UNIVERSITÀ DEGLI STUDI DI CAMERINO

SCHOOL OF ADVANCED STUDIES

DOCTORAL COURSE IN

CHEMICAL AND PHARMACEUTICAL SCIENCES AND BIOTECHNOLOGY

CYCLE XXXIII

SYNTHESIS AND DERIATIZATION OF HETEROCYCLIC SYSTEMS UNDER SUSTAINABLE CONDITIONS

PHD STUDENT
ELENA CHIURCHIÙ

SUPERVISORS
ALESSANDRO PALMIERI

“Sola dosis facit venenum”
Paracelsus

List of Abbreviations

AE: Atom economy

MW: Microwave

EWG: Electron-withdrawing group

EDG: Electron-donating group

R.t.: Room temperature

FC: Friedel Craft

PTFE: Polytetrafluoroethylene

DCM: Dichloromethane

NMP: *N*-Methylpyrrolidone

MeCN: Acetonitrile

EtOAc: Ethyl acetate

2-MeTHF: 2-Methyl tetrahydrofuran

Hex: Hexane

PS: Polystyrene

RBF: Round-bottom flask

TBD: 1,5,7-Triazabicyclo[4.4.0]dec-5-ene

DMAP: 4-(Dimethylamino)pyridine

BEMP: 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2 diazaphosphorine

B.P.: Boiling point

M.P.: Melting point

SolFC: Solvent free conditions

MEK: Methyl Vinyl ketone

NCS: *N*-Chlorosuccinimmide

Hal: Halogen

Het: Heteroatom

1. Heterocycles

Heterocyclic systems are of exceptional importance in most of the chemistry fields and it is one of the main research areas in organic chemistry. They can find applications in electronic, biology, optic, pharmacology, material sciences and so on.

Heterocycles are cyclic molecules containing, at least, two different types of atoms in the ring. In organic chemistry, heterocycles are ring structures containing atoms different from carbon, in general sulphur, nitrogen or oxygen. As shown in Figure 1, there is plenty of natural and synthetic drugs and biologically active molecules containing an heterocycle in the core structure, according to CMC 2001.1 database 56.8% of approved drugs.[1] These drugs are used as antibacterial, antifungal, treatment for CNS disorders and more.[2]

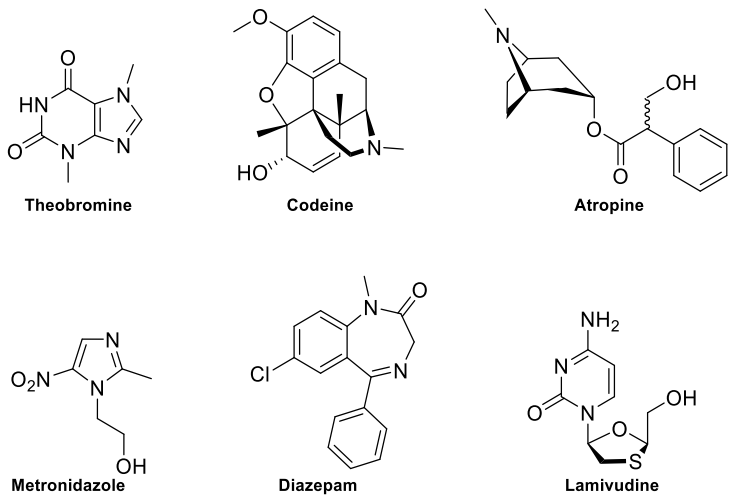


Figure 1. Examples of biologically active heterocycles

Why heterocycles are so ubiquitous? Because this class of compound is involved in a considerable extent of reactions. In fact, according to the pH of the reaction media, for example, heterocycles can act as a base or an acid and promote further reactions; they can form metal complex of biological importance[3] and, the presence of a heteroatom in the structure, gives new qualities to the compound, which displays more flexibility and often better response to biochemical systems.[4] Moreover,

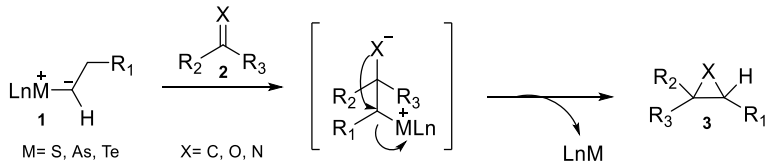
also physical-chemical properties like lipophilicity, polarity and H-bonding ability are affected by the presence of an heteroatom.

1.1 Three-membered ring

The usual three-membered heterocycles are aziridines, azirines and oxiranes (Figure 2), they are of paramount utility in organic synthesis.[5] In fact, this small reactive species found applications in pharmaceutical sector as building blocks for more complex molecules or as a catalysts.[6]

Figure 2. Most common three-membered rings

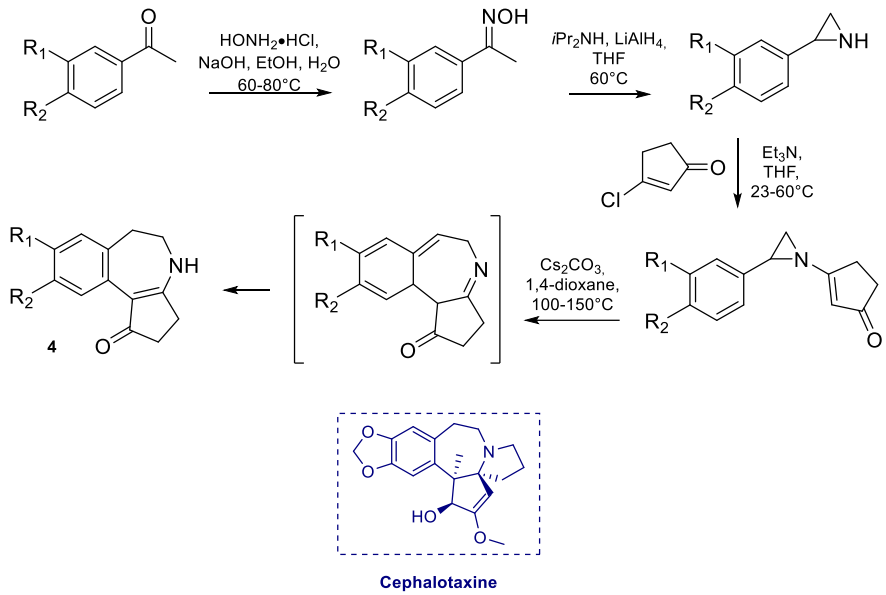
An interesting synthesis for both *N*- and *O*- containing saturated three membered ring was recently proposed by Dai *et al.*[7] starting from a nucleophilic addition of an ylide type **1** to an electrophilic carbon provided by an imine or a carbonyl respectively (**2**). The addition is followed by a cyclization to afford the three membered rings **3** with controlled stereochemistry, additionally, this procedure works also for the formation of cyclopropanes (Scheme 1).



Scheme 1. Three-membered ring formation.

Oxiranes find their main applications in the field of material sciences in the preparation of epoxydic resins[8] or poly-carbonates.[9]

Differently, a useful application of aziridine is in the synthesis of larger ring by expansion reaction, as for the preparation of *Cephalotaxine* analogues where this is the key step.[10] The study was performed developing the synthesis for substituted 2,3-dihydro-1H-3-benzazepine type **4**, the ring expansion in the final step is thermally activated and it is promoted by the presence of a base (Scheme 2).



Scheme 2. Synthesis of Chephalotaxine analogues

1.2 Four-membered ring

The interest in four-membered rings has been increasing in the last decades. The reason of this tendency is to find in the unexplored potential of such molecular structure and in the need to find unpatented compounds for pharmaceutical applications. A principal utilization for four-membered ring is in the formation of spiroketals,[11] which are a bicyclic compound where an atom belongs to both rings. Spiroketals are rigid compounds with a specific stereochemistry which make them really attractive in the field of medicinal chemistry.

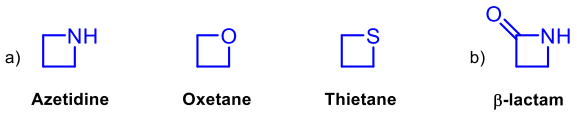
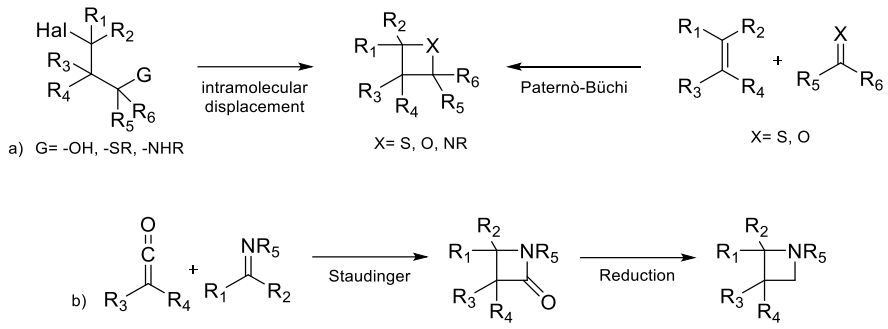


Figure 3. Common four-membered rings

The main synthetic routes to *S,O,N*-containing four-membered heterocycles (Scheme 3) involves a photo-promoted approach, like in Paternò-Buchi reaction where a ketone or a thioketone reacts with an alkene to produce the corresponding ring (oxetane or thietane). Similarly, Staudinger reaction is used to access, in a photo-catalytical way, β-lactams which can be, in turn, reduced to obtain azetidines (Scheme 3b).

Alternatively, an intramolecular nucleophilic substitution, may be performed to synthetize the target heterocycle (Scheme 3a).



Scheme 3. Synthetic approach for *S,N,O*-containing four-membered heterocycles

β-lactams (Figure 3b) are extensively used in pharmaceutical and medicinal chemistry as antibiotics core. Penicillin (Figure 4a), which shows a bicyclic core including a β-lactams ring, is basically the progenitor of antibiotics and was used successfully for the first time in 1930 by Paine for a gonococcal infection.[12] Its large-scale production began during WWII, moving the manufacturing from Europe to US.

Penicillin, and in general β-lactam-based antibiotics, act on membrane enzymes of bacteria called PBPs (Penicillin-Binding Proteins) which are, essentially, enzymes able to interact with β-lactam. These enzymes work for producing peptidoglycan, responsible for the cell wall synthesis and involved in osmotic processes.[13]

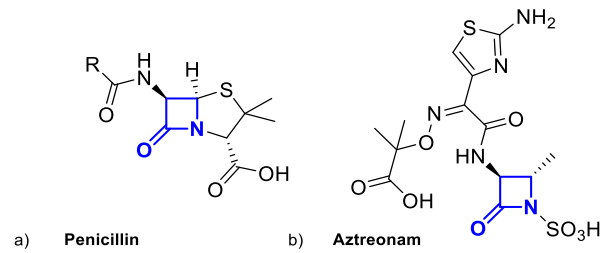


Figure 4. β-lactam containing drugs

Aztreonam (Figure 4b), is a monobactams, a monocyclic β-lactam antibiotic. This kind of antibiotics are effective only with Gram-negative bacteria.

1.3 Five-membered ring

In recent times, rising interest has been put in the chemistry of five-membered rings, especially in *N,O,S*-containing aromatic ones (Figure 5). In fact, they can be considered as isosteres of benzene, but the presence of a heteroatom gives them a peculiar metabolic behavior, conferring them a different SMR (Structure-Metabolism-Relationship) compared to their carbonaceous analogues.[14]

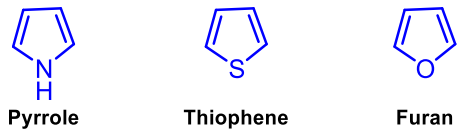


Figure 5. Most common five-membered heterocyclic ring

Five-membered aromatic heterocyclic ring are planar, sp^2-hybridized, 6-π-electrons systems which can be considered aromatic according to the Hückel's rule (π= 4n + 2). Comparably to cyclopentadiene anion, they have six electrons over five atoms and are regarded as electron-rich systems. Four of the six π-electrons are given by the two conjugated double bonds, the remaining two are shared by the heteroatom. The resonance structures (Figure 6) explain why five-membered heterocycles are subjected to electrophilic substitution at C and not at heteroatom: negative charge is essentially on carbons and the positive on X (X= het). Moreover, aromaticity of these compounds is affected by the electronegativity of the heteroatom; considering furans, oxygen is less prone to participate with its two electrons to the π-system, behaving more like a conjugated diene than as an aromatic system.

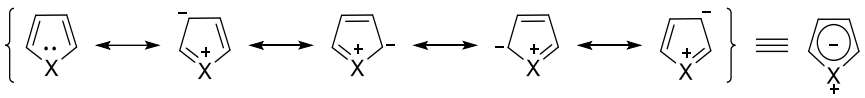
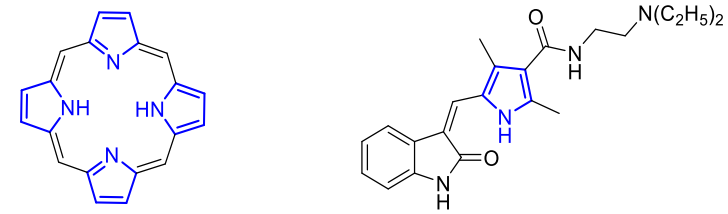


Figure 6. Five-membered ring heterocycles resonance structures and π-orbitals aromatic system

Pyrroles. Pyrrole (Figure 5) is defined "privileged scaffold", which is a high-affinity ligand able to bind to different receptors.[15] In fact, pyrrole is a ubiquitous ring in biologically active molecules used in the treatment of most varied diseases, like inflammation,[16] cancer,[17] virus.[18] Pyrrole is a constituent of porphyrins (Figure 7a), a hetero-macrocyclic compound

present in heme, chlorophyll and vitamin B_{12}, molecules of vital importance, and in countless other natural compounds.

It is possible to cite hundreds of cases of commercial pyrrole-containing drugs, since the presence of pyrrole in the structure gives to the molecule a peculiar behavior.[19] An example is Sunitinib (Figure 7b) which is a small-molecule drug used in the treatment of renal carcinoma and gastrointestinal stromal tumor. It is able to act on three different receptors (RTKs, VEGFR and PDGFR) and shows great bioavailability compared to its predecessors.[20]

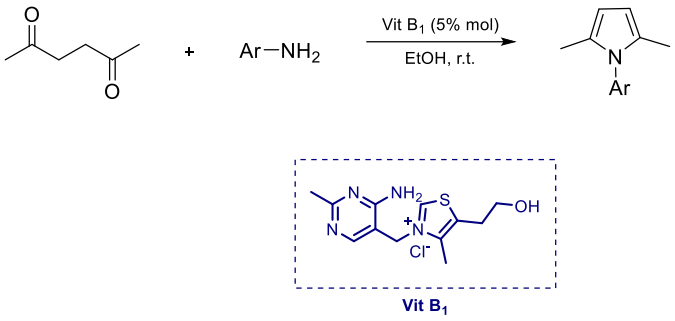


a) **Porphyrin** b) **Sunitinib**

Figure 7. Examples of pyrrole-containing molecules

A typical synthetic procedure for the preparation of pyrroles is the well-known Paal-Knorr where a 1,4-dicarbonyl compound reacts with ammonia or a primary ammine to generate a substituted pyrrole.

Recent developments are proposed in literature, for example a curious approach is suggested by Darabi *et al.*[21] where vitamin B_1 is used as a green catalyst for the synthesis of substituted pyrroles (Scheme 4). Even if the methodology reports the use of 2,5-hexanedione as a unique di-ketone, the procedure works pretty well at mild conditions with aryl amines (yields=28-89%).



Scheme 4. Vitamin B_1-catalyzed synthesis of pyrroles

Furans. Furan ring (Figure 5) is component of numerous natural products such as furoflavonoids, furanolactones, furano-coumarins and natural terpenoid and found extensive applications in pharmaceutical chemistry.[22]

In recent times, several microorganisms resulted to be resistant to typical antibiotic drugs based on β-lactams, macrolides or quinolones, so it became fundamental to find different scaffold.[23] Furantoin (Macrobid, Figure 8) is a furan-containing antibiotic used in the treatment of UTIs (Urinary Tract Infections), it demonstrated to be almost immune to antibiotic resistance, in fact, even if its first use was registered in 1953 it is still active against several type of bacteria.[24]

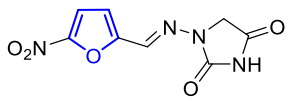


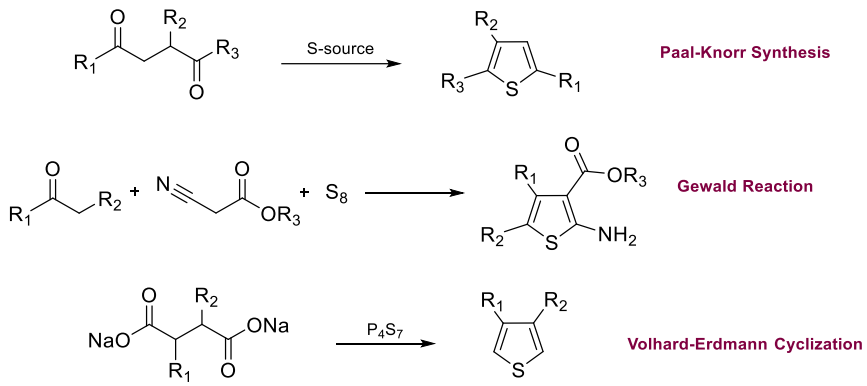
Figure 8. Nitrofurantoin

A common industrial preparation for furan is from furfural, generated from sugar-containing raw material like corncobs. Recently, the use of sugars as renewable feedstock of raw material is increasing, in fact biomass is an inexhaustible source of furanoses and hexoses which can be easily converted into furan-based molecules.[25] Especially 5-HMF (5-hydroxymethyl furfural), 2,5-FDCA (2,5-furan dicarboxylic acid) and 2,5-DMF (2,5-dimethyl furan), derived from hexoses, are considered as "sleeping giants" for chemical intermediates.

Thiophenes. Thiophenes (Figure 5) is a *S*-containing five-membered aromatic ring. Its derivatives are broadly used in material science,[26] as a

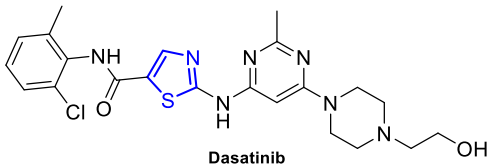
matter of fact, thiophene-based oligomers and polymers show compelling semiconductor and luminescence properties. These oligomers and polymers can arrange in a supramolecular organization, due to weak interaction (Van der Waals, CH…S, S-S, π-π) and, according to the polymorphism obtained, they can have different characteristics. Thiophene-based Covalent Organic Frameworks (COFs), are gaining interest in the field of electronics,[27] as well as printed Organic Thin-Film Transistor (OTFTS) produced from thiophene-based polymer are making their way in alternative to silicon-based material.[28] Moreover, thiophene-based π-conjugated systems has emerged as important class of compounds in organic solar cell. Their defined molecular structure confers to this kind of oligomers peculiar chemical characteristics which make them fascinating for photovoltaic applications.[29]

Representative synthetic procedures for thiophene preparation are based on classical Paal-Knorr synthesis, Gewald reaction or Volhar-Erdmann cyclization (Scheme 5).

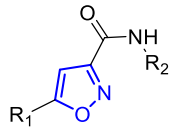


Scheme 5. Typical thiophenes synthesis

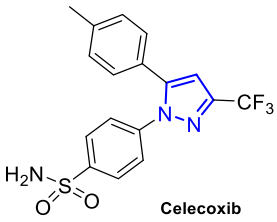
Five-membered ring containing more than one heteroatom. As an example, herein are reported some five-membered rings containing more than one heteroatom. Pyrazoles,[30] imidazoles,[31] thiazoles,[32] isoxazoles[33] and many others are omnipresent in nature and in industries, in fact, they are core structures for many commercial drugs (Figure 9), ingredients for dyes, or find employment in material sciences.



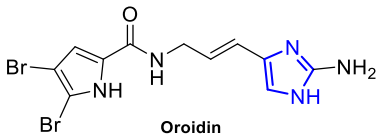
Dasatinib
for the treatment of cancer



3-carboxamido-5-aryl-isoxazoles
for the treatment of colitis



Celecoxib
anti-inflammatory activity



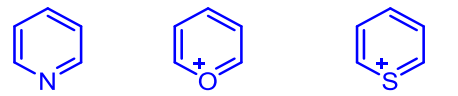
Oroidin
anti-microbial activity

Figure 9. Few examples of heterocycles containing more than one heteroatom

1.4 Six-membered ring

Six-membered heterocycles, as most of the heterocyclic systems, are largely present in nature. A striking example of this are pyranose sugars, six membered cyclic saccharides where one of the members is an oxygen.

Considering aromatic systems, the most common one is pyridine, a *N*-containing aromatic six-membered ring. The *O*- and *S*- analogues of pyridine, pyrilium and thiopyrilium, exist only in their cationic form (Figure 10) and are not frequent.



Pyridine **Pyrilium ion** **Thiopyrilium ion**

Figure 10. Six-membered aromatic ring

Pyridines. Pyridines is widely present in natural products (Figure 11)[34] and in biological systems, and it is broadly used as a reagent or solvent in organic chemistry. It is naturally contained in coal tar and bone oil, a smelly lubricant almost abolished after Geneve's Protocol, since pyridine's presence in the environment is considered a concern and very few literature is present regarding its degradation.[35]

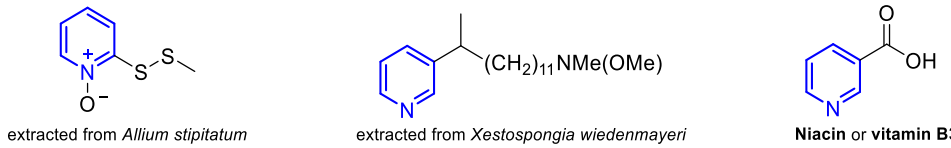


Figure 11. Pyridine in natural product

Niacin (Vitamin B_3, Figure 11), it is a naturally occurring pyridine derivatives and plays a fundamental role in biological systems. In fact, it is a precursor of cofactors NAD and NADP, important for carbohydrates, fats and proteins catabolism and for fatty acid or cholesterol synthesis, respectively.

The main industrial application for pyridine is maybe as a pesticide, even if it is homocyclic to benzene, the presence of the nitrogen confers to the molecule and its derivatives different reactivity. Some of the best-seller pesticides are pyridine-based, like Paraquat or picloram (Figure 12).[36]

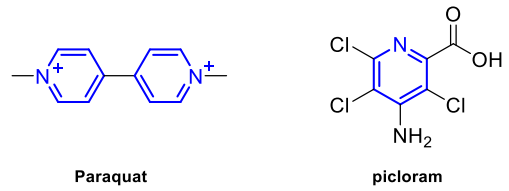
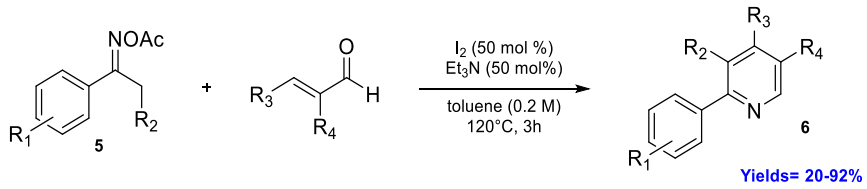


Figure 12. Pyridine-based pesticides

An appealing synthesis of poly-substituted pyridines is proposed by Huang *et al.*[37] In this work, pyridines are prepared from *O*-acetyl ketoxime **5** reacting with α,β-unsaturated aldehydes catalyzed by a metal-free system. Molecular iodine and triethylamine promote the addition-cyclization in a regioselective process, leading to the product **6** in good to excellent yields (Scheme 6). Moreover, different substituents are tolerated both on the *O*-acetyl ketoxime **5** and on the α,β-unsaturated aldehyde.



Scheme 6. Synthesis of poly-substituted pyridines

Pyridazines. Pyridazines (Figure 13), or 1,2-diazines, are six-membered ring heterocycles containing two adjacent nitrogen atoms, they can be considered a sort of cyclic hydrazones. Their presence in nature is quite rare, probably because hydrazines, their precursor, are not that common. Pyridazine-containing structures have been isolated mainly from *Streptomyces* culture broth, and really few information are available about their natural synthesis or degradation.[38] That's why they took long time to become "important" and, by now, they find wide application in the preparation of pesticides[39] and in pharmaceutical chemistry[40] as isosteres of phenyl or other heteroaromatic ring. In fact, their presence in a pharmacophore affect its chemical-physical properties, like complexation ability and bioavailability. Moreover, compared to other diazines, they show quite basic behavior (pk_a=2.2) explained by resonance structure **c** in Figure 13 exhibiting a molecular dipole and, deeply, by the HOMO energy. For sure, the presence of a strong dipole affects pyridazine ability to form H-bond,[41] which is a captivating aptitude, since it influences biological and chemical processes, like interaction with receptors or water solubility.[42] Analyzing the resonance structures, using different techniques, appeared quite obvious that structures **a** in Figure 13 contributes more in the hybrid.

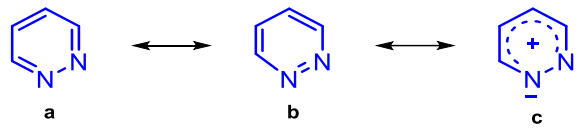
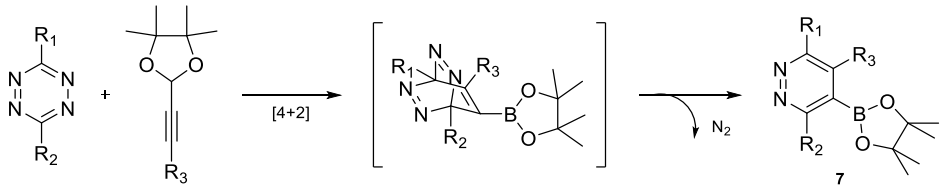


Figure 13. Resonance structures of pyridazine

Pyridazines first preparation was performed by Fisher during his studies about indole synthesis,[43] making phenylhydrazine react with levulinic acid. The characteristic preparation involves the use of hydrazines and 1,4-diketons as starting materials. Nowadays, different synthetic procedures are available in literature, here it is presented an intriguing approach using boronic esters in a Diels-Alder type reaction to produce substituted pyridizane-boronic esters **7**. [44] The cycloaddition is regioselective even using a non-symmetrical tetrazine.



Scheme 7. Synthesis of pyridazines boronic esters.

Compound **7** can undergo to further reactions exploiting the possibility to functionalize the C-B bond in a Suzuki coupling, obtaining new C-C or C-O bonds. Nevertheless, protodeboronation side reactions could still be a challenge, but using electron-rich phosphines to promote the reaction, this obstacle was cleared.

1.5 Benzo-fused systems

Indole. The name indole comes from indigo which is a natural dye extracted originally extracted from *Indigofera* (Figure 14a). Indoles are bicyclic systems made by a pyrrole and a benzene fused together, they are all-over in natural products and extensively present in synthetic drugs. For example, it is present in tryptophan (Figure 14b), which is an essential α-amino acid and its core structure for many drugs, including anti-cancer (Figure 14c).[45]

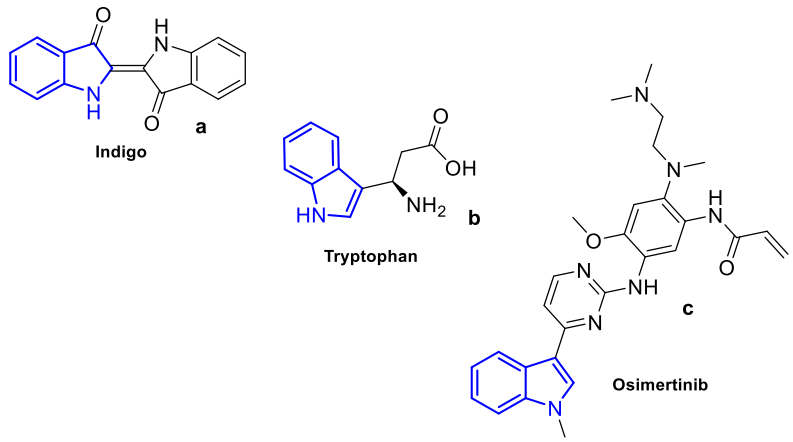
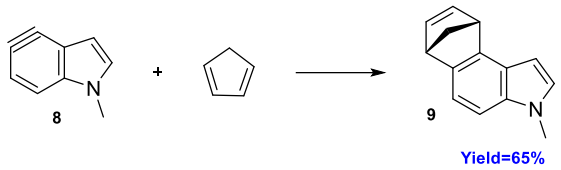


Figure 14. Indole-containing molecules

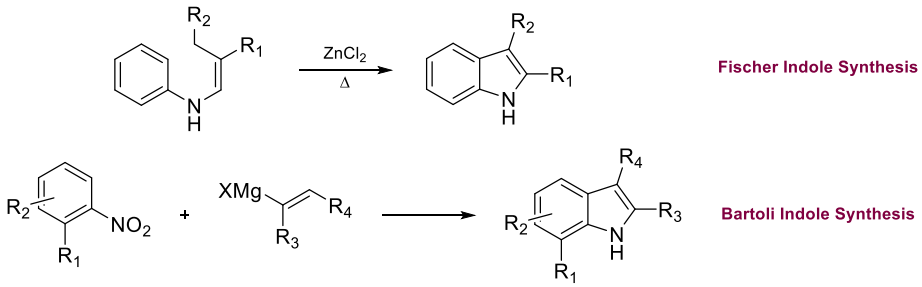
The typical reactivity of indole concerns its nucleophilic character to undergo to substitution in 3-potition, just like an enamine. Benzene moiety reactivity is, in general, neglected but, pretty much recently,

different behavior of indole has been realized and exploited. Taking into consideration 4,5-indolyne type **8**, they can be considered as electrophiles, reversing indole typical nucleophilic behavior. In fact, they can be used in combination to diene in Diels-Alder reactions to obtain indoles substituted at C5 and C4 positions (**9**).[46]



Scheme 8. Indolyne in Diels-Alder reactions

There is plenty of reported synthesis in literature for preparing this class of compounds, some of the most famous ones are based on Fischer or Bartoli synthesis (Scheme 9).



Scheme 9. Typical Indole Synthesis

Quinolines. Quinolines, namely pyridine benzoderivatives, are an attractive class of heterocycles. In fact, their derivatives have been deeply and widely studied for various applications in pharmaceutical chemistry, for instance they show anticancer, antimycobacterial, antimicrobial, anticonvulsant, anti-inflammatory and cardiovascular activities.[47]

Quinine (Figure 15), a quinolone derivative, is a traditional anti-malaria drug,[48] it has been used for 400 years and is still in use. It was accidentally discovered in 17th century, extracted from *cinchona tree* and used, successfully, since that time to treat malaria.

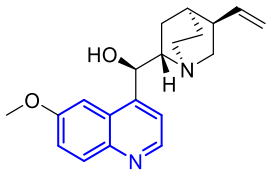
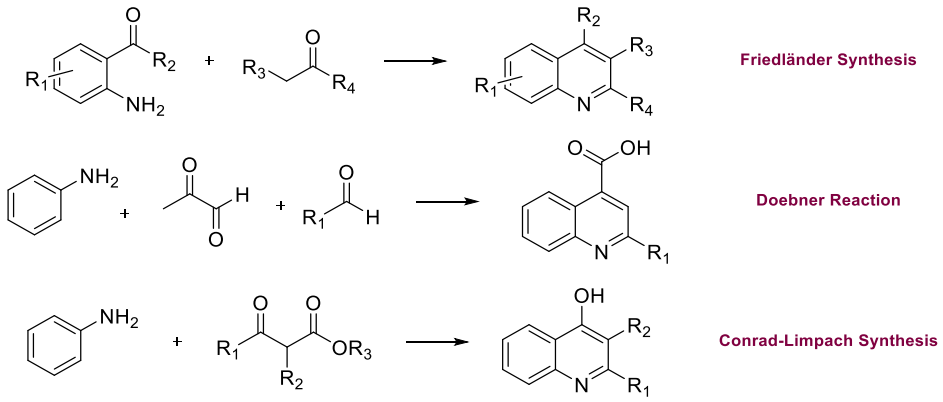


Figure 15. Quinine structure

Due to their importance in many fields, there are hundreds synthetic procedure for obtaining substituted quinolines. In Scheme 10 are listed the model reactions used for their preparation.



Scheme 10. Typical quinoline synthesis

Flavones. Flavones are a subclass of flavonoid which are generally diffused in nature and their typical backbone is reported in Figure 16. They are secondary metabolites in plants who are involved in signaling and defense, they are pigments in white-colored flowers, they can act as a protection for UVB filter and for oxidative stress and more.[49] Flavones are also studied for their benefic effect on human health, they are introduced in digestive system mainly in the form of 7-*O*-glycosydes or 6-*C*-glycosides, but the first one are more common and digestible.

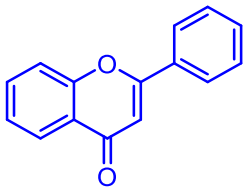
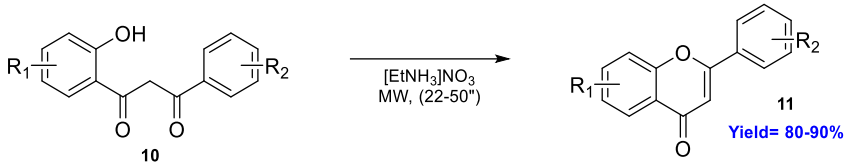


Figure 16. Flavones backbone

In particular, flavones polyphenolic derivatives have been studied as antioxidant,[50] antimicrobial[51] and for their cytotoxic activity.[52]

The title compounds can be prepared from 1,3-diketons type **10** which, under microwave irradiation, produce the target molecule in few seconds, according to the proposed methodology. This procedure involves the use of ionic liquid as a solvent, which can be recovered at the end and re-used, reducing the impact of the method.[53]



Scheme 11. Synthetic procedure for preparing flavones

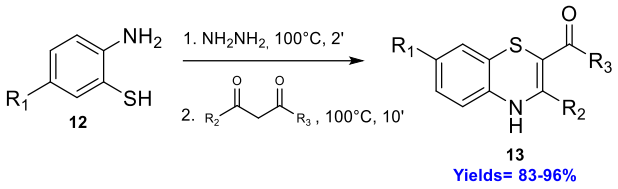
Thiazine derivatives: Benzo- and Pheno-thiazines. Several thiazine-based heterocycles have been studied for their potential pharmacological activity.[54]

Figure 17. Thiazine derivatives

Specifically, benzothiazine derivatives (Figure 17), which naturally occur in pheomelanin and are responsible for red hair and freckles, found application as potential analgesic,[55] antibacterial,[56] anticancer,[57] antiviral and more over. In the last decades, they have been studied as efflux pump inhibitors (EPIs) which, in combination with antibiotic, reduce the bacterial resistance to drug membrane-penetration.[58] Since they have different active sites, studies on 1,4-benzothiazines have demonstrated that substituents on *N* and oxidation state of *S* will affect their reactivity and therapeutic effect.[59]

A green preparation of 1,4-benzothiazines appeared in *Green Chemistry* journal in 2003, where a typical reaction between *o*-aminothiophenol **12** and a 1,3-diketon is promoted by catalytic amount of hydrazine leading

to the final product **13**, in solvent-free conditions and excellent yields (83-96%).[60]



Scheme 12. Synthesis of benzothiazines derivatives

Concerning phenothiazines derivatives (Figure 18), two of the most known ones are Promazine (PMZ) and Promethazine (PMT) hydrochloride (Figure 18, a and b respectively).

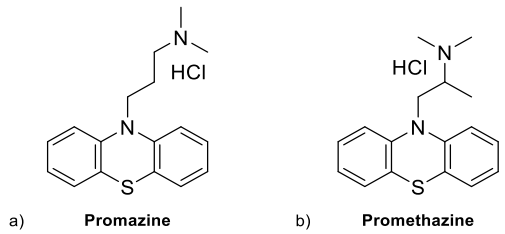
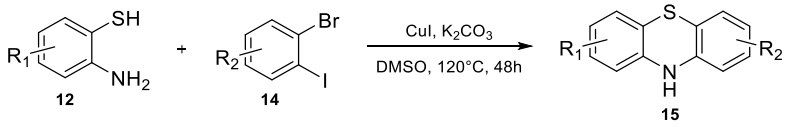


Figure 18. Phenothiazine-containing drugs

PMZ and PMT, despite showing just a conformation difference, they are used for the treatment of different disease. The former one is a molecule with antipsychotic activity, while the second one is just a sedative and can be used also as an antihistaminic.[61]

A typical synthesis for phenothiazine **15** is proposed by Dai. *et al.*, which involves a ligand-free CuI-catalyzed cascade coupling between an *ortho*-dihalide **14** and a 2-aminobenzenethiol (Scheme 13). The interesting part is the proposed catalytic cycle in which the 2-aminothiophenol itself act as a Cu-ligand to promote the Ulmann type coupling.[62]



Scheme 13. Phenothiazines synthesis

1.6 Larger ring systems

Benzodiazepines. Benzodiazepines (Figure 19) are bicyclic systems where one is a seven-membered ring containing two nitrogen and are defined as "privileged structures". They are a group of psychoactive drugs acting on GABA receptors ensuing a sedative, hypnotic, anti-anxiety, anticonvulsant, and muscle relaxant effect.[63]

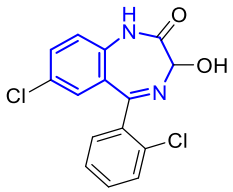
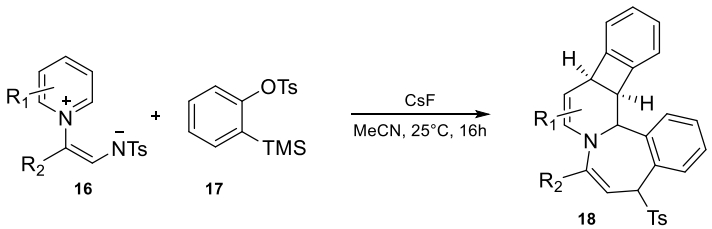


Figure 19. Lorazepam, example of benzodiazepine-based drug

Despite benzodiazepine side effects, like addiction, dependence or deficit in cognitive function, they are still one of the most commonly prescribed psycho-active drugs since they show great variability of application and administration.[64] Recently, fused polycyclic benzodiazepine-based system have been tested for their biological activity,[65] making necessary the development of synthetic strategies. With this purpose, Shin *et al.*,[66] developed a method for the preparation of such 1,4-benzodiazepine derivatives involving a cascade cycloaddition processes. Cycloadditions reactions allow the formation of complex product in one-step and, for this reason, they are desirable process in organic synthesis. In this particular case, pyridinium zwitterion derivatives **16** react as a 1,5-dipole with aryne precursor **17** to form the seven-membered ring in a [5+2] cycloaddition reaction. This intermediate automatically undergoes to a [2+2] with the aryne forming the final product **18**. The methodology proceeds avoiding the presence of any catalyst.



Scheme 14. Synthesis of benzodiazepine-based polycyclic systems

Macrolides. The name "macrolide" comes from *macro* (large) and *-olide* which is the suffix for a lactone, in fact they are a class of compound marked out by a large lactone ring, typically 14 to 16 members, functionalized with a sugar residue. They act as inhibitor of protein synthesis and show strong antibacterial activity. These compounds are active toward Gram-positive and some Gram-negative bacteria. But, unfortunately, in the last decades, many bacteria demonstrated a macrolide-based drug resistance, so different generation of such compound have been studied, like ketolides.[67] Resistance mechanisms are mainly related with the alteration of the binding site or in the antibiotic transportation.

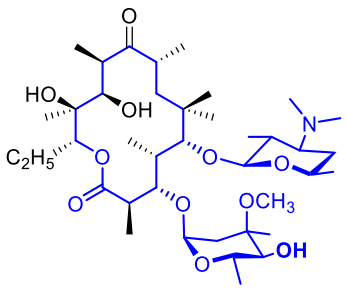


Figure 20. Erythromycin

The ancestor of macrolides is erythromycin, commercialized in 1953 and still extensively used in case of respiratory tract or skin infections, chlamydia or syphilis. It is the main alternative to treat people allergic to penicillin.

Due to the typical complexity of these molecules, which bear double bonds, stereocenter and different substituent, their synthetic approach is strictly related to the nature of the specific target molecule.[68]

2. Green Chemistry

In these days, environmental concerns are of primary importance: both pollution and human health are the two main problems to face in every branch of economy and, for this reason, at the beginning of 90's lots of programs and government initiatives appeared to deal with it.

During 60s and 70s, the publications of *Silent Spring* and *Closing Circle* shed light on the negative effect of chemical products on the environment. The attention was focused to an industrial development centralized mainly on a single fossil fuel which would inevitably bring to a limitation of the growth but also to a dramatic effect on the nature. The publication of *Our Common Future*, in 1987, by the World Commission on Environment and Development was the point of no return, a new definition of sustainable development was given: ''development that meets the needs of the present generation without compromising the ability of future generations to meet their own needs".

The idea of chemistry comes often with the idea of negativity, danger and, in general, something bad; a new viewpoint for chemistry and rules for an eco-friendly management of chemical industries and academical research seem to be essential. In this sense, chemistry must be no longer the problem but the solution.[69]

2.1 History and meaning of Green Chemistry

The first to promote this trend was President Nixon introducing the Citizen's Advisory Committee on Environmental Quality and a Cabinet-level Environmental Quality Council (CEQ) with NEPA (National Environmental Policy Act), this act established national policies and goals about pollution prevention and defined the role of national agencies.

After that, in 1970 EPA (Environmental and Protection Agency) was founded to face with environmental existing issues such as the wide use of DDT. Later on, this agency, established the OPPT (Office of Pollution, Prevention and Toxics) an institution formed to manage programs aimed control, prevent and evaluate pollution.

In 1990, EPA (Environmental Protection Agency) emitted the *Pollution Prevention Act* which was basically proposed to promote a more "green" approach to the productivity.

In 1991, EPA launched a research grant program which was expanded in 1993 and named "Green Chemistry Program" where, for the first time, the term Green Chemistry was used, coined by Anastas and co-workers.

Green Chemistry is defined as the ''design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances",[70] hence the purpose of green chemistry is not only to clean the world but to promote a new point of view for chemists and industries. The main point is to prevent and minimize the risk reducing the hazard, raising awareness about the need of developing new processes which are, by definition, less impactful for environment. A green process is not green by accident, is thought to be green. There's premeditation in a better use, handling, treatment, and disposal of substances.

In order to push people through this concept of "green", in 1995, President Clinton introduces "The Green Chemistry Challenge Awards" to reward both academic and industrial innovations. And, after 2 years, the

first Ph.D. in Green Chemistry was instituted in Massachusetts which was the first step of an educational project involving symposium, conferences and awards. Finally, in 1999, the journal *Green Chemistry* was launched by Royal Society of Chemistry in UK.

During 90's, also in Europe and in Japan, lots of program and institution were proposed: INCA, in Italy, which is a multi-university consortium involving about thirty universities and research groups working on different fields of chemistry, such as environmental, organic, inorganic, industrial, biochemical. The task of this consortium is to study and prevent the impact of chemical processes on human health and environment. In 2000, GSCN (Green and Sustainable Chemistry Network) was born in Japan with similar purpose and renamed JACI (Japan Association for Chemical Innovation) in 2011.[71] JACI is a platform conceived to share ideas and innovations with the intention to promote green and sustainable chemistry, it also promotes awards and conferences to spread its believes in Asia but also in other continents.

2.2 The twelve principle

In 1998, Anastas introduced the Twelve Principles of Green Chemistry, basically twelve rules to help in the design of a safer process.[70a,72] This set of principles are aim to reduce the intrinsic hazard of a chemical process embracing the whole life-cycle of the project.

The risk of a process is related both to the intrinsic hazard but also to the exposure:

$$\text{Risk} = f\,(\text{Hazard X Exposure})$$

1. Prevention. *It is better to prevent waste than to treat or clean up waste after it is formed.*

Waste is maybe the most important part in quantifying the impact of a process. Everything that is not included in the final product can be considered waste: materials, solvents, side-products, excess of energy. And, according to the way they are disposed or their nature, wastes can have different effect on the environment and human health. During

these years, several metrics have been introduced to define how much a process is green and the most widely used is the *E*-factor. Such parameter has been introduced for the first time by Roger Sheldon in 1992[73] and helps to quantify the impact of a process, including in the calculations the amount of waste produced, all the auxiliaries, solvents, energy, purification materials and so on. Finally, another important point is the recycle of the waste and its application in another process, which make a waste not a waste anymore but a raw material for another process.

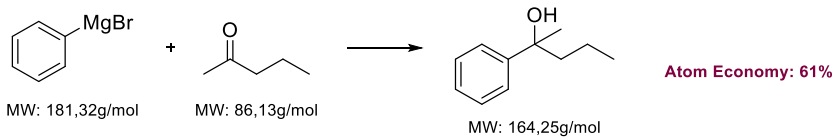
2. Atom Economy. *Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.*

The concept of Atom Economy was firstly introduced in 1991 by Barry Trost and it is defined as "maximize the number of atoms of all raw materials that end up in the product".[74]

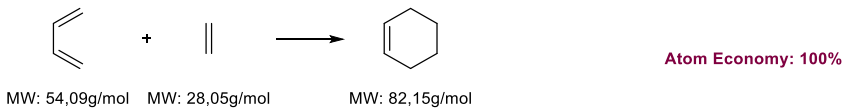
$$AE = \frac{\text{MW of Product}}{\text{MW of Reagents}}$$

In this sense, the formation of any side-product should be avoided and, when it is not possible, push the reaction to the formation of innocuous ones. There are some reactions which are, due to their mechanism, ideal for the atom economy, for example: Diels-Alder reactions where two molecules bond together thanks to a simple movement of electrons, keeping in the product all the reactants' atoms. On the contrary, synthesis involving Grignard reagents, despite their great importance, possess low atom economy, as depicted in Scheme 15.

Example of a Grignard Reaction:



Example of a Diels-Alder Reaction:



Scheme 15. Calculation of Atom Economy in typical organic reactions

3. Less Hazardous Chemical Synthesis. *Whenever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.*

As stated in the first principle, it is better to prevent the formation of a side product or waste rather than find the best way to dispose it. But how it is possible to prevent? The answer it's easy: designing a better and greener process. And how it is possible to do that? Applying the know-how of chemistry, exploiting the technological innovations developed and using the new reactions that have been discovered during these years. Reactions that are most likely to be use are the classical cycloadditions,[75] rearrangement,[76] multi-component coupling[77] or the more innovative cascade or tandem reactions,[78] one-pot synthesis,[79] C-H activation,[80] metathesis,[81] enzymatic catalyst[82] and so on.

4. Designing Safer Chemicals. *Chemical products should be designed to preserve efficacy of the function while reducing toxicity.*

Toxicity depends on three factors: exposure, bioavailability and the intrinsic toxicity of the substance.[83] Using the knowledge concerning the toxic mechanism of a chemicals and, also, studying the SAR (Structure-Activity Relationship) it is possible to design chemicals less toxic for humans and for environment, reducing their adsorption or varying the nature of metabolites formed.

This rational design of chemicals it is central both for drug-design and in every branch of chemistry. Few examples are pesticides, designed more selective and less persistent in environment and also less impactful like essential oil,[84] or polymer, studied to degrade at after disposal,[85] or dyes not having heavy metals.[86]

5. Safer Solvents and Auxiliaries. *The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary whenever possible and, when used, innocuous.*

Auxiliaries are substances used in the reaction system that do not participate in the reaction. Auxiliaries such as purification or separation agents can be avoided eliminating intermediate purification steps, whenever possible.

Solvents are still the main source of waste and energy-consumption part of the process and, hence, they influence cost, safety, and impact. Innovative "greener" solvents have been implemented to the classical list of traditional ones, for instance bio-based solvents,[87] supercritical fluids,[88] ionic liquids[89] or water.[90] But, most of them still show both advantages and drawback, the idea is to promote processes and reactions performed in solvent-free conditions avoiding any disadvantages.[91]

There are two main guidelines to define how green is a solvent: EHS and LCA. EHS (Health, Environmental and safety) parameter classifies solvents according to their physical and chemical properties and defines their classification according to toxicity, explosivity, air and water hazard and so on (Figure 21).[92]

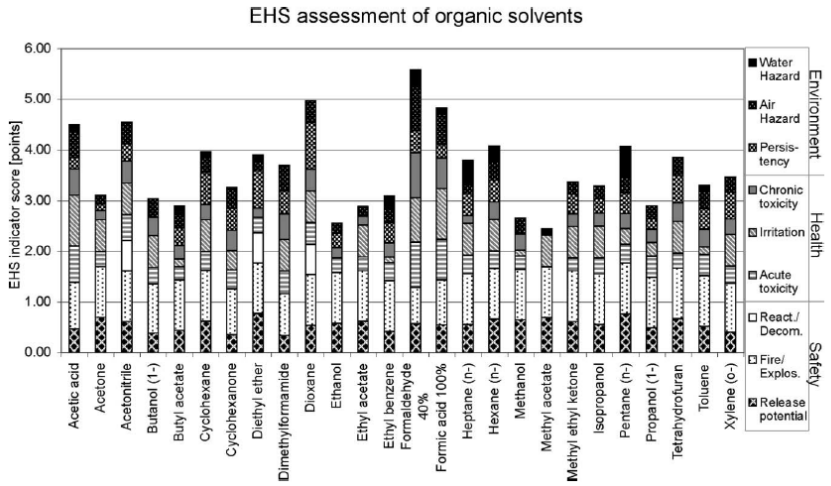


Figure 21. Results of the EHS for some organic solvents (Picture taken from Ref[92])

LCA (Life-Cycles Assessment) method consider the whole life-cycle of a solvent, like the energy needed to obtain it, the source (renewable or not), the energy recoverable after incineration and, finally, the indirect impact of the solvent disposal, for example gases or pollutant released into the environment after incineration (Figure 22).[93]

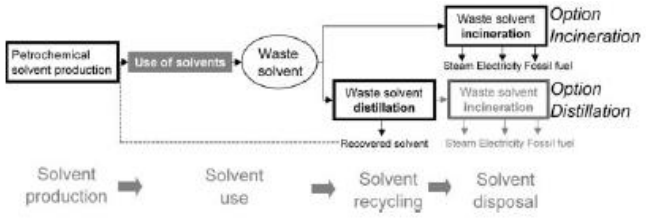


Figure 22. System model for LCA method (Picture taken from Ref[93])

Both methods must be taken into account when choosing the proper solvent for a chemical process.

6. Design for Energy Efficiency. *Energy requirements of chemical process should be recognized for their environmental and economic impact and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.*

Find a match between competitivity and eco-friendly it is a hard challenge for industries and government. Indeed, it is not easy to find a balance among short-term profit and a long- term plan that is in

agreement with a sustainable development but, for sure, reduce the energy consumption is the first step.[94] Reduce the energy consumption means less pollution due to petroleum extraction but also less thermal pollution due to oil processes. Another issue might be the use and expansion of renewable source of energy such as biofuels,[95] solar power,[96] wind power, hydrogen fuel cells.[97]

Talking about chemistry, it is possible to reduce the thermal barrier of reactions by using catalyst or following different synthetic strategies which do not implies the use of harsh thermal conditions. Whenever it is not possible, it is reasonable to increase the energy efficiency of the system in order to reduce the heat dispersion.

7. Use of Renewable Feedstocks. *A raw material of feedstock should be renewable rather than depleting whenever technically and economically practicable.*

The sustainability of a process starts analysing the origin of raw materials and energy.[98] The extraction and use of fossil fuels are faster than their production by nature, that's why they are considered non-renewable, on the contrary, renewable feedstocks are a never-ending source of raw material and energy, one of the most abundant is bio-mass. Everything coming from nature can be considered bio-mass like wood, crops, agricultural and food wastes.[99] Lignin is a suitable example of bio-mass that can be used as a bio-fuel but also as a raw-material for the preparation of bio-based products.[100]

8. Reduce derivatives. *Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.*

Whenever possible, it is better to reduce the formation of derivatives, because every step of derivatization might include a following step of deprotection and, therefore, the production of waste or energy to form a new covalent bond. Recently, a new way of derivatizing product is born: non-covalent derivatization, which implies the creation of a derivatives

which is not covalently bound, but is formed using H-bond or Van der Waals interaction. [101]

9. Catalysis. *Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.*

Catalyst are important for two reasons: they lower the activation energy of reactions and increase the selectivity toward the product reducing the formation of undesired side product and so the waste. Moreover, the use of heterogeneous catalyst can also facilitate and reduce the work-up to a simple filtration avoiding extraction or distillation of the product.[102]

10. Design for degradation. *Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.*

Persistency and pollution are strictly related, in fact a substance that might be toxic, if promptly degraded into innocuous derivatives, is not a problem to the environment. But monitoring showed that some function in molecules, such as halogen, branched chains, quaternary carbons, tertiary amines, and others, increase persistence of a molecule. In this sense, it is possible to boost the decomposition introducing some functional group, such as esters or amides, that are typically degraded by enzymes.[103]

11. Real-Time Analysis for Pollution Prevention. *Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.*

In agreement with the principle of prevention, in-line analysis seems to be vital to the detection and elimination of eventual side-products. Another point to consider is the impact of the analytical techniques itself, after the publication of the 12 principles of Green Chemistry, a new branch grew and was named Green Analytical Chemistry.[104]

12. Inherently Safer Chemistry for Accident Prevention. *Substances and the form of a substance used in a chemical process should be chosen to*

minimize the potential for chemical accidents, including releases, explosions, and fires.

When designing a process, it is mandatory consider the large-scale system. In fact, the release of heat or dangerous side-reactions might be difficult to keep under control. For this reason, according to the "Chemical accident prevention and the clean air act amendments of 1990", all kind of hazard: nature of chemicals, explosivity, and toxicity must be examined when studying a process.[105]

Considering the parameter, Poliakoff and co-workers coined the acronym PRODUCTIVELY, to make the twelve principles easier to memorize (Figure 23).[106]

P – prevent wastes
R – renewable materials
O – omit derivatization steps
D – degradable chemical products
U – use safe synthetic methods
C – catalytic reagents
T – temperature, pressure ambient
I – in-process monitoring
V – very few auxiliary substances
E – *E*-factor
L – low toxicity chemical products
Y – yes, it is safe!

Figure 23. Mnemonic acronym for the 12 principles

2.3 *E*-Factor, PMI and EQ: useful green metrics

Green metrics are parameters used to quantify the sustainability and effect on environment of a chemical process. During these years, several

metrics have been proposed, but the most common are *E*-factor, PMI and EQ

E-factor

E-factor (Environmental factor) was proposed by Sheldon in 1992[107] and introduced solvents and auxiliary used to evaluate the efficiency of a process and not only the atom economy. The *E*-factor is calculated dividing the kilograms of waste produced in a process by the kilograms of product recovered, everything that it is not included in the final product is considered waste.

$$E\text{-factor} = \frac{\text{kg of waste}}{\text{kg of product}}$$

This parameter combines the AE, solvents, purification materials, yield and, in principle, even energy required, but it does not include water coming from work-ups because it will affect too much the value, making comparison between processes quite tricky. The calculation is made gate-to-gate, namely considering from the raw material entering the factory to the product leaving, but nothing is said about the production of the raw material.[108]

The ideal *E*-factor is 0, which correspond to a 0kg of waste produced, and it was useful to point out that pharmaceutical processes are much more impactful then oil refinery, for example. In Table 1, some typical value of *E*-factor for different chemistry sectors of industries are reported.

Table 1. Typical value of E-factor and tonnage of product produced in chemical industries

Sector	Product tonnage	*E*-factor
Petrochemistry	10^6-10^8	≈0.1
Bulk chemistry	10^4-10^6	1-5
Fine chemistry	10^2-10^4	5-50
Pharmaceutical chemistry	10-10^3	25-100

Petrochemistry shows the best *E*-factor and, even if the production is bigger, it is not the main source of waste.

Pharmaceutical processes show such a big *E*-factor since the target molecules are much more complex and require several steps and intermediate purifications. But reducing the *E*-factor it is a synonym of reducing costs concerning waste disposal or energy consumption and, for this reason, pharmaceutical industries are trying to move toward this direction.

PMI

PMI (Process Mass Intensity)[109] is similar to *E*-factor, it is the mass of all the materials used in the process, divided by the mass of the product obtained, but it is more complete since it includes water.

$$\text{PMI} = \frac{\text{kg of input materials}}{\text{kg of product}}$$

It is easier to calculate compared to *E*-factor, but it is related to it by an arithmetical relationship:

$$\text{PMI} = E\text{-factor} + 1$$

The best PMI for a process in equal to 1.

EQ (Environmental Quotient)

EQ (Environmental Quotient)[110] it is an extension of the *E*-factor and considers the nature of the waste. It is calculated using this equation:

$$\text{EQ} = (E\text{-factor}) \cdot Q$$

Q is an arbitrary parameter that consider the "unfriendliness" of the waste and depends on the toxicity, persistency, ease of recycling and so on. Since there is not a specific rule for the calculation of Q, the EQ metric gives just an indicative value.

2.4 Tools for a sustainable production

In this century of innovations and improved technologies, great importance is given to those so-called "Enabling technologies", but what are them? An enabling technology is a modernization or novelty that brings a strong upgrade to the existing one.[111] Enabling technologies do

not introduce new reactions but new set-up for processes. Microwave heating, one-pot processes and flow chemistry stand out among enabling technologies.

Microwave apparatus demonstrated to be one of the most efficient methods for heating reactions and its use has drastically increased recently. One-pot processes brought to a great improvement in terms of minimizing wastes but also time, minimizing work-up. Flow-chemistry led to considerable enhancement of process selectivity conducting to an increased yield.

One-pot Processes

One-pot reactions,[112] as it is said in the name, are performed in a single reaction vessel. It is possible to add reagents, change solvent and reaction conditions, but any purifications or isolations of intermediates are not allowed (Figure 24). Such procedures aim to minimize time and waste, avoiding purification steps and are in fully agreement with Principle 1 of Green Chemistry, introducing the concept of Pot-Economy.[113]

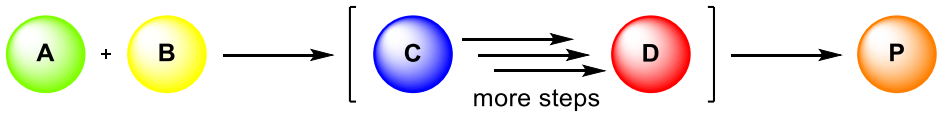


Figure 24. General scheme for one-pot reactions

Cascade or domino reactions are defined as a sequence of two or more transformations that occur in the same vessel, with the same reaction conditions, not adding any promoter and every transformation is a consequence of the previous one, bypassing isolation or purification of intermediates.[114] Such procedures are crucial for total synthesis since it should be possible to obtain complex molecules considerably reducing the waste but also increasing the practical efficiency. For this reason, cascade reactions find wide applications in modern organic synthesis. An additional distinction can be done introducing tandem reactions, which are transformation happening in two distinguished part of the molecules

by adding only one reagent. Cascade or domino and tandem reactions can be considered a sub-class of one-pot processes.

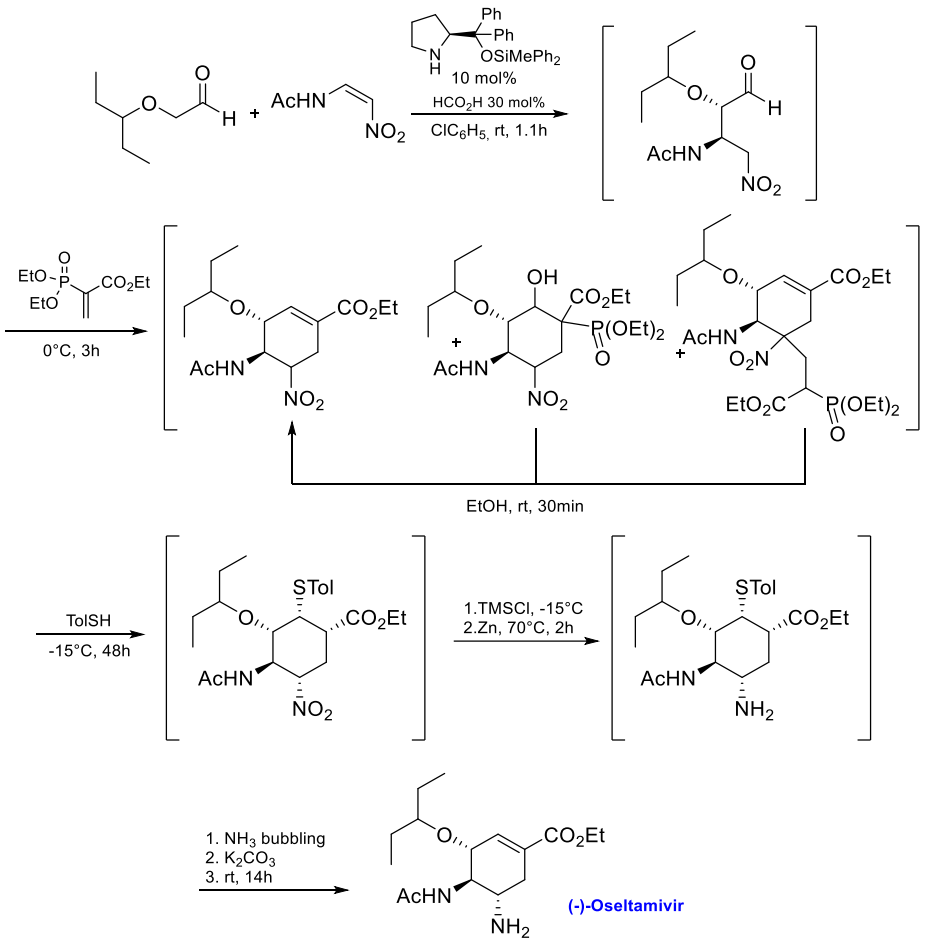
Situations in which is wise to use one-pot procedure are when:

- Intermediates are unstable and isolation bring to lower yield
- There is an equilibrium between two intermediates, but both can be converted to the desired product
- There is an equilibrium between the starting material and the intermediate
- Side-products can be converted to the desired product
- Same reagents are used in more than one reaction step

Similar to one-pot reactions are "telescope reactions" which are not a sub-class. In this case, work-up such as filtration or separation are allowed, but not the isolation of pure intermediates or even crude, like evaporating solvent.

One-pot methodology also shows some drawbacks, related mainly to the fundamental feature of the method: one vessel. In fact, every reagents used in each step rest in the vessel which means that excess of reactants is not advisable, as much as are not suitable reaction leading to the formation of salts or other side products, trying to respect Principle 2. All this material may interfere in reaction mechanisms of the following reaction steps.

A representative example of one-pot methodology applied to pharmaceutical synthesis is the (-)-Oseltamivir preparation. (-)-Oseltamivir is one of the most effective drug for influenza and, for this reason, there are plenty of synthesis reported in literature,[115] here is presented the one proposed by Hayashi and co-workers in 2013, obtaining an overall yield of 36% (Scheme 16).[116]



Scheme 16. One-pot synthesis of (-)-Oseltamivir

Microwave-Assisted Organic Synthesis (MAOS)

Microwave radiations have a frequency ranging from 300GHz and 300MHz, corresponding from 1 mm to 1 m as wavelength, and they are placed between radio waves and infrared (Figure 25).

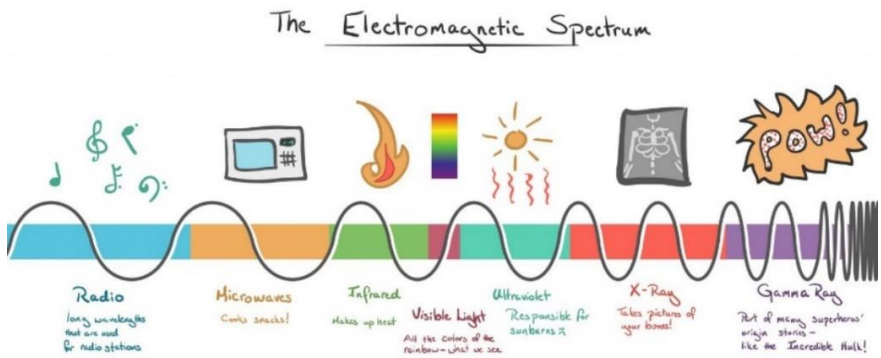


Figure 25. Electromagnetic Spectrum.[117]

Domestic microwave ovens, just like laboratory ones, work with a frequency of 2450MHZ (12.25 cm) between Radar (1-25 cm) and frequency used telecommunications.

The first study of reactions performed exploiting microwave heating appeared in 1988,[118] and it was mainly focused on the observation that, under microwave conditions, reaction time seems to decrease for different kind of reaction performed in a polar solvent.

MAOS appeared to be revolutionary,[119] since it demonstrated several advantages, such as:

- Uniform heating of the sample
- Lower energy usage (Principle 6)
- Better reproducibility
- Shorter reaction time
- Higher yield
- Ease to reduce or remove solvent (Principle 5)

Conventional heating is strictly dependent on the convection current in the solution but also on the thermal conductivity of both flak material and solvent. For this reason, the temperature is usually higher close to

the wall and lower in the middle, in MW warming the distribution of temperature is kind of reversed (Figure 26).

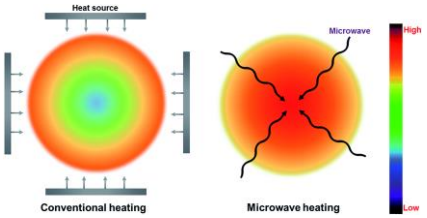


Figure 26. Comparison between Conventional and microwave heating[120]

In MW, heating is due to two different mechanism dependents on the nature of the solvent: *i)* dipolar polarization and *ii)* ionic conduction, and the process is known as *dielectric heating*.

Dipolar polarization is related to the dielectric constant of molecules. The oscillating electric field generated by the MW radiations push molecules (of both solvent and reagent) to align with it at every oscillation, this movement cause a loss of energy which is released as heat. The energy lost is connected to the molecular friction and the dielectric loss and is described by the Loss Tangent (Tanδ).

$$\text{Tan}\delta = \frac{\varepsilon''}{\varepsilon'}$$

ε" is the dielectric loss, which is basically the efficiency of solvent to convert the radiation into heat. While ε' is the dielectric constant which display the polarizability of the molecule.

As we can infer from the equation, the more polar is the solvent the more efficient is the heating and this is the reason why polar solvent are the preferable for MW synthesis. Tanδ for common solvents are listed in Table 2.[121]

Table 2. Loss factors for organic solvents, measured at 20°C and 2.45GHz

Solvent	Tanδ	Solvent	Tanδ
Ethylene Glycol	1.35	Chloroform	0.091
Ethanol	0.941	Acetonitrile	0.062
DMSO	0.825	Ethyl Acetate	0.059
Nitrobenzene	0.589	Tetrahydrofuran	0.047
NMP	0.275	DCM	0.040
Water	0.123	Hexane	0.020

The classification as microwave absorbing solvent can be done according to the value of Tanδ:

- High= Tanδ > 0.5
- Medium= Tanδ 0.1-0.5
- Low= Tanδ <0.1

A low Tanδ does not mean that a solvent can't be used in microwave-assisted reactions, in fact heating is still possible if reactant or catalyst are polar and absorb the radiation or a polar additive (like ionic liquid) can be used to promote the warming.

The second point of the dielectric heating, ionic conduction, is related to the ability of ions to move along an electric field, that is why solvent containing more ions are easier to warm, such as tap water compared distilled one.

What is important to point out is that MW radiation is not enough energetic neither to ionize molecules nor to break atom bonds, so it does not change the molecular structure of reactants and the radiation itself can't induce the reaction.

Considering that two molecules must collide for reacting, the Arrhenius equation (below) describes the kinetic (k) of a reaction as related to both activation energy (E_a) and temperature (T).

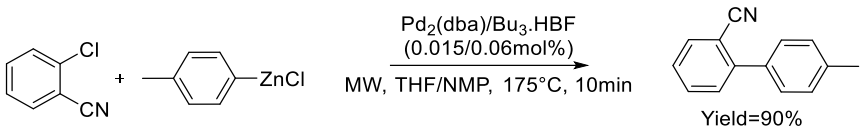
$$k=Ae^{\frac{-E_a}{RT}}$$

A is called "frequency factor" and represent the frequency of collisions, $e^{\frac{-E_a}{RT}}$ is the fraction of collision with enough energy to react.

Observing the equation, the kinetic is directly proportional to the temperature and inversely proportional to the activation energy.

Nowadays there are debates still open about a non-thermal effect of MW radiations. The so-called microwaves effect should be observed in polar reactant molecules interacting with radiations and changing the value of E_a or A in the Arrhenius' equation.[122] But, in general, it is considered that all the advantages of microwave heating come from thermal effect, both direct and indirect like super-heating of solvents which is impossible to obtain in traditional heating, selective heating of some heterogeneous catalyst with high absorbing level of MW, elimination of "wall effect" due to a different heating method of the reaction.[123]

The instantaneous heating of the solvent, usually over the set temperature, lead to a speed up in yield or reaction time, or both. To give an example, the Scheme 17 shows a synthetic methodology Pd-catalyzed for bi-aryls in MW conditions proposed by Walla and Kappe. [124] Using this procedure, it is possible to obtain the desired product in just 10 min with 90% of yield. This method can be compared with other ones present in literature, such as the one presented by Day and Fu[125] where the same product is obtained, employing a Pd-catalyst, after 24h at 100°C.



Scheme 17. Synthesis of biaryls in MW conditions and Pd Catalyzed.

Another property that might affect the effectiveness of heating is the penetration depth of radiations, the depth at which the radiation has the 37% of the initial value and it is a feature of the material or of the solvent.

Despite the spread of MW apparatus in organic laboratories, few drawbacks are still mining their applications.[126] In fact, it is not possible to measure accurately the temperature but only set the power of radiation, leading often to an initial over-heating of the vessel. Even if the reaction is reproducible using the same apparatus, it is hard to replicate the

reaction conditions using a different instrument since in most paper the description of the MW is not reported. Moreover, the efficient and homogeneous heating is shown in small scale vessel, but for industrial application the penetration depth affects the efficiency of the reaction.

Flow-Chemistry

Flow-chemistry has been developing in the last two decades, when the need to promote process in agreement with the principles of green chemistry became urgent.

Flow process are based on the reaction of two or more reactant dissolved in a liquid medium and pushed through a tube or pipe where the reaction occurs (Figure 27).

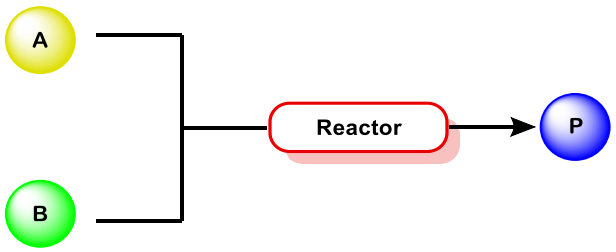


Figure 27. General scheme for flow reactor

But which are the innate principles of green chemistry in flow conditions?

First of all, it is fundamental to underline that in flow process all reactions occur inside a tube, so there is a safer handling of toxic reactant (Principle 12). It is possible to combine a series of transformation with flow technology avoiding any manipulation of intermediates which might be toxic or unstable. Due to the controlled contact between reactant, side reactions are limited leading to an increase in the yield. Other enabling technologies can be combined with flow, like photochemistry or MW irradiation to promote the reaction enhancing the energy efficiency of the whole process (Principle 11).

In-line analysis are often combined to flow instrumentation to evaluate, step-by-step the trend of the process (Principle 6). Flow-chemistry will be deeply discussed in the following chapter.

3. Flow Chemistry in Organic Synthesis

Flow chemistry flourished recently due to its huge influence in the field of organic synthesis since it can be considered a connection between laboratory research and industry and, in general, flow technique brings considerable advantages in synthetic procedures, for instance:

- Better control on heat transfer and on other reaction parameter
- Increased mixing ability
- Ease to scale-up
- Simplicity to perform serial reactions
- Controlled use of toxic materials
- Control on reactive intermediate
- Possibility to add in-line analysis and purification
- Higher working pressure limit

All these advantages lead, substantially, to a better selectivity in reactions and, consequently, to an improved efficiency and yield. The limited contact between intermediate and product or between reagent and product, reduces the formation of side- and by-products.

Flow apparatus exist both commercial and laboratory-built using tubes and connector and both can be classified according to the diameter of the tube in micro- (I.D. 50-500 µm, surface-to-area ratio 5.000-50.000 m^2/m^3),[127] mini- (I.D. 500-2000 µm) or and mesoreactors (I.D. > 2000 µm, surface-to-area ratio 100-10.000 m^2/m^3).

The main limitations of flow chemistry are linked to physical problem of the instrumentation. In fact, the small dimensions of tube, especially for microfluidic systems, is often responsible for blockage or clogging and the compatibility of materials (such as for O-ring) with solvents are still an issue.

Residence time and stoichiometry

Stoichiometry and residence time calculations are different for flow processes compared to batch synthesis. In fact, the stoichiometry comes from the correlation between concentration of reagents and streams

flow rate, while residence time is defined as the time between the beginning and the end of the transformation and it is given, generally, by reactor volume and flow rate, according to the formula:

$$t_{res} = \frac{V}{v}$$

where V is the volume (or length of the path) and v is the flow rate. Sometimes, especially when using packed-bed reactors, it is tricky to calculate the volume with a formula, so it is easier to measure it manually. For an accurate residence time, it is important to ensure a correct quench of the reaction.

Heat – exchange

Temperature is decisive for the yield of a reaction. In fact, especially in cases where the activation energy of the side-products is close to the one of the desired products, temperature play a crucial role. In batch conditions, especially for a bigger scale, it is tricky to obtain a homogenous distribution of temperature. The ability to control precisely temperature is pledged also in terms of safety, indeed having an easier cooling path helps in reducing runway episodes. Runway is an event in which the heat produced by an exothermic reaction, lead to an uncontrolled over-heating of the whole system ending often in an explosion.

The following equation gives the heat transfer rate (q):

$$q = U \cdot A \cdot \Delta T_{LM}$$

U is the heat transfer coefficient, ΔT_{LM} is the logarithmic mean temperature difference and A is the heat transfer surface area, which is proportionally related to the heat exchange rate, confirming that control on temperature benefit from an increased surface area.

The last consideration to do is about the material of tubing whose conductivity affect the heat transfer, moreover the dimension of tube section must be enough small to guarantee no gradient of temperature from the wall to the center.

Mixing in flow chemistry and multi-phase systems

Adequate mixing is essential for performing a reaction. In general, flow can be of three different type: *i)* laminar, *ii)* turbulent or *iii)* transitional. The size of the tube, flow rate, viscosity of fluid or density set the kind of flow in a tube and can be determined using Reynolds number. Reynolds number (Re) it is a dimensionless number indicator of the flow pattern and it is, basically, the ratio between internal forces to the viscous forces of the fluid. Its value is calculated according to the following equation:

$$Re = \frac{\rho \cdot u \cdot D}{\mu}$$

Where ρ and μ are, respectively, density and dynamic viscosity of the fluid, u is the speed and D the I.D. of the tube. For low Reynolds (Re<2300) number the flow pattern is laminar and viscous forces are prevailing. When Re>4000, principal forces are the internal ones and the flow is turbulent. For all the values in the middle, flow is transitional.

Due to the excellent surface-area-to-volume ratio, flow systems, especially microfluidic, outperform batch conditions especially in multi-phase system (141 m^2/m^3 for 5 ml RBF half-filled VS. 3400-18000 m^2/m^3 for microchannel).

Gases are usually good reactant from an atom economical viewpoint, but not from stoichiometric one since they must be used in large excess due to their poor solubility in liquid. In a gas-liquid multi-phase system, flow bring advantages both to mixing and to solubility. For small tubes (0.25-0.75 mm I.D.) flow reveal a slug fashion increasing the mass transfer and, so, the reaction rate. Moreover, considering the Henry's law for gas solubility:

$$p = C \cdot K_H$$

where p is the pressure, C the concentration of a gas in the liquid and K_H a temperature-dependent constant, it comes out that the pressure of a system is directly proportional to the concentration of the gas. Using a

flow system, according to the tube material, it is possible to achieve incredibly high pressure which notably increase the solubility of gases.

Considering solid-liquid system, different considerations must be done. Solid catalyst or reagent can be supported by covalent bond or absorbed on an insoluble material or on a monolith structure.

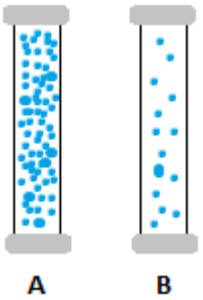


Figure 28. Packed (A) and fluidized (B) reactors

Considering the case of solid supported species, beads are blocked in a glass column and can be packed or fluidized (Figure 28), in the first case the heat-exchange is not really efficient but the flow is less turbulent, in the second situation the flow is turbulent to keep particles in suspension but the heat-exchanged is improved. The main problem with this kind of reactor is the broad distribution of the average residence time.

The last, but not the least, case of multi-phasic system is the liquid-liquid. In this situation, laminar and slug flow are the most common. Laminar is typical for large tube and viscous liquid, while slug flow can be obtained using a T-mixer (Figure 29).

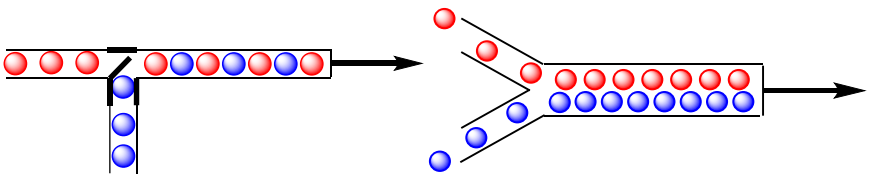


Figure 29. Slug VS laminar flow for two immiscible liquid

At high flow rates, the reactor conformation it is important to determine the kind of flow and the mixing, using a tortured path, which is realized by filling the tube with inert material, it is possible to boost the mixing

and mass transfer. The nature of flow it is important when the size of droplet or the emulsion homogeneity affect the reaction efficiency.

3.1 Combining technologies

Photo-flow

The modest section of a flow reaction goes hand in hand with the efficiency of photochemical reactions. The typical depth for a micro-reactor is in a range of 50-500 µm so the intensity of light is high even for concentrates solutions and it is deducible from the Beer-Lambert law for the attenuation of light (A):

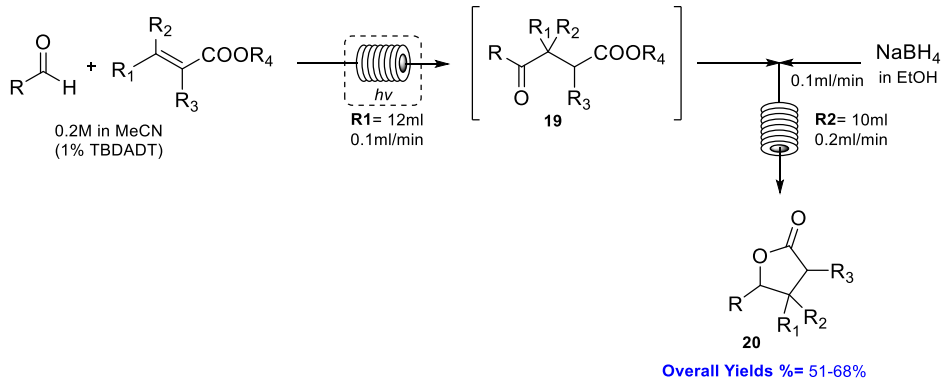
$$A = \varepsilon \cdot C \cdot l$$

Where ε is the molar attenuation coefficient, C is the concentration of reagents in the reaction solutions and l is the length of the light path.

Usually, photochemistry is not suitable for industry scale systems but using photo-flow reactors several parallel reactions can be set up increasing the productivity. An additional advantage given by flow, compared to batch, is the increased control on heat exchange and temperature. As a matter of fact, one big issue with photochemical reactions is the temperature raise which typically brings to formation of side product or degradation of materials, such problems are overcome in flow.

Immobilized species in reactors can be used as a photocatalyst, for examples TiO_2 is used in a continuous flow system for the degradation of azo-dyes[128] or for the decomposition of nonionic surfactant[129] before their emission to the environment.

To report an example of photo-flow reaction, in Scheme 18, is described the synthesis of γ-lactones. The two-steps synthesis proposed by Fagnoni *et al.*[130] involves a first photo-promoted radical conjugate addition followed by reduction of keton **19** and cyclization to give the final γ-lactones **20**.



Scheme 18. Flow-synthesis of γ-lactones

Microwave irradiation in flow

Flow reactions have commonly short residence time and a fast heating is paramount, microwave irradiation can provide it. In fact, MW not only provides fast heating but also shorter reaction time.

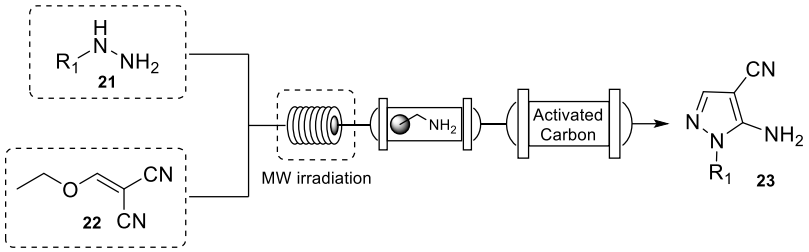
Reactors must be made with a MW-transparent material such as PTFE or glass to guarantee an optimum heating and immobilized species can still be used as promoters for reactions.

In the end, performing a high-temperature reaction in flow presents advantages regardless of the heating mode. Actually, due the set-up of a flow apparatus, only the reactor where transformations occur is heated and not the reservoir containing starting materials or products, which means less degradation problems.[131]

An interesting example of combining flow and MW is proposed by Ley and co-workers for the synthesis of 5-amino-4-cyanopyrazoles (Scheme 30).[132] Pyrazoles are structures widely present in pharmaceuticals and agrochemicals.

The reported synthesis involves the use of aryl hydrazines **21** and ethoxymalonitrile **22**, the two solutions containing the starting material are pumped through a MW-irradiated coil reactor for a short period of time (0.8-4'). The reaction solution pass then a scavenger column, packed with supported benzylamine, and a second column filled with active

carbon to remove any impurity. The yields of the process are in a range of 62-96% for compound **23**.



Scheme 19. Flow microwave synthesis of 5-amino-4-cyanopyrazoles

Flow and solid supported species

Solid-supported species are inert material, generally spherically shaped, insoluble in reaction conditions, whose surface is functionalized with reactive species (simple functional groups or metal complexes). In flow, supported systems can be blocked in a column, called packed-bed reactor (Figure 30a), and reaction occurs by flowing the reagent solution through the column.

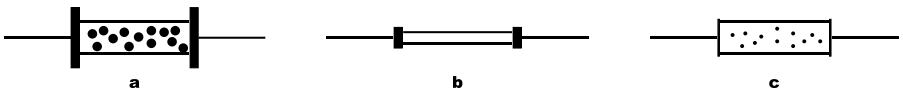
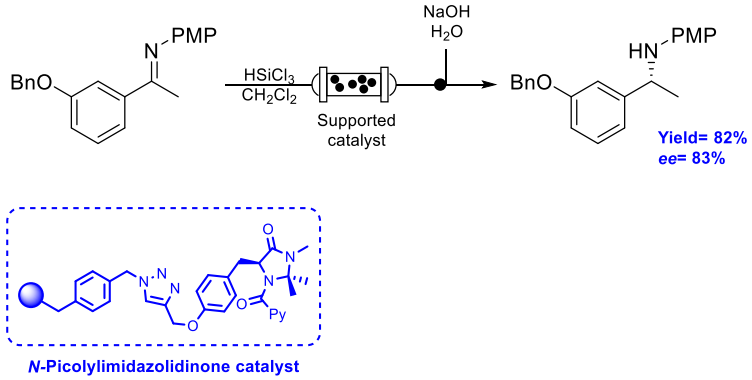


Figure 30. Flow reactors for heterogeneous catalysis

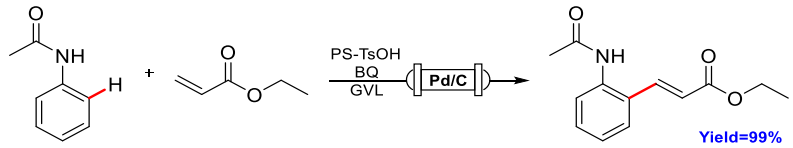
Further types of flow reactors for heterogeneous catalysis are available: catalytic capillary (Figure 31b) and monolith reactors (Figure 31c). The first one, are functionalized on the internal wall using chemical methods. The latter is a unique microporous material where catalyst can be both adsorbed or incorporated in the structure. Heterogeneous systems, in flow, allow the product recovery without any purification since the solid is trapped in the column.

In Scheme 20, is presented the synthesis of chiral amines proposed by Benaglia *et. al*[133] using supported chiral *N*-Picolylimidazolidinones as heterogeneous catalyst in flow conditions.



Scheme 20. Synthesis of chiral amine using heterogeneous supported catalyst

Another valuable example is proposed by Vaccaro and co-workers[134] for Fujiwara-Moritani reaction in flow (Scheme 21). This work is particularly interesting since the reaction is performed in a biomass-derived solvent, γ-valerolactone, and the solid catalytic system showed great durability in such media. In fact, even after several hours the metal leaching is still in the order of 4 ppm, allowing the production of 4g/h of material.



Scheme 21. Continuous-flow Fujiwara-Moritani reaction

3.2 Anatomy of flow reactors

The different parts of a flow reactor can be put in eight categories (Figure 31):[135]

1- Fluid and reagent delivery
2- Mixing
3- Reactor
4- Quenching
5- Pressure regulation
6- Collection
7- Analysis
8- Purification

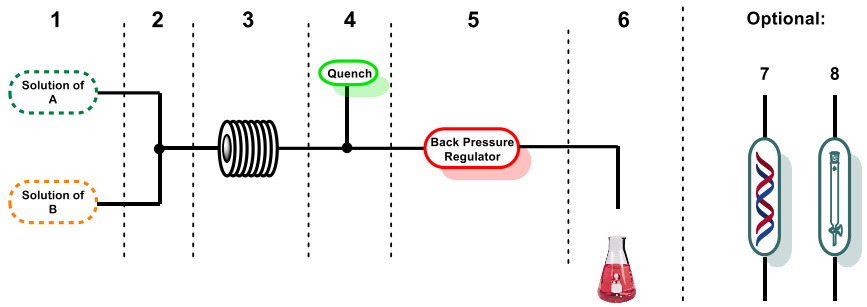
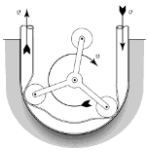


Figure 31. General set-up for a flow apparatus

1. Liquid Delivery. The system used for liquid and reagents delivery plays an important role in the reaction, in fact it affects stoichiometry and efficiency. Delivery systems for liquid can be grouped in three categories: *i)* HPLC pump, *ii)* syringe pump and *iii)* peristaltic pump (Table 3).

Table 3. Advantages and disadvantages of different pumps

i)		·Flow rate > 0.1 ml/min ·Suitable for large-scale reservoir	·Issue with volatile solvents ·Liquid in contact with pump, no way to prevent it from blockage
ii)		·High precision even at low rate < 0.1 ml/min ·Suitable for small-scale optimization ·Easy to use ·Flow rate remain constant	·Limited reservoir to the syringe volume
iii)		·No blockage problem ·No contact or contamination by the fluid to the pump ·Less susceptible in pressure change ·Ability to manage slurry and viscous fluid	·Tubing deteriorates faster affecting the efficiency ·Pulsed flow

2. Mixing. As much as delivery system, mixing it is crucial to the yield of reactions. Mixing can be active, when there is an external aid, or passive, when it depends only on the nature of fluid, flow rate and mixing piece.

When the reaction mixture forms a single phase or a biphasic liquid-liquid system, a simple T- or Y- piece can be used for slow reactions (reaction time longer than mixing time), if the reaction is fast, special mixing pieces are commercially available (Figure 32).

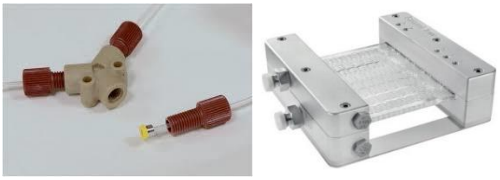


Figure 32. T-mixing piece and glass microreactor

When it is a gas-liquid system to face, there are different solutions to mix the two different phases. It is possible to prepare a saturated solution of the gas in the reaction solvent or a tube-in-tube system (Figure 34).[136]

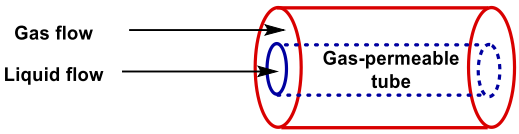
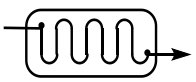
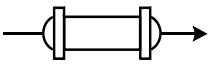


Figure 33. Tube-in-tube system

3. Reactor. Three different class of reactors are listed in Table 4. Shape and material of a reactor are chosen according to the nature of reactant and to the kind of reaction. Perhaps, stainless steel reactors are preferable if high pressure are needed, or chip reactors are superior when the temperature must be accurate.

Table 4. Different type of flow reactors

	CHIP REACTOR: ·suitable for optimization ·best heat transfer ·small volume ·made of glass ·mixing zone might be included ·easy to clog ·expensive
	COIL REACTOR: ·cheap ·most widely used ·made of inert fluoro-polymer or stainless steel
	PACKED-BED REACTOR: ·used for heterogeneous species ·excellent ratio solid species/reagent ·no separation step needed ·made of glass, polymer, or stainless steel ·leaking of the supported species

4. Quenching unit. To ensure the right reaction time, it might be necessary to quench the reaction before collection. If the reaction is thermally activated, it would be enough to cool down the reactor. But if it is chemically activated, the quenching solution can be added to the reaction stream using a T-valve. There are specific in-line liquid/liquid

extractors like FLLEX by Syrris[137] or other by Zaitput.[138] In this in-line system (Figure 34), separation is performed by membranes rather than gravity and such technology allows the separation of liquid with similar density and typically miscible like THF and water. The liquid stream is divided by the two components: the wetting phase that pass through the membrane and the non-wetting phase, the separation is guaranteed by the correct pressure system.

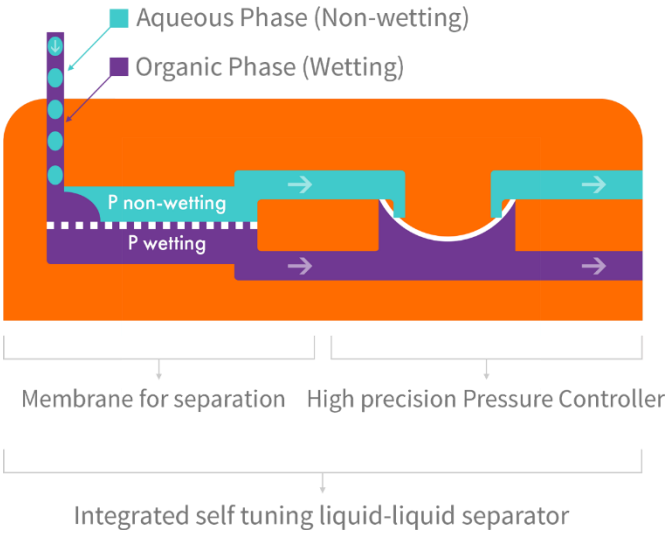


Figure 34. Scheme taken from Zaitput website (ref[138])

The applications of these in-line liquid/liquid separators are more than simple work-up. In fact, they can be used for biphasic reaction, for homogeneous catalyst recovery, for solvent switch between two reactions, for the separation of hazardous material formed in-situ and so on.

5. Pressure regulation. When reaction is operated at temperature close to the boiling point of the solvent or if gases are present in the reactor, a back-pressure regulator it is crucial to provide the correct reaction time and so the reproducibility of the reaction. Back-pressure regulator can be pre-set at one pressure or adjustable.

6. Collection. Collection can be made in a simple RBF or a flask, according to the following steps of the process.

7. Analysis. In-line or off-line analysis are usually performed to check the trend of a reaction, to verify that no toxic intermediates are forming and so on. In-line analysis are automated, the sample is analyzed during the flow process by GC-MS, HPLC, NMR or similar. In off-line analysis, the sample is manually transferred and analyzed.

8. Purification. Flow chemical synthesis often involves several transformations starting from the raw material to get the product and, for this reason, in-line purifications might be appropriate. Typically, liquid-liquid separations are maybe the most common, this type of separations are performed in flow using a membrane-based setup which allows the separation of organics and aqueous phase.[139] Continuing the list, Ley[140] suggests the use of reusable scavenger column to trap excess of reagents in a continuous flow system. More complex separation techniques include the use of Simulated Moving-Bed chromatography (SMB),[141] continuous crystallization processes or centrifugal partition chromatography (CPC).[142]

In CPC there is not a solid stationary phase which eliminates the two typical linked complication: column degradation and irreversible absorption of material. Both stationary phase and eluent are liquid but immiscible and must guarantee a correct partition coefficient to ensure the separation. The stationary phase is kept inside the rotating column by centrifugal forces and the mobile phase can extract the product in two different ways: ascending mode (AM) and descending mode (DM). In the first one, the mobile phase is the upper one, in DM the mobile phase is the lower one (Figure 35).

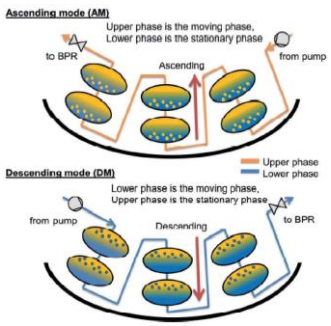


Figure 35. AM and DM in centrifugal partition chromatography (scheme taken from ref[142])

Working alternating the two mode, it is possible to obtain a continuous purification that can be coupled with a flow process for the purification of intermediates or final products.

At the beginning, SMB chromatography was used in oil refining industry to separate xylene isomers, hard to divide by distillation. The principle is to use several small columns instead of one bigger, all the columns are packed with a solid adsorbent (the beds). Beds move in the opposite direction respect with the eluent flow, creating a countercurrent which enhance the separation. The movement of beds is provided by valves interspersed between columns and, instead of collecting fraction after one column, feed is constantly pushed through the system for a continuous purification (Figure 36).

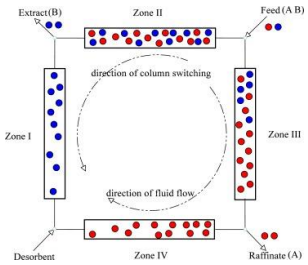


Figure 36. Simulated Moving-Bed chromatography scheme (scheme taken from ref[141])

SMB chromatography found application also in the field of chiral purification.[143]

3.3 Flow technique for the preparation of natural products

In drug discovery, the "rate-limiting" step is the preparation of libraries. Hundreds of compounds need to be ready for further evaluation in a short time. The development and increased automation of flow systems help in saving time for this preliminary step. Flow technologies favor the preparation of complex molecules reducing manual operation and, hence, found vast application in the synthesis of various heterocycles and natural product. Figure 37 shows a general scheme for a flow system.

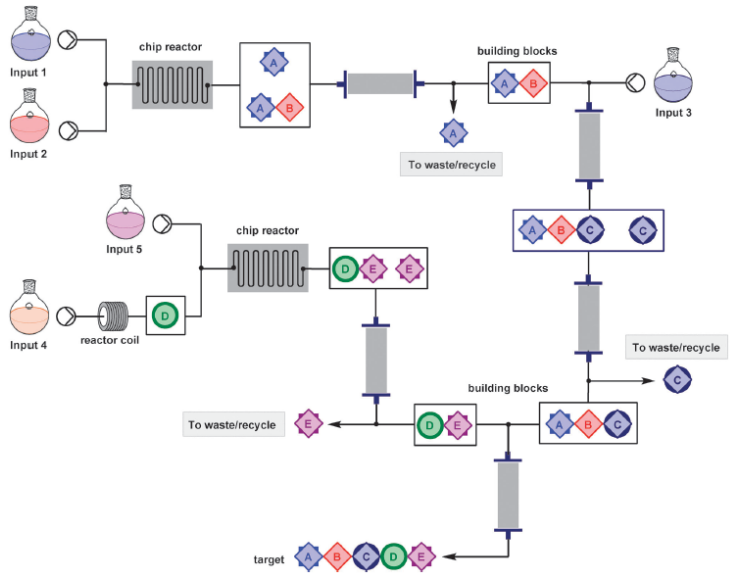
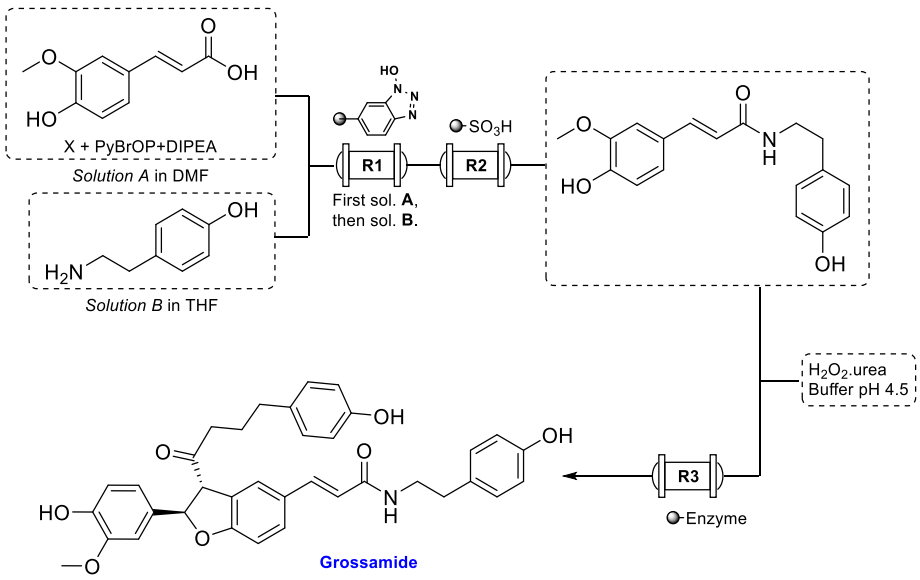


Figure 37. Example of fully automated flow system[144] (scheme taken from ref[145])

The preparation of Grossamide was the first total flow synthesis reported in literature, here is reported the fully automated flow preparation proposed by Ley and co-workers in 2006 (Scheme 22).[145] Grossamide showed anti-inflammatory effect[146] and can be generally extracted from Bell Pepper.[147]



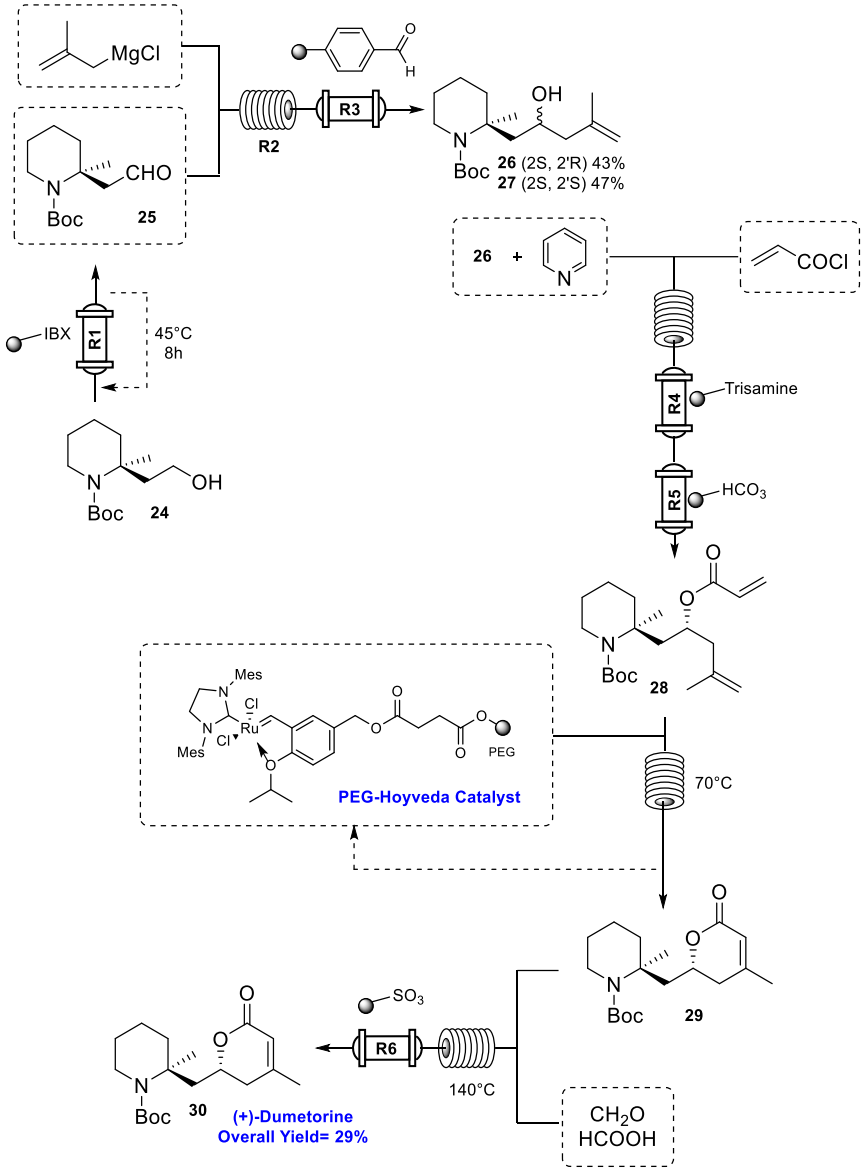
Scheme 22. Total flow synthesis of Grossamide

The process starts with an amide coupling between tyramine and ferulic acid promoted, in **R1**, by supported HOBt (1-Hydroxybenzotriazole). *Solution A* is pumped as first for ester activation, then *Solution B* for the coupling. **R2** act as a scavenger and, after it, a buffering solution is pumper into the system. The solution flush inside **R3** containing an immobilized peroxidase enzyme which allows the dimerization.

Another interesting example of total flow synthesis is provided by the preparation of (+)-Dumetorine (Scheme 23).[148] This natural compound was firstly extracted in 1985 from *Discorea Dumetorum* and was used in traditional African medicine.[149] The total synthesis proposed involves five steps to produce the final products in an overall yield of 29%.

The first step is the oxidation of alcohol **24** to the corresponding aldehyde **25**, the solution is pumped through the column **R1** packed with supported IBX until complete conversion. The following step is the Grignard addition performed at room temperature in a coil reactor **R2**, the excess of Grignard is trapped by the supported benzaldehyde in the successive column **R3**. At this point, a chromatographic separation of the two diastereomer is required, and it is the only one of the whole process.

Diastereomer **26** is then acylated to provide the starting material for the following metathesis. The ring closure is catalyzed by a PEG-supported Hoveyda-Grubbs Ru-based catalyst, such system allows to work in homogeneous phase, recovering the catalyst through a solvent-promoted precipitation.



Scheme 23. Total Flow synthesis of (+)-Dumetorine

In the end, Boc-protection is removed to give afford the final product **30** with an overall yield of 29%.

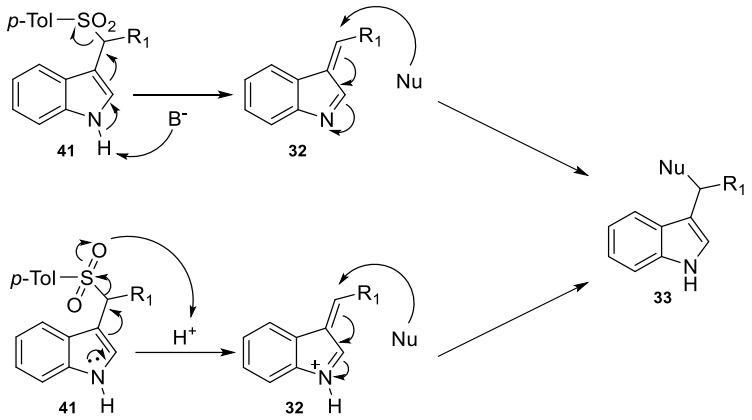
4. Thesis work

In present days, the role of chemistry in every field of technology it is crucial. During the PhD period, with the aim to reduce the impact of chemical process, several protocols were developed in agreement with the principles of green chemistry. The use of enabling techniques has demonstrated to be of countless importance to achieve target products in higher yield and selectivity. Herein are reported some of the research carried out in this period.

4.1 Sulfonyl Indoles and their chemistry

Since the omnipresence of the indole core in medicinal and pharmaceutical chemistry, the development and disclosure of new protocols focused to obtain functionalized indoles is an imperative. The typical procedures usually involve the use of metal catalysts or Friedel-Craft reaction, but all these procedures suffer of several limitations. For example, numerous sensitive or coordinating functional groups (-OH, -NH_2, -OR) are not suitable under the habitual acidic conditions for Friedel-Craft reaction.

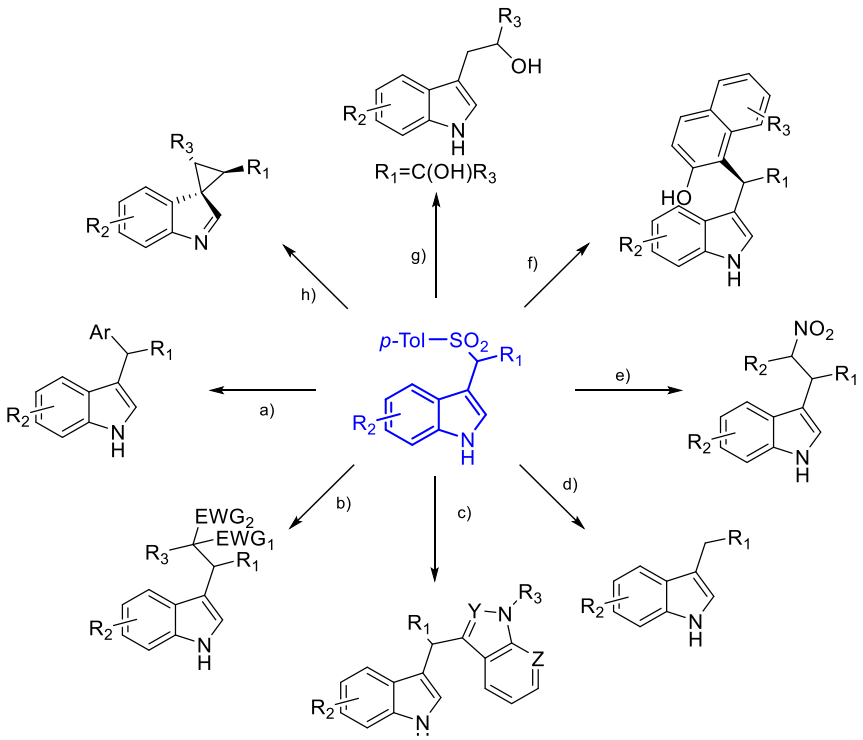
Sulfonyl indoles derivatives **41**, appeared in literature in 2006 and, since then, they have been exploited for benzylic functionalization of 3-substituted indoles as gramine analogues. This class of compounds can be considered stable precursor of indolenine **32** (vinylogous imino derivatives), significant intermediate for the functionalization of indole motif (Scheme 24).



Scheme 24. Base and acid promoted benzylic functionalization of indoles

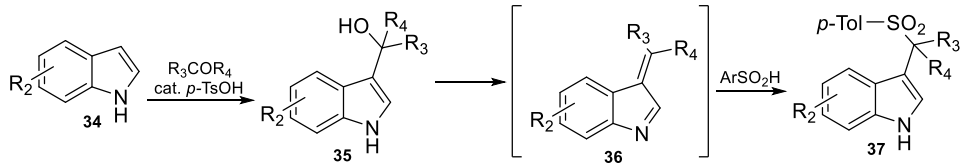
Indolenine intermediate **32**, in fact, undergoes to nucleophilic attack in the benzylic position leading to the formation of branched 3-substituted indoles **33**.

As depicted in Scheme 25, according to the reaction conditions, sulfonyl indoles are involved in a surprising variety of reactions. In fact, they can be functionalized with alkyl or aryl substituent or with enolate analogues or active methylene compounds, they can undergo to Nu-attack by another hetero-aromatic system or can also be reduced to 3-aliphatic derivatives and so on.



Scheme 25. a) Ref;[150] b) Ref;[151] c) Ref;[152] d) Ref;[153] e) Ref;[154] f) Ref;[155] g) Ref[156]

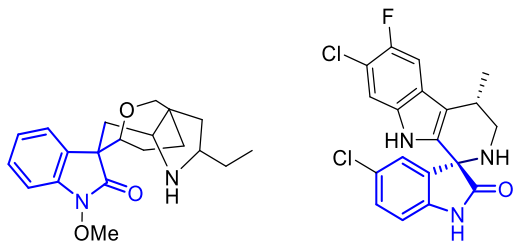
Sulfonyl indoles are typically prepared from an indole reacting with an aldehyde in the presence of aryl sulfinic acid. The indole **34** firstly goes through Friedel-Craft alkylation to form the alcohol **35** which, after dehydration, produce the indolenine **36** that is trapped by the aryl sulfinic acid to produce the target sulfonyl indoles **37** (Scheme 26).[157]



Scheme 26. Reaction mechanism for the preparation of sulfonyl indoles

4.1.1 Flow chemical oxidation of sulfonyl indoles for the formation of 3-alkylidene-2-oxindoles[158]

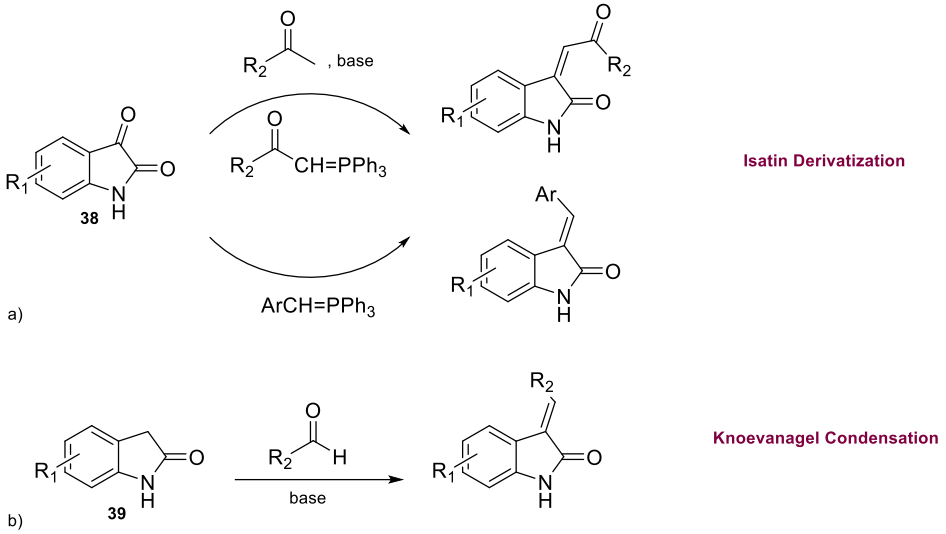
3-Alkylidene-2-oxyndoles **40**, are an important class of indoles derivatives. In fact, the exocyclic double bond in 3 position can be easily converted to form 3-3'-spyronyndoles, which are a promising class of compound profoundly studied in the last decades. Indeed, they have been found as a main motif in many naturally occurring alkaloid[159] and they gave encouraging results in different medical applications, as in the treatment of cancer or as anti-malaria drugs (Figure 38).[160]



Gelsemicine **NITD609**

Figure 38. Naturally occurring spirooxyndole-containing molecules and anti-malaria drug candidate NITD609

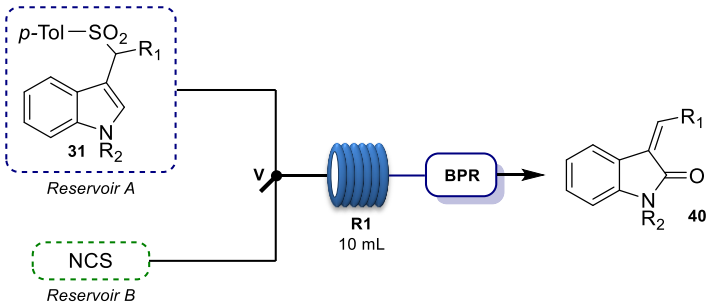
The vast majority of the reported methods for the construction of these compounds regard the derivatization of Isatin **38** (Scheme 27a),[161] occurring preferentially in the 3-position, or the functionalization of 2-oxindoles **39** in a Knoevanagel type reaction with aldehydes (Scheme 27b).[162]



Scheme 27. Typical preparation for 3-alkyliden-2-oxindoles

In this work, after a literature overview, 3-alkylidene-2-oxindoles **40** are produced by the direct oxidation of sulfonyl indoles using *N*-chlorosuccinimmide.

As a first attempt, the reaction was performed in batch conditions to verify the effectiveness of the oxidant. Actually, it was possible to isolate the final product, but in really few yields since the crude was obtained as a complex mixture of products, probably due to the over-oxidation of desired product. Based on the experience of the research group, the attention was moved to the employment of flow technique in order to minimize the contact time between product and oxidant. Specifically, the apparatus was constituted by two HPLC pump pushing the two solutions in a PTFE coil reactor, using a T-mixing piece as a connector and a BPR (Back Pressure Regulator) to keep the constant pressure of 2 atm (Scheme 28).



Scheme 28. Flow apparatus for this work

Preliminary tests demonstrated that *N*-protection is essential for the reaction to proceed. We selected sulfonyl indoles **31a** (R_1= *n*-C_5H_{11}, R_2=Bn, Me or TIPS) as a lead in the screening of the best reaction conditions, the evaluations were about the ratio between the two solvents (THF:H_2O), the stoichiometry of the two reagents and the nature of *N*-protecting group (Table 5).

Table 5. Optimization trials

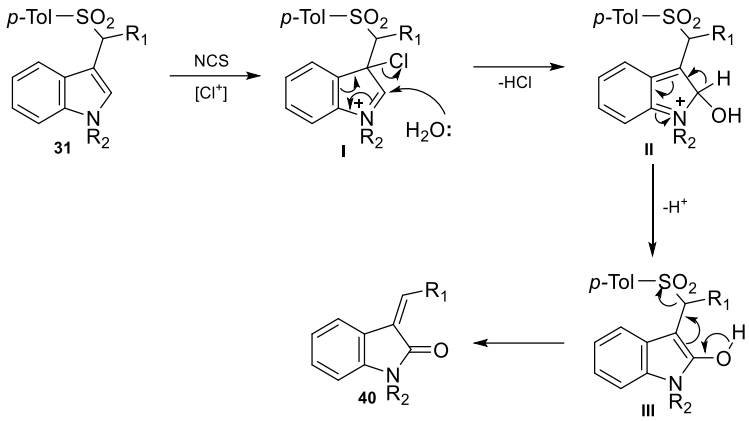
Entry	**[31a]** M	R_2	[NCS] M	Temp (°C)	Flow rate[a]	THF/H_2O	Yield of **41a**%[c]
1	0.1	Bn	0.2	r.t.	1.25	2:1	15
2	0.1	Bn	0.2	60	1.25	2:1	44
3	0.07	Bn	0.14	60	1.25	2:1	52
4	0.05	Bn	0.10	60	1.25	2:1	51
5	0.07	Bn	0.14	60	1.25	3:1	55
6	0.07	Bn	0.14	60	1.25	7:3	61
7	0.07	Bn	0.14	60	1.66	7:3	65
8	0.07	Bn	0.14	60	2.00	7:3	51
9	0.07	Bn	0.14	80	1.66	7:3	Trace
10	0.07	Bn	0.21	60	1.66	7:3	33
11	0.07	Me	0.14	60	1.66	7:3	12
12	0.07	TIPS	0.14	60	1.66	7:3	12
13[b]	0.07	Bn	0.14	60	1.66	7:3	Trace

[a]Flow rate: mL/h/pump. Reactor volume= 10 mL
[b]Reaction performed using Chloramine T as oxidant
[c]Yield of the pure isolated product

As shown in Table 5, the effect of temperature has a great influence in the yield and 60°C revealed to be the more appropriate. Apparently, not only the presence, but also the nature of protecting group seems to be crucial. According to Entry 11-13, switching from benzyl to methyl or TIPS, the yield decreases dramatically. Finally, the solvent ratio appears to be the less influencing feature but tuning its ratio to 7:3 gave the best result.

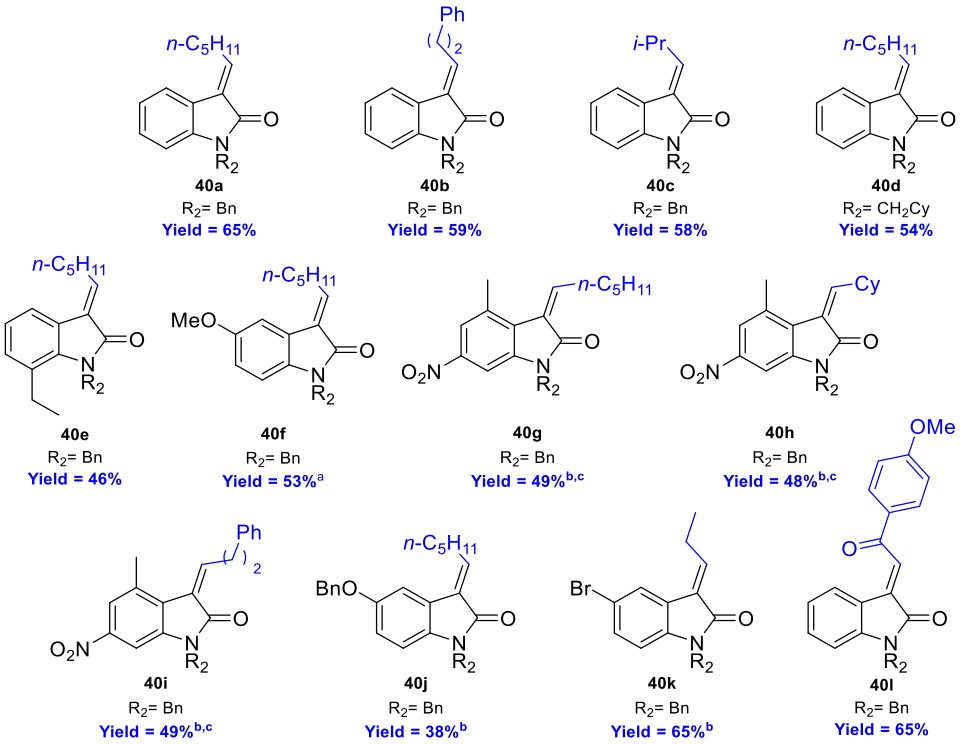
In agreement with Entry 7, the final product was isolated in 65% using the best reaction conditions.

The plausible reaction mechanism involves a first C-3 chlorination (intermediate **I**), followed by the nucleophilic attack of water in 2 position which promote the elimination of the chlorine to produce the cationic intermediate **II**. After deprotonation, a formal rearrangement of electrons, give the hydroxylated intermediate **III** which undergoes to a retro-enolization ending with the elimination of sulfinic acid to furnish the title compound **40** (Scheme 29).



Scheme 29. Proposed reaction mechanism for the oxidation of sulfonyl indoles

To prove the versatility of the new methodology, several sulfonyl indoles were examined under the best reaction conditions. Interestingly, the procedure works pretty well with aliphatic derivatives (R_1= Alkyl) which is a fascinating result. In fact, most of the reported methods work mainly on aryl (R_1= Aryl) functionalized indole derivatives with only few exceptions.[163] Moreover, different substituents are tolerated both on the aryl moiety of indole and on R_1, the substrate scope is evidenced in Figure 39 and all products were obtained from satisfying to good yields.



[a]Flow Rate= 0.83 mL/h/pump
[b]Starting material reservoir kept at 60°C
[c]Z configuration

Figure 39. Substrate scope for the proposed method

The configuration of the double bond was determined by NOE analysis and was established as *E* (dr>95:5), with the only exceptions of compound **40g**, **40h**, **40l** showing a *Z* configuration. For solubility reasons, reservoir of starting material for compound **40g**, **40h**, **40i**, **40l**, **40m** was kept at 60°C.

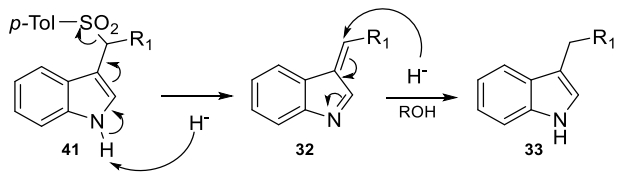
General procedure for the preparation of 40. The flow apparatus was built according to Scheme 28. Sulfonyl indole **31** (0.7 mmol) was dissolved in a 7:3 solution of THF/H_2O (10 mL) and filled in *Reservoir A*, NCS was dissolved in a 7:3 solution of THF/H_2O (10 mL) and filled in *Reservoir B*. The two solutions were pumped using two HPLC pumps through a T-connector and a 10 mL (flow rate 1.66 mL/h/pump, residence time 3h) PTFE coil reactor kept at 60°C, with a BPR set at 2 atm. The outflow was concentrated under reduced pressure and treated with

water. The water phase was extracted using EtOAc and the aqueous layer was dried over Na_2SO_4. After filtration and evaporation, the crude product was purified by flash chromatography to afford the final pure product.

4.1.2 Flow chemical reduction and synthesis of sulfonyl indoles[164]

3-Alkyl indole **33**, as well as other indole derivatives, demonstrated to be ubiquitous core structure in many biologically active compounds. Analyzing the literature, extensive number of papers have been published on this topic. The main procedures involve Friedel-Crafts alkylation, metal-catalyzed functionalization, or acid catalyzed addition of alkyl halide, terminal alkynes or ketones.[165] Recently, even alcohol have been used in a metal redox catalyzed procedure to originate 3-substituted indoles. But main reported method present limitations on substrate scope, in fact, on Friedel Crafts alkylation the presence of acid catalyst limit the possible functional group present in both moieties. In metal catalyzed reactions, the expensive catalyst might inhibit the scalability of the process,[166] while in metal redox catalyzed processes the applicability is reduced by the nature of alcohol.[167]

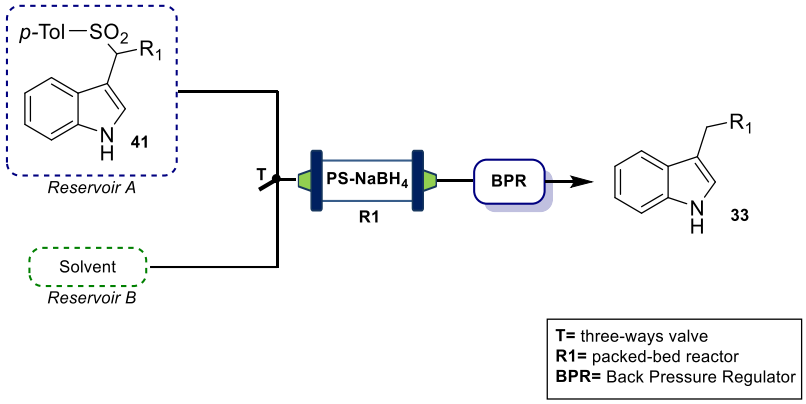
In this context, the presented methodology involves the use of sulfonyl indole **41** as valuable precursor of 3-alkylidene indoles which can bear both aliphatic and arylic substituent in R_1 position increasing the substrate scope of the reaction. Based on previous experiences,[155,152a] sulfonyl indoles are reduced in the presence of hydride source which both act as a base to promote the formation of indolenine intermediate **32** and as a nucleophile to furnish the target indole derivatives (Scheme 30).



Scheme 30. Reaction mechanism for hydride-promoted reduction

In this circumstance, $NaBH_4$ has been use as H^- source, since it is a milder reducing agent compared to the parent $LiAlH_4$. Moreover, the use of solid supported reagent in combination with flow chemistry produce an easy-to-handle procedure involving just solvent evaporation as work-up step.

In this regard, the PS-immobilized borohydride was filled in a packed-bed reactor, sulfonyl indole was dissolved in a solvent a pumped through the column. A three-ways valves (**v**) permit to switch from starting material solution to the solvent in order to wash the resin and recover all the crude product (Scheme 31).



Scheme 31. Flow equipment for the reduction of sulfonyl indoles

Sulfonyl indole **41a** (R_1= *n*-C_5H_{11}) have been selected for the optimization trials concerning solvent, molarity and residence time. Using a 0.03M solutions of **41a** and considering 45' as residence time (column packed with 3 equivalents of PS-$NaBH_4$) different solvent has been tested (Table 6).

Table 6. Solvent optimization

Entry	Solvent[a]	Yield of **33a**%[b]
1	Toluene	-
2	EtOAc	-
3	Dioxane	-
4	2-MeTHF	-
5	DCM	5
6	MeCN	9
7	EtOH	61
8	MeOH	54
9	*i*-PrOH	53
10	γ-valerolacton	-

[a]0.03M solution, 45' as residence time
[b]Yield of the pure isolated product

As expected, an overview of Table 6 delineates alcoholic solvent as the best for performing reduction reaction, with ethanol giving the higher yield (Entry 7, Table 7). At this point, the focus was moved to the molarity of the solutions, with the aim to increase the productivity.

Table 7. Concentration screening

Entry	**[41a]** M[a]	Yield of **33a**%[b]
1	0.03	61
2	0.04	60
3	0.02	59
4	0.05	63
5	0.06	-[c]

[e]Ethanolic solutions
[b]Yield of pure isolated product
[c]Solubility issues

Unfortunately, concentration higher than 0.05M could not be achieved for solubility reasons, but the desired reduced product at this molarity was isolated with a good yield (63%, Entry 4, Table 7). The possibility to use a co-solvent led to an elongation of reaction time but still produce high yielding results.

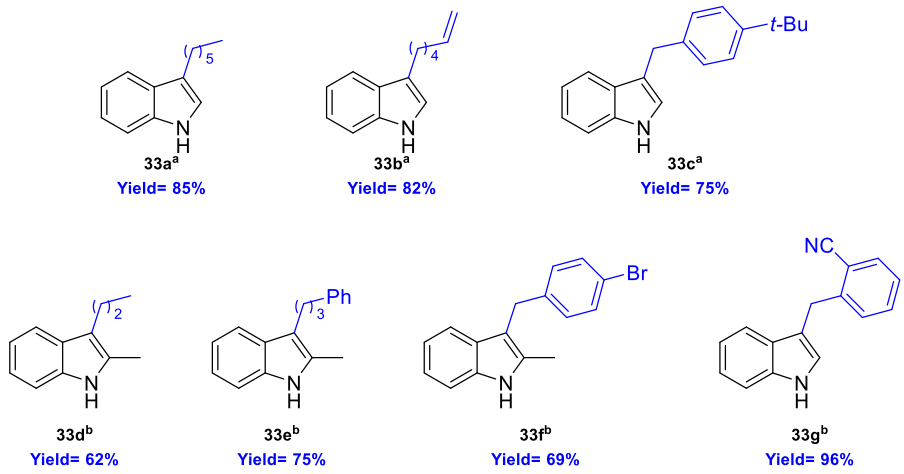
The final screening was focused on the residence time, modifying both flow rate and the stoichiometry of the resin (Table 8). Notably, doubling the amount of PS-BH_4, the reaction time could be reduced to 20' obtaining the target compound **41a** in very good yield (85%, Entry 6, Table 8).

Table 8. Residence time and $NaBH_4$ stoichiometry screening

Entry	PS-BH_4 (eq.)	Residence time[a]	Yield of **33a**%[b]
1	3	45'	63
2	4.5	45'	75
3	6	45'	83
4	7.5	45'	81
5	6	30'	84
6	6	20'	85
7	6	10'	57

[a]0.05 M ethanolic solution
[b]Yield of pure isolated product

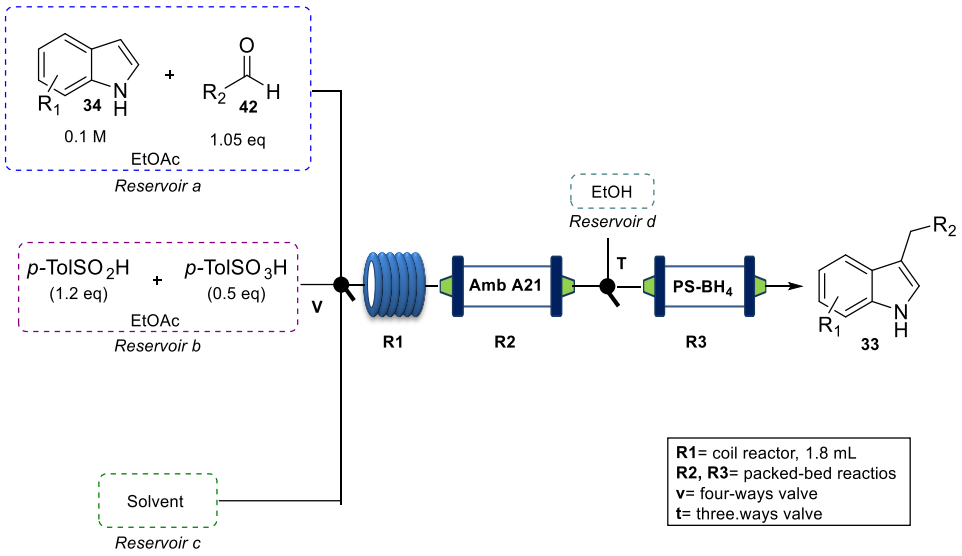
With the purpose to prove the versatility of the method, assorted sulfonyl indoles were tested (Figure 40). As demonstrated in Figure 41, all products are obtained in very good to excellent yields and reducible functional groups are stable under the reaction conditions. In case of 2-substituted indoles, it has been necessary to use 2-MeTHF as a co-solvent because of poor solubility in solely ethanol. The use of a co-solvent is converted in the need to increase the residence time to obtain a full conversion of starting material.



[a]0.05M in EtOH, residence time= 20'
[b]0.05M in EtOH/2-MeTHF (8:2), residence time= 40'

Figure 40. Sulfonyl indoles reduction substrate scope

In the end, the continuous flow synthesis starting from the sulfonyl indoles precursor followed by the reduction has been tested. The idea was to provide the final 3-alkylated indoles **33** avoiding the batch preparation of sulfonyl intermediate **41**. In this respect, batch conditions were fit into a flow system (Scheme 32), implemented with four different *Reservoir*: *A* and *B* for starting materials and sulfonylating agents, respectively, *Reservoir C* providing the solvent to wash reactors **R1** and **R2**, and *Reservoir D* to wash reactor **R3**. The formation of sulfonyl indole happens in **R1**, were reactant are simply mixed thanks to the four-ways valve, then **R2** is packed with A21 to trap the acid excess which will interfere with the reduction step. In the end, in **R3**, there will be the final reduction step to provide final alkylated indole **33**.



Scheme 32. Continuous flow system for the preparation of 3-alkylated indoles starting from indole and aldehyde

With this protocol, different 3-alkylindoles **33** have been synthetized varying the nature of both indoles and aldehydes counterparts demonstrating the applicability of the methodology (Figure 41).

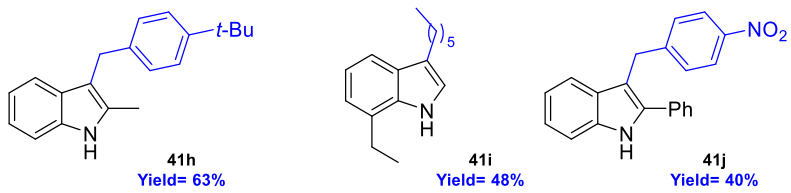


Figure 41. Examples of 3-alkylated indoles produced in a continuous flow system

In conclusion, the application of flow conditions and solid supported systems displayed to be a powerful mean for the synthesis of 3-alkylated indoles **41**, with the possibility to change both the substituent oh the indole moiety and the nature of aldehyde with the only "limitation" to keep the indole nitrogen free.

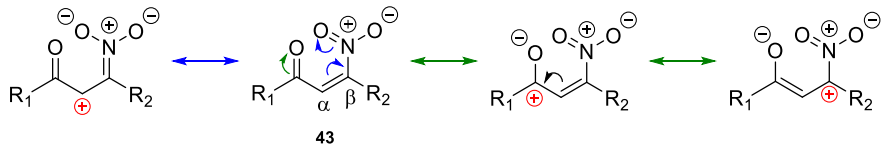
General procedure for reduction of sulfonyl indoles 41. The flow apparatus was implemented according to Scheme 31. Sulfonyl indoles type **41** (0.25 mmol) is dissolved in ethanol (5 mL, or 8:2 EtOH/2-MeTHF for compounds **41e**, **41f**, **41g**, **41h**) filled in *Reservoir A*. *Reservoir B* is filled with solely ethanol. Reactor **R1** is packed with 6 eq. of supported PS-BH_4 (1.2 mmol, residence time 20 min, or 40 min for **41e**, **41f**, **41g**,

41h) and BPR is set at 2 atm to guarantee a constant flow rate. Solution A is pumped with a flow rate of 0.05ml/min (0.025 ml/min for **41e**, **41f**, **41g**, **41h**) into reactor **R1** (residence time 20'). Once all solution in *Reservoir A* is pumped, the valve **v** is switched to let EtOH from *Reservoir B* to wash the reactor and the outflow is collected into an RBF. Solvent is evaporated under reduced pressure to obtain the crude **33**, which is then purified by flash chromatography (9:1 Hex/EtOAc).

General procedure for the one-pot synthesis of 3-alkylated indoles. The flow apparatus was implemented according to Scheme 32. Appropriate aldehyde **42** (0.32 mmol) and indole **34** (0.3 mmol) were dissolved in EtOAc (3 mL) and filled into *Reservoir A*. *p*-$TolSO_3H•H_2O$ (0.15 mmol) and *p*-$TolSO_2H$ (0.36 mmol) were dissolved into EtOAC (3 mL) and filled into *Reservoir B*. The two solutions are pumped through **R1** (1.8 mL coil reactor, residence time= 3h) and **R2** with a flow rate of 0.005 mL/min. **R2** was packed with 0.5g Amberlyst A21. The outflow is mixed at **T** with EtOH (flow rate 0.04 mL/min) and pumped through **R3** packed with PS-BH_4 (1.2 mmol, residence time 20'). The three reactors are washed with pure EtOAc and EtOH to recover all the material and the outcoming stream is collected into an RBF. The crude product was concentrated under reduced pressure and purified by flash chromatography.

4.2 β-Nitroenones: valuable precursor of heterocyclic systems and other precious intermediates

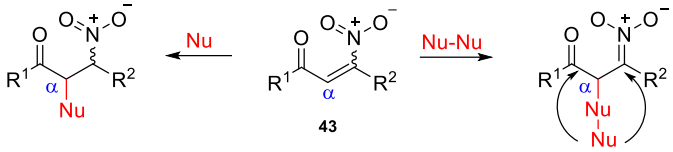
β-Nitroenones **43** are a peculiar class of nitroolefins bearing a ketone in α-position. The resonance structures evidence the presence of three possible electrophilic centers and two nucleophilic centers (Figure 42).



43

Figure 42. Resonance structures of β-nitroenones

Due to the enhanced EWG character of the nitro group, compared to the ketone, the first nucleophilic attack occurs preferentially in α-positions, unless the reaction is performed under kinetic control.[168] Using a di-nucleophilic compound, it might be possible to exploit the other electrophilic center to obtain a ring closure (Scheme 33).

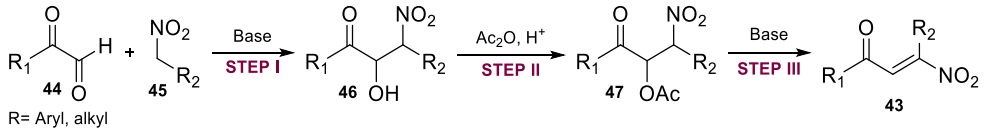


Scheme 33. Nucleophilic attack on β-nitroenones

Moreover, the presence of nitro group might be exploited for its conversion to a plethora of other functionalities such as amine, oxime, nitrile and many others.

Reviewing the literature, they have been used for the derivatization of indoles and pyrroles to produce chiral products,[169] they undergo to nucleophilic attack producing chiral β-nitroketones[170] or, due to the reverse reactivity of the α-carbon, they have been employed to produce α-substituted enones.[171] In our research group, we studied their reactivity for the preparation of 1,4-diketons[172] which can be used as a valuable precursor of substituted heterocycles or, they can be selectively reduced at the double bond to produce β-nitroketons.[173]

β-nitroenones **43** are prepared in a three steps synthesis starting from an aryl (or alkyl) glyoxales **44** and a nitroalkane **45** which undergo to a Henry addition (Step I, Scheme 34). The outcoming nitro alcohol type **46** is treated with acetic anhydride in the presence of an acidic promoter to obtain the acetylated intermediate **47** (Step II, Scheme 34) which, under basic conditions, experience the acetic acid elimination to produce the targeted β-nitroenones **43** (Step III, Scheme 34).

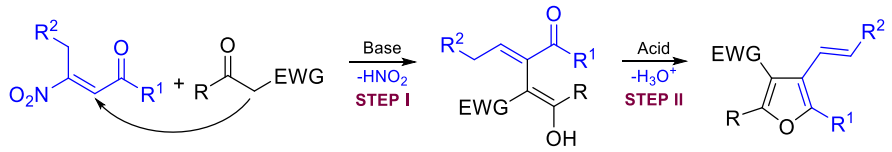


Scheme 34. Synthetic preparation for β-nitroenones

4.2.1 Fully substituted furans from β-nitroenones[174]

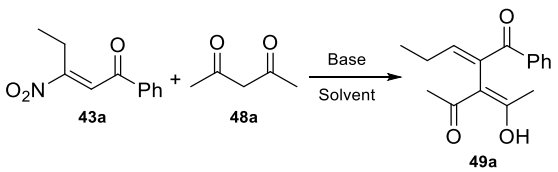
Furans are important key structures in countless biologically active compounds,[175] in polymer chemistry[176] and their natural occurrence in food is responsible for its organoleptic properties;[177] hence, their synthesis and derivatization have been deeply exploited during the years.

With the intent to prepare fully substituted furans, reactivity of β-nitroenons have been studied in the presence of an active methylene compound. Active methylene compound is, in this case, an α-substituted ketone bearing an EWG group in the carbon adjacent to it, the nature of the substituent, make the α-hydrogen particularly acidic facilitating the enolate formation. The proposed procedure involves a two steps reaction to produce the title compound consisting in a first domino Michael addition/elimination of nitrous acid (Step I, Scheme 35) of the generated enolate to the β-nitroenones, followed by an intramolecular cyclization (Step II, Scheme 34).



Scheme 35. Two steps synthesis for fully substituted furans

Compounds reported in Scheme 36 have been selected as test reactant for the optimization studies. For the first step has been performed a screening of base and solvents. As reported in Table 9, the evaluation was carried out on solid supported bases in order to simplify the work up and facilitate the procedure.



Scheme 36. Test reaction for the study of the first step

The best result was obtained using 1 eq. PS-carbonate (Entry 1, Table 9) in acetonitrile solution and no other bases showed similar outcome.

Table 9. Bases screening for the first step

Entry	Supported Base[a]	Eq.	Yield of **49a**%[b]
1	PS-carbonate	1	85
2	PS-TBD	1	45
3	PS-DMAP	1	37
4	KF/Al2O3	1	40
5	PS-F	1	31
6	PS-BEMP	1	37
7	PS-carbonate	0,8	81
8	PS-carbonate	1,2	55

[a]Reaction performed in MeCN at r.t.
[b]Yield of the pure isolated product

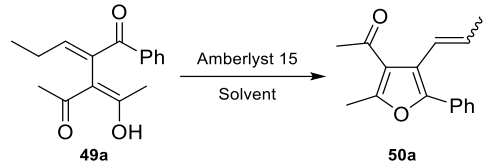
Once selected the optimum base, a second screening concerned the solvent. But even trying different reaction media, the higher yield is still obtained in acetonitrile (Table 10, Entry 4) which has been selected as the best solvent for this step, with the only comparable result in ethyl acetate (Table 10, Entry 1).

Table 10. Solvent screening for the first addition-elimination step

Entry	Solvent[a]	Yield of **49a**%[b]
1	EtOAc	72
2	CPME	55
3	2-MeTHF	21
4	MeCN	85
5	EtOH	37
6	Toluene	45

[a]Reaction performed using 1 eq. of PS-carbonate at r.t.
[b]Yield of the pure isolated product

At this point, the focus was on the second step. Amberlyst 15 has been selected as solid supported acidic promoter of the cyclization step (Scheme 37), and further screening were carried out regarding solvent, temperature, and stoichiometry. All reactions are performed under microwave conditions because it makes possible to reach temperature higher than the solvent boiling point.



Scheme 37. Second step test reaction

Comparing Entry 1, 2, 3, 4 (Table 11) it is evident that ethyl acetate demonstrated to be the best solvent and, hence, a quick screening concerning stoichiometry and temperature has been performed. The optimization proved that 80°C, 2h and 0.6 eq. of Amberlyst 15 represent the best reaction conditions for the cyclization (Entry 9, Table 11).

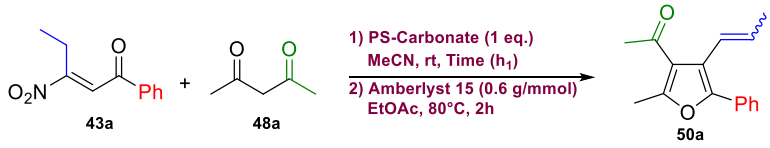
Table 11. Second step optimization

Entry	Amberlyst 15 (g/mmol)	Solvent	Temp. (°C)	Time (h)	Yield of **50a**%[a]	*E:Z*[b] (dr)
1	1	MeCN	80	2	53	96:4
2	1	EtOAc	80	2	76	96:4
3	1	Toluene	80	2	68	82:18
4	1	2-MeTHF	80	2	58	90:10
5	1	EtOAc	100	1	74	90:10
6	1	EtOAc	60	4	45	96:4
7	1.2	EtOAc	80	2	82	96:4
8	0.8	EtOAc	80	2	89	96:4
9	0.6	EtOAc	80	2	91	96:4
10	0.4	EtOAc	80	2	85	96:4

[a]Yield of pure isolated product
[b]Determined by ^{1}H-NMR analysis

The use of solid supported promoter for both steps, enable the chance to perform a simple filtration and evaporation of solvent after the first step, and treat the crude intermediate **49** with the appropriate conditions for the second step.

In the optimized conditions (Scheme 38) and without the purification of the intermediate **49a**, product **50a** was collected in 74% of yield (*E:Z*= 96:4).



Scheme 38. Optimized conditions for the preparation of fully substituted furans

In attempt to confirm the versatility of the method, a valuable variety of activated ketones and β-nitroenones have been tested under the best reaction conditions. Actually, not only α-substituted ketones were suitable as active methylene compounds, but also α-substituted esters, sulfones or cyanides.

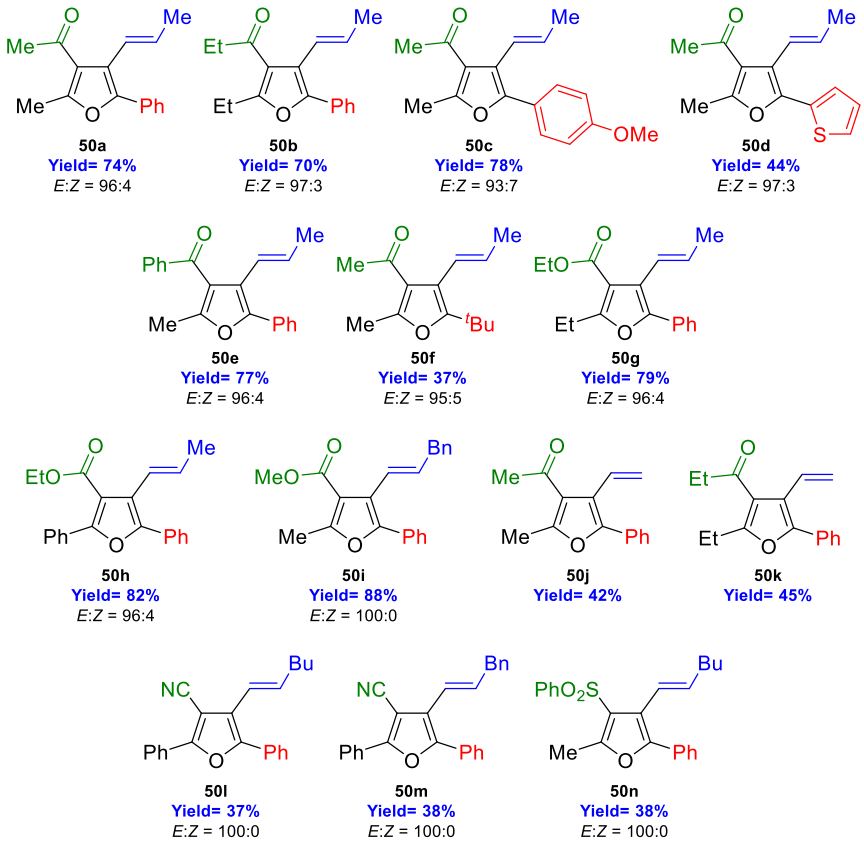


Figure 43. Substrates scope

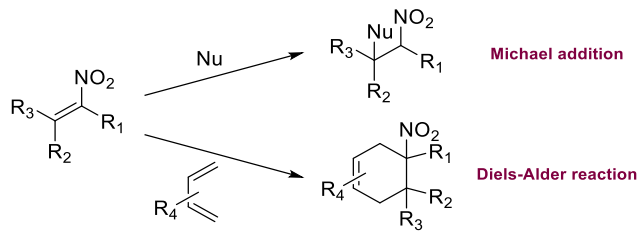
All products are obtained in good to very good yields with excellent diastereoselectivity determined by ^{1}H-NMR analysis. Reaction time for the first step in case of compounds **50e**, **50f**, **50m**, **50n**, **50l** was slightly longer (**50a-d**, **g-i**= 2h; **50e**= 4h; **50f**, **50m**, **50n**= 3h; **50l**= 5h).

By virtue of mild rection conditions, sensible functional groups such as sulfones of cyanides are well tolerated, and the reaction mechanisms allows the formation of terminal double bonds. Moreover, the employment of solid supported systems gives the advantage to avoid any aqueous wasteful work-up.

General procedure for the synthesis of fully substituted furans 50. The appropriate β-nitroenone **43** (1 mmol) and ketone **48** (1 mmol) were dissolved in acetonitrile (2 mL, 0.05M) and PS-carbonate (0.286 g, 1 mmol) was added. The solution was stirred at r.t. for the proper time. Once reached the full conversion, PS-carbonate was filtered-off and washed with additional EtOAc (10 mL), after that solvents were evaporated under reduced pressure. Then, EtOAc (12 mL) and Amberlyst 15 was added and the resulting solution was irradiated in Biotage® Initiator^{+} apparatus, at 80°C for 2h. In the end, Amberlyst A15 was filtered-off and washed with fresh EtOAc (10 mL). The crude material was concentrated under reduced pressure and purified by flash chromatography (95:5 Hexane/Et_2O) to afford the final pure products **50**.

4.2.2 Isomerization of (*E*)-β-nitroenones into β-nitro-β,γ-unsaturated ketones and their application[178]

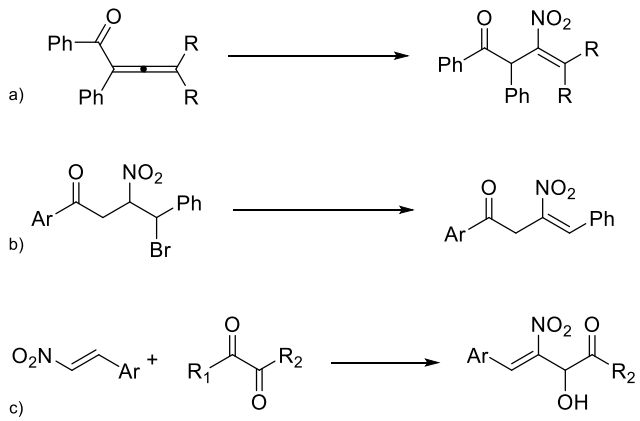
β-Nitro-β,γ-unsaturated ketones are a special class of nitroolefins, which can undergo to the typical reaction of these class of compounds (Scheme 39) and, additionally, ketone functionality can be used for further functionalization.



Scheme 39. Reactivity of nitroolefins

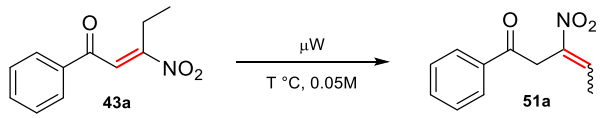
There is no general synthetic procedure for such molecules, in fact, the few reported methods suffer from low substrate scope and poor

versatility (Scheme 40). β-Nitro-β,γ-unsaturated ketones can be prepared from nitration of allenyl ketones,[179] by elimination of hydrobromic acid from γ-brominated β-nitroketones [180] or by Morita-Baylis-Hillmann coupling between a nitroolefins and dicarbonyl compounds.[181]



Scheme 40. Synthetic procedure for β-nitro-β,γ-unsaturated ketones

In the proposed procedure, β-Nitro-β,γ-unsaturated ketones **51** are prepared by isomerization of β-nitroenones **43** promoted by MW irradiation (Scheme 41).



Scheme 41. β-Nitroenone isomerization

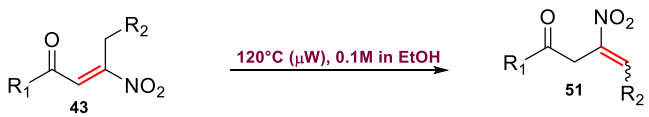
Preliminary results demonstrated that, irradiating at 120°C a solution of β-nitroenones **43a**, an isomerization of the double bond from α,β to β,γ occurred. As listed in Table 12, different solvents have been tested exhibiting strong effect on the reaction trend. In fact, alcoholic solvent (Entry 1-4) evidenced both better diastereoselectivity in the product and greater yields.

Table 12. Solvent screening for isomerization

Entry	Solvent[a]	Time (h)	Yield of **51a**%[b]	*E:Z* (dr)[c]
1	EtOH	2,5	72	83:17
2	*i*-PrOH	2,5	71	80:20
3	*n*-PrOH	2,5	67	85:15
4	MeOH	2,5	65	82:18
5	CPME	2,5	43	65:35
6	EtOAc	2,5	44	55:45
7	Toluene	2,5	45	60:40
8	1,4-Dioxane	2,5	59	80:20

[a]0.05M solutions
[b]Yield of pure isolated product
[c]Determined by ^{1}H-NMR analysis

Since ethanol provided the best results, a small screening of temperature was performed. It was observed that lowering the temperature to 100°C, the reaction needed 4h to have a complete conversion and the yield decrease to 57%. While, raising the temperature to 140°C the reaction proceeds faster (1 h), but the yield is anyway lower (66%). Keeping the optimal temperature of 120°C for the ethanolic solution, with the aim to increase the productivity of the method, more concentrated solutions 0.1M and 0.15M are irradiated under the same reaction conditions obtaining 76% and 66% of yield respectively (*E/Z*= 90:10 for both). The optimized conditions are resumed in Scheme 42.

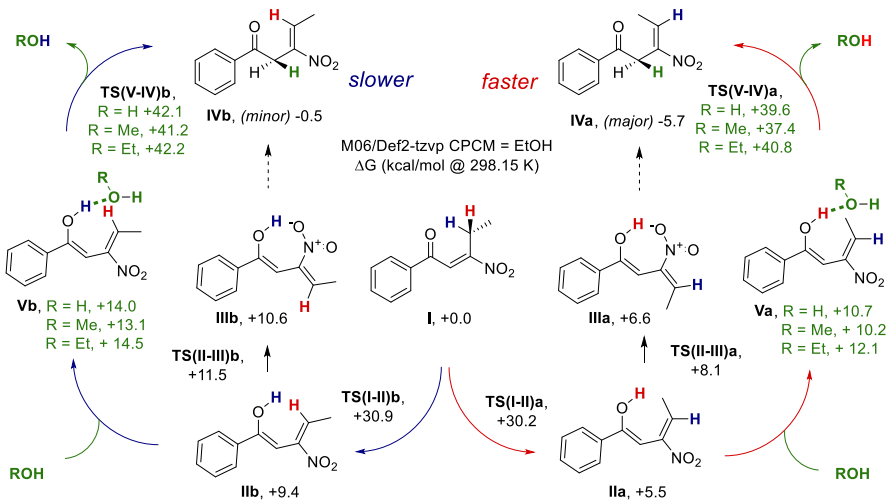


Scheme 42. Optimized reaction conditions for the isomerization

The use of microwave seems to be essential for the reaction progression, in fact, it is impossible to achieve temperature higher than the boiling point in batch conditions (B.P. for EtOH= 78°C) and performing the reaction under reflux the product was isolated in 10% of yield (*E/Z*= 70:30).

The proposed reaction mechanism (Scheme 43) has been implemented with DFT calculations to explain both the diastereoselectivity and the role

of solvent. The two hydrogens of starting material **I** are both likely to undergo to a 1,5-sigmatropic rearrangement to produce an enol, conjugated with the shifted double bond (intermediates **IIa** and **IIb**). But, according to which proton is involved, the intermediate will present different energy and diastereoselectivity. Intermediates **II** can then isomerize into **III** and undergo to a formal retro-enolization to give the target products **IV**. In this process, the difference in energy of the transition states and the difference in energy barrier do not justify the stereoselectivity. Moreover, the energy involved for going from **II** and **III** to **IV** seems to be to high (above +50 kcal/mol). Despite this latter limitation could be overcome by microwave, the diastereoselectivity is still not explained unless it is considered a catalytic action of the solvent. In fact, the retro-enolization step, involving the proton coming from solvent, involves smaller energy barrier (+29.3 kcal/mol) allowing the formation of **IV** from **V** in a concerted mechanism.



Scheme 43. Proposed reaction mechanism for isomerization and DFT calculations

The energy involved in the red catalytic cycles, are converted into a higher turnover frequency that produce more *E* product compared to *Z*. The involvement of solvent proton in the reaction mechanisms has been proved by performing the reaction in ethanol-*d*. In fact, examining the ^{13}C-NMR spectra of the product, it was possible to detect the triplet given by the α-carbon which couple with the deuterium (Figure 44).

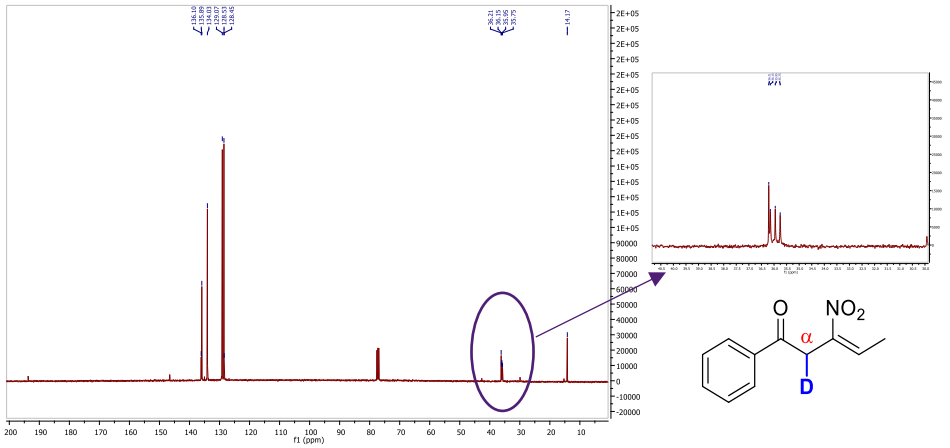


Figure 44. ^{13}C-NMR of deuterated product and magnification of the interesting peak

The catalytic cycle explains also the results got from the solvent screening, in fact, in aprotic polar solvent the reaction proceeds with less difference between the transition state from a thermodynamic point of view.

At this point, in order to demonstrate the flexibility of the method, several β-nitroenones were irradiated under the same reaction conditions and the results are depicted in Figure 45.

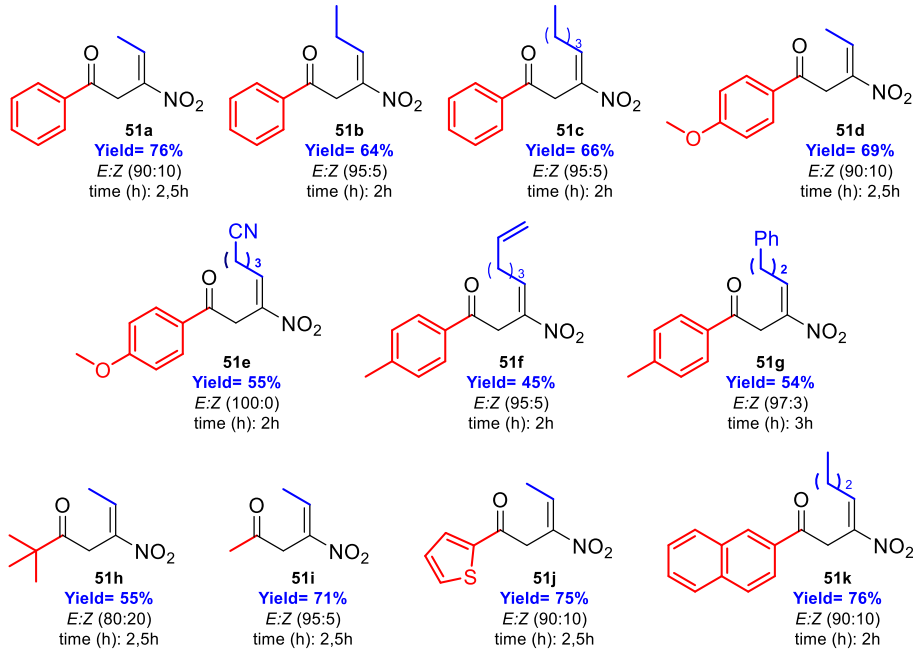
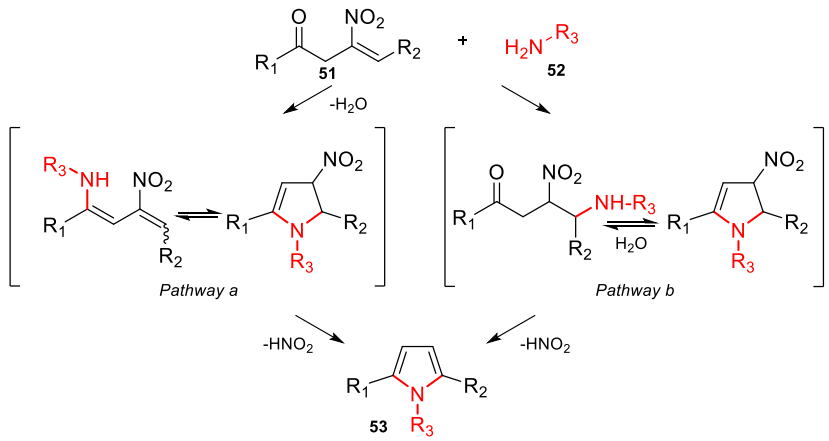


Figure 45. Substrate scope for β-nitroenones isomerization

Finally, with the intent to prove the synthetic utility of the isomerized compound, they were treated with primary amines to form disubstituted pyrroles. A possible reaction mechanism to achieve the formation of the pyrroles presumes a first enamine formation on the carbonyl moiety, followed by an intramolecular Michael addition (*Pathway a*, Scheme 44) or, on the other way round, a first Michael addition, followed by intramolecular enamine formation (*Pathway b*, Scheme 44). In both cases, after the elimination of nitrous acid, it is possible to obtain the final aromatic product **53**.



Scheme 44. The two possible reaction mechanisms for the formation of pyrroles

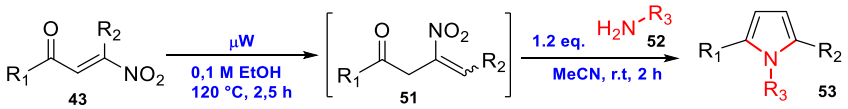
Performing the two reaction in a one-pot fashion was not achievable. In fact, treating β-nitro-β,γ-unsaturated ketones **51a** with 1.2 equivalent of pentylamine produced only 25% of yield (Table 13).

Table 13. Solvent screening for pyrrole formation

Entry	Solvent	Yield of **53a**%[a]
1	EtOH	25
2	EtOAc	57
3	MeCN	72
4	2-MeTHF	48

[a]Yield of pure isolated product

Switching the solvent from ethanol to acetonitrile for the second step, the yield increased to 72% for the overall process. As reported in Scheme 45, the crude intermediate type **51** was concentrated under reduced pressure, diluted in acetonitrile, and treated with primary amines **52** to obtain the targeted disubstituted pyrrole **53**.



Scheme 45. Optimized reaction conditions for the overall process

The method works also starting from different β-nitroenones treated with diverse primary amines (Figure 46). The variety of obtained pyrrole illustrates the versatility of the methodology which allows the

introduction of specific functionalization also on the nitrogen. For example, compound **53c** bear a triple bond which can be used for further reaction in the field of click chemistry.

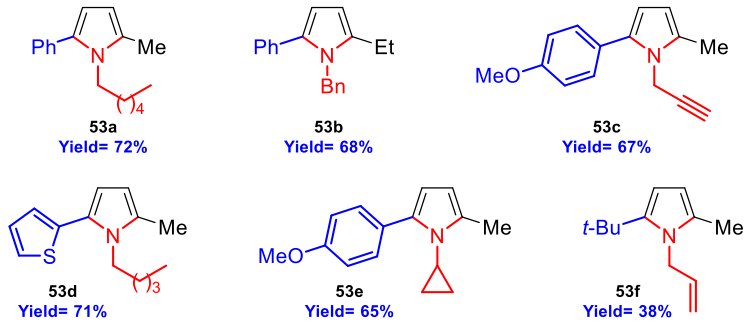


Figure 46. Substrate scope for pyrrole synthesis

General procedure for the isomerization of β-nitroenones into β-nitro-β,γ-unsaturated 51. β-nitroenones **43** (1 mmol) was dissolved in ethanol (10 mL, 0.1M) and irradiated by Biotage® Initiator^{+} at 120°C for the proper time. Once the reaction underwent to completeness, solvent was evaporated under reduced pressure and the crude product **51** was purified by flash chromatography (8:2 Hex/EtOAc).

General procedure for the one-pot preparation of disubstituted pyrrole 53. β-nitroenones **43** (1 mmol) was dissolved in ethanol (10 mL, 0.1M) and irradiated by Biotage® Initiator^{+} at 120°C for the proper time. Once the reaction underwent to completeness, solvent was evaporated under reduced pressure and acetonitrile (10 mL) was added. Then, the appropriate amine **52** (1.2 mmol) was added and the solution was stirred for two hours at room temperature. At the end, the solvent is evaporated under reduced pressure and the product **53** was purified by flash chromatography (95:5 Hex/EtOAc).

4.3 Reactivity of β-nitroacrylates

Similar to β-nitroenones, β-nitroacrylates present an interesting chemistry which have been profoundly exploited during the years (Figure 47). Indeed, they have been used for the synthesis of a huge variety of heterocycles, as well as highly functionalized molecules that can be used in further transformations. The presence of both ester and nitro group,

makes this compound excellent Michael acceptor leaving the carboxylic functionality free.

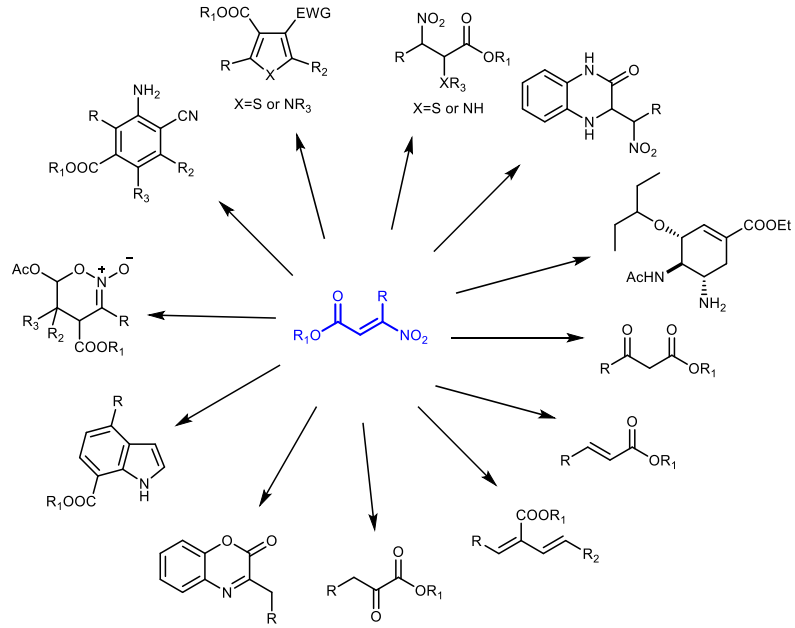
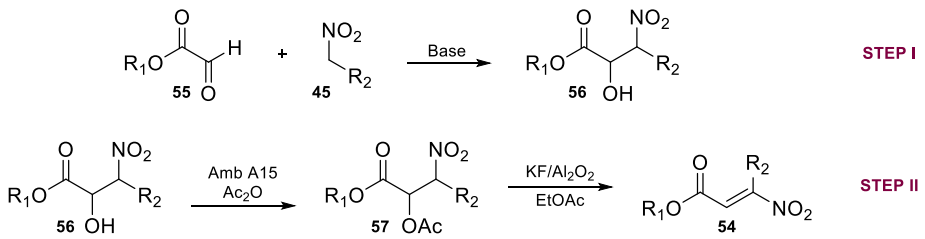


Figure 47. Synthetic application of β-nitroacrylates

The most used and versatile procedure for the preparation of β-nitroacrylates **54** is the dehydration of nitroalcohol **56** (Step II, Sheme 46),[182] using a recently proposed green procedure involving the use of solid supported system and in solvent free conditions. Nitroalcohol **56** can be prepared following an henry-type reaction between a nitroalkane **45** and a glyoxalate **55** (Step I, Scheme 46).



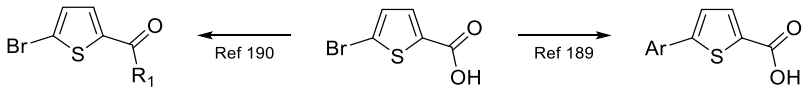
Scheme 46. Two-steps preparation for β-nitroacrylates

Moreover, the nature of R_2 is not limited to the only alkyl groups, in fact, according to the nitro compound used for the Henry reaction, different functional groups can be introduced in the target compound.

4.3.1 β-nitroacrylates for the preparation of thiophenes-2-carboxylates[183]

Thiophenes-2-carboxylates are attractive scaffolds in organic synthesis, they both contain an heterocyclic core and a carboxylic function which can be exploited for derivatization.[184] They demonstrated to have biological activity itself[185] but found application also in the field of catalysis,[186] liquid crystals[187] and coordination polymers.[188]

5-substituted-thiophene-2-carboxylates can be obtained by derivatization of commercially available 5-bromothiophene-2-carboxylic acid, exploiting cross coupling reactions like Suzuki-Miyaura[189] or the reactivity of carboxylic group (Scheme 47).[190]



Scheme 47. Derivatization of 5-substituted-thiophene-2-carboxylates scaffold

In this procedure, the intriguing reactivity of β-nitroacrylates type **58** (Figure 50) has been adventured for the preparation of title compounds. Such peculiar class of β-nitroacrylates bear a masked carbonyl functionality which can be released and used at a later time. The synthetic utility of compounds type **58** has been already proved by the research group for the preparation of substituted pyrroles[191] and indoles.[192]

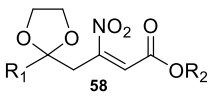
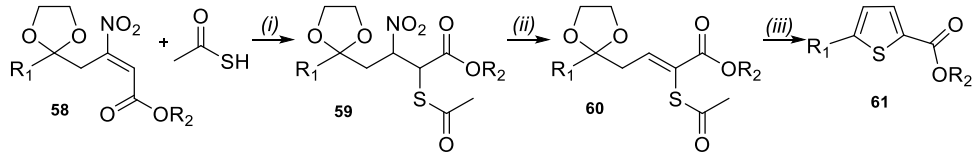


Figure 48. β-nitroacrylates tipe x

The idea was to propose a one-pot three-steps synthesis involving *(i)* a first Michael addition of thioacetic acid to the β-nitroacrylates **58**, followed by *(ii)* nitrous aid elimination and a finally *(iii)* cleavage of the protecting group to induce the cyclization and aromatization (Scheme 48).



Scheme 48. Synthetic procedure for the preparation of 5-substituted 2-carboxythiophene 61

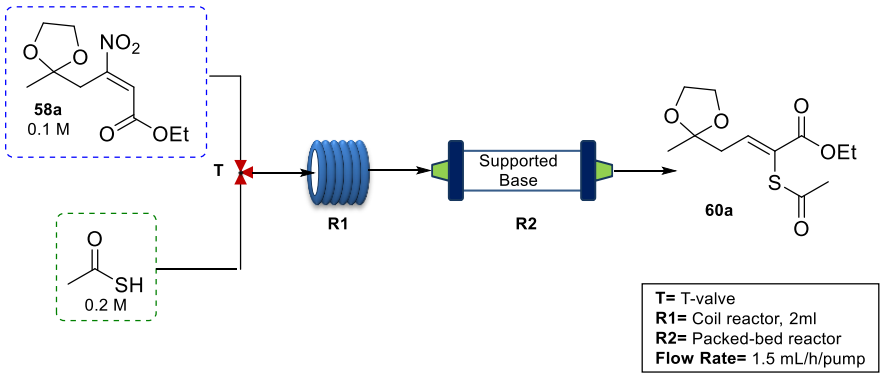
The three steps were, initially, studied separately using β-nitroacrylates **58a** (R_1= Me, R_2= Et) as a lead for the optimization tests. The decision to move from batch to flow conditions came out after a first trial for the Michael addition which produce a complex mixture of products. Probably because the dioxolane ring is not stable under protracted acidic conditions due to the presence of thioacetic acid. Even moving from batch to flow, the encouraging but not plenty satisfying result (69% of isolated yield, Entry 9, Table 14) for the first step, shed light on the possibility that intermediate **59a** was not stable under purification conditions.

Table 14. First step optimization

Entry[a]	**[58a]** M	[AcSH] M	Flow rate[b] (mL/h/pump)	Yield of **59a**%[c]
1	0.4	0.44	0.5	49
2	0.2	0.22	0.5	53
3	0.1	0.11	0.5	58
4	0.05	0.055	0.5	57
5	0.1	0.11	1	56
6	0.1	0.11	1.5	59
7	0.1	0.11	2	53
8	0.1	0.15	1.5	62
9	0.1	0.2	1.5	69
10	0.1	0.25	1.5	63

[a]Reactions performed in MeCN
[b]Reactor volume= 2 mL
[c]Yield of pure isolated product

Aiming to increase the yield, the decision to couple the first two steps seemed to be precious. Concerning the nitrous acid elimination, several bases have been tested, the choice of solid supported ones was prompted by the use of flow equipment (Scheme 49).



Scheme 49. Flow apparatus for step *(i)* and *(ii)*

The screening reported in Table 15, identifies PS-carbonate as the best base, and both acetonitrile (Entry 7) or toluene (Entry 9) the preferable solvents.

Table 15. Optimization of the coupled *(i)* Michael addition- *(ii)* HNO_2 elimination steps

Entry	Supported Base (eq.)	Solvent	Yield of **60a**%[a]
1	PS-TBD (1)	MeCN	41
2	PS-BEMP (1)	MeCN	52
3	PS-F (1)	MeCN	33
4	PS-DMAP (1)	MeCN	28
5	PS- Carbonate (1)	MeCN	62
6	PS-Carbonate (1.5)	MeCN	78
7	PS-Carbonate (2)	MeCN	97
8	PS-Carbonate (2)	EtOAc	75
9	PS-Carbonate (2)	Toluene	91
10	PS-Carbonate (2)	2-MeTHF	61

[a]Yield of pure isolated product

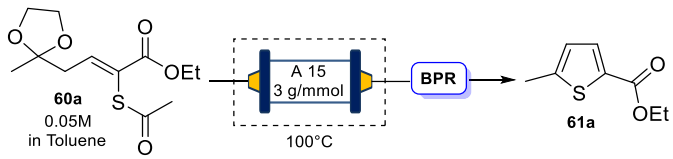
Lately, the attention was focused on the last step. For the acid catalyzed ring cleavage, Amberlyst 15 has been selected based on the know-how of the research group. The scan of the best reaction conditions has firstly been performed in a sealed vial using microwave. In fact, the need of high reaction temperature with low boiling point solvent, such as acetonitrile, forced the use of system that allows to work under pressure.

Table 16. Third step optimization

Entry	Amberlyst 15	Temp (°C)	Solvent[a]	Yield of **61a**%[b]
1	1	80	MeCN	26
2	1	100	MeCN	35
3	1	110	MeCN	30
4	1	100	Toluene	58
5	2	100	Toluene	77
6	3	100	Toluene	93
7	3	100	2-MeTHF	51
8	3	100	EtOAc	68

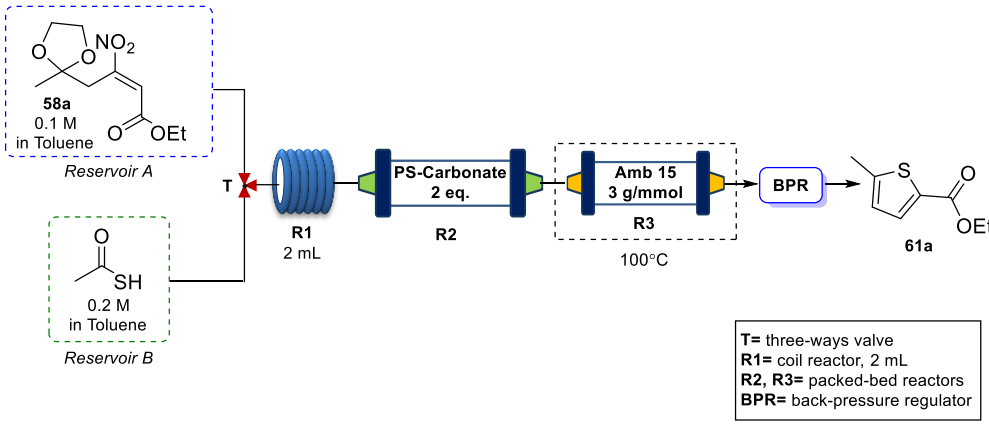
[a]0.05M solutions
[b]Yield of pure isolated product

The higher yield obtained in toluene at 100°C (Entry 6, Table 16), enabled the possibility to switch back to flow system. In fact, just applying the same conditions to the flow apparatus depicted in Scheme 50, the targeted thiophene was isolated in same yield.



Scheme 50. Flow conditions for the third step

Finally, the three steps were put together in a continuous flow systems (Scheme 51) which produced the final thiophene **61a** with an overall yield of 84% of pure product in the optimized conditions (Flow rate= 1.5 mL/h/pump, toluene, 0.1M for β-nitroacrylates and 2 eq. of AcSH, 2 eq. of PS-Carbonate, 3 g/mmol Amb 15 at 100°C). A BPR was fixed at the end of the flow apparatus to keep a constant pressure all over the system to guarantee a correct flow rate.



Scheme 51. Continuous flow system for the synthesis of thiophenes-2-carboxylate 61

In order to verify the skillfulness of the continuous flow system, different β-nitroacrylates type **58** have been testes demonstrating that it was possible to obtain the targeted compounds from good to excellent yield for the overall process (Figure 49).

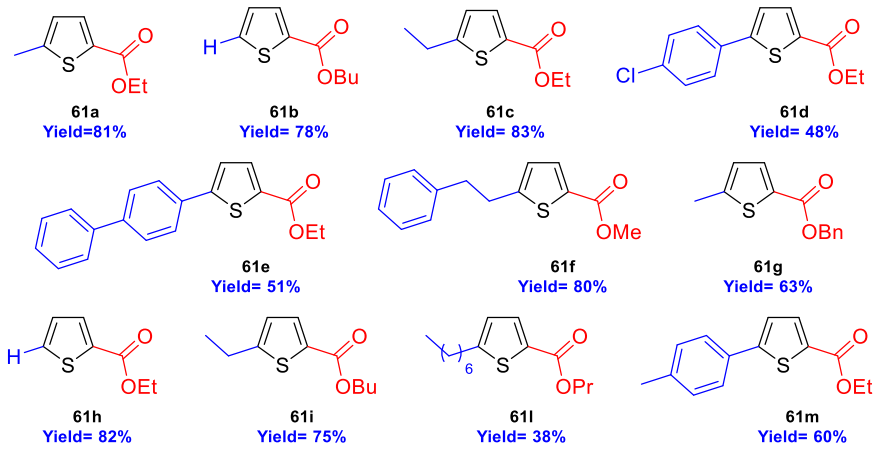


Figure 49. Thiophenes-2-carboxylate substrate scope

In conclusion, this procedure enables the synthesis of title compound in good yield starting from β-nitroacrylates **58**, allowing the preparation on a great variety of both aliphatic and aromatic derivatives avoiding the use of any expensive metal catalysts or harmful reactants. The continuous flow system avoids any intermediate purification reducing time and material wasting, desirable condition from a sustainable viewpoint.

General procedure for the synthesis of thiophenes-2-carboxylates 61. The flow equipment was implemented according to Scheme 51. At the

end of the apparatus, BPR was set at 2 atm. The appropriate β-nitroacrylates **58** (1 mmol) was dissolved in toluene (10 mL) and filled in *Reservoir A*. Thioacetic acid (2 mmol) was dissolved in toluene (10 mL) and filled in *Reservoir B*. The solutions are pumper with a flow rate of 1.5 ml/h/pump into the T-connector to mix them and the resulting solution flows through **R1**, **R2** and **R3** and is collected at the end in an RBF. **R1** was a 2 mL PTFE coil reactor, **R2** is a packed-bed reactor filled with 2 eq. PS-carbonate, **R3** is a packed-bed reactor filled with 3 g/mmol of Amberlyst 15 and is kept at 100°C. The solvent is then evaporated under reduced pressure and the product **61** purified by flash chromatography.

4.4 Allyl nitro compounds

Allyl nitro compound (Figure 50), as well as other unsaturated nitro compounds, demonstrated their synthetic utility all over the years. In fact, they can both act as nucleophiles or as electrophiles, and the nitro group can be converted in other functionalities (amine, carbonyl, oxime) and exploited for further transformations. Moreover, nitro group can be replaced in a Pd-catalyzed nucleophilic substitution to obtain allylic substituted alkenes.[193]

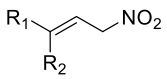
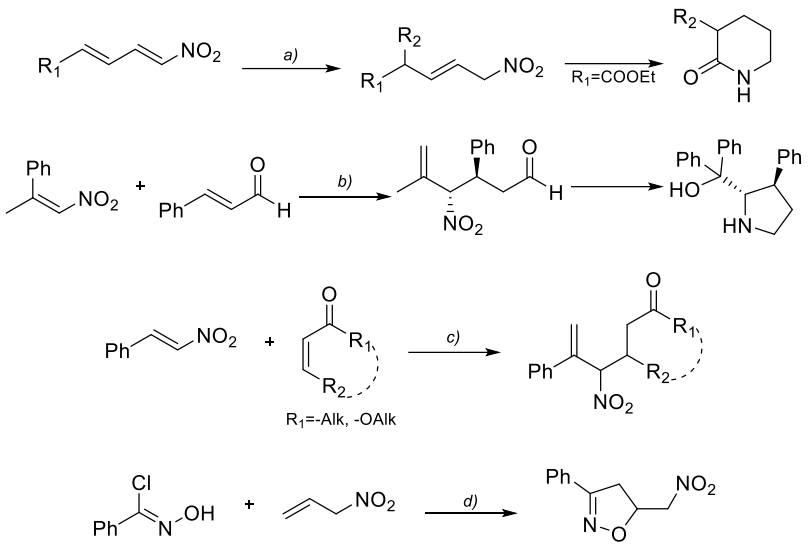


Figure 50. Typical structure for allyl nitro compounds

They can be prepared by deoxygenation of vicinal diol,[194] or by Cu-catalyzed addition to nitrodienoate,[195] Morita-Bayles-Hillman reaction,[196] Knoevagel condensation,[197] or Michael addition of nitroolefins to α,β-unsaturated compounds[198] (Scheme 52).



Scheme 52. Some synthetic preparations and applications of allyl nitro compounds. a) Ref;[194] b) Ref;[196a] c) Ref;[196c] d) Ref[198]

Additionally, allyl nitrocompounds demonstrated to be versatile for the cyclization leading to the formation of both carbo- and heterocycles.[196,199]

4.4.1 Preparation of (2-acetoxy)allyl nitro compounds[200]

(2-Acetoxy)allyl nitro compounds **62**, are an innovative class of allyl nitro compounds bearing an acetoxy group in vinylic position. The presence of this additional functional groups discloses a plethora of new reactions in which the title compounds might be involved. In fact, as shown in Figure 51, the acetoxy could release a carbonyl group, the α-carbon to the nitro act both as an electrophilic or a nucleophilic center and, finally, the cleavage of the acetoxy group, lead to the formation of an enolate which act as a nucleophile.

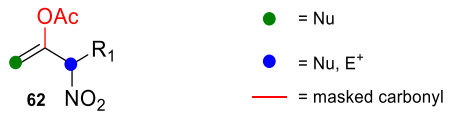
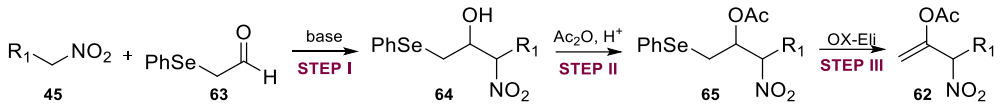


Figure 51. (2-Acetoxy)allyl nitro compounds: general structure

Title compounds have been prepared in a three-steps synthesis (Scheme 53) involving a base-promoted Henry reaction (Step I), acetylation of the

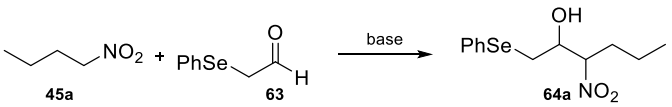
nitro alcohol (Step II), and oxidation-elimination to produce the target compound (Step III).



Scheme 53. Three-steps synthesis for the preparation of (2-Acetoxy)allyl nitro compounds

The key step is the oxidation of selenium which is converted to selenium oxide, eliminating in the end phenylselanol. The elimination is thermally promoted and lead to the formation of the desired double bond.

The optimization of the procedure was divided into the study of the three isolated steps. Reaction depicted in Scheme 54 has been selected for the screening and several bases have been tested for the nitro-aldol reaction.



Scheme 54. First step

As shown by the Table 17, particular attention has been given to the solid supported bases, obtaining higher yields using basic alumina (Entry 10). The choice of the base it is pivotal to avoid decomposition of selenyl aldehyde.

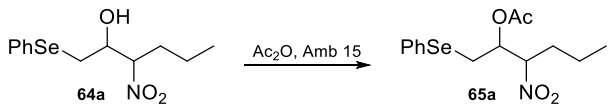
Table 17. Base screening

Entry	Base	Solvent	Yield of **64a**%[a]	Time (h)
1	DBU (0.4 eq.)	THF	36	2
2	Amb A21 (200 mg/mmol)	THF	41	5
3	PS-TBD (1 eq.)	EtOAc	49	6
4	PS-BEMP (1 eq.)	EtOAc	Traces	5
5	CTAOH (0.1 eq.)	H_2O	24	6
6	K_2CO_3 (1 eq.)	MeCN	44	4
7	Carb. On Silica (0.2 eq.)	Neat	52	5
8	Neutral Al_2O_3 (250 mg/mmol)	EtOAc	48	5
9	Basic Al_2O_3 (250 mg/mmol)	EtOAc	51	5
10	Basic Al_2O_3 (500 mg/mmol)	EtOAc	54	5
11	Basic Al_2O_3 (1 g/mmol)	EtOAc	48	5

[a]Yield of pure isolated product, reactions performed at r.t

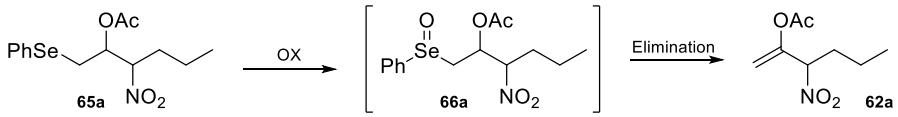
Keeping the same reaction conditions of Entry 10 and switching the solvent to 2-MeTHF, the yield can be increased up to 63%, using a slightly excess of the nitroalkane (1.2 eq).

For the second step (Scheme 55), based on the experience of similar reactions, Amberlyst 15 has been selected as the acidic promoter to enhance the acetate formation using acetic anhydride as acetylating agent.[181]



Scheme 55. Second step

Performing the reaction in solvent free conditions and at room temperature, the acetylated adduct **65a** was obtained in 93% of yield in the presence of 80 mg/mmol of Amberlyst 15 and 3 eq. of acetic anhydride.



Scheme 56. Third step

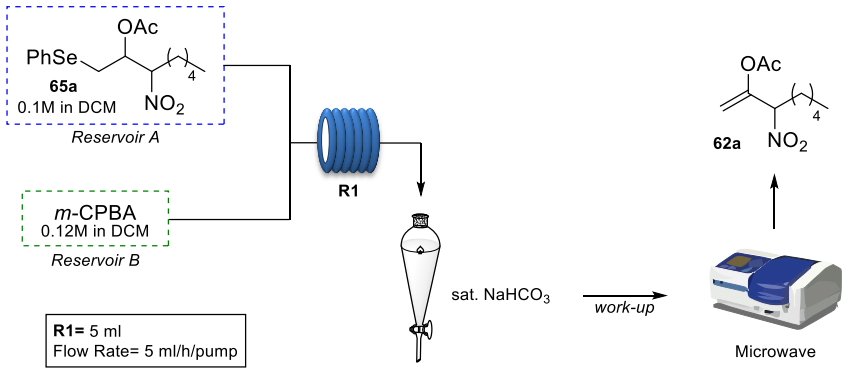
The third and last step revealed to be the trickiest one, in fact, it is constituted by two reactions: a first oxidation of selenium to selenium oxide, followed by the elimination of the phenylselanol to provide the final terminal alkene (Scheme 56). The oxidized intermediate **66a** was never isolated, just an aqueous work-up was performed and the crude was heated to promote the elimination. Based on the literature,[201] three different oxidizing agents have been tested, *m*-CPBA, H_2O_2, SO_2Cl_2. According to Table 18, *m*-CPBA gave better results and tuning the conditions for the elimination step (Entry 4), the target compound could be isolated in 63% of yield for the third step.

Table 18. Third step optimization: Oxidation - Elimination

Entry	Oxidizing Agent (eq.)	Tim (h)	Elimination Conditions[a]	Yield of **62a**%[a]
1	*m*-CPBA (1.1)	1	110°C, 0.5h	33
2	*m*-CPBA (1.2)	1	110°C, 0.5h	51
3	*m*-CPBA (1.5)	1	110°C, 0.5h	49
4	*m*-CPBA (1.2)	0.5	110°C, 0.5h	63
5	*m*-CPBA (1.2)	3	110°C, 0.5h	55
6	H_2O_2 (1.9)	0.5	110°C, 0.5h	35
7	SO_2Cl_2 (1)	0.5	110°C, 0.5h	37
8	*m*-CPBA (1.2)	0.5	110°C, 1h	58
9	*m*-CPBA (1.2)	0.5	100°C, 0.5h	51
10	*m*-CPBA (1.2)	0.5	80°C, 0.5h	39
11	*m*-CPBA (1.2)	0.5	120°C, 0.5h	61

[a]All reactions have been performed under microwave irradiation and using toluene as a solvent
[b]Yield of pure isolated product.

At the end, to avoid further over-oxidation side reactions, the oxidation was performed in flow followed by the elimination in microwave conditions (Scheme 57), improving the yield up to 78%.



Scheme 57. Flow apparatus for oxidation

At this point, once optimized the reaction conditions for the three steps, the flexibility of the method was proved using several nitroalkane, bearing also additional functional groups or derivatizations (Figure 52). All intermediates were isolated, and the respective yields are reported in Table 19.

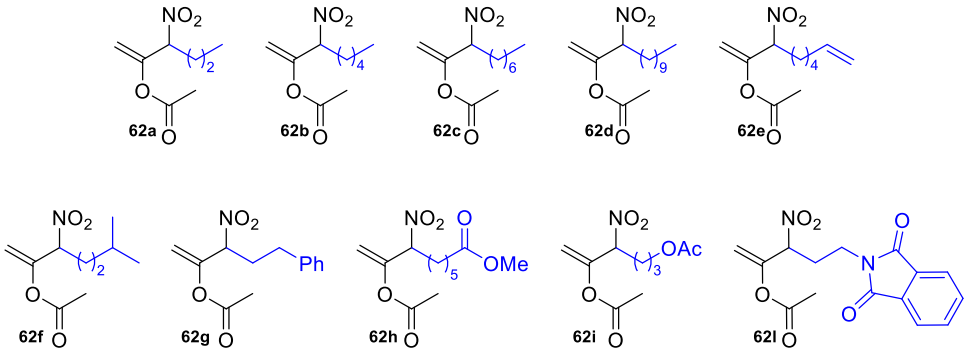
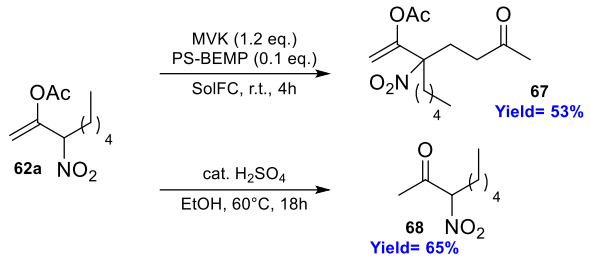


Figure 52. Substrate scope

Table 19. Isolated yields % of the intermediates and products

Substrate	64	65	62
a	63	91	78
b	65	85	78
c	61	88	81
d	53	82	67
e	62	90	65
f	59	79	74
g	62	95	58
h	60	95	73
i	70	80	69
j	68	92	52

Furthermore, a small demonstration of the synthetic utility has been shown. The obtained (2-acetoxy)allyl nitro compounds have been put in acidic conditions to provide the α-nitroketon **68**[202] or it was made react with MVK to produce the Michael adduct **67** (Scheme 58).[203]



Scheme 58. Examples of synthetic applications for (2-acetoxy)allyl nitro compounds

General procedure for preparation of 64. Nitroalkanes **45** (1.2 mmol) and aldehyde **63** (1 mmol) were dissolved in 2-MeTHF (2 mL), then Al_2O_3 (500 mg) was added and the solution is stirred at r.t. for 5 h. When the reaction is complete, Al_2O_3 was filtered off and washed with fresh EtOAc (15 mL). The solvent is then removed under reduced pressure and crude nitro alcohol **64** was obtained and purified by flash chromatography.

General procedure for preparation of 65. β-Nitroalcohol **64** (1 mmol) was dissolved in acetic anhydride (3 mmol), then Amberlyst 15 (80 mg) was added and the solution stirred at room temperature for 4 h. When the reaction was complete, Amberlyst 15 was filtered-off and washed

with fresh EtOAc (15 mL). Solvents are removed under reduced pressure and the crude acetylated product **65** was purified by flash chromatography.

General procedure for the flow chemical preparation of 62. The flow apparatus was set up according to Scheme 55. Intermediate **65** (1 mmol) was dissolved in CH_2Cl_2 (10 mL) and filled in a *Reservoir A*, *m*-CPBA (1.2 mmol) was dissolved in CH_2Cl_2 (10 mL) and filled in *Reservoir B*. The two solutions were pumped at the same time into **R1** (5 ml coil reactor) with a flow rate of 5 mL/h/pump. The outflow stream was directly quenched with a saturated solution of $NaHCO_3$ (20 mL). The two phases are then separate, and the water phase extracted twice with CH_2Cl_2 (2x20mL). The combined organic phases were dried over Na_2SO_4 which is then filtered off and the solvent evaporated under reduced pressure. The crude material is dissolved in toluene (10 mL) and irradiated under Biotage Initiator$^+$ for 30 minutes at 110°C. Solvent is removed under reduced pressure and the product **62** purified by flash chromatography.

5. Experimental section

^{1}H-NMR analyses were recorded at 400MHz on a Varian Mercury Plus 400. ^{13}C-NMR analyses were recorded at 100MHz. IR spectra were recorded with a PerkinElmer FT-IR spectrometer Spectrum Two UATR. Microanalyses were performed with CHNS-O analyzer Model EA 1108 from Fisons Instruments. GC-MS analyses were obtained on Hewlett-Packard GC/MS 6890N that works with EI technique (70 eV). Microwave irradiations were performed by the means of a Biotage Initiator^{+}.

5.1 Spectroscopic Data For 3-alkylidene-2-oxindoles

***(E)*-1-Benzyl-3-hexylideneindolin-2-one (40a).** Pale yellow viscous oil, Yield: 65%. IR (neat): 3061, 3030, 1704, 1607, 1465, 1347, 1174, 745, 694 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.7 Hz, 1 H), 7.30 (d, *J* = 4.3 Hz, 2 H), 7.33–7.21 (m, 3 H), 7.19–7.11 (m, 2 H), 7.01 (dt, *J* = 0.9, 7.7 Hz, 1 H), 6.72 (d, *J* = 8.1 Hz, 1 H), 4.96 (s, 2 H), 2.70 (q, *J* = 7.7 Hz, 2 H), 1.73–1.62 (m, 2 H), 1.50–1.31 (m, 4 H), 0.93 (t, *J* = 7.3 Hz, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.2, 143.2, 142.9, 136.4, 129.0, 128.9, 127.7, 127.6, 127.5, 123.7, 122.7, 122.3, 109.3, 43.8, 31.9, 29.6, 28.6, 22.8, 14.3. MS (EI): m/z (%) = 305 (40, [M^{+}]), 262 (21), 235 (10), 91 (100), 65 (11). Anal. Calcd for $C_{21}H_{23}NO$ (305.42): C, 82.58; H, 7.59; N, 4.59. Found: C, 82.50; H, 7.55; N, 4.63.

***(E)*-1-Benzyl-3-(3-phenylpropylidene)indolin-2-one (40b).** Orange oil, Yield: 59%. IR (neat): 3062, 3033, 1465, 1301, 1138, 1077, 735 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.3 Hz, 1 H), 7.38–7.22 (m, 10 H), 7.19–7.14 (m, 2 H), 7.00 (dt, *J* = 0.9, 7.7 Hz, 1 H), 6.72 (d, *J* = 7.7 Hz, 1 H), 4.96 (s, 2 H), 3.07–2.94 (m, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.1, 143.0, 141.3, 140.9, 136.3, 129.1, 129.0, 128.9, 128.6, 128.1, 127.8, 127.5, 126.6, 123.8, 122.5, 122.4, 109.3, 43.9, 34.9, 31.5. MS (EI): m/z (%) = 339 (36, [M^{+}]), 248 (41), 91 (100), 65 (13). Anal. Calcd for $C_{24}H_{21}NO$ (339.44): C, 84.92; H, 6.24; N, 4.13. Found: C, 84.99; H, 6.20; N, 4.08.

***(E)*-1-Benzyl-3-(2-methylpropylidene)indolin-2-one (40c).** Yellow waxy solid, Yield: 58%. IR (neat): 3737, 2881, 2359, 1794, 1630, 1535, 1402, 1211, 790 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.3 Hz, 1 H), 7.38–7.21 (m, 6 H), 7.19–7.12 (m, 1 H), 7.04–6.94 (m, 1 H), 6.72 (d, *J* = 8.1 Hz, 1 H), 4.96 (s, 2 H), 3.36–3.20 (m, 1 H), 1.23 (d, *J* = 6.8 Hz, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.6, 149.2, 136.3, 132.0, 129.3, 129.0, 128.9, 127.7, 127.5, 127.4, 123.7, 122.3, 109.3, 43.5, 28.8, 22.1. MS (EI): m/z (%) = 277 (100, [M^+]), 262 (12), 186 (20), 158 (11), 91 (81), 65 (10). Anal. Calcd for $C_{19}H_{19}NO$ (277.37): C, 82.28; H, 6.90; N, 5.05. Found: C, 82.32; H, 6.92; N, 5.09.

***(E)*-1-(Cyclohexylmethyl)-3-hexylideneindolin-2-one (40d).** Yellow viscous oil, Yield: 54%. IR (neat): 2924, 2853, 1704, 1607, 1465, 1357, 1174, 745 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.6 Hz, 1 H), 7.27–7.22 (m, 1 H), 7.10–7.01 (m, 2 H), 6.86 (d, *J* = 7.8 Hz, 1 H), 3.59 (d, *J* = 7.3 Hz, 2 H), 2.69 (q, *J* = 7.3 Hz, 2 H), 1.87–1.61 (m, 8 H), 1.49–1.34 (m, 4 H), 1.24–1.15 (m, 3 H), 1.13–1.00 (m, 2 H), 0.94 (t, *J* = 7.3 Hz, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.4, 142.7, 128.8, 128.5, 123.6, 121.9, 121.6, 119.0, 108.8, 46.4, 36.7, 31.9, 31.2, 29.6, 28.5, 26.5, 26.0, 22.7, 14.2. MS (EI): m/z (%) = 311 (100, [M^+]), 294 (12), 268 (30), 228 (54), 215 (78), 200 (31), 186 (18), 158 (18), 145 (34), 130 (46), 115 (15), 55 (18). Anal. Calcd for $C_{21}H_{29}NO$ (311.47): C, 80.98; H, 9.39; N, 4.50. Found: C, 81.08; H, 9.33; N, 4.46.

***(E)*-1-Benzyl-7-ethyl-3-hexylideneindolin-2-one (40e).** Yellow waxy solid, Yield: 46%. IR (neat): 3030, 2924, 1697, 1439, 1342, 1165, 694 cm^{-1}. 1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.45 (m, 1 H), 7.32–7.11 (m, 6 H), 7.04–6.97 (m, 2 H), 5.22 (s, 2 H), 2.72 (q, *J* = 7.7 Hz, 2 H), 2.58 (q, *J* = 7.7 Hz, 2 H), 1.73–1.64 (m, 2 H), 1.50–1.32 (m, 4 H), 1.08 (t, *J* = 7.3 Hz, 3 H), 0.93 (t, *J* = 7.3 Hz, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.4, 143.0, 140.2, 138.0, 131.4, 129.0, 127.3, 127.2, 126.7, 125.9, 123.7, 122.6, 121.8, 45.4, 31.9, 29.6, 28.6, 24.9, 22.8, 16.8, 14.3. MS (EI): m/z (%) = 333 (47, [M^+]), 290 (16), 186 (15), 172 (10), 91 (100). Anal. Calcd for $C_{23}H_{27}NO$ (333.48): C, 82.84; H, 8.16; N, 4.20. Found: C, 82.80; H, 8.12; N, 4.17.

***(E)*-1-Benzyl-3-hexylidene-5-methoxyindolin-2-one (40f).** Pale orange waxy solid, Yield: 53%. IR (neat): 2914, 2848, 1704, 1479, 1179, 1026, 695 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 5 H), 7.19–7.11 (m, 2 H), 6.69 (dd, *J* = 2.6, 8.5 Hz, 1 H), 6.59 (d, *J* = 8.5 Hz, 1 H), 4.93 (s, 2 H), 3.78 (s, 3 H), 2.67 (q, *J* = 7.7 Hz, 2 H), 1.73–1.62 (m, 2 H), 1.50–1.30 (m, 4 H), 0.92 (t, *J* = 7.3 Hz, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.1, 155.6, 143.5, 136.7, 136.4, 129.0, 127.9, 127.7, 127.5, 123.7, 112.7, 111.6, 109.4, 56.1, 43.9, 31.9, 29.6, 28.5, 22.7, 14.2. MS (EI): m/z (%) = 335 (44, [M^+]), 292 (13), 91 (100), 65 (9). Anal. Calcd for $C_{22}H_{25}NO_2$ (335.45): C, 78.77; H, 7.51; N, 4.18. Found: C, 78.84; H, 7.54; N, 4.23.

***(Z)*-1-Benzyl-3-hexylidene-4-methyl-6-nitroindolin-2-one (40g).** Yellow solid, Yield: 49%; m.p.= 95–97 °C. IR (neat): 3066, 3030, 2924, 2895, 1702, 1515, 1337, 1220, 705 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74–7.72 (m, 1 H), 7.43–7.40 (m, 1 H), 7.36–7.22 (m, 6 H), 4.99 (s, 2 H), 3.16 (q, *J* = 7.7 Hz, 2 H), 2.57 (s, 3 H), 1.69–1.58 (m, 2 H), 1.49–1.32 (m, 4 H), 0.92 (t, *J* = 7.3 Hz, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.2, 152.8, 147.2, 142.3, 135.6, 134.1, 129.2, 128.1, 127.6, 127.2, 126.5, 120.6, 101.8, 43.7, 32.0, 29.3, 29.2, 22.7, 21.5, 14.2. MS (EI): m/z (%) = 282 (28), 91 (100), 65 (11). Anal. Calcd for $C_{22}H_{24}N_2O_3$ (364.44): C, 72.51; H, 6.64; N, 7.69. Found: C, 72.44; H, 6.60; N, 7.73.

***(Z)*-1-Benzyl-3-(cyclohexylmethylene)-4-methyl-6-nitroindolin-2-one (40h).** Yellow solid, Yield: 48%; m.p.= 181–184 °C. IR (neat): 3092, 3081, 2919, 1707, 1525, 1337, 1226, 965, 740 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74–7.71 (m, 1 H), 7.42–7.40 (m, 1 H), 7.38–7.23 (m, 5 H), 7.04 (d, *J* = 9.8 Hz, 1 H), 4.99 (s, 2 H), 4.06–3.94 (m, 1 H), 2.56 (s, 3 H), 1.93–1.70 (m, 4 H), 1.54–1.38 (m, 2 H), 1.36–1.16 (m, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.1, 157.4, 147.2, 142.4, 135.6, 134.2, 129.2, 128.1, 127.6, 126.7, 125.7, 120.6, 101.8, 43.8, 37.2, 32.7, 26.1, 25.6, 21.5. MS (EI): m/z (%) = 376 (30, [M^+]), 295 (11), 282 (27), 91 (100). Anal. Calcd for $C_{23}H_{24}N_2O_3$ (376.46): C, 73.38; H, 6.43; N, 7.44. Found: C, 73.45; H, 6.38; N, 7.48.

***(Z)*-1-Benzyl-4-methyl-6-nitro-3-(3-phenylpropylidene)indolin-2-one (40i).** Yellow solid, Yield: 49%; m.p.= 170–173 °C. IR (neat): 3061, 3026, 2924, 2853, 1703, 1515, 1332, 1221, 740 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 7.73–7.70 (m, 1 H), 7.42–7.39 (m, 1 H), 7.38–7.11 (m, 11 H), 4.99 (s, 2 H), 3.50 (q, *J* = 7.7 Hz, 2 H), 2.96 (t, *J* = 7.7 Hz, 2 H), 2.48 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.1, 150.7, 147.3, 142.5, 140.9, 135.5, 134.2, 129.2, 128.7, 128.1, 127.7, 127.6, 126.6, 126.3, 120.6, 101.9, 43.7, 35.3, 30.7, 21.3. MS (EI): m/z (%) = 282 (25), 91 (100), 65 (12). Anal. Calcd for $C_{25}H_{22}N_2O_3$ (398.46): C, 75.36; H, 5.57; N, 7.03. Found: C, 75.35; H, 5.65; N, 7.07.

***(E)*-1-Benzyl-5-(benzyloxy)-3-hexylideneindolin-2-one (40j).** Orange waxy solid, Yield: 38%. IR (neat): 3061, 3030, 2924, 2853, 1701, 1454, 1175, 799, 698 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.46–7.21 (m, 11 H), 7.16–7.09 (m, 1 H), 6.77 (dd, *J* = 2.6, 8.5 Hz, 1 H), 6.59 (d, *J* = 8.5 Hz, 1 H), 5.02 (s, 2 H), 4.93 (s, 2 H), 2.64 (q, *J* = 7.7 Hz, 2 H), 1.69–1.59 (m, 2 H), 1.46–1.32 (m, 4 H), 0.93 (t, *J* = 7.3 Hz, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.1, 154.8, 143.5, 137.2, 137.0, 136.4, 129.0, 128.9, 28.3, 127.8, 127.7, 127.6, 127.5, 123.6, 114.1, 112.6, 109.3, 71.2, 43.9, 31.9, 29.6, 28.6, 22.8, 14.3. MS (EI): m/z (%) = 221 (20), 205 (41), 180 (54), 165 (100), 137 (34), 91 (18), 57 (73), 43 (32). Anal. Calcd for $C_{28}H_{29}NO_2$ (411.54): C, 81.72; H, 7.10; N, 3.40. Found: C, 81.80; H, 7.05; N, 3.41.

***(E)*-1-Benzyl-5-bromo-3-propylideneindolin-2-one (40k).** Yellow waxy solid, Yield: 44%. IR (neat): 3059, 3031, 2965, 1707, 1601, 1454, 1165, 815, 698 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65–7.63 (m, 1 H), 7.33–7.22 (m, 6 H), 7.15 (t, *J* = 7.7 Hz, 1 H), 6.57 (d, *J* = 8.1 Hz, 1 H), 4.93 (s, 2 H), 2.75–2.66 (m, 2 H), 1.28 (t, *J* = 7.37 Hz, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.7, 146.1, 141.7, 135.9, 131.4, 129.0, 127.9, 127.5, 126.6, 126.3, 124.4, 115.0, 110.6, 43.9, 23.2, 13.3. MS (EI): m/z (%) = 341 (43, [M$^+$]), 91 (100). Anal. Calcd for $C_{18}H_{16}BrNO$ (342.24): C, 63.17; H, 4.71; N, 4.09. Found: C, 63.23; H, 4.67; N, 4.11.

***(E)*-1-Benzyl-3-[2-(4-methoxyphenyl)-2-oxoethylidene]indolin-2-one (40l).** Orange solid, Yield: 40%; m.p.= 115–117 °C. IR (neat): 3061, 3025, 1709, 1597, 1465, 1240, 1169, 949, 750, 699 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 7.7 Hz, 1 H). 8.15–8.09 (m, 2 H), 7.93 (s, 1 H), 7.39–7.19 (m, 6 H), 7.02–6.94 (m, 3 H), 6.70 (d, *J* = 7.7 Hz, 1 H), 4.98 (s, 2 H), 3.90 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 189.9, 168.4, 164.5, 145.1,

135.7, 132.4, 131.6, 130.9, 129.1, 128.0, 127.8, 127.7, 127.5, 127.2, 123.0, 120.5, 114.4, 109.4, 55.8, 44.1. MS (EI): m/z (%) = 369 (74, [M^+]), 341 (61), 234 (19), 206 (31), 135 (43), 91 (100), 78 (21), 65 (12). Anal. Calcd for $C_{24}H_{19}NO_3$ (369.42): C, 78.03; H, 5.18; N, 3.79. Found: C, 77.96; H, 5.16; N, 3.85.

5.2 Spectroscopic Data of 3-alkylated indoles

3-Hexyl-1H-indole (33a). Yellow oil, Yield: 85%. IR (neat): 3413, 2924, 2857, 1455, 738 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.81 (br s, 1H), 7.68 (d, 1H, *J* = 7.7 Hz), 7.37 (d, 1H, *J* = 7.7 Hz), 7.25 (t, 1H, *J* = 7.7 Hz), 7.18 (t, 1H, J = 7.7 Hz), 6.97 (s, 1H), 2.81 (t, 2H, *J* = 7.7 Hz), 1.85-1.70 (m, 2H), 1.57-1.27 (m, 6H), 0.96 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100, $CDCl_3$ MHz): δ = 136.6, 127.9, 122.1, 121.3, 119.3, 117.4, 111.3, 32.1, 30.5, 29.7, 25.5, 23.0,14.5. MS (EI): m/z (%) =201 (44, [M^+]), 130 (100), 103 (9), 77 (10). Anal. Calcd for $C_{14}H_{19}N$ (201.31): C, 83.53; H, 9.51; N, 6.96. Found: C, 83.57; H, 9.48; N, 6.99.

3-(Hex-5-enyl)-1H-indole (33b). Yellow oil, Yield= 82%. IR (neat): 3415, 2925, 1455, 909, 740 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.89 (br s, 1H), 7.62 (d, 1H, *J* = 8.33 Hz), 7.36 (d, 1H, *J* = 8.11 Hz), 7.22-7.17 (m, 1H), 7.15-7.10 (m, 1H), 6.98 (s, 1H), 5.89-5.78 (m, 1H), 5.05-4.93 (m, 2H), 2.77 (t, 1H, *J* = 7.54), 2.12 (q, 2H, *J* = 6.75, 8.14 Hz), 1.79-1.69 (m, 2H), 1.56-1.46 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.3, 136.6, 127.8, 122.1, 121.3, 119.3, 119.2, 117.2, 114.6, 111.3, 33.9, 29.9, 29.1, 25.2. MS (EI): m/z (%) = 199 (19, [M^+]), 156 (14), 130 (100), 103 (6), 77 (7). Anal. Calcd for $C_{14}H_{17}N$ (199.30): C, 84.37; H, 8.60; N, 7.03. Found: C, 84.41; H, 8.57; N, 7.05.

3-(4-tert-Butylbenzyl)-1H-indole (33c). Pale yellow solid, Yield= 75%, m.p.= 124-126°C. IR (neat): 3404, 2960, 1455, 818, 742 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.89 (br s, 1H), 7.60 (d, 1H, *J* = 8.1 Hz), 7.39-7.32 (m, 3H), 7.28-7.19 (m, 3H), 7.13 (t, 1H, *J* = 7.7 Hz), 6.95-6.91 (m, 1H), 4.13 (s, 2H), 1.34 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.9, 138.4, 136.7, 128.6, 127.8, 125.5, 122.6, 122.3, 119.6, 119.5, 116.2, 111.2, 34.6, 31.7, 31.2. MS (EI): m/z (%) = 263 (100, [M^+]), 244 (61), 232 (10), 206 (23), 130

(46), 110 (9). Anal. Calcd for $C_{19}H_{21}N$ (263.38): C, 86.64; H, 8.04; N, 5.32. Found: C, 86.68; H, 8.01; N, 5.35.

2-Methyl-3-propyl-1H-indole (33d). Pinkish oil, Yield= 62%. IR (neat): 3404, 2956, 2929, 1459, 1298, 738 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68 (br s, 1H), 7.52 (d, 1H, *J* = 7.3 Hz), 7.28-7.25 (m, 1H), 7.14-7.04 (m, 2H), 2.68 (t, 2H, *J* = 7.3 Hz), 2.37 (s, 3H), 1.72-1.60 (m, 2H), 0.95 (t, 3H, *J* = 7.3Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 135.5, 131.0, 129.1, 121.0, 119.2, 118.4, 112.5, 110.3, 26.4, 24.1, 14.3, 11.9. MS (EI): m/z (%) = 173 (48, [M^+]), 144 (100), 115 (10), 77 (9). Anal. Calcd for $C_{12}H_{15}N$ (173.26): C, 83.19; H, 8.73; N, 8.08. Found: C, 83.23; H, 8.70; N, 8.11.

2-Methyl-3-(3-phenylpropyl)-1H-indole (33e). Pale yellow solid, Yield= 75%, m.p.= 76-79°C. IR (neat): 3413, 3054, 2920, 2848, 1459, 1298, 738, 702 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (br s, 1H), 7.53 (d, 1H, *J* = 7.3 Hz), 7.36-7.09 (m, 8H), 2.79 (t, 2H, *J* = 7.7 Hz), 2.73 (t, 2H, *J* = 7.7 Hz), 2.36 (s, 3H), 2.08-1.97 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 142.9, 135.5, 131.1, 129.0, 128.7, 128.5, 125.9, 121.1, 119.3, 118.4, 112.1, 110.4, 36.0, 32.5, 24.1, 12.0. MS (EI): m/z (%) = 249 (72, [M^+]), 144 (100), 130 (14), 115 (10), 91 (10), 77 (10). Anal. Calcd for $C_{18}H_{19}N$ (249.36): C, 86.70; H, 7.68; N, 5.62. Found: C, 86.74; H, 7.71; N, 5.59.

3-(4-Bromobenzyl)-2-methyl-1H-indole (33f). Pale yellow solid, Yield= 69%, m.p.= 122-125°C. IR (neat): 3440, 2902, 1486, 1459, 1437, 1011, 747 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (br s, 1H) 7.39-7.34 (m, 3H), 7.29 (d, 1H, *J* = 8.1 Hz), 7.16-7.01 (m, 4H), 4.02 (s, 2H), 2.38 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 140.9, 135.5, 132.0, 131.5, 130.2, 128.9, 121.4, 119.6, 118.4, 110.5, 110.1, 29.8, 12.0. MS (EI): m/z (%) = 299 (49), 284 (20), 204 (12), 144 (100), 109 (14), 102 (17). Anal. Calcd for $C_{16}H_{14}BrN$ (300.2): C, 64.02; H, 4.70; N, 4.67. Found: C, 64.06; H, 4.73; N, 4.70.

2-((1H-Indol-3-yl)methyl)benzonitrile (33g). Pale yellow viscous oil, Yield= 96%. IR (neat): 3411, 3063, 2225, 1455, 732 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.10 (br s, 1H), 7.65 (d, 1H, *J* = 7.64 Hz), 4.35 (s, 2H), 7.55 (d, 1H, *J* = 8.0 Hz), 7.39-7.34 (m, 2H), 7.27 (t, 1H, *J* = 6.8), 7.22 (t, 1H, *J* = 8.2), 7.15-7.06 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.4, 136.6, 133.1, 130.0, 127.3, 126.8, 123.3, 122.5, 119.9, 119.1, 118.6, 113.4,

112.5, 111.6, 30.5. MS (EI): m/z (%) = 232 (100), 204 (10), 130 (75), 102 (10). Anal. Calcd for $C_{16}H_{12}N_2$ (232.29): C, 82.73; H, 5.21; N, 12.06. Found: C, 82.77; H, 5.24; N, 12.04.

3-(4-tert-Butylbenzyl)-2-methyl-1H-indole (33h). Pale yellow solid, Yield= 63%, mp= 136-138°C. IR (neat): 3395, 2956, 1463, 830, 744 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (br s, 1H), 7.44 (d, 1H, *J* = 7.7 Hz), 7.30-7.25 (m, 3H), 7.17 (d, 2H, *J* = 8.1 Hz), 7.12 (dt, 1H, *J* = 0.8, 7.3 Hz), 7.05 (dt, 1H, *J* = 0.8, 7.3 Hz), 4.05 (s, 2H), 2.40 (s, 3H), 1.30 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.6, 138.8, 135.5, 131.8, 129.2, 128.1, 125.4, 121.2, 119.4, 118.7, 111.0, 110.4, 34.5, 31.7, 29.8, 12.1. MS (EI): m/z (%) = 277 (100, [M^+]), 262 (57), 220 (14), 144 (71). Anal. Calcd for $C_{20}H_{23}N$ (277.41): C, 86.59; H, 8.36; N, 5.05. Found: C, 86.63; H, 8.39; N, 5.08.

7-Ethyl-3-hexyl-1H-indole (33i). Pale yellow oil, Yield= 48%. IR (neat): 3419, 2929, 1432, 1076, 744 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.86 (br s, 1H), 7.48 (d, 1H, *J* = 7.7 Hz), 7.12-7.01 (m, 2H), 6.98 (s, 1H), 2.86 (q, 2H, *J* = 7.7 Hz), 2.75 (t, 2H, *J* = 7.7 Hz), 1.77-1.66 (m, 2H), 1.46-1.28 (m, 9H), 0.90 (t, 3H, J 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 131.4, 127.6, 126.6, 120.8, 120.6, 119.6, 117.9, 117.0, 32.0, 30.4, 29.6, 25.5, 24.3, 23.0, 14.4, 14.1. MS (EI): m/z (%) = 229 (28, [M^+]), 158 (100), 143 (10). Anal. Calcd for $C_{16}H_{23}N$ (229.37): C, 83.79; H, 10.11; N, 6.11. Found: C, 83.76; H, 10.08; N, 6.08.

3-(4-Nitrobenzyl)-2-phenyl-1H-indole (33j). Yellow viscous oil, Yield= 48%. IR (neat): 3407, 3059, 1708, 1597, 1514, 1459, 1340, 732 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.24 (br s, 1H), 8.10 (d, 2H, *J* = 8.5 Hz), 7.50-7.33 (m, 9H), 7.24 (dt, 1H, *J* = 0.9, 8.1 Hz), 7.10 (dt, 1H, *J* = 0.9, 8.1 Hz), 4.36 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.7, 136.2, 132.7, 129.3, 129.2, 128.4, 128.1, 124.0, 123.0, 120.4, 119.3, 111.3, 109.6, 30.8. MS (EI): m/z (%) = 328 (100, [M^+]), 281 (10), 206 (83), 178 (8). Anal. Calcd for $C_{21}H_{16}N_2O_2$ (328.37): C, 76.81; H, 4.91; N, 8.53. Found: C, 76.85; H, 4.94; N, 8.56.

5.3 Spectroscopic data of fully substituted furans

3-(1-hydroxyethylidene)-1-phenyl-2-propylidenepentane-1,4-dione (49a). Clear oil. IR (neat): 1646, 1597, 733 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 15.77 (s, 1H), 7.73-7.69 (m, 2H), 7.59-7.54 (m, 1H), 7.50-7.44 (m, 2H), 6.65 (t, *J* = 7.5 Hz, 1H), 2.24 (qui, *J* = 7.5 Hz, 2H), 2.01 (s, 6H), 1.07 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 197.0, 191.3, 191.2, 153.2, 138.5, 136.5, 132.2, 129.6, 128.6, 107.9, 23.9, 23.8, 12.9. MS (EI): m/z (%) = 253 (13, [M^+]), 229 (100), 187 (14), 151 (26), 105 (56),77 (49), 43 (77). Anal. Calcd. for $C_{16}H_{18}O_3$ (253.32): C, 74.40; H, 7.02. Found: C, 74.44; H, 6.98.

(*E*)-1-(2-methyl-5-phenyl-4-(prop-1-en-1-yl)furan-3-yl)ethan-1-one (50a). Pale yellow oil, Yield= 74%. IR (neat): 2919, 1667, 950, 764, 693 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.66 (m, 2H), 7.40-7.35 (m, 2H), 7.29-7.25 (m, 1H), 6.46 (dq, *J* = 1.8, 15.9 Hz, 1H), 5.81 (dq, *J* = 6.6, 15.9Hz, 1H), 2.58 (s, 3H), 2.44 (s, 3H), 1.87 (dd, *J* = 1.8, 6.6 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.5, 156.8, 147.4, 132.4, 131.1, 128.6, 127.7, 126.4, 125.4, 121.8, 119.3, 31.4, 19.0, 14.7. MS (EI): m/z (%) = 240 (100, [M^+]), 225 (50), 197 (25), 183 (12), 155 (14), 153(13), 152 (12), 105 (19), 77 (26), 43 (47). Anal. Calcd. for $C_{16}H_{16}O_2$ (240.3): C, 79.97; H, 6.71. Found: C, 80.02; H, 6.75.

(*E*)-1-(2-ethyl-5-phenyl-4-(prop-1-en-1-yl)furan-3-yl)propan-1-one (50b). Yellow waxy solid, Yield= 70%. IR (neat): 2974, 2939, 1671, 927, 764, 689 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.65 (m, 2H), 7.41-7.35 (m, 2H), 7.29-7.24 (m, 1H), 6.46 (dq, *J* = 1.8, 15.9 Hz, 1H), 5.77 (dq, *J* = 6.6, 15.9 Hz, 1H), 2.91 (q, *J* = 7.5 Hz, 2H), 2.72 (q, *J* = 7.3 Hz, 2H), 1.87 (dd, *J* = 1.8, 6.6 Hz, 3H), 1.29, (t, *J* = 7.54 Hz, 3H), 1.14 (t, *J* = 7.31 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.4, 160.6, 147.3, 132.1, 131.2, 128.6, 127.6, 126.4, 125.4, 122.0, 119.0, 36.6, 21.8, 19.0, 12.7, 8.5. MS (EI): m/z (%) = 268 (76, [M^+]), 239 (100), 211(18), 155 (15), 105 (3), 77 (26), 57 (25), 29 (10). Anal. Calcd. for $C_{18}H_{20}O_2$ (268.36): C, 80.56; H, 7.51. Found: C, 7.55; H, 7.54.

(*E*)-1-(5-(4-methoxyphenyl)-2-methyl-4-(prop-1-en-1-yl)furan-3-yl)ethan-1-one (50c). Yellow oil, Yield= 78%. IR (neat): 2935, 2839, 1667, 1505, 1246, 1176, 1026, 831, 732 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.61-7.57 (m, 2H), 6.93-6.87 (m, 2H), 6.42 (dq, *J* = 1.8, 15.9 Hz, 1H), 5.78 (dq, *J* = 6.6, 15.9 Hz, 1H), 3.83 (s, 3H), 2.54 (s, 3H), 2.40 (s, 3H), 1.86 (dd, *J* = 1.8, 6.6 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.6, 159.2, 156.3, 147.6, 132.0, 127.9, 126.9, 123.8, 122.0, 117.9, 114.1, 55.5, 31.4, 19.0, 14.7. MS (EI): m/z (%) = 270 (100, [M^+]), 255(25), 227 (24), 213 (16), 185 (13), 135 (14), 43 (34). Anal. Calcd. for $C_{17}H_{18}O_3$ (270.33): C, 75.53; H, 6.71. Found: C, 75.48; H, 6.67.

(*E*)-1-(2-methyl-4-(prop-1-en-1-yl)-5-(thiophen-2-yl)furan-3-yl)ethan-1-one (50d). Orange oil, Yield= 44%. IR (neat): 2966, 2931, 1667, 1505, 1247, 950, 835 cm^{-1}. ^{1}H-NMR (400 Hz, $CDCl_3$): δ = 7.32 (dd, *J* = 1.2, 3.6 Hz, 1H), 7.23 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.03 (dd, *J* = 3.6, 5.1 Hz, 1H), 6.38 (dq, *J* = 1.8, 15.9 Hz, 1H), 5.94 (dq, *J* = 6.6, 15.9 Hz, 1H), 2.55 (s, 3H), 2.40 (s, 3H), 1.91 (dd, *J* = 1.7, 6.6 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.1, 156.9, 143.7, 133.7, 132.7, 127.3, 124.8, 124.4, 124.1, 121.3, 118.8, 31.4, 19.0, 14.8. MS (EI): m/z (%) = 248 (5, [M+2$^+$]), 246 (100, [M^+]), 231 (31), 203 (20), 189 (13), 161 (17), 111 (21), 43(39). Anal. Calcd. for $C_{14}H_{14}O_2S$ (246.32): C, 68.27; H, 5.73; S, 13.02. Found: C, 68.33; H, 5.69; S, 12.98.

(*E*)-(2-methyl-5-phenyl-4-(prop-1-en-1-yl)furan-3-yl)(phenyl)methanone (50e). Yellow oil, Yield= 77%. IR (neat): 3061, 2914, 2851, 1651, 1596, 1445, 1330, 906, 764, 693 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88-7.84 (m, 2H), 7.69-7.65 (m, 2H), 7.58-7.53 (m, 1H), 7.47-7.39 (m, 4H), 7.33-7.28 (m, 1H), 6.30 (dq, *J* = 1.7, 15.9 Hz, 1H), 5.61 (dq, *J* = 6.6, 15.9 Hz, 1H), 2.30 (s, 3H), 1.6 (dd, *J* = 1.7, 6.6 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.6, 154.6, 147.8, 138.7, 133.2, 131.4, 131.1, 129.9, 128.8, 128.7, 127.8, 126.6, 122.7, 120.4, 119.9, 19.0, 13.7. MS (EI): m/z (%) = 302 (100, [M^+]), 288 (18), 105 (61), 77 (45). Anal. Calcd. for $C_{21}H_{18}O_2$ (302.37): C, 83.42; H, 6.00. Found: C, 83.47; H, 6.04.

1-(5-(tert-butyl)-2-methyl-4-(prop-1-en-1-yl)furan-3-yl)ethan-1-one (50f) (*E:Z* = 65:35). Pale yellow oil, Yield= 37%. IR (neat): 2966, 2930, 1667, 1505, 1247, 1176, 1029, 950, 835, 633 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ

= 6.34-6.29 (m, 1H, (*E,Z*)), 5.81 (dq, *J* = 6.6, 11 Hz, (*Z*), 0.35H), 5.56 (dq, *J* = 6.6, 15.9 Hz, (*E*), 0.65H), 2.47 (s, (*Z*), 1.05H), 2.43 (s, (*E*), 1.95H), 2.31 (s, (*E*), 1.95H), 2.30 (s, (*Z*), 1.05H), 1.83 (dd, *J* = 1.8, 6.6 Hz, (*E*), 1.95H), 1.53 (dd, *J* = 1.8, 6.6 Hz, (*Z*), 1.05H), 1.28 (s, (*E*), 5.85H), 1.25 (s, (*Z*), 3.15H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 197.1, 196.6, 156.1, 155.7, 155.6, 154.5, 131.5, 130.3, 124.0, 123.7, 123.6, 123.0, 116.2, 113.2, 34.1, 33.9, 31.5, 30.1, 30.0, 29.4, 18.7, 14.8, 14.7, 14.4. MS (EI): m/z (%) = 220 (35, [M^+]), 205 (100), 163 (10), 145 (12), 43 (37). Anal. Calcd. for $C_{14}H_{20}O_2$ (220.31): C, 76.33; H,9.15. Found: C, 76.37; H, 9.18.

Ethyl (*E*)-2-ethyl-5-phenyl-4-(prop-1-en-1-yl)furan-3-carboxylate (50g). Yellow oil, Yield= 79%. IR (neat): 2978, 2938, 1707, 1211, 1097, 764, 693 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39-7.34 (m, 2H), 7.71-7.68 (m, 2H), 7.29-7.24 (m, 1H), 6.50 (dq, *J* = 1.8, 16.0 Hz, 1H), 5.94 (dq, *J* = 6.6, 16.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.00 (q, *J* = 7.5 Hz, 2H), 1.83 (dd, *J* = 1.8, 6.6 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.7, 163.1, 131.4, 130.9, 128.6, 127.7, 126.7, 125.4, 121.4, 119.9, 113.9, 60.3, 21.9, 19.1, 14.5, 12.6. MS (EI): m/z (%) = 284 (100, [M^+]), 269 (12), 255 (50), 239(16), 237 (35), 223 (11), 211 (11), 209 (10), 195 (11), 182 (13), 181 (12), 165 (10), 153 (11), 152 (12), 105 (34),77 (32). Anal. Calcd. for $C_{18}H_{20}O_3$ (284.35): C, 76.03; H, 7.09. Found: C, 75.98; H, 7.04.

Ethyl (*E*)-2,5-diphenyl-4-(prop-1-en-1-yl)furan-3-carboxylate (50h). Yellow oil, Yield= 82%. IR (neat): 2978, 2934, 2910, 1714, 1485, 1223, 1065, 764, 689 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.82-7.74 (m, 4H), 7.46-7.30 (m, 6H), 1.32 (t, *J* = 7.1 Hz, 3H), 6.51 (dq, *J* = 1.8, 16 Hz, 1H), 6.00 (dq, *J* = 6.6, 16 Hz, 1H), 4.34 (q, *J* = 7.1Hz, 2H), 1.88 (dd, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.5, 153.9, 148.8, 130.9, 130.2, 129.1, 128.8, 128.5, 128.3, 128.1, 127.7, 126.9, 125.7, 120.9, 115.8, 61.2, 19.2, 14.3. MS (EI): m/z (%) = 332 (100, [M^+]), 285(33), 269 (25), 215 (13), 105 (57), 77 (29). Anal. Calcd. for $C_{22}H_{20}O_3$ (332.40): C, 79.50; H, 6.07. Found: C, 79.47; H, 6.03.

Methyl (*E*)-2-methyl-5-phenyl-4-(3-phenylprop-1-en-1-yl)furan-3-carboxylate (50i). Yellow waxy solid, Yield= 88%. IR (neat) 3025, 2950,

2907, 2851, 1707, 1441, 1211, 1093, 966, 760, 693 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68-7.64 (m, 2H), 7.35-7.20 (m, 8H), 6.59 (dt, *J* = 1.6, 16 Hz, 1H), 6.07 (dt, *J* = 7.1, 16 Hz, 1H), 3.53 (dd, *J* = 1.4, 7.1 Hz, 2H), 3.81 (s, 3H), 2.61 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 156.2, 158.8, 148.0, 140.1, 134.2, 131.0, 128.7, 128.7, 128.6, 127.8, 126.8, 126.32, 121.6, 119.5, 114.6, 51.4, 40.0, 14.6. MS (EI): m/z (%) = 332 (100, [M^+]), 300 (100), 284 (40), 257 (22), 241 (19), 230 (29), 223 (44), 209 (19), 182 (9), 165 (10), 152(15), 115 (15), 105 (29), 91 (29), 77 (33), 43 (14). Anal. Calcd. for $C_{22}H_{20}O_3$ (332.40): C, 79.50; H, 6.07. Found: C, 79.54; H, 6.10.

1-(2-methyl-5-phenyl-4-vinylfuran-3-yl)ethan-1-one (50j). Clear oil, Yield= 42%. IR (neat) 2954, 2922, 1667, 1390, 1132, 1069, 950, 768, 693, 665 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.66 (m, 2H), 7.32-7.27 (m, 1H), 7.41-7.35 (m, 2H), 6.84 (dd, *J* = 11.2, 17.7 Hz, 1H), 5.44 (dd, *J* = 1.7, 17.7 Hz, 1H), 5.41 (dd, *J* = 1.7, 24.4 Hz, 1H), 2.57 (s, 3H), 2.44 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.7, 31.5, 119.5, 120.7, 124.2, 126.7, 128.0, 128.7, 128.8, 130.7, 148.0, 156.8, 196.3. MS (EI): m/z (%) = 226 (100, [M^+]), 225 (77), 211 (22), 183 (40), 165 (15), 155 (23), 141 (22), 115 (19), 105 (18), 77 (25), 43 (41). Anal. Calcd. for $C_{15}H_{14}O_2$ (226.27): C, 79.62; H, 6.24. Found: C, 79.67; H, 6.20.

1-(2-ethyl-5-phenyl-4-vinylfuran-3-yl)propan-1-one (50k). Yellow waxy solid, Yield= 45%. IR (neat): 2978, 2938, 1671, 926, 768, 693 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.65 (m, 2H), 7.41-7.36 (m, 2H), 7.32-7.27 (m, 1H), 6.83 (dd, *J* = 11.2, 17.7 Hz, 1H), 5.41 (dd, *J* = 1.7, 11.2Hz, 1H), 5.35 (dd, *J* = 1.7, 17.7 Hz, 1H), 2.91 (q, 2H, *J* = 7.5), 2.75 (q, 2H, *J* = 7.3Hz), 1.30 (t, 3H, *J* = 7.5 Hz), 1.14 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.3, 160.5, 147.9, 130.9, 128.7, 128.7, 127.9, 126.7, 123.1, 120.3, 119.2, 36.7, 21.7, 12.8, 8.5. MS (EI): m/z (%) = 254 (100, [M^+]), 253 (40), 235 (20), 225 (68), 197 (23), 141 (27), 115 (13), 105 (50), 77 (29), 57 (23), 29 (10). Anal. Calcd. for $C_{17}H_{18}O_2$ (254.33): C, 80.28; H, 7.13. Found: C, 80.24; H, 7.10.

(*E*)-4-(hex-1-en-1-yl)-2,5-diphenylfuran-3-carbonitrile (50l). Pale yellow waxy solid, Yield= 37%. IR (neat): 2954, 2926, 2859, 2225, 1489, 962, 764, 685 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.09-8.05 (m, 2H), 7.70-7.66 (m,

2H), 7.53-7.37 (m, 6H), 6.63 (dt, *J* = 6.9, 16.1 Hz, 1H), 6.43 (dt, *J* = 1.5, 16.1 Hz, 1H), 2.32-2.25 (m, 2H), 1.56-1.37 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.0, 149.0, 136.8, 130.3, 129.8, 129.3, 129.0, 128.8, 128.3, 127.0, 125.8, 121.0, 117.9, 115.9, 93.0, 33.6, 31.4, 22.5, 14.2. MS (EI): m/z (%) = 327 (100, [M^+]), 284 (34), 250 (29), 206 (10), 105 (48), 77 (33). Anal. Calcd. For $C_{23}H_{21}NO$ (327.43): C, 84.37; H, 6.46; N, 4.28. Found: C, 84.41; H, 6.42; N, 4.31.

(*E*)-2,5-diphenyl-4-(3-phenylprop-1-en-1-yl)furan-3-carbonitrile (50m). Yellow waxy solid, Yield= 38%. IR (neat): 3058, 3023, 2924, 2231, 1491, 766, 691, 671 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.09-8.04 (m, 2H), 7.62 (m, 2H), 7.54-7.17 (m, 11H), 6.82 (dt, *J* = 6.7, 16.1 Hz, 1H), 6.46 (dt, *J* = 1.6, 16.1 Hz, 1H), 3.63 (dd, *J* = 1.2, 6.7 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.2, 149.5, 139.5, 134.5, 130.4, 129.6, 129.3, 129.0, 128.9 (2C), 128.8, 128.2, 127.0, 126.6, 125.8, 120.6, 119.5, 115.8, 92.8, 39.9. MS (EI): m/z (%) = 361 (100, [M^+]), 360 (89), 270 (14), 269 (13), 105 (29), 77 (26). Anal. Calcd. for $C_{26}H_{19}NO$ (361.44): C, 86.40; H, 5.30; N, 3.88. Found: C, 86.45; H, 5.33; N, 3.84.

(*E*)-3-(hex-1-en-1-yl)-5-methyl-2-phenyl-4-(phenylsulfonyl)furan (50n). Yellow oil, Yield= 38%. IR (neat): 2958, 2926, 1445, 2859, 1318, 1160, 685, 605, 558 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.94-7.86 (m, 2H), 7.66-7.62 (m, 2H), 7.59-7.24 (m, 6H), 6.29 (dt, *J* = 1.6, 16.1 Hz, 1H), 5.78 (dt, *J* = 7.7, 16.1 Hz, 1H), 2.73 (s, 3H), 2.12-2.06 (m, 2H), 1.37-1.23 (m, 4H), 0.9 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): δ = 156.9, 148.2, 142.9, 138.7, 133.2, 130.3, 129.1, 128.6, 128.2, 128.0, 127.3, 126.7, 122.8, 118.1, 33.2, 31.1, 22.5, 14.2, 14.0. MS (EI): m/z (%) = 382 (7, [M+2$^+$]), 380 (100, [M^+]), 232 (31), 311 (69), 196 (36), 182 (53),153 (25), 125 (15), 105 (73), 77 (75), 43 (29). Anal. Calcd. for $C_{23}H_{24}O_3S$ (380.50): C, 72.60; H, 6.36; S,8.43. Found: C, 72.65; H, 6.39; S, 8.39.

5.4 Spectroscopic data for β-nitro-β,γ-unsaturated ketones and disubstituted pyrroles

3-Nitro-1-Phenylpent-3-en-1-one (51a). Yellow dark oil, Yield= 76%, *E/Z*= 90:10. IR (neat): 1682, 1516, 1447, 1331, 1213, 755, 685 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04-7.94 (m, 2H), 7.65-7.45 (m, 3.9H), 6.19 (q, 0.10H, *J* = 7.3 Hz), 4.30 (s, 1.8H), 4.22 (s, 0.2H), 2.20 (d, 0.3H, *J* = 7.4 Hz), 1.91 (d, 2.7H, *J* = 7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 193.7, 14.2, 15.3(Z), 146.6, 136.1, 135.9, 135.0(Z), 134.1, 129.1, 129.0(Z), 128.5, 128.4(Z), 42.7(Z), 36.2. MS (EI): m/z (%) = 105 (100), 77 (35), 51 (8). Anal. Calcd. For $C_{11}H_{11}NO_3$ (205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.32; H, 5.37; N, 6.80.

3-Nitro-1-Phenylhex-3-en-1-one (51b). Yellow dark oil, Yield= 64%, *E:Z*= 95:5. IR (neat): 1685, 1521, 1446, 1333, 1211, 751, 686 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.03-7.93 (m, 2H), 7.65-7.57 (m, 1H), 7.53-7.41 (m, 2.95H), 6.04 (t, 0.05H, *J* = 7.4 Hz), 4.29 (s, 1.9H), 4.21 (s, 0.1H), 2.73-2.63 (m, 0.1H), 2.29-2.19 (m, 1.9H), 1.15 (t, 2.85H, *J* = 7.5 Hz), 1.13 (t, 0.15H, *J* = 7.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 193.8, 145.3, 142.0(Z), 141.8, 136.1, 134.0, 129.1, 128.5, 128.4 (Z), 42.7(Z), 36.4, 22.6(Z), 22.2, 13.6, 13.1(Z). MS (EI): m/z (%) = 105 (100), 77 (33), 51 (6). Anal. Calcd. For $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.79; H, 6.02; N, 6.36.

3-Nitro-1-Phenyloct-3-en-1-one (51c). Yellow dark oil, Yield= 66%, *E:Z*= 95:5. IR (neat): 1690, 1519, 1448, 1331, 1213, 756, 688 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06-7.92 (m, 2H), 7.66-7.59 (m, 1H), 7.55-7.44 (m, 2.95H), 6.06 (t, 0.05H, *J* = 7.3 Hz), 4.29 (s, 1.9H), 4.22 (s, 0.1H), 2.68 (q, 0.1H, *J* = 7.4 Hz), 2.23 (q, 1.9H, *J* = 7.4 Hz), 1.58-1.47 (m, 2H), 1.44-1.31 (m, 2H), 1.07 (t, 0.15H, *J* = 7.4 Hz), 0.92 (t, 2.85H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 193.7, 145.6, 140.8, 136.1, 134.0, 129.1, 128.5, 42.7(Z), 36.5, 30.6, 28.4, 22.6, 14.0. MS (EI): m/z (%) = 105 (100), 77 (24), 51 (3). Anal. Calcd. For $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 68.05; H, 6.96; N, 5.63.

1-(4-Methoxyphenyl)-3-Nitropent-3-en-1-one (51d). Pale yellow solid, Yield= 69%, m.p.= 98–100 °C, *E:Z*= 90:10. IR (neat): 3066, 1670, 1515, 1429, 1337, 1260, 1176, 1020, 826, 610 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, 2H, *J* = 9.0 Hz), 7.54 (q, 0.9H, *J* = 7.4 Hz), 6.97 (d, 2H, *J* = 9.0 Hz), 6.17 (q, 0.1H, *J* = 7.4 Hz), 4.25 (s, 1.8H), 4.17 (s, 0.2H), 3.89 (s, 2.7H), 3.88 (s, 0.3H), 2.19 (d, 0.3H, *J* = 7.4 Hz), 1.92 (d, 2.7H, *J* = 7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 192.1, 164.3, 146.9, 135.7, 134.6(Z), 130.9, 130.8(Z), 129.2, 114.2, 55.8, 42.3(Z), 35.8, 15.3(Z), 14.2. MS (EI): m/z (%) = 135 (100), 107 (5), 92 (7), 77 (10), 64 (3). Anal. Calcd. For $C_{12}H_{13}NO_4$ (235.24): C, 61.27; H, 5.57; N, 5.95. Found: C, 61.22; H, 5.60; N, 5.91.

(*E*)-8-(4-Methoxyphenyl)-6-Nitro-8-Oxooct-5-Enenitrile (51e). Yellow oil, Yield= 55%. IR (neat): 2247, 1676, 1598, 1519, 1332, 1169, 833. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, 2H, *J* = 8.9 Hz), 7.35 (t, 1H, *J* = 8.0 Hz), 6.97 (d, 2H, *J* = 8.9 Hz), 4.28 (s, 2H), 3.88 (s, 3H), 2.46-2.37 (m, 4H), 1.96-1.87 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 192.1, 164.4, 147.6, 137.1, 131.0, 128.9, 119.1, 114.3, 55.8, 36.1, 27.2, 24.2, 16.9. MS (EI): m/z (%) = 241 (43), 187 (100), 173 (45), 135 (64), 77 (26). Anal. Calcd. For $C_{15}H_{16}N_2O_4$ (288.30): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.54; H, 5.63; N, 9.75.

3-Nitro-1-(p-Tolyl)nona-3,8-Dien-1-One (51f). Yellow oil, Yield= 45%, *E:Z*= 95:5. IR (neat): 3033, 1686, 1604, 1519, 1332, 1181, 811, 574 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.92-7.84 (m, 2H), 7.45 (t, 0.95H, *J* = 8.0 Hz), 7.34-7.26 (m, 2H), 6.04 (t, 0.05H, *J* = 7.3 Hz), 5.82-5.68 (m, 1H), 5.06-4.95 (m, 2H), 4.25 (s, 1.9H), 4.19 (s, 0.1H), 2.68 (1, 0.1H, *J* = 7.4 Hz), 2.44 (s, 2.85H), 2.42 (s, 0.15H), 2.23 (q, 1.9H, *J* = 7.4 Hz), 2.15-2.07 (m, 2H), 1.70-1.59 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 194.2(Z), 193.3, 146.0, 145.0, 140.1, 140.0, 137.7, 133.6, 129.7, 128.9(Z), 128.7, 115.9, 115.6(Z), 42.6(Z), 36.4, 33.5(Z), 33.3, 28.6(Z), 28.3(Z), 27.9, 27.6, 22.0. MS (EI): m/z (%) = 119 (100), 91 (20), 65 (5). Anal. Calcd. For $C_{16}H_{19}NO_3$ (273.14): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.26; H, 6.97; N, 5.11.

3-Nitro-6-Phenyl-1-(p-Tolyl)Hex-3-en-1-one (51g). Dark red oil, Yield= 54%, *E:Z*= 97:3. IR (neat): 3028, 1685, 1605, 1520, 1453, 1333, 1181, 811, , 700, 570 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88-7.76 (m, 2H), 7.47 (t, 0.97H, *J* = 8.0 Hz), 7.35-7.13 (m, 7H), 6.05 (t, 0.03H, *J* = 7.1 Hz), 4.17 (s,

0.06H), 4.13 (s, 1.94H), 3.01 (q, 0.06H, *J* = 7.5 Hz), 2.89-2.81 (m, 2H), 2.54 (q, 1.94H, *J* = 7.6 Hz), 2.43 (s, 2.91H), 2.42 (s, 0.09H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 194.1(Z), 193.3, 146.5, 145.0, 140.1, 139.0, 133.6, 129.7, 128.9, 128.6, 126.8, 126.6(Z), 42.6 (Z), 36.3, 34.9(Z), 34.5, 30.6, 22.0. MS (EI): m/z (%) = 262 (10), 171 (93), 158 (30), 128 (27), 119 (100), 91 (40), 65 (14). Anal. Calcd. For $C_{19}H_{19}NO_3$ (309.37): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.82; H, 6.23; N, 4.50.

2,2-Dimethyl-5-Nitrohept-5-en-3-One (51h). Yellow oil, Yield= 55%, *E:Z*=80:20. IR (neat): 1711, 1518, 1478, 1336, 1066 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (q, 0.8H, *J* = 7.4 Hz), 6.06 (q, 0.2H, *J* = 7.4 Hz), 3.79 (s, 1.6H), 3.71 (s, 0.4H), 2.14 (d, 0.6H, *J* = 7.4 Hz), 1.84 (d, 2.4H, *J* = 7.4 Hz), 1.24 (s, 7.2H), 1.19 (s, 1.8H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 210.5(Z), 209.4, 147.0, 145.9(Z), 135.4, 134.7(Z), 44.7, 44.4(Z), 41.1(Z), 34.5, 26.6, 26.5(Z), 15.2 (Z), 14.0. MS (EI): m/z (%) = 85 (14), 57 (100), 41 (21). Anal. Calcd. For $C_9H_{15}NO_3$ (185.22): C, 58.36; H, 8.16; N, 7.56. Found: C, 58.42; H, 8.20; N, 7.52.

4-Nitrohex-4-en-2-one (51i). Yellow oil, Yield= 71%, *E:Z*= 95:5. IR (neat): 1715, 1524, 1481, 1332, 1063 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.41 (q, 0.95H, *J* = 7.3 Hz), 6.11 (q, 0.05H, *J* = 7.3 Hz), 3.68 (s, 1.9H), 2.98 (s, 0.1H), 2.26 (s, 2.85H), 2.21 (s, 0.15H), 2.13 (d, 0.15H, *J* = 7.5 Hz), 1.86 (d, 2.85H, *J* = 7.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.2, 146.5, 135.7, 47.0(Z), 40.6, 30.0, 15.2 (Z),14.1. MS (EI): m/z (%) = 53 (8), 43 (100), 39 (9). Anal. Calcd. For $C6H_9NO_3$ (143.14): C, 50.35; H, 6.34; N, 9.79. Found: C, 50.39; H, 6.31; N, 9.83.

3-Nitro-1-(Thiophen-2-yl)Pent-3-en-1-one (51j). Pink solid, Yield= 75%, m.p.= 99–102 °C, *E:Z*= 90:10. IR (neat): 3049, 1657, 1511, 1417, 1329, 1221, 1063, 733, 588 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, 0.9H, *J* = 3.8, 1.1 Hz), 7.78 (dd, 0.1H, *J*= 3.8, 1.2 Hz), 7.65-7.19 (m, 1H), 7.53 (q, 0.9H, *J* = 7.4 Hz), 7.20-7.12 (m, 1H), 6.23 (q, 0.1H, *J* = 7.3 Hz), 4.23 (s, 1.8H), 4.13 (s, 0.2H), 2.18 (d, 0.3H, *J* = 7.4 Hz), 1.93 (d, 2.7H, *J* = 7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 187.4(Z), 186.5, 146.1, 142.9, 136.4, 135.6(Z), 134.9, 133.0, 132.9(Z), 128.6, 43.1(Z), 36.7, 15.3(Z), 14.3. MS (EI): m/z (%) = 111 (100), 83 (8), 39 (12). Anal. Calcd. For $C_9H_9NO_3S$

(211.24): C, 51.17; H, 4.29; N, 6.63; S, 15.18. Found: C, 51.11; H, 4.26; N, 6.59; S, 15.22.

1-(Naphthalen-2-yl)-3-Nitrohept-3-en-1-one (51k). Waxy yellow solid, Yield= 76%, *E:Z*= 90:10 IR (neat): 3060, 1683, 1627, 1517, 1468, 1331, 1185, 1123, 858, 821, 746. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.54 (d, 0.9H, *J* = 1.6 Hz), 8.48 (d, 0.1H, *J* = 1.6 Hz), 8.05-7.84 (m, 4H), 7.66-7.53 (m, 2H), 7.50 (t, 0.9H, *J* = 7.9 Hz), 6.09 (t, 0.1H, *J* = 7.2 Hz), 4.43 (s, 1.8H), 4.35 (s, 0.2H), 2.67 (q, 0.2H, *J* = 7.4 Hz), 2.24 (q, 1.8H, *J* = 7.5 Hz), 0.99 (t, 0.3H, *J* = 7.4 Hz), 1.65-1.53 (m, 2H), 0.98 (t, 2.7H, *J* = 7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 194.7(Z), 193.7, 145.9, 140.6(Z), 140.5, 133.5, 133.4(Z), 132.7, 130.4, 130.3(Z), 129.9, 129.1, 129.0, 128.1, 127.3, 127.2(Z), 124.0, 123.9(Z), 42.8(Z), 36.6, 31.2(Z), 30.7, 22.4(Z), 21.9, 14.1, 14.0(Z). MS (EI): m/z (%) = 236 (39), 207 (100), 179 (18), 155 (13), 127 (35). Anal. Calcd. For $C_{17}H_{17}NO_3$ (288.33): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.12; H, 6.01; N, 4.90.

2-Methyl-1-Pentyl-5-Phenyl-1H-Pyrrole (53a). Clear oil, Yield= 72%. IR (neat): 1602, 1401, 1311, 747, 699 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.44-7.22 (m, 5H), 6.12-6.06 (m, 1H), 5.99-5.92 (m, 1H), 3.92-3.79 (m, 2H), 2.32 (s, 3H), 1.65-1.48 (m, 2H), 1.33-1.05 (m, 4H), 0.85-0.76 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 134.7, 134.1, 129.9, 129.2, 128.5, 126.8, 107.9, 106.9, 44.4, 31.0, 29.0, 22.4, 14.1, 13.0. MS (EI): m/z (%) = 227 ([M^+], 65), 170 (100), 156 (22), 128 (10). Anal. Calcd. For $C_{16}H_{21}N$ (227.35): C, 84.53; H, 9.31; N, 6.16. Found: C, 84.59; H, 9.35; N, 6.19.

1-Benzyl-2-Ethyl-5-Phenyl-1H-Pyrrole (53b). Clear oil, Yield= 68%. IR (neat): 1602, 1452, 1304, 749, 728, 697 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34-7.20 (m, 8H), 6.95-6.90– (m, 2H), 6.29 (d, 1H, *J* = 3.5 Hz), 6.10 (dt, 1H, *J* = 1.0, 3.5 Hz), 5.16 (s, 2H), 2.46 (dq, 2H, *J* = 1.0, 7.4 Hz), 1.24 (t, 3H, *J* =7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.3, 136.9, 134.9, 134.0, 129.0, 128.9, 128.6, 127.2, 126.9, 125.8, 108.2, 105.3, 47.7, 20.1, 12.7. MS (EI): m/z (%) = 261 ([M^+], 100), 246 (78), 170 (77), 91 (80). Anal. Calcd. For $C_{19}H_{19}N$ (261.37): C, 87.31; H, 7.33; N, 5.36. Found: C, 87.36; H, 7.37; N, 5.33.

2-(4-Methoxyphenyl)-5-Methyl-1-(Prop-2-yn-1-yl)-1HPyrrole

(53c). White solid, Yield= 67%, m.p.= 102–104 °C. IR (neat): 3243, 2116, 1525, 1442, 1307, 1249, 770, 665, 544 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, 2H, *J* = 8.4 Hz), 6.97 (d, 2H, *J* = 8.4 HZ), 6.09 (d, 1H, *J* = 3.4 Hz), 5.98 (d, 1H, *J* = 3.4 Hz), 4.53 (d, 2H, *J* = 2.4 Hz), 3.85 (s, 3H), 2.40 (s, 3H), 2.37 (t, 1H, *J* = 2.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.0, 133.9, 130.3, 129.9, 126.2, 114.2, 107.5, 107.2, 79.8, 72.7, 55.6, 34.3, 12.7. MS (EI): m/z (%) = 225 ([M^+], 100), 210 (15), 186 (76), 143 (15). Anal. Calcd. For $C_{19}H_{19}N$ (225.29): C, 79.97; H, 6.71; N, 6.22. Found: C, 80.02; H, 6.67; N, 6.25.

2-Methyl-1-Pentyl-5-(Thiophen-2-yl)-1H-Pyrrole (53d). Clear oil, Yield= 71%. IR (neat): 1531, 1406, 842, 752, 689 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.27-7.23 (m, 1H), 7.07-7.03 (m, 1H), 6.99-6.96 (m, 1H), 6.21 (s, 1H), 5.92 (s, 1H), 3.94-3.87 (m, 2H), 2.30 (s, 3H), 1.71-1.55 (m, 2H), 1.37-1.16 (m, 4H), 0.87 (t, 3H, *J* = 7.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 136.0, 130.6, 127.4, 125.8, 125.3, 124.7, 109.6, 107.0, 44.6, 31.2, 29.1, 22.5, 14.2, 12.9. MS (EI): m/z (%) = 233 ([M^+], 100), 176 (70), 162 (46). Anal. Calcd. For $C_{14}H_{19}NS$ (233.37): C, 72.05; H, 8.21; N, 6.00; S, 13.74. Found: C, 72.10; H, 8.25; N, 6.04; S, 13.71.

1-Cyclopropyl-2-(4-Methoxyphenyl)-5-Methyl-1H-Pyrrole (53e). Clear oil, Yield= 65%. IR (neat): 1611, 1523, 1482, 1242, 1030, 833, 755, 579 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, 2H, *J* = 8.9 Hz), 6.92 (d, 2H, *J* = 8.9 Hz), 6.04 (br s, 1H), 5.91 (br s, 1H), 3.86 (s, 3H), 2.39 (s, 3H), 1.30-1.24 (m, 1H), 0.96-0.85 (m, 2H), 0.66-0.55 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.3, 134.7, 132.3, 129.8, 127.4, 113.6, 106.9, 106.4, 55.5, 26.9, 13.7, 9.6. MS (EI): m/z (%) = 227 ([M^+], 100), 212 (64), 186 (19), 143 (8). Anal. Calcd. For $C_{15}H_{17}NO$ (227.31): C, 79.26; H, 7.54; N, 6.16; S. Found: C, 79.30; H, 7.58; N, 6.19.

1-Allyl-2-(Tert-Butyl)-5-Methyl-1H-Pyrrole (53f). Pale yellow oil, Yield= 38%. IR (neat): 1645, 1467, 1401, 1304, 923, 750. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.95-5.77 (m, 3H), 5.16-5.14 (m, 1H), 4.77-4.66 (m, 1H), 4.63-4.58 (m, 2H), 2.15 (s, 3H), 1.33 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 140.9, 135.3, 130.1, 115.9, 105.1, 103.5, 47.6, 32.2, 31.2, 12.7. MS (EI): m/z (%) = 177 ([M^+], 38), 162 (100), 147 (13), 121 (17). Anal. Calcd. For

$C_{12}H_{19}N$ (177.29): C, 81.30; H, 10.80; N, 7.90. Found: C, 81.25; H, 10.76; N, 7.87.

5.5 Spectroscopic data of thiophenes-2-carboxylates

Ethyl 5-methylthiophene-2-carboxylate (61a). Pale yellow oil, Yield= 84%. IR (neat): 1708, 1540, 1464, 1256, 1089, 815, 749 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, 1H, *J* = 3.8 Hz), 6.76-6.73 (m, 1H), 4.31 (q, 2H, *J* = 7.3 Hz), 2.51 (s, 3H), 1.35 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.5, 148.0, 133.9, 131.6, 126.5, 61.1, 16.0, 14.6. MS (EI): m/z (%) = 170 ([M^+], 29), 142 (19), 125 (100), 97 (16), 53 (15). Anal. Calcd. for $C_8H_{10}O_2S$ (170.23): C, 56.45; H, 5.92; S, 18.83. Found: C, 56.41; H, 5.89; S, 18.87.

Ethyl thiophene-2-carboxylate (61b). Pale yellow oil, Yield= 86%. IR (neat): 1703, 1526, 1420, 1258, 1091, 750, 718 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.81-7.79 (m, 1H), 7.55-7.53 (m, 1H), 7.11-7.08 (m, 1H), 4.35 (q, 2H, *J* = 6.8 Hz), 1.37 (t, 3H, *J* = 6.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.5, 134.3, 133.5, 132.4, 127.9, 61.4, 14.6. MS (EI): m/z (%) = 156 ([M^+], 19), 128 (25), 111 (100), 83 (7), 57 (5), 39 (15). Anal. Calcd. for $C_7H_8O_2S$ (156.20): C, 53.83; H, 5.16; S, 20.53. Found: C, 53.88; H, 5.19; S, 20.56.

Ethyl 5-ethylthiophene-2-carboxylate (61c). Pale yellow oil, Yield= 88%. IR (neat): 1705, 1464, 1454, 1278, 1246, 1088,749 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, 1H, J=3.8 Hz), 6.76–6.79 (m, 1H), 4.31 (q, 2H, *J*= 7.3 Hz), 2.86 (q, 2H, *J*= 7.3 Hz), 1.35 (t, 3H, *J*= 6.8 Hz), 1.31 (t, 3H, *J*= 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.6, 155.6, 133.7, 131.2, 124.7, 61.1, 24.1, 15.9, 14.6. MS (EI): m/z (%) = 184 ([M^+], 47), 169 (37), 156 (12), 141 (48), 139 (100), 111 (12), 97 (10), 77 (9). Anal. Calcd. for $C_9H_{12}O_2S$ (184.25): C, 58.67; H, 6.56; S, 17.40. Found: C, 58.63; H, 6.52; S, 17.36.

Ethyl 5-(4-chlorophenyl)thiophene-2-carboxylate (61d). White solid, Yield= 48%, m.p.= 75-77 °C. IR (neat): 1682, 1448, 1290, 1091, 812, 749 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, 1H, *J* = 3.8 Hz), 7.55 (d, 2H, *J* = 8.5 Hz), 7.37 (d, 2H, *J* = 8.5 Hz), 7.25 (d, 1H, *J* = 3.8 Hz), 4.36 (q, 2H, *J* =

6.8 Hz), 1.39 (t, 3H, *J* = 6.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.4, 149.8, 134.8, 134.5, 133.2, 132.2, 129.5, 127.6, 124.1, 61.5, 14.6. MS (EI): m/z (%) = 266 ([M^+], 81), 237 (48), 220 (100), 193 (22), 149 (51), 114 (10), 79 (8). Anal. Calcd. for $C_{13}H_{11}ClO_2S$ (266.74): C, 58.54; H, 4.16; S, 12.02. Found: C, 58.58; H, 4.12; S, 11.99.

Ethyl 5-([1,1'-biphenyl]-4-yl)thiophene-2-carboxylate (61e). White solid, Yield= 55%, m.p.= 136–138 °C. IR (neat): 1702, 1268, 1098, 904, 727, 650 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, 1H, *J* = 3.8 Hz), 7.74-7.70 (m, 2H), 7.66-7.60 (m, 4H), 7.49-7.43 (m, 2H), 7.40-7.35 (m, 1H), 7.33 (d, 1H, *J* = 3.8 Hz), 4.38 (q, 2H, *J* = 7.3 Hz), 1.40 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.5, 150.9, 141.8, 140.4, 134.5, 132.7, 132.6, 129.1, 128.0, 127.9, 127.2, 126.8, 123.8, 61.4, 14.6. MS (EI): m/z (%) = 308 ([M^+], 100), 280 (46), 263 (47), 236 (17), 191 (48), 131 (13), 95 (12). Anal. Calcd. for $C_{19}H_{16}O_2S$ (308.39): C, 74.00; H, 5.23; S, 10.40. Found: C, 74.04; H, 5.20; S, 10.37.

Methyl 5-phenethylthiophene-2-carboxylate (61f). White solid, Yield= 80%, m.p.= 50–52 °C. IR (neat): 3033, 3009, 1703, 1461, 1254, 1091, 824, 740 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, 1H, *J* = 3.8 Hz), 6.75 (d, 1H, *J* = 3.8 Hz), 7.33-7.15 (m, 5H), 3.86 (s, 3H), 3.18-3.12 (m, 2H), 3.03-2.97 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.0, 152.7, 140.6, 133.9, 131.1, 128.7, 128.6, 126.6, 125.8, 52.2, 37.8, 32.5. MS (EI): m/z (%) = 246 ([M^+], 31), 155 (100), 126 (10), 91 (47), 65 (48). Anal. Calcd. for $C_{14}H_{14}O_2S$ (246.32): C, 68.27; H, 5.73; S, 13.02. Found: C, 68.32; H, 5.77; S, 12.98.

Benzyl 5-methylthiophene-2-carboxylate (61g). Pale yellow oil, Yield= 63%. IR (neat): 1691, 1451, 1371, 1268, 1076, 1035, 814, 744, cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, 1H, *J* = 3.8 Hz), 7.46-7.30 (m, 5H), 6.76 (d, 1H, *J* = 3.8 Hz), 5.32 (s, 2H), 2.52 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.3, 148.5, 136.2, 134.4, 131.1, 128.8, 128.4, 128.3, 126.6, 66.7, 16.0. MS (EI): m/z (%) = 232 ([M^+], 45), 187 (11), 125 (100), 91 (48). Anal. Calcd. for $C_{13}H_{12}O_2S$ (232.30): C, 67.22; H, 5.21; S, 13.80. Found: C, 67.17; H, 5.18; S, 13.76.

Butyl thiophene-2-carboxylate (61h). Pale yellow oil, Yield= 78%. IR (neat): 1705, 1526, 1419, 1257, 1092, 750, cm^{-1}. ^{1}H-NMR (400 MHz,

$CDCl_3$): δ = 7.80-7.78 (m, 1H), 7.55-7.53 (m, 1H), 7.11-7.08 (m, 1H), 4.30 (t, 2H, *J* = 6.8 Hz), 1.77-1.65 (m, 2H), 1.41-1.40 (m, 2H), 0.97 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.6, 134.3, 133.5, 132.4, 127.9, 65.2, 31.0, 19.4, 14.0. MS (EI): m/z (%) = 184 ([M^+], 9), 128 (60), 111 (100), 83 (8), 56 (8), 39 (19). Anal. Calcd. for $C_9H_{12}O_2S$ (184.25): C, 58.67; H, 6.56; S, 17.40. Found: C, 58.62; H, 6.60; S, 17.37.

Butyl 5-ethylthiophene-2-carboxylate (61i). Pale yellow oil, Yield= 75%. IR (neat): 1705, 1526, 1449, 1278, 1253, 1089, 750 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, 1H, *J* = 3.8 Hz), 6.79-6.77 (m, 1H), 4.26 (t, 2H, *J* = 6.8 Hz), 2.86 (q, 2H, *J* = 7.3 Hz), 1.75-1.67 (m, 2H), 1.50-1.39 (m, 2H), 1.32 (t, 3H, *J* = 7.3 Hz), 0.96 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.7, 155.6, 133.7, 131.2, 124.7, 65.0, 31.0, 24.1, 19.4, 15.9, 14.0. MS (EI): m/z (%) = 212 ([M^+], 20), 156 (78), 141 (100), 139 (90), 124 (7), 111 (14). Anal. Calcd. for $C_{11}H_{16}O_2S$ (212.31): C, 62.23; H, 7.60; S, 15.10. Found: C, 62.27; H, 7.57; S, 15.13.

Propyl 5-heptylthiophene-2-carboxylate (61j). Pale yellow oil, Yield= 38%. IR (neat): 1708, 1461, 1281, 1258, 1086, 748, 733 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, 1H, *J* = 3.8 Hz), 6.77 (d, 1H, *J* = 3.8 Hz), 4.22 (t, 2H, *J* = 6.8 Hz), 2.82 (t, 2H, *J* = 7.7 Hz), 1.81-1.62 (m, 4H), 1.41-1.21 (m, 8H), 1.00 (t, 3H, *J* = 7.3 Hz), 0.88 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.7, 154.2, 133.7, 131.2, 125.3, 66.7, 32.0, 31.7, 30.7, 29.2, 22.9, 22.4, 14.3, 10.7. MS (EI): m/z (%) = 268 ([M^+], 45), 209 (64), 183 (96), 141 (100), 97 (51), 43 (25). Anal. Calcd. for $C_{15}H_{24}O_2S$ (268.41): C, 67.12; H, 9.01; S, 11.94. Found: C, 67.17; H, 9.05; S, 11.91.

Propyl 5-(p-tolyl)thiophene-2-carboxylate (61k). White solid, Yield= 60%, m.p.= 54–56 °C. IR (neat): 1701, 1539, 1447, 1344, 1263, 1234, 1086, 806, 747 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, 1H, *J* = 3.8 Hz), 7.53 (d, 2H, *J* = 8.1 Hz), 7.25 (d, 1H, *J* = 3.8 Hz), 7.21 (d, 2H, *J*= 8.1 Hz), 4.26 (t, 2H, *J* = 6.8 Hz), 2.38 (s, 3H), 1.85-1.72 (m, 2H), 1.03 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.6, 151.6, 139.1, 134.4, 132.2, 131.0, 130.0, 126.3, 123.3, 66.9, 22.4, 21.5, 10.7. MS (EI): m/z (%) = 260 ([M^+], 71), 218 (100), 201 (67), 173 (18), 129 (40). Anal. Calcd. for $C_{15}H_{16}O_2S$ (260.35): C, 69.20; H, 6.19; S, 12.31. Found: C, 69.25; H, 6.22; S, 12.34.

5.6 Spectroscopic data for (2-acetoxy)allyl nitro compounds and intermediates

3-Nitro-1-(phenylselanyl)hexan-2-ol (64a). Yellow oil, Yield= 63%, *dr*= (65:35). IR (neat): 3469, 1546, 1374, 737, 691 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57-7.50 (m, 2H), 7.33-7.26 (m, 3H), 4.66-4.56 (m, 1H), 4.04-3.96 (m, 1H), 3.12 (dd, 0.65H, *J* = 4.3, 13.3 Hz), 3.07 (dd, 0.35H, *J* = 4.3, 13.3 Hz), 3.00-2.92 (m, 1H), 2.78 (br s, 1H), 2.10-1.88 (m, 1H), 1.83-1.72 (m, 0.35H), 1.66-1.53 (m, 0.65H), 1.42-1.18 (m, 2H), 0.94-0.86 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 133.8, 133.6, 129.8, 129.7, 128.3, 128.2, 91.5, 91.1, 71.1, 70.9, 32.8, 32.4, 32.3, 31.2, 19.4, 19.2, 13.6, 13.5. Anal. Calcd for $C_{12}H_{17}NO_3Se$ (302.23): C, 47.69; H, 5.67; N, 4.63. Found: C, 47.58; H, 5.64; N, 4.65.

3-Nitro-1-(phenylselanyl)octan-2-ol (64b). Yellow oil, Yield= 65%, dr= 60:40. IR (neat): 3503, 1543, 1438, 1367, 736, 691 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57-7.49 (m, 2H), 7.35-7.27 (m, 3H), 4.63-4.56 (m, 1H), 4.05-3.95 (m, 1H), 3.12 (dd, 0.6H, *J* = 4.3, 13.3 Hz), 3.07 (dd, 0.4H, *J* = 4.3, 12.8 Hz), 3.00-2.92 (m, 1H), 2.90 (br s, 1H), 2.09-1.87 (m, 1H), 1.85-1.74 (m, 0.4H), 1.69-1.56 (m, 0.6H), 1.34-1.14 (m, 6H), 0.90-0.81 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 133.8, 133.6, 129.8, 128.5, 128.3, 128.2, 91.8, 91.4, 71.1, 70.9, 32.8, 32.3, 31.3, 31.2, 30.4, 29.2, 25.7, 25.5, 22.5, 22.4, 14.2, 14.1. Anal. Calcd for $C_{14}H_{21}NO_3Se$ (330.29): C, 50.91; H, 6.41; N, 4.24. Found: C, 50.83; H, 6.43; N, 4.27.

3-Nitro-1-(phenylselanyl)decan-2-ol (64c). Yellow oil, Yield= 61%, dr= 60:40. IR (, neat): 3460, 1478, 1438, 737, 691 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59-7.47 (m, 2H), 7.37-7.23 (m, 3H), 4.64-4.52 (m, 1H), 4.04-3.93 (m, 1H), 3.16-3.03 (m, 1H), 3.02-2.91 (m, 1H), 2.85 (br s, 1H), 2.11-1.86 (m, 1H), 1.82-1.71 (m, 0.4H), 1.68-1.49 (m, 0.6H), 1.35-1.07 (m, 10H), 0.87 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 133.8, 133.6, 129.8, 129.7, 128.5, 128.3, 128.2, 91.8, 91.4, 71.1, 70.9, 32.8, 32.2, 31.9, 31.8, 30.4, 29.1, 29.0, 26.0, 22.8, 14.3. Anal. Calcd for $C_{16}H_{25}NO_3Se$ (358.34): C, 53.63; H, 7.03; N, 3.91. Found: C, 53.79; H, 7.06; N, 3.94.

3-Nitro-1-(phenylselanyl)tridecan-2-ol (64d). Yellow oil, Yield= 53%, dr= 60:40. IR (neat): 3503, 1550, 1438, 1371, 736, 691 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.61-7.48 (m, 2H), 7.36-7.21 (m, 3H), 4.66-4.49 (m, 1H), 4.04-3.94 (m, 1H), 3.16-3.03 (m, 1H), 3.00-2.91 (m, 1H), 2.86 (br s, 1H), 2.10-1.87 (m, 1H), 1.85-1.73 (m, 0.4H), 1.68-1.51 (m, 0.6H), 1.36-1.10 (m, 16H), 0.88 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 134.0, 133.6, 131.7, 129.8, 129.4, 128.3, 128.2, 91.8, 91.4, 71.1, 70.8, 32.8, 32.3, 32.1, 30.4, 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 26.0, 25.8, 22.9, 14.4. Anal. Calcd for $C_{19}H_{31}NO_3Se$ (400.42): C, 56.99; H, 7.80; N, 3.50. Found: C, 57.11; H, 7.83; N, 3.52.

3-Nitro-1-(phenylselanyl)non-8-en-2-ol (64e). Pale yellow oil, Yield= 62%, dr= 50:50. IR (neat): 3497, 1544, 1436, 1362, 738, 694 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60-7.48 (m, 2H), 7.34-7.25 (m, 3H), 5.82-5.66 (m, 1H), 5.03-4.90 (m, 2H), 4.66-4.53 (m, 1H), 4.06-3.93 (m, 1H), 3.15-3.04 (m, 1H), 3.01-2.92 (m, 1H), 2.87-2.81 (br s, 1H), 2.13-1.89 (m, 3H), 1.88-1.76 (m, 0.5H), 1.72-1.49 (m, 0.5H), 1.48-1.13 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 138.4, 138.3, 133.8, 133.7, 129.8, 128.4, 128.2, 115.2, 115.1, 91.6, 91.3, 71.1, 70.8, 33.5, 33.5, 32.8, 32.3, 30.2, 29.1, 28.3, 25.4, 25.2. Anal. Calcd for $C_{15}H_{21}NO_3Se$ (342.30): C, 52.63; H, 6.18; N, 4.09. Found: C, 52.56; H, 6.15; N, 4.06.

6-Methyl-3-nitro-1-(phenylselanyl)heptan-2-ol (64f). Pale yellow oil, Yield= 59%, dr= 50:50. IR (, neat): 3503, 1547, 1437, 1368, 737, 697 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64-7.48 (m, 2H), 7.36-7.22 (m, 3H), 4.63-4.50 (m, 1H), 4.08-3.94 (m, 1H), 3.16-3.05 (m, 1H), 3.02-2.92 (m, 1H), 2.87 (br s, 1H), 2.10-1.77 (m, 1.5H), 1.20-1.02 (m, 2H), 0.90-0.77 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 133.9, 133.7, 131.7, 129.8, 128.3, 128.2, 92.0, 91.7, 71.1, 70.8, 34.9, 34.6, 32.8, 32.4, 28.4, 27.9, 27.8, 27.3, 22.7, 22.6, 22.3. Anal. Calcd for $C_{14}H_{21}NO_3Se$ (330.29): C, 50.91; H, 6.41; N, 4.24. Found: C, 51.07; H, 6.45; N, 4.28.

3-Nitro-5-phenyl-1-(phenylselanyl)pentan-2-ol (64g). Yellow oil, Yield= 62%, dr= 50:50. IR (neat): 3446, 1546, 1478, 1437, 737, 691 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64-7.46 (m, 2H), 7.40-7.21 (m, 6H), 7.20-7.04 (m, 2H), 4.87-4.43 (m, 1H), 4.06-3.92 (m, 1H), 3.16-2.89 (m, 2H), 2.86 (d, 0.5

Hz, *J* = 5.8 Hz), 2.83 (d, 0.5H, *J* = 3.1 Hz), 2.79-2.70 (m, 0.5H), 2.69-2.59 (m, 0.5H), 2.60-2.49 (m, 1H), 2.48-2.27 (m, 1H), 2.22-2.09 (m, 0.5H), 2.05-1.92 (m, 0.5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.6, 139.4, 133.7, 133.5, 129.6, 129.5, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 126.7, 126.6, 90.5, 90.1, 32.5, 32.1, 31.9, 31.8, 31.7, 30.8. Anal. Calcd for $C_{17}H_{19}NO_3Se$ (364.30): C, 56.05; H, 5.26; N, 3.84. Found: C, 56.15; H, 5.29; N, 3.87.

Methyl 7-Hydroxy-6-nitro-8-(phenylselanyl)octanoate (64h). Yellow oil, Yield= 60%, dr= 60:40. IR (neat): 3452, 1547,1437, 1367, 739, 692 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59-7.52 (m, 2H), 7.35-7.28 (m, 3H), 4.66-4.57 (m, 1H), 4.08-3.97 (m, 1H), 3.68 (s, 3H), 3.16-3.07 (m, 1H), 3.04-2.85 (m, 2H), 2.34-2.25 (m, 2H), 2.17-1.93 (m, 1H), 1.92-1.80 (m, 0.4H), 1.74-1.49 (m, 2.6H), 1.41-1.26 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.7, 173.6, 133.6, 133.4, 129.6, 129.5, 128.3, 128.1, 128.0, 91.2, 90.9, 70.9, 70.6, 51.6, 33.5, 33.4, 32.5, 32.1, 29.8, 28.7, 25.3, 25.1, 24.2, 24.1. Anal. Calcd for $C_{15}H_{21}NO_5Se$ (374.30): C, 48.13; H, 5.66; N, 3.74. Found: C, 48.21; H, 5.68; N, 3.71.

5-Hydroxy-4-nitro-6-(phenylselanyl)hexyl Acetate (64i). Yellow oil, Yield= 70%, dr= 50:50. IR (neat): 3451, 2961, 1735, 1548, 1366, 1244, 740, 692 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.58-7.49 (m, 2H), 7.36-7.26 (m, 3H), 4.70-4.57 (m, 1H), 4.16-3.94 (m, 3H), 3.15-3.04 (m, 1H), 3.01-2.84 (m, 2H), 2.04 (s, 1.5H), 2.03 (s, 1.5H), 2.20-1.86 (m, 1.5H), 1.83-1.49 (m, 2.5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.2, 133.8, 133.6, 129.8, 129.7, 128.4, 128.3, 91.1, 90.8, 71.1, 70.9, 63.4, 63.3, 32.6, 32.4, 27.1, 26.0, 25.3, 25.1, 21.1. Anal. Calcd for $C_{14}H_{19}NO_5Se$ (360.27): C, 46.67; H, 5.32; N, 3.89. Found: C, 46.54; H, 5.28; N, 3.86.

2-(4-Hydroxy-3-nitro-5-(phenylselanyl)pentyl)isoindoline-1,3-dione (64j). Yellow oil, Yield= 68%, dr= 50:50. IR (neat): 3464, 1703, 1547, 1378, 719 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.95-7.80 (m, 2H), 7.78-7.67 (m, 2H), 7.59-7.45 (m, 2H), 7.36-7.19 (m, 3H), 4.78-4.58 (m, 1H), 4.18-4.08 (m, 0.5H), 4.07-3.98 (m, 0.5H), 3.89-3.64 (m, 2H), 3.13 (dd, 0.5H, *J* = 4.2, 12.8 Hz), 3.08-2.84 (m, 2.5H), 2.59-2.35 (m, 1H), 2.33-2.09 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.3, 134.6, 134.5, 133.8, 133.7, 132.1, 132.0, 129.8, 128.2, 123.7, 123.6, 88.4, 88.3, 71.0, 70.7, 34.9, 34.6, 32.4,

32.2, 29.1, 27.7. Anal. Calcd for $C_{19}H_{18}N_2O_5Se$ (433.32): C, 52.66; H, 4.19; N, 6.46. Found: C, 52.55; H, 4.15; N,6.42.

3-Nitro-1-(phenylselanyl)hexan-2-yl Acetate (65a). Yellow oil, Yield= 91%, dr= 65:35. IR (neat): 1747, 1551, 1372, 1225, 739, 692 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.61-7.49 (m, 2H), 7.38-7.22 (m, 3H), 5.40-5.25 (m, 1H), 4.98-4.88 (m, 0.65H), 4.85−4.77 (m, 0.35H), 3.35-3.27 (dd, 0.65H, *J* = 5.1, 14.3 Hz), 3.12-2.98 (m, 1.35H), 1.94 (s, 1.05H), 1.85 (s, 1.95H), 1.98-1.80 (m, 1H), 1.66-1.43 (m, 1H), 1.39-1.14 (m, 2H), 0.90 (t, 3H, *J* = 7.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9, 133.9, 133.8, 129.7, 129.6, 129.0, 128.2, 128.1, 89.1, 88.9, 72.7, 72.5, 31.9, 31.1, 28.4, 27.4, 20.8, 20.7, 19.3, 19.0, 13.6, 13.5. MS (EI): m/z (%) = 345 ([M+1$^+$], 14), 239 (39), 157 (33), 91 (32), 43 (100). Anal. Calcd for $C_{14}H_{19}NO_4Se$ (344.27): C, 48.84; H, 5.56; N, 4.07. Found: C, 49.00; H, 5.59; N,4.09.

3-Nitro-1-(phenylselanyl)octan-2-yl Acetate (65b). Yellow oil, Yield= 85%, dr= 65:35. IR (neat): 1748, 1552, 1372,1225, 739, 692 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62-7.48 (m, 2H), 7.39-7.24 (m, 3H), 5.39-5.34 (m, 0.65H), 5.33-5.27 (m, 0.35H), 4.96-4.87 (m, 0.65H), 4.82-4.75 (m, 0.35 H), 3.31 (dd, 0.65H, *J* = 5.1, 14.1 Hz), 3.12-2.98 (m, 1.35H), 1.94 (s, 1.05H), 1.85 (s, 1.95H), 2.07-1.79 (m, 1H), 1.67-1.49 (m, 1H), 1.36-1.13 (m, 6H), 0.86 (t, 3H, *J* = 6.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9, 133.9, 129.8, 129.7, 129.6, 129.0, 128.9, 128.2, 128.1, 89.4, 89.2, 72.7, 72.5, 31.1, 29.9, 29.2, 28.4, 27.4, 25.6, 25.3, 22.5, 20.8, 20.7, 14.1. MS (EI): m/z (%) = 373 ([M+1$^+$], 16), 267 (48), 157 (29), 91 (37), 43 (100). Anal. Calcd for $C_{16}H_{23}NO_4Se$ (372.32): C, 51.61; H, 6.23; N, 3.76. Found: C, 51.73; H, 6.27; N, 3.79.

3-Nitro-1-(phenylselanyl)decan-2-yl Acetate (65c). Yellow oil, Yield= 88%, dr= 70:30. IR (neat): 2926, 2856, 1747, 1551, 1371, 1225, 1022, 738, 691 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59-7.50 (m, 2H), 7.33-7.25 (m, 3H), 5.39-5.34 (m, 0.7H), 5.33-5.27 (m, 0.3H), 4.95-4.87 (m, 0.7H), 4.83-4.76 (m, 0.3H), 3.32 (dd, 0.7H, *J* = 5.1, 14.1 Hz), 3.14-2.96 (m, 1.3H), 1.95 (s, 0.9H), 1.85 (s, 2.1H), 2.08-1.82 (m, 1H), 1.51−1.65 (m, 1H), 1.35-1.13 (m, 10H), 0.87 (t, 3H, *J* = 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.0, 169.9, 133.9, 133.8, 129.6, 129.5, 129.1, 128.1, 128.0, 89.4, 89.2, 72.7,

72.5, 31.8, 30.0, 29.2, 29.1, 29.0, 28.4, 27.4, 26.0, 25.6, 22.8, 20.8, 20.7, 14.2. MS (EI): m/z (%) = 401 ([M+1$^+$], 18), 295 (58), 244 (15), 197 (12), 157 (29), 81 (39), 43 (100). Anal. Calcd for $C_{18}H_{27}NO_4Se$ (400.38): C, 54.00; H, 6.80; N, 3.50. Found: C, 53.85; H, 6.83; N, 3.53.

3-Nitro-1-(phenylselanyl)tridecan-2-yl Acetate (65d). Yellow oil, Yield= 82%, dr= 70:30. IR (neat): 1749, 1553, 1371, 1226, 738, 691 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65-7.40 (m, 2H), 7.39-7.14 (m, 3H), 5.40-5.33 (m, 0.7H), 5.33-5.26 (m, 0.3H), 4.96-4.86 (m, 0.7H), 4.84-4.75 (m, 0.3H), 3.32 (dd, 0.7H, *J* = 5.1, 13.7 Hz), 3.14-2.95 (m, 1.3H), 1.95 (s, 0.9H), 1.85 (s, 2.1H), 2.04-1.78 (m, 1H), 1.63-1.52 (m, 1H), 1.34-1.16 (m, 16H), 0.88 (t, 3H, *J* = 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9, 133.9, 133.8, 129.7, 129.6, 128.1, 89.4, 89.2, 72.7, 72.5, 32.1, 29.9, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 29.0, 28.4, 27.4, 25.9, 25.6, 22.9, 20.8, 20.7, 14.4. MS (EI): m/z (%) = 443 ([M+1$^+$], 9), 337 (38), 286 (9), 157 (19), 67 (25), 43 (100). Anal. Calcd for $C_{21}H_{33}NO_4Se$ (442.46): C, 57.01; H, 7.52; N, 3.17. Found: C, 57.11; H, 7.53; N, 3.20.

3-Nitro-1-(phenylselanyl)non-8-en-2-yl Acetate (65e). Yellow oil, Yield= 90%, dr= 50:50. IR (neat): 3074, 1747, 1640, 1551, 1370, 1224, 738 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59-7.51 (m, 2H), 7.32-7.24 (m, 3H), 5.80-5.66 (m, 1H), 5.41-5.26 (m, 1H), 5.02-4.88 (m, 2.5H), 4.82-4.76 (m, 0.5H), 3.31 (dd, 0.5H, *J* = 5.1, 14.1 Hz), 3.11-3.00 (m, 1.5H), 1.95 (s, 1.5H), 1.86 (s, 1.5H), 2.08-1.83 (m, 3H), 1.68-1.53 (m, 1H), 1.46-1.17 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.0, 169.9, 138.2, 133.8, 134.0, 129.7, 129.6, 128.9, 128.2, 128.1, 115.3, 89.2, 89.1, 72.7, 72.4, 33.4, 29.8, 29.0, 28.4, 28.3, 28.2, 27.4, 25.4, 25.1, 20.8, 20.7. MS (EI): m/z (%) = 385 ([M+1$^+$], 21), 279 (38), 228 (15), 157 (31), 117 (31), 91 (48), 43 (100). Anal. Calcd for $C_{17}H_{23}NO_4Se$ (384.33): C, 53.13; H, 6.03; N, 3.64. Found: C, 53.29; H, 6.07; N, 3.66.

6-Methyl-3-nitro-1-(phenylselanyl)heptan-2-yl Acetate (65f). Pale yellow oil, Yield= 79%, dr= 50:50. IR (neat): 1747, 1555, 1374, 1221, 734, 697 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.58-7.51 (m, 2H), 7.32-7.24 (m, 3H), 5.40-5.27 (m, 1H), 4.98-4.91 (m, 0.6H), 4.81-4.79 (m, 0.4H), 3.32 (dd, 0.6H, *J* = 5.1, 14.1 Hz), 3.11-2.99 (m, 1.4H), 1.95 (s, 1.2H), 1.85 (s, 1.8H),

2.07-1.80 (m, 1H), 1.68-1.41 (m, 2H), 1.23-1.01 (m, 2H), 0.86-0.81 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 170.0, 169.9, 134.0, 133.8, 129.7, 129.6, 129.0, 128.9, 128.2, 128.1, 89.6, 89.4, 72.7, 72.4, 34.8, 34.4, 28.4, 27.9, 27.8, 27.7, 27.4, 27.2, 22.7, 22.6, 22.3, 22.2, 20.8, 20.7. MS (EI): m/z (%) = 373 ([M+1$^+$], 14), 267 (23), 157 (25), 109 (76), 91 (32), 67 (27), 43 (100). Anal. Calcd for $C_{16}H_{23}NO_4Se$ (372.32): C, 51.62; H, 6.23; N, 3.76. Found: C, 51.71; H, 6.26; N, 3.78.

3-Nitro-5-phenyl-1-(phenylselanyl)pentan-2-yl Acetate (65g). Yellow oil, Yield= 95%, dr= 70:30. IR (neat): 1746, 1550, 1371, 692, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57-7.48 (m, 2H), 7.36-7.21 (m, 6H), 7.15-7.05 (m, 2H), 5.42-5.32 (m, 1H), 4.96-4.88 (m, 0.7H), 4.86-4.79 (m, 0.3H), 3.25 (dd, 0.7H, *J* = 5.1, 14.1 Hz), 3.16-2.95 (m, 1.3H), 2.74-2.21 (m, 3.3H), 1.95 (s, 0.9H), 1.89 (s, 2.1H), 2.04-1.79 (m, 0.7H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9, 139.56, 139.4, 134.0, 133.8, 129.7, 129.0, 128.9, 128.8, 128.7, 128.6, 128.2, 128.1, 126.9, 88.4, 88.2, 72.7, 72.3, 32.1, 31.9, 31.8, 30.8, 28.4, 27.5, 20.8, 20.7. MS (EI): m/z (%) = 326 (31), 236 (41), 221 (100), 178 (22), 91 (41). Anal. Calcd for $C_{19}H_{21}NO_4Se$ (406.34): C, 56.16; H, 5.21; N, 3.45. Found: C, 56.32; H, 5.25; N, 3.49.

Methyl 7-Acetoxy-6-nitro-8-(phenylselanyl)octanoate (65h). Yellow oil, Yield= 95%, dr= 60:40. IR (neat): 2950, 1735, 1551, 1370, 1225, 740, 692 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75-7.46 (m, 2H), 7.38-7.15 (m, 3H), 5.39-5.34 (m, 0.6H), 5.33-5.27 (m, 0.4H), 4.94-4.86 (m, 0.6H), 4.83-4.75 (m, 0.4), 3.66 (s, 3H), 3.29 (dd, 0.6H, *J* = 5.1, 13.7 Hz), 3.11-2.95 (m, 1.4H), 2.27 (t, 2H, *J* = 7.3 Hz), 1.94 (s, 1.2H), 1.85 (s, 1.8H), 2.10-1.82 (m, 1H), 1.70-1.62 (m, 3H), 1.18-1.10 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.7, 16972.4,.9, 133.9, 133.8, 129.7, 129.6, 129.0, 128.2, 128.1, 89.0, 88.8, 72.7, 51.9, 33.7, 29.6, 28.8, 28.3, 27.5, 25.5, 25.2, 24.4, 24.3, 20.8, 20.7. MS (EI): m/z (%) = 3 .14 (100), 234 (31), 157 (90), 77 (45). Anal. Calcd for $C_{17}H_{23}NO_6Se$ (416.33): C, 49.04; H, 5.57; N, 3.36. Found: C, 49.16; H, 5.61; N, 3.40.

4-Nitro-6-(phenylselanyl)hexane-1,5-diyl diacetate (65i). Yellow oil, Yield= 80%, dr= 60:40. IR (neat): 1737, 1551, 1367, 1225, 1022, 739, 691 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.58-7.50 (m, 2H), 7.33-7.24 (m, 3H),

5.38-5.30 (m, 1H), 4.98-4.91 (m, 0.6H), 4.87-4.80 (m, 0.4H), 4.09-3.93 (m, 2H), 3.28 (dd, 0.6H, *J* = 5.5, 14.1 Hz), 3.10-2.99 (m, 1.4H), 2.04 (s, 1.2H), 2.03 (s, 1.8H), 2.22-1.94 (m, 1H), 1.94 (s, 1.2H), 1.86 (s, 1.8H), 1.78-1.45 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 169.9, 169.8, 133.9, 133.7, 129.7, 129.6, 128.9, 128.2, 128.1, 88.6, 88.5, 72.7, 72.3, 63.3, 63.1, 28.3, 27.4, 26.8, 25.8, 25.2, 24.9, 21.1, 20.7, 20.6. MS (EI): m/z (%) = 403 ([M^+], 11), 297 (8), 237 (31), 157 (23), 79 (34), 43 (100). Anal. Calcd for $C_{16}H_{21}NO_6Se$ (402.31): C, 47.77; H, 5.26; N, 3.48. Found: C, 47.66; H, 5.23; N, 3.44.

5-(1,3-Dioxoisoindolin-2-yl)-3-nitro-1-(phenylselanyl)pentan-2-yl Acetate (65j). Yellow waxy solid, Yield= 92%, dr= 50:50. IR (neat): 1708, 1552, 1370, 720, 692 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91-7.80 (m, 2H), 7.79-7.67 (m, 2H), 7.61-7.40 (m, 2H), 7.39-7.12 (m, 3H), 5.44-5.31 (m, 1H), 5.01-4.85 (m, 1H), 3.96-3.61 (m, 2H), 3.22 (dd, 0.5H, *J* = 5.1, 13.7 Hz), 3.16-3.03 (m, 1H), 2.95 (dd, 0.5H, *J* = 6.4, 13.7 Hz), 2.55-2.34 (m, 1H), 2.15-2.02 (m, 1H), 1.94 (s, 1.5H), 1.90 (s, 1.5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9, 169.6, 168.3, 168.2, 134.6, 134.4, 133.8, 133.6, 132.0, 129.7, 129.6, 129.1, 128.8, 128.2, 128.0, 123.7, 86.2, 85.8, 72.7, 72.0, 34.8, 34.4, 28.9, 28.1, 27.3, 27.2, 20.7, 20.6. MS (EI): m/z (%) = 314 (98), 234 (34), 157 (100), 117 (10), 77 (74), 51 (29). Anal. Calcd for $C_{21}H_{20}N_2O_6Se$ (475.36): C, 53.06; H, 4.24; N, 5.89. Found: C, 53.14; H, 4.26; N, 5.92.

3-Nitrohex-1-en-2-yl Acetate (62a). Yellow oil, Yield= 78%.IR (neat): 2932, 1768, 1557, 1371, 1170, 905 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.30 (d, 1H, *J* = 2.6 Hz), 5.26 (d, 1H, *J* = 2.6 Hz), 4.99 (dd, 1H, *J* = 5.9, 8.9 Hz), 2.18 (s, 3H), 2.24-2.12 (m, 1H), 1.99-1.88 (m, 1H), 1.45-1.35 (m, 2H), 0.98 (t, 3H, *J* = 7.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.8, 148.1, 108.7, 89.1, 32.6, 21.1, 19.3, 13.6. MS (EI): m/z (%) = 141 (2), 99 (14), 91 (17), 43 (100) . Anal. Calcd for $C_8H_{13}NO_4$ (187.19): C, 51.33; H, 7.00; N, 7.48. Found: C, 51.22; H, 6.96; N, 7.45.

3-Nitrooct-1-en-2-yl Acetate (62b). Yellow oil, Yield= 78%. IR (neat): 2931, 1767, 1555, 1369, 1173, 903 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.29 (d, 1H, *J* = 2.6 Hz), 5.25 (d, 1H, *J* = 3.4 Hz), 4.97 (dd, 1H, *J* = 6.4, 8.9

Hz), 2.17 (s, 3H), 2.32-2.04 (m, 1H), 2.02-1.86 (m, 1H), 1.45-1.21 (m, 6H), 0.88 (t, 3H, *J* = 6.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.7, 148.1, 100.7, 89.2, 31.2, 30.6, 25.5, 22.5, 21.0, 14.1. MS (EI): m/z (%) = 127 (13), 109 (8), 67 (11), 55 (9), 43 (100). Anal. Calcd for $C_{10}H_{17}NO_4$ (215.25): C, 55.80; H, 7.96; N, 6.51. Found: C, 55.93; H, 8.00; N, 6.54.

3-Nitrodec-1-en-2-yl Acetate (62c). Yellow oil, Yield= 81%. IR (, neat): 2928, 1768, 1556, 1369, 1180, 1019, 901 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.29 (d, 1H, *J* = 2.6 Hz), 5.25 (d, 1H, *J* = 2.6 Hz), 4.97 (dd, 1H, *J* = 5.9, 9.4), 2.23-2.11 (m, 1H), 2.17 (s, 3H), 2.23-1.41 (m, 10H), 2.03-1.88 (m, 1H), 0.87 (t, 3H, *J* = 6.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.7, 148.1, 108.7, 89.2, 31.8, 30.7, 29.1, 29.0, 25.9, 22.8, 21.1, 14.3. MS (EI): m/z (%) = 234 (18), 163 (17), 149 (14), 136 (15), 124 (100), 69 (15), 55 (10), 41 (10). Anal. Calcd for $C_{12}H_{21}NO_4$ (243.30): C, 59.24; H, 8.70; N, 5.76. Found: C, 59.32; H, 8.74; N, 5.79.

3-Nitrotridec-1-en-2-yl Acetate (62d). Yellow oil, Yield= 67%. IR (neat): 2924, 1769, 1557, 1369, 1178, 1019 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.29 (d, 1H, *J* = 2.6 Hz), 5.26 (d, 1H, *J* = 2.6 Hz), 4.97 (dd, 1H, *J* = 5.9, 8.9 Hz), 2.17 (s, 3H), 2.21-2.11 (m, 1H), 2.03-1.87 (m, 1H), 1.62-1.15 (m, 16H), 0.87 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.7, 148.1, 108.7, 89.2, 32.1, 30.7, 29.7, 29.6, 29.5, 29.4, 29.1, 25.9, 22.9, 21.1, 14.3. MS (EI): m/z (%) = 197 (13), 95 (10), 79 (8), 67 (6), 43 (100). Anal. Calcd for $C_{15}H_{27}NO_4$ (285.38): C, 63.13; H, 9.54; N, 4.91. Found: C, 63.23; H, 9.56; N, 4.94.

3-Nitronona-1,8-dien-2-yl Acetate (62e). Yellow oil, Yield= 65%. IR (neat): 1770, 1668, 1557, 1370, 1184, 1020, 907 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.83-5.68 (m, 1H), 5.29 (d, 1H, *J* = 2.6 Hz), 5.26 (d, 1H, *J* = 2.6 Hz), 5.04-4.92 (m, 3H), 2.17 (s, 3H), 2.56-2.11 (m, 1H), 2.09-1.91 (m, 3H), 1.53-1.16 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.7, 148.1, 138.2, 115.2, 108.7, 89.1, 33.4, 30.6, 28.3, 25.3, 21.0. MS (EI): m/z (%) = 139 (5), 121 (5), 93 (6), 79 (11), 43 (100). Anal. Calcd for $C_{11}H_{17}NO_4$ (227.26): C, 58.14; H, 7.54; N, 6.16. Found: C, 58.01; H, 7.50; N, 6.13.

6-Methyl-3-nitrohept-1-en-2-yl Acetate (62f). Clear oil, Yield 74%. IR (neat): 1766, 1664, 1555, 1369, 1174, 1019 cm^{-1}. ^{1}H-NMR (400 MHz,

$CDCl_3$): δ = 5.30 (d, 1H, *J* = 2.6 Hz), 5.26 (d, 1H, *J* = 2.6 Hz), 4.94 (dd, 1H, *J* = 6.4, 9.0 Hz), 2.17 (s, 3H), 2.24-2.10 (m, 1H), 2.04-1.91 (m, 1H), 1.65-1.51 (m, 1H), 1.33-1.12 (m, 2H), 0.91 (d, 3H, *J* = 1.7 Hz), 0.9 (d, 3H, *J* = 1.7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 168.7, 148.1, 108.8, 89.4, 34.7, 28.7, 27.8, 22.5, 22.4, 21.1. MS (EI): m/z (%) = 127 (8), 109 (10), 69 (9), 55 (7), 43 (100). Anal. Calcd for $C_{10}H_{17}NO_4$ (215.25): C, 55.80; H, 7.96; N, 6.51. Found: C, 55.99; H, 7.99; N, 6.55.

3-Nitro-5-phenylpent-1-en-2-yl Acetate (62g). Yellow oil, Yield= 58%. IR (neat): 2918, 1767, 1554, 1370, 742, 699 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39-7.29 (m, 2H), 7.24-7.12 (m, 3H), 5.31 (s, 2H), 4.97 (dd, 1H, *J* = 6.0, 8.6 Hz), 2.69 (t, 2H, *J* = 7.3 Hz), 2.60-2.47 (m, 1H), 2.33-2.21 (m, 1H), 2.18 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.7, 147.7, 139.5, 129.0, 128.7, 127.0, 109.3, 88.3, 32.3, 31.9, 21.1. MS (EI): m/z (%) = 161 (15), 143 (17), 107 (20), 91 (73), 65 (10), 43 (100). Anal. Calcd for $C_{13}H_{15}NO_4$ (249.27): C, 62.64; H, 6.07; N, 5.62. Found: C, 62.75; H, 6.11; N, 5.66.

Methyl 7-Acetoxy-6-nitrooct-7-enoate (62h). Yellow oil, Yield= 73%. IR (neat): 1767, 1733, 1552, 1369, 1175, 1020 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.29 (d, 1H, *J* = 2.6 Hz), 5.26 (d, 1H, *J* = 2.9 Hz), 4.97 (dd, 1H, *J* = 6.4, 8.9 Hz), 3.66 (s, 3H), 2.32 (t, 2H, *J* = 7.7 Hz), 2.17 (s, 3H), 2.26-2.11 (m, 1H), 2.05-1.92 (m, 1H), 1.75-1.58 (m, 2H), 1.49-1.29 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.8, 168.7, 147.8, 108.9, 88.9, 51.9, 33.7, 30.6, 25.3, 24.3, 21.1. MS (EI): m/z (%) = 171 (7), 139 (12), 97 (20), 79 (11), 55 (10), 43 (100). Anal. Calcd for $C_{11}H_{17}NO_6$ (259.26): C, 50.96; H, 6.61; N, 5.40. Found: C, 50.86; H, 6.57; N, 5.38.

4-Nitrohex-5-ene-1,5-diyl Diacetate (62i). Yellow oil, Yield= 69%. IR (neat): 1762, 1733, 1662, 1553, 1369, 1172 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.31 (d, 1H, *J* = 2.6 Hz), 5.28 (d, 1H, *J* = 2.6 Hz), 5.01 (dd, 1H, *J* = 6.0, 8.6 Hz), 4.16-4.01 (m, 2H), 2.36-2.19 (m, 1H), 2.17 (s, 3H), 2.05 (s, 3H), 2.13-1.96 (m, 1H), 1.81-1.60 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.1, 168.7, 147.7, 109.1, 88.6, 63.2, 27.5, 25.2, 21.1, 21.0. MS (EI): m/z (%) = 139 (6), 113 (7), 97 (20), 79 (11), 43 (100). Anal. Calcd for $C_{10}H_{15}NO_6$ (245.23): C, 48.98; H, 6.17; N, 5.71. Found: C, 49.09; H, 6.20; N, 5.74.

5-(1,3-Dioxoisoindolin-2-yl)-3-nitropent-1-en-2-yl Acetate (62j). Clear oil, Yield= 52%. IR (neat): 1770, 1707, 1556, 1396, 1372, 1178, 1015, 722 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88-7.81 (m, 2H), 7.75-7.68 (m, 2H), 5.41 (d, 1H, *J* = 2.6 Hz), 5.33 (d, 1H, *J* = 2.6 Hz), 5.06 (t, 1H, *J* = 7.3 Hz), 3.79 (t, 2H, *J* = 6.8 Hz), 2.64-2.53 (m, 1H), 2.47-2.37 (m, 1H), 2.17 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.5, 168.3, 146.8, 134.5, 132.0, 123.7, 110.1, 86.6, 34.5, 29.5, 21.1. MS (EI): m/z (%) = 200 (5), 160 (100), 133 (9), 104 (8), 76 (11). Anal. Calcd for $C_{15}H_{14}N_2O_6$ (318.28): C, 56.60; H, 4.43; N, 8.80. Found: C, 56.72; H, 4.46; N, 8.84.

3-Nitro-3-(3-oxobutyl)oct-1-en-2-yl Acetate (67). Clear oil, Yield= 53%. IR (neat): 1774, 1741, 1552, 1364, 1172 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.33-5.30 (m, 2H), 2.54-2.23 (m, 4H), 2.15 (s, 3H), 2.12 (s, 3H), 2.23-2.06 (m, 1H), 1.99-1.83 (m, 1H), 1.38-1.21 (m, 5H), 1.19-1.02 (m, 1H), 0.95-0.80 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.0, 149.6, 107.3, 95.3, 38.1, 33.3, 31.8, 30.3, 26.2, 23.5, 22.5, 21.2, 14.1. Anal. Calcd for $C_{14}H_{23}NO_5$ (285.34): C, 58.93; H, 8.13; N, 4.91. Found: C, 59.14; H, 8.17; N, 4.94.

3-Nitrooctan-2-one (68). Clear oil, Yield= 65%. IR (neat): 1733, 1556, 1361, 1167 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.11 (dd, 1H, *J* = 4.7, 10.3 Hz) 2.28 (s, 3H), 2.26-2.14 (m, 1H), 2.09-1.91 (m, 1H), 1.42-1.12 (m, 6H), 0.96-0.80 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 197.2, 95.1, 31.2, 29.8, 26.7, 25.6, 22.4, 14.0. MS (EI): m/z (%) = 130 (8), 71 (13), 55 (20), 43 (100). Anal. Calcd for $C_8H_{15}NO_3$ (173.21): C, 55.47; H, 8.73; N, 8.09. Found: C, 55.40; H, 8.70; N, 8.05.

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