University of Szeged

Doctoral School of Pharmaceutical Sciences

Educational Program: Pharmaceutical Chemistry and Drug Research

Programme director: Dr. István Szatmári

Institute: Institute of Pharmaceutical Chemistry

Supervisors: Dr. Márta Palkó

Prof. Dr. Ferenc Fülöp

Mohamed EL HAIMER

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

Complex exam committee:

Head: Prof. Dr. Loránd Kiss

Members: Prof. Dr. Anikó Borbás

Prof. Dr. János Wölfling

Reviewer committee:

Head: Prof. Dr. György Dombi

Reviewers: Prof. Dr. Tamás Kálai

Dr Gerda Szakonyi

Members: Dr. Andrea Vasas

Dr. Anita Sztojkov-Ivanov

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. As a solution to this challenging problem, multistep, one-pot procedure has been developed. These protocols minimize time consumption and chemical waste generation, based on several transformations with bond forming taking place in a domino reaction manner. Therefore, the preparation of complex structures using reaction sequences, that assembles 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, because of the difficulty of performing "one-pot" domino reactions with high diastereoselectivity, the task is still challenging.

N-Propargylamines/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. Recently, 2-amino-*N*-propargyl aromatic amides were the subject of various transformations via domino reaction processes, to prepare diverse and complex heterocyclic systems.

Following the work of our research group on the synthesis and transformation of β-amino acids, 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. Subsequently, CuAAC was applied in a regioselective manner to investigate 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]

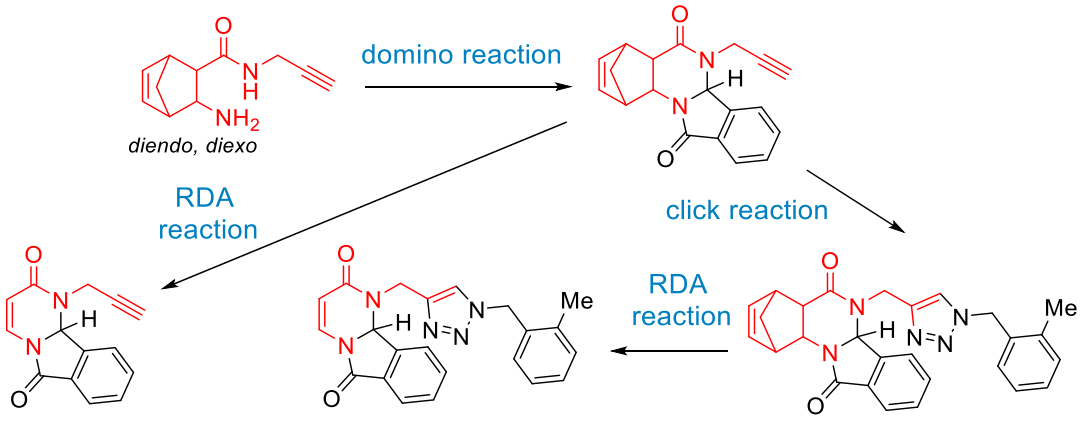


Figure 1

Our second aim was the synthesis of various alicyclic *N*-propargyl-substituted amino acids and to develop a one-pot, two-step, five-centered cascade process to synthesise alicyclic derivatives of quinazolinotriazolobenzodiazepines and to examine the diastereoselectivity of the domino ring-closure process [II]. Our further goal was the syntheses of 2-methylene-substituted thiazolo[2,3-*b*]quinazolinone derivatives through a tandem bicyclisation strategy [III] (Figure 2). Finally we wanted to investigate the possibility of RDA decomposition of the created norbornene derivatives and scrutinize the biological activity of aromatic and alicyclic derivatives *in vitro*.

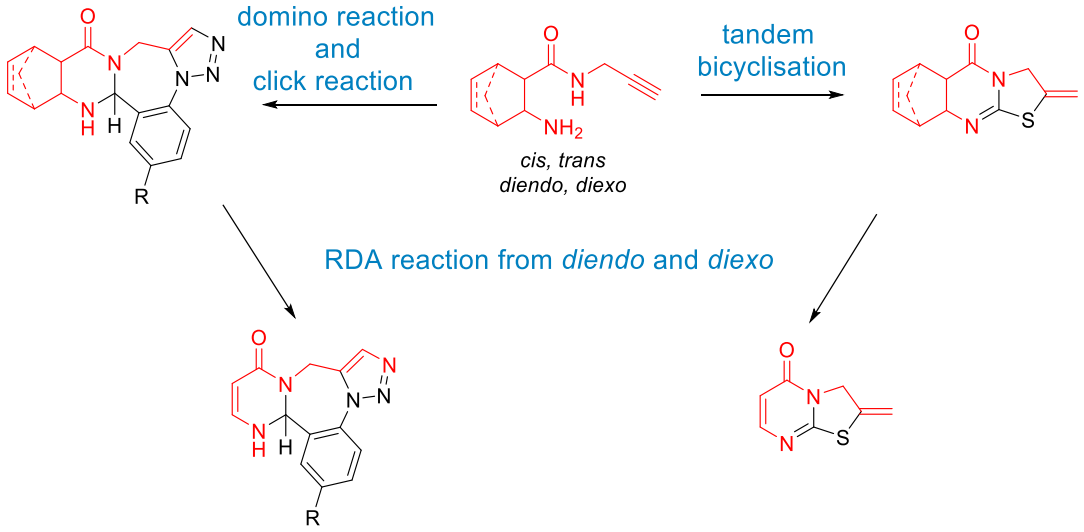
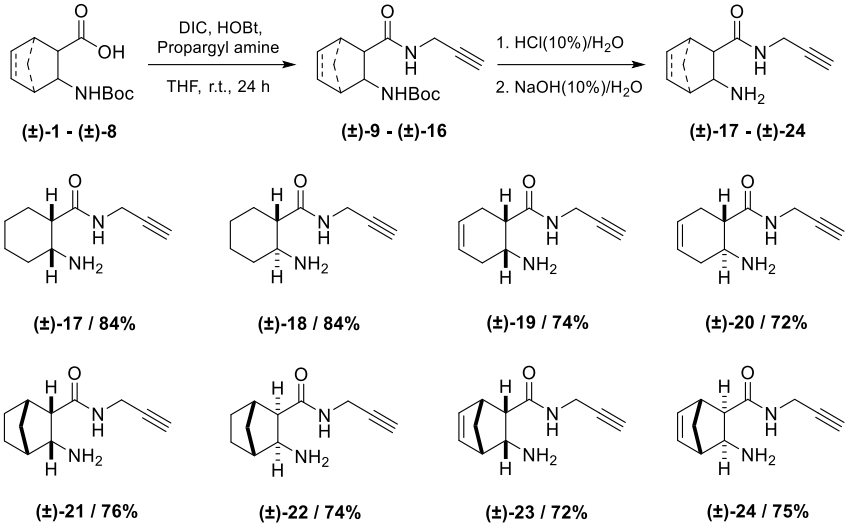


Figure 2

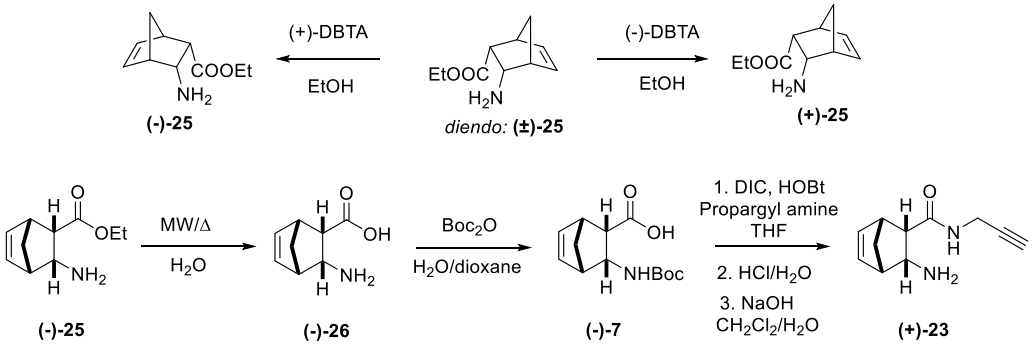
2. RESULTS AND DISCUSSIONS

Simple and efficient routes have been developed for the preparation of new racemic and enantiomeric norbornane-β-amino-*N*-propargyl carboxamides bearing *cis*- and *trans*-cyclohexene, cyclohexane as well as *diendo*- and *diexo*-norbornene rings. Starting from racemic alicyclic *N*-Boc-protected amino acids (±)-**1**–(±)-**8,** using HOBt and DIC as coupling agent, they were transformed to alicyclic *N*-propargyl amino carboxamides (±)-**17**–(±)-**24** after acidic deprotection (Scheme 1).

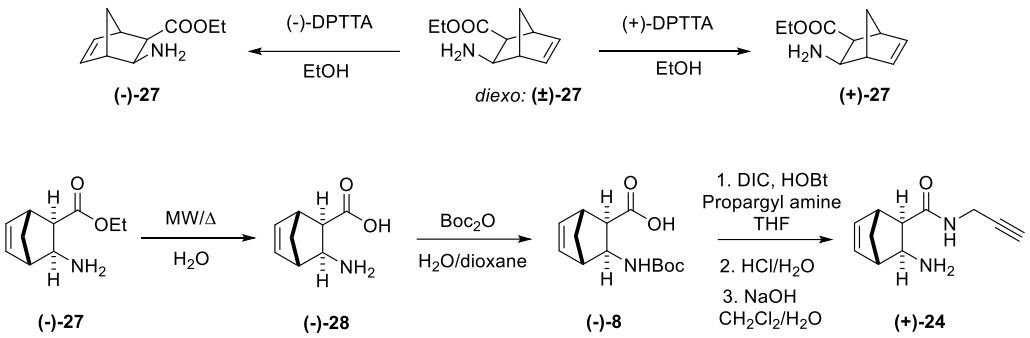


Scheme 1

Optically enriched *N*-propargyl amino carboxamides (−)-**23**, (+)-**23**, (−)-**24** and (+)-**24** 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 by resolution of racemic esters via diastereomeric salt formation with commercially available resolution agents (DBTA and DPTTA). The *ee* values of ester enantiomers were determined by HPLC measurements (Schemes 2 and 3).

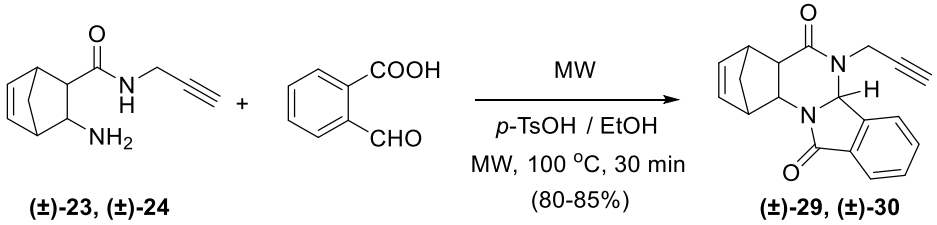


Scheme 2



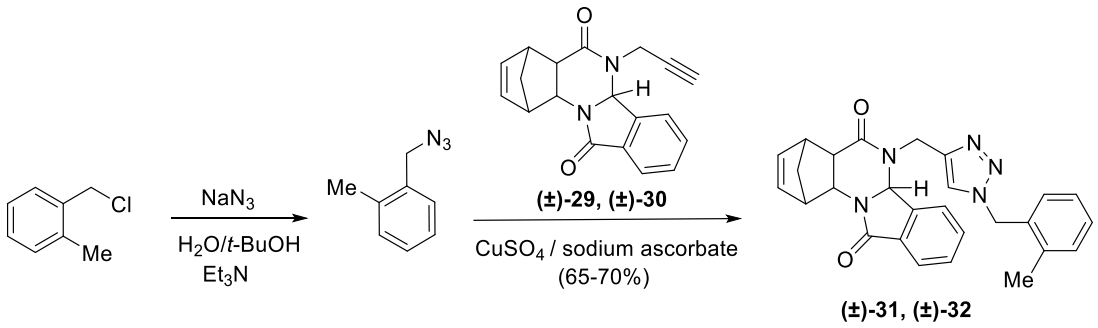
Scheme 3

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 (±)-**23** or (±)-**24** were reacted with 2-formylbenzoic acid, leading to the formation of alicyclic isoindolo[2,1-*a*]quinazoline (±)-**29** and (±)-**30** (Scheme 4). The reactions were first carried out with racemic compounds and then extended to enantiomeric carboxamides as well.



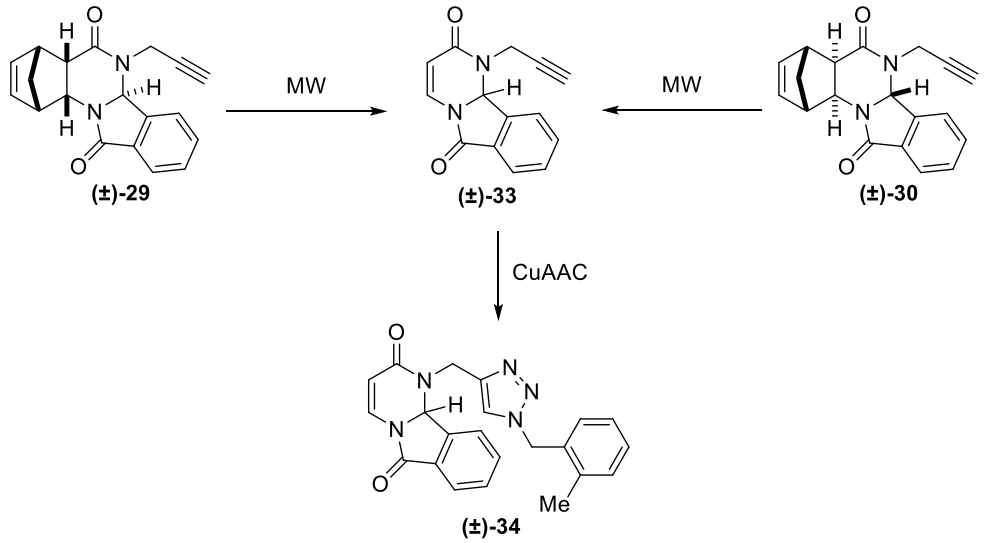
Scheme 4

Successful product formation was confirmed by full NMR signal assignment. The ^{1}H NMR spectra, in both cases, revealed the formation of the single epimers isoindolo[2,1-*a*]quinazoline (±)-**29** and (±)-**30**. The stereochemical information of the newly formed stereogenic centres of isoindoloquinazolinones (±)-**29** and (±)-**30** 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 (+)-**23** and (−)-**23** and *diexo* 3-amino-*N*-propargyl carboxamides (+)-**24** and (–)-**24** allowed to determine the absolute configuration of the final products. Moreover, the terminal alkyne moiety was subjected to CuAAC leading to the formation of racemic and enantiomeric 1,2,3-triazole pharmacophore-based isoindolo[2,1-*a*]quinazolinones (±)-**31**, (−)-**31**, (+)-**31**, (±)-**32**, (−)-**32** and (+)-**32** (Scheme 5).



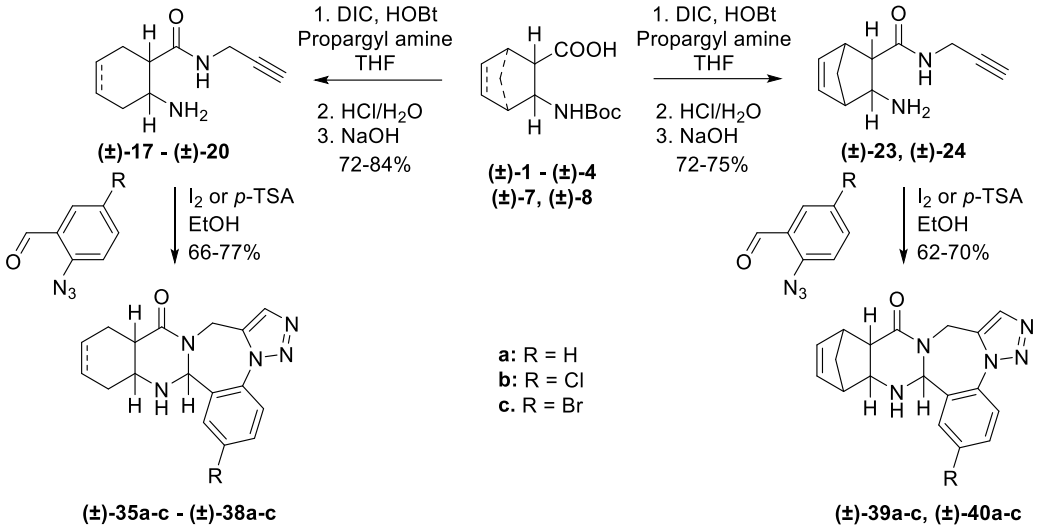
Scheme 5

Following the same CuAAC procedure, starting from RDA products (±)-**33**, product molecules (±)-**34** were produced with the same regioselectivity of the original pathway (Scheme 6).



Scheme 6

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 (±)-**17**–(±)-**20**, (±)-**23** and (±)-**24**, under reflux in EtOH in the presence of a catalytic amount iodine or *p*-TSA as catalyst under green conditions in good yields (Scheme 7). In all cases, the ^{1}H NMR spectra revealed the formation of the single epimers of alicyclic derivatives of quinazolinotriazolobenzodiazepine (±)-**35a–c**, (±)-**36a–c**, (±)-**37a–c**, (±)-**38a–c,** (±)-**39a–c** and (±)-**40a–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, this was shown to be consistent throughout the studied scope.



Scheme 7

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 (−)-**23** and (+)-**23**. The enantiomeric quinazolinotriazolobenzodiazepine (+)-**39a** and (−)-**39a** were obtained with a relatively good enantiomeric excess of *ee* > 84% and *ee* > 95%, respectively (Figure 3).

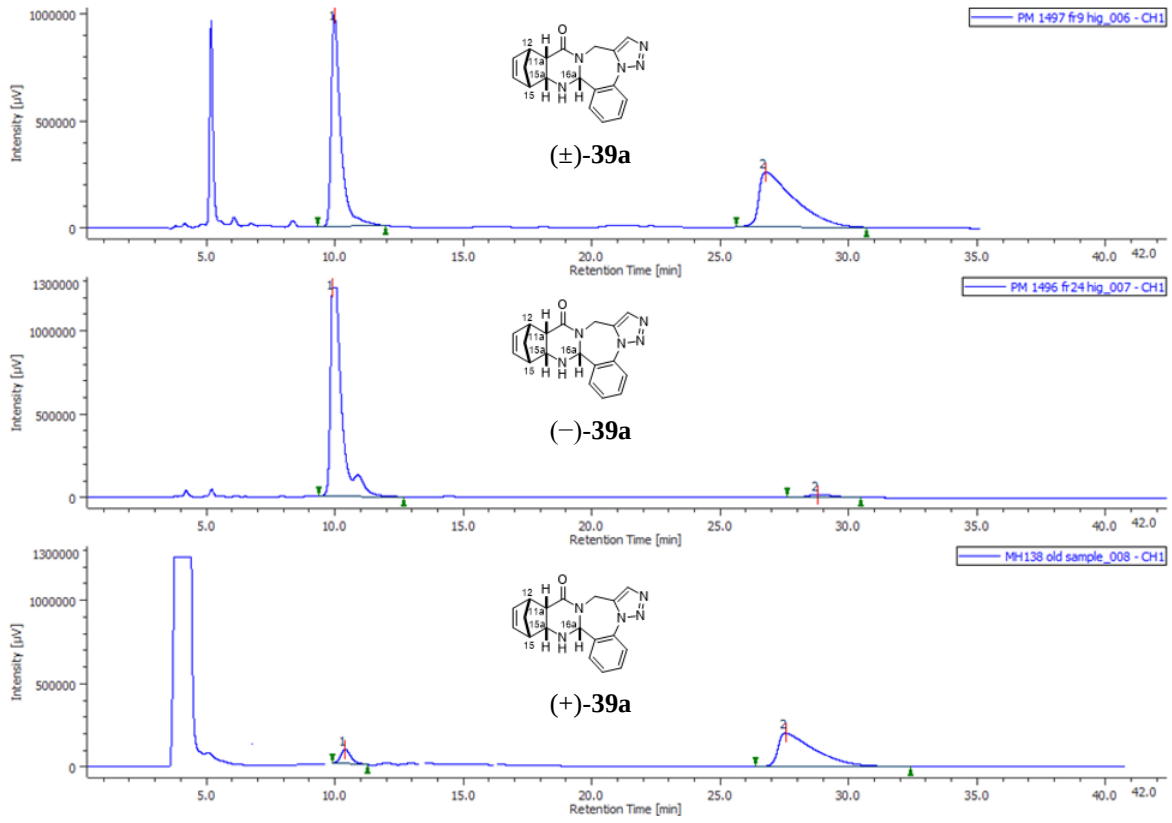
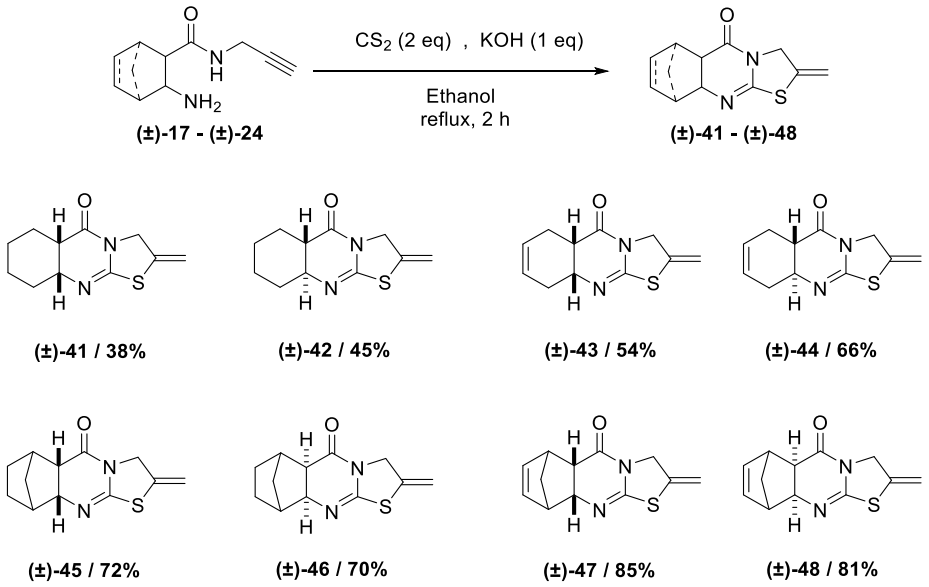


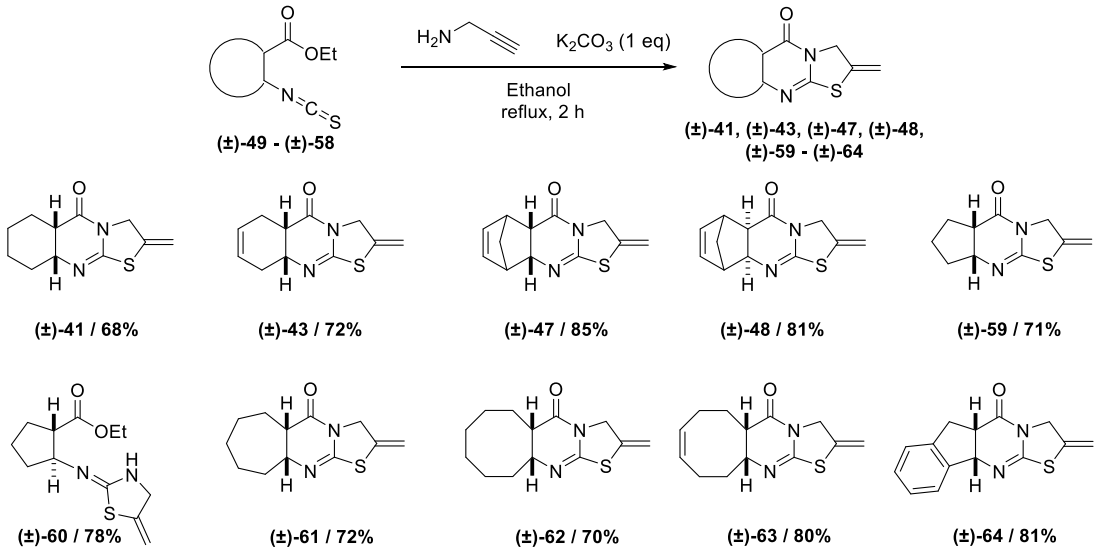
Figure 3

By means of the highly regioselective domino reaction process, several alicyclic 2-methylene-substituted thiazolo[2,3-*b*]quinazolinones (±)-**41**–(±)-**48** were synthesised (Scheme 8). Although the reactions of cyclic and alicyclic β-amino-*N*-propargyl carboxamides (±)-**17**–(±)-**24** 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.



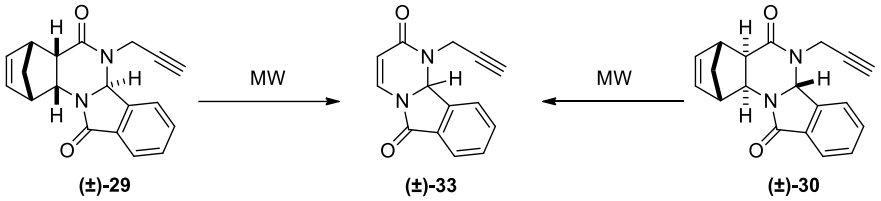
Scheme 8

On the other hand, a comparative study was performed using the reaction of ethyl 2-isothiocyanatocarboxylates (±)-**49**–(±)-**58** with propargylamine for the synthesis of several alicyclic 2-methylene-substituted thiazolo[2,3-*b*]quinazolinones (±)-**41**, (±)-**43**, (±)-**47**, (±)-**48** and (±)-**59**–(±)-**64** affording higher yields (Scheme 9).

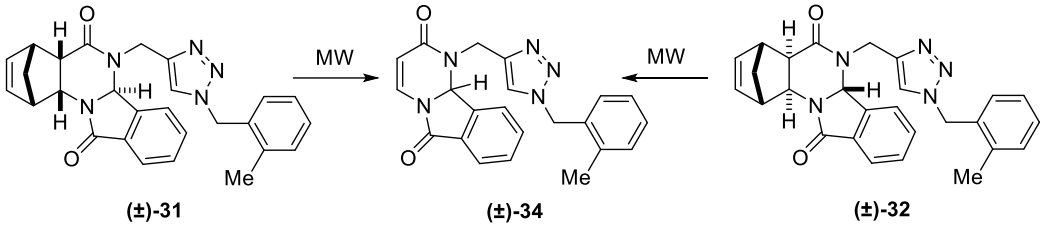


Scheme 9

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 (Scheme 10 and 11). Starting from isoindoloquinazoline derivatives, a traceless chirality transfer was achieved leading to pyrimido[2,1-*a*]isoindole. Under the same RDA reaction protocol, the enantiomeric isoindoloquinazoline derivatives (−)-**29**, (+)-**29**, (−)-**30**, (+)-**30**, (−)-**31**, (+)-**31**, (−)-**32** or (+)-**32** were transformed into enantiomeric pyrimido[2,1-*a*]isoindole derivatives (−)-**33**, (+)-**33**, (−)-**34** and (+)-**34**. Moreover, the absolute configuration of these final pyrimido[2,1-*a*]isoindole products was also determined.

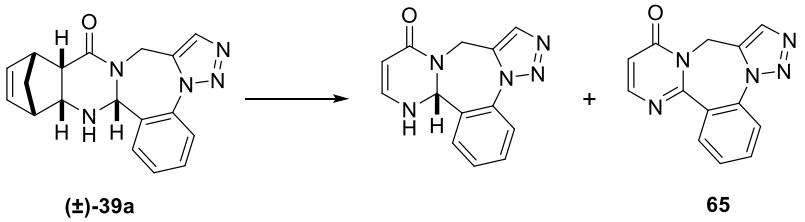


Scheme 10



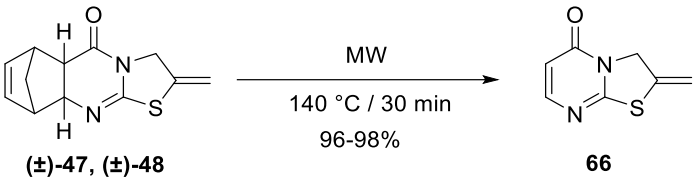
Scheme 11

The RDA decomposition of *diendo*-quinazolinotriazolobenzodiazepine derivative (±)-**39a** proved to be more challenging. In fact the traceless chirality transfer was not successful. On the other hand, after testing several conditions, an oxidation method resulted in benzo[*f*]pyrimido[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepine **65**, which has a novel *N*-heterocyclic ring system (Scheme 12).



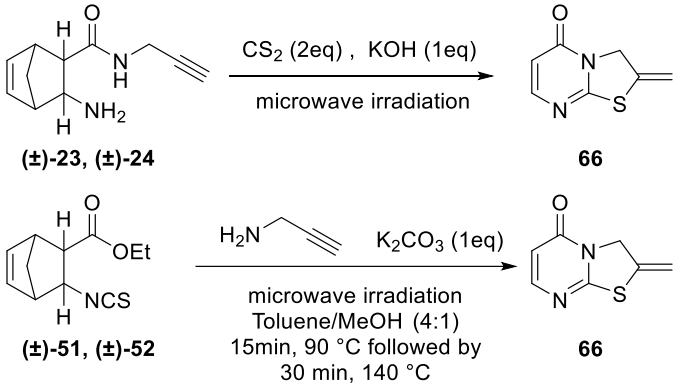
Scheme 12

2-Methylene-2*H*-thiazolo[3,2-*a*]pyrimidin-5(3*H*)-one **66** was prepared directly from *diendo*- and *diexo*-thiazolo[2,3-*b*]quinazolinones (±)-**76** and (±)-**77** following a microwave-promoted RDA procedure. It proceeded remarkably well leading to very high yields (Scheme 13).



Scheme 13

Moreover, this newly prepared 2-methylene-2*H*-thiazolo[3,2-*a*]pyrimidin-5(3*H*)-one **66** derivative could also be obtained from β-amino-*N*-propargyl carboxamides (±)-**23** and (±)-**24**, and ethyl 2-isothiocyanatocarboxylate (±)-**51** and (±)-**52**, following a one-pot process without the isolation of thiazolo[2,3-*b*]quinazolinones (±)-**47** and (±)-**48** (Scheme 14).



Scheme 14

3. PUBLICATIONS

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**

4. 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.