Universidade de Lisboa
Faculdade de Farmácia

New synthetic asymmetric methodologies for the synthesis of bioactive building blocks and potential scale up/out

Rafael Filipe Teixeira Arbuéz Gomes

Orientador: Professor Doutor Carlos Alberto Mateus Afonso
Co-orientador: Doutor Ricardo Filipe de Jesus Gonçalves Mendonça

Tese especialmente elaborada para obtenção do grau de doutor em Farmácia, especialidade de Química Farmacêutica e Terapêutica.

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6. Alexandre F. Trindade, Jaime A. S. Coelho, **Rafael F. A. Gomes**, João P. M. António, Raquel F. M. Frade, Carlos A. M. Afonso, "5-hidroximetilfurfural: plataforma para obtenção de diversidade molecular", *Química*, **2018**, 42 (151), pp 236-240.

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Abbreviations and Symbols

2-FBBA = 2-formylbenzene boronic acid

ACP = amino cyclopentenone

ACN = acetonitrile

API = active pharmaceutical ingredient

Bn = benzyl

BAF = barbituric acid activated furfural

BzAld = Benzaldehyde

CP = Cyclopentenone

DCP = *trans*-4,5-diamino-cyclopent-2-enone

DASA = Donor-Aceptor Stenhouse Salt

DCM = dichloromethane

EtOH = ethanol

HMF = 5-hydroxymethylfurfural

HCP = hydroxyl cyclopentenone

LCP = δ-Lactone-fused cyclopentenones

MAF = meldrum’s acid activated furfural

MCP = morpholino cyclopentenone

MeOH = methanol

NMR = Nuclear Magnetic Resonance

OTf = trifluoromethanesulfonate

PMB = 4-methoxybenzaldehyde

PDMB = 4-(dimethylamino)-benzaldehyde

PPA = 3-phenylpropanal

SACP = sulfur-amino cyclopentenone

SS = Stenhouse Salt

SalAld = Salicylaldehyde

Abstract

Preparation of medicinal relevant small molecules from biomass is a field of interest due to 1) structural diversity obtained in biomass modification, 2) being sustainable and an environmentally friendly approach, 3) low cost of starting materials most likely lead to low cost of final product.

Amoungst biomass, the furans have been given special attention by the scientific community, namely furfural and 5-hydroxymethylfurfural (HMF). They can be obtained by de dehydration of non-edible carbohydrates and have been described as key building blocks for the future.

On the other hand, cyclopentenones (CP) are a class of molecules that has used for medicinal purposes. The transformation of furfural to *trans*-4,5-diamino-cyclopent-2-enones or other CP derivatives has been reported by several different methodologies being available. However there has been no attempts on taking advantage of this sustainable transformation towards the development of new bioactive molecules.

Also, although the transformation of furfural, Meldrum's acid activated furfural and furyl alcohols to cyclopentenones has been studied, the same transformation using HMF has yet to be succeeded.

In this thesis we studied the transformation of furans to CP, taking into consideration sustentability and possible scale up/out, and evaluate their biological activity. We observed that diferent families of CP prepared from furfural have remarkable anticancer and antibacterial activity, while CP prepared from HMF present antimalarial activity.

The issue on HMF stability is also address during the course of this thesis, as well as the formation of aminals. The formation of aminals was used as means to protect furfural but was explored as a common protective group of aldehydes, as a way to scavenge genotoxic impurities and as a stimuli-responsive dynamic linker.

Keywords: Sustainability, Furfurals, Cyclopentenones, Continuous Flow Chemistry, Medicinal Chemistry

Resumo

A preparação de pequenas moléculas com relevância medicinal é um campo de interesse devido a 1) diversidade estrutural obtida durante a modificação de biomassa, 2) ser uma abordagem sustentável e amiga do ambiente, 3) baixo custo dos materiais de partida que possivelmente levarão ao baixo custo do produto final.

De vários compostos presentes na biomassa, os furanos têm sido objecto de especial atenção pela comunidade cientifica, em particular furfural e 5-hidroximetilfurfural (HMF). Podem ser obtidos pela desidratação de carbohidratos não comestíveis e foram descritos como materiais de partida importantes do futuro.

Por outro lado, ciclopentenonas (CP) são uma classe de moléculas que têm sido usadas para efeitos medicinais. A transformação de furfural em *trans*-4,5-diamino-ciclopent-2-enonas foi previamente descrita, estando disponível várias metodologias para esta transformação. Apesar disso não houve qualquer tentativa de usar esta transformação sustentável para o desenvolvimento de novas moléculas biologicamente relevantes.

Apesar da transformação de furfural, furfural activado por ácido de Meldrum e alcóis furfurílicos em CP ser bem conhecida, a mesma transformação usando HMF ainda não foi bem sucedida.

Nesta tese estudamos a transformação de furanos em CP, tendo em consideração a sustentabilidade e possível aumento de escala, e avaliamos a sua actividade biológica. Observámos que diferentes famílias de CP preparadas do furfural apresentam marcada actividade anticancerígena e antibacteriana, enquanto as CP preparadas do HMF apresentam actividade antimalárica.

O problema da instabilidade do HMF também é resolvido nesta tese, tal como a formação de aminais. A formação de aminais foi usada para a proteção do furfural mas foi explorada como um grupo de proteção comum de aldeídos, na remoção de impurezas genotoxicas e como uma ligação responsiva a um estímulo.

Começamos o estudo da transformação do furfural em CP testando vários catalisadores em meio aquoso. Verificámos que triflato de cobre ($Cu(OTf)_2$) catalisa eficientemente a reação e conseguimos reutilizar o catalisador até 4 vezes. No seguimento deste trabalho preparámos catalisadores heterogénios baseados em cobre para estudarmos a possibilidade de reação em fluxo contínuo. Escolhemos imobilizar sulfato de cobre (CuSO4) por ser um sal de cobre barato e facilmente disponível, e imobilizámos o catlizador em vários suportes sólidos como silica, alumina e hidroxiapatite. Verificámos

que o catalisador adsorvido em silica promove eficientemente a formação de CP a partir de furfural em fluxo contínuo

As actividades biológicas destas CP foram testadas e verificou-se que derivados de adição de Michael tinham actividades anticancerígenas bastante promissoras. Por outro lado as CP também apresentam actividade antimicrobiana com inclusive em estirpes multirresistentes de MRSA.

A transformação de HMF em CP também foi estudada. Para esse efeito activou-se o HMF através de condensação de Knoevanagel com ácido de meldrum. Esta reação para preparar derivado activado do HMF causava vários problemas como baixo rendimento e formação de precipitados insolúveis. Esta instabilidade do HMF é bastante conhecida e já nos tínhamos deparado com ela em trabalhos anteriores. Foi possível eliminar a formação destes produtos secundários usando como aditivo ditionito de sódio. Este aditivo conseguiu estabilizar o HMF tanto a temperatura como em várias condições reacionais. Isto permitiu por exemplo a destilação do HMF que até agora não era possível.

Com o problema da instabilidade resolvido, procedemos ao estudo de formação de CP a partir dos derivados activados do HMF. Verificámos que a reação em solventes halogenados ocurria com posterior lactonização intramolecular, catalizada por BINOL. Preparámos várias novas ciclopentenonas bicíclicas e derivados.

Estes derivados foram testados para actividade biológica e verificou-se em ensaios preliminares que algumas CP derivadas do HMF tinham actividade anti malárica.

Por fim testou-se a possibilidade de usar o grupo aminal como grupo de proteção de aldeídos. Devido à instabilidade do HMF, a sua proteção como acetal leva a decomposição como por exemplo a formação de dímeros ou homo-acetais. Nesta linha tentámos desenvolver um método suave, sem recurso a ácidos fortes normalmente usados para a formação de acetais, para a formação de aminais.

A formação de aminais foi desenvolvida em meio aquoso como vários catalisadores, sendo que quantidades mínimas de triflato de cobre promoveram a formação do aminal em menos de 5 minutos á temperatura ambiente. A formação do aminal leva à precipitação do mesmo na mistura reacional, sendo que podemos obter o produto puro após simples filtração.

A estabilidade de vários aminais foi avaliada, sendo que aminais cíclicos de 6 membros obtidos através da condensação de aldeídos com *N,N'*-metil-propilenodiamina e a partir de aminas aromáticas são mais estáveis.

A desproteção do aminal é feita numa mistura de THF:água com ácido acético. O potencial uso do aminal como grupo de proteção foi avaliado através de reações na presença do grupo aminal e verificou-se que o aminal se manteve após condições de 1) redução, 2) oxidação, 3) adição de Grignard, 4) amidação, 5) litiação.

Entre várias impurezas que aparecem em produtos finais como ingredientes activos, os aldeídos podem estar presentes. Infelizmente muitos aldeídos são impurezas genotóxicas, daí serem impurezas com níves bastante controlados pelas autoridades. Tirando vantagem do nosso método eficiente para formação de aminais, usámos uma resina comercial contendo uma diamina para a remoção de aldeídos. Empacotámos uma coluna de cromatografia líquida em alta pressão (HPLC) vazia com a resina e ao passar uma mistura de aldeídos e triflato de cobre conseguimos reter os aldeídos na coluna.

Usámos como caso de estudo um modelo de substancia activa que é preparado a partir de aldeídos. A remoção do aldeído duma mistura de produto/aldeído foi bem sucedida usando o nosso método.

Por fim estudámos a possibilidade de usar o grupo aminal como ligação covalente dinâmica que pode ser quebrada por um estímulo. Verificámos que usando um aldeído com ácido borónico na posição ortho, conseguimos aumentar a estabilidade do grupo aminal, que em condições acídicas hidrolisa.

Em conclusão, no decorrer desta tese desenvolvemos um método para preparar CP a partir de furfural em água e em fluxo contínuo. Estudámos a sua actividade biológica e de derivados. Também preparámos CP a partir de HMF e estudámos a sua actividade biológica. Por fim desenvolvemos um método para a preparação de aminais e estudámos a sua utilização como 1) grupo de proteção de aldeídos; 2) remoção de aldeídos genotóxicos; 3) ligação covalente dinâmica mediante estímulo.

Palavras-chave: Sustentabilidade, Furfurales, Ciclopentenonas, Química em fluxo contínuo, Química Medicinal

Abreviaturas e Símbolos

2-FBBA = ácido 2-formylbenzeno borónico

ACP = amino ciclopentenona

ACN = acetonitrilo

API = substancia activa

Bn = benzilo

BAF = furfural activado por ácido barbitúrico

BzAld = Benzaldeído

CP = Ciclopentenona

DCP = *trans*-4,5-diamino-ciclopent-2-enona

DASA = sal de stanhouse doador-aceitador

DCM = dichlorometano

EtOH = etanol

HMF = 5-hidroximetilfurfural

HCP = hidroxil ciclopentenona

LCP = cyclopentenona δ-Lactona-fundida

MAF = furfural activado por ácido de meldrum

MCP = morfolino ciclopentenona

MeOH = metanol

NMR = ressonância magnética nuclear

OTf = trifluoromethanesulfonato

PMB = 4-methoxybenzaldeído

PDMB = 4-(dimethilamino)-benzaldeído

PPA = 3-fenilpropanal

SACP = tio-amino ciclopentenona

SS = sal de stenhouse

SalAld = Salicilaldeído

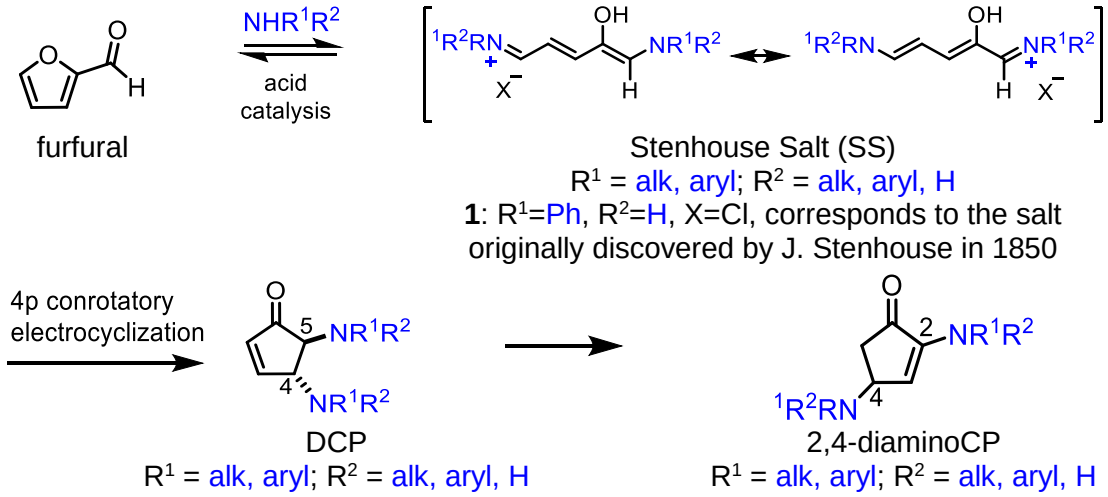
Chapter I

I. State of the art - Transformation of furans to cyclopentenone scaffolds

Abstract: The transformation of furans to CP has been thoroughly studied by several research groups from the early XXth century. Recent advances point towards more sustainable approaches for the preparation of CP and the use of activated furfurals in order to avoid the use of catalyst. Although several methodologies for the preparation of CP from furfural derivatives have been reported, the transformation of HMF to CP has yet to be discovered.

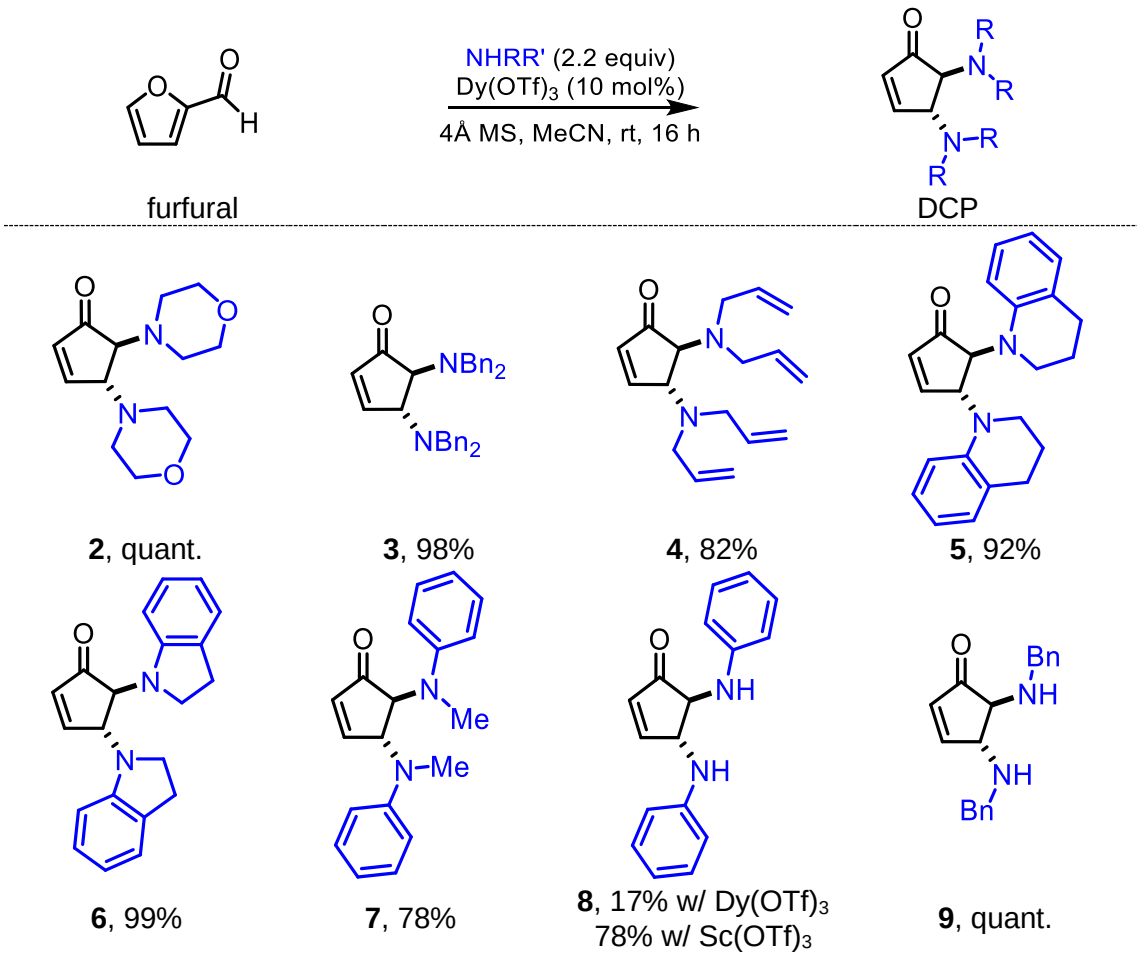
I.1. Synthesis of trans-4,5-diamino-2-cyclopentenones

First reported in 1850, Stenhouse salts (SSs) result from the furan ring-opening reaction upon condensation of furfurals and amines (**Scheme 1**). These salts are named after J. Stenhouse, who first described the formation of **1**, the product of reacting aniline with a furfural-containing crude oil obtained upon acidic treatment of various vegetable plants.[1,2] Early studies revealed that SS undergo a thermal 4π-electrocyclization reaction under acidic conditions to give the corresponding colorless 4,5-diamino-2-cyclopentenones (DCPs), which further rearrange into the thermodynamically more stable 2,4-isomer (**Scheme 1**).[3,4]



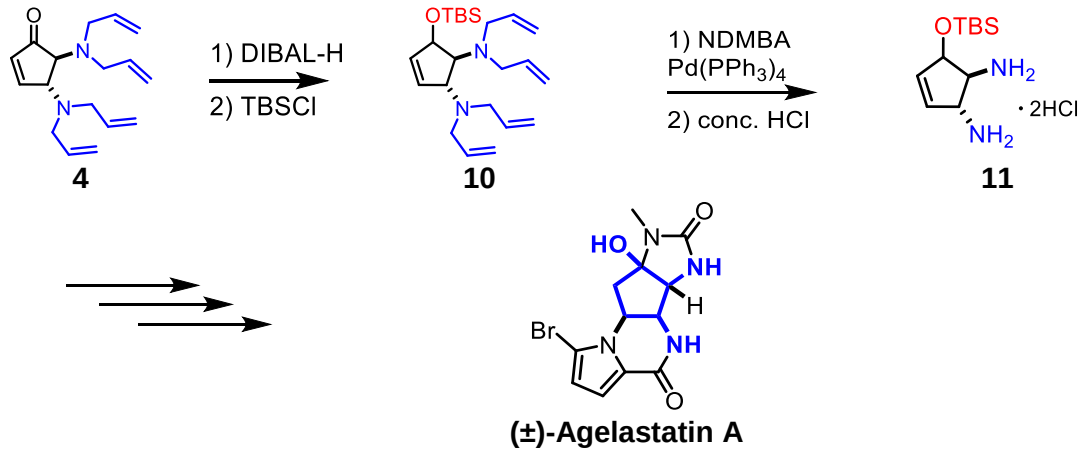
Scheme 1 General formation of Stenhouse salts; and subsequent 4π-cyclization into the 4,5-diamino-cyclopenten-2-ones followed by the isomerization into 2,4-diamino-cyclopenten-2-ones.

In 2007, Batey and Li successfully developed the selective synthesis of DCP by Lewis acid catalysis under mild reaction conditions (acetonitrile at room temperature, **Scheme 2**).[5] Several secondary anilines and aliphatic amines successfully reacted with furfuraldehyde promoted by dysprosium(III) trifluoromethanesulfonate ($Dy(OTf)_3$) to afford the corresponding CP in very good to excellent yields (**Scheme 2**). Furthermore, the use of scandium(III) trifluoromethanesulfonate ($Sc(OTf)_3$) allowed for the less reactive primary anilines to undergo the rearrangement efficiently.



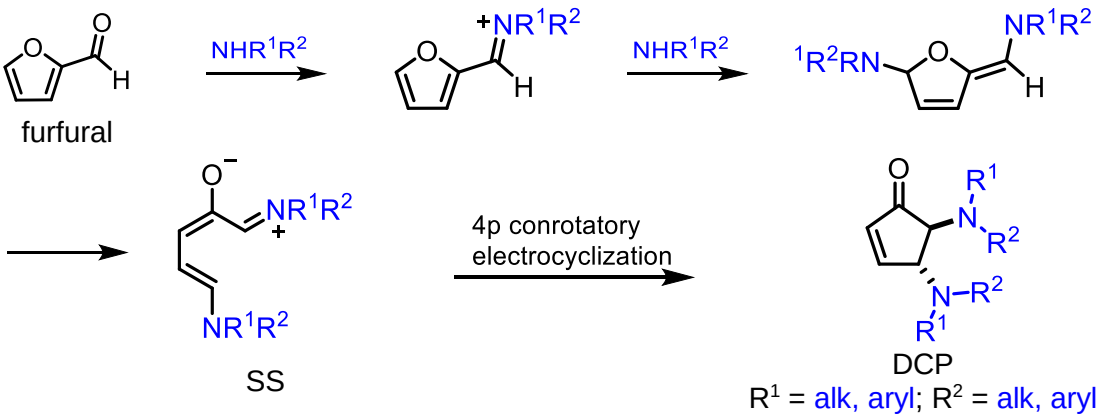
Scheme 2 Lanthanide(III)-catalyzed reaction of furfural with several amines to afford DCP.

Moreover, the use of amines bearing labile substituents such as the allyl group, allowed for the synthesis of NH_2- containing CP derivatives upon removal of the protecting group. Thus, the same research group later reported the synthesis of the natural product (±)-Agelastatin A from furfural and diallylamine (**Scheme 3**).[6]



Scheme 3 DCP as starting point for the synthesis of (±)-agelastatin A. NDMBA stands for *N,N*-dimethyl barbituric acid

Mechanistic studies revealed that ring closure is a fast process and first order with respect to the SS, which suggest that formation of SS intermediate is the rate-determining step (**Scheme 4**). Computational studies at the UHF/6-31G** level of theory on the ring-closure step supported a thermal conrotatory 4π-electrocyclization consistent with a Nazarov-like mechanism in which the trans product is favored.[5]



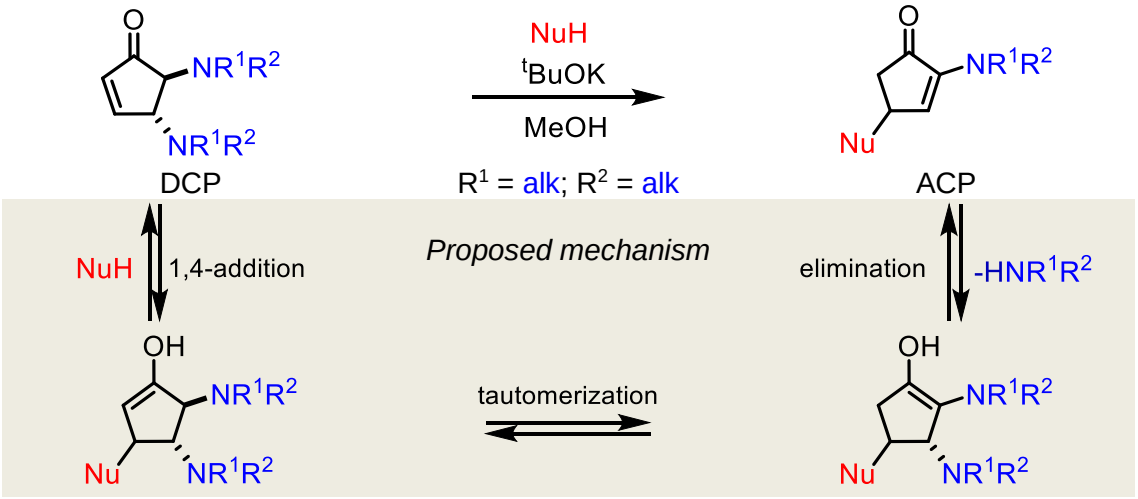
Scheme 4 Proposed mechanism for the formation of DCP from furfural

Inspired by the pioneering work of Batey, several other authors reported alternative reaction conditions for the selective synthesis of *trans*-4,5-diamino-CPs. In 2009, Venkateswarlu and co-workers reported the use of the acidic ionic liquid 1-methylimidazoliumtetrafluoroborate as reusable reaction medium. Under this reaction conditions, several CPs were obtained in high yields after short reaction times (up to 98% yield in around 5 min).[7] In 2013, Yu, Wang and co-workers reported the use of p-toluenesulfonamide catalysis, which allowed the reaction of furfural and secondary amines to be performed at 80 ºC under metal-free conditions.[8] Therein, the reaction of the N-sulfonylimine intermediate with several amines was also described. It is worth mentioning that anilines gave poor yields under these reaction conditions. In 2015 Kostakis and co-workers reported the use of a heteronuclear cluster with general formula $[Ni^{II}_2Dy^{III}_2L_4Cl_2(CH_3CN)_2]\cdot 2CH_3CN$ as catalyst (H_2L=(E)-2-(2-hydroxy-3-methoxybenzylidene-amino)phenol). The reaction of furfural with several secondary amines in the presence of 1 mol% of this cluster afforded the corresponding CPs in up to quantitative yield after 16 h, at room temperature and under air. Interestingly, under these conditions, primary amines afforded the corresponding deprotonated SSs and subsequent acidic treatment gave the corresponding CP. This process is industrially appealing as it allows the reaction to be performed under air and heterogeneous conditions. [9,10] In 2013, Procopio and co-workers reported the use of erbium(III) chloride and ethyl lactate (catalyst and solvent, respectively) as a more sustainable alternative.[11] Later on, Afonso *et al.* reported the use of erbium(III) immobilized on silica as a reusable

catalyst.[12] In 2017, a method to prepare CP in water under microwave irradiation (60 ºC, 5 min) was described by Nardi and co-workers. [13]

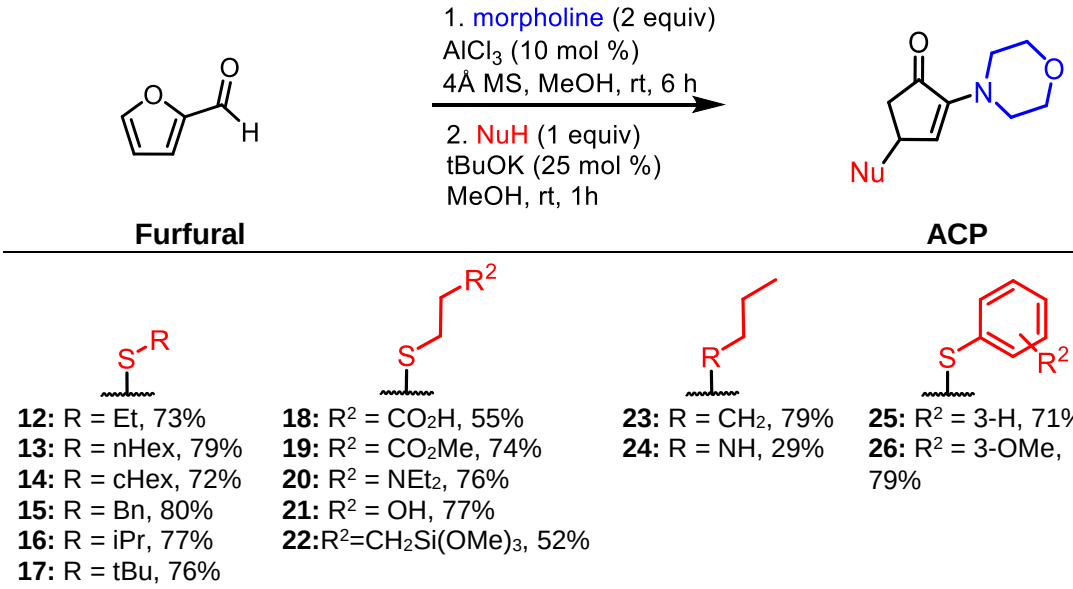
I.2. Synthesis of the 2,4-bifunctionalized-cyclopent-2-enones

Regioisomeric 2,4-bifunctionalized-aminocyclopentenones (ACP) can be prepared from furfural via formation of DCP **2** followed by a consecutive intermolecular 1,4-addition (thiols were used as the nucleophile in most of the cases), isomerization via ketoenol tautomerization and elimination of the amine to reform the CP core (**Scheme 5**).[14]



Scheme 5 Tandem process for the formation of ACP from DCP.

Several alkyl and aryl thiols were successfully employed in this process to yield the corresponding 4-thio-2-morpholino-2-CPs 14–26 in up to 80% yield (**Scheme 6**). In addition, Gilman reagent $LiCu(nBu)_2$ smoothly reacted with the diamine intermediate to yield **23** in 79% yield (**Scheme 6**). Primary amine propanamine afforded the desired mixed 2,4-diaminocyclopentenone **24** in low yield (29% yield, **Scheme 6**). The isolation of the byproducts 4-morpholino (20%) and 4-methoxy (20%) 2-morpholino-2-CP accounted for the mass balance.

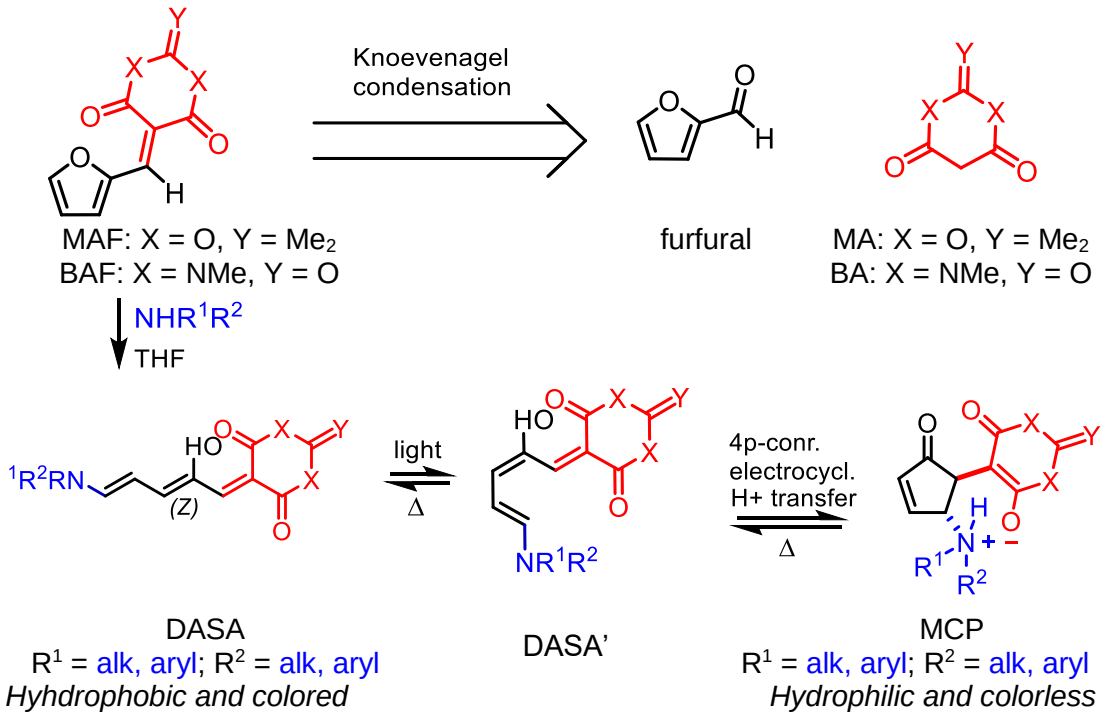


Scheme 6 Nucleophile scope for the formation of ACP from furfural

I.3. Donor–Acceptor Stenhouse Adducts (DASA)

In 2014, Alaniz and co-workers reported the synthesis of a novel type of Stenhouse adducts with remarkable properties as visible light activated photochromes. The structure of these molecules comprises an amine (donor) and a dicarboxylate moiety (acceptor) from either Meldrum's or 1,3-dimethylbarbituric acids at the terminal positions of the conjugated π-system. These new class of Stenhouse adducts are known as donor-acceptor Stenhouse adducts (DASA, **Scheme 7**).[15,16]

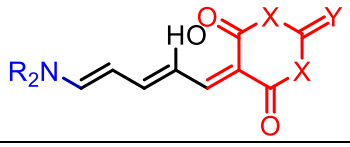
DASA are highly-colored hydrophobic molecules that undergo reversible Nazarov-type 4π-electrocyclization into the corresponding colorless hydrophilic zwitterionic Meldrum's acid-CP (MCP)[15,17] upon irradiation with wavelengths spanning from 450 to 750 nm, depending on the amine moiety.[18,19] The synthesis of DASA was accomplished by preparation of the corresponding activated furan, MAF or BAF, via Knoevenagel condensation of furfural and Meldrum's acid or 1,3-dimethylbarbituric acid, respectively, followed by reaction with a secondary amine or aniline.[15]

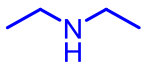
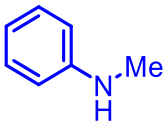
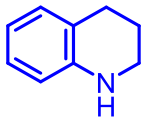
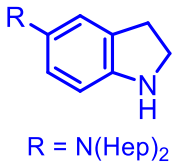


Scheme 7 Donor-acceptor Stenhouse Adducts formation.

The use of activated furans allowed the reaction to proceed in the absence of catalyst in excellent yields, which allowed the easy access to small libraries of these molecules.[16] Photoisomerization of amine-based DASA was found to be highly solvent dependent. Polar protic solvents stabilize the zwitterionic CP inhibiting the reverse ring-opening into the Stenhouse adduct form. On the other hand, it was found that halogenated solvents favor the triene form. Aromatic solvents such as toluene proved to be the most suitable solvent for the photoswitch turn-on/turn-off. Complete photoisomerization of the Stenhouse adduct into the corresponding CP was observed in toluene, confirmed by the decrease on the UV/Vis absorption profile. The absence of a photo-stimulus resulted in the re-establishment of the UV/Vis absorption profile caused by retrocyclization. Nevertheless, the use of aniline-based DASA overcame the solvent restriction, allowing the photoswitching to occur in polar solvents such as DCM, THF, ethyl acetate or acetonitrile.[18] Selected photochemical properties of some DASA are depicted in **Table 1**. A bathochromic shift (21–25 nm) is observed on moving from MAF-derived DASA to BAF-derived DASA. Within the same acceptor class, similar absorption trend is observed on moving from alkyl to aromatic amines. In particular, the highest λ_{max} was observed with the BAF-derived DASA containing the most electron-donating amine substituents (669 nm, **Table 1**, entry 4). On the other hand, the lowest λ_{max} was observed with the MAF-derived DASA containing diethylamine (545 nm, **Table 1**, entry 1). Molar absorption coefficients are not influenced by either the acceptor or the amine. The photoisomerization is faster in the DASA containing barbituric acid as the acceptor.

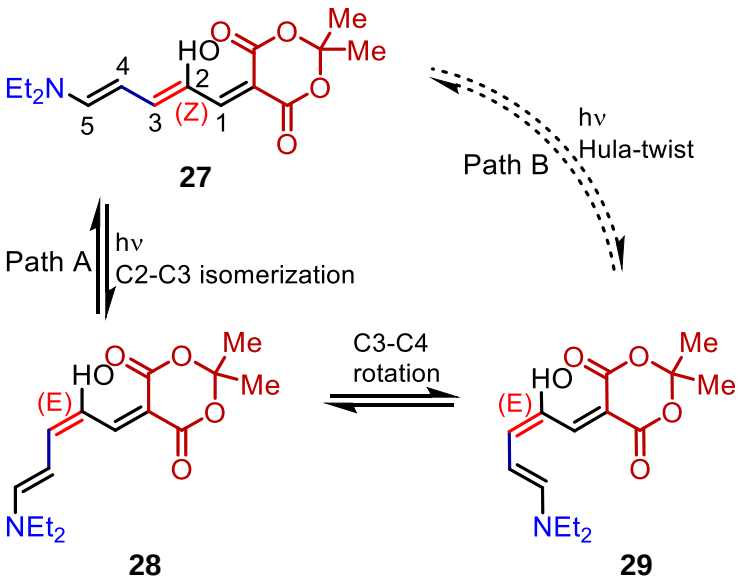
Table 1 Photochemical properties of DASA.[a][16,17,19]



amine	X = O, Y = Me_2	X = NMe, Y = O
	λ_{max} (toluene) = 545 nm $\varepsilon = 1 \times 10^5$ $M^{-1}cm^{-1}$ Ref. 17	λ_{max} (toluene) = 570 nm $\varepsilon = 1 \times 10^5$ $M^{-1}cm^{-1}$ Ref. 17
	λ_{max} (CH_2Cl_2) = 558 nm $\varepsilon = 1.1 \times 10^5$ $M^{-1}cm^{-1}$ PI rate[b] = 1.32 × 100 s^{-1} Ref. 19	λ_{max} (CH_2Cl_2) = 582 nm $\varepsilon = 1.1 \times 10^5$ $M^{-1}cm^{-1}$ PI rate[b] = 2.93 × 100 s^{-1} Ref. 16
	λ_{max} (CH_2Cl_2) = 575 nm PI rate[b] = 2.35 × 100 s^{-1} Ref. 47	λ_{max} (CH_2Cl_2) = 599 nm $\varepsilon = 8.9 \times 10^4$ $M^{-1}cm^{-1}$ PI rate[b] = 2.36 × 100 s^{-1} Ref. 47
 R = $N(Hep)_2$	λ_{max} (CH_2Cl_2) = 648 nm PI rate[c] = 1.72 × 100 s^{-1} Ref. 16	λ_{max} (CH_2Cl_2) = 669 nm PI rate[c] = 3.15 × 100 s^{-1} Ref. 16

[a] Values not represented are not described in the literature; [b] measured in toluene; [c] measured in hexane:toluene

DASA showed good fatigue resistance with no degradation up to 20 cycles of irradiation/dark.[15] Moreover, dynamic phase transfer was possible due to solubility alterations upon isomerization. A colored DASA solution in toluene layered over colorless water underwent rapid color loss upon irradiation caused by the complete migration of the hydrophilic CP to the water layer. The stabilization effect of the water stopped the retrocyclization of the CP.[15] Feringa and co-workers studied the mechanism for the photoisomerization of DASA using UV/Vis absorption spectroscopy[20] and a combination of ultrafast visible and IR pump-probe spectroscopies and TD-DFT calculations.[21] The proposed mechanism starts with a *Z–E* isomerization to intermediate **28** followed by rotation of the C3-C4 sigma bond to **29**. The resulting conformer is in place for the thermal conrotatory 4π-electrocyclization to form MCP (**Scheme 8**, path A). Alternative Hula-twist mechanism that bypasses the formation of intermediate **28** was excluded because this intermediate was trapped at low temperature (**Scheme 8**, path B).

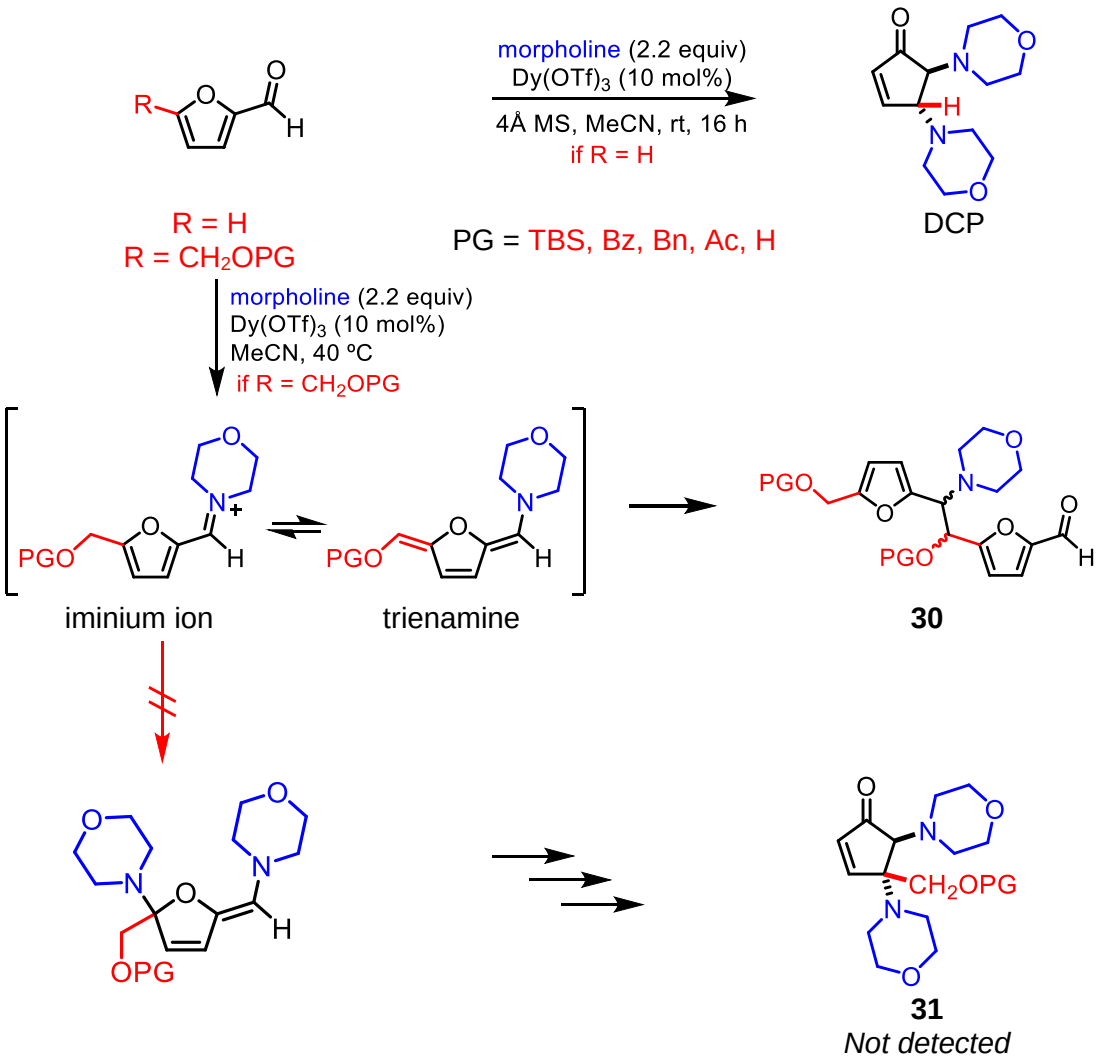


Scheme 8. Isomerization mechanism of the DASA elucidated by Feringa and co-workers

I.4. Attempts towards formation of Cyclopentenones from 5-hydroxymethylfurfural

Early attempts at the formation of complex cyclopentenones from 5-hydroxymethylfurfural (HMF) were unsuccessful. While furfural reacts with morpholine in the presence of $Dy(OTf)_3$ to form previously described DCP, HMF derivatives undergoes an unexpected homo-bisvinylogous Mannich reaction *via in situ* formation of trienamine that reacts with the corresponding iminium ion to form dimer 30 (**Scheme 9**).[22] Traces of CP **31** resulting from the ring opening and Nazarov electrocyclization were never detected.

When the same conditions were carried out in the presence of arylamines such as *N*-methyl-aniline another product was formed corresponding to the Friedel-Crafts alkylation reaction of the HMF aldehyde and the arylamine. Further optimization lead to the development of a methodology for the preparation of triarylmethanes (TRAM) promoted by Lewis acid Ytterbium trifluoromethanosulfonate ($Yb(OTf)_3$) that was significantly accelerated by high pressure (**Scheme 10**). [23]

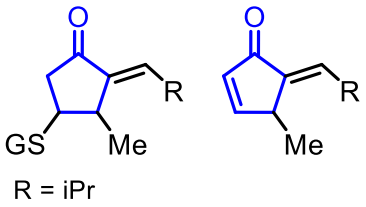


Scheme 9 Unexpected homo-bisvinylogous Mannich reaction of HMF derivatives in the presence of morpholine.

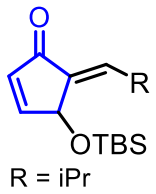
Scheme 10. Formation of TRAM from the LA promoted condensation of HMF derivatives and *N*-methyl-aniline

I.5. Examples of medicinal relevant cyclopentenone

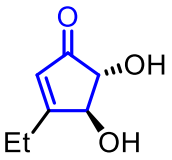
Several natural products containing a cyclopentenone core present remarkable biological activity (**Figure 1**), from anti-inflamatory[24], antiviral[25,26], antitumoral[27–33], pro-apoptotic[34] and antifungal[35].



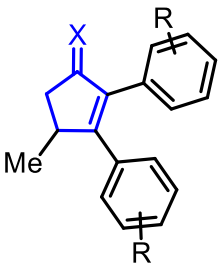
NF-kB inhibitors
Bickley *et al.*[35]



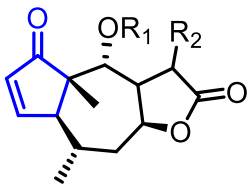
CTC-35 - synthetic inducer of apoptose in ER negative breast cancer cells
Santoro *et al.*[29]



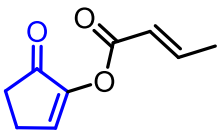
Trichoderone - natural product cytotoxic
Chen *et al.*[28]



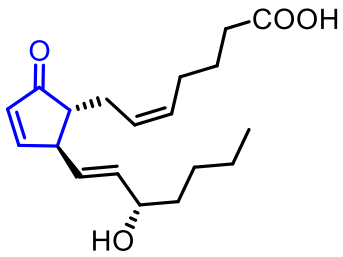
Synthetic cyclopentenones
Anticancer
Agarwal *et al.*[31]



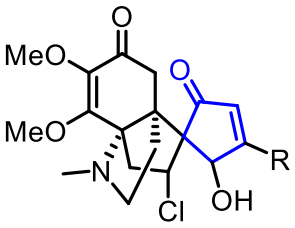
Helenalin - natural product cytotoxic
Schmidtb *et al.*[30]
Kumar *et al.*[36]



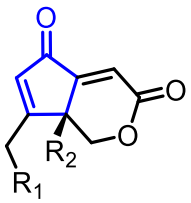
Synthetic B16 cells growth inhibitor
Creighton *et al.*[37]



PGA2
Several biological activities
Pérez-Sala *et al.*[33]



Hypserpanine A
Antiviral - anti HBV
Ji-jun Chen *et al.*[26]



Iridoid glucosides derived from aucubin
Active against L1210 and KB cell lines
Deguin *et al.*[32]

Figure 1 Selected relevant biologically active cyclopentenones

Most activities result of the electrophilic character of the CP ring. Several examples have been reported where the biological target, usually a protein containing a free cystein, undergoes a Michael addition on the α,β-unsaturated ketone forming an inactive CP-protein complex. Some of the known targets are proteins and transcription factors involved in the cell proliferation and cell protection (**Figure 2**).[25,27,29,33,34,38]

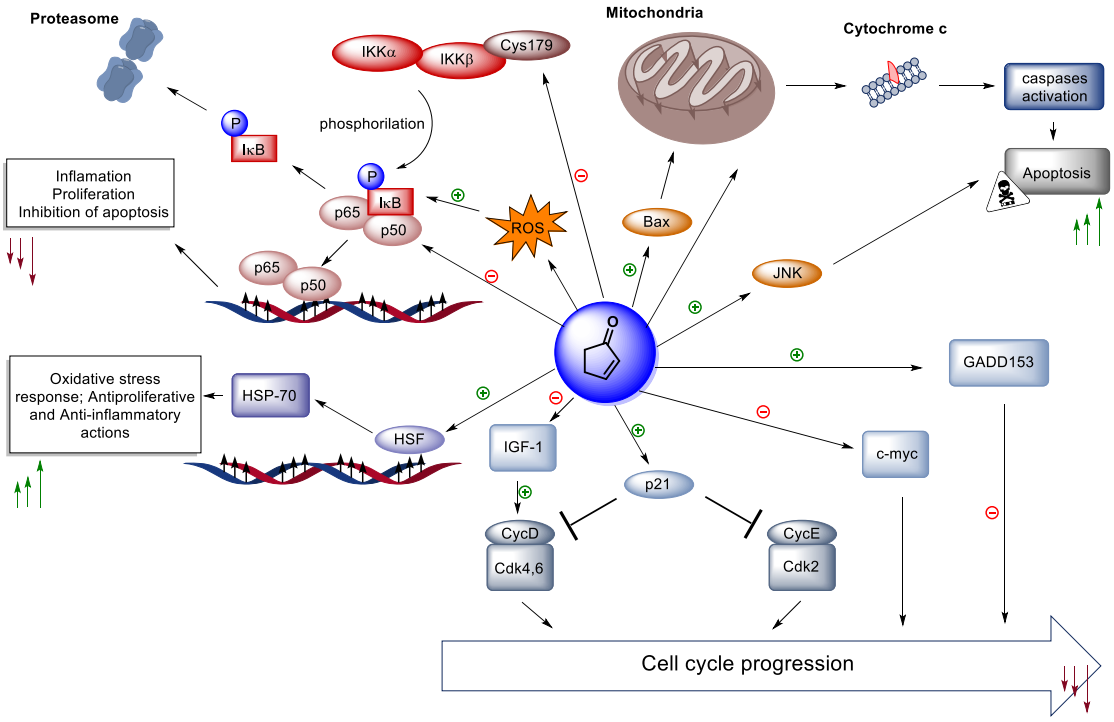


Figure 2 Cyclopentenone known intracellular targets

Preparation of biologically active products from biomass allows for cheaper and accessible drug products.[23] However, despite the formation of CP from biomass derived furans being well known as depicted in the previous sub-chapters, there has been no reports on the preparation of medicinal relevant CPs from biomass.

I.6. Final remarks

In this chapter we can see that the formation of CP core is an active area of research. Several methodologies have been described for the formation of CP promoted by Lewis acids or catalyst free in the case of activated furfurals. Focusing in the CP prepared from biomass there is no toxicological information nor biological activity described. Moreover there is no reports on the formation of complex CP from 5-hydroxymethylfurfural.

Chapter II

II. Transformation of furfural to *trans-4*,5-diamino-cyclopent-2-enones and derivatives as new scaffolds for drug discovery

Abstract: The transformation of furfural to *trans*-4,5-diamino-cyclopent-2-enones has been studied with a wide range of catalysts. Although these CP have been used for the preparation of a natural product, (±)-agelastatin A, there has been no biological activities of these class of molecules reported nor an efficient scale-up process.

In this Chapter we developed a methodology to prepare CP from furfural in water and prepare a continuous flow system for the scaling up/out of this reaction. The reaction in aqueous conditions is promoted by $Cu(OTf)_2$ while the continuous flow is promoted by silica supported $CuSO_4$ catalyst.

A new class of mixed CP is described from the reaction of furfural and two distinct amines that undergoes with high regioselectivity that is highly dependent on the stabilization of the iminium ion.

Michael addition to these CP affords new derivatives that present remarkable anticancer activity, while retaining a low electrophilic character. The common pain of having a reactive enone that usually leads to poor pharmacokinetics and side effects is overcome with this strategy.

The CPs also show remarkable antibacterian activity, even against MRSA.

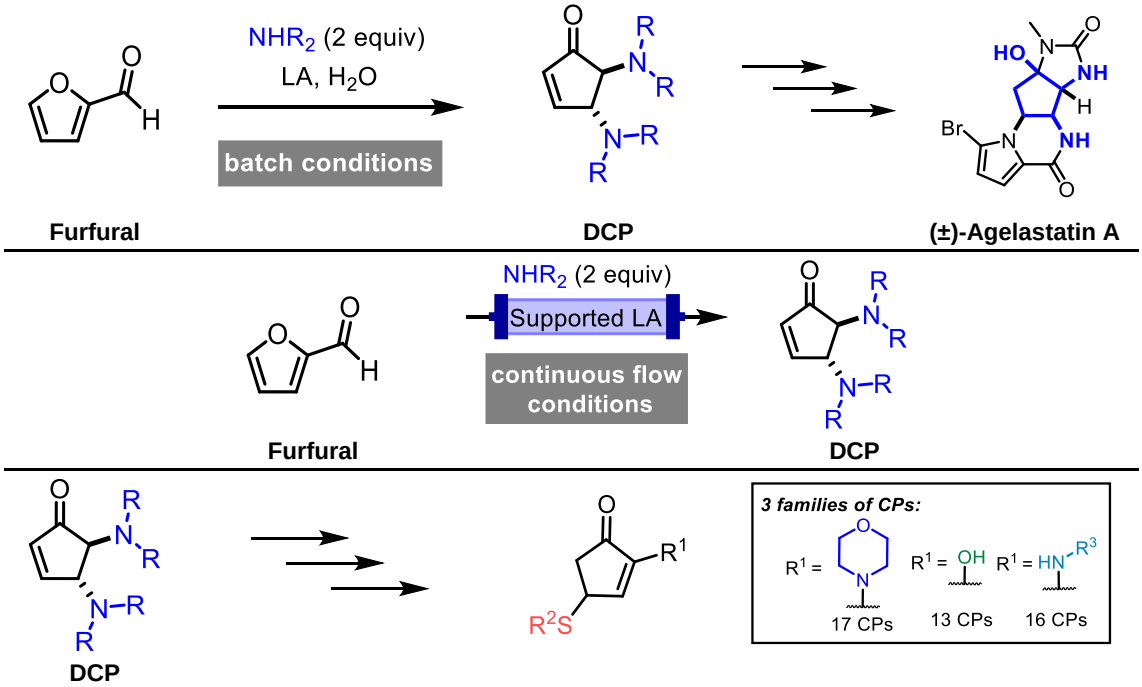
II.1. Rationale and Goals

Cyclic enones such as cyclopentenones (CPs) and cyclohexanones have been reported to have cytotoxic activity against several cancer cell lines.[29,36,38,39] New families of bioactive molecules containing CP scaffold can be obtained from highly versatile *trans*-4,5-diamino-CPs (DCP). Moreover new methodologies for sustainable and scalable production of DCP are of importance due to the use of diallyl-DCP as precursor for total synthesis of cytotoxic marine sponge alkaloid (±)-Agelastatin A.[6]

Water is considered as a green environmentally friendly solvent. The mechanism for the transformation of furfural in DCP starts from the condensation with an amine to form the corresponding iminium ion as depicted in Chapter I. Formation of imines can be performed in aqueous solvents. Considering this we aimed at screening Lewis acids to find the appropriate LA for this transformation in water.

Upon finding the appropriate LA the immobilization in solid support allow for the development of a continuous flow system. Continuous flow has been described as an easily scalable methodology that will allow the formation of DCP in high productivity.

Transformation of DCP in 3 families of 2,4-substituted CPs can be performed upon thio-Michael addition, followed by hydrolysis and condensation with primary amines. The novel CPs scaffolds will then be screened for several biological activities such as anticancer, antimicrobial, anti-HIV and anti-malarial. (**Scheme 11**)



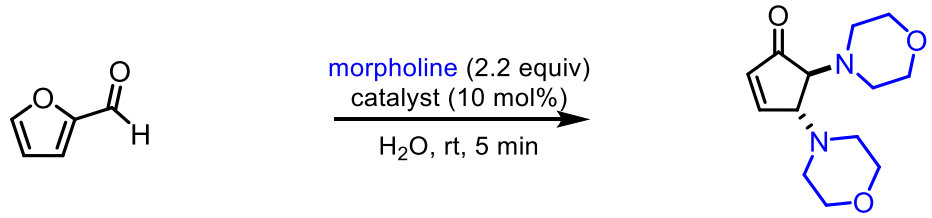
Scheme 11 Overview of the formation of DCP in batch and continuous flow conditions abd preparation of novel 2,4-substituted CPs from DCP developed in this thesis.

II.2. Results and discussion

II.2.1. Preparation of DCP in aqueous media

The reaction of furfural with morpholine in water resulted in the formation of traces amount of the desired product **2** after 5 min (**Table 2**, entry 1). Based on that, we started this study by testing several Lewis acids catalysts under the same reaction conditions. To our delight, 10 mol % of $Dy(OTf)_3$ afforded **2** in 53% yield (**Table 2**, entry 2). Other Lewis acids, such as $GdCl_3 \cdot 6H_2O$, $ErCl_3$, $ZnCl_2$, or $AlCl_3$, were not able to catalyze the reaction (**Table 2**, entries 7-11, up to 42% yield). Remarkably, $Cu(OTf)_2$ afforded **2** in outstanding isolated yield (quantitative) (**Table 2**, entry 3). It is noteworthy that full conversion was observed in most cases. Remarkably, the use of 10 mol % of $Cu(OTf)_2$ results in full conversion of the starting materials in <1 min. Next, we investigated the influence of the copper ligand by evaluating several different copper salts under the same reaction conditions (**Table 2**, entries 3-6). The tested salts afforded up to 50% yield of **2** in opposite to an outstanding yield obtained with the trifluoromethanesulfonate salt. Furthermore, the Brønsted acids p-toluenosulfonic acid and triflic acid afforded low yield of **2** (**Table 2**, entries 12-13, 25% and 32% yield, respectively). Further reduction of $Cu(OTf)_2$ loading to 1 mol % did not affect the performance, and **2** was obtained in excellent yield after 10 min reaction time (**Table 2**, entry 14, quantitative). In addition, the combined scale up to 10 g of furfural and reduction of catalyst load to 0.1 mol % afforded the product in 93% yield after 8 h as a 6.7:1 mixture of **2** and the thermodynamically more stable regioisomer 2,4-dimorpholino-cyclopent-2-enone (**Table 2**, entry 15).[14] Full conversion to the 2,4 regioisomer was observed after 24 h. Finally, similar efficiency of the catalyst was observed in an organic solvent (acetonitrile, **Table 2**, entry 16 quantitative yield of **2**).

Table 2 Optimization of the reaction conditions for the synthesis of *trans*-4,5-dimorpholino-cyclopent-2-enone[a]



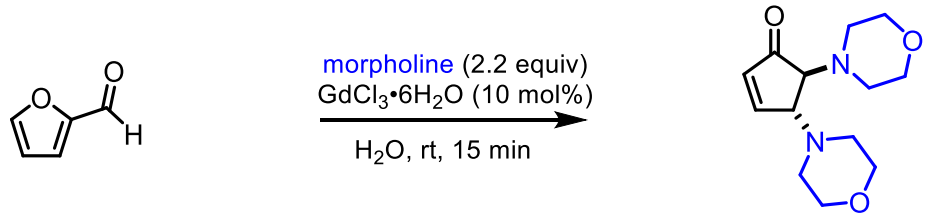
furfural **2**

Entry	Catalyst	Yield (%)[b]
1	none	traces
2	$Dy(OTf)_3$ (10 mol %)	53
3	$Cu(OTf)_2$ (10 mol %)	quant (quant.)[c]
4	$Cu(OAc)_2$ (10 mol %)	38
5	$Cu(SO_4)$ (10 mol %)	46
6	CuCl (10 mol %)	30
7	$GdCl_3.6H_2O$ (10 mol %)	10
8	$ErCl_3$ (10 mol %)	10
9	$ZnCl_2$ (10 mol %)	14
10	$FeCl_3$ (10 mol %)	9
11	$AlCl_3$ (10 mol %)	10
12	pTsOH (10 mol %)	25
13	TfOH (20 mol %)	32
14	$Cu(OTf)_2$ (1 mol %)	quant. (10 min)
15[d]	$Cu(OTf)_2$ (0.1 mol %)	93[e] (8h)
16[f]	$Cu(OTf)_2$ (10 mol %)	quant.

[a] Reaction conditions: furfural (0.2 mmol), morpholine (2.2 equiv), catalyst (10 mol %), H2O (0.2 mL), rt, 5 min. [b] Isolated yield. [c] The reaction time is 1 minute. [d] Reaction performed using 10 gram of furfural. The reaction was stirred for 1h in an ice bath, after which was allowed to warm until room temperature. [e] The product was isolated as a 6.7:1 mixture of **2** and the corresponding 2,4-isomer. [f] The reaction solvent is acetonitrile (2 mL).

To further understand the low yield of **2** in the reaction catalyzed by other Lewis acids, we first note that full conversion was obtained in all cases. For example, the reaction of furfural with morpholine in water catalyzed by $GdCl_3$ afforded the desired product in 10% yield (Scheme 12A). A negligible decomposition (Scheme 12B) of the product in the presence of $GdCl_3$ in water points toward an unselective catalysis, in which $GdCl_3$ as well as the other Lewis acids tested promote the undesired side reactions of furfural or intermediates.

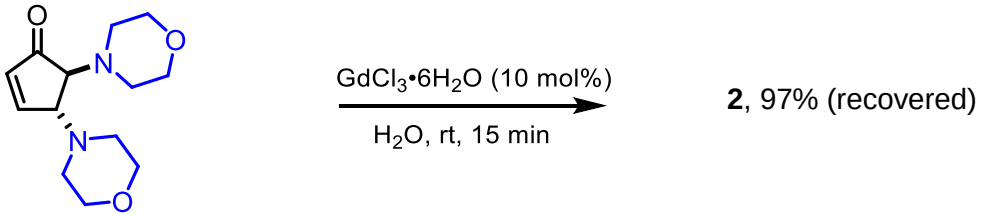
A. *Reaction catalyzed by $GdCl_3 \cdot 6H_2O$*



furfural

2, 10%

B. *Stability of* **2** *in the presence of $GdCl_3 \cdot 6H_2O$*



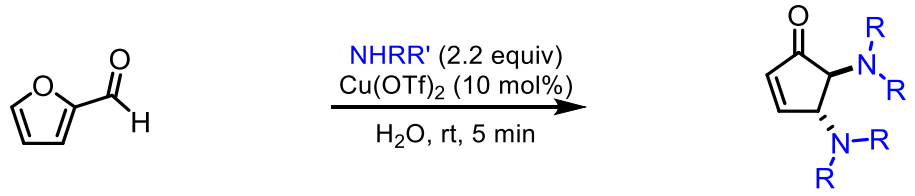
2

2, 97% (recovered)

Scheme 12 Stability study of cyclopentenone **2** in the presence of LA in aqueous medium.

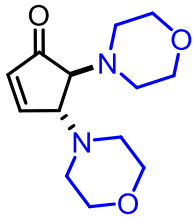
With the optimized conditions in hands, the amine scope was evaluated (Scheme 13). Several secondary amines, including cyclic amines and secondary anilines were well tolerated and afforded the corresponding product in excellent yield (up to >99% yield) in a very short reaction time (1 min). Diallylamine also reacted with furfural to give the corresponding product **4** in 72% yield (80% conversion) after 4 h reaction. When pyrrolidine or N-methyl-piperazine were employed, if the mixture was allowed to react for longer periods of time, isomerization to the more stable 2,4-diamino-cyclopent-2-enones was observed. The more challenging primary amines[5] such as aniline and benzylamine did not offer the desired product, and the intermediate imine was isolated in these cases.

In general, the synthesis of CP was a very efficient reaction under the conditions reported herein, and water was the only byproduct generated. Based on that, we envisioned that the ability to easily extract the product from the aqueous reaction medium using an organic solvent (diethyl ether) would allow reuse of catalyst. Remarkably, $Cu(OTf)_2$ was reused 4 times without considerable loss of catalytic activity. Furthermore, the yield of **2** remained >50% after 7 times. The results obtained during 7 cycles are summarized in **Figure 3**.

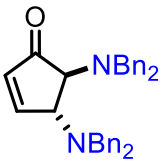


furfural

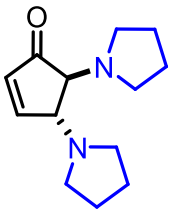
DCP



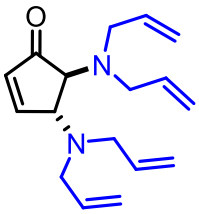
2, quant.



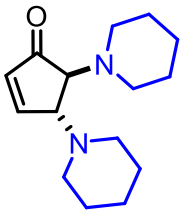
3, 98%



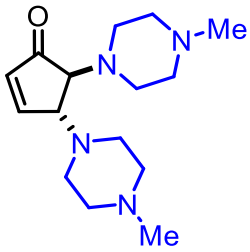
32, 97%



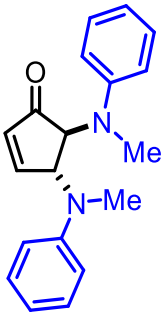
4, 72%[b]



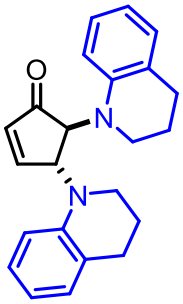
33, quant.



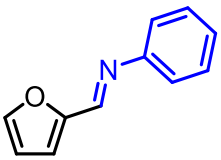
34, quant.



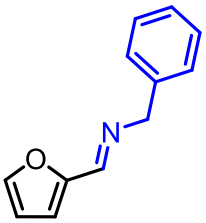
7, quant.



5, quant.



35, quant.



36, quant.

Scheme 13 Reaction scope for the formation of *trans*-4,5-diamino-cyclopent-2-enones under the optimized conditions. [a] Reaction conditions: furfural (1.0 mmol), amine (2.2 equiv), $Cu(OTf)_2$ (10 mol %), H_2O (1 mL), rt, 1 min. The average yield of 3 experiments are shown [b] Reaction time is 4 h.

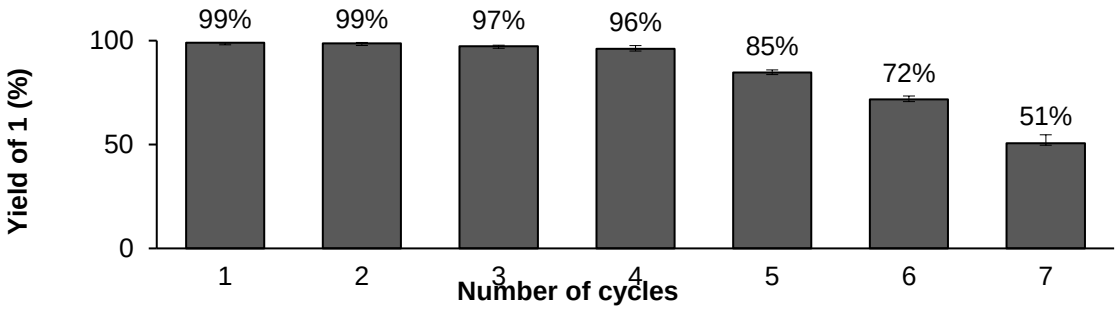
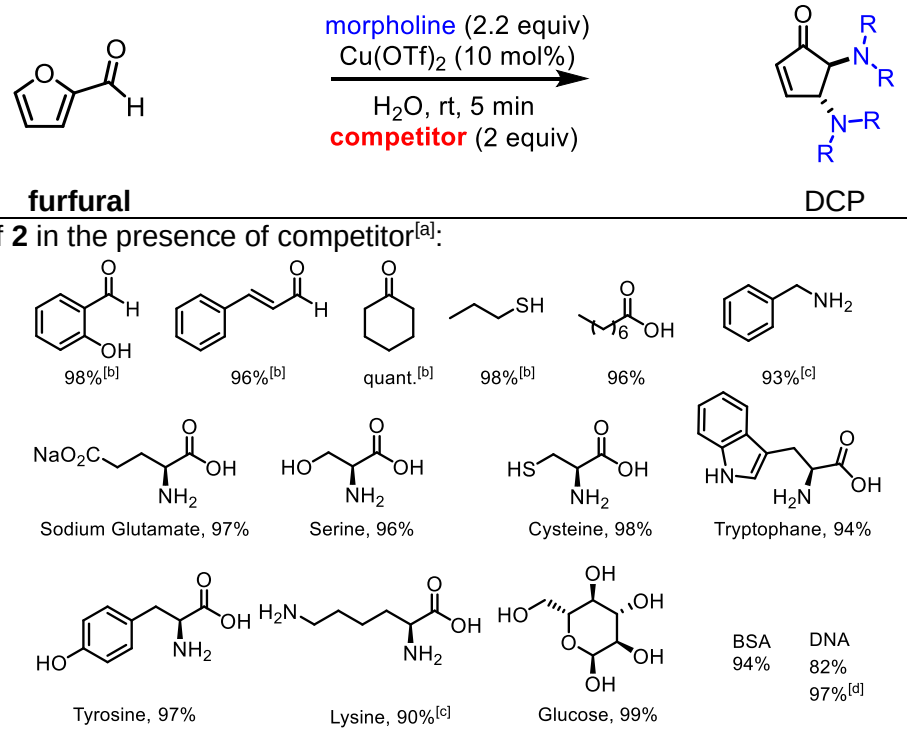


Figure 3. Catalyst reuse on the synthesis of 2 in aqueous media. Reaction conditions: furfural (1.0 mmol), morpholine (2.2 equiv), $Cu(OTf)_2$ (10 mol %), H_2O (1 mL), rt, 1 min. Isolated yield by diethyl ether extraction. All the experiments were performed in triplicate.

Conjugation of small molecules with biomolecules is a very challenging field that has attracted the interest of several research groups.[40,41] In this context, it is important to develop new strategies for chemo and site selective introduction of non-natural functionalities in biomolecules. In this way, we can bypass the difficult process of introducing non-natural amino acids on the protein skeleton.[42–44] Such reactions should meet the following requirements: 1) be compatible with aqueous media, 2) have fast kinetics and complete conversion, 3) be orthogonal. We envisioned that the selective formation of cyclopentenones bearing secondary amines, not often found in biological media, could be an easy and cheap procedure to insert both an external secondary amine and an enone that can be further functionalized.

Knowing that this methodology meets the first 2 requirements, we next sought to study the functional group tolerance of the reaction by performing the $Cu(OTf)_2$-catalyzed reaction of furfural with morpholine in the presence of selected molecules bearing different functional groups (Scheme 14). Both aldehydes and ketones can potentially inhibit the reaction by reaction of the amine substrate with these electrophiles. Surprisingly, the yield of **2** was not significantly affected in the presence of salicylaldehyde, cinnamaldehyde, or cyclohexanone. Thiols, commonly found as detoxification platforms due to their nucleophilic and antioxidant character, were also tested. In this case the concern was the known ability of thiols to undergo 1,4-addition, however, **2** was isolated in 98% yield under our reaction conditions. Carboxylic acids, commonly found in the C-terminal region of proteins and in several biomolecules, were also tested because of their potential ability to protonate amines. Gladly, the reaction proceeded smoothly in the presence of 2 equiv of octanoic acid, and **2** was isolated in 96%. Primary amines, frequently found in proteins (e.g., as lysine regions), and one of the most used sites for bioconjugation, were of great concern because of the potential competition with the secondary amine substrate. Furthermore, the reaction with primary

amines gives the corresponding imine in nearly quantitative yield, as observed in the amine substrate scope study. In fact, the $Cu(OTf)_2$-catalyzed reaction of furfural with morpholine in the presence of 2 equiv of benzylamine offered the imine when performed in acetonitrile. However, the use 4.4 equiv of morpholine and water as the solvent allowed the isolation of the desired product 1 in very good yield (93% yield, Scheme 14). Similarly, the reaction in the presence of lysine required an excess of morpholine in order to achieve very good yield of **2**. Several other amino acids such as tryptophan, serine, cysteine, sodium glutamate, and tyrosine were tested with no significant inhibition of the reaction. In addition, the presence of glucose in the reaction medium was also well tolerated with no decrease in yield or apparent reaction rate. Finally, the reaction efficiency was also studied in the presence of selected macromolecules. The presence of bovine serum albumin (BSA), chosen as a model protein, did not affect the reaction yield, affording 94% of **2** in the presence of 200% w/w of BSA (relative to furfural). However, we observed a decrease to 82% yield of **2** (100% yield based on recovered furfural) in the presence of 200% w/w of DNA from salmon. Remarkably, extension of the reaction time to 15 min afforded the product in 97% yield. Based on that, we propose that the apparent decrease of the reaction rate is due to the trapping of the catalyst by the DNA rather than undesired reactions of the morpholine. No other products were identified during the competition assays.



Scheme 14 $Cu(OTf)_2$-catalyzed reaction of furfural with morpholine in the presence of an external additive. [a] The values correspond to the isolated yield of 2. [b] Yield determined by ^1H NMR yield after extraction. [c] Reaction performed with 4.4 equivalents of morpholine. [d] Reaction time is 15 minutes

In conclusion, we described in this study a fast methodology for the synthesis of *trans*-4,5-diamino-cyclopent-2-enones (DCP) in water at room temperature using $Cu(OTf)_2$ as catalyst. This protocol is distinguished by its operational simplicity, mild reaction conditions, great efficiency, high tolerance to the presence of external molecules with several functional-groups, and amenability to gram-scale synthesis.

II.2.2. Preparation of DCP under flow conditions

In continuation of the previous subchapter, we decided to develop a methodology for the formation of DCP **2** under continuous flow conditions. Continuous flow has seen an increase interest by the synthetic organic community due to the ease in scale-out process, higher selectivity amongst others.[45–47] Knowing that $Cu(OTf)_2$ can promote DCP formation reaction we opted to immobilize Cu catalyst in different solid supports. In this way, we hoped to find an heterogeneous catalyst based on cheap Cu catalyst that could be used under flow conditions. We started this work by preparing solid supported copper catalysts. The catalyst were prepared by stirring the solid support with inexpensive $CuSO_4$ in aqueous media (silica and alumina) or in acetone ($Ca_5(PO_4)_3(OH)$). Although under batch conditions $Cu(OTf)_2$ proved to be best at promoting the reaction, we chose the sulfate salt that was significantly cheaper (9.000 €/kg *vs* 63 €/kg, Sigma-Aldrich). The supported catalyst were used for the condensation between furfural and morpholine to the formation of DCP **2**. We know from our previous work that protic solvents favor the copper promoted reaction. Unfortunately most protic solvents are too polar and would leech the copper from the solid support, so we chose a mixture of isopropanol (IPA) and hexane. The copper was immobilized in silica, basic alumina and hydroxyapatite that was packed inside an empty HPLC column (**Figure 4**). The initial screening showed that both hydroxyapatite and silica supported catalysts (Table 3, Entries 2 and 3) were promising although silica afforded higher yields. At lower catalyst loadings the reaction is highly impaired (Table 3, Entries 4-6) and in the absence of copper no product is formed therefore the silica is not promoting the reaction.

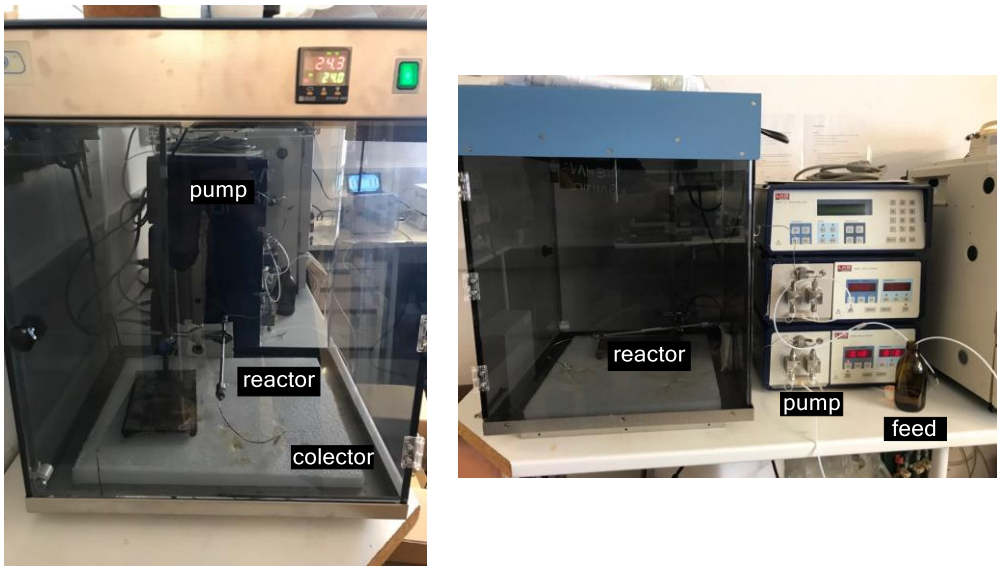
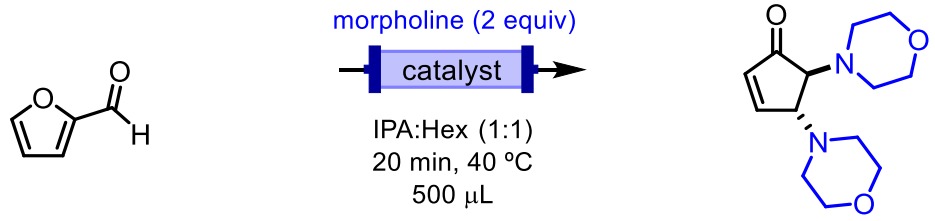


Figure 4 Continuos flow reaction apparatus in a T controlled oven.

Table 3. Catalyst screening[a]



furfural **2**

Entry	Solid suport	$CuSO_4$ (w/w %)	Yield (%)[b]
1	Al_2O_3	20	24
2	$Ca_5(PO_4)_3(OH)$	20	87
3	SiO_2	20	100
4	SiO_2	2.5 to 5	traces
6	SiO_2	0	0

[a] Reaction conditions: furfural (20 mg, 0.2 mmol), morpholine (38 mg, 0.43 mmol, 2.1 equiv), IPA:hexane 1:1 (2 mL), 40 ºC, flow rate 25 µL min^{-1}. [b]Yield determined by ^1H NMR using trimethoxybenzene as internal standard.

The ratio of isopropanol and hexane was studied. We observed that the catalyst remains active even in low ratios of IPA:Hexane (Table 4, Entries 4 and 5), although no product was formed in the absence of isopropanol (Table 4, Entry 6). The reaction was also performed in ethyl acetate:hexane (9:1) and no product was formed, which highlights the importance of a protic solvent under these conditions. Although the reaction in higher ratios of IPA afforded excellent yields (Table 4, Entry 1), we observed visible amounts of silica leeched from the reactor, which would utterly hinder the reutilization of the catalyst.

Table 4 Solvent and temperature optimization[a]

Entry	IPA:Hexane ratio	T (º C)	Yield (%)[b]
1	1.0	40	100
2	0.8	40	100
3	0.5	40	100
4	0.2	40	100
5	0.1	40	98
6	0	40	0
7	0.5	50	100
8	0.5	30	100
7	0.5	24	98

[a] Reaction conditions: furfural (20 mg, 0.2 mmol), morpholine (38 mg, 0.43 mmol, 2.1 equiv), isopropanol:hexane in the corresponding ratio (2 mL), flow rate 25 µL min^{-1}. [b] Yield determined by ^1H NMR using trimethoxybenzene as internal standard.

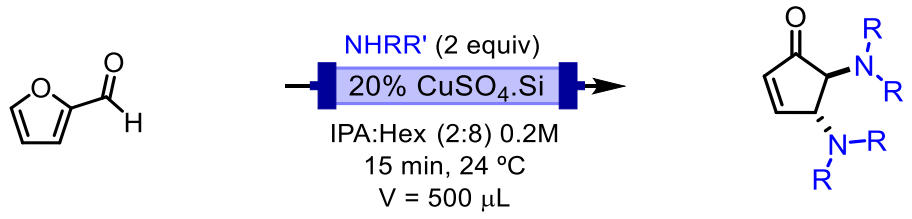
By screening different concentrations of furfural in isopropanol:hexane 2:8, we observed that 0.2 M affords the highest amount of pure product (Table 5, Entry 4). Even though 0.3 M affords appealing 87% yield (Table 5, Entry 3), the product required further purification. We attempted to reduce the residence time (RT) but were only able to reduce to 15 min without significant decrease in yield (Table 5, Entries 5-7).

Table 5 Concentration and residence time optimization[a]

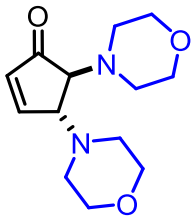
Entry	Concentration (M)	RT	Yield (%)[b]
1	1.0	20	24
2	0.5	20	62
3	0.3	20	87
4	0.2	20	98
5	0.1	20	100
6	0.1	15	100
7	0.1	10	87

[a] Reaction conditions: furfural (in the corresponding amount), morpholine (2.1 equiv), isopropanol:hexane 2:8 (2 mL). [b] Yield determined by ^{1}H NMR using trimethoxybenzene as internal standard.

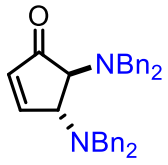
With the best conditions in hands we extended the reaction to different amines (Scheme 15). We were able to isolate pure products in high yields just by evaporation off the reaction mixture obtained from the reactor in high yields. The scope included cyclic amines such as morpholine and piperidine, aromatic amines such as tetrahydroquinoline and methyl-aniline, dibenzylamine and diallylamine.



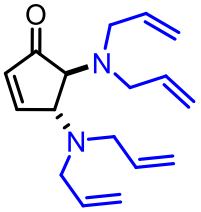
furfural DCP



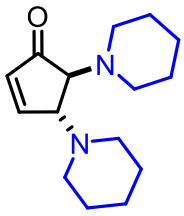
2, 99%



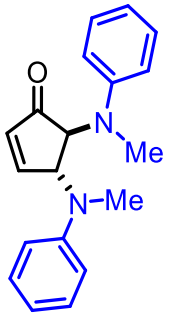
3, 99%



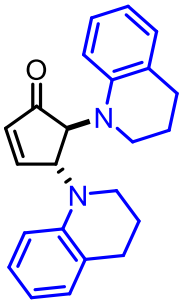
4, 96%



33, 94%



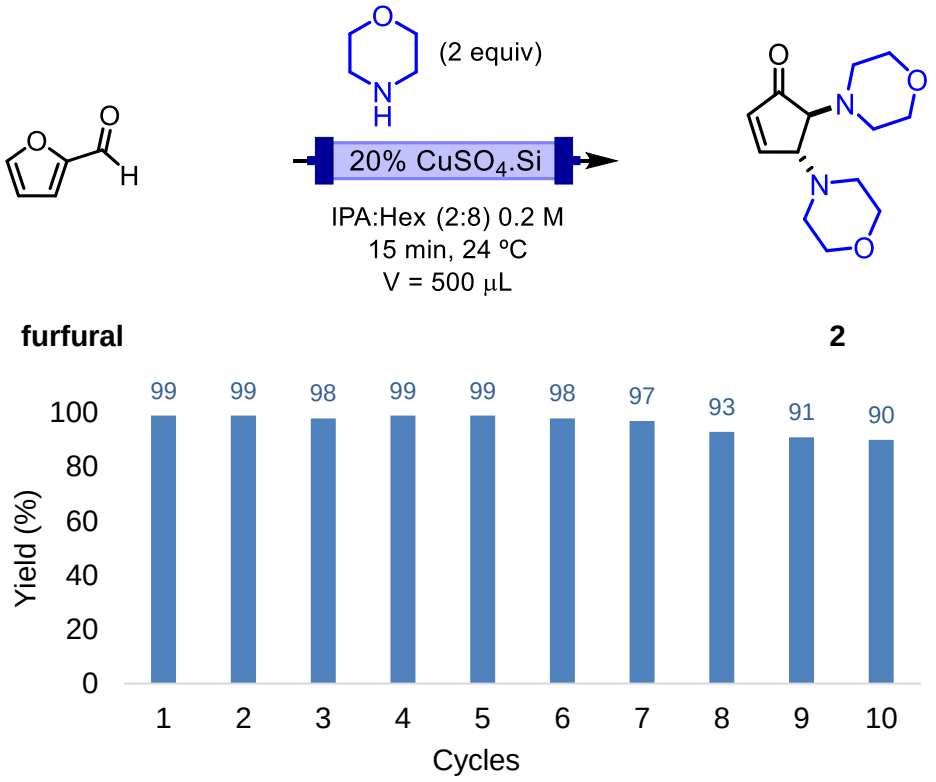
7, 98%



5, 98%

Scheme 15 Amine scope for formation of DCP under continuous flow conditions. Reaction conditions: furfural (20 mg, 0.2 mmol), amine (0.43 mmol, 2.1 equiv), 20% $CuSO_4$.Si (471 mg), IPA:hexane 2:8 (2 mL), temperature is 24 ºC, flow rate 25 µL min^{-1}.

Finally, we selected the substrates **2** and **4** and studied the robustness of the system by measuring the yield by continuously feeding the reactor with the reaction mixture (Figure 5). In this way we were able to prepare 1.2 g of **4** in 3.5h. This corresponds to a productivity of 14 g L^{-1} h^{-1}. Substrate **2** was prepared with productivity of 34 g L^{-1} h^{-1}.



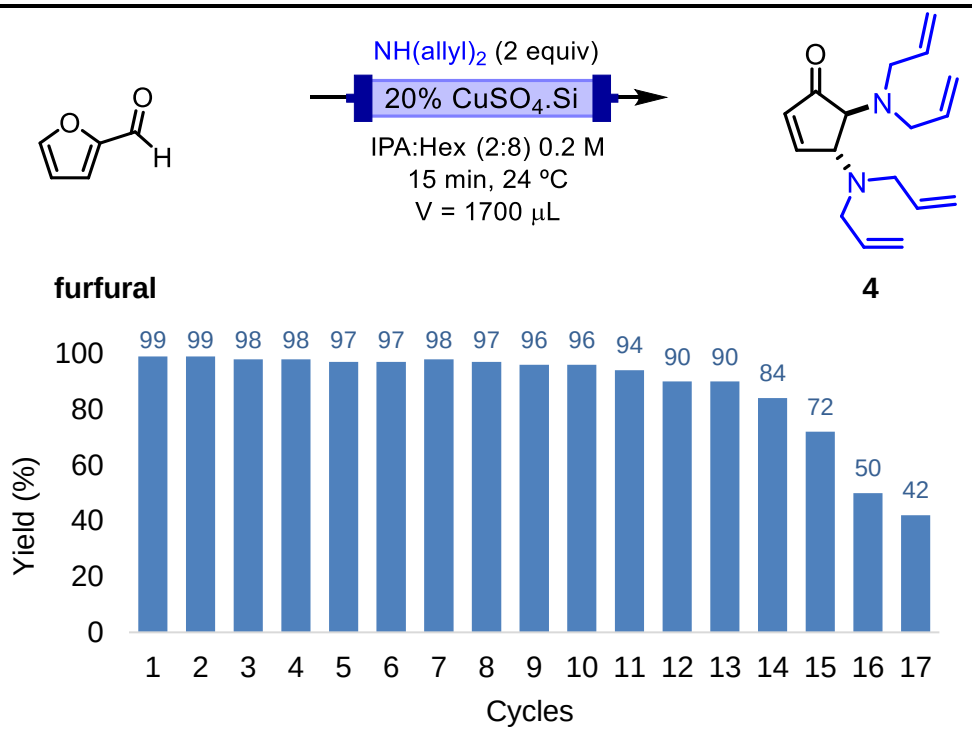


Figure 5 Continuous flow approach for the production of **2** (top) and **4** (bottom).

Focusing in DCP **4** we observed a significant decrease in activity after 14 cycles of reaction. We wondered if this could be attributed to copper leaching from the reactor. The copper content of samples from different cycles was obtained by inductively coupled plasma (ICP) analysis. Although there is copper detected in the samples, the sum of all the copper leached in 17 cycles corresponds to less than 1 % of the initial copper content in the reactor (initial copper content is 20%). Another possibility for the decrease in catalyst activity could be organic material adsorbed in the catalyst. Gratifyingly we observed by Attenuated total reflection Fourier-transform infrared spectroscopy (ATR-FTIR) that the supported catalyst after 17 runs is contaminated with organic material, namely amines and cyclopentenone (1450 cm^{-1} and 1645 cm^{-1}, Figure 6).

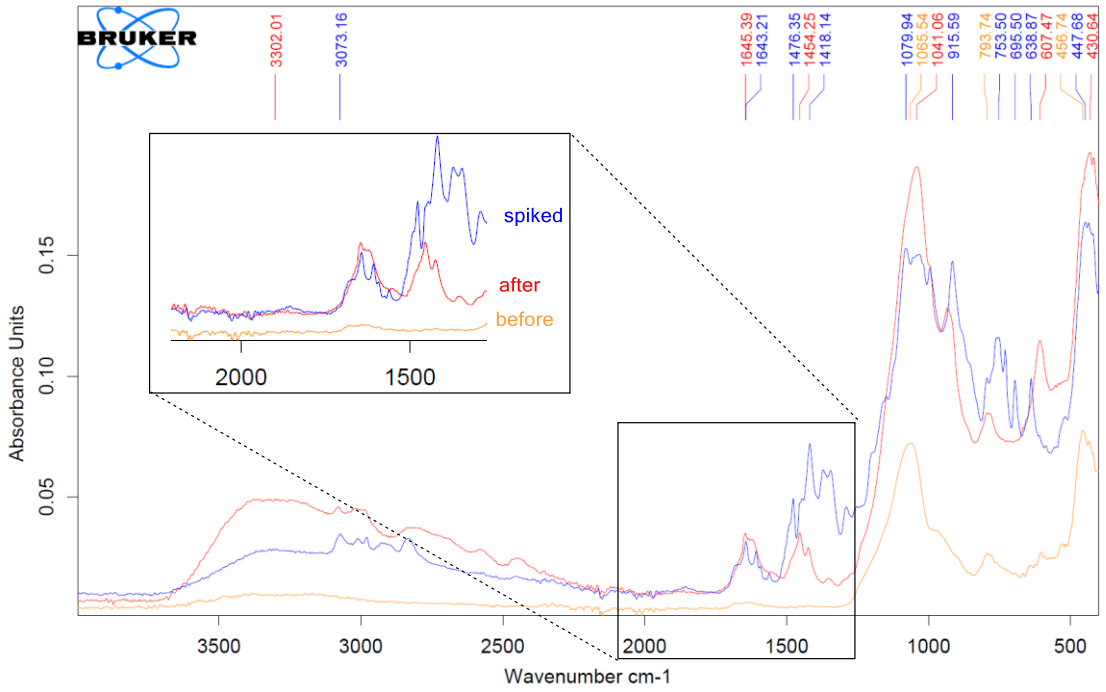


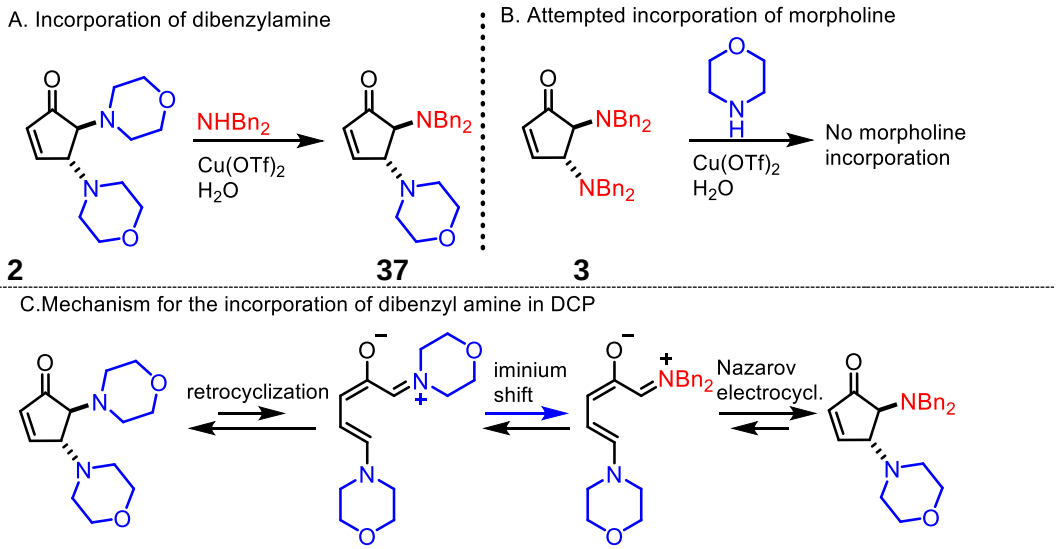
Figure 6 FTIR analysis of the $CuSO_4$.Si catalyst before the flow reaction (orange), after the flow reaction (red) and spiked with 10 % (w/w) of **4** and diallylamine (blue).

In summary we describe in this study a continuous flow approach using silica immobilized copper catalyst for the production of *trans*-4,5-diamino-cyclopentenones. The supported catalyst is prepared from inexpensive reagents (silica and $CuSO_4$). We were able to scale the reaction up to a productivity of 14 g L^{-1} h^{-1} for *trans*-4,5-diallyl-cyclopentenone that can be used as starting material for the preparation of cytotoxic marine sponge derived alkaloid (±)-agelastatin A (See **Scheme 3**, Chapter I).

II.2.3. Preparation of mixed *trans*-4,5-diamino-cyclopent-2-enones

Despite the formation of DCP being well known, there has been no reports on the formation of mixed DCP using two different amines. During the course of our previous studies we observed retro-electrocyclization of DCP products to the corresponding furfural in a small extent during column chromatography of DCP products. This reversibility, aligned with the reversibility of the CP-DASA systems previously reported by Alaniz and depicted in Chapter I, lead us to study the possible reversibility of the DCP formation. We envisioned to harness this properties of the CP system to prepare new DCP with two different amines in position 4 and 5. This would be of importance due to the large amount of cyclopentanes observed in natural products that could now be accessed by this strategy by using two amines with different orthogonal protecting groups.

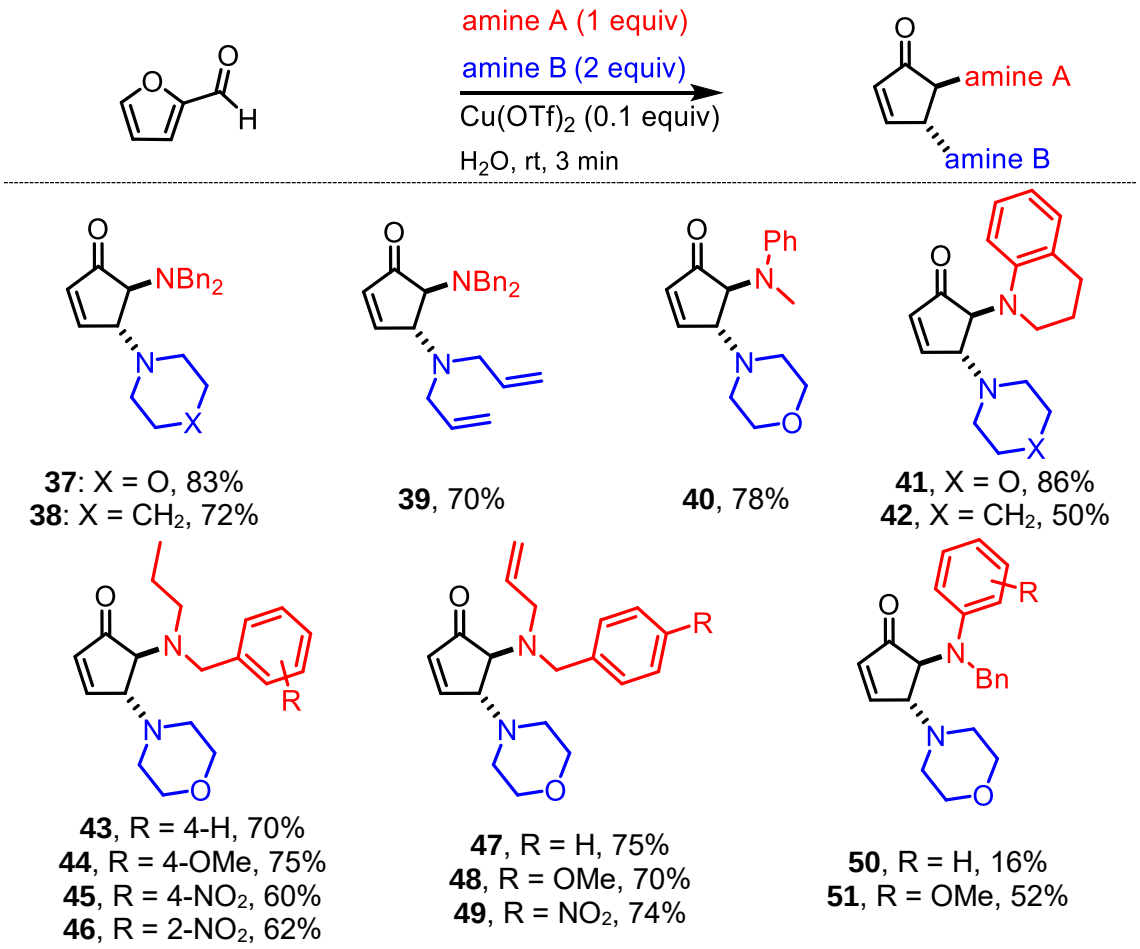
We started this work by stirring DCP **2** in the presence of dibenzylamine (DBA) under the reaction conditions (**Scheme 16**A). Gratifyingly we observed the formation of product **37** in a small extent. Remarkably only the morpholine in position 5 was replaced by the dibenzylamine. On the other hand, DCP **3** did not underwent morpholine incorporation under the same condition in the presence of excess morpholine (**Scheme 16**B). This lead us to believe that the mechanism for the formation of the new CP is occurring *via* the formation of the Stenhouse salt that undergoes iminium shift to the more stable iminium, that in this case is the DBA iminium (**Scheme 16**C).



Scheme 16 Copper promoted incorporation of external amines in *trans*-4,5-diamino-cyclopentenones (A. incorporation of dibenzylamine in **2**; B. incorporation of morpholine in **3**; C. Mechanism for incorporation of dibenzylamine).

We attempted to transpose this selectivity to a one pot reaction by directly react furfural with a mixture of morpholine and DBA. To our delight we were able to isolate 83% of the desired product **37**, 4% of the bisdibenzylproduct **3** and no formation of the bismorpholine product **2**.

With the optimized conditions in hand the reaction was extended to other amines (**Scheme 17**). In the presence of DBA both cyclic amines morpholine, piperidine and diallylamine afforded the mixed product. When the reaction was performed with tetrahydroquinoline (THQ) and morpholine the major product was the CP with THQ in position 5, similar to DBA. There was formation of bisTHQ product and no bismorpholine was observed. In the presence of *N*-methylaniline (NMA) and morpholine the major product was the CP with NMA in position 5, although there were traces of product with NMA in position 4 that could not be properly purified for characterization. There was also formation of bisNMA product in small amounts. In order to prepare CP that could be further functionalized we decided to use amines that could be deprotected under different conditions. It is known that 1) 4-methoxybenzylamine can be deprotected under oxidative conditions such as DDQ and CAN; 2) 4-nitrobenzylamine can be deprotected under basic conditions; 3) 2-nitrobenzylamine can be deprotected under UV irradiation and 4) allylamine can undergo deallylation by several methods. The desired amines were prepared by reductive amination and were reacted with furfural in the presence of morpholine. All this amines afforded the desired product as the major product. In the presence of dibenzylamine both morpholine and piperidine afforded the mixed product **37** and **38** with excellent selectivity in 83 and 72% yield respectively. In the presence of dibenzylamine and diallylamine we observe that the same tendency ocurrs, with dibenzylamine remaining in position 5 while diallyamine goes for position 4 as can be seen in product **39**. When using arylamine such as N-methylaniline and morpholine the arylamine is incorporated in position 5 while morpholine remains in position 4 as can be seen in CP **40**. Tetrahydroquinolines behaves similar in the presence of both morpholine and piperidine as can be seen in CP **41** and **42**. Despite this, the product in the presence of piperidine is obtained in lower yields, with an increase of the formation of bis-tetrahydroquinoline product. The reaction with different substituted benzylamine underwent smoothly with yields ranging from 60-75% for CPs **43-49** with the exception of aryl substituents that afforded low selectivties as can bee seen in CPs **50** and **51**.

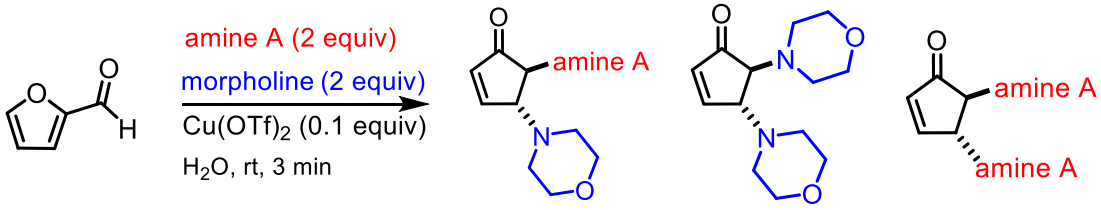


Scheme 17 Amine scope for the formation of mixed DCPs directly from furfural. Reaction conditions: furfural (200 mg, 2.1 mmol), amine A (1 equiv, 2.1 mmol), amine B (2.0 equiv, 4.2 mmol), $Cu(OTf)_2$ (10 mol %, 75 mg, 0.2 mmol), H_2O (2 mL).

In an attempt to understand the selectivity for the formation of mixed DCP we performed the reaction with morpholine and substituted benzyl-anilines with electron donating and electron withdrawing groups (**Table 6**). We observe that 4-methoxy-N-benzylaniline afforded the desired product in greater proportions when compared with N-benzylaniline. Electron poor 4-trifluoromethyl-N-benzylaniline did not afford the mixed product neither the bis aniline product.

This result indicates that formation of a stable iminium ion, promoted by electron donor substituents, is key for the selectivity towards position 5.

Table 6 Studies on the effect of the electronic effect on the selectivity for the formation of mixed DCP



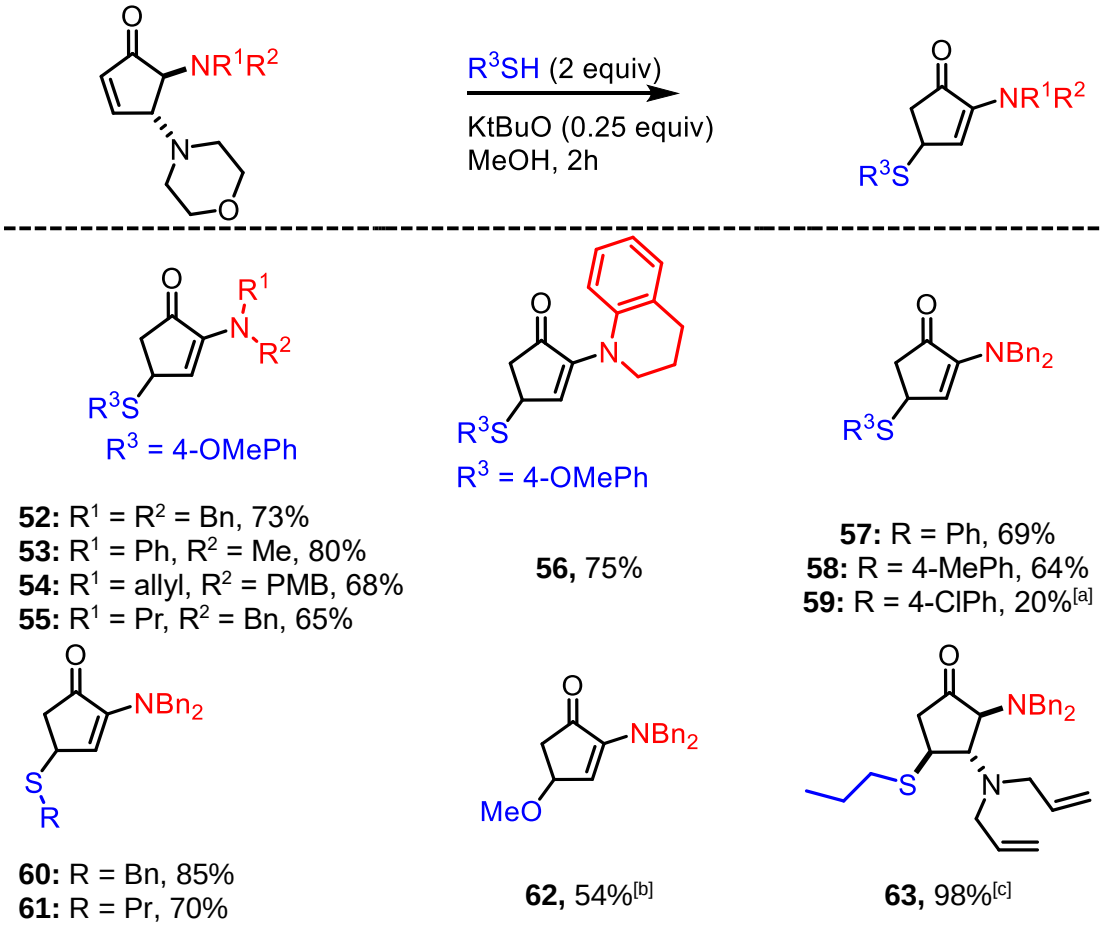
Amine A = NHBn(4-R-Ph) A B C

Entry	R	A (%)	B (%)	C (%)
1	H	16	37	0
2	OMe	56	16	28
3	CF_3	0	100	0

Having the amine scope established we further functionalized the CP core by Michael-addition of thiols. It has been previously reported by our group that bismorpholine CP undergoes Michael addition with thiols in basic conditions followed by elimination of the morpholine in position 4 to re-establish the enone.[13,48] When bisdibenzyl CP was submited to the same conditions no product was isolated.

Despite this, mixed CPs in the presence of thiols undergo the same 1,4-addition, affording aminoCP (ACP) with diverse amine substituents in position 2. Selected DCPs **37**, **40**, **41**, **43** and **48** underwent addition with 4-methoxythiophenol affording the corresponding adducts **52-56** in good yields (65-70 %) (**Scheme 18**). These studies indicate that morpholine in position 4 is more important for the Michael addition than the substituent in position 5. Reaction of **37** with different aryl thiols afforded the corresponding products. Electron donor groups favoured the addition (**Scheme 18**, **58** vs **59**).

The reaction with 4-chloro-thiophenol required excess of thiol and we could only isolate 20% of the desired product **59**, with **62** as side product. Product **62** can be explained by *in situ* formation of methoxide anion promoted by *t*BuOK and posterior addition. Reaction with alkyl thiols was also possible and CP **60** and **61** were isolated in good yields (85 and 70% respectively). Reaction with NaOMe afforded **62** in 54% yield by the addition of the alkoxide to the enone. When the thiol addition reaction was performed in the absence of base the sole isolated product corresponded to the trisubstituted cyclopentanone **63**, which highlight the importance of the base for the elimination.



Scheme 18 Scope for the Michael addition to mixed DCP. Reaction conditions: DCP (0.3 mmol), thiol (0.3 equiv), tBuOK (25 mol %, 0.075 mmol), MeOH (3 mL). [a]required 5 eq thiol; [b] NaOMe (1.25 eq) was used; [c] no base was used.

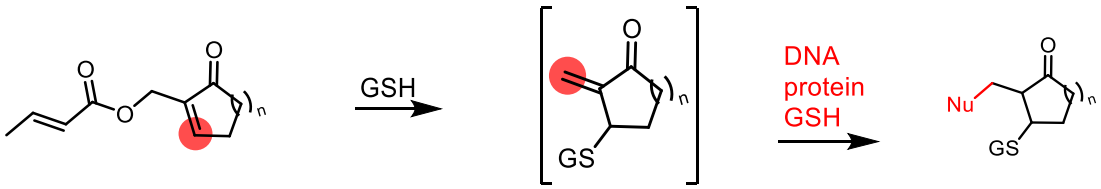
In summary during this study we explored the formation of mixed DCP directly from furfural using two different amines. The formation of mixed DCP is highly regioselective with electron donating groups favouring the substitution in position 5. This is indicative that the stabilization of iminium ion of the Stenhouse salt is crucial for the formation o mixed DCP. Michael addition of thiols to the new mixed CP allowed for the formation of new ACPs by elimination of the morpholine in position 4.

II.2.4. Anticancer activity of novel cyclopentenones

This work was performed in the framework of MSc thesis of Késsia Andrade.

Cyclic enones such as cyclopentenones (CPs) and cyclohexanones have been reported to possess cytotoxic activity against several cancer cell lines. [29,36,38,39] An example of simple cyclic enones with relevant activities are COMCs.[49–51] Creighton and coworkers observed that formation of a highly reactive exocyclic enone is responsible for the activity (Scheme 19).[37] This activated species is capable of alkylating critical biomacromolecules such as DNA or proteins.[52] The exocyclic enone is formed in the presence of GSH by thio-Michael addition to the cyclopentenone. Moreover it was shown that the cytotoxicity of COMC correlates to the level of expression of GSTP1-1 when MCF-7^{piGST} and MCF-7wt breast tumor cells were incubated with the cytotoxic agents.[39] This indicates that the exocyclic enones which require GSTP1-1 to be formed are important for cytotoxicity, corroborating the hypothesis that alkylation of critical biomacromolecules is indeed responsible for activity.

However, the presence of this highly reactive Michael acceptor is cause of concern due to possible promiscuity which can lead to severe side effects.[53,54] In fact Michael acceptors are included in the list of compounds that furnished false positives due to high reactivity and lead to the development of filters to exclude the so called Pan Assay Interference Compounds (PAINS) in biological screening.[55]



COMC-5, n = 1
COMC-6, n = 2
COMC-7, n = 3

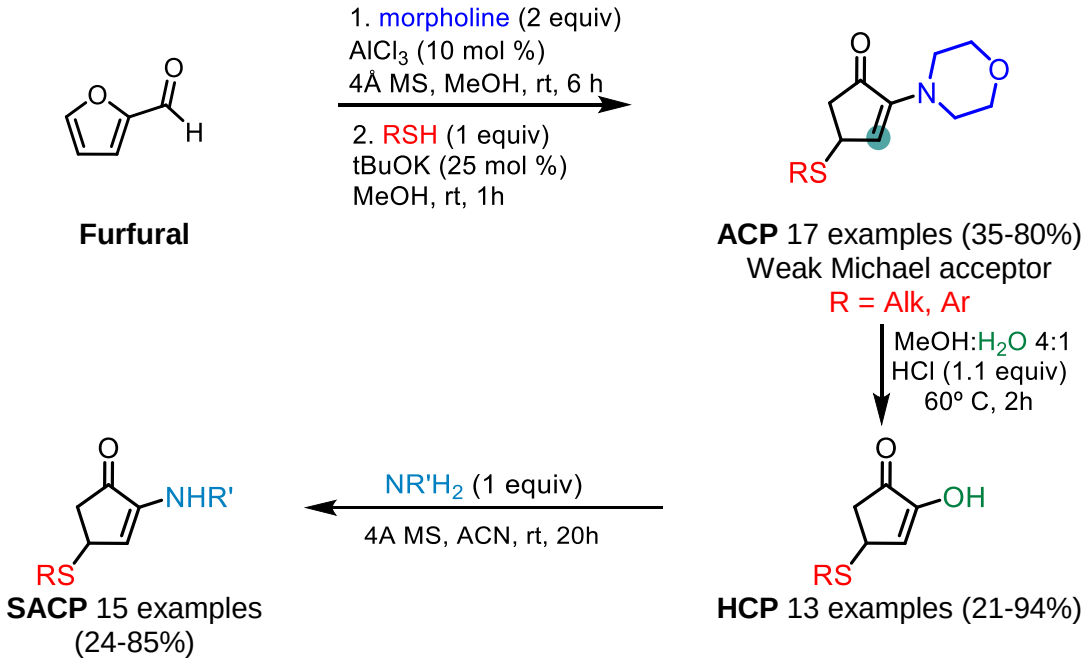
Highly reactive enone

Reactive Michael acceptor:
- side effects
- poor ADME properties

Scheme 19. Cytotoxic cyclic enones described by Creighton and coworkers**.**

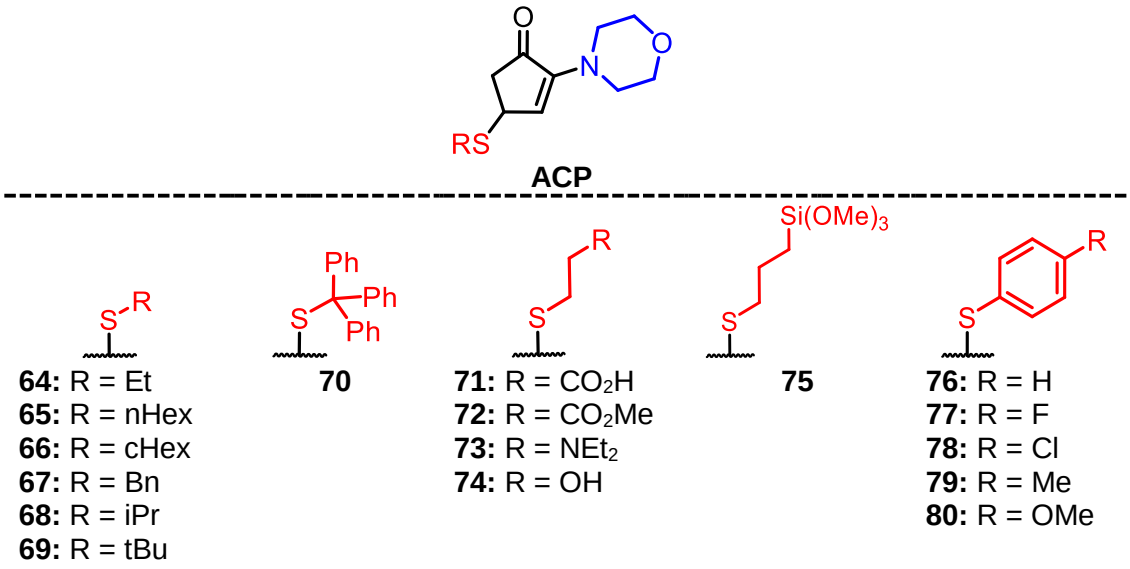
Our group described the addition of a thiol to the enone under basic conditions is followed by consequent elimination of an amine in position 4 to reestablish the enone motif.[48] However, no second addition of the excess thiol to the newly formed enone was observed. Herein we envisioned that the development of CP containing very poor

Michael acceptor character that could retain the cytotoxic activity through a mechanism of action other than non-specific macromolecule alkylation as depicted in **Scheme 20**.



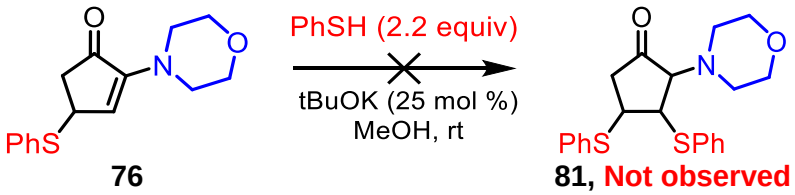
Scheme 20. Strategy for the preparation of cyclopentenones with poor Michael acceptor character.

Following the procedure previously described in Chapter I.4, 17 ACPs were prepared from furfural (**Scheme 21**). The new ACPs may be less prone to a second Michael addition due to the decrease of electrophilicity of the olefin which is also an enamine.



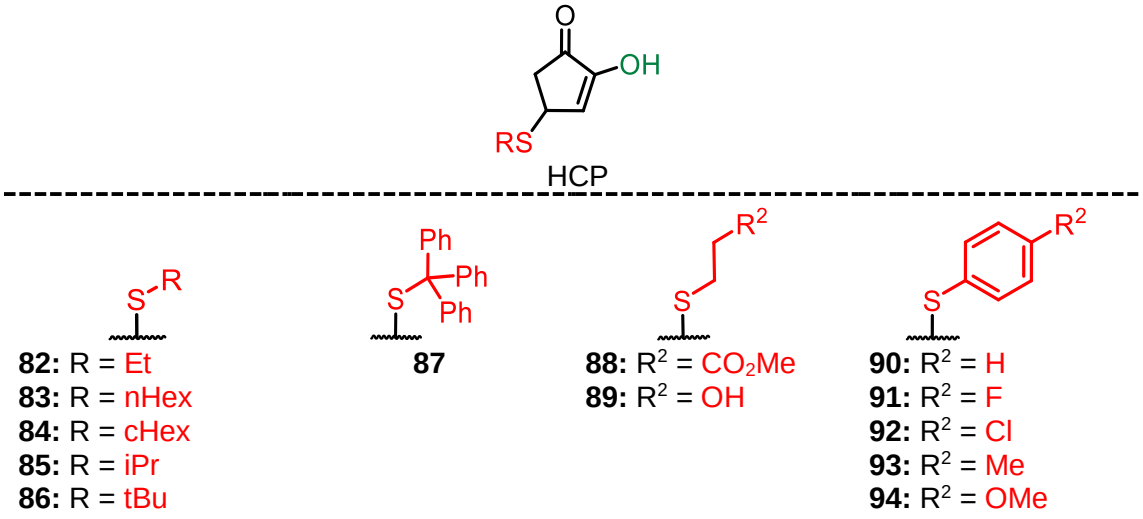
Scheme 21. ACP prepared for the biological assays.

When ACP **76** was put with an excess of thiol in the presence of *t*BuOK the product **81** was not observed, corroborating the hypothesis that **76** is a weak Michael acceptor (**Scheme 22**).



Scheme 22. Stability of ACP **76** under thio-Michael addition conditions.

Next we envisioned that hydrolysis of **64**-**80** to 2-hydroxy-4-substituted-CPs (HCPs) **82**-**94** would: 1) enhance the solubility in aqueous media; 2) the free alcohol would allow for additional H bond since it behaves as H bond donor, potentiating interaction with the unknown target; 3) decrease the electrophilic character of the enone even further, since the olefin is also an enol. Although tautomerism to diketone is possible, the diketone was never observed. This can be explained by the increased thermodynamic stability of α,β-unsaturated system. The hydrolysis is promoted under acidic conditions (HCl 1.1 equiv) in a MeOH:H_2O mixture at 60ºC as previously described (**Scheme 23**).[48]

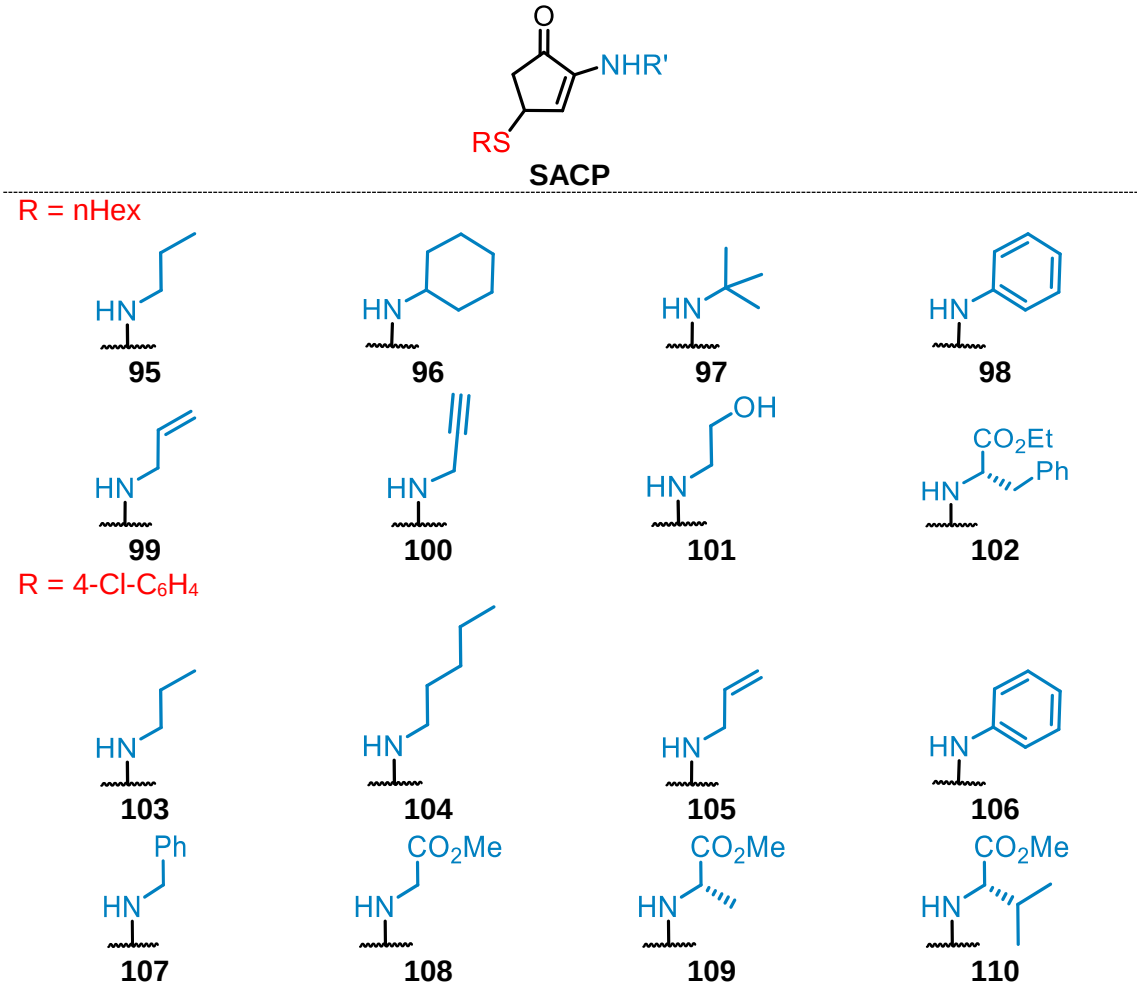


Scheme 23. HCP prepared for the biological assays.

To continue our study on the importance of the substituent in position 2 we prepared CPs with secondary amines (SACP) in the corresponding position. This amines retain the H-bond donor character of the free alcohol and allowed an addition alkyl chain potentiating Van-der-Waals interaction with unknown targets. Moreover the amines can protonate in the active site to form favorable ionic bonds with anions present in the target.

Incorporation of the amines is performed in acetonitrile with 4A molecular sieves to remove water following the reported procedure (**Scheme 24**). The CPs **95** to **102** were prepared from **83** containing an aliphatic thiol and alkyl, allyl, propargyl and aryl amines. An aminoacid derivative, phenylalanine ethyl ester, was also incorporated. The CPs **103**

to **110** were prepared from **92** containing an arylthiol and alkyl, allyl, and aryl amines. Aminoacid derivatives such as glycine, alanine and leucine methyl esters were also incorporated.



Scheme 24 Prepared SACPs for biological evaluation.

With the different families of compounds in hands firstly, the activity of the new derivatives was evaluated for the anti-proliferative activity in the Neutral Red assay at a fixed concentration of 20 μM in HT-29, MCF-7 and NCI-H460 cells. There was no significant activity observed by DCP **2** nor the ACPs **65**-**75** containing thioalkyl substituents. However for DCP **3**, **7** and **5** we observed significant reduced viability at 20 μM (6-28 % viability). Although we observe in ACP containing the morpholine enamine **76** to **80** activity in HT-29 cell lines, in particular those with electron withdrawing groups (**77** and **78**) we observe a significant increase in activity upon replacement of the morpholine with OH in CPs **90** to **94** (40 *vs* 81 % viability in HT-29 when comparing **78** *vs* **92**). Moreover we observed the morpholine containing compounds (**76**-**80**) were most active in MCF-7 cell lines while the hydrolyzed analogs (**90**-**94**) were more active in HT-29. The increased activity indicates that the OH group may be involved in important H-

bond interaction. As such the incorporation of secondary amines that retain the ability for H-bond interaction in SACPs **103** to **110** show increase of activity. The activity of the most promising compounds was evaluated for the anti-proliferative activity in the MTT assay at a fixed concentration of 20 μM in healthy Human Embryonic Kidney 293 cells (HEK 293T) cell lines. We observe that while CPs **3**, **7** and **5** were most active (6-28 % viability), they also show some toxicity in HEK 293 (72-92 % viability). In contrast, both HCP **92** and SACP **103** show no toxicity in healthy cell lines, while showing significant activity in the tumorous cell lines (29-38% viability). Overall aromatic thiol substituents with electron withdrawing groups show increased activity when compared with other thiols, the morpholine substituent show increased activity in MCF-7 cell lines while the hydrolyzed analogs were more active in HT-29, alkyl amines show better activity than arylamines, with small chains being favored. Also when aminoacid derivatives were used we observed decreased activity with higher branching of the side chain, which indicates that steric hindrance is disfavored.

Table 7 Heatmap of viability assays (%) at 20 μM CPs on different cell lines.

	HT-29	NCI-H460	MCF-7	HEK 293		HT-29	NCI-H460	MCF-7	HEK 293		HT-29	NCI-H460	MCF-7	HEK 293
2	100	100	100		**76**	83	79	60		**94**	77	100	100	
3	12	8	6	92	**77**	76	78	64		**95**	100	100	100	
4	100	100	100		**78**	81	52	58		**96**	100	100	100	
5	13	7	6	72	**79**	100	100	84		**97**	100	100	100	
7	28	26	20	90	**80**	80	81	69		**98**	100	100	100	
64	100	100	100		**82**	100	100	100		**99**	100	100	100	
65	100	100	100		**83**	100	100	100		**100**	100	100	100	
66	100	100	100		**84**	100	100	100		**101**	100	100	100	
67	100	100	100		**85**	100	100	100		**102**	100	100	100	
68	100	100	100		**86**	100	100	100		**103**	31	38	26	98
69	100	100	100		**87**	100	100	100		**104**	50	62	77	
70	100	100	100		**88**	100	100	100		**105**	33	30	22	68
71	100	100	100		**89**	100	100	100		**106**	71	58	59	
72	100	100	100		**90**	59	77	92		**107**	36	47	29	83
73	100	100	100		**91**	55	69	100		**108**	63	76	67	
74	100	100	100		**92**	40	60	76	100	**109**	69	57	55	
75	100	100	100		**93**	74	100	100		**110**	100	100	100	

0% 100%

[a] Data are the mean of at least three independent experiments

The electronic character of the aromatic substituent appears to have influence over the activity. The electronic effect of the thioaryl substituents was evaluated by Hammett plot in HT-29 and NCI-H460 cell lines. When comparing the results of HCPs **90** to **94** we observe a strong correlation between activity and electronegativity of the aromatic substituent of the thiol. The plot of viability at 20 µM vs Hammet σ_{para} coefficient of the corresponding substituents provided linear correlation with a ρ value of -7.88 and -1.04 in HT-29 and NCI-H60 cell lines respectively (**Figure 7**). This correlation indicates that electron withdrawing groups indeed favor the cytotoxic activity of the CPs.

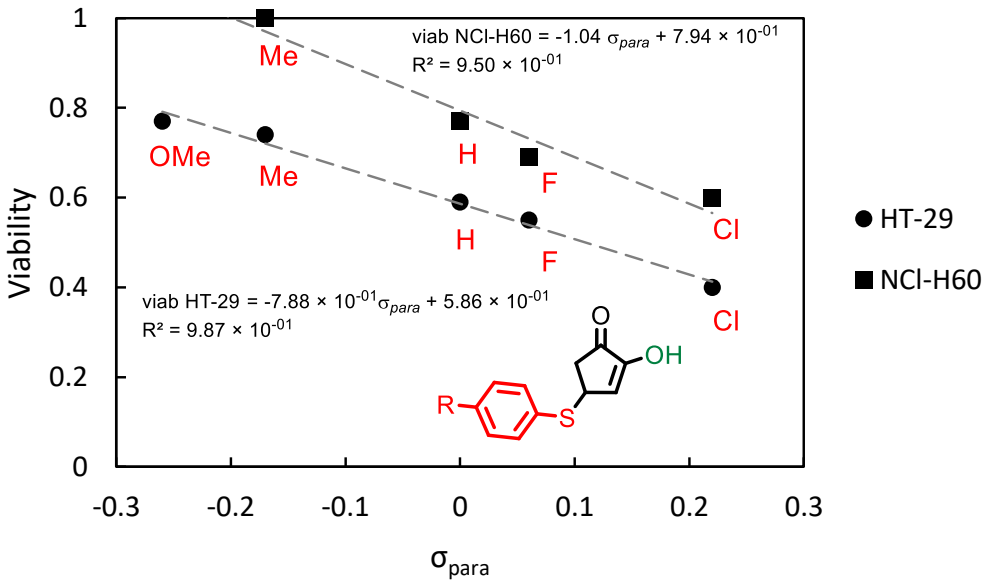


Figure 7 Hammett plot of the thioaryl substituents.

Prompted by these results we measured the IC_{50} values of the most active compounds **3**, **5** and **7** belonging to the first family of highly electrophilic CP and **103**, **105**, **107** belonging to the last family of CPs after incorporation of amine.

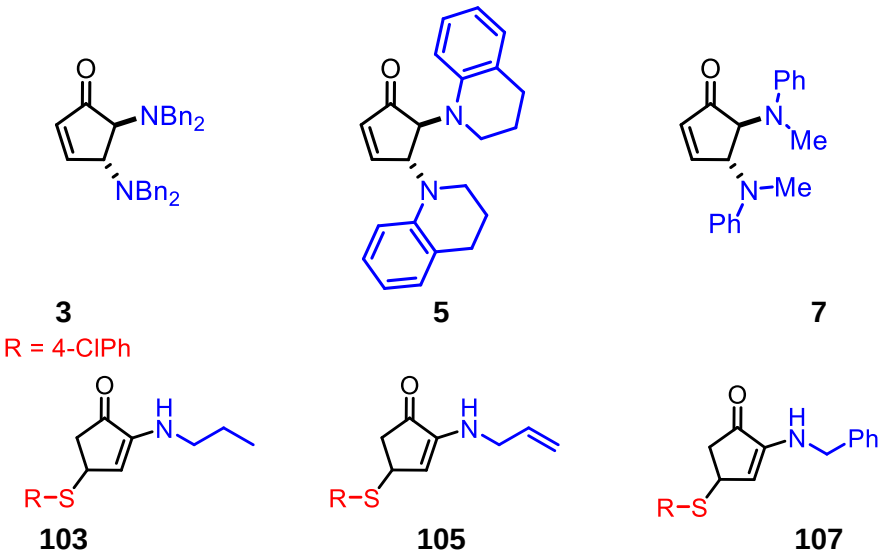
We observed low IC_{50} values in the first DCPs (**Table 8**, Entries 1-3). However this compounds show slight toxicity in HEK 293 cell lines (viabilities at 20 µM of 83%, 68% and 78% respectively) and present a highly electrophilic enone which is prone to react with nucelophiles present in critical macrobiomolecules. This is shown by the reduced stability in the presence of glutathione (GSH) shown in the assays bellow.

SACP **103** resulted as the most potent in HT-29 amongst the non-toxic CP with an IC_{50} of 7.07 µM (Table 8, Entry 4). The activity is almost halved in NCI-H460 and MCF-7 cell lines. This indicates a certain degree of specificity against this cell lines.

Substitution of the propyl amine with allyl amine in **105** led to a slight decrease of activity in HT-29 although the compound was found to be the most potent in NCI-H460 cell lines with an IC_{50} off 7.34 µM (Table 2, Entry 5) amongst the non-toxic CP. The three SACPs show only moderate IC_{50} in MCF-7 cell lines

Table 8 IC_{50} (µM) of the most promising CPs.

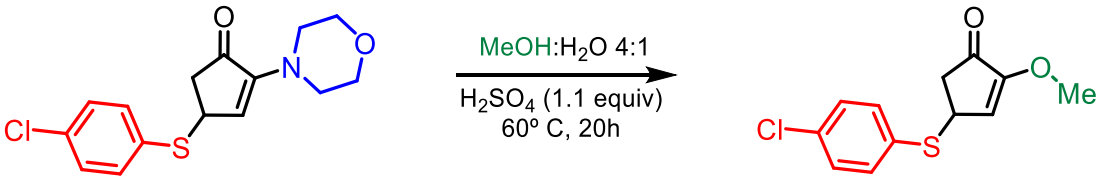
		IC_{50} (µM)		
Entry	CP	HT-29	NCI-H460	MCF-7
1	**3**	3.27 ± 0.60	2.16 ± 0.93	1.80 ± 0.37
3	**5**	3.17 ± 0.67	2.38 ± 0.33	2.02 ± 0.35
2	**7**	7.60 ± 2.48	5.57 ± 1.03	1.31 ± 0.69
4	**103**	7.07 ± 1.78	11.97 ± 3.33	12.27 ± 1.89
5	**105**	8.57 ± 1.65	7.34 ± 3.29	14.35 ± 1.53
6	**107**	9.24 ± 2.09	9.61 ± 1.80	10.19 ± 0.54



3 **5** **7**

103 **105** **107**

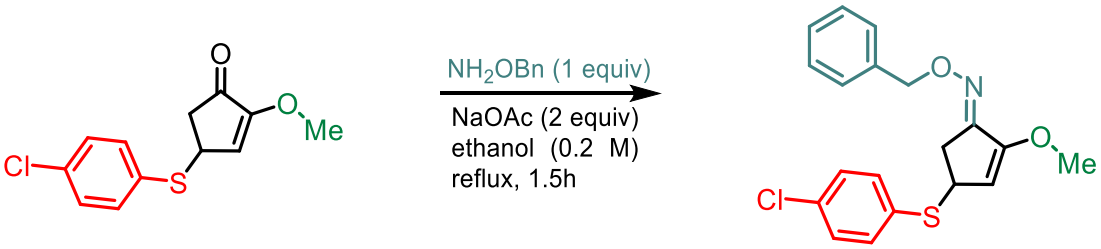
With the information in hands that arylthiols present better activity, in particular 4-chloroaryl, and that both the free alcohol and a secondary amine in position 2 favor the cytotoxic activity we decided to explore further the structure-activity relationship of these CPs. At first glance it appears that H-bond donors are important for the activity. As such we prepared **111**, the methylated derivative of **92** which loses the possibility of H-bond donation in order to support the hypothesys of this parameter on the activity. The methylated compound was prepared by methanolysis of **78**.



78 **111**

Scheme 25. Preparation of methylated derivative of ACP **78**

CP **112,** the oxime derivative of **111** was also prepared in order to highlight the importance of the ketone in the activity (**Scheme 26**).



111 **112**

Scheme 26. Preparation of the oxime derivative of **111**

With the compounds in hands we evaluate the activity of the new derivatives of **20** for the anti-proliferative activity at a fixed concentration of 20 μM in HT-29, MCF-7 and NCI-H460 cells (**Table 9**). We observed a remarkable decrease in activity on HT-29 cell lines when the substituent in position 2 is not capable of forming H bond interactions (**92** vs **78** and **111**). However, this decrease is not observed in MCF-7 cell lines, it is in fact the opposite with increased activities of **78** and **111**. When the oxime is formed activity decreased even further, highlighting the importance of the ketone in activity (**111** vs **112**).

With the overall information in hand we proposed the following SAR depicted in Figure 8.

Table 9 Viability assays of derivatives of CP **92** on different cell lines.

Compound	%Viability (20μM)[a]		
	HT-29	NCI-H460	MCF-7
78	81	52	60
92	40	60	76
111	80	82	60
112	94	>100	96

[a] Data are the mean of at least three independent experiments

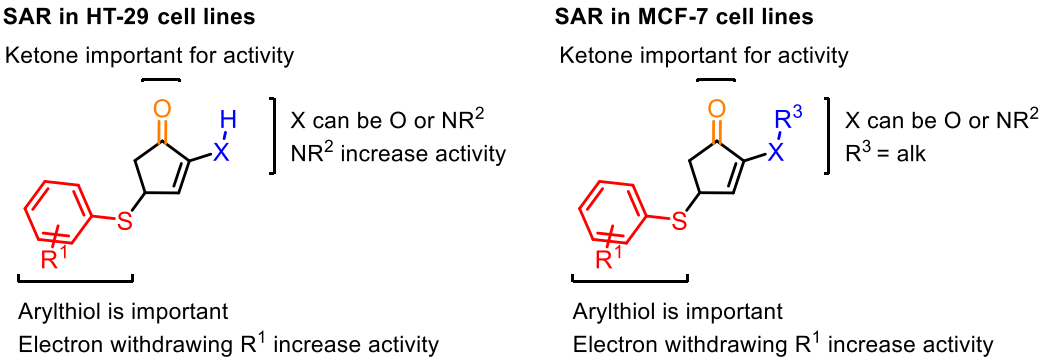


Figure 8 SAR study of the CP thio-adducts.

With the activity of the compounds evaluated we studied their stability both in human plasma but also in a glutathione solution at 24 ºC. One of the main drawbacks to enones in medical chemistry applications is the promiscuity of the enone. By evaluating the stability in presence GSH we measure the promiscuity of the enone. Incubation of DCP **2** in human plasma show no degradation by ^{1}H-NMR after 24h. However in the presence of GSH we observed complete conversion of **2** by ^{1}H-NMR in 3 min. The absence of an olefinic proton and the reappearance over time of the olefinic proton indicates initial formation of intermediate **113** followed by elimination to product **114** (Figure 9, top).

Incubation of CP **78, 92 and 105** in human plasma show no degradation by ^{1}H-NMR after 24h. However in the presence of GSH new aromatic signals consistent with the incorporation of GSH in the CP start appearing. As expected this CP in comparison with **2** is not susceptible to Michael addition, but undergoes amine exchange with the primary amine in GSH to form CP **115**. This may occur due to hydrolysis of the morpholine to CP **92** followed by the incorporation of the amine *via* a mechanism similar to our preparation of **SACPs**. After 3 minutes we observed 20% conversion to the new CP. After 24 h CP **78** has converted in 34 % to CP **115** (Figure 9). Similar to **78** the HCP **92** undergoes the same incorporation even faster**.** After 5 minutes we observe 80% incorporation of the GSH (**Figure 9**).

Finally the stability of CP **105** was evaluated and we observed reduced incorporation of GSH, with only 18 % conversion of the CP after 24 h (**Figure 9**).

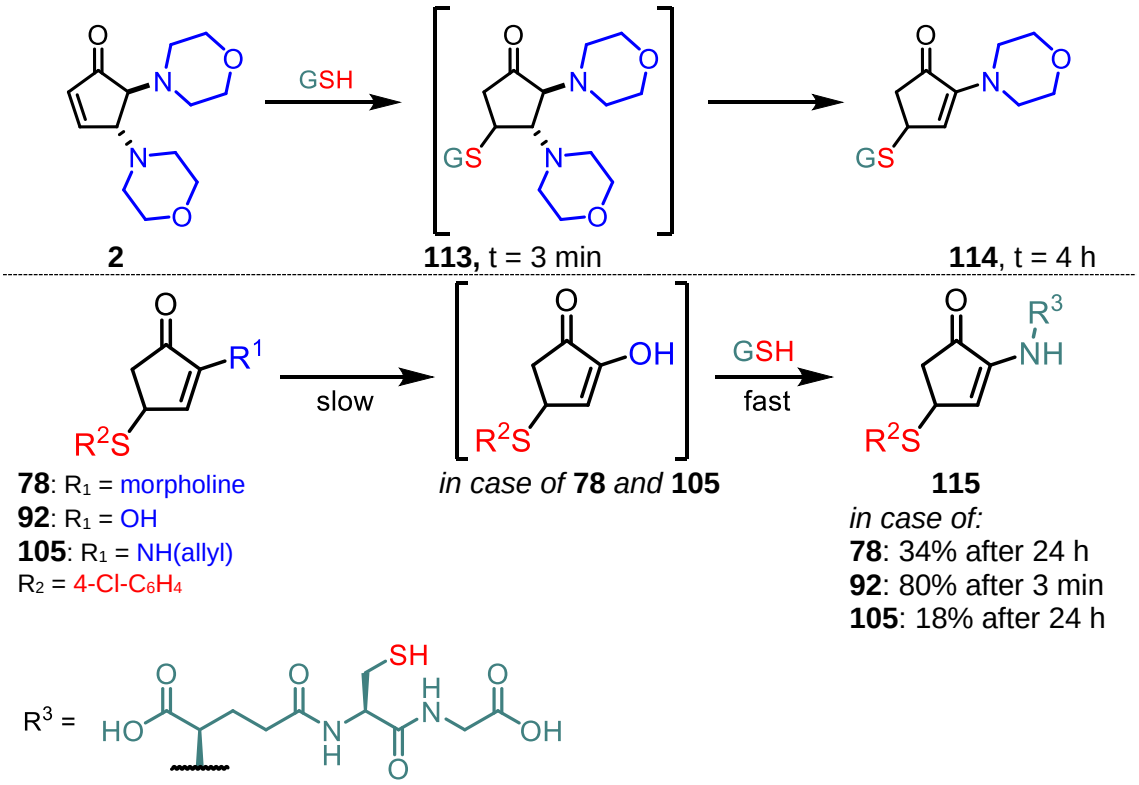


Figure 9 Stability (by ^{1}H-NMR) of CP **2** and **78** (0.1 M) in the presence of glutathione (2 equiv) at 24 ºC.

The drug-like properties of the new CP were calculated (**Table 10**). The active compounds present good drug-like properties, with low molecular weights, calcLogP between 2.52 to 4.31, with the exception of CP **3** where the cLogP is 5.49. Hydrogen bond donors (HBD) between 0-1 and only 2-3 hydrogen bond acceptors (HBA). TPSA between 23, 55 and 37.3. The calculated properties fits the Lipinski's rule of 5 and also the rules described by Veber *et al.* [56] <140 PSA and <12 rotable bonds.

Table 10 Calculated properties of the most promising CPs.

Entry	CP	cLogP	HBD	HBA	MW	TPSA	FR
1	**3**	5.49	0	3	472.6	23.55	10
2	**5**	4.31	0	3	344.5	23.55	2
3	**7**	3.29	0	3	292.4	23.55	4
4	**33**	2.52	1	2	240.7	37.3	2
5	**44**	3.63	1	2	281.8	29.1	5
6	**46**	3.40	1	2	279.8	29.1	5
7	**48**	4.15	1	2	329.8	29.1	5

In conclusion in this study we evaluated the anticancer properties of the new cyclopentenones. These compounds show promising results as anticancer agents against HT-29, MCF-7 and NCI-H460 cells lines. Unlike the commonly used enone cytotoxic agents, the new cyclopentenones lack the strong electrophilic character that lead to noxious side effects *via* unselective alkylation of critical macrobiomolecules. Moreover we observe that the new cyclopentenones are very stable in human plasma and in the presence of gluthathione. Computational studies indicate good drug-like properties according to the Lipinski rules of 5.

II.2.5. Antibacterial activity of DCP

Infectious diseases are a serious cause of morbidity and mortality. Amongst the several pathogens involved in infectious diseases, *Staphylococcus aureus* has shown the ability to develop resistance to most antibiotics. Barber described in 1961 methicillin resistant *S. aureus* (MRSA) strains in clinical isolates derived from an hospital in England[57]. From that point on, MRSA infections have seen a dramatic increase.[58,59] Vancomycin is the gold standard for MRSA infections. Unfortunately vancomycin has some drawbacks such as the low oral bioavailability that limits its use to intravenous[60], and vancomycin-associated nephron and ototoxicity that leads to the need of constant monitoring of serum vancomycin concentrations.[61] The appearance of vancomycin intermediate *S. aureus* (VISA) and vancomycin resistant *S. aureus* (VRSA) is a cause of concern.[62] For this reason the search for new molecules with antibiotic properties, especially against MRSA[63–65] is urgent. Natural products containing a cyclopentenone (CP) scaffold such as nigrosporione A-B[66] and palmenone A-B[67] have demonstrated antimicrobial activity (Figure 10). In this sub chapter we studied the antimicrobial activity of the DCP family and some derivatives described in the previous chapter. The antimicrobial assays were performed by Vera Isca, PhD student from Dr. Patrícia Rijo from Lusófona.

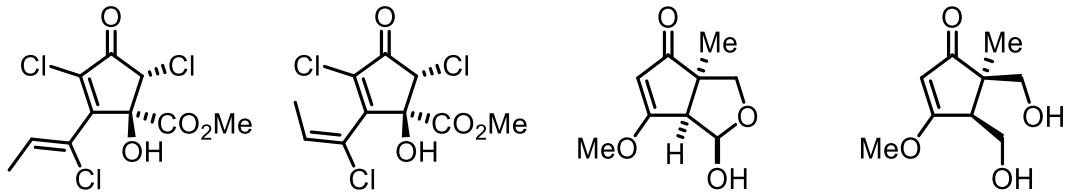
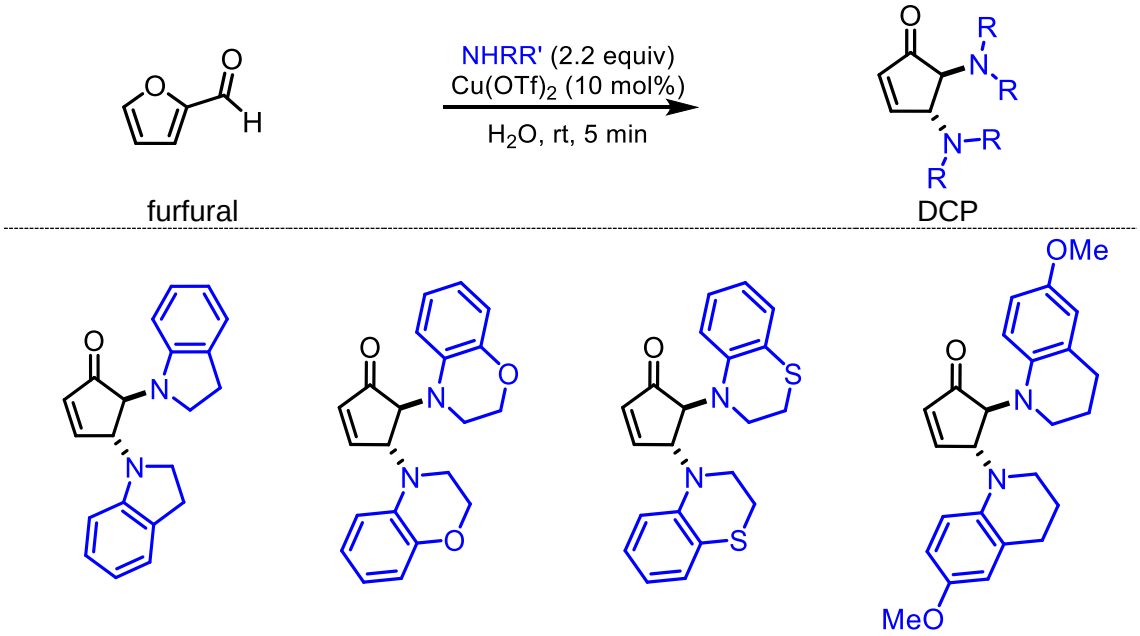


Figure 10. Natural ocurring cyclopentenones with antimicrobial activity:

An initial screening was performed by evaluating the minimum inhibitory concentrations (MICs) against a Gram-positive bacteria strain (*Staphylococcus aureus*), a Gram-negative bacteria strain (*Escherichia coli*) and two fungal strains (*Candida albicans* and *Sacharomyces cereviseae*).

The initial screening revealed that amongst the DCP family only **5** presented significant antimicrobial activity (**Table 11**). As such new DCP were prepared according to the method previously described in subchapter II.2.1 containing amines similar to tetrahydroquinoline (**Scheme 27**).



Scheme 27. New diaminocyclopentenones from tetrahydroquinolone analogs.

Electron donating groups in the tetrahydroquinoline decreases activity (**5** vs **118**). Although **5** is very active in *S. aureus* its activity is impaired in MRSA. Despite this, the O and S analogs **116** and **117** are active with MIC of 3.91 μg.mL^{-1} In the ACP family and the corresponding hydrolyzed HCPs was observed no antimicrobial activity (**76-80** and **90-94**).

Table 11 Minimum inhibitory concentration values of prepared cyclopentenones

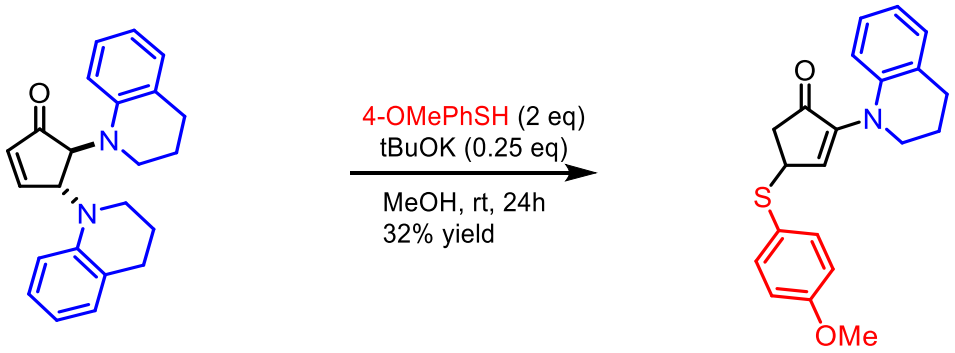
	S. aureus		*MRSA*		*S. cereviseae*	
CP	MIC	MBC	MIC	MBC	MIC	MBC
2, 3, 4	125	>500			62.5	125
5	3.91	>31.2	15.6	250	31.2	125
6	62.5	>500	62.5	>500		
7	62.5	125			>125	125
116	7.81	>62.5	3.91	>31.2		
117	3.91	>31.2	3.91	>31.2		
118	7.81	250	62.5	250	31.2	125
76-80	>250	250			62.5	250
90-94	125	250			31.2	62.5
Vanco	1.95	1.95	0.48		0.98	nt

[a] Data are the mean of at least three independent experiments

Focusing on the tetrahydroquinoline DCP derivatives it was possible that the CP underwent non-specific Michael addition in the bacteria cells releasing the corresponding

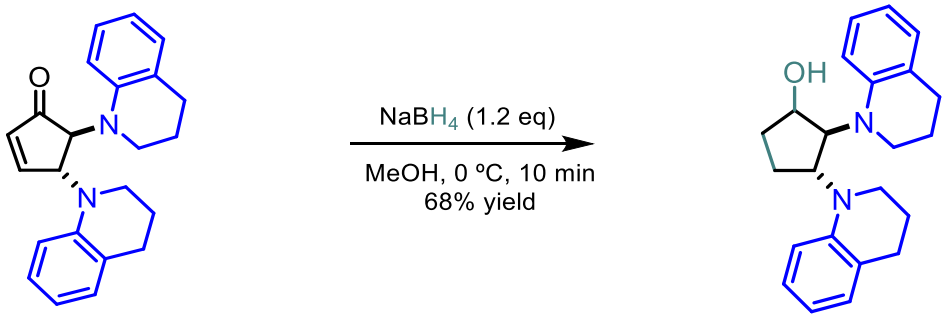
ACP compound and tetrahydroquinoline (THQ). Both the ACP and the THQ could be responsible for the activity and as such we decided to evaluate their antimicrobial inhibition. ACP **119** was prepared as depicted in Scheme 28. Also reduced derivative **120** was prepared to evaluate the importance of the enone.

A. Thio-michael addition of 4-OMe-PhSH to diaminocyclopentenone **5**



5 **119**

B. Reduction of diaminocyclopentenone **5**



5 **120**

Scheme 28 Synthetic derivatives of cyclopentenone **5** prepared by Michael addition (A) and reduction (B).

Table 12 Minimum inhibitory concentration values of active cyclopentenone derivatives.

	S. aureus	
Compounds	MIC	MBC
5	3.91	>31.2
119	125	>500
120	62.5	>500
THQ	125	>500

[a] Data are the mean of at least three independent experiments

A complete loss of activity is observed upon reduction of the enone. Gratifyingly we observed no activity neither when the CP is conjugated with a thiol nor by the free amine. Those combined results indicates that the mechanism of action does not involve the formation of active thio-CP adducts nor liberation of toxic amines (**Table 12**).

Finally the drug-like properties of the enones were accessed in Table 13. CPs **5, 116** and **117** present good drug-like properties, with low molecular weights, calcLogP between 3.03 to 4.31. No hydrogen bond donors (HBD) and only 3-5 hydrogen bond acceptors (HBA). TPSA between 23 and 42. The calculated properties fits the Lipinski's rule of 5 and also the rules described by Veber *et al.*[56] <140 PSA and <12 rotable bonds.

Table 13 Calculated properties of relevant cyclopentenones.

CP	cLogP	MW	HBA	HBD	TPSA
5	4.31	344.4	3	0	23.55
116	3.03	348.4	5	0	42.02
117	3.79	380.5	3	0	23.55

In conclusion in this subchapter we observe that *trans-4,5*-diamino-cyclopent-2-enones are promising antibacterial agents. In particular tetrahydroquinoline analogs show activity against MRSA and present good calculated drug-like properties. Future work in on optimizing this scaffold is ongoing.

II.3. Conclusions

In the Chapter II we described an environmentally friendly procedure to prepare DCP from biomass derived furfural in water promoted by catalytical amounts of $Cu(OTf)_2$. This catalyst can be reused up to 4 times. Immobilization of $CuSO_4$ in silica allowed for the first example of the preparation of DCP under continuous flow conditions. This approach facilitates the scale-up/out of DCP important for the preparation of natural product (±)-agelastatin A. Using the $Cu(OTf)_2$ in water system we prepared mixed DCP by reacting furfural in the presence of two distinct amines. The reaction is highly regioselective and dependent in the formation of a stable iminium ion. Biological evaluation of these compounds revealed DCP to be a promising scaffold for antimicrobial studies, with low IC_{50} even in MRSA strains. ACP and HCP obtained from Michael addition to DCP revealed to be a promising scaffold for tumor growth inhibition. These CP are also non-electrophilic, which is the case of most previously used CP scaffolds for drug discovery and often led to the discontinuation of the studies due to toxicity related to non specific alkylation.

Chapter III

III. Transformation of 5-hydroxymethylfurfural to δ-Lactone-fused cyclopent-2-enones and derivatives as new scaffolds for drug discovery

Abstract: In this Chapter III we described the formation of CP from HMF. Following the pioneer work of Batey on the Dysprosium promoted transformation of furfural to CP, our group have previously observed that under the same conditions HMF undergoes a vinilogous addition. The formation of CP from HMF would allow an increase in complexity to the system. Recent advances have shown that furfural if activated by Knovanaegel condensation with Meldrum's acid undergoes CP formation in the absence of catalyst. This increase in reactivity led us to prepare activated derivatives of HMF and attempt the formation of CP with these furans. We observed that the HMF-Meldrum's acid in the presence of diethylamine undergoes the formation of CP and in the presence of BINOL further decomposition of the Meldrum's acid leads to a lactonization. The mechanism of this reaction is thoroughly studied by NMR and DFT.

We prepared several derivatives namely derived from thio-Michael addition, that leads to a remote lactone activation that then undergoes methanolysis. We used DFT calculation to explain why the previously unreactive lactone undergoes spontaneous methanolysis after the Michael addition.

The prepared CP underwent an array of biological screening and the thio-adducts have shown antimalarial activity.

III.1. Rationale and Goals

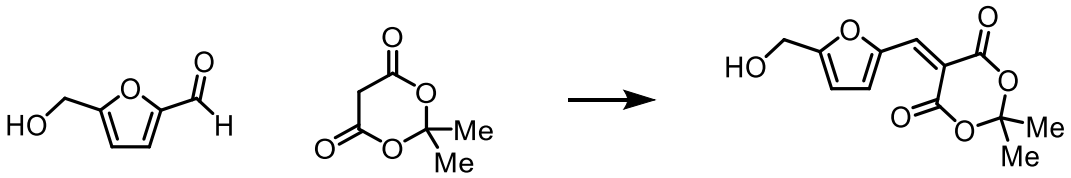
As described in section I, CPs may contain several biological activities. In section II we prepared DCPs and derivatives with anticancer and antimicrobial activity. In this context we decided to develop CPs with increased complexity by taking advantage on our expertise on 5-hydroxymethylfurfural (HMF) chemistry [23,68]. HMF, similar to furfural, is a biomass derived furan of high potential[69]. However several drawbacks of the HMF platform have been reported[70,71], namely its instability[70]. By using known methods such as Lewis acid catalysis and aldehyde activation that have been used in the transformation of furfural to CP we aimed to prepare complex CP from HMF with potential bioactivity. For this purpose we started by overcoming the instability issue on HMF by screening several additives that will impair the acid promoted decomposition of HMF, which yields the corresponding dimer[72], and the oxidative pathways that lead to insoluble black tars described as humins[73,74]. Then, we prepared different activated HMF derivatives by Knovanaegel condensation and screened different conditions for the formation of CP. After obtaining the initial family of CP model reactions was synthesized different families of compounds that have been tested for anticancer, antimicrobial and antiviral activity.

III.2. Results and discussion

III.2.1. Stabilization of 5-hydroxymethylfurfural

5-Hydroxymethylfurfural (HMF) was included by US Department of Energy in the previous “Top 10” list of bio-based chemicals.[75] However, the broad application of HMF, namely for large scale processes still suffers from several drawbacks, which limits the production and purification by distillation due to thermal and storage/transportation instability and general occurrence of side reactions, such as the formation of humins[73,74] and dimerization to the corresponding ether[72] 5,5′-oxy(bis-methylene)-2-furaldehyde (OBMF). As depicted in section III.1, we prepared **121** as starting material for the formation of complex CPs. During our attempts to carry out Knoevenagel condensation of HMF with Meldrum’s acid, as recently reported for furfural,[16] we observed the occurrence of side reactions. Under base free conditions or in presence of catalytic amount of $NaHCO_3$ moderate yields of 74% and 78% of **121** were achieved, respectively, accompanied by the common dark appearance of the reaction mixtures and formation of insoluble black tars (**Table 14**, entries 1 and 3). Surprisingly, in presence of only 1% w/w of $Na_2S_2O_4$ the formation of black tars in course of the reaction was suppressed to a large extend resulting in an outstanding yield of 96% and yellowish appearance of the reaction mixture (**Table 14**, entry 2).

Table 14 Knoevenagel condensation of HMF with Meldrum’s acid[a]



HMF MA **121**

Entry	Reaction mixture	Additive	**121** (%)[b]	HMF (%)[b]	Humins (%)[c]
1		None	74	10	16
2		$Na_2S_2O_4$	96	traces	traces
3		$NaHCO_3$	78	13	9

[a] Reaction conditions: HMF (100 mg, 0.79 mmol), Meldrum’s acid (110 mg, 0.79 mmol, 1 equiv.), H_2O (8 mL), additive (0.01 equiv.), 75°C, 0.5h. [b] Yields determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Yield calculated from the mass balance between 5-HMF and **121**.

The lack of significant improvement of the reaction outcome in presence of $NaHCO_3$ led to the idea that $Na_2S_2O_4$ promotes unprecedented inhibition of the side reactions rather than efficient basic catalysis. We foresaw this property as an unexplored strategy that may contribute to overcoming some of the present limitations of the HMF platform.

As reported by Galkin *et al.,*[70] during aging in oil state, HMF tend to undergo two general degradation pathways, namely dimerization to OBMF and not clearly understood oligomerization to form insoluble tarry carbonaceous materials, known as humins. Encouraged by our results we attempted to overcome this issue by exploring several additives for their property to preserve HMF upon heating (120°C, 4h, neat). Given the reducing properties of $Na_2S_2O_4$ we elected several commonly used antioxidants together with choline chloride (ChCl)[76] and DMSO,[77] which were reported to stabilize 5-HMF when used as solvents (**Table 15**).

In the absence of any additive only 37% of HMF was preserve at the end of the experiment and formation of 33% OBMF together with 30% of humins was observed (**Table 15**, entry 1). The addition of DMSO did not led to any pronounced advantage (**Table 15**, entry 2). The presence of antioxidants led to significant suppression of the formation of humins (**Table 15**, entries 3, 4 and 5), which indicates that oxidative pathways are likely to be involved in the oligomerization of HMF. However, the acidity of ascorbic acid and BHT catalyzes the formation of OBMF, thus leading to significant loss of HMF (**Table 15**, entries 3, and 4). No dimer formation was observed in presence of urea, which is likely to be due to the basic conditions caused by the liberation of ammonia *via* formation of carbonates, as observed by us in previous studies.[11] However, significant amount of humins was formed and only 63% HMF was preserved (**Table 15**, entry 6). Surprisingly, the addition of 1% w/w ChCl promoted considerable stabilization, effecting both the dimerization and formation of humins, nevertheless the HMF sample significantly changed in color (**Table 15**, entry 7). Both sodium metabisulfite and sodium dithionite exhibited remarkable effect over the 5-HMF stability (**Table 15**, entries 8 and 9). It is worth mentioning that in both cases the visual appearance of HMF after its processing significantly differed from all the other stabilizers (**Table 15**). However, $Na_2S_2O_4$ was the only additive to exhibit unprecedented effect on the stability of HMF, promoting absence of any degradation (**Table 15**, entry 9). Moreover, $Na_2S_2O_4$ showed significant effect over the long term storage. After 2 months of aging under ambient conditions crude HMF sample in oil state underwent 40% degradation in absence of stabilizer, whereas only 18% degradation was detected in presence of 1% w/w $Na_2S_2O_4$. In addition, in both cases no possible reduction of the aldehyde function of HMF was observed.[78]

Table 15 Stability effect promoted by the addition of additives[a]

Entry	Additive[b]	HMF (%)[c]	Dimer (%)[c]	Humins (%)[d]
1	-	37	33	30
2	DMSO	46	33	21
3	Ascorbic acid	42	49	8
4	BHT	48	43	9
5	Zn^0	71	10	19
6	Urea	63	0	47
7	ChCl	86	14	Traces
8	$Na_2S_2O_5$	85	6	9
9	$Na_2S_2O_4$	100	0	0

[a] Reaction conditions: 5-HMF (100 mg, 0.79 mmol), 120°C, 4h. [b] 1% w/w [c] Yields determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [d] Yield calculated from the mass balance between HMF and dimer.

NMR tube (Entry 1)

NMR tube (Entry 7)

NMR tube (Entry 8)

NMR tube (Entry 9)

Furthermore, self-diffusion NMR measurements were conducted in Bulgaria Academy of Science by Yavor N. Mitrev in order to give some insight into the observed stabilization properties. The significantly lower diffusion coefficient of ChCl in the presence of HMF, regardless of the similar molecular weights of the two compounds, indicates extensive aggregation of ChCl with the formation of high stoichiometry associates (**Table 16**, entry 1). The reorganization of the HMF network is also supported by the chemical shift changes in the presence of different amounts of ChCl (**Figure 11**), with the most pronounced differences near aldehyde and alcohol functions. Hence, the most plausible explanation of the stabilization properties of ChCl is the disturbance of the non-covalent network of the HMF molecules, as the close self-arrangement in the network is considered favorable for the oligomerization.[70]

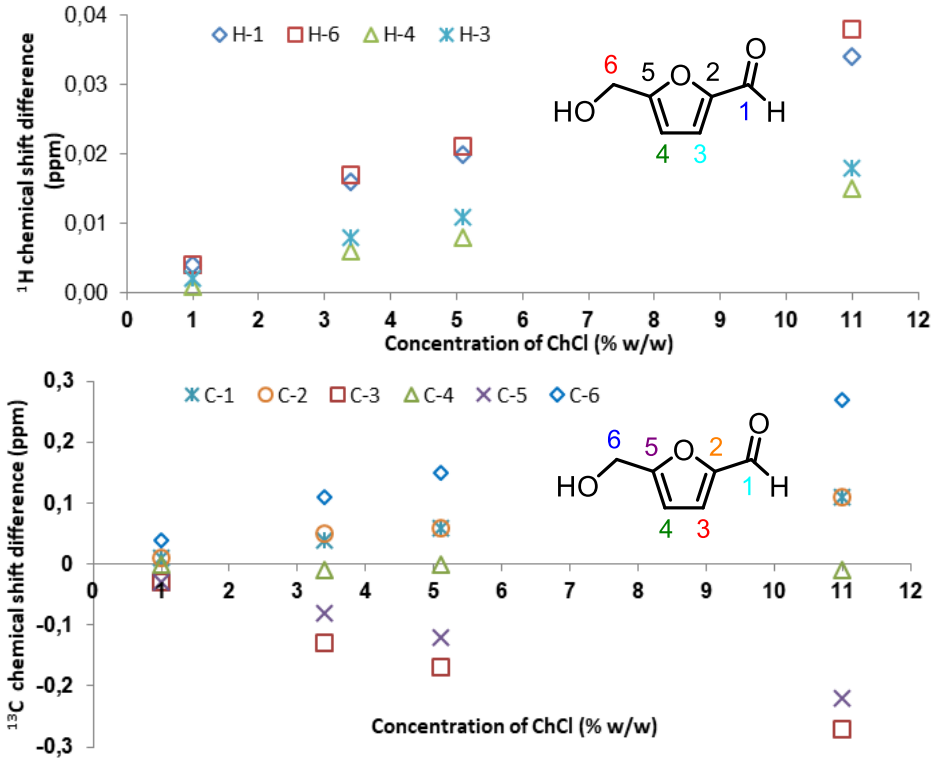


Figure 11 Chemical shift difference of HMF in the presence of ChCl. (Chemical shift difference is calculated by $\Delta\delta=\delta_{(pure)}-\delta_{(doped)}$ of HMF protons and carbons upon addition of ChCl)

Driven by this considerations, we anticipated that the effect of ChCl may be limited only to the aging and thermal stability of neat HMF, as in this case the self-arrangement in the network will have the predominant effect over the decomposition. This was experimentally confirmed in one instance, where ChCl was used as additive in the Knoevenagel condensation, as expected no positive effect was observed and only 49% yield of **121** was achieved. On the contrary, although the nature of the $Na_2S_2O_4$ hampers its direct observation in ^{1}H experiments, thus requiring more sophisticated approaches (e.g. ^{23}Na DOSY experiments), the addition of either BHT or $Na_2S_2O_4$ did not change significantly the NMR behavior of HMF (**Table 16**, entries 2 and 3), suggesting that indeed different stabilization mechanism is at play. Hence, given the similar antioxidant properties of BHT, $Na_2S_2O_5$ and $Na_2S_2O_4$ and their effect over the HMF stability, we believe that the ability of $Na_2S_2O_4$ to suppress the oxidative pathways towards humins formation combined with its mild basicity to prevent HMF dimerization is the most plausible explanation.

Table 16 Self-diffusion coefficient (*10^{-10}) of 1M HMF

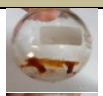
Entry	Additive[a]	HMF[b]	Additive
1[b]	ChCl	8.81 (9.1)	4.55
2[b]	BHT	9.41 (9.1)	8.90
3[c]	$Na_2S_2O_4$	3.67 (3.68)	-

[a] 1 % w/w additive. [b] Data for pure HMF is given in parenthesis. [b] Spectra in $CDCl_3$, 303 K. [c] Spectra in DMSO-d6, 303 K.

As the stabilization effect of $Na_2S_2O_4$ is not limited to the simple disturbance of the neat HMF self-arrangement in the network one may expect that its effect will be of a much wider scope compared to ChCl. Hence, driven by these considerations we further explored the utility of $Na_2S_2O_4$ as stabilizer for HMF synthesis, purification and various synthetic transformations.

A long lasting challenge in the preparation of HMF from carbohydrates are the low yields sometimes observed simultaneously with high yields of humins. A number of research groups have reported different approaches to overcome this problem. Sugar dehydration under aqueous conditions with an *in situ* extraction of the HMF in an organic phase was intensively studied.[69] However, although in some examples the undesired side reactions were suppressed to a large extent many limitations are still to overcome. To this end, we explored the stabilization effect of $Na_2S_2O_4$ for the synthesis of HMF from fructose using simple biphasic system aq. NaCl/THF and HCl as catalyst. The so prepared biphasic system was heated for 2h at 170°C in a sealed reaction tube. Under these conditions, the presence of only 1% $Na_2S_2O_4$ led to significant improvement of the yield and purity (**Table 17**, entry 1 vs 2). The visual inspection of the reaction`s courses revealed that in presence of $Na_2S_2O_4$ the organic phase was slightly yellow, whereas in its absence dark brown color caused by the formation of side products was observed. Moreover, the appearance of the isolated crude product was an orange oil when the reaction was carried out in presence of $Na_2S_2O_4$, while darker color and significant amount of solid black by-products were observed in its absence.

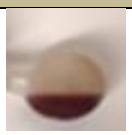
Table 17 Biphasic preparation of HMF from fructose[a]

Entry	Crude HMF	$Na_2S_2O_4$	Crude HMF yield (%)[b]	HMF purity (%)[c]
1		1%	98	92
2		-	67	83

[a] Reaction conditions: Fructose (106 mg, 0.59 mmol), NaCl aqueous solution (pH 2) (1mL), THF (2 mL), 170°C, 2h. [b] Isolated Yield. [c] Purity determined by ^{1}H-NMR.

Vacuum distillation is typically used to obtain pure HMF. However, the distillation of crude HMF was recognized to be troublesome due to its thermal decomposition leading to the formation of tarry carbonaceous materials. Under classical vacuum distillation the isolated yield of pure HMF from the crude typically lies in the region of 45-60%.[79] Therefore, we further explored the effect of $Na_2S_2O_4$ in solving this issue. Two batches of 6.0 g crude HMF obtained *via* previously described by us protocol were distilled under reduced pressure. We were pleased to observe that the presence of only 2% w/w of $Na_2S_2O_4$ promoted largely positive effect on the outcome of the distillation leading to 85% recovery of highly pure HMF, whereas only 52% of impure HMF were recovered in its absence (**Table 18**). It is worth mentioning that in the absence of stabilizer the NMR analysis of the remaining residues showed mainly degradation products, whereas in presence of $Na_2S_2O_4$ the residues contained predominantly HMF (**Figure 12**), which was not possible to distil due to the limitations of our distillation set up. Hence, we anticipate that better yield may be achieved if the distillation is carried out on a larger scale. In addition, as described by Galkin *et al*.,[70] the crystalline HMF with purity greater than 99.9% is a stable product, while rapid aging of the oil form is observed even in 97-99% purity. The HMF sample obtained from the distillation in presence of $Na_2S_2O_4$ meets the purity requirements and smoothly solidified to form crystalline HMF, which without any further treatment was stable under prolonged storage.

Table 18 Stability effect on HMF distillation[a]

Entry	HMF vapor	Distilled HMF	$Na_2S_2O_4$	HMF (%)
1			-	52
2			2% w/w	85

[a] The distillations were performed at 120ºC and $5x10^{-4}$ bar using diffusion pump.

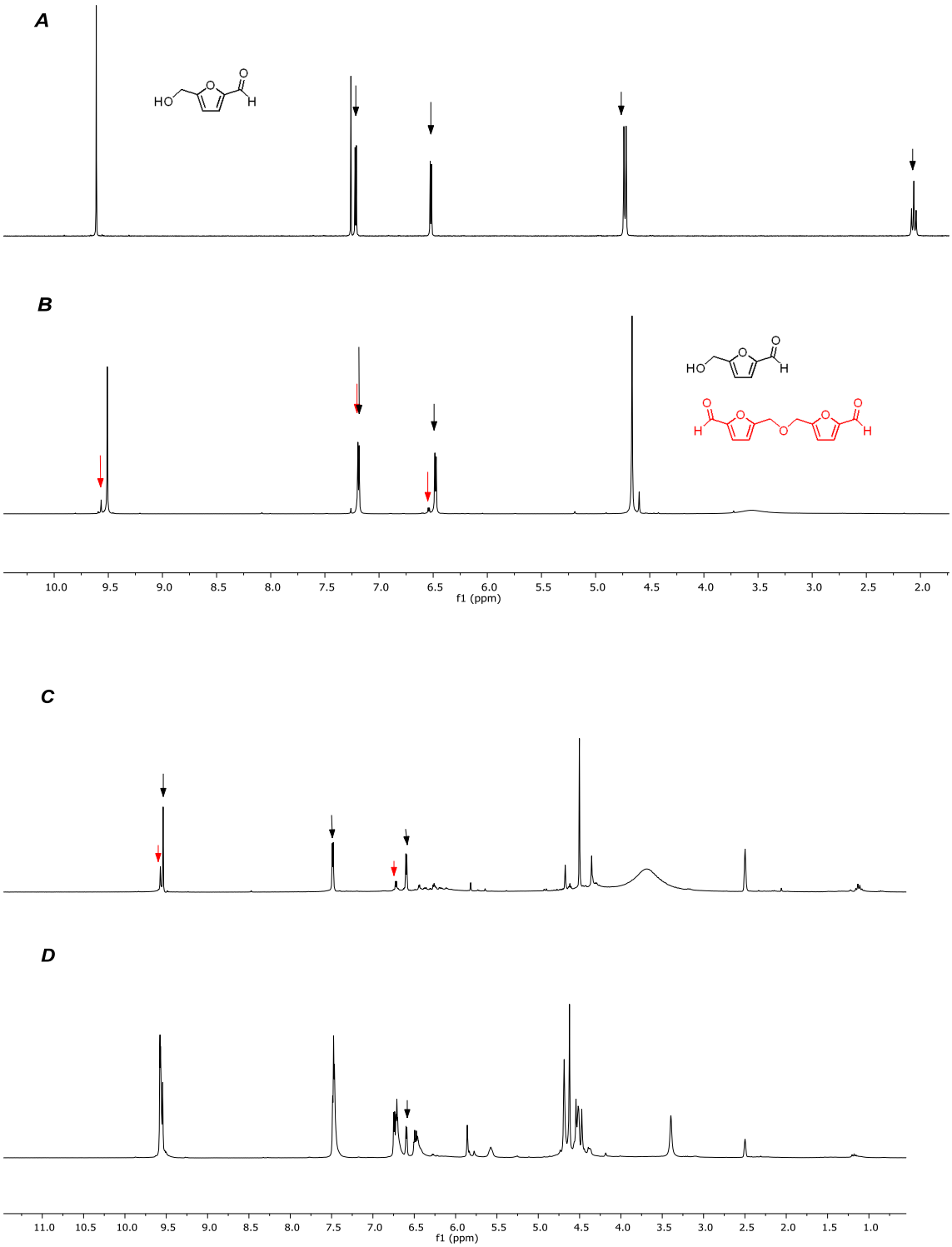
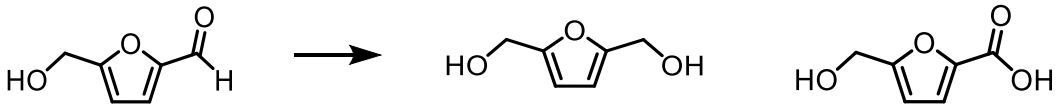


Figure 12 ^{1}H NMR ($CDCl_3$) of the distilled HMF in presence of stabilizer (A) and in the absence of stabilizer (B) and of the remaining residues in presence of stabilizer (C) and in the absence of stabilizer (D).

Encouraged by these very promising results we further focused our attention on the effect of $Na_2S_2O_4$ on the synthetic transformations of HMF, by exploring two examples, namely Cannizzaro reaction and synthesis of pyridinium salts. As previously reported by us,[68] HMF readily undergoes Cannizzaro reaction in presence of strong bases to yield simultaneously the important 2,5-dihydroxymethylfurfural (DHMF) and 5-hydroxymethyl-2-carboxylic acid (HMCA) in up to 82% and 81% yield, respectively. However, the formation of black side products was always observed, which was a reason for troublesome purification of the reaction mixtures. Under our previous conditions in presence of 1% $Na_2S_2O_4$ the formation of tars was fully omitted resulting in quantitative yields of DHMF and HMCA (**Table 19**). Moreover, we observed unexpected improvement of the reaction rate, which allowed full conversion of HMF in only 1h compared to 36h in our previous studies. The isolation of both DHMF and HMFCA underwent smoothly under the previously reported by us conditions[68] to give 96% and 94% yield, respectively.

Table 19 Stability effect on Cannizzaro reaction of HMF[a]



HMF **DHMF** **HMCA**

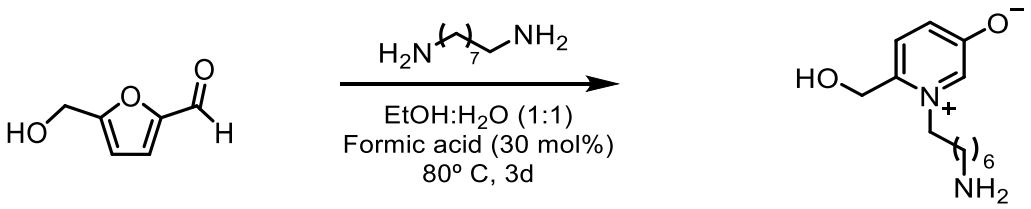
Entry	Isolated HMFCA	$Na_2S_2O_4$	DHMF (%)[b]	HMCA (%)[b]
1		-	81 (82)[c]	84 (85)[c]
2		1% w/w	100 (96)[c]	100 (94)[c]

[a] Reaction conditions: HMF (100 mg, 0.79 mmol), water (0.5 mL), NaOH aq. solution (30 mg in 0.5 mL). [b] Yields determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated Yield.

Recently, we described[80] the formation of various pyridinium salts from the acid catalyzed condensation of HMF with primary amines. However, the final products were isolated as black solids and in some examples only moderate yields were achieved. Treatment with charcoal allowed to remove the black color to a large extend. However, when stored, even at -12°C, the so prepared pyridinium salts tend to become black again. Therefore, the observed stabilization effect of $Na_2S_2O_4$ was foreseen by us as a promising approach to overcome these drawbacks. To this end, as a proof-of-concept

example we elected the reaction of 1,8-diaminooctane and HMF, which was known to be troublesome. Under the previously reported conditions, **122** was obtained as black oil in 60% yield. A simple addition of 1% w/w $Na_2S_2O_4$ led to significant improvement allowing the isolation of **122** as white solid in 88% yield, which maintained its color under long storage, up to 2 months (**Table 20**).

Table 20 Stability effect on Acid catalysed pyridinium salt formation[a]



HMF **122**

Entry	Pyridinium salt **122**	$Na_2S_2O_4$	**122** (%)[b]
1		-	60
2		1% w/w	88

[a] Reaction conditions: HMF (100 mg, 0.79 mmol), ethanol (5 mL), 1,8-diaminooctane (171 mg, 1.19 mmol). After stirring for 30 min, formic acid aq solution (9 µL formic acid in 5mL water). [b] Isolated Yield.

Albeit the use of 1%-2% w/w of $Na_2S_2O_4$ could be considered insignificant for proof-of-concept and laboratory scale processing of HMF, when considering the integration of HMF into commercial operations it is of pivotal importance to address the production cost issues by limiting the amount of the downstream chemicals. To this end, we explored the minimum amount of $Na_2S_2O_4$ that significantly affects the Knoevenagel condensation (**Table 21**). We were pleased to observe that even after 100-fold decrease, from 1% (**Table 14**, entry 2) to 0.01% w/w (**Table 21**, entry 3), significant stabilization effect was still in play. As may be expected, the effective amount of $Na_2S_2O_4$ will vary according to the different type of processes, however this result indicates that upon optimization very low doses of $Na_2S_2O_4$ are viable. In addition, $Na_2S_2O_4$ is readily available, non-toxic salt of an industrial importance, used for instance as bleaching agent in textile, wood pulp and paper industries. Besides being low toxic itself, it dissociates under aerobic conditions into non-toxic products such as sulfite, thiosulfate, and sulfate salts.[81] Hence, it may be considered as promising stabilizer in the large scale HMF processing, as the development of recycling procedures driven by cost or environmental issues are not of a pivotal importance.

Table 21 Dosage effect over Knoevenagel condensation[b]

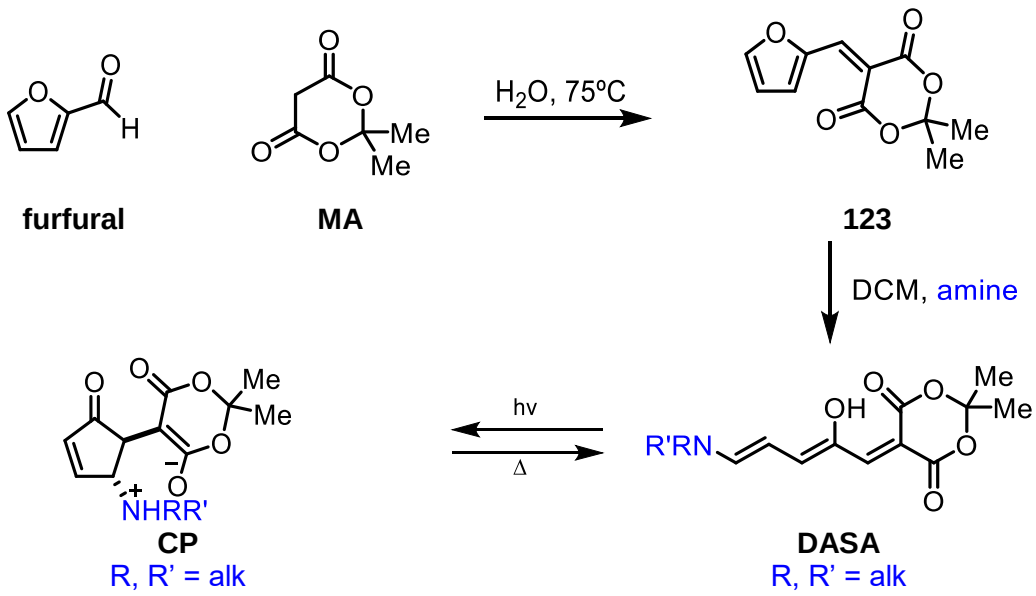
Entry	$Na_2S_2O_4$	**121** (%)[b]	HMF (%)[c]
1	0.1% w/w	95	Traces
2	0.05% w/w	94	3
3	0.01% w/w	89	3

[a] Reaction conditions: HMF (100 mg, 0.79 mmol), Meldrum's acid (110 mg, 0.79 mmol, 1 equiv.), H_2O (8 mL), 75°C, 0.5h. [b] Yields determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard.

In summary in this sub-chapter not only we improved the yield on the Knoevenagel condensation to prepare activated HMF derivatives but also unprecedented low dosage $Na_2S_2O_4$ promoted stabilization of HMF. Our studies revealed that the balanced antioxidant properties accompanied by the mild basicity of this inorganic salt are the key properties for this distinctive stabilization. Although being a non-conventional solution, the observed stability effect is highly versatile affecting the synthesis, purification, shelf-life and synthetic transformations of HMF. Hence, we believe that these results may help in overcoming the present limitations of the HMF platform, which albeit very promising at first glance still suffer serious drawbacks associated with the unstable nature of this compound.

III.2.2. Preparation of δ-Lactone-fused cyclopentenones

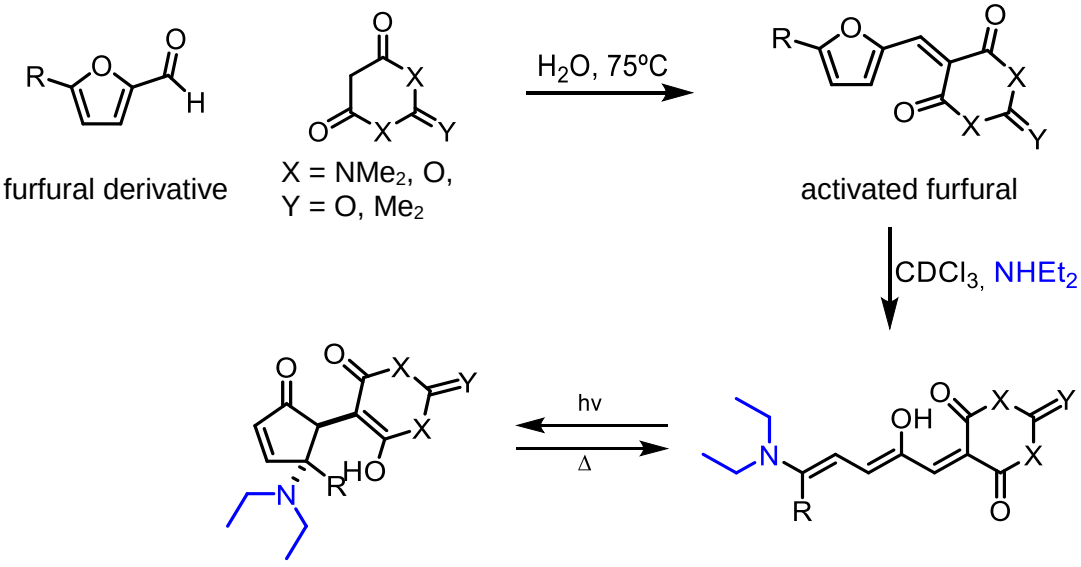
Recent advances by Read de Alaniz and co-workers on the formation of CP led to the development of activated furfurals that react with secondary amines in the absence of catalyst to form stable Stenhouse Salts. Those salts may undergo light mediated 4π-electrocyclization to the corresponding CP (**Scheme 29**).



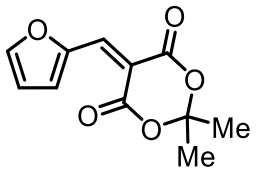
Scheme 29 Catalyst free preparation of DASA-cyclopentenone system from activated furfural described by Read de Alaniz and co-workers.

CPs bearing a quaternary carbon center at C4 have been previously accessed by intramolecular Piancatelli[82] or aza-Piancatelli[83]rearrangements of 5-substitued furylcarbinols, affording spiro-CP. These reported precedents show that nucleophilic addition to the C5 position of furans is feasible. We envisioned that extension of the methodology developed by Read de Alaniz and co-workers, i.e., the use of activated furans, to HMF would lead to new highly functionalized CP scaffolds containing a quaternary carbon center.

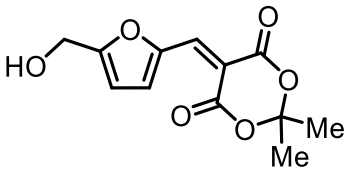
In this line, we prepared activated derivatives of HMF by Knovanaegel condensation with barbituric acid and Meldrum's acid. The silylilated derivative was prepared by protection of **121** with TBSCl (**Scheme 30**).



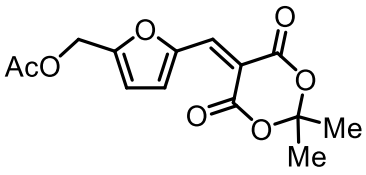
Scope of activated furfurals used for the condensation with diethylamine:



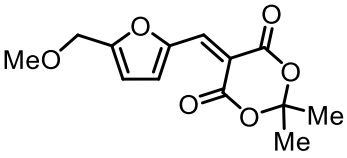
123



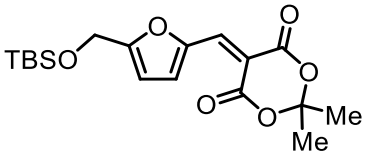
121



125



126



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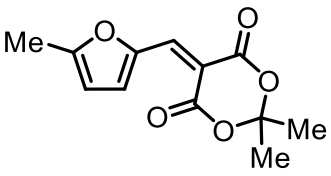
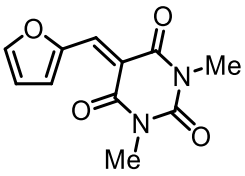
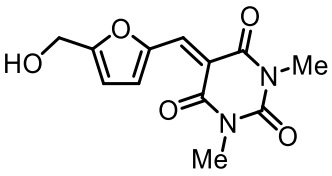


128



129



130

Scheme 30 Strategy for the formation of complex cyclopentenones. Scope of activated furfurals.

We performed a first model reaction with the activated furfural **123** described by Read de Aalaniz and coworkers in deuterated chloroform with diethylamine. Instead of the SS we observed the selective formation of the corresponding cyclopentenone by ^{1}H NMR analysis (**Figure 13**).

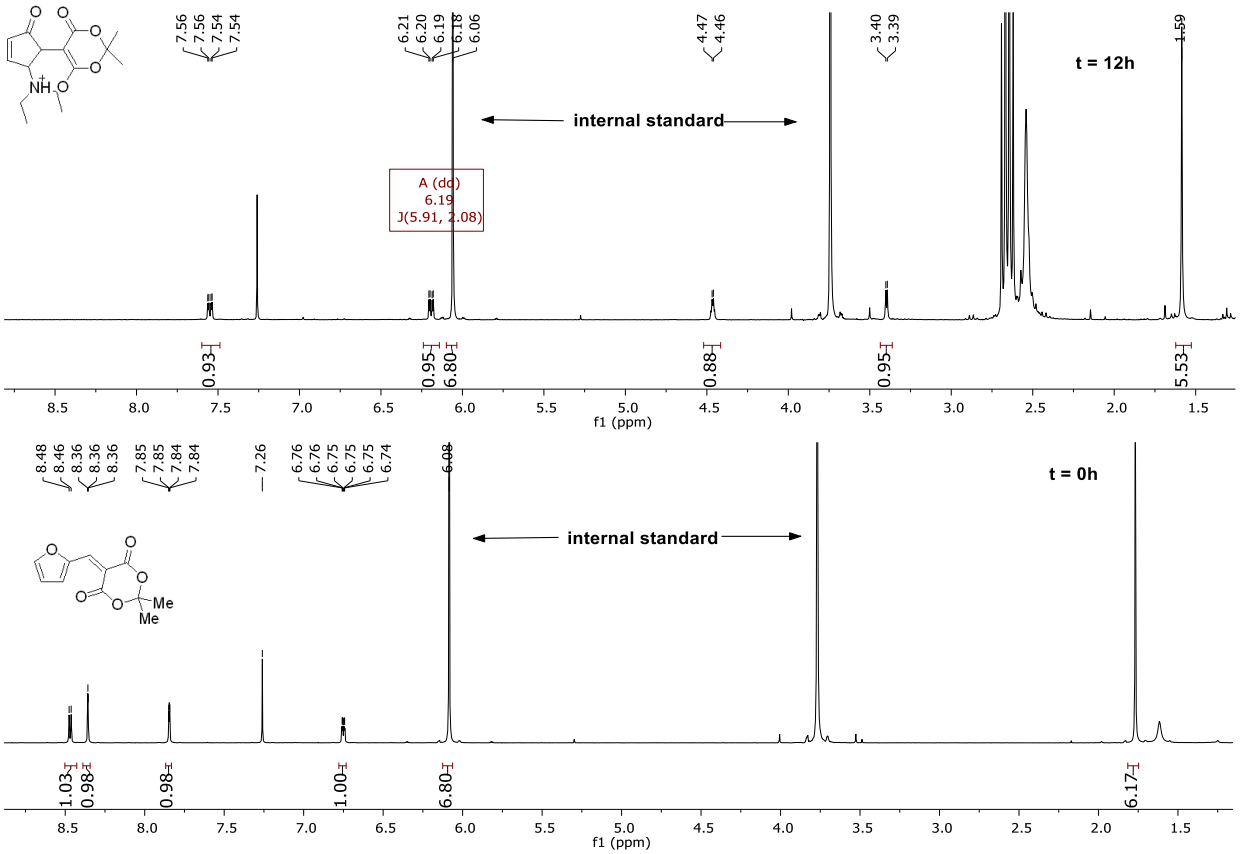


Figure 13. Overlay of ^{1}H-NMR spectra of the reaction of **123** and diethylamine in $CDCl_3$ showing the selective formation of the corresponding CP product (95% NMR yield, using trimethoxybenzene as internal standard). Diethylamine was added after performing the ^{1}H NMR analysis at t=0.

After that, we reacted the activated HMF derivatives (**121**, **125**-**128**) with diethylamine under the same conditions and analyzed the reaction profiles by quantitative ^{1}H NMR.

The TBDMS derivative **127** did not form the corresponding SS and only traces of the desired CP was observed. Instead there was unselective decomposition of the SS leading to a decrease in mass balance. Similar to the TBDMS derivative, the methylated derivative **126** also led mainly to unselective side products formation. In the case of **128** there is formation of the corresponding SS but the electrocyclization to the desired CP is not observed. Instead we observed unselective decomposition of the SS leading to a decrease in mass balance (**Figure 14**).

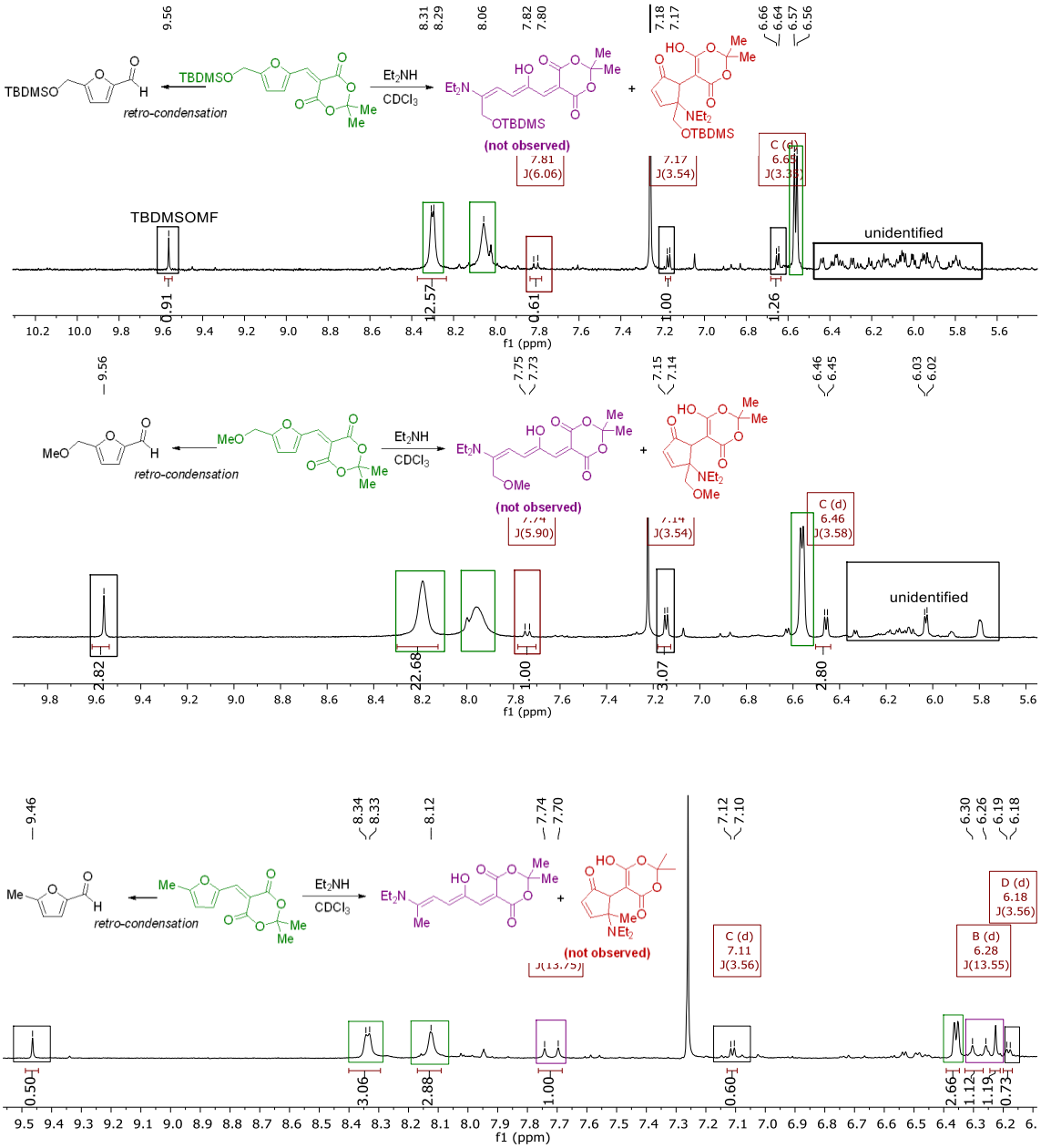


Figure 14 Spectrum of the reaction of **127**, **126** and **128** with diethylamine in $CDCl_3$ after 24 hours. Unidentified products can be observed from 5.8 to 6.4 ppm.

On the other hand, when the free alcohol **121** was used, we observed the formation of the desired CP **131**. Surprisingly the CP was being consumed followed by the formation of a single product, corresponding to the intramolecular lactonization (**Figure 15**). The reaction was repeat in batch conditions and we obtained 30% isolated yield of CP **132**. The reaction profile revealed that the formation of **131** was fast and complete, but a slow transformation to **132** led to formation of unidentified side products and as such low yield.

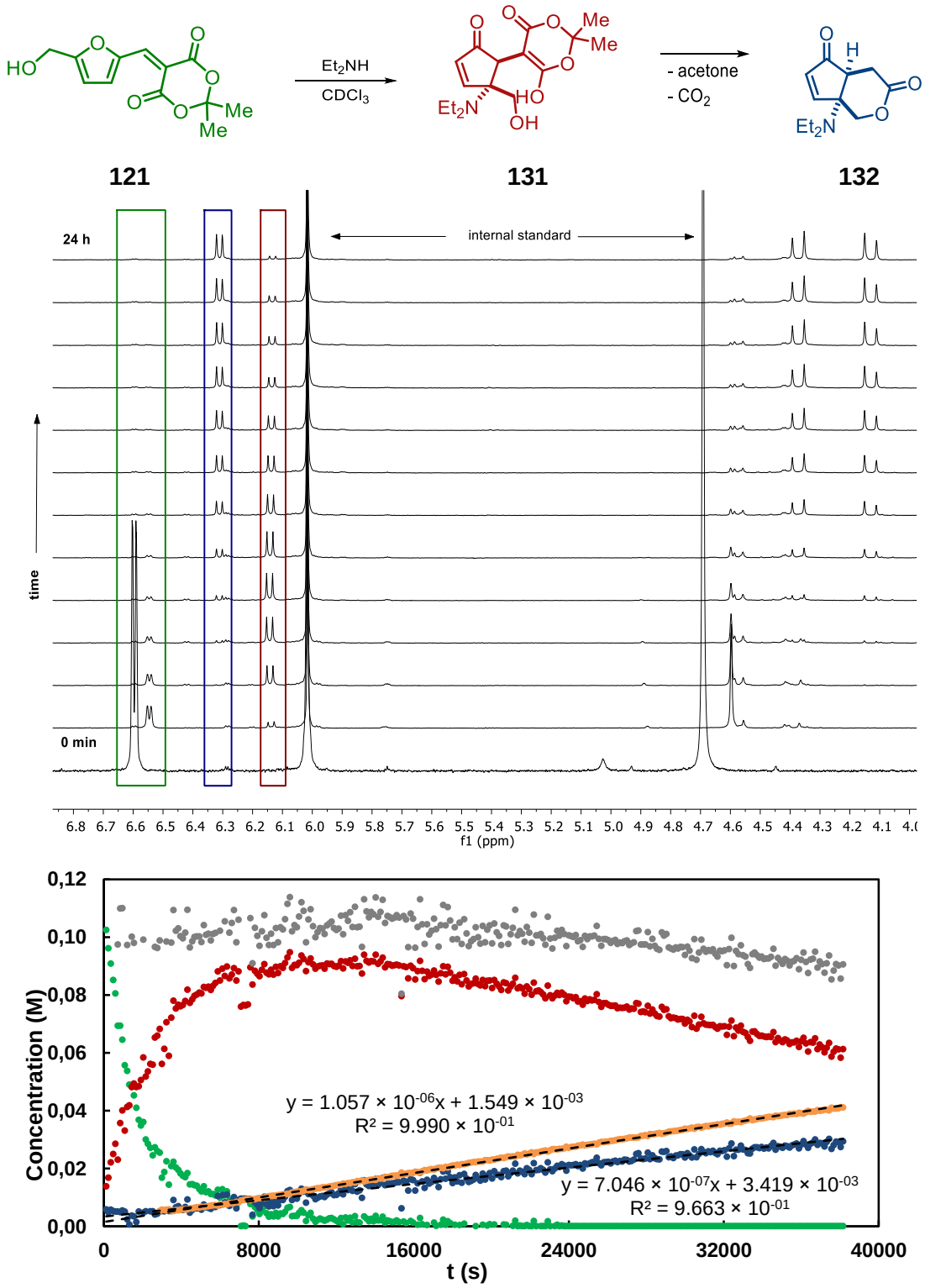
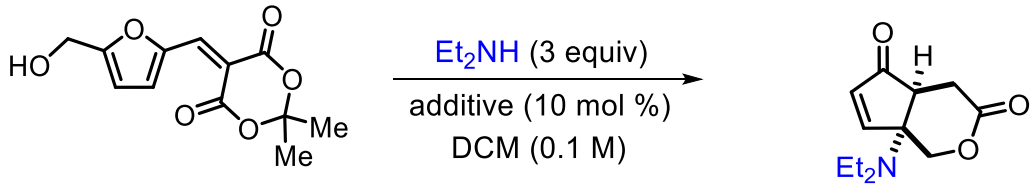


Figure 15 Profile of the reaction of **121** and diethylamine. Legend: **121** (green), **131** (red), **132** (blue), acetone (orange), mass balance (grey, sum of **121**, **131** and **132**). The reaction profile shows greater formation of acetone than product **132**, which is presumably due to decomposition of intermediate **131** to form side products and acetone.

We attempted to improve the yield by screening different additives, namely Lewis and Bronsted acids. (**Table 22**)

Table 22 Screening of additives[a]

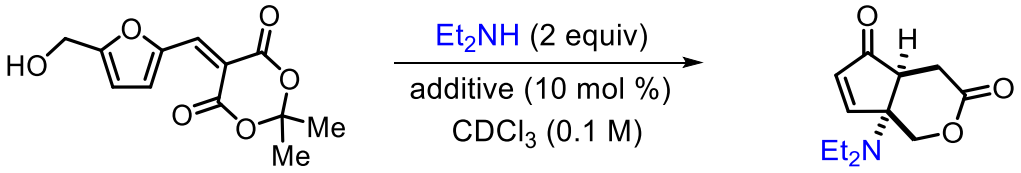


121 **132**

Additive	Yield **132** (%)[a]		
	1 h	7 h	24 h
None	0	28	45
$RuCl_3$	0	36	34[b]
$FeCl_3 \cdot 7H_2O$	30	39	54[b]
$CoCl_2 \cdot 6H_2O$	0	30	0[b]
$Cu(OTf)_2$	0	35	41
ZnI_2	0	25	26
$AlCl_3$	0	30	38
$LaCl_3 \cdot 7H_2O$	0	24	24
$CeCl_3 \cdot 7H_2O$	21	43	51
$GdCl_3 \cdot 6H_2O$	0	25	25
$Dy(OTf)_3$	0	29	46
$Yb(OTf)_3$	0	26	40
TEA	0	27	43
DBU	0	32	38
t-BuOK	0	30	49
PTSA	19	31	37
CSA	20	34	41
PhCOOH	20	34	41
TfOH	0	18	18

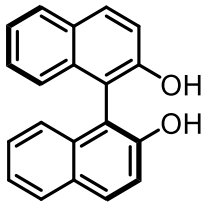
[a]Yield determined by GC analysis of crude reaction mixture using dodecane as internal standard. [b]28 h Reaction time

Unfortunately we did not observe significant increase in yield with the different acidic and basic promoters. Surprisingly we observed that H-bond donor *(R)*-BINOL promoted the reaction up to 70% yield (**Scheme 31**) It is noteworthy that emplying the *(S)*-BINOL we observed similar yield.

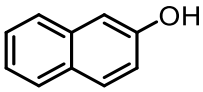


121 **132**

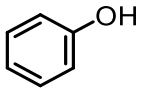
H-donors



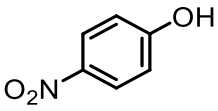
70% of **132**



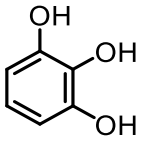
31% of **132**



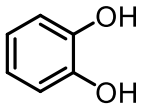
36% of **132**



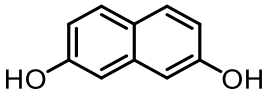
33% of **132**



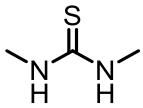
27% of **132**



32% of **132**



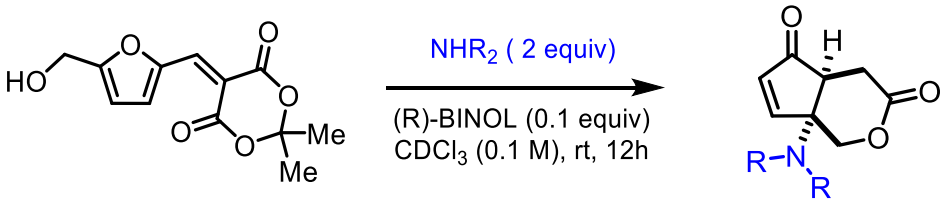
36% of **132**



35% of **132**

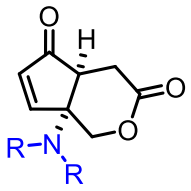
Scheme 31 Screening of additives. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard

With the optimized conditions established, we proceeded to investigate the amine scope of the tandem electrocyclization–lactonization process in the presence and absence of *(R)*-BINOL. In the absence of BINOL, acyclic amines bearing a methyl (**137**, **138**), an allyl or benzyl groups (**136** and **141** to **144**) afforded the corresponding products in high yield (up to 82% yield; **Scheme 32**). An exception is dibenzylamine and *N*-(4-nitrobenzyl)- *N* -allyl-amine, which afforded the corresponding products **139** and **144** in lower yield. Other acyclic dialkylamines afforded the corresponding product in significantly lower yields (up to 46% yield; **108** to **135**, **138**, **Scheme 32**). Finally, cyclic amines afforded the product in up to 65% yield (**145** to **147**). In general, the use of 10 mol% of *(R)*-BINOL resulted in increased yield in up to 82% yield. Several other amines, such as those in five-membered rings, anilines, and α-branched amines did not afford the desired CP products (**Scheme 32**).

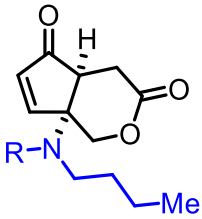


121

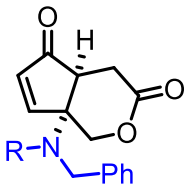
Amine scope (yields in brackets were obtained in the absence of (R)-BINOL catalyst):



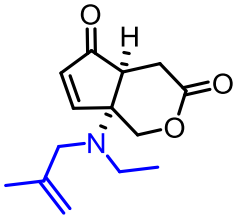
108: R = Et, 60% (35%)
133: R = n-hex, 70% (40%)
134: R = n-oct, 74% (43%)
135: R = n-dec, 72% (46 %)
136: R = $(allyl)_2$, 70% (60%)



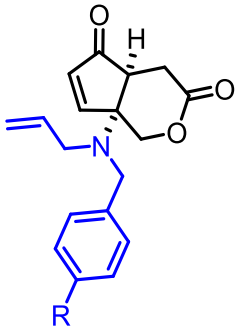
137: R = Me, 72% (78%)
138: R = Et, 71% (36%)



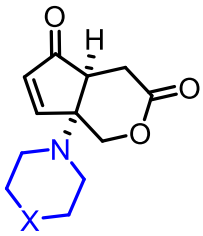
139: R = Bn, 26% (25%)
140: R = Me, 76% (78%)



141, 68% (58%)

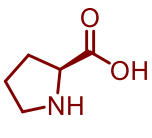


142: R = H, 78%
143: R = OMe, 82% (76%)
144: R = NO_2, 52%

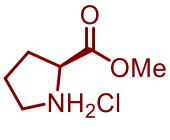


145: X = CH_2, 56% (48%)
146: X = O, 68% (65%)
147: X = NMe, 57% (63%)

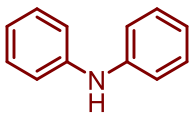
Amines that did not form the desired product:



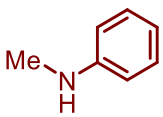
0% conv.



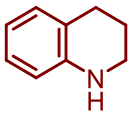
0% conv.



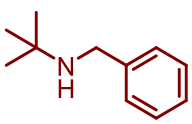
0% conv.



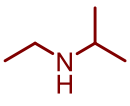
2% conv.



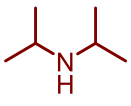
20% conv.



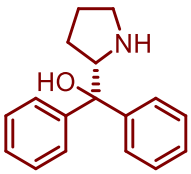
20% conv.



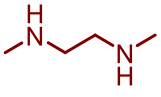
70% conv.



73% conv.



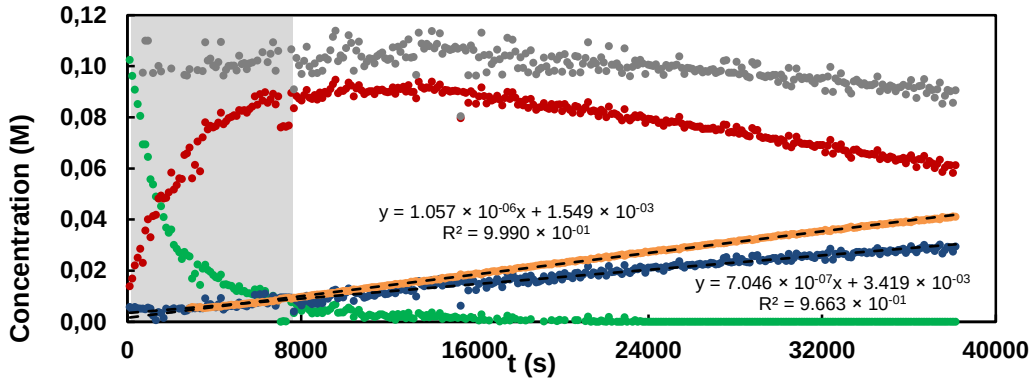
55% conv.



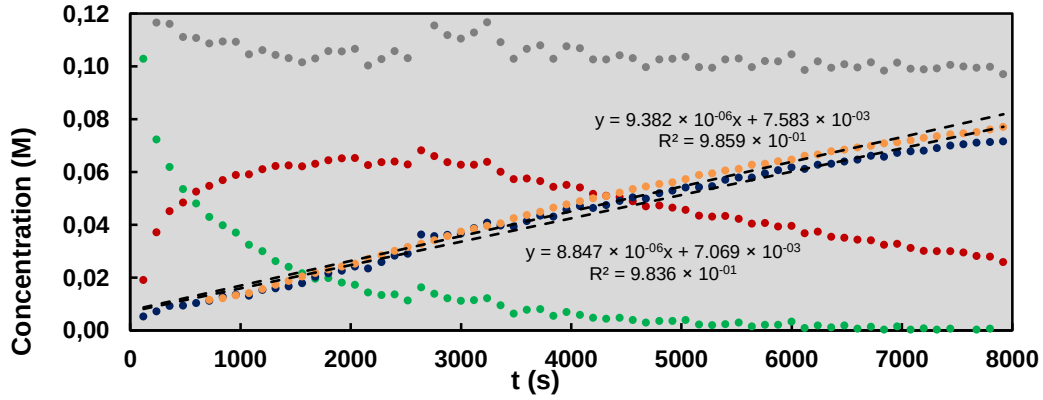
very complex mixture

Scheme 32 Amine scope for the formation of δ-Lactone-fused cyclopentenones

Intrigued by the fact that lactonization was taking place under mild reaction conditions, we decided to investigate the reaction mechanism by a combination of experimental and density functional theory (DFT) calculations. We monitored the reaction of **121** and diethylamine by using ^{1}H NMR spectroscopy. In the absence of BINOL catalyst, immediate conversion of starting material to **131** is observed, reaching a maximum concentration at 1 h reaction time (**Figure 16**, top). Although isolation of intermediate **131** was not possible, its structure was elucidated by ^{1}H and ^{13}C NMR spectroscopy of the reaction mixture. The structure of **131** resembles the structure of **124**, the product obtained by DASA cyclization. Additionally, the presence of the Meldrum's acid moiety in the structure of **131** was indirectly confirmed by the absence of acetone formation during the initial moments of the reaction. In fact, acetone formation correlates with consumption of **131** and consequent formation of product **132** (**Figure 16**, top). The reaction profile using BINOL catalyst is very different, as intermediate 3iia does not accumulate under these reaction conditions (**Figure 16**, bottom).



Reaction profile in the absence of 10 % (R)-BINOL



Reaction profile in the presence of 10 % (R)-BINOL

Figure 16. Reaction profile in the absence (top) and presence (bottom) of 10 % *(R)*-BINOL. Legend: **121** (green), **131** (red), **132** (blue), acetone (orange), mass balance (grey, sum of **121**, **131** and **132**).

These observations suggested that cyclization occurs first to generate CP **131** followed by BINOL-catalyzed Meldrum's acid decomposition/lactonization to form the final lactone product **132**.To further investigate the mechanism of the reaction, kinetic studies were performed. The reaction exhibited zero-order dependence in diethylamine (**Figure 17**E), suggesting that amine addition is not rate determining. In contrast, a positive order dependence on [*(R)*-BINOL] was determined, with a double logarithmic plot of the data shown in **Figure 17**C indicating a reaction order of 0.33 based on the catalyst concentration. By considering the reaction mechanism divided into two elementary steps, the first step—formation of intermediate **131** from **121**—exhibited a first order kinetics in diethylamine (**Figure 17**D) and zero order in (R)-BINOL (**Figure 17**A). Thus, the combined data from NMR experiments suggest that the free amine is not involved in the lactonization process and that BINOL catalyzes exclusively the lactonization step. This observation is in agreement with the fact that enantiomerically pure BINOL did not deliver the product with enantioselectivity, as it is not involved in the C-C bond formation.

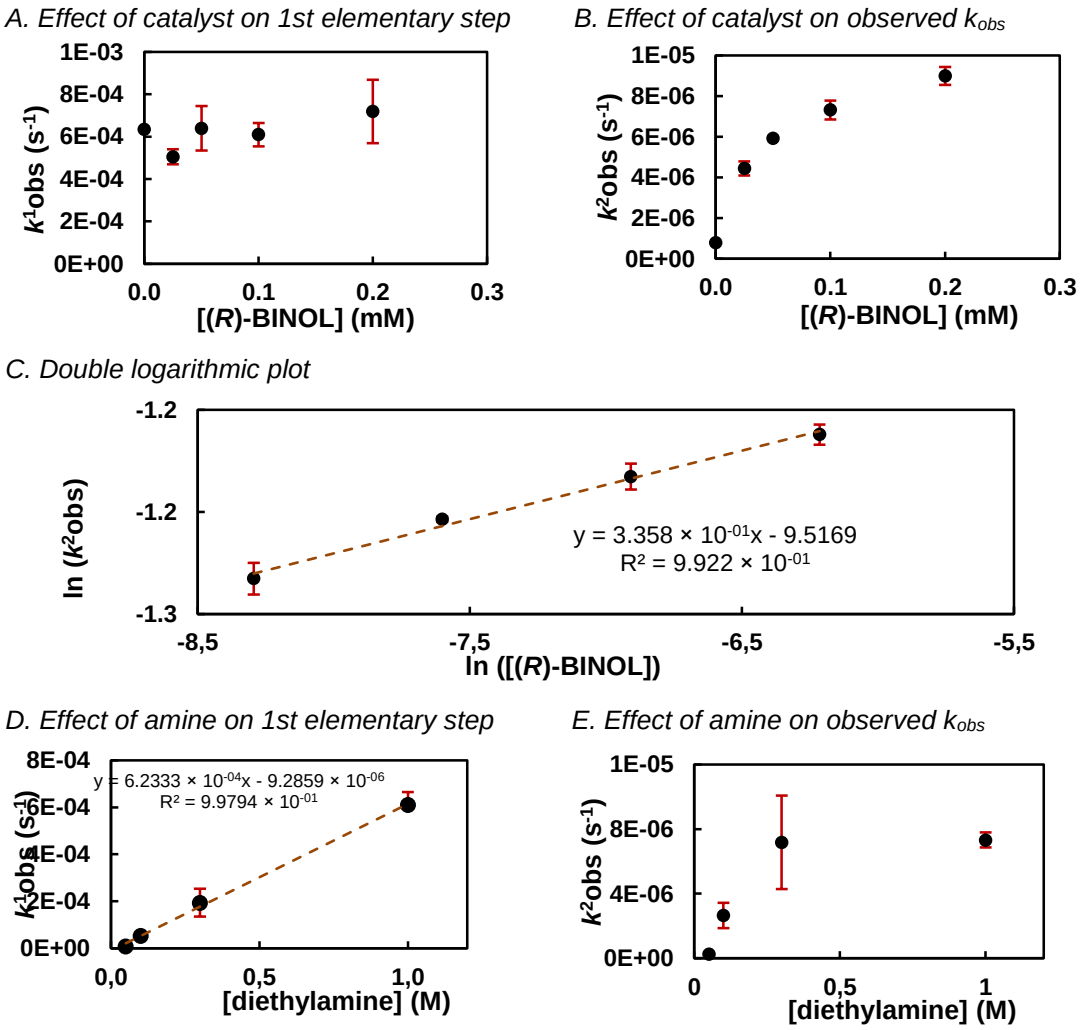


Figure 17 ^{1}H NMR reaction kinetic studies

To understand the role of BINOL in the lactonization step, and to address the fundamental question why intermediate **131** is less stable than its analogue **124**, we turned our attention to DFT calculations. We modeled the reaction of **121** and diethylamine at the B3LYP/6-31G(d) level of theory as implemented by Gaussian 09. Formation of cyclopentenone intermediate proceeds in a diastereoselective fashion as shown by other studies.[5] The electrocyclization is favored for the Stenhouse adduct adopting *E,E* configuration rather than *E,Z*, which is consistent with selective formation of the trans isomer (**Figure 18**).

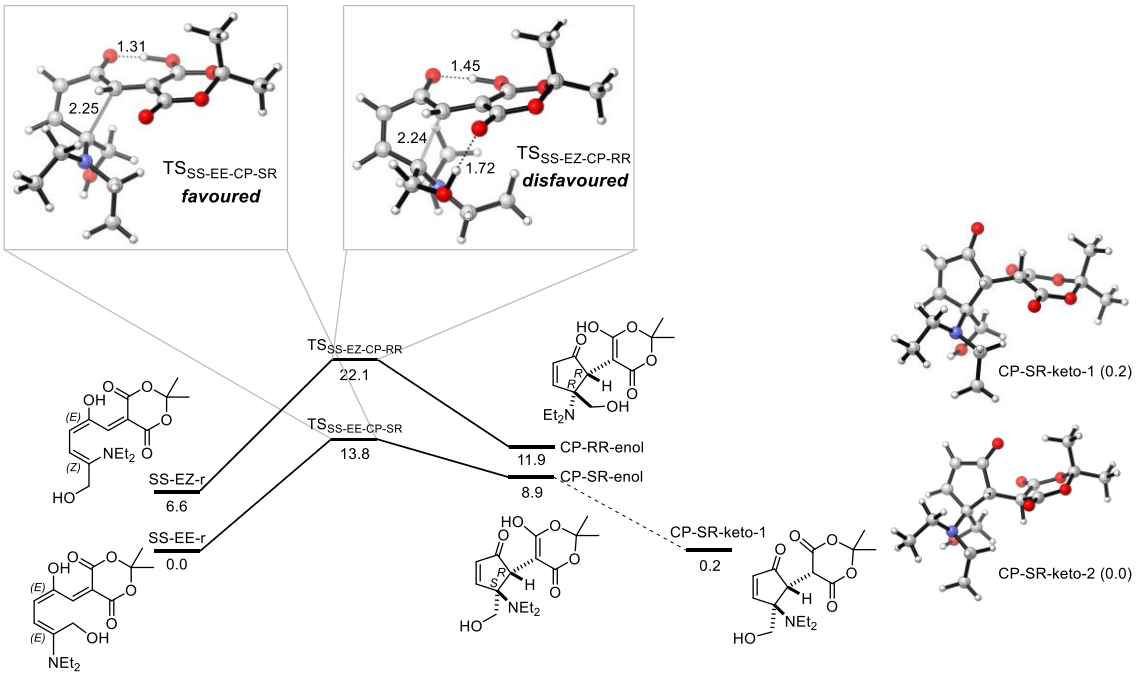


Figure 18 Free energy profiles for the cyclization of SS-r to CP-SR-keto. DFT calculations were performed at the B3LYP-D3/6-311++G(d,p)/SMD(DCM) level of theory using geometries optimized by B3LYP/6-31G(d). The distances shown are in Å, and energies are in kcal/mol.

Next, the intramolecular lactonization was investigated. First we studied the reaction in the absence of any catalyst. Several approaches were considered, including: i) Ketene formation followed by esterification; ii) acetone loss promoted by the intramolecular addition of the nitrogen to the carbonyl group of the Meldrum's acid moiety followed by esterification; iii) alkoxy formation enabled by intramolecular proton abstraction by the tertiary amine followed by alkoxy addition and consequent loss of acetone and CO2. Whereas the first two approaches did not result in formation of the desired product, the third approach is consistent with product formation via a two-step sequence with an overall barrier of 35.8 kcalmol^{-1} (**Figure 19**, black profile). The calculations suggest that

lactonization proceeds through addition of the primary alcohol to the carbonyl with assistance of the tertiary amine, which transfers the hydroxyl proton to the carbonyl oxygen, resulting in the formation of an orthoester (**Figure 19**, ii). Orthoester iii then undergoes loss of acetone and CO_2 to form the product as the enol tautomer. The transition state for the tautomerization that leads to the formation of the final product **108** was not investigated. Next, a conformational search for interactions between biphenol (BIPOL) and i was performed to locate possible adducts for studying the effect of the BINOL in the lactonization reaction.

To reduce the computational cost, BIPOL was used as a model instead of BINOL, which is not expected to significantly alter the geometry around the reaction center. From this analysis, iB was the most stable conformation found. This adduct has two hydrogen-bonding interactions between the CP intermediate I and BIPOL, contributing to an 18.5 $kcalmol^{-1}$ decrease in the free energy of the system (**Figure 19**, blue profile). One of the hydrogen bonds—that between the hydroxy group hydrogen and the dioxinone oxygen—is analogous to that reported by Moon, Hawker, and co-workers.[84] Moreover, this adduct was the only one that contributed to product formation. In general, these interactions between i and BIPOL resulted in a decrease in the relative energy barriers (**Figure 19**, black vs. blue profiles). Furthermore, the calculations suggest a five-step sequence from iB to viB with an overall barrier of 29.5 $kcalmol^{-1}$, which is consistent with the observed reaction acceleration. The calculations suggest that the catalyzed lactonization proceeds by the following steps: proton abstraction (via TS1; **Figure 20**), alkoxy addition to the Meldrum's acid carbonyl group (via TS2; **Figure 20**), loss of acetone (via TS3; **Figure 20**), hydrogen bonding alteration from ivB to vB to stabilize the intermediate bearing the dioxinone oxygen, and finally loss of CO_2 (via TS4; **Figure 20**). Based on the mechanism proposed herein, we believe that the difference in reactivity of **124** (derived from furfural) and **131** (derived from HMF) comes from the different tautomeric form of the meldrum's acid moiety. Whereas **124** has been described as an enolate,[16] **131** most likely adopts the enol form. Thus, the electrophilicity of **131** is responsible for its reactivity and instability. Another evident difference between these two structures is that **131** bears a hydroxymethyl group while no alcohol is present in **124**. However, even using an external alcohol, no Meldrum's acid decomposition was observed for **124**. Altogether, the mechanism for the formation of LCP is depicted in Figure 21.

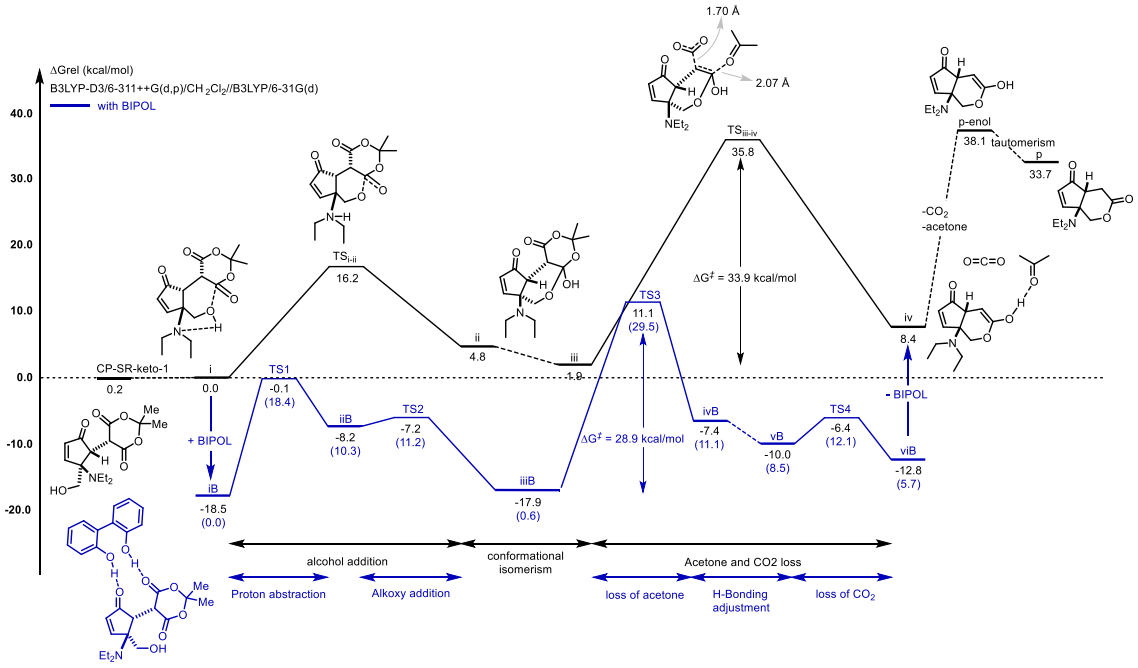


Figure 19 Free energy profiles for the lactonization step. DFT calculations were performed at the B3LYP-D3/6-311++G(d,p)/SMD(DCM) level of theory using geometries optimized by B3LYP/6-31G(d). The distances shown are in Å, and energies are in kcal/mol.

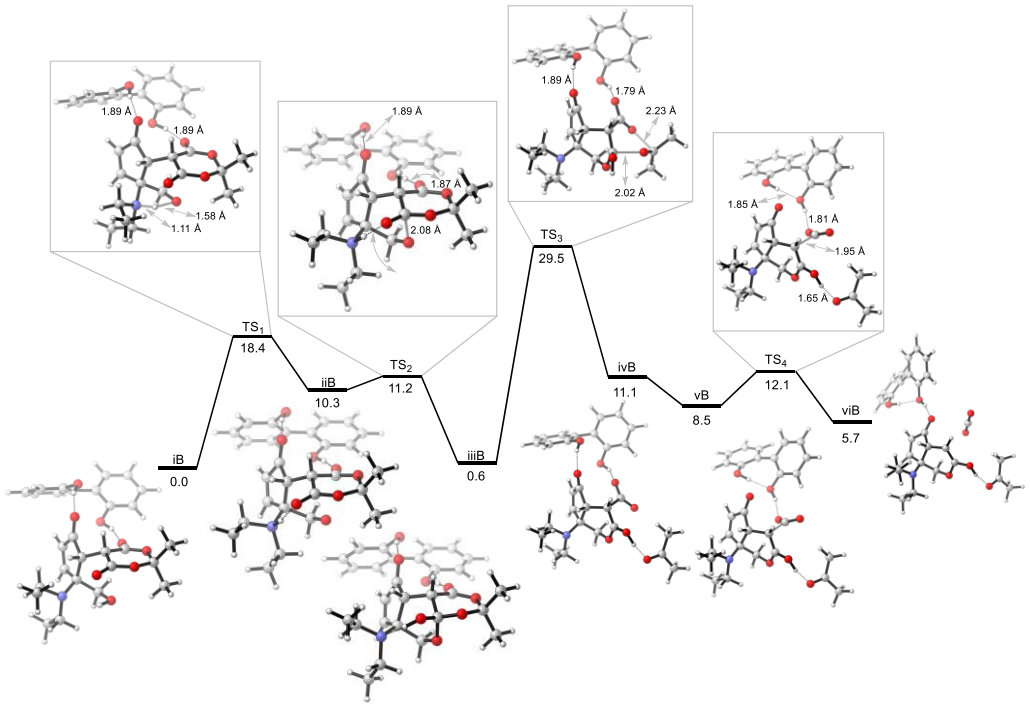


Figure 20 Free energy profiles for the lactonization of iB into viB promoted by BIPOL. DFT calculations were performed at the B3LYP-D3/6-311++G(d,p)/SMD(DCM) level of theory using geometries optimized by B3LYP/6-31G(d). The distances shown are in Å, and energies are in kcal/mol.

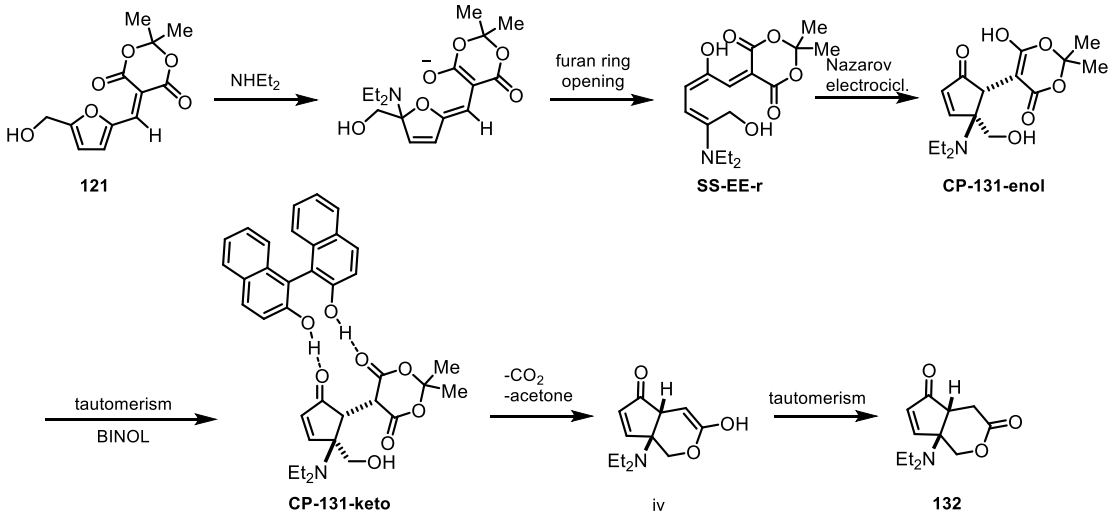
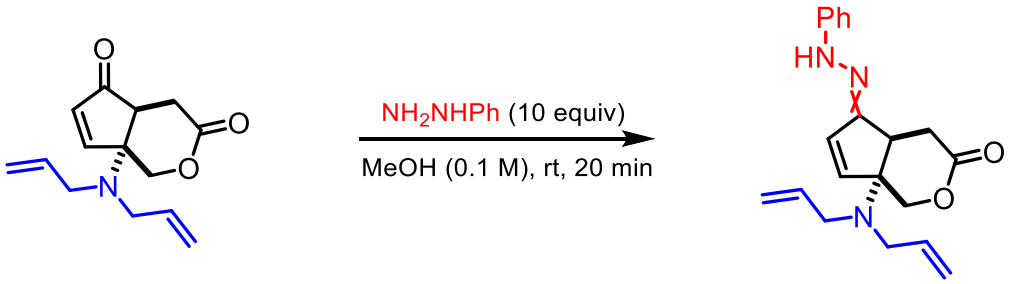


Figure 21 General mechanism for the formation of LCP.

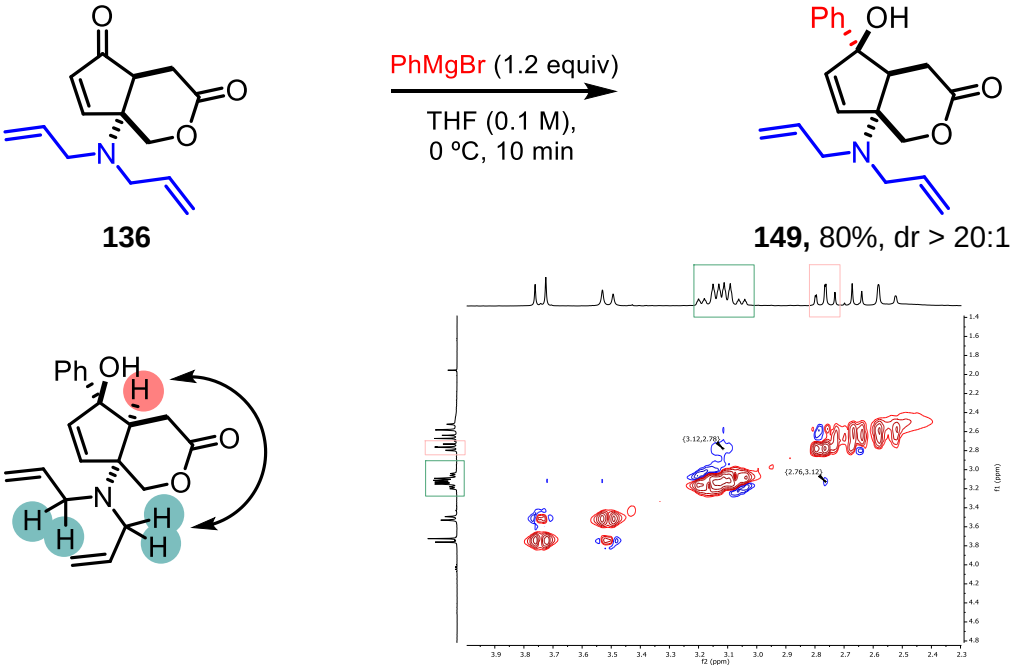
Finally, we envisioned that elaboration of LCP scaffold would be important for displaying its importance in synthetic chemistry and small molecule diversification. Herein, we describe selective synthetic strategies for modification of highly functionalized LCP. Reaction of **136** and phenylhydrazine in methanol at room temperature afforded the corresponding hydrazone **148** in 76% yield as a 1:1.5 mixture of isomers (**Scheme 33**). A common issue of hydrazone formation in enone systems, namely the DCP described in chapter II, is the aza-Michael addition. It is notewoethy that we did not observe neither aza-Michael nor lactone opening by hydrazine addition.



136 **148,** 76%, 1:1.5

Scheme 33 Formation of hydrazone from LCP **136**

Grignard addition of phenylmagnesium bromide to the carbonyl group of **136** afforded **149** in 80% yield as a single diastereomer (**Scheme 34**). The addition to the carbonyl was anti to the α substituent affording the corresponding diastereomer as can be seen by NOESY experiment depicted in **Scheme 34**. There was no addition to the lactone under these conditions.

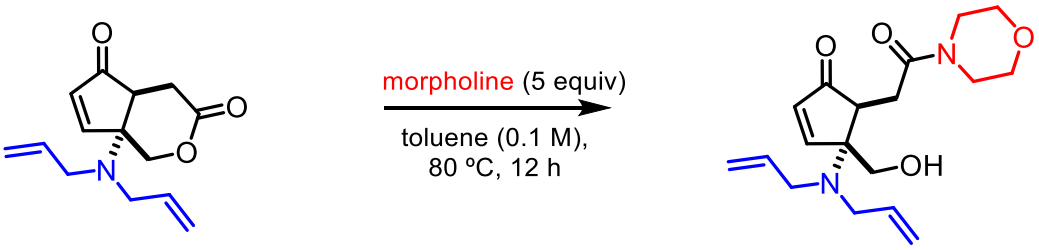


136 **149,** 80%, dr > 20:1

NOESY correlations *NOESY experiment*

Scheme 34 Grignard addition of phenylmagnesium bromide to LCP **136**

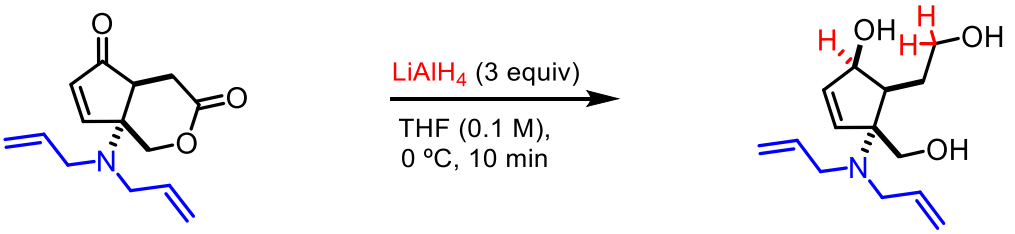
We attempted hydrolysis and methanolysis of the lactone ring. Unfortunately we were not successful in neither reaction, both in basic (KOH in THF:H_2O at 0ºC or NaOMe in MeOH at reflux) and acidic conditions (HCl in THF:H_2O at rt or Acetyl chloride in MeOH at reflux). Gratifyingly we were able to perform ring opening of **136** in the presence of morpholine (5 equiv) in toluene at 80 ºC to afford the corresponding amide **150** in 80% yield. We did not observe formation of the product at room temperature.



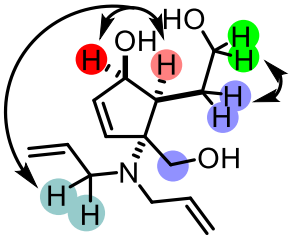
136 **150,** 80%

Scheme 35. Lactone ring opening with morpholine

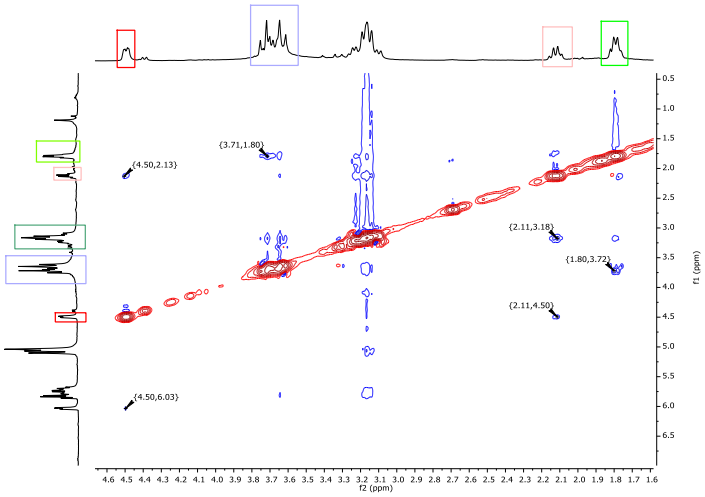
Reduction of **136** by using lithium aluminum hydride resulted in the reduction of the ketone and lactone moieties affording triol **151** in 70% yield as a 5:1 mixture of diastereomers. We did not observe 1,4 reduction of the enone. Similar to the Grignard addition there was preferential *anti* addition of the hydride in relation to the α substituent.



136 **151,** 70%, d.r. 5:1



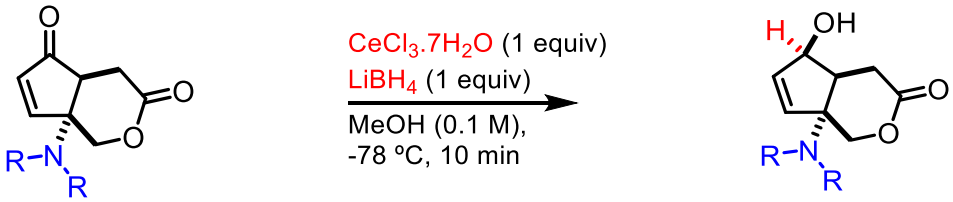
NOESY correlations



NOESY experiment

Scheme 36 Reduction of **136** with lithium aluminium hydride.

We next turned our attentions to the diastereoselective Luche reduction of **136**. We observe that the $CeCl_3/LiBH_4$ system at -40 ºC afforded the best diastereoselectivity of **152**. The reaction was carried out with LCP **132** and **139** and we achieve good yields with high diastereoslectivity. Moreover when LCP **139** was employed the reaction could be carried out at only -5 ºC with good d.r. possibly due to increased steric effects (**Scheme 37**).

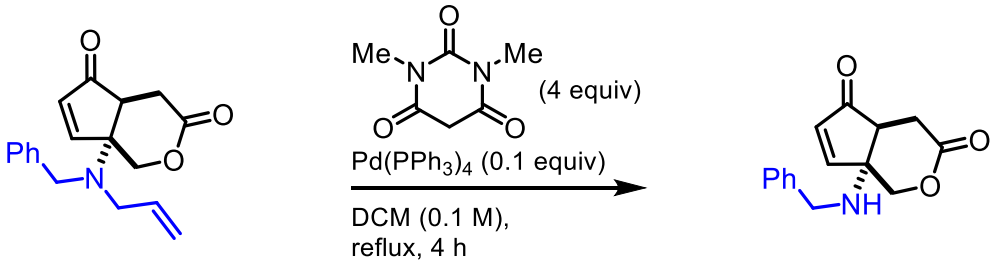


152, 83%, d.r. > 20:1

153, 72%, d.r. > 20:1

154, 97%, d.r. > 20:1
Reaction was carried out at -5 ºC

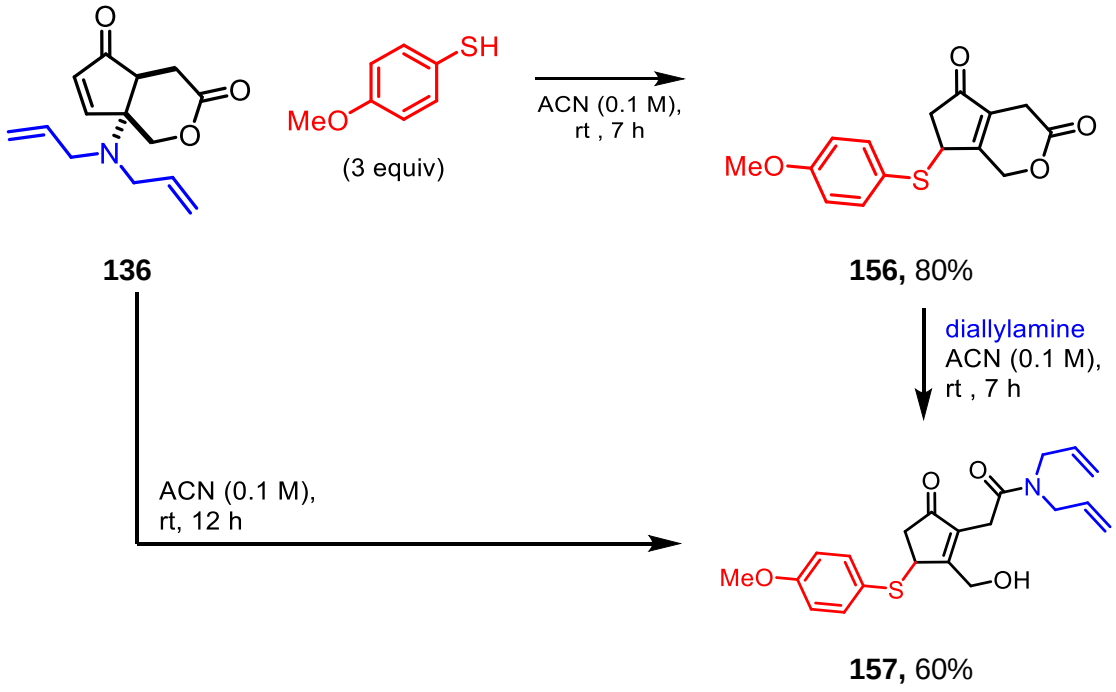
Scheme 37 Diastereoselective Luche reduction of **132**, **136** and **139**.



Scheme 38 Deprotection of allyl amine in LCP **142**

Removal of the N-allyl protecting group under palladium-catalyzed reduction afforded secondary amine **155** in 92% yield (**Scheme 38**).

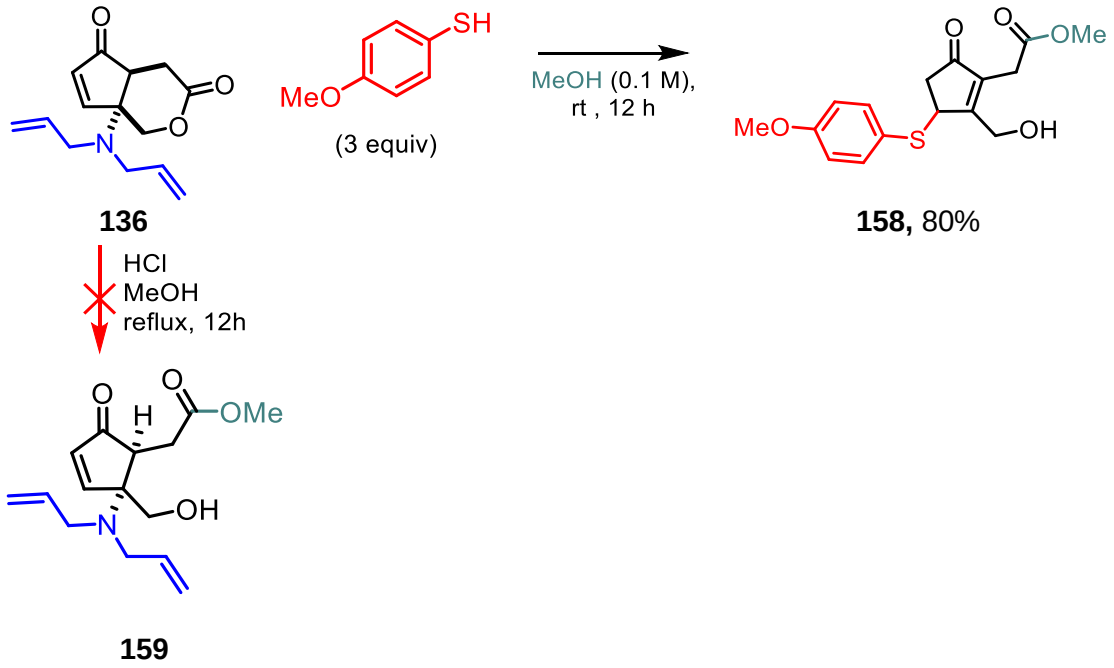
We had previously described thio-Michael addition to CP systems as depicted in Chapter II. We extended the scope of the addition to LCPs. Reaction of 4-methoxybenzenethiol and **136** afforded product **156** in 82% yield, which resulted from a thio-Michael addition and consequent amine elimination (**Scheme 39**). However if the reaction was allowed to stir longer periods of time we observed the diallylamine which was eliminated after the addition was spontaneously opening the lactone ring to form CP **157** (**Scheme 39**). We found this curious due to the high stability towards hydrolysis observed in LCPs.



Scheme 39 Thio-Michael addition to LCP **136** in acetonitrile

We became interested in this remote ester activation and in the functional complexity of the new CP that could present interesting medicinal applications. We performed the reaction in methanol and observed that the same ester activation was occurring and the

previously stable LCP now underwent methanolysis (**Scheme 40**). These results prompted us to study the reactivity in more detail as depicted in the next chapter.



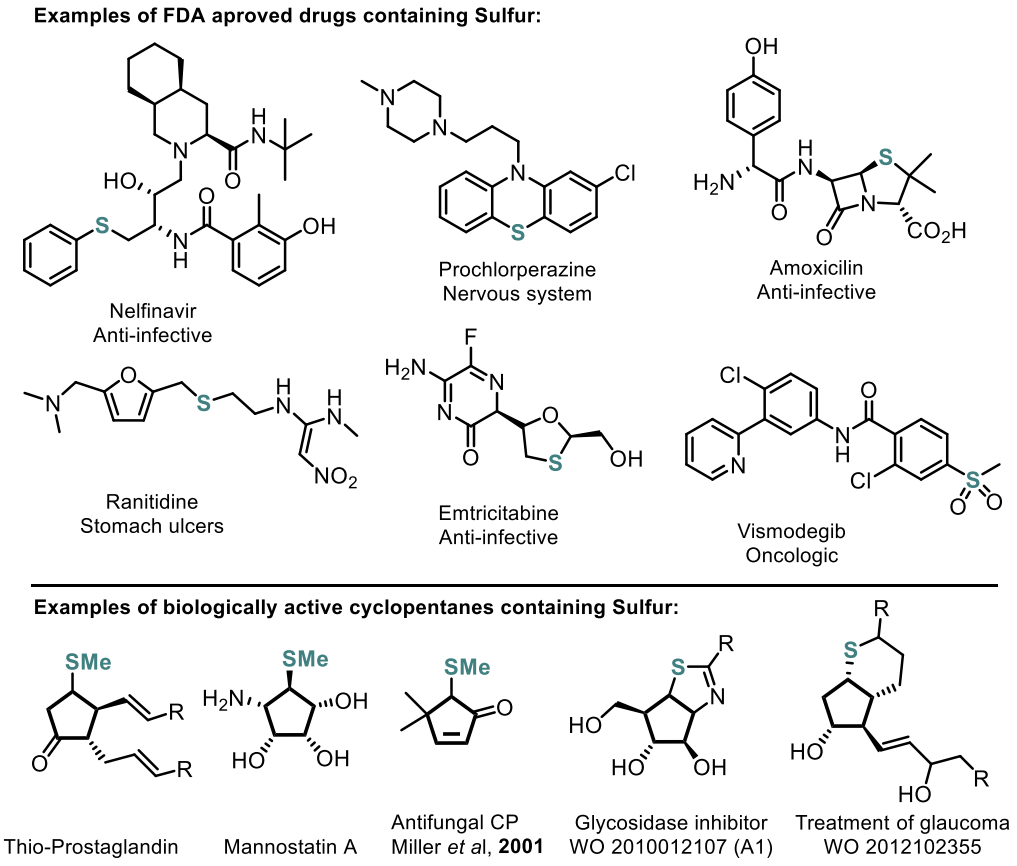
Scheme 40 Thio-Michael addition to LCP **136** in methanol

In conclusion in this sub-chapter we studied the transformation of activated 5-hydroxymethylfurfural (HMF) derivatives in δ-Lactone-fused cyclopentenones (LCP). The new mechanism for the formation of LCP was thoroughly studied, both by quantitative NMR experiments and DTF calculations. Synthetic derivatives of LCP were prepared by model textbook reactions. The new cyclopentenones and derivatives will be subjected to biological evaluation.

III.2.3. Preparation of thiosubstituted highly functionalized cyclopentenones with antimalarial activity

Sulfur containing scaffolds are important in medicinal chemistry being one of the most abundant heteroatoms in FDA approved drugs, usually introduced as sulfonamide, sulfone or sulfide (**Scheme 41**).[85] Studies have shown that sulfur is a key constituent of over 20% FDA approved drugs.[86] A recent study on the role of sulfur interaction in drug design show that S-aromatic and S-O/N interaction have a significant favorable impact on binding to the target.[87]

On the other hand several sulfur containing cyclopentanes have been reported to have relevant biological activities (**Scheme 41**). Thio-prostanglandines have shown relevant bronchodilator properties.[88] Mannostatin A is a sulfur containing aminocyclopentitol with α-mannosidase inhibitory activity. [89] Miller and coworkers reported a sulfur containing cyclopentenones (CP) with remarkable antifungal activity.[90] Some sulfur containing cyclopentanes have been patented as glycosidase inhibitors[91] and for the treatment of glaucoma[92]. Due the importance of sulfur containing molecules we attempted to incorporate thiophenol by Michael addition to the new δ-Lactone-fused cyclopentenones.

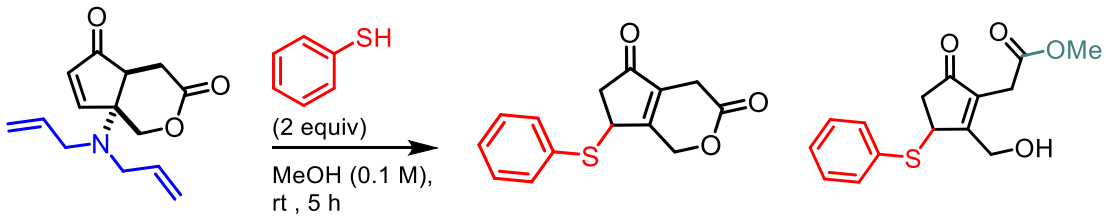


Scheme 41 Examples of medicinal relevant molecules containing sulfur,

We observed on the previous sub-chapter that upon Michael-addition in methanol there was elimination of the amine to reestablish the enone. Similar results were previously reported on the addition to 4,5-diaminoCP (DCP) in the presence of base.[13,14] Moreover the lactone that was previously unreactive towards hydrolysis and methanolysis underwent spontaneous methanolysis in these conditions caused by a remote lactone activation (**Scheme 40**).

We started this study by screening different conditions for the addition of thiophenol to LCP **136**. In the absence of base we observe 80% conversion after 5h, although the main product is the closed lactone **160** (**Table 23**, Entry 1). After 12h full methanolysis to **161** was observed (**Table 23**, Entry 2). Both sodium methoxyde and potassium tert-butoxyde promoted the reaction, affording 60 and 70% yield of **161** after 5h (**Table 23**, Entries 3 and 4). These results indicate that the base improves the rate for the methanolysis, although only a slight increase of conversion is observed. Unlike previous findings where the addition to DCP could not be performed in the presence of sodium methoxide due to the formation of a side product result of methoxide addition[14], we did not detect such side products. Both potassium carbonate and sodium hydroxide afforded the product although in low yields (**Table 23**, Entries 5 and 6). Hydrolysis of the lactone promoted by sodium hydroxide may lead to the formation of a free acid as final product.

Table 23. Reaction optimization[a]

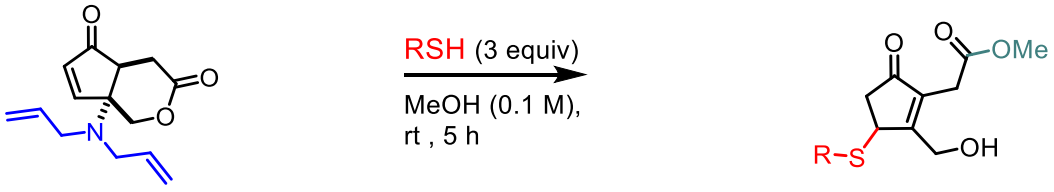


136 **160** **161**

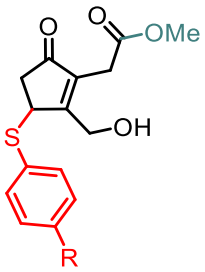
Entry	Base	**160** (%)[b]	**161** (%)[b]	Conversion (%)[b]
1	None	70	10	80
2[c]	None	0	80	100
3	K^{t}BuO	0	70	100
4	NaOMe	0	60	100
5	K_2CO_3	0	20	100
6	NaOH	0	40	100

[a] Reaction conditions: **136** (20 mg, 0.8 mmol), PhSH (18 mg, 1.6 mmol), MeOH (0.8 mL) and base (0.25 equiv). The reaction was stirred for 5h, diluted with water and extracted with AcOEt; [b] Yield calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard; [c] reaction time is 12h

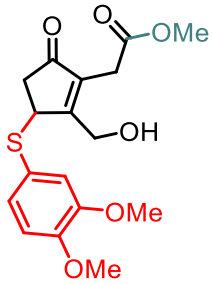
The thiol scope of the Michael addition was studied and the reaction withstands several substituted aryl thiols, alkyl thiols and propanedithiol (**Scheme 42**). Electron donor substituted arylthiols afforded the corresponding product in excellent yields (**162**, **163** and **167**), while electron withdrawing substituents afford medium to good yields (**164**, **165** and **166**). The reaction was successful with benzylthiol and propanethiol with good yields (**168** and **169**). Propanedithiol was employed and neither dimerization or dithiolane formation was observed providing only **170** in 80% yield. The reaction was also performed in ethanol using thiophenol and 4-methoxythiophenol affording **171** and **172** in 79 and 70% yield. **171** was prepared in 1 g scale for further functionalization. The addition also occurred in water using propanethiol and a carboxylic acid thiol affording the corresponding salt with diallylamine **173** and **174**.



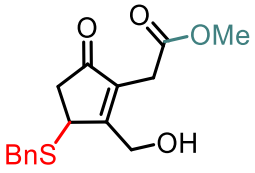
136



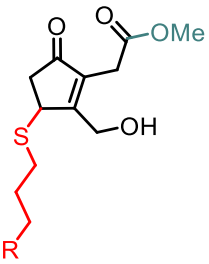
161: R = H, 82%
162: R = Me, 80%
163: R = OMe, 76%
164: R = F, 75%
165: R = Cl, 75%
166: R = CF_3, 63%



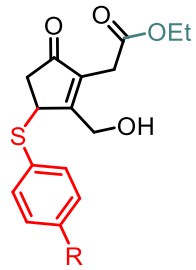
167, 80%



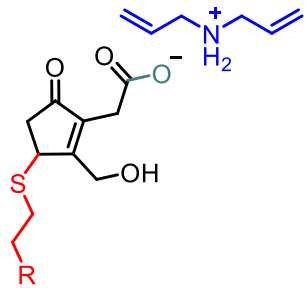
168, 93%



169: R = H, 85%
170: R = SH, 80%



171: R = H, 79%[a]
172: R = OMe, 70%[a]



173: R = Me, 87%[b]
174: R = CO_2H, 92%[b]

Scheme 42 Thio-Michael addition scope. Reaction conditions: **136** (100 mg, 4.0 mmol), RSH (3 eq, 12 mmol) and MeOH (4 mL). [a] Reaction was carried using ethanol as solvent. [b] Reaction was carried using water as solvent.

Considering both the established key reactivity of LCP **136** in aqueous environment and that a wide variety of CP are known to react via 1, 4- addition with endogenous nucleophiles, we decided to inquire whether or not this scaffold could quickly react with more complex structures under bioconjugation conditions to generate conjugates bearing the resulting sugar biomimetic.

For this purpose laminin fragment model peptide, a non-internalizing peptide containing a single cysteine at the *N*-terminal position was used as model. Gratifyingly, by employing **136** (25 equiv.) in ammonium acetate buffer (20 mM, pH 8.0) at 25 ˚C for 1h, the expected construct (*m/z* 1135) was formed as observed by ESI-MS (**Figure 21**). Due to the highly diluted environment, ring-opening hydrolysis of the 1, 4-lactone intermediate promptly occurs and the ring-closed lactone was never observed even after 1 minute reaction. Despite considerably less reactive than gold-standard bionconjugation tools such as maleimides and other activated Michael acceptors, **136** still proved useful for the modification of more complex biological scaffolds in dilute conditions. On the other hand, important chemoselectivity towards cysteines was observed, with no aza-Michael cross-reactivity with amine nucleophiles observed when performing the reaction in peptides containing lysines (*e.g* ovalbumin fragment) even using a large excess of **136** (100 equiv.) (**Figure 21**). Moreover, incubation of the Laminin-CP conjugate with excess thiol did not cause the disappearance of the conjugate peak by MS, which renders unlikely the problem of thiol scramble that is a cause of concern on Michael addition based conjugates.

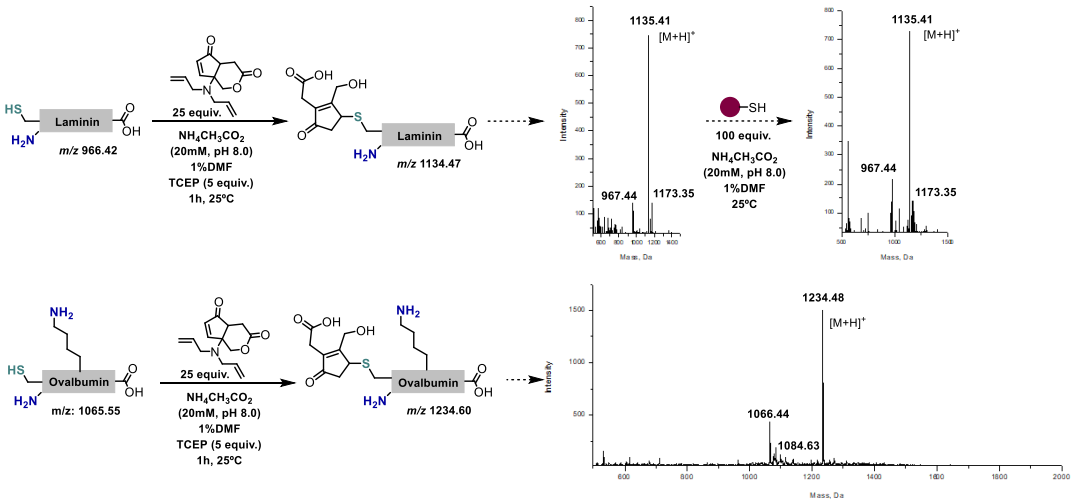
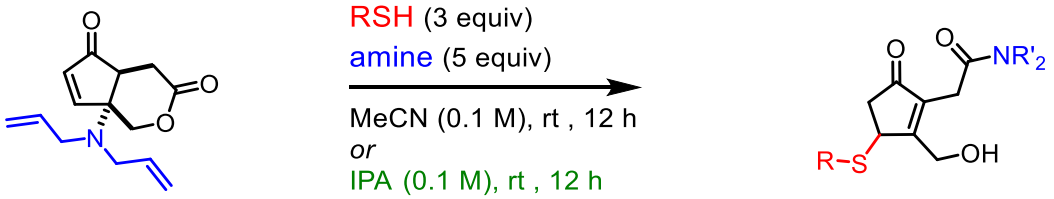


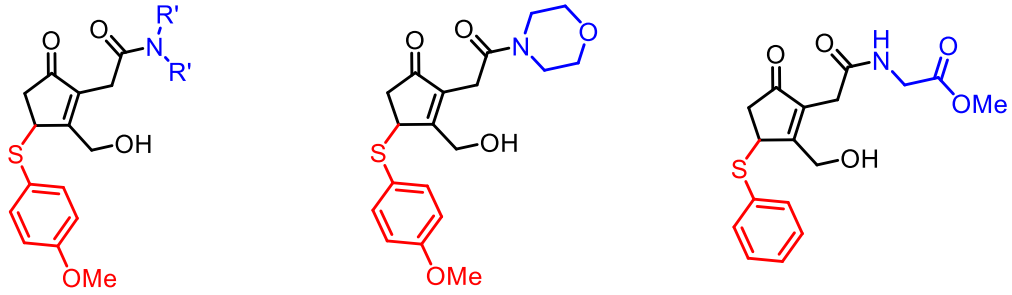
Figure 21 Peptide modification using **136**. Laminin modification (top) and Ovalbumin modification (Bottom).

As depicted in **Scheme 39** in the previous sub-chapter, in acetonitrile the diallylamine eliminated from the starting material was incorporated in the final product. As such we performed the thiol addition in non-nucleophilic solvents (ACN, iPrOH) in the presence of an external amine. As model reaction we reacted 4-methoxythiophenol with LCP **136** in the presence of excess morpholine. After 12h the sole observable product was the result of the thiol addition with incorporation of morpholine **167**. We performed the reaction in the presence of different amines which were used in excess to reduce the completion with diallyl amine released from the starting material. The amidation occurred in the presence of morpholine, diallylamine and dibenzylamine (**167, 157** and **175**) in good yields both in acetonitrile and isopropanol. The protic solvent afforded better yields of the desired product except when diallylamine was used. When we attempted to incorporate a primary amine, namely the aminoacid derivative glycine methyl ester, the reaction in acetonitrile was not complete and formation of side products was observed. When the reaction was performed in isopropanol we were able to isolate the desired product **177** in 70% yield.



136

Amine scope (yields in brackets were obtained in isopropanol):



R' = allyl: **157**, 84% (76%)
R' = Bn: **175**, 65% (80%)

176, 70% (82%)

177, (70%)

Scheme 43 Amine scope for the Lactone ring opening. Reaction conditions: **136** (100 mg, 4.0 mmol), RSH (3 eq, 12 mmol), Amine (5 eq, 20 mmol) and solvent (4 mL).

Intrigued by the reaction mechanism we monitored the reaction of **136** and thiol by using ^{1}H-NMR spectroscopy. The reaction profile shows rapid monoexponential consumption of **136** accompanied by the formation of intermediate **178** that could not be isolated. Formation of **160** is accompanied by the release of diallylamine. Finally is observed the methanolysis to product **161** (**Figure 22**)

The effect of the thiol substituent was evaluated by performing the reaction between **136** and an excess of aryl thiols with different substituents on *para* position. Quantitative ^{1}H-NMR kinetics were traced for the different thiols and we observe a correlation between k1 and the electronegativity of the substituent. Moreover the Hammet plot of $\log(k_{obs}/k_H)$ vs σ_{para} was linear with a ρ value of -4.49 (**Figure 22**). This indicates the Michael addition to be mainly influenced by the nucleophilicity of the thiol, with eletron donnor groups increasing the reaction rate. We found no correlation between the substituent and k2 or k3. This indicates that the thiol electronegativity is not contributing for the amine elimination neither to the methanolysis. We observe upon reaction of **136** with sodium thiophenolate there is no significant increase in k_1, k_2 or k_3 versus thiophenol. This result is in line with the base screening which indicates that the base is not involved in the addition. Instead the base is increasing the rate of lactone methanolysis.

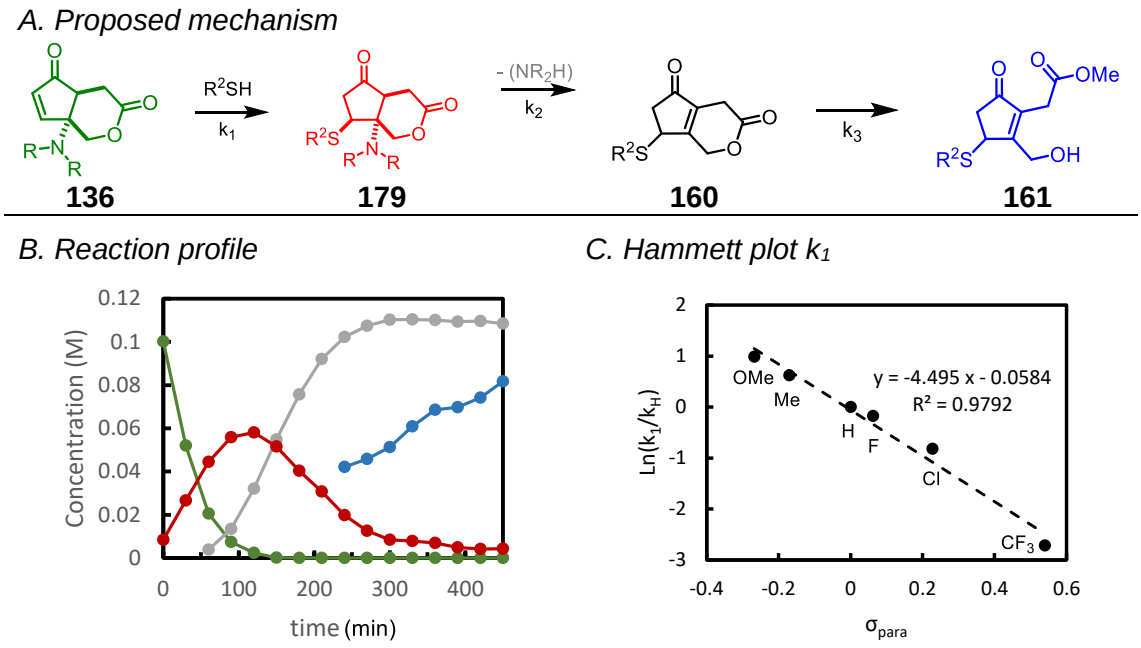


Figure 22 ^{1}H NMR Mechanistic studies for the thio-Michael addition to LCP **136**. R = allyl; R^2 = Ph.

In order to explain the spontaneous lactone methanolysis that occurs upon formation of the thio-adduct in comparison with the non reactive LCP we turned our attention to DFT calculations. We modelled the methanolysis reaction of Ia and IIa at the B3LYP-D3/6-311+G(d,p) /SMD(MeOH) level of theory as implemented by Gaussian 09 (**Figure 23**). Although reaction occurs in both substrates, the overall barrier of methanolysis for Ia and IIa is 32.3 kcal mol^{-1} and 28.7 kcal mol^{-1} respectively. Moreover formation of Ic is thermodynamically disfavored (ΔG=5. kcal/mol^{-1}), whereas methanolysis product IIc is favored (ΔG= -2.7. kcal mol^{-1}).

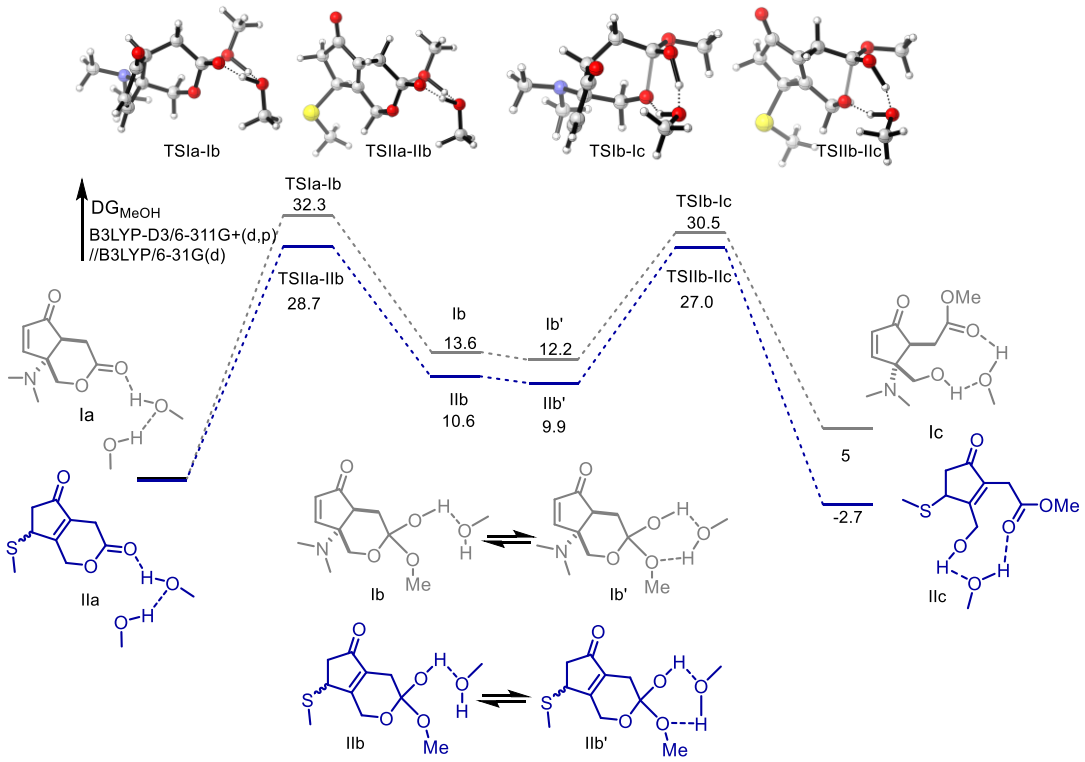
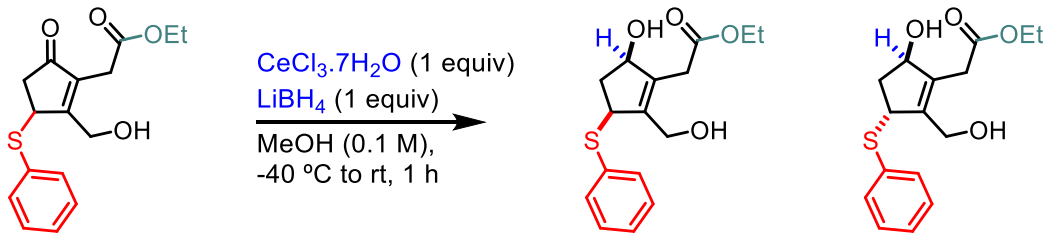


Figure 23 Free energy profiles for the lactone opening step. DFT calculations were performed at the B3LYP-D3/6-311++G(d,p)/SMD(MeOH) level of theory using geometries optimized by B3LYP/6-31G(d). The energies shown are in kcal/mol.

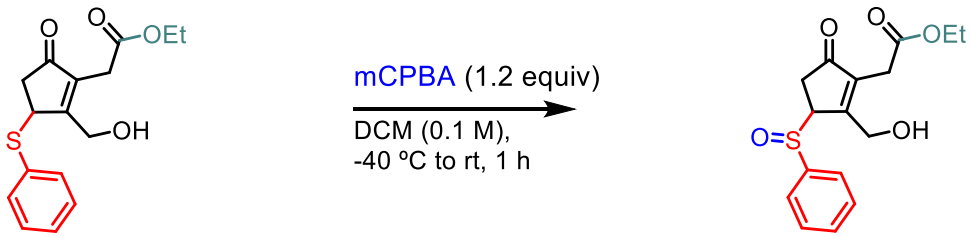
Due to the importance of small molecule diversification in the development of possible hits for medicinal chemistry purposes, we envision possible modifications to scaffold **171**. Luche reduction afforded two diastereomers **180** and **181** that were easily separated by chromatography (**Scheme 44**). Unlike the previous examples of Luche reduction the absence of chirality on the α position lead to complete loss of diastereoselectivity.



171 **180** and **181**, 47% + 43%

Scheme 44 Luche reduction of CP **171**

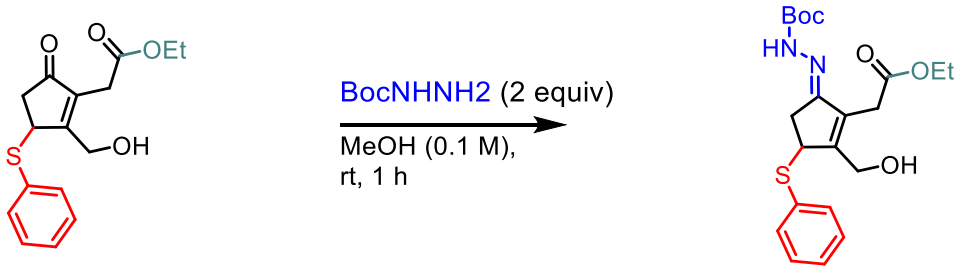
Oxidation to the sulfoxide promoted by mCPBA afforded **182** in 81% yield (**Scheme 45**). There was no formation of the sulfone nor Baeyer-Villiger reaction.



171 **182**, 81%

Scheme 45 Oxidation of CP **171**.

Reaction with Boc-hydrazine afforded the hydrazone **183** in excellent yield (Scheme 46). No Michael addition was observed upon reaction with the hydrazine. Unlike hydrazone formation of LCP (**Scheme 33**) only one isomer was identified.



171 **183**, 81%

Scheme 46 Hydrazone formation from CP **171**.

In conclusion in this sub-chapter we perform thio-Michael additions to the previously described δ-Lactone-fused cyclopentenones (LCP) prepared from 5-hydroxymethylfurfural (HMF). The Michael addition is followed by amine elimination to restore the enone system and an unexpected remote lactone activation to hydrolysis is observed. We prepared new cyclopentenone sulfur-containing derivatives and study the mechanism of the reaction by quantitative NMR kinetic experiments and DFT calculations. The new cyclopentenones and derivatives will be subjected to biological evaluation.

III.2.4. Biological activity of new cyclopentenones prepared from 5-hydroxymethylfurfural

Having the different families of cyclopentenones prepared from HMF we screened for different biological activities.

Firstly, the activity of the new derivatives was evaluated for the anti-proliferative activity in the Neutral Red assay at a fixed concentration of 20 μM in HT-29, MCF-7 and NCI-H460 cells. Unfortunately no activity was observed with the exception of LCP **135** that due to the length of the alkyl side chains may intercalate in membranes and cause non-specific cytotoxicity.

The compounds were also tested for antimicrobial activity. An initial screening was performed by evaluating the minimum inhibitory concentrations (MICs) against a Gram-positive bacteria strain (*Staphylococcus aureus*), a Gram-negative bacteria strain (*Escherichia coli*) and two fungal strains (*Candida albicans* and *Sacharomyces cereviseae*). Unfortunately no activity was observed in none of the CP derivatives. However, when the CP were incubated with the assexual form of *Plasmodium falciparum* we observed inhibition of the parasite growth. Amongst the tested compounds the DCP and MCP described in Chapter II show promising activity. Moreover a reduced form of the DCP also present activity. On the other hand, the CP obtained from the Michael addition to LCP also present activity.

These are only preliminary results and further studies on the full array of CPs and reduced CP are ongoing.

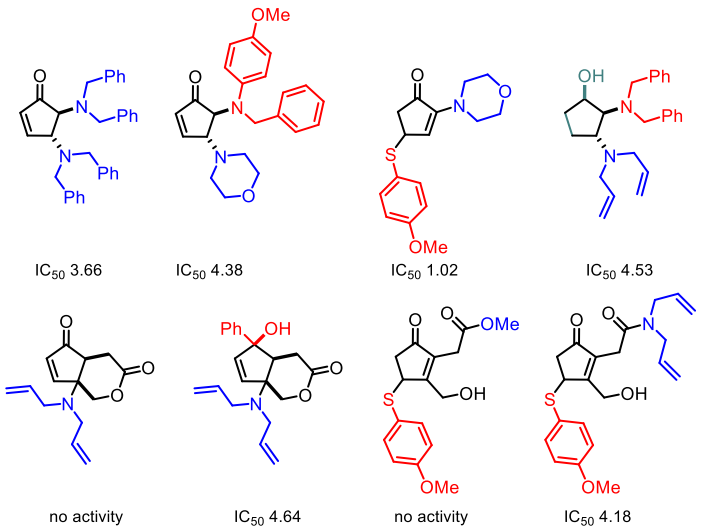


Figure 24 Relevant CP and the corresponding IC50 against assexual form of *Plasmodium falciparum*. IC_{50} in μM.

III.3. Conclusions

In the Chapter III we describe the first preparation of CP from biomass derived HMF. This was possible by the Knovanaegel condensation of Meldrum's acid with HMF forming activated furfural MAF. MAF undergoes condensation with amines to form an intermediary CP that through BINOL mediated decomposition of the Meldrum's acid leads to a δ-Lactone-fused cyclopentenone LCP. The mechanism of this reaction was thoroughly studied by NMR studies and DFT calculations. Synthetic derivatizations of the LCP core were performed, with particular attention to the Michael addition to the LCP core. The addition is followed by elimination of the amine and a remote lactone activation that leads to methanolysis. All the new CP were screened for biological activities and the thio-CP present promising results on the inhibition of malaria's parasite *Plasmodium falciparum*.

Moreover the instability issues of HMF were accessed and a variety of stabilizers were screened. We observe that sodium dithionite show remarkable properties on the stabilization of HMF both during its aging, distillation or under reaction condtions.

Chapter IV

IV. Aminals: A new tool for aldehyde protection

Abstract: In this Chapter IV we develop a mild methodology for the preparation of aminals from aldehydes promoted by $Cu(OTf)_2$. This mild preparation allows us to now use the aminal group as a tool for aldehyde protection. The stability of different aminals is accessed and we observe that 5 membered ring aminals have the desired balance between stability/hydrolysis to be used as protection group. We showcase this by performing commonly used reactions in the presence of aminals.

On the otherhand, we know that aldehydes may appear as genotoxic impurities in the process of preparing active pharmaceutic ingredients (API). By taking advantage of our method we use a diamine resin and develop a method for the scavenging of aldehydes. We showcase this by preparing a model API and removing the starting aldehyde from a product:starting aldehyde mixture.

Finally we observe that the presence of an *ortho* boronic acid in benzaldehyde stabilize the aminal ligation. Taking advantage of this we study the use of the aminals as a possible stimuli-responsive linker.

IV.1. Rational and Goals

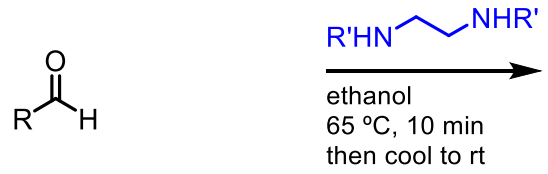
During the course of preparing derivatives of Meldrum's acid activated 5-hydroxymethylfurfural (HMF) we attempted to prepare secondary alcohols in position 5. We attempted two approaches, 1) lithiation of position 5 of furfural and react with an aldehyde to prepare our desired furan derivative in one pot. Further Knovanaegel reaction with meldrum's acid would yield the desired product for the condensation with diethyl amine to form new cyclopentenones; 2) protection of HMF aldehyde, followed by oxidation of the alcohol to aldehyde, Grignard addition and deprotection. In order to perform the reaction depicted in the first approach, the aldehyde need to be protected otherwise would undergo addition by the lithiating agent (nBuLi) affording the corresponding butylic alcohol. We observed that acetal protection did not afford the desired product. On the other hand it was reported that by protecting the aldehyde as an aminal the lithiation would undergo smoothly. As such we prepared the aminal and reacted with nBuLi and benzaldehyde, which afforded the desired product that underwent Knovanaegel condensation.

On the other hand protection of HMF with ethylenoglycol in the presence of pTSA afforded side-products such as the dimer due to the acidic conditions. In this way we believed it was useful to develop mild methodologies for the preparation of aminals as an alternative to the acetal group. The following sub-chapter depicts the commonly used conditions for the preparation of aminal (e.g. toluene under reflux, ethanol under reflux) and their applications.

IV.2. State of the art

Aminals are the N,N analogs of the commonly used protection group acetal. The preparation and applications of this scaffolds are described in this chapter.

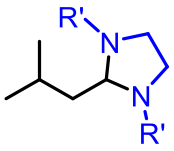
Caswell and coworkers in 1952 showed the formation of solid derivatives of aldehydes from the condensation of aldehydes with *N,N'*-(*p*-methoxybenzyl)ethylenediamine in absolute ethanol at 65 ºC (**Scheme 47**).[93] The reaction afforded no product when formaldehyde or acetaldehyde was used. Moderate yields (44-52%) were obtained when propanaldehyde, butyraldehyde or pentylaldehyde were employed. The reaction withstood isobutylaldehyde, affording the product in 63% yield. No reaction was observed when 2-phenylacetaldehyde was used. The reaction with aromatic aldehydes was highly dependent on the substituents. Both the unsubstituted benzaldehyde and 4-MeObenzaldehyde afforded no product, along with 3,4-dimethylenedioxybenzaldehyde. Overall when electro donor groups were employed the yields were poor (28-57%) with the exception of 4-methylbenzaldehyde. When electron withdrawing groups were used the yield increased. The scope included 2-naphtylaldehyde and cinnamaldehyde, which afforded the product in 36 and 56% yield respectively. Formation of the imidazolidine with heteroaromatic aldehyde was successful in poor yields with 3-thienylaldehyde but the furan derivatives such as furfural, 5-methylfurfural and 5-hydroxymethylfurfural were unreactive.



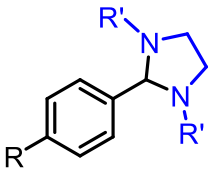
aldehyde

aminal
R' = CH_2(4-OMe)-Ph

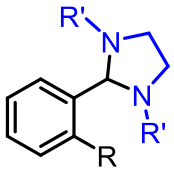
184: R = H, N.R.
185: R = Me, N.R.
186: R = Et, 44%
187: R = Pr, 57%
188: R = Bu, 52%
189: R = Bn, N.R.



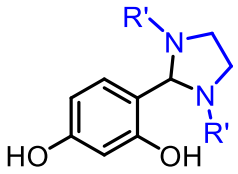
190, 63%



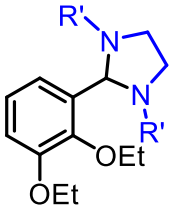
191: R = H, N.R.
192: R = OH, 28%
193: R = OMe, N.R.
194: R = Me, 85%
195: R = NO2, 56%
196: R = Cl, 72%
197: R = NMe2, 57%
198: R = NEt2, 54%



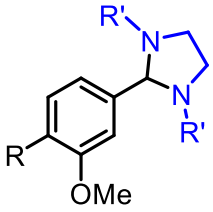
199: R = OH, 71%
200: R = NO2, 27%
201: R = Cl, 58%



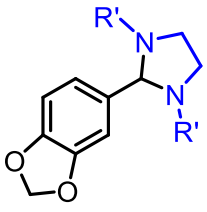
202, 58%



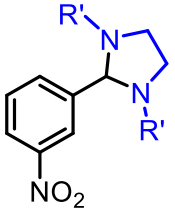
203, 69%



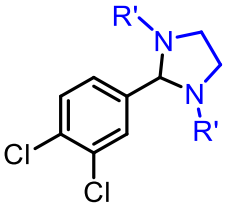
204: R = OH, 36%
205: R = OMe, 58%



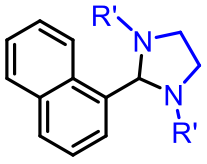
206, N.R.



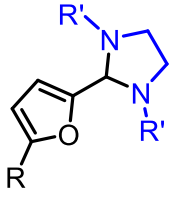
207, 80%



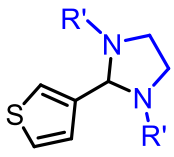
208, 72%



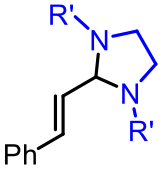
209, 36%



210: R = H, N.R.
211: R = Me, N.R.
212: R = CH2OH, N.R.



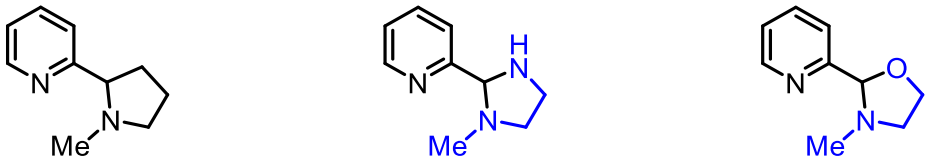
213, 13%



214, 56%

Scheme 47. Formation of aminal described by Caswell and coworkers.

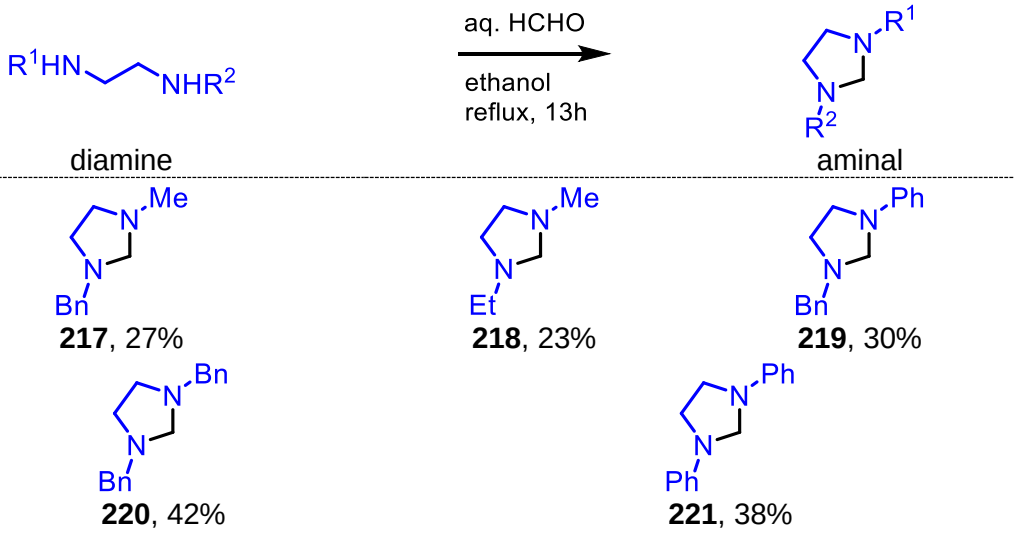
In an attempt to produce biologically active analogs of nicotine, Castle *et al*. replaced the pyrrolidine ring for an imidazolidine and oxazolidine (**Scheme 48**) by refluxing the corresponding aldehyde with diamine/aminoalcohol in benzene, achieving moderate yields (around 60%). This analogs showed no pharmacological activity due to hydrolysis to the corresponding aldehyde in aqueous media.[94]



nicotine **215** **216**

Scheme 48 Imidazolidine and oxazolidine analofs of nicotine prepared by Castle and coworkers.

Lambert *et al*. reported the preparation of unsymmetric imidazolidines, by refluxing the ethylenodiamine with a formaldehyde aqueous solution in ethanol.[95,96] The scope included *N,N'*-bisalkyl, bisaryl and alky,aryl ethylenediamines (**Scheme 49**). Overall yields were poor, with slightly increase yields when aryl substituents were present.



diamine aminal

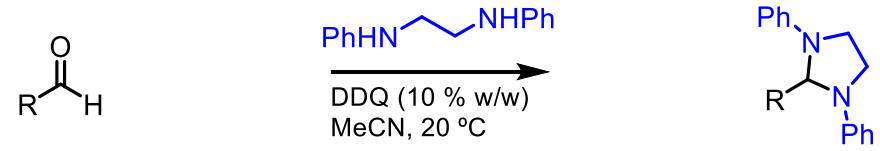
217, 27% **218**, 23% **219**, 30%

220, 42% **221**, 38%

Scheme 49 Preparation of unsymmetric imidazolidines described by Lambert and coworkers.

In 1995 Eynde and coworkers observed that catalytic amounts of 3,4-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) promoted the condensation of ethylenediamines with aldehydes to imidazolidines (**Scheme 50**).[97] Even in the cases of furfural, benzaldehyde and 2-chlorobenzaldehyde where only traces of the product were formed in the absence of DDQ, the catalyst promoted the formation of imidazolidine in 90, 85 and 85% respectively. The same group reported the use of bentonite K10 clay as catalyst for

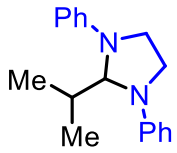
several amine derivatives, including imidazolidines. The scope is equal to the previous study with similar yields.[98]



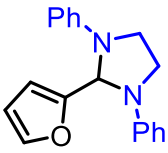
aldehyde aminal

Yield without DDQ under brackets:

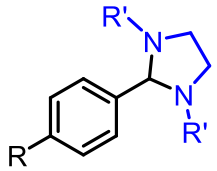
222: R = Et, 85% (70%)
223: R = Pr, 85%(40%)



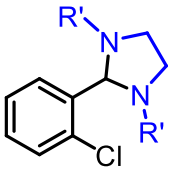
224, 90% (30%)



225, 90 % (traces)



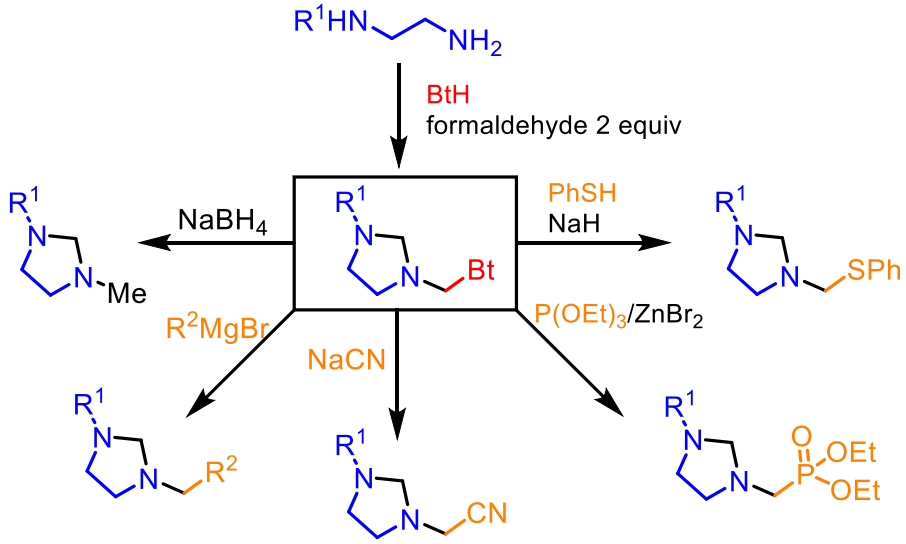
226: R = H, 85% (traces)
227: R = OMe, 95% (10%)
228: R = NO2, 90% (10%)



229, 85 % (traces)

Scheme 50 Preparation of aminals promoted by DDQ described by Eynde and coworkers

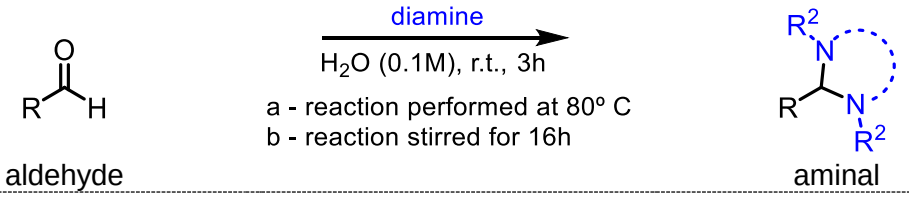
Preparation of a versatile family of *N*-benzotriazole derived aminals has been described by Katritzky and coworkers (**Scheme 51**). The adducts were formed in a mixture of BtH, formaldehyde and a primary amine in a proportion of 2:3:2. This structures were further functionalized by addition of a Grignard reagent or KCN.[99] The same group applied this method for the preparation of unsymmetrical imidazolidines. Reacting a *N*-monosubstituted diamine with BtH and formaldehyde 1:1:2 affords an unsymmetric imidazolidine with a readily functionalizable *N*-benzotriazole. Reduction with sodium borohydride affords the *N*-methyl subtituent whereas addition of a Grignard affords the *N*-alkylated product. Reaction with NaCN afforded the acetonitrile substituted imidazolidine. The authors also reported thiophenol addition promoted by sodium hydride and the $ZnBr_2$ catalyzed addition of a phosphonate.[100]

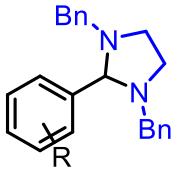


Scheme 51 Preparation of benzotriazol functionalized aminals and their derivatization studied by Katritzky and coworkers.

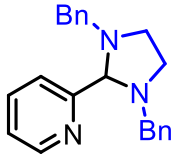
In 2004 a first example of imidazolidines prepared in water from ethylenediamines was reported by Wilhelm and co-workers (**Scheme 52**). The authors claim that under neat conditions the reaction originated several side products and lower yields. However by stirring the aldehydes and diamines in a concentrated aqueous solution were able to isolate the aminals in good yield (42-99 %).[101] The authors comment that the reaction is not as efficient when solid aldehydes are employed and the reaction had to be heated to the melting point of the corresponding aldehyde. The scope was very broad including C2, C3 and C4 diamines, cyclohexyldiamine and even piperidine to form the acyclic aminal.

Xiao and coworkers reported in 2011 a photoredox system for the intramolecular cyclization of ethylenodiamines to imidazolidines (**Scheme 53**). The use of visible light to induce chemical transformation is a recent hot topic of great importance. The authors envision the use of chirally enriched substrates to induce chirality to the final imidazolidine. The photoreaction runs under 36 W fluorescent light and is promoted by catalytic ammounts of $Ru(bpy)_3Cl_2$ in the presence of O_2 in protic solvents (ethanol and methanol). Base should be used to increase the efficiency of the reaction, tBuOK afforded the best yield/diastereoselectivity. The scope whithstands several aromatic substituents on the amine, both electron donnor and electron withdrawing. The elecrophilic character of the benzylic group also doesn't seem to affect the reaction. The enantiomerically defined α substintuent can be benzylic or alkylic.[102]

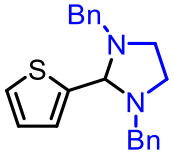




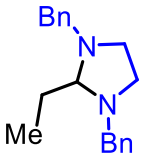
230: R = 4-H, 91%
231: R = 2-Cl, 96%
232: R = 2-OMe, 94%
233: R = 2,4-Cl[a], 96%
234: R = 2,3,4,5,6-F, 92%
235: R = 4-Cl[a], 91%
236: R = 2,6-Cl[a], 88%



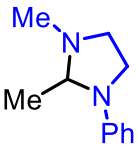
237, 99%



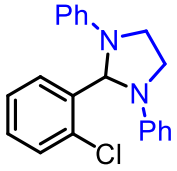
238, 99%



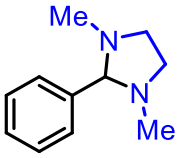
239, 85%b



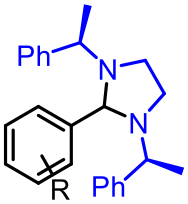
240, 42%[a]



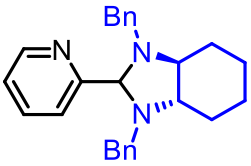
241, 98[a,b]



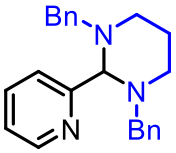
242, 67%



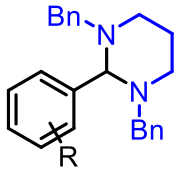
243: R = 2-Cl[b], 81%
244: R = 4-Cl[a,b], 80%



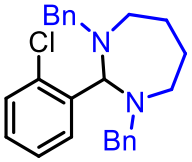
245, 95%



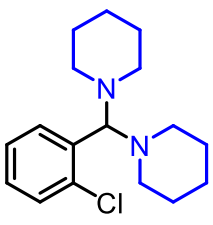
246, 93%



247: R = 4-H, 96%
248: R = 2-Cl, 88%

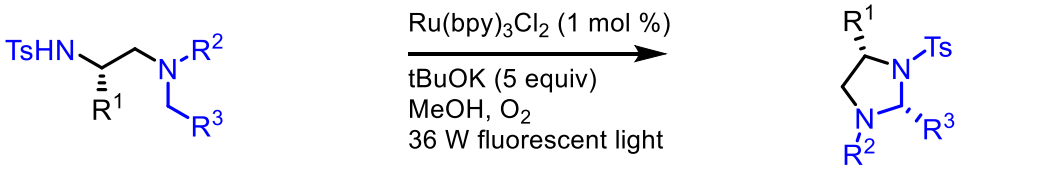


249, 99%

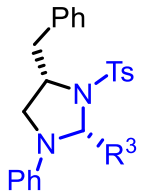


250, 99%

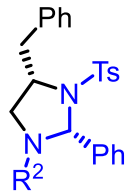
Scheme 52 Preparation of imidazolidines in water described by Wilhelm and co-workers.



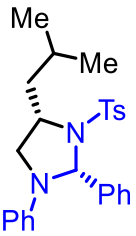
diamine aminal



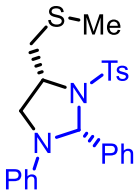
251: R^3 = Ph, 92% 10:1 dr
252: R^3 = 4-MePh, 93% >19:1 dr
253: R^3 = 4-MeOPh, 90% >19:1 dr
254: R^3 = 2-MeOPh, 92% >19:1 dr
255: R^3 = 4-ClPh, 92% >19:1 dr
256: R^3 = 4-BrPh, 92%, 8:1 dr



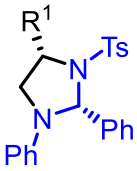
257: R^2 = 4-MePh, 94% >19:1 dr
258: R^2 = 4-MeOPh, 91% >19:1 dr
259: R^2 = 4-ClPh, 94% >19:1 dr



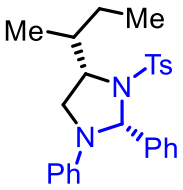
260, 94% >19:1 dr



261, 45%, 3:1 dr



262: R^1 = Me, 92% >19:1 dr
263: R^1 = iPr, 89% >19:1 dr

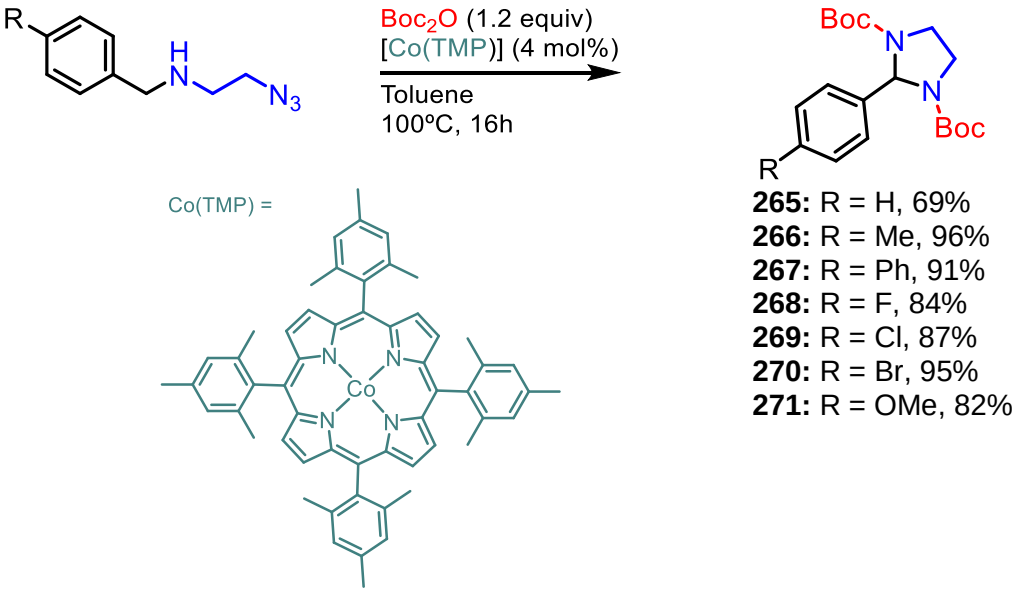


264, 90% 2:1 dr

Scheme 53 Photoredox system for the intramolecular cyclization of ethylenodiamines to imidazolidines described by Xiao and co-workers.

Bruin and co-workers have prepared several heterocycles, including imidazolidines, through the activation of azides by a cobalt-porphyrin complex. The mechanism involves the formation of a nitrene radical followed by HAT to form a carbon centered radical. This leads to ring closure forming the heterocycle. The reaction needs Boc_2O to protect the final amine which would lead to product inhibition of the catalyst if let unprotected (**Scheme 54**).[103]

Enantioselective preparation of aminals was described in 2016 by Smith and co-workers. In this work the condensation of an aldehyde with a primary amine affords the corresponding imine which under base catalysis in the presence of a chiral cinchonidinium chloride derivative undergoes Aza-Michael addition (**Scheme 55**). A scope was performed with different aromatic and alkyl aldehydes. Electron donor groups seem to decrease the yields but afford better er. Electron withdrawing groups afford better yields but reduced er. The reaction was also successful when methyl/ethyl CF_3 ketone was employed, with excellent yield and enantiomeric excess.[104]

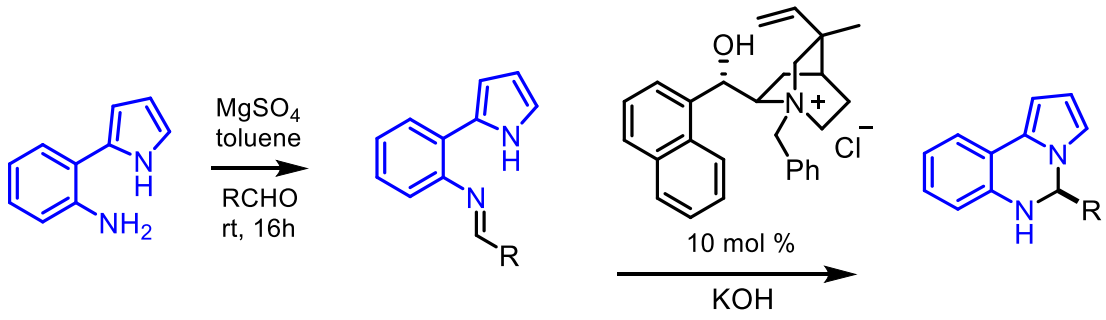


Scheme 54 Radical based formation of imidazolidines described by Bruin and co-workers.

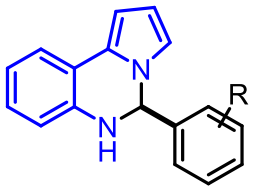
The imidazolidine was used as a method to selectively functionalize one of the diamine nitrogen (**Scheme 56**). Gao and coworkers observed that *via* formation of an aminal one could mask a secondary amine as a tertiary one, rendering it unreactive towards electrophiles. Using this method several amides were prepared through by treatment of acylation agents with imidazolidine obtained from the condensation of N-(phosphonoethyl)ethylenodiamine and benzaldehyde. [105]

The equilibrium between aminal-imine when a primary amine is present has been thoroughly studied. In 2000 Boca and coworkers prepared aminal derivatives from 2-pyrdinecarboxaldehyde *N*-oxide (PNO) with polyamines. The authors observed that the formation of terminal cyclic aminals is favored (**Scheme 57**).[106] There is no formation of di-imines.

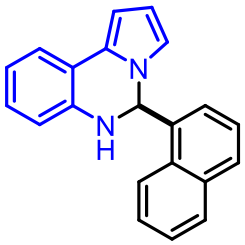
Similar studies on the equilibrium of aminal-imine were performed by Kukharev and coworkers using *N*-(2-vinyloxyethyl)ethylenodiamine (**Scheme 58**). The authors report that condensation with benzaldehyde affords a mixture of the imidazolidine and imine in a 0.59:1 ratio. Condensation with heteroaryl groups such as pyridin-4-yl and pyridin-3-yl affords a mixture of imidazolidine and imine in a 4.52:1 and 1.99:1 ratio respectively. When ketones were used the sole product formed was the imine. In the case of formaldehyde the condensation of 3 amines with 3 formaldehydes lead to the formation of a triazine.[107]



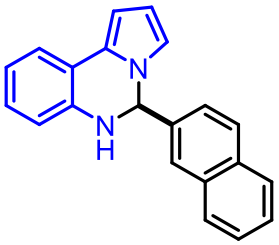
272 **272** imine aminal



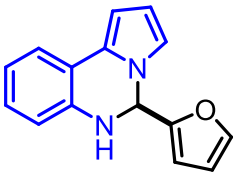
273: R = 4-H, 85%, 86:14 er
274: R = 2-OMe, 77%, 92:8 er
275: R = 3-OMe, 86%, 82:18 er
276: R = 4-OMe, 73%, 78:22 er
277: R = 2-Me, 73%, 96:4 er
278: R = 3-Me, 74%, 89:11 er
279: R = 4-Me, 95%, 76:24 er
280: R = 2-CN, 94%, 61:39 er
281: R = 3-CN, 92%, 70:30 er
282: R = 4-CN, 76%, 62:38 er
283: R = 2-F, 85%, 81:19 er
284: R = 2-Br, 71%, 82:18 er



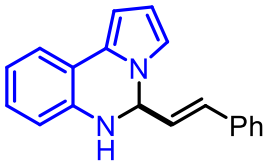
285, 80%, 88:12 er



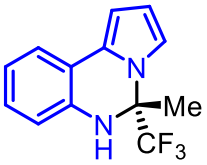
286, 82%, 91:9



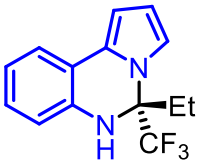
287, 90%, 70:30 er



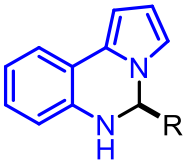
288, 99%, 60:40 er



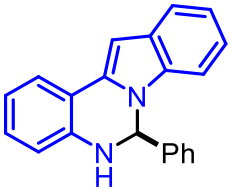
289, 90%, 98:2 er



290, 96%, 99:1 er



291: R = *n*Bu, 83%, 83:17 er
292: R = *i*Pr, 83%, 77:33 er
293: R = cyclohexyl, 86%, 92:8
294: R = *t*Bu 84%, 72:28 er

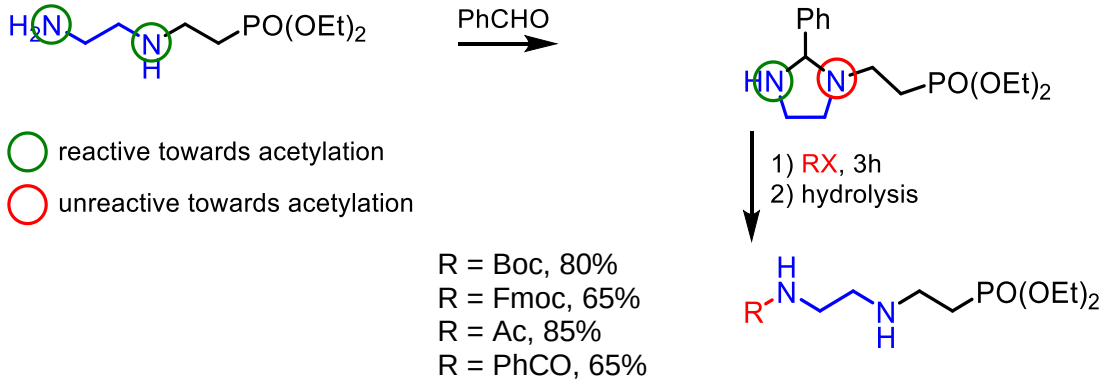


295[a], 76%, 63:37

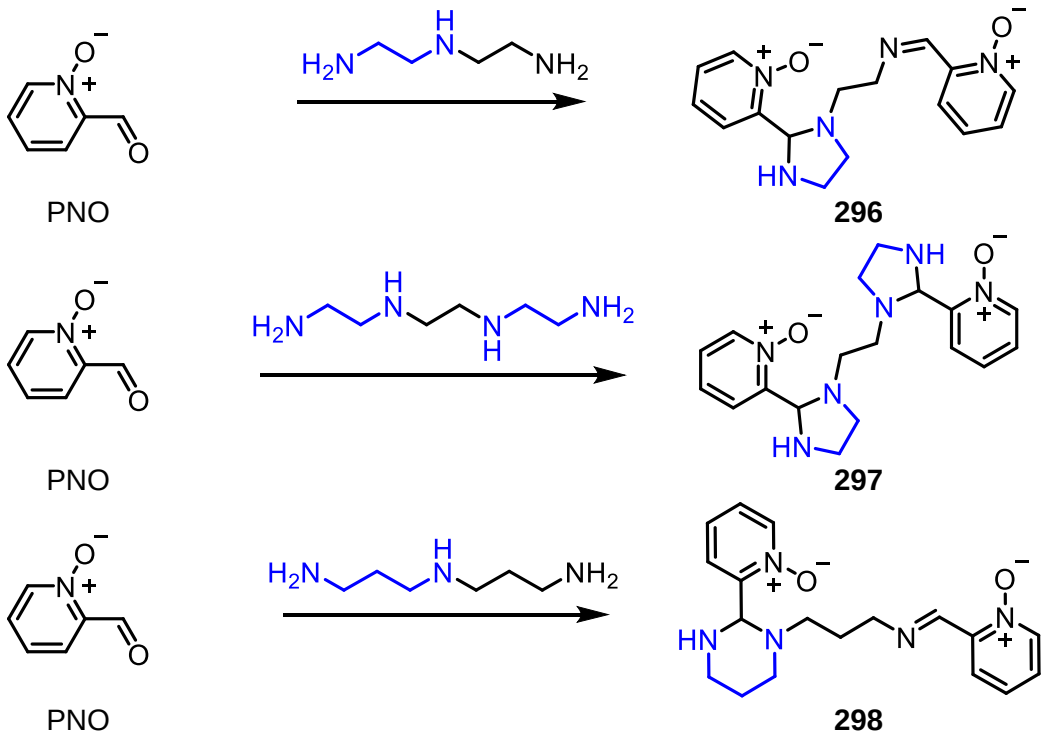
[a]*Imine formation by reacting benzaldehyde (1.1 equiv), pyrrolidine (10 mol%), 3 Å molecular sieves, CH_2Cl_2, 60 °C, 1 h. The crude imine was used without purification in the cyclization step.*

Scheme 55 Enantioselective preparation of aminals described by Smith and co-workers

The same group later reported the study for the condensation of *N*-(2-vinyloxyethyl)ethylenodiamine with fluorinate benzaldehyde derivatives (**Scheme 59**). Unlike the previous study, the equilibrium between the imine and imidazolidine is reach in almost 1:1 ratio. Moreover the authors compared with the condensation of an aminoalcohol where they observe the predominant product to be the imine and not the oxazolidine. [108]

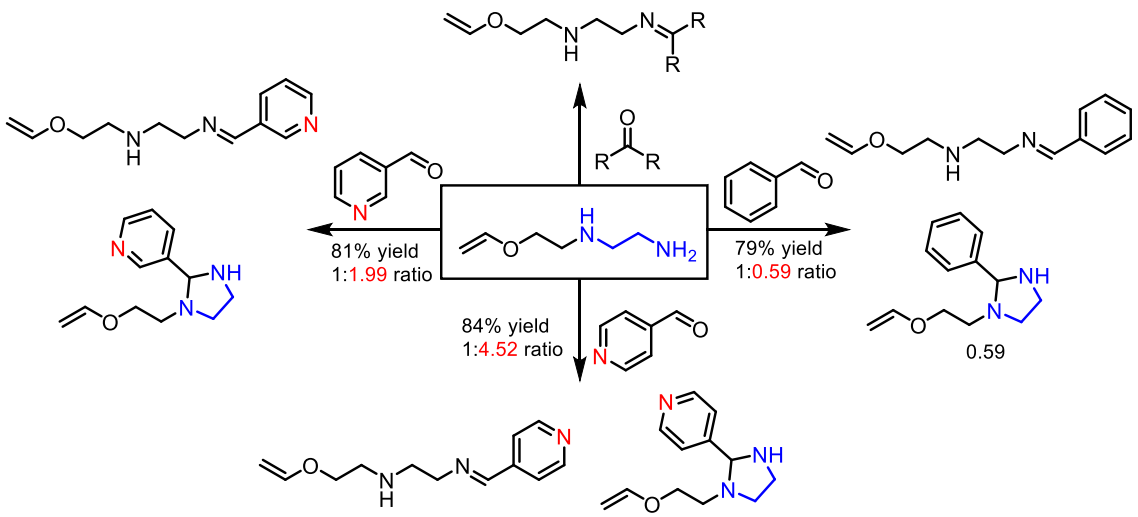


Scheme 56 Selective acetylation of primary amines in the presence of secondary amines *via* aminal formation described by Gao and coworkers.

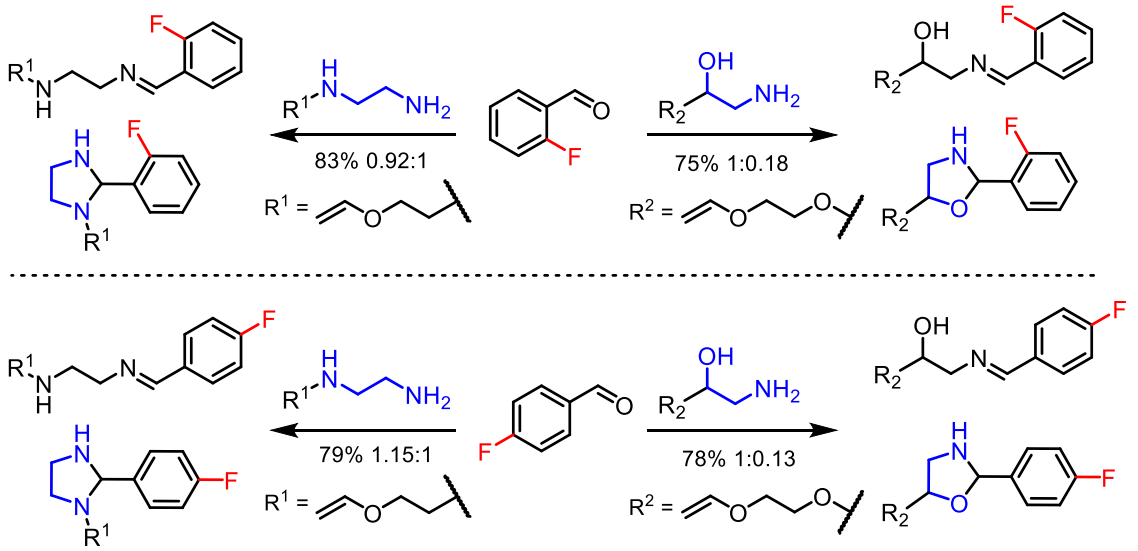


Scheme 57 Formation of aminals by condensation of PNO and polyamines. Formation of di-imine or internal aminal is not observed.

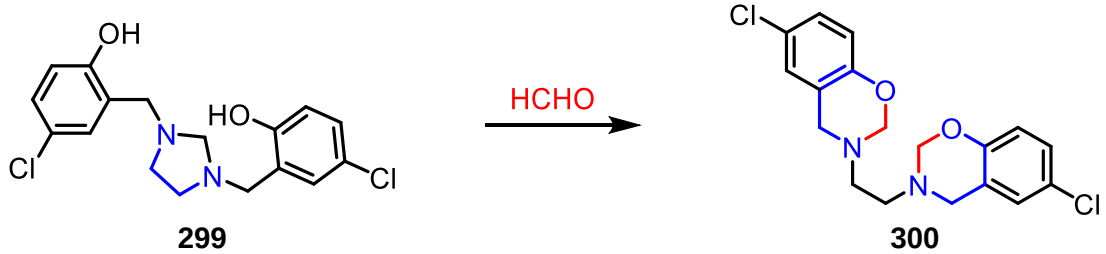
Rivera and coworkers studied the interconversion of imidazolidine in the presence of other aldehydes. The diamine used contains a free OH in position 2 of the aromatic ring. In the presence of formaldehyde there is displacement of the imidazolidine to form a benzoxazine (**Scheme 60**).[109] When other aldehydes were used a complex mixture was obtained. In the case of aryl aldehydes when the starting materials were refluxed in dioxane for 3 days the imidazolidine exchange was observed in low yields (**Scheme 61**).[110]



Scheme 58 Studies on the equilibrium of aminal-imine described by Kukharev and coworkers using *N*-(2-vinyloxyethyl)ethylenodiamine.

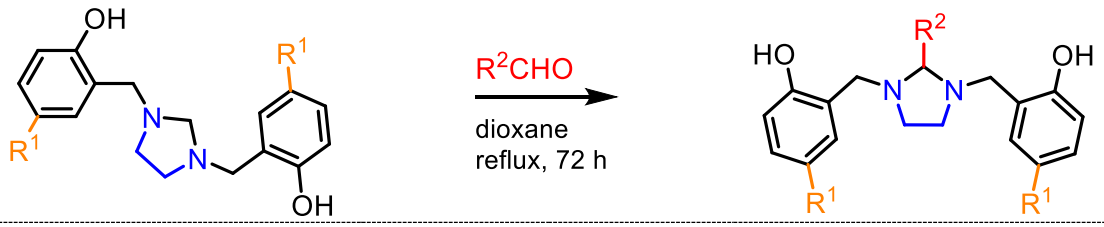


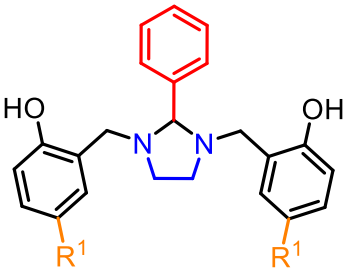
Scheme 59 Studies on the equilibrium of aminal-imine described by Kukharev and coworkers using Fluoro-benzaldehyde derivatives.



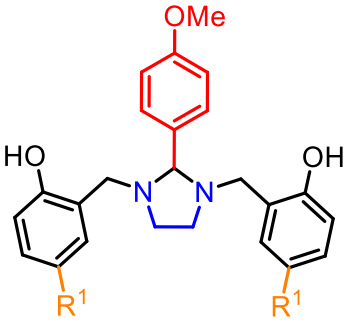
299 **300**

Scheme 60 formaldehyde promoted displacement of imidazolidine to benzoxazine described by Rivera and coworkers.





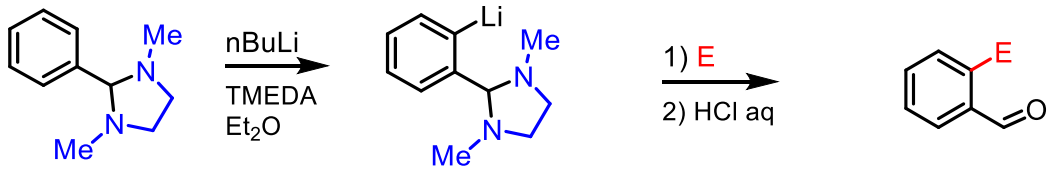
301: R = H, 35%
302: R = Me, 29%
303: R = Cl, 40%



304: R = H, 28%
305: R = Me, 18%
306: R = Cl, 25%

Scheme 61 Aminal exchange in the presence of benzaldehyde and 4-OMe-benzaldehyde described by Rivera and coworkers.

Imidazolidines prepared form the condensation of aromatic aldehydes and diamines in refluxing benzene were used by Harris and coworkers as an easily removable directing group for *ortho* lithiations (**Scheme 62**). The aminal was formed by refluxing the aldehyde and *N,N'*-dimethylethylenediamine in the presence of *p*-toluenosulphonic acid. Treatment of the imidazolidine with 3 equiv of n-BuLi in anhydrous diethyl ether for 7h afforded the corresponding *ortho* lithiated imidazolidine which could then be quenched with an electrophile.[111]

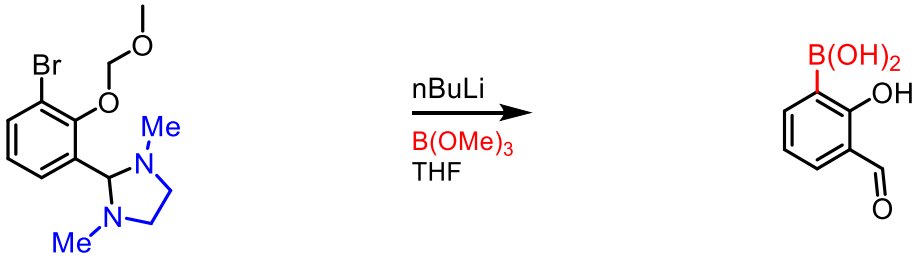


aminal Lithiated aminal E = electrophile Aldehyde

Scheme 62 *Ortho* lithiation directed by aminal group described by Harris and coworkers.

This procedure has been used for the bromination of substituted benzaldehydes as intermediaries in total synthesis. [112–118]

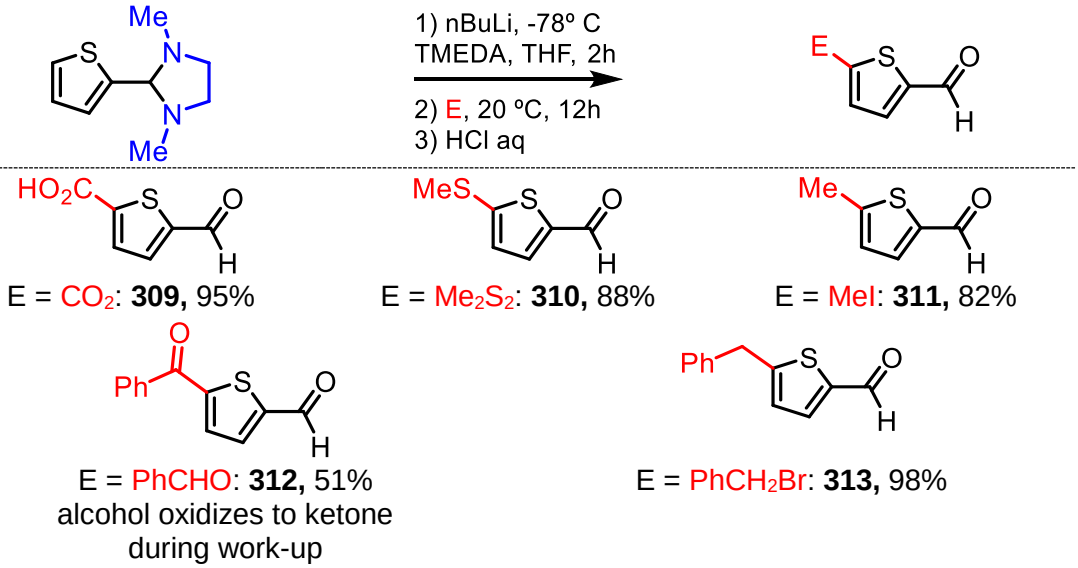
The imidazolidine has been used by Shinkai and coworkers as protection group for the borylation of a bromo benzaldehyde derivative (**Scheme 63**). The boronic acids were then used as chiral salen-Co(II) complexes.[119] The starting imidazolidine **307** was prepared by refluxing the corresponding aldehyde with the diamine in benzene for 2 h.



307 **308**

Scheme 63 Borylation of bromo-benzaldehyde derivative described by Shinkai and coworkers.

The same method was used by Chadwick and coworkers for the lithiation of heteroaromatic aldehydes such as furfural and thiophene.[120] The authors claim the imidazoline to be a mild protection methodology, since the aldehydes could be easily obtained by treatment of the final product with a dilute acid aqueous solution or by treatment with MeI in diethylether. The latter allowed for the deprotection of the aminal even in the presence of an acetal. The authors prepared several 5-substituted heteroaromatic aldehydes by lithiation of the imidazolidine protected aldehyde in the position 5, followed by quenching with the corresponding electrophile (**Scheme 64** and **Scheme 65**). The thiophene was successfully carboxylated in the presence of CO_2. Alkylation with methyl iodide and benzyl bromide afforded the products in excellent yield (82 and 98% correspondingly). Reaction with Me_2S_2 afforded the sulphide. Upon reacting with an aldehyde instead of the corresponding alcohol the authors isolated the ketone product of aerobic oxidation in 51% yield. Other authors have used this methodology to prepare several thiophene analogues.[121–123]



E = CO_2: **309,** 95%

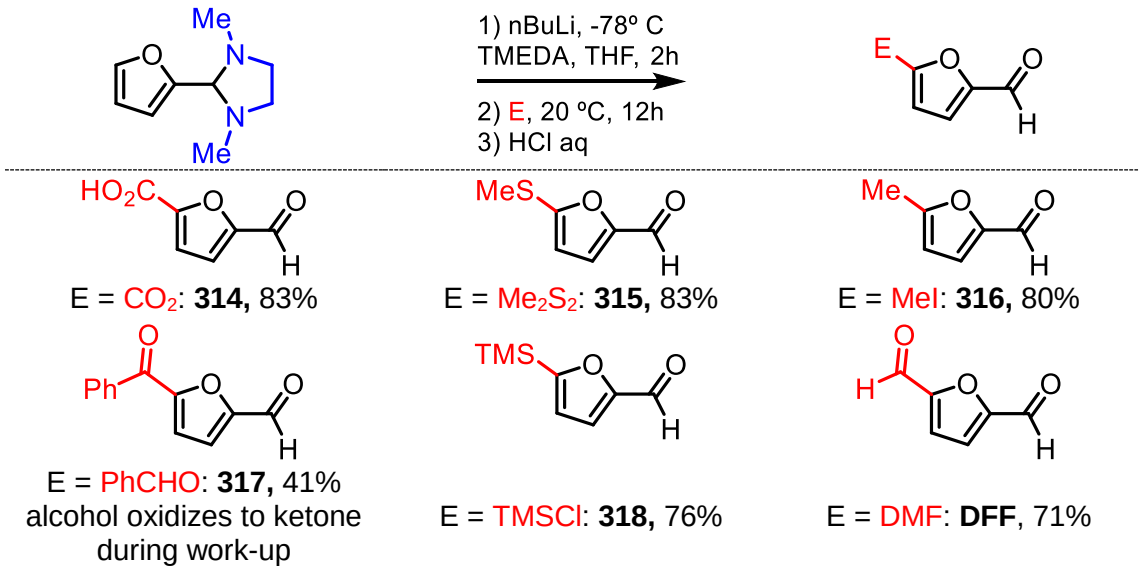
E = Me_2S_2: **310,** 88%

E = MeI: **311,** 82%

E = PhCHO: **312,** 51%
alcohol oxidizes to ketone
during work-up

E = $PhCH_2Br$: **313,** 98%

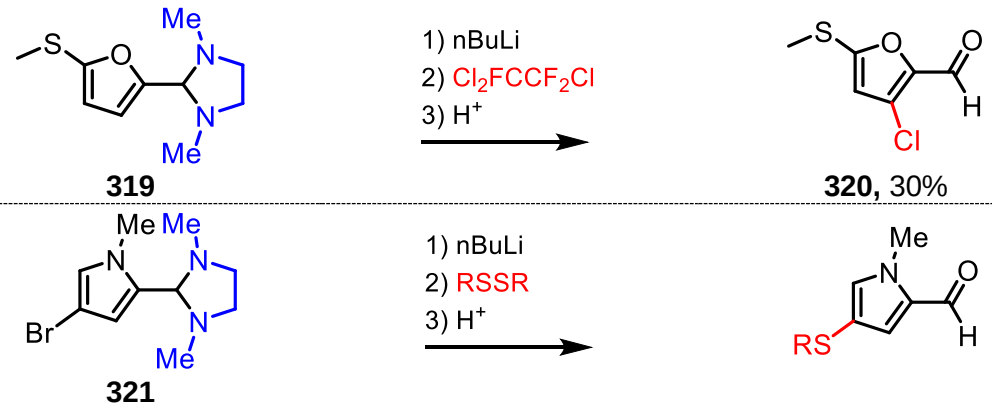
Scheme 64 Scope of thiophene functionalization described by Chadwick and coworkers.



Scheme 65 Scope of furan functionalization described by Chadwick and coworkers.

Lithiation in position 3 of the furan ring was attempted but the aminal group proved to be unsuccessful in such metalations. Instead the oxazoline showed remarkable selectivity towards β substitutions.[124]

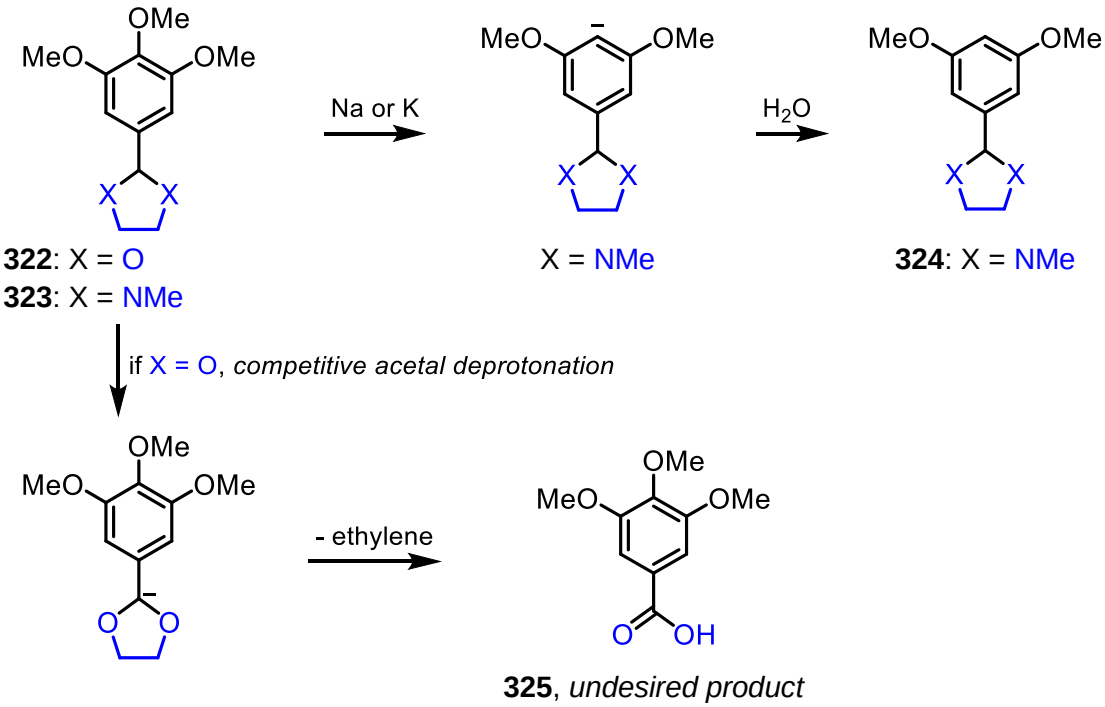
Later in 2008 Basarab and coworkers use the imidazolidine as an aldehyde protection group for the lithiation of a substituted furan **319** and were able to obtain the chlorinated product **320** in 30% yield (**Scheme 66**). The same authors use the imidazolidine for the protection of an *N*-substituted pyrrol aldehyde **321** during a halogen-lithium exchange (**Scheme 66**). The substituted heterocycles were used in the design of *Helycobacter pylori* galatamase racemase inhibitors.[125]



Scheme 66 Formation of chlorinated furfural derivatives (top) and halogen-lithium exchange in pyrrol aldehyde (bottom) described by Basarab and coworkers.

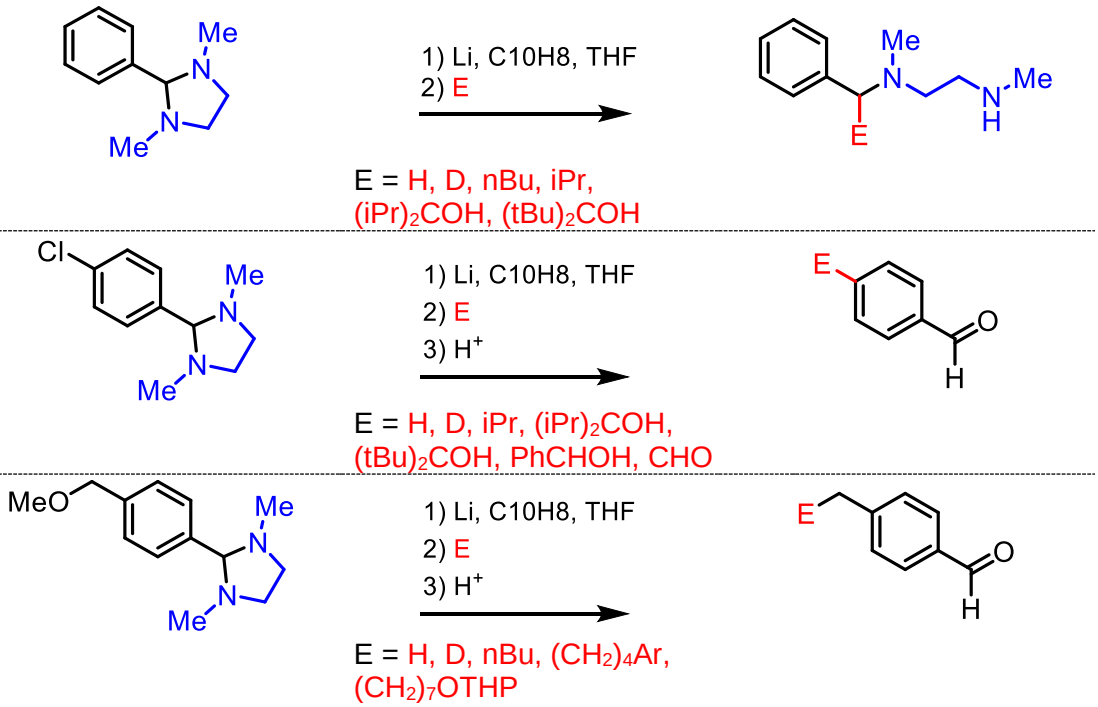
Azzena and coworkers in the early 90s were interested in methods for the selective demethoxylation of trimethoxybenzene[126]. The most common method was the reductive

cleavage with metallic Na or K. In the case of 1,2,3-trimethoxybenzene substituted in position 5 with an aldehyde the common methods lead to decomposition products so a suitable protection group was developed. The acetal under these conditions underwent deprotonation leading to side products, while the aminal proved to be stable under basic conditions leading to the desired product in 80 % yield (**Scheme 67**).[127]



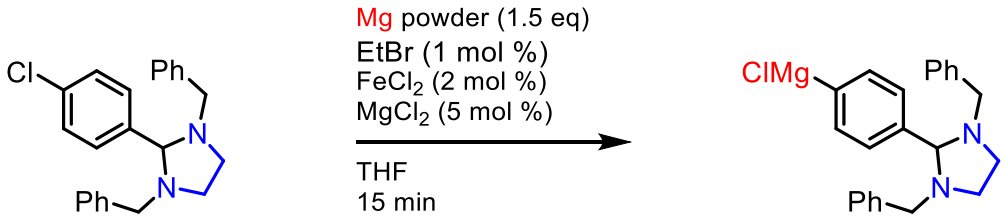
Scheme 67 Demethoxylation of trimethoxybenzaldehyde in the presence of aminal described by Azzena and coworkers. Formation of undesired side products in the case of substrate protected by acetal.

Azzena and coworkers explored the Lithium reductive metalation of imidazolidines. The unsubstituted aromatic imidazolidine underwent reductive metalation on the aminal carbon, which could then be quenched with an electrophile. This afforded N,N‘,N‘-trisubstituted benzylic ethylenodiamines with α-substituints depending on the quenching electrophile. The 4-chloro aromatic imidazolidine suffered a halogen-lithium exchange and after quenching afforded the substituted benzaldehydes. The 4-methoxy aromatic imidazolidines underwent dealkoxylation and could be quenched with different electrophiles to afford the substituted benzaldehydes (**Scheme 68**).[128]



Scheme 68 Lithium reductive metalation of benzaldehyde derivatives explored by Azzena and coworkers.

The aminals have shown to be compatible with Grignard reagents and Bogdanovic and coworkers have prepared imidazolidine containing Grinard **327**. The authors describe a mild system for Grignard preparation using Mg powder with EtBr/$FeCl_2$/$MgCl_2$ system for Grignard preparation (**Scheme 69**).[129]

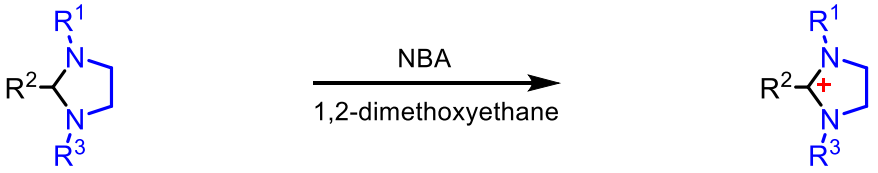


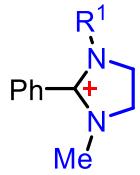
326 **327**

Scheme 69 Preparation of Grignard reagent from aryl aminal described by Bogdanovic and coworkers.

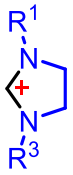
In 2000 Perillo and coworkers described the preparation of imidazolium salts *via* dehydrogenation of imidazolidines (**Scheme 70**). The authors screened several dehydrating agents such as DDQ, chloranil, carbon tetrachloride, Hg(II)/EDTA, PCC, N-bromosuccinimide (NBS), N-iodosuccinimide (NIS), N-bromoacetamide (NBA). The latter showed higher yields and less side products formation. Chloranil and carbon tetrachloride proved to be efficient in the case of C-unsubstituted imidazolidines (where

R^2 = H).[130] The same group latter reported the use of 1,3-dibromo-5,5-dimethylhydantoin as a new dehydrogenating agent.[131]

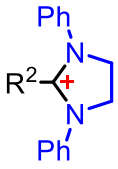




328: R^1 = Ph
329: R^1 = 4-MePh
330: R^1 = 4-OMePh



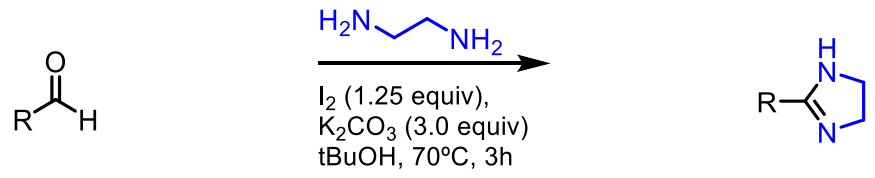
331: R^1 = R^3 = 4-MePh
332: R^1 = R^3 = 4-MeOPh
333: R^1 = R^3 = 4-EtOPh
334: R^1 = 4-ClPh, R^3 = Bn
335: R^1 = 4-ClPh, R^3 = 4-ClPh



336: R^2 = Ph
337: R^2 = Me

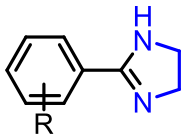
Scheme 70 Scope of preparation of imidazolium salts described by Perillo and coworkers.

In 2006 Togo and coworkers prepared imidazolines from aldehydes and ethylenodiamine *via* formation of imidazolidine followed by iodine in the presence of potassium carbonate (**Scheme 71**). The imidazolines could be further oxidized with (diacetoxy)iodobenezene to the corresponding imidazoles (**Scheme 72**).[132]

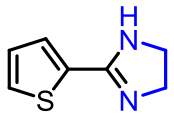


aldehyde

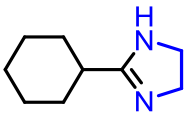
imidazoline



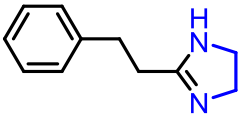
338: R = H, 100%
339: R = 4-Me, 100%
340: R = 4-Br, 97%
341: R = 4-MeO, 100%
342: R = 4-NO_2, 99%
343: R = 4-CN, 98%
344: R = 2-Cl, 99%



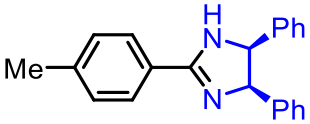
345, 94%



347, 50%

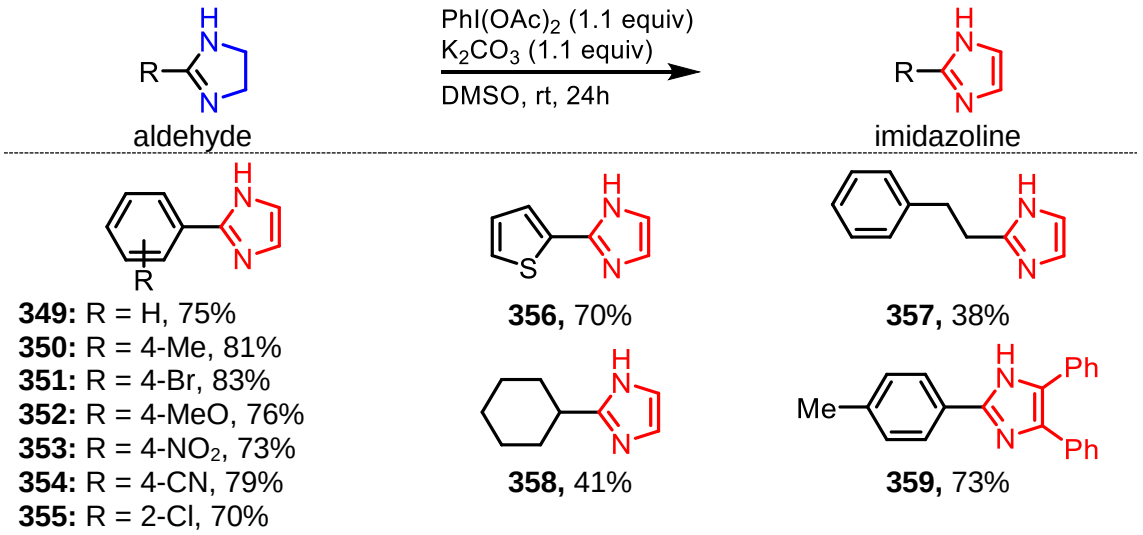


346, 53%



348, 92%

Scheme 71 Scope for the formation of imidazolines from aldehydes described by Togo and coworkers.

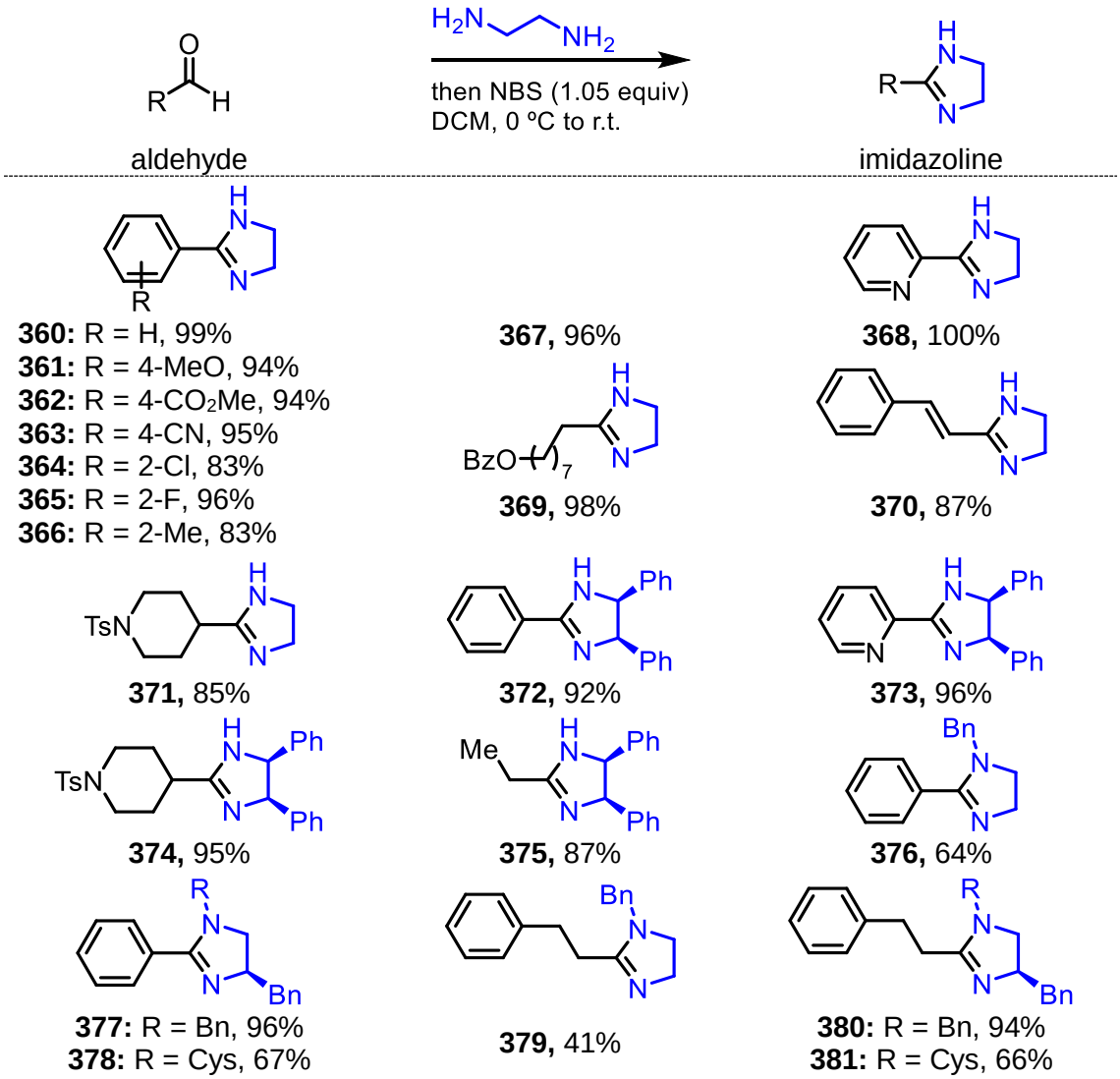


Scheme 72 Scope for the formation of imidazoles from imidazolines described by Togo and coworkers.

A similar study by Kita and coworkers in 2007 use NBS as the oxidant for the one-pot preparation of imidazolines from aldehydes and diamines.[133] The reaction is efficient at room temperature unlike the previously reported. The broad scope tolerates unsymetric N and C substituted ethylenediamines (**Scheme 73**).

Reduction of the imidazolidine ring has been reported by hydrogenation using Raney nickel[134], BH_3.THF[135] and excess $NaBH_4$.[136] Northrop and coworkers in the course of imidazolidine reactivity studies noticed the reduction by BH_3.THF to afford trisubstituted ethylenodiamines. BH_3.THF was also able to reduce oxazolidine to the corresponding aminoalcohol. [135] Perillo and coworkers have reported the reduction of imidazolidines to prepare *N,N,N'*-trisubstituted ethylenediamines (**Scheme 74**). The authors refluxed the N,N'-disubstituted ethylenediamines with the corresponding aldehydes in ethanol and *in situ* reduced the imidazolidine with an excess of sodium borohydride. In the cases of unsymmetrical imidazolidines the reduction occurred regioselectively to afford the substituted ethylenediamine on the alkyl nitrogen. Moreover the authors claim the imidazolidines prepared from electron deficient aldehydes or anilines were not sucessfully reduced. [136]

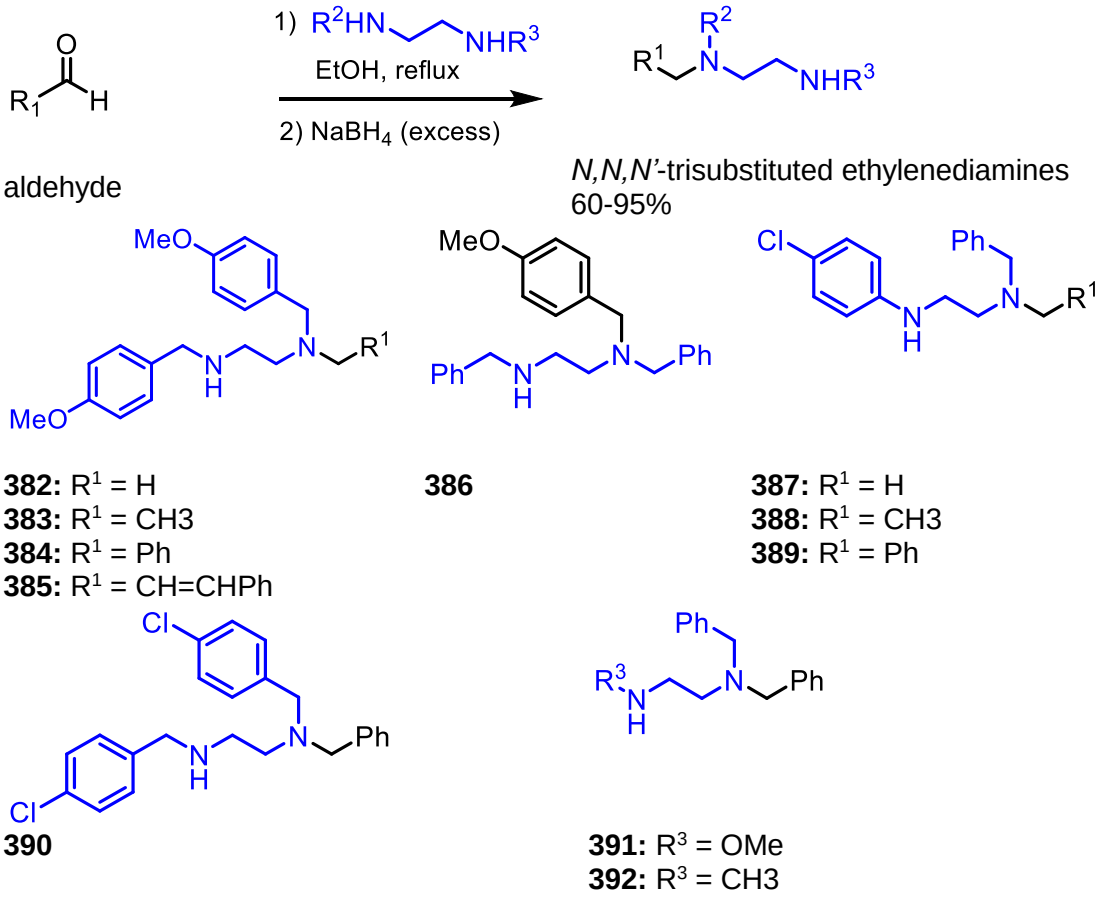
The need for regioselective diamine functionalization lead to the development of a strategy that took advantage of the equilibrium between imine and imidazolidine. Lehn and coworkers observed that diamines in the presence of salicyl aldehyde preferred to form the imine, whereas in the presence of 2-pyridyl aldehyde preferred to form the imidazolidine (**Scheme 75**). Moreover the authors claim that if more than one aminal can be formed (5 membered vs 6 membered ring) the imidazolidine is favoured.



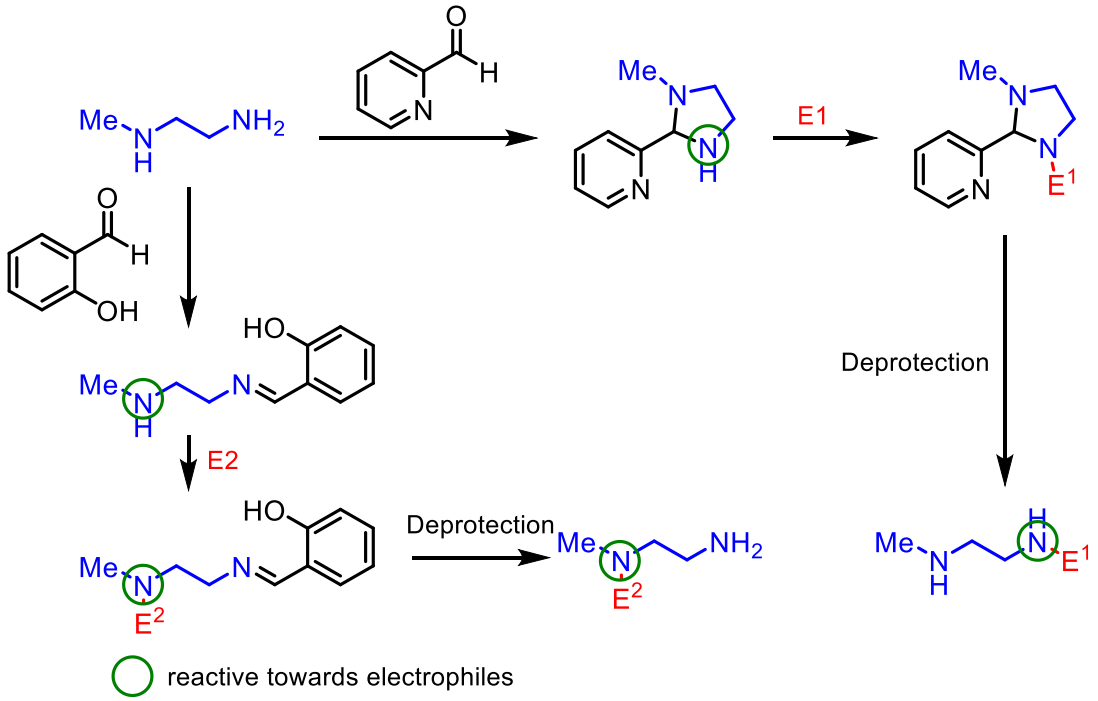
Scheme 73 Scope for the formation of imidazolines from aldehydes described by Kita and coworkers.

Following this observation the authors selectively functionalized diamines with different electrophiles. [137]

Aminals have been used as metal ligands both for catalysis and medicinal applications. Manganese complex **395** was prepared by Panja and coworkers from imidazolidine **393** as catalysts for the oxidation of *o*-aminophenol. The ligands are complexed to the manganese (II) ion through the imidazolidine (**Scheme 76**A). [138] Zinc complexes **397a-e** were prepared from imidazolidine **396** by Montazerozohori and coworkers as antimicrobial agents (**Scheme 76B**). The complexes were prepared under ultrasounds and presented enhance antimicrobial activity when compared with the free imidazolidines.



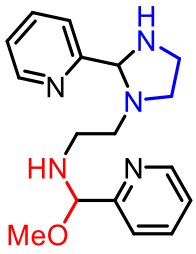
Scheme 74 Scope for the preparation of trisubstituted ethylenediamines from aldehydes described by Perillo and coworkers.



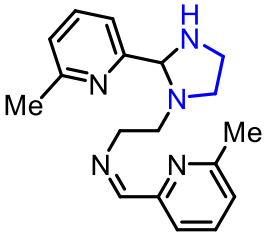
Scheme 75 Chemoselective functionalization of primary/secondary amines in a diamine system described by Lehn and coworkers.

Studies show that a potential mechanism of action involves cleavage of plasmid DNA.[139] The same group prepared cadmium complexes **399a-e** with increased antimicrobial activity (**Scheme 76C**).[140]

A. Manganese complexes with aminal ligands described by Panja and coworkers



393



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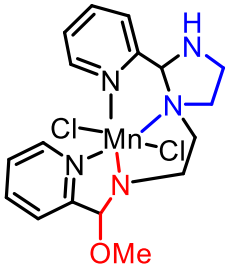
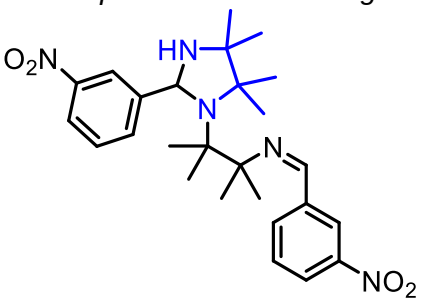


395

B. Zinc complexes with aminal ligands described by Montazerozohori and coworkers



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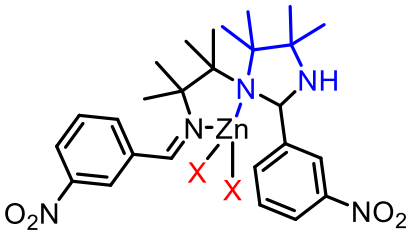
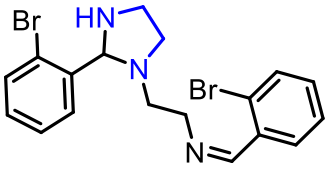
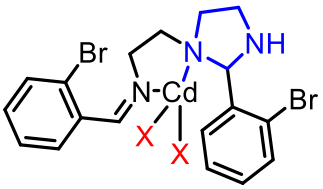


397 a-e: X = Cl, Br, I, SCN, N_3

C. Cadmium complexes with aminal ligands described by Montazerozohori and coworkers



398

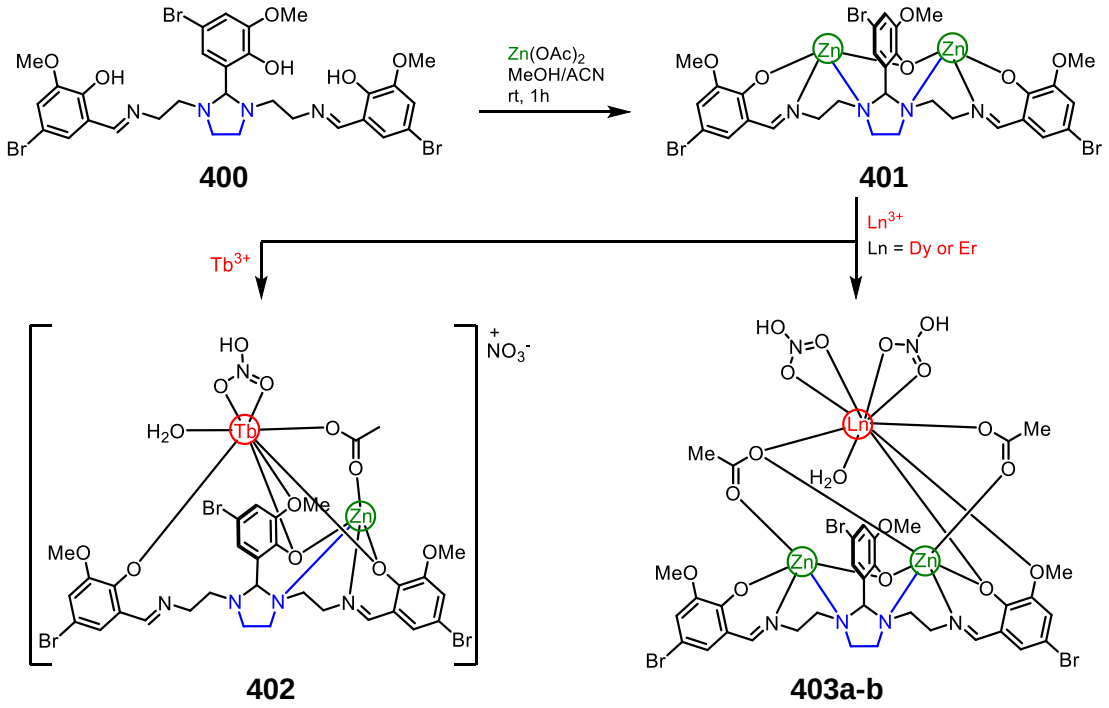


399 a-e: X = Cl, Br, I, SCN, N_3

Scheme 76 Metal complexes with aminal ligands described by A: Panja and coworkers; B and C: Montazerozohori and coworkers.

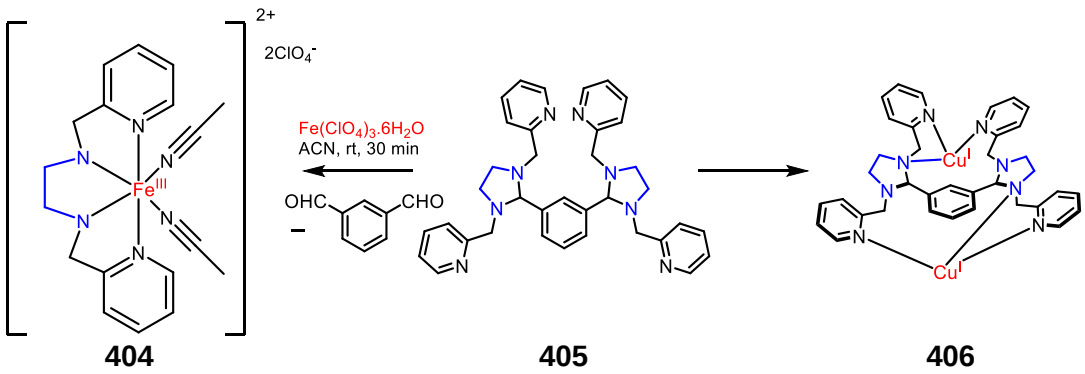
Fondo and coworkers prepared zinc-lathanide complexes with imidazolidines containing multiple complexation sites (**Scheme 77**). The authors envision the zinc to complex with imidazolidine **400**, forming complex **401**. This leaves leaving the remaining sites to complex with a second metal such as Tb, Dy and Er to form complexes **402** and **403**a-b respectively.[141]

In a study by the same group imidazolidines were not stable when attempted to complex with Cu (II). The main product of complexation was the Cu-diamine, which can be explained by the hydrolysis of the imidazolidine. The hydrolysis released the free diamine which then complexed with the Cu.[142] Avenier and coworkers explored this phenomena and observed that the cleavage of the imidazolidine is highly dependent of the Lewis acidity of the metal.



Scheme 77 Zinc-Lathanide complexes with aminal ligands described by Fondo and coworkers

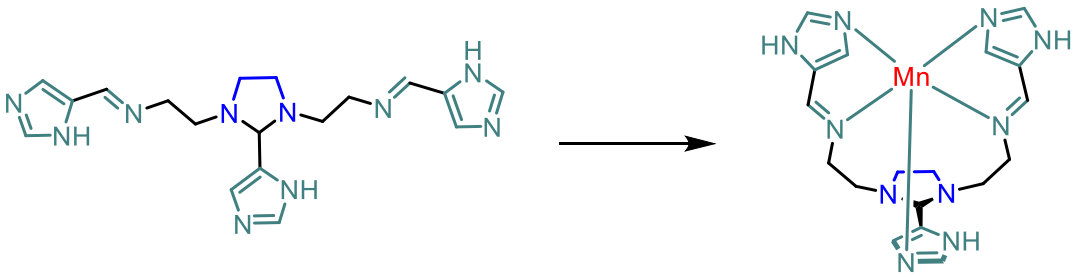
The imidazolidine **404** prepared from isophtaldehyde and two equivalents of *N*,*N'*-bis(2-pyridylmethyl)-ethylenodiamine was used as model (**Scheme 78**). Using soft Lewis acids such as Cu (I) complex **406** was formed, whereas the use of Fe (III), Zn (II) and Cu (II) lead to hydrolysis and formation of the corresponding metal-diamine complex such as **405**.[103]



Scheme 78 Complexation of diaminal with Fe(III) and Cu(I) salts described by Fondo and coworkers. The aminal is hydrolysed in the presence of the Fe(III) salt, forming the corresponding Fe-diamine complex.

Louloudi and coworkers prepared heterogeneous Mn(II) catalysts such as **408** for alkene epoxidation with hydrogen peroxide by complexing imidazolidines **407** with Mn[143] and further graphting to the surface of an oxidized activated carbon and an oxidized pyrolytic

carbon from recycled tire char. The authors claim the complexation with the manganese ion to be on the imidazoles and imines instead of the imidazolidine (**Scheme 79**). [144]

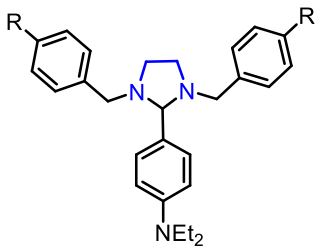


407 **408**

Scheme 79 Manganese complexes with aminal ligands described by Louloudi and coworkers.

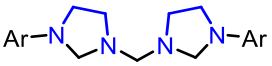
The pharmacological properties of imidazolidines has been studied as depicted in **Scheme 80** . Sharma and coworkers reported in 2001 the Anti-inflammatory and analgesic properties of a series of imidazolidines. [145]. Imidazolidines prepared from benzylic diamines presented best results. Electron donor substituents increase the pharmacologic activity. Perillo and coworkers reported in 2005 the preparation of imidazolidine dimers from the condensation of N-substituted ethylenodiamines with an excess of formaldehyde.[146] The new imidazolidine dimers were screened for antimicrobial activity and were positive for anti Gram-negative and Gram-positive bacterial.[146] The dimers also presented antifungal activy against *Aspergillus niger* and *Candida albicans*.[146] In 2013 the dimers were tested as antineoplasic agents against several cell lines according to the NCI assay and some examples were positive.[147] The same group reported in 2008 the anti-*Trypanosoma cruzi* activity of the imidazolidines.[148] Most of the active imidazolidines (IC_{50} in µM range) are prepared from the condensation of *N,N'*-4-chlorobenzylethylenodiamine and aromatic aldehydes. The free diamine has IC_{50} in the µM range and as such the release of free diamine in *T. cruzi* can be one of themechanism of action. Moreover QSAR studies revealed the most important factor for the activity to be lipophilicity, possibly due to the increase uptake of the imidazolidine.[148] Westcott and coworkers prepared aminals from phenylboronic esters and acids as antifungal[149,150], antibacterial[149,150] and antituberculosis agents[151]. Most of the aminals were prepared from the condensation of diamines with the corresponding acetylboronic acid/ester or formylboronic acid/ester in ether or dichloromethane. The product precepitates from the reaction mixture and can be easily recovered as pure product. Moreover in 2017 the group observed increased antimicrobial effect when the product was complexed with zinc, similar to the previous findings by Montazerozohori.

Anti-inflamatory and analgesic:



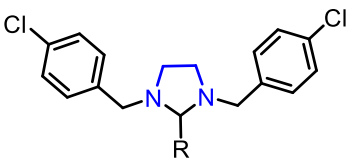
409 (R = NMe_2, NEt_2, OMe)

Antimicrobial and antineoplasic:



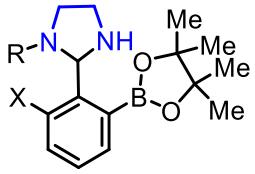
410

Anti-Trypanosoma cruzei:

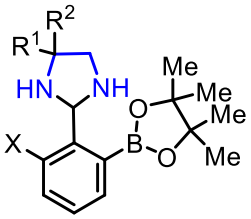


411 (R= Ph, 2-furyl, 4-OMePh, 3-OHPh, 2-OHPh, 3-ClPh)

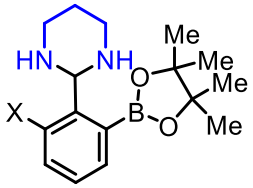
Antifungal and antimicrobial:



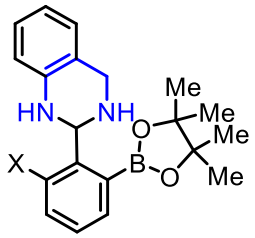
412 (R = Ph, $CH_2CH_2NH_2$; X = H, F)



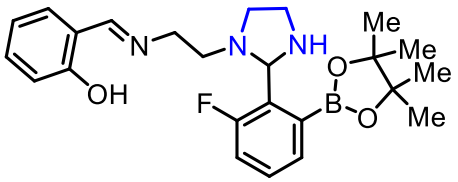
413: R_1 = H, R_2 = Me, X = H
414: R_1 = R_2 = H, X = F
415: R_1 = R_2 = Me, X = F



416: X = H
417: X = F



418: X = H
419. X = F



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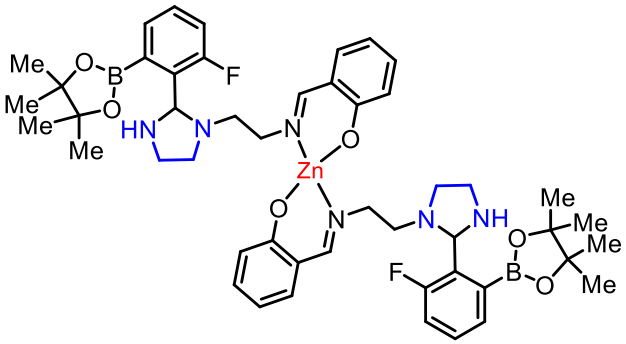
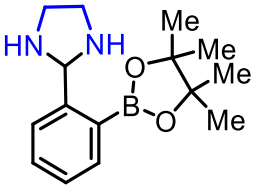


421

Antituberculosic:



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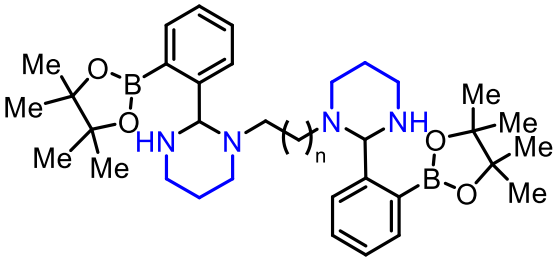
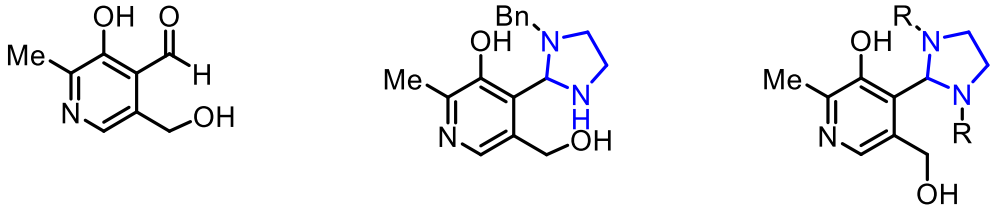


423: n = 1
424: n = 3

Scheme 80 Pharmacological properties of imidazolidines.

For this the authors formed the imine from salicylaldehyde with a free amine substituent on the imidazolidine and then reacted with diethylzinc.

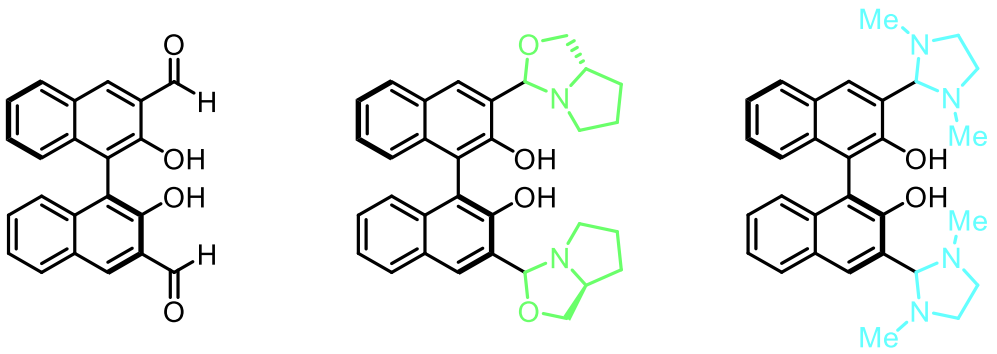
Pudovik and coworkers prepared several derivatives of vitamine B6 (pyridoxal). Amongst these derivatives, imidazolidines **425**, **426** and **427** were prepared from the condensation of pyridoxal and the corresponding diamines (**Scheme 81**).[152]



Vit B6 (pyridoxal) **425** **426:** R = Me
427: R = Bn

Scheme 81 Imidazolidine derivatives of vitamin B6 described by Pudovik and coworkers.

Pu and coworkers prepared a fluorescent off-on system based on imidazolidine/oxazolidine formation (**Scheme 82**). 2,2'-dihydroxy-[1,1'-binaphthalene]-3,3'-dicarbaldehyde (**428**) is the aldehyde derivative of 1,1'-bi-2-naphtol (BINOL), and shows no fluorescence. When treated with amino alcohols such as prolinol or *N,N'*-dimethyl-ethylenodiamine the conjugated aldehyde is transformed into unconjugated oxazolidine **429** or imidazolidine **430**, enhancing the product fluorescence. [153]



428 **429** **430**

Scheme 82 Fluorescent turn on system based on oxazolidine and imidazolidine described by Pu and coworkers.

Lim and coworkers encapsulated imidazolidines prepared from benzaldehyde in poly(lactic acid) fibers by electrospinning as a way to protect the food preservatives from oxidation and to reduce volatility. The release of the benzaldehyde could be acomplished by addition of 1N citric acid. [154]

One of the first publications on the synthesis of six-membered cyclic aminals goes back to 1913 by Branch and coworkers.[155] The condensation of 1,3-diaminopropane (monoacetate or monohydrochloride salts) and aqueous formaldehyde was described to

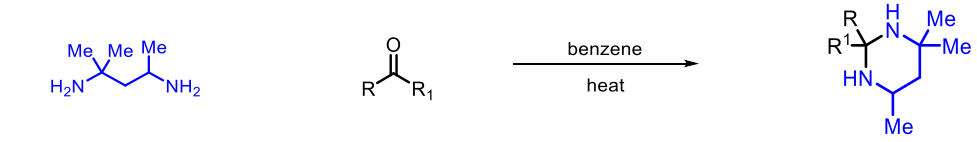
yield a mixture of salts - hexahydropyrimidine cyclic form and its open-chain tautomer methylene-1,3-diaminopropane – in which the open form predominates (Scheme 83). [155]

diamine salts formaldehyde hexahydropyrimidine form

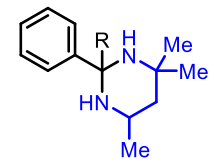
Scheme 83. Synthesis of hexahydropyrimidine salt forms from condensation of 1,3-diaminopropane salt forms and formaldehyde in water described by Branch and coworkers.

A derivative of 1,3-diaminopropane (2,4-diamino-4-methylpentane) was reported by Zimkin and coworkers to react easily and in good yields, with carbonyl compounds in benzene solution (Scheme 84). This method was applied to aldehydes boiling above 63 ºC, including benzaldehyde, 2-ethylhexanal and 2-ethyl-2-hexenal, to produce aminals **431**, **433** and **434** in good yields, with exception of aminal **434** (Scheme 84).

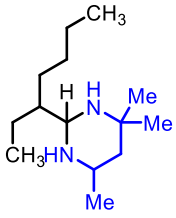
Several ketones (e.g. acetophenone, methyl isobutyl ketone, cyclohexanone and 3-methyl-3-butanol-2-one) were also suitable reagents producing aminals **432** and **435**-**437** in relative to good yields (Scheme 84). However, higher temperatures (> 125 ºC) were necessary to achieve conversion. [156]



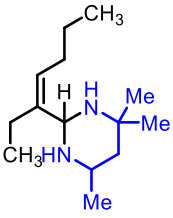
2,4-diamino-4-pentane



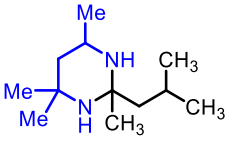
431: R = H, 81 %
432: R = -CH_3, 60 %



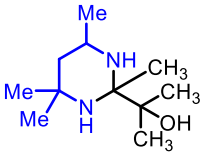
433, 91 %



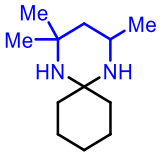
434, 22 %



435, quant.



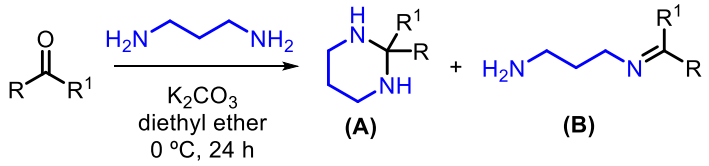
436, 84 %



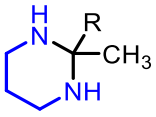
437, 58 %

Scheme 84. Scope of six-membered cyclic aminals from the condensation of 2,4-diamino-4-methylpentane and carbonyl compounds (aldehydes and ketones) in benzene solution described by Zimkin and coworkers.

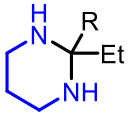
Alekseyev and co-workers studied the interaction of aliphatic and aromatic aldehydes and aliphatic ketones with 1,3-diaminopropane in diethyl ether at 0 ℃, in the presence of K_2CO_3 for 24 hours (Scheme 85). The authors also studied the ring-chain tautomerism usually observed in these types of structures. They concluded that derivatives of unbranched aliphatic aldehydes (e.g. **438**, **440** and **443**) exist only in hexahydropyrimidine form. The ring-chain tautomerism was observed in all the other compounds. For isobutyraldehyde (**445**) and ketone derivatives (**439**, **441**, **444**, **446**, **458** and **459**) was observed that the content of the linear tautomer increased with increasing size of substituents R and/or R^1. In the case of aromatic aldehydes (**447**-**457**), the presence of the hexahydropyrimidine form generally predominates, except in some cases where it is absent (**455**) or exists in lower proportion (**452**,**453** and **456**). Electron-withdrawing substituents stabilized the cyclic hexahydropyrimidine form as observed in compounds **448**-**450** (Scheme 85).[157]



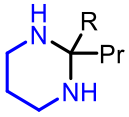
*Ratios of aminals **(A)**/open-chain tautomers **(B)** are given in parenthesis*



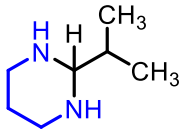
438: R = H, 60 % (100/0)
439: R = Me, 51 % (90/10)



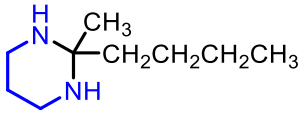
440: R = H, 59 % (100/0)
441: R = Me, 52 % (89/11 *Z*+*E*)
442: R = Et, 91 % (78/22 E)



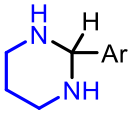
443: R = H, 63 % (100/0)
444: R = Me, 49 % (65/35 *Z*+*E*)



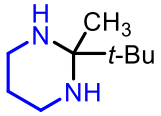
445, 55 % (95/5)



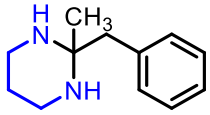
446: 60 % (61/39 *Z*+*E*)



447: -Ph, quant. (87/13)
448: 4-F Ph, quant. (89/11)
449: 4-Cl Ph, quant. (90/10)
450: 4-Br Ph, quant. (92/8)
451: 4-OCH_3 Ph, quant. (65/35)
452: 4-$N(CH_3)_2$ Ph, quant. (24/76)
453: 4-$N(CH_2CH_3)_2$ Ph, quant. (10/90)
454: 4-(CO_2CH_3) Ph, quant. (100/0)
455: 2-OH Ph, 95 % (0/100)
456: 3,4-OCH_3 Ph, quant. (28/72)
457: 2-Cl-6-NO_2 Ph, quant. (84/16)



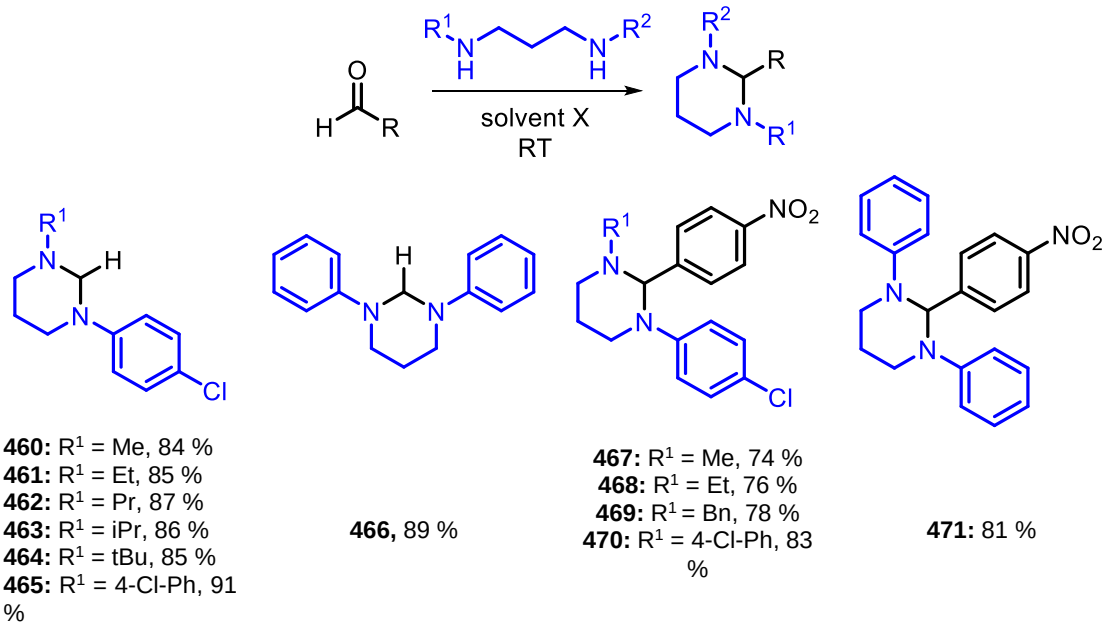
458: 45 % (20/22 *Z*+*E*)



459: 83 % (80/20 *E*)

Scheme 85. Synthesis of six-membered cyclic aminals described by Alekseyev and co-workers.

Orelli and co-workers reported the synthesis of *N*-arylhexahydropyrimidines (**460**-**471**) by condensation of *N*-aryl-*N'*-alkyl- (or *N'*-aryl)-1,3-propanediamines with aldehydes (Scheme 86). Reactions with formaldehyde proceeded in aqueous methanol towards formation of aminals **460**-**466**, while condensation with aromatic aldehydes required the use of anhydrous solvents –dichloromethane for aminals **467**-**469** or ethanol for aminals **470**-**471**.[96]



460: R^1 = Me, 84 %
461: R^1 = Et, 85 %
462: R^1 = Pr, 87 %
463: R^1 = iPr, 86 %
464: R^1 = tBu, 85 %
465: R^1 = 4-Cl-Ph, 91 %

466, 89 %

467: R^1 = Me, 74 %
468: R^1 = Et, 76 %
469: R^1 = Bn, 78 %
470: R^1 = 4-Cl-Ph, 83 %

471: 81 %

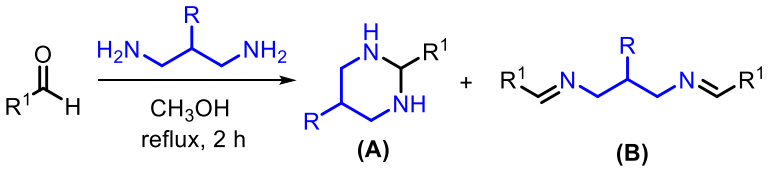
Scheme 86. Scope of N-arylhexahydropyrimidines from condensation of N-aryl-N'-alkyl-(or N'-aryl)-1,3-propanediamines with aldehydes described by Orelli and co-workers.

Crumbie and co-workers claimed that the condensation of 1,3-diamines with aldehydes (or ketones) leads to the formation of two products, the hexahydropyrimidine **(A)** and the bisimine **(B)** forms. This statement is comparable with the results observed by Alekseyev and co-workers where they identified the formation of monoimine open-chain tautomers.[157]

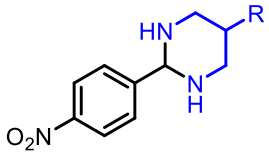
The reaction between a range of aromatic aldehydes and 1,3-diaminopropane or 1,3-diamino-2-propanol in refluxing methanolic solution for 2 hours was reported with formation of a scope of cyclic aminals and the corresponding bisimines (**472**-**488**) in relative to good yields (**Scheme 87**). [158]

Experimental results indicated that the hexahydropyrimidine formation is favored by less nucleophilic amines and by the presence of electron-withdrawing substituents on the

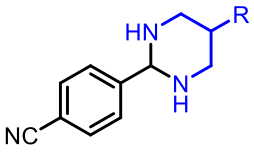
para-positions of the benzaldehyde ring as observed in compounds **450** and **472**-**477** (**Scheme 87**). Aminal **449** gave contradictory results, also comparing with previous results from Alekseyev and coworkers. DFT calculations (at HF/6-311G* level) indicated a stabilization of the LUMO (e.g. decrease of LUMO energy) and consequent increase of the hexahydropyrimidine proportion, corroborating the experimental results. [158]



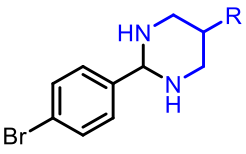
*Ratios of aminals **(A)**/open-chain tautomers **(B)** are given in parenthesis*



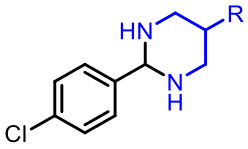
472: R = H, quant. (70/30)
473: R = OH, 87 % (80/7)



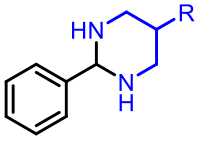
474: R = H, quant. (81/19)
475: R = OH, 83 % (75/8)



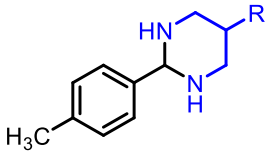
450: R = H, quant. (68/32)
476: R = OH, 79 % (69/10)



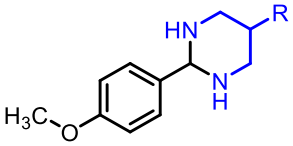
449: R = H, quant. (0/100)
477: R = OH, 78 % (57/21)



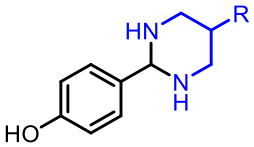
447: R = H, quant. (52/48)
478: R = OH, 80 % (70/10)



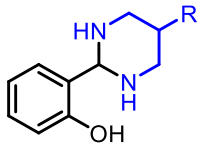
479: R = H, 59 % (11/48)
480: R = OH, 80 % (60/20)



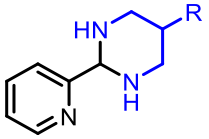
481: R = H, quant. (0/100)
482: R = OH, 70 % (38/32)



483: R = H, quant. (57/43)
484: R = OH, 54 % (46/8)



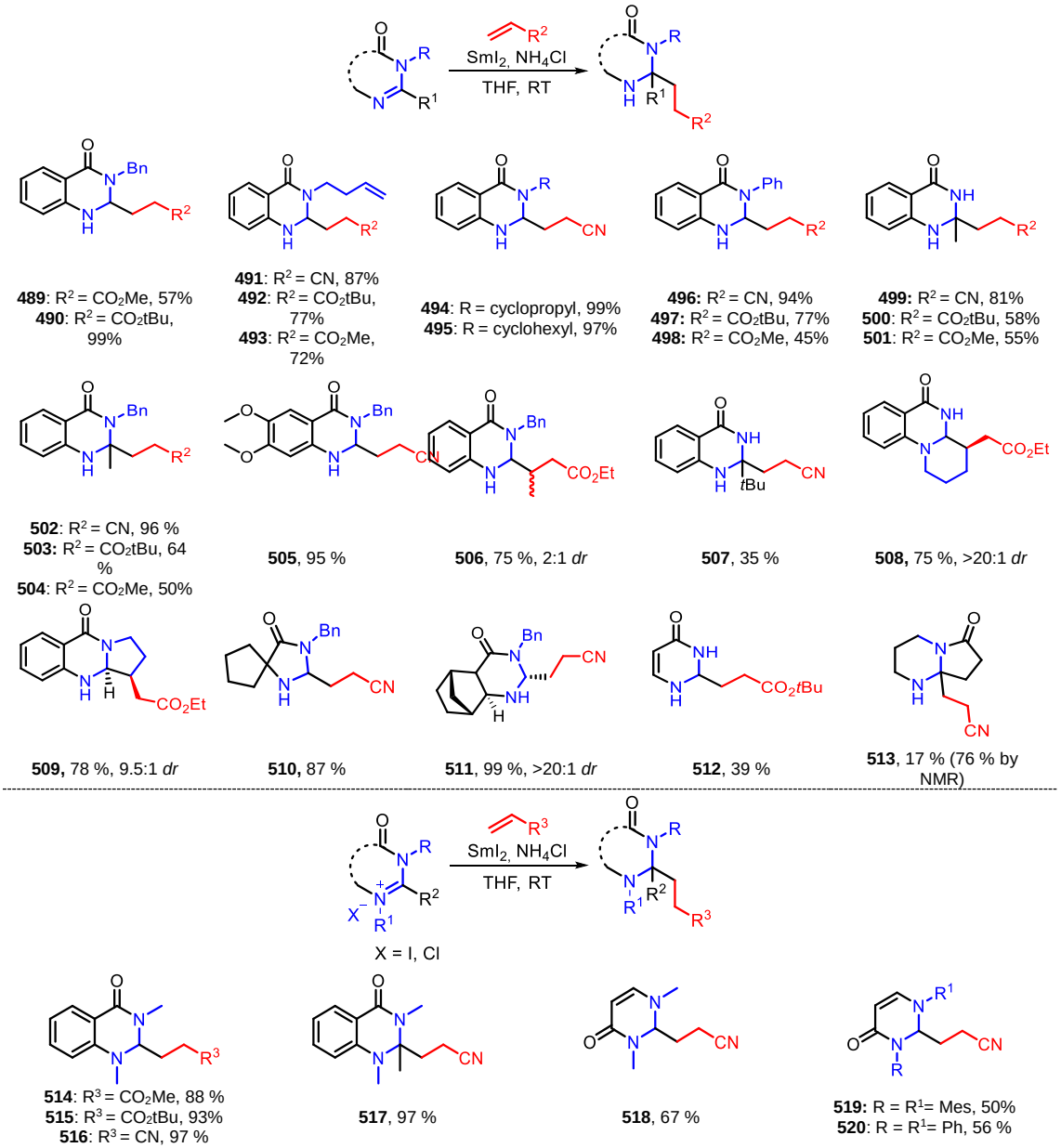
485: R = H, quant. (0/100)
486: R = OH, 65 % (0/100)



487: R = H, quant. (82/18)
488: R = OH, quant. (100/0)

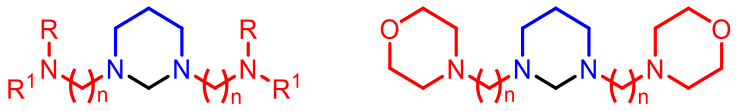
Scheme 87. Scope of hexahydropyrimidines from the condensation of aromatic aldehydes and 1,3-diaminopropane or 1,3-diamino-2-propanol in refluxing methanolic solution described by Crumbie and co-workers.

Schiedler and co-workers reported the synthesis of aminals through reduction of amidines and amidinium ions using SmI_2, producing a broad scope in relative to good yields (**Scheme 88**). The radical chemistry of aminals have been known in the literature, however this paper brought additional synthetic utility to these intermediates, being effective in both inter- and intramolecular contexts.[159]



Scheme 88. Scope of aminals synthesized from the reduction of amidines and amidinium ions using SmI_2 described by Schiedler and co-workers

The search for applications of hexahydopyrimidines in medicinal chemistry field started when Van Hook & Craig patented the synthesis of 1,3-bis(dialkylaminoalkyl)- **(I)** and 1,3-bis-(heterocyclicaminoalkyl)hexahydropyrimidines **(II)** (**Figure 25**) and their antifungal, antibiotic and antiviral properties. [160,161]

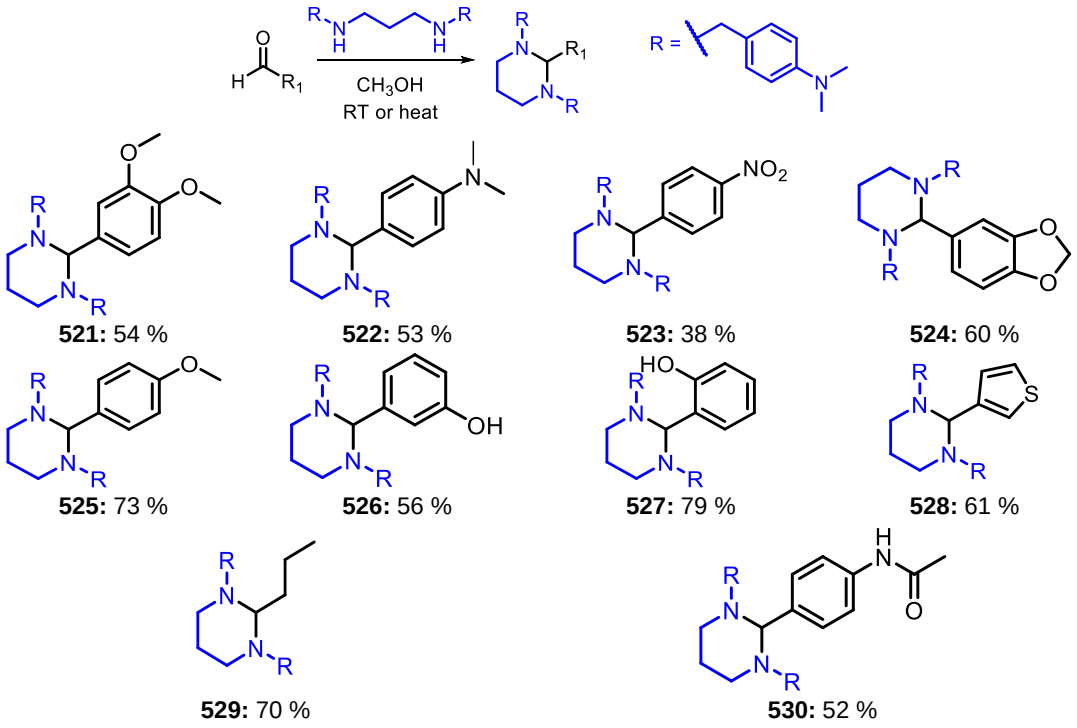


[I] **[II]**

Figure 25. 1,3-bis(dialkylaminoalkyl)- (I) and 1,3-bis-(heterocyclicaminoalkyl)hexahydropyrimidines (II) molecular structures.

Based on the previous work from Van Hook & Craig, Dormen and co-worker prepared a number of 2-substituted 1,3-bis(*p*-dimethylaminobenzyl)hexahydropyrimidines (**521**-**530**) in moderate to good yields (**Scheme 89**). Methanol was a convenient solvent and in general the reactions proceeded smoothly at room temperature or on heating at moderate temperatures.

Although compounds **521**-**530** where though to display similar pharmacological activity to compouns **[I]** and **[II]** (**Figure 25**), they failed to show any biological properties of significant interest. [160]

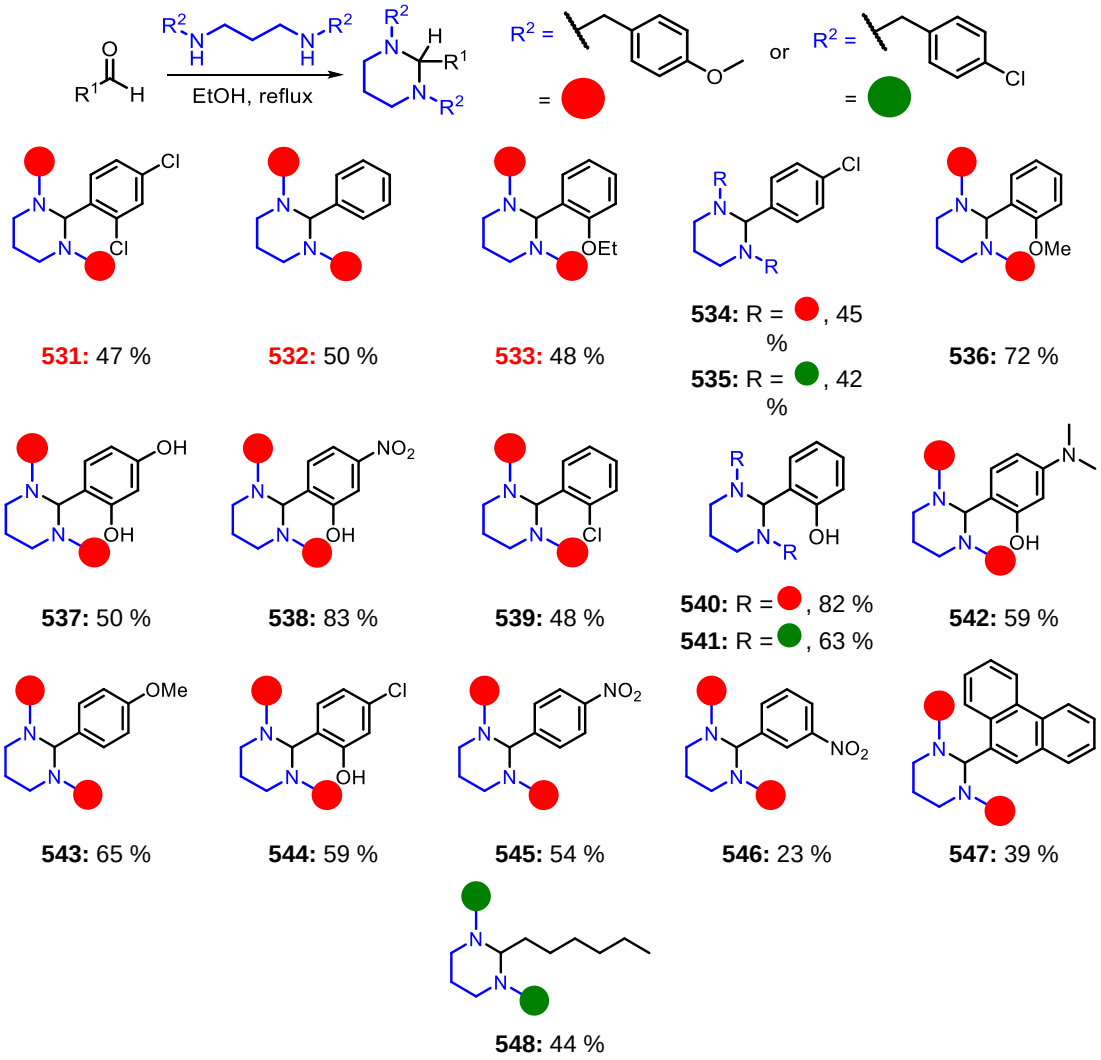


Scheme 89. Scope of six-membered cyclic aminals from the condensation of 1,3-bis(p-dimethylamino)propane and several aldehydes described by Dormen and co-worker.

The medicinal activity of six-membered cyclic aminals continued to be studied by Billman & Meisenheimer with the synthesis of 2-substituted 1,3-bis-(*p*-methoxybenzyl)hexahydropyridines (**531**-**534**, **536**-**540** and **542**-**547**) and 2-substituted 1,3-bis-(*p*-chlorobenzyl)hexahydropyridines (**535**, **541** and **548**) producing a diverse scope of compounds (**Scheme 90**).

Since hexahydropyrimidines can be hydrolyzed under mild acidic conditions to regenerate the aldehydes known to cause tumor regression, this class of compounds were thought to be effective transporting the aldehyde to a tumor site, behaving as a prodrug.

All the compounds were tested for antitumor activity *in vivo*, in rodent (e.g. Sarcoma 180, Carcinoma 755, Leukemia 1210), and *in vitro*, in tissue culture cell lines. They displayed no significant activity against any of the *in vivo* test systems. However, compounds **531**-**533** have given reproducible ED_{50} values below 4 mg/mL level in tissue culture cells, highlighted in red (**Scheme 90**). [162]



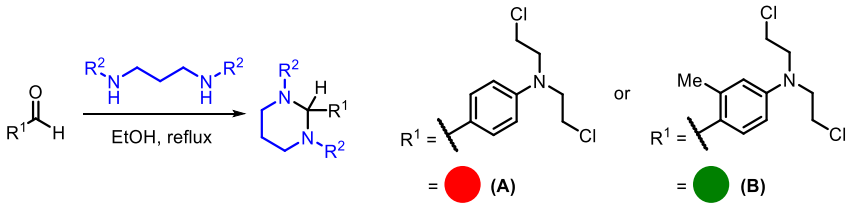
Scheme 90. Scope of 2-substituted 1,3-bis-(p-methoxybenzyl)hexahydropyridines and 2-substituted 1,3-bis-(p-chlorobenzyl)hexahydropyridines tested for antitumor activity (red – high relative inhibition) described by Billman & Meisenheimer.

In line with these results, the same authors prepared a serie of hexahydropyrimidines (**549**-**554**) derived from potent cytotoxic aldehydes - benzaldehyde nitrogen mustard **(A)** and *ortho*-tolualdehyde nitrogen mustard **(B)** (**Scheme 91**).

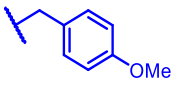
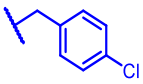
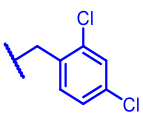
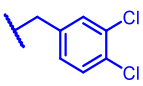
The compounds were tested *in vivo* using a Walker 256 carcinoma model. Hexahydropyrimidines derived from *ortho*-tolualdehyde nitrogen mustard (**550**, **552** and **554**) exhibited greater tumor inhibition than the related compounds derived from benzaldehyde nitrogen mustard (**549**, **551** and **553**). This indicated that the presence of electron-donating groups at the benzyl group were important to increase tumor inhibition. Compound **550** revealed 100 % tumor inhibition with no animal deaths at doses of 100 mg/Kg, while compound **549** only inhibited 93 % of the tumor (**Scheme 91**).

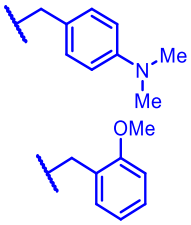
The introduction of electron-withdrawing groups (e.g. chlorine) at the benzylamine group decreased the potential of inhibition as observed in compounds **551**-**554** (**Scheme 91**). [163]

The degree of antitumor activity appeared to be related to the electron-donating ability of the substituents on the nitrogens of the hexahydropyrimidine ring. Therefore, two new hexahydropyrimidines **556**-**557** were prepared later, from *ortho*-tolualdehyde nitrogen mustard **(B)**, and tested for anticancer activity using the same *in vivo* model. Both exhibited good tumor growth inhibition at doses of 100 mg/Kg. Yet the introduction of a dimethylamine at the benzylamine group **556** displayed better tumor inhibition than the introduction of a methoxy group **557** (Scheme 91).[164]



Percentages of tumor inhibition are given in parenthesis

R^2:		
	**549,** 43 % *(93 %)*	**550,** 47 % *(100 %)*
	**551,** 39 %	**552,** 42 % *(71 %)*
	**553,** 82 %	**554,** 44 % *(22 %)*
		**555,** 58 %



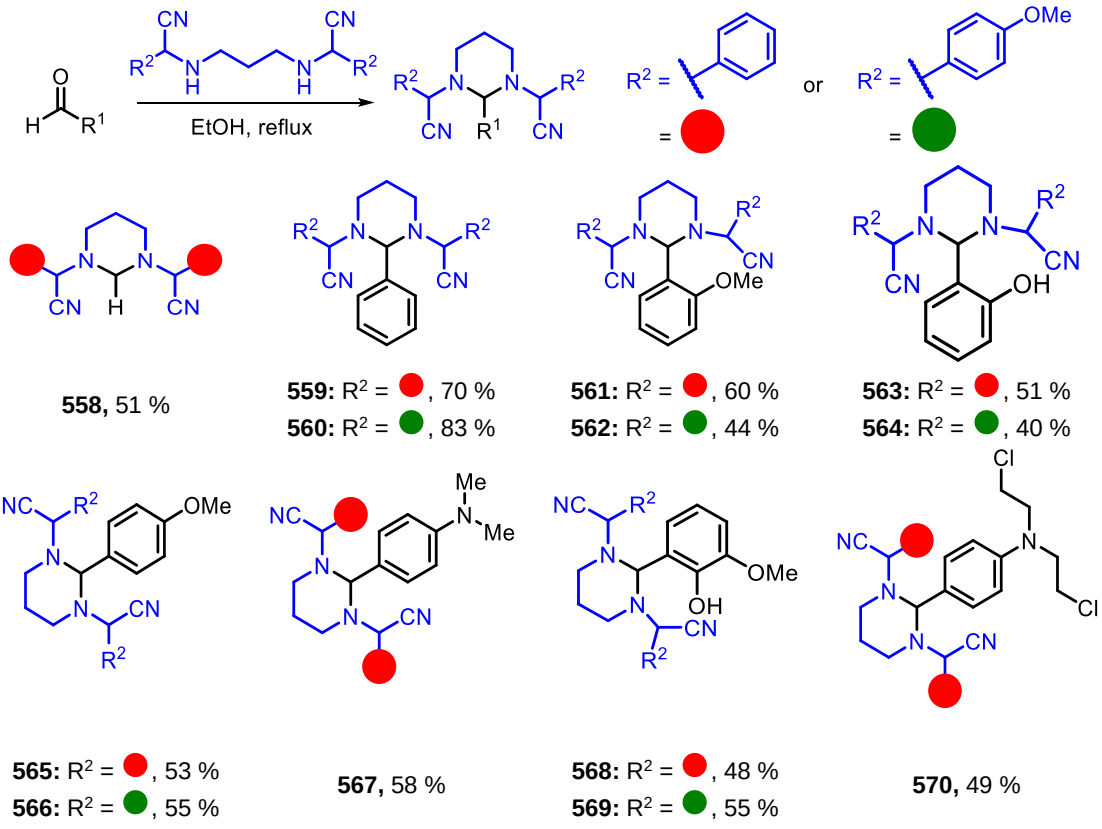
556, 32 % *(95 %)*

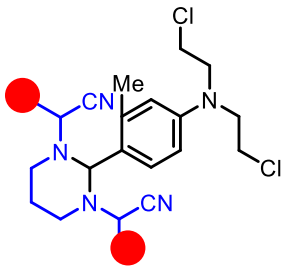
557, 30 % *(77 %)*

Scheme 91. Scope of hexahydropyrimidines derived from ortho-tolualdehyde and benzaldehyde nitrogen mustard and their relative antitumoral properties (green – low; yellow – medium; red - high).

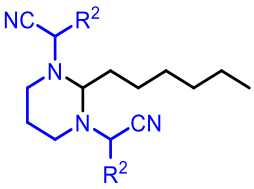
In 1965, Billman & Khan reported the synthesis of 2-substituted 1,3-bis-(cyanobenzyl)hexahydropyrimidines and 2-substituted 1,3-bis-(*α*-cyano-*p*-methoxybenzyl)hexahydropyrimidines (**558**-**573**). They were prepared through the condensation of aldehydes and the corresponding diamines in refluxing ethanolic solution, obtaining a diverse scope of aminals in relative to good yields (Scheme 92).

The compounds were screened for anticancer activity in mice in doses up to 200 mg/Kg for Walker 256, Sarcoma 180, Leukemia L1210 and Dunning ascites leukemia, displaying no significant tumor inhibition in these *in vivo* models. However, hexahydropyrimidine **558** showed an ED_{50} value of less than 4 μg/mL in KB human epidermoid carcinoma. [165]





571, 42 %

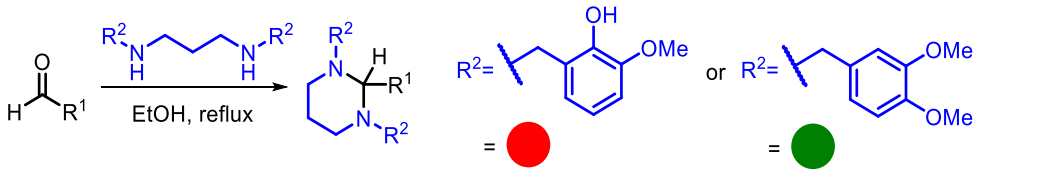


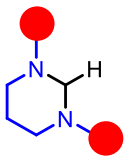
572: R^2 = ●, 47 %
573: R^2 = ●, 35 %

Scheme 92. Scope of hexahydropyrimidines derived from condensation of α-cynanobenzyldiamines or α-cynano-p-methoxybenzyldiamines and aldehydes described by Billman & Khan.

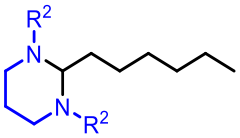
Billman & Khan reported the synthesis of 2-substituted 1,3-bis-(2-hydroxy-3-methoxybenzyl)hexahydropyrimidines and 2-substituted 1,3-bis-(3,4-dimethoxybenzyl)hexahydropyrimidines (**574**-**591**) under previously reported conditions, in relative to good yields (**Scheme 93**).

All the compounds were screened for antitumor activity at doses up to 500 mg/Kg *in vivo* and in cell culture tests. None were active against Walker 256, Sarcoma 180, lymphoid leukemia L1210, Lewis lung carcinoma, solid Friend virus leukemia, Dunning ascites leukemia and lymphosarcoma P1798 *in vivo* models. However, compound **589** has given an ED_{50} value of 3.7 μg/mL in a KB human epidermoid carcinoma cell culture test. [166]

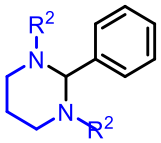




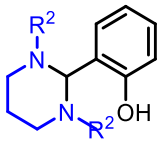
574, 99 %



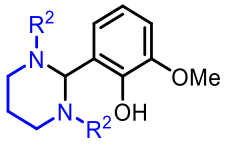
575: R = ●, 98 %
576: R = ●, 80 %



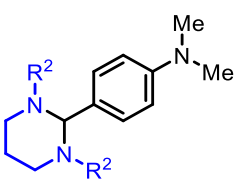
577: R = ●, 70 %
578: R = ●, 76 %



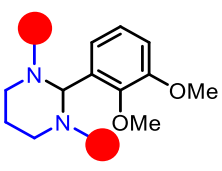
579: R = ●, quant.
580: R = ●, 78 %



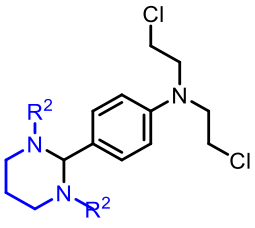
581: R = ●, 99 %
582: R = ●, 81 %



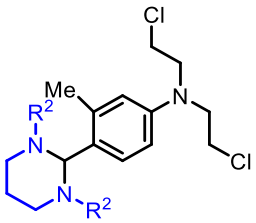
583: R = ●, 97 %
584: R = ●, 72 %



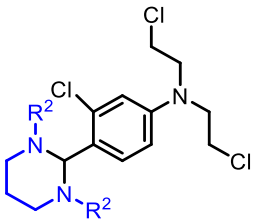
585, 91 %



586: R = ●, 80 %
587: R = ●, 83 %



588: R = 🔴, 90 %
589: R = 🟢, 83 %



590: R = 🔴, 83 %
591: R = 🟢, 86 %

Scheme 93. Scope of synthesized 2-substituted 1,3-bis-(2-hydroxy-3-methoxybenzyl)hexahydropyrimidines and 2-substituted 1,3-bis-(3,4-dimethoxybenzyl)hexahydropyrimidines described by Billman & Khan.

Later in 1968, Billman & Khan reported the synthesis of 2-substituted 1,3-bis-{4-[*N,N*-bis-(2-chloroethyl)amino]benzyl}hexahydropyrimidines and 2-substituted 1,3-bis-{2-methyl-4-[*N,N*-bis-(2-chloroethyl)amino]benzyl}hexahydropyrimidines) (**592**-**620**) in methanol at room temperature (**Scheme 94**). The reaction times vary from 3 to 18 hours depending on the aldehyde.

The introduction of the two nitrogen mustard moieties at the benzylamine group was thought to have similar antitumor activity has the aforementioned hexahydropyrimidines containing these groups from *ortho*-toluadehyde nitrogen mustard and benzaldehyde nitrogen mustard.

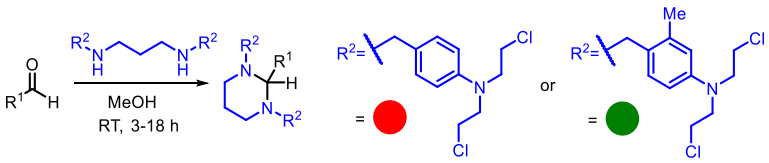
All the compounds were tested for antitumor activity in doses up to 200 mg/Kg/day in rats and in cell culture tests. The toxicity was also evaluated using a dose range of 3-100 mg/Kg in rats by intraperitoneal daily injection, for 5 days. Compounds **594**, **596**, **613**, **617**, **619** and **620** were toxic at dose level of 100 mg/Kg.

The hexahydropyrimidines presented in Scheme 94 displayed moderate activity against Walker 256 carcinoma *in vivo* model. All the compounds had given a reproducible ED_{50} values of 0.17-0.0047 mg/mL in a KB human epidermoid carcinoma *in vitro* cell culture, some of them reported in Scheme 94. [167]

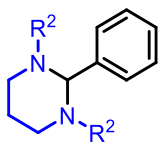
The compounds were submitted to cytotoxic studies in tissue culture and animal testing for antitumor activity. All of them have a moderate activity against Walker 256 carcinoma model. At a dose level of 50 mg/mL some hexahydropyrimidines exhibited good tumor inhibition – compound **593** (50 %), **612** (79 %), **614** (67 %) and **616** (84 %). Notably, compound **608** was able to inhibit the tumor for 86 % at dose level of 15 mg/mL (Scheme 94). [168]

Parrinello & Mülhaupt prepared six-membered cyclic aminals **621**-**627** from the condensation of equimolar proportions of *N*-substituted propane diamines and aldehydes in refluxing toluene (Scheme 95).

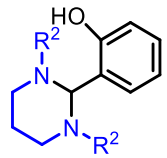
The authors investigated the reaction of these cyclic aminals with isocyanates. This transformation will allow the functionalization of isocyanates through urea linkages and introduce an imine function or a heterocycle, and could be useful for polymer functionalization and other applications[169]



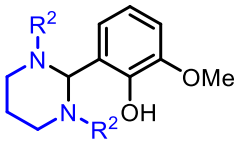
ED_{50} (mg/mL) or percentage of tumor inhibition values are given in parenthesis



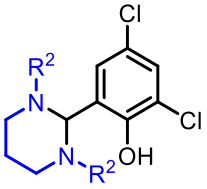
592: R = ●, 64 % *(0.17 mg/mL)*
593: R = ●, 70 % *(50 %)*



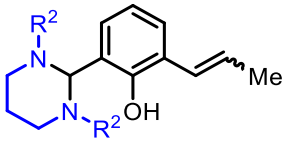
594: R = ●, 71 % *(1.5 mg/mL)*
595: R = ●, 60 %



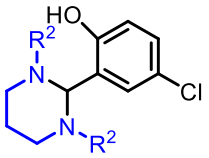
596: R = ●, 61 %
597: R = ●, 67 %



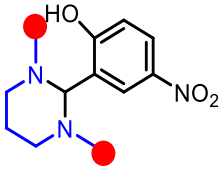
598: R = ●, 70 %
599: R = ●, 74 %



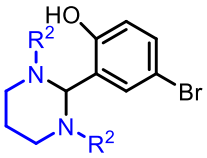
600: R = ●, 70 %
601: R = ●, 64 %



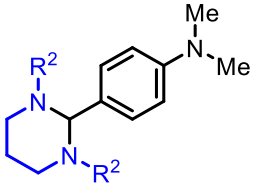
602: R = ●, 82 % *(0.0047 mg/mL)*
603: R = ●, 71 %



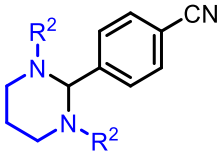
604: 73 % *(0.31 mg/mL)*



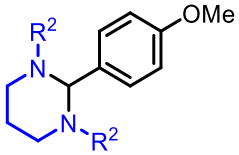
605: R = ●, 98 % *(0.03 mg/mL)*
606: R = ●, 72 %



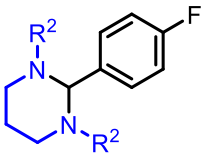
607: R = ●, 86 %
608: R = ●, 80 % *(80 %)*



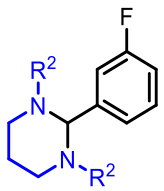
609: R = ●, 73 %
610: R = ●, 78 %

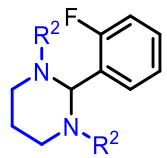


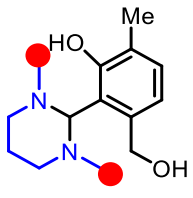
611: R = ●, 70 %
612: R = ●, 85 % *(79 %)*

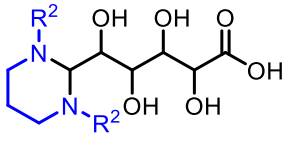


613: R = ●, 97 %
614: R = ●, 57 % *(67 %)*



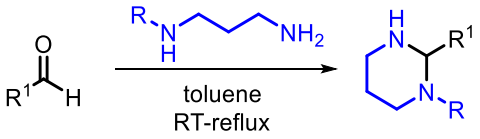


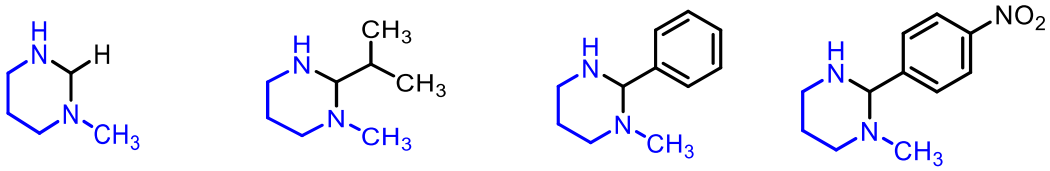




615: R = 🔴, 70 %
616: R = 🟢, 89 % *(84 %)*
617: R = 🔴, 81 %
618: R = 🟢, 60 %
619, 70 %
620, 94 %

Scheme 94. Synthesis of 2-substituted 1,3-bis-{4-[N,N-bis-(2-chloroethyl)amino]benzyl}hexahydropyrimidines and 2-substituted 1,3-bis-{2-methyl-4-[N,N-bis-(2-chloroethyl)amino]benzyl}hexahydropyrimidines in methanolic solution.





621 **622** **623** **624**

625 **626** **627**

Scheme 95. Synthesis of six-membered cyclic aminals **206-212** from N-substituted propane diamines and aldehydes in refluxing toluene.

Herrmann *et al.* studied the reversibility of the C-N bond of aminals in aqueous medium for the controlled release of volatile bioactive compounds (e.g. fragrances) by slow evaporation into the environment.

The condensation between *N,N'*-dibenzylpropane-1,3-diamine and benzaldehyde **(C)** was used as preliminary study for the evaluation of the reversibility of the reaction in dynamic mixtures of THF(D_8)/D_2O 3:1 or 2:1 (using a phosphate buffer at pH c.a. 8.5) through NMR experiments (**Scheme 96**).

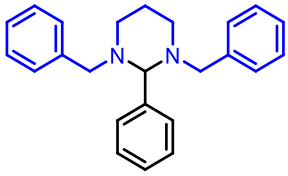
The evaporation of fragrance carbonyl compounds (Scheme 96) in the presence or absence of the diamine was evaluated by GC analysis. *N,N'*-dibenzyl diamines showed an efficient release profile, prolonging the duration of evaporation from surfaces such as

cotton. This indicated that the substituents at the *N*-atom influence the efficiency of the delivery system. Nevertheless, the size of the aminal heterocycle seemed to be less important.[170,171]

Bunz *et al.* described the use of distyrylbenzenes with appended-aldehydes for amine recognition in water. The amine-responsive properties were studied and it was observed the formation of imines or cyclic aminals depending on the employed amine.

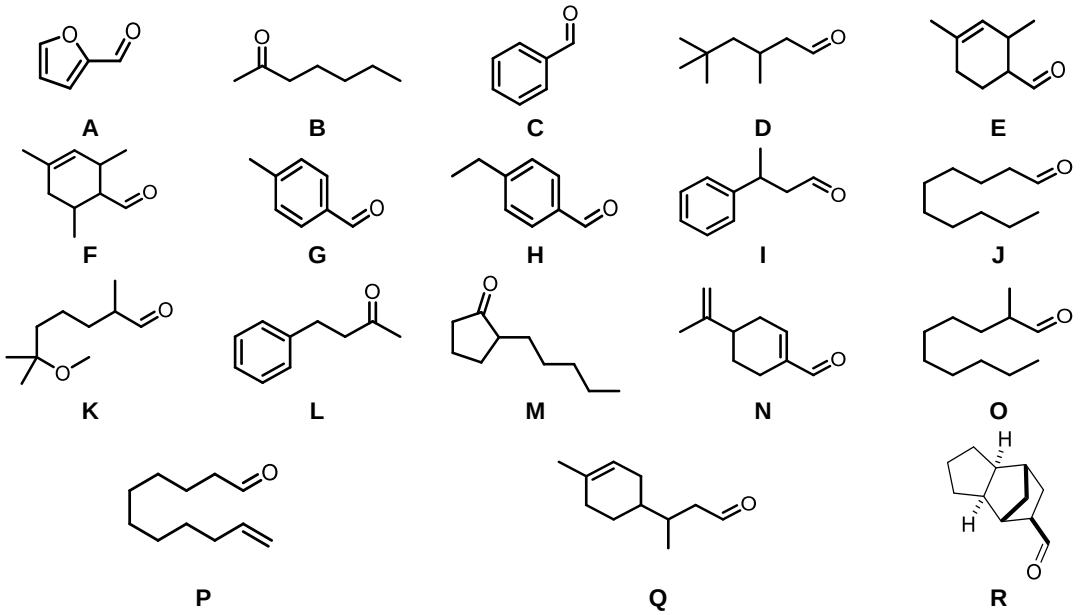
Changes in the color and fluorescence emission shifts of aqueous solutions of **(A)** and **(B)** were observed upon exposal of the aldehydes to the different amines.

N,N'-dibenzylpropane-1,3-diamine



Aminal

	Diamine/Aminal Ratio (%)		
THF(D_8)/D_2O	*Formation*	*Hydrolysis*	*Time (days)*
3:1	33/67	21/79	25
2:1	22/78	20/80	26



Scheme 96. Study of the C-N bond reversibility of 1,3-dibenzyl-2-phenylhexahydropyrimidine in dynamic mixtures of THF(D_8)/D_2O and volatile carbonyl compounds tested **(A-R)**.

With dialdehyde **(A)** it was possible to discern and identify different biogenic amines and aminoacids that can undergo aminal (e.g. arginine, lysine) and thioacetal (e.g. cysteine) formation. [172]

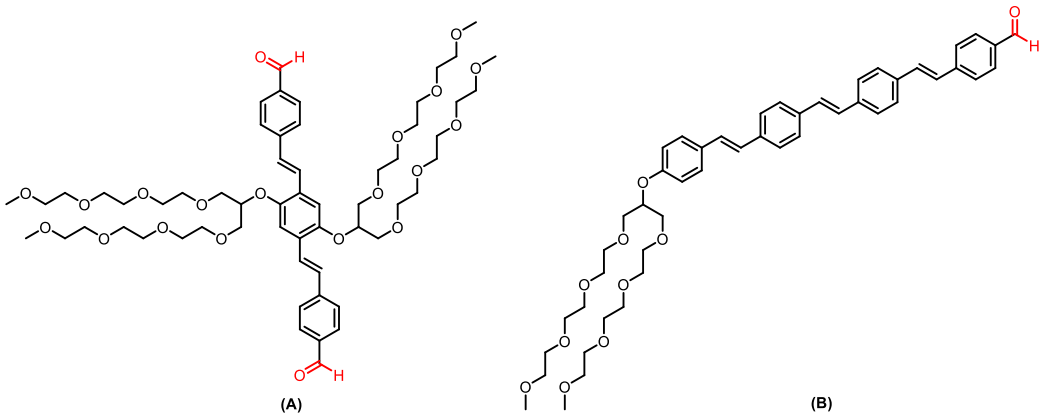
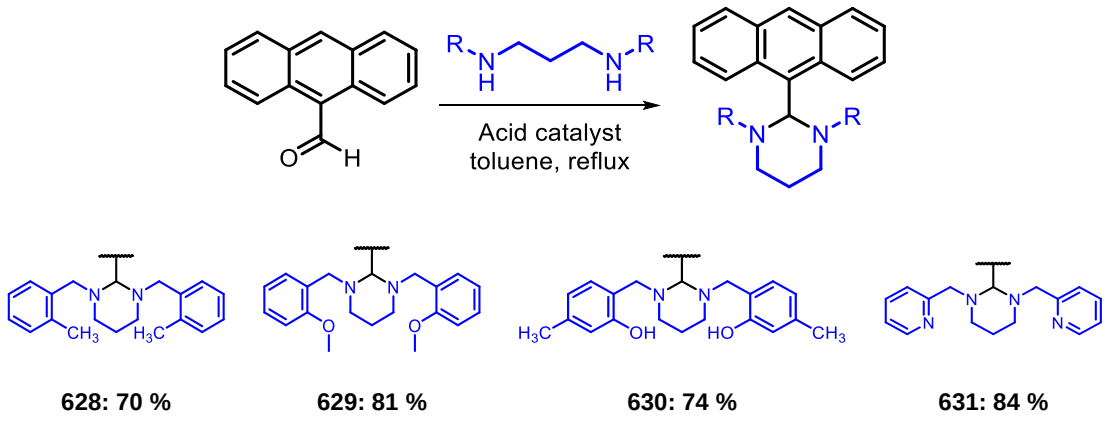


Figure 26. Aldehyde-substituted distyrylbenzenes **(A)** and **(B)**.

Tolpygin synthesized a serie of 2-(anthracen-9-aryl)-substituted hexahydropyrimidines through reaction of *N,N'*-bis[aryl(hetaryl)methyl]propane-1,3-diamines (**628**-**631**) with anthracene-9-carbaldehyde in the presence of an acid catalyst in refluxing toluene (Scheme 97).

The compounds showed chemosensor activity towards heavy metal cations, such as Cd^{2+}, Cu^{2+} and Hg^{2+}. [173]



628: 70 % **629: 81 %** **630: 74 %** **631: 84 %**

Scheme 97. Scope of N,N'-bis[aryl(hetaryl)methyl]propane-1,3-diamines (213-216) with chemosensor activity.

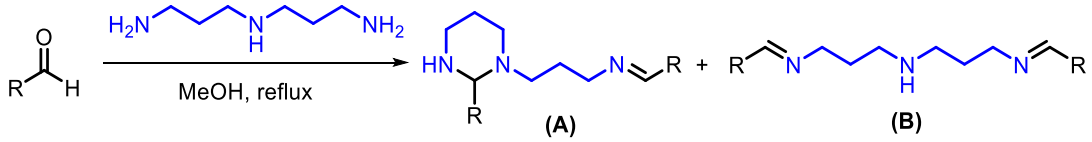
Briand *et al.* described the use of aromatic aldehydes for the regiospecific protection of primary amines in the polyamine norspermidine (**Scheme 98**). This reaction proceeded under mild conditions, in methanol at room temperature, in high yields to form mixtures of aminal and open-chain tautomer (**632**-**638**).

The interesting application of this reaction relies on its utility for imine protection of primary amine groups in polyamines and the further development in their synthesis and applications. [174]

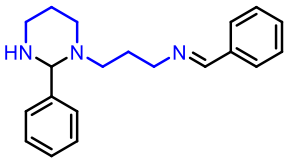
Windisch *et al.* identified a hit compound containing a hexahydropyrimidine core, for the development of novel anti-hepatitis C virus (HCV) agents. This compound **639** was selected from high throughput screening results using a cell culture derived HCV system, exhibiting an EC_{50} value of 4.3 μM.

To explore the structure-activity relationship (SAR), a serie of hexahydropyrimidines (**639**-**658**) were synthesized, from the condensation of 1,3-propanediamines and aldehydes, in refluxing water (Scheme 99).

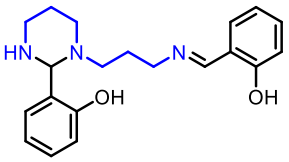
During the cell-based SAR study, the conversion of the cyclic hexahydropyrimidine into a linear diamine was observed. The diamine was identified as the active component, inhibiting HCV with similar antiviral activity to the hexahydropyrimidine compound.



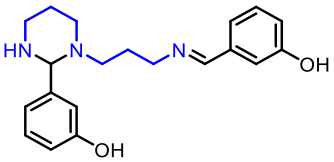
*Ratios of aminals **(A)**/open-chain tautomers **(B)** are given in parenthesis*



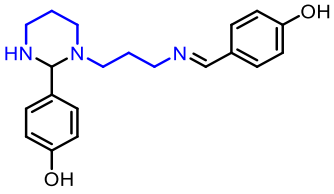
632: quant. (59/41)



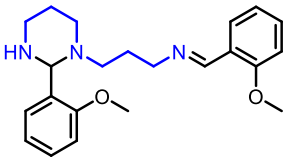
633: quant. (5/95)



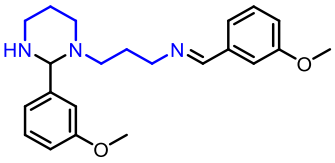
634: quant. (55/45)



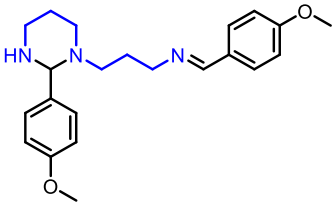
635: 0 % (quinoid structure)



636: quant. (57/43)



637: quant. (74/26)



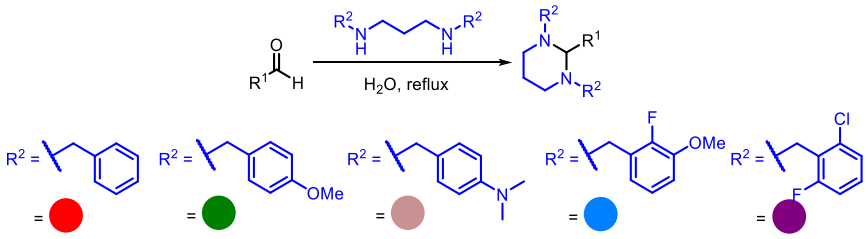
638: quant. (55/45)

Scheme 98. Scope of products (aminal/bisimine mixtures) from the condensation of norsperdimine and aromatic aldehydes.

For the diamine to be potent is required to have more than two carbon units between two nitrogen atoms and to be a basic diamine with sp3-hybridized nitrogen. [175]

Beaudry *et al.* demonstrated that aminal radical intermediates may be generated via radical translocation, using AIBN and a stoichiometric hydrogen atom donor (Scheme 100).

Carbon-carbon bond formation was observed after addition of these radicals to electron-poor alkenes in high yields, producing a large scope of compounds with six-membered ring aminal (**659**-**677** and **680**) or with five-membered ring aminal (**678**, **679**, **681** and **682**) cores (Scheme 100). Exploring this reactivity can lead to the production of fully substituted aminal stereocenters and formation of carbon quaternary stereocenters. [159]



EC_{50} values (μM) are given in parenthesis

639: R^1 = 4-Py, (4.5)

640: R^1 = 4-NMe2-Ph, 63 % *(25)*

641: R^1 = 3-CF_3-Ph, 54 % *(6.5)*

642: R^1 = 5-Me furane, 15 % *(>50)*

643: R^1 = Me, 36 % *(3.7)*

644: R^1 = H, 45 % *(>50)*

645: R^1 = ketone, 42 % *(>50)*

646: R^1 = 4-Py, 56 % *(1.5)*

647: R^1 = 4-CF_3-Ph, 30 % *(1.6)*

648: R^1 = 3-CF_3-Ph, 12 % (3.2)
649: R^1 = 4-CN-Ph, 33 % (1.5)
650: R^1 = 4-F-Ph, 14 % (1.9)
651: R^1 = 3-F-4-CN-Ph, 49 % (1.9)
652: R^1 = 4-Me_2N-Ph, 56 % (1.3)

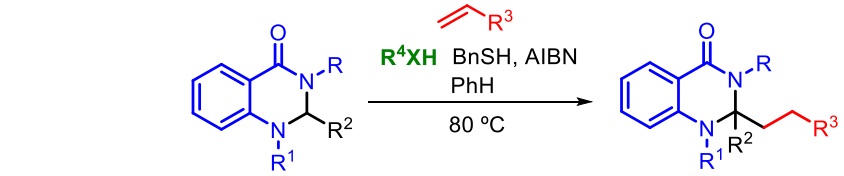
653: R^1 = 4-Py, 31 % (0.83)
654: R^1 = 4-F-Ph, 45 % (1.3)
655: R^1 = 4-CF_3-Ph, 24 % (1.5)

656: R^1 = 4-Py, (2.7)
657: R^1 = 4-CF_3-Ph, (11)

658: R^1 = 3-CF_3-Ph, (11)

Scheme 99. Scope of hexahydropyrimidines synthesized based on the hit compound obtained from high throughput screening.

Lin Pu *et al.* observed that 1,3-diaminopropane enhanced the fluorescence of 1,1'-bi-naphthol-based aldehydes after reaction in methanol. A six-membered ring aminal was formed as the major product **683** (Scheme 101). Other primary (e.g. butan-1-amine, 2-methylpropan-2-amine, cyclohexanamine, benzylamine), secondary (e.g. diethylamine) and tertiary (e.g. triethylamine) amines were tested, as well as primary diamines with different chain sizes (e.g. 1,2-diaminoethane, 1,4-diaminobutane, 1,5-diaminopentane). However, these monoamines and diamines caused much smaller fluorescent response under the same conditions.



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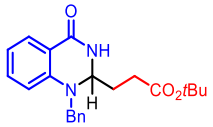
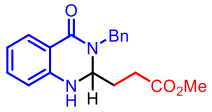
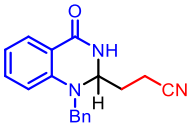


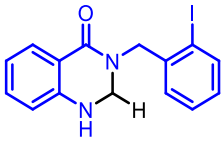
659: Bu_3SnH, 65 %
$(TMS)_3SiH$, 22 %

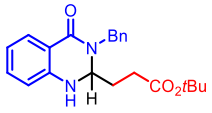


660: Bu_3SnH, 73 %
$(TMS)_3SiH$, 75 %

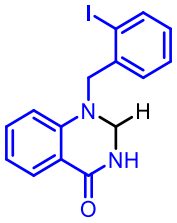


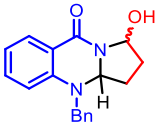
661: Bu_3SnH, 79 %
$(TMS)_3SiH$, 56 %



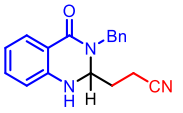


662: Bu_3SnH, 67 %
$(TMS)_3SiH$, 44 %

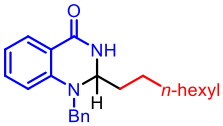




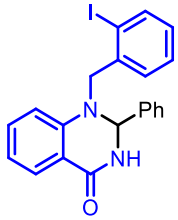
663:Bu_3SnH, 57%,1:1dr
$(TMS)_3SiH$, 20 %, 1:1 *dr*

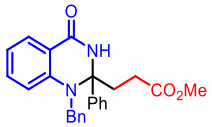


664: Bu_3SnH, 72 %
$(TMS)_3SiH$, 25 %

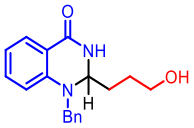


665: Bu_3SnH, **0 %**

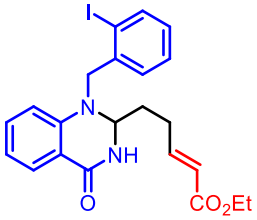


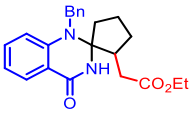


666: Bu_3SnH, 0 %

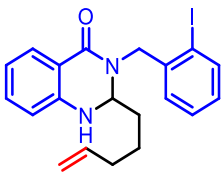


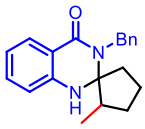
667: Bu_3SnH, 0 %





668: Bu_3SnH, **0 %**

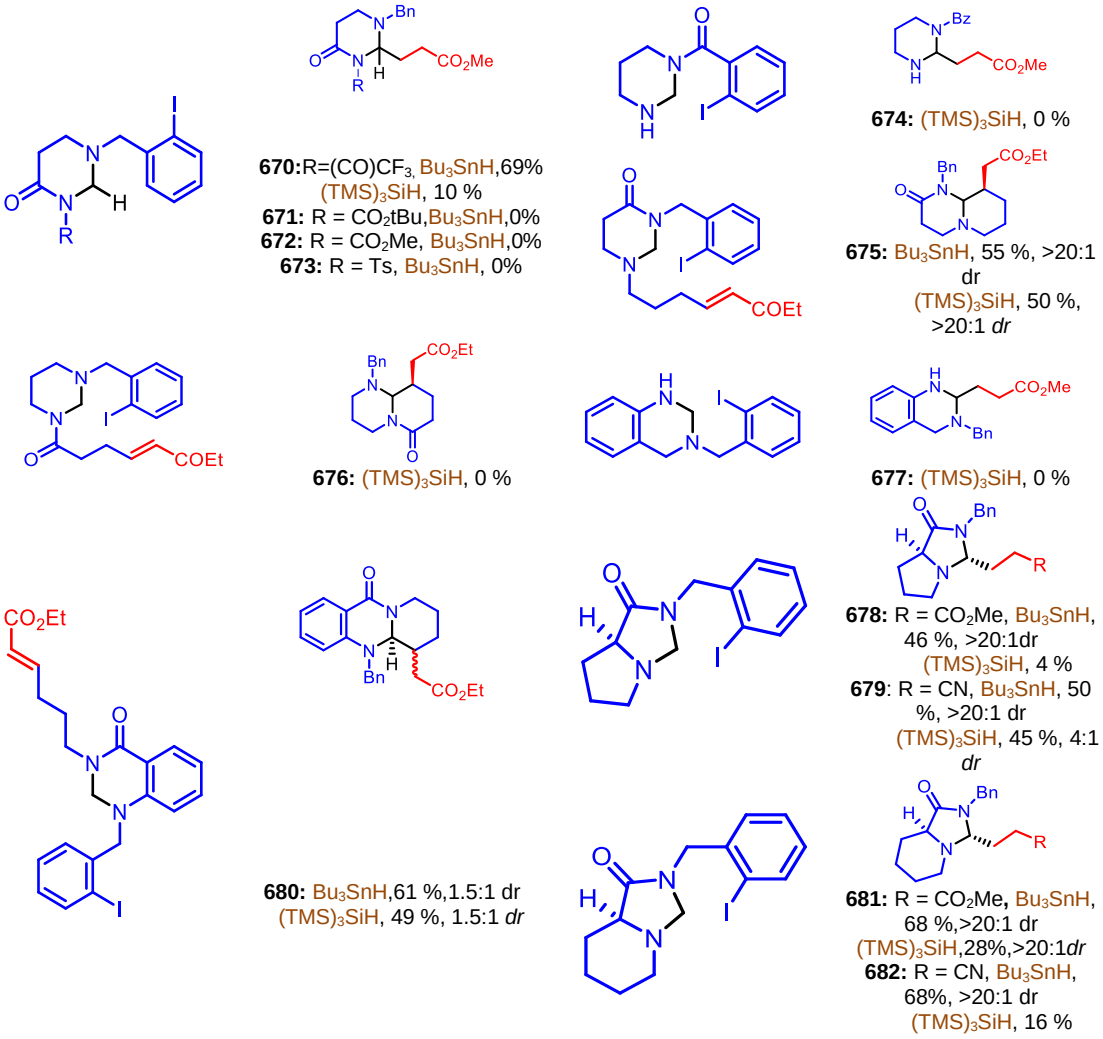




669: $(TMS)_3SiH$, 0 %

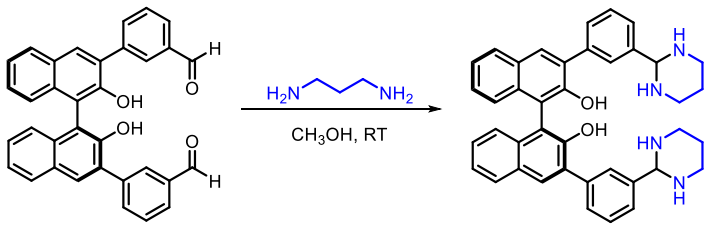
Additional scopes

Substrate *Product* *Substrate* *Product*



Scheme 100. Substrate scope and radical acceptor examination of the radical translocation method using AIBN.

These molecules act as highly selective fluorescent probes for the recognitions of 1,3-diaminopropane and could be useful for the study of the biological functions of polyamines. [176]



683

Scheme 101. Reaction conditions for the condensation of 1,1'-bi-2-naphtol (BINOL)-based aldehydes with 1,3-diaminopropane to form aminal **268**.

IV.3. Results and discussion

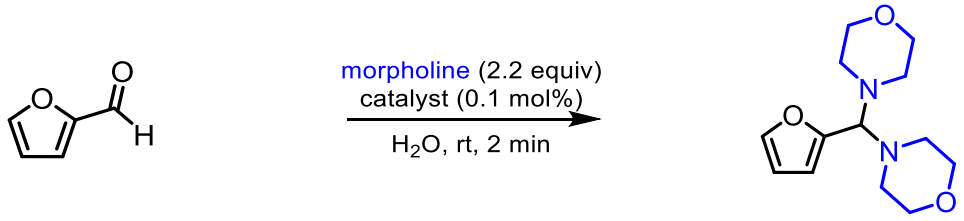
This work was performed in collaboration with Juliana Pereira and João António.

IV.3.1. Preparation of aminals promoted by Cu(II)

We aimed at the development of a methodology to prepare aminals under mild conditions that would not cause decomposition in furan aldehydes. As such we started this work by reacting furfural with morpholine to prepare aminal **684**. Wilhelm and coworkers reported the formation of aminals in water although in long reaction times and in some cases high temperature.[101] We initiated a screening of bronsted and Lewis acids (**Table 24**) in water. In the absence of a catalyst no conversion of the aldehyde was observed (**Table 24**, Entry 1) after 2 minutes. Due to the unstable nature of furfural most Lewis acids lead to the formation of insoluble black tars with total consumption of the aldehyde (**Table 24**, Entries 2-5). Moreover is described in Chapter II that furfural in the presence of secondary amines may undergo rearrangement to CP, and indeed we observe formation of CP as a side product. When trifluoromethanosulphonic acid (TfOH) was used we observe formation of 81% aminal, but also formation of side products such as CP (**Table 24**, Entry 6). Surprisingly the reaction in the presence of $Cu(OTf)_2$ afforded the aminal **684** in quantitative analytical yield after 2 minutes (**Table 24**, Entry 7). If the reaction was allowed to stir further 8h, no aminal was detected, only the corresponding CP (**Table 24**, Entry 8). The fact that other copper salts did not afford the aminal but instead lead to decomposition highlight the importance of the triflate anion. The reaction was quite robust to variations of concentration, with no loss of yield from 0.1 to 4 M concentration. The reaction using $Cu(OTf)_2$ was scaled up to 10 g, affording 25.5 g (96%) of the corresponding aminal **684** which precipitates directly from the reaction media. Acetonitrile can be an organic alternative to water with the disadvantage that the product does not precipitate from the reaction media. Instead, addition of water cause the precipitation to occur (**Table 24**, Entry 9).

With the optimized conditions in hands, the substrate scope was explored by using different aromatic aldehydes and amines. The reaction was equally efficient in the presence of electron poor and electron rich aromatic aldehydes (**692-703, Scheme 102**). Heteroaromatic aldehydes such as furfural and HMF derivatives also afforded the desired aminal product (**685**-**688**, **Scheme 102**). When using HMF no side products such as the homo-acetals were detected. Also there was no deprotection of the silyl group neither hydrolysis of the acetyl ester (**687-688**, **Scheme 102**).

Table 24 Reaction optimization for the formation of aminal **684**[a]



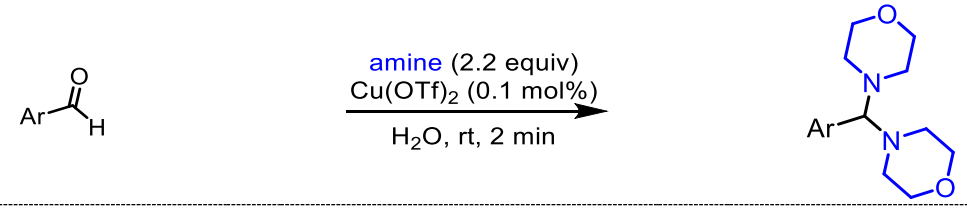
furfural **684**

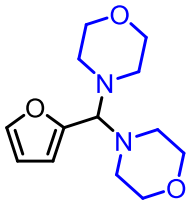
Entry	Cat (0.1 mol%)	**684** (%)[b]	Conversion (%)[b]
1	none	0	0
2	$FeCl_3 \cdot 6H_2O$	0	100
3	$CuSO_4 \cdot 5H_2O$	0	100
4	$CuCl_2 \cdot 2H_2O$	0	81
5	$Dy(OTf)_3$	0	90
6	TfOH	81	92
7	$Cu(OTf)_2$	Quant (96) [c]	100
8[d]	$Cu(OTf)_2$	0	100
9[e]	$Cu(OTf)_2$	97	100

[a] Reaction conditions: furfural (0.1 mmol), morpholine (0.22 mmol, 2 equiv), cat (0.1 mol%), H_2O (0.1 mL). The reaction was stirred for 2 min and extracted with ethyl acetate. [b] Yields determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield, 10 g scale. [d] Reaction time is 8h, formation of cyclopentenone. [e] Acetonitrile was used as solvent.

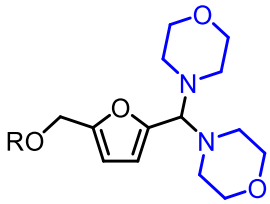
Reaction with a dialdehyde such as terephtaldehyde afforded the mono aminal **702** in 90% yield. The scope of amines (**704-712, Scheme 102**) included cyclic amines such as morpholine, piperidine, methylpiperazine and pyrrolidine , *N*-methyl-aminoaniline and diamines. The scope also included aminoalcohols to form *N,O*-acetals of benzaldehyde and HMF. The reaction was not impaired by carboxylic acid and proceeded smoothly to afford aminal **701**.

In conclusion, is described a mild procedure to prepare aminals under aqueous conditions. Catalytic amounts of $Cu(OTf)_2$ promote the reaction at room temperature in only 2 minutes. The scope of the reaction included several benzaldehyde derivatives with electron donating and electron withdrawing groups. Also acid sensitive molecules such as furfural and HMF, both highly important biomass derived building blocks that are known to form side products such as levulinic acid and humins under acidic conditions were included in the scope.

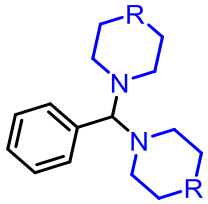




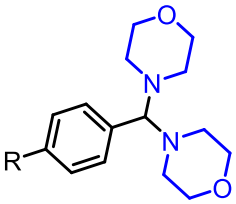
685, quant



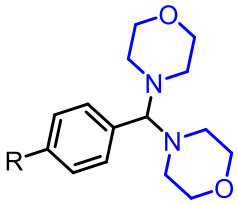
686: R = H, quant
687: R = Ac, quant
688: R = TBS, quant



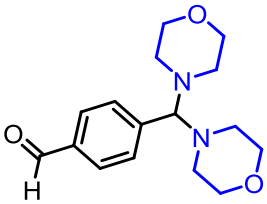
689: R = O, quant
690: R = CH_2, quant
691: R = NMe, quant



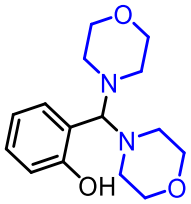
692: R = Me, quant
693: R = OMe, quant
694: R = OH, quant



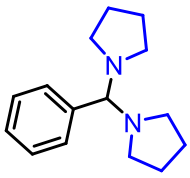
695: R = F, quant
696: R = Cl, quant
697: R = Br, quant
698: R = CF_3, quant
699: R = NO_2, quant
700: R = CN, quant
701: R = CO_2H, quant



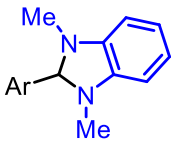
702, 90%



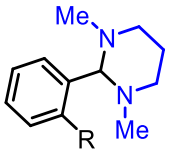
703, quant



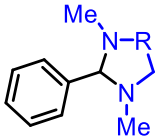
704, quant



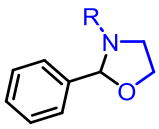
705: Ar = Ph, quant
706: Ar = HMF, quant



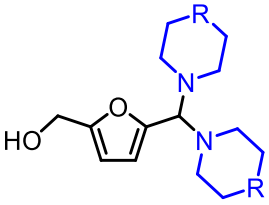
707: R = OH, quant
708: R = $B(OH)_2$, quant



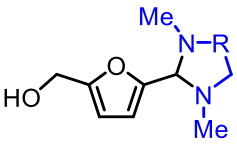
709: R = CH_2, quant
710: R= C_2H_4, quant



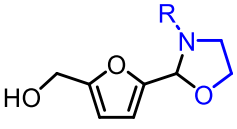
711: R = Pr, quant
712: R = Ph, quant



713: R = CH_2, quant
714: R = NMe, quant



715: R = CH_2, quant
716: R= C_2H_4, quant



717: R = Pr, quant
718: R = Ph, quant

Scheme 102 Amine and aldehyde scope for aminal formation

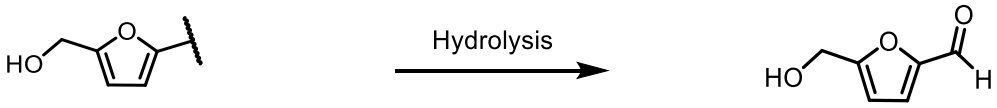
IV.3.2. Aminals as protection group

As depicted in the rational and goals for this chapter we aimed at the development of aminals as a new protection group. To this goal we performed stability assays. The assays were performed by quantitative ^{1}H-NMR in D_2O using sodium acetate as internal standard using different aminals derived from HMF. The first stability test was performed at pH 7 (**Figure 27**, A), and we observed that the aminal **686** prepared from morpholine, **717** prepared from aminoalcohol and imidazolidine **715** reverted to the aldehyde in the first minutes. The hexahydropyrimidine **716** reverted to 60 % aldehyde in 10 hours. The aminal prepared from *N,N*-dimethyl-α-aminoaniline **706** did not revert to the aldehyde even after 25h.

We studied the stability of **716** at higher pH (Figure 2, B) and observed that at pH 8 the equilibrium is reached at 40% aldehyde after 20h and at pH 9 at 18% after 10h. The aminal **706** remained stable under acidic conditions at pH 4.5 and basic conditions at pH 9 and pH 12 (**Figure 27**, B).

Ideally a protection group should be selectively deprotected under mild conditions. We observe that aminal **706** is the most stable amongst the studied aminals and *N,O*-acetals. Unfortunately hydrolysis of **706** under acidic conditions (pTSA or HCl aq) was not successful. As such we moved our focus to aminal **716** that although not as stable as **706** was stable enough to be used as protection group. Both pTSA and acetic acid were able to hydrolize **716** to the free aldehyde (**Figure 28**, A).

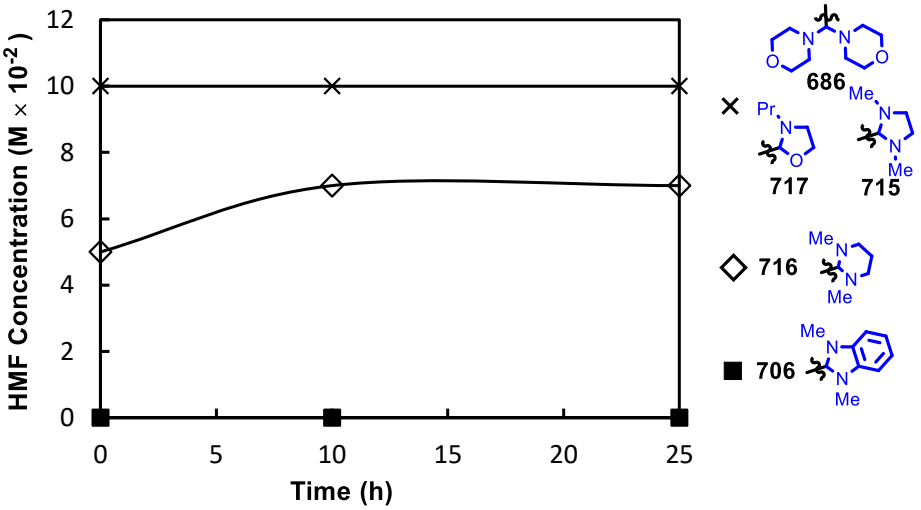
Using the chosen HMF aminal **716** we assessed the robustness of this protecting group under 1) reduction conditions; 2) amidation conditions; 3) presence of strong nucleophile; 4) oxidative conditions (**Figure 28**, B). The reduction of 4-nitrobenzaldehyde by $NaBH_4$ was not impaired by the presence of **716**, affording the corresponding 4-nitrobenzylic alcohol in 91% isolated yield. As such we can use the aminal as protection group under reductive conditions. Only when large excess of $NaBH_4$ was used, a side product formed by the reduction of **716** was detected. Addition of a Grignard such as PhMgBr to benzaldehyde afforded the corresponding alcohol in 70% isolated yield. No side products of the addition of the nucleophile to the aminal or the corresponding HMF aldehyde were detected. Acetals have been used to protect aldehydes during amidations with primary amines.[177,178] We observed that benzoic acid underwent Steglich coupling with pentylamine successfully in the presence of **716**. The corresponding HMF imine was not detected. The amide was obtained in 47 % isolated yield.



686, **717**, **715**, **716**, **706** (C = 0.10 M)

HMF

A. Stability at pH 7



B. Stability at pH 4.5, 8, 9 and 12 for aminal **716** *and* **706**

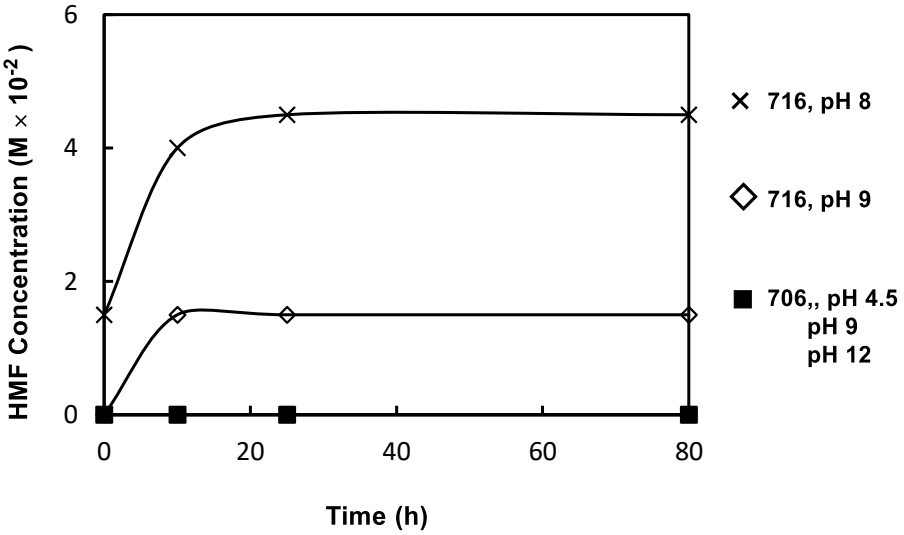
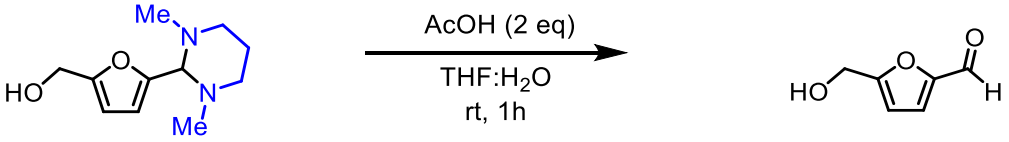


Figure 27 Stability assays for the hydrolysis of HMF aminals in D_2O. Starting concentration is 0.1 M; A. represents the formation of HMF at pH 7 for aminals **686, 706, 715, 716** and**717**; B represents the formation of HMF at pH 8 and 9 for aminal **716** and at pH 4.5, 9 and 12 for aminal **706**

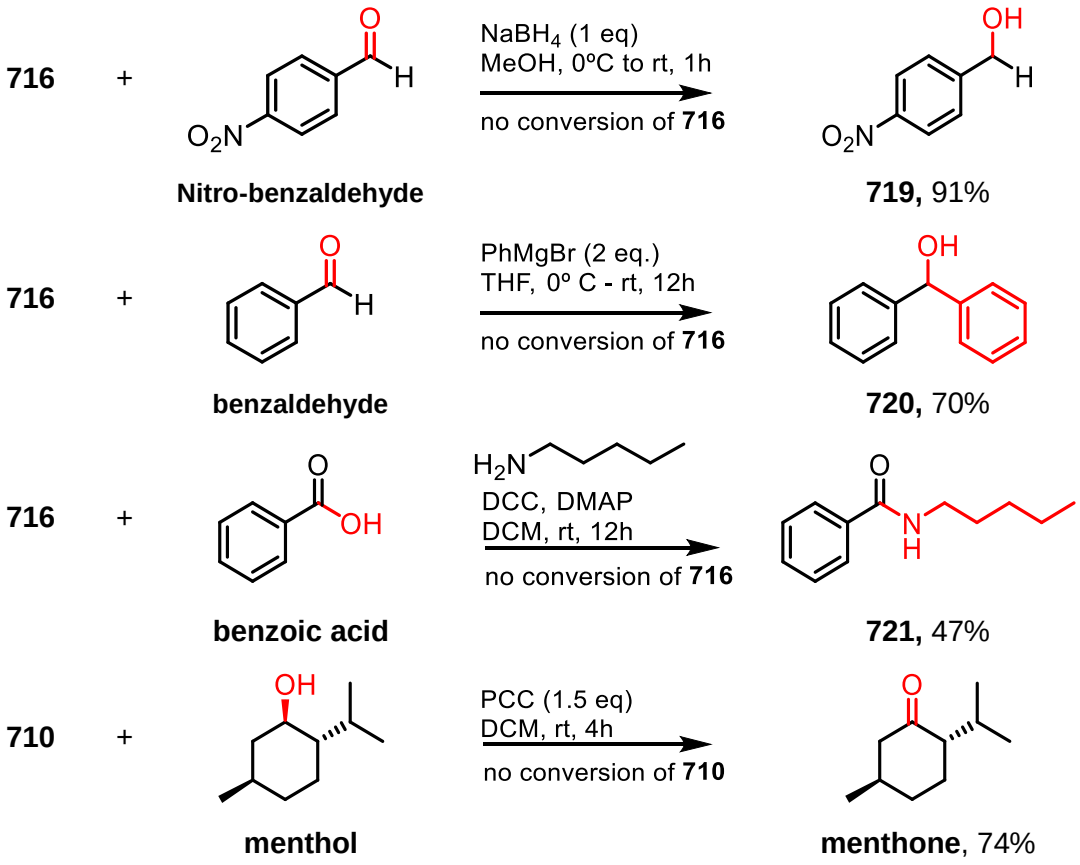
Oxidation of menthol to menthone using pyridinium cromium chloride (PCC) in the presence of benzaldehyde protected aminal **710** was successful, with no formation of oxidation side products of the aminal group. Mentone was obtained in 74% isolated yield.

*A. Deprotection of aminal **716***



716 **HMF**

*B. Selected examples of reaction in the presence of aminal **716** or **710** (1 mol equiv)*



Nitro-benzaldehyde **719,** 91%

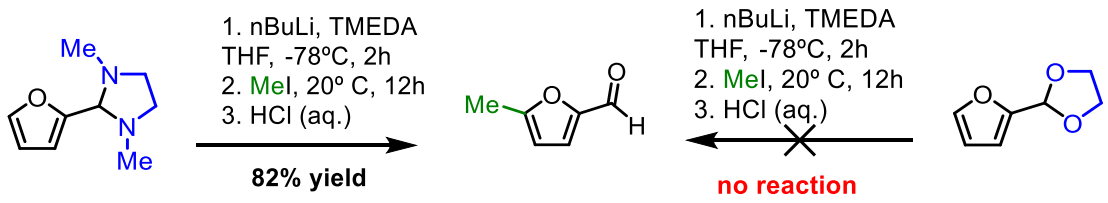
benzaldehyde **720,** 70%

benzoic acid **721,** 47%

menthol **menthone**, 74%

Figure 28. A. Deprotection of aminal **716** under mildly acidic conditions; B. Selected examples of common reactions in the presence of aminals: Reduction; Grignard addition; Steglich coupling; PCC oxidation (from top to bottom).

In an attempt to methylate position 5 of furfural we performed a tandem lithiation-methylation of acetal protected and aminal protected furfural (**Scheme 103**). Using nBuLi as lithiating agent and MeI as electrophile no reaction was observed in acetal protected furfural **723**. The aminal protected furfural **722** underwent methylation and we were able to reproduce the reported conditions[179] affording 5-methylfurfural in 82% yield.



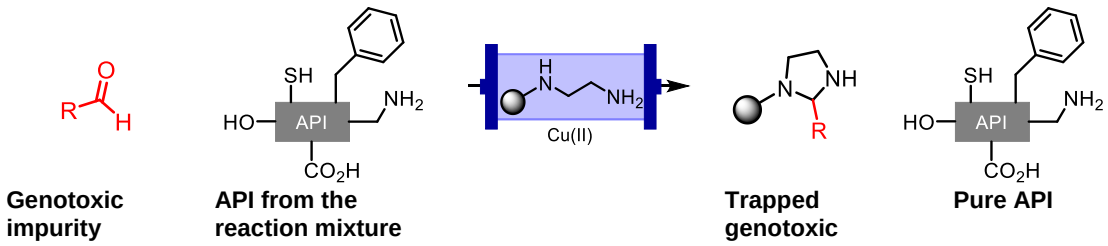
722 **5MF** **723**

Scheme 103 Methylation of furfural *via* lithiation of the furan ring in the presence of an acetal and aminal protection group.

In conclusion in this sub-chapter we observed that aromatic diamines afford the most stable aminals but are unsuited to be used as protection groups due to the lack of reversibility. Propane diamines are the most suited as protection group due to a balance between stability and deprotection under mildly acidic conditions. The aminal was deprotected with 2 eq acetic acid. The aminal was compatible with common reaction conditions and the group withstood both reductive and oxidative conditions, basic conditions and the presence of nucleophiles such as phenyl Grignard. It was also possible to perform an amidation with a primary amine in the presence of an aldehyde by protecting the aldehyde as an aminal. As a case example we performed a methylation via lithiation in aminal protected furfural versus acetal protected furfural. We hope that the aminal moiety adds value to the protection of aldehydes in cases where the acetal group is not suited.

IV.3.3. Aminals as tools for genotoxic aldehyde scavenging

When preparing active pharmaceutical ingredients (API) there is concern of impurities that can be formed during the preparation/storage of the API. The impurities are highly regulated due to the toxicity or unknown toxicity profiles that may lead to undesired side effects when the API is administered. Genotoxic impurities may induce chromosomal breaks, chromosomal rearrangements and genetic mutations. The European Medicines Agency (EMA) in 2006 published a guideline where is recommended that the concentration limits in ppm of genotoxic impurity in the API can be calculated by the formula Concentration limit (ppm) = threshold of toxicological concern (TTC) (µg/day) / dose (g/day).[180] Aldehydes are amongst the possible genotoxic impurities due to their electrophilicity and are considered highly reactive.[181] In some cases the calculated risk of the aldehyde is enough for the action to be taken in order to actively remove the aldehyde used as starting material or to find an alternate path altogether.[182] However studies point towards the need to actively remove the genotoxic instead of rearranging an alternate synthetic route.[183] Diamine resins have been used for the removal of aldehydes from Grignard addition reactions, by the formation of an imine.[184] This methodology is not always efficient and involves stirring the resin in the reaction mixture for long periods of times to remove the aldehyde. Having developed an efficient system for the formation of aminals from aldehydes we envisioned the formation of aminals with resin supported diamines for the removal of aldehydes from reaction mixtures (**Scheme 104**) in a continuous flow system.

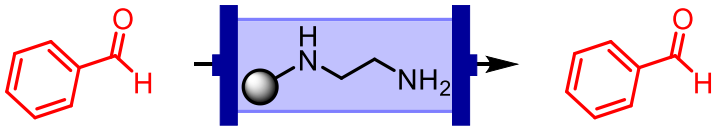


Scheme 104 Strategy for the scavenging of genotoxic aldehyde impurities.

We started this study by packing a small HPLC column with commercial diamine resin, containing 4-5.7 mmol/g diamine, and reacted a benzaldehyde and $Cu(OTf)_2$ (0.1 mol %) solution in methanol:water (9:1) with a residence time of 60 minutes (**Table 25**, Entry 1). We analyzed the aliquots after the mixture reacted with the diamine resin by HPLC and no aldehyde was detected. Next we reduced the residence time for 10 and 5 minutes and gratifyingly observed that the system remained efficient for benzaldehyde removal (**Table 25**, Entries 2 and 3). Also the reaction was performed with increased amounts of water (**Table 25**, Entry 4) and by replacing the methanol for industrial friendly ethanol,

and we observed the same aldehyde scavenging reaction (**Table 25**, Entry 5). Moreover we observe that increasing the concentration of benzaldehyde to 1 M does not affect the resin efficiency and by decreasing the concentration to 0.2 mM we also did not detect aldehyde. It is of importance that the system be able to remove aldehydes in small concentration due to its application in impurity scavenging.

Table 25 Residence time and solvent screening for the scavenging of benzaldehyde.



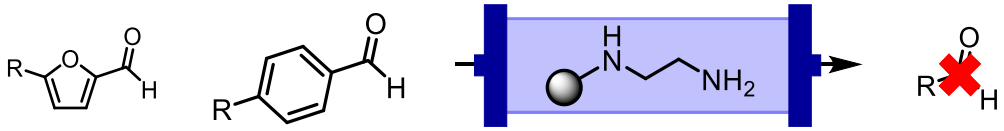
$Cu(OTf)_2$ (0.1 mol %)
$ROH:H_2O$ (0.1M), r. t.

Benzaldehyde				**Recovered Benzaldehyde**
Entry	RT	alcohol	alcohol:H_2O ratio	Recovered benz (%)
1	60	methanol	9:1	0
2	10	methanol	9:1	0
3	5	methanol	9:1	0
4	5	methanol	1:1	0
5	5	ethanol	1:1	0
6[a]	5	ethanol	1:1	0
7[b]	5	ethanol	1:1	0

Reaction conditions: benzaldehyde (0.035 mmol), alcohol:H_2O (0.35 mL). Benzaldehyde measured by HPLC. [a]Reaction performed at 1 M concentration. [b]Reaction performed at 2 mM concentration

Next we extended the scope of our system. We performed two sets of reactions in the presence of multiple aldehydes and analyzed the recovered aliquots by HPLC. The first set was carried out with benzaldehyde and derivatives containing electron-withdrawing substituents, furfural and HMF (**Figure 29**) and the removal was successful.

The second set of aldehydes corresponded to the electron rich aryl aldehydes, which were inherently less prone to react with the resin. Indeed we observe that after passing 0.1 mmol of aldehydes there is 0.2% of recovered naphtaldehyde and 0.08% of 4-methylbenzaldehyde (**Figure 30**).



R = H
R = CH2OH

R = H
R = Br
R = CHO

No recovered aldehyde

Overlaid HPLC chromatograms of benzaldehyde, 4-bromobenzaldehyde, terephthalaldeyde, furfural and HMF.

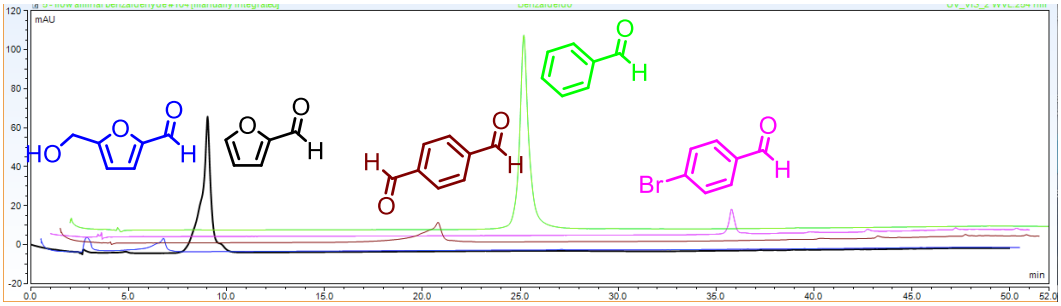
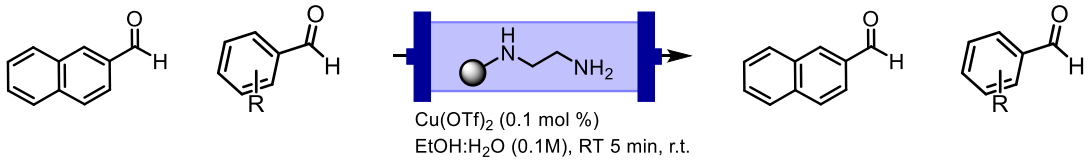


Figure 29 Scavenging of electron poor aryl aldehydes and furyl aldehydes.



R = 2-OH
R = 4-OMe
R = 4-Me

0.2%

R = 4-Me, 0.08%

Overlaid HPLC chromatograms of salicylaldehyde, 4-methoxybenzaldehyde, 4-methylbenzaldehyde and naphtaldehyde.

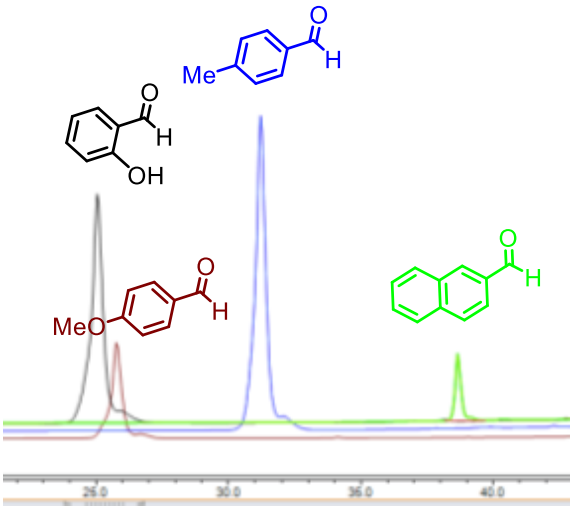
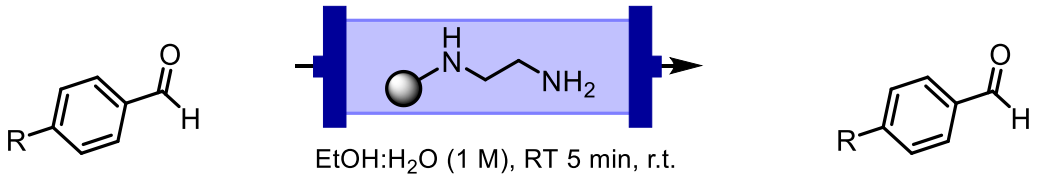


Figure 30 Scavenging of electron rich aryl aldehydes.

Finally we tested how much aldehyde could be efficiently removed from a mixture using our system. For this purpose we selected electron rich aryl aldehyde that we knew were problematic and run the reaction at 1M concentration. The selected aldehydes were 4-methoxybenzaldehyde (PMB) and 4-(dimethylamino)-benzaldehyde (PDMB). The reaction was performed in the presence and in the absence of copper catalyst. Although the reaction is still occurring in the absence of catalyst, the capture of both aldehyde is greatly enhanced by the presence of catalyst (**Table 26**). In the case of PMB we observed efficient capture even after feeding the system with 1 mmol aldehyde mixture (**Table 26**, Entry 4). In the case of less reactive PDMB the scavenging resin starts losing efficiency after 0.7 mmol aldehyde input (**Table 26**, Entry 3).

Table 26 Saturation of the resin with aldehydes in the presence and absence of catalyst



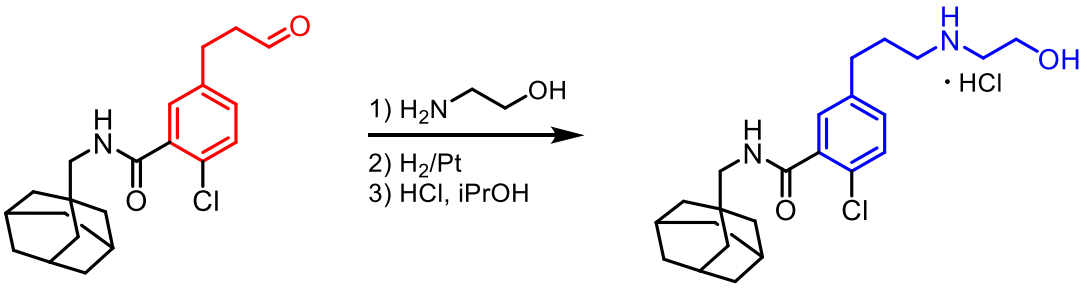
PMB, R = 4-OMe
PDMB, R = 4-NMe_2

Recovered aldehyde

		Recovered aldehyde **PMB/PDMB** (%)	
Entry	Total aldehyde input	No catalyst	0.1 mol% $Cu(OTf)_2$
1	0.35 mmol	10/12	0/0
2	0.70 mmol	22/30	1/4
3	1 mmol	32/40	7/40
4	1.4 mmol	77/100	18/55
5	1.7 mmol	100/100	23/56

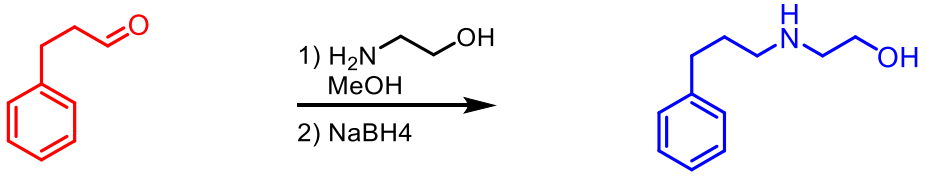
As previously discussed, it is of importance to be able to remove genotoxic aldehydes from APIs. One such example corresponds to the preparation of AZD 9056, an API under development for rheumatoid arthritis. Its preparation involves a reductive amination of the corresponding AZD 9056 aldehyde.[181,182] This aldehyde remains as a genotoxic impurity due to its low volatility. To study the efficiency of our system in this particular case we prepared model amine **724** by reductive amination of 3-phenylpropanal (PPA). Using the best condition we feed the reactor with a mixture of PPA and model amine **724** in a 1:1 ratio and after evaporating the output of the reactor we obtained 100% of pure **724**.

A. AZD 9056 HCl preparation from genotoxic aldehyde



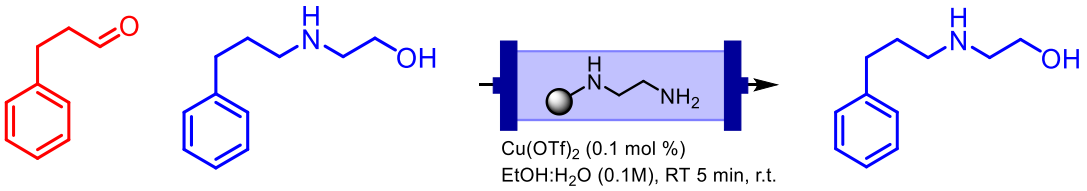
AZD 9056 aldehyde AZD 9056 HCl salt

*B. AZD 9056 model amine **724** preparation*



PPA **724**

*C. Removal of PPA from a PPA:**724** mixture*



PPA **724** Pure **724**

Figure 31 Strategy for the case study of impurity scavenging. A. AZD 9056 HCl preparation from genotoxic aldehyde; B. AZD 9056 model amine **724** preparation; C. Removal of PPA from a PPA:**724** mixture by our approach.

In summary during this sub-chapter a methodology for the removal of aldehydes in mixtures based in the formation on aminals was developed. The system was used to remove an aldehyde from a mixture containing a model amino alcohol that mimetize API AZD 9056.

IV.3.4. Aminals as stimuli responsive dynamic linkers

A gradual revolution has been occurring recently in medicinal chemistry where the main focus of research is shifting from traditional small molecule-based therapies to more precise targeted therapies. This change is particularly visible in cancer treatment where cytotoxic drugs that were deemed too active to be therapeutically useful, due to their off-site toxicity, are now being safe and effectively used attached to targeting warheads. The success of this approach is represented by the five FDA-approved Antibody-Drug conjugates (ADC) already on the market as well as the multiple ones currently in clinical trials. Recent reports have demonstrated that small-molecules can also be employed as effective targeting moieties. One key aspect of ADC development which is often overlooked is the linker technology. Despite being used solely as inert spacers in the first generations of conjugates, the new generations present linkers as functional components who play a major role in the success of the conjugate. The new-generation linkers are not only responsible for preventing random release of the payload in circulation, but should also be responsive to a predetermined stimulus to promote drug release specifically at the intended site of action.

To further explore their potential, we envisioned that aminals could work as a dynamic covalent linker that is specifically responsive to particular chemical/environmental *stimuli*. A commonly explored chemical trigger in cancer targeting is acidic pH. Two FDA-approved ADCs (Mylotarg® and Besponsa®) contain acid-sensitive hydrazone linkages that are hydrolysed in the acidic tumour microenvironment. Furthermore, several drug-delivery systems have also employed acid-sensitive acetal linkers for tumour delivery of cytotoxic drugs. With these examples in hand and recognizing the similarities between acetals and aminals as potentially reversible covalent linkages, we set out to explore the stability of aminals at different pHs.

The first step was the selection of the appropriate aminal. As previously demonstrated, non-cyclic aminals were not stable at pH 7 (compound **686**, **Scheme 102**), thus being unsuited as a potential linker. On the other hand, aminals from aromatic diamines show incredible stability even at pH 4.5 (compound **706**, **Scheme 102**), precluding the intended reversibility in acidic conditions. Therefore, aminals derived from 1,3-propanediamine were selected for the subsequent assays as they offer the best compromise between stability and reversibility.

We started by synthesizing aminal **709** and assessing its stability at pH 7.0 and 4.5 by UV-Vis spectroscopy (**Figure 32**). At neutral pH, aminal **709** was hydrolysed to

benzaldehyde in approximately 20 minutes. However, under acidic conditions aminal **709** was entirely hydrolysed upon the first UV-Vis measurement (<1 minute). As expected, this preliminary result demonstrates that aminals could in fact be used as a pH-responsive group. However, aminal **709**'s stability at pH 7 was still far from adequate for biological applications and it was necessary to improve it.

To do so, we proposed that the presence of adjacent groups could help stabilize the aminal and improve its half-life at neutral pH. With this idea in mind, we synthesized aminal **707** derived from salicylaldehyde to evaluate the effect of a possible intramolecular hydrogen bond, and aminal **708** derived from 2-formylbenzene boronic acid (2-FBBA) to explore the well-documented boron-nitrogen interaction. Surprisingly, aminal **707** was shown to be very unstable at pH 7.0, being hydrolysed to salicylaldehyde after just 5 minutes. Once more, at pH 4.5 aminal **707** was entirely degraded upon the first measurement (**Figure 32**). On the contrary, aminal **708** was shown to be much more stable than **709** and **707**, requiring around 7-8 hours to be hydrolysed. Auspiciously, aminal **708** maintained its reversibility as the molecule reverts immediately to 2-FBBA in acidic conditions (**Figure 32**). These encouraging results indicate that boronic acid-stabilized aminals can potentially be employed as acid-responsive linkers in drug delivery systems.

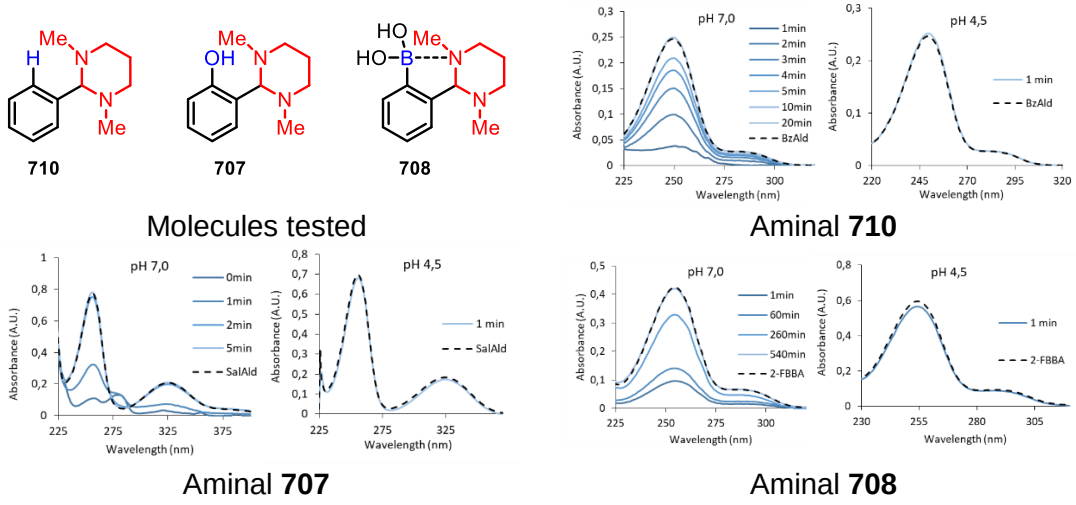


Figure 32 Stability in pH 7.0 and 4.5 of aminal **709**, **707** and **708** containing different *ortho* groups. Abbreviations: BzAld = Benzaldehyde; SalAld = Salicylaldehyde; 2-FBBA = 2-formylbenzene boronic acid.

IV.4. Conclusions

In the Chapter IV we study a mild and efficient methodology for the preparation of aminals from aldehydes by using catalytic amounts of Cu(OTf)2 (0.1 mol %) in water. The aminals precipitate under this conditions affording quantitative yields of the aminal product.

A concise study on the stability of the aminals allow us to select the cyclic aminals prepared from 1,3-propanediamine as protection group for aldehydes. A consistent study on this highlights the possibility of using these under several reaction conditions.

Also a diamine resin was used as scavenger for aldehydes. Since aldehydes may appear as genotoxic impurities in APIs we develop the methodology and apply in a model API/aldehyde system.

Finally we envision the aminal to be a dynamic bond that can release an aldehyde under a pH stimuli. We observe that a boronic acid in *ortho* position of the aldehyde significantely increase the aminal stability.

V. Final Conclusions and Future Perspectives

In this thesis we developed an environmentally friendly procedure to prepare DCP from biomass derived furfural in water promoted by $Cu(OTf)_2$. This catalyst can be reused up to 4 times. Immobilization of $CuSO_4$ in silica allowed for the first example of the preparation of DCP under continuous flow conditions. This facilitates the scale-up/out of DCP important for the preparation of natural product (±)-agelastatin A.

We also prepared mixed DCP by reacting furfural in the presence of two distinct amines. The reaction is highly regioselective and dependent in the formation of a stable iminium ion.

Biological evaluation of these compounds revealed DCP to be a promising scaffold for antimicrobial studies, with MIC of 3.91 $\mu g.mL^{-1}$ in MRSA strains. ACP and HCP obtained from Michael addition to DCP revealed to be a promising scaffold for tumor growth inhibition achieving IC_{50} of 7.07 ± 1.78 in HT-29 cell lines. These CP are also non-electrophilic, which is the case of most previously used CP scaffolds for drug discovery and often led to the discontinuation of the studies due to toxicity related to non specific alkylation.

Future work on the DCP family involves developing the scaffold as antimicrobial agent, for exemple by transforming the enone to an oxime as a pro-drug strategy that can be hydrolized in the bacteria. Also the development of natural product (±)-agelastatin A analogs are of great interest in a MedChem prespective.

We also describe the first preparation of CP from biomass derived HMF. This was possible by the Knovanaegel condensation of Meldrum's acid with HMF forming activated furfural HMF-MAF. HMF-MAF undergoes condensation with amines to form an intermediary CP that through BINOL mediated decomposition of the Meldrum's acid leads to a δ-Lactone-fused cyclopentenone LCP. Synthetic derivatizations of the LCP scaffold were performed, with particular attention to the Michael addition to the LCP core. The addition is followed by elimination of the amine and a remote lactone activation that leads to methanolysis. All the new CP were screened for biological activities and the thio-CP present promising results on the inhibition of malaria's parasite *Plasmodium falciparum*.

Future work on the LCP family involves the continuation of the ongoing studies of antimalaric CPs.

Finally we study a mild and efficient methodology for the preparation of aminals from aldehydes by using catalytic amounts of $Cu(OTf)_2$ (0.1 mol %) in water. The aminals precipitate under these conditions affording quantitative yields of the aminal product.

A concise study on the stability of the aminals allow us to select the cyclic aminals prepared from 1,3-propanediamine as protection group for aldehydes. A consistent study on this highlights the possibility of using aminals under several reaction conditions.

Also a diamine resin was used as scavenger for aldehydes. Since aldehydes may appear as genotoxic impurities in APIs we develop the methodology and apply in a model API/aldehyde system.

Finally we envision the aminal to be a dynamic bond that can release an aldehyde under a pH stimuli. We observe that a boronic acid in *ortho* position of the aldehyde significantely increase the aminal stability.

Future work on the aminal chemistry involves the use of aminals as an Umpolung strategy of the carbonyl group for the formation of α-keto-acids or other α-keto-functionalized molecules. Also the use of the aminal bond as a potential biorthogonal handle for drug delivery is of interest due to the increased rate of hydrolysis upon transformation of an *ortho*-boronic acid aminal to an *ortho*-phenol aminal.

VI. Experimental Section

VI.1. Chapter II

General Remarks

All solvents were distilled prior use. Furfural was distilled and stored at 4°C. Unless otherwise stated, all reagents were used as received from commercial suppliers. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel F254 with 0.2 mm thickness. ^{1}H and ^{13}C NMR spectra were acquired on Bruker MX300 spectrometer.

General procedure for the synthesis of *trans*-4,5-dimorpholino-cyclopent-2-enone 2 in water

To a solution of a selected catalyst (10 mol%) in water (0.2 mL) was added morpholine (40 µL, 0.45 mmol, 2.2 equiv) and furfural (20 mg, 0.2 mmol). The reaction was allowed to stir vigorously at room temperature for 5 minutes. Then the reaction mixture was diluted with water (0.8 mL) and extracted with diethyl ether (3 × 1 mL). The organic phase was dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude mixture was analysed by ^{1}H-NMR.

Stability of *trans*-4,5-dimorpholino-cyclopent-2-enone 2

To a solution of $GdCl_3 \cdot 6H_2O$ (7 mg, 0.019 mmol, 10 mol%) in water (0.1 mL) was added an aqueous solution of *trans*-4,5-dimorpholino-cyclopent-2-enone (50 mg, 0.2 mmol in 0.1 mL water). The mixture was allowed to stir vigorously at room temperature for 15 minutes. The solution was diluted with water (0.8 mL) and extracted with diethyl ether (3 × 1 mL). The solvent was evaporated under reduced pressure and the crude mixture was analysed by ^{1}H-NMR.

General procedure for the catalyst reuse in the preparation of *trans*-4,5-dimorpholino-cyclopent-2-enone 2

To a solution of $Cu(OTf)_2$ (40 mg, 10 mol%) in water (1 mL) was added morpholine (225 µL, 2.29 mmol, 2.2 equiv) and furfural (100 mg, 1.04 mmol). The reaction was allowed to stir vigorously at room temperature for 1 minutes. Diethyl ether was added to the reaction mixture (2 mL) and after 1 min of vigorous stirring the phases were separated. The process was repeated one more time and the collected organic phases were dried with MgSO4 and evaporated under reduced pressure to yield the pure *trans*-4,5-dimorpholino-cyclopent-2-enone. The remaining aqueous layer was loaded with more

morpholine (200 µL, 2.29 mmol, 2.2 equiv.) and furfural (100 mg, 1.04 mmol) and the process repeated for 7 cycles.

General procedure for the preparation of *trans*-4,5-dimorpholino-cyclopent-2-enone 2 in the presence of small molecules competitors

To a solution of $Cu(OTf)_2$ (8 mg, 10 mol%) in water (0.2 mL) was added the corresponding competitor (2 equiv), morpholine (40 µL, 0.45 mmol, 2.2 equiv) and furfural (20 mg, 0.2 mmol). The reaction was allowed to stir vigorously at room temperature for 5 minutes. Then the reaction mixture was diluted with water (0.8 mL) and extracted with diethyl ether (3 × 1 mL). The organic phase was dried with MgSO4 and the solvent was evaporated under reduced pressure. The crude mixture was analysed by ^{1}H-NMR.

Procedure for the preparation of *trans*-4,5-dimorpholino-cyclopent-2-enone 2 in the presence of BSA

To a solution of $Cu(OTf)_2$ (8 mg, 10 mol%) in water (0.2 mL) was added BSA (40 mg), morpholine (40 µL, 0.45 mmol, 2.2 equiv) and furfural (20 mg, 0.2 mmol). The reaction was allowed to stir vigorously at room temperature for 5 minutes. Then the reaction mixture was diluted with cold acetone (2 mL) and left at -20°C for 1 h. The sample was centrifuged and the supernatant was evaporated under reduced pressure. Water (1 mL) was added to the crude mixture and the reaction was extracted with diethyl ether (3 × 2 mL). The collected organic phases were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the final product in 94% yield.

Procedure for the preparation of *trans*-4,5-dimorpholino-cyclopent-2-enone 2 in the presence of DNA

To a solution of $Cu(OTf)_2$ (8 mg, 10 mol%) in water (0.2 mL) was added DNA (40 mg), morpholine (40 µL, 0.45 mmol, 2.2 equiv) and furfural (20 mg, 0.2 mmol). The reaction mixture was allowed to stir vigorously at room temperature for 5 minutes. Then the reaction mixture was diluted with cold ethanol (2 mL) and left at -20°C for 1 h. The sample was centrifugated to remove the precipitated DNA and the supernatant was evaporated under reduced pressure. Water (1 mL) was added to the crude mixture and the reaction was extracted with diethyl ether (3 × 2 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude mixture was analysed by ^{1}H-NMR.

Procedure for the preparation of *trans*-4,5-dimorpholino-cyclopent-2-enone 2 in a 10-gram scale

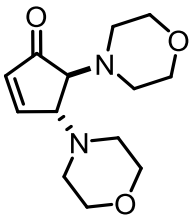
To a round bottom flask loaded with a $Cu(OTf)_2$ (4 mg, 0.1 mol%) and water (100 mL) were added morpholine (20 mL, 229 mmol, 2.2 equiv) and furfural (10 g, 104 mmol) in an ice bath. The reaction was allowed to stir vigorously for 1 h. Then the ice bath was removed and the reaction was allowed to stir at room temperature. Aliquots of 0.1 mL were taken at 3 h and 8 h, extracted with $CDCl_3$ and analysed by ^{1}H-NMR. After 8 h, 50 mL of the homogenous reaction mixture was collected from the flask, diluted with water (200 mL) and extracted with MTBE (3 × 200 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to give a crude product (12.2 g, 93%) as a 6.7:1 mixture of isomers **1** and 2,4-dimorpholino-cyclopent-2-enone. The remaining 50 mL of the reaction mixture were stirred for an additional 16 h after which similar work-up protocol was performed to yield the regioisomer 2,4-dimorpholino-cyclopent-2-enone in 87% yield (11.4 g).

General procedure for the preparation of *trans*-4,5-diamino-cyclopent-2-enones

To a solution of $Cu(OTf)_2$ (40 mg, 10 mol%) in water (1 mL) was added amine (2.29 mmol, 2.2 equiv.) and furfural (100 mg, 1.04 mmol). The reaction was allowed to stir vigorously at room temperature for 1 minutes. Then the reaction mixture was diluted with water (9 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to yield the pure cyclopent-2-enones as shown by ^{1}H-NMR analysis.

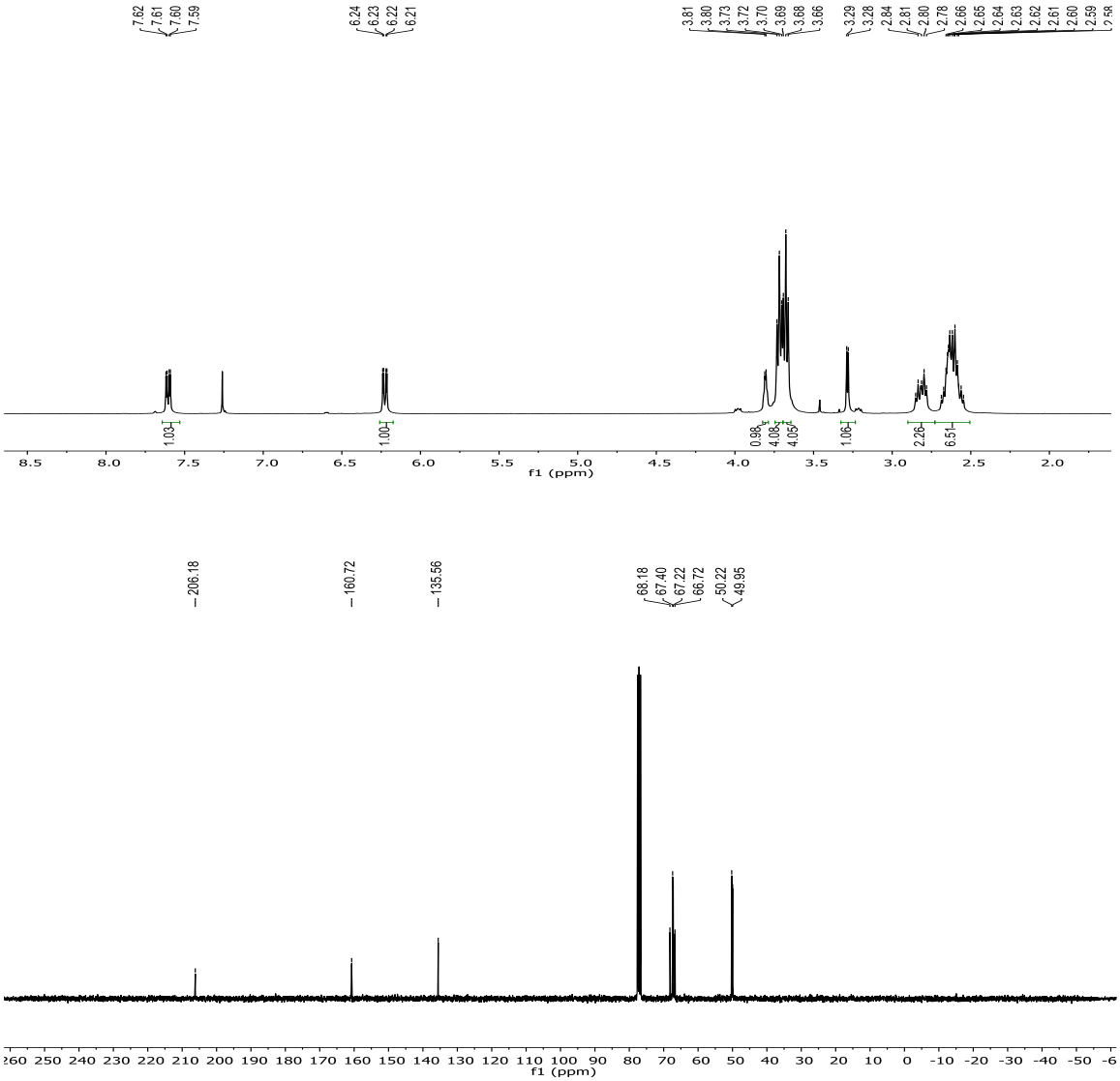
Product characterization

***trans*-4,5-bismorpholino-cyclopent-2-enone 2**

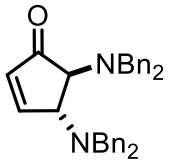


The product was isolated as a yellow solid (262 mg, quantitative yield). The spectral data are in agreement with the literature[196]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 6.2, 2.2 Hz, 1H) 6.23 (dd, *J* = 6.2, 1.8 Hz, 1H) 3.81 (m, 1H) 3.72 (t, *J* = 4.6 Hz, 4H) 3.68 (t, *J* = 4.6 Hz, 4H) 3.28 (d, *J* = 3.0 Hz, 1H) 2.78-2.85 (dt, *J* = 11.5, 4.6 Hz, 2H) 2.55-2.69 (m, 6H) **^{13}C NMR (75 MHz, $CDCl_3$)** δ 49.9, 50.2, 66.7, 67.2, 67.4, 68.2, 135.6, 160.7, 206.2.

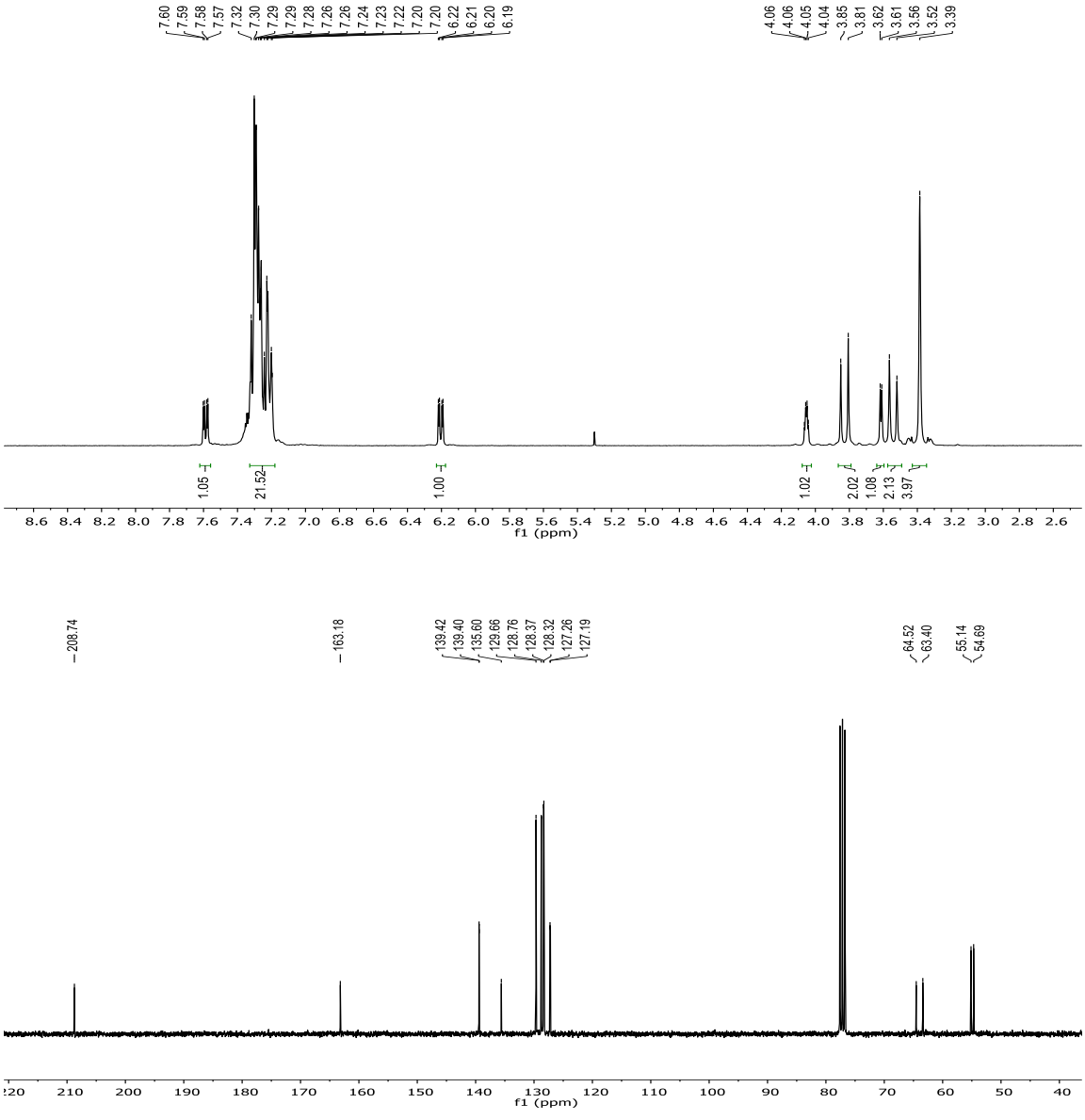


***trans*-4,5-bis(dibenzylamine)-cyclopent-2-enone 3**

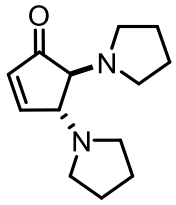


The product was isolated as a yellow solid (482mg, 98% yield). The spectral data are in agreement with the literature[196]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 6.2, 2.2 Hz, 1H) 7.20-7.32 (m, 20H) 6.20 (dd, *J* = 6.2, 1.9 Hz, 1H) 4.05 (m, 1H) 3.83 (d, *J* = 13.2 Hz, 2H) 3.61 (d, *J* = 2.9 Hz, 1H) 3.54 (d, *J* = 13.2 Hz, 2H) 3.39 (s, 4H) **^{13}C NMR (75 MHz, $CDCl_3$)** δ 54.7, 55.1, 63.4, 64.5, 127.2, 127.3, 128.3, 128.4, 128.8, 129.7, 135.6, 139.4, 139.4, 163.2, 208.7.

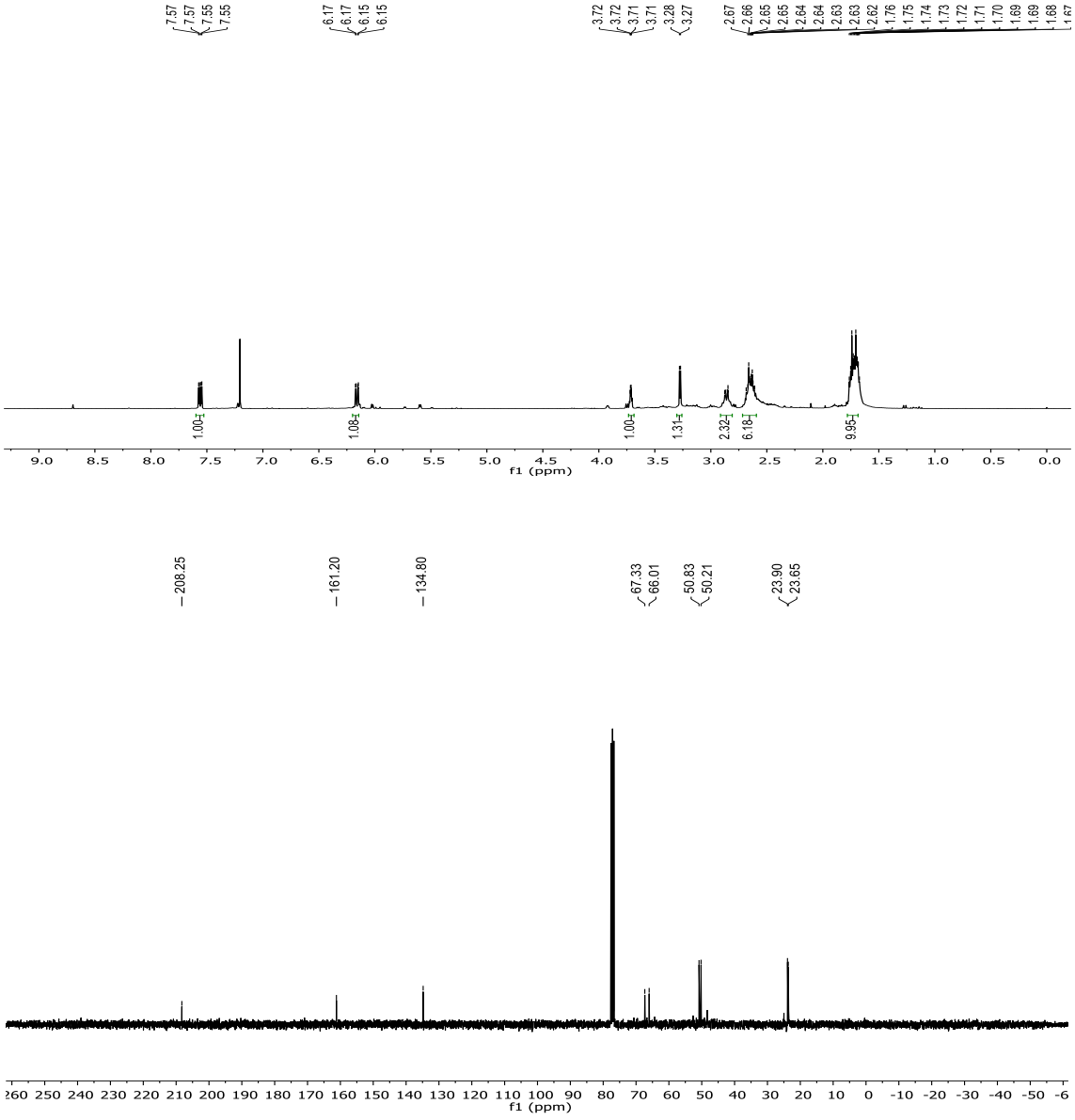


***trans*-4,5-bispyrrolidine-cyclopent-2-enone 32**

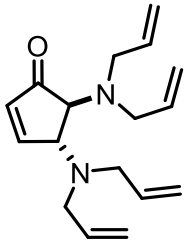


The product was isolated as a yellow oil (222 mg, 97% yield). The spectral data are in agreement with the literature[196]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 6.2, 2.2 Hz, 1H) 6.16 (dd, *J* = 6.1, 1.6 Hz, 1H) 3.71 (m, 1H) 3.28 (d, *J* = 2.7 Hz, 1H) 2.85-2.88 (m, 2H) 2.61-2.68 (m, 6H) 1.67-1.76 (m, 8H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 23.6, 23.9, 50.2, 50.8, 66.0, 67.3, 134.8, 161.2, 208.2.

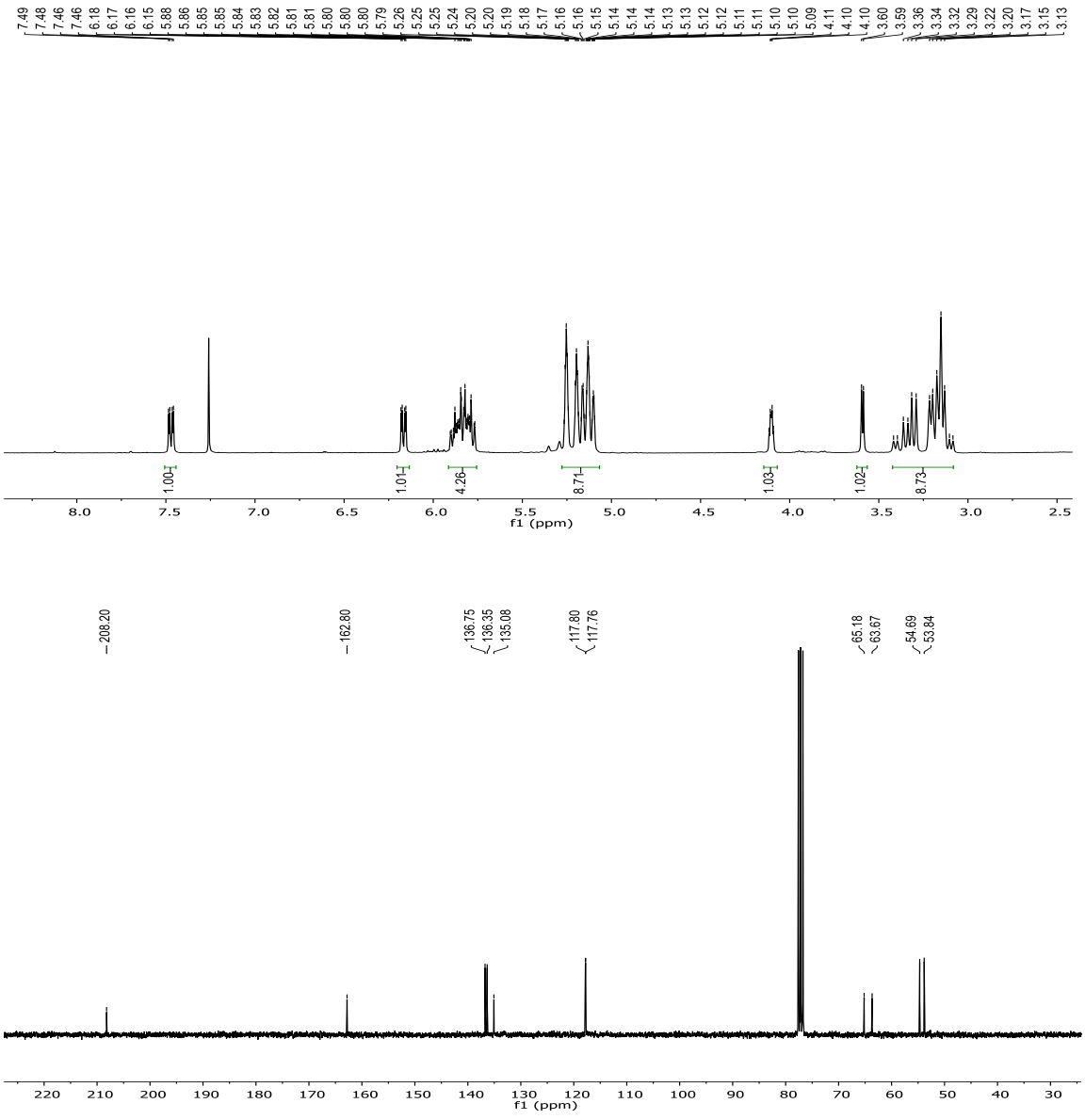


***trans*-4,5-bis(diallylamine)-cyclopent-2-enone 4**

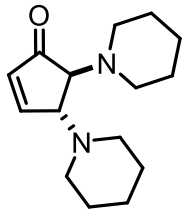


The product was isolated as a brown oil (204 mg, 72% yield). The spectral data are in agreement with the literature[196]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 6.2, 2.1 Hz, 1H) 6.17 (dd, *J* = 6.2, 1.9 Hz, 1H) 5.77-5.90 (m, 4H) 5.10-5.26 (m, 8H) 4.10 (m, 1H) 3.59 (d, *J* = 3.3 Hz, 1H) 3.08-3.42 (m, 8H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 53.8, 54.7, 63.7, 65.2, 117.8, 117.8, 135.1, 136.4, 136.8, 162.8, 208.2.

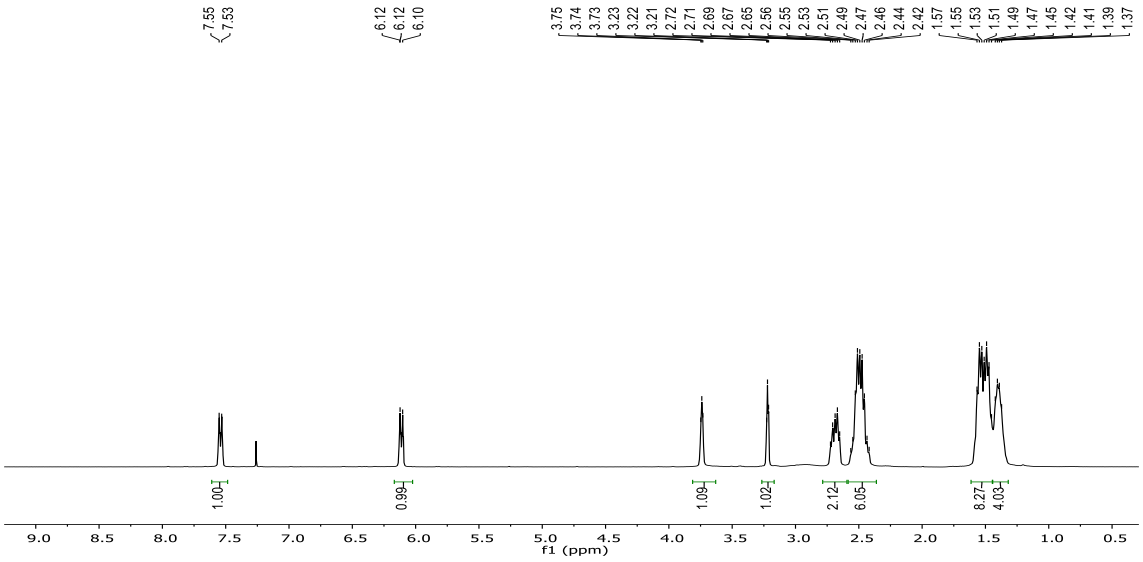


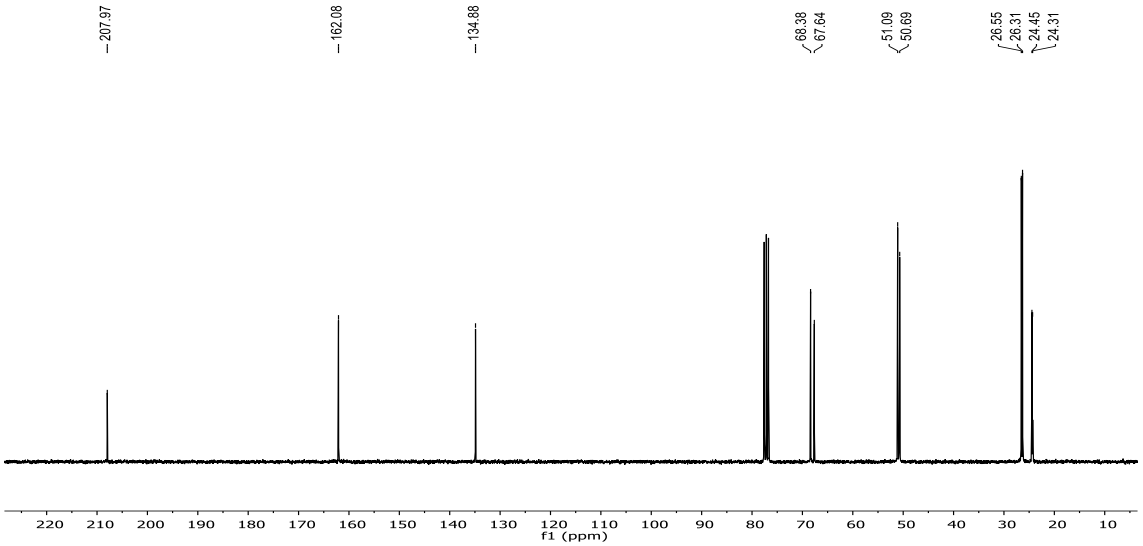
***trans*-4,5-bispiperidino-cyclopent-2-enone 33**



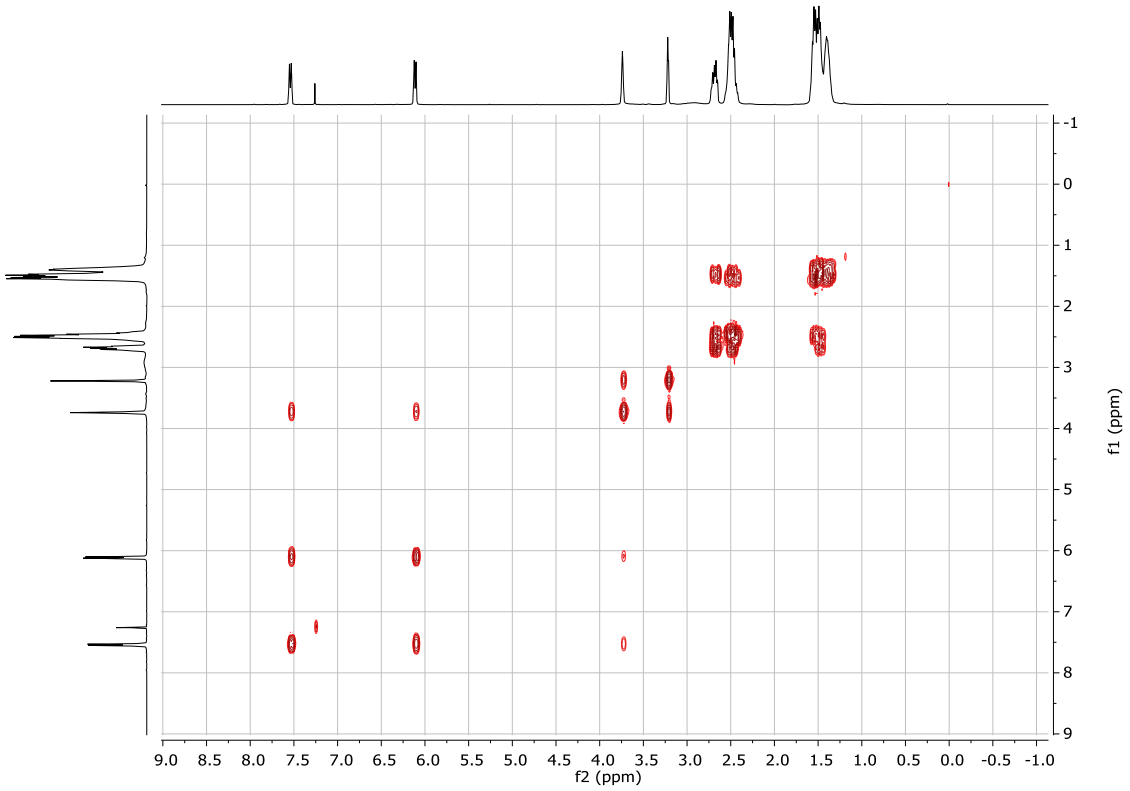
The product was isolated as a yellow oil (258 mg, quantitative yield). The spectral data are in agreement with the literature[196]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.1 Hz, 1H) 6.11 (d, *J* = 6.1 Hz, 1H) 3.74 (m, 1H) 3.22 (m, 1H) 2.65-2.72 (m, 2H) 2.42-2.56 (m, 6H) 1.47-1.57 (m, 8H) 1.37-1.45 (m, 4H) **^{13}C NMR (75 MHz, $CDCl_3$)** δ 24.3, 24.5, 26.3, 26.6, 50.7, 51.1, 67.6, 68.4, 134.9, 162.1, 208.0.

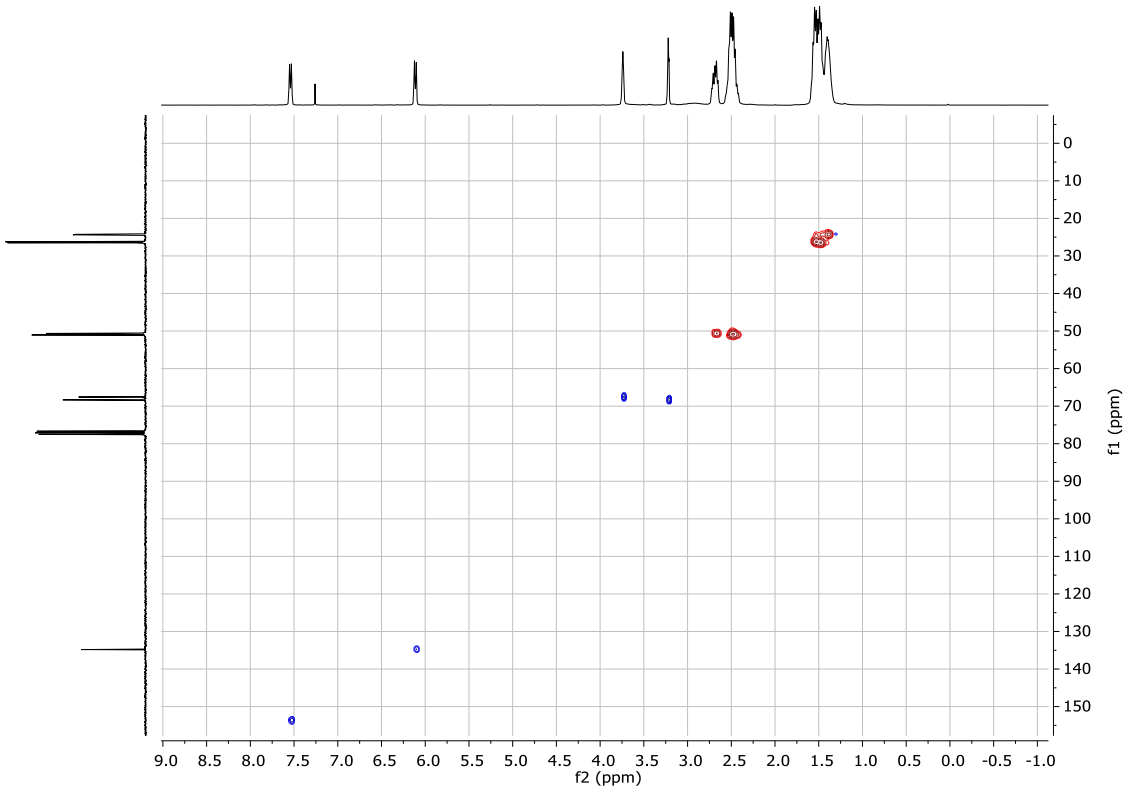




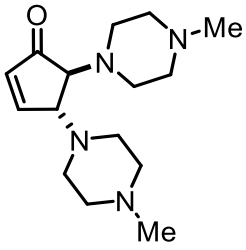
HMBC



HSQC

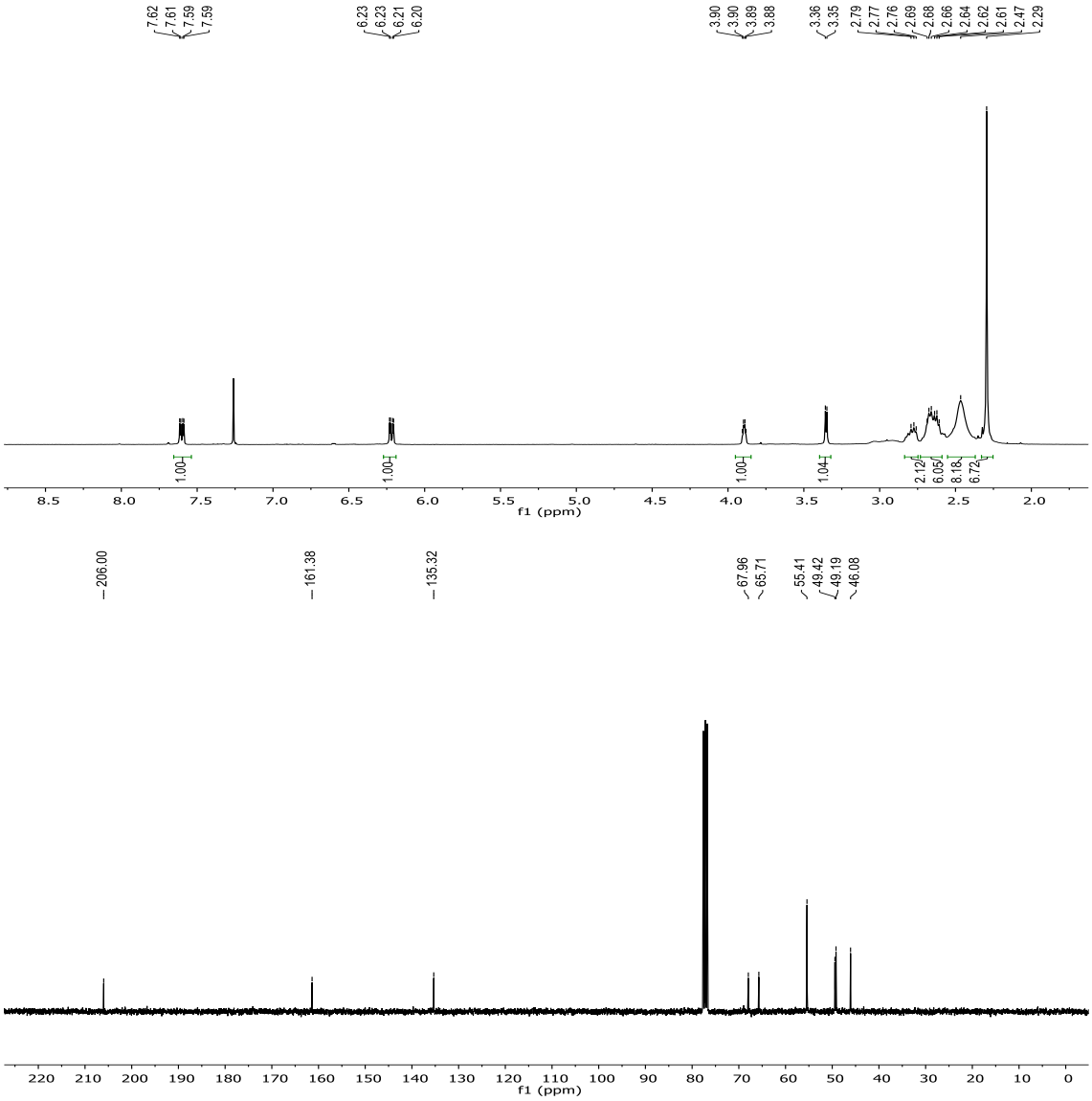


***trans*-4,5-bis(*N*-methylpiperazine)-cyclopent-2-enone 34**

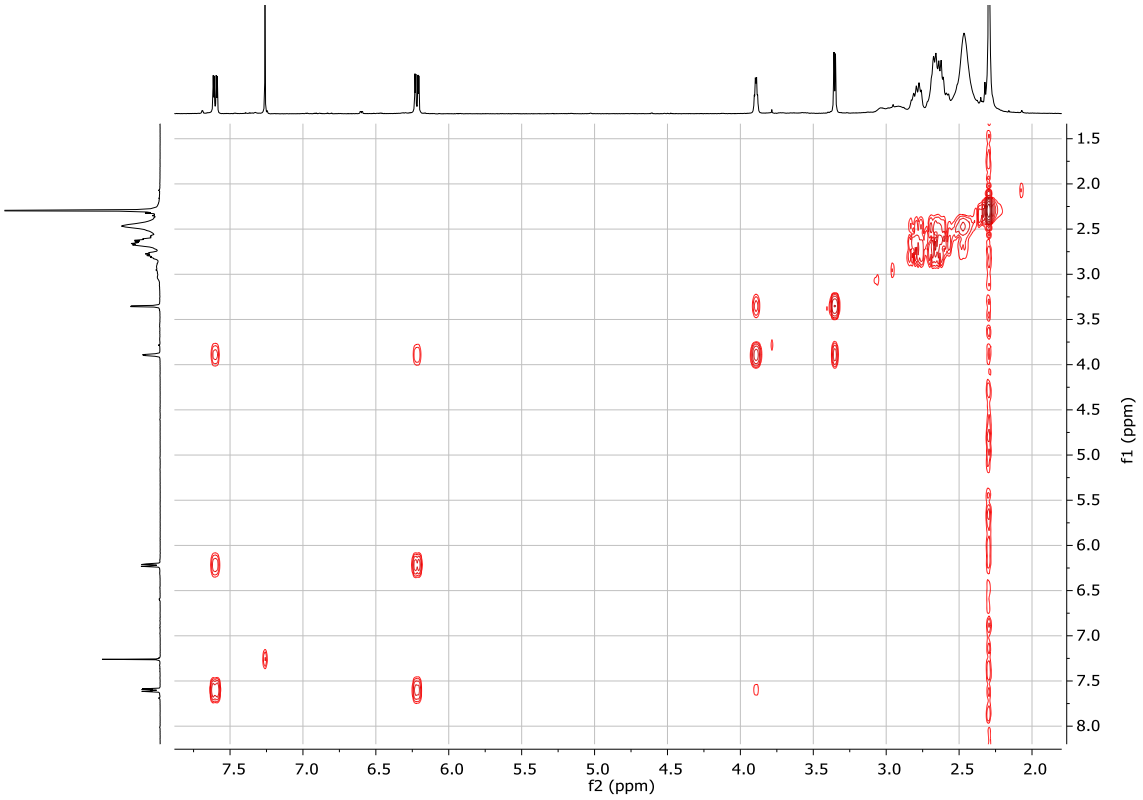


The product was isolated as an orange oil (290 mg, quantitative yield). The spectral data are in agreement with the literature[196]

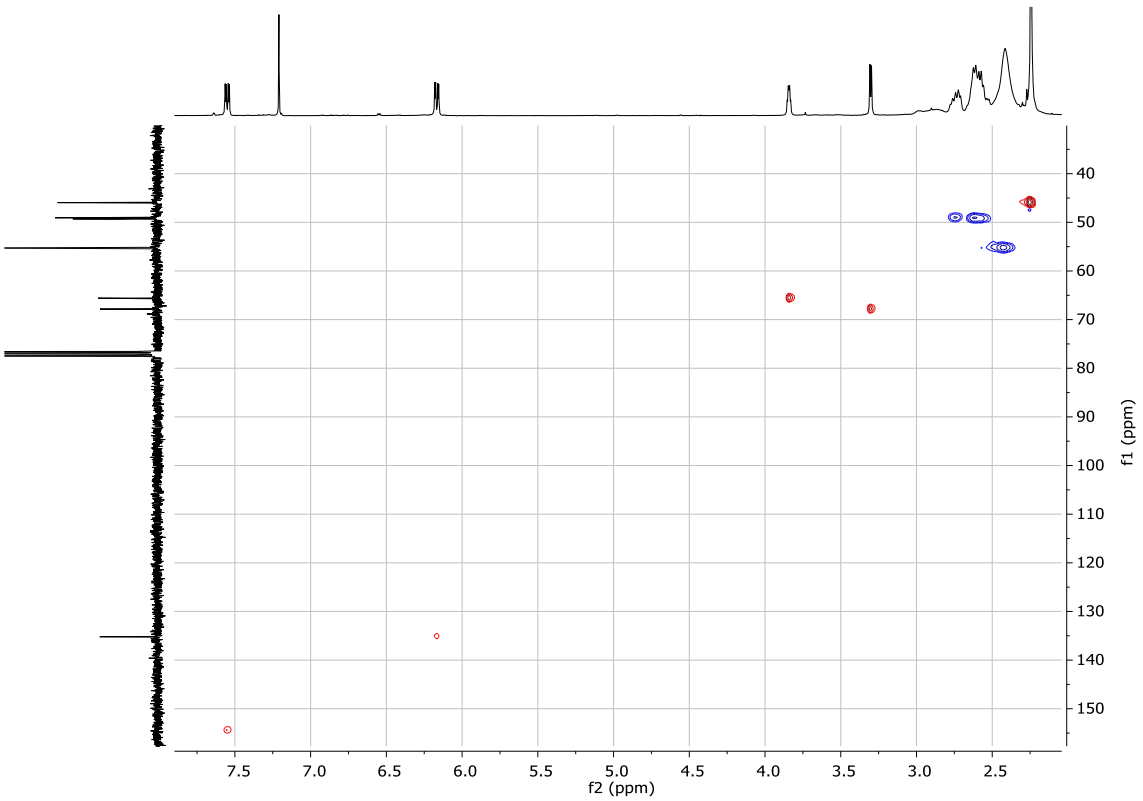
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 6.2, 2.2 Hz, 1H) 6.22 (dd, *J* = 6.2, 1.8 Hz, 1H) 3.89 (m, 1H) 3.35 (d, *J* = 3.0 Hz, 1H) 2.76-2.79 (m, 2H) 2.61-2.69 (m, 6H) 2.47 (broad s, 8H) 2.29 (s, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 46.1, 49.2, 49.4, 55.4, 65.7, 67.9, 135.3, 161.4, 206.0.



COSY


1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)

HSQC


40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
7.5
7.0
6.5
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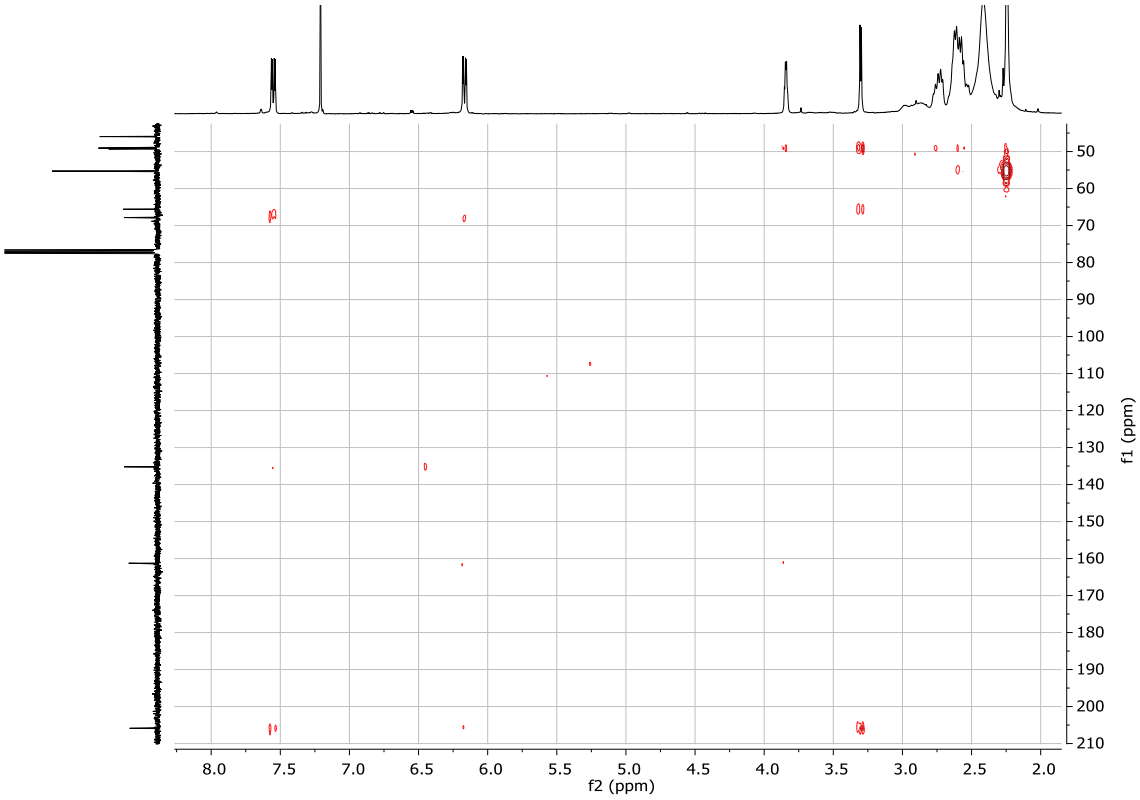
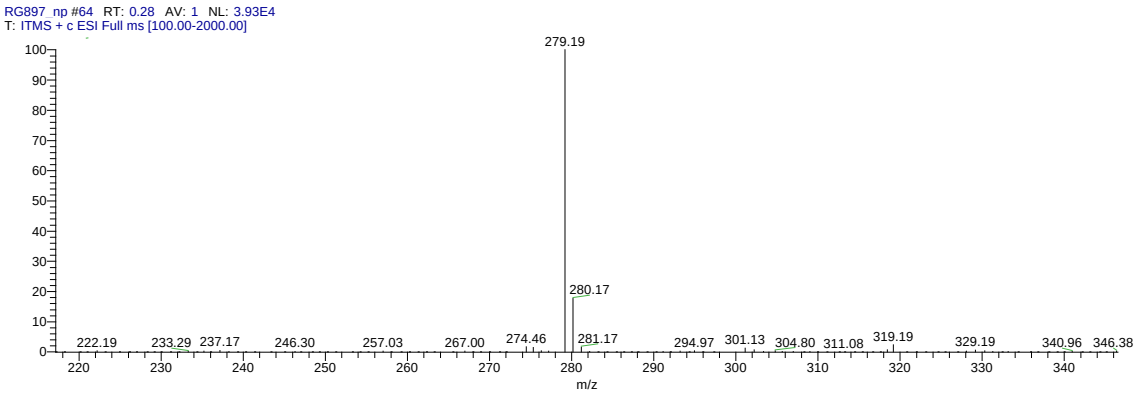
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f2 (ppm)

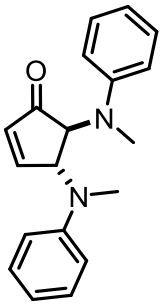
HMBC


f2 (ppm)
f1 (ppm)

MS

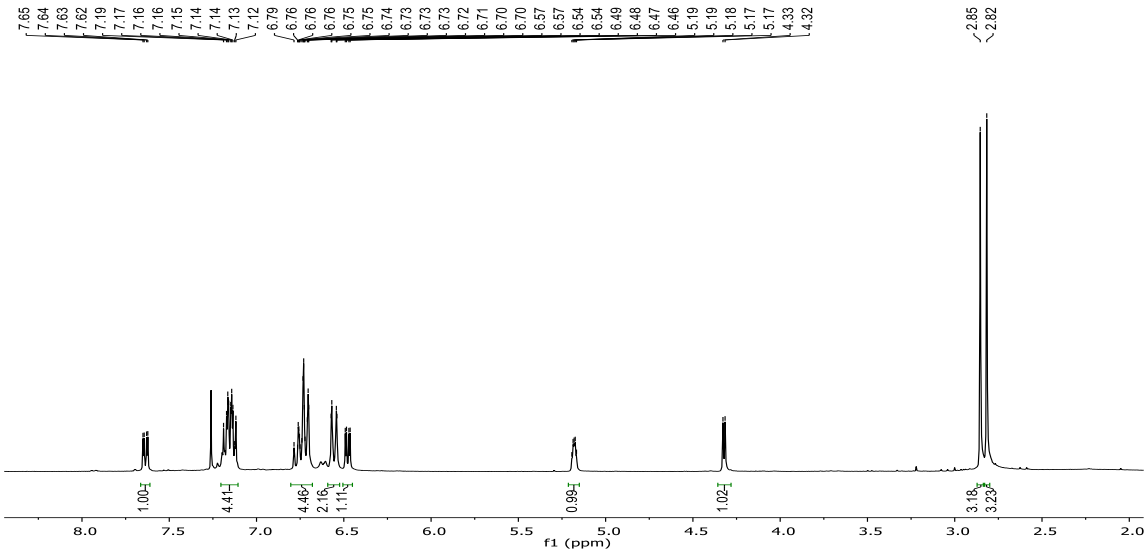

RG897_np #64 RT: 0.28 AV: 1 NL: 3.93E4
T: ITMS + c ESI Full ms [100.00-2000.00]
279.19
280.17
281.17
m/z

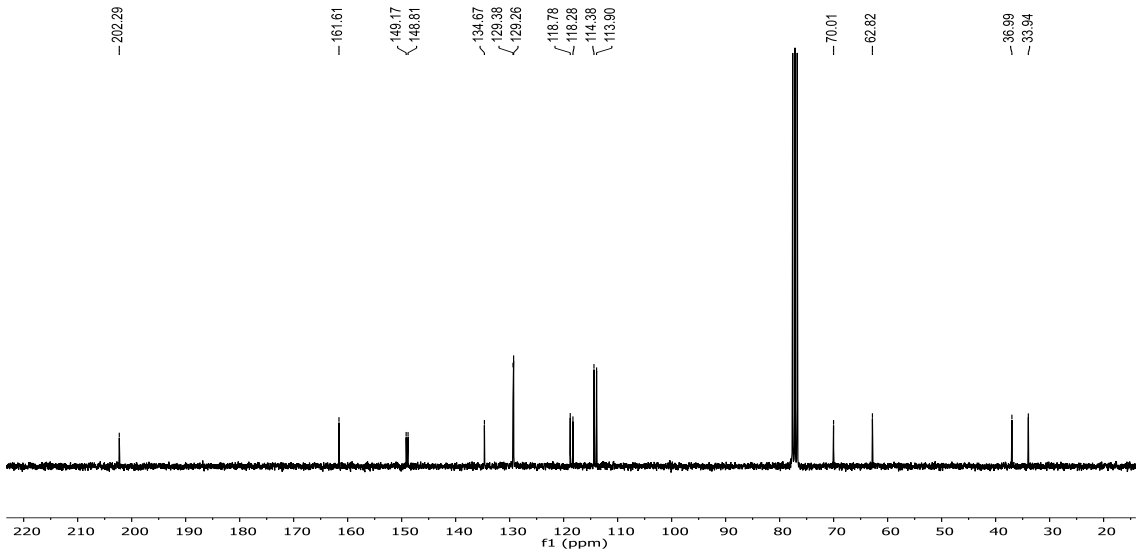
***trans*-4,5-bis(*N*-methylaniline)-cyclopent-2-enone 7**



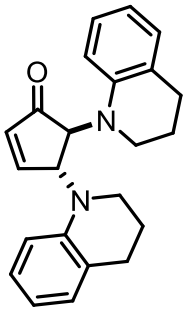
The product was isolated as a red oil (304 mg, quantitative yield). The spectral data are in agreement with the literature[196]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 6.3, 2.1 Hz, 1H) 7.15 (m, 4H) 6.73 (m, 4H) 6.56 (d, *J* = 8.9 Hz, 2H) 6.48 (dd, *J* = 6.3, 2.1 Hz, 2H) 5.18 (m, 1H) 4.32 (d, *J* = 3.6 Hz, 1H) 2.85 (s, 3H) 2.82 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 33.9, 36.9, 62.8, 70.0, 113.9, 114.4, 118.3, 118.8, 129.3, 129.4, 134.7, 148.8, 149.2, 161.6, 202.3



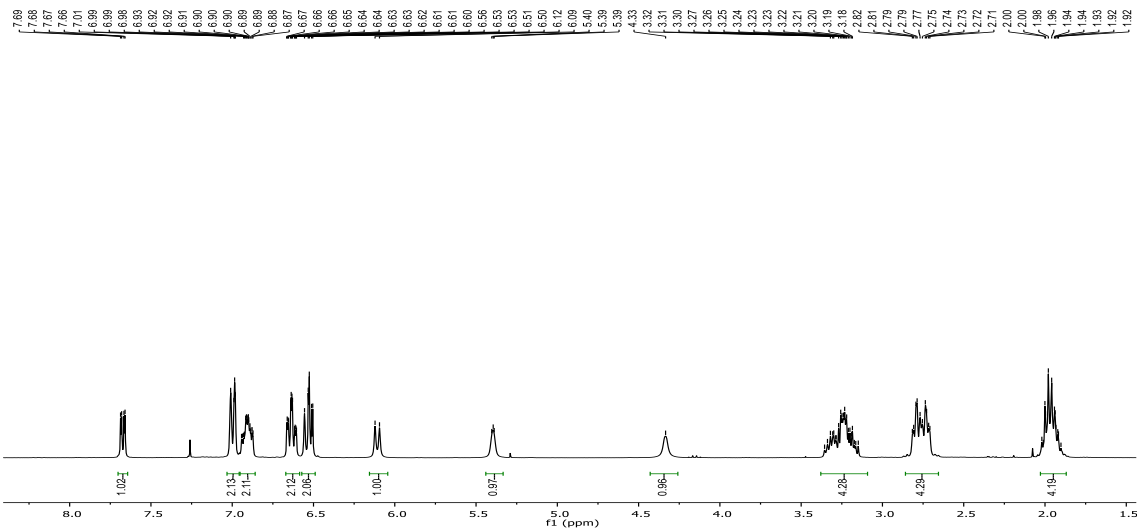


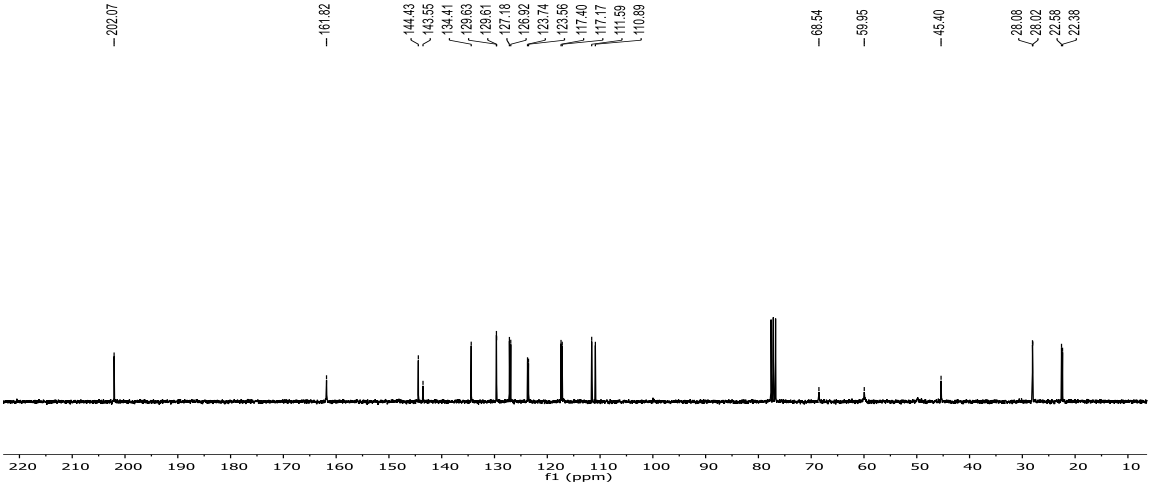
***trans*-4,5-bis(dihydroquinoline)-cyclopent-2-enone 5**



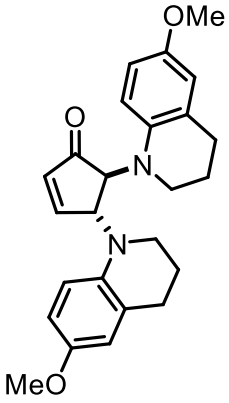
The product was isolated as a yellow solid (358 mg, quantitative yield). The spectral data are in agreement with the literature[196]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 6.2, 2.0 Hz, 1H) 7.0 (d, *J* = 7.4 Hz, 2H) 6.87-6.94 (m, 2H) 6.63 (tdd, *J* = 7.3, 2.5, 1.1 Hz, 2H) 6.53 (m, 2H) 6.11 (d, *J* = 8.2 Hz, 1H) 5.40 (s, 1H) 4.33 (s, 1H) 3.15-3.36 (m, 4H) 2.71-2.72 (m, 4H) 1.90-2.02 (m, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 22.4, 22.6, 28.0, 28.1, 45.4, 59.9, 68.5, 110.9, 111.6, 117.2, 117.4, 123.6, 123.7, 126.9, 127.2, 129.6, 129.6, 134.4, 143.6, 144.4, 161.8, 202.1



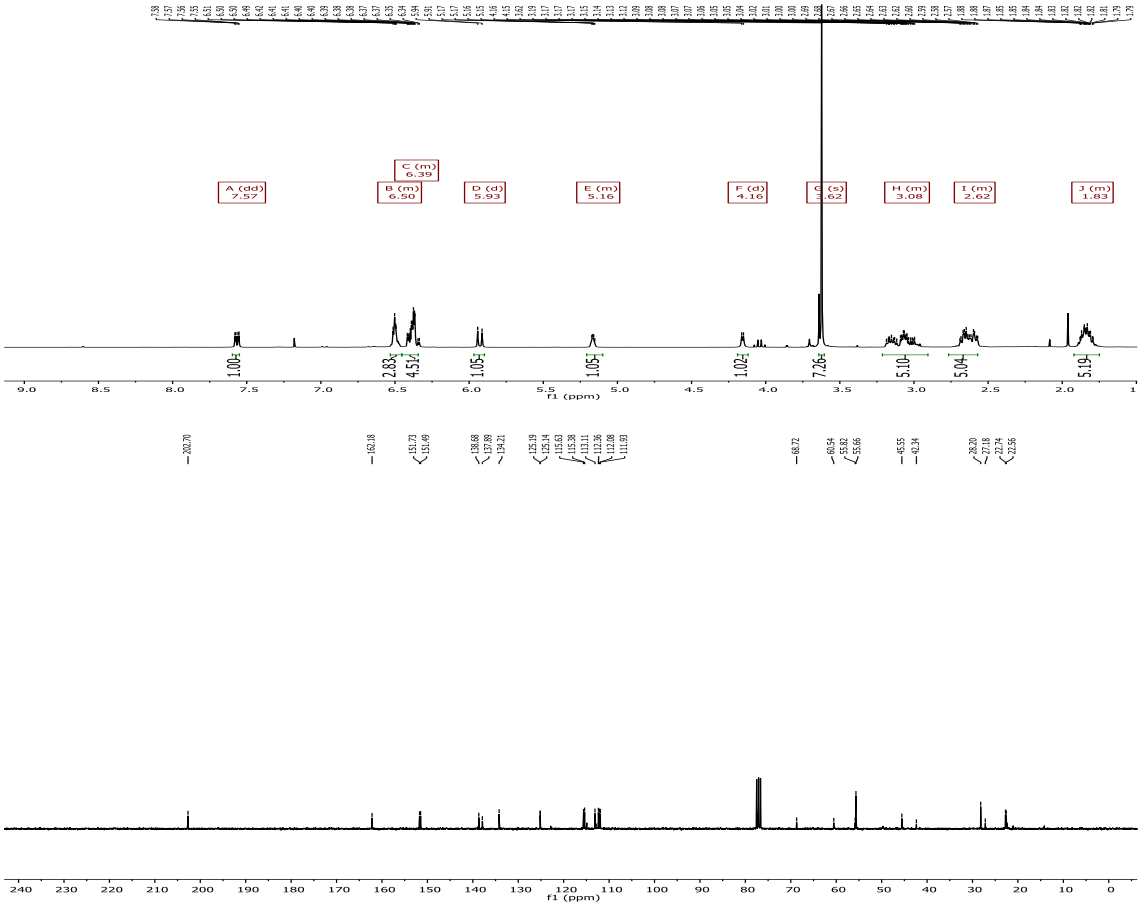


***trans*-4,5-bis(6-methoxy-3,4-dihydroquinolin-1(2H)-yl)cyclopent-2-en-1-one 117**

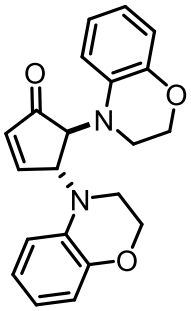


The product was isolated as a yellow solid (416 mg, 99% yield). The spectral data are in agreement with the literature[196]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, J = 6.3, 2.0 Hz, 1H), 6.69 – 6.48 (m, 2H), 6.45 – 6.24 (m, 4H), 5.93 (d, J = 8.8 Hz, 1H), 5.23 – 5.02 (m, 1H), 4.16 (d, J = 3.6 Hz, 1H), 3.62 (s, 6H), 3.35 – 2.90 (m, 4H), 2.72 – 2.55 (m, 4H), 1.90 – 1.70 (m, 4H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.70, 162.18, 151.73, 151.49, 138.68, 137.89, 134.21, 125.19, 125.14, 115.63, 115.38, 113.11, 112.36, 112.08, 111.93, 68.72, 60.54, 55.66, 45.55, 28.20, 22.74, 22.56.

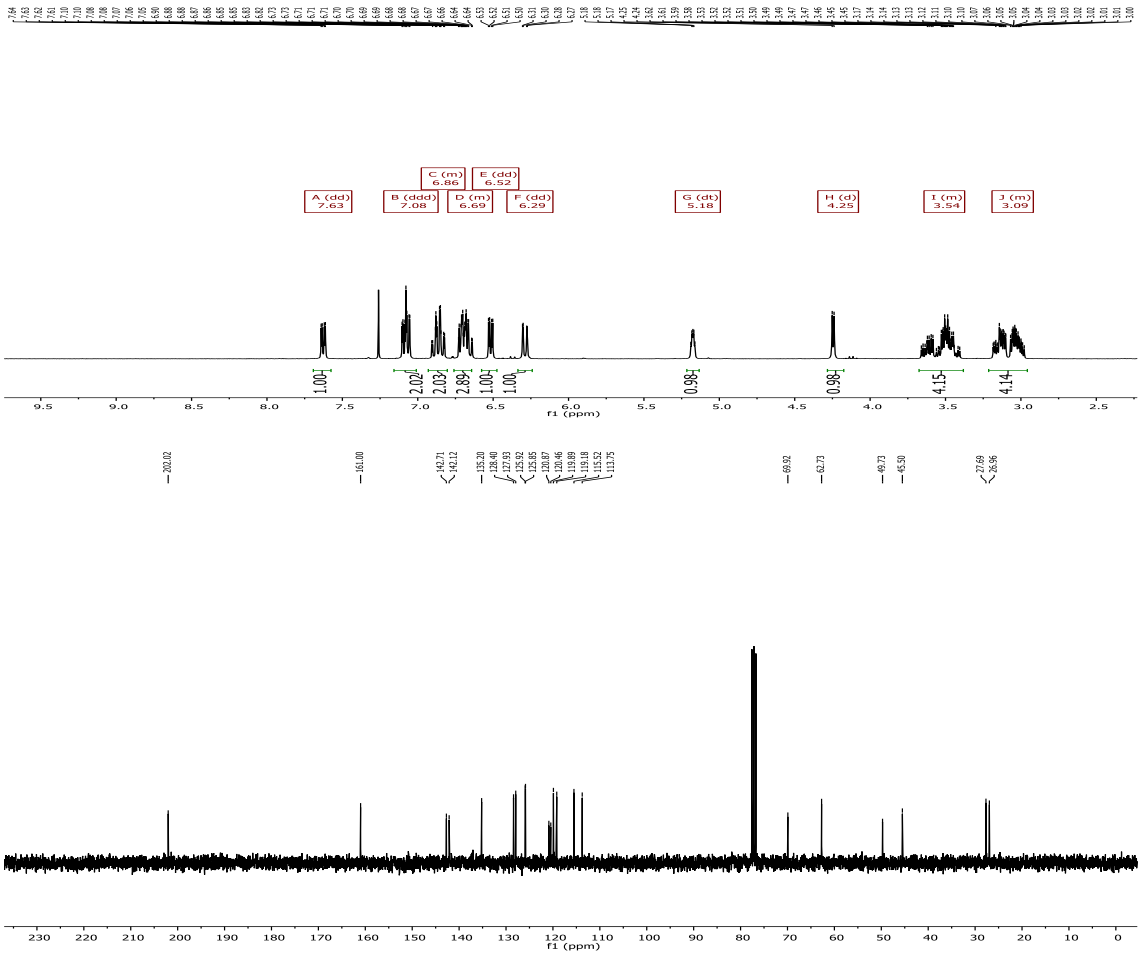


***trans*-4,5-bismorpholino-cyclopent-2-enone 116**

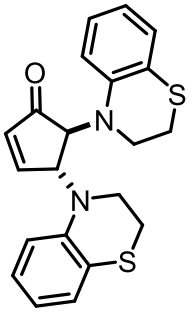


The product was isolated as a yellow solid (272 mg, 75% yield).

^{1}H NMR (300 MHz, $CDCl_3$ δ 7.63 (dd, J = 6.3, 2.1 Hz, 1H), 7.08 (ddd, J = 7.7, 5.8, 1.6 Hz, 2H), 6.97 – 6.77 (m, 2H), 6.78 – 6.61 (m, 3H), 6.52 (dd, J = 6.3, 2.1 Hz, 1H), 6.29 (dd, J = 8.3, 1.2 Hz, 1H), 5.18 (m, 1H), 4.25 (d, J = 3.7 Hz, 1H), 3.84 – 3.34 (m, 4H), 3.24 – 2.92 (m, 4H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.02, 161.00, 142.71, 142.12, 135.20, 128.40, 127.93, 125.92, 125.85, 120.87, 120.46, 119.89, 119.18, 115.52, 113.75, 69.92, 62.73, 49.73, 45.50, 27.69, 26.96.

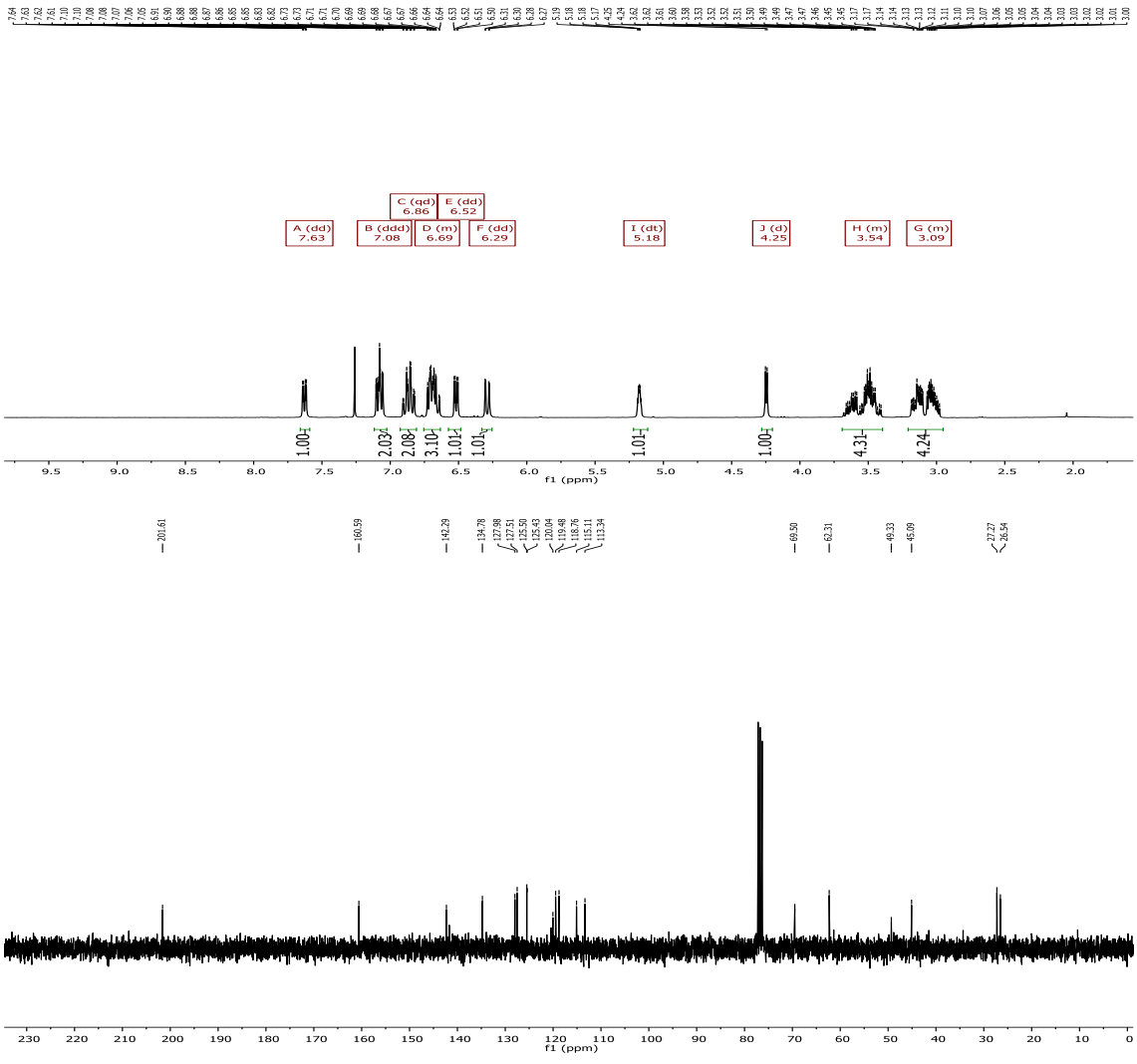


***trans*-4,5-bismorpholino-cyclopent-2-enone 117**

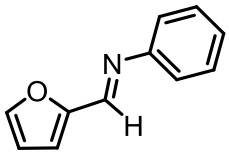


The product was isolated as a yellow solid (321 mg, 81% yield).

^{1}H NMR (300 MHz, $CDCl_3$ δ 7.63 (dd, J = 6.3, 2.1 Hz, 1H), 7.08 (ddd, J = 7.7, 5.8, 1.5 Hz, 2H), 6.86 (qd, J = 8.2, 1.7 Hz, 2H), 6.76 – 6.60 (m, 3H), 6.52 (dd, J = 6.3, 2.1 Hz, 1H), 6.29 (dd, J = 8.2, 1.2 Hz, 1H), 5.18 (m, 1H), 4.25 (d, J = 3.7 Hz, 1H), 3.74 – 3.35 (m, 4H), 3.23 – 2.91 (m, 4H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 201.61, 160.59, 142.29, 134.78, 127.98, 127.51, 125.50, 125.43, 120.04, 119.48, 118.76, 115.11, 113.34, 69.50, 62.31, 45.09, 27.27, 26.54.



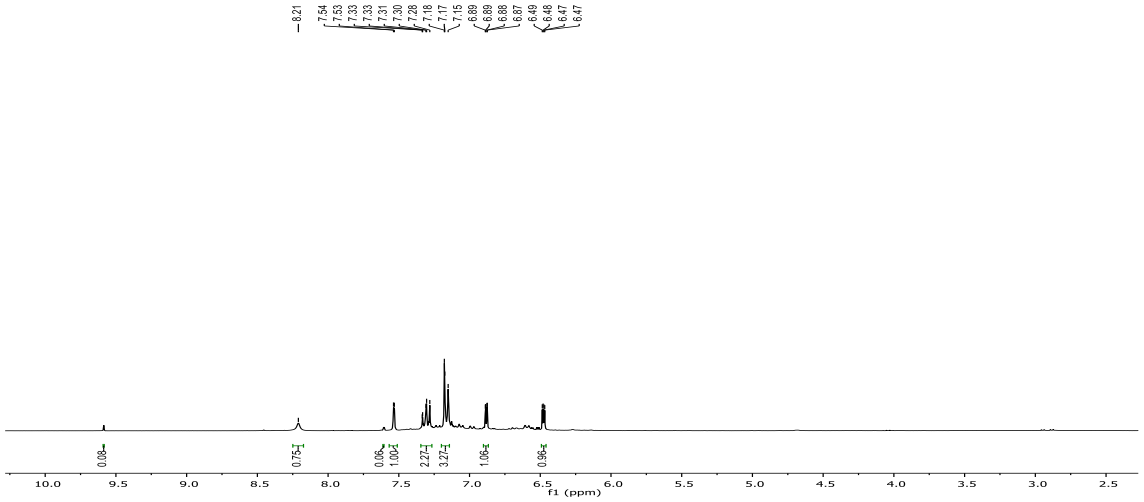
1-(furan-2-yl)-*N*-phenylmethanimine 35

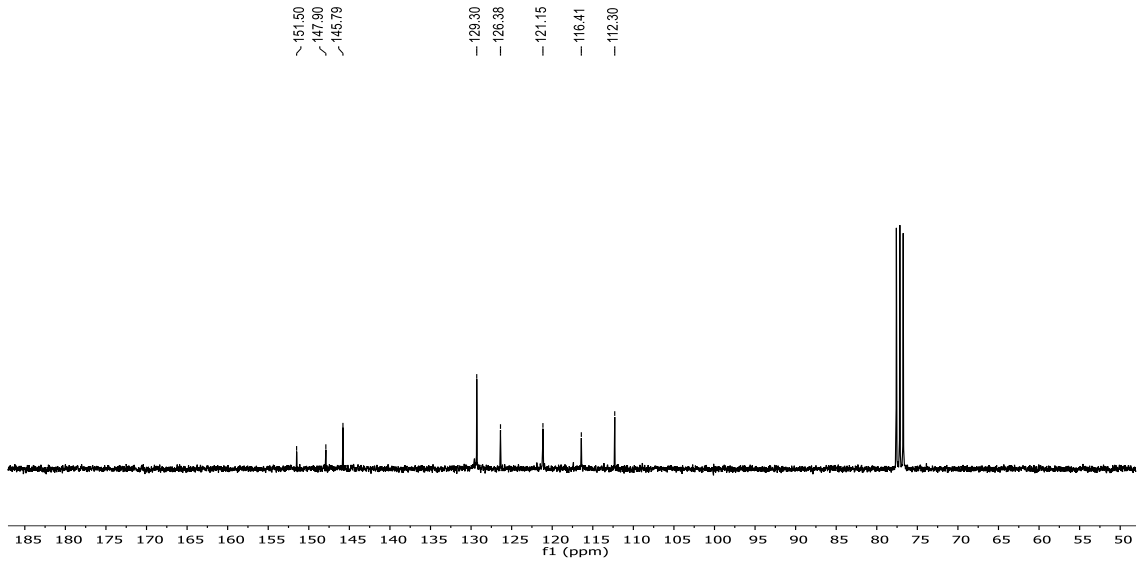


The product was isolated as a brown oil (178 mg, quantitative yield, 93% purity). The spectral data are in agreement with the literature[196]

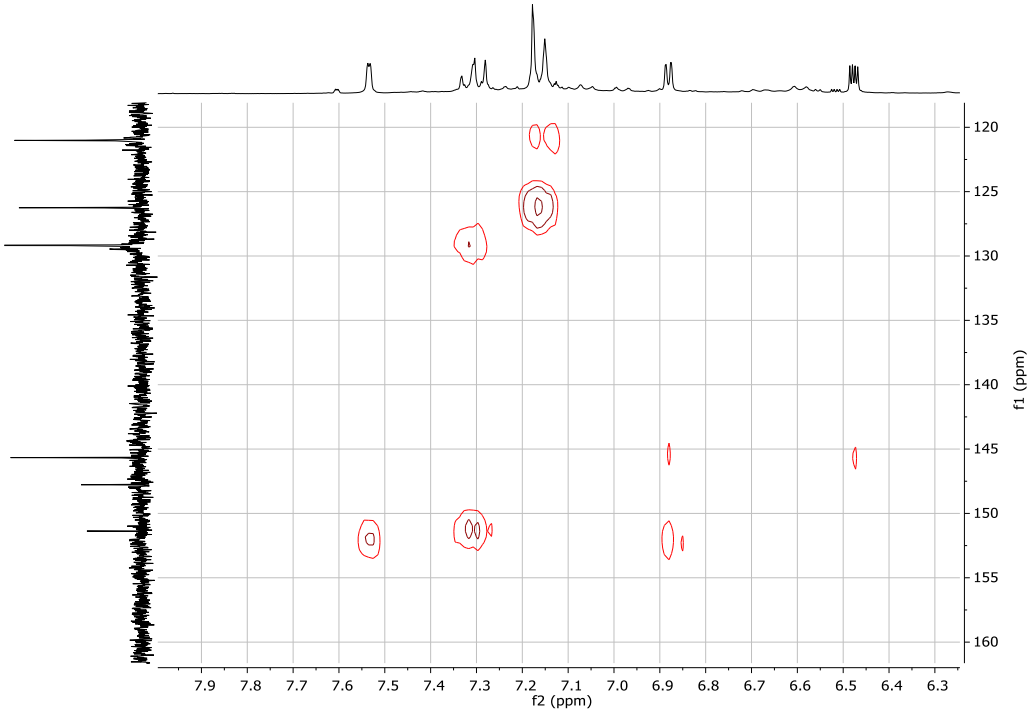
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H) 7.53 (d, *J* = 1.7 Hz, 1H) 7.28-7.33 (m, 2H) 7.15-7.18 (m, 3H) 6.88 (dd, *J* = 3.4, 0.7 Hz, 1H) 6.48 (dd, *J* = 3.5, 1.8 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 112.3, 116.4, 121.2, 126.4, 139.3, 145.8, 147.9, 151.5, 151.9.

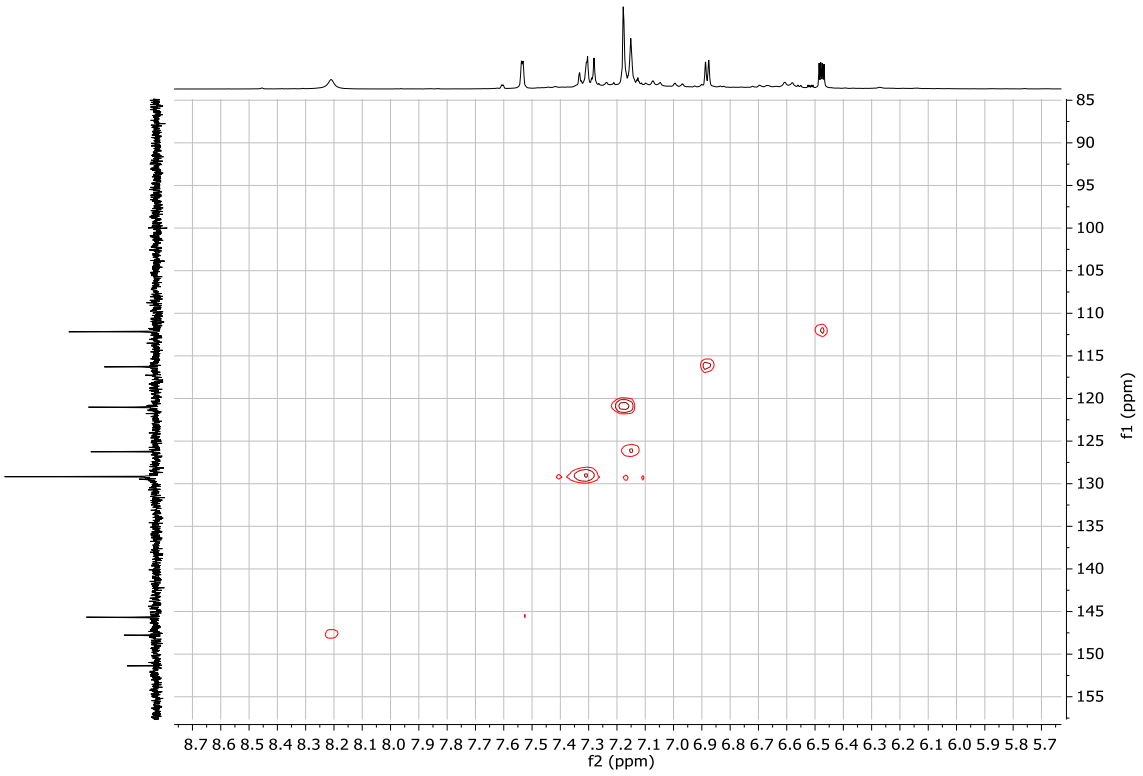




HMBC


120
125
130
135
140
145
150
155
160
f1 (ppm)
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3
f2 (ppm)

HSQC


85
90
95
100
105
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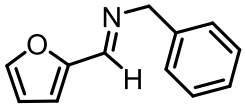
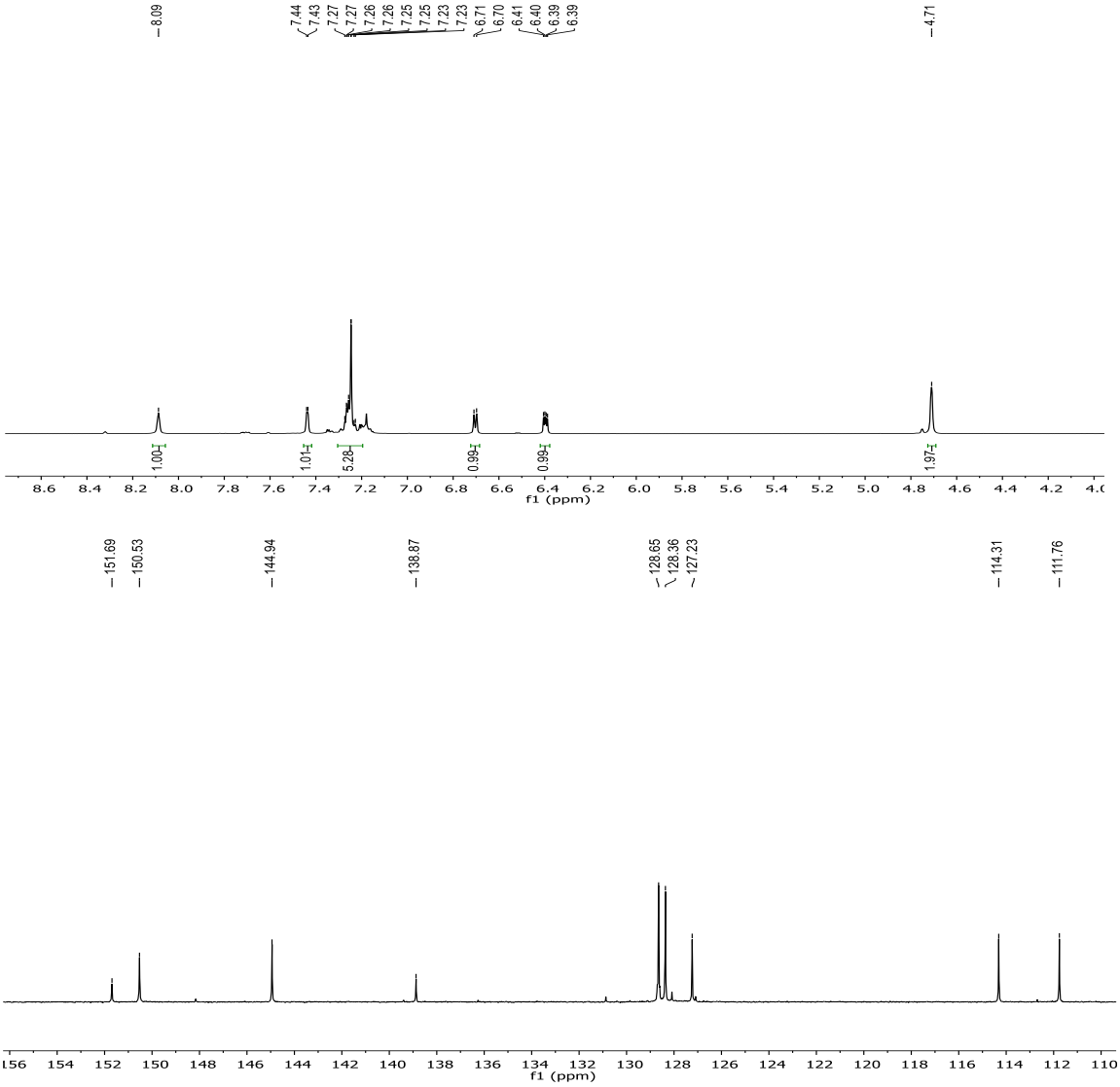
115
120
125
130
135
140
145
150
155
f1 (ppm)
8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7
f2 (ppm)

N-benzyl-1-(furan-2-yl)methanimine 36

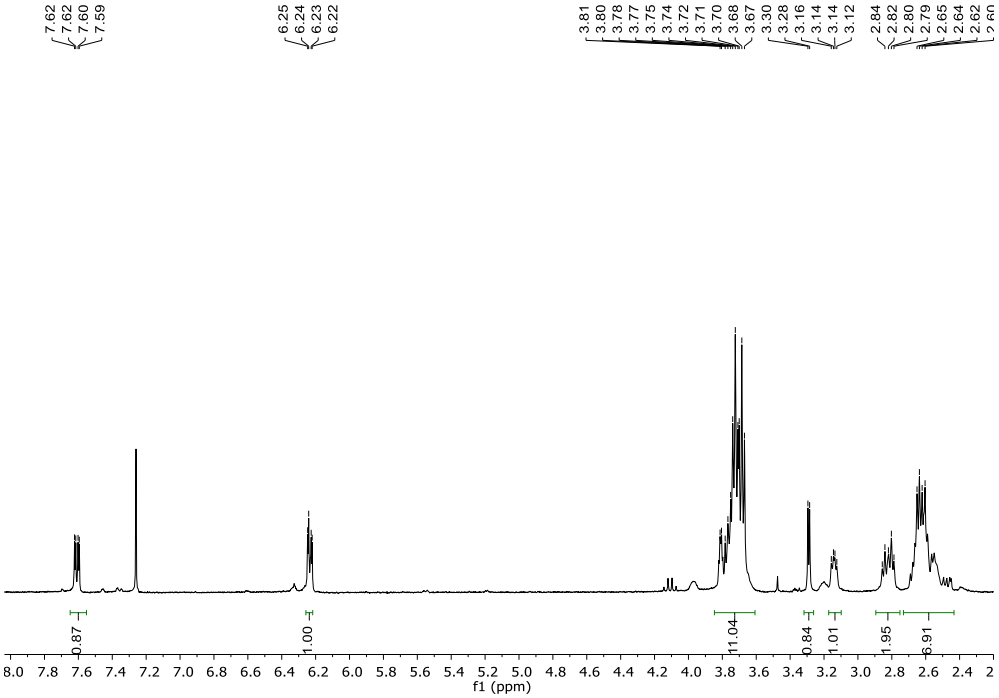


The product was isolated as a brown oil (192 mg, quantitative yield). The spectral data are in agreement with the literature[196]

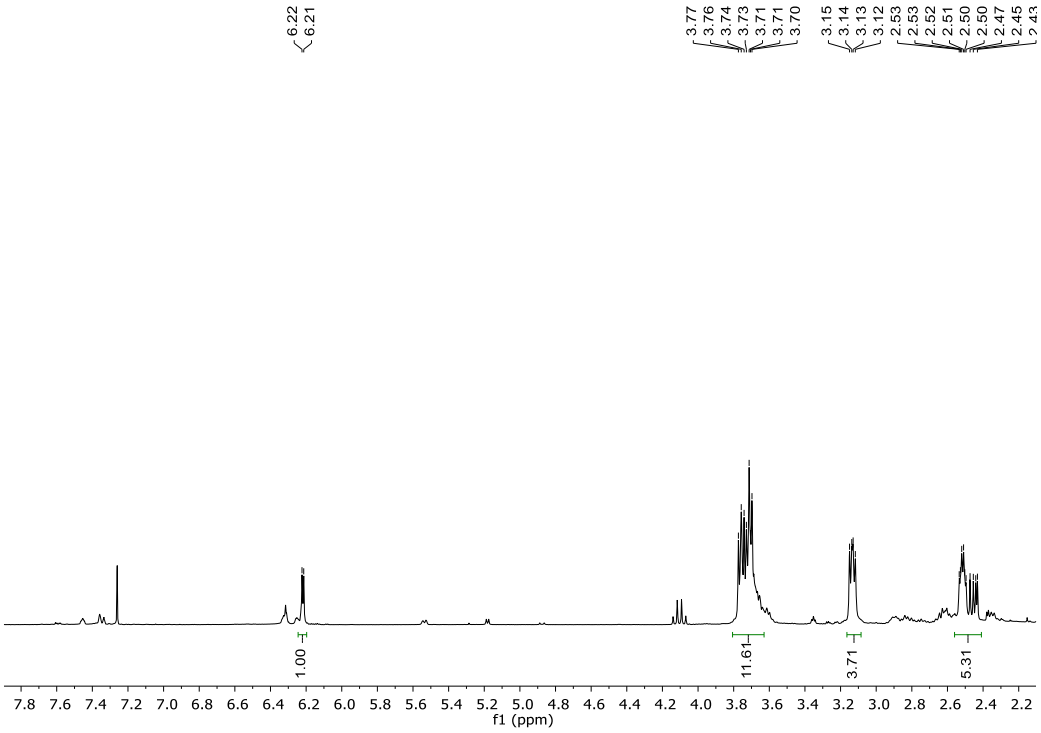
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H) 7.44 (d, *J* = 1.7 Hz, 1H) 7.25 (m, 5H) 6.70 (d, *J* = 3.4 Hz, 1H) 6.40 (dd, *J* = 3.4, 1.8 Hz, 1H) 4.71 (s, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 65.2, 111.8, 114.3, 127.2, 128.4, 128.7, 138.9, 144.9, 150.5, 151.7.



Gram scale reaction NMRs



^{1}H-NMR of the isolated 10 gram scale reaction of furfural and morpholine in the presence of 0.1 mol % of $Cu(OTf)_2$ after 8h. Regioisomer 2,4-dimorpholino-cyclopent-2-enone present in a 0.87:0.13 (6.7:1) ratio of product **2** to regioisomer.



^{1}H-NMR of the crude 10 gram scale reaction of furfural and morpholine in the presence of 0.1 mol % of $Cu(OTf)_2$ after 24h. The spectral data is in agreement with the literature[13]

Preparation of solid supported copper catalysts

General procedure for the copper immobilization in silica (2.5%, 5% and 20%)

To a solution of $CuSO_4$ (from 0.25 g to 2 g) in water (50 mL) was added silica (from 9.75 g to 8.0 g). The suspension was allowed to stir for 10 minutes. The solvent was evaporated under reduced pressure and the light blue solid was dried in an oven at 110 ºC for 24h.

Procedure for the copper immobilization in alumina (20%)

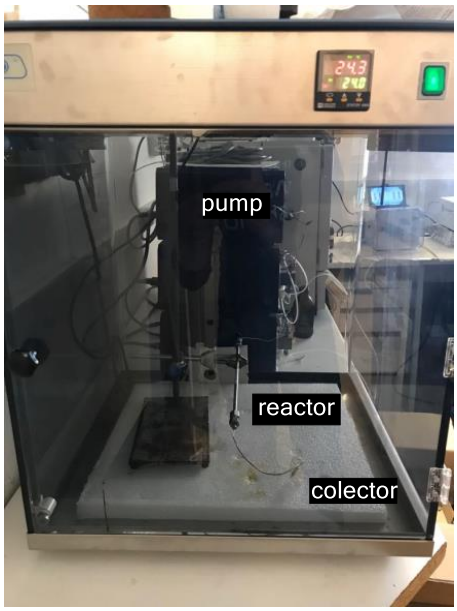
To a solution of $CuSO_4$ (1 g) in water (25 mL) was added basic alumina (4 g). The suspension was allowed to stir for 10 minutes. The solvent was evaporated under reduced pressure and the deep blue solid was dried in an oven at 110 ºC for 24h.

Procedure for the copper immobilization in hydroxyapatite $Ca_5(PO_4)_3(OH)$ (20%)

To a solution of $CuSO_4$ (0.2 g) in acetone (5 mL) was added $Ca_5(PO_4)_3(OH)$ (0.8 g). The suspension was allowed to stir for 10 minutes. The solvent was evaporated under reduced pressure and the light green solid was dried in an oven at 110 ºC for 24h.

General procedure for the development of the continuous flow method to prepare *trans*-4,5-dimorpholino-cyclopent-2-enone

A solution of the furfural (1 equiv) and morpholine (2.1 equiv) in a mixture of isopropanol:hexane (2 mL) was injected in the continuous flow reactor at the corresponding flow rate inside a controlled temperature air circulating oven. Another 1 mL of solvent mixture was injected at the corresponding flow rate. 1,3,5-trimethoxybenzene (0.33 equiv) was added to the crude mixture. The solvent was evaporated and the sample analysed by ^1H NMR.



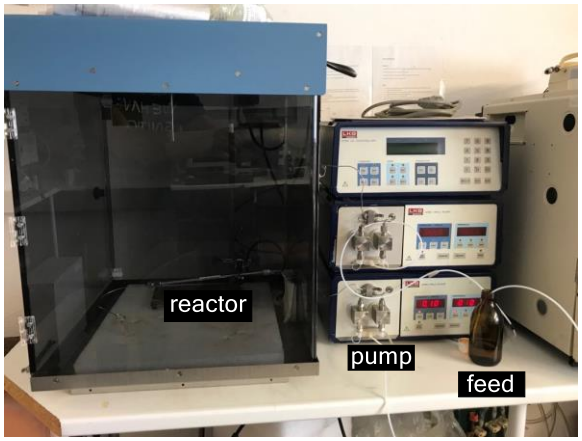


Figure 33 Pictures of the used reactor

Table 27 Data from the used flow system

Flow chemistry approach	
Reactor (empty HPLC column, ID= 4.6 mm, L= 50 mm, g)	62.366
Reactor + catalyst (g)	62.837
catalyst (mg)	471
Reactor + catalyst + Solvent (g)	63.164
Solvent	0.327 g solvent (0.500 mL hexane)

General procedure for the continuous flow method to prepare *trans*-4,5-diamino-cyclopent-2-enones

A solution of the furfural (20 mg, 0.2 mmol, 1 equiv) and the corresponding amine (0.43 mmol, 2.1 equiv) in a mixture of isopropanol:hexane 2:8 (2 mL) was injected in the continuous flow reactor at 25 µL min^{-1} flow rate in a controlled temperature air circulating oven at 24 ºC. Another 1 mL of solvent mixture was injected at the corresponding flow rate. The solvent was evaporated and the pure products were analysed by ^{1}H NMR.

***trans*-4,5-bis(diallylamine)-cyclopent-2-enone**

The title compound was prepared from diallyamine according to general procedure and isolated as an orange oil (54 mg, 96% yield).

***trans*-4,5-bismorpholino-cyclopent-2-enone**

The title compound was prepared from morpholine according to general procedure and isolated as a yellow solid (52 mg, 99% yield).

***trans*-4,5-bispiperidino-cyclopent-2-enone**

The title compound was prepared from piperidine according to general procedure and isolated as a yellow oil (48 mg, 94% yield).

***trans*-4,5-bis(dihydroquinoline)-cyclopent-2-enone**

The title compound was prepared from piperidine according to general procedure and isolated as a brown oil (70 mg, 98% yield).

***trans*-4,5-bis(*N*-methylaniline)-cyclopent-2-enone**

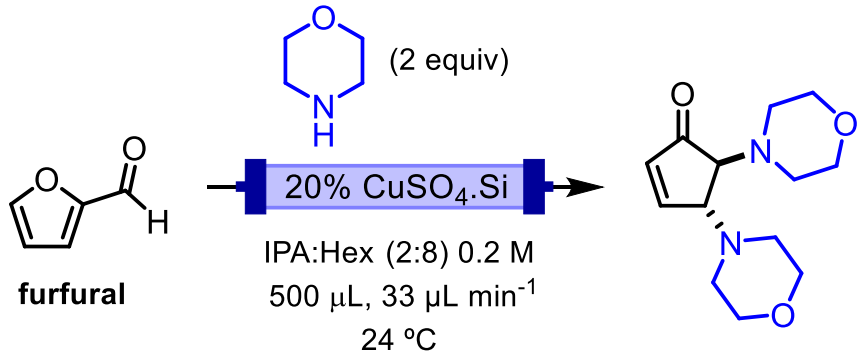
The title compound was prepared from piperidine according to general procedure and isolated as a brown oil (59 mg, 98% yield).

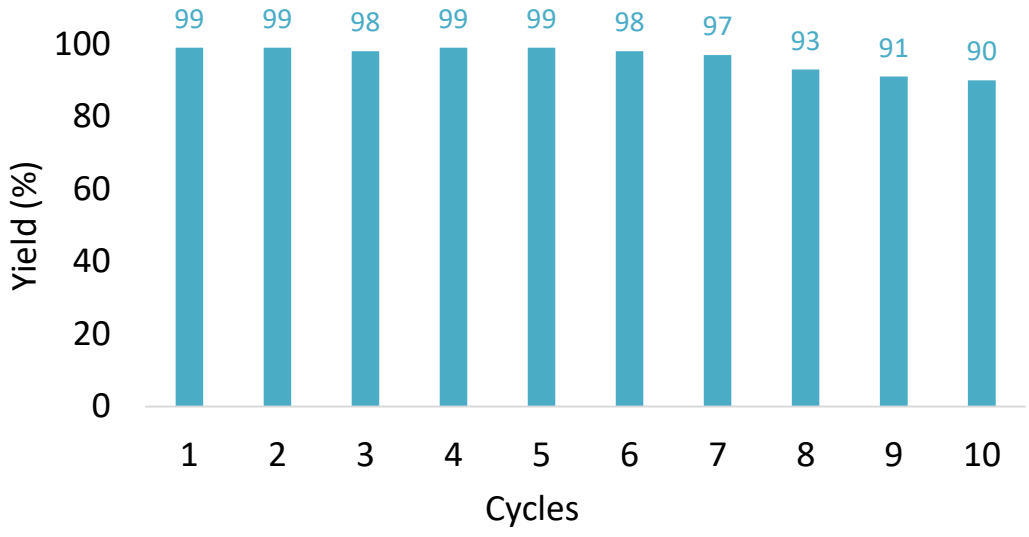
***trans*-4,5-bis(dibenzylamine)-cyclopent-2-enone**

The title compound was prepared from piperidine according to general procedure and isolated as a brown oil (97 mg, 99% yield).

Procedure for the continuous flow method to prepare *trans*-4,5-dimorpholino-cyclopent-2-enone 2

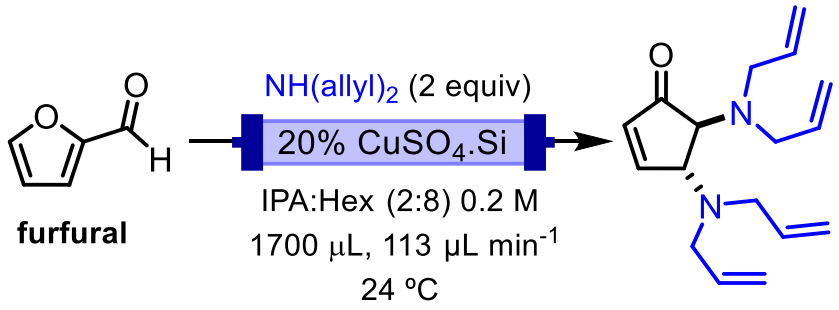
A solution of the furfural (100 mg, 1 mmol, 1 equiv) and morpholine (190 mg, 2.1 mmol, 2.1 equiv) in a mixture of isopropanol:hexane 2:8 (5 mL) was injected in the continuous flow reactor at 33 µL min^{-1} flow rate in a in a controlled temperature air circulating oven at 24 ºC. Another 1 mL of solvent mixture was injected at the corresponding flow rate. In total 10 aliquots of 500 µl were collected. The solvent was evaporated and the samples were analysed by ^{1}H NMR.

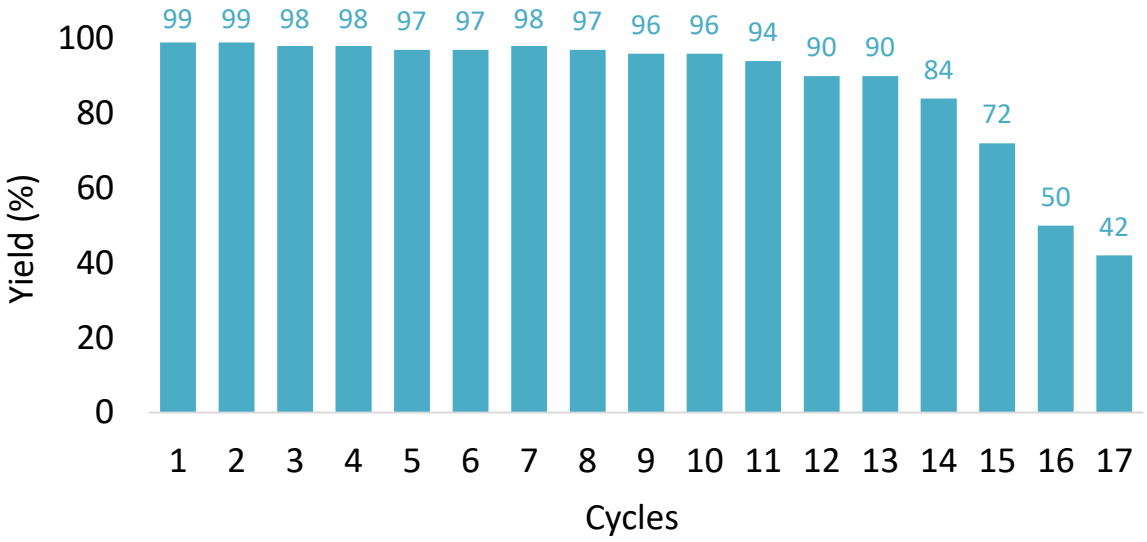




Procedure for the continuous flow method to prepare *trans*-4,5-diallyl-cyclopent-2-enone 4

A solution of the furfural (554 mg, 5.77 mmol, 1 equiv) and diallylamine (1.18 g, 12.1 mmol, 2.1 equiv) in a mixture of isopropanol:hexane 2:8 (29 mL) was injected in the continuous flow reactor at 33 µL min^{-1} flow rate in a in a controlled temperature air circulating oven at 24 ºC. Another 1 mL of solvent mixture was injected at the corresponding flow rate. In total 17 aliquots of 1700 µl were collected. The solvent was evaporated and the samples were analysed by ^{1}H NMR. The copper content of the aliquots was measured by inductively coupled plasma (ICP) analysis.





FTIR analysis of the $CuSO_4$.Si catalyst before the flow reaction, after the flow reaction and spiked with 10 % (w/w) of DCP and diallylamine

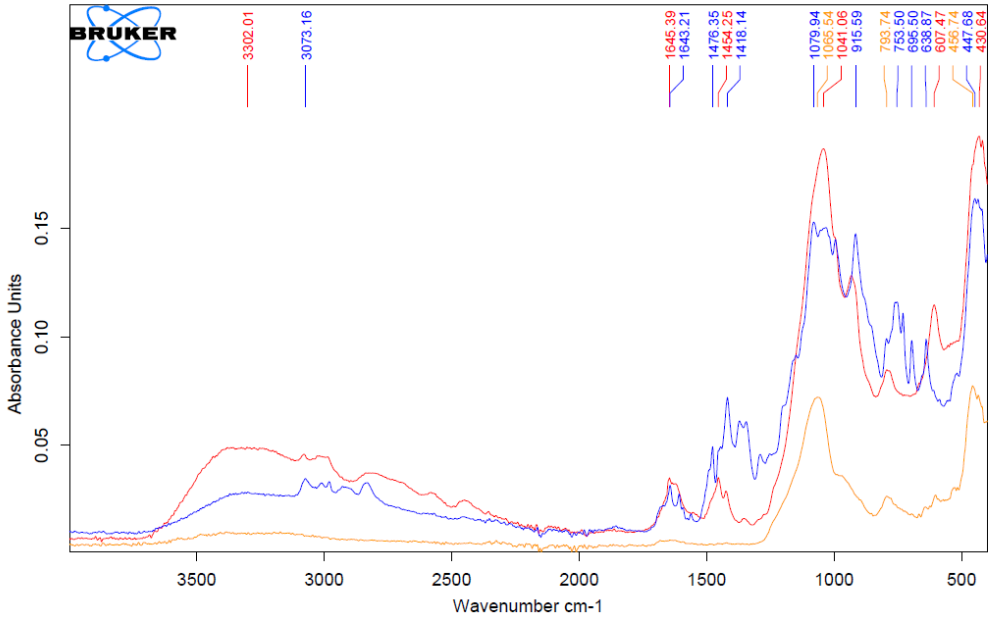
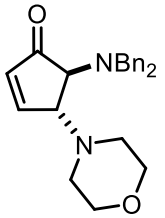


Figure 34**.** FTIR analysis of the CuSO4.Si catalyst before the flow reaction (orange), after the flow reaction (red) and spiked with 10 % (w/w) of **DCP** and diallylamine (blue).

General procedure for the preparation of mixed *trans*-4,5-diamino-cyclopent-2-enones

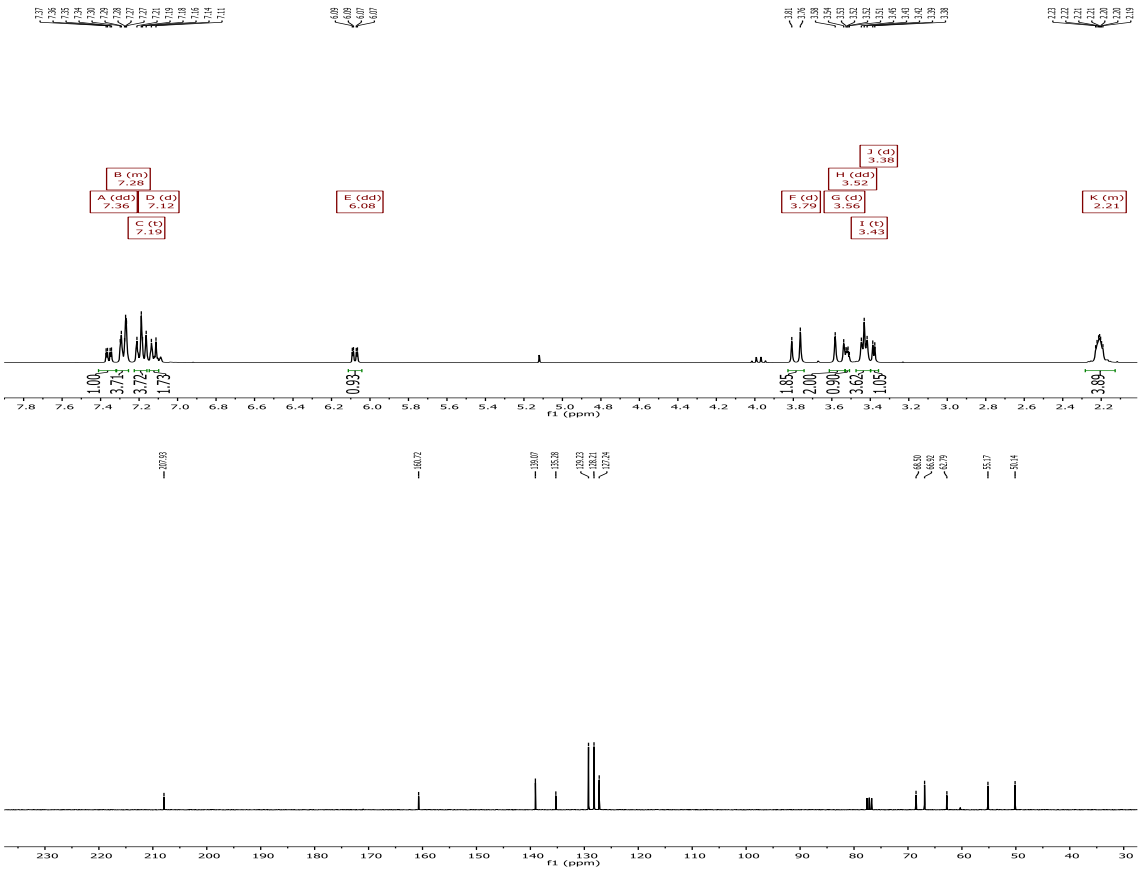
To a solution of $Cu(OTf)_2$ (40 mg, 10 mol%) in water (1 mL) was added amine A (2.08 mmol, 2 equiv.), amine B (1.04 mmol, 1 equiv.), and furfural (100 mg, 1.04 mmol). The reaction was allowed to stir vigorously at room temperature for 1 minutes. Then the reaction mixture was diluted with water (9 mL) and extracted with diethyl ether (3 $\times$ 10 mL). The combined organic phases were dried with $MgSO_4$, the solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography.

5-(dibenzylamino)-4-(piperidin-1-yl)cyclopent-2-en-1-one 37

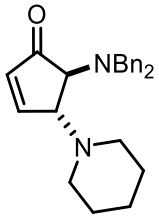


The title compound was prepared using morpholine as amine A and dibenzylamine as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 125 mg (83%) of pure product as a yellow crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, J = 6.3, 2.1 Hz, 1H), 7.32 – 7.25 (m, 4H), 7.19 (t, J = 7.2 Hz, 4H), 7.12 (d, J = 7.1 Hz, 2H), 6.08 (dd, J = 6.2, 1.8 Hz, 1H), 3.79 (d, J = 13.3 Hz, 2H), 3.56 (d, J = 13.2 Hz, 2H), 3.52 (dd, J = 3.4, 1.8 Hz, 1H), 3.43 (t, J = 4.5 Hz, 4H), 3.38 (d, J = 3.2 Hz, 1H), 2.24 – 2.14 (m, 4H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 208.0, 160.8, 139.1, 135.3, 129.3, 128.3, 127.3, 68.6, 67.0, 62.8, 55.2, 50.2. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{22}H_{27}N_2O_2$ $[M + H]^+$ 363.20670, found 363.20742.

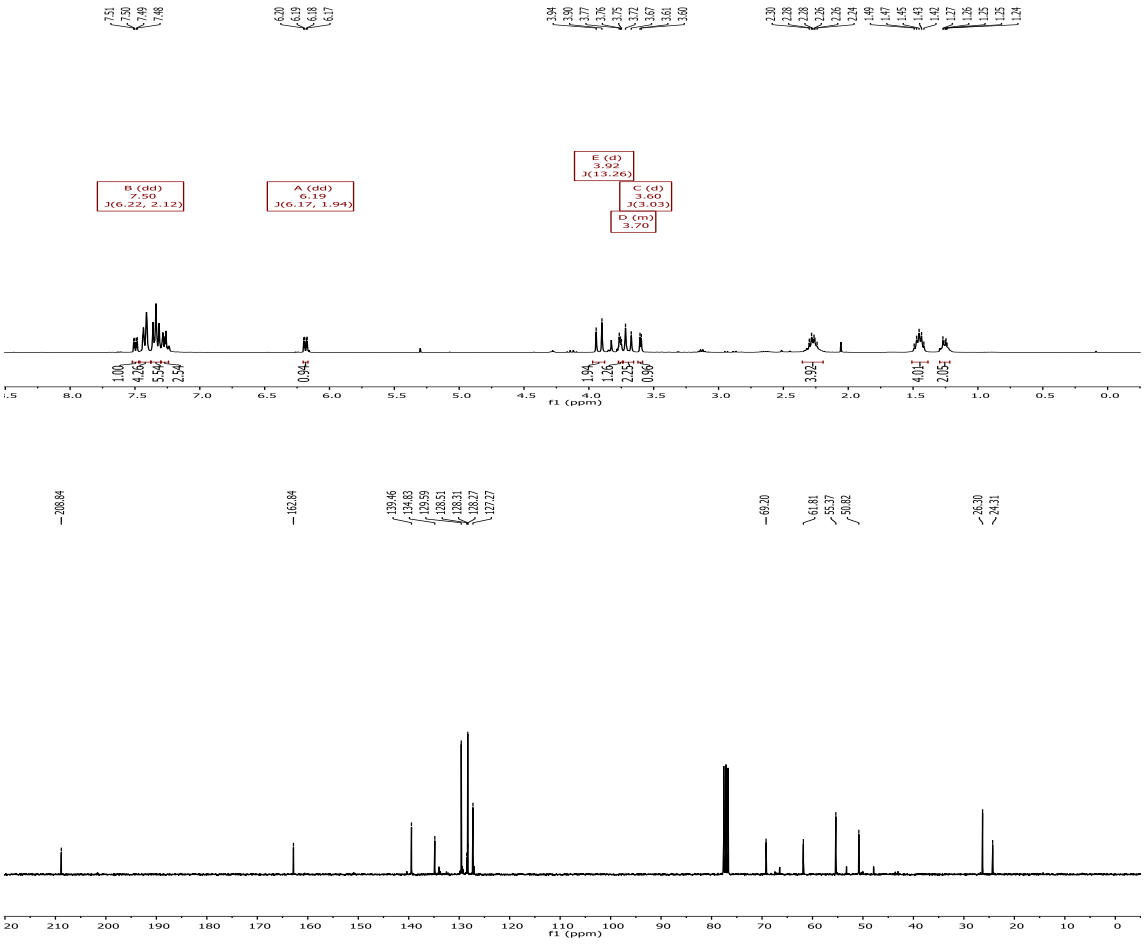


5-(dibenzylamino)-4-(piperidin-1-yl)cyclopent-2-en-1-one 38

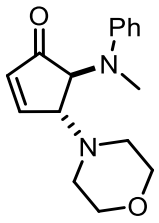


The title compound was prepared using piperidine as amine A and dibenzylamine as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 108 mg (72%) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 6.2, 2.1 Hz, 1H), 7.48 – 7.20 (m, 10H), 6.19 (dd, J = 6.2, 1.9 Hz, 1H), 3.92 (d, J = 13.3 Hz, 2H), 3.76 (m, 1H), 3.78 – 3.64 (m, 2H), 3.60 (d, J = 3.0 Hz, 1H), 2.49 – 2.19 (m, 4H), 1.44 (q, J = 5.6 Hz, 4H), 1.36 – 1.17 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 208.84, 162.84, 139.46, 134.83, 129.59, 128.31, 127.27, 69.2, 61.81, 55.37, 50.82, 26.30, 24.31. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{24}H_{29}N_2O$ $[M + H]^+$ 361.22744, found 361.22713.

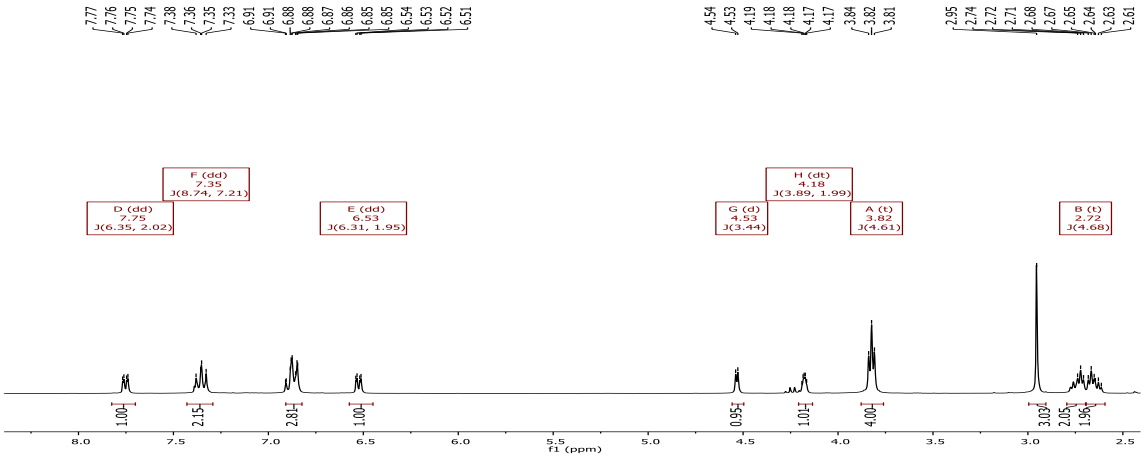


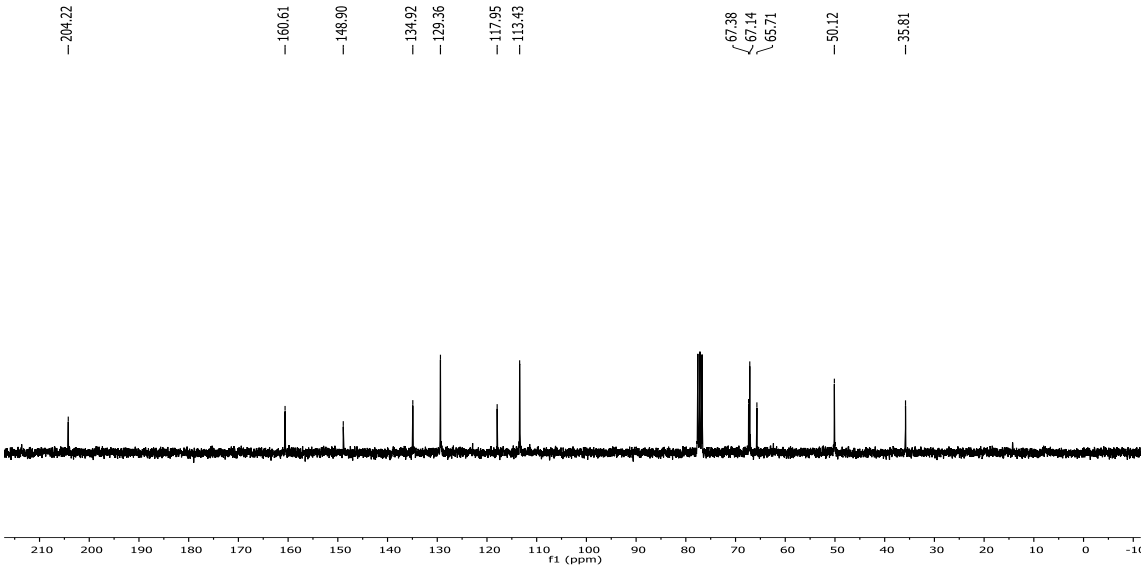
5-(methyl(phenyl)amino)-4-morpholinocyclopent-2-en-1-one 40



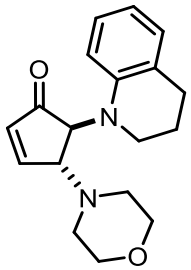
The titled compound was prepared using morpholine as amine A and *N*-methylaniline as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 88 mg (78%) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 6.3, 2.0 Hz, 1H), 7.35 (dd, *J* = 8.7, 7.2 Hz, 2H), 6.53 (dd, *J* = 6.3, 1.9 Hz, 2H), 4.53 (d, *J* = 3.4 Hz, 1H), 4.18 (m, 1H), 3.82 (t, *J* = 4.6 Hz, 1H), 2.74 (dt, *J* = 9.4, 4.6 Hz, 4H),2.95 (s, 3H) 2.65 (dt, *J* = 11.3, 4.6 Hz, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.2, 160.6, 148.9, 134.9, 129.3, 117.9, 113.4, 67.3, 67.1, 65.7, 50.1, 35.8. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{16}H_{21}N_2O_2$ $[M + H]^+$ 273.15975, found 273.15945.



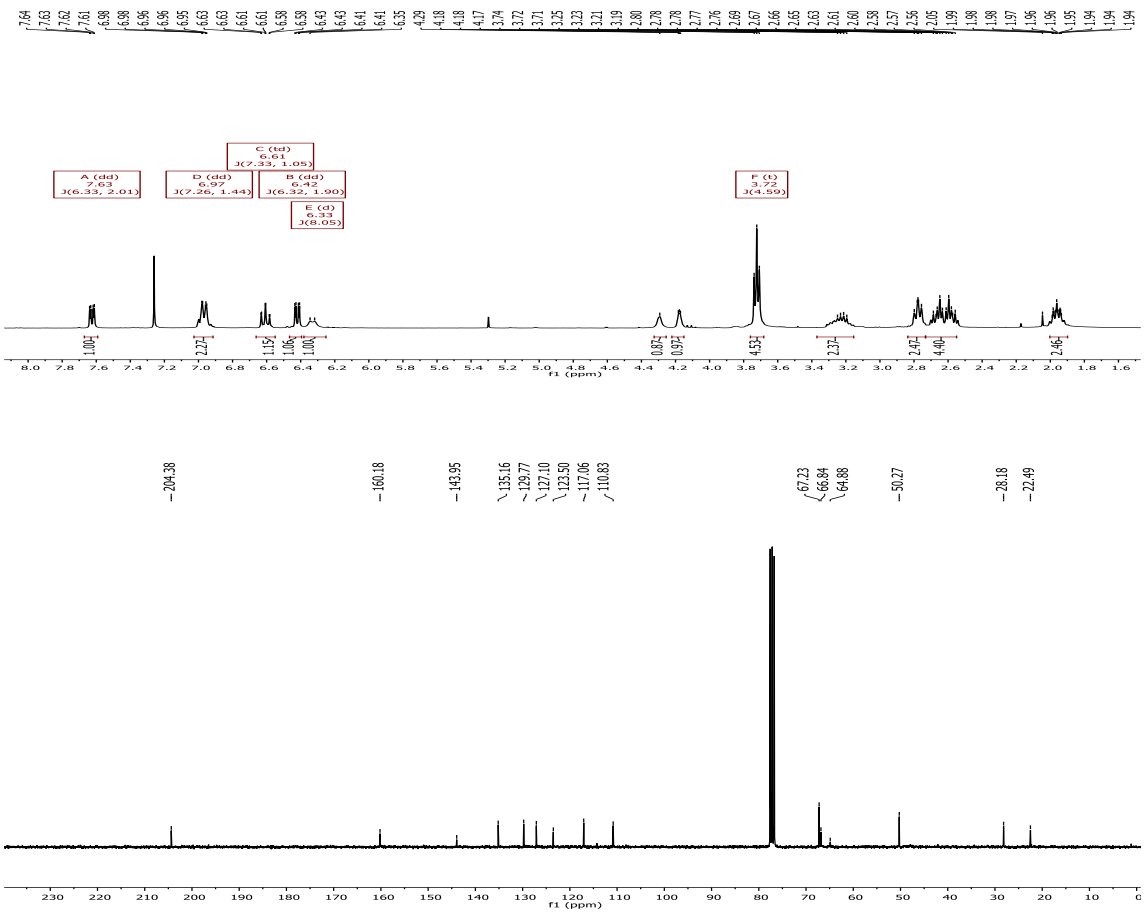


5-(3,4-dihydroquinolin-1(2H)-yl)-4-morpholinocyclopent-2-en-1-one 41

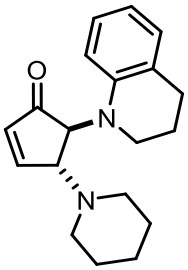


The titled compound was prepared using morpholine as amine A and tetrahydroquinoline as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 106 mg (86%) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, J = 6.3, 2.0 Hz, 1H), 6.97 (dd, J = 7.3, 1.4 Hz, 2H), 6.61 (td, J = 7.3, 1.1 Hz, 1H), 6.42 (dd, J = 6.3, 1.9 Hz, 1H), 6.33 (d, J = 8.0 Hz, 1H), 4.29 (s, 1H), 4.21 – 4.15 (m, 1H), 3.72 (t, J = 4.6 Hz, 4H), 3.22 (dd, J = 10.9, 5.5 Hz, 2H), 2.86 – 2.71 (m, 2H), 2.70 – 2.37 (m, 4H), 2.01 – 1.83 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.3, 160.1, 143.9, 135.1, 129.7, 127.1, 123.5, 117.0, 110.8, 67.2, 66.8, 50.2, 28.1, 22.4. **HRMS (ESI-MS)** *m/z* calcd For compound $C_{18}H_{23}N_2O_2$ $[M + H]^+$ 299.17540, found 299.17513.

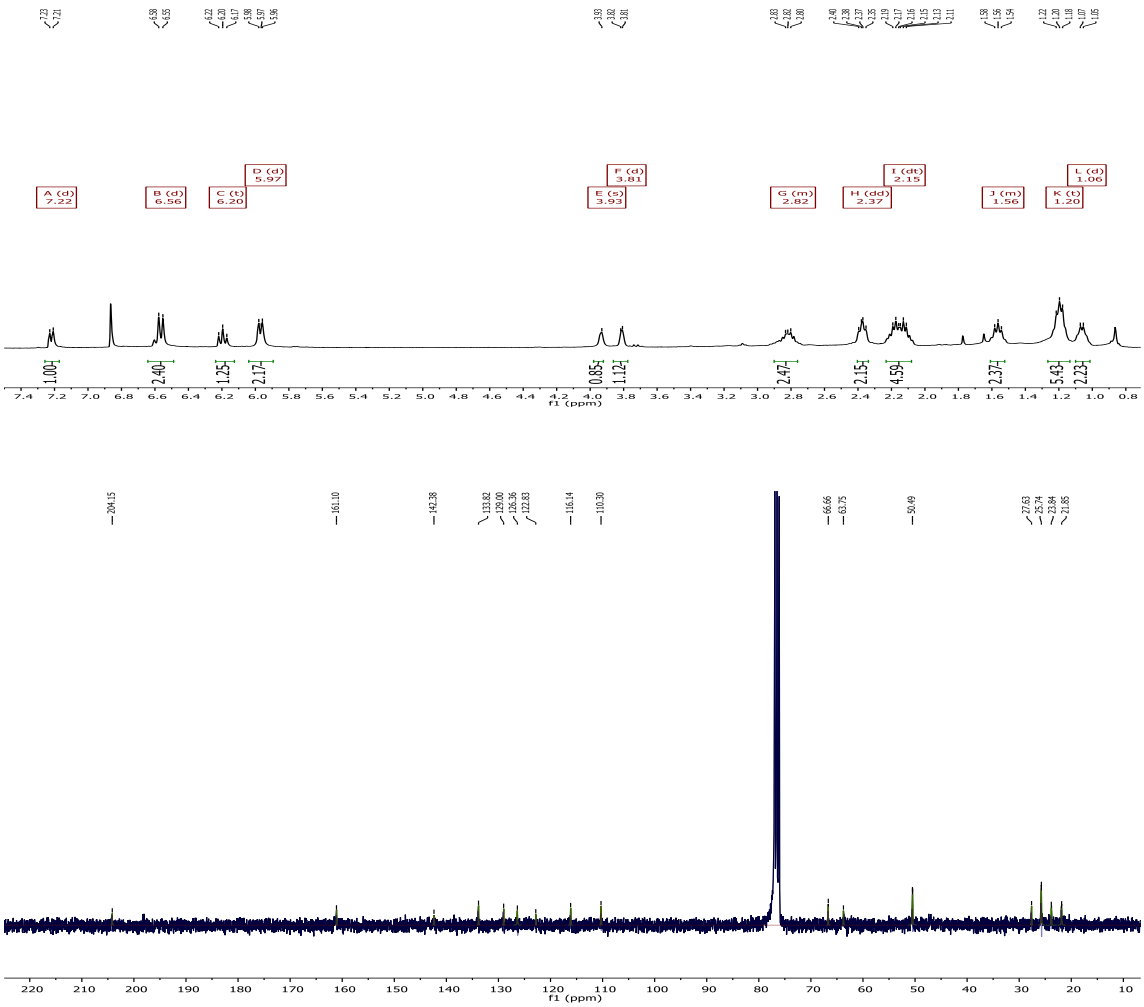


5-(3,4-dihydroquinolin-1(2H)-yl)-4-(piperidin-1-yl)cyclopent-2-en-1-one 42

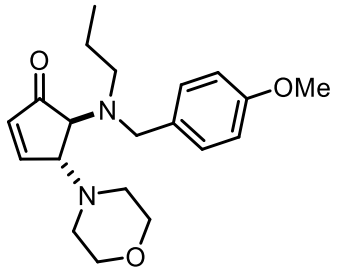


The titled compound was prepared using piperidine as amine A and tetrahydroquinoline as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 61 mg (50%) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 6.3 Hz, 1H), 6.56 (d, J = 7.4 Hz, 2H), 6.20 (t, J = 7.3 Hz, 1H), 5.97 (d, J = 6.5 Hz, 2H), 3.93 (s, 1H), 3.81 (d, J = 3.1 Hz, 1H), 3.09 – 2.62 (m, 1H), 2.37 (m, 2H), 2.15 (m, 4H), 1.65 – 1.48 (m, 2H), 1.20 (m, 5H), 1.06 (m, 2H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.1, 161.1, 142.3, 133.8, 129.0, 126.3, 122.8, 116.1, 110.3, 66.6, 63.7, 50.4, 27.7, 25.7, 23.8, 21.8. **HRMS (ESI-MS)** *m/z* calcd For compound $C_{19}H_{25}N_2O$ $[M + H]^+$ 297.19614, found 297.19702.



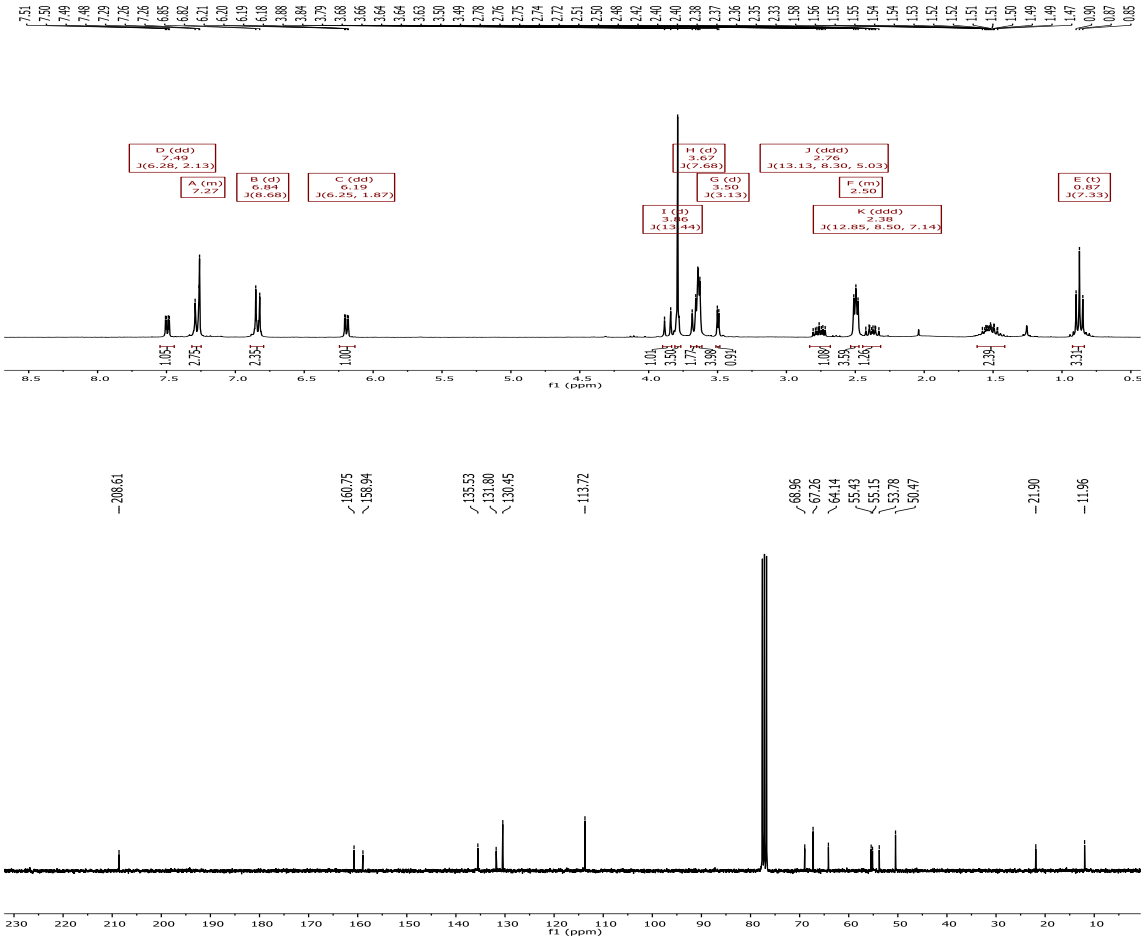
5-((4-methoxybenzyl)(propyl)amino)-4-morpholinocyclopent-2-en-1-one 44



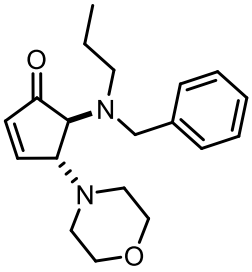
The titled compound was prepared using morpholine as amine A and *N*-propyl-4(OMe)-benzyl-amine as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 107 mg (75%) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, J = 6.3, 2.1 Hz, 1H), 7.36 – 7.16 (m, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.19 (dd, J = 6.2, 1.9 Hz, 1H), 3.86 (d, J = 13.4 Hz, 1H), 3.79 (s, 3H), 3.67 (d, J = 7.7 Hz, 1H), 3.64 (m, 4H), 3.50 (d, J = 3.1 Hz, 1H), 2.76 (ddd, J = 13.1, 8.3, 5.0 Hz, 1H), 2.63 – 2.31 (m, 4H), 2.38 (ddd, J = 12.9, 8.5, 7.1 Hz, 1H), 1.67 – 1.39 (m,

2H), 0.87 (t, J = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 208.6, 160.7, 158.9, 135.5, 131.8, 130.4, 113.7, 68.9, 67.2, 64.1, 55.4, 55.1, 53.7, 50.4, 21.9, 11.9. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{20}H_{29}N_2O_3$ $[M + H]^+$ 345.21727, found 345.21702.

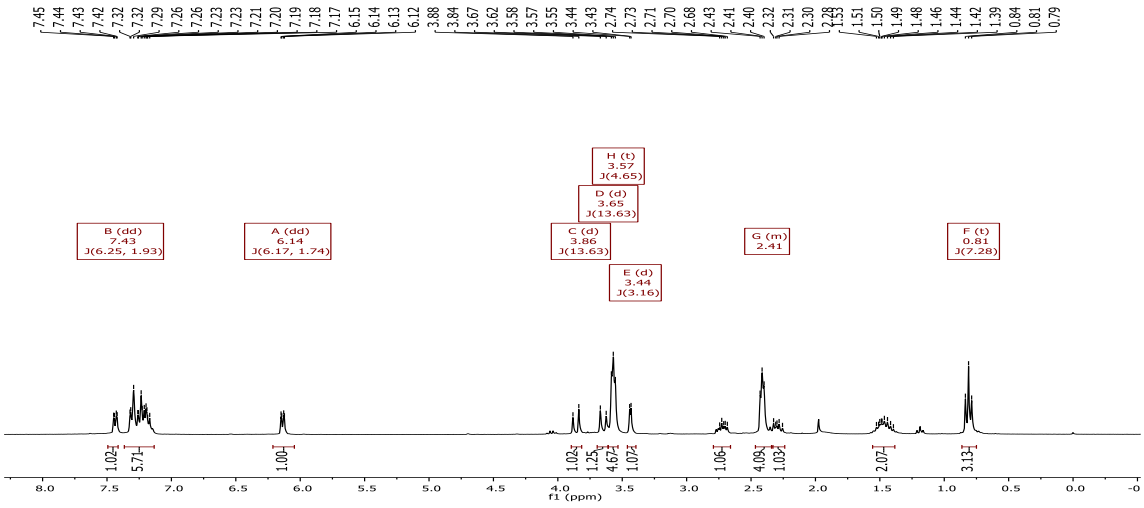


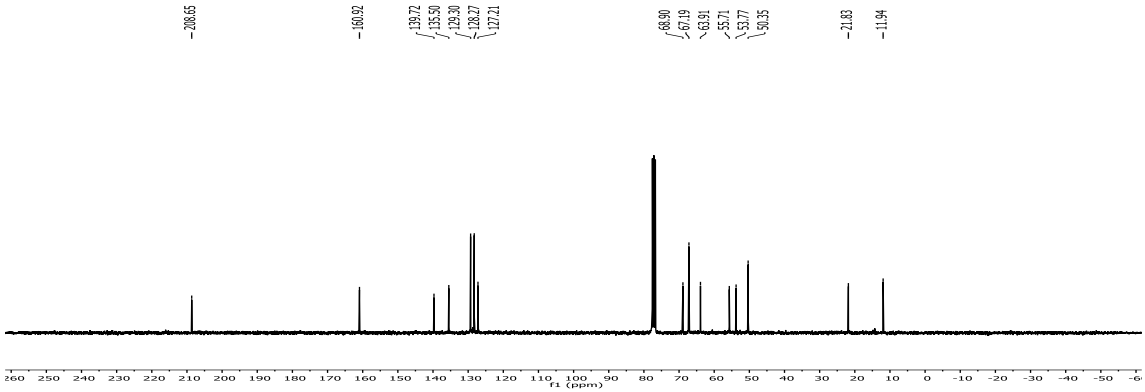
5-(benzyl(propyl)amino)-4-morpholinocyclopent-2-en-1-one 43



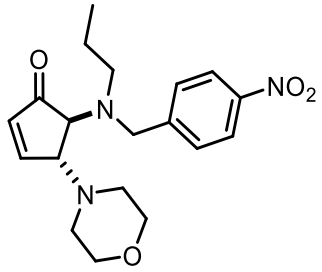
The titled compound was prepared using morpholine as amine A and *N*-propyl-benzyl-amine as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 91 mg (70%) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 6.3, 1.9 Hz, 1H), 7.36 – 7.09 (m, 5H), 6.14 (dd, J = 6.2, 1.7 Hz, 1H), 3.86 (d, J = 13.6 Hz, 1H), 3.65 (d, J = 13.6 Hz, 1H), 3.57 (t, J = 4.7 Hz, 4H), 3.44 (d, J = 3.2 Hz, 1H), 2.71 (m, 1H), 2.51 – 2.27 (m, 4H), 2.27 (m, 1H), 1.46 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 208.6, 160.9, 139.7, 135.5, 129.3, 128.2, 127.2, 68.9, 67.1, 63.9, 55.7, 53.7, 50.3, 21.8, 11.9. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{19}H_{27}N_2O_2$ $[M + H]^+$ 315.20670, found 315.20592.



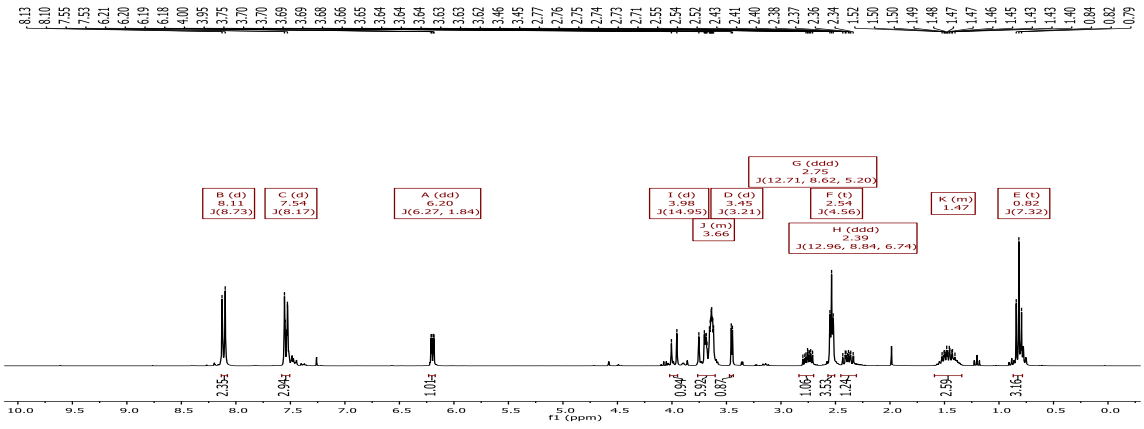

208.65
160.92
139.72
135.50
129.30
128.27
127.21
68.90
67.19
63.91
55.71
53.77
50.35
21.83
11.94
f1 (ppm)

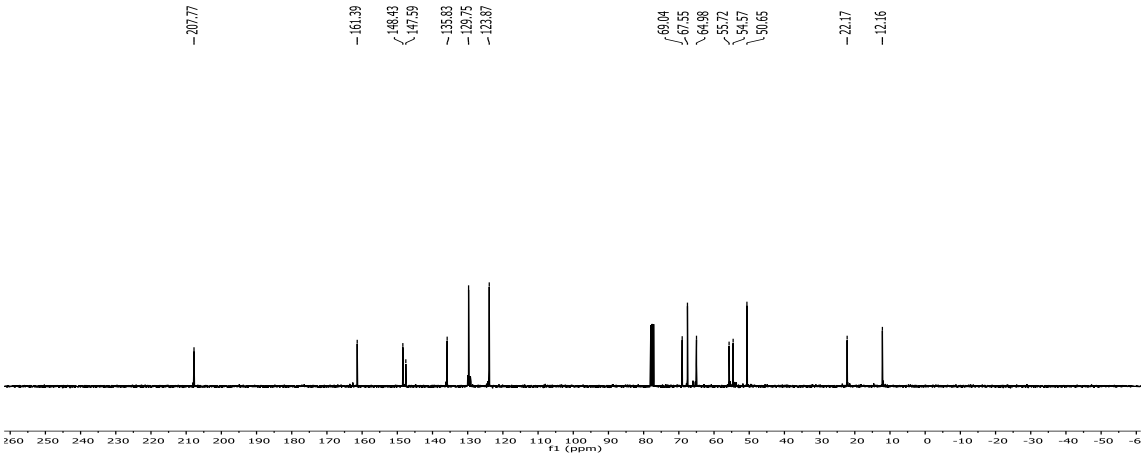
4-morpholino-5-((4-nitrobenzyl)(propyl)amino)cyclopent-2-en-1-one 45



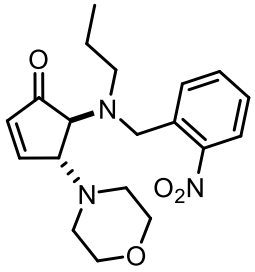
The titled compound was prepared using morpholine as amine A and *N*-propyl-4(NO_2)-benzyl-amine as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 89 mg (60%) of pure product as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.2 Hz, 3H), 6.20 (dd, J = 6.3, 1.8 Hz, 1H), 3.98 (d, J = 15.0 Hz, 1H), 3.83 – 3.58 (m, 6H), 3.45 (d, J = 3.2 Hz, 1H), 2.75 (ddd, J = 12.7, 8.6, 5.2 Hz, 1H), 2.54 (t, J = 4.6 Hz, 4H), 2.39 (ddd, J = 13.0, 8.8, 6.7 Hz, 1H), 1.62 – 1.35 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 207.7, 161.3, 148.4, 147.5, 135.8, 129.7, 123.8, 69.0, 67.5, 64.9, 55.7, 54.5, 50.6, 22.1, 12.1. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{19}H_{26}N_3O_4$ $[M + H]^+$ 360.19178, found 360.19052.



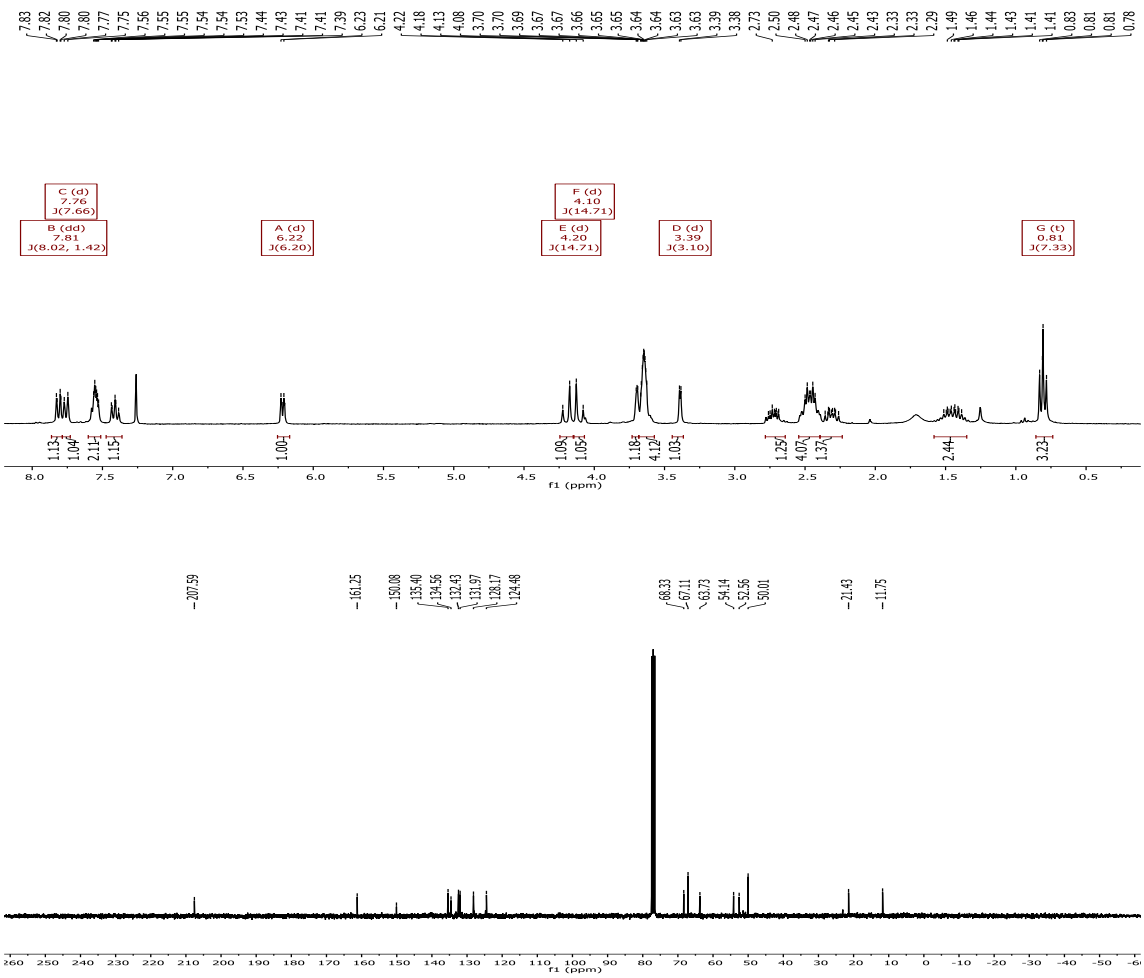


4-morpholino-5-((2-nitrobenzyl)(propyl)amino)cyclopent-2-en-1-one 46

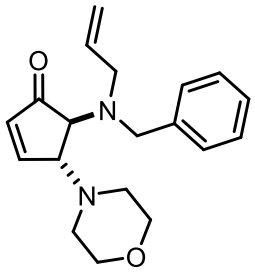


The titled compound was prepared using morpholine as amine A and *N*-propyl-2(NO_2)-benzyl-amine as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 93 mg (62%) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.0, 1.4 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.55 (dt, J = 6.0, 2.3 Hz, 2H), 7.46 – 7.36 (m, 1H), 6.22 (d, J = 6.2 Hz, 1H), 4.20 (d, J = 14.7 Hz, 1H), 4.10 (d, J = 14.7 Hz, 1H), 3.82 – 3.68 (m, 1H), 3.89 – 3.48 (m, 4H), 3.39 (d, J = 3.1 Hz, 1H), 2.96 – 2.58 (m, 1H), 2.69 – 2.26 (m, 4H), 2.33 (m, 1H), 1.45 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 207.6, 161.2, 150.1, 135.4, 134.6, 132.4, 131.9, 128.2, 124.5, 68.3, 67.1, 63.7, 54.1, 52.6, 50.0, 21.4, 11.7. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{19}H_{26}N_3O_4$ $[M + H]^+$ 360.19178, found 360.19052.



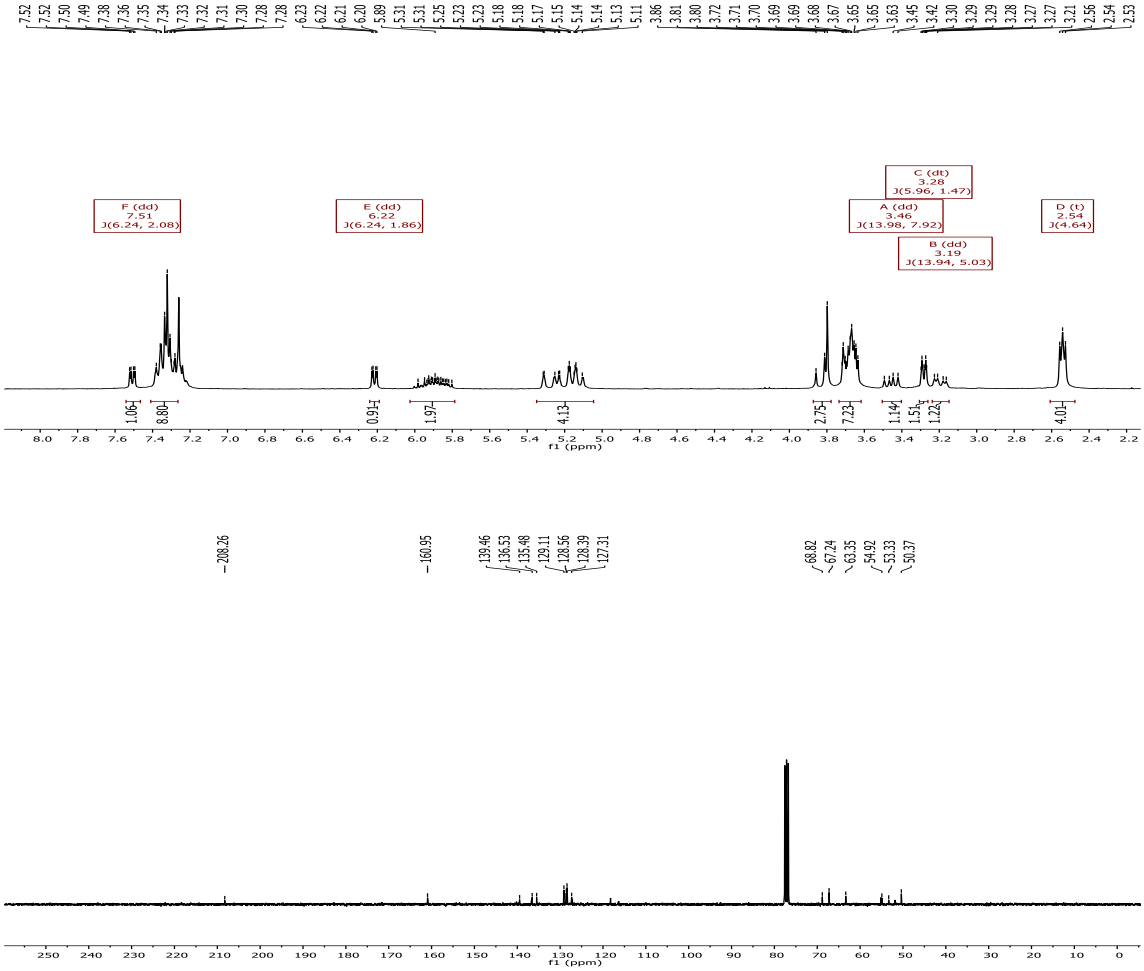
5-(allyl(benzyl)amino)-4-morpholinocyclopent-2-en-1-one 47



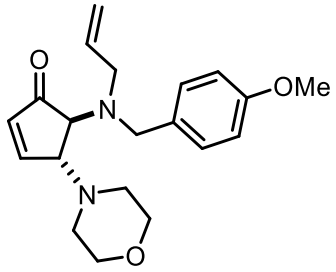
The titled compound was prepared using morpholine as amine A and *N*-allyl-benzyl-amine as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 97 mg (75%) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, J = 6.2, 2.1 Hz, 1H), 7.40 – 7.20 (m, 5H), 6.22 (dd, J = 6.2, 1.9 Hz, 1H), 6.02 – 5.74 (m, 1H), 5.41 – 4.87 (m, 2H), 3.95 – 3.78 (m, 1H), 3.67 (m, 6H), 3.46 (dd, J = 14.0, 7.9 Hz, 1H), 3.28 (d, J = 6.0, 1H), 3.19 (dd, J = 13.9, 5.0 Hz, 1H), 2.54 (t, J = 4.6 Hz, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 208.2, 160.9, 136.5,

135.4, 129.1, 128.5, 128.3, 127.3, 68.8, 67.2, 63.3, 54.9, 53.3, 50.4. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{19}H_{26}N_2O_2$ $[M + H]^+$ 313.19105, found 313.19109.

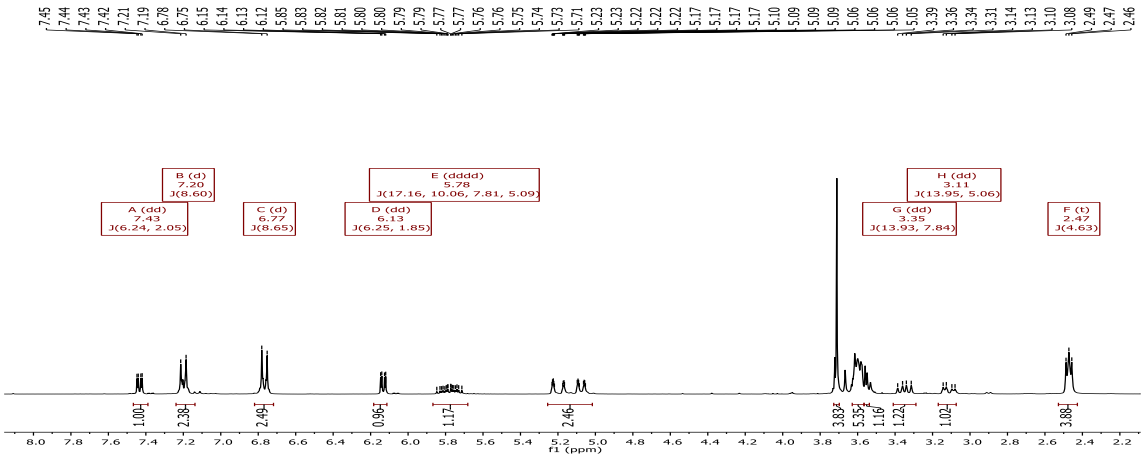


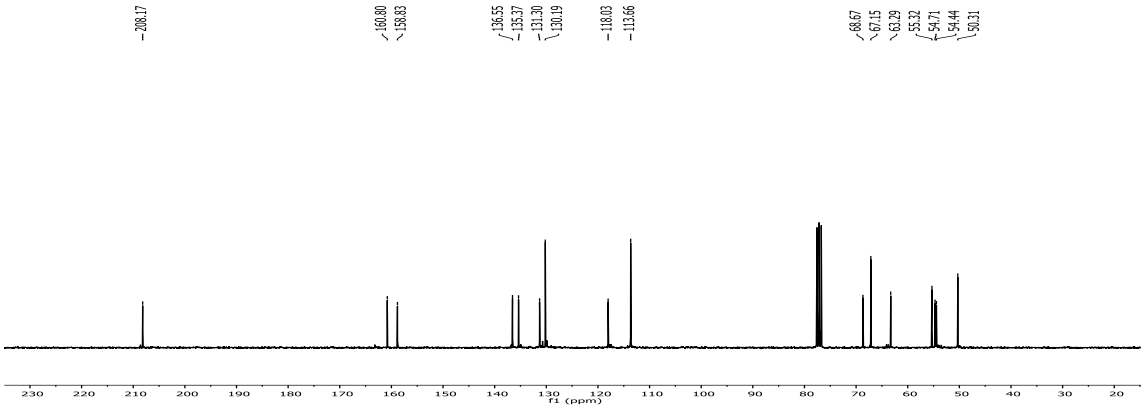
5-(allyl(4-methoxybenzyl)amino)-4-morpholinocyclopent-2-en-1-one 48



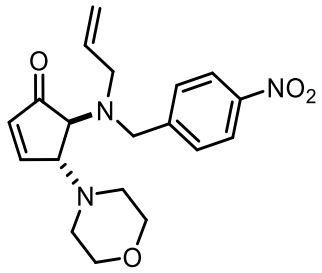
The titled compound was prepared using morpholine as amine A and *N*-allyl-4(OMe)-benzyl-amine as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 100 mg (70%) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 6.2, 2.0 Hz, 1H), 7.20 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.6 Hz, 2H), 6.13 (dd, J = 6.3, 1.8 Hz, 1H), 5.85 – 5.71 (m, 1H), 5.40 – 4.93 (m, 2H), 3.71 (s, 3H), 3.65 – 3.57 (m, 4H), 3.55 (d, J = 3.2 Hz, 1H), 3.35 (dd, J = 13.9, 7.8 Hz, 1H), 3.11 (dd, J = 14.0, 5.1 Hz, 1H), 2.47 (t, J = 4.6 Hz, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 208.1, 160.8, 158.8, 136.5, 135.4, 131.3, 130.2, 118.0, 113.7, 68. 7, 67.2, 63.3, 55.3, 54.7, 54.4, 50.3. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{20}H_{27}N_2O_3$ $[M + H]^+$ 343.20162, found 343.20153.



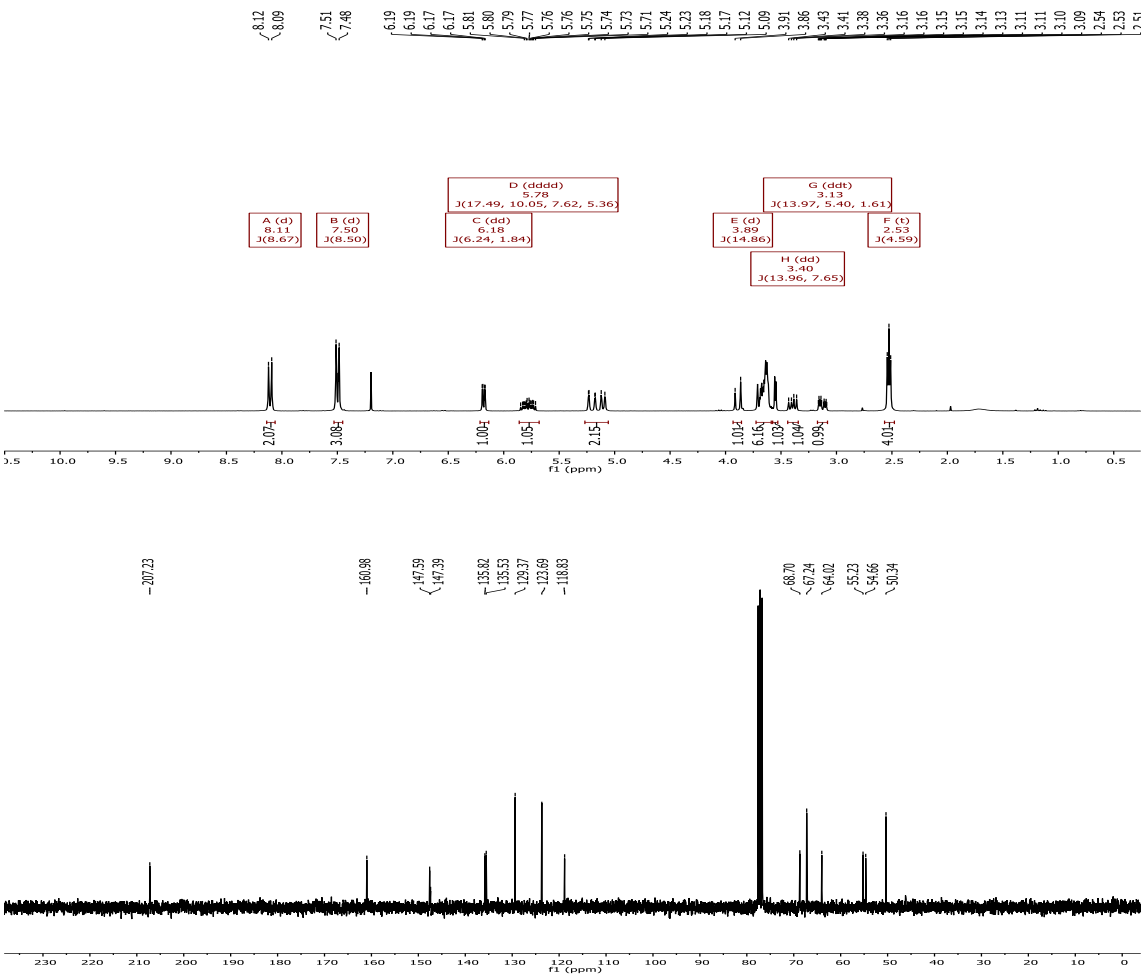


5-(allyl(4-nitrobenzyl)amino)-4-morpholinocyclopent-2-en-1-one 49

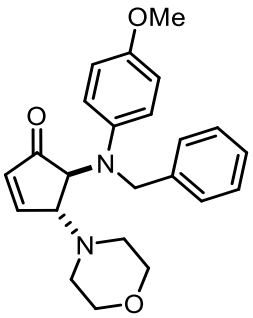


The titled compound was prepared using morpholine as amine A and *N*-allyl-4(NO_2)-benzyl-amine as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 110 mg (74%) of pure product as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.5 Hz, 3H), 6.18 (dd, J = 6.2, 1.8 Hz, 1H), 5.85 – 5.71 (m, 1H), 5.32 – 4.83 (m, 2H), 3.89 (d, J = 14.9 Hz, 1H), 3.69 (d, J = 11.3 Hz, 1H), 3.63 (m, 4H), 3.55 (d, J = 3.3 Hz, 1H), 3.40 (dd, J = 14.0, 7.6 Hz, 1H), 3.13 (dd, J = 14.0, 5.4, 1H), 2.53 (t, J = 4.6 Hz, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 207.2, 160.9, 147.5, 147.3, 135.8, 135.5, 129.3, 123.7, 118.8, 68.7, 67.2, 64.0, 55.2, 54.7, 50.3. **HRMS (ESI-MS)** *m/z* calcd For compound $C_{19}H_{24}N_3O_4$ $[M + H]^+$ 358.17613, found 358.17601.



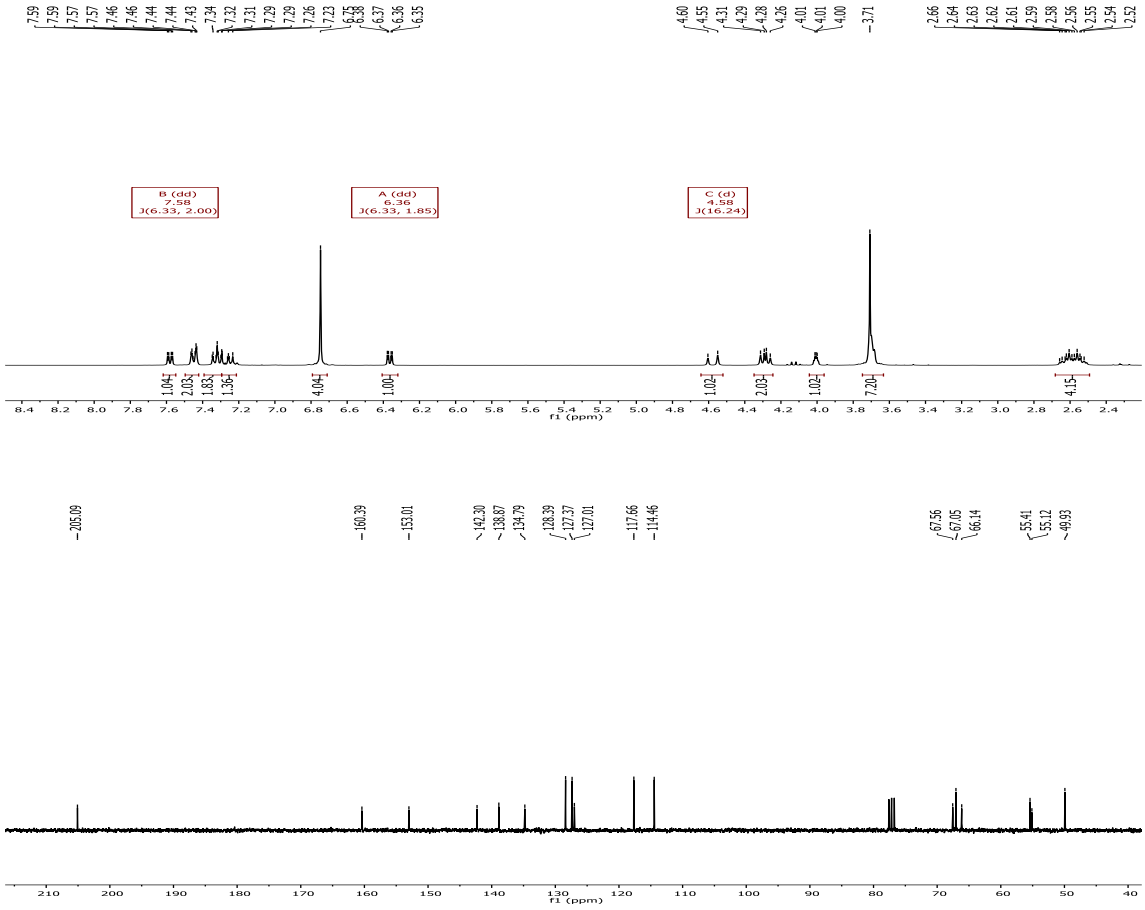
5-(benzyl(4-methoxyphenyl)amino)-4-morpholinocyclopent-2-en-1-one 51



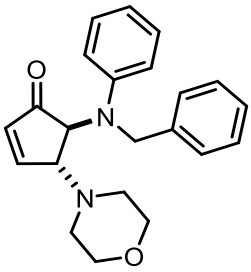
The titled compound was prepared using morpholine as amine A and *N*-benzyl-4-methoxyaniline as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 82 mg (52%) of pure product as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 6.3, 2.0 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.37 – 7.28 (m, 2H), 7.28 – 7.21 (m, 1H), 6.75 (s, 4H), 6.36 (dd, J = 6.3, 1.8 Hz, 1H), 4.58 (d, J = 16.2 Hz, 1H), 4.29 (m, 2H), 4.01 (m, 1H), 3.71 (s, 7H), 2.87 – 2.40 (m, 4H). **^{13}C NMR**

(75 MHz, $CDCl_3$) δ 205.1, 160.4, 153.0, 142.3, 138.9, 134.8, 128.4, 127.4, 127.0, 117.7, 114.5, 67.6, 67.1, 66.1, 55.4, 55.1, 49.9. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{23}H_{27}N_2O_3$ $[M + H]^+$ 379.20162, found 379.20288.

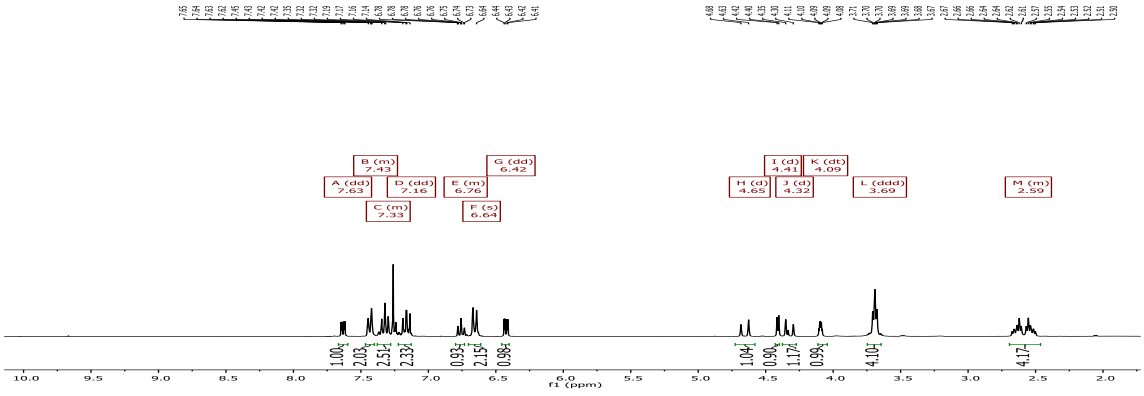


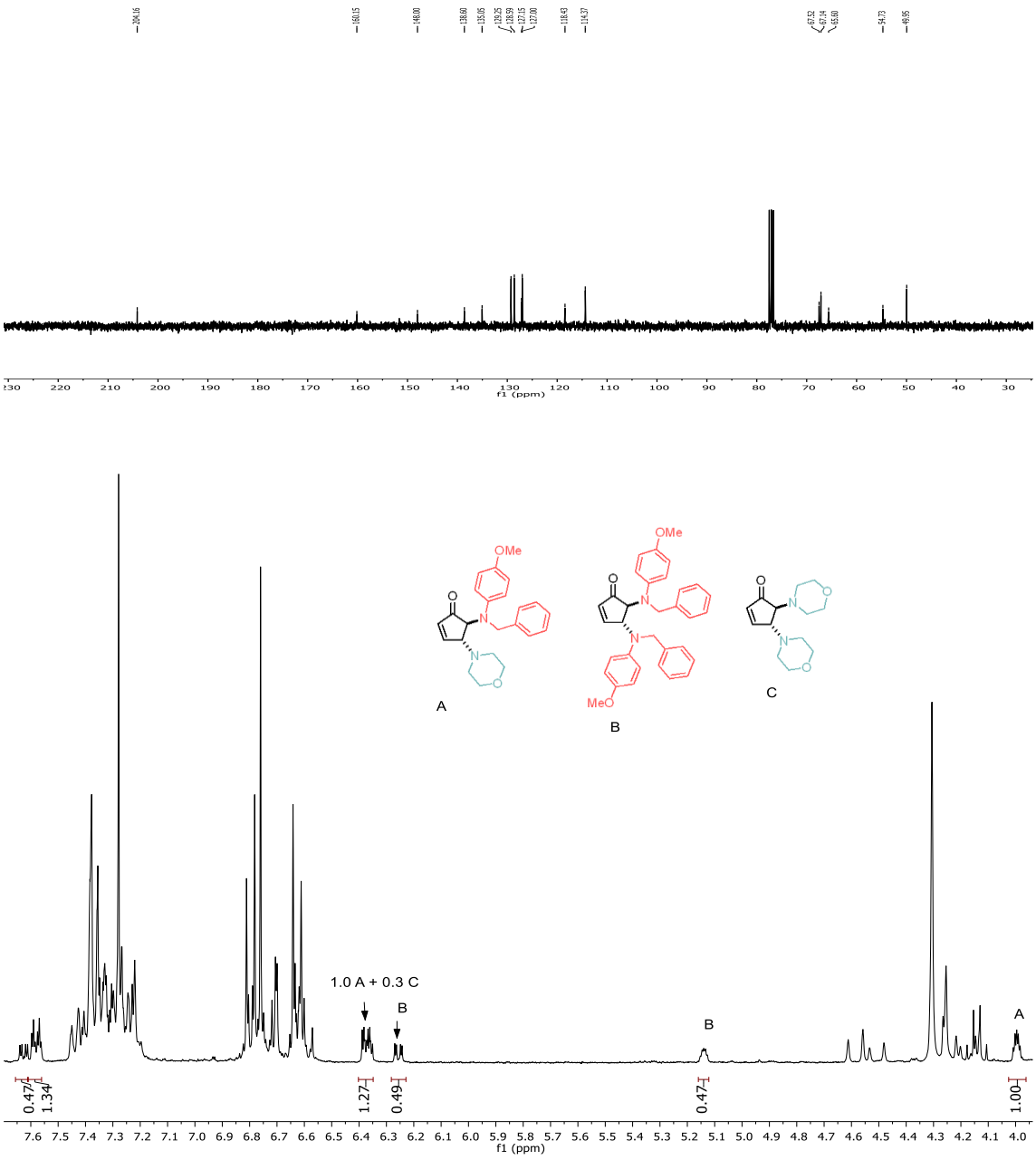
5-(benzyl(phenyl)amino)-4-morpholinocyclopent-2-en-1-one 50



The titled compound was prepared using morpholine as amine A and *N*-benzylaniline as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 23 mg (16%) of pure product as a yellow solid.

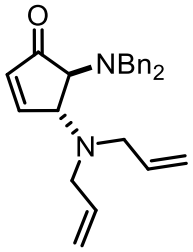
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, J = 6.4, 2.0 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.32 (dd, J = 8.2, 6.4 Hz, 2H), 7.16 (dd, J = 8.8, 7.3 Hz, 2H), 6.89 – 6.69 (m, 1H), 6.66 (dd, J = 8.9, 1.0 Hz, 2H), 6.42 (dd, J = 6.3, 1.9 Hz, 1H), 4.65 (d, J = 17.0 Hz, 1H), 4.41 (d, J = 3.6 Hz, 1H), 4.32 (d, J = 17.0 Hz, 1H), 4.09 (m, 1H), 3.69 (m, 4H), 2.76 – 2.43 (m, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.1, 160.1, 148.0, 138.6, 135.1, 129.3, 128.6, 127.2, 127.0, 118.4, 114.4, 67.5, 67.1, 65.6, 54.7, 49.9. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{22}H_{25}N_2O_2$ $[M + H]^+$ 349.19105, found 349.19123.





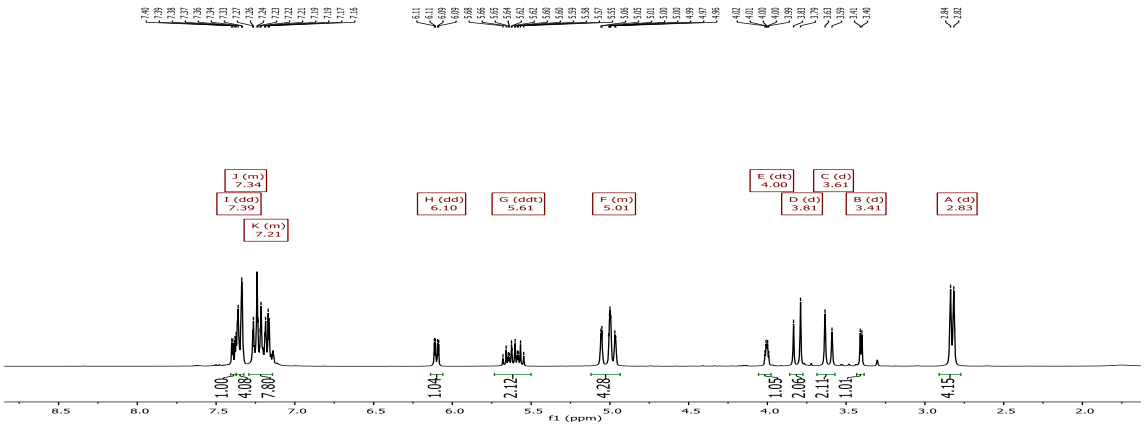
Crude mixture

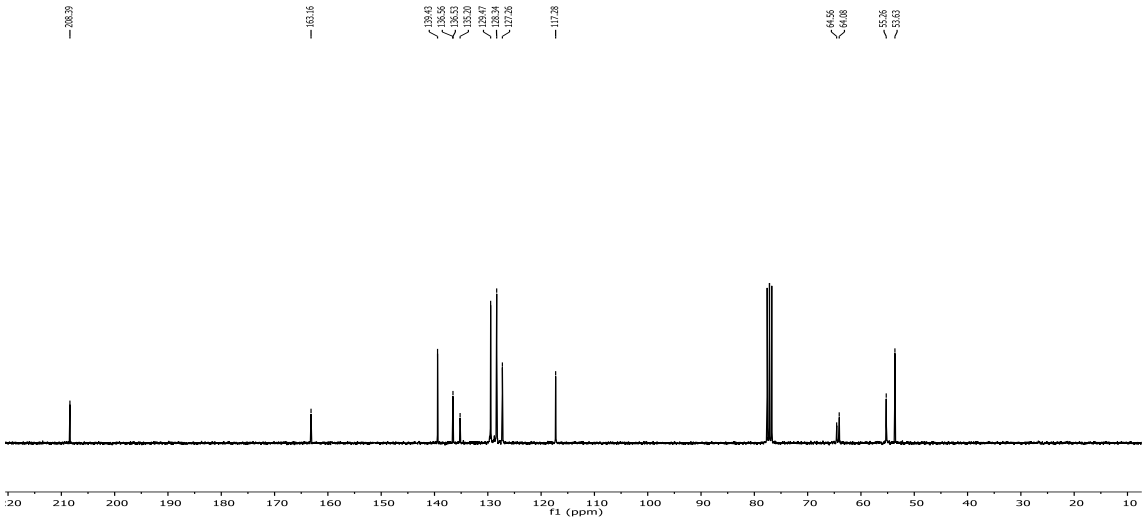
5-(benzyl(phenyl)amino)-4-morpholinocyclopent-2-en-1-one 39



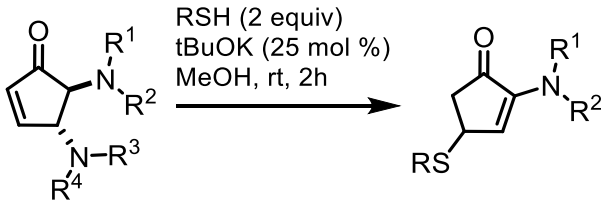
The titled compound was prepared using diallylamine as amine A and dibenzylamine as amine B according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 108 mg (70%) of pure product as a low boiling point yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, J = 6.2, 2.2 Hz, 1H), 7.37 – 7.32 (m, 4H), 7.29 – 7.14 (m, 6H), 6.10 (dd, J = 6.2, 2.0 Hz, 1H), 5.61 (m, 2H), 5.16 – 4.88 (m, 4H), 4.00 (m, 1H), 3.81 (d, J = 13.3 Hz, 2H), 3.61 (d, J = 13.3 Hz, 2H), 3.41 (d, J = 3.1 Hz, 1H), 2.83 (d, J = 6.2 Hz, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 208.4, 163.2, 139.4, 136.5, 135.2, 129.5, 128.3, 127.3, 117.3, 64.6, 64.1, 55.3, 53.6. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{25}H_{29}N_2O$ $[M + H]^+$ 373.22744, found 373.22651.



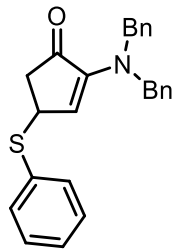

208.39
163.16
139.43
136.56
136.53
135.20
129.47
128.34
127.26
117.28
64.56
64.08
55.26
53.63
f1 (ppm)

General Procedure for the Preparation of 2-morpholino-4-thio cyclopentenones from 2-furaldehyde



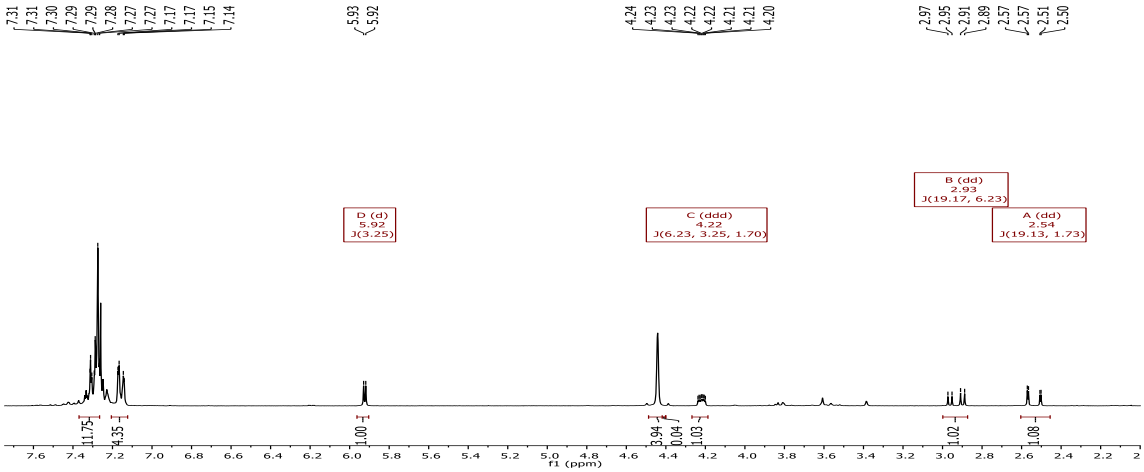
The mixed CP (0.2 mmol, 1 equiv) was dissolved in MeOH (2 mL) Then, was added 2 equivalents of the corresponding substituted thiol (0.4 mmol) and KO^{t}Bu (5.6 mg, 0.25 equiv, 0.05 mmol). The mixture was stirred at room temperature under nitrogen atmosphere for 2h. Afterwards, the crude was filtered through a short plug of celite and the filter cake was washed with DCM (6 mL). To the filtrate was added AcOH/NaOAc buffer solution at pH 5 (2 mL) and brine (4 mL). The organic layer was separated, and the aqueous layer was further extracted with DCM (2×6 mL), and the combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was further purified by column chromatography.

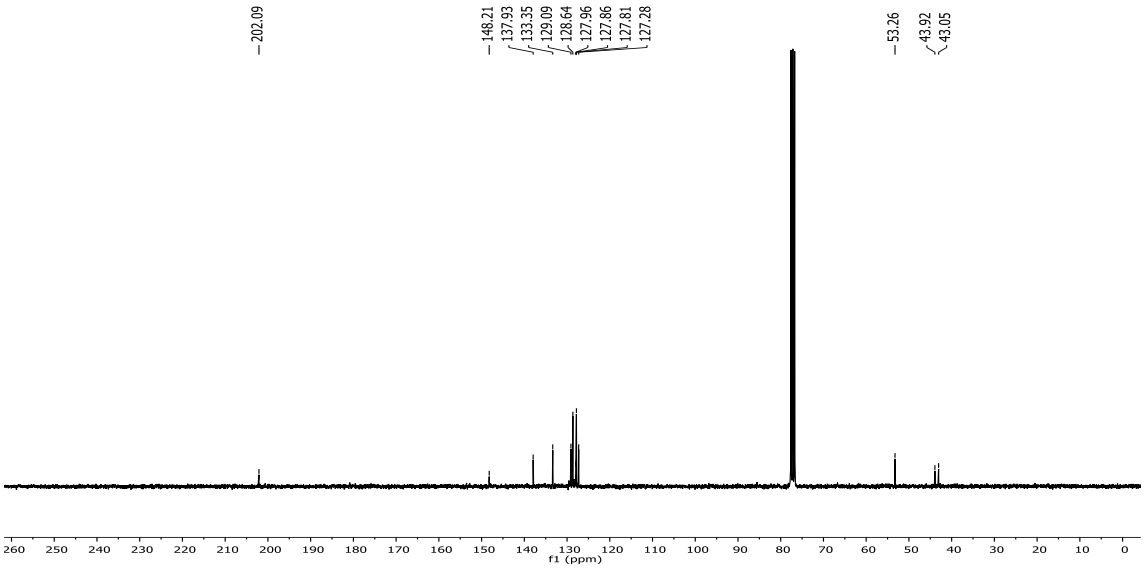
2-(dibenzylamino)-4-(phenylthio)cyclopent-2-en-1-one 57



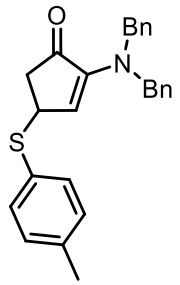
The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 53 mg (69%) of pure product as a brown oil. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{25}H_{24}NOS$ $[M + H]^+$ 386.15731, found 386.15691.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.23 (m, 9H), 7.20 – 6.99 (m, 4H), 5.92 (d, *J* = 3.2 Hz, 1H), 4.44 (s, 4H), 4.22 (ddd, *J* = 6.2, 3.2, 1.7 Hz, 1H), 2.93 (dd, *J* = 19.2, 6.2 Hz, 1H), 2.54 (dd, *J* = 19.1, 1.7 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.1, 148.2, 137.9, 133.3, 129.1, 128.6, 127.9, 127.9, 127.8, 127.3, 53.3, 43.9, 43.1.



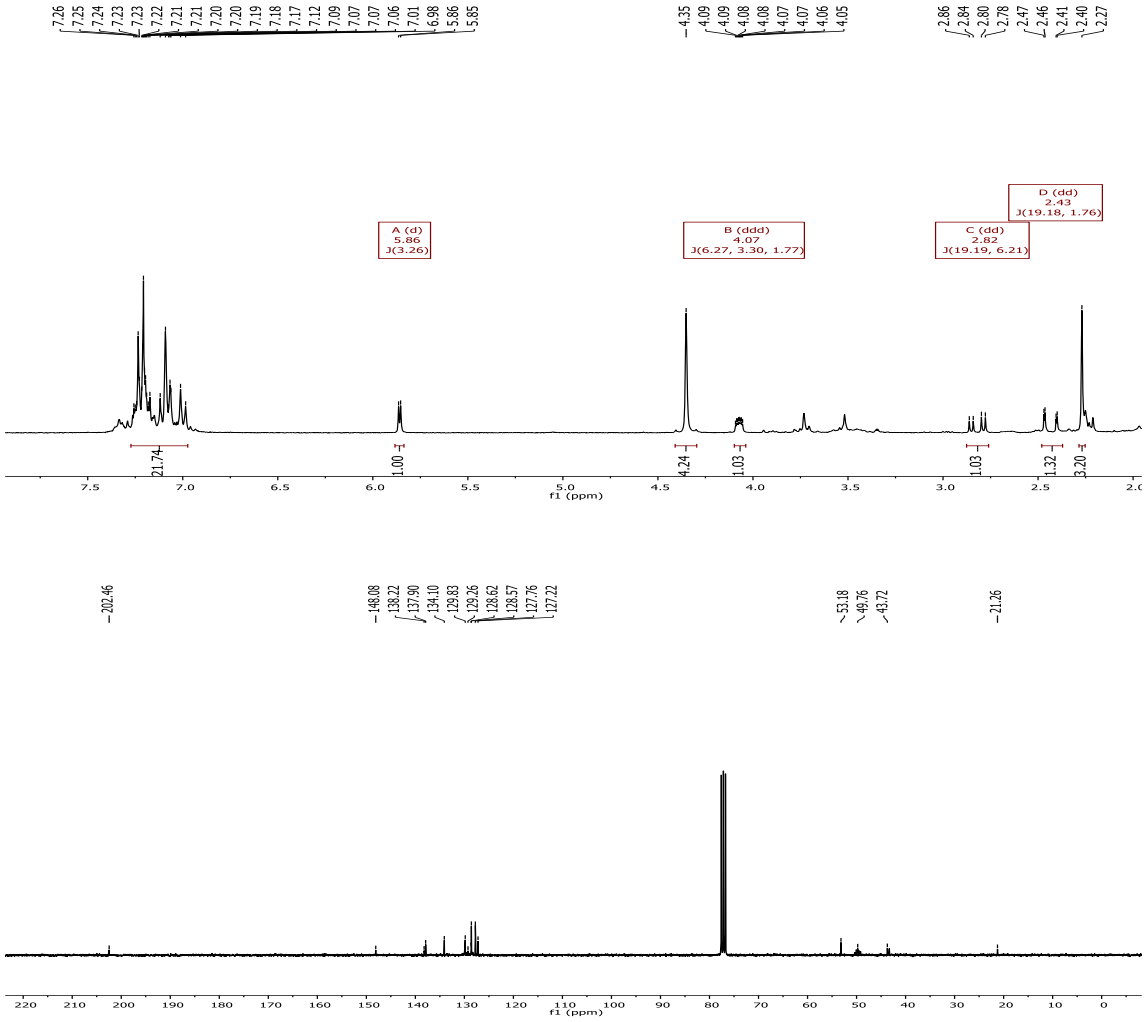


2-(dibenzylamino)-4-(p-tolylthio)cyclopent-2-en-1-one 58

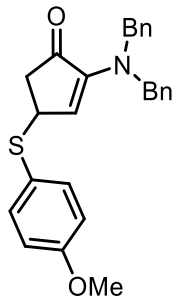


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 51 mg (64%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 6.85 (m, 17H), 5.86 (d, J = 3.3 Hz, 1H), 4.35 (s, 4H), 4.07 (ddd, J = 6.3, 3.3, 1.8 Hz, 1H), 2.82 (dd, J = 19.2, 6.2 Hz, 1H), 2.43 (dd, J = 19.2, 1.8 Hz, 1H), 2.27 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.5, 148.1, 138.2, 137.9, 134.1, 129.8, 128.6, 128.6, 127.8, 127.2, 53.2, 49.8, 43.7, 21.3. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{26}H_{26}NOS$ $[M + H]^+$ 400.17296, found 400.17224.

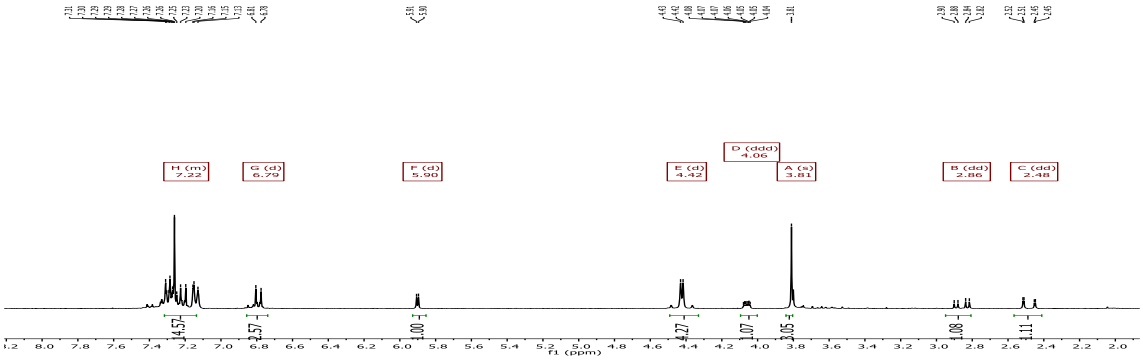

7.26
7.25
7.24
7.23
7.23
7.22
7.21
7.21
7.20
7.20
7.19
7.18
7.17
7.12
7.09
7.07
7.07
7.06
7.01
6.98
5.86
5.85
4.35
4.09
4.09
4.08
4.08
4.07
4.07
4.06
4.05
2.86
2.84
2.80
2.78
2.47
2.46
2.41
2.40
2.27
A (d)
5.86
J(3.26)
B (ddd)
4.07
J(6.27, 3.30, 1.77)
C (dd)
2.82
J(19.19, 6.21)
D (dd)
2.43
J(19.18, 1.76)
21.74
1.00
4.24
1.03
1.03
1.32
3.20
f1 (ppm)
202.46
148.08
138.22
137.90
134.10
129.83
129.26
128.62
128.57
127.76
127.22
53.18
49.76
43.72
21.26
f1 (ppm)

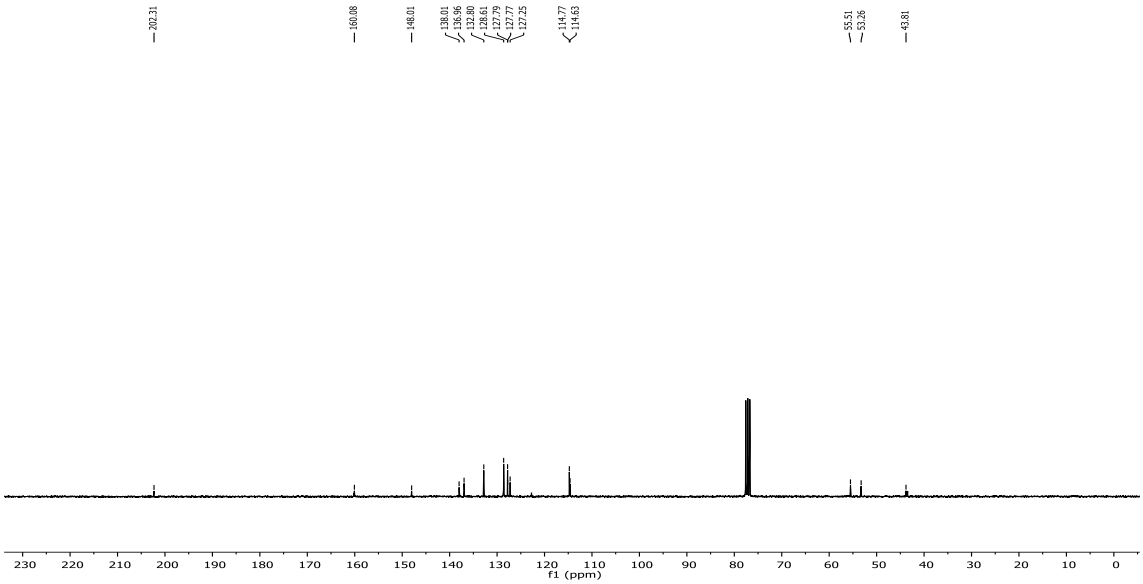
2-(dibenzylamino)-4-(p-methoxythio)cyclopent-2-en-1-one 52



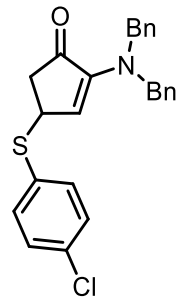
The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 61 mg (73%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.04 (m, 12H), 6.79 (d, J = 8.8 Hz, 2H), 5.90 (d, J = 3.3 Hz, 1H), 4.42 (d, J = 4.2 Hz, 4H), 4.06 (ddd, J = 5.3, 3.2, 1.8 Hz, 1H), 3.81 (s, 3H), 2.86 (dd, J = 19.2, 6.3 Hz, 1H), 2.48 (dd, J = 19.1, 1.8 Hz, 1H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.3, 160.1, 138.0, 136.9, 132.8, 128.6, 127.8, 127.8, 127.2, 114.8, 114.6, 55.5, 53.3, 43.8. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{26}H_{26}NO_2S$ $[M + H]^+$ 416.16788, found 416.16698.



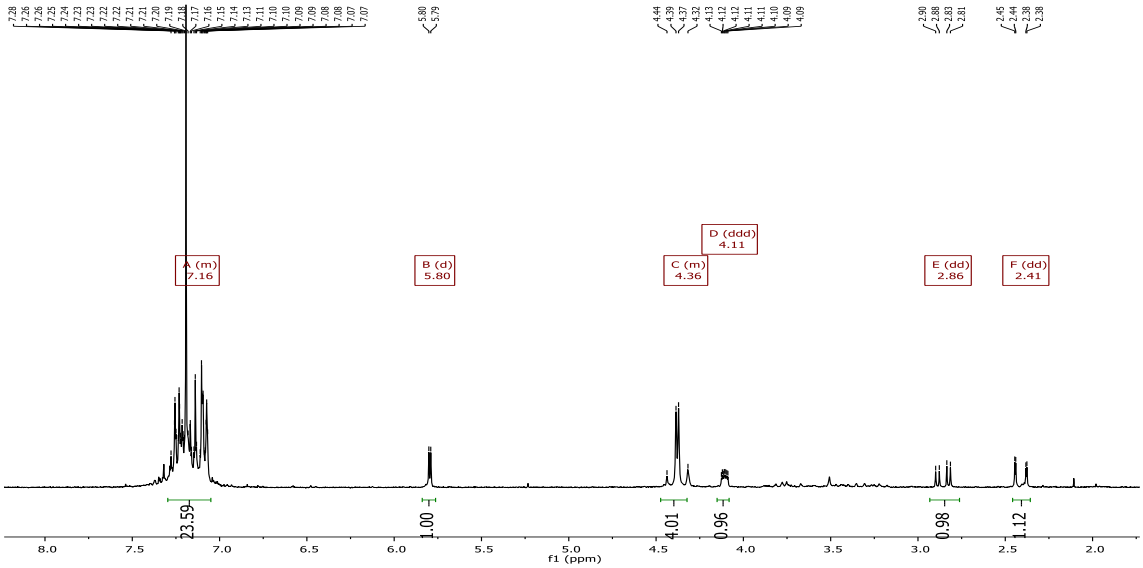


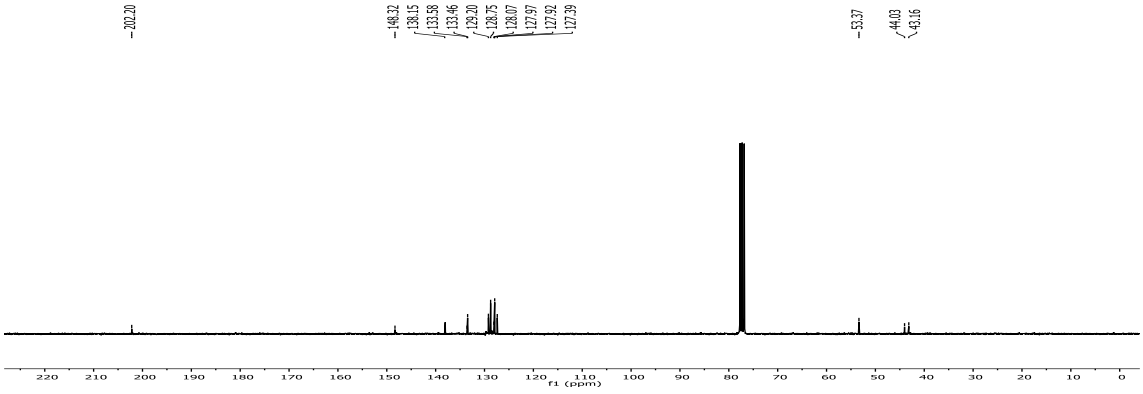
2-(dibenzylamino)-4-(p-chlorothio)cyclopent-2-en-1-one 59



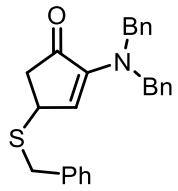
The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 17 mg (20%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 6.79 (m, 14H), 5.80 (d, *J* = 3.3 Hz, 1H), 4.65 – 4.22 (m, 4H), 4.11 (ddd, *J* = 6.3, 3.3, 1.7 Hz, 1H), 2.86 (dd, *J* = 19.1, 6.3 Hz, 1H), 2.41 (dd, *J* = 19.1, 1.7 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.2, 148.3, 138.2, 133.6, 133.5, 129.2, 128.8, 128.1, 127.9, 127.4, 53.4, 44.0, 43.2 and **HRMS (ESI-MS)** *m/z* calcd for compound $C_{25}H_{23}ClNOS$ $[M + H]^+$ 420.11834, found 420.11910.


A (m)
7.16
B (d)
5.80
C (m)
4.36
D (ddd)
4.11
E (dd)
2.86
F (dd)
2.41
23.59
1.00
4.01
0.96
0.98
1.12
f1 (ppm)

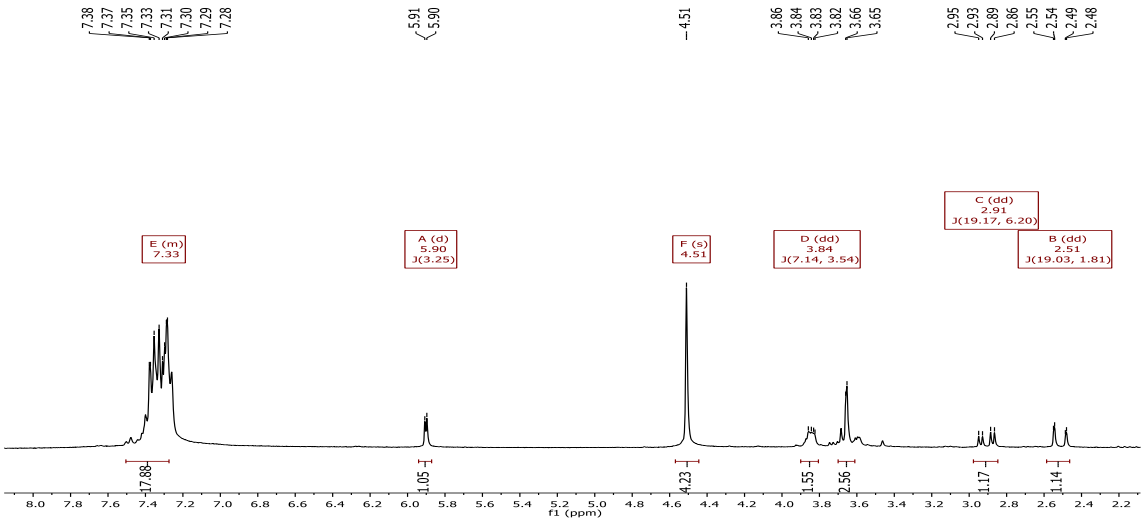

202.20
148.32
138.15
133.58
133.46
129.20
128.75
128.07
127.97
127.92
127.39
53.37
44.03
43.16
f1 (ppm)

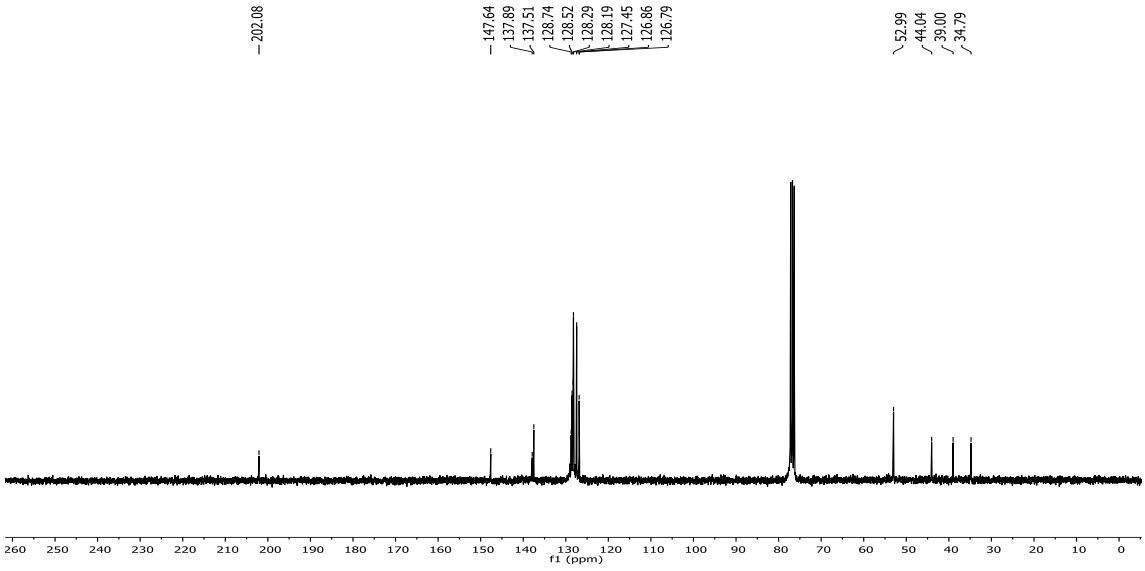
4-(benzylthio)-2-(dibenzylamino)cyclopent-2-en-1-one 60



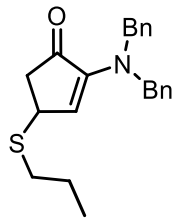
The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 69 mg (85%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 6.98 (m, 15H), 5.90 (d, J = 3.2 Hz, 1H), 4.51 (s, 4H), 3.84 (m, 1H), 3.66 (m, 2H), 2.91 (dd, J = 19.2, 6.2 Hz, 1H), 2.51 (dd, J = 19.0, 1.8 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.1, 147.6, 137.9, 137.5, 128.7, 128.5, 128.3, 128.2, 127.5, 126.9, 126.8, 52.9, 44.0, 39.0, 34.8. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{26}H_{26}NOS$ $[M + H]^+$ 400.17296, found 400.17340.



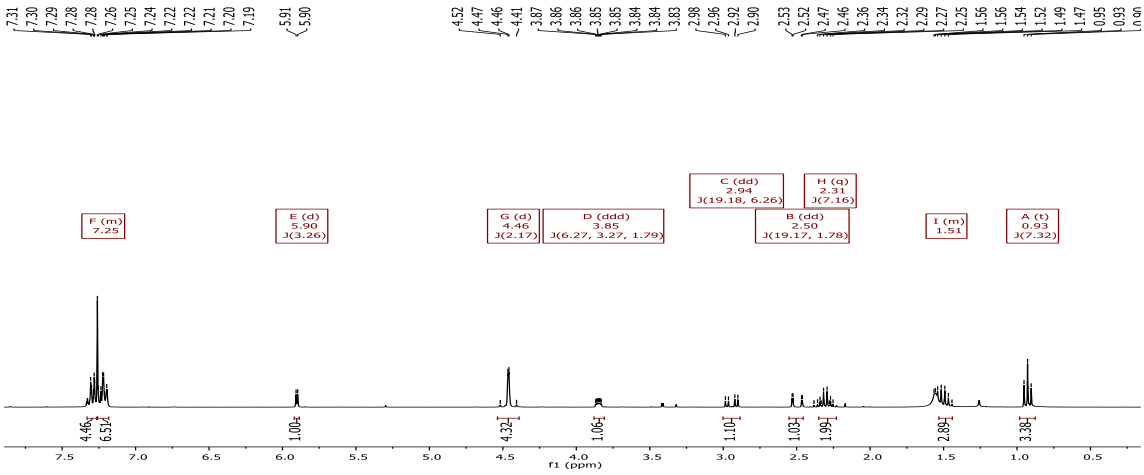

202.08
147.64
137.89
137.51
128.74
128.52
128.29
128.19
127.45
126.86
126.79
52.99
44.04
39.00
34.79
260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

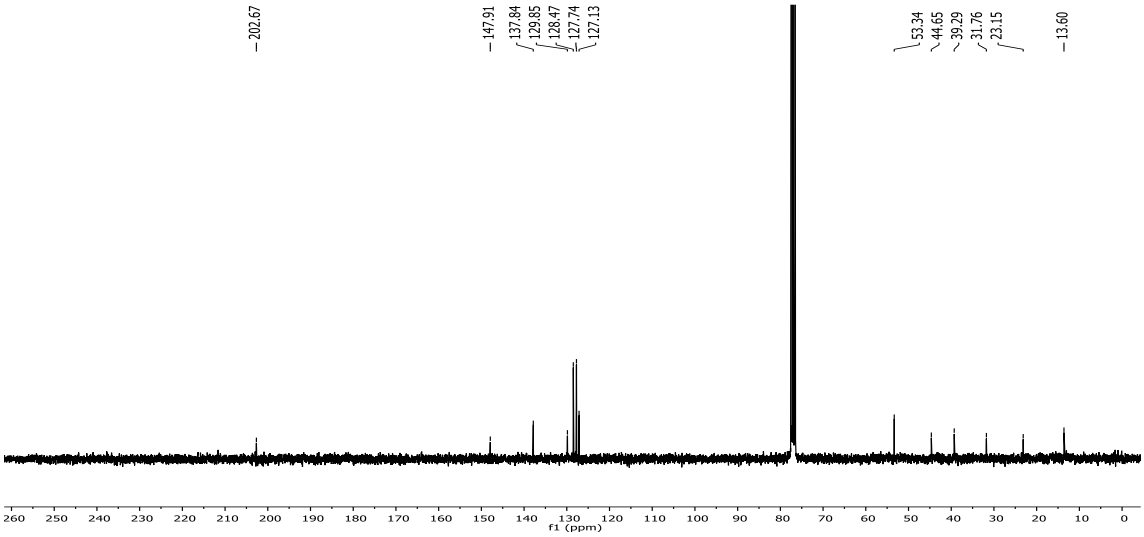
2-(dibenzylamino)-4-(propylthio)cyclopent-2-en-1-one 61



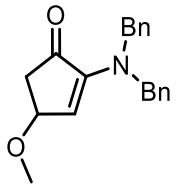
The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 49.5 mg (70%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.08 (m, 10H), 5.90 (d, J = 3.3 Hz, 1H), 4.46 (d, J = 2.2 Hz, 4H), 3.85 (ddd, J = 6.3, 3.3, 1.8 Hz, 1H), 2.94 (dd, J = 19.2, 6.3 Hz, 1H), 2.50 (dd, J = 19.2, 1.8 Hz, 1H), 2.31 (q, J = 7.2 Hz, 2H), 1.70 – 1.36 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.7, 147.9, 137.8, 129.9, 128.5, 127.7, 127.1, 53.3, 44.7, 39.3, 31.8, 23.1, 13.6. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{22}H_{26}NOS$ $[M + H]^+$ 352.17296, found 352.17285.



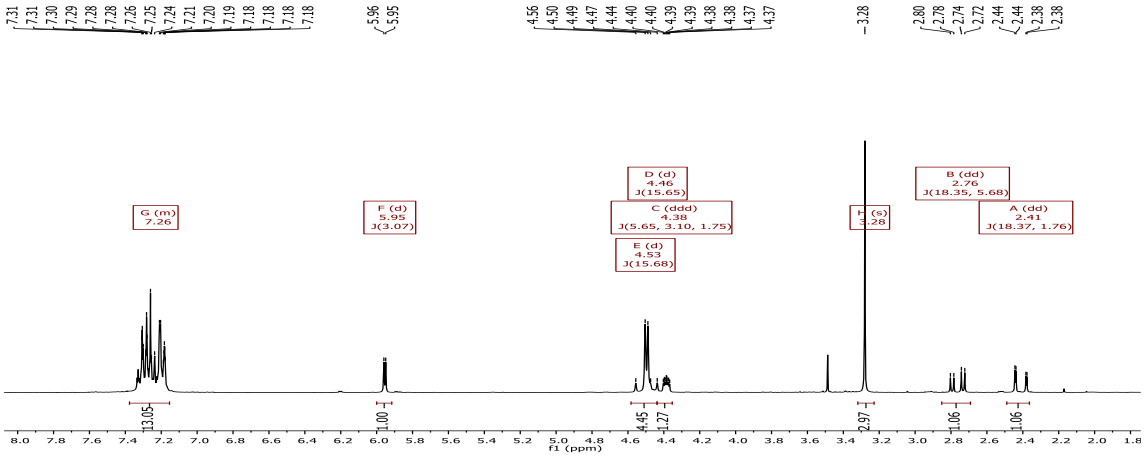


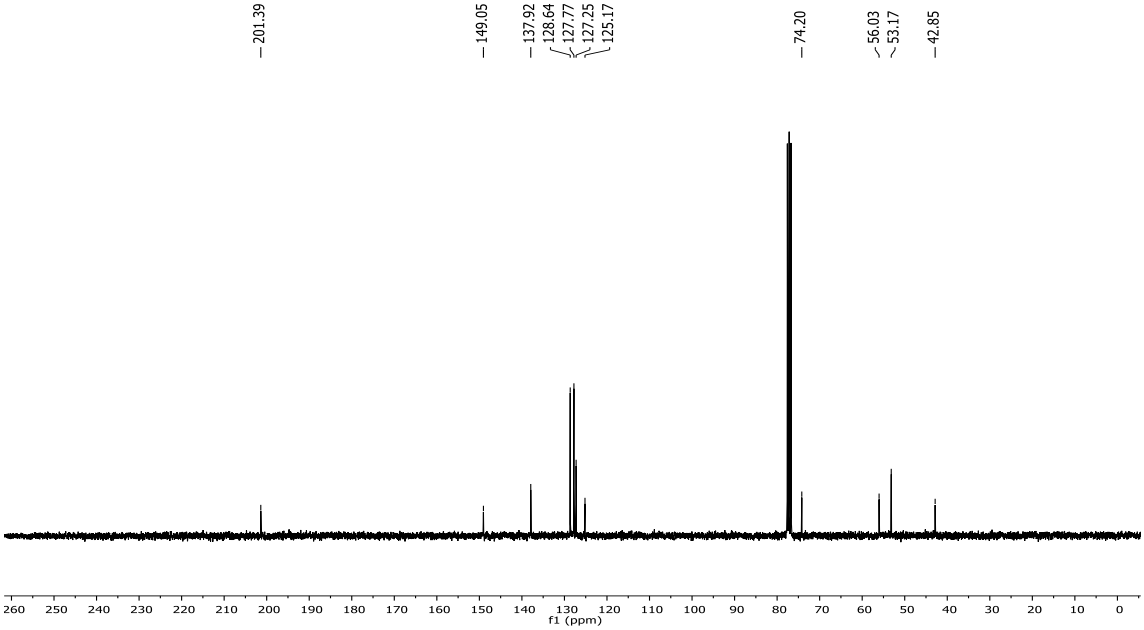
2-(dibenzylamino)-4-methoxycyclopent-2-en-1-one 62



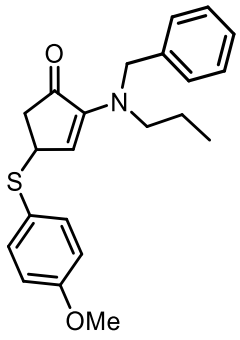
The titled compound was prepared according to general procedure without the use of any thiol and using NaOMe as base. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 33 mg (54%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.00 (m, 10H), 5.95 (d, *J* = 3.1 Hz, 1H), 4.53 (d, *J* = 15.7 Hz, 2H), 4.46 (d, *J* = 15.6 Hz, 2H), 4.38 (ddd, *J* = 5.7, 3.1, 1.8 Hz, 1H), 3.28 (s, 3H), 2.76 (dd, *J* = 18.3, 5.7 Hz, 1H), 2.41 (dd, *J* = 18.4, 1.8 Hz, 1H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 201.4, 149.1, 137.9, 128.6, 127.8, 127.3, 125.2, 74.2, 56.0, 53.2, 42.9. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{20}H_{22}NO_2$ $[M + H]^+$ 308.16451, found 308.16504.



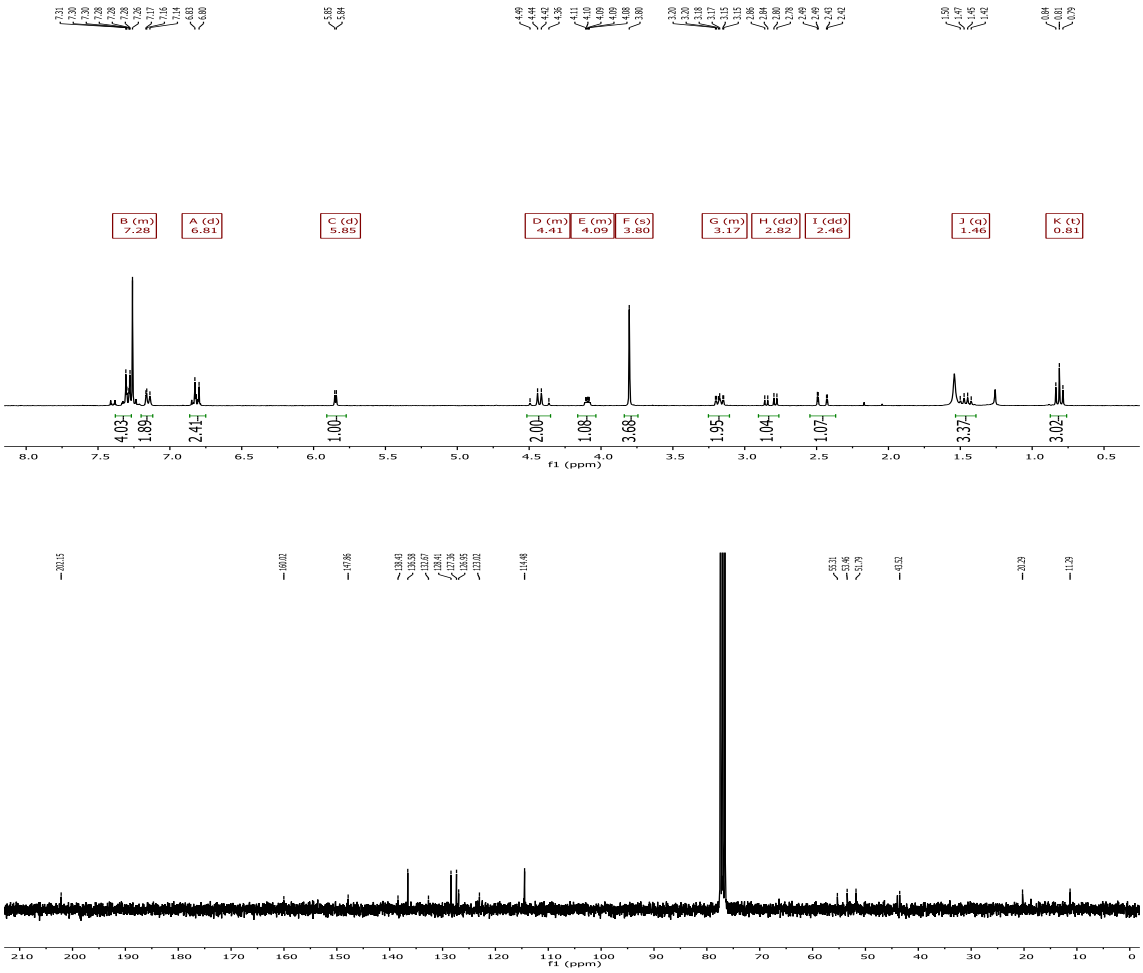


2-(benzyl(propyl)amino)-4-((4-methoxyphenyl)thio)cyclopent-2-en-1-one 55



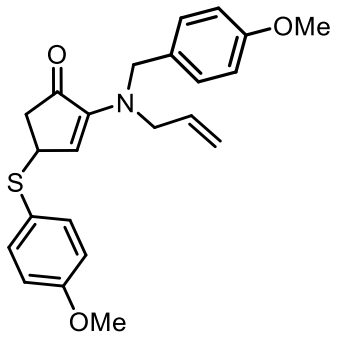
The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 45 mg (65%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.06 (m, 6H), 6.81 (d, J = 8.8 Hz, 1H), 5.85 (d, J = 3.3 Hz, 1H), 4.72 – 4.31 (m, 1H), 4.21 – 4.02 (m, 1H), 3.80 (s, 2H), 3.29 – 3.02 (m, 1H), 2.82 (dd, J = 19.1, 6.2 Hz, 1H), 2.46 (dd, J = 19.1, 1.7 Hz, 1H), 1.46 (q, J = 7.8 Hz, 1H), 0.81 (t, J = 7.4 Hz, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.2, 160.0, 147.9, 138.4, 136.6, 132.7, 128.4, 127.4, 126.9, 123.0, 114.5, 55.3, 53.5, 51.8, 43.5, 20.3, 11.3. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{22}H_{26}NO_2S$ $[M + H]^+$ 368.16788, found 368.16738.



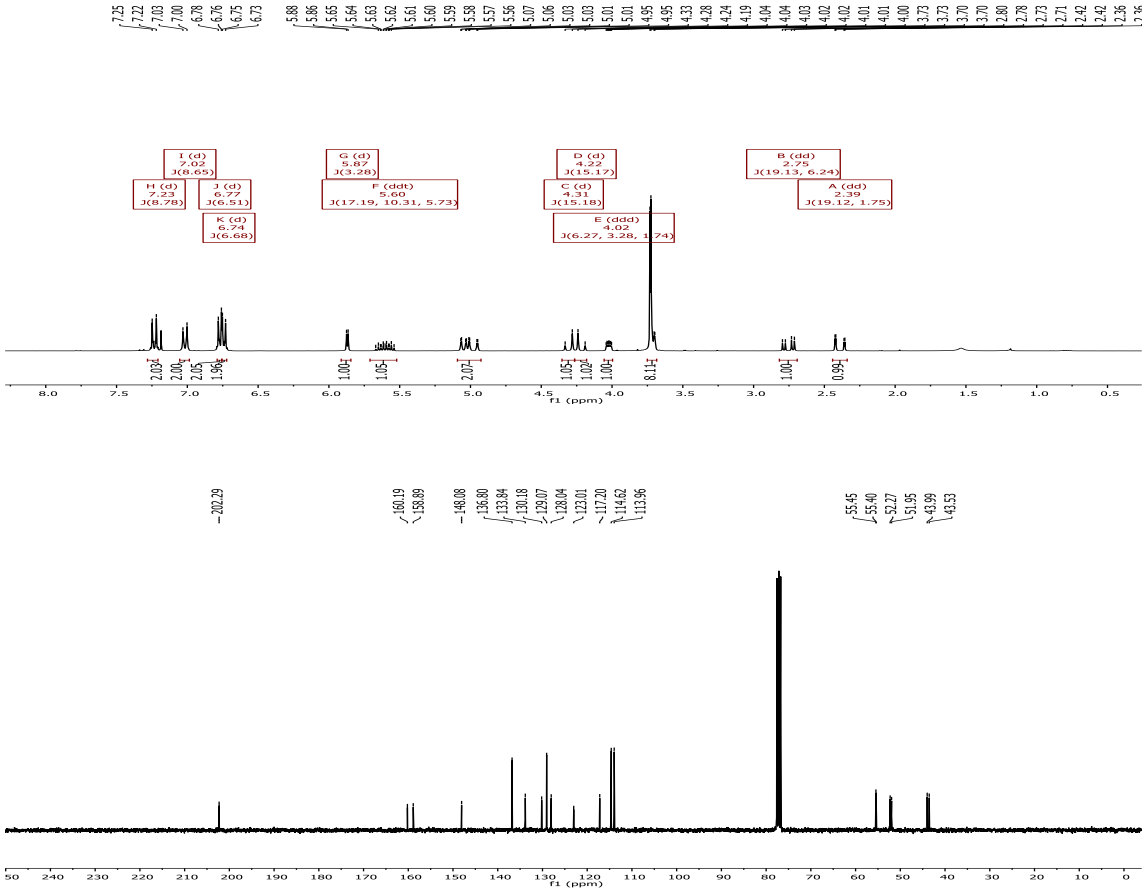
2-(allyl(4-methoxybenzyl)amino)-4-((4-methoxyphenyl)thio)cyclopent-2-en-1-one

54

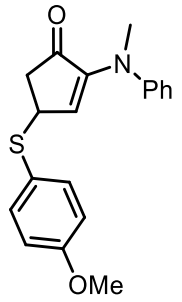


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 54 mg (68%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 6.5 Hz, 2H), 6.74 (d, J = 6.7 Hz, 2H), 5.87 (d, J = 3.3 Hz, 1H), 5.60 (m, 1H), 5.19 – 4.90 (m, 2H), 4.31 (d, J = 15.2 Hz, 1H), 4.22 (d, J = 15.2 Hz, 1H), 4.02 (ddd, J = 6.3, 3.3, 1.7 Hz, 1H), 3.73 (d, J = 2.0 Hz, 8H), 2.75 (dd, J = 19.1, 6.2 Hz, 1H), 2.39 (dd, J = 19.1, 1.7 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.3, 160.2, 158.9, 148.1, 136.8, 133.8, 130.2, 129.1, 128.0, 123.0, 117.2, 114.6, 113.9, 55.4, 55.4, 52.3, 51.9, 43.9, 43.5. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{23}H_{26}NO_3S$ $[M + H]^+$ 396.16279, found 396.16164.

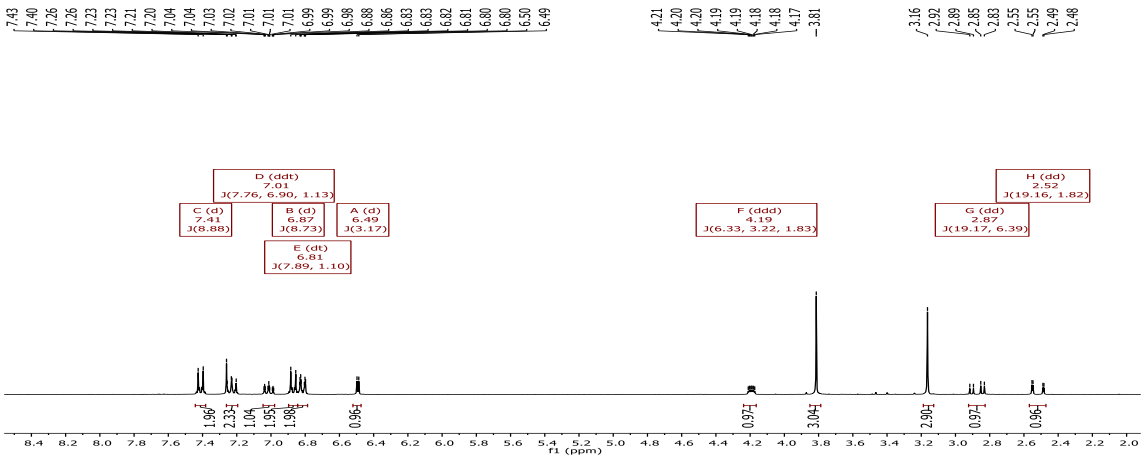


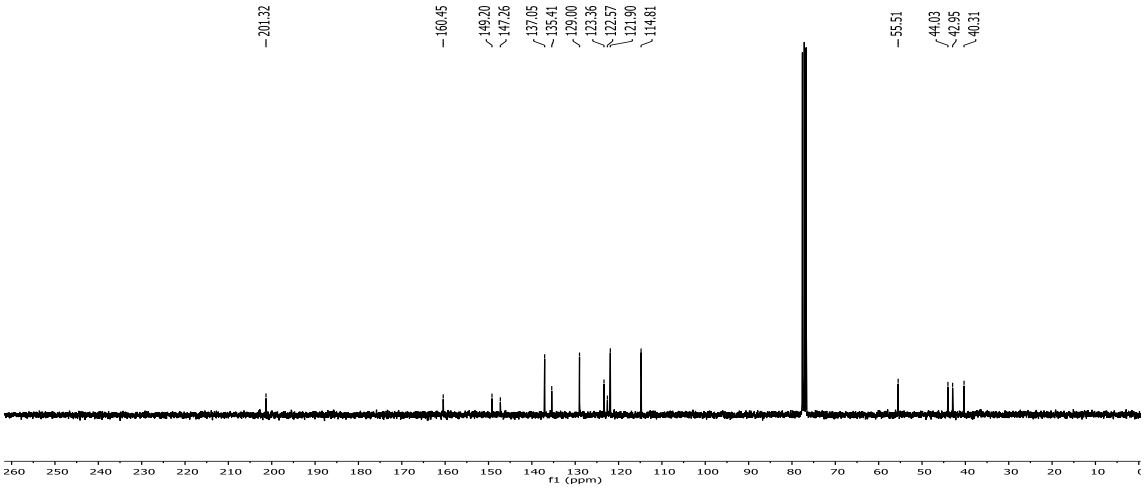
4-((4-methoxyphenyl)thio)-2-(methyl(phenyl)amino)cyclopent-2-en-1-one 53



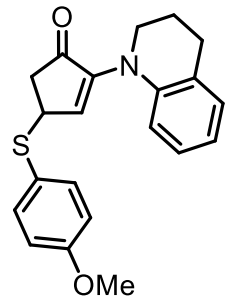
The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 52 mg (80%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.9 Hz, 2H), 7.27 – 7.15 (m, 2H), 7.01 (ddt, *J* = 7.8, 6.9, 1.1 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.81 (dt, *J* = 7.9, 1.1 Hz, 2H), 6.49 (d, *J* = 3.2 Hz, 1H), 4.19 (ddd, *J* = 6.3, 3.2, 1.8 Hz, 1H), 3.81 (s, 3H), 3.16 (s, 3H), 2.87 (dd, *J* = 19.2, 6.4 Hz, 1H), 2.52 (dd, *J* = 19.2, 1.8 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 201.3, 160.5, 149.2, 147.3, 137.0, 135.4, 129.0, 123.4, 122.6, 121.9, 114.8, 55.5, 44.0, 42.9, 40.3. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{19}H_{20}NO_2S$ $[M + H]^+$ 326.12093, found 326.12121.



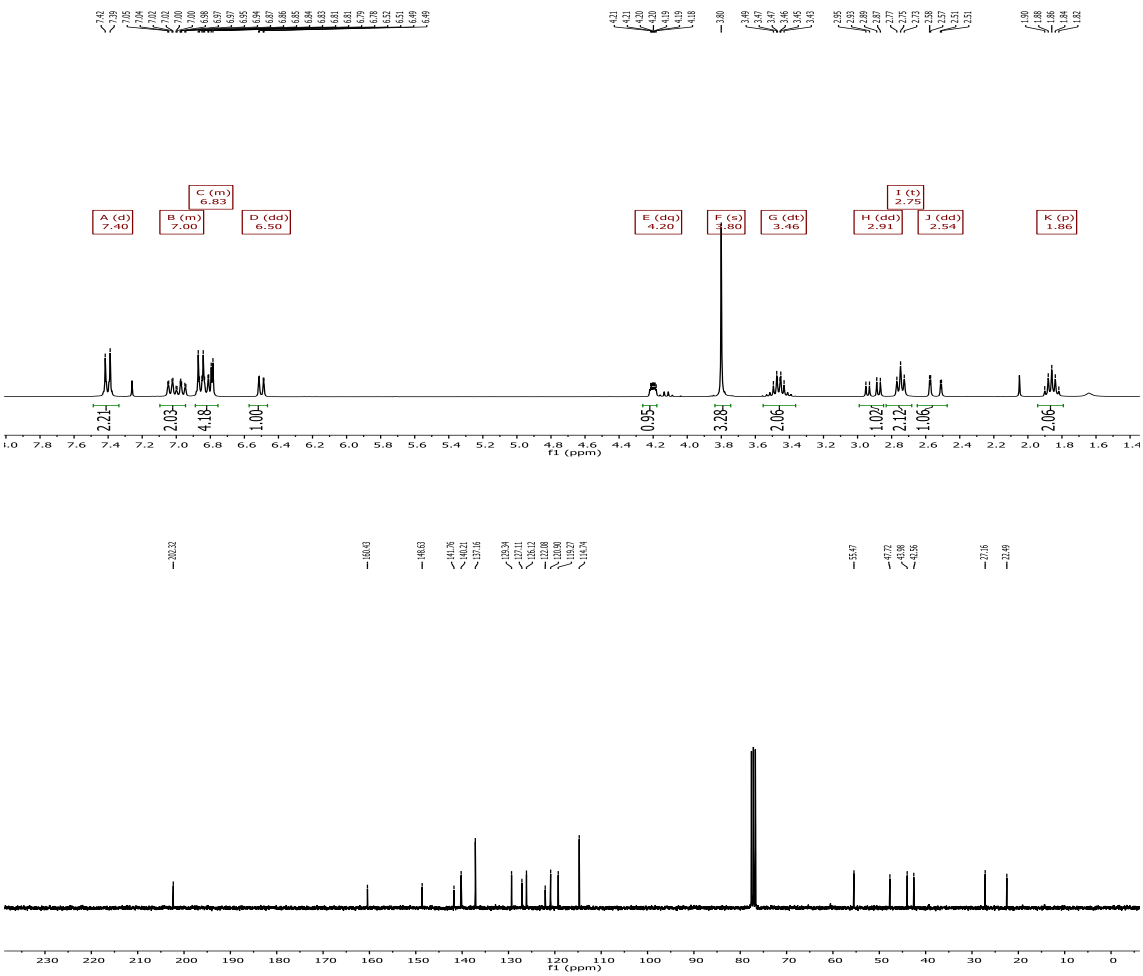


2-(3,4-dihydroquinolin-1(2H)-yl)-4-((4-methoxyphenyl)thio)cyclopent-2-en-1-one56

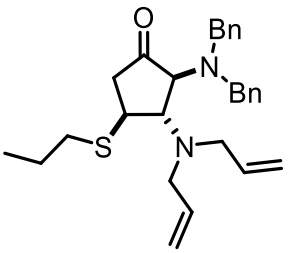


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 53 mg (75%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 2H), 7.08 – 6.91 (m, 2H), 6.90 – 6.70 (m, 4H), 6.50 (dd, J = 8.2, 1.2 Hz, 1H), 4.20 (dq, J = 5.0, 1.6 Hz, 1H), 3.80 (s, 3H), 3.46 (m, 2H), 2.91 (dd, J = 19.2, 6.4 Hz, 1H), 2.75 (t, J = 6.5 Hz, 2H), 2.54 (dd, J = 19.2, 1.8 Hz, 1H), 1.86 (p, J = 6.2 Hz, 2H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.3, 160.4, 148.6, 141.8, 140.2, 137.2, 129.3, 127.1, 126.1, 122.1, 120.9, 119.3, 114.7, 55.47, 47.7, 43.9, 42.6, 27.2, 22.5. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{21}H_{22}NO_2S$ $[M + H]^+$ 352.12658, found 352.12548.

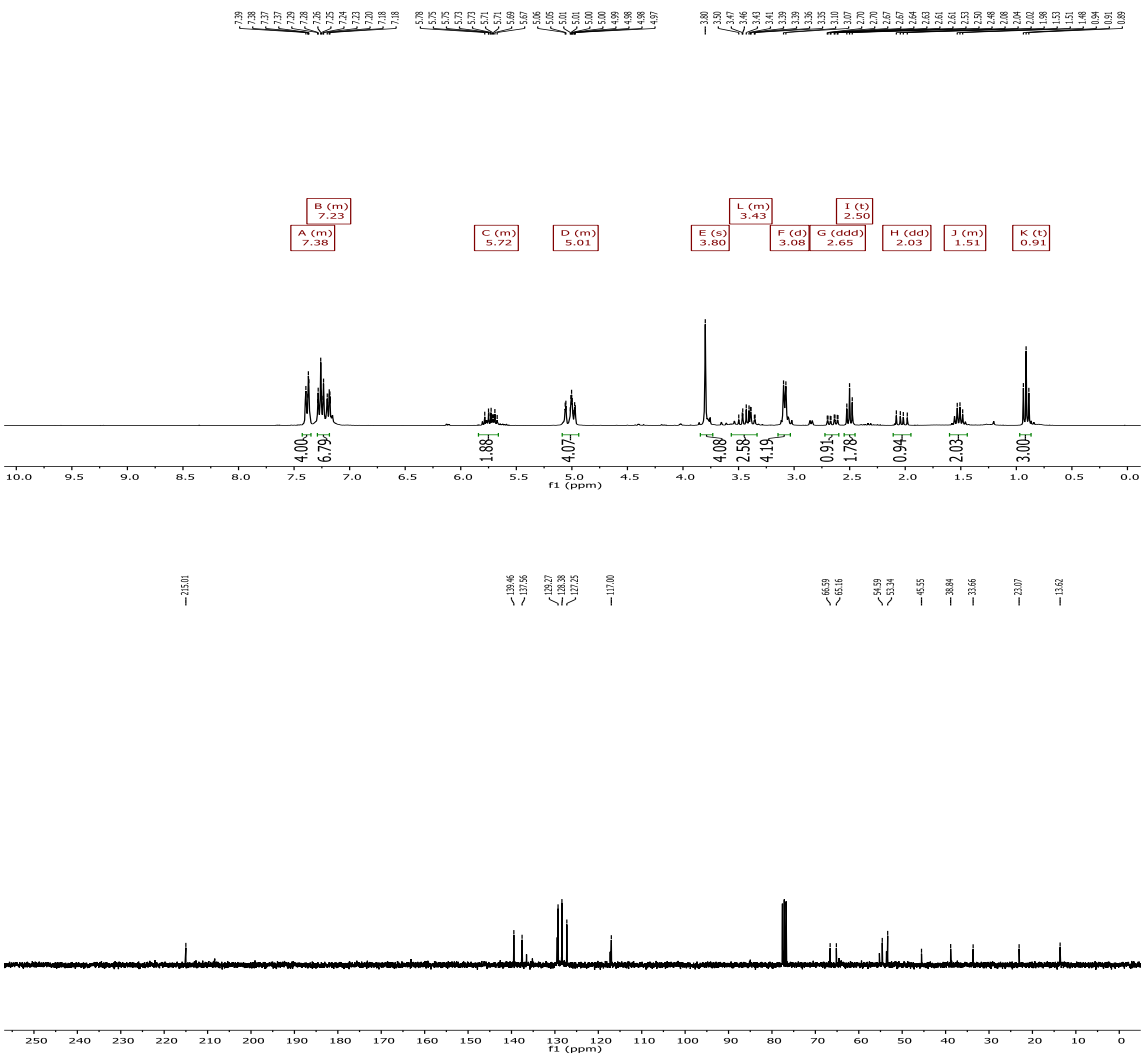


3-(diallylamino)-2-(dibenzylamino)-4-(propylthio)cyclopentan-1-one 63

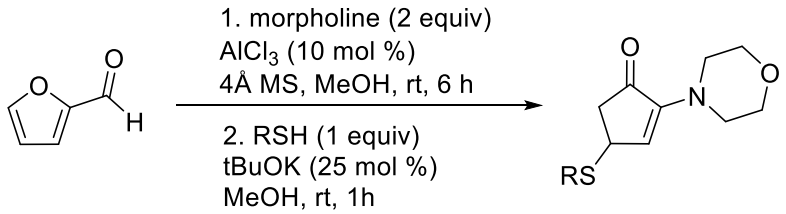


The titled compound was prepared according to general procedure in the absence of base. The crude mixture was evaporated affording 88 mg (98%) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.34 (m, 4H), 7.33 – 7.05 (m, 6H), 6.03 – 5.59 (m, 2H), 5.39 – 4.88 (m, 4H), 3.80 (s, 4H), 3.35 – 3.50 (m, 2H), 3.08 (d, J = 6.3 Hz, 4H), 2.65 (dd, J = 18.9, 8.1, Hz, 1H), 2.50 (t, J = 7.3 Hz, 2H), 2.03 (dd, J = 18.8, 10.7 Hz, 1H), 1.68 – 1.27 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 215.0, 139.5, 137.6, 129.3, 128.4, 127.2, 117.0, 66.6, 65.2, 54.6, 53.4, 45.5, 38.8, 33.7, 23.1, 13.6. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{28}H_{37}N_2OS$ $[M + H]^+$ 449.26211, found 449.26398.



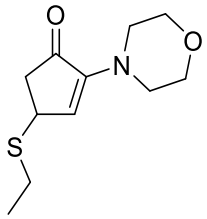
General Procedure B for the Preparation of 2-morpholino-4-thio cyclopentenones from 2-furaldehyde



To a solution of 2-furaldehyde (0.41 mL, 5 mmol) in dry MeOH (20 mL, 0.25M) was added morpholine (0.86 mL, 2.2 equiv, 10 mmol), $AlCl_3$ (67 mg, 0.1 equiv, 0.5 mmol) and 4Å molecular sieves (0.2 g/mmol of 2-furaldehyde). The mixture was stirred for six hours at room temperature under nitrogen atmosphere. Then, was added 1 equivalent of the corresponding substituted thiol and KO^tBu (140 mg, 0.25 equiv, 1.25 mmol). The mixture was stirred at room temperature under nitrogen atmosphere for 1-2h. Afterwards, the crude was filtered through a short plug of celite and the filter cake was washed with DCM

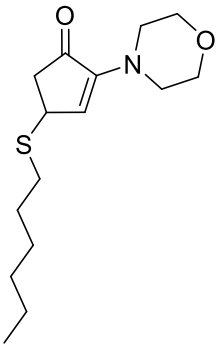
(60 mL). To the filtrate was added AcOH/NaOAc buffer solution at pH 5 (20 mL) and brine (10 mL). The organic layer was separated, and the aqueous layer was further extracted with DCM (2×20 mL), and the combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the pure products

4-(ethylthio)-2-morpholinocyclopent-2-enone 64



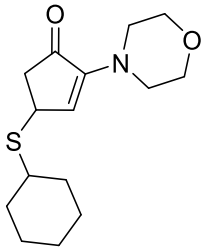
The titled compound was prepared using ethanethiol (0.37mL) according to general procedure **B**. The product was purified by flash chromatography on silica using petroleum ether/DCM/EtOAc (10:10:1 v/v) and was isolated as an orange oil in 73% (829 mg). Spectroscopic data are in accordance to the literature. [48]

4-(hexylthio)-2-morpholinocyclopent-2-enone 65



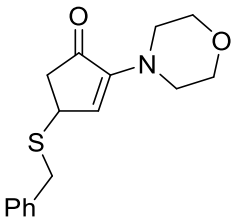
The titled compound was prepared using 1-hexanethiol (0.7 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using petroleum ether/DCM/EtOAc (10:10:1 v/v) and was isolated as an orange oil in 79% (1.1 g). Spectroscopic data are in accordance to the literature. [48]

4-(cyclohexylthio)-2-morpholinocyclopent-2-enone 66



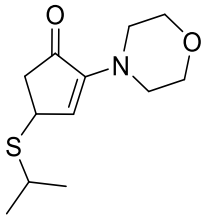
The titled compound was prepared using cyclohexanethiol (0.625 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using petroleum ether/DCM/EtOAc (10:10:1 v/v) and was isolated as an orange oil in 72% (1 g). Spectroscopic data are in accordance to the literature. [48]

4-(benzylthio)-2-morpholinocyclopent-2-enone 67



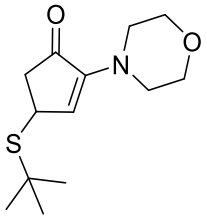
The titled compound was prepared using benzylthiol (0.587 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using petroleum ether/DCM/EtOAc (10:10:1 v/v) and was isolated as an orange oil in 80% (1.1 g). Spectroscopic data are in accordance to the literature. [48]

4-(isopropylthio)-2-morpholinocyclopent-2-enone 68



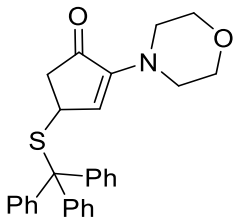
The titled compound was prepared using 2-propanethiol (0.464 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using petroleum ether/DCM/EtOAc (10:10:1 v/v) and was isolated as an orange oil in 77% (924 mg). Spectroscopic data are in accordance to the literature. [48]

4-(*tert*-butylthio)-2-morpholinocyclopent-2-enone 69



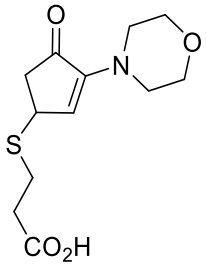
The titled compound was prepared using 2-methyl-2-propanethiol (0.56 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using petroleum ether/DCM/EtOAc (10:10:1 v/v) and was isolated as a yellow-white solid in 76% (975 mg). Spectroscopic data are in accordance to the literature. [48]

2-morpholino-4-(tritylthio)-cyclopent-2-enone 70



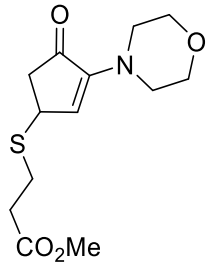
The titled compound was prepared using trityl thiol (1.38 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using petroleum ether/DCM/EtOAc (10:10:1 v/v) and was isolated as a yellow-white solid in 63% (1.4 g). Spectroscopic data are in accordance to the literature. [48]

3-(3-morpholino-4-oxocyclopent-2-enylthio)-propanoic acid 71



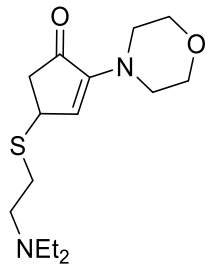
The titled compound was prepared using 3-mercaptopropionic acid (0.436 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using DCM/ethanol (20:1 v/v) and was isolated as an orange-brown solid in 55% (743 mg). Spectroscopic data are in accordance to the literature. [48]

Methyl 3-(3-morpholino-4-oxocyclopent-2-enylthio)-propanoate 72



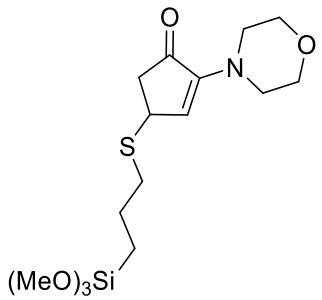
The titled compound was prepared using methyl-3-mercaptopropionate (0.542 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using DCM/EtOAc (10:1 v/v) and was isolated as an orange oil in 71% (973 mg). Spectroscopic data are in accordance to the literature. [48]

4-(2-(diethylamino)ethylthio)-2-morpholinocyclopent-2-enone 73



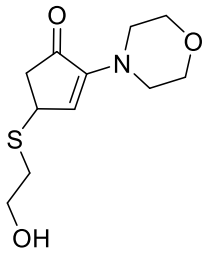
The titled compound was prepared using 2-(diethylamino)-ethanethiol (0.75 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as an orange oil in 76% (1.13 g). Spectroscopic data are in accordance to the literature. [48]

4-(3-(trimethoxysilyl)-propylthio)-2-morpholinocyclopent-2-enone 75



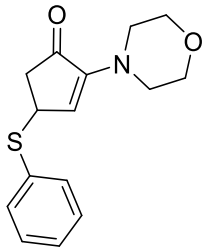
The titled compound was prepared using 2-(trimethoxysilyl)ethane-1-thiol (0.93 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using DCM/ethanol (20:1 v/v) and was isolated as an orange oil in 52% (940 mg). Spectroscopic data are in accordance to the literature. [48]

4-(2-hydroxyethylthio)-2-morpholinocyclopent-2-enone 74



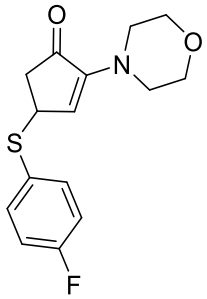
The titled compound was prepared using 2-mercaptoethanol (0.35 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using DCM/ethanol (20:1 v/v) and was isolated as an orange oil in 77% (940 mg). Spectroscopic data are in accordance to the literature. [48]

2-morpholino-4-(phenylthio)-cyclopent-2-enone 76



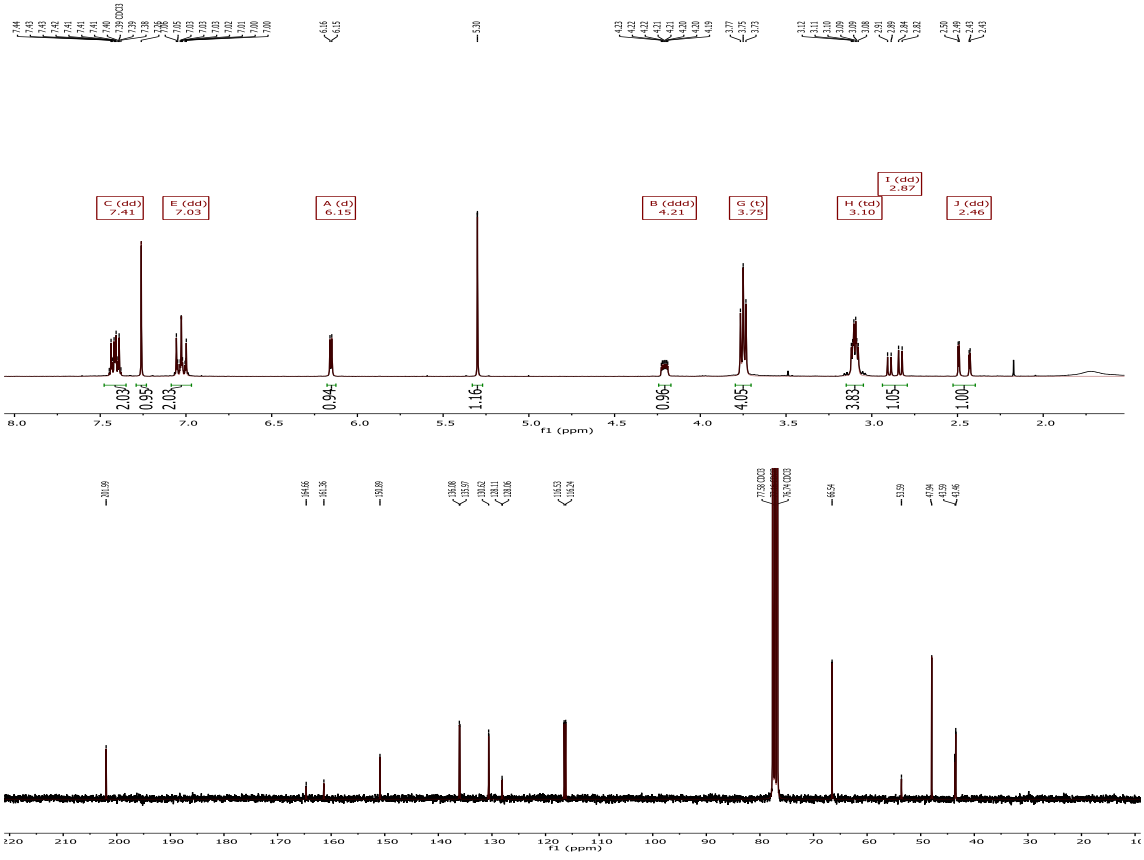
The titled compound was prepared using thiophenol (0.513 mL) according to general procedure **B**. The product was purified by flash chromatography on silica using petroleum ether/DCM/EtOAc (10:10:1 v/v) and was isolated as an orange oil in 71% (973 mg). Spectroscopic data are in accordance to the literature. [48]

4-((4-fluorophenyl)thio)-2-morpholinocyclopent-2-en-1-one 77

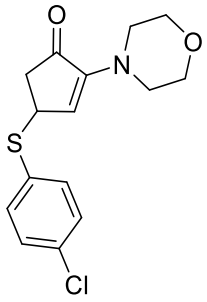


The titled compound was prepared using 4-fluorobenzenethiol (640 mg) according to general procedure **B**. The product was purified by flash chromatography on silica using EtOAc/n-hexane (1:9 v/v) and was isolated as a light brown solid in 43% (631 mg). m.p. 88-89 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (1H, dd, *J* = 19.2, 1.8 Hz), 2.87 (1H, dd, *J* = 19.2, 6.3 Hz), 3.10 (4H*, td, J* = 4.4, 2.4 Hz), 3.75 (4H, t, *J* = 4.8 Hz), 4.21 (1H, ddd, *J* = 6.3, 3.1, 1.8 Hz), 6.15 (1H, d, *J* = 3.1 Hz), 7.03 (2H, dd, *J* = 8.9, 8.5 Hz), 7.41 (2H, dd, *J* = 8.9, 5.3 Hz) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 43.5, 43.6, 47.9, 66.5, 116.2, 116.5, 128.1, 128.1, 130.6, 135.9, 136.1, 150.9, 201.9 **HRMS (ESI-MS)** *m/z* calcd for $C_{15}H_{16}FNO_2S$ $[M + H]^+$ 294.0959, found 294.0959

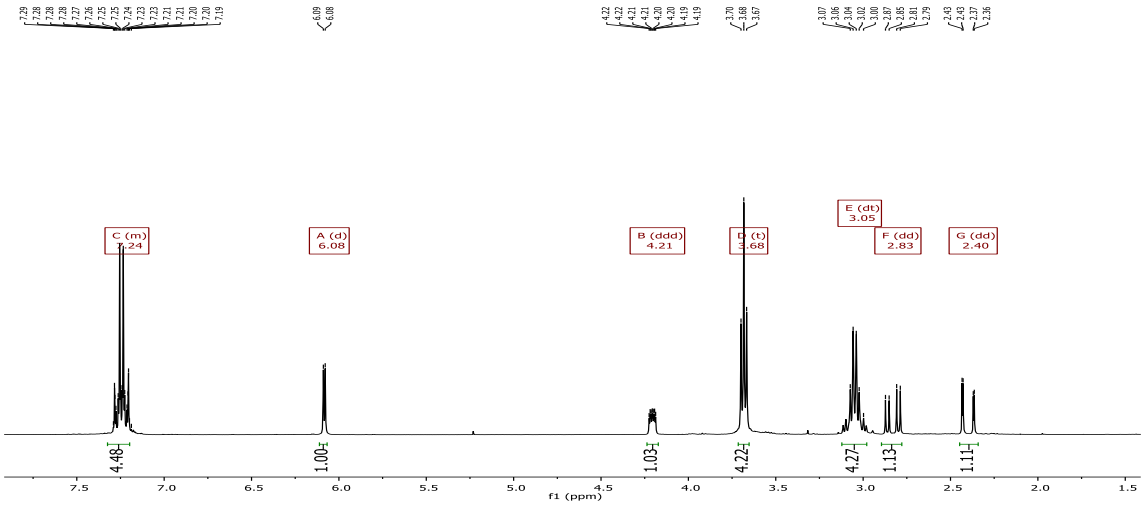


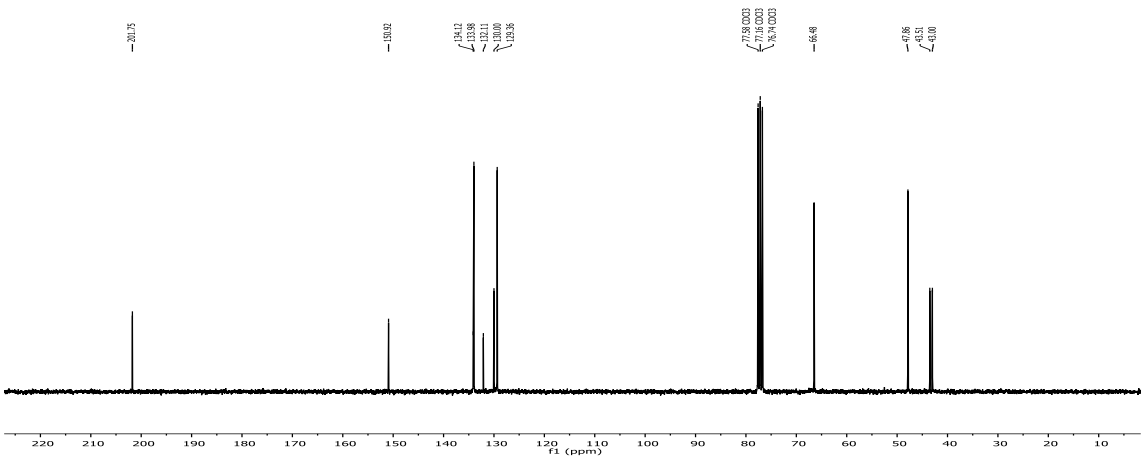
4-((4-chlorophenyl)thio)-2-morpholinocyclopent-2-en-1-one 78



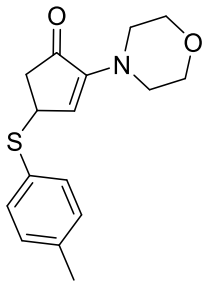
The titled compound was prepared using 4-chlorobenzenethiol (723 mg) according to general procedure **B**. The product was purified by flash chromatography on silica using EtOAc/n-hexane (1:9 v/v) and was isolated as a dark yellow solid in 54% (836 mg). m.p. 88 -90 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (1H, dd, *J* = 19.2, 1.8 Hz), 2.83 (1H, dd, *J* = 19.2, 6.3 Hz), 3.05 (4H, dt, *J* = 6.0, 4.7 Hz), 3.68 (4H, t, J= 4,8 Hz), 4.21 (1H, ddd, J = 6.3, 3.2, 1.8 Hz), 6.08 (1H, d, *J* = 3.2 Hz), 7.31 -7.19 (4H, m) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 43.0, 43.5, 47.8, 66.5, 129.4, 130.0, 132.1, 133.9, 134.1, 150.9, 201.8 **HRMS (ESI-MS)** m/z calcd for $C_{15}H_{16}ClNO_2S$ $[M + H]^+$ 310.0663, found 310.0660



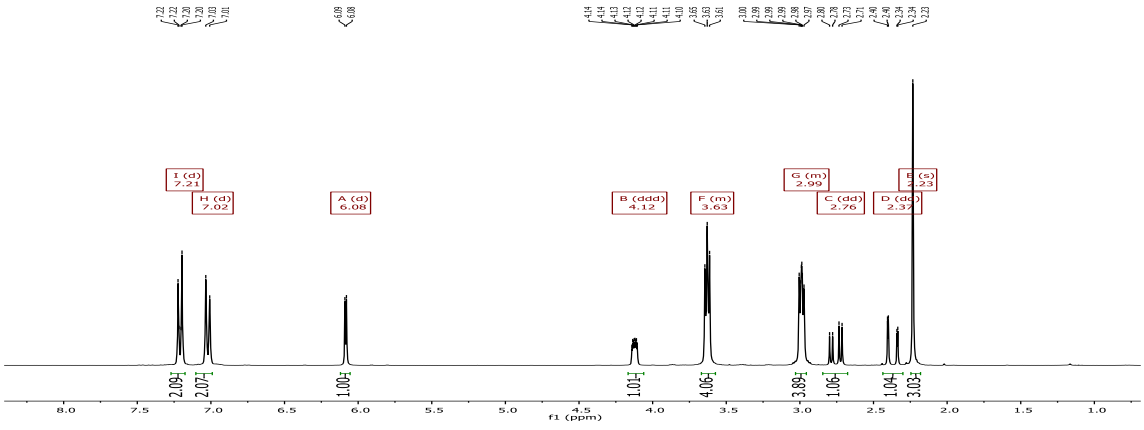

201.75
150.02
134.12
133.98
132.11
130.00
129.36
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
66.48
47.86
43.51
43.00
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

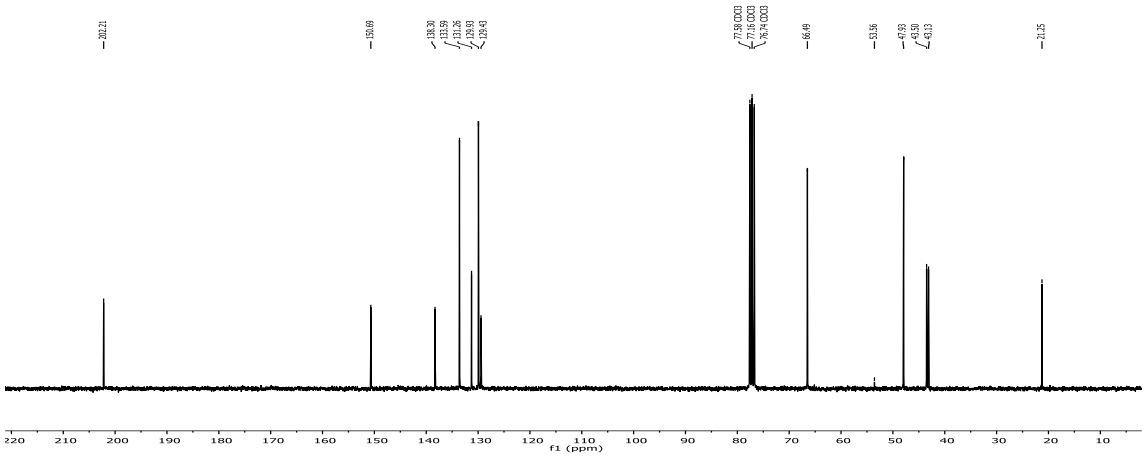
2-morpholino-4-(p-tolylthio)cyclopent-2-en-1-one 79



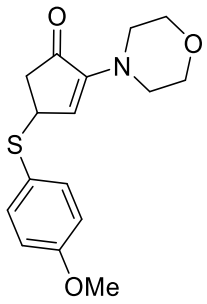
The titled compound was prepared using 4-methylbenzenethiol (621 mg) according to general procedure **B**. The product was purified by flash chromatography on silica using EtOAc/n-hexane (1:9 v/v) and was isolated as a dark brown solid in 35% (506 mg). m.p. 87-88 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (3H, s), 2.37 (1H, dd, *J* = 19.2, 1.8 Hz), 2.76 (1H, dd, *J* = 19.2, 6.2 Hz), 3.03 – 2.96 (4H, m), 3.67 – 3.57 (4H, m), 4.12 (1H, ddd, J = 6.3, 3.2, 1.8 Hz), 6.08 (1H, d, *J* = 3.2 Hz), 7.02 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.0 Hz) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 21.3, 43.1, 43.5, 47.9, 66.5, 129.4, 129.9, 131.3, 133.6, 138.3, 150.7, 202.2 **HRMS (ESI-MS)** *m/z* calcd for $C_{16}H_{19}NO_2S$ $[M + H]^+$ 290.1209 , found 290.1208



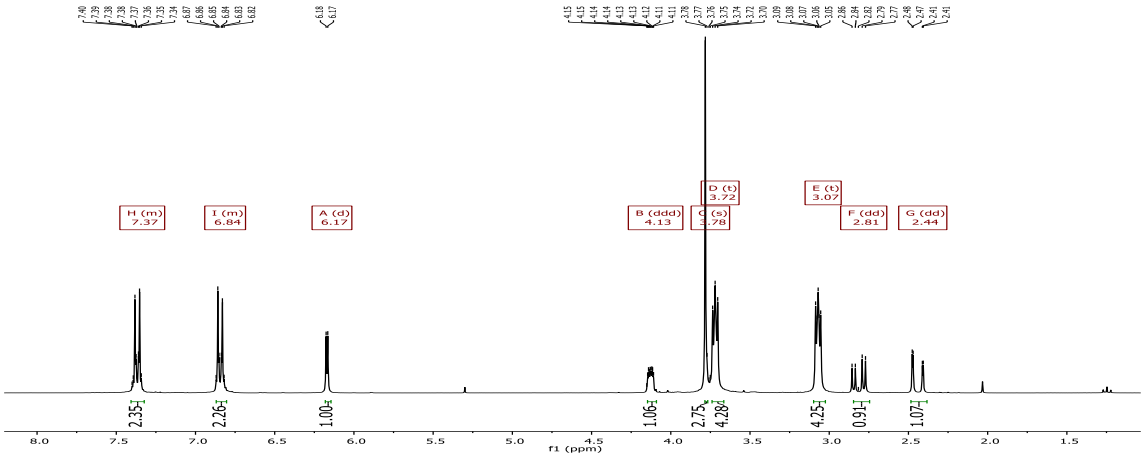

202.21
150.69
138.30
133.59
131.26
129.93
129.43
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
66.49
53.16
47.93
43.50
43.13
21.25
f1 (ppm)

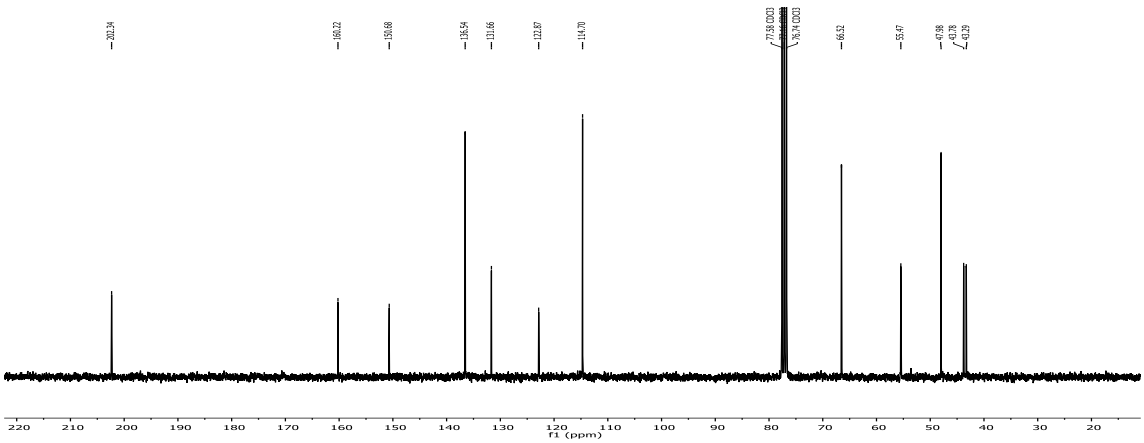
4-((4-methoxyphenyl)thio)-2-morpholinocyclopent-2-en-1-one 80



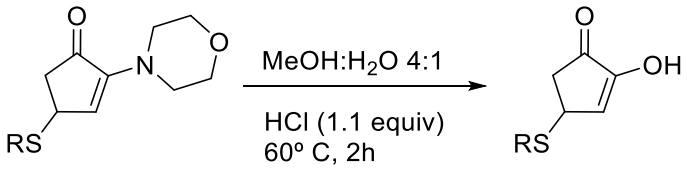
The titled compound was prepared using 4-methoxybenzenethiol (701 mg) according to general procedure **B**. The product was purified by flash chromatography on silica using EtOAc/n-hexane (1:9 v/v) and was isolated as a brown solid in 47% (718 mg). m.p. 105 - 107 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (1H, dd, J = 19.2, 1.7 Hz), 2.81 (1H, dd, J = 19.2, 6.3 Hz), 3.07 (4H, t, J = 3.8 Hz), 3.72 (4H, t, J = 3.8 Hz), 3.78 (3H, s), 4.13 (1H, ddd, J = 6.3, 3.1, 1.7 Hz), 6.17 (1H, d, J = 3.2 Hz), 6.84 (2H, m), 7.97 (2H, m) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 43.3, 43.8, 47.9, 55.5, 66.5, 114.7, 122.9, 131.7, 136.5, 150.7, 160.2, 202.3.0. **HRMS (ESI-MS)** m/z calcd for $C_{16}H_{19}NO_2S$ $[M + H]^+$ 306.1158, found 306.11520.



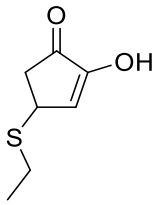


General Procedure C for the Preparation of 2-hydroxyl cyclopentenones



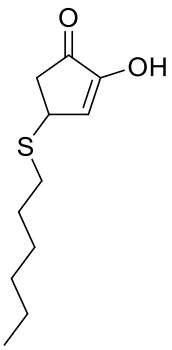
To a solution of the selected 2-morpholino-4-thio-cyclopentenone (1 mmol) in a mixture of MeOH/water (0.2M, 4:1 v/v) was added HCl 37% (0.094 ml, 1.1 equiv, 1.1 mmol). The mixture was stirred at 60 ºC for 2 hours. Afterwards, water (4 mL) and DCM (12 mL) were added, and layers were separated. Aqueous layer was further extracted with DCM (12 mL). Combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow low melting point solid or an orange oil which was purified by flash chromatography on silica.

4-(ethylthio)-2-hydroxycyclopent-2-enone 82



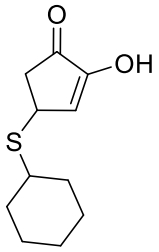
The titled compound was prepared according to general procedure **C**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as a pale-yellow low melting point solid in 79% (125 mg). Spectroscopic data are in accordance to the literature. [48]

4-(hexylthio)-2-hydroxycyclopent-2-enone 83



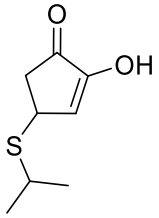
The titled compound was prepared according to general procedure **C**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as a pale-yellow low melting point solid in 83% (166 mg). Spectroscopic data are in accordance to the literature. [48]

4-(cyclohexylthio)-2-hydroxycyclopent-2-enone 84



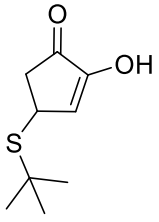
The titled compound was prepared according to general procedure **C**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as a pale-yellow low melting point solid in 92% (195 mg). Spectroscopic data are in accordance to the literature. [48]

2-hydroxy-4-(isopropylthio)-cyclopent-2-enone 85



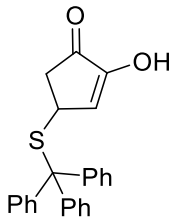
The titled compound was prepared according to general procedure **C**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as a pale-yellow low melting point solid in 82% (141 mg). Spectroscopic data are in accordance to the literature. [48]

4-(*tert*-butylthio)-2-hydroxycyclopent-2-enone 86



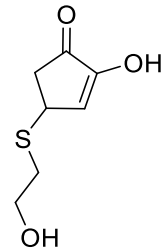
The titled compound was prepared according to general procedure **C**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as a pale-yellow low melting point solid in 94% (176 mg). Spectroscopic data are in accordance to the literature. [48]

2-hydroxy-4-(tritylthio)-cyclopent-2-enone 87



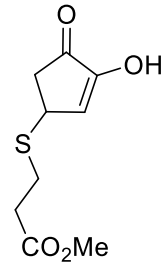
The titled compound was prepared according to general procedure **C**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as a pale-yellow low melting point solid in 82% (304 mg). Spectroscopic data are in accordance to the literature. [48]

4-(2-hydroxyethylthio)-2-hydroxycyclopent-2-enone 89



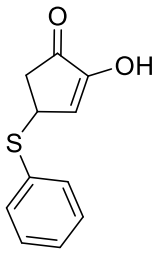
The titled compound was prepared according to general procedure **C**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as an orange oil in 80% (140 mg). Spectroscopic data are in accordance to the literature.[48]

Methyl-3-(3-hydroxy-4-oxocyclopent-2-enylthio)-propanoate 88



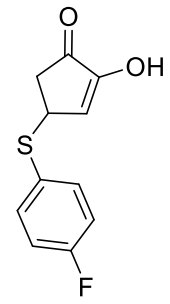
The titled compound was prepared according to general procedure **C**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as an orange oil in 78% (170 mg). Spectroscopic data are in accordance to the literature. [48]

2-hydroxy-4-(phenylthio)-cyclopent-2-enone 90



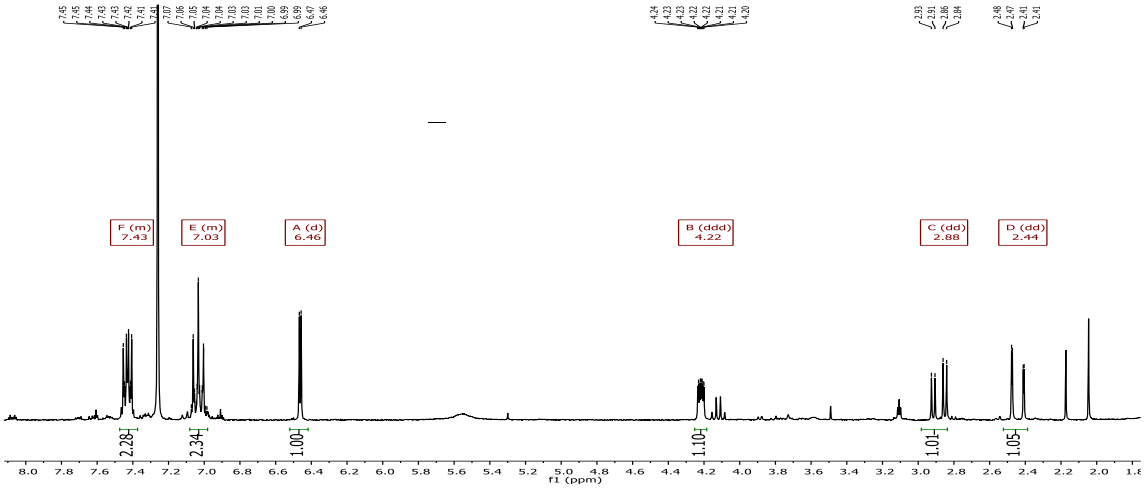
The titled compound was prepared according to general procedure **C**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as a pale yellow low melting point solid in 49% (134 mg). Spectroscopic data are in accordance to the literature.[48]

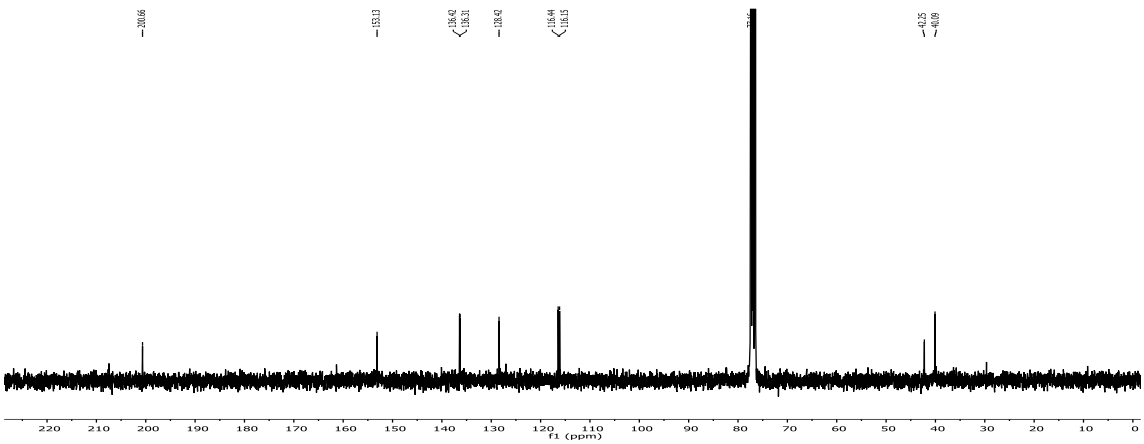
4-((4-fluorophenyl)thio)-2-hydroxycyclopent-2-en-1-one 91



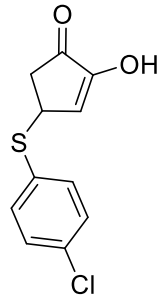
The titled compound was prepared according to general procedure **C**. The product was purified by flash chromatography on silica using DCM/MeOH (20:1 v/v) and was isolated as a brown low melting point solid in 27% (60 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (1H, dd, *J* = 19.6, 1.5 Hz), 2.88 (1H, dd, *J* = 19.6, 6.0 Hz), 4.22 (1H, ddd, *J* = 6.0, 3.1, 1.5 Hz), 6.46 (1H, d, *J* = 3.0 Hz), 7.08 – 6.98 (2H, m), 7.47 – 7.37 (2H, m) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 40.1, 42.2, 116.2, 116.4, 128.4, 136.3, 136.4, 153.1, 200.7 **HRMS (ESI-MS)** m/z calcd for $C_{11}H_9FO_2S$ $[M + H]^+$ 223.0235, found 223.0233



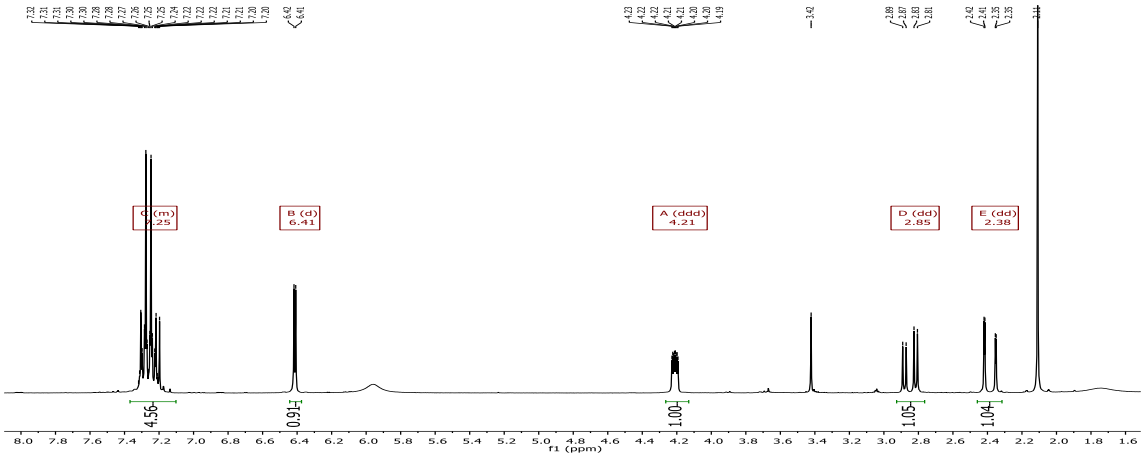


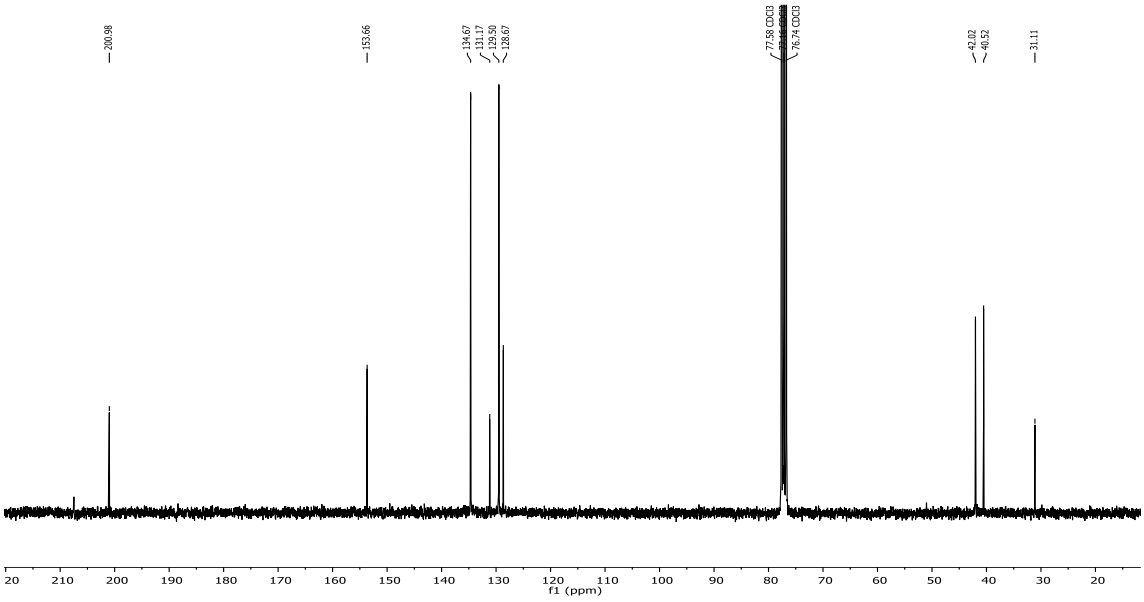
4-((4-chlorophenyl)thio)-2-hydroxycyclopent-2-en-1-one 92



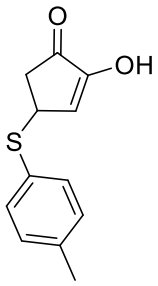
The titled compound was prepared according to general procedure **C**. The product was isolated by precipitation as a brown solid in 25% (60 mg). m.p. 135 ºC - 138 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (1H, dd, *J* = 19.6, 1.5 Hz), 2.85 (1H, dd, *J* = 19.6, 6.0 Hz), 4.21 (1H, ddd, J = 6.0, 3.1, 1.5 Hz), 6.41 (1H, d, *J* = 3.0 Hz), 7.39 -7.23 (5H, m) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 31.1, 40.5, 42.0, 128.7, 129.5, 131.2, 134.7, 153.7, 200.9. **HRMS (ESI-MS)** m/z calcd for $C_{11}H_9ClO_2S$ $[M + H]^+$ 241.0081, found 241.0072.



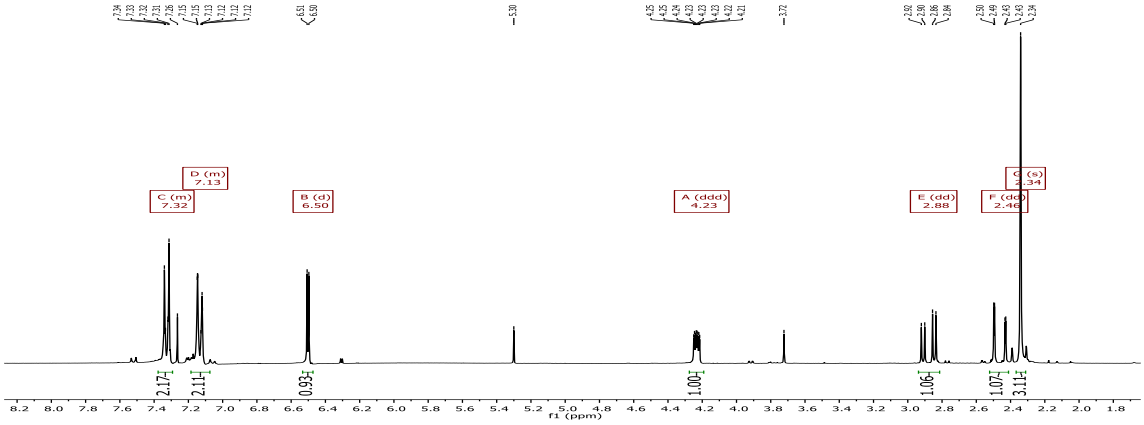

200.98
153.66
134.67
131.17
129.50
128.67
77.58 CDCl3
76.74 CDCl3
42.02
40.52
31.11
f1 (ppm)

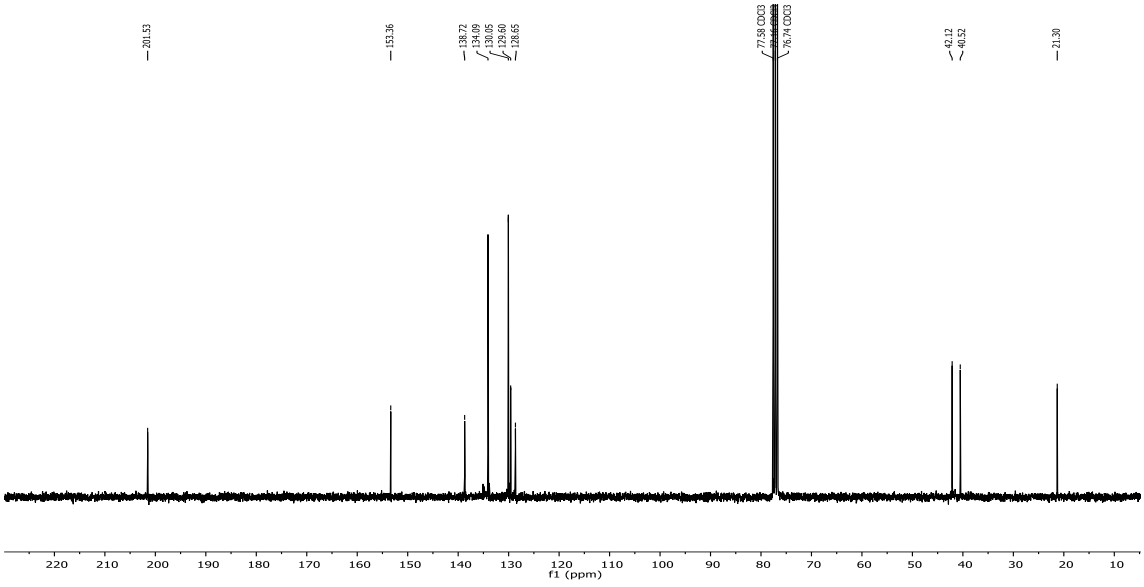
2-hydroxy-4-(p-tolylthio)cyclopent-2-en-1-one 93



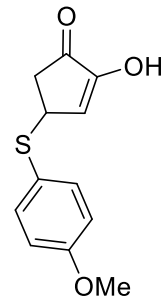
The titled compound was prepared according to general procedure **C**. The product was isolated by precipitation as a brown solid in 24% (53 mg). m.p. 62 ºC - 64 ºC

^{1}H NMR (300 MHz, CDCl3) δ 2.34 (3H, s), 2.46 (1H, dd, *J* = 19.7, 1.5 Hz), 2.88 (1H, dd, *J* = 19.6, 5.9 Hz), 4.23 (1H, ddd, J = 5.9, 3.0, 1.5 Hz), 6.5 (1H, d, *J* = 3.0 Hz), 7.13 (2H, m, *J* = 8.1 Hz), 7.32 (2H, m, *J* = 8.1 Hz) **^{13}C NMR (75 MHz, CDCl3) δ** 21.3, 40.5, 42.1, 128.6, 129.6, 130.0, 134.1, 138.7, 153.4, 200.5. **HRMS (ESI-MS)** m/z calcd for $C_{12}H_{12}O_2S$ $[M + H]^+$ 221.0631, found 221.0680.



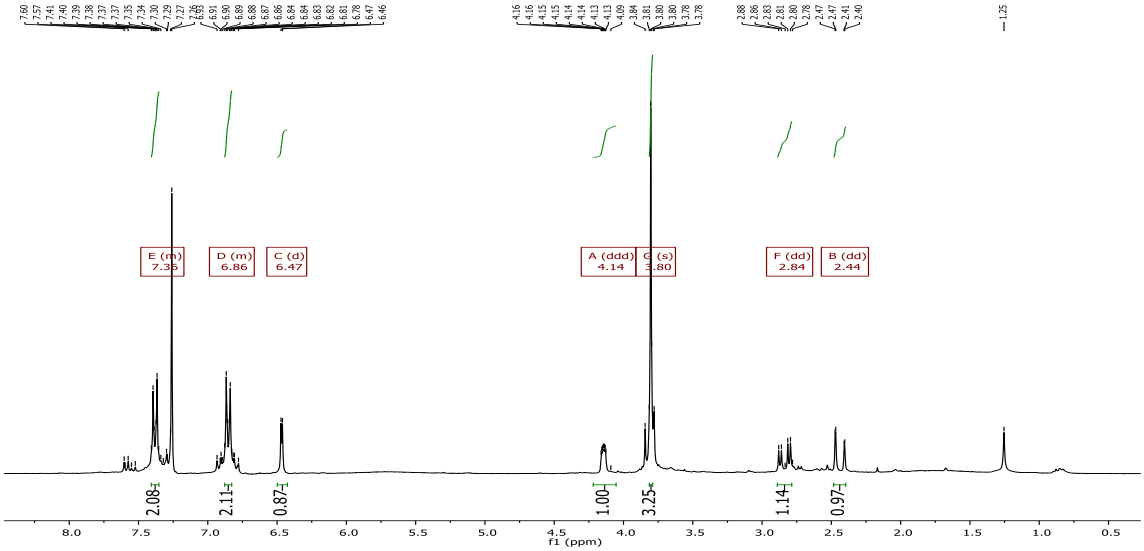


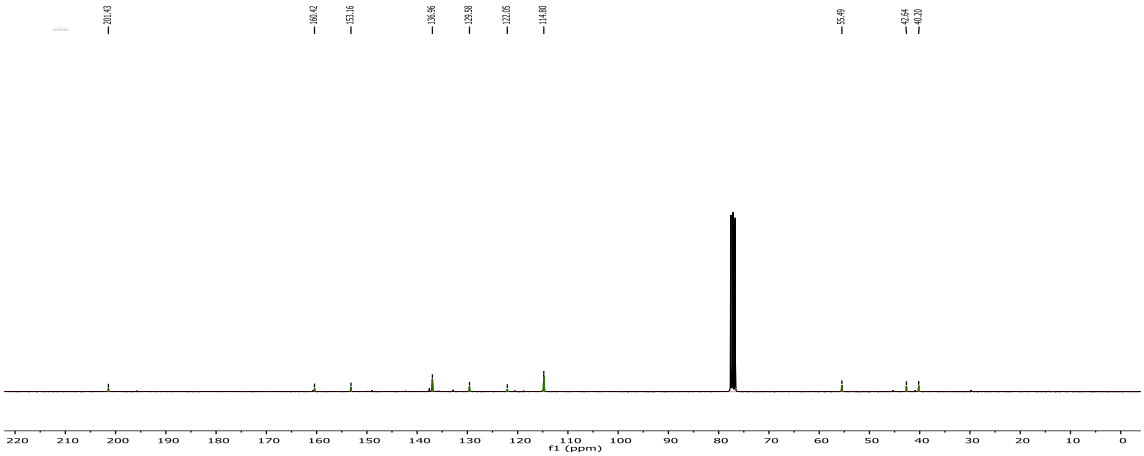
2-hydroxy-4-((4-methoxyphenyl)thio)cyclopent-2-en-1-one 94



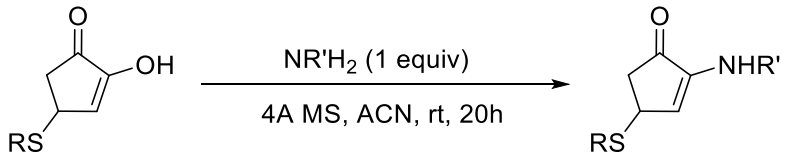
The titled compound was prepared according to general procedure **C**. The product was isolated by precipitation as a brown solid in 21% (50 mg) as a 9:1 mixture of product and SM.

^{1}H NMR (300 MHz, CDCl3) δ 2.44 (1H, dd, J = 19.5, 1.5 Hz), 2.84 (1H, dd, J = 19.6, 5.9 Hz), 3.80 (s, 3H), 4.14 (1H, ddd, J = 6.1, 3.1, 1.5 Hz), 6.47 (1H, d, J = 3.1 Hz), 6.96 – 6.74 (4H, m), 7.64 – 7.30 (4H, m) **^{13}C NMR (75 MHz, CDCl3) δ** 40.2, 42.6, 55.5, 114.8, 122.1, 129.6, 136.9, 153.2, 160.4, 201.4. **HRMS (ESI-MS)** m/z calcd for $C_{12}H_{12}O_3S$ [M + H]$^+$ 237.0580, found 237.0532.



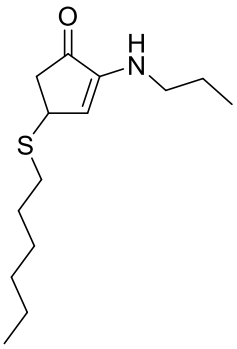

201.43
166.42
153.16
136.96
129.58
122.05
114.80
55.49
42.64
40.20
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

General Procedure D for the Preparation of 2-amino-4-thio cyclopentenones



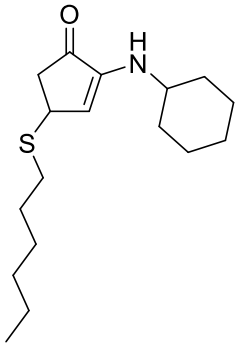
To a solution of the selected hydrolysed cyclopentenone (0.5 mmol) in dry MeCN (0.25 M) was added the selected amine (1 eq.) and 4Å molecular sieves (0.2 g/mmol of diketone). The mixture was stirred at room temperature for the corresponding time to each compound. Afterwards, the reaction mixture was filtered through a short plug of celite and the filter cake was washed with DCM. The filtrate was concentrated under reduced pressure to yield a dark brown oil which was purified by flash chromatography on silica.

4-(hexylthio)-2-(propylamino)-cyclopent-2-enone 95



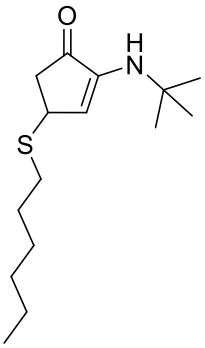
The titled compound was prepared according to general procedure **D** for 20 hours. The product was purified by flash chromatography on silica with petroleum ether/DCM/EtOAc (10:10:1 v/v) and was isolated as a clear oil with a slight brown hue, that gets progressively darker over time, in 51% (66 mg). Spectroscopic data are in accordance to the literature. [48]

2-(cyclohexylamino)-4-(hexylthio)-cyclopent-2-enone 96



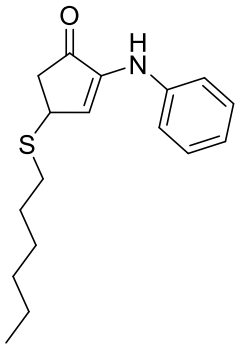
The titled compound was prepared according to general procedure **D** for 20 hours. The product was purified by flash chromatography on silica with petroleum ether/EtOAc (20:1 v/v) and was isolated as a clear oil with a slight brown hue, that gets progressively darker over time, in 64% (94 mg). Spectroscopic data are in accordance to the literature. [48]

2-(*tert*-butylamino)-4-(hexylthio)-cyclopent-2-enone 97



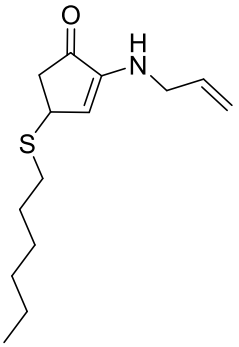
The titled compound was prepared according to general procedure **D** for 20 hours. The product was purified by flash chromatography on silica with petroleum ether/EtOAc (20:1 v/v) and was isolated as a clear oil with a slight brown hue, that gets progressively darker over time, in 24% (32 mg). Spectroscopic data are in accordance to the literature. [48]

4-(hexylthio)-2-(phenylamino)-cyclopent-2-enone 98



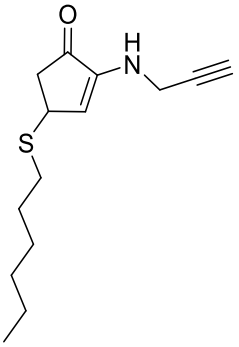
The titled compound was prepared according to general procedure **D** for 20 hours. The product was purified by flash chromatography on silica with DCM and was isolated as a brown oil, that gets progressively darker over time, in 31% (38 mg). Spectroscopic data are in accordance to the literature. [48]

2-(allylamino)-4-(hexylthio)-cyclopent-2-enone 99



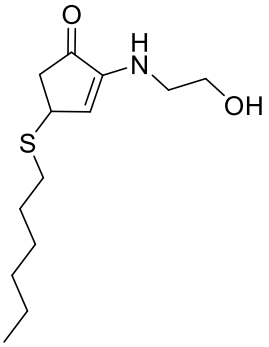
The titled compound was prepared according to general procedure **D** for 20 hours. The product was purified by flash chromatography on silica with DCM and was isolated as a clear oil with a slight brown hue, which gets progressively darker over time, in 66% (84 mg). Spectroscopic data are in accordance to the literature. [48]

4-(hexylthio)-2-(prop-2-ynylamino)-cyclopent-2-enone 100



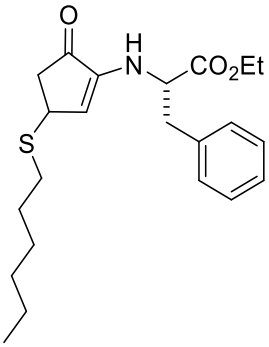
The titled compound was prepared according to general procedure **D** for 20 hours. The product was purified by flash chromatography on silica with DCM and was isolated as a brown oil, which gets progressively darker over time, in 31% (38 mg). Spectroscopic data are in accordance to the literature. [48]

2-(2-hydroxyethylamino)-4-(hexylthio)-cyclopent-2-enone 101



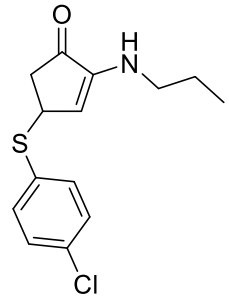
The titled compound was prepared according to general procedure **D** for 20 hours. The product was purified by flash chromatography on silica with DCM/ethanol (20:1 v/v) and was isolated as a brown oil, which gets progressively darker over time, in 51% (66 mg). Spectroscopic data are in accordance to the literature. [48]

(*S*)-ethyl 2-(3-(hexylthio)-5-oxocyclopent-1-enylamino)-3-phenylpropanoate 102



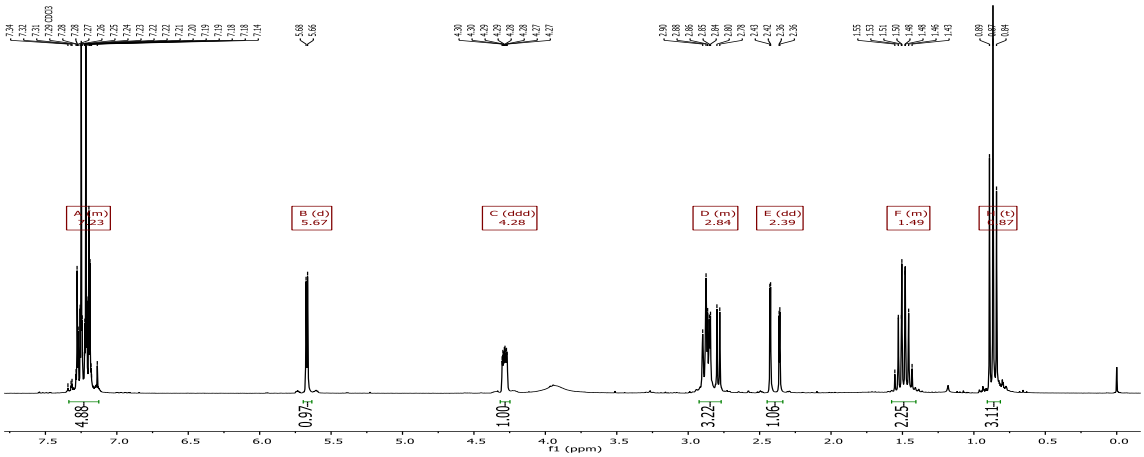
The titled compound was prepared according to general procedure **D** for 20 hours. The product was purified by flash chromatography on silica with petroleum ether/EtOAc (10:1 v/v) and was isolated a separable diastereomeric mixture of diastereomer **102** as a brown oil in 17% (34 mg) and diastereomer **102** as a brown oil in 20% (40 mg). Spectroscopic data are in accordance to the literature. [48]

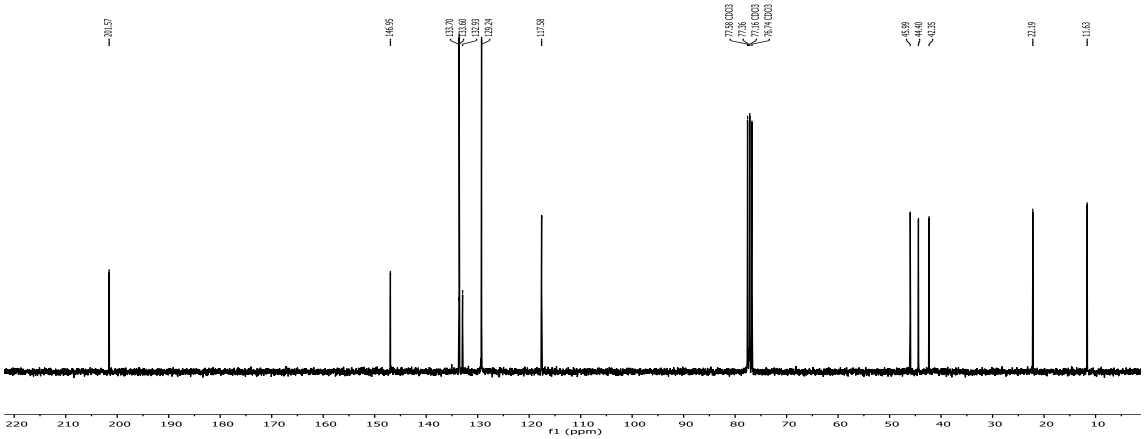
4-((4-chlorophenyl)thio)-2-(propylamino)cyclopent-2-en-1-one 103



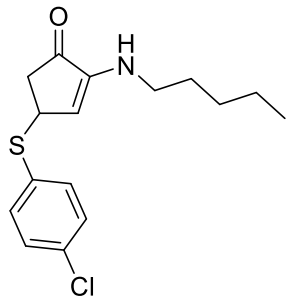
The titled compound was prepared according to general procedure **D** for 3 hours. The product was purified by flash chromatography (EtOAc/*n*-hexane 1:9) and was isolated as a light brown oil in 82% yield (116 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.4 Hz), 1.56 - 1.42 (2H, m), 2.39 (1H, dd, *J* = 19.4, 1.6 Hz), 2.93 – 2.75 (3H, m), 4.28 (1H, ddd, *J* = 6.0, 3.2, 1.6 Hz), 4.28 (1H, ddd, *J* = 6.0, 3.2, 1.6 Hz), 5.67 (1H, d, *J* = 3.2 Hz); 7.37 - 7.09 (4H, m) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 11.6, 22.2, 42.3, 44.4, 45.9, 117.6, 129.2, 132.9, 133.6, 133.7, 146.9, 201.6. **HRMS (ESI-MS)** m/z calcd for $C_{14}H_{16}ClNOS$ $[M + H]^+$ 282.0714, found 282.05871.



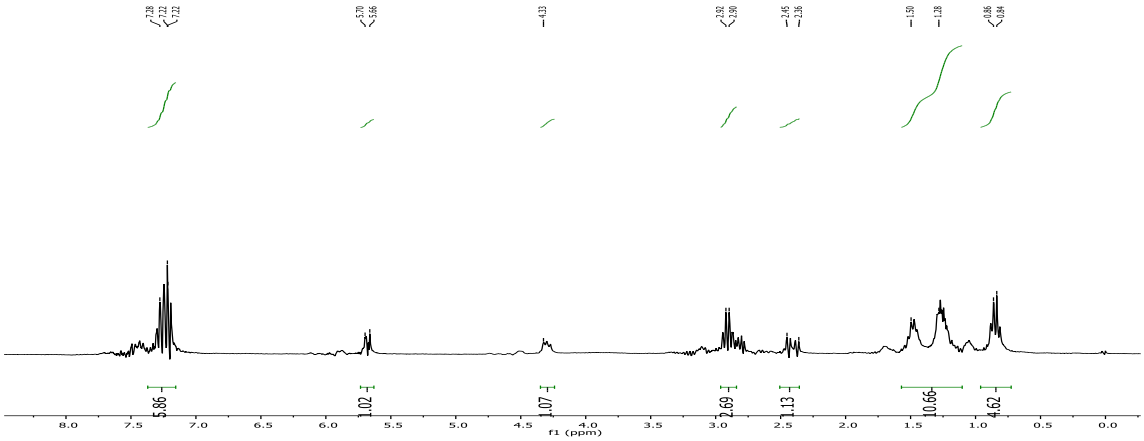


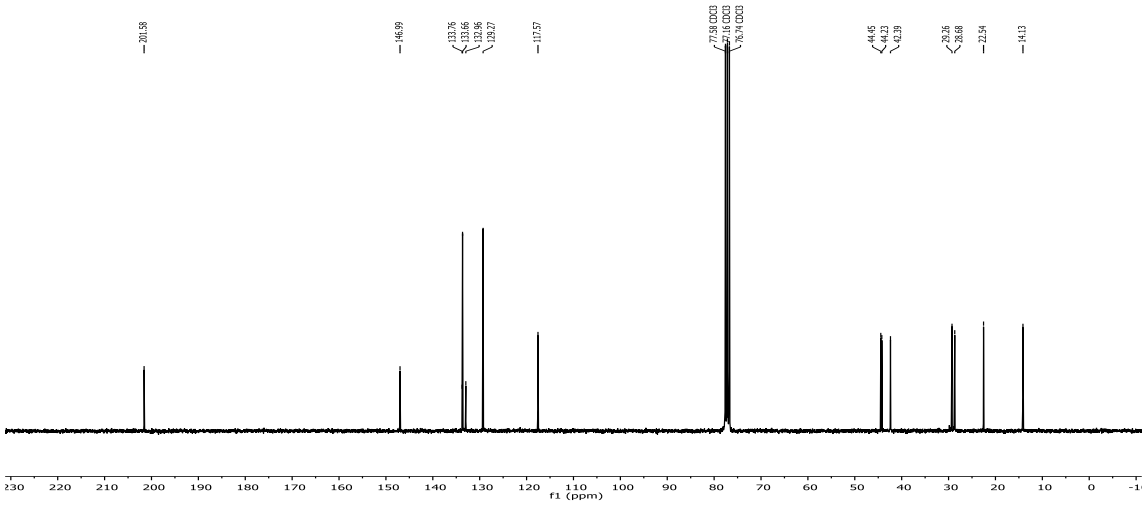
4-((4-chlorophenyl)thio)-2-(pentylamino)cyclopent-2-en-1-one 104



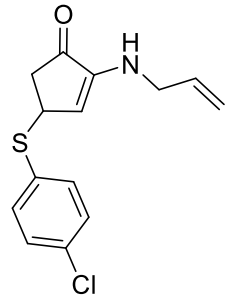
The titled compound was prepared according to general procedure **D** for 3 hours. The product was purified by flash chromatography (EtOAc/*n*-hexane 1:9) and was isolated as a light brown oil in 76% yield (118 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.4 Hz, 3H, H12), 1.49 (h, 2H, H11), 2.39 (dd, *J* = 19.4, 1.6 Hz, 1H, H5), 2.93 – 2.75 (m, 3H, H10, H5), 4.28 (ddd, *J* = 6.0, 3.2, 1.6 Hz, 1H), 4.28 (ddd, *J* = 6.0, 3.2, 1.6 Hz, 1H, H4), 5.67 (d, *J* = 3.2 Hz, 1H, H3) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 14.1, 22.5, 28.7, 29.3, 42.4, 44.2, 44.5, 117.6, 129.3, 132.9, 133.7, 133.8, 146.9, 201.6. **HRMS (ESI-MS)** m/z calcd for $C_{16}H_{20}ClNOS$ $[M + H]^+$ 310.1027, found 310.09021.



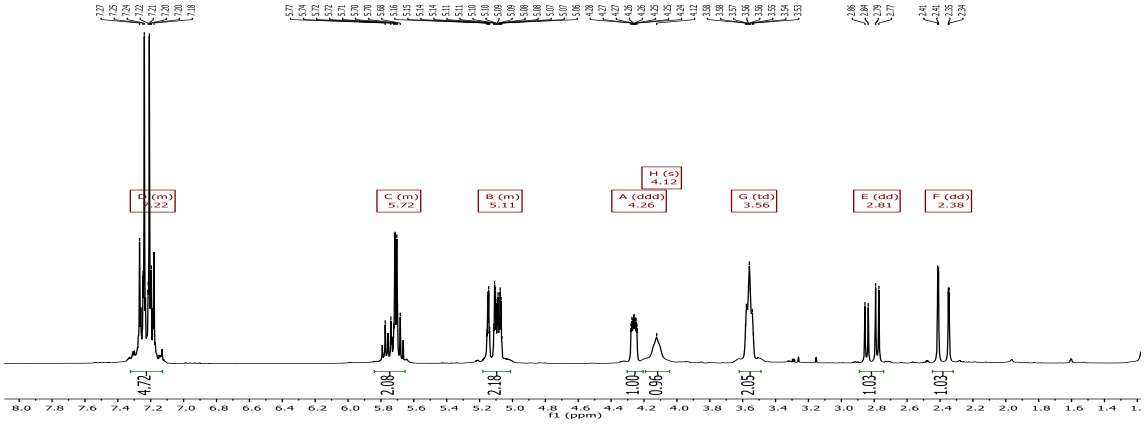

201.58
146.99
133.76
133.06
132.96
129.77
117.57
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
44.45
44.23
42.39
29.26
28.88
22.54
14.13
f1 (ppm)

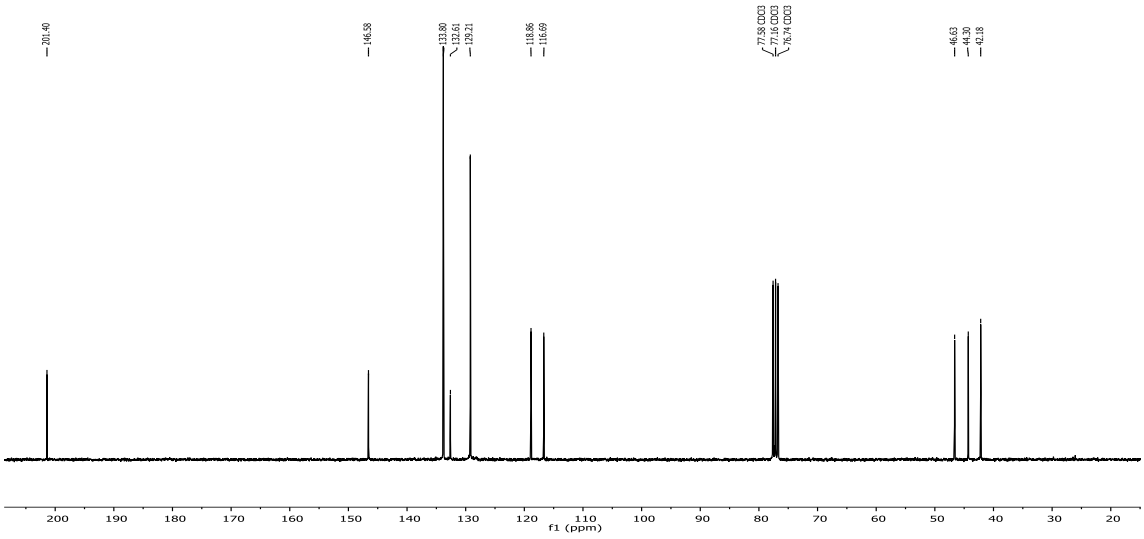
2-(allylamino)-4-((4-chlorophenyl)thio)cyclopent-2-en-1-one 105



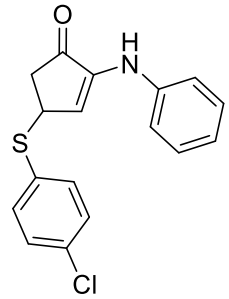
The titled compound was prepared according to general procedure **D** for 3 hours. The product was purified by flash chromatography (EtOAc/*n*-hexane 1:9) and was isolated as a dark brown oil in 85% yield (119 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (1H, dd, *J* = 19.5, 1.5 Hz), 2.81 (1H, dd, *J* = 19.5, 6.0 Hz), 3.56 (2H, td, *J* = 5.3, 4.6, 2.6 Hz), 4.12 (1H, s), 4.26 (1H, ddd, J = 6.0, 3.1, 1.6 Hz), 5.18 – 5.01 (2H, m), 5.84 – 5.65 (2H, m), 7.32– 7.13 (4H, m) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 42.4, 44.3, 46.6, 116.7, 118.9, 129.2, 132.6, 133.8 (2C), 146.6, 201.4. **HRMS (ESI-MS)** m/z calcd for $C_{14}H_{14}ClNOS$ $[M + H]^+$ 280.0557, found 280.05487



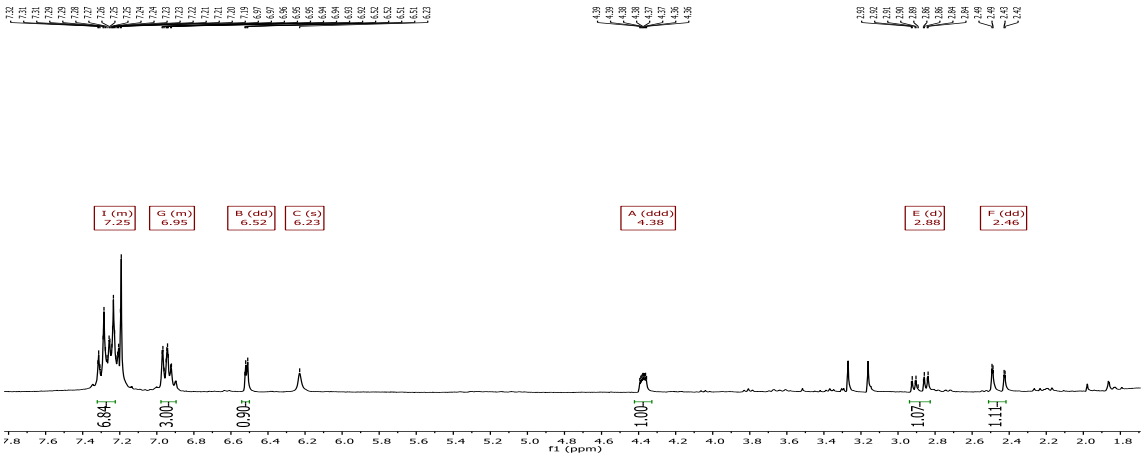

201.40
146.58
133.80
132.61
129.21
118.86
116.69
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
46.63
45.30
42.16
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

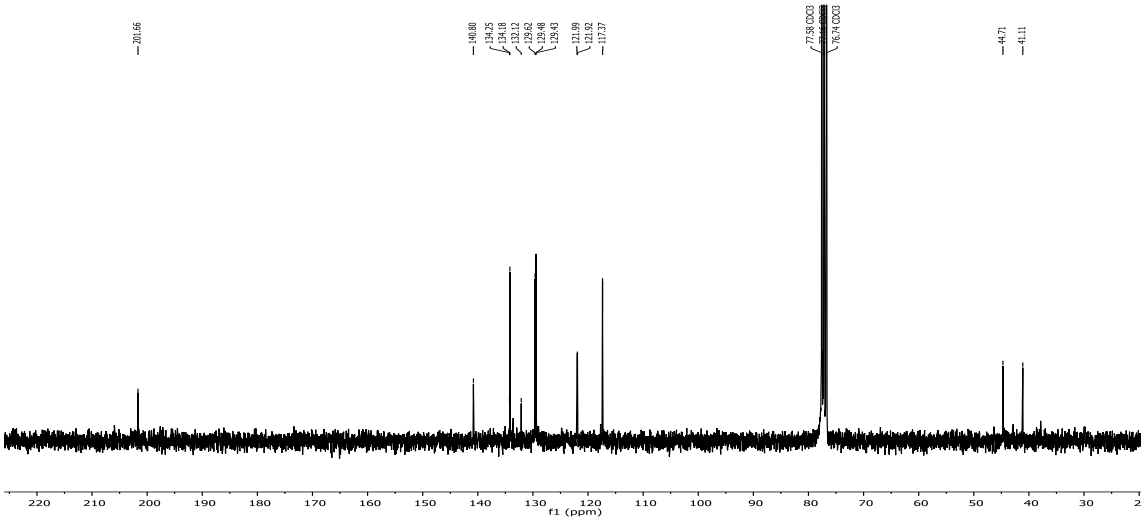
4-((4-chlorophenyl)thio)-2-(phenylamino)cyclopent-2-en-1-one 106



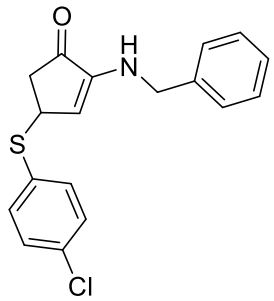
The titled compound was prepared according to general procedure **D** for 6 hours. The product was purified by flash chromatography (EtOAc/*n*-hexane 1:9) and was isolated as a dark brown oil in 45% yield (71 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (1H, dd, J = 19.6, 1.6 Hz), 2.88 (1H, d, J = 19.6, 6.1, 1.3 Hz), 4.38 (1H, ddd, J = 6.1, 3.2, 1.6 Hz), 6.23 (1H, s), 6.52 (1H, dd, J = 3.3, 1.3 Hz), 6.98 – 6.87 (3H, m), 7.35 – 7.18 (6H, m) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 41.1, 44.7, 117.4, 121.9, 121.9, 129.4, 129.5, 129.6, 132.1, 134.2, 134.3, 140.8, 201.7. **HRMS (ESI-MS)** m/z calcd for $C_{17}H_{15}ClNOS$ $[M + H]^+$ 316.0557, found 316.05457



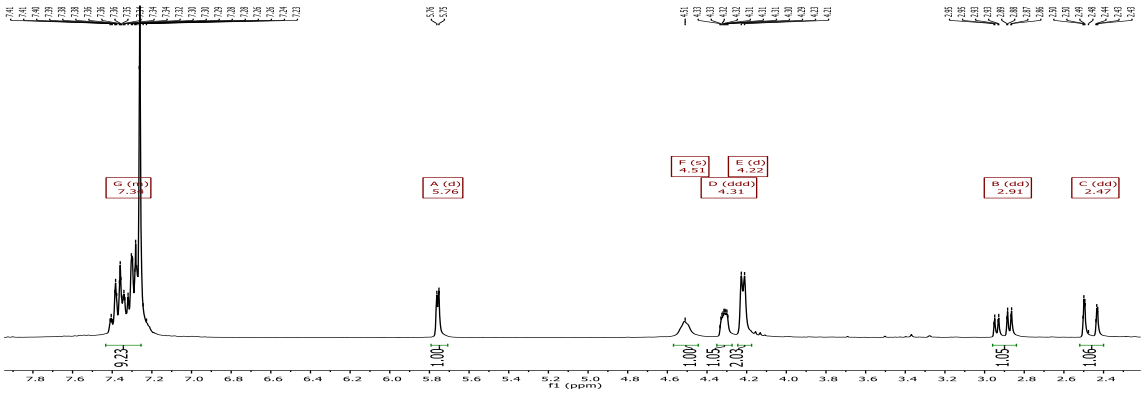

201.66
140.80
134.75
134.18
132.12
129.62
129.48
129.43
121.99
121.52
117.37
77.58 CDCl3
76.74 CDCl3
44.71
41.11
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
2
f1 (ppm)

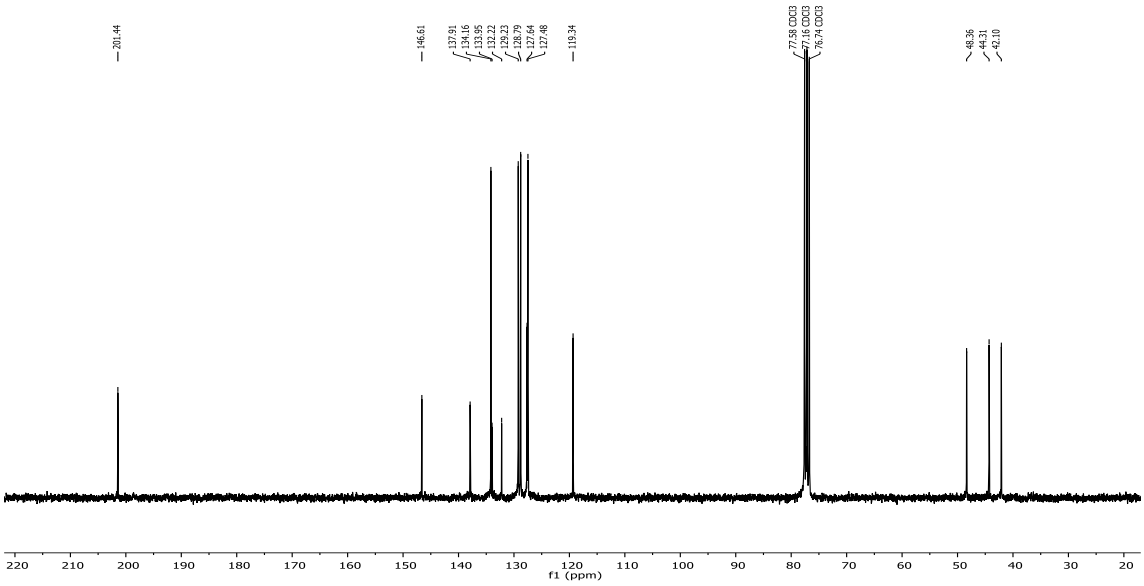
2-(benzylamino)-4-((4-chlorophenyl)thio)cyclopent-2-en-1-one 107



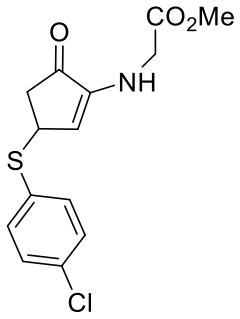
The titled compound was prepared according to general procedure **D** for 6 hours. The product was purified by flash chromatography (EtOAc/*n*-hexane 1:9) and was isolated as a light brown oil in 70% yield (115 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (1H, dd, J = 19.5, 1.4 Hz), 2.91 (1H, dd, *J* = 19.5, 6.0 Hz), 4.22 (2H, d, J = 4.9 Hz), 4.31 (1H, ddd, J = 6.0, 3.1, 1.4 Hz), 4.51 (1H, s), 5.76 (1H, d, J = 3.1 Hz), 7.48 – 7.28 (5H, m) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 42.1, 44.3, 48.4, 119.3, 127.5, 127.6, 128.8, 129.2, 132.2, 133.9, 134.2, 137.9, 146.6, 201.4. **HRMS (ESI-MS)** m/z calcd for $C_{18}H_{16}ClNOS$ $[M + H]^+$ 330.0714, found 330.07050



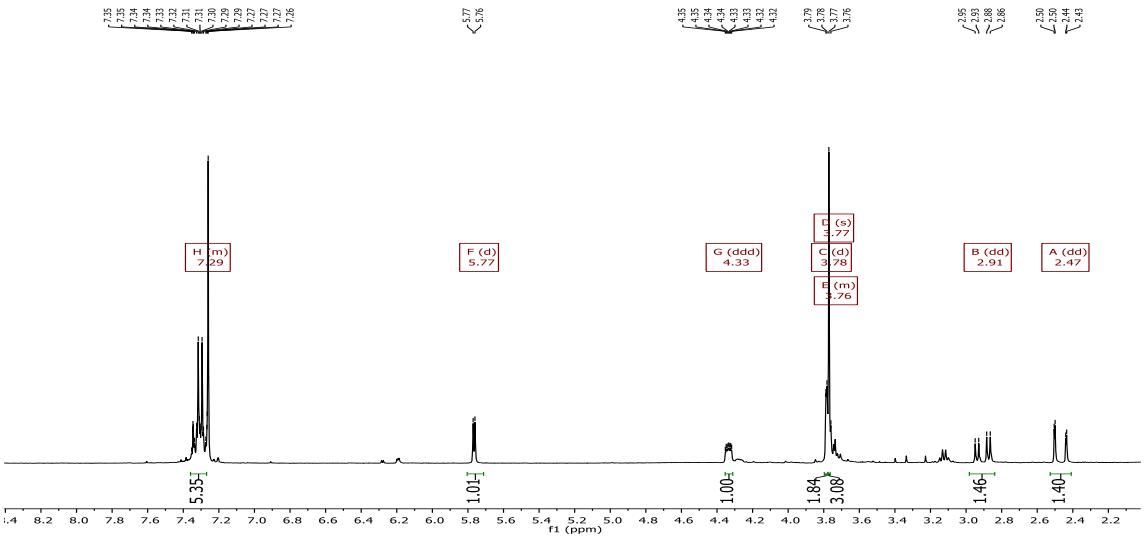

201.44
146.61
137.91
134.16
133.95
132.22
129.23
128.79
127.64
127.48
119.34
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
48.36
44.31
42.10
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

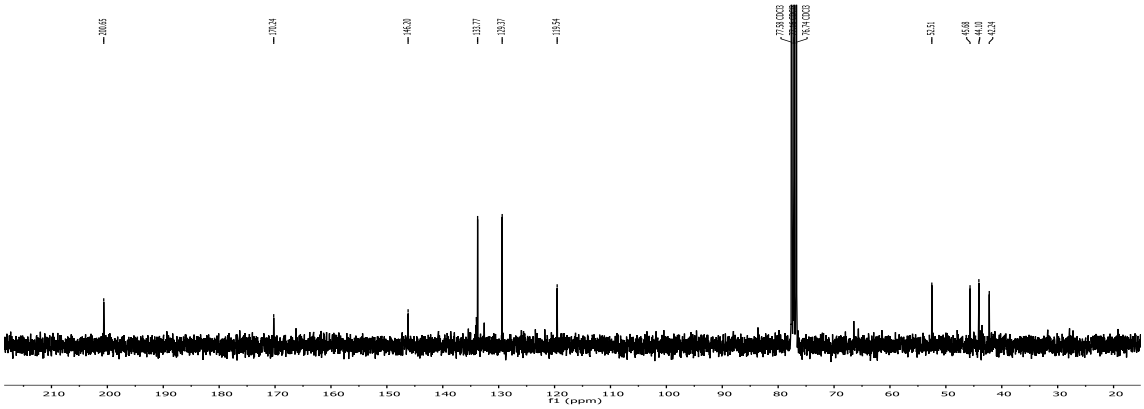
Methyl (3-((4-chlorophenyl)thio)-5-oxocyclopent-1-en-1-yl)glycinate 108



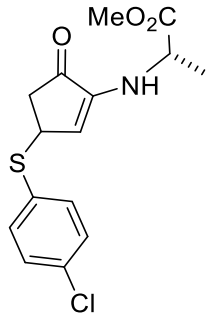
The titled compound was prepared according to general procedure **D** for 6 hours. The product was purified by flash chromatography (EtOAc/*n*-hexane 1:9) and was isolated as a light brown oil in 34% yield (53 mg).

1H NMR (300 MHz, CDCl3) δ 2.47 (1H, dd, *J* = 19.5, 1.6 Hz), 2.91 (1H, dd, J = 19.5, 6.1 Hz), 3.77 (3H, s), 3.78 (2H, d, *J* = 1.8 Hz), 4.33 (1H, ddd, J = 4.7, 3.1, 1.5 Hz), 5.77 (1H, d, *J* = 3.1 Hz), 7.41 – 7.23 (5H, m) **^{13}C NMR (75 MHz, CDCl$_3$) δ** 42.2, 44.1, 45.7, 52.5, 119.5, 129.4, 133.8, 146.2, 170.2, 200.7. **HRMS (ESI-MS)** m/z calcd for $C_{14}H_{14}ClNO_3S$ $[M + H]^+$ 312.0456, found 312.04364



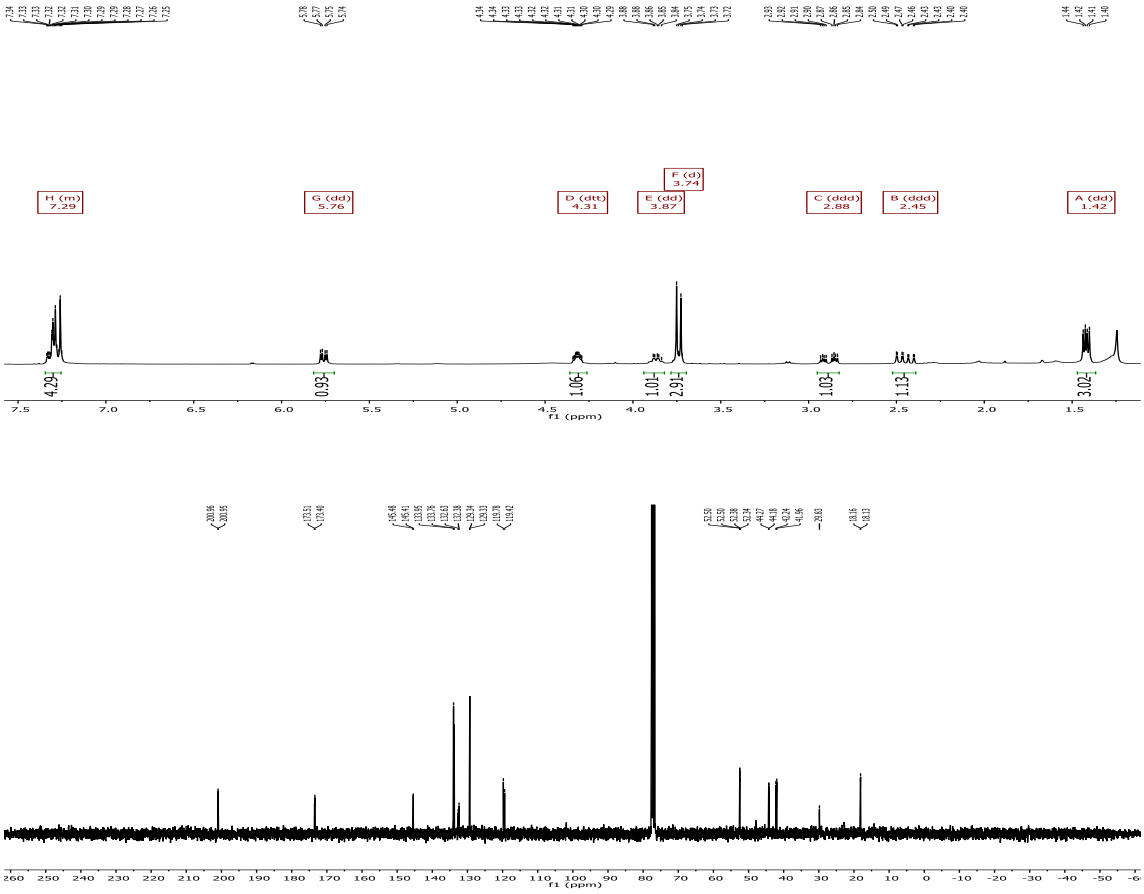


Methyl (3-((4-chlorophenyl)thio)-5-oxocyclopent-1-en-1-yl)-L-alaninate 109

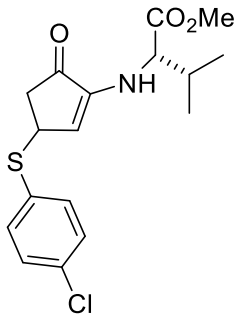


The titled compound was prepared according to general procedure **D** for 6 hours. The product was purified by flash chromatography (EtOAc/*n*-hexane 1:9) and was isolated as a light brown oil in 34% yield (53 mg) as a mixture of diastereosimers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (3H, dd, J = 7.0, 3.7 Hz), 2.45 (1H, ddd, J = 19.5, 9.6, 1.6 Hz), 2.88 (1H, ddd, J = 19.5, 6.0, 3.5 Hz), 3.74 (3H, d, J = 7.4 Hz), 3.87 (1H, dd, J = 7.0, 2.5 Hz), 4.31 (1H, dtt, J = 4.6, 3.1, 1.6 Hz), 5.76 (1H, dd, J = 7.9, 3.1 Hz), 7.40 – 7.22 (4H, m) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 18.1, 18.2, 29.8, 41.9, 42.2, 44.2, 44.3, 52.3, 52.4, 52.5, 52.5, 119.4, 119.8, 129.3, 129.3, 132.4, 132.6, 133.8, 133.9, 145.4, 145.5, 173.4, 173.5, 200.9, 200.9. **HRMS (ESI-MS)** m/z calcd for $C_{15}H_{16}ClNO_3S$ $[M + H]^+$ 326.0612, found 326.06046

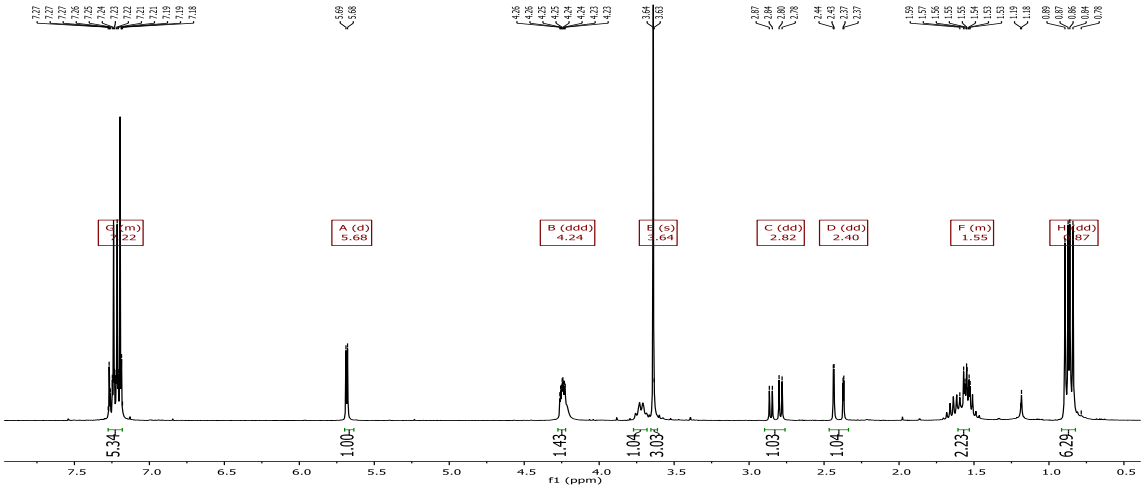


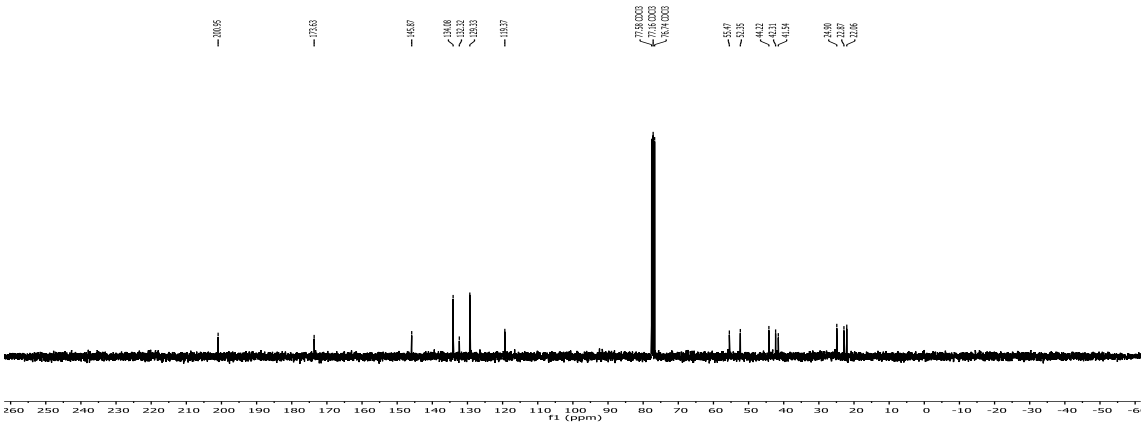
Methyl (3-((4-chlorophenyl)thio)-5-oxocyclopent-1-en-1-yl)-L-valinate 110



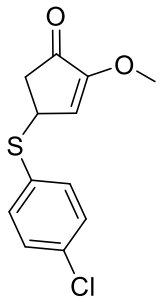
The titled compound was prepared according to general procedure **D** for 12 hours. The product was purified by flash chromatography (EtOAc/*n*-hexane 1:9) and was isolated as a dark brown oil in 44% yield (78 mg)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (6H, dd, *J* = 9.7, 6.3 Hz), 1.70 – 1.46 (4H, m), 2.40 (1H, dd, *J* = 19.5, 1.5 Hz), 2.82 (1H, dd, J = 19.5, 6.0 Hz), 3.64 (3H, s), 3.73 (1H, ddd, *J* = 8.6, 6.2 Hz), 4.24 (2H, ddd, *J* = 6.0, 3.1, 1.5 Hz), 5.68 (1H, d, *J* = 3.2 Hz), 7.28 – 7.17 (4H, m) **^{13}C NMR (75 MHz, $CDCl_3$) δ** 22.1, 22.9, 24.9, 41.5, 42.3, 44.2, 52.4, 55.5, 119.4, 129.3, 132.3, 134.1, 145.9, 173.6, 200.9. **HRMS (ESI-MS)** m/z calcd for $C_{17}H_{20}ClNO_3S$ $[M + H]^+$ 354.0925, found 354.09253


G (m)
7.22
A (d)
5.68
B (ddd)
4.24
E (s)
3.64
C (dd)
2.82
D (dd)
2.40
F (m)
1.55
H (dd)
0.87
5.34
1.00
1.43
1.04
3.03
1.03
1.04
2.23
6.29
f1 (ppm)

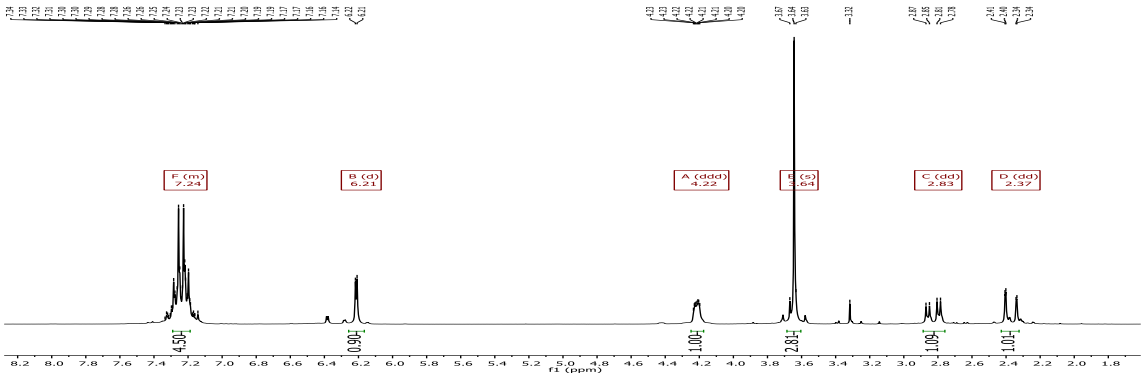

200.95
173.63
145.87
134.08
132.12
128.33
119.37
77.38 CDCl3
77.16 CDCl3
76.74 CDCl3
55.47
53.35
44.22
42.21
41.54
24.98
23.37
12.86
f1 (ppm)

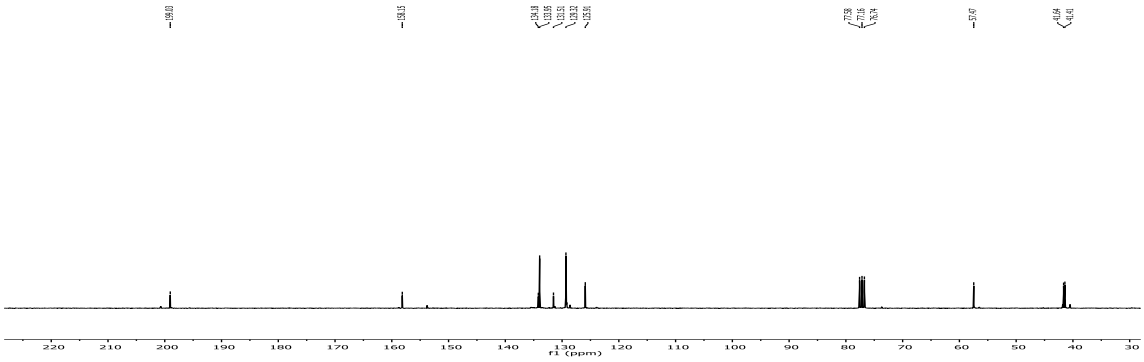
Procedure for the preparation of 4-((4-chlorophenyl)thio)-2-methoxycyclopent-2-en-1-one 111



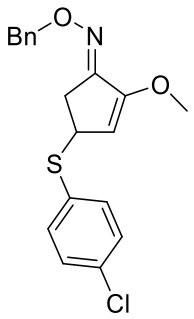
To a solution of the selected enone **78** (1.2 g, 3.87 mmol) in a mixture of MeOH/water (0.25 M 4:1 v/v) was added H_2SO_4 (0.62 mL, 3 equiv., 11.6 mmol). The mixture was stirred at 60 ºC for 20 hours. Afterwards, water (30 mL) and DCM (20 mL) were added and the aqueous layer was further extracted with DCM (30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The compound was purified by flash chromatography (EtOAc/*n*-hexane 1:9) and was isolated as a brown solid in 81% (799 mg). m.p. 62 ºC - 64 ºC

^{1}H NMR (300 MHz, $CDCl_3$): 2.37 (1H, dd, *J* = 19.5, 1.5 Hz), 2.83 (1H, dd, *J* = 19.5, 6.2 Hz, 1H), 3.64 (3H, s, 3H), 4.22 (1H, ddd, J = 6.6, 3.1, 1.7 Hz), 6.21 (1H, d, *J* = 2.9 Hz), 7.32 -7.16 (4H, m) **^{13}C NMR (75 MHz, $CDCl_3$):** 41.4, 41.6, 57.5, 125.9, 129.3, 131.5, 133.9, 134.2, 158.2, 199.0. **HRMS (ESI-MS)** m/z calcd for $C_{12}H_{11}ClO_2S$ $[M + H]^+$ 255.0241, found 255.02360



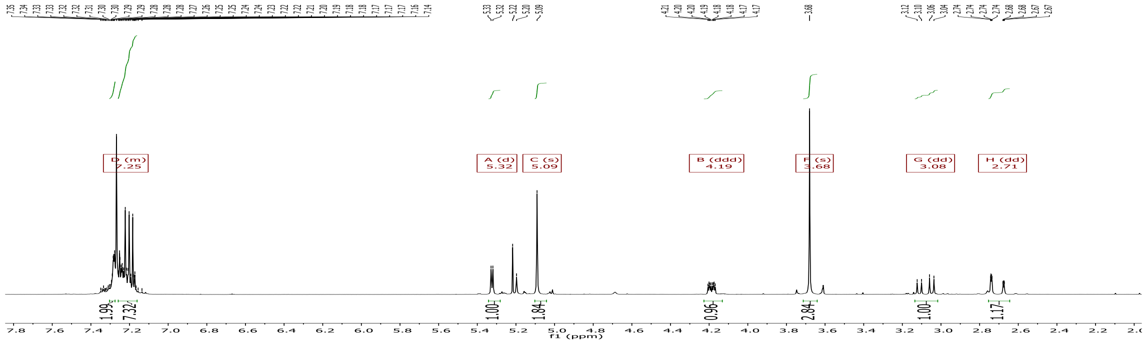


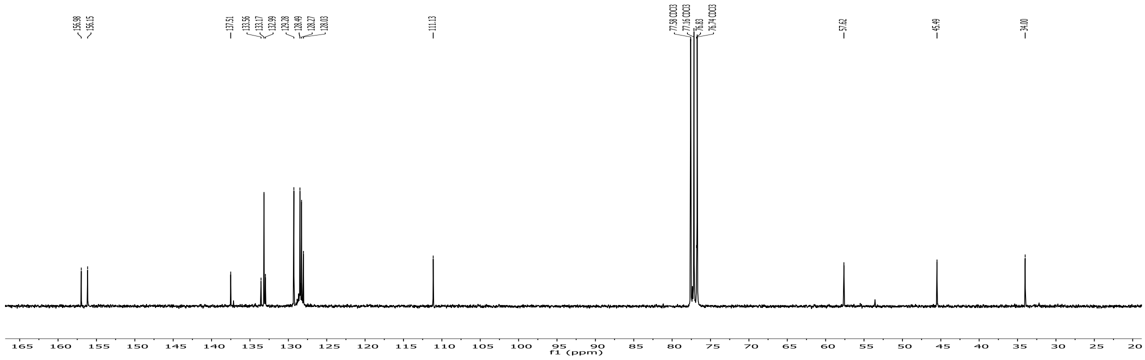
Procedure for the preparation of (E)-4-((4-chlorophenyl)thio)-2-methoxycyclopent-2-en-1-one O-benzyl oxime 112



To a solution of the selected enone **111** (50mg, 0.196 mmol) in ethanol (0.2 M) was added O-benzylhydroxylamine (0.023 ml, 1 equiv.) and NaOAc (2 equiv.) The mixture was refluxed for 1.5 hours and afterwards washed with water (20mL) and extracted with DCM (20mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The compound was purified by flash chromatography (EtOAc/*n*-hexane 1:9) and was isolated as a dark brown oil in 49% (34.6 mg).

^{1}H NMR (300 MHz, $CDCl_3$): 2.71 (1H, dd, *J* = 19.2, 1.7, 0.6 Hz), 3.08 (1H, dd, *J* = 19.2, 6.8 Hz), 3.68 (3H, s), 4.19 (1H, ddd, *J* = 6.8, 2.8, 1.7 Hz), 5.09 (2H, s), 5.32 (1H, d, *J* = 2.8 Hz), 7.50 – 7.07 (9H, m) **^{13}C NMR (75 MHz, $CDCl_3$)** 34.0, 45.5, 57.5, 76.8, 111.1, 128.0, 128.3, 128.5, 129.3, 132.9, 133.2, 133.6, 137.5, 156.2, 156.9. **HRMS (ESI-MS)** m/z calcd for $C_{19}H_{18}ClNO_2S$ $[M + H]^+$ 255.0241, found 255.02360.





Biological Assays

Cell Culture

These biological assays were performed by MSc Késsia Andrade.

The Human breast cancer cells line (MCF-7), human colorectal cancer cells line (HT-29), human lung cancer cells line (NCI-H460) and human embryonic kidney 293T healthy cells line (HEK 293T) were purchased from the American Type Culture Collection (ATCC). The cancer cells were cultured in RPMI-1640 medium supplemented with 10% FBS and antibiotic antimycotic solution in 75 cm^2 tissue culture flasks and the healthy cells in DMEM medium supplemented with 10% FBS and antibiotic antimycotic solution (1%) in 75 cm^2 tissue culture flasks, both incubated with a humidified 5% CO_2 atmosphere and at 37 ºC.

Cell culture RPMI-1640 Medium, Dulbecco's Modified Eagle's Medium, trypsin–EDTA solution and stabilized antibiotic antimycotic solution (100x) were purchased from Sigma; and fetal bovine serum (FBS) from VWR.

Viability assay

Seeded plates were incubated for several days until reaching approximately confluence. Viability assay was carried out in RPMI-1640 with 10%FBS and antibiotic antimycotic solution (HT-29, MCF-7, NCI-H460), and DMEM with 10%FBS and antibiotic antimycotic solution (HEK 293T). Cells were incubated with different concentrations for 24h: $1x10^5$ cell/mL (HT-29), $5x10^4$ cell/mL (NCI-H460), $1{,}5x10^5$ cell/mL (MCF-7) and $7x10^4$ cell/mL (HEK 293T).

Stock solutions were prepared in dimethyl sulfoxide (DMSO - purchased from Carbo Erba), and then diluted with the cell culture media to obtain the desirable concentrations (the final concentration of DMSO in culture medium during treatment did not exceed 0.5% (v/v)). The assays were run in triplicate. After incubation for more 48h, plate was treated with medium 10%FBS with Neutral Red reagent (50 µg/mL) and returned to the incubator for 3h. Media was removed, the plate was washed and PBS and one organic solution (20 mL ethanol + 20 mL H_2O + 400 µL glacial acetic acid) was added. The absorbance was measured by spectrophotometry at 540 nm and the ratio of the

absorbance of treated cells and the absorbance of control cells was determined (viability). The percentage of viability versus LOG 10 of the concentration was plotted. The dose to attain 50% viability (IC_{50}) was determined using GraphPad Prism 5.

VI.2. Chapter III

General Experimental

All solvents were distilled prior use. Unless otherwise stated, all other reagents were used as received from commercial suppliers. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel F_{254} with 0.2 mm thickness. $Na_2S_2O_4$ Merck Ref. 6507. The distillation experiments were carried out using Edwards model B30402210 diffusion pump, coupled with Edwards rotatory pump model RV5.

All 1D NMR spectra were acquired on Bruker MX300 spectrometer. All diffusion and ROESY experiments were recorded on Bruker AVII+ spectrometer, working at 600.01 MHz ^{1}H frequency, equipped with a BBO probehead (maximum gradient strength 53.5 G/cm). The temperature was maintained at 303K. The diffusion coefficient measurements were conducted with convection compensated double stimulated echo pulse sequence (*dstegp3s*), with diffusion time 100 ms, gradient encoding pulses of 3.5 ms and relaxation delay of 10 s. All spectra were acquired with 32 points in the diffusion dimension, following squared gradient ramp, which was optimised for every sample. These NMR experiments were conducted in Bulgaria Academy of Science by Yavor N. Mitrev.

General procedure for the synthesis of 5-((5-(hydroxymethyl)furan-2-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione

To a solution of 5-HMF (100 mg, 0.79mmol) in water (8 mL, 0.1M) was added Meldrum's acid (110 mg, 0.79 mmol, 1 equiv.). Additionally an aqueous solution of the corresponding additive (0.1 mL of a 10 mg/mL solution) was added. The reaction mixture was stirred at 75°C for 30 minutes and then extracted with dichloromethane (10 mL, 3 x). The organic layers were combined, dried with anhydrous sodium sulphate and concentrated under reduced pressure. The crude mixtures were analysed by ^{1}H-NMR without further purification using trimethoxybenzene (133 mg, 0.79 mmol, 1 equiv.) as internal standard.

entry	Additive	Yield 120 (%)	HMF (%)	Humins (%)
1	None	74	10	16
2	$Na_2S_2O_4$	96	traces	traces
3	$NaHCO_3$	78	13	9

General procedure for the termal stability assays of 5-HMF

Neat 5-HMF (100 mg, 0.79 mmol) was stirred at 100°C for 4h in presence of the corresponding additive (1% w/w). The resulting mixtures were directly analysed by ^{1}H-NMR using trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

entry	Additive	HMF (%)	Dimer (%)	Humins (%)
1	None	37	33	30
2	DMSO	46	33	21
3	Ascorbic acid	42	49	8
4	BHT	48	43	9
5	Zn^0	71	10	19
6	Urea	63	0	47
7	ChCl	86	14	Traces
8	$Na_2S_2O_5$	85	6	9
9	$Na_2S_2O_4$	100	0	0


NMR tube (Entry 1)


NMR tube (Entry 2)


NMR tube (Entry 3)


NMR tube (Entry 4)


NMR tube (Entry 5)


NMR tube (Entry 6)


NMR tube (Entry 7)


NMR tube (Entry 8)


NMR tube (Entry 9)

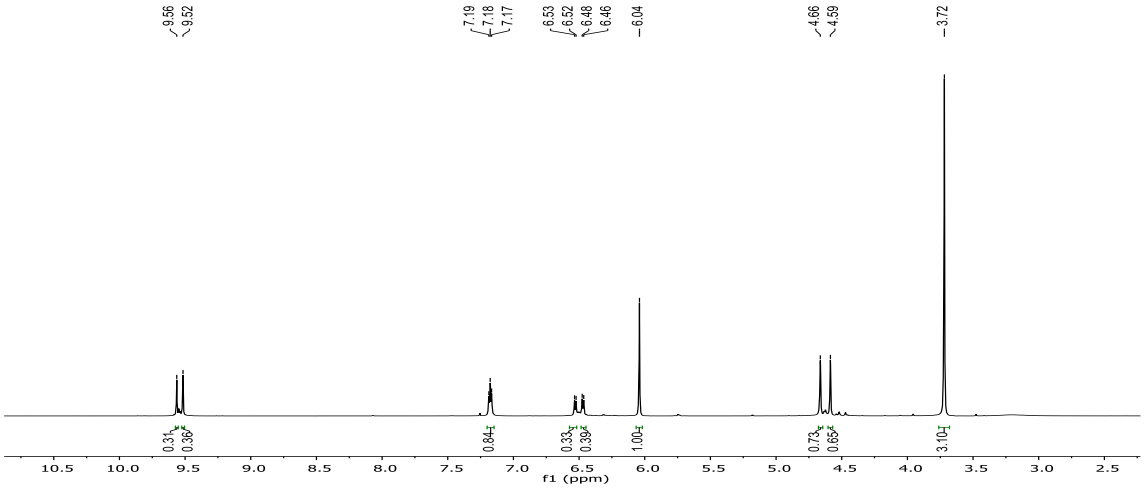


Figure 35 ^{1}H NMR ($CDCl_3$) of the thermal decomposition of 5-HMF (4h at 100°C) in absence of additive (entry 1). Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

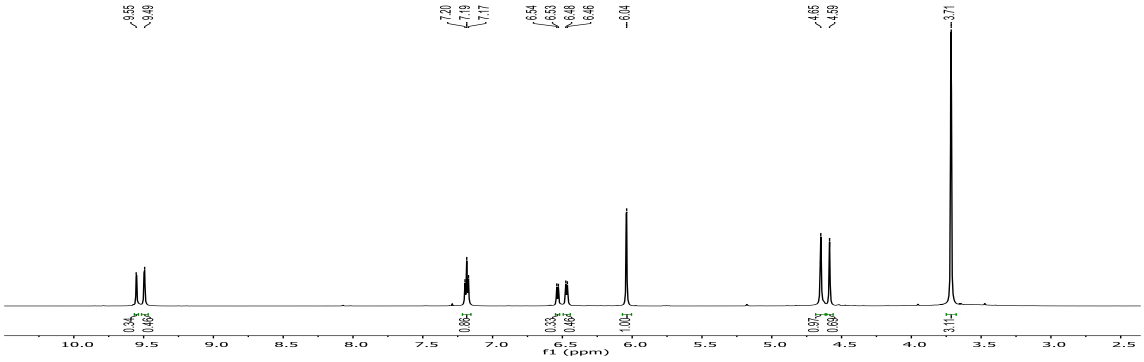


Figure 36 ^{1}H NMR ($CDCl_3$) of the thermal decomposition of 5-HMF (4h at 100°C) in presence of DMSO (entry 2). Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

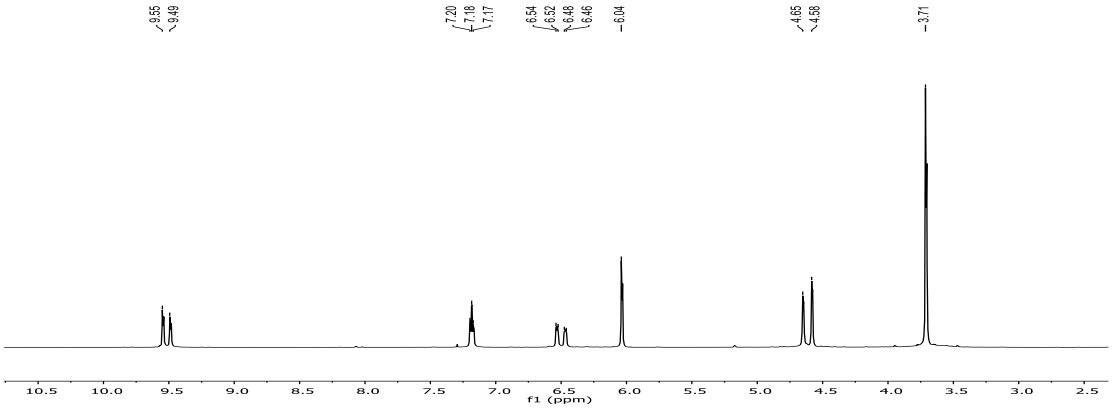


Figure 37 ^{1}H NMR ($CDCl_3$) of the thermal decomposition of 5-HMF (4h at 100°C) in presence of ascorbic acid (entry 3). Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

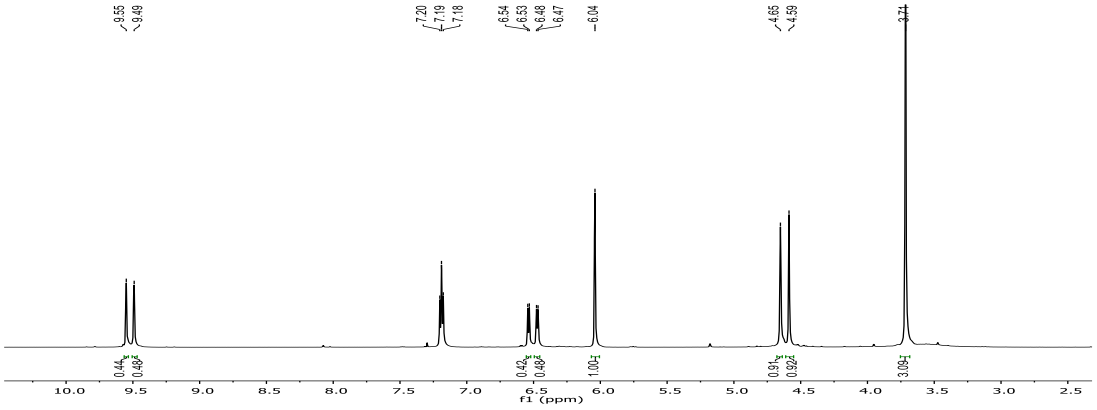


Figure 38 ^{1}H NMR ($CDCl_3$) of the thermal decomposition of 5-HMF (4h at 100°C) in presence of BHT (entry 4). Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

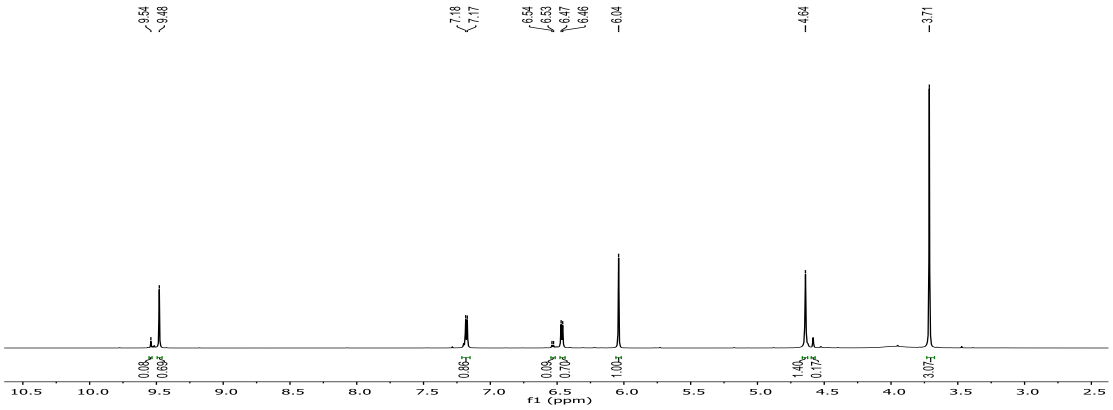


Figure 39 ^{1}H NMR ($CDCl_3$) of the thermal decomposition of 5-HMF (4h at 100°C) in presence of Zn^0 (entry 5). Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

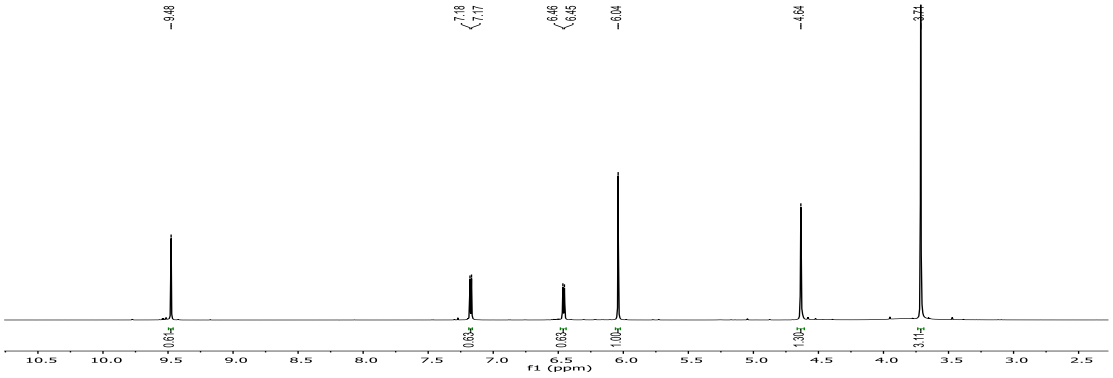


Figure 40 ^{1}H NMR ($CDCl_3$) of the thermal decomposition of 5-HMF (4h at 100°C) in presence of urea (entry 6). Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

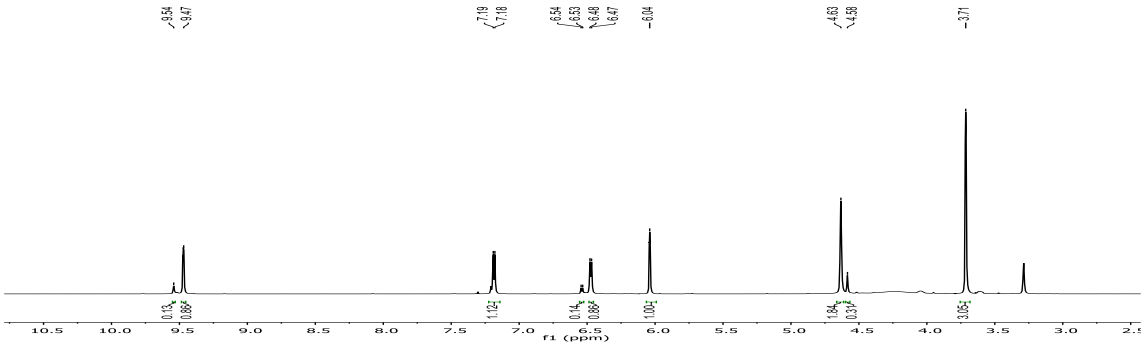


Figure 41 ^{1}H NMR ($CDCl_3$) of the thermal decomposition of 5-HMF (4h at 100°C) in presence of ChCl (entry 7). Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

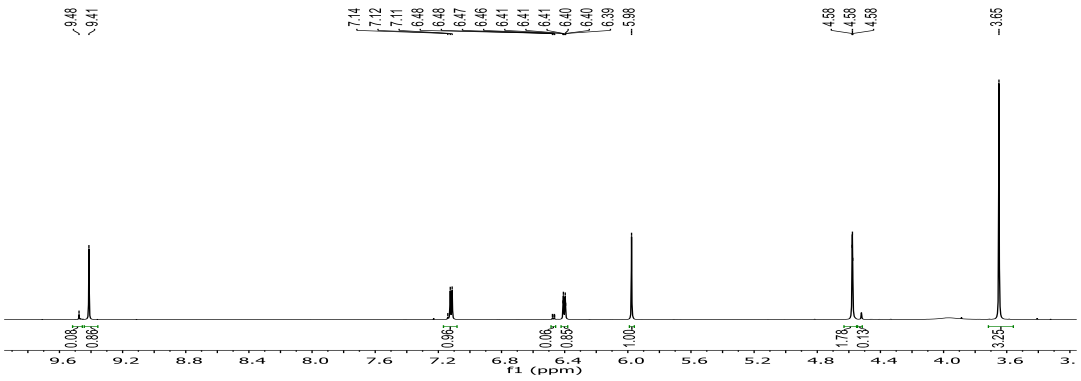


Figure 42 ^{1}H NMR ($CDCl_3$) of the thermal decomposition of 5-HMF (4h at 100°C) in presence of 1% w/w $Na_2S_2O_5$ (entry 8). Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard

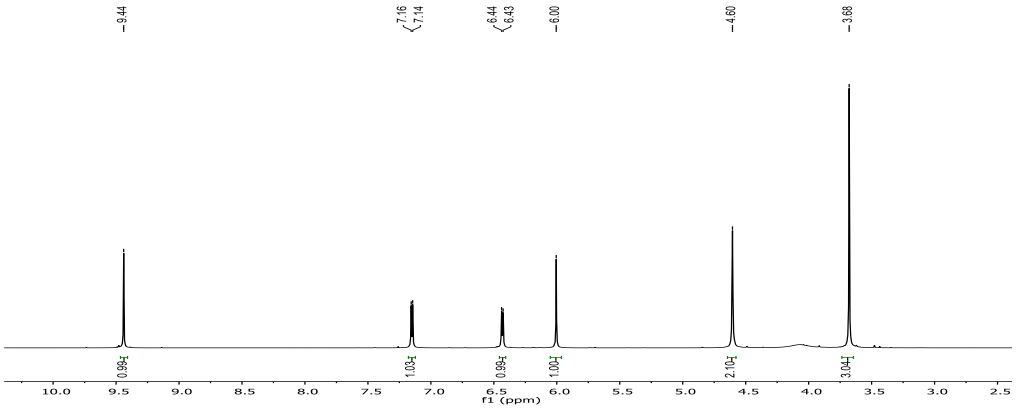


Figure 43 ^{1}H NMR ($CDCl_3$) of the thermal decomposition of 5-HMF (4h at 100°C) in presence of 1% w/w $Na_2S_2O_4$ (entry 9). Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

General procedure for the bench stability of crude HMF

Two batches of HMF (100 mg, 0.79 mmol) were kept for 1 month in open vials under ambient conditions (temperature scaled from 25 to 29ºC) in presence or absence of 1% w/w $Na_2S_2O_4$. The resulting mixtures were directly analysed by ^{1}H-NMR using trimethoxybenzene (44 mg, 0.26mmol, 0.33 equiv.) as internal standard.

Figure 44 HMF after 1 month aging in absence of $Na_2S_2O_4$ (left) and in presence of $Na_2S_2O_4$ (right)

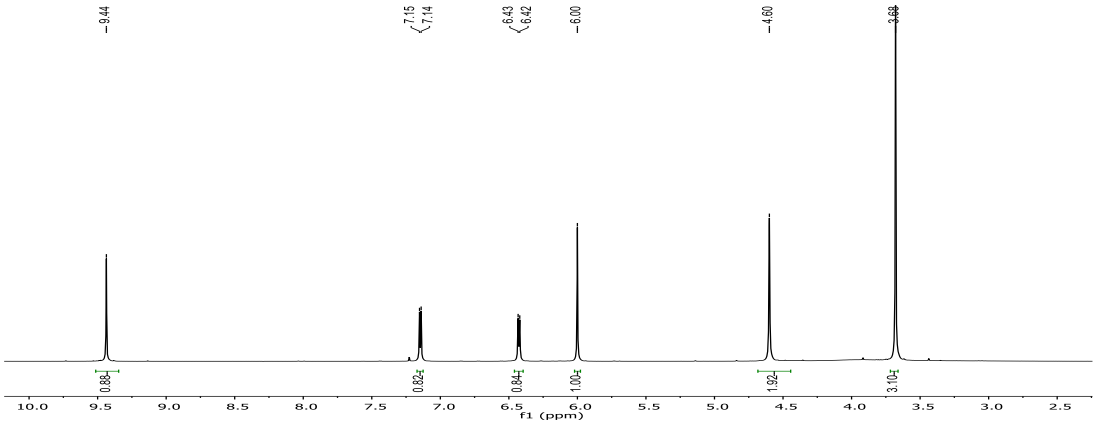


Figure 45 ^{1}H-NMR ($CDCl_3$) of 5-HMF after 1 month aging at r.t. in presence of 1% w/w $Na_2S_2O_4$. Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

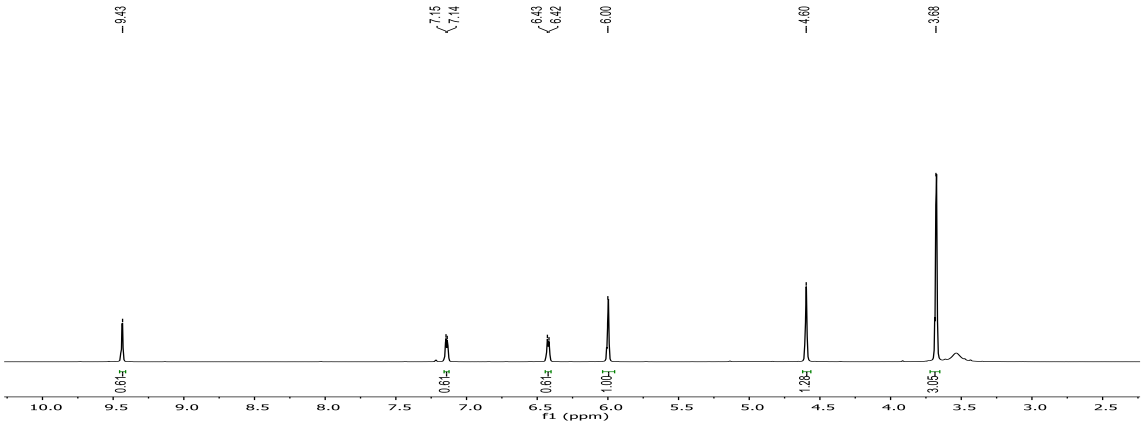


Figure 46 ^{1}H-NMR ($CDCl_3$) of 5-HMF without $Na_2S_2O_4$ after 1 month aging at r.t. Trimethoxybenzene (44 mg, 0.26 mmol, 0.33 equiv.) as internal standard.

Synthesis of 5-HMF using biphasic system

To a brine solution was added concentrated HCl until pH 2. To 1 mL of the so prepared solution in a pressure reaction vessel were added THF (2 mL) and fructose (106 mg,

0.59 mmol). $Na_2S_2O_4$ (1 mg, 1% w/w) was added when appropriate. The reaction was heated with stirring at 170ºC for 2h. The THF phase was separated and the aqueous phase was washed with THF (2 mL, 2 x). The organic layers were combined, dried with sodium sulphate and evaporated under reduced pressure. The yields were determined by ^{1}H-NMR without further purification using trimethoxybenzene (100 mg, 0.59 mmol, 1 equiv.) as internal standard.

entry	$Na_2S_2O_4$	Crude HMF yield [%]	HMF purity [%]
1	1% w/w	98	92
2	-	67	83

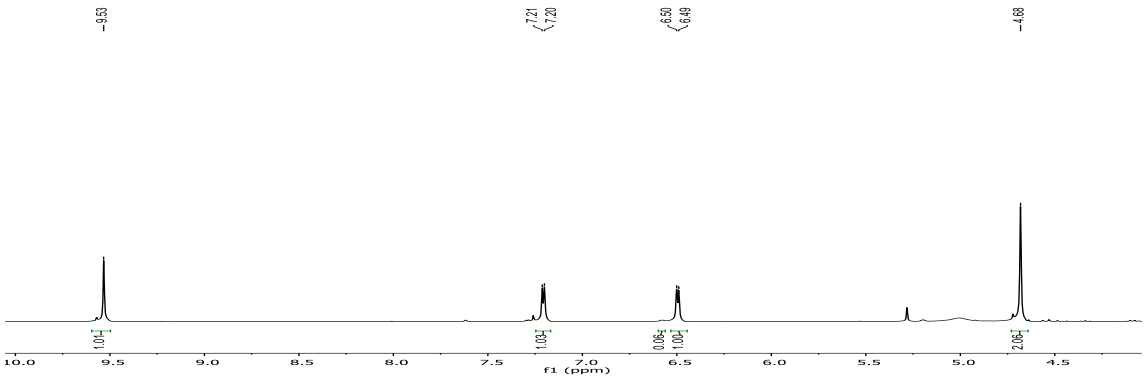


Figure 47 ^{1}H-NMR ($CDCl_3$) of crude 5-HMF synthesized in presence of 1% w/w $Na_2S_2O_4$. Trimethoxybenzene (100 mg, 0.59 mmol, 1 equiv.) as internal standard.

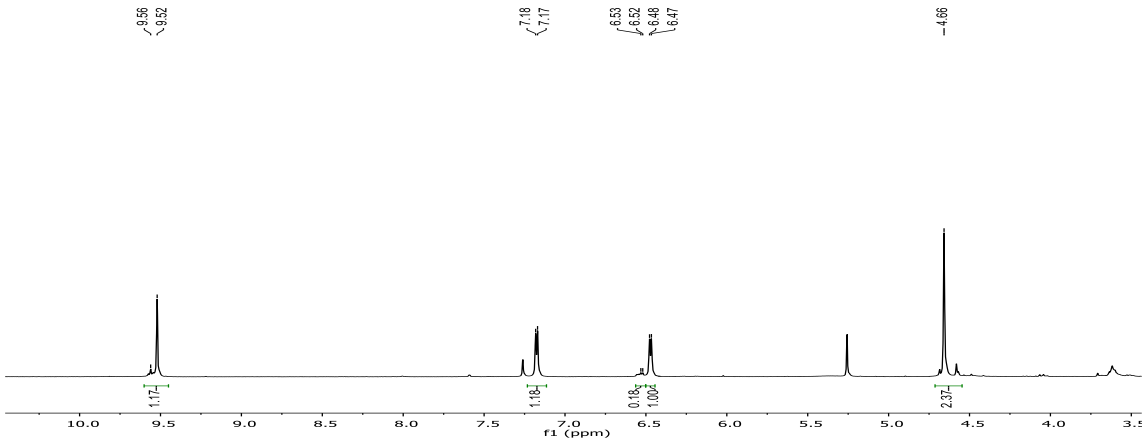


Figure 48 ^{1}H-NMR ($CDCl_3$) of crude 5-HMF synthesized in absence of $Na_2S_2O_4$. Trimethoxybenzene (100 mg, 0.59 mmol, 1 equiv.) as internal standard.

Synthesis of crude 5-HMF for the distillation experiments

A 500-mL single-necked, round-bottomed flask was charged with tetraethylammonium bromide (45 g, 214 mmol), distilled water (5 mL) and fructose (10 g, 0.056 mol). The flask was placed in an oil bath at 100°C. The reaction temperature was monitored by a thermometer placed inside the reaction mixture. When the internal temperature reached 90°C, Amberlyst® 15 (1 g, 10%w/w) was added. The stirring was continued for 15 min, during which time the internal temperature reached 96–98°C. After this period the flask was removed from the heat source and the hot solution separated from the Amberlyst® 15 by decantation into a 2-L single-necked round-bottomed flask. Absolute ethanol (20–30 mL) was used to wash the catalyst after the transfer. The mixture was placed on a rotary evaporator for 1 h (15 mmHg, 50°C). The solid was dissolved in hot absolute anhydrous ethanol (25 mL), followed by immediate addition of ethyl acetate under vigorous stirring. Immediate precipitation of the tetraethylammonium bromide was observed. The precipitate was vacuum-filtered through a fritted filter and the cake rinsed with ethyl acetate (100 mL). The collected filtrate was vacuum-filtered through a pad of silica gel (30 g) using a fritted filter and the silica gel was rinsed with ethyl acetate (100 mL). The filtrate was concentrated by rotary evaporation (32°C, 15 mmHg). The oily residue is transferred into a 50 mL single-necked round-bottomed flask and the residual organic solvent was removed under vacuum (0.5 mmHg). The crude 5-HMF was obtained as deeply orange oil (6.0 g, 86%), which was directly subjected to vacuum distillation as further described.

Distillation of crude 5-HMF without $Na_2S_2O_4$

Crude 5-HMF (6.0 g) was placed in 25 mL round bottom flask equipped with magnetic stirrer. The flask was connected to a glass distillation apparatus and heated to 120°C using oil bath. The distillation was carried out under stirring at 5.10^{-4} bar using diffusion pump. After completion of the distillation 3.12 g (52%) of 5-HMF were obtained as deeply brown liquid that solidified in the freezer (-12°C).

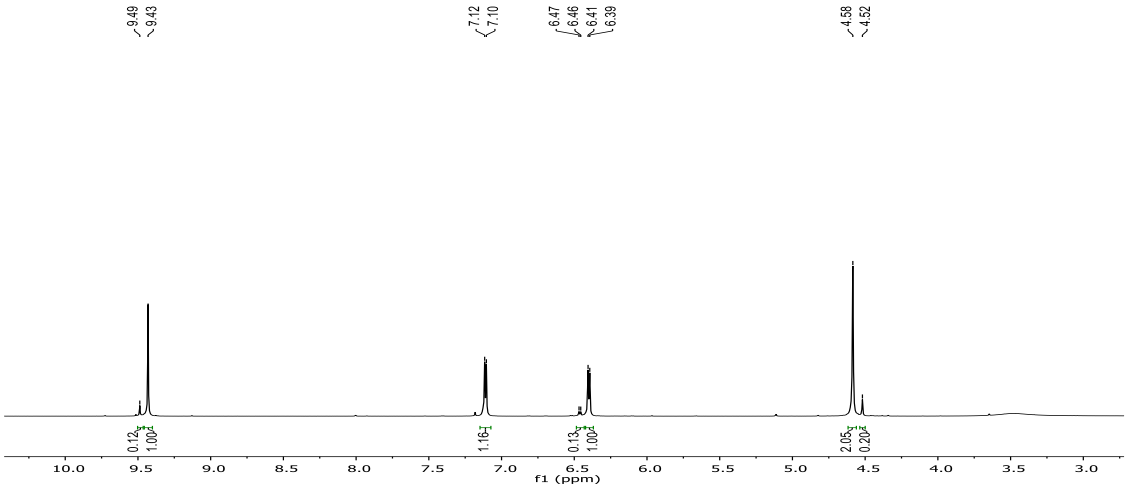


Figure 49 ^{1}H NMR ($CDCl_3$) of the distilled 5-HMF in absence of $Na_2S_2O_4$.

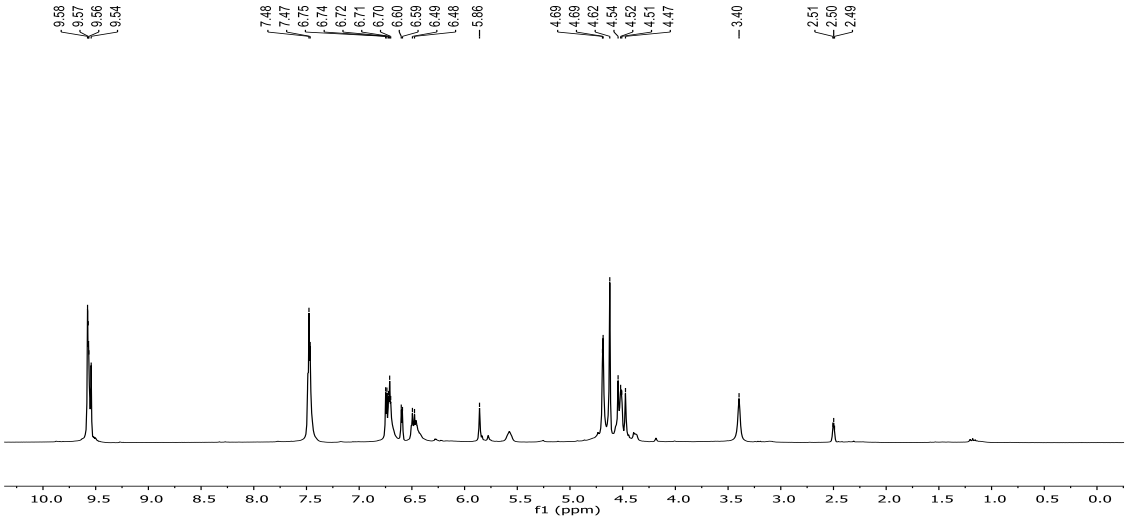


Figure 50 ^{1}H NMR ($CDCl_3$) of the residues after the distillation in absence of $Na_2S_2O_4$.

Figure 51 HMF vapour during the distillation without $Na_2S_2O_4$ (left) and collected 5-HMF (-12°C) (right).

Distillation of crude 5-HMF in presence of $Na_2S_2O_4$

Crude 5-HMF (6.0 g) was placed in 25 mL round bottom flask equipped with magnetic stirrer, then 120 mg $Na_2S_2O_4$ was added. The flask was connected to a glass distillation apparatus and heated to 120°C using oil bath. The distillation was carried out under stirring at 5.10^{-4} bar using diffusion pump. After completion of the distillation 5.1 g (85%) of 5-HMF was obtained as colourless liquid that solidified in the freezer (-12°C).

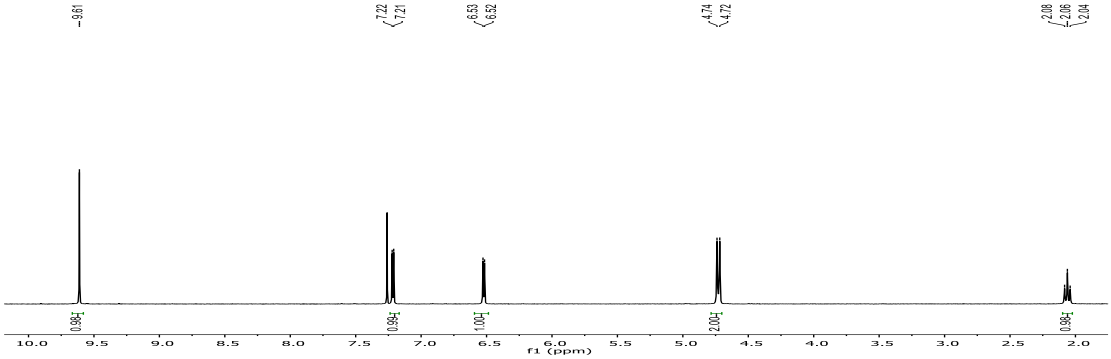


Figure 52 ^1H NMR ($CDCl_3$) of the distilled 5-HMF in presence of 2% w/w $Na_2S_2O_4$.

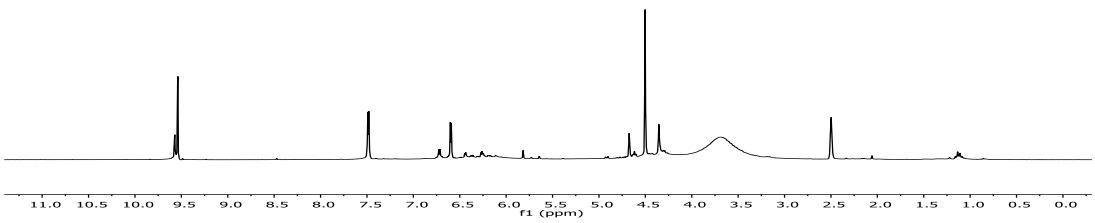
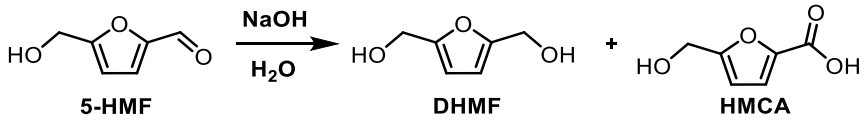


Figure 53 ^1H NMR ($CDCl_3$) of the residues after the distillation in presence of 2% w/w $Na_2S_2O_4$.

Figure 54 HMF vapour during the distillation in presence of $Na_2S_2O_4$ (left), freshly distilled 5-HMF (middle) and collected 5-HMF (-12°C) (right)

Synthesis of 5-hydroxymethyl-2-carboxylic acid (HMCA) and 2,5-dihydroxymethylfurfural (DHMF) *via* Cannizarro reaction of 5-HMF



To a solution of 5-HMF (200 mg, 1.58 mmol) in water (1 mL) was added aqueous solution of $Na_2S_2O_4$ (0.1 mL, 20 mg/mL solution). Then aq. NaOH (60 mg, 1.54 mmol, 1 equiv. in 0.5 mL H_2O) was added dropwise at 0ºC. The reaction was stirred for 1h. The solvent was evaporated under vacuum and the crude mixture was dissolved in ethanol. Then MTBE was added and precipitation of HMCA as a brownish solid was observed (122 mg, 94% yield). The solvent was decanted and concentrated under reduced pressure to give DHMF as a yellowish solid (97 mg, 96% yield).

DHMF - ^{1}H NMR (300 MHz, D_2O) δ 6.22 (s, 2H), 4.41 (s, 4H)

HMCA - ^{1}H NMR (300 MHz, D_2O) δ 6.81 (d, J = 3.4 Hz, 1H), 6.33 (d, J = 3.4 Hz, 1H), 4.45 (s, 2H).

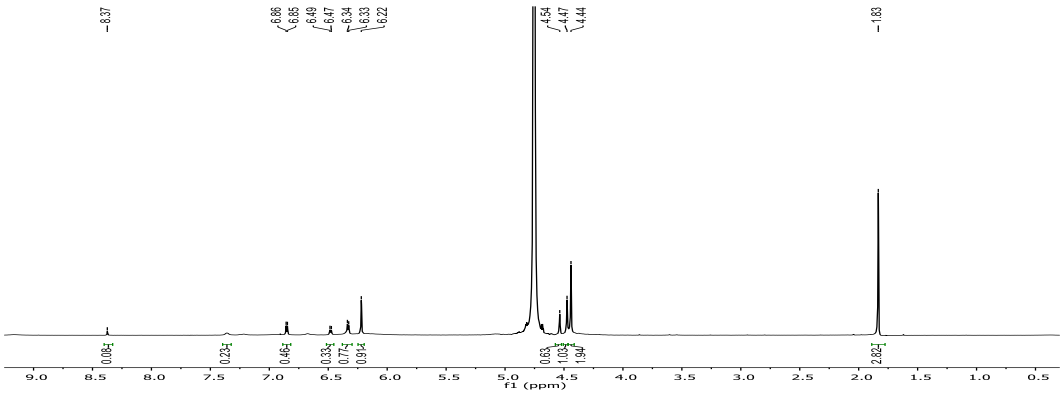


Figure 55 ^{1}H NMR (D_2O) of the Cannizzaro reaction in absence of $Na_2S_2O_4$.

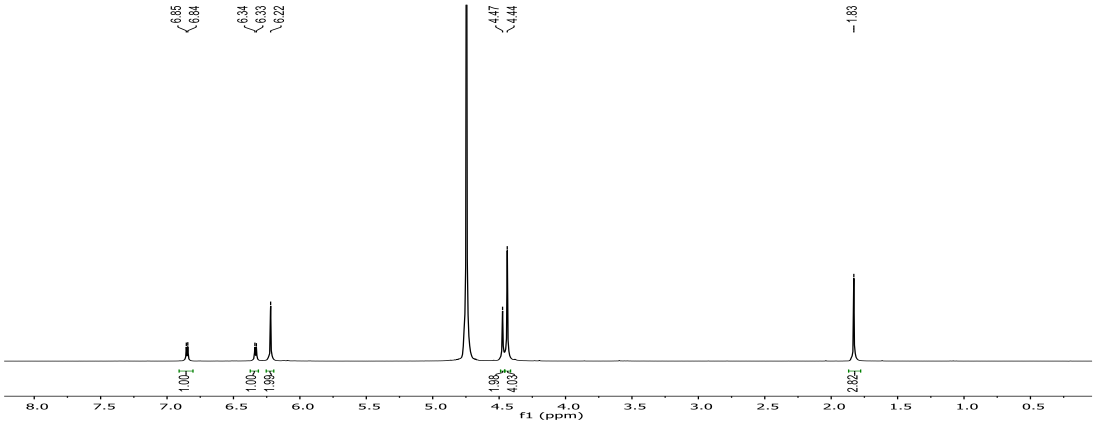


Figure 56 ^{1}H NMR (D_2O) of the Cannizzaro reaction in presence of 1% w/w $Na_2S_2O_4$

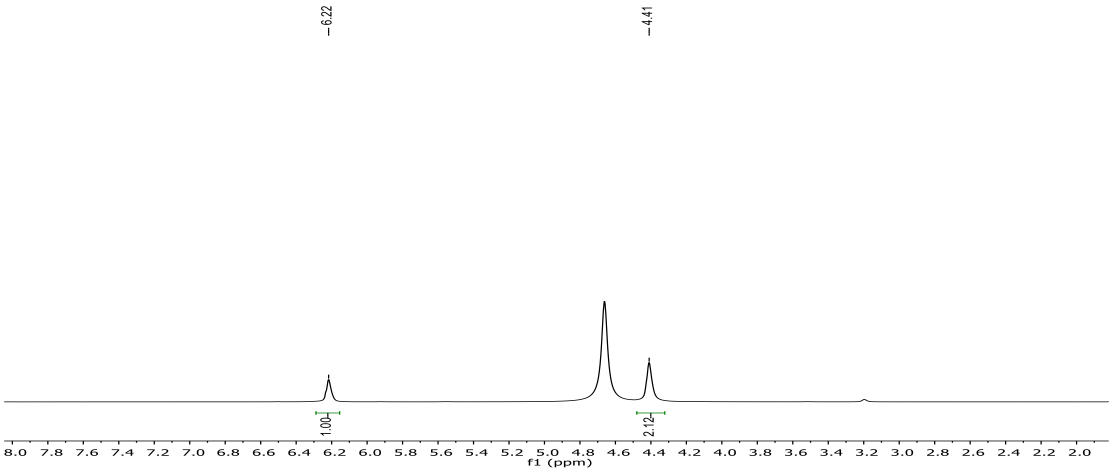


Figure 57 ^{1}H-NMR (D_2O) of DHMF.

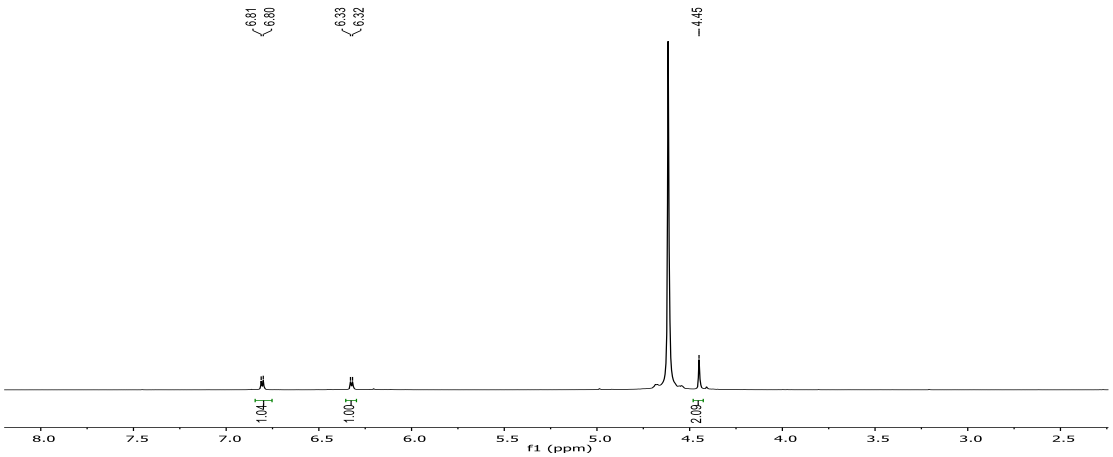
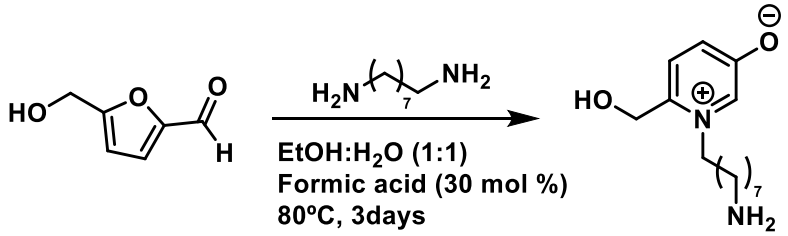


Figure 58 ^{1}H-NMR (D_2O) of HMCA.

Synthesis of pyridinium salt 122



To a solution of 5-HMF (100 mg, 0.79 mmol) in ethanol (5 mL) was added 1,8-diaminooctane (171 mg, 1.19 mmol, 1.5 equiv.). $Na_2S_2O_4$ (1 mg, 1% w/w) was added when appropriate and the reaction was stirred for 30 min at r.t. Then aqueous solution of formic acid (9 µL formic acid in 5 mL distilled H_2O) was added to the reaction mixture and stirred for 3 days at 80ºC. The crude mixture was diluted with 100 mL H_2O, stirred with activated charcoal for 5 minutes and filtered through a pad of celite. The filtrate was

concentrated under vacuum to give **6** as white crystals in 88% yield when in presence of $Na_2S_2O_4$ or as brown oil in 60% yield in absence of $Na_2S_2O_4$.

^{1}H NMR (300 MHz, D_2O**)** δ 8.28 (s, 1H), 7.57 (d, *J* = 2.8 *Hz*, 1H), 7.39 (d, *J* = 8.9 *Hz*, 1H), 7.21 (dd, *J* = 2.7, 8.9 *Hz*, 1H), 4.59 (s, 2H), 4.15-4.20 (t, *J* = 7.7 *Hz*, 2H), 1.68-1.74 (m, 2H), 1.00-1.33 (m, 12H)

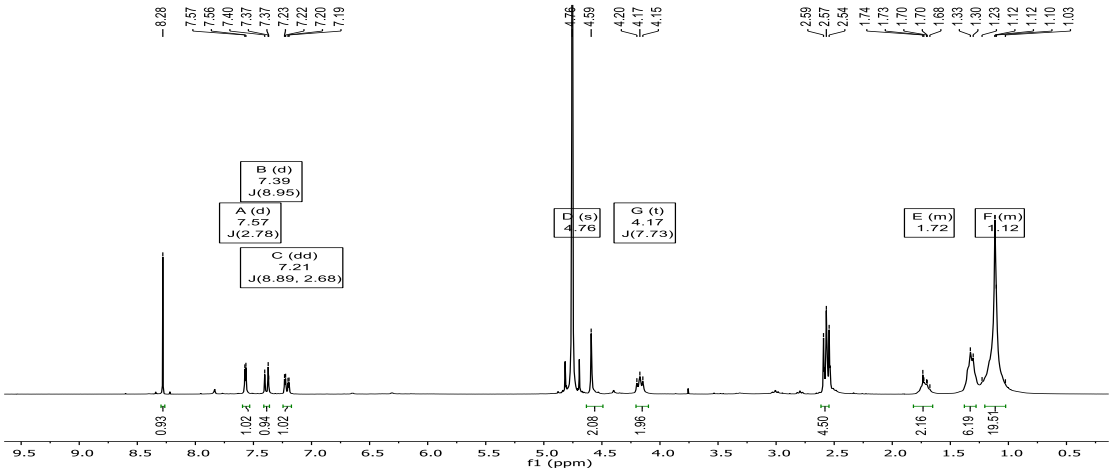
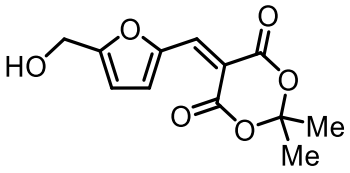


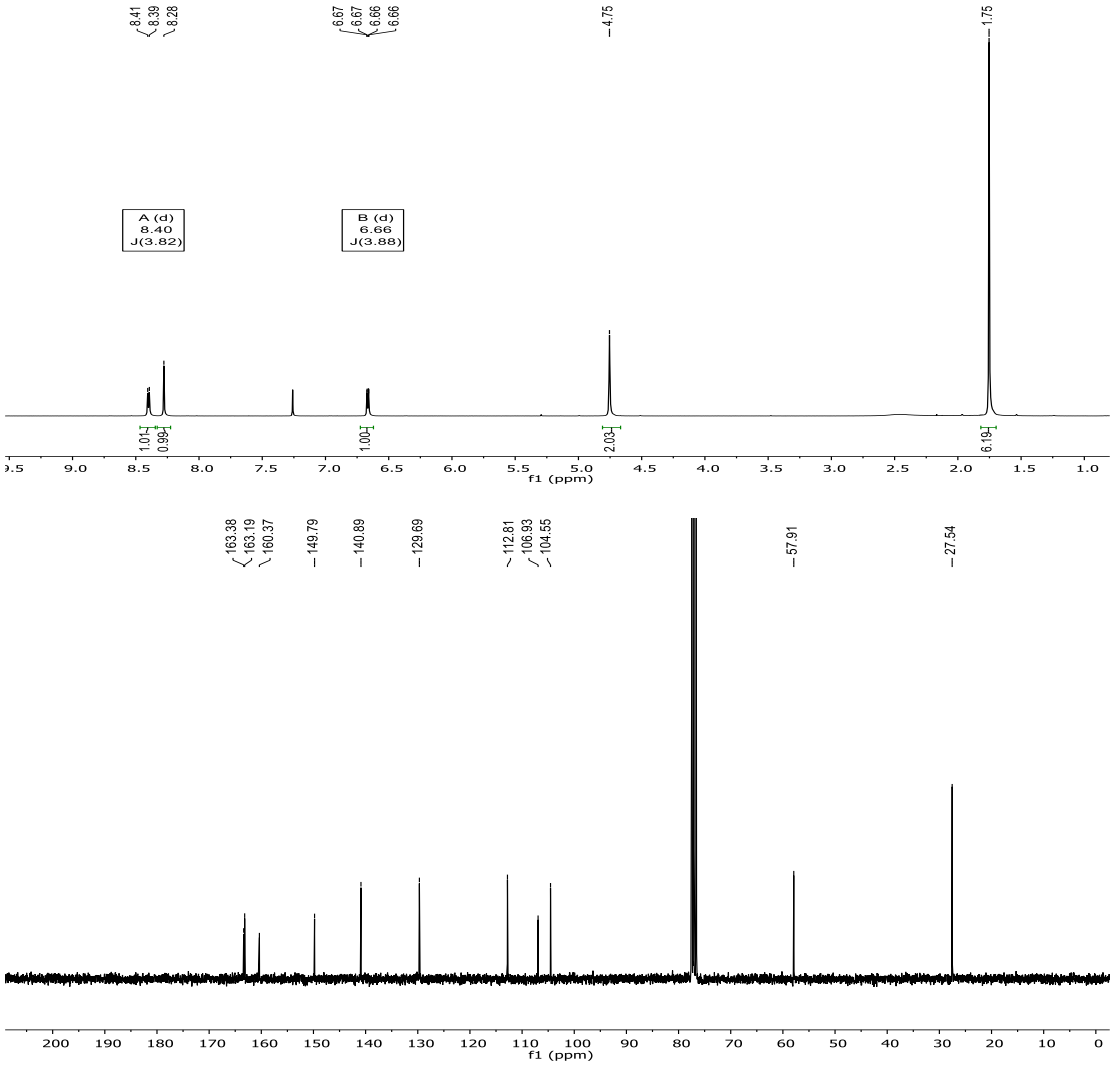
Figure 59 ^{1}H-NMR (D_2O) of **6** obtained in presence of 1% w/w $Na_2S_2O_4$.

Synthesis of 121 under optimized conditions

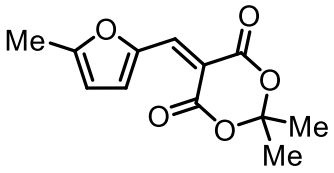


To a solution of HMF (1 g, 7.9 mmol) in water (80 mL, 0.1M) was added Meldrum's acid (1.14 g, 7.9 mmol, 1 equiv.) and $Na_2S_2O_4$ (10 mg, 1% w/w). The reaction mixture was stirred at 75°C for 30 minutes and then cooled down in an ice bath leading to precipitation of the product as yellow crystals. The crystals were filtered and rinsed with cold water to give 1.8 g, 91% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 3.8 *Hz*, 1H), 8.28 (s, 1H), 6.67 (d, *J* = 3.8 *Hz*, 1H), 4.75 (s, 2H), 1.75 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 27.5, 57.9, 104.6, 106.9, 112.8, 129.7, 140.9, 149.8, 160.4, 163.2, 163.4 **HRMS (ESI-MS)** *m/z* calcd for $C_{12}H_{12}O_6$ $[M + H]^+$ 253.07121, found 253.07237..

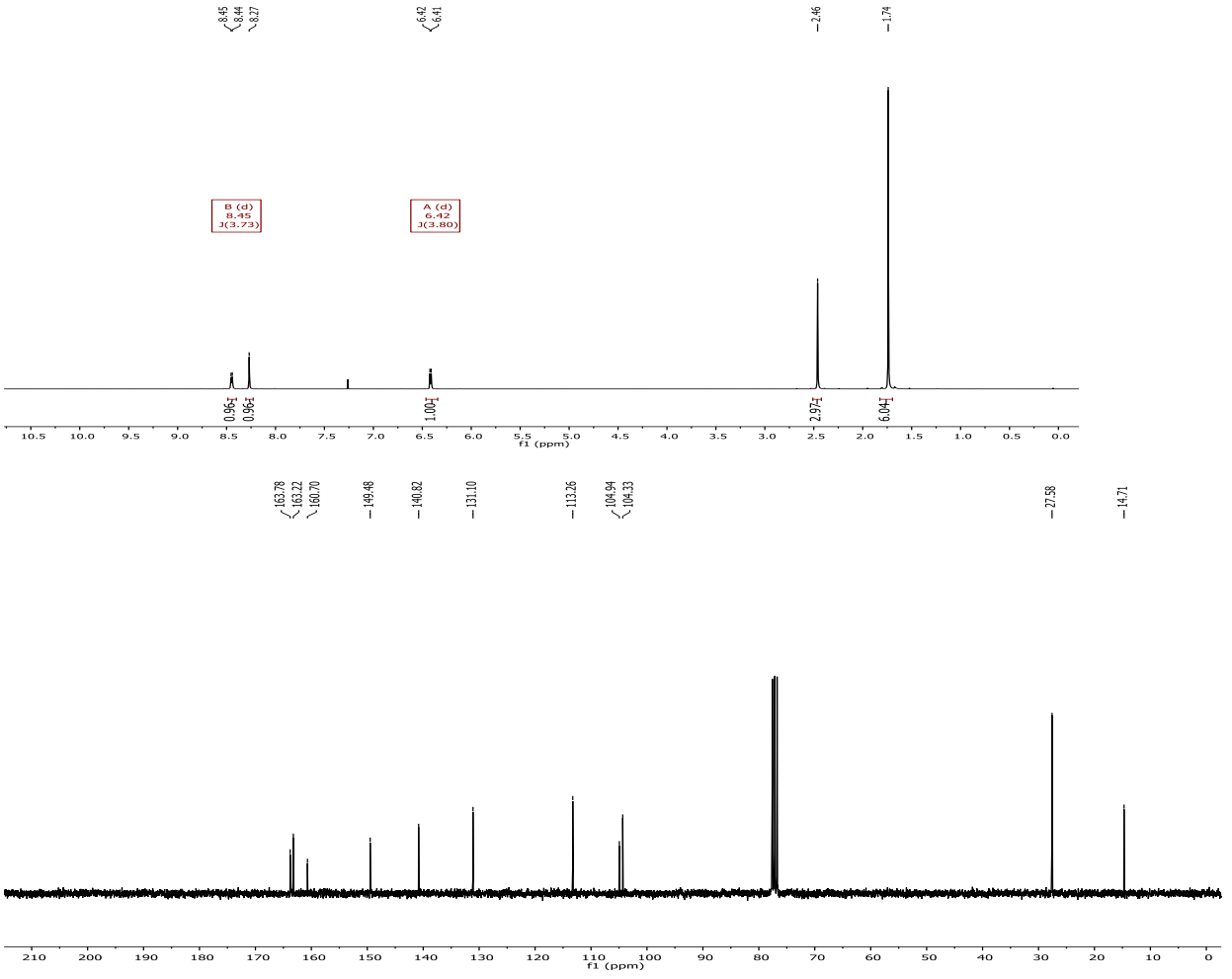


2,2-dimethyl-5-((5-methylfuran-2-yl)methylene)-1,3-dioxane-4,6-dione 128

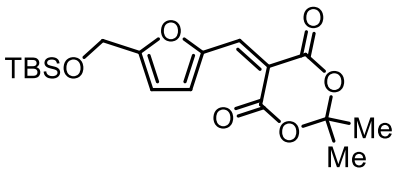


To a solution of 5-methylfurfural (0.75 mL, 7.5 mmol) in water (23 mL, 0.33 M) was added Meldrum's acid (1.13 g, 7.8 mmol, 1.05 equiv). The reaction mixture was stirred at 75°C for 2.5 h and then cooled down to RT. A sat. aq. sol. of $NaHCO_3$ was added (10 mL) and the product was extracted with DCM (3 × 25 mL). The collect organic layers were dried over Na_2SO_4 and concentrated in *vacuo* to give the desired product as a yellow solid (1.3 g, 73% yield). m.p. 110-112 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (1H, d, *J* = 3.7 Hz), 8.27 (1H, s), 6.42 (1H, d, *J* = 3.8 Hz), 2.46 (s, 3H), 1.74 (s, 6H). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 163.8, 163.2, 160.7, 149.5, 140.8, 131.1, 113.3, 104.9, 104.3, 27.6, 14.7. **HRMS (ESI-MS)** *m/z* calcd for $C_{12}H_{12}O_5$ $[M + Na]^+$ 259.0577, found 259.0576.

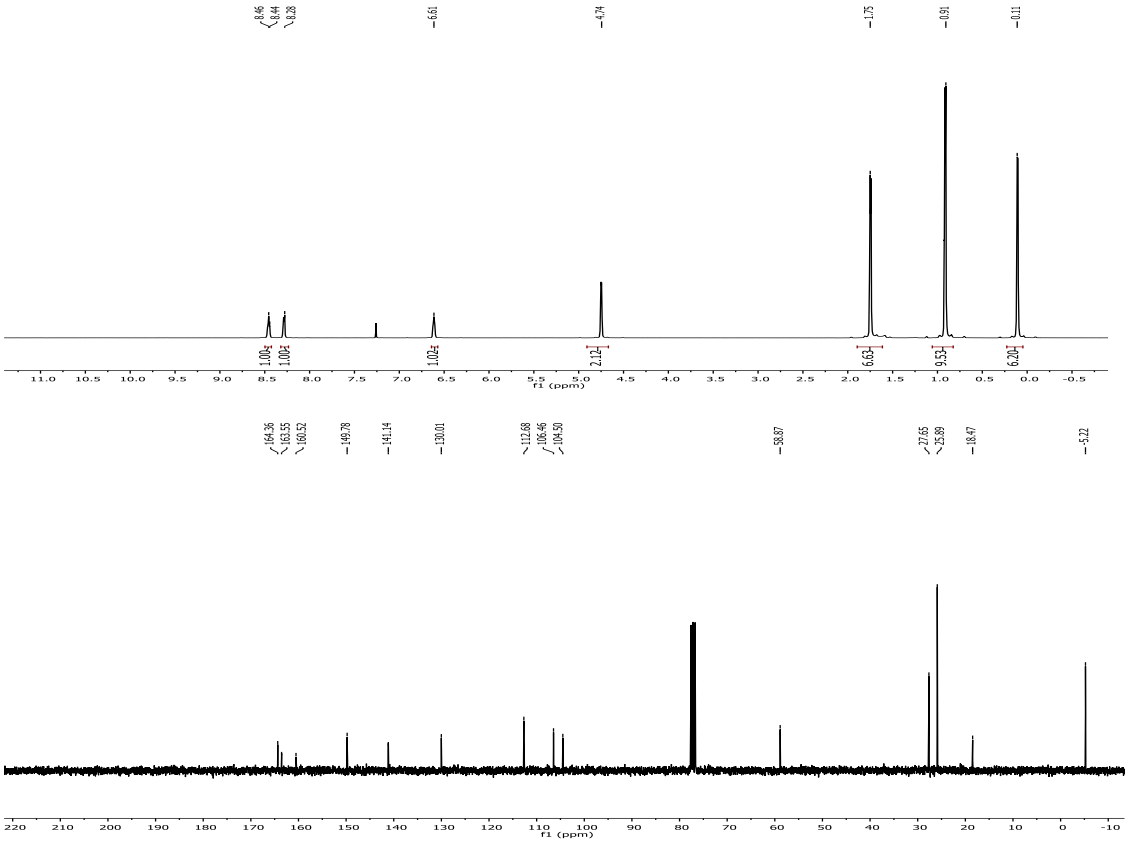


5-((5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione 127

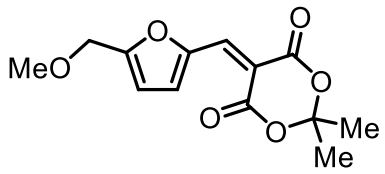


To a mixture of **121** (1.0 g, 3.96 mmol) and imidazole (0.54 g, 7.9 mmol, 2 equiv) in DCM (7 mL) was slowly added a solution of *tert*-butyldimethylsilyl chloride (TBDSCl, 0.72 g, 4.8 mmol, 1.2 equiv) in DCM (7 mL) at 0ºC. The reaction mixture was stirred and allowed to warm to RT. After completion of the reaction (TLC analysis, 16 h), water (15 mL) was added. The aqueous phase was extracted with DCM (3 × 25 mL), the collect organic layers dried over Na_2SO_4 and concentrated in *vacuo*. The obtained crude product was purified by column chromatography on silica gel (hexane-EtOAc = 1:9) to give the desired product as a yellow solid (0.81 g, 56% yield). m.p. 85-87 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (1H, m), 8.28 (1H, s), 6.61 (1H, m), 4.74 (2H, s), 1.75 (6H, s), 0.91 (9H, s), 0.11 (6H, s). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 164.4, 163.6, 160.5, 149.8, 141.1, 130.0, 112.7, 106.5, 104.5, 58.9, 27.7, 25.9, 18.5, -5.22. **HRMS (ESI-MS)** *m/z* calcd for $C_{18}H_{26}O_6Si$ $[M + Na]^+$ 389.1391, found 389.1395.

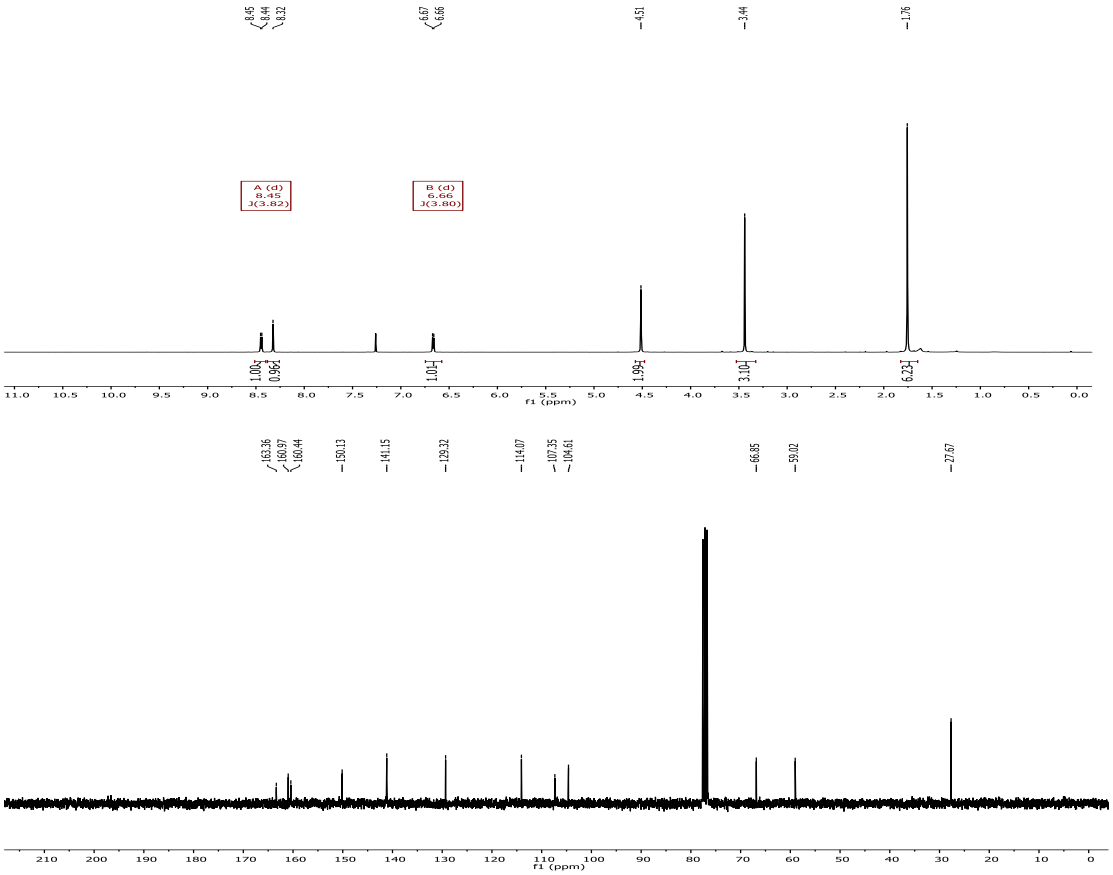


5-((5-(methoxymethyl)furan-2-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione 126



To a solution of 5-(methoxymethyl)furfural (0.2 g, 1.4 mmol) in water (4.2 mL, 0.33 M) was added Meldrum's acid (216 mg, 1.5 mmol, 1.05 equiv). The reaction mixture was stirred at 75°C for 2 h and then cooled down to RT. A sat. aq. sol. of $NaHCO_3$ was added (5 mL) and the product was extracted with DCM (3 × 15 mL). The collect organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The obtained crude product was purified by column chromatography on silica gel (hexane-EtOAc = 7:3) to give the desired product as a yellow solid (65 mg, 17% yield). m.p. 43-45 ºC

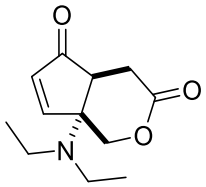
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (1H, d, *J* = 3.8 Hz), 8.44 (1H, s), 6.66 (1H, d, *J* = 3.8 Hz), 4.51 (2H, s), 3.44 (3H, s) 1.76 (6H, s). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 163.4, 161.0, 160.4, 150.1, 141.2, 129.3, 114.1, 107.4, 104.6, 66.9, 59.0, 27.7. **HRMS (ESI-MS)** *m/z* calcd for $C_{13}H_{14}O_6$ $[M + Na]^+$ 389.0683, found 389.0684.



General Procedure for the synthesis of LCP

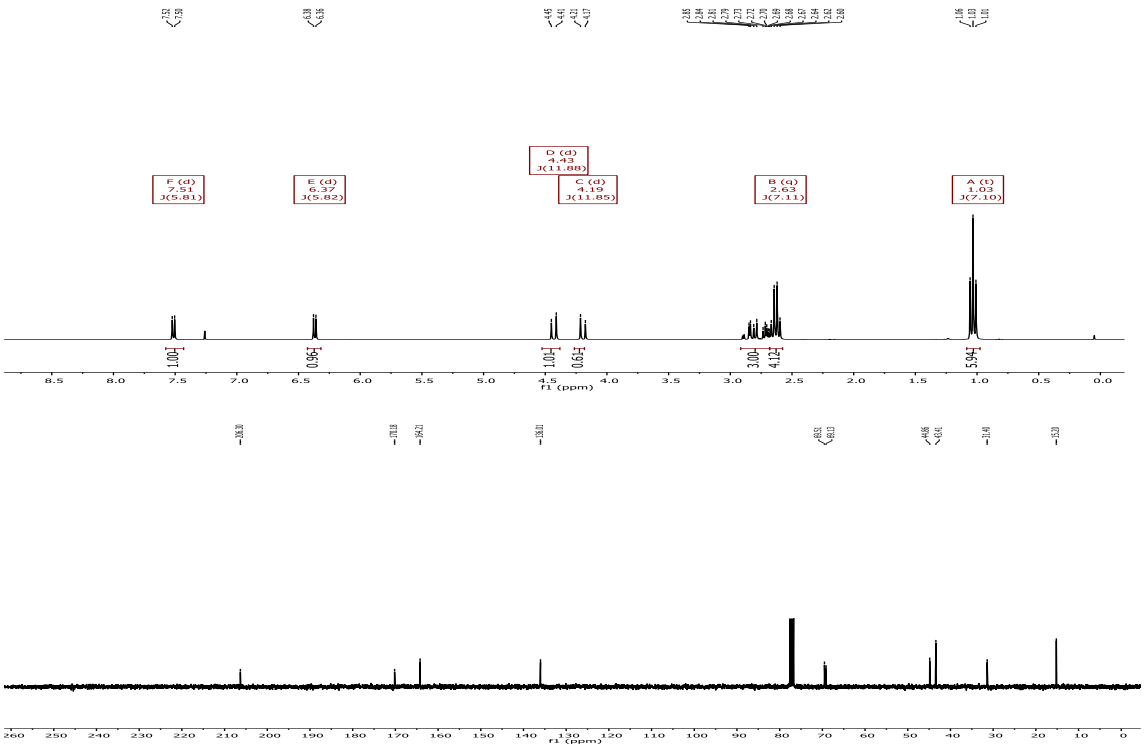
To a solution of **121** (100 mg, 0.40 mmol) in DCM (4 mL) was added the corresponding amine (1.5 equiv, 0.65 mmol), upon which the yellowish solution turns red. (*R*)-BINOL (0.1 equiv, 11.4 mg, 0.04 mmol) was added and the mixture was allowed to stir for 24 h. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography.

7a-(diethylamino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 108

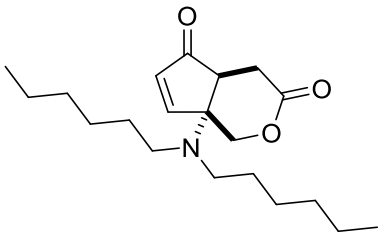


The titled compound was prepared using diethylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (8:2 to 2:8) affording 53 mg (60% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, d, *J* = 5.8 Hz), 6.37 (1H, d, *J* = 5.8 Hz), 4.43 (1H, d, *J* = 11.9 Hz), 4.19 (1H, d, *J* = 11.9 Hz), 2.67-2.85 (3H, m), 2.63 (4H, t, *J* = 7.1 Hz), 1.03 (6H, t, *J* = 7.1 Hz); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 206.3, 170.2, 164.2, 136.0, 69.5, 69.1, 44.9, 43.4, 31.4, 15.2; **HRMS (ESI-MS)** *m/z* calcd for $C_{12}H_{17}NO_3$ $[M + H]^+$ 224.1281, found 224.1285.

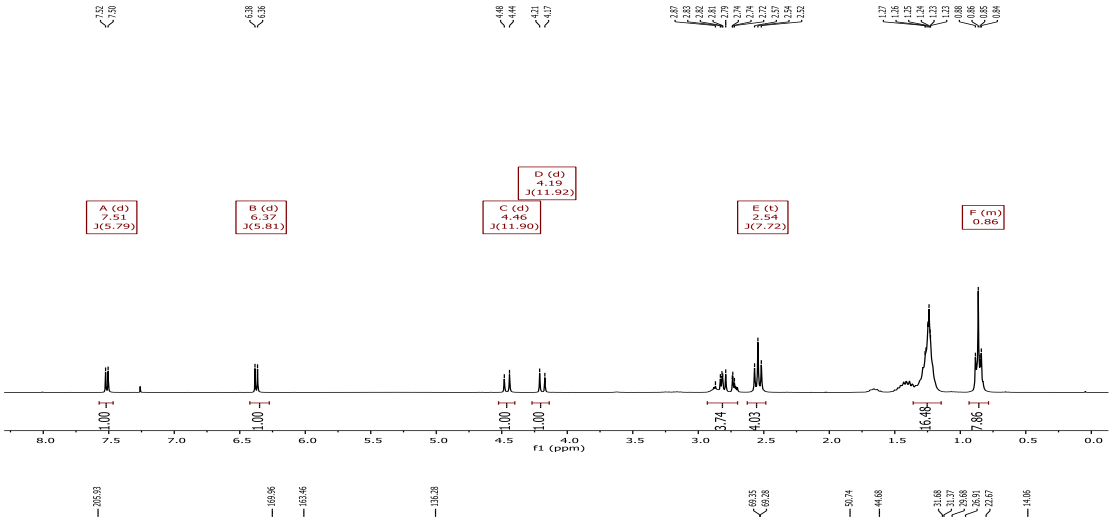


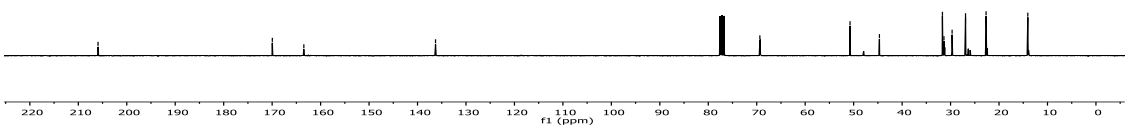
7a-(dihexylamino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 133



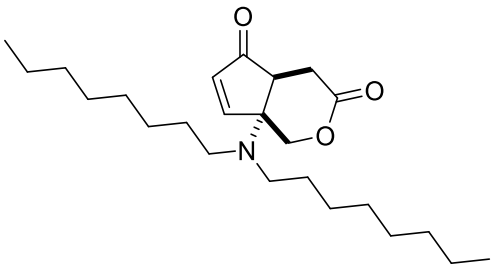
The titled compound was prepared using dihexylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 93 mg (70%) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, d, *J* = 5.8 Hz), 6.37 (1H, d, *J* = 5.8 Hz), 4.46 (1H, d, *J* = 11.9 Hz), 4.19 (1H, d, *J* = 11.9 Hz) 2.72-2.87 (3H, m) 2.54 (4H, t, *J* = 7.7 Hz) 1.23-1.27 (16H, m) 0.84-0.88 (6H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.9, 170.0, 163.5, 136.3, 66.4, 69.3, 50.7, 44.7, 31.7, 31.4, 29.7, 26.9, 22.7, 14.1;**HRMS (ESI-MS)** *m/z* calcd for $C_{20}H_{33}NO_3$ $[M + H]^+$ 336.25387, found 336.25303.



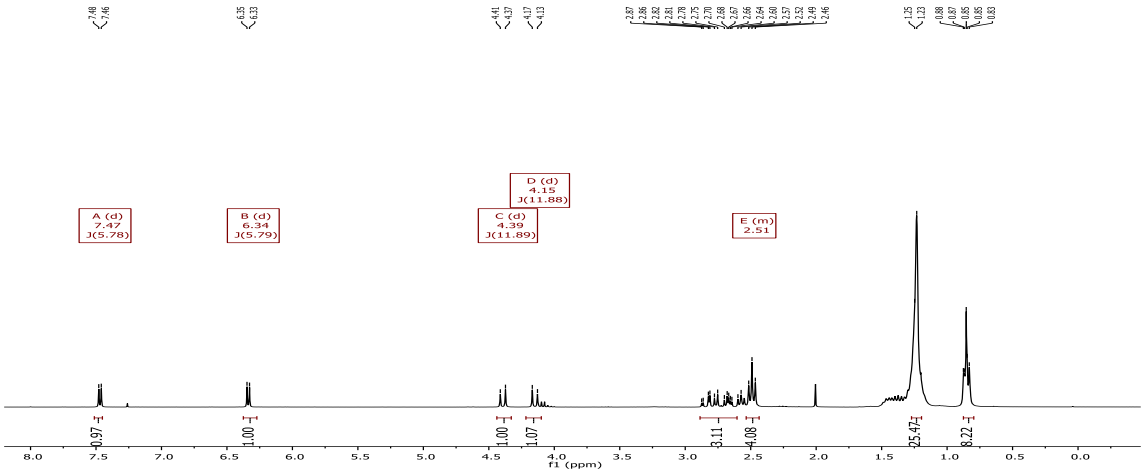


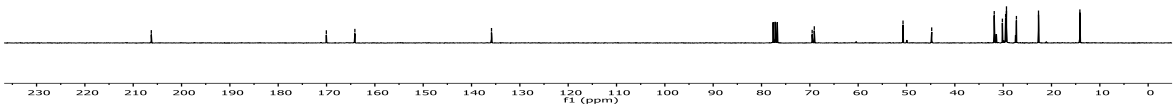
7a-(dioctylamino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 134



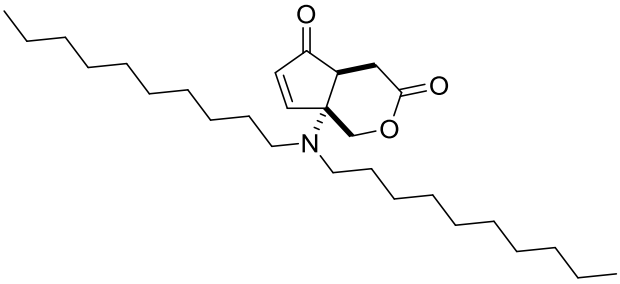
The titled compound was prepared using dioctylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 115 mg (74% yield) pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 5.8 Hz), 6.34 (1H, d, *J* = 5.8 Hz), 4.39 (1H, d, *J* = 11.9 Hz), 4.15 (1H, d, *J* = 11.9 Hz) 2.57-2.87 (3H, m) 2.51 (4H, m) 1.23-1.25 (20H, m) 0.83-0.88 (6H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 206.3, 170.0, 164.1, 135.9, 69.5, 69.1, 50.7, 44.8, 31.9, 30.2, 29.5, 29.3, 27.3, 22.7, 14.1. **HRMS (ESI-MS)** *m/z* calcd for $C_{24}H_{41}NO_3$ $[M + H]^+$ 392.31647, found 392.31534.



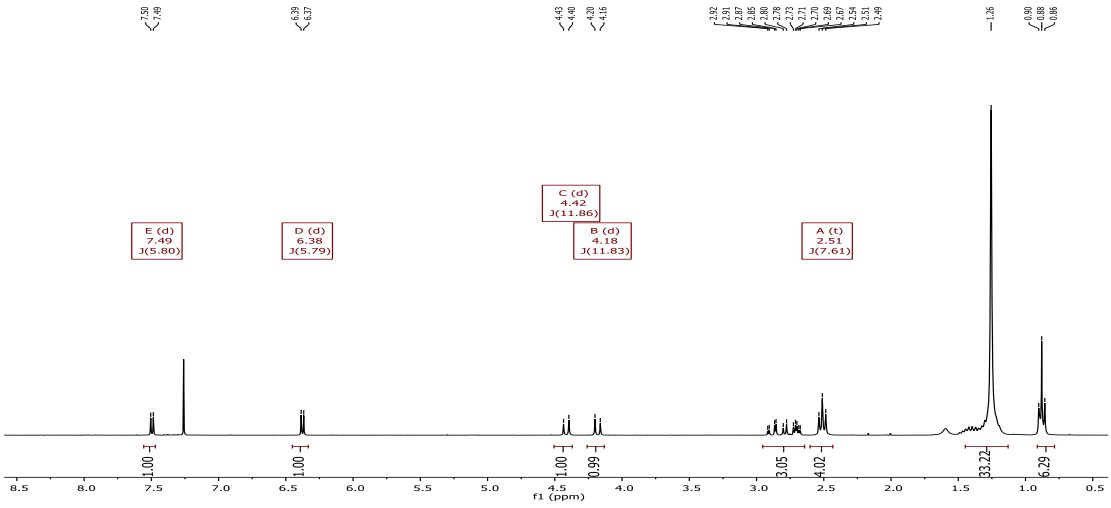


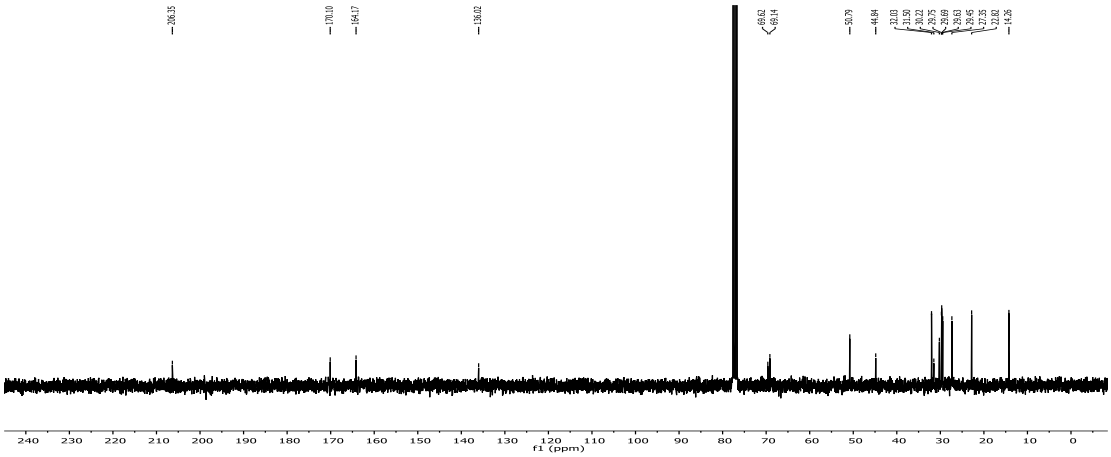
7a-(didecylamino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 135



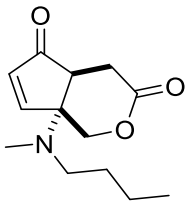
The titled compound was prepared using didecylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9.5:0.5 to 8:2) affording 129 mg (72% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (1H, d, *J* = 5.8 Hz), 6.38 (1H, d, *J* = 5.8 Hz), 4.42 (1H, d, *J* = 11.9 Hz), 4.18 (1H, d, *J* = 11.9 Hz) 2.567-2.92 (3H, m) 2.51 (4H, t, *J* = 7.6 Hz) 1.26 (32H, m) 0.86-0.90 (6H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 206.4, 170.1, 164.2, 136.0, 69.6, 69.1, 50.8, 44.8, 32.0, 31.5, 30.2, 29.8, 29.7, 29.6, 29.5. 27.4, 22.8, 14.3. **HRMS (ESI-MS)** *m/z* calcd for $C_{28}H_{49}NO_3$ $[M + H]^+$ 448.37907, found 448.37792.



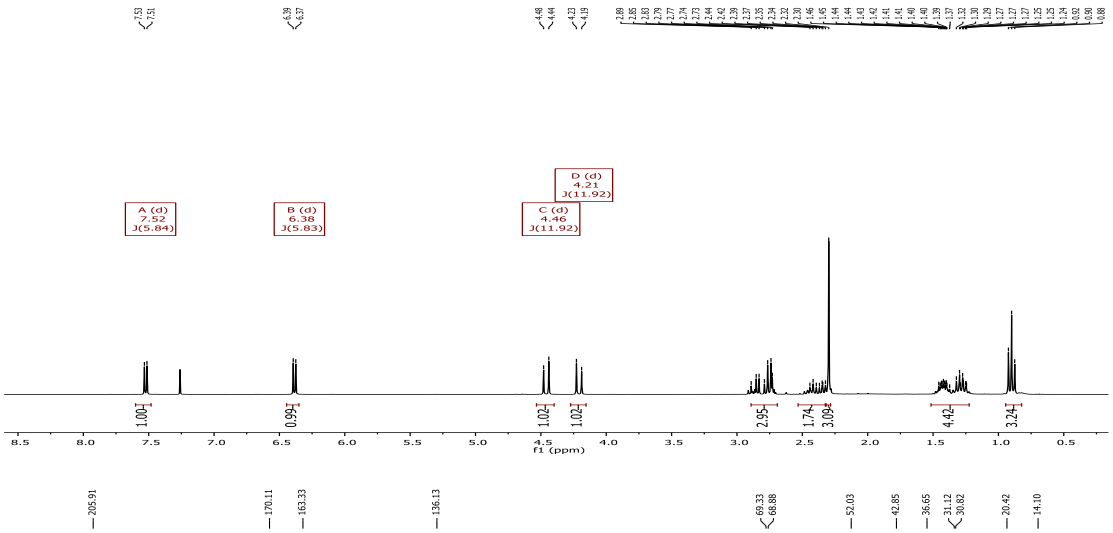


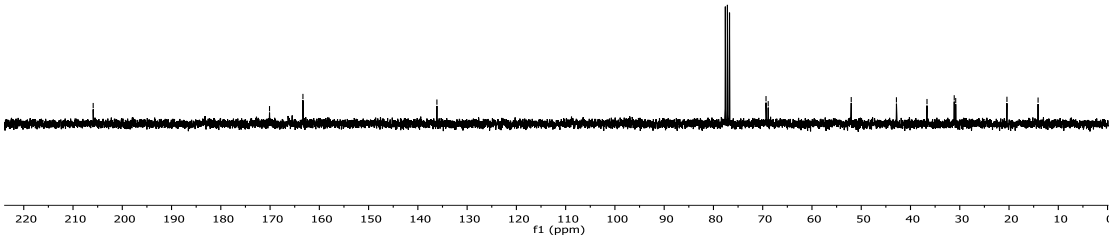
7a-(butyl(methyl)amino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 137



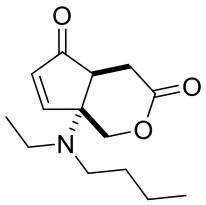
The titled compound was prepared using *N*-methylbutylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 6:4) affording 68 mg (72% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 5.8 Hz), 6.38 (1H, d, *J* = 5.8 Hz), 4.46 (1H, d, *J* = 11.9 Hz), 4.21 (1H, d, *J* = 11.9 Hz) 2.73-2.89 (3H, m) 2.32-2.44 (2H, m) 2.30 (3H, s) 1.25-1.46 (4H, m) 0.88-0.92 (3H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.9, 170.1, 163.3, 136.1, 69.3, 28.9, 52.0, 42.9, 36.6, 31.1, 30.8, 20.4, 14.1. **HRMS (ESI-MS)** *m/z* calcd for $C_{13}H_{19}NO_3$ $[M + H]^+$ 238.14432, found 238.14311.



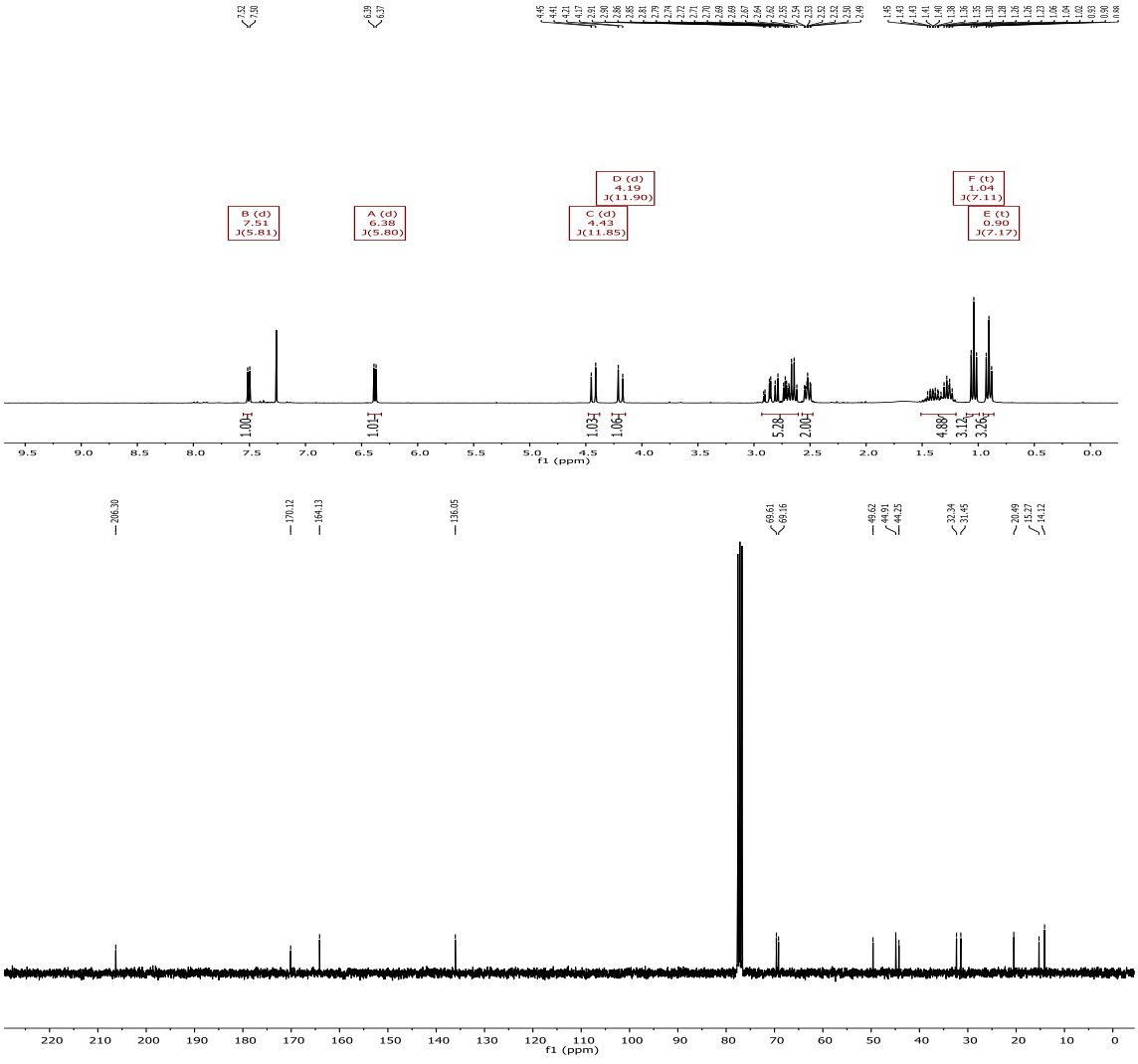


7a-(butyl(ethyl)amino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 138

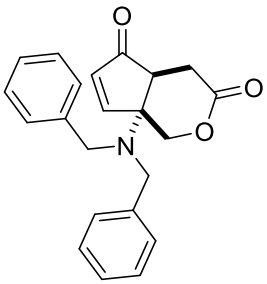


The titled compound was prepared using *N*-ethylbutylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 6:4) affording 70 mg (71% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, d, *J* = 5.8 Hz), 6.38 (1H, d, *J* = 5.8 Hz), 4.43 (1H, d, *J* = 11.9 Hz), 4.19 (1H, d, *J* = 11.9 Hz), 2.64-2.91 (5H, m), 2.49-2.55 (2H, m), 1.35-1.45 (4H, m), 1.04 (3H, t, *J* = 7.1 Hz), 0.9 (3H, t, *J* = 7.1 Hz); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 206.3, 170.1, 164.1, 136.1, 69.6. 69.2, 49.6, 44.9, 44.3, 32.3, 31.5, 20.5, 15.3, 14.1. **HRMS (ESI-MS)** *m/z* calcd for $C_{14}H_{21}NO_3$ $[M + H]^+$ 252.15997, found 252.15917.

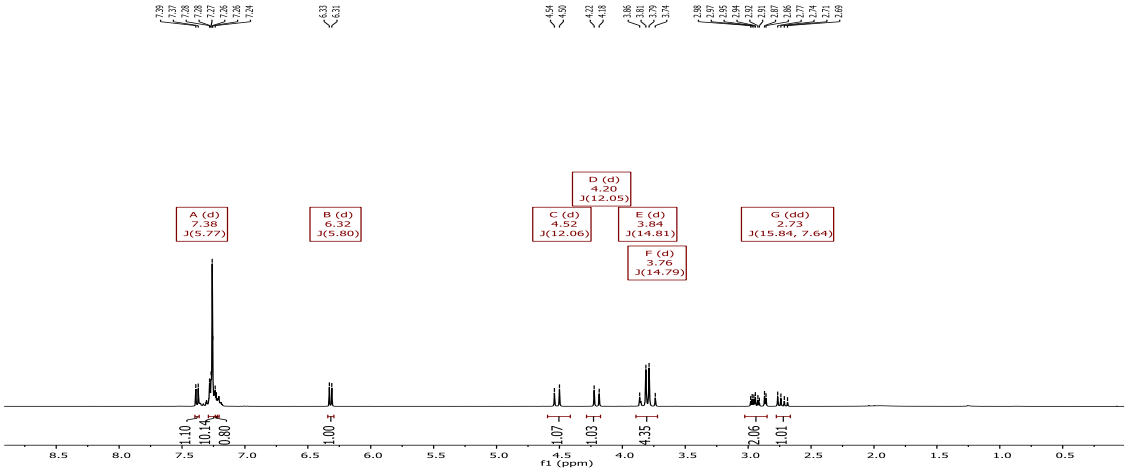


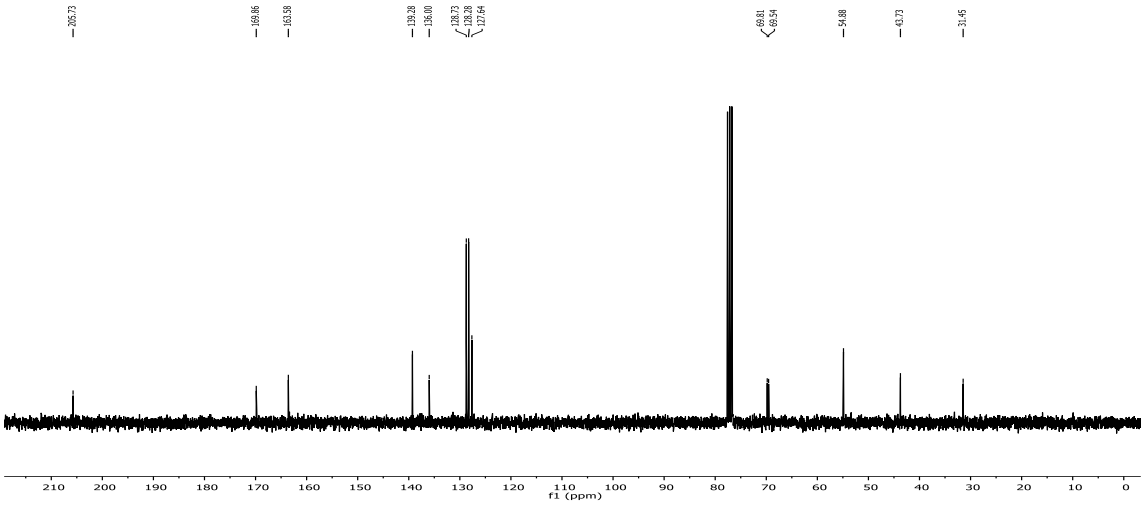
7a-(dibenzylamino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 139



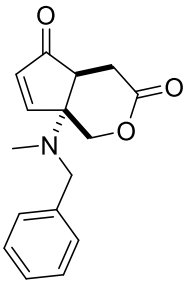
The titled compound was prepared using dibenzylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 6:4) affording 36 mg (26% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (1H, d, *J* = 5.8 Hz), 7.24-7.28 (10H, m), 6.32 (1H, d, *J* = 5.8 Hz), 4.52 (1H, d, *J* = 12.0 Hz), 4.20 (1H, d, *J* = 12.0 Hz), 3.84 (2H, d, *J* = 14.8 Hz), 3.76 (2H, d, *J* = 14.8 Hz), 2.86-2.98 (2H, m) 2.73 (1H, dd, *J* = 15.8, 7.6 Hz) ; **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.7, 169.9, 163.6, 139.3, 136.0, 128.7, 128.3, 127.6, 69.8, 69.5, 54.9, 43.7, 31.5. **HRMS (ESI-MS)** *m/z* calcd for $C_{22}H_{21}NO_3$ $[M + H]^+$ 348.15997, found 348.15888.



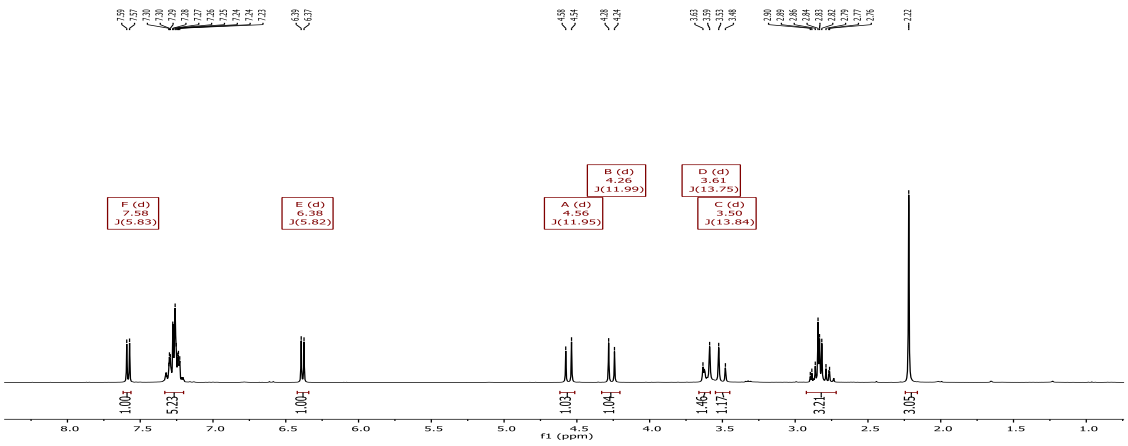


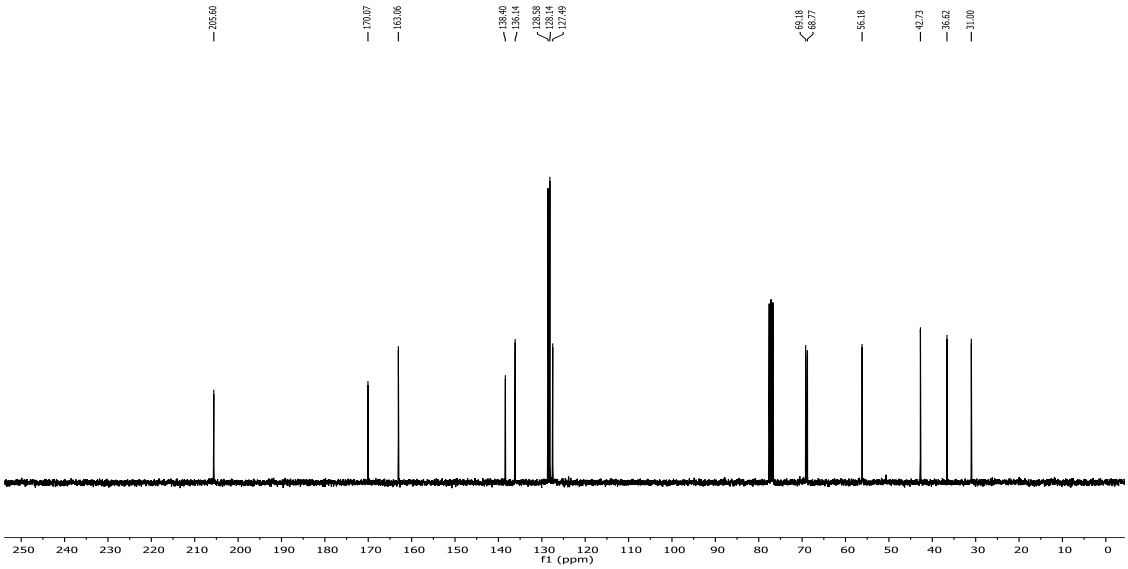
7a-(benzyl(methyl)amino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 140



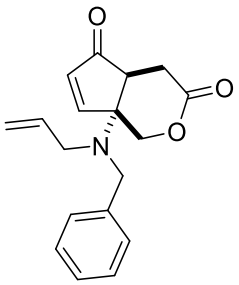
The titled compound was prepared using *N*-benzylmethylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 6:4) affording 82 mg (76% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 5.8 Hz), 7.23-7.30 (5H, m), 6.38 (1H, d, *J* = 5.8 Hz), 4.56 (1H, d, *J* = 12.0 Hz), 4.26 (1H, d, *J* = 12.0 Hz), 3.61 (1H, d, *J* = 13.8 Hz), 3.50 (1H, d, *J* = 13.8 Hz), 2.76-2.90 (3H, m) 2.22 (3H, s); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.6, 170.1, 163.1, 138.4, 136.1, 128.6, 128.1, 17.5, 69.2, 68.8, 56.2, 42.7, 36.6, 31.0. **HRMS (ESI-MS)** *m/z* calcd for $C_{16}H_{17}NO_3$ $[M + H]^+$ 272.12867, found 272.12762.



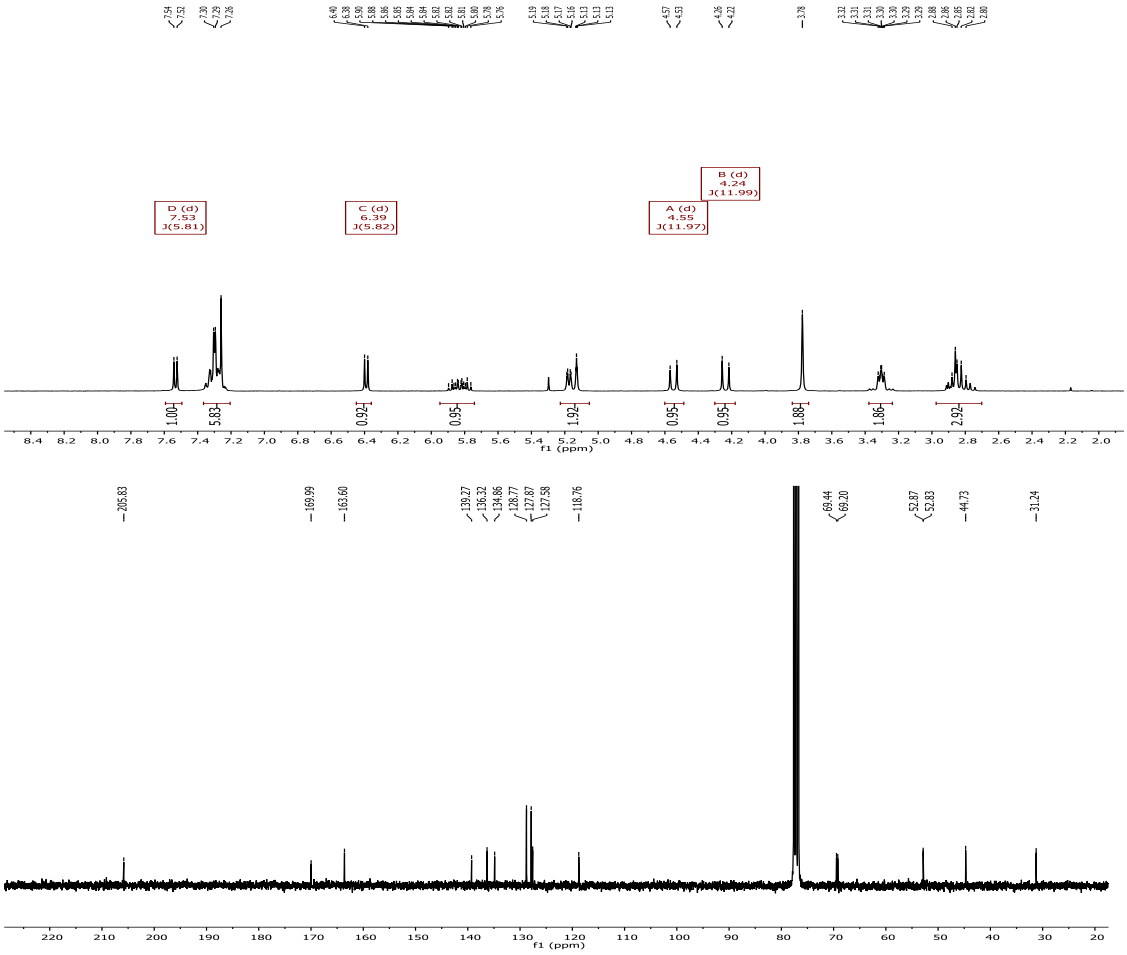


7a-(allyl(benzyl)amino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 142

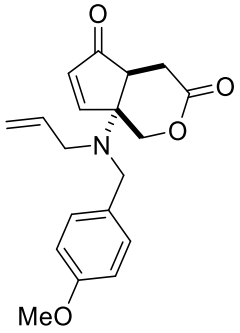


The titled compound was prepared using *N*-allylbenzylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 6:4) affording 92 mg (78% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ δ 7.53 (1H, d, *J* = 5.8 *Hz*), 7.26-7.30 (5H, m), 6.39 (1H, d, *J* = 5.8 *Hz*), 5.76-5.90 (1H, m), 5.13-5.19 (2H, m) 4.55 (1H, d, *J* = 12.0 *Hz*), 4.24 (1H, d, *J* = 12.0 *Hz*), 3.78 (2H, s) 3.29-3.32 (2H, m) 2.80-2.88 (3H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.8, 170.0, 163.6, 139.3, 136.3, 134.9, 128.8, 127.9, 127.6, 118.8, 69.4, 69.2, 52.9, 52.8, 44.8, 31.2. **MS (ESI-MS)** *m/z* calcd for $C_{18}H_{19}NO_3$ $[M + H]^+$ 298.1438, found 298.1443.



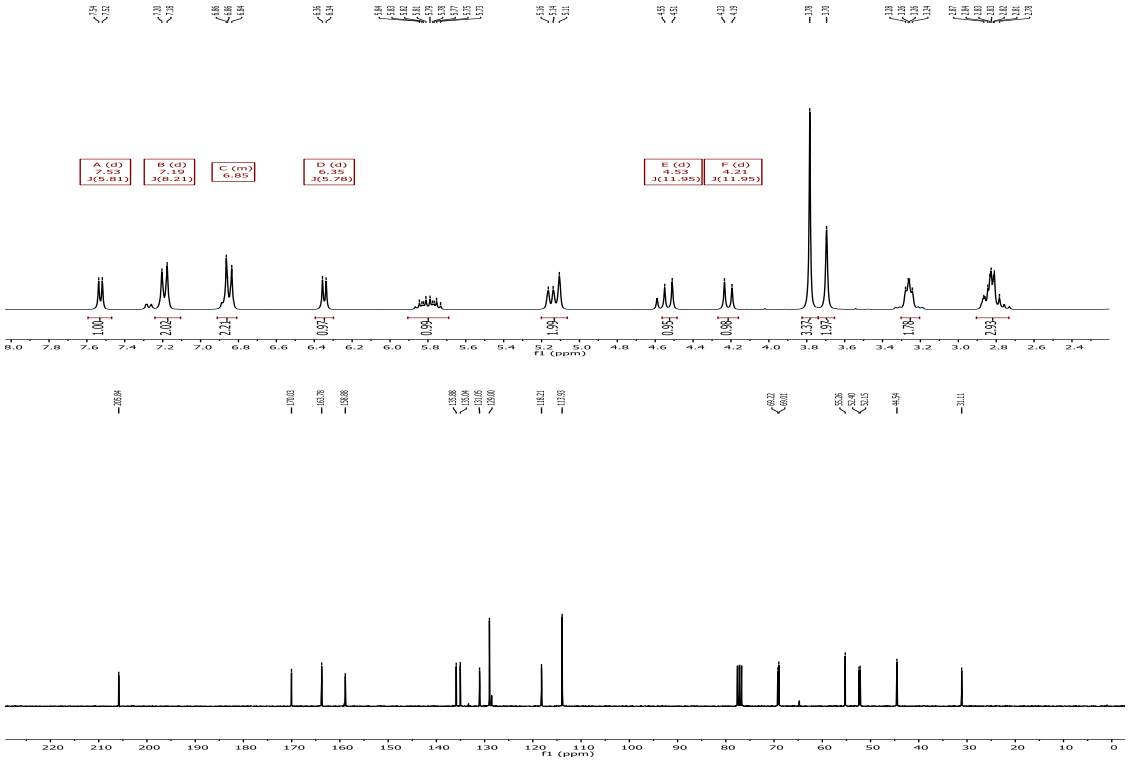
7a-(allyl(4-methoxybenzyl)amino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 143



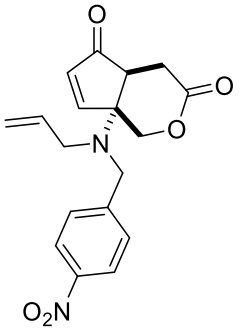
The titled compound was prepared using *N*-(4-methoxybenzyl)allylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 6:4) affording 106 mg (82% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 5.8 Hz), 7.19 (2H, d, *J* = 8.2 Hz), 6.85 (2H, m), 6.35 (1H, d, *J* = 5.8 Hz), 5.73-5.84 (1H, m), 5.11-5.16 (2H, m), 4.53 (1H, d, *J* = 12.0 Hz), 4.21 (1H, d, *J* = 12.0 Hz), 3.78 (3H, s), 3.70 (2H, s), 3.24-3.28 (2H, m), 2.78-2.87

(3H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.8, 170.0, 163.8, 158.9, 135.9, 135.0, 131.0, 129.0, 118.2, 113.69, 69.2, 69.0, 55.3, 52.4, 52.2, 44.5, 31.1. **HRMS (ESI-MS)** *m/z* calcd for $C_{19}H_{21}NO_4$ $[M + Na]^+$ 350.1363, found 350.1369.



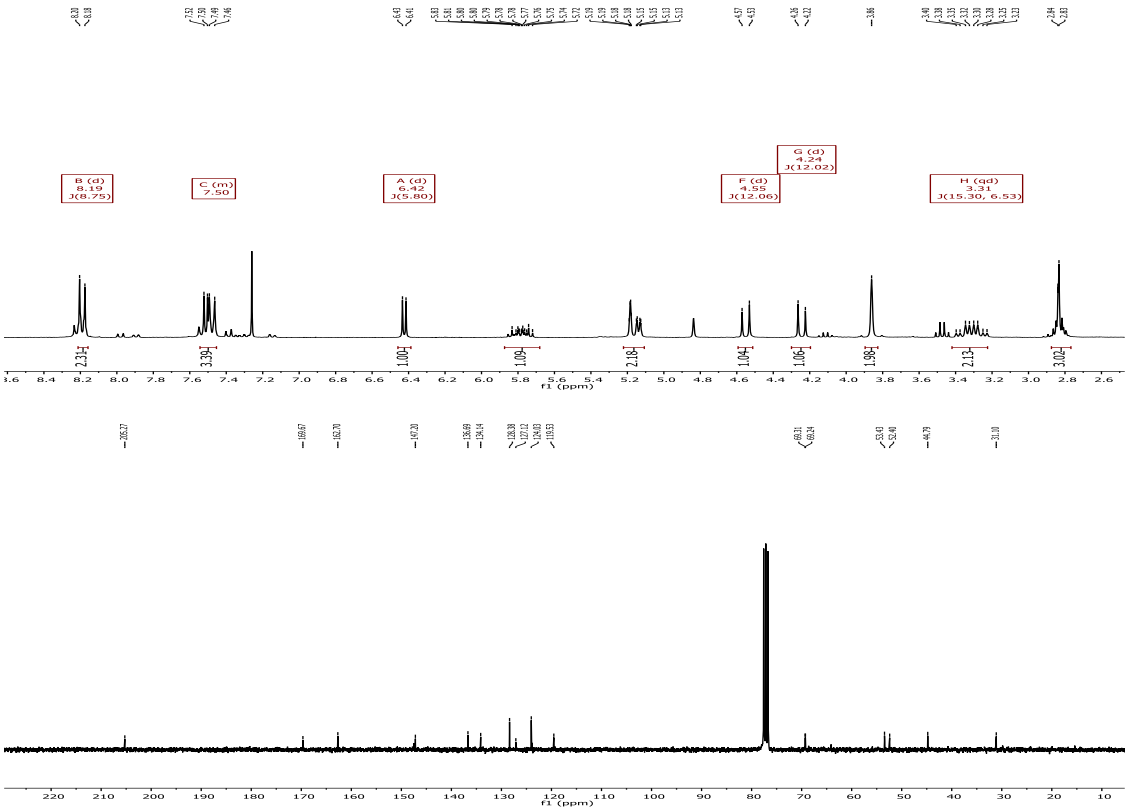
7a-(allyl(4-nitrobenzyl)amino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 144



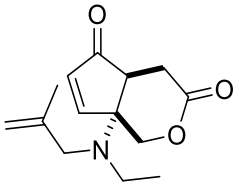
The titled compound was prepared using *N*-(4-nitrobenzyl)allylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 6:4) affording 70 mg (52% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (2H, d, *J* = 8.8 Hz), 7.5 (3H, m), 6.42 (1H, d, *J* = 5.8 Hz), 5.72-5.83 (1H, m), 5.13-5.19 (2H, m), 4.55 (1H, d, *J* = 12.0 Hz), 4.24 (1H, d, *J* = 12.0 Hz), 3.86 (2H, s), 3.31 (2H, qd, *J* = 15.3, 6.5 Hz), 2.83-2.84 (3H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.3, 169.7, 162.7, 147.2, 136.7, 134.1, 128.4, 127.1, 124.0, 119.5,

69.3, 69.2, 53.4, 52.4, 44.8, 31.1. **HRMS (ESI-MS)** *m/z* calcd for $C_{18}H_{18}N_2O_5$ [M + H]$^+$ 343.1288, found 343.1293.

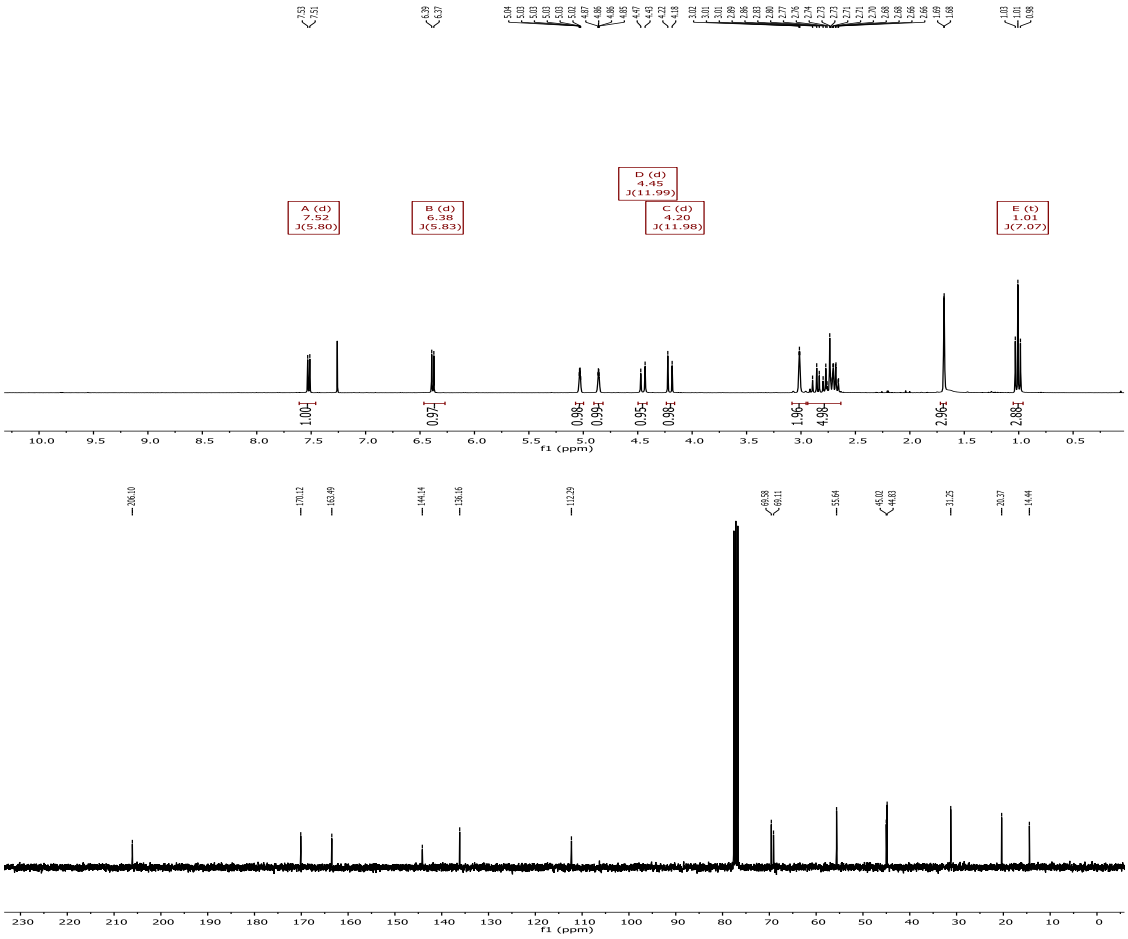


7a-(ethyl(2-methylallyl)amino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 141

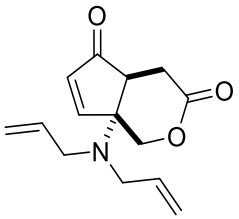


The titled compound was prepared using *N*-ethyl-2-methylallylamine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 4:6) affording 67 mg (68% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 5.8 Hz), 6.38 (1H, d, *J* = 5.8 Hz), 5.02-5.04 (1H, m), 4.85-4.86 (1H, m), 4.45 (1H, d, *J* = 12.0 Hz), 4.20 (1H, d, *J* = 12 Hz), 2.80-3.02 (2H, m), 2.66-2.77 (5H, m), 1.68 (3H, s), 1.01 (3H, t, *J* = 7.1 *H*); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 206.1, 170.1, 163.5, 144.1, 136.2, 112.3, 69.6, 69.1, 55.6, 45.0, 44.8, 31.3, 20.4, 14.4. **HRMS (ESI-MS)** *m/z* calcd for $C_{14}H_{19}NO_3$ [M + H]$^+$ 250.14432, found 250.14362.

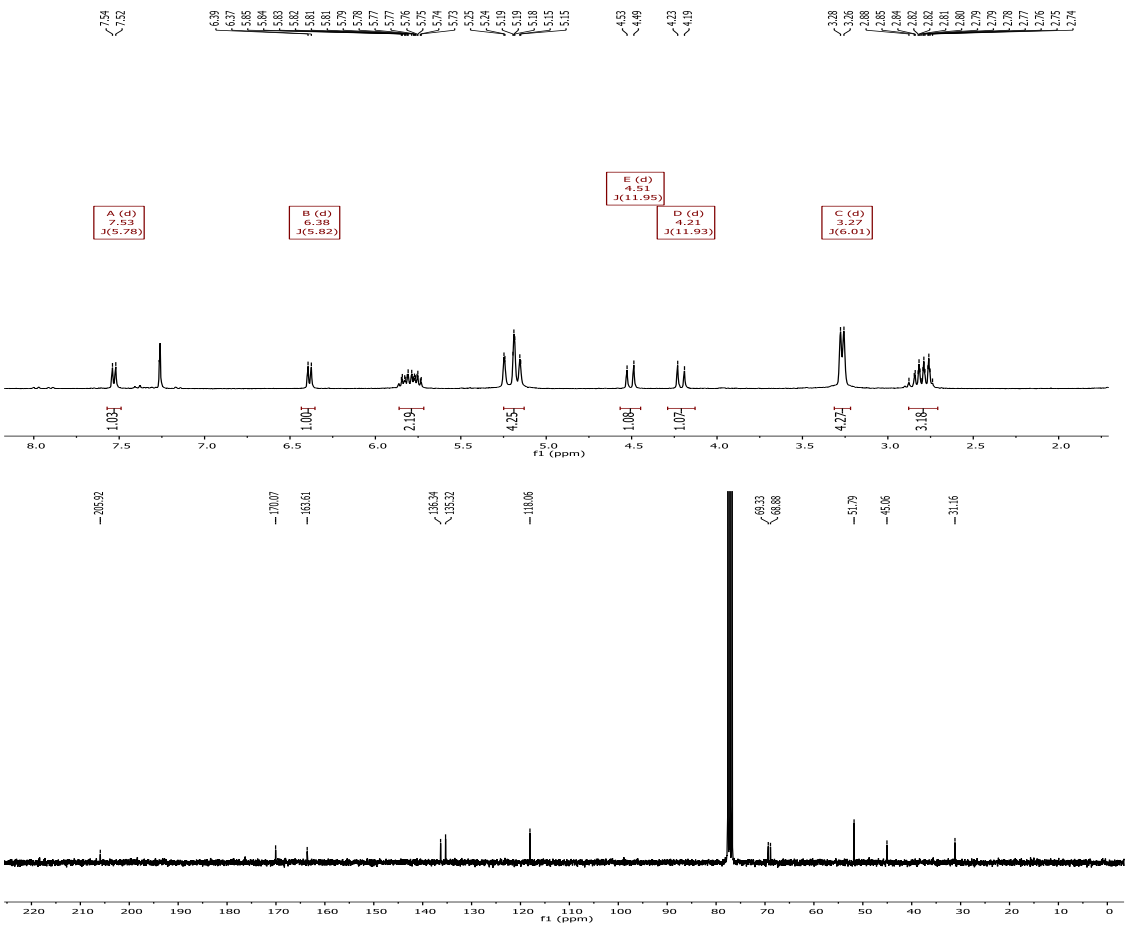


7a-(diallylamino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 136

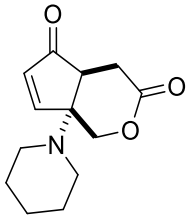


To a solution of **1ii** (5 g, 19.8 mmol) in DCM (200 mL) was added diallylamine (2.0 equiv, 4.9 mL, 39.6 mmol), upon which the yellowish solution turns red. (*R*)-BINOL (0.1 equiv, 568 mg, 1.98 mmol) was added and the mixture was allowed to stir for 24 h. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography using hexane:ethyl acetate (9:1 to 4:6) affording the pure product as a yellow crystals (3.43 g, 70% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 5.8 Hz), 6.38 (1H, d, *J* = 5.8 Hz), 5.73-5.85 (2H, m), 5.15-5.25 (4H, m), 4.51 (1H, d, *J* = 12.0 Hz), 4.21 (1H, d, *J* = 11.9 Hz), 3.27 (4H, d, *J* = 6.0 Hz), 2.74-2.88 (3H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.9, 170.1, 163.6, 136.3, 135.3, 118.0, 69.3, 68.9, 51.8, 45.1, 31.2; **HRMS (ESI-MS)** *m/z* calcd for $C_{14}H_{17}NO_3$ $[M + H]^+$ 248.12867, found 248.12777.

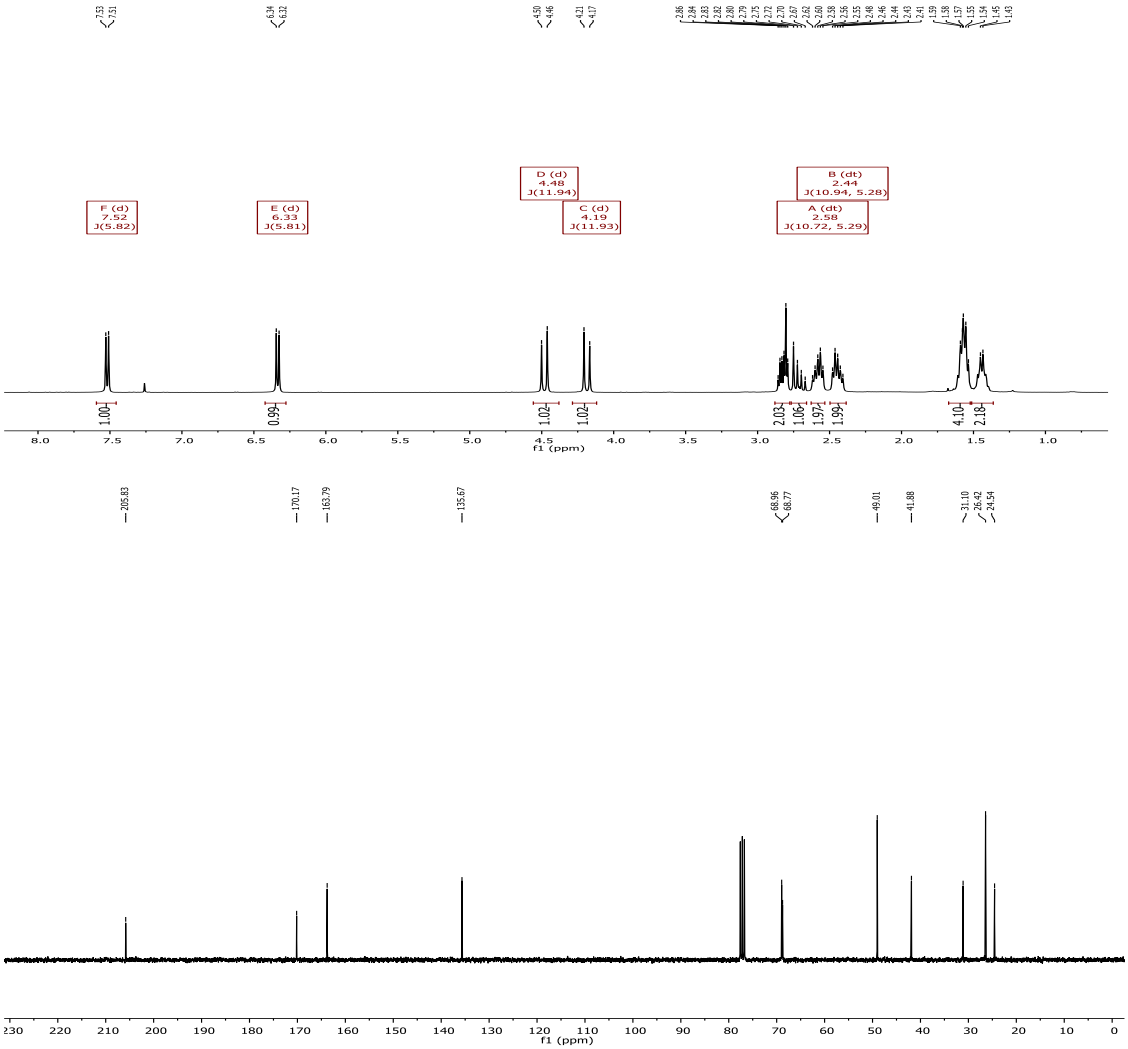


7a-(piperidin-1-yl)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 145

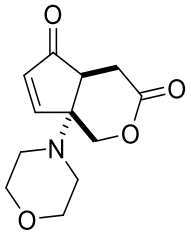


The titled compound was prepared using piperidine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 4:6) affording 52 mg (56% yield) of pure product as a yellow powder. m.p. 156-158 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 5.8 Hz), 6.33 (1H, d, *J* = 5.8 Hz), 4.48 (1H, d, *J* = 11.9 Hz), 4.19 (1H, d, *J* = 11.9 Hz), 2.79-2.86 (2H, m) 2.67-2.75 (1H, m), 2.58 (2H, dt, *J* = 5.3, 10.7 Hz), 2.44 (2H, dt, *J* = 5.3, 10.9 Hz), 1.54-1.59 (4H, m), 1.43-1.45 (2H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.8, 170.2, 163.8, 135.7, 69.0, 68.8, 49.0, 41.9, 31.1, 26.4, 24.5. **HRMS (ESI-MS)** *m/z* calcd for $C_{13}H_{17}NO_3$ $[M + H]^+$ 236.12084, found 236.12775

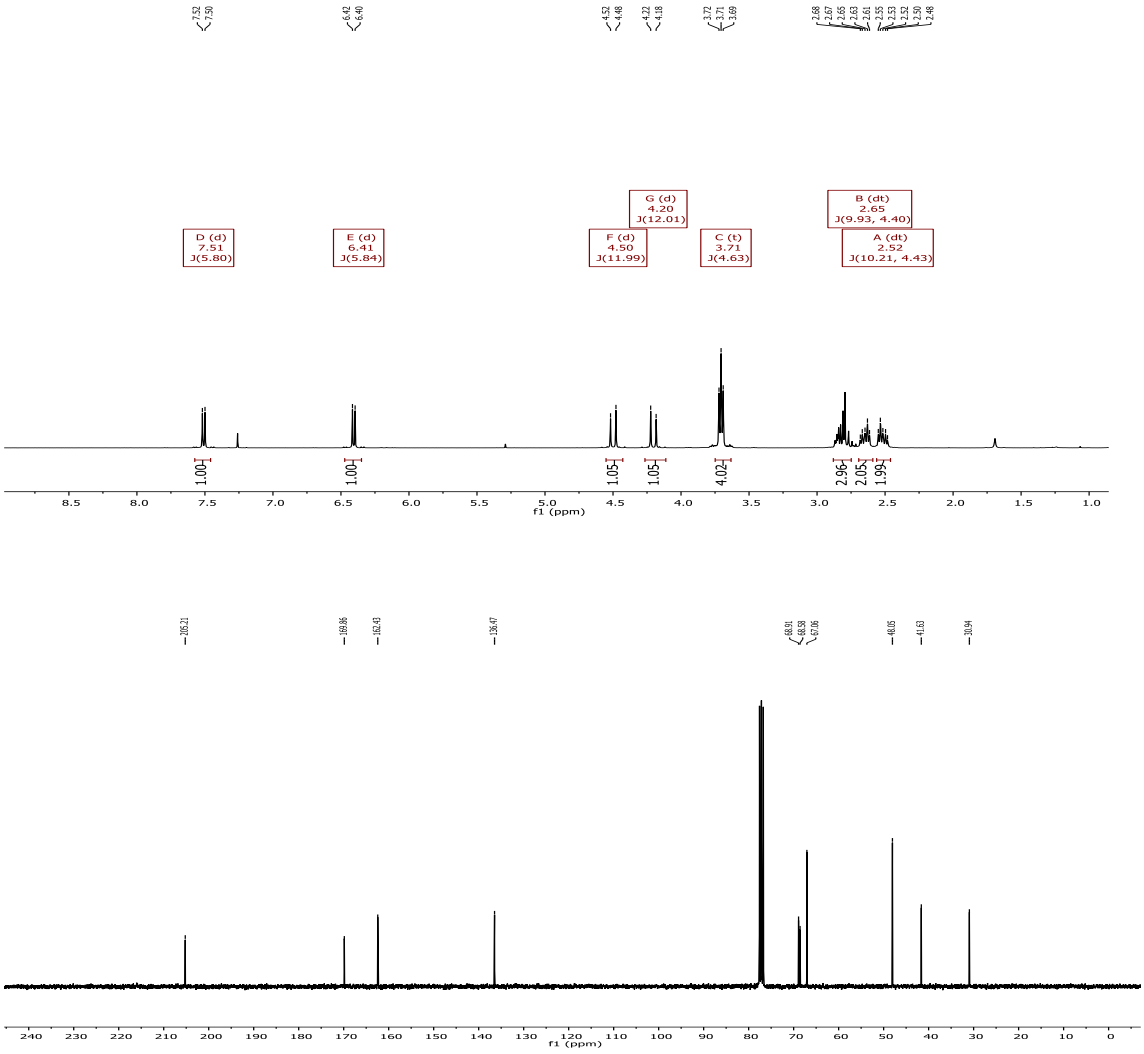


7a-morpholino-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 146

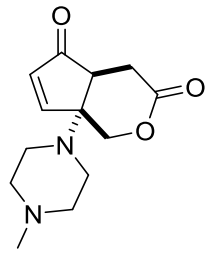


The titled compound was prepared using morpholine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (7:3 to 1:9) affording 64 mg (68% yield) pure product as a yellow powder. m.p. 187-188 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, d, *J* = 5.8 Hz), 6.41 (1H, d, *J* = 5.8 Hz), 4.50 (1H, d, *J* = 12.0 Hz), 4.20 (1H, d, *J* = 12.0 Hz), 3.71 (4H, t, *J* = 4.6 Hz), 2.61-2.68 (3H, m), 2.65 (2H, dt, *J* = 4.4, 9.9 Hz), 2.52 (2H, dt, *J* = 4.4, 10.2 Hz); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.2, 169.9, 162.4, 136.5, 68.9, 68.6, 67.1, 48.1, 51.6, 30.9. **HRMS (ESI-MS)** *m/z* calcd for $C_{12}H_{15}NO_4$ $[M + H]^+$ 238.10793, found 238.10601.



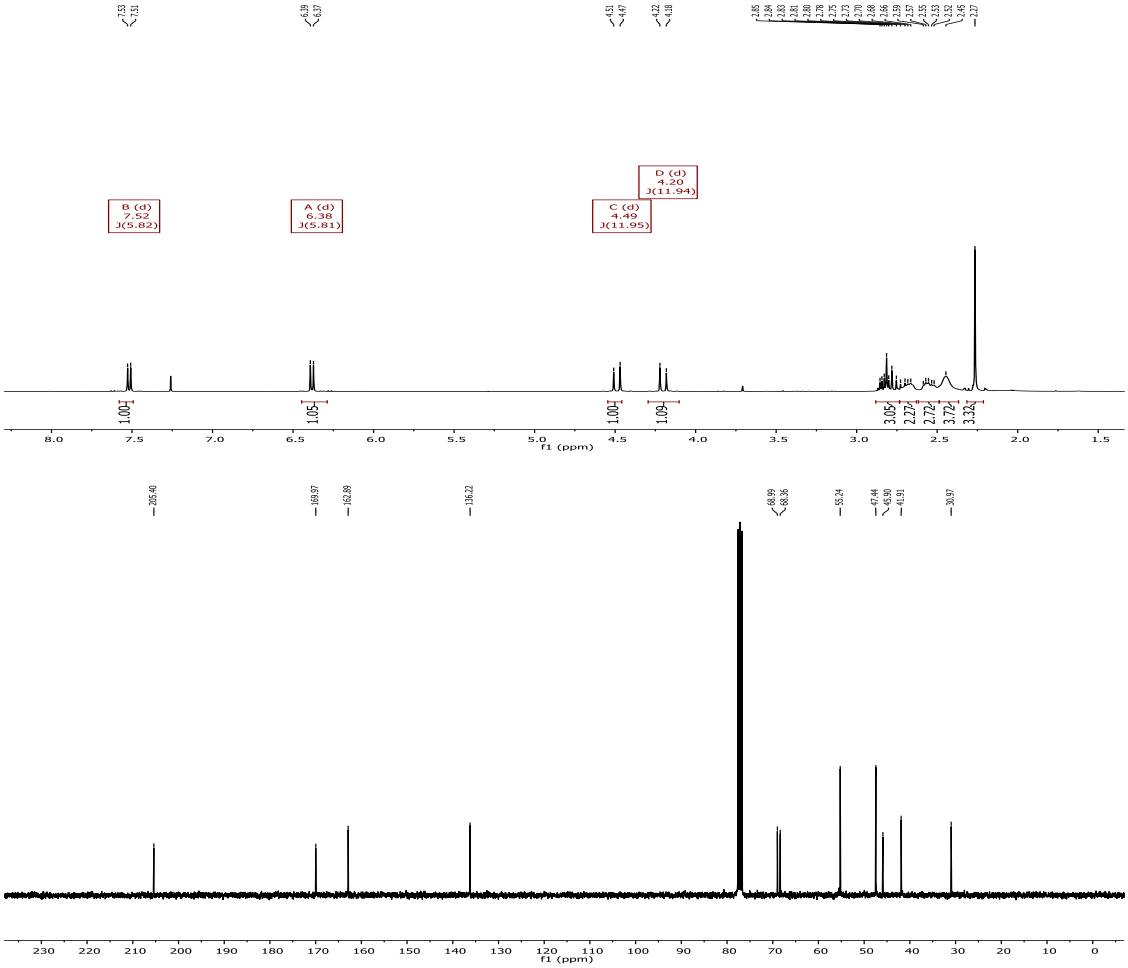
7a-(4-methylpiperazin-1-yl)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 147



The titled compound was prepared using *N*-methylpiperazine according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (7:3 to 1:9) affording 57 mg (57% yield) of pure product as a yellow oil.

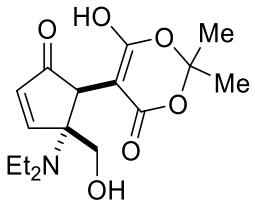
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 5.8 Hz), 6.38 (1H, d, *J* = 5.8 Hz), 4.49 (1H, d, *J* = 12.0 Hz), 4.20 (1H, d, *J* = 12.0 Hz), 2.78-2.85 (3H, m), 2.59-2.75 (2H, m), 2.53-2.55 (2H, m), 2.45 (2H, broad s), 2.27 (3H, s); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.4, 170.0,

162.9, 136.2, 69.0, 68.4, 55.2, 47.54, 45.9, 41.9, 31.0. **HRMS (ESI-MS)** *m/z* calcd for $C_{13}H_{18}N_2O_3$ $[M + H]^+$ 251.13957, found 251.13839

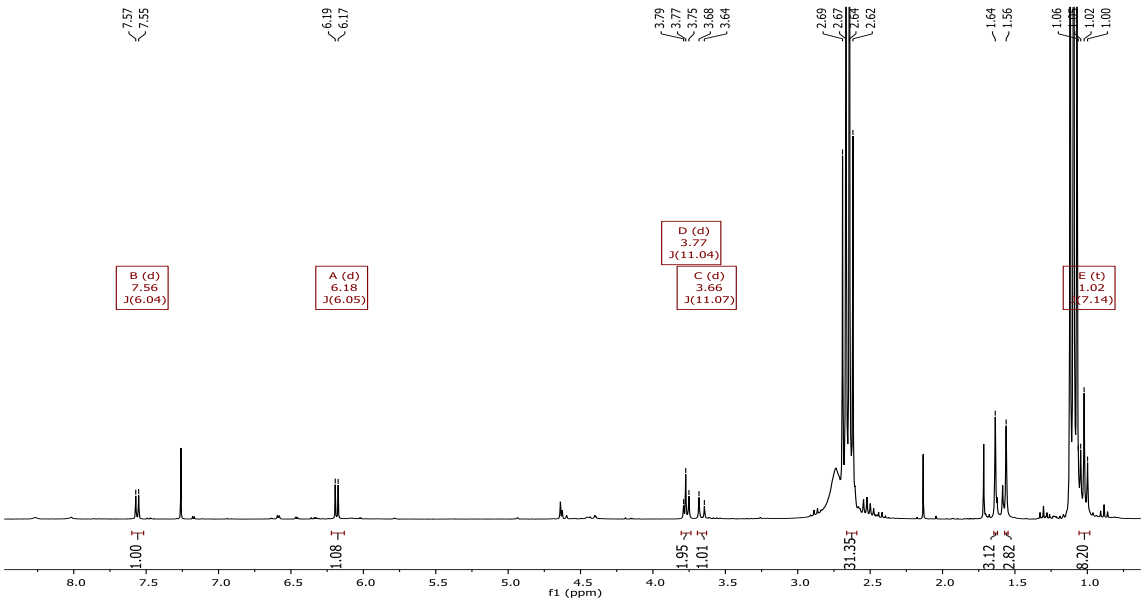


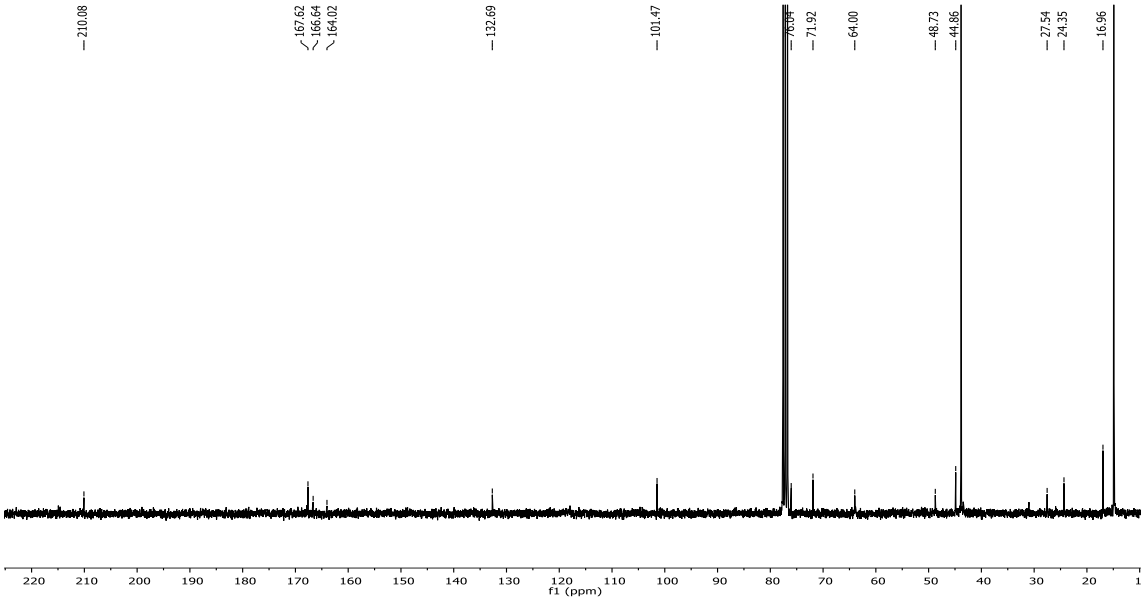
Identification of reaction intermediate

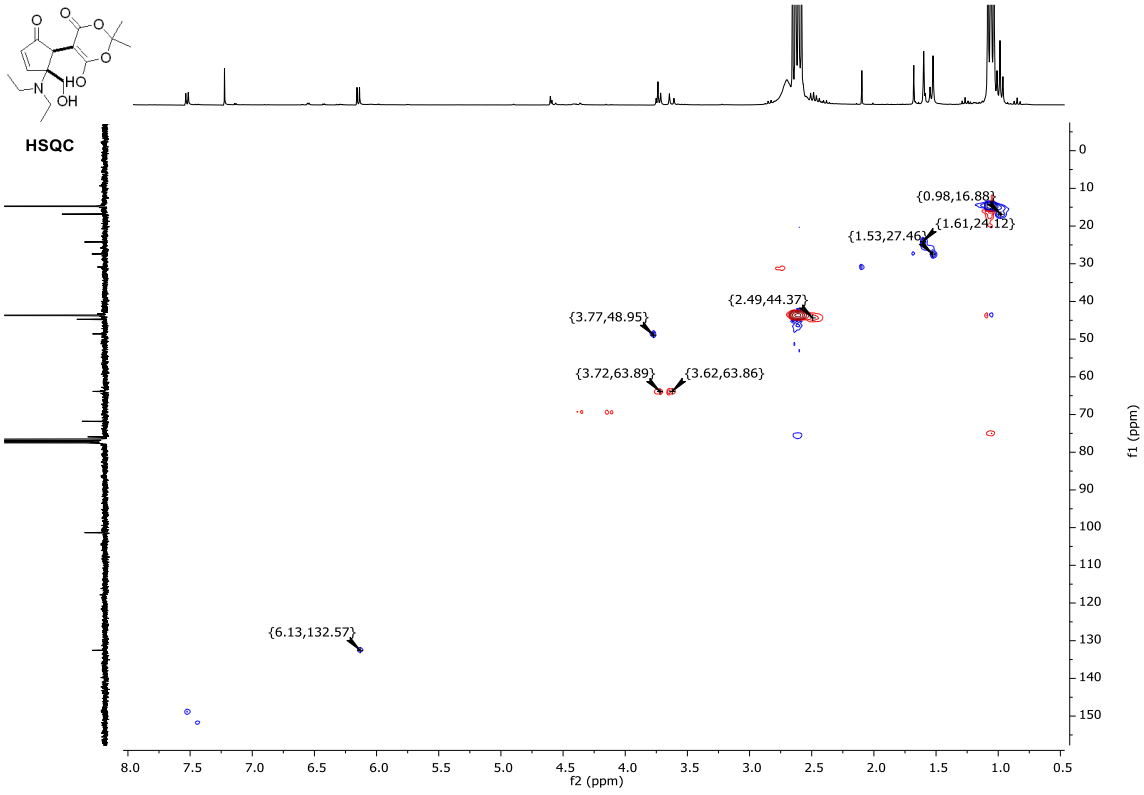
To a solution of **121** (10 mg, 0.04 mmol) in $CDCl_3$ (0.4 mL) was added diethylamine (10 equiv, 0.4 mmol) and the resulting mixture transfer to an NMR tube. The reaction was monitored by ^1H NMR every 30 min. After achieving maximum formation of **reaction intermediate** (*ca.* 6 h), additional ^{13}C and two-dimensional NMR experiments were performed to characterize the structure of this intermediate.



^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 6.0 Hz), 6.18 (1H, d, *J* = 6.0 Hz), 3.77 (1H, d, *J* = 11.0 Hz), 3.75 (1H, s), 3.66 (1H, d, *J* = 11.0 Hz) 2.62 (4H, m), 1.64 (3H, s), 1.56 (3H, s), 1.02 (6H, t, *J* = 7.1 Hz); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 210.1, 167.6, 166.6, 164.0, 132.7, 101.5, 76.0, 71.9, 64.0, 48.7, 44.9, 27.5, 24.4, 17.0.




210.08
167.62
166.64
164.02
132.69
101.47
76.04
71.92
64.00
48.73
44.86
27.54
24.35
16.96
f1 (ppm)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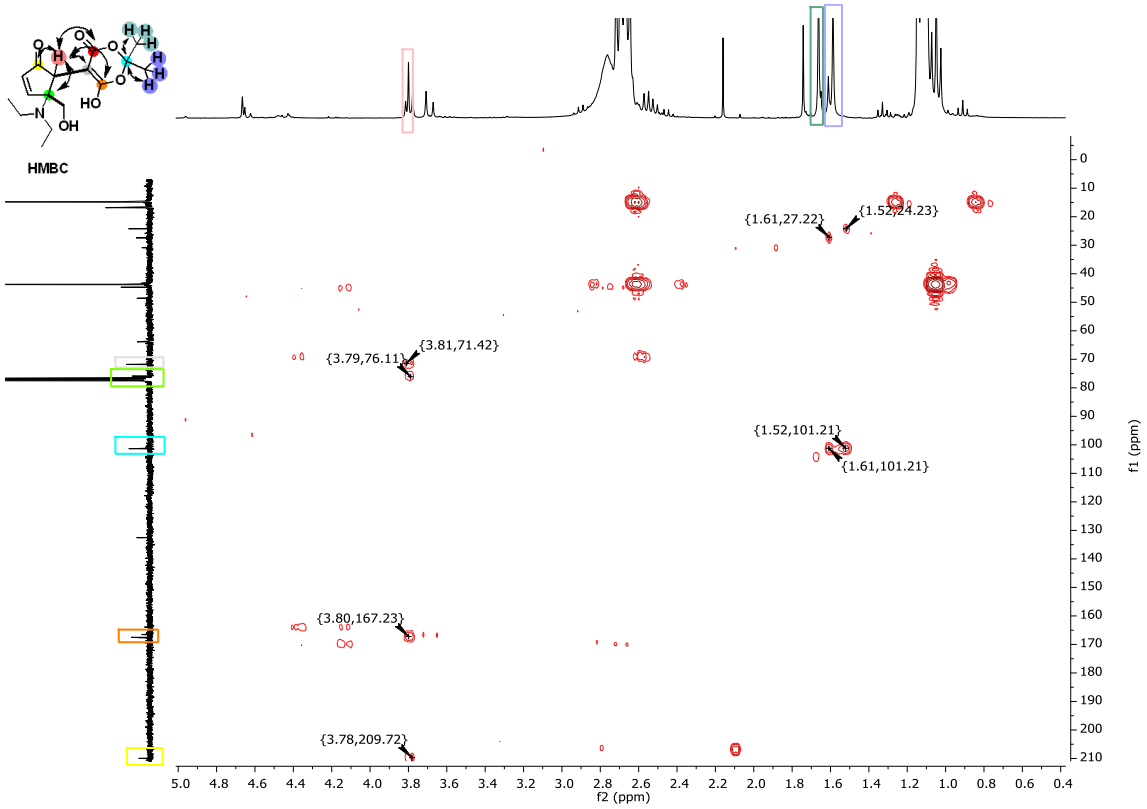
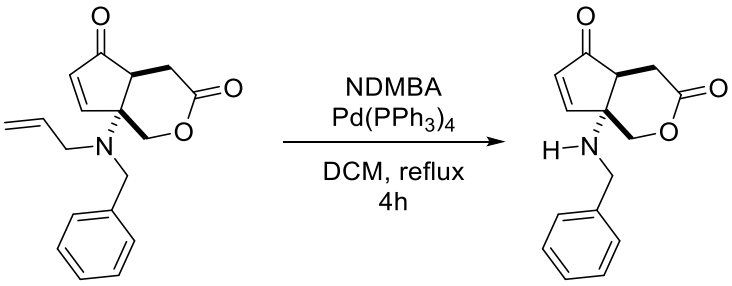
{1.53,27.46}
{2.49,44.37}
{3.77,48.95}
{3.72,63.89}
{3.62,63.86}
{6.13,132.57}
f2 (ppm)
f1 (ppm)

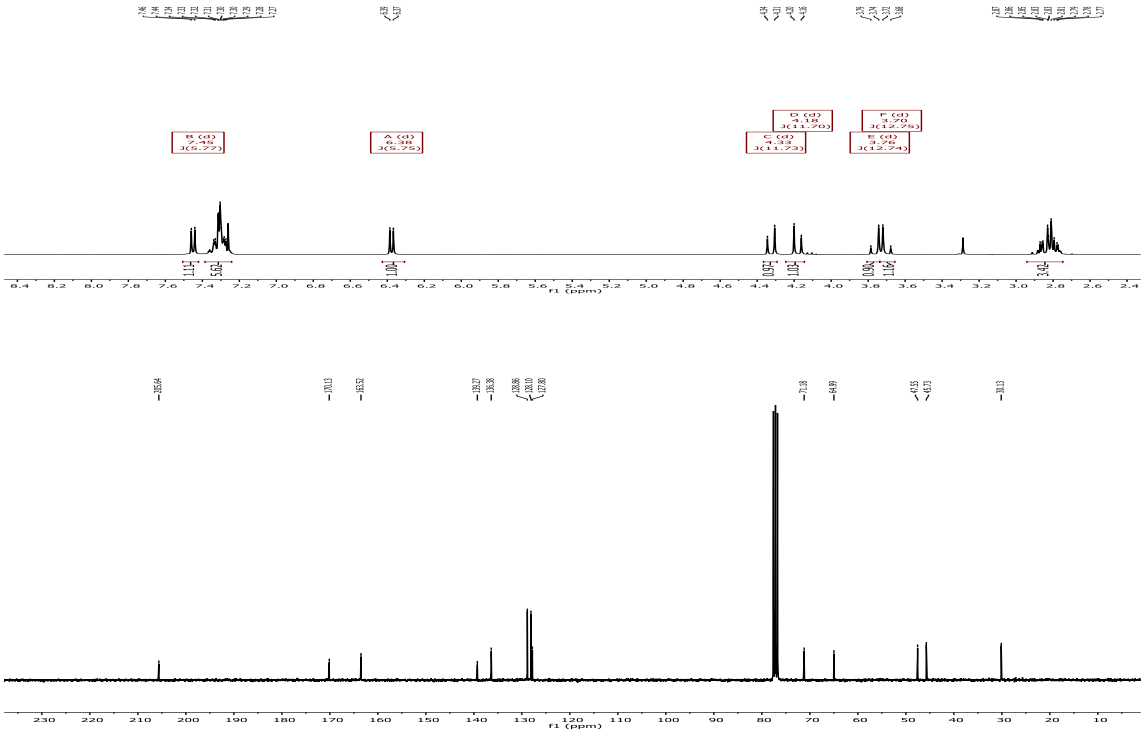

HMBC
{1.61,27.22}
{1.52,24.23}
{3.79,76.11}
{3.81,71.42}
{1.52,101.21}
{1.61,101.21}
{3.80,167.23}
{3.78,209.72}
f2 (ppm)
f1 (ppm)

7a-(benzylamino)-1,4,4a,7a-tetrahydrocyclopenta[c]pyran-3,5-dione 155

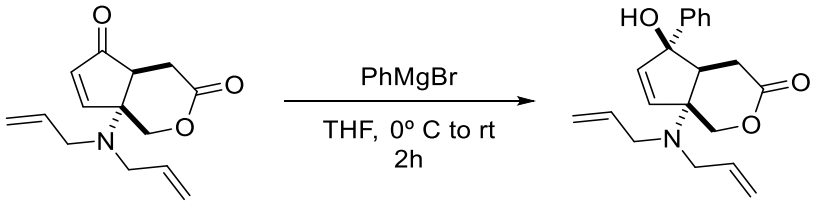


A previously flame dried Schleck was loaded with $Pd(PPh)_3$ (39 mg, 0.034 mmol). A solution of **142** (100 mg, 0.34 mmol) in anhydrous DCM (3 mL) was added. *N,N*-dimethylbarbituric acid (NDMBA, 210 mg, 1.35 mmol) was added and the mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure and the crude mixture was dissolved in ethyl acetate (10 mL) and washed with 1 N NaOH (aq.) (10 mL) and then brine (10 mL). The organic phase was dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the product was further purified by flash chromatography using hexane:ethyl acetate (8:2 to 1:9) affording 79.5 mg (92% yield) of pure product as white crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (1H, d, *J* = 5.8 Hz), 7.27-7.34 (5H, m), 6.38 (1H, d, *J* = 5.8 Hz), 4.33 (1H, d, *J* = 12.0 Hz), 4.18 (1H, d, *J* = 12.0 Hz), 3.76 (1H, d, *J* = 12.8 Hz), 3.70 (1H, d, *J* = 12.8 Hz), 2.77-2.87 (3H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 205.6, 170.1, 163.5, 139.4, 128.9, 128.1, 127.8, 71.18, 65.0, 47.6, 45.7, 30.1 **HRMS (ESI-MS)** *m/z* calcd for $C_{15}H_{15}NO_3$ $[M + H]^+$ 258.1130, found 258.1135.

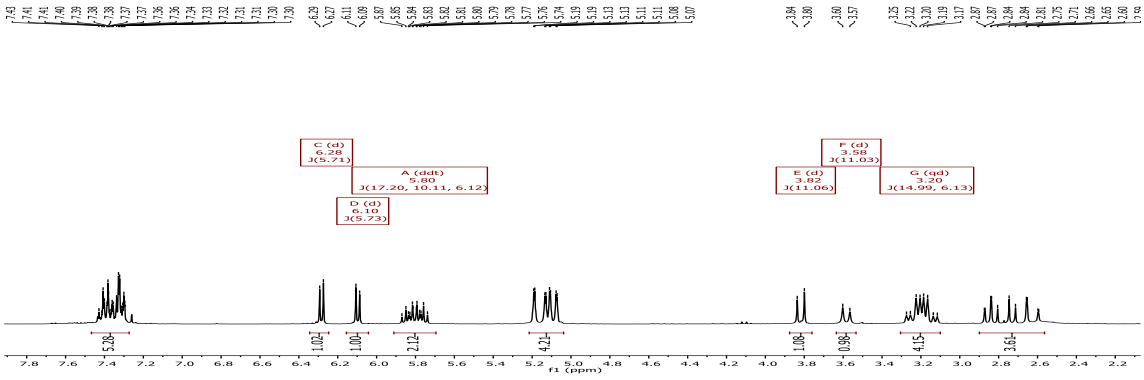


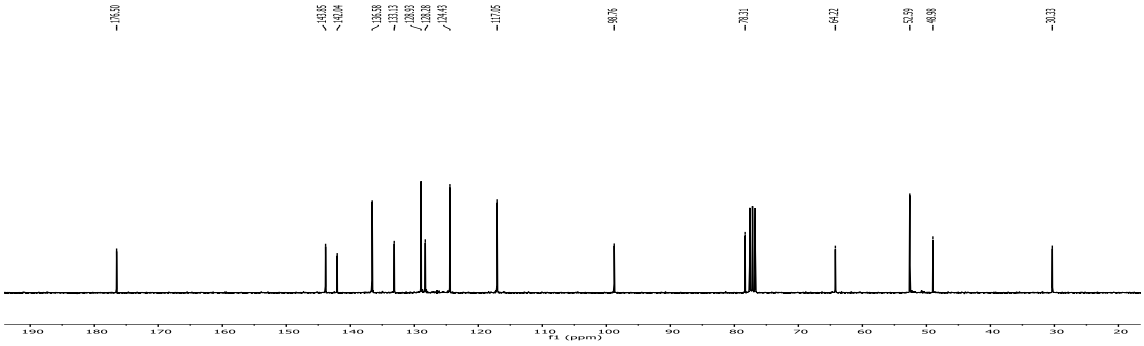
7a-(diallylamino)-5-hydroxy-5-phenyl-4,4a,5,7a-tetrahydrocyclopenta[c]pyran-3(1H)-one 149



A previously flame dried Schleck was loaded with a solution of **136** (100 mg, 0.4 mmol) in anhydrous THF (4 mL). A PhMgBr solution in THF (1 M, 404 µL, 1 equiv, 0.4 mmol) was added at 0ºC and the reaction was stirred and allowed to warm up to room temperature for 2 h. The reaction was quenched by addition of a sat. aq. sol. of NH_4Cl (15 mL) and extracted with DCM (3 × 15 mL). The combined organic phases were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the product was purified by flash chromatography using hexane:ethyl acetate (9:1 to 5:5) affording 105 mg (80% yield) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.43 (5H, m), 6.28 (1H, d, *J* = 5.7 Hz), 6.10 (1H, d, *J* = 5.7 Hz), 5.8 (2H, ddt, *J* = 17.2, 10.1, 6.1 Hz), 5.07-5.19 (4H, m), 3.82 (1H, d, *J* = 11.1 Hz), 3.58 (1H, d, *J* = 11.0 Hz), 3.20 (4H, qd, *J* = 15.0, 6.1 Hz), 2.59-2.87 (3H, m). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 176.5, 143.9, 142.0, 136.6, 133.1, 128.9, 128.3, 235.4, 117.1, 98.8, 78.3, 64.2, 52.6, 49.0, 30.3. **HRMS (ESI-MS)** *m/z* calcd for $C_{20}H_{23}NO_3$ $[M + H]^+$ 326.17562, found 326.17554.

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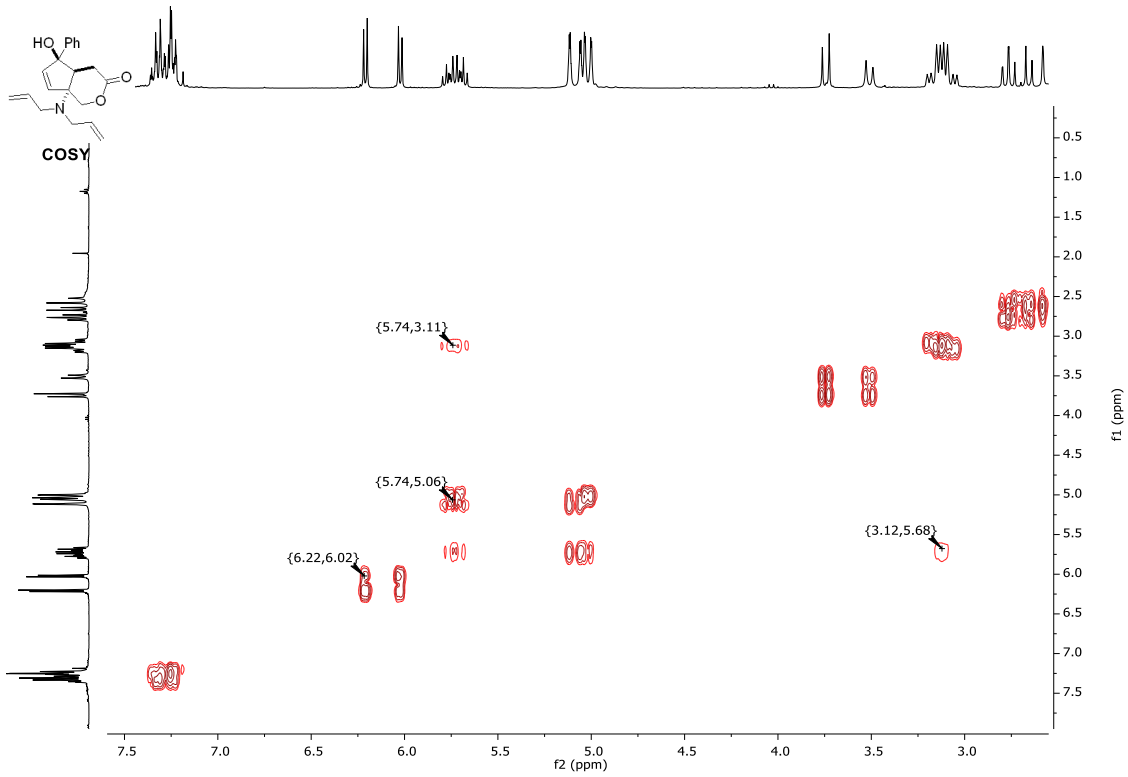
143.85
142.04
136.58
133.13
128.93
128.28
124.45
117.05
98.76
70.31
64.22
52.39
48.08
30.33
f1 (ppm)


HO
Ph
O
O
N
COSY
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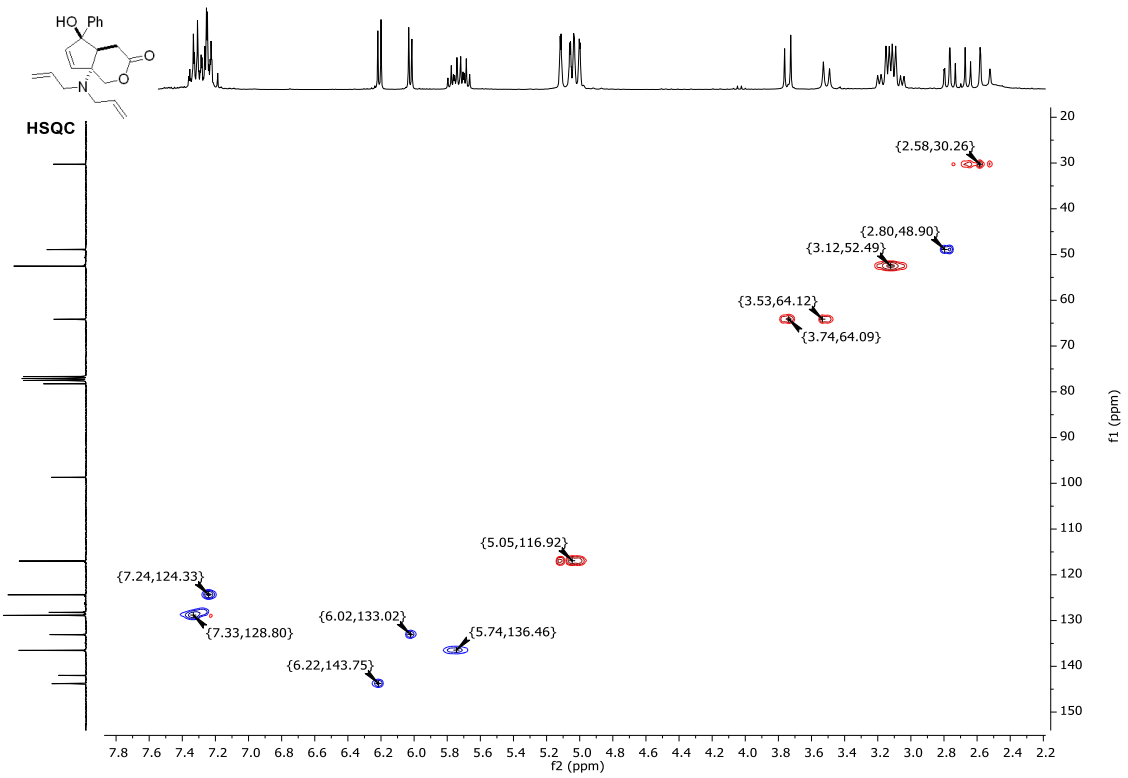
{5.74,5.06}
{6.22,6.02}
{3.12,5.68}
f2 (ppm)
f1 (ppm)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Ph
O
N
O
HSQC
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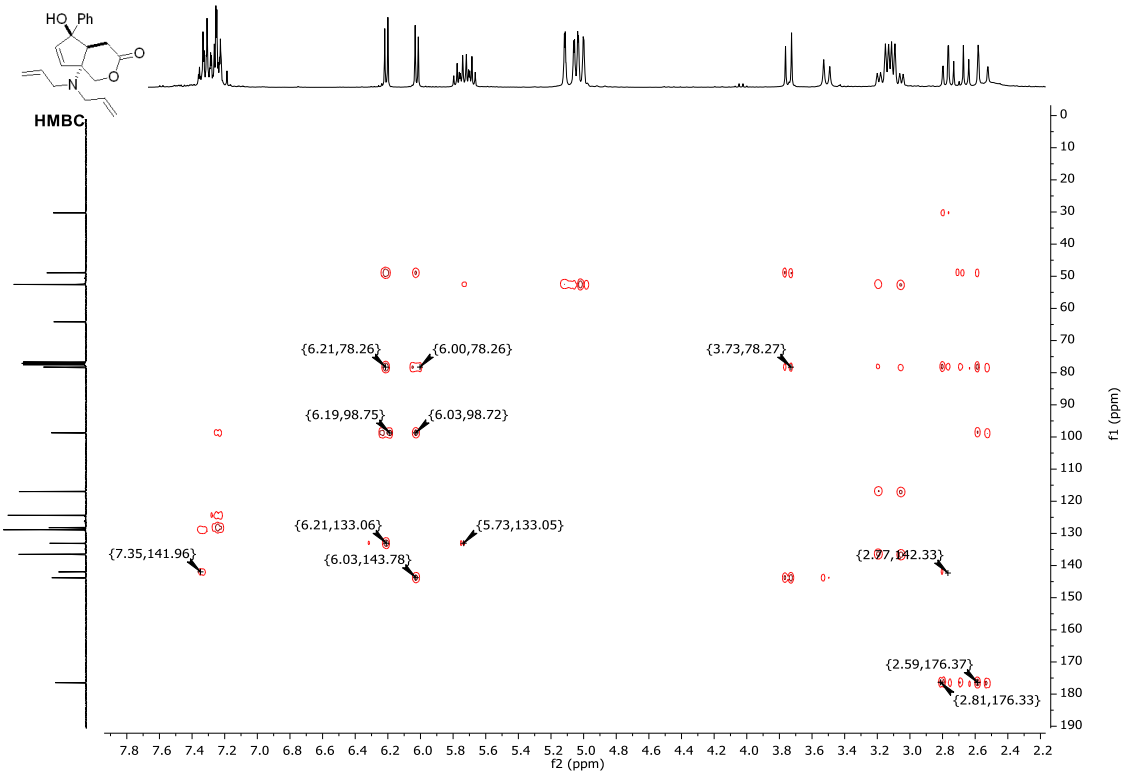
{6.22,143.75}
f1 (ppm)
f2 (ppm)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Ph
O
N
O
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{6.03,143.78}
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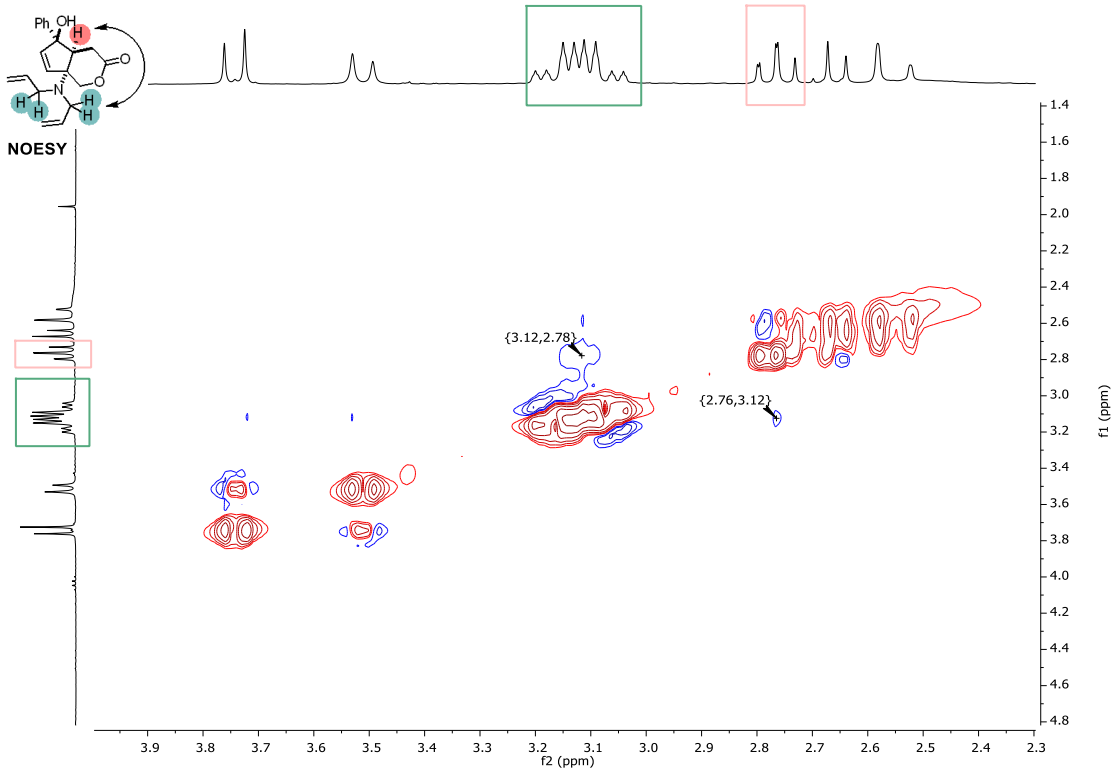
{2.81,176.33}
f1 (ppm)
f2 (ppm)


NOESY
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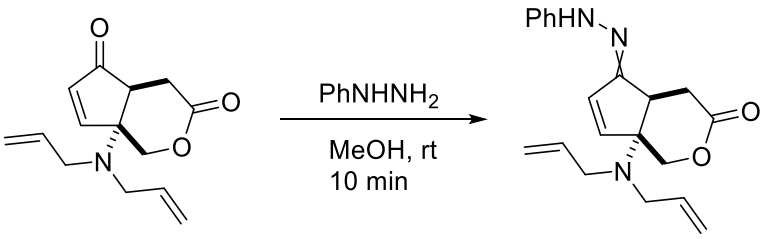
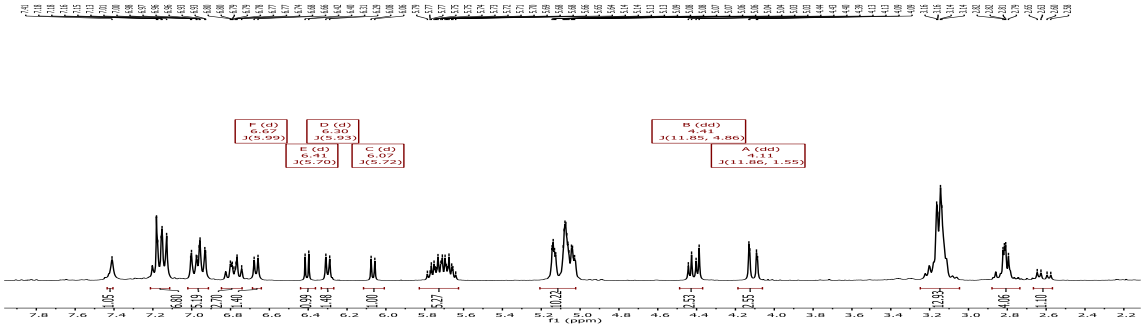
{2.76,3.12}
f2 (ppm)
f1 (ppm)

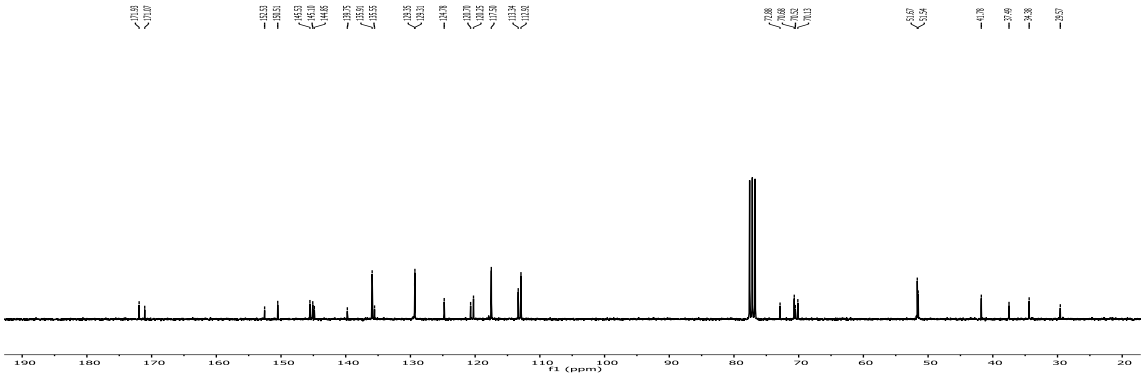
7a-(diallylamino)-5-(2-phenylhydrazineylidene)-4,4a,5,7a-tetrahydrocyclopenta[c]pyran-3(1H)-one 148

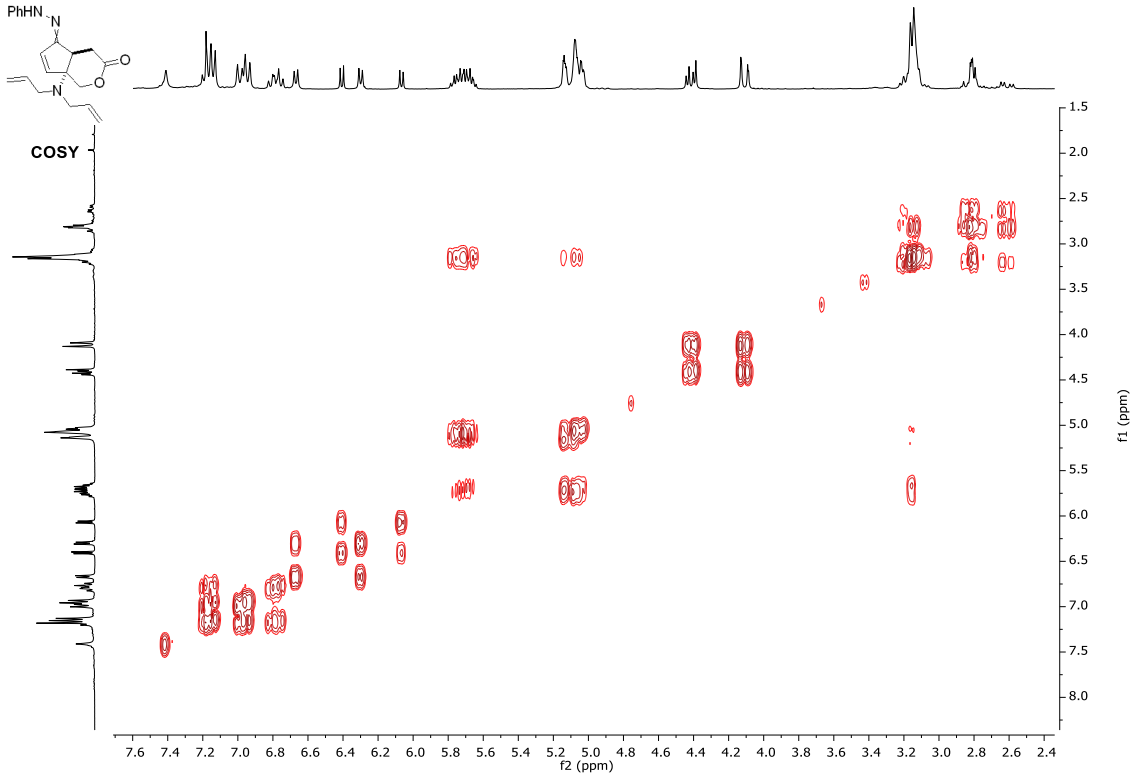


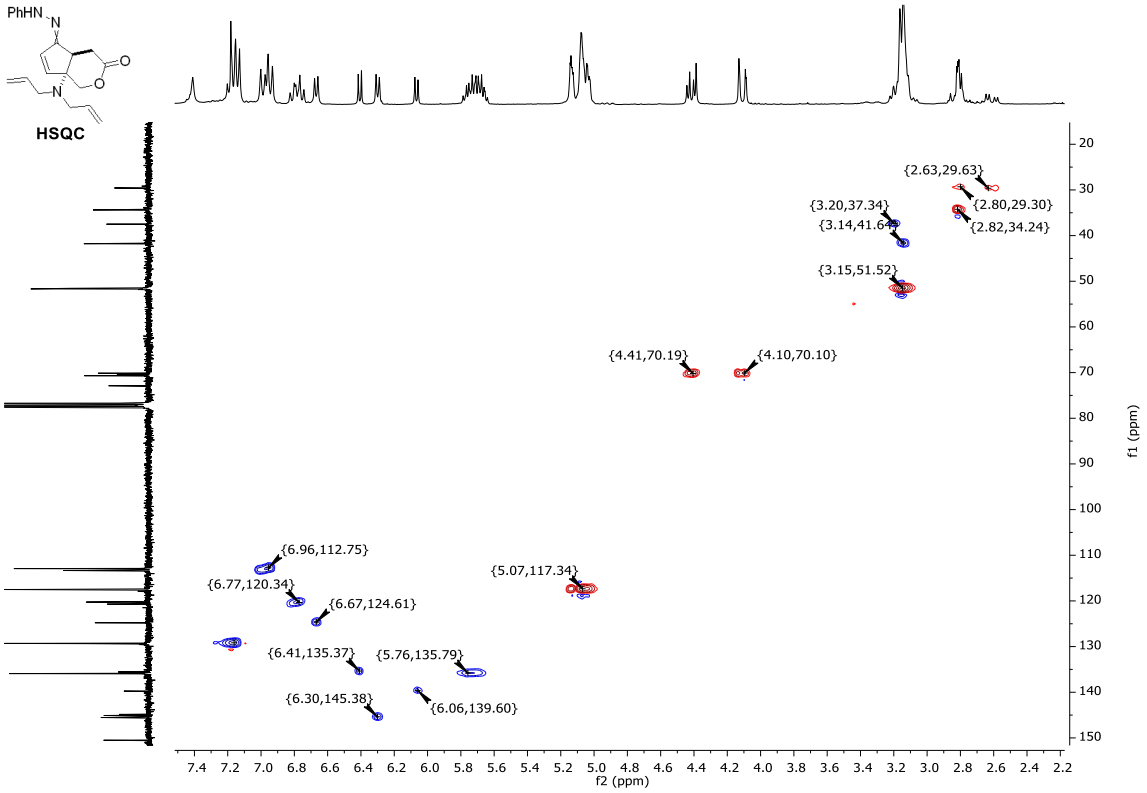
To a solution of **136** (100 mg, 0.4 mmol) in anhydrous MeOH (4 mL) was added phenylhydrazine (5 equiv, 200 µl, 2.02 mmol). The solution was allowed to stir for 10 min. The solvent was evaporated under reduce pressure, the crude mixture was washed with cold diethyl ether to remove excess hydrazine. The product was further purified by flash chromatography using hexane:ethyl acetate (9:1 to 5:5) affording 103 mg (76% yield) of a mixture of two isomers as a brown oil.

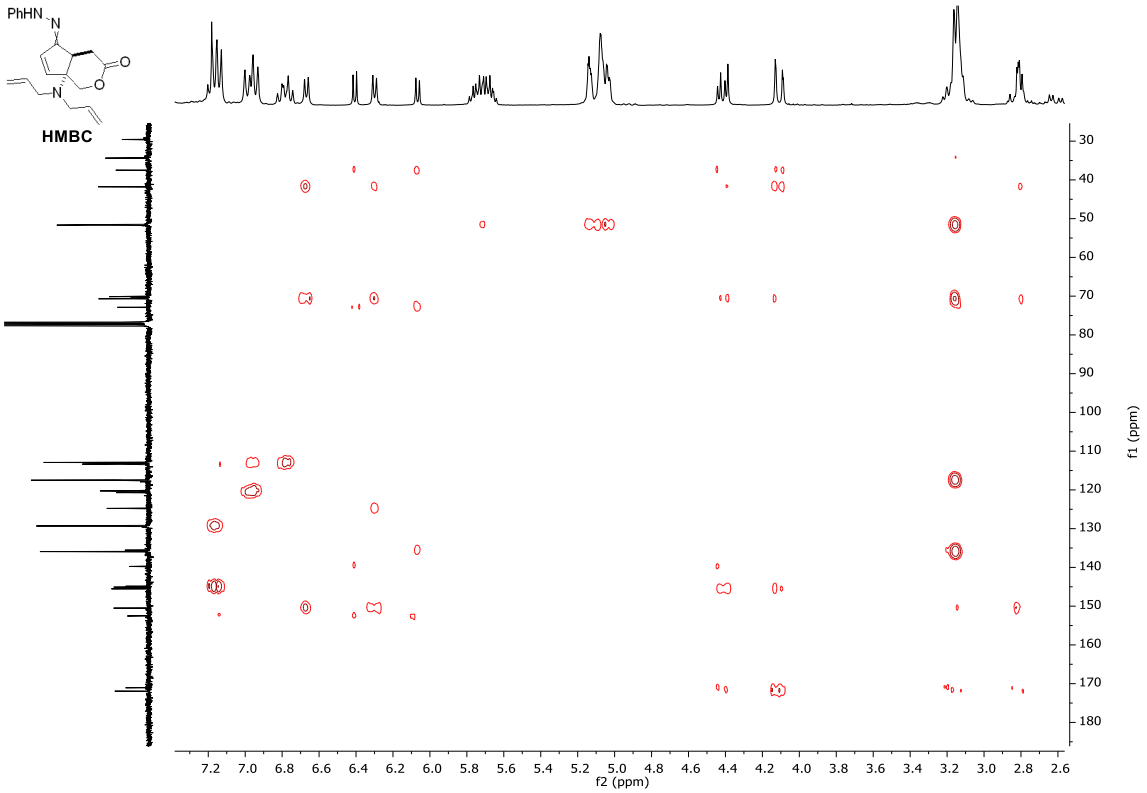
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, broad s), 7.00-7.18 (6H, m), 6.93-6.98 (5H, m), 6.74-6.8 (2H, m) 6.67 (1.4H, d, J = 6.0 Hz), 6.41 (1H, d, J = 5.7 Hz), 6.30 (1.4H, d, J = 5.9 Hz), 6.07 (1H, d, J = 5.7 Hz), 5.64-5.79 (2H, m), 5.03-5.14 (4H, m), 4.41 (2.5H, dd, J = 11.9, 4.9 Hz), 4.11 (2.5H, dd, J = 11.9, 1.6 Hz), 3.14-3.16 (12H, m), 2.79-2.82 (4H, m), 2.58-2.65 (1H, m); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 171.9, 171.1, 152.5, 150.5, 145.5, 145.1, 144.9, 139.8, 135.9, 135.6, 129.4, 129.3, 124.8, 120.7, 120.3, 117.5, 113.3, 112.9, 72.9, 70.7, 70.5, 70.1, 51.7, 51.5, 41.8, 37.5, 34.4, 29.6. **HRMS (ESI-MS)** *m/z* calcd for $C_{20}H_{22}N_3O_2$ $[M - H]^-$ 336.17175, found 336.17059.

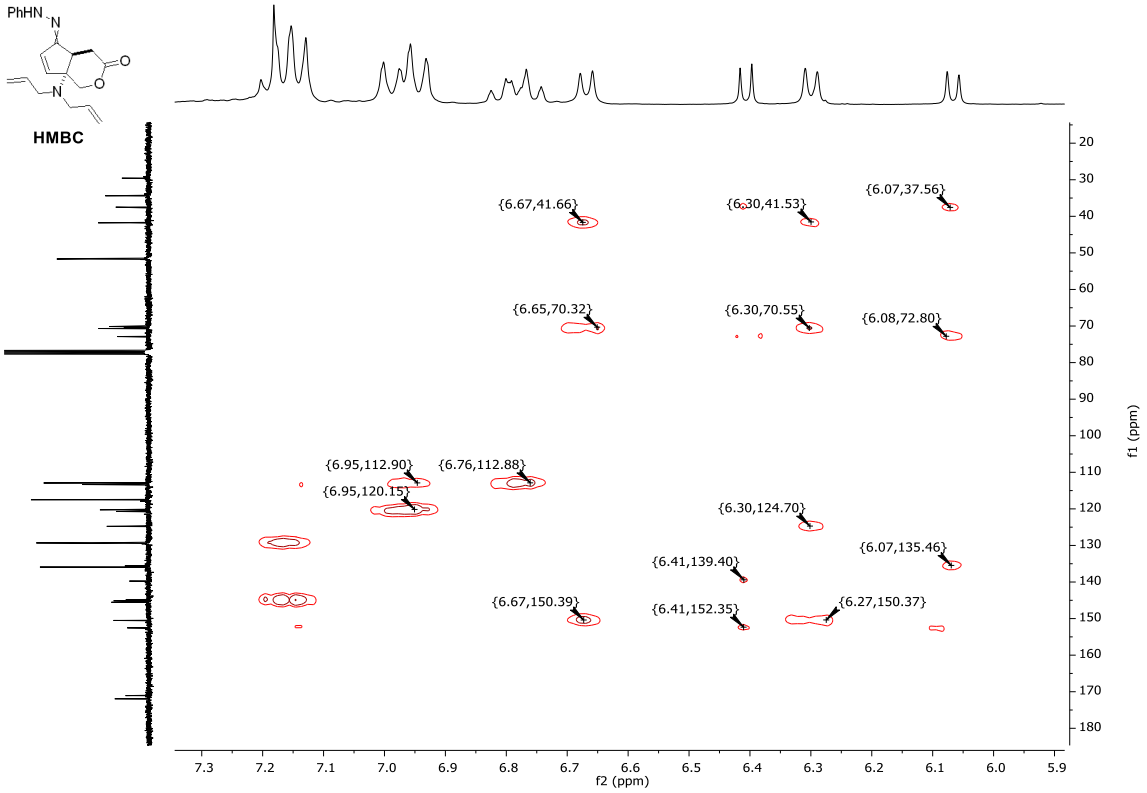


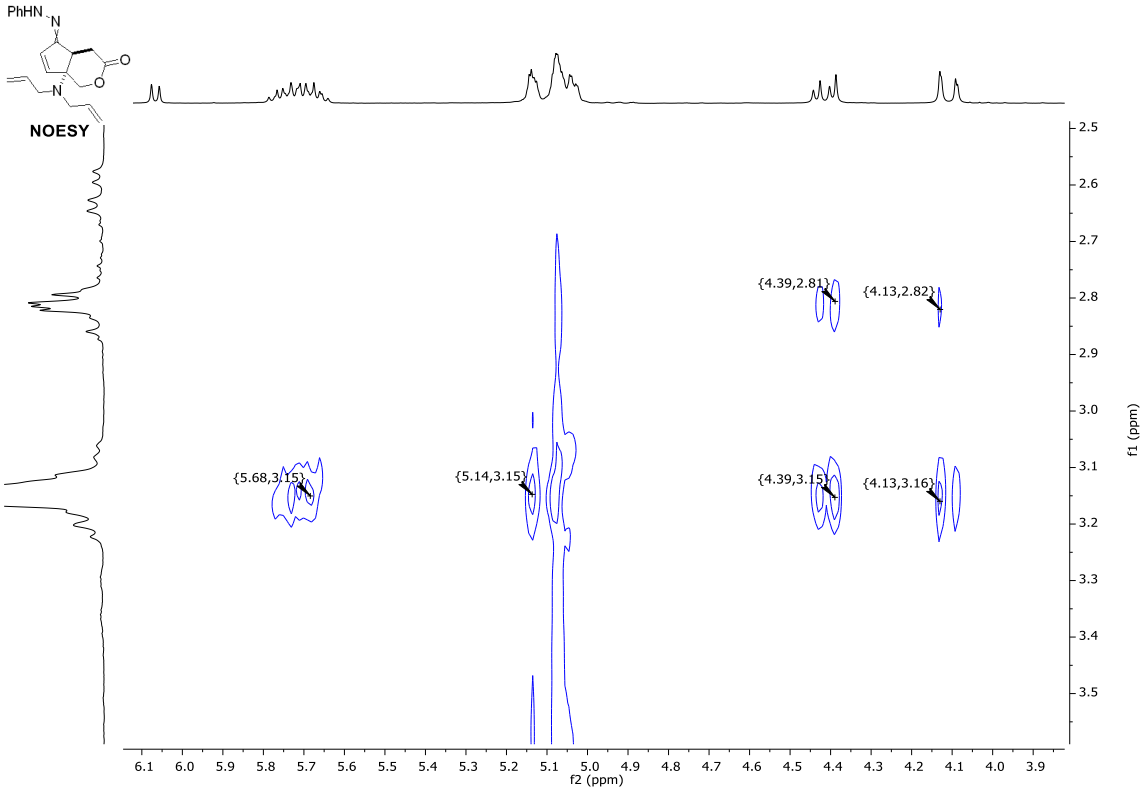



PhHN
N
O
O
N
COSY
f2 (ppm)
f1 (ppm)

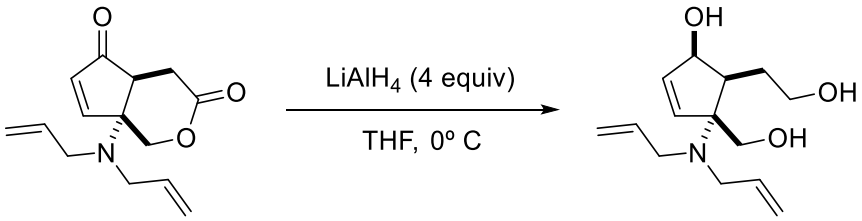

PhHN
N
O
O
N
HSQC
{2.63,29.63}
{2.80,29.30}
{2.82,34.24}
{3.20,37.34}
{3.14,41.64}
{3.15,51.52}
{4.41,70.19}
{4.10,70.10}
{6.96,112.75}
{6.77,120.34}
{6.67,124.61}
{5.07,117.34}
{6.41,135.37}
{5.76,135.79}
{6.30,145.38}
{6.06,139.60}
f1 (ppm)
f2 (ppm)


PhHN
N
O
O
N
HMBC
f1 (ppm)
f2 (ppm)


PhHN
N
O
O
N
HMBC
{6.67,41.66}
{6.30,41.53}
{6.07,37.56}
{6.65,70.32}
{6.30,70.55}
{6.08,72.80}
{6.95,112.90}
{6.76,112.88}
{6.95,120.15}
{6.30,124.70}
{6.07,135.46}
{6.41,139.40}
{6.67,150.39}
{6.41,152.35}
{6.27,150.37}
f1 (ppm)
f2 (ppm)

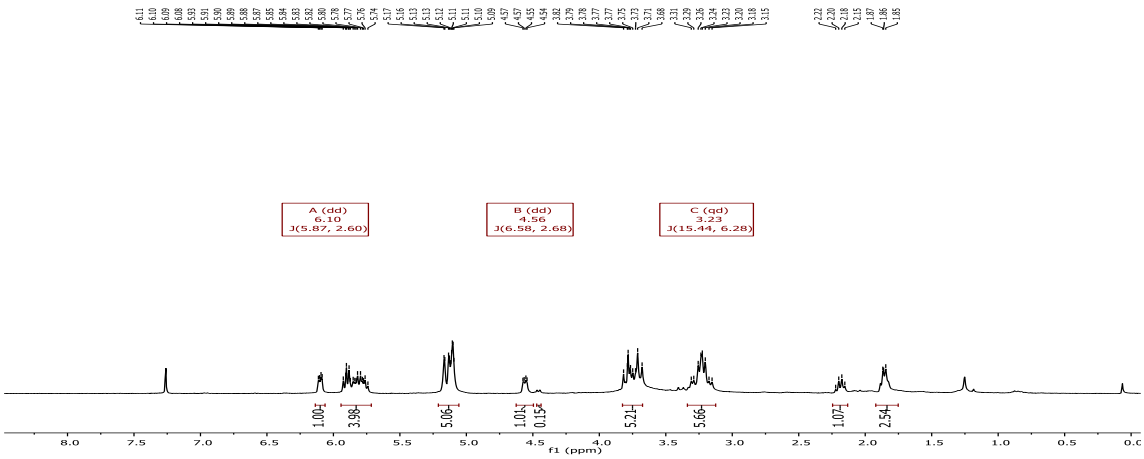

PhHN
N
O
O
N
NOESY
{4.39,2.81}
{4.13,2.82}
{5.68,3.15}
{5.14,3.15}
{4.39,3.15}
{4.13,3.16}
f1 (ppm)
f2 (ppm)

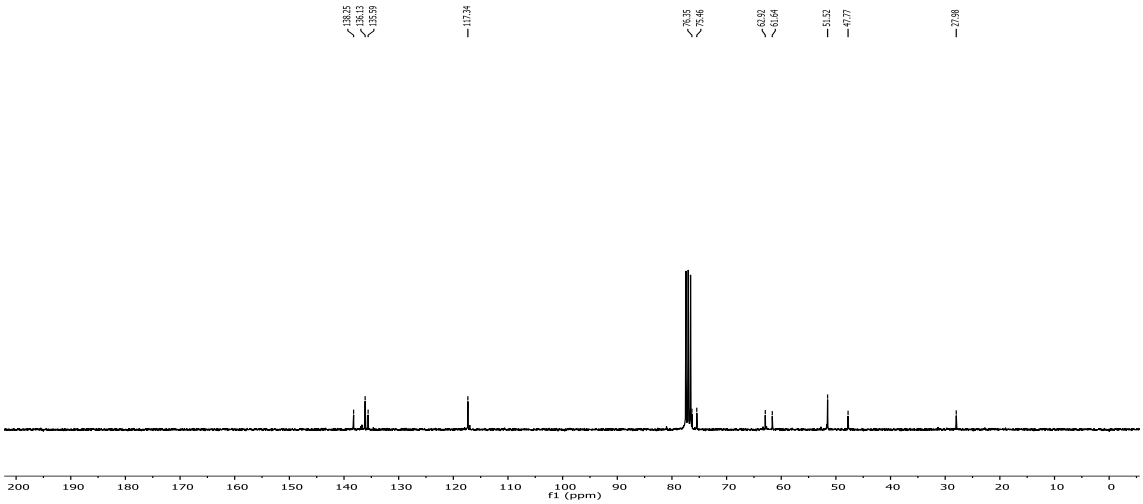
4-(diallylamino)-5-(2-hydroxyethyl)-4-(hydroxymethyl)cyclopent-2-en-1-ol 151

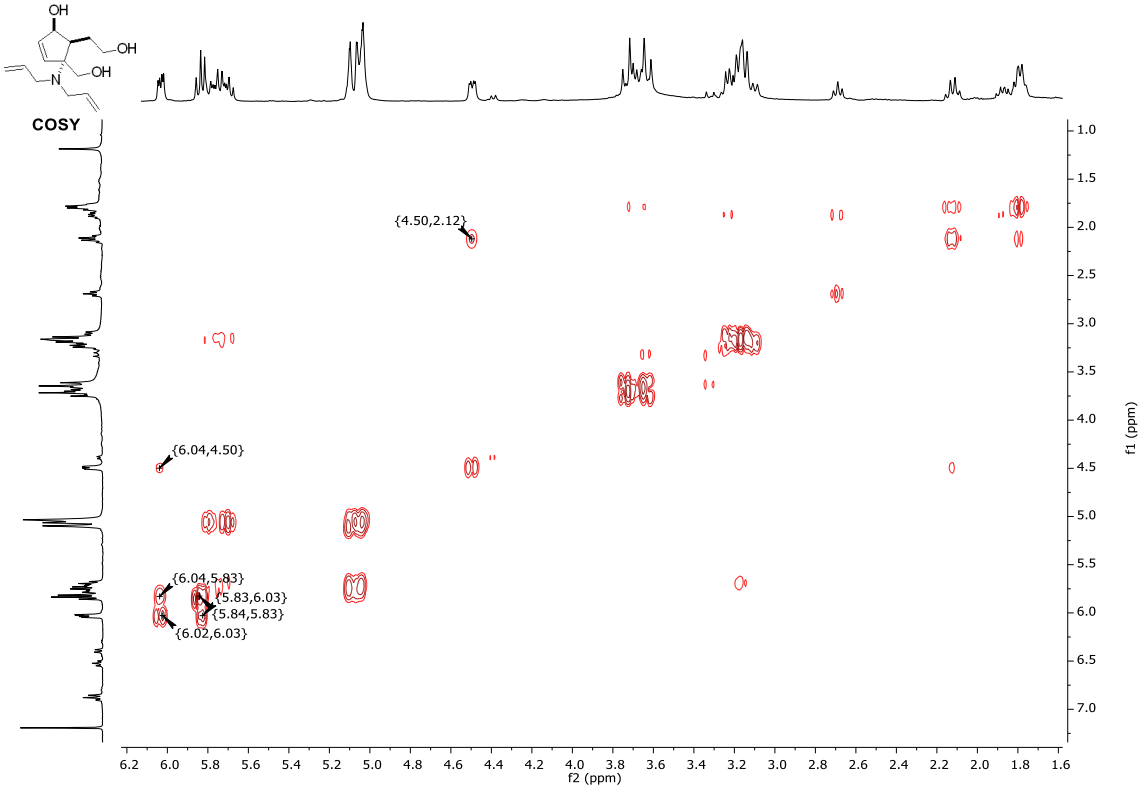


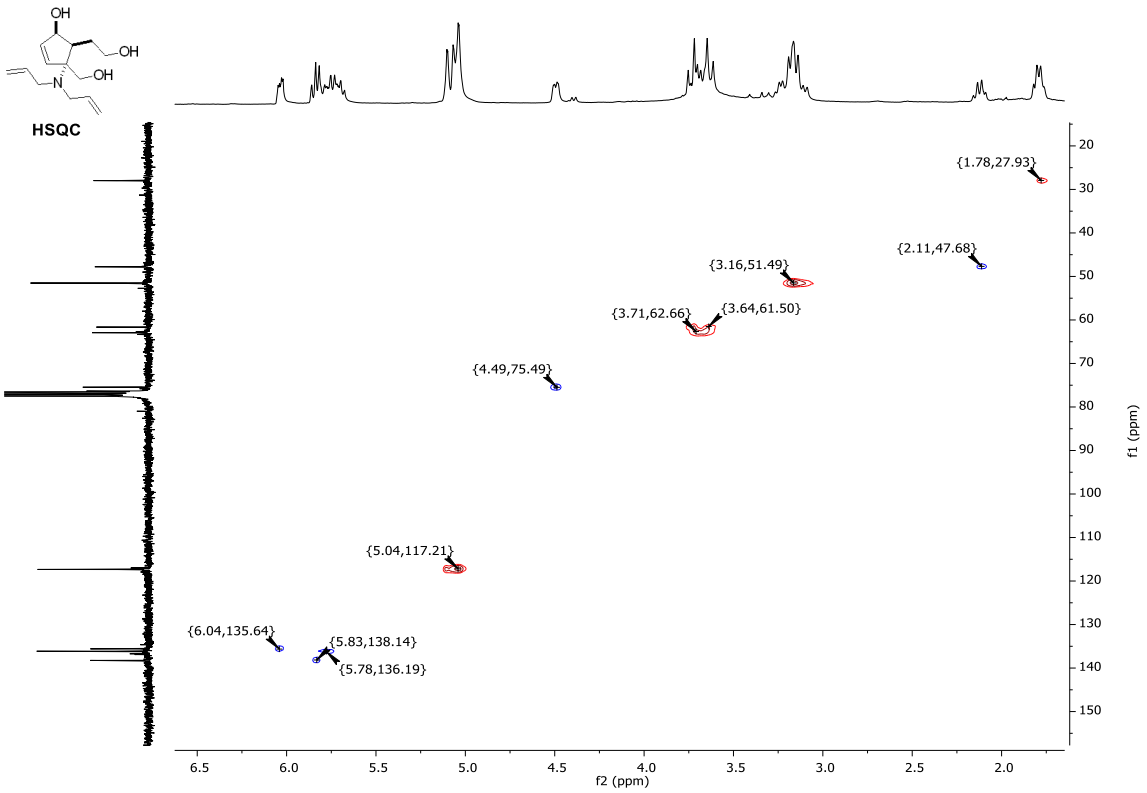
To a solution of **136** (100 mg, 0.4 mmol) in anhydrous THF (4 mL) was added $LiAlH_4$ (4 equiv, 61 mg, 1.62 mmol) at 0º C. The reaction was stirred until total consumption of the starting material. The reaction was quenched by the addition of water (30 µL) and the Li salts were filtered through a pad of celite. The solvent was evaporated under reduced pressure affording 72 mg (70% yield) of pure product as a white oil.

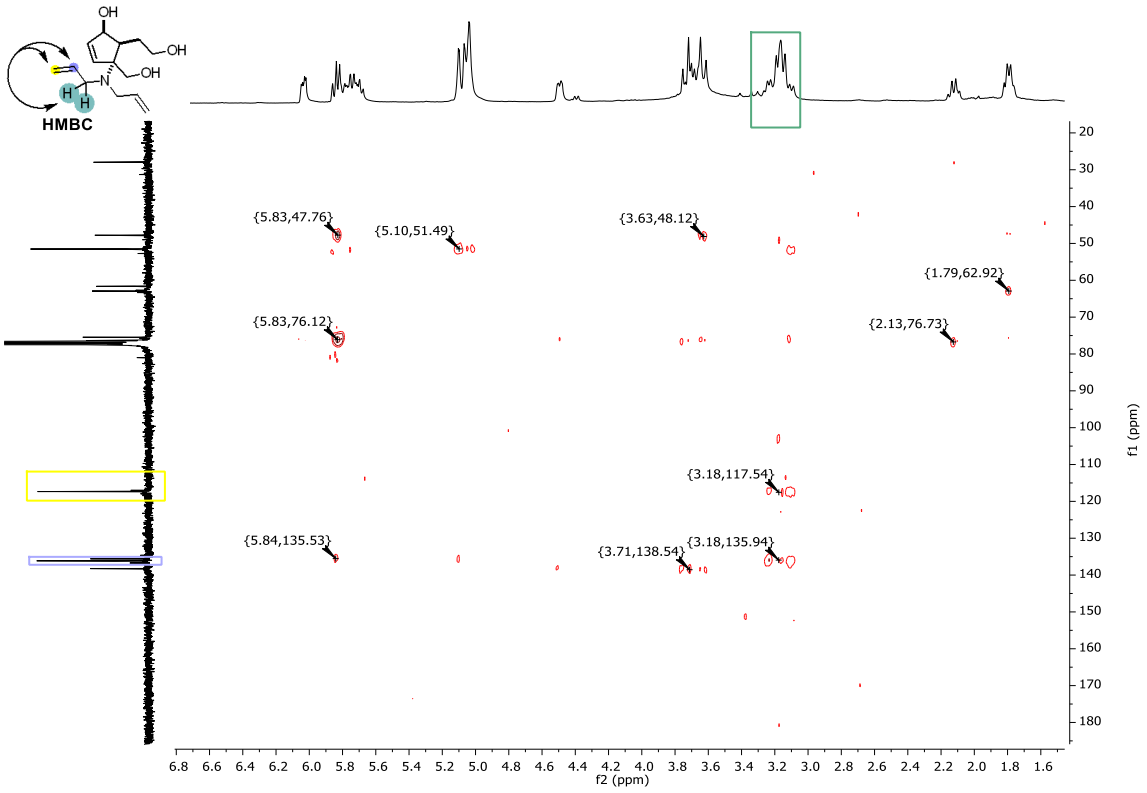
^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.10 (1H, dd, *J* = 5.9, 2.6 Hz), 5.74-5.93 (3H, m), 5.09-5.17 (4H, m), 4.56 (1H, dd, *J* = 6.6, 2.7 Hz), 3.68-3.82 (4H, m), 3.23 (4H, qd, *J* = 15.4, 6.3 Hz), 2.15-2.22 (1H, m), 1.85-1.87 (2H, m); **^{13}C NMR**: (75 MHz, $CDCl_3$) δ 138.3, 136.1, 135.6, 117.3, 76.4, 75.5, 62.9, 61.6, 51.5, 47.8, 28.0; **HRMS (ESI-MS)** *m/z* calcd for $C_{14}H_{23}NO_3$ $[M + H]^+$ 254.17562, found 254.17757.

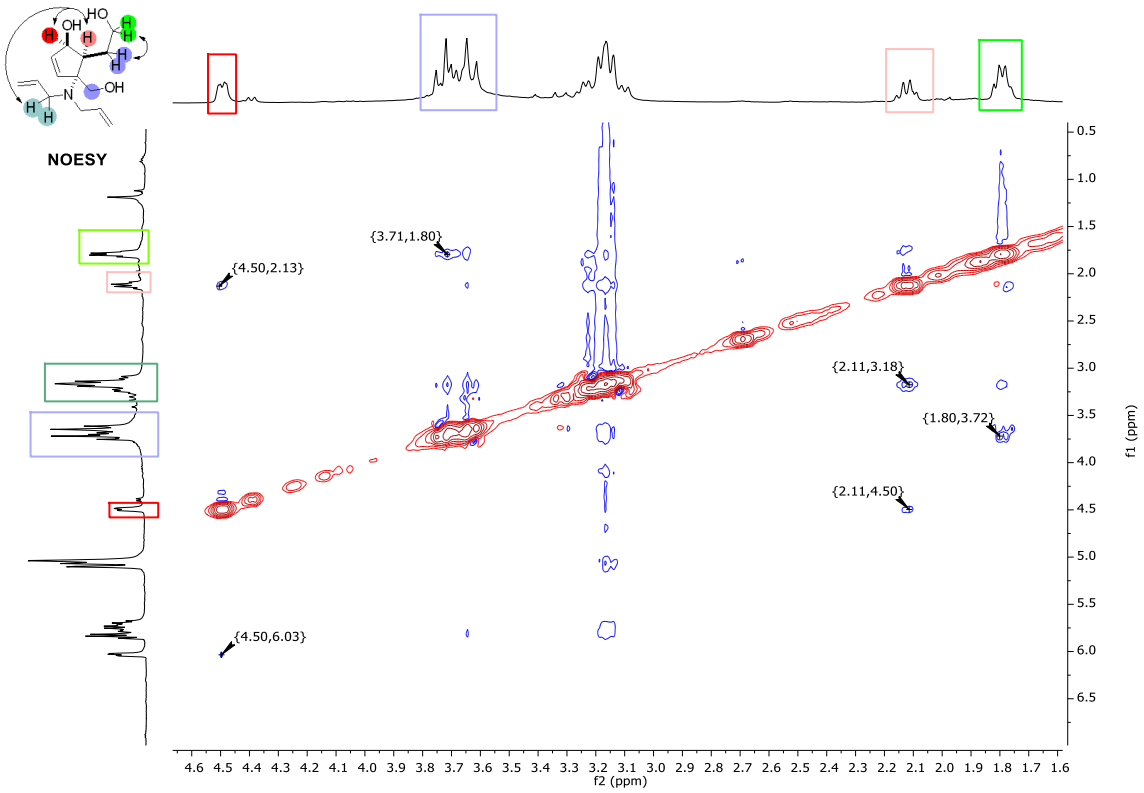



138.25
136.13
135.59
117.34
76.35
75.46
61.92
61.64
51.52
47.77
27.98
f1 (ppm)

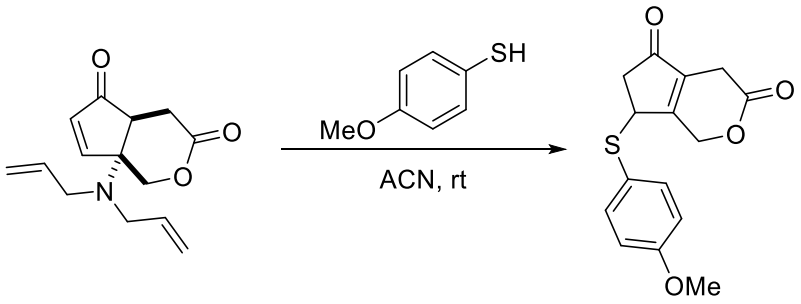

OH
OH
OH
N
COSY
{4.50,2.12}
{6.04,4.50}
{6.04,5.83}
{5.83,6.03}
{5.84,5.83}
{6.02,6.03}
f2 (ppm)
f1 (ppm)


HSQC
{1.78,27.93}
{2.11,47.68}
{3.16,51.49}
{3.71,62.66}
{3.64,61.50}
{4.49,75.49}
{5.04,117.21}
{6.04,135.64}
{5.83,138.14}
{5.78,136.19}
f1 (ppm)
f2 (ppm)


HMBC
{5.83,47.76}
{5.10,51.49}
{3.63,48.12}
{1.79,62.92}
{5.83,76.12}
{2.13,76.73}
{3.18,117.54}
{5.84,135.53}
{3.71,138.54}
{3.18,135.94}
f1 (ppm)
f2 (ppm)

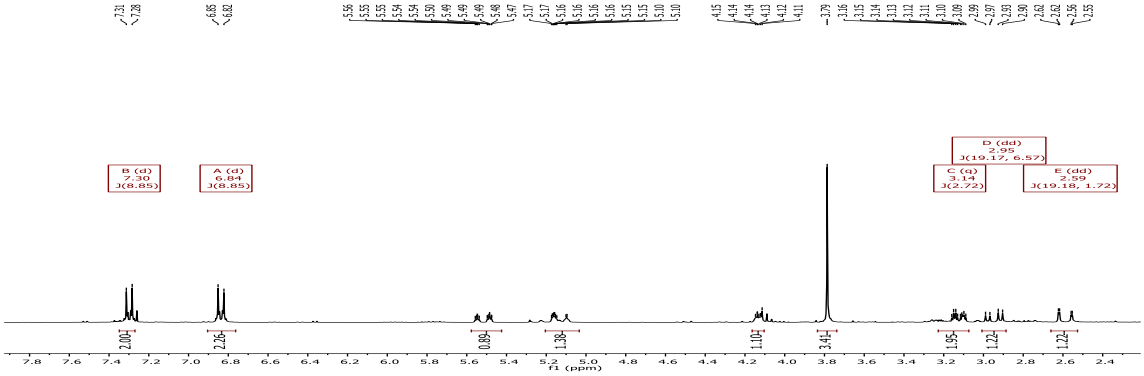

NOESY
{3.71,1.80}
{4.50,2.13}
{2.11,3.18}
{1.80,3.72}
{2.11,4.50}
{4.50,6.03}
f2 (ppm)
f1 (ppm)

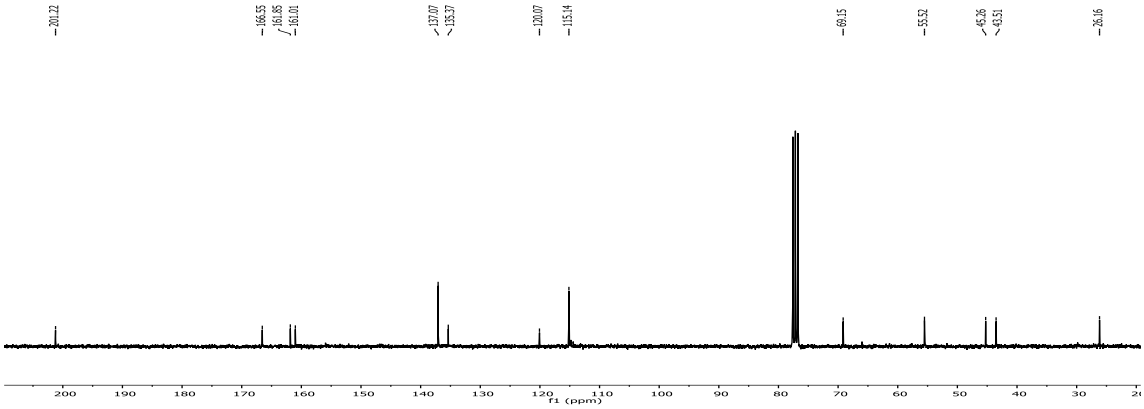
Preparation of 7-((4-methoxyphenyl)thio)-1,4,6,7-tetrahydrocyclopenta[c]pyran-3,5-dione 156

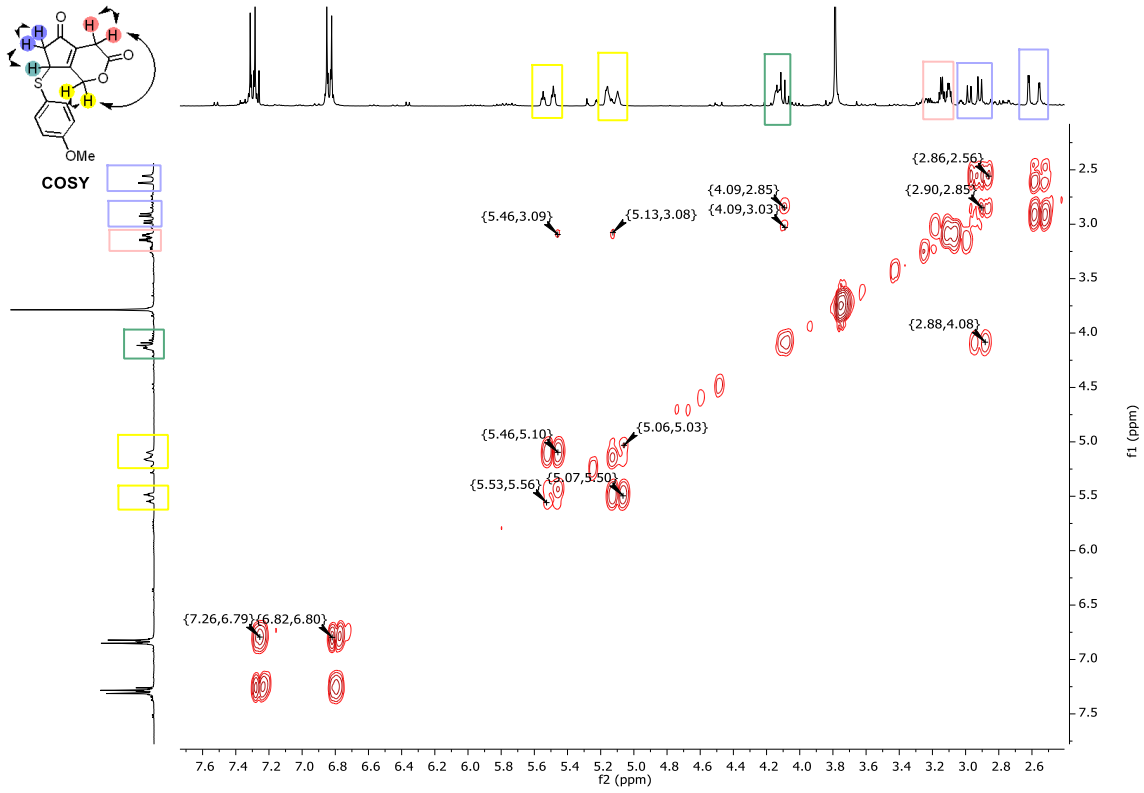


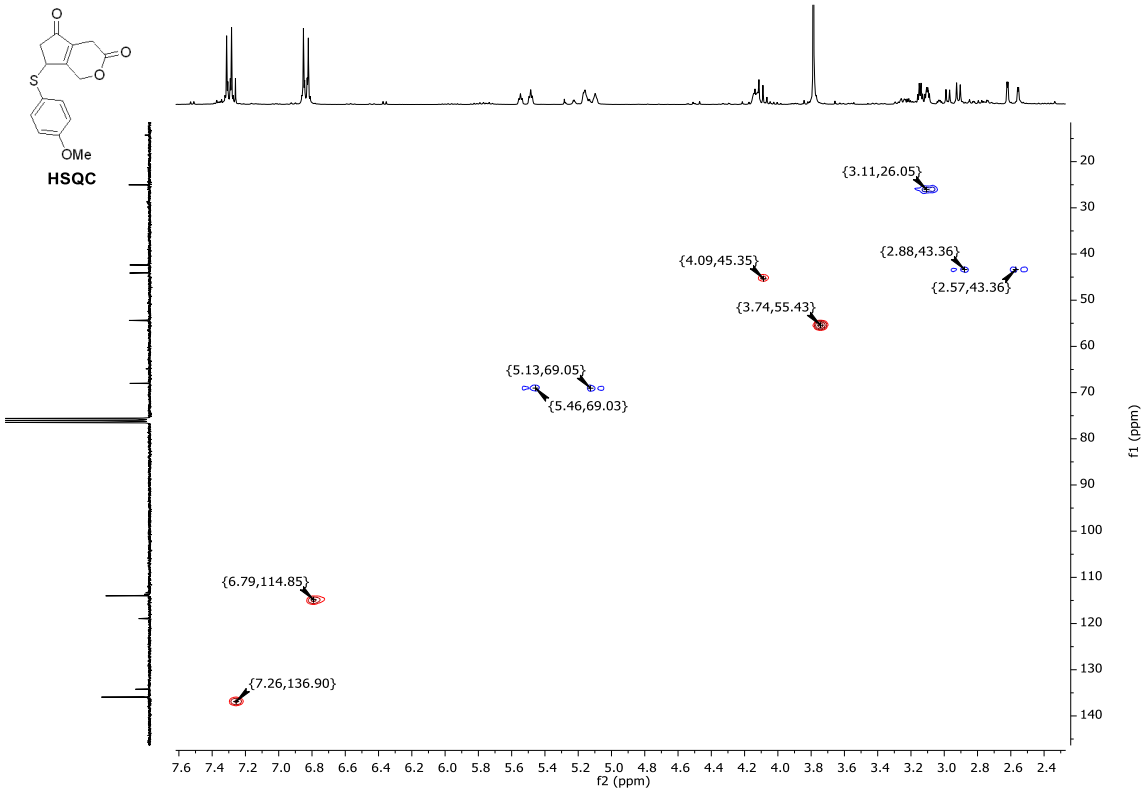
To a solution of **136** (100 mg, 0.40 mmol) in acetonitrile (4 mL) was added 4-methoxythiophenol (100 µl, 0.81 mmol, 2 equiv). The reaction was stirred for 7 h. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography using hexane:ethyl acetate (9:1 to 4:6) affording 96 mg (82% yield) of pure product as a brown oil.

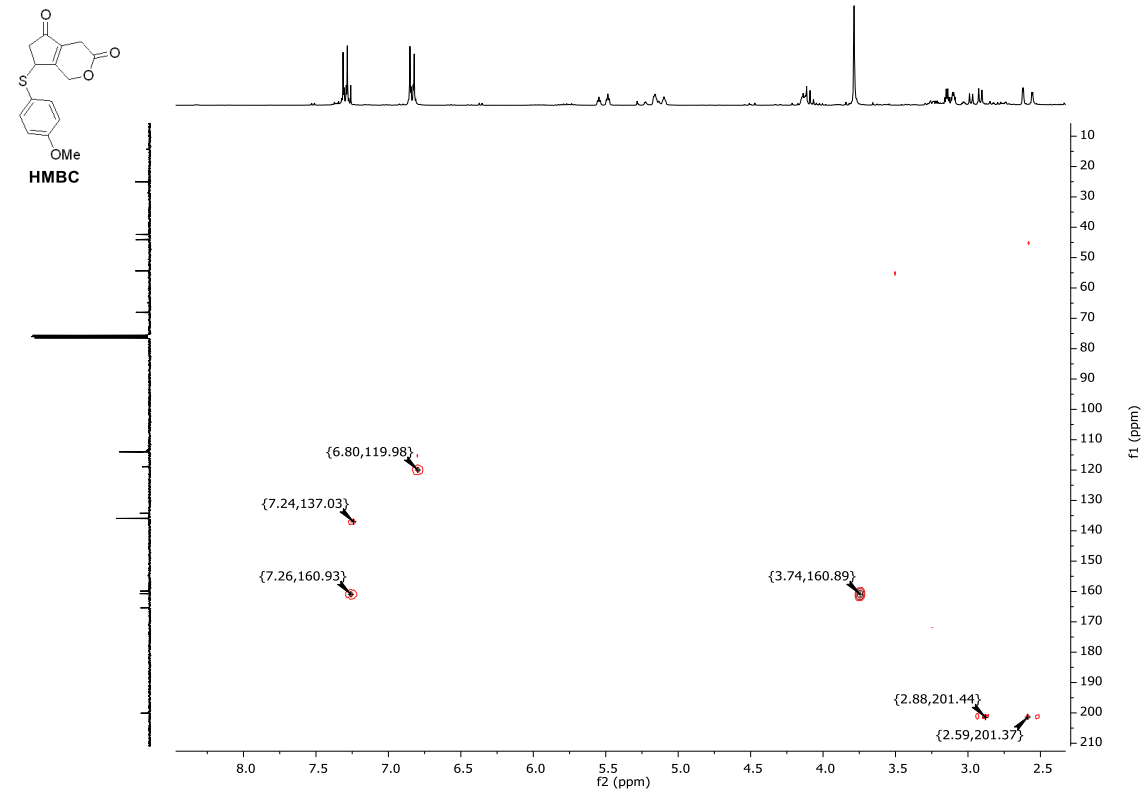
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.9 Hz), 6.84 (2H, d, *J* = 8.9 Hz), 5.47-5.56 (1H, m), 5.10-5.17 (1H, m), 4.11-4.15 (1H, m), 3.79 (3H, s), 3.09-3.16 (2H, m), 2.95 (1H, dd, *J* = 19.2, 6.6 Hz), 2.59 (1H, dd, *J* = 19.2, 1.7 Hz). **^{13}C NMR (75 MHz, $CDCl_3$) δ** 201.2, 166.6, 161.9, 161.0, 137.0, 135.4, 120.1, 115.1, 69.2, 55.5, 45.3, 43.5, 26.1. **HRMS (ESI-MS)** *m/z* calcd for $C_{12}H_{19}NO_3$ $[M + MeOH + H]^+$ 323.0946, found 323.0948. Calcd for $C_{12}H_{19}NO_3$ $[M + MeOH + Na]^+$ 345.0766, found 345.0767.



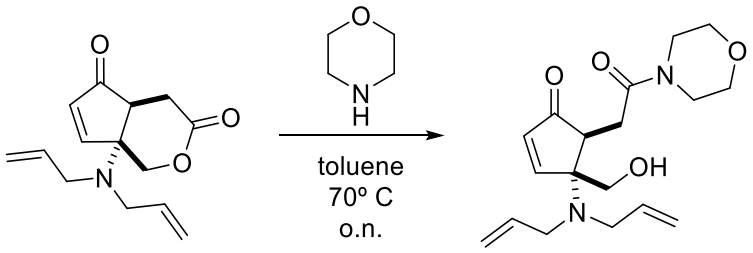

201.22
166.55
161.85
161.01
137.07
135.37
120.07
115.14
69.15
55.52
45.26
43.51
26.16
f1 (ppm)


OMe
COSY
{2.86,2.56}
{4.09,2.85}
{2.90,2.85}
{4.09,3.03}
{5.46,3.09}
{5.13,3.08}
{2.88,4.08}
{5.46,5.10}
{5.06,5.03}
{5.53,5.56}
{5.07,5.50}
{7.26,6.79}
{6.82,6.80}
f2 (ppm)
f1 (ppm)


HSQC
{3.11,26.05}
{4.09,45.35}
{2.88,43.36}
{2.57,43.36}
{3.74,55.43}
{5.13,69.05}
{5.46,69.03}
{6.79,114.85}
{7.26,136.90}
f1 (ppm)
f2 (ppm)

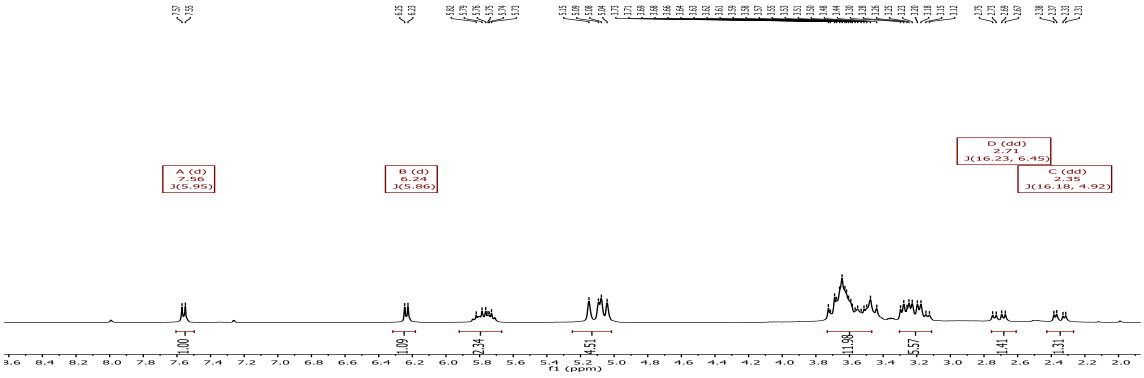

HMBC
{6.80,119.98}
{7.24,137.03}
{7.26,160.93}
{3.74,160.89}
{2.88,201.44}
{2.59,201.37}
f1 (ppm)
f2 (ppm)

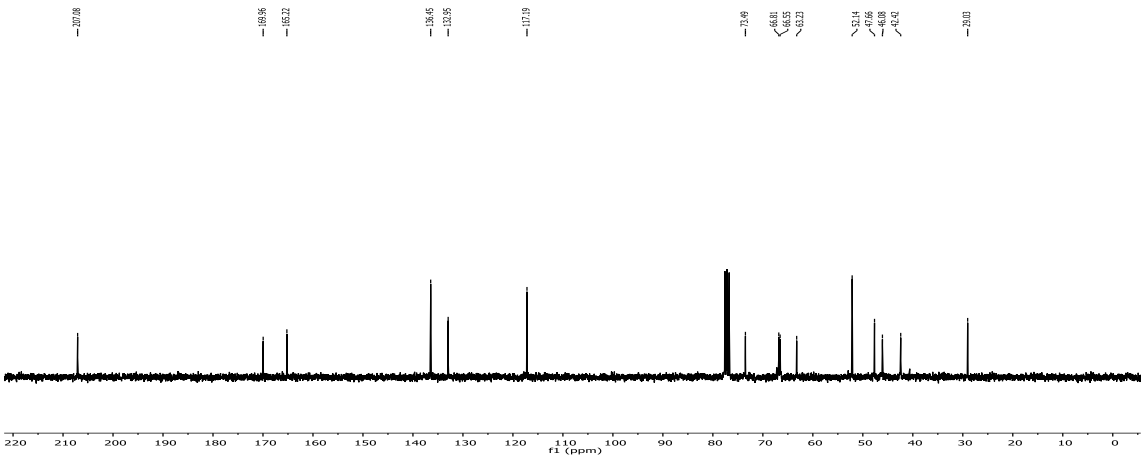
4-(diallylamino)-4-(hydroxymethyl)-5-(2-morpholino-2-oxoethyl)cyclopent-2-en-1-one 150



To a solution of **136** (100 mg, 0.40 mmol) in toluene (4 mL) was added morpholine (176 µl, 2.02 mmol, 5 equiv). The reaction was stirred at 70º C overnight. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography using hexane:ethyl acetate (5:5 to 1:9) affording 108 mg (80% yield) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 6.0 Hz), 6.24 (1H, d, *J* = 5.9 Hz), 5.73-5.82 (2H, m), 5.04-5.15 (4H, m), 3.44-3.73 (11H, m), 3.12-3.30 (4H, m), 2.71 (1H, dd, *J* = 16.2, 6.5 Hz), 2.35 (1H, dd, *J* = 16.2, 4.9 Hz); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 207.1, 170.0, 165.2, 136.5, 133.0, 117.2, 73.5, 66.8, 66.6, 63.2, 52.1, 47.7, 46.1, 42.4, 29.0; **HRMS (ESI-MS)** *m/z* calcd for $C_{18}H_{26}N_2O_4$ $[M + H]^+$ 335.1965, found 335.1971.



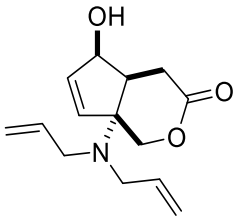


Luche reduction

General Procedure (GPC)

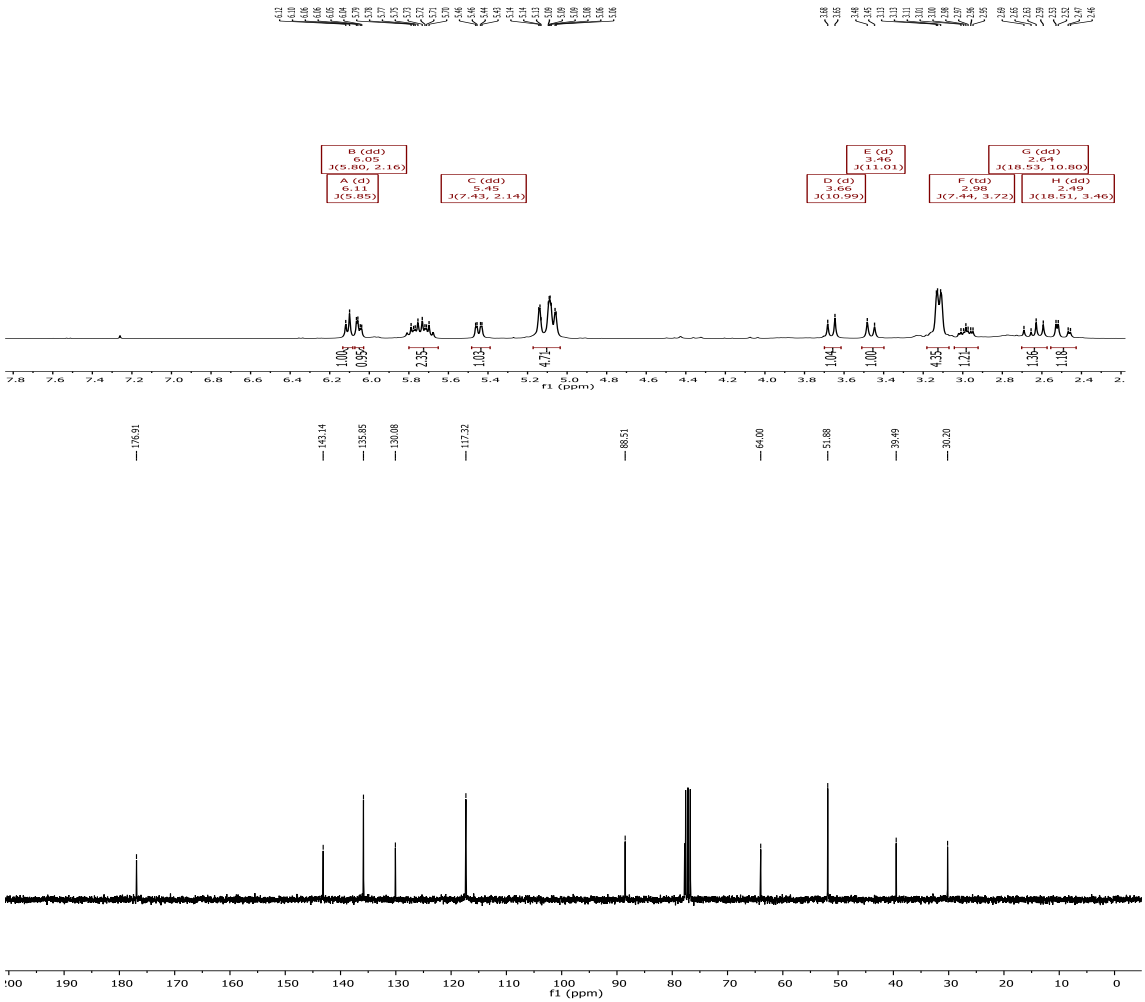
To a solution of a specific **LCP** (0.4 mmol) in anhydrous MeOH (4 mL) was added $CeCl_3.7H_2O$ (150 mg, 0.4 mmol, 1 equiv) at the corresponding temperature. $LiBH_4$ (9 mg, 0.4 mmol, 1 equiv) was added and the reaction was stirred until total consumption of the starting material. The reaction was quenched by the addition of a sat. aq. sol. NH_4Cl (15 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic phases were dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure affording pure product

7a-(diallylamino)-5-hydroxy-4,4a,5,7a-tetrahydrocyclopenta[c]pyran-3(1H)-one
152



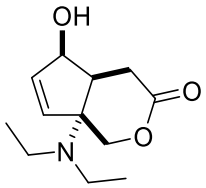
The product was prepared from **136** according to GPC and obtained as a brown oil (82 mg, 83% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (1H, d, *J* = 5.9 Hz), 6.05 (1H, dd, *J* = 5.8, 2.1 Hz), 5.70-5.79 (2H, m), 5.45 (1H, dd, *J* = 7.4, 2.1 Hz), 5.06-5.14 (4H, m), 3.66 (1H, d, *J* = 11.0 Hz), 3.46 (1H, d, *J* = 11.0 Hz), 3.11-3.13 (4H, m), 2.98 (1H, td, *J* = 7.4, 3.7 Hz), 2.64 (1H, dd, *J* = 18.5, 10.8 Hz), 2.49 (1H, dd, *J* = 18.5, 3.5); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 176.9, 143.1, 135.9, 130.1, 117.3, 88.5, 64.0, 51.9, 39.5, 30.2. **HRMS (ESI-MS)** *m/z* calcd for $C_{14}H_{19}NO_3$ $[M + H]^+$ 250.14432, found 250.14413



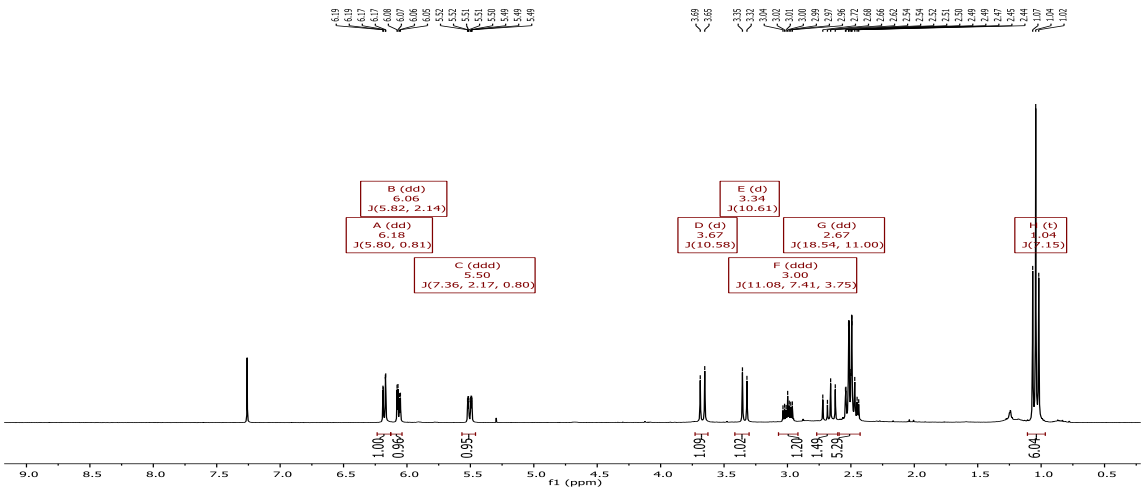
7a-(diethylamino)-5-hydroxy-4,4a,5,7a-tetrahydrocyclopenta[c]pyran-3(1H)-one

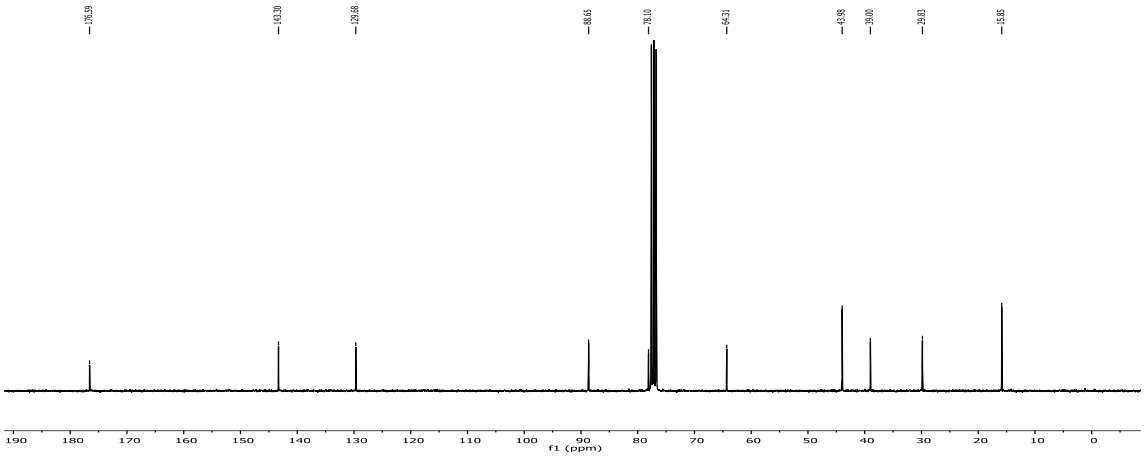
153

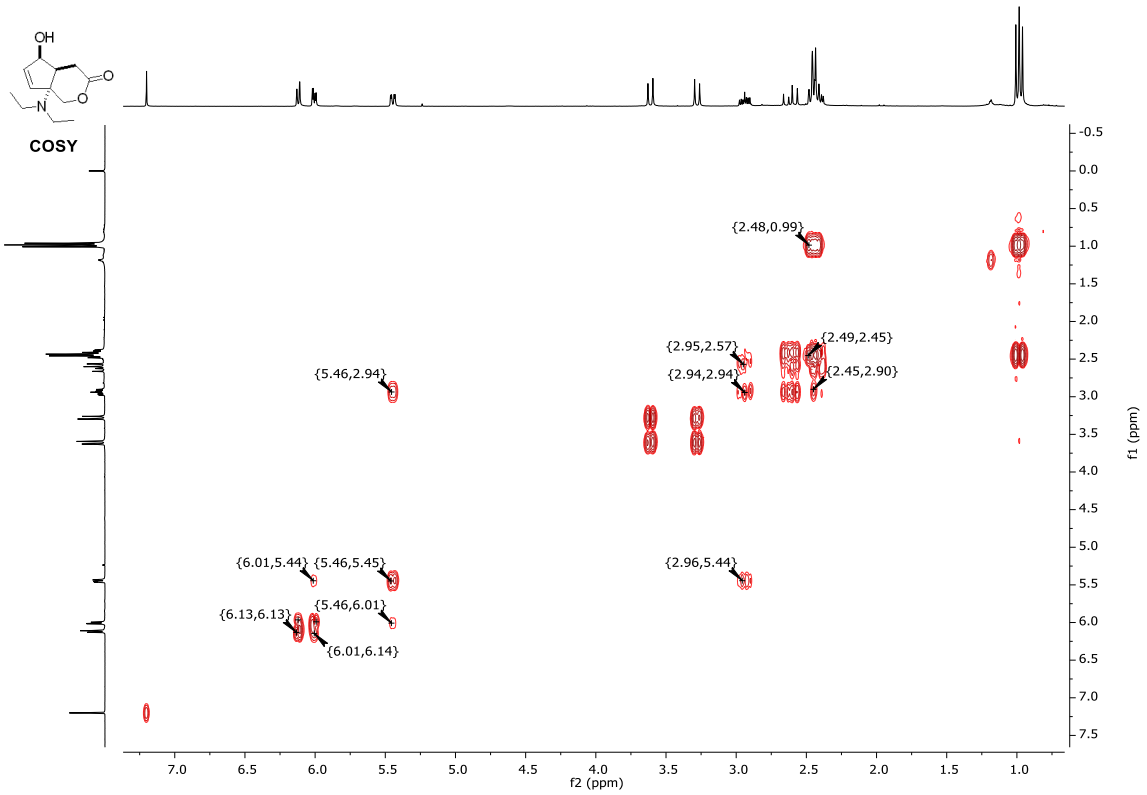


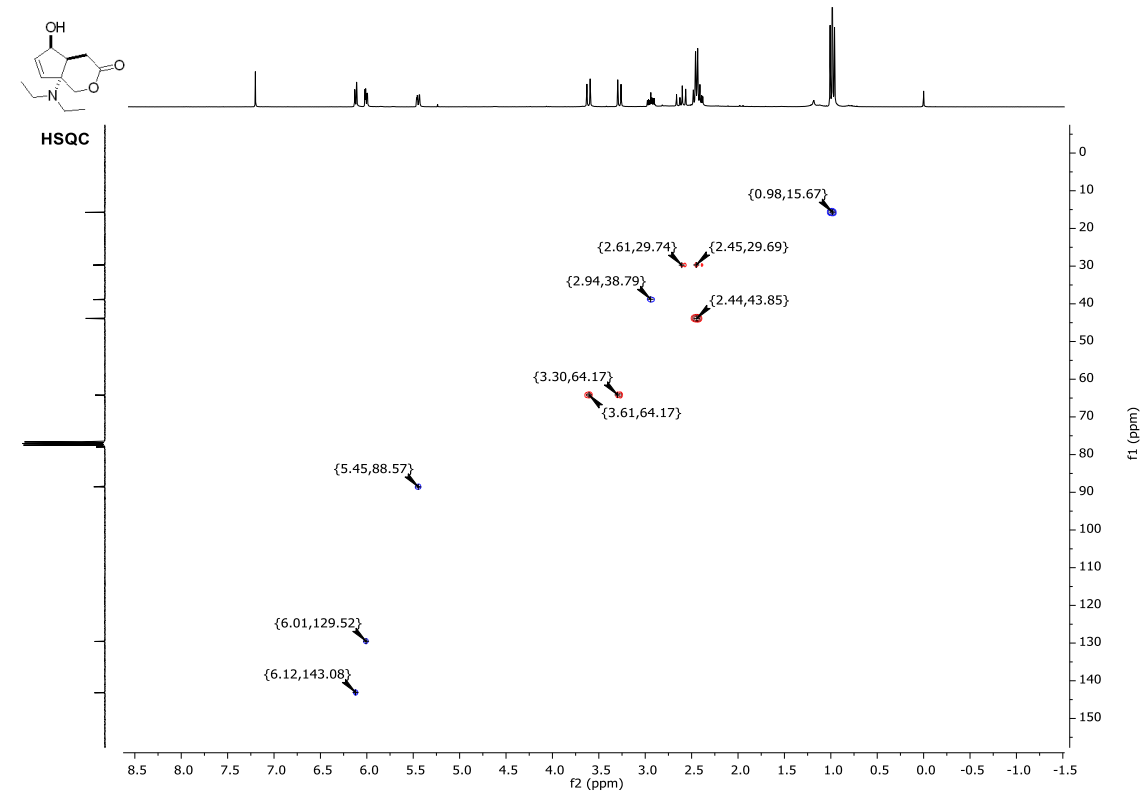
The product was prepared from **108** according to GPC and obtained as a colorless oil (64 mg, 72% yield).

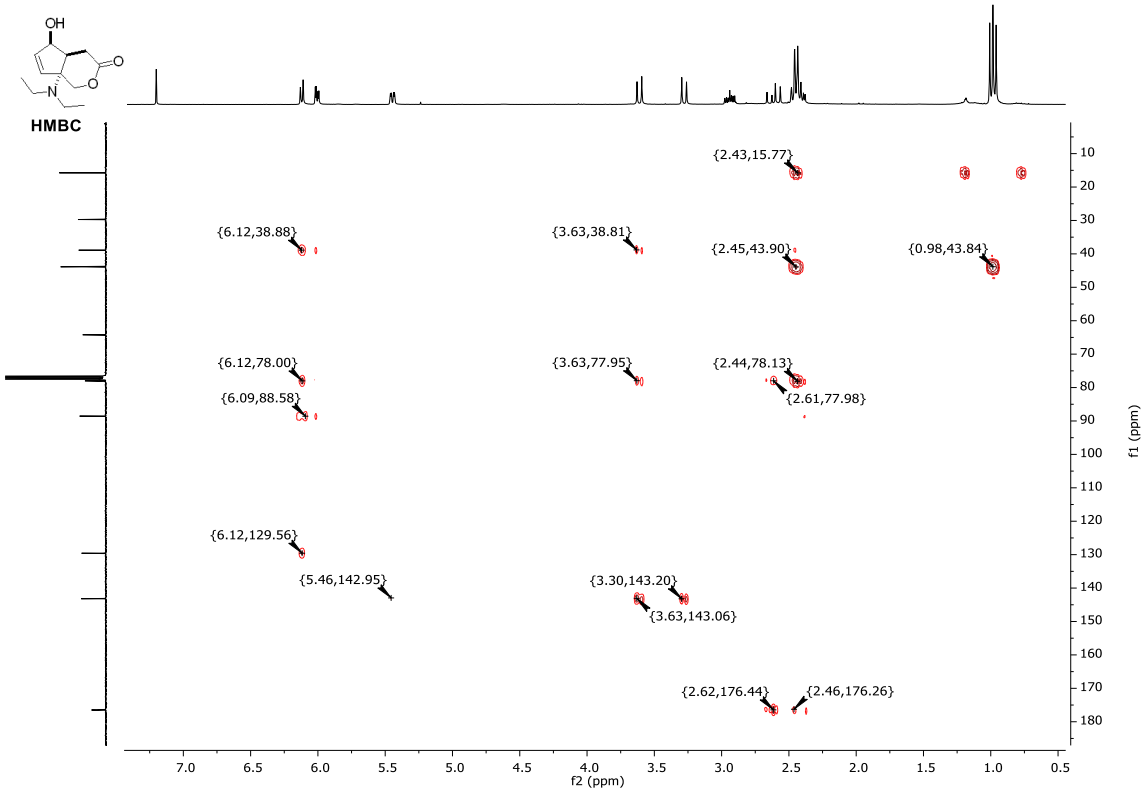
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (1H, dd, J = 5.8, 0.8 Hz), 6.06 (1H, dd, *J* = 5.8, 2.1 Hz), 5.50 (1H, ddd, *J* = 7.4, 2.2, 0.8 Hz), 3.67 (1H, d, *J* = 11.0 Hz), 3.34 (1H, d, *J* = 11.0 Hz), 3.00 (1H, ddd, *J* = 11.1, 7.4, 3.8), 2.67 (1H, dd, *J* = 18.5, 11.0 Hz), 2.44-2.68 (5H, m), 1.04 (1H, t, *J* = 7.2 Hz); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 176.6, 143.3, 129.7, 88.7, 78.1, 64.3, 44.0, 39.0, 29.8, 15.9; **HRMS (ESI-MS)** *m/z* calcd for $C_{12}H_{19}NO_3$ $[M + H]^+$ 226.14432, found 226.14380

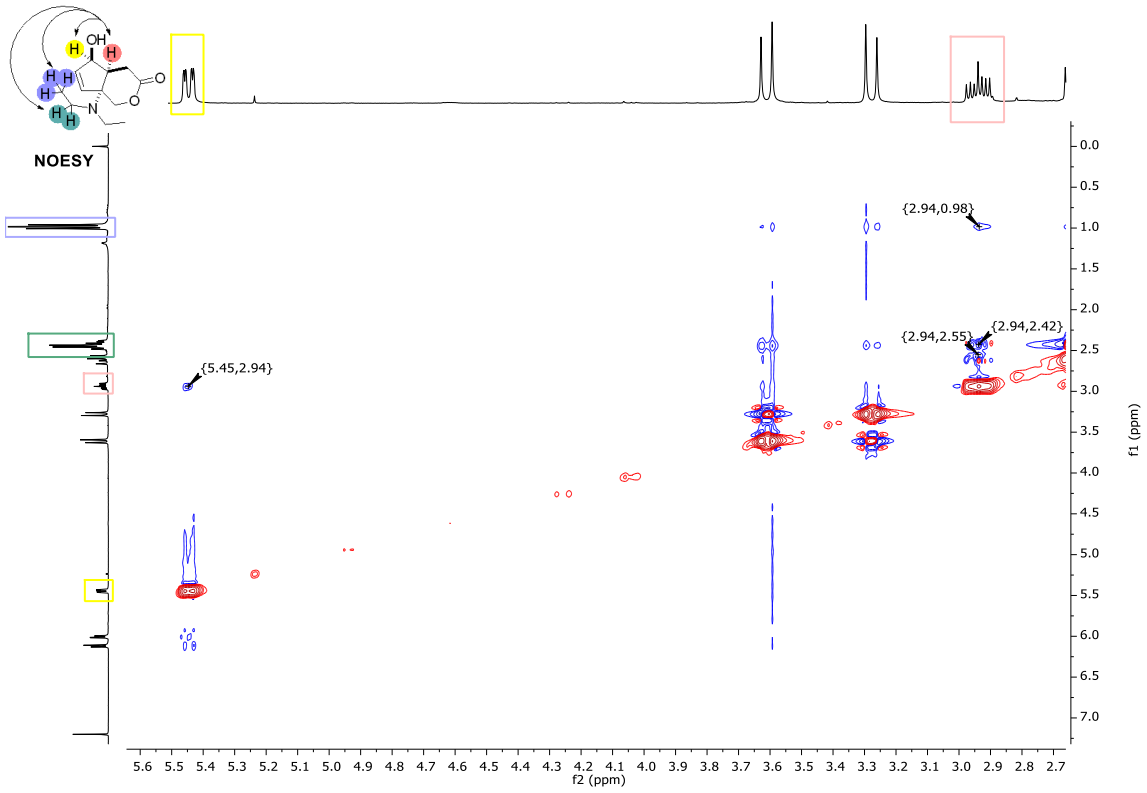




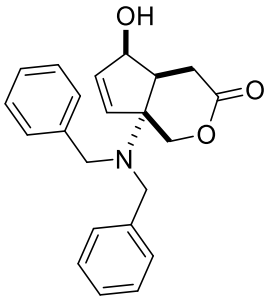

COSY
{2.48,0.99}
{2.49,2.45}
{2.95,2.57}
{2.94,2.94}
{2.45,2.90}
{5.46,2.94}
{6.01,5.44}
{5.46,5.45}
{2.96,5.44}
{5.46,6.01}
{6.13,6.13}
{6.01,6.14}
f2 (ppm)
f1 (ppm)


HSQC
{0.98,15.67}
{2.61,29.74}
{2.45,29.69}
{2.94,38.79}
{2.44,43.85}
{3.30,64.17}
{3.61,64.17}
{5.45,88.57}
{6.01,129.52}
{6.12,143.08}
f2 (ppm)
f1 (ppm)


HMBC
{2.43,15.77}
{6.12,38.88}
{3.63,38.81}
{2.45,43.90}
{0.98,43.84}
{6.12,78.00}
{3.63,77.95}
{2.44,78.13}
{6.09,88.58}
{2.61,77.98}
{6.12,129.56}
{5.46,142.95}
{3.30,143.20}
{3.63,143.06}
{2.62,176.44}
{2.46,176.26}
f2 (ppm)
f1 (ppm)

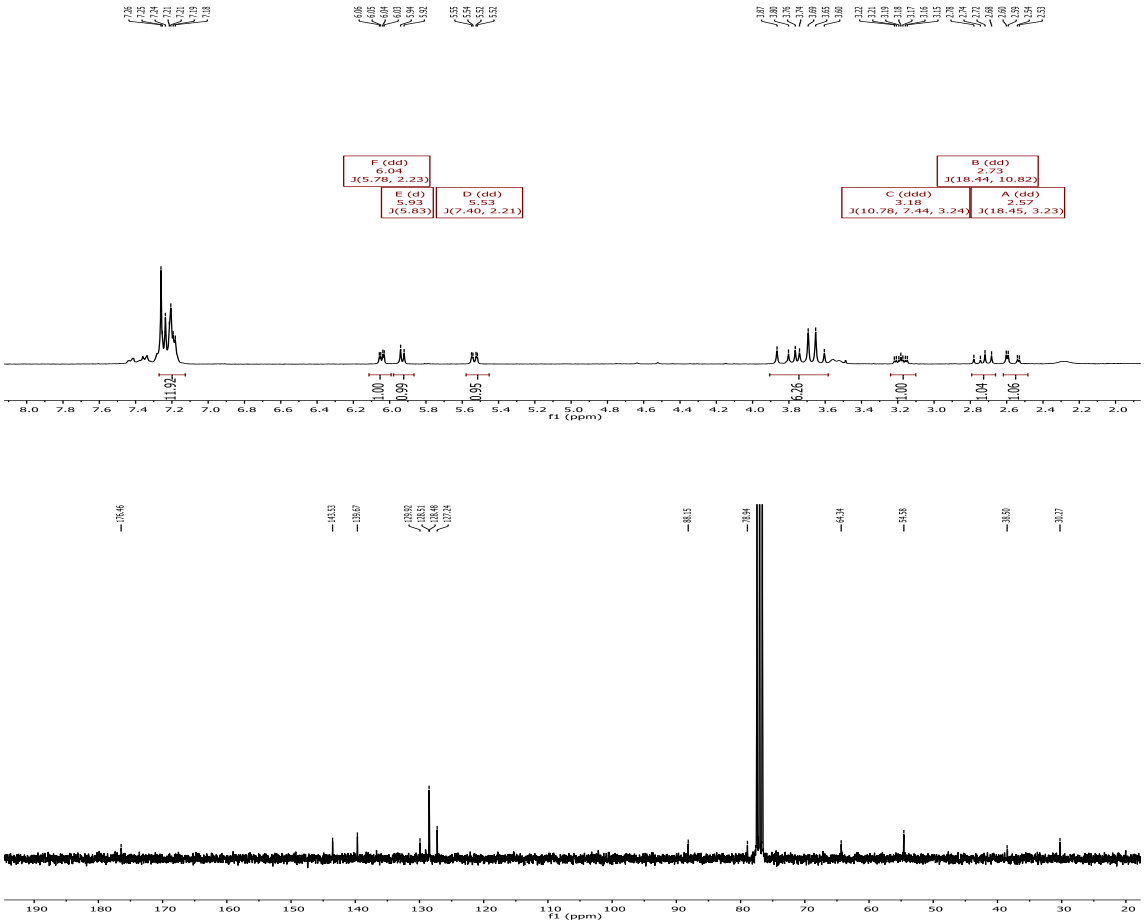

NOESY
{2.94,0.98}
{2.94,2.55}
{2.94,2.42}
{5.45,2.94}
f2 (ppm)
f1 (ppm)

7a-(dibenzylamino)-5-hydroxy-4,4a,5,7a-tetrahydrocyclopenta[c]pyran-3(1H)-one
154



The product was prepared from **139** according to GPC and obtained as a red oil (134 mg, 97% yield).

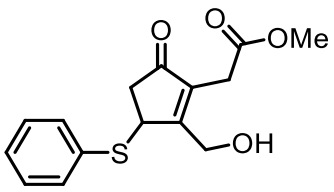
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.26 (10H, m), 6.04 (1H, dd, *J* = 5.8, 2.2 Hz), 5.93 (1H, d, *J* = 5.8 Hz), 5.53 (1H, dd, *J* = 7.4, 2.2 Hz), 3.60-3.87 (6H, m), 3.18 (1H, ddd, *J* = 10.8, 7.4, 3.2 Hz), 2.73 (1H, dd, *J* = 18.5, 10.8 Hz), 2.57 (1H, d, *J* = 18.5, 3.2 Hz); **^{13}C NMR (75 MHz, $CDCl_3$) δ** 176.5, 143.5, 139.7, 129.9, 128.5, 128.5, 127.2, 88.2, 78.9, 64.3, 54.6, 38.5, 30.3; **HRMS (ESI-MS)** *m/z* calcd for $C_{22}H_{23}NO_3$ $[M + H]^+$ 350.17562, found 350.17294.



General Procedure for the synthesis of LCP-thioadducts in nucleophilic solvents

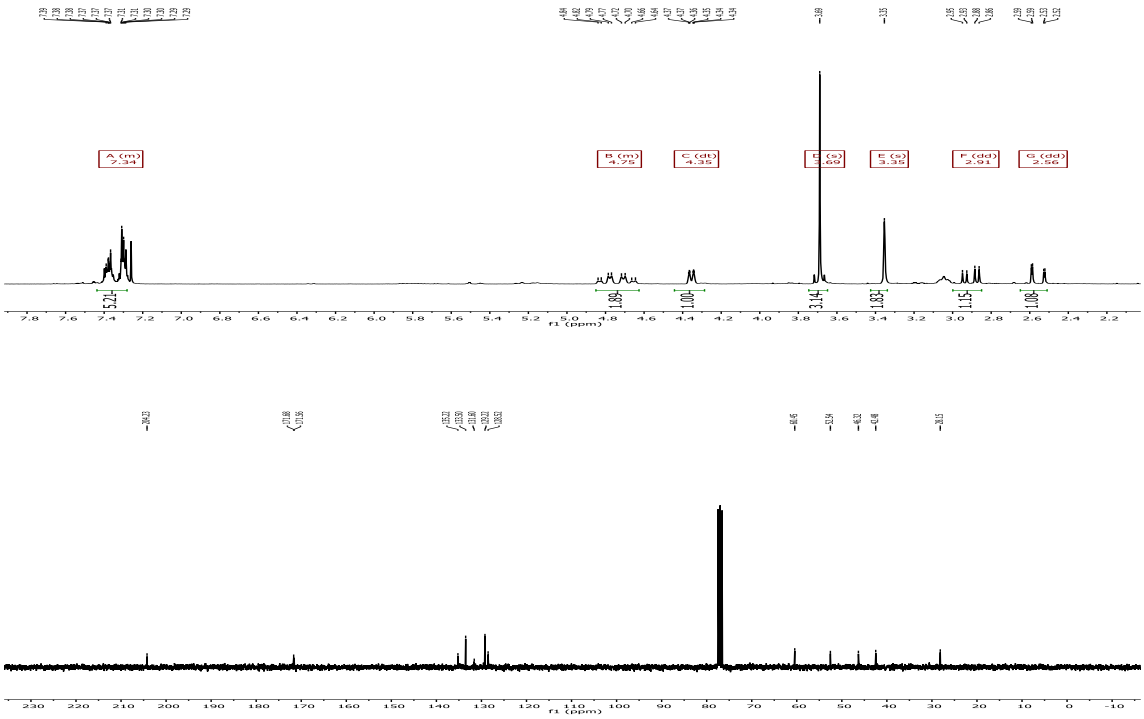
To a solution of **136** (100 mg, 0.40 mmol) in MeOH (4 mL) was added the corresponding thiol (3 equiv, 1.2 mmol) and the mixture was allowed to stir for 5 h. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography.

methyl 2-(2-(hydroxymethyl)-5-oxo-3-(phenylthio)cyclopent-1-en-1-yl)acetate 161

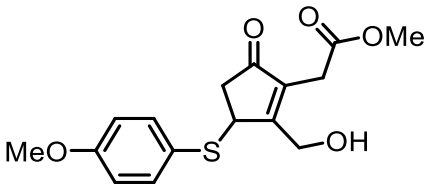


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 100 mg (82% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.29 (m, 5H), 5.02 – 4.56 (m, 2H), 4.35 (dt, J = 6.7, 1.0 Hz, 1H), 3.69 (s, 3H), 3.35 (s, 2H), 2.91 (dd, J = 19.2, 6.7 Hz, 1H), 2.56 (dd, J = 19.2, 1.8 Hz, 1H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 208.4, 163.2, 139.4, 136.5, 135.2, 129.5, 128.3, 127.26, 117.3, 64.6, 64.1, 55.3, 53.6. **HRMS (ESI-MS)** *m/z* calcd for $C_{15}H_{17}O_4S$ $[M + H]^+$ 293.08475, found 293.08492

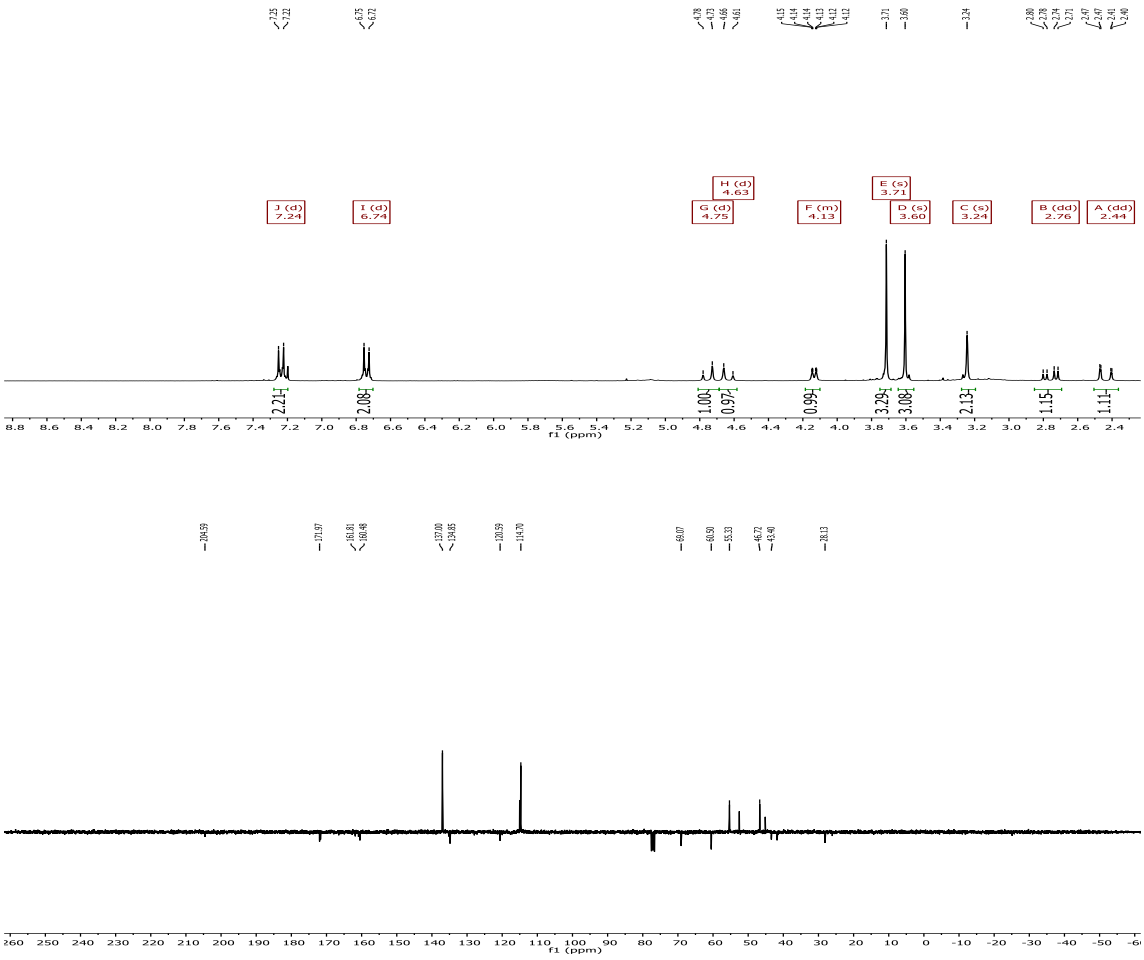


methyl 2-(2-(hydroxymethyl)-3-((4-methoxyphenyl)thio)-5-oxocyclopent-1-en-1-yl)acetate 163

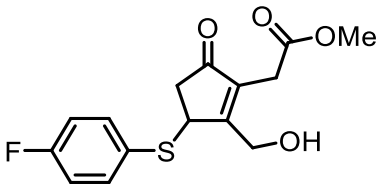


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 99 mg (76% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.9 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 4.75 (d, J = 16.1 Hz, 1H), 4.63 (d, J = 16.1 Hz, 1H), 4.20 – 4.07 (m, 1H), 3.71 (s, 3H), 3.60 (s, 3H), 3.24 (s, 2H), 2.76 (dd, J = 19.2, 6.8 Hz, 1H), 2.44 (dd, J = 19.2, 1.8 Hz, 1H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.6, 171.9, 161.8, 160.5, 137.0, 134.9, 120.6, 114.7, 69.1, 60.5, 55.3, 46.7, 43.4, 28.1. **HRMS (ESI-MS)** *m/z* calcd for $C_{16}H_{19}O_5S$ $[M + H]^+$ 323.09532, found 323.09515

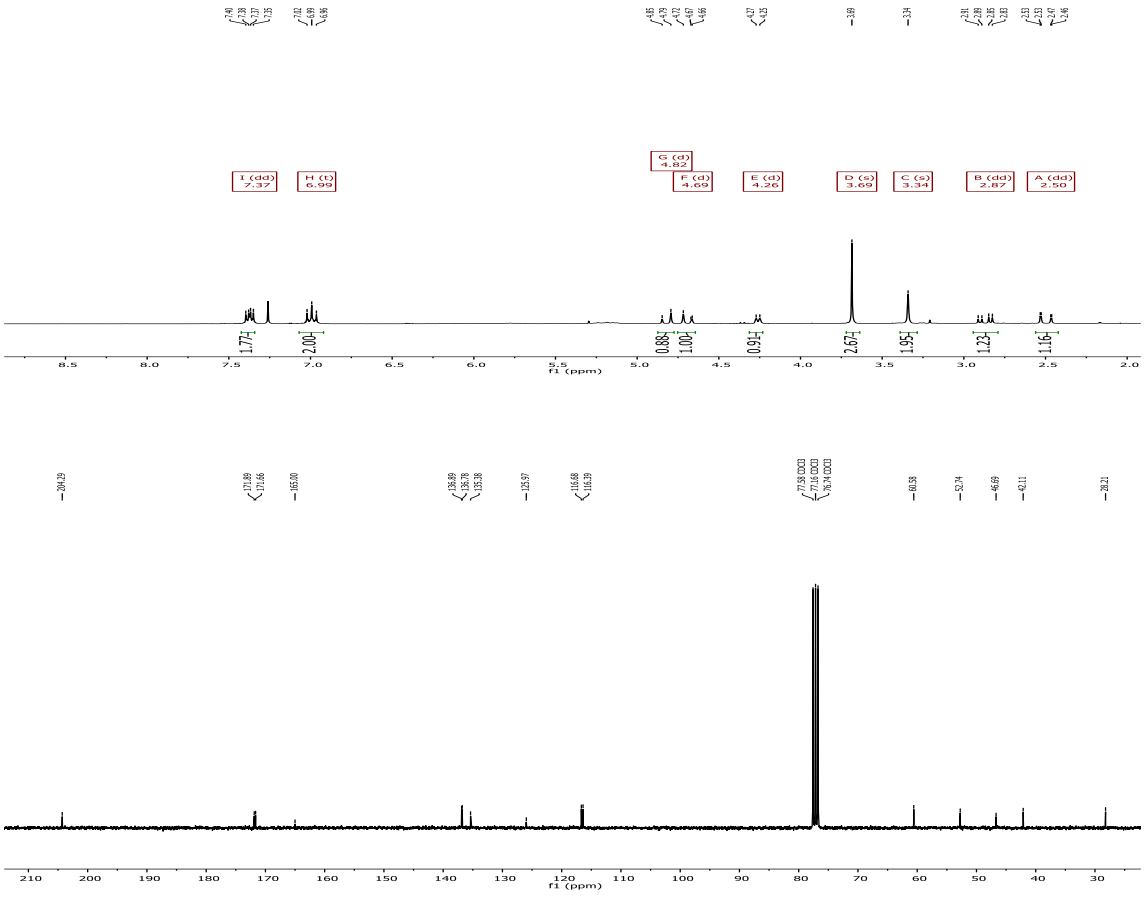


methyl 2-(3-((4-fluorophenyl)thio)-2-(hydroxymethyl)-5-oxocyclopent-1-en-1-yl)acetate 164

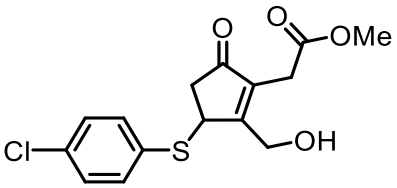


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 94 mg (75% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, J = 8.8, 5.2 Hz, 2H), 6.99 (t, J = 8.6 Hz, 2H), 4.82 (d, J = 16.1 Hz, 1H), 4.69 (d, J = 16.3 Hz, 1H), 4.26 (d, J = 6.7 Hz, 1H), 3.69 (s, 3H), 3.34 (s, 2H), 2.87 (dd, J = 19.3, 6.8 Hz, 1H), 2.50 (dd, J = 19.2, 1.7 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.3, 171.9, 171.7, 165.0, 136.9, 136.8, 135.4, 125.9, 116.7, 116.4, 60.6, 52.7, 46.7, 42.1, 28.2. **HRMS (ESI-MS)** *m/z* calcd for $C_{15}H_{16}FO_4S$ $[M + H]^+$ 311.07533, found 311.07520

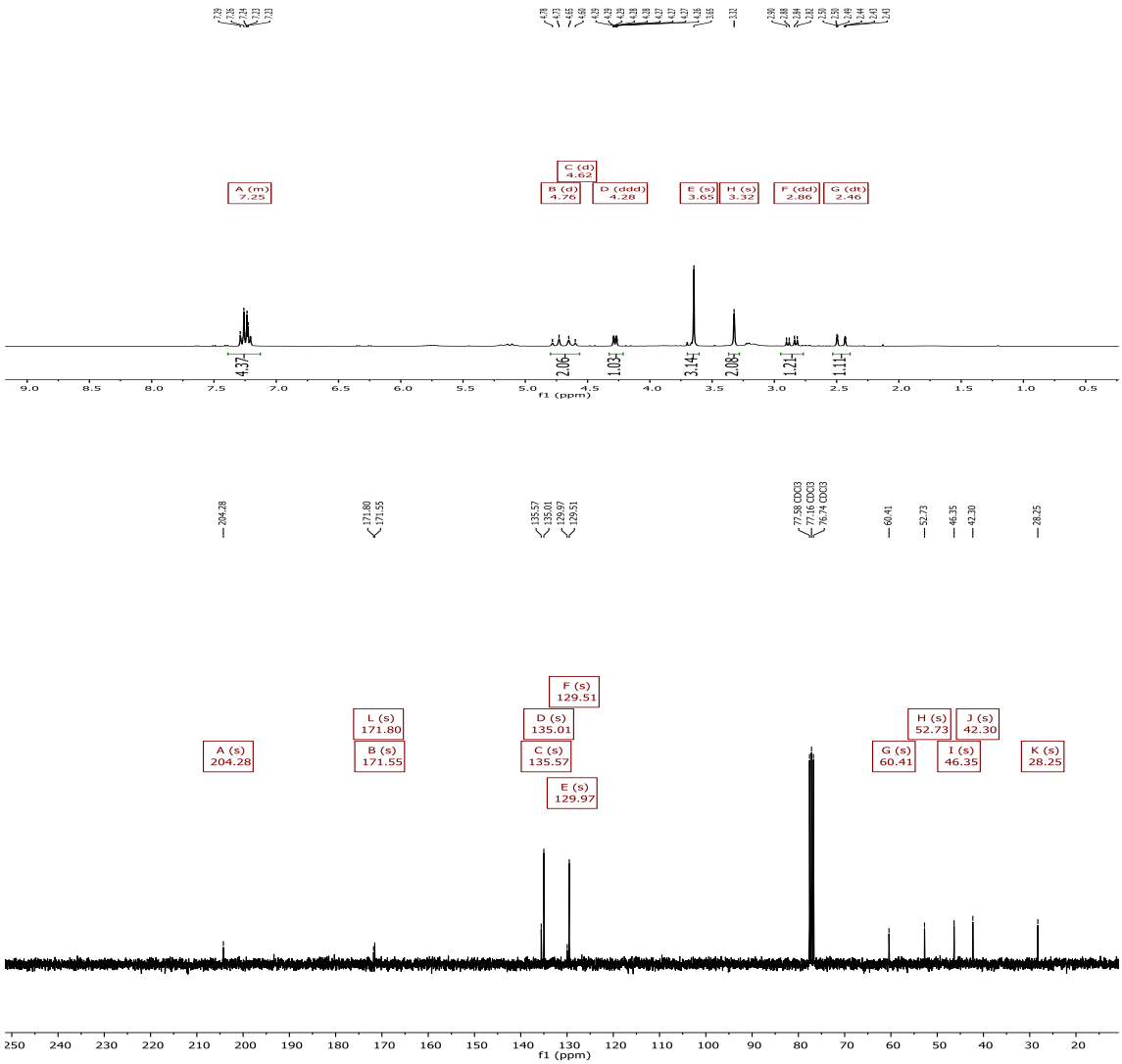


methyl 2-(3-((4-chlorophenyl)thio)-2-(hydroxymethyl)-5-oxocyclopent-1-en-1-yl)acetate 165

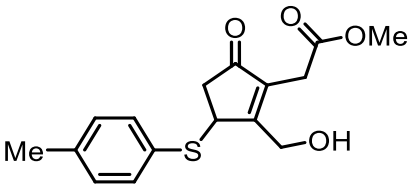


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 99 mg (75% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 6.97 (m, 4H), 4.76 (d, J = 16.0 Hz, 1H), 4.62 (d, J = 15.9 Hz, 1H), 4.28 (ddd, J = 6.7, 1.9, 0.9 Hz, 1H), 3.65 (s, 3H), 3.82 (s, 2H), 2.86 (dd, J = 19.3, 6.7 Hz, 1H), 2.46 (dt, J = 19.3, 1.4 Hz, 1H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.3, 171.8, 171.6, 135.6, 135.0, 129.9, 129.5, 60.41, 52.7, 46.4, 42.3, 28.3. **HRMS (ESI-MS)** *m/z* calcd for $C_{15}H_{16}ClO_4S$ $[M + H]^+$ 327.04578, found 327.04580

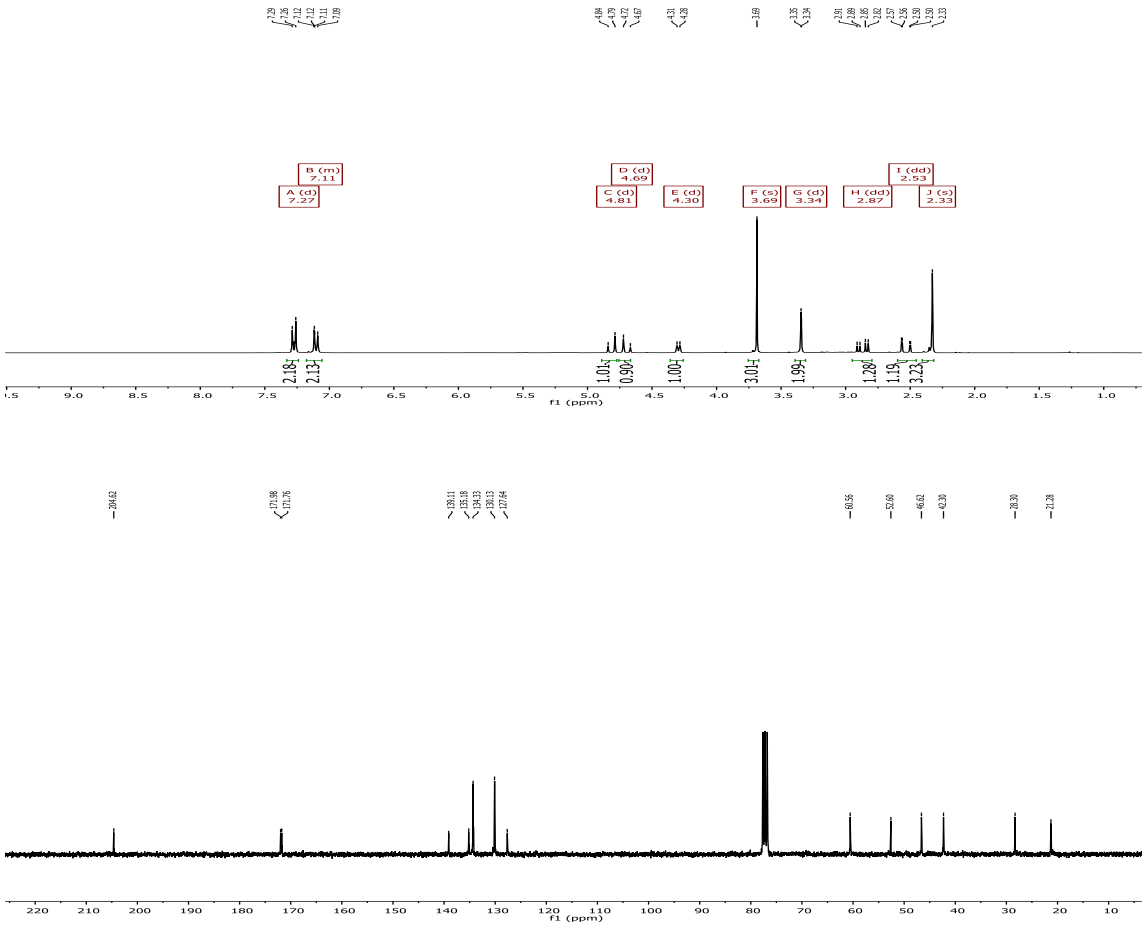


methyl 2-(3-((4-methylphenyl)thio)-2-(hydroxymethyl)-5-oxocyclopent-1-en-1-yl)acetate 162

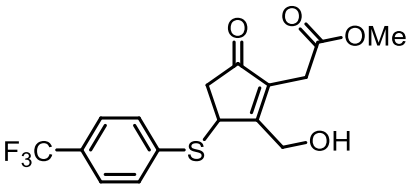


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 99 mg (80% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.1 Hz, 2H), 7.20 – 6.96 (m, 2H), 4.81 (d, J = 16.0 Hz, 1H), 4.69 (d, J = 16.1 Hz, 1H), 4.30 (d, J = 6.7 Hz, 1H), 3.69 (s, 3H), 3.34 (d, J = 1.0 Hz, 2H), 2.87 (dd, J = 19.2, 6.7 Hz, 1H), 2.53 (dd, J = 19.2, 1.8 Hz, 1H), 2.33 (s, 3H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.6, 171.9, 171.8, 139.1, 135.2, 134.3, 130.1, 127.6, 60.6, 52.6, 46.6, 42.3, 28.3, 21.3. **HRMS (ESI-MS)** *m/z* calcd for $C_{16}H_{19}O_4S$ $[M + H]^+$ 307.10040, found 307.10012

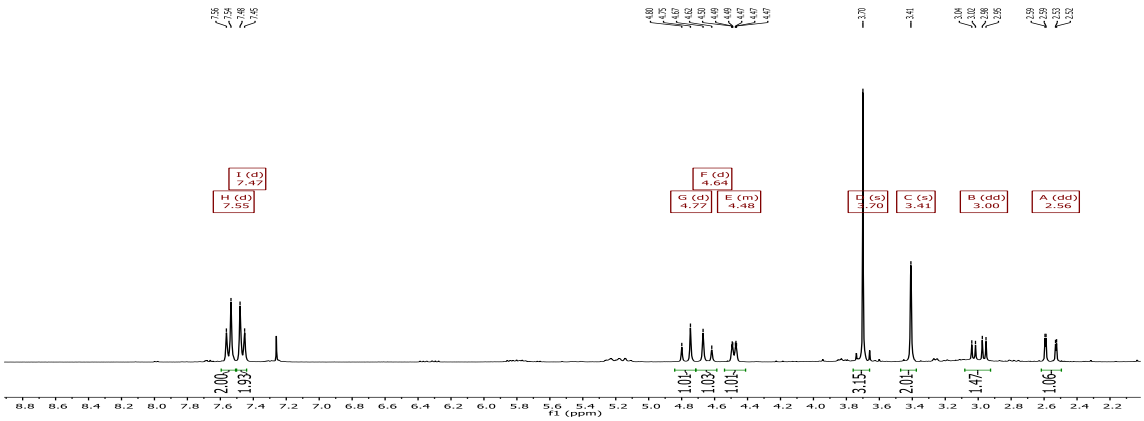


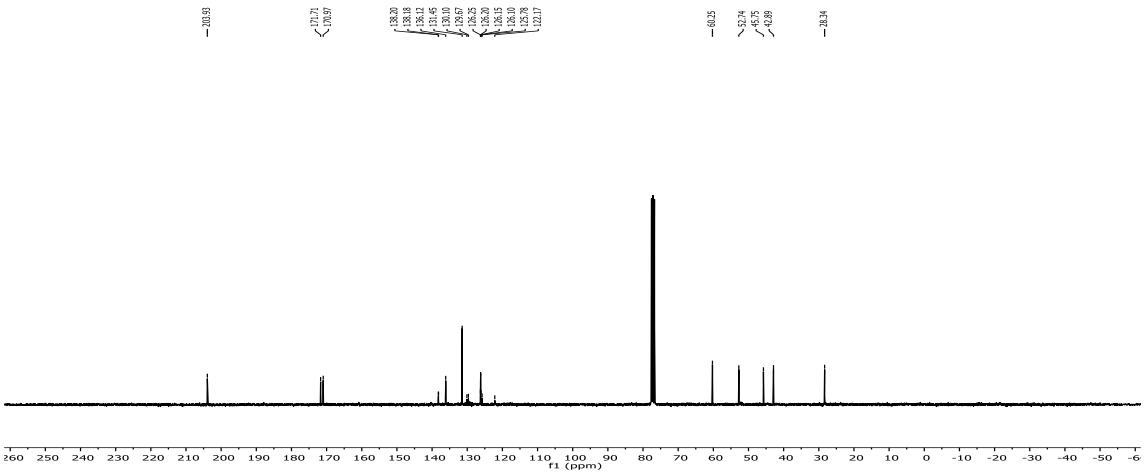
methyl 2-(3-((4-trifluoromethylphenyl)thio)-2-(hydroxymethyl)-5-oxocyclopent-1-en-1-yl)acetate 166



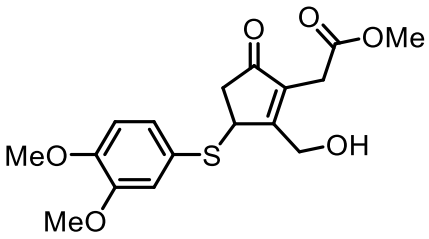
The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 92 mg (63% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 4.77 (d, J = 15.8 Hz, 1H), 4.64 (d, J = 15.8 Hz, 1H), 4.52 – 4.37 (m, 1H), 3.70 (s, 3H), 3.41 (s, 2H), 3.00 (dd, J = 19.2, 6.7 Hz, 1H), 2.56 (dd, J = 19.2, 1.9 Hz, 1H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 203.9, 171.7, 170.9, 138.2, 136.1, 131.4, 129.7, 126.2, 126.2, 126.2, 126.1, 125.8, 60.3, 52.7, 45.8, 42.9, 28.3. **HRMS (ESI-MS)** *m/z* calcd for $C_{16}H_{16}F_3O_4S$ $[M + H]^+$ 361.07214, found 361.07195



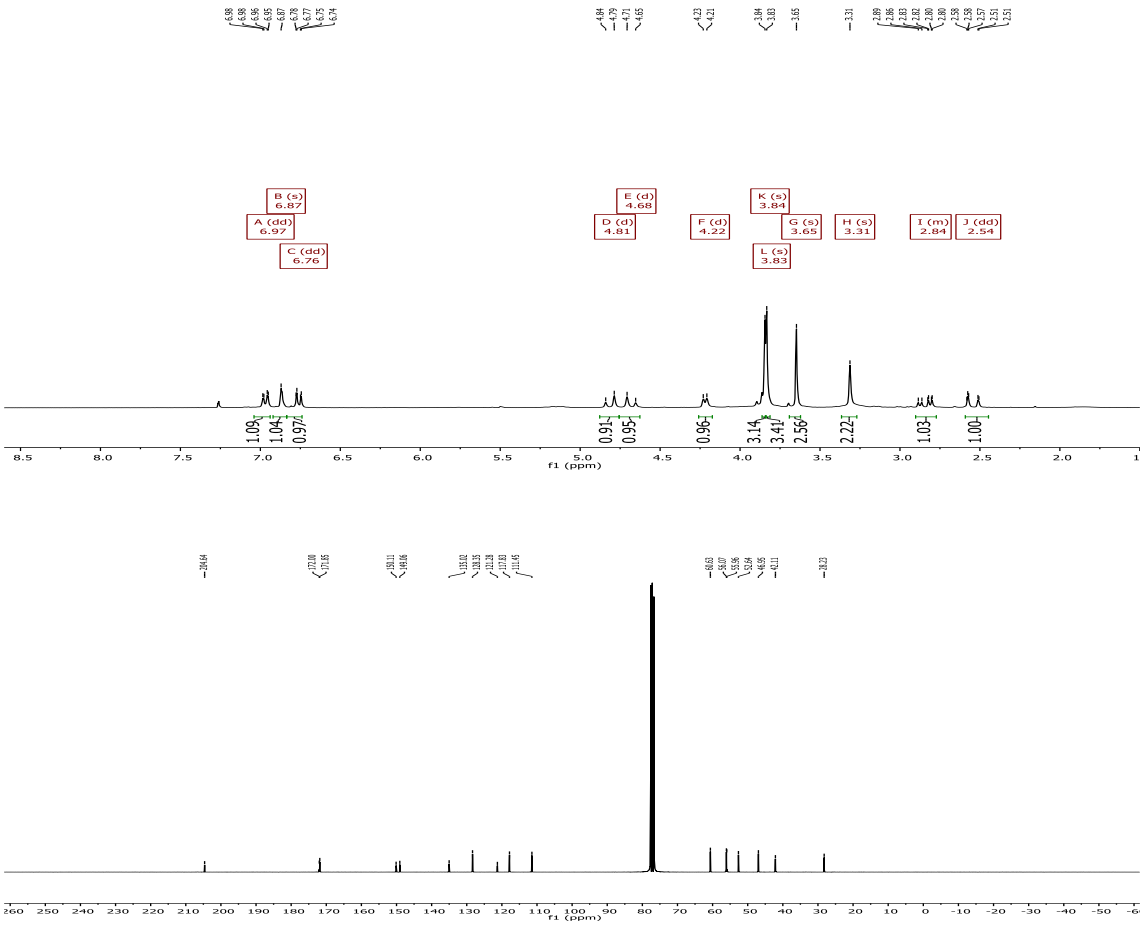


methyl 2-(3-((3,4-dimethoxyphenyl)thio)-2-(hydroxymethyl)-5-oxocyclopent-1-en-1-yl)acetate 167

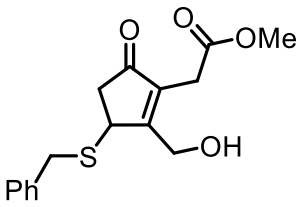


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 114 mg (80% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$). δ 6.97 (dd, J = 8.3, 1.9 Hz, 1H), 6.87 (s, 1H), 6.76 (dd, J = 8.3, 1.5 Hz, 1H), 4.81 (d, J = 16.1 Hz, 1H), 4.68 (d, J = 16.1 Hz, 1H), 4.22 (d, J = 6.7 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.65 (s, 3H), 3.31 (s, 2H), 2.96 – 2.74 (m, 1H), 2.54 (dd, J = 19.2, 1.7 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.6, 172.0, 171.9, 150.1, 149.1, 135.0, 128.4, 121.3, 117.8, 111.5, 60.6, 56.1, 55.9, 52.6, 46.9, 42.1, 28.2. **HRMS (ESI-MS)** *m/z* calcd for $C_{17}H_{21}O_6S$ $[M + H]^+$ 353.10588, found 353.10585

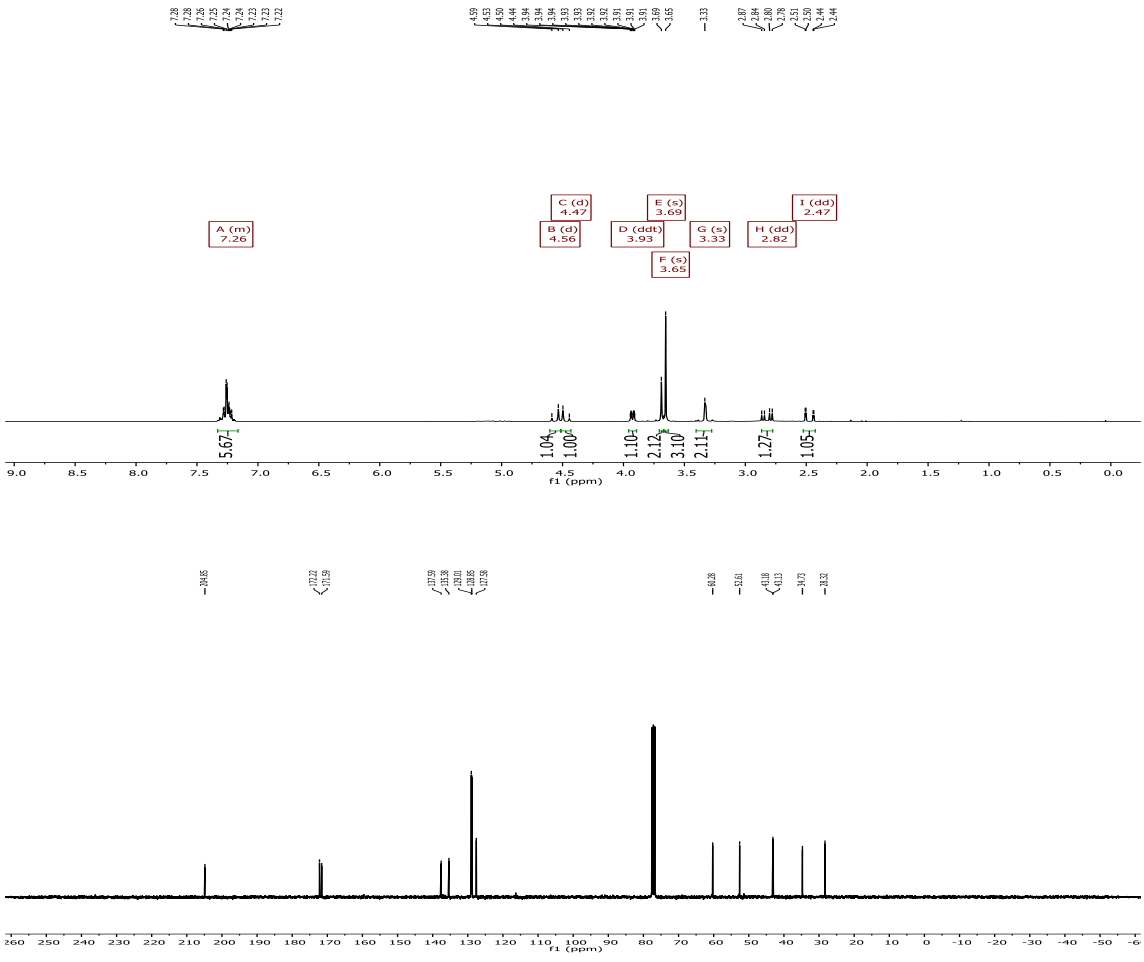


methyl 2-(3-(benzylthio)-2-(hydroxymethyl)-5-oxocyclopent-1-en-1-yl)acetate 168

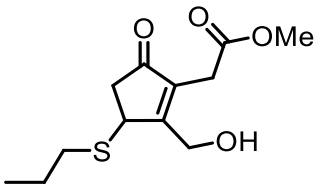


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 115 mg (93% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.13 (m, 5H), 4.56 (d, J = 16.0 Hz, 1H), 4.47 (d, J = 16.0 Hz, 1H), 3.93 (ddt, J = 6.8, 2.0, 1.0 Hz, 1H), 3.69 (s, 2H), 3.65 (s, 3H), 3.33 (s, 2H), 2.82 (dd, J = 19.3, 6.7 Hz, 1H), 2.47 (dd, J = 19.3, 1.8 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.9, 172.2, 171.6, 137.6, 135.4, 129.0, 128.9, 127.6, 60.3, 52.6, 43.2, 43.1, 34.7, 28.3. **HRMS (ESI-MS)** *m/z* calcd for $C_{16}H_{19}O_4S$ $[M + H]^+$ 307.10040, found 307.10042.

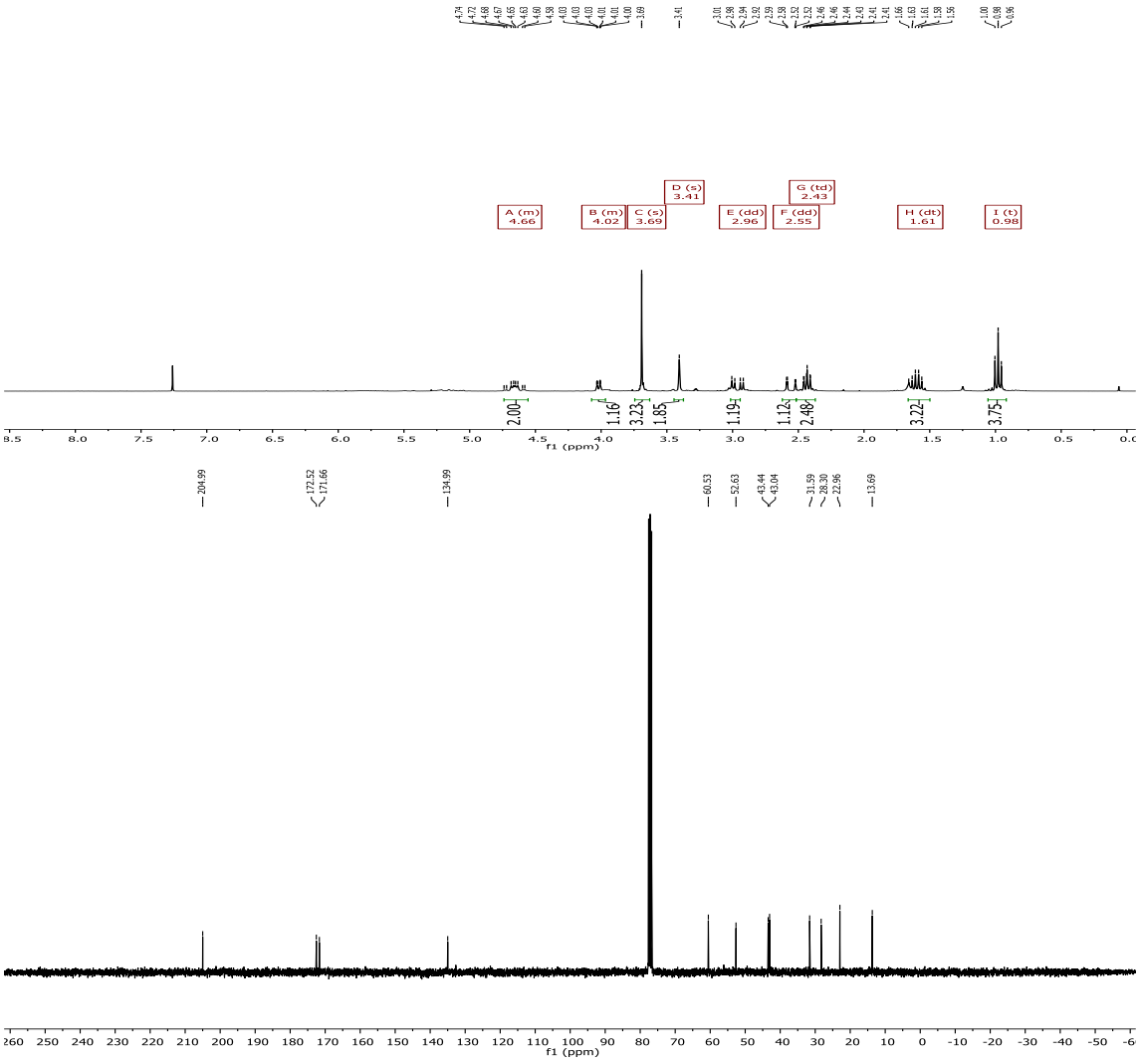


methyl 2-(2-(hydroxymethyl)-5-oxo-3-(propylthio)cyclopent-1-en-1-yl)acetate 169

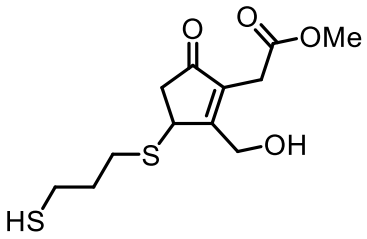


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 89 mg (85% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 – 4.47 (m, 2H), 4.17 – 3.90 (m, 1H), 3.69 (s, 3H), 3.41 (s, 2H), 2.96 (dd, J = 19.3, 6.8 Hz, 1H), 2.55 (dd, J = 19.3, 1.8 Hz, 1H), 2.43 (td, J = 7.3, 1.1 Hz, 2H), 1.61 (dt, J = 14.6, 7.6 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.9, 172.5, 171.7, 134.9, 60.5, 52.6, 43.4, 43.0, 31.6, 28.3, 22.9, 13.7. **HRMS (ESI-MS)** *m/z* calcd for $C_{12}H_{19}O_4S$ $[M + H]^+$ 259.10040, found 259.10031.

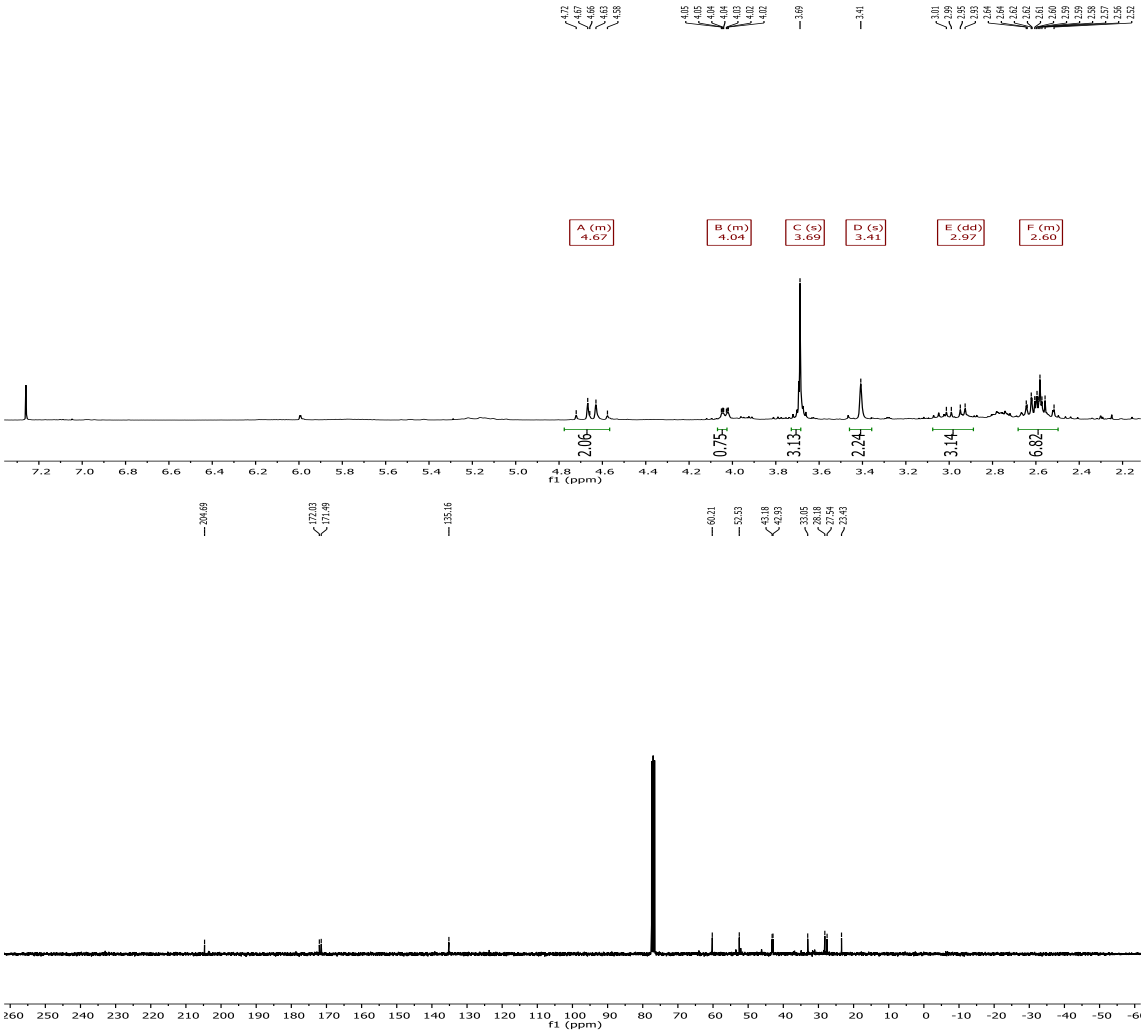


methyl 2-(2-(hydroxymethyl)-3-((3-mercaptopropyl)thio)-5-oxocyclopent-1-en-1-yl)acetate 170

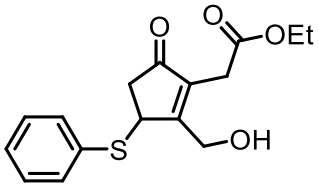


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 93 mg (80% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 – 4.51 (m, 2H), 4.17 – 3.97 (m, 1H), 3.69 (s, 3H), 3.41 (s, 2H), 2.97 (dd, J = 19.2, 6.8 Hz, 3H), 2.73 – 2.43 (m, 6H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.7, 172.0, 171.5, 135.2, 60.2, 52.5, 43.2, 42.9, 33.1, 28.2, 27.5, 23.4. **HRMS (ESI-MS)** *m/z* calcd for $C_{12}H_{19}O_4S_2$ $[M + H]^+$ 291.07248, found 291.07239.

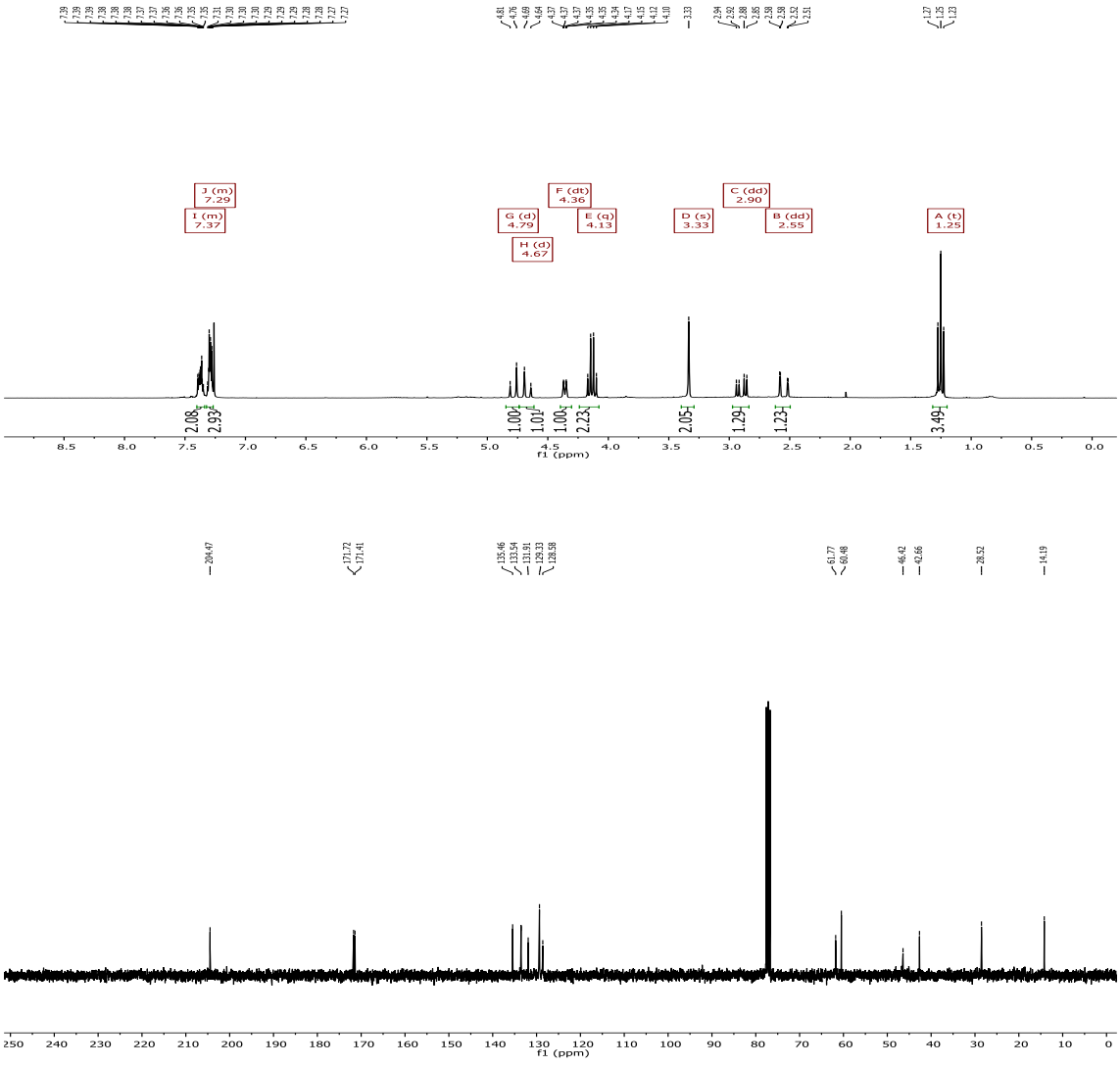


ethyl 2-(2-(hydroxymethyl)-3-(phenylthio)-5-oxocyclopent-1-en-1-yl)acetate 171

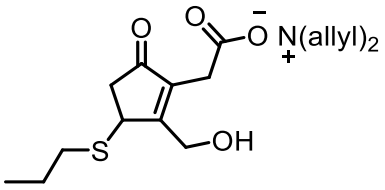


The titled compound was prepared according to general procedure using ethanol as solvent. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 97 mg (79% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 7.32 – 7.27 (m, 3H), 4.79 (d, J = 15.9 Hz, 1H), 4.67 (d, J = 15.9 Hz, 1H), 4.36 (dt, J = 6.7, 0.9 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.33 (s, 2H), 2.90 (dd, J = 19.2, 6.7 Hz, 1H), 2.55 (dd, J = 19.2, 1.8 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.5, 171.7, 171.4, 135.5, 133.5, 131.9, 129.3, 128.5, 61.7, 60.5, 46.4, 42.7, 28.5, 14.2. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{16}H_{19}O_4S$ $[M + H]^+$ 307.09986, found 307.09875.

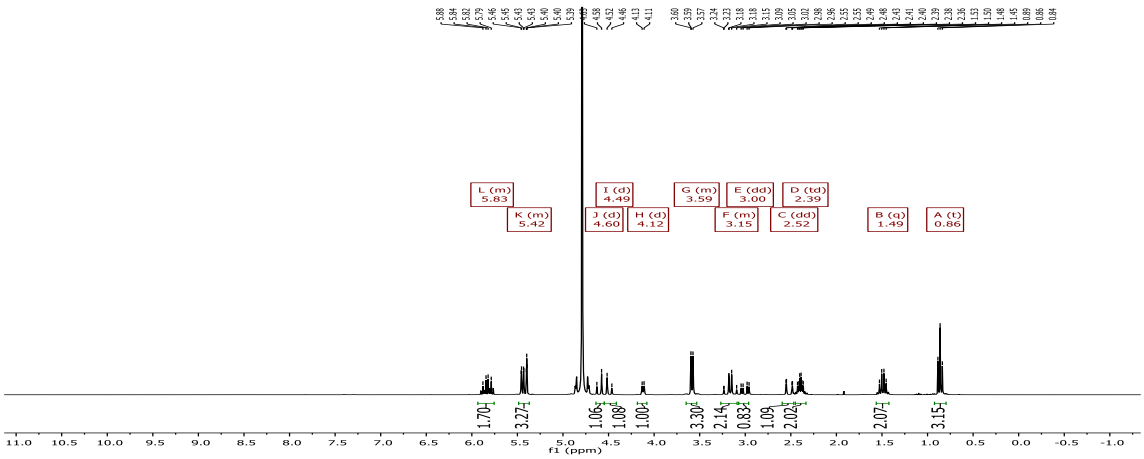


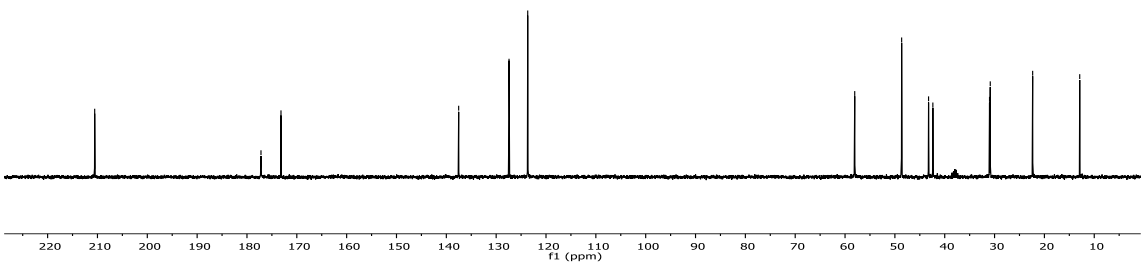
Diallyamine 2-(2-(hydroxymethyl)-5-oxo-3-(propylthio)cyclopent-1-en-1-yl)aceticetate 173



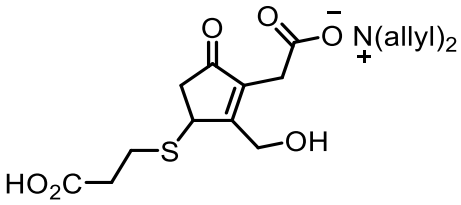
The titled compound was prepared according to general procedure using water as solvent. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 119 mg (87% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 – 4.51 (m, 2H), 4.17 – 3.97 (m, 1H), 3.69 (s, 3H), 3.41 (s, 2H), 2.97 (dd, J = 19.2, 6.8 Hz, 3H), 2.73 – 2.43 (m, 6H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 210.6, 177.2, 173.2, 137.5, 127.4, 123.7, 58.1, 48.6, 43.2, 42.4, 31.0, 30.9, 22.4, 12.9. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{11}H_{15}O_4S$ [M – $C_6H_{10}N$]$^-$ 243.06965, found 243.06950.



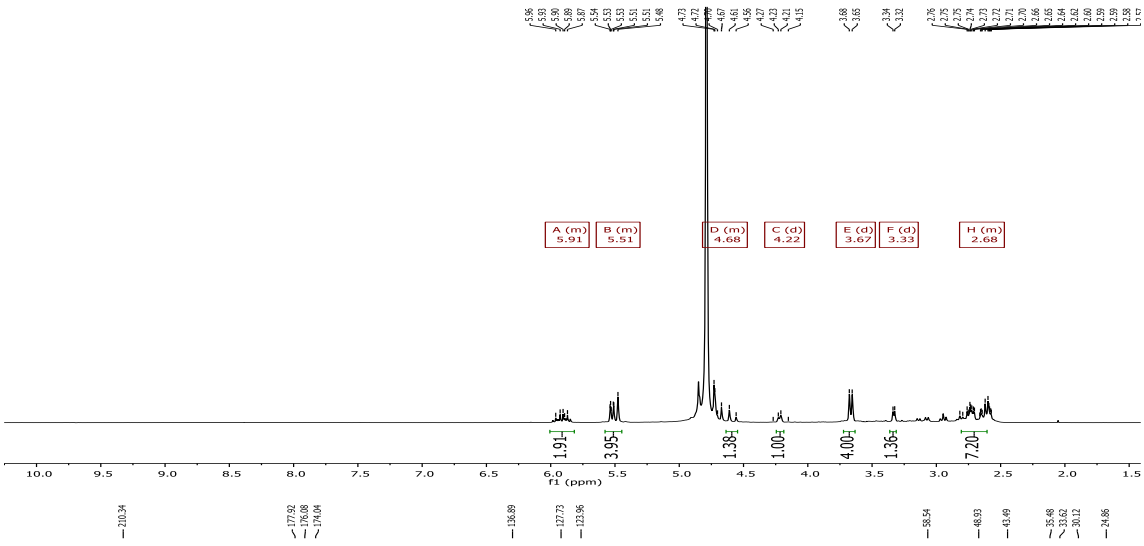


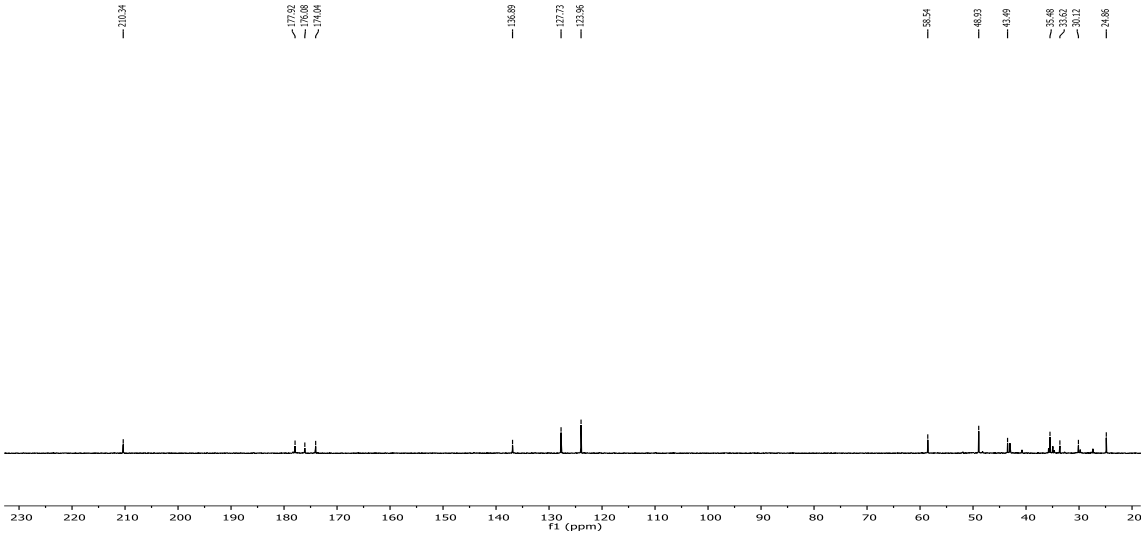
Diallyamine 3-((3-(carboxymethyl)-2-(hydroxymethyl)-4-oxocyclopent-2-en-1-yl)thio)propanate 174



The titled compound was prepared according to general procedure using water as solvent. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (9:1 to 2:8) affording 137 mg (92% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 – 5.78 (m, 1H), 5.64 – 5.39 (m, 4H), 4.73 – 4.45 (m, 7H), 4.22 (d, J = 5.9 Hz, 1H), 3.67 (d, J = 6.7 Hz, 2H), 3.33 (d, J = 4.0 Hz, 1H), 2.83 – 2.51 (m, 7H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 210.3, 177.9, 176.1, 174.0, 136.9, 127.7, 123.9, 58.5, 48.9, 43.5, 33.6, 24.9. **HRMS (ESI-MS)** *m/z* calcd For compound $C_{11}H_{13}O_6S$ $[M - C_6H_{10}N]^-$ 273.04383, found 273.04420.

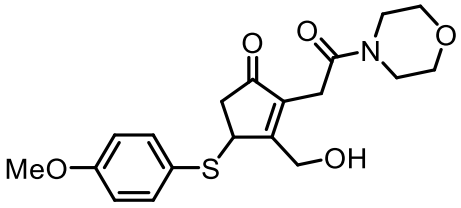




General Procedure for the synthesis of LCP-thioadducts in nucleophilic solvents

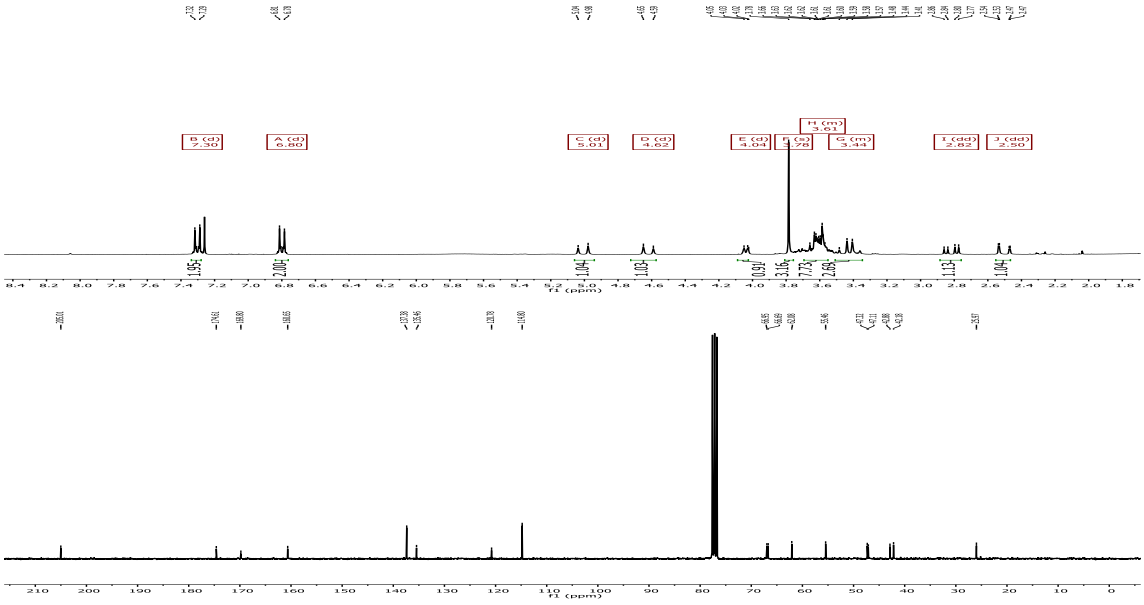
To a solution of **LCP** (100 mg, 0.40 mmol) in ACN (or iPrOH) (4 mL) was added the corresponding thiol (3 equiv, 1.2 mmol) and corresponding amine (5 equiv, 2.0 mmol) and the mixture was allowed to stir for 12 h. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography.

3-(hydroxymethyl)-4-((4-methoxyphenyl)thio)-2-(2-morpholino-2-oxoethyl)cyclopent-2-en-1-one 176

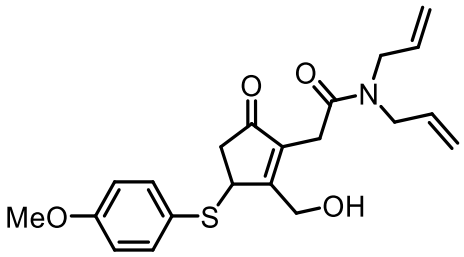


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (7:3 to 1:9) affording 106 mg (70% yield) of pure product as a yellow oil in ACN and 125 mg (82% yield) of pure product in iPrOH.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 5.01 (d, J = 17.8 Hz, 1H), 4.62 (d, J = 17.8 Hz, 1H), 4.04 (d, J = 6.5 Hz, 1H), 3.78 (s, 3H), 3.69 – 3.52 (m, 8H), 3.49 – 3.24 (m, 2H), 2.82 (dd, J = 19.3, 6.7 Hz, 1H), 2.50 (dd, J = 19.3, 1.7 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 205.01, 174.61, 169.80, 160.65, 137.38, 135.46, 120.78, 114.80, 66.95, 66.69, 62.08, 55.46, 47.32, 47.11, 42.88, 42.18, 25.97. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{19}H_{24}NO_5S$ $[M + H]^+$ 378.13697, found 378.13645.

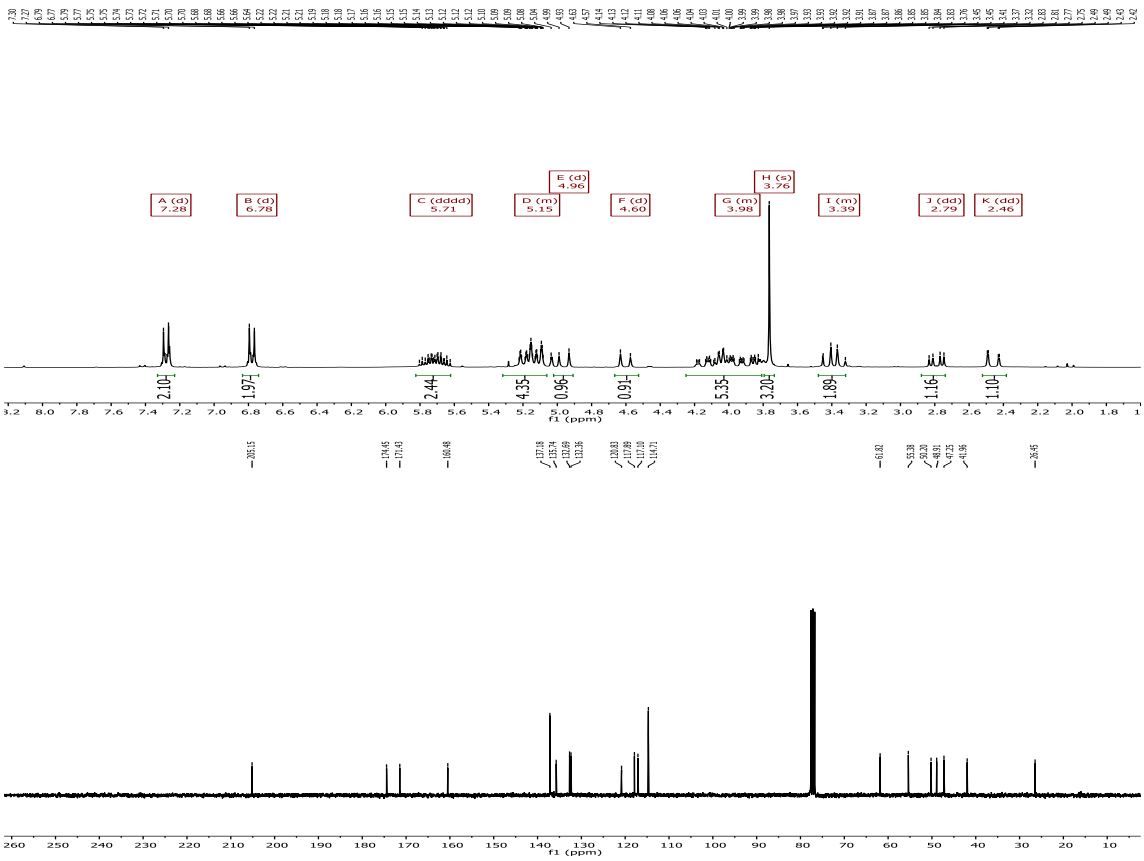


N,N-diallyl-2-(2-(hydroxymethyl)-3-((4-methoxyphenyl)thio)-5-oxocyclopent-1-en-1-yl)acetamide 157

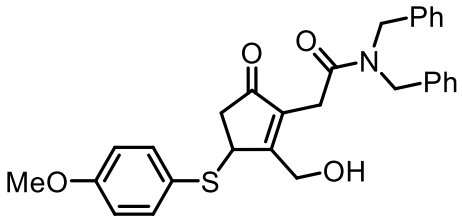


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (7:3 to 1:9) affording 131 mg (84% yield) of pure product as a yellow oil in ACN and 119 mg (76% yield) of pure product in iPrOH.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 5.71 (dddd, J = 22.9, 11.7, 10.2, 5.5 Hz, 2H), 5.42 – 5.03 (m, 4H), 4.96 (d, J = 17.4 Hz, 1H), 4.60 (d, J = 17.5 Hz, 1H), 4.33 – 3.82 (m, 5H), 3.76 (s, 3H), 3.60 – 3.23 (m, 2H), 2.79 (dd, J = 19.2, 6.7 Hz, 1H), 2.46 (dd, J = 19.2, 1.7 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 205.15, 174.45, 171.43, 160.48, 137.18, 135.74, 132.69, 132.36, 120.83, 117.89, 117.10, 114.71, 61.82, 55.38, 50.20, 48.91, 47.25, 41.96, 26.45. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{21}H_{26}NO_4S$ $[M + H]^+$ 388.15771, found 388.15623.

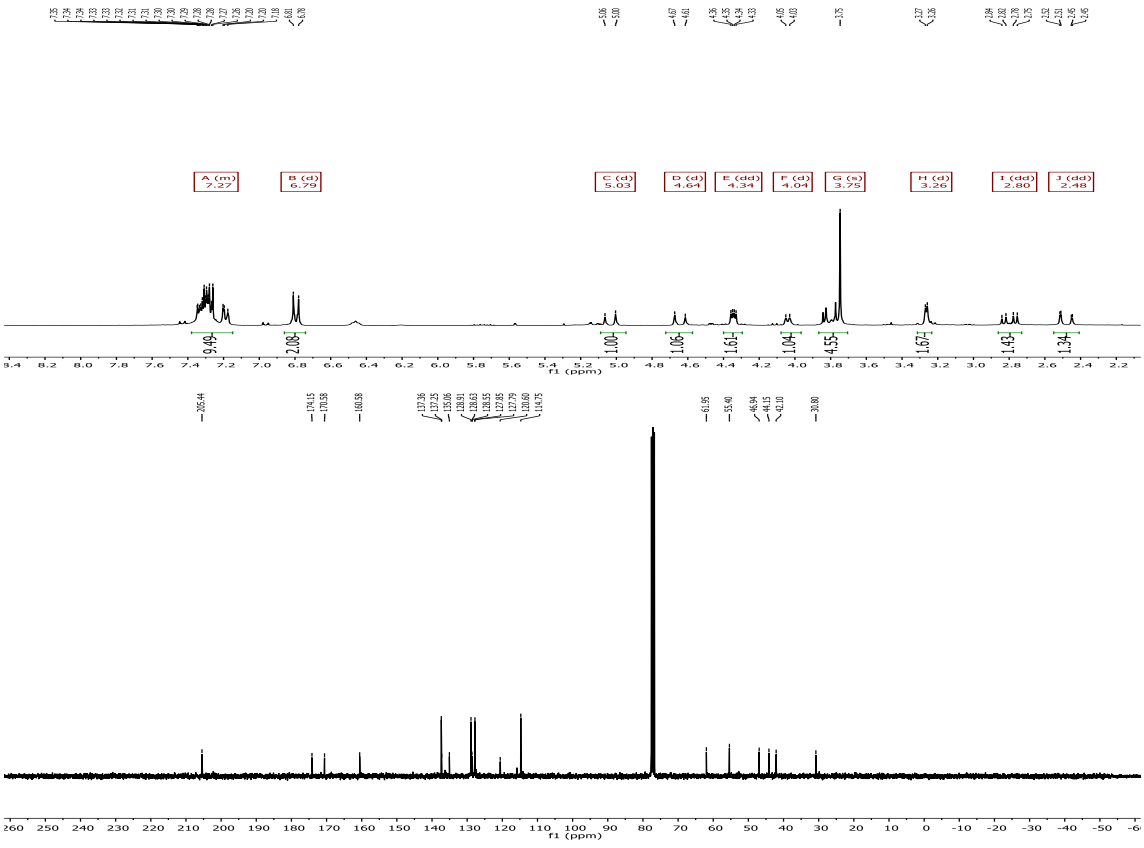


***N,N*-dibenzyl-2-(2-(hydroxymethyl)-3-((4-methoxyphenyl)thio)-5-oxocyclopent-1-en-1-yl)acetamide** R' = Bn: **175**

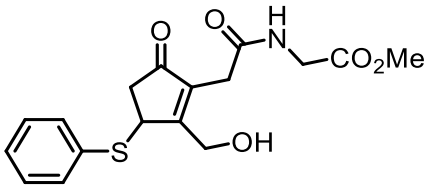


The titled compound was prepared according to general procedure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (7:3 to 1:9) affording 128 mg (65% yield) of pure product as a yellow oil in ACN and 157 mg (80% yield) of pure product is iPrOH.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.08 (m, 7H), 6.79 (d, J = 8.8 Hz, 2H), 5.03 (d, J = 17.8 Hz, 1H), 4.64 (d, J = 17.8 Hz, 1H), 4.34 (dd, J = 5.7, 2.9 Hz, 1H), 4.04 (d, J = 6.5 Hz, 1H), 3.75 (s, 4H), 3.26 (d, J = 3.3 Hz, 2H), 2.80 (dd, J = 19.2, 6.7 Hz, 1H), 2.48 (dd, J = 19.3, 1.7 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 205.44, 174.15, 170.58, 160.58, 137.36, 137.25, 135.06, 128.91, 128.63, 128.55, 127.85, 127.79, 120.60, 114.75, 61.95, 55.40, 46.94, 44.15, 42.10, 30.80. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{29}H_{30}NO_4S$ $[M + H]^+$ 488.18901, found 488.18945.

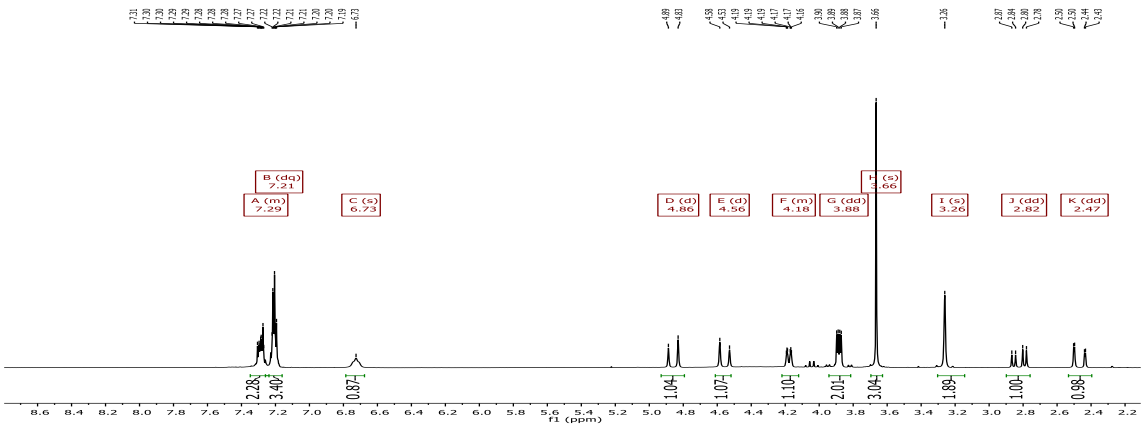


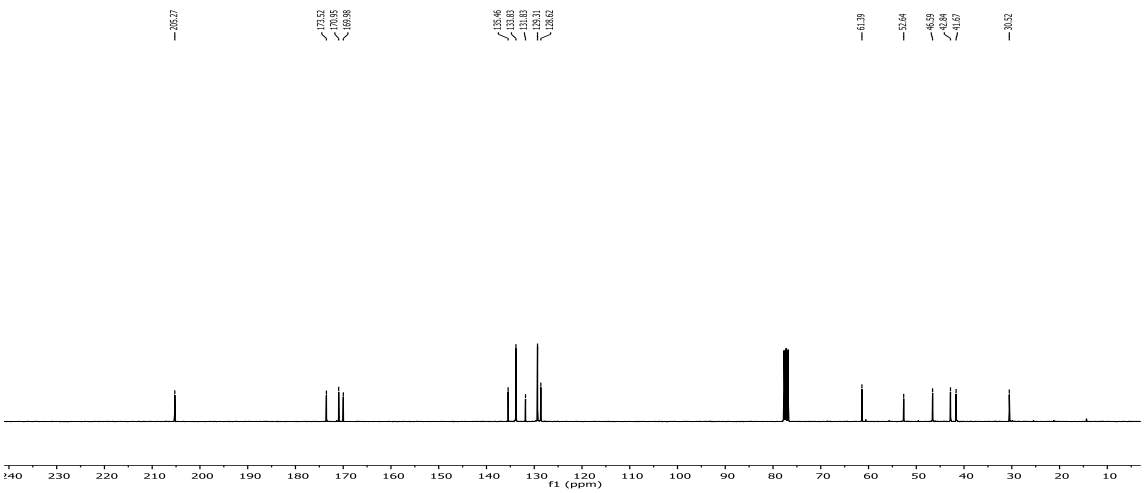
methyl (2-(2-(hydroxymethyl)-3-((4-methoxyphenyl)thio)-5-oxocyclopent-1-en-1-yl)acetyl)glycinate 177



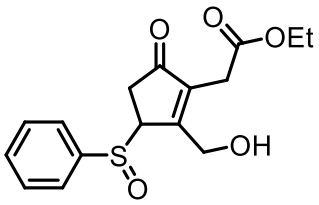
The titled compound was prepared according to general procedure in iPrOH. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (7:3 to 1:9) affording 99 mg (70% yield) of pure product as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$ δ 7.45 – 7.23 (m, 2H), 7.21 (dq, J = 3.5, 2.1, 1.7 Hz, 3H), 6.73 (s, 1H), 4.86 (d, J = 17.1 Hz, 1H), 4.56 (d, J = 17.2 Hz, 1H), 4.33 – 4.01 (m, 1H), 3.88 (dd, J = 5.5, 2.6 Hz, 2H), 3.66 (s, 3H), 3.26 (s, 2H), 2.82 (dd, J = 19.2, 6.7 Hz, 1H), 2.47 (dd, J = 19.3, 1.8 Hz, 1H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 205.27, 173.52, 170.95, 169.98, 135.46, 133.83, 131.83, 129.31, 128.62, 61.39, 52.64, 46.59, 42.84, 41.67, 30.52. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{17}H_{19}NNaO_5S$ $[M + Na]^+$ 372.08761, found 372.08750.



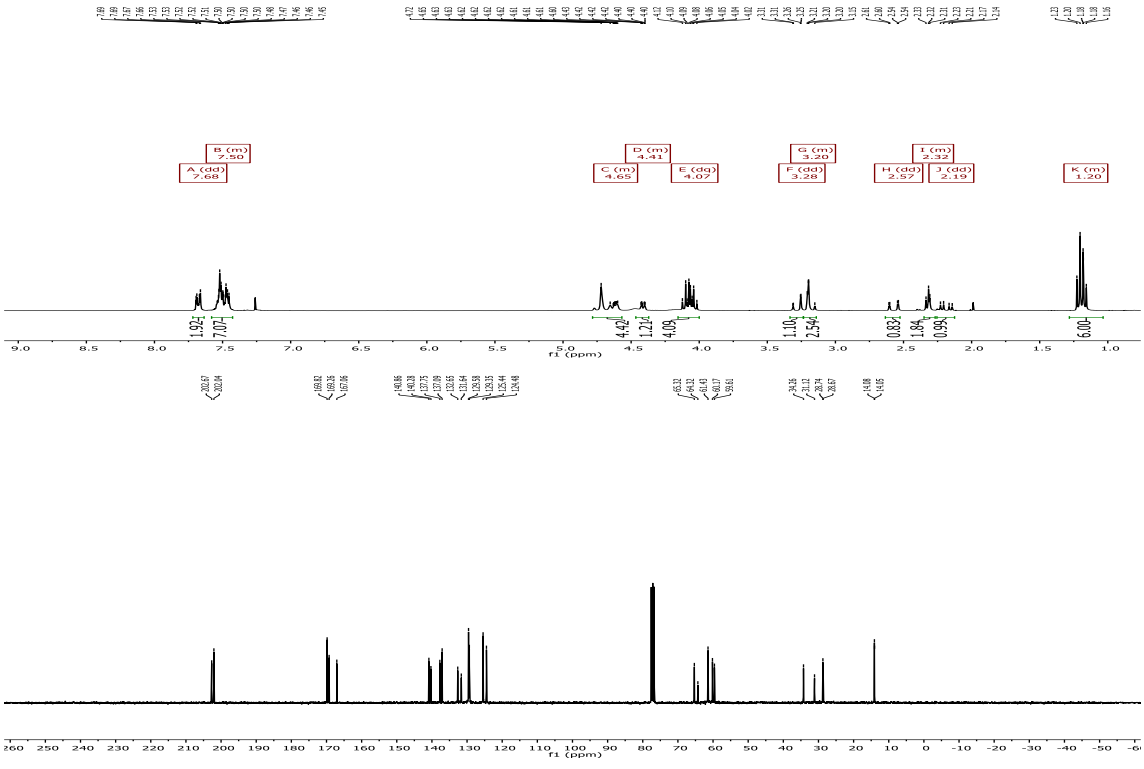


Oxidation of thio-adduct CP to ethyl 2-(2-(hydroxymethyl)-5-oxo-3-(phenylsulfinyl)cyclopent-1-en-1-yl)acetate 182

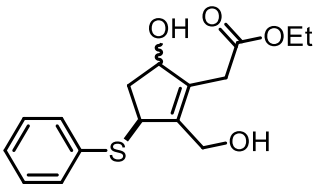


To a solution of **CP** (100 mg, 0.32 mmol) in DCM (3.2 mL) was added mCPBA (56 mg, 1 equiv, 0.32 mmol) at -40 ºC and the mixture was allowed to stir for 1 h. The reaction was quenched with Na_2SO_3 (aq) and the mixture was extracted with DCM (2 x 5 mL). The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography using hexane:ethyl acetate (7:3 to 1:9) affording 85 mg (81% yield) of pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$ δ 7.68 (dd, J = 7.7, 1.9 Hz, 2H), 7.62 – 7.38 (m, 8H), 4.91 – 4.49 (m, 4H), 4.54 – 4.35 (m, 1H), 4.07 (dq, J = 10.5, 7.1 Hz, 4H), 3.28 (dd, J = 16.7, 1.0 Hz, 1H), 3.24 – 3.08 (m, 2H), 2.57 (dd, J = 19.0, 1.9 Hz, 1H), 2.48 – 2.27 (m, 2H), 2.19 (dd, J = 19.0, 6.9 Hz, 1H), 1.54 – 1.02 (m, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 202.67, 202.04, 169.82, 169.26, 167.06, 140.86, 137.75, 137.09, 132.65, 131.64, 129.58, 129.35, 125.44, 124.48, 65.32, 64.32, 61.43, 60.17, 59.61, 34.26, 31.12, 28.74, 28.67, 14.08, 14.05. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{16}H_{19}O_5S$ $[M + H]^+$ 323.09477, found 323.09512.



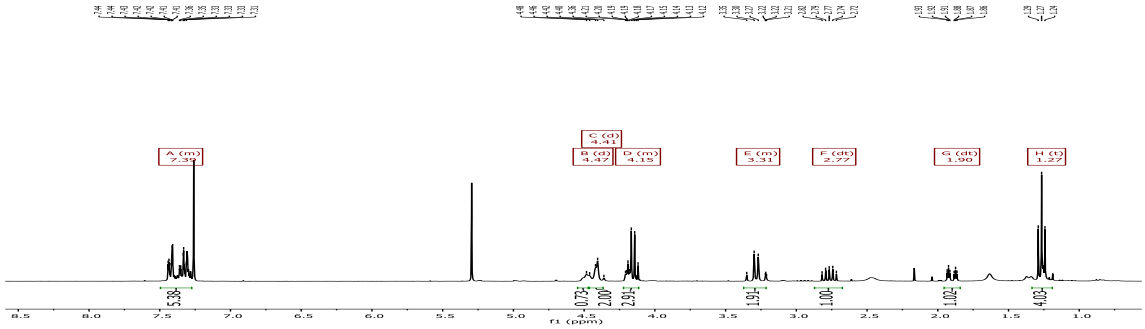
ethyl 2-((3,5)-5-hydroxy-2-(hydroxymethyl)-3-(phenylthio)cyclopent-1-en-1-yl)acetate 180, 180

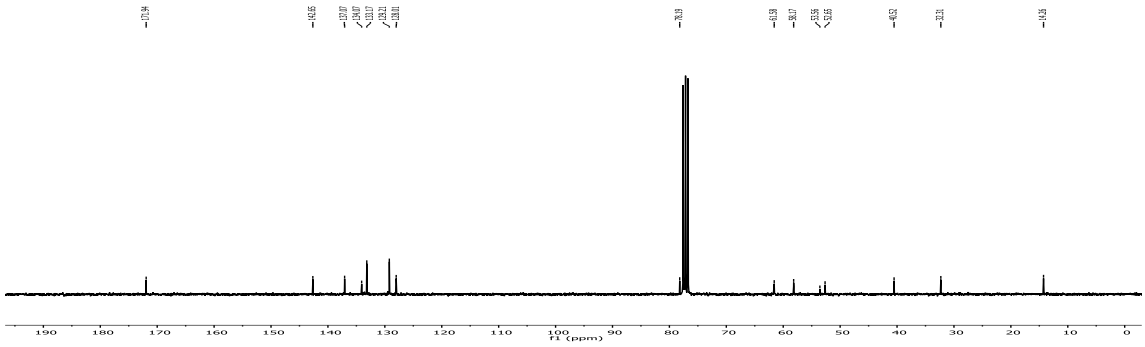


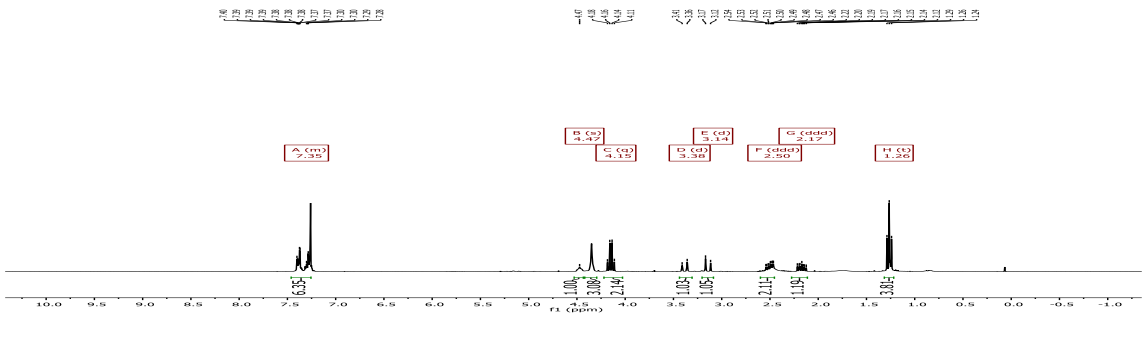
To a solution of a CP (100 mg, 0.32 mmol) in anhydrous MeOH (3.2 mL) was added $CeCl_3.7H_2O$ (121 mg, 0.32 mmol, 1 equiv) at -40 ºC. $LiBH_4$ (7 mg, 0.32 mmol, 1 equiv) was added and the reaction was stirred until total consumption of the starting material. The reaction was quenched by the addition of a sat. aq. sol. NH_4Cl (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phases were dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The crude mixture was purified by flash chromatography using hexane:ethyl acetate (1:1) affording two fractions, one 47 mg (47% yield) of pure product as a yellow oil and the othe diastereoisomer in 43 mg (47% yield) of pure product as a yellow oil.

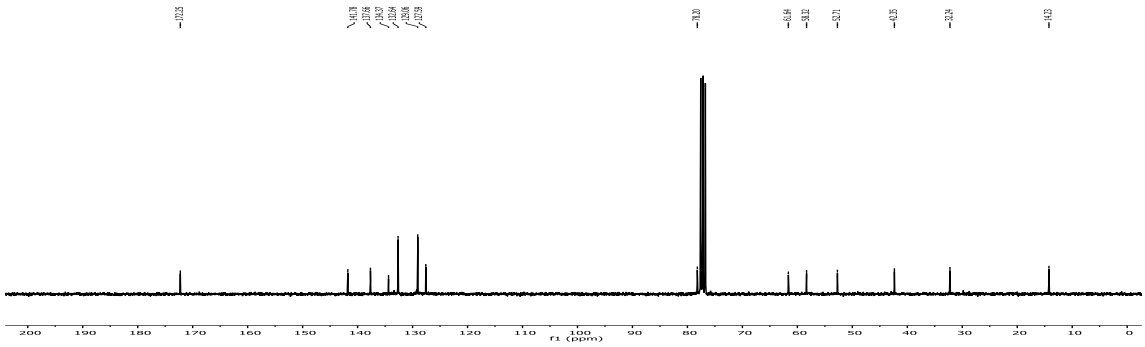
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.31 (m, 5H), 4.47 (d, J = 6.6 Hz, 1H), 4.41 (d, J = 4.5 Hz, 2H), 4.32 – 3.75 (m, 3H), 3.44 – 3.10 (m, 2H), 2.77 (dt, J = 15.3, 7.6 Hz, 1H), 1.90 (dt, J = 15.0, 2.9 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 171.94, 142.65, 137.07, 134.07, 133.17, 129.21, 128.01, 61.58, 58.17, 53.56, 52.65, 40.52, 32.31, 14.26. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{16}H_{20}O_4S$ $[M + Na]^+$ 331.09745, found 331.09579.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5H), 4.47 (s, 1H), 4.35 (s, 3H), 4.15 (q, J = 7.1 Hz, 2H), 3.38 (d, J = 15.7 Hz, 2H), 3.14 (d, J = 15.7 Hz, 1H), 2.50 (ddd, J = 14.1, 7.1, 2.3 Hz, 1H), 2.17 (ddd, J = 13.9, 8.0, 5.6 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 172.25, 141.78, 137.66, 134.37, 132.64, 129.06, 127.59, 61.64, 58.32, 52.71, 42.35, 32.24, 14.23. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{16}H_{20}O_4S$ $[M + Na]^+$ 331.09745, found 331.09579.

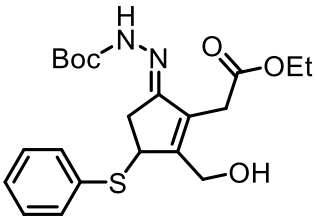

A (m)
7.35
C (d)
4.41
B (d)
4.47
D (m)
4.15
E (m)
3.31
F (dt)
2.27
G (dt)
1.90
H (t)
1.27
5.38
0.73
2.00
2.91
1.94
1.00
1.00
4.03
f1 (ppm)


f1 (ppm)


A (m)
7.35
B (s)
4.47
C (q)
4.15
D (d)
3.39
E (d)
3.14
F (ddd)
2.50
G (ddd)
2.17
H (t)
1.26
6.25
1.04
3.08
2.14
1.03
1.05
2.11
1.19
3.04
f1 (ppm)

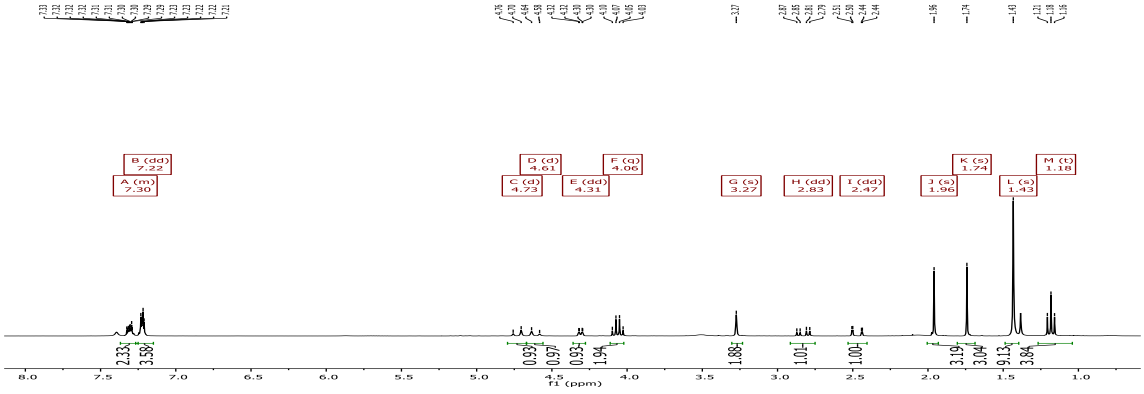

f1 (ppm)

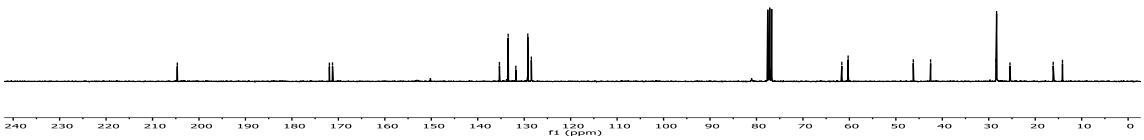
tert-butyl (E)-2-(2-(2-ethoxy-2-oxoethyl)-3-(hydroxymethyl)-4-(phenylthio)cyclopent-2-en-1-ylidene)hydrazine-1-carboxylate 183



To a solution of **CP** (100 mg, 0.32 mmol) in anhydrous MeOH (3.2 mL) was added boc-hydrazine (2 equiv, 86 mg, 0.64 mmol). The solution was allowed to stir for 10 min. The solvent was evaporated under reduce pressure, the crude mixture was washed with cold diethyl ether to remove excess hydrazine. The product was further purified by flash chromatography using hexane:ethyl acetate (1:1) affording 111 mg (81% yield) of a pure product as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.22 (dd, J = 3.9, 2.5 Hz, 3H), 4.73 (d, J = 15.9 Hz, 1H), 4.61 (d, J = 16.0 Hz, 1H), 4.31 (dd, J = 6.7, 1.0 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 3.27 (s, 2H), 2.83 (dd, J = 19.2, 6.7 Hz, 1H), 2.47 (dd, J = 19.2, 1.8 Hz, 1H), 1.96 (s, 3H), 1.74 (s, 3H), 1.43 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.67, 171.94, 171.26, 135.33, 133.45, 131.80, 129.23, 128.46, 61.64, 60.27, 46.25, 42.52, 28.46, 28.37, 28.31, 25.44, 16.13, 14.13 **HRMS (ESI-MS)** *m/z* calcd For compound $C_{21}H_{29}N_2O_5S$ $[M + H]^+$ 421.17917, found 421.17803.



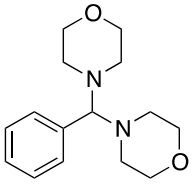


VI.3. Chapter IV

General procedure for the preparation of aminals

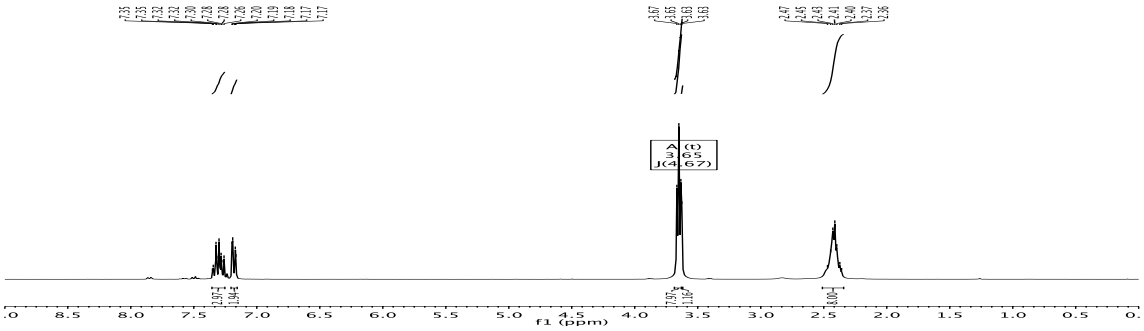
To a solution of aldehyde (1.88 mmol, 200 mg) in water (4 M) was added the corresponding amine (2.2 eq, 4.15 mmol) or diamine/aminoethanol (1.2 eq, 2.56 mmol) and a solution of $Cu(OTf)_2$ (0.1 mol%). The reaction mixture was stirred at room temperature for 2 minutes and then the precipitation of the desired product occurred in quantitative yield. All the compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy.

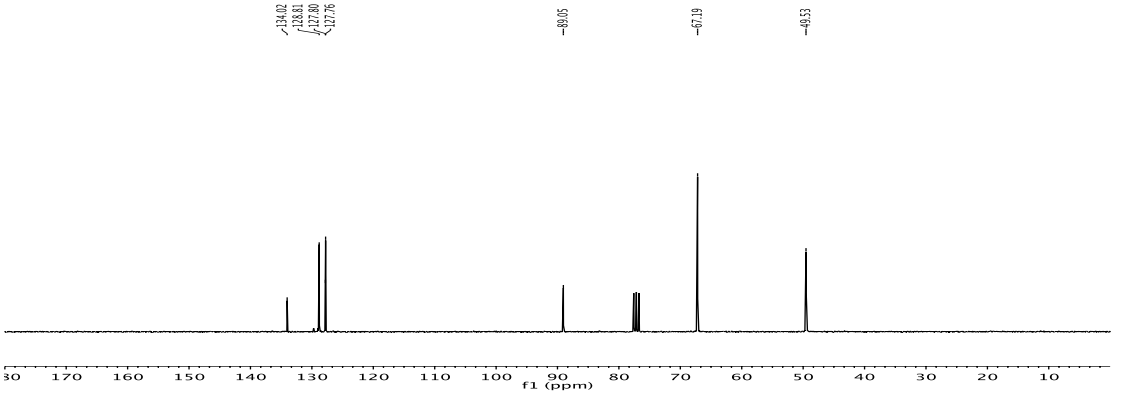
4,4'-(phenylmethylene)dimorpholine 685



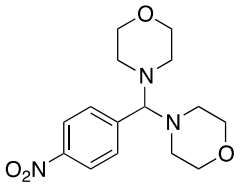
The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (493 mg) as a yellow/white solid. The spectral data are in agreement with the literature.[185]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.26 (m, 3H), 7.20-7.17 (m, 2H), 3.66 (t, J = 4.67 Hz, 8H), 3.63 (s, 1H), 2.47-2.36 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 134.0, 128.8, 127.8, 127.8, 89.1, 67.2, 49.5 ppm.



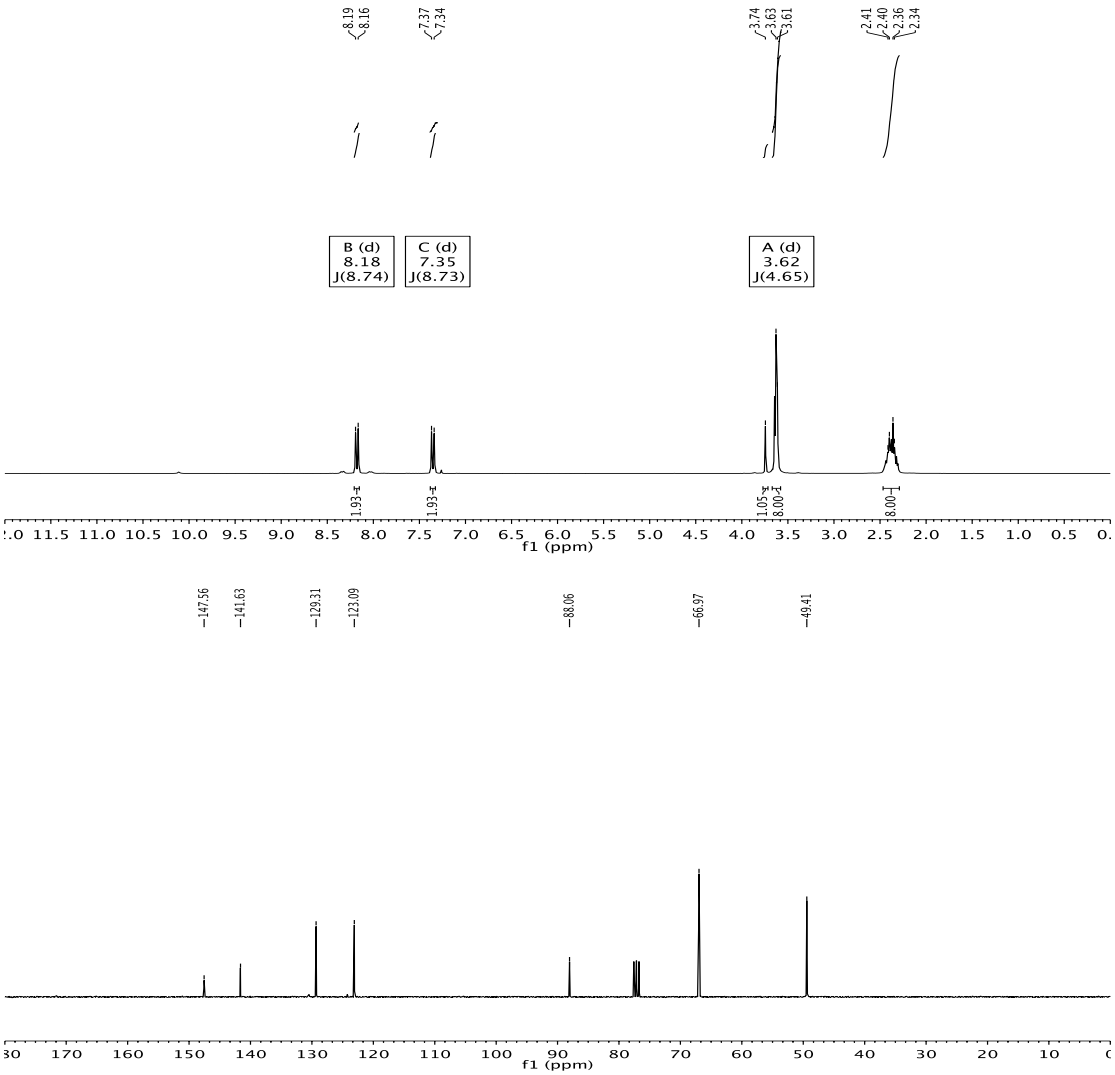


4,4'-((4-nitrophenyl)methylene)dimorpholine 699

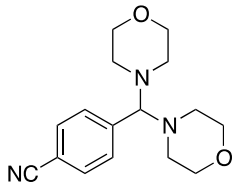


The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (407 mg) as a brownish solid. The spectral data are in agreement with the literature.[186,187]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 8.74 Hz, 2H), 7.35 (d, J = 8.73 Hz, 2H), 3.74 (s, 1H), 3.62 (t, J = 4.65 Hz, 8H), 2.41-2.34 (m, 8H) ppm.**^{13}C NMR (75 MHz, $CDCl_3$) δ** 147.6, 141.6, 129.3, 123.1, 88.1, 67.0, 49.4 ppm.

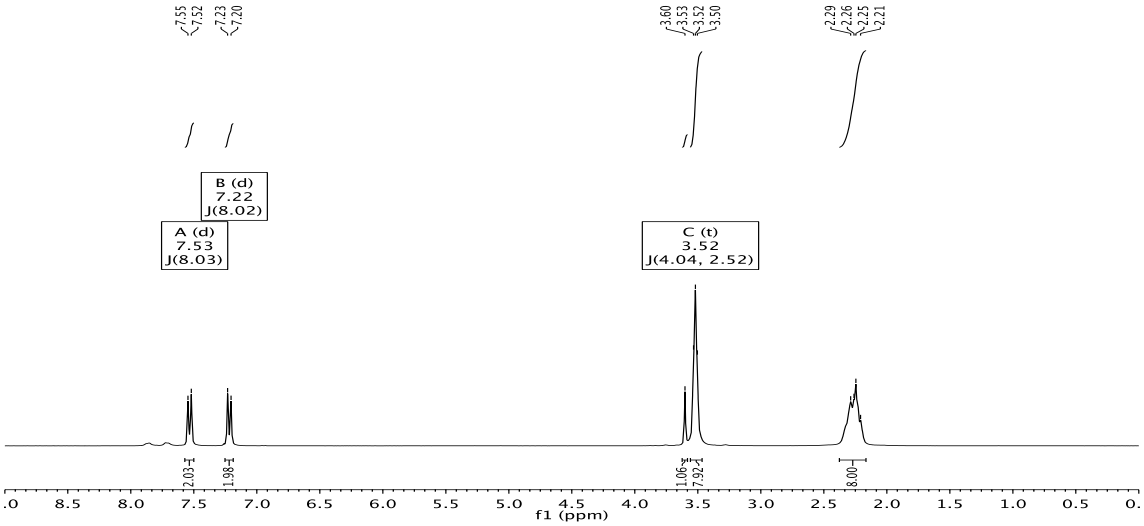


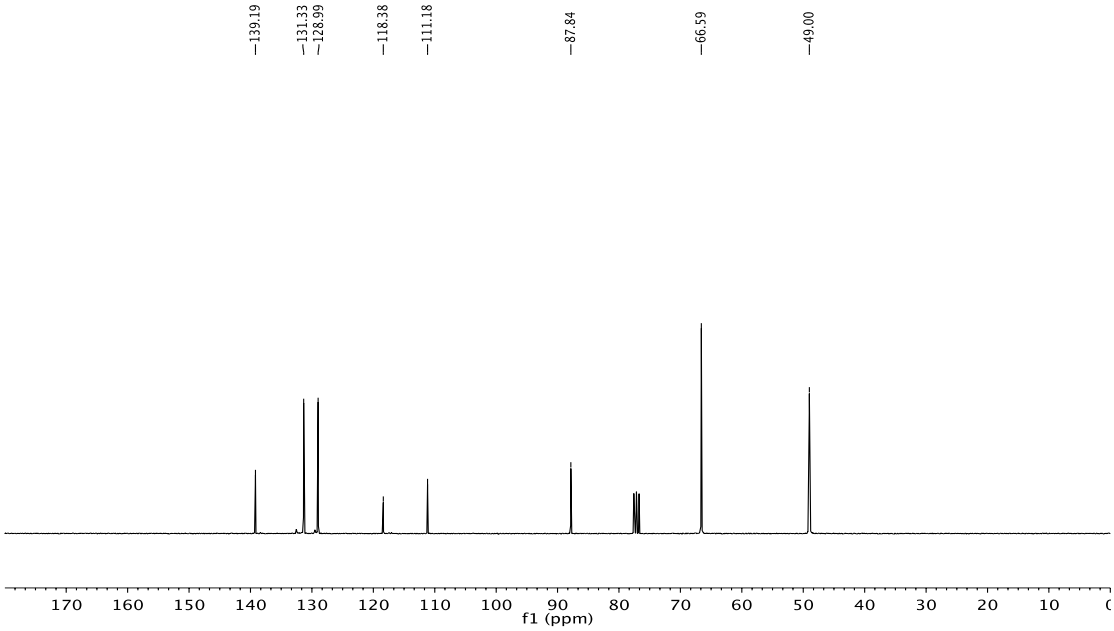
4-(dimorpholinomethyl)benzonitrile 700



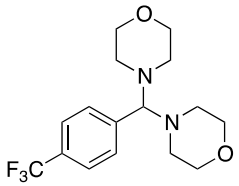
The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (439 mg) as a faint yellow solid. The spectral data are in agreement with the literature.[186]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.03 Hz, 2H), 7.22 (d, J = 8.02 Hz, 2H), 3.60 (s, 1H), 3.52 (t, J = 4.04 Hz, J = 2.52 Hz, 8H), 2.29-2.21 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 139.2, 131.3, 129.0, 118.4, 111.2, 87.8, 66.6, 49.00 ppm.



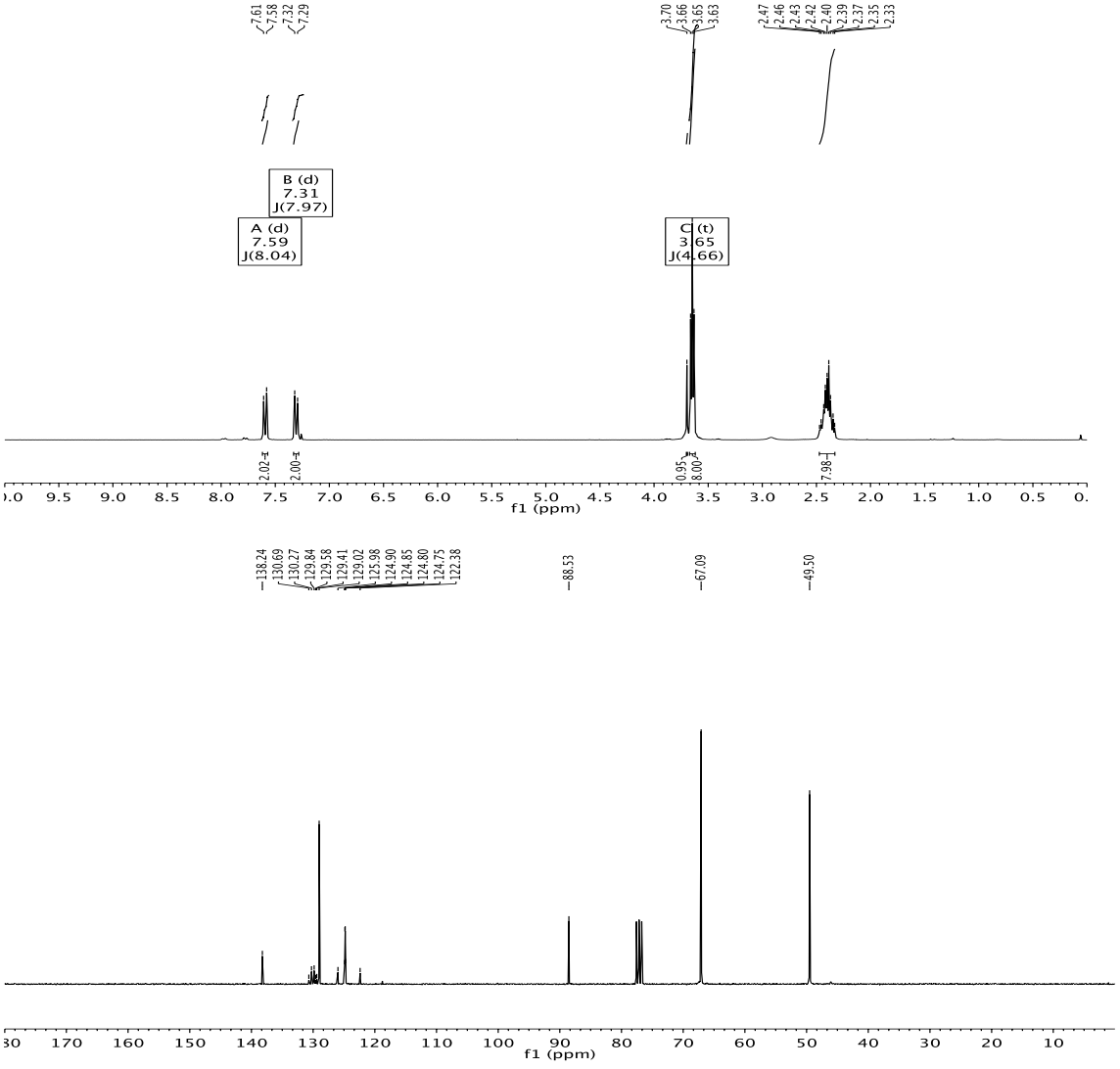


4,4'-((4-(trifluoromethyl)phenyl)methylene)dimorpholine 698

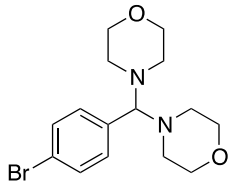


The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (379 mg) as a white solid. The spectral data are in agreement with the literature.[186]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.04 Hz, 2H), 7.31 (d, J = 7.97 Hz, 2H), 3.70 (s, 1H) 3.65 (t, J = 4.66 Hz, 8H), 2.47-2.33 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 138.2, 130.7, 130.3, 129.8, 129.6, 129.4, 129.0, 126.0, 124.9, 124.9, 124.8, 124.8, 122.4, 88.5, 67.1, 49.5 ppm.

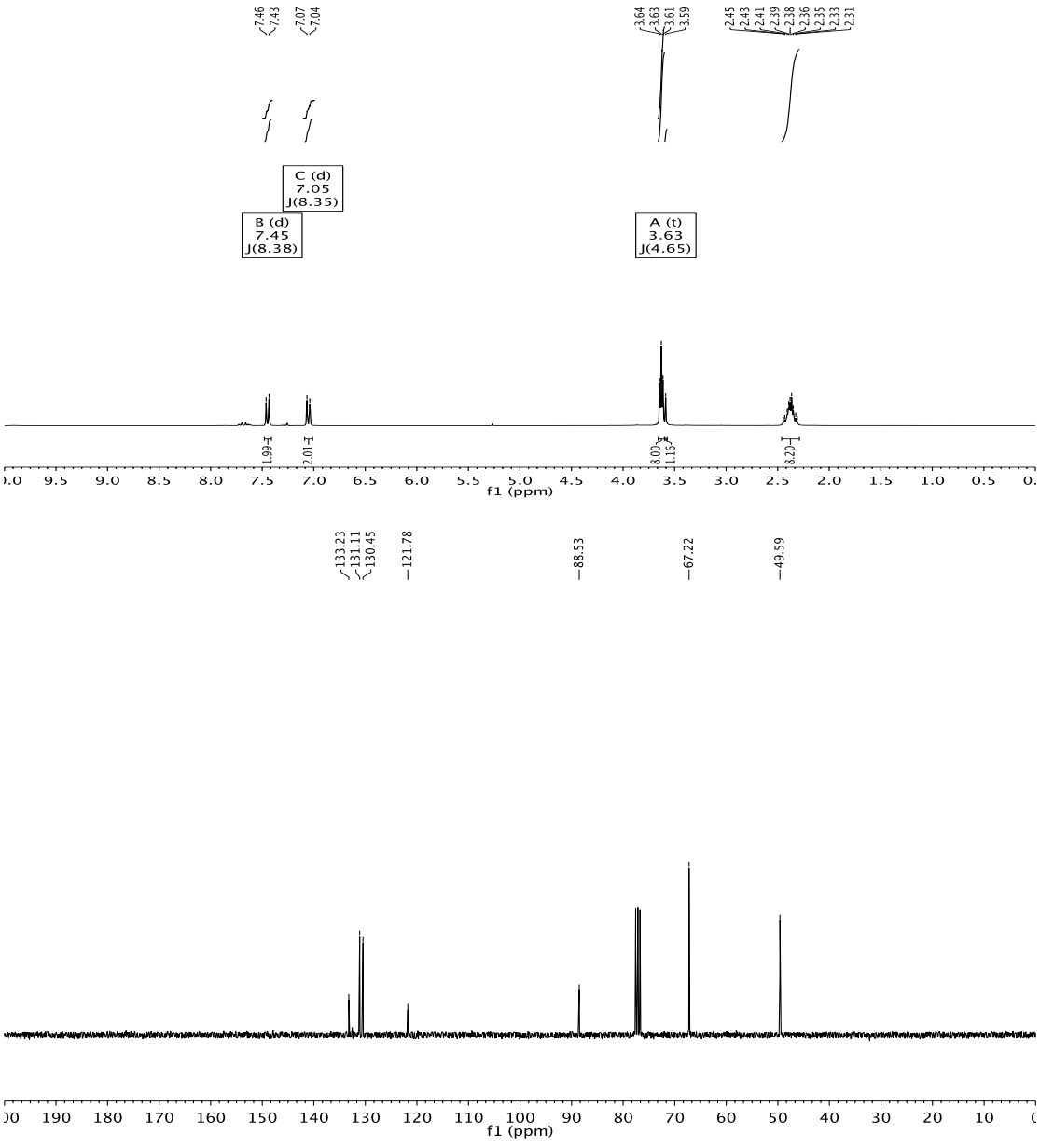


4,4'-((4-bromophenyl)methylene)dimorpholine 697

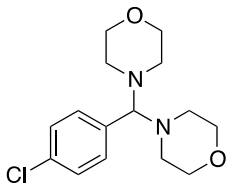


The title compound was prepared according to the general procedure. The product was prepared according to GPA in 100 mg scale. The product was isolated in quantitative yield (184 mg) as a white solid. The spectral data are in agreement with the literature.[188]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.38, 2H), 7.05 (d, J = 8.35 Hz, 2H), 3.63 (t, J = 4.65 Hz, 8H), 3.59 (s, 1H), 2.45-2.31 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 133.2, 131.1, 130.5, 121.8, 88.5, 67.2, 49.6 ppm.

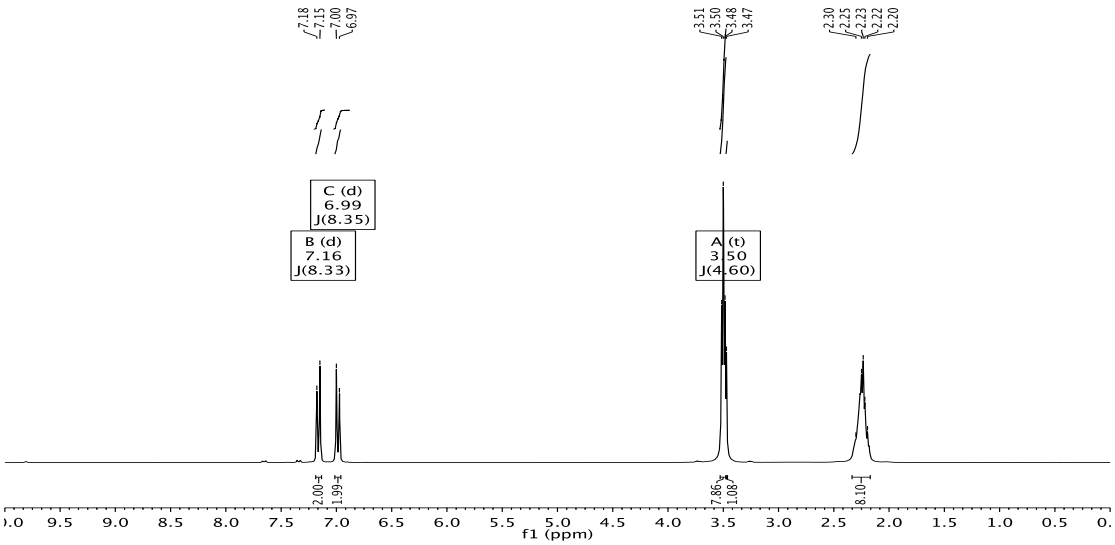


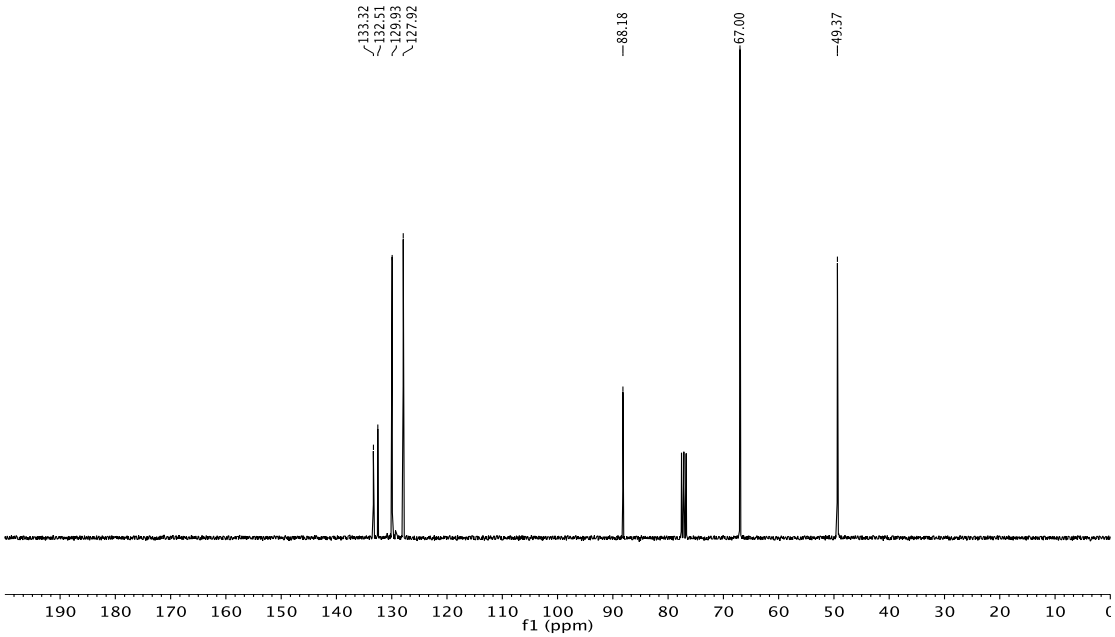
4,4'-((4-chlorophenyl)methylene)dimorpholine 696



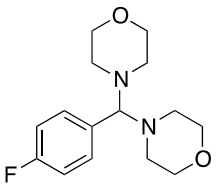
The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (422 mg) as a yellow/white solid. The spectral data are in agreement with the literature.[186]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.33 Hz, 2H), 6.99 (d, J = 8.35 Hz, 2H), 3.50 (t, J = 4.60 Hz, 8H), 3.47 (s, 1H), 2.30-2.20 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 133.3, 132.5, 129.9, 127.9, 88.2, 67.0, 49.4 ppm.





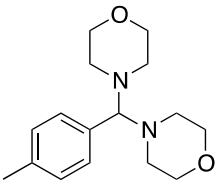
4,4'-((4-fluorophenyl)methylene)dimorpholine 695



The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (450 mg) as a yellow solid. The spectral data are in agreement with the literature.[189]

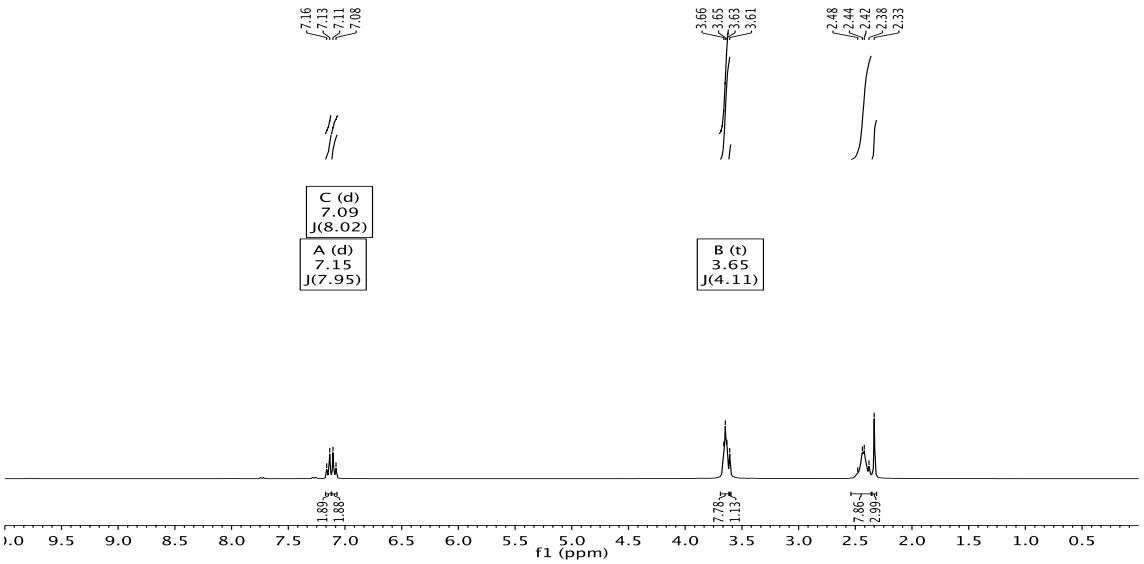
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (dd, J = 8.70 Hz, J = 5.62 Hz, 2H), 6.99 (t, J = 8.70 Hz, 2H), 3.62 (t, J = 4.66 Hz, 8H), 3.59 (s, 1H), 2.38-2.30 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 163.9, 160.6, 130.2, 130.1, 129.9, 129.8, 114.8, 114.5, 88.2, 67.1, 49.4 ppm.

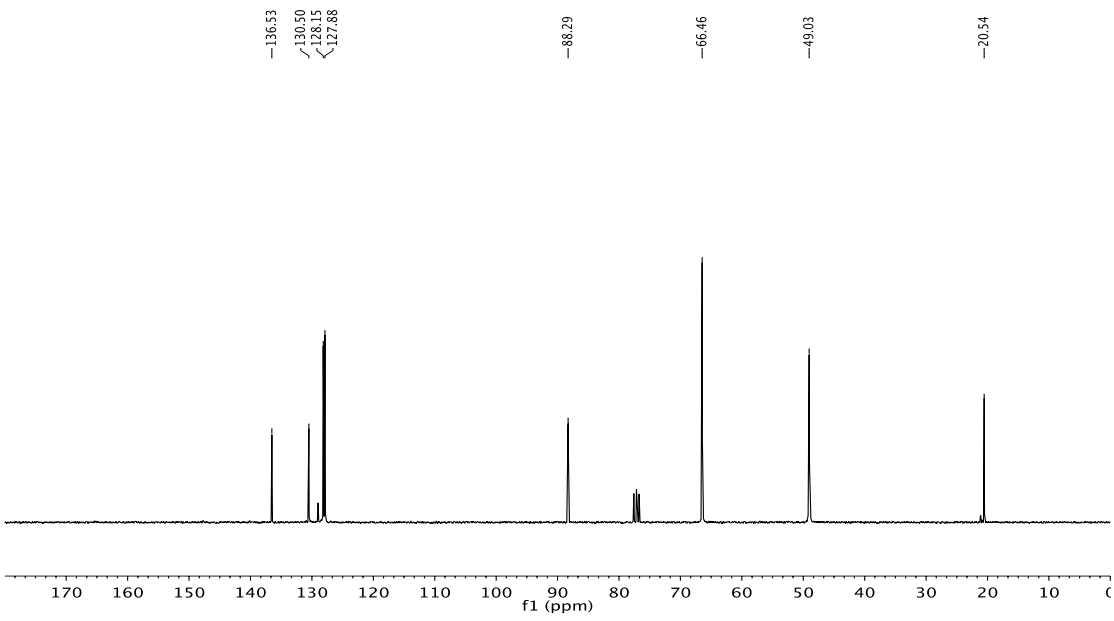
4,4'-(p-tolylmethylene)dimorpholine 692



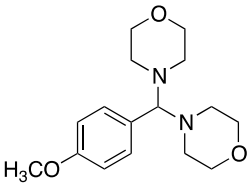
The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (460 mg) as a yellow/white solid. The spectral data are in agreement with the literature.[186,187]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 7.95 Hz, 2H), 7.09 (d, J = 8.02 Hz, 2H), 3.65 (t, J = 4.11 Hz, 8H), 3.61 (s, 1H), 2.48-2.38 (m, 8H), 2.33 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 136.5, 130.5, 128.2, 127.9, 88.3, 66.5, 49.0, 20.5 ppm.



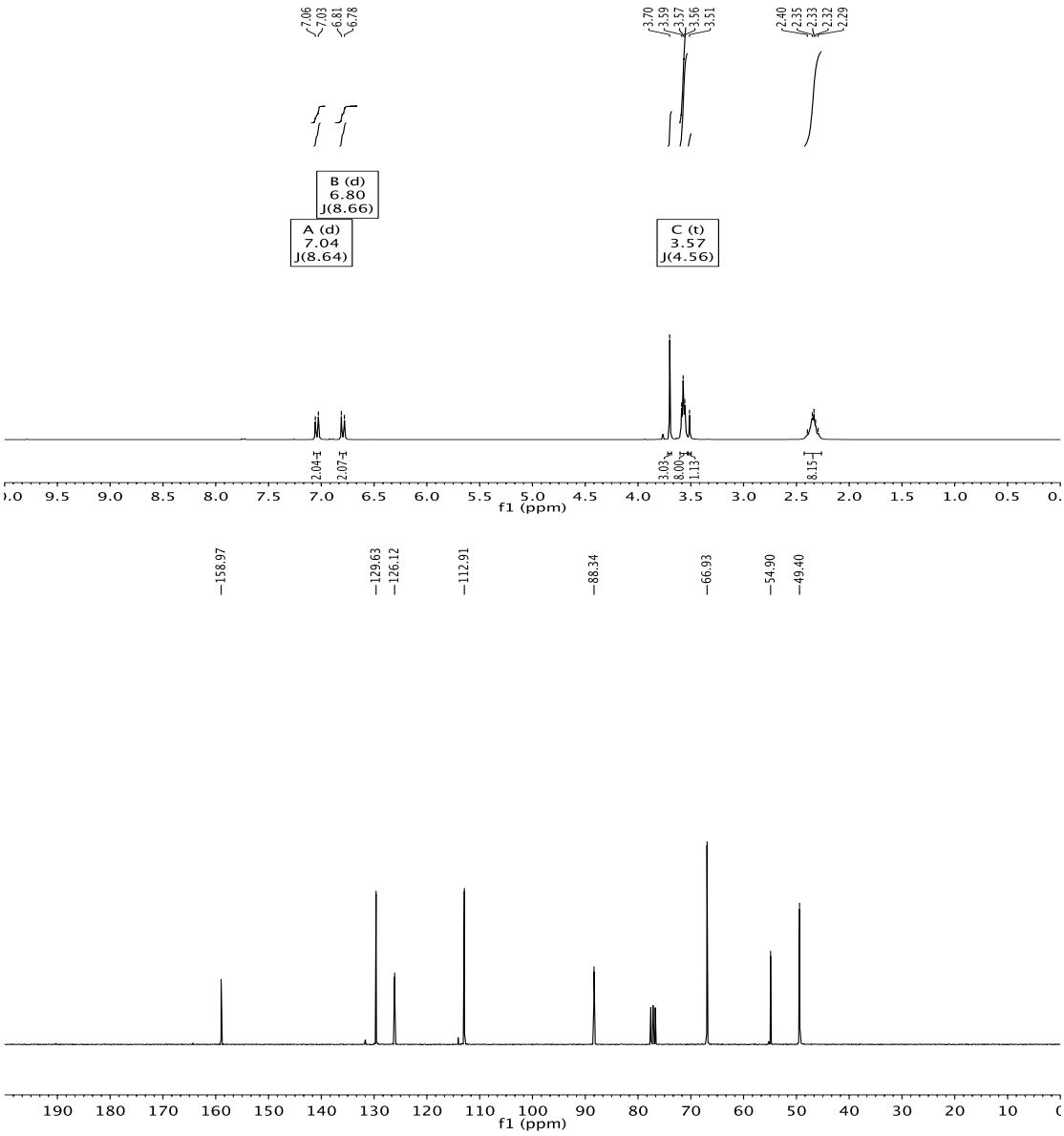


4,4'-((4-methoxyphenyl)methylene)dimorpholine 693

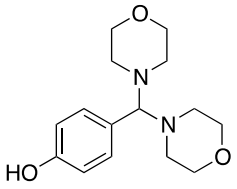


The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (429 mg) as a yellow/white solid. The spectral data are in agreement with the literature.[186]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J = 8.64 Hz, 2H), 6.80 (d, J = 8.66 Hz, 2H), 3.70 (s, 3H), 3.57 (t, J = 4.56 Hz, 8H), 3.51 (s, 1H), 2.40-2.29 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 159.0, 129.6, 126.1, 112.9, 88.3, 66.9, 54.9, 49.4 ppm.

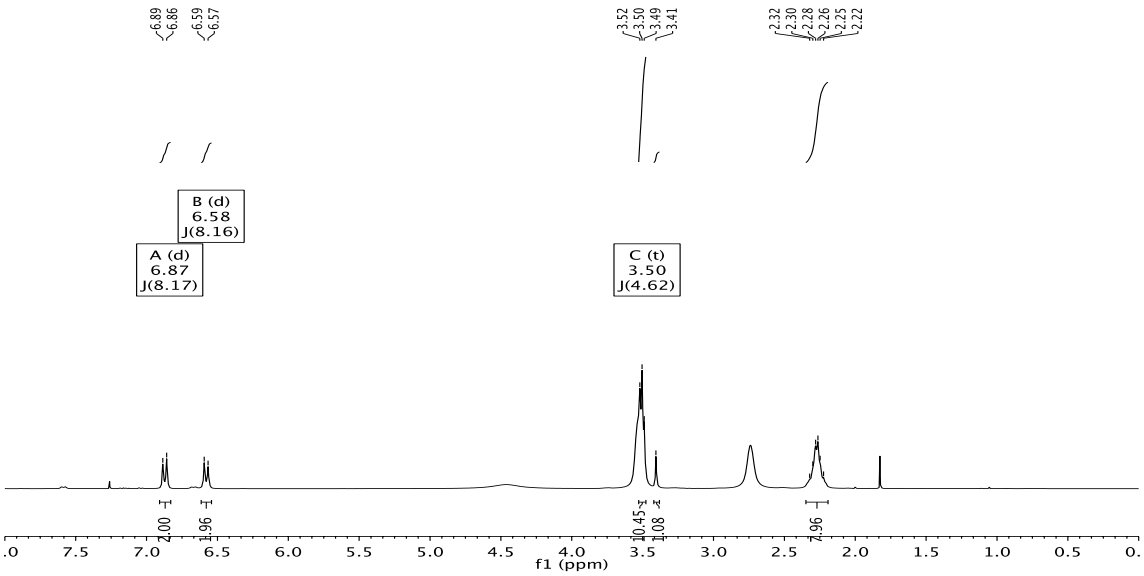


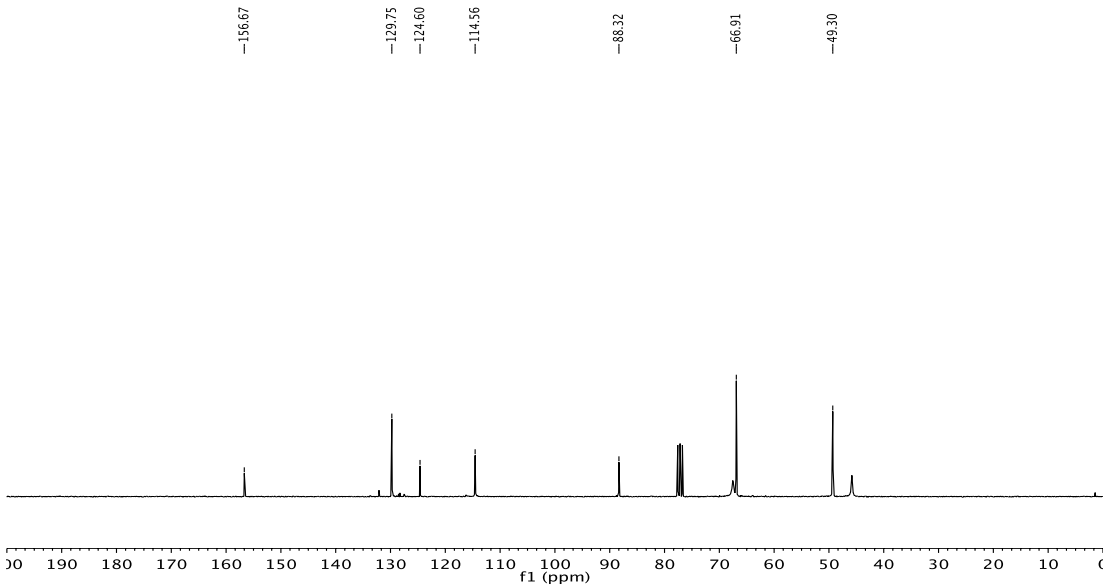
4- (dimorpholinomethyl)phenol 694



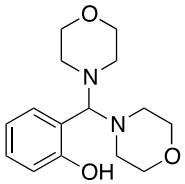
The title compound was prepared according to the general procedure in 50 mg scale. The product was isolated in quantitative yield (114 mg) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, J = 8.17 Hz, 2H), 6.58 (d, J = 8.16 Hz, 2H), 3.50 (t, J = 4.62 Hz, 8H), 3.41 (s, 1H), 2.32-2.22 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 156.7, 129.8, 124.6, 114.6, 88.3, 66.9, 49.3 ppm. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{15}H_{22}N_2KO_3$ [M+K^+] 317.1262, found 317.12610.



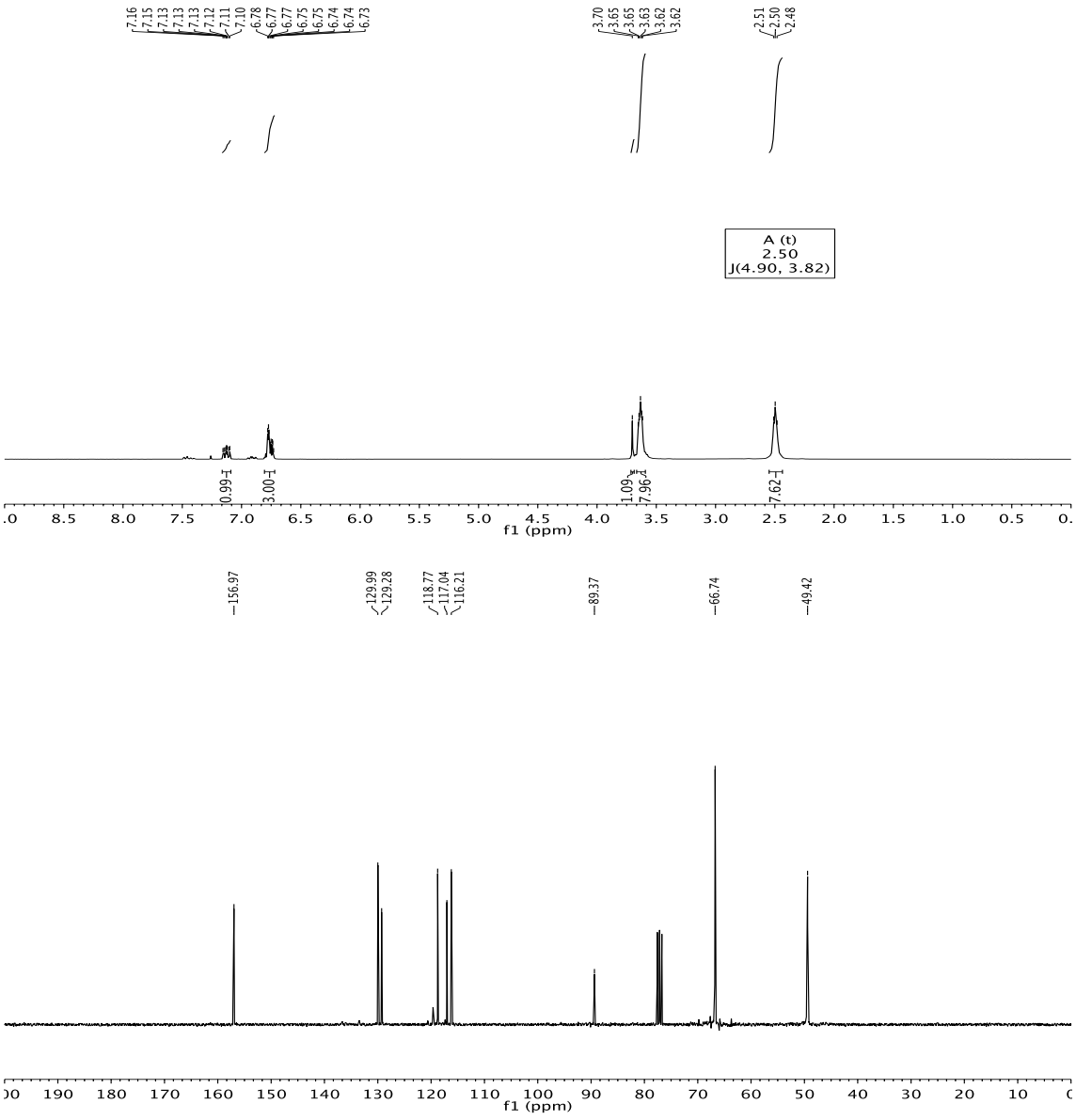


2-(dimorpholinomethyl)phenol 703

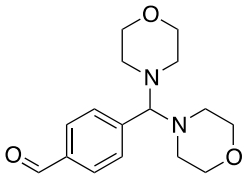


The title compound was prepared according to the general procedure in 50 mg scale. The product was isolated in quantitative yield (114 mg) as a brown oil. The spectral data are in agreement with the literature.[190]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.10 (m, 1H), 6.78-6.73 (m, 3H), 3.70 (s, 1H), 3.65-3.62 (m, 8H), 3.50 (t, J = 4.90 Hz, J = 3.82 Hz, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 157.0, 130.0, 129.3, 118.8, 117.0, 116.2, 89.4, 66.7, 49.4 ppm.

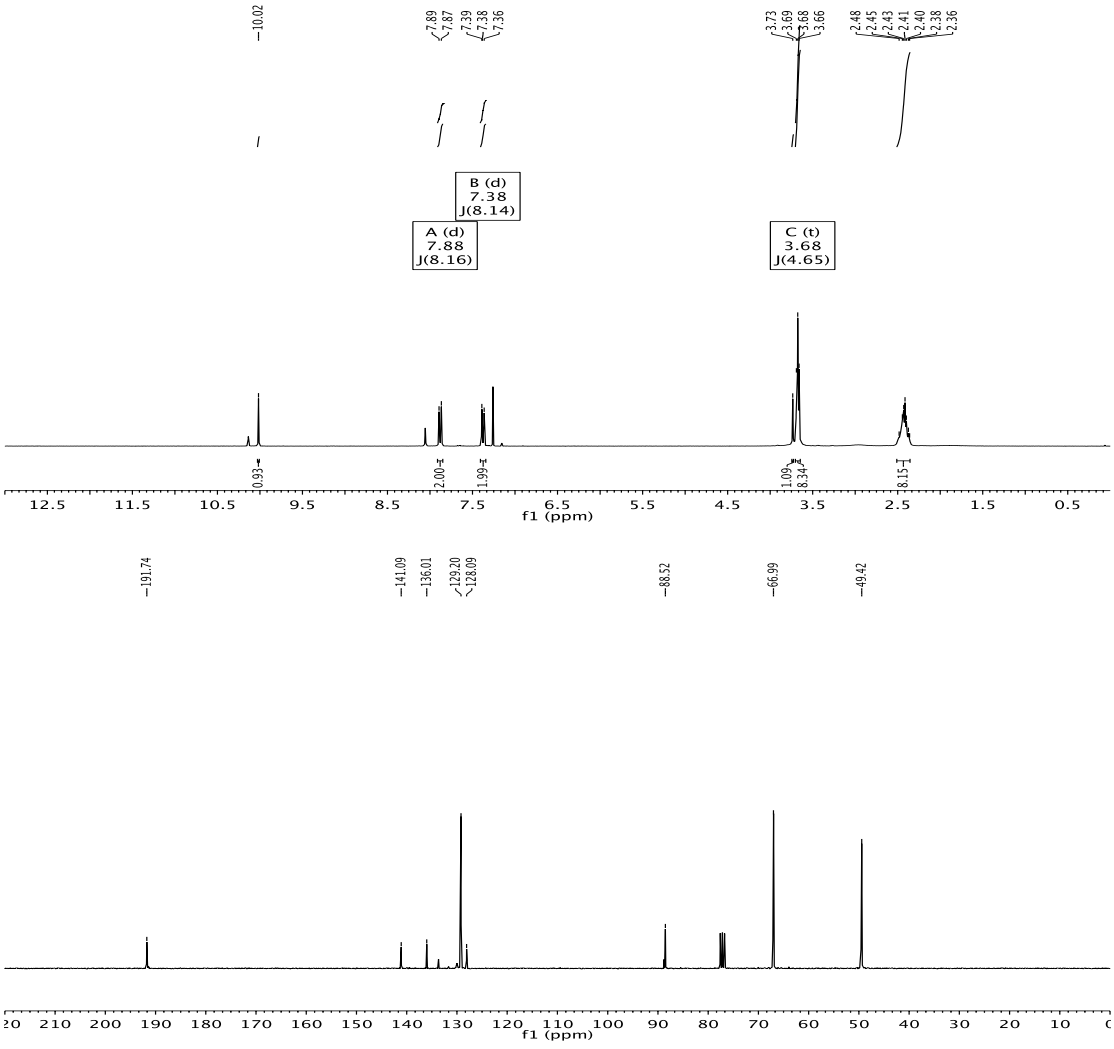


4-(dimorpholinomethyl)benzaldehyde 702

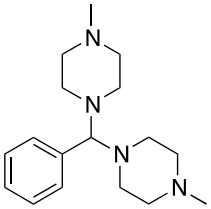


The title compound was prepared according to the general procedure. The product was isolated as a mixture of the monoaminal and diaminal product in a ratio of 1:0.01 (404 mg) as a yellowish solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.88 (d, J = 8.16 Hz, 2H), 7.38 (d, J = 8.14 Hz, 2H), 3.73 (s, 1H), 3.68 (t, J = 4.65 Hz, 8H), 2.48-2.36 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 191.7, 141.1, 136.0, 129.2, 128.1, 88.5, 67.0, 49.4 ppm. **HRMS (ESI):** m/z calculated for $C_{16}H_{23}N_2O_3$ [M+H$^+$] 291.1703, found 291.1684; m/z calculated for $C_{16}H_{22}N_2NaO_3$ [M+Na$^+$] 313.1523, found 313.1609.

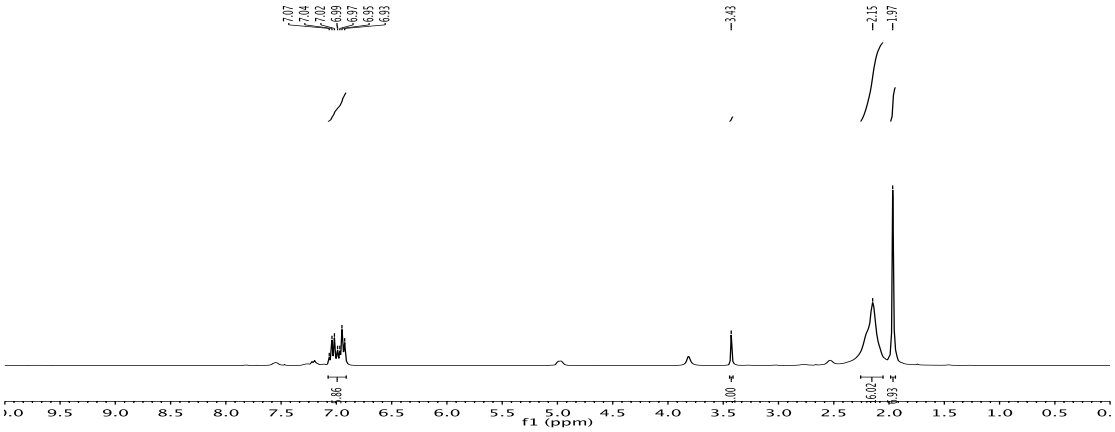


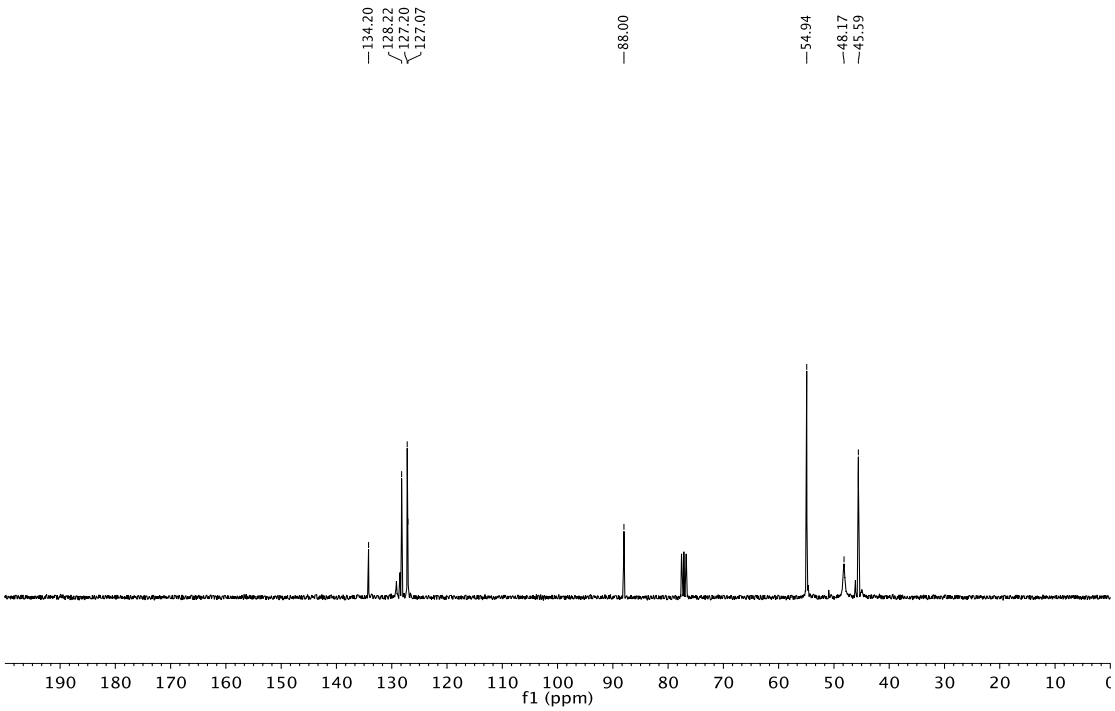
4,4'-(phenylmethylene)bis(1-methylpiperazine) 691



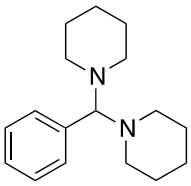
The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (544 mg) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07-6.93 (m, 5H), 3.43 (s, 1H), 2.15 (s, 16H), 1.97 (s, 6H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 134.2, 128.2, 127.2, 127.1, 88.0, 54.9, 48.2, 45.6 ppm. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{17}H_{29}N_4$ [M+H$^+$] 289.23867, found 289.23591.



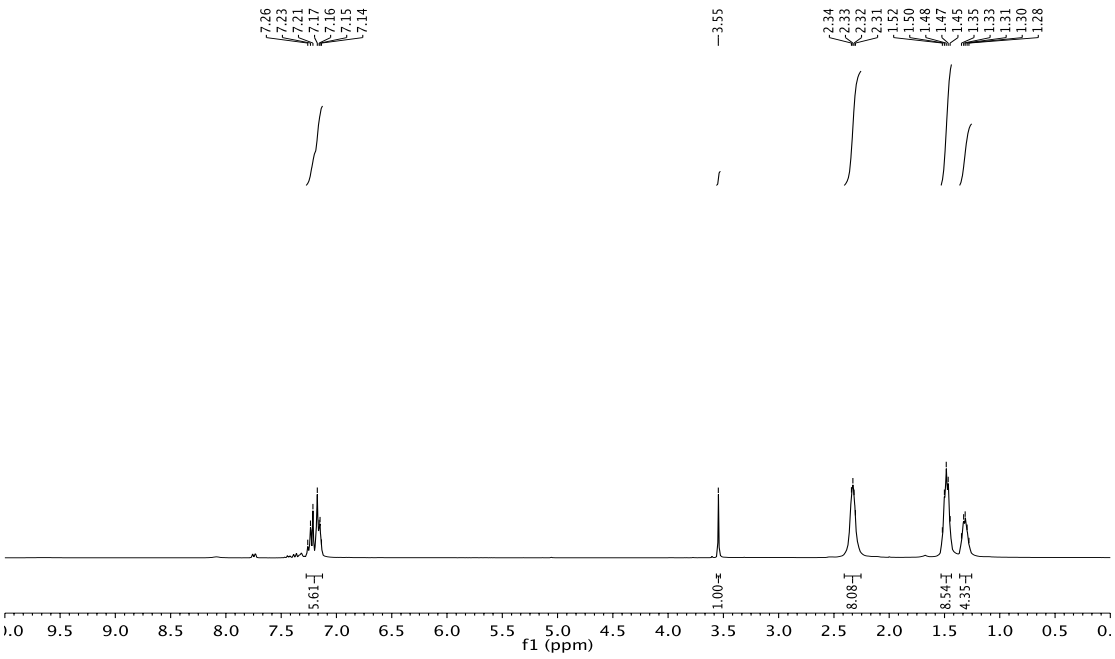


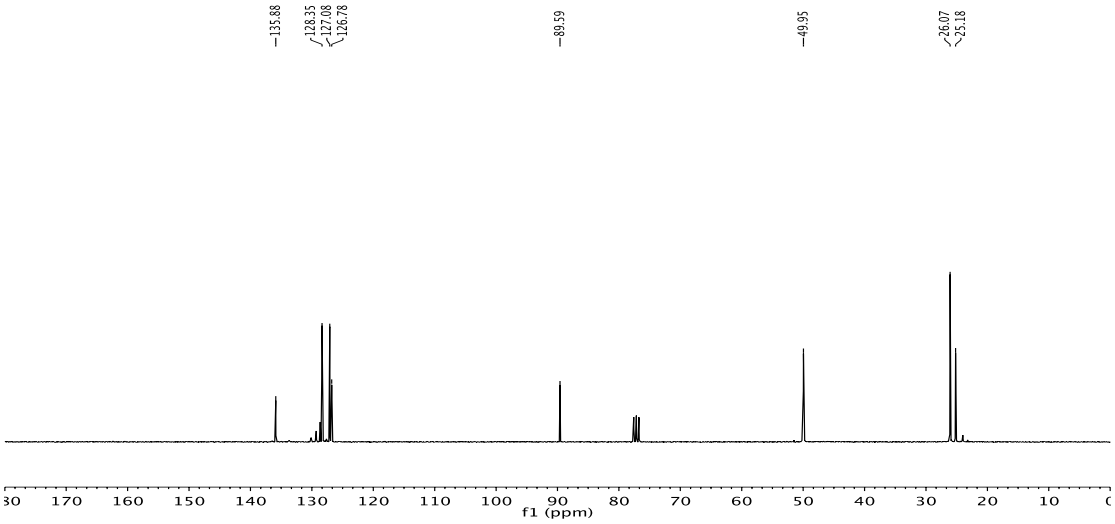
1,1'-(phenylmethylene)dipiperidine 690



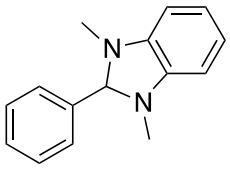
The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (486 mg) as a white solid. The spectral data are in agreement with the literature.[191]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.14 (m, 5H), 3.55 (s, 1H), 2.34-2.31 (m, 8H), 1.52-1.45 (m, 8H), 1.35-1.28 (m, 4H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 135.9, 128.4, 127.1, 126.8, 89.6, 50.0, 26.1, 25.2 ppm.



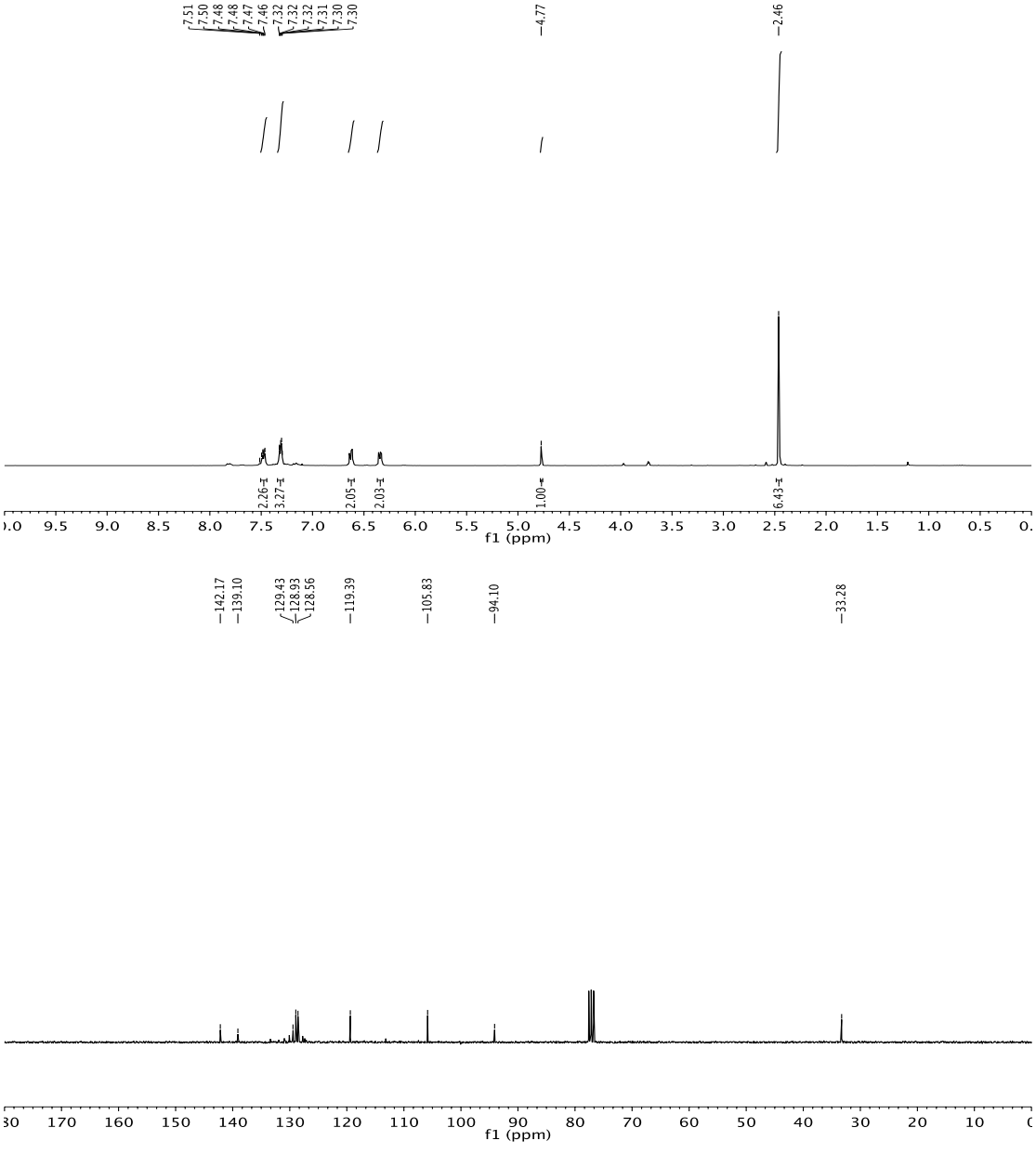


1,3-dimethyl-2-phenyl-2,3-dihydro-1H-benzo[d]imidazole 705

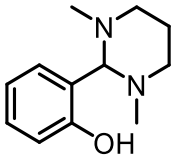


The title compound was prepared according to the general procedure in 50 mg scale. The product was isolated in quantitative yield (106 mg) as a dark brown oil. The spectral data are in agreement with the literature.[192,193]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.46 (m, 2H), 7.32-7.30 (m, 3H), 6.64-6.61 (m, 2H), 6.36-6.33 (m, 2H), 4.77 (s, 1H), 2.46 (s, 6H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 142.2, 139.1, 129.4, 128.9, 128.6, 119.4, 105.8, 94.1, 33.3 ppm.

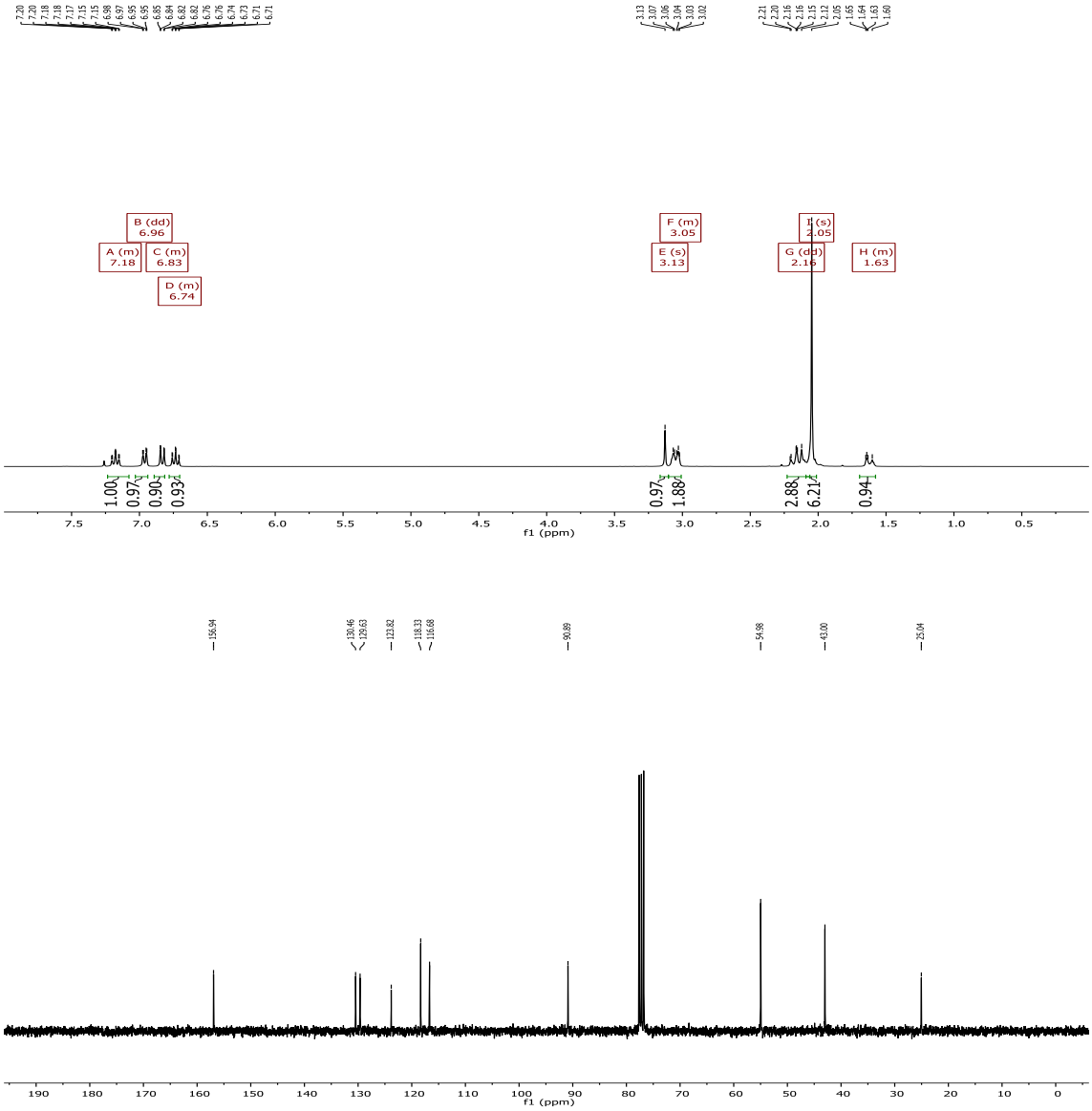


1,3-dimethyl-2-phenylimidazolidine 707

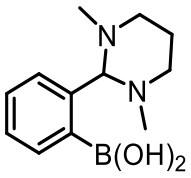


The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (360 mg) as a transparent oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.10 (m, 1H), 6.96 (dd, J = 7.4, 1.6 Hz, 1H), 6.89 – 6.79 (m, 1H), 6.79 – 6.63 (m, 1H), 3.13 (s, 1H), 3.10 – 2.89 (m, 2H), 2.16 (dd, J = 12.7, 10.6 Hz, 3H), 2.05 (s, 6H), 1.65 – 1.60 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 156.94, 130.46, 129.63, 123.82, 118.33, 116.68, 90.89, 54.98, 43.00, 25.04. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{13}H_{23}N_2O_2$ [M+CH_3OH+H^+] 239.17540, found 239.17494.

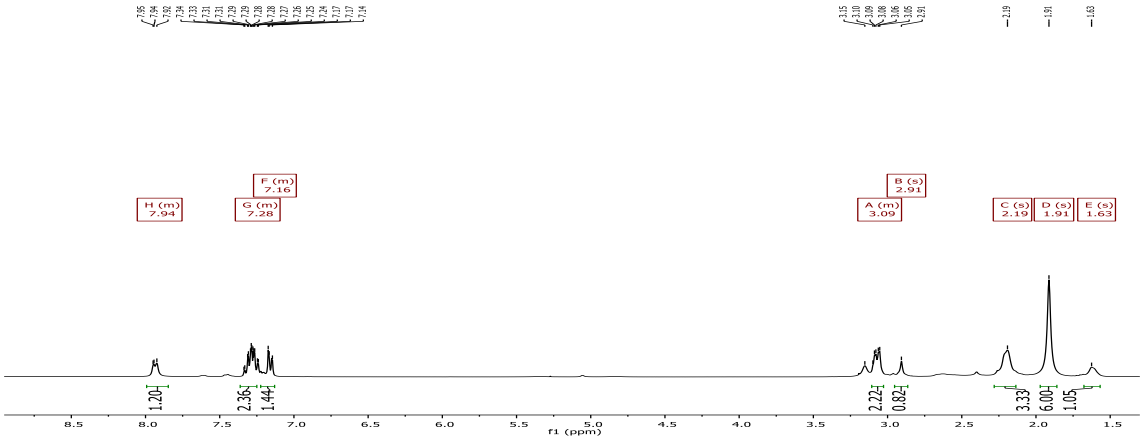


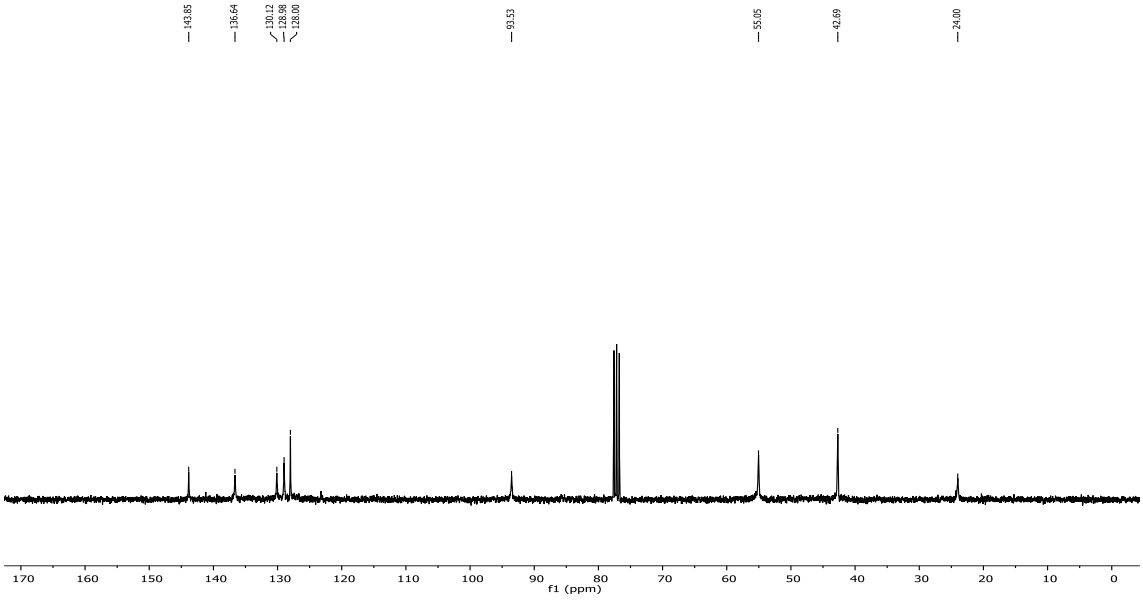
1,3-dimethyl-2-phenylimidazolidine 708



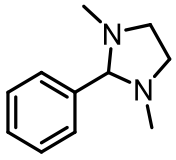
The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (360 mg) as a transparent oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 – 7.82 (m, 1H), 7.40 – 7.20 (m, 2H), 7.21 – 7.11 (m, 1H), 3.25 – 3.00 (m, 2H), 2.91 (s, 1H), 2.19 (s, 3H), 1.91 (s, 6H), 1.63 (s, 1H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 143.85, 136.64, 130.12, 128.98, 128.00, 93.53, 55.05, 42.69, 24.00. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{12}H_{20}BN_2O_2$ [M+H$^+$] 235.1612, found 235.15527.



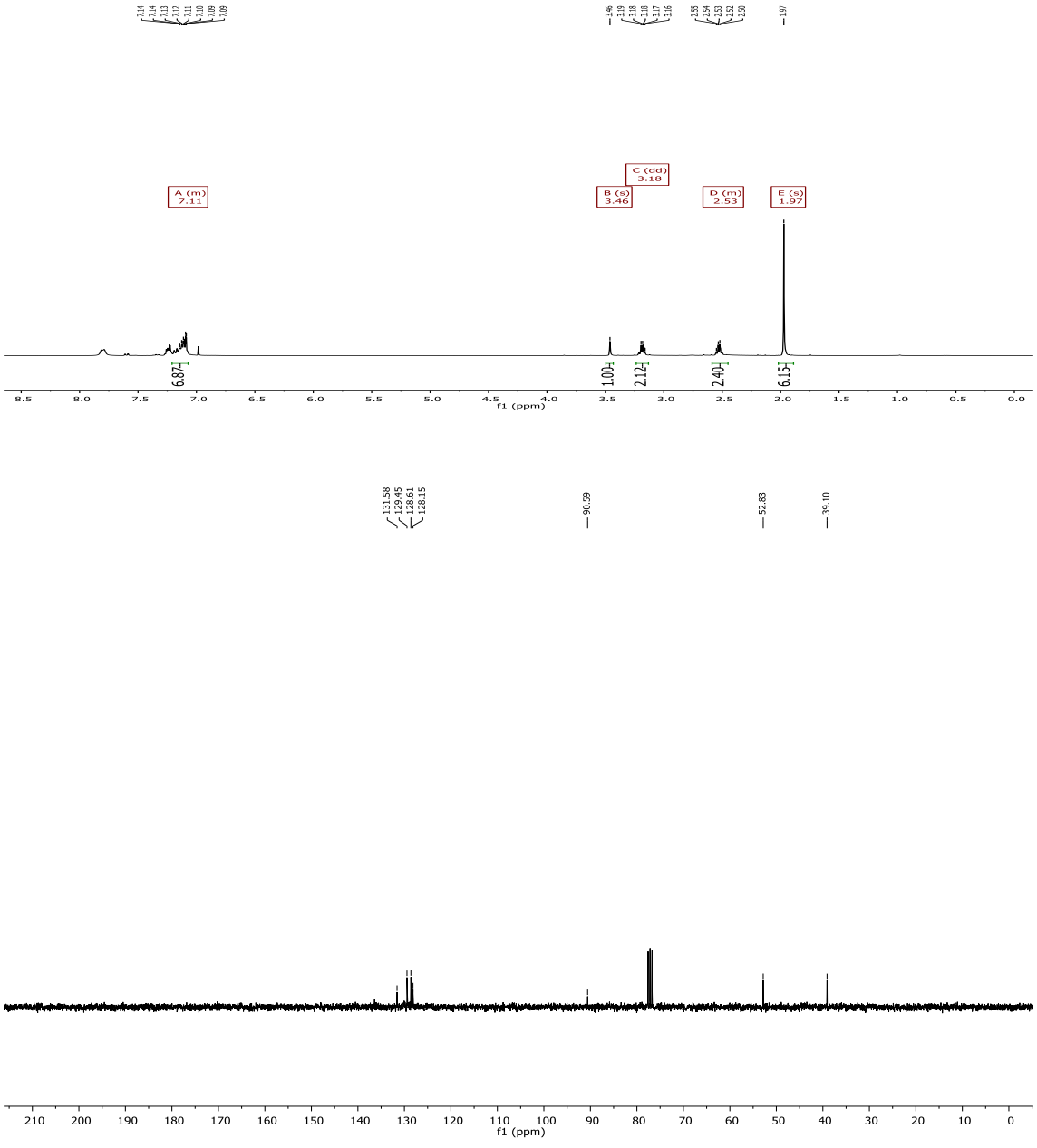


1,3-dimethyl-2-phenylimidazolidine 709

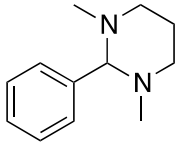


The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (360 mg) as a transparent oil. The spectral data are in agreement with the literature.[186]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 – 6.99 (m, 5H), 3.46 (s, 1H), 3.18 (dd, J = 5.0, 3.8 Hz, 2H), 2.68 – 2.36 (m, 2H), 1.97 (s, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 131.58, 129.45, 128.61, 128.15, 90.59, 52.83, 39.10.

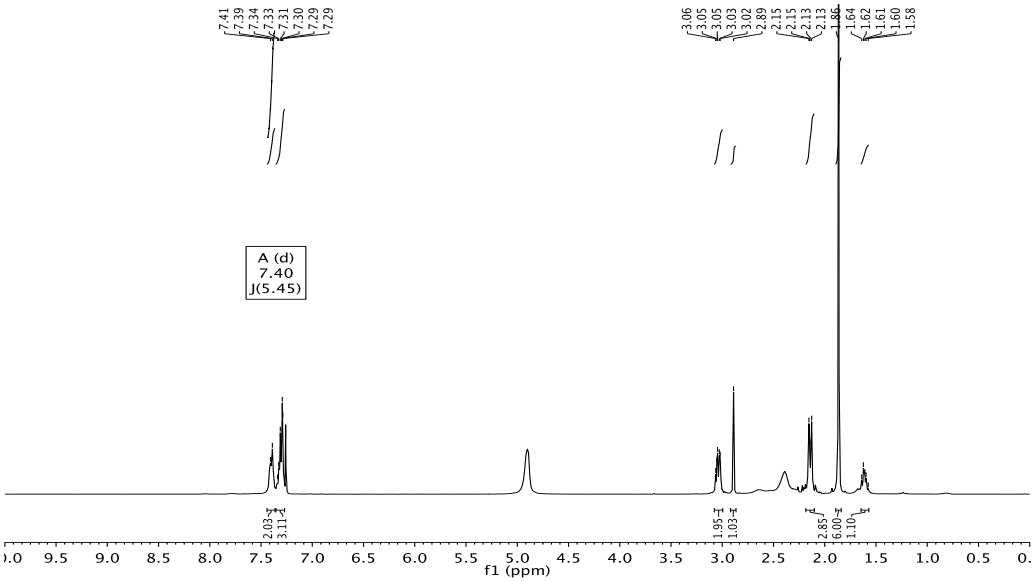


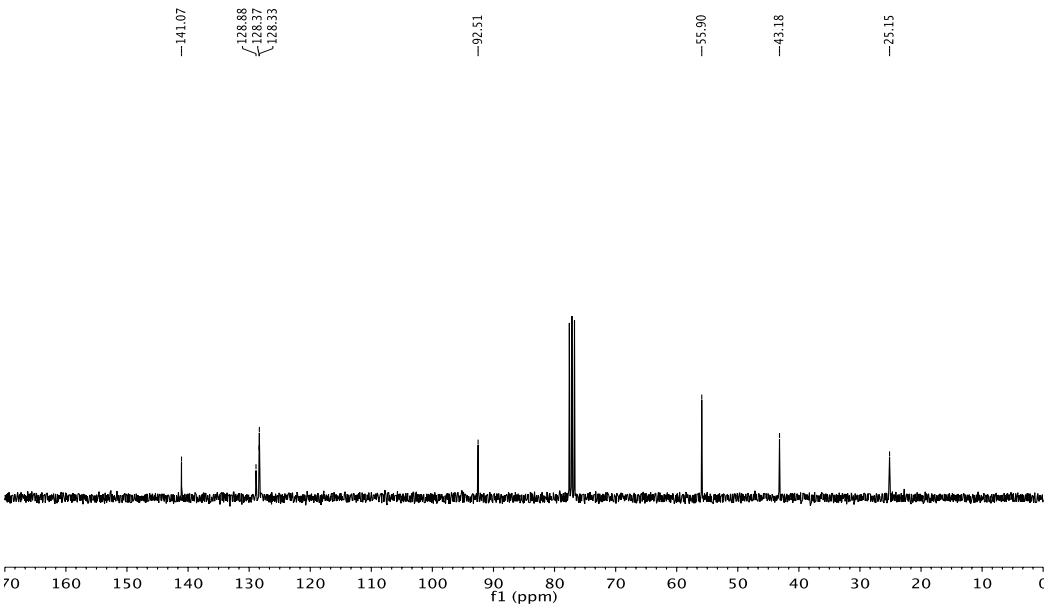
1,3-dimethyl-2-phenylhexahydropyrimidine 710



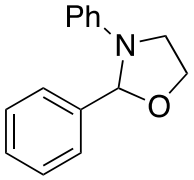
The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (360 mg) as a transparent oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 5.45 Hz, 2H), 7.34-7.29 (m, 3H), 3.06-3.02 (m, 2H), 2.89 (s, 1H), 2.15-2.13 (m, 3H), 1.86 (s, 6H), 1.64-1.58 (m, 1H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 141.1, 128.9, 128.4, 128.3, 92.5, 55.9, 43.2, 25.2 ppm. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{13}H_{23}N_2O$ [M+CH_3OH+H^+] 223.18049, found 223.17528.



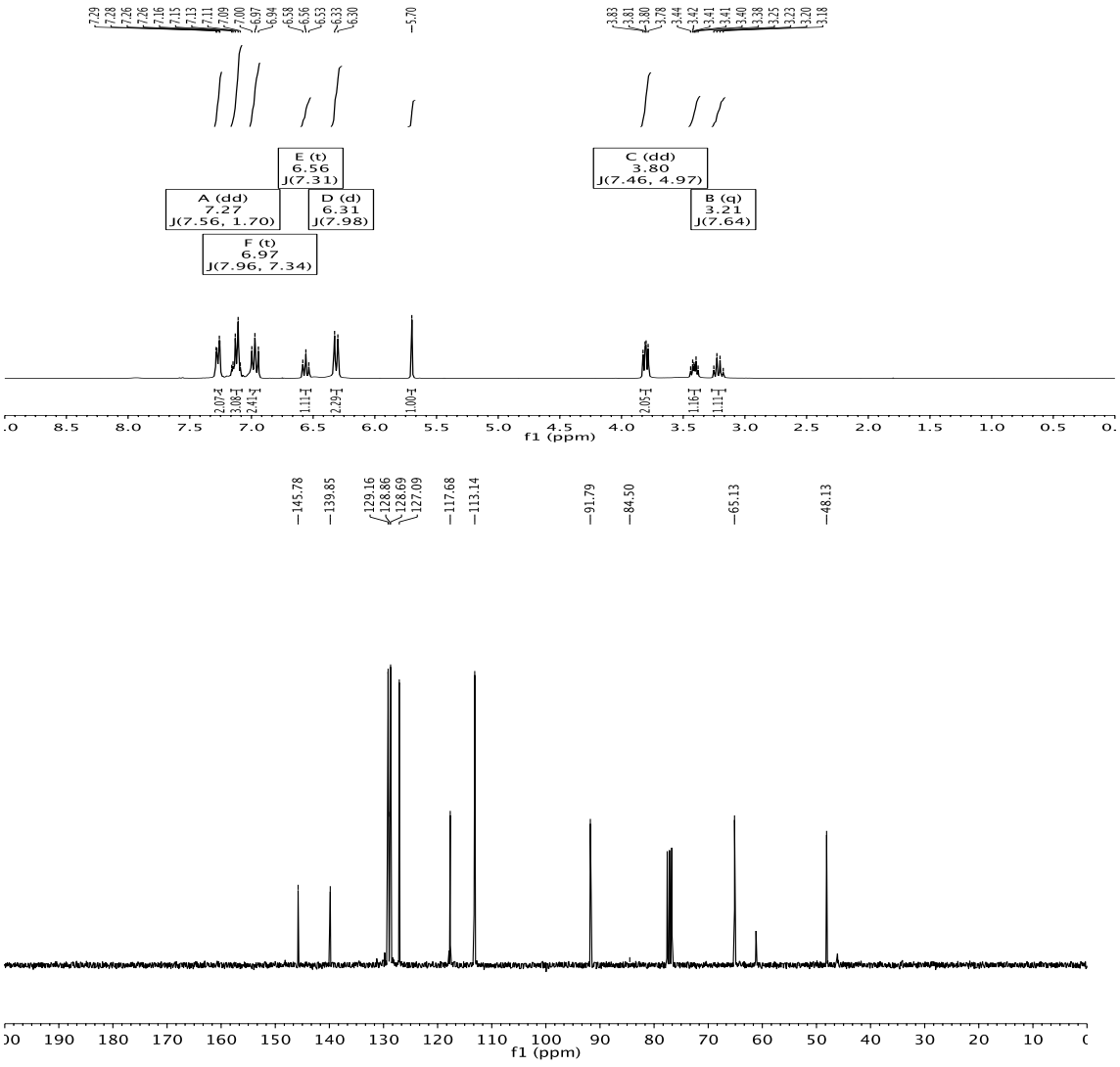


2,3-diphenyloxazolidine 712

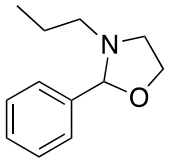


The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (424 mg) as a brownish oil. The spectral data are in agreement with the literature.[194]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, J = 7.56 Hz, J = 1.70 Hz, 2H), 7.16-7.09 (m, 3H), 6.97 (t, J = 7.96 Hz, J = 7.34 Hz, 2H), 6.56 (t, J = 7.31 Hz, 1H), 6.31 (d, J = 7.98 Hz, 2H), 5.70 (s, 1H), 3.80 (dd, J = 7.46 Hz, J = 4.97 Hz, 2H), 3.44-3.38 (m, 1H), 3.21 (q, J = 7.64 Hz, 1H) ppm**. ^{13}C NMR (75 MHz, $CDCl_3$)** δ 145.8, 139.9, 129.2, 128.9, 128.7, 127.1, 117.7, 113.1, 91.8, 65.1, 48.1 ppm.

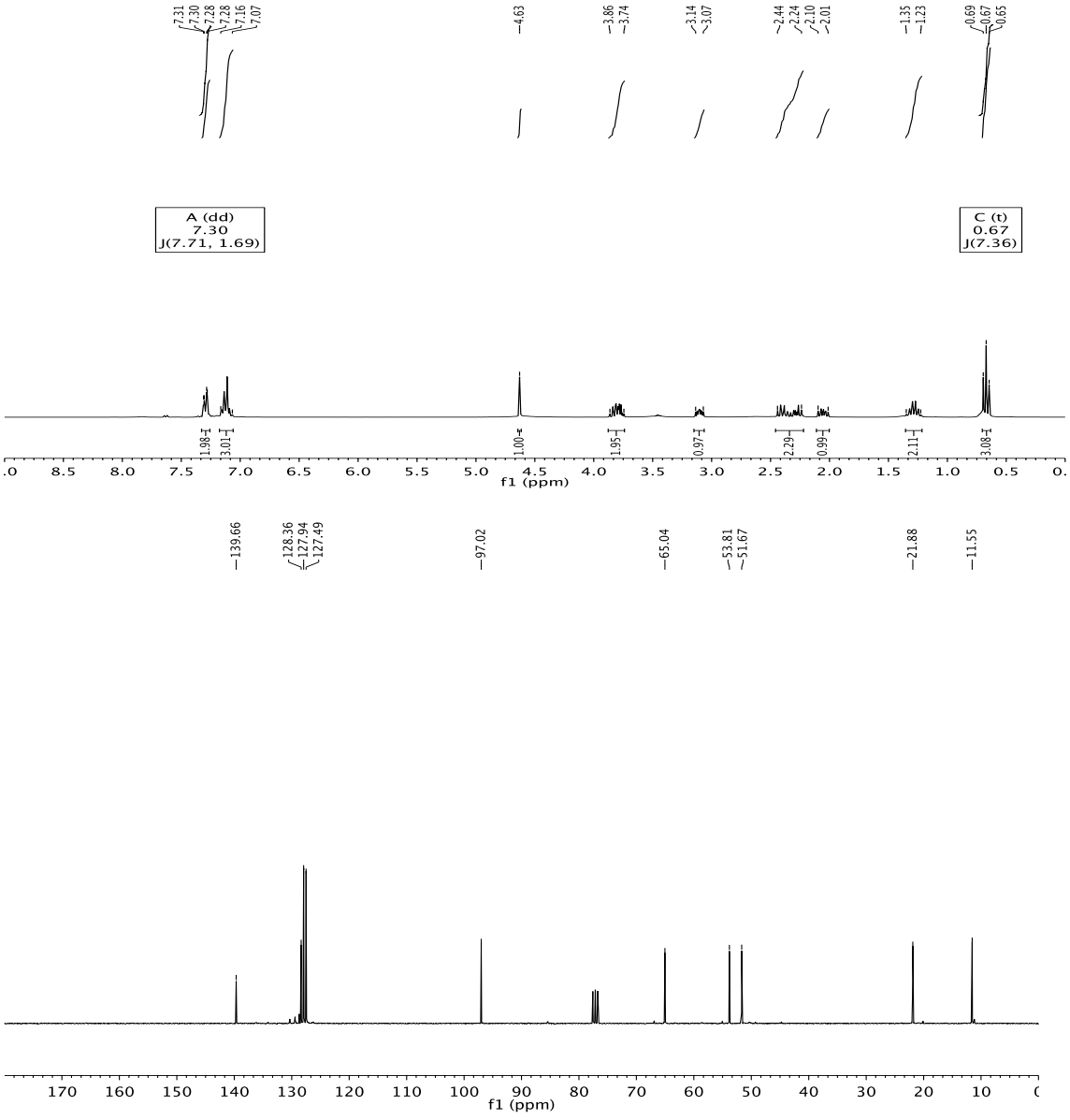


2-phenyl-3-propyloxazolidine 711

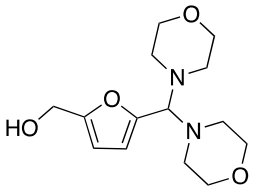


The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (360 mg) as a clear blue liquid. The spectral data are in agreement with the literature.[195]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (dd, J = 7.71 Hz, J = 1.69 Hz, 2H), 7.16-7.07 (m, 3H), 4.63 (s, 1H), 3.86-3.74 (m, 2H), 3.14-3.07 (m, 1H), 2.44-2.24 (m, 2H), 2.10-2.01 (m, 1H), 1.35-1.23 (m, 2H), 0.67 (t, J = 7.36 Hz, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 139.7, 128.4, 127.9, 127.5, 97.0, 65.0, 53.8, 51.7, 21.9, 11.6 ppm.

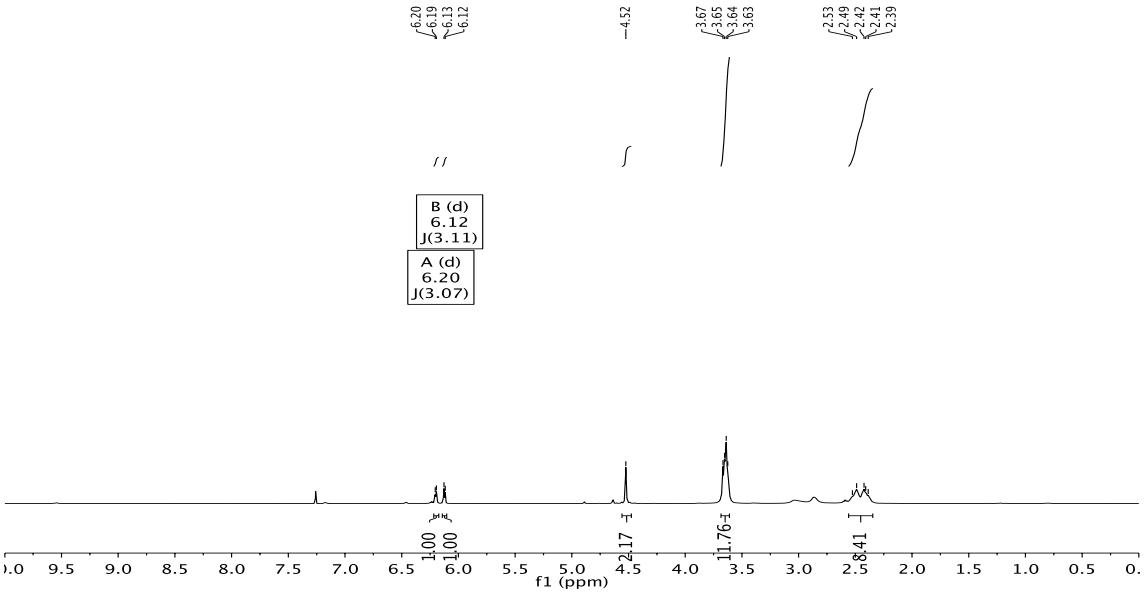


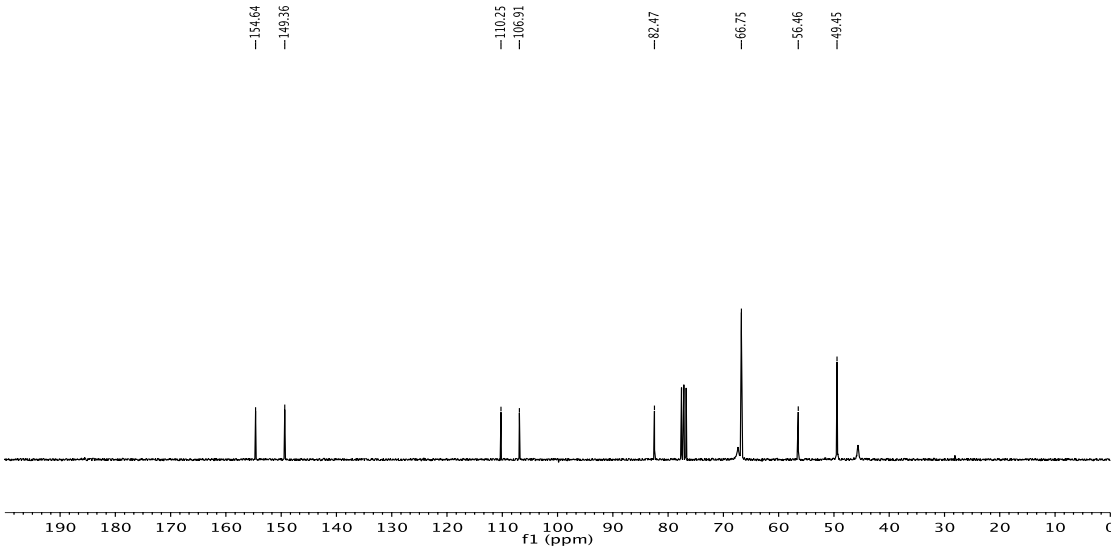
(5-(dimorpholinomethyl)furan-2-yl)methanol 686



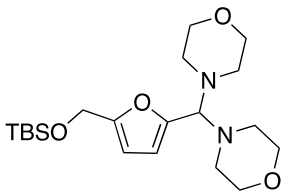
The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (224 mg) as brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, J = 3.07 Hz, 1H), 6.12 (d, J = 3.11 Hz, 1H), 4.52 (s, 2H), 3.67-363 (m, 9H), 2.53-2.39 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 154.6, 149.4, 110.3, 106.9, 82.5, 66.8, 56.5, 49.5 ppm. **HRMS (ESI)** *m/z* calcd for $C_{14}H_{22}N_2O_4$ [M + H^+] 283.1652, found 283.1640.



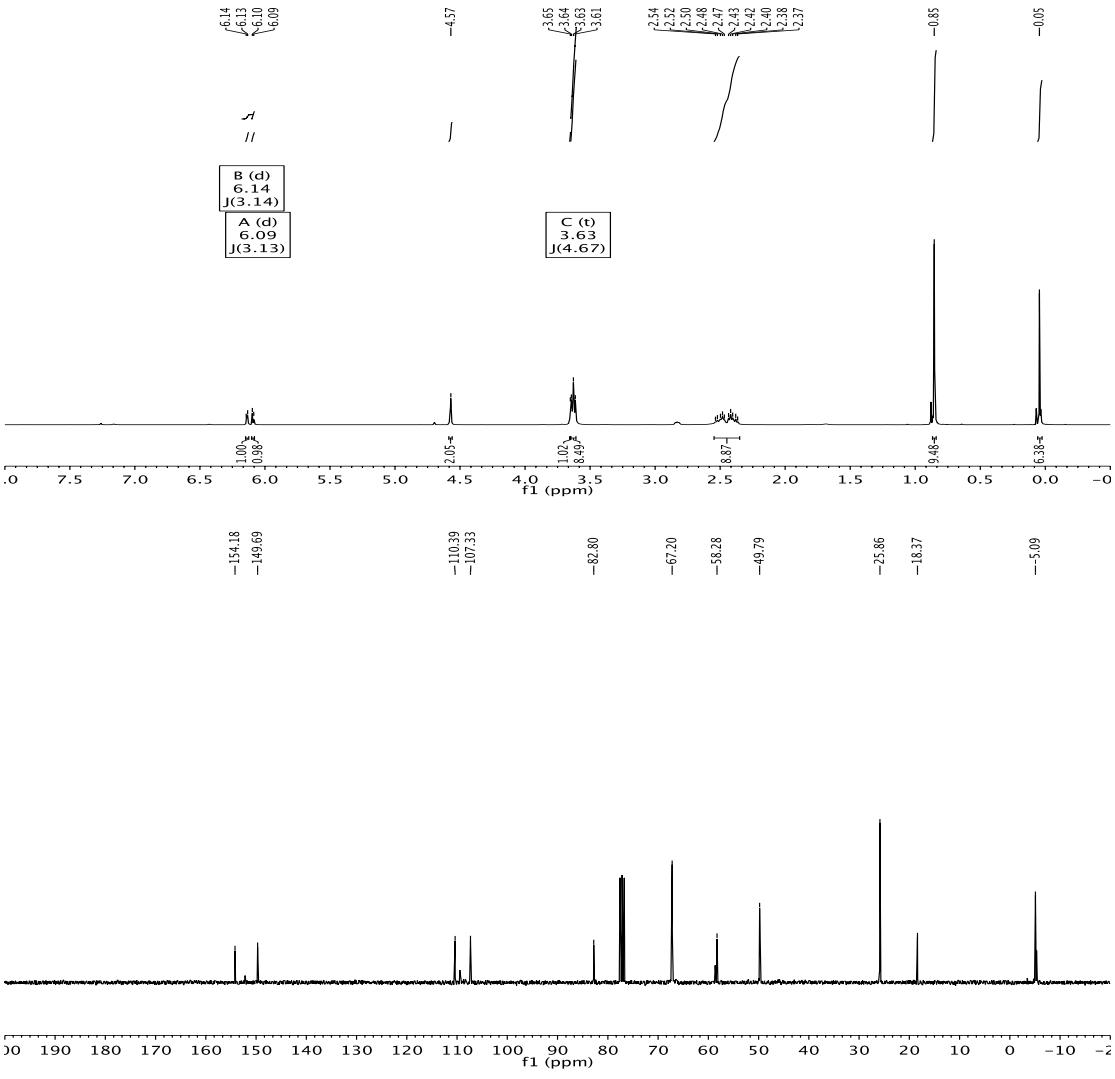


4,4'-((5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)methylene)dimorpholine
688

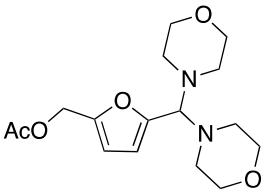


The title compound was prepared according to the general procedure in 50 mg scale. The product was isolated in quantitative yield (82 mg) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, J = 3.14 Hz, 1H), 6.09 (d, J = 3.13 Hz, 1H), 4.57 (s, 2H), 3.65 (s, 1H) 3.63 (t, J = 4.67 Hz, 8H), 2.54-2.37 (m, 8H), 0.85 (s, 9H), 0.05 (s, 6H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 154.2, 149.7, 110.4, 107.3, 82.8, 67.2, 58.3, 49.8, 25.9, 18.4, -5.1 ppm. **HRMS (ESI)** *m/z* calcd for $C_{20}H_{37}N_2O_4Si$ [M + H^+] 397.2517, found 397.2509; *m/z* calcd for $C_{20}H_{36}N_2NaO_4Si$ [M + Na^+] 419.2337, found 419.2337.

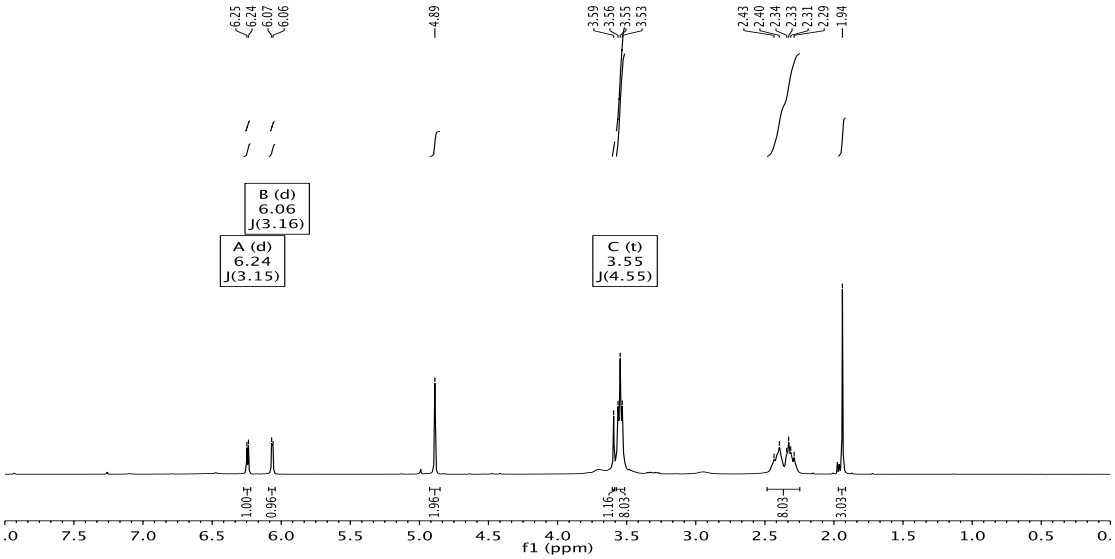


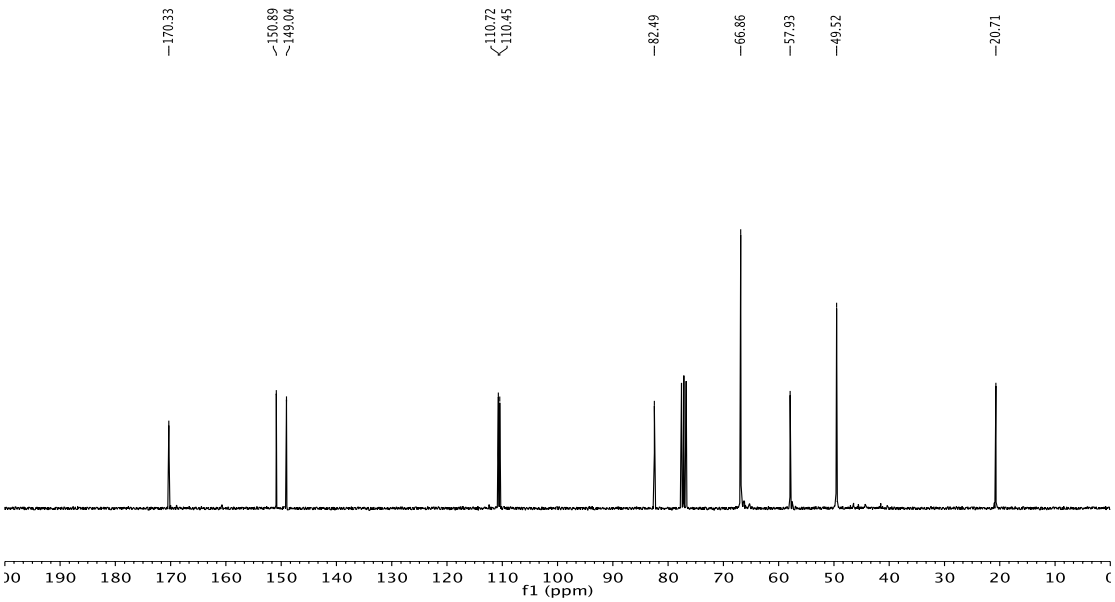
(5-(dimorpholinomethyl)furan-2-yl)methyl acetate 687



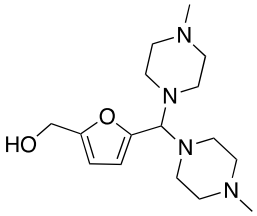
The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (193 mg) as an orange solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (d, J = 3.15 Hz, 1H), 6.06 (d, J = 3.16 Hz, 1H), 4.89 (s, 2H), 3.59 (s, 1H), 3.55 (t, J = 4.55 Hz, 8H), 2.43-2.29 (m, 8H), 1.94 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 170.3, 150.9, 149.0, 110.7, 110.5, 82.5, 66.9, 57.9, 49.5, 20.7 ppm. **HRMS (ESI)** *m/z* calcd for $C_{16}H_{25}N_2O_5$ [M + H^+] 325.1758, found 325.1754.



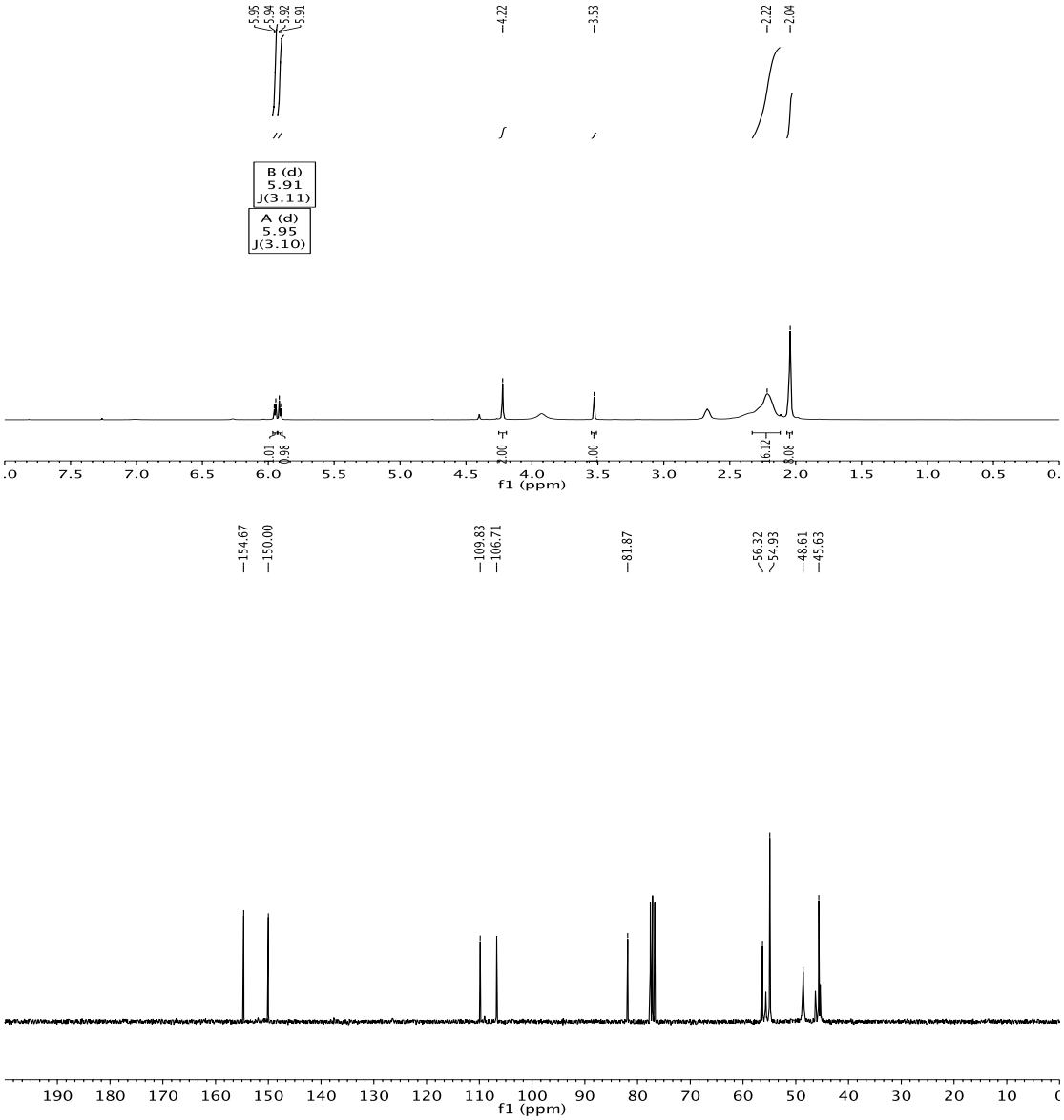


(5-(bis(4-methylpiperazin-1-yl)methyl)furan-2-yl)methanol 691

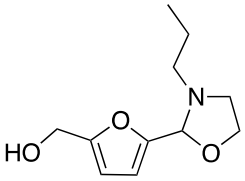


The title compound was prepared according to the general procedure in 50 mg scale. The product was isolated in quantitative yield (122 mg) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (d, J = 3.10 Hz, 1H), 5.91 (d, J = 3.11 Hz, 1 H), 4.22 (s, 2H), 3.53 (s, 1H), 2.22 (s, 16H), 2.04 (s, 6H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 154.7, 150.0, 109.8, 106.7, 81.9, 56.3, 54.9, 48.6, 45.6 ppm. **HRMS (ESI)** *m/z* calcd for $C_{11}H_{19}N_2O_2$ [M-$C_5H_{11}N_2$+H^+] 211.14410, found 211.14351.

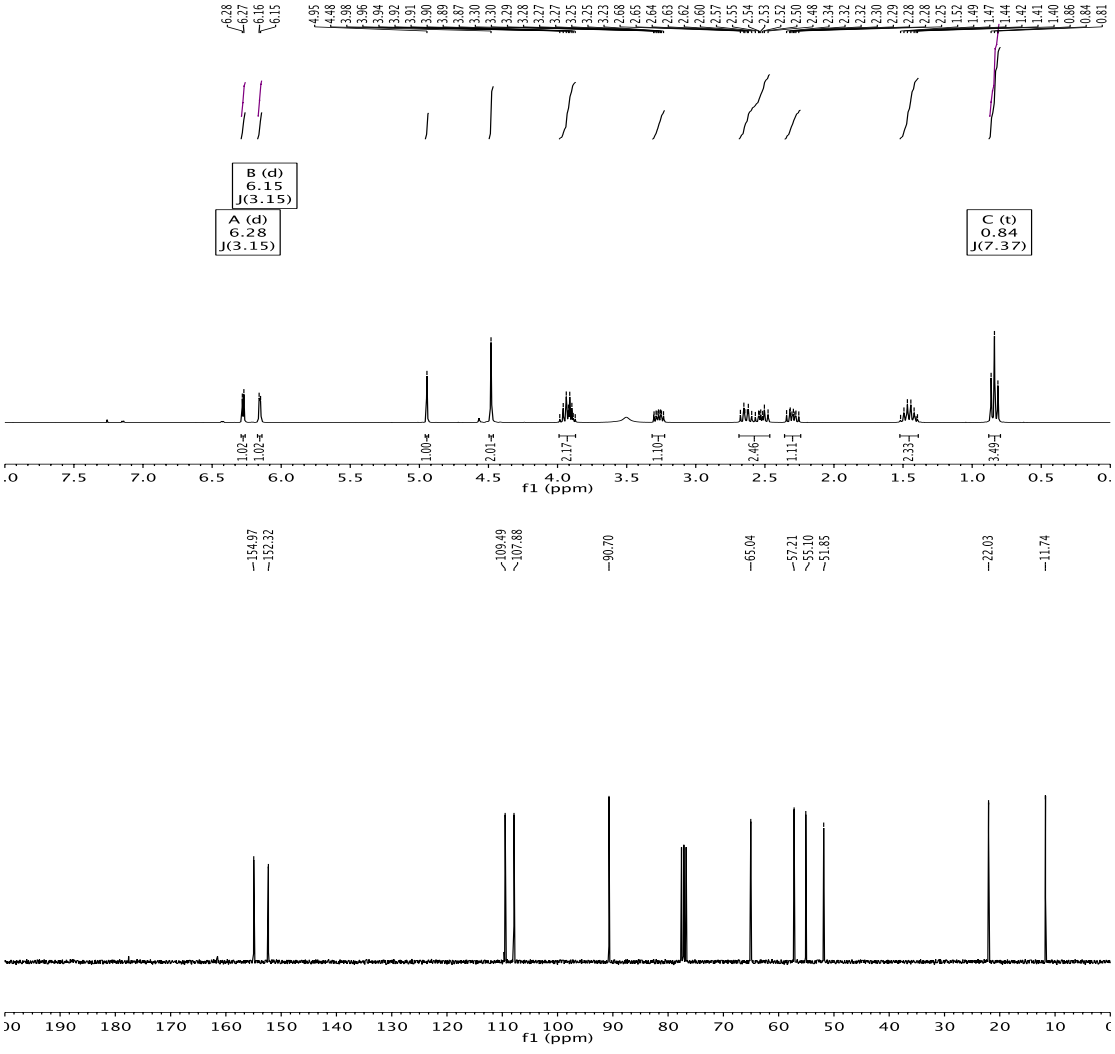


(5-(3-propyloxazolidin-2-yl)furan-2-yl)methanol 717

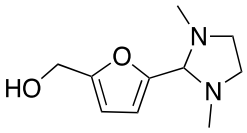


The title compound was prepared according to the general procedure in 50 mg scale. The product was isolated in quantitative yield (84 mg) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (d, J = 3.15 Hz, 1H), 6.15 (d, J = 6.15 Hz, 1H), 4.95 (s, 1H), 4.48 (s, 2H), 3.98-3.87 (m, 2H), 3.30-3.23 (m, 1H), 2.68-2.48 (m, 2H), 2.34-2.25 (m, 1H), 1.52-1.40 (m, 2H), 0.84 (t, J = 7.37 Hz, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 155.0, 152.3, 109.5, 107.9, 90.7, 65.0, 57.2, 55.1, 51.9, 22.0, 11.7 ppm. **HRMS (ESI)** *m/z* calcd for $C_{11}H_{18}NO_3$ [M+H$^+$] 212.1281, found 212.1273; *m/z* calcd for $C_{16}H_{17}NNaO_3$ [M+Na$^+$] 234.1101, found 234.1101.

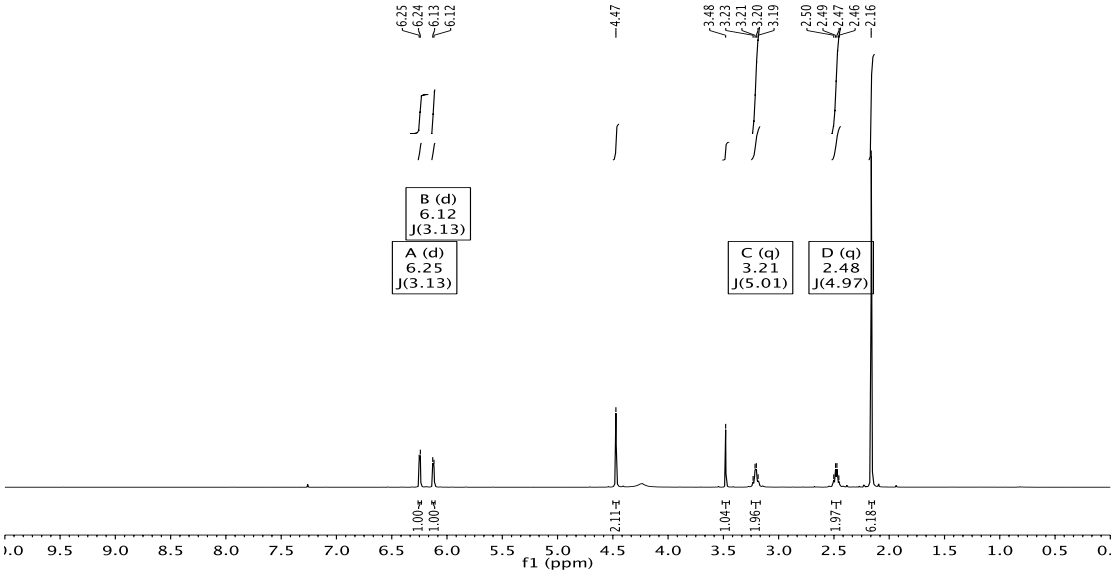


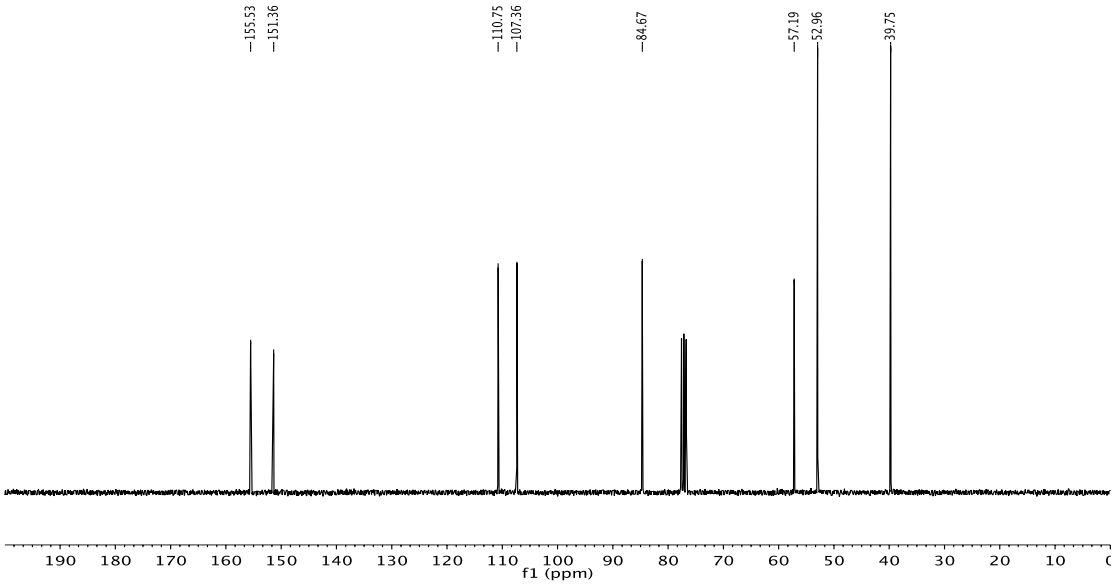
(5-(1,3-dimethylimidazolidin-2-yl)furan-2-yl)methanol 715



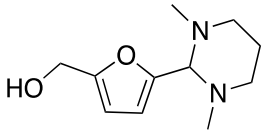
The title compound was prepared according to the general procedure in 50 mg scale. The product was isolated in quantitative yield (70 mg) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (d, J = 3.13 Hz, 1H), 6.12 (d, J = 3.13 Hz, 1H), 4.47 (s, 2H), 3.48 (s, 1H), 3.21 (q, J = 5.01 Hz, 2H), 2.48 (q, J = 4.97 Hz, 2H), 2.16 (s, 6H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 155.5, 151.4, 110.7, 107.4, 84.7, 57.2, 53.0, 39.8 ppm. **HRMS (ESI)** *m/z* calculated for $C_{10}H_{17}N_2O_2$ [M + H^+] 197.1285, found 197.1277.



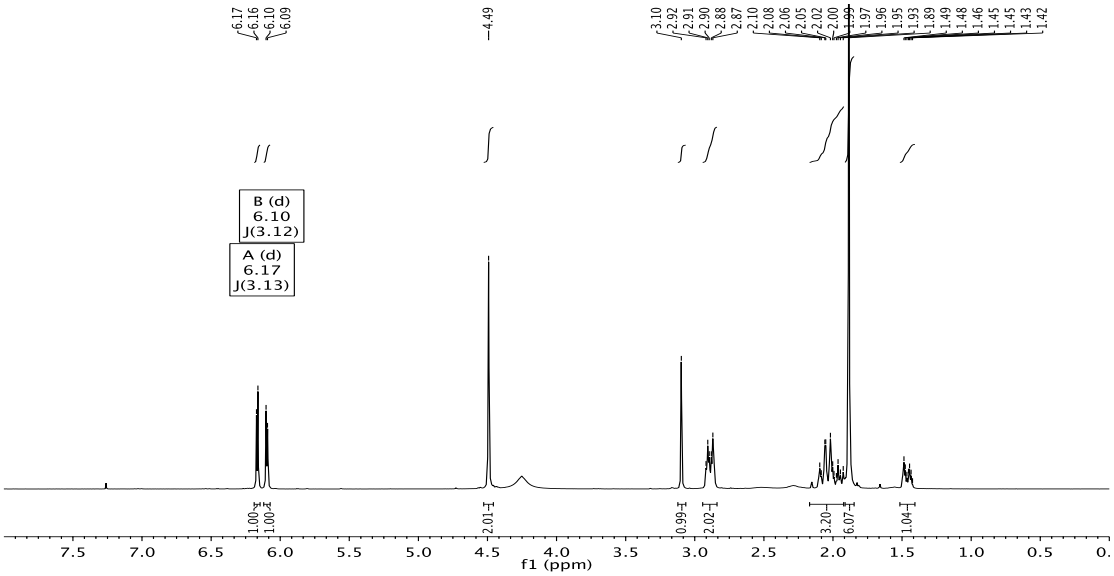


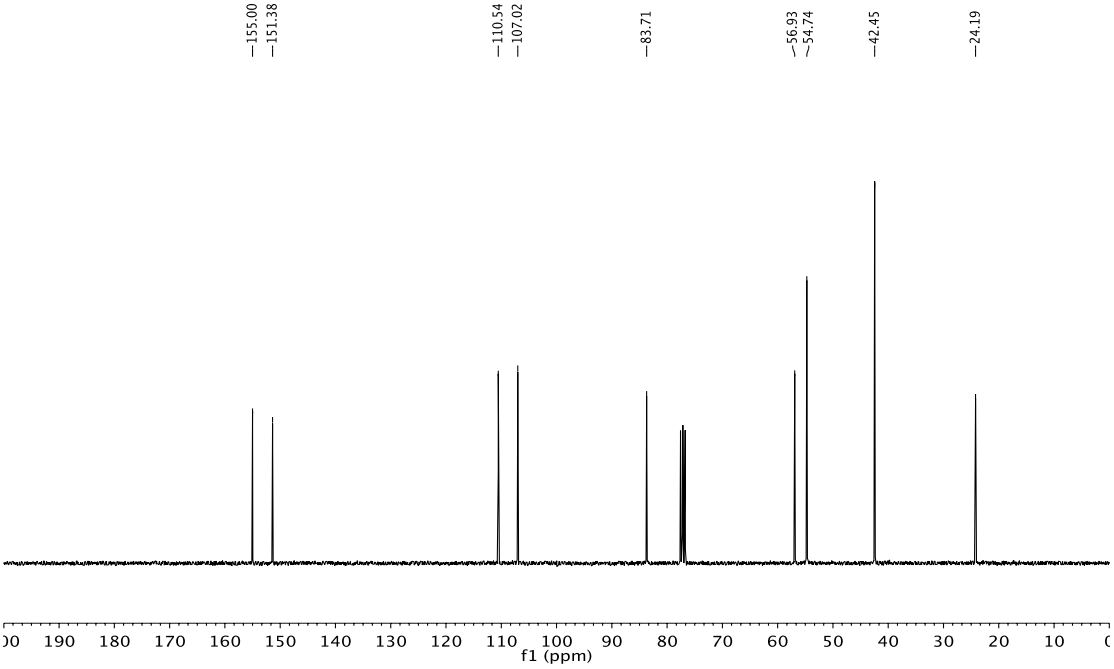
(5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol 716



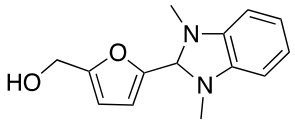
The title compound was prepared according to the general procedure in 400 mg scale. The product was isolated in quantitative yield (666 mg) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (d, J = 3.13 Hz, 1H), 6.10 (d, J = 3.12 Hz, 1H), 4.49 (s, 2H), 3.10 (s, 1H), 2.92-2.87 (m, 2H), 2.10-1.89 (s, 6H), 1.49-1.42 (m, 1H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 155.0, 151.4, 110.5, 107.0, 83.7, 56.9, 54.7, 42.5, 24.2 ppm. **HRMS (ESI)** *m/z* calculated for $C_{11}H_{19}N_2O_2$ [M + H^+] 211.1441, found 211.1436.



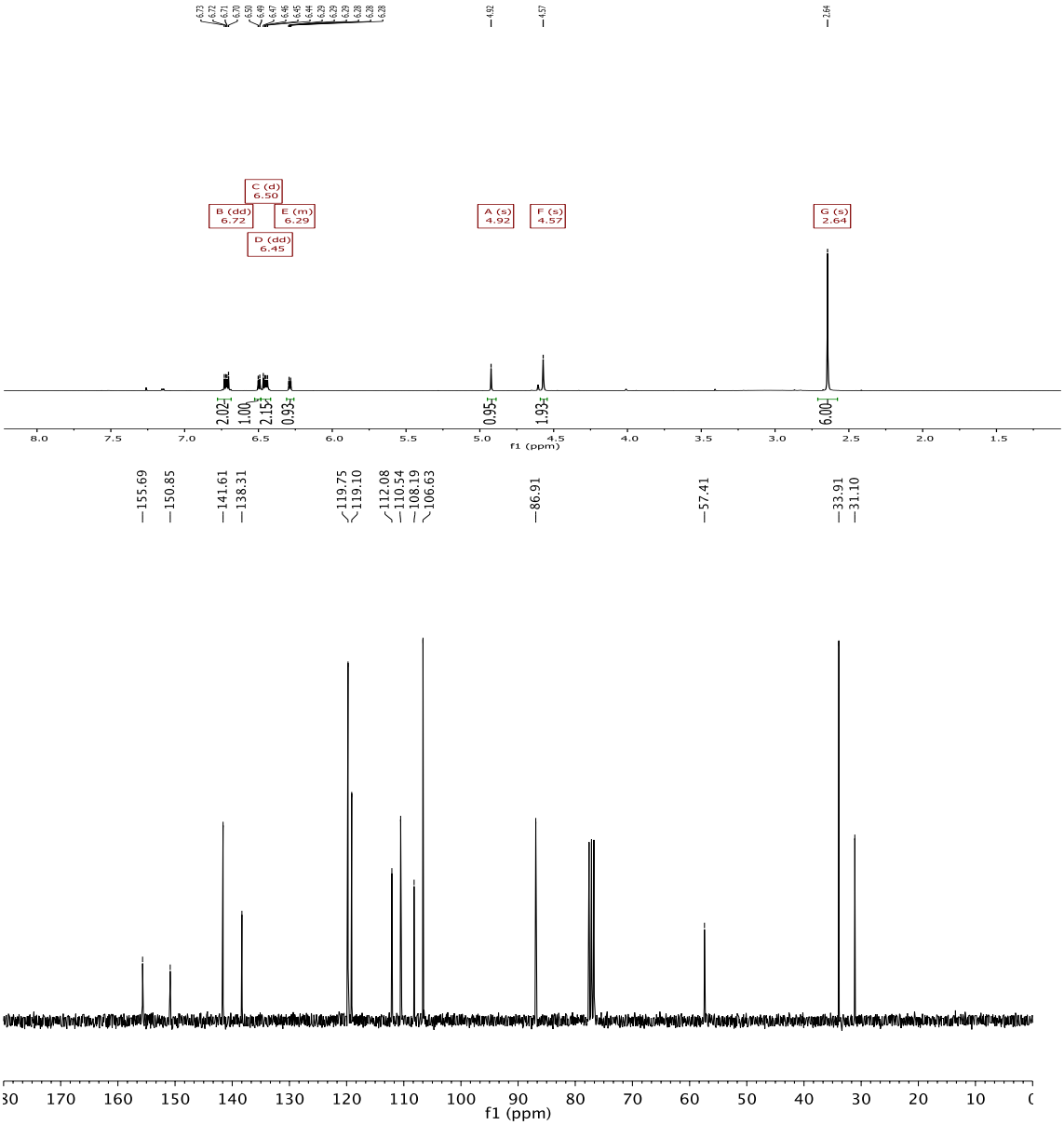


1,3-dimethyl-2-phenyl-2,3-dihydro-1H-benzo[d]imidazole 706

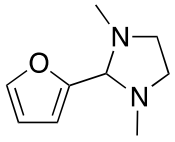


The title compound was prepared according to the general procedure. The product was isolated in quantitative yield (387 mg) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (dd, J = 5.46 Hz, J = 3.18 Hz, 2H), 6.52 (d, J = 3.20 Hz, 1H), 6.48 (dd, J = 5.45 Hz, J = 3.20 Hz, 2H), 6.30 (d, J = 3.15 Hz, 1H), 4.93 (s, 1H), 4.59 (s, 2H), 2.66 (s, 6H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 155.7, 150.9, 141.6, 138.3, 119.8, 119.1, 112.1, 110.5, 108.2, 106.6, 86.9, 57.4, 33.9, 31.1 ppm. **HRMS (ESI)** *m/z* calculated for $C_{14}H_{17}N_2O_2$ [M + H^+] 245.12845, found 245.13411.

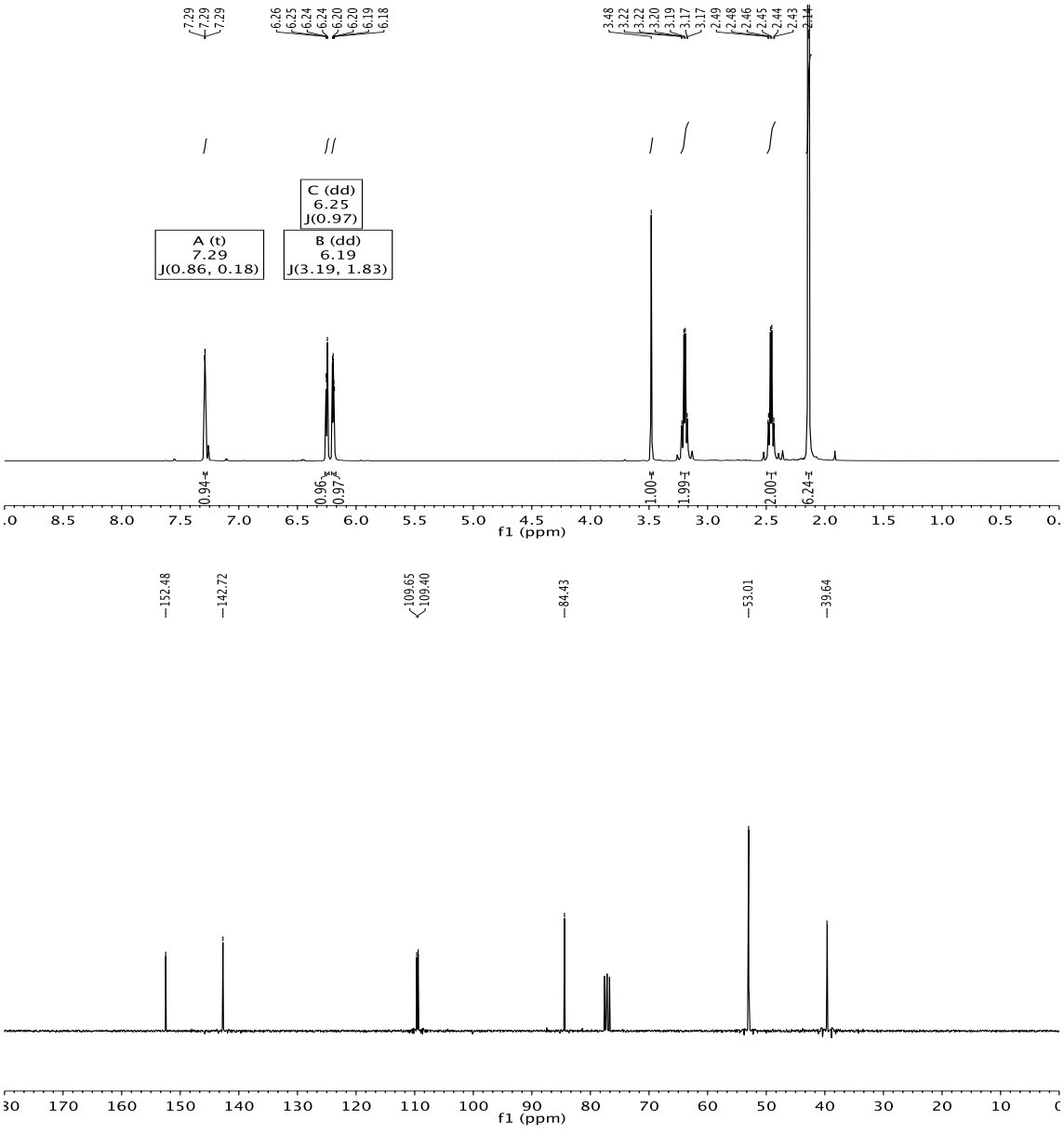


2-(furan-2-yl)-1,3-dimethylimidazolidine 722

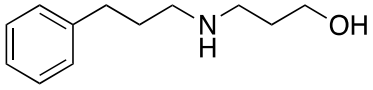


The title compound was prepared according to the general procedure in 50 mg scale. The product was isolated in quantitative yield (87 mg) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 0.86 Hz, J = 0.18 Hz, 1H), 6.25 (dd, J = 0.97 Hz, 1H), 6.19 (dd, J = 3.19 Hz, J = 1.83 Hz, 1H), 3.48 (s, 1H), 3.22-3.17 (m, 2H), 2.49-2.43 (m, 2H), 2.14 (s, 6H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 152.48, 142.72, 109.65, 109.40, 84.43, 53.01, 39.64 ppm.

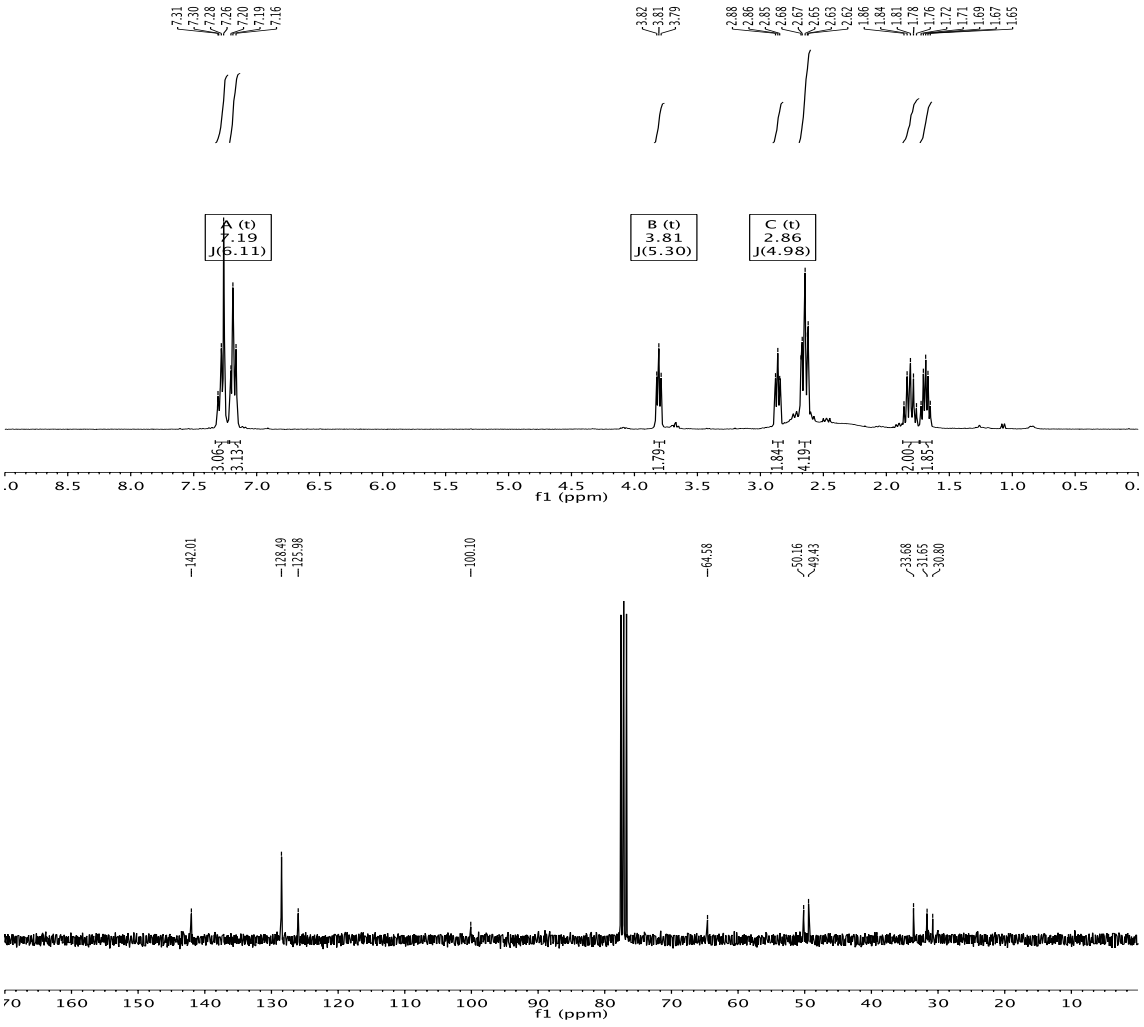


Synthesis of 3-((3-phenylpropyl)amino)propan-1-ol



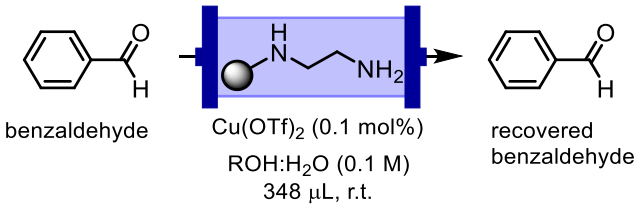
To a solution of 3-phenylpropanal (198 µL, 1.49 mmol) in methanol (1.49 mL, 1M) was added 3-aminopropan-1-ol (136 µL, 1.79 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour and then sodium borohydride was slowly added (68 mg, 1.79 mmol), stirred for 30 minutes followed by dropwise addition of water. Then, the mixture was extracted with dichloromethane (2x 20 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The 3-((3-phenylpropyl)amino)propan-1-ol was isolate in 94% yield (251 mg) as a transparent yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.19 (t, *J* = 6.11 Hz, 3H), 3.81 (t, *J* = 5.30 Hz, 2H), 2.86 (t, *J* = 4.98 Hz, 2H), 2.68-2.62 (m, 4H), 1.86-1.76 (m, 2H), 1.72-1.65 (m, 2H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 142.0, 128.5, 126.0, 100.1, 64.6, 50.2, 49.4, 33.7, 31.7, 30.8 ppm.



General procedure for optimization of scavenging benzaldehyde

To a solution of benzaldehyde in a mixture of alcohol:water (0.006 - 1M) was added $Cu(OTf)_2$ (0-10 mol%) catalyst. The mixture was injected with a syringe pump into the flow reactor comprised of an empty HPLC column (ID= 4.6 mm, L= 50 mm), filled with polymer-bound ethylenediamine resine (Aldrich Ref. 472093, 395 mg, 4-5.7 mmol/g), at room temperature. The flow rate was set at the appropriate flow. The resultant solution was collected and analysed by HPLC.



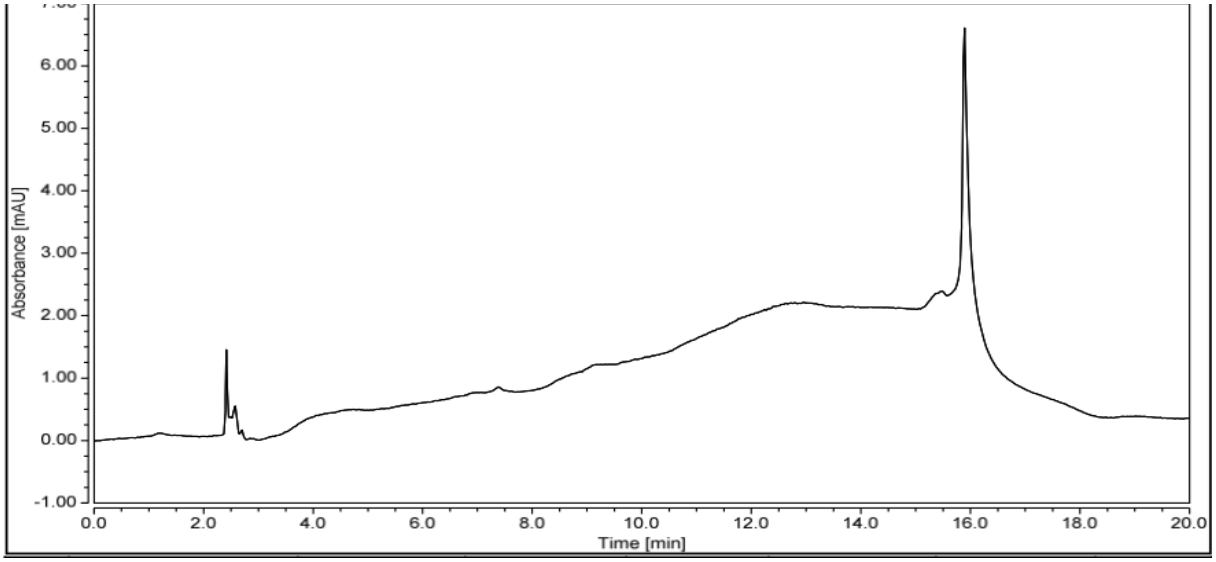


Figure 60. Representative chromatogram of benzaldehyde scavenging with 0.1 mol% of $Cu(OTf)_2$ and a residence time of 1 hour. Conditions: 0.0348 mmol of benzaldehyde, 0.348 mL of MeOH:H_2O (9:1).

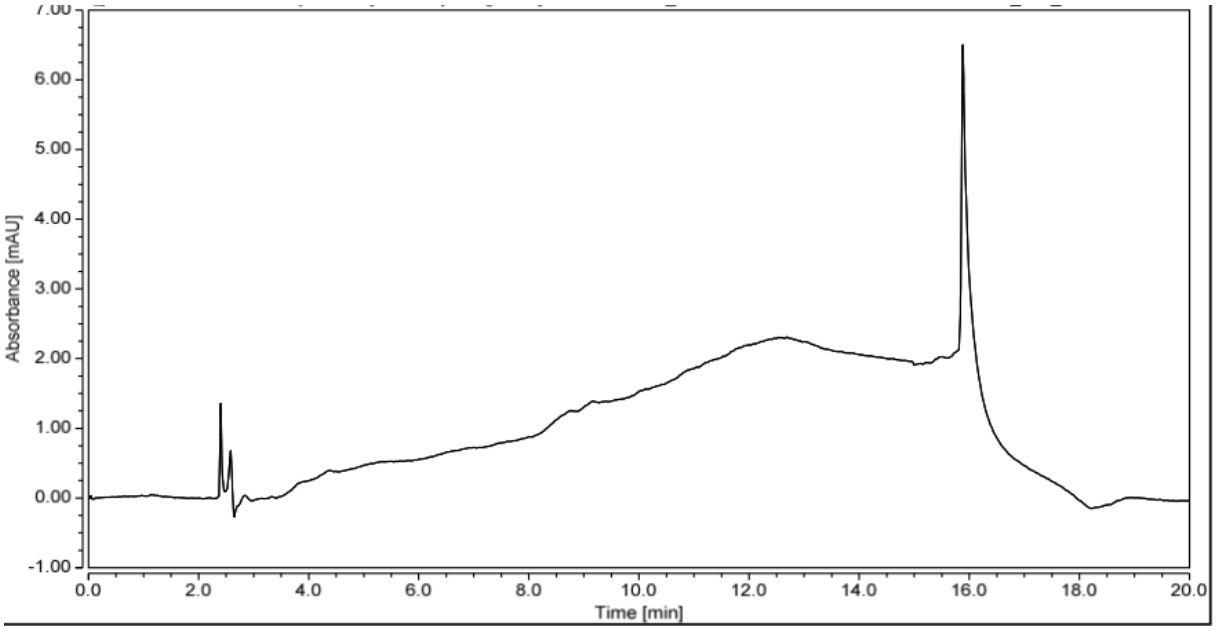


Figure 61 Representative chromatogram of benzaldehyde scavenging with 0.1 mol% of $Cu(OTf)_2$ and a residence time of 10 minutes. Conditions: 0.0348 mmol of benzaldehyde, 0.348 mL of MeOH:H_2O (9:1).

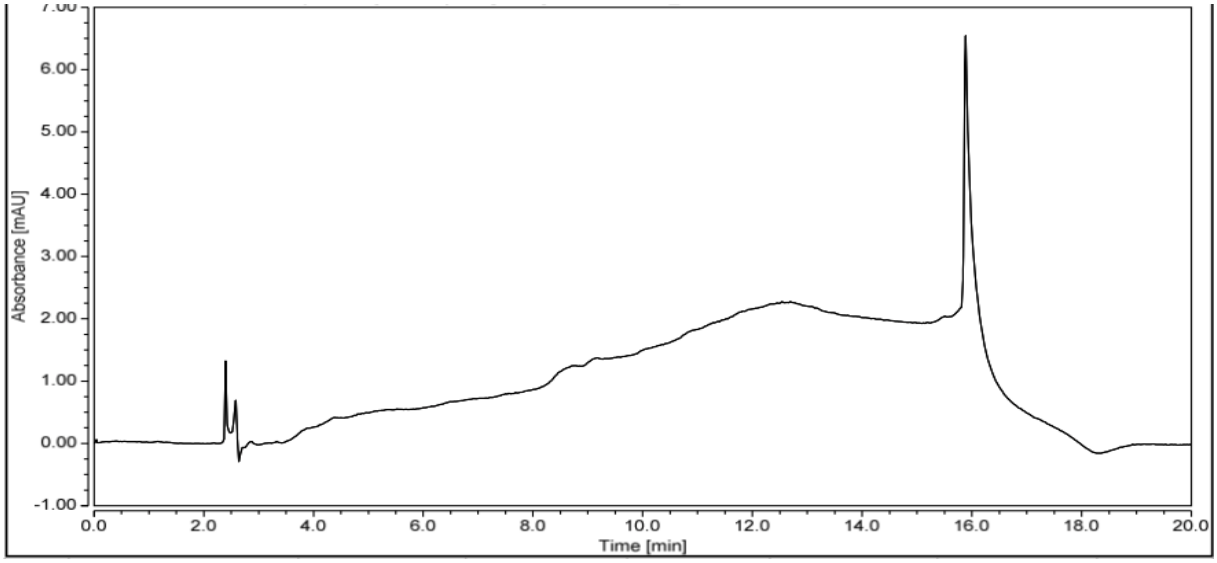


Figure 62 Representative chromatogram of benzaldehyde scavenging with 0.1 mol% of $Cu(OTf)_2$ and a residence time of 5 minutes. Conditions: 0.0348 mmol of benzaldehyde, 0.348 mL of MeOH:H_2O (9:1).

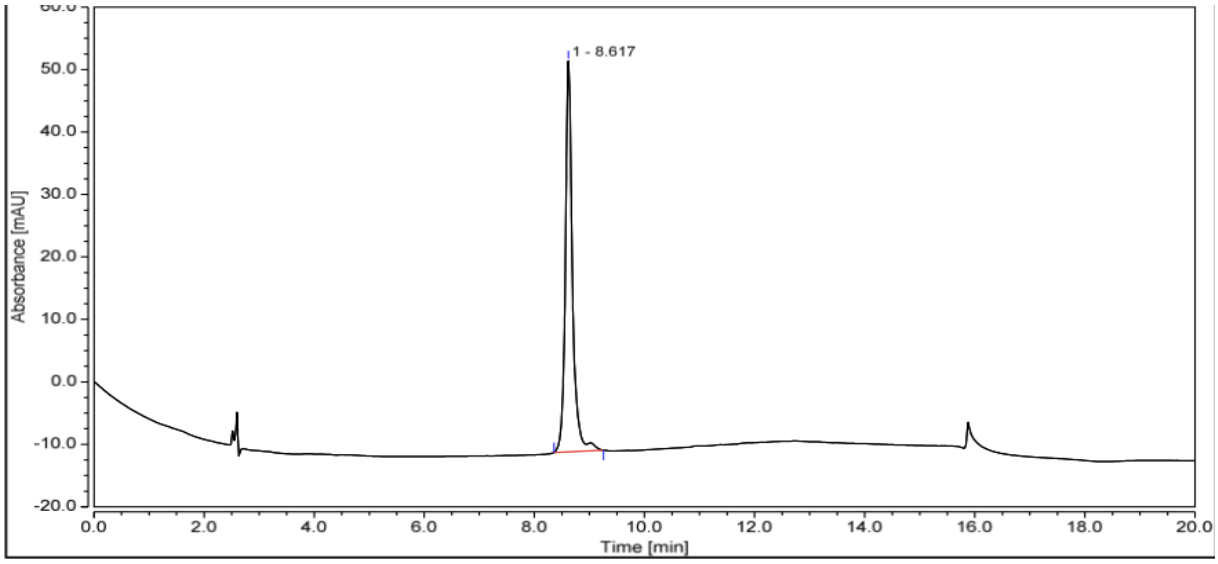


Figure 63 Representative chromatogram of benzaldehyde scavenging with 0.1 mol% of $Cu(OTf)_2$. Conditions: 1.11 mmol of the benzaldehyde; 1.4 mL of EtOH:H_2O (1:1).

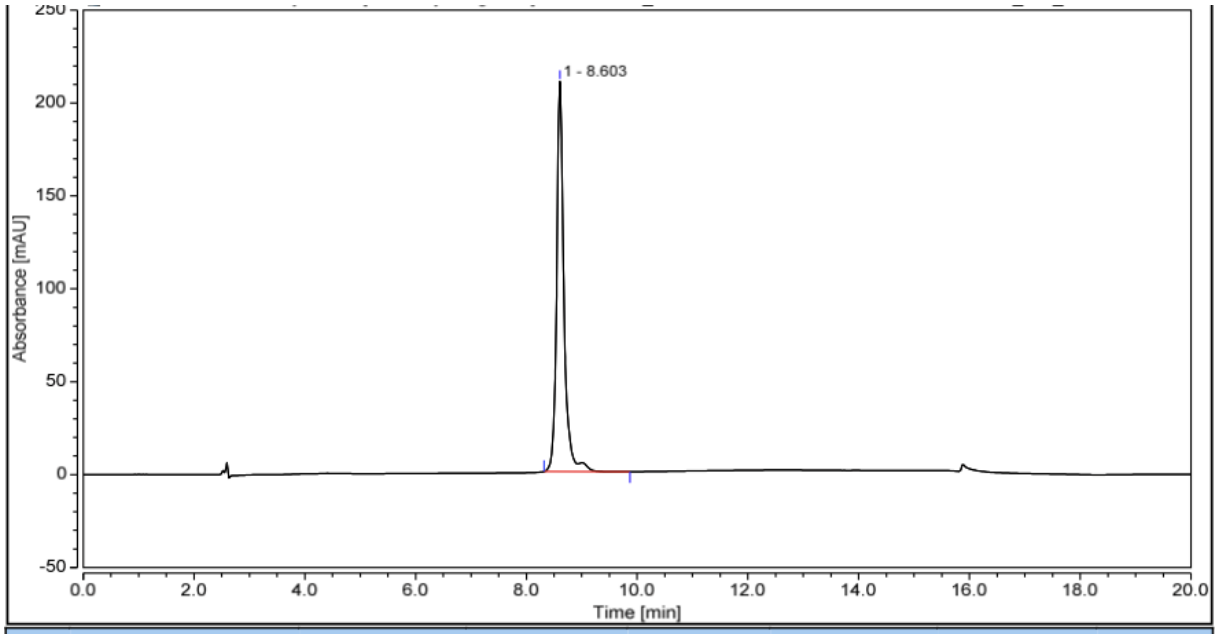
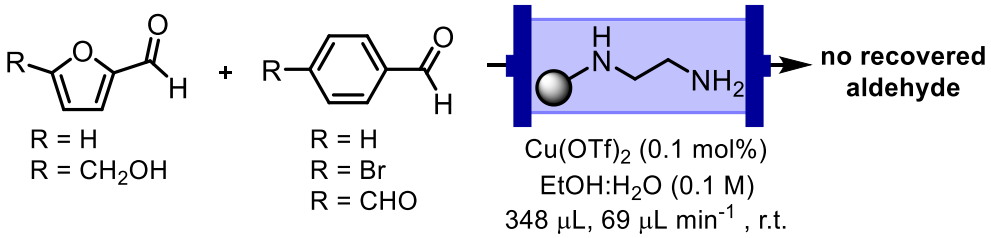


Figure 64 Representative chromatogram of benzaldehyde scavenging with 0.1 mol% of $Cu(OTf)_2$. Conditions: 1.4 mmol of the benzaldehyde; 1.74 mL of EtOH:H_2O (1:1).

Scavenging of different aromatic aldehydes and furfural derivatives



To a solution of benzaldehyde, 4-bromobenzaldehyde, terephthalaldehyde, furfural and 5-hydroxymethylfurfural in a mixture of EtOH:H_2O (1:1) (0.1 M of total aldehydes, 0.02 M each aldehyde) was added $Cu(OTf)_2$ (0.1 mol%) catalyst. The mixture was injected with a syringe pump into the flow reactor (ID= 4.6 mm, L= 50 mm), containing polymer-bound ethylenediamine resine (395 mg, 4-5.7 mmol/g), at room temperature. The flow rate was set at 69.6 µL min^{-1} corresponding to a residence time of 5 minutes. The resultant solution was collected and analysed by HPLC.

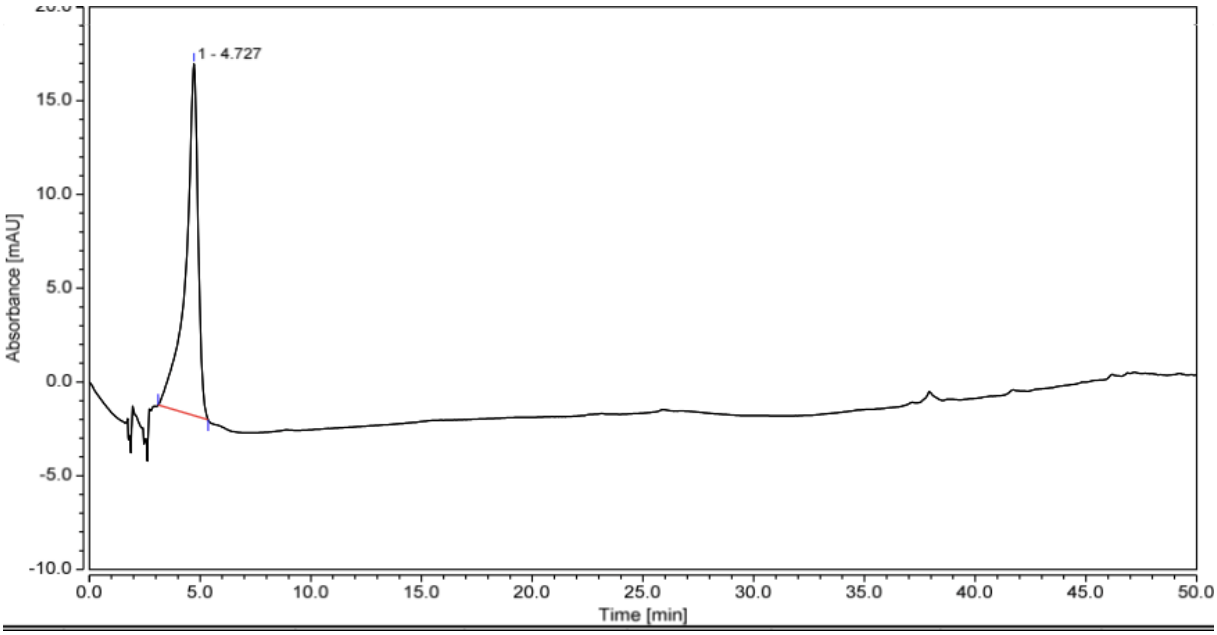


Figure 65 Representative chromatogram of aldehydes scavenging with 0.1 mol% of $Cu(OTf)_2$. Conditions: 0.035 mmol of the aldehydes (total), 0.348 mL of EtOH:H_2O (1:1)

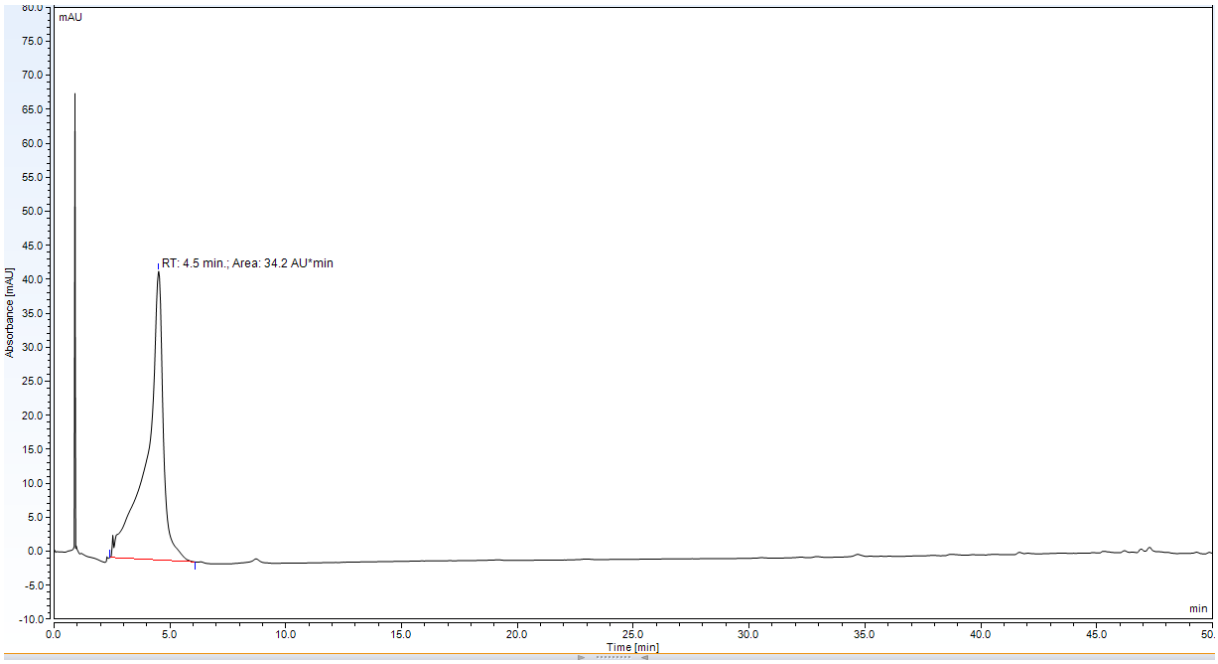
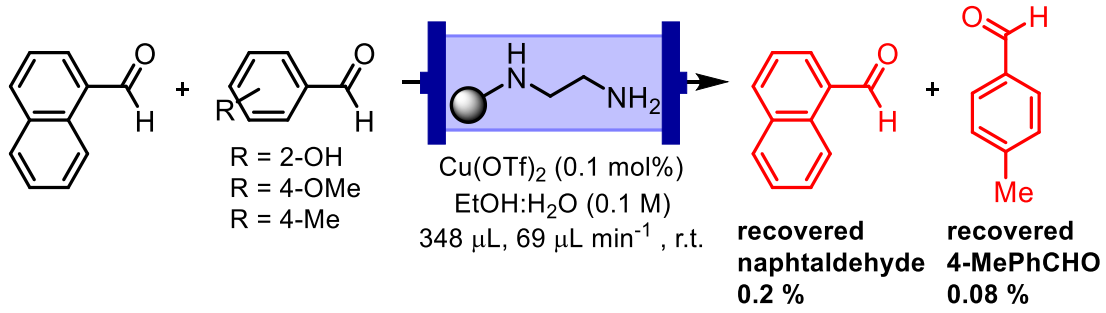


Figure 66 Representative chromatogram of aldehydes scavenging with 0.1 mol% of $Cu(OTf)_2$. Conditions: 0.14 mmol of the aldehydes (total), 1.4 mL of $EtOH:H_2O$ (1:1)



To a solution of 2-naphthaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde and salicyladehyde in a mixture of $EtOH:H_2O$ (1:1) (0.1 M of total aldehydes, 0.025 M each aldehyde) was added $Cu(OTf)_2$ (0.1 mol%) catalyst. The mixture was injected with a syringe pump into the flow reactor (ID= 4.6 mm, L= 50 mm), containing polymer-bound ethylenediamine resine (395 mg, 4-5.7 mmol/g), at room temperature. The flow rate was set at 69.6 $\mu L \cdot min^{-1}$ corresponding to a residence time of 5 minutes. The resultant solution was collected and analysed by HPLC.

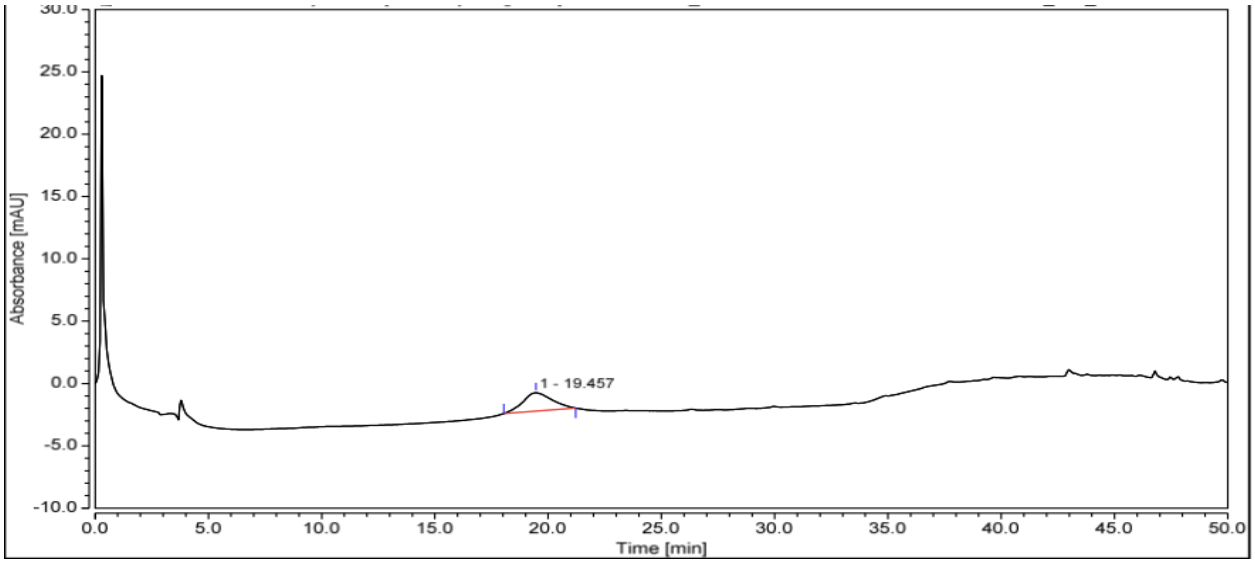


Figure 67 Representative chromatogram of aldehydes scavenging with 0.1 mol% of $Cu(OTf)_2$. Conditions: 0.08 mmol of the aldehydes (total), 1 mL of EtOH:H_2O (1:1).

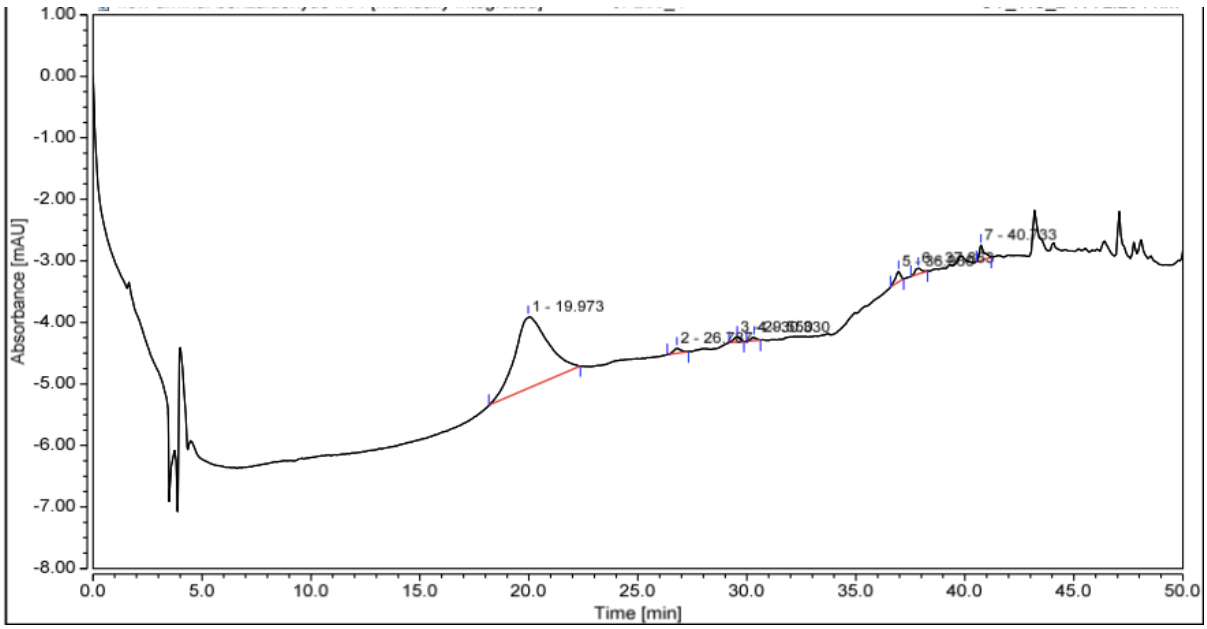
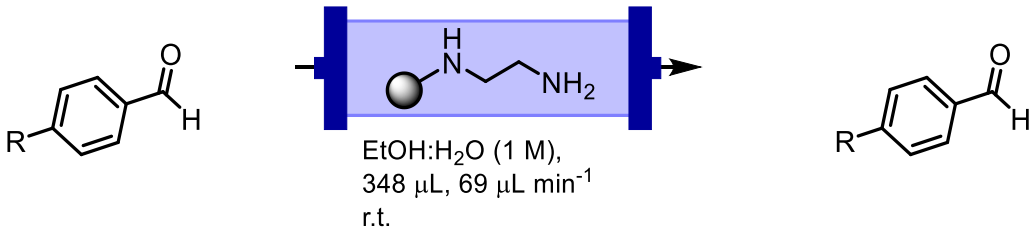


Figure 68 Representative chromatogram of aldehydes scavenging with 0.1 mol% of $Cu(OTf)_2$. Conditions: 0.11 mmol of the aldehydes (total), 1.4 mL of EtOH:H_2O (1:1)

Resin capability for the scavenging of 4-methoxybenzaldehyde and 4-(dimethylamino) benzaldehyde

To a solution of 4-methoxybenzaldehyde (PMB) and 4-(dimethylamino)benzaldehyde (PDMB) in a 1:1 molar ratio in a mixture of EtOH:H_2O (1:1) (1M) was added $Cu(OTf)_2$ (0-0.1 mol%) catalyst. The mixture was injected with a syringe pump into the flow reactor (ID= 4.6 mm, L= 50 mm), containing polymer-bound ethylenediamine resine (395 mg, 4-5.7 mmol/g), at room temperature. The flow rate was set at 69.6 µL min^{-1} corresonding to a residence time of 5 minutes. The resultant solution was collected and analysed by HPLC.

Table 28 Saturation of the resin with aldehydes in the presence and absence of catalyst



PMB, R = 4-OMe

PDMB, R = 4-NMe2

Recovered aldehyde

		Recovered aldehyde PMB/PDMB (%)	
Entry	Total aldehyde input	No catalyst	0.1 mol% Cu(OTf)2
1	0.35 mmol	10/12	0/0
2	0.70 mmol	22/30	1/4
3	1 mmol	32/40	7/40
4	1.4 mmol	77/100	18/55
5	1.7 mmol	100/100	23/56

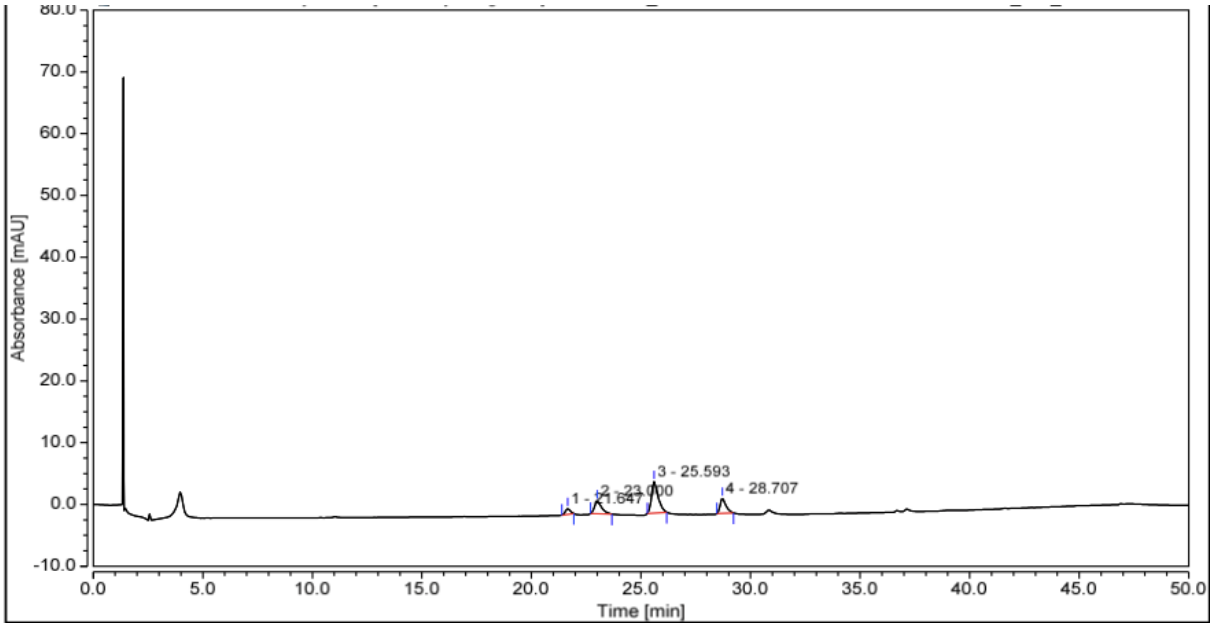


Figure 69 Representative chromatogram of aldehydes scavenging without catalyst. Conditions: 0.348 mmol of the aldehydes (total); 0.348 mL of EtOH:H_2O (1:1).

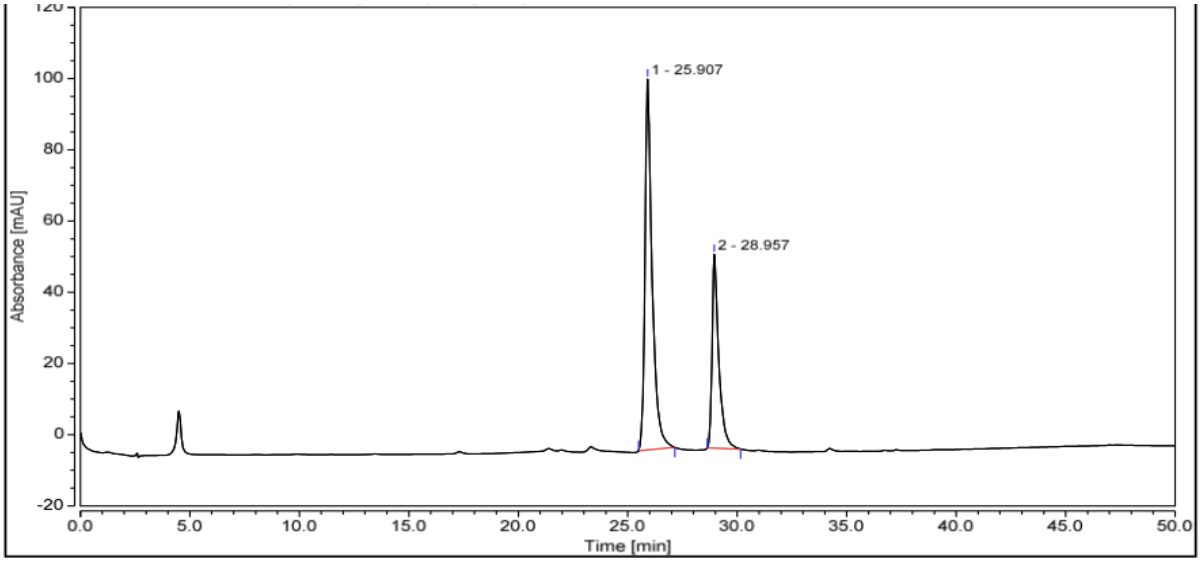


Figure 70 Representative chromatogram of aldehydes scavenging without catalyst. Conditions: 1.74 mmol of the aldehydes (total); 1.74 mL of EtOH:H_2O (1:1).

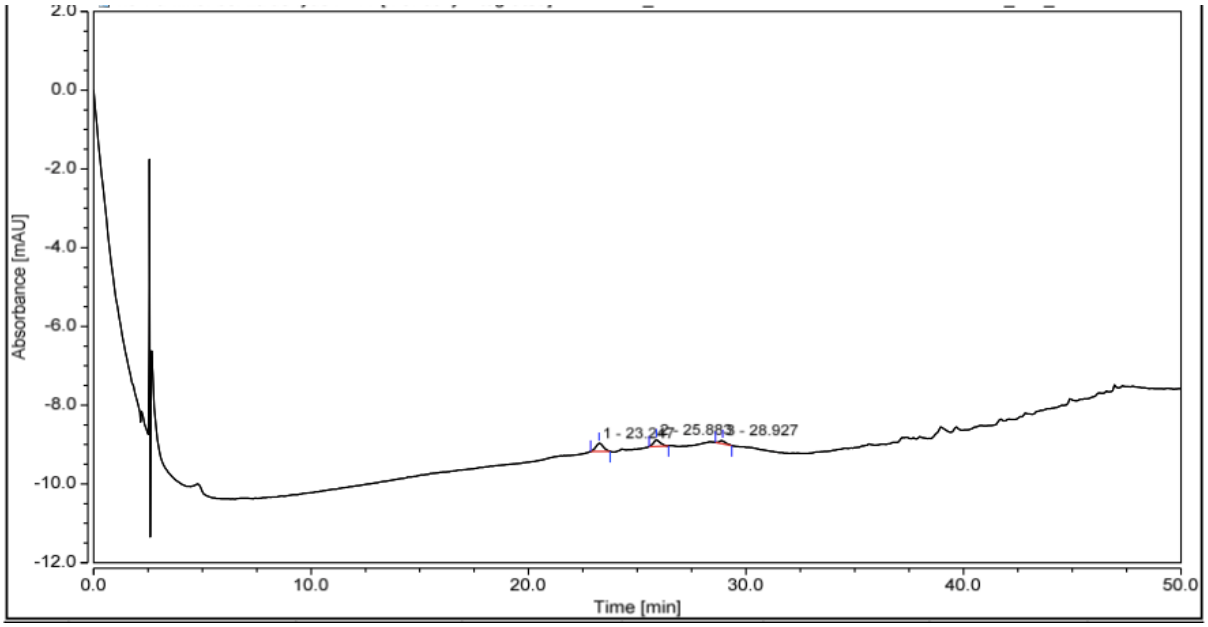


Figure 71 Representative chromatogram of aldehydes scavenging with 1 mol% of $Cu(OTf)_2$. Conditions: 0.348 mmol of the aldehydes (total); 0.348 mL of EtOH:H_2O (1:1).

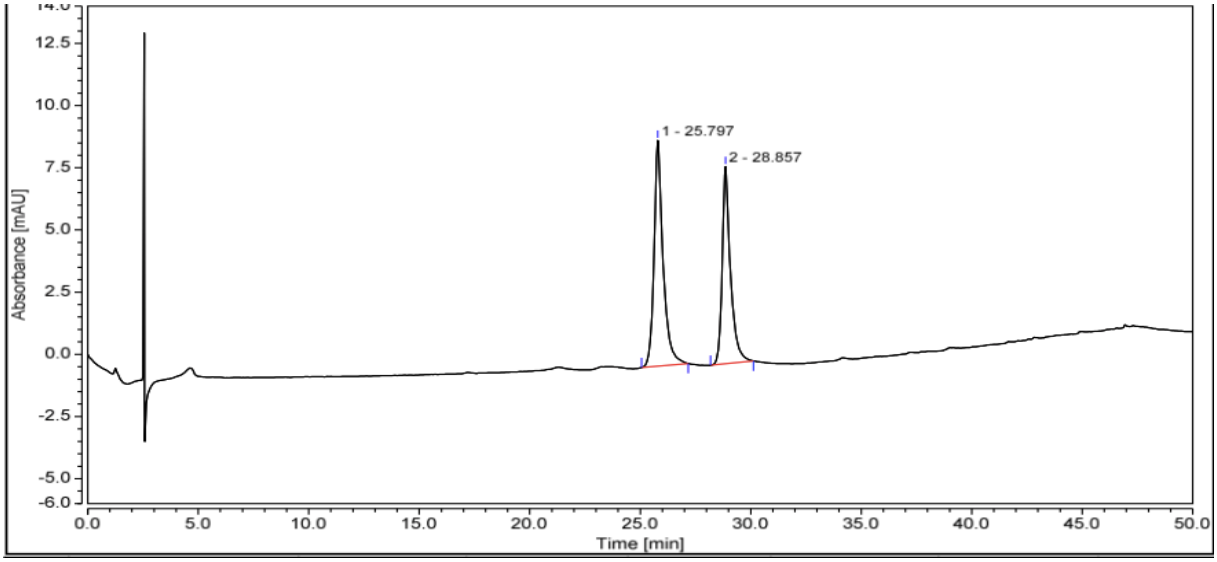
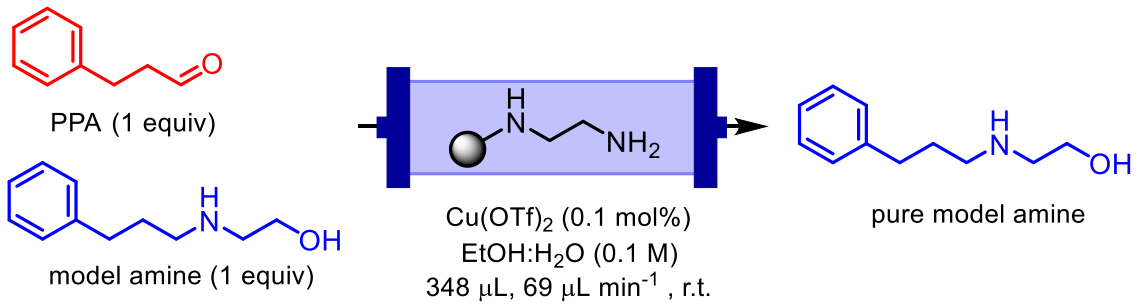


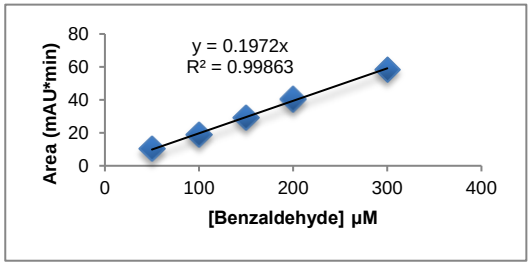
Figure 72 Representative chromatogram of aldehydes scavenging with 1 mol% of $Cu(OTf)_2$. Conditions: 1.74 mmol of the aldehydes (total); 1.74 mL of EtOH:H_2O (1:1).

Scavenging of 3-phenylpropanal 41 in the presence of 3-((3-phenylpropyl)amino)propan-1-ol

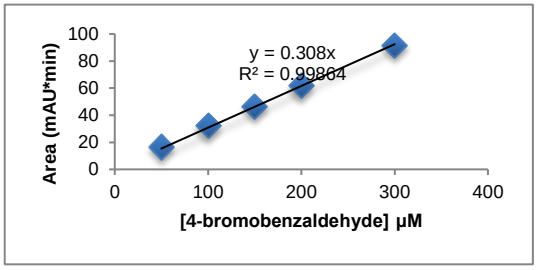


To a solution of 3-phenylpropanal (13 mg, 0.1 mmol) and 3-((3-phenylpropyl)amino)propan-1-ol (18 mg, 0.1 mmol) in a mixture of ethanol:water (1:1) (1 mL, 0.1 M) was added $Cu(OTf)_2$ catalyst (0.1 mol%). The mixture was injected with a syringe pump into the flow reactor (ID= 4.6 mm, L= 50 mm), containing polymer-bound ethylenediamine resine (395 mg, 4-5.7 mmol/g), at room temperature. The flow rate was set at 69.6 µL min^{-1} corresonding to a residence time of 5 minutes. The resultant solution was collected and evaporated to obtain 18 mg of pure product.

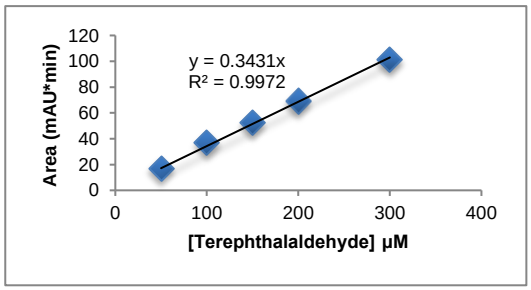
Calibration curves for HPLC analysis



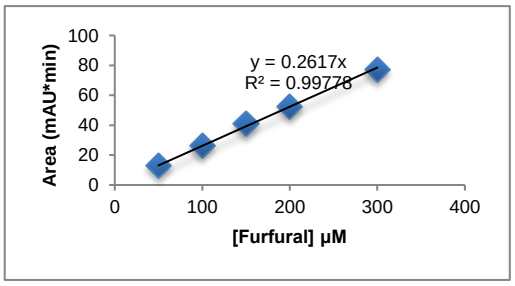
benzaldehyde at 254 nm.



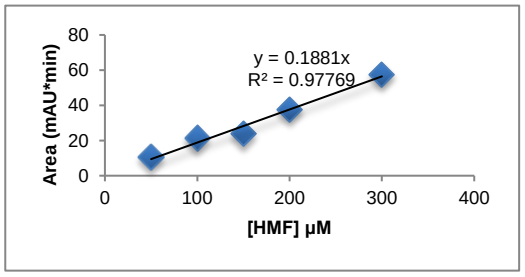
4-bromobenzaldehyde at 254 nm.



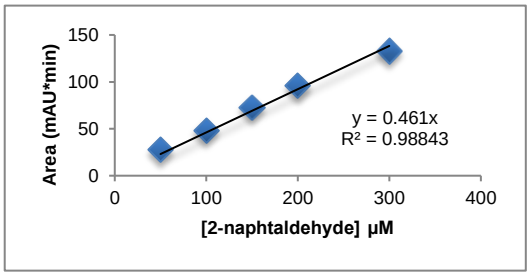
terephthaldehyde at 254 nm.



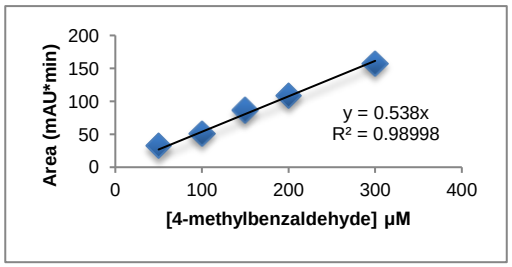
furfural at 254 nm.



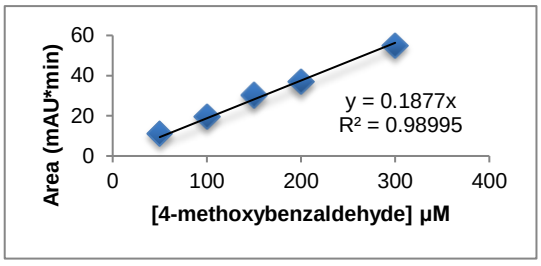
HMF at 280 nm.



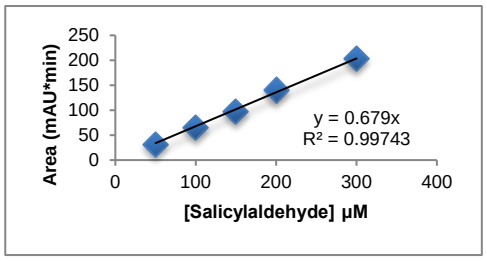
2-naphtaldehyde at 254 nm.

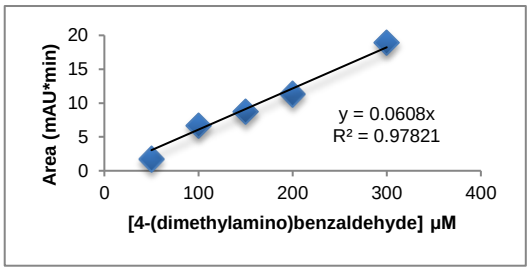


4-methylbenzaldehyde at 254 nm.



4-methoxybenzaldehyde at 254 nm.





salicylaldehyde at 210 nm

4-(dimethylamino)benzaldehyde at 254 nm.

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