PALACKY UNIVERSITY OLOMOUC

Faculty of Science

Department of Organic Chemistry

Development of Strategies for Solid-Phase Synthesis of Nitrogenous Heterocyclic Compounds Based on the 2- and 4-Nitrobenzenesulfonamide Chemistry

Ph.D. Thesis

Author: Mgr. Veronika Fülöpová

Supervisor: doc. RNDr. Miroslav Soural, Ph.D.

Supervisor-consultant: RNDr. Viktor Krchňák, CSc.

Olomouc   2015

Bibliographic details

Title	Development of Strategies for Solid-Phase Synthesis of Nitrogenous Heterocyclic Compounds Based on the 2- and 4-Nitrobenzenesulfonamide Chemistry.
Nadpis	Vývoj strategií pro přípravu dusíkatých heterocyklických sloučenin založených na 2- a 4-nitrobenzensulfonamidové chemii s využitím syntézy na pevné fázi.
Type	Ph.D. Thesis
Author	Mgr. Veronika Fülöpová
Supervisor	doc. RNDr. Miroslav Soural, Ph.D.
University	Palacky University Olomouc
Study programme	P1417 Chemistry
Field of study	Organic Chemistry
Department	Organic Chemistry
Language	English
Year	2015
Pages	141
Available at	http://portal.upol.cz

Declaration of originality

I hereby declare that this Ph.D. thesis represents my original work made with the best of my knowledge and that I have used no other sources except as referred by citations. Neither the thesis nor any of its substantial parts were previously used for awarding of any other academic degree.

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Acknowledgement

Abstract

Solid-phase synthesis in connection with combinatorial chemistry represents one of the essential approaches leading to considerable array of diverse compounds collections (so called chemical libraries) in relatively short time. Such technique, widely used in the field of medicinal chemistry, facilitates the detailed structure-activity relationship (SAR) studies enabling a rapid detection of novel drug candidates. In this context, the submitted doctoral thesis deals with the development of simple procedures applicable for the preparation of libraries of selected heterocyclic compounds. In all of the introduced procedures, the immobilized 2- or 4-nitrobenzenesulfonamides were used as the key intermediates. Different scenarios have been used in which the nitrobenzenesulfonyl (Nos) group was applied (1) only as a protective/activating group for Fukuyama selective monoalkylation followed by the cleavage of the sulfonamide scaffold, (2) as a building block after previous Fukuyma alkylation, or (3) as a building block without application of Fukuyama alkylation.

The major part of the research was focused on the preparation of compounds derived from the benzodiazepin-5-one and benzothiadiazepine 1,1-dioxide scaffold. Firstly, a method for synthesis of trisubstituted 3*H*-benzo[*e*][1,4]diazepin-5(4*H*)-one derivatives (**A**, **B**) was developed based on the scenario (1). Fukuyama alkylation of 4-nitrobenzenesulfonamides provided the corresponding intermediates that were deprotected and subsequently converted to the target products under different cyclization conditions. Conversely, the corresponding benzothiadiazepine 1,1-dioxides (**C**) were obtained via the scenario (2). After alkylation of the starting nitrobenzenesulfonamide, the Nos group was kept in the structure as a building block to give the target scaffold. In this case, some of the prepared derivatives were not stable and unprecedented rearrangement was observed that yielded benzothiazine 1,1-dioxides **D**. Another part of this thesis was targeted to the synthesis of structurally different scaffolds. The corresponding nitrobenzenesulfonamides were converted to the trisubstituted benzoylquinazoline derivatives **E** with use of scenario (2). However, unlike the previous case, the final compounds were prepared via *C*-arylated intermediates. The last contribution was dedicated to the preparation of Anagrelide sulfonyl analogues **F**. In this case, 2-nitrobenzensulfonylchloride was used exclusively as a building block according to scenario (3).

General overview of the target scaffolds

Y=CO; SO$_2$

X=scaffold of the immobilized amine
including a substituent R^1
Pol=polymer support; L=linker

Souhrn

Syntéza na pevné fázi ve spojení s kombinatoriální chemií představuje jeden ze základních přístupů vedoucích k řadě rozmanitých sérií sloučenin (tzv. chemických knihoven) získaných v relativně krátkém čase. Tato technika, široce používaná v medicinální chemii, usnadňuje detailní studium vztahů mezi strukturou a biologickou aktivitou látek, což umožňuje rychle rozpoznat potenciální kandidáty na nová léčiva. V této souvislosti se předložená doktorská práce zabývá vývojem jednoduchých postupů aplikovatelných na syntézu knihoven vybraných heterocyklických sloučenin. Základem všech navržených metodik je příprava imobilizovaných 2- nebo 4-nitrobenzensulfonamidů jakožto klíčových meziproduktů, jejichž nitrobenzensulfonylová (Nos) skupina může být v syntéze využita třemi různými způsoby: (1) jako protektivní/aktivační jednotka umožňující Fukuyama selektivní monoalkylaci (po této reakci je Nos odštěpen), (2) jako stavební jednotka, která je následně po Fukuyama alkylaci ve struktuře zachována, nebo (3) jako stavební jednotka bez aplikace Fukuyama alkylace.

Hlavní část práce byla zaměřena na přípravu sloučenin odvozených od struktur benzodiazepin-5-onu a benzothiadiazepin 1,1-dioxidu. V tomto případě byla nejdříve vyvinuta metodika založená na přístupu (1), která byla následně aplikována na syntézu derivátů 3*H*-benzo[*e*][1,4]diazepin-5(4*H*)-onu (**A**, **B**). Fukuyama alkylace 4-nitrobenzensulfonamidů poskytla příslušné intermediáty, které byly deprotekovány a následně převedeny na cílové sloučeniny za různých cyklizačních podmínek. Naopak benzothiadiazepin 1,1-dioxidy (**C**) byly získány využitím přístupu (2). Po alkylaci výchozího nitrobenzensulfonamidu byla ve struktuře Nos skupina zachována pro výstavbu finálního skeletu. Některé z takto připravených derivátů nebyly stabilní, přičemž byl pozorován nečekaný přesmyk vedoucí k benzothiazin 1,1-dioxidům **D**. Další část práce byla zacílená na syntézu strukturně odlišných skeletů. Příslušné nitrobenzensulfonamidy byly převedeny na trisubstituované benzoylchinazoliny **E** s využitím přístupu (2). Nicméně, na rozdíl od předchozí syntézy, finální sloučeniny byly připraveny přes *C*-arylované intermediáty. Poslední příspěvek byl věnován přípravě sulfonyl analog Anagrelidu **F**. V tomto případě byl 2-nitrobenzensulfonylchlorid použit výhradně jako stavební jednotka podle přístupu (3).

Contents

1. Introduction

Over the last two hundred years, the traditional (solution-phase) organic chemistry has undergone a tumultuous development. At the beginning of the 19th century, it was only a branch of chaos that was later unified thanks to understanding of various theories, postulates, experimental basics and syntheses of the first organic compounds. Clarification of the structural concepts and introduction of the chemical nomenclature triggered a considerable development of industry and chemistry of natural materials.[1] To gain a broader spectrum of derivatives based on naturally-occurring motifs, chemists have been searching for novel and more efficient synthetic procedures. One of these methods involves reactions on insoluble polymer support, so called solid-phase synthesis. This technique was introduced in 1963, when Robert Bruce Merrifield published an article[2] describing a simple and highly effective method for the preparation of peptides utilizing polystyrene matrix as a support. With respect to the significant advantages of the method, such as simple isolation of reaction intermediates resulting in the quick synthesis of target compounds collections, the contribution was later awarded by a Nobel Prize. Solid-phase technique have been widely used as a powerful tool in combinatorial chemistry, particularly for medicinal and pharmaceuticals goals. Less time-consuming syntheses and sufficient structural variability of chemical libraries has allowed a rapid identification of novel, biologically active molecules.

During our long-term research, we have been applying the advantages of solid-phase synthesis and paid our attention to a development of convenient protocols compatible with high-throughput synthesis of chemical entities based on privileged heterocyclic scaffolds. This work summarizes our recent results from this field.

2. Aims of the work

The general goal of this work consisted in a development of high-throughput solid-phase syntheses of selected heterocyclic compounds and determination of scope and limitations of the proposed synthetic pathways. In the individual reaction sequences, the polymer-supported nitrobenzenesulfonamides were used as the key intermediates for different chemical transformations to obtain the final derivatives. The first part of the research, based on the synthesis of benzodiazepine derivatives and Anagrelide sulfonyl analogues (Figures 1, 2 and 6), was carried out at the Institute of Molecular and Translational Medicine (IMTM) under the auspices of Department of Organic Chemistry, Palacky University in Olomouc. Preparation of benzothiadiazepine 1,1-dioxides, benzothiazine1,1-dioxides and benzoylquinazolines (Figures 3,4 and 5) was achieved during the internship at the University of Notre Dame, USA. Benzoylquinazoline derivatives were synthesized by American undergraduate students under the author's supervision.

2.1 Summary of the presented aims

Figure 1. Retrospective synthesis of benzo[1,4]-diazepin-5-one derivatives.[3]

Figure 2. Retrospective synthesis of benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-6(5*H*)-ones and their sulfonyl analogues.[4]

Figure 3. Retrospective synthesis of 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide derivatives.[5]

Figure 4. Retrospective synthesis of 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides.[6]

Figure 5. Retrospective traceless synthesis of benzoylquinazoline derivatives.[7]

Figure 6. Retrospective synthesis of Anagrelide Sulfonyl Analogues.[8]

X=scaffold of the immobilized amine
including a substituent R^1

n=1-3

3. State of the art

3.1 Brief introduction into nitrobenzenesulfonamide chemistry on solid-phase

Based on the publication: Fülöpová, V.; Soural, M. 2015, Article under review.[9]

Compounds containing a benzenesulfonamide scaffold belong to the most intensively studied sulfurous organic derivatives. Their utility originated in the field of medicinal chemistry, which introduced benzenesulfonamides as pharmacologically important compounds.[10-13] A number of these molecules have applications in human medicine, particularly as potent antidepressant,[14] antitumor,[15-17] antiviral[18] and antimicrobial[19,20] agents. In the field of synthetic organic chemistry, a special group of derivatives is represented by 2-nitrobenzenesulfonamides and 4-nitrobenzenesulfonamides derived from primary amines. Such compounds are easily accessible from 2-nitrobenzenesulfonyl chloride (2-NosCl) or 4-nitrobenzenesulfonyl chloride (4-NosCl), respectively. In 1995, a milestone in nitrobenzenesulfonamide application in preparative synthesis was achieved by Fukuyama, who reported their use for the selective monoalkylation of primary amines.[21,22] Although alternative methods had been developed earlier (e.g., reductive alkylation or acylation followed by amide reduction),[23-25] the Fukuyama procedure quickly became the method of choice. Even strategies based on a similar approach using *p*-toluenesulfonamides and trifluoroacetamides could not compete with Fukuyama method due to the relatively harsh conditions needed to cleave the activating/protecting Tosyl and trifluoroacetyl groups.[21] Alkylation of nitrobenzenesulfonamides with either alkyl halides, alcohols[26,27] or α,β-unsaturated ketones (Michael's addition)[28] is followed by the cleavage of a Nos group under mild reaction conditions, typically using various thiols. Because of its simplicity and only few limitations,[29,30] the Fukuyama strategy has subsequently been employed by many 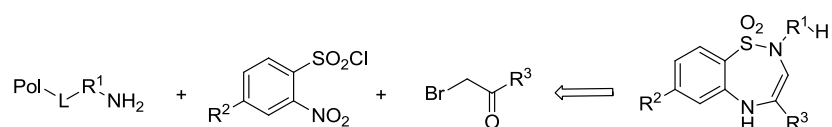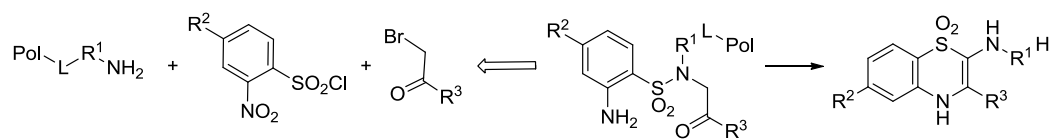chemists for the regioselective monoalkylation of diverse intermediates. In addition to traditional solution-phase synthesis, Fukuyama protection/activation is also efficient in SPS using an excess of alkylating species. Miller initially used this technique in 1997[31] to selectively *N*-methylate peptides. The mild cleavage conditions compared to alternative acid/base methods (such as Benoiton, Freidinger or Grieco)[32] are preferred in SPS because they are compatible with a number of acid/base-labile linkers. For this reason, the Fukuyama alkylation significantly impacted solid-phase synthesis in the following decade.

In 2008, solid-phase Fukuyama alkylation with haloketones unexpectedly provided novel indazole-*N*-oxide derivatives.[33] Rearrangement was based on *C*-arylation followed by

cleavage of sulfur dioxide moiety. This discovery ushered in a new era of NosCls in organic synthesis. Instead of the standard Fukuyama alkylation, nitrobenzenesulfonamides have been advanced intermediates in DOS of various heterocyclic scaffolds.[34] Later research showed that also intramolecular *N*-arylations can occur depended on the type of substrate and the reaction conditions.[35] Apart from planar heterocyclic scaffolds, also compounds with 3D architecture (presence of sp^3 carbons) and derivatives with stereoselective formation of stereogenic centres were accessible to cover the larger part of a chemical space.

The following subchapters summarize the entire history of polymer-supported 2- and 4-nitrobenzensulfonamides. Three general different approaches are distinguished: (i) Nos as standard protecting group for monoalkylation followed by cleavage of the Nos group (scenario A, Scheme 1), (ii) Nos as activation species for Fukuyama or Fukuyama-Mitsunobu alkylation while preserving the Nos scaffold (or just the aromatic portion) in the final structure (scenario B, Scheme 1) and (iii) NosCls as common building blocks without application of Fukuyama alkylation (scenario C, Scheme 1).

Scheme 1. Three different scenarios for application of NosCls in solid-phase synthesis.
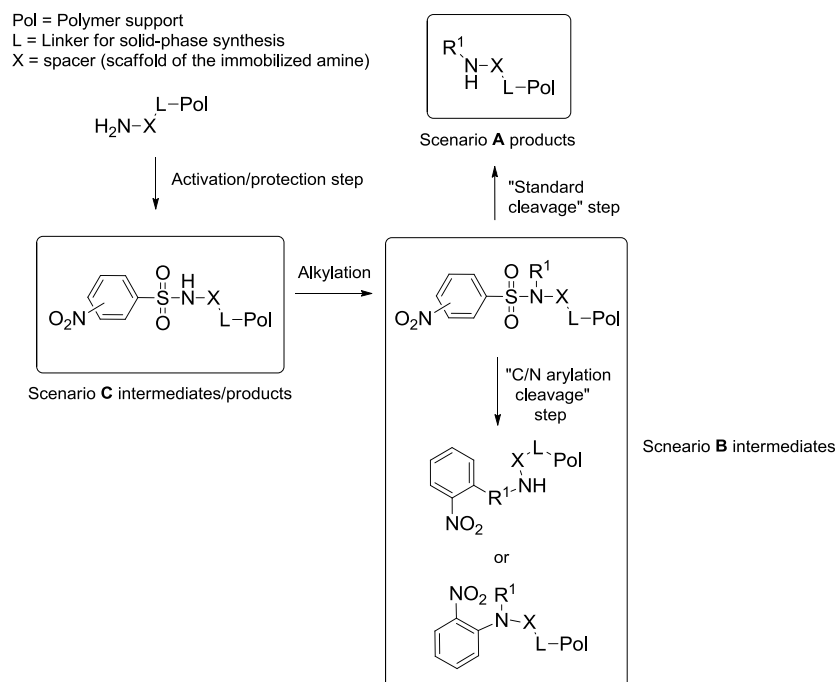
3.2 Scenario A: Protecting/activating function for the regioselective alkylation

Incorporation of the Nos group to obtain the corresponding nitrobenzenesulfonamide is typically carried out with NosCls in a presence of a base (e.g., collidine, DIEA, TEA or 2,6-lutidine)[36-39] in different solvents such as DMF, NMM,[40] THF or DCM. The resulting nitrobenzenesulfonamide intermediate is subjected to alkylation with different species followed by deprotection of the Nos moiety. In addition to protecting/activating function, the most important feature of the Nos group is its mild cleavage conditions. In accordance with the original Fukuyama procedure (Scheme 2),[21] deprotection of intermediate **2** is mediated by diverse thiols (e.g., thiophenol, mercaptoethanol, mercaptoacetic acid, 1*H*,1*H*,2*H*,2*H*-perfluorodecane-1-thiol or 2,2′-(ethylenedioxy)diethanethiol)[41-46] in the presence of a suitable base, such as potassium carbonate, collidine, propylamine or DBU, via a Meisenheimer complex **3**. The typical solvent is DMF or NMP. Ionic liquids[47] have also been used in solution-phase chemistry. However, the most frequently applied procedure in SPS consists of the combination of mercaptoethanol, DBU and DMF.

Scheme 2. Mechanism of Nos deprotection according to Fukuyama[21] (demonstrated for 4-Nos).[a]

R^1= Bn, Pr, PhCH$_2$CH$_2$, CH$_3$CHCOOEt R^2=Ph, HOOC-CH$_2$
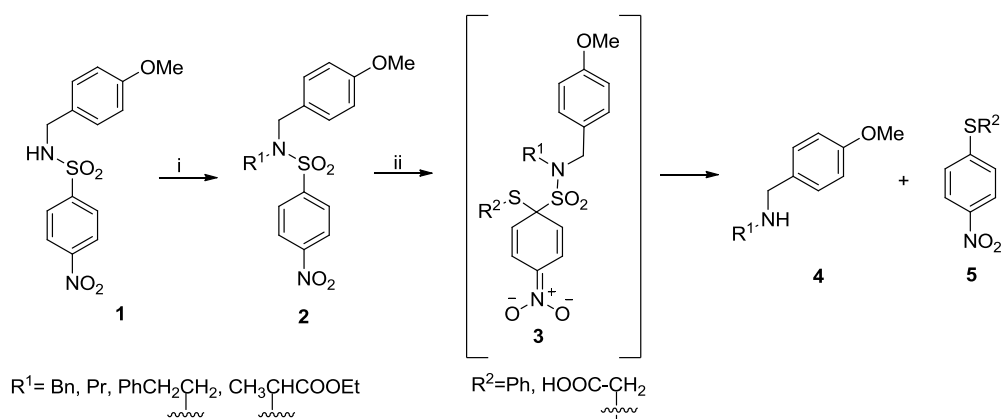
[a]Reagents: (i) R^1OH, DEAD, PPh$_3$, DCM or R^1X, K$_2$CO$_3$, DMF; (ii) R^2SH, K$_2$CO$_3$, DMF.

In the context of scenario A, the following subchapters summarize the individual approaches sorted according to the type of the alkylating agent.

3.2.1 Alkylation with alkyl halides

The historical solid-phase Fukuyama alkylation belongs in this category.[31] Miller and Scalan automated the SPS of a thrombin-receptor agonist peptide amide (SFLLRN) with the cheaper *N*-2-Nos protected *N*-unalkylated amino acid in place of the commonly applied Fmoc-AA-OH.[48] In contrast to Fmoc deprotection, cleavage of the 2-Nos group of peptide **7** by thiophenol produced compound **9a** and a yellow chromophore; which allowed the process to be inspected visually (Scheme 3). To expand the developed method, the starting *N*-2-Nos peptide **7** underwent selective *N*-alkylation (**8b**) or allylation (**8c**) prior to deprotection. After selective removal of the Nos group from compound **8b**, the subsequent coupling of immobilized *N*-alkylated peptide **9b** with 2-Nos-AA-OH was effortless. On the other hand, coupling of *N*-allylated peptide **9c** with 2-Nos-AA-OH was more complicated due to the formation of side products. To increase the coupling yield, peptide **9c** was coupled with 2-Nos-AA-Cls. The developed strategy was compatible with the Fmoc protecting group and can therefore also be combined with Fmoc-AA-OH.[49]

Scheme 3. Use of *N*-2-Nos protected amino acids in peptide synthesis.[a]
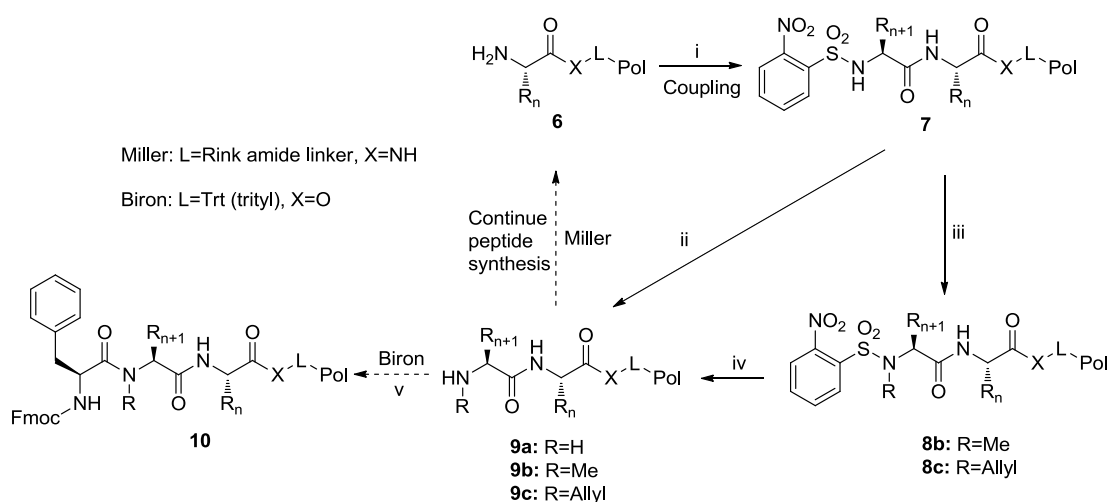
[a]Reagents: (i) 2-Nos-AA-OH or 2-Nos-Phe-Cl, HBTU, NMM, DMF; (ii) PhSH, K_2CO_3 DMF; (iii) a) methyl 4-nitrobenzenesulfonate, MTBD, DMA or b) allyl methyl carbonate, Pd_2dba_3, $CHCl_3$, PPh_3, THF; (iv) 2-mercaptoethanol, DBU, DMF; (v) Fmoc-Phe-OH, HATU, HOAt, DIEA, NMP.

The methylation of non-natural α-amino acids was described by Bolton and Hodges,[50] who developed a procedure for the intramolecular Heck cyclization of solid-supported allyl intermediates **13**. *N*-Methylated sulfonamide **12** was deprotected by thiolate and then acylated

with 2-iodobenzoyl chloride (Scheme 4). The final Heck cyclization of **13** was accomplished under Pd(II) catalysis.

Scheme 4. Fukuyama methylation of the unnatural amino acid sulfonamide for the Heck reaction.[a]
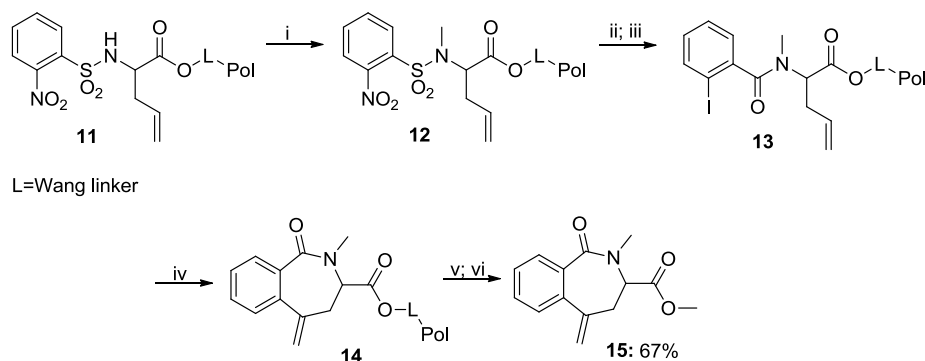
[a]Reagents: (i) MTBD, MeI, DMF; (ii) PhSH, K$_2$CO$_3$, DMF; (iii) 2-iodobenzoyl chloride, TEA, DCM; (iv) Pd(OAc)$_2$, PPh$_3$, Bu$_4$NCl, potassium acetate, DMF, 70 °C; (v) 50% TFA in DCM; (vi) CH$_2$N$_2$.

In addition to solid-supported α-amino acids, alkylation of other immobilized amines has also been described.[51] The following example shows the alkylation of a 1,2-diaminoethane intermediate **16**, which spontaneously afforded solid-supported benzodiazepinone derivatives **18** after cleavage of the Nos group (Scheme 5).

Scheme 5. Use of Nos protecting group for the alkylation of immobilized diamine.[a]
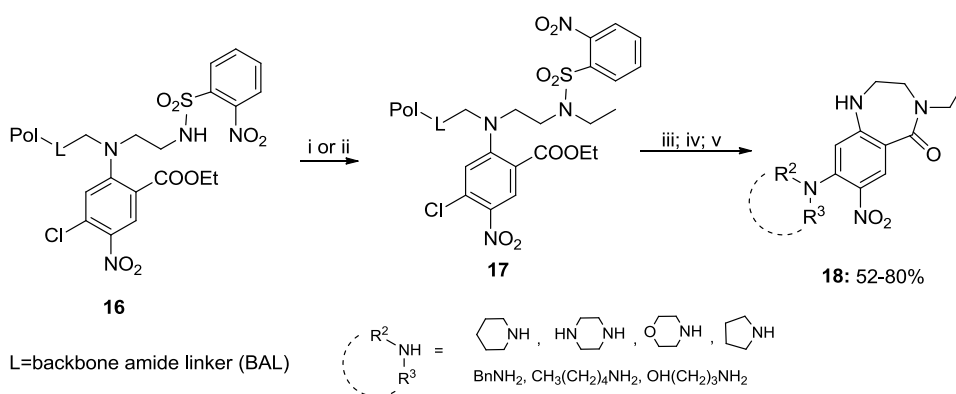
[a]Reagents: (i) ethyl iodide, DBU, DMF; (ii) EtOH, DIAD, PPh$_3$, anhydrous THF; (iii) amine, DMSO, MW (200 W, 150 °C); (iv) 2-mercaptoethanol, DBU, DMF; (v) 50% TFA in DCM.

Functionalized alkyl halides have been used to construct additional heterocyclic scaffolds. For example, *N*-alkylation of immobilized Nos-dipeptide **19** with 1,2-

17

dibromoethane was followed by spontaneous intramolecular cyclization to yield *N*-2-Nos-oxopiperazines **20** (Scheme 6).[52] Cleavage of the 2-Nos group provided the target compounds **21** which can be further derivatized with another amino acid.

Scheme 6. Intramolecular alkylation of a Nos-protected dipeptide with 1,2-dibromoethane.[a]

L=Barlos linker
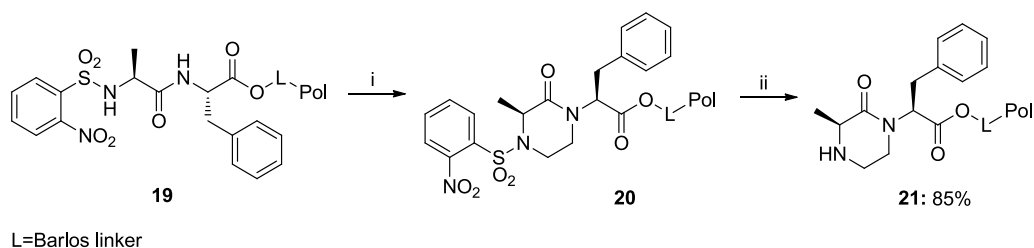
[a]Reagents: (i) 1,2-dibromoethane, K$_2$CO$_3$, DMF, 60 °C; (ii) DBU, 2-mercaptoethanol, DMF.

Similarly, propargyl bromides were used to construct 1,2,3-triazole scaffold. Intermediate **22** was alkylated with different substituted propargyl bromides, followed by deprotection of the 4-Nos group (Scheme 7).[4] Subsequent acylation of intermediate **24** with 2-azidobenzoic acids or 2-azidobenzenesulfonyl chloride spontaneously afforded benzotriazolodiazepinones and their sulfonyl analogues **26**.

Scheme 7. Intramolecular cyclization via 1,3-dipolar cycloaddition.[a]

L=Wang linker, X=O
L=Rink amide linker, X=NH
L=BAL, X=NPr or NBn

26: 32-77%
R^1=H, Me, Ph
R^2=H, Me, OMe, Br, Cl, NO$_2$

Y=CO, SO$_2$
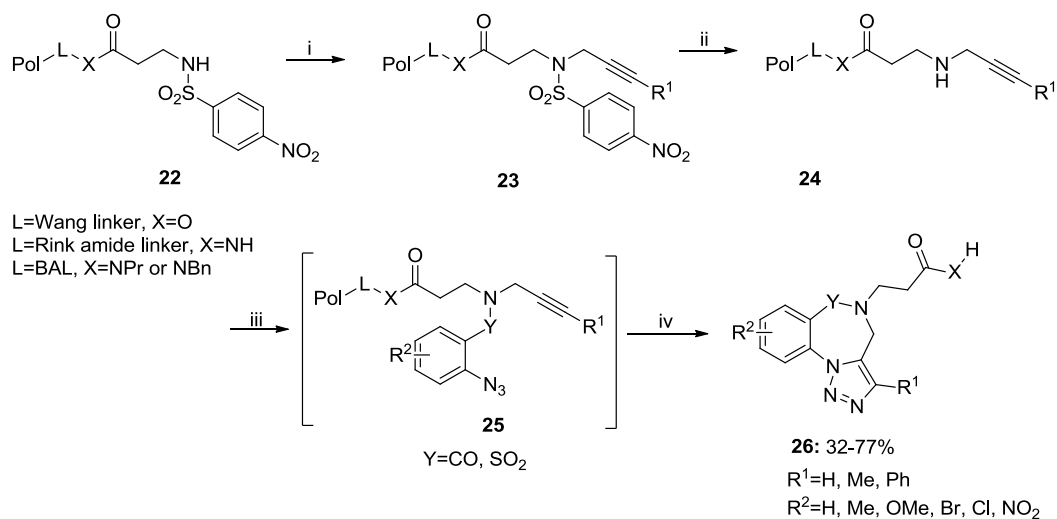
[a]Reagents: (i) propargyl bromide, DBU, DMSO; (ii) 2-mercaptoethanol, DBU, DMF; (iii) 2-azidobenzoic acid (Y=CO), HOBt, DIC; or 2-azidobenzenesulfonyl chloride (Y=SO$_2$), 2,6-lutidine, DCM; (iv) 50% TFA in DCM.

In 2009, Pudelová and Krchňák[53] developed a DOS[54] of various heterocycles through α-acylamino ketone/ester intermediates **30** (Scheme 8). The starting 4-nitrobenzenesulfonamides **27** were alkylated with different substituted α-haloketones. Deprotection of the Nos group and subsequent acylation of **29** with acids or their halogen derivatives provided the key intermediate **30** that was subjected to different cyclization reactions leading to heterocycles **31**, **32** and **33**. α-Acylamino ketones were also used to prepare trisubstituted 1-*H*-imidazoles **34**.[55]

Recently, trisubstituted benzo[1,4]-diazepin-5-one derivatives **35** were synthesized by a similar approach (Scheme 8).[3] Unlike the previous case, the deprotected precursor **29** was first acylated with 2-nitrobenzoic acid, and further reduction of the nitro group was followed by spontaneous intramolecular on-resin cyclization.

Scheme 8. Use of nitrobenzenesulfonamides and haloketones in the synthesis of different nitrogenous heterocycles.[a]

35: 14-47%
R^1=thiophene, 4-OMePh, 4-MePh
R^2=H, Br, OMe, Me
Y=H, N

34: 6-81%
R^1=4-MePh, 4-FPh, 4-ClPh, 4-OMePh
R^2=Me, $NH_2CH_2CH_2$, Py derivatives

29

28

27

30

33: 16%, 29%
R^1=4-MePh, 4-OMePh

31: 6-77%
R^1=4-MePh, 4-OMePh, OEt
4-NH_2-3,5-diCl-Ph
R^2 included R^3=H, Me, Et

32: 5%, 15%
R^1=4-MePh, 4-OMePh
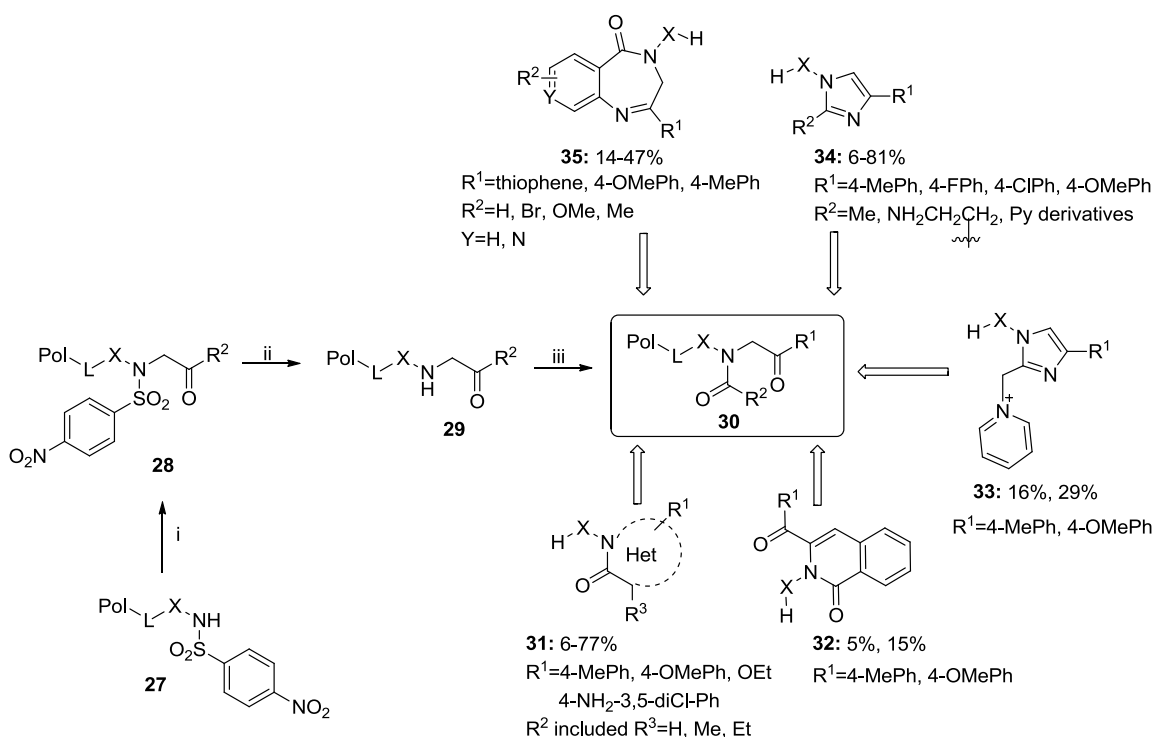
L=Wang or Rink amide linker or BAL

Selected examples of X-H= H_2NOC PrHNOC HOOC HO H_2N

[a]Reagents: (i) haloketone, DIEA, DMF; (ii) 2-mercaptoethanol, DBU, DMF; (iii) α-bromocarboxylic acid, DIC, DCM, DIEA; or Fmoc-α-AA-OH, DIC, DCM/DMF; or 2-nitrobenzoic acid, DIC, DMF.

The analogous, but reversed strategy was described by Biron et al.[56] for the synthesis of peptoids by an alternative path in the submonomer approach. This procedure utilized the alkylation of 2-nitrobenzenesulfonamide, prepared from 2-NosCl, with immobilized bromoketone **36** (Scheme 9). Surprisingly, the common protocol for removing 2-Nos was not successful in this case. To avoid incomplete deprotection of intermediate **37**, Biron's group developed suitable conditions to use *p*-methoxybenzenethiol with Cs_2CO_3 or DBU.

Scheme 9. Reverse alkylation of nitrobenzenesulfonylamides with polymer-supported halogene derivatives.[a]
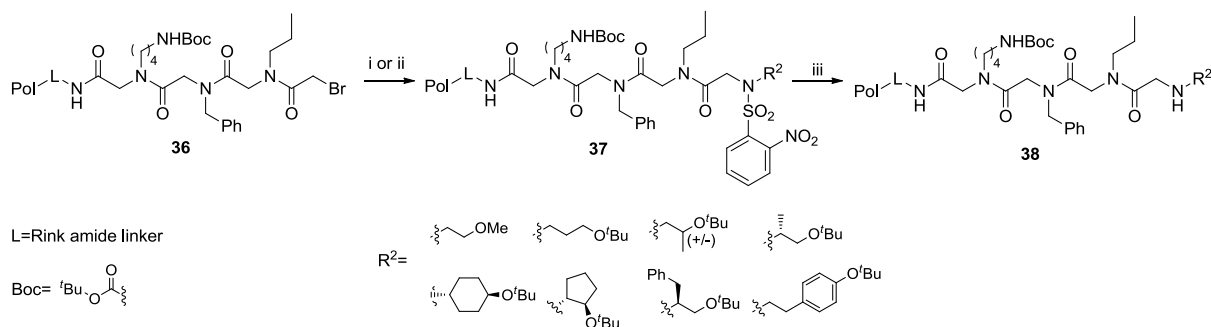
[a]Reagents: (i) 2-Nos-NHR[2], Cs_2CO_3, DMF (repeated once); (ii) 2-Nos-NHR[2], Cs_2CO_3, DMF, MW (70 ºC); (iii) *p*-OMePhSH, Cs_2CO_3 or DBU, DMF.

3.2.2 Alkylation with alcohols

The efficacy of Nos-activation was significantly enhanced through use of the Mitsunobu reaction with alcohols as an alternative procedure to Fukuyama alkylation with alkyl halides. One of the first applications of the solid-phase Fukuyama-Mitsunobu procedure was described in 1997 by Murray et al.,[57] who later also developed *N*-Boc-2-nitrobenzenesulfonamide linkers **39** for the preparation of primary **42** and secondary **44** amines (Scheme 10).[58]

Scheme 10. *N*-Boc-2-nitrobenzenesulfonamide linkers for the preparation of primary/secondary amines.[a]
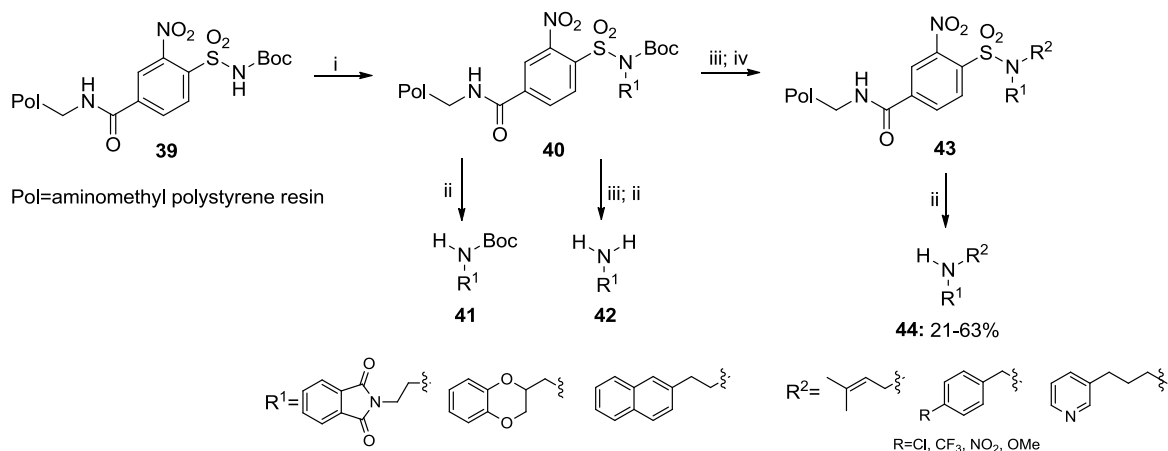
[a]Reagents: (i) R[1]OH, PPh$_3$, DEAD, anhydrous THF; (ii) 2-mercaptoethanol, DBU, MeCN; (iii) TFA, DCM; (iv) R[2]OH, PPh$_3$, DEAD, anhydrous THF.

A similar approach developed a set of novel benzyloxy, benzylamine and benzhydrylamine linkers.[28,59,60] Whereas linkers **48** and **49** have been designed for synthesis of *N*-alkyl and *N*-aryl hydroxamates (discussed in subchapter 3.3.1, Scheme 24),[39] linkers **50** and **51** have been developed as an alternative to BAL.[61] Scheme 11 depicts the individual types of linkers along with a representative example of the synthetic procedure. It is based on the acylation of the aminomethylene polystyrene/divinylbenzene (PS/DVB) resin with 4-(4-hydroxymethyl-3-methoxy-phenoxy)butyric acid (HMPB linker) **45** via HOBt activation. The subsequent Mitsunobu reaction of resin **46** with *N*-hydroxypthalimide resulted in the intermediate **47**, which was cleaved with hydrazine and treated with 2-NosCl to yield the resin-bound linker **48**.

Scheme 11. Synthesis of *N*-benzyloxy-2-nitrobenzenesulfonamide linker and examples of similar individual linkers.[a]

Structures 49, 50, 51.
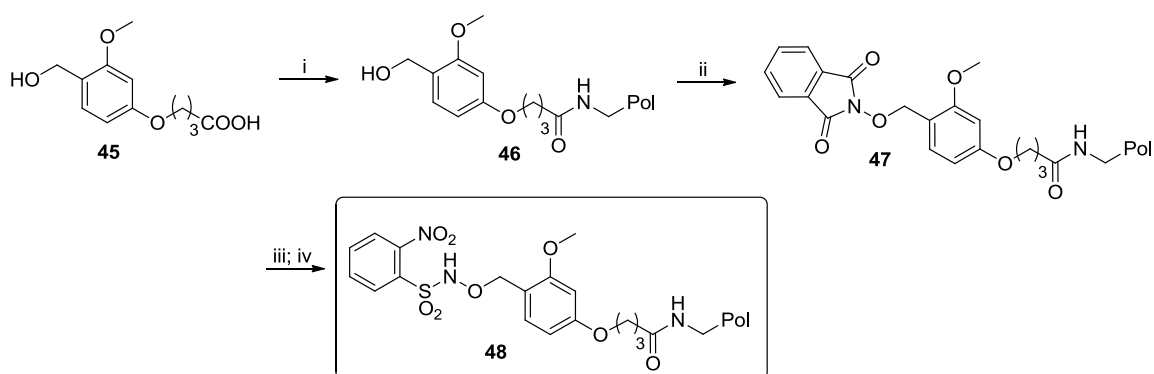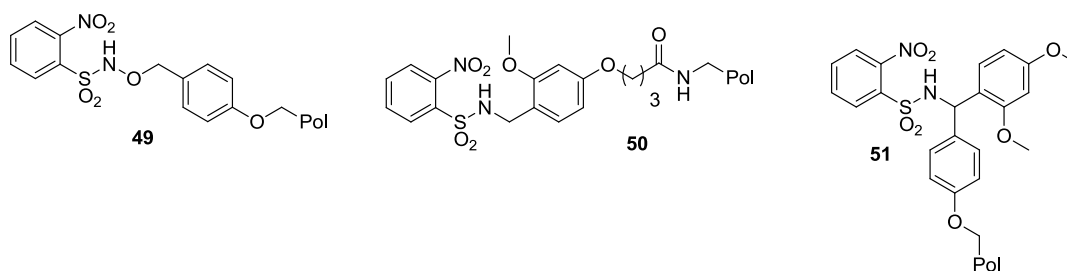
*Reagents: (i) Aminomethylene PS/DVB resin, DIC, HOBt, DMF; (ii) *N*-hydroxypthalimide, PPh₃, DIAD, anhydrous THF; (iii) 5% hydrazine hydrate, 50% THF in MeOH; (iv) NosCl, 2,6-lutidine, DCM.

Aside from mono hydroxy derivatives, alkylation with diols has also been described. An example is given in Scheme 12 that shows the solid-phase synthesis of Philanthotoxin-related compounds **56**.[62] Two alternative approaches were combined in the reaction sequence, Fukuyama-Mitsunobu alkylation with either solid-supported (step i) or solution-phase (step iii) nosylamides. To avoid potential crosslinking, the propylene glycol moiety was monoprotected by silylation.

Scheme 12. Synthesis of Philanthotoxin-433 analogues.*
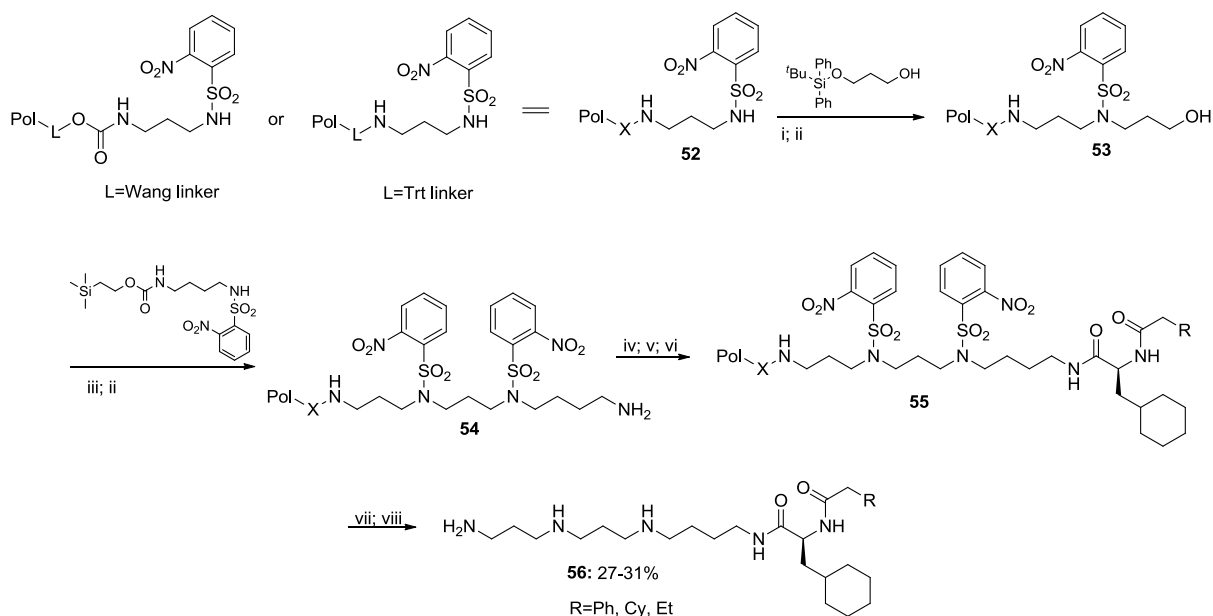
*Reagents: (i) PMe₃, ADDP, THF, DCM, N₂; (ii) TBAF, THF, 50°C; (iii) PBu₃, ADDP, THF, DCM, N₂; (iv) (S)-*N*-Fmoc-Cha-OPfp, DIEA, HODhbt, DMF, N₂; (v) 20% PIP in DMF; (vi) PhCH₂COOPfp or CyCH₂COOPfp or C₃H₇COOPfp, DIEA, HODhbt, N₂; (vii) 2-mercaptoethanol, DBU, DMF; (viii) TFA/DCM/triisopropylsilane/H₂O (47.5:47.5:2.5:2.5).

As in the Fukuyama procedure with functionalized halides, diverse functionalized hydroxy derivatives have been frequently used to synthesize various heterocycles based on Fukuyama-Mitsunobu alkylation. For example, *N*-Alloc-ethanolamine was used in the SPS synthesis of Enkephalin analogues (Scheme 13).[58] After alkylation of intermediate **57** with *N*-Alloc-ethanolamine and cleavage of the Alloc group, intermolecular cyclization promoted by HBTU/HOBt yielded the 13-membered cycle **58**. Deprotection of the 2-Nos group and introducing of R substituent afforded the final compound **60**.

Scheme 13. Synthesis of Enkephalin analogues.[a]
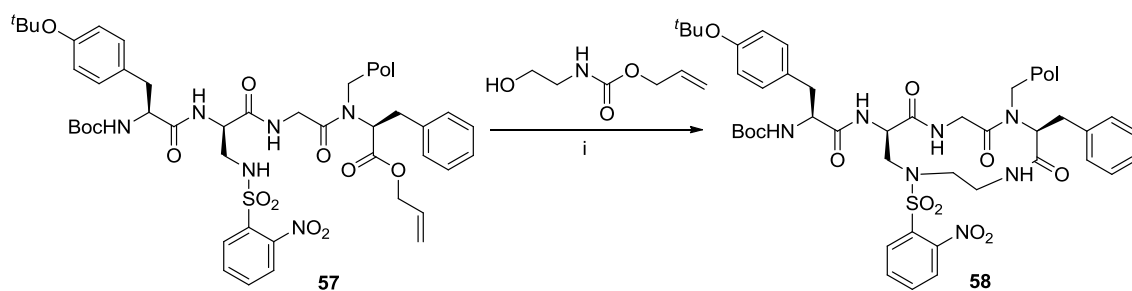
Pol=2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene resin
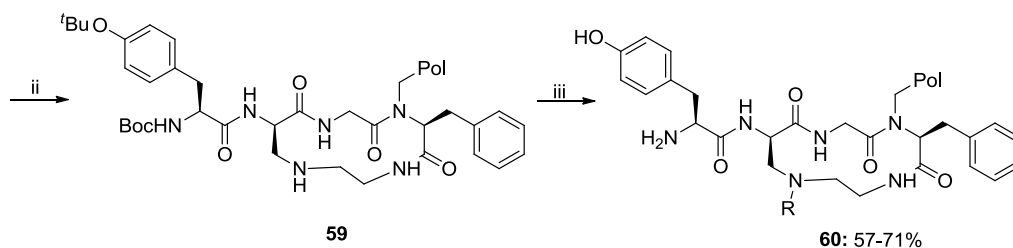
[a]Reagents: (i) (a) DIAD, PPh$_3$, THF, (b) PhSiH$_3$, Pd(PPh$_3$)$_4$, DCM, (c) HBTU, HOBt, 2,6-lutidine, DCM/DMF (1:1); (ii) DBU, 2-mercaptoethanol, DMF; (iii) reductive amination, alkylation or acylation to introduce the substituent R.

Ladlow showed that intramolecular cyclization can release the product from the resin (i.e. cyclative cleavage) when amino alcohols are involved.[63] The intermediate **61** was alkylated with *N*-Dde-phenylalaninol, and after cleavage of both protecting groups, the target monoketopiperazinones **63** were obtained (Scheme 14).

Scheme 14. Cyclative cleavage after Fukuyama-Mitsunobu alkylation.[a]

Pol=ArgoGel[TM] amine resin
L=2,4-dimethoxybenzylarylhydrazine (DMBAH) linker

Dde=
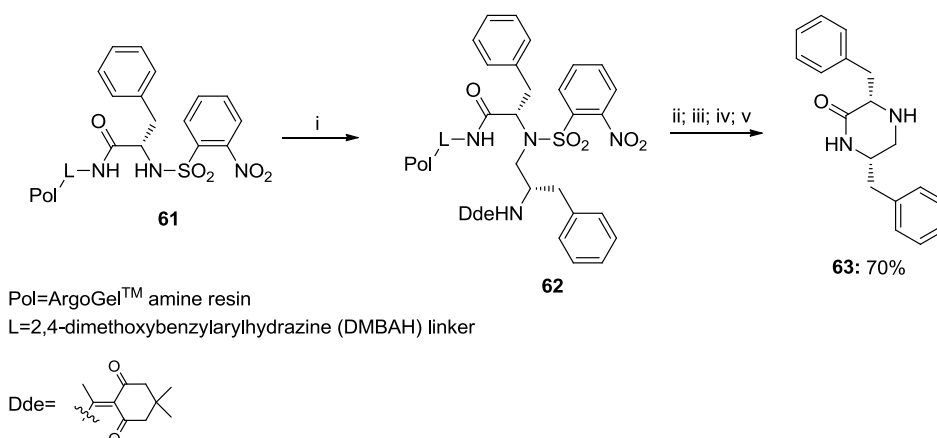
[a]Reagents: (i) Ph$_3$P, TBAD, N-Dde-phenylalaninol, DCM; (ii) PhSNa, DMF, (iii) N$_2$H$_4$· H$_2$O/ DMF (1:5); (iv) 5% TFA in DCM; (v) Cu(OAc)$_2$, Py, MeCN.

Alkylation with unsaturated alcohols yielded oxazepane derivatives **66** through *C-C* coupling.[64] The *N*-2-Nos protected hydroxylamine intermediate **64** was reacted with but-3-en-1-ol derivatives followed by intramolecular metathesis of compound **65** under Ru(II) catalysis (Scheme 15).

Scheme 15. Intramolecular metathesis leading to 1,2-oxazepanes.[a]

Pol-Trt = polystyrene trityl

R^1=Me, Bn, 4-COOEt-Bn, ^{i}Bu, N$_3$(CH$_2$)$_2$CH$_2$

R^2=
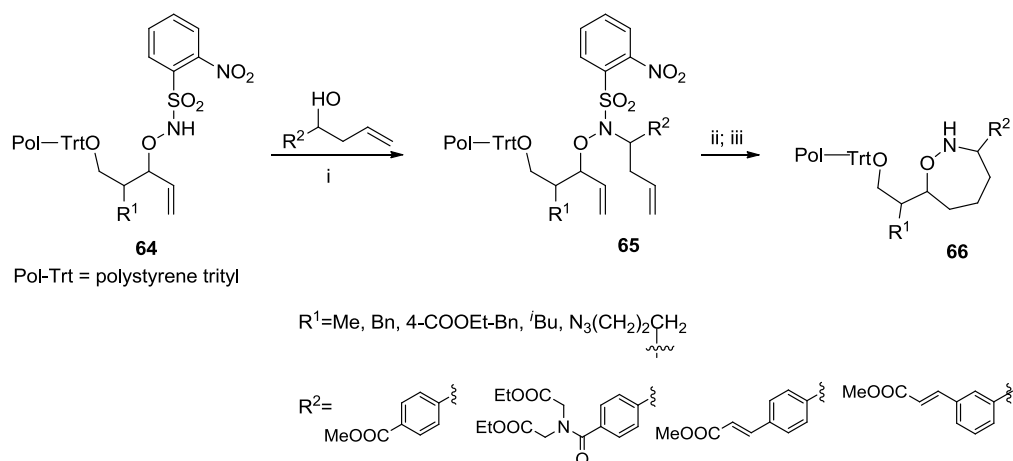
[a]Reagents: (i) PPh$_3$, ^{i}PrO$_2$C-N=N-CO$_2$^{i}Pr or ^{t}BuO$_2$C-N=N-CO$_2$^{t}Bu, THF; (ii) Cl$_2$Ru(PCy$_3$)$_2$=CHPh, DCM; (iii) RSH, DBU, DCM or NMP.

Recently, hydroxyaldehydes with the aldehyde group protected as the acetal **67** have been extensively employed in the alkylation of polymer-supported nitrobenzenesulfonamides. After cleavage from the polymer support with TFA, the unmasked aldehyde provided many

different heterocyclic scaffolds via formation of the corresponding iminium salts. This research has been primarily targeted at the incorporation of various heterocyclic scaffolds in a peptide backbone.[65-68] Representative examples are depicted in Scheme 16. In many cases, the Nos building block remained in the final structures, and these results are therefore also mentioned in the next chapter.

Scheme 16. Examples of various heterocyclic scaffolds synthesized via the acetal intermediate **67**.

L (**69**)=Rink amide linker
L (**70, 71**)=Wang linker, Rink amide linker or BAL
L (**72, 73**) =BAL, Rink amide linker
L (**68**)=Rink amide linker
Selected examples of X (**69**)=
Selected examples of X-H (**70-73**)=
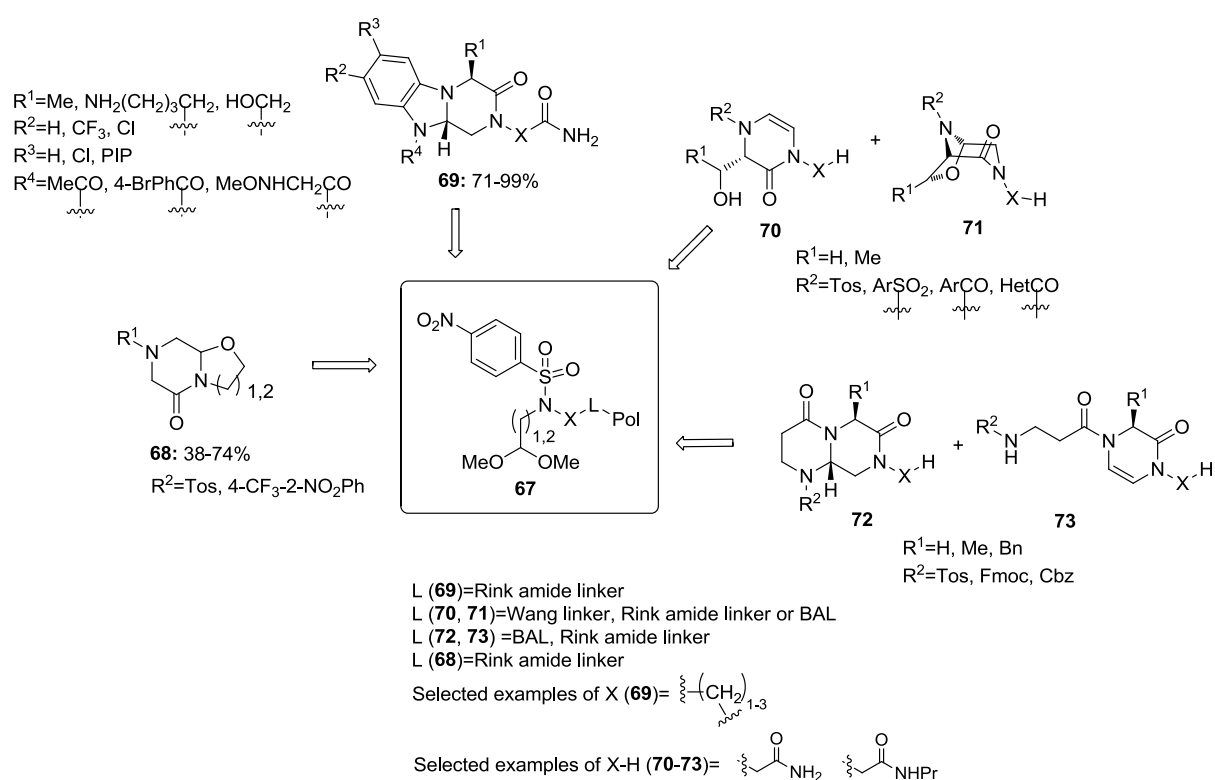
To access a new heterocyclic moiety through Nos activation, the functional group does not necessarily need to be introduced through external alkylation of a sulfonamide, as in all of the previous cases. The following example demonstrates the activation of the amino group of intermediate **74** followed by the attack of the neighbouring alcohol leading to the target tricyclic scaffold **76** (Scheme 17).[69]

Scheme 17. Intramolecular cyclization under Fukuyama-Mitsunobu conditions.[a]
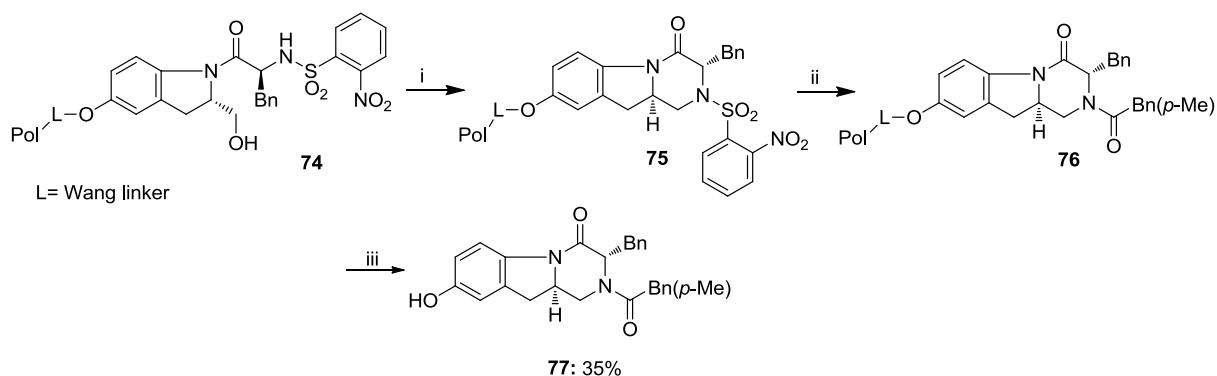
[a]Reagents: (i) DEAD, Ph$_3$P, THF; (ii) (a) PhSH, DBU, DMF, (b) HOBt, DIC, Bn-(p-Me)-COOH, DMF; (iii) 10% TFA in DCM.

Polymer-supported alcohols can be used similarly to immobilize alkyl halides (see Scheme 9) as the alkylation species. An example of this strategy has been already given in Scheme 12. Alternatively, Raveglia and co-workers[70] used reversed Mitsunobu alkylation (Scheme 18) to prepare amino intermediates **80** that were later applied in the split-mix synthesis of a complex library with considerable diversity.

Scheme 18. The reversed Mitsunobu alkylation of nitrobenzenesulfonamides.[a]
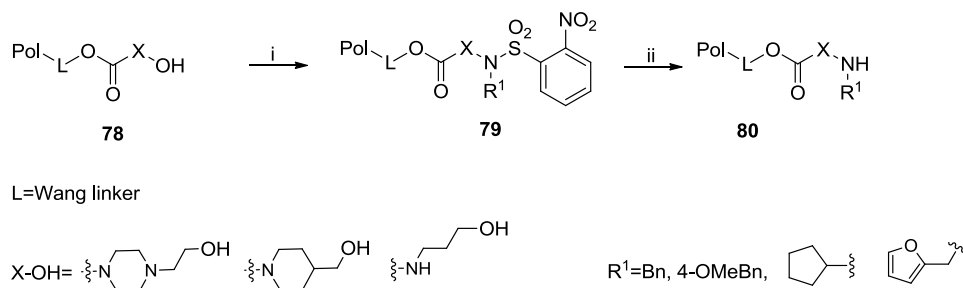
[a]Reagents: (i) 2-Nos-NHR^1, PPh$_3$, DTAD, DCM/THF (1:1); (ii) 2-mercaptoethanol, DBU, DMF.

3.2.3 Alkylation with unsaturated ketones

Michael's addition of activated olefins can incorporate *N*-substituent into nitrobenzenesulfonamides,[28] except in nucleophilic substitution with alcohols or alkyl halides. This alternative is not common, but the alkylation of sulfonamide linker **81** is given in Scheme 19 as an example. In addition, the intermediate **82** can be used for the synthesis of *N*-alkyl hydroxamic acids.[59]

Scheme 19. Synthesis of *N*-alkyl amines with unsaturated ketones.[a]

81
L=Wang linker, PAL linker

82
R=Me, Et, OMe

83
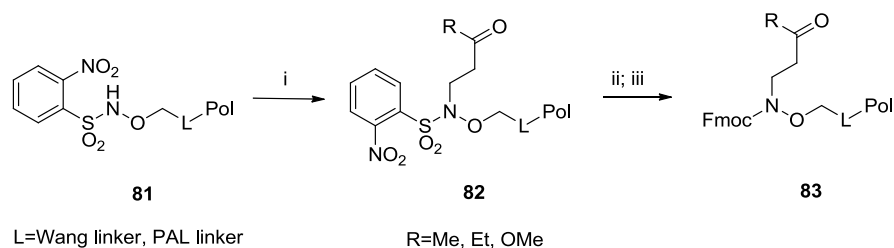
[a]Reagents: (i) α,β-unsaturated ketones, BEMP, anhydrous THF; (ii) 2-mercaptoethanol, DBU, DMF; (iii) Fmoc-OSu, DCM.

3.3 Scenario B: Combined function of the Nos group

In the previous chapter, we summarized different strategies in which the Nos group was applied only as a standard activating/protecting group. Accordingly, the Nos group was cleaved after alkylation. Numerous examples also exist that omit this cleavage. Furthermore, certain reactions are triggered by a base that do not cleave the Nos group, but result in *C/N* intramolecular arylations. In both cases, the Nos group was used as the activating/protecting group for alkylation, but the benzenesulfonamide moiety or only its aromatic portion (in the case of *C/N* arylations) was preserved in the final molecule.

3.3.1 Preservation of the Nos group to give linear nitrobenzenesulfonamides

The term "linear nitrobenzenesulfonamides" refers to compounds in which the sulfonyl group is not included in the cyclic moiety. There are three general reasons why the Nos group is preserved in the final product structure after Fukuyama or Fukuyama-Mitsunobu alkylation: (i) the nitrobenzenesulfonamide scaffold serves as a chromophore to allow for a simple HPLC-UV detection of UV-VIS inactive intermediates, (ii) it increases the structural diversity of the synthesized molecules or (iii) it provides the reactive internal nucleophile.

One of the frequent methods leading to linear benzenesulfonamides is iminium chemistry, mentioned in subchapter 3.2.2. Scheme 20 outlines the preparation of other heterocycles via the masked aldehyde **84** as the key intermediate.[71,72] In each case, the nitrobenzenesulfonamide scaffold remained in the final structure.

Scheme 20. Examples of linear sulfonamides synthesized via a masked aldehyde intermediate.
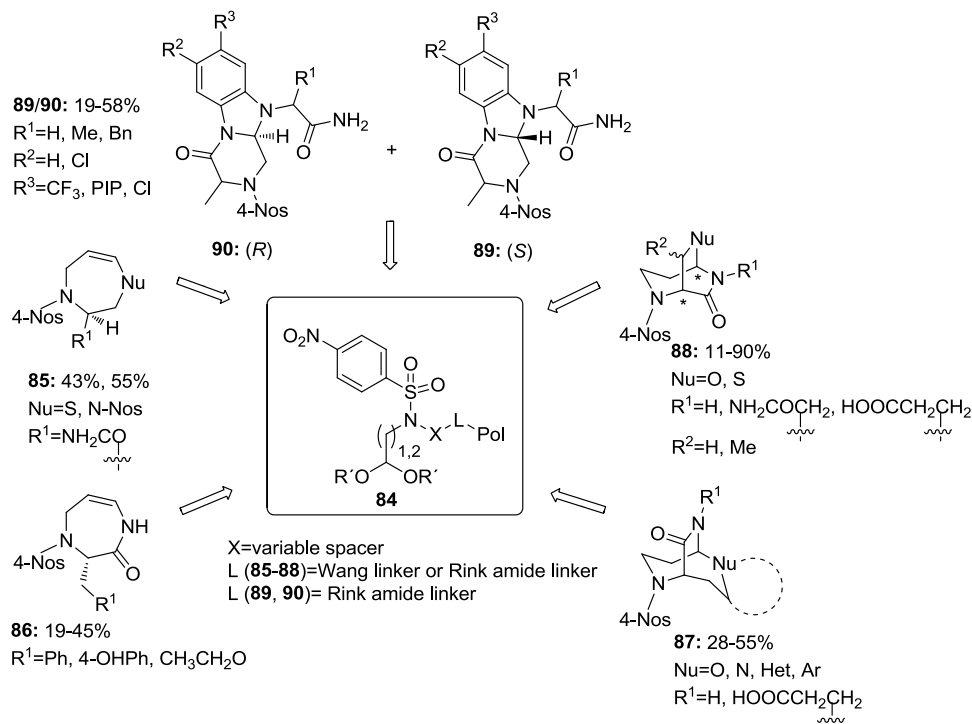
Ketone groups in acyclic precursors can also be used to produce *N*-alkyliminium intermediates, as in the synthesis of trisubstituted tetrahydropyrazines and piperazines (Scheme 21).[73] First, the *N*-Nos protected terminal amino group of intermediate **91** was alkylated with a bromoketone. Subsequent treatment of intermediate **92** with 50% TFA yielded the target tetrahydropyrazines **93**. Advantageously, addition of the reduction agent TES into the cleavage cocktail formed the corresponding piperazine derivatives **94**.

Scheme 21. Synthesis of piperazines and tetrahydropyrazines via a ketone-acyclic precursor.[a]
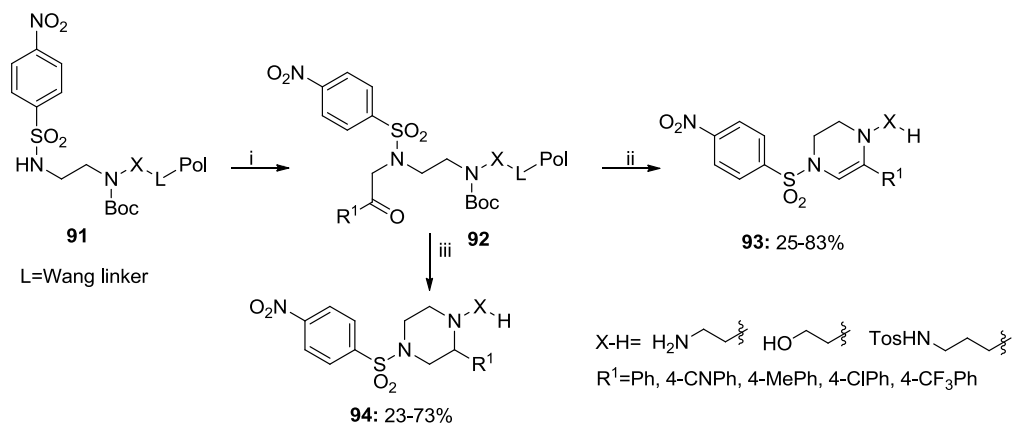
[a]Reagents: (i) bromoketone, DIEA, DMF; (ii) 50% TFA in DCM; (iii) 10% TES, 50% TFA, 40% DCM.

Intramolecular azomethine ylide cycloaddition has also been used to produce nitrogenous Nos-heterocycles in the stereoselective synthesis of polycyclic compounds.[74] Immobilized α-N-Boc-β-N-Nos-diaminopropionic acid served as a starting material for the construction of α-N-imine and β-N-Nos-olefin residues **95** (Scheme 22). Subsequent application of the suitable catalytic system triggered the ylide formation to yield the bicyclic pyrrolidines **96**. Nosylated bicycles were either cleaved from the polymer support (compound **97**) or further modified to afford the tricyclic triazacyclopenta[*c*]pentalene **99**.

Scheme 22. Synthesis of polycyclic compounds via the azomethine ylide transition state.[a]
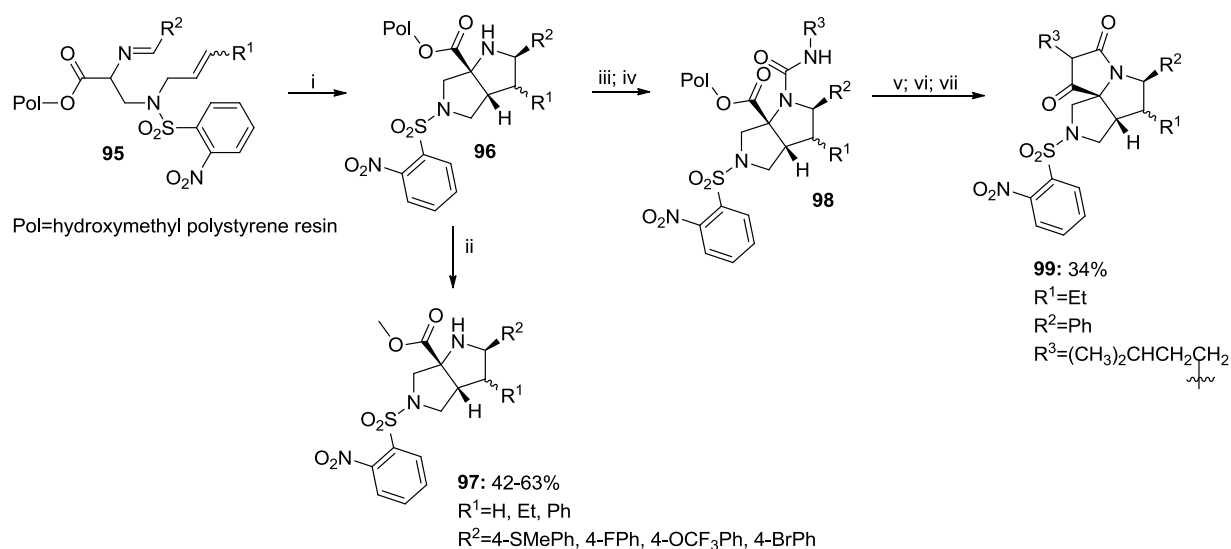
[a]Reagents: (i) Zn(OAc)$_2$, DBU, anhydrous MeCN; (ii) MeOH, KOH; (iii) phosgene, DIEA, DCM; (iv) R^{3}NH$_2$, DCM; (v) PhSNa, DMF; (vi) re-nosylation: 2-NosCl, TEA, DCM (reductive alkylation or acylation is also possible); (vii) ^{t}BuOK, THF.

Olsen et al.[75] described the first example of aminolysis of *N*-Nos-activated/protected aziridine-2-carboxylic acids on resin (Scheme 23). Starting aziridines **100** were exposed to different amines with terminal hydroxy or amino groups, and the final ring closure of intermediate **101** was accomplished under Mitsunobu conditions or with CSIm$_2$ to yield enantiomerically pure heterocycles **102** and **103**.

Scheme 23. Aminolysis of resin-bound aziridines to synthesize enantiopure heterocycles.[a]
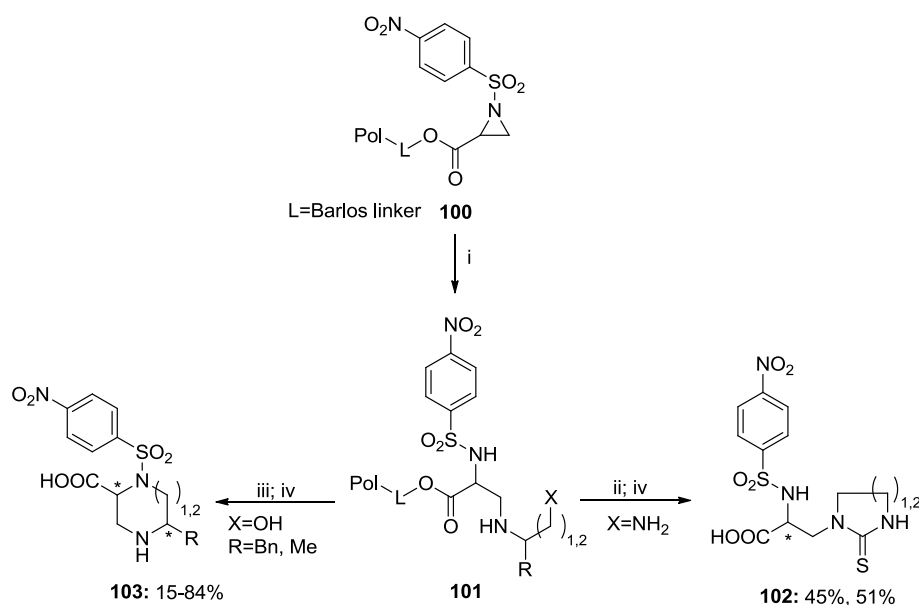
[a]Reagents: (i) diamines or aminoalcohols, THF; (ii) CSIm$_2$, DCM; (iii) DEAD, PEt$_3$ or ADDP, PMe$_3$; (iv) TFA, DCM.

In 2006, Krchňák and Stanger[39] developed an efficient procedure for the synthesis of both *N*-H and *N*-R hydroxamates from *O*-linked hydroxylamines **104** (Scheme 24), which was later used to prepare a small library of *β*-sulfonamide-hydroxamates **106**. These were tested for inhibition of breast cancer cell proliferation,[76] compound **107** was the best inhibitor.

Scheme 24. Synthesis of *N*-alkyl hydroxamates.[a]
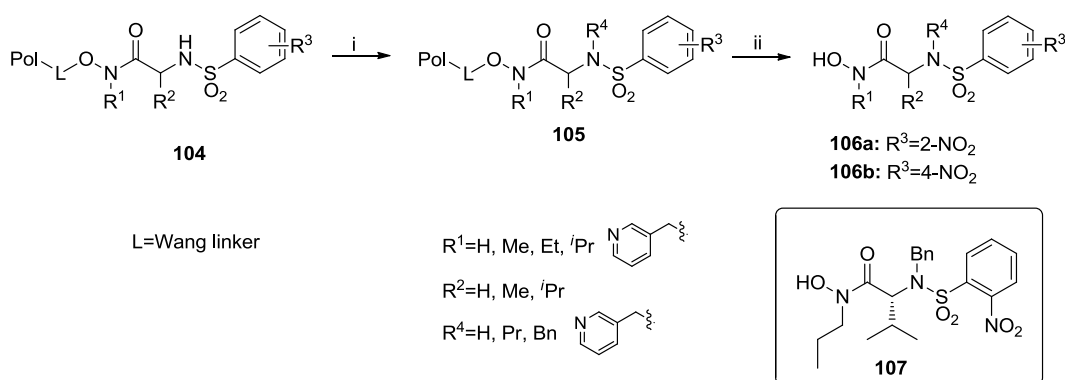
[a]Reagents: (i) benzyl alcohols, PPh$_3$, DIAD, anhydrous THF; (ii) TFA, DCM.

3.3.2 Incorporation of 2-Nos group resulting in cyclic sulfonamides

This alternative has been typically applied with 2-nitrobenzensulfonamides. When the nitro group of suitable intermediates was reduced, the intramolecular cyclization reaction yielded the cyclic benzenesulfonamides. A typical example is the preparation of tetrahydrobenzopyrazino-thiadiazinone dioxides **111** (Scheme 25).[77] 4-NosCl was primarily used to synthesize the masked aldehyde precursor **67**, whereas substituted 2-NosCls were subsequently applied as synthons to produce intermediates **109**. After reduction of the nitro group, the target compounds **111** were obtained via the corresponding *N*-sulfonyl iminium intermediates.

Scheme 25. Synthesis of cyclic sulfonamides by *N*-sulfonyl iminium chemistry.[a]
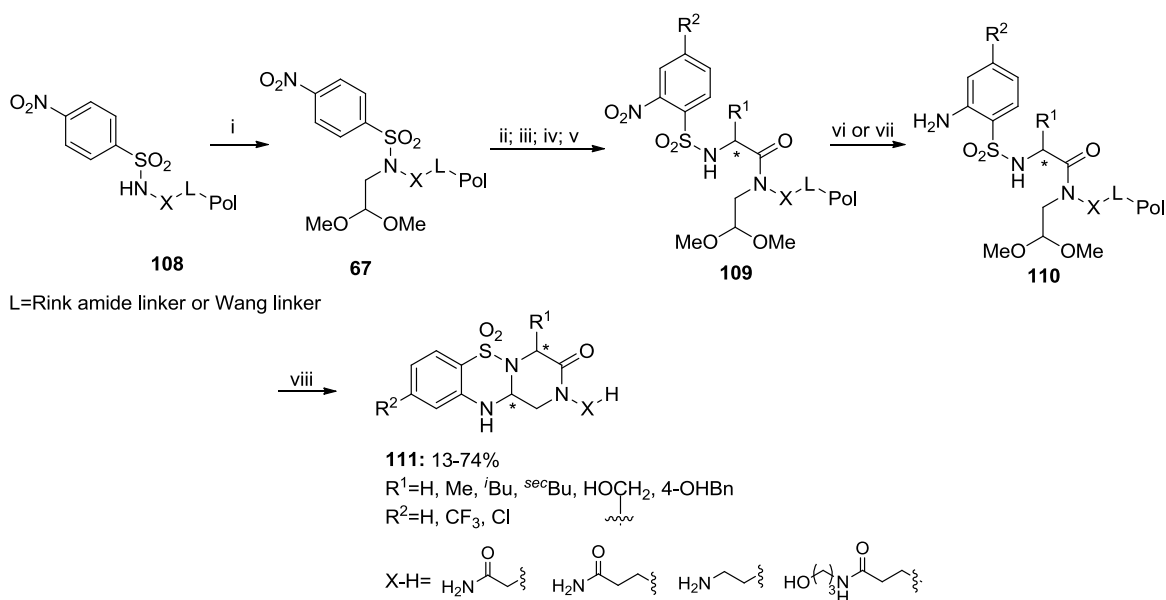
[a]Reagents: (i) glycolaldehyde dimethyl acetal, PPh$_3$, DIAD, anhydrous THF, 0-50 ℃; (ii) 2-mercaptoethanol, DBU, DMF; (iii) Fmoc-α-AA-OH, HOBt, DIC, DCM/DMF (1:1); (iv) 50% PIP in DMF; (v) 2-NosCls, 2,6-lutidine, DCM; (vi) SnCl$_2$ · 2H$_2$O, DIEA, DMF (saturated with N$_2$), 50 ℃; (vii) Na$_2$S$_2$O$_4$, TBAHS, K$_2$CO$_3$, DCM/H$_2$O (1:1); (viii) 50% TFA in DCM.

In the same year, synthesis of dihydrobenzothiadiazepine 1,1-dioxides **117** was published (Scheme 26).[5] First, the immobilized sulfonamide **112** was alkylated with various bromoketones. After reduction of the nitro group, cleavage from the polymer support yielded the mixture of compounds **115** and **116** in variable ratios. Further NMR investigation of the mixtures demonstrated that linear sulfonamides **115** were spontaneously cyclized in DMSO-

d_6. Cyclization time was remarkably accelerated for compounds bearing a methoxy group in position R^2.

Scheme 26. Synthesis of dihydrobenzothiadiazepine 1,1-dioxides.[a]
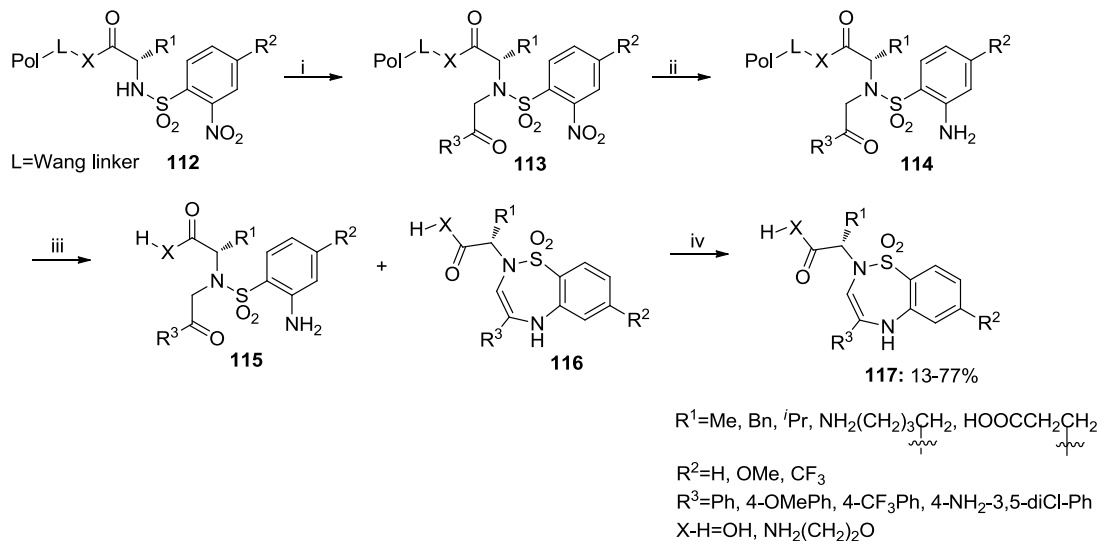
[a]Reagents: (i) bromoketone, DIEA, DMF; (ii) $Na_2S_2O_4$, K_2CO_3, TBAHS, DCM/H_2O (1:1); (iii) 50% TFA in DCM; (iv) DMSO-d_6.

Subsequent experiments (LC/MS, 1D-NMR) revealed that dihydrobenzothiadiazepine 1,1-dioxides **117** (Scheme 26) were not stable in DMSO-d_6 at room temperature, and 2D-NMR confirmed an unprecedented ring contraction that yielded 4H-benzo[b][1,4]thiazine 1,1-dioxides **119** (Scheme 27).[6] Target compounds **119** do not belong to the cyclic benzenesulfonamides, but the rearrangement is included here to show the synthetic possibilities of the nitrobenzenesulfonamide chemistry.

Scheme 27. Synthesis of thiazine dioxides via ring contraction of thiadiazepine dioxides.[a]
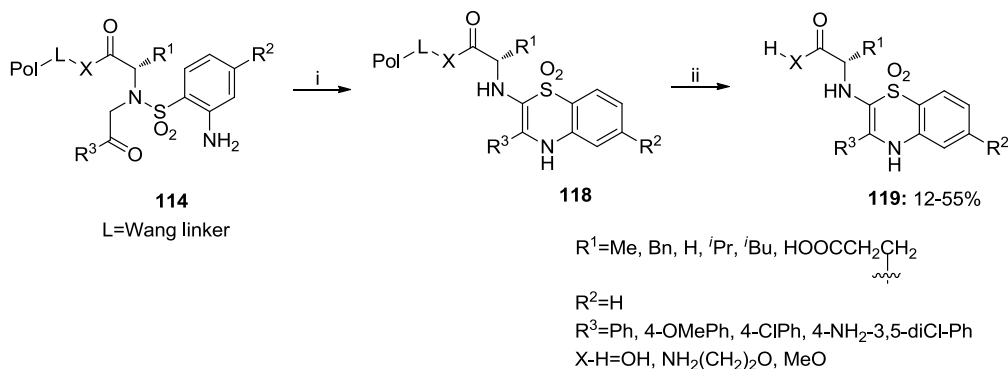
[a]Reagents: (i) 5% AcOH in DMSO, 80 °C; (ii) 50% TFA in DCM.

3.3.3 Application of the Nos group for Fukuyama alkylation followed by the *C/N*-arylation

Seven years ago, a striking difference in the reactivity of 2-nitrobenzenesulfonamides and 4-nitrobenzenesulfonamides was observed. The treatment of 4-Nos derivatives **120** with mercaptoethanol and DBU afforded the standard deprotected product **121**, whereas cleavage of 2-Nos derivatives **122** caused the *C*-arylation followed by release of sulfur dioxide (**124**) and spontaneous cyclization to give indazole oxide derivatives **125** (Scheme 28).[33] Rearrangement was enabled by the acidic methylene group hyperconjugated by the carbonyl functionality originating from the alkylating agents such as bromoketones, bromoacetates, benzyl alcohols or pyridylmethanols. The electron withdrawing groups of the aryl building blocks in the position R^2 facilitated *C*-arylation to give benzhydrylamine derivatives **126**.[78]

Scheme 28. Different reactivity of 2-Nos and 4-Nos derivatives towards DBU.[a]
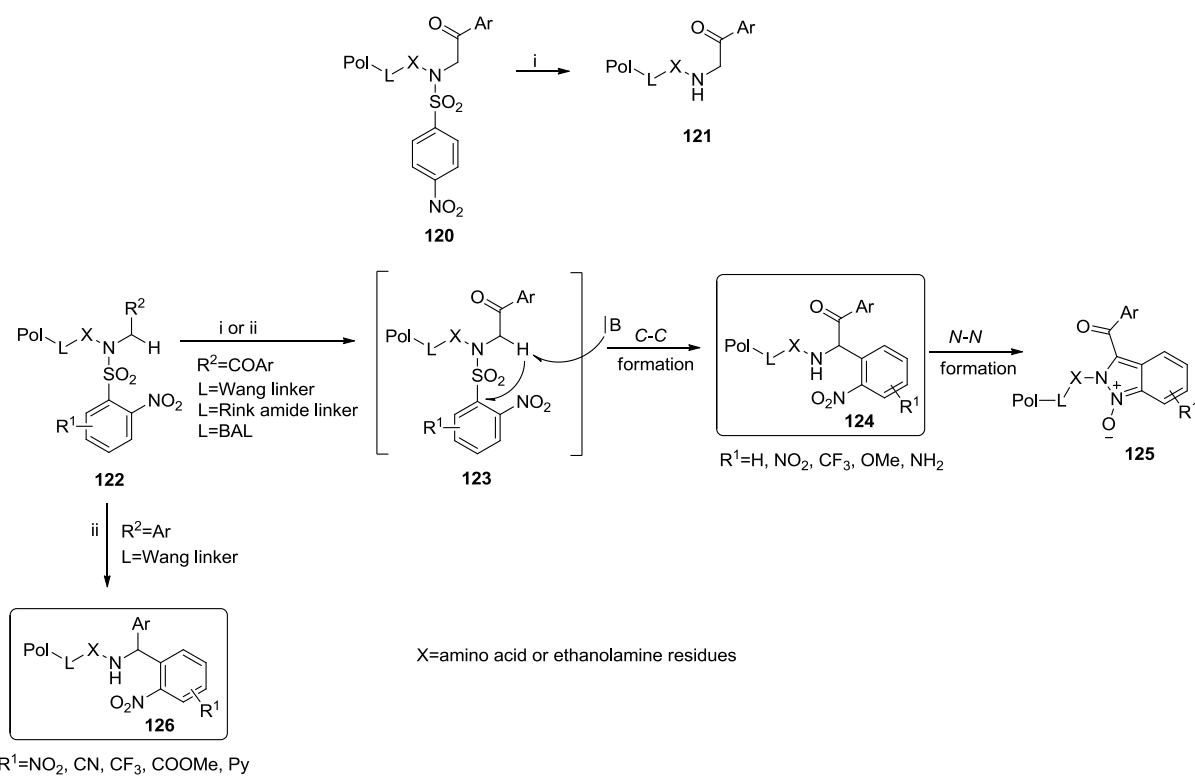
^{a}Reagents: (i) 2-mercaptoethanol, DBU, DMF; (ii) DBU, DMF.

Application of this tandem *C-C* and *N-N* rearrangement has been widely used to give diverse scaffolds. Depending on the reaction conditions, type of base, substitution pattern and structure of the individual linkers, *C*-arylated intermediates **127** were converted into variable

indazole oxides and their iminium salts suitable for other chemical transformations (Scheme 29).[33,34,78-81]

Scheme 29. Examples of diverse indazole-based heterocycles generated from *C*-arylated precursors.

133a: Y=N-O; 23-99%
133b: Y=N; 31-97%
R^1=H, CF_3, NO_2

134: 19-83%
R^1=H

135: 23-71%
R^1=H, CF_3, NO_2

132a: Y=N-O; 47-64%
132b: Y=N; 63%
R^1=H

128a: Y=N-O; 17-99%
128b: Y=N; 23%, 48%
R^1=H, OMe, CF_3, NO_2, NH_2

131a: Y=N-O
131b: Y=N; 11-73%
R^1=H, CF_3, NO_2

130: 16-96%
R^1=H, OMe, CF_3, NO_2

129: 17-64%
R^1=H, OMe, CF_3

127
L=Wang or Rink amide linker or BAL
X=variable spacer
R^2=ArCO or Ar
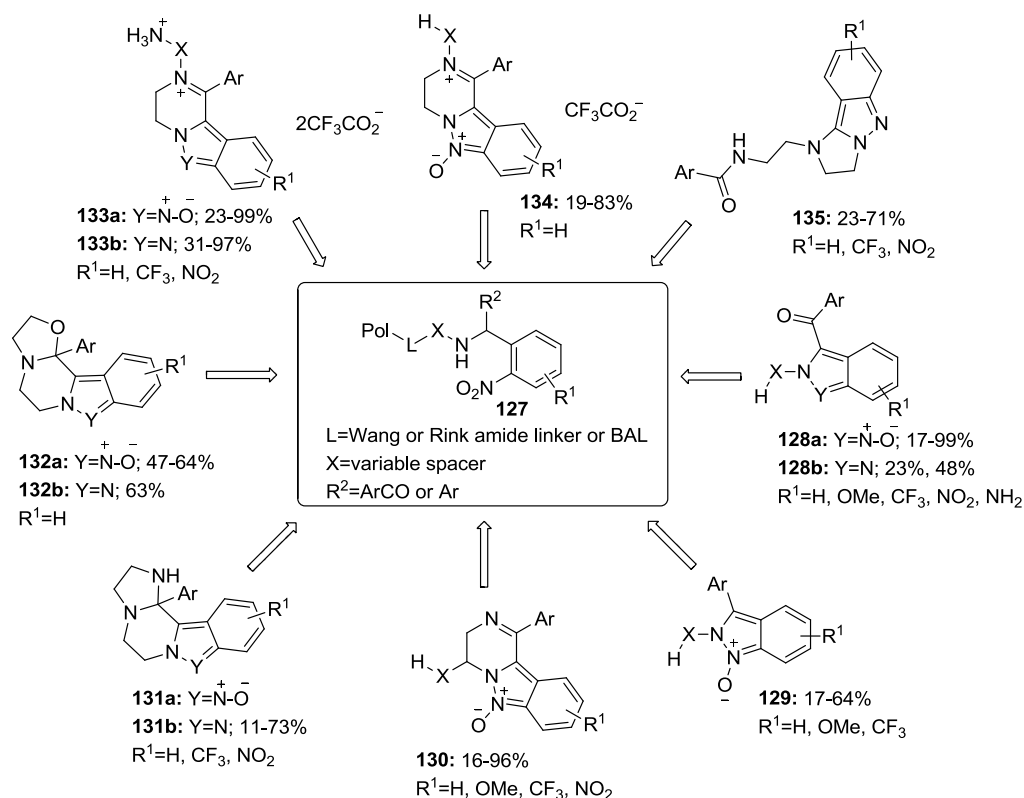
To access the parent 2*H*-indazoles, several methods for the reduction of indazole oxides have been evaluated, with mesyl chloride and TEA being the most efficient reagents.[33] This procedure was used for the traceless synthesis of 3,4-dihydropyrazino[1,2-*b*]indazoles (Scheme 30). The immobilized and deoxygenated product **137** was treated with 50% TFA that caused release of the desired pyrazino indazoles **138**. In contrast, the cyclization was performed by TEA in MeOH to yield the final derivatives **140** when a carboxylate substituent was in the R^3 position.

Scheme 30. Traceless synthesis of 3,4-dihydropyrazino[1,2-*b*]indazoles.[a]

L=Wang linker
R[1]=H, Me
R[2]=H, NO$_2$, OMe, CF$_3$

R[3]=OEt

136

137

138: 7-99%
R[4]=Me, Cl, OMe

139

140: 33%
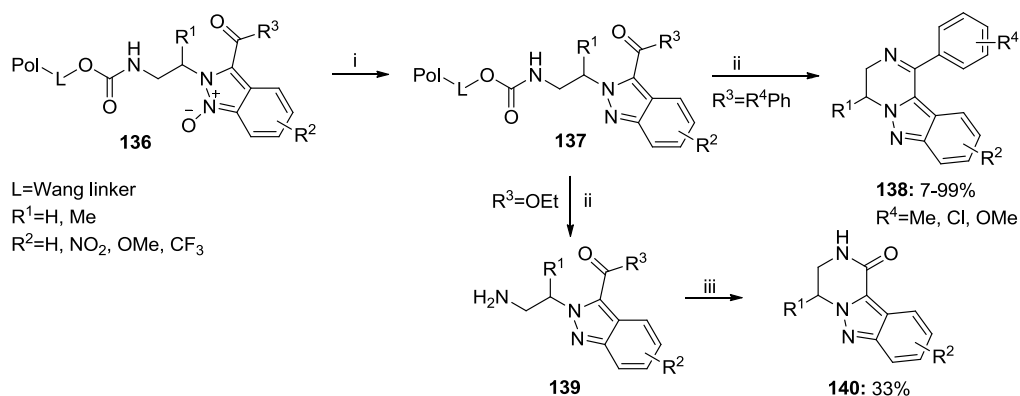
[a]Reagents: (i) methanesulfonyl chloride, TEA, DCM; (ii) 50% TFA in DCM; (iii) TEA, MeOH.

Attempts to expand the scope of indazole-oxide transformations led to discovery of a novel ring expansion (Scheme 31).[82] A proposed mechanism for this reaction consisted of a base-mediated compensation for electron deficit on the nitrogen of the *N*-oxide group (**142**). After scission of the *N-N*-bound intermediate **143**, subsequent rearrangement provided the quinazoline derivatives **144**. 4-Aryl-quinazolines **146** were obtained in the same manner.[78]

Scheme 31. Rearrangement of indazole oxide leading to quinazolines.[a]

R[2]=COAr
L=Wang linker
L=Rink amide linker
L=BAL

141

i; ii | R[2]=Ar
L=Wang linker

142

143

144

146: 51%
R[1]=H, CF$_3$, OMe

X-H=

145: 10-48%
R[1]=H, CF$_3$, NO$_2$

X-H=
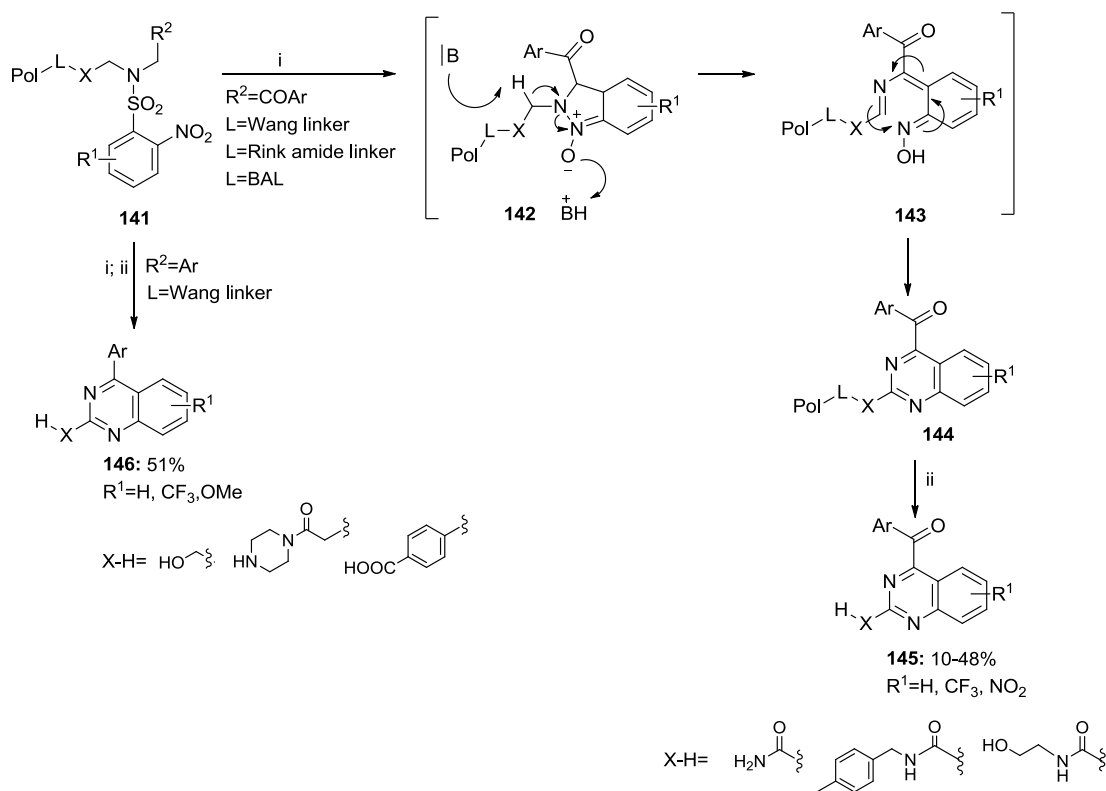
[a]Reagents: (i) DBU, DMF; (ii) 50% TFA in DCM.

35

In addition to different indazole or quinazoline derivatives, *C*-aryl intermediates were applied in the preparation of trisubstituted 1*H*-indoles.[34] Encore of a base to the acyclic intermediate **123** induced the *C*-arylation yielding the compound **147** (Scheme 32). After nitro-group reduction, an unprompted cyclization afforded the 1*H*-indoles **148**. Final compounds **149** were obtained after cleavage from the polymer support. Nevertheless, in the case of linkers **123e-g**, it was necessary to protect the amino group of *C*-arylated precursor **147** to avoid undesirable indazole oxide formation.

Scheme 32. Synthesis of 2-aryl-3-alkylamino-1*H*-indoles from *C*-arylated precursors.*[a]*
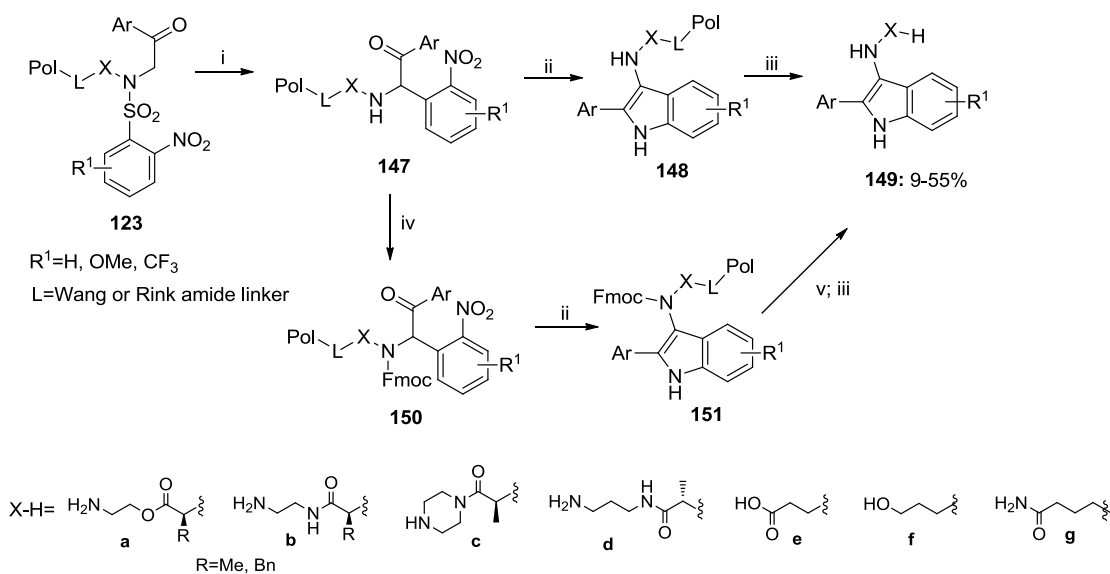
*[a]*Reagents: (i) DABCO or TEA, DMF; (ii) $Na_2S_2O_4$, K_2CO_3, TBAHS, H_2O/DCM (1:1); (iii) TFA/DCM (1:1) or TFA/TES/DCM (5:1:4) for Fmoc protected compounds; (iv) Fmoc-Cl, DCM; (v) PIP, DMF.

The effects of different linkers, amino acids and benzyl alcohols on *C*-aryl formation evaluated the scope and limitations of these reactions.[35] Surprisingly, DBU-mediated arylation of compound **152** containing alanine anchored to an ester-based linker and 2-NO_2Ph group in R^2 position afforded a mixture of benzylic sp^3-arylated (**153a**) and α-*C*-arylated (**154a**) compounds (Scheme 33). However, introduction of more bulky amino acids resulted in direct sp^3 arylation and creation of expected products **154a** mostly in excellent purity. The assessed piperazine linker resulted in either benzylic sp^3-arylated (**153b**) or α-*C*-arylated (**154b**) compounds according to the building blocks and reaction conditions used. Secondary amide-based dual substrates were also evaluated in this context. Unexpectedly, the DBU-mediated reaction did not afford α-*C*-arylation, but rather the *N*-arylated compound **155** (for

proposed reaction mechanism, see Scheme 34). The benzylic sp³ product **153c** could also be prepared depending on the substitution of the benzyl ring.

Scheme 33. Examples of base-mediated α-*C*-arylation and *N*-arylation.

153a: 18-51%, X-H= H_2N
153b: 26-58%, X-H= HN

154a: 7-86%, X-H= H_2N
154b: 15-76%, X-H= HN

153c: 18-67%, X-H= HO
155: 17-54%, X-H= HO

152

L=Wang linker
R^1=H, Me, ^{i}Pr, ^{sec}Bu, Bn
R^2=H, 4-MePh, 4-NO_2Ph, 2-NO_2Ph, 4-CF_3Ph,
     4-COOMePh, 4-FPh, 2,6-diClPh, Py
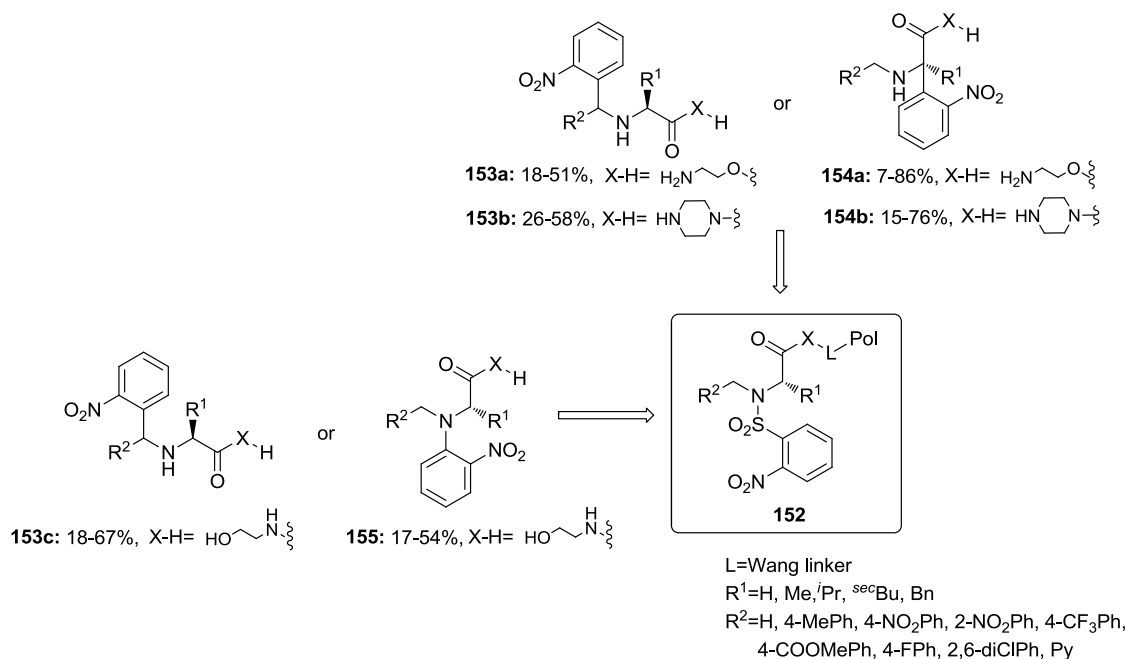
Scheme 34. Proposed mechanism of *N*-arylation.

spiro-Meisenheimer intermediate
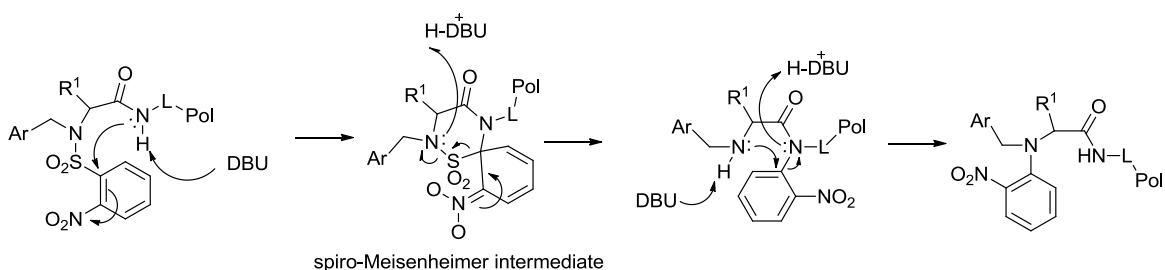
N-Arylation has been observed previously in both the solution[83] and solid phase. Bienz et al.[84] developed methodology leading to cyclic polyamines. One of the proposed synthetic routes utilized 2,4-dinitrobenzenesulfonyl chloride as an alternative to 2-NosCl in the subsequent Mitsunobu reaction (Scheme 35). However, after cleavage of **157** from the polymer support followed by methanolysis, *N*-arylated compounds **159** and **160** were obtained instead of the desired product **158**. Attempts to release the 2,4-dinitrobenzenesulfonyl group prior to cleavage from the resin led to the major compound **159**.

Scheme 35. Smile-type rearrangements in the synthesis of cyclic amines.[a]
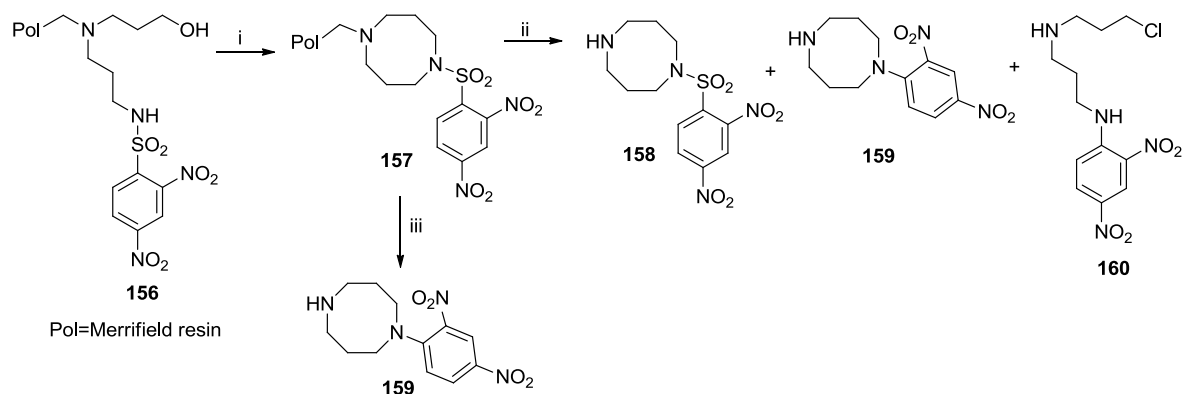
[a]Reagents: (i) PPh₃, DEAD, anhydrous THF; (ii) (a) ACE-Cl, DCE, (b) MeOH, reflux; (iii) mercaptoacetic acid, DIEA or PhSH, K₂CO₃.

3.4 Scenario C: Nos group used exclusively as a synthon

The applications of polymer-supported nitrobenzenesulfonamides in Fukuyama or Fukuyama-Mitsunobu alkylation were summarized in the previous chapters. These applications are the most common, but 2-NosCl and 4-NosCl have also been applied as common building blocks without alkylation of the corresponding sulfonamides. In such cases, the benzenesulfonamide moiety is either integrated into the target scaffold to access reactive intermediates for further derivatization, or due to the skeletal similarity of target compounds to biologically active molecules.

In 1998, Jung and Richter[85] developed the first version of the Baylis-Hillman reaction in the solid-phase (Scheme 36). The one-pot procedure was based on the reaction of immobilized olefin **161** with aldehyde **162** and 4-nitrobenzenesulfonamide **163** catalyzed by DABCO. The final cleavage of resulting compounds **164** from polymer support was accomplished by TFA in DCM.

Scheme 36. One-pot Baylis-Hillman reaction on a solid support.[a]

L=Barlos linker   R¹=4-CF₃Ph
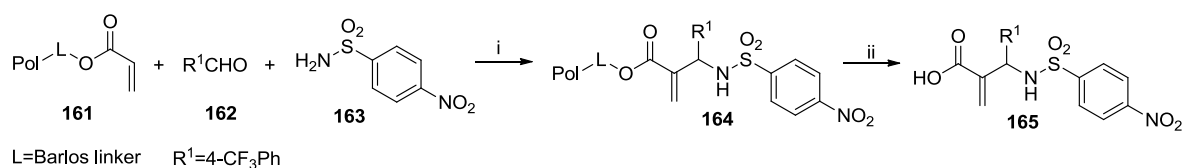
[a]Reagents: (i) DABCO, dioxane, 70 ℃; (ii) TFA/DCM (5:95).

Four years later, another one-pot polymer-supported synthesis of α-sulfonylamino amide derivatives was published.[86] This study targeted the scope and limitation of the Ugi condensation reaction (Scheme 37). The optimized conditions were compatible with carboxy polystyrene resin **166**, 2-/4-nitrobenzenesulfonamides and *tert*-butyl isocyanide, which provided the desired products **168** in high overall yields.

Scheme 37. Ugi-type four-component condensation.[a]

Pol-COOH=carboxy polystyrene resin

168a: R^1=2-NO$_2$; 93%
168b: R^1=4-NO$_2$; 87%
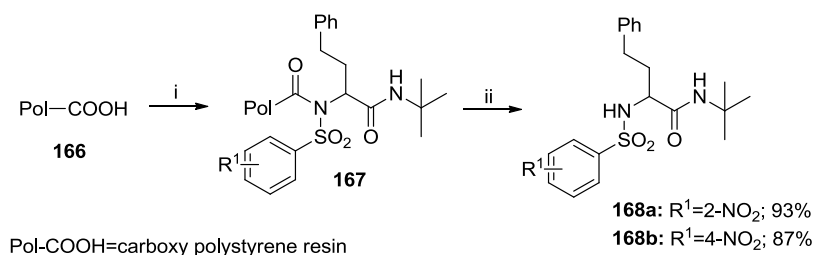
[a]Reagents: (i) hydrocinnamaldehyde, arylsulfonamide, *tert*-butyl isocyanide, THF, MeOH, 60 °C; (ii) 40% aq. MeNH$_2$/THF (v/v, 1:1).

Gong and co-workers[38] synthesized *N*-hydroxypiperazine derivatives from phenethylpiperazine linkers **169** derivatized by 4-NosCl. The corresponding 4-nitrophenylsulfonylpiperazine **170** was converted to the *N*-oxide intermediate **171** through oxidation with *m*-chloroperoxybenzoic acid (Scheme 38). The final transformation leading to release of the product **172** from the polymer support was accomplished through a Cope *β*-elimination reaction.

Scheme 38. Synthesis of hydroxypiperazine derivatives via oxidation-Cope elimination.[a]

Pol=Merrifield resin

172: 49%   **173**
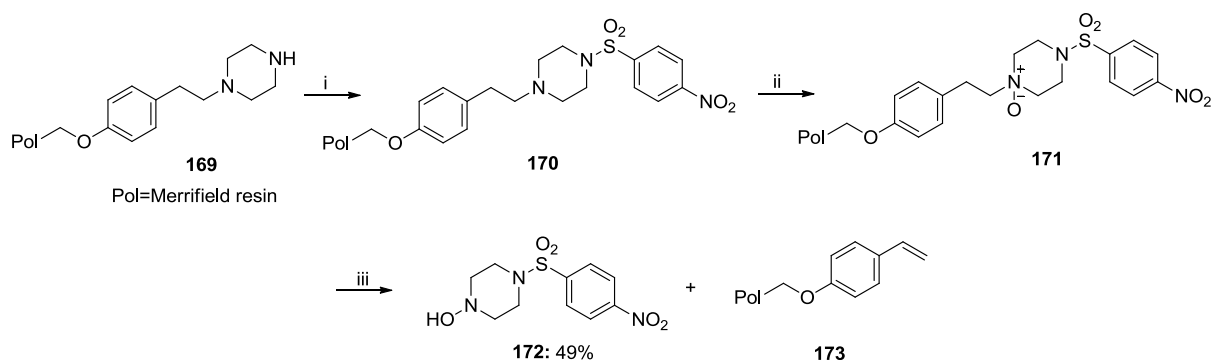
[a]Reagents: (i) 4-NosCl, TEA, DMF; (ii) *m*-CPBA, DCM; (iii) toluene, 90 °C.

Maclean et al.[87] used the polymer-supported 4-nitrobenzenesulfonamide derivative **174** to construct a safety-catch linker. Previously, the original *S*-immobilized-*N*-

acylsulfonamide (Kenner)[88] linker had been widely used in peptide synthesis, and several of its modifications have been reported, including the sulfonamide carbamate (reversed Kenner) linker. The nitro group of the key intermediate **174** was reduced and subsequently used to prepare thiazolidinone products (Scheme 39). Depending on the cleavage conditions, different thiazolidinones **178** or their succinate analogues **179** were obtained.

Scheme 39. Synthesis of *N*-alkyl-sulfonamides via "reversed Kenner" linkers.*a*
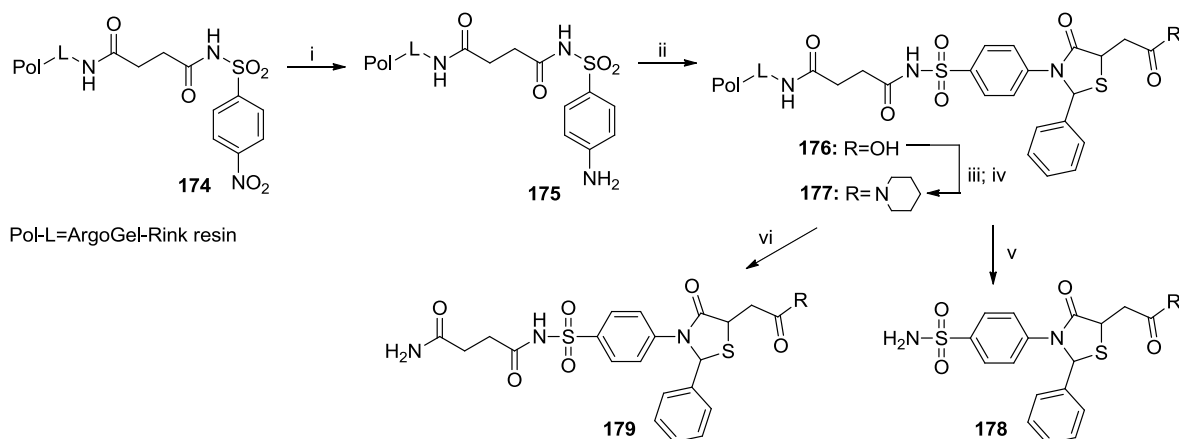
*a*Reagents: (i) SnCl$_2$, DMF; (ii) PhCHO, mercaptosuccinic acid, 4 Å molecular sieves, THF, 70 °C; (iii) pentafluorophenyl trifluoroacetate/Py/DMF (1:1:1); (iv) 20% PIP in DMF; (v) NH$_3$, MeOH; (vi) 50% TFA in DCM.

Incorporation of the Nos group can also introduce analogs of biologically active compounds. A convenient solid-phase technique prepared simple arylsulfonamide molecules derived from putrescine.[40] Nucleophilic displacement of carbonate **191** by putrescine provided immobilized amine **192** that was further exposed to NosCls (Scheme 40). The desired compounds **193** were prepared as potential ligands of serotonin 5-HT$_6$ receptors.

Scheme 40. Synthesis of sulfonamide ligands of 5-HT$_6$ receptors.*a*
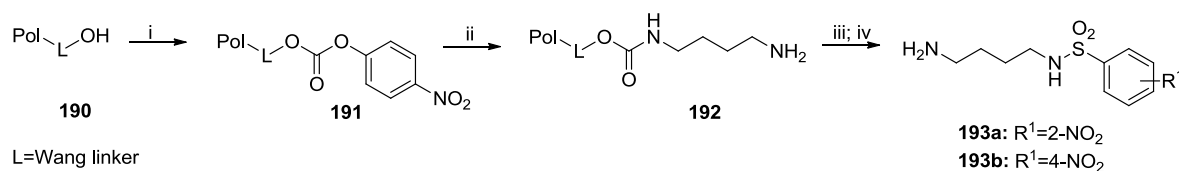
*a*Reagents: (i) 4-nitrophenylchloroformate, NMM, DCM; (ii) putrescine, DCM; (iii) NosCl, NMM, DCM; (iv) 50% TFA in DCM.

Nicolaou and co-workers[89] utilized the previously developed procedure in the split-and-pool synthesis of a large natural product-like library based on the benzopyran scaffold. The starting aldehyde **194** was immobilized onto a selenium resin via ring closure (intermediate **195**) (Scheme 41). The subsequent condensation and reductive amination yielded the intermediate **196**. After reaction with NosCl and final oxidative cleavage, the target scaffold **198** was obtained. Subsequent modification in the solution phase led to diverse sulfonamide products **199**.[90]

Scheme 41. Synthesis of benzopyran derivatives by Nicolaou.[a]
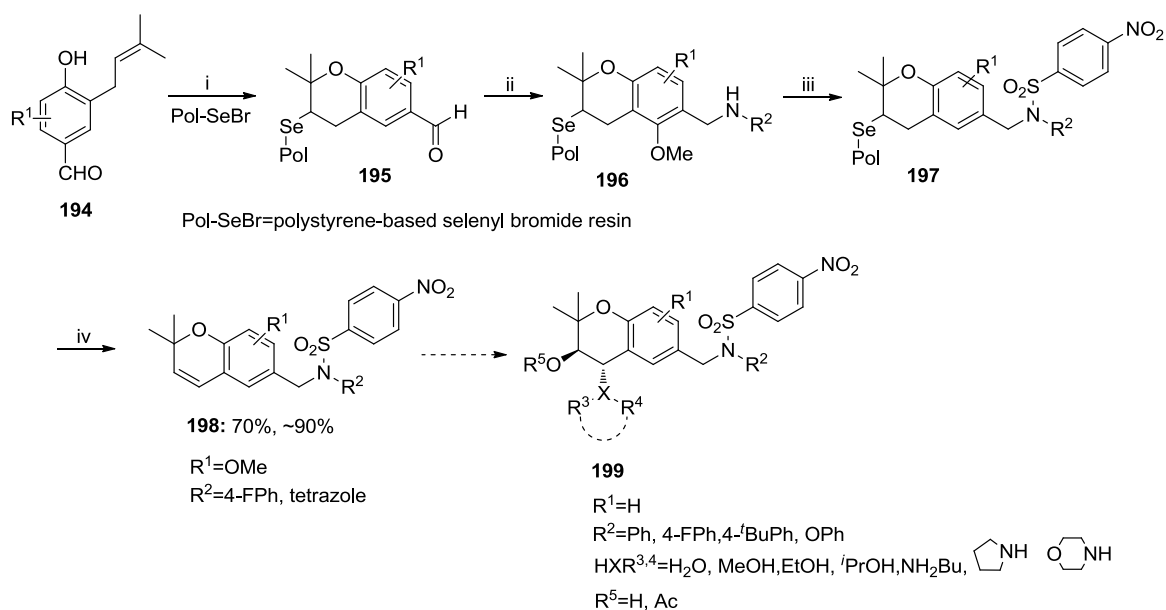
[a]Reagents: (i) DCM; (ii) (a) R^2NH_2, THF, 65 °C (b) NaCNBH$_3$, THF/MeOH (10:1), 65 °C; (iii) 4-NosCl, TEA, DMAP, DCM; (iv) H$_2$O$_2$, THF.

In 2002, solid-phase method was used to synthesize 1,2,4-benzothiadiazin-3-one 1,1-dioxides on solid supports for the first time.[91] The synthesis is based on the sulfonylation of anchored 4-aminophenylacetic acid **200** (Scheme 42). After reduction of an appropriate nitro group, the key cyclization was effortlessly achieved by reaction of compound **202** with CDI. To increase the diversity, the compound **203** was treated with various alkyl halides yielding products **204**.

Scheme 42. Synthesis of 1,2,4-benzothiadiazin-3-one 1,1-dioxides.[a]
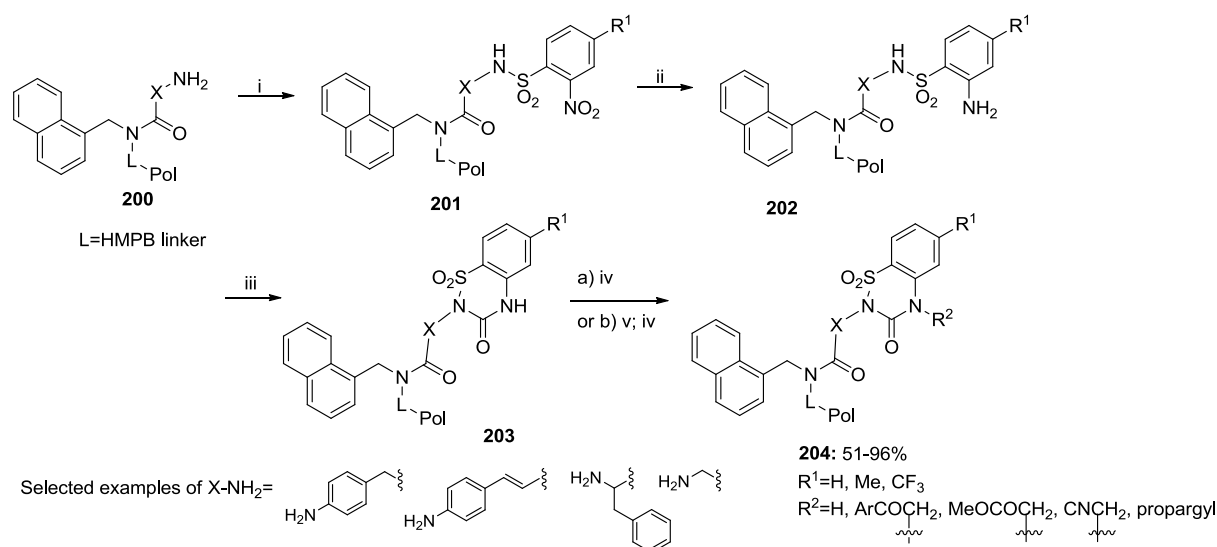
[a]Reagents: (i) 4-R[1]-2-NosCl, 2,6-di-*tert*-butyl-4-methylpyridine, DCM; (ii) SnCl$_2$ · 2H$_2$O, NMP, EtOH; (iii) CDI, DCM; (iv) 95% TFA in H$_2$O; (v) R^{2}X, DIEA, NMP.

The most recent contribution involves the solid-phase synthesis of Anagrelide sulfonyl analogues.[8] The simple procedure was based on the immobilization of various natural amino acids that were treated with 2-NosCl (Scheme 43). Reduction of the nitro group of compounds **205** followed by exposure to Fmoc-NCS provided Fmoc-thiourea intermediates **207**. After DIC-triggered ring closure, final deprotection of the Fmoc group was followed by spontaneous cyclative cleavage to afford the target products **210**.

Scheme 43. Synthesis of Anagrelide sulfonyl analogues.[a]
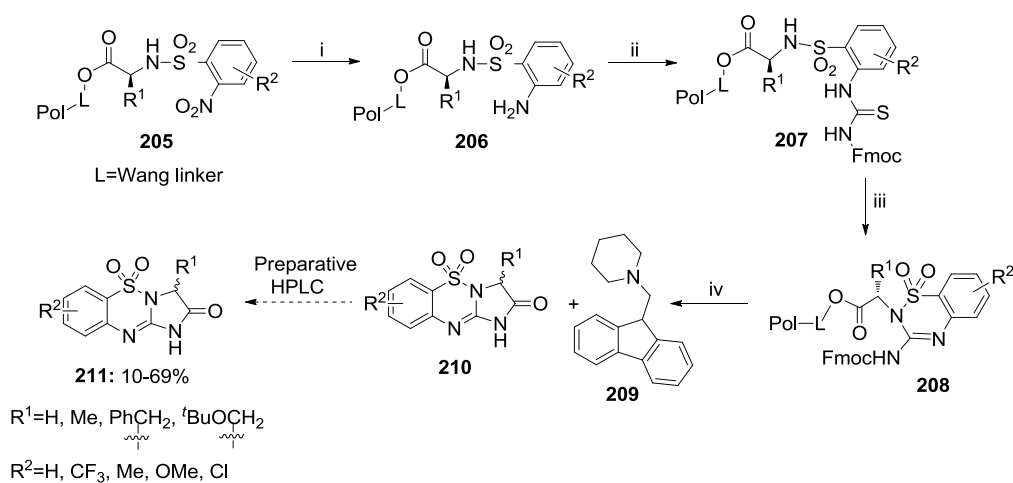
[a]Reagents: (i) Na$_2$S$_2$O$_4$, K$_2$CO$_3$, TBAHS, DCM/H$_2$O (1:1); (ii) Fmoc-NCS, THF; (iii) DIC, DMF; (iv) PIP, DMF.

4. Results and discussion

Numbering of the compounds, linkers and building blocks used in the individual sections is adopted from author´s articles.

4.1 Solid-phase synthesis of trisubstituted benzo[1,4]-diazepin-5-one derivatives

Based on the publication: Fülöpová, V.; Gucký, T.; Grepl, M.; Soural, M. *ACS Comb. Sci.* 2012, *14* (12), 651-656.[3]

The chemistry described in this subchapter takes advantage of the convenient solid-phase technique with application of the standard Fukuyama protocol (scenario A, subchapter 3.2). In such case, the Nos group served as an activation unit for the alkylation with α-haloketones. After the cleavage of the 4-Nos group, the corresponding α-aminoketones were acylated with various *o*-nitrobenzoic acids. Reduction of the nitro group followed by spontaneous on-resin ring closure gave the target immobilized benzodiazepines. After acid-mediated cleavage the products were obtained in very good, crude purity and satisfactory overall yields.

4.1.1 Brief introduction into 1,4-benzodiazepinone motif

In the entire history of 1,4-benzodiazepine scaffold containing substances, 5-substituted-1,3-dihydro-benzo[*e*][1,4]diazepin-2-ones **I** (Figure 7) have been studied most extensively particularly because of their influence on a central nervous system (CNS).[92,93] The most frequently observed effects which resulted in an introduction of more than 30 market benzodiazepine drugs are sedative-hypnotic,[94] anxiolytic,[95] muscle relaxant[96] and anticonvulsant[97] activities. The commercial success of benzodiazepine drugs (such as clonazepam, diazepam, bromazepam or flunitrazepam, see Figure 7) caused exhaustive research in this area and preparation of large number of benzodiazepine derivatives has been described. In contrast, structurally isomeric 2-phenyl-3,4-dihydro-benzo[*e*][1,4]diazepin-5-ones **II** have been studied rarely and only a few articles dedicated to the preparation and properties of such compounds have been published.[98-101]

Figure 7. General structures of benzodiazepine drugs **I** and target substance **II**.

Diazepam   Bromazepam   Clonazepam   Flunitrazepam
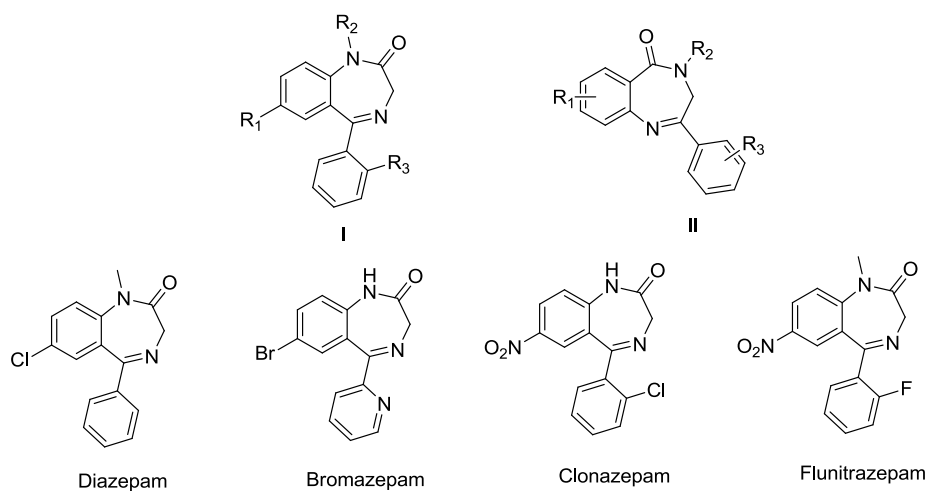
4.1.2 Synthesis

The key building blocks for the preparation of the target substances were primary amines, α-bromoketones and *o*-nitrobenzoic acids. To expand the diversity of R^1 position as much as possible, starting amines of various structures were attached to the polystyrene resin via suitable acid-labile linkers (Scheme 44). To introduce an aliphatic chain with a terminal amino group, hydroxy group or carboxy group respectively, Wang resin[102] was used and ethylendiamine **1**(*1*), 2-(Fmoc-amino)ethanol **1**(*2*)**,** and Fmoc-*β*-Ala-OH **1**(*3*) were immobilized. To introduce an aliphatic ligand with the terminal unsubstituted carboxamide group, Rink amide resin[103] was used and acylated with Fmoc-*β*-Ala-OH to give aminoderivative **1**(*4*). To include *N*-substituted carboxamide, the aminomethylated polystyrene resin equipped with BAL[61] was reductively aminated with two model amines (propylamine and benzylamine) which were subsequently acylated with Fmoc-*β*-Ala-OH to give intermediates **1**(*5*) and **1**(*6*).

Scheme 44. Preparation of immobilized amines **1**(R^1).*a*
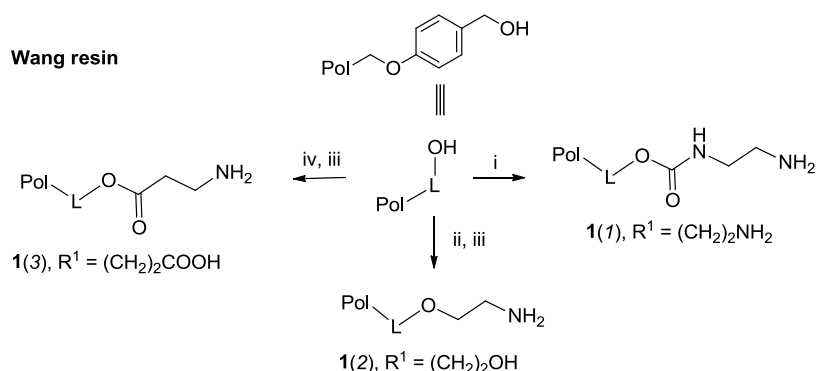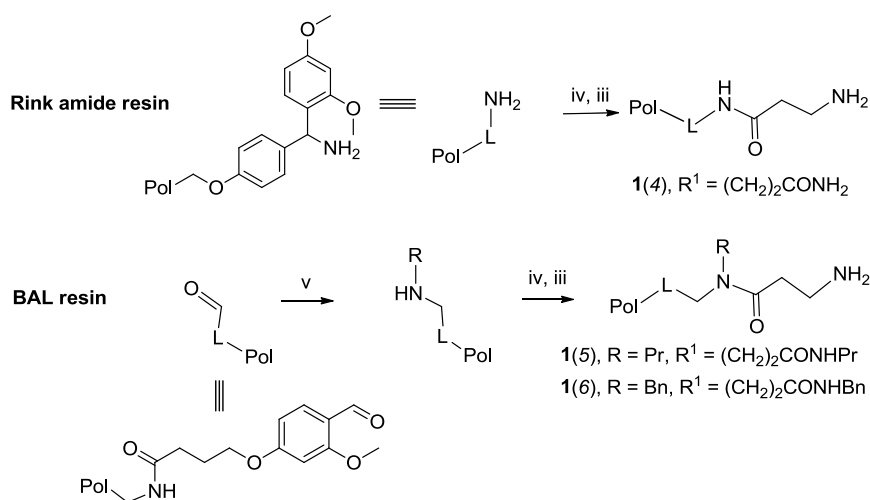
*Reagents: (i) (a) CDI, Py, DCM, rt, 3 h, (b) ethylendiamine, DCM, rt, 3 h; (ii) (a) trichloroacetonitrile, DBU, anhydrous DCM, rt, 1 h, (b) 2-(Fmoc-amino)ethanol, BF$_3$ · Et$_2$O, anhydrous THF, rt, 30 min; (iii) 50% PIP in DMF, rt, 10 min; (iv) Fmoc-β-Ala-OH, HOBt, DIC, DMAP (not for Rink and BAL resin), DMF/DCM (1:1), rt, overnight; (v) (a) 10% Et$_3$N in DCM, rt, 10 min, (b) 4-(4-formyl-3-methoxyphenoxy)butyric acid, HOBt, DIC, DMF/DCM (1:1), rt, overnight, (c) primary amine, 10% AcOH in anhydrous DMF, rt, overnight, (d) NaBH(OAc)$_3$, 5% AcOH in anhydrous DMF, rt, 4 h, (e) 20% PIP in DMF, rt, 10 min.

Following the Scheme 45, the immobilized amines **1** were transformed to the corresponding α-aminoketones **4**. Surprisingly, sulfonylation of aminoderivatives with 4-NosCl was not quantitative in most cases (resins **1**(*1*), **1**(*3-5*)) and the reaction had to be repeated for completion. For the verification of the subsequent alkylation we used compound **2**(*3*) and five aromatic bromoketones substituted with electron-withdrawing as well as electron-donating groups were tested. Also one heterocyclic and one aliphatic haloketone was included (see Figure 8).

Scheme 45. General synthetic route leading to the target benzodiazepines.*
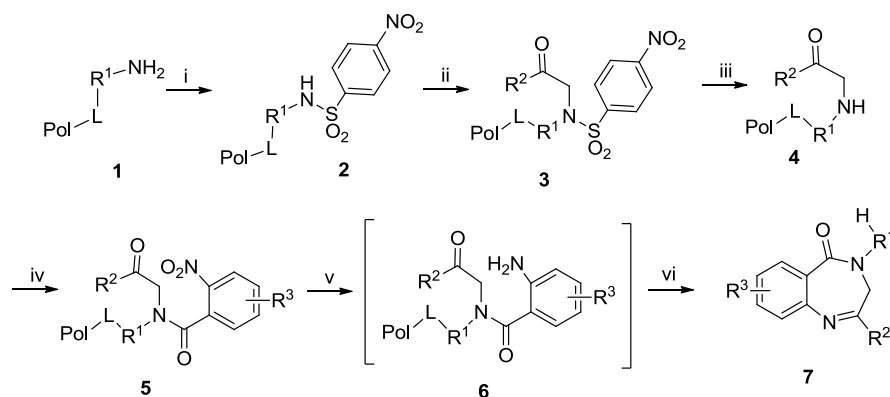
45

[a]Reagents: (i) 4-NosCl, 2,6-lutidine, DCM, rt, overnight; (ii) bromoketone, DIEA, DMF, rt, overnight; (iii) 2-mercaptoethanol, DBU, rt, 10 min; (iv) *o*-nitrobenzoic acids, DIC, DMF, rt, overnight; (v) SnCl$_2$ · 2H$_2$O, DIEA, deoxygenated DMF, rt, overnight (repeated); (vi) 50% TFA in DCM, rt, 30 min.

Figure 8. List of used building blocks for substitution R^2 and R^3.

Alkylation with bromoketones *1-6* afforded sulfonamides **3**(*3,1-6*) with excellent purity (more than 90%, traces at 200-600 nm). A different result was obtained when chloroacetone *7* was used. Alkylation with this agent gave the desired intermediate **3**(*3,7*) in limited purity (up to 75 %). First, we tried to optimize the reaction conditions with use of different solvents, bases and temperature (see Table 1) but we did not manage to increase the overall purity. Additionally, repetition of reaction conditions was tested but the purity decreased due to secondary products formation.

Table 1. Various reaction conditions for the preparation of intermediate **3**(*3,7*).

Reaction Conditions	Purity (%)[a]
DIEA, DMF, rt, 16 h	49
DIEA, DMF, rt, 16 h, repeated	70
DIEA, DMF, 40°C, 16 h	75
DIEA, DMF, 40°C, 16 h, repeated	46
proton sponge, DMF, rt, 16 h	70
DBU, DMF, rt, 16 h	mixture of compounds
DIEA, THF, rt, 16 h	mixture of compounds

[a]Calculated from LC traces at 200-600 nm after cleavage from the polymer support.

Denosylation of intermediates **3** afforded the corresponding aminoketones **4** that were acylated with *o*-nitrobenzoic acid. It should be noted that denosylation of intermediate **3**(*6,1*) required a significantly longer reaction time (60 min instead of typical 10 min procedure). After the acylation step, we observed formation of a side product, which was identified with the use of LC/MS analysis as the dealkylated byproduct **5-D**(R^1,-,*1*) (Scheme 46). Further investigation (cleavage of resins **5**(R^1,R^2,*1*) was performed for various time periods and identical mixtures of compounds were obtained) showed that the side product was not formed during the cleavage of intermediates **5** from the resin but during the acylation of intermediates **4** with *o*-nitrobenzoic acid.

Scheme 46. Dealkylation during acylation with *o*-nitrobenzoic acid.[a]

[a]Reagents: (i) *o*-nitrobenzoic acid, DIC, DMF, rt, 16 h.

In most of the tested cases, the dealkylation did not decrease the overall purity significantly and the intermediates **5** were obtained in a sufficient purity ranging from 72 to 99% (LC traces at 200-600 nm). However, in the case of intermediate **4**(*3,7*) prepared from chloroacetone, we obtained only a mixture of compounds without corresponding product. The use of intermediate prepared from 3-bromo-2′-bromoacetophenone (*5*) led to quantitative dealkylation, intermediate prepared from 4-fluoro-2′-bromoacetophenone (*6*) dealkylated from 60% so the both building blocks were excluded. To suppress the side reaction we tested the acylation of intermediate **4**(*3,1*) with alternative agents (such as isatoic anhydride or anthranilic acid) and species (HOBt ester, symmetrical anhydride) but the purity of intermediates **5** was usually decreased (see Table 2). The best results were obtained with the use of a symmetrical anhydride prepared in situ from the corresponding *o*-nitrobenzoic acids in *N,N*-dimethylformamide.

Table 2. Summary of alkylated/dealkylated product ratio with use of intermediate **4**(*3,1*) and different acylating methods species.

Reagents	Alkylated (%)[a]	Dealkylated (%)[a]
o-nitrobenzoic acid, DIC, HOBt, DMF/DCM	64	30
o-nitrobenzoic acid, DIC, DMF	93	6
isatoic anhydride, DIPEA, DMF	0	21
anthranilic acid, DIC, HOBt, DMF/DCM	13	31
3-nitropthalic anhydride, DIEA, anhydrous THF	52	33
3-nitropyridine-2-carboxylic acid, DIC, DMF	85	2
4-bromo-2-nitrobenzoic acid, DIC, DMF	82	13
4-methyl-2-nitrobenzoic acid, DIC, DMF	72	20
5-methoxy-2-nitrobenzoic acid, DIC, DMF	87	12

[a]Calculated from LC traces at 200-600 nm after cleavage from the polymer support.

To introduce the third diversity position, various *o*-nitrobenzoic acids were used (see Figure 8) to acylate intermediates **4**. After subsequent reduction of the nitro group and cleavage of the resulting material from the resin we did not detect the linear intermediates **6** but only the final products **7** (Scheme 47). When the sample of the resin **6**(*1,1,1*) was treated with Fmoc-Cl and cleaved, the corresponding *N*-Fmoc intermediate was not detected which indicates the ring closure took place on-resin after reduction of the nitro group. After the reduction step, we detected the appearance of a side product in each case (10-30%, LC traces at 200-600 nm). From LC traces, we have concluded that the structure of the side products corresponds to *N*-hydroxyderivatives **8** formed after incomplete reduction of the nitro group to hydroxylamine derivative. After repeating the reduction step, the side products **8** were not detected, which is in accordance with the theory of hydroxylamine intermediate formation.

Scheme 47. Side product formation after first-round reduction of precursors **5**.[a]

[a]Reagents: (i) SnCl$_2$ · 2H$_2$O, DIEA, deoxygenated DMF, rt, 16 h; (ii) 50% TFA in DCM, rt, 30 min.

The final compounds **7** were generally obtained in very good crude purity (see Table 3), and their final purification was achieved by the use of flash chromatography on reversed phase C^{18} cartridges and subsequent reverse phase semipreparative HPLC. The use of C^{18} cartridges was necessary to remove tin(II) and tin(IV) salts otherwise HPLC column was clogged during purification. During the isolation process, an unexpected instability of amino group containing derivatives **7**(*1*,R^2,R^3) was observed. Because of their decomposition, such substances have not been isolated in a pure form. The structure of the final compounds was confirmed with the help of ^{1}H and ^{13}C NMR spectrometry and HRMS.

We also investigated the tautomerism of prepared 1,4-benzodiazepine-5-ones since at least two possible tautomeric form **7A** and **7B** have to be considered. We observed a broad singlet at around 4.20 ppm in the ^{1}H NMR spectra of the studied compounds which corresponds to a methylene group of tautomeric from **7A**. The tautomer **7A** seems to be the only present of the studied compounds under the experimental conditions used. We have proven this suggestion with the help of ^{1}H-^{1}H COSY and ^{1}H-^{13}C edited HSQC experiments in the case of compound **7**(*5,1,1*).

Figure 9. Two possible tautomeric forms of the final products.

Table 3. List of final compounds **7**.

Cmpd	R^1H	R^2	R^3	Purity (%)^a (C^{18})	Purity (%)^a (HPLC)	Yield (%)^b
7(*1,1,1*)	(CH$_2$)$_2$NH$_2$	4-MePh	H	77	-	NI
7(*1,2,1*)	(CH$_2$)$_2$NH$_2$	4-OMePh	H	78	-	NI
7(*1,3,1*)	(CH$_2$)$_2$NH$_2$	4-NH$_2$-3,5-di-ClPh	H	63	-	NI
7(*1,4,1*)	(CH$_2$)$_2$NH$_2$	thiophene cycle	H	58	-	NI
7(*2,1,1*)	(CH$_2$)$_2$OH	4-MePh	H	97	99	30

7(*3,1,1*)	(CH$_2$)$_2$COOH	4-MePh	H	72	99	26
7(*3,2,1*)	(CH$_2$)$_2$COOH	4-OMePh	H	93	99	47
7(*3,3,1*)	(CH$_2$)$_2$COOH	4-NH$_2$-3,5-di-ClPh	H	88	99	33
7(*3,4,1*)	(CH$_2$)$_2$COOH	thiophene cycle	H	83	99	22
7(*3,1,2*)	(CH$_2$)$_2$COOH	4-MePh	8-Br	85	99	24
7(*3,1,3*)	(CH$_2$)$_2$COOH	4-MePh	7-OMe	73	99	14
7(*3,1,4*)	(CH$_2$)$_2$COOH	4-MePh	8-Me	87	99	15
7(*3,1,5*)	(CH$_2$)$_2$COOH	4-MePh	NA	76	96	28
7(*4,1,1*)	(CH$_2$)$_2$CONH$_2$	4-MePh	H	79	96	30
7(*5,1,1*)	(CH$_2$)$_2$CONHPr	4-MePh	H	96	99	26
7(*6,1,1*)	(CH$_2$)$_2$CONHBn	4-MePh	H	85	99	29

[a]Calculated from LC traces at 200-600 nm. [b]Calculated from NMR spectra. NI = Not Isolated due to the decomposition during semiprep. HPLC isolation. NA = Not applicable.

4.2 Solid-phase synthesis of trisubstituted benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-6(5*H*)-ones and their sulfonyl analogues under mild reaction conditions

Based on the publication: Fülöpová, V.; Funk, P.; Popa, I.; McMaster, C.; Soural, M. *Eur. J. Org. Chem.* 2015, *2015* (16), 3551-3557.[4]

This subchapter describes the extension of the above summarized chemistry for the preparation of 1,4-benzodiazepinones with a condensed 1,2,3-triazole cycle. The designed seven-step synthetic strategy utilized the polymer-supported 4-nitrobenzenesulfonamides that were alkylated with various propargyl derivatives. Cleavage of the 4-Nos group from each of the key intermediates was followed by the acylation with different 2-azidobenzoic acids, leading to spontaneous intramolecular (Huisgen) 1,3-dipolar cycloaddition. After cleavage from the polymer support, target compounds were obtained in excellent crude purity and very good overall yields.

4.2.1 Brief introduction into fused 1,4-benzodiazepinone motif

As it was already mentioned, 1,4-benzodiazepines belong to a group of compounds frequently reported as "privileged structures" with high pharmacological, medicinal and clinical importance.[104] In addition, molecules that contain the fused heterocyclic system of the 1,4-benzodiazepinone scaffold with an imidazol (Midazolam, Bretazenil, Flumazenil), or a

1,2,4-triazol (Alprazolam, Estazolam, Triazolam, Pyrazolam) moiety (Figure 10) constitute a specific group of benzodiazepine CNS drugs. The majority of these agents have been clinically used for the treatment of anxiety[105] and depression.[106] In contrast, Flumazenil is primarily used for the treatment of benzodiazepine overdoses.[107] Due to the structural similarity to commercially successful drugs (such as Dormicum, Xanax, Anexate) a deeper attention has recently been paid to benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-6(5*H*)-ones. These scaffolds have already been prepared with use of traditional solution-phase synthesis and thermal or catalyzed 1,3-dipolar azide cycloaddition.[108-113]

Figure 10. Selected fused 1,4-benzodiazepine drugs compared to target scaffold.

Pyrazolam   Triazolam   Alprazolam   Estazolam

Midazolam   Bretazenil   Flumazenil   Target scaffold

Y = CO or SO$_2$
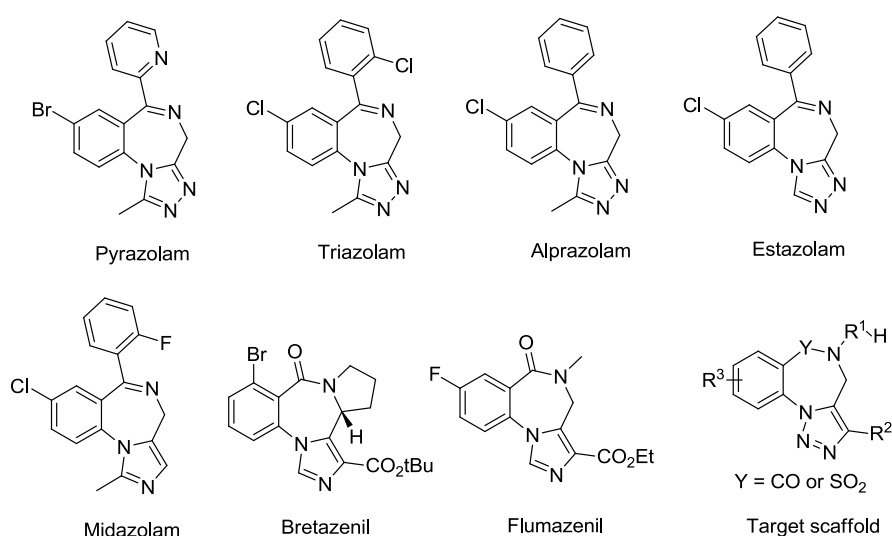
4.2.2 Synthesis

The general synthetic strategy leading to the target triazolobenzodiazepinones is described in Scheme 48. To diversify target molecules in position R^1, various starting amines have been anchored onto resin according to procedures described in experimental part. To introduce carboxylic, hydroxy and amino groups into the structure at position R^1, Fmoc-*β*-Ala-OH **1**(*1*), Fmoc-Ala-OH **1**(*2*), 2-(Fmoc-amino)ethanol **1**(*3*) and ethylendiamine **1**(*4*) were attached to Wang resin followed by the cleavage of Fmoc protecting groups with piperidine. *N*-Unsubstituted carboxamides were achieved by acylation of Rink amide resin **1**(*5*) with Fmoc-*β*-alanine. Furthermore, two polymer-supported secondary amides (aliphatic **1**(*6*) and aromatic **1**(*7*)) have been synthesized with use of the corresponding resin bound amines, immobilized on aminomethylated resin equipped with BAL linker (Figure 11).

Figure 11. List of immobilized starting amines.
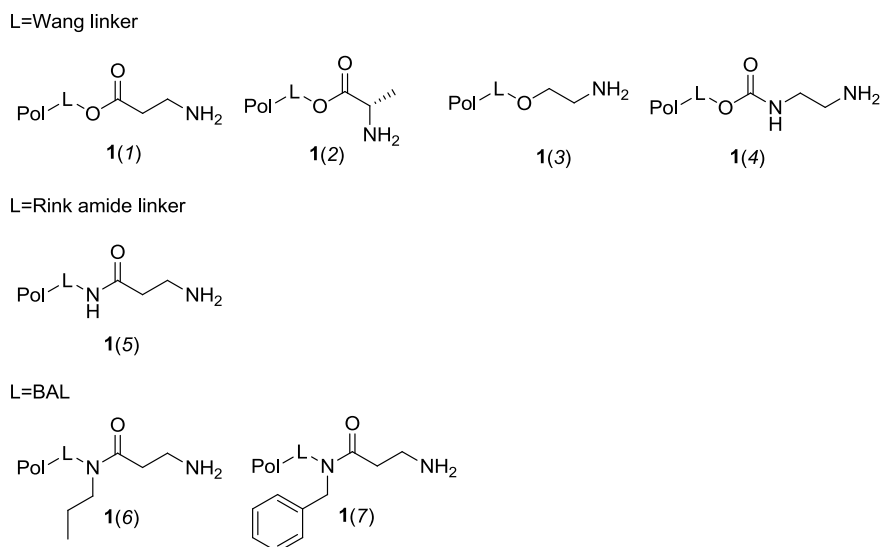
To test the suggested synthetic pathway, resin bound amine **1**(*1*) was sulfonylated with 4-NosCl. The corresponding sulfonamide **2**(*1*) was then alkylated with propargyl bromide according to the Fukuyama procedure[21] to give the propargyl derivative **3**(*1,1*) in excellent purity. After cleavage of the 4-Nos group with mercaptoethanol and DBU, the unmasked propargylamine **4**(*1,1*) was treated with a solution of 2-azidobenzoic acid in the presence of HOBt and DIC. Subsequent cleavage from the polymer support, with use of TFA in DCM, gave the target product **7**(*1,1,1*) in a crude purity of 86% (calculated from LC traces at 200-500 nm) and overall yield of 32% (after semipreparative HPLC purification). From this result we concluded that the Huisgen reaction took place spontaneously on the resin, giving the polymer supported product **6**(*1,1,1*). On the other hand, TFA mediated cyclization of intermediate **5**(*1,1,1*) during the acidic cleavage was also possible. To distinguish between the two alternatives, resin **6**(*1,1,1*) was submitted to a FTIR study. In the IR spectrum we did not observe the presence of a characteristic signal for -C≡C- stretch in the region 2100-2260 cm^{-1} which points to the formation of resin-bound triazolobenzodiazepinones **6**. The same evidence for quantitative conversion was used in paper[114] published in 2012.

Scheme 48. Synthesis of triazolobenzodiazepinones **7**.[a]
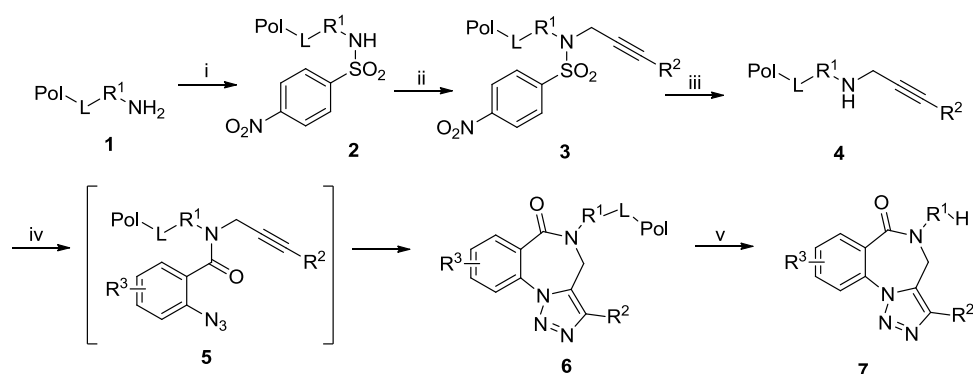
[a]Reagents: (i) 4-NosCl, 2,6-lutidine, DCM, rt, overnight; (ii) propargyl bromide derivative, DBU, DMSO, rt, overnight; (iii) 2-mercaptoethanol, DBU, DMF, rt, 30 min.; (iv) 2-azidobenzoic acid, HOBt, DIC, 50% DMF/DCM, rt, overnight; (v) 50% TFA in DCM, rt, 1 h.

Encouraged by the result, we subsequently tested the applicability of the synthetic strategy for the preparation of analogical triazolobenzothiadiazepine dioxides **10** (Scheme 49). Intermediate **4**(*1,1*) was treated with a solution of 2-azidobenzenesulfonyl chloride in the presence of 2,6-lutidine. As in the previous case, subsequent cleavage gave directly the desired product **10**(*1,1,7*), again with a very good crude purity of 75% and an overall yield of 71%.

Scheme 49. Synthesis of triazolobenzothiadiazepine dioxides **10**.[a]
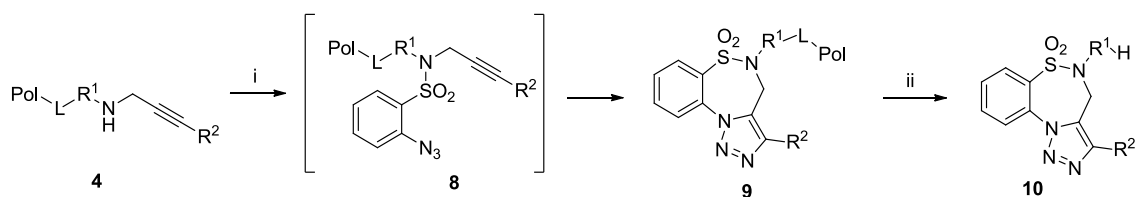
[a]Reagents: (i) 2-azidobenzenesulfonyl chloride, 2,6-lutidine, DCM rt, overnight; (ii) 50% TFA in DCM, rt, 1 h.

To evaluate the scope and limitations of this method, various *C*-substituted propargyl bromides were used in combination with unsubstituted 2-azidobenzoic acid. Similarly, a set of 2-azidobenzoic acids substituted with both electron donating and withdrawing groups were tested in combination with propargyl bromide and resin **1**(*1*). Finally, all the starting resin bound amines (see Figure 11) were tested in combination with unsubstituted 2-azidobenzoic acids and propargyl bromides. Applicability of the sequence for the preparation of

triazolobenzothiadiazepine dioxides **10** was tested for various polymer supported amines in combination with unsubstituted 2-azidobenzenesulfonyl chloride and propargyl bromide. The list of propargyl and azido building blocks is displayed in Figure 12; all synthesized compounds are summarized in Table 4.

Figure 12. List of tested building blocks.

Building blocks for (R^2) substitution:

Building blocks for (R^3) substitution:

Table 4. Synthesized derivatives **7** and **10**.

Cmpd	Y	R^{1}H	R^2	R^3	Purity (%)^a	Yield (%)^b
7(*1,1,1*)	CO	(CH$_2$)$_2$COOH	H	H	86	32
7(*1,2,1*)	CO	(CH$_2$)$_2$COOH	Me	H	95	64
7(*1,3,1*)	CO	(CH$_2$)$_2$COOH	Ph	H	93	52
7(*1,1,2*)	CO	(CH$_2$)$_2$COOH	H	10-Me	81	77
7(*1,1,3*)	CO	(CH$_2$)$_2$COOH	H	10-OMe	89	69
7(*1,1,4*)	CO	(CH$_2$)$_2$COOH	H	8,10-di-Br	93	71
7(*1,1,5*)	CO	(CH$_2$)$_2$COOH	H	8-Cl	80	58
7(*1,1,6*)	CO	(CH$_2$)$_2$COOH	H	8-NO$_2$	86	64
7(*2,1,1*)	CO	(CH$_2$)$_2$OH	H	H	82	44
7(*3,1,1*)	CO	(CH$_2$)$_2$NH$_2$	H	H	89	36
7(*4,1,1*)	CO	(CH$_2$)$_2$CONH$_2$	H	H	83	68
7(*5,1,1*)	CO	(CH$_2$)$_2$CONHPr	H	H	84	70
7(*6,1,1*)	CO	(CH$_2$)$_2$CONHBn	H	H	94	76

10(*1,1,7*)	SO$_2$	(CH$_2$)$_2$COOH	H	H	75	71
10(*2,1,7*)	SO$_2$	(CH$_2$)$_2$OH	H	H	85	60
10(*3,1,7*)	SO$_2$	(CH$_2$)$_2$NH$_2$	H	H	93	38
10(*4,1,7*)	SO$_2$	(CH$_2$)$_2$CONH$_2$	H	H	83	67
10(*6,1,7*)	SO$_2$	(CH$_2$)$_2$CONHBn	H	H	91	62

[a]Calculated from LC traces at 200-500 nm. [b]Calculated from NMR spectra.

The developed methodology was also tested for immobilized Fmoc-Ala-OH (resin **1**(*2*)) in order to introduce the α-amino acid framework into the final structure. Surprisingly, alkylation of sulfonamide **2**(*2*) with propargyl bromide did not afford the intermediate **3**(*2,1*). Instead of this, LC/MS analysis showed the presence of an unknown product with MW = 248 and a high crude purity of 81%. Such molecular weight could correspond to reaction products **X**, **Y** or **Z** (Scheme 50). Rearrangement of various polymer supported 2-nitrobenzenesulfonamides based either on *C*- or *N*-arylation have been recently reported by Krchňák.[33,35] To identify the correct structure with NMR, the cleaved product was isolated by semipreparative HPLC, freeze dried and submitted to NMR study. Unfortunately, we observed full decomposition of the compound during the process which did not allow for the structural determination.

Scheme 50. Formation of unknown side product after propargylation of intermediate **2**(*7*).[a]
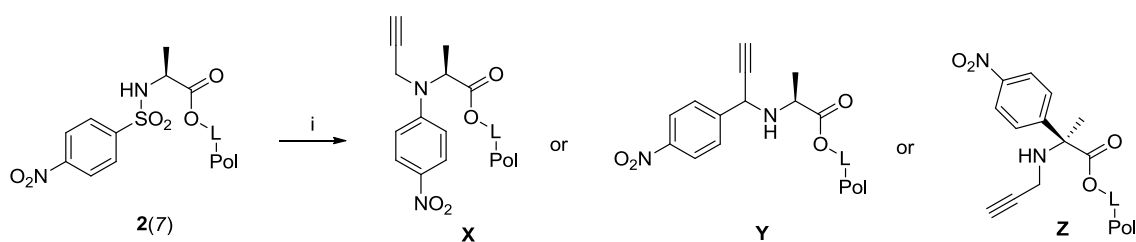
[a]Reagents: (i) propargyl bromide, DBU, DMSO, rt, overnight.

Aside from triazolobenzodiazepinones, we also focused on possible applications of the synthetic pathway for the preparation of the corresponding dihydrotriazolobenzodiazepinone derivatives. For this purpose, the intermediate **2**(*7*) was alkylated with allyl bromide (Scheme 51). In contrast to the chemistry of triazolobenzodiazepinones described above, desulfonylation followed by acylation with 2-azidobenzoic acid and the final cleavage provided only the linear precursor **13**(*7,4,1*). Conventional heating of the resin **12**(*7,4,1*) to 60ºC did not furnish the desired product **14**(*7,4,1*). Further heating above 75 ºC led only to

slow decomposition of the starting material to give a mixture of unknown compounds. Interestingly, microwave heating at 120 ºC for 5 minutes provided compound **15** as the major product. The analogous 2-azidobenzoic *N*-allylamides have previously been reported to follow a similar reaction course in solution-phase synthesis.[115,116] To compare the stability of the corresponding triazoles, compounds **7**(*1,1,1*) and **10**(*1,1,7*) were subjected to microwave heating, but no decomposition was observed.

Scheme 51. Unsuccessful preparation of dihydrotriazolobenzodiazepinones **14**.[a]
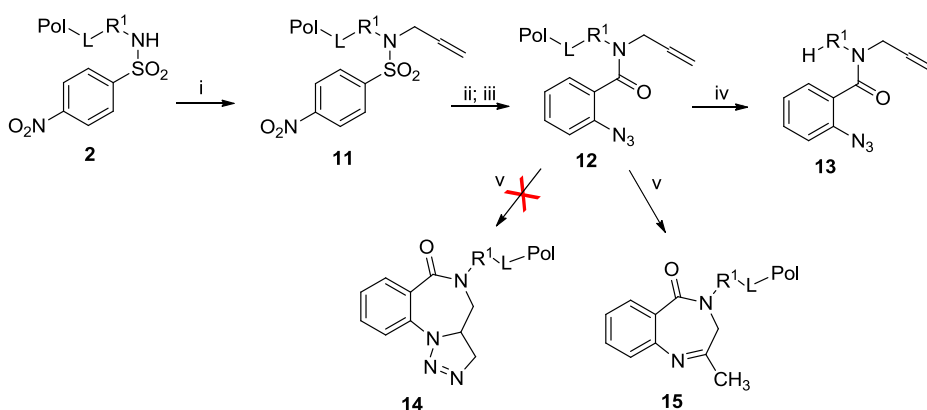
[a]Reagents: (i) allyl bromide, DBU, DMSO, rt, overnight; (ii) mercaptoethanol, DBU, DMF, rt, 30 min.; (iii) 2-azidobenzoic acid, HOBt, DIC, 50% DMF/DCM, rt, overnight; (iv) 50% TFA in DCM; (v) DMSO, MW, 120 ºC, 5 min.

4.3 Solid-phase synthesis of trisubstituted 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide derivatives

Based on the publication: Fülöpová, V.; Krchňák, V. *ACS Comb. Sci.* 2014, *16* (8), 412-420.[5]

This subchapter is dedicated to the solid-phase synthesis of sulfonyl analogues of the previously described benzodiazepine derivatives **A** (General overview of the target scaffolds, Abstract). In this case, the 2-Nos group was preserved in the structure of nitrobenzenesulfonamide intermediates as a synthon according to scenario B (subchapter 3.3). After Fukuyama alkylation with variable bromoketones, the acyclic precursors were subjected acid-mediated release from the resin and the final cyclization was completed in solution-phase.

4.3.1 Brief introduction into benzodiazepine sulfonyl analogues

Derivatives with structure **III** (Figure 13) belong to the benzodiazepine class which has seldom been studied, and only a few reports have described their synthesis or properties.[117,118] In this regard, some derivatives with an introduced imidazole ring, such it is displayed in the compounds **IV**, possesses an anti-HIV-1 activity.[119]

Figure 13. Examples of benzodiazepine sulfonyl analogues scaffolds.
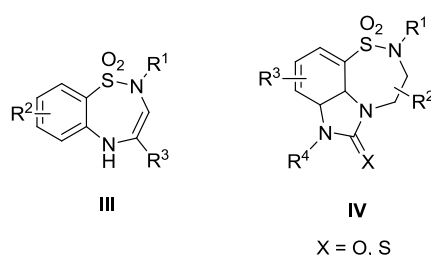
4.3.2 Synthesis

The solid-phase synthesis of 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxides was performed on resin-bound amines **1**, which were prepared by immobilization of Fmoc-protected α- or β-amino acid (see Figure 15) on commercially available Wang **1**(*1-7*) and Rink amide **1**(*8*) resins (Figure 14). To increase the diversity of the target compounds and to study the effect of ester group, the Fmoc-Ala-OH was also attached to the Wang resin via an acidic/basic-labile ethanolamine linker **1**(*9*).

Figure 14. Amino acids immobilized on various linkers for R^1 substitution.
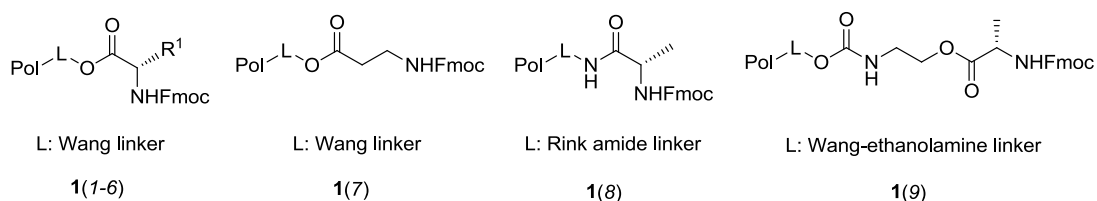
The Fmoc group was cleaved with piperidine, and the deprotected primary amines **2** were transformed to the corresponding 2-nitrobenzenesulfonamides **3** with an excellent rate of conversion (more than 93%, LC traces at 205-450 nm). The activating 2-Nos group of intermediates **3** enabled Fukuyama alkylation using aromatic bromoketones with both electron-withdrawing and electron-donating groups (Figure 15). This step afforded compounds **4** with good crude purity (from 73% to 93%, LC traces at 205–450 nm).

Alkylation was not quantitative despite attempts to alkylate valine **3**(*4,1,1*) three times and lysine **3**(*5,1,1*) twice.

Scheme 52. Solid-phase synthesis of the target compounds.[a]
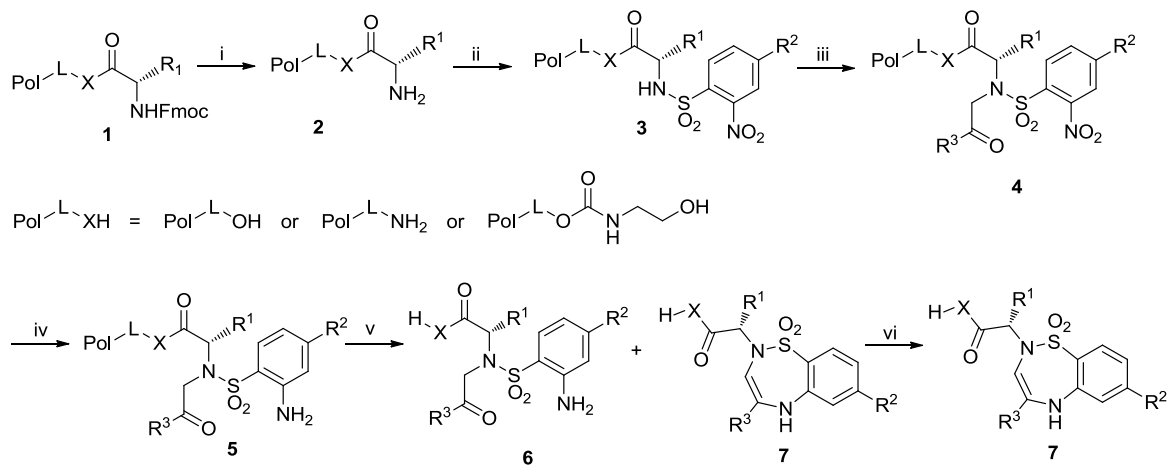
[a]Reagents: (i) 50% PIP in DMF, rt, 30 min.; (ii) 2-NosCl, 2,6-lutidine, DCM, rt, overnight; (iii) bromoketone, DIEA, DMF, rt, overnight; (iv) $Na_2S_2O_4$, K_2CO_3, TBAHS, 50% H_2O/DCM, rt, overnight; (v) 50% TFA in DCM, rt, 1 h.; (vi) DMSO-d_6, rt, see Table 5 for the reaction time.

Figure 15. Structures and numbering of the tested building blocks.
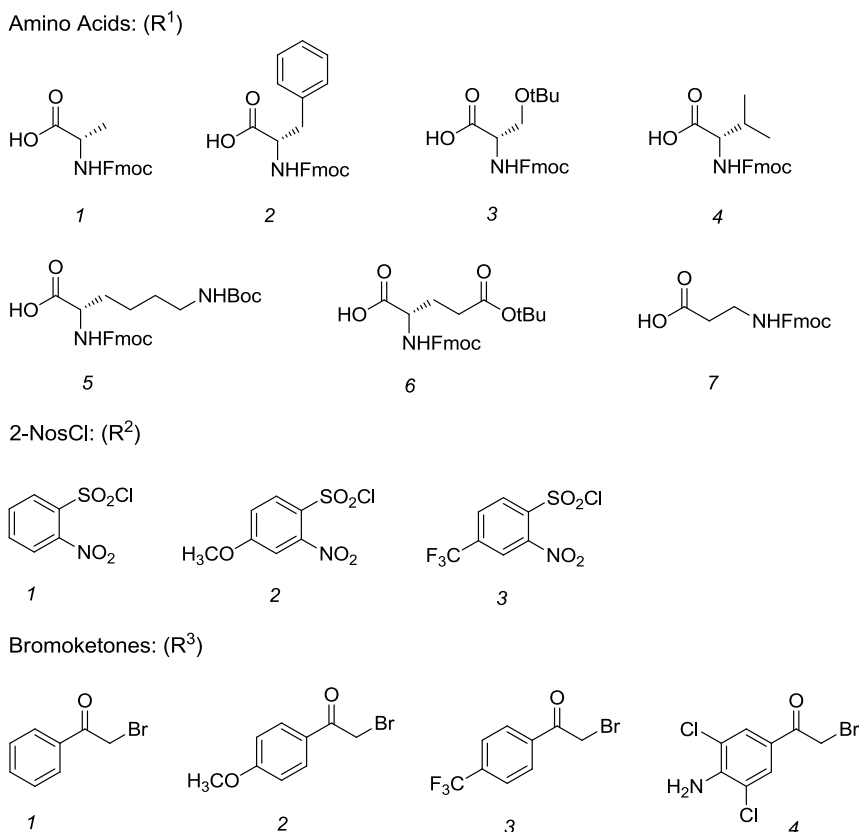
Resins **4** were exposed to a phase-transfer catalyzed nitro group reduction developed for polymer-supported synthesis.[120] The acyclic resin-bound precursors **5** were treated with a TFA cleavage cocktail to release the products from the resin. Because the described research has been more challenging, we have divided our observation into three parts.

Structure determination:

The LC/MS analysis of the crude products revealed the presence of two major components, the mass spectra showed the appropriate positive and negative molecular ions corresponding to the acyclic compounds **6** and cyclized products **7**. To confirm their structures, the crude products were purified by reverse-phase semipreparative HPLC using mobile phases consisting of MeCN and 0.1% aqueous TFA. The acyclic compounds **6** spontaneously cyclized and formed **7**, however majority of compounds did not cyclize completely and the rate of cyclization depended on the linker and substituents R. The ^{1}H NMR spectra indicated complete cyclization to target products **7**(*1,1,2*), **7**(*2,1,1*), and **7**(*4,1,1*). On the other hand, compound **6**(*9,1,2*) contained only 5% of cyclic form **7**(*9,1,2*).

Analysis of the ^{1}H-NMR spectrum of **6**(*9,1,2*) enabled identification of diagnostic resonances of acyclic compound **6**: methylene protons as two doublets at 4.78–5.00 and 4.98–5.18 ppm with a *J* value of 19.0-19.3 Hz. The carbon with the chemical shift at 193.1–195.7 ppm corresponded to the carbonyl carbon of the linear ketones **6**. LC/MS analysis showed the appropriate positive and negative molecular ions, and HRMS analysis confirmed the molecular formula.

Two tautomeric forms, **7** and **8**, are possible for the cyclic derivatives (Figure 16). In our previous work (subchapter 4.1.2), we investigated the tautomeric forms of cyclic benzodiazepinone derivatives **II** (Figure 7, subchapter 4.1.1).[3] The broad singlet at 4.20 ppm in the proton spectra corresponded to the methylene group and confirmed the structure of **II**. In contrast to benzodiazepinone, we observed diagnostic resonances for the aniline proton at 8.32–9.03 ppm and for the olefinic proton at 5.25–5.38 ppm, confirming the tautomer **7**. The olefinic proton appeared as a singlet or a doublet with a very small *J* value (0.4–0.8 Hz), but long distance coupling of the corresponding proton was not observed. The olefinic carbon signal was present at 101.3–105.5 ppm in the ^{13}C-NMR spectrum and was confirmed by an HSQC experiment. Previously reported synthesis afforded the same tautomer.[117] A potential cause for the presence of tautomer **7** could be the extended conjugation involving two sp^2

carbons, whereas the sulfonamide is not planar. The presence of could also be a result of the electron-withdrawing effect of the sulfonyl group, which is stronger than the effect of the carbonyl in structure **II**. The tautomer **8** has never been observed in this case.

Figure 16. Two possible tautomeric forms.
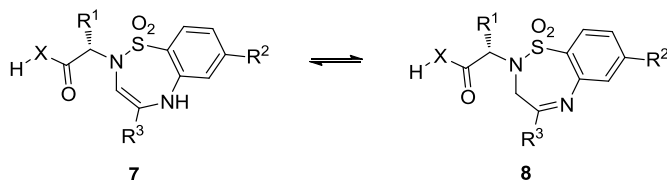
Cyclization:

A subset of the compounds was not completely cyclized, and a mixture of linear **6** and cyclic **7** compounds was obtained (Figure 17 and 18). We utilized the NMR diagnostic signals to calculate the **6/7** ratio and to study the progress of cyclization as a function of time. The cyclization time depended on substituents R^2 and R^3 and the linker (Table 5). To accelerate the cyclization by using different solvent and elevated temperature resulted in transformation of the target compounds **7** and deteriorating the overall purity. Thus, we used spontaneous cyclization in the DMSO solution at room temperature to prepare products **7**. Only compounds **6**(*9,1,2*) did not cyclized completely and attempts to force the cyclization (elevated temperature) resulted in decomposition.

Figure 17. ^{1}H NMR spectrum of a mixture of **6**(*1,2,1*) and **7**(*1,2,1*).
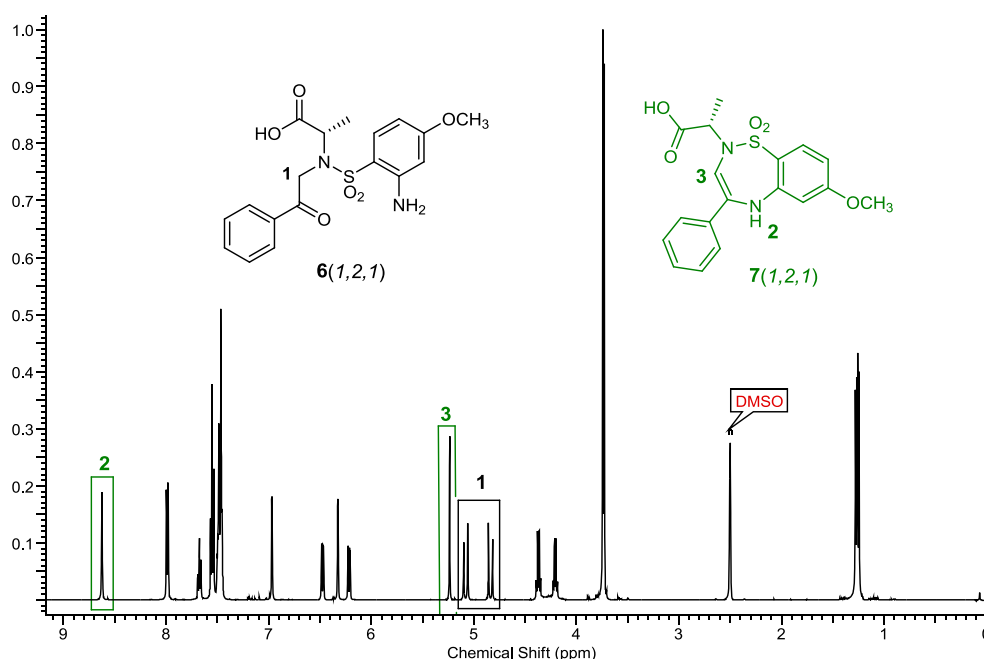
Figure 18. Expansion of the ^{1}H NMR aliphatic region.

Table 5. Synthesized compounds **7**.

Cmpd	XH	R^1	R^2	R^3	Ratio **6/7** (%)[a]	Cycl. time (days)	Purity (%)[c]
7(*1,1,1*)	OH	Me	H	Ph	13:87	1.3	53
7(*1,1,2*)	OH	Me	H	4-OMePh	<1:>99	[b]	71
7(*1,1,3*)	OH	Me	H	4-CF$_3$Ph	14:86	1.3	77
7(*1,1,4*)	OH	Me	H	4-NH$_2$-3,5-di-ClPh	51:49	1.3	69
7(*1,2,1*)	OH	Me	H	Ph	50:50	3.3	67
7(*1,3,1*)	OH	Me	OMe	Ph	21:79	6.3	33
7(*2,1,1*)	OH	Bn	CF$_3$	Ph	<1:>99	[b]	65
7(*3,1,1*)	OH	CH$_2$OH	H	Ph	NI	NI	NI
7(*4,1,1*)	OH	^{i}Pr	H	Ph	<1:>99	[b]	67
7(*5,1,1*)	OH	(CH$_2$)$_4$NH$_2$	H	Ph	67:33	1.0	72
7(*6,1,1*)	OH	(CH$_2$)$_2$COOH	H	Ph	27:73	3.3	74
7(*7,1,1*)	OH	NA	H	Ph	9:91	[b]	71

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7(*8,1,1*)	NH$_2$	Me	H	Ph	NI	NI	NI
7(*9,1,1*)	O(CH$_2$)$_2$NH$_2$	Me	H	Ph	67:27	6.3	65
7(*9,1,2*)	O(CH$_2$)$_2$NH$_2$	Me	H	4-OMePh	97:3	NI	NI
7(*9,1,3*)	O(CH$_2$)$_2$NH$_2$	Me	H	4-CF$_3$Ph	NI	NI	NI

[a]The ratio was calculated from the NMR spectra obtained after purification and overnight lyophilization; [b]NMR spectra indicated >90% of cyclic product **7** after purification and overnight lyophilization. [c]Crude purity of **6** + **7** estimated from LC traces at 205-450 nm. NA = Not Applicable and NI = Not Isolated (see the text).

<u>Scope and limitation</u>:

The NMR spectra and LC/MS data were used to evaluate the effects of the linker and the R groups on the transformation and to establish the scope and limitation of the benzothiadiazepine synthesis. In addition to the cyclization rate, we analysed the crude reaction products to determine the presence of side-products. During the *N*-alkylation of compound **3** by bromoketones in the presence of DIEA, the presence of the Nos group is known to cause intramolecular *C*-arylation followed by the formation of indazole oxide (Scheme 53). Base-mediated *C*-arylation and exploitation of this carbon-carbon bond formation for the synthesis of 2*H*-indazole-1-oxides via *C*-aryl intermediates have already been reported.[33] We analysed all crude reaction products by LC/MS and found that the derivatives with strongly electron-withdrawing CF$_3$ groups underwent partial *C*-arylation; in addition to the main products **4**, the *C*-aryl derivatives **9** and indazole oxide **10** were also present. As a result of the presence of the *C*-arylated compound, after reduction of the nitro group, *C*-aryl **9** was converted to the indole derivative **11**. The indazole oxide **10**, also present on the resin, was reduced to indazole **12** (for the yield of the individual side-products, see the experimental section). In addition, nitro reduction of compound **4**(*9,1,3*) afforded dealkylated product **13**(*9,1*) (16%, LC traces at 205–250 nm) and the indole derivative **11**(*9,1,3*) (32%, LC traces at 205–450 nm). No linear **6**(*9,1,3*) or cyclic **7**(*9,1,3*) compounds were observed.

We also evaluated the effects of the carboxy terminal functional groups of acids, amides, and esters. In the case of α-amino acids attached to the Wang resin, the indole-side products **11** were detected in the preparations, except for the Ala-derived compound. To confirm the structures, four indoles **11** and one indazole **12**(*1,3,1*) were isolated and fully characterized.

To address the effect of the amides, the Ala-derived, resin-bound acyclic intermediate was synthesized on a Rink amide resin. We observed substantial dealkylation during nitro reduction of compound **4**(*8,1,1*), and the dealkylated substance **13**(*8,1*) was isolated as a main

product (45%, LC traces at 205–450 nm). We also detected the formation of indole **11**(*8,1,1*); however, the target amide **7**(*8,1,1*) was only obtained in a minute amount.

Substitutions on the two aromatic rings (R groups) did not have a remarkable effect; notably, only the electron donating OMe group in the R^2 position accelerated cyclization of the compound synthesized on the Wang linker. However, NMR monitoring revealed significant effects of the ethanolamine linker (amino acids 2-aminoethyl esters). The acyclic compounds **6**(*9*,R^2,R^3) were present at a substantially higher ratio, and their conversion was significantly slower than those of other substances. In addition, cyclic products **7**(*9*,R^2,R^3) underwent spontaneous O-N shifts after HPLC repurification in MeCN–ammonium acetate aqueous buffer.

To show that the benzothiadiazepine synthesis was also compatible with a general primary amino group, we also performed the synthesis on polymer-supported *β*-Ala-OH. As expected, there was no difference compared with α-amino acids, and the final product **7**(*7,1,1*) was isolated.

Scheme 53. Side-product formation during the alkylation and reduction steps.[a]
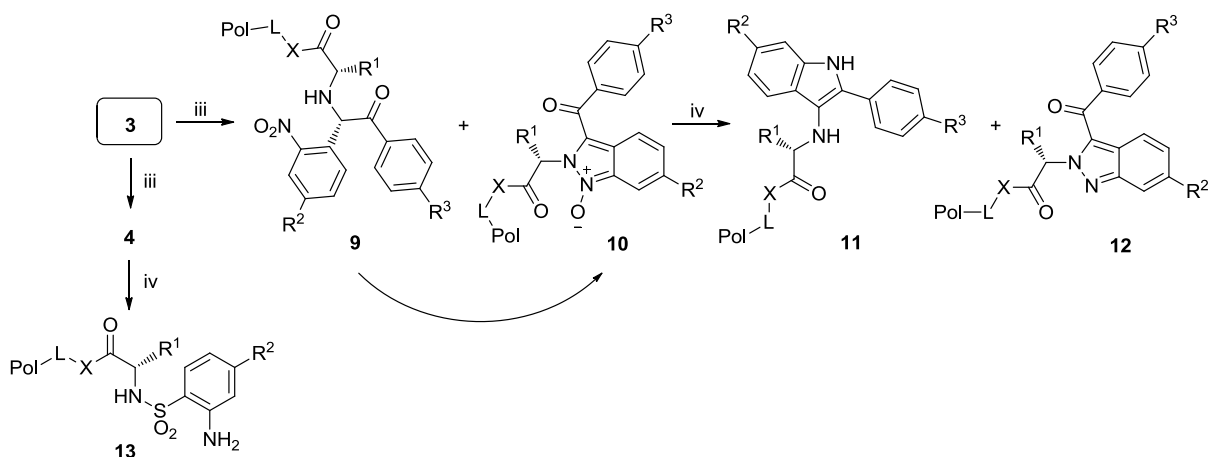
[a]Reagents: (iii) bromoketone, DIEA, DMF, rt, overnight; (iv) $Na_2S_2O_4$, K_2CO_3, TBAHS, 50% H_2O/DCM, rt, overnight.

The compound prepared using Ser(*t*Bu) yielded morpholine derivatives. The *tert*-butyl group of **4**(*3,1,1*) was cleaved using a TFA-based cleavage cocktail, and the morpholine derivative **14** was formed (Scheme 54). After nitro reduction and subsequent cleavage from the resin, the benzodiazepine ring **7**(*3,1,1*) was not formed, but morpholine **15** was isolated in 43% yield.

Scheme 54. Morpholine derivative formation during acidic cleavage.[a]
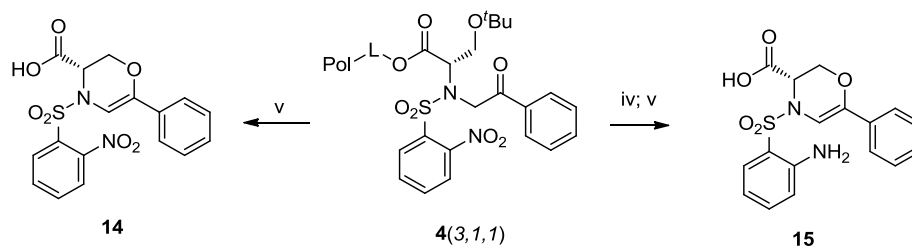
[a]Reagents: (iv) Na$_2$S$_2$O$_4$, K$_2$CO$_3$, TBAHS, 50% H$_2$O/DCM, rt, overnight; (v) 50% TFA in DCM, rt, 60 min.

4.4 Ring contraction of 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxides: Access to 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides

Based on the publication: Fülöpová, V.; Krchňáková, A.; Schütznerová, E.; Zajíček, J.; Krchňák, V. *J. Org. Chem.* 2015**,** *80* (3), 1795-1801.[6]

During the previuos research we observed that some of prepared benzo[*f*][1,2,5]thiadiazepine 1,1-dioxides **III** (Figure 13, subchapter 4.3.1) were not stable and they were converted to 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides.[121-125] This subchapter describes the conversion leading to discover of unanticipated rearrangement involving carbon-sulfur bond formation under mild reaction conditions.

Brief description of investigation:

Compounds **1** (Scheme 55) were prepared according to previously described synthetic pathway (Scheme 52, subchapter 4.3.2), then cleaved from the resin with TFA in DCM and purified by reverse-phase HPLC. We evaluated the stability of target compounds **3** at room temperature and at -20 °C in DMSO, which is typically used for high-throughput screening. Whereas no significant instability was observed at the lower temperature, a new compound was formed at room temperature. This transformed product exhibited an MS ionization pattern identical with that of benzothiadiazepine dioxide **3** and was eluted with a shorter retention time during LC/MS analysis. To obtain a preparative quantity of the new compound for a structure determination, the DMSO solution was exposed to elevated temperature (70 °C) to accelerate the transformation. Almost quantitative conversion was observed.

The new compound was isolated and purified. Its structure was determined as benzothiazine 1,1-dioxide **4** (Scheme 55). Because of the pharmacological relevance of benzothiazine 1,1-dioxides **4** and the unprecedented and clean rearrangement of benzothiadiazepine 1,1-dioxides **3** to **4**, we prepared a set of model compounds **1** and focused on the scope and limitations of this interesting and synthetically useful ring contraction. Model compounds **1** were prepared using six amino acids (Ala (*1*), Phe (*2*), Glu (*3*), Val (*4*), Leu (*5*), Gly (*6*)) attached to Wang resin either directly or via an ethanolamine linker. We also used several types of NosCls and bromoketones with R^2 and R^3 groups containing neutral (H), electron-donating (OCH_3), and electron-withdrawing (CF_3) substituents (see Table 8 for synthesized compounds).

Scheme 55. Synthesis of benzothiazine 1,1-dioxides **4**.[a]
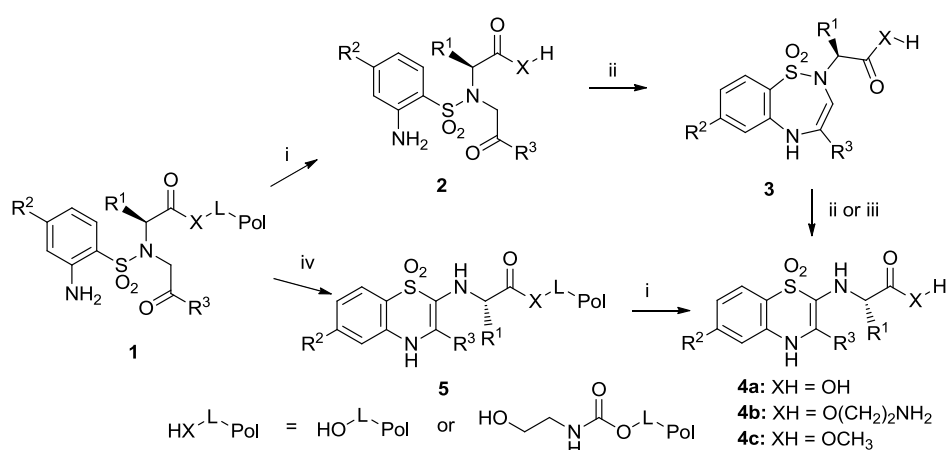
[a]Reagents: (i) 50% TFA in DCM, rt, 1 h.; (ii) DMSO-d_6, rt, see Supplementary information for the reaction time; (iii) DMSO, 70 °C, see Supplementary information for the reaction time; (iv) 5% AcOH, DMSO, 80 °C, overnight.

Scope and limitations:

We assessed the effects of R groups and linkers on the ring contraction rate. Diagnostic peak in the ^{1}H-NMR spectra of compounds **2**, **3** and **4** allowed straightforward monitoring of the reaction (Figures 19 and 20). The type of amino acid, linker, and R^2 substituent did not significantly affect the rate of rearrangement (Table 6). In contrast, we observed a significant effect of the R^3 substituent. Whereas an electron-donating methoxy group at R^3 accelerated the reaction, a strongly electron-withdrawing CF_3 group gave no product **4**(*1,1,3*). The time course of rearrangement at room temperature for selected compounds is tabulated in the Supplementary information.

Figure 19. ^{1}H-NMR spectrum of a mixture of **2b**(*1,1,2*), **3b**(*1,1,2*) and **4b**(*1,1,2*).
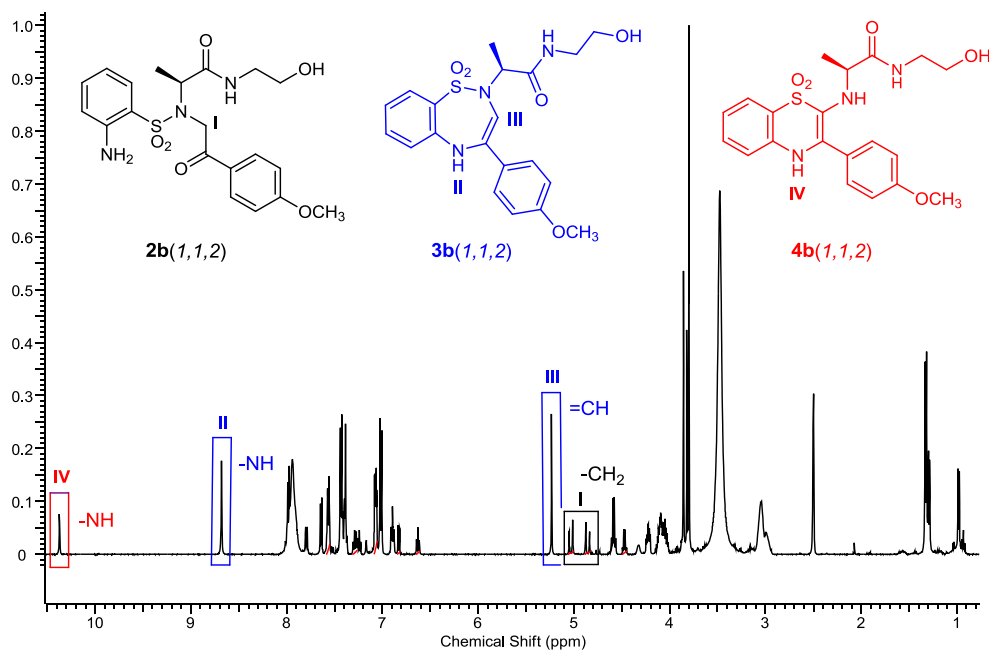
Figure 20. Expansion of the ^{1}H-NMR aliphatic region: methoxy protons of a mixture of **2b**(*1,1,2*), **3b**(*1,1,2*) and **4b**(*1,1,2*).

Experiment	Days	[a]**2b**(*1,1,2*) (%)	[a]**3b**(*1,1,2*) (%)	[a]**4b**(*1,1,2*) (%)
1.	Start	85	10	5
2.	2.3	52	38	10
3.	4.3	31	47	22
4.	5.3	24	49	27
5.	22.3	9	9	82
6.	41.3	8	4	88
7.	54.3	0	1	99
8.	57.3	0	0	100

[a]Ratio **2b/3b/4b** was calculated from NMR spectra.

Table 6. Effect of substituents on the formation of **4**.

Cmpd	Amino acid	R^2	R^3	**4** (%)[a]
4a(*1,1,1*)	Ala	H	H	10

66

4a(*1,1,2*)	Ala	H	OMe	56
4a(*1,1,3*)	Ala	H	CF$_3$	0
4a(*1,2,1*)	Ala	OMe	H	9
4a(*1,3,1*)	Ala	CF$_3$	H	20
4a(*2,1,1*)	Phe	H	H	42
4b(*1,1,1*)	Ala	H	H	54
4b(*1,1,2*)	Ala	H	OMe	82

[a]Calculated from ^{1}H-NMR spectra after ~23 days at room temperature.

The experiments in solution provided important information concerning the rate and mechanism of the ring contraction. Nevertheless, from the preparative point of view, we wished to carry out the contraction on resin as the last step of the synthesis, thereby allowing isolation of the final compounds by cleavage from the polymer support. We evaluated several different reaction conditions and observed that 5% AcOH in DMSO at 80 °C overnight cleanly provided the expected products (Table 7). Synthesized compounds are listed in Table 8.

Table 7. Reaction conditions for ring contraction of compound **1**(*1,1,1*) on resin.

Solvent	Additive	T (°C)	SM (%)[a]	Thiazine (%)[a]
DMSO	5% H$_2$O	80	50	50
DMSO	5% AcOH	80	3	97
DMF	5% H$_2$O	80	99	<1
DMF	5% AcOH	80	90	10
DMSO	5% AcOH	70	92	8
DMSO	none	70	99	<1

[a]Relative ratio SM/Thiazine was calculated from LC traces at 205-450 nm.

Table 8. Synthesized benzothiadiazine 1,1-dioxides **4**.

| Cmpd	R^1	R^2	R^3	Method[a]	Reaction time(h)[a]	Purity (%)[b]	Yield (%)[c]
4a(*1,1,1*)	Me	H	Ph	B	16	65	41
4a(*1,1,4*)	Me	H	4-ClPh	B	16	40	25
4a(*1,1,5*)	Me	H	4-NH$_2$-3,5-di-ClPh	B	16	30	19
4b(*1,1,2*)	Me	H	4-OMePh	A	3.3	88	33
4b(*2,1,1*)	Bn	H	Ph	B	16	77	41
4b(*3,1,1*)	(CH$_2$)$_2$COOH	H	Ph	B	16	81	55
4b(*4,1,1*)	^{i}Pr	H	Ph	B	16	65	35
4b(*5,1,1*)	CH$_2$CH(CH$_3$)$_2$	H	Ph	B	16	83	49
4b(*6,1,1*)	H	H	Ph	B	16	59	15
4c(*1,1,5*)	Me	H	4-NH$_2$-3,5-di-ClPh	B	16	21	12

[a]Method: (A) ring contraction in DMSO at 70 °C; (B) ring contraction on resin at 80°C. [b]Crude purity estimated from LC traces at 205-450 nm. [c]Yield of six-step synthesis calculated from the NMR spectra.

Structure determination:

The structure of **4** was unambiguously determined by analysis of 2D homonuclear (DQFCOSY and TOCSY) and heteronuclear (^{13}C/^{15}N HSQC and HMBC) NMR spectra. Proton connectivities were established from the DQFCOSY and TOCSY spectra. Resonances of carbon and nitrogen atoms with attached protons were assigned using ^{13}C and ^{15}N HSQC spectra, respectively. The ^{13}C HMBC spectrum was then used to assign the signals of quaternary carbons and (together with the ^{15}N HMBC spectrum) to verify the connectivities inferred from the other spectra. In the ^{13}C-HMBC spectrum, the 7a proton signal (δ 10.37 ppm) exhibited cross-peaks with the carbon signals at δ 114.72, 117.82, 123.06, 125.54, 136.82, and 141.03 ppm corresponding to C-5, CH-8, C-12, C-14, C-7, and C-6, respectively (Figure 21). The carbonyl C-3 signal (δ 172.75 ppm) exhibited cross-peaks with the methyl CH$_3$-13, methylene CH$_2$-2, methine CH-4, and amide NH-5a proton signals. Additionally, the NH-5a proton signal displayed a cross-peak with the C-6 carbon signal as well as the CH-15 and CH-19 proton signals. The ^{15}N HMBC spectrum revealed cross-peaks between the NH$_2$-1a nitrogen signal and the methylene CH$_2$-2 proton signals, the NH-5a nitrogen and the CH$_3$-20 protons, and the NH-7a nitrogen and the CH-8 proton. The complete ^{1}H, ^{13}C, and ^{15}N resonance assignments for **4b**(*1,1,2*) are given in Supplementary information (Table 13).

Figure 21. Numbering of atoms.
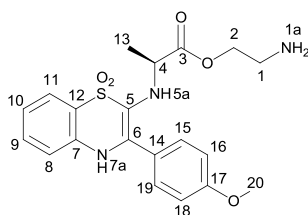
Unlike esters **4b**, ^{1}H-NMR spectra of the free acids **4a** did not show the 5a proton resonance signal. To prove that this signal was absent due to a free acid, we esterified compound **4a**(*1,1,5*) and prepared a methyl ester **4c**. As expected, the ^{1}H-NMR spectra of methyl ester **4c** exhibited this signal.

Mechanism of rearrangement:

Compounds **3** were purified by reverse phase HPLC using 0.1% aqueous TFA and MeCN. After purification the solution was lyophilized, and it contained residual traces of TFA. We initially observed spontaneous rearrangement of HPLC-purified benzothiadiazepine 1,1-dioxides **3** in DMSO-d_6 solution at room temperature. The on-resin cyclization experiments confirmed the effect of an acid (Table 7). On the basis of these results, we surmised that the key step of the ring contraction is the attack of sulfur by the alkene electron pair, supported by the beneficial effect of electron-donating R groups (Scheme 56). There are two plausible pathways: ring opening followed by ring closure and direct contraction.

Scheme 56. Proposed mechanisms of 2-(alkylamino)-3-aryl-4*H*-benzo[*b*][1,4]thiazine 1,1-dioxide formation.
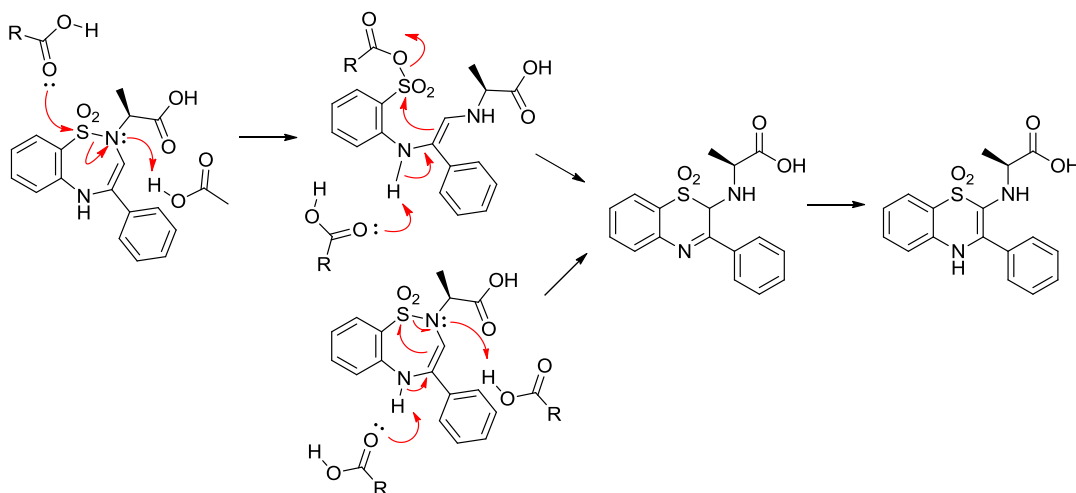
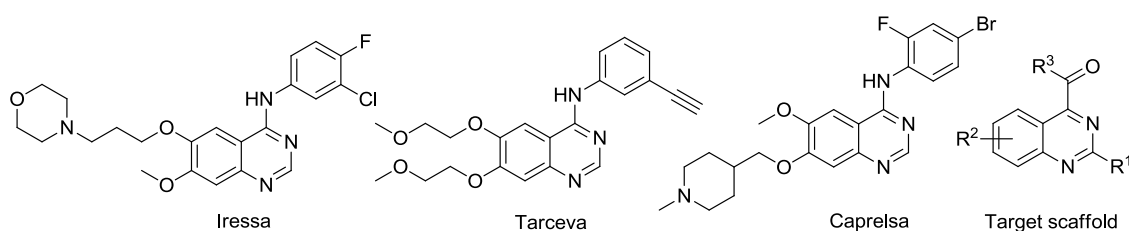## 4.5 Traceless solid-phase synthesis of trisubstituted quinazolines

Based on the publication: Fülöpová, V.; Cziesla, L.; Fleming, M.; Lu, Y.; Voelker, A.; Krchňák, V. *ACS Comb. Sci.* 2015, Article in press.[7]

 This subchapter describes the solid phase synthesis of quinazoline derivatives using scenario B (subchapter 3.3) via *C*-aryl and then *N*-oxide intermediate formation. The acyclic benzenesulfonamide precursor underwent base-catalyzed rearrangement involving carbon-carbon and nitrogen-nitrogen bond formation followed by ring expansion and yielded resin-bound dihydroquinazoline-2-carboxylic acid. Subsequent release from resin with TFA and base-mediated decarboxylation led to the target quinazolines. Final compounds listed in Table 9 have been prepared in the USA during undergraduate student's project under the supervision of author.

4.5.1 Brief introduction into quinazoline motif

 Natural and synthetic quinazolines are particularly important class of biologically active nitrogenous heterocycles with known insecticidal,[126] antibacterial,[127] antiviral[128] and anticancer[129] effects. Quinazoline derivatives are used in the agrochemical, veterinary and pharmaceutical industry. Several commercial antitumor drugs such as Iressa, Tarceva or Caprelsa (Figure 22) are potent tyrosine kinase inhibitors.[130] Quinazolines condensed with different heterocycles were shown to act as antitumor DNA ligands targeting DNA topoisomerase.[131] In this context, development of novel synthetic routes to access pharmacologically relevant quinazolines represents an attractive and practical task. Interestingly, although countless reports described preparation and properties of structurally diverse quinazolines, only a few articles dealt with the synthesis and properties of 4-ketoderivatives (Figure 22, Target scaffold).[132-134]
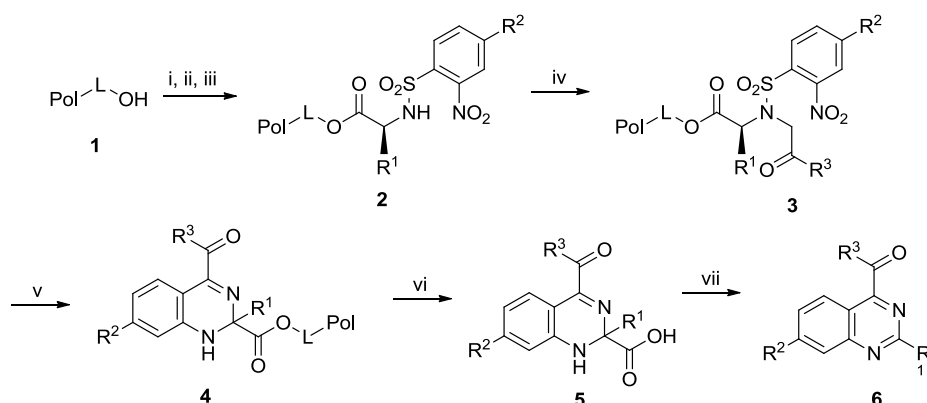
Figure 22. Structure of commercially successful quinazoline drugs.

Iressa Tarceva Caprelsa Target scaffold

4.5.2 Synthesis

Traceless solid-phase synthesis of 4-benzoylquinazolines was carried out according to the Scheme 57 using three types of commercially available building blocks: Fmoc-protected α-amino acids, 2-NosCls and α-bromoacetophenones (for structures and numbering of the building blocks, refer to Figure 23). The first reaction step involved immobilization of Fmoc-α-amino acids on Wang resin **1** via an ester bond. Removal of the Fmoc group provided the polymer-supported amines, which underwent sulfonylation with 2-NosCls to yield resin **2**. In the next step, the activating/protecting 2-Nos group allowed Fukuyama alkylation of the sulfonamide intermediates **2** with diversely substituted α-bromoacetophenones, thereby yielding resins **3** (typically > 65% as indicated by LC traces at 205–450 nm). To complete the conversion, alkylation step was repeated two times with **2**(*1,1*) and three times with **2**(*3,2*) and **2**(*4,1*).

Scheme 57. Synthetic route for preparation of the target 4-benzoylquinazolines.[a]

[a]Reagents: (i) Wang resin, Fmoc-α-amino acid, DMAP, DIC, DCM/DMF (1:1), rt, overnight; (ii) 50% PIP in DMF, rt, 15 min; (iii) 2-NosCl, 2,6-lutidine, DCM, rt, overnight; (iv) α-bromoacetophenone, DIEA, DMF, rt, overnight; (v) DBU, DMF, rt, overnight or 30 min for **3**(*1,1,1*) and **3**(*3,1,2*); (vi) 50% TFA in DCM, rt, 1 h; (vii) neutralization with ammonium acetate, for reaction time see Table 9.

Figure 23. Fmoc-α-amino acids, 2-NosCl and α-bromoacetophenones used for the synthesis.
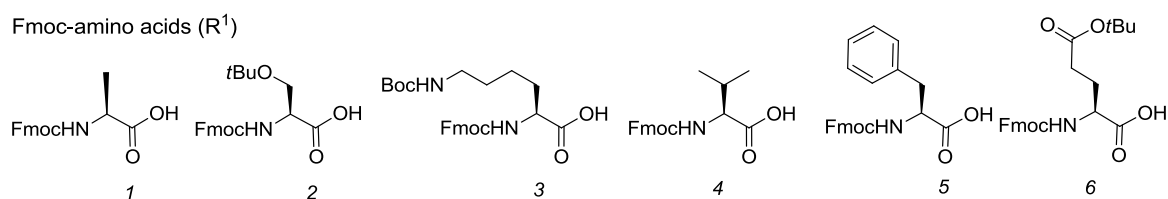
2-Nos-Cl (R^2)

1   2   3   4

Bromoketones (R^3)

1   2   3   4
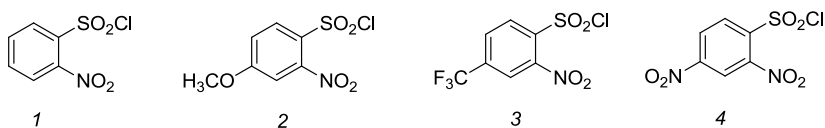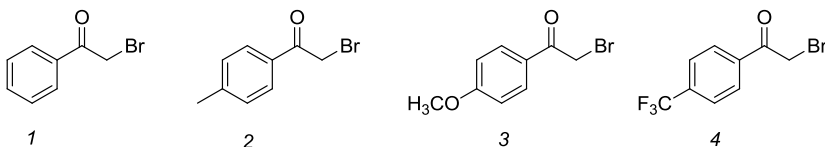
Polymer-supported acyclic alkylated sulfonamides **3** were treated with DBU to trigger base-catalyzed tandem carbon-carbon bond formation followed by cyclization to indazole oxides via nitrogen-nitrogen bond formation[33] and conversion of the indazole oxides to quinazolines **4**.[82] Resin-bound quinazolines were cleaved from the polymer support by a cleavage cocktail of 50% TFA in DCM, yielding carboxylates **5**. To determine the decarboxylation reaction conditions, cleaved crude samples were purified by reversed-phase HPLC in an aqueous ammonium acetate buffer. We observed that the ammonium acetate buffer that neutralized the crude prepa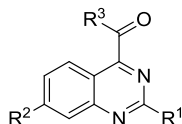rations triggered spontaneous decarboxylation at ambient temperature. The rate of decarboxylation, which was monitored by LC/MS, was dependent on the character of the substituents on the aromatic rings; it slowed, as expected, in the case of electron-withdrawing substituents. In contrast, when the HPLC purification was carried out in aqueous 0.1% TFA, only a trace amount of decarboxylated product was detected by LC/MS analysis. For practical syntheses, the HPLC purification of the crude samples after cleavage from the resin was eliminated and replaced by simple solid-phase extraction (SPE). The crude samples were neutralized with ammonium acetate, adsorbed onto octadecyl-functionalized silica gel and eluted with 80% acetonitrile in aqueous ammonium acetate buffer. Elimination of the C18 cartridge pre-purification step reduced the overall purity of crude compounds. The final products were purified by semi-preparative HPLC in acetonitrile-ammonium acetate aqueous buffer. The decarboxylation times for individual compounds are included in Table 9.

To address the scope and limitation of this route to quinazolines, we prepared resin-bound intermediates **4** using a set of α-amino acids, and 2-NosCls and α-bromoacetophenones containing electron-withdrawing and electron-donating groups (Figure 23). The synthesis was fully compatible with all of the tested building blocks, with the exception of 4-methoxy-2-

NosCl (*2*). The purities of the final crude compounds ranged from 52% to 70%, and the total yields were respectable given the 7-step synthesis (Table 9).

**Table 9.** Synthesized derivatives of quinazolines **6**.

Cmpd	R^1	R^2	R^3	Purity (%)[a]	Decarb. time[b]	Yield (%)[c]
6(*1,1,1*)	Me	H	Ph	52	1 d	12
6(*1,1,2*)	Me	H	4-MePh	53	2 d	56
6(*1,1,3*)	Me	H	4-OMePh	70	1d	16
6(*1,3,1*)	Me	CF_3	Ph	55	4 d	41
6(*1,4,1*)	Me	NO_2	Ph	69	5 d	8
6(*2,1,1*)	CH_2OH	H	Ph	64	1 d	23
6(*3,1,2*)	$(CH_2)_4NH_2$	H	4-MePh	52	1 d	35
6(*4,1,1*)	^{i}Pr	H	Ph	54	1 d	23
6(*4,1,4*)	^{i}Pr	H	4-CF_3Ph	63	5 d	28
6(*5,1,1*)	Bn	H	Ph	51	1 d	24
6(*6,1,1*)	$(CH_2)_2COOH$	H	Ph	59	1 d	38

[a]Purity of the crude product **5**. [b]Decarboxylation time. [c]Yield of HPLC-purified compounds **6** prepared after the 7-step synthesis.

The yields of compounds **6**(*1,1,1*) and **6**(*1,4,1*) were substantially lower compared to those of the other compounds. We analyzed the crude reaction mixture for **6**(*1,4,1*) and isolated the major purity, in addition to the expected product. The crude product mixture contained *N*-oxide derivative **7**(*1,4,1*), which was also isolated and characterized.

Figure 24. Formation of the *N*-oxide side-product **7**(*1,4,1*).

6(*1,4,1*)   **7**(*1,4,1*)
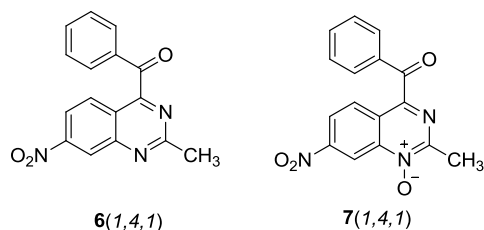
## 4.6 Solid-phase synthesis of Anagrelide sulfonyl analogues

Based on publication: McMaster, C.; Fülöpová, V.; Popa, I.; Grepl, M.; Soural, M. *ACS Comb. Sci.* 2014, *16*, (5), 221-224.[8]

In the last contribution, we paid attention to development of the synthesis leading to Anagrelide sulfonyl analogues. For this purpose, the scenario C (subchapter 3.4) excluding the Fukuyama alkylation was utilized. Designed methodology was successful and used for the solid-phase synthesis of chemical library involving twenty 1,2,4-benzothiadiazine-1,1-dioxide scaffolds.[8] In this context, we were also interested in the modification of the target structure based on the ring expansion or introduction of substituent in N^1-position.

4.6.1 Brief introduction into Anagrelide motif

Anagrelide (Figure 25), commercially known as Agrylin or Xagrid,[135] is being widely used for the treatment of essential thrombocytosis,[136,137] overproduction of blood platelets or chronic myeloid leukemia.[138] On the other hand, biological properties of its sulfonyl analogues have never been reported. With respect to the single published article dealing with the synthesis of the Anagrelide sulfonyl analogues,[139] we have been motivated to develop a novel solid-support methodology for the preparation of desired compounds.

Figure 25. General structures of target compound and Anagrelide.

Target scaffold   Anagrelide
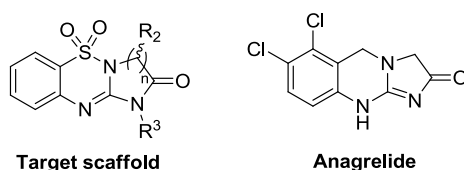
4.6.2 Synthesis

We have developed a general synthetic approach displayed in Scheme 58. The first two steps are based on a traditional solid-phase peptide synthesis using Wang resin and Fmoc-amino acid. After immobilization of Fmoc-α-Ala, the protecting Fmoc group was cleaved with piperidine. The intermediate **2** was reacted with 2-NosCl and subsequently the nitro group of sulfonamide **3** was reduced using the sodium dithionite method. Reaction of **4** with Fmoc-NCS gave the corresponding Fmoc-thiourea **5** which after treatment with DIC, furnished intermediate **6** in excellent crude purity (96%, calculated from LC traces at 200-500

nm). Cleavage of the Fmoc protecting group was followed by spontaneous intramolecular aminolysis of ester bond and the target product **7** was released from the polymer support by a cyclative cleavage. Separation of the product from fluorenylmethylpiperidine by-product **8** formed after Fmoc protecting group removal was easily accomplished by reverse phase semipreparative HPLC. The model compound **7** was obtained in a very good overall yield of 45%. This methodology was successfully used for the split-and-split[140] solid-phase synthesis of chemical library involving twenty 3,10-Dihydro-2*H*-benzo[*e*]imidazo[1,2-*b*][1,2,4]thiadiazin-2-one 5,5-dioxide derivatives.[8]

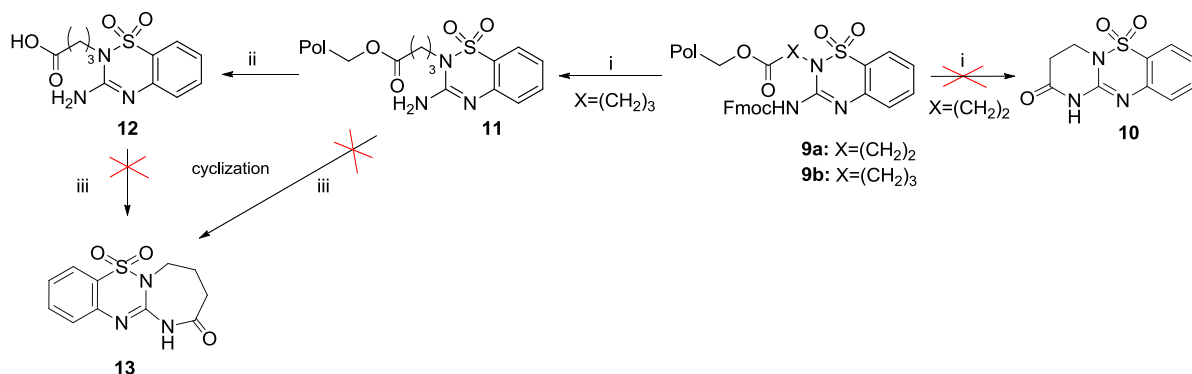**Scheme 58.** Synthetic pathway leading to target compounds.*a*
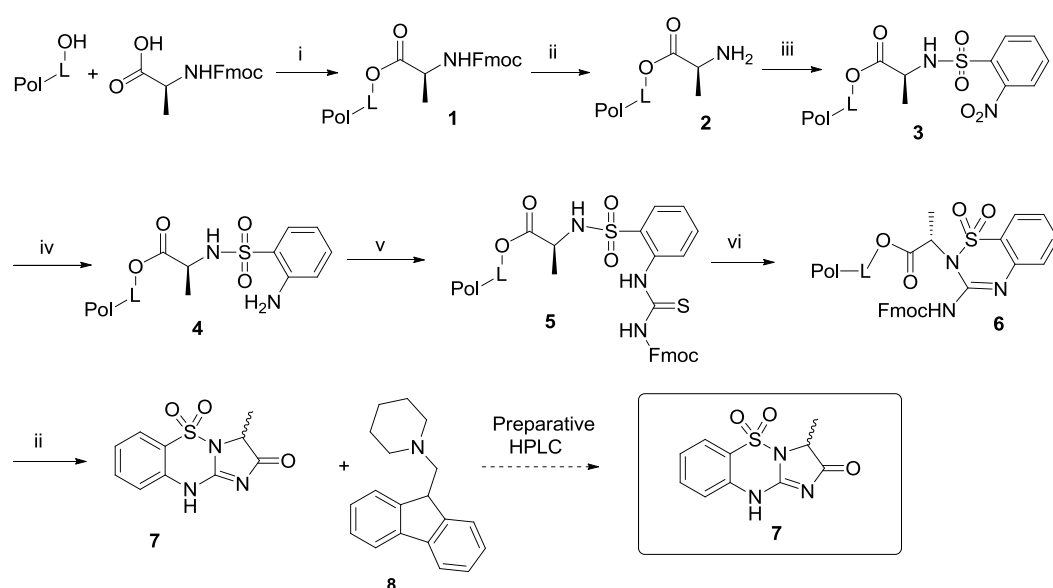
*a*Reagents and conditions: (i) DIC, HOBt, DMAP, DCM, DMF, rt, overnight; (ii) 50% PIP in DMF, rt, 30 min; (iii) 2-NosCl, 2,6-lutidine, DCM, rt, overnight; (iv) Na$_2$S$_2$O$_4$, K$_2$CO$_3$, TBAHS, H$_2$O, rt, 2 h; (v) Fmoc-NCS, THF, rt, overnight; (vi) DIC, DMF, rt, overnight.

To expand this area, we tested the developed synthetic pathway for the preparation of benzothiadiazine dioxide derivatives with expanded imidazole ring (Scheme 59). For this purpose, the Fmoc-*β*-Ala-OH and Fmoc-GABA-OH were immobilized on the Wang resin. Following the Scheme 59, the intermediates **9a** (80%, LC traces at 200-500 nm) and **9b** (95% LC traces at 200-500 nm) were prepared according to procedure described above. In the case of compound **9a**, the Fmoc-deprotection resulted in the cleavage of final compounds from the polymer support. Unexpectedly, LC/MS analysis of the reaction solution showed only 10% of product **10** and mixture of unknown compounds. Fmoc cleavage of GABA intermediate **9b** led to the deprotected compound **11** that was subsequently submitted to cyclization

experiments (Table 10). However, none of the attempts provided the desired product **13**. For the cyclization in solution, the intermediate **11** was released from the resin by the cleavage cocktail consisting of TFA and DCM (1:1).

Scheme 59. Unsuccessful expansion of the developed synthetic pathway.[a]

[a]Reagents and conditions: (i) 50% PIP in DMF, rt, 30 min; (ii) 50% TFA in DCM, rt, 30 min; (iii) see Table 10 for reaction conditions.

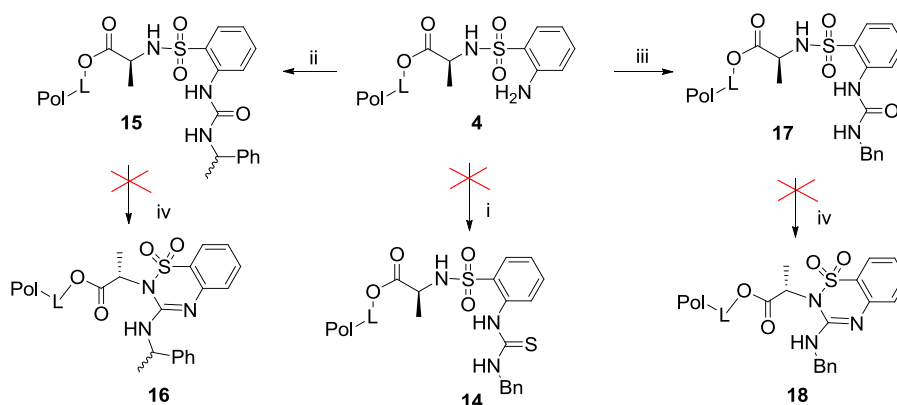**Table 10.** Cyclization experiment with intermediates **11** and **12**.

SM	Solvent	Temperature (ºC)	MW	Reaction time	SM/13 (%)[a]	Purity (%)[b]
11	DMSO	100	-	on	100/0	95
11	DMSO	120	✓	10 min	100/0	95
11	DMSO	120	✓	45 min	100/0	50
11	Diglyme	120	✓	10 min	100/0	55
12	DMSO	100	-	on	98/2	95
12	DMSO	120	✓	10 min	100/0	85
12	DMSO	120	✓	45 min	100/0	85

[a]Ratio **SM/13** calculated from LC traces at 200-500 nm. [b]Crude purity of **SM** + **13** calculated from LC traces at 200-500 nm.

In addition, we investigated a possible use of the developed reaction sequence for the preparation of N^1-substituted derivatives of compounds **7**. For this purpose, Fmoc-NCS was replaced with benzyl-NCS, benzyl-NCO or α-methylbenzyl-NCO (Scheme 60). Surprisingly, the reaction of **4** with benzyl-NCS did not take place, even at elevated temperature. Reaction with α–methylbenzyl-NCO led to 30% of compound **15** (LC traces at 200-500 nm). However, the subsequent cyclization with DIC did not afford the desired product **16**. Benzyl-NCO provided the intermediate **17** in excellent purity (95%, LC traces at 200-500 nm) but

unfortunately, the following cyclization with DIC was not successful and only the starting material was recovered. When the resin **17** was heated to reflux in toluene, the compound was partially decomposed to give a mixture of unknown compounds. Optimization experiments are displayed in the Tables 11 and 12.

Scheme 60. Attempt to increase diversity of target compounds – N^1 substitution.

[a]Reagents and conditions: (i) Bn-NCS; (ii) α-MeBn-NCO; (iii) Bn-NCO, (iv) cyclization with DIC; see Table 11 and 12 for more details.

Table 11. Optimization attempts for reaction with Bn-NCS, α-MeBn-NCO and Bn-NCO.

Agent	Solvent	Temperature (ºC)	React. time	**SM/P** (%)[a]	Purity (%)[b]
0.2 M Bn-NCS	THF	rt	on	**4/14** (100/0)	85
0.2 M Bn-NCS	DMF	rt	on	**4/14** (100/0)	85
0.2 M Bn-NCS	DMF	rt	on	**4/14** (90/10)	80
0.5 M Bn-NCS	Toluene	110	1 h	**4/14** (100/0)	85
0.5 M Bn-NCS	Toluene	110	on	**4/14** (100/0)	30
0.5 M MeBn-NCO	DMSO	rt	on	**4/15** (95/5)	79
0.5 M MeBn-NCO	THF	50	on	**4/15** (100/0)	85
0.5 M MeBn-NCO	Toluene	110	1h	**4/15** (70/30)	90
0.5 M MeBn-NCO	Toluene	110	on	**4/15** (70/30)	90
1.0 M MeBn-NCO	Toluene	110	on	**4/15** (70/30)	90
0.5 M Be-NCO	Toluene	110	1 h	**4/17** (0/100)	95

[a]Ratio **SM/P** calculated from LC traces at 200-500 nm. [b]Crude purity of **SM/P** calculated from LC traces at 200-500 nm.

Table 12. Cyclization experiment with intermediates **15** and **17**.

Cmpd	Agent	Solvent	Temperature (ºC)	React. time	SM/P (%)^a	Purity (%)^b
4/15 (70/30)	0.2 M DIC	DMF	rt	on	**15/16** (100/0)	30
17	0.2 M DIC	DMF	rt	on	**17/18** (100/0)	95
17	0.2 M DIC	DMF	50	on	**17/18** (100/0)	95
17	-	Toluene	112	1 h	**17/18** (100/0)	50

^{a}Ratio **SM/P** calculated from LC traces at 200-500 nm. ^{b}Crude purity of **SM** + **P** calculated from LC traces at 200-500 nm.

5. Conclusion

Polymer-supported nitrobenzenesulfonamides prepared from 2-NosCls and 4-NosCls represent an important class of multifunctional intermediates suitable for many applications leading to less or more complex compounds. Apart from standard or modified Fukuyama alkylation protocol, the Nos group can be introduced into the structures also as a synthon. In such case, different interesting chemical transformations of 2-Nos intermediates have been observed. In this context, we applied a concept of the sulfonamide chemistry for the development of convenient and simple methodologies generating the novel heterocyclic derivatives.

The first part of the research was dedicated to the solid-phase synthesis of benzodiazepine derivatives **A** and **B**. For this purpose, we prepared benzenesulfonamide intermediates serving as precursors for subsequent Fukuyama alkylation with alkyl halides (α-bromoketones or propargyl bromides) followed by the deprotection of protecting/activating Nos group (scenario A, subchapter 3.2). The resulting compounds were then converted to the appropriate heterocyclic products through the acylation with different functionalized benzoic acids and the final cyclization. In the case of benzo[*e*][1,4]diazepin-5-ones, we synthesized a small library of desired compounds; however, some limitations were observed: (i) the developed synthesis seems not to be applicable for bromoketones substituted with only electron withdrawing ligands due to formation of significant side-products, and (ii) derivatives with amino-alkyl chain in position N-R^1 exhibited an unexpected instability and decomposed during the semipreparative HPLC purification. Chemical library of eighteen benzodiazepine derivatives modified by the triazole ring was also prepared. The developed synthetic pathway was not successful for α-amino acids anchored on Wang linker due to formation of numerous by-products. However, according to latest results, it seems that the corresponding benzo-triazolobenzodiazepinones can be prepared from α-Ala-OH if piperazine linker attached on Wang resin is used.

Benzodiazepine sulfonyl analogues **C** were prepared according to similar procedures, but Nos group was kept in the final scaffold as a synthon (scenario B, subchapter 3.3). In this case, we revealed limitation for CF$_3$ derivatives that underwent the substantial *C*-arylation during the alkylation step. Further, the carboxy-terminal functional group of cleaved linear compounds exhibited a significant effect on the cyclization outcome. Whereas the free acids provided the expected products, the amides did not afford desired compounds. In the case of

an ester-type linker, the conversion of the linear intermediates to the target thiadiazepine 1,1-dioxides was remarkably slower. During our investigations of thiadiazepine 1,1-dioxides in DMSO solution at room temperature, we discovered an unanticipated rearrangement yielding benzothiazine 1,1-dioxides **D**. For the preparative purpose, we developed a new method involving on-resin cyclization at elevated temperature.

The second part was focused on the traceless solid-phase synthesis of trisubstituted quinazoline derivatives **E**. The proposed methodology utilized the ability of 2-Nos group to undergo the basic-catalyzed *C*-arylation followed by formation of indazole oxide intermediate (scenario B, subchapter 3.3). For the preparation of benzenesulfonamide precursors, variable-substituted 2-NosCls were used. However, only in the case of 4-NO$_2$-2-NosCl, the yield of product was significantly lower due to formation of the *N*-oxide 4-benzoyl-2-methyl-7-nitroquinoline that was also isolated. Despite this fact, the synthesis was compatible with a range of substituents on all building blocks.

Finally, we developed solid-phase methodology that was used for high-throughput synthesis of Anagrelide sulfonyl analogues **F** with two diversity positions.[8] The Nos group of benzenesulfonamide intermediate was kept in the final scaffold without the prior Fukuyama alkylation (scenario C, subchapter 3.4). The reduction of a nitro group allowed the Fmoc-thiourea formation that was subsequently cyclized by treating with DIC. The final deprotection of Fmoc group afforded the target derivatives. We also tried to apply the developed procedure for further modification of the target scaffold (ring expansion, N^1-substitution), but the desired compounds were not obtained.

In conclusion, despite minor limitations, we have developed high-throughput solid-phase syntheses of various heterocyclic compounds involving six types of different scaffolds (see Structures of prepared compounds). With respect to simplicity of the synthetic protocols and number of available building blocks, the methodologies can be applied for the quick preparation of sizable chemical libraries to access large collections of pharmacologically promising compounds.

Structures of prepared compounds
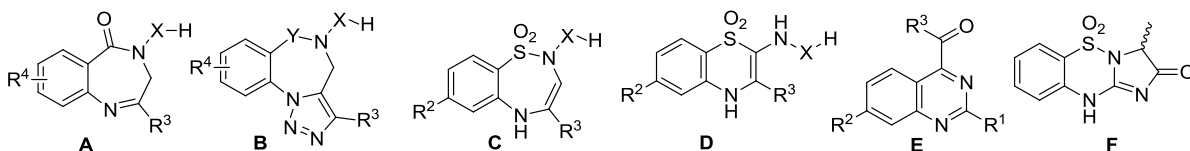
6. Experimental part

6.1 Material and methods

Solvents, chemicals and the polystyrene resins were purchased from Sigma-Aldrich (Milwaukee, IL, www.sigmaaldrich.com), Acros (Geel, Belgium, www. acros.cz), Aaron Chemistry GmbH (Mittenwald, Germany, www.aaron-chemistry.de) and AKos GmbH (Steinen, Germany, www.akosgmbh.de). The Rink amide resin (100-200 mesh, 1% DVB, 0.57, 0.6 and 0.9 mmol/g) the aminomethylene resin (100-200 mesh, 1% DVB, 0.98 mmol/g), Wang resin (100-200 mesh, 1% DVB, 0.52, 0.9 and 1 mmol/g) and 4-(4-Formyl-3-methoxyphenoxy)butyric acid were obtained from AAPPTec (Louisville, KY, www.aapptec.com). Synthesis was carried out on Domino Blocks in disposable polypropylene reaction vessels (Torviq, Niles, MI, www.torviq.com).

All reactions were carried out at ambient temperature (21 ^{o}C) unless stated otherwise. The volume of wash solvent was 10 mL per 1 g of resin. For washing, resin slurry was shaken with the fresh solvent for at least 1 min before changing the solvent. After adding a reagent solution, the resin slurry was manually vigorously shaken to break any potential resin clumps. Resin-bound intermediates were dried by a stream of nitrogen for prolonged storage and/or quantitative analysis.

Characteristic of LC/MS, Department of Organic Chemistry, Palacky University Olomouc: The LC/MS analyses were carried out on UHPLC-MS system consisting of UHPLC chromatograph Accela with photodiode array detector and triple quadrupole mass spectrometer TSQ Quantum Access (both Thermo Scientific, CA, USA), using Nucleodur Gravity C18 column at 30 °C and flow rate of 800 µL/min (Macherey-Nagel, 1.8 µm, 2.1 × 50 mm, Germany). Mobile phase was (A) 0.1% ammonium acetate in water, and (B) 0.1% ammonium acetate in acetonitrile, linearly programmed from 10% to 80% B over 2.5 min, kept for 1.5 min. The column was re-equilibrated with 10% of solution B for 1 min. The APCI source operated at discharge current of 5 µA, vaporizer temperature of 400 °C and capillary temperature of 200 ^{o}C.

Characteristic of LC/MS, Institute of Molecular and Translational Medicine, Olomouc: The LC/MS analyses were carried out on UHPLC-MS system consisting of UHPLC chromatograph Acquity with photodiode array detector and single quadrupole mass

spectrometer (Waters), using X-Select C18 column at 30 °C and flow rate of 600 μL/min. Mobile phase was (A) 0.01 M ammonium acetate in water, and (B) acetonitrile, linearly programmed from 10% to 80% B over 2.5 min, kept for 1.5 min. The column was re-equilibrated with 10% of solution B for 1 min. The ESI I source operated at discharge current of 5 μA, vaporizer temperature of 350 °C and capillary temperature of 200 °C. Purification was carried out on C18 reverse phase column 19 × 100 mm, 5 μm particles; gradient was formed from 10 mM aqueous ammonium acetate and acetonitrile, flow rate 15 mL/min.

Characteristic of LC/MS, Department of Chemistry and Biochemistry, University of Notre Dame, USA: The LC/MS analyses were carried out using the instrument, which comprised a 3 × 50 mm C18 reverse phase column, 5 μm particles. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 5% to 80% of B in 10 minutes, flow rate of 0.7 mL/min. The MS electrospray source operated at capillary voltage 3.5 kV and a desolvation temperature 300 °C. Purification was carried out on C18 reverse phase column 20 × 100 mm, 5 μm, gradient was formed from 10 mM aqueous ammonium acetate (or 0.1% TFA) and acetonitrile, flow rate 15 mL/min.

For the LC/MS analysis a sample of resin (~5 mg) was treated by 50% TFA in DCM (0.5 mL), the cleavage cocktail was evaporated by a stream of nitrogen, and cleaved compounds extracted into 1 mL of MeOH (in USA) and 1 mL of 50% MeOH/H_2O (in Olomouc).

Purification was carried out on C18 reverse phase column 19 (or 20) × 100 mm, 5 μm, gradient elution was formed from 10 mM aqueous ammonium acetate (or 0.1% TFA) and acetonitrile, flow rate 15 (or 20) mL/min.

Characteristic of NMR, Farmak a. s., Olomouc: All ^{1}H, ^{13}C NMR and 2D spectra were obtained on a Bruker Avance (300 MHz) instrument. NMR spectra were recorded at ambient temperature (21 °C) in DMSO-d_6 solutions and referenced to the resonance signal of DMSO. Chemical shifts (δ) are reported in ppm and coupling constants J in Hz.

Characteristic of NMR, Institute of Molecular and Translational Medicine, Olomouc: All ^{1}H, ^{13}C NMR and 2D experiments were performed with using Jeol ECX4500SS at magnetic field strengths of 11.749 T corresponding to 1H and 13C resonance frequencies of 500.16 MHz and 125.77 MHz at ambient temperature (25 °C, in DMSO-d_6 or CDCl$_3$). [1]H and ^{13}C spectra

were referenced relative to the signal of TMS. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are reported in Hertz (Hz).

Characteristic of NMR, Department of Chemistry and Biochemistry, University of Notre Dame, USA: All ^{1}H, ^{13}C NMR and 2D were obtained on Bruker Avance (500 MHz or 400 MHz) instruments. Spectra were recorded at ambient temperature (21 ^{o}C) in DMSO-d_6 solutions and referenced to the resonance signal of DMSO at δ = 2.50 ppm (^{1}H spectra) and δ = 39.51 ppm (^{13}C spectra). Chemical shifts, δ, are reported in ppm and coupling constants, J, in Hz.

Acetate salts exhibited singlet at 1.7–1.9 ppm in the ^{1}H NMR spectrum and two resonances at 173 and 23 ppm in ^{13}C spectrum. Trifluoroacetates exhibited typical quarters at 158-159 and 111-119 ppm in the ^{13}C spectrum.

Characteristic of HRMS, Department of Growth Regulators, Centre of the Region Hana for Biotechnological and Agricultural Research, Olomouc: HRMS analyses were measured with Thermo Exactive instrument (Thermo Scientific, USA). The injection was performed by autosampler of HPLC apparatus Accela 1250. The chromatographic preseparation parameters: column Luna C18, 3 μm, 50 × 2mm i.d. column (Phenomenex, USA), mobile phase acetonitrile/water 70/30 with 0.1% of formic acid, flow rate 200 μL/min, the column temperature 30 ^{o}C. High resolution mass spectrometer Exactive based on orbitrap mass analyser was equipped with Heated Electrospray Ionization (HESI). The spectrometer was tuned to obtain maximum response for m/z 75-700. The source parameters were set to the following values: HESI temperature 250°C, spray voltage +3.0kV (positive mode), transfer capillary temperature 300 ^{o}C, sheath gas/aux gas (nitrogen) flow rates 35/10. Sample preparation was obtained using following procedure: The 1 mg of sample was dissolved in 10 mL of a mixture acetonitrile/water 7/3 (1 min sonication) and then 50 μL of this solution and 950 μL of the same solution were added into vial and mixed before injection of 3 μl.

Characteristic of HRMS, Institute of Molecular and Translational Medicine, Olomouc: HRMS analysis was performed using an Orbitrap Elite high-resolution mass spectrometer (Thermo Fischer Scientific, MA, USA) operating at positive full scan mode (120 000 FWMH) in the range of 200–900 m/z. The settings for electrospray ionization were as follows: oven temperature of 300 °C, sheath gas of 8 arb. units and source voltage of 1.5 kV. The acquired data were internally calibrated with diisooctyl phthalate as a standard in methanol (m/z 391.2843). Samples were diluted to a final concentration of 20 μmol/L by 0.1% formic acid in

water and methanol (50:50, v/v). The samples were injected by direct infusion into the mass spectrometer.

The identification of the respective structures was performed with less than 3 ppm difference between experimental and theoretically calculated value.

6.2. Procedures for SPS of trisubstituted benzo[1,4]-diazepin-5-one derivatives

Based on publication: Fülöpová, V.; Gucký, T.; Grepl, M.; Soural, M. *ACS Comb. Sci.* 2012, *14* (12), 651-656.[3]

Immobilization of ethylendiamine: synthesis of linker (*1*)

Wang resin (1 g, 1 mmol/g) was washed 3 × with DCM. The solution of CDI (810 mg, 5 mmol) and pyridine (400 µL, 5 mmol) in DCM (10 mL) was added to the resin. This reaction mixture was shaken for three hours at room temperature. The resin was washed 3 × with DCM and solution of ethylendiamine (335 µL, 5 mmol) in DCM (10 mL) was added. Resin slurry was shaken for three hours and washed 3 × with DCM, MeOH and dried in a stream of nitrogen. Calculated loading was 0.6 mmol/g.

Immobilization of 2-(Fmoc-amino)ethanol: synthesis of linker (*2*)

Wang resin (1 g, 1 mmol/g) was washed 3 × with anhydrous DCM. The solution of trichloroacetonitrile (1.5 mL, 1.5 mmol) in anhydrous DCM (10 mL) was added. Another syringe was charged with solution of DBU (100 µL, 0.65 mmol) in anhydrous DCM (2 mL) and both syringes were connected and put into a freezer for 30 min. Then both solutions were combined and slurry was shaken for an hour at room temperature. Resin was washed 3 × with DCM and anhydrous THF. Subsequently solution of 2-(Fmoc-amino)ethanol (850 mg, 3 mmol) in anhydrous THF (10 mL) was added to the resin, followed by dropwise addition of $BF_3 \cdot Et_2O$ (63 µL, 0.5 mmol). Then the reaction mixture was shaken for 30 min at room temperature, washed 3 × with THF, DCM, MeOH and dried in a stream of nitrogen. Calculated loading was 0.4 mmol/g.

Immobilization of Fmoc-amino acid: synthesis of linkers (*3*) and (*4*)

The Fmoc-amino group of the Rink resin was first deprotected according to procedure described below (Deprotection of Fmoc goup). After this reaction, Wang resin (1 g, 1

mmol/g) and deprotected Rink amide resin (1 g, 0.9 mmol/g) were subsequently washed 3 ×
with DCM. A solution of Fmoc-amino acid (2 mmol), HOBt (306 mg, 2 mmol), DMAP (61
mg, 0.5 mmol, not used for the Rink amide and aminomethylated BAL resins), and DIC (312
μL, 2 mmol) in DMF/DCM (50%, 10 mL) was added to the resin, and the slurry was shaken
at ambient temperature overnight. The resins were washed 3 × in DMF, 3 × in DCM and dried
in a stream of nitrogen. Calculated loadings were: (3) 0.5 mmol/g and (4) 0.37 mmol/g.

Immobilization of primary amines: synthesis of linkers (5) and (6)

a) Acylation with BAL linker: Aminomethylene resin (1 g, 0.98 mmol/g) was washed 3 ×
with DCM, treated with 10% of Et$_3$N in DCM (10 mL) for 10 min at room temperature
and washed 5 × with DCM. The solution of 4-(4-formyl-3-methoxyphenoxy)butyric acid
(524 mg, 1.96 mmol), HOBt (229 mg, 1.96 mmol), and DIC (300 μL, 1.96 mmol) in
DMF/DCM (1:1; 10 ml) was added to the resin. Reaction mixture was shaken overnight
at room temperature. The resin was washed 3 × with DMF and 3 × with DCM. Sample of
resin (~5 mg) was checked for the presence of free amino group by drop of bromophenol
blue (BB) in DCM (0.5 mL).

b) Reaction with primary amines: Aminomethylene resin with BAL linker (1g) was washed
3 × with anhydrous THF and 3 × with anhydrous DMF. A solution of primary amine (5
mmol) of 10% AcOH in anhydrous DMF (10 mL) was added and the slurry was shaken
overnight at room temperature. The next day, reduction agent NaBH(OAc)$_3$ (2,2 g, 10
mmol) was added in three portions during four hours. After the first portion in solution of
5% AcOH and anhydrous DMF (5 mL), the syringe was punctured with a needle under
the plunger allowing escape of hydrogen gas. Other portions were added as a solid
powder. After four hours the resin was washed 5 × with DMF, neutralized with 20%
piperidine in DMF (10 mL) for 10 min, and washed 5 × with DMF and DCM.

c) Resulting BAL resin with immobilized amine was treated with Fmoc-amino acid
according to procedure above (Immobilization of Fmoc-amino acid). Calculated loading
was 0,6 mmol/g for (5) and (6).

Quantification of resin

After immobilization step, the sample of resin (~30 mg) was reacted with Fmoc-OSu (0.2
mmol, 65 mg) in DCM (0.5 mL) for 30 min at room temperature. The resin was washed 5 ×
with DCM and divided into two samples (2 × 10 mg). Both samples were cleaved from the
resin by treating with 50% TFA in DCM (2 × 0.5 mL) for 30 min at ambient temperature. The

cleavage cocktail was evaporated by a stream of nitrogen and oil residue was extracted into 1 mL of MeOH. This sample was diluted four times by MeOH and analyzed by HPLC-UV-MS. The loading of resin was calculated with the use of an external standard (Fmoc-Ala-OH, 0.5 mg/mL). In the case of samples containing the Fmoc group from the immobilized Fmoc-amino compound, the quantification was carried out without reaction with Fmoc-OSu.

Deprotection of Fmoc group: synthesis of resin 1

The solution of 50% piperidine in DMF (10 mL) was added to the Fmoc-protected linkers (*2-6*) (1 g) and the slurry was shaken for 10 min. Then it was washed 5 × with DMF and 3 × with DCM.

Reaction with 4-NosCl

The resin **1** (300 mg) was washed 3 × with DCM and the solution of 4-NosCl (201 mg, 0.9 mmol) and 2,6-lutidine (114 μL, 0.99 mmol) in DCM (3 mL) was added. The resin slurry was shaken overnight at room temperature. The reaction step was repeated in each case except resin **1**(*2*). Finally, the resin was washed 5 × with DCM.

Alkylation with haloketones

Resin **2** (300 mg) was washed 3 × with DMF and solution of haloketone (1.5 mmol) and DIEA (522 μl, 1.5 mmol) in DMF (3 mL) was added. The reaction mixture was shaken overnight at room temperature and then washed 5 × with DMF.

Cleavage of 4-Nos group

To resin **3** (300 mg) solution of 2-mercaptoethanol (126 μL, 1.8 mmol) and DBU (30 μL, 0.6 mmol) in DMF (3 mL) was added and the slurry was shaken for 10 min at room temperature. In the case of **1**(*6*) the reaction time was prolonged from 10 to 60 min. The resin was washed 3 × with DMF and five times with DCM.

Acylation with *o*-nitrobenzoic acids

To resin **4** (300 mg) solution of appropriate acid (0.6 mmol) and DIC (48 μL, 0.3 mmol) in DMF (3 mL) was added. The reaction mixture was shaken overnight at room temperature, washed 3 × with DMF and DCM.

Reduction of nitro group

The solution of tin(II)chloride dihydrate (675 mg, 3 mmol) and DIEA (522 μL, 1.5 mmol) in deoxygenated DMF (3 mL) was added to resin **5**. The reaction mixture was shaken overnight

(3 days for compounds **5**(*3,1,2*), **5**(*3,1,5*) and **5**(*4,1,1*)) at room temperature and washed 5 ×
with DMF. Then the reduction step was repeated once, with the exception of compound
5(*4,1,1*), and the resin was washed 5 × with DMF and 5 × with DCM.

Cleavage and isolation

Resin **6** was treated with TFA/DCM (50%) for 1 h. The TFA solution was collected
and concentrated using a stream of nitrogen. The oily product was dissolved in MeCN
(2.5 mL) and purified by semi-preparative reverse phase HPLC in a mobile phase
consisting of 10 mM ammonium acetate buffer and MeCN. After lyophilization, the
amorphous powder was dissolved in 650 μL of DMSO-d_6 and the NMR spectra were
obtained.

6.2.1 Analytical data

4-(2-hydroxy-ethyl)-2-*p*-tolyl-3,4-dihydro-benzo[*e*][1,4]diazepin-5-one 7(*2,1,1*)
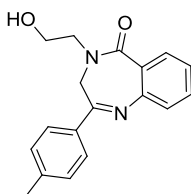
Purity of the crude product 97%; purity of the purified product 99%; 10,6 mg; yield 30%; MS
[M+H]$^+$=295.02; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.40 (s, 3 H) 3.47 (t, *J*=6.15 Hz, 2 H)
3.54 - 3.60 (m, 2 H) 4.27 (br. s., 2 H) 4.81 (br. s., 1 H) 7.31 - 7.41 (m, 4 H) 7.56 - 7.58 (m, 1
H) 7.60 (td, *J*=7.60, 1.40 Hz, 1 H) 7.88 (dd, *J*=8.17, 1.65 Hz, 1 H) 8.08 (d, *J*=8.34 Hz, 2 H);
^{13}C NMR (75 MHz, DMSO-d$_6$) δ ppm 167.1, 166.2, 146.8, 142.3, 133.8, 132.0, 130.7, 130.1,
128.6, 127.7, 127.1, 126.1, 59.5, 50.7, 45.4, 21.6, HRMS (ESI) *m/z* calcd for C$_{18}$H$_{19}$N$_2$O$_2$ [M
+ H]$^+$ 295.1446, found 295.1441.

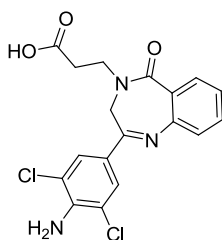**3-(5-oxo-2-*p*-tolyl-3,5-dihydro-benzo[*e*][1,4]diazepin-4-yl)propionic acid 7(*3,1,1*)**
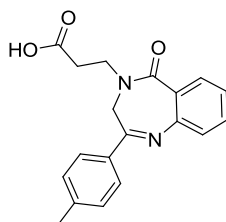
Purity of the crude product 72%; purity of the purified product 99%; MS [M+H]$^+$=322.96; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.34 - 2.47 (m, 5 H) 3.64 - 3.75 (m, 2 H) 4.25 (br. s., 2 H) 7.25 - 7.51 (m, 4 H) 7.55 - 7.66 (m, 1 H) 7.86 (dd, J=8.14, 1.37 Hz, 1 H) 8.12 (d, J=8.42 Hz, 2 H) 12.34; ^{13}C (75 MHz, DMSO-d$_6$) δ ppm 167.0, 166.2, 146.8, 142.4, 133.6, 132.0, 130.7, 130.1, 128.6, 127.6, 127.1, 126.1, 44.8, 44.6, 34.1, 33.4, 21.6, HRMS (ESI) m/z calcd for C$_{19}$H$_{19}$N$_2$O$_3$ [M + H]$^+$ 323.1395, found 323.1390.

3-[2-(4-methoxy-phenyl)-5-oxo-3,5-dihydro-benzo[e][1,4]diazepin-4-yl]propionic acid 7(3,2,1)
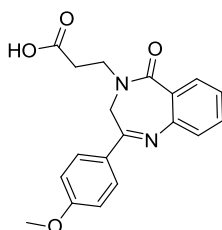
Purity of the crude product 93%; purity of the purified product 99%; MS [M+H]$^+$=339.00; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.42 - 2.48 (m, 2 H) 3.62 - 3.75 (m, 2 H) 3.86 (s, 3 H) 4.24 (br. s., 2 H) 7.11 (d, J=8.97 Hz, 2 H) 7.33 (s, 2 H) 7.59 (t, J=8.80 Hz, 1 H) 7.85 (d, J=6.95 Hz, 1 H) 8.19 (d, J=8.78 Hz, 2 H) 12.33 (br. s., 1 H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ ppm 175.4, 174.3, 166.8, 165.7, 162.7, 147.0, 131.8, 130.7, 130.5, 128.9, 127.8, 127.0, 125.8, 56.0, 45.7, 44.3, 36.6, HRMS (ESI) m/z calcd for C$_{19}$H$_{19}$N$_2$O$_4$ [M + H]$^+$ 339.1344, found 339.1339.

3-[2-(4-amino-3,5-dichloro-phenyl)-5-oxo-3,5-dihydro-benzo[e][1,4]diazepin-4-yl] propionic acid 7(3,3,1)

Purity of the crude product 88%; purity of the purified product 99%; MS [M+H]$^+$=391.91; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.41 - 2.48 (m, 2 H) 3.61 - 3.77 (m, 2 H) 4.19 (br. s., 2 H) 6.34 (s, 2 H) 7.26 - 7.36 (m, 2 H) 7.57 (t, J=7.70 Hz, 1 H) 7.84 (d, J=8.05 Hz, 2 H) 8.12 (s, 2 H) 12.32 (br. s., 1 H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ ppm 174.3, 167.0, 164.0, 146.8,

144.7, 131.9, 130.7, 128.5, 127.7, 127.2, 125.8, 124.8, 118.6, 45.0, 43.9, 35.2, HRMS (ESI) m/z calcd for $C_{18}H_{16}Cl_2N_3O_3$ [M + H]$^+$ 392.0568, found 392.0561.

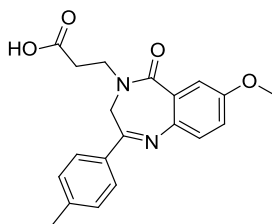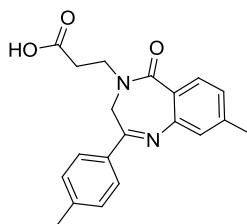**3-(5-oxo-2-thiophen-2-yl-3,5-dihydro-benzo[e][1,4]diazepin-4-yl)propionic acid 7(3,4,1)**
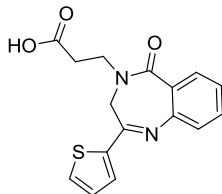
Purity of the crude product 83%; purity of the purified product 99%; MS [M+H]$^+$=314.88; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.37 - 2.43 (m, 2 H) 3.65 (t, J=7.00 Hz, 2 H) 4.15 (br. s., 2 H) 7.23 - 7.30 (m, 2 H) 7.52 (td, J=7.63, 1.57 Hz, 1 H) 7.64 - 7.68 (m, 1 H) 7.69 - 7.72 (m, 1 H) 7.79 (dd, J=7.83, 1.57 Hz, 1 H) 8.58 (dd, J=2.74, 1.17 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ ppm 166.9, 161.9, 146.5, 140.8, 132.0, 131.6, 130.6, 128.6, 127.5, 127.1, 127.0, 126.0, 46.0, 44.6, 40.8, 33.3, HRMS (ESI) m/z calcd for $C_{16}H_{15}N_2O_3S$ [M + H]$^+$ 315.0803, found 315.0799.

3-(8-bromo-5-oxo-2-p-tolyl-3,5-dihydro-benzo[e][1,4]diazepin-4-yl)propionic acid 7(3,1,2)
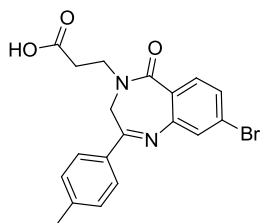
Purity of the crude product 85%; purity of the purified product 99 %; MS [M+H]$^+$= 400.86; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.35 - 2.42 (m, 5 H) 3.70 (t, J=7.04 Hz, 2 H) 4.29 (br. s., 2 H) 7.39 (d, J=8.05 Hz, 2 H) 7.51 (d, J=2.01 Hz, 1 H) 7.55 (s, 1 H) 7.80 (d, J=8.60 Hz, 1 H) 8.12 (d, J=8.23 Hz, 2 H); ^{13}C (75 MHz, DMSO-d$_6$) δ ppm 167.6, 166.3, 156.3, 148.2, 142.9, 133.2, 132.7, 130.2, 129.3, 128.9, 128.8, 126.8, 125.1, 44.8, 44.7, 33.8, 21.6, HRMS (ESI) m/z calcd for $C_{19}H_{20}BrN_2O_3$ [M + H]$^+$ 403.0657, found 403.0476.

3-(7-methoxy-5-oxo-2-p-tolyl-3,5-dihydro-benzo[e][1,4]diazepin-4-yl)propionic   acid 7(3,1,3)
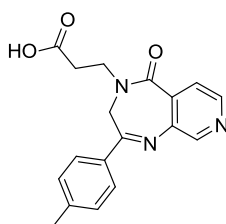
Purity of the crude product 73%; purity of the purified product 99%; MS [M+H]$^+$= 353.08; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.39 (br. s., 3 H) 3.18 (s, 2 H) 3.64 - 3.73 (m, 2 H) 4.26 (br. s., 2 H) 7.26 - 7.40 (m, 3 H) 7.73 (d, J=8.60 Hz, 1 H) 7.86 (d, J=7.68 Hz, 1 H) 8.09 (d, J=8.05 Hz, 2 H); ^{13}C (75 MHz, DMSO-d_6) δ ppm 166.6, 164.4, 157.3, 141.9, 140.7, 133.8, 130.1, 129.8, 129.3, 128.7, 128.6, 128.3, 128.0, 56.0, 44.9, 44.6, 34.4, 21.6, HRMS (ESI) m/z calcd for $C_{20}H_{20}N_2O_4$ [M + H]$^+$ 353.1501, found 353.1496.

3-(8-methyl-5-oxo-2-*p*-tolyl-3,5-dihydro-benzo[*e*][1,4]diazepin-4-yl)propionic acid 7(*3,1,4*)

Purity of the crude product 87%; purity of the purified product 99%; MS [M+H]$^+$= 336.99; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.33 - 2.44 (m, 8 H) 3.61 - 3.72 (m, 2 H) 4.26 (br. s., 2 H) 7.13 - 7.19 (m, 2 H) 7.37 (d, J=8.05 Hz, 2 H) 7.76 (d, J=8.60 Hz, 1 H) 8.10 (d, J=8.23 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 167.0, 165.9, 146.8, 142.3, 142.0, 133.6, 130.7, 130.1, 128.5, 127.3, 127.1, 127.0, 124.9, 44.7, 44.6, 33.9, 21.6, 21.4, HRMS (ESI) m/z calcd for $C_{20}H_{20}N_2O_3$ [M + H]$^+$ 337.1552, found 324.1548.

3-(5-oxo-2-*p*-tolyl-3,5-dihydro-pyrido[3,4-*e*][1,4]diazepin-4-yl)propionic acid 7(*3,1,5*)

Purity of the crude product 76%; purity of the purified product 96%; MS [M+H]$^+$=323.94; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.30 - 2.43 (m, 5 H) 3.65 - 3.75 (m, 2 H) 4.34 (br. s., 2 H)

7.39 (d, J=8.05 Hz, 2 H) 7.76 (d, J=5.12 Hz, 1 H) 8.16 (d, J=8.05 Hz, 2 H) 8.51 (d, J=5.12 Hz, 1 H) 8.66 (s, 1 H); ^{13}C (75 MHz, DMSO-d$_6$) δ ppm 168.8, 165.4, 149.2, 146.5, 142.9, 141.6, 133.3, 133.2, 130.1, 128.7, 123.3, 44.5, 44.4, 40.6, 32.9, 21.5, HRMS (ESI) m/z calcd for C$_{18}$H$_{17}$N$_3$O$_3$ [M + H]$^+$ 324.1348, found 324.1343.

**3-(5-oxo-2-*p*-tolyl-3,5-dihydro-benzo[*e*][1,4]diazepin-4-yl)propionamide 7(*4,1,1*)**
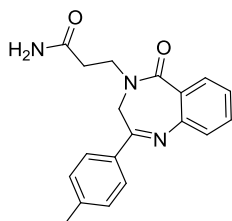
Purity of the crude product 79%; purity of the purified product 82%; MS [M+H]$^+$=321,94; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.33 - 2.43 (m, 5 H) 3.59 - 3.72 (m, 2 H) 4.15 - 4.32 (m, 2 H) 6.91 (br. s., 2 H) 7.33 - 7.43 (m, 4 H) 7.56 - 7.65 (m, 1 H) 7.87 (dd, J=8.05, 1.46 Hz, 1 H) 8.11 (d, J=8.23 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ ppm 172.8, 167.0, 166.2, 146.8, 142.4,133.6, 132.0, 130.7, 130.2, 128.5, 127.6, 127.1, 126.1, 44.8, 44.6, 34.5, 21.6, HRMS (ESI) m/z calcd for C$_{19}$H$_{20}$N$_3$O$_2$ [M + H]$^+$ 322.1555, found 322.1550.

3-(5-oxo-2-*p*-tolyl-3,5-dihydro-benzo[*e*][1,4]diazepin-4-yl)-*N*-propyl-propionamide 7(*5,1,1*)
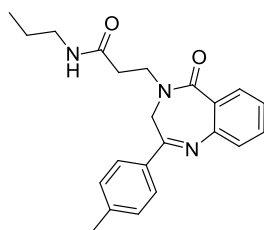
Purity of the crude product 96%; purity of the purified product 99%; MS [M+H]$^+$=364.07; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.81 (t, J=7.32 Hz, 3 H) 1.36 (sxt, J=7.30 Hz, 2 H) 2.33 - 2.43 (m, 5 H) 2.98 (q, J=6.50 Hz, 2 H) 3.62 - 3.77 (m, 2 H) 4.22 (br. s., 2 H) 7.29 - 7.44 (m, 4 H) 7.60 (t, J=7.60 Hz, 1 H) 7.87 (d, J=9.50 Hz, 1 H) 7.92 (br. s., 1 H) 8.10 (d, J=8.23 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ ppm 170.4, 167.0, 166.1, 146.8, 142.4, 133.6, 132.0, 130.7, 130.2, 128.5, 127.6, 127.1, 126.1, 45.0, 44.6, 40.9, 34.9, 22.8, 21.6, 11.9, HRMS (ESI) m/z calcd for C$_{22}$H$_{26}$N$_3$O$_2$ [M + H]$^+$ 364.2025, found 364.2019.

_N_-benzyl-3-(5-oxo-2-_p_-tolyl-3,5-dihydro-benzo[_e_][1,4]diazepin-4-yl)propionamide 7(_6_,_1_,_1_)
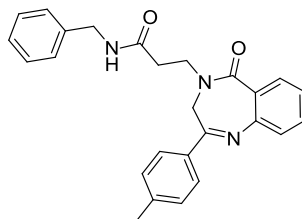
Purity of the crude product 85%; purity of the purified product 99%; MS [M+H]$^{+}$=412,07; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.37 - 2.49 (m, 5 H) 3.68 - 3.81 (m, 2 H) 4.19 (br. s., 1 H) 4.25 (d, _J_=5.85 Hz, 2 H) 7.19 - 7.28 (m, 4 H) 7.32 - 7.42 (m, 5 H) 7.57 - 7.65 (m, 1 H) 7.88 (dd, _J_=8.05, 1.28 Hz, 1 H) 8.09 (d, _J_=8.05 Hz, 2 H) 8.45 (br. s., 1 H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ ppm 170.6, 167.0, 166.0, 146.8, 142.4, 139.9, 133.6, 132.1, 130.7, 130.2, 128.8, 128.5, 127.8, 127.6, 127.3, 127.1, 126.1, 45.0, 44.7, 42.7, 34.8, 21.6, HRMS (ESI) _m/z_ calcd for $C_{26}H_{26}N_3O_2$ [M + H]$^{+}$ 412.2025, found 412.2020.

6.3. Procedures for SPS of trisubstituted benzo[_f_][1,2,3]triazolo[1,5-_a_][1,4]diazepin-6(5_H_)-ones and their sulfonyl analogues under mild reaction conditions

Based on publication: Fülöpová, V.; Funk, P.; Popa, I.; McMaster, C.; Soural, M. _Eur. J. Org. Chem._ 2015, _2015_ (16), 3551-3557.[4]

Preparation of resin-bound amines 1(_1_), 1(_2_), 1(_3_), 1(_4_), 1(_5_), 1(_6_), and 1(_7_)

Starting materials were immobilized on the Wang (0.52 or 0.9 mmol/g), Rink (0.6 mmol/g) and aminomethylene BAL (0.98 mmol/g) linkers according to procedures described in the subchapter 6.2. After quantification of resins, the Fmoc group was deprotected according to procedure reported in subchapter 6.4. Overall yields were calculated according to loadings determined after the first immobilization step: **1**(_1_) 0.43 and 0.51 mmol/g, **1**(_2_) 0.29 mmol/g, **1**(_3_) 0.75 mmol/g, **1**(_4_) 0.23 mmol/g, **1**(_5_) 0.25 mmol/g, **1**(_6_) and **1**(_7_) 0.3 mmol/g.

Reaction with 4-NosCl

Resin **1** (250 mg) was washed 3 × with DCM. A solution of 4-NosCl (166 mg, 0.75 mmol) and 2,6-lutidine (95 μL, 0.75 mmol) in DCM (2.5 mL) was added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 5 × with DCM.

Alkylation with propargyl bromide derivatives

Resin **2** (250 mg) was washed 3 × with DCM and 3x with DMSO. A solution of propargyl bromide derivatives (2.5 mmol) and DBU (250 μL, 1.67 mmol) in DMSO (2.5 mL) was then added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 3 × with DMSO and 3 × with DCM.

Cleavage of 4-Nos group

Resin **3** (250 mg) was washed 3 × with DCM and 3 × with DMF. A solution of 2-mercaptoethanol (126 μL, 1.80 mmol) and DBU (90 μL, 0.60 mmol) in DMF (3 mL) was then added to the resin, and the slurry was shaken at ambient temperature for 30 minutes. The resin was washed 3 × with DMF and 3 × DCM.

Acylation with 2-azidobenzoic acids

Resin **4** (250 mg) was washed 3 × with DCM. A solution of 2-azidobenzoic acid (0.75 mmol), HOBt (103 mg, 0.68 mmol) and DIC (116 μL, 0.75 mmol) in DMF/DCM (2.5 mL) was added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 5 × with DCM.

**Acylation with 2-azidobenzenesulfonyl chloride**

Resin **4** (250 mg) was washed 3 × with DCM. A solution of 2-azidobenzenesulfonyl chloride (273 mg, 1.25 mmol) and 2,6-lutidine (146 μL, 1.25 mmol) in DCM (2.5 mL) was added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 5 × with DCM.

Cleavage and isolation

Cleavage and isolation of resins **7** and **10** was carried out according to procedure described in subchapter 6.2. After lyophilization, the amorphous powder was dissolved in 600 μL of DMSO-d_6 (or CDCl$_3$-d), and the NMR spectra were obtained.
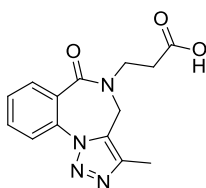
6.3.1 Analytical data

**3-(6-oxo-4***H***-benzo[***f***][1,2,3]triazolo[1,5-***a***][1,4]diazepin-5(6***H***)-yl)propanoic acid 7(*1,1,1*)**
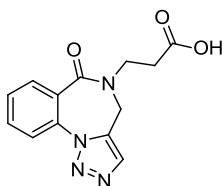
Yield 11.7 mg (32%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.97 (dd, J=8.0, 1.5 Hz, 1 H), 7.91 (s, 1 H), 7.93 (m, 1 H), 7.80 (td, J=7.7, 1.5 Hz, 1 H), 7.64 (td, J=8.0, 1.1 Hz, 1 H), 4.66 (br. s, 2 H), 3.75 (t, J=7.2 Hz, 2 H), 2.53 (t, J=7.2 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.6, 165.4, 136.2, 132.9, 132.2, 132.00, 130.9, 128.9, 127.2, 124.1, 44.5, 32.5, one carbon is hidden in DMSO. HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{12}N_4O_3$ [M+H]$^+$ 273.0982, found 273.0981.

3-(3-methyl-6-oxo-4*H***-benzo[***f***][1,2,3]triazolo[1,5-***a***][1,4]diazepin-5(6***H***)-yl)propanoic acid 7(*1,2,1*)**
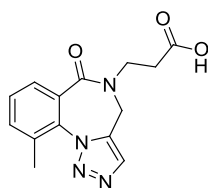

Yield 21.8 mg (64%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.96 (dt, J=7.9, 1.2 Hz, 1 H), 7.86 - 7.90 (m, 1 H), 7.73 - 7.77 (m, 1 H), 7.58 - 7.62 (m, 1 H), 4.60 (br. s., 2 H), 3.77 (t, J=7.1 Hz, 2 H), 2.52 (m, 2 H) 2.40 (s, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.5, 165.5, 138.7, 132.9, 132.7, 132.6, 132.0, 128.6, 127.0, 121.9, 44.4, 39.0, 32.6, 9.6. HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{14}N_4O_3$ [M+H]$^+$ 287.1139, found 287.1136.

3-(6-oxo-3-phenyl-4*H***-benzo[***f***][1,2,3]triazolo[1,5-***a***][1,4]diazepin-5(6***H***)-yl)propanoic acid 7(*1,3,1*)**
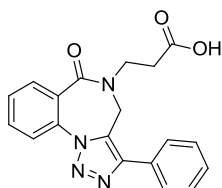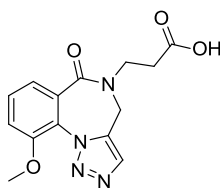
Yield 19.0 mg (52%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.01 (dd, J=8.0, 1.5 Hz, 1 H), 7.98 (dd, J=7.8, 1.2 Hz, 1 H), 7.81 - 7.89 (m, 3 H), 7.67 (td, J=8.0, 1.2 Hz, 1 H), 7.53 - 7.56 (m, 2 H), 7.43 - 7.47 (m, 1 H), 4.89 (br. s., 2 H), 3.71 (t, J=6.9 Hz, 2 H), 2.41 (t, J=6.9 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.7, 165.5, 142.1, 133.0, 132.5, 132.4, 131.9, 129.8, 129.1, 129.1, 128.5, 127.1, 127.0, 122.4, 44.6, 40.1, 32.8. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{16}N_4O_3$ [M+H]$^+$ 349.1295, found 349.1293.

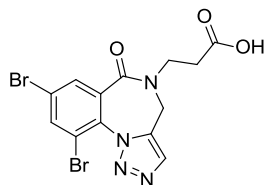**3-(10-methyl-6-oxo-4H-benzo[f][1,2,3]triazolo[1,5-a][1,4]diazepin-5(6H)-yl)propanoic acid 7($1,1,2$)**

Yield 15.3 mg (77%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.91 (s, 1 H), 7.72 (d, J=7.5 Hz, 1 H), 7.67 (d, J=7.5 Hz, 1 H), 7.53 (t, J=7.5 Hz, 1 H), 4.80 (d, J=16.0 Hz, 1 H), 4.39 (d, J=16.0 Hz, 1 H), 3.70 (t, J=7.3 Hz, 2 H), 2.50 (m, 2 H, overlap with DMSO), 2.44 (s, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.6, 165.9, 137.4, 134.9, 132.4, 130.9, 130.0, 129.7, 129.1, 128.9, 44.2, 39.6, 32.4, 19.9. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{14}N_4O_3$ [M+H]$^+$ 287.1139, found 287.1136.

**3-(10-methoxy-6-oxo-4H-benzo[f][1,2,3]triazolo[1,5-a][1,4]diazepin-5(6H)-yl)propanoic acid 7($1,1,3$)**

Yield 27.1 mg (69%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.87 (s, 1 H), 7.57 (t, J=8.0 Hz, 1 H), 7.47 (dd, J=8.5, 1.3 Hz, 1 H), 7.41 (dd, J=8.0, 1.3 Hz, 1 H), 4.83 (d, J=16.0 Hz, 1 H), 4.33 (d, J=16.0 Hz, 1 H), 3.85 (s, 3 H), 3.63 (sxt, J=6.6 Hz, 2 H), 2.23 (q, J=6.6 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.7, 165.6, 152.2, 137.2, 130.8, 130.2, 129.2, 122.3, 121.3, 116.2, 56.8, 44.2, 39.7, 32.5. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{14}N_4O_4$ [M+H]$^+$ 303.1088, found 303.1086.

**3-(8,10-dibromo-6-oxo-4*H*-benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-5(6*H*)-yl)propanoic acid 7(*1,1,4*)**

Yield 38,6 mg (71%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.36 - 8.40 (m, 1 H), 8.00 (d, *J*=2.2 Hz, 1 H), 7.96 (s, 1 H), 4.84 (d, *J*=16.0 Hz, 1 H), 4.59 (d, *J*=16.0 Hz, 1 H), 3.69 (td, *J*=7.1, 3.8 Hz, 2 H), 2.50 - 2.53 (m, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.6, 163.6, 139.4, 137.5, 133.3, 133.0, 130.2, 130.1, 122.5, 118.1, 44.4, 32.4, one carbon is hidden in DMSO. HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{10}Br_2N_4O_3$ [M+H]$^+$ 428.9192, found 428.9194.

3-(8-chloro-6-oxo-4*H*-benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-5(6*H*)-yl)propanoic acid 7(*1,1,5*) – a proof of structure
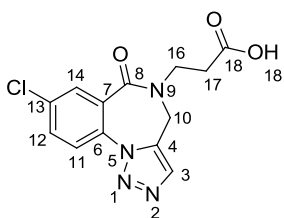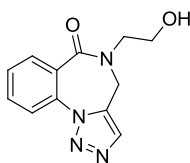

Yield 19.0 mg (58%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.92 (d, *J*=8.6 Hz, 1 H, HC^{11}), 7.90 (d, *J*=2.5 Hz, 1 H, HC^{14}), 7.88 (s, 1 H, HC^3), 7.82 (dd, *J*=8.6, 2.5 Hz, 1 H, HC^{12}), 4.68 (br. s., 2 H, HC^{10}), 3.69 (t, *J*=7.1 Hz, 2 H, HC^{16}), 2.39 (t, *J*=7.1 Hz, 2 H, HC^{17}). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 173.1 (C18), 164.0 (C8), 136.2 (C4), 133.3 (C6), 132.7 (C12), 131.4 (C14), 131.1 (C3), 131.0 (C13), 128.9 (C7), 124.2 (C11), 45.2 (C16), 33.7 (C17), one carbon is hidden in DMSO. ^{15}N-NMR, d_6-DMSO, relatively nitromethan (electronic), at 25 °C, δ (ppm), *J* (Hz): 122.80$^{3.69, s, HC16 (l. int.); 2.39, s, HC17 (h. int.)}$ N9; 246.48$^{7.92, s,}$ $^{HC11 (h. int.); 7.88, s, HC3 (h. int.); 4.68, s, HC10 (l. int.)}$ N5; 353.15$^{7.88, s, HC3 (h. int.)}$ N2; 363.18$^{7.92, s, HC11 (l. int.);}$ $^{7.88, s, HC3 (l. int.)}$ N1, h. int., l. int. – high and low intensity, relatively. HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{11}ClN_4O_3$ [M+H]$^+$ 307.0592, found 307.0595.

**3-(8-nitro-6-oxo-4*H*-benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-5(6*H*)-yl)propanoic acid 7(*1,1,6*)**
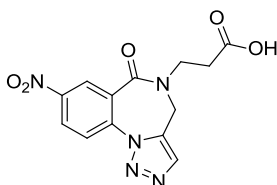
Yield 16.5 mg (42%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.69 (d, J=2.8 Hz, 1 H), 8.56 (d, J=8.9, 2.8 Hz, 1 H), 8.21 (d, J=8.9 Hz, 1 H), 7.97 (s, 1 H), 4.78 (s, 2 H), 3.75 (t, J=7.1 Hz, 2 H), 2.42 (t, J=7.1 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.6, 163.8, 146.7, 136.6, 136.4, 131.5, 128.1, 127.6, 127.4, 124.0, 44.8, 32.3, one carbon is hidden in DMSO. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{11}N_5O_5$ [M+H]$^{+}$ 318.0833, found 318.0832.

**5-(2-hydroxyethyl)-4H-benzo[f][1,2,3]triazolo[1,5-a][1,4]diazepin-6(5H)-one 7(2,1,1)**

Yield 8.9 mg (44%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.98 (dd, J=8.0, 1.5 Hz, 1 H), 7.94 (dd, J=7.8, 1.1 Hz, 1 H), 7.90 (s, 1 H), 7.80 (td, J=7.8, 1.5 Hz, 1 H), 7.65 (td, J=8.0, 1.1 Hz, 1 H), 4.80 (t, J=5.2 Hz, 1H), 4.66 (br. s, 2 H), 3.62 (t, J=5.8 Hz, 2 H), 3.55 (t, J=5.8 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 165.4, 136.1, 132.8, 132.2, 132.1, 130.9, 128.8, 127.4, 122.1, 58.7, 50.6, 40.0. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{12}N_4O_2$ [M+H]$^{+}$ 245.1033, found 245.1033.

**5-(2-aminoethyl)-4H-benzo[f][1,2,3]triazolo[1,5-a][1,4]diazepin-6(5H)-one 7(3,1,1)**
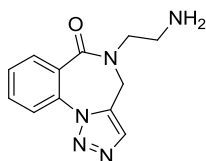
Yield 18.5 mg (36%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.98 (dd, J=8.0, 1.5 Hz, 1 H), 7.94 (dd, J=7.8, 1.1 Hz, 1 H), 7.91 (s, 1 H), 7.79 (td, J=7.8, 1.5 Hz, 1 H), 7.64 (td, J=8.0, 1.1 Hz, 1 H), 4.69 (br. s, 2 H), 3.69 (t, J=7.2 Hz, 2 H), 2.89 (t, J=7.2 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.8, 165.8, 136.1, 132.9, 132.2, 130.8, 128.8, 127.3, 122.1, 49.5, 38.8, one carbon is hidden in DMSO. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{13}N_5O$ [M+H]$^{+}$ 244.1193, found 244.1195.

**3-(6-oxo-4*H*-benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-5(6*H*)-yl)propanamide 7(*4,1,1*)**
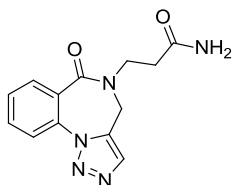
Yield 12.7 mg (68%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.97 (dd, J=8.1, 1.5 Hz, 1 H), 7.93 (dd, J=7.7, 1.2 Hz, 1 H), 7.90 (s, 1 H), 7.79 (td, J=7.7, 1.5 Hz, 1 H), 7.64 (td, J=8.1, 1.2 Hz, 1 H), 7.36 (br. s., 1 H), 6.89 (br. s., 1 H), 4.66 (br. s, 2 H), 3.74 (t, J=7.1 Hz, 2 H), 2.37 (t, J=7.1 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.2, 165.3, 136.1, 132.9, 132.1, 131.9, 131.0, 128.9, 127.3, 122.1, 45.1, 33.6, one carbon is hidden in DMSO. HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{13}N_5O_2$ [M+H]$^+$ 272.1142, found 272.1145.

**3-(6-oxo-4*H*-benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-5(6*H*)-yl)-*N*-propylpropanamide 7(*5,1,1*)**
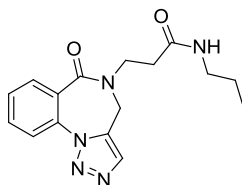
Yield 19.6 mg (70%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.95 - 7.98 (m, 1 H), 7.91 - 7.95 (m, 1 H), 7.89 (s, 1 H), 7.85 (t, J=5.4 Hz, 1 H), 7.79 (t, J=7.7 Hz, 1 H), 7.61 - 7.67 (m, 1 H), 4.64 (br. s., 2 H), 3.75 (t, J=6.9 Hz, 2 H), 2.98 (q, J=6.5 Hz, 2 H), 2.38 (t, J=6.9 Hz, 2 H), 1.37 (sxt, J=7.2 Hz, 2 H), 0.81 (t, J=7.2 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 169.7, 165.3, 136.1, 132.9, 132.1, 131.9, 130.9, 128.9, 127.2, 122.1, 45.3, 40.3, 39.7, 33.9, 22.3, 11.4. HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{19}N_5O_2$ [M+H]$^+$ 314.1612, found 314.1615.

***N*-benzyl-3-(6-oxo-4*H*-benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-5(6*H*)-yl)propanamide 7(*6,1,1*)**
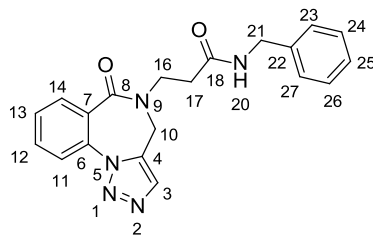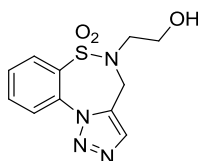
Yield 15.5 mg (53%) of amorphous solid. ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 7.99 (dd, J=8.0, 1.0 Hz, 1 H), 7.95 (dd, J=7.4, 1.2 Hz, 1 H), 7.80 (s, 1 H), 7.71 (td, J=8.0, 1.2 Hz, 1 H), 7.55 (td, J=7.4, 1.0 Hz, 1 H), 7.19 - 7.32 (m, 5 H, overlap with chloroform), 6.90 (br. s., 1 H), 4.86 (br. s., 2 H, H$_b$C^{21}), 4.62 (br. s., 2 H), 4.41 (br. s., 2 H, H$_a$C^{21}), 3.95 (t, J=5.8 Hz, 2 H), 2.65 (t, J=5.8 Hz, 2 H), a and b are proton conformational isomers of the group HC^{21}. ^{13}C NMR (126 MHz, CHLOROFORM-d) δ = 170.9, 166.6, 137.5, 135.3, 133.0, 132.6, 132.0, 130.8, 129.1, 128.7, 127.8, 127.6, 126.9, 122.6, 46.2, 43.9, 41.5, 35.0. HRMS (ESI-TOF) m/z calcd for C$_{20}$H$_{19}$N$_5$O$_2$ [M+H]$^+$ 362.1612, found 362.1615.

3-(6,6-dioxidobenzo[*f*][1,2,3]triazolo[5,1-*d*][1,2,5]thiadiazepin-5(4*H*)-yl)propanoic acid 10(*1,1,7*)
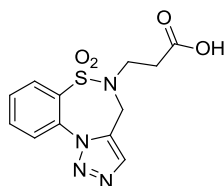
Yield 37.0 mg (71%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.13 (dd, J=8.0, 1.1 Hz, 1 H), 8.01 (dd, J=7.8, 1.5 Hz, 1 H), 7.93 - 7.97 (m, 2 H), 7.77 (td, J=7.8, 1.1 Hz, 1 H), 4.61 - 4.63 (m, 2 H), 3.42 (t, J=7.3 Hz, 2 H), 2.58 (t, J=7.3 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.2, 134.9, 134.1, 133.4, 132.8, 131.2, 129.8, 127.5, 125.2, 47.0, 41.3, 32.6. HRMS (ESI-TOF) m/z calcd for C$_{12}$H$_{12}$N$_4$O$_4$S [M+H]$^+$ 309.0652, found 309.0654.

5-(2-hydroxyethyl)-4,5-dihydrobenzo[f][1,2,3]triazolo[5,1-d][1,2,5]thiadiazepine 6,6-dioxide 10(*2,1,7*)

Yield 8.8 mg (60%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.13 (dd, J=8.0, 1.4 Hz, 1 H), 7.92 - 7.99 (m, 3 H), 7.75 (td, J=7.8, 1.4 Hz, 1 H), 4.89 (t, J=5.3 Hz, 1 H), 4.67 (d, J=0.6 Hz, 2 H), 3.56 (q, J=5.6 Hz, 2 H), 3.26 (t, J=5.6 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 134.7, 133.9, 133.8, 132.8, 131.7, 129.6, 127.4, 125.0, 59.0, 52.8, 41.8. HRMS (ESI-TOF) m/z calcd for $C_{11}H_{12}N_4O_3S$ [M+H]$^{+}$ 281.0703, found 281.0702.

5-(2-aminoethyl)-4,5-dihydrobenzo[*f*][1,2,3]triazolo[5,1-*d*][1,2,5]thiadiazepine 6,6-dioxide 10(*3,1,7*)

Yield 19.7 mg (38%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.14 (dd, J=8.0, 1.4 Hz, 1 H), 7.98 - 8.00 (m, 1 H), 7.93 - 7.97 (m, 2 H), 7.76 (td, J=7.8, 1.4 Hz, 1 H), 4.66 (d, J=0.6 Hz, 2 H), 3.17 (t, J=6.6 Hz, 2 H), 2.74 (t, J=6.6 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 134.8, 133.9, 133.8, 132.8, 131.5, 129.7, 127.5, 125.1, 53.1, 41.5, one carbon is hidden in DMSO. HRMS (ESI-TOF) m/z calcd for $C_{11}H_{13}N_5O_2S$ [M+H]$^{+}$ 280.0863, found 280.0862.

3-(6,6-dioxidobenzo[*f*][1,2,3]triazolo[5,1-*d*][1,2,5]thiadiazepin-5(4*H*)-yl)propanamide 10(*4,1,7*)
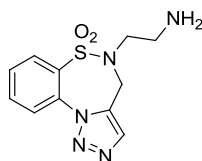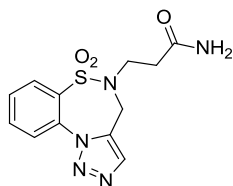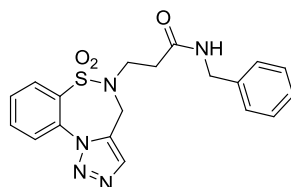

Yield 16.7 mg (77%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.13 (dd, J=8.0, 1.4 Hz, 1 H), 8.01 (dd, J=7.7, 1.2 Hz, 1 H), 7.94 - 7.98 (m, 2 H), 7.77 (td, J=7.7, 1.4 Hz, 1 H), 7.42 (br. s., 1 H), 6.92 (br. s., 1 H), 4.59 - 4.63 (m, 2 H), 3.39 (t, J=7.2 Hz, 2 H), 2.41 (t, J=7.2 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 171.6, 134.9, 134.0, 133.5, 132.8, 131.2, 129.8, 127.5, 125.1, 47.5, 41.4, 33.8. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{13}N_5O_3S$ [M+H]$^{+}$ 308.0812, found 308.0811.

***N*-benzyl-3-(6,6-dioxidobenzo[*f*][1,2,3]triazolo[5,1-*d*][1,2,5]thiadiazepin-5(4*H*)-yl) propanamide 10(*6,1,7*)**

Yield 27.0 mg (62%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.47 (t, J=5.9 Hz, 1 H), 8.12 (dd, J=8.0, 1.2 Hz, 1 H), 8.00 (dd, J=7.7, 1.5 Hz, 1 H), 7.95 (td, J=8.0, 1.5 Hz, 1 H), 7.91 (s, 1 H), 7.76 (td, J=7.7, 1.2 Hz, 1 H), 7.20 - 7.31 (m, 5 H), 4.60 (d, J=0.4 Hz, 2 H), 4.25 (d, J=5.9 Hz, 2 H), 3.44 (t, J=7.1 Hz, 2 H), 2.49 - 2.52 (m, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 169.5, 139.2, 134.9, 134.0, 133.5, 132.8, 131.3, 129.8, 128.3, 127.5, 127.2, 126.8, 125.1, 47.7, 42.1, 41.4, 34.1. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{19}N_5O_3S$ [M+H]$^{+}$ 398.1281, found 398.1283.

6.4 Procedures for SPS of trisubstituted 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide derivatives

Based on publication: Fülöpová, V.; Krchňák, V. *ACS Comb. Sci.* 2014, *16* (8), 412-420.[5]

Immobilization of ethanolamine linker: synthesis of 1(*9*)

Wang resin (1 g, 1 mmol/g) was washed 3 × with DCM. A solution of CDI (800 mg, 5 mmol) and pyridine (400 μL, 5 mmol) in DCM (10 mL) was added to the resin, and the slurry was shaken at ambient temperature for 2 h. The resin was washed 3 × with DCM, and a solution of ethanolamine (300 μL, 5 mmol) in DCM (10 mL) was then added to the resin. The slurry was shaken at ambient temperature for 3 h, and then washed 5 × with DCM and dried in a stream of nitrogen. Calculated loading was 0.43 mmol/g.

Immobilization of Fmoc-amino acids: synthesis of 1(*1-6*), 1(*7*), and 1(*8*)

Wang (1 g, 1 mmol/g) or Rink amide (1 g, 0.57 mmol/g) resins were treated with Fmoc-amino acid solution according to procedure described in subchapter 6.2. Calculated loadings were: **1**(*1-6*) 0.51 mmol/g, **1**(*7*) 0.52 mmol/g and **1**(*8*) 0.25 mmol/g.

Deprotection of Fmoc group

Resin **1** (1 g) was washed 3 × with DMF. A solution of piperidine in DMF (50%, 10 mL) was then added to the resin, and the slurry was shaken at ambient temperature for 30 min. The resin was washed 3 × with DMF and 3 × with DCM.

Reaction with NosCl

Resin **2** (1 g) was washed 3 × with DCM. A solution of NosCl (3 mmol) and 2,6-lutidine (381 µL, 3 mmol) in DCM (10 mL) was added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 5 × with DCM.

Reaction with bromoacetophenone

Resin **3** (250 mg) was washed 3 × with DMF. A solution of bromoacetophenone (0.5 mmol) and DIEA (218 µL, 0.5 mmol) in DMF (2.5 mL) was then added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 3 × with DMF and 3 × with DCM.

Reduction of a nitro group

Resin **4** (250 mg) was washed 3 × with DCM. A solution of $Na_2S_2O_4$ (525 mg, 3 mmol), K_2CO_3 (480 mg, 3.5 mmol), and TBAHS (85 mg, 0.25 mmol) in H_2O/DCM (50%, 5 mL) was then added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 3 × with H_2O/DCM (50%), 3 × with MeOH/DCM (50%), and 3 × with DCM.

Cleavage and isolation

Resins **5** (250 mg, resins **5**(*5,1,1*), **5**(*6,1,1*), **5**(*7,1,1*), **5**(*9,1,1*), 500 mg) were treated with TFA/DCM (50%) for 1 h. The TFA solution was collected and concentrated using a stream of nitrogen. The oily product was dissolved in MeOH (2.5 mL) and purified by semi-preparative reverse phase HPLC in a MeCN–0.1% aqueous TFA mobile phase. After lyophilization, the amorphous powder was dissolved in 750 µL of DMSO-d_6, and the NMR spectra were obtained. Compounds that contained the acyclic precursor were cyclized in the DMSO solution at room temperature till they spontaneously cyclized (for the cyclization times, see Table 5). Cyclized compounds were purified in MeCN–10 mM ammonium acetate buffer.

6.4.1 Analytical data

2-aminoethyl 2-(2-amino-*N*-(2-(4-methoxyphenyl)-2-oxoethyl)phenylsulfonamido) propanoate 6(*9,1,2*)
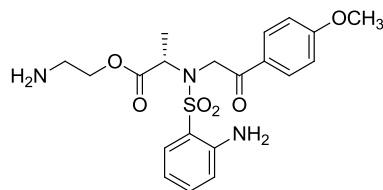
Yield 10.5 mg (37%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.95 - 8.00 (m, 4 H), 7.56 (dd, J=8.1, 1.5 Hz, 1 H), 7.29 (ddd, J=8.3, 7.0, 1.5 Hz, 1 H), 7.05 - 7.09 (m, 2 H), 6.83 (dd, J=8.3, 1.0 Hz, 1 H), 6.63 (ddd, J=8.1, 7.0, 1.0 Hz, 1 H), 5.03 (d, J=19.0 Hz, 1 H), 4.86 (d, J=19.0 Hz, 1 H), 4.47 (q, J=7.2 Hz, 1 H), 4.01 - 4.13 (m, 2 H), 3.86 (s, 3 H), 3.00 - 3.07 (m, 2 H), 1.29 (d, J=7.2 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 193.1, 170.4, 163.5, 147.1, 134.2, 130.4, 129.9, 127.5, 118.4, 117.3, 115.3, 114.0, 61.2, 55.6, 54.4, 50.0, 37.7, 15.5. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{25}N_3O_6S$ [M+H]$^+$ 436.1537, found 436.1520.

2-(1,1-dioxido-4-phenylbenzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)propanoic acid 7(*1,1,1*)
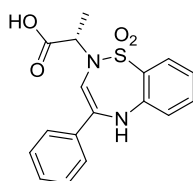

Yield 36.5 mg (74%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.72 (s, 1 H), 7.63 (dd, J=8.0, 1.1 Hz, 1 H), 7.45 - 7.51 (m, 5 H), 7.37 - 7.39 (m, 2 H), 6.87 (ddd, J=8.0, 6.0, 2.2 Hz, 1 H), 5.25 (d, J=0.7 Hz, 1 H), 4.40 (q, J=7.3 Hz, 1 H), 1.26 (d, J=7.3 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 172.1, 141.9, 140.0, 136.2, 133.0, 129.3, 128.5, 127.7, 127.7, 126.5, 120.1, 118.4, 101.7, 56.2, 15.3. LC/MS (ESI) m/z 345.2 [M+H]$^+$ 345.2.

2-(4-(4-methoxyphenyl)-1,1-dioxidobenzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)propanoic acid 7(*1,1,2*)
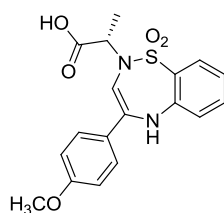
Yield 35.0 mg (66%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.65 (s, 1 H), 7.63 (d, J=8.1 Hz, 1 H), 7.41 - 7.45 (m, 2 H), 7.36 - 7.38 (m, 2 H), 7.00 - 7.03 (m, 2 H), 6.87 (ddd, J=8.1, 4.8, 3.4 Hz, 1 H), 5.20 (d, J=0.4, 1 H), 4.4 (q, J=7.3 Hz, 1 H), 3.79 (s, 3 H), 1.25 (d, J=7.3 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.3, 160.3, 142.1, 140.0, 133.0, 129.6, 129.1, 128.4, 126.7, 120.2, 118.4, 113.9, 100.7, 56.3, 55.4, 15.3. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{18}N_2O_5S$ [M+H]$^+$ 375.1009, found 375.1030.

2-(1,1-dioxido-4-(4-(trifluoromethyl)phenyl)benzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)propanoic acid 7(*1,1,3*)
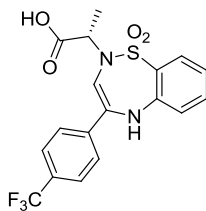
Yield 8.0 mg (19%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.76 (s, 1 H), 7.81 - 7.84 (m, 2 H), 7.71 - 7.74 (m, 2 H), 7.63 (dd, *J*=8.0, 1.6 Hz, 1 H), 7.40 (ddd, *J*=8.4, 7.1, 1.6 Hz, 1 H), 7.32 (dd, *J*=8.4, 0.9 Hz, 1 H), 6.89 (ddd, *J*=8.0, 7.1, 0.9 Hz, 1 H), 5.35 (d, *J*=0.5 Hz, 1 H), 4.42 (q, *J*=7.3 Hz, 1 H), 1.28 (d, *J*=7.3 Hz, 3 H). HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{15}F_3N_2O_4S$ [M+H]$^+$ 413.0777, found 413.0781.

2-(4-(4-amino-3,5-dichlorophenyl)-1,1-dioxidobenzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)propanoic acid 7(*1,1,4*)
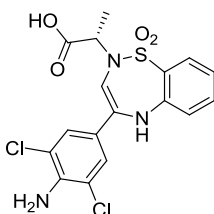
Yield 22.3 mg (46%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.56 (s, 1 H), 7.60 (dd, *J*=8.0, 1.4 Hz, 1 H), 7.36 (ddd, *J*=8.3, 6.9, 1.4 Hz, 1 H), 7.31 - 7.34 (m, 3 H), 6.86 (ddd, *J*=8.0, 6.9, 1.4 Hz, 1 H), 5.85 (s, 2 H), 5.25 (s, 1 H), 4.31 (q, *J*=7.2 Hz, 1 H), 1.21 (d, *J*=7.3 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.3, 142.1, 139.9, 139.8, 132.9, 129.8, 127.1, 126.5, 124.5, 120.1, 118.4, 117.6, 101.5, 56.8, 15.5. HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{16}Cl_2N_2O_4S$ [M+H]$^+$ 428.0233, found 428.0239.

2-(7-methoxy-1,1-dioxido-4-phenylbenzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)propanoic acid 7(*1,2,1*)

Yield 35.2 mg (74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.61 (s, 1 H), 7.54 (d, J=8.9 Hz, 1 H), 7.45 - 7.51 (m, 5 H), 6.97 (d, J=2.4 Hz, 1 H), 6.47 (dd, J=8.9, 2.4 Hz, 1 H), 5.24 (s, 1 H), 4.37 (q, J=7.3 Hz, 1 H), 3.75 (s, 3 H), 1.25 (d, J=7.3 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 172.1, 162.6, 141.5, 141.4, 136.3, 129.2, 128.5, 128.4, 127.6, 122.7, 105.5, 103.8, 101.6, 56.2, 55.3, 15.3. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{18}N_2O_5S$ [M+H]$^+$ 375.1009, found 375.1033.

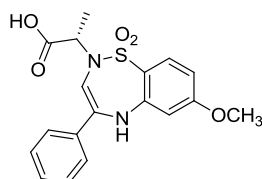## 2-(1,1-dioxido-4-phenyl-7-(trifluoromethyl)benzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl) propanoic acid 7(*1,3,1*)
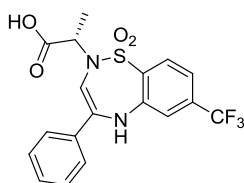
Yield 17.3 mg (20%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 9.03 (s, 1 H), 7.83 (d, J=8.3 Hz, 1 H), 7.80 (s, 1 H), 7.44 - 7.56 (m, 5 H), 7.16 (dd, J=8.3, 1.0 Hz, 1 H), 5.38 (s, 1 H), 4.48 (q, J=7.2 Hz, 1 H), 1.34 (d, J=7.3 Hz, 3 H). HRMS (ESI-TOF) m/z calcd for $C_{18}H_{15}F_3N_2O_4S$ [M+H]$^+$ 413.0777, found 413.0770.

2-(1,1-dioxido-4-phenylbenzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)-3-phenylpropanoic acid 7(*2,1,1*)

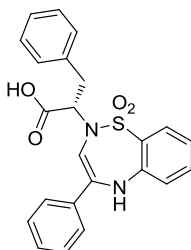Yield 47.3 mg (76%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.33 (s, 1 H), 7.43 - 7.52 (m, 5 H), 7.37 (dd, J=7.9, 1.5 Hz, 1 H), 7.19 (ddd, J=8.6, 7.2, 1.5 Hz, 1 H), 7.06 - 7.11 (m, 3 H), 6.94 - 7.03 (m, 3 H), 6.68 (ddd, J=7.9, 7.2, 1.0 Hz, 1 H), 5.31 (s, 1 H), 4.63 (dd, J=10.4, 5.1 Hz, 1 H), 3.22 (dd, J=14.3, 5.1 Hz, 1 H), 3.01 (dd, J=14.3, 10.4 Hz, 1 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 171.5, 140.1, 139.7, 137.4, 132.4, 129.8, 128.6, 128.5, 127.8, 127.6, 126.1, 125.3, 119.9, 117.6, 102.5, 62.1, 35.9. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{20}N_2O_4S$ [M+H]$^+$ 421.1217, found 421.1231.

2-(1,1-dioxido-4-phenylbenzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)-3-methylbutanoic acid 7(*4,1,1*)
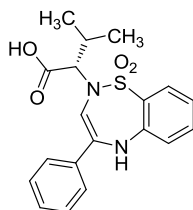
Yield 5.0 mg (13%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.56 (s, 1 H), 7.56 - 7.59 (m, 1 H), 7.42 - 7.48 (m, 5 H), 7.30 - 7.33 (m, 2 H), 6.81 (ddd, *J*=8.0, 5.8, 2.4 Hz, 1 H), 5.44 (s, 1 H), 3.95 (d, *J*=9.3 Hz, 1 H), 2.16 - 2.26 (m, 1 H), 0.90 (d, *J*=6.7 Hz, 3 H), 0.88 (d, *J*=6.7 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 171.3, 140.5, 139.5, 136.5, 132.8, 129.7, 129.1, 128.5, 127.5, 125.8, 119.7, 103.5, 66.4, 28.4, 19.2, 19.2. HRMS (ESI-TOF) *m/z* calcd for C$_{19}$H$_{20}$N$_2$O$_4$S [M+H]$^+$ 373.1217, found 373.1248.

6-amino-2-(1,1-dioxido-4-phenylbenzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)hexanoic acid 7(*5,1,1*)
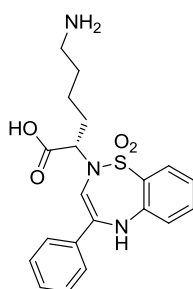
Yield 110.0 mg (71%).^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.64 (s, 1 H), 7.57 - 7.63 (m, 1 H), 7.42 - 7.53 (m, 5 H), 7.32 - 7.37 (m, 2 H), 6.84 (ddd, *J*=8.1, 4.9, 3.3 Hz, 1 H), 5.27 (s, 1 H), 4.33 (dd, *J*=9.9, 5.5 Hz, 1 H), 2.52 - 2.71 (m, 2 H), 1.75 - 1.92 (m, 2 H), 1.46 (quin, *J*=7.5 Hz, 2 H), 1.17 - 1.40 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 173.3, 140.7, 138.9, 136.9, 132.4, 130.8, 128.8, 128.4, 127.3, 125.7, 119.5, 117.6, 104.9, 62.3, 38.3, 30.2, 26.6, 22.9. HRMS (ESI-TOF) *m/z* calcd for C$_{20}$H$_{23}$N$_3$O$_4$S [M+H]$^+$ 402.1482, found 402.1515.

2-(1,1-dioxido-4-phenylbenzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)pentanedioic acid 7(*6,1,1*)
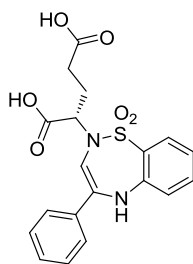
Yield 21.0 mg (24%).^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.48 (s, 1 H), 7.53 - 7.58 (m, 1 H), 7.41 - 7.49 (m, 5 H), 7.28 - 7.32 (m, 2 H), 6.79 (ddd, J=8.0, 4.8, 3.4 Hz, 1 H), 5.55 (s, 1 H), 4.18 (t, J=7.8 Hz, 1 H), 2.16 - 2.26 (m, 1 H), 1.99 - 2.11 (m, 2 H), 1.63 - 1.74 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 174.4, 172.6, 140.5, 139.7, 136.7, 132.6, 130.6, 129.0, 128.5, 127.4, 125.9, 119.7, 117.8, 104.7, 61.6, 32.2, 26.7. HRMS (ESI-TOF) *m/z* calcd for C$_{19}$H$_{18}$N$_2$O$_6$S [M+H]$^+$ 403.0958, found 403.0986.

3-(1,1-dioxido-4-phenylbenzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)propanoic acid 7(*7,1,1*)
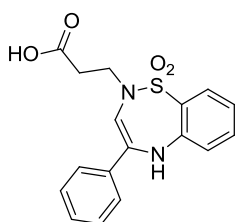
Yield 109.0 mg (77%).^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.84 (s, 1 H), 7.71 (dd, J=8.1, 1.3 Hz, 1 H), 7.50 - 7.54 (m, 2 H), 7.42 - 7.48 (m, 5 H), 6.94 (ddd, J=8.1, 6.4, 1.7 Hz, 1 H), 5.39 (d, J=0.8 Hz, 1 H), 3.29 (t, J=7.0 Hz, 2 H), 2.57 (t, J=7.0 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 172.5, 141.3, 139.5, 136.0, 133.2, 129.4, 128.5, 128.0, 127.9, 127.6, 120.4, 118.8, 105.5, 46.8, 33.0. HRMS (ESI-TOF) *m/z* calcd for C$_{17}$H$_{16}$N$_2$O$_4$S [M+H]$^+$ 345.0904, found 345.0916.

2-(1,1-dioxido-4-phenylbenzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)-*N*-(2-hydroxyethyl) propanamide 7(*9,1,1*)
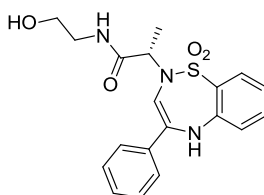
Yield 55.0 mg (75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.72 (s, 1 H), 7.87 (t, J=5.6 Hz, 1 H), 7.63 - 7.67 (m, 1 H), 7.45 - 7.51 (m, 5 H), 7.38 - 7.41 (m, 2 H), 6.89 (ddd, J=8.1, 5.9, 2.3

Hz, 1 H), 5.35 (d, *J*=0.7 Hz, 1 H), 4.25 (q, *J*=7.1 Hz, 1 H), 3.35 - 3.40 (m, 2 H), 3.06 - 3.16 (m, 2 H), 1.17 (d, *J*=7.1 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-*d*₆) δ = 170.1, 141.7, 139.9, 136.3, 133.2, 129.3, 129.1, 128.5, 127.7, 127.0, 120.2, 118.4, 102.5, 59.6, 57.4, 41.5, 15.4. HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{21}N_3O_4S$ [M+H]$^+$ 388.1326, found 388.1346.

2-((2-phenyl-6-(trifluoromethyl)-1*H*-indol-3-yl)amino)propanoic acid 11(*1,3,1*)
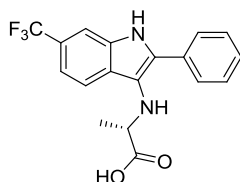
Yield 27.2 mg (37%). ^{1}H NMR (400 MHz, DMSO-*d*₆) δ = 11.50 (s, 1 H), 7.94 - 7.99 (m, 2 H), 7.90 (d, *J*=8.5 Hz, 1 H), 7.58 (s, 1 H), 7.48 - 7.54 (m, 3 H), 7.33 - 7.38 (m, 1 H), 7.24 (d, *J*=8.5 Hz, 1 H), 3.70 (q, *J*=6.9 Hz, 1 H), 1.31 (d, *J*=7.1 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-*d*₆) δ = 175.7, 133.0, 131.9, 128.8, 128.8, 128.1, 127.5, 125.4 (q, *J*=267.7 Hz), 126.4, 121.9 (q, *J*=31.1 Hz), 121.2, 119.7, 114.3 - 114.5 (m), 108.1 - 108.4 (m), 56.3, 18.5. LC/MS (ESI) *m/z* 349.2 [M+H]$^+$ 349.2.

3-((2-phenyl-1*H*-indol-3-yl)amino)propanoic acid 11(*7,1,1*)
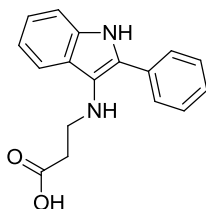
Yield 9.0 mg (8%). ^{1}H NMR (400 MHz, DMSO-*d*₆) δ = 11.61 (br. s., 1 H), 7.79 - 7.83 (m, 2 H), 7.75 (d, *J*=8.0 Hz, 1 H), 7.52 - 7.59 (m, 3 H), 7.40 - 7.48 (m, 2 H), 7.18 - 7.23 (m, 1 H), 7.09 - 7.14 (m, 1 H), 3.47 (t, *J*=6.3 Hz, 2 H), 2.62 (t, *J*=6.6 Hz, 2 H). LC/MS (ESI) *m/z* 281.2 [M+H]$^+$ 281.3

2-((2-phenyl-1*H*-indol-3-yl)amino)propanamide 11(*8,1,1*)
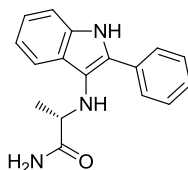
Yield 0.9 mg (3%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 11.22 (br. s., 1 H), 7.88 (m, J=7.5 Hz, 2 H), 7.70 (d, J=8.1 Hz, 1 H), 7.46 - 7.52 (m, 3 H), 7.30 - 7.37 (m, 2 H), 7.08 - 7.12 (m, 1 H), 7.00 (t, J=7.4 Hz, 1 H), 3.74 - 3.79 (m, 1 H), 1.27 (d, J=6.5 Hz, 3 H). LC/MS (ESI) m/z 280.2 [M+H]$^+$ 280.3.

2-aminoethyl 2-((2-(4-(trifluoromethyl)phenyl)-1H-indol-3-yl)amino)propanoate 11(9,1,3)
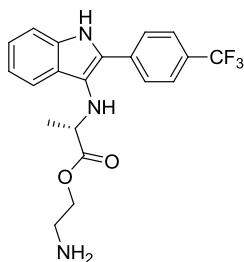
Yield 4.0 mg (10%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.13 (s, 1 H), 8.18 - 8.23 (m, 2 H), 7.93 (s, 1 H), 7.78 - 7.85 (m, 4 H), 7.70 (d, J=8.0 Hz, 1 H), 7.31 (d, J=8.1 Hz, 1 H), 7.09 - 7.14 (m, 1 H), 6.96 - 7.01 (m, 1 H), 3.94 - 4.08 (m, 2 H), 3.68 - 3.76 (m, 1 H), 2.93 - 2.99 (m, 2 H), 1.40 (d, J=7.0 Hz, 3 H). LC/MS (ESI) m/z 392.2 [M+H]$^+$ 392.4.

2-(3-benzoyl-6-(trifluoromethyl)-2H-indazol-2-yl)propanoic acid 12(1,3,1)
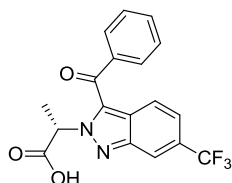
Yield 14.3 mg (19%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.37 (s, 1 H), 7.75 - 7.83 (m, 3 H), 7.60 - 7.67 (m, 2 H), 7.42 (d, J=8.9 Hz, 1 H), 7.12 (d, J=8.9 Hz, 1 H), 6.02 (q, J=7.1 Hz, 1 H), 1.93 (d, J=7.2 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 185.5, 170.8, 144.9, 137.8, 133.7, 132.1, 129.5, 128.9, 126.9 (q, J=31.8 Hz), 124.2 (q, J=272.0 Hz), 123.7, 122.2, 120.1 (m), 117.0 (q, J=4.9), 60.5, 16.8. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{13}F_3N_2O_3$ [M+H]$^+$ 363.0951, found 363.0986.

2-(2-aminophenylsulfonamido)propanamide 13(8,1)
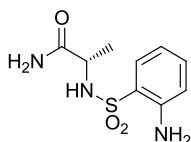
Yield 7.0 mg (26%).^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.73 (d, J=8.2 Hz, 1 H), 7.47 (dd, J=8.0, 1.5 Hz, 1 H), 7.24 (ddd, J=8.3, 7.0, 1.5 Hz, 1 H), 7.20 (br. s., 1 H), 7.02 (br. s., 1 H), 6.77 (dd, J=8.3, 1.0 Hz, 1 H), 6.58 (ddd, J=8.0, 7.0, 1.0 Hz, 1 H), 5.95 (br. s, 2 H), 3.51 - 3.58 (m, 1 H), 1.02 (d, J=7.1 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 173.3, 146.2, 133.5, 129.0, 120.2, 116.8, 114.9, 51.1, 19.0. HRMS (ESI-TOF) m/z calcd for $C_9H_{13}N_3O_3S$ [M+H]$^+$ 244.0750, found 244.0751.

4-((2-aminophenyl)sulfonyl)-6-phenyl-3,4-dihydro-2H-1,4-oxazine-3-carboxylic acid 15(3,1,1)
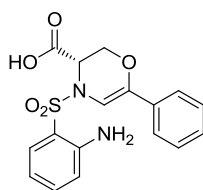
Yield 27.2 mg (43%, acidic purification). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.54 (dd, J=8.2, 1.5 Hz, 1 H), 7.45 - 7.48 (m, 2 H), 7.23 - 7.34 (m, 4 H), 6.81 - 6.84 (m, 2 H), 6.61 (ddd, J=8.2, 7.1, 1.1 Hz, 1 H), 4.96 (dt, J=2.9, 1.5 Hz, 1 H), 4.64 (dd, J=10.9, 1.5 Hz, 1 H), 3.27 (dd, J=10.9, 2.9 Hz, 1 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 168.9, 147.2, 138.7, 134.7, 133.1, 129.5, 128.4, 127.8, 123.2, 117.6, 116.5, 115.6, 101.6, 64.8, 54.6. HRMS (ESI-TOF) m/z calcd for $C_{17}H_{16}N_2O_5S$ [M+H]$^+$ 361.0853, found 361.0858.

6.5 Procedures for SPS of 4H-benzo[b][1,4]thiazine 1,1-dioxides

Based on publication: Fülöpová, V.; Krchňáková, A.; Schütznerová, E.; Zajíček, J.; Krchňák, V. *J. Org. Chem.* 2015, *80* (3), 1795-1801.[6]

Synthesis of Benzothiazine 1,1-dioxide 4

Resin **1** (250 mg) was washed (3 × DCM, 3 × DMSO). Five milliliters of 5% AcOH in DMSO was added, and the resin slurry was shaken in an incubator at 80 °C, overnight. The resin was subsequently washed (5 × DCM).

Cleavage and isolation

Resin **5** was treated with TFA/DCM (50%) for 1 h. The TFA solution was collected and concentrated using a stream of nitrogen. The oily product was dissolved in MeOH (2.5 mL) and purified by semi-preparative reverse phase HPLC in a mobile phase

consisting of 10 mM ammonium acetate buffer and MeCN. After lyophilization, the amorphous powder was dissolved in 750 μL of DMSO-d_6 and the NMR spectra were obtained.

6.5.1 Analytical data

2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)propanoic acid 4a(*1,1,1*)
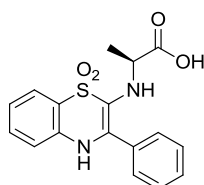
Yield 34.6 mg (41%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.35 (br. s., 1 H), 7.80 (dd, *J*=8.2, 1.2 Hz, 1 H), 7.46 - 7.61 (m, 6 H), 7.41 (dd, *J*=8.5, 0.5 Hz, 1 H), 7.22 (ddd, *J*=8.1, 7.1, 1.0 Hz, 1 H), 3.34 (q, *J*=6.9 Hz, 1 H), 0.85 (d, *J*=6.9 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 175.4, 138.2, 137.2, 133.7, 131.9, 129.4, 129.3, 128.3, 122.4, 122.2, 121.9, 117.7, 116.1, 56.5, 18.5. HRMS (FAB) *m/z* calcd for $C_{17}H_{16}N_2O_4S$ [M+H]$^+$ 345.0904, found 345.0891.

2-((3-(4-chlorophenyl)-1,1-dioxido-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)propanoic acid 4a(*1,1,4*)
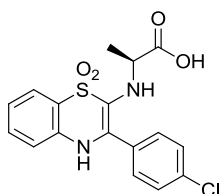
Yield 22.3 mg (25%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.38 (s, 1 H), 7.81 (dd, *J*=8.2, 1.5 Hz, 1 H), 7.62 - 7.67 (m, 2 H), 7.54 - 7.59 (m, 3 H), 7.38 (dd, *J*=8.5, 0.6 Hz, 1 H), 7.25 (ddd, *J*=8.1, 7.1, 1.1 Hz, 1 H), 3.56 (q, *J*=6.9 Hz, 1 H), 0.95 (d, *J*=6.9 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 174.8, 139.3, 136.9, 134.1, 132.2, 132.1, 131.5, 128.3, 123.0, 122.3, 122.2, 117.8, 115.5, 56.4, 18.4. HRMS (FAB) *m/z* calcd for $C_{17}H_{15}ClN_2O_4S$ [M+H]$^+$ 379.0514, found 379.0542.

2-((3-(4-amino-3,5-dichlorophenyl)-1,1-dioxido-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino) propanoic acid 4a(*1,1,5*)
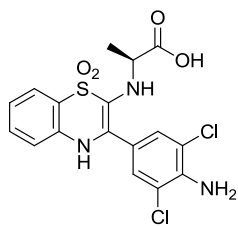
Yield 19.8 mg (19%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ =10.23 (br. s., 1H), 7.77 (dd, *J*=8.2, 1.2 Hz, 1 H), 7.51 - 7.57 (m, 3 H), 7.40 (dd, *J*=8.5, 0.5 Hz, 1 H), 7.21 (ddd, *J*=8.1, 7.1, 1.0 Hz, 1 H), 5.90 (s, 2 H), 3.45 (q, *J*=6.9 Hz, 1 H), 0.94 (d, *J*=6.9 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 175.1, 142.0, 137.0, 136.6, 131.8, 129.1, 122.6, 122.0, 121.9, 121.5, 117.8, 117.2, 115.8, 56.4, 18.5. HRMS (FAB) *m/z* calcd for $C_{17}H_{15}Cl_2N_3O_4S$ [M+H]$^+$ 428.0233, found 428.0218.

2-aminoethyl 2-((3-(4-methoxyphenyl)-1,1-dioxido-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino) propanoate 4b(*1,1,2*)
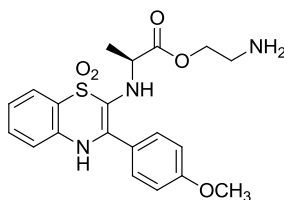
Yield 6.9 mg (33%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.36 (s, 1 H), 7.78 (dd, *J*=8.1, 1.4 Hz, 1 H), 7.52 - 7.58 (m, 3 H), 7.41 (d, *J*=7.9 Hz, 1 H), 7.23 (ddd, *J*=8.1, 7.1, 1.0 Hz, 1 H), 7.03 - 7.08 (m, 2 H), 4.32 (d, *J*=6.4 Hz, 1 H), 3.99 - 4.14 (m, 2 H), 3.81 (s, 3 H), 3.01 - 3.08 (m, 2 H), 0.97 (d, *J*=7.0 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.7, 160.1, 141.0, 136.8, 132.0, 130.9, 125.4, 123.1, 122.3, 122.2, 117.8, 114.7, 113.6, 60.6, 57.5, 55.4, 37.9, 18.2. HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{23}N_3O_5S$ [M+H]$^+$ 418.1431, found 418.1464.

2-aminoethyl 2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)-3-phenyl propanoate 4b(*2,1,1*)
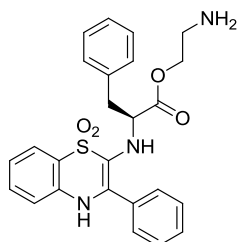
Yield 12.8 mg (41%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-d_6) δ = 10.53 (s, 1 H), 7.81 (d, J=8.2 Hz, 1 H), 7.63 - 7.60 (m, 2 H), 7.60 - 7.56 (m, 1 H), 7.55 - 7.51 (m, 3 H), 7.42 (d, J=8.5 Hz, 1 H), 7.28 - 7.24 (m, 1 H), 7.18 - 7.11 (m, 3 H), 6.81 (d, J=6.7 Hz, 2 H), 4.56 (d, J=8.5 Hz, 1 H), 4.01 (td, J=11.5, 5.5 Hz, 1 H), 3.92 (td, J = 11.5, 5.6 Hz, 1 H), 3.42 - 3.36 (m, 1 H), 2.98 - 2.92 (m, 2 H), 2.68 - 2.63 (m, 1 H), 2.62 - 2.57 (m, 1 H). ^{13}C NMR (151MHz, DMSO-d_6) δ = 171.0, 140.6, 136.9, 136.8, 133.3, 132.2, 129.6, 129.4, 128.9, 128.5, 128.2, 126.5, 123.0, 122.5, 122.3, 117.9, 115.8, 65.0, 60.3, 37.9. HRMS (ESI-TOF) m/z calcd for $C_{25}H_{26}N_3O_4S$ [M+H]$^+$ 464.1639, found 464.1627.

5-(2-aminoethoxy)-4-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)-5-oxopentanoic acid 4b(*3,1,1*)

Yield 19.6 mg (55%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-d_6) δ = 10.48 (s, 1 H), 7.81 (d, J=8.2 Hz, 1 H), 7.60 - 7.54 (m, 3 H), 7.53 - 7.48 (m, 3 H), 7.40 (d, J=8.2 Hz, 1 H), 7.26 (t, J=7.6 Hz, 1 H), 4.40 (d, J=8.2 Hz, 1 H), 4.15 - 4.09 (m, 1 H), 4.05 - 3.99 (m, 1 H), 3.36 - 3.30 (m, 1 H), 3.06 (br. s., 2 H), 1.87 - 1.80 (m, 1 H), 1.73 - 1.66 (m, 1 H), 1.63 - 1.50 (m, 2 H). ^{13}C NMR (151MHz, DMSO-d_6) δ = 174.1, 172.1, 141.9, 136.8, 133.3, 132.3, 129.6, 129.5, 128.4, 123.3, 122.5, 122.3, 117.9, 115.3, 62.6, 60.7, 38.0, 29.2, 28.1. HRMS (ESI-TOF) m/z calcd for $C_{21}H_{24}N_3O_6S$ [M+H]$^+$ 446.1380, found 446.1419.

2-aminoethyl 2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)-3-methyl butanoate 4b(*4,1,1*)
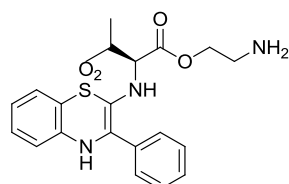
Yield 11.5 mg (35%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-d_6) δ = 10.46 (s, 1 H), 7.80 (d, J=8.2 Hz, 1 H), 7.59 - 7.55 (m, 3 H), 7.54 - 7.48 (m, 3 H), 7.40 (d, J=8.2 Hz, 1 H),

7.25 (t, *J*=7.9 Hz, 1 H), 4.35 (d, *J*=9.1 Hz, 1 H), 4.19 - 4.13 (m, 1 H), 4.09 - 4.02 (m, 1 H), 3.09 (br. s., 2 H), 2.98 (dd, *J*=9.1, 6.5 Hz, 1 H), 1.64 - 1.56 (m, 1 H), 0.49 (d, *J*=6.7 Hz, 3 H), 0.44 (d, *J*=6.7 Hz, 3 H). ^{13}C NMR (151MHz, DMSO-*d6*) δ = 171.8, 141.6, 136.8, 133.5, 132.2, 129.7, 129.5, 128.3, 123.2, 122.4, 122.2, 117.8, 116.0, 69.7, 60.3, 38.1, 31.3, 18.5, 18.2. HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{26}N_3O_4S$ [M+H]$^+$ 416.1639, found 416.1620.

2-aminoethyl 2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)-4-methyl pentanoate 4b(*5,1,1*)
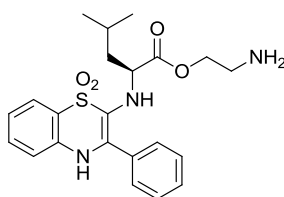
Yield 13.5 mg (39%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-*d₆*) δ = 10.46 (s, 1 H), 7.80 (d, *J*=7.9 Hz, 1 H), 7.61 - 7.55 (m, 3 H), 7.54 - 7.49 (m, 3 H), 7.40 (d, *J*=8.5 Hz, 1 H), 7.25 (t, *J*=7.5 Hz, 1 H), 4.37 (d, *J*=8.8 Hz, 1 H), 4.19 - 4.12 (m, 1 H), 4.10 - 4.02 (m, 1 H), 3.15 - 3.05 (m, 3 H), 1.31 - 1.24 (m, 1 H), 1.17 - 1.07 (m, 1 H), 0.66 (td, *J*=14.4, 7.5 Hz, 1 H), 0.60 - 0.55 (m, 3 H), 0.48 (d, *J*=6.7 Hz, 3 H). ^{13}C NMR (151MHz, DMSO-*d₆*) δ = 171.5, 141.5, 136.8, 133.5, 132.1, 129.6, 129.4, 128.2, 123.2, 122.3, 122.2, 117.8, 116.0, 68.2, 60.3, 38.2, 38.0, 24.7, 14.9, 11.4. HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{28}N_3O_4S$ [M+H]$^+$ 430.1795, found 430.1766.

2-aminoethyl 2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)acetate 4b(*6,1,1*)
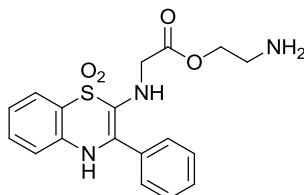
Yield 4.1 mg (15%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-*d₆*) δ = 10.42 (s, 1 H), 7.82 (dd, *J*=8.4, 1.1 Hz, 1 H), 7.63 - 7.59 (m, 2 H), 7.57 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1 H), 7.53 - 7.49 (m, 3 H), 7.40 (d, *J*=8.4 Hz, 1 H), 7.27 - 7.22 (m, 1 H), 4.16 - 4.12 (m, 2 H), 4.11 (t, *J*=5.3 Hz, 1 H), 3.64 (d, *J*=5.3 Hz, 2 H), 3.05 (br. s., 2 H). ^{13}C NMR (151MHz, DMSO-*d₆*) δ = 170.5, 140.7, 137.3, 133.6, 132.6, 130.0, 129.6, 128.8, 123.4, 122.7, 122.6, 118.2, 116.4,

61.1, 52.0, 38.4. HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{20}N_3O_4S$ [M+H]$^+$ 374.1169, found 374.1160.

**methyl 2-((3-(4-amino-3,5-dichlorophenyl)-1,1-dioxido-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)propanoate 4c(*1,1,5*)**
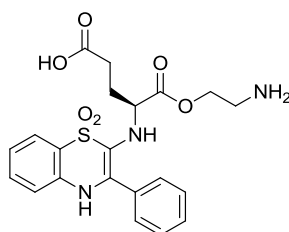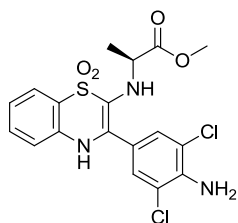

Yield 13.4 mg (12%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.25 (s, 1 H), 7.78 (dd, *J*=8.1, 1.3 Hz, 1 H), 7.53 - 7.58 (m, 3 H), 7.41 (dd, *J*=8.5, 0.6 Hz, 1 H), 7.23 (ddd, *J*=8.1, 7.1, 1.1 Hz, 1 H), 5.92 (s, 2 H), 4.28 (d, *J*=6.1 Hz, 1 H), 3.53 (dq, *J*=6.9, 6.1 Hz, 1 H), 3.44 (s, 3 H), 1.07 (d, *J*=6.9 Hz, 3 H). ^{13}C NMR (101MHz, DMSO-d_6) δ = 173.6, 142.1, 138.4, 136.8, 131.8, 129.2, 123.2, 122.2, 122.0, 121.1, 117.9, 117.1, 115.4, 57.0, 51.34, 18.4. HRMS (FAB) *m/z* calcd for $C_{18}H_{17}Cl_2N_3O_4S$ [M+H]$^+$ 442.0390, found 442.0380.

6.6 Procedures for traceless SPS of trisubstituted quinazolines

Based on publication: Fülöpová, V.; Cziesla, L.; Fleming, M.; Lu, Y.; Voelker, A.; Krchňák, V. *ACS Comb. Sci.* 2015, Article in press.[7]

Immobilization of Fmoc-amino acids

Fmoc-amino acids were immobilized on the Wang resin **1** (1 g, 1 mmol/g) according to procedure described in subchapter 6.2.

Deprotection of Fmoc group

Immobilized α-amino acids (1 g of resin) were treated with the solution of piperidine in DMF (50%, 10 mL) and the slurry was shaken at ambient temperature for 15 min. The resin was washed 3 × with DMF and 3 × with DCM.

Reaction with NosCl

Immobilized and deprotected α-amino acids (1 g resin) were treated with solution of NosCl according to procedure described in subchapter 6.4.

Reaction with bromoacetophenone

Resin **2** (250 mg) was reacted with solution of α-bromoacetophenone according to procedure reported in subchapter 6.4.

Cyclization with DBU

Resin **3** (250 mg) was washed 3 × with DMF. The solution of 0.5 M DBU (224 μL, 1.5 mmol) in DMF (3 mL) was added to the resin and the slurry was shaken at ambient temperature overnight or 30 min for **3**(*1,1,1*) and **3**(*3,1,2*). The resin was washed 5 × with DMF, 5 × DCM.

Cleavage, decarboxylation and isolation of quinazolines 6

Resins **4** (typically 100 - 250 mg) were treated with 50% TFA in DCM (1-3 mL) at room temperature for 90 min. The TFA solution was collected, the resin was washed 3× with 50% TFA in DCM (3 mL), and the combined extracts were evaporated by a stream of nitrogen. The oily residue **5** was dissolved in 2 mL of MeCN and diluted with 18 mL of 10 mM aqueous ammonium acetate. Depending on the type of compound, a solution or opalescent solution, occasionally with precipitation, was formed. The pH of the solution was adjusted to approximately 8 using solid ammonium acetate. A 10 mL SPE column was charged with 2 g of octadecyl-functionalized silica gel, and the plug was covered with a porous disc. The sorbent was wetted with 5 mL of MeCN and washed with 5 mL of 10 mM aqueous ammonium acetate. The solution of the target compound was passed through the column and washed with 5 mL of 10 mM aqueous ammonium acetate. The target compound was eluted with 10 mL of MeCN. The solution was analyzed by LC/MS to determine the decarboxylation progress. After decarboxylation was complete, typically overnight, the target compound was purified by semi-preparative reversed-phase HPLC. All products **6** were isolated as amorphous solids by freeze drying and were subsequently characterized by LC/MS, HRMS and ^{1}H and ^{13}C NMR.

6.6.1 Analytical data

(2-methylquinazolin-4-yl)(phenyl)methanone 6(*1,1,1*)
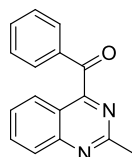
Yield 2.4 mg (12%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.05 - 8.07 (m, 2 H), 7.89 - 7.92 (m, 3 H), 7.74 - 7.79 (m, 1 H), 7.69 (ddd, J=8.3, 5.4, 2.7 Hz, 1 H), 7.56 - 7.61 (m, 2 H), 2.83 (s, 3 H). ^{13}C NMR (151MHz, DMSO-d$_6$) δ = 193.1, 164.3, 162.8, 150.8, 135.1, 134.9, 134.7, 130.3, 129.1, 128.2, 128.0, 125.4, 119.0, 25.9. HRMS (ESI-TOF) *m/z* calcd for C$_{16}$H$_{13}$N$_2$O [M+H]$^{+}$ 249.1022, found 249.1032.

(2-Methylquinazolin-4-yl)(*p*-tolyl)methanone 6(*1,1,2*)
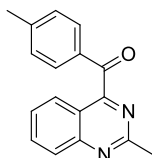
Yield 11.8 mg (56%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.01 - 8.10 (m, 2 H), 7.86 (d, J=8.3 Hz, 1 H), 7.79 (d, J=8.1 Hz, 2 H), 7.63 - 7.71 (m, 1 H), 7.39 (d, J=8.1 Hz, 2 H), 2.82 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 192.6, 164.7, 162.9, 150.7, 145.9, 135.1, 132.4, 130.5, 129.7, 128.1, 128.0, 125.4, 119.0, 26.0, 21.4. HRMS (ESI-TOF) *m/z* calcd for C$_{17}$H$_{15}$N$_2$O [M+H]$^{+}$ 263.1179, found 263.1153.

(4-Methoxyphenyl)(2-methylquinazolin-4-yl)methanone 6(*1,1,3*)
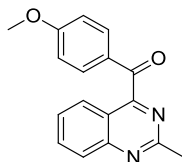
Yield 7.1 mg (16%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.01 - 8.07 (m, 2 H), 7.83 - 7.89 (m, 3 H), 7.67 (ddd, J=8.2, 5.6, 2.5 Hz, 1 H), 7.07 - 7.12 (m, 2 H), 3.87 (s, 3 H), 2.82 (s, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ =191.4, 164.9, 164.5, 162.9, 150.7, 135.0, 132.9, 128.0, 128.0, 127.7, 125.4, 119.1, 114.5, 55.8, 26.0. HRMS (ESI-TOF) *m/z* calcd for C$_{17}$H$_{14}$N$_2$O$_2$ [M+H]$^{+}$ 279.1149, found 279.1128.

(2-Methyl-7-(trifluoromethyl)quinazolin-4-yl)(phenyl)methanone 6(*1,3,1*)
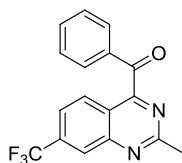
Yield 25.5 mg (41%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-d_6) δ = 8.45 (s, 1 H), 8.19 (d, J = 8.8 Hz, 1 H), 7.97 - 7.93 (m, 3 H), 7.81 - 7.75 (m, 1 H), 7.62 - 7.57 (m, 2 H), 2.87

(s, 3 H). ^{13}C NMR (151MHz, DMSO-d$_6$) δ = 192.5, 164.5, 165.4, 150.3, 135.1, 134.2 (q, J = 32.7 Hz), 130.6, 129.1, 127.8, 125.7 - 125.8 (m), 123.3 (q, J = 272.8 Hz) , 123.3 - 123.4 (m), 120.7, 26.0. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{12}F_3N_2O$ [M+H]$^+$ 317.0896, found. 317.0889.

(2-Methyl-7-nitroquinazolin-4-yl)(phenyl)methanone 6(*1,4,1*)
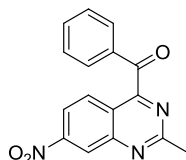
Yield 1.2 mg (8%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-*d$_6$*) δ = 8.82 (dd, J = 0.4, 2.3 Hz, 1 H), 8.36 (dd, J = 2.3, 9.1 Hz, 1 H), 8.23 (dd, J = 0.4, 9.1 Hz, 1 H), 8.01 - 7.93 (m, 2 H), 7.82 - 7.74 (m, 1 H), 7.64 - 7.56 (m, 2 H), 2.89 (s, 3 H). HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{12}N_3O_3$ [M+H]$^+$ 294.0873, found 294.0868.

(2-(Hydroxymethyl)quinazolin-4-yl)(phenyl)methanone 6(*2,1,1*)
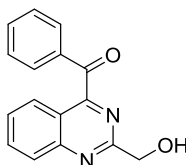
Yield 8.1 mg (23%) of amorphous solid. ^{1}H NMR (500MHz, DMSO-*d$_6$*) δ = 8.17 - 8.13 (m, 1 H), 8.12 - 8.07 (m, 1 H), 7.94 (td, J = 0.6, 8.3 Hz, 1 H), 7.91 (dd, J = 1.3, 8.4 Hz, 2 H), 7.79 - 7.71 (m, 2 H), 7.61 - 7.57 (m, 2 H), 4.82 (s, 2 H). ^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ = 193.1, 164.8, 164.5, 150.5, 135.3, 135.0, 134.7, 130.4, 129.1, 128.6, 128.3, 125.5, 119.8, 65.1. HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{13}N_2O_2$ [M+H]$^+$ 265.0972, found 265.0973.

4-(4-(4-Methylbenzoyl)quinazolin-2-yl)butan-1-aminium acetate 6(*3,1,2*)
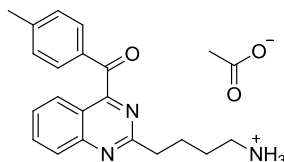
Yield 9.0 mg (35%) of amorphous solid. ^{1}H NMR (400MHz, DMSO-*d$_6$*) δ = 8.12 - 8.01 (m, 2 H), 7.88 (d, J = 7.9 Hz, 1 H), 7.81 - 7.76 (m, 2 H), 7.69 (ddd, J = 1.6, 6.4, 8.2 Hz, 1 H), 7.42 - 7.37 (m, 2 H), 3.08 (t, J = 7.5 Hz, 2 H), 2.67 (t, J = 7.3 Hz, 2 H), 2.41 (s, 3 H), 1.87 (quin, J = 7.6 Hz, 2 H), 1.53 (quin, J = 7.5 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-*d$_6$*) δ = 192.6, 165.7,

164.6, 150.7, 145.8, 135.0, 132.4, 130.4, 129.7, 128.2, 128.1, 125.4, 119.2, 38.5, 29.8, 25.1, 22.9, 21.4. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{21}N_3O$ [M+H]$^+$ 320.1773, found 320.1757.

(2-Isopropylquinazolin-4-yl)(phenyl)methanone 6(*4,1,1*)
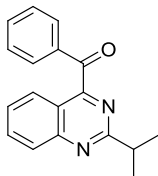
Yield 3.7 mg (23%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-d_6) δ = 8.11 - 8.08 (m, 1 H), 8.06 (dd, J = 1.3, 6.6 Hz, 1 H), 7.93 (qd, J = 0.8, 8.3 Hz, 1 H), 7.91 - 7.89 (m, 2 H), 7.76 (tt, J = 1.3, 7.5 Hz, 1 H), 7.70 (ddd, J = 1.3, 6.8, 8.3 Hz, 1 H), 7.61 - 7.57 (m, 2 H), 3.33 (td, J = 6.9, 13.8 Hz, 1 H), 1.36 (d, J = 7.0 Hz, 6 H). ^{13}C NMR (151MHz, DMSO-d_6) δ = 193.2, 169.8, 164.3, 150.8, 135.2, 135.0, 134.8, 130.4, 129.2, 128.4, 128.4, 125.5, 119.4, 37.2, 21.6. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{17}N_2O$ [M+H]$^+$ 277.1335, found 277.1358.

(2-Isopropylquinazolin-4-yl)(4-(trifluoromethyl)phenyl)methanone 6(*4,1,4*)
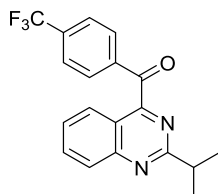
Yield 4.9 mg (28%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-d_6) δ = 8.16 (d, J = 8.2 Hz, 2 H), 8.14 - 8.05 (m, 3 H), 7.97 (d, J = 8.2 Hz, 2 H), 7.74 (td, J = 1.2, 7.5 Hz, 1 H), 3.35 - 3.31 (m, 1 H), 1.37 (d, J = 6.7 Hz, 6 H). ^{13}C NMR (151MHz, DMSO-d_6) δ = 192.2, 169.5, 162.6, 151.1, 138.1, 135.1, 131.3, 128.4, 128.3, 125.9 (q, J = 3.8 Hz), 125.5, 119.4, 37.0, 21.5 (CF$_3$ carbon was not identified). HRMS (ESI-TOF) m/z calcd for $C_{19}H_{16}F_3N_2O$ [M+H]$^+$ 345.1209, found 345.1197.

(2-Benzylquinazolin-4-yl)(phenyl)methanone 6(*5,1,1*)
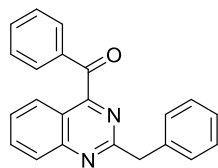
Yield 3.9 mg (24%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-d_6) δ = 8.13 - 8.10 (m, 1 H), 8.09 - 8.05 (m, 1 H), 7.96 - 7.92 (m, 1 H), 7.87 - 7.83 (m, 2 H), 7.77 - 7.73 (m, 1 H), 7.71

(ddd, J = 1.3, 6.8, 8.3 Hz, 1 H), 7.57 - 7.52 (m, 2 H), 7.36 - 7.32 (m, 2 H), 7.31 - 7.27 (m, 2 H), 7.24 - 7.18 (m, 1 H), 4.42 (s, 2 H). ^{13}C NMR (151MHz, DMSO-d_6) δ = 192.8, 164.5, 164.4, 150.9, 138.3, 135.3, 134.9, 134.6, 130.4, 129.1, 129.0, 128.6, 128.5, 128.3, 126.5, 125.5, 119.3, 45.2. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{17}N_2O$ [M+H]$^+$ 325.1335, found 325.1357.

3-(4-Benzoylquinazolin-2-yl)propanoic acid 6(*6,1,1*)
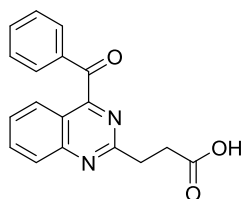
Yield 5.8 mg (38%) of amorphous solid. ^{1}H NMR (600MHz, DMSO-d_6) δ = 8.10 - 8.01 (m, 2 H), 7.96 - 7.88 (m, 3 H), 7.79 - 7.74 (m, 1 H), 7.72 - 7.67 (m, 1 H), 7.61 - 7.54 (m, 2 H), 3.31 (t, J = 7.0 Hz, 3 H), 2.83 (t, J = 7.0 Hz, 2 H). ^{13}C NMR (151MHz, DMSO-d_6) δ = 193.0, 174.1, 164.7, 164.0, 150.7, 135.2, 135.0, 134.7, 130.4, 129.1, 128.3, 128.2, 125.5, 119.3, 33.9, 31.6. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{15}N_2O_3$ [M+H]$^+$ 307.1107, found 307.1079.

4-Benzoyl-2-methyl-7-nitroquinazoline 1-oxide 7(*1,4,1*)
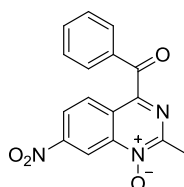
Yield 10.2 mg (51%) of amorphous solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 9.16 (d, J = 2.3 Hz, 1 H), 8.57 (d, J = 9.1 Hz, 1 H), 8.50 (dd, J = 2.3, 9.1 Hz, 1 H), 8.03 (dd, J = 1.0, 8.2 Hz, 2 H), 7.75 (tt, J = 1.3, 7.4 Hz, 1 H), 7.64 - 7.55 (m, 2 H), 2.77 (s, 3 H). ^{13}C NMR (151MHz, DMSO-d_6) δ = 191.6, 153.3, 150.6, 146.2, 143.6, 135.5, 134.5, 130.9, 129.8, 128.8, 125.4, 123.1, 114.5, 19.9. HRMS (ESI-TOF) m/z calcd for $C_{16}H_{12}N_3O_4$ [M+H]$^+$ 310.0822, found 310.0817

6.7 Procedures for SPS of Anagrelide sulfonyl analogues

Chemical library based on the scaffold **7** was prepared according to procedure described in the reported publication.[8]

Optimization experiments displayed in Tables 10, 11 and 12

Resins **4**, **11**, **15** and **17** (50 mg) were washed 3 × with appropriate reaction solvent. This solvent (1 mL) was added to the corresponding resin and the reaction proceeded according to conditions outlined in the Tables 10, 11 and 12. For the cyclization in solution, the analytical sample of resin **11** (50 mg) was first treated with 50% TFA in DCM for 30 min at ambient temperature. After this reaction, the TFA solution was evaporated under a stream of nitrogen and the appropriate reaction solvent (1 mL) was then added to the compound **12**. Intermediate **12** was subsequently subjected the cyclization conditions described in the Table 10.

6.7.1 Analytical data

3-methyl-1*H*-benzo[*e*]imidazo[1,2-*b*][1,2,4]thiadiazin-2(3*H*)-one 5,5-dioxide 7
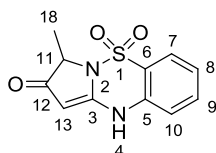
Cleaved from 180 mg of resin **6** (0.48 mmol/g, 0.086 mmol substrate). Yield 9.7 mg (0.038 mmol, 45%. Purity before final cyclisation 96%; Purity of purified product 99%; ESI-MS *m/z* = 250.02 [M-H]. ^{1}H-NMR, d_6-DMSO, δ (ppm), *J* (Hz): 1.54, 3H, *d*, 6.9, HC^{18}; 5.01, 1H, *q*, 6.9, HC^{11}; 7.38, 1H, *d*, 8.0, HC^{10}; 7.40, 1H, *t*, 8.0, HC^8; 7.71, 1H, *td*, 8.0, 1.5, HC^9; 7.91, 1H, *dd*, 8.0, 1.5, HC^7; 11.90, 1H, *br*, HN^4. ^{13}C-NMR, d_6-DMSO, δ (ppm): 17.15 (C18); 55.08 (C11); 122.44 (C7); 125.57 (C6); 125.86 (C8); 126.38 (C10); 135.40 (C9); 142.61 (C5); 151.67 (C3); 173.29 (C12).

6.8 Supplementary information

6.8.1 Data for 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides

Based on publication: Fülöpová, V.; Krchňáková, A.; Schütznerová, E.; Zajíček, J.; Krchňák, V. *J. Org. Chem.* 2015, *80* (3), 1795-1801.[6]

NMR study of rearrangement at room temperature

Resin **1** was cleaved with TFA in DCM, purified in MeCN/0.1% aqueous TFA, freeze dried, and dissolved in DMSO-d_6. The ratio of **2**:**3**:**4** was calculated from diagnostic resonances in ^{1}H NMR spectra. The first entry (time zero days) represents the **2**:**3**:**4** ratio after purification and overnight freeze-drying.

2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)propanoic acid 4a(*1,1,1*)
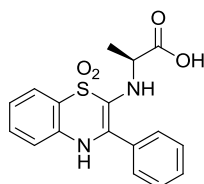
Entry	Time (d)	2 (%)	3 (%)	4 (%)
1	0	13	87	0
2	1.3	0	98	2
3	9.3	0	97	3
4	17.3	0	94	6
5	20.3	0	93	7
6	23.3	0	90	10
7	32.3	0	88	12

2-((3-(4-methoxyphenyl)-1,1-dioxido-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)propanoic acid 4a(*1,1,2*)
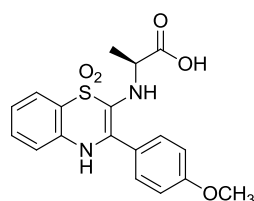
Entry	Time (d)	2 (%)	3 (%)	4 (%)
1	0	0	97	3

2	1.3	0	93	7
3	3.3	0	85	15
4	7.3	0	72	28
5	11.3	0	62	38
6	22.3	0	44	56
7	25.3	0	38	62
8	38.3	0	28	72

2-((1,1-dioxido-3-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino) propanoic acid 4a(*1,1,3*)
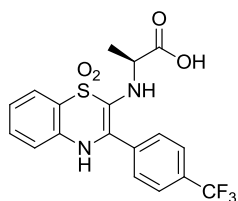
Entry	Time (d)	2 (%)	3 (%)	4 (%)
1	0	14	86	0
2	1.3	0	100	0
3	6.3	0	93	0
4	10.3	0	89	0
5	23.3	0	84	0
6	33.3	0	74	0

2-((6-methoxy-1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)propanoic acid 4a(*1,2,1*)
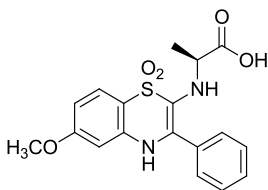
Entry	Time (d)	2 (%)	3 (%)	4 (%)
1	0	50	50	0
2	3.3	0	100	0
3	5.3	0	97	3
4	9.3	0	96	4
5	22.3	0	91	9

2-((1,1-dioxido-3-phenyl-6-(trifluoromethyl)-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino) propanoic acid 4a(*1,3,1*)
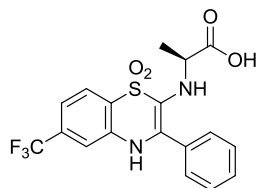
Entry	Time (d)	**2** (%)	**3** (%)	**4** (%)
1	0	21	79	0
2	2.3	10	88	3
3	6.3	2	92	6
4	19.3	0	84	16
5	29.3	0	78	22

2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)-3-phenylpropanoic acid 4a(*2,1,1*)
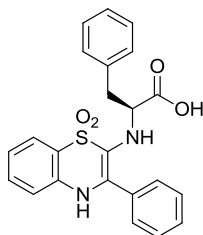
Entry	Time (d)	**2** (%)	**3** (%)	**4** (%)
1	0	0	95	5
2	3.3	0	86	14
3	5.3	0	81	19
4	9.3	0	75	25
5	22.3	0	58	42

2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)-*N*-(2-hydroxyethyl) propanamide 4b(*1,1,1*)
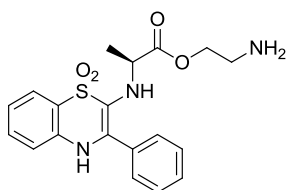
Entry	Time (d)	2 (%)	3 (%)	4 (%)
1	0	67	27	5
2	2.3	42	50	9
3	4.3	24	64	12
4	6.3	13	68	19
5	13.3	7	55	38
6	17.3	7	47	46
7	21.3	7	39	54
8	32.3	6	24	70
9	35.3	5	21	74
10	48.3	5	13	82

N-(2-hydroxyethyl)-2-((3-(4-methoxyphenyl)-1,1-dioxido-4H-benzo[b][1,4]thiazin-2-yl)amino)propanamide 4b(1,1,2)
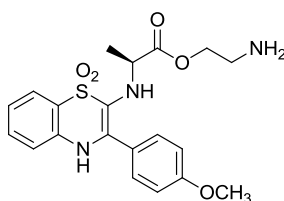
Entry	Time (d)	2 (%)	3 (%)	4 (%)
1	0	85	10	5
2	2.3	52	38	10
3	4.3	31	47	22
4	5.3	24	49	27
5	22.3	9	9	82
6	41.3	8	4	88
7	54.3	0	1	99
8	57.3	0	0	100

LC/MS study of rearrangement at elevated temperature

Compounds **3** were purified in MeCN/aqueous ammonium acetate unless otherwise stated and were subsequently lyophilized overnight and dissolved in DMSO-d_6. A sample of DMSO-d_6 solution (10 µL) was diluted with DMSO or MeOH (800 µL). The **3**:**4** ratio was calculated from LC traces at 205–450 nm. The first entry (time zero hours) indicates the **3**:**4** ratio after purification and overnight freeze-drying.

2-((3-(4-methoxyphenyl)-1,1-dioxido-4H-benzo[b][1,4]thiazin-2-yl)amino)propanoic acid 4a(1,1,2)
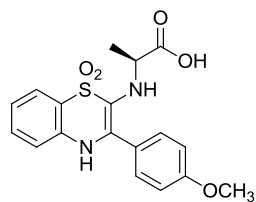
Entry	Solvent	T (°C)	Time (h)	3 (%)	4 (%)
1	DMSO	rt	0	100	0
2	DMSO	70	3.3	24	63
3	DMSO	70	4.3	18	68
4	DMSO	70	6.6	0	82
5	DMSO	70	8.0	0	68

2-((3-(4-amino-3,5-dichlorophenyl)-1,1-dioxido-4H-benzo[b][1,4]thiazin-2-yl)amino) propanoic acid 4a(1,1,5)
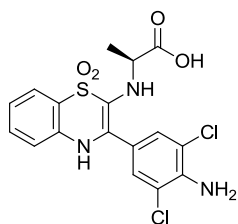
Entry	Solvent	T (°C)	Time (h)	3 (%)	4 (%)
1	DMSO	rt	0	83	9
2	DMSO	70	3.3	13	75
3	DMSO	70	4.3	0	75
4	DMSO	70	6.6	0	71
5	DMSO	70	8.0	0	62

2-((1,1-dioxido-3-phenyl-6-(trifluoromethyl)-4H-benzo[b][1,4]thiazin-2-yl)amino) propanoic acid 4a(1,3,1)
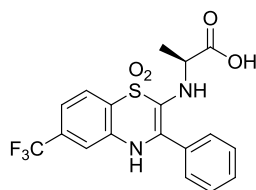
Entry	Solvent	T (°C)	Time (h)	3 (%)	4 (%)
1	MeOH	rt	0	80	20

2	MeOH	50	1.0	73	21
3	MeOH	50	21.0	40	45
4	DMSO	70	3.3	31	69
5	DMSO	70	4.3	26	74
6	DMSO	70	6.6	19	81
7	DMSO	70	8.0	12	61

2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)-3-phenylpropanoic acid 4a(*2,1,1*)
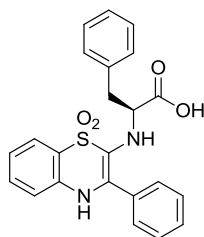
Entry	Solvent	T (ºC)	Time (h)	3 (%)	4 (%)
1	DMSO	rt	0	100	0
2	DMSO	70	3.3	33	60
3	DMSO	70	4.3	18	71
4	DMSO	70	5.3	10	83
5	DMSO	70	6.6	0	87
6	DMSO	70	8.0	0	85

2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)-4-methylpentanoic acid 4a(*4,1,1*)

Entry	Solvent	T (ºC)	Time (h)	3 (%)	4 (%)
1	MeOH	rt	0	100	0
2	DMSO	70	1.0	63	37
3	DMSO	70	2.0	61	39
4	DMSO	70	3.0	21	79

5	DMSO	70	4.4	9	79

Experiment after purification in 0.1% TFA/MeCN:

Entry	Solvent	T (ºC)	Time (h)	3 (%)	4 (%)
1	MeOH	rt	0	82	8
2	DMSO	70	1.0	60	35
3	DMSO	70	2.0	35	61
4	DMSO	70	3.0	31	65
5	DMSO	70	4.0	22	66
6	DMSO	70	5.0	14	66

6-amino-2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)hexanoic acid 4a(*5,1,1*)

Entry	Solvent	T (ºC)	Time (h)	3 (%)	4 (%)
1	MeOH	rt	0	92	4
2	DMSO	70	1.0	70	20
3	DMSO	70	3.0	34	27
4	DMSO	70	5.0	20	31
5	DMSO	70	7.0	14	27

2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)pentanedioic acid 4a(*6,1,1*)

Entry	Solvent	T (ºC)	Time (h)	3 (%)	4 (%)
1	MeOH	rt	0	87	0
2	DMSO	70	1.0	64	22

3	DMSO	70	3.0	34	43
4	DMSO	70	5.0	24	51
5	DMSO	70	7.0	19	56
6	DMSO	70	9.0	12	49

3-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)propanoic acid 4a(*7,1,1*)

Entry	Solvent	T (ºC)	Time (h)	3 (%)	4 (%)
1	MeOH	rt	0	78	1
2	DMSO	70	1.0	74	9
3	DMSO	70	2.0	68	16
4	DMSO	70	4.0	57	25
5	DMSO	70	6.0	49	34
6	DMSO	70	8.0	43	42
7	DMSO	70	12.0	31	56
8	DMSO	70	14.0	26	59
9	DMSO	70	16.5	22	64
10	DMSO	70	18.5	18	66
11	DMSO	70	19.7	16	64

2-((1,1-dioxido-3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)-*N*-(2-hydroxyethyl) propanamide 4b(*1,1,1*)
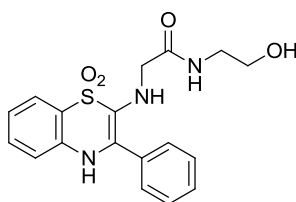
Entry	Solvent	T (ºC)	Time (h)	3 (%)	4 (%)
1	DMSO	rt	0	88	12
2	DMSO	70	2.0	48	49
3	DMSO	70	3.0	41	54
4	DMSO	70	5.0	30	62
5	DMSO	70	7.0	25	65

6	DMSO	70	9.0	19	67
7	DMSO	70	11.0	16	67
8	DMSO	70	13.0	13	67
9	DMSO	70	14.0	12	68
10	DMSO	70	16.4	1	75

2-aminoethyl 2-((3-(4-methoxyphenyl)-1,1-dioxido-4*H*-benzo[*b*][1,4]thiazin-2-yl)amino)propanoate 4b(*1,1,2*)
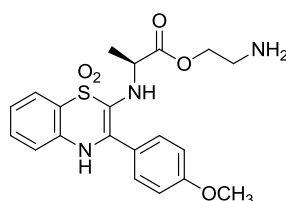
Experiment after purification in 0,1% TFA/MeCN:

Entry	Solvent	T (ºC)	Time (h)	3 (%)	4 (%)
1	MeOH	rt	0	91	9
2	DMSO	70	3.3	12	88
3	DMSO	70	4.3	11	87
4	DMSO	70	6.6	10	87
5	DMSO	70	8.0	7	87
6	MeOH	100	5.0	16	31

Table 13. ^{1}H and ^{13}C NMR data for thiazine **4b**(*1,1,2*) in DMSO at 298 K.
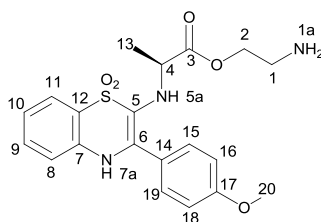
Substructural unit	δ_C (ppm)	δ_H (ppm)	Proton multiplicity $J(H_i,H_j)$ [Hz]	
CH$_2$-1	37.91	3.06	bt	2
CH$_2$-2	60.60	4.04	ddd, 4.2, 6.3, 11.9	1
		4.13	ddd, 4.2, 6.3, 11.9	
C-3	172.75			2 4 13 5a
CH-4	57.50	3.47	dq, 6.6, 6.7	13
C-5	114.72			4 7a
C-6	141.03			15 19 5a 7a

C-7	136.82			9 11 7a
CH-8	117.82	7.42	ddd, 8.4, 1.0, 0.5	9 10 7a
CH-9	131.99	7.56		8 10 11
CH-10	122.26	7.24	ddd, 8.1, 7.1, 1.0	8 9
CH-11	122.15	7.79	dd, 8.1, 1.3	8 9 10
C-12	123.06			8 10 7a
CH$_3$-13	18.21	0.98	d, 7.2	4
C-14	125.54			15 16 18 19 7a
CH-15,CH-19	130.91	7.55	mt, δJ=14.7	16 18
CH-16,CH-18	113.55	7.07	mt, δJ=14.7	15 19
C-17	160.05			15 16 18 19 20
CH$_3$-20	55.33	3.82	s	
NH$_2$-1a	28.19[c]	7.88	bs	2
NH-5a	34.53[c]	4.38	d, 6.7	13
NH-7a	116.08[c]	10.37	s	8

a) Due to numerous overlaps of several proton signals the values of coupling constants or δJ could not be always extracted.

b) HMBC correlations, optimized for 6 Hz, are from proton(s) stated to the indicated carbon/nitrogen.

c) ^{15}N chemical shifts values.

7. List of abbreviations

ACE-Cl	1-chloroethyl chloroformate
AcOH	acetic acid
ADDP	1,1′-(azodicarbonyl)-dipiperidine
Alloc	allyloxycarbonyl
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
CDI	carbonyldiimidazole
Cha	cyclohexylalanine
CSIm$_2$	1,1′-thiocarbonyldiimidazole
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIC	*N,N*′-diisopropylcarbodiimide
DIEA	*N,N*-diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-(*N,N*)-dimethylaminopyridine
DMSO	dimethyl sulfoxide
DOS	diversity-oriented synthesis
DTAD	di-*tert*-butylazodicarboxylate
Fmoc-OSu	*N*-(9-Fluorenylmethoxycarbonyloxy)succinimide
H-AA-OH	amino acid (it can be protected by Fmoc/Nos group)
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBTU	*N,N,N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uranium hexafluorophosphate
HMPB	4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole hydrate

HODhbt	3,4-dihydro-5-hydroxy-4-oxo-1,2,3-benzotriazine
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
m-CPBA	3-chloroperoxybenzoic acid
MeCN	acetonitrile
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene
MW	microwave
NMM	*N*-methylmorpholine
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
OAc	acetoxy
PEt$_3$	triethylphosphine
Pfp	pentafluorophenyl
PIP	piperidine
PMe$_3$	trimethylphosphine
PPh$_3$	triphenylphosphine
PS/DVB	polystyrene/divinylbenzene
Py	pyridine
SPS	solid-phase synthesis
TBAD	tetrabutylammonium dodecanoate
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrogen sulfate
TEA	triethylamine
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofurane

8. References

1. http://www.ped.muni.cz/wchem/sm/hc/hist/19/organickachemie.html, **2011**.

2. Merrifield, R. B. Solid Phase Peptide Synthesis. I. *J. Am. Chem. Soc.* **1963,** *85* (14), 2149-2154.

3. Fülöpová, V.; Gucký, T.; Grepl, M.; Soural, M. *ACS Comb. Sci.* **2012,** *14* (12), 651-656.

4. Fülöpová, V.; Funk, P.; Popa, I.; McMaster, C.; Soural, M. *Eur. J. Org. Chem.* **2015,** *2015* (16), 3551-3557.

5. Fülöpová, V.; Krchňák, V. *ACS Comb. Sci.* **2014,** *16* (8), 412-420.

6. Fülöpová, V.; Krchňáková, A.; Schütznerová, E.; Zajíček, J.; Krchňák, V. *J. Org. Chem.* **2015,** *80* (3), 1795-1801.

7. Fülöpová, V.; Cziesla, L.; Fleming, M.; Lu, Y.; Voelker, A.; Krchňák, V. *ACS Comb. Sci.* **2015,** Article in press.

8. McMaster, C.; Fülöpová, V.; Popa, I.; Grepl, M.; Soural, M. *ACS Comb. Sci.* **2014,** *16* (5), 221-224.

9. Fülöpová, V.; Soural, M. **2015,** Article under review.

10. Igwe, C. N.; Okoro, U. C. *Org. Chem. Int.* **2014,** 419518-1-419518/5.

11. Ko, S. K.; Jin, H.; Jung, D. W.; Tian, X.; Shin, I. *Angew. Chem. Int. Ed.* **2009,** *48* (42), 7809-7812.

12. Wani, M. Y.; Bhat, A. R.; Azam, A.; Choi, I.; Athar, F. *Eur. J. Med. Chem.* **2012,** *48* (0), 313-320.

13. Gioiello, A.; Rosatelli, E.; Teofrasti, M.; Filipponi, P.; Pellicciari, R. *ACS Comb. Sci.* **2013,** *15* (5), 235-239.

14. Giannotti, D.; Viti, G.; Sbraci, P.; Pestellini, V.; Volterra, G.; Borsini, F.; Lecci, A.; Meli, A.; Dapporto, P.; Paoli, P. *J. Med. Chem.* **1991,** *34* (4), 1356-1362.

15. Owa, T.; Yoshino, H.; Okauchi, T.; Yoshimatsu, K.; Ozawa, Y.; Sugi, N. H.; Nagasu, T.; Koyanagi, N.; Kitoh, K. *J. Med. Chem.* **1999,** *42* (19), 3789-3799.

16. Ren, J.; Wang, Y.; Wang, J.; Lin, J.; Wei, K.; Huang, R. *Steroids* **2013,** *78* (1), 53-58.

17. Kim, D. H.; Yun, B. H.; Choi, E. W.; Oh, S. M.; Alam, M.; Lee, K. T.; Lee, Y. S. *Bull. Korean Chem. Soc.* **2013,** *34* (8), 2507-2510.

18. Flosi, W. J.; DeGoey, D. A.; Grampovnik, D. J.; Chen, H. j.; Klein, L. L.; Dekhtyar, T.; Masse, S.; Marsh, K. C.; Mo, H. M.; Kempf, D. *Bioorg. Med. Chem.* **2006,** *14* (19), 6695-6712.

19. Barea, C.; Pabón, A.; Castillo, D.; Zimic, M.; Quiliano, M.; Galiano, S.; Pérez-Silanes, S.; Monge, A.; Deharo, E.; Aldana, I. *Bioorg. Med. Chem. Lett.* **2011,** *21* (15), 4498-4502.

20. Samala, G.; Devi, P. B.; Nallangi, R.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2013,** *69* (0), 356-364.

21. Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995,** *36* (36), 6373-6374.

22. Kan, T.; Fukuyama, T. *Chem. Commun.* **2004,** (4), 353-359.

23. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996,** *61* (11), 3849-3862.

24. Pillai, R. B. C.. *J. Mol. Catal.* **1993,** *84* (1), 125-129.

25. Smith, M. B.; March, J. In *March′s Advanced Organic Chemistry;* Sixth ed.; John Wiley & Sons: New Jersey, **2001**.

26. Mitsunobu, O. *Synthesis* **1981,** (1), 1-28.

27. Hughes, D. L. *Org. React. (N. Y.)* **1992,** *42*, 335-656.

28. Krchňák, V.; Slough, G. A. *Tetrahedron Lett.* **2004,** *45* (22), 4289-4291.

29. Patino, N.; Di Giorgio, C.; Dan-Covalciuc, C.; Peytou, V.; Terreux, R.; Cabrol-Bass, D.; Bailly, C.; Condom, R. *Eur. J. Med. Chem.* **2002,** *37* (7), 573-584.

30. Stuhr-Hansen, N.; Solling, T. I.; Stromgaard, K. *Org. Biomol. Chem.* **2013,** *11* (14), 2288-2293.

31. Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997,** *119* (9), 2301-2302.

32. Yang, L.; Chiu, K. *Tetrahedron Lett.* **1997,** *38* (42), 7307-7310.

33. Bouillon, I.; Zajíček, J.; Pudelová, N.; Krchňák, V. *J. Org. Chem.* **2008,** *73* (22), 9027-9032.

34. Schütznerová, E.; Krchňák, V. *ACS Comb. Sci.* **2014,** *17* (2), 137-146.

35. Smyslová, P.; Kisseljova, K.; Krchňák, V. *ACS Comb. Sci.* **2014,** *16* (9), 500-505.

36. Hou, W.; Zhang, X.; Li, F.; Liu, C. F. *Org. Lett.* **2011,** *13* (3), 386-389.

37. Chhabra, S. R.; Khan, A. N.; Bycroft, B. W. *Tetrahedron Lett.* **2000,** *41* (7), 1099-1102.

38. Seo, J. s.; Kim, H. w.; Yoon, C. M.; Ha, D. C.; Gong, Y. D. *Tetrahedron* **2005,** *61* (39), 9305-9311.

39. Stanger, K. J.; Krchňák, V. *J. Comb. Chem.* **2006,** *8* (3), 435-439.

40. Renault, J.; Fabis, F.; Dauphin, F.; Lebranchu, M.; Roch, M. L.; Butt, S.; Uriac, P.; Rault, S. *J. Pharm. Pharmacol.* **2001,** *53* (7), 969-972.

41. Le Pera, A.; Leggio, A.; Liguori, A. *Tetrahedron* **2006,** *62* (25), 6100-6106.

42. Tsuda, S.; Shigenaga, A.; Bando, K.; Otaka, A. *Org. Lett.* **2009,** *11* (4), 823-826.

43. Christensen, C.; Clausen, R. P.; Begtrup, M.; Kristensen, J. L. *Tetrahedron Lett.* **2004,** *45* (43), 7991-7993.

44. Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2004,** *7* (2), 307-310.

45. Nihei, K. i.; Kato, M. J.; Yamane, T.; Palma, M. S.; Konno, K. *Synlett* **2001,** *2001* (07), 1167-1169.

46. Fang, W. J.; Yakovleva, T.; Aldrich, J. V. *Biopolymers* **2011,** *96* (6), 715-722.

47. Di Gioia, M. L.; Barattucci, A.; Bonaccorsi, P.; Leggio, A.; Minuti, L.; Romio, E.; Temperini, A.; Siciliano, C. *RSC Adv.* **2014,** *4* (6), 2678-2686.

48. Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1998,** *120* (11), 2690-2691.

49. Biron, E.; Chatterjee, J.; Kessler, H. *J. Peptide Sci.* **2006,** *12* (3), 213-219.

50. Bolton, G. L.; Hodges, J. C. *J. Comb. Chem.* **1999,** *1* (2), 130-133.

51. Lemrová, B.; Soural, M. *ACS Comb. Sci.* **2012,** *14* (12), 645-650.

52. Mohamed, N.; Bhatt, U.; Just, G. *Tetrahedron Lett.* **1998,** *39* (45), 8213-8216.

53. Pudelová, N.; Krchňák, V. *J. Comb. Chem.* **2009,** *11* (5), 851-859.

54. Cankařová, N.; Krchňák, V. In *Diversity-Oriented Synthesis*, John Wiley & Sons, Inc.: **2013**; pp 201-252.

55. Kočí, J.; Pudelová, N.; Krchňák, V. *J. Comb. Chem.* **2009,** *11* (3), 397-402.

56. Vézina-Dawod, S.; Derson, A.; Biron, E. *Tetrahedron Lett.* **2015,** *56* (2), 382-385.

57. Kay, C.; Murray, P. J.; Sandow, L.; Holmes, A. B. *Tetrahedron Lett.* **1997,** *38* (39), 6941-6944.

58. Congreve, M. S.; Kay, C.; Scicinski, J. J.; Ley, S. V.; Williams, G.; Murray, P. J.; McKeown, S. C.; Watson, S. P. *Tetrahedron Lett.* **2003,** *44* (21), 4153-4156.

59. Krchňák, V.; Slough, G. A. *Tetraheron Lett.* **2004,** *45* (24), 4649-4652.

60. Krchňák, V. In *Mini-Reviews in Medicinal Chemistry*, **2006**; pp 27-36.

61. Jensen, K. J.; Alsina, J.; Songster, M. F.; Vágner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998,** *120* (22), 5441-5452.

62. Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Synlett* **2004,** *2004* (03), 473-476.

63. Berst, F.; Holmes, A. B.; Ladlow, M.; Murray, P. J. *Tetrahedron Lett.* **2000,** *41* (34), 6649-6653.

64. Koide, K.; Finkelstein, J. M.; Ball, Z.; Verdine, G. L. *J. Am. Chem. Soc.* **2000,** *123* (3), 398-408.

65. Cankařová, N.; Krchňák, V. *J. Org. Chem.* **2012,** *77* (13), 5687-5695.

66. Schütznerová, E.; Oliver, A. G.; Zajíček, J.; Krchňák, V. *Eur. J. Org. Chem.* **2013,** *2013* (15), 3158-3165.

67. La Venia, A.; Lemrová, B.; Krchňák, V. *ACS Comb. Sci.* **2012,** *15* (1), 59-72.

68. La Venia, A.; Dolenský, B.; Krchňák, V. *ACS Comb. Sci.* **2013,** *15* (3), 162-167.

69. Arya, P.; Wei, C. Q.; Barnes, M. L.; Daroszewska, M. *J. Comb. Chem.* **2003,** *6* (1), 65-72.

70. Bianchi, I.; La Porta, E.; Barlocco, D.; Raveglia, L. F. *J. Comb. Chem.* **2004,** *6* (5), 835-845.

71. Ventosa-Andréss, P.; Hradilová, L.; Krchňák, V. *ACS Comb. Sci.* **2014,** *16* (7), 359-366.

72. La-Venia, A.; Ventosa-Andrés, P.; Hradilová, L.; Krchňák, V. *J. Org. Chem.* **2014,** *79* (21), 10378-10389.

73. Vaňková, B.; Brulíková, L.; Wu, B.; Krchňák, V. *Eur. J. Org. Chem.* **2012,** *2012* (26), 5075-5084.

74. Peng, G.; Sohn, A.; Gallop, M. A. *J. Org. Chem.* **1999,** *64* (22), 8342-8349.

75. Olsen, C. A.; Christensen, C.; Nielsen, B.; Farah, M. M.; Witt, M.; Clausen, R. P.; Kristensen, J. L.; Franzyk, H.; Jaroszewski, J. W. *Org. Lett.* **2006,** *8* (15), 3371-3374.

76. Stanger, K. J.; Sliva, D.; Jiang, J.; Krchňák, V. *Comb. Chem. High Throughput Screen.* **2006,** *9* (9), 651-661.

77. Cankařová, N.; La Venia, A.; Krchňák, V. *ACS Comb. Sci.* **2014,** *16* (6), 293-302.

78. Kisseljova, K.; Smyslová, P.; Krchňák, V. *ACS Comb. Sci.* **2014,** *16* (10), 573-577.

79. Pudelová, N.; Krchňák, V. *J. Comb. Chem.* **2009,** *11* (3), 370-374.

80. Kočí, J.; Krchňák, V. *J. Comb. Chem.* **2010,** *12* (1), 168-175.

81. Kočí, J.; Oliver, A. G.; Krchňák, V. *J. Org. Chem.* **2009,** *75* (2), 502-505.

82. Křupková, S.; Slough, G. A.; Krchňák, V. *J. Org. Chem.* **2010,** *75* (13), 4562-4566.

83. Fukuyama, T.; Cheung, M.; Jow, C. K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997,** *38* (33), 5831-5834.

84. Bisegger, P.; Manov, N.; Bienz, S. *Tetrahedron* **2008,** *64* (32), 7531-7536.

85. Richter, H.; Jung, G. *Tetrahedron Lett.* **1998,** *39* (18), 2729-2730.

86. Campian, E.; Lou, B.; Saneii, H. *Tetrahedron Lett.* **2002,** *43* (47), 8467-8470.

87. Maclean, D.; Hale, R.; Chen, M. *Org. Lett.* **2001,** *3* (19), 2977-2980.

88. Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc. D* **1971,** (12), 636-637.

89. Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G. Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000,** *122* (41), 9954-9967.

90. Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G. Q. *J. Am. Chem. Soc.* **2000,** *122* (41), 9968-9976.

91. Makino, S.; Nakanishi, E.; Tsuji, T. *J. Comb. Chem.* **2003,** *5* (1), 73-78.

92. Sternbach, L. H. *J. Med. Chem.* **1979,** *22* (1), 1-7.

93. Mohler, H.; Fritschy, J.; Rudolph, U. *J. Pharmacol. Exp. Ther.* **2002,** *300* (1), 2-8.

94. McKernan, R. M.; Rosahl, T. W.; Reynolds, D. S.; Sur, C.; Wafford, K. A.; Atack, J. R.; Farrar, S.; Myers, J.; Cook, G.; Ferris, P.; Garrett, L.; Bristow, L.; Marshall, G.; Macaulay, A.; Brown, N.; Howell, O.; Moore, K. W.; Carling, R. W.; Street, L. J.; Castro, J. L.; Ragan, C. I.; Dawson, G. R.; Whiting, P. J. *Nat. Neurosci.* **2000,** *3* (6), 587-592.

95. Löw, K.; Crestani, F.; Keist, R.; Benke, D.; Brünig, I.; Benson, J. A.; Fritschy, J. M.; Rülicke, T.; Bluethmann, H.; Möhler, H.; Rudolph, U. *Science* **2000,** *290* (5489), 131-134.

96. Crestani, F.; Löw, K.; Keist, R.; Mandelli, M. J.; Möhler, H.; Rudolph, U. *Mol. Pharmacol.* **2001,** *59* (3), 442-445.

97. Rudolph, U.; Crestani, F.; Benke, D.; Brünig, I.; Benson, J. A.; Fritschy, J. M.; Martin, J. R.; Bluethmann, H.; Möhler, H. *Nature* **1999,** *401* (6755), 796-800.

98. Hradil, P.; Grepl, M.; Hlaváč, J.; Soural, M.; Maloň, M.; Bertolasi, V. *J. Org. Chem.* **2005,** *71* (2), 819-822.

99. Fray, M. J.; Cooper, K.; Parry, M. J.; Richardson, K.; Steele, J. *J. Med. Chem.* **1995,** *38* (18), 3514-3523.

100. Marcaccini, S.; Miliciani, M.; Pepino, R. *Tetrahedron Lett.* **2005,** *46* (4), 711-713.

101. Sanudo, M.; García-Valverde, M.; Marcaccini, S.; Delgado, J. J.; Rojo, J.; Torroba, T. *J. Org. Chem.* **2009,** *74* (5), 2189-2192.

102. Wang, S. S. *J. Amer. Chem. Soc.* **1973,** *95* (4), 1328-1333.

103. Rink, H. *Tetrahedron Lett.* **1987,** *28* (33), 3787-3790.

104. Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *Proc. Natl. Acad. Sci.* **1994,** *91* (11), 4708-4712.

105. Snyder, P. J.; Werth, J.; Giordani, B.; Caveney, A. F.; Feltner, D.; Maruff, P. *Hum. Psychopharmacol. Clin. Exp.* **2005,** *20* (4), 263-273.

106. Greenblatt, D. J.; Harmatz, J. S.; Shapiro, L.; Engelhardt, N.; Gouthro, T. A.; Shader, R. I. *N Engl J Med* **1991,** *324* (24), 1691-1698.

107. Klotz, U.; Kanto, J. *Clin-Pharmacokinet.* **1988,** *14* (1), 1-12.

108. Thomas, A. W. *Bioorg. Med. Chem. Lett.* **2002,** *12* (14), 1881-1884.

109. Chowdhury, C.; Kumar Sasmal, A.; Achari, B. *Org. Biomol. Chem.* **2010,** *8* (21), 4971-4977.

110. Chambers, C. S.; Patel, N.; Hemming, K. *Tetrahedron Lett.* **2010,** *51* (37), 4859-4861.

111. Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004,** *45* (46), 8439-8441.

112. Mohapatra, D. K.; Maity, P. K.; Shabab, M.; Khan, M. I. *Bioorg. Med. Chem. Lett.* **2009,** *19* (17), 5241-5245.

113. Majumdar, K. C.; Ganai, S. *Synthesis* **2013,** *45* (18), 2619-2625.

114. Cornier, P. G.; Boggián, D. B.; Mata, E. G.; Delpiccolo, C. M. L. *Tetrahedron Lett.* **2012,** *53* (6), 632-636.

115. Beccalli, E.; Broggini, G.; Paladino, G.; Pilati, T.; Pontremoli, G. *Tetrahedron: Asymmetry* **2004,** *15* (4), 687-692.

116. Molteni, G.; Broggini, G.; Pilati, T. *Tetrahedron: Asymmetry* **2002,** *13* (22), 2491-2495.

117. Sternbach, L. H.; Field, G. F.; Zally, W. J. *J. Org. Chem.* **1971,** *36* (20), 2968-2972.

118. Migliara, O.; Petruso, S.; Sprio, V. *J. Heterocycl. Chem.* **1979,** *16* (5), 835-837.

119. Di Santo, R.; Costi, R.; Artico, M.; Ragno, R.; Lavecchia, A.; Novellino, E.; Gavuzzo, E.; La Torre, F.; Cirilli, R.; Cancio, R.; Maga, G. *ChemMedChem* **2006,** *1* (1), 82-95.

120. Kaplánek, R.; Krchňák, V. *Tetrahedron Lett.* **2013,** *54* (21), 2600-2603.

121. Goyal, K.; Gautam, N.; Khandelwal, N.; Gautam, D. C. *Nucleosides Nucleotides Nucleic Acids* **2013,** *32* (2), 81-97.

122. Hendricks, R. T.; Fell, J. B.; Blake, J. F.; Fischer, J. P.; Robinson, J. E.; Spencer, S. R.; Stengel, P. J.; Bernacki, A. L.; Leveque, V. J. P.; Pogam, S. L.; Rajyaguru, S.; Najera, I.; Josey, J. A.; Harris, J. R.; Swallow, S. *Bioorg. Med. Chem. Lett.* **2009,** *19* (13), 3637-3641.

123. de Vicente, J.; Hendricks, R. T.; Smith, D. B.; Fell, J. B.; Fischer, J.; Spencer, S. R.; Stengel, P. J.; Mohr, P.; Robinson, J. E.; Blake, J. F.; Hilgenkamp, R. K.; Yee, C.; Adjabeng, G.; Elworthy, T. R.; Tracy, J.; Chin, E.; Li, J.; Wang, B.; Bamberg, J. T.; Stephenson, R.; Oshiro, C.; Harris, S. F.; Ghate, M.; Leveque, V.; Najera, I.; Le Pogam, S.; Rajyaguru, S.; Ao-Ieong, G.; Alexandrova, L.; Larrabee, S.; Brandl, M.; Briggs, A.; Sukhtankar, S.; Farrell, R.; Xu, B. *Bioorg. Med. Chem. Lett.* **2009,** *19* (13), 3642-3646.

124. de Vicente, J.; Hendricks, R. T.; Smith, D. B.; Fell, J. B.; Fischer, J.; Spencer, S. R.; Stengel, P. J.; Mohr, P.; Robinson, J. E.; Blake, J. F.; Hilgenkamp, R. K.; Yee, C.; Zhao, J.; Elworthy, T. R.; Tracy, J.; Chin, E.; Li, J.; Lui, A.; Wang, B.; Oshiro, C.; Harris, S. F.; Ghate, M.; Leveque, V. J. P.; Najera, I.; Pogam, S. L.; Rajyaguru, S.; Ao-Ieong, G.; Alexandrova, L.; Fitch, B.; Brandl, M.; Masjedizadeh, M.; Wu, S. y.; Keczer, S. d.; Voronin, T. *Bioorg. Med. Chem. Lett.* **2009,** *19* (19), 5648-5651.

125. Ellis, D. A.; Blazel, J. K.; Webber, S. E.; Tran, C. V.; Dragovich, P. S.; Sun, Z.; Ruebsam, F.; McGuire, H. M.; Xiang, A. X.; Zhao, J.; Li, L. S.; Zhou, Y.; Han, Q.; Kissinger, C. R.; Showalter, R. E.; Lardy, M.; Shah, A. M.; Tsan, M.; Patel, R.; LeBrun, L. A.; Kamran, R.; Bartkowski, D. M.; Nolan, T. G.; Norris, D. A.; Sergeeva, M. V.; Kirkovsky, L. *Bioorg. Med. Chem. Lett.* **2008,** *18* (16), 4628-4632.

126. Latli, B.; Wood, E.; Casida, J. E. *Chem. Res. Toxicol.* **1996,** *9* (2), 445-450.

127. Bedi, P. M. S.; Kumar, V.; Mahajan, M. P. *Bioorg. Med. Chem. Lett.* **2004,** *14* (20), 5211-5213.

128. Rojas-Aguirre, Y.; Hernández-Luis, F.; Mendoza-Martínez, C.; Sotomayor, C. P.; Aguilar, L. F.; Villena, F.; Castillo, I.; Hernández, D. J.; Suwalsky, M. *Biochim. Biophy. Acta.* **2012,** *1818* (3), 738-746.

129. Gundla, R.; Kazemi, R.; Sanam, R.; Muttineni, R.; Sarma, J. A. R. P.; Dayam, R.; Neamati, N. *J. Med. Chem.* **2008,** *51* (12), 3367-3377.

130. Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem.* **2009,** *74* (14), 4934-4942.

131. Malecki, N.; Carato, P.; Rigo, B.; Goossens, J. F.; Houssin, R.; Bailly, C.; Hénichart, J. P. *Bioorg. Med. Chem.* **2004,** *12* (3), 641-647.

132. Miyashita, A.; Matsuda, H.; Suzuki, Y.; Iwamoto, K.; Higashino, T. *Chem. Pharm. Bull.* **1994,** *42* (10), 2017-2022.

133. Zhao, D.; Zhu, M. X.; Wang, Y.; Shen, Q.; Li, J. X. *Org. Biomol. Chem.* **2013,** *11* (37), 6246-6249.

134. Toh, K. K.; Sanjaya, S.; Sahnoun, S.; Chong, S. Y.; Chiba, S. *Org. Lett.* **2012,** *14* (9), 2290-2292.

135. Fleming, J. S.; Buyniski, J. P. *Thromb. Res.* **1979,** *15* (3), 373-388.

136. Reilly, J. T. *Hematology* **2009,** *14* (1), 1-10.

137. Pescatore, S. L.; Lindley, C. Anagrelide: *Expert Opin. Pharmacother.* **2000,** *1* (3), 537-546.

138. Trapp, O. M.; Beykirch, M. K.; Petrides, P. E. *Blood Cells, Molecules, and Diseases* **1998,** *24* (1), 9-13.

139. Hirota, S.; Sakai, T.; Kitamura, N.; Kubokawa, K.; Kutsumura, N.; Otani, T.; Saito, T. *Tetrahedron* **2010,** *66* (3), 653-662.

140. Hlaváč, J.; Soural, M.; Krchňák, V. In *Solid-Phase Organic Synthesis*, John Wiley & Sons, Inc.: **2011**; pp 95-130.

PALACKY UNIVERSITY OLOMOUC

Faculty of Science

Department of Organic Chemistry

Development of Strategies for Solid-Phase Synthesis of Nitrogenous Heterocyclic Compounds Based on the 2- and 4-Nitrobenzenesulfonamide Chemistry

Summary of Ph.D. Thesis

Author: Mgr. Veronika Fülöpová

Supervisor: doc. RNDr. Miroslav Soural, Ph.D.

Supervisor-consultant: RNDr. Viktor Krchňák, CSc.

Olomouc   2015

The doctoral thesis is based on a research carried out within the study programme P1417 Chemistry (field of study Organic Chemistry) at the Department of Organic Chemistry, Faculty of Science, Palacky University in Olomouc.

Author (Ph.D. candidate):　　　**Mgr. Veronika Fülöpová**
Department of Organic Chemistry, Faculty of Science, Palacky University Olomouc

Supervisor:　　　**doc. RNDr. Miroslav Soural, Ph.D.**
Department of Organic Chemistry, Faculty of Science, Palacky University Olomouc

Supervisor-consultant:　　　**RNDr. Viktor Krchňák, CSc.**
Department of Organic Chemistry, Faculty of Science, Palacky University Olomouc

Department of Chemistry and Biochemistry, Research Faculty, University of Notre Dame, South Bend, Indiana, USA

Opponents:　　　**Dr hab. Paweł Zajdel**
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jagiellonian University, Kraków, Poland

The summary was distributed on …………………, **2015**

The oral defence will take place on ………………… in front of the committee for defence of the doctoral thesis at the Department of Organic Chemistry, Faculty of Science, Palacky University in Olomouc, 17. listopadu 12, Olomouc.
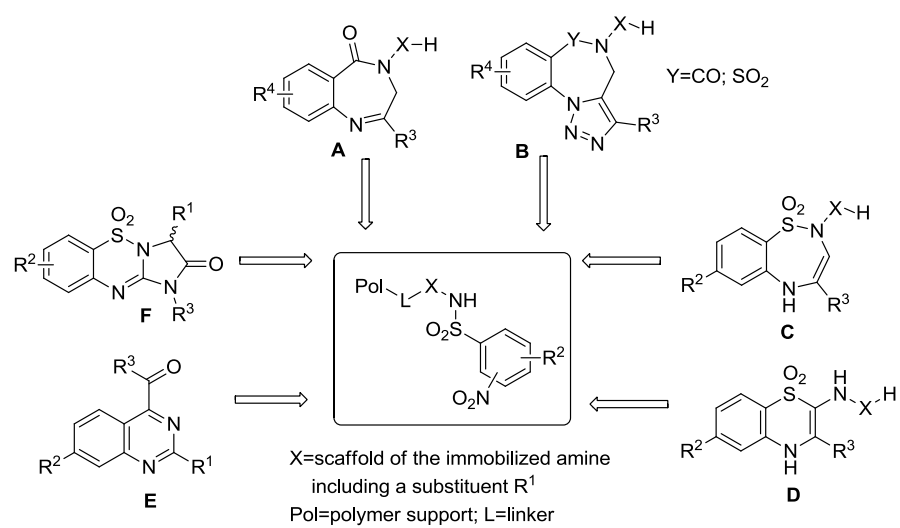
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Abstract

Solid-phase synthesis in connection with combinatorial chemistry represents one of the essential approaches leading to considerable array of diverse compounds collections (so called chemical libraries) in relatively short time. Such technique, widely used in the field of medicinal chemistry, facilitates the detailed structure-activity relationship (SAR) studies enabling a rapid detection of novel drug candidates. In this context, the submitted doctoral thesis deals with the development of simple procedures applicable for the preparation of libraries of selected heterocyclic compounds. In all of the introduced procedures the immobilized 2- or 4-nitrobenzenesulfonamides were used as the key intermediates. Different scenarios have been used in which the nitrobenzenesulfonyl (Nos) group was applied (1) only as a protective/activating group for Fukuyama selective monoalkylation followed by the cleavage of the sulfonamide scaffold, (2) as a building block after previous Fukuyma alkylation, or (3) as a building block without application of Fukuyama alkylation.

The major part of the research was focused on the preparation of compounds derived from the benzodiazepin-5-one and benzothiadiazepine 1,1-dioxide scaffolds. Firstly, a method for synthesis of trisubstituted 3*H*-benzo[*e*][1,4]diazepin-5(4*H*)-one derivatives (**A**, **B**) was developed based on the scenario (1). Fukuyama alkylation of 4-nitrobenzenesulfonamides provided the corresponding intermediates that were deprotected and subsequently converted to the target products under different cyclization conditions. Conversely, the corresponding benzothiadiazepine 1,1-dioxides (**C**) were obtained via the scenario (2). After alkylation of the starting nitrobenzenesulfonamide, the Nos group was kept in the structure as a building block to give the target scaffold. In this case, some of the prepared derivatives were not stable and unprecedented rearrangement was observed that yielded benzothiazine 1,1-dioxides **D**. Another part of this thesis was targeted to the synthesis of structurally different scaffolds. The corresponding nitrobenzenesulfonamides were converted to the trisubstituted benzoylquinazoline derivatives **E** with use of scenario (2). However, unlike the previous case, the final compounds were prepared via *C*-arylated intermediates. The last contribution was dedicated to the preparation of Anagrelide sulfonyl analogues **F**. In this case, 2-nitrobenzensulfonylchloride was used exclusively as a building block according to scenario (3).

General overview of the target scaffolds

X=scaffold of the immobilized amine
including a substituent R^1
Pol=polymer support; L=linker

Y=CO; SO$_2$

Souhrn

Syntéza na pevné fázi ve spojení s kombinatoriální chemií představuje jeden ze základních přístupů vedoucích k řadě rozmanitých sérií sloučenin (tzv. chemických knihoven) získaných v relativně krátkém čase. Tato technika, široce používaná v medicinální chemii, usnadňuje detailní studium vztahů mezi strukturou a biologickou aktivitou látek, což umožňuje rychle rozpoznat potenciální kandidáty na nová léčiva. V této souvislosti se předložená doktorská práce zabývá vývojem jednoduchých postupů aplikovatelných na syntézu knihoven vybraných heterocyklických sloučenin. Základem všech navržených metodik je příprava imobilizovaných 2- nebo 4-nitrobenzensulfonamidů jakožto klíčových meziproduktů, jejichž nitrobenzensulfonylová (Nos) skupina může být v syntéze využita třemi různými způsoby: (1) jako protektivní/aktivační jednotka umožňující Fukuyama selektivní monoalkylaci (po této reakci je Nos odštěpen), (2) jako stavební jednotka, která je následně po Fukuyama alkylaci ve struktuře zachována, nebo (3) jako stavební jednotka bez aplikace Fukuyama alkylace.

Hlavní část práce byla zaměřena na přípravu sloučenin odvozených od struktur benzodiazepin-5-onu a benzothiadiazepin 1,1-dioxidu. V tomto případě byla nejdříve vyvinuta metodika založená na přístupu (1), která byla následně aplikována na syntézu derivátů 3*H*-benzo[*e*][1,4]diazepin-5(4*H*)-onu (**A**, **B**). Fukuyama alkylace 4-nitrobenzensulfonamidů poskytla příslušné intermediáty, které byly deprotekovány a následně převedeny na cílové sloučeniny za různých cyklizačních podmínek. Naopak benzothiadiazepin 1,1-dioxidy (**C**) byly získány využitím přístupu (2). Po alkylaci výchozího nitrobenzensulfonamidu byla ve struktuře Nos skupina zachována pro výstavbu finálního skeletu. Některé z takto připravených derivátů nebyly stabilní, přičemž byl pozorován nečekaný přesmyk vedoucí k benzothiazin 1,1-dioxidům **D**. Další část práce byla zacílená na syntézu strukturně odlišných skeletů. Příslušné nitrobenzensulfonamidy byly převedeny na trisubstituované benzoylchinazoliny **E** s využitím přístupu (2). Nicméně, na rozdíl od předchozí syntézy, finální sloučeniny byly připraveny přes *C*-arylované intermediáty. Poslední příspěvek byl věnován přípravě sulfonyl analog Anagrelidu **F**. V tomto případě byl 2-nitrobenzensulfonylchlorid použit výhradně jako stavební jednotka podle přístupu (3).

Contents

9. Introduction

Over the last two hundred years, the traditional (solution-phase) organic chemistry has undergone a tumultuous development. At the beginning of the 19th century, it was only a branch of chaos that was later unified thanks to understanding of various theories, postulates, experimental basics and syntheses of the first organic compounds. Clarification of the structural concepts and introduction of the chemical nomenclature triggered a considerable development of industry and chemistry of natural materials.[1] To gain a broader spectrum of derivatives based on naturally-occurring motifs, chemists have been searching for novel and more efficient synthetic procedures. One of these methods involves reactions on insoluble polymer support, so called solid-phase synthesis. This technique was introduced in 1963, when Robert Bruce Merrifield published an article[2] describing a simple and highly effective method for the preparation of peptides utilizing polystyrene matrix as a support. With respect to the significant advantages of the method, such as a simple isolation of reaction intermediates resulting in the quick synthesis of target compounds collections, the contribution was later awarded by a Nobel Prize. Solid-phase technique have been widely used as a powerful tool in combinatorial chemistry, particularly for medicinal and pharmaceuticals goals. Less time-consuming syntheses and sufficient structural variability of chemical libraries has allowed a rapid identification of novel, biologically active molecules.

During our long-term research, we have been applying the advantages of solid-phase synthesis and paid our attention to a development of convenient protocols compatible with high-throughput synthesis of chemical entities based on privileged heterocyclic scaffolds. This work summarizes our recent results from this field.

10. Aims of the work

The general goal of this work consisted in a development of high-throughput solid-phase syntheses of selected heterocyclic compounds and determination of scope and limitations of the proposed synthetic pathways. In the individual reaction sequences, the polymer-supported nitrobenzenesulfonamides were used as the key intermediates for different chemical transformations to obtain the final derivatives. The first part of the research, based on the synthesis of benzodiazepine derivatives and Anagrelide sulfonyl analogues (Figures 1, 2 and 6), was carried out at the Institute of Molecular and Translational Medicine (IMTM) under the auspices of Department of Organic Chemistry, Palacky University in Olomouc. Preparation of benzothiadiazepine 1,1-dioxides, benzothiazine1,1-dioxides and benzoylquinazolines (Figures 3,4 and 5) was achieved during the internship at the University of Notre Dame, USA. Benzoylquinazoline derivatives were synthesized by American undergraduate students under the author's supervision.

2.1 Summary of the presented aims

Figure 1. Retrospective synthesis of benzo[1,4]-diazepin-5-one derivatives.[3]

Figure 2. Retrospective synthesis of benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-6(5*H*)-ones and their sulfonyl analogues.[4]

Figure 3. Retrospective synthesis of 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide derivatives.[5]

Figure 4. Retrospective synthesis of 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides.[6]

Figure 5. Retrospective traceless synthesis of benzoylquinazoline derivatives.[7]

Figure 6. Retrospective synthesis of Anagrelide Sulfonyl Analogues.[8]

X=scaffold of the immobilized amine
including a substituent R^1

n=1-3

11. Results and discussion

Numbering of the compounds, linkers and building blocks used in the individual sections is adopted from author´s articles.

3.1 Solid-phase synthesis of trisubstituted benzo[1,4]-diazepin-5-one derivatives

Based on the publication: Fülöpová, V.; Gucký, T.; Grepl, M.; Soural, M. *ACS Comb. Sci.* 2012, *14* (12), 651-656.[3]

The chemistry described in this subchapter takes advantage of the convenient solid-phase technique with application of the standard Fukuyama protocol (scenario (1), Abstract). In such case, the Nos group served as an activation unit for the alkylation with α-haloketones. After the cleavage of the 4-Nos group, the corresponding α-aminoketones were acylated with various *o*-nitrobenzoic acids. Reduction of the nitro group followed by spontaneous on-resin ring closure gave the target immobilized benzodiazepines. After acid-mediated cleavage the products were obtained in very good, crude purity and satisfactory overall yields.

3.1.1 Synthesis

The key building blocks for the preparation of the target substances were primary amines, α-bromoketones and *o*-nitrobenzoic acids. Following the Scheme 1, the immobilized amines **1** (Figure 7) were transformed to the corresponding α-aminoketones **4**. Surprisingly, sulfonylation of aminoderivatives with 4-NosCl was not quantitative in most cases (resins **1**(*1*), **1**(*3-5*)) and the reaction had to be repeated for completion. For the verification of the subsequent alkylation we used compound **2**(*3*) and five aromatic bromoketones substituted with electron-withdrawing as well as electron-donating groups were tested. Also one heterocyclic and one aliphatic haloketone was included (Figure 7).

Scheme 1. General synthetic route leading to the target benzodiazepines.[a]
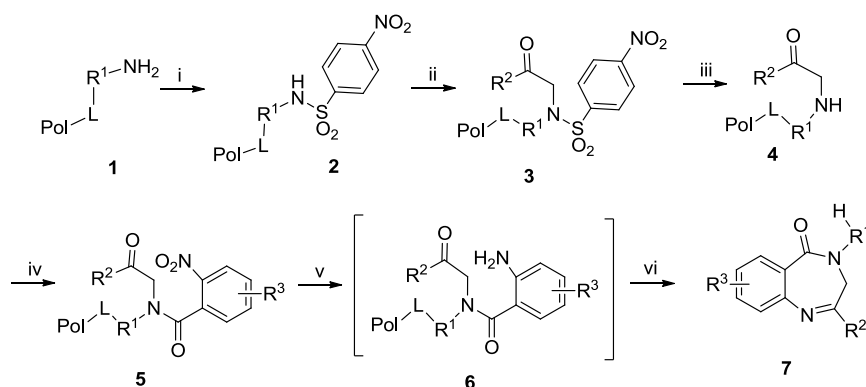
[a]Reagents: (i) 4-NosCl, 2,6-lutidine, DCM, rt, overnight; (ii) bromoketone, DIEA DMF, rt, overnight; (iii) 2-mercaptoethanol, DBU, rt, 10 min; (iv) o-nitrobenzoic acids, DIC, DMF, rt, overnight; (v) SnCl$_2$ · 2H$_2$O, DIEA, deoxygenated DMF, rt, overnight (repeated); (vi) 50% TFA in DCM, rt, 30 min.

Figure 7. List of used building blocks for substitution R^1, R^2 and R^3.

Alkylation with bromoketones *1-6* afforded sulfonamides **3**(*3,1-6*) with excellent purity (more than 90%, traces at 200-600 nm). A different result was obtained when chloroacetone *7* was used. Alkylation with this agent gave the desired intermediate **3**(*3,7*) in limited purity (up to 75 %). First, we tried to optimize the reaction conditions with use of different solvents, bases and temperature (see Table 1) but we did not manage to increase the

overall purity. Additionally, repetition of reaction conditions was tested but the purity decreased due to secondary products formation.

Table 1. Various reaction conditions for the preparation of intermediate **3**(*3,7*).

Reaction Conditions	Purity (%)[a]
DIEA, DMF, rt, 16 h	49
DIEA, DMF, rt, 16 h, repeated	70
DIEA, DMF, 40°C, 16 h	75
DIEA, DMF, 40°C, 16 h, repeated	46
proton sponge, DMF, rt, 16 h	70
DBU, DMF, rt, 16 h	mixture of compounds
DIEA, THF, rt, 16 h	mixture of compounds

[a]Calculated from LC traces at 200-600 nm after cleavage from the polymer support.

Denosylation of intermediates **3** afforded the corresponding aminoketones **4** that were acylated with *o*-nitrobenzoic acid. It should be noted that denosylation of intermediate **3**(*6,1*) required a significantly longer reaction time (60 min instead of typical 10 min procedure). After the acylation step, we observed formation of a side product, which was identified with the use of LC/MS analysis as the dealkylated byproduct **5-D**(R^1,-,*1*) (Scheme 2). Further investigation (cleavage of resins **5**(R^1,R^2,*1*) was performed for various time periods and identical mixtures of compounds were obtained) showed that the side product was not formed during the cleavage of intermediates **5** from the resin but during the acylation of intermediates **4** with *o*-nitrobenzoic acid.

Scheme 2. Dealkylation during acylation with *o*-nitrobenzoic acid.[a]

[a]Reagents: (i) *o*-nitrobenzoic acid, DIC, DMF, rt, 16 h.

In most of the tested cases, the dealkylation did not decrease the overall purity significantly and the intermediates **5** were obtained in a sufficient purity ranging from 72 to 99% (LC traces at 200-600 nm). However, in the case of intermediate **4**(*3,7*) prepared from chloroacetone, we obtained only a mixture of compounds without corresponding product. The

use of intermediate prepared from 3-bromo-2′-bromoacetophenone (*5*) led to quantitative dealkylation, intermediate prepared from 4-fluoro-2′-bromoacetophenone (*6*) dealkylated from 60% so the both building blocks were excluded. To suppress the side reaction we tested the acylation of intermediate **4**(*3,1*) with alternative agents (such as isatoic anhydride or anthranilic acid) and species (HOBt ester, symmetrical anhydride) but the purity of intermediates **5** was usually decreased (see Table 2). The best results were obtained with the use of a symmetrical anhydride prepared in situ from the corresponding *o*-nitrobenzoic acids in *N,N*-dimethylformamide.

Table 2. Summary of alkylated/dealkylated product ratio with use of intermediate **4**(*3,1*) and different acylating methods species.

Reagents	Alkylated (%)[a]	Dealkylated (%)[a]
o-nitrobenzoic acid, DIC, HOBt, DMF/DCM	64	30
o-nitrobenzoic acid, DIC, DMF	93	6
isatoic anhydride, DIPEA, DMF	0	21
anthranilic acid, DIC, HOBt, DMF/DCM	13	31
3-nitropthalic anhydride, DIEA, anhydrous THF	52	33
3-nitropyridine-2-carboxylic acid, DIC, DMF	85	2
4-bromo-2-nitrobenzoic acid, DIC, DMF	82	13
4-methyl-2-nitrobenzoic acid, DIC, DMF	72	20
5-methoxy-2-nitrobenzoic acid, DIC, DMF	87	12

[a]Calculated from LC traces at 200-600 nm after cleavage from the polymer support.

To introduce the third diversity position various *o*-nitrobenzoic acids were used (see Figure 7) to acylate intermediates **4**. After subsequent reduction of the nitro group and cleavage of the resulting material from the resin we did not detect the linear intermediates **6** but only the final products **7** (Scheme 3). When the sample of the resin **6**(*1,1,1*) was treated with Fmoc-Cl and cleaved, the corresponding *N*-Fmoc intermediate was not detected which indicates the ring closure took place on-resin after reduction of the nitro group. After the reduction step, we detected the appearance of a side product in each case (10-30%, LC traces at 200-600 nm). From LC traces, we have concluded that the structure of the side products corresponds to *N*-hydroxyderivatives **8** formed after incomplete reduction of the nitro group to hydroxylamine derivative. After repeating the reduction step, the side products **8** were not detected, which is in accordance with the theory of hydroxylamine intermediate formation.

Scheme 3. Side product formation after first-round reduction of precursors **5**.[*a*]

[*a*]Reagents: (i) $SnCl_2 \cdot 2H_2O$, DIEA, deoxygenated DMF, rt, 16 h; (ii) 50% TFA in DCM, rt, 30 min.

The final compounds **7** were generally obtained in very good crude purity (see Table 3), and their final purification was achieved by the use of flash chromatography on reversed phase C^{18} cartridges and subsequent reverse phase semipreparative HPLC. The use of C^{18} cartridges was necessary to remove tin(II) and tin(IV) salts otherwise HPLC column was clogged during purification. During the isolation process, an unexpected instability of amino group containing derivatives **7(*1*,R^2,R^3)** was observed. Because of their decomposition, such substances have not been isolated in a pure form. The structure of the final compounds was confirmed with the help of ^1H and ^{13}C NMR spectrometry and HRMS.

We also investigated the tautomerism of prepared 1,4-benzodiazepine-5-ones since at least two possible tautomeric form **7A** and **7B** have to be considered. We observed a broad singlet at around 4.20 ppm in the ^1H NMR spectra of the studied compounds which corresponds to a methylene group of tautomeric from **7A**. The tautomer **7A** seems to be the only present of the studied compounds under the experimental conditions used. We have proven this suggestion with the help of ^1H-^1H COSY and ^1H-^{13}C edited HSQC experiments in the case of compound **7(*5,1,1*)**.

Figure 8. Two possible tautomeric forms of the final products.

Table 3. List of final compounds **7**.

Cmpd	R^{1}H	R^2	R^3	Purity (%)^a (C^{18})	Purity (%)^a (HPLC)	Yield (%)^b
7(*1,1,1***)**	(CH$_2$)$_2$NH$_2$	4-MePh	H	77	-	NI
7(*1,2,1***)**	(CH$_2$)$_2$NH$_2$	4-OMePh	H	78	-	NI
7(*1,3,1***)**	(CH$_2$)$_2$NH$_2$	4-NH$_2$-3,5-di-ClPh	H	63	-	NI
7(*1,4,1***)**	(CH$_2$)$_2$NH$_2$	thiophene cycle	H	58	-	NI
7(*2,1,1***)**	(CH$_2$)$_2$OH	4-MePh	H	97	99	30
7(*3,1,1***)**	(CH$_2$)$_2$COOH	4-MePh	H	72	99	26
7(*3,2,1***)**	(CH$_2$)$_2$COOH	4-OMePh	H	93	99	47
7(*3,3,1***)**	(CH$_2$)$_2$COOH	4-NH$_2$-3,5-di-ClPh	H	88	99	33
7(*3,4,1***)**	(CH$_2$)$_2$COOH	thiophene cycle	H	83	99	22
7(*3,1,2***)**	(CH$_2$)$_2$COOH	4-MePh	8-Br	85	99	24
7(*3,1,3***)**	(CH$_2$)$_2$COOH	4-MePh	7-OMe	73	99	14
7(*3,1,4***)**	(CH$_2$)$_2$COOH	4-MePh	8-Me	87	99	15
7(*3,1,5***)**	(CH$_2$)$_2$COOH	4-MePh	NA	76	96	28
7(*4,1,1***)**	(CH$_2$)$_2$CONH$_2$	4-MePh	H	79	96	30
7(*5,1,1***)**	(CH$_2$)$_2$CONHPr	4-MePh	H	96	99	26
7(*6,1,1***)**	(CH$_2$)$_2$CONHBn	4-MePh	H	85	99	29

^{a}Calculated from LC traces at 200-600 nm. ^{b}Calculated from NMR spectra. NI = Not Isolated due to the decomposition during semiprep. HPLC isolation. NA = Not applicable.

3.2 Solid-phase synthesis of trisubstituted benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-6(5*H*)-ones and their sulfonyl analogues under mild reaction conditions

Based on the publication: Fülöpová, V.; Funk, P.; Popa, I.; McMaster, C.; Soural, M. *Eur. J. Org. Chem.* 2015, *2015* (16), 3551-3557.[4]

This subchapter describes the extension of the above summarized chemistry for the preparation of 1,4-benzodiazepinones with a condensed triazole cycle. The designed seven-step synthetic strategy utilized the polymer-supported 4-nitrobenzenesulfonamides that were

alkylated with various propargyl derivatives. Cleavage of the 4-Nos group from each of the key intermediates was followed by the acylation with different 2-azidobenzoic acids, leading to spontaneous intramolecular (Huisgen) 1,3-dipolar cycloaddition. After cleavage from the polymer support, target compounds were obtained in excellent crude purity and very good overall yields.

3.2.1 Synthesis

To test the suggested synthetic pathway (Scheme 4), resin bound amine **1**(*1*) (Figure 9) was sulfonylated with 4-NosCl. The corresponding sulfonamide **2**(*1*) was then alkylated with propargyl bromide according to the Fukuyama procedure[9] to give the propargyl derivative **3**(*1,1*) in excellent purity. After cleavage of the 4-Nos group with mercaptoethanol and DBU, the unmasked propargylamine **4**(*1,1*) was treated with a solution of 2-azidobenzoic acid in the presence of HOBt and DIC. Subsequent cleavage from the polymer support, with use of TFA in DCM, gave the target product **7**(*1,1,1*) in a crude purity of 86% (calculated from LC traces at 200-500 nm) and overall yield of 32% (after semipreparative HPLC purification). From this result we concluded that the Huisgen reaction took place spontaneously on the resin, giving the polymer supported product **6**(*1,1,1*). On the other hand, TFA mediated cyclization of intermediate **5**(*1,1,1*) during the acidic cleavage was also possible. To distinguish between the two alternatives, resin **6**(*1,1,1*) was submitted to a FTIR study. In the IR spectrum we did not observe the presence of a characteristic signal for -C≡C- stretch in the region 2100-2260 cm^{-1} which points to the formation of resin-bound triazolobenzodiazepinones **6**. The same evidence for quantitative conversion was used in paper[10] published in 2012.

Scheme 4. Synthesis of triazolobenzodiazepinones **7**.[a]
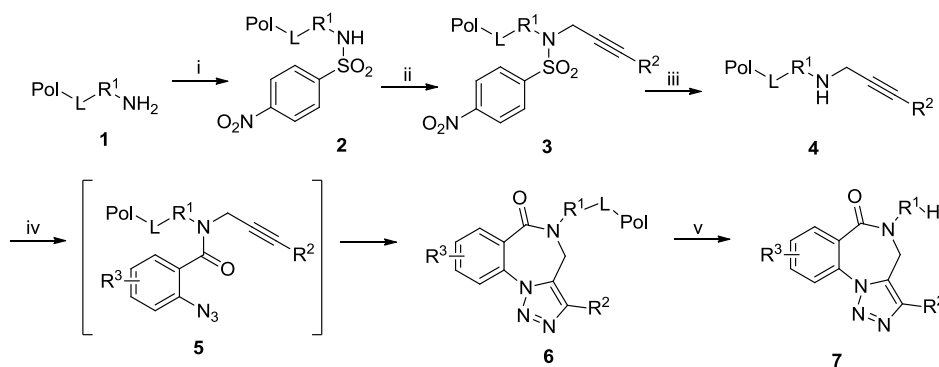
<superscript>a</superscript>Reagents: (i) 4-NosCl, 2,6-lutidine, DCM, rt, overnight; (ii) propargyl bromide derivative, DBU, DMSO, rt, overnight; (iii) 2-mercaptoethanol, DBU, DMF, rt, 30 min.; (iv) 2-azidobenzoic acid, HOBt, DIC, 50% DMF/DCM, rt, overnight; (v) 50% TFA in DCM, rt, 1 h.

Encouraged by the result, we subsequently tested the applicability of the synthetic strategy for the preparation of analogical triazolobenzothiadiazepine dioxides **10** (Scheme 5). Intermediate **4**(*1,1*) was treated with a solution of 2-azidobenzenesulfonyl chloride in the presence of 2,6-lutidine. As in the previous case, subsequent cleavage gave directly the desired product **10**(*1,1,7*), again with a very good crude purity of 75% and an overall yield of 71%.

Scheme 5. Synthesis of triazolobenzothiadiazepine dioxides **10**.<superscript>a</superscript>
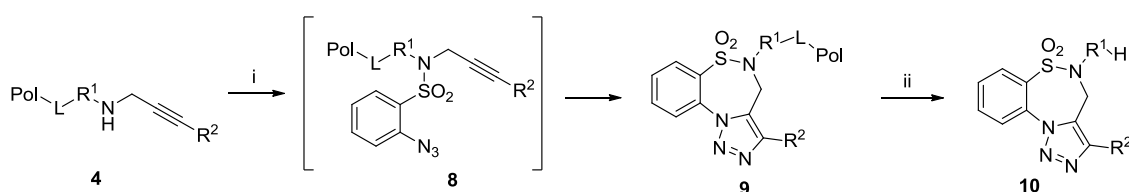
<superscript>a</superscript>Reagents: (i) 2-azidobenzenesulfonyl chloride, 2,6-lutidine, DCM rt, overnight; (ii) 50% TFA in DCM, rt, 1 h.

To evaluate the scope and limitations of this method, various *C*-substituted propargyl bromides were used in combination with unsubstituted 2-azidobenzoic acid. Similarly, a set of 2-azidobenzoic acids substituted with both electron donating and withdrawing groups were tested in combination with propargyl bromide and resin **1**(*1*). Finally, all the starting resin bound amines (see Figure 9) were tested in combination with unsubstituted 2-azidobenzoic acids and propargyl bromides. Applicability of the sequence for the preparation of triazolobenzothiadiazepine dioxides **10** was tested for various polymer supported amines in combination with unsubstituted 2-azidobenzenesulfonyl chloride and propargyl bromide. The list of propargyl and azido building blocks is displayed in Figure 9; all synthesized compounds are summarized in Table 4.

Figure 9. List of tested building blocks.

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L=Rink amide linker: (structure) **1**(*5*)   L=BAL: (structure) **1**(*6*)   (structure) **1**(*7*)

Building blocks for (R^2) substitution:

1   2   3   4

Building blocks for (R^3) substitution:

1   2   3   4   5   6   7

Table 4. Synthesized derivatives **7** and **10**.

Cmpd	Y	R^{1}H	R^2	R^3	Purity (%)^a	Yield (%)^b
7(*1,1,1*)	CO	(CH$_2$)$_2$COOH	H	H	86	32
7(*1,2,1*)	CO	(CH$_2$)$_2$COOH	Me	H	95	64
7(*1,3,1*)	CO	(CH$_2$)$_2$COOH	Ph	H	93	52
7(*1,1,2*)	CO	(CH$_2$)$_2$COOH	H	10-Me	81	77
7(*1,1,3*)	CO	(CH$_2$)$_2$COOH	H	10-OMe	89	69
7(*1,1,4*)	CO	(CH$_2$)$_2$COOH	H	8,10-di-Br	93	71
7(*1,1,5*)	CO	(CH$_2$)$_2$COOH	H	8-Cl	80	58
7(*1,1,6*)	CO	(CH$_2$)$_2$COOH	H	8-NO$_2$	86	64
7(*2,1,1*)	CO	(CH$_2$)$_2$OH	H	H	82	44
7(*3,1,1*)	CO	(CH$_2$)$_2$NH$_2$	H	H	89	36
7(*4,1,1*)	CO	(CH$_2$)$_2$CONH$_2$	H	H	83	68
7(*5,1,1*)	CO	(CH$_2$)$_2$CONHPr	H	H	84	70
7(*6,1,1*)	CO	(CH$_2$)$_2$CONHBn	H	H	94	76
10(*1,1,7*)	SO$_2$	(CH$_2$)$_2$COOH	H	H	75	71
10(*2,1,7*)	SO$_2$	(CH$_2$)$_2$OH	H	H	85	60
10(*3,1,7*)	SO$_2$	(CH$_2$)$_2$NH$_2$	H	H	93	38
10(*4,1,7*)	SO$_2$	(CH$_2$)$_2$CONH$_2$	H	H	83	67

10(*6,1,7*)	SO$_2$	(CH$_2$)$_2$CONHBn	H	H	91	62

*[a]*Calculated from LC traces at 200-500 nm. *[b]*Calculated from NMR spectra.

The developed methodology was also tested for immobilized Fmoc-Ala-OH (resin **1**(*2*)) in order to introduce the *α*-amino acid framework into the final structure. Surprisingly, alkylation of sulfonamide **2**(*2*) with propargyl bromide did not afford the intermediate **3**(*2,1*). Instead of this, LC/MS analysis showed the presence of an unknown product with MW = 248 and a high crude purity of 81%. Such molecular weight could correspond to reaction products **X**, **Y** or **Z** (Scheme 6). Rearrangement of various polymer supported 2-nitrobenzenesulfonamides based either on *C*- or *N*-arylation have been recently reported by Krchňák.[11,12] To identify the correct structure with NMR, the cleaved product was isolated by semipreparative HPLC, freeze dried and submitted to NMR study. Unfortunately, we observed full decomposition of the compound during the process which did not allow for the structural determination.

Scheme 6. Formation of unknown side product after propargylation of intermediate **2**(*7*).*[a]*
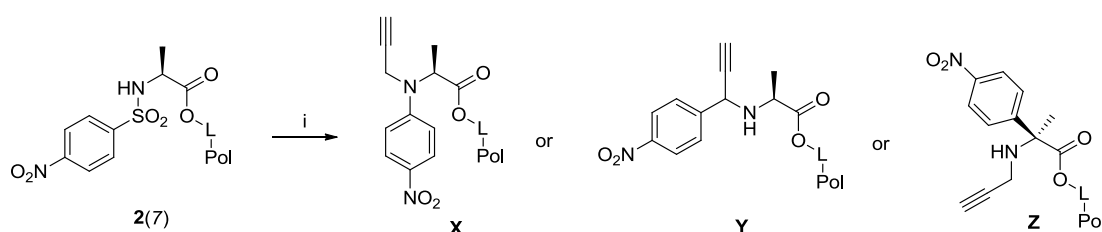
*[a]*Reagents: (i) propargyl bromide, DBU, DMSO, rt, overnight.

Aside from triazolobenzodiazepinones, we also focused on the possible applications of the synthetic pathway for the preparation of the corresponding dihydrotriazolobenzodiazepinone derivatives. For this purpose, the intermediate **2**(*7*) was alkylated with allyl bromide (Scheme 7). In contrast to the chemistry of triazolobenzodiazepinones described above, desulfonylation followed by acylation with 2-azidobenzoic acid and the final cleavage provided only the linear precursor 1**3**(*7,4,1*). Conventional heating of the resin **12**(*7,4,1*) to 60ºC did not furnish the desired product **14**(*7,4,1*). Further heating above 75 ºC led only to slow decomposition of the starting material to give a mixture of unknown compounds. Interestingly, microwave heating at 120 ºC for 5 minutes gave compound **15** as the major product. The analogous 2-azidobenzoic *N*-allylamides have previously been reported to follow a similar reaction course in solution-phase synthesis.[13,14]

Scheme7. Unsuccessful preparation of dihydrotriazolobenzodiazepinones **14**.[a]
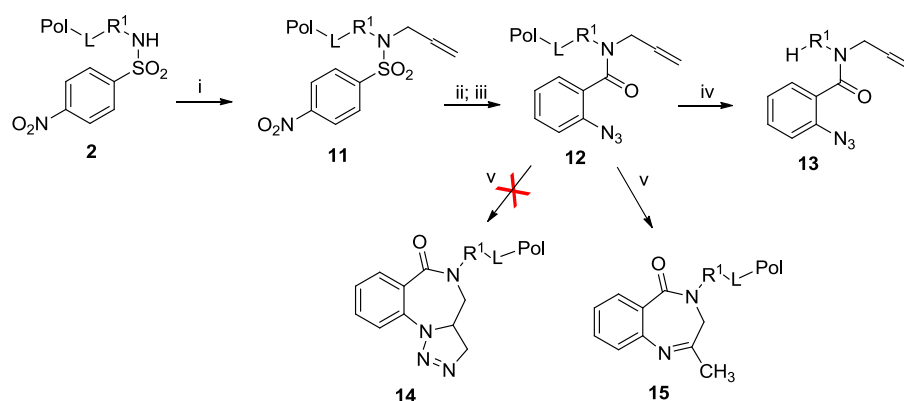
[a]Reagents: (i) allyl bromide, DBU, DMSO, rt, overnight; (ii) mercaptoethanol, DBU, DMF, rt, 30 min.; (iii) 2-azidobenzoic acid, HOBt, DIC, 50% DMF/DCM, rt, overnight; (iv) 50% TFA in DCM; (v) DMSO, MW, 120ºC, 5 min.

3.3 Solid-phase synthesis of trisubstituted 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide derivatives

Based on the publication: Fülöpová, V.; Krchňák, V. *ACS Comb. Sci.* 2014, *16* (8), 412-420.[5]

This subchapter is dedicated to the solid-phase synthesis of sulfonyl analogues of the previously described benzodiazepine derivatives **A** (General overview of the target scaffolds, Abstract). In this case, the 2-Nos group was preserved in the structure of nitrobenzenesulfonamide intermediates as a synthon according to scenario (2) (Abstract). After Fukuyama alkylation with variable bromoketones, the acyclic precursors were subjected acid-mediated release from the resin and the final cyclization was completed in solution-phase.

3.3.1 Synthesis

The solid-phase synthesis of 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxides was performed on resin-bound amines **1** (Figure 10). The Fmoc group was cleaved with piperidine, and the deprotected primary amines **2** were transformed to the corresponding 2-nitrobenzenesulfonamides **3** with an excellent rate of conversion (more than 93%, LC traces at 205-450 nm). The activating 2-Nos group of intermediates **3** enabled Fukuyama alkylation using aromatic bromoketones with both electron-withdrawing and electron-donating groups (Figure 10). This step afforded compounds **4** with good crude purity (from 73% to 93%, LC

traces at 205–450 nm). Alkylation was not quantitative despite attempts to alkylate valine **3**(*4,1,1*) three times and lysine **3**(*5,1,1*) twice.

Scheme 8. Solid-phase synthesis of the target compounds.[a]

[a]Reagents: (i) 50% PIP in DMF, rt, 30 min.; (ii) 2-NosCl, 2,6-lutidine, DCM, rt, overnight; (iii) bromoketone, DIEA, DMF, rt, overnight; (iv) Na$_2$S$_2$O$_4$, K$_2$CO$_3$, TBAHS, 50% H$_2$O/DCM, rt, overnight; (v) 50% TFA in DCM, rt, 1 h.; (vi) DMSO-d_6, rt, see Table 5 for the reaction time.

Figure 10. Structures and numbering of the tested building blocks.

21
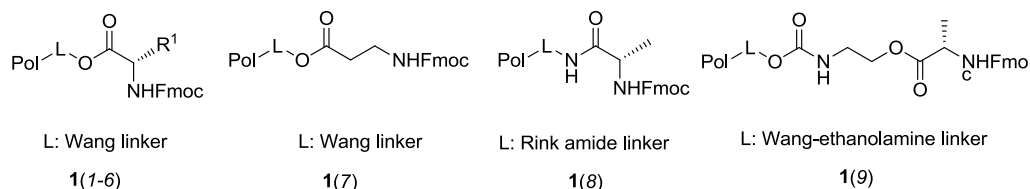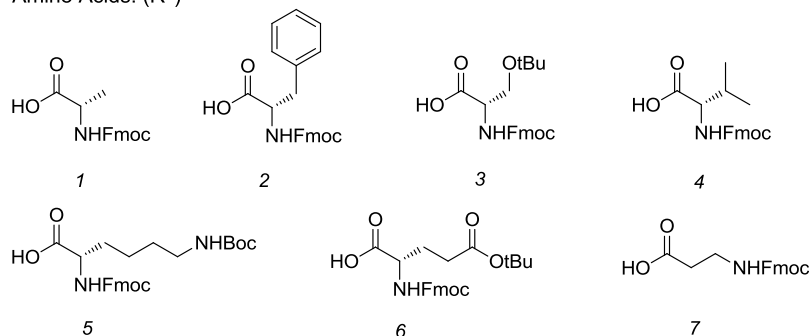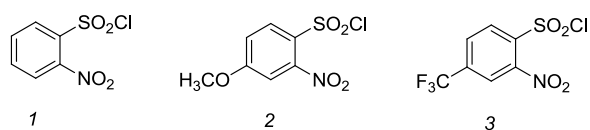
Bromoketones: (R³)
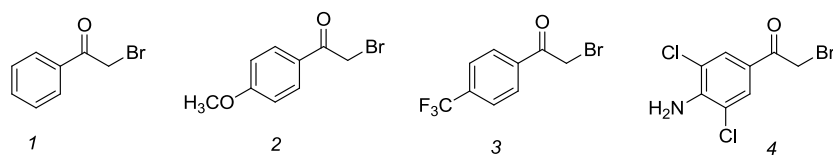
Resins **4** were exposed to a phase-transfer catalyzed nitro group reduction developed for polymer-supported synthesis.[15] The acyclic resin-bound precursors **5** were treated with a TFA cleavage cocktail to release the products from the resin.

The LC/MS analysis of the crude products revealed the presence of two major components, the mass spectra showed the appropriate positive and negative molecular ions corresponding to the acyclic compounds **6** and cyclized products **7**. To confirm their structures, the crude products were purified by reverse-phase semipreparative HPLC using mobile phases consisting of MeCN and 0.1% aqueous TFA. The acyclic compounds **6** spontaneously cyclized and formed **7**, however majority of compounds did not cyclize completely and the rate of cyclization depended on the linker and substituents R. The ^{1}H NMR spectra indicated complete cyclization to target products **7**(*1,1,2*), **7**(*2,1,1*), and **7**(*4,1,1*). On the other hand, compound **6**(*9,1,2*) contained only 5% of cyclic form **7**(*9,1,2*).

Structure determination:

Two tautomeric forms **7** and **8** (Figure 11) were investigated. We observed diagnostic resonances for the aniline proton at 8.32–9.03 ppm and for the olefinic proton at 5.25–5.38 ppm, confirming the tautomer **7**. Previously reported synthesis afforded the same tautomer.[16] A potential cause for the presence of tautomer **7** could be the extended conjugation involving two sp^2 carbons, whereas the sulfonamide is not planar. The presence of **7** could also be a result of the electron-withdrawing effect of the sulfonyl group. The tautomer **8** has never been observed in this case.

Figure 11. Two possible tautomeric forms.
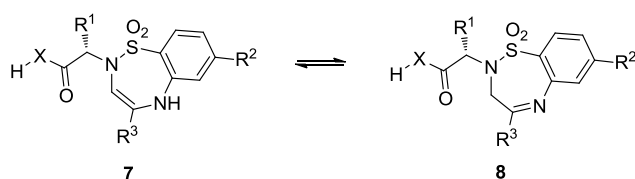
Cyclization:

A subset of the compounds was not completely cyclized, and a mixture of linear **6** and cyclic **7** compounds was obtained (Figure 12). We utilized the NMR diagnostic signals to calculate the **6**/**7** ratio and to study the progress of cyclization as a function of time. The cyclization time depended on substituents R^2 and R^3 and the linker (Table 5). To accelerate the cyclization by using different solvent and elevated temperature resulted in transformation of the target compounds **7** and deteriorating the overall purity. Thus, we used spontaneous cyclization in the DMSO solution at room temperature to prepare products **7**. Only compounds **6**(*9,1,2*) did not cyclized completely and attempts to force the cyclization (elevated temperature) resulted in decomposition.

Figure 12. ^{1}H NMR spectrum of a mixture of **6**(*1,2,1*) and **7**(*1,2,1*).

Table 5. Synthesized compounds **7**.

Cmpd	XH	R^1	R^2	R^3	Ratio **6**/**7** (%)^a	Cycl. time (days)	Purity (%)^c
7(*1,1,1*)	OH	Me	H	Ph	13:87	1.3	53

7(*1,1,2*)	OH	Me	H	4-OMePh	<1:>99	*b*	71
7(*1,1,3*)	OH	Me	H	4-CF$_3$Ph	14:86	1.3	77
7(*1,1,4*)	OH	Me	H	4-NH$_2$-3,5-di-ClPh	51:49	1.3	69
7(*1,2,1*)	OH	Me	H	Ph	50:50	3.3	67
7(*1,3,1*)	OH	Me	OMe	Ph	21:79	6.3	33
7(*2,1,1*)	OH	Bn	CF$_3$	Ph	<1:>99	*b*	65
7(*3,1,1*)	OH	CH$_2$OH	H	Ph	NI	NI	NI
7(*4,1,1*)	OH	^{i}Pr	H	Ph	<1:>99	*b*	67
7(*5,1,1*)	OH	(CH$_2$)$_4$NH$_2$	H	Ph	67:33	1.0	72
7(*6,1,1*)	OH	(CH$_2$)$_2$COOH	H	Ph	27:73	3.3	74
7(*7,1,1*)	OH	NA	H	Ph	9:91	*b*	71
7(*8,1,1*)	NH$_2$	Me	H	Ph	NI	NI	NI
7(*9,1,1*)	O(CH$_2$)$_2$NH$_2$	Me	H	Ph	67:27	6.3	65
7(*9,1,2*)	O(CH$_2$)$_2$NH$_2$	Me	H	4-OMePh	97:3	NI	NI
7(*9,1,3*)	O(CH$_2$)$_2$NH$_2$	Me	H	4-CF$_3$Ph	NI	NI	NI

[a]The ratio was calculated from the NMR spectra obtained after purification and overnight lyophilization; [b]NMR spectra indicated >90% of cyclic product **7** after purification and overnight lyophilization. [c]Crude purity of **6** + **7** estimated from LC traces at 205-450 nm. NA = Not Applicable and NI = Not Isolated (see the text).

<u>Scope and limitation:</u>

The NMR spectra and LC/MS data were used to evaluate the effects of the linker and the R groups on the transformation and to establish the scope and limitation of the benzothiadiazepine synthesis. In addition to the cyclization rate, we analysed the crude reaction products to determine the presence of side-products. LC/MS analysis revealed that the derivatives with strongly electron-withdrawing CF$_3$ groups underwent previously described partial *C*-arylation.[11] Thus, in addition to the main products **4**, the *C*-aryl derivatives **9** and indazole oxide **10** were also observed (Scheme 9). As a result of the presence of the *C*-arylated compound, after reduction of the nitro group, *C*-aryl **9** was converted to the indole derivative **11**. The indazole oxide **10**, also present on the resin, was reduced to indazole **12**. In addition, nitro reduction of compound **4**(*9,1,3*) afforded dealkylated product **13**(*9,1*) (16%, LC traces at 205–250 nm) and the indole derivative **11**(*9,1,3*) (32%, LC traces at 205–450 nm). No linear **6**(*9,1,3*) or cyclic **7**(*9,1,3*) compounds were observed.

We also evaluated the effects of the carboxy terminal functional groups of acids, amides, and esters. In the case of α-amino acids attached to the Wang resin, the indole-side products **11** were detected in the preparations, except for the Ala-derived compound. To confirm the structures, four indoles **11** and one indazole **12**(*1,3,1*) were isolated and fully characterized.

To address the effect of the amides, the Ala-derived, resin-bound acyclic intermediate was synthesized on a Rink amide resin. We observed substantial dealkylation during nitro reduction of compound **4**(*8,1,1*), and the dealkylated substance **13**(*8,1*) was isolated as a main product (45%, LC traces at 205–450 nm). We also detected the formation of indole **11**(*8,1,1*); however, the target amide **7**(*8,1,1*) was only obtained in a minute amount.

Substitutions on the two aromatic rings (R groups) did not have a remarkable effect; notably, only the electron donating OMe group in the R^2 position accelerated cyclization of the compound synthesized on the Wang linker. However, NMR monitoring revealed significant effects of the ethanolamine linker (amino acids 2-aminoethyl esters). The acyclic compounds **6**(*9*,R^2,R^3) were present at a substantially higher ratio, and their conversion was significantly slower than those of other substances.

Developed benzothiadiazepine synthesis was also compatible with the polymer-supported *β*-Ala-OH **1**(*7*). As expected, there was no difference compared with α-amino acids, and the final product **7**(*7,1,1*) was isolated.

Scheme 9. Side-product formation during the alkylation and reduction steps.[a]
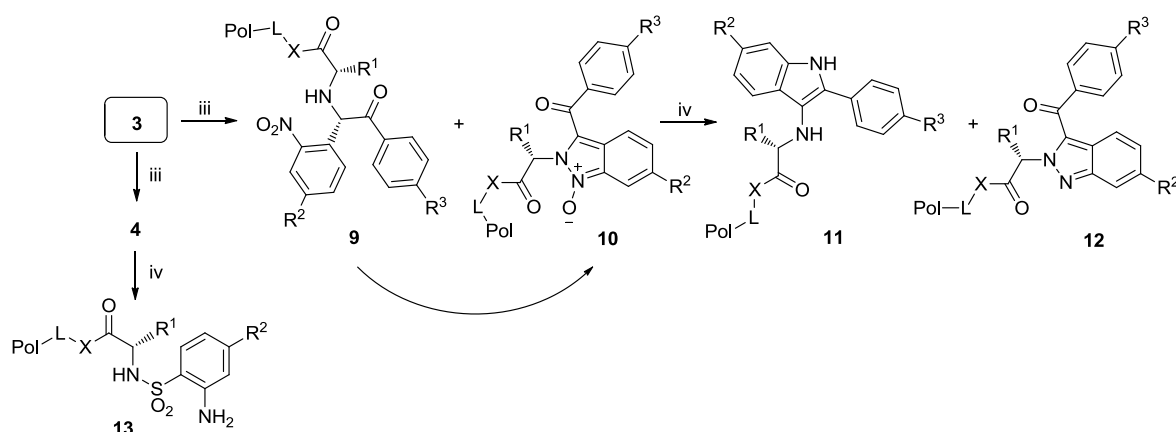
[a]Reagents: (iii) bromoketone, DIEA, DMF, rt, overnight; (iv) $Na_2S_2O_4$, K_2CO_3, TBAHS, 50% H_2O/DCM, rt, overnight.

The compound prepared using Ser(^{t}Bu) yielded morpholine derivatives. The *tert*-butyl group of **4**(*3,1,1*) was cleaved using a TFA-based cleavage cocktail, and the morpholine derivative **14** was formed (Scheme 10). After nitro reduction and subs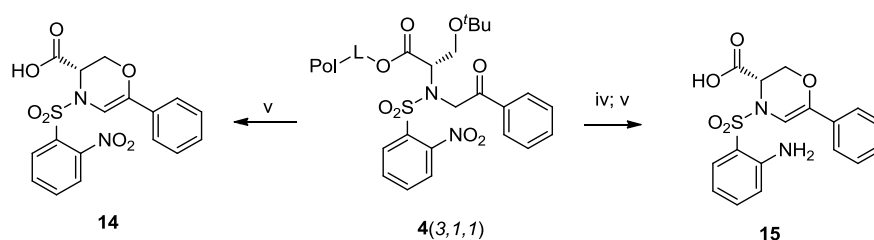equent cleavage from the resin, the benzodiazepine ring **7**(*3,1,1*) was not formed, and morpholine **15** was isolated in 43% yield.

Scheme 10. Morpholine derivative formation during acidic cleavage.[*a*]

[*a*]Reagents: (iv) Na$_2$S$_2$O$_4$, K$_2$CO$_3$, TBAHS, 50% H$_2$O/DCM, rt, overnight; (v) 50% TFA in DCM, rt, 60 min.

3.4 Ring contraction of 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxides: Access to 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides

Based on the publication: Fülöpová, V.; Krchňáková, A.; Schütznerová, E.; Zajíček, J.; Krchňák, V. *J. Org. Chem.* 2015**,** *80* (3), 1795-1801.[6]

During the previuos research we observed that some of prepared benzo[*f*][1,2,5]thiadiazepine 1,1-dioxides were not stable and they were converted to 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides. This subchapter describes the conversion leading to discover of unanticipated rearrangement involving carbon-sulfur bond formation under mild reaction conditions.

Brief description of investigation:

Compounds **1** (Scheme 11) were prepared according to previously described synthetic pathway (Scheme 8, subchapter 3.3.1), then cleaved from the resin with TFA in DCM and purified by reverse-phase HPLC. We evaluated the stability of target compounds **3** at room temperature and at -20 °C in DMSO, which is typically used for high-throughput screening. Whereas no significant instability was observed at the lower temperature, a new compound was formed at room temperature. This transformed product exhibited an MS ionization pattern identical with that of benzothiadiazepine dioxide **3** and was eluted with a shorter

retention time during LC/MS analysis. To obtain a preparative quantity of the new compound for a structure determination, the DMSO solution was exposed to elevated temperature (70 °C) to accelerate the transformation. Almost quantitative conversion was observed.

The new compound was isolated and purified. Its structure was determined as benzothiazine 1,1-dioxide **4**. Because of the pharmacological relevance of benzothiazine 1,1-dioxides **4** and the unprecedented and clean rearrangement of benzothiadiazepine 1,1-dioxides **3** to **4**, we prepared a set of model compounds **1** and focused on the scope and limitations of this interesting and synthetically useful ring contraction. Model compounds **1** were prepared using six amino acids (Ala (*1*), Phe (*2*), Glu (*3*), Val (*4*), Leu (*5*), Gly (*6*)) attached to Wang resin either directly or via an ethanolamine linker. We also used several types of NosCls and bromoketones with R^2 and R^3 groups containing neutral (H), electron-donating (OCH_3), and electron-withdrawing (CF_3) substituents (see Table 8 for synthesized compounds).

Scheme 11. Synthesis of benzothiazine 1,1-dioxides **4**.[a]
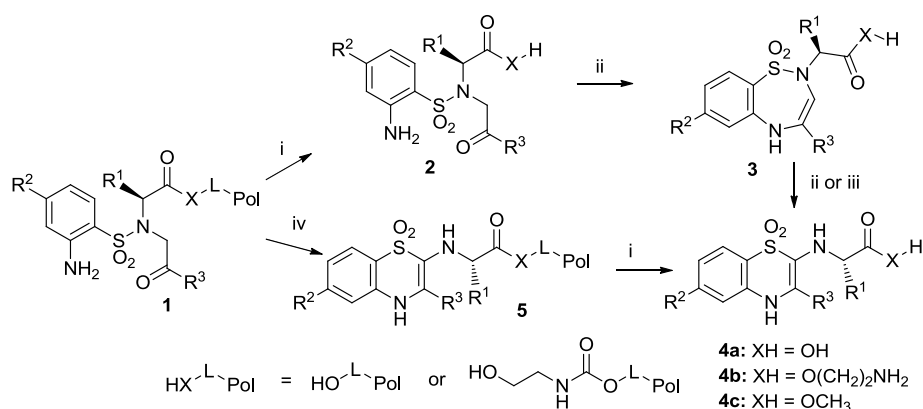
[a]Reagents: (i) 50% TFA in DCM, rt, 1 h.; (ii) DMSO-d_6, rt, see Supplementary information in the Ph.D thesis for the reaction time; (iii) DMSO, 70 °C, see Supplementary information in the Ph.D. thesis for the reaction time; (iv) 5% AcOH, DMSO, 80 °C, overnight.

Scope and limitations:

We assessed the effects of R groups and linkers on the ring contraction rate. Diagnostic peak in the ^{1}H-NMR spectra of compounds **2**, **3** and **4** allowed straightforward monitoring of the reaction (Figures 13). The type of amino acid, linker, and R^2 substituent did not significantly affect the rate of rearrangement (Table 6). In contrast, we observed a significant effect of the R^3 substituent. Whereas an electron-donating methoxy group at R^3 accelerated the reaction, a strongly electron-withdrawing CF_3 group gave no product **4**(*1,1,3*).

The time course of rearrangement at room temperature for selected compounds is tabulated in Supplementary information of the Ph.D. thesis.

Figure 13. ^{1}H-NMR spectrum of a mixture of **2b**(*1,1,2*), **3b**(*1,1,2*) and **4b**(*1,1,2*).
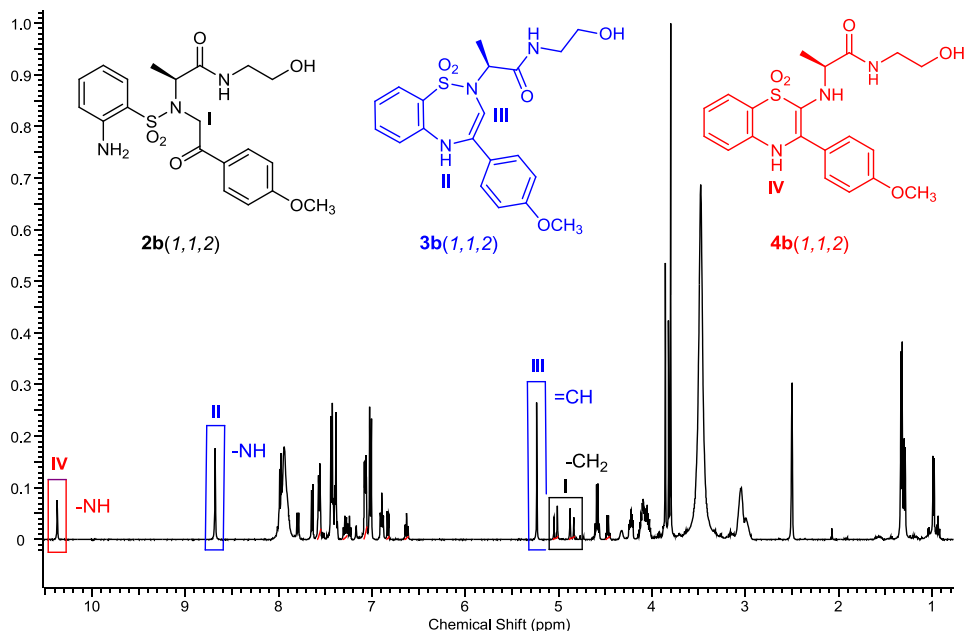
Table 6. Effect of substituents on the formation of **4**.

Cmpd	Amino acid	R[2]	R[3]	4 (%)[a]
4a(*1,1,1*)	Ala	H	H	10
4a(*1,1,2*)	Ala	H	OMe	56
4a(*1,1,3*)	Ala	H	CF$_3$	0
4a(*1,2,1*)	Ala	OMe	H	9
4a(*1,3,1*)	Ala	CF$_3$	H	20
4a(*2,1,1*)	Phe	H	H	42
4b(*1,1,1*)	Ala	H	H	54
4b(*1,1,2*)	Ala	H	OMe	82

[a]Calculated from ^{1}H-NMR spectra after ~23 days at room temperature.

The experiments in solution provided important information concerning the rate and mechanism of the ring contraction. Nevertheless, from the preparative point of view, we wished to carry out the contraction on resin as the last step of the synthesis, thereby allowing isolation of the final compounds by cleavage from the polymer support. We evaluated several different reaction conditions and observed that 5% AcOH in DMSO at 80 °C overnight

cleanly provided the expected products (Table 7). Synthesized compounds **4** are listed in Table 8 and their structure was unambiguously determined by analysis of 2D homonuclear (DQFCOSY and TOCSY) and heteronuclear ($^{13}C/^{15}N$ HSQC and HMBC) NMR spectra.

Table 7. Reaction conditions for ring contraction of compound **1**(*1,1,1*) on resin.

Solvent	Additive	T (°C)	SM (%)[a]	Thiazine (%)[a]
DMSO	5% H_2O	80	50	50
DMSO	5% AcOH	80	3	97
DMF	5% H_2O	80	99	<1
DMF	5% AcOH	80	90	10
DMSO	5% AcOH	70	92	8
DMSO	none	70	99	<1

[a]Relative ratio SM/Thiazine was calculated from LC traces at 205-450 nm.

Table 8. Synthesized benzothiadiazine 1,1-dioxides **4**.

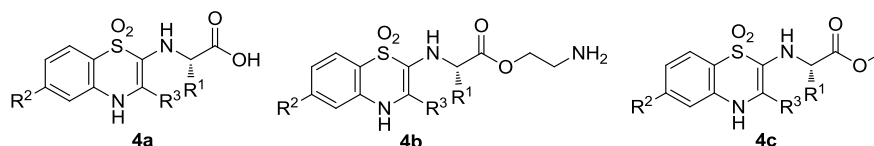| Cmpd	R^1	R^2	R^3	Method[a]	Reaction time(h)[a]	Purity (%)[b]	Yield (%)[c]
4a(*1,1,1*)	Me	H	Ph	B	16	65	41
4a(*1,1,4*)	Me	H	4-ClPh	B	16	40	25
4a(*1,1,5*)	Me	H	4-NH_2-3,5-di-ClPh	B	16	30	19
4b(*1,1,2*)	Me	H	4-OMePh	A	3.3	88	33
4b(*2,1,1*)	Bn	H	Ph	B	16	77	41
4b(*3,1,1*)	$(CH_2)_2COOH$	H	Ph	B	16	81	55
4b(*4,1,1*)	^iPr	H	Ph	B	16	65	35
4b(*5,1,1*)	$CH_2CH(CH_3)_2$	H	Ph	B	16	83	49
4b(*6,1,1*)	H	H	Ph	B	16	59	15
4c(*1,1,5*)	Me	H	4-NH_2-3,5-di-ClPh	B	16	21	12

[a]Method: (A) ring contraction in DMSO at 70°C; (B) ring contraction on resin at 80°C. [b]Crude purity estimated from LC traces at 205-450 nm. [c]Yield of six-step synthesis calculated from the NMR spectra.

Mechanism of rearrangement:

Compounds **3** were purified by reverse phase HPLC using 0.1% aqueous TFA and MeCN. After purification the solution was lyophilized, and it contained residual traces of TFA. We initially observed spontaneous rearrangement of HPLC-purified benzothiadiazepine 1,1-dioxides **3** in DMSO-d_6 solution at room temperature. The on-resin cyclization experiments confirmed the effect of an acid (Table 7). On the basis of these results, we surmised that the key step of the ring contraction is the attack of sulfur by the alkene electron pair, supported by the beneficial effect of electron-donating R groups (Scheme 12). There are two plausible pathways: ring opening followed by ring closure and direct contraction.

Scheme 12. Proposed mechanisms of 2-(alkylamino)-3-aryl-4*H*-benzo[*b*][1,4]thiazine 1,1-dioxide formation.
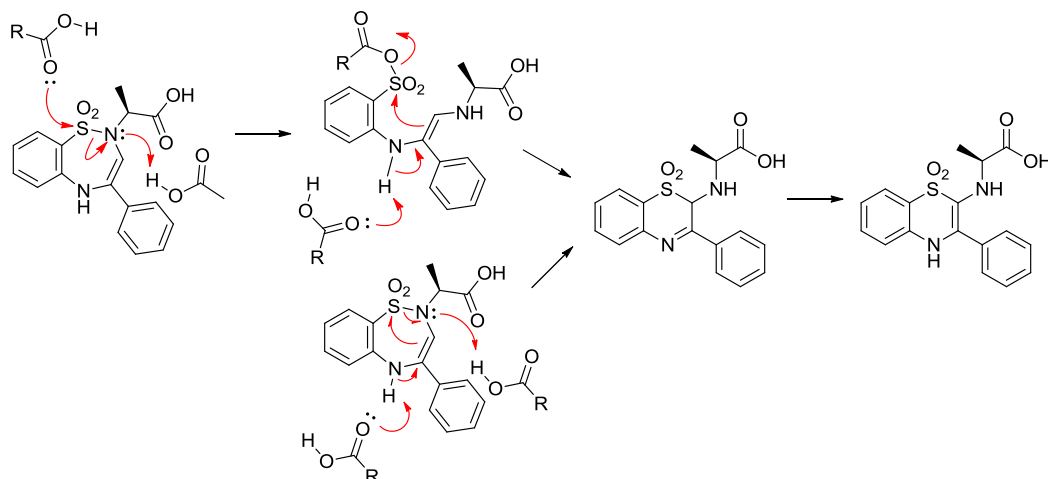
3.5 Traceless solid-phase synthesis of trisubstituted quinazolines

Based on the publication: Fülöpová, V.; Cziesla, L.; Fleming, M.; Lu, Y.; Voelker, A.; Krchňák, V. *ACS Comb. Sci.* 2015, Article in press.[7]

This subchapter describes the solid phase synthesis of quinazoline derivatives using scenario (2) (Abstract) via *C*-aryl and then *N*-oxide intermediate formation. The acyclic benzenesulfonamide precursor underwent base-catalyzed rearrangement involving carbon-carbon and nitrogen-nitrogen bond formation followed by ring expansion and yielded resin-bound dihydroquinazoline-2-carboxylic acid. Subsequent release from resin with TFA and base-mediated decarboxylation led to the target quinazolines. Final compounds listed in Table

9 have been prepared in the USA during undergraduate student's project under the supervision of author.

3.5.1 Synthesis

Traceless solid-phase synthesis of 4-benzoylquinazolines was carried out according to the Scheme 13 using three types of commercially available building blocks: Fmoc-protected α-amino acids, 2-NosCls and α-bromoacetophenones (Figure 14). The first reaction step involved immobilization of Fmoc-α-amino acids on Wang resin **1** via an ester bond. Removal of the Fmoc group provided the polymer-supported amines, which underwent sulfonylation with 2-NosCls to yield resin **2**. In the next step, the activating/protecting 2-Nos group allowed Fukuyama alkylation of the sulfonamide intermediates **2** with diversely substituted α-bromoacetophenones, thereby yielding resins **3** (typically > 65% as indicated by LC traces at 205–450 nm). To complete the conversion, alkylation step was repeated two times with **2(***1,1***)** and three times with **2(***3,2***)** and **2(***4,1***)**.

Scheme 13. Synthetic route for preparation of the target 4-benzoylquinazolines.[a]
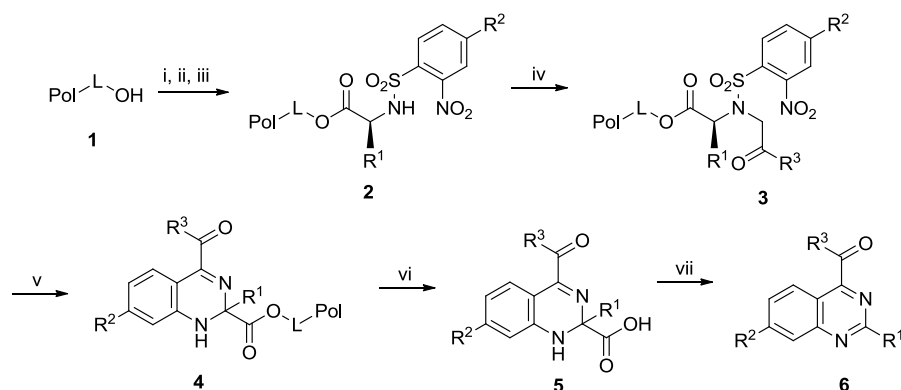
[a]Reagents: (i) Wang resin, Fmoc-α-amino acid, DMAP, DIC, DCM/DMF (1:1), rt, overnight; (ii) 50% PIP in DMF, rt, 15 min; (iii) 2-NosCl, 2,6-lutidine, DCM, rt, overnight; (iv) α-bromoacetophenone, DIEA, DMF, rt, overnight; (v) DBU, DMF, rt, overnight or 30 min for **3(***1,1,1***)** and **3(***3,1,2***)**; (vi) 50% TFA in DCM, rt, 1 h; (vii) neutralization with ammonium acetate, for reaction time see Table 9.

Figure 14. Fmoc-α-amino acids, 2-NosCl and α-bromoacetophenones used for the synthesis.
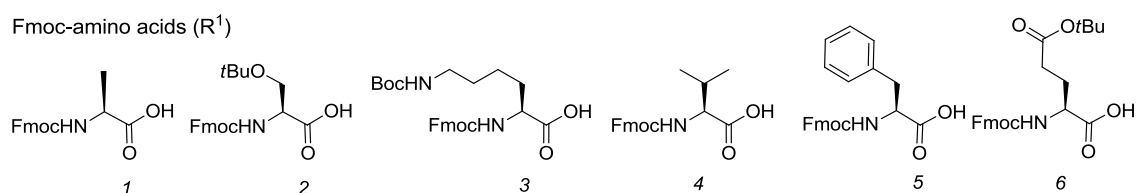
2-Nos-Cl (R^2)
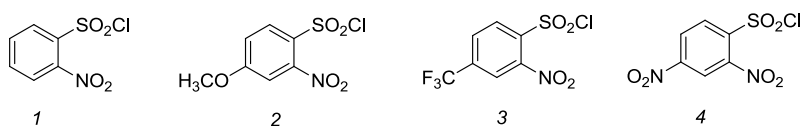
Bromoketones (R^3)
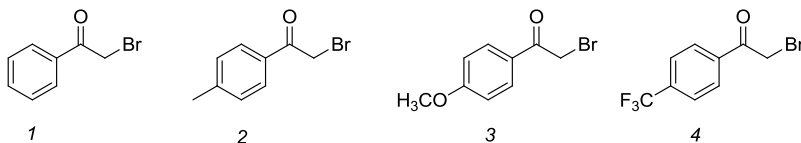
Polymer-supported acyclic alkylated sulfonamides **3** were treated with DBU to trigger base-catalyzed tandem carbon-carbon bond formation followed by cyclization to indazole oxides via nitrogen-nitrogen bond formation[11] and conversion of the indazole oxides to quinazolines **4**.[17] Resin-bound quinazolines were cleaved from the polymer support by a cleavage cocktail of 50% TFA in DCM, yielding carboxylates **5**. To determine the decarboxylation reaction conditions, cleaved crude samples were purified by reversed-phase HPLC in an aqueous ammonium acetate buffer. We observed that the ammonium acetate buffer that neutralized the crude preparations triggered spontaneous decarboxylation at ambient temperature. The rate of decarboxylation, which was monitored by LC/MS, was dependent on the character of the substituents on the aromatic rings; it slowed, as expected, in the case of electron-withdrawing substituents. In contrast, when the HP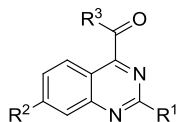LC purification was carried out in aqueous 0.1% TFA, only a trace amount of decarboxylated product was detected by LC/MS analysis. For practical syntheses, the HPLC purification of the crude samples after cleavage from the resin was eliminated and replaced by simple solid-phase extraction (SPE). The crude samples were neutralized with ammonium acetate, adsorbed onto octadecyl-functionalized silica gel and eluted with 80% acetonitrile in aqueous ammonium acetate buffer. Elimination of the C18 cartridge pre-purification step reduced the overall purity of crude compounds. The final products were purified by semi-preparative HPLC in acetonitrile-ammonium acetate aqueous buffer. The decarboxylation times for individual compounds are included in Table 9.

To address the scope and limitation of this route to quinazolines, we prepared resin-bound intermediates **4** using a set of α-amino acids, and 2-NosCls and α-bromoacetophenones containing electron-withdrawing and electron-donating groups (Figure 14). The synthesis was fully compatible with all of the tested building blocks, with the exception of 4-methoxy-2-

NosCl (*2*). The purities of the final crude compounds ranged from 52% to 70%, and the total yields were respectable given the 7-step synthesis (Table 9).

Table 9. Synthesized derivatives of quinazolines **6**.

Cmpd	R^1	R^2	R^3	Purity (%)[a]	Decarb. time[b]	Yield (%)[c]
6(*1,1,1*)	Me	H	Ph	52	1 d	12
6(*1,1,2*)	Me	H	4-MePh	53	2 d	56
6(*1,1,3*)	Me	H	4-OMePh	70	1d	16
6(*1,3,1*)	Me	CF$_3$	Ph	55	4 d	41
6(*1,4,1*)	Me	NO$_2$	Ph	69	5 d	8
6(*2,1,1*)	CH$_2$OH	H	Ph	64	1 d	23
6(*3,1,2*)	(CH$_2$)$_4$NH$_2$	H	4-MePh	52	1 d	35
6(*4,1,1*)	^{i}Pr	H	Ph	54	1 d	23
6(*4,1,4*)	^{i}Pr	H	4-CF$_3$Ph	63	5 d	28
6(*5,1,1*)	Bn	H	Ph	51	1 d	24
6(*6,1,1*)	(CH$_2$)$_2$COOH	H	Ph	59	1 d	38

[a]Purity of the crude product **5**. [b]Decarboxylation time. [c]Yield of HPLC-purified compounds **6** prepared after the 7-step synthesis.

The yields of compounds **6(*1,1,1*)** and **6(*1,4,1*)** were substantially lower compared to those of the other compounds. We analyzed the crude reaction mixture for **6(*1,4,1*)** and isolated the major purity, in addition to the expected product. The crude product mixture contained *N*-oxide derivative **7(*1,4,1*)**, which was also isolated and characterized.

Figure 15. Formation of the *N*-oxide side-product **7(*1,4,1*)**.
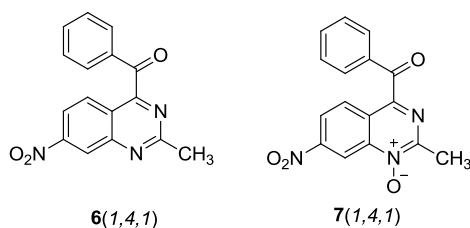
3.6 Solid-phase synthesis of Anagrelide sulfonyl analogues

Based on the publication: McMaster, C.; Fülöpová, V.; Popa, I.; Grepl, M.; Soural, M. *ACS Comb. Sci.* 2014, *16*, (5), 221-224.[8]

In the last contribution, we paid attention to development of the synthesis leading to Anagrelide sulfonyl analogues. For this purpose, the scenario (3) (Abstract) excluding the Fukuyama alkylation was utilized. Designed methodology was successful and used for the solid-phase synthesis of chemical library involving twenty 1,2,4-benzothiadiazine-1,1-dioxide scaffolds.[8] In this context, we were also interested in the modification of the target structure based on the ring expansion or introduction of substituent in N^1-position.

3.6.1 Synthesis

We have developed a general synthetic approach displayed in Scheme 14. The first two steps are based on a traditional solid-phase peptide synthesis using Wang resin and Fmoc-amino acid. After immobilization of Fmoc-α-Ala, the protecting Fmoc group was cleaved with piperidine. The intermediate **2** was reacted with 2-NosCl and subsequently the nitro group of sulfonamide **3** was reduced using the sodium dithionite method. Reaction of **4** with Fmoc-NCS gave the corresponding Fmoc-thiourea **5** which after treatment with DIC, furnished intermediate **6** in excellent crude purity (96%, calculated from LC traces at 200-500 nm). Cleavage of the Fmoc protecting group was followed by spontaneous intramolecular aminolysis of ester bond and the target product **7** was released from the polymer support by a cyclative cleavage. Separation of the product **7** from fluorenylmethylpiperidine by-product **8** was easily accomplished by reverse phase semipreparative HPLC. This methodology was successfully used for the split-and-split[18] solid-phase synthesis of chemical library involving twenty 3,10-Dihydro-2*H*-benzo[*e*]imidazo[1,2-*b*][1,2,4]thiadiazin-2-one 5,5-dioxide derivatives.[8]

To expand this area, we tested the developed synthetic pathway for the preparation of benzothiadiazine dioxide derivatives with expanded imidazole ring (Scheme 15). For this purpose, the Fmoc-*β*-Ala-OH and Fmoc-GABA-OH were immobilized on the Wang resin. Following the Scheme 15, the intermediates **9a** (80%, LC traces at 200-500 nm) and **9b** (95% LC traces at 200-500 nm) were prepared according to procedure described above. In the case of compound **9a**, the Fmoc-deprotection resulted in the cleavage of final formations from the

polymer support. Unexpectedly, LC/MS analysis of the reaction solution showed only 10% of product **10** and mixture of unknown compounds. Fmoc cleavage of GABA intermediate **9b** led to the deprotected compound **11** that was subsequently submitted to cyclization experiments (Table 10). However, none of the attempts provided the desired product **13**. For the cyclization in solution, the intermediate **11** was released from the resin by the cleavage cocktail consisting of TFA and DCM (1:1).

Scheme 14. Synthetic pathway leading to target compounds.[a]
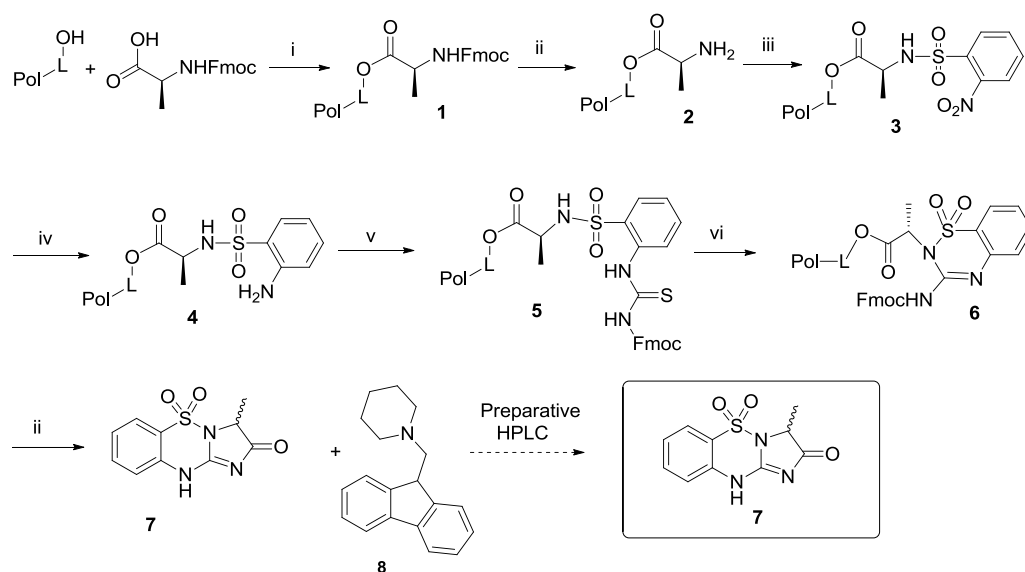
[a]Reagents and conditions: (i) DIC, HOBt, DMAP, DCM, DMF, rt, overnight; (ii) 50% PIP in DMF, rt, 30 min; (iii) 2-NosCl, 2,6-lutidine, DCM, rt, overnight; (iv) $Na_2S_2O_4$, K_2CO_3, TBAHS, H_2O, rt, 2 h; (v) Fmoc-NCS, THF, rt, overnight; (vi) DIC, DMF, rt, overnight.

Scheme 15. Unsuccessful expansion of the developed synthetic pathway.[a]

[a]Reagents and conditions: (i) 50% PIP in DMF, rt, 30 min; (ii) 50% TFA in DCM, rt, 30 min; (iii) see Table 10 for reaction conditions.

Table 10. Cyclization experiment with intermediates **11** and **12**.

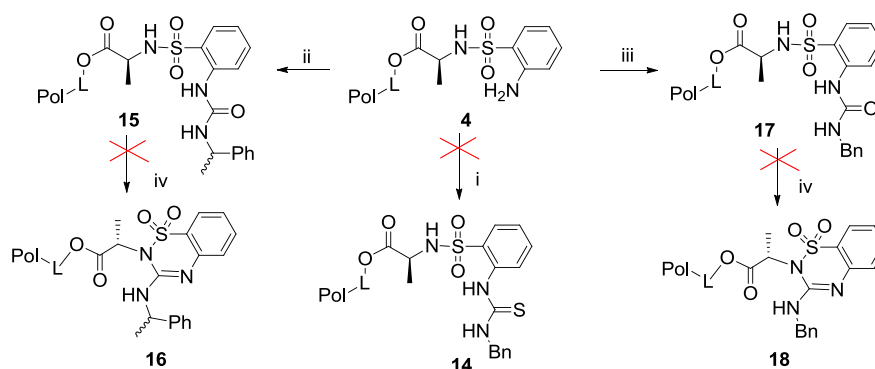| SM	Solvent	Temperature (ºC)	MW	Reaction time	SM/13 (%)[a]	Purity (%)[b]
11	DMSO	100	-	on	100/0	95
11	DMSO	120	✓	10 min	100/0	95
11	DMSO	120	✓	45 min	100/0	50
11	Diglyme	120	✓	10 min	100/0	55
12	DMSO	100	-	on	98/2	95
12	DMSO	120	✓	10 min	100/0	85
12	DMSO	120	✓	45 min	100/0	85

[a]Ratio **SM/13** calculated from LC traces at 200-500 nm. [b]Crude purity of **SM** + **13** calculated from LC traces at 200-500 nm.

In addition, we investigated a possible use of the developed reaction sequence for the preparation of N^1-substituted derivatives of compounds **7**. For this purpose, Fmoc-NCS was replaced with benzyl-NCS, benzyl-NCO or α-methylbenzyl-NCO (Scheme 16). Surprisingly, the reaction of **4** with benzyl-NCS did not take place, even at elevated temperature. Reaction with α–methylbenzyl-NCO led to 30% of compound **15** (LC traces at 200-500 nm). However, the subsequent cyclization with DIC did not afford the desired product **16**. Benzyl-NCO provided the intermediate **17** in excellent purity (95%, LC traces at 200-500 nm) but unfortunately, the following cyclization with DIC was not successful and only the starting material was recovered. When the resin **17** was heated to reflux in toluene, the compound was partially decomposed to give a mixture of unknown compounds. Optimization experiments are displayed in the Table 11 and 12.

Scheme 16. Attempt to increase diversity of target compounds – N^1 substitution.

[a]Reagents and conditions: (i) Bn-NCS; (ii) α-MeBn-NCO; (iii) Bn-NCO, (iv) cyclization with DIC; see Table 11 and 12 for more details.

Table 11. Optimization attempts for reaction with Bn-NCS, α-MeBn-NCO and Bn-NCO.

Agent	Solvent	Temperature (ºC)	React. time	**SM/P** (%)[a]	Purity (%)[b]
0.2 M Bn-NCS	THF	rt	on	**4/14** (100/0)	85
0.2 M Bn-NCS	DMF	rt	on	**4/14** (100/0)	85
0.2 M Bn-NCS	DMF	rt	on	**4/14** (90/10)	80
0.5 M Bn-NCS	Toluene	110	1 h	**4/14** (100/0)	85
0.5 M Bn-NCS	Toluene	110	on	**4/14** (100/0)	30
0.5 M MeBn-NCO	DMSO	rt	on	**4/15** (95/5)	79
0.5 M MeBn-NCO	THF	50	on	**4/15** (100/0)	85
0.5 M MeBn-NCO	Toluene	110	1h	**4/15** (70/30)	90
0.5 M MeBn-NCO	Toluene	110	on	**4/15** (70/30)	90
1.0 M MeBn-NCO	Toluene	110	on	**4/15** (70/30)	90
0.5 M Be-NCO	Toluene	110	1 h	**4/17** (0/100)	95

[a]Ratio **SM/P** calculated from LC traces at 200-500 nm. [b]Crude purity of **SM/P** calculated from LC traces at 200-500 nm.

Table 12. Cyclization experiment with intermediates **15** and **17**.

Cmpd	Agent	Solvent	Temperature (ºC)	React. time	**SM/P** (%)[a]	Purity (%)[b]
4/15 (70/30)	0.2 M DIC	DMF	rt	on	**15/16** (100/0)	30
17	0.2 M DIC	DMF	rt	on	**17/18** (100/0)	95
17	0.2 M DIC	DMF	50	on	**17/18** (100/0)	95
17	-	Toluene	112	1 h	**17/18** (100/0)	50

[a]Ratio **SM/P** calculated from LC traces at 200-500 nm. [b]Crude purity of **SM** + **P** calculated from LC traces at 200-500 nm.

12. Conclusion

Polymer-supported nitrobenzenesulfonamides prepared from 2-NosCls and 4-NosCls represent an important class of multifunctional intermediates suitable for many applications leading to less or more complex compounds. Apart from standard or modified Fukuyama alkylation protocol, the Nos group can be introduced into the structures also as a synthon. In such case, different interesting chemical transformations of 2-Nos intermediates have been observed. In this context, we applied a concept of the sulfonamide chemistry for the development of convenient and simple methodologies generating the novel heterocyclic derivatives.

The first part of the research was dedicated to the solid-phase synthesis of benzodiazepine derivatives **A** and **B**. For this purpose, we prepared benzenesulfonamide intermediates serving as precursors for subsequent Fukuyama alkylation with alkyl halides (α-bromoketones or propargyl bromides) followed by the deprotection of protecting/activating Nos group (scenario (1), Abstract). The resulting compounds were then converted to the appropriate heterocyclic products through the acylation with different functionalized benzoic acids and the final cyclization. In the case of benzo[*e*][1,4]diazepin-5-ones, we synthesized a small library of desired compounds; however, some limitations were observed: (i) the developed synthesis seems not to be applicable for bromoketones substituted with only electron withdrawing ligands due to formation of significant side-products, and (ii) derivatives with amino-alkyl chain in position *N*-R[1] exhibited an unexpected instability and decomposed during the semipreparative HPLC purification. Chemical library of eighteen benzodiazepine derivatives modified by the triazole ring was also prepared. The developed synthetic pathway was not successful for α-amino acids anchored on Wang linker due to formation of numerous by-products. However, according to latest results, it seems that the corresponding benzo-triazolobenzodiazepinones can be prepared from α-Ala-OH if piperazine linker attached on Wang resin is used.

Benzodiazepine sulfonyl analogues **C** were prepared according to similar procedures, but Nos group was kept in the final scaffold as a synthon (scenario (2), Abstract). In this case, we revealed limitation for CF$_3$ derivatives that underwent the substantial *C*-arylation during the alkylation step. Further, the carboxy-terminal functional group of cleaved linear compounds exhibited a significant effect on the cyclization outcome. Whereas the free acids provided the expected products, the amides did not afford desired compounds. In the case of
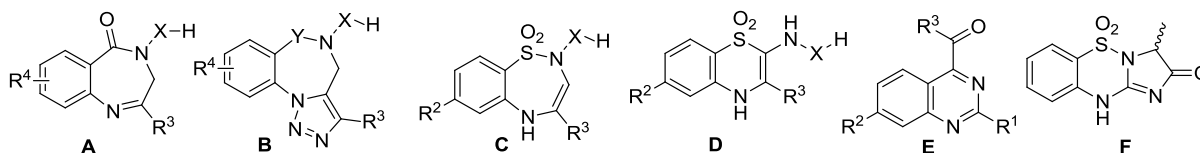
an ester-type linker, the conversion of the linear intermediates to the target thiadiazepine 1,1-dioxides was remarkably slower. During our investigations of thiadiazepine 1,1-dioxides in DMSO solution at room temperature, we discovered an unanticipated rearrangement yielding benzothiazine 1,1-dioxides **D**. For the preparative purpose, we developed a new method involving on-resin cyclization at elevated temperature.

The second part was focused on the traceless solid-phase synthesis of trisubstituted quinazoline derivatives **E**. The proposed methodology utilized the ability of 2-Nos group to undergo the basic-catalyzed *C*-arylation followed by formation of indazole oxide intermediate (scenario (2), Abstract). For the preparation of benzenesulfonamide precursors, variable-substituted 2-NosCls were used. However, only in the case of 4-NO$_2$-2-NosCl, the yield of product was significantly lower due to formation of the *N*-oxide 4-benzoyl-2-methyl-7-nitroquinoline that was also isolated. Despite this fact, the synthesis was compatible with a range of substituents on all building blocks.

Finally, we developed solid-phase methodology that was used for high-throughput synthesis of Anagrelide sulfonyl analogues **F** with two diversity positions.[8] The Nos group of benzenesulfonamide intermediate was kept in the final scaffold without the prior Fukuyama alkylation (scenario (3), Abstract). The reduction of a nitro group allowed the Fmoc-thiourea formation that was subsequently cyclized by treating with DIC. The final deprotection of Fmoc group afforded the target derivatives. We also tried to apply the developed procedure for further modification of the target scaffold (ring expansion, N^1-substitution), but the desired compounds were not obtained.

In conclusion, despite minor limitations, we have developed high-throughput solid-phase syntheses of various heterocyclic compounds involving six types of different scaffolds. With respect to simplicity of the synthetic protocols and number of available building blocks, the methodologies can be applied for the quick preparation of sizable chemical libraries to access large collections of pharmacologically promising compounds.

Structures of prepared compounds

13. References

1. http://www.ped.muni.cz/wchem/sm/hc/hist/19/organickachemie.html, **2011**.

2. Merrifield, R. B. *J. Am. Chem. Soc.* **1963,** *85* (14), 2149.

3. Fülöpová, V.; Gucký, T.; Grepl, M.; Soural, M. S *ACS Comb. Sci.* **2012,** *14* (12), 651.

4. Fülöpová, V.; Funk, P.; Popa, I.; McMaster, C.; Soural, M. *Eur. J. Chem.* **2015**, *2015* (16), 3551.

5. Fülöpová, V.; Krchňák, V. *ACS Comb. Sci.* **2014,** *16* (8), 412.

6. Fülöpová, V.; Krchňáková, A.; Schütznerová, E.; Zajíček, J.; Krchňák, V. *J. Org. Chem.* **2015,** *80* (3), 1795.

7. Fülöpová, V.; Cziesla, L.; Fleming, M.; Lu, Y.; Voelker, A.; Krchňák, V. *ACS Comb. Sci.* **2015**, Article in press.

8. McMaster, C.; Fülöpová, V.; Popa, I.; Grepl, M.; Soural, M. *ACS Comb. Sci.* **2014,** *16* (5), 221.

9. Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995,** *36* (36), 6373.

10. Cornier, P. G.; Boggián, D. B.; Mata, E. G.; Delpiccolo, C. M. L. *Tetrahedron Lett.* **2012,** *53* (6), 632-636.

11. Bouillon, I.; Zajíček, J.; Pudelová, N.; Krchňák, V. *J. Org. Chem.* **2008,** *73* (22), 9027.

12. Smyslová, P.; Kisseljova, K.; Krchňák, V. *ACS Comb. Sci.* **2014,** *16* (9), 500.

13. Beccalli, E.; Broggini, G.; Paladino, G.; Pilati, T.; Pontremoli, G. *Tetrahedron: Asymmetry* **2004,** *15* (4), 687.

14. Molteni, G.; Broggini, G.; Pilati, T. *Tetrahedron: Asymmetry* **2002,** *13* (22), 2491.

15. Kaplánek, R.; Krchňák, V. *Tetrahedron Lett.* **2013,** *54* (21), 2600.

16. Sternbach, L. H.; Field, G. F.; Zally, W. J. *J. Org. Chem.* **1971,** *36* (20), 2968.

17. Křupková, S.; Slough, G. A.; Krchňák, V. *J. Org. Chem.* **2010,** *75* (13), 4562.

18. Hlaváč, J.; Soural, M.; Krchňák, V. In *Solid-Phase Organic Synthesis*, John Wiley & Sons, Inc.: **2011**; 95.