Bicyclic 6-6 Systems With One Bridgehead Nitrogen Atom: One Extra Heteroatom 1:0☆

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

Abbreviations

1GrCat	Grubb's first-generation catalysts
2GrCat	Grubb's second-generation catalysts
5-FU	5-Flurouracil
AcChl	Acryloyl chloride
ADC	Acetylenedicaboxylate
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BHA	Baylis Hillman acetate
CAE	Cyanoacetic ester
CDI	Carbonyldiimidazole
DAP	2,6-Diaminopyridine
DGl	Diglyme
DHPM	3,4-Dihydropyrimidin-2(1*H*)-one
DMAD	Dimethyl acetylenedicarboxylate
DOX	Doxorubicin
EG	Ethylene glycol
FA-AC	Fluorine-activated acetylenecarboxylate
IBX	2-Iodoxybenzoic acid
MBH bromides	Morita–Baylis–Hillman bromides
MCR	Multicomponent reaction
MWI	Microwave irradiation
NDesML	*N*-desmethyl levofloxacin
NICS	Nucleus independent chemical shift
NOS inhibitors	Nitric oxide synthases inhibitors
OflP	Ofloxacin precursor

☆*Change History*: March 2020. MV Slivka made changes to the text and references.

OMS-2	Manganese oxide octahedral molecular sieves
PPA	Polyphosphoric acid
PS-NEt$_2$	Diethylaminomethyl polystyrene
PSTPP	Polystyryl triphenylphosphine
PTC	Phase transfer catalysis
PTSA	*p*-Toluenesulfonic acid
RCM reactions	Ring-closing metathesis reactions
TEMED	Tetramethylethylenediamine
TFMCPs	Trifluoromethylcyanovinyl phosphonates
THIQs	Tetrahydroisoquinolines
TMSCl	Chlorotrimethylsilane

1 Introduction

This chapter covers bicyclic 6-6 ring systems with one bridgehead nitrogen atom and one extra heteroatom, and their benzo-fused derivatives. It reviews the literature from 2007 to early 2019. This review is the continuation of the previous III edition of CHEC[1] covering the literature up to 2006. The contour structures for the fused bicyclic systems are shown in Table 1. The condensed heterocycles discussed in this chapter are grouped in four sections:

Section 2: Systems **1-4** with extra *O* atom, 1:0 and their benzo analogs.
Section 3: Systems **5-7** with extra *S* atom, 1:0 and their benzo analogs.
Section 4: Systems **8-11** with extra *N* atom, 1:0 and their benzo analogs.
Section 5: Systems **12** and **13** with extra *B* and *Se* atoms, 1:0 and their benzo analogs.
No system with heteroatoms different from above has been reported in the reviewed period.

The synthesis, reactivity, structural features, application and important compounds are discussed within each section. Compounds given in patents without chemical properties or synthesis are not described in this review.

Table 1 Contour structures of bicyclic 6-6 *N*-bridgehead systems with one extra heteroatom 1:0.

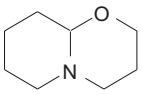
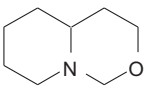
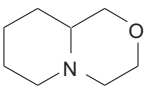
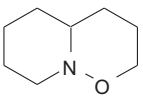
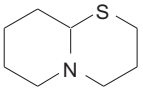
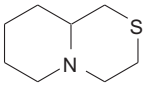
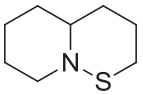
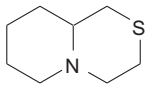
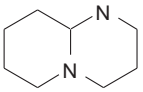
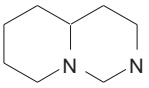
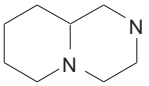
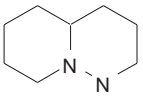
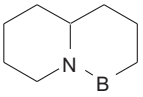
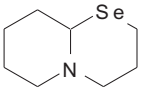
Fused system number	*Ring system*	*Name of basic structure*
Section 2		
Pyridooxazines 1-4		
1		Pyrido[2,1-*b*][1,3]oxazine
2		Pyrido[1,2-*c*][1,3]oxazine
3		Pyrido[2,1-*c*][1,4]oxazine
4		Pyrido[1,2-*b*][1,2]oxazine
Section 3		
Pyridothiazines 5-7		
5		Pyrido[2,1-*b*][1,3]thiazine
6		Pyrido[2,1-*c*][1,4]thiazine

Table 1 (Continued)

Fused system number	*Ring system*	*Name of basic structure*
7		Pyrido[1,2-*b*][1,2]thiazine
Section 4 Pyridodiazines 8-11		
8		Pyrido[1,2-*a*]pyrimidine
9		Pyrido[1,2-*c*]pyrimidine
10		Pyrido[1,2-*a*]pyrazine
11		Pyrido[1,2-*b*]pyridazine
Section 5 Pyridoazaborine 12 and pyridoselenazines 13		
12		Pyrido[2,1-*f*][2,1]azaborine
13		Pyrido[2,1-*b*][1,3]selenazine

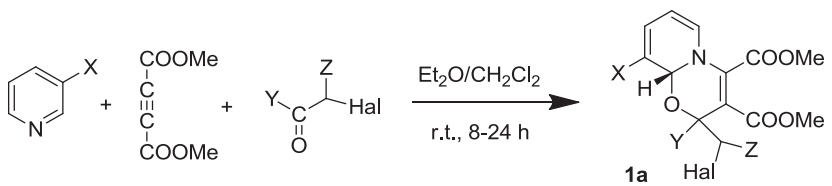
The benzo-fused derivatives (not shown) are also discussed in this review.

2 Pyrido[2,1-*b*][1,3]oxazines 1, pyrido[1,2-*c*][1,3]oxazines 2, pyrido[2,1-*c*][1,4]oxazines 3, pyrido[1,2-*b*][1,2]oxazines 4 and their benzo analogs

2.1 Synthesis

Fused pyridooxazines with a bridgehead nitrogen-atom have both natural and synthetic origins; the key synthetic approaches were reviewed by Hermecz in 2008[1] and 2011.[2]

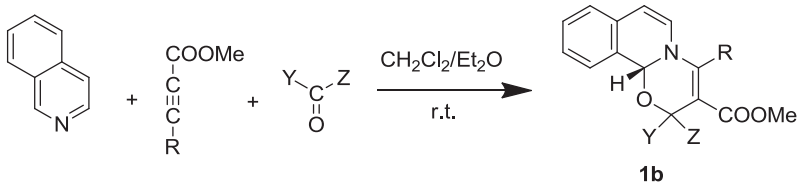
The effective three-component reaction of a 3-substituted pyridine, dimethyl acetylenedicarboxylate (DMAD), and a haloketone was described by Asghari[3] for the regioselective and stereoselective synthesis of pyrido[2,1-*b*][1,3]oxazine system **1** (diester **1a**) in high yield under mild conditions. All individual reactions selectively furnished the pyrido[2,1-*b*][1,3]oxazine derivatives without formation of any isomeric indolizine products (Eq. 1). The scope and limitations of this approach were analyzed. The simplicity of the described procedure makes it an interesting alternative to other approaches.



(1)

X = H, Me, Hal; Y = Me, CH_2Cl, Ar; Z = H, Cl.

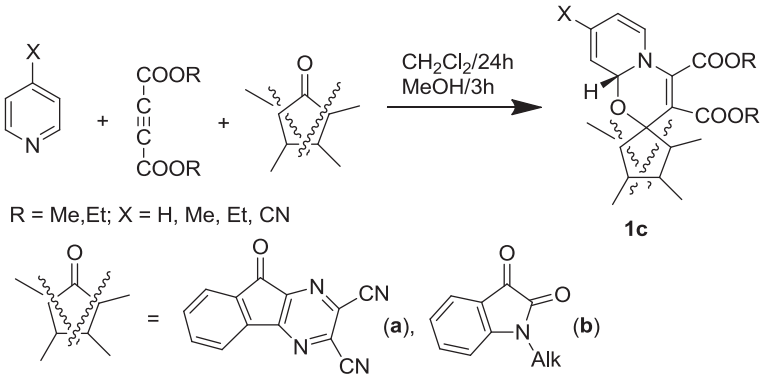
A similar route is also applicable as a convenient approach to corresponding benzo analogs – [1,3]oxazino[2,3-*a*]isoquinoline derivatives **1b** (Eq. 2).[4]



1b (2)

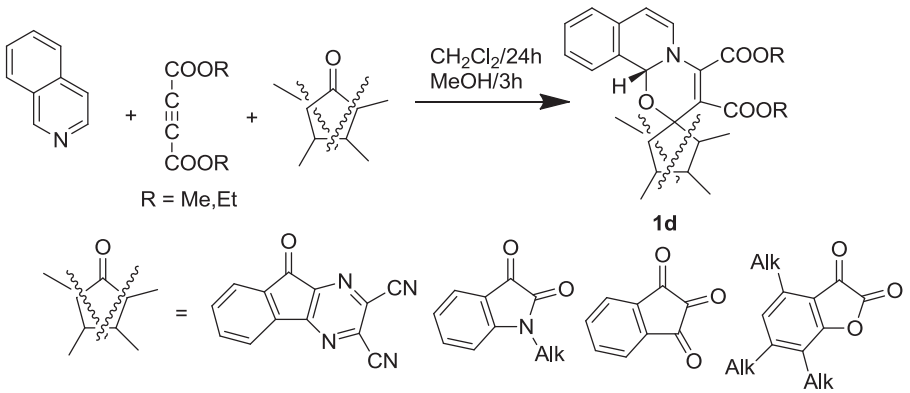
R = COOMe, C_2F_5; Y = Me, CH_2Cl, Ar; Z = H, CH_2Cl, $CHCl_2$, $CHCl\text{-}CH_3$, CF_3, CN.

Short reaction times, good to excellent yields, mild reaction conditions, and the simplicity of the procedure, based on one-pot three-component reaction of isoquinoline and dimethyl acetylenedicarboxylate in the presence of α-chloro and α-bromo ketone derivatives, make it an interesting alternative to complex multistep approaches.[4] It has also been shown that many activated ketones[5,6] and aldehydes can also be used as starting carbonyl components for the reaction with fluorine-activated acetylenecarboxylate (FA-AC)[7] (Eq. 2). The synthesis described above starting with pyridine derivatives, DMAD (or analogs) and activated carbonyl compounds is a powerful means of creating not only different fused pyrido[1,3]oxazines and corresponding benzo analogs, but also their policondensed and spiro derivatives. The use of cyclic ketones (like 9-oxo-9*H*-indeno[1,2-*b*]pyrazine-2,3-dicarbonitrile and *N*-alkylisatins), acetylenedicaboxylates (ADC) and 4-substituted pyridines as starting materials allows to synthesize in good yields the spiroderivatives of fused pyrido[2,1-*b*][1,3]oxazines **1c** by stirring the reaction mixture for 3 h in MeOH[8] or for 24 h in CH_2Cl_2[9] (Eq. 3).



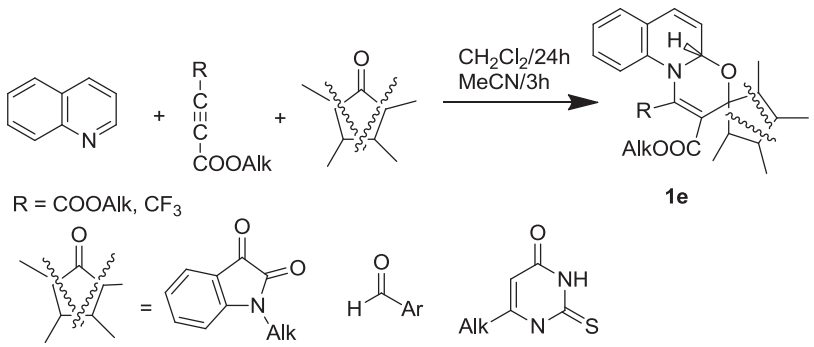
(3)

In order to gain a better insight into these transformations, the reactions were performed with isoquinoline with a number of ketones. The corresponding benzo analogs of spiro-[1,3]oxazino[2,3-*a*]isoquinolines **1d** were obtained in good yields (Eq. 4).[8–10]



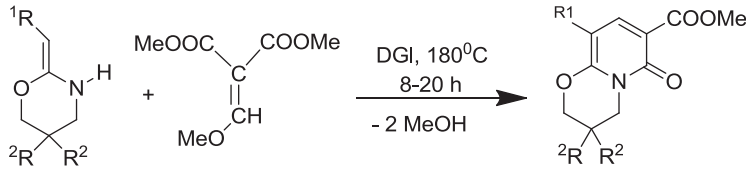
(4)

The use of a quinoline[9,11–13] in the three-component reactions described above (Eqs. 1–4) results in the formation of isomeric benzo analogs of title fused system – [1,3]oxazino[3,2-*a*]quinolines **1e** (Eq. 5). The reaction proceeds smoothly in boiling acetonitrile,[11] toluene[12,13] or at room temperature in CH_2Cl_2[9] to give the desired [1,3]oxazino[3,2-*a*]quinolines **1e**. Aromatic aldehydes or cyclic ketones, and ADC or FA-AC, and quinolone were used as starting compounds as well.



(5)

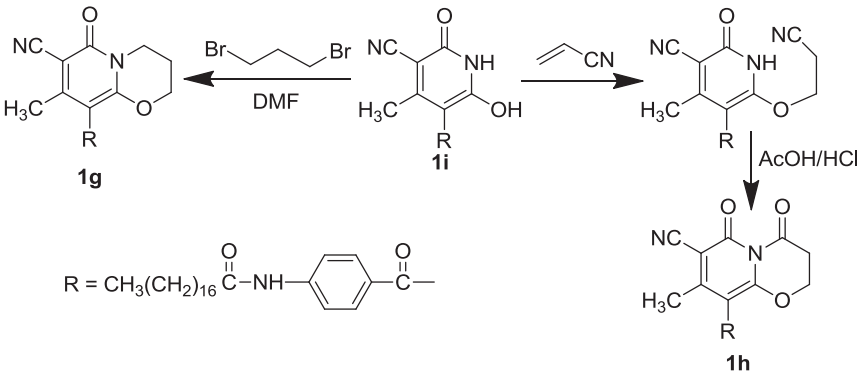
Ihara[14] described an efficient synthesis of pyrido[2,1-*b*]-1,3-oxazine derivatives **1f** via cycloaddition reaction of 2-benzyl-5,6-dihydro-4*H*-1,3-oxazines with dimethyl 2-(methoxymethylene)malonate (Eq. 6).



(6)

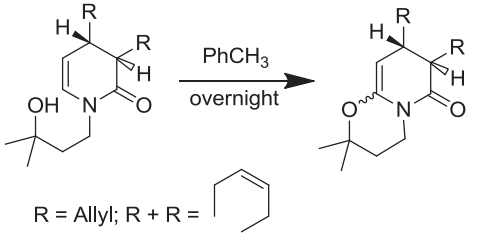
^{1}R = Ar; ^{2}R = H, CH_3.

The reaction between 5-cyano-2-hydroxy-6-oxo-3-(4-stearamidobenzoyl)pyridine **1i** with 1,3-dibromopropane in DMF or with acrylonitrile followed by acidic treatment (Scheme 1) furnished the fused pyrido[2,1-*b*][1,3]oxazine **1g** or **1h** under mild conditions in good yields.[15]



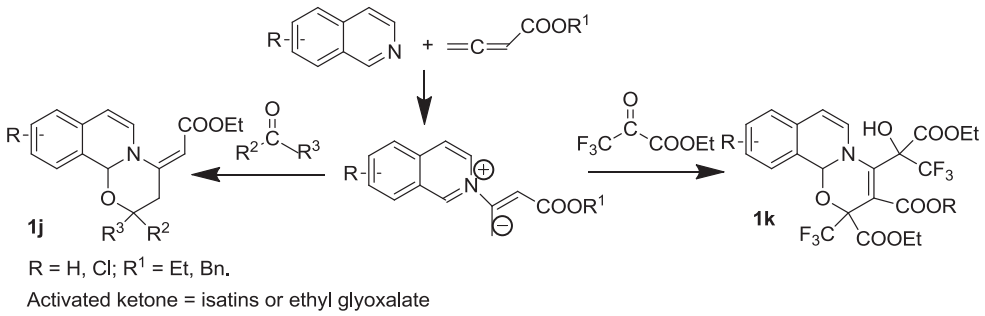
Scheme 1

A convenient stereoselective synthesis of pyrido[2,1-*b*]-1,3-oxazine derivatives uses ring-closure metathesis (RCM) reactions[16] (Eq. 7) of 3-hydroxypropyl-*N*-substituted pyridines.



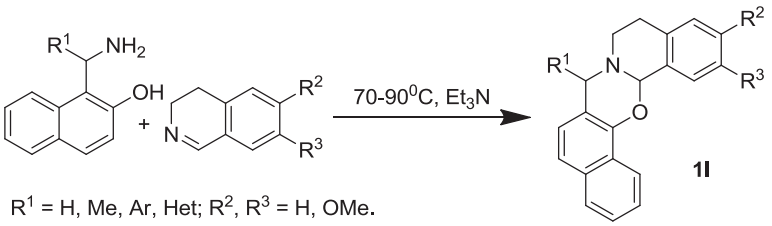
(7)

A variety of synthetic routes to pyridooxazine benzo analogs are known. The multicomponent reaction of isoquinoline, an allenoate ester and an activated ketone was reported by Yang.[17] It affords [1,3]oxazino[2,3-*a*]isoquinoline derivatives **1j** and **1k** in moderate yields along with moderate diastereoselectivities via 1,4-dipolar cycloaddition (Scheme 2).



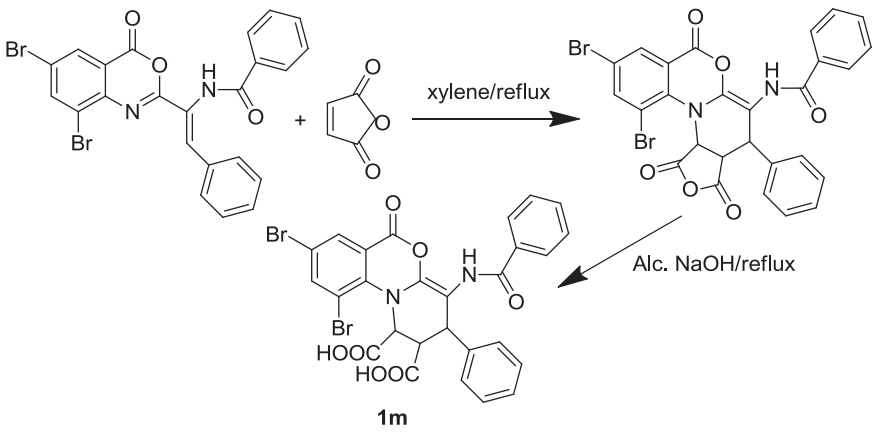
Scheme 2

A series of novel unsubstituted and substituted napht[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines **1l** were prepared by the reaction of 1-aminomethyl-2-naphthol or substituted 1-aminobenzyl-2-naphthol derivatives with 3,4-dihydroisoquinolines (Eq. 8).[18–21]



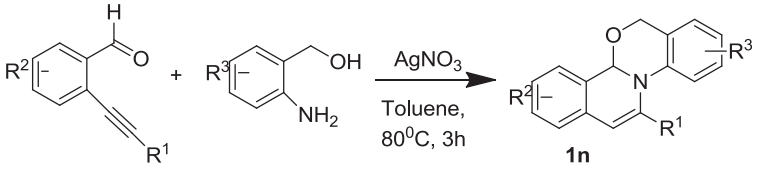
(8)

The reaction of a 4(*H*)-3,1-benzoxazin-4-one with maleic anhydride followed by treatment with NaOH furnished pyrido[1,2-*a*][3,1]benzoxazine derivative **1m** (Scheme 3)[22].



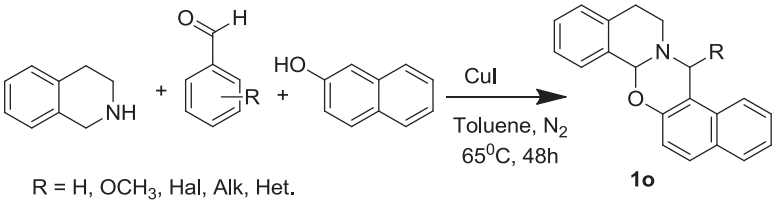
Scheme 3

One-pot synthesis of dihydrobenzo [4,5][1,3]oxazino[2,3-*a*]isoquinolines **1n** via a silver(I)-catalyzed cascade approach was developed using 2-(phenylethynyl)benzaldehyde and (2-aminophenyl)methanol as model substrates (Eq. 9).[23]



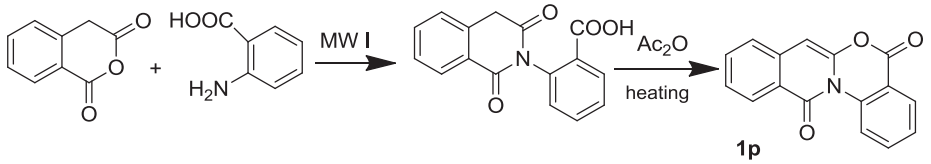
(9)

A highly regio and diastereoselective copper catalyzed three-component reaction of tetrahydroisoquinolines (THIQs), aldehydes, and naphthols to furnish naphthoxazine derivatives under mild conditions was developed. The initial generation of iminium ion followed by the nucleophilic attack of naphthol was suggested in this synthesis of [1,3]oxazino[2,3-*a*]isoquinoline derivatives **1o** (Eq. 10).[24]



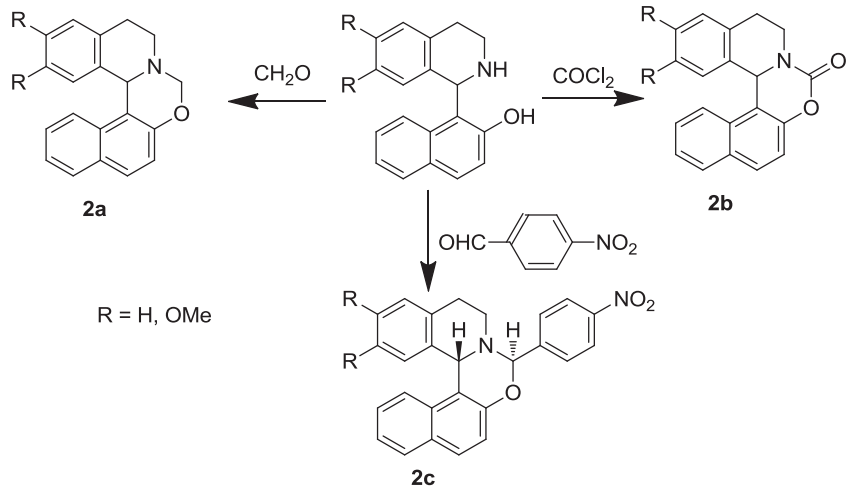
(10)

An efficient and convenient synthesis of [1,3]oxazino[3,2-*b*]isoquinoline-5,12-dione **1p** was achieved by the reaction of anthranilic acid with homophthalic anhydride under microwave irradiation (MWI), followed by cyclization with acetic anhydride (Scheme 4).[25]



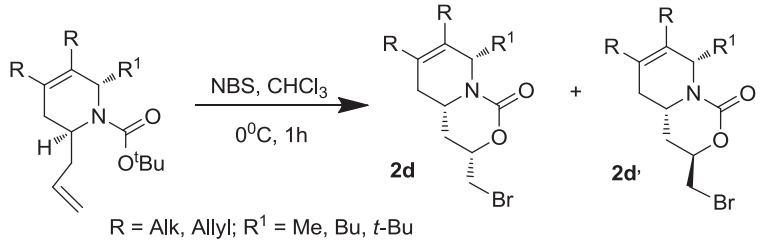
Scheme 4

Through the cyclization of 1-(β-hydroxynaphthyl)isoquinolines in the presence of formaldehyde, phosgene or *p*-nitrobenzaldehyde, the benzo analogs of pyrido[1,2-*c*][1,3]oxazine system **2** (8-substituted 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino [4,3-*a*]isoquinolines **2a-c**) were prepared (Scheme 5).[26]



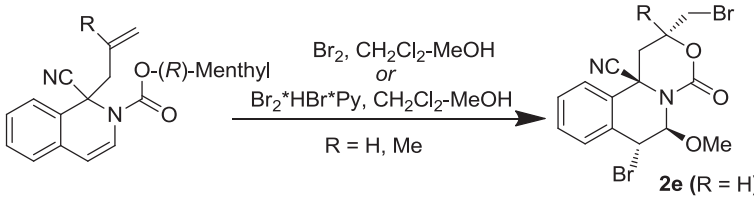
Scheme 5

2,6-Disubstituted (alkyl)(allyl)- and diallylpiperidines containing C=C bonds can be transformed into a mixture of stereoisomers **2d** and **2d′**. With R^1 = *t*-Bu in the starting compound, a good level of diastereoselectivity was observed (Eq. 11).[27]



(11)

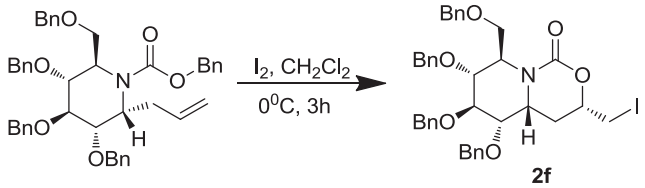
The bromination reaction of an 1-allyl-2-menthyloxycarbonyl derivative of isoquinoline (R = H) resulted in the formation of fused tricyclic 2-bromomethyl-[1,3]oxazino[4,3-*a*]isoquinoline-4-one **2e** by treatment with bromine or pyridinium tribromide (Eq. 12).[28] The methyl homolog (R = Me) also undergoes this cyclization reaction. A plausible explanation of this process involves



(12)

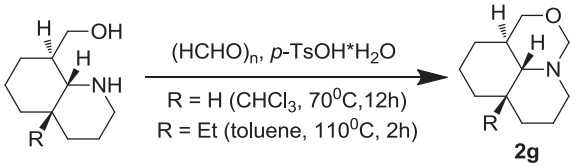
transformation of the alkene double bond of the allyl moiety in the starting isoquinoline into a bromonium ion. Subsequent intramolecular attack at the carbonyl oxygen atom generates the oxazine ring, while the *R*-menthyloxy moiety is eliminated.

The iodocyclization reaction between the double bond of 2-allyl-1-benzyloxycarbonylpiperidine and the benzyloxy group of the ester afforded the bicyclic iodo derivative **2f** in 92% yield and de >95% in favor of the *S*-isomer (Eq. 13).[29]



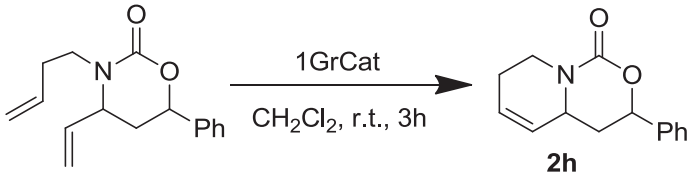
(13)

The treatment of 8-hydroxymethylperhydroquinolines with $(HCHO)_n$ and *p*-TsOH*H_2O in boiling $CHCl_3$ gave perhydro[1,3]oxazino[5,4,3-*ij*]quinolines **2g** (Eq. 14).[30,31]



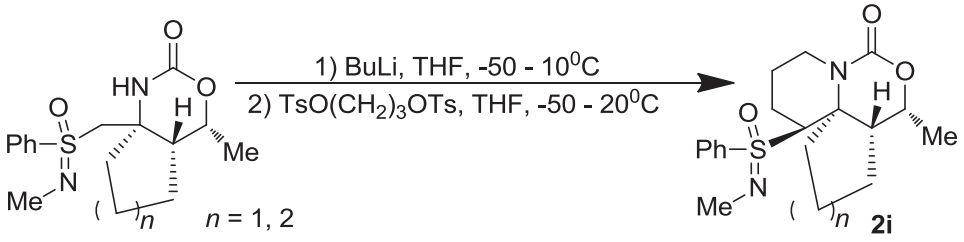
(14)

An unsaturated [1,3]oxazin-2-one underwent ring-closing methathesis efficiently on treatment with the Grubbs first-generation catalysts to yield tetrahydro-1*H*,3*H*-pyrido[1,2-*c*]-[1,3]oxazin-1-one **2h** (Eq. 15).[20]



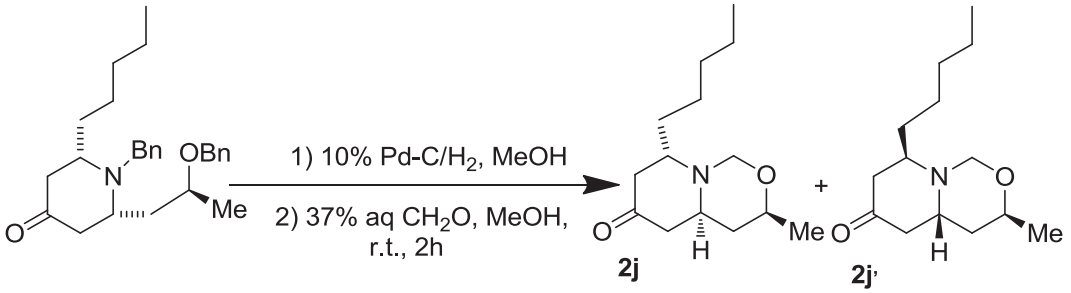
(15)

The annulation of the heterocyclic ring by cycloalkylation of the intermediate *C,N*-dianion furnished the spiropyrido[1,2-*c*]-1,3-oxazinone **2i** with high diastereoselectivity (Eq. 16).[32]



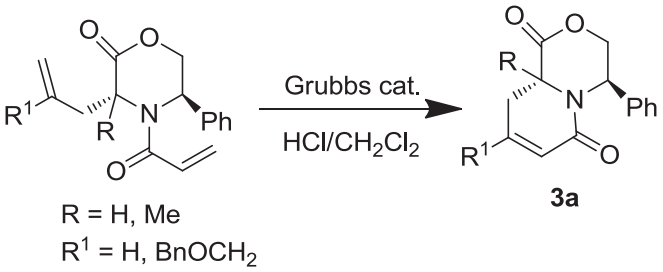
(16)

The diastereomeric mixture of a piperidin-4-one was resolved into two oxaquinolizidines **2j** and **2j′** upon reductive cyclization (HCHO/MeOH/rt) to give a 3:1 product ratio and 65% combined yield (Eq. 17).[33] The two products **2j** and **2j′** were initially thought to be **2j** and its C8-epimer.



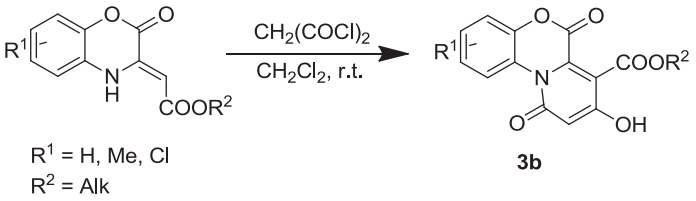
(17)

The cyclization of unsaturated morpholin-2-one was reported by Sun and Fustero[34,35] for asymmetric synthesis of pyrido[2,1-*c*][1,4]oxazine system **3** ((4R,9aR)-4-phenyl-3,4,9,9a-tetrahydro-6*H*-pyrido[2,1-*c*][1,4]oxazin-1-ones **3a**) in quantative yield under catalytic conditions (Eq. 18).



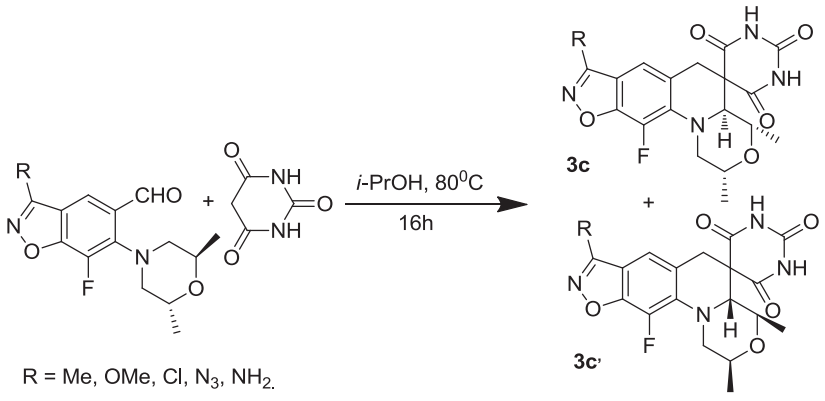
(18)

An efficient synthesis of alkyl 6,10-dioxo-6,10-dihydropyrido[2,1-*c*][1,4]benzoxazine-7-carboxylates **3b** was described by Yavari.[36] It involves the reaction between malonyl dichloride and alkyl 2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetates in CH_2Cl_2 at room temperature (Eq. 19).



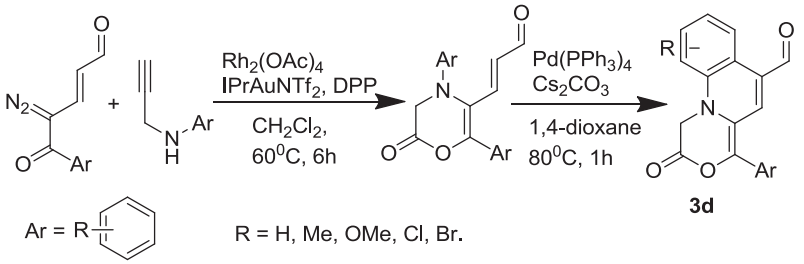
(19)

Efficient synthetic procedures were devised for analogs of the antibacterial drug PNU 286607. Products were separated into stereoisomers **3c** and **3c'**[37] (Eq. 20).



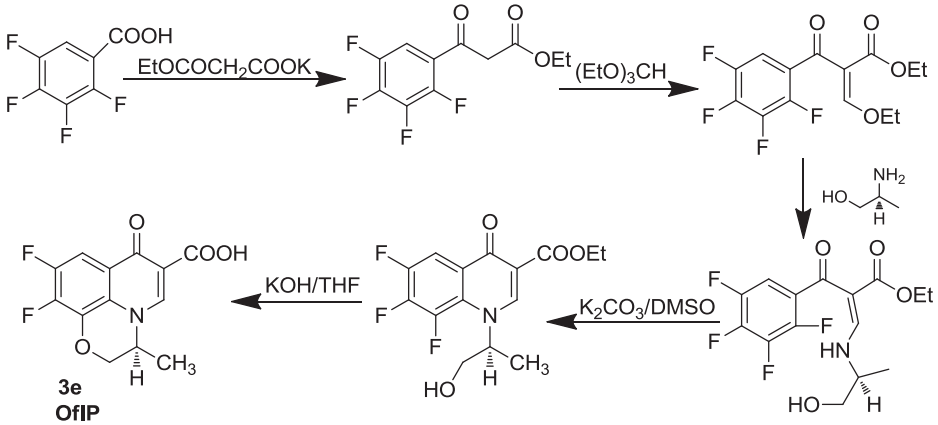
(20)

A novel rhodium-catalyzed dienamine activation of diazoenals generates γ-functionalized donor-acceptor dienamines. The synthetic utility of these dienamines was demonstrated in a cooperative rhodium(II)/Bronsted acid and gold(I)-catalyzed direct [3+3] annulation of enaldiazo ketones with *N*-propargylanilines, leading to highly substituted enal-functionalized 1,4-oxazines that underwent ring closure to form [1,4]oxazino[4,3-*a*]quinolones **3d** (Scheme 6).[38]



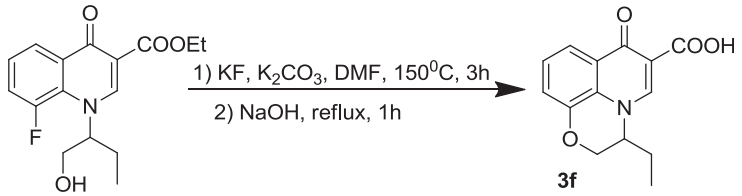
Scheme 6

Many synthetic protocols are devoted to substituted [1,4]oxazino[2,3,4-*ij*]quinolines which constitute a basic structure of well-known antibacterial drugs ofloxacin and levofloxacin.[39,40] For example, modification of the amino moiety was carried out using the ofloxacin precursor (OflP) **3e**, which can be synthesized from tetrafluorosubstituted benzoic acid as shown in Scheme 7.[41]



Scheme 7

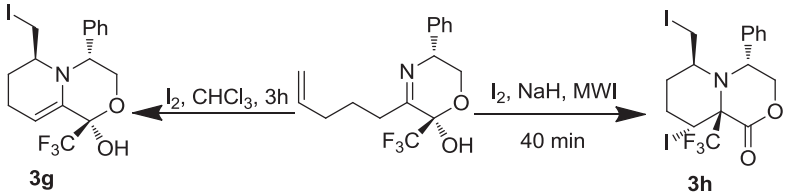
A similar ring closure was described for synthesis of ethyl analogs of ofloxacin **3f** (Eq. 21).[42] Taking advantage of the easy displacement of the fluorine substituent, the tricyclic acid **3f.**



(21)

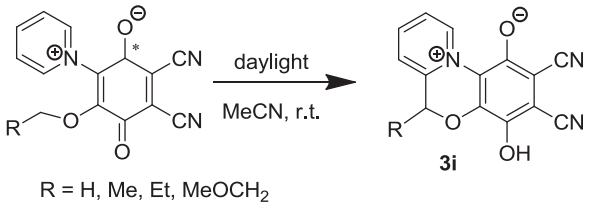
was obtained by treating the quinolone with potassium fluoride/potassium carbonate in DMF at 150 °C followed by alkaline hydrolysis of the ester group.

Trifluoromethyl substituted imino lactol containing an unsaturated side chain (Scheme 8) is a substrate for cyclization reactions. For instance, when treated with iodine in order to promote an iodoamination reaction, bicyclic iodide **3g** was obtained as a single isomer.[43] However, under harsher conditions (I_2, NaH, MWI), this lactol was stereoselectively transformed into diiodide **3h.**[43]



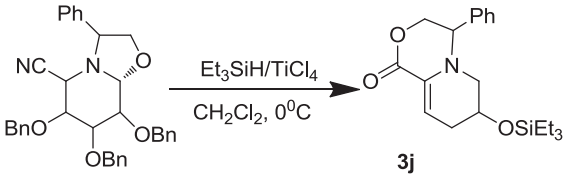
Scheme 8

A simple and efficient photoinduced reaction starting from easily accessible stable semiquinone radicals was performed to construct pyrido[2,1-*c*][1,4]oxazinium derivatives **3i** via intramolecular dehydrogenative coupling of a C(sp^3) center adjacent to an oxygen atom with a C(sp^2) center in positively charged heterocycle (Eq. 22).[44]



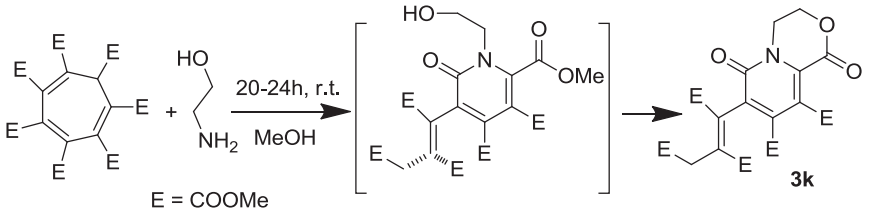
(22)

The treatment of 3,4,5-tribenzyloxy-1-(2′-hydroxy-1′(*R*)-phenylethylpiperidine-2-carbonitrile with triethylsilane used as a reducing agent, in the presence of titanium(IV) chloride, at 0 °C led to exclusive formation of bicyclic lactone **3j** (Eq. 23).[45]



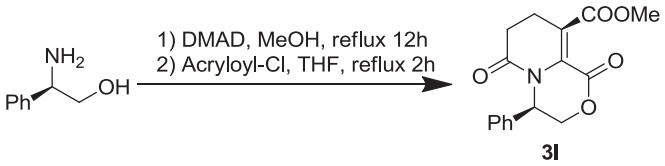
(23)

The reaction of a cycloheptatriene with 2-aminoethanol generates a 3-vinylpyridin-2-one exclusively, regardless of the solvent. This intermediate product underwent further cyclization into the bicyclic lactone **3k** which was easily isolated from the reaction mixture by crystallization in a yield of 77% as the *E*-isomer exclusively (Scheme 9).[46] The structural assignment of compound **3k** was strongly supported by ^{1}H–^{1}H HMBC, and ^{1}H–^{13}C HMQC NMR experiments.



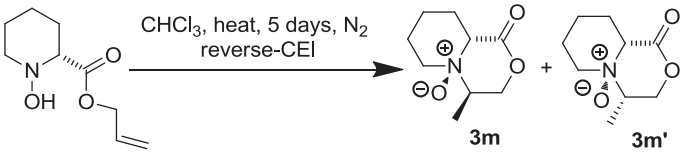
Scheme 9

The condensation of dimethyl acetylenedicarboxylate with (*R*)-phenylglycinol and further azaannulation with acryloyl chloride yielded the bicyclic enamido ester **3l** (Eq. 24).[47]



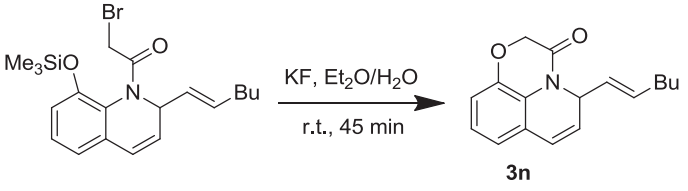
(24)

Heating a hydroxylamine substrate in chloroform under nitrogen under reflux for 5 days gave an inseparable mixture of starting hydroxylamine and bicyclic lactone *N*-oxide as two diastereomers **3m** and **3m′** in a ratio of 5:1 (Eq. 25).[48]



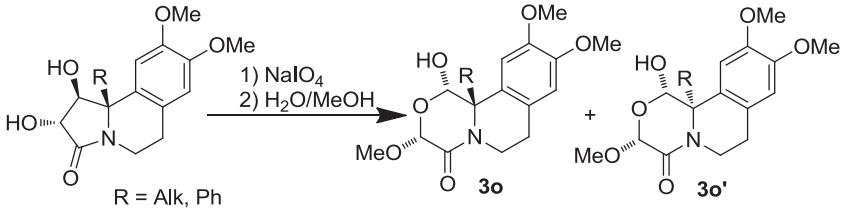
(25)

An *N*-bromacetylquinoline was transformed into tricyclic product **3n** in good yield slowly or through a faster pathway in the presence of KF under phase transfer conditions (Eq. 26).[49]



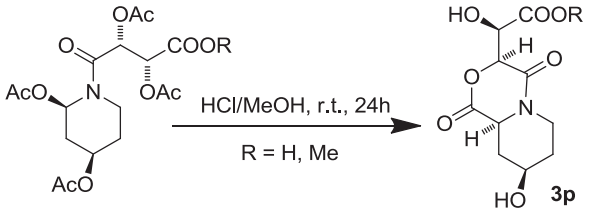
(26)

The (*S*)-1,2-dihydroxy-pyrrolo-isoquinolines were investigated in the reaction of glycolic cleavage with sodium periodate in water-methanol solution to yield the diastereomeric mixture of bicyclic hemiacetals **3o** and **3o′** (Eq. 27).[50] Due to the steric hindrance, oxidation of the *trans*-diol was slow (4–5 days) and required 4 equiv. of sodium periodate for completion. Under similar conditions the glycolic cleavage of the respective *cis*-epimer gave hemiacetals **3o** and **3o′** in high yield.



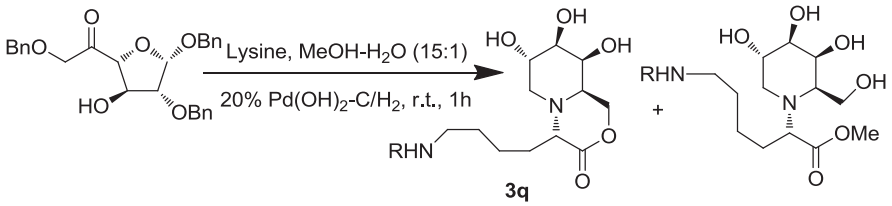
(27)

Bicyclic pyrido[2,1-*c*][1,4]oxazine-1,4-diones **3p** were obtained from piperidine derivatives by stirring in MeOH saturated with HCl gas overnight at room temperature (Eq. 28).[51]



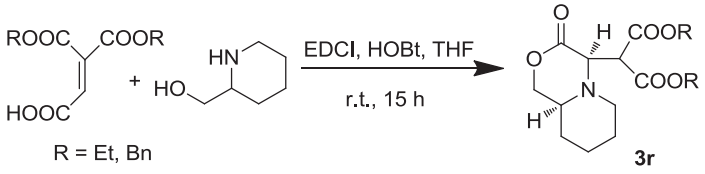
(28)

Cyclization by double reductive amination of *L*-arabinose over $Pd(OH)_2/C$ catalyst in MeOH-H_2O (15:1) for 1 h at room temperature with suitably protected *D*- or L-lysine derivative provided an inseparable mixture of pyrido[2,1-*c*][1,4]oxazin-3-one **3q** and a tetrahydroxypiperidine (Eq. 29).[52]



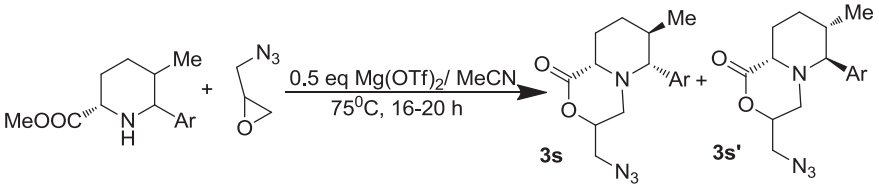
(29)

The one-pot reaction of an unsaturated ester with 2-piperidinemethanol in the presence of EDCI and HOBt in THF gave exclusively a bicyclic *N,O*-containing heterocycle **3r** as a single diastereomer in good yield (Eq. 30).[53]



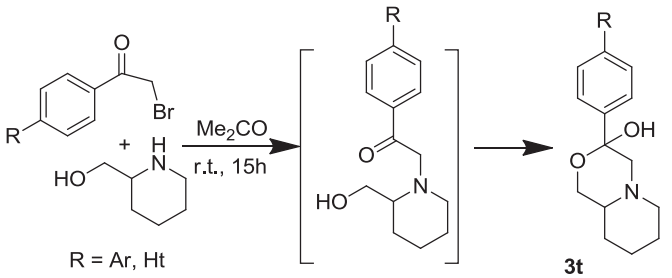
(30)

The stereocontrolled synthesis of pyridooxazinones **3s** and **3s′** by $Mg(OTf)_2$-promoted epoxide ring-opening with use of chiral pipecolates as nucleophiles was described by Chen and co-workers (Eq. 31).[54] Reaction was carried out in MeCN at 75 °C in a sealed tube.



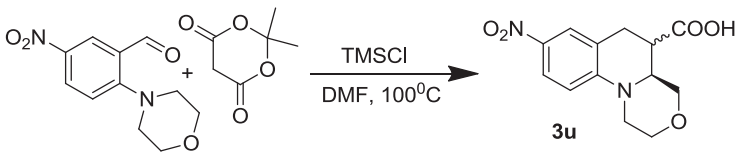
(31)

The fused pyrido[2,1-*c*][1,4]oxazine derivatives **3t** (hemiketals) were obtained by a spontaneous cyclization of 1-(2-aryl-2-oxoethyl)-2-piperidinemethanols, generally in very good yields (Scheme 10).[55]



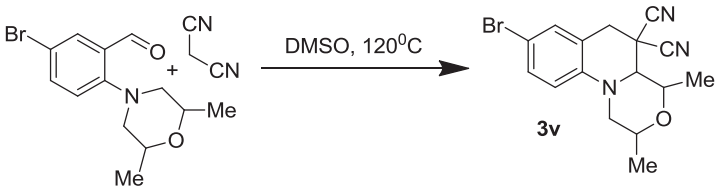
Scheme 10

Heating of equimolar mixture of a morpholin-1-yl substituted aldehyde with Meldrum's acid in DMF at 100 °C with dropwise addition of TMSCl led to a diastereomeric mixture of hexahydro[1,4]oxazino[4,3-*a*]quinoline-5-carboxylic acid **3u** (Eq. 32).[56]



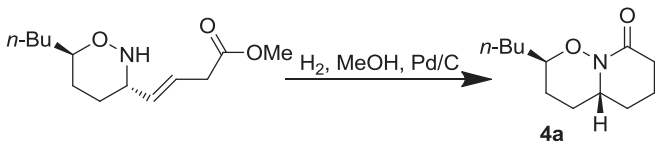
(32)

The analogous cycloaddition of 5-bromo-2-(2,6-dimethylmorpholin-4-yl)benzaldehyde with malononitrile in DMSO at 120 °C furnished [1,4]oxazino[4,3-*a*]quinoline **3v** in good yield (Eq. 33).[57]



(33)

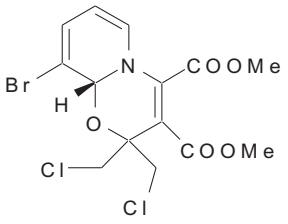
An alkenyl substituted 1,2-oxazine derivative underwent hydrogenation over Pt catalyst with simultaneous lactamization to give the bicyclic perhydropyrido[1,2-*b*][1,2[oxazin-8-one **4a** (Eq. 34).[58]



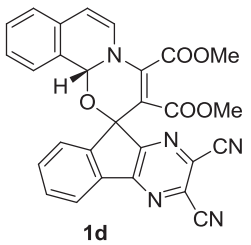
(34)

2.2 Reactivity and structural features

The crystal structure of the dimethyl 9-bromo-2,2-bis(chloromethyl)-2*H*,9a*H*-pyrido[2,1-*b*]-[1,3]oxazine-3,4-dicarboxylate **1a**, which contains one chiral center, was determined by means of an X-ray diffraction analysis.[3]

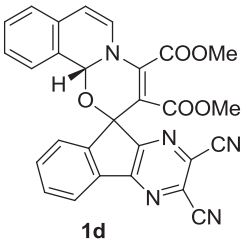


1a



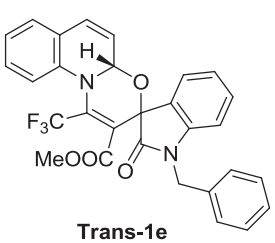
1d

The formation of a diastereomer of *trans*-methyl 2-(2,3-dichlorophenyl)-4-(pentafluoroethyl)-2,11*b*-dihydro-[1,3]oxazino[2,3-*a*]isoquinoline-3-carboxylate **1b** was clearly shown by XDR analyses of a monocrystal.[7]

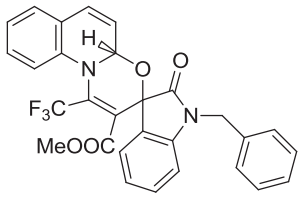


1d

The stereochemistry of dimethyl 2,3-dicyano-11b′-*H*-spiro[indeno[1,2-*b*]pyrazine-9,2′-[1,3]oxazino[2,3-*a*]isoquinoline]-3′,4′-dicarboxylate **1d** was confirmed by X-ray crystallographic analysis.[8]



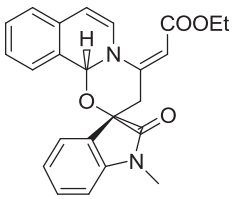
Trans-1e



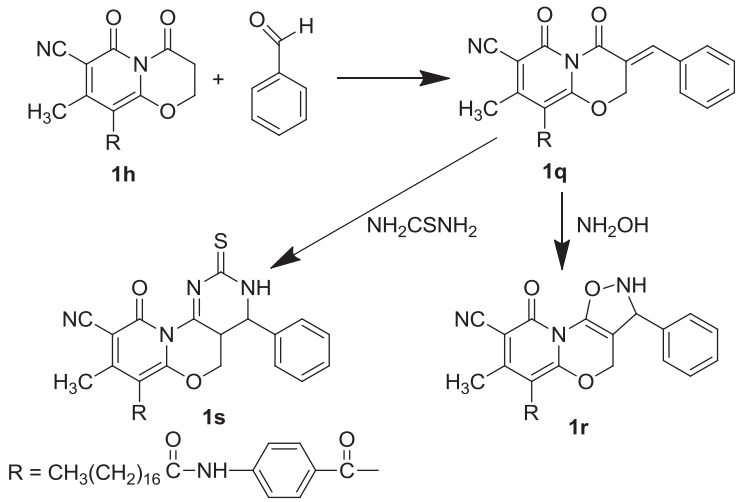
Cis-1e

A pair of *trans*/*cis*-diastereoisomers was obtained in good yield with a 1:0.6 ratio for methyl 1-methyl-2-oxo-1′-(trifluoromethyl)-4a′*H*-spiro[indoline-3,3′-[1,3]oxazino[3,2-*a*]quinoline]-2′-carboxylate **1e**. The mixture was purified by column chromatography on silica gel eluting with PE/EtOAc to give individual *trans*- and *cis*-diastereoisomers, which was clearly confirmed by X-ray crystallographic analysis.[1]

The condensation of an oxo-derivative of pyrido[2,1-*b*]-[1,3]oxazine **1h** with benzaldehyde afforded the corresponding benzylidene derivative **1q**, which is a precursor to compounds **1r** and **1s** (Scheme 11).[15] The structure of compound **1j** was also confirmed by X-ray diffraction analysis.[17]

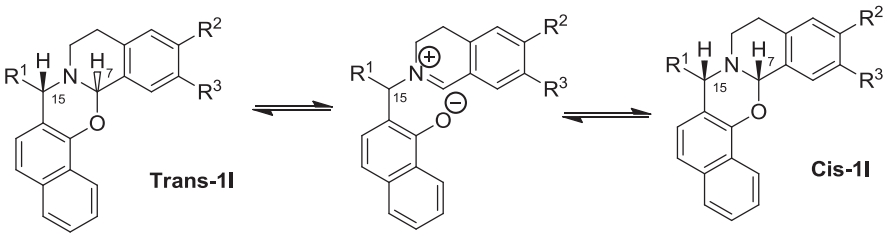


1j



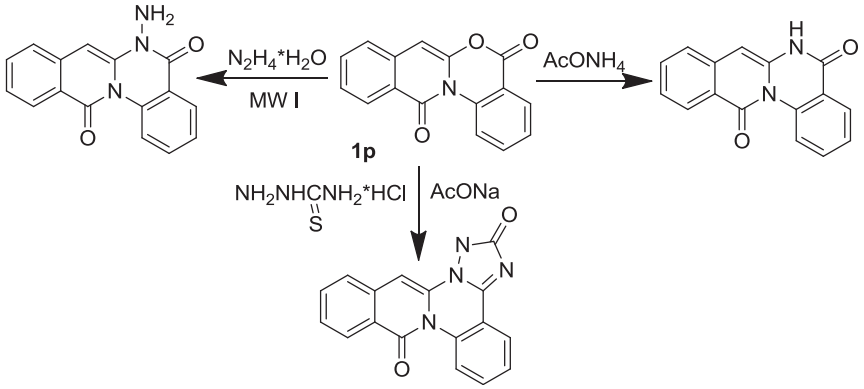
Scheme 11

The stereochemistry of compounds **1l** was studied by dynamic NMR spectroscopy and molecular modelling.[18] It was found that for all compounds the most stable diastereomer contains the *trans* arrangement of H-15 and H-7a, which was also indicated by the DFT geometry optimization (Scheme 12). For substituted napht[2,1-*e*]-[1,3]oxazino[2,3-*a*]isoquinolines, the dynamic equilibrium between the *trans* and *cis* forms was observed in solution.



Scheme 12

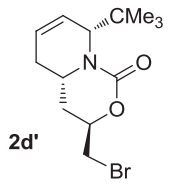
The aminolysis of [1,3]oxazino[3,2-*b*]isoquinoline-5,12-dione **1p** was investigated under different conditions (Scheme 13).[25] The generation of various isoquinolino[2,3-*a*]quinazolines was suggested.



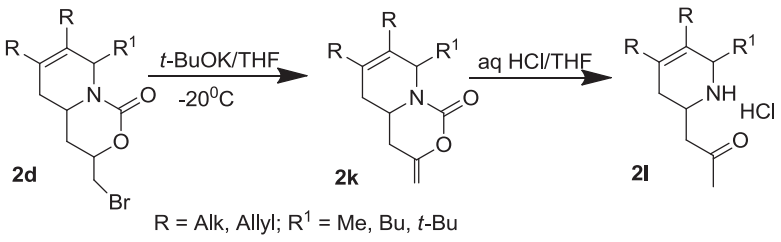
Scheme 13

Conformational analysis of both the piperidine and the 1,3-oxazine moieties of fused heterocycles **2a-c** (Scheme 5) by 2D NMR spectroscopy and an accompanying theoretical study revealed that these two conformationally flexible six-membered ring moieties prefer twisted chair conformers.[26] The anisotropic effects of the phenyl and naphthyl moieties in series of 1,3-oxazino[4,3-*a*] isoquinolines **2a-c** on the ^{1}H chemical shifts of the isoquinoline protons were calculated by employing the Nucleus Independent Chemical Shift (NICS) concept and visualized as anisotropic cones by a through-space NMR shielding grid.[59]

The structure of compound **2d′** was unambiguously established by X-ray single-crystal crystallographic analysis.[27]

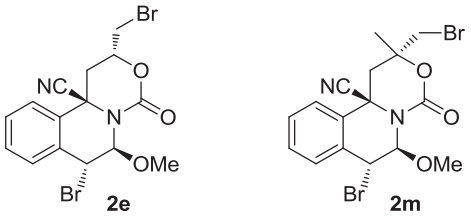


The X-ray diffraction study revealed that **2d′** is a bicyclic compound containing two six-membered rings in an unsymmetrical half-chair conformation with deviations of the C2, C3, C4 and N1 atoms from the mean plane of the remaining ring atoms.[27] It was found that bromomethyl derivatives **2d** undergo a rapid dehydrobromination (at −20 °C in minutes) with *t*-BuOK in THF (Scheme 14). Cyclic enol esters **2k** obtained in this way have high analytical purity and can be converted directly into amino ketone hydrochlorides **2l** by treatment with HCl solution in high yields.[27]

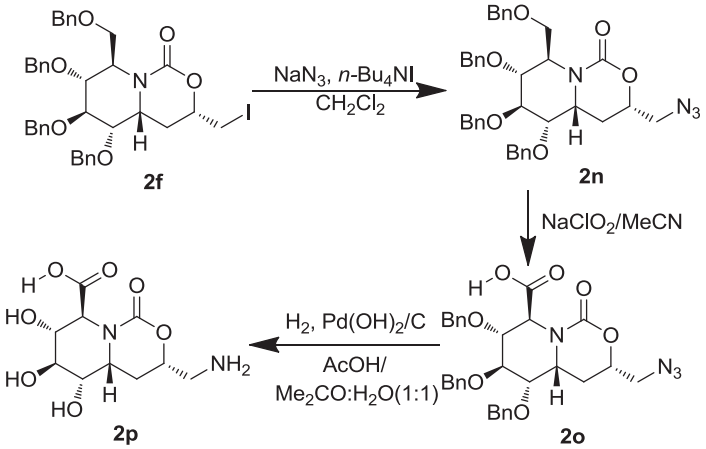


Scheme 14

The structure of the [1,3]oxazino[4,3-*a*]isoquinolines **2e** and **2m** was established by X-ray crystallographic analysis which revealed that the bromine atom is located at the concave side of the bowl-shaped [1,3]oxazino[4,3-*a*]isoquinoline ring system.[28]

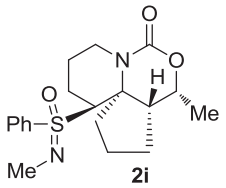


Stereochemistry of the iodo derivative **2f** was determined by NOESY experiments. The compound was functionalized by nucleophilic substitution of iodine with sodium azide in dry *N,N*-dimethylformamide to afford the azidobicyclic derivative **2n** (reflux, 88% yield). Then, compound **2n** was oxidized to **2o** and finally deprotected by hydrogenolysis, with simultaneous reduction of the azido function to the amino group yielding compound **2p** (Scheme 15).[29]

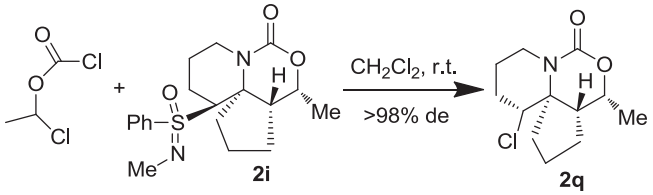


Scheme 15

The configuration of spirosulfoximine **2i** was determined by X-ray crystal structure analysis.[32]

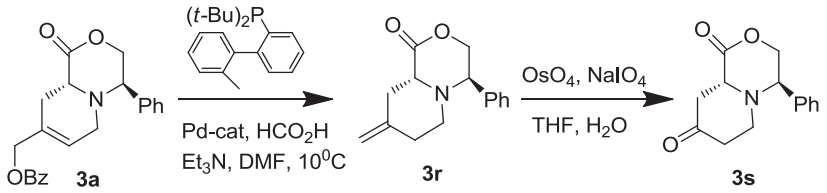


The use of spiropyrido[1,2-*c*]-1,3-oxazinones **2i** for the synthesis of azaspirocyclic natural products requires a substitution of the sulfoximine group. It was accomplished by treatment of sulfoximine **2i** with $ClCO_2CH(Cl)Me$, which gave tricyclic chloride **2q** with high diastereoselectivity in good yield. The configuration was determined by a combination of TOCSY and NOE experiments. It was shown that the substitution of the sulfoximine moiety occurs with retention of configuration (Eq. 35).[32]



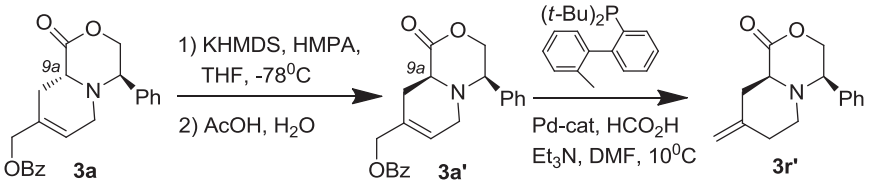
(35)

4R,9aR-8-Benzoyloxymethyl-4-phenyl-3,4,9,9a-tetrahydro-6*H*-pyrido[2,1-*c*][1,4]oxazin-1-one **3a** was converted to the *exo*-olefin **3r** (Scheme 16),[34] the subsequent oxidation of which led to the formation of dioxopyrido[2,1-*c*][1,4]oxazine **3s** in good yield.



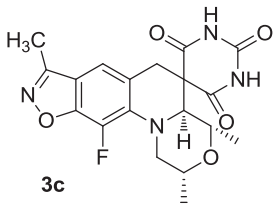
Scheme 16

In the formation of the diastereomeric pyrido[2,1-*c*][1,4]oxazine **3r′**, the 9a stereocenter of **3a** was inverted by a deprotonation/protonation protocol[60] to give diastereomer **3a′** which was then converted to the corresponding *exo*-olefin **3r′** (Scheme 17).[34]

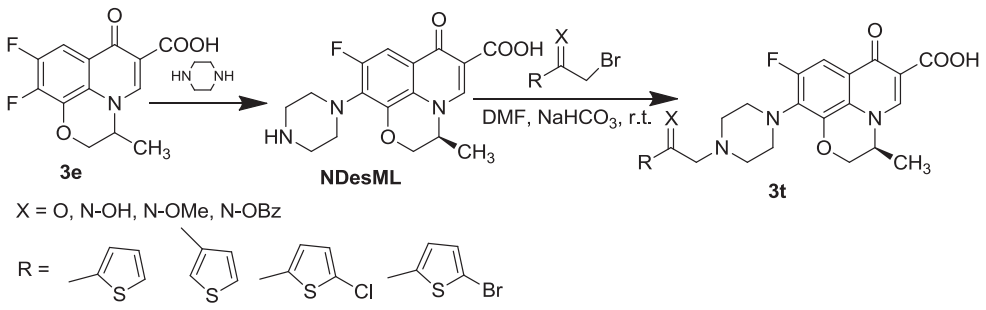


Scheme 17

The configuration of 11-fluoro-2,4,8-trimethyl-2,4,4a,6-tetrahydro1*H*,1′*H*-spiro[isoxazolo-[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5′-pyrimidine]-2′,4′,6′(3′*H*)-trione **3c** was confirmed by X-ray crystallographic analysis showing that the morpholine ring exists in a lower energy chair conformation with the two pendant methyl substituents in equatorial orientations.[37]



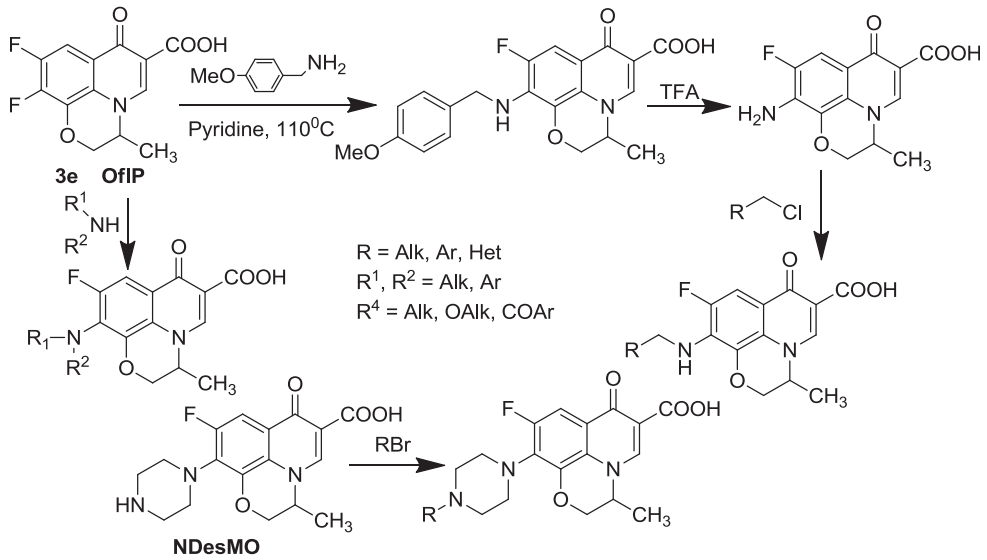
An effective synthetic approach to a new series of levofloxacin derivatives was reported by Mohammadhosseini via nucleophilic reaction of *N-des*-methyllevofloxacin (NDesML, obtained from **3e**) with thienylethyl bromide derivatives. The *N*-substituted



Scheme 18

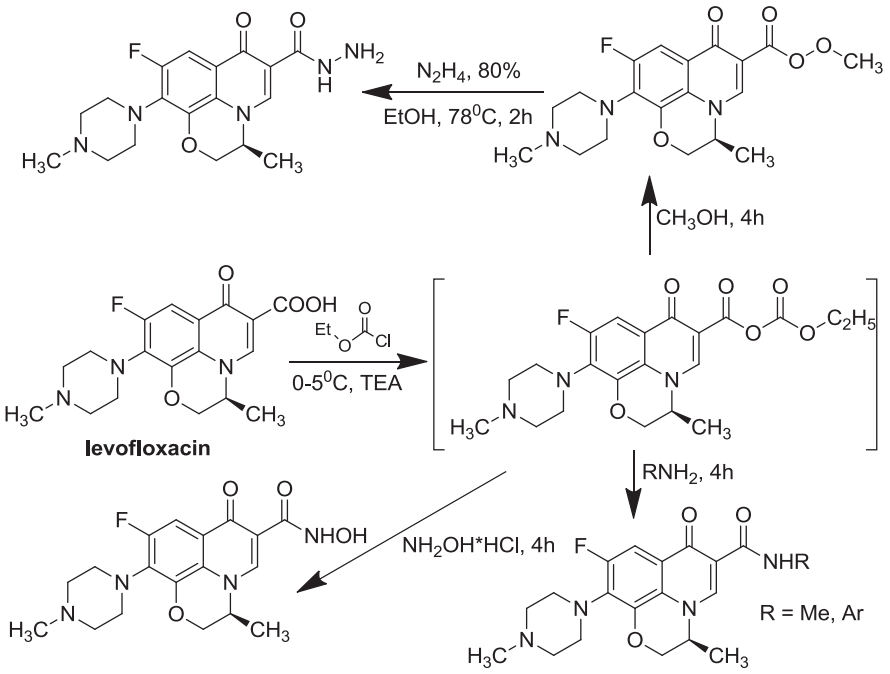
antibacterial analogs of levofloxacin **3t** were obtained (Scheme 18).[61]

A variety of amino analogs of ofloxocin were synthesized by aminolysis of ofloxacin precursor (**OflP**) **3e** and *des*-methylofloxacin **(NDesMO)** (Scheme 19).[41,62] This simple chemical modification of drug precursors allowed to obtain efficiently bioactive samples.



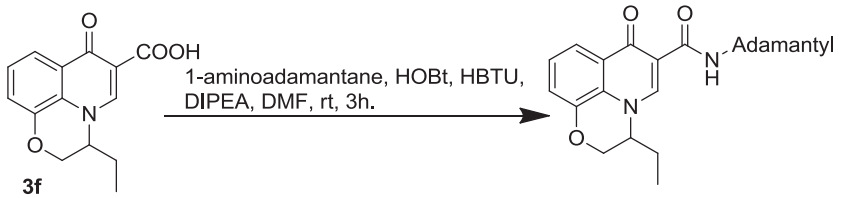
Scheme 19

New hydroxamic acid, peroxy, hydrazide and amide derivatives of levofloxacin were prepared and characterized by spectroscopic techniques (Scheme 20).[63,64]



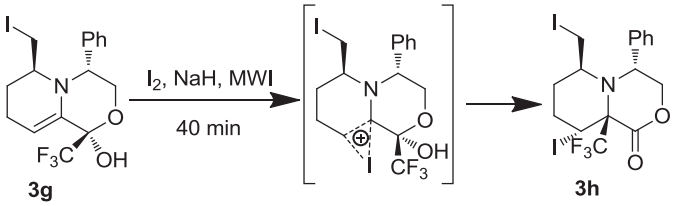
Scheme 20

Compound **3f** was subjected to coupling with 1-aminoadamantane to furnish the corresponding amide in 8% overall yield (Eq. 36).[42]



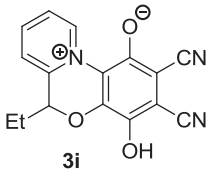
(36)

A second iodine atom was introduced to compound **3g** after iodination under MWI condition, presumably through an iodonium cation intermediate which evolved into compound **3h** by the rearrangement of the CF_3 group with concomitant regeneration of the lactone functionality (Scheme 21).[43]

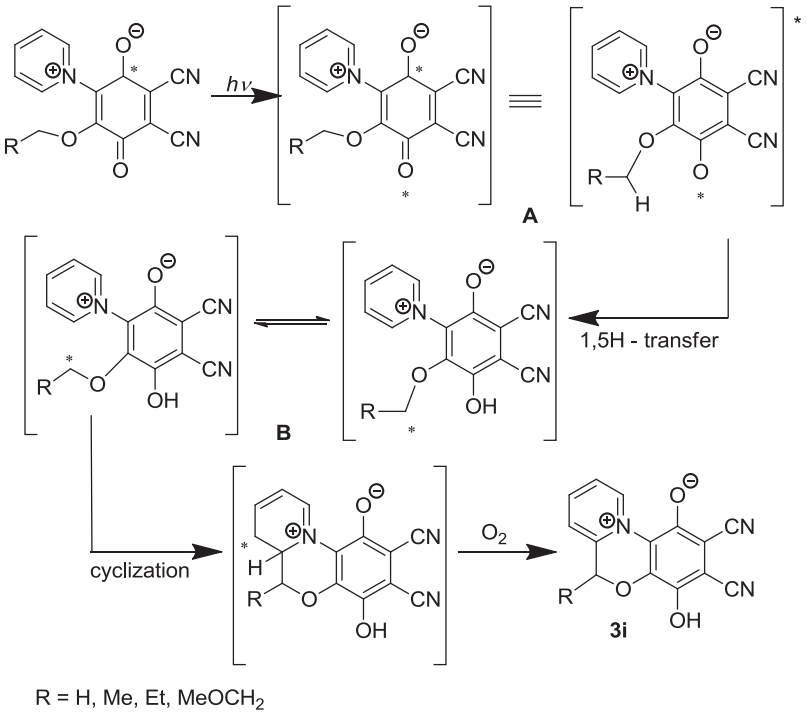


Scheme 21

X-Ray crystal structure analysis of ethyl substituted (*R*)-enantiomer of **3i** showed that the oxazine moiety adopts slightly twisted conformation.[44]



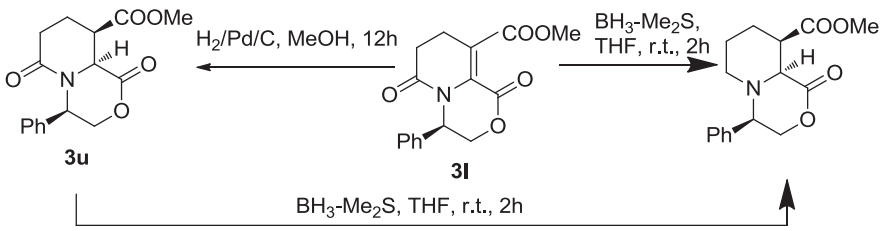
Synthesis and mechanism of **3i** are presented in Scheme 22.[44] Irradiation of starting radical generates the excited phenoxy radical **A** that undergoes a remarkably selective intramolecular 1,5-hydrogen-atom transfer analogous to a Norrish-type-II reaction. The reaction gives rise to the 1-aryloxyalkyl radical **B**, which is transformed into the heterocyclic product **3i** via a homolytic aromatic substitution process involving cyclization followed by a rearomatization process. Intramolecular radical additions to pyridinium salts are well documented (Scheme 22).[65] The mechanism of the rearomatization step most probably involves oxygen from air as an oxidizing agent.[44]



Scheme 22

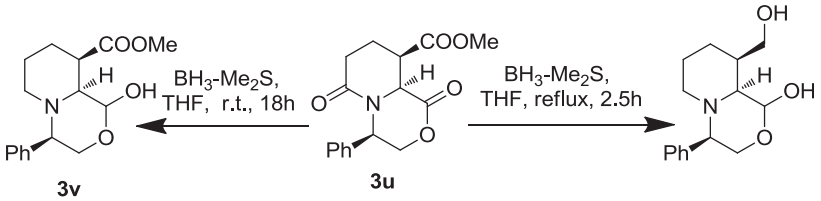
Fused chiral derivative **3l** has been recognized as a precursor of enantiopure 2,3-disubstituted piperidines. The chemoselective reduction of pyrido[2,1-*c*][1,4]oxazine **3l** was reported (Scheme 23).[47] The ethylenic double bond of compound **3l** was

diastereoselectively hydrogenated to give the cis-adduct **3u**. Then, reduction of the amidic function with 2 equivalents of the BH_3-Me_2S complex over 2 h in THF afforded the expected bicyclic product after chromatography on silica gel.



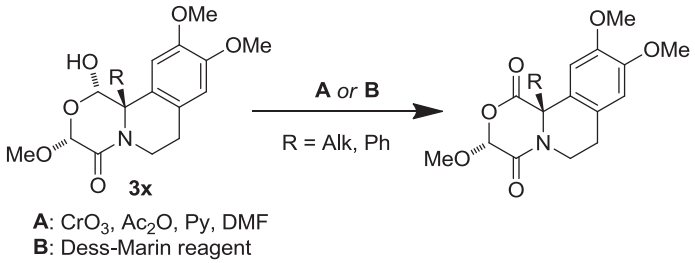
Scheme 23

Noteworthy, the reduction of the amide function of **3u** is chemoselective using 2 equivalents of BH_3-Me_2S under reflux conditions leading to a single product shown in Scheme 24. If this reaction was conducted at room temperature for 18 h, hemiacetal **3v** was obtained as a single stereoisomer after chromatography on silica gel in 45% yield.[47]



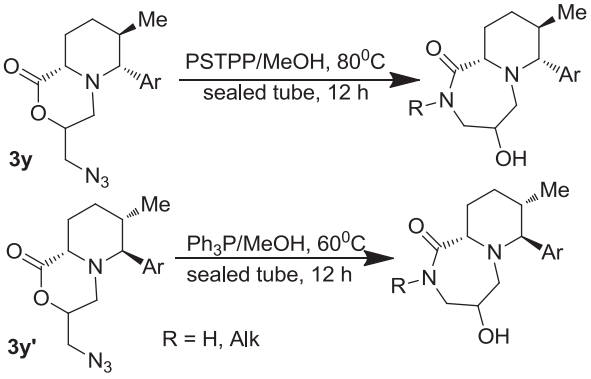
Scheme 24

The oxidation of hemiacetals **3** × using Corey's procedure with chromium(VI) reagent gave the expected lactones in good yields. The lactones were also obtained using the Desse-Marin reagent (Eq. 37).[50]



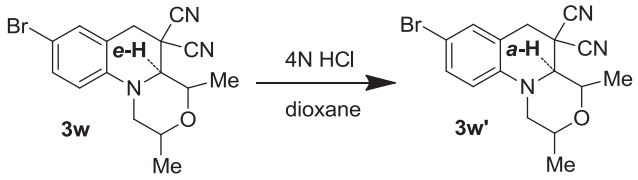
(37)

Pyridooxazinone products **3y** and **3y′** derived from azido-epoxides can be further rearranged to the corresponding seven-membered pyridodiazepinones by azide reduction using the venerable Staudinger reaction (Scheme 25).[54]



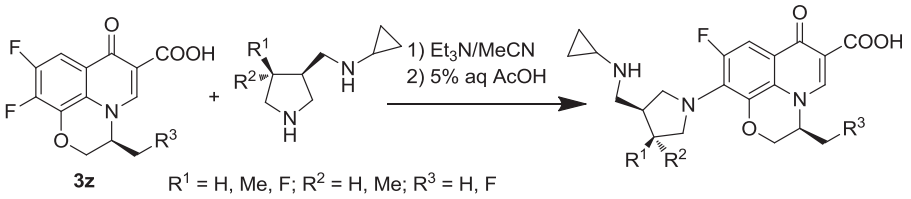
Scheme 25

Upon stirring of **3w** in 4N HCl/dioxane for 1 h, bis-nitrile **3w′** was formed (Eq. 38).[57] The stereochemical assignments of **3w** and **3w′**, were confirmed by ^{1}H NMR analysis. In particular, the coupling constants between hydrogens H(C4) and H(C4a) were diagnostic ($J = 3$ Hz for compound **3w** and $J = 9$ Hz for compound **3w′**).[57]



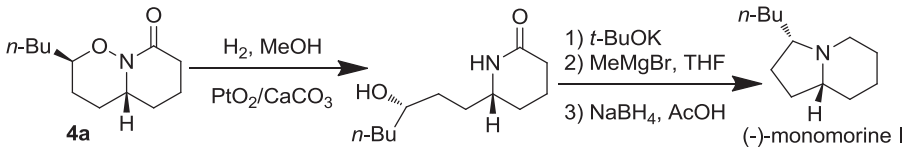
(38)

Novel pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid derivatives carrying a 3-cyclopropylaminomethyl-4-substituted-1-pyrrolidinyl moiety at the C-10 position were synthesized from tricyclic system **3z**[66] as shown in Eq. (39).[67]



(39)

Perhydropyrido[1,2-*b*][1,2]oxazine **4a** was used in the total synthesis of (−)-monomorine I, an indolizidine alkaloid, to control the stereoselectivity (Scheme 26).[58]



Scheme 26

2.3 Application and important compounds

The introduction a long alkyl chain in pyrido[2,1-*b*][1,3]oxazine derivatives **1h** (Scheme 1) results in bioactive compounds with favorable hydrophilic-lypophilc balance and low toxicity to humans and which are environmentally friendly.[15] The antimicrobial activity of compounds **1h** and **1q-s** (Scheme 11) were examined. Croy[21] described the development of PCS1055 ([1,3]oxazino[2,3-*a*]isoquinoline **1l**), a M4-receptor antagonist, which may prove to be a valuable pharmacological tool for evaluating M4 receptor signaling mechanisms. The 1,2,3,6-tetrahydrobenzo[*d*]pyrido-[2,1-b][1,3]ox-azine-1,2-dicarboxylic acid **1m** (Scheme 3) shows significant antimicrobial and anti-inflammatory activities comparable to ampicillin, mycostatine and indomethacin positive controls[22]. Compounds **1p** and related derivatives show cytotoxic activity against three anticancer cell lines.[25] Compound **2p** (Scheme 15), featuring a cyclic carbamate group is active against α-glucosidase, with inhibition potency higher than that of the reference 1-deoxynojirimycin. It was also tested in antibacterial assays against *Enterococcus faecium* (Gram positive), *Staphylococcus aureus* (Gram positive), *Escherichia coli* (Gram negative) and *Pseudomonas aeruginosa* (Gram negative) bacteria.[29] A novel mode of inhibition of DNA gyrase was demonstrated without loss of susceptibility to bacteria resistant to fluoroquinolones and aminocoumarins.[37] Discovery of novel DNA gyrase inhibiting spiropyrimidinetriones **3c** (Eq. 20) with *N*-Linked oxazolidinone substituents resulted in identification of a clinical candidate (ETX0914).[68] The results of antibacterial screening of *N*-substituted derivatives of levofloxacin **3t** (Scheme 20) against Gram-positive and Gram-negative bacteria revealed that the introduction of a functionalized thienylethyl moiety on the piperazine ring of levofloxacin can improve the bioactivity.[61] A modification of amino moiety in ofloxacin (Scheme 19) resulted in increasing of activity in the inhibition of the supercoiling activity of DNA gyrase with an IC_{50} of 10.0 μg/mL[41] and against organisms expressing efflux pumps from the MFS, MATE and RND classes of pump systems.[62] It was shown that compounds shown in Scheme 20 are active against the urease splitting bacteria, *Proteus mirabilis*. The urease inhibitory activity was investigated using the indophenol method. Most of the tested compounds show better activity than the reference acetohydroxamic acid (AHA). The levofloxacin hydroxamic acid (Scheme 20) is the most active ($IC_{50} = 2.20$ μM). Molecular docking study revealed high spontaneous binding ability of the tested compounds to the active site of urease.[63] Compounds shown in Scheme 20 significantly inhibit the phosphorylation of Axl and dose dependently inhibited cell invasion and migration in TGF-β 1 induced MDA-MD-231 breast cancer cells.[64] Pasquini reported that pharmacological screening shows that compound **3f** (Eq. 21) shows high affinity toward the human CB2 receptor, while no affinity for the human CB1 receptor.[42] A number of newly synthesized 2-pyrido[2,1-*c*][1,4]oxazines derivatives were found to inhibit lipid peroxidation (IC_{50} of the most potent agent is

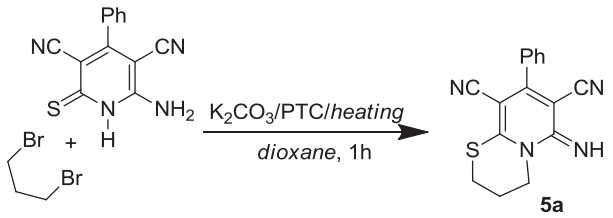
20 μM) as well as rat squalene synthase (IC_{50} for most agents is between 1 and 10 μM). Most of the novel compounds are more active than the reference compound biphenyl-morpholine, pointing to useful structural approaches for the design of antiatherosclerotic agents.[55] Another 1,4-oxazine derivative (Eq. 39) which has a *cis*-oriented 4-methyl or 4-fluoro-3-cyclopropylaminomethyl-1-pyrrolidinyl moiety at the C-10 position, exhibits 2-to 16-fold more potent *in vitro* antibacterial activity than clinafloxacin against quinolone-resistant Gram-positive clinical isolates. Introduction of a fluorine atom to the C-4 position of the 3-cyclopropylaminomethyl-1-pyrrolidinyl moiety reduces intravenous single-dose acute toxicity and the convulsion inductive ability, and introduction of a fluorine atom to the C-3 methyl group of the pyridobenzoxazine nucleus eliminates the phototoxicity.[67]

3 Pyrido[2,1-*b*][1,3]thiazines 5, pyrido[2,1-*c*][1,4]thiazines 6, pyrido[1,2-*b*][1,2]thiazines 7 and their benzo analogs

3.1 Synthesis

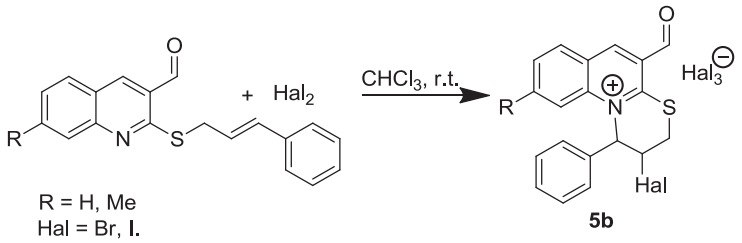
Fused pyridothiazines with a bridgehead nitrogen-atom have both natural and synthetic origins; the key synthetic approaches were reviewed by Hermecz in 2008[1] and 2011.[2] It should be noted that there is no information about pyrido[1,2-*c*][1,3]thiazine system for the reviewed period of 2007–2019. This system was abbreviated as **8** in CHC III, and in the current CHC IV edition the number **8** is for pyrido{1,2-*a*]pyrimidine system.

The effective approach to the synthesis of 6-imino-8-phenyl-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-7,9-dicarbonitrile **5a** was described by Abdel-Ghany[69] via cycloalkylation of starting pyridinethione with 1,3-dibromopropane by heating under PTC conditions (Eq. 40).



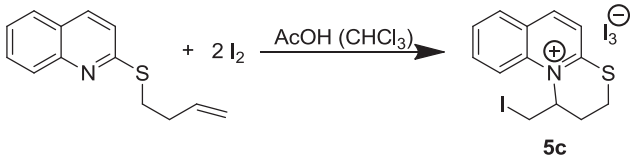
(40)

The original procedure for synthesis of [1,3]thiazino[3,2-*a*]quinolin-11-ium salts **5b** via electrophilic haloheterocyclization was described by Onysko.[70] The target tricyclic halides **5b** were obtained under mild conditions in good yields (Eq. 41).



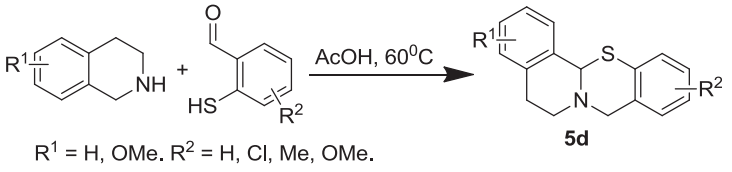
(41)

1-Iodomethyl-2,3-dihydro-1*H*-[1,3]thiazino[3,2-*a*]quinolin-11-ium triiodide **5c** was similarly obtained upon treatment of 2-(but-3-en-1-ylsulfanyl)quinoline with iodine in glacial acetic acid or chloroform at room temperature (Eq. 42).[71]



(42)

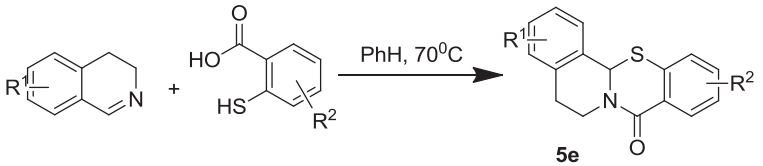
Conventional synthetic approach to the construction of ring-fused 1,3-thiazine scaffolds includes redox-neutral α-sulfenylation of secondary amines with thiosalicylaldehydes (Eq. 43).[72] This route is useful for the synthesis of tetracyclic ring-fused pyrido-1,3-benzothiazines **5d.**



R1 = H, OMe. R2 = H, Cl, Me, OMe.

(43)

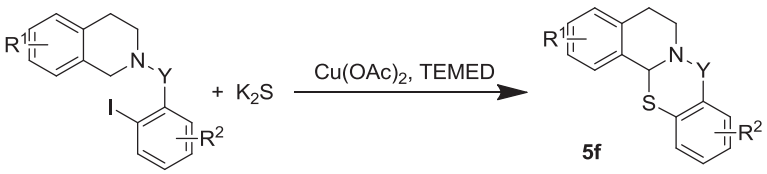
Direct imine acylation reaction with thiosalicylic acid furnished benzo[1,3]thiazino[2,3-*a*]isoquinoline derivatives **5e** in a good yield (Eq. 44).[73,74]



(44)

R^1 = H, OMe. R^2 = H, Cl, Me, OMe.

An efficient and straightforward synthesis of similar isoquinoline-fused 1,3-benzothiazines **5f** involves copper-catalyzed cross-coupling of 2-(2-iodobenzoyl) substituted or 2-(2-iodobenzyl) substituted 1,2,3,4-tetrahydroisoquinolines with potassium sulfide (Eq. 45).[75] The main features of this preparation are: (1) the C(sp^3)-S bond and C(sp^2)-S bond are efficiently constructed in a single step; (2) readily available potassium sulfide has low toxicity and is odorless; (3) the desired tetracyclic pyridothiazines are potentially bioactive compounds.

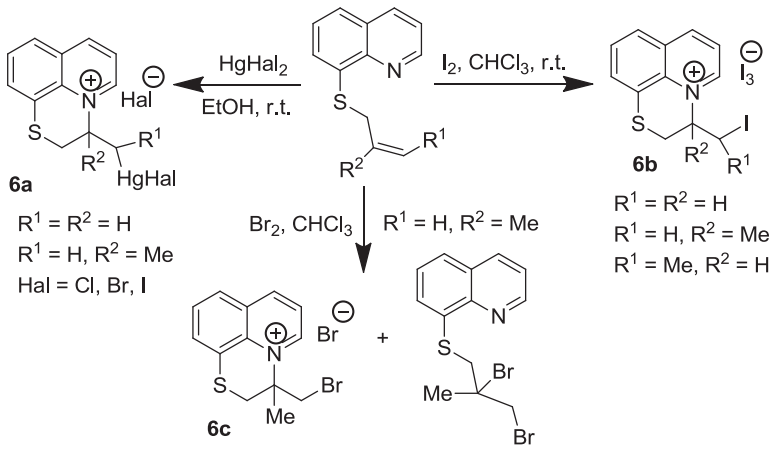


(45)

R^1 = H, OMe. R^2 = H, Cl, F, Me, OMe, CF_3.

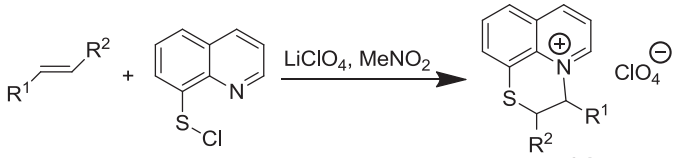
Y = CH_2, C=O.

A multi-component reaction has been developed allowing direct access to substituted [1,4]thiazino[3,4-*a*]isoquinolines.[76] General access to [1,4]thiazino[2,3,4-*ij*]quinolin-4-ium salts **6a-c** was elaborated by Kim and co-workers[77–79] via electrophilic heterocyclization of alkenyl thioethers of quinoline (Scheme 27). Reactions were performed under the mild conditions in the presence of iodine and mercurium(II) halides as electrophilic reagents.



Scheme 27

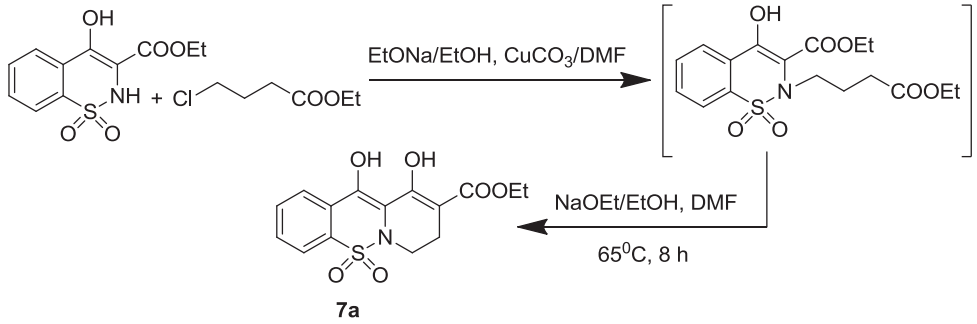
The polar cycloaddition reaction of 8-quinolylsulfenyl chloride with a carbon–carbon multiple bond is shown in Eq. (46).[80] This reaction proceeds readily upon mixing of the reagents in nitromethane in the presence of lithium perchlorate at 20 °C and furnishes 2,3-dihydro[1,4]thiazino[2,3,4-*ij*]quinolin-4-ium salts **6d**.



(46)

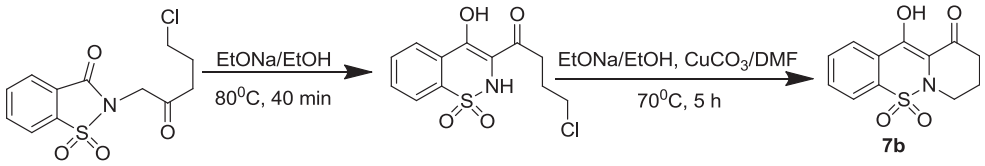
R^1 = H, Ph, PhCH=CH; R^2 = H, Ph, Me_3Si; R^1+ R^2 = $(CH_2)_3$

The *N*-alkylation of a sulfonamide with ethyl 4-chlorobutyrate was performed in the presence of copper(II) carbonate to avoid the formation of *O*-alkylated product (Scheme 28). The generated *N*-alkylsufonamide, without isolation was transformed into tricyclic pyrido[1,2-*b*][1,2]benzothiazine **7a** via a Dieckmann-condensation catalyzed by excess sodium ethoxide in 47% yield.[81]



Scheme 28

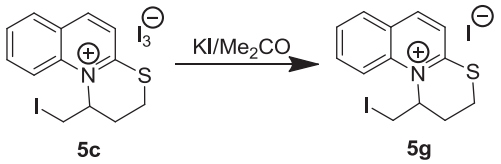
Tricyclic 1-oxo-9,10,11,12-tetrahydro-4*H*-pyrido[1,2-*b*][1,2]benzothiazine-5,5-dioxide **7b** was prepared in satisfactory yield starting from commercially available saccharin and 1,5-dichloropentan-2-one, as shown in Scheme 29. Saccharine was alkylated in a one-pot procedure and the resultant product was subjected to Gabriel-Colman rearrangement. This reaction was followed by base catalyzed ring closure using excess sodium ethoxide in anhydrous ethanol. Moisture plays a key role in the last ring addition step. After the fast Gabriel-Colman rearrangement, copper(II) carbonate was added to the mixture to exclude lactone formation by preventing *O*-alkylation and to assure selective ring closure to linearly condensed tricyclic product **7b** (Scheme 29).[81]



Scheme 29

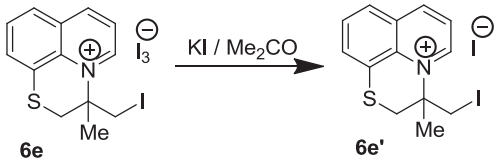
3.2 Reactivity and structural features

1-Iodomethyl-2,3-dihydro-1*H*-[1,3]thiazino[3,2-*a*]quinolin-11-ium triiodide **5c** was treated with potassium iodide in acetone at room temperature to change the anion to monoiodide **5g** (Eq. 47).[71]



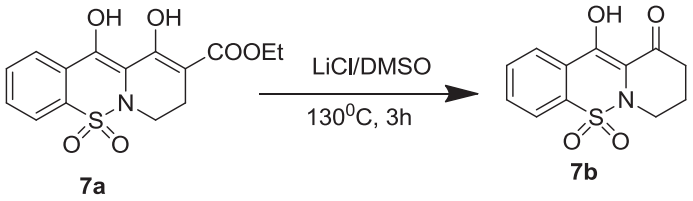
(47)

3-Iodomethyl-3-methyl-2,3-dihydro[1,4]thiazino[2,3,4-*ij*]quinolinium triiodide **6e** upon treatment with potassium iodide in acetone at room temperature was transformed into monoiodide **6e′** (Eq. 48).[77]



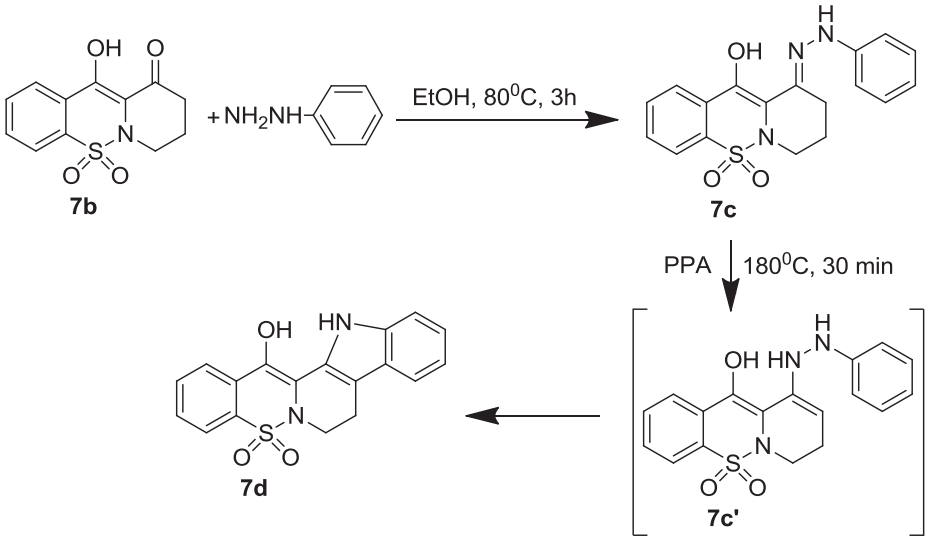
(48)

Ketoester **7a,** which exists in the enol form shown, was transformed into tricyclic 1-oxo-9,10,11,12-tetrahydro-4*H*-pyrido[1,2-*b*][1,2]benzothiazine-5,5-dioxide **7b** in a good yield. The reaction was carried out by heating compound **7a** at 130 °C in DMSO solution in the presence of a catalytic amount of lithium chloride (Eq. 49).[81]



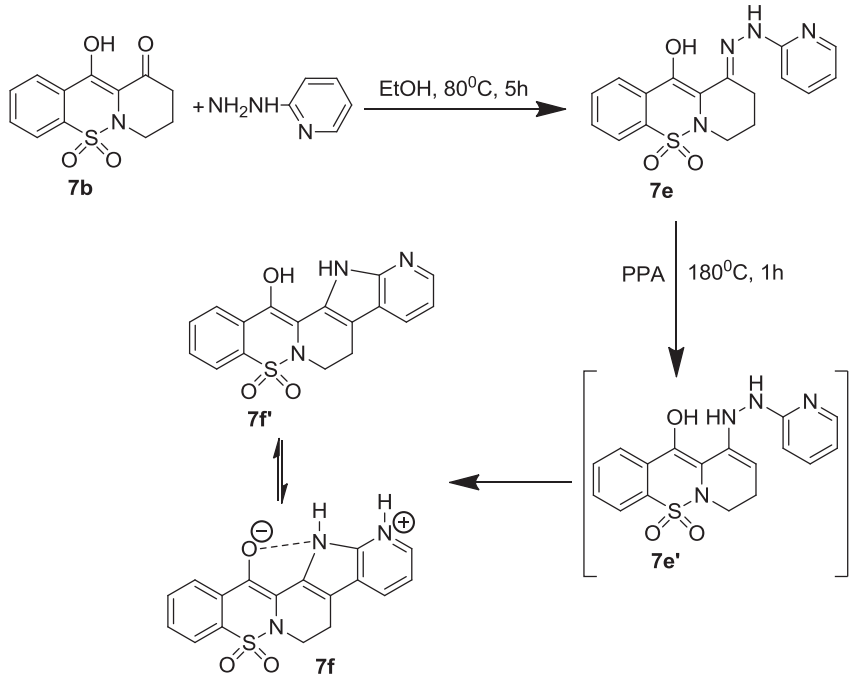
(49)

The pyridobenzothiazinone **7b** was allowed to react with phenylhydrazine in ethanol at 80 °C for 3 h to form hydrazone **7c** in excellent yield (Scheme 30).[81]



Scheme 30

Compound **7b** was subjected to Fischer indole synthesis.[82] Thus, heating the hydrazone **7c** in polyphosphoric acid (PPA) at 180 °C for 30 min furnished, through the intermediary of **7c'**, the indole derivative **7d** in good yield (Scheme 30).[81] In a similar way, condensation of **7b** with 2-pyridylhydrazine furnished the hydrazone **7e** in a high yield (Scheme 31).[81] Fischer indolization of hydrazone **7e** was carried out in PPA at 180 °C for 1 h to give 7-azaindolopyridoquinazoline **7f.** The pyridine nitrogen in compound **7f** is protonated by the acidic enolic hydroxy group, and the enolate forms a strong intramolecular hydrogen bond with the indole NH. The stable zwitterionic form **7f** is in equilibrium with the neutral form **7f'**.[81]



Scheme 31

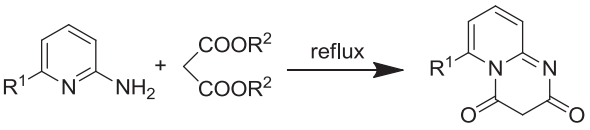
3.3 Application and important compounds

Through synthetic modifications of the pentacyclic ring systems of **7d** and **7f**, which are analogs of the anti-inflammatory agent rutaecarpine, new anti-inflamatory agents were obtained.[81]

4 Pyrido[1,2-*a*]pyrimidines 8, Pyrido[1,2-*c*]pyrimidines 9, Pyrido[1,2-*a*]pyrazines 10, Pyrido[1,2-*b*]pyridazines 11 and their benzo analogs

4.1 Synthesis

Fused pyridodiazines with a bridgehead nitrogen-atom have both natural and synthetic origins; the key synthetic approaches were reviewed previously by Hermecz in 2008[1] and 2011.[2] Additional important information concerning synthesis and properties of condensed pyrimidines can be found in reviews.[83–85]

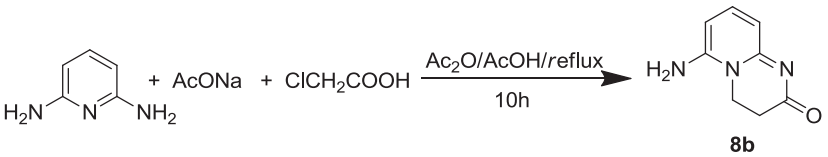


R^1 = H, Alk, Cl, NH_2
R^2 = H, Et, Ar

(50)

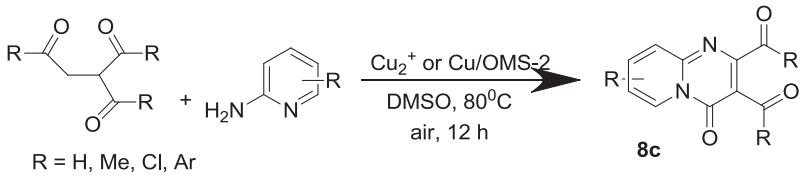
Synthetic procedures based on 2-aminopyridines are the most convenient techniques for construction of a pyrido[1,2-*a*]pyrimidine system **8**. Dioxo derivatives **8a′** were synthesized from substituted 2-aminopyridines and malonic acid/esters by heating (Eq. 50).[86–91]

Similar reaction between 2,6-diaminopyridine and chloroacetic acid afforded a single product identified as 6-amino-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one **8b** (Eq. 51).[86]



(51)

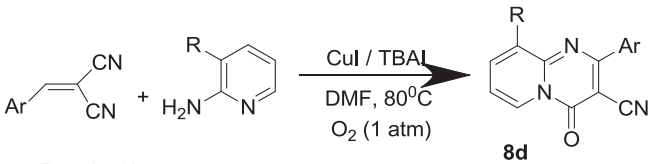
4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones **8c** were synthesized in the presence of a copper catalyst as shown.
In Eq. (52).[92,93]



R = H, Me, Cl, Ar

(52)

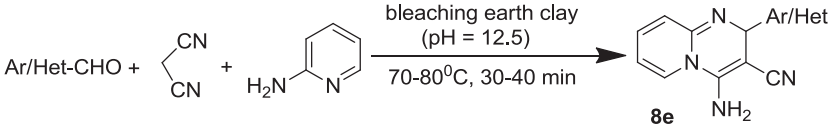
A new strategy has been developed for the synthesis of 4-oxo-pyrido[1,2-*a*]pyrimidine-3-carbonitriles **8d** by Cu(I)-catalyzed annulation of 2-aminopyridines with arylidenemalononitriles under oxygen atmosphere (Eq. 53).[94]



R = Ar, Het

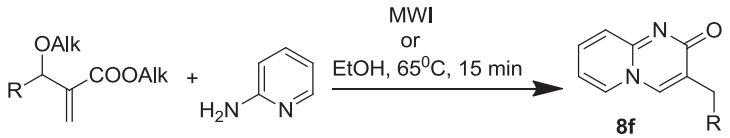
(53)

A simple, green one-pot three-component approach to the synthesis of pyrido[1,2-*a*]-pyrimidine-3-carbonitrile derivatives **8e** directly from 2-aminopyridine, aldehydes, and malononitrile in the presence of a recyclable catalytic system is shown in Eq. (54).[95]



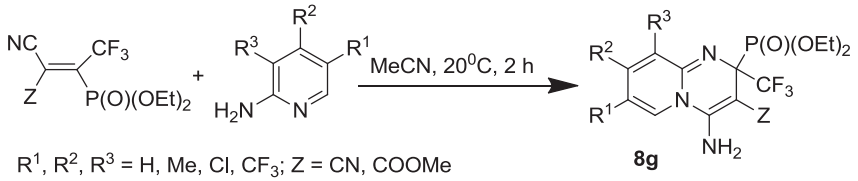
(54)

A highly efficient cyclocondensation reaction for synthesis of structurally diverse 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones **8f** starting with 2-aminopyridine is shown in Eq. (55).[96–98] The transformation involves one-pot sequential aza-Michael addition, intramolecular acyl substitution, and a [1,3]-H shift. The reaction is catalyst free, environmentally benign and cost-effective.



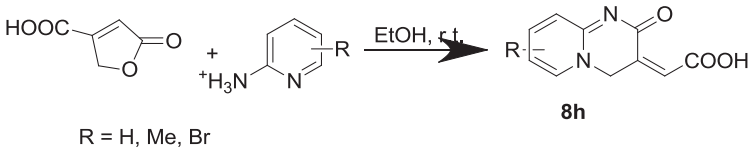
(55)

Heterocyclization reactions with 2-aminopyridines can be used for synthesis of fused 2*H*-pyrido[1,2-*a*]pyrimidines **8g** containing trifluoromethyl and diethoxyphosphoryl substituents (Eq. 56).[99]



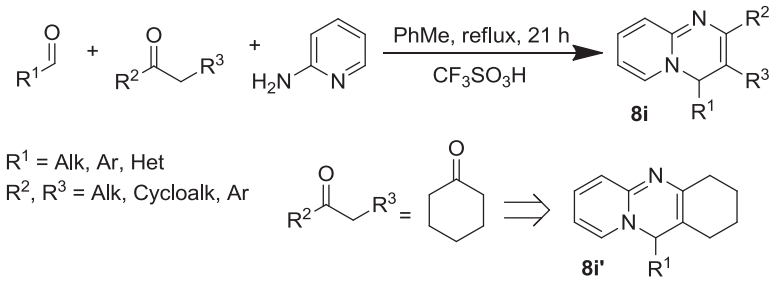
(56)

A highly efficient one-pot simple synthesis of 2-[2-oxo-2*H*-pyrido[1,2-*a*]pyridmidin-3(4*H*)-ylidene)]acetic acids **8h** starts from 2-aminopyridines and aconic acid. The reaction was carried out in alcohol at room temperature and furnished products **8h** in good yields (Eq. 57).[100]



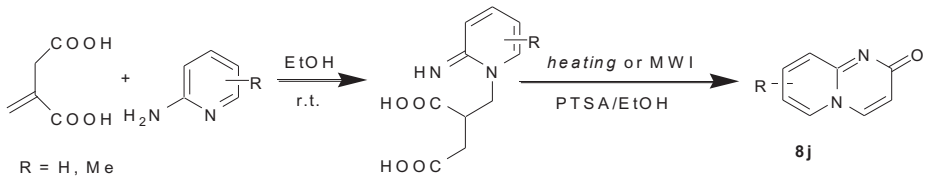
(57)

A three-component reaction of 2-aminopyridine, an aldehyde and a ketone in the presence of trifluoromethanesulfonic acid yields 4*H*-pyrido[1,2-*a*]pyrimidines **8i** in moderate to high yields (Eq. 58).[101] The reaction is also suitable for the synthesis of analogs **8i'** of 4*H*-pyrido[1,2-*a*]pyrimidine.



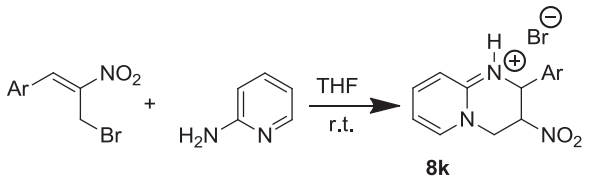
(58)

Sharulatha[102] reported a two-step procedure for synthesis of 2*H*-pyrido[1,2-*a*]pyrimidine-2-ones **8j** under classical and microwave conditions. Treatment of a 2-aminopyridines with itaconic acid yields imino-1,2(*H*)-pyridine-substituted itaconic acid derivatives, heating of which in ethanol in the presence of PTSA yields 2*H*-pyrido[1,2-*a*]pyrimidine-2-ones **8j** (Scheme 32).[102]



Scheme 32

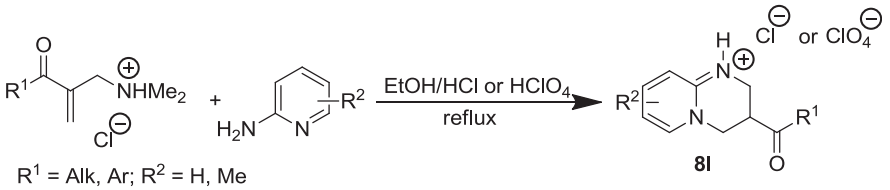
A simple approach to the synthesis of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines **8k** is shown in Eq. (59).[103] The products, in their hydrobromide salt form, are conveniently isolated and purified by crystallization.



(59)

8k

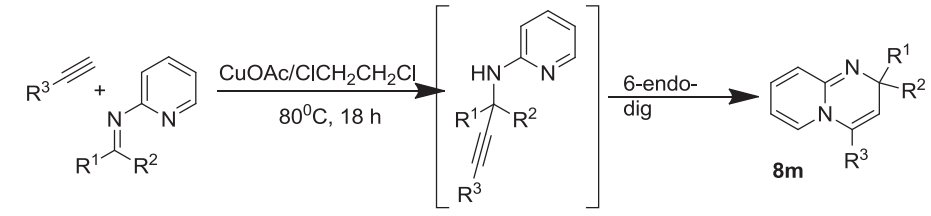
A series of 3-aroylpyrido[1,2-*a*]pyrimidines **8l** were prepared by condensation of 2-aminopyridines with enone Mannich bases via a simple procedure in good yields (Eq. 60).[104,105]



(60)

8l

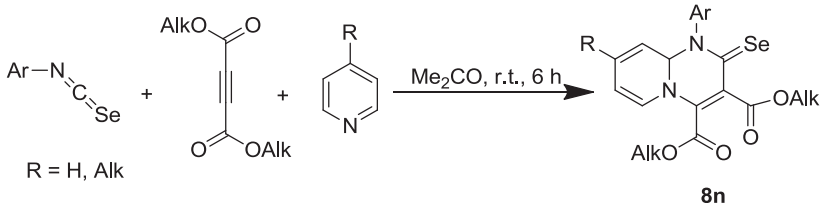
Pyrido[1,2-*a*]pyrimidines **8m** were synthesized by copper-catalyzed [4+2] cycloaddition of *N*-(2-pyridyl)ketimines and terminal alkynes in good yields (Scheme 33).[106] This reaction generates a propargylamine intermediate, and the product is obtained via 6-*endo*-dig cyclization.



3 **8m**

Scheme 33

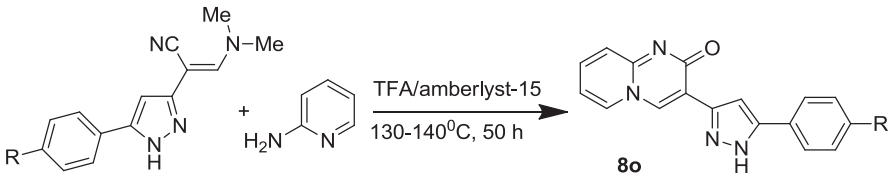
The reaction of aryl isoselenocyanates with acetylenic esters and substituted pyridines leads to formation of 2-selenoxo-1,9a-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine derivatives **8n** in good yields (Eq. 61).[107]



(61)

8n

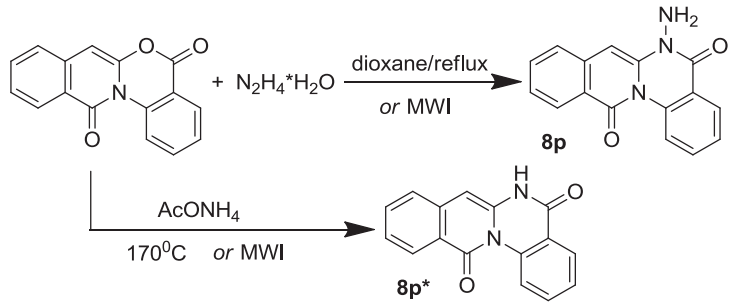
5-Aryl-2-pyrazol-3-yl-3-dimethylaminoacrylonitriles undergo a reaction with 2-aminopyridine in TFA in the presence of amberlyst-15 affording 3-(5-aryl-1*H*-pyrazol-3-yl)-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones **8o** (Eq. 62).[108] The reaction proceeds with elimination of NMe_2 moiety followed by intramolecular cyclization and hydrolysis.



(62)

8o

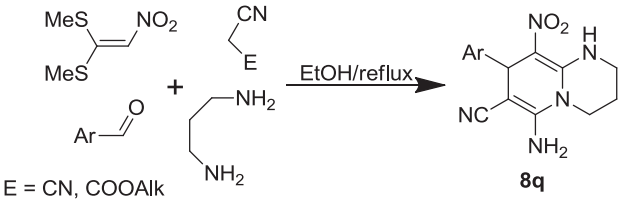
Heating under reflux of a [1,3]oxazino[3,2-*b*]isoquinolinone derivative with hydrazine in dioxane afforded 6-amino-5*H*-isoquinolino[2,3-*a*]quinazoline-5,12(6*H*)-dione **8p** as the sole product in good yield (Scheme 34).[25]



Scheme 34

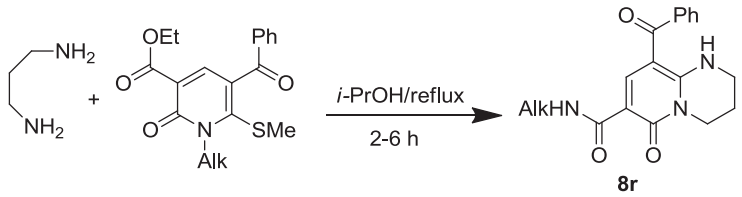
However, fusion of the same substrate with ammonium acetate on an oil bath at 170 °C or under MWI afforded 5*H*-isoquinolino[2,3-*a*]quinazoline-5,12(6*H*)-dione **8p*** (Scheme 34).[25]

An efficient, one-pot synthetic protocol for pyrido[1,2-*a*]pyrimidines **8q** was reported starting from 1,1-bis(methylthio)-2-nitroethylene, 1,3-propanediamine, an arylaldehyde, and malononitrile or its ester derivative (Eq. 63).[109,110] The reactions were completed within 12–15 h under reflux conditions in the presence of 10 mol% of piperidine as a basic catalyst and produced the desired bicyclic compounds **8q** in 60–75% yields.



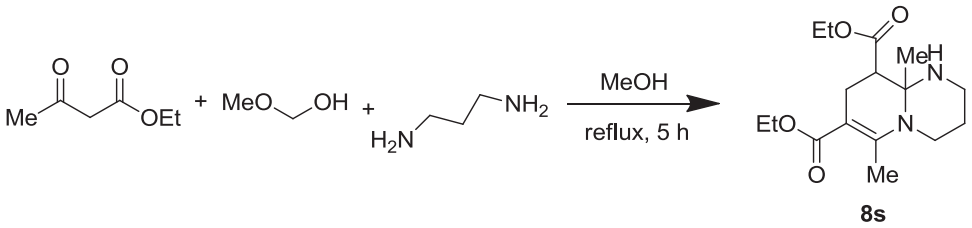
(63)

The reaction of 1-alkyl-5-benzoyl-3-ethoxycarbonyl-6-methylthio-1,2-dihydropyridin-2-one with an excess of 1,3-propanediamine yielded 7-alkylcarbamoyl-9-benzoyl-6-oxo-1,2,3,5-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidine **8r** (Eq. 64).[111]



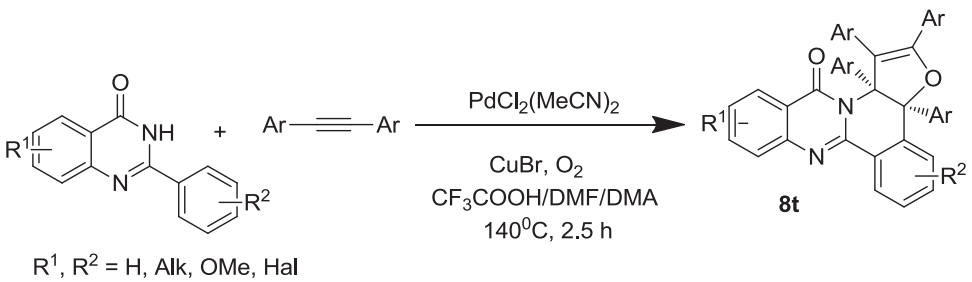
(64)

Bicyclic compound **8s** was synthesized in 98% yield by one-pot three-component condensation of ethyl acetoacetate with methoxymethanol and 1,3-propanediamine in methanol in the presence of *tert*-butyl alcohol (Eq. 65).[112]



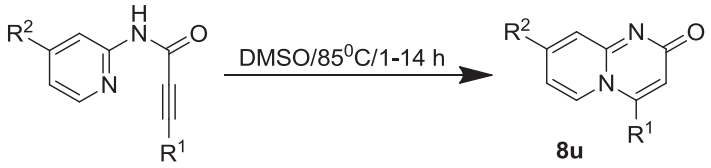
(65)

Treatment of 2-arylquinazolin-4(3*H*)-ones with diarylacetylenes using $PdCl_2(MeCN)_2$ as a catalyst in the presence of CuBr and O_2 as the reoxidizing reagent system furnished 1,2,3a,14a-tetraaryl-3a,14a-dihydro-13*H*-furo[3′,2′:3,4]isoquinolino[1,2-*b*]quinazolin-13-ones **8t** (Eq. 66).[113,114]



(66)

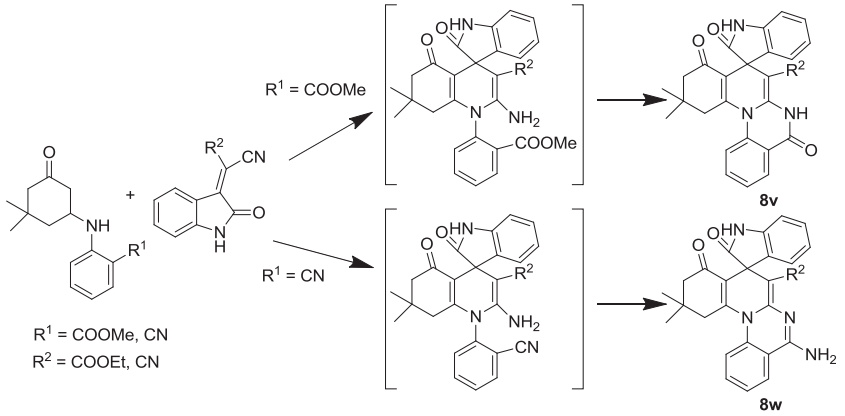
Synthesis of several pyrido[1,2-*a*]pyrimidine derivatives was reported previously[1] and their properties and application were discussed more recently.[115–119] A novel efficient approach to pyrido[1,2-*a*]pyrimidine derivatives **8u** is shown in Eq. (67).[120]



(67)

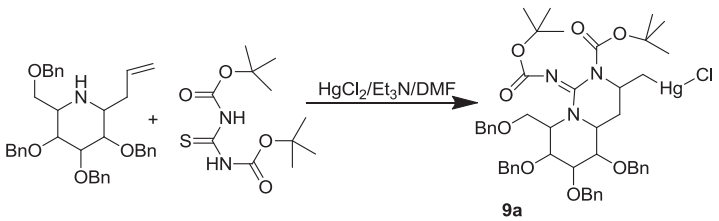
R^1 = Me, CF_3; R^2 = H, Ph, Cl, Br, CN, CF_3, COOEt, OAlkyl

One-pot synthesis of hexahydrospiro[indoline-3,8′-quinolino[1,2-*a*]quinazoline] derivatives **8v** and **8w** was described recently (Scheme 35).[121]



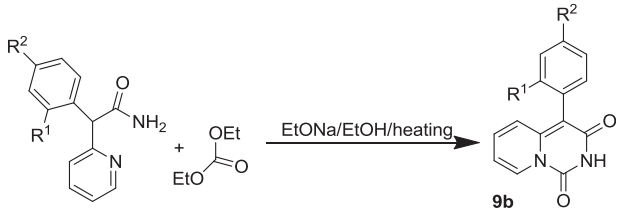
Scheme 35

A saturated pyrido[1,2-*c*]pyrimidine derivative **9a** was synthesized by the reaction of an allylpiperidine with *N,N′*-bis-(*tert*-butoxycarbonyl)thiourea in the presence of $HgCl_2$ and Et_3N in dry DMF medium (Eq. 68).[29]



(68)

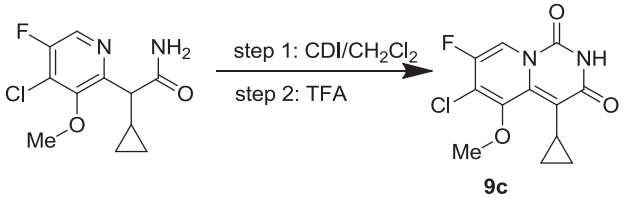
New derivatives of 4-aryl-pyrido[1,2-*c*]pyrimidine **9b** were synthesized as shown in Eq. (69).[122–124]



(69)

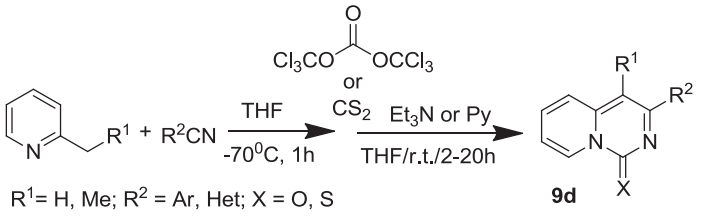
R^1 = H, F; R^2 = H, Me, OMe, F, Cl

Pyrido[1,2-*c*]pyrimidine-1,3-dione **9c** is a core structure of a new fluoroquinolone-like class of antibacterial agents[125] (Eq. 70).



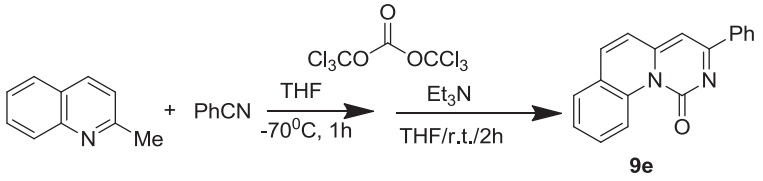
(70)

Three-component coupling reaction was developed for the synthesis of 3,4-fused pyrimidin-2-(thio)ones **9d** from a pyridine, a nitrile and triphosgene or carbon disulfide[126] (Scheme 36).



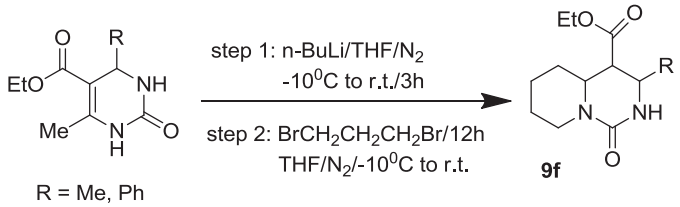
Scheme 36

Moreover, the use of 2-methylquinoline as starting compound (Scheme 37) furnished tricyclic pyrimidine derivatives **9e** in a good yield under similar conditions.[126]



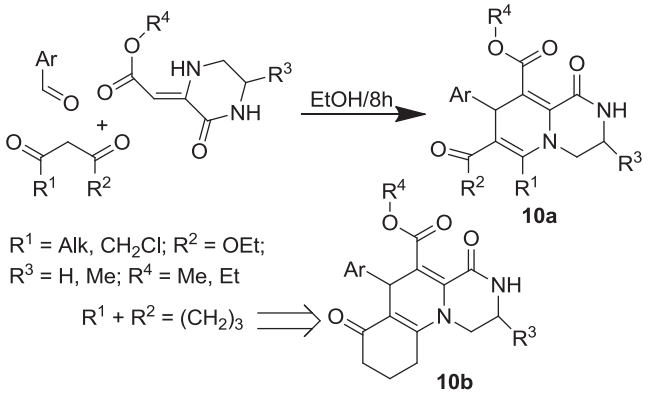
Scheme 37

6-Methyldihydropyrimidine-2-ones are readily lithiated at the C-6 methyl position along with two NH moieties upon treatment with *n*-butyllithium at 10 °C. The trianion thus generated undergoes a reaction with 1,3-dibromopropane to afford bicyclic derivatives **9f**[127] (Eq. 71).



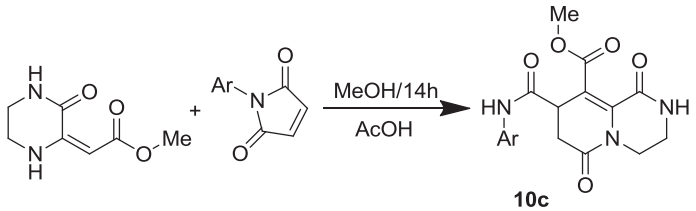
(71)

An efficient, general method for the synthesis of pyrido[1,2-*a*]pyrazines **10a** and pyrazino[1,2-*a*]quinolones **10b** by one-pot three-component reaction between cyclic enaminones, aromatic aldehydes, and 1,3-dicarbonyl compounds was reported by Vovk[128] (Eq. 72). Pyrido[1,2-*a*]pyrazine-7,9-dicarboxylates **10a** and pyrazino[1,2-*a*]quinoline-5-carboxylates **10b** were obtained in moderate (40–51%) to high (71–73%) yields, respectively, after reflux for 8 h of the mixture in ethanol.



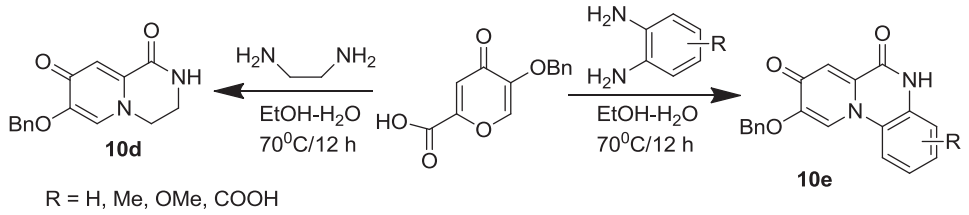
(72)

A similar approach was described starting from methyl-(3-oxopiperazin-2-ylidene)-acetate and arylmaleimides[129] (Eq. 73). The desired 6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrazine-9-carboxylates **10c** were obtained upon heating a solution in methanol in the presence of a catalytic amount of acetic acid.



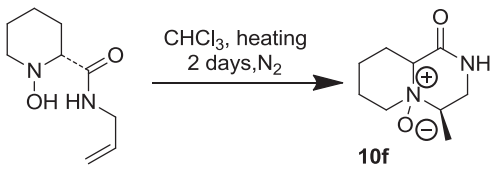
(73)

Treatment of the pyranone shown in Scheme 38 with a range of 1,2-diamines with heating resulted in an intermolecular condensation to produce the corresponding bicyclic lactam **10d** and its benzo analogs **10e**[130] (Scheme 38). It should be mentioned that the reaction with 4-substituted benzene-1,2-diamine yields two isomeric products.



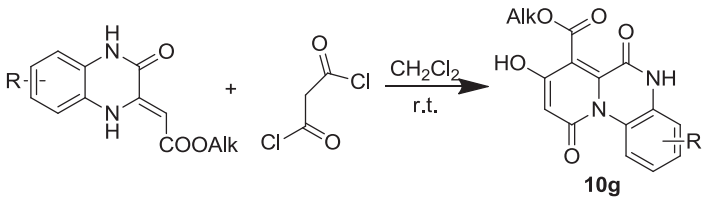
Scheme 38

A reverse Cope elimination of a cyclic hydroxylamine, shown in Eq. (74), at room temperature furnishes bicyclic lactam *N*-oxide **10f**. This reaction is greatly accelerated by heating in chloroform under nitrogen to give an 87% yield of *N*-oxide **10f** as a single diastereoisomer (Eq. 74).[33]



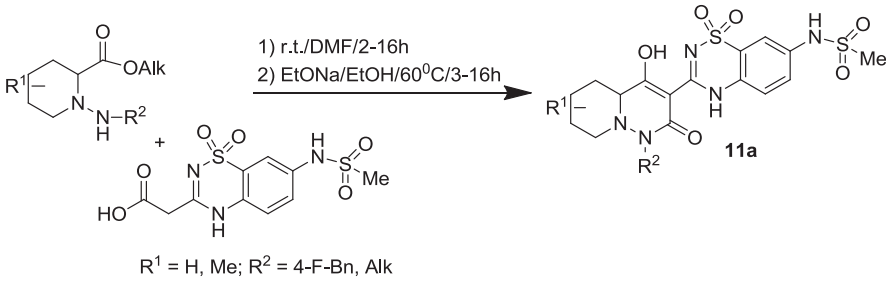
(74)

An efficient and convenient synthetic route to alkyl 8-hydroxy-6,10-dioxo-6,10-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-7-carboxylates **10g** by the reaction between malonyl dichloride and alkyl 2-[3,4-dihydro-3-oxoquinoxaline-2(1*H*)-ylidene]acetates in CH_2Cl_2 at room temperature was reported by Yavari (Eq. 75).[36]



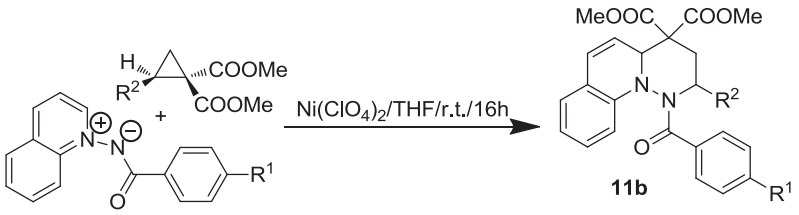
(75)

N-Substituted hydrazines were coupled with a heteroaryl acid and subsequently cyclized in the presence of sodium ethoxide to give the desired hexahydro-1*H*-pyrido[1,2-*b*]pyridazin-2-ones **11a** (Eq. 76).[131]



(76)

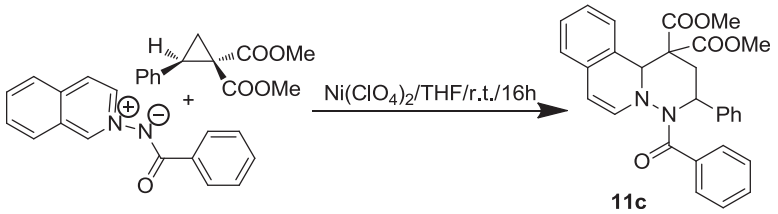
The cycloaddition of quinolinium azomethine imines to 1,1-cyclopropane diesters was achieved using $Ni(ClO_4)_2$ as catalyst. This methodology gives access to unique tricyclic dihydroquinoline derivatives **11b** in good yield (Eq. 77).[132]



(77)

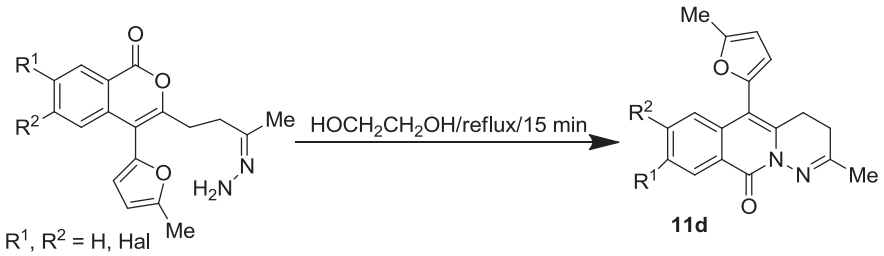
R^1 = H, CF_3, OMe; R^2 = H, $CH{=}CH_2$, Ar

In a similar way, the reaction of *N*-benzoyliminoisoquinolinium ylide with a cyclopropane dicarboxylate furnished the adduct **11c** in modest yield (Eq. 78).[132]



(78)

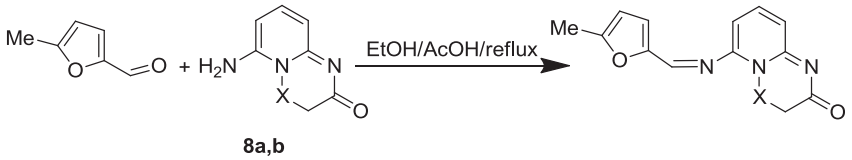
An efficient approach to the synthesis of pyridazino[1,6-*b*]isoquinolinones **11d** is based on a facile substitution of an endocyclic isochromone oxygen atom by nitrogen-containing nucleophiles such as hydrazines (Eq. 79).[133]



(79)

4.2 Reactivity and structural features

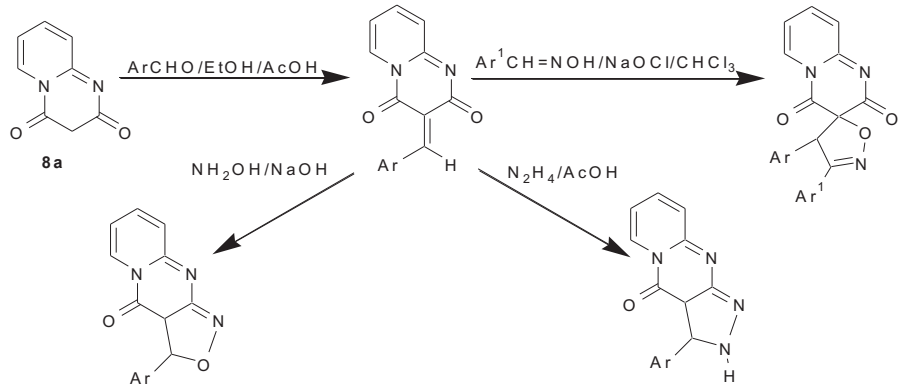
Amino-substituted pyrido[1,2-*a*]pyrimidin-2,4-dione **8a** and pyrido[1,2-*a*]pyrimidin-2-one **8b** are convenient substrates for a chemical modification. Their treatment with 5-methylfuran-2-carbaldehyde in refluxing ethanol containing a few drops of acetic acid yielded 6-((4-methylfuran-2-yl)methyleneamino)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one and 6-((4-methylfuran-2-yl) methyleneamino)-2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-dione (Eq. 80).[86]



(80)

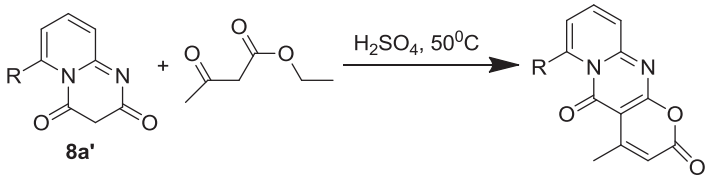
X = CH_2, C=O

2*H*-Pyrido[1,2-*a*]pyrimidine-2,4(3*H*)dione **8a** underwent Claisen condensation with aromatic aldehydes to afford chalcones. These chalcones were allowed to react with aromatic oximes, hydroxylamine and hydrazine hydrate to furnish cyclized products 4-(aryl)-3-(3-substituted phenyl)4*H*-spiro[isoxazole-5,3-pyrido[1,2-*a*]pyrimidine]-2,4-dione, 3-(aryl)-3*H*-isoxazole[3,4-*d*]pyrido[1,2-*a*]pyrimidin-4-(3a*H*)-one and 3-(aryl)-3,3a-dihydropyrazolo[3,4-*d*]pyrido[1,2-*a*]pyrimidin-4-(2*H*)-one (Scheme 39).[87]



Scheme 39

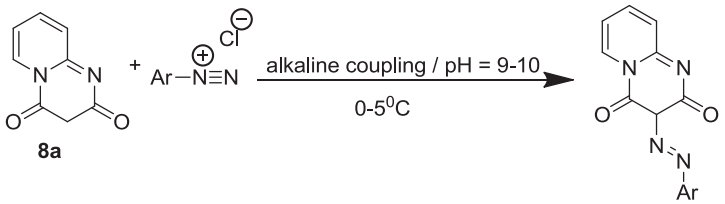
Treatment of 2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)diones **8a′** in conc. H_2SO_4 with ethyl acetoacetate afforded fluorescent whitening compounds after heating for 1 h at 50 °C (Eq. 81).[88]



(81)

The fluorescent whitening agents based on 4-methyl-2*H*,5*H*-pyrane derivatives of 2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-dione were characterized by ^{1}H, ^{13}C NMR, and HRMS.[88] Photophysical properties in various microenvironments were studied out experimentally and correlated with optical absorption and fluorescence emission using global hybrid (B3LYP) and long range separated functional (CAM-B3LYP) with the Pople's 6–31G(d) basis set and in combination with polarizable continuum model. The experimental and theoretical photophysical properties were in a good agreement with each other.[88]

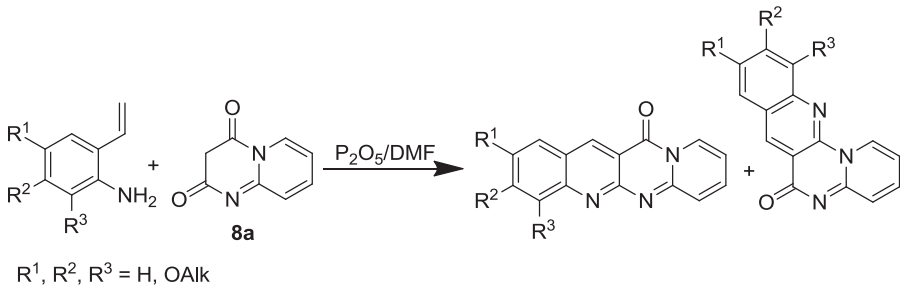
The bicyclic dione **8a** was used in diazo-coupling reaction for synthesis of pyrido[1,2-*a*]pyrimidine-containing dyes (Eq. 82).[89]



(82)

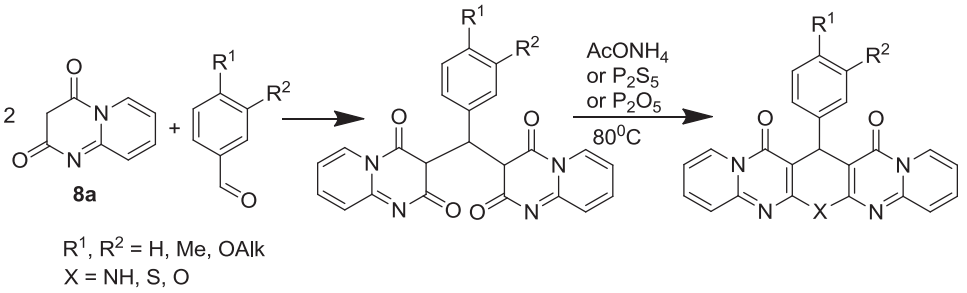
These dyes were characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and elemental analysis. They were applied on nylon, silk, and wool. Their fastness properties were evaluated and color on the fabric was assessed. Yellow, brown, and crimson colors with good fastness properties were obtained.[89]

The interaction of bicyclic diketone **8a** with carbonyl compounds expands the boundaries of the synthetic design of polycyclic heterocyclic systems.[90] For example, condensation of **8a** with 2-aminostyrenes produced mainly the linear products and the angular dyes as minor products (Eq. 83).



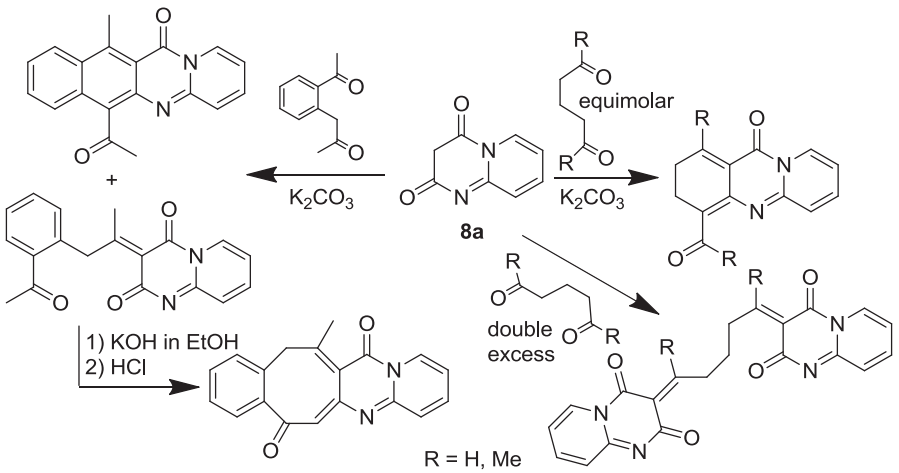
(83)

The condensation of **8a** with aromatic aldehydes in ethylene glycol in the absence of any catalyst furnished the symmetrical pentacyclic systems, as shown in Scheme 40.[90]



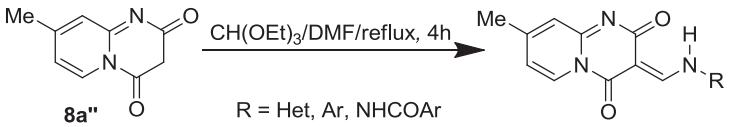
Scheme 40

The cyclocondensation of **8a** with 1,5-diketones afforded linear systems, as shown in Scheme 41.



Scheme 41

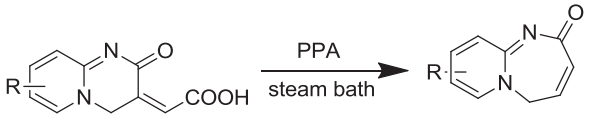
Amino derivatives of pyrido[1,2-*a*]pyrimidine were prepared by refluxing equimolar quantities of 8-methyl-2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)dione **8a″** with respective anilines, aminopyridines, or hydrazides in the presence of triethylorthoformate (Eq. 84).[91]



(84)

Single crystal X-ray diffraction analysis of **8d** (Eq. 53, Ar = 2-BrPh) confirmed the structure of the product.[94]

The rearrangement of 2-[2-oxo-2*H*-pyrido[1,2-*a*]pyridmidin-3(4*H*)-ylidene)]acetic acid **8h** promoted by heating in PPA in a steam bath yielded a seven-membered pyridodiazepines after decarboxylation and ring expansion (Eq. 85).[100]



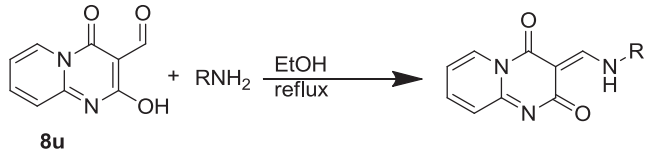
(85)

The mechanism of the intramolecular aza-Michael addition with formation of bicyclic products **8k** [Eq. 59, Ar = 3,4-di(OMe)Ph] and the molecular structures of the products were investigated.[103] The X-ray diffraction analysis revealed that the partially reduced pyrimidine ring exists in a half-chair conformation and the dihedral angle between Ar and NO_2 is ~165°.

The NMR spectroscopic data of a series of 34 3-acylpyrido[1,2-*a*]pyrimidinium salts **8l** (Eq. 60) were analyzed.[105] Unequivocal assignment of all resonances was achieved via two-dimensional $^{1}H,^{1}H$-COSY measurements, $^{1}H,^{13}C$ and $^{1}H,^{15}N$ HSQC as well as HMBC experiments, and important diagnostic CH and NH couplings in the heteroaromatic ring system were recorded. The influence of the methyl substituents on the proton, carbon and nitrogen chemical shifts was analyzed. A significant effect of the counter ion on some chemical shifts of the pyridopyrimidines under discussion was found, allowing an indirect detection of the anion.[105]

The structure of **8m** (Scheme 33, R^1 = Ph, R^2 = CF_3, R^3 = cyclohexyl) was determined using X-ray crystallographic analysis, and 2D NMR measurements fully supported this structure.[106]

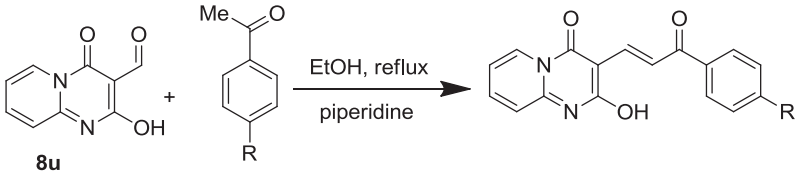
Reactivity of 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde **8u** toward *N*- nucleophiles was studied.[115] Bicyclic aldehyde **8u** was heated under reflux with primary amines, semicarbazide, thiosemicarbazide, hydrazides and hydrazines in absolute ethanol to give the corresponding 3-[(R-NH)-methylene)pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-diones in a good yield (Eq. 86).[115]



8u (86)

R = Alk, Ar, $NHCSNH_2$, $NHCONH_2$, NHCOAr, NHHet

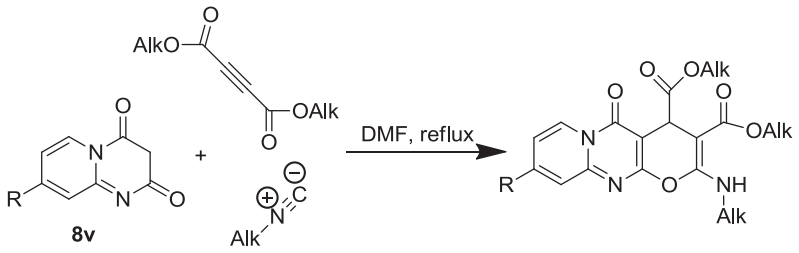
The Knoevenagel condensation reaction of aldehyde **8u** with methyl ketones in the presence of piperidine furnished chalcones (Eq. 87).[115]



8u (87)

R = H, Alkyl, OMe, Hal

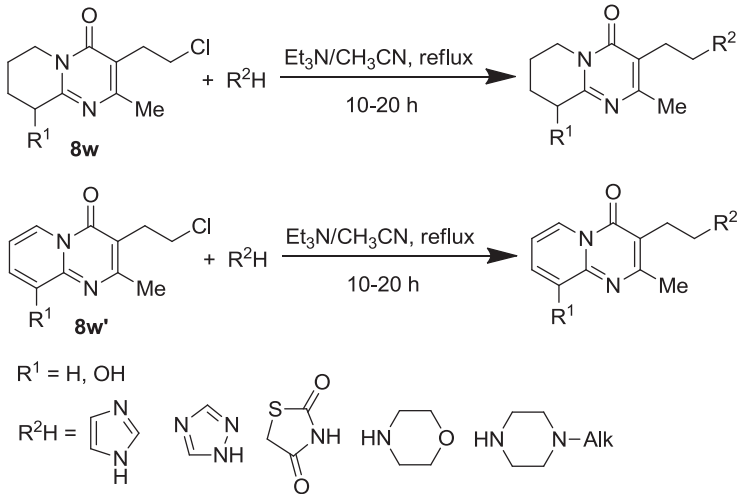
The reaction between 2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-dione **8v**, isocyanides and dialkyl acetylenedicarboxylates afforded tricyclic fused pyrano[2,3-*d*]pyrido[1,2-*a*]pyrimidines (Eq. 88).[116] The products were obtained in good to excellent yields over short reaction times and with a simple work-up procedure.



8v (88)

R = H, Me

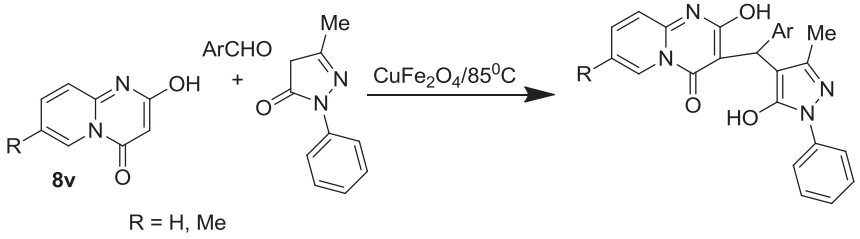
The synthesis of pyrido[1,2-*a*]pyrimidines substituted with various (heterocyclic amino)ethyl moieties starting with chloroethyl-substituted fused pyrimidinones **8w** and **8w′** is shown in Scheme 42.[117]



Scheme 42

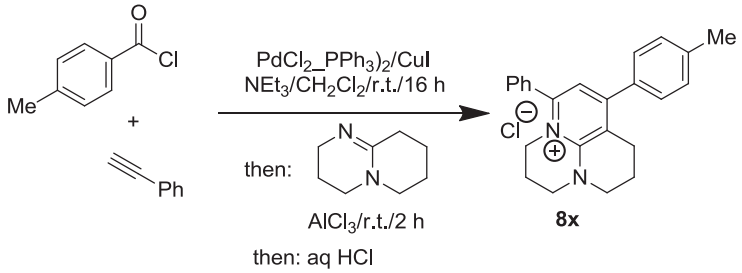
The structures of synthesized heterocyclic derivatives derived from substrate **8w′** were confirmed by spectral and analytical techniques. In one case (R^1 = H, R^2 = 1,2,4-triazol-1-yl), an X-ray diffraction analysis was carried out.

An efficient one-pot three-component synthesis of highly functionalized benzylpyrazolyl-substituted pyrido[1,2-*a*]-pyrimidine derivatives starting with substrate **8v** in the presence of $CuFe_2O_4$ nanoparticles under solvent-free conditions is shown in Eq. (89).[118]



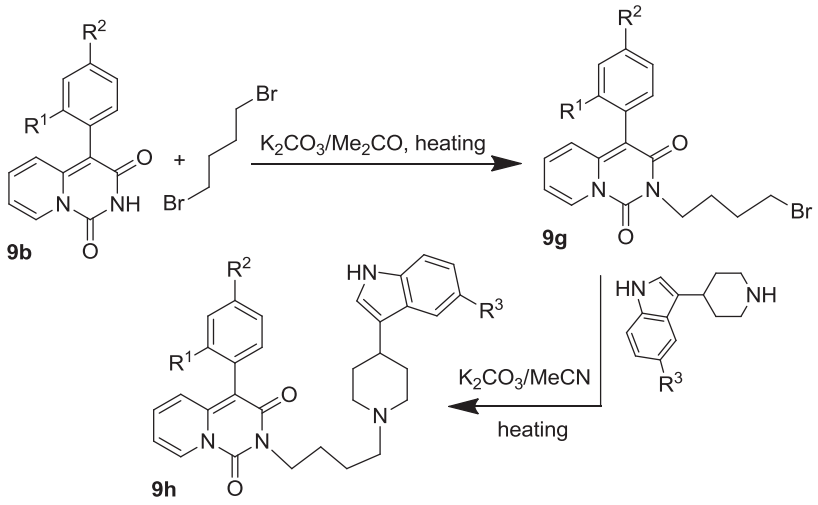
(89)

In the highly efficient synthesis of the fused tricyclic product **8×**, p-tolyoyl chloride was coupled with phenylacetylene, and the generated intermediate product was allowed to react with hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine (Eq. 90).[119] Analytically pure compound **8×** was obtained upon treatment of the mixture with aqueous hydrochloric acid.

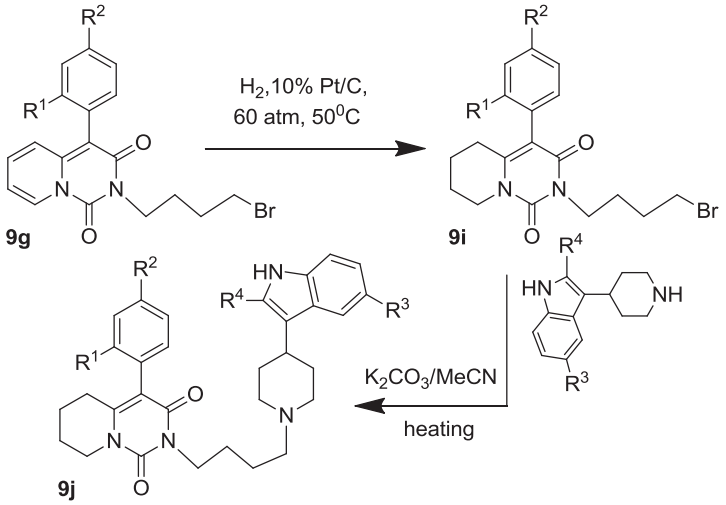


(90)

Compounds **9h** of pharmacological interest were synthesized by mono-alkylation of substrate **9b** with 1,4-dibromobutane, followed by coupling of the resultant intermediate product **9g** with a piperidyl-substituted indole (Scheme 43).[122] The structure of **9h** (R^1 = H, R^2 = Cl, R^3 = H) was confirmed by using an XRD experiment. The saturated analogs **9i** and **9j** were also synthesized starting with hydrogenation of the substrate **9g**, as shown in Scheme 44.[123,124]



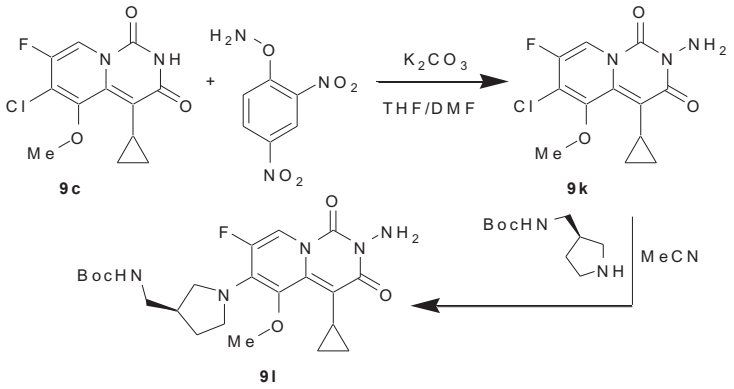
Scheme 43



R^1 = H, F; R^2 = H, Me, OMe, F, Cl; R^3 = H, OMe; R^4 = H, Me

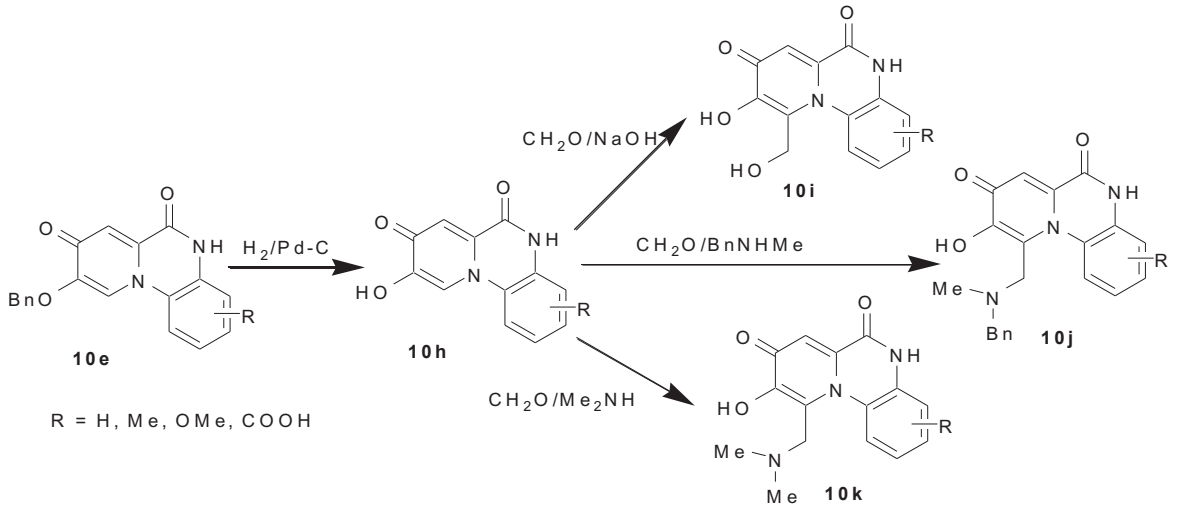
Scheme 44

N-Amination of **9c** was achieved by treatment with *O*-(2,4-ditrophenyl)hydroxylamine to supply 1,3-dione **9k** in high yield[125] (Scheme 45). Compound **9k** was transformed into **9l** which is a scaffold for the development of quinolone-like antibacterial compounds.



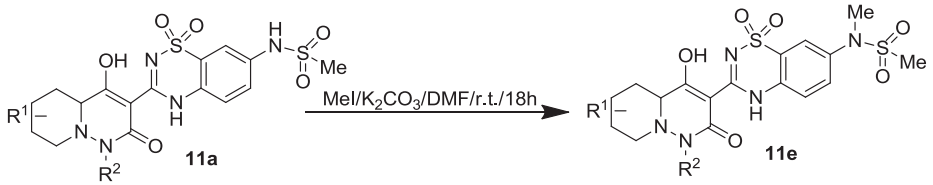
Scheme 45

The protected lactams **10e** in ethanol were subjected to hydrogenolysis in the presence of 5% Pd/C catalyst for 5 h to afford high yields of fluorescent chelators **10h**[130] (Scheme 46). These products were further transformed into derivatives **10i, 10j** and **10k**.



Scheme 46

Treatment of compounds **11a** with iodomethane yielded *N*-methylated analogs **11e** (Eq. 91).[131]



(91)

Stereochemistry of **11b** (Eq. 77, $R^1 = H$, $R^2 = Ph$) was studied using X-ray diffraction analysis state. This compound exists preferentially in a boat conformation.[132]

4.3 Application and important compounds

The ability of various pyrido[1,2-*a*]pyrimidines **8** to inhibit the HIV integrase was reviewed by Patel.[134] Several derivatives of **8** were also screened for antitumor activity against liver (HEPG2) cell line.[86] The biochemical effects of the compounds on some enzymes such as AST, ALT and (ALP), in addition to albumin, globulins, creatinine, total lipids, cholesterol, triglycerides and bilirubin in serum of mice were studied in comparison to 5-FU and DOX. The antitumor activity results indicated that these compounds show good growth inhibition activity against the tested cell line but with varying potency in comparison to the known anticancer drugs 5-FU and DOX.[86]

The spiro compounds **8v** and **8w** (Scheme 35) show excellent activity against both bacterial and fungal strains. The zone of inhibition for some of these samples was substantial against the *S. aureus*, *B. subtilis* and the fungus *C.albicans*.[87] These compounds were also screened for *in vitro* antiinflammatory activity against hyaluronidase enzyme.[117]

Several fused derivatives of pyrido[1,2-*a*]pyrimidine **8** have been screened for bronchodilatory and antimicrobial activities with promising results[90]; some of them were found to be significantly more potent inhibitors of urease activity in comparison to thiourea, a standard urease inhibitor as a reference [91].

The pyrido[1,2-*a*]pyrimidine-3-carbonitrile derivatives **8e** (Eq. 54) exhibit varying patterns of antibacterial and antifungal activities. The test results of *in vitro* antibacterial activity revealed that some of the synthesized compounds exhibit equipotent activity in comparison with standard drug ampicillin and also inhibit *E. coli*, *B. subtilis* and *S. aureus*.[95]

The cytotoxic activity of some of the bicyclic compounds **8g** (Eq. 56) has been investigated *in vitro* by the National Cancer Institute (USA) on a standard panel consisting of 60 human tumor-cell lines. Most of the tested compounds exhibit cytotoxic activity without a clear selectivity for cell lines belonging to different subpanels.[99]

3-Aroylpyrido[1,2-*a*]pyrimidines **8l** (Eq. 60) were evaluated as NOS inhibitors.[104] The influence of a substituent in the pyrimidine moiety on bioactivity of compound was investigated experimentally using a structure–activity relationship analysis. Compounds with a biphenyloyl, benzyloxybenzoyl or naphthoyl group display the highest inhibitory effects which are further increased by introduction of a methyl group in position 8 of the pyrido[1,2-*a*]pyrimidine system. Some of the compounds exhibit promising inhibitory effects with selectivity toward the purified inducible nitric oxide synthases (iNOS) and are also active against iNOS expressed in stimulated RAW 264.7 cells.

Tricyclic salt **8** × (Eq. 90) exhibits a remarkable light emission in dichloromethane, water and in the solid state.[119] The intensely blue to turquoise luminophore displays high fluorescent quantum yield. This salt is well suited for development of tailored fluorescence probes for labeling of biomolecules *in vitro* and in vivo as well as on surfaces.

In vitro experiments showed that 4-aryl-pyrido[1,2-*c*]pyrimidines **9g-j** (Schemes 43 and 44) exhibit high to moderate binding to the 5-HT_{1A} receptor and to the 5-HT transporter.[122,123]

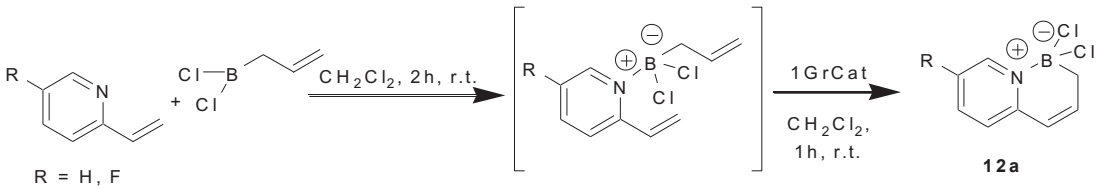
The compounds **10e** and **10h-k** (Scheme 46) have been developed in order to replace the traditional fluorescent probes for the quantification of intracellular labile iron pools.[130] The relatively low pKa values of the ligands result from an inductive effect of the amido group at the 6-position. As a result of the decreased competition with protons, the pFe^{3+} values are increased.

Hexahydro-1*H*-pyrido[1,2-*b*]pyridazin-2-ones **11a, 11e** (Eq. 91) are a novel class of inhibitors of genotype 1 HCV NS5B polymerase.[131] In particular, compound **11a** displays potent inhibitory activities in biochemical and replicon assays and good stability toward human liver microsomes.

5 Pyrido[2,1-*f*][2,1]azaborines 12 and a pyrido[2,1-*b*][1,3]selenazine 13a

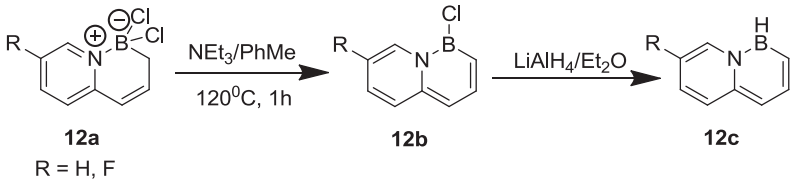
5.1 Synthesis and structural features

Selenium-nitrogen[70,135] and boron-nitrogen[136,137] fused heterocyclic systems hold great promise for practical applications in many areas of chemistry. The BN/CC isosterism, the replacement of a CC unit with a BN unit, has emerged as an effective strategy to expand the chemical space of organic molecules. The quite unstable compounds **12a** of the parental BN naphthalene series were synthesized by a simple procedure from commercially available 2-vinylpyridine using Grubbs' first generation metathesis catalyst $(Cy_3P)_2(PhCH)RuCl_2$ (Scheme 47).[136]



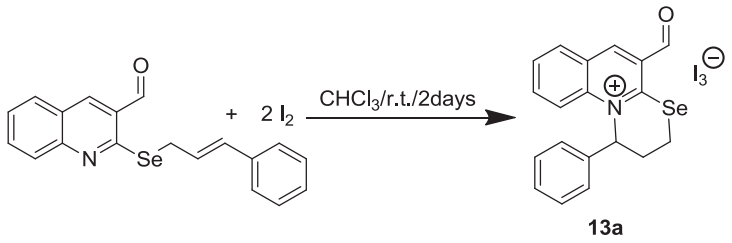
Scheme 47

The elimination of HCl from compound **12a** in the presence of triethylamine as base furnished the B–Cl substituted BN-naphthalene derivative **12b** (Scheme 48).[133] Subsequent reduction of **12b** with lithium aluminium hydride gave the parent 1,2-BN-naphthalene **12c** – the model structure for theoretical and experimental investigations.[136,137] Notably, the synthesis of 1*H*-pyrido[2,1-*f*][2,1]azaborine **12c** allowed Liu[137] to discern certain trends regarding the electronic structure of 1,2-BN-naphthalenes with respect to the orientation of the BN unit within the bicyclic structure. The X-ray diffraction analysis of fluorine-substituted **12c** (R = F) unambiguously established the connectivity in the bicyclic fused system. Analysis of the crystal packing of **12c** revealed a "herringbone" motif much like in its all-carbon analog. Thus, the unique packing is a direct result of BN/CC isosterism.[136]



Scheme 48

Electrophilic cyclization of 2-(3-phenyl-2-propenylselanyl)-3-quinolinecarbaldehyde upon treatment with iodine in chloroform at room temperature for 2 days furnished fused [1,3]selenazino[3,2-*a*]quinolinium triiodide **13a** (Eq. 92).[70]



(92)

5.2 Application and important compounds

BN/CC isosterism can influence the crystal packing, resulting in a face-to-face π-stacking motif for BN-9,1-Naph **12c** vs a herringbone motif for its carbonaceous isostere 2-fluoronaphthalene.[136,137] The established trends may be general for other BN acenes. Thus, the described findings are important for targeted syntheses of BN acenes for optoelectronic applications.

References

1. Hermecz, I.; Vasva'ri-Debreczy, L. 12.02 Bicyclic 6-6 Systems with one bridgehead (ring junction) nitrogen atom: One extra heteroatom 1:0. In *Comprehensive Heterocyclic Chemistry III*; Katrizky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 2008; vol. 12, pp 77–141.
2. Hermecz, I. *Adv. Heterocycl. Chem.* **2011**, *104*, 1–126.
3. Asghari, S.; Habibi, A. K. *Tetrahedron* **2012**, *68*, 8890–8898.
4. Asghari, S.; Habibi, A. K. *Heteroatom Chem.* **2017**, *28*, e21378–e21386.
5. Yavari, I.; Hossaini, Z.; Moradi, L. *Monatsh Chem.* **2008**, *139*, 953–956.
6. Lei, M.; Tian, W.; Hu, R.; Li, W.; Zhang, H. *Synthesis* **2012**, *44*, 2519–2526.
7. Zhiliang Xu, Z.; Sun, T.; Cai, Q.; Ni, F.; Han, J.; Chen, J.; Deng, H.; Shao, M.; Zhang, H.; Cao, W. *J. Fluorine Chem.* **2016**, *181*, 45–50.
8. Sayadian, H.; Yavari, I.; Halvagar, M. R. *Monatsh Chem.* **2018**, *149* (8), 1469–1474.
9. Yavari, I.; Hossaini, Z.; Sabbaghan, M.; Ghazanfarpour-Darjani, M. *Monatsh Chem.* **2007**, *138*, 677–681.
10. Esmaeili, A. A.; Nazer, M. *Synlett* **2009**, *13*, 2119–2122.
11. Liu, G.; Wu, Y.; Han, J.; He, W.; Chen, J.; Deng, H.; Shao, M.; Zhang, H.; Cao, C. *Synthesis* **2018**, *50* (23), 4668–4682.
12. Nair, V.; Devipriya, S.; Eringathodi, S. *Tetrahedron Lett.* **2007**, *48*, 3667–3670.
13. Yavari, I.; Hojatia, M.; Azad, L.; Halvagar, M. R. *Synlett* **2018**, *29*, 1024–1027.
14. Ihara, S.; Soma, T.; Yano, D.; Aikawa, S.; Yoshida, Y. *J. Heterocycl. Chem.* **2011**, *48*, 577–581.

15. El-Sayed, R. *J. Oleo Sci.* **2015**, *64* (7), 761–774.
16. Sośnicki, J. G.; Struk, L. *Synlett* **2010**, *8*, 1209–1214.
17. Yang, H.-B.; Zhao, Y.-Z.; Sang, R.; Tang, X.-Y.; Shi, M. *Tetrahedron* **2013**, *69*, 9205–9211.
18. Szatmari, I.; Heydenreich, M.; Koch, A.; Fulop, F.; Kleinpeter, E. *Tetrahedron* **2013**, *69*, 7455–7465.
19. Szatmari, I.; Fulop, F. *Tetrahedron* **2011**, *52*, 4440–4442.
20. Osyanin, V. A.; Ivleva, E. A.; Rybakov, V. B.; Klimochkin, Y. N. *Crystal. Rep.* **2015**, *60*, 67–71.
21. Croy, C. H.; Chan, W. Y.; Castetter, A. M.; Watt, M. L.; Quets, A. T.; Felder, C. C. *Eur. J. Pharmacol.* 2016, 782, 70–76.
22. El-Hashash, M. A. E.-A.; Azab, M. E.; Faty, R. A. E.-A.; Amr, A. E.-G. E. *Chem. Pharm. Bull.* 2016, 64, 263–271.
23. Jiang, B.; Zhou, Y.; Kong, Q.; Jiang, H.; Liu, H.; Li, J. *Molecules* **2013**, *18*, 814–831.
24. Malapaka, C.; Daggupati, R. V.; Kankatala, G. S.; Botla, V.; Balasubramanian, S. *New J. Chem.* **2016**, *40*, 6389–6395.
25. Hekal, M. H.; El-Azm, F. S. M. A. *J. Heterocyclic Chem.* **2017**, *54*, 3056–3064.
26. Heydenreich, M.; Koch, A.; Szatmari, I.; Fulop, F.; Kleinpeter, E. *Tetrahedron* **2008**, *64*, 7378–7385.
27. Kuznetsov, N. Y.; Khrustalev, V. N.; Godovikov, I. A.; Yu.N., B. *Eur. J. Org. Chem.* **2015–2021**, *2007*.
28. Fuchs, C.; Bender, C.; Ziemer, B.; Liebscher, J. *J. Heterocyclic. Chem.* **2008**, *45*, 1651–1658.
29. Cipolla, L.; Fernandes, M. R.; Gregori, M.; Airoldi, C.; Nicotra, F. *Carbohydrate Research* **2007**, *342*, 1813–1830.
30. Burrell, A. J. M.; Coldham, L.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, *74*, 2290–2300.
31. Burrell, A. J. M.; Coldham, L.; Oram, N. *Org. Lett.* **2009**, *11* (7), 1515–1518.
32. Adrien, A.; Gais, H.-J.; Kohler, F.; Runsink, J.; Raabe, G. *Org. Lett.* **2007**, *9* (11), 2155–2158.
33. Krishna, P. R.; Sreeshailam, A. *Tetrahedron Lett.* **2007**, *48*, 6924–6927.
34. Sun, C.-S.; Lin, Y.-S.; Hou, D.-R. *J. Org. Chem.* **2008**, *73*, 6877–6880.
35. Fustero, S.; Mateu, N.; Albert, L.; Acena, J. L. *J. Org. Chem.* **2009**, *74*, 4429–4432.
36. Yavari, I.; Souri, S.; Sirouspour, M.; Bayat, M. J. *Synlett* **2009**, *12*, 1921–1922.
37. Basarab, G. S.; Brassil, P.; Doig, P.; Galullo, V.; Haimes, H. B.; Kern, G.; Kutschke, A.; McNulty, J.; Schuck, V. J. A.; Stone, G.; Gowravaram, M. *J. Med. Chem.* **2014**, *57* (21), 9078–9095.
38. Kalepu, J.; Katukojvala, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 7831–7835.
39. Sarro, A. D.; Sarro, G. D. *Curr. Med. Chem.* **2001**, *8*, 371–384.
40. Anderson, V. E.; Osheroff, N. *Curr. Pharm. Des.* **2001**, *7*, 339–355.
41. Dinakaran, M.; Senthilkumar, P.; Yogeeswari, P.; China, A.; Nagarajab, V.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1229–1236.
42. Pasquini, S.; De Rosa, M.; Pedani, V.; Mugnaini, C.; Guida, F.; Luongo, L.; De Chiaro, M.; Maione, S.; Dragoni, S.; Frosini, M.; Ligresti, A.; Di Marzo, V.; Corelli, F. *J. Med. Chem.* **2011**, *54*, 5444–5453.
43. Fustero, S.; Albert, L.; Acen, J. L.; Sanz-Cervera, J. F.; Asensio, A. *Org. Lett.* **2008**, *10* (4), 605–608.
44. Yi, C.; Liu, S.-X.; Neels, A.; Renaud, P.; Decurtins, S. *Org. Lett.* 2009, 11 (23), 5530–5533.
45. Tsimilaza, A.; Tite, T.; Boutefnouchet, B.; Lallemand, M.-C.; Tillequina, F.; Husson, H.-P. *Tetrahedron Asymmetry* **2007**, *18*, 1585–1588.
46. Tomilov, Y. V.; Platonov, D. N.; Okonnishnikova, G. P. *Tetrahedron Lett.* 2009, 50, 5605–5608.
47. Calosso, M.; Wagner, M.; Gendrineau, T.; Petit, M.; Puchot, C. R.; Dechoux, L. *Lett. Org. Chem.* **2007**, *4*, 4–6.
48. Ellis, G. L.; O'Neil, I. A.; Ramos, V. E.; Cleator, E.; Kalindjian, S. B.; Chorltonc, A. P.; Tapolczay, D. J. *Tetrahedron Lett.* **2007**, *48*, 1683–1686.
49. Signore, G.; Malanga, C.; Menicagli, R. *Tetrahedron* **2008**, *64*, 197–203.
50. Kaluza, Z.; Mostowicz, D.; Dolega, G.; Wo'jcik, R. *Tetrahedron* **2008**, *64*, 2321–2328.
51. Boutefnouchet, S.; Moldvai, I.; Gács-Baitz, E.; Bello, C.; Vogel, P. *Eur. J. Org. Chem.* **2007**, 3028–3037.
52. Steiner, A. J.; Schitter, G.; Stütz, A. E.; Wrodnigg, T. M.; Tarling, C. A.; Withers, S. G.; Fantur, K.; Mahuran, D.; Paschke, E.; Tropak, M. *Bioorg. Med. Chem.* **2008**, *16*, 10216–10220.
53. Yamazaki, S.; Iwata, Y.; Fukushima, Y. *Org. Biomol. Chem.* **2009**, *7*, 655–659.
54. Chen, Y.; Porco, J. A.; Panek, S., Jr.; Panek, J. S. *Org. Lett.* **2007**, *9* (8), 1529–1532.
55. Kourounakis, A. P.; Charitos, C.; Rekka, E. A.; Kourounakis, P. N. *J. Med. Chem.* **2008**, *51*, 5861–5865.
56. Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Pipko, S. E.; Tolmachev, A. A. *Synth. Commun.* **2008**, *38*, 3032–3043.
57. Ruble, G. C.; Hurd, A. R.; Johnson, T. A.; Sherry, D. A.; Barbachyn, M. R.; Toogood, P. L.; Bundy, G. L.; Graber, D. R.; Kamilar, J. M. *J. Am. Chem. Soc.* 2009, 131, 3991–3997.
58. Bates, R. W.; Song, P. *Synthesis* **2009**, *4*, 655–659.
59. Kleinpeter, E.; Szatmari, I.; Lazar, L.; Koch, A.; Heydenreich, M.; Fulop, F. *Tetrahedron* **2009**, *65*, 8021–8027.
60. Hou, D. R.; Hung, S.-Y.; Hu, C.-C. *Tetrahedron Asymmetry* **2005**, *16* (23), 3858–3864.
61. Mohammadhosseini, N.; Zahra Alipanahi, Z.; Alipour, E.; Emami, S.; Faramarzi, M. A.; Samadi, N.; Khoshnevis, N.; Shafiee, A.; Foroumadi, A. *DARU J. Pharm. Sci.* **2012**, *20*, 2231–2236.
62. German, N.; Wei, P.; Kaatz, G. W.; Kerns, R. J. *Eur. J. Med. Chem.* **2008**, *43*, 2453–2463.
63. Abdullah, M. A. A.; Abuo-Rahma, G. E.-D.; Abdelhafez, E. M. N.; Hassan, H. A.; AbdelBaky, R. M. *Bioorg. Chem.* **2017**, *70*, 1–11.
64. Tan, L.; Zhang, Z.; Gao, D.; Chan, S.; Luo, J.; Tu, Z.-C.; Zhang, Z.-M.; Ding, K.; Ren, X.; Lu, X. *Eur. J. Med. Chem.* **2019**, *166*, 318–327.
65. Harrowven, D. C.; Sutton, B. J. *Prog. Heterocycl. Chem.* **2004**, *16*, 27–53.
66. Kawakami, K.; Namba, K.; Tanaka, M.; Matsuhashi, N.; Sato, K.; Takemura, M. *Antimicrob. Agents Chemother.* **2000**, *44*, 2126–2129.
67. Asahina, Y.; Takei, M.; Kimura, T.; Fukuda, Y. *J. Med. Chem.* **2008**, *51*, 3238–3249.
68. Basarab, G. S.; Doig, P.; Galullo, V.; Kern, G.; Kimzey, A.; Kutschke, A.; Newman, J.; Morningstar, M.; Mueller, J.; Otterson, L.; Vishwanathan, K.; Zhou, F.; Gowravaram, M. *J. Med. Chem.* **2015**, *58* (15), 6264–6282.
69. Abdel-Ghany, H.; El-Sayed, A. M.; Amer, A. A.; Ahmed, A. M. *J. Heterocycl. Chem.* **2015**, *53*, 2013–2019.
70. Onysko, M.; Filak, I.; Lendel, V. *Heterocycl. Commun.* **2017**, *23* (4), 309–312.
71. Kim, D. G.; Vershininaa, E. A.; Ezhikova, M. A.; Kodess, M. I. *Russ. J. Org. Chem.* **2015**, *51* (9), 1313–1317.
72. Jarvis, C. L.; Richers, M. T.; Breugst, M.; Houk, K. N.; Seidel, D. *Org. Lett.* **2014**, *16* (13), 3556–3559.
73. Unsworth, W. P.; Kitsiou, C.; Taylor, R. J. K. *Org. Lett.* **2013**, *15* (2), 258–261.
74. Kitsiou, C.; Unsworth, W. P.; Coulthard, G.; Taylor, R. J. K. *Tetrahedron.* **2014**, *70*, 7172–7180.
75. Dang, P.; Zheng, Z.; Liang, Y. *J. Org. Chem.* **2017**, *82* (4), 2263–2268.
76. Hopkin, M. D.; Baxendale, I. R.; Ley, S. V. *Synthesis* 2008, (11), 1688–1702.
77. Batalov, V. I.; Kim, D. G.; Slepukhin, P. A. *Chem. Heterocycl. Compd.* **2013**, *49* (7), 1092–1096.
78. Slepukhin, P. A.; Batalov, V. I.; Kim, D. G.; Charushin, V. N. *J. Struct. Chem.* **2012**, *53* (1), 145–150.
79. Batalov, V. I.; Dikhtiarenko, A.; Yushina, I. D.; Bartashevich, E. V.; Kim, D. G.; García-Granda, S. *Z. Kristallogr. NCS* **2014**, *229* (3), 195–196.
80. Borisov, A. V.; Osmanov, V. K.; Borisova, G. N.; Matsulevich, Z. V.; Fukin, G. K. *Mendeleev Commun.* **2009**, *19*, 49–51.
81. Bubenyák, M.; Noszál, B.; Kóczián, K.; Takács, M.; Béni, S.; Hermecz, I.; Kökösi, J. *Tetrahedron Lett.* **2008**, *49*, 5711–5713.

82. Kökösi, J.; Hermecz, I.; Szász, G.; Mészáros, Z. *Tetrahedron Lett.* **1981**, *22* (48), 4861–4862.
83. Lozinskii, M. O.; Il'chenko, A. Y. *Chem. Heterocycl. Compd.* **2009**, *45* (4), 376–399.
84. Voskoboynik, O. Y.; Kolomoets, O. S.; Berest, G. G.; Nosulenko, I. S.; Martynenko, Y. V.; Kovalenko, S. I. *Chem. Heterocycl. Compd.* **2017**, *53* (3), 256–272.
85. Elattar, K. M.; Rabie, R.; Hammouda, M. M. *Synth. Commun.* **2016**, *46* (18), 1477–1498.
86. Bassyouni, F. A.; Tawfik, H. A.; Soliman, A. M.; Rehim, M. A. *Res Chem Intermed* **2012**, *38*, 1291–1310.
87. Bishnoi, A.; Singh, S.; Tiwari, A. K.; Srivastava, K.; Raghuvir, R.; Tripathi, C. M. *J. Chem. Sci.* **2013**, *125* (2), 305–312.
88. Gawale, J.; Sekar, N. *J. Luminesc.* 2018, 194, 248–256.
89. Gawale, J.; Jadhav, A.; Sekar, N. *Fib. Polym.* 2018, 19 (8), 1678–1686.
90. Gupta, P.; Gupta, S.; Sachar, A.; Sharma, R. L. J. *Heterocyclic Chem.* **2010**, *47*, 1188–1199.
91. Rauf, A.; Liaqat, S.; Qureshi, A. M.; Yaqub, M.; Rehman, A. U.; Hassan, M. U.; Chohan, Z. H.; Nasim, F. U. H.; Hadda, T. B. *Med. Chem. Res.* **2012**, *21*, 60–74.
92. Zhang, J.; Meng, X.; Yu, C.; Chena, G.; Zhao, P. *RSC Adv.* **2015**, *5*, 87221–87227.
93. Yang, Y.; Shu, W.-M.; Yu, S.-B.; Ni, F.; Gao, M.; Wu, A.-X. *Chem. Commun.* 2013, 49, 1729–1731.
94. Mishra, S.; Hajra, A. *Tetrahedron Lett.* **2015**, *56* (41), 5651–5655.
95. Hese, S. V.; Kamble, R. D.; Mogle, P. P.; Kadam, S. S.; Hebade, M. J.; Ambhore, A. N.; Dawane, B. S. *Pharm. Chem.* **2015**, *7* (4), 249–256.
96. Inturi, S. B.; Kalita, B.; Ahamed, A. J. *Synth. Commun.* 2018, 48 (16), 2037–2045.
97. Satyanarayana, S.; Kumar, K. P.; Reddy, P. L.; Narender, R.; Narasimhulu, G.; Subba Reddy, B. V. *Tetrahedron Letters* **2013**, *54* (36), 4892–4895.
98. Sreevani, R.; Manjula, A.; Vittal Rao, B. J. *Heterocyclic Chem.* **2011**, *48*, 586–591.
99. Shidlovskii, A. F.; Peregudov, A. S.; Bulychev, Y. N.; Chkanikov, D. N. *Pharm. Chem. J.* **2009**, *43* (10), 549–559.
100. Venugopal, S.; Sundaram, S. *J. Heterocyclic Chem.* **2016**, *53*, 882–886.
101. Yang, K.; Xiang, J.; Bao, G.; Dang, Q.; Bai, X. *ACS Comb. Sci.* **2013**, *15* (9), 519–524.
102. Sharulatha, V.; Indumathi, U.; Priyadharshini, S. *IJRET* **2014**, *3* (8), 1–4.
103. Satham, L.; Namboothiri, I. N. N. *J. Org. Chem.* **2017**, *82*, 6482–6488.
104. Bluhm, U.; Boucher, J.-L.; Buss, U.; Clement, B.; Friedrich, F.; Girreser, U.; Heber, D.; Lam, T.; Lepoivre, M.; Rostaie-Gerylow, M.; Wolschendorf, U. *Eur. J. Med. Chem.* **2009**, *44*, 2877–2887.
105. Girreser, U.; Bluhm, U.; Clement, B.; Heber, D. *Magn. Reson. Chem.* **2013**, *51*, 714–721.
106. Tatsumi, K.; Fujihara, T.; Teraoa, J.; Tsuji, Y. *Adv. Synth. Catal.* **2018**, *360* (17), 3245–3248.
107. Shahroudia, M.; Zhiani, R. *J. Chem. Res.* **2018**, *42* (7), 377–379.
108. Maurya, H. K.; Gupta, A. *Tetrahedron Lett.* **2014**, *55*, 1715–1719.
109. Alizadeh, A.; Firuzyar, T.; Mikaeili, A. *J. Heterocyclic Chem.* **2013**, *50*, 676–679.
110. Bayat, M.; Rezaei, M. *Monatsh Chem* **2017**, *148* (12), 2097–2106.
111. Britsun, V. N.; Esipenko, A. N.; Gootov, A. V.; Chernega, A. N.; Lozinskii, M. O. *Chem. Heterocycl. Compd.* **2009**, *45* (4), 445–453.
112. Ishmiyarova, E. R.; Rakhimova, N. T.; Latypova, D. R.; Spirikhina, L. V.; Abdullina, M. I.; Dokichev, V. A. *Russ. J. Org. Chem.* **2015**, *51* (12), 1770–1773.
113. Feng, Y.; Tian, N.; Li, Y.; Jia, C.; Li, X.; Wang, L.; Ciu, X. *Org. Lett.* **2017**, *19*, 1658–1661.
114. Gabriele, B.; Mancuo, R.; Veltri, L.; Ziccarelli, I.; Della, C. N. *Eur. J. Org. Chem.* **2019** https://doi.org/10.1002/ejoc.201900481.
115. Abass, M.; Ismail, M. M.; Abdel-Monem, W. R.; Mayas, A. S. *Chem. Pap.* **2010**, *64* (1), 72–83.
116. Esmaeili, A. A.; Salehan, F.; Habibi, A.; Fakhari, A. R. *Tetrahedron Lett.* **2016**, *57* (1), 100–102.
117. Meti, G.; Kattimani, P.; Kamble, R.; Devarajegowda, H. C.; Kumbar, M.; Prasad, D. J.; World, J. *Pharm. Sci.* **2015**, *3* (2), 277–287.
118. Jannati, S.; Esmaeili, A. A. *Res. Chem. Intermed.* **2017**, *43* (12), 1–17.
119. Bakulina, O.; Merkt, F. K.; Knedel, T.-O.; Janiak, C.; Müller, T. J. J. Angew. Chem., Int.. *Ed.* **2018**, *57* (52), 17240–17244.
120. Alanine, T. A.; Galloway, W. R. J. D.; Bartlett, S.; Ciardiello, J. J.; McGuireb, T. M.; Spring, D. R. *Org. Biomol. Chem.* **2016**, *14*, 1031–1038.
121. Ghozlan, S. A. S.; Mohamed, M. F.; Ahmed, A. G.; Shouman, S. A.; Attia, Y. M.; Abdelhamid, I. A. *Arch. Pharm. Chem. Life Sci.* **2015**, *348*, 113–124.
122. Herold, F.; Chodkowski, A.; Izbicki, L.; Kro'l, M.; Kleps, J.; Turio, J.; Nowak, G.; Stachowicz, K.; Dybala, M.; Siwek, A. *Eur. J. Med. Chem.* 2009, 44, 1710–1717.
123. Herold, F.; Izbicki, L.; Chodkowski, A.; Dawidowski, M.; Kro'l, M.; Kleps, J.; Turio, J.; Wolska, I.; Nowak, G.; Stachowicz, K.; Dybala, M.; Siwek, A.; Nowak, M.; Pieniazek, M.; Jaron'czyk, M.; Sylte, I.; Mazurek, A. P. *Eur. J. Med. Chem.* 2009, 44, 4702–4715.
124. Herold, F.; Chodkowski, A.; Izbicki, L.; Turio, J.; Dawidowski, M.; Kleps, J.; Nowak, G.; Stachowicz, K.; Dybala, M.; Siwek, A.; Mazurek, A. P.; Mazurek, A.; Plucinski, F. *Eur. J. Med. Chem.* **2011**, *46*, 142–149.
125. Rosen, J. D.; German, N.; Kerns, R. J. *Tetrahedron Lett.* **2009**, *50*, 785–789.
126. Sasada, T.; Moriuchi, M.; Sakai, N.; Konakahara, T. *Eur. J. Org. Chem.* **2009**, 5738–5743.
127. Singh, K.; Singh, S. *Tetrahedron* **2008**, *64*, 11718–11723.
128. Eften'eva, R. I.; Kushnir, O. V.; Lyavinets, O. S.; Mangalagiu, I. I.; Vovk, M. V. *Monatsh Chem* **2016**, *147* (12), 2127–2133.
129. Medvedeva, S. M.; Shikhaliev, K. S. *J. Mater. Sci. Eng.* **2015**, *5* (7–8), 310–313.
130. Ma, Y.; Kong, X.; Abbate, V.; Hider, R. C. *Sens. Actuat. B* **2015**, *213*, 12–19.
131. Ruebsam, F.; Sun, Z.; Ayida, B. K.; Webber, S. E.; Zhou, Y.; Zhao, Q.; Kissinger, C. R.; Showalter, R. E.; Shah, A. M.; Tsan, M.; Patel, R.; LeBrun, L. A.; Kamran, R.; Sergeeva, M. V.; Bartkowski, D. M.; Nolan, T. G.; Norris, D. A.; Kirkovsky, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5002–5005.
132. Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* 2008, 10 (5), 689–692.
133. Butin, A. V.; Dmitriev, A. S.; Kostyukova, O. N.; Abaev, V. T.; Trushkov, I. V. *Synthesis* **2007**, *14*, 2208–2214.
134. Patel, R. V.; Keum, Y.-S.; Park, S. W. *Eur. J. Med. Chem.* **2015**, *97*, 649–663.
135. Koketsu, M.; Ishihara, H. *Curr. Org. Chem.* **2003**, *7* (2), 175–185.
136. Liu, Z.; Ishibashi, J. S. A.; Darrigan, C.; Dargelos, A.; Chrostowska, A.; Li, B.; Vasiliu, M.; Dixon, D. A.; Liu, S.-Y. *J. Am. Chem. Soc.* **2017**, *139*, 6082–6085.
137. Giustra, Z. X.; Liu, S.-Y. *J. Am. Chem. Soc.* **2018**, *140*, 1184–1194.