Syntheses and domino ring closure reactions of novel *N*-propargyl-substituted alicyclic β-amino acids

PhD Thesis

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ABBREVIATIONS AND SYMBOLS

CDI	1,1-carbonyldiimidazole
CuAAC	Cu(I)-catalyzed azide/alkyne cycloaddition
DBTA	*O*,*O*-dibenzoyltartaric acid
DCB	1,2-dichlorobenzene
DFT	discrete Fourier transform
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIC	*N*,*N*′-diisopropylcarbodiimide
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DPTTA	*O*,*O*-di-*p*-toluoyltartaric acid
ee	enantiomeric excess
HOBt	hydroxybenzotriazole
HPLC	high performance liquid chromatography
IPA	isopropyl alcohol
GC	gas chromatography
NMR	nuclear magnetic resonance spectroscopy
PPh_3	triphenylphosphane
p-TSA	*p*-toluenesulfonic acid
RDA	retro Diels–Alder reaction
TEA	triethylamine
TFA	trifluoroacetic acid
TLC	thin-layer chromatography
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride

PUBLICATIONS

Papers related to the thesis

I. Márta Palkó, **Mohamed El Haimer**, Zsanett Kormányos and Ferenc Fülöp
Synthesis of Novel *N*-Heterocyclic Compounds Containing 1,2,3-Triazole Ring System via Domino, "Click" and RDA Reactions
Molecules **2019**, *24*, 772. DOI: 10.3390/molecules24040772 **IF: 4.411**

II. **Mohamed El Haimer**, Márta Palkó, Matti Haukka, Márió Gajdács, István Zupkó and Ferenc Fülöp
Synthesis and biological evaluation of the new ring system benzo[*f*]pyrimido[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepine and its cycloalkane and cycloalkene condensed analogues
RSC Adv., **2021**, *11*, 6952-6957. DOI: 10.1039/D0RA10553H **IF: 3.245**

III. **Mohamed El Haimer**, Tünde Faragó, Zsuzsanna Schelz, István Zupkó and Márta Palkó
Synthesis of alicyclic 2-Methylenethiazolo[2,3-*b*]quinazolinone derivatives via base-promoted cascade reaction
Synthesis, 2021, xx,xxxx-xxxx DOI: 10.1055/s-0040-1720028 **IF: 3.157**

CONFERENCE LECTURES

I. **Mohamed El Haimer**, Márta Palkó and Ferenc Fülöp:
Synthesis of Novel *N*-Heterocyclic Compounds Containing 1,2,3-Triazole Ring through a traceless chirality transfer strategy.
Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése Balatonszemes, June 3-5, 2019.

II. Márta Palkó, **Mohamed El Haimer** and Ferenc Fülöp:
Synthesis of novel *N*-heterocycles via domino-, click and RDA reactions.
20th Tetrahedron Symposium, Bangkok, Thailand, June 18-21, 2019.

III. **Mohamed El Haimer**, Márta Palkó and Ferenc Fülöp:
Synthesis of novel *N*-heterocycles via traceless chirality transfer.
18th Blue Danube Symposium on Heterocyclic Chemistry, Ljubljana, September 18-21, 2019.

IV. **Mohamed El Haimer** and Márta Palkó:
Regioselective domino reactions towards novel *N*-heterocycles.
Royal Society of Chemistry, #RSCPoster Twitter Conference, Ljubljana, Marsh 1-2, 2022.

1. INTRODUCTION AND AIMS

The development and synthesis of architecturally diverse and complex molecules with efficient, stereoselective, environmentally benign and atom-economic fashion have become extremely important in the last several decades [1–3]. As a solution to this challenging problem, multistep, one-pot procedures have been developed. These protocols, involving bond forming taking place in a domino reaction manner, minimize time consumption and chemical waste generation, based on several transformations [4]. Therefore, the preparation of complex structures using reaction sequences, that assemble several components or transformations engaging several reactive centres is an ideal solution. In general, the number of possible diastereomers increases along with the number of components. Although several successful examples have been reported [5–7], because of the difficulty of performing "one-pot" domino reactions with high diastereoselectivity, the task is still challenging [8–12].

N-Propargyl amines/amides are one of the most specific class of alkynes having diverse reaction patterns. It is well known that they can undergo several cyclization reactions to produce various significant nitrogen-containing heterocycles, which made them suitable for various domino reaction processes [13]. Recently, 2-amino-*N*-propargyl-substituted aromatic amides were the subject of various transformations via domino reactions processes, to prepare diverse and complex heterocyclic systems.

Continuing the work of our research group on the syntheses and transformation of β-amino acids [14–19], my PhD work focused on the synthesis of racemic and enantiomeric *N*-propargyl-substituted *diendo*- and *diexo*-2-aminonorbornenecarboxylic amides, the study of their domino ring-closure reaction with 2-formylbenzoic acid and examination of the diastereoselectivity of this process. Next, we used CuAAC in a regioselective manner and studied the RDA reaction to create isoindolo[2,1-*a*]quinazolinones, and to extend this methodology to obtain different racemic and enantiomeric pyrimido[2,1-*a*]isoindole derivatives containing a triazole ring (Figure 1) [I].

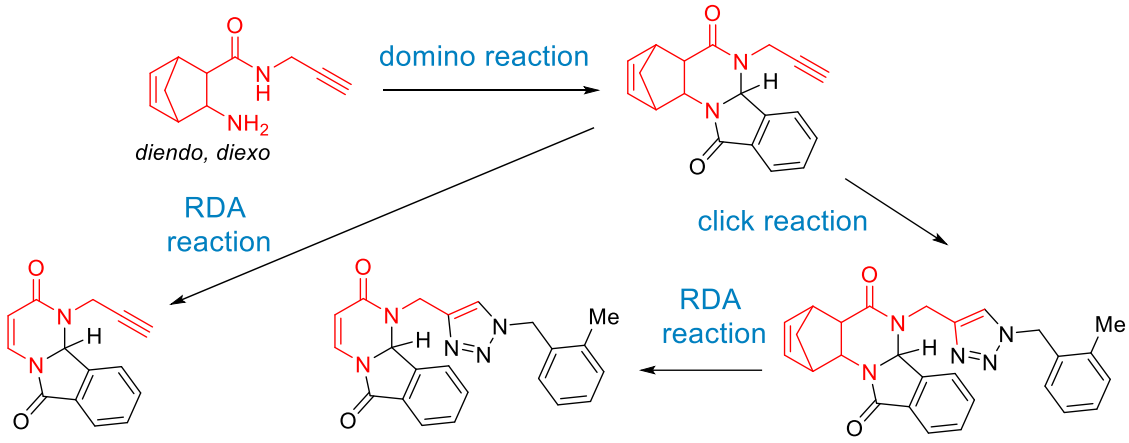


Figure 1

Another aim was to synthesise alicyclic *N*-propargyl-substituted amino acids and to develop a one-pot, two-step, five-centre cascade synthesis for alicyclic derivatives of quinazolino-triazolobenzodiazepine and to explore the diastereoselectivity of the domino reaction [II].

Our further aim was the syntheses of 2-methylene-substituted thiazolo[2,3-*b*]quinazolinone derivatives through a tandem bicyclisation strategy [III]. We investigated the possibility of RDA decomposition of the created norbornene derivatives and scrutinized in vitro biological activity of the aromatic and alicyclic derivatives.

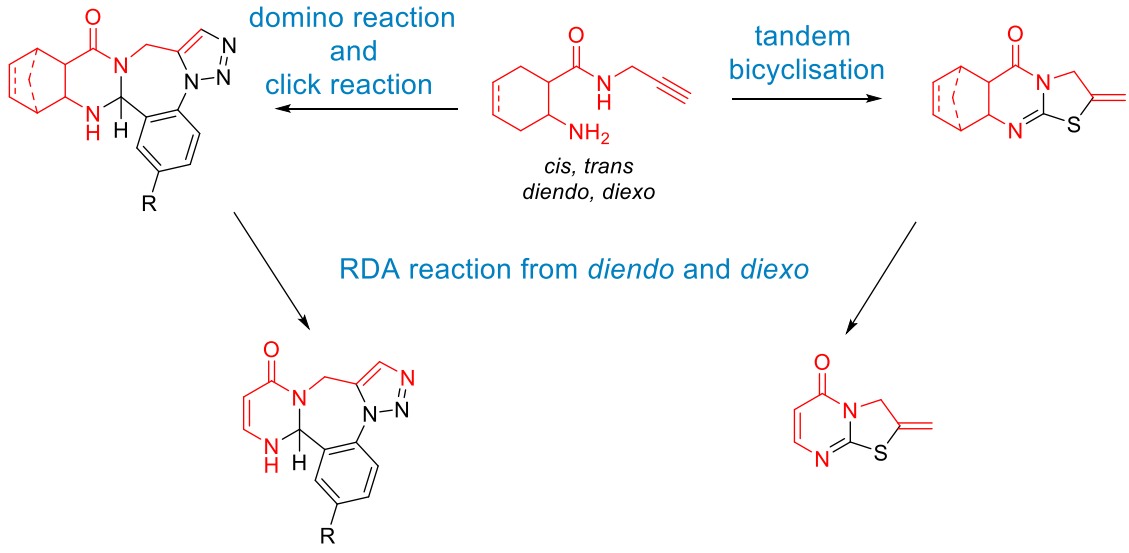
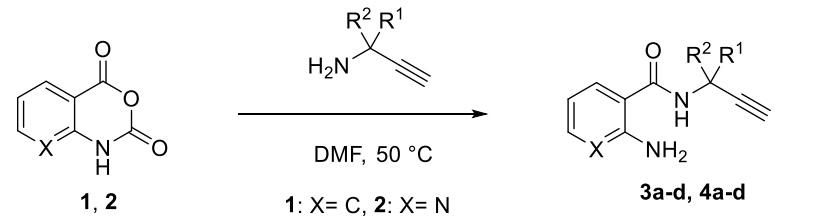


Figure 2

2. THEORETICAL BACKGROUND

2.1. Preparation of 2-amino-*N*-propargylbenzamides

The first known synthesis of 2-amino-*N*-propargylbenzamide (**3a**) was published by Reisch *et al.* in 1989 [20]. It was obtained by the ring opening of isatoic anhydrid (**1**) with propargylamine. In the process, isatoic anhydride **1** was first heated in DMF, then a solution of propargylamine derivative in equal volume of DMF was added dropwise over a period of 30 min. The reaction mixture was maintained at 50 °C for 24 h until the full consumption of isatoic anhydride was observed in TLC. Then the mixture was cooled to room temperature, poured into water and the pH was adjusted to 9 using a NaOH solution. The precipitate was isolated by filtration and washed by three portions of water to remove all traces of NaOH. Finally the solid was purified by column chromatography using DCM as eluent. In 1992, the same group successfully prepared alkyl-substituted 2-amino-*N*-propargylnicotinamid **4a** applying the same procedure (Scheme 1) [21].

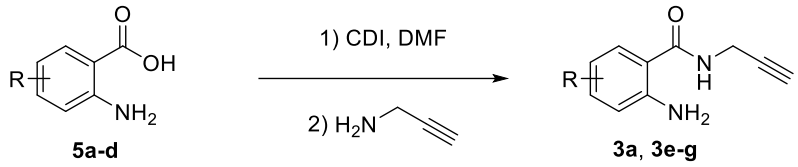


Scheme 1

This method was optimised by Farjadmand *et al.* using aqueous media [22]. Specifically, the synthesis of 2-amino-*N*-propargylbenzamide (**3a**) was performed by reacting a mixture of isatoic anhydride (**1**) and propargylamine in water under stirring at room temperature for 4 h. After completion of the reaction (checked by TLC), the resulting colourless precipitate was filtered off and used in additional reaction steps without further purification.

These two procedures were widely used to prepare 2-amino-*N*-propargylbenzamides. However, they have limitations for the synthesis of substituted derivatives due to limited availability of substituted isatoic anhydrides as an ideal starting material in these methods [23].

Fortunately, substituted 2-amino-*N*-propargylbenzamides (**3e**: R^1 = 3-OMe; **3f**: R^1 = 4-OMe; **3g**: R^1 = 5-Br) can also be prepared by CDI-mediated coupling of substituted anthranilic acids **5a-d** with propargylamine without any protection of the amine moiety of aniline [24]. Guggenheim *et al.* used this protocol to synthesise several substituted 2-amino-*N*-propargylbenzamides [23]. A reaction mixture of substituted anthranilic acid **5a-d** and dry DMF was stirred under N_2, and CDI was added to the solution in one portion. The reaction mixture was stirred overnight at 40 °C under N_2. Next, propargylamine was charged to the flask via syringe addition. The resulting solution was stirred overnight at room temperature, the crude mixture was taken up in water, extracted with EtOAc and washed with brine. The desired products were purified by flash chromatography (Scheme 2).

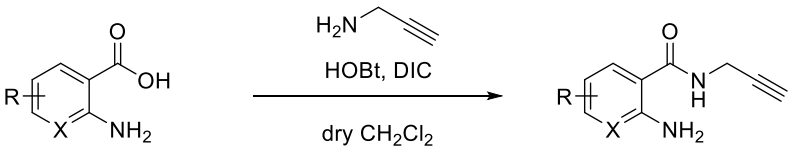


5a-d **3a**, **3e-g**

3a: R= H; 3**e**: R= 3-OMe; 3**f**: R= 4-OMe; **3g**: R= 5-Br

Scheme 2

In accordance with the procedure published by Jablonski *et al.* in 2012 [25], Mahdavi *et al.* reported the synthesis of several 2-amino-*N*-propargylbenzamides (**3**) by the coupling reaction of 2-aminobenzoic acids **5a**, **5e-k** with propargylamine using HOBt and DIC in DCM for 48 h at room temperature (Scheme 3). The products of these reactions (**3a, 3h-m, 4a**) were used in subsequent steps without isolation or purification [26].



5a, **5e-k** **3a**, **3h-m, 4a**

X= C: **5a, 3a**: R= H; **5e,3h**: R= 5-Me; **5f,3i**: R= 4,5-$(OMe)_2$; **5g,3j**: R= 4-Cl; **5h,3k**: R= 5-Cl; **5i,3l**: R= C_4H_4 (3-amino-2-naphthoic acid); **5j,3m**: R= 4-NO_2; X= N: **5k,4a**: R= H

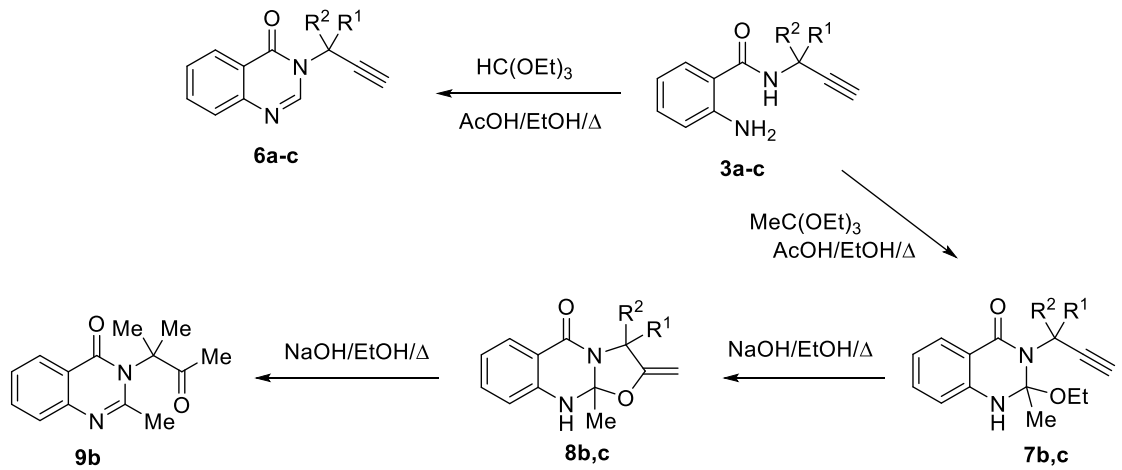
Scheme 3

A relatively new procedure was communicated by Ramakrishna *et al.* in 2017 [27]. Anthranilic acid (**5a**) or 2-amino-4-chlorobenzoic acid (**5g**) was dissolved in dry DMF, the flask was degassed with nitrogen, cooled to 0 °C, then HOBt, DMAP and DIC were added to the reaction mixture. After 10 min, propargylamine was added and the reaction mixture was stirred overnight at ambient temperature. The crude mixture was taken up

in water and extracted with EtOAc. The combined organic extracts were washed with brine and purified by column chromatography (EtOAc/*n*-hexane = 4:1) to afford the desired compounds.

2.2. Ring-closure reactions of 2-amino-*N*-propargylbenzamides

Various transformations of 2-amino-*N*-propargylbenzamides **3a-c** were studied by Reisch *et al.* in 1990. Under a blanket of N_2, the reaction of 2-amino-*N*-propargylbenzamides **3a-c** with triethyl orthoformate in the presence of glacial acetic acid in EtOH yielded 3-propynyl-substituted quinazolines **6a-c** in good yields (Scheme 4). Using methyl-substituted and cyclohexenyl-substituted amides **3b** and **3c**, decreasing yields were observed with increasing reaction time (unsubstituted > Me > cyclohexyl). The reaction of **3b** and **3c** with triethyl orthoacetate gave ethoxy-substituted products **7b** and **7c**. Heating the ethanolic solution of these derivatives with sodium hydroxide, dealkylation took place, followed by cyclisation affording oxazoloquinazolinones **8b** and **8c**. Compound **8b** could be isolated by stopping the reaction after 1 hour. Moreover, the heating of **8b** in the reaction mixture led to the formation of **9b** in low yield [28].

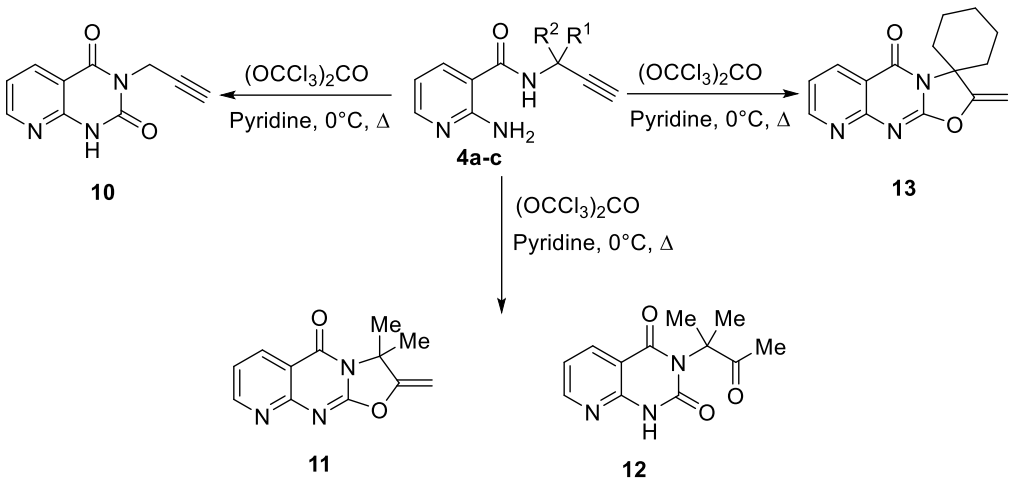


a: $R^1 = R^2 = H$; **b**: $R^1 = R^2 = Me$; **c**: $R^1 = R^2 = -(CH_2)_5-$

Scheme 4

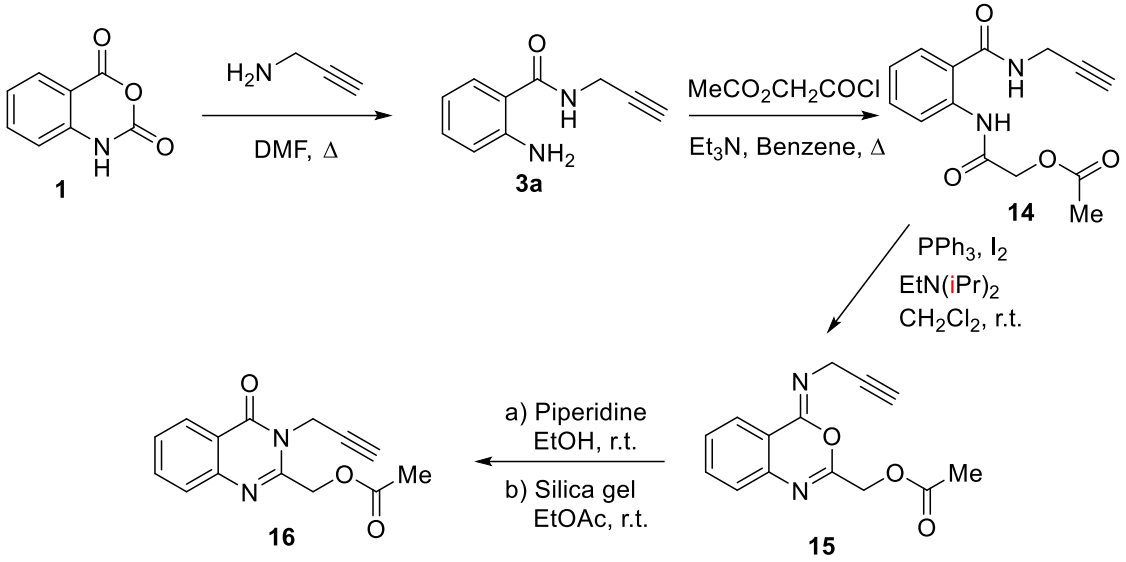
Reisch *et al.* also studied the ring-closure reaction of nicotinamides with triphosgene [21]. The transformation of nicotinamides **4a-c** with triphosgene in pyridine yielded pyrido[2,3-*d*]pyrimidinones **10**–**13**, depending on the substituent of nicotinamide. When R_1=R_2=H, 3-propargylpyrido[2,3-*d*]pyrimidin-2,4-dione (**10)** was obtained. Oxazolopyrido[2,3-*d*]pyrimidin-5-ones **11** and **13**, in turn, were isolated, when

R_1=R_2=Me or R_1=R_3=cyclohexyl, which indicates that the substitution influences the production of the desired tricyclic compounds (Scheme 5). By-product 3-(1,1-dimethylacetonyl)pyrido[2,3-*d*]pyrimidin-2,4-dione (**12**) was also isolated, which could have resulted from hydration of **11** [28].



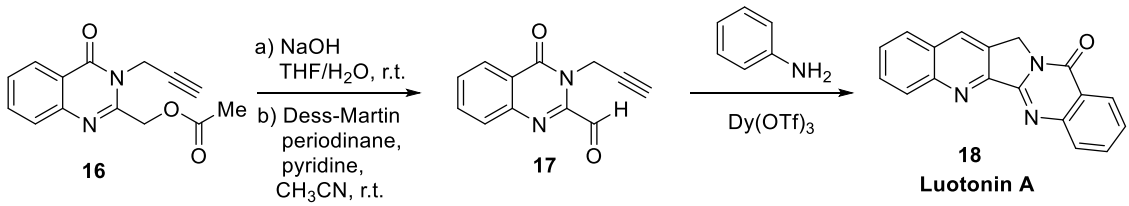
Scheme 5

Twin *et al.* reported a concise intramolecular Povarov strategy for the formation of pyrrolo[3,4-*b*]quinolines that has been applied in a formal synthesis of camptothecin as well as in the total synthesis of Luotonin A (**18**). The total synthesis of Luotonin A (**18**) requires the use of quinazolinone aldehyde precursor **17** [29]. To obtain this precursor, 2-amino-*N*-propargylbenzamide **3a** was prepared on the basis of the procedure reported previously [20]. *N*-Acylation of **3a** was performed using acetoxyacetyl chloride, a reaction step, which can be carried out on a multigram scale, giving **14** in good yield (Scheme 6). The research group investigated various methods in order to obtain the quinazolinone ring system, such as treatment of **14** with sodium carbonate [30]. Unfortunately, it resulted in side reactions, whereas no reaction occurred in the presence of TMSCl [31]. Intermediate **15**, in turn, was made by applying the method developed independently by Snider [32] and Ganesan [33]. Namely, amide **14** was reacted with PPh_3 and iodine in the presence of Hünig's base furnishing **15** in high yield. A two-step, one-pot rearrangement of **15** was elaborated using piperidine followed by silica gel to obtain quinazolinone **16** in 85% yield.



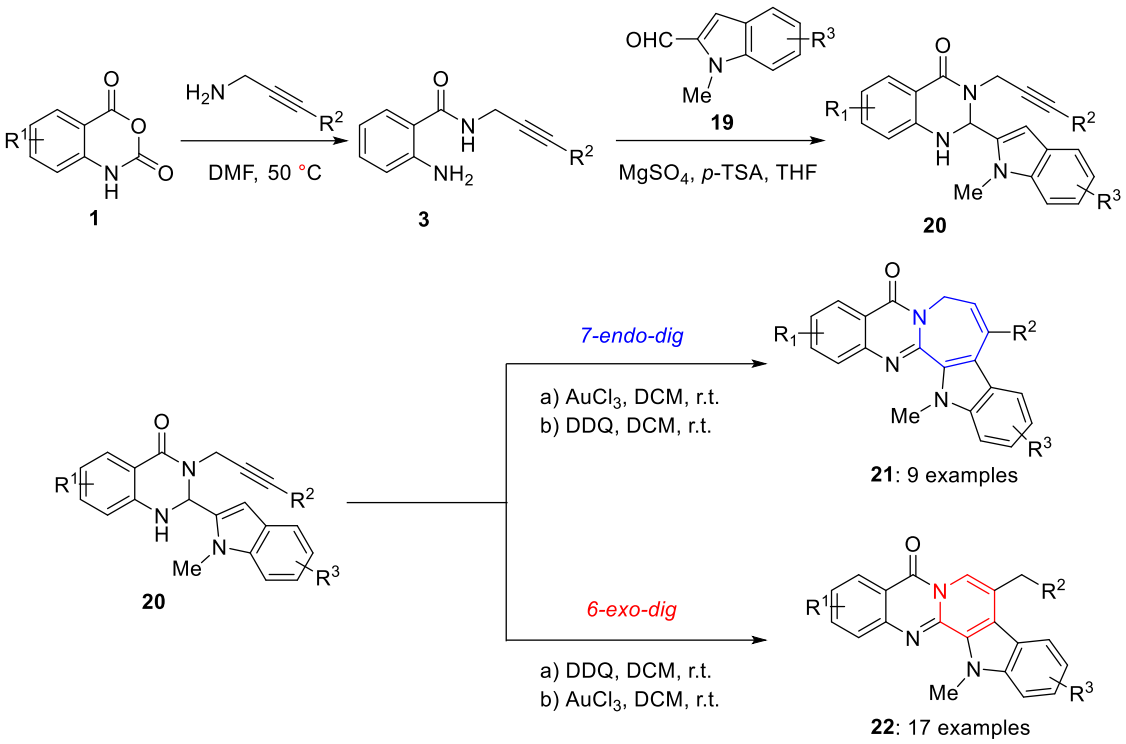
Scheme 6

The final steps in the synthesis of Luotonin A (**18**) involved the removal of the acetyl group of **16** and subsequent oxidation using Dess-Martin periodinane to give aldehyde precursor **17** in good yield in the two steps. Luotonin A (**18**) was finally obtained by an intramolecular Povarov reaction between aniline and aldehyde **17** in acetonitrile in the presence of 10 mol% $Dy(OTf)_3$ in 24 h at room temperature (Scheme 7) [29].



Scheme 7

An efficient method for the synthesis of Rutaecarpine derivatives **21** via gold-catalyzed selective cyclization of alkyne-tethered indoles **20** under mild conditions was described by Kong *et al*. Tethered indole derivatives **20** were prepared by a ring-closure reaction between alkynyl aniline and indole-2-carboxaldehyde in the presence of anhydrous $MgSO_4$ in THF followed by treatment with **19** in the presence of *p*-TSA under N_2 [34]. The alkyne-tethered indoles thus formed can undergo 6-*exo-dig* cyclization by oxidation followed by gold catalysis, while it goes through 7-*endo-dig* cyclization by gold catalysis and subsequent oxidation.



Scheme 8

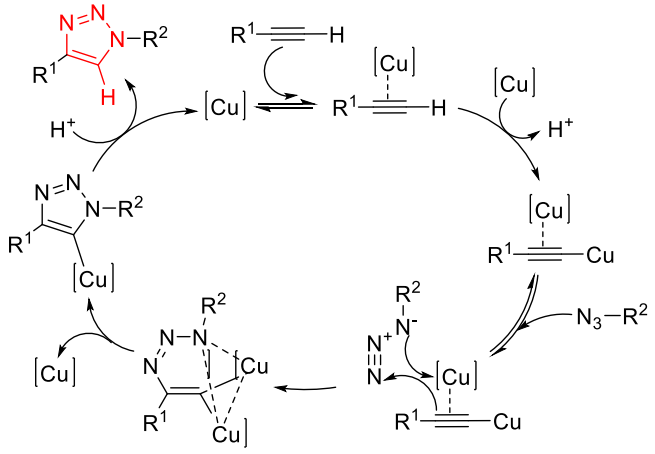
The investigation of the formation of 7-*endo-dig* product **21** indicated that various alkyne-tethered indoles (**20**) can be converted to 7-*endo-dig* product **21** in moderate yields accompanied by minor 6-*exo-dig* product **22** by gold catalysis and subsequent oxidation with DDQ in a one-pot reaction (Scheme 8). The products could be purified easily by flash column chromatography. This also provided a new entry to access the 7-*endo-dig* cyclization products for further studies in the synthesis of pharmaceuticals [34].

Furthermore the research group studied the possibility of 6-*exo-dig* cyclisation of alkyne-tethered indoles. Initially, an oxidation of **20** was performed using DDQ in methanol, followed by a sequential treatment with catalytic amount of $AuCl_3$ in DCM at room temperature to obtain the desired **22** products (Scheme 8). The generality of this catalytic system for 6-*exo-dig* cyclization was also explored. A variety of substituents (R^1, R^2, R^3) of compound **20** were well tolerated and allowed the synthesis of product **22** with uniformly high efficiency [34].

2.3. Click transformations of 2-amino-*N*-propargylbenzamides

Since its discovery by Sharpless [35], the copper-catalyzed 1,3-dipolar cycloaddition between an azide and an alkyne (CuAAC) has become one of the most widely used click-chemistry methods enabling the efficient synthesis of a variety of compounds from simple to complex structures with high selectivity [36–39].

The mechanism of this process was thoroughly explored using kinetic studies and DFT calculations [40–43]. First a bimetallic mechanism was proposed in which the alkynyl moiety was coordinated to one of the copper centres, whereas the azide attacked a second one. A bimetallic structure was also involved in this mechanism, because a π-complexation of the α-alkynyl-Cu(I) species was suggested to enhance the reactivity of the alkynyl ligand by decreasing the electron density of the Csp carbon atoms [40, 41]. DFT calculations confirmed that the second Cu(I) atom interacted with the Cu(I)-acetylide [40–43]. The azide attack was followed by formation of a Cu(III) vinylidene metallacycle. According to Fokin, tris(triazolylmethyl)amine ligands are labile enough to be easily displaced by substrates and, at the same time, they are strong enough to avoid the formation of higher unreactive or less reactive Cu(I) aggregates. Under these conditions, the μ_2-ligated σ–π-alkynyl dicopper transition state was proposed (Scheme 9) [41].

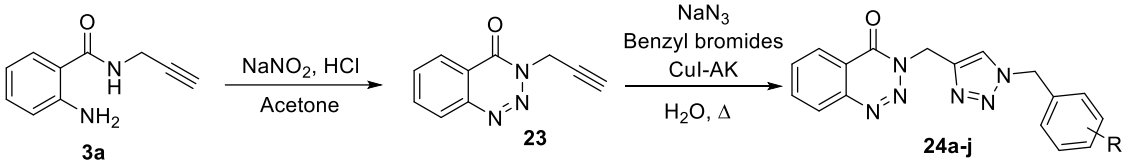


Scheme 9

Various applications of the click reaction have acquired tremendous importance in different fields such as organic chemistry, synthetic carbohydrate chemistry, biotherapeutics, catalysis, biochemistry, medical science, and material science. The development of new methods for the synthesis of 1,2,3-disubstituted triazoles is still

of interest due to the importance of this function. The presence of the propargyl substitution on 2-amino-*N*-propargylbenzamide made it the subject of several different click reactions.

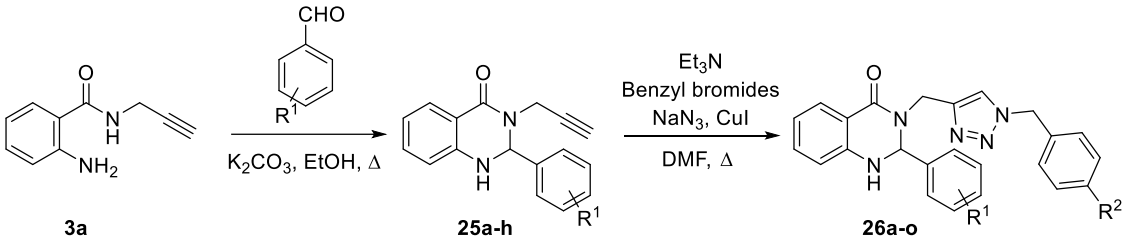
Moghimi *et al.* described an approach for the synthesis of benzotriazinone-triazole systems. Starting with 2-amino-*N*-propargylbenzamides **3a**, its exposure to acidic solution of sodium nitrite at 0 °C for 1 h resulted in intramolecular nitrogen–nitrogen bond formation (Scheme 10). Subsequently, the formed benzotriazinone **23** was subjected to click reaction with copper nano-catalyst CuI-AK on a modified silica-based KIT-5 support, in the presence of NaN_3, with 10 different benzyl bromides. The desired products **24a-j** were obtained after 3 h in good to excellent yields [44].



24a: R= H; **24b**: R= 2-Me; **24c**: R= 3-Me; **24d**: R= 4-Me; **24e**: R= 3-F; **24f**: R= 2-Cl; **24g**: R= 2,3-Cl_2; **24h**: R=3,4-Cl_2 ; **24i**: R= 2-Br; **24j**: R= 4-NO_2;

Scheme 10

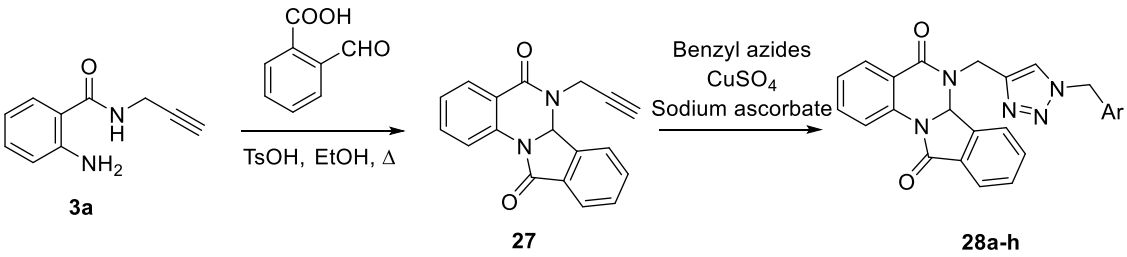
Farjadmand *et al.* preformed a ring-closure reaction between 2-amino-*N*-propargylbenzamide **3a** and substituted benzaldehydes using potassium carbonate in ethanol at reflux temperature producing quinazolinone **25a-h** derivatives with a yield range of 62–77%. The obtained quinazolinones were subjects of a click reaction at the terminal triple bonds attached to the C3-position using benzyl bromide derivatives, sodium azide, triethyl amine and CuI in DMF. Both unsubstituted and substituted benzylbromide derivatives possessing various electron-withdrawing groups provided excellent yields of triazole products **26a-o** (Scheme 11) [22].



26a: R^1= H; R^2= H; **26b**: R^1= H; R^2= Cl;
26c: R^1= 4-Me; R^2= Cl; **26d**: R^1= 4-Me; R^2= Br;
26e: R^1= 4-OMe; R^2= Cl; **26f**: R^1= 4-OMe; R^2= Br; **26g**: R^1= 3-OMe; R^2= Cl;
26h: R^1= 3,4-OMe; R^2= H; **26i**: R^1= 3,4-OMe; R^2= Cl; **26j**: R^1= 3,4-OMe; R^2= Br;
26k: R^1= 3,4,5-OMe; R^2= F; **26l**: R^1= 3,4,5-OMe; R^2= Cl;
26m: R^1= 4-Cl; R^2= F; **26n**: R^1= 4-Cl; R^2= Cl; **26o**: R^1= 4-Cl; R^2= Br;

Scheme 11

Esmaeili-Marandi *et al.* elaborated a domino ring-closure reaction by reacting 2-amino-*N*-propargylbenzamide **3a** with 2-formylbenzoic acid for the preparation of 6-propargyl-6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione **27** in high yield (85%) using *p*-TSA in EtOH under reflux (Scheme 12). Next, under click reaction condition, using sodium ascorbate and a catalytic amount of $CuSO_4$, compound **27** was reacted with freshly prepared azides, possessing electron-donating and electron-withdrawing groups as well as halogens, leading to the formation of different isoindolo[2,1-*a*]quinazolinedione-coupled 1,2,3-triazoles **28a-h** [45].

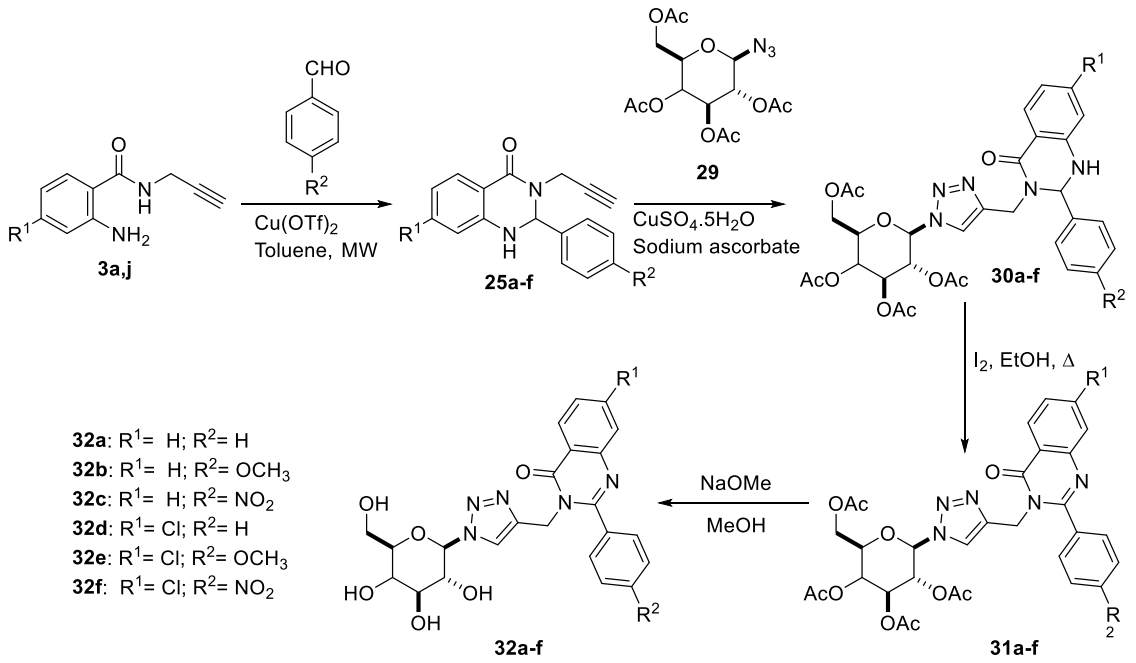


28a: Ar= Ph; **28b**: Ar= 2-Me-C_6H_4; **28c**: Ar= 4-F-C_6H_4; **28d**: Ar= 2-Cl-C_6H_4; **28e**: Ar= 2,3-Cl-C_6H_3;
28f: Ar= 3,4-Cl-C_6H_3; **28g**: Ar= 2-Br-C_6H_4; **28h**: Ar= 2-NO_2-C_6H_4

Scheme 12

Ramakrishna *et al.* used 2-amino-*N*-propargyl benzamides **3a,j** for a ring-closure reaction with different benzaldehydes to obtain various 2-phenyl-3-propargyl-2,3-dihydroquinazolin-4-(1*H*)-one **25** under optimal conditions (20 mol% of $Cu(OTf)_2$, toluene, microwave irradiation, 30 min). In addition to high yields, shorter reactions and reduction of the by-products were also observe by employing microwave irradiation (Scheme 13) [27].

The obtained ring-closed products were subjected to CuAAC reactions with freshly prepared glycosyl azides **29** using equimolar quantities of the reagents, $CuSO_4.5H_2O$ and sodium ascorbate in *t*-BuOH/H_2O (1:1) at room temperature. The reactions afforded epimeric mixtures of peracetyl glycosyltriazolyl 2,3-dihydroquinazolin-4(1*H*)-ones **30** in good yields.



Scheme 13

2.4. Domino reactions and transformations of 2-amino-*N*-propargylbenzamide

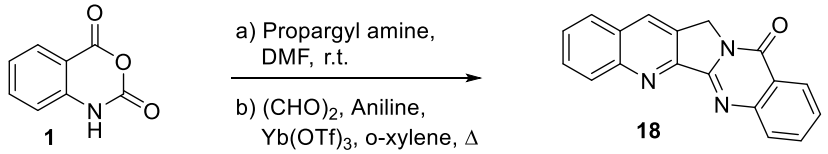
The development and synthesis of architecturally diverse and complex molecules with efficient, environmentally benign and atom-economic fashion have become extremely important in the last several decades [1–3]. As a solution to this challenging problem, a multistep, one-pot procedure has been developed. Such processes, involving several transformations with bond forming taking place in a domino reaction manner are also referred to as “pot economy” [4]. Major benefits are both minimal time consumption and chemical waste generation.

Therefore, the development of a reaction sequence, that assembles several components or transformations engaging several reactive centres, is ideal for preparing complex structures. In general, the number of possible diastereomers increases along with the number of components. Although several successful examples have been reported

[5–7], because of the difficulty of performing “one-pot” domino reactions with high diastereoselectivity, the task is still challenging [8–12].

The use of one-, two- and multi-component domino reactions in asymmetric synthesis is continuously increasing [46–50]. Such single-step reactions allow the synthesis of a wide range of structurally diverse and complex chiral molecules from simple substrates in an economically favourable manner, by avoiding the use of costly and time-consuming protection–deprotection processes as well as purification procedures of intermediates [51–54].

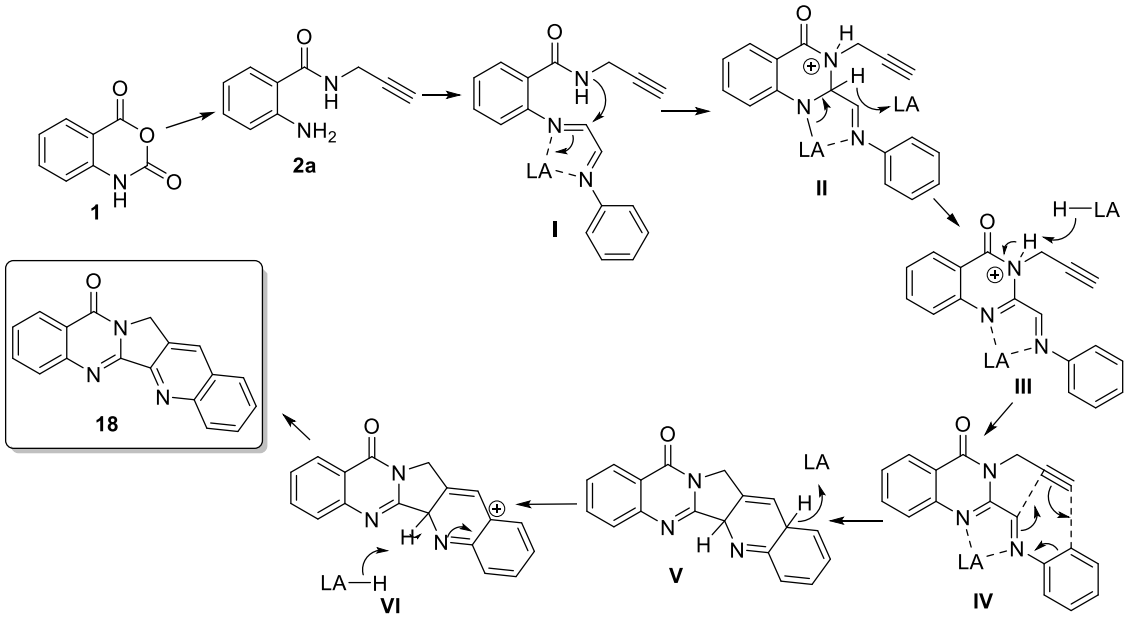
A literature survey described the use of 2-amino-*N*-propargylbenzamide as a key material for some recent domino reaction procedures. Tseng *et al.* achieved a self-directed chemical process with the aid of a single metal triflate to concomitantly construct quinazoline and pyrroloquinoline cores to afford the synthesis of Luotonin A **18** (Scheme 14) [55]. The process involves five reactions sequences: (*i*) imine formation, (*ii*) quinazolinone formation, (*iii*) intramolecular aza-Diels–Alder reaction and, finally, (*iv*) dehydrogenation and (*v*) aromatization. The procedure is activated and catalyzed by metal triflates, using commercially available isatoic anhydride as starting material. The first step of the synthesis was performed in DMF with propargylamine. After removal of excess propargylamine under vacuum, formed 2-amino-*N*-propargylbenzamide **2a** was reacted with aniline (10 equiv), in the presence of $Yb(OTf)_3$ (20 mol %) and aqueous glyoxal (40%, 15 equiv) at reflux temperature in a solution of *o*-xylene for 12 h, furnishing fluorescent product **18** isolated in 35% yield after column chromatography.



Scheme 14

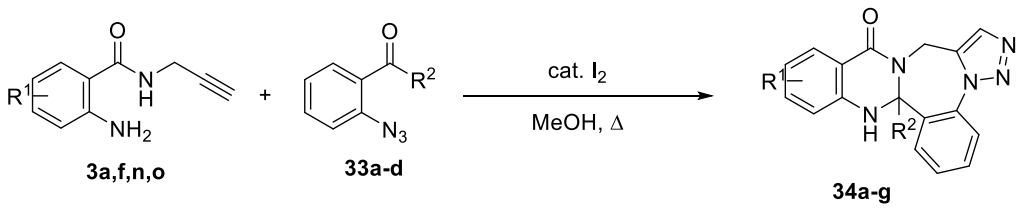
A plausible mechanism for the synthesis of **18** is presented in Scheme 15. First, propargylamine was reacted with isatoic anhydride **1** to form an isolable intermediate **2a** followed by the Lewis acid-mediated formation of imine **I**, concomitantly leading to ring-closed product **II**. Subsequently, dehydrogenation of **III** forms the stable D ring in **IV**, and then aromatization of **V** to **VI** takes place. Finally, **18** can be readily formed through Lewis acid-catalyzed H-abstraction and deprotonation of the cyclohexadienyl cation intermediate. The aromatization of cyclohexadiene ring in **V** and related hydrocarbons

promoted by Lewis acids is well-documented in the literature [56, 57]. As one of the key steps in this proposed mechanism, the transformation of **IV** to **V** could be rationalized (as elegantly proposed by Yu *et al.* [58]) using a Lewis acid-catalyzed inverse electron-demand aza-Diels–Alder [4+2] cycloaddition reaction, in an intramolecular fashion (IADA), between *N*-chelated *N*-phenyliminium azadiene and the electron-rich alkyne dienophile moiety in **IV**.



Scheme 15

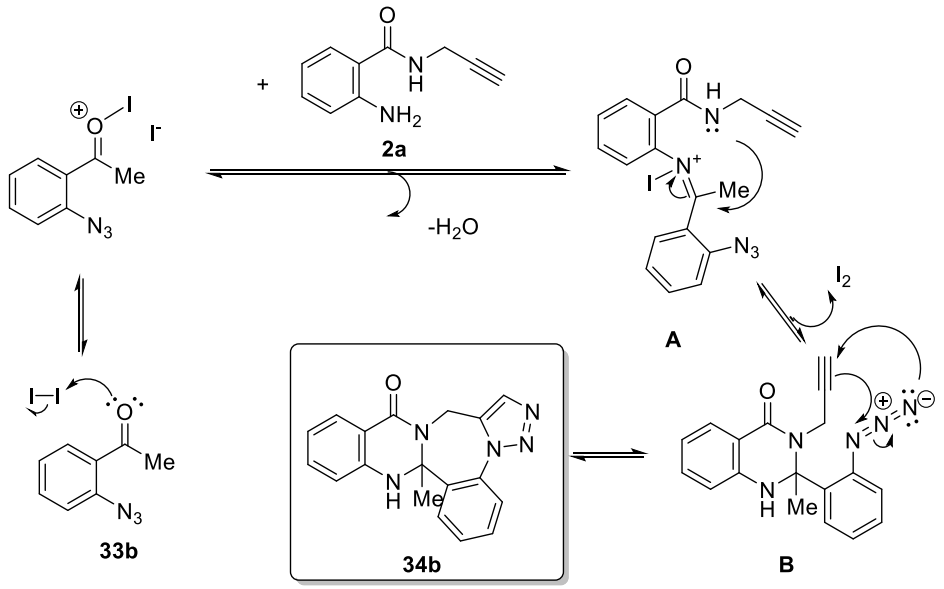
Guggenheim *et al.* developed a one-pot, two-step cascade method to prepare quinazolinotriazolobenzodiazepines **34** using substituted and unsubstituted 2-amino-*N*-propargylbenzamides (**3a**) as a starting material [23]. According to a general method, the starting materials were reacted with 1-(2-azidophenyl)ethenone **33a-d** at reflux temperature in methanol in the presence of iodine as catalyst **(**Scheme 16). The use of varied substrates allowed to study the generality of the process.



34a: R^1= H; R^2= H; **34b**: R^1= H; R^2= Me; **34c**: R^1= H; R^2= Ph; **34d**: R^1= 3-Br; R^2= Me; **34e**: R^1= 4-OMe; R^2= Me; **34f**: R^1= 5-OMe; R^2= Me; **34g**: R^1= 5-OMe; R^2= Ph;

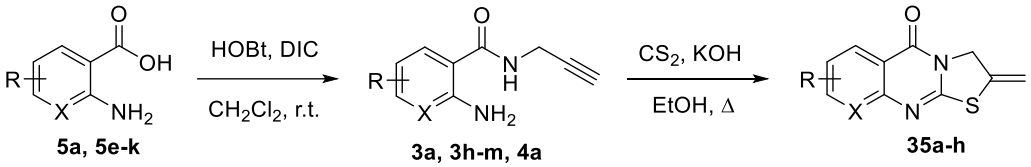
Scheme 16

The first step of the proposed mechanism consists of aniline–keto condensation to form Schiff base **A** and subsequent nucleophilic attack by the amide nitrogen onto the imine to give quinazolinone **B**. These two iodine-promoted condensations pre-organize the alkyne and azide for an intramolecular 1,3-dipolar cycloaddition (step two) to form complex pentacyclic system **34b (**Scheme 17).



Scheme 17

Mahdavi *et al.* performed an efficient synthesis of 2-methylenethiazolo[2,3-*b*]quinazolinone derivatives **35a-h** starting from propargyl-substituted amides [26]. The reaction proceeded by a cyclization reaction of 2-amino-*N*-propargylbenzamide derivatives **3a, 3h-m, 4a** promoted by potassium hydroxide followed by selective 5-*exo-dig* ring closure in the presence of CS_2 to give the corresponding products **35a-h** in relatively short reactions (3–8 h) in good yields (Scheme 18).



35a: R= H; **35b**: R= 5-Me; **35c**: R= 4,5-$(OMe)_2$; **35d**: R= 4-Cl; **35e**: R= 5-Cl;
35f: R= C_4H_4 (3-amino-2-naphthoic acid);**35g**: R= 4-NO_2; **35h**: X = N, R = H

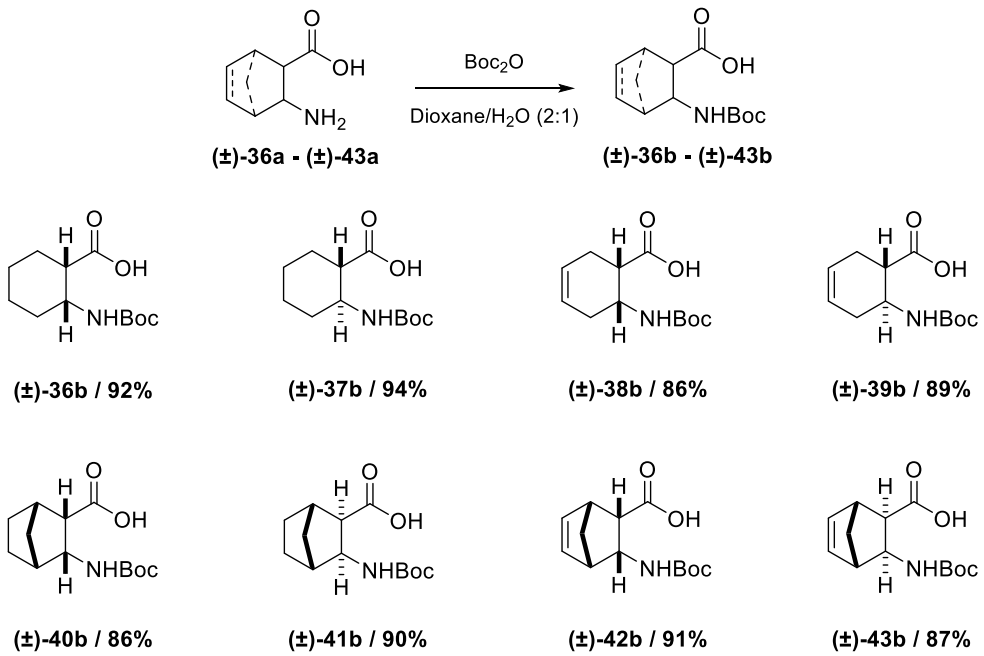
Scheme 18

3. RESULTS AND DISCUSSIONS

3.1. Preparation of key starting materials

3.1.1. Preparation of racemic alicyclic 3-amino-*N*-propargyl carboxamides

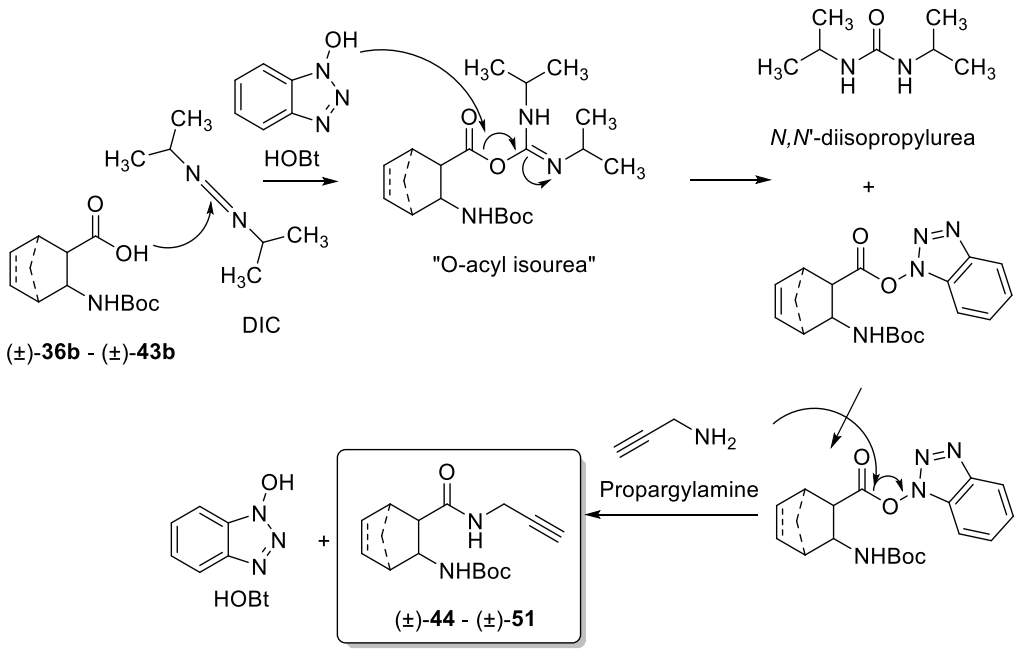
Racemic alicyclic *N*-Boc-protected amino acids (±)-**36b**–(±)-**43b** were produced from the corresponding *cis*- and *trans*-2-aminocyclohexane-1-carboxylic acids (±)-**36a** and (±)-**37a**, *cis*- and *trans*-6-aminocyclohex-3-ene-1-carboxylic acids (±)-**38a** and (±)-**39a**, *diendo*- and *diexo*-3-aminobicyclo[2.2.1]heptane-2-carboxylic acids (±)-**40a** and (±)-**41a** and *diendo*- and *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids (±)-**42a** and (±)-**43a** according to a literature procedure [59]. To a solution of the appropriate β-amino acid in a 2:1 dioxane/H_2O mixture, 1 M NaOH was added. The solution was cooled to 0 °C followed by the addition of 1.1 equivalent of Boc_2O. The mixture was stirred at 0 °C for 1 h, warmed to room temperature, stirred for 4 h and, finally, dioxane was evaporated from the solution. The residue was acidified with 10% H_2SO_4 to pH = 2.5 and the resulting mixture was extracted with EtOAc, the crude product was filtered off from Et_2O and recrystallised from iPr_2O.



Scheme 19

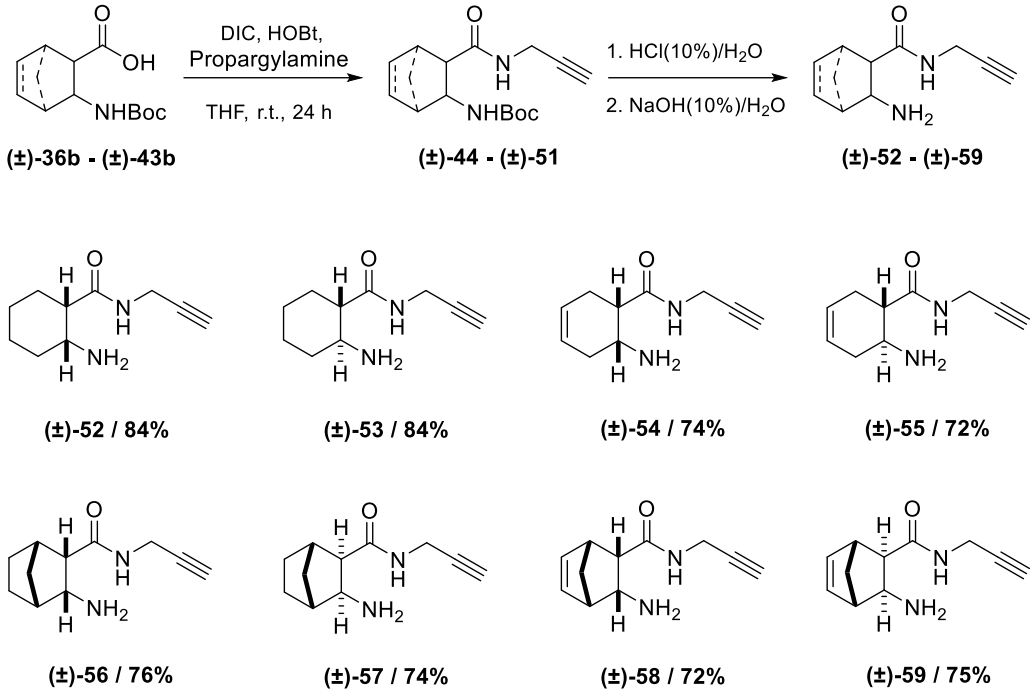
Alicyclic *N*-Boc-protected propargylamides (±)-**44**–(±)-**51** were easily obtained, following a slightly modified coupling reaction using a literature procedure [26]. In the

process, the appropriate *N*-Boc-protected amino acids (±)-**36b**–(±)-**43b** are reacted in a mixture of DIC, HOBt and *N*-propargylamine in THF (Scheme 20). DIC is often used for solution-phase peptide couplings since its urea by-product can be removed by washing during aqueous work-up. The solution was moderately stirred overnight at room temperature. After the reaction was completed, checked by thin layer chromatography, the reaction mixture was evaporated and then the residue was dissolved in EtOAc and washed with water. The purification was hindered due to the presence of HOBt and urea-type side-product formed form DIC, which could not be washed with water. However, the purification of the residue was performed successfully by a fast column chromatography over silica gel with EtOAc as eluent.



Scheme 20

Afterwards, the deprotection of Boc-protected amides (±)-**44**–(±)-**51** was performed using a mixture of the appropriate Boc-protected amide with 10% aqueous HCl solution under stirring at room temperature for 6 h (Scheme 21). The aqueous layer was neutralized with 10% aqueous NaOH solution and extracted with CH_2Cl_2. The combined organic phase was dried and the solvent was evaporated. The resulting racemic alicyclic β-amino-*N*-propargyl carboxamides (±)-**52**–(±)-**59** were used for the next steps without purification.



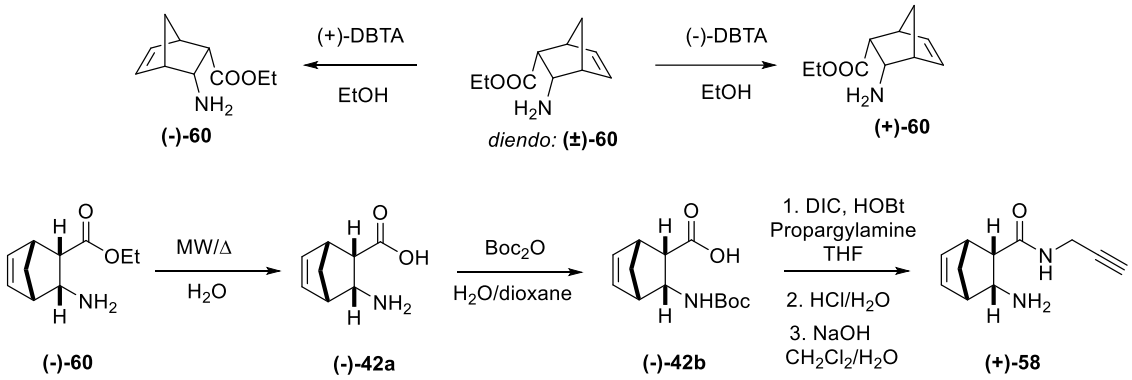
Scheme 21

3.1.2. Synthesis of enantiomeric norbornene 3-amino-*N*-propargyl carboxamides

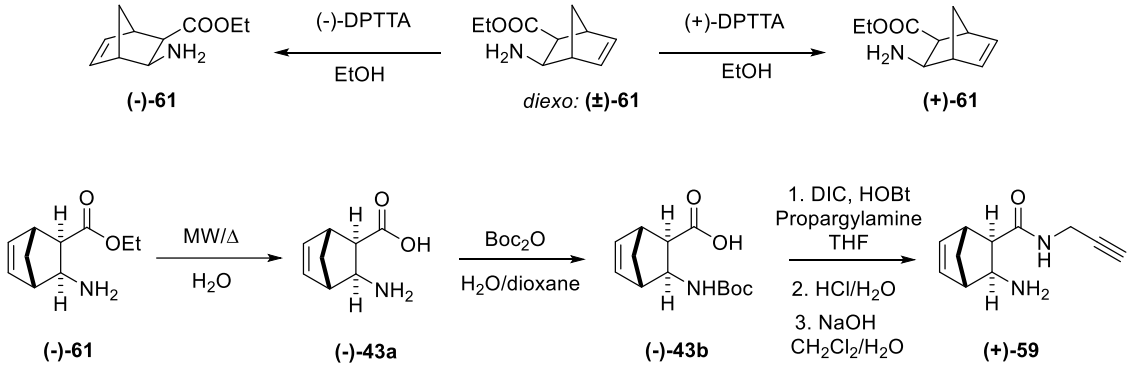
The synthesis of enantiomeric Boc-protected amino acids (−)-**42b** and (−)-**43b** started from enantiomeric 2-aminonorbornene esters (−)-**60** and (−)-**61** as depicted in Scheme 22 and Scheme 23. The starting enantiomeric 2-aminonorbornene esters (−)-**60** (*ee* > 95%) and (−)-**61** (*ee* > 96%) were prepared from racemic amino esters (±)-**60** and (±)-**61** by diastereomeric salt formation with DPTTA and DBTA as previously published [60]. The *ee* values of (+)-**60** and (−)-**60** were determined by a literature method [60]. The *ee* values for (+)-**61** (92%) and (−)-**61** (98%) were determined by HPLC using Phenomenex-IA column after derivatisation with benzoyl chloride in the presence of TEA.

To obtain the enantiomeric 2-aminonorbornene acids (−)-**42a** and (−)-**43a**, the corresponding enantiomeric 2-aminonorbornene esters were diluted in water in a 10 mL pressurized reaction vial, and the solution was stirred and warmed to 100 °C and kept at this temperature for 30 min under 300 W microwave irradiation. The solvent was evaporated and the crude product was filtered off from acetone and recrystallised from water/acetone.

The furnished amino acids (−)-**42a** and (–)-**43a** were then reacted with Boc_2O affording *N*-Boc-protected amino acids (−)-**42b** and (−)-**43b**. These were then transformed into propargylamides (−)-**50** and (−)-**51** in tetrahydrofuran using propargylamine in the presence of DIC and HOBt, utilising the same procedure used for the racemic compounds. After acidic deprotection of amides (−)-**50** and (−)-**51**, free amide bases (+)-**58** and (+)-**59** were applied in the next step without purification. In Scheme 22 and 23 only a single enantiomer is represented for evidence, but the opposite enantiomer of free amide bases (–)-**58** and (–)-**59** were also synthesized.



Scheme 22



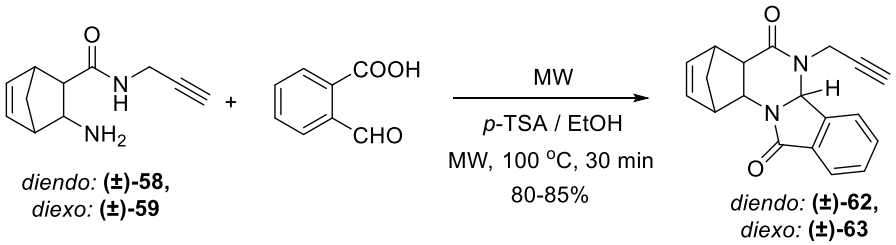
Scheme 23

3.2. Domino reactions towards *N*-heterocyclic compounds

3.2.1. Synthesis of isoindolo[2,1-*a*]quinazolinones

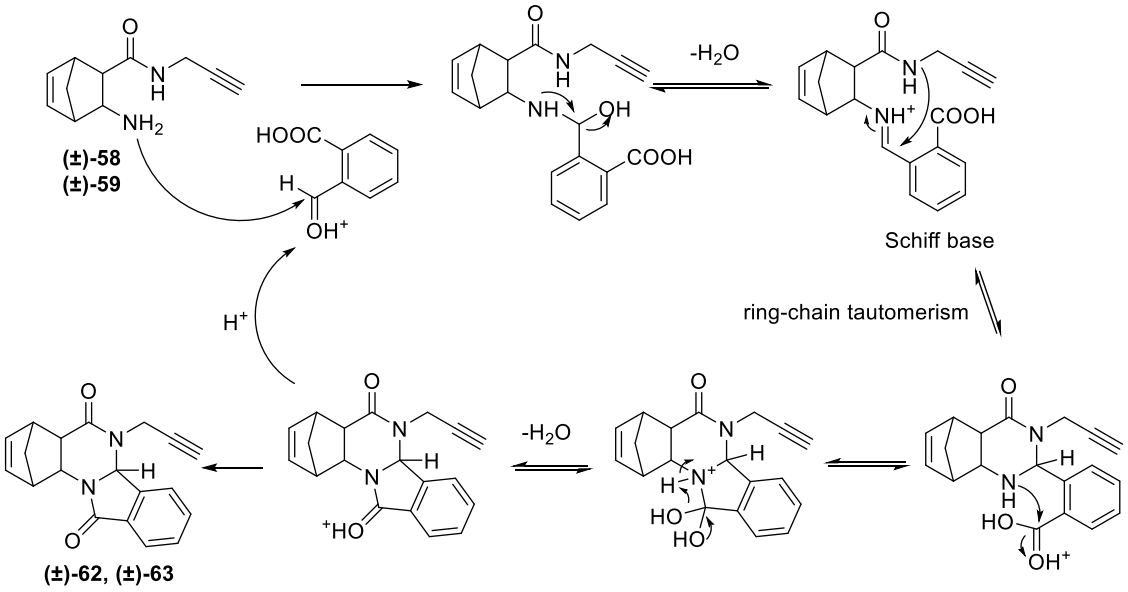
The alicyclic derivatives of isoindolo[2,1-*a*]quinazolinones were synthesised in a one-step procedure. First, all methods were performed and optimized with racemic starting materials followed by repeating the syntheses with the enantiomers. The reaction was implemented by dissolving *diendo*-(±)-**58** and *diexo*-(±)-**59** in ethanol using one equivalent of 2-formylbenzoic acid and stirring the solution at 100 °C for 30 min under

microwave irradiation at 300 W in the presence of *p*-TSA. Upon completion of the reaction (monitored by TLC), the solvent was evaporated and the crude solid was filtered off from Et_2O and recrystallised from EtOH. The ^1H NMR spectra revealed the formation of the alicyclic isoindolo[2,1-*a*]quinazolines (±)-**62** and (±)-**63** (Scheme 24).



Scheme 24

The reaction of alicyclic propargylamides (±)-**58** and (±)-**59** with 2-formylbenzoic acid is interpreted in a plausible manner as a domino process, in which the first step is Schiff base formation [15, 61]. Then it undergoes ring closure to give isoindolo[2,1-*a*]quinazolinones (±)-**62** and (±)-**63**, respectively (Scheme 25).



Scheme 25

Full NMR signal assignment was carried out for compounds (±)-**62** and (±)-**63**. According to the characteristic NOE crosspeaks, the relative configuration of the new hydrogen in the product from the *diendo* isomer is in *trans* arrangement relative to the annelated hydrogen atoms in (±)-**62**. The characteristic crosspeak for (±)-**62** was found between protons C(6a)-H and C(3)-H (Figure 1).

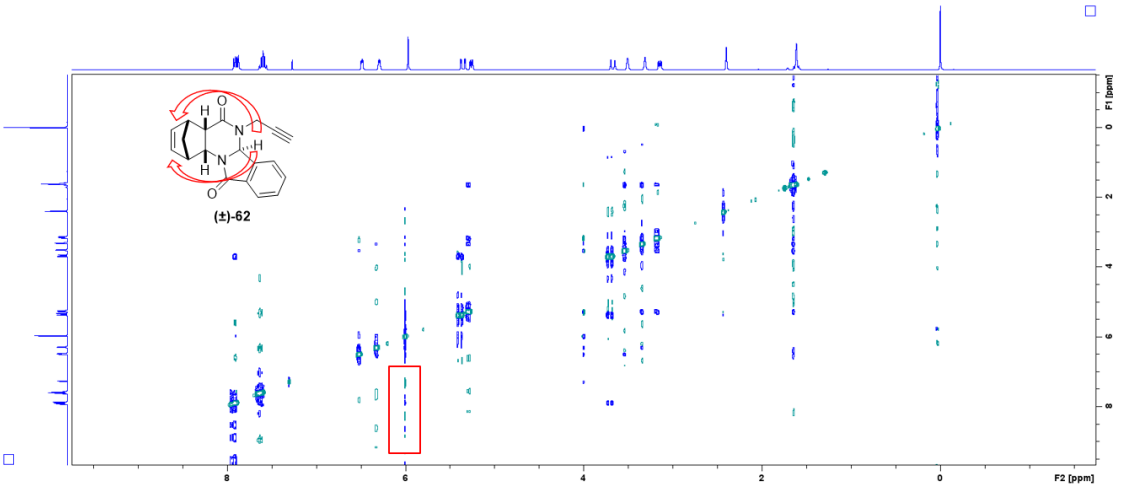


Figure 1

On the other hand, considering the *diexo* isomer, according to the characteristic NOE crosspeaks, the relative configuration of the new hydrogen is in *trans* arrangement with the annelated hydrogen atoms in (±)-**63**. The characteristic crosspeak was found for (−)-**63** between protons C(6a)-H and C(13)-H (Figure 2).

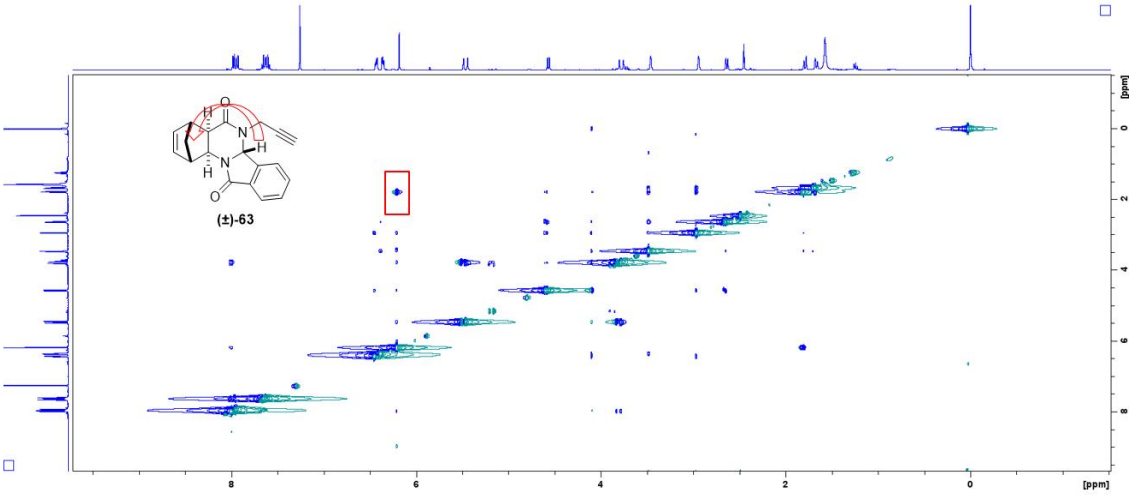
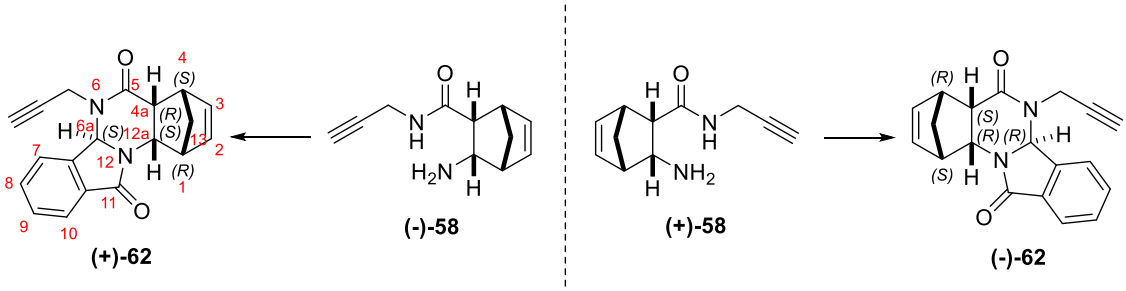


Figure 2

The reaction was repeated starting from enantiomeric *diendo*-(+)-**58** and *diendo*-(−)-**58** as well as *diexo*-(+)-**59** and *diexo*-(–)-**59**. Following the same procedure, (1*S*,4*R*,4a*S*,6a*R*,12a*R*)-6-(prop-2-yn-1-yl)-1,4,4*a*,6,6*a*,12*a*-hexahydro-1,4-methanoisoindolo[2,1-*a*]quinazoline-5,11-dione [(–)-**62**)] and (1*R*,4*S*,4a*R*,6a*S*,12a*S*)-6-(prop-2-yn-1-yl)-1,4,4*a*,6,6*a*,12*a*-hexahydro-1,4-methano-isoindolo-[2,1-*a*]quinazoline-5,11-dione [(+)-**62**)] were isolated starting from (+)-**58** and (–)-**58**, respectively (Scheme 26). The *ee* values for (+)-**62** (92%) and (−)-**62** (94%) were determined by HPLC using Phenomenex-IA column (Figure 3).



Scheme 26

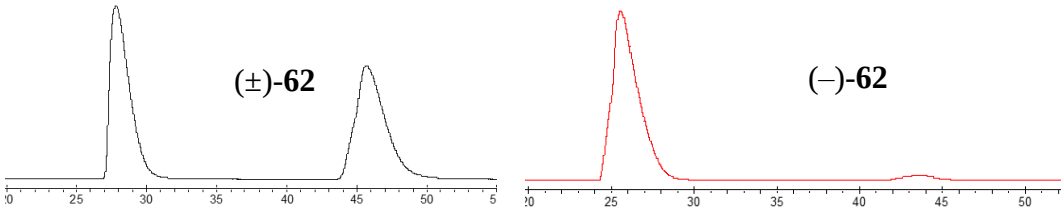
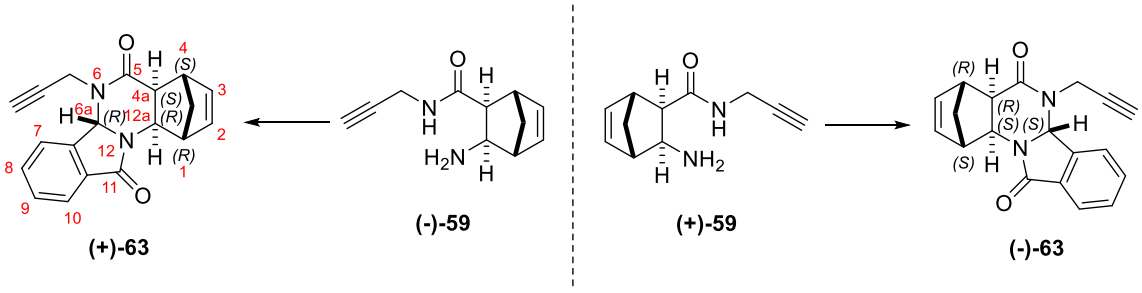


Figure 3. HPLC chromatograms of (±)-**62** and (–)-**62**

n-hexane/IPA 60:40; 1 ml/min; 254 nm; IA

In addition, starting from *diexo*-(−)-**59** and *diexo*-(+)-**59** (1*R*,4*S*,4a*S*,6a*R*,12a*R*)-6-(prop-2-yn-1-yl)-1,4,4*a*,6,6*a*,12*a*-hexahydro-1,4-methanoisoindolo[2,1-*a*]quinazoline-5,11-diones, (+)-**63** and (–)-**63** (1*S*,4*R*,4a*R*,6a*S*,12a*S*)-6-(prop-2-yn-1-yl)-1,4,4*a*,6,6*a*,12*a*-hexahydro-1,4-methanoiso-indol[2,1-*a*]quinazoline-5,11-diones were isolated (Scheme 27). The *ee* values for (+)-**63** (96%) and (−)-**63** (93%) were determined by HPLC using Phenomenex-IA column (Figure 4).



Scheme 27

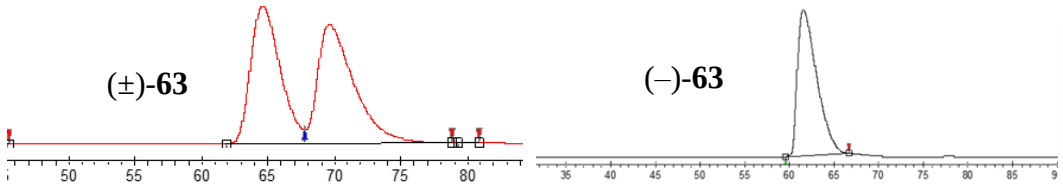
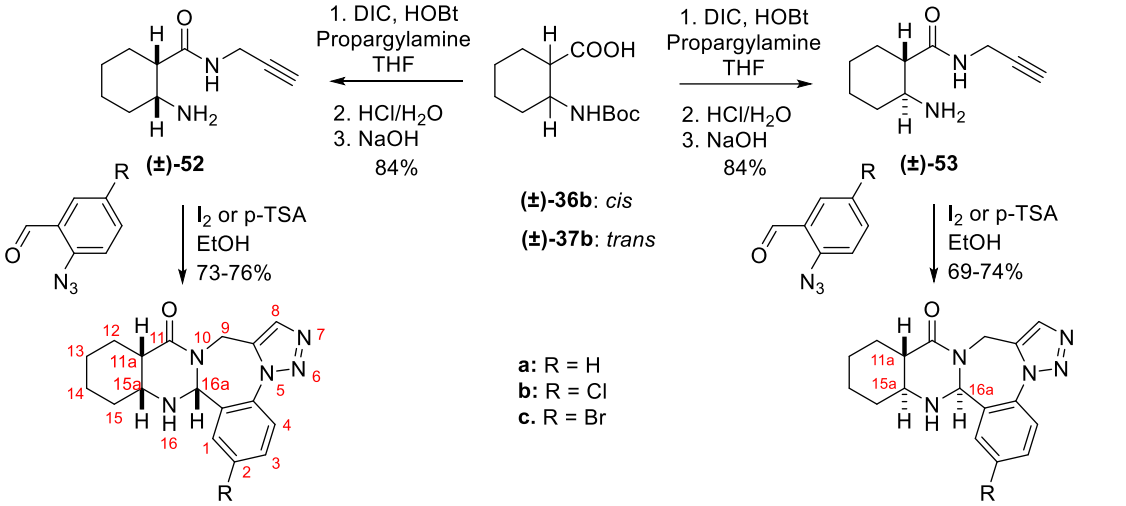


Figure 4. HPLC chromatograms of (±)-**63** and (–)-**63**

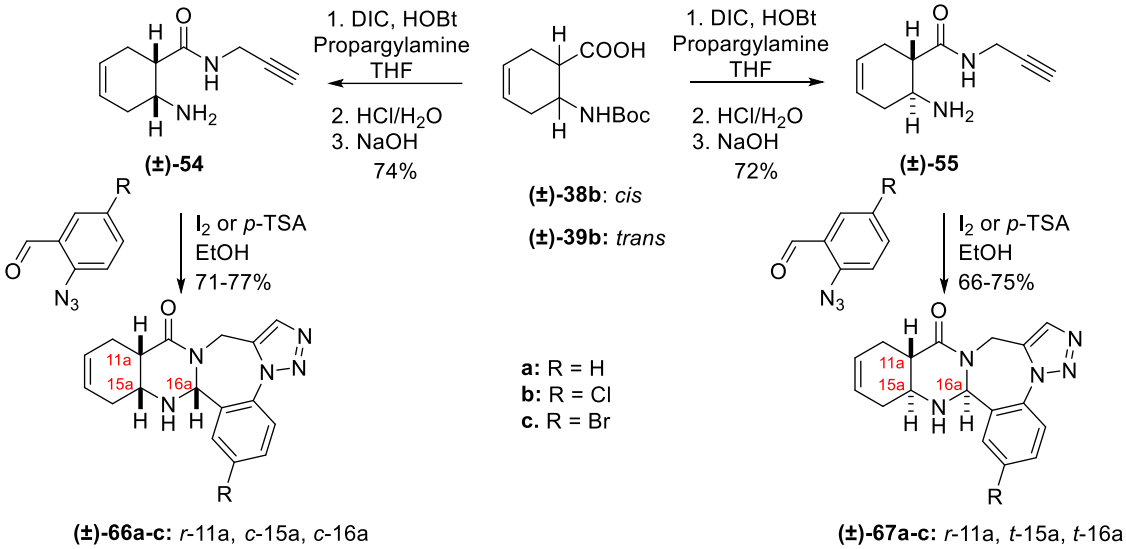
n-hexane/IPA 70:30; 0.15 ml/min; 254 nm; ODH

3.2.2. Synthesis of alicyclic quinazolinotriazolobenzodiazepines

A one-pot, two-step cascade process was carried out by reacting chloro- or bromo-substituted and unsubstituted azidobenzaldehydes with *cis*- and *trans*- cyclohexane and cyclohexene skeletons bearing *N*-propargyl carboxamides under reflux in EtOH in the presence of a catalytic amount iodine or *p*-TSA for 2 h. The main products (±)-**64a–c**, (±)-**65a–c**, (±)-**66a–c** and (±)-**67a–c** were obtained after crystallization from Et_2O followed by recrystallization from a 5:1 mixture of iPr_2O–EtOH (Schemes 28 and 29).



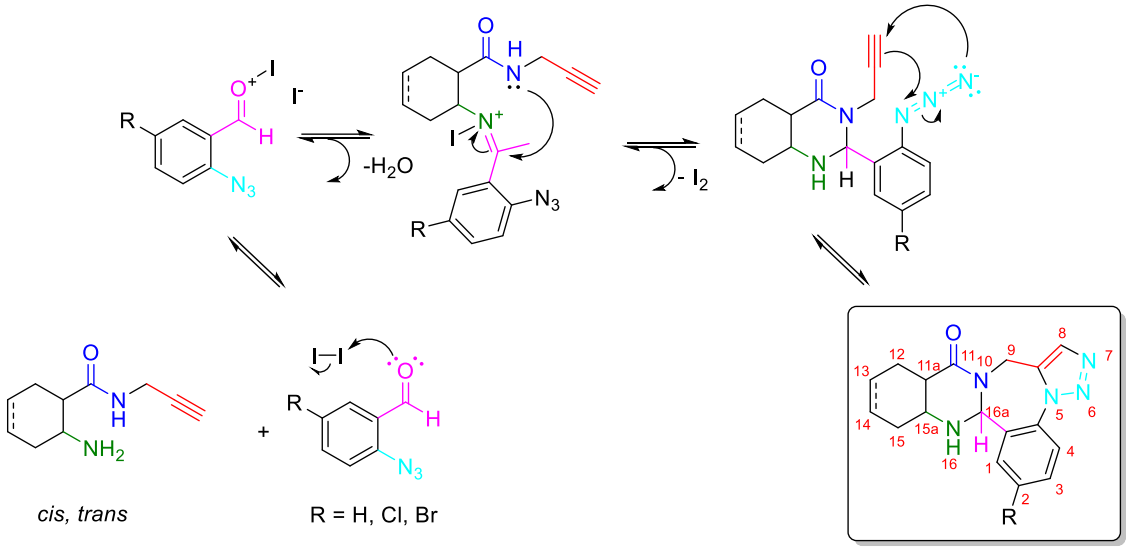
Scheme 28



Scheme 29

In the cascade process of alicylic 2-aminocarboxamides with 2-azidobenzaldehydes involving five reactive centres, first a Schiff base is produced, which undergoes a ring-

closure reaction to give quinazoline epimers through a ring–chain tautomerism. The next step is an intramolecular azide–alkyne 1,3-dipolar cycloaddition delivering the pentacyclic ring systems (Scheme 30) [23].



Scheme 30

This designed cascade process is atom economic as described by Trost [62, 63], since it maximizes the incorporation of both reagents into the final compound without any by-product, with a given consideration to the use of stoichiometric quantities for both reagents [64]. Moreover, it also employs environmentally benign iodine as a catalyst. Furthermore, the process is step economic, minimising the number of reactions steps to a bare minimum, as described by Wender [65, 66], with the possibility to form two epimers of (±)-**64a–c**, (±)-**65a–c**, (±)-**66a–c** and (±)-**67a–c**.

In all cases, the ^{1}H NMR spectra revealed the formation of the single epimers of quinazolino[1,2,3]triazolo[1,4]benzodiazepines (±)-**64a–c**, (±)-**65a–c**, (±)-**66a–c** and (±)-**67a–c**. Full NMR signal assignment was carried out for these compounds. Characteristic NOE crosspeaks were found between the protons C(11a)-H, C(15a)-H, and C(16a)-H for cyclohexane *cis*-condensed (±)-**64a–c** and between the protons C(15a)-H, and C(16a)-H for cyclohexane *trans*-condensed (±)-**65a–c**. This allowed the deduction of the relative configuration of the new asymmetric centre, which is in *cis* arrangement with the C(11a)-H and C(15a)-H hydrogens. Furthermore, the stereochemistry of (±)-**64a** and (±)-**65a** was also confirmed by X-ray diffraction analysis (Figure 5).

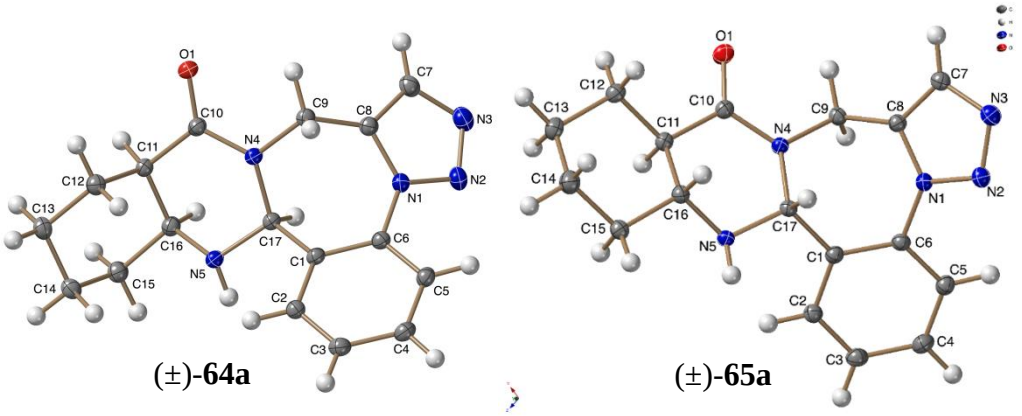


Figure 5. ORTEP plot of the X-ray structure of (±)-**64a**, and (±)-**65a**

For cyclohexene *cis*-condensed (±)-**66a–c** and cyclohexene *trans*-condensed (±)-**67a–c**, the relative configuration of the new asymmetric centre C(16a)-H is in *cis* arrangement with the C(15a)-H proton as shown by their NOE crosspeaks (Figure 6).

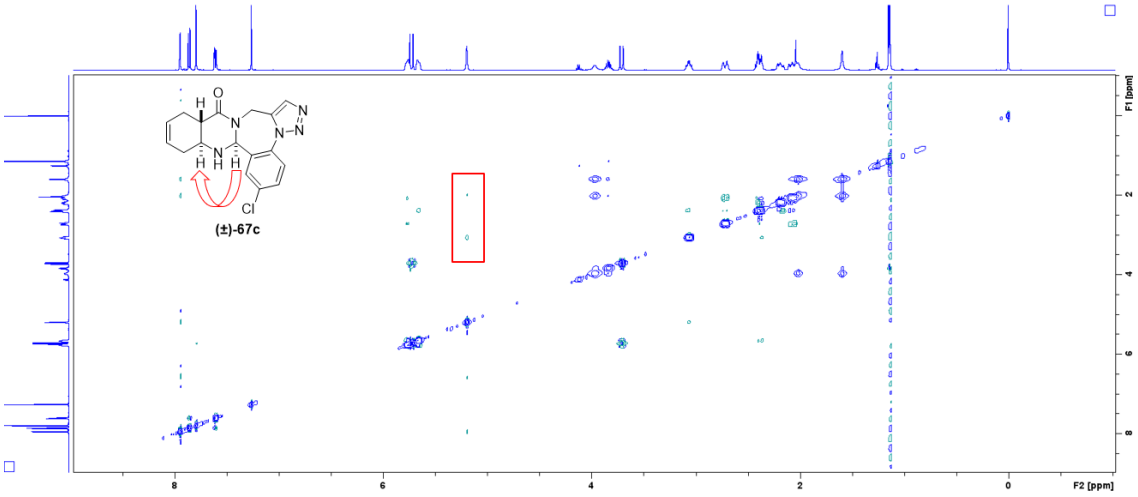
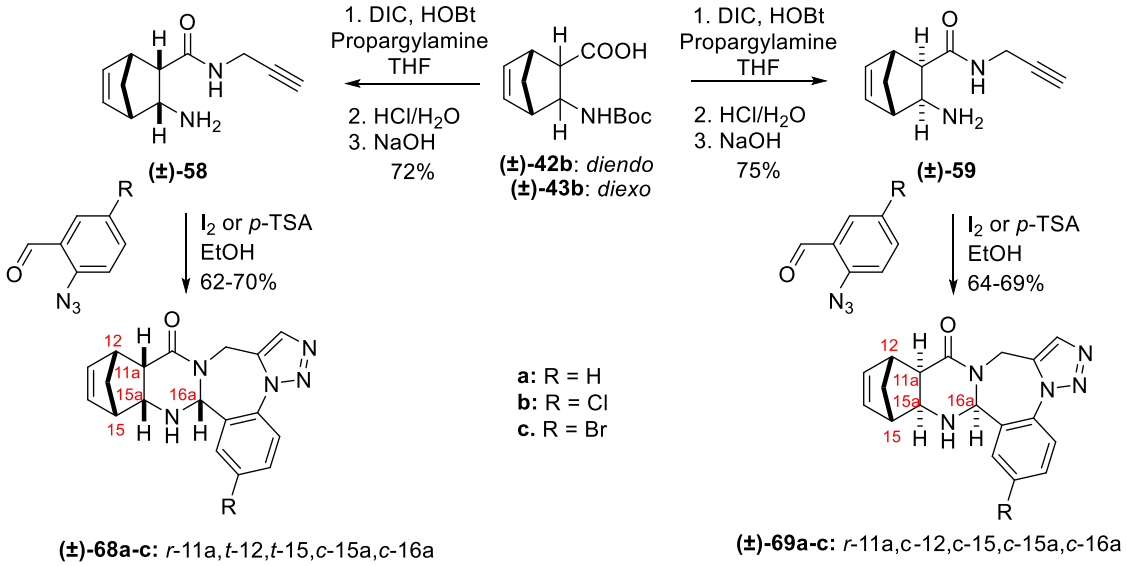


Figure 6

Our study was extended to racemic norbornene derivatives (Scheme 31) for further examination. The reaction was performed with enantiomerically pure norbornene starting materials to obtain enantiomerically pure products. The racemic *N*-Boc-protected amino acids were prepared from the corresponding amino acids according to an earlier method. Following the same cascade reaction procedure, the synthetic route was fully diastereoselective giving single epimers (±)-**68a–c** and (±)-**69a–c**.



Scheme 31

Full NMR signal assignment followed by stereochemistry investigation by NOE crosspeaks revealed the relative configuration of the C(16a)-H protons to be in a *cis* arrangement with the annelated hydrogen atoms C(11a)-H and C(15a)-H for *diendo* (±)-**68a–c** and *diexo* (±)-**69a–c** derivatives (Figure 7 and 8). The stereochemistry was further confirmed by X-ray diffraction analysis of the single crystal of (±)-**68c** (Figure 9).

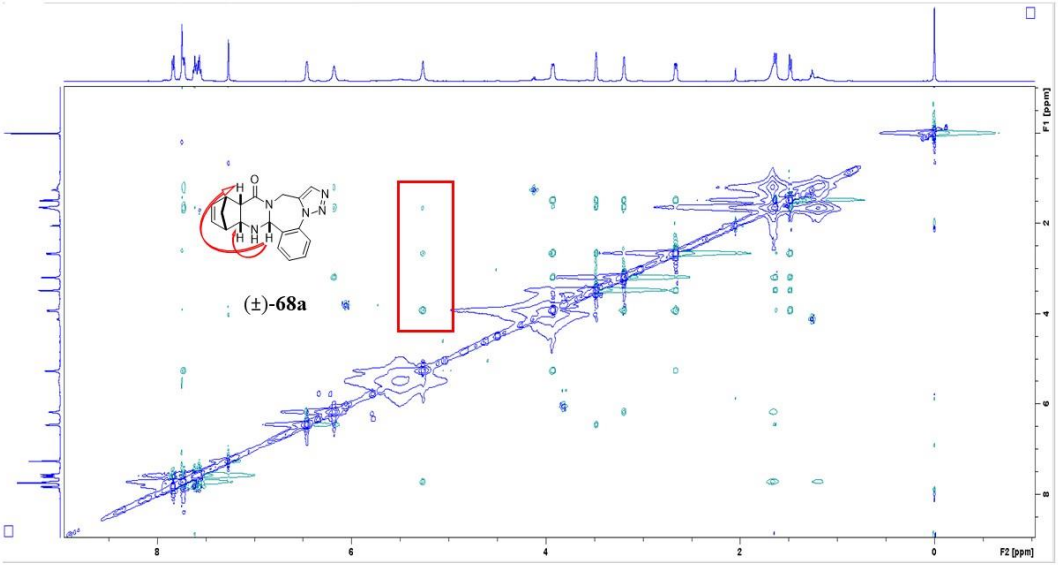


Figure 7

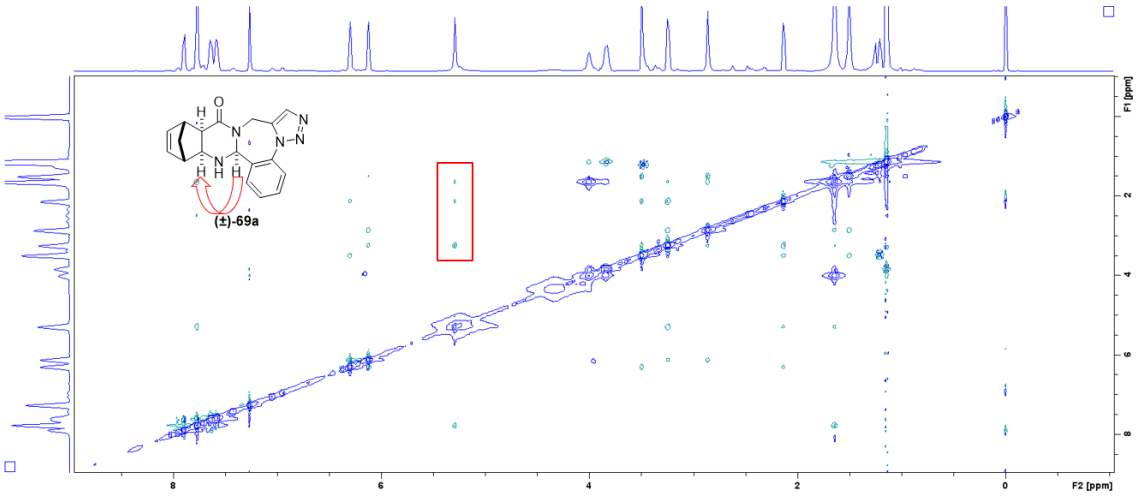


Figure 8

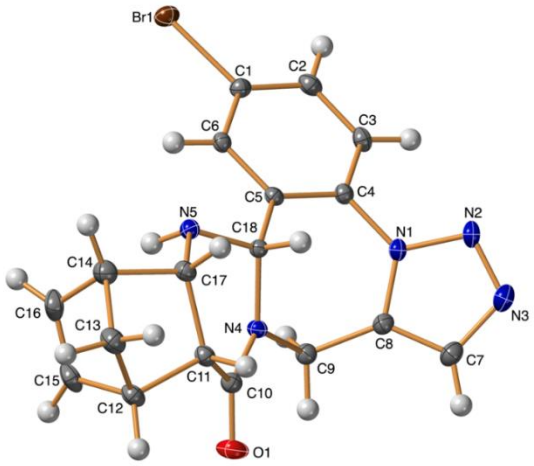
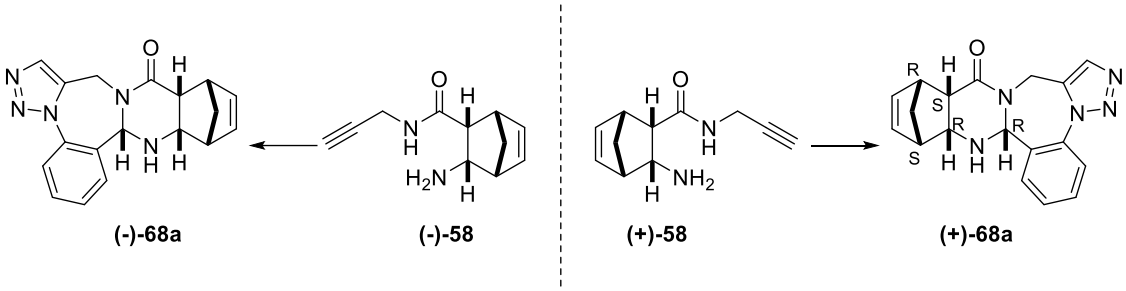


Figure 9. ORTEP plot of the X-ray structure of (±)-**68c**

In further studies, enantiomerically pure *diendo N*-Boc-protected amino acids, prepared by following the procedure described in a previous work [14], were used as chiral sources (Scheme 32). The reaction was performed with both (+)-**58** and (−)-**58**. The synthesis was carried out under conditions applied previously, starting from enantiomerically pure propargylamide (−)-**58** to obtain product (−)-**68a** with high enantiomeric excess (*ee* > 95%). On the other hand, (+)-**68a** was isolated with good enantiomeric excess (*ee* > 84%) starting from (+)-**58** (Figure 9).



Scheme 32

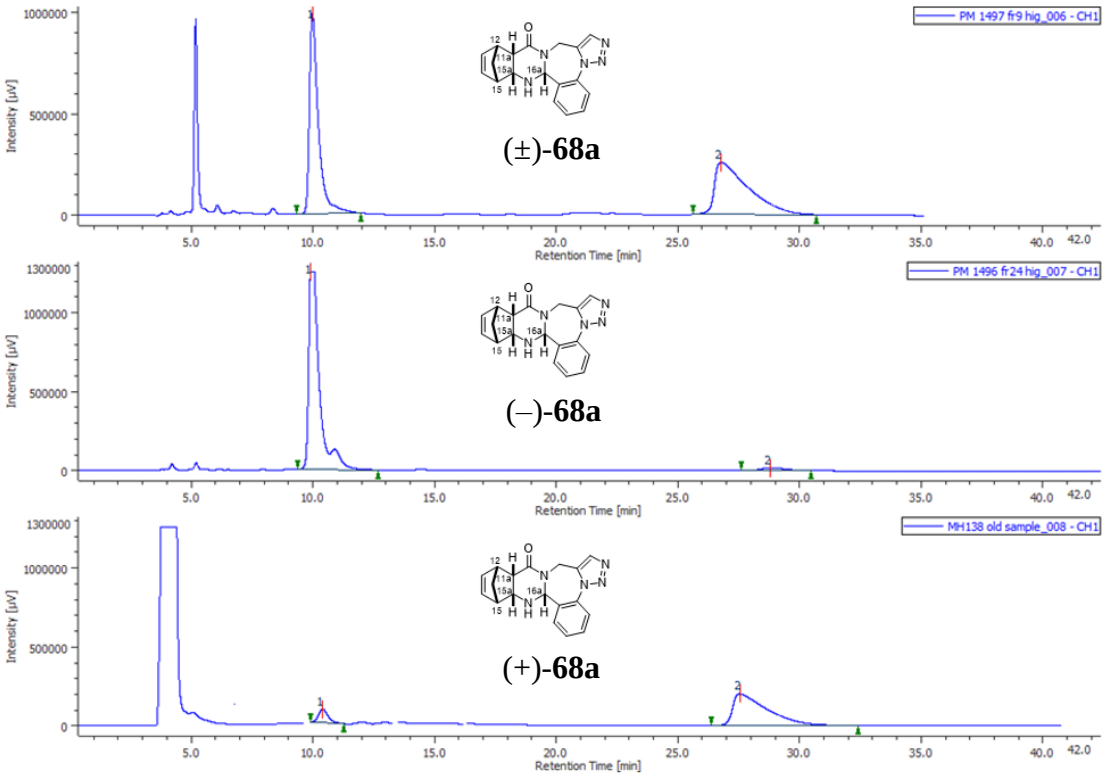
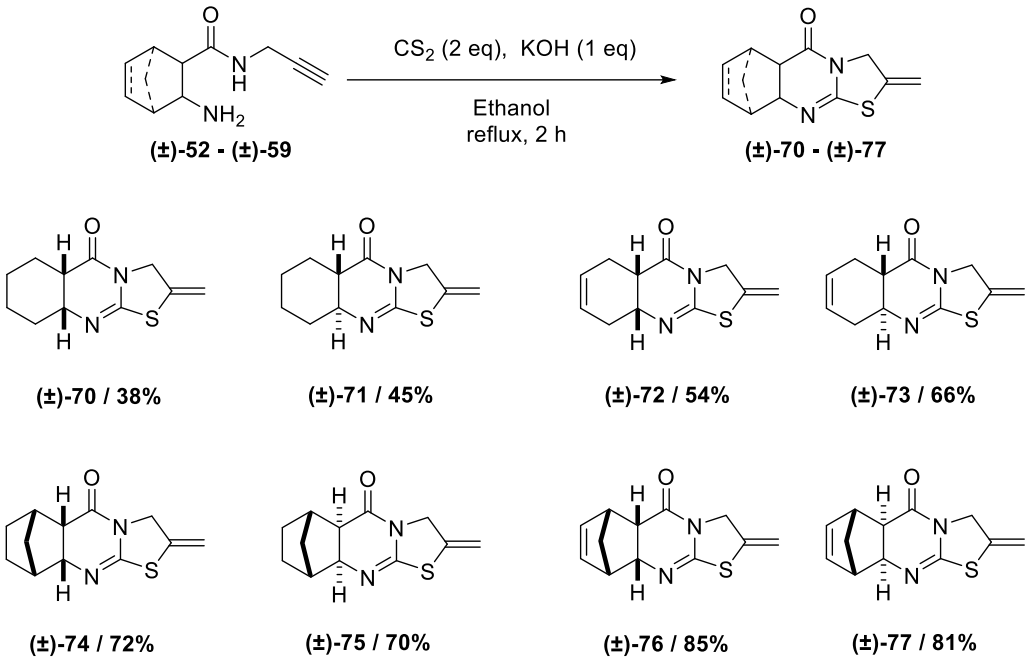


Figure 9. HPLC chromatograms of (±)-**68a**, (+)-**68a** and (–)-**68a**
n-hexane/IPA 60:40; 0.5 ml/min; PDA detector; IA

3.2.3. Synthesis of alicyclic 2-methylene-substituted thiazolo[2,3-*b*]-quinazolinones form alicyclic 3-amino-*N*-propargyl carboxamides

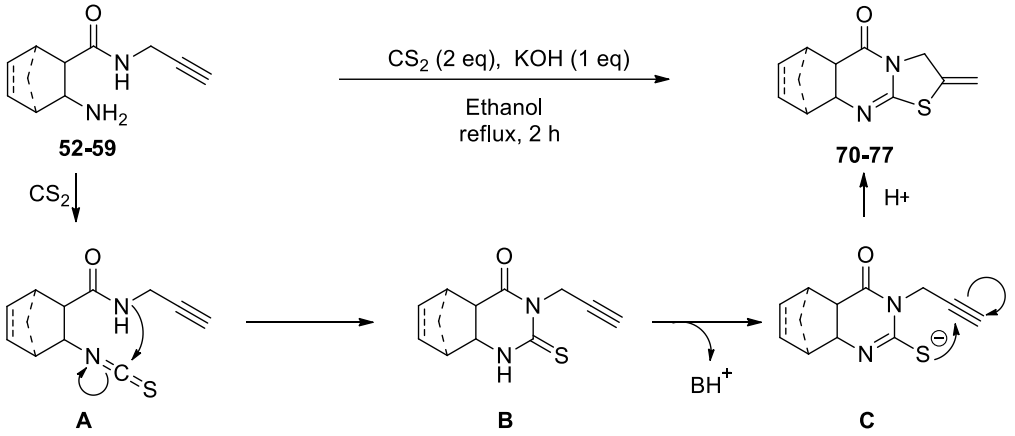
Domino ring-closure reactions between 3-amino-*N*-propargyl carboxamides and carbon disulfide can lead to two different ring systems. Namely to 6-*endo-dig* compounds and 2-methylene-substituted thiazolo[2,3-*b*]-quinazolinones, which are 5-*exo-dig* compounds. The straightforward reaction of alicyclic 3-amino-*N*-propargyl carboxamides (±)-**52**–(±)-**59** with carbon disulfide in ethanol in the presence of potassium hydroxide showed regioselectivity in the second ring closure, leading only to 5-*exo-dig* ring products.

The result showed a noticeable increase in the yield of the final product with the decrease in the flexibility of the starting alicyclic amino propargylamide. The yield changed from a mere 38% for cyclohexane derivative (±)-**70** to 72–81% for tetracyclic derivatives (±)-**74**, (±)-**75**, (±)-**76** and (±)-**77**. Moreover, the presence of one equivalent of potassium hydroxide induced partial epimerisation in the case of *cis*-cyclohexane (±)-**70** and *cis*-cyclohexene (±)-**72** to *trans*-cyclohexane (±)-**71** and *trans*-cyclohexene (±)-**73**, respectively. This accounts for the somewhat lower yields observed for these final products (Scheme 33).



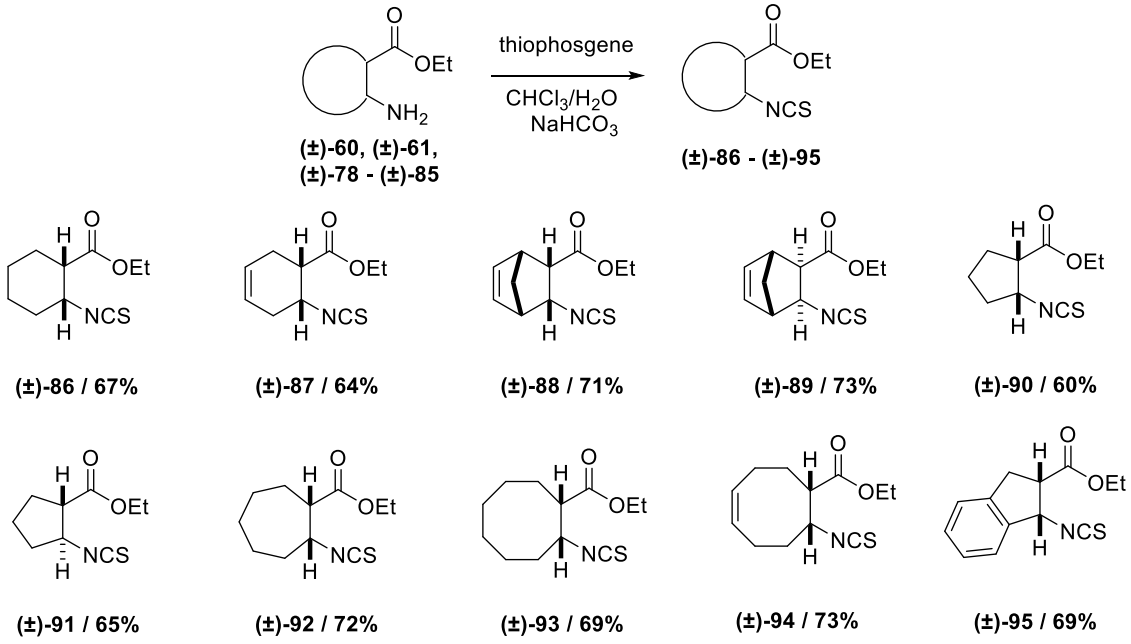
Scheme 33

These reactions proceed through a two-step cascade process starting with the formation of isothiocyanate **A** followed by the first ring closure giving 2-thioxo-2,3-dihydroquinazolinone intermediate **B**. Finally, a favoured 5-*exo*-*dig* ring closure takes place leading to our desired alicyclic 2-methylene-substituted thiazolo[2,3-*b*]quinazolinones (±)-**70**–(±)-**77** (Scheme 34).



Scheme 34

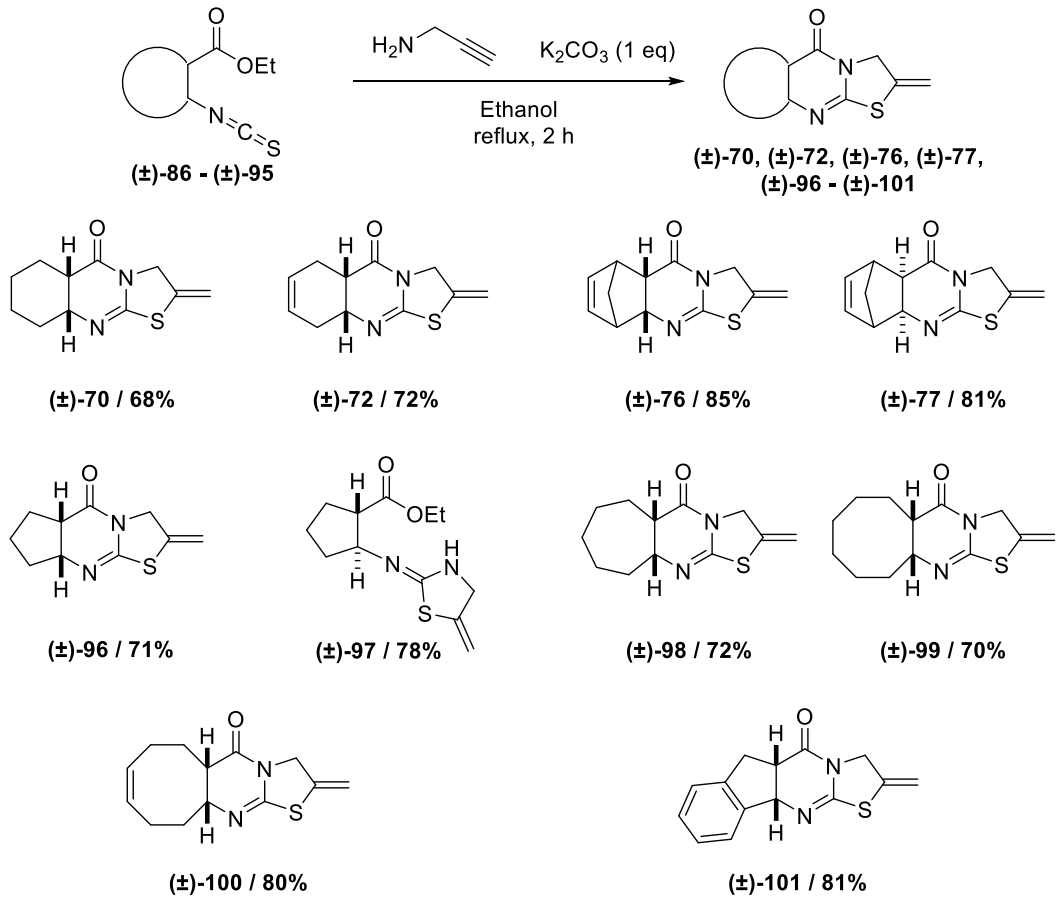
The alternative syntheses of fused thiazolo derivatives from alicyclic isothiocyanates bearing an ester group using bifunctional reagents, such as propargylamine, are feasible [I, 67]. The preparation of racemic alicyclic ethyl 2-isothiocyanatocarboxylates (±)-**86**–(±)-**95** was easily performed in one-step reactions from the corresponding 2-amino esters (±)-**60**, (±)-**61** and (±)-**78**–(±)-**85** upon reacting with thiophosgene in relatively high yields (Scheme 35). To a stirred mixture of $CHCl_3$, water, thiophosgene and $NaHCO_3$, a solution of alicyclic ethyl esters (±)-**60**, (±)-**61** and (±)-**78**–(±)-**85**) in water was added dropwise followed by stirring for 3 hours at 40 °C. The analytical data of the purified compounds (±)-**88**–(±)-**91** were identical to those in the literature [68, 69].



Scheme 35

Alicyclic ethyl 2-isothiocyanatocarboxylates (±)-**86**–(±)-**95** were treated using one equivalent each of propargylamine and potassium carbonate at reflux condition in ethanol then stirring at room temperature to perform a comparative study.

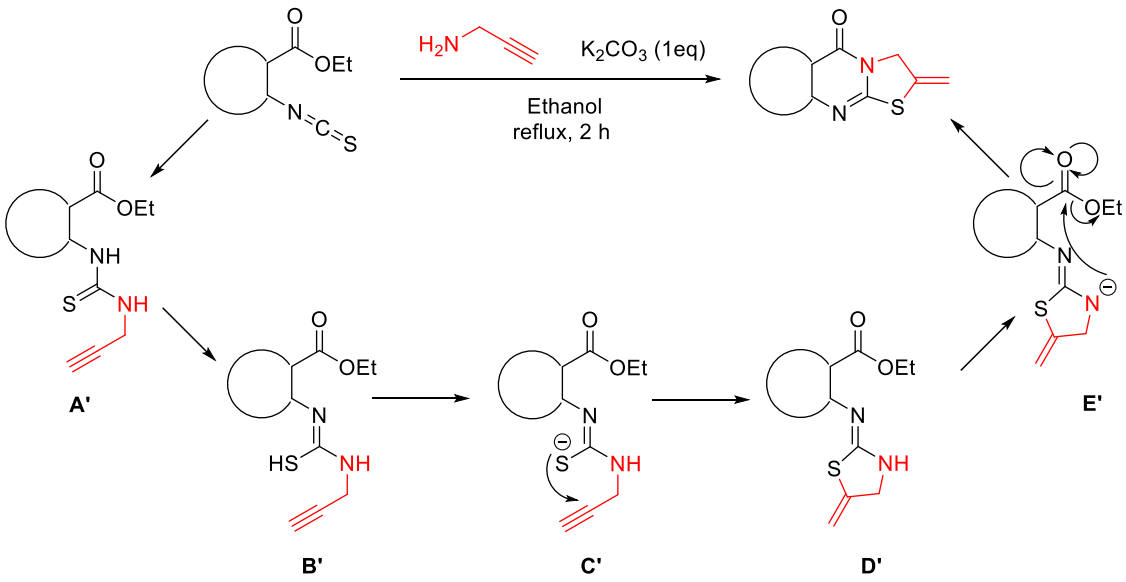
Products (±)-**70**, (±)-**72**, (±)-**76**, (±)-**77** and (±)-**96**–(±)-**101** obtained in this procedure were isolated with relatively high yields ranging from 68% to 85%. This reaction process showed no yield decrease when using more flexible alicyclic starting materials. Moreover, with the use of a slightly weaker base such as potassium carbonate, partial epimerisation of *cis*-cyclohexane (±)-**70** and *cis*-cyclohexene (±)-**72** derivatives could be avoided (Scheme 36).



Scheme 36

Product formation involves a two-step cascade reaction starting by the formation of thiourea intermediate **A′**, followed by a favoured base-catalysed intramolecular 5-*exo-dig* ring closure leading to methylenethiazolidin-2-ylidene intermediate **D′**. Finally, a base-catalysed amidation delivers the target ring system (Scheme 37).

According to a proposed mechanistic pathway, intramolecular 5-*exo-dig* ring closure takes place first. This can be supported by the information, that in the reaction of *trans*-ethyl-2-(3-(prop-2-yn-1-yl)thioureido)cyclopentane-1-carboxylate (±)-**91**, carried out under the same condition, only methylenethiazolidin-2-ylidene intermediate (±)-**97** was isolated and characterised by NMR. Similar reactivity was observed in earlier studies related to cyclisation of the *cis* and *trans* 1,3-bifunctional 1,2-disubstituted cyclopentane derivatives, such as *cis*- and *trans*-2-amino-1-cyclopentane-carboxylic acids and their isothiocyanate esters. Note that *cis* isomers react readily, whereas their *trans* counterparts do not undergo ring closure in most of the cases [68, 69].

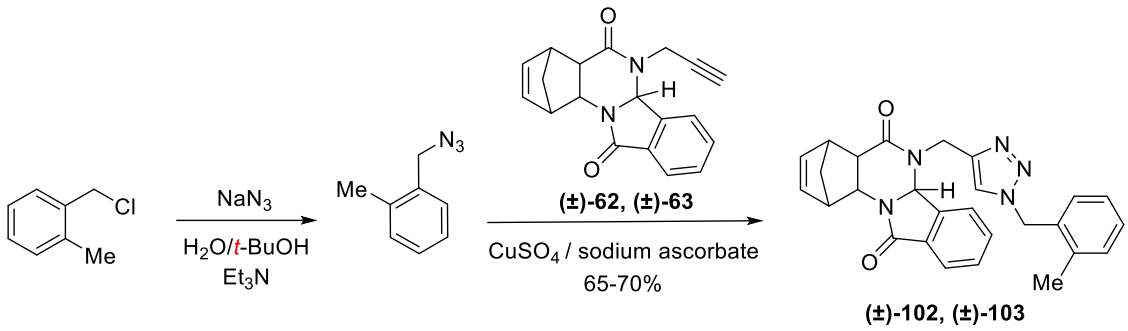


Scheme 37

3.3. Click reaction

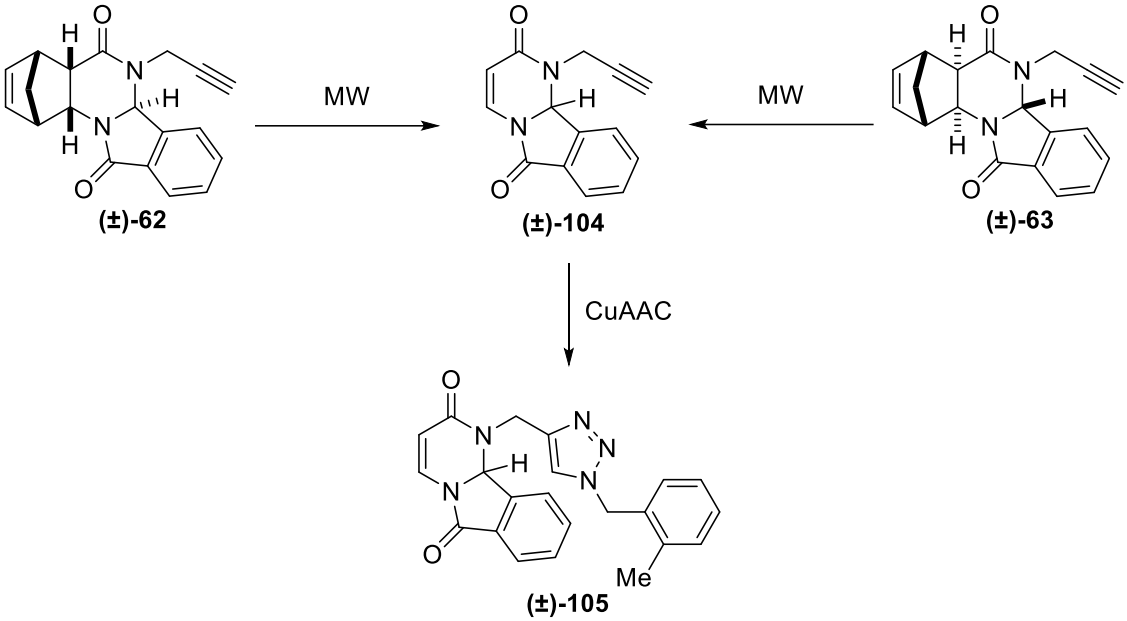
The 1,4-disubstituted 1,2,3-triazole function, as a pharmacophore, still plays an important role in drug discovery and it can affect the pharmacokinetic properties of a compound, which justifies the continuous advancement of new strategies for their synthesis. One of the most widely used click-chemistry methods in this field is the copper-catalyzed 1,3-dipolar cycloaddition between an alkyne and an azide (CuAAC), due to its simplicity and high selectivity.

The 1,2,3-triazole ring was formed by click reaction using Cu(I)-catalyzed azide/alkyne cycloaddition (CuAAC). The azide was synthesized in situ by dissolving sodium azide in the mixture of 2-methylbenzyl chloride, trimethylamine, and *tert*-butyl alcohol under stirring at room temperature for 1 h [45]. Afterwards, pentacylic compounds (±)-**62** or (±)-**63** was added along with copper(II) sulfate and sodium ascorbate as a reducing agent. Nascent copper(I) acting as the catalyst is responsible for the regioselectivity (Scheme 38) [45]. The mixture was diluted with H_2O and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and the solvent was evaporated off. Purification of the residue by column chromatography over silica gel with EtOAc gave the desired products. The CuAAC reaction of the terminal alkyne moiety of (±)-**62** and (±)-**63** was completely regioselective affording 1,4-disubstituted triazoles (±)-**102** and (±)-**103**.



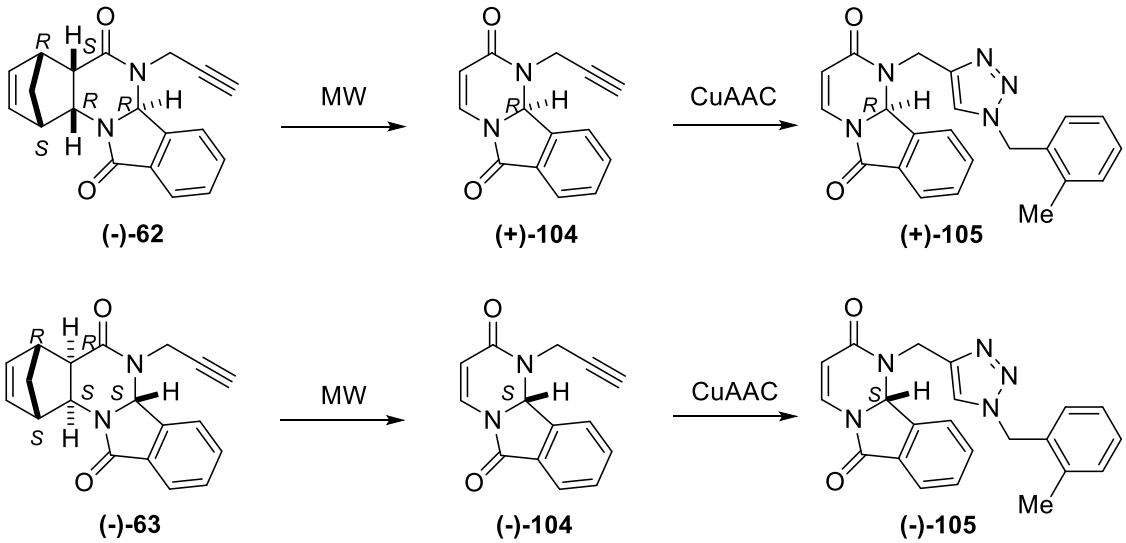
Scheme 38

Cu(I)-catalyzed azide/alkyne cycloaddition was also implemented after the RDA reaction of (±)-**62** and (±)-**63** (Scheme 39). Following the same CuAAC procedure, starting from RDA product (±)-**104**, the reaction provided product (±)-**105** with the same regioselectivity of the original pathway described in Scheme 38.



Scheme 39

The same procedure was applied using the enantiomeric norbornene 3-amino-*N*-propargyl carboxamides and the results are illustrated in Scheme 40. The result will be discussed in details in a further part related to RDA reaction.

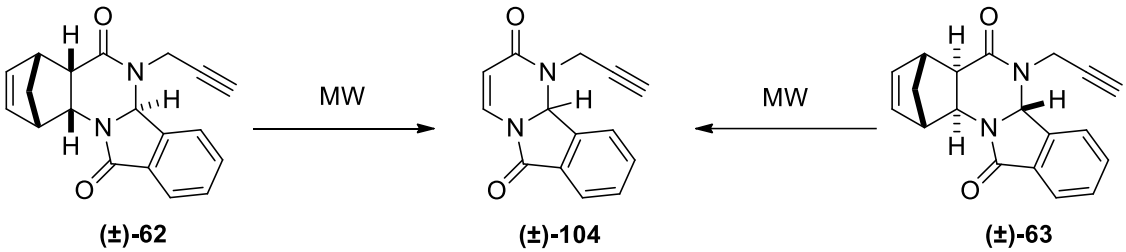


Scheme 40

3.4. RDA protocols towards novel *N*-heterocyclic compounds

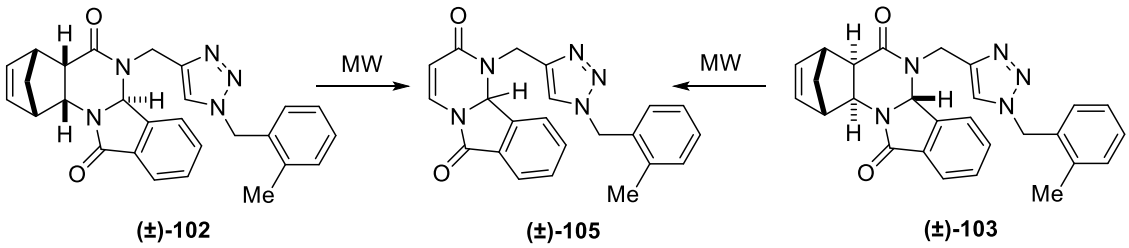
3.4.1. Synthesis of pyrimido[2,1-*a*]isoindols

The RDA reaction was performed with (±)-**62** and (±)-**63** resulting in new ring products pyrimido[2,1-*a*]isoindole (±)-**104** (Scheme 41). Isoindoloquinazoline derivatives [(±)-**62** or (±)-**63**] were dissolved in 1,2-dichlorobenzene. The solution was stirred and heated to 220 °C for 60 min under microwave irradiation at 300 W. Then the solvent was evaporated and the residue was purified by column chromatography to afford pyrimido[2,1-*a*]isoindole derivative (±)-**104**.



Scheme 41

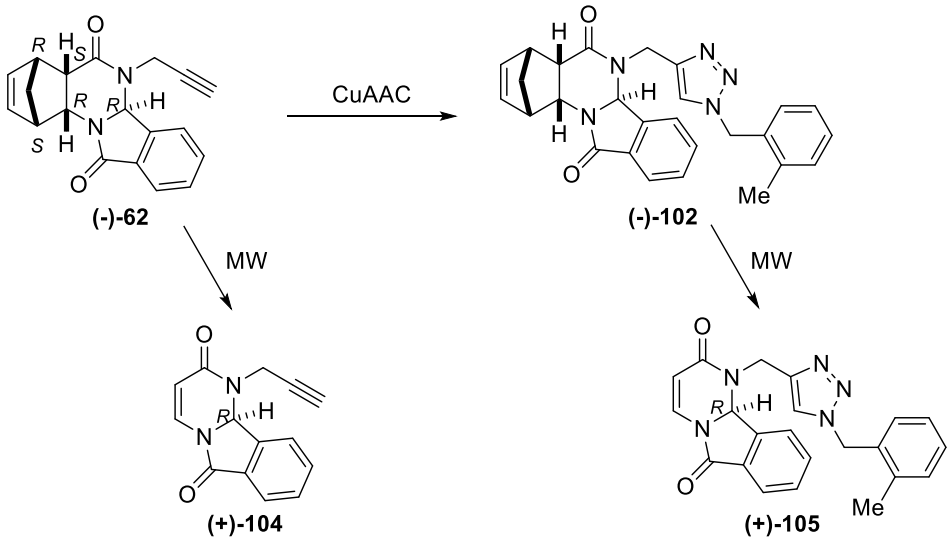
An alternative pathway for the transformation of (±)-**102** and (±)-**103** was also tested. The RDA process was implemented after the CuAAC reaction of (−)-**62** and (−)-**63** and, as expected, it provided the product molecule (±)-**105** with the same ring system formed in the original pathway (Scheme 42).



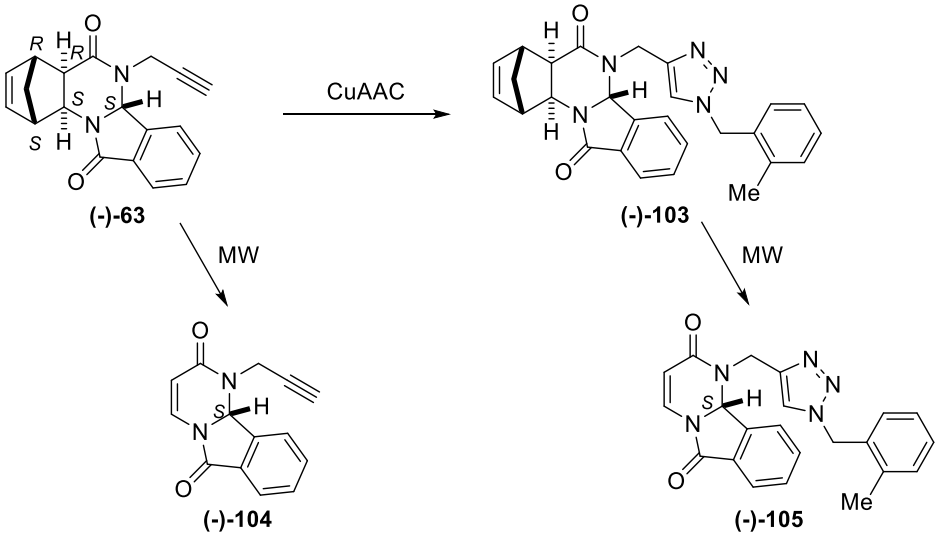
Scheme 42

Upon success of the RDA reaction procedure for racemic *diendo*- and *diexo*-isoindoloquinazoline derivatives, the method was implemented for enantiomeric *diendo*- and *diexo*-isoindoloquinazoline derivatives as well in order to achieve a traceless chirality transfer (Scheme 43 and 44).

Under the same RDA reaction procedure, the enantiomeric compounds (−)-**62**, (+)-**62**, (−)-**63**, (+)-**63**, (−)-**102**, (+)-**102**, (−)-**103** or (+)-**103** were transformed into enantiomeric pyrimido[2,1-*a*]isoindole derivatives (−)-**104**, (+)-**104**, (−)-**105** and (+)-**105**. Knowing already the relative configuration of the new chiral centre, proved by NOE cross peaks, the absolute configuration of the chiral centre of the enantiomeric isoindoloquinazoline derivatives can be determined. Therefore, we were able to determine the absolute configuration of the enantiomeric pyrimido[2,1-*a*]isoindole derivatives obtained in the RDA reaction process. Note that in Schemes 43 and 44, only a single enantiomer is represented for evidence.



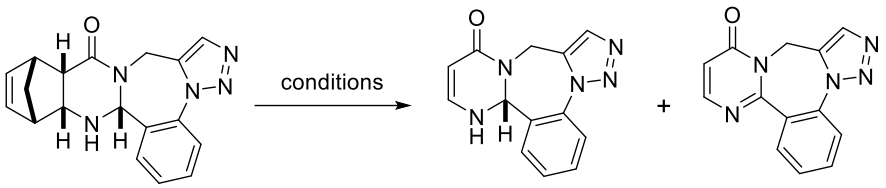
Scheme 43



Scheme 44

3.4.2. Synthesis of benzo[f]pyrimido[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepine

The investigation of the RDA reaction conditions was performed on both *diendo* (±)-**68a** and *diexo* (±)-**69a** derivatives. Unfortunately, *diexo* (±)-**69a** led only to degradation or no reaction under all tested conditions. Consequently, only the transformation of *diendo* (±)-**68a** derivative shown in Scheme 45 is discussed below.



Scheme 45

Table 1 lists the results of our efforts to find appropriate reaction conditions for the transformation of (±)-**68a** including both classic and modern organic synthesis techniques for the synthesis of compound **106**. The flow reactor showed temperature limitations not reaching high enough temperatures necessary to our procedure. Likewise, the use of classic batch reaction gave unsatisfactory results even at high temperature.

Table 1 RDA reaction of (±)-**68a** investigated under varied conditions

Methods	Conditions	Compound (yield)
Batch reaction	Toluene, reflux, 30 min	No reaction
Batch reaction	1,2-Dichlorobenzene, reflux, 30 min	**106** (traces)
Batch reaction	Solvent free, 220 °C, 30 min	**106** (traces)
Flow reactor	Toluene, 180 °C, 30 min	No reaction
Flow reactor	Toluene/Methanol (4 : 1), 180 °C, 30 min	No reaction
Microwave reactor	Toluene, 180 °C, 30 min	No reaction
Microwave reactor	1,2-Dichlorobenzene, 220 °C, 30 min	**106** (66%)

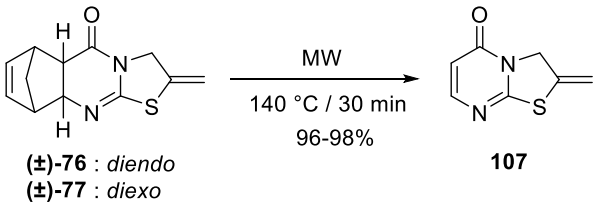
The only successful attempt was the use of microwave irradiation in a microwave vial in 1,2-dichlorobenzene as solvent at 220 °C for 30 min, resulting in pyrimidotriazolobenzodiazepine **106**, a novel *N*-heterocyclic ring system. The NMR signal assignment of the obtained product shows the loss of both the cyclopentadiene moiety and the hydrogen of the asymmetric centre. These results can be explained by the instability of quinazolinotriazolo-benzodiazepine (±)-**68a** under high temperature

leading to an oxidation of the starting compound of the domino process before the RDA reaction can take place. This statement can also be confirmed by the result of a literature study, where a similar oxidation side product was isolated even at a temperature much lower than that used in our RDA reaction [23].

3.4.3. Synthesis of 2-methylene-2*H*-thiazolo[3,2-*a*]pyrimidin-5(3*H*)-one

The possibility of the RDA reaction of both *diendo* (±)-**76** and *diexo* **(±)-77** norbornene derivatives was explored under microwave irradiation. A portion of *diendo* (±)-**76** or *diexo* (±)-**77** norbornene derivative was dissolved in toluene/methanol (4:1) and heated under microwave irradiation at 140 °C for 30 min leading to the formation of new ring system 2-methylene-2*H*-thiazolo[3,2-*a*]pyrimidin-5(3*H*)-on **107**.

The final product was obtained after evaporation of the solvent and crystallization from ether and then it was characterised by NMR. Surprisingly, the yield of the RDA decomposition was extremely high, notably 96% starting from *diendo* isomer (±)-**76** and 98% starting from *diexo* (±)-**77**. This result can be easily accounted for by the high electron delocalisation throughout the ring system of product **107** (Scheme 46).



Scheme 46

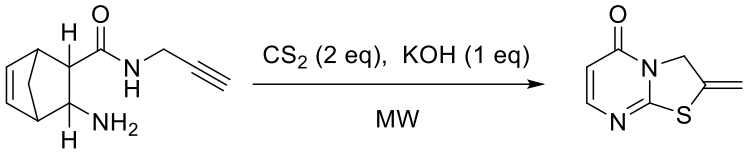
The extremely high yield of the RDA decomposition was intriguing and prompted us to explore the possibility of converting both *diendo* and *diexo* norbornene 3-amino-*N*-propargyl carboxamides (±)-**58** and (±)-**59** and *diendo* and *diexo* norbornene ethyl 2-isothiocyanatocarboxylate (±)-**88** and (±)-**89** to 2-methylene-2*H*-thiazolo[3,2-*a*]pyrimidin-5(3*H*)-on (**107**) in the one-pot domino-RDA process under microwave irridiation.

Because both domino processes work under the same optimal conditions, the optimisation of the conditions of the new one-pot domino-RDA process was investigated only with norbornene 3-amino-*N*-propargyl carboxamides (±)-**58** and (±)-**59**.

Afterwards, the optimal conditions were applied on norbornene ethyl 2-isothiocyanatocarboxylate (±)-**88** and (±)-**89** as well.

While using ethanol alone as solvent for the reaction, the temperature barrier couldn't be reached and only the product of domino reaction was detected. Afterwards, the use of an ethanol/water (2:1) mixture was investigated, which led to a decomposition detecting neither the domino nor the RDA product. The same result was obtained using a mixture of toluene/methanol (4:1) for 60 min and 30 min at 140 °C (Table 2).

Table 2 One-pot synthesis of 2-methylene-2*H*-thiazolo[3,2-*a*]pyrimidin-5(3*H*)-one **107**



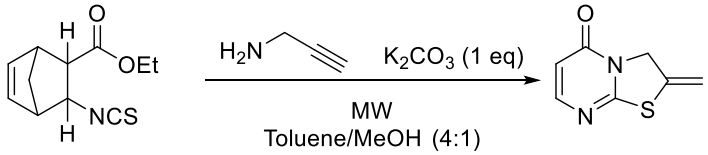
(±)-58: *diendo*
(±)-59: *diexo*

107

Solvent	Conditions	Yield of the product
EtOH	60 min, 120 °C	Only domino product
EtOH/H_2O (2:1)	60 min, 140 °C	Decomposition
Toluene/MeOH (4:1)	60 min, 140 °C	Decomposition
Toluene/MeOH (4:1)	30 min, 140 °C	Decomposition
Toluene/MeOH (4:1)	30 min, 90 °C followed by 30 min, 140 °C	60%
Toluene/MeOH (4:1)	15 min, 90 °C followed by 30 min, 140 °C	68%

Therefore, the use of two different temperature barriers was investigated. Indeed, the one-pot domino-RDA reaction worked successfully using 90 °C for 30 min followed by 140 °C for 30 min. The optimal result was achieved at 90 °C for 15 min and 140 °C for 30 min with toluene/methanol (4:1) as solvent (Scheme 47).

The one-pot procedure was then performed with norbornene ethyl 2-isothiocyanatocarboxylate (±)-**88** and (±)-**89** under optimal conditions. Regardless of the similar yield of the reaction, the final product needed purification by column chromatography.



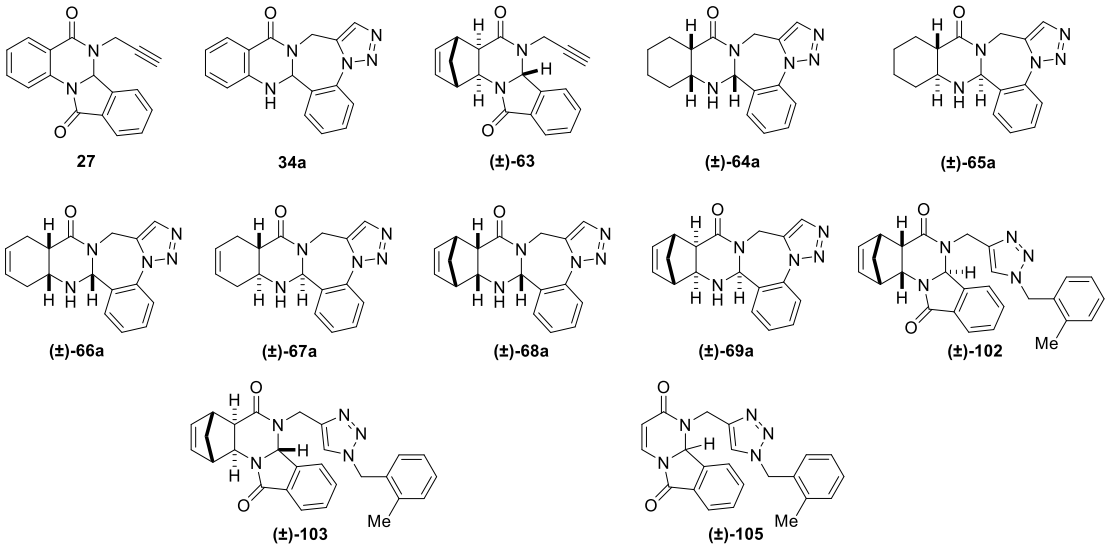
(±)-88: *diendo*
(±)-89: *diexo*

107

Scheme 47

3.5. Examination of in vitro antiproliferative activities

The effects of the tested compounds on cell growth were determined using a standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay on a selection of human gynaecological cancer cell lines of epidemiological significance: MCF-7 (ER+, PR+, and HER2- breast cancer), MDA-MB-231 (ER-, PR- and HER2- breast cancer), HeLa (human papilloma virus [HPV] 18 positive cervical cancer), SiHa (HPV 16 positive cervical cancer) and A2780 (ER- ovarian cancer) [70]. The cell lines – apart from SiHa – were obtained from ECACC (European Collection of Cell Cultures, Salinsbury, UK). SiHa was obtained from ATCC (American Tissue Culture Collection, Manassas, VA, USA). Murine fibroblast NIH/3T3 cell line was additionally included to obtain data related to the cancer selectivity of the tested alicyclic *N*-heterocyclic quinazoline derivatives (Scheme 48). Cells were propagated in minimal essential medium supplemented with 10% fetal bovine serum, 1% non-essential amino acids and a 1% penicillin–streptomycin mixture at 37 °C in a humidified atmosphere containing 5% CO_2. All media and culture supplements were purchased from Lonza Group Ltd. (Based, Switzerland). Cells were seeded into 96-well microtiter plates (at a cell density of 5x103/well) and incubated with the tested compounds at 10 µM and 30 µM under cell-culture conditions for 72 h. Subsequently, the MTT solution (5 mg/mL) was added to each well, which were further incubated for 4 h. The medium was removed and the precipitated formazan crystals were dissolved in 0.1 mL DMSO during a 1 h shaking at 37 °C [70]. The absorbance in the wells was measured at 545 nm using a microplate reader. Untreated cells served as controls during the measurements. Results presented in the paper have been obtained from two independent experiments with five wells per each condition. Cisplatin (Ebewe Pharmaceuticals, Unterach, Austria) was used a reference agent. Calculations were performed using GraphPad Prism 5.01 software (GraphPad Software Inc., San Diego, CA, USA).



Scheme 48

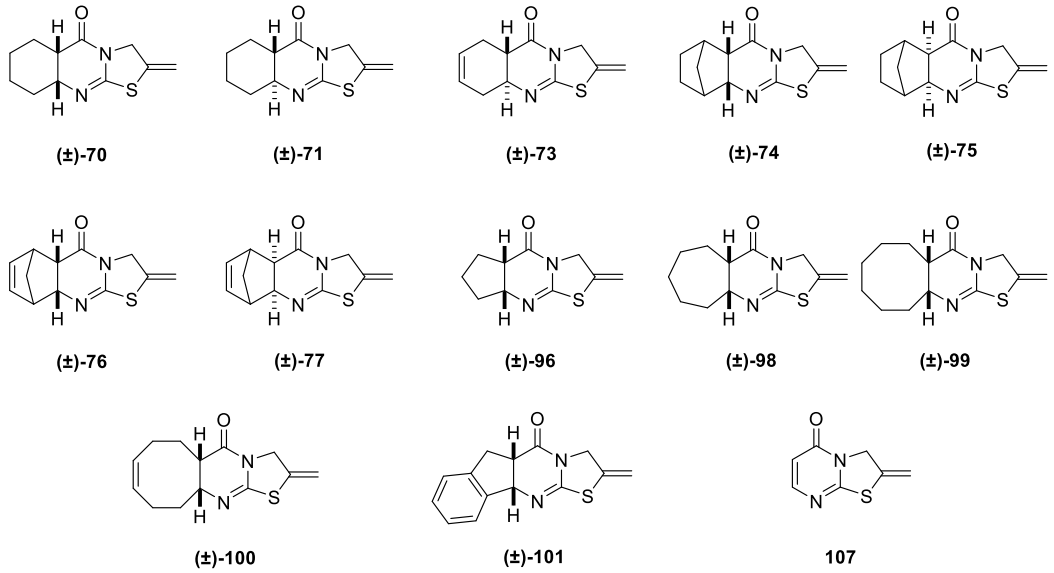
Most of the compounds elicited negligible growth inhibiting action against the utilised cancer cells. None of the substances elicited >10% inhibition on ovarian (A2780) cancer cells. MCF-7 (breast) and HeLa (cervical) cells are more sensitive than SiHa (cervical) or MDA-MB-231 (breast) cell lines. Concerning the diazepine analogues, the condensed aromatic ring may confer some limited activity and the configuration of the annelation seems irrelevant. The importance of the aromatic ring has been confirmed in the case of quinazoline derivatives with **27** being the most effective compound in the current set.

Table 3 Antiproliferative activities of **27**, **34a**, (±)-**63**, (±)-**64a**–(±)-**69a**, (±)-**102**, (±)-**103** and (±) **105**

Comp.	Conc. (μM)	Inhibition of cell proliferation (%) ± SEM				
		HeLa	MCF-7	A2780	MDA-MB-231	SiHa
27	10	17.59 ± 0.88	–	–	–	–
	30	70.86 ± 2.29	67.39 ± 2.37	–	–	26.03 ± 0.98
34a	10	–*	–	–	–	15.56 ± 1.82
	30	25.52 ± 1.32	55.34 ± 2.15	–	–	19.07 ± 1.34
(±)-63	10	–	–	–	–	–
	30	–	–	–	–	–
(±)-64a	10	–	–	–	–	–
	30	–	–	–	–	–
(±)-65a	10	–	–	–	–	–
	30	–	–	–	–	–
(±)-66a	10	–	–	–	–	–
	30	–	–	–	–	11.17 ± 1.84
(±)-67a	10	–	–	–	–	–
	30	–	–	–	–	–
(±)-68a	10	–	–	–	11.08 ± 1.06	–
	30	15.04 ± 2.16	36.74 ± 3.51	–	14.06 ± 0.92	17.81 ± 1.19
(±)-69a	10	–	–	–	–	16.32 ± 1.85
	30	–	–	–	–	19.07 ± 1.34
(±)-102	10	–	–	–	–	–
	30	–	19.38 ± 1.17	–	11.45 ± 0.88	–
(±)-103	10	–	–	–	–	–
	30	–	–	–	–	–
(±)-105	10	–	–	–	–	–
	30	12.07 ± 1.12	39.19 ± 1.98	–	–	12.44 ± 2.10
Cisplatin	10	50.54 ± 2.19	37.27 ± 2.22	36.64 ± 0.53	52.87 ± 0.50	76.74 ± 1.26
	30	76.81 ± 1.25	88.14 ± 2.32	89.64 ± 0.82	86.13 ± 0.57	96.90 ± 0.25

[1] Cell growth inhibition values lower than 10% were considered negligible and were not given numerically.

Concerning the antiproliferative properties of the presented alicyclic 2-methylene-substituted thiazolo[2,3-*b*]quinazolinones analogs (Scheme 49), modest antiproliferative actions could be detected. MCF-7 was shown to be the most sensitive cell line to almost all tested compounds with the maximum of above 60% growth inhibition by (5a*S**,10b*S**)-2-methylene-2,3,5a,6-tetrahydroindeno[1,2-*d*]thiazolo[3,2-*a*]pyrimidin-5(10b*H*)-one (±)-**101** at 30 μM concentration. Compound (±)-**101** exerted more than 10% antiproliferative effect on all tested cell lines with a slight selectivity to cancer cell lines. MCF-7, which is an estrogen receptor positive and HER2-negative breast cancer cell line and MDA-MB-231 (triple negative) breast cancer cell line were the most sensitive to the tested quinazolinone analogs. The indane moiety in the molecular structure seems to contribute to the in vitro anticancer effect.



Scheme 49

Table 4 Antiproliferative actions of alicyclic 2-methylene-substituted thiazolo[2,3-*b*]quinazolinones

Comp.	Conc. (μM)	Inhibition of cell proliferation (%) ± SEM				
		HeLa	MCF-7	A2780	MDA-MB-231	NIH/3T3
(±)-70	10	–*	10.67 ± 2.98	–	–	–
	30	–	20.49 ± 2.25	–	–	–
(±)-71	10	–	13.06 ± 3.32	–	–	–
	30	–	21.20 ± 3.01	–	–	–
(±)-73	10	–	–	–	–	–
	30	–	16.79 ± 1.64	–	11.84 ± 1.10	–
(±)-74	10	–	20.50 ± 3.15	–	–	–
	30	–	31.44 ± 1.71	–	20.09 ± 1.58	–
(±)-75	10	–	–	–	–	–
	30	–	–	–	–	–
(±)-76	10	–	19.32 ± 1.71	–	–	–
	30	–	35.32 ± 1.70	–	–	–
(±)-77	10	–	25.10 ± 0.77	–	–	–
	30	–	29.07 ± 2.48	–	–	–
(±)-96	10	–	14.86 ± 2.83	–	–	–
	30	–	26.49 ± 3.21	–	–	–
(±)-98	10	–	–	–	–	–
	30	–	–	–	–	–
(±)-99	10	–	–	–	–	–
	30	–	–	–	11.77 ± 2.64	–
(±)-100	10	–	10.73 ± 3.23	–	–	–
	30	–	17.87 ± 3.36	–	16.66 ± 1.78	–
(±)-101	10	–	53.41 ± 1.89	–	12.58 ± 3.03	–
	30	19.39 ± 2.17	60.14 ± 1.42	24.31 ± 1.20	31.01 ± 3.04	13.10 ± 1.99
107	10	–	12.32 ± 1.92	–	–	–
	30	–	20.56 ± 3.19	–	13.41 ± 2.43	–
Cisplatin	10	50.54 ± 2.19	37.27 ± 2.22	36.64 ± 0.53	52.87 ± 0.50	76.74 ± 1.26
	30	76.81 ± 1.25	88.14 ± 2.32	89.64 ± 0.82	86.13 ± 0.57	96.90 ± 0.25

[1] Cell growth inhibition values lower than 10% were considered negligible and were not given numerically.

4. SUMMARY

Simple and efficient routes have been developed for the preparation of new racemic and enantiomeric *cis*- and *trans*-cyclohexene-, cyclohexane-, *diendo*- and *diexo*-norbornene- and norbornane-β-amino-*N*-propargyl carboxamides. Racemic alicyclic *N*-Boc-protected amino acids (±)-**36b**–(±)-**43b**, using HOBt and DIC as coupling agent, were transformed to alicyclic *N*-propargyl amino carboxamides (±)-**52**–(±)-**59** after acidic deprotection. Optically enriched *N*-propargyl amino carboxamides (−)-**58**, (+)-**58**, (−)-**59** and (+)-**59** were successfully prepared as well by the synthetic methods mentioned above starting from enantiomeric amino esters. The starting *diendo*- and *diexo*-norbornene amino ester enantiomers were synthesized from racemic esters by resolution via diastereomeric salt formation with commercially available resolution agents (DBTA and DPTTA). The *ee* values of ester enantiomers were determined via HPLC measurements.

We also studied the reactivity and selectivity of the domino ring-closure reaction of alicyclic *N*-propargyl amino carboxamides (±)-**52**–(±)-**59** with oxocarboxylic acids, azido benzaldehydes and carbon disulfide.

An efficient domino reaction procedure for the synthesis of novel *N*-propargyl isoindolo[2,1-*a*]quinazolinones was performed. In the presence of *p*-TSA, *diendo*- and *diexo*-norbornene 3-amino-*N*-propargyl carboxamides (±)-**58** or (±)-**59** were reacted with 2-formylbenzoic acid, leading to the formation of alicyclic isoindolo[2,1-*a*]quinazoline (±)-**62** and (±)-**63**. Reactions were first carried out with racemic compounds then extended to enantiomeric carboxamides as well.

In all cases, stereochemical assignment by ^{1}H NMR spectra revealed the formation of the single epimers of isoindolo[2,1-a]quinazoline (±)-**62** and (±)-**63**. The stereochemical information of the newly formed stereogenic centres of isoindoloquinazolinones (±)-**62** and (±)-**63** facilitated by the high rigidity of the norbornene skeleton was fully determined by characteristic NOE crosspeaks. The implementation of this domino procedure to enantiomeric *diendo*-norbornene 3-amino-*N*-propargyl carboxamides (+)-**58** and (−)-**58** and *diexo* 3-amino-*N*-propargyl carboxamides (+)-**59** and (–)-**59** led to the determination of the absolute configuration of the final products. Moreover, the terminal alkyne was subjected to CuAAC leading to the

formation of racemic and enantiomeric 1,2,3-triazole pharmacophore-based isoindolo[2,1-*a*]quinazolinones (±)-**102**, (−)-**102**, (+)-**102**, (±)-**103,** (−)-**103** and (+)-**103**.

A one-pot, two-step cascade process was carried out by reacting chloro- or bromo-substituted and unsubstituted azidobenzaldehydes with *cis*- and *trans*-cyclohexane and cyclohexene skeletons bearing *N*-propargyl carboxamides (±)-**52**–(±)-**59** under reflux in EtOH in the presence of a catalytic amount iodine or *p*-TSA under green conditions in good yields. In all cases, the ^{1}H NMR spectra revealed the formation of the single epimers of alicyclic derivatives of quinazolinotriazolobenzodiazepine (±)-**64a–c**, (±)-**65a–c**, (±)-**66a–c**, (±)-**67a–c,** (±)-**68a–c** and (±)-**69a–c**. The stereoselectivity of the three-step cascade process engaging five reactive centres (amide, amine, carbonyl, azide, and alkyne) was proved by NMR and X-ray methods. Moreover, these features were shown to be consistent throughout the studied scope. The simplicity of this process with the use of accessible starting materials and the wide scope are the major features to make the current protocol valuable. The study of the process was further extended to enantiomeric *diendo* *N*-propargyl carboxamides (−)-**58** and (+)-**58**. Enantiomeric quinazolinotriazolobenzodiazepines (+)-**68a** and (−)-**68a** were obtained with a relatively good enantiomeric excess (*ee* > 84% and *ee* > 95%, respectively).

By means of the highly regioselective domino reaction process, alicyclic 2-methylene-substituted thiazolo[2,3-*b*]quinazolinones (±)-**70**−(±)-**77** were synthesised. Although the reactions of cyclic and alicyclic β-amino-*N*-propargyl carboxamides (±)-**52**–(±)-**59** with carbon disulfide took place in a regioselective manner and led only to the favoured 5-*exo*-*dig* products, the obtained yields were relatively low for the flexible cyclic amides. On the other hand, a comparative study was performed using the reaction of ethyl 2-isothiocyanatocarboxylates (±)-**86**−(±)-**95** with propargylamine for the synthesis of several alicyclic 2-methylene-substituted thiazolo[2,3-*b*]quinazolinones (±)-**70**, (±)-**72**, (±)-**76**, (±)-**77** and (±)-**96**–(±)-**101** leading to higher yields.

The synthesis of novel ring systems was achieved following an RDA reaction procedure using microwave irradiation. The main advantages of this protocol are simplicity, high yield, short time, mild reaction conditions and easy work-up. The configuration remains constant during the RDA reaction, which allowed to define the absolute configuration of the final products. Starting from isoindoloquinazoline derivatives, a traceless chirality transfer into pyrimido[2,1-*a*]isoindols was achieved.

Under the same RDA reaction protocol, enantiomeric isoindoloquinazoline derivatives (−)-**62**, (+)-**62**, (−)-**63**, (+)-**63**, (−)-**102**, (+)-**102**, (−)-**103** or (+)-**103** were transformed into enantiomeric pyrimido[2,1-*a*]isoindole derivatives (−)-**104**, (+)-**104**, (−)-**105** and (+)-**105**. In addition, the absolute configuration of these final pyrimido[2,1-*a*]isoindole products was also determined.

The RDA decomposition of *diendo*-quinazolinotriazolobenzodiazepine derivative (±)-**68a** proved to be more challenging, that is the traceless chirality transfer was not successful. On the other hand, after testing several conditions, an oxidation was observed, resulting in benzo[*f*]pyrimido[1,2-*d*][1,2,3]triazolo[1,5-a][1,4]diazepine **106,** which has a novel *N*-heterocyclic ring system.

2-Methylene-2*H*-thiazolo[3,2-*a*]pyrimidin-5(3*H*)-one (**107**) was prepared directly from *diendo*- and *diexo*-thiazolo[2,3-*b*]quinazolinones (±)-**76** and (±)-**77**, following a microwave-promoted RDA procedure. The transformation proceeded remarkably well leading to very high yields. Moreover, newly prepared derivative **107** could also be obtained from β-amino-*N*-propargyl carboxamides (±)-**58** and (±)-**59** and ethyl 2-isothiocyanatocarboxylate (±)-**88** and (±)-**89**, following a one-pot two-step process without the isolation of thiazolo[2,3-*b*]quinazolinones (±)-**76** and (±)-**77**.

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ANNEX