Bicyclic 6-6 Systems With One Bridgehead Nitrogen Atom: Two Extra Heteroatoms 1:1

Mikhailo V Slivka, Maksym M Fizer, and Nataliya I Korol, Department of Organic Chemistry, Chemical Faculty, Uzhhorod University, Uzhhorod, Ukraine

Email addresses: mikhailslivka@gmail.com (M.V. Slivka); mmfizer@gmail.com (M.M. Fizer); nataliya.korol@uzhnu.edu.ua (N.I. Korol)

Nomenclature

ADMA Asymmetric dimethylarginine
AIBN Azobisisobutyronitrile
AIM Atoms-in-molecules
BODIPY 4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene
CDI Carbonyl diimidazole
DCM Dichloromethane
DDAH Dimethylarginine dimethylaminohydrolase
DDQ 2,3-Dichloro-5,6-dicyanobenzoquinone
DEAD Diethyl azodicarboxylate
DFT Density functional theory
DIEA Diisopropylethylamine
DMA Dimethylacetamide
ECP Effective core potential
FQA Fumiquinazoline A
FQF Fumiquinazoline F
GIAO Gauge-independent atomic orbital
HDDA Hexadehydro-Diels-Alder
HFIP 1,1,1,3,3,3-Hexafluoropropanol-2
L-Ala L-Alanine
LiHMDS Lithium hexamethyldisilazide
L-Trp L-Tryptophan
mCPBA Meta-chloroperoxybenzoic acid
MCR Multicomponent reaction
MS Molecular sieves
MWI Microwave irradiation
NBO Natural bond orbital
NCTS *N*-Cyano-4-methyl-*N*-phenylbenzenesulfonamide
NRPS Nonribosomal peptide synthetase
PIDA Phenyliodine diacetate
PMB *p*-Methoxybenzyl
TBAF Tetra-*n*-butylammonium fluoride
TD-DFT Time-dependent density functional theory
TES Triethylsilane
TFA Trifluoroacetic acid
TFE 2,2,2-Trifluoroethanol
THDTAP 2,3,4,6-Tetrahydro-1,6-dithia-3a-azaphenalene
TTMSS Tris(trimethylsilyl)silane

1 Introduction

This article covers bicyclic 6-6 ring systems with one bridgehead nitrogen atom and two extra heteroatoms and their benzo-fused derivatives. It reviews the literature from 2007 to early 2019 and is the continuation of previous edition of CHEC III[1] covering the literature up to 2006. Condensed heterocycles discussed in this article are grouped into six sections:

Section 2 Systems with two extra O atoms, 1:1, and their benzo analogs.
Section 3 Systems with one N and one O extra atoms, 1:1, and their benzo analogs.
Section 4 Systems with one O and one S extra atoms, 1:1, and their benzo analogs.
Section 5 Systems with two extra N atoms, 1:1, and their benzo analogs.
Section 6 Systems with one extra N atom and one extra S atom, 1:1, and their benzo analogs.
Section 7 Systems with two extra S atoms, 1:1, and their benzo analogs.

No system with heteroatoms different from above has been reported in the reviewed period.. Compounds given in patents without chemical properties and synthesis are not part of this review. Synthesis, reactivity, structural features, application and important compounds are discussed within each section. Nomenclature is shown in **Table 1**.

2 Systems with two O extra atoms, 1:1, and their benzo analogs

2.1 [1,2]Oxazino[2,3-*b*][1,2]oxazines and their benzo analogs

The [3 + 3]cycloaddition of nitronates with donor-acceptor cyclopropanes leads to stereoselective formation of polysubstituted [1,2]oxazino[2,3-*b*][1,2]oxazines **2-1-1.**[1] In two cases, a mixture of **2-1-1** and **2-1-2** with the domination of the first product was obtained (Eq. **1**). The reaction is catalyzed by ytterbium trifluoromethanesulfonate. The use of common Lewis acids like $SnCl_4$ and $TiCl_4$, led only to the decay products. The use of molecular sieves or non-hydrated Lewis acids is of key importance: the yield of product decreases in the

Table 1 Bicyclic 6-6 N-bridgehead systems with two extra heteroatoms, 1:1, and their benzo-fused derivatives discussed in this review.

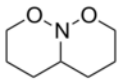
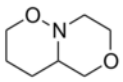
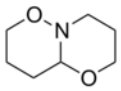
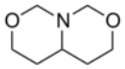
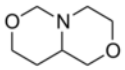
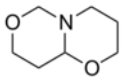
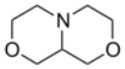
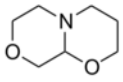
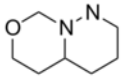
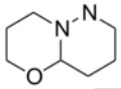
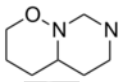
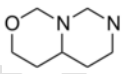
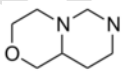
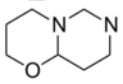
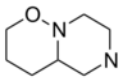
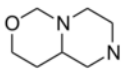
Fused system number	*Ring system*	*Chemical Abstract Name of Basic Structure* *Autonom name (if different from CA name)*
Section 2		
2-1		[1,2]Oxazino[2,3-*b*][1,2]oxazine
2-2		[1,4]Oxazino[4,3-*b*][1,2]oxazine
2-3		[1,3]Oxazino[3,2-b][1,2]oxazine
2-4		[1,3]Oxazino[3,4-*c*][1,3]oxazine
2-5		[1,4]Oxazino[4,3-*c*][1,3]oxazine
2-6		[1,3]Oxazino[4,3-*b*][1,3]oxazine
2-7		[1,4]Oxazino[3,4-*c*][1,4]oxazine
2-8		[1,4]Oxazino[3,4-*b*][1,3]oxazine
Section 3		
3-1		Pyridazino[1,6-*c*][1,3]oxazine
3-2		Pyridazino[6,1-*b*][1,3]oxazine
3-3		Pyrimido[1,6-*b*][1,2]oxazine
3-4		Pyrimido[1,6-*c*][1,3]oxazine
3-5		Pyrimido[6,1-*c*][1,4]oxazine
3-6		Pyrimido[6,1-*b*][1,3]oxazine
3-7		Pyrazino[1,2-*b*][1,2]oxazine
3-8		Pyrazino[1,2-*c*][1,3]oxazine

Table 1 (Continued)

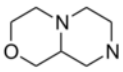
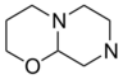
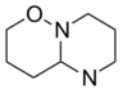
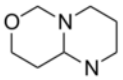
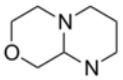
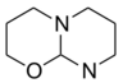
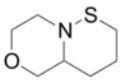
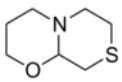
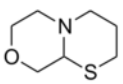
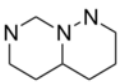
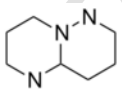
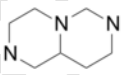
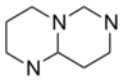
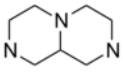
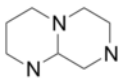
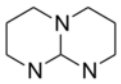
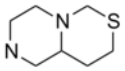
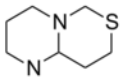
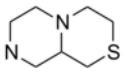
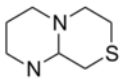
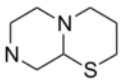
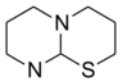
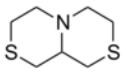
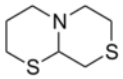
Fused system number	*Ring system*	*Chemical Abstract Name of Basic Structure* *Autonom name (if different from CA name)*
3-9		Pyrazino[2,1-*c*][1,4]oxazine
3-10		Pyrazino[2,1-*b*][1,3]oxazine
3-11		Pyrimido[1,2-*b*][1,2]oxazine
3-12		Pyrimido[1,2-*c*][1,3]oxazine
3-13		Pyrimido[2,1-*c*][1,4]oxazine
3-14		Pyrimido[2,1-*b*][1,3]oxazine
Section 4		
4-1		[1,2]Thiazino[3,2-*c*][1,4]oxazine
4-2		[1,4]Thiazino[3,4-*b*][1,3]oxazine
4-3		[1,3]Thiazino[2,3-*c*][1,4]oxazine
Section 5		
5-1		Pyrimido[1,6-*b*]pyridazine
5-2		Pyrimido[1,2-*b*]pyridazine
5-3		Pyrazino[1,2-*c*]pyrimidine
5-4		Pyrimido[1,6-*a*]pyrimidine
5-5		Pyrazino[1,2-*a*]pyrazine
5-6		Pyrazino[1,2-*a*]pyrimidine

Table 1 (Continued)

Fused system number	*Ring system*	*Chemical Abstract Name of Basic Structure* *Autonom name (if different from CA name)*
5-7		Pyrimido[1,2-*a*]pyrimidine
Section 6		
6-1		Pyrazino[1,2-*c*][1,3]thiazine
6-2		Pyrimido[1,2-*c*][1,3]thiazine
6-3		Pyrazino[2,1-*c*][1,4]thiazine
6-4		Pyrimido[2,1-*c*][1,4]thiazine
6-5		Pyrazino[2,1-*b*][1,3]thiazine
6-6		Pyrimido[2,1-*b*][1,3]thiazine
Section 7		
7-1		[1,4]Thiazino[3,4-*c*][1,4]thiazine
7-2		[1,4]Thiazino[3,4-*b*][1,3]thiazine

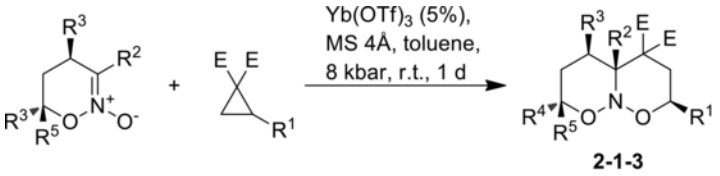
presence of $Yb(OTf)_3*6H_2O$ without MS 4 Å.

(1)

E = COOMe
R^1 = 4-$MeOC_6H_4$, 4-ClC_6H_4-, Ph
R^2 = H R^3 = Me, Ph, n-Pr; R^2R^3 = $(CH_2)_4$
R^4 = H, Me R^5 = Ph, 4-Cl-C_6H_4, 4-$MeOC_6H_4$, 2-thienyl

A similar [3 + 3]-cycloaddition of cyclopropane dicarboxylates with 3-methyl-5,6-dihydro-4*H*-1,2-oxazine *N*-oxides was published.[2] The authors developed a synthetic method under hyperbaric conditions in the presence of $Yb(OTf)_3$ (Eq. **2**). The proposed mechanism is similar to that of the reaction of donor-acceptor cyclopropanes with nitrones and involves O-attack of nitronate on a Lewis acid coordinated cyclopropane with a concomitant ring closure. The investigated [3 + 3]-cycloaddition is highly stereoselective, and target

nitroso acetals **2-1-3** were obtained in high yields.



(2)

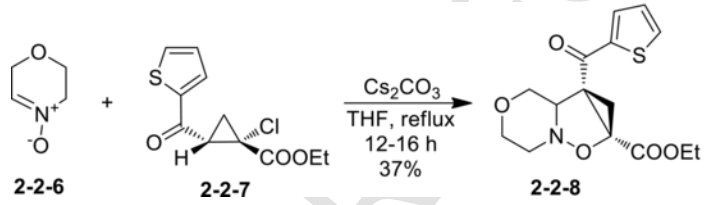
E = COOMe;
R^1 = CH=CH_2, (*E*)-CH=CH-Ph, 4-ClC_6H_4-, Ph;
R^2 = Me, Et; R^3 = H, Ph, 4-$MeOC_6H_4$-;
R^4 = H, Me, CH_2Cl, *n*-Pr, Ph; R^5 = H, Me. E = COOMe;

Stereoelectronic interactions in an O–N–O unit was experimentally and theoretically studied by Nelyubina and Lyssenko.[3] The analysis of electron density computed at B3LYP/6-311G(d,p) level of theory in terms of Atoms-In-Molecules (AIM) theory clearly indicates the energy loss of the oxygen atom that acts as a donor of a lone pair, while energy for the nitrogen and the second oxygen atom remains relatively constant. The AIM-based atomic energies within the ONO unit, both calculated and obtained experimentally, provided the estimates for the strength of the stereoelectronic interaction lp-O(1)–N(1)–O(2) that are consistent with the natural bond orbital (NBO) analysis.

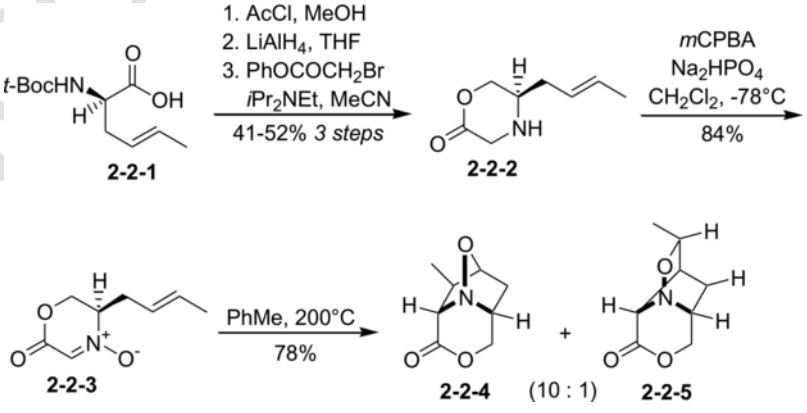
2.2 [1,4]Oxazino[4,3-*b*][1,2]oxazines

Tricyclic system with [1,4]oxazino[4,3-*b*][1,2]oxazine structure was obtained as a byproduct in.[4] The free morpholinone **2-2-2** was obtained in three steps starting from **2-2-1** (**Scheme 1**). Removal of the *t*-Boc group in **2-2-1** with the formation of a methyl ester followed by lithium aluminium hydride reduction led to the optically pure crotyl glycinol which then was treated with α-bromophenyl acetate. Oxidation of the resultant product **2-2-2** was performed by treatment with purified *m*CPBA in dichloromethane to give an 84% yield of the corresponding oxazinone N-oxide **2-2-3**. Heating of **2-3-3** to elevated temperatures gave the mixture (10:1) of tricyclic systems **2-2-4** and **2-2-5** in 78% isolated yield.

In a study of the cycloaddition reactions of alkyl cyclopropenecarboxylates, generated in situ, with nitrones, a number of 1,2-oxazinanes were synthesized; one of the products contained the [1,4]oxazino[4,3-b][1,2]oxazine skeleton.[4] The initial reaction of oxide **2-2-6** with polysubstituted cyclopropane **2-2-7** was carried out in the presence of Cs_2CO_3 in THF at 70 °C (Eq. **3**). The desired cycloaddition product **2-2-8** was isolated in 37% yield. The stereochemistry of this process was determined by NMR spectroscopic techniques.[5]



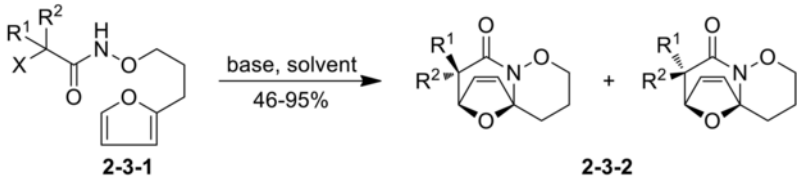
(3)



Scheme 1

2.3 [1,3]Oxazino[3,2-*b*][1,2]oxazines

Jeffrey and co-workers reported the synthesis of polyheterocyclic scaffolds with a [1,3]oxazino[3,2-*b*][1,2]oxazine skeleton through the intramolecular aza-[4 + 3] cycloaddition reactions of aza-oxyallylic cations with cyclic dienes.[6] The reaction was conducted by adding the base to a cooled (0 °C) solution of the substrate **2-3-1** in a solvent (Eq. 4). After the addition, the mixture was allowed to warm to room temperature until complete consumption of starting material. 2,2,2-Trifluoroethanol (TFE), 1,1,1,3,3,3-hexafluoropropanol-2 (HFIP) or diethyl ether was used as solvent. Cycloadducts **2-3-2** were formed as a diastereoisomeric mixture.



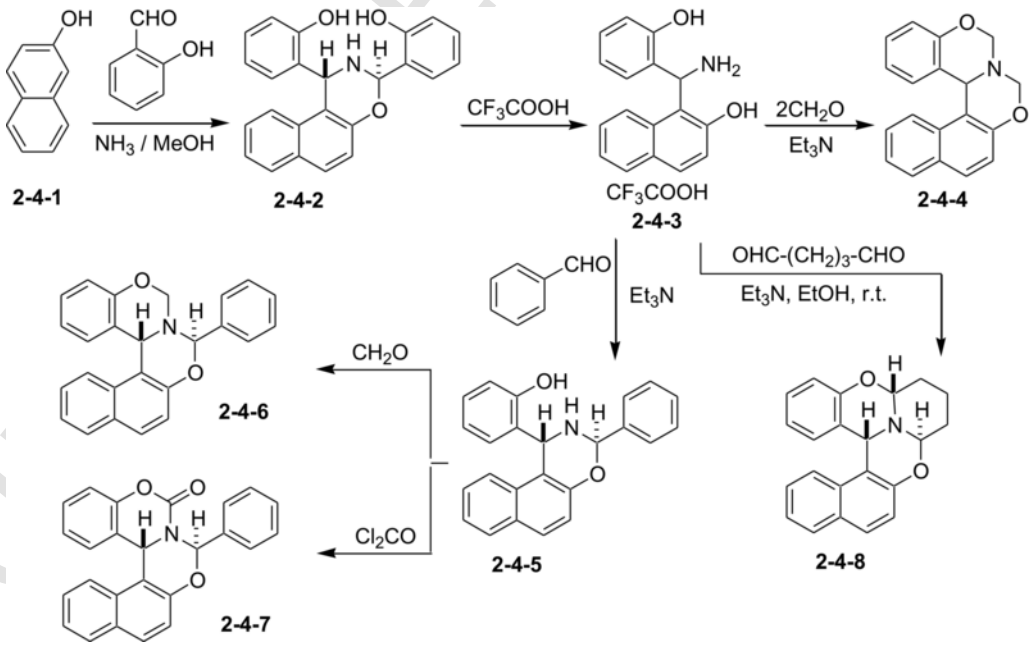
(4)

R^1 = H, Me R^2 = Me, Et, Cl X = Cl, Br
base = Et_3N, Na_2CO_3 solvent = TFE, Et_2O, HFIP

2.4 [1,3]Oxazino[3,4-*c*][1,3]oxazines and their benzo analogs

Naphthoxazinobenzoxazines **2-4-6** and **2-4-7** were obtained with practically full stereoselectivity, which was confirmed by NMR spectroscopic data.[7] The starting *ortho*-functionalized Betti base **2-4-2** was prepared by condensation of 2-naphthol **2-4-1**, salicylaldehyde and ammonia. Subsequent acidic hydrolysis with trifluoroacetic acid (TFA) led to the aminobenzylnaphthol trifluoroacetate **2-4-3**. The *ortho*-functionalized Betti base derivative **2-4-3** readily decomposes; for this reason, it was used as the trifluoroacetate salt in the further transformations. The ring-closure reaction of **2-4-3** with 2 equivalents of formaldehyde led to the parent naphtho[1,3]oxazino[3,4-*c*][1,3]benzoxazine **2-4-4** (**Scheme 2**). Naphthoxazine **2-4-5**, derived from **2-4-3**, was then allowed to react with formaldehyde or phosgene to yield 8-phenylnaphth[1,3]oxazino[3,4-*c*][1,3]benzoxazine **2-4-6** and 8-phenylnaphth[1,3]oxazino[3,4-*c*][1,3]-benzoxazin-10-one **2-4-7**, respectively.

Similarly, authors have synthesized the poly benzo analog with a [1,3]oxazino[3,4-*c*][1,3]oxazine skeleton **2-4-8.**[8] In order to transform **2-4-3** to the desired piperidine-fused benzoxazinonaphthoxazine derivative **2-4-8**, aminodiol **2-4-3** was dissolved in ethanol and treated with glutardialdehyde. The white crystalline product separated out from the mixture during 1 day period. The structure of **2-4-8**



Scheme 2

was established through 2D NMR measurements. Density functional theory (DFT) calculations at the B3LYP/6-31G** level of theory were carried out over different conformers to find the minimum and most probable structures.[7,8]

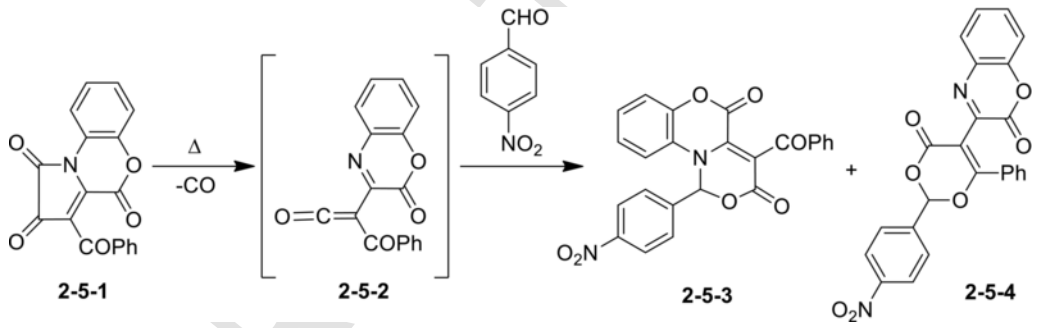
2.5 [1,4]Oxazino[4,3-*c*][1,3]oxazines and their benzo analogs

A mixture of 4-benzoyl-1-(4-nitrophenyl)-1,3-dihydro-5H-[1,3]oxazino[4,3-*c*][1,4]benzoxazine-3,5-dione **2-5-3** and 3-[2-(4-nitrophenyl)-4-oxo-6-phenyl-4H-1,3-dioxin-5-yl]-2H-1,4-benzoxazin-2-one **2-5-4** at a ratio of 5:3 was obtained by heating a solution of 3-benzoylpyrrolo[2,1-*c*]-[1,4]benzoxazine-1,2,4-trione **2-5-1** and 4-nitrobenzaldehyde in pseudocumene at 168–169 °C over a period of 15 min, until a violet color for compound **2-5-1** disappeared.[9] Autors stated that target compounds **2-5-3** and **2-5-4** are formed as a result of thermal decarbonylation of starting 3-benzoylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-trione **2-5-1** with generation of ketene **2-5-2** which immediately undergoes the [4 + 2]-cycloaddition reaction with 4-nitrobenzaldehyde (**Scheme 3**).

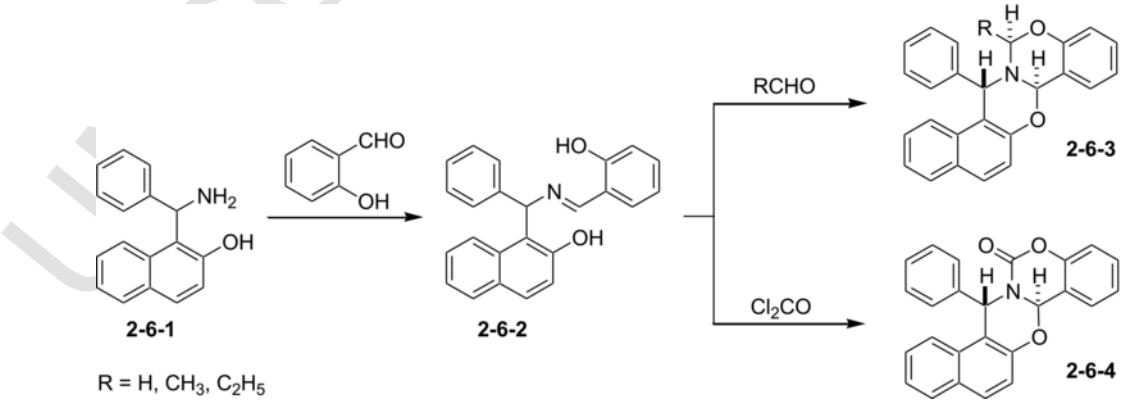
2.6 [1,3]Oxazino[4,3-*b*][1,3]oxazines and their benzo analogs

Compound **2-6-2**, obtained by condensation of amine **2-6-1** with salicylic aldehyde (**Scheme 4**), was converted by the ring-closure reaction with aldehydes (formaldehyde, acetaldehyde, propionaldehyde) or phosgene to the desired naphtho[1,3]oxazino[3,2-*c*][1,3]benzoxazine derivatives **2-6-3** and **2-6-4.**[7] This reaction proceeds with exceptional stereoselectivity, as no minor diastereomers were detected even in the crude products. The high diastereoselectivity was explained in terms of the kinetic control governing the second ring closures of the tautomeric cyclic intermediates.

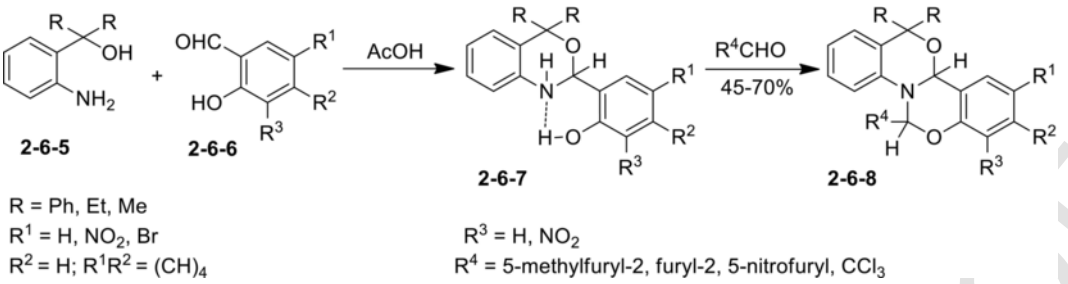
A series of 2,4,4-trisubstituted 1,2-dihydro-4*H*-3,1-benzoxazines **2-6-7** was obtained by treating the carbinols **2-6-5** with the *ortho*-hydroxy aromatic aldehydes **2-6-6** (substituted salicylaldehydes or 3-hydroxy-2-naphthaldehyde) in acetic acid (**Scheme 5**).[10] The dihydrobenzoxazines **2-6-7** undergo a reaction with aliphatic aldehydes in acetic acid to give 45%–70% yields of the corresponding tetra(penta)cyclic structures **2-6-8** (3,1-benzoxazino[1,2-*c*][1,3]-benzoxazines and 3,1-benzoxazino[1,2-*c*][1,3]naphthoxazines). The size of the attacking aliphatic aldehyde affects the yields and ease of carrying out the reaction. For example, with formaldehyde, the reaction occurs at room temperature, whereas in the case of heptanal a higher temperature (34–36 °C) is needed for 3 h to give the products in 35%–45% yield.



Scheme 3



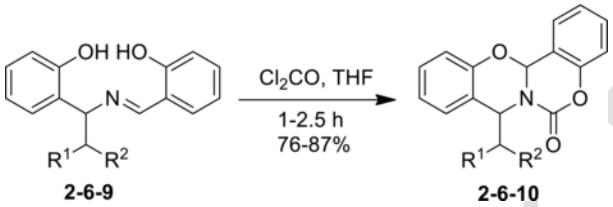
Scheme 4



Scheme 5

According to the proposed mechanism of formation of the 3,1-benzoxazino[1,2-*c*][1,3]benz(naphth)oxazines **2-6-8**, the first stage is likely a nucleophilic addition of the amino group of the dihydrobenz(naphth)oxazines **2-6-7** to the carbonyl group. Next reaction step can occur by two routes which are determined by the structure both of the benzoxazines and the aldehyde. The formation of the structure **2-6-8** takes place only in the case of aliphatic aldehydes. Using of more bulky or aromatic aldehydes (chloral, furfural, nitrofurfural, or methylfurfural) leads to the exchange reaction with the starting substrate **2-6-7**.

Phosgene was tested as electrophile in the reaction with Shiff bases **2-6-9** (Eq. 5) to give tetracyclic benzoxazine compounds **2-6-10.**[11] Final confirmation of the structure of compounds **2-6-10** was obtained by XRD analysis of one of the benzoxazines. Because of using the toxic gas phosgene in this synthetic approach, the reaction should be performed in a very efficient hood and all the glassware should be washed with the ethanol-ammonia mixture before removing from the hood.



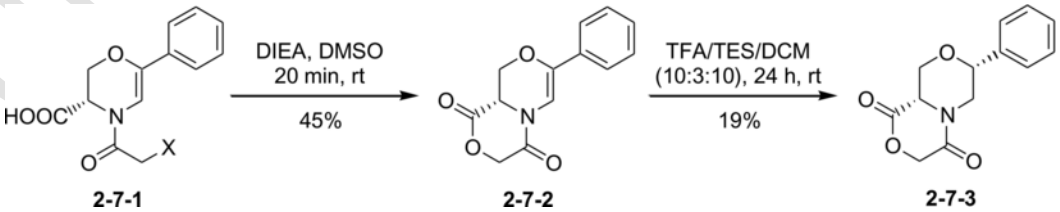
(5)

2.7 [1,4]Oxazino[3,4-*c*][1,4]oxazines and their benzo analogs

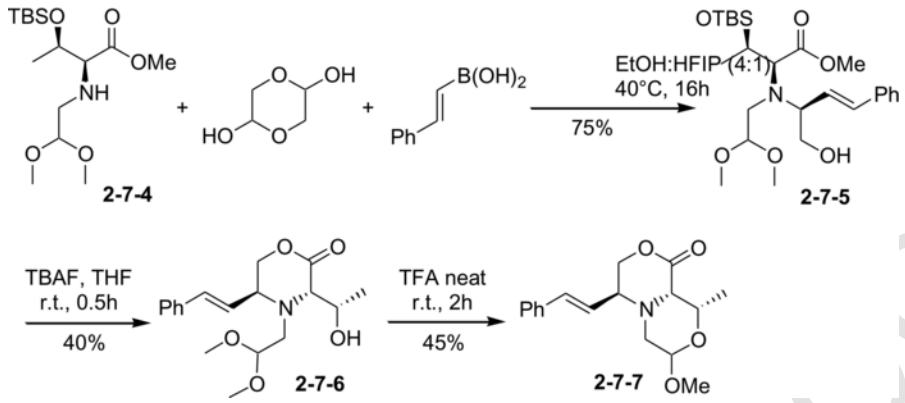
A solid-phase synthesis of oxazino[3,4-*c*][1,4]oxazine-dione **2-7-2** from dihydrooxazine-3-carboxylic acid **2-7-1** by the base-catalyzed cyclization using *N*,*N*-diisopropylethylamine (DIEA) in DMSO solution was reported.[12] After only 20 min, the quantitative formation of the expected product **2-7-2** was observed (**Scheme 6**). After it was freeze-dried from DMSO/DIEA, crude compound **2-7-2** was reduced by treatment with triethylsilane-trifluoroacetic acid (TES/TFA) to **2-7-3**. Reduction of the dihydroxazine scaffold was fully stereoselective.

Treatment of *tert*-butyldimethylsilyl ether of *N*-substituted threonine **2-7-4** in the Petasis reaction in the presence of 20% hexafluoro-2-propanol (HFIP) in ethanol as catalyst, furnished product **2-7-5** (**Scheme 7**).[13] The intermediate product **2-7-5** was transformed into morpholine **2-7-6** in 75% yield by deprotection of the TBS group of the threonine fragment with tetra-*n*-butylammonium fluoride (TBAF). Treatment of **2-7-6** with trifluoroacetic acid furnished bicyclic compound **2-7-7**.

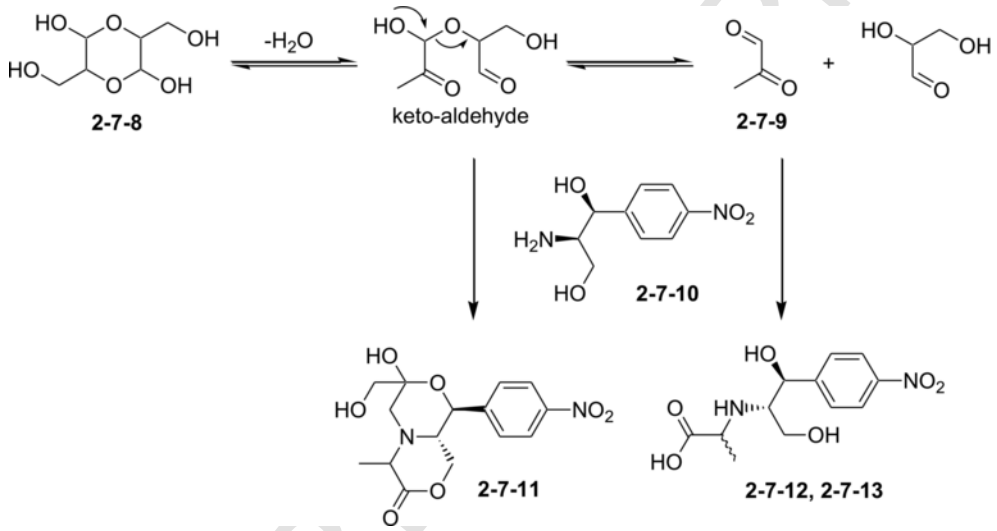
A reaction o a chiral primary alkyl amine, (1*S*,2*S*)-2-amino-1-(4-nitrophenyl) propane-1,3-diol **2-7-10**, with DL-glyceraldehyde dimer **2-7-8** was investigated.[14] The acidic condition was used to dissociate the DL-glyceraldehyde dimer **2-7-8** to its monomers in situ. It must be noted that under the reaction conditions (25% acetic acid at 90 °C), the formation of pyruvaldehyde **2-7-9** also takes place, as shown in **Scheme 8**. The reaction was monitored by HPLC, and after 1 h three major products **2-7-11, 2-7-12** and **2-7-13** were observed in the reaction mixture. After 15 h, the quantity of products **2-7-12** and **2-7-13** increased, while the amount of the bicyclic product **2-7-11**



Scheme 6



Scheme 7



Scheme 8

decreased. It was suggested that product **2-7-11** is an intermediate of products **2-7-12/13** as the increase in the sum of the amounts of **2-7-12** and **2-7-13** was nearly equal to the decrease of product **2-7-11.**

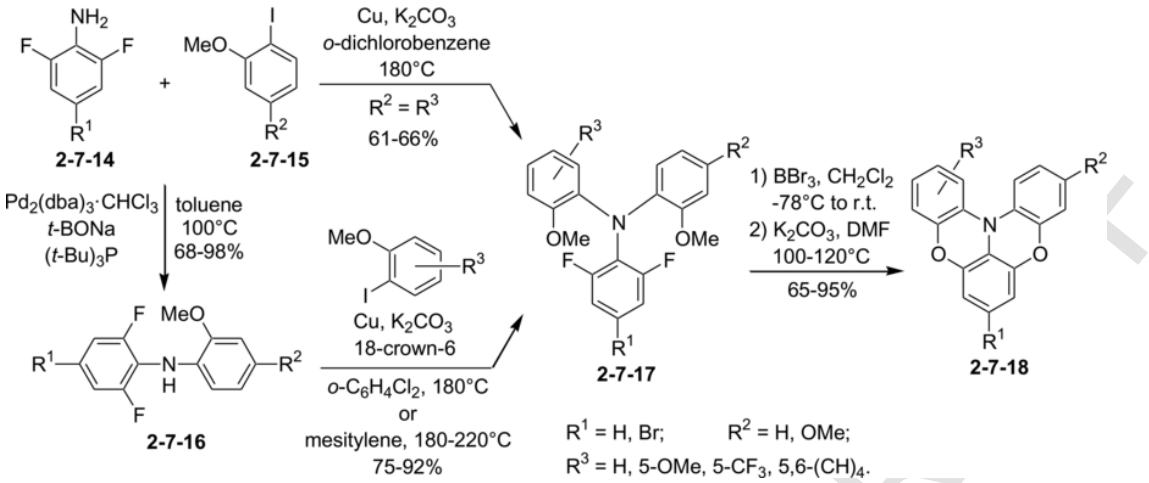
A multistep synthesis of benzo analogs of [1,4]oxazino[3,4-c][1,4]oxazines **2-7-18** via the intermolecular cyclization reaction of substituted 2,6-difluoro-*N,N*-bis(2-methoxyphenyl)anilines **2-7-17.**[15–17] Compounds **2-7-17** were synthesized by the direct reacion of 2,6-difluoroanilines **2-7-14** with **2-7-15** and through the intermediary of **2-7-16** (**Scheme 9**).

Homocoupling of brominated benzo[1,4]oxazino[3,4-*c*][1,4]oxazines **2-7-19** in the presence of nickel cycloocta-1,5-dieneate in a bipyridine/cycloocta-1,5-diene/THF mixture yielded the corresponding dimers **2-7-20** and **2-7-21** (54%–98%) as pale yellow solids (**Scheme 10**).[15]

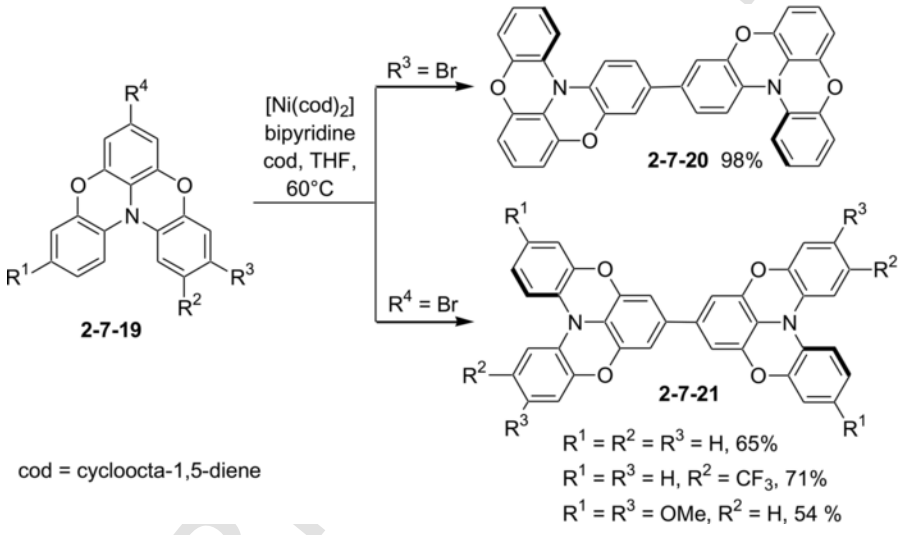
Benzo analogue of [1,4]oxazino[3,4-*c*][1,4]oxazine **2-7-22** was derivatized to **2-7-23** and **2-7-24.**[16] These structures, functionalized at the 4-position of the naphthyl moiety, were easily prepared by subjecting **2-7-22** to the selective Vilsmeier − Haack reaction (**Scheme 11**). The monoformyl product **2-7-23** was selectively obtained by treatment of **2-7-22** with $POCl_3$ in DMF in 80% yield. Consequently, mono-2,2-dicyanovinyl derivative **2-7-24** was prepared by the reaction of **2-7-23** with malononitrile in the presence of triethylamine. The purple solid of **2-7-24** was obtained in 91% yield.

Treatment [1,4]oxazino[3,4-*c*][1,4]oxazines **2-7-25** with NBS led to the selective formation of the corresponding bromoaryl substituted products **2-7-26** in 72%–88% yields.[17] The palladium-catalyzed Suzuki-Miyaura cross-coupling reactions of **2-7-26** with 1,3,5,7-tetra(Bpin)azulene, which was synthesized by the direct borylation of azulene using an iridium catalyst, furnished the target products **2-7-27** in 42%–69% yields (**Scheme 12**).

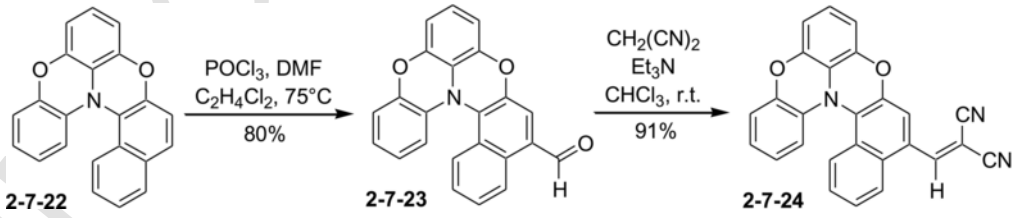
A conveniet method for the introduction of heterocycles to benzo analogs of [1,4]oxazino[3,4-*c*][1,4]oxazine **2-7-28** was described.[18–20] Thus, the reaction of bromo-substituted **2-7-28** with bis(pinacolato)diboron, 1,1′-bis[(diphenylphosphino)ferrocene]dichloropalladium(II) and potassium acetate in dioxane led to the target pinacol ester of arylboric acid



Scheme 9

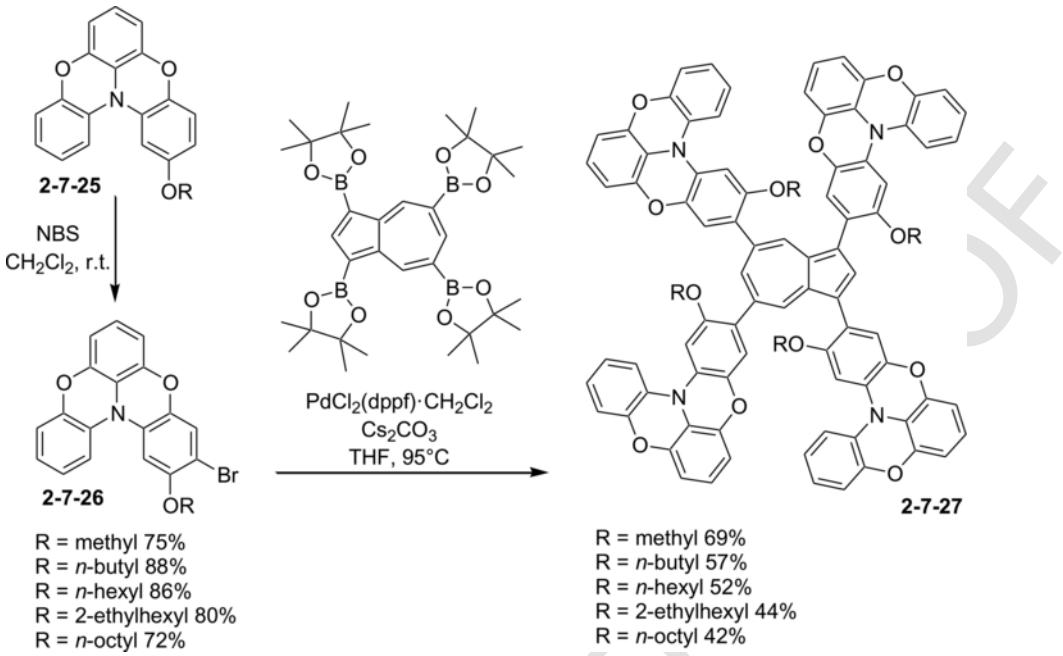


Scheme 10

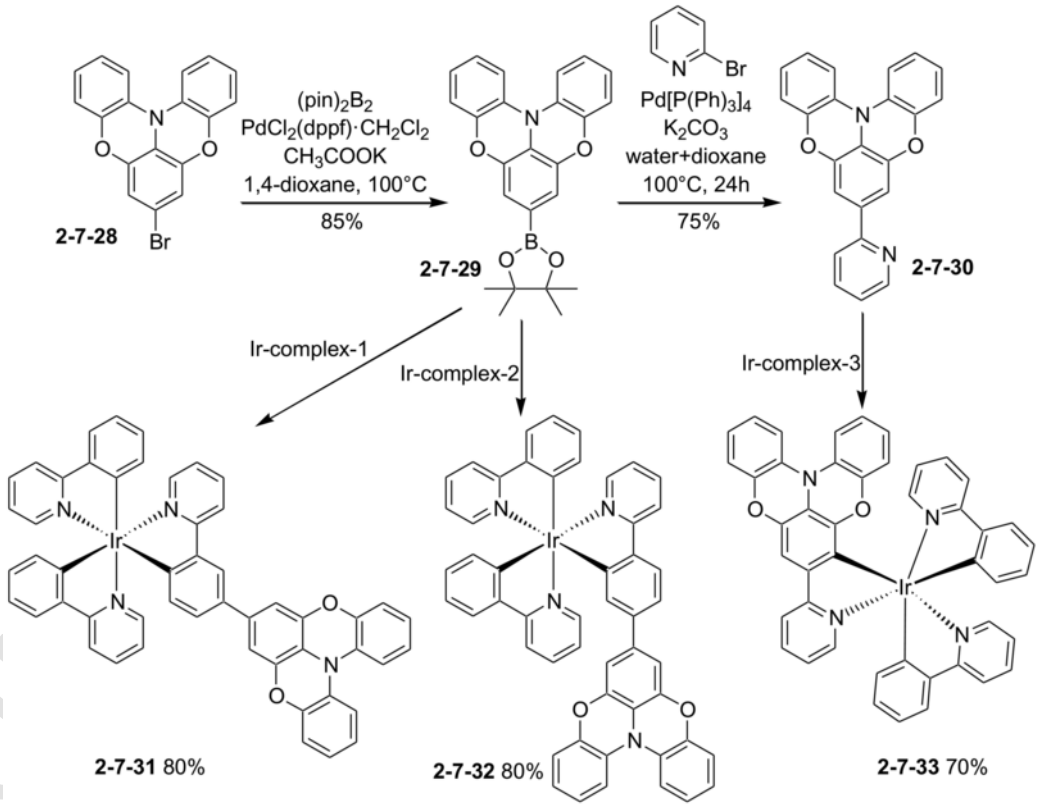


Scheme 11

2-7-29 (**Scheme 13**). Arylation of **2-7-29** with 2-bromopyridine was performed to obtain **2-7-30** that subsequently was used for the preparation of iridium complex **2-7-33** in 70% yield.[18] Moreover, **2-7-29** was used for a direct modification of bipyridyl iridium complexes in the synthesis of **2-7-31** and **2-7-32** in 80% yield.[20]



Scheme 12



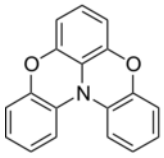
Scheme 13

Quantum chemical DFT computations at the B3LYP/6-31G(d) level of theory were performed to study inversion barrier for the flipping of the two phenyl rings in **2-7-18**. At the same time, theoretical calculations at the PW91/DZP level were conducted to evaluate the charge-transfer integrals in crystals of **2-7-20.**[15,21]

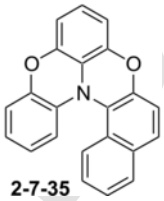
Diphenylnaphthylamine derivatives **2-7-23** and **2-7-24**, containing different functional groups, were investigated for their optical properties both in solution and in the solid-state.[16] In solution, these substances exhibit full-color emission from blue to deep red. To better understand the electronic structures, photophysical properties and electron transitions upon excitations, the DFT and TD-DFT calculations were carried out on these compounds at the B3LYP/6-31G(d) level of theory.[16]

In compounds **2-7-27** the alkoxy groups can attain dfferent orientation relative to the azulene plane, which leads to multiple conformational isomers that can interconvert in the case of low energy barriers. To investigate the interconversion, the smallest compound with methyl substituents was chosen for DFT calculations at the B3LYP/6–31G(d) level of theory. It was found that the difference in free energy among six proposed conformations is lower than 1.40 kcal/mol.[17,22] Theoretical study of the absorption spectrum was performed in time-dependent DFT (TD-DFT) formalism at the CAM-B3LYP/6-31G(d) level of theory. The S0 → S1 transition corresponds to the HOMO → LUMO excitation. The electronic transitions S0 → S2 and S0 → S3 can be mainly attributed to the HOMO → LUMO + 1 and HOMO − 1 → LUMO + 1 excitations.

To better understand the excited state optical properties of iridium complexes **2-7-31**, **2-7-32**, and **2-7-33**, theoretical calculations were carried out.[18–20] It was shown that the lowest triplet excited state is dominated by the HOMO → LUMO transitions. It was noticed that the HOMO of all three complexes are mainly distributed on oxygen-bridged triarylamine polycyclic unit of cyclometalated ligand part. The LUMO of the complexes is mainly localized on partial moieties of cyclometalated ligand and iridium(III) center.



2-7-34



2-7-35

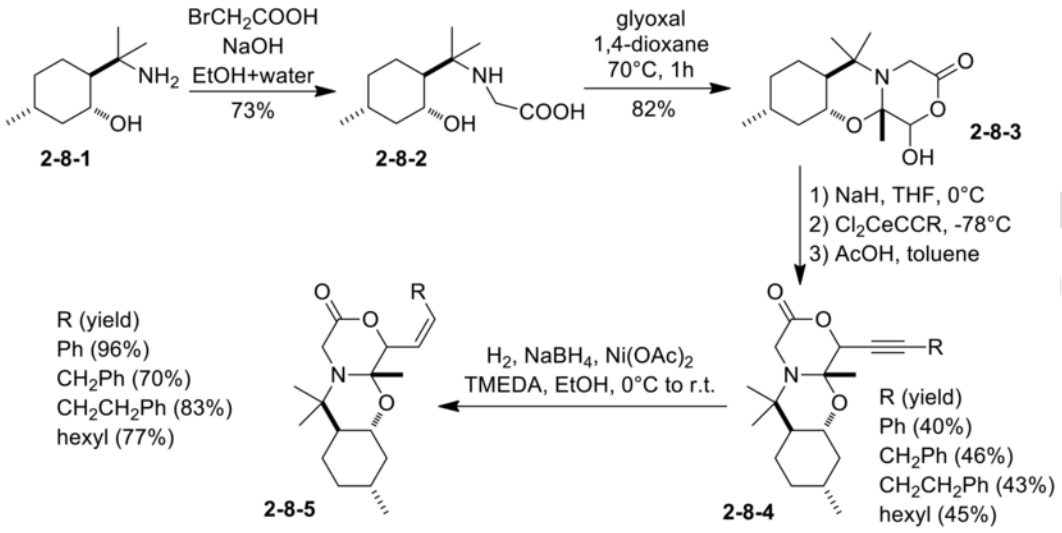
DFT computations at B3PW91/6-311G(d,p) level of theory were used to analyze the spectral properties and nonlinear optical response of the oxo and thio-bridged triarylamine heterohelicenes **2-7-34** and **2-7-35.**[23] The out-of-phase stretchings of the three fused aromatic rings provide contributions to the mid-infrared region (1300–1650 cm^{-1}) of the simulated infrared and vibrational circular dichroism spectra. It was shown that upon the increase in electron-donating capacity of substituents, the hyperpolarizability increases due to the decrease in the optical band gap. It was suggested that the oxo- and thia-bridged heterohelicenes could be used for nonlinear optical device and their nonlinear optical response can be enhanced by the extension in π-conjugation or addition of electron-donating substituents.

When tetrasubstituted azulene **2-7-27** was used as a hole-transporting material in perovskite solar cells, the observed performance was superior to that of the Spiro-OMeTAD, which is currently considered as hole-transporting material standard.[24] The power conversion efficiency of **2-7-27** is about 16.5%. The key factors required for hole-transporting materials to act efficiently in perovskite solar cells are the hole mobility, the ability to control the HOMO and LUMO levels, and the hole-collection efficiency at the perovskite/hole-transporting material interface.

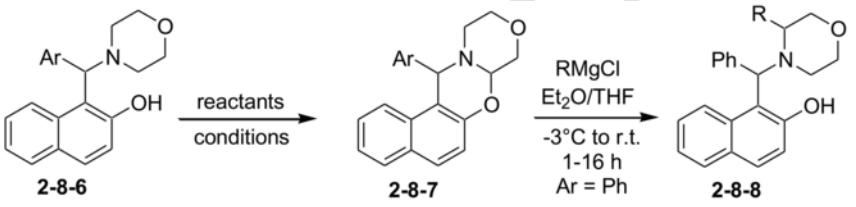
2.8 [1,4]Oxazino[3,4-*b*][1,3]oxazines and their benzo analogs

Alkylation of amino-substituted menthol **2-8-1** with bromoacetic acid furnished the amino acid **2-8-2** in 73% yield.[25] Condensation of this amino acid with glyoxal led to the carboxylactol **2-8-3** in 82% yield, the treatment of which with sodium hydride followed by addition of the appropriately substituted organocerium reagents produced the target lactones **2-8-4** with yields of about 45%. Selective partial hydrogenation of alkynes **2-8-4** using Brown's method produced the corresponding cis-alkenes **2-8-5** (with Z/E > 99:1) in 70%–96% yields (**Scheme 14**).

An efficient, diastereoselective and green copper-catalyzed synthesis of naphtho- and benzo-2,3-dihydro-1,3-oxazines through regioselective C—H bond activation and cyclization (**Scheme 15**) was developed.[26–28] The main reactants for the above cyclization are: silver(I) oxide in xylene,[26] copper(II) acetate monohydrate in xylene with heating[27] or (diacetoxyiodo)benzene in dichloromethane at room temperature.[28] It was shown that the direct C–H functionalization of the obtained *N*-heterocycles **2-8-7** can be performed in a



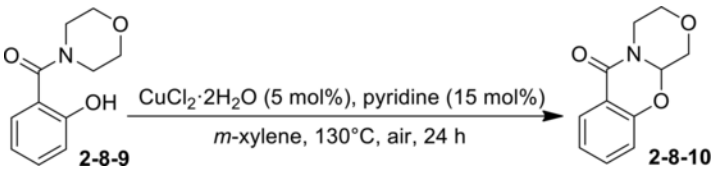
Scheme 14



reactants/conditions:
Ag_2O, xylene, 140°C: Ar = Ph (45%), *m*-NO_2Ph (55%);
$Cu(OAc)_2 \cdot H_2O$ (5 mol%), *p*-xylene, 130°C, air, 7 h: Ar = Ph (58%);
$PhI(OAc)_2$ (2.2 equiv.), CH_2Cl_2, r.t., 16 h: Ar = Ph (67%).

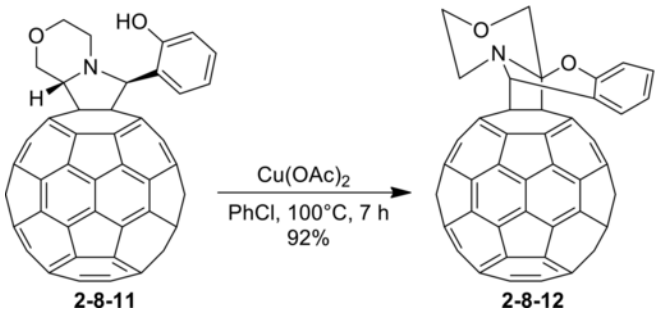
Scheme 15

straightforward manner by treatment with Grignard reagents.[29] Corresponding substituted morpholines **2-8-8** were obtained (**Scheme 15**).



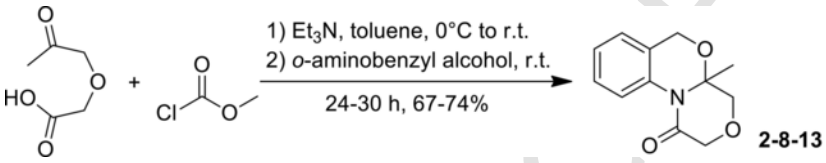
(6)

A similar functionalization of morpholine was published.[30] Thus, treatment of the amide **2-8-9** with $CuCl_2$ and pyridine in *m*-xylene produced 1,3,4,11a-tetrahydro-6*H*-[1,4]oxazino[3,4-*b*][1,3]benzoxazin-6-one **2-8-10** in 15% yield (Eq. **6**).



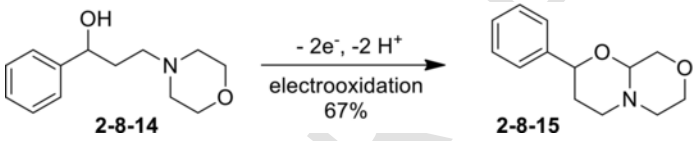
(7)

Functionalization of the C_{60} derivative **2-8-11** by treatment with copper(II) acetate in non-polar aromatic solvent furnished C_{60}-derivatized [1,4]oxazino[3,4-*b*][1,3]benzoxazine **2-8-12** (Eq. **7**).[31]



(8)

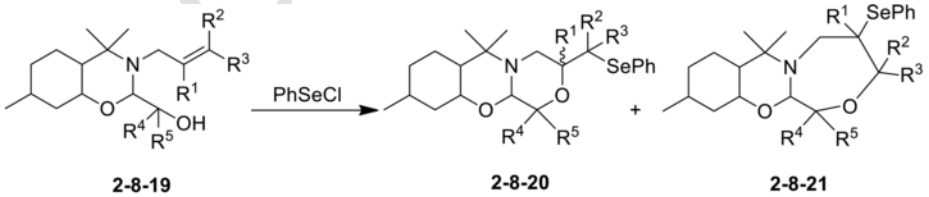
A simple synthesis of substituted [1,4]oxazino[4,3-a][3,1]benzoxazine **2-8-13** involves threatment of (2-oxopropoxy)acetic acid with methyl chloroformate followed by reaction with *o*-aminobenzyl alcohol (Eq. **8**).[32]



(9)

Electrooxidative cyclization of 3-morpholino-1-phenylpropanol **2-8-14** is a convenient method of annulation of the perhydro-[1,3]oxazine ring.[33] The target 2-phenylhexahydro-2*H*-[1,4]oxazino[3,4-*b*][1,3]oxazine **2-8-15** was prepared in 67% yield (Eq. **9**).

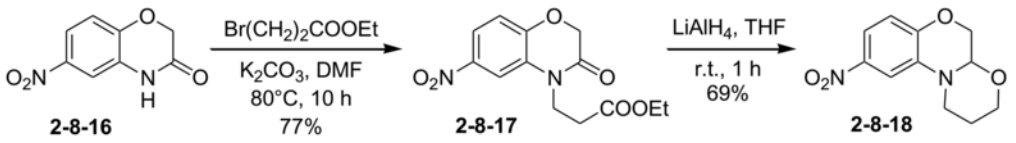
The reaction of benzoxazinone **2-8-16** with ethyl 3-bromopropionate furnishes *N*-alkylated product **2-8-17** (**Scheme 16**). A subsequent reduction with $LiAlH_4$ is accompanied by simultaneous cyclization to give the target substance **2-8-18.**[34]



(10)

R^1 = H, Me; R^2 = H, Me; R^3 = Me, Ph; R^4 = H, Me, *i*Pr, Ph; R^5 = H, Me, Ph

Selenium induced electrophilic cyclization of *N*-alkenyl oxazines **2-8-19** by treatment with benzeneselenenyl chloride leads to the formation of [1,4]oxazino[3,4-*b*][1,3]oxazines **2-8-20** in a mixture with **2-8-21**. Reaction is highly condition-dependent (Eq. **10**).[35,36]



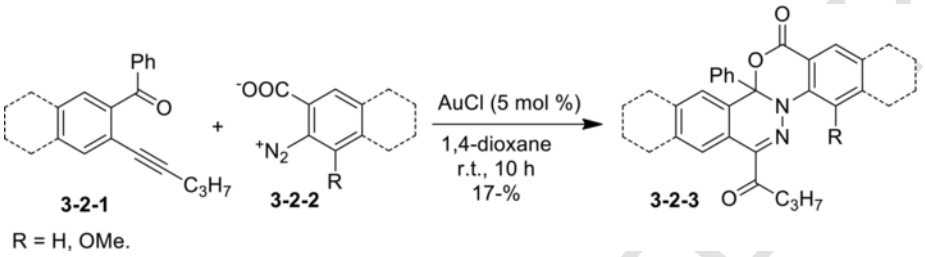
Scheme 16

3 Systems with one N and one O extra atoms, 1:1, and their benzo analogs

3.1 Pyridazino[1,6-*c*][1,3]oxazines and their benzo analogs

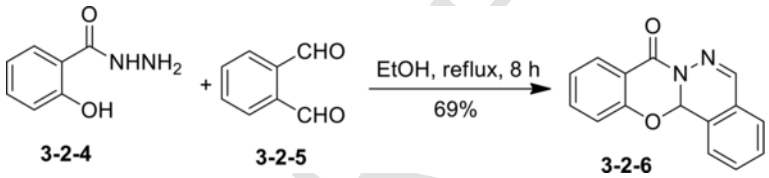
Oxidation of [2-(1′-methylene-2-propenyl)-3-pentene-1,5-diyl]iron complex **3-1-1** furnished cycloheptadiene **3-1-2**, the treatment of which with 4-phenyl-1,2,4-triazoline-3,5-dione in aprotic solvent produced pyridazino[1,6-*c*][1,3]oxazine **3-1-3** (Scheme 17).[37]

3.2 Pyridazino[6,1-*b*][1,3]oxazines and their benzo analogs



(11)

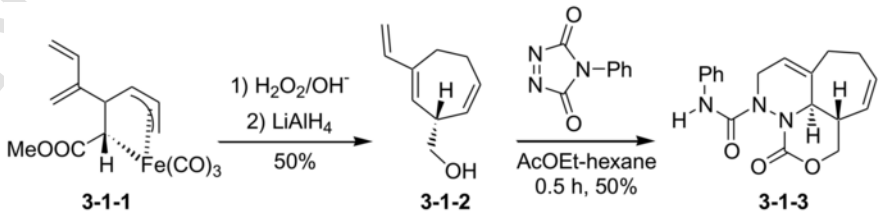
While exploring the benzannulation of benzyne, Sato and co-workers examined the AuCl-catalyzed reaction of **3-2-1** with **3-2-2** in 1,4-dioxane at room temperature (Eq. 11).[38] In the case of non-substituted reagents, the small amount of corresponding phthalazine derivative **3-2-3** was obtained along with other products. It was noted that yield of **3-2-3** increased up to 40% when $AuCl_3$ was used as catalyst, whereas some other catalysts were less effective. Moreover, when the reaction was performed with *ortho*-alkynylnaphthyl ketone, yield of the target phthalazines **3-2-3** was increased up to 91%.



(12)

In an attempt to synthesize and study Schiff-bases as fluorescence reagents, Wang and co-workers designed a pyridazino[6,1-*b*][1,3]oxazine ligand **3-2-6.**[39] The synthesis is based on the condensation of salicylhydrazide **3-2-4** with *ortho*-phthalaldehyde **3-2-5** (Eq. 12).

The fluorescent chemosensor **3-2-6** was investigated about its chemosensing properties. Lone electron pairs on nitrogen and oxygen atoms determined high selectivity for Al^{3+} ion in abiotic and living systems. The ligand/Al^{3+} reaction ratio is 2:1.



Scheme 17

The structure of the **3-2-6**–Al^{3+} complex was studied in terms of density functional theory. Calculations were performed using the poplar B3LYP/6-31G(d) combination of exchange functional and double-zeta basis sets, except aluminum atom for which the LANL2DZ effective core potential (ECP) was used. The metal coordination number was determined as 6 and the corresponding Al—N, Al—O, and Al—O(water) bond lengths were 2.03, 1.86, and 2.04 Å, respectively.

3.3 Pyrimido[1,6-*b*][1,2]oxazines and their benzo analogs

The domino aza-Michael addition of ureas **3-3-1** containing electron-rich 3,4-dimethoxybenzyl and (1-methyl-1*H*-indol-2-yl)methyl groups with **3-3-2** in the presence of a catalytic amount of α,α-diphenylprolinol trimethylsilyl ether and acetic acid in trifluoromethyl benzene prodced tricyclic products **3-3-3** and **3-3-4** (**Scheme 18**).[40]

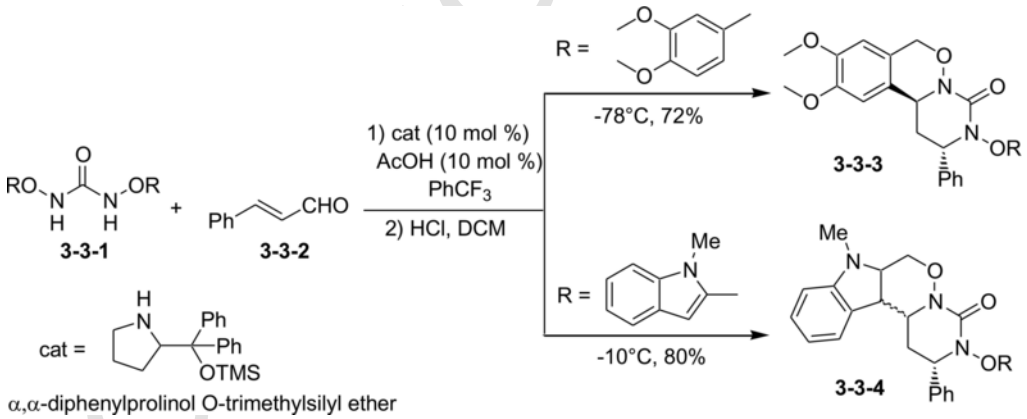
3.4 Pyrimido[1,6-*c*][1,3]oxazines and their benzo analogs

1-(Allyloxymethyl)uracil **3-4-2** was conveniently prepared by selective alkylation of uracil **3-4-1** using chloromethyl allyl ether.[41] Alkenyl substituted uracil **3-4-2** was subjected to photocycloaddition reaction conditions (**Scheme 19**) resulting in the intramolecular formation of the tricyclic cyclobutane adduct **3-4-3** in 89% yield. Treatment of **3-4-3** with a 1 M solution of NaOH at 80 °C for 10 h led to formation of the cyclobutane amino acid **3-4-4** in quantitative yield.

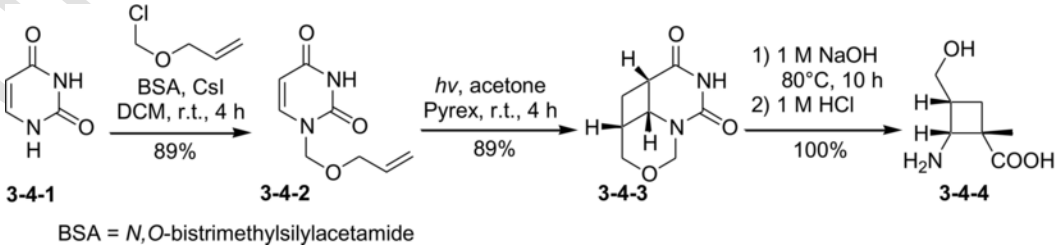
Treatment of aminonaphtol **3-4-5** with 2 equivalents of aqueous formaldehyde in chloroform for 1.5 h at room temperature produced a naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline derivative **3-4-6.**[42] The use of pentandial also leads to construction of [1,3]oxazino[3,4-*c*]quinazoline system **3-4-7** (**Scheme 20**).[8]

The direct ring-closure reaction of diamine **3-4-5** is also possible by treatment with 4 equivalents of triphosgene in toluene in the presence of Na_2CO_3. After 8.5 h mixing at room temperature, product **3-4-8** separated in 67% yield. Moreover, a Shiff base **3-4-9** was transformed into the heterocyclic system via the reaction with phosgene. When **3-4-9** was allowed to react with 4 equivalents of triphosgene in toluene for 6.5 h at room temperature, the pyrimido-oxazine product **3-4-10** was isolated in a yield of 31%.

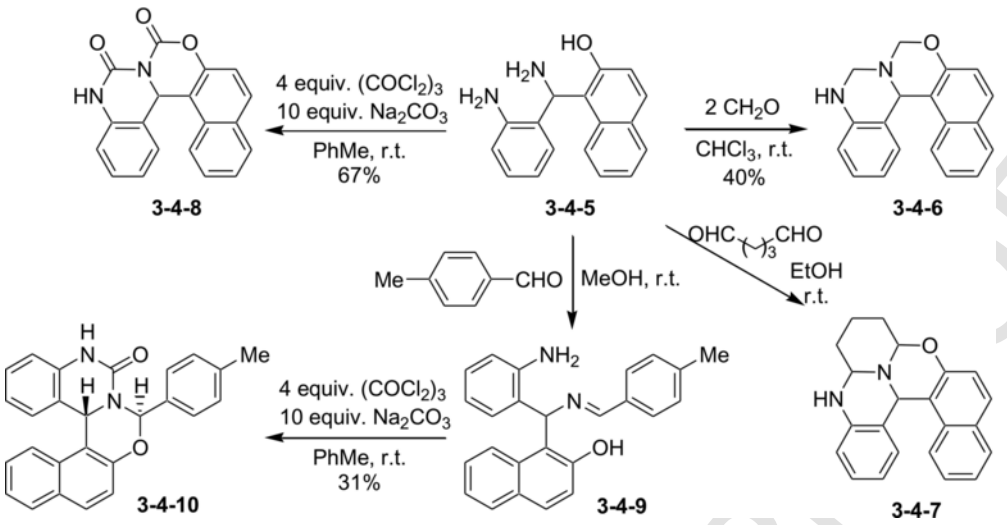
Theile and McLaughlin in their synthetic approach to 6,5′-cyclouridines converted the hydroxy group in the 5′ position of uracil **3-4-11** to iodo group in 87% yield using Moffatt's chemistry (**Scheme 21**).[43] Next radical cyclization of **3-4-12** with azobisisobutyronitrile (AIBN) and Bu_3SnH and further dehydrohalogenation with sodium methoxide led to **3-4-13** in 72% yield. Compound **3-4-13** was readily oxidized to ketone **3-4-14** by treatment with SeO_2 in hot 1,4-dioxane. It was found that the acetonide group of **3-4-13** can be easily replaced with acetates to give **3-4-15** in a good yield.



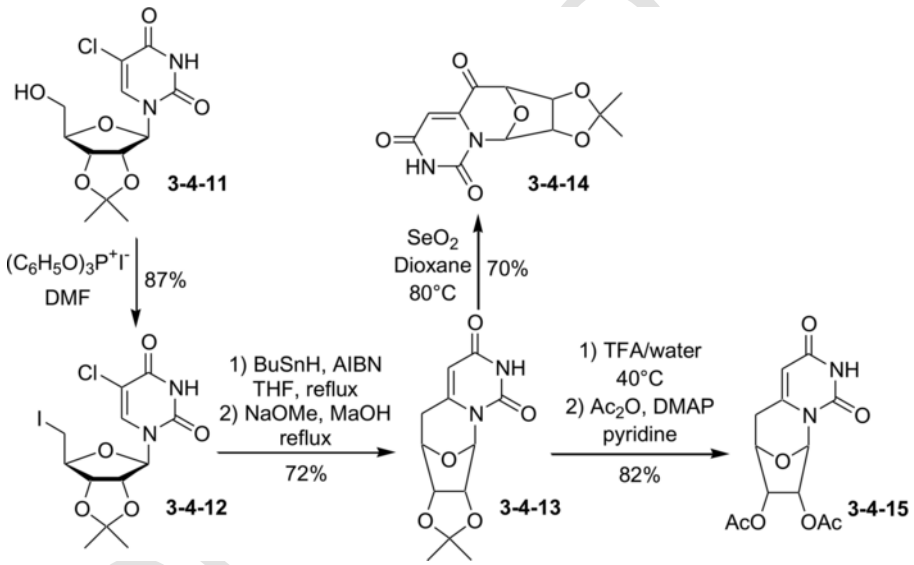
Scheme 18



Scheme 19



Scheme 20

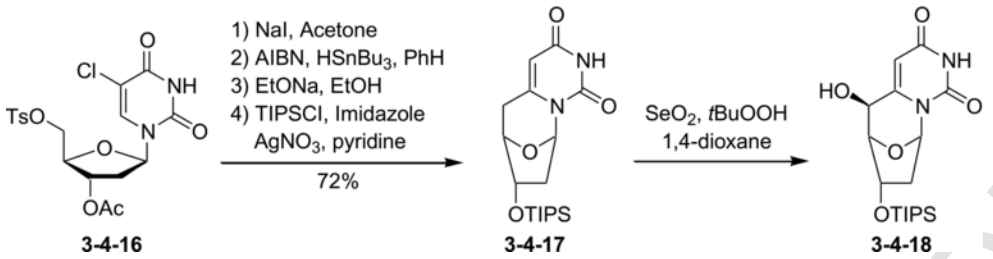


Scheme 21

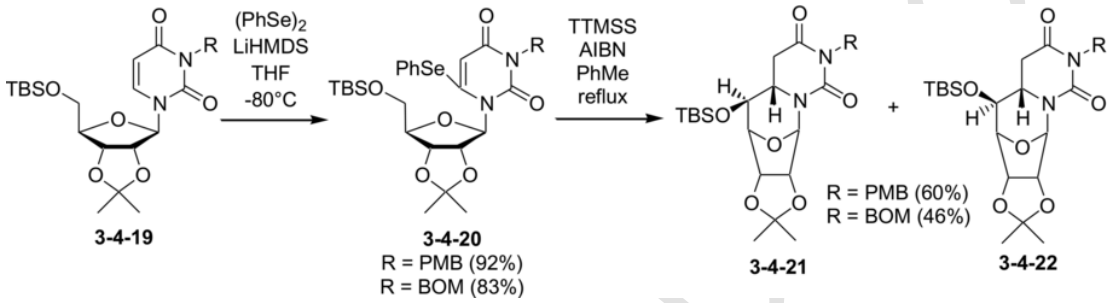
Similar cyclization was achieved for uracil **3-4-16** using a mixture of AIBN and $HSnBu_3$ in benzene. Oxidation of the product **3-4-17** with selenium dioxide furnished alcohol **3-4-18**[44] (**Scheme 22**).

The reaction of **3-4-19** with lithium hexamethyldisilazide (LiHMDS) in the presence of diphenyl diselenide gave 6-phenylseleno derivatives **3-4-20** in good yields. With the aim to examine the tandem radical cyclization of **3-4-20**, a toluene solution of tris(trimethylsilyl)silane (TTMSS) and azobisisobutyronitrile (AIBN) was added over one hour. The desired products **3-4-21** and **3-4-22** were obtained in satisfactory yields[45] (**Scheme 23**).

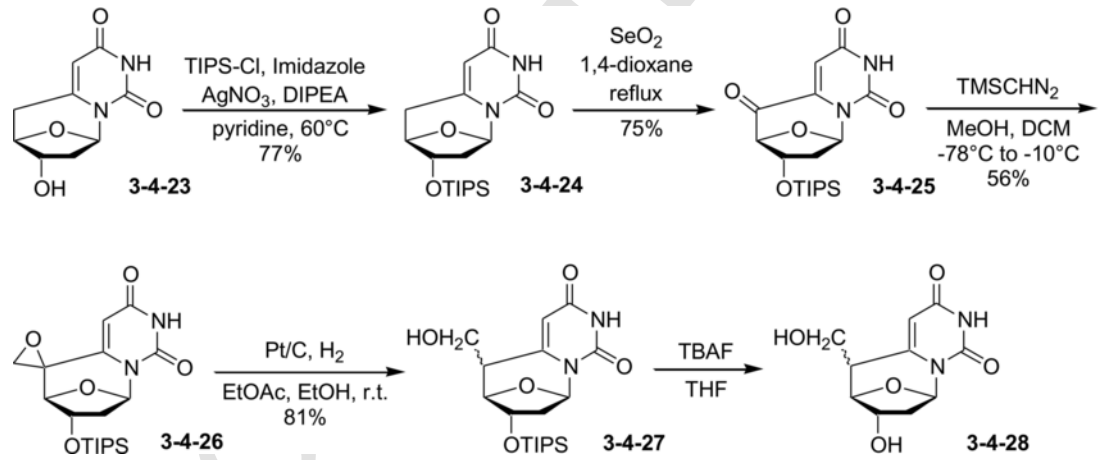
Both diastereomers of 5′-(hydroxymethyl)-6,5′-cyclo-2′,5′-dideoxyuridine nucleosides **3-4-28** were synthesized starting with **3-4-23** trough intermediaries of **3-4-24** to **3-4-27**, as shown in **Scheme 24.**[46] The addition of a methylene group to 6,5′-cyclo-2′-deoxyuridine increases the distance between the hydrogen bonding face of the nucleobase and the primary hydroxy group, which was determined by the



Scheme 22

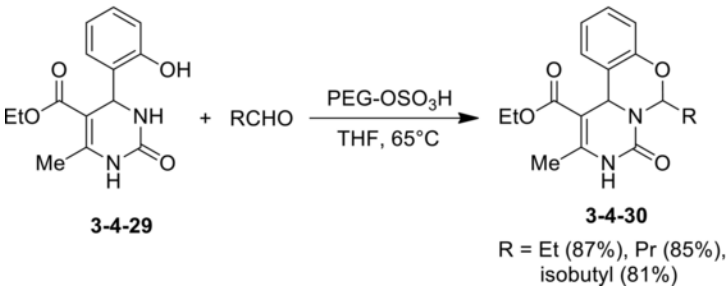


Scheme 23



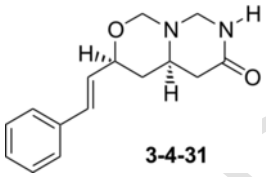
Scheme 24

analysis of the crystal structures of these two cyclonucleosides.



(13)

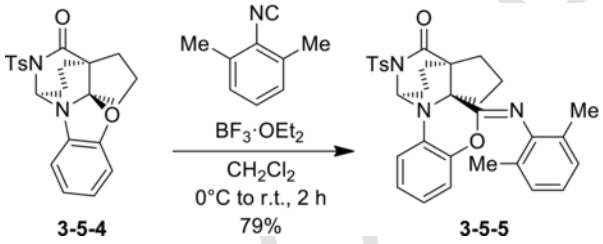
The reaction between 2-hydroxyphenyl-3,4-dihydropyrimidinones **3-4-29** with propionaldehyde, butyraldehyde and 3-methylbutyraldehyde gave tetrahydrobenzo[*e*]pyrimido[1,6-*c*][1,3]oxazine derivatives **3-4-30** with high yields.[47]



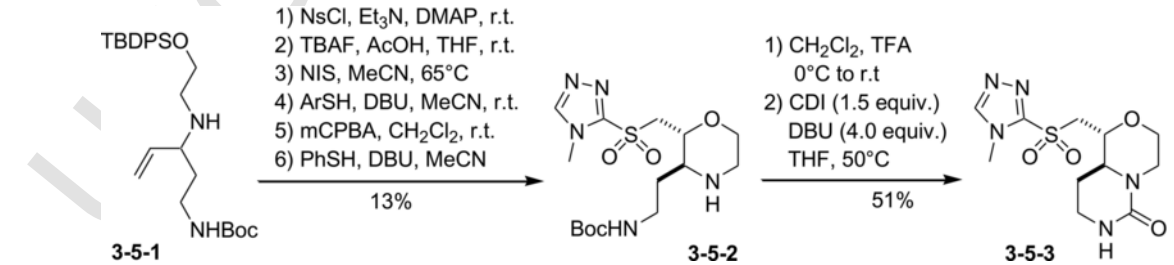
In the study of cytotoxicity of components isolated from the stem bark extracts of G. tapisoides, compound **3-4-31** (goniomicin D) with the pyrimido[1,6-*c*][1,3]oxazine skeleton was analyzed. NOESY spectrum and X-ray diffraction analysis were used for the determination of the relative stereochemistry of goniomicin D.[48]

3.5 Pyrimido[6,1-*c*][1,4]oxazines and their benzo analogs

Iodocyclization of substrate **3-5-1**, as shown in **Scheme 25**, furnished polysubstituted morpholine **3-5-2**. A subsequent cyclization, also used as a Boc-deprotection, followed by reaction with carbonyl diimidazole (CDI) furnished the bicyclic product **3-5-3.**[49]

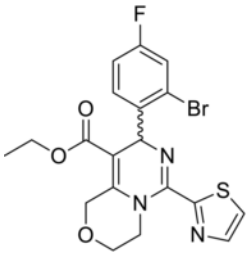


(14)



Scheme 25

Constantieux and co-workers have investigated the reaction of **3-5-4** with 2,6-dimethylphenyl isocyanide afforded imidate **3-5-5** in good yield[50] (Eq. **14**).

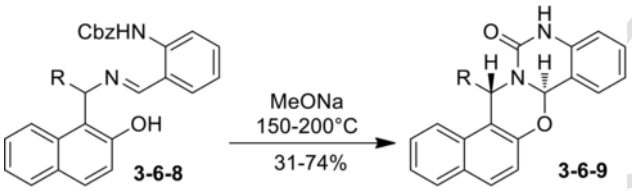


3-5-6

Condensed pyrimidines were studied as capsid assembly inhibitors for the treatment of hepatitis B virus.[51] Among many compounds, the antivirus potency of the structure **3-5-6** from pyrimido[6,1-*c*][1,4]oxazine family was tested. However, its activity was relatively low.

3.6 Pyrimido[6,1-*b*][1,3]oxazines and their benzo analogs

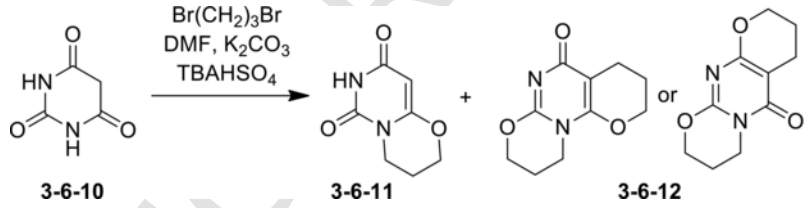
Synthesis of O^6-cyclonucleoside analogs with H, Cl, Br substituents in the pyrimidine ring was described.[52] (±)-*Cis*-1-[2-(hydroxymethyl)cyclohexyl]uracil **3-6-1** was used as a precursor to **3-6-2** to **3-6-7**. Cyclization of the hydroxymethyl group with the heterocyclic nucleophilic center afforded a stable six-membered ring (**Scheme 26**).



3-6-8 **3-6-9** (15)

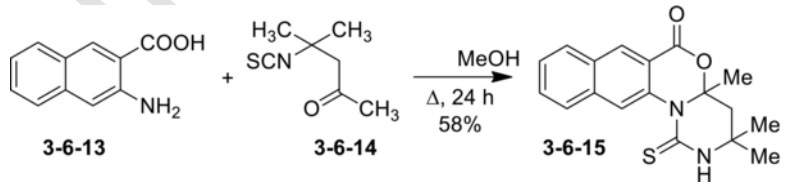
R = H, 4-ClPh, Ph, 4-MeOPh, 1-naphthyl, 2-naphthyl

Benzyloxycarbonyl-protected intermediates **3-6-8** were treated with MeONa (Eq. **15**). After 10–40 min of heating at the melting temperatures of substrates **3-6-8**, the mixtures were cooled and the products **3-6-9** were isolated by extraction with ethanol.[53] Possible conformational structures of synthesized compounds were studied using PM3 geometry minimization protocol.

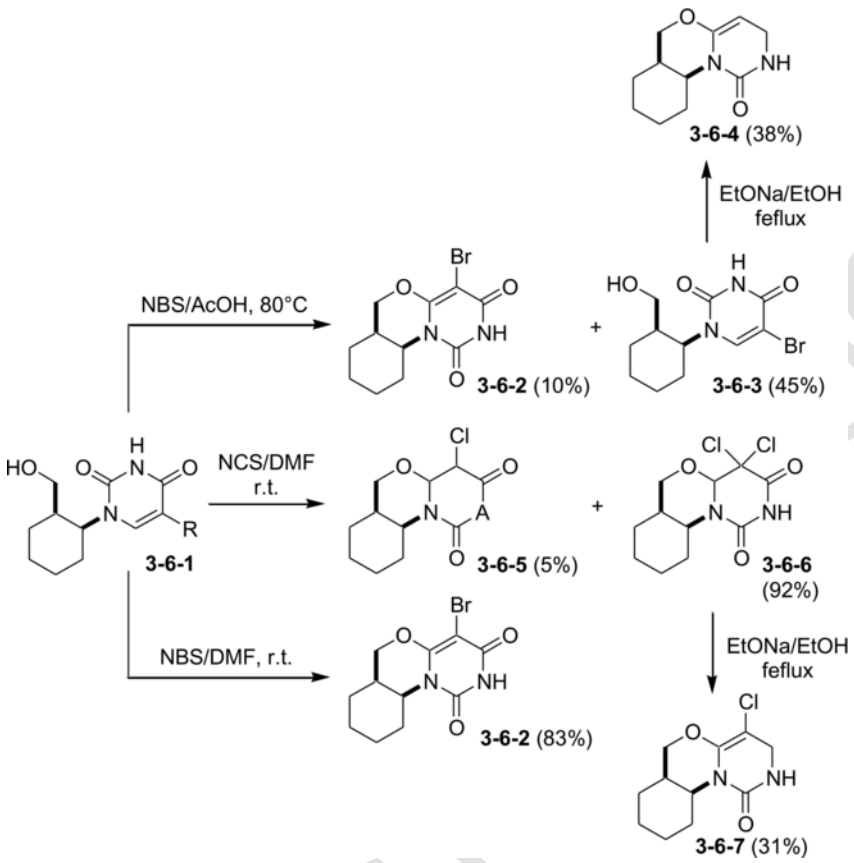


3-6-10 **3-6-11** **3-6-12** (16)

Alkylation of barbituric acid **3-6-10** with 1,3-dibromopropane furnished a derivative of pyrimido[6,1-*b*][1,3]oxazine **3-6-11** as the main product and a minor product **3-6-12**[54] (Eq. **16**).

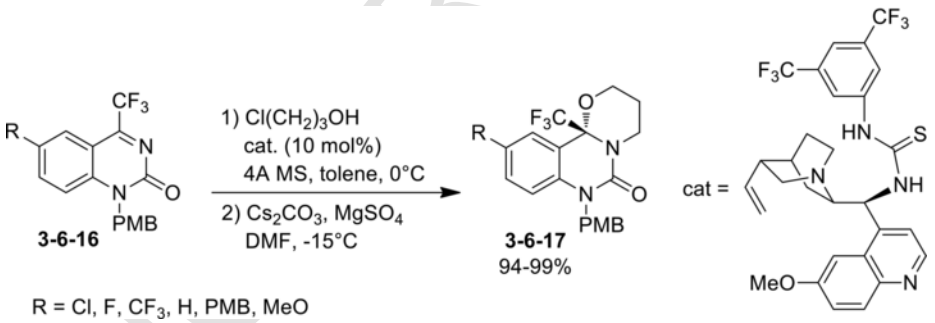


3-6-13 **3-6-14** **3-6-15** (17)



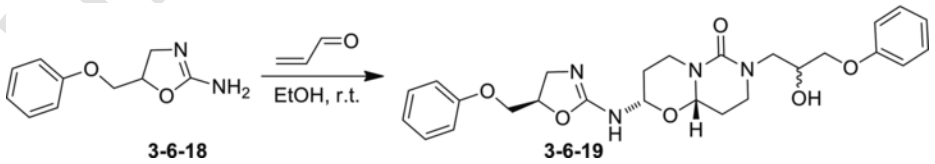
Scheme 26

The condensation reaction of 4-isothiocyanato-4-methylpentan-2-one **3-6-14** with diverse amino acids was studied.[55] It was found that reatment of 3-amino-2-naphthoic acid **3-6-13** with **3-6-14** furnished tetracyclic compound **3-6-15** (Eq. **17**).



(18)

Asymmetric addition reaction of cyclic *N*-*p*-methoxybenzyl (PMB) ketimines **3-6-16** with 3-chloro-1-propanol followed by cyclization reaction led to [1,3]oxazino[3,2-*c*]quinazolines **3-6-17**. As a catalyst, the thioureido-substituted quinine was used[56] (Eq. **18**).

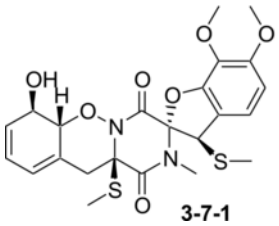


(19)

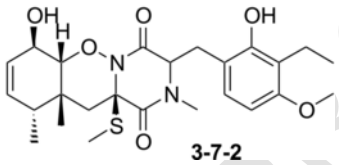
Pyrimido[6,1-*b*][1,3]oxazin-6-one **3-6-19** was synthesized from **3-6-18** as shown in Eq. **19** and its structure was analyzed using X-ray crystallography. The proposed mechanism involves the formation of an adduct via a Michael reaction, followed by a ring closure through a Dimroth-like rearrangement[57] (Eq. **19**).

3.7 Pyrazino[1,2-*b*][1,2]oxazines and their benzo analogs

The pyrazino[1,2-*b*][1,2]oxazine class of compounds is mostly represented by natural alkaloids.

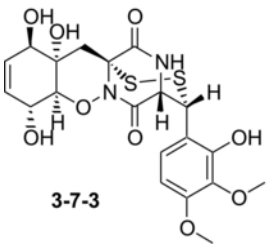


3-7-1

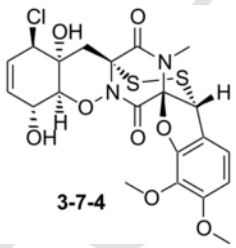


3-7-2

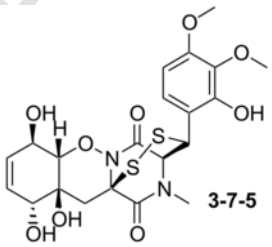
The structure and antimicrobial activity of two peniciadametizines **A** and **B**, **3-7-1** and **3-7-2**, respectively, were studied.[58] These substances were obtained from a fungal extract of an unidentified sponge collected at the Hainan Island of China.



3-7-3

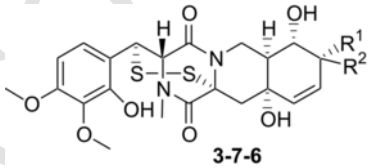


3-7-4



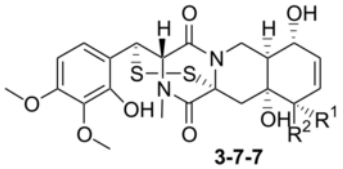
3-7-5

New austalides were obtained from a marine-derived *Aspergillus* strain isolated from a specimen of the Mediterranean sponge *Tethya aurantium*.[59] Several alkaloids, including **3-7-3**, were isolated. The mechanism of inhibition of a heat shock protein 90 (Hsp90) with **3-7-4** (Penicisulfuranol **A**), was investigated for a possible use in cancer therapy.[60] A new epithiodiketopiperazine natural product outovirin **B**, **3-7-5**, was identified in extracts of *Penicillium raciborskii*, an endophytic fungus isolated from *Rhododendron tomentosum*.[61]



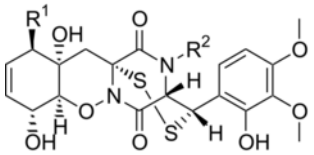
3-7-6

R^1 = H, OH; R^2 = H, OH, Cl.

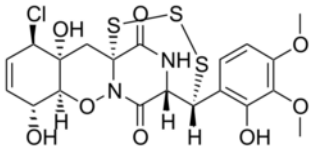


3-7-7

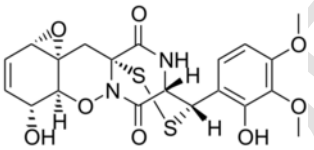
Yurchenko with colleagues, during their study of structurally novel bioactive metabolites from marine-derived fungi, isolated compounds **3-7-6** and **3-7-7.**[62]



3-7-8

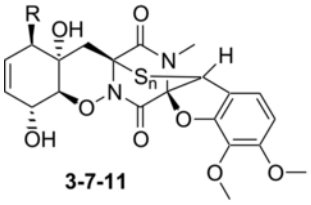


3-7-9

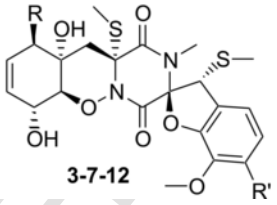


3-7-10

A cytotoxic epidithiodiketopiperazine **3-7-8** was isolated from hyper saline lake derived Penicillium sp. and characterized.[63] A group of Yamazaki investigated marine-derived compound **3-7-8**, chlorotrithiobrevamide **3-7-9** and gliovirin **3-7-10.**[64,65]



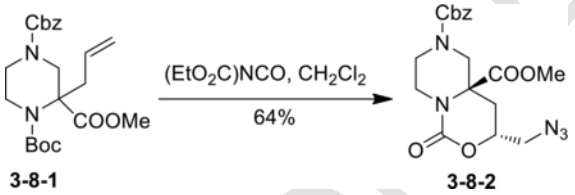
3-7-11



3-7-12

Zhu and co-workers isolated six new epipolythiodioxopiperazine alkaloids **3-7-11** and **3-7-12**, penicisulfuranols **A-F**, from the mangrove endophytic fungus *Penicillium janthinellum.*[66] Spectroscopic data and ECD calculations were used for determination of the absolute configurations of all structures. It was found that compounds **3-7-11** and **3-7-12** are highly cytotoxic.

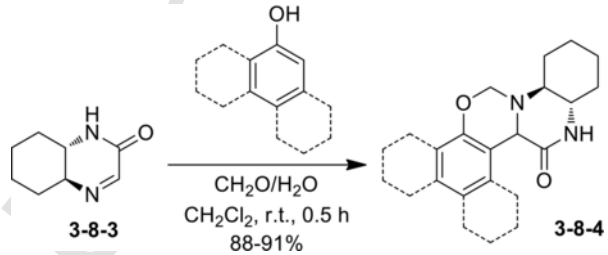
3.8 Pyrazino[1,2-*c*][1,3]oxazines and their benzo analogs



3-8-1 **3-8-2**

(20)

Foley with colleagues, considering high bioactivity of 1,2-amino alcohols and 1,2-diamines, developed a systematic approach to diverse agents from α,α-disubstituted amino acids and their functionalized derivatives. An example is synthesis of **3-8-2** from **3-8-1** (Eq. **20**).[67]

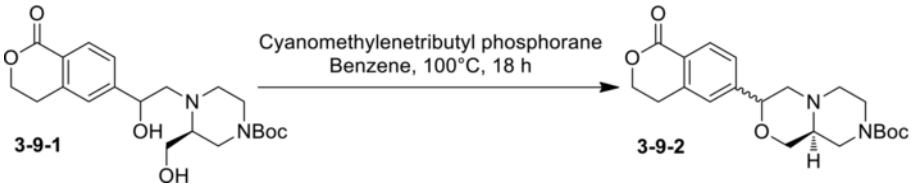


3-8-3 **3-8-4**

(21)

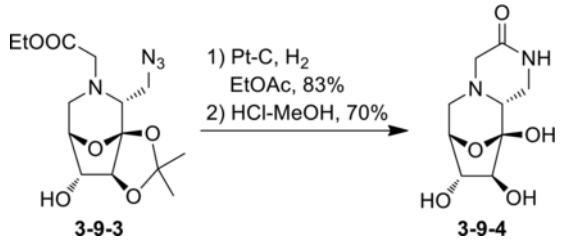
A new synthetic route to naphthoxazinoquinoxalinone derivatives **3-8-4** was developed starting with **3-8-3.**[68] An individual aminonaphthol isomer was allowed to react with formaldehyde to produce the desired derivative **3-8-4** in good yield (Eq. **21**).

3.9 Pyrazino[2,1-*c*][1,4]oxazines and their benzo analogs



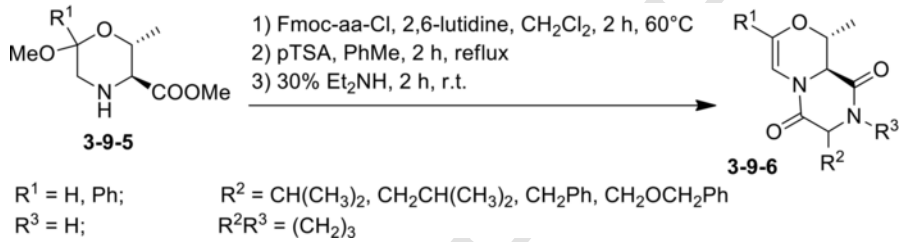
(22)

Octahydropyrazino[2,1-*c*][1,4]oxazines are potent and selective ROMK inhibitors.[69] Synthesis of active compound **3-9-2** from **3-9-1** is presented in Eq. **(22)**.



(23)

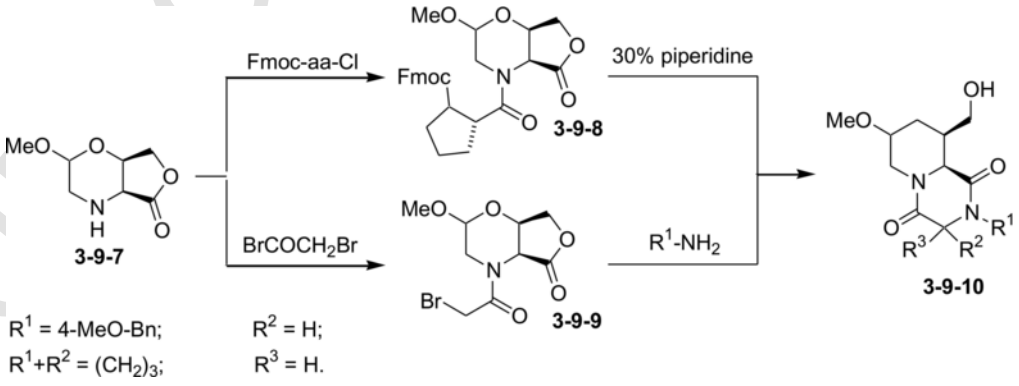
Synthesis of polyfunctional bicyclic iminocyclitols via intramolecular Huisgen cycloaddition was described.[70] Catalytic reduction of the azide **3-9-3** generated an amine that underwent spontaneous cyclization to a lactam. Tricyclic derivative **3-9-4** was obtained in 58% yield after subsequent removal of the acetonide by treatment with HCl/MeOH (Eq. **23**).



(24)

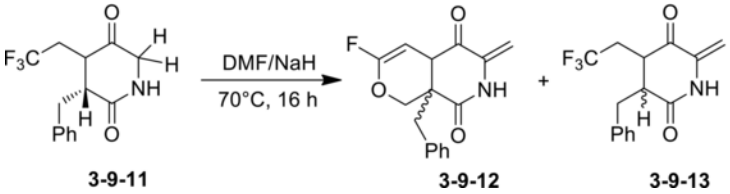
Synthesis of bicyclic compounds **3-9-6** containing 1,4-dihydrooxazine and diketopiperazine moieties.[71] involves coupling of morpholine derivatives **3-9-5** with Fmoc-protected α-amino acyl chlorides in the presence of 2 equivalents of 2,6-lutidine as a base. At the next step, 5 equivalents of *p*-toluenesulfonic acid in toluene were added. The final treatment with an excess of diethylamine gave the target diketopiperazine **3-9-6**. This process is effective for a number of amino acids (Eq. **24**).

Small molecule modulators of cell growth **3-9-10** were synthesized by two pathways presented in **Scheme 27**. Bicyclic lactone **3-9-7** was used as the starting material.[72] Coupling **3-9-7** with 9-fluorenylmethoxycarbonyl L-proline chloride (Fmoc-L-Pro-Cl) or bromoacetyl



Scheme 27

bromide generated the intermediate products **3-9-8** and **3-9-9**, respectively. Subsequent cyclization by treatment with amines produces target diketopiperazines **3-9-10**.



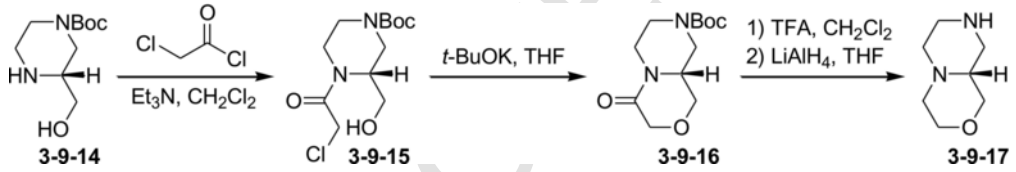
(25)

Deprotonation of **3-9-11** by treatment with sodium hydride in DMF led to the formation of two compounds **3-9-12** and **3-9-13** in 46% and 39% yields, respectively (Eq. **25**). Photophysical properties of these compounds were studied.[73]

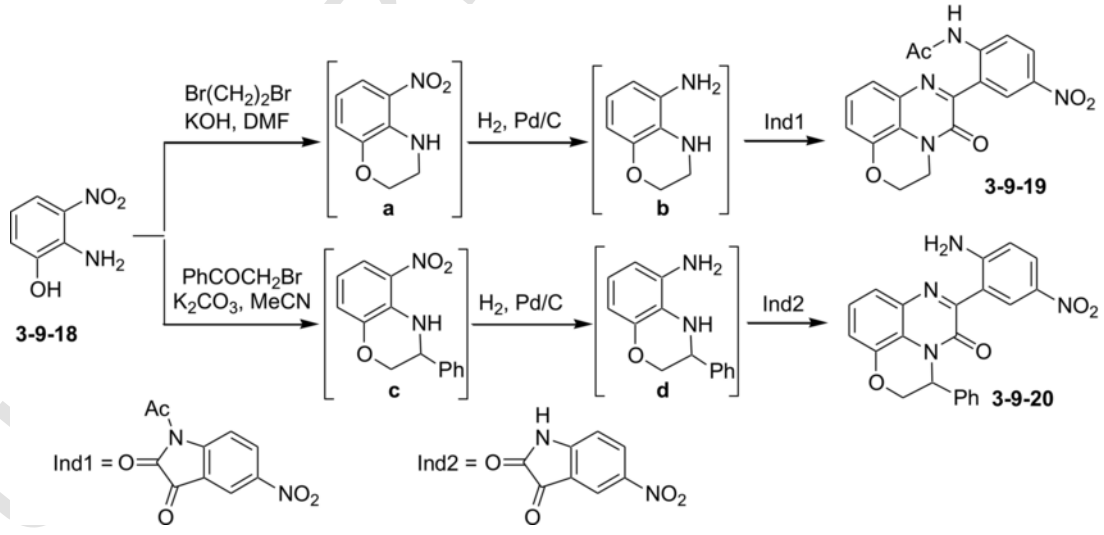
With the aim to develop a novel generation of anti-tuberculosis agents, pyrazino[2,1-*c*][1,4]oxazine **3-9-17** was synthesized.[74] (*R*)-1-Boc-3-(hydroxymethyl)piperazine **3-9-14** was allowed to react with chloroacetyl chloride to give **3-9-15**, which was cyclized to bicyclic *N*-protected intermediate product **3-9-16**. Synthesis was completed by deprotection of *tert*-butyloxycarbonyl (Boc) using trifluoroacetic acid and subsequent reduction with lithium aluminium hydride (**Scheme 28**).

Biologically active pyrazino[2,1-*c*][1,4]oxazines **3-9-19** and **3-9-20** were synthesized[75] (**Scheme 29**). At the first step, 2-amino-3-nitrophenol **3-9-18** was alkylated with 1,2-dibromoethane and β-bromoacetophenone and the resultant intermediate products **a** and **c** were reduced to **b** or **d**, respectively. Condensation of the diamines **b** or **d** with 5-nitroindoline-2,3-diones led smoothly to products **3-9-19** and **3-9-20**.

The 5-HT_{2C} receptor agonists **3-9-25** with potential anorectic activity were synthesized.[76] Heating *o*-nitrofluorobenzenes **3-9-21** with a 2-cyanopiperazine **3-9-22** in DMF/triethylamine solution furnished *o*-nitrophenylpiperazines **3-9-23** which, in turn, were reduced to **3-9-24** by treatment with iron in acetic acid. The last step consists of diazotization, followed by hydroxylation of the aryldiazonium salts and

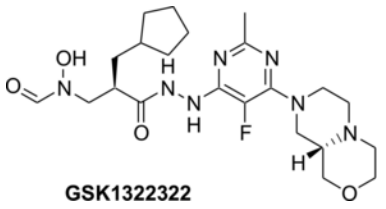


Scheme 28



Scheme 29

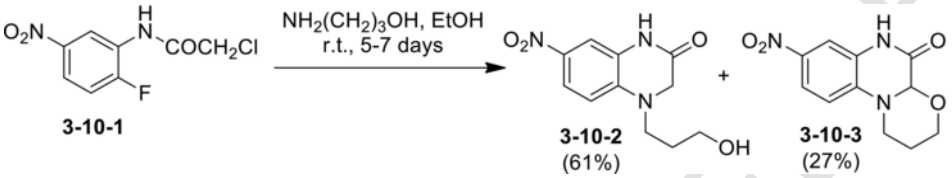
lactonization to give the benzoxazinones **3-9-25** (**Scheme 30**).



GSK1322322

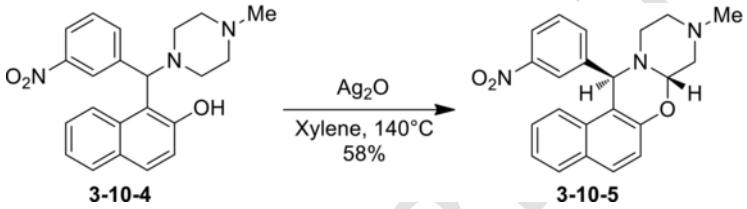
GSK1322322 is a novel peptide deformylase inhibitor[77] that was intensively investigated by different research groups for its metabolism.[78] This compound is also active against *Staphylococcus aureus*.[79]

3.10 Pyrazino[2,1-*b*][1,3]oxazines and their benzo analogs

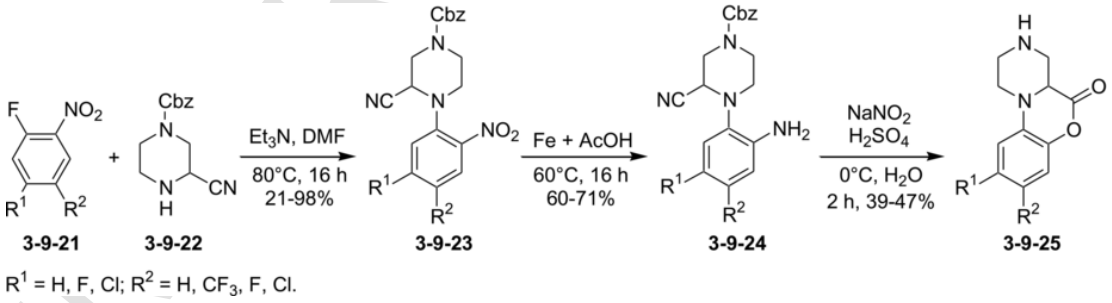


(26)

In an attempt to develop novel trichomonacidal agents, nitroquinoxalin-2-one **3-10-2** was synthesized starting from 2-chloroacetanilide **3-10-1**. Compound **3-10-2** was accompanied by pyrazino[2,1-*b*][1,3]oxazine **3-10-3** as a minor product[80] (Eq. **26**).

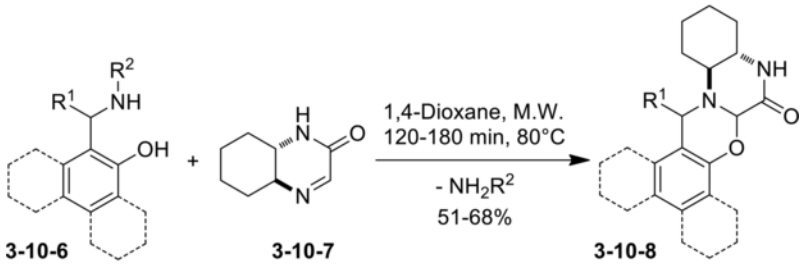


(27)



Scheme 30

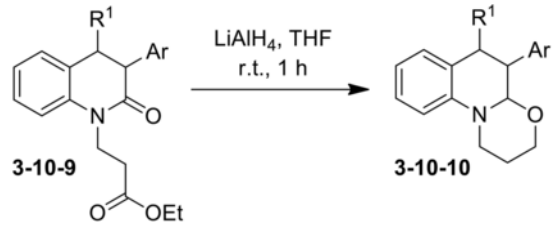
Diastereoselective cyclization of a substituted 2-naphthol **3-10-4** to pyrazino[2,1-*b*][1,3]oxazine derivative **3-10-5** by treatment with silver(I) oxide in xylene is shown in Eq. **27**.[26] This is an efficient route to other ring-fused oxazines as well.



(28)

R^1 = Ph, 1-naphthyl, 2-naphthyl
R^2 = H, benzyl

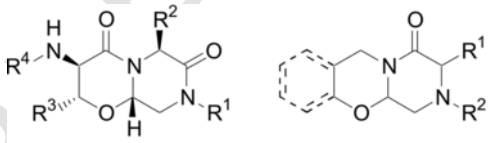
Equivalent amounts of aminonaphthols **3-10-6** and cyclic imine **3-10-7** were heated under MWI in 1,4-dioxane for 2–3 h and corresponding pyrazino[2,1-*b*][1,3]oxazines **3-10-8** were isolated (Eq. **28**).[68] The DFT calculations were used to investigate the conformations of synthesized compounds.



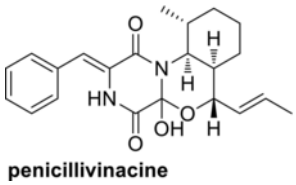
(29)

R^1 = CH_2Ph, $COOCH_2Ph$
Ar = Ph, 4-F-Ph

Compounds **3-10-10** were synthesized by reductive cyclization of ethoxycarbonylethyl - substituted quinoxalines **3-10-9** (Eq. **29**).[81]

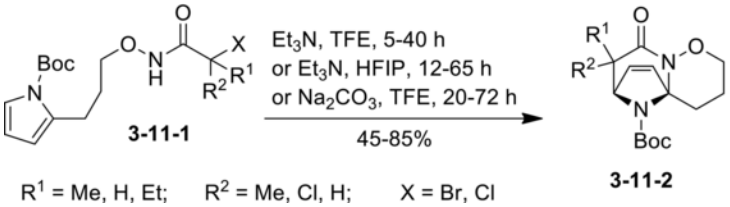


A solid-phase synthetic approach to fused bicyclic and tricyclic lactams of structures **3-10-11** and **3-10-12** was developed.[82–84] The cyclization step was performed using acid-mediated *N*-acylium ion formation followed by the O-/C-nucleophilic addition.



The diketopiperazine alkaloid penicillivinacine was isolated from the marine-derived fungus *Penicillium vinaceum*.[85] The structure was established by using spectroscopic techniques and high-resolution mass spectrometry. The activity against human breast cancer cells and antimicrobial activity against different pathogens was noted.

3.11 Pyrimido[1,2-*b*][1,2]oxazines



(30)

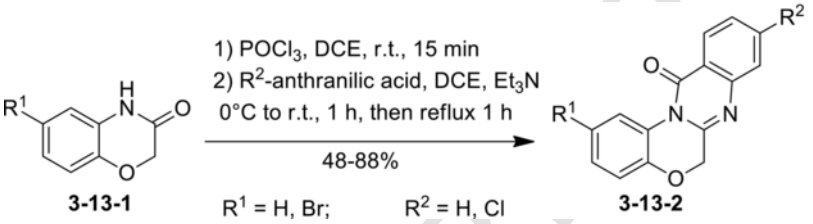
Intramolecular aza-[4 + 3] cycloaddition reactions of α-halohydroxamates **3-11-1** in 2,2,2-trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) in the presence of triethylamine or sodium carbonate furnished **3-11-2.**[6] (Eq. **30**).

3.12 Pyrimido[1,2-*c*][1,3]oxazines and their benzo analogs

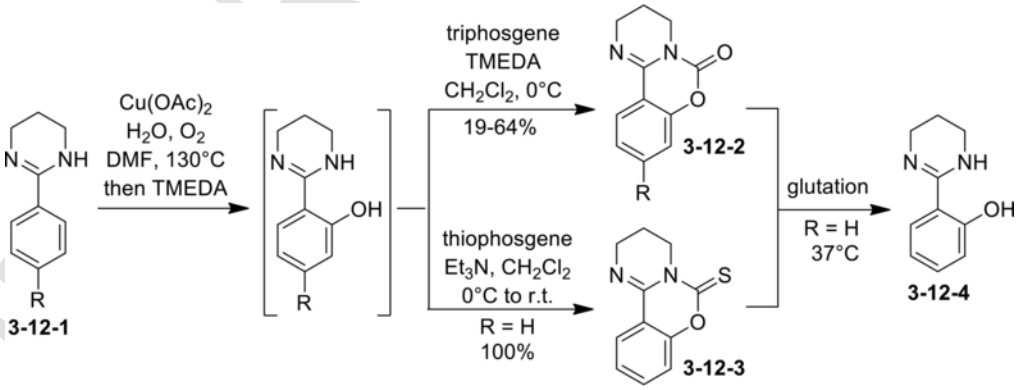
Mishara investigated the Cu(II)-mediated oxidative aromatic C–H functionalization of aryl-substituted tetrahydropyrimidines **3-12-1.**[86,87] In the presence of *N,N,N′,N′*-tetramethylethylenediamine the reaction is efficient for the selective introduction of oxygen to the *ortho*-position of the aryl substituent, and the subsequent reaction with triphosgene or thiophosgene leads to **3-12-2** or **3-12-13**, respectively (**Scheme 31**). In an attempted study bioactivity of synthesized compounds, it was found that in concentrated glutathione solutions at 37 °C, that mimic the intracellular environment, the ureido groups of **3-12-2** and **3-12-3** underwent decomposition and phenols **3-12-4** were isolated.[88]

In another investigation of intramolecular C-H bond activation, tetracyclic compounds **3-12-6** were synthesized in excellent yields by refluxing substituted 2-(2-hydroxyphenyl)-3-*R*-2,3-dihydroquinazolin-4(*1H*)-ones **3-12-5** with formaldehyde in ethanol at 80 °C for 10 h (**Scheme 32**). It was shown that benzoxazine-fused quinazolinones with the 2-bromophenyl substituent at the 2 position readily undergo oxidative biaryl Pd-catalyzed C–C coupling to form polycyclic scaffolds **3-12-7.**[89]

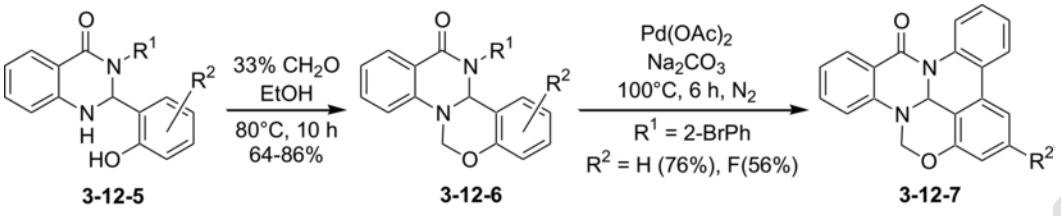
3.13 Pyrimido[2,1-*c*][1,4]oxazine and their benzo analogs



(31)



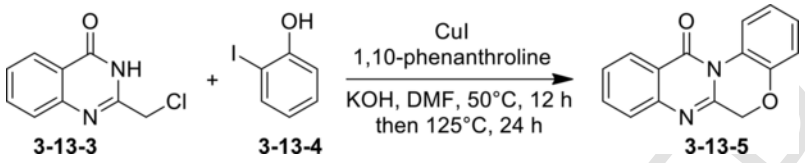
Scheme 31



R^1 = Ph, 4-MeOPh, 4-EtOPh, 4-MePh, 4-FPh, 4-ClPh, 4-BrPh, $PhCH_2$, 2-BrPh;
R^2 = H, 3-MeO, 2-MeO, 3-F.

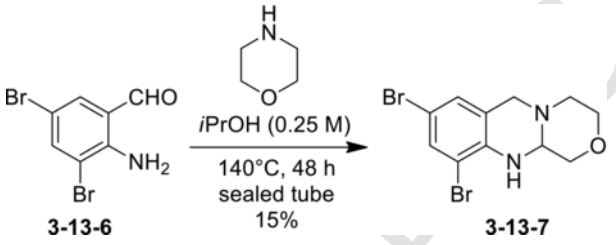
Scheme 32

In an attempt to develop biologically active oxadiazole inhibitors of soluble guanylyl cyclase, structures **3-13-2** were synthesized[90]. The reaction mixture was a suspension of 1,4-benzoxazin-3(4*H*)-one **3-13-1** and phosphoryl chloride in dichloroethane. After 15 min of stirring, a mixture of triethylamine and anthranilic acid was added (Eq. **31**). It was found that the replacement of the oxadiazole ring by a quinazoline system decreases activity.



(32)

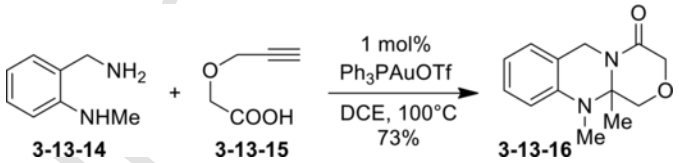
During the investigation of copper-catalyzed synthesis of 1,4-oxazino-, 1,4-thiazino-, and 1,4-oxazepinoquinazolinones, polycyclic system **3-13-5** were synthesized. A reaction mixture was a suspension of 2-chloromethylquinazolin-4-one **3-13-3**, 2-iodophenol **3-13-4**, CuI, 1,10-phenanthroline, and solid KOH in dry DMF (Eq. **32**).[91]



(33)

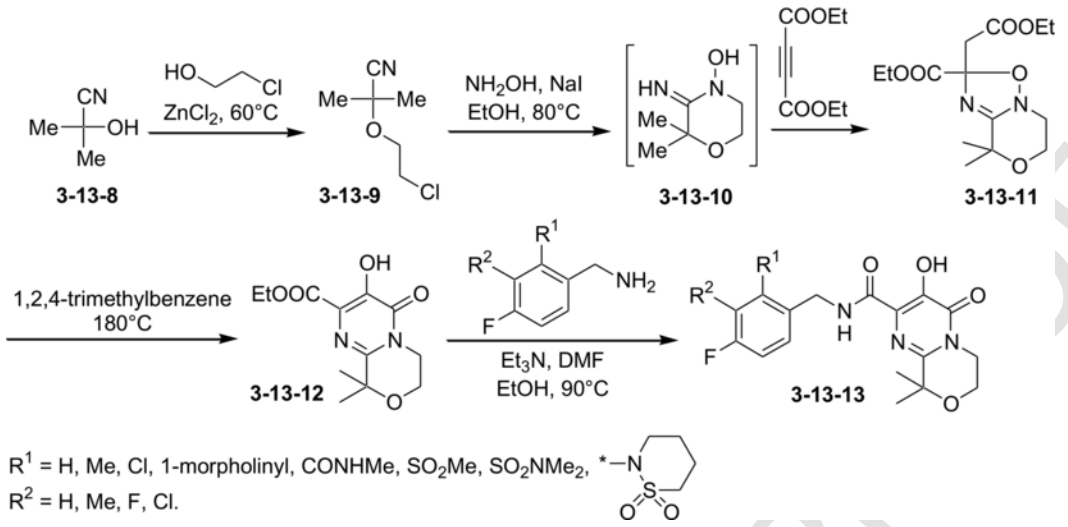
During the investigation of metal-free α-amination of secondary amines, tricyclic system **3-13-7** were synthesized by condensation of morpholine with aminobenzaldehyde **3-13-6**. Isopropanol was used as solvent and the reaction mixture was heated to 140 °C for 48 h in a sealed tube (Eq. **33**).[92]

Bicyclic pyrimidinone carboxamides **3-13-13** were synthesized for evaluation as HIV-1 integrase strand transfer inhibitors. These pyrimido[2,1-*c*][1,4]oxazines were prepared from acetone cyanohydrin **3-13-8** through intermediaries of **3-13-9** to **3-13-12**, as shown in **Scheme 33**.[93]



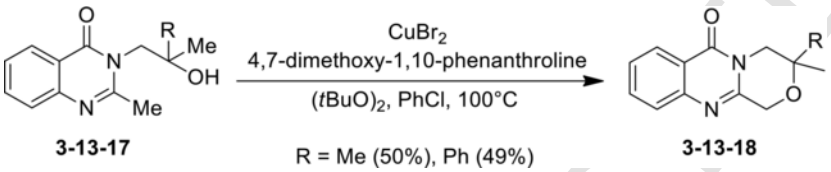
(34)

Tricyclic system **3-13-16** was constructed during investigation of the Au(I)-catalyzed cascade reaction involving formal double hydroamination of alkynes. Compound **3-13-16** was synthesized by condensation of diamine **3-13-14** with propargyloxyacetic acid **3-13-**



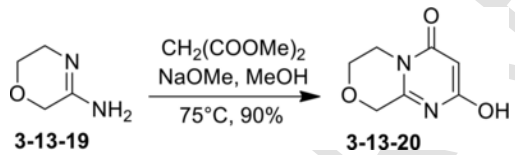
Scheme 33

15 (Eq. **34**).[94]



(35)

Copper-catalyzed benzylic C(sp^3)-H alkoxylation of heterocyclic compounds was investigated. The intramolecular alkoxylation of **3-13-17** on a gram scale was achieved using $CuBr_2$ with 4,7-dimethoxyphenanthroline and *tert*-butyl peroxide as a catalyst and an oxidant, respectively (Eq. **35**).[95]



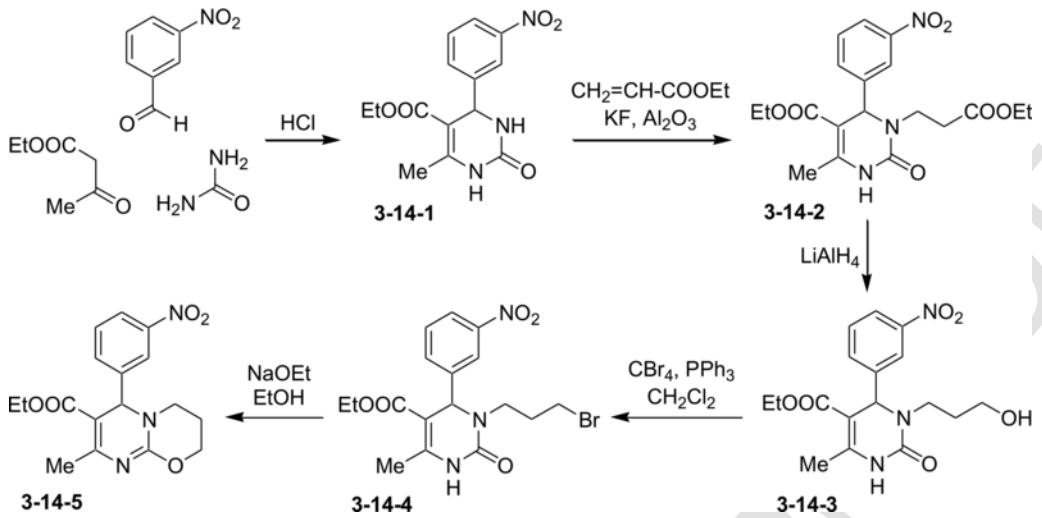
(36)

Synthesis of **3-13-20** from **3-13-19** was described in the work related to discovery and characterization of (*R*)-6-neopentyl-2-(pyridin-2-ylmethoxy)-6,7-dihydropyrimido[2,1-*c*][1,4]oxazin-4(9H)-one (PF-06462894) (Eq. **36**).[96]

3.14 Pyrimido[2,1-*b*][1,3]oxazines and their benzo analogs

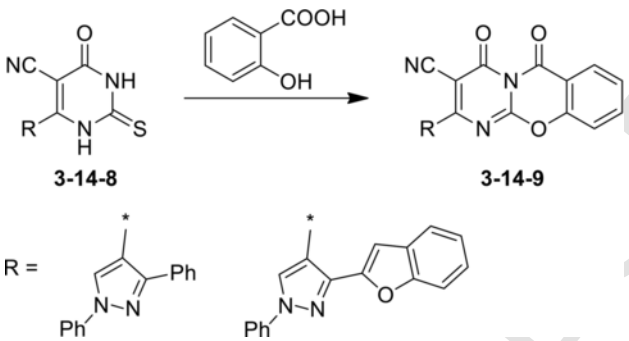
With the aim to design and synthesize substituted dihydropyrimidines with L-/T-type calcium channel blocking activities, the bicyclic structure **3-14-5** was obtained according to pathway **3-14-1** to **3-14-4** presented in **Scheme 34**.[97]

It was shown shown that the intermediate product generated in the reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates readily undergoes a reaction with 5-substituted uracils to produce highly functionalized pyrimido[2,1-*b*



Scheme 34

][1,3]oxazines **3-14-6** and **3-14-7** in high yields (**Scheme 35**).[98]



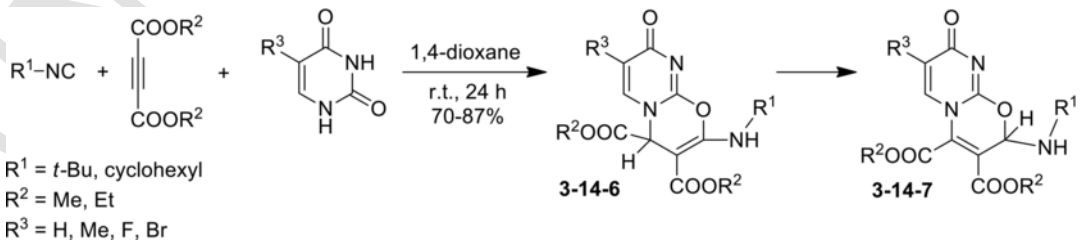
(37)

New pyrimido[2,1-*b*][1,3]oxazines **3-14-9** were synthesized and studied as possible antibacterial agents.[99,100] An equimolar mixture of thiouracils **3-14-8** and salicylic acid in absolute ethanol was heated under reflux for 10–12 h. According to minimal inhibition concentration values, products **3-14-9** display high antibacterial and antifungal potency.

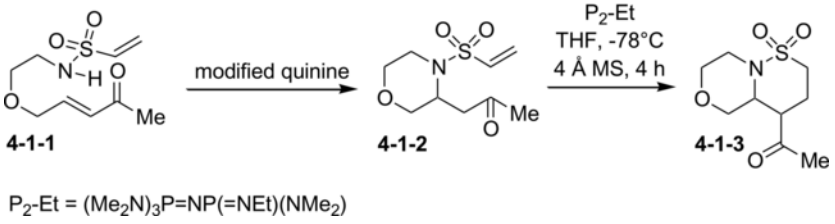
4 Systems with one O and one S extra atoms, 1:1, and their benzo analogs

4.1 [1,2]Thiazino[3,2-*c*][1,4]oxazines and their benzo analogs

A new strategy for the synthesis of enantiomerically enriched bicyclic δ-sultam of [1,2]thiazino[3,2-*c*][1,4]oxazine **4-1-3** is presented in **Scheme 36.**[101] The initial organocatalytic intramolecular aza-Michael reaction of vinyl sulfonamide **4-1-1** gives a conjugated ketone **4-1-**



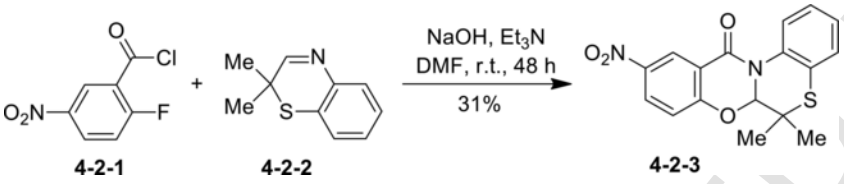
Scheme 35



Scheme 36

2. Next step is the intramolecular conjugate addition of the vinyl sulfone moiety and α-methylene group (**Scheme 36**). The key point of this methodology is the use of starting vinyl sulfonamides as nitrogen nucleophiles and Michael acceptors.

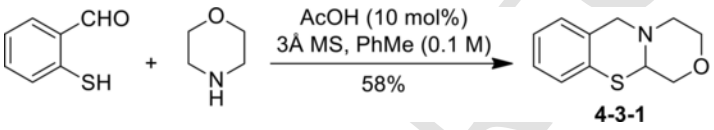
4.2 [1,4]Thiazino[3,4-*b*][1,3]oxazines and their benzo analogs



(38)

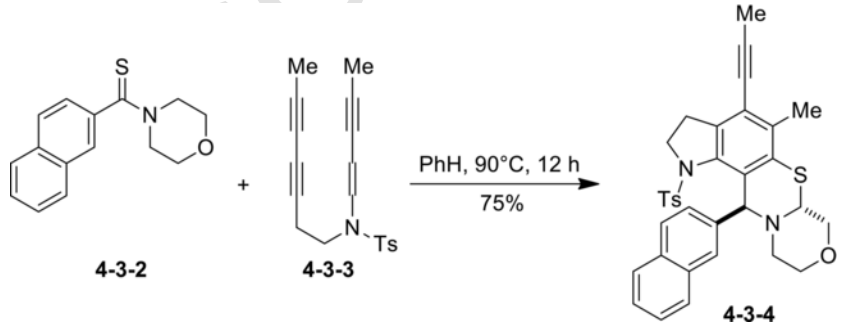
An efficient synthesis of a new [1,4]thiazino[3,4-*b*][1,3]oxazine **4-2-3** by reaction of readily accessible cyclic imine **4-2-2** with acid chloride **4-2-1** was described. The convenient strategy enables the access to different polyheterocyclic scaffolds. The reaction mixture consists of the imine, acyl chloride, sodium hydroxide, Et_3N and DMF as solvent. The reaction was performed under an argon atmosphere (Eq. **38**).[102]

4.3 [1,3]Thiazino[2,3-*c*][1,4]oxazines and their benzo analogs



(39)

Secondary amines undergo a reaction with thiosalicylaldehydes to produce ring-fused N,S-acetals.[103] It was found that a broad range of amines undergo α-sulfenylation, including morpholine, thiomorpholine and piperazine. For example, the tricyclic system **4-3-1** was obtained by the reaction of thiosalicylaldehyde with morpholine. Acetic acid and 3 Å molecular sieves were used as a catalyst system (Eq. **39**). Theoretical DFT studies at M06-2X-D3/def2-TZVPP//TPSS-D2/6-31 + G(d,p) level of theory with employing IEFPCM toluene solvent model were performed for the calculation of energy barriers of reaction steps.



(40)

During the study of reactions of hexadehydro-Diels-Alder (HDDA)-derived benzynes with thioamides, a powerful synthetic methodology was developed for synthesis of [1,3]thiazino[2,3-*c*][1,4]oxazines.[104] For example, the reaction of thioamide **4-3-2** with benzyne precursor **4-3-3** in benzene upon heating produces system **4-3-4**. The reaction involves benzyne intermediate generated by thermal cycloisomerization of **4-3-3** (Eq. **40**).

5 Systems with two extra N atoms, 1:1, and their benzo analogs

5.1 Pyrimido[1,6-*b*]pyridazines

5.1.1 Synthesis of pyrimido[1,6-b]pyridazines

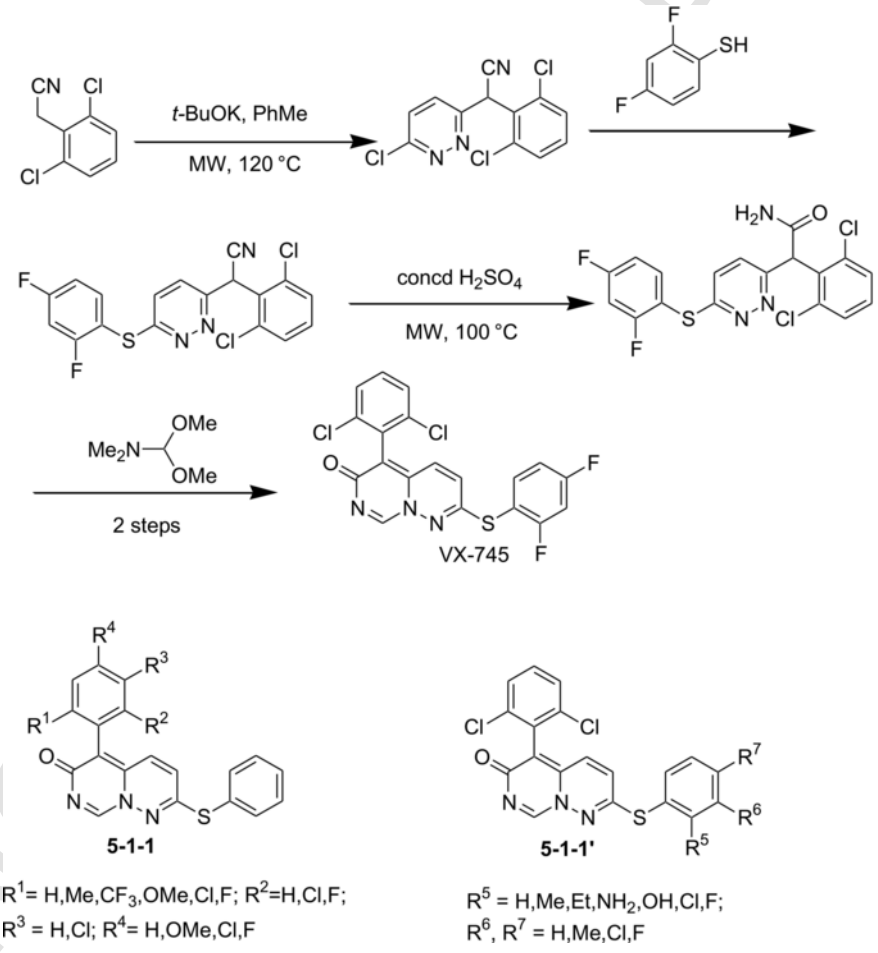
Compounds **5-1-1** and **5-1-1′** containing the fused bicyclic pyrimido[1,6-*b*]pyridazine system are synthetic analogs of the biologically active agent VX-745 (**Scheme 37**). Their synthesis can be conducted on a multi-gram scale.[105–107]

5.1.2 Reactivity and structural features of pyrimido[1,6-b]pyridazines

The application of structural information from enzyme-ligand complexes guided the selection of compounds **5-1-1** and **5-1-1′** for screening, leading to the identification of a novel class of p38R inhibitors containing a pyrimido[1,6-*b*]pyridazine system.[107] Advancing the SAR analysis of this series led to the discovery of 5-(2,6-dichlorophenyl)-2-(2,4-difluorophenylthio)-6*H*-pyrimido[1,6-*b*]pyridazin-6-one (VX-745).

5.1.3 Applications and important pyrimido[1,6-b]pyridazines

Recent advances on the understanding of the interaction of receptors such as TLRs, interleukins and p38R with pyrimido[1,6-*b*]pyridazine derivatives, as well as recent strategies for developing small molecule antagonists using rational models are discussed by Bello.[108]

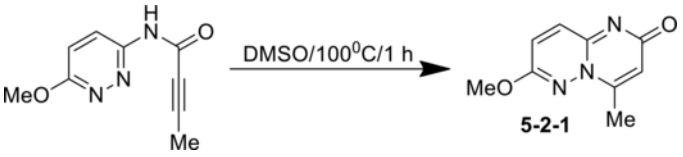


Scheme 37

5.2 Pyrimido[1,2-*b*]pyridazines and their benzo analogs

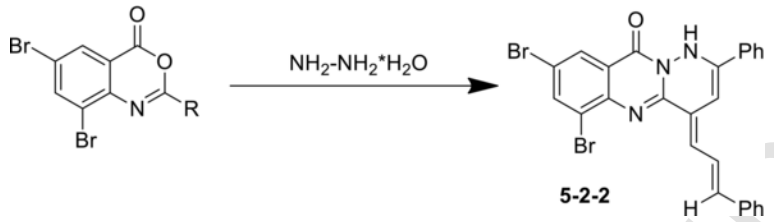
5.2.1 Synthesis of pyrimido[1,2-b]pyridazines and their benzo analogs

An effective and modular strategy for the concise synthesis of pyrimido[1,2-*b*]pyridazines **5-2** is briefly summarized in **Scheme 38.**[109] A particular example of **5-2-1** is illustrated in Eq. **41**. This approach is suitable for the construction of other isomeric pyrimidopyrimidines and pyrimidopyrazines.



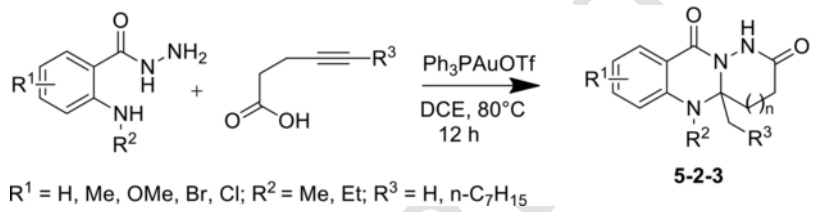
(41)

N-Substituted pyridazino[6,1-*b*]quinazoline derivative **5-2-2** was obtained by the reaction of 2-[(1*Z*,3*E*)-1-benzamido-4-phenyl-1,3-butadien-1-yl]-6,8-dibromo[3,1]benzoxazin-4(*H*)-one with hydrazine hydrate in boiling *n*-butanol for 20 h (Eq. **42**).[110]



(42)

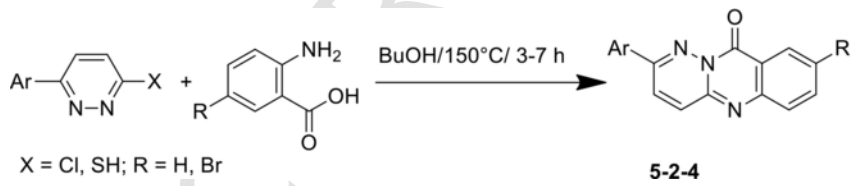
A robust library-based approach to pyridazino[6,1-*b*]quinazolines **5-2-3** involves the gold(I)-catalyzed reaction between a 2-aminobenzohydrazide and a pent-4-ynoic acid (Eq. **43**).[111] An equimolar mixture of the starting 2-aminobenzohydrazide and pent-4-ynoic acid in the presence of $Ph_3PAuOTf$ was heated in DCE at 80 °C for 12 h yielding single regioisomer **5-2-3**.



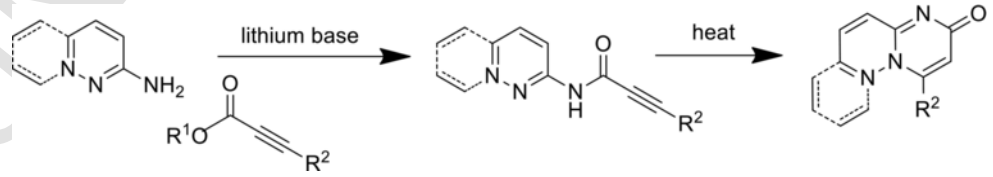
(43)

R^1 = H, Me, OMe, Br, Cl; R^2 = Me, Et; R^3 = H, n-C_7H_{15}

3-Chloro-6-aryl-pyridazines undergo a reaction with an anthranilic acid, in DMF affording pyridazino[3,2-*b*]quinazolinones **5-2-4** (Eq. **44**).[112–115] A mixture of starting compounds was heated in an oil bath at 150 °C for 3–7 h, cooled and triturated with ethanol.



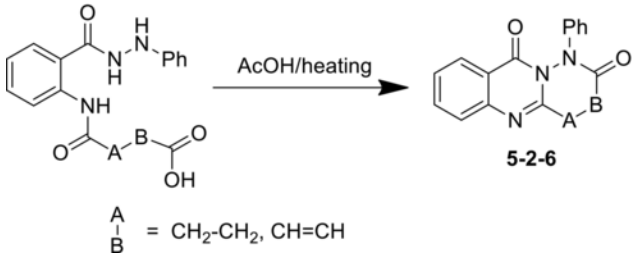
(44)



Scheme 38

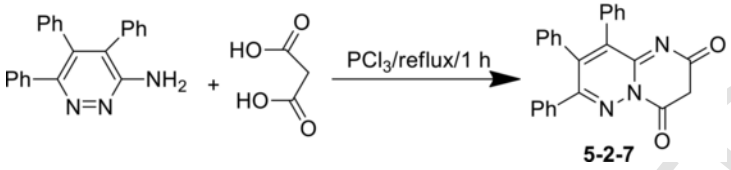
In an efficient synthetic route to 5*H*-quinazolino[3,2-*b*]cinnoline-7,13-diones **5-2-5**, 2′-bromoacetophenone was treated with iodine in DMSO at 110 °C during 3 h, then *N*′-phenyl-2-aminobenzohydrazide and K_2CO_3 were added to the reaction vessel. After stirring at room temperature for 5 h, the mixture was heated to 100 °C for another 6 h (**Scheme 39**).[116]

Upon heating of the substituted anthranilic acid hydrazides in glacial acetic acid, pyridazino[3,2-*b*]quinazolinones **5-2-6** were obtained in good yield (Eq. **45**).[117] This technique is also suitable for synthesis of tetracyclic analogs of pyridazino[3,2-*b*]quinazolinones.



(45)

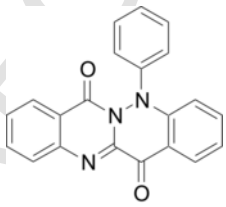
A convenient synthetic approach to a pyrimido[1,2-*b*]pyridazinone **5-2-7** involves treatment of 3-amino-4,5,6-triphenylpyridazine with malonic acid in the presence of phosphoryl chloride (Eq. **46**).[118]



(46)

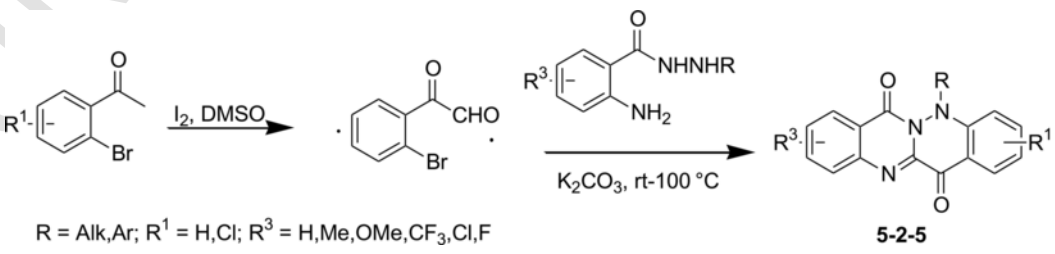
5.2.2 Reactivity and structural features of pyrimido[1,2-b]pyridazines and their benzo analogs

The structure of 5-phenyl-5*H*-quinazolino[3,2-*b*]cinnoline-7,13-dione **5-2-5** was unambiguously confirmed by X-ray diffraction analysis.[116]

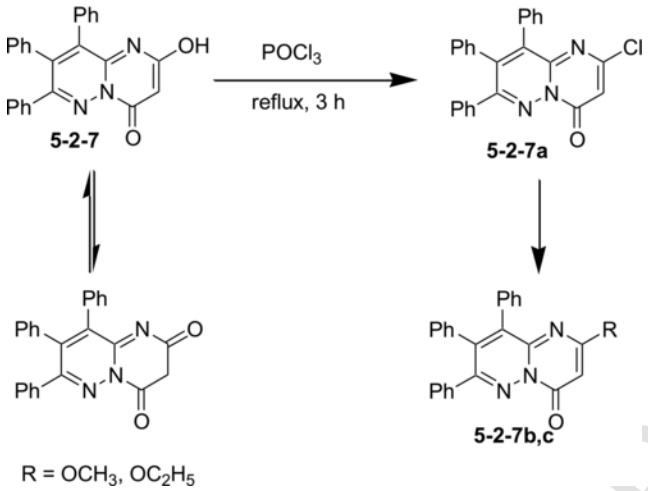


Pyrimido[1,2-*b*]pyridazinone **5-2-7** is an excellent precursor for the synthesis of various derivatives of this system.[119] For example, chlorination of **5-2-7** by treatment with phosphoryl chloride led to the 2-chloro derivative **5-2-7a** (**Scheme 40**),[119] the nucleophilic substitution reactions of which furnished derivatives **5-2-7b,c**.

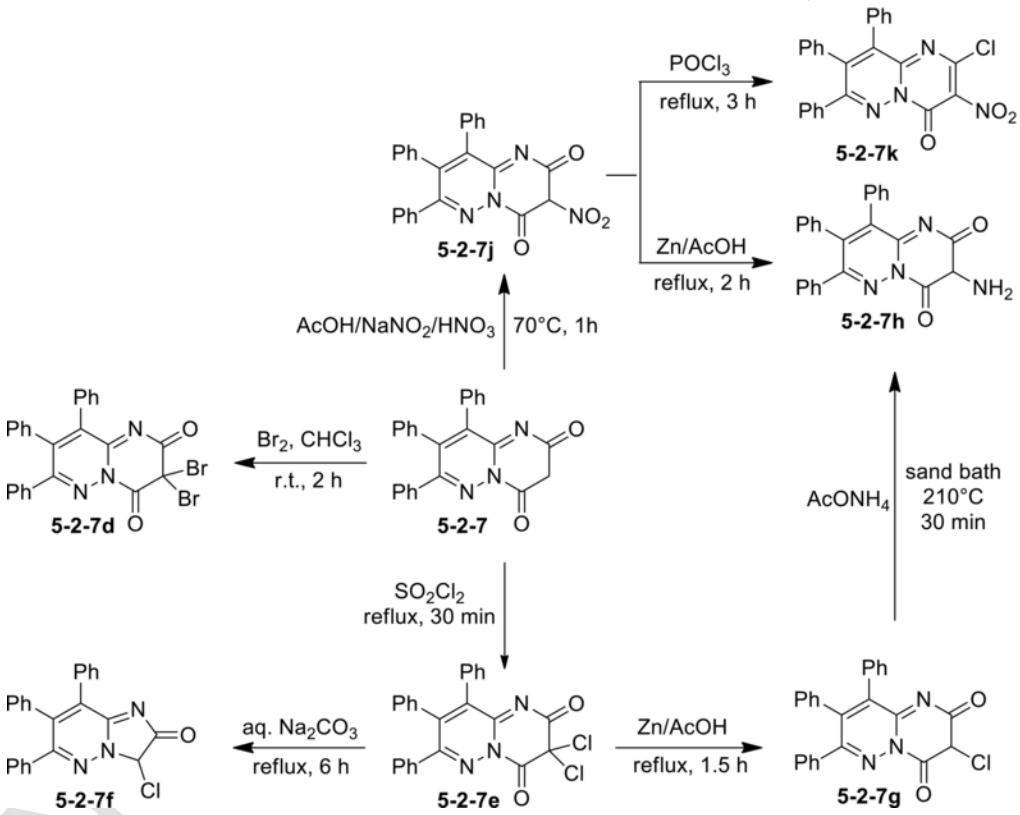
Bromination of pyrimido[1,2-*b*]pyridazinone **5-2-7** with an excess of bromine furnished a dibromo derivative **5-2-7d** (**Scheme 41**).[119] Chlorination of title compound **5-2-7** with sulfuryl chloride led to 3,3-dichloro-7,8,9-triphenyl-2*H*-pyrimido[1,2-*b*]pyridazine-2,4(3*H*)-



Scheme 39



Scheme 40



Scheme 41

dione **5-2-7e**. This compound underwent ring contraction upon boiling in an aqueous solution of sodium carbonate to afford 3-chloro imidazo[1,2-*b*]pyridazin-2(3*H*)-one **5-2-7f**. Treatment of compound **5-2-7e** with zinc in acetic acid under reflux furnished 3-chloro derivative **5-2-7g** in a good yield, the direct amination of which by fusion with ammonium acetate at 210 °C for 30 min gave 3-amino-7,8,9-triphenyl-2*H*-pyrimido[1,2-*b*]pyridazine-2,4(3*H*)-dione derivative **5-2-7h**. Nitration of **5-2-7** by nitric acid in acetic acid in the presence of sodium nitrite as a catalyst, gave 3-nitropyrimidopyridazinone derivative **5-2-7j**. Treatment of the nitro derivative **5-2-7j** with phosphoryl chloride gave the corresponding 2-chloro derivative **5-2-7k**. Finally, reduction of **5-2-7j** by treatment with zinc dust in acetic acid under reflux furnished the 3-amino derivative **5-2-7h** (Scheme 41).[119]

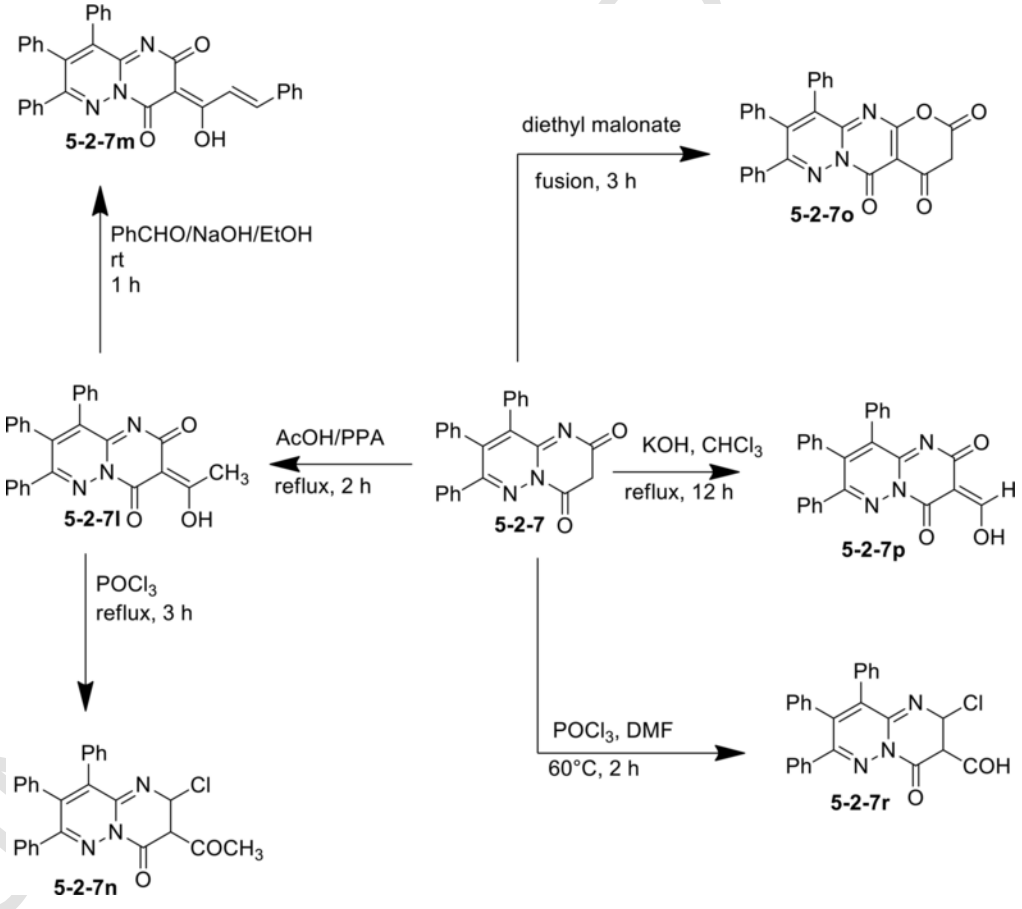
Introduction of an acetyl group into the 3-position of the pyrimidopyridazinone **5-2-7** was achieved by direct *C*-acetylation with acetic acid in polyphosphoric acid yielding 3-acetyl derivative **5-2-7l** (**Scheme 42**).[119] The α,β-unsaturated ketone **5-2-7m** was synthesized employing Claisen-Schmidt reaction by treating the 3-acetyl derivative **5-2-7l** with benzaldehyde in the presence of a base. Treatment of compound **5-2-7l** with phosphoryl chloride under reflux, furnished 3-acetyl-2-chloropyrimidopyridazinone **5-2-7n**. Condensation of **5-2-7** with diethyl malonate under reflux conditions furnished pyranopyrimidopyridazinone **5-2-7o** (**Scheme 42**).[119]

Formylation of compound **5-2-7** at position 3 was achieved by reaction with chloroform in the presence of potassium hydroxide. This reaction yielded 3-(hydroxymethylidene)-7,8,9-triphenyl-2*H*-pyrimido[1,2-*b*]pyridazine-2,4(3*H*)-dione **5-2-7p**. The reaction of compound **5-2-7** with Vilsmeier reagent led to the analogous pyridazine-3-carbaldehyde **5-2-7r**, which was also obtained by the reaction of compound **5-2-7p** with phosphoryl chloride (**Scheme 42**).[119]

5.2.3 Applications and important pyrimido[1,2-b]pyridazines and their benzo analogs

A number of drugs containing pyrimido[1,2-*b*]pyridazine moiety **5-2** have been in clinical use for inhibition of CYP2D6.[120] The heterocyclic derivatives **5-2-3** significantly inhibit the proliferation of lung cancer cells A549 and breast cancer cells MDA-MB-231 and MCF-7 in vitro. These compounds could be used for finding leads for lung and breast cancer therapies.[111]

Cytotoxicity of compounds **5-2-4** against three human cancer cell lines in vitro was tested: MCF7 (breast carcinoma), HEPG2 (hepatocellular carcinoma) and HCT116 (colon carcinoma).[114] Compounds **5-2-4** also show moderate antimicrobial activity against *Escherichia coli, Staphylococcus aureus, Bacillus subtilis* and *Salmonella typhi* bacterial strains and *Aspergillums niger* and *Candida albicans* fungal strains.[115] Compound **5-2-7g** is highly active against *Staphylococcus aureus*.[119] On the other hand, compounds **5-2-7b-f,j,m,o-r** show moderate activity against both *Staphylococcus aureus* and *Escherichia coli*. Compounds **5-2-7c,g** show antifungal activity against *Candida albicans*.[119]



Scheme 42

5.3 Pyrazino[1,2-*c*]pyrimidines and their benzo analogs

5.3.1 Synthesis of pyrazino[1,2-c]pyrimidines and their benzo analogs

The cyclocondensation of 3-alkoxycarbonylmethylidenepiperazin-2-ones with α-chlorobenzyl isocyanates gave alkyl 8-aryl-1,6-dioxo-1,3,4,6,7,8-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-9-carboxylates **5-3-1** (**Scheme 43**).[121] It is most likely that this reaction takes place by initial addition of the nucleophilic carbon atom of the exocyclic alkoxycarbonylmethylidene group of starting compounds to the C═N bond of the *N*-chloroformylimino form of the isocyanates to yield the intermediates **A**, which then undergo cyclization to the target compounds **5-3-1**.

A different result was obtained for the reaction of the same piperazin-2-ones with 1-aryl-2,2,2-trifluoroethyl isocyanates in toluene under reflux conditions—the 6-aryl-1,8-dioxo-6-trifluoromethyl-1,3,4,6,7,8-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-9-carboxylic acid esters **5-3-2** were formed (**Scheme 44**).[121]

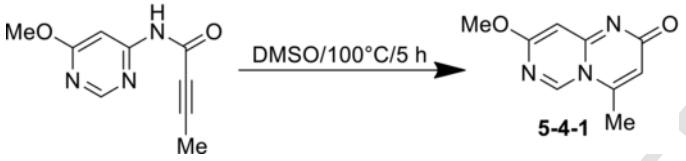
Cyclization of aroyl or (4,6-dimethylpyrimidin-2-yl)cyanamides with methyl 2-(3-oxopiperazin-2-yl)acetate furnished 2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione derivatives **5-3-3** (**Scheme 45**).[122]

At the first step, the reaction of cyanamides with piperazinone generates an ionic compound **B** (**Scheme 45**), which upon heating undergoes the Woehler rearrangement with the formation of guanidine **C**.[122]

5.4 Pyrimido[1,6-*a*]pyrimidines and their benzo analogs

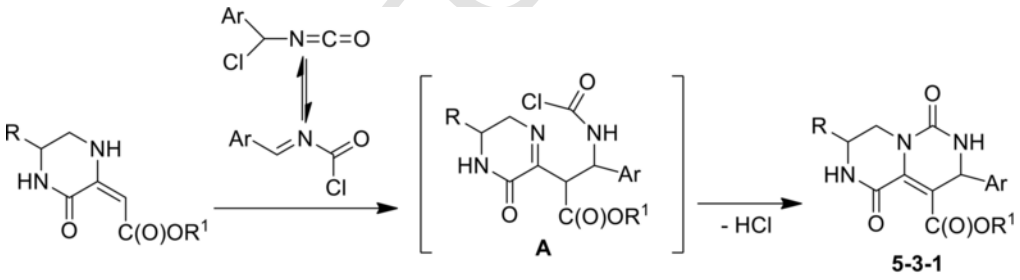
5.4.1 Synthesis of pyrimido[1,6-a]pyrimidines and their benzo analogs

A general approach of Scheme 38can be used for the preparation of pyrimido[1,6-*a*]pyrimidines **5-4.**[109] A particular example of the synthesis of **5-4-1** is presented in Eq. **47**.



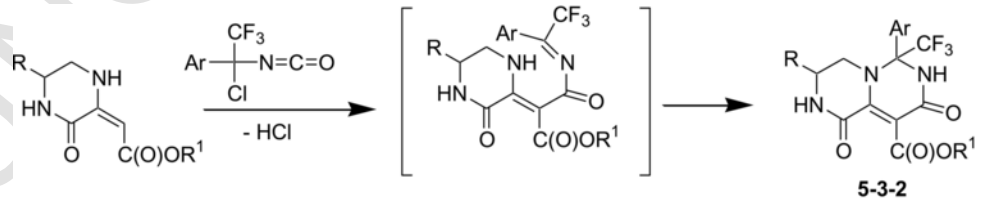
(47)

Reliable reviews of the application of microwave irradiation in synthesis of six-membered bicyclic heterocyclic systems, including pyrimido[1,6-*a*]pyrimidines **5-4**, as well as their benzo analogs, were published.[123,124]



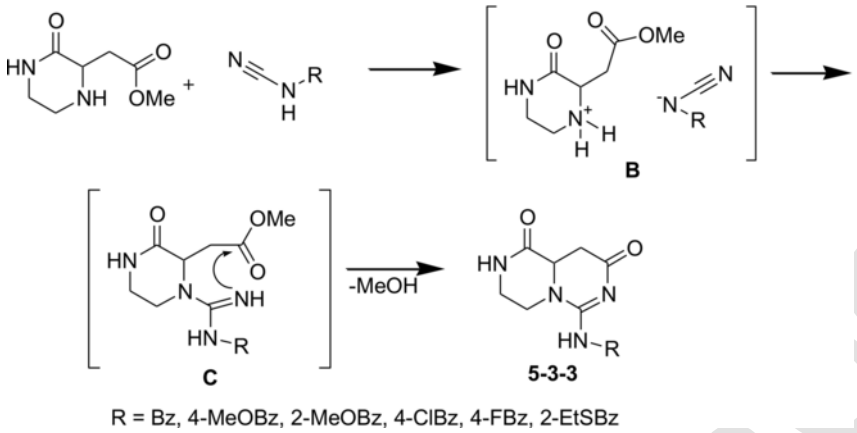
R = H, Me; R^1 = Me, Et; Ar = Ph, 2-FC_6H_4, 3-BrC_6H_4, 4-$NO_2C_6H_4$, 3,4-$Cl_2C_6H_3$

Scheme 43



R = H, Me; R^1 = Me, Et; Ar = Ph, 4-FC_6H_4, 4-MeC_6H_4

Scheme 44



Scheme 45

A concise and efficient route for the synthesis of pyrimido[1,6-*a*]pyrimidines **5-4-2** and **5-4-3** was developed by simply refluxing a mixture of *N,N′*-bis(arylmethylidene)arylmethane and different diamines in the presence of 1,1-bis(methylthio)-2-nitroethylene for 8–10 h (**Scheme 46**).[125] Different solvents, such as methanol, ethanol, acetonitrile, tetrahydrofuran and dichloromethane were explored; the best results were obtained using EtOH.

A polysubstituted pyrimidine was allowed to react with 3-chloropentane-2,4-dione (a typical β-diketone) in acetic acid in the presence of zinc dust to afford 1,3,4,6-tetrahydro-2*H*-pyrimido[1,6-*a*]pyrimidines **5-4-4** in a good yield (**Scheme 47**).[126] The suggested intermediate products are shown.

5.4.2 Reactivity and structural features of pyrimido[1,6-a]pyrimidines and their benzo analogs

The 3-chloro-pyrimido[1,6-*a*]pyrimidines **5-4-4** undergo **a** reaction with piperazine or morpholine in boiling methanol to give the corresponding 3,6,8-tripiperazin-1-yl **5-4-4-a** or 3,6,8-trimorpholin-1-yl **5-4-4b** derivatives (**Scheme 48**).[126]

5.4.3 Applications and important pyrimido[1,6-a]pyrimidines and their benzo analogs

Compounds **5-4-4, 5-4-4a, 5-4-4b** exhibit potent antiinflammatory and analgesic activities.[126]

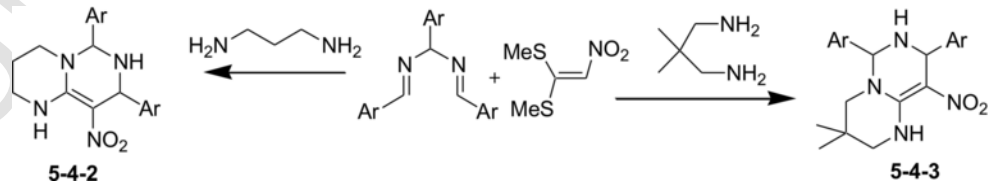
5.5 Pyrazino[1,2-*a*]pyrazines and their benzo analogs

5.5.1 Synthesis of pyrazino[1,2-a]pyrazines and their benzo analogs

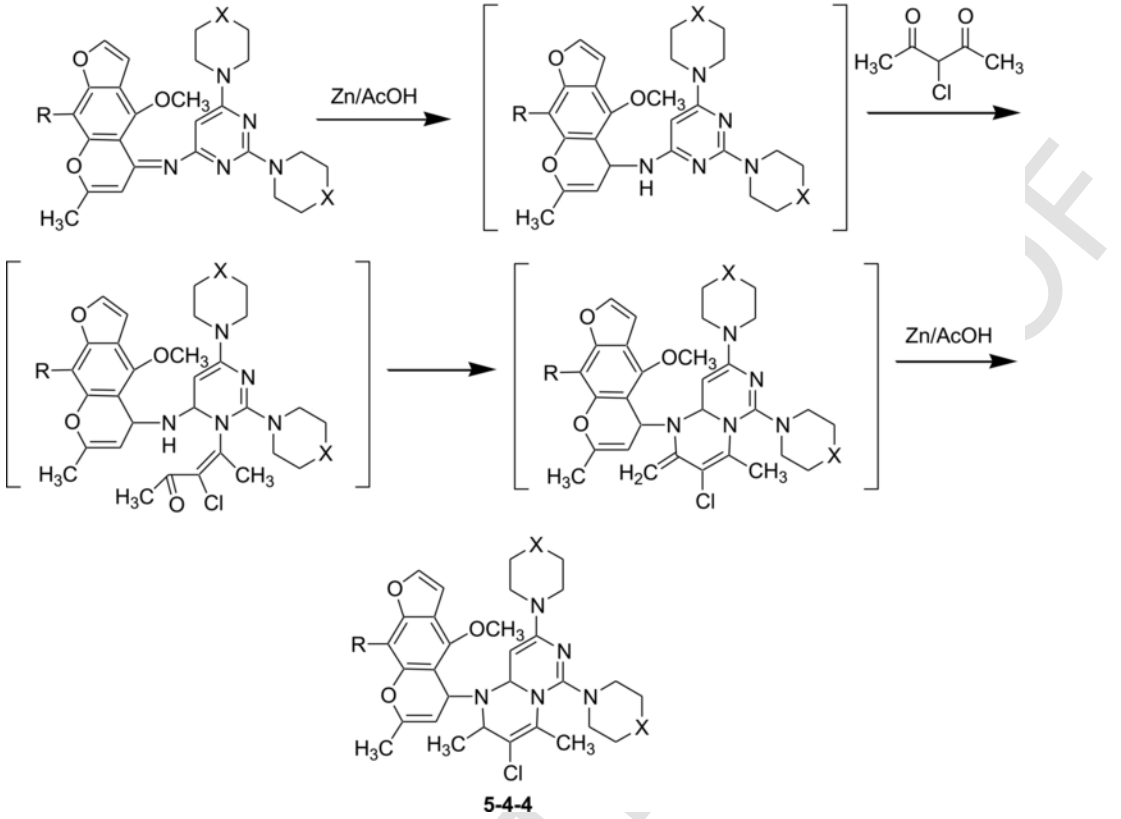
Synthesis of pyrazino[1,2-*a*]-pyrazine derivatives **5-5-1** is shown in **Scheme 49.**[127,128] Acylation with a subsequent removal of the *N*-Boc group was achieved by treatment with an excess of methanolic HCl, and the resulting aminoterminal dipeptide fragment in the deprotected compound was cyclized by heating in toluene at 90 °C to furnish the fully protected oxopyrazino[1,2-*a*]pyrazinedione **5-5-1** containing the rigidified retro-RGD (Arg-Gly-Asp) tripeptide motif with a β-amino acid analog of arginine.

Treatment of 3-alkanoylquinoxalin-2-ones with NH_4OAc in a benzene-DMSO mixture with azeotropic removal of water produced purple-colored bipyrazinylimine as the main product, the continuing heating of which furnished a burgundy colored pyrazino[1,2-*a*]quinoxaline **5-5-2** (**Scheme 50**).[129] A series of analogous compounds **5-5-3** (not shown) were also synthesized through the intermediaries of dimeric products.[130]

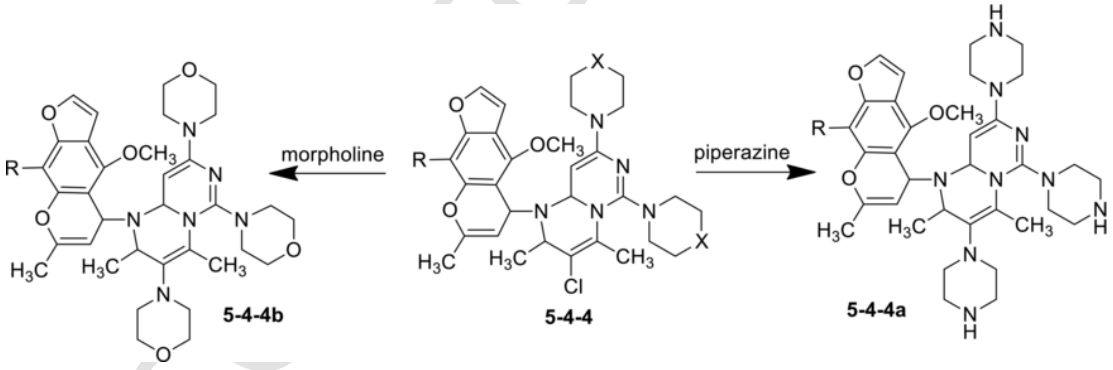
A series of enantiomerically pure hexahydro-1*H*-pyrazino[1,2-*a*]quinoxalines **5-5-4** were synthesized from a protected diamine derivative in three steps, as shown in **Scheme 51**.[131,132]



Scheme 46



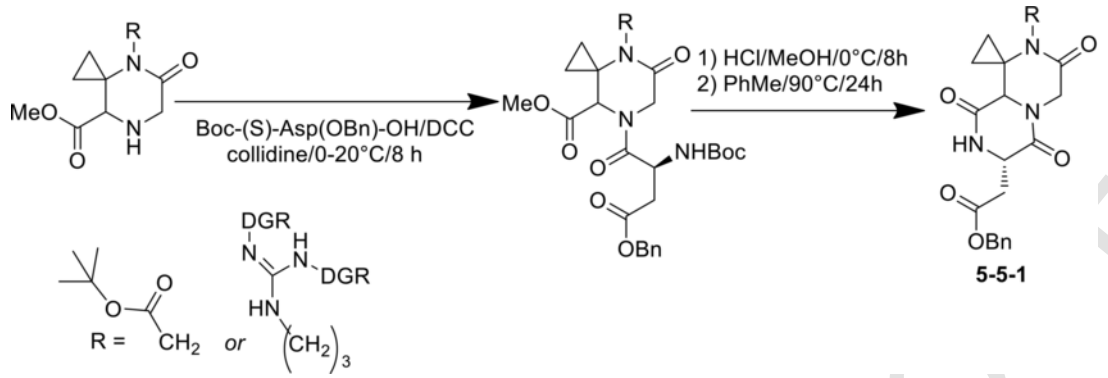
Scheme 47



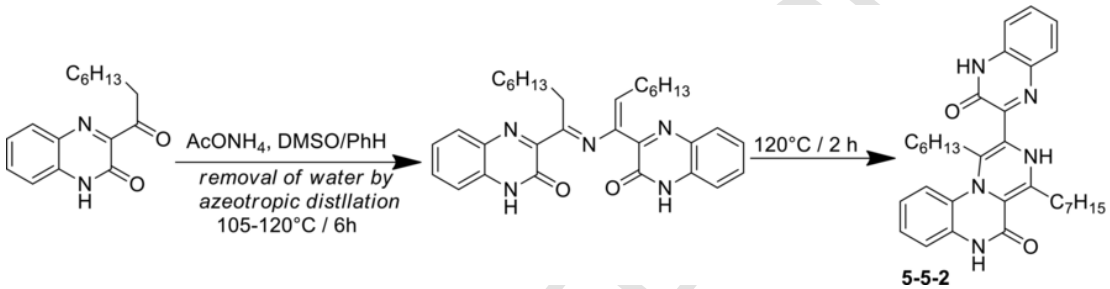
Scheme 48

5.5.2 Reactivity and structural features of pyrazino[1,2-a]pyrazines and their benzo analogs

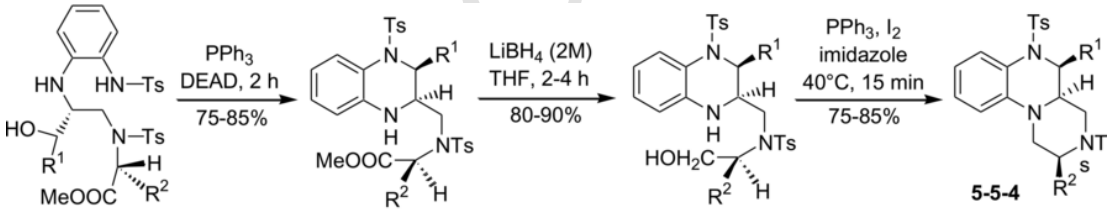
The inseparable 1:1 mixture of diastereomers **5-5-1** was deprotected by catalytic hydrogenation in methanol over palladium on charcoal. The crude mixture was purified by filtration over CeliteR to prevent any loss of the DGR tripeptide mimic **5-5-1a**, which is extremely



Scheme 49



Scheme 50

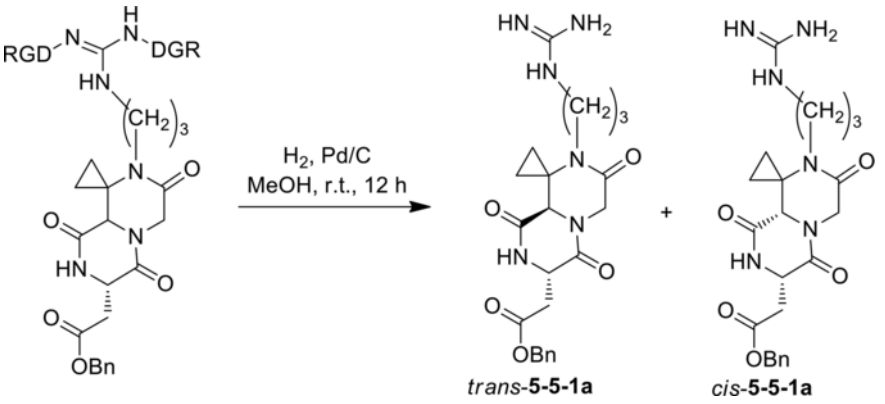


R^1 = H, Me;

R^2 = Me, *i*-Pr, CH_2CHMe_2,CH_2Ph, $CH_2C_6H_4OBn$.

Scheme 51

soluble in water (Eq. 48).[128] The 1:1 mixture of *trans*- and *cis*-**5-5-1a** was obtained as a colorless solid in quantitative yield.



(48)

5.5.3 Applications and important pyrazino[1,2-a]pyrazines and their benzo analogs

These benzofused pyrazino[1,2-*a*]quinoxalines **5-5-4** had promising biological activity in hormonal related disorders.[132]

5.6 Pyrazino[1,2-*a*]pyrimidines and their benzo analogs

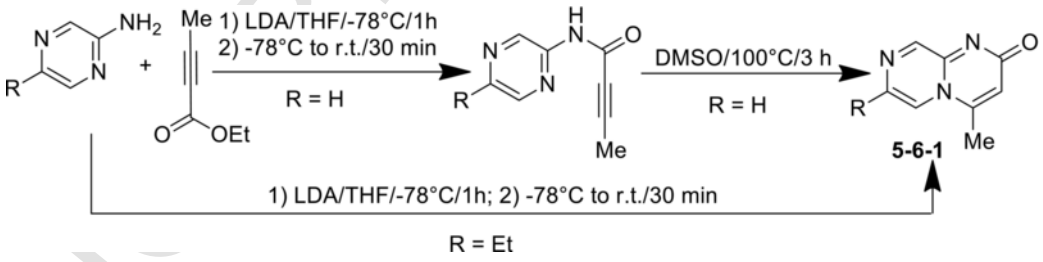
5.6.1 Synthesis of pyrazino[1,2-a]pyrimidines and their benzo analogs

Microwave irradiation assisted synthesis of pyrazino[1,2-*a*]pyrimidines **5-6** and their benzo analogs were reviewed.[124,133–137] Approximately 80 naturally-occurring secondary metabolites that are structurally-related to pyrazino[1,2-*a*]pyrimidines were isolated, mainly from marine sources. The data on isolation, structure elucidation, biological activities, biosynthetic pathways, and synthetic studies of these natural products were reviewed in detail.[138,139]

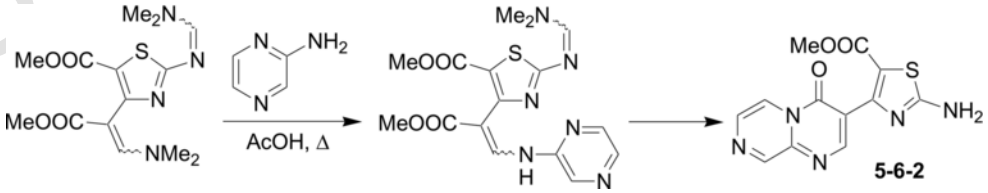
An effective and modular strategy for the concise synthesis of pyrazino[1,2-*a*]pyrimidines **5-6** and related fused compounds is shown in **Scheme 38**.[109] Application of this strategy to synthesis of pyrazino[1,2-*a*]pyrimidines **5-6-1** in excellent yield is shown in **Scheme 52**.[109] Noteworthy, the acylation of ethyl substituted pyrazine directly leads to desired bicyclic system **5-6-1** without isolation of the intermediate amide.

Synthesis of thiazole substituted pyrazino[1,2-*a*]pyrimidines **5-6-2** is presented in **Scheme 53**.[140]

Using zinc triflate, the direct one-pot double cyclodehydration of linear tripeptides in the total synthesis of pyrazino[2,1-*b*]quinazoline-3,6-diones **5-6-3** on solid support was achieved with (mostly) good overall yields in short reaction time. These syntheses of the pyrazino[2,1-*b*]quinazoline-3,6-diones **5-6-3** were conveniently achieved in only three steps, starting from the amino acid-bound Wang



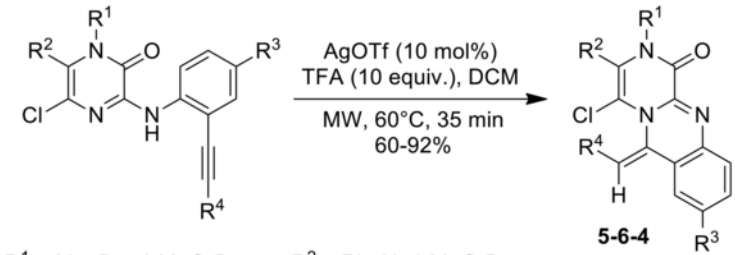
Scheme 52



Scheme 53

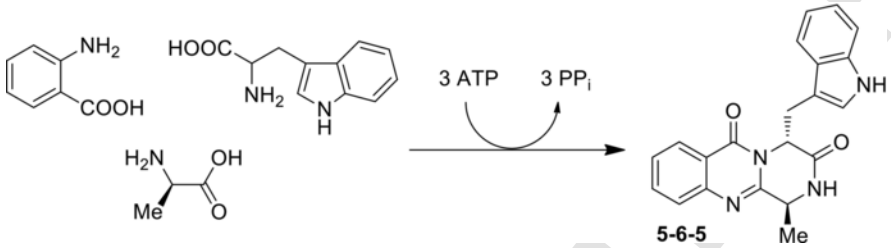
resin (**Scheme 54**).[141,142] It was shown[143] that microwave irradiation for a period of 10 min gave desired pyrazino[2,1-*b*]quinazolines **5-6-3** in excellent yields.

Microwave-assisted synthesis of pyrazino[2,1-*b*]quinazolines **5-6-4** employing silver(I)-catalyzed protocols is shown in Eq. **49**.[144] The scope and limitations of this process were investigated and the optimal conditions for maximal regioselectivity were found.



(49)

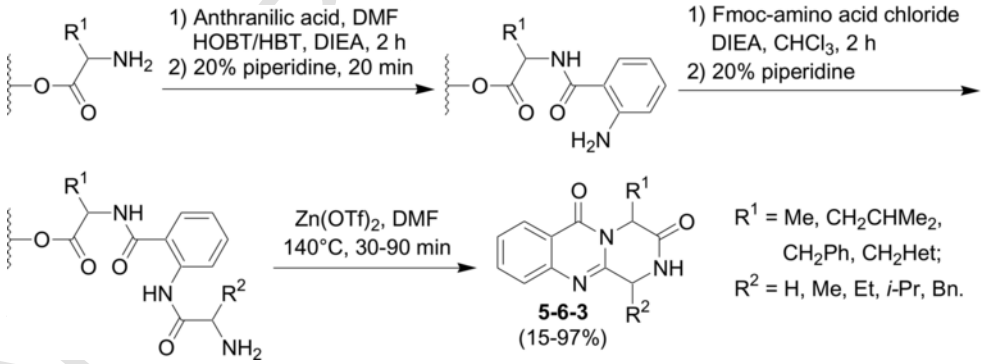
Enzyme-controlled one-step biosynthesis of fumiquinazoline F **5-6-5** from three amino acids, anthranilic acid, L-Trp and L-Ala, was improved by addition of the trimodular nonribosomal peptide synthetase Af12080[145] or enzyme TqaA[146] (Eq. **50**).



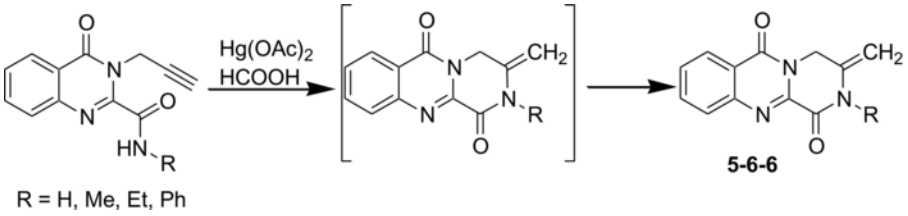
(50)

Starting from 3-propargylquinazolin-4(3*H*)-ones bearing a primary or secondary carboxamide group at the position 2, an intramolecular alkyne hydroamination reaction, catalyzed by mercury(II) acetate, afforded 2*H*-pyrazino[2,1-*b*]quinazoline-1,6-diones **5-6-6** in a two-step process that involves a rearrangement of the primary cyclization products (**Scheme 55**).[147]

Facile synthesis of 4*H*-pyrazino[1,2-*a*]pyrimidine-4,9(8*H*)-diones **5-6-7** from 3-amino-2(1*H*)-pyrazinones and β-ketoesters involves Conrad-Limpach condensation (Eq. **51**).[148] The standard procedure for this transformation involves heating a β-keto-ester with 3-amino-

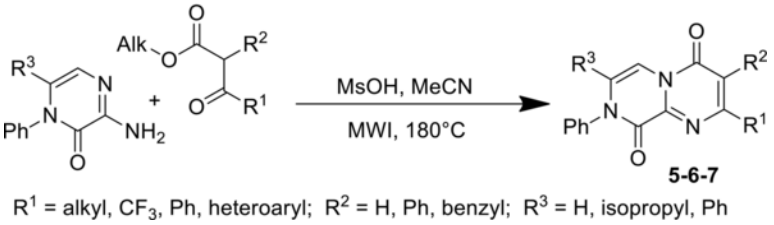


Scheme 54



Scheme 55

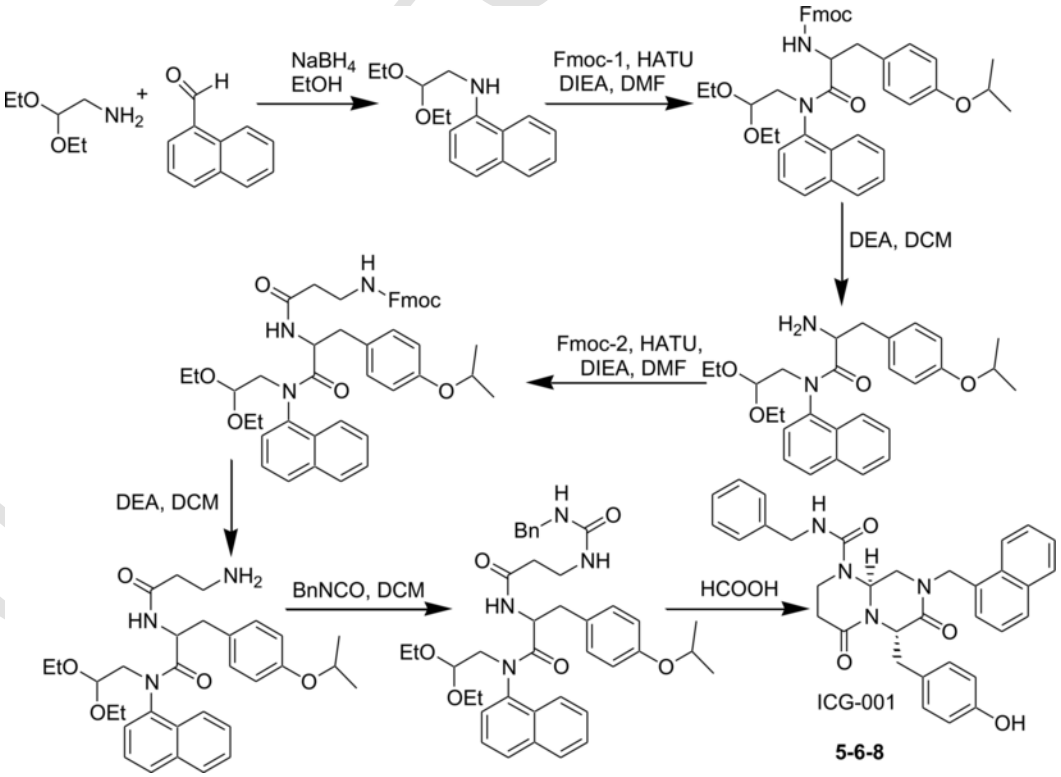
2(1*H*)-pyrazinones in acidic medium.



(51)

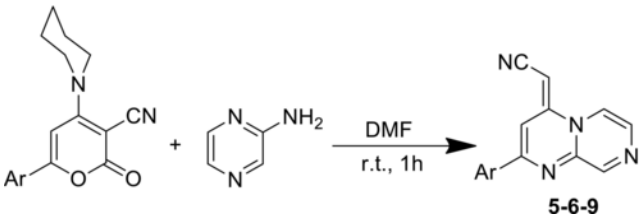
The β-turn peptidomimetic compound **5-6-8**, ICG-001, is a selective inhibitor of Wnt/β-catenin signalling, which is important for both initiation and progression of cancers of different tissues and has been exploited as an extremely useful chemogenomic tool. The solution-phase synthesis of **5-6-8** is shown in **Scheme 56**.[149] This route is particularly suitable for the multigram scale preparation.

An innovative and efficient synthesis of pyrazino[1,2-*a*]pyrimidines **5-6-9** via base-catalyzed ring transformations of suitably functionalized 2*H*-pyran-2-ones using 2-aminopyrazine and arylamidinium salts was reported (Eq. **52**).[150] Thus, a mixture of 6-aryl-4-amino-2*H*-pyran-2-one-3-carbonitrile and 2-aminopyrazine was stirred in DMF at room temperature for 1 h followed by the addition of powdered KOH. The stirring was continued for an additional 1 h and then the mixture was poured onto crushed ice with vigorous stirring



Scheme 56

and neutralized with 10% aqueous HCl.



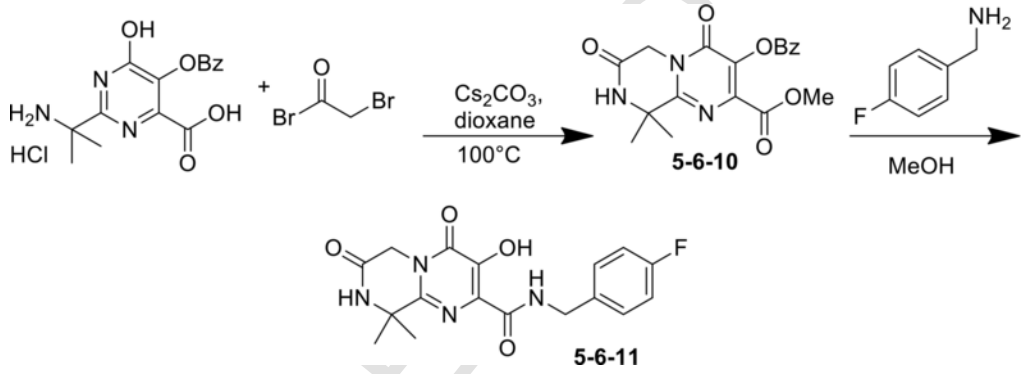
5-6-9 (52)

A variety of pyrazino[1,2-*a*]pyrimidines**,** including **5-6-10** and **5-6-11** were derived from earlier described[151] polysubstituted pyrimidines.[152] The preparation is illustrated in **Scheme 57.**[151]

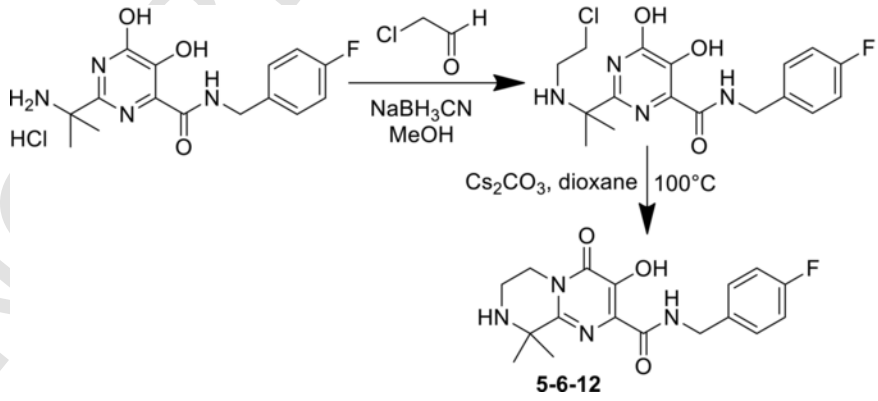
After introduction of a chloroethyl moiety into the pyrimidine core and a subsequent ring closure, the formation of pyrazino[1,2-*a*]pyrimidine **5-6-12** was observed (**Scheme 58**).[152]

Substituted pyrazino[1,2-*a*]pyrimidin-6-ones **5-6-13** and **5-6-13′** were synthesized stereoselectively by a multi-step procedure, as shown in **Scheme 59.**[153] The formation of a single diastereomer is due to the low energy of the chair-like conformation of its bicyclic structure.

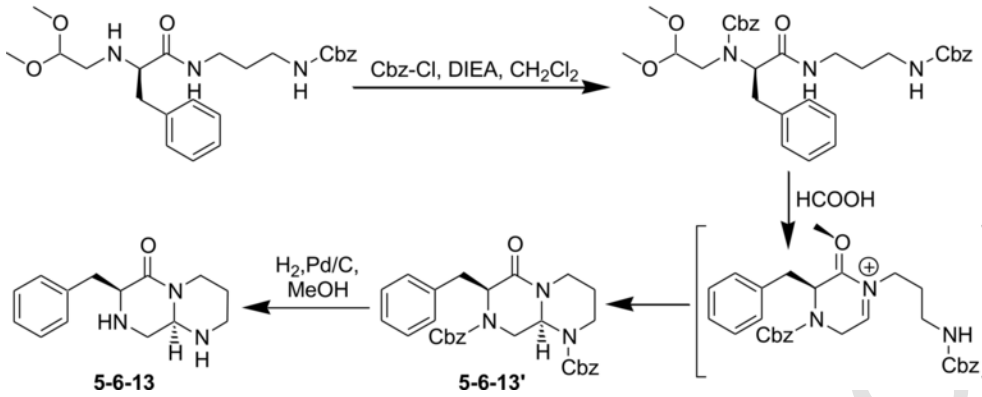
One-pot three-component synthesis 4*H*-pyrazino[1,2-*a*]pyrimidines **5-6-14** was conducted by mixing an acetylenic ester and an *N*-(2-pyrazinyl)amide in dry dichloromethane followed by addition of an isocyanide (Eq. **53**).[154] The reaction proceeded smoothly at ambient



Scheme 57

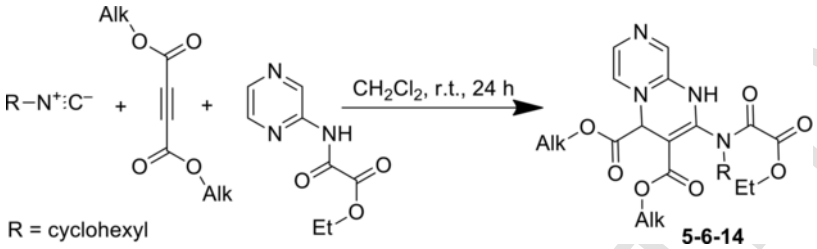


Scheme 58



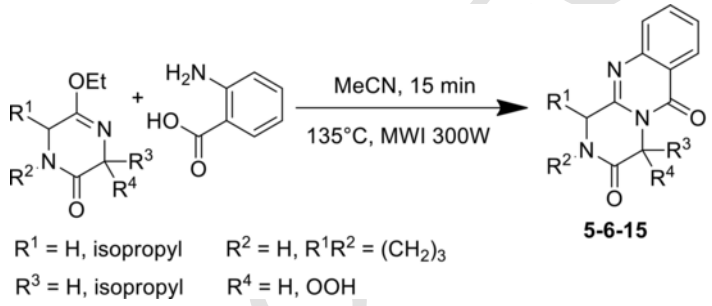
Scheme 59

temperature and was completed within 24 h.



(53)

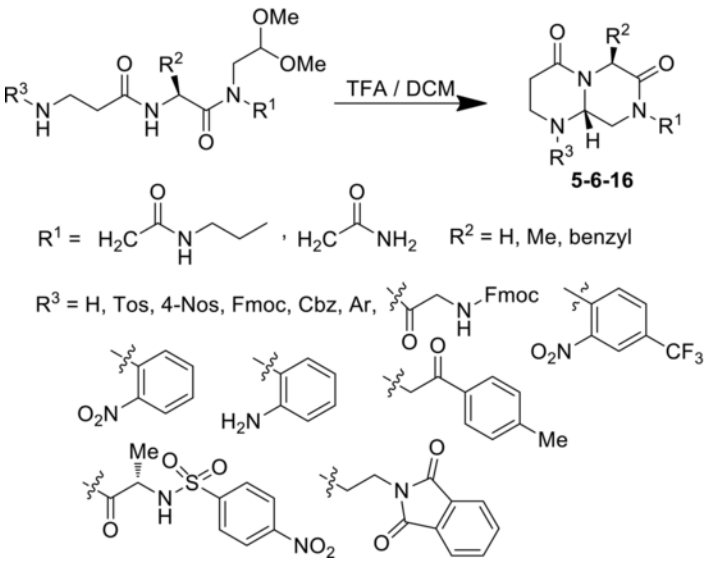
Condensation of lactim ethers with anthranilic acid furnished the corresponding pyrazinoquinazolines **5-6-15** (Eq. 54).[155] The reaction was performed with 1.1–2.4-equivalents of anthranilic acid in acetonitrile under microwave irradiation at 135 °C during 15 min yielding desired products in a good yield.



(54)

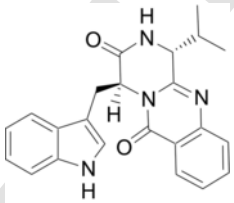
Synthesis of pyrazino[1,2-*a*]pyrimidine-4,7-diones **5-6-16** by the tandem *N*-acyliminium ion cyclization-nucleophilic addition is shown in Eq. (55).[83] Exposure of the tripeptide substrate to trifluoroacetic acid in dichloromethane caused cleavage but deprotection of

the aldehyde generated iminium ions which are the precursors to the target pyrazino[1,2-*a*]pyrimidine-4,7-diones **5-6-16** (Eq. **55**).[83]



(55)

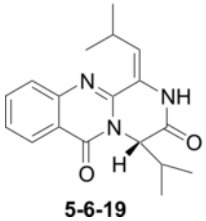
The quinazolinone-containing alkaloid fiscalin **5-6-17** is present in the strain BRF082 of *Dichotomomyces cejpii*.[156] Fiscalin was obtained by a large-scale fermentation of BRF082 in potato dextrose broth followed by chromatographic purification of the bioactive fractions.[156]



5-6-17

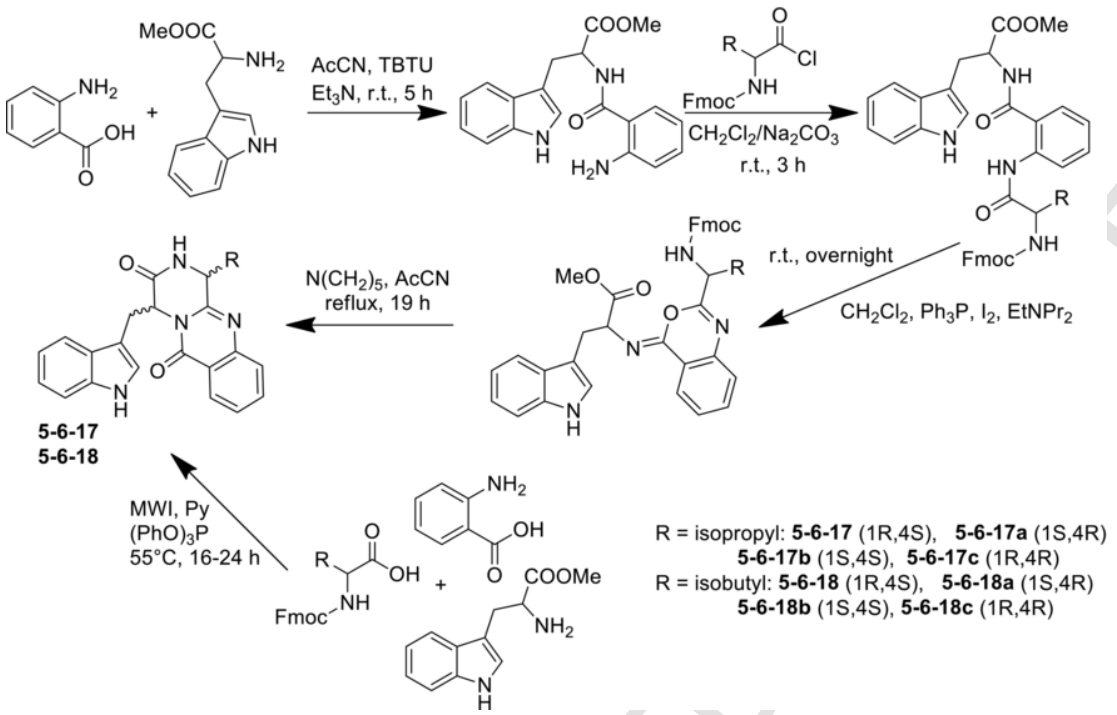
Synthesis of the marine natural product fiscalin **5-6-17** and analogs **5-6-18** is shown in **Scheme 60.**[157] The *anti*-enantiomers **5-6-17a, 5-6-18,** and **5-6-18a** were synthesized using a one-pot approach, while the *syn*-enantiomers **5-6-17b,c** and **5-6-18b,c** were prepared by a multi-step procedure. These strategies used anthranilic acid, chiral *N*-protected α-amino acids, and tryptophan derivatives for construction of the pyrazino[2,1-*b*]quinazoline system.

Isomers of **5-6-19**, carnequinazolines A-C, were isolated from the marine-derived fungus *Aspergillus carneus* (*Trichocomaceae*) KMM 4638.[158]



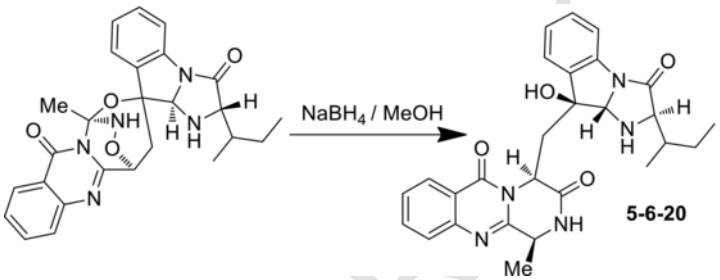
5-6-19

Chemical examination of a coral-associated *fungus Aspergillus* resulted in the isolation of six new polycyclic alkaloids including versiquinazoline *O* **5-6-20.**[159] The structure of versiquinazoline *O* **5-6-20** was determined by extensive analyses of spectroscopic data, including quantum ECD calculation. The versiquinazoline *O* **5-6-20** was also synthesized from another natural alkaloid versiquinazoline



Scheme 60

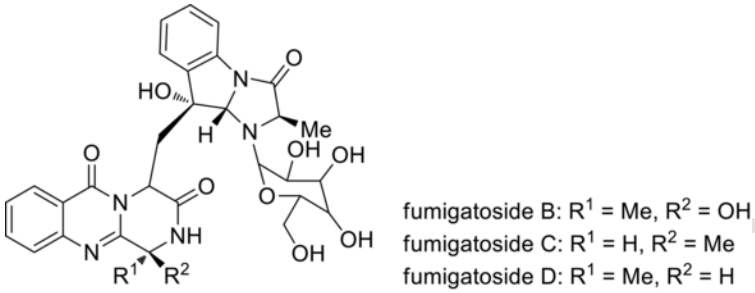
N via simple reduction by $NaBH_4$ in alcohol medium (Eq. **56**).[159]



(56)

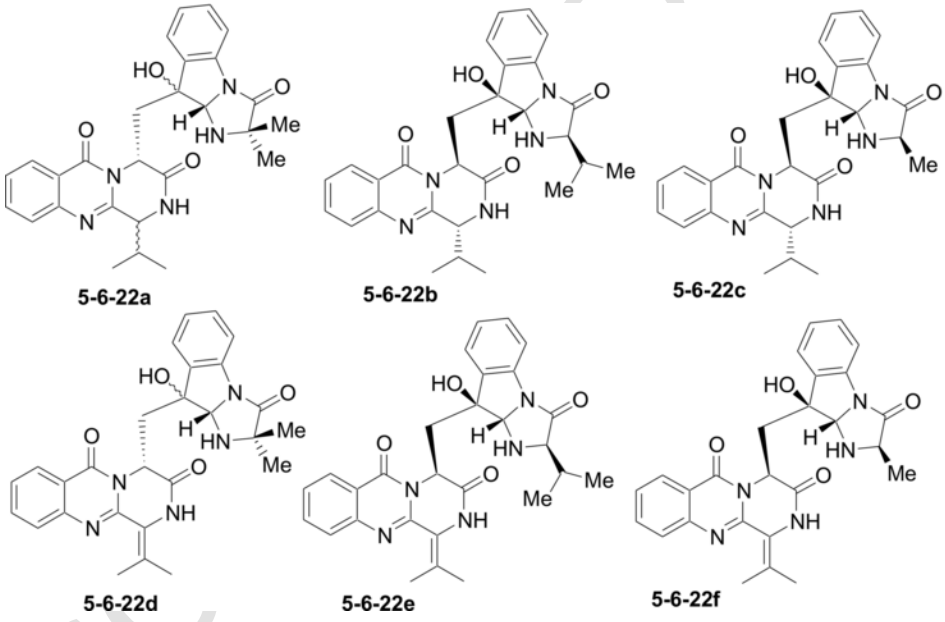
Three new pyrazinoquinazoline indole glucosides **5-6-21** were isolated from the fungus *Aspergillus fumigatus* derived from the jellyfish *Nemopilema nomurai*. Compounds **5-6-21** represent the first examples of natural glycosidated fumiquinzoline-type alkaloids.[160]

Neither antibacterial activity nor cytotoxicity was observed for compounds **5-6-21.**[160]



5-6-21

By feeding various amino acids to the marine fungus *Scedosporium apiospermum* F41-1, twenty two diverse alkaloids, including compounds with a skeleton of a pyrazino[2,1-*b*]-quinazoline and an imidazoindolone/indolone **5-6-22a-f**, were obtained.[161]

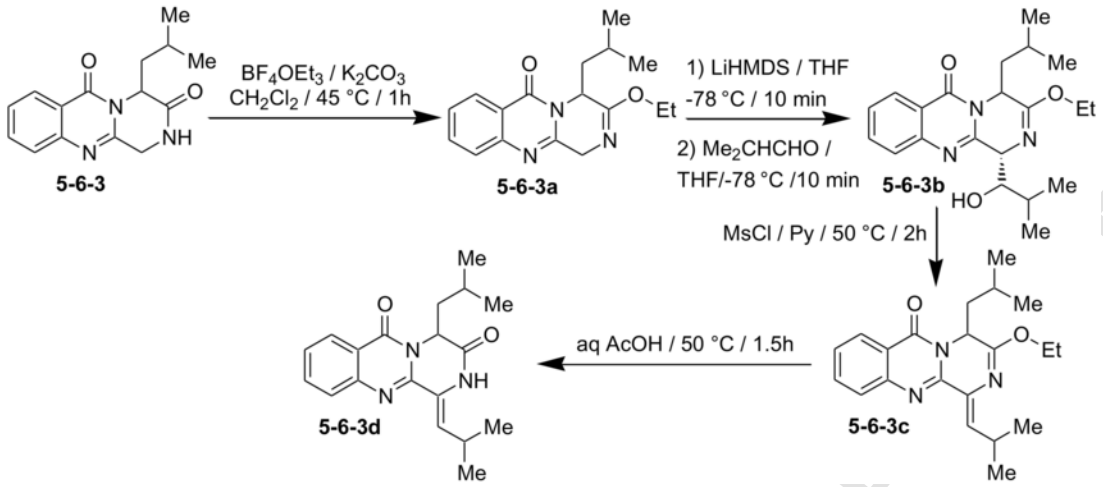


5-6-22a **5-6-22b** **5-6-22c**

5-6-22d **5-6-22e** **5-6-22f**

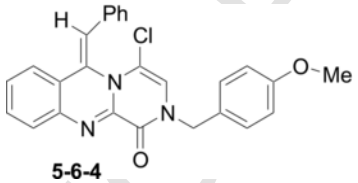
5.6.2 Reactivity and structural featuress of pyrazino[1,2-a]pyrimidines and their benzo analogs

Strategies for the asymmetric bio-synthesis of a putative precursor to natural *janoxepin* and *aurantiomide C* were investigated using the pyrazino[2,1-*b*]quinazoline **5-6-3.**[143] The key steps are shown in **Scheme 61**. The structure of the target product **5-6-3d** was reliably confirmed by ^{1}H and ^{13}C NMR spectroscopy in conjunction with COSY and HSQC experiments. The NOE correlations confirmed that the enamine is in the desired *Z*-configuration, and further proof of this was provided by X-ray crystallographic analysis (**Scheme 61**).[143]

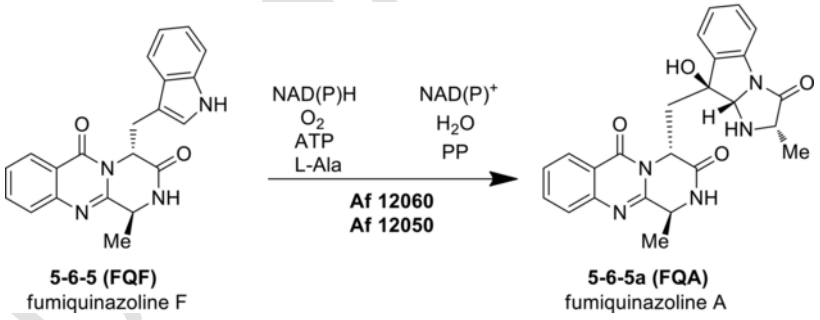


Scheme 61

The X-ray crystallographic analysis of pyrazino[2,1-*b*]quinazoline **5-6-4** supports the mechanism-based suggestion about the origin of this compound.[144]



Fumiquinazoline F (FQF) **5-6-5** is the proposed biological precursor to fumiquinazoline A (FQA) **5-6-5a** in which the pendant indole side chain has been modified via oxidative coupling of an additional molecule of alanine, yielding a fused imidazoindolone **5-6-5a**. It was shown that two proteins Af12050 and Af12060 are necessary to convert FQF **5-6-5** to FQA **5-6-5a** (Eq. 57).[145] Af12060 oxidizes the 2′,3′-double bond of the indole side chain of FQF **5-6-5**, and the three-domain protein Af12050 activates L-Ala as the adenylate, installs it as the pantetheinyl thioester on its carrier protein domain, and acylates the oxidized indole for subsequent intramolecular cyclization to create the **5-6-5a** imidazolindolone (FQA).

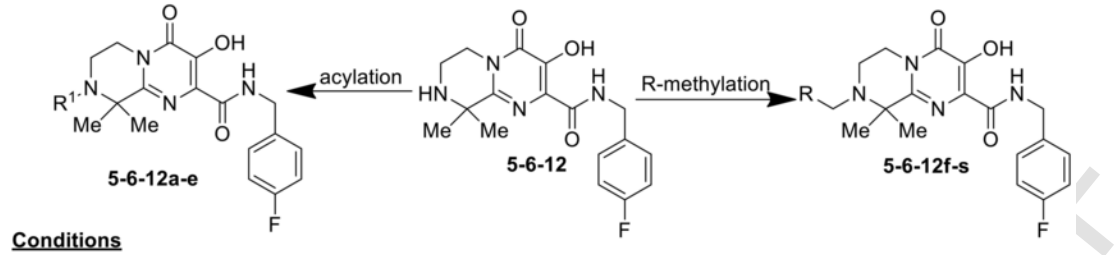


(57)

Functionalization of pyrazino[1,2-*a*]pyrimidine **5-6-12** was carried out as one-pot procedure (**Scheme 62**).[152] A variety amino-derivatives of *N*-(4-fluorobenzyl)-3-hydroxy-9,9-dimethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrazino[1,2-*a*]pyrimidine-2-carboxamides **5-6-12a-s** were obtained.

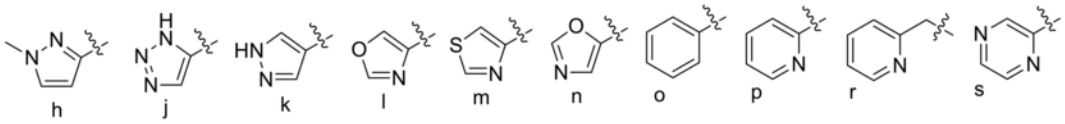
Benzylation of the hydroxy group in pyrazino[1,2-*a*]pyrimidine **5-6-12** led to the formation of ether **5-6-12t**, a precursor to the alkylation products **5-6-12u,x** (**Scheme 63**).[152]

To confirm the configuration of compound **5-6-13**, density functional theory (DFT) calculations were performed using the GAUSSIAN 03 program. Structure optimization followed by a frequency calculation was performed on **5-6-13** at the B3LYP/6-31G(d)

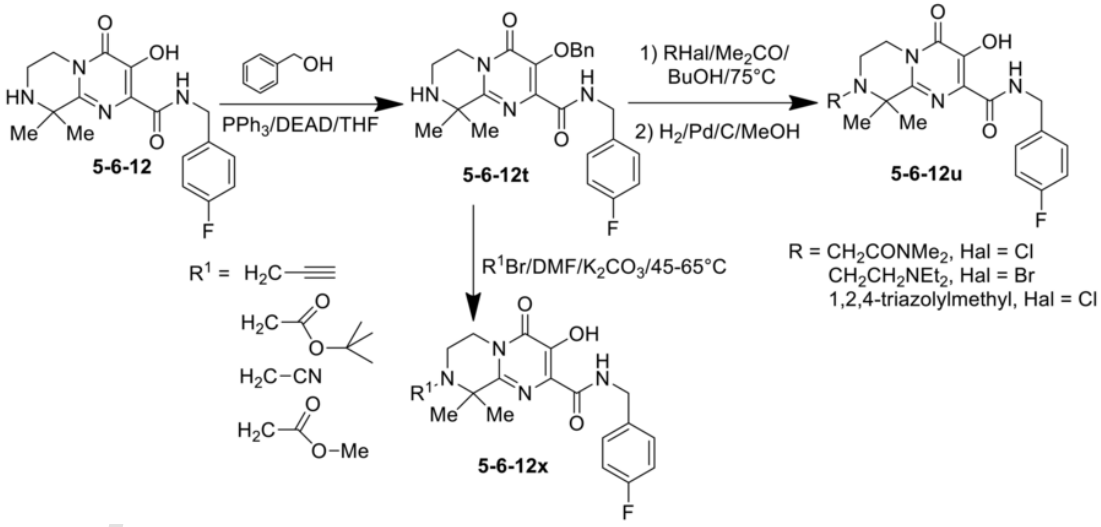


Conditions

(a) R^1 = COMe; 1) Ac_2O/TEA/DMAP/$CHCl_3$/reflux; 2) NaOH/MeOH/40°C
(b) R^1 = $COCONMe_2$; 1) ClCOCOOMe/Py/50°C; 2) Me_2NH/THF
(c) R^1 = SO_2Me; 1) $MeSO_2Cl$/Py; 2) NaOH/MeOH/40°C
(d) R^1 = SO_2NMe_2; 1) MsCl/Py/55°C
(e) R^1 = CONHEt; 1) EtNCO/TEA/THF
(f) R = H; 1) CH_2O/$NaBH_3CN$/MeOH
(g) R = CH_2NMe_2; 1) $BocNHCH_2CHO$/AcOH/$NaBH_3CN$/MeOH; 2) DCM/TFA; 3) CH_2O/$NaBH_3CN$/MeOH
(h-s) = R = Het; 1) HetCHO/AcOH/$NaBH_3CN$/MeOH

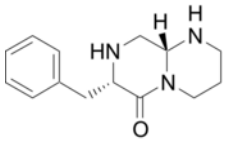


Scheme 62



Scheme 63

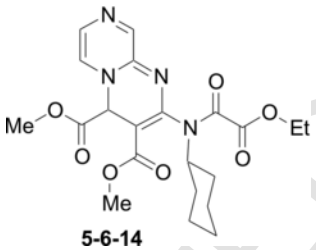
level.[153] Compound **5-6-13** was studied to compare the obtained calculated conformation with its X-ray crystal structure.[153]



5-6-13

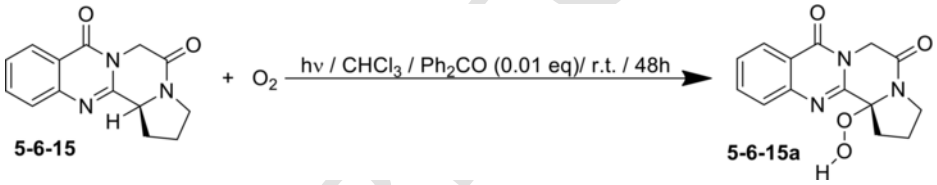
The calculated structure of **5-6-13** was in a good agreement with the X-ray crystal structure.[153]

The structures of the 4*H*-pyrazino[1,2-*a*]pyrimidines **5-6-14** were confirmed by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, mass spectrometry, and X-ray diffraction data.[154]



5-6-14

A combined quantum mechanical and experimental studies of oxidation of chiral pyrazinoquinazolines **5-6-15** were performed (Eq. **58**).[155] Pyrazinoquinazolines **5-6-15** are oxidized with molecular oxygen to the corresponding hydroperoxides **5-6-15a**. As can be seen, the oxidation site is the tertiary α-C-H bond next to an *N*-aryl-imino moiety.

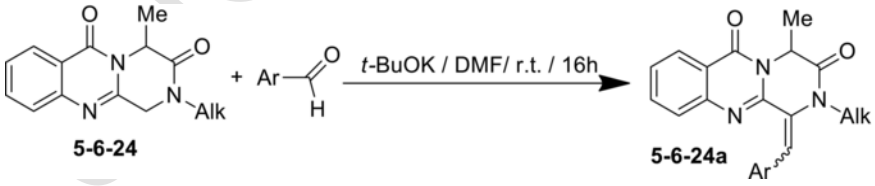


5-6-15 **5-6-15a** (58)

The structures of the natural products **5-6-17** to **5-6-22** were elucidated by spectroscopic methods and ECD/TD-DFT calculations.[156–161]

Novel spin traps **5-6-23a** derived from **5-6-23** were developed (**Scheme 64**).[162] The structural variations comprise the steric and electronic features of the aryl substituent at the nitrone α-carbon of pyrimidoquinoxalines **5-6-23**. The addition rate constants, the spin adducts decomposition rate constants and the corresponding half-life times were determined. DFT and MP2 calculations were used.[162]

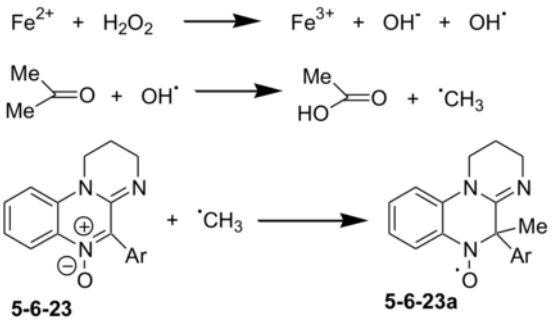
The reaction between 2-alkylpyrazino[2,1-*b*]quinazoline-3,6-diones **5-6-24** and aromatic aldehydes in the presence of *t*-BuOK afforded the corresponding 1-arylmethylene derivatives **5-6-24a** as the major *Z* isomers (Eq. **59**).[163] This diastereoselectivity is the result of the thermodynamic control, as suggested by *ab initio* calculations.



5-6-24 **5-6-24a** (59)

5.6.3 Applications and important pyrazino[1,2-a]pyrimidines and their benzo analogs

Biological activity of pyrazino[1,2-*a*]pyrimidines **5-6** of natural and synthetic origin was reviewed.[138,139,164] An oxidative annulation biosynthetic strategy likely shared among several classes of polycyclic fungal alkaloids was described.[145]



Scheme 64

A class of *N*-(4-fluorobenzyl)-3-hydroxy-9,9-dimethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrazino[1,2-*a*]pyrimidine-2-carboxamides **5-6-10** to **5-6-12** was identified as HIV-1 integrase inhibitors.[152] These compounds have excellent antiviral activity equivalent to that shown by Raltegravir.

Compound **5-6-17** is cytotoxic against the tumor cell lines HCT-116.[156] Compounds **5-6-17, 5-6-18** were evaluated for their growth inhibitory effect against two tumor cell lines in vitro.[157] The quinazolinone derivatives, carnequinazolines A-C **5-6-19** were assayed for cytotoxic activities against T-47D, SK-Mel-5, and SK-Mel-28 cell lines. None of the tested compounds showed activity against these cell lines up to 100 μM.[158] Compounds **5-6-19** showed no inhibitory activity in agar diffusion assays against *Staphylococcus aureus* ATCC 21027, *Bacillus cereus* ATCC 10702, *Escherichia coli* ATCC 15034, *Pseudomonas aeruginosa* ATCC 27853 and *Candida albicans* KMM 453.[158]

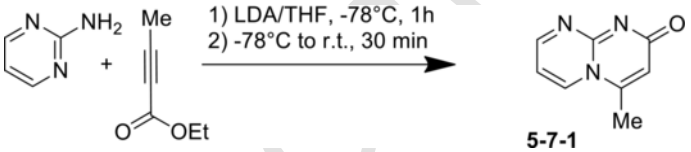
Versiquinazoline *O* **5-6-20** exhibits significant inhibition of thioredoxin reductase (TrxR).[159] The weak cytotoxicity and potent inhibition of TrxR suggest that versiquinazoline *O* **5-6-20** is of potential interest for microenvironmental regulation of tumor progression and metastasis.

Among alkaliods from marine fungus *Scedosporium apiospermum* F41 − 1, scequinadoline *D* **5-6-22b** displays significant antiviral activity against hepatitis C.[161]

5.7 Pyrimido[1,2-*a*]pyrimidines and their benzo analogs

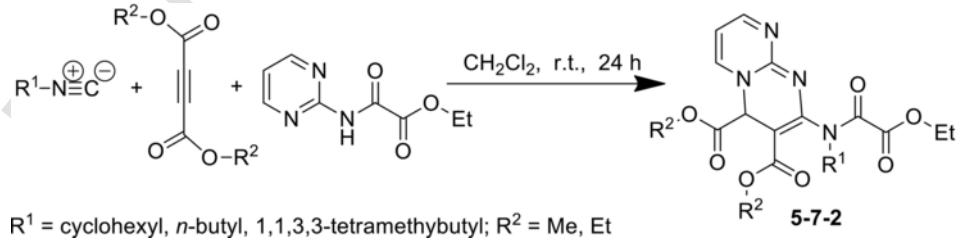
5.7.1 Synthesis of pyrimido[1,2-a]pyrimidines and their benzo analogs

A review of the developments in chemistry of pyrimido[1,2-*a*]pyrimidine system **5-10** was published.[134] An effective and modular strategy for the concise synthesis of pyrimido[1,2-*a*]pyrimidines **5-7** and related fused compounds **5-2, 5-4** and **5-6** was shown in **Scheme 38.**[109] A particular example of **5-7-1** is illustrated in Eq. **(60)**. As stated previously, the product **5-7-1** and analogous products were obtained in excellent yield without isolation of the intermediate amide (Eq. **60**).[109]



(60)

One-pot three-component synthesis of 4*H*-pyrimido[1,2-*a*]pyrimidines **5-7-2** was conducted by mixing acetylenic ester and *N*-(2-pyrimidinyl)amide dry CH_2Cl_2 followed by the addition of isocyanide (Eq. **61**).[154] The reaction proceeded smoothly at ambient temperature and was complete after 24 h to afford the 4*H*-pyrimido[1,2-*a*]pyrimidines **5-7-2**.

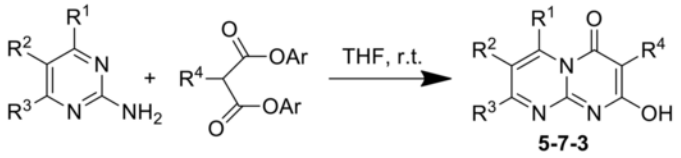


(61)

R^1 = cyclohexyl, *n*-butyl, 1,1,3,3-tetramethybutyl; R^2 = Me, Et

A facile synthesis of pyrimido[1,2-*a*]pyrimidin-4-ones **5-7-3** was conducted starting with highly reactive malonates and 2-aminopyrimidines at room temperature under basic catalysis (Eq. **62**).[165] After optimization of the conditions (heating to 60–150 °C in

THF or DMF), products **5-7-3** were obtained in quantitate yields.

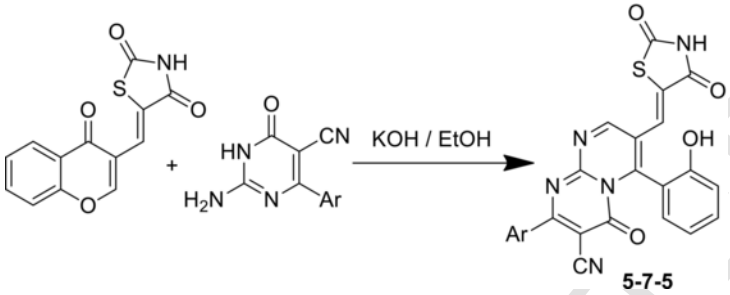


5-7-3 (62)

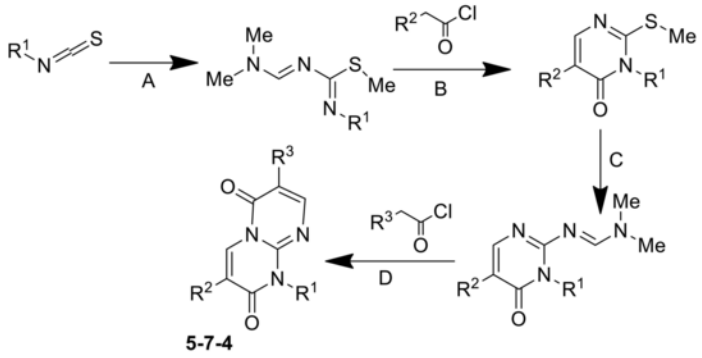
R^1 = H, Me, Cl; R^2 = H, *n*-butyl, Cl; R^3 = H, Me, OH, OMe, morpholin-4-yl; R^4 = H, *n*-butyl, allyl

The multi-step synthesis of 1,3,7-trisubstituted pyrimido[1,2-*a*]pyrimidinediones **5-7-4** starting from isothiocyanates was achieved using an iterative sequence of functionalization/cyclocondensation reactions (**Scheme 65**).[166] The synthesis is based on an iterative sequence (diazadiene formation followed by cyclization reaction) and consists of four parts: (A) functionalization of an isothiocyanate into a diazadienic chain, (B) cycloaddition reaction providing a pyrimidinone, (C) introduction of a second diazadienic chain onto the structure and (D) second cycloaddition reaction furnishing a pyrimidopyrimidinedione (**Scheme 65**).[166]

The reaction of a chromenylthiazolidine derivative with a 2-aminopyrimidine proceeds via attack of the nucleophile at the C-2 position of the chromone system with the concomitant opening of the γ-pyrone ring followed by cyclocondensation to furnish products **5-7-5** (Eq. **63**).[167] The reaction was carried out in ethanol in the presence of KOH under reflux for 4 h.



5-7-5 (63)



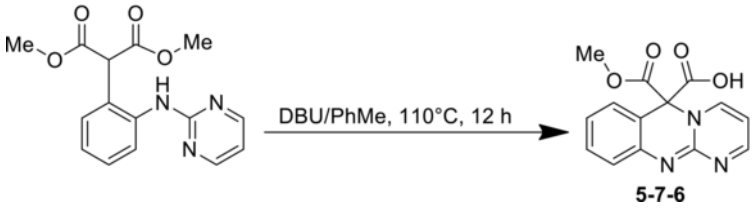
5-7-4

R^1 = *p*-tolyl; R^2 = H, Ph, CF_3, OMe, $CONH_2$, COOMe; R^3 = H, OMe, COOMe

Step A: (i) NH_3/MeOH ; (ii) N,N-dimethylhydrazine (1 equiv), EtOH, then HCl, H_2O; (iii) DMF, DMA (1.2 equiv), CH_2Cl_2; (iv) MeI (1.05 equiv), THF; (v) saturated aqueous $NaHCO_3$, Et_2O.
Step B: (i) R^2CH_2COCl (3 equiv), NEt_3 (4 equiv), CH_2Cl_2.
Step C: (i) NH_3/ MeOH (5 equiv); (ii) DMFDMA (1.2 equiv), CH_2Cl_2.
Step D: R^3CH_2COCl (3 equiv), NEt_3 (3 equiv), CH_2Cl_2, reflux.

Scheme 65

Intramolecular cyclization between ester and amine groups of starting substituted 2-amino-pyrimidine under basic conditions furnished a tricyclic 6*H*-pyrimido[2,1-*b*]quinazoline **5-7-6** in moderate yield (Eq. 64).[168]

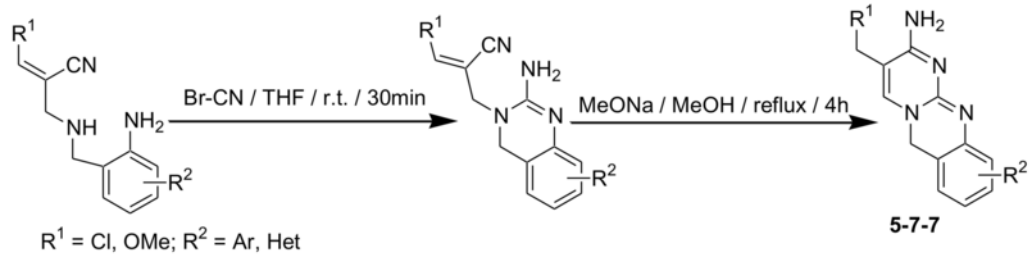


(64)

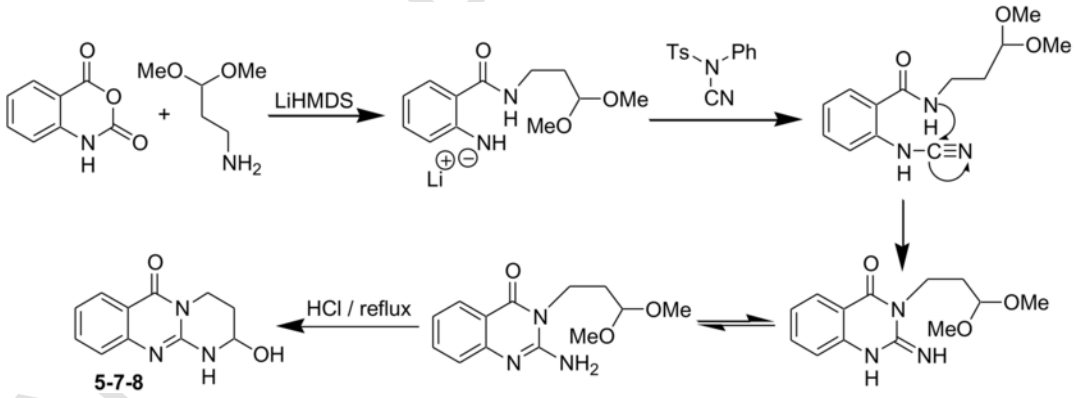
An efficient synthetic approach to pyrimido[2,1-*b*]quinazolines **5-7-7** from the primary aromatic allyl-substituted amines is shown in Scheme 66.[169]

Novel synthesis of pyrimido-[2,1-*b*]quinazoline **5-7-8** starting with isatoic anhydride and 3,3′-dimetoxypropylamine is shown in Scheme 67.[170] The synthesis of **5-7-8** involves a nucleophilic attack of an amino group on the carbonyl group of isatoic anhydride followed by ring opening and subsequent decarboxylation, nucleophilic addition of amine to nitrile, and heterocyclization.

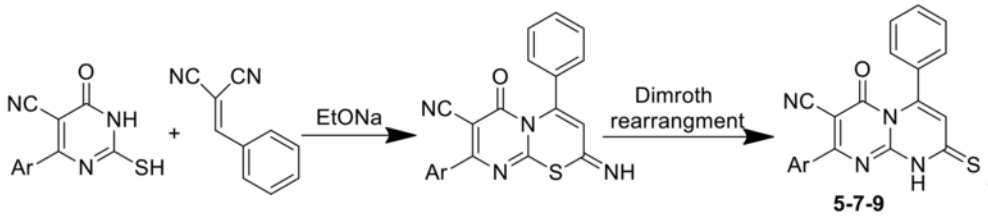
Cycloaddition of benzylidene-substituted malononitrile with a mercaptopyrimidine generated a non-isolable Michael type adduct (thiazinopyrimidine system), which underwent base-induced ring transformation via the addition of nucleophilic sulphur to the cyano function and subsequent elimination of HCN to give pyrimido[1,2-*a*]pyrimidine **5-7-9** afterr the Dimorth rearrangement (Scheme 68).[171]



Scheme 66

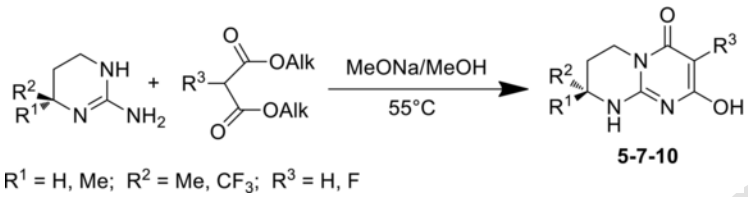


Scheme 67



Scheme 68

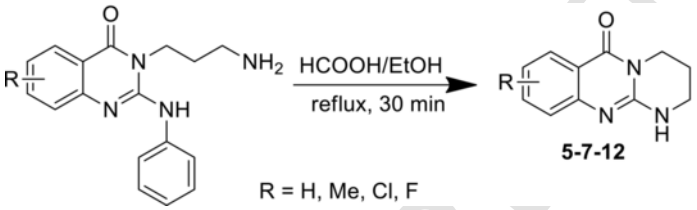
One-step ring annulation of 2-aminopyrimidines by treatment with malonates under basic conditions furnished pyrimido[1,2-*a*]pyrimidinones **5-7-10** (Eq. **65**).[172]



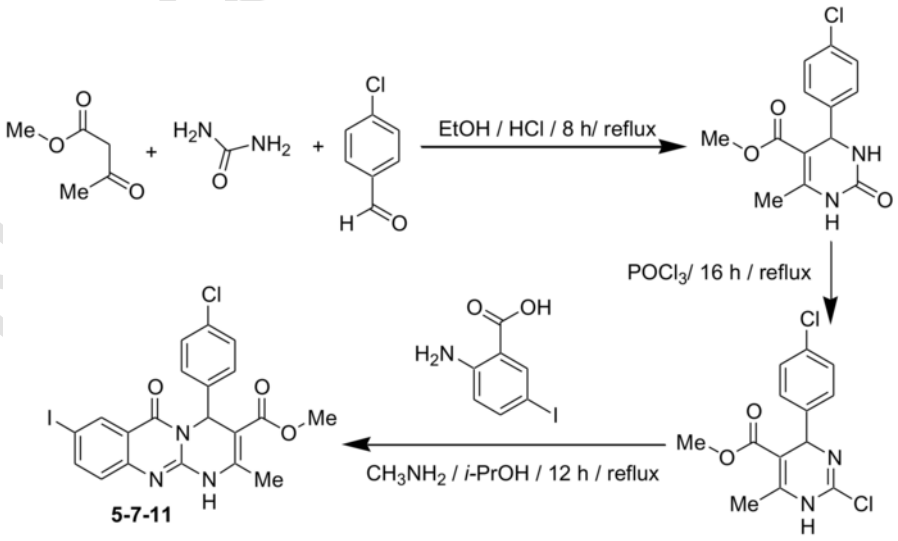
(65)

Synthesis of methyl 4-(4-chlorophenyl)-8-iodo-2-methyl-6-oxo-1,6-dihydro-4*H*-pyrimido[2,1-*b*]quinazoline-3-carboxylate **5-7-11** was achieved by a three-step procedure starting with Biginelli reaction (**Scheme 69**).[173]

Bioactive tricyclic 3,4-dihydro-1*H*-pyrimido[2,1-*b*]quinazolin-6(2*H*)-ones **5-7-12** were synthesized by the formic acid-catalyzed intramolecular cyclization of 3-(2-aminoalkyl)-2-(phenylamino)quinazolin-4(3*H*)-ones in high yields (Eq. **66**).[174] A mechanism of the cyclization step was proposed.

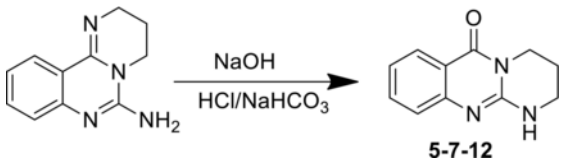


(66)



Scheme 69

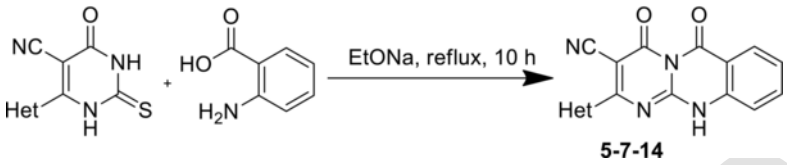
The unsubstituted compound **5-7-12** was also obtained by rearrangement of a pyrimidoquinazoline in the presence of NaOH (Eq. **67**).[175]



(67)

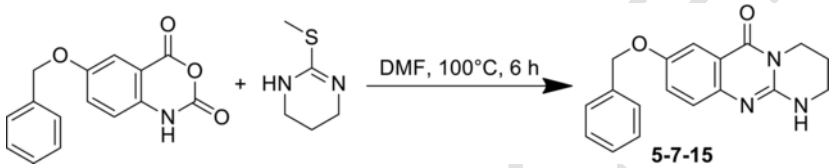
The reaction of aromatic azides with triphenylphosphine and an isocyanate produced 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-diones **5-7-13** in the presence of sodium ethoxide by a tandem aza-Wittig/nucleophilic addition/intramolecular cyclization/isomerization reaction (**Scheme 70**).[176] It is noteworthy that the reaction takes place at room temperature and the overall transformation is run as a one-pot procedure after the addition of azides. Various isocyanates can be used in this one-pot cyclization to prepare 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-diones **5-7-13**.

A cyanopyrimidine was condensed with anthranilic acid in the presence of sodium ethoxide under reflux for 10 h, yielding 2-heteroaryl-6,11-dihydro-4,6-dioxo-4*H*-pyrimido[2,1-*b*]-quinazoline-3-carbonitrile **5-7-14** (Eq. **68**).[99,177]

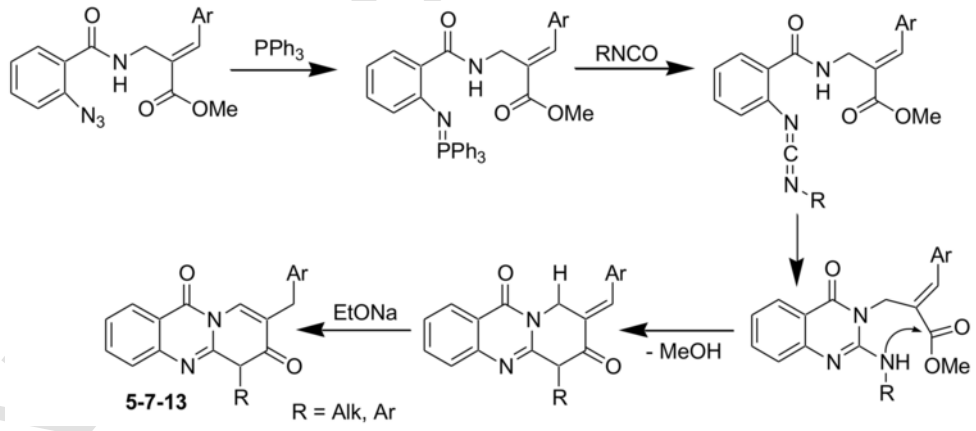


(68)

8-(Benzyloxy)-3,4-dihydropyrimido[2,1-*b*]quinazolin-6(2*H*)-one **5-7-15** was obtained by fusion of the 6-(benzyloxy)-1*H*-benzo[*d*][1,3]oxazine-2,4-dione with 2-methylthio-1,4,5,6-tetrahydropyrimidine in DMF at 100 °C (Eq. **69**).[178]

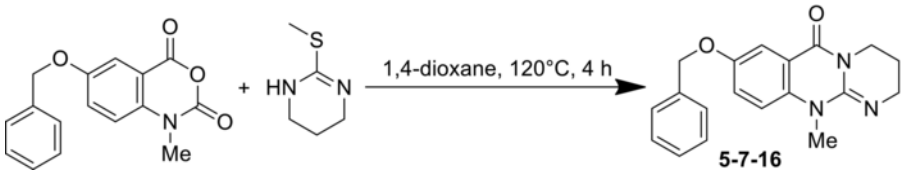


(69)



Scheme 70

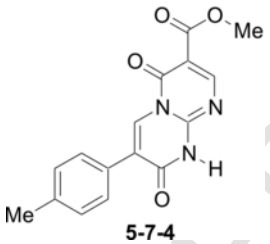
A similar fusion reaction of the methylated starting material with the methylthio substrate in 1,4-dioxane at 120 °C furnished 8-benzyloxy-11-methyl-3,4-dihydro-2*H*-pyrimido[2,1-*b*]quinazolin-6(11*H*)-one **5-7-16** (Eq. 70).[178]



(70)

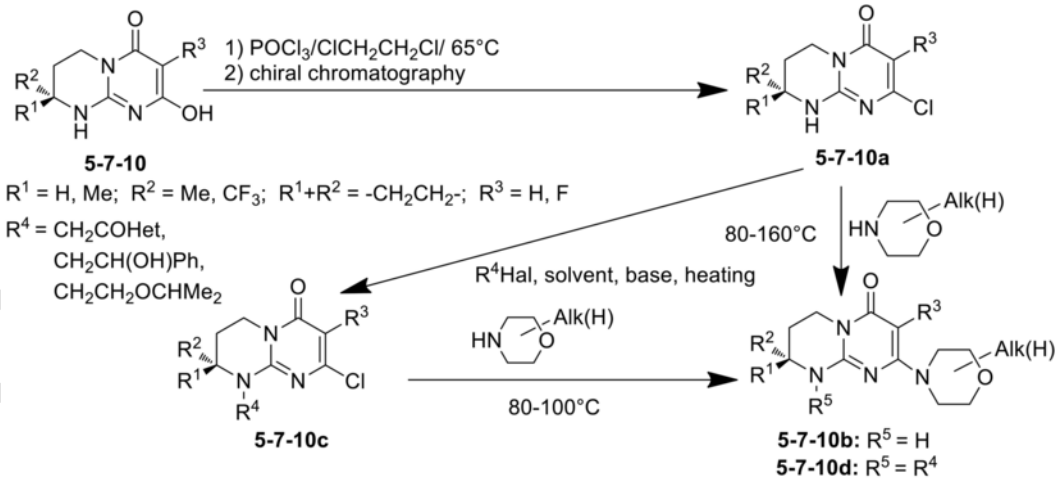
5.8 Reactivity and structural features of pyrimido[1,2-*a*]pyrimidines and their benzo analogs

The structure of compound **5-7-4** was determined by single-crystal X-ray diffraction analysis.[166] It was pointed out that the COOMe group (R^3) slightly deviates from the mean plane of the bicyclic group, while the *para*-tolyl group forms a large dihedral angle.



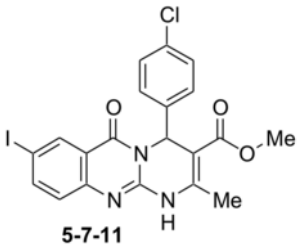
The pyrimido[1,2-*a*]pyrimidinones **5-7-10** contain two active centers of high reactivity. Chloro-substituted pyrimido[1,2-*a*]pyrimidinones **5-7-10a** were obtained by the reaction of $POCl_3$ with **5-7-10** (Scheme 71).[172] Aminolysis of compounds **5-7-10a** by morpholine derivatives led to the nucleophilic substitution of the chlorine atom, yielding compounds **5-7-10b**. On the other hand, compounds **5-7-10a** were alkylated at the saturated cyclic amino nitrogen, yielding products **5-7-10c**. Noteworthy, alkylation of morpholine-substituted pyrimido[1,2-*a*]pyrimidinones **5-7-10b** afforded compounds **5-7-10d**—the products substituted at both of the reactive centers (Scheme 71).[172]

The 4-(4-chlorophenyl)-8-iodo-2-methyl-6-oxo-1,6-dihydro-4*H*-pyrimido[2,1-*b*]quinazoline-3-carboxylate **5-7-11** was characterized by IR, NMR, LC-MS, elemental analysis, and single-crystal X-ray studies.[173] Compound **5-7-11** shows polymorphism with differences in the preference of hydrogen and/or halogen bonding intermolecular interactions. The crystallographic details clearly show the existence of



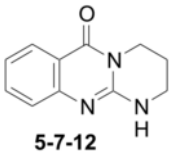
Scheme 71

two different crystalline forms compound **5-7-11**.



5-7-11

The structure of 3,4-dihydro-1*H*-pyrimido[2,1-*b*]quinazolin-6(2*H*)-one **5-7-12** was determined by single-crystal X-ray analysis.[174]



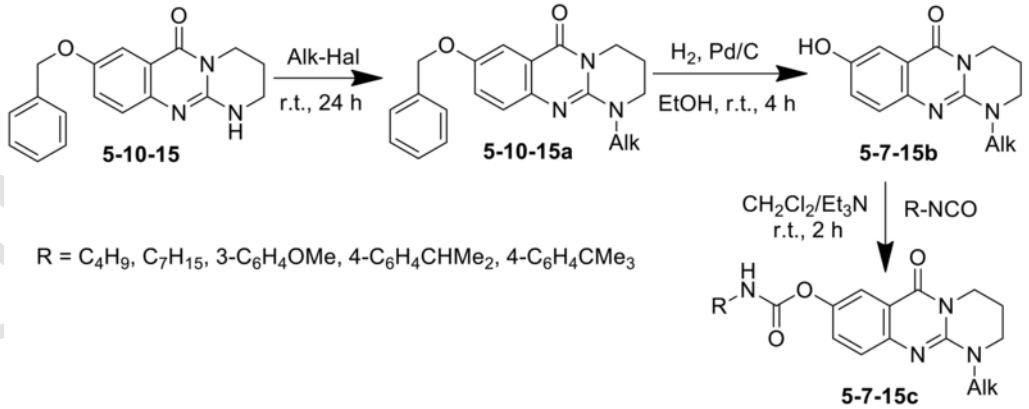
5-7-12

8-(Benzyloxy)-3,4-dihydropyrimido[2,1-*b*]quinazolin-6-ones **5-7-15** and **5-7-16** were employed as efficient synthetic precursors to substituted cyclic guanidine moieties.[178] Thus, alkylation of the NH group of compound **5-7-15** with iodomethane, benzyl bromide, or 1-(3-bromopropyl)-piperidine, respectively, in the presence of sodium hydride in THF gave the corresponding alkylated guanidine compounds **5-7-15a**. Quantitative debenzylation by catalytic hydrogenation using Pd/C in ethanol at room temperature gave the corresponding phenolic guanidine compounds **5-7-15b**. The carbamoylated products **5-7-15c** were obtained by treatment of **5-7-15b** witht isocyanates in dichloromethane in the presence of triethylamine as a base (**Scheme 72**).[178]

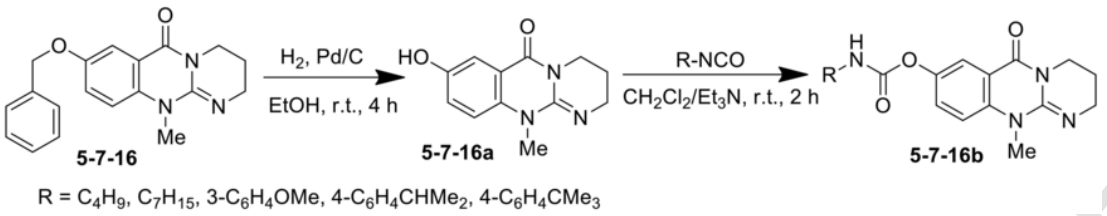
Quantitative debenzylation of 8-benzyloxy-3,4-dihydro-pyrimido[2,1-*b*]quinazolin-6-one **5-7-16** by catalytic hydrogenation using Pd/C gave compound **5-7-16a**. Treatment of **5-7-16a** with isocyanates, as described above for **5-7-15b** in **Scheme 72**, yielded compounds **5-7-16b** (**Scheme 73**).[178]

Reduction of the carbonyl group in **5-7-15a** using $NaBH_4$ and $AlCl_3$ gave cyclic guanidine compound **5-7-15d**, debenzylation of which furnished phenolic product **5-7-15e**. Treatment of **5-7-15e** with isocyanates gave compounds **5-7-15f** (**Scheme 74**).[178]

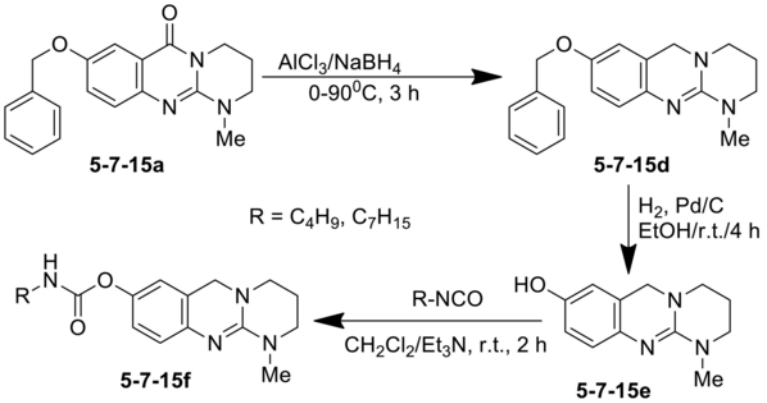
Introduction of the additional aza-heterocycle into the fused bicyclic system **5-7** is a facile route to substituted bidentate and tridentate ligands **5-7-17a,b** that are capable of forming six-membered chelates with transition metal ions (Eqs. 71 and 72).[179]



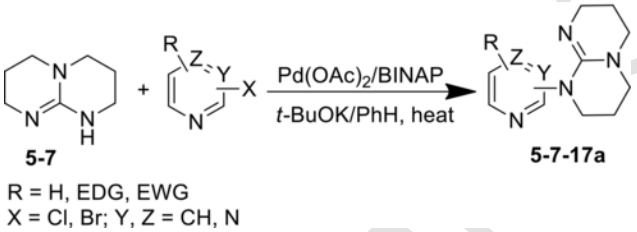
Scheme 72



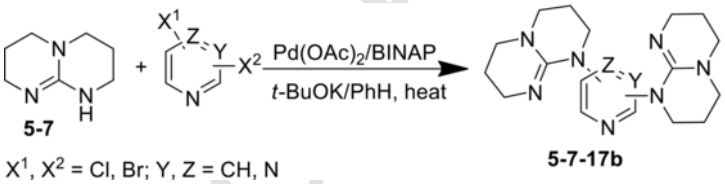
Scheme 73



Scheme 74

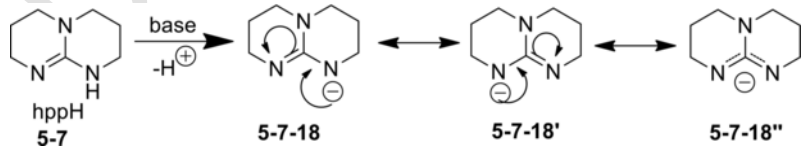


(71)



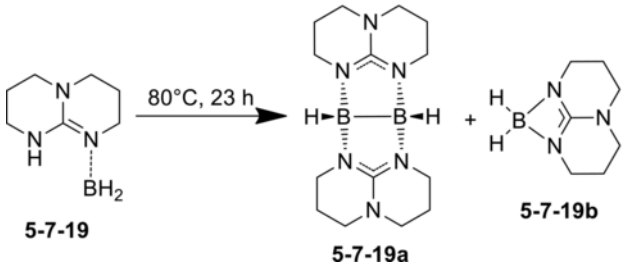
(72)

Several studies were devoted to the formation and properties of anion **5-7-18** derived from the general system **5-7** (Eq. **73**). A DFT analysis of the neutral guanidine hppH **5-7** was performed for comparison with other liner and cyclic guanidines.[180] A theoretical investigation of anion **5-7-18** was conducted.[181] On the basis of of X-ray crystallography, CPMAS NMR (^{13}C and ^{15}N) and theoretical calculations it was suggested that a double proton transfer takes place in the $(hppH)_2$ dimer.[182]

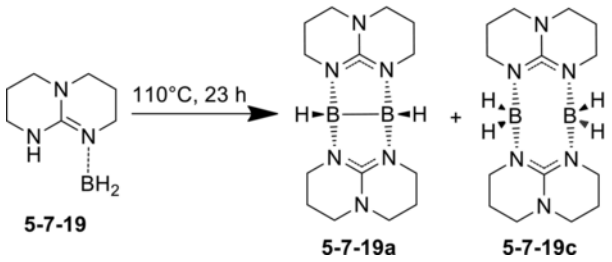


(73)

Theoretical calculations helped understand the differences in the thermal dehydrogenation reactions between guanidine-borane **5-7-19** and its derivatives **5-7-19a-c** under different conditions (Eqs. 74 and 75).[183]



(74)



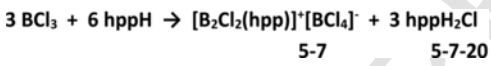
(75)

Compound **5-7-19c** was crystallized from DMSO and its molecular structure according to an X-ray diffraction analysis was identified unambiguously as $[H_2B(\mu\text{-hpp})]_2$.[183] There are two essentially identical crystallographically independent centrosymmetric half molecules in the asymmetric unit. In agreement with the results of quantum chemical calculations, the two BH_2 groups are located above and below the approximate plane hosting the guanidinate moieties.[183]

The oxidative sulfuration of $[HB(\mu\text{-hpp})]_2$ complex **5-7-19a** with S_8 leading to the formation of $[HB(\mu\text{-hpp})]_2(\mu\text{-S})$ system **5-7-19d** is an example of an oxidative insertion into the B–B bond (**Scheme 75**).[184] The reaction with the disulfides Ph_2S_2 and Bn_2S_2 led to formation of complexes $[HB(\mu\text{-hpp})]_2(\mu\text{-S})$ **5-10-19d** as well as the substitution products $[HB(\mu\text{-hpp})_2SAr]$ **5-7-19e** and $[ArS(\mu\text{-hpp})]_2$ **5-7-19f**.

All products **5-7-19d-f** were structurally characterized by NMR and X-ray diffraction analysis.[184]

The analogous guanidine-borane chloride complexes **5-7-20** was synthesized from the base heterocycle hppH **5-7** and boron chloride (Eq. **76**).[185]



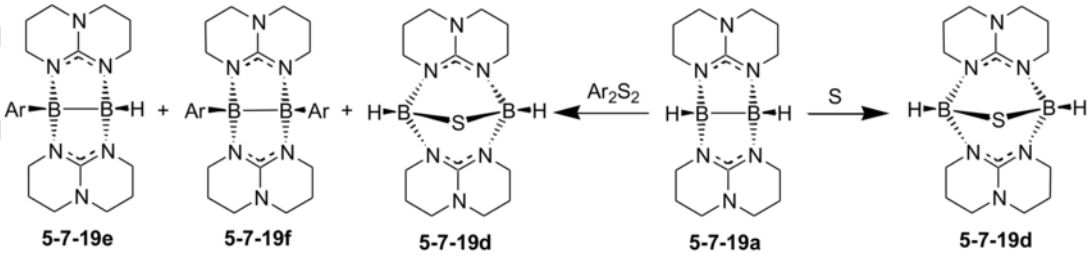
(76)

Other metal complexes **5-7-21** with the [hpp] anion **5-7-18** were synthesized and characterized by NMR spectroscopy and single-crystal X-ray diffraction analysis (not shown). The metals included potassium, manganese and zinc.[186,187]

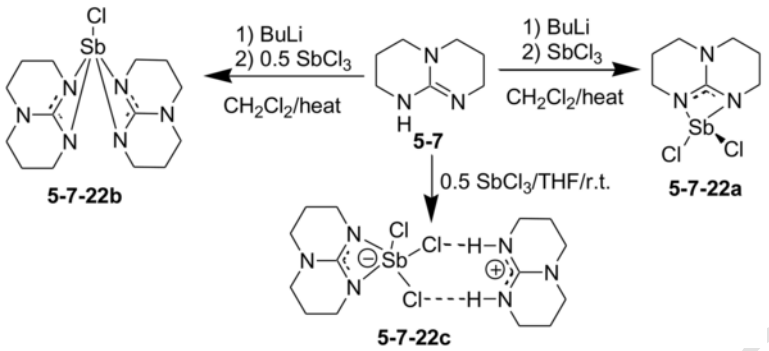
The reaction of the in situ generated Li salt of the bicyclic system **5-7** with 1 equivalent of $SbCl_3$ gave colorless crystals of $Sb(hpp)Cl_2$ **5-7-22a** after stirring and heating for 1h followed by extraction with dichloromethane (**Scheme 76**).[188] The analogous procedure with 0.5 equivalents of anitimony(III) chloride afforded the bis(guanidinate) complex $Sb(hpp)_2Cl$ **5-7-22b**. The reaction between 2 equivalents of hppH **5-7** and $SbCl_3$ afforded colorless crystals of **5-7-22c**.

Products **5-7-22a-c** were characterized by NMR spectra and X-ray diffraction analysis.[188]

The coordination chemistry of gold(II) with different organic ligands including pyrimido-[1,2-*a*]pyrimidine core **5-7** was reviewed previously.[189] Some chemical properties of Au-hppH complexes were studied. For example, attempts to remove the halide atoms from



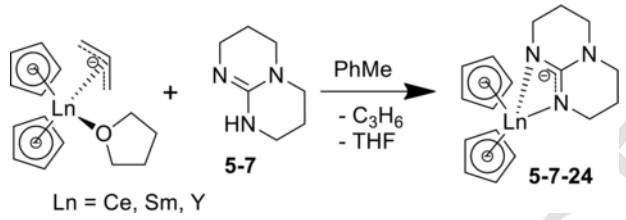
Scheme 75



Scheme 76

$[Au_2(hpp)_2Cl_2]$ **5-7-23** with Ag(I) benzoate led to the formation of the Au(I)–Ag(I) product $[(PhCOO)_2Au_4(hpp)_4Ag_2(PhCOO)_4]$ **5-7-23a** (**Scheme 77**).[190] The stoichiometry of the reaction was not determined but no other crystalline products were observed by XRD analysis.

Lanthanide metallocene guanidinate complexes $(C_5Me_5)_2$(hpp)Ln **5-7-24** derived from the ligand **5-7** were synthesized (Eq. 77).[191] These complexes were synthesized by protonolysis reaction of the equimolar mixture of $(C_5Me_5)_2Ln(\eta^3\text{-}CH_2CHCH_2)$-(THF) (Ln = Ce, Sm, Y) and hppH **5-7**.



(77)

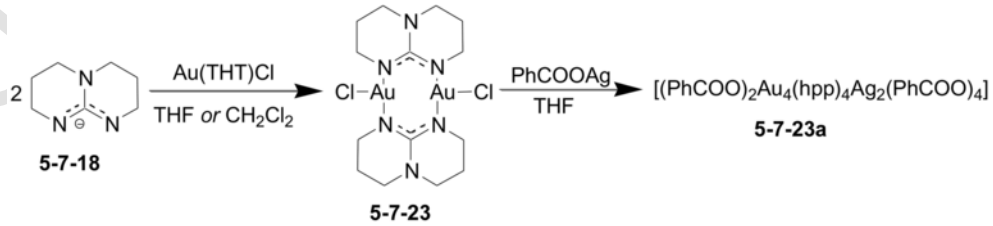
In the synthesis of uranium complex **5-10-25**, the complex $(C_5Me_5)_2UMe_2$ was allowed to react with 1 equivalent of Hhpp **5-7**. The complex (C_5Me_5)2(hpp)UCl **5-7-25a** was synthesized from $(C_5Me_5)_2UCl_2$ by reaction with potassium salt of ionic form **5-7-18** (**Scheme 78**).[192] The substitution reactions of halogen in the complex **5-7-25a** furnished (U-hpp)-derivatives **5-7-25b-d.**[193] The structures of **5-7-25**, **5-7-25a-d** were determined by X-ray crystallographic diffraction analysis.

The reaction between the guanidine derivative hppH **5-7** and K_2PtCl_4 in water furnished the salt $[hppH_2]_2[PtCl_4]$ **5-7-26** which, upon treatment with with lithium salt of **5-7-18** in THF was transformed into *cis*-$[(hppH)_2PtCl_2]$ **5-7-26a** (**Scheme 79**).[194] The corresponding *trans*-isomer **5-7-26b** was obtained by the reaction between $[(DMSO)_2PtCl_2]$ (prepared from DMSO and K_2PtCl_4) and hppH **5-7**. Additional molecule of hppH **5-7** can easily replace another chloride ligand to give $[(hppH)_3PtCl]^+ Cl^-$ **5-7-26c**.

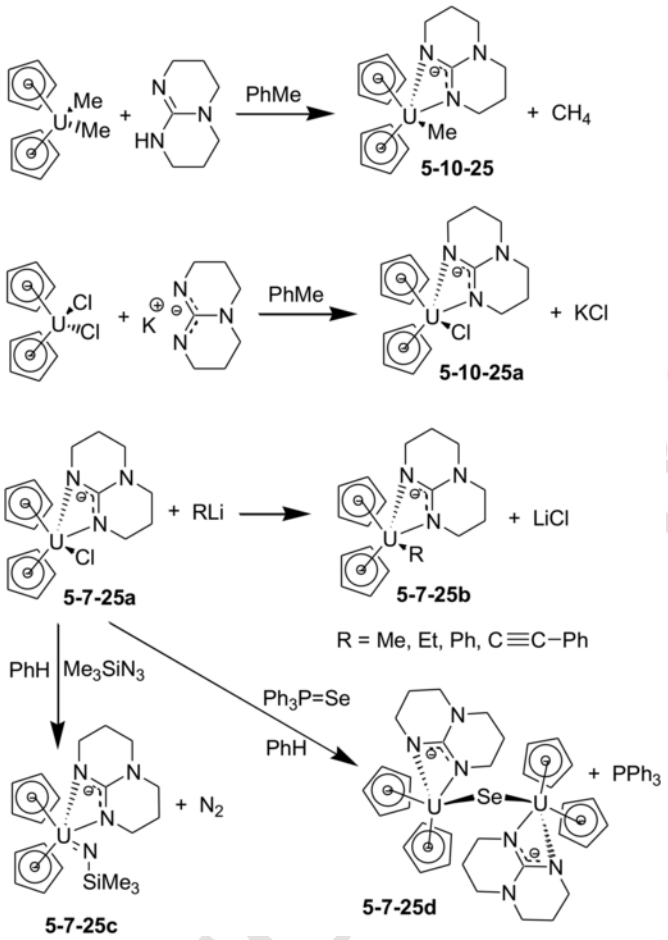
The crystal structures of all synthesized complexes **5-7-26** and **5-7-26a-c** were solved using XRD methodology. Finally, quantum chemical calculations provided further insight into the structures and properties of these compounds.[194]

5.8.1 Applications and important pyrimido[1,2-a]pyrimidines and their benzo analogs

Some of the thiazolidine-2,4-dione-containing pyrimido[1,2-*a*]pyrimidines **5-7-5** exhibit moderate antimicrobial and strong antifungal activities.[167] The pyrimido[1,2-*a*]pyrimidinone derivatives **5-7-10** are useful agents in cancer chemotherapy.[172] Compound **5-7-11** was evaluated for antimosquito properties.[173] Compound **5-7-14** shows moderate activity against the bacteria *Bacillus subtilis*, *Staphylococcus aureus and Escherichia coli* and high activity against fungus *C. albicans.*[177] The SAR analyses of pyrimido[2,1-*b*]quinazolin-6-one carbamates **5-7-15a,f** and **5-7-16b** were described.[195–197]



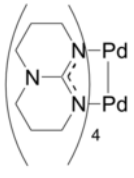
Scheme 77



Scheme 78

Interestingly, the two isomeric sets of carbamates **5-7-15a** and **5-7-16b** show different biological profiles.[178]

The application of a dinuclear palladium(II) complex Pd_2(hexahydro-2*H*-pyrimido[1,2-*a*]-pyrimidinium)$_4$ **5-7-27** as a catalyst for the chemo- and regioselective *R*-hydroxylation reaction of carbonyl compounds with molecular oxygen as the oxidant was investigated.[198]



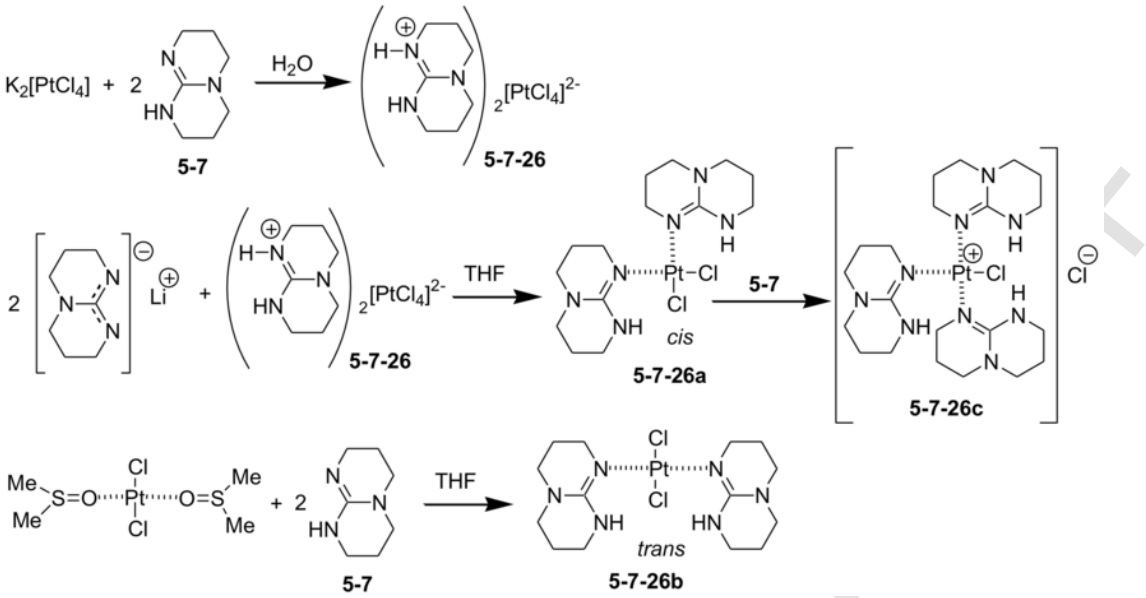
5-7-27

6 Systems with one extra N atom and one extra S atom, 1:1, and their benzo analogs

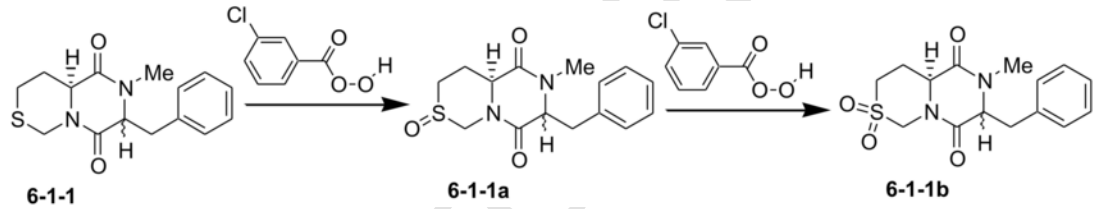
6.1 Pyrazino[1,2-*c*][1,3]thiazines

Construction of the title bicyclic system was reviewed in previous edition of CHC III.[199]

Cyclic sulfoxide **6-1-1a** and sulfone **6-1-1b** were prepared by a stepwise in situ oxidation of sulfide **6-1-1** with *meta*-chloroperbenzoic acid (*m*CPBA) in an NMR tube in a $CDCl_3$ solution (**Scheme 80**).[200] The oxidation reactions were monitored by taking the ^1H and ^{13}C



Scheme 79



Scheme 80

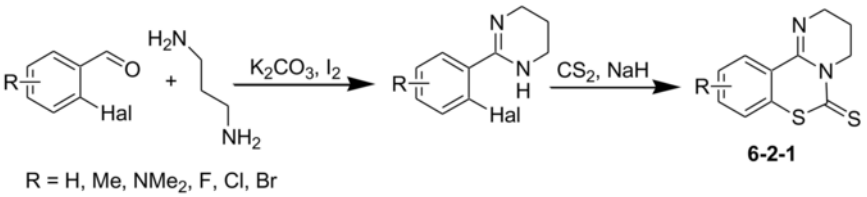
NMR spectra. The addition of *m*CPBA was finished when the sulfide was completely oxidized to the sulfone and a small amount of unreacted *m*CPBA was observed (the final molar ratio of added *m*CPBA to sulfone was about 2.1:1).

The geometries of the compounds **6-1-1a,b** were optimized using the DFT B3LYP/6-31G** method, and the ^{13}C and ^{1}H NMR chemical shifts were calculated for geometry-optimized structures with the DFT B3LYP/6-31 ++G** method. The calculated ^{13}C NMR chemical shifts induced by oxidation are in very good agreement with the experimental data and can be used to determine the oxidation state of the sulfur atom (–S–, –SO–, –SO_2–). The characteristic differences of the induced oxidation chemical shifts of carbon atoms at the α- and β-position to sulfur were successfully used for distinguishing between the diastereoisomeric sulfoxides.

6.2 Pyrimido[1,2-*c*][1,3]thiazines and their benzo analogs

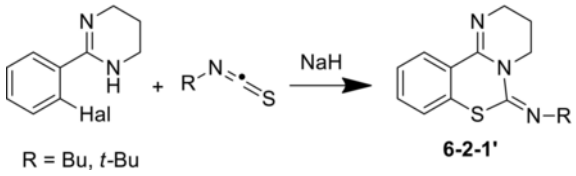
6.2.1 Synthesis pyrimido[1,2-c][1,3]thiazines and their benzo analogs

A simple and practical synthetic method of pyrimido[1,2-*c*][1,3]benzothiazines **6-2-1** by treatment of 2-(2-haloaryl)-tetrahydropyrimidines with NaH and carbon disulfide in DMF provides the desired cyclization products through a regioselective S_NAr-type reaction (**Scheme 81**).[201–203] The starting 2-(2-haloaryl)-tetrahydropyrimidines can be easily obtained from the corresponding 2-halo-substituted aromatic aldehydes.



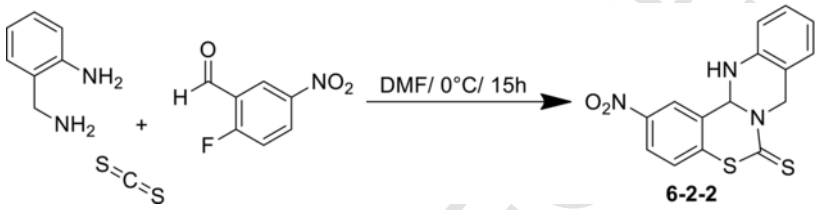
Scheme 81

Analogous fused tricyclic *N*-substituted systems **6-2-1′** were obtained using butylisothiocyanates as heterocumulenes in the synthetic route described above (Eq. **78**).[202,203]



(78)

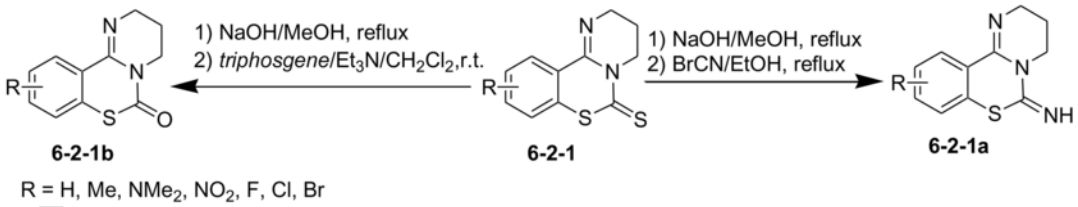
2-Aminobenzylamine was used in synthesis of 2-nitro-6,8,13,13a-tetrahydro-5-thia-7,13-diazatetraphene-6-thione **6-2-2** (Eq. **79**).[204] This multicomponent reaction was carried out by mixing at 0 °C all staring reagents: a solution of 2-fluoro-5-nitrobenzaldehyde in DMF, a solution of amine in DMF, and CS_2. After stirring for 15 h at room temperature, ethyl acetate was added to the mixture, and product **6-2-2** was isolated by addition of water.



(79)

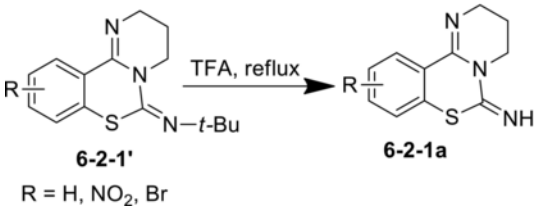
6.2.2 Reactivity and structural features of pyrimido[1,2-c][1,3]thiazines and their benzo analogs

Structural modifications of the central pyrimido-1,3-thiazine core in **6-2-1** were conducted.[87,202] For example, alkaline hydrolysis of the carbamodithioate moiety followed by treatment with cyanogen bromide afforded the imino-substituted compounds **6-2-1a** (**Scheme 82**),[87,202] which are analogs with the known drug PD 404182.[205–207] On the other hand, when triphosgene and triethylamine in dichloromethane were used in the last step—the oxo-derivatives of pyrimido[1,2-*c*][1,3]thiazine **6-2-1b** were obtained.



Scheme 82

The treatment of *N*-*t*-butyl-substituted pyrimido-1,3-thiazin-2-imines **6-2-1′** with TFA under reflux furnished unsubstituted imines **6-2-1a** (Eq. **80**).[87,202]

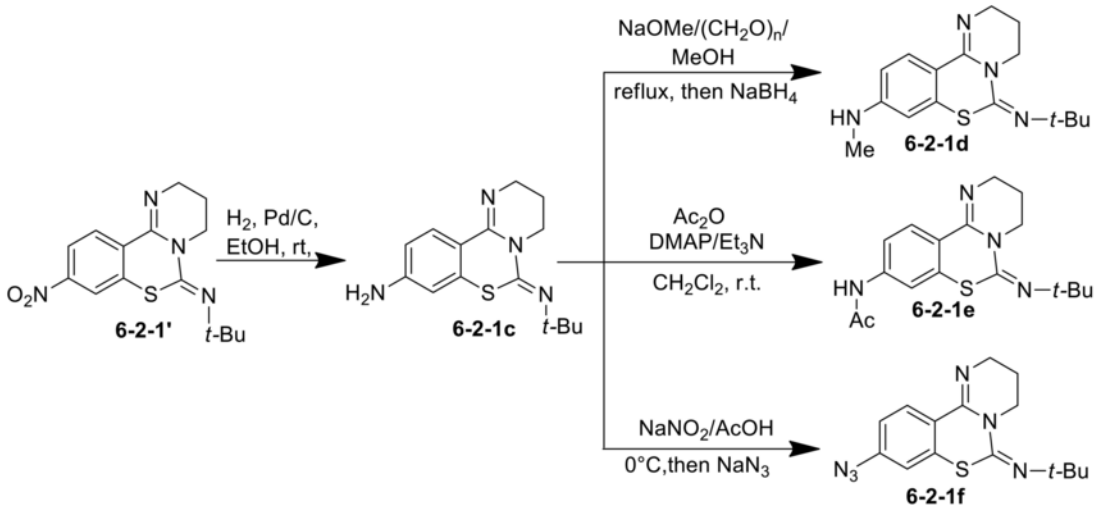


(80)

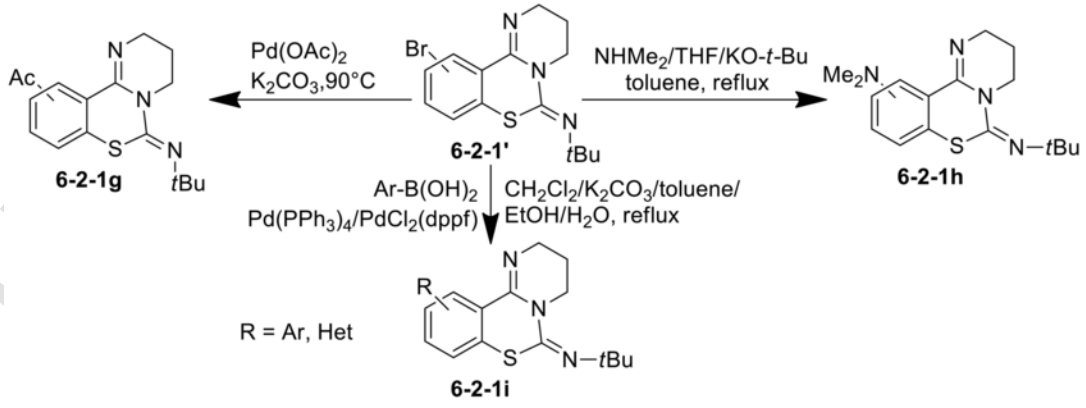
The nitro group in **6-2-1′** was reduced to the amino group. The resultant product **6-2-1c** was further modified at the amino group to give compounds **6-2-1d-f** (**Scheme 83**).[87]

Compounds **6-2-1′**, substituted with a bromine atom at position 9 or 10 at the benzene moiety undergo substitution reactions to give derivatives **6-2-1g-i** in good yields (**Scheme 84**).[87,203,208]

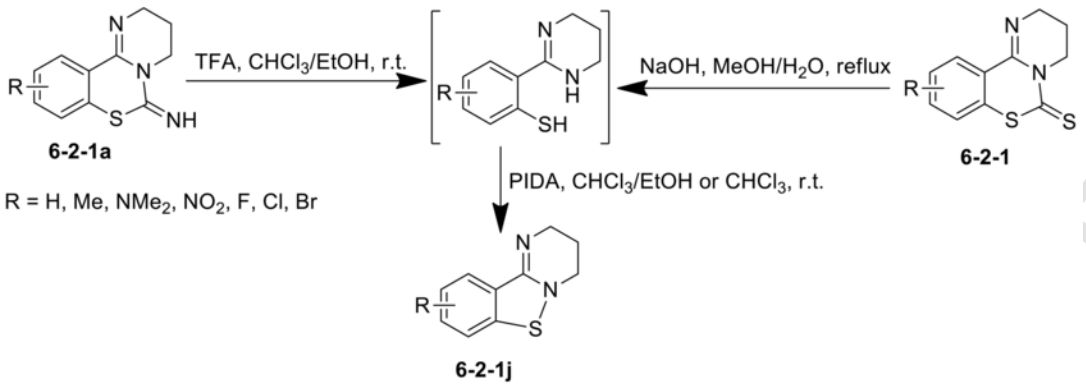
Ethanolysis of the imino or thio group in pyrimido[1,2-*c*][1,3]benzothiazines **6-2-1** or **6-2-1a** generated an intermediate thiophenol derivative which, without isolation, was transformed into benzo[4,5]isothiazolo[2,3-*a*]pyrimidines **6-2-1j** by phenyliodine diacetate (PIDA) mediated oxidation (**Scheme 85**).[203]



Scheme 83



Scheme 84



Scheme 85

6.2.3 *Applications and important pyrimido[1,2-c][1,3]thiazines and their benzo analogs*

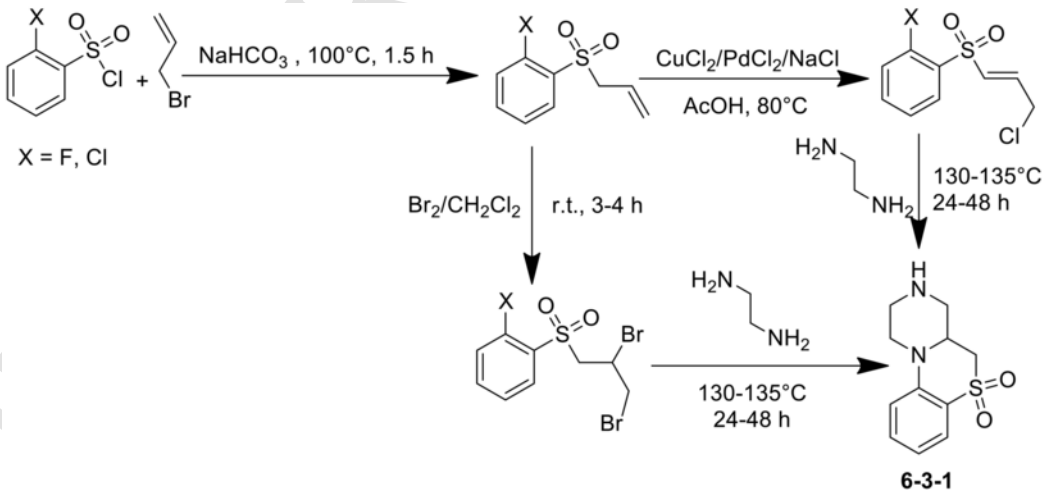
Pyrimido[1,2-*c*][1,3]benzothiazines **6-2-1, 6-2-1′** and **6-2-1a-i** are analogs of known anti-HIV agent PD 404182[87,201,203,205–209] Comprehensive SAR studies demonstrated that the 6-6-6 fused pyrimido[1,2-*c*]-[1,3]benzothiazine scaffold and the heteroatom arrangement in the thiazinimine moiety are indispensable for the inhibitory activity of PD 404182 against HIV infection. Optimization studies of the benzene and cyclic amidine rings indicated that the introduction of a hydrophobic group on the benzene ring and the amidine group is effective in improving the antiviral activity. Some compounds are competitive inhibitors of nitric oxide (NO) synthase.[210]

6.3 Pyrazino[2,1-*c*][1,4]thiazines and their benzo analogs

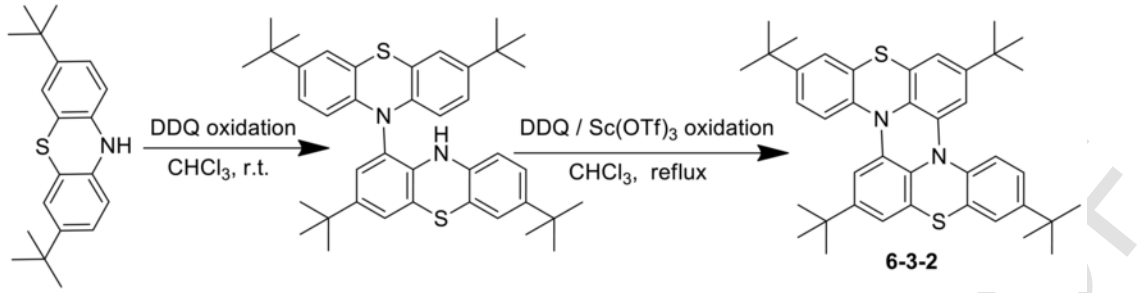
6.3.1 *Synthesis of pyrazino[2,1-c][1,4]thiazines and their benzo analogs*

Expeditious routes to pyrazino[2,1-*c*][1,4]benzothiazine-6,6-dioxide **6-3-1** were developed starting from allyl substituted sulfones (**Scheme 86**).[204,211] The key steps in a cascade of reactions are a 1,4-addition, nitrogen alkylation, and aromatic substitution.

A double hetero[4]helicene consisting of two phenothiazines **6-3-2** was synthesized by using 3,7-di-*tert*-butylphenothiazine as a building block.[212] The dimerization of starting phenothiazine by treatment with DDQ gave a good yield of the intermediate dimer in a short reaction time. A subsequent oxidation in the presence of of DDQ and $Sc(OTf)_3$ resulted in the intramolecular C—N bond formation and gave a doubly fused phenothiazine dimer **6-3-2** (**Scheme 87**).[212]

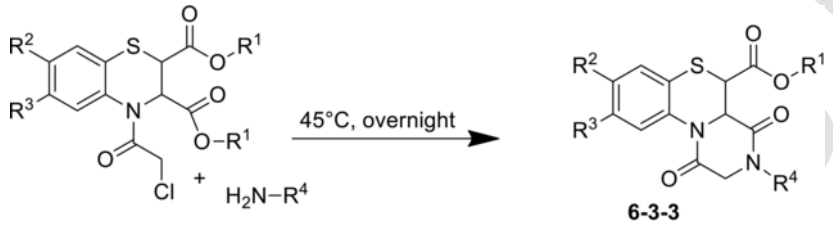


Scheme 86



Scheme 87

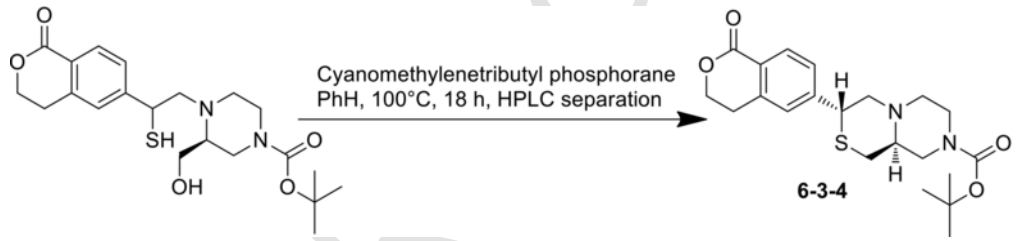
Aminolysis of the phenothiazine shown below smoothly furnished 1,4-dioxo-1,2,3,4,4a,5-hexahydrobenzo[*b*]pyrazino[1,2-*d*][1,4]thiazine-5-carboxylates **6-3-3** after stirring of the reaction mixture at 45 °C overnight (Eq. **81**).[213]



(81)

$R^1 = R^2 = Me, Et; R^2, R^3 = H, Cl, Br; R^4 = propyl, propargyl, benzyl, Hal\text{-}benzyl$

Following the discovery of small molecule acyl piperazine ROMK inhibitors, the acylpyrazino[2,1-*c*][1,4]thiazines **6-3-4** were synthesized (Eq. **82**).[69]

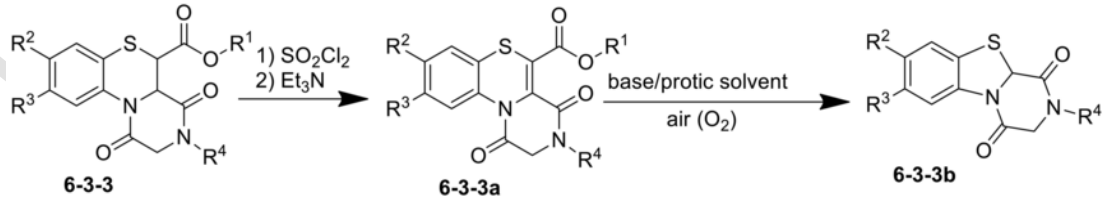


(82)

6.3.2 Reactivity and structural features of pyrazino[2,1-c][1,4]thiazines and their benzo analogs

The structure of doubly fused phenothiazine dimer **6-3-2** was determined by the X-ray single crystal analysis. As expected, dimer **6-3-2** exists in a double hetero[4]helicene structure, and two enantiomers are present in the unit cell in the ratio of 1:1.

The treatment of compounds **6-3-3** with SO_2Cl_2 and Et_3N gave unsaturated derivatives **6-3-3a** (**Scheme 88**).[213] An unexpected ring-contraction from benzo[*b*]pyrazino[1,2-*d*][1,4]thiazine-1,4-diones **6-3-3a** to benzo[4,5]thiazolo[3,2-*a*]pyrazine-1,4-diones **6-3-3b** was observed. The preliminary mechanistic studies suggested that the transformation involves two independent steps: (1) the Michael addition



$R^1 = R^2 = Me, Et; R^2, R^3 = H, Cl, Br; R^4 = propyl, propargyl, benzyl, benzyl\text{-}Hal$

Scheme 88

of a protic solvent, in the presence of base, to the C-2–C-3 double bond of compound **6-3-3a** and (2) a ring contraction induced by migration of a sulfur atom from C-2 to C-3 position.[213]

Cyclic sulfoxides **6-3-5a** and sulfones **6-3-5b** were prepared by a stepwise in situ oxidation of the sulfide **6-3-5** with *m*CPBA in an NMR tube in a $CDCl_3$ solution (**Scheme 89**).[200] The oxidation reactions were monitored by the ^1H and ^{13}C NMR spectra. The addition of *m*CPBA was finished when the sulfide was completely oxidized to the corresponding sulfone and a small amount of unreacted *m*CPBA was observed (the final molar ratio of added *m*CPBA to sulfone was about 2.1:1).

The geometries of compounds **6-3-5a,b** were optimized using the DFT B3LYP/6-31G** method and the ^{13}C and ^1H NMR chemical shifts were calculated for geometry-optimized structures with the DFT B3LYP/6-31 ++G** method.

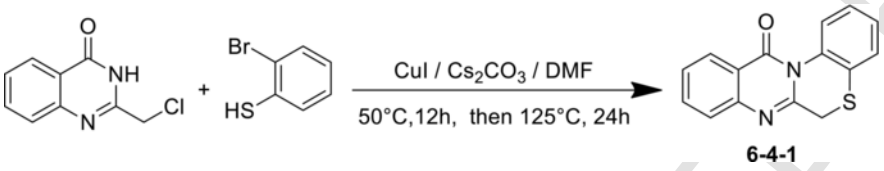
6.3.3 Applications and important pyrazino[2,1-c][1,4]thiazines and their benzo analogs

Compound **6-3-4** is a ROMK inhibitor with potency that is superior to many other ROMK inhibitors, and shows improved pharmacokinetic properties.[69]

6.4 Pyrimido[2,1-*c*][1,4]thiazines and their benzo analogs

6.4.1 Synthesisof pyrimido[2,1-c][1,4]thiazines and their benzo analogs

1,4-Thiazino[2,3-*b*]quinazolinone **6-4-1** was synthesized by a copper-catalyzed tandem reaction of 2-chloromethylquinazolin-4-one with 2-bromothiophenol (Eq. **83**).[91]



6-4-1

(83)

6.5 Pyrazino[2,1-*b*][1,3]thiazines and their benzo analogs

6.5.1 Synthesis of pyrazino[2,1-b][1,3]thiazines and their benzo analogs

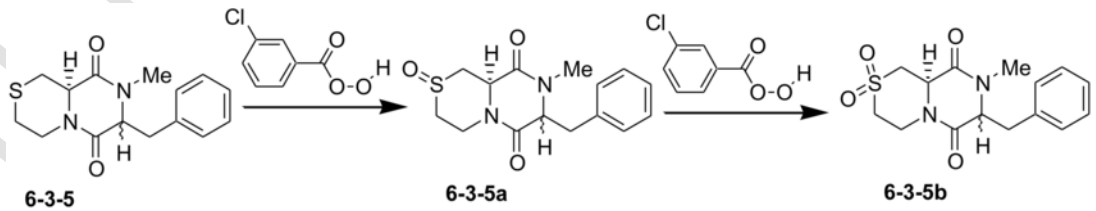
Analogs of pyrazino[2,1-*b*][1,3]thiazine scaffold-based tripeptidomimetic CXCR4 antagonists **6-5-1** were synthesised from linear precursor **D**. Synthesis of **D** required coupling of three building blocks **A–C** (**Scheme 90**).[214–216] Treatment of **D** with trifluoroacetic acid liberates the aldehyde from the dimethyl acetal, which is then attacked by the amide nitrogen atom to form the *N*-acyliminium ion **E**. Finally, nucleophilic attack by the thiol results in the formation of the bicyclic ring system **6-5-1**.

A relatively mild and effective approach to ring fused pyrazino[2,1-*b*][1,3]benzothiazines **6-5-2** involves treatment of thiosalicylaldehyde with secondary amines in the presence of a catalytic amount of acetic acid (**Scheme 91**).[103] Computational studies employing density functional theory indicate that acetic acid reduces the energy barriers of two steps shown below, both of which involve proton transfer and water elimination.[103]

6.5.2 Reactivity and structural features of pyrazino[2,1-b][1,3]thiazines and their benzo analogs

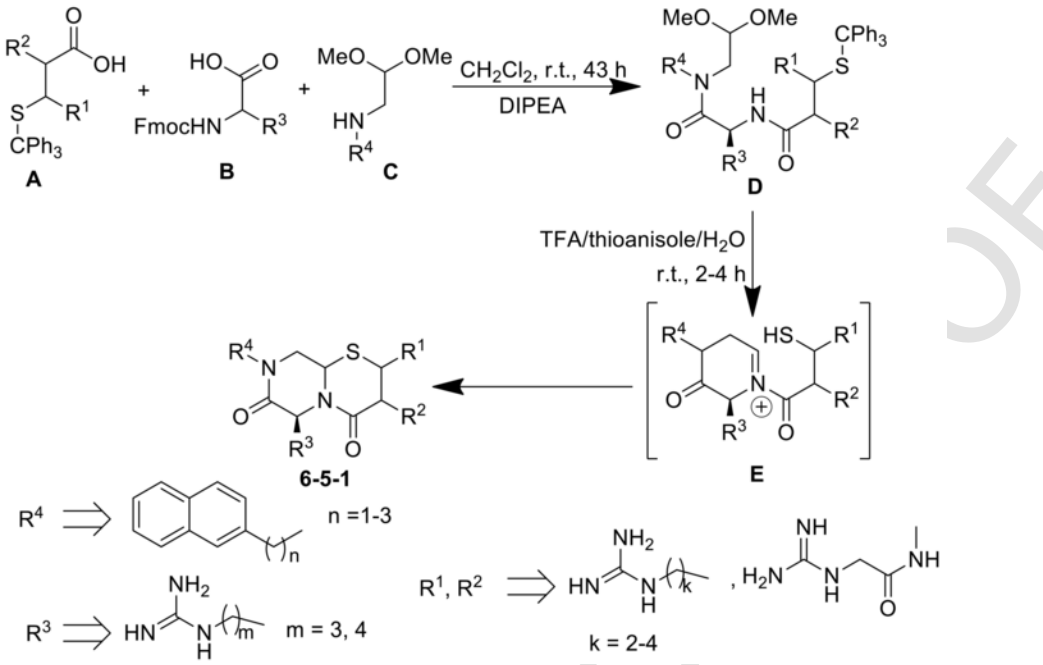
Cyclic sulfoxide **6-5-3a** and sulfone **6-5-3b** were prepared by a stepwise in situ oxidation of the sulfide **6-5-3** with *m*CPBA in an NMR tube in a $CDCl_3$ solution (**Scheme 92**).[200] The oxidation reactions were monitored by analysis of the ^1H and ^{13}C NMR spectra. The addition of *m*CPBA was finished when the sulfide was completely oxidized to the corresponding sulfone and a small amount of unreacted *m*CPBA was observed (the final molar ratio of added *m*CPBA to sulfone was about 2.1:1).

The geometries of all of the compounds **6-5-3a,b** were optimized using the DFT B3LYP/6-31G** method and the ^{13}C and ^1H NMR chemical shifts were calculated for geometry-optimized structures with the DFT B3LYP/6-31 ++G** method.

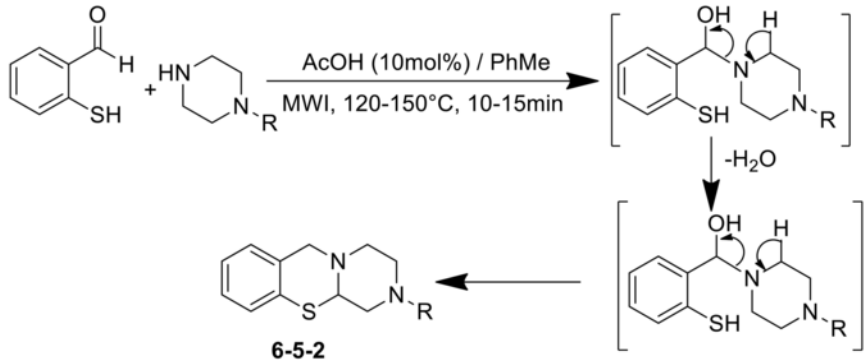


6-3-5 **6-3-5a** **6-3-5b**

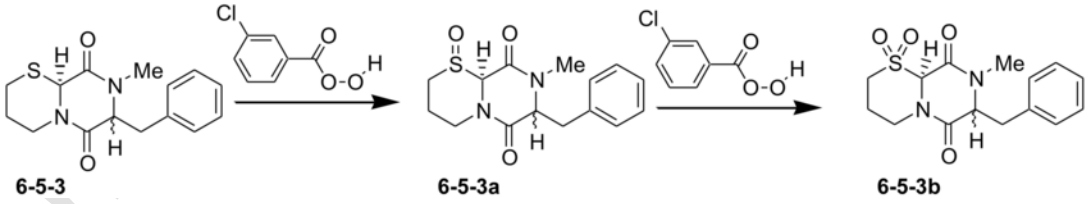
Scheme 89



Scheme 90



Scheme 91



Scheme 92

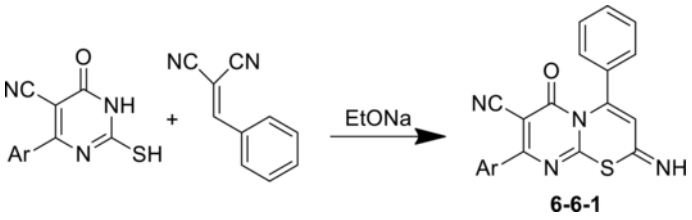
6.5.3 Applications and important pyrazino[2,1-b][1,3]thiazines and their benzo analogs

Biological testing of pyrazino[2,1-*b*][1,3]thiazine scaffold-based tripeptidomimetic CXCR4 antagonists **6-5-1** concerning the antagonistic potency toward CXCR4 showed that they represent new peptidomimetic hits. Importantly, the modular nature of the scaffold provides an interesting starting point for future optimization of side substituents.[214–216]

6.6 Pyrimido[2,1-*b*][1,3]thiazines and their benzo analogs

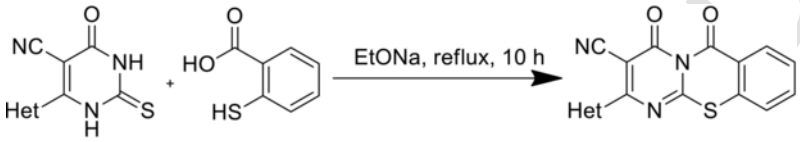
6.6.1 Synthesis of pyrimido[2,1-b][1,3]thiazines and their benzo analogs

Treatment of 4-(4-chlorophenyl)-2-mercapto-6-oxo-1,6-dihydropyrimidine-5-carbonitrile with benzylidenemalononitrile furnished pyrimido[2,1-*b*][1,3]thiazines **6-6-1**. The reaction involves generation of the non-isolable Michael-type adduct followed by addition of the nucleophilic sulphur to the cyano function and subsequent elimination of HCN (Eq. **84**).[171]



6-6-1 (84)

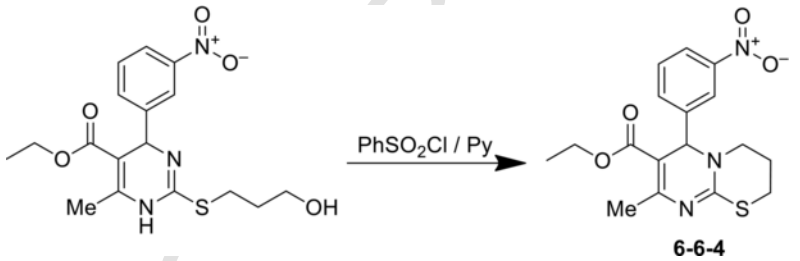
The cyanopyrimidines were allowed to react with thiosalicylic acid in the presence of sodium ethoxide under reflux for 10 h, yielding 2-heteroaryl-6,11-dihydro-4,6-dioxo-4*H*-pyrimido[2,1-*b*]-[1,3]benzothiazines **6-6-2** (Eq. **85**).[99]



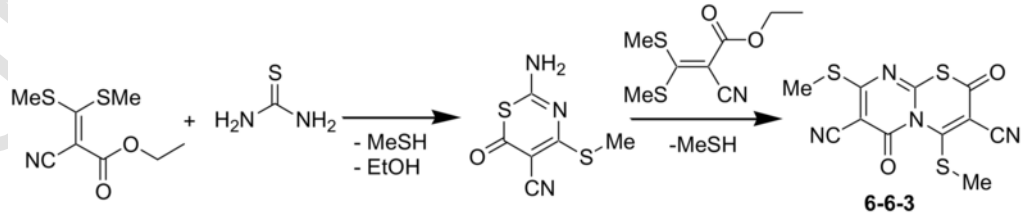
6-6-2 (85)

Simple and efficient synthesis of a fused bicyclic heterocyclic compound **6-6-3** by the reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate and thiourea in the presence of potassium carbonate in DMF under reflux conditions is shown in (**Scheme 93**).[217] The optimized molar ratio of the substrates is 2:1 in agreement with the proposed mechanistic pathway.

Stirring a mixture of ethyl 2-(3-hydroxypropylsulfanyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydro-pyrimidine-5-carboxylate and benzenesulfonyl chloride in dry pyridine overnight at room temperature afforded a good yield the ethyl 8-methyl-6-(3-nitrophenyl)-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazine-7-carboxylate **6-6-4** (Eq. **86**).[218]



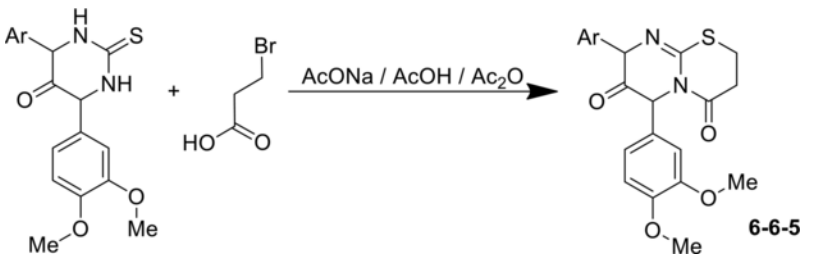
6-6-4 (86)



6-6-3

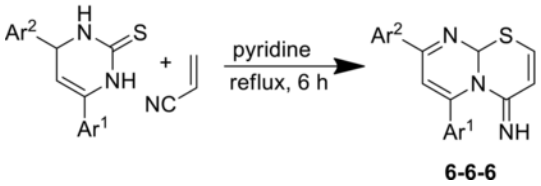
Scheme 93

Treatment of 6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-thioxo-tetrahydropyrimidin-5(6*H*)-ones with 2-bromopropionic acid or 3-bromopropionic acid in a mixture of acetic acid/acetic anhydride in the presence of anhydrous sodium acetate furnished the corresponding pyrimido[2,1-*b*][1,3]thiazinones **6-6-5** (Eq. **87**).[219] The antiviral screening of **6-6-5** showed that it has a good antiviral activity comparable to acyclovir as reference control.[219]



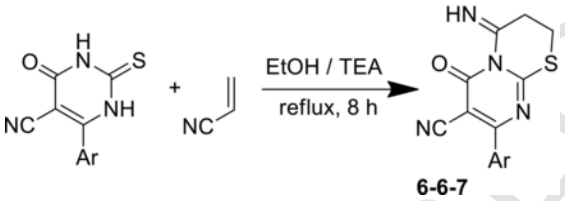
(87)

Cyanoethylation of 6-(4-methylphenyl)-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-pyrimidin-2(*H*)-thiones with acrylonitrile in boiling pyridine afforded 4-imino-pyrimido[2,1-*b*][1,3]-thiazine derivatives **6-6-6** (Eq. **88**).[220] The reaction was performed with pyrimidin-2-thione and a twofold amount of acrylonitrile in pyridine under reflux for 6 h.



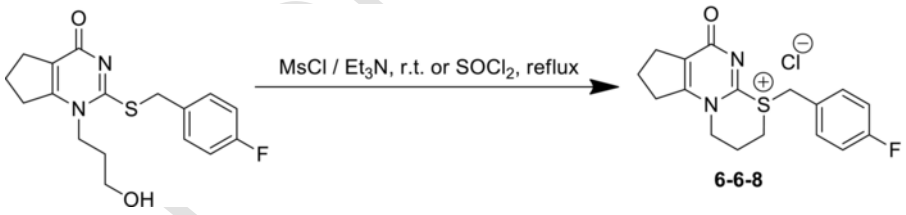
(88)

A similar cyclization process was observed for the synthesis of 4-imino-8-(4-methoxyphenyl)-6-oxo-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*]-[1,3]thiazine-7-carbonitrile **6-6-7** (Eq. **89**).[221]



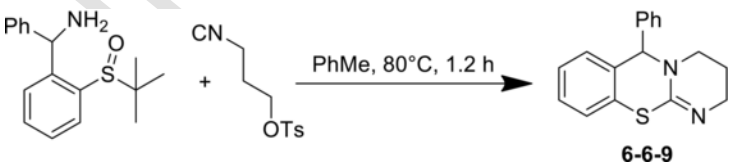
(89)

The treatment of 2-(4-fluorobenzylthio)-1-(2-hydroxyethyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidin-4(5*H*)-one with MsCl in the presence of Et_3N in dichloromethane produced bicyclic sulfonium salt **6-6-8** as a single product, instead of the expected mesylate ester (Eq. **90**).[222] This outcome may be attributable to the powerful nucleophilicity of the sulfur atom which displaces the mesyloxy group by an S_N2 pathway. A similar outcome was observed for the reaction with thionyl chloride.[222]



(90)

A convenient synthesis of pyrimido[2,1-*b*][1,3]thiazine **6-6-9** is depicted in Eq. **91**.[223]



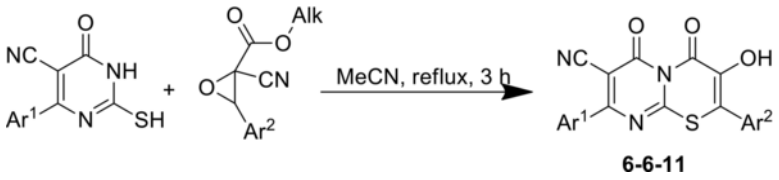
(91)

As shown in Eq. **92**, the reaction of dihydropyrimidines with 1,3-dibromopropane furnishes 2,3,4,6-tetrahydro-8-methyl-pyrimido[2,1-*b*][1,3]thiazine-7-carboxamide **6-6-10**. In a conventional method, the reaction was carried out in methanol or dimethylformamide in the

presence of potassium carbonate as a base.[224] While performing this reaction under microwave irradiation, it was found that it proceeds without a catalyst, leading rapidly to the formation of product **6-6-10** in excellent yields (Eq. **92**).[224]

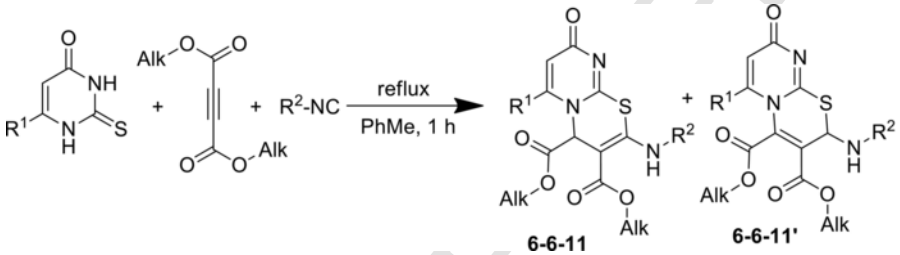
(92)

A one-pot procedure for the synthesis of the 4,6-dioxo-pyrimido[2,1-*b*][1,3]thiazine-7-carbonitriles **6-6-11** involves a reaction of dihydropyrimidines with α-functionalized epoxides (Eq. **93**).[225] The elaborated protocol offers several advantages of high yields, short reaction times, operational simplicity, mild reaction conditions, ease of isolation of products, and a green aspect by avoiding the need for a catalyst.



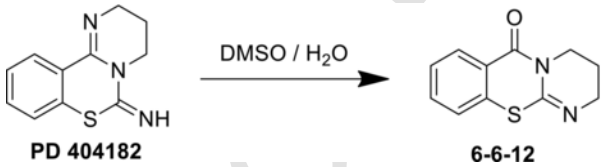
(93)

A facile and direct synthesis of pyrimido[2,1-*b*][1,3]thiazin-6-ones **6-16-11** and **6-16-11′** involves a one-pot multi-component reaction of dialkyl acetylenedicarboxylates with alkyl or aryl isocyanides and 2-thioxopyrimidin-4-ones in good overall yields (Eq. **94**).[226] The regioisomers **6-6-11** and **6-6-11′** were isolated and purified by column chromatography on silica gel eluting with *n*-hexane/AcOEt, 3:1.



(94)

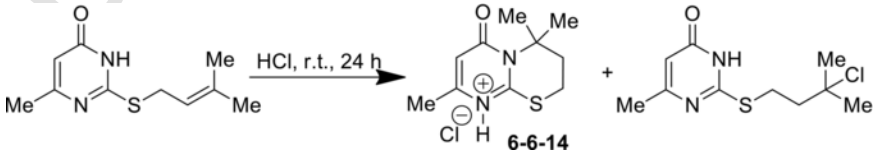
It was observed that the antiviral activity of DMSO solution of the drug PD 404182[205–207] decreases with time.[88] X-ray crystallographic analysis of the decomposition product revealed 3,4-dihydro-2*H*,6*H*-benzo[*e*]pyrimido[2,1-*b*][1,3]thiazin-6-one **6-6-12** (Eq. **95**).[88]



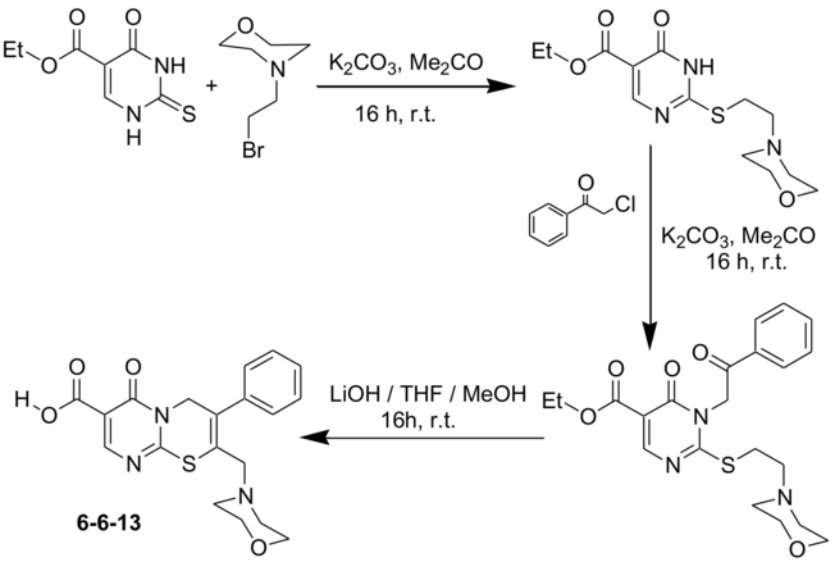
(95)

The pyrimido[2,1-*b*][1,3]thiazine derivative **6-6-13** bearing a morpholine moiety was synthesized from 2-mercapto-5-ethoxycarbonylpyrimidin-4 one using a multi-step protocol (**Scheme 94**).[227] Alkylation of the thio moiety with bromoethylmorpholine gave an intermediate product, further alkylation of which at the N-3 position with bromoacetophenone yielded a dialkylated pyrimidine. Treatment of this product with lithium hydroxide furnished a bicyclic pyrimido[2,1-*b*][1,3]thiazine derivative **6-6-13.**[227]

Treatment of 6-methyl-2-prenylsulfanyl-pyrimidin-4(3*H*)-one with HCl furnished a mixture of the addition product and the product of electrophilic cyclization reaction involving the N(3) atom, 4,4,8-trimethyl-6-oxo-3,4-dihydro-pyrimido[2,1-*b*][1,3]thiazinium chloride **6-6-14** (Eq. **96**).[228]



(96)

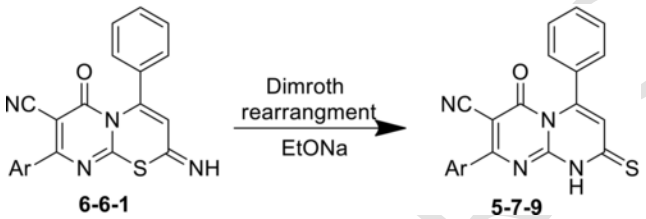


Scheme 94

The reaction was carried out by a slow addition of a concentrated hydrochloric acid over 24 h to acetone solution of the starting prenyl thioether.

6.6.2 Reactivity and structural featuress of pyrimido[2,1-b][1,3]thiazines and their benzo analogs

Pyrimido[2,1-*b*][1,3]thiazines **6-6-1** undergo base-induced Dimorth rearrangement to give pyrimido[1,2-*a*]pyrimidine **5-7-9** (Eq. **97**).[171]



(97)

Pyrimido[2,1-*b*][1,3]benzothiazine **6-6-3** contains methylthio groups (SMe) at positions 4 and 8 that are activated by adjacent ring nitrogen atoms and electron-withdrawing groups towards a nucleophilic displacement. Compound **6-6-3** was derivatized by using a synthetic strategy that is based on suitability of the substituted pyrimido[2,1-*b*][1,3]thiazine system **6-6-3** to react as a bis-electrophilic species towards various nucleophiles yielding derivatives **6-6-3a,b** (**Scheme 95**).[217]

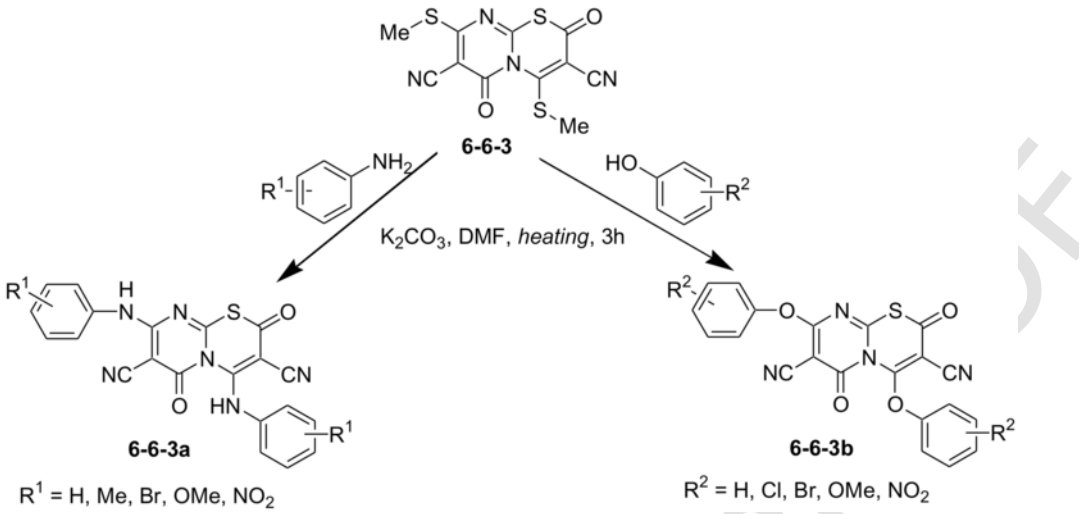
Spectral data (IR, ^{1}H NMR, ^{13}C NMR) of the ethyl 8-methyl-6-(3-nitrophenyl)-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazine-7-carboxylate **6-6-4** lacked the signals for NH and the side chain phenylsulfonate moiety confirming the cyclic structure.[218] Cyclization regioselectivity of compound **6-16-4** was unequivocally established by HMBC and confirmed by X-ray crystallographic analysis.

7 Systems with two extra S atoms, 1:1, and their benzo analogs

7.1 [1,4]Thiazino[3,4-*c*][1,4]thiazines and their benzo analogs

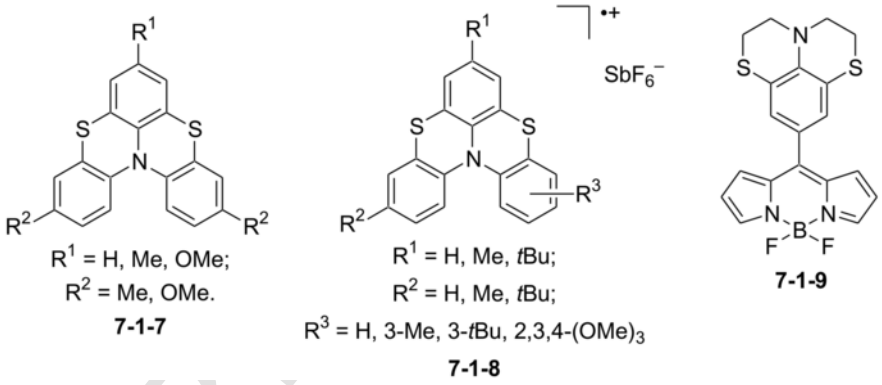
Three thia-bridged triphenylamine heterohelicenes **7-1-1**, **7-1-2** and **7-1-3** were synthesized.[229–231] These novel organic dyes were studied as dye-sensitized solar cells. It was shown that the device based on compound **7-1-1** has excellent long-term stability. Synthesis of these dyes is shown in **Scheme 96**.

[1,4]Thiazino[3,4-*c*][1,4]thiazine derivatives, such as **7-1-6**, can be used as water-soluble fluorescent metal complex probes.[232] Four-step synthesis of the precursor **7-1-5** from *m*-anisidine **7-1-4** is presented in **Scheme 97**. Compound **7-1-6** was also used in the synthesis of



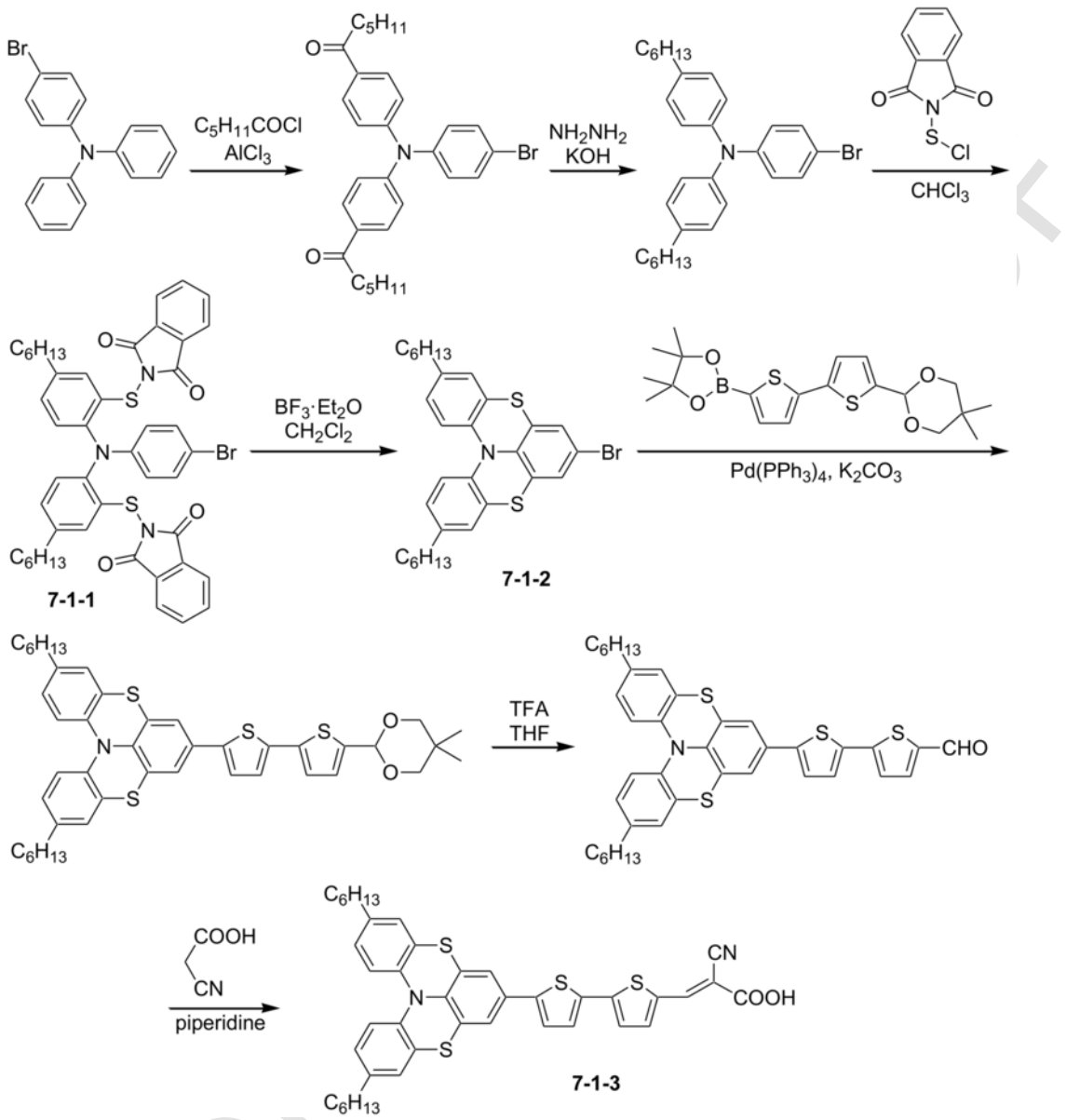
Scheme 95

Zn-salens.

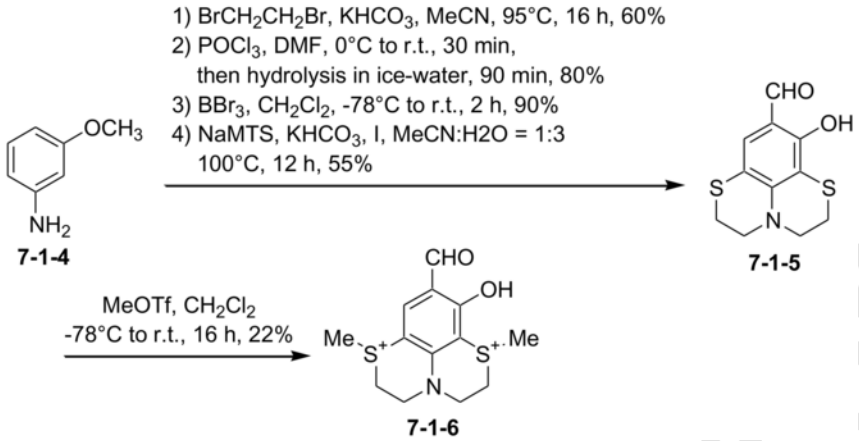


Many articles are devoted to quantum chemical investigations of compounds with a [1,4]thiazino[3,4-*c*][1,4]thiazine system. For example, theoretical TD-DFT calculations of **7-1-3** at B3LYP/3-21G* level of theory suggest that the HOMO-1 and HOMO of this dye are delocalized over the π-conjugated system.[229] Chiro-optical and nonlinear optical studies of heterohelicenes **7-1-7**, **7-1-8** and **7-1-9** were described.[232] DFT calculations at B3PW91/6-311G(d,p) level were employed to analyze the nonlinear optical response and spectral properties of the triarylamine heterohelicenes. It was concluded that these heterohelicenes can be used as good materials for nonlinear optical devices and addition of electron donating substituents can increase their nonlinear optical response due to the extension in π-conjugation.

The structure, stability and redox potentials of thia-bridged triarylamine heterohelicene radical cations **7-1-8** were analyzed.[233,234] Crystalline samples of corresponding hexafluoroantimonates were obtained and investigated using XRD and DFT methods. Analogous

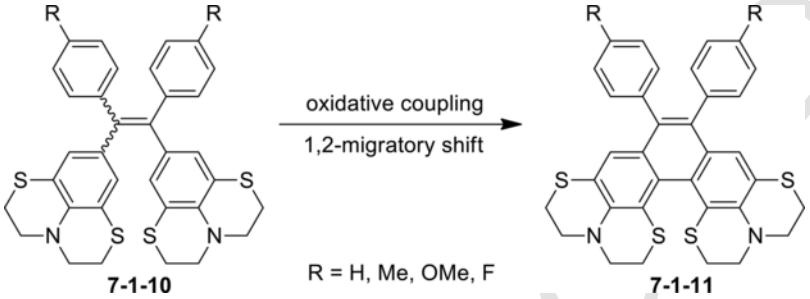

Br
C5H11COCl
AlCl3
C5H11
NH2NH2
KOH
C6H13
CHCl3
BF3·Et2O
CH2Cl2
Pd(PPh3)4, K2CO3
7-1-1
7-1-2
TFA
THF
CHO
COOH
CN
piperidine
7-1-3

Scheme 96



Scheme 97

compounds were studied in a similar way.[235]



(98)

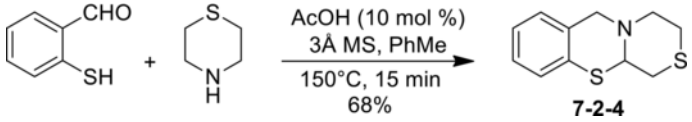
Oxidative cyclodehydrogenation reaction of tetraphenylethylenes **7-1-10** containing electron-rich THDTAP moieties was investigated (Eq. **98**).[236] The four substances show the aggregation-induced emission with yellowish-green photoluminescence in the solid state and in tetrahydrofuran-water solution. Compounds **7-1-10** during the oxidative cyclodehydrogenation reaction undergo the 1,2-migratory shift and are transformed into **7-1-11**.

7.2 [1,4]Thiazino[3,4-*b*][1,3]thiazines and their benzo analogs

(99)

$R^1 = R^2$ = Me [yield 20%]
$R^1 R^2 = (CH_2)_5$ [yield 27%]

The reaction shown in Eq. **99** is a simple route to benzothiazinones **7-2-3.**[102] A mixture of *o*-fluorobenzoyl chloride **7-2-1**, imine **7-2-2**, sodium hydrosulfide and triethylamine in DMF under an argon atmosphere was kept at room temperature for 2 days. Although the yields are low, considering the simplicity of the reaction and availability of starting materials, the method will definitely find its niche among the arsenal of synthetic reactions.



(100)

Treatment of thiosalicylaldehyde with thiomorpholine furnished **7-2-4.**[103] A toluene solution of the aldehyde in a microwave vial equipped with a magnetic stir bar and 3 Å molecular sieves was treated with thiomorpholine in glacial acetic acid. After 15 min of irradiation at 150 °C, the crude product **7-2-4** was purified using silica gel chromatography (Eq. **100**).

References

1.. E.O. Gorbacheva, A.A. Tabolin, R.A. Novikov, Y.A. Khomutova, Y.V. Nelyubina, Y.V. Tomilov, S.L. Ioffe, Org. Lett. 15 (2) (2013) 350–353.
2.. A.A. Tabolin, R.A. Novikov, Y.A. Khomutova, A.A. Zharov, G.A. Stashina, Y.V. Nelyubina, Y.V. Tomilov, S.L. Ioffe, Tetrahedron Lett. 56 (2015) 2102–2105.
3.. Y.V. Nelyubina, K.A. Lyssenko, J. Phys. Chem. A 117 (2013) 3084–3092.
4.. R.E. Looper, M.T.C. Runnegar, R.M. Williams, Tetrahedron 62 (2006) 4549–4562.
5.. J. Hu, M. Zhang, Y. Gong, Eur. J. Org. Chem. 9 (2015) 1970–1978.
6.. A. Acharya, J.A. Eickhoff, C.S. Jeffrey, Synthesis 45 (2013) 1825–1836.
7.. M. Heydenreich, A. Koch, S. Klod, I. Szatmari, F. Fulop, E. Kleinpeter, Tetrahedron 62 (2006) 11081–11089.
8.. R. Csutortoki, I. Szatmari, M. Heydenreich, A. Koch, I. Starke, F. Fulop, E. Kleinpeter, Tetrahedron 68 (2012) 6284–6288.
9.. V.A. Maslivets, A.N. Maslivets, Russ. J. Org. Chem. 49 (2013) 1092–1093.
10.. E.V. Gromachevskaya, T.P. Kosulina, A.A. Borodavko, Chem. Heterocycl. Compd. 42 (8) (2006) 1068–1077.
11.. V. Tena Pérez, Á.L. Fuentes de Arriba, L.M. Monleón, L. Simón, O.H. Rubio, F. Sanz, J.R. Morán, Eur. J. Org. Chem. 15 (2014) 3242–3248.
12.. P. Králová, S. Benická, M. Soural, ACS Comb. Sci. 21 (3) (2019) 154–157.
13.. E. Lenci, A. Rossi, G. Menchi, A. Trabocchi, Org. Biomol. Chem. 15 (2017) 9710–9717.
14.. Y. Huang, C. Pathirana, Q. Ye, V. Palaniswamy, Tetrahedron Lett. 56 (2015) 4516–4519.
15.. A. Wakamiya, H. Nishimura, T. Fukushima, F. Suzuki, A. Saeki, S. Seki, I. Osaka, T. Sasamori, M. Murata, Y. Murata, H. Kaji, Angew. Chem. Int. Ed. 53 (2014) 1–6.
16.. H. Nishimura, K. Tanaka, Y. Morisaki, Y. Chujo, A. Wakamiya, Y. Murata, J. Org. Chem. 82 (2017) 5242–5249.
17.. M.A. Truong, J. Lee, T. Nakamura, J.-Y. Seo, M. Jung, M. Ozaki, A. Shimazaki, N. Shioya, T. Hasegawa, Y. Murata, S.M. Zakeeruddin, M. Grätzel, R. Murdey, A. Wakamiya, Chem. Eur. J. 25 (2019) 6741–6752.
18.. Q. Li, X. Zhang, Y. Cao, C. Shi, P. Tao, Q. Zhao, A. Yuan, Dalton Trans. 48 (2019) 4596–4601.
19.. Q. Li, C. Shi, X. Zhang, P. Tao, Q. Zhao, A. Yuan, Eur. J. Inorg. Chem. 10 (2019) 1343–1348.
20.. Q. Li, X. Zhang, Y. Cao, C. Shi, P. Tao, Q. Zhao, A. Yuan, ChemistryOpen 8 (2019) 339–343.
21.. H. Nishimura, T. Fukushima, A. Wakamiya, Y. Murata, H. Kaji, Bull. Chem. Soc. Jpn. 89 (2016) 726–732.
22.. H. Nishimura, Y. Hasegawa, A. Wakamiya, Y. Murata, Chem. Lett. 46 (2017) 817–820.
23.. N. Islam, A.H. Pandith, J. Mol. Struct. 1142 (2017) 1–10.
24.. H. Nishimura, N. Ishida, A. Shimazaki, A. Wakamiya, A. Saeki, L.T. Scott, Y. Murata, J. Am. Chem. Soc. 137 (2015) 15656–15659.
25.. E. Bond, A.-M. Beausoleil, J. Howell, A. Wong, J. Robichaud, J. Org. Chem. 76 (2011) 2488–2493.
26.. S. Mahato, S. Haldar, C.K. Jana, Chem. Commun. 50 (2014) 332–334.
27.. M.L. Deb, S.S. Dey, I. Bento, M.T. Barros, C.D. Maycock, Angew. Chem. Int. Ed. 52 (2013) 9791–9795.
28.. N.A. Waghmode, A.H. Kalbandhe, P.B. Thorat, N.N. Karade, Tetrahedron Lett. 57 (2016) 680–683.
29.. S. Mahato, C.K. Jana, Org. Biomol. Chem. 15 (2017) 1655–1660.
30.. A. Modak, U. Dutta, R. Kancherla, S. Maity, M. Bhadra, S.M. Mobin, D. Maiti, Org. Lett. 16 (2014) 2602–2605.
31.. H.-T. Yang, Y.-C. Tan, J. Ge, H. Wu, J.-X. Li, Y. Yang, X.-Q. Sun, C.-B. Miao, J. Org. Chem. 81 (2016) 11201–11209.
32.. A. Jha, A.B. Naidu, A.M. Abdelkhalik, Org. Biomol. Chem. 11 (2013) 7559–7565.
33.. M. Okimoto, K. Ohashi, H. Yamamori, S. Nishikawa, M. Hoshi, T. Yoshida, Synthesis 44 (2012) 1315–1322.
34.. V. Rajachandrasekhar, B.G. Vineel, S. Venkataiaha, P.K. Dubey, Asian J. Chem. 26 (2014) 5263–5267.
35.. R. Pedrosa, C. Andrés, P. Mendiguchıa, J. Nieto, J. Org. Chem. 71 (2006) 8854–8863.
36.. J. Nieto, C. Andrés, A. Pérez-Encabo, Org. Biomol. Chem. 13 (2015) 9118–9126.
37.. R.K. Pandey, L. Wang, N.J. Wallock, S. Lindeman, W.A. Donaldson, J. Org. Chem. 73 (2008) 7236–7245.
38.. K. Sato, Menggenbateer, T. Kubota, N. Asao, Tetrahedron 64 (2008) 787–796.
39.. L. Wang, W. Qin, X. Tang, W. Dou, W. Liu, Q. Teng, X. Yao, Org. Biomol. Chem. 8 (2010) 3751–3757.
40.. Z.-Q. He, Q. Zhou, L. Wu, Y.-C. Chena, Adv. Synth. Catal. 352 (2010) 1904–1908.
41.. A. Mondiere, R. Peng, R. Remuson, D.J. Aitken, Tetrahedron 64 (2008) 1088–1093.
42.. R. Csutortoki, I. Szatmari, A. Koch, M. Heydenreich, E. Kleinpeter, F. Fulop, Tetrahedron 67 (2011) 8564–8571.
43.. C.S. Theile, L.W. McLaughlin, Chem. Commun. 48 (2012) 5587–5589.
44.. H. Yueh, H. Yu, C.S. Theile, A. Pal, A. Horhota, N. Greco, C.V. Christianson, L.W. McLaughlin, Nucleosides Nucleotides Nucleic Acids 31 (2012) 661–679.
45.. Y. Yoshimura, Y. Yamazaki, K. Wachi, S. Satoh, H. Takahata, Synlett 1 (2007) 0111–0114.
46.. H. Yu, M.K. Schlegel, L.W. McLaughlin, RSC Adv. 4 (2014) 32588–32593.
47.. L.-J. Yang, J.-G. Lo, X.-C. Wang, Heterocycles 94 (2017) 1027–1039.
48.. R.P.T. Kim, V. Bihud, K. Bin Mohamad, K.H. Leong, J. Bin Mohamad, F. Bin Ahmad, H. Hazni, N. Kasim, S.N.A. Halim, K. Awang, Molecules 18 (2013) 128–139.
49.. R.G. Doveston, P. Tosatti, M. Dow, D.J. Foley, H.Y. Li, A.J. Campbell, D. House, I. Churcher, S.P. Marsden, A. Nelson, Org. Biomol. Chem. 13 (2015) 859–865.
50.. H. Du, Y. Dudognon, M.M. Sanchez Duque, S. Goudedranche, D. Bonne, J. Rodriguez, X. Bugaut, T. Constantieux, Synthesis 48 (2016) 3479–3503.
51.. X. Li, K. Zhou, H. He, Q. Zhou, Y. Sun, L. Hou, L. Shen, X. Wang, Y. Zhou, Z. Gong, S. He, H. Jin, Z. Gu, S. Zhao, L. Zhang, C. Sun, S. Zheng, Z. Cheng, Y. Zhu, M. Zhang, J. Li, S. Chen, ACS Med. Chem. Lett. 8 (2017) 969–974.
52.. D. Vina, E. Quezada, L. Santana, E. Uriartea, Tetrahedron 62 (2006) 9949–9952.
53.. R. Csutortoki, I. Szatmari, A. Koch, M. Heydenreich, E. Kleinpeter, F. Fulop, Tetrahedron 68 (2012) 4600–4608.

54.. P. Singh, K. Paul, Indian J. Chem. 45B (2006) 247–251.
55.. S.M. Sondhi, S. Jain, A.D. Dwivedi, R. Shukla, R. Raghubir, Indian J. Chem. 47B (2008) 136–143.
56.. D. Zhou, X. Yu, J. Zhang, W. Wang, H. Xie, Org. Biomol. Chem. 14 (2016) 6193–6196.
57.. J. Guillon, S. Rubio, S. Savrimoutou, F. Halle, S. Moreau, P. Sonnet, M. Marchivie, C. R. Chim. 21 (2018) 987–992.
58.. Y. Liu, A. Mándi, X.-M. Li, L.-H. Meng, T. Kurtán, B.-G. Wang, Mar. Drugs 13 (2015) 3640–3652.
59.. Y. Zhou, A. Debbab, A. Mándi, V. Wray, B. Schulz, W.E.G. Müller, M. Kassack, W. Lin, T. Kurtán, P. Proksch, A.H. Aly, Eur. J. Org. Chem. 2013 (2013) 894–906.
60.. J. Dai, A. Chen, M. Zhu, X. Qi, W. Tang, M. Liu, D. Li, Q. Gu, J. Li, Biochem. Pharmacol. 163 (2019) 404–415.
61.. M. Kajula, J.M. Ward, A. Turpeinen, M.V. Tejesvi, J. Hokkanen, A. Tolonen, H. Häkkänen, P. Picart, J. Ihalainen, H.-G. Sahl, A.M. Pirttilä, S. Mattila, J. Nat. Prod. 79 (2016) 685–690.
62.. A.N. Yurchenko, O.F. Smetanina, E.V. Ivanets, A.I. Kalinovsky, Y.V. Khudyakova, N.N. Kirichuk, R.S. Popov, C. Bokemeyer, G. von Amsberg, E.A. Chingizova, S.S. Afiyatullov, S.A. Dyshlovoy, Mar. Drugs 14 (2016) 122.
63.. R.S. Orfali, A.H. Aly, W. Ebrahim, M.S. Abdel-Aziz, W.E.G. Muller, W. Lin, G. Daletos, P. Proksch, Phytochem. Lett. 11 (2015) 168–172.
64.. H. Yamazaki, O. Takahashi, K. Murakami, M. Namikoshi, Tetrahedron Lett. 56 (2015) 6262–6265.
65.. H. Yamazaki, H. Rotinsulu, R. Narita, R. Takahashi, M. Namikoshi, J. Nat. Prod. 78 (2015) 2319–2321.
66.. M. Zhu, X. Zhang, H. Feng, J. Dai, J. Li, Q. Che, Q. Gu, T. Zhu, D. Li, J. Nat. Prod. 80 (2017) 71–75.
67.. D.J. Foley, R.G. Doveston, I. Churcher, A. Nelson, S.P. Marsden, Chem. Commun. 51 (2015) 11174–11177.
68.. I. Szatmári, P. Barta, G. Tóth, A. Balázs, J. Halász, F. Fülöp, Eur. J. Org. Chem. 2017 (2017) 5537–5545.
69.. Y. Zhu, R.K. de Jesus, H. Tang, S.P. Walsh, J. Jiang, X. Gu, N. Teumelsan, A. Shahripour, B. Pio, F.-X. Ding, S. Ha, B.T. Priest, A.M. Swensen, M. Alonso-Galicia, J.P. Felix, R.M. Brochu, T. Bailey, B. Thomas-Fowlkes, X. Zhou, L.-Y. Pai, C. Hampton, M. Hernandez, K. Owens, J. Ehrhart, S. Roy, G.J. Kaczorowski, L. Yang, E.R. Parmee, K. Sullivan, M.L. Garcia, A. Pasternak, Bioorg. Med. Chem. Lett. 26 (2016) 5695–5702.
70.. C. O'Reilly, C. O'Brien, P.V. Murphy, Tetrahedron Lett. 50 (2009) 4427–4429.
71.. L. Ciofi, M. Morvillo, F. Sladojevich, A. Guarna, A. Trabocchi, Tetrahedron Lett. 51 (2010) 6282–6285.
72.. A. Trabocchi, I. Stefanini, M. Morvillo, L. Ciofi, D. Cavalieri, A. Guarna, Org. Biomol. Chem. 8 (2010) 5552–5557.
73.. D.D. DesMarteau, C. Lu, D. Vanderveer, Tetrahedron Lett. 50 (2009) 3741–3745.
74.. S.D. Markad, P. Kaur, B.K.K. Reddy, M. Chinnapattu, A. Raichurkar, R. Nandishaiah, M. Panda, P.S. Iyer, Med. Chem. Res. 24 (2015) 2986–2992.
75.. J.-H. Son, J.S. Zhu, P.-W. Phuan, O. Cil, A.P. Teuthorn, C.K. Ku, S. Lee, A.S. Verkman, M.J. Kurth, J. Med. Chem. 60 (2017) 2401–2410.
76.. G. Yoon, H.J. Jeong, J.J. Kim, S.H. Cheon, Arch. Pharm. Res. 31 (2008) 989–994.
77.. F. Lv, C. Chen, Y. Tang, J. Wei, T. Zhu, W. Hu, Bioorg. Med. Chem. Lett. 26 (2016) 3714–3718.
78.. D. Mamaril-Fishman, J. Zhu, M. Lin, C. Felgate, L. Jones, P. Stump, E. Pierre, C. Bowen, O. Naderer, E. Dumont, P. Patel, P.D. Gorycki, B. Wen, L. Chen, Y. Deng, Drug Metab. Dispos. 42 (2014) 1314–1325.
79.. F. Peyrusson, D. Butler, P.M. Tulkens, F. Van Bambeke, Antimicrob. Agents Chemother. 59 (2015) 5747–5760.
80.. A. Ibanez-Escribano, F. Reviriego, J.J. Nogal-Ruiz, A. Meneses-Marcel, A. Gomez-Barrio, J.A. Escario, V.J. Aran, Eur. J. Med. Chem. 94 (2015) 276–283.
81.. V. Rajachandrasekhar, C. Hariprasad, V. Venugopala Rao, S. Venkataiah, P.K. Dubey, Asian J. Chem. 26 (2014) 3161–3165.
82.. A. La Venia, B. Dolenský, V. Krchňák, ACS Comb. Sci. 15 (2013) 162–167.
83.. A. La Venia, B. Lermova, V. Krchňák, ACS Comb. Sci. 15 (2013) 59–72.
84.. V. Giménez-Navarro, V. Krchňák, Molecules 23 (2018) 1090.
85.. I.A.M. Asiri, J.M. Badr, D.T.A. Youssef, Phytochem. Lett. 13 (2015) 53–58.
86.. T. Mizuhara, S. Inuki, S. Oishi, N. Fujii, H. Ohno, Chem. Commun. 2009 (2009) 3413–3415.
87.. T. Mizuhara, S. Oishi, H. Ohno, K. Shimura, M. Matsuoka, N. Fujii, Org. Biomol. Chem. 10 (2012) 6792–6802.
88.. S. Okazaki, S. Oishi, T. Mizuhara, K. Shimura, H. Murayama, H. Ohno, M. Matsuoka, N. Fujii, Org. Biomol. Chem. 13 (2015) 4706–4713.
89.. P.K. Gupta, N. Yadav, S. Jaiswal, M. Asad, R. Kant, K. Hajela, Chem. A Eur. J. 21 (2015) 13210–13215.
90.. M. von Wantoch Rekowski, A. Pyriochou, N. Papapetropoulos, A. Stößel, A. Papapetropoulos, A. Giannis, Bioorg. Med. Chem. 18 (2010) 1288–1296.
91.. E. Abele, J. Popelis, Y. Višnevska, Chem. Heterocycl. Compd. 48 (2012) 1119–1121.
92.. A. Dieckmann, M.T. Richers, A.Y. Platonova, C. Zhang, D. Seidel, K.N. Houk, J. Org. Chem. 78 (2013) 4132–4144.
93.. B.N. Naidua, M.A. Walker, M.E. Sorenson, Y. Ueda, J.D. Matiskella, T.P. Connolly, I.B. Dicker, Z. Lin, S. Bollini, B.J. Terry, H. Higley, M. Zheng, D.D. Parker, D. Wu, S. Adams, M.R. Krystal, N.A. Meanwell, Bioorg. Med. Chem. Lett. 28 (2018) 2124–2130.
94.. N.T. Patil, A.K. Mutyala, P.G.V.V. Lakshmi, B. Gajula, B. Sridhar, G.R. Pottireddygari, T.P. Rao, J. Org. Chem. 75 (2010) 5963–5975.
95.. N. Takemura, Y. Kuninobu, M. Kanai, Org. Biomol. Chem. 12 (2014) 2528–2532.
96.. A.F. Stepan, M.M. Claffey, M.R. Reese, G. Balan, G. Barreiro, J. Barricklow, M.J. Bohanon, B.P. Boscoe, G.D. Cappon, L.K. Chenard, J. Cianfrogna, L. Chen, K.J. Coffman, S.E. Drozda, J.R. Dunetz, S. Ghosh, X. Hou, C. Houle, K. Karki, J.T. Lazzaro, J.Y. Mancuso, J.M. Marcek, E.L. Miller, M.A. Moen, S. O'Neil, I. Sakurada, M. Skaddan, V. Parikh, D.L. Smith, P. Trapa, J.B. Tuttle, P.R. Verhoest, D.P. Walker, A. Won, A.S. Wright, J. Whritenour, K. Zasadny, M.M. Zaleska, L. Zhang, C.L. Shaffer, J. Med. Chem. 60 (2017) 7764–7780.
97.. M. Teleb, O.H. Rizk, F.-X. Zhang, F.R. Fronczek, G.W. Zamponi, H. Fahmye, Bioorg. Chem. 83 (2019) 354–366.
98.. R. Baharfar, S.M. Baghbanian, J. Heterocyclic Chem. 49 (2012) 310–314.
99.. M.I. El-Zahar, S.S. Abd El-Karim, M.E. Haiba, M.A. Khedr, Acta Pol. Pharm. 68 (2011) 357–373.
100.. N.M. Khalifa, A.S. El-Sayed, S.S. Abd El-Karim, E.S. Hassan, E.S. Nossier, A.G. Shalaby, Russ. J. Gen. Chem. 88 (2018) 2646–2652.
101.. C. Mulet, M. Escolano, S. Llopis, S. Sanz, C.R. de Arellano, M. Sánchez-Roselló, S. Fustero, C. del Pozo, Adv. Synth. Catal. 360 (2018) 2885–2893.
102.. D. Kröger, T. Schlüter, M. Fischer, I. Geibel, J. Martens, ACS Comb. Sci. 17 (2015) 202–207.
103.. C.L. Jarvis, M.T. Richers, M. Breugst, K.N. Houk, D. Seidel, Org. Lett. 16 (2014) 3556–3559.
104.. V. Palani, J. Chen, T.R. Hoye, Org. Lett. 18 (2016) 6312–6315.
105.. M.C. Bagley, T.D. Davis, M.C. Dix, V. Fusillo, M. Pigeaux, M.J. Rokicki, D.J. Kipling, Org. Chem. 74 (21) (2009) 8336–8342.
106.. M.C. Bagley, T.D. Davis, M.C. Dix, V. Fusillo, M. Pigeaux, M.J. Rokicki, D.J. Kipling, Future Med. Chem. 2 (9) (2010) 1417–1427.
107.. J.P. Duffy, E.M. Harrington, F.G. Salituro, J.E. Cochran, J. Green, H. Gao, G.W. Bemis, G. Evindar, V.P. Galullo, P.J. Ford, U.A. Germann, K.P. Wilson, S.F. Bellon, G. Chen, P. Taslimi, P. Jones, C. Huang, S. Pazhanisamy, Y.-M. Wang, M.A. Murcko, M.S.S. Su, ACS Med. Chem. Lett. 2 (2011) 758–763.
108.. A.M. Bello, M.K. Purohit, T.G. Yang Cui, S.B. Stead, L.P. Kotra, Anti-Inflammatory Anti-Allergy Agents Med. Chem. 10 (2011) 121–131.

109. T.A. Alanine, W.R.J.D. Galloway, S. Bartlett, J.J. Ciardiello, T.M. McGuireb, D.R. Spring, Org. Biomol. Chem. 14 (2016) 1031–1038.
110. M.A.I. Salem, M.E. Azab, I.S.A. Mabrouk, Int. J. Sci. Eng. Res. 5 (5) (2014) 1137–1150.
111. N.T. Patil, P.G.V.V. Lakshmi, B. Sridhar, S. Patra, M.P. Bhadra, C.R. Patra, Eur. J. Org. Chem. (2012) 1790–1799.
112. A.N.F. El-Ghaffar, M.K. Mohamed, M.S. Kadah, A.M. Radwan, G.H. Sayed, S.N. Abd Elal, J. Chem. Pharm. Res. 3 (3) (2011) 248–259.
113. A. Mohammad, Asian J. Chem. Pharm. Sci. 1 (1) (2016) 41–52.
114. A.N.F. El-Ghaffar, M.S. Kadah, G.H. Sayed, A.M. Radwan, S.N. Abd Elal, J. Chem. Pharm. Res. 4 (10) (2012) 4562–4569.
115. M.A.A. El-Hashash, A.Y. Soliman, I.E. El-Shamy, Turk. J. Chem. 36 (2012) 347–366.
116. S. Guo, J. Zhai, X. Fan, Org. Biomol. Chem. 15 (2017) 1521–1529.
117. L.A. Shemchuk, V.P. Chernykh, O.S. Krys'kiv, Russ. J. Org. Chem. 44 (7) (2008) 1006–1008.
118. A. Deeb, F. El-Mariah, H.K. Abd El-Mawgoud, Eur. J. Chem. 6 (2) (2015) 211–218.
119. A. Deeb, F. El-Mariah, H.K. Abd El-Mawgoud, Eur. J. Chem. 6 (2) (2015) 204–210.
120. B.L. Bourdonnec, L.K. Leister, Curr. Med. Chem. 16 (2009) 3093–3121.
121. M.V. Vovk, O.V. Kushnir, N.V. Mel'nichenko, I.F. Tsymbal, Chem. Heterocycl. Compd. 47 (8) (2011) 989–995.
122. K.S. Shikhaliev, A.S. Shestakov, S.M. Medvedeva, N.V. Gusakova, Russ. Chem. Bull. Int. Ed. 57 (1) (2008) 170–176.
123. N. Kaur, Synth. Commun. 45 (2015) 1599–1631.
124. N. Kaur, Synth. Commun. 45 (2015) 300–330.
125. A. Alizadeh, J. Mokhtari, M. Ahmadi, Tetrahedron 68 (2012) 319–322.
126. A.A. Abu-Hashem, M.M. Youssef, Molecules 16 (2011) 1956–1972.
127. M. Limbach, A. Lygin, M. Es-Sayed, A. Meijere, Eur. J. Org. Chem. (2009) 1357–1364.
128. M. Limbach, V.S. Korotkov, M. Es-Sayed, A. Meijere, Org. Biomol. Chem. 6 (2008) 3816–3822.
129. A.A. Kalinin, V.A. Mamedov, Chem. Heterocycl. Compd. 50 (2) (2014) 195–203.
130. X. Zhang, G. Song, H. Cui, Z. Xu, J. Zhu, Z. Chen, Sci. China Chem. 58 (7) (2015) 1239–1242.
131. K. Samanta, G. Panda, Org. Biomol. Chem. 8 (2010) 2823–2828.
132. Shagufta, I. Ahmad, G. Panda, Eur. J. Med. Chem. 133 (2017) 139–151.
133. N. Joshi, G. Anju, Int. J. Pharm. Erud. 1 (2) (2011) 1–9.
134. L. He, H. Li, J. Chen, X.-F. Wu, RSC Adv. 4 (2014) 12065–12077.
135. C. Avendano, E. Cuesta, Curr. Org. Synth. 6 (2009) 143–168.
136. M. Demeunynck, I. Baussanne, Curr. Med. Chem. 20 (2013) 794–814.
137. D.A. Patil, P.O. Patil, G.B. Patil, S.J. Surana, Mini Rev. Med. Chem. 11 (2011) 633–641.
138. D.I.S.P. Resende, P. Boonpothong, E. Sousa, A. Kijjoa, M.M.M. Pinto, Nat. Prod. Rep. 36 (2019) 7–34.
139. U.A. Kshirsagar, Org. Biomol. Chem. 13 (2015) 9336–9352.
140. M. Žugelj, A. Albreht, U. Uršič, J. Svete, B. Stanovnik, ARKIVOC 6 (2009) 137–145.
141. M.-C. Tseng, Y.-H. Chu, Tetrahedron 64 (2008) 9515–9520.
142. M.-C. Tseng, H.-Y. Yang, Y.-H. Chu, Org. Biomol. Chem. 8 (2010) 419–427.
143. R.G. Doveston, R.J.K. Taylor, Tetrahedron Lett. 53 (2012) 2533–2536.
144. D.D. Vachhani, V.P. Mehta, S.G. Modha, K.V. Hecke, L.V. Meervelt, E.V. Van der Eycken, Adv. Synth. Catal. 354 (8) (2012) 1593–1599.
145. B.D. Ames, X. Liu, C.T. Walsh, Biochemistry 49 (2010) 8564–8576.
146. X. Gao, Y.-H. Chooi, B.D. Ames, P. Wang, C.T. Walsh, Y.J. Tang, Am. Chem. Soc. 133 (2011) 2729–2741.
147. J. Zhang, N. Haider, ARKIVOC 3 (2016) 125–133.
148. P. Raubo, N. Ladwa, Synlett 23 (2012) 2935–2938.
149. A. Piergentili, F. Del Bello, F. Gentili, M. Giannella, W. Quaglia, C. Vesprini, R.J. Thomas, G.M. Robertson, Tetrahedron 63 (2007) 12912–12916.
150. R. Pratap, S.P. Kushwaha, A. Goel, V.J. Ram, Tetrahedron Lett. 48 (2007) 549–553.
151. P. Pace, M.E. Di Francesco, C. Gardelli, S. Harper, E. Muraglia, E. Nizi, F. Orvieto, A. Petrocchi, M. Poma, M. Rowley, R. Scarpelli, R. Laufer, O. Gonzalez Paz, E. Monteagudo, F. Bonelli, D. Hazuda, K.A. Stillmock, V. Summa, J. Med. Chem. 50 (2007) 2225–2239.
152. A. Petrocchi, F. Jones, M. Rowley, F. Fiore, V. Summa, Bioorg. Med. Chem. Lett. 19 (2009) 4245–4249.
153. B.J. Min, X. Gu, T. Yamamoto, R.R. Petrov, H. Qu, Y.S. Lee, V.J. Hruby, Tetrahedron Lett. 49 (2008) 2316–2319.
154. M. Adib, M.H. Sayahi, H. Ziyadi, H.R. Bijanzadeh, L.-G. Zhu, Tetrahedron 63 (2007) 11135–11140.
155. W. Argyrakis, C. Koppl, H.-J. Werner, W. Frey, A. Baro, S. Laschat, J. Phys. Org. Chem. 24 (2011) 682–692.
156. B.S.F. Rodriguesa, B.D.B. Sahm, P.C. Jimenez, F.C.L. Pinto, J. Mafezoli, M.C. Mattos, E. Rodrigues-Filho, L.H. Pfenning, L.M. Abreu, L.V. Costa-Lotufo, M.C.F. Oliveira, Chem. Biodivers. 12 (2015) 432–442.
157. S. Long, D.I.S.P. Resende, A. Kijjoa, A.M.S. Silva, A. Pina, T. Fernández-Marcelo, M.H. Vasconcelos, E. Sousa, M.M.M. Pinto, Mar. Drugs 16 (2018) 261–278.
158. O.I. Zhuravleva, S.S. Afiyatullov, V.A. Denisenko, S.P. Ermakova, N.N. Slinkina, P.S. Dmitrenok, N.Y. Kim, Phytochemistry 80 (2012) 123–131.
159. Z. Cheng, D. Liu, W. Cheng, P. Prokschc, W. Lin, RSC Adv. 8 (2018) 31427–31439.
160. J. Liu, X. Wei, E.L. Kim, X. Lin, X.-W. Yang, X. Zhou, B. Yang, J.H. Jung, Y. Liu, Tetrahedron 71 (2) (2015) 271–275.
161. L.-H. Huang, M.-Y. Xu, H.-J. Li, J.-Q. Li, Y.-X. Chen, W.-Z. Ma, Y.-P. Li, J. Xu, D.-P. Yang, W.-J. Lan, Org. Lett. 19 (2017) 4888–4891.
162. N. Gruber, L.L. Piehl, E.R. Celis, J.E. Dıaz, M.B. Garcıa, P. Stipa, L.R. Orelli, RSC Adv. 5 (2015) 2724–2731.
163. P. Cledera, M. Villacampa, C. Avendano, J.C. Menendez, ARKIVOC 3 (2011) 72–98.
164. R.V. Patel, Y.-S. Keum, S.W. Park, Eur. J. Med. Chem. 97 (2015) 649–663.
165. M. Gullu, A. Dincsonmez, O. Ozyavas, Eur. J. Org. Chem. (2010) 2113–2120.
166. S. Grosjean, S. Triki, J.-C. Meslin, K. Julienne, D. Deniaud, Tetrahedron 66 (2010) 9912–9924.
167. M.A. Ibrahim, M.A.-M. Abdel-Hamed, N.M. El-Gohary, J. Braz. Chem. Soc. 22 (6) (2011) 1130–1139.
168. I.S. Kim, N.K. Mishra, M. Choi, H. Jo, Y. Oh, S. Sharma, S.H. Han, T. Jeong, S. Han, S. Lee, Chem. Commun. 51 (2015) 17229–17232.
169. S. Nag, A. Mishra, S. Batra, Tetrahedron 64 (2008) 10162–10171.
170. V.N. Murthy, S.P. Nikumbh, S.P. Kumar, L.V. Rao, A. Raghunadh, Tetrahedron Lett. 56 (2015) 5767–5770.
171. E. Abdelghani, S. Aly Said, M.G. Assy, A.M. Abdel Hamid, Arab. J. Chem. 10 (2017) 2926–2933.

172. B. Pasquier, Y. El-Ahmad, B. Filoche-Romme, C. Dureuil-Sizaire, F. Fassy, P.-Y. Abecassis, M. Mathieu, T. Bertrand, T. Benard, C. Barriere, S. El Batti, J.-P. Letallec, V. Sonnefraud, M. Brollo, L. Delbarre, V. Loyau, F. Pilorge, L. Bertin, P. Richepin, J. Arigon, J.-R. Labrosse, J. Clement, F. Durand, R. Combet, P. Perraut, V. Leroy, F. Gay, D. Lefrançois, F. Bretin, J.-P. Marquette, N. Michot, A. Caron, C. Castell, L. Schio, G. McCort, H. Goulaouic, C. Garcia-Echeverria, B.P. Ronan, J. Med. Chem. 58 (1) (2015) 376–400.
173. K.N. Venugopala, S.K. Nayak, R.M. Gleiser, M.E. Sanchez-Borzone, D.A. Garcia, B. Odhav, Chem. Biol. Drug Des. 88 (2016) 88–96.
174. X. Yang, M. Wu, S. Sun, C. Huan, H. Guo, J. Wan, J. Lee, Y. Xing, Mol. Divers. 20 (2) (2016) 551–556.
175. P. Yin, N. Liu, Y.X. Deng, Y. Chen, Y. Deng, L. He, J. Org. Chem. 77 (2012) 2649–2658.
176. D. Yuan, H.-H. Kong, M.-W. Ding, Tetrahedron 71 (2015) 419–423.
177. M.S. Mohamed, S.M. Awad, N.M. Ahmed, J. Appl. Pharm. Sci. 1 (5) (2011) 76–80.
178. F.H. Darras, B. Kling, E. Sawatzky, J. Heilmann, M. Decker, Bioorg. Med. Chem. 22 (2014) 5020–5034.
179. A.K. Pala, P.K. Mandalia, D.-K. Chand, G.S. Hanan, Synlett 26 (2015) 1408–1412.
180. M.S. Khalaf, M.P. Coles, P.B. Hitchcock, Dalton Trans. (2008) 4288–4295.
181. J.I. Martínez-Araya, J. Math. Chem. 53 (2015) 451–465.
182. M.P. Coles, M.S. Khalaf, R.M. Claramunt, M.A. Garcia, I. Alkortac, J. Elguero, J. Phys. Org. Chem. 23 (2010) 526–535.
183. O. Ciobanu, F. Allouti, P. Roquette, S. Leingang, M. Enders, H. Wadepohl, H.-J. Himmel, Eur. J. Inorg. Chem. (2008) 5482–5493.
184. N. Schulenberg, O. Ciobanu, E. Kaifer, H. Wadepohl, H.-J. Himmel, Eur. J. Inorg. Chem. (2010) 5201–5210.
185. O. Ciobanu, A. Fuchs, M. Reinmuth, A. Lebkücher, E. Kaifer, H. Wadepohl, H.-J.Z. Himmel, Anorg. Allg. Chem. 636 (2010) 543–550.
186. M.P. Coles, P.B. Hitchcock, Aust. J. Chem. 66 (2013) 1124–1130.
187. K. Zelga, M. Leszczynski, I. Justyniak, A. Kornowicz, M. Cabaj, A.E.H. Wheatley, J. Lewinski, Dalton Trans. 41 (2012) 5934–5938.
188. B.M. Day, M.P. Coles, P.B. Hitchcock, Eur. J. Inorg. Chem. (2012) 841–846.
189. A.A. Mohamed, H.E. Abdou, H.P. Fackler Jr., Coord. Chem. Rev. 254 (2010) 1253–1259.
190. A.A. Mohamed, H.E. Abdou, H.P. Fackler Jr., J. Clust. Sci. 19 (2008) 551–559.
191. W.J. Evans, E. Montalvo, D.J. Dixon, J.W. Ziller, A.G. DiPasquale, A.L. Rheingold, Inorg. Chem. 47 (2008) 11376–11381.
192. W.J. Evans, E. Montalvo, J.W. Ziller, A.G. DiPasquale, A.L. Rheingold, Inorg. Chem. 49 (2010) 222–228.
193. E. Montalvo, J.W. Ziller, A.G. DiPasquale, A.L. Rheingold, W.J. Evans, Organometallics 29 (2010) 2104–2110.
194. U. Wild, P. Roquette, E. Kaifer, J. Mautz, O. Hubner, H. Wadepohl, H.-J. Himmel, Eur. J. Inorg. Chem. (2008) 1248–1257.
195. F.H. Darras, B. Kling, J. Heilmann, M. Decker, ACS Med. Chem. Lett. 3 (11) (2012) 914–919.
196. S.S. Chaudhaery, K.K. Roy, N. Shakya, G. Saxena, S.R. Sammi, A. Nazir, C. Nath, A.K. Saxena, J. Med. Chem. 53 (17) (2010) 6490–6505.
197. W. Luo, Q.-S. Yu, S.S. Kulkarni, D.A. Parrish, H.W. Holloway, D. Tweedie, A. Shafferman, D.K. Lahiri, A. Brossi, N.H. Greig, J. Med. Chem. 49 (7) (2006) 2174–2185.
198. G.J. Chuang, W. Wang, E. Lee, T. Ritter, J. Am. Chem. Soc. 133 (2011) 1760–1762.
199. I. Hermecz, L. Vasvári-Debreczy, in: A.R. Katrizky, C.W. Rees, E.F.V. Scriven (Eds.), Comprehensive Heterocyclic Chemistry III, Vol. 12, Pergamon, Oxford, 2008, pp. 257–320.
200. M. Dracinsky, R. Pohl, L. Slavetinska, J. Janku, M. Budesinsky, Tetrahedron Asymmetry 22 (2011) 356–366.
201. A. Kleinschek, C. Meyners, E. Digiorgio, C. Brancolini, F.-J. Meyer-Almes, ChemMedChem 11 (2016) 2598–2606.
202. T. Mizuhara, S. Oishi, N. Fujii, H. Ohno, J. Org. Chem. 75 (2010) 265–268.
203. S. Okazaki, T. Mizuhara, K. Shimura, H. Murayama, H. Ohno, S. Oishi, M. Matsuoka, N. Fujii, Bioorg. Med. Chem. 23 (2015) 1447–1452.
204. T. Stalling, J. Pauly, D. Kroger, J. Martens, Tetrahedron 71 (2015) 8290–8301.
205. M.R. Birck, T.P. Holler, R.W. Woodard, J. Am. Chem. Soc. 122 (2000) 9334–9335.
206. A. Golebiowski, S.R. Klopfenstein, D.E. Portlock, Curr. Opin. Chem. Biol. 5 (2001) 273–284.
207. C. Sansom, Drug Discov. Today 6 (2001) 499–500.
208. T. Mizuhara, S. Oishi, H. Ohno, K. Shimura, M. Matsuoka, N. Fujii, Bioorg. Med. Chem. 20 (2012) 6434–6441.
209. T. Mizuhara, S. Oishi, H. Ohno, K. Shimura, M. Matsuoka, N. Fujii, Bioorg. Med. Chem. 21 (2013) 2079–2087.
210. Y.T. Ghebremariam, D.A. Erlanson, J.P. Cooke, J. Pharmacol. Exp. Ther. 348 (2014) 69–76.
211. R.C. Bernotas, R.J. Dooley, Tetrahedron 66 (2010) 2273–2276.
212. D. Sakamaki, D. Kumano, E. Yashima, S. Seki, Chem. Commun. 51 (2015) 17237–17240.
213. S.-R. Liao, Y. Tang, L. Xu, X.-F. Zhou, J.-F. Wang, B. Yang, Y.-H. Liu, Tetrahedron 73 (2017) 98–107.
214. M. Baumann, L.M. Nome, Z.G. Zachariassen, S. Karlshoj, T. Fossen, M.M. Rosenkilde, J. Vabeno, B.E. Haug, Tetrahedron 73 (2017) 3866–3877.
215. Z.G. Zachariassen, S. Thiele, E.A. Berg, P. Rasmussen, T. Fossen, M.M. Rosenkilde, J. Vabeno, B.E. Haug, Bioorg. Med. Chem. 22 (2014) 4759–4769.
216. M. Baumann, M.M. Hussain, N. Henne, D.M. Garrote, S. Karlshoj, T. Fossen, M.M. Rosenkilde, J. Vabeno, B.E. Haug, Bioorg. Med. Chem. 25 (2017) 646–657.
217. S.P. Vartale, S.B. Sirsat, N.K. Halikar, Heterocycl. Commun. 19 (3) (2013) 215–218.
218. M. Teleba, O.H. Rizk, F.-X. Zhang, F.R. Fronczeke, G.W. Zamponid, H. Fahmy, Bioorg. Chem. 88 (2019) 102915–102924.
219. S.F. Mohamed, E.M. Flefel, A.E.G.E. Amr, D.N.A. El-Shafy, Eur. J. Med. Chem. 45 (2010) 1494–1501.
220. M.R. Mahmoud, M.M. El-Shahaw, Phosphorus Sulfur Silicon Relat. Elem. 183 (2008) 3097–3108.
221. N.F.H. Mahmoud, E.A. Ghareeb, J. Heterocyclic Chem. 56 (2019) 81–91.
222. Y. Wang, W. Xu, H. Shao, Y. Xie, J. Wang, Chin. J. Chem. 29 (2011) 2039–2048.
223. S. Wu, X. Lei, E. Fan, Z. Sun, Org. Lett. 20 (2018) 522–525.
224. V.R. Virsodia, N.R. Vekariya, A.T. Manvar, R.C. Khunt, B.R. Marvania, B.S. Savalia, A.K. Shah, Phosphorus Sulfur Silicon Relat. Elem. 184 (2009) 34–44.
225. H. Serrar, S. Boukhris, A. Hassikou, A. Souizi, J. Heterocyclic Chem. 52 (2014) 1269–1272.
226. K. Yadollahzadeh, J. Azizian, H. Sanaeishoar, Phosphorus Sulfur Silicon Relat. Elem. 190 (2015) 2023–2030.
227. S. Mundra, V. Thakur, A.M. Bello, S. Rathore, M. Asad, L. Wei, J. Yang, S.K. Chakka, R. Mahesh, P. Malhotra, A. Mohmmed, L.P. Kotra, Bioorg. Med. Chem. 25 (2017) 5662–5677.
228. T.V. Frolova, D.G. Kim, P.A. Slepukhin, K.Y. Osheko, Russ. Chem. Bull. Int. Ed. 66 (4) (2017) 690–693.
229. C. Kim, H. Choi, S. Paek, J.-J. Kim, K. Song, M.-S. Kang, J. Ko, J. Photochem. Photobiol., A 225 (2011) 17–25.
230. G. Lamanna, C. Faggi, F. Gasparrini, A. Ciogli, C. Villani, P.J. Stephens, F.J. Devlin, S. Menichetti, Chem. A Eur. J. 14 (2008) 5747–5750.

231. S. Menichetti, C. Faggi, M. Onori, S. Piantini, M. Ferreira, S. Rocchi, V. Lupi, I. Marin, M. Maggini, C. Viglianisi, Eur. J. Org. Chem. 2019 (2019) 168–175.
232. J. Tang, D. Xie, H.-Y. Yin, J. Jing, J.-L. Zhang, Org. Biomol. Chem. 14 (2016) 3360–3368.
233. S. Menichetti, S. Cecchi, P. Procacci, M. Innocenti, L. Becucci, L. Franco, C. Viglianisi, Chem. Commun. 51 (2015) 11452–11454.
234. B.D. Gliemann, A.G. Petrovic, E.M. Zolnhofer, P.O. Dral, F. Hampel, G. Breitenbruch, P. Schulze, V. Raghavan, K. Meyer, P.L. Polavarapu, N. Berova, M. Kivala, Chem. Asian J. 12 (2017) 31–35.
235. T. Xu, C. Yan, Y. Wu, C. Yuan, X. Shao, Dyes Pigments 168 (2019) 235–247.
236. Y. Wu, C. Yan, D. Li, C. Yuan, J. Sun, S. Zhou, H.-L. Zhang, X. Shao, Chem. Asian J. 14 (2019) 1860–1869.