Three Heterocyclic Rings Fused (5-6-6)

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

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

Abbreviations

[BMIm]B Ionic liquid 1-butyl-3-methylimidazolium bromide
CHP Cumene hydroperoxide
DABCO,4 Diazabicyclo[2.2.2]octane
DCM Dichloromethane
DEAD Diethyl azodicarboxylate
DIPEA *N,N*-Diisopropylethylamine
DMAD Dimethyl acetylenedicarboxylate
DMCDA *N,N*-Dimethylcyclohexanamine
DME 1,2-Dimethoxyethane
DMEDA 1,2-Dimethylethylenediamine
DM *N,N*-Dimethylformamide
DMSO Dimethyl sulfoxide
EDCHCl 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EG Ethylene glycol
HOBt Hydroxybenzotriazole
IBX 2-Iodoxybenzoic acid
LiHMDS Lithium bis(trimethylsilyl)amide
MW Microwave heating
Ns-Cl Trithiazyl trichloride
p-TSA *p*-Toluenesulfonic acid
TBABr Tetra-*n*-butylammonium bromide
TEA Triethylamine
TFA Trifluoroacetic acid
THF Tetrahydrofuran

1 Introduction

This chapter covers fused tricyclic 5-6-6 ring systems. It reviews the literature from 2007 to early 2019. Condensed heterocycles are grouped in four sections:

- Fused Tricyclic Heterocycles with no Ring Junction Heteroatom (**Section 2**).
- Fused Tricyclic Heterocycles with a 5:6 Ring Junction Heteroatom (**Section 3**).
- Fused Tricyclic Heterocycles with a 6:6 Ring Junction Heteroatom (**Section 4**).
- Cycl[3.3.2]azines and Related Systems (**Section 5**).

Each section contains synthetic routes to target compounds, their chemical properties and investigations of biological, biochemical, spectral and physical characteristics.

2 Fused tricyclic heterocycles with no ring junction heteroatom

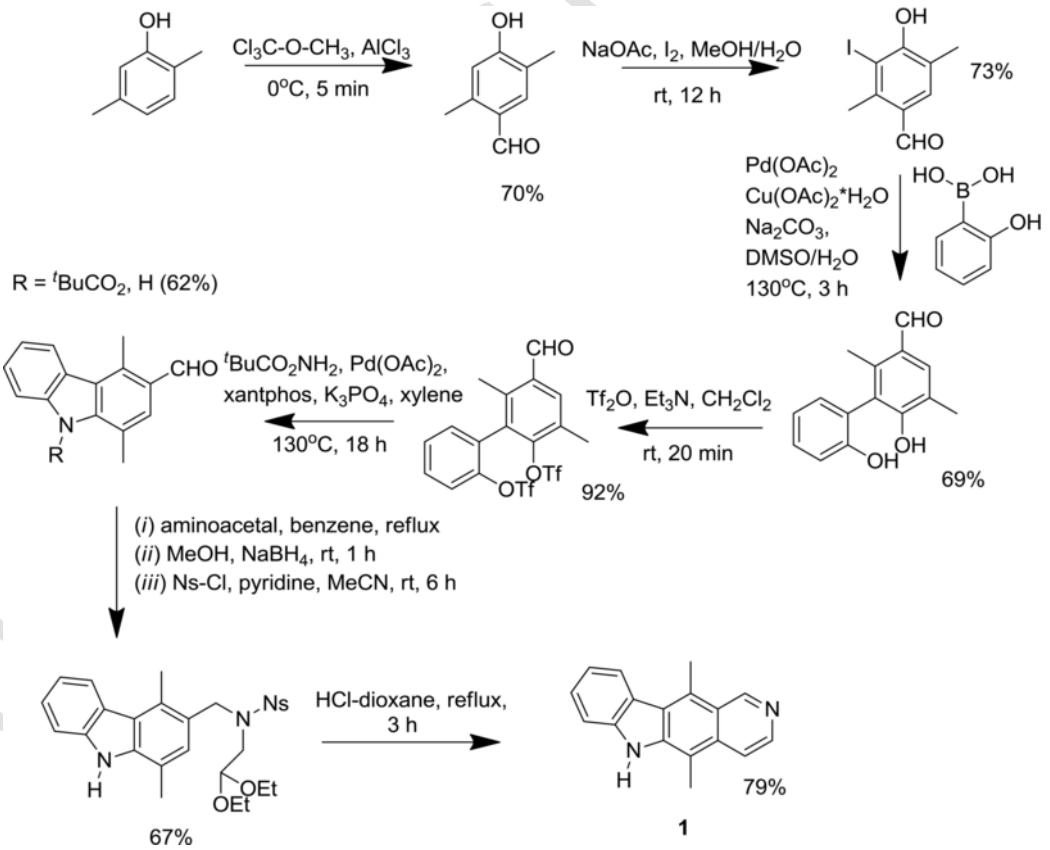
2.1 Linearly fused systems

2.1.1 Azolonaphthyridines and analogues

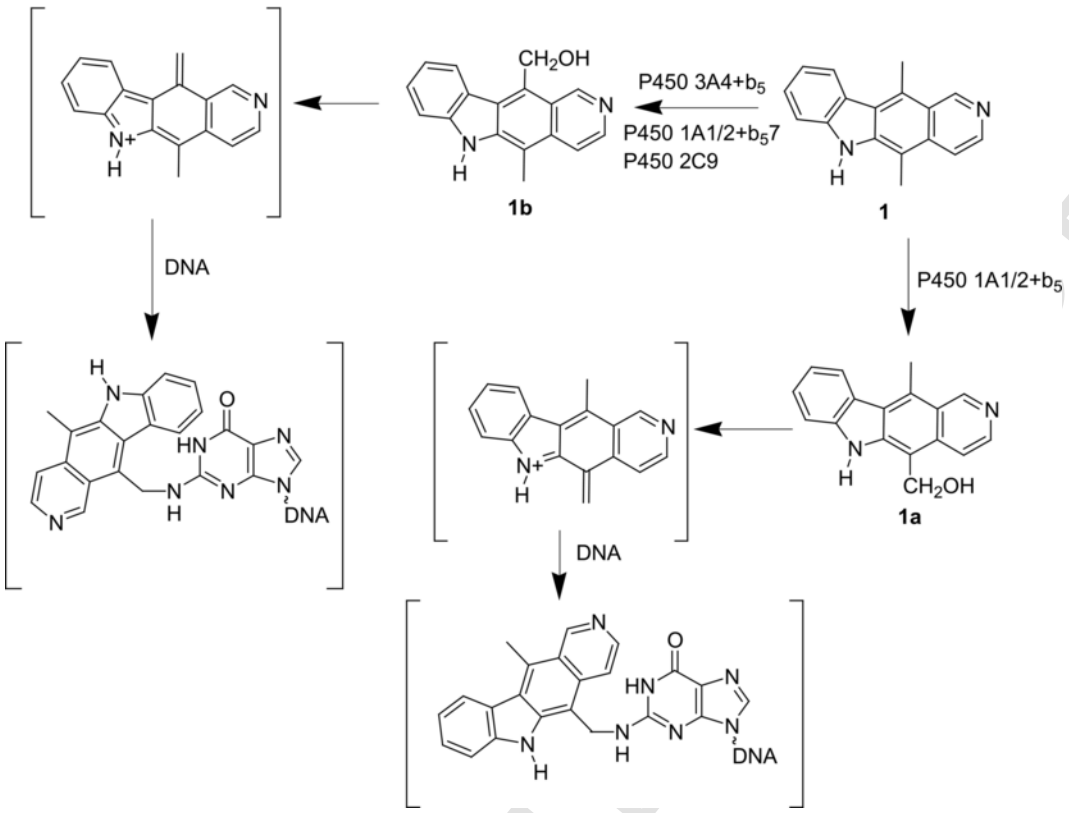
Many studies were concentrated on the synthesis and biological evaluation of analogues of the alkaloid ellipticine **1** which is as a proven anticancer agent. Total synthesis of ellipticine **1** was developed via the Suzuki-Miyaura coupling of sterically sensitive 2-hydroxybenzeneboronic acid with a multifunctional aryl halide using $Pd(OAc)_2$ as a catalyst[1] (**Scheme 1**).

Biochemical and physical properties of ellipticine **1** were studied including its cytotoxicity to human cancer cell lines.[2] For the first time it was shown that ellipticine is toxic to thyroid cancer cell lines.[3] It was found that the P450 3A4 enzyme oxidizes ellipticine to five metabolites, mainly to 13-hydroxy-**1a** and 12-hydroxyellipticine **1b**, the metabolites responsible for the formation of ellipticine-13-ylium and ellipticine-12-ylium ions that generate covalent DNA adducts[4] (**Scheme 2**).

The high photostability of ellipticine **1** in polar media[5] and the origin of dual fluorescence in alcoholic solvents were investigated.[6] The dual emission of ellipticine **1** in methanol originates from the photoexcited normal and protonated forms of the molecule with the latter generated as a result of proton transfer from the solvent. It appears that the excited state reaction involves solvent reorganization around ellipticine to form the "cyclic" solvated species followed by rapid proton transfer (relay) along the chain. The two emission bands arise from the normal and tautomeric forms of ellipticine. The ease of formation of the cyclic complex with two molecules of ethylene glycol, compared with the requirement of three molecules of methanol explains why the excited state reaction is faster in EG compared

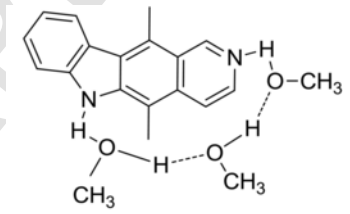


Scheme 1



Scheme 2

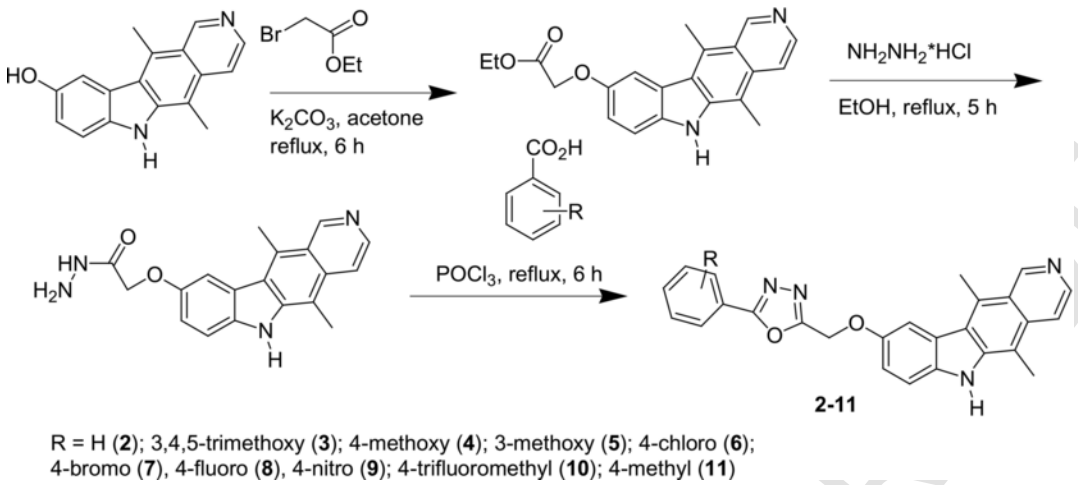
to methanol, even though the hydrogen bond donating ability of the latter is more than the former.[6]



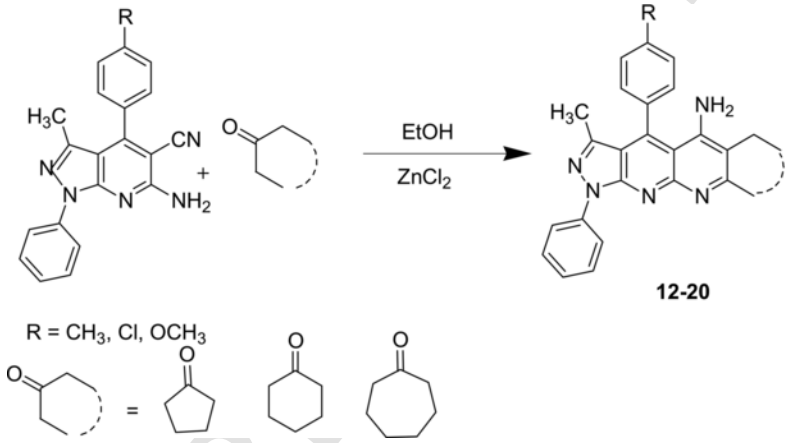
ellipticine-methanol complex

Synthesis of the new 1,3,4-oxadiazole incorporated ellipticine derivatives **2–11** is shown in **Scheme 3**. 5,11-Dimethyl-6*H*-pyrido[4,3-*b*]carbazol-9-ol underwent esterification with ethyl bromoacetate in the presence K_2CO_3. The intermediate ester was allowed to react with hydrazine hydrochloride to afford acid hydrazide. This intermediate product was cyclized by treatment with different substituted aromatic acids in $POCl_3$ at reflux for 6 h to afford compounds **2–11**. Anticancer activity of compounds **2–11** was studied. Most of the compounds show significant anticancer activity against four different human Colo-205, MCF-7, A-549, and KB cancer cell lines. Compounds **2–4**, **10** and **11** are more potent than etoposide.[7]

A microwave-assisted synthesis of novel pyrazolo[3,4-*g*][1,8]naphthyridin-5-amines **12–20** by Friedländer condensation of *o*-aminonitrile with cyclic ketones in the presence of zinc chloride as a catalyst, was described[8] (**Scheme 4**). The reaction was performed under MWI, providing significant improvements evidenced by better yields of the target products **12–20** in comparison to the classical approach. The presented synthetic procedure is environmentally friendly, simple, and efficient for the preparation of target compounds. The whole series of compounds were tested against standardized strains of the clinically important fungi, *C. albicans* and *C. neoformans*. Compounds **12**, **15** and **18**, all possessing a *p*-tolyl substituent, but different fused rings, are the most active structures. The antitumor evaluation data revealed that compounds **12** and **16** exhibit remarkable activity against different cancer cell lines.



Scheme 3



Scheme 4

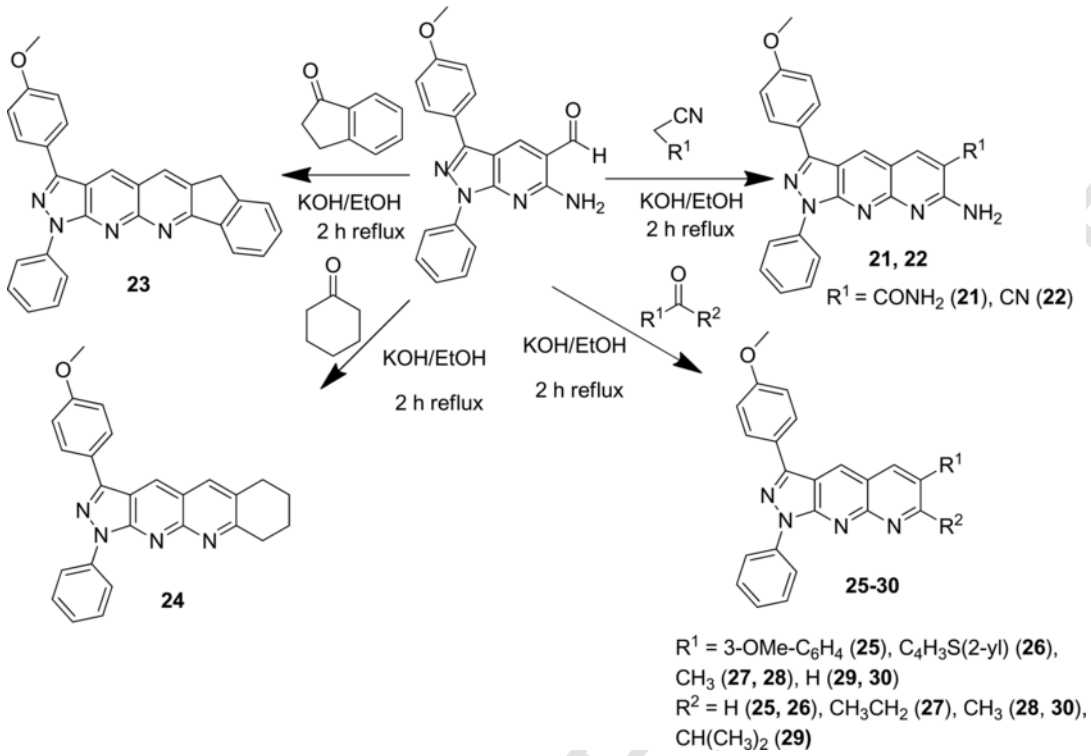
Simple and efficient approach to the synthesis of highly functionalized 6-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbaldehyde was described.[9] The Friedlander condensation of this 6-aminopyrazolo[3,4-*b*]pyridine-5-carbaldehyde with reactive methylene compounds was studied. The condensation with cyanoacetamide in ethanolic potassium hydroxide solution under reflux for 2 h furnished compounds **21** and **22** (**Scheme 5**). The condensation with 1-indanone under similar conditions yielded a yellowish brown solid of **23**. In a similar way, cyclohexanone was condensed with the *o*-amino aldehyde substrate to yield a tetracyclic heterocycle **24**. Finally, the condensation with acetophenones and alkyl ketones in ethanolic potassium hydroxide yielded the pyrazolonaphthyridine derivatives **25–30** in good yield (**Scheme 5**). Pyrazolo[3,4-*b*][1,8]naphthyridines **21–30** are strongly fluorescent compounds that may find applications in optic electronic devices.[9]

An efficient green synthesis of 1*H*-pyrazolo[3,4-*b*][1,6]naphthyridin-5(4*H*)-one derivatives **31–35** was conducted in an ionic liquid by a reaction of an aromatic aldehyde, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and piperidine-2,4-dione under catalyst-free conditions and under nitrogen atmosphere (**Scheme 6**). The three-component reactions gave non-aromatic pyrazolonaphthyridinones **31–35**.[10]

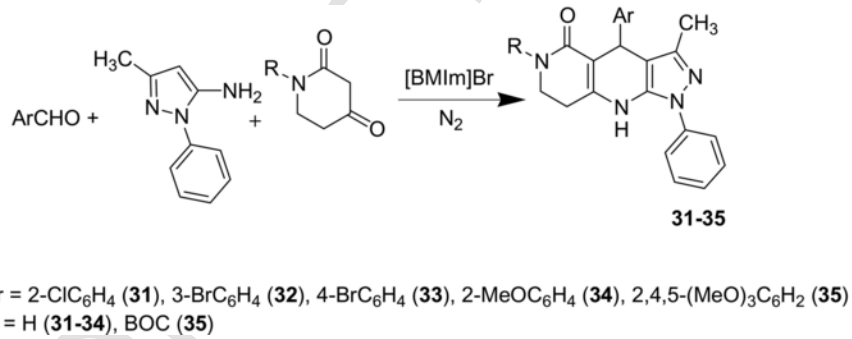
Heating of enamines with pentane-2,4-dione in polyphosphoric acid at 130–140 °C or in diphenyl ether at 250 °C promotes an annulation reaction. For example, 1,3-dialkyl-5,7-dimethyl-2-oxo-2*H*-imidazo[5,4-*b*][1,8]naphthyridines **36–38** were obtained in 47–70% yield by using this approach (**Scheme 7**). In a similar way, analogous products **39–41** were obtained in 35–70% yields starting with ethyl acetoacetate. In both cases an intermediate enamino ketone undergoes an intramolecular cyclization.[11]

2.1.2 Furanonaphthyridines

The development of a highly efficient approach to multi-functionalized furo[3,4-*b*][1,8]naphthyridine derivatives **42** through new three-component domino reaction of aldehyde, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and enaminone was reported (**Scheme 8**). The



Scheme 5



Scheme 6

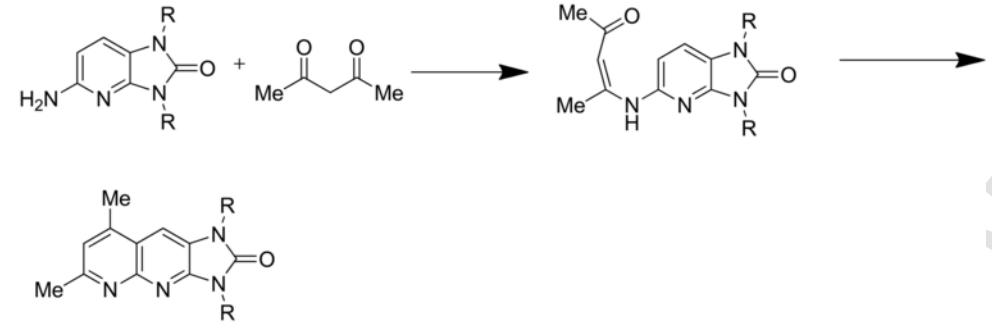
reaction was carried out in ethanol at 100 °C under microwave irradiation. The best yield of products **42** (about 83%) was obtained in the presence of sodium ethoxide with the temperature increased to 120 °C.[12]

2.2 Angularly fused systems

2.2.1 Pyrazolonaphthyridines

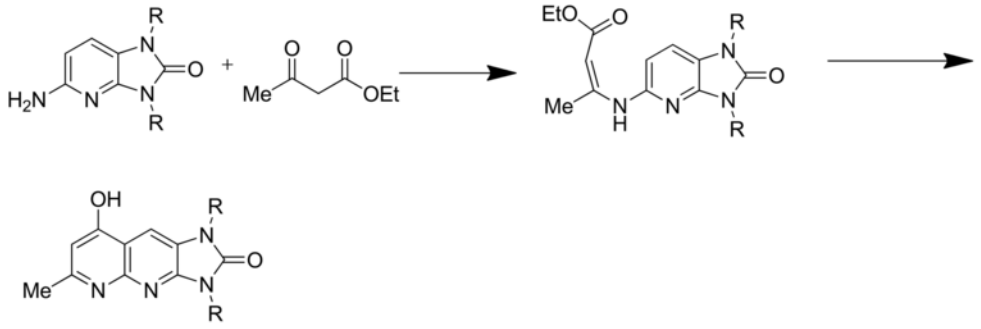
2-[4,6-Diaryl-3-cyano-6-methyl-5,6-dihydropyridin-2(1*H*)-ylidene]malononitrile undergoes a reaction with hydrazine hydrate and phenyl hydrazine to afford the pyrazolonaphthyridine derivatives **43**, **44**, respectively (**Scheme 9**).[13] The reaction mixture was heated under reflux in ethanol for 2 h in each case.

The Friedlander condensation of *o*-aminoaldehyde with propiophenone in ethanolic potassium hydroxide solution under reflux yielded 3,9-dimethyl-2,7-diphenyl-7H-pyrazolo[3,4-*h*][1,6]-naphthyridine **45** (**Scheme 10**). The reaction of dimethyl 1,3-acetonedicarboxylate with 5-aminopyrazolo-4-aldehyde resulted in the formation of the diester **46**. Similarly, the reaction of 5-aminopyrazolo-4-aldehyde with phenylacetonitrile afforded naphthyridine **47** in 76% yield (**Scheme 10**). Furthermore, the Friedlander condensation of *o*-aminoaldehyde, shown in **Scheme 11**, with cyclic ketones under similar reaction conditions produced the corresponding pyrazolonapthyridines **48a–g**.[14]



36-38

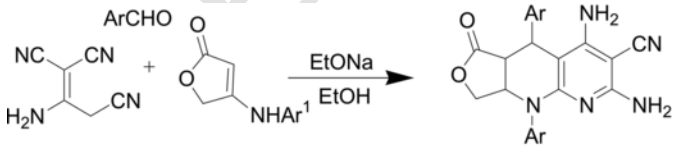
R = Me (**36**), Et (**37**), $PhCH_2$ (**38**)



39-41

R = Me (**39**), Et (**40**), $PhCH_2$ (**41**)

Scheme 7



42

Scheme 8

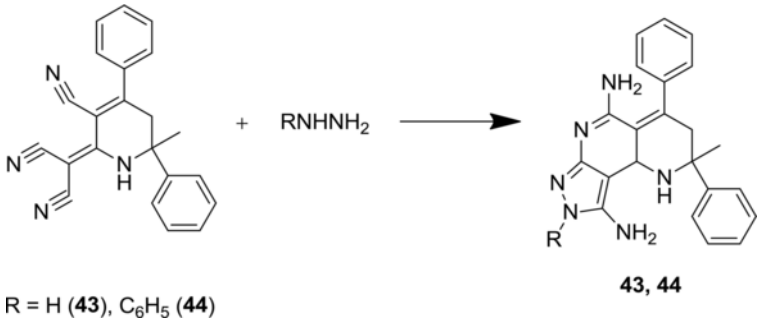
A known synthetic approach was used for the preparation of new 3*H*-benzo[*b*]pyrazolo[3,4-*b*]-1,6-naphthyridine derivatives **49** and **50**, starting from two ethyl 4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylates as the substrates.[15] The reaction conditions and corresponding yields are shown in **Scheme 12**.

A similar synthetic approach was used for synthesis of compounds **51** (**Scheme 13**).[16]

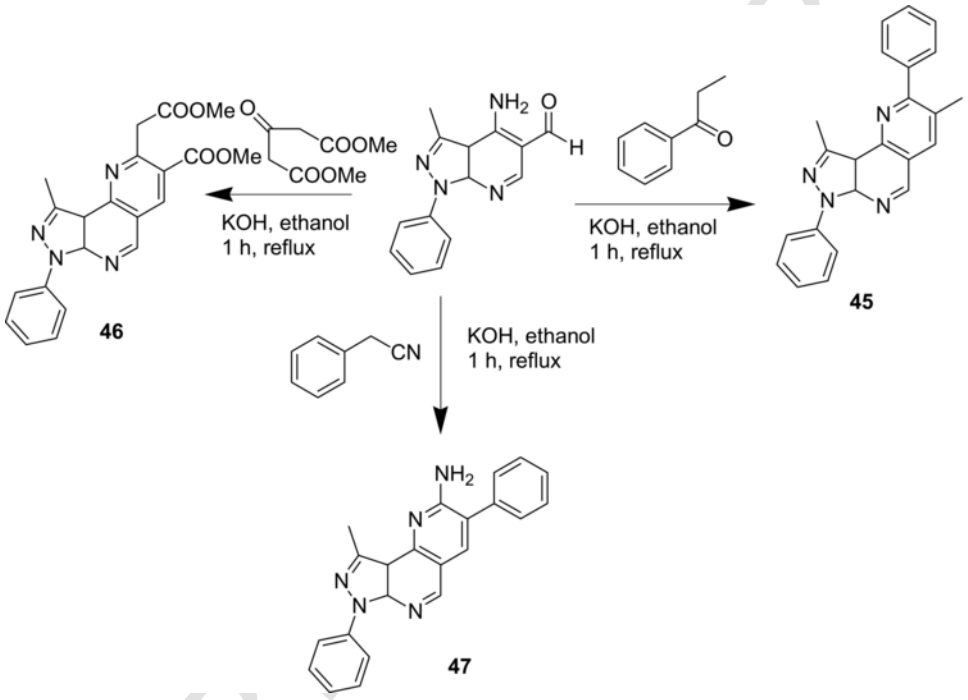
On the other hand, all attempts to cyclize a thiosemicarbazide, shown in **Scheme 14**, by heating in boiling dimethylformamide containing a catalytic amount of triethylamine or by refluxing in glacial acetic acid in the presence of freshly fused sodium acetate failed to produce the expected pyrazolo-naphthyridine derivative **52** (**Scheme 14**).[17]

4-Amino-3-(4-phenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde was synthesized by reduction of an azido derivative with LAH followed by oxidation of the resultant amino alcohol with MnO_2. The Friedländer condensation the amino aldehyde product with acetophenones in the presence of base furnished pyrazolo[3,4-*h*][1,6]naphthyridines **53** in excellent yields (**Scheme 15**). Photophysical properties of **53** were studied.[18]

Friedländer condensation of the same amino aldehyde with active methylene compounds was studied in ethanolic potassium hydroxide under reflux conditions. Thus, heating a mixture of the amino aldehyde with malononitrile, acetylacetone, ethyl acetoacetate, acetone, ethyl cyanoacetate or diethyl malonate furnished pyrazolo[3,4-*h*][1,6]naphthyridines **54–65** in good yields (**Scheme 16**).[19]



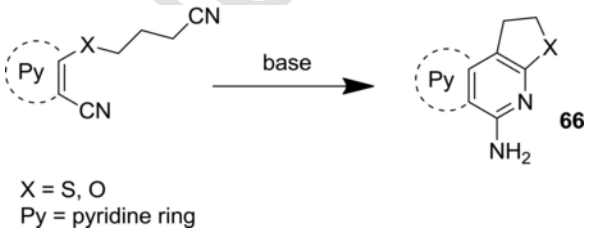
Scheme 9



Scheme 10

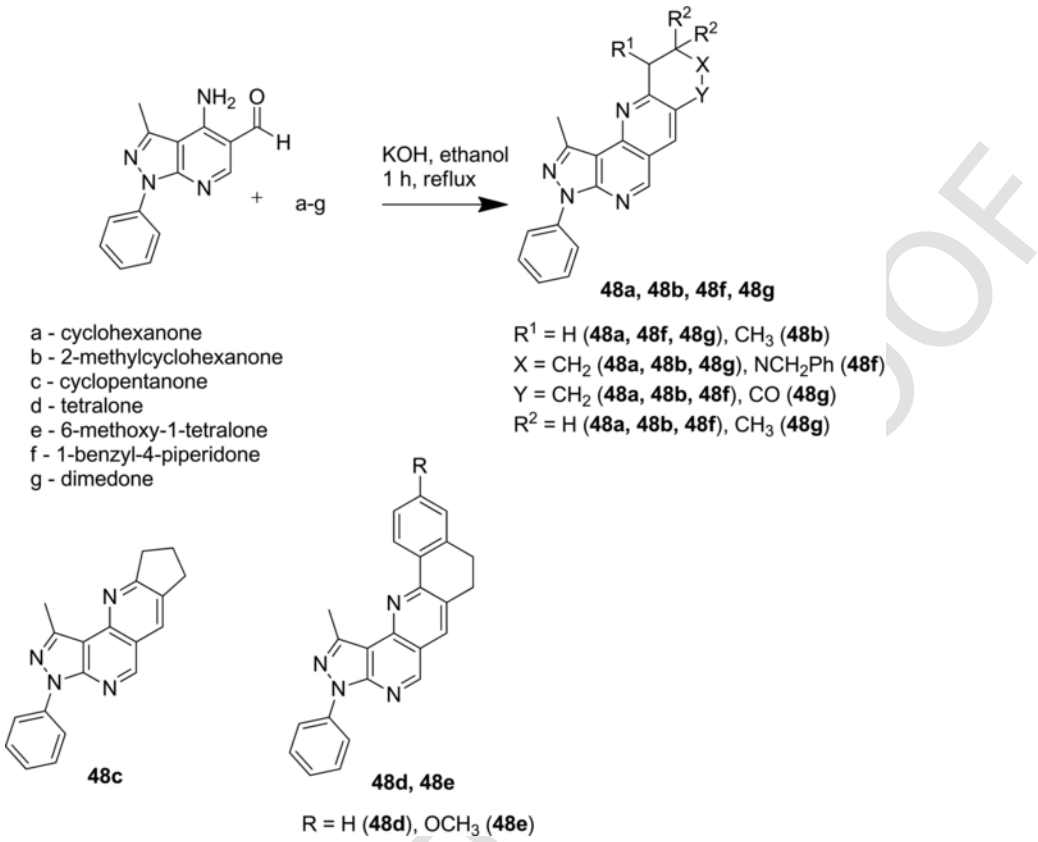
2.2.2 *Thienonaphthyridines and furanonaphthyridines*

The Truce-Smiles rearrangement for the synthesis of many aromatic fused dihydrothieno- or dihydrofuronaphthyridines **66** in one step from cyanopyridines having a 3-cyanopropyloxy or 3-cyanopropylthio group adjacent to a cyano group (Eq. **1**) was reported.[20]



(1)

The reaction of (3-cyanopiperidin-2-ylidene)malononitriles with a thiol functionalized anilide (**Scheme 17**) in refluxing alcohol in the presence of Et_3N proceeded through an initial attack by the RS anion at one of the nitrile groups of the $=C(CN)_2$ moiety. The



Scheme 11

generated cyclization products, 1,6-naphthyridines, under the reaction conditions underwent intramolecular Thorpe-Ziegler cyclization, forming the expected thieno-[2,3-*h*][1,6]naphthyridines **67**–**69** (**Scheme 17**).[21]

2.2.3 Systems containing an additional nitrogen atom in the six-membered ring

Iminophosphorane shown in **Scheme 18** was allowed to react with 4-chlorophenyl or 4-fluorophenyl isocyanate to generate a carbodiimide. This intermediate product was inert in toluene in the presence of phenols under reflux conditions. However, 2-aryloxy-8,9,10,11-tetrahydrobenzo [4,5]thieno[3,2,5,6]pyrido[4,3-*d*]pyrimidin-4(3H)-ones **70**, **71** were produced when the reaction was carried out in the presence of a catalytic amount of K_2CO_3 under otherwise identical conditions (**Scheme 18**).[22]

A similar reaction of the iminophosphorane with 4-chlorophenyl isocyanate followed by treatment of the intermediate isocyanate with amines R_1R_2NH furnished 2-substituted 3-(4-chlorophenyl)-5,8,9-trimethylthieno[3′,2′: 5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **72** (**Scheme 19**). The cyclization with the amines proceeded smoothly in CH_2Cl_2 in the presence of a catalytic amount of NaOEt at room temperature and gave satisfactory yields of **72**.[23]

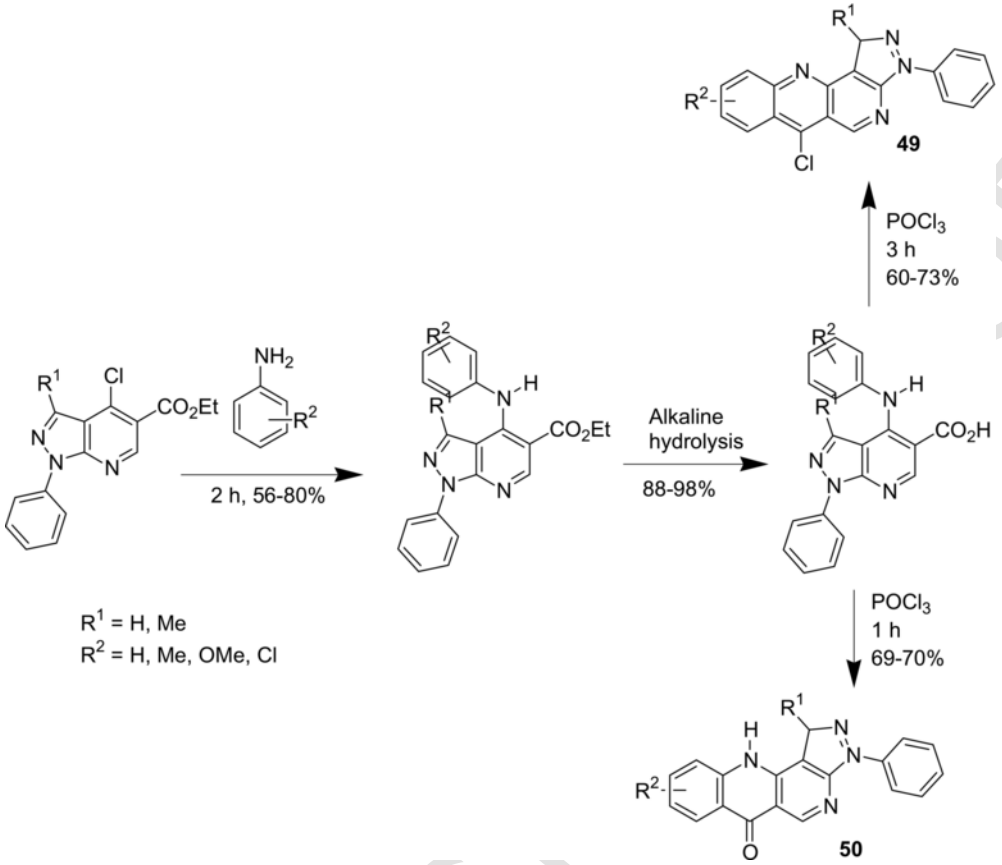
Synthesis of target compounds **73**, **74** is shown in **Scheme 20**. The Gewald reaction of cyclohexanone generated 2-amino-4,5,6,7-tetrahydrobenzothiophene-3-carbonitrile which was transformed into a thienopyridine, as shown. Treatment of the thienopyridine with triethyl orthoformate in acetic anhydride generated the key intermediate product as a reddish-brown oil that was allowed to react directly without any purification with the corresponding amines and hydrazine hydrate to give the respective target compounds **73** and **74**.[24]

3 Fused tricyclic heterocycles with a 5:6 ring junction heteroatom

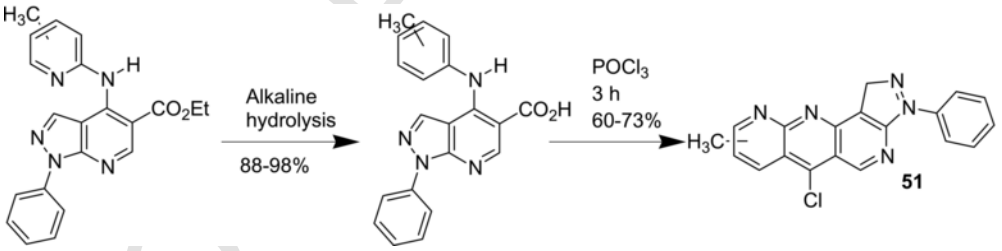
3.1 Linearly fused systems

3.1.1 Pyrrolonaphthyridines

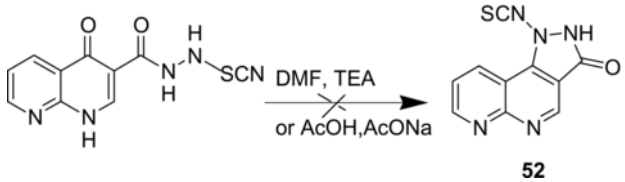
Transformation of a chiral tetrahydropyrrole derivative to indolizino[7,6-*c*]quinolone **75** is shown in **Scheme 21**.[25] The intermediate isatin derivative is unstable and was used without purification. It was hydrolyzed under alkaline conditions to give a substituted oxoacetic acid. This material was then subjected to an intramolecular aldol condensation reaction to give a substituted 2-quinolone. Both the direct treatment of this material with $SOCl_2$ and a two-step process (Boc deprotection with HCl/MeOH followed by EDCI mediated coupling) produced indolizino[7,6-*c*]quinolone **75** in good yield (**Scheme 21**).[25]



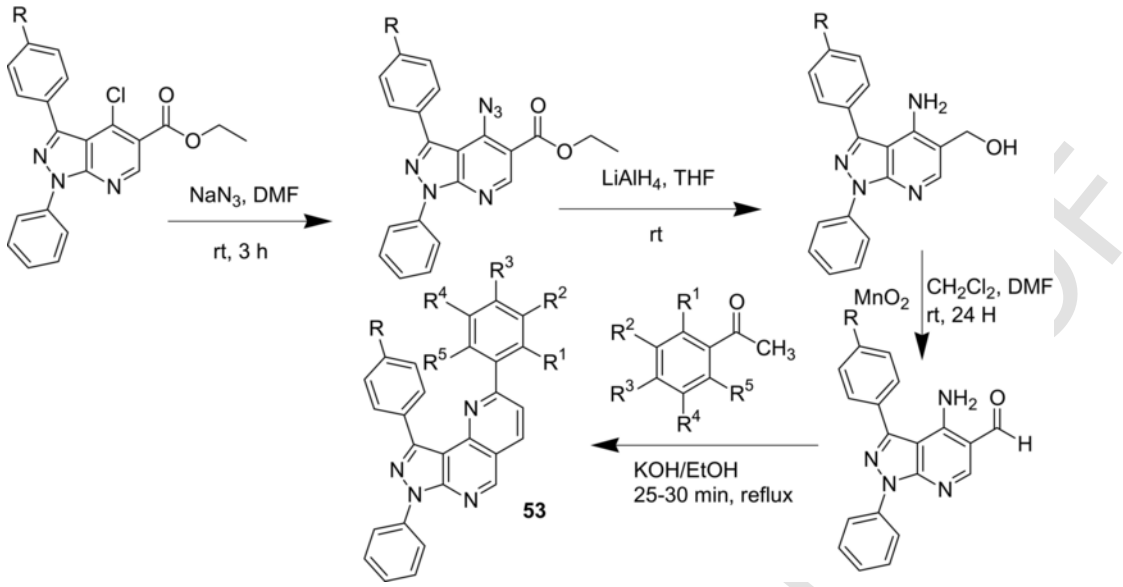
Scheme 12



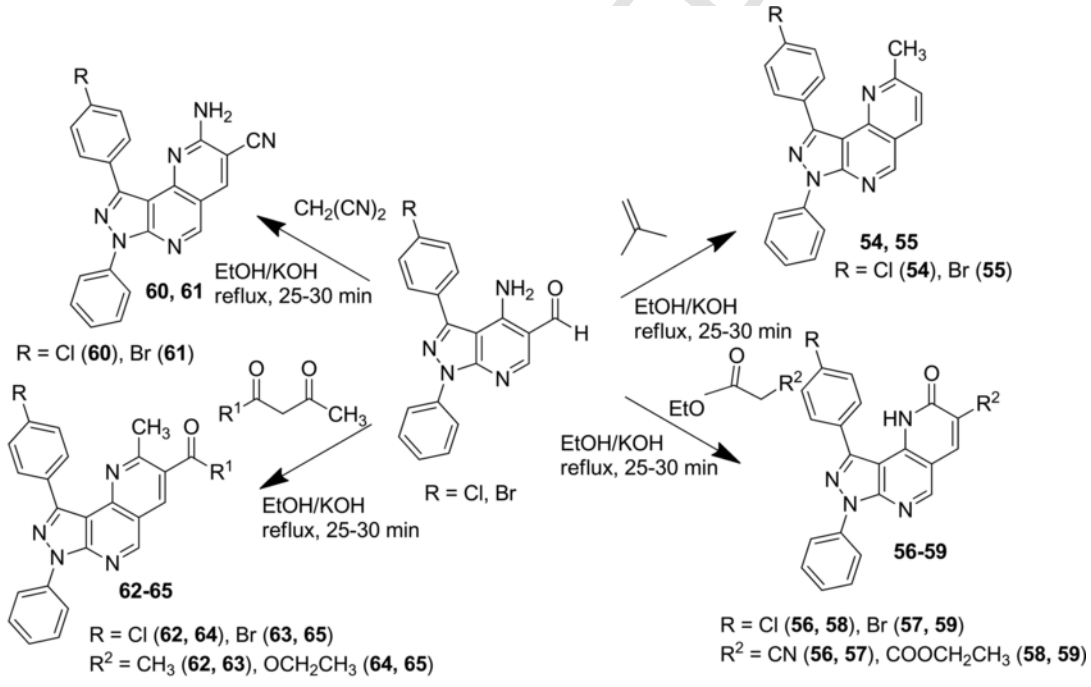
Scheme 13



Scheme 14



Scheme 15

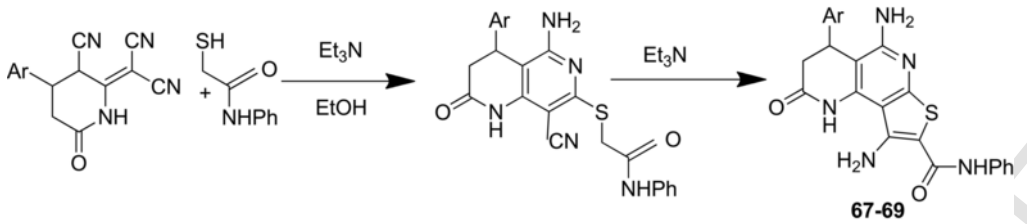


Scheme 16

Scheme 16

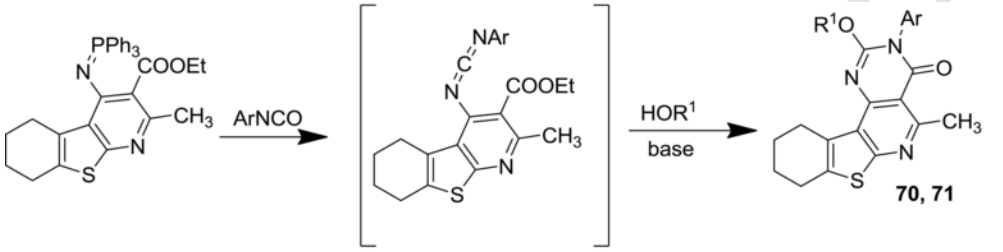
3.1.2 *Pyranoindolizines*

New guanidine-*bis*-urea bifunctional organocatalysts **76** bearing chirality at the outer side of the urea groups were synthesized.[26] These catalysts were effective in enantioselective α-hydroxylation of a pyranoindolizine derivative to product **77**, as shown in Eq. **(2)**. Catalysts bearing an aryl group with an electron-donating substituent or a 1-naphthyl group provided selectivity of 61–69%. Even



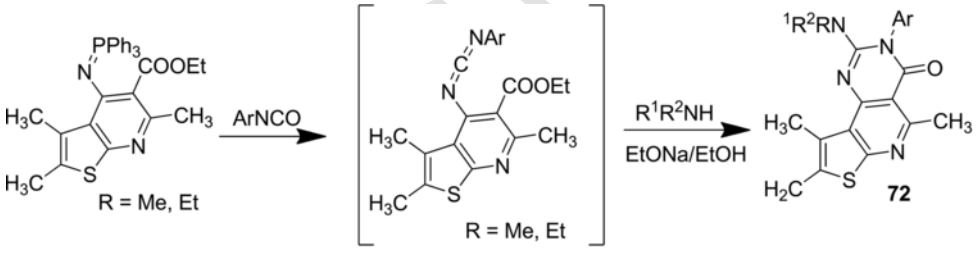
Ar = Ph (**67**), 4-MeOC$_6$H$_4$ (**68**), 3,4-(MeO)$_2$C$_6$H$_3$ (**69**)

Scheme 17



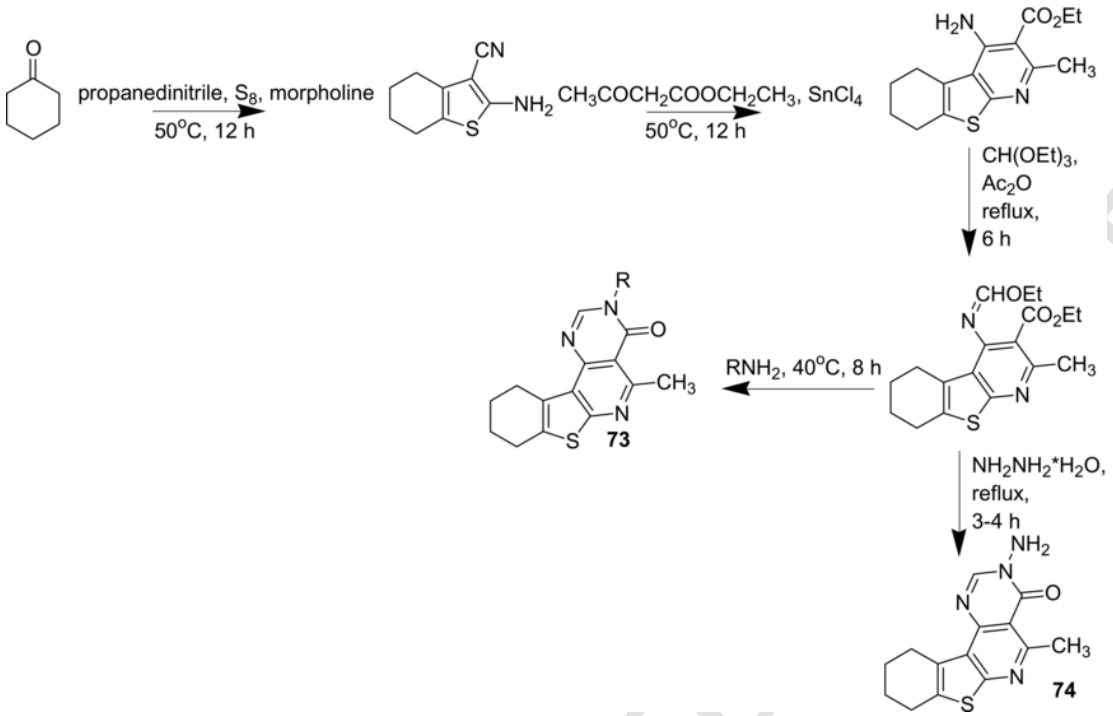
Ar = 4-Cl-Ph (**70**), 4-F-Ph (**71**)
R^1 = Ph (**70**), 4-Cl-Ph (**71**)

Scheme 18

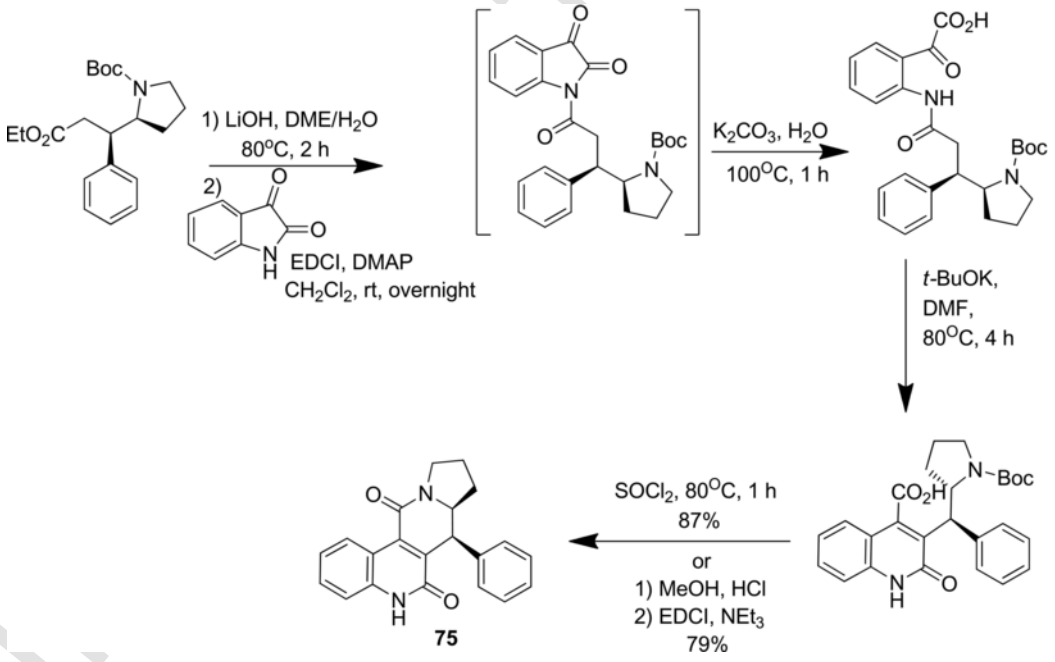


R^1, R^2 = H or alkyl
Ar = 4-Cl-C$_6$H$_4$

Scheme 19

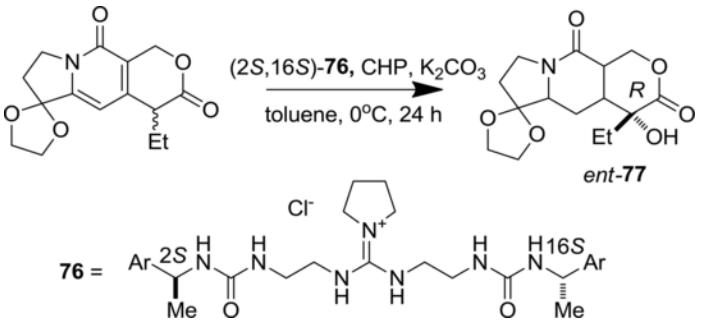


Scheme 20



Scheme 21

higher enantioselectivity was observed for catalysts **76** bearing chirality at both the outer and inner sides of the urea moieties.

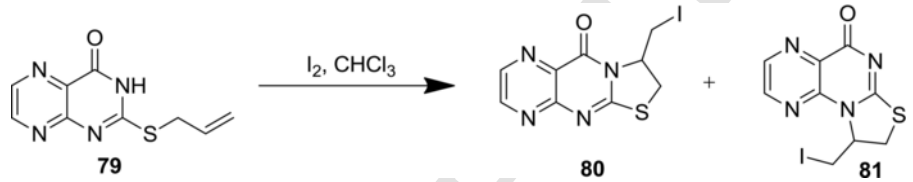


(2)

3.1.3 Pteridine analogues

Treatment of 5,6-diamino-2-thiopyrimidine derivatives with 2,2-dipyridil in boiling ethanol furnished 6,7-bis(2-pyridyl)pteridine-2-thiones. Alkylation with phenacyl chloride and 4-methoxyphenacyl chloride gave the *S*-alkylpteridine derivatives in 78% and 74% yields, respectively. Cyclization of the *S*-alkylpteridine derivatives in polyphosphoric acid at 80 °C afforded the thiazole analogues **78** in the respective yields of 63% and 58%. (**Scheme 22**). The regioselectivity of the cyclization step may be due to a difference in the electron density at the *N*1 and *N*3 positions of 2-thiopteridine, where the higher electron density of the *N*3 atom results in exclusive cyclization at this position.[27] All compounds were evaluated for their antiviral activity against the replication of HIV-1 and HIV-2. Some of the synthesized compounds were tested against bacterial species *Escherichia coli* and *Staphylococcus aureus* as well as fungal species *Candida tropicalis* and *Candida albicans*.[27]

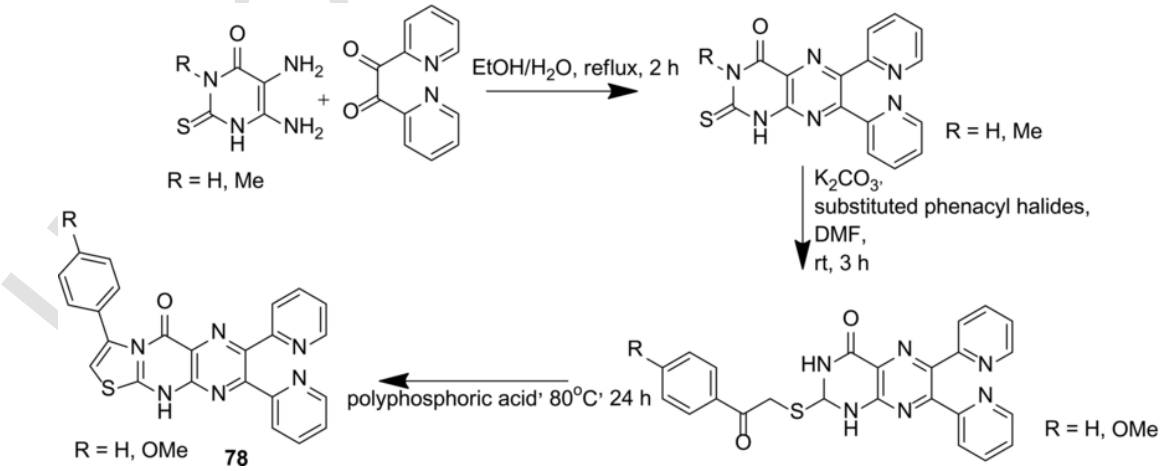
The reaction of compound **79** with iodine in chloroform furnished a mixture of the linear compound **80** and angular compound **81** in a 1:1 ratio. This result is apparently due to the influence of the fused substrate on the stability of the intermediate iodonium cation leading to a decrease in the reaction selectivity (Eq. **3**).[28]



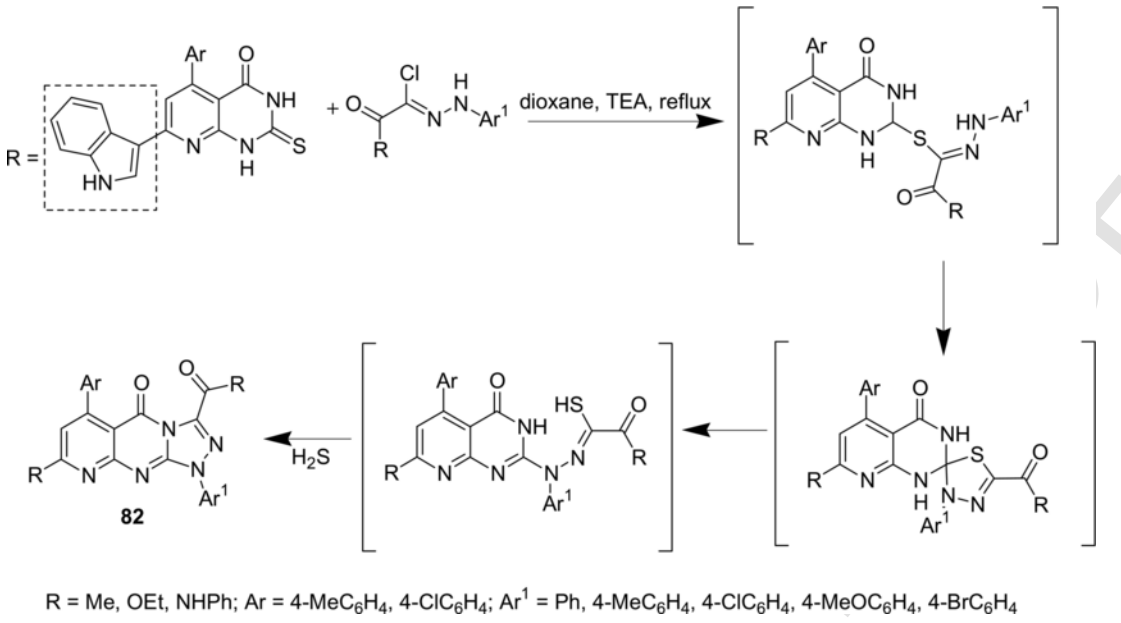
(3)

3.1.4 Aza analogues of azolonaphthyridines

The mechanism in **Scheme 23** outlines the most plausible pathways for the formation of product **82** by the reaction of a thione with hydrazonoyl derivatives. In the first step, 1,3-addition of the thiol tautomer to the nitrilimine would generate the thiohydrazonate ester, which would undergo nucleophilic cyclization to a spiro intermediate product. Ring opening followed by cyclization with loss



Scheme 22

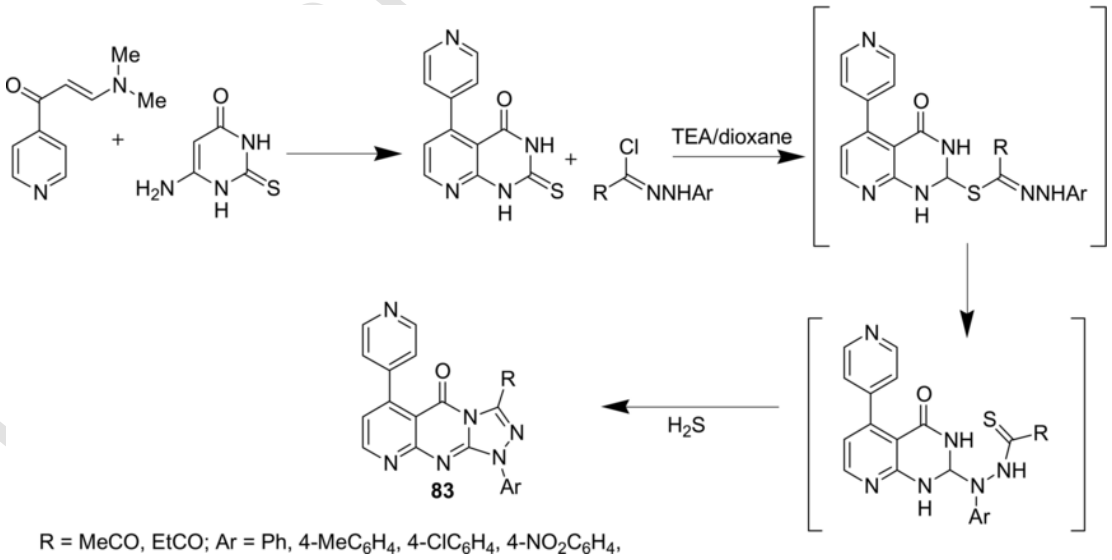


Scheme 23

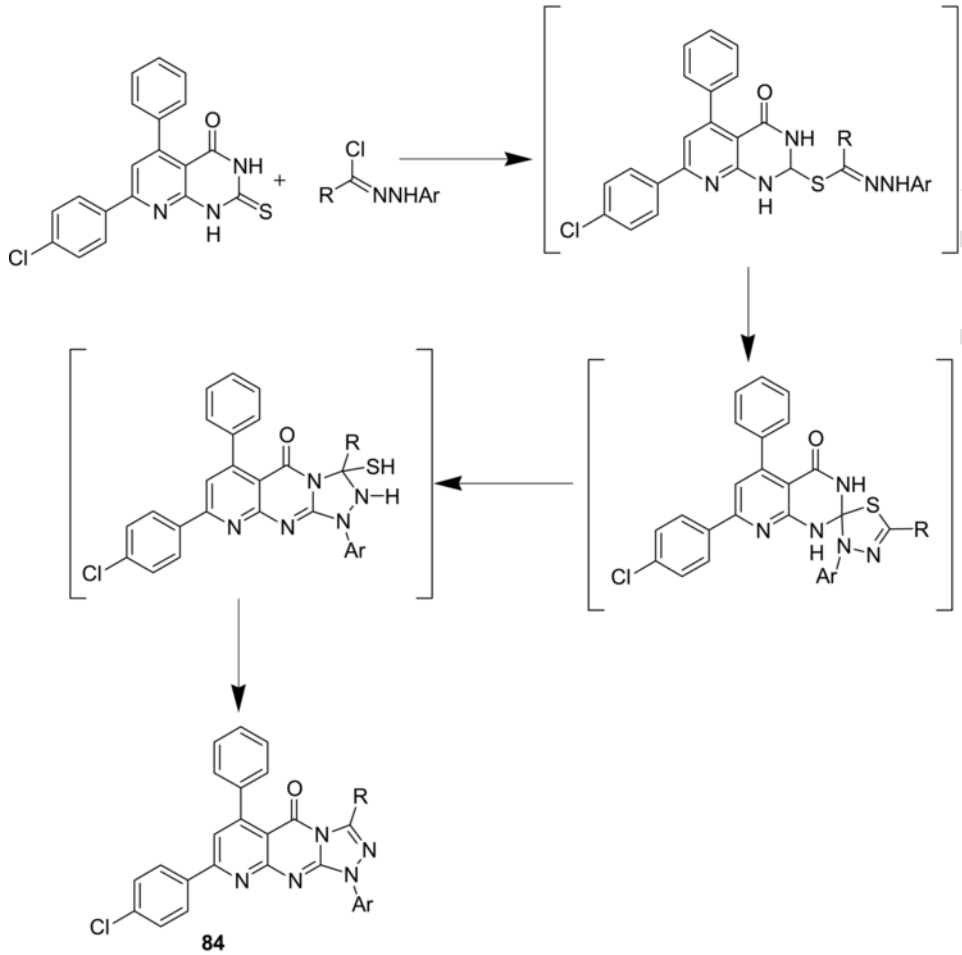
of hydrogen sulfide would then yield **82**. In the second step, an initial 1,3-cycloaddition of nitrilimine to the C═S double bond would give spiro compound directly. Attempts to isolate the thiohydrazonate ester, spiro and thiohydrazide compounds did not succeed, even under mild conditions as they readily undergo in situ cyclization followed by elimination of hydrogen sulfide to give the final product **82**. This structural assignment is also consistent with literature reports from early years, which indicate that reaction of hydrazonoyl halides with 2-thioxopyrimidin-4-one yields regioselectively the corresponding 1,2,4-triazolo[4,3-*a*]pyrimidin-5-one derivatives.[29]

A similar methodology was used to obtain 1,2,4-triazolo[4,3-*a*]pyrimidin-5-one derivatives **83**. As depicted in **Scheme 24**, the reaction proceeds through *S*-alkylation to give the non-isolable *S*-alkylated intermediates followed by Smiles rearrangement to generate the thiohydrazide intermediates, which undergo in situ cyclization via hydrogen sulfide elimination to give the final products **83**.[30]

A similar reaction apparently takes place between pyrido[2,3-*d*]pyrimidines derivatives and hydrazonoyl chlorides to form pyridotriazolopyrimidines **84**, as depicted in **Scheme 25**. Thus, pyrido[2,3-*d*]pyrimidines were allowed to react with hydrazonoyl



Scheme 24



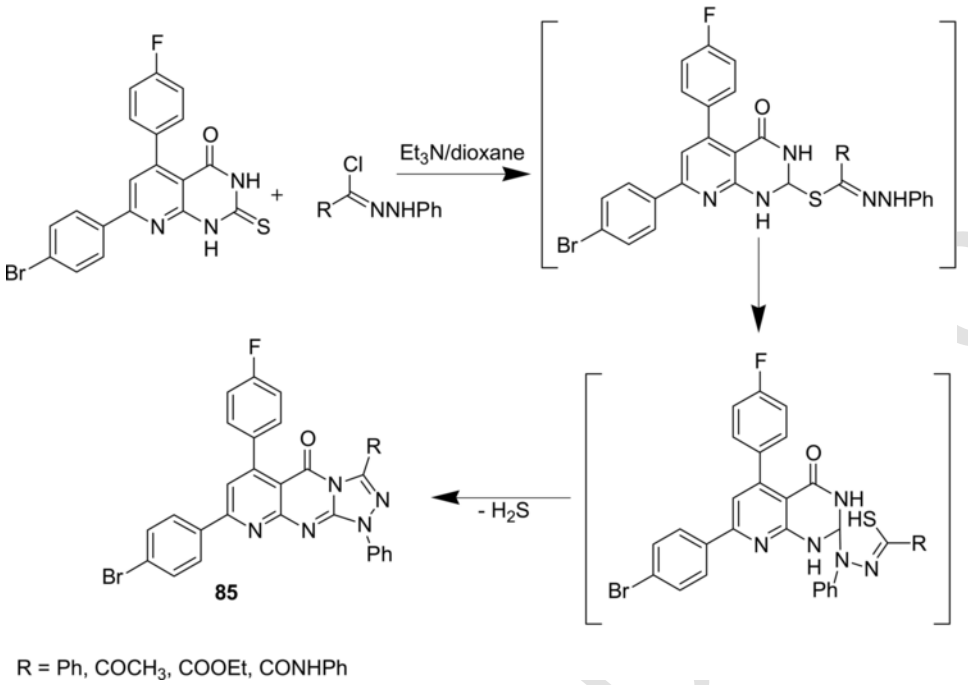
Scheme 25

chloride in dry chloroform in the presence of a few drops of triethylamine under reflux for 20–30 h under TLC control to afford 8-(4-chlorophenyl)-6-phenyl-5*H*-pyrido[2,3-*d*][1,2,4]triazolo[4,5-*a*]pyrimidin-5-ones **84** (**Scheme 25**).[31]

A similar procedure was used to obtain a series of compounds **85** (**Scheme 26**). As can be seen, reaction with hydrazonoyl chlorides in dioxane in the presence of triethylamine yielded one isolable product **85** in each case. The mechanism apparently involves cyclization with loss of hydrogen sulfide.[32]

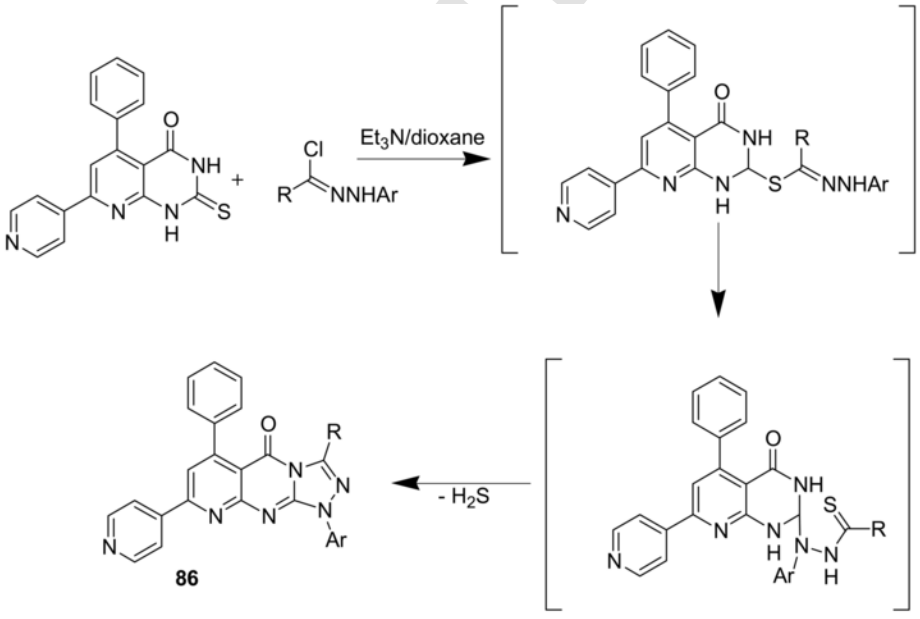
A similar pathway was suggested in the synthesis of 8-(4-pyridyl)-substituted compounds **86** (**Scheme 27**).[33]

Compound **87**, 8-amino-1,5-dihydro-3-methyl-5-oxo-6-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-7-carbonitrile was prepared by heating the hydrazine derivative of a pyridopyrimidine in a mixture of acetic acid and acetic anhydride under reflux conditions (**Scheme 28**).[34] This hydrazine derivative was also transformed into 8-amino-3-(4-chlorophenyl)-1,2,3,5-tetrahydro-5-oxo-6-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-8-carbonitrile **88** in good yield (87%) and into the analogue triazolopyridopyrimidine **89**, as shown in (**Scheme 28**).[34] These two reactions were conducted in pyridine under reflux conditions.



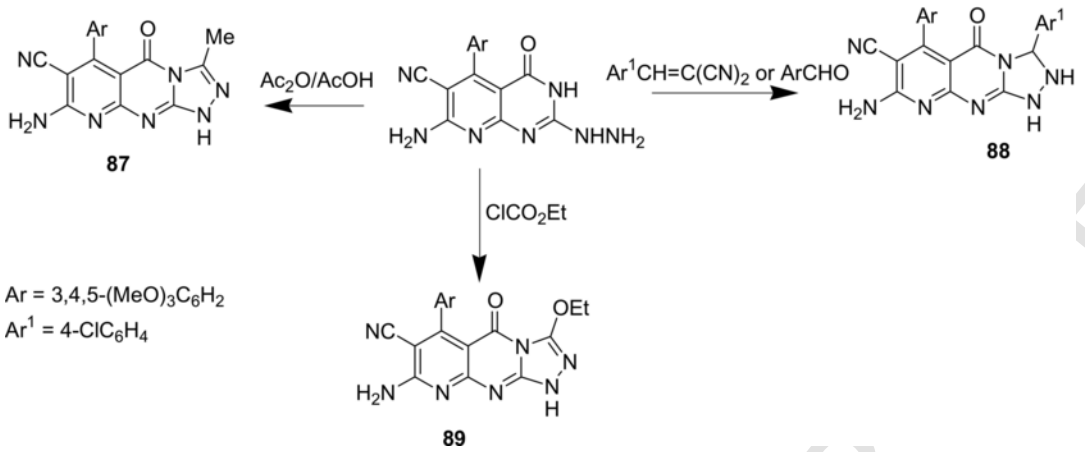
R = Ph, $COCH_3$, COOEt, CONHPh

Scheme 26



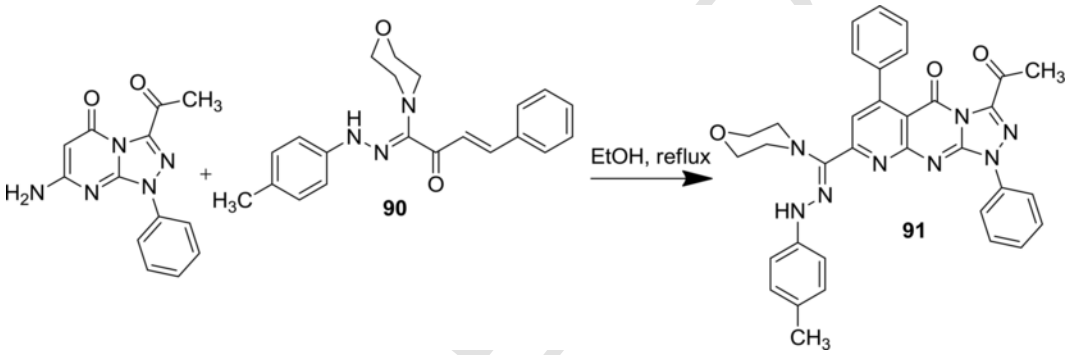
R = $COCH_3$, COOEt; Ar = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4

Scheme 27



Scheme 28

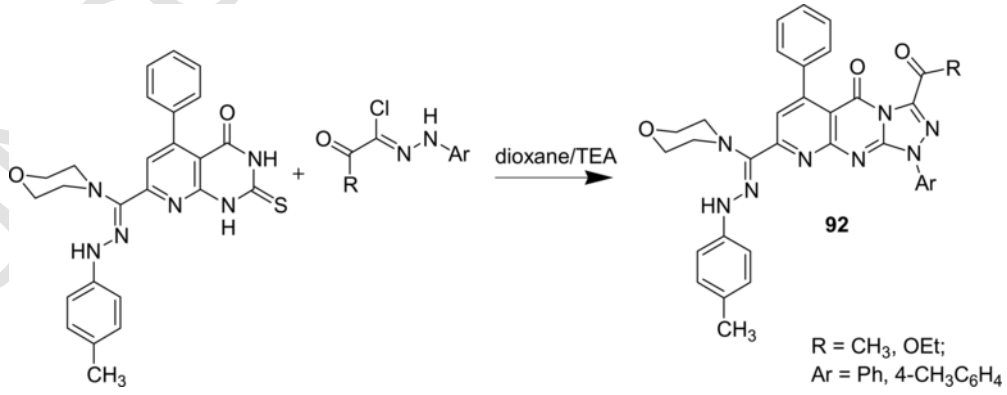
In the synthesis of the pyridotriazolopyrimidine derivative **91**, a solution of compound **90** and 3-acetyl-7-amino-1-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one in ethanol was heated under reflux (Eq. **4**).[35]



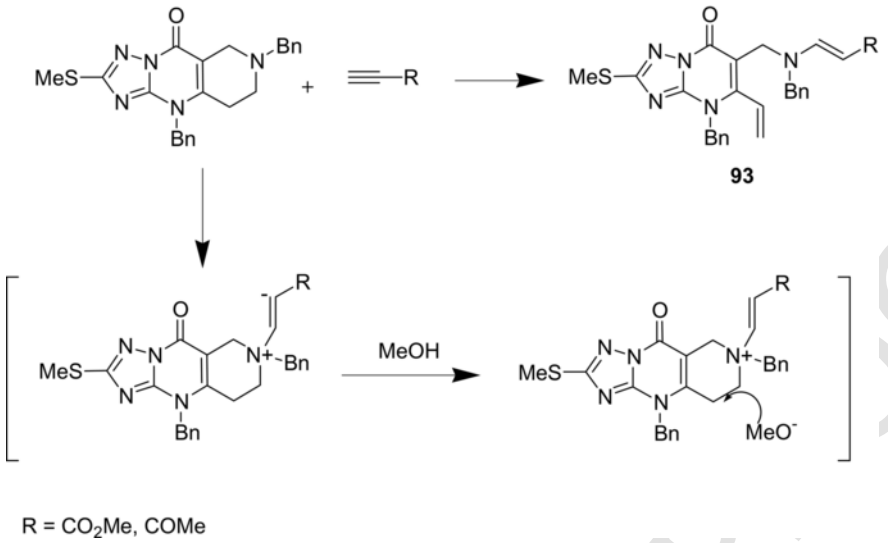
(4)

On the other hand, the treatment of a thione, shown in **Scheme 29**, with hydrazonoyl halides in dioxane in the presence of triethylamine furnished 1,5-dihydropyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine derivatives **92**.[35]

It was expected that the reaction of triazolopyridopyrimidine derivative, shown in **Scheme 30**, with acetylacetylene and methyl propiolate in methanol would give the respective tetrahydrotriazolopyrimidoazocine. Instead, the Hofmann cleavage of the tetrahydropyridine ring resulted in the formation of 5-vinyl[1,2,4]triazolo[1,5-*a*]pyrimidines **93** in 85% and 89% yields, respectively (**Scheme 30**).[36]



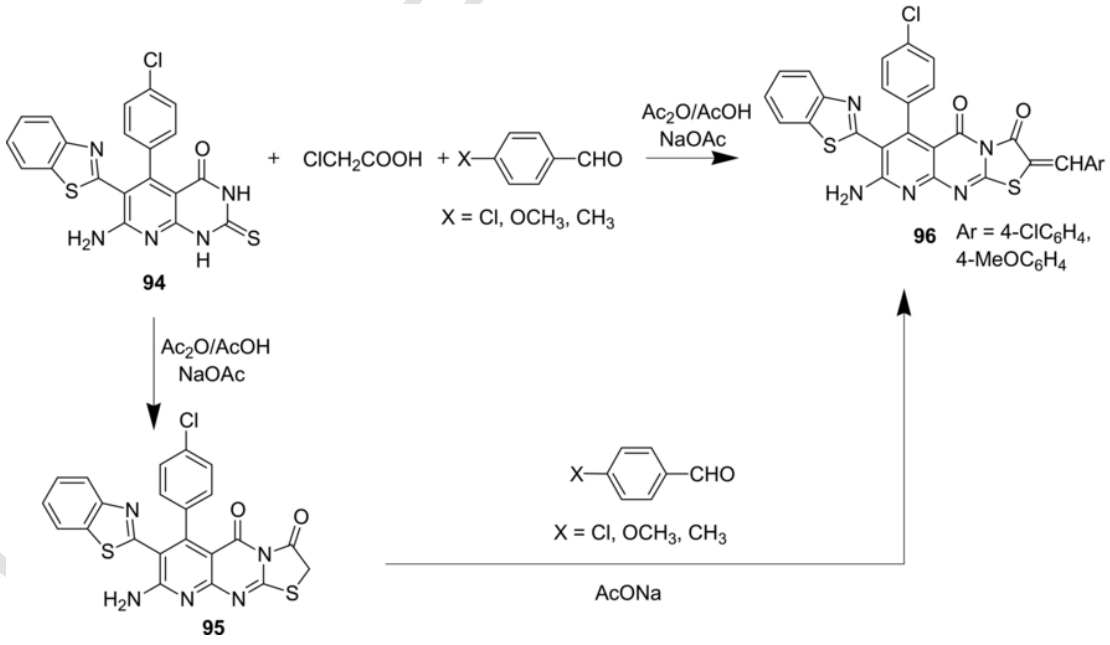
Scheme 29



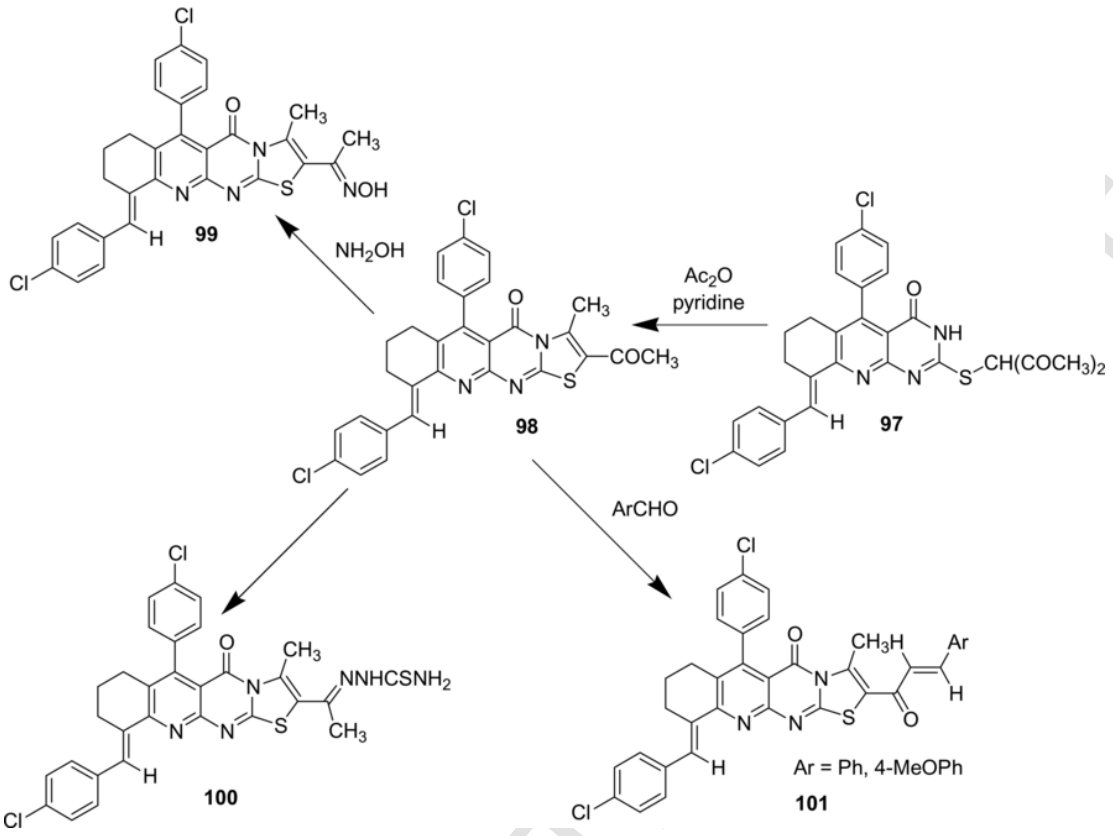
Scheme 30

Compound **94** was condensed with aromatic aldehydes in a ternary mixture of chloroacetic acid, acetic acid and acetic anhydride, in the presence of anhydrous sodium acetate to give 2-arylmethylene-8-amino-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-[1,3]thiazolo[4,5-*a*]pyrido[2,3-d]pyrimidine-3,5-dione derivatives **96** in high yield as shown in **Scheme 31**.[37]

Heating of **97** under reflux in an acetic anhydride/pyridine mixture led to cyclization with the formation of product **98** in good yield. Treatment of **98** with hydroxylamine hydrochloride and thiosemicarbazide gave the respective oxime and thiosemicarbazone derivatives **99** and **100**. Moreover, treatment of compound **98** with an aryl aldehyde in the presence of a catalytic amount of piperidine yielded the fused tetracyclic derivatives **101** (**Scheme 32**).[38]



Scheme 31

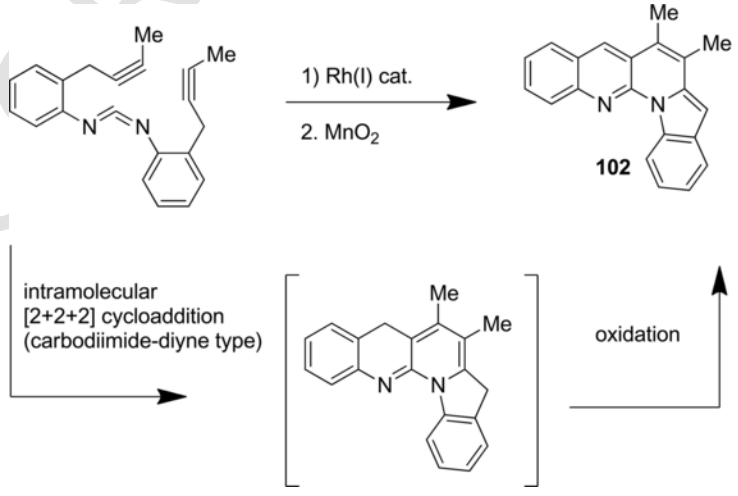


Scheme 32

3.2 Angularly fused systems

3.2.1 Indolizines and their hetero analogues fused to a six-membered heterocycle

A synthetic method for the L-shaped π-extended pentacycle, dibenzopyrrolo[1,2-*a*][1,8]naphthyridine **102**, via intramolecular hetero[2 + 2 + 2]cycloaddition using carbodiimide with two alkyne moieties was developed (**Scheme 33**).[39]

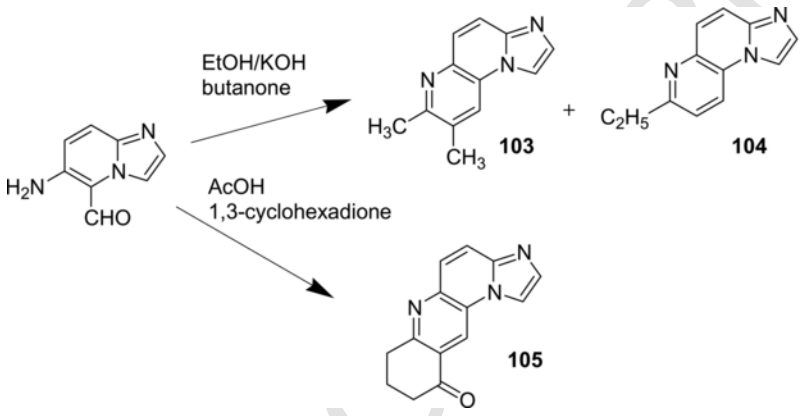


Scheme 33

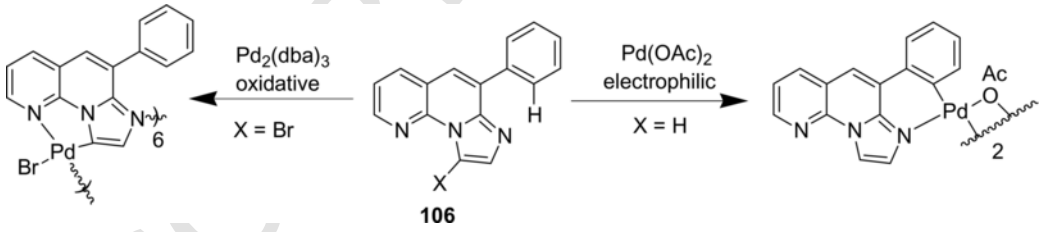
The preparation of imidazo[1,2-*a*][1,5]naphthyridines **103** and **104** was carried out using anhydrous EtOH/KOH 10% in butanone, as shown in **Scheme 34**. This reaction yielded the dimethyl derivative **103** and the ethyl derivative **104** in 22% and 5% yields, respectively. Treatment of the imidazole substrate with 1,3-cyclohexadione under similar conditions gave no trace of the desired tetracyclic system **105**. After prolonged reaction time, unchanged starting material was recovered together with an unidentified material. Finally, compound **105** was prepared in 30% yield by the reaction conducted in acetic acidic (**Scheme 34**).[40]

Cyclometalation on the substituted imidazo[1,2-*a*][1,8]naphthyridine **106** platform involves either the *C*3-aryl or *C*4′-aryl *ortho* carbon and the imidazole nitrogen *N*3′. The higher donor strength of the imidazole nitrogen in comparison to that of the naphthyridine nitrogen aids regioselective *ortho* metalation at the *C*3/*C*4′-aryl ring with Cp*IrIII (Cp* = η5-pentamethylcyclopentadienyl). A longer reaction time led to double cyclometalations at *C*3-aryl and imidazole *C*5′-H, creating six- and five-membered metallacycles on a single skeleton. Mixed-metal Ir/Sn compounds are accessed by insertion of $SnCl_2$ into the Ir—Cl bond. The use of $Pd(OAc)_2$ afforded an acetate-bridged dinuclear *ortho* metalated product involving the *C*3-aryl unit. Metalation at the imidazole carbon *C*5′ was achieved via an oxidative route by the reaction of the bromo derivative with the Pd(0) precursor $Pd_2(dba)_3$ (dba = dibenzylideneacetone). Regioselective C–H/Br activation on a rigid and planar imidazonaphthyridine system is shown in **Scheme 35**.[41]

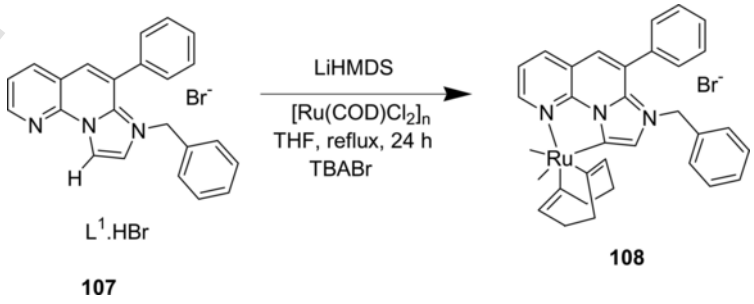
Compound **107** (L1 · HBr) (**Scheme 36**) is a difficult ligand for metalation. Nevertheless, the complex $[Ru(COD)(L^1)Br_2]$ **108** was isolated in yield of 81% via the reaction of **107** with $Li[N(SiMe_3)_2]$ followed by addition of $[Ru(COD)Cl_2]_n$ and subsequent



Scheme 34



Scheme 35

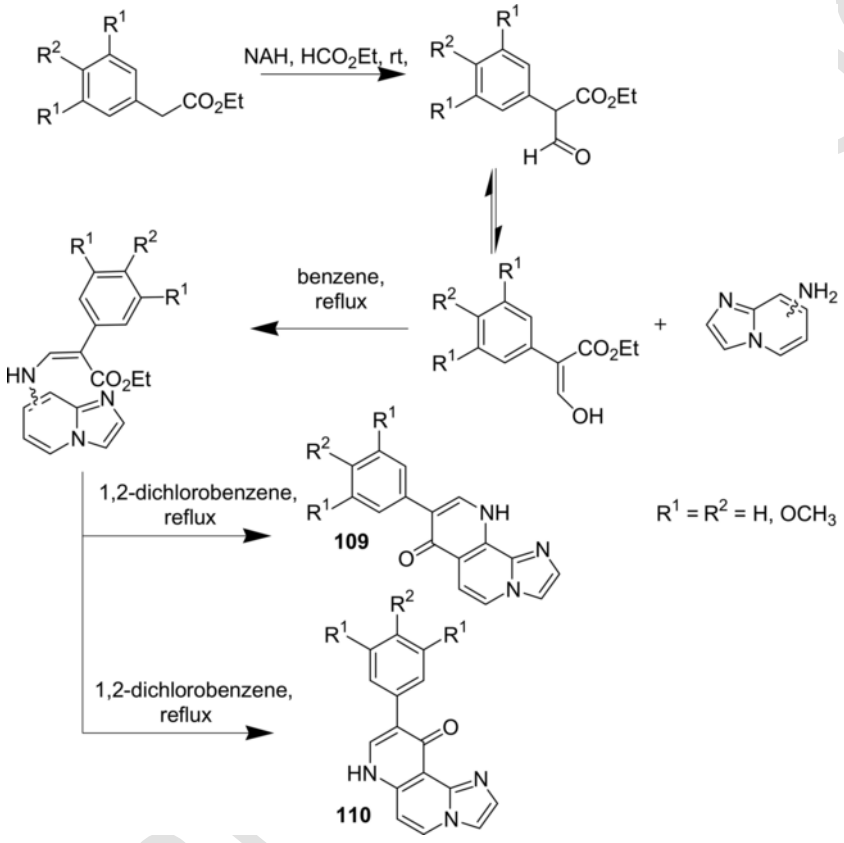


Scheme 36

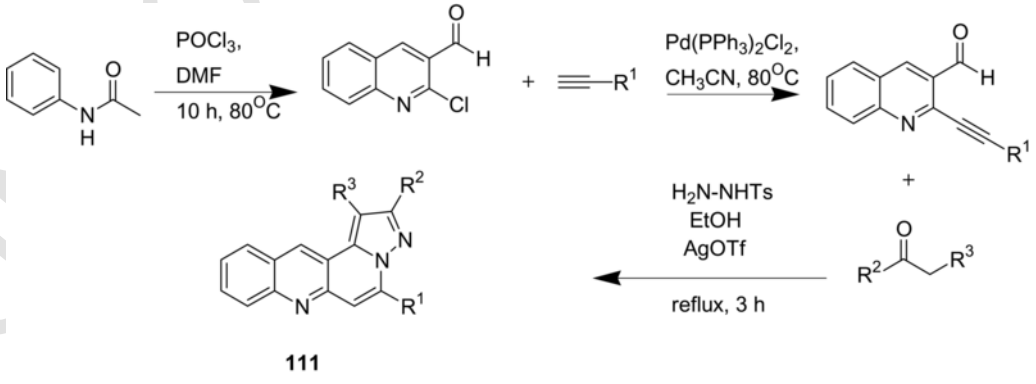
treatment with *n*-Bu_4NBr. This is the first report[42] of a ruthenium complex that contains COD (cyclooctadiene), a labile ligand under oxidative conditions.

The preparation of imidazonaphthyridinones **109** and **110**, which are potential ligands for metal complexation, is shown in **Scheme 37**.[43] These compounds were obtained in moderate yields of 53–83%.[43]

As shown in **Schemes 38**, 2-chloroquinoline-3-carbaldehyde was prepared by Vilsmeier reaction of acetanilide. The Sonogashira coupling of this aldehyde with various alkynes afforded the 2-alkynyl-3-formylquinolines, the cyclization of which with tosylhydrazine and various carbonyl compounds in the presence of silver triflate (AgOTf) and a base, afforded the benzo[*b*]pyrazolo[5,1-*f*



Scheme 37



Scheme 38

][1,6]naphthyridines **111** in 56–82% yields (**Scheme 38**). The best yields were obtained under reflux conditions with K_3PO_4 as base in ethanol. The reaction in the absence of AgOTf or the use of other Lewis acids resulted in a decrease of the yield.[44]

2-Amino-3-(tetrazol-5-yl)-4-trifluoromethyl-6-phenylpyridine was allowed to react with acid chlorides in pyridine at room temperature to form *N*-acyl derivatives **112**. Compounds **112** upon reflux in toluene in the presence of *p*-TSA (*para*-toluenesulfonic acid) as a catalyst for 2 h were cyclized to pyrido[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines **113**. Alternatively, the substrate was allowed to react with acid chlorides in pyridine at 100 °C to furnish directly the cyclized products **113** in a single step (**Scheme 39**).[45]

A facile approach to synthesis of thiazolopyridines **114** via one-pot, four-component, domino reaction between α-enolic dithioesters, cysteamine, arylglyoxal monohydrate and cyclic 1,3-diketones under solvent-free conditions at 90 °C is shown in **Scheme 40**.[46]

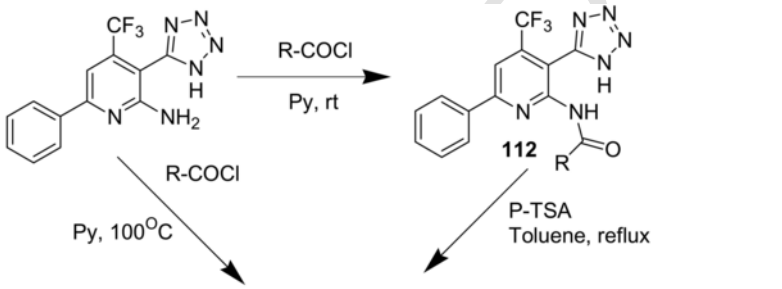
The series of structurally related thiazolonaphthyridines **115** was obtained in a similar way (**Scheme 41**).[46]

Naphtopyranotriazolopyrimidine amidoximes **116** can easily be functionalized as shown in **Scheme 42**.[47] In a similar way, the substrate **117** can be transformed into a number of derivatives by using common reagents (**Scheme 43**).[48] Synthesis of angularly fused pentacyclic derivatives **118** is shown in **Scheme 44**.[49] Another transformation of the tetracyclic system of **117** into the pentacyclic fused system of **119** is presented in **Scheme 45**.[50]

Treatment of 10-amino-10,11-dihydro-11-imino-3-methoxy-12-(*p*-chloro/bromo phenyl)-12*H*-naphtho[2,1-*b*]pyrano-[2,3-*d*]pyrimidines with ethyl chloroformate in dry benzene afforded 11-methoxy-14-(*p*-chloro/bromophenyl)-2-oxo-2*H*,3*H*,14*H*-naphtho[2,1-*b*]-pyrano[3,2-*e*].

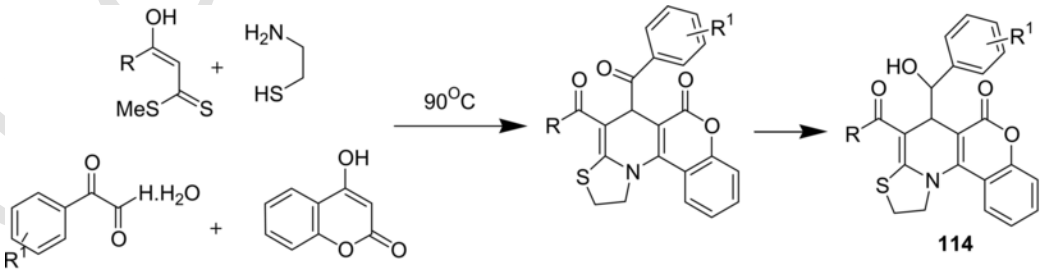
[1,2,4]triazolo[1,5-*c*]pyrimidines **120**. Reaction of the same compounds with CS_2 in the presence of KOH in ethanol gave triazolo-2-thiones **120** (**Scheme 46**).[50]

Thiazolo[3′,2′:1,6]pyrido[2,3-*d*]pyrimidine derivative **122** was obtained by refluxing a solution of compound **121** in formic acid (**Scheme 47**). Cyclocondensation of compound **121** with formamide under reflux furnished the corresponding thiazolo-



R = CH_3, C_2H_5, C_3H_7, $CH(CH_3)_2$, $C(CH_3)_3$, C_6H_5, 4-FC_6H_4, 4-CNC_6H_4, 4-$MeOC_6H_4$, 3-ClC_6H_4, 3-BrC_6H_4, 3-$NO_2C_6H_4$, 3-$MeOC_6H_4$, 3-FC_6H_4

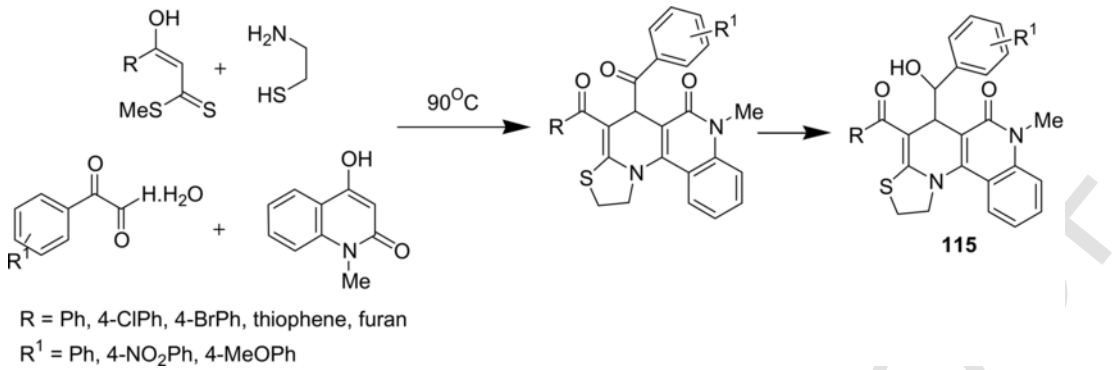
Scheme 39



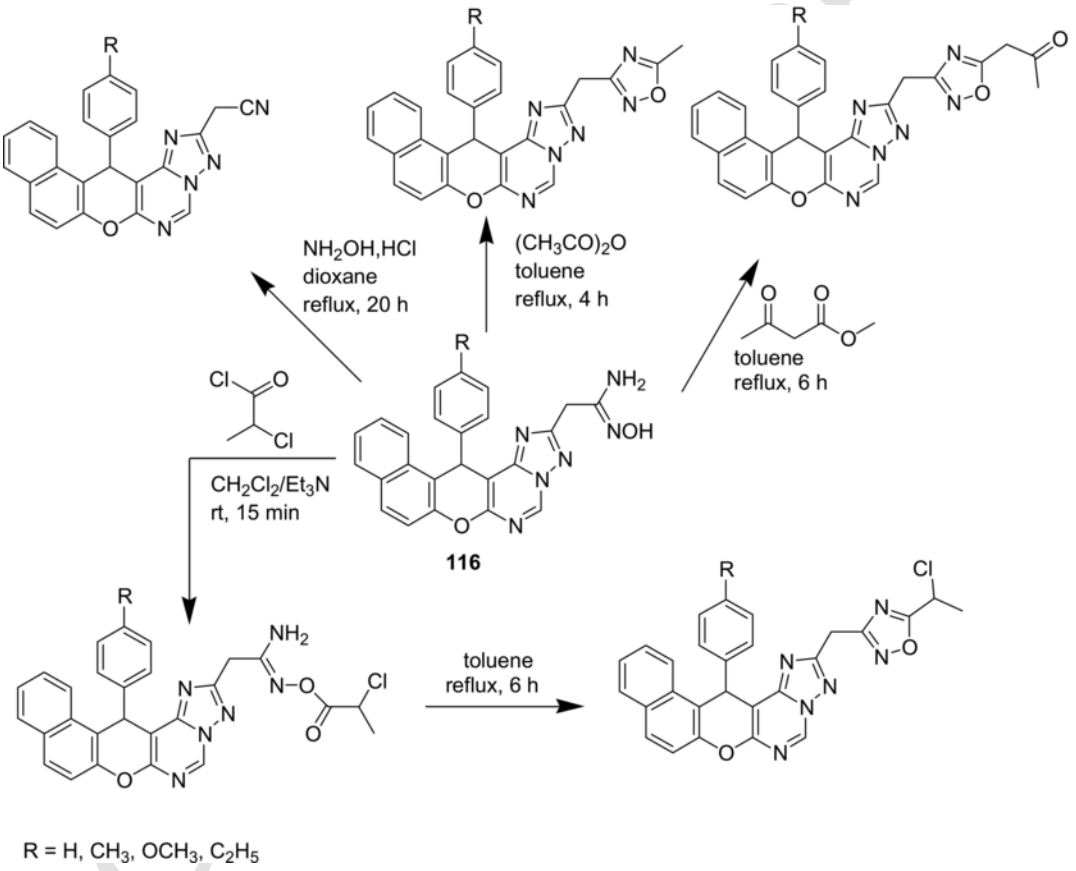
R = Ph, 4-ClPh, 4-BrPh, thiophene, furan

R^1 = Ph, 4-NO_2Ph, 4-MeOPh

Scheme 40



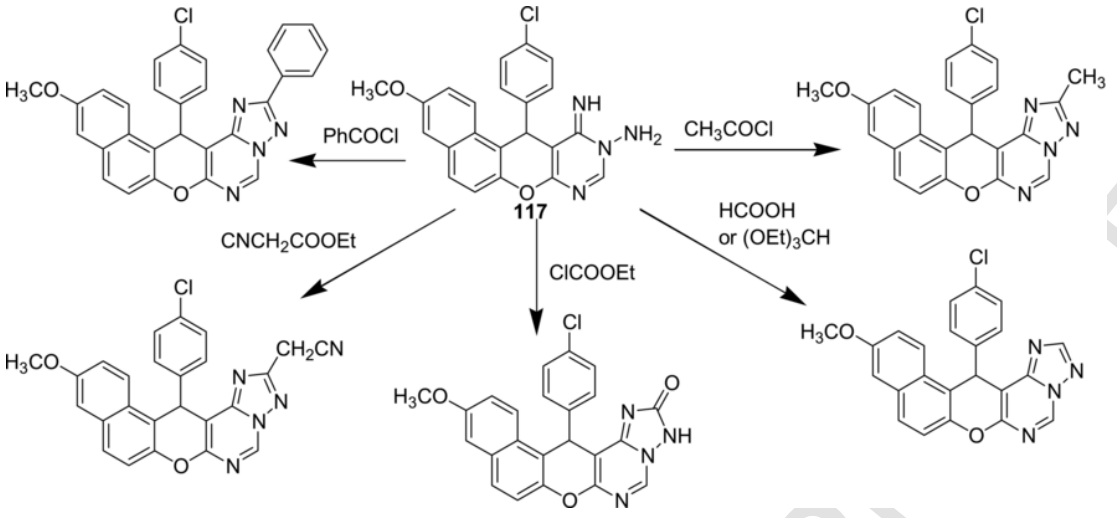
Scheme 41



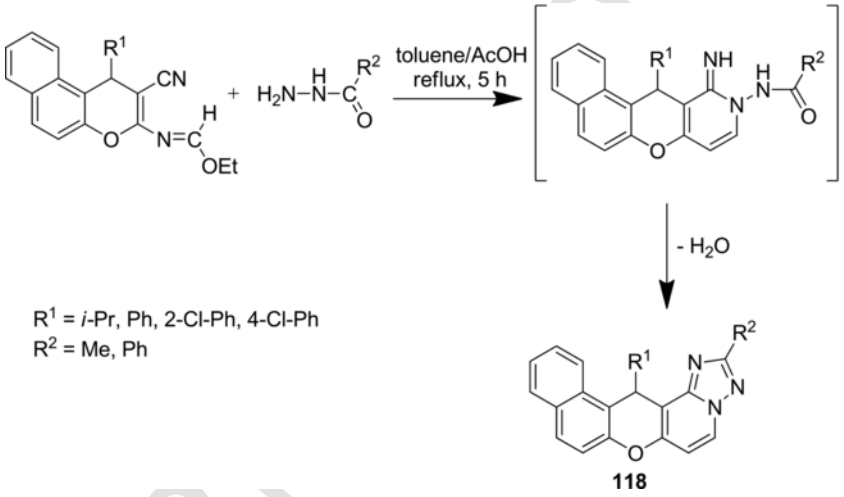
Scheme 42

[3′,2′:1,6]pyrido[2,3-*d*]pyrimidine derivative **123** (Scheme 47).[51] Products **122** and **123** were also obtained using an alternative synthetic route.[52]

Treatment of compound **125** with cyclohexylamine in boiling ethanol afforded the thiazolopyridopyrimidine derivative **126** (Scheme 48). On the other hand, the reaction of substrate **124** with carbon disulfide in ethanolic KOH furnished 8-amino-2-(4-chlorobenzylidene)-9-(*N,N*-dimethyl-4-aminophenyl)-10-ethoxycarbonyl-3-oxo-9*H*-thiazolo[3,2-*a*]pyrido[2,3-*d*]1,3-thiazin-6(*H*)thione **127** (Scheme 48).[53]



Scheme 43

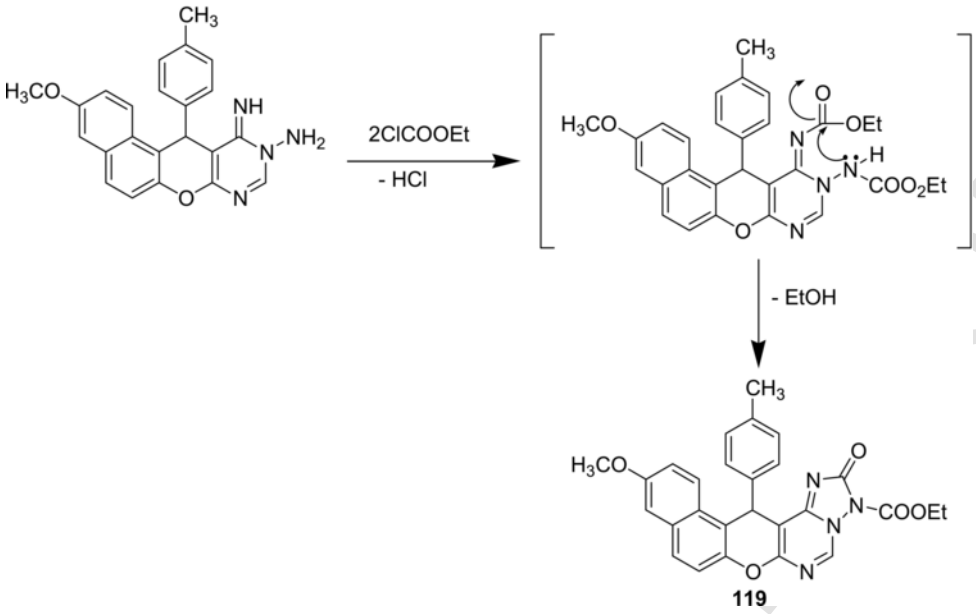


Scheme 44

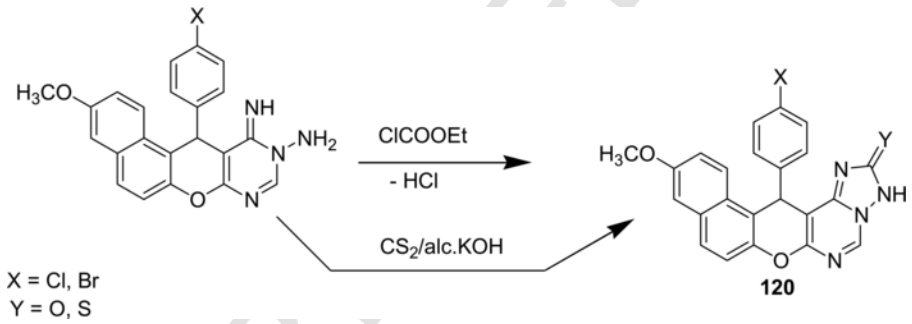
3.3 *Peri*-fused systems

3.3.1 Canthines

During the review period, a new canthin-6-one alkaloid **128** and two known alkaloids **129**, **130** were isolated for the first time from the stem bark of *P. huberi*. The structure of the new compound **128** was elucidated by analysis of spectroscopic data. The isolates

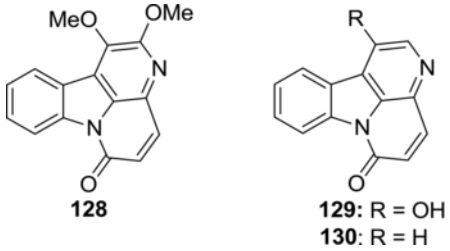


Scheme 45

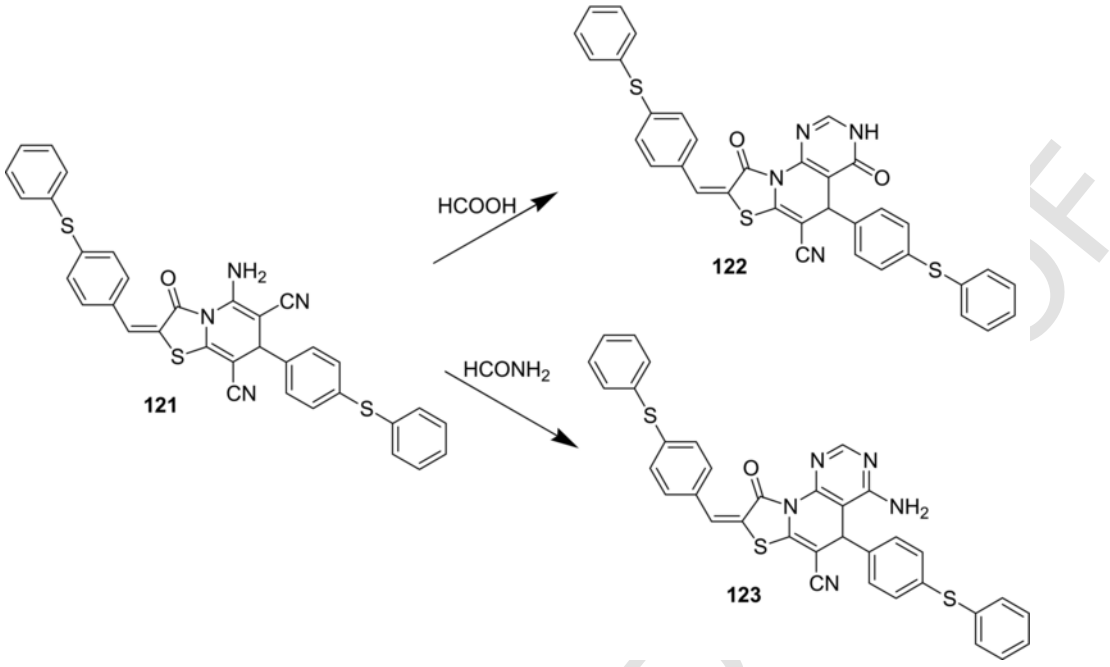


Scheme 46

were screened for inhibitory activity.



against *Plasmodium falciparum* strains. Compounds **128** and **129** showed no effective antiplasmodial activity.[54] In a subsequent study,[55] 22 cationic 10-methoxycanthin-6-one derivatives **131** were synthesized (**Scheme 49**). Their antibacterial activity was evaluated against three bacterial strains including two kinds of agricultural pathogenic bacteria. Four compounds displayed eightfold superiority against *R. solanacearum* and *P. syringae* compared to agrochemical streptomycin sulfate.

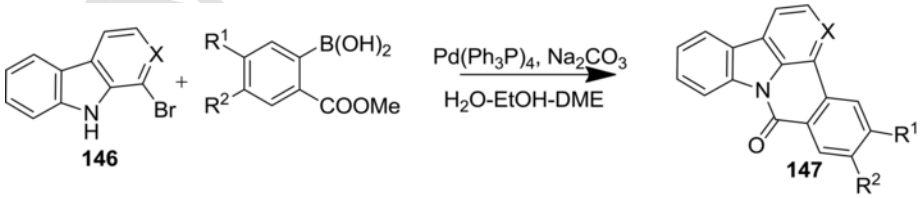


Scheme 47

The enantioselective synthesis of some analogues of compounds **128–131** is shown in **Scheme 50**. The substrate (±)-**132** on treatment with magnesium in a methanol/benzene mixture underwent a smooth *N*-detosylation and was transformed into (±)-20-epihydroxydesethyleburnamonine **133** in 87% yield. The lactamization process to form (−)-**133** with *trans* ring-fusion was very fast due to the 1,2-equatorial-equatorial orientations of the cyclizing groups. The (±)-β-hydroxyester **132** on treatment with the Burgess reagent underwent stereoselective dehydration to form a chromatographically separable mixture of the corresponding (±)-*Z*-**134** (52%) and (±)-E-**135** (10%) products in a total yield of 62% with a 5:1 isomeric ratio. Compound (±)-*Z*-**134** upon treatment with magnesium in a methanol/benzene mixture (1:1) was transformed into (±)-aminolactam **136** in 82% yield with preservation of the carbon-carbon double bond. Catalytic hydrogenation of the major isomer (±)-*Z*-**134** furnished the diastereomeric mixture of products (±)-cis-**137** and (±)-trans-**138** in 96% yield with a 2:5 ratio (**Scheme 50**). Detosylation of the major isomer (±)-**138** directly furnished the cyclized product (±)-20-epidesethyleburnamonine **139** in 73% yield. The transformation of (±)-**139** to (±)-vindeburnol **140** was accomplished by hydride reduction followed by an acid-catalyzed epimerization at the aminohydrin carbon through the dehydration-rehydration pathway. Detosylation of compound (±)-**137** initially generated the non-cyclized product (±)-**141** in 83% yield which, upon treatment with K_2CO_3 in refluxing methanol, was transformed into the desired cyclized product (±)-desethyleburnamonine **142** in 77% yield. Desethyleburnamonine **142** is an important bioactive agent.[56]

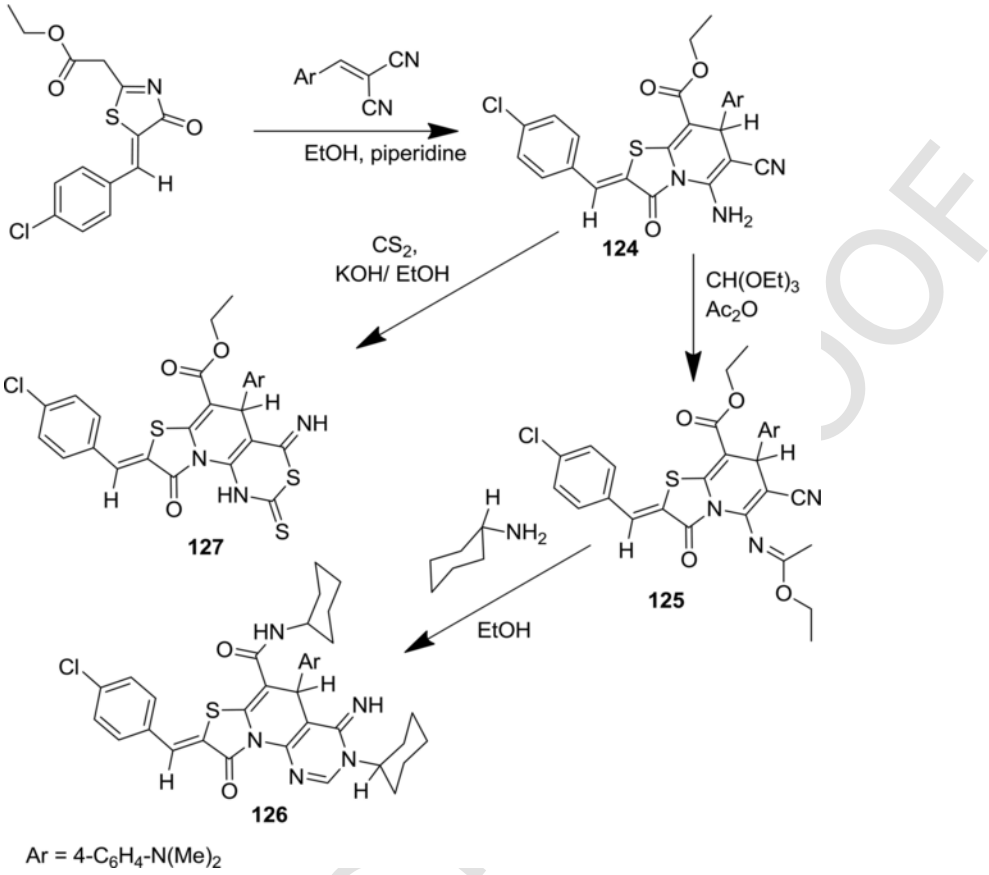
Detosylation of (±)-**143** by treatment with magnesium with a concomitant intramolecular cyclization furnished the lactam (±)-**144** in 83% yield (**Scheme 51**). Reduction of (±)-**144** gave the kinetically controlled product (±)-isovindeburnol **145** in 68% yield. Acid-catalyzed epimerization at the *gem*-aminohydrin center of **145** furnished the thermodynamically more stable (±)-vindeburnol **140**, which was mentioned in **Scheme 50**.[56,57]

Cross-coupling of pyrrole derivatives **146** with 2-methoxycarbonylphenylboronic acid under standard Suzuki conditions was accelerated by microwave irradiation. The coupling was followed by lactamization to give the corresponding benzocanthin-6-one derivatives **147** in high yields (Eq. **5**).[58] Antifungal activity of canthin-6-one derivatives was studied.[59]



X = CH, N
R^1 = H, Cl, OMe
R^2 = H, OMe

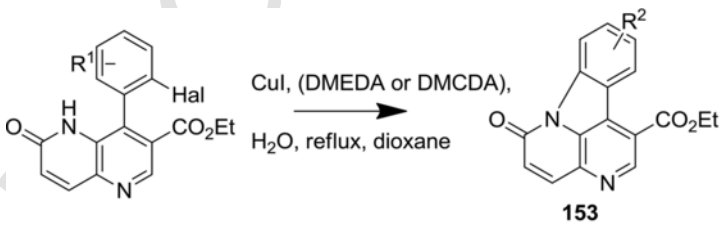
(5)



Scheme 48

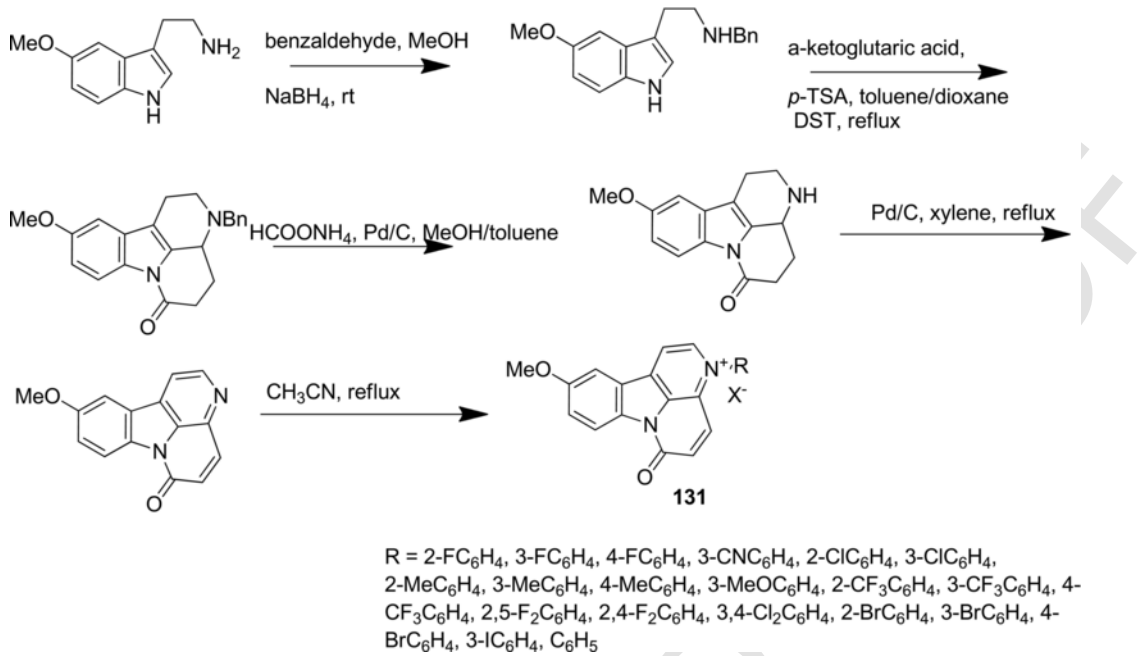
Treatment of compound **148** with prenyl bromide in the presence of Cs_2CO_3 smoothly afforded the *N*-prenylated acetal **149** in 91% yield (**Scheme 52**). Use of aqueous acetic acid or aqueous trifluoroacetic acid (TFA) promoted the deprotection of **149** instead of producing the aldehyde **150** and led to the formation of a new canthine **151** in 62% yield (**Scheme 52**). In the synthesis of **150**, aldehyde **152** was directly treated with prenyl bromide in the presence of Cs_2CO_3 in anhydrous *N,N*-dimethylformamide (DMF) at room temperature. This reaction furnished the required product **150** in 78% yield. Heating of **150** with $ZnBr_2$ in anhydrous benzene to reflux temperature smoothly afforded **151** in 91% yield in 12 h. This reaction was observed to be diastereoselective in favour of the *syn*-isomer (98:2). Prenylated aldehyde **150** was subjected to heating with $ZnBr_2$ in anhydrous benzene to afford **151** in 90% yield with *syn*-stereoselectivity. Reaction of **150** with $Yb(OTf)_3$ in anhydrous acetonitrile under heating at reflux also furnished **151** in 80% yield; the reaction was completed in 3 h.[60]

Treatment of ethyl 4-(2-bromo(chloro)phenyl)-6-oxo-1,5-naphthyridine-3-carboxylate derivatives under typical Buchwald conditions [CuI (5 mol%), DMEDA (10 mol%) Cs_2CO_3(2 equiv.), water (2 equiv.) in refluxing dioxane, 1 h] furnished the canthinone-1-carboxylate derivatives **153** in excellent yields (Eq. **6**).[61]



(6)

Hal = Br, Cl
R^1 = H, 3-Cl, 4-Cl, 4-F_3C, 4-Me, 4-MeO, 4-F, 5-Cl, 5-F_3C, 3-aza, 4-aza
R^2 = H, 8-Cl, 9-F_3C, 9-Me, 9-MeO, 9-F, 10-Cl, 10-F_3C, 8-aza, 9-aza

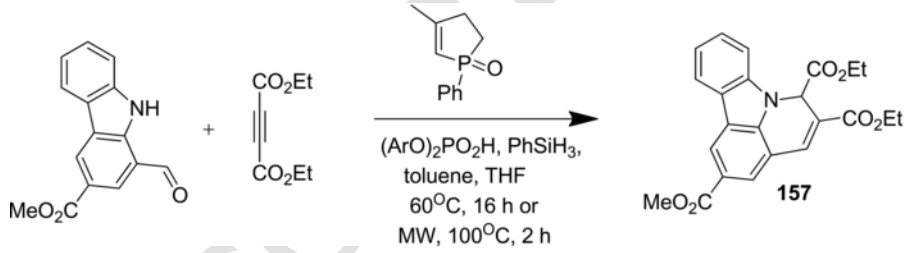


Scheme 49

In the synthesis of product **154** (**Scheme 53**), indole was formylated using Vilsmeier-Haack reaction to give indole-3-carbaldehyde which was then *N*-alkylated with 4-chlorobutan-1-ol. Henry reaction of this product furnished an unsaturated nitro-hydroxy derivative, the oxidation of which using *o*-iodoxybenzoic acid (IBX) produced a nitro-aldehyde. Treatment of this product with hydroxylamine hydrochloride in the presence of sodium acetate in toluene produced the cyclized product **154** in 67% yield (**Scheme 53**).[62]

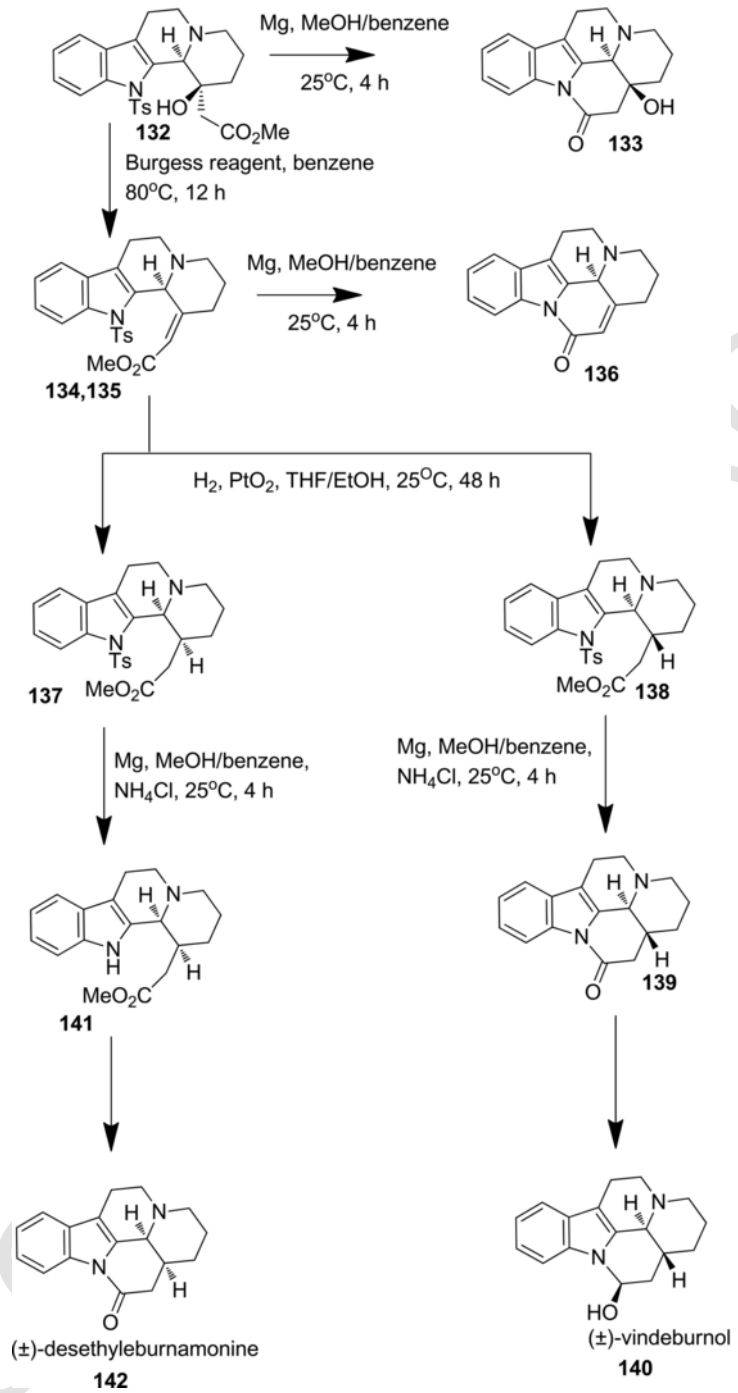
The Stille coupling reaction provided 9*H*-pyrido[3,4-*b*]indoles **155a–c** in good yields. Heating of **155a** in the presence of *p*-TsOH at 120 °C furnished 4*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6(5*H*)-one **156** in 75% yield (**Scheme 54**).[63]

Triester **157** was obtained in 86% yield starting from methyl 1-formyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate substrate. Solubility problems of the starting material were overcome by using THF as a co-solvent to ensure a decent yield (Eq. 7).[64]



(7)

The elaborated synthetic approach to the natural product cordatanine **167** is depicted in **Scheme 55**.[65] The reaction of tryptamine **158** with freshly prepared methoxymaleic anhydride **159** in refluxing *o*-dichlorobenzene delivered methoxymaleimide **160** in 84% yield via regioselective ring opening of **159**, followed by the intramolecular dehydrative cyclization. Regioselective $NaBH_4$ reduction of **160** exclusively generated the lactamol **161** in 97% yield. Acid-catalyzed intramolecular dehydrative cyclization of lactamol **161** furnished the pyrrolotetrahydrocarbazole **162** in 87% yield. Treatment of **162** with *p*-toluenesulfonic acid (*p*-TSA) in MeOH at room temperature under atmospheric conditions directly provided the completely aromatized ester **166** in yield of 50% in 24 h. Repetition of the same reaction with a balloon of oxygen delivered product **166** in 88% yield in just 4 h. After the reaction of **162** with *p*-TSA/MeOH at room temperature under an oxygen atmosphere was arrested after 1 h, it was possible to isolate the intermediate pyrrolotetrahydrocarbazole **163**, bearing a labile angular methoxy group, in 47% yield. Intermediate product **163** upon treatment with *p*-TSA/MeOH at room temperature under an oxygen atmosphere also was transformed into the expected product **166** in good yield. Thus, **163** upon protonation followed by elimination of methanol is transformed into the reactive iminium ion intermediate **164**, which quickly undergoes methanolysis to the dihydroester **165**. The ester is oxidized in situ to the stable aromatic product **166**. Both the K_2CO_3/MeOH-catalyzed intramolecular cyclization of ester **166** (R═Me) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI)-induced intramolecular dehydrative cyclization of acid **166** (R═H) furnish the natural product cordatanine **167** in 93% and 84% yields, respectively.[65]

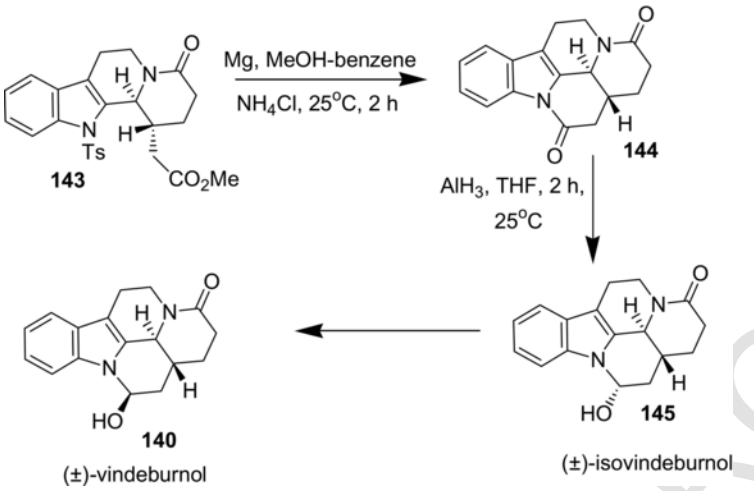


Scheme 50

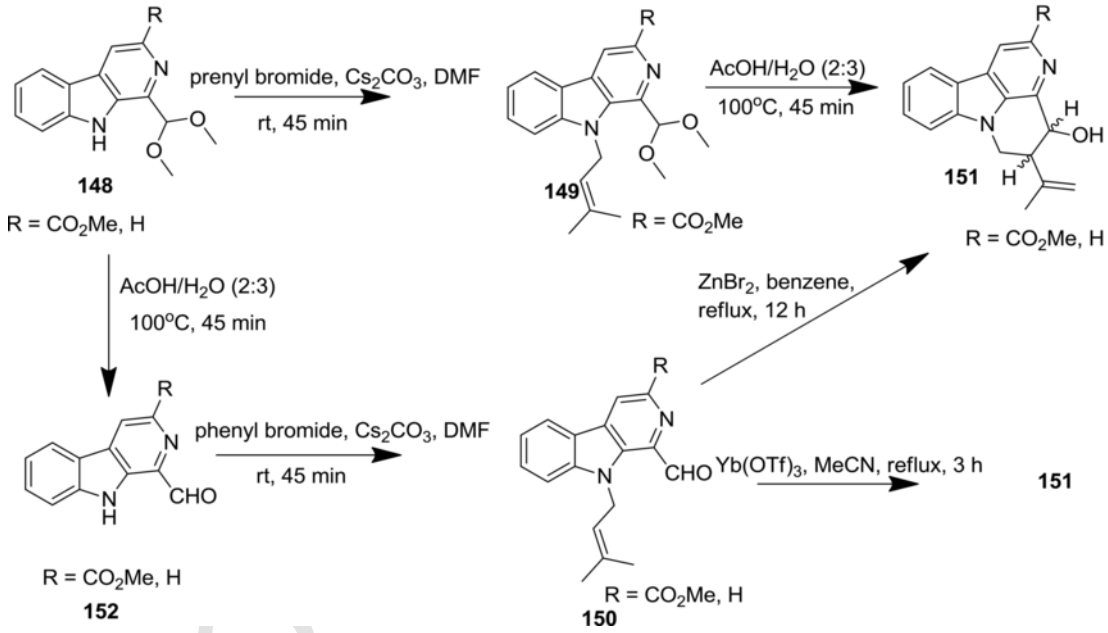
The Baylis-Hillman reaction of **168** with acrylonitrile was investigated.[66] This reaction was completed in 3–5 h in the presence of 1.0 equiv. of DABCO, giving the desired adducts **169** (**Scheme 56**). Treatment of **169** with K_2CO_3 in DMF at room temperature smoothly gave the canthine products **170** by an intramolecular Michael reaction.[66]

The same study,[66] produced diverse products using this chemistry starting from a new aldehyde **171**. The Baylis-Hillman reaction of **171** with acrylonitrile followed by intramolecular cyclization of the resultant adduct **172** furnished the new canthine analogue **173** (**Scheme 57**).[66]

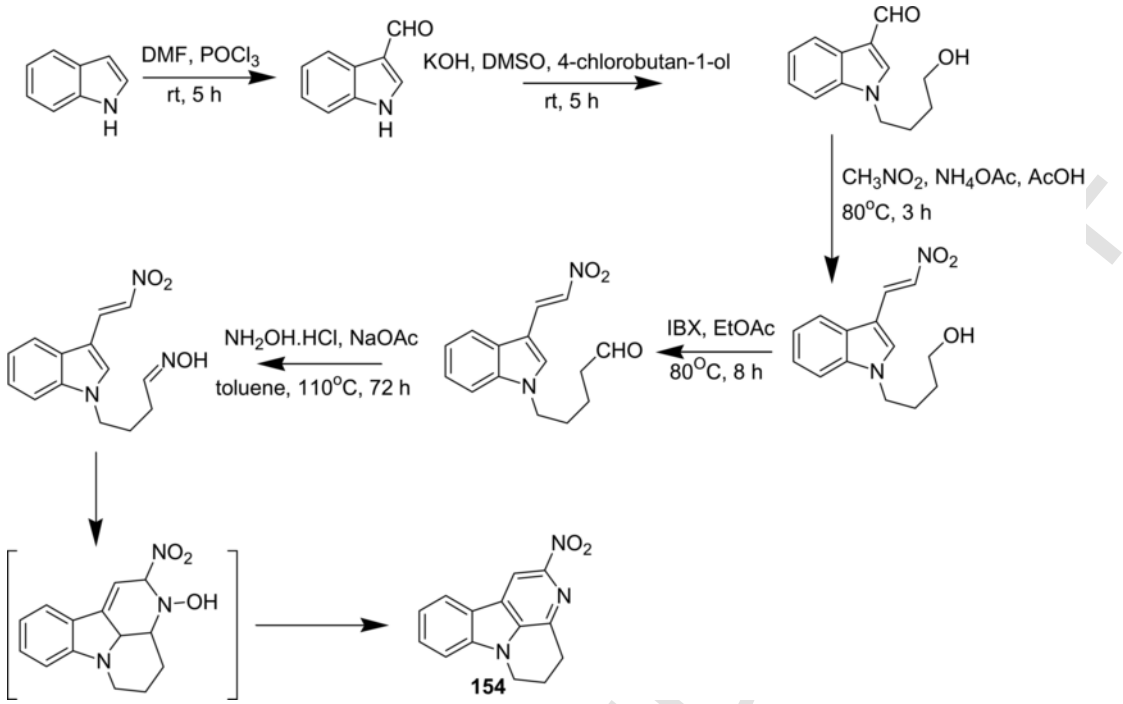
Novel fluorescent alkaloid amarastelline A **174** was isolated from *Quassia amara*.[67] Compound **174** shows unique fluorescence in a variety of solvents, illuminating all areas of living HeLa cells with the exception of their nuclei. This feature could be utilized in



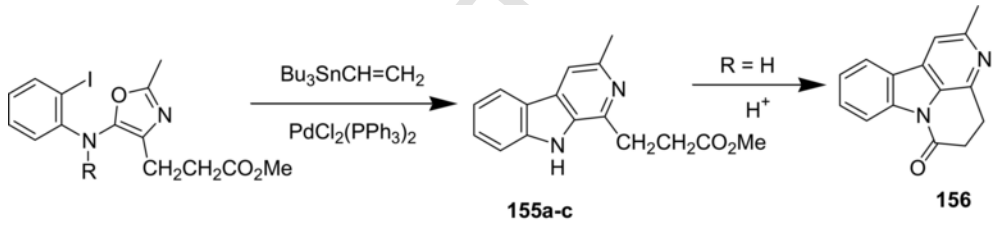
Scheme 51



Scheme 52

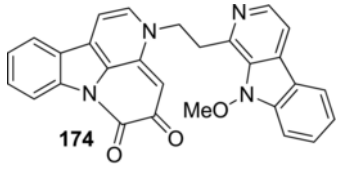


Scheme 53



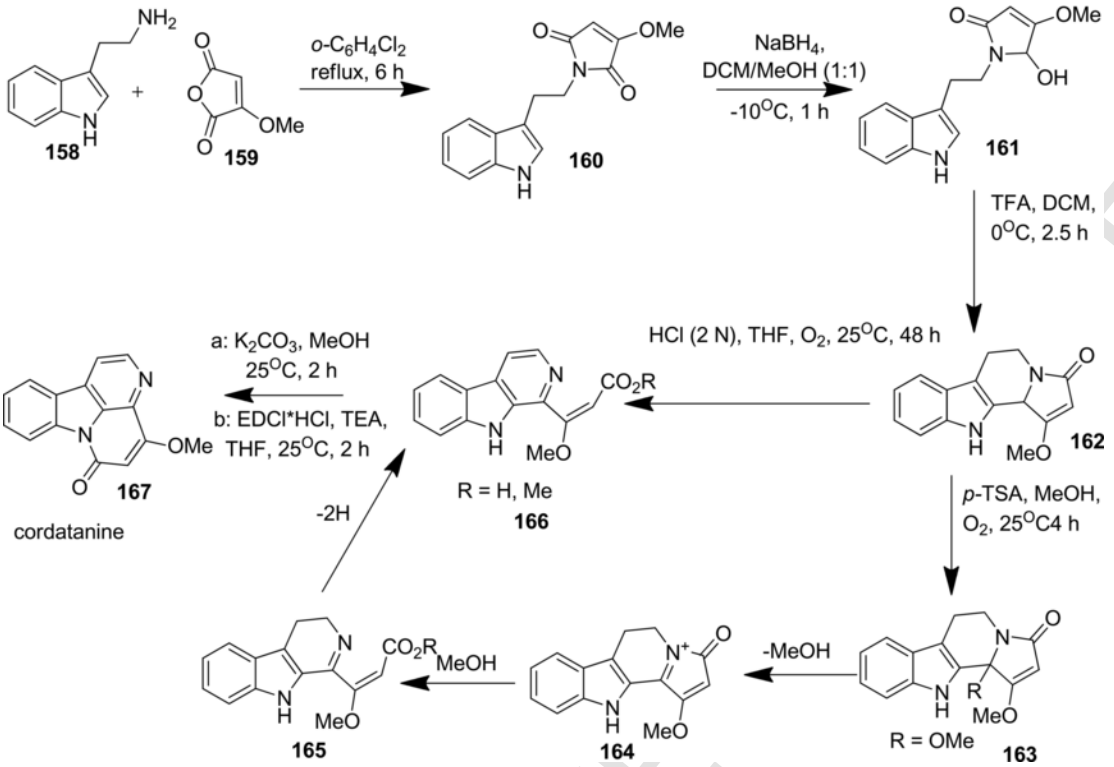
Scheme 54

cellular biology and to develop novel fluorescent sensors.[67]

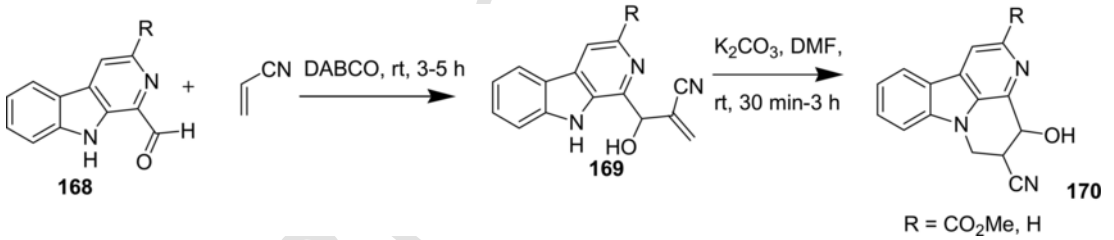


Canthine-4-ones **176** were prepared by intramolecular Claisen-type condensation of 1,3-diketones **175**. 1-Isoxazolyl-*b*-carbolines **177** were also considered as versatile precursors to **176** through intermediary of primary enaminoketones **178** upon reductive ring cleavage (**Scheme 58**).[68]

Canthin-4-ones were identified as a novel class of antibacterial agents, with a surprising selectivity for *S. entericus*.[69] Analysis of the *in vitro* antibacterial activities of the (hetero)aryl-canthin-4-one series does not include structure-activity relationships, despite the



Scheme 55



Scheme 56

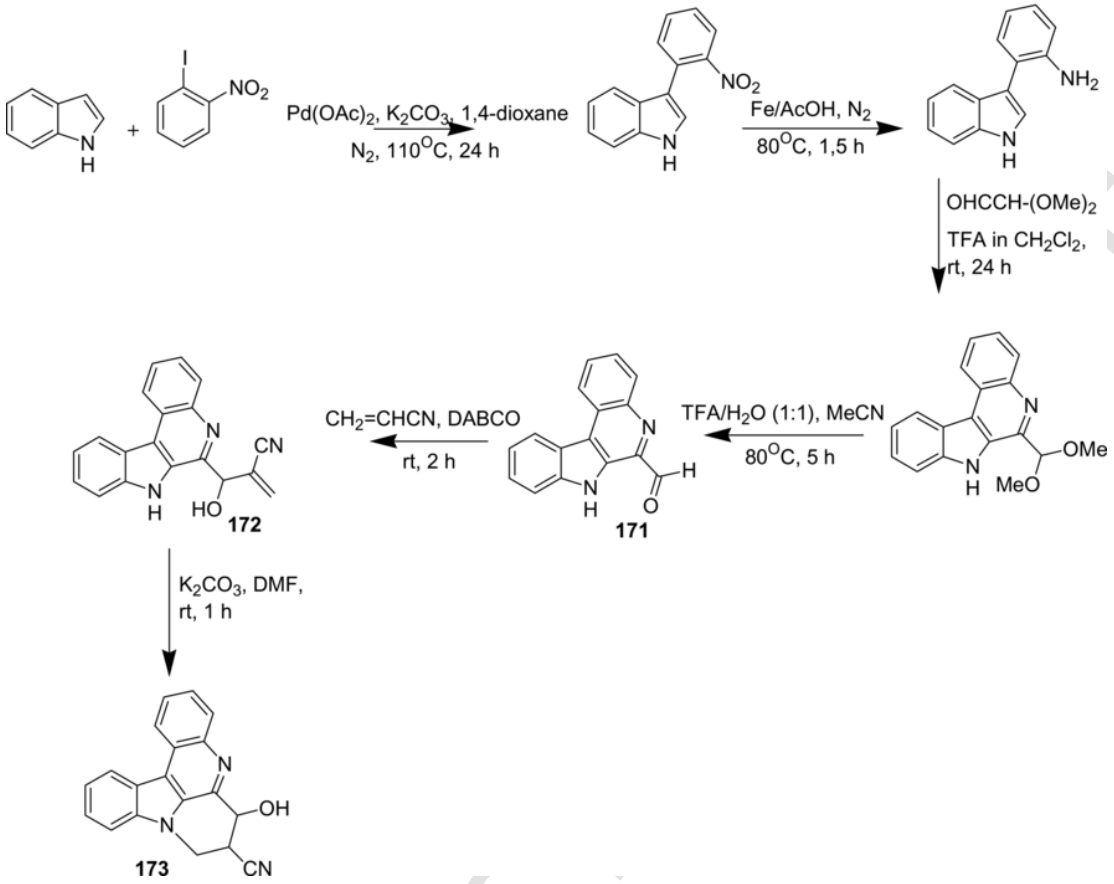
large number of compounds in this subtype. The most active compounds do not show undesired cytotoxicity for mammalian cells, so these compounds might be new leads for the development of novel narrow spectrum antibiotics. Some canthin-6-one alkaloids, commonly found in *Eurycoma* and *Picrasma* plants (*Simaroubaceae* family), show *in vitro* inhibition of several cancer cell lines, including A-388, A549, MCF-7 and Bel-7402.[70]

The synthetic route used for the target compounds **181** is outlined in **Scheme 59**. The natural product 10-methoxycanthin-6-one **179** was synthesized with 5-methoxytryptamine as the starting material. 10-hydroxycanthin-6-one **180**, was obtained by treating compound **179** with boron tribromide under an argon atmosphere, with anhydrous dichloromethane as solvent. At 0 °C, a new series of ester derivatives of 10-hydroxycanthin-6-one **181** was obtained in 48–86% yield by the reaction of compound **180** with the corresponding acyl chloride in the presence of triethylamine. In this study, two naturally occurring canthine-6-ones and 24 novel ester derivatives of 10-hydroxycanthin-6-one were synthesized and their *in vitro* antimicrobial activity was evaluated. Most of the synthesized compounds showed potential antibacterial and antifungal activity.[71]

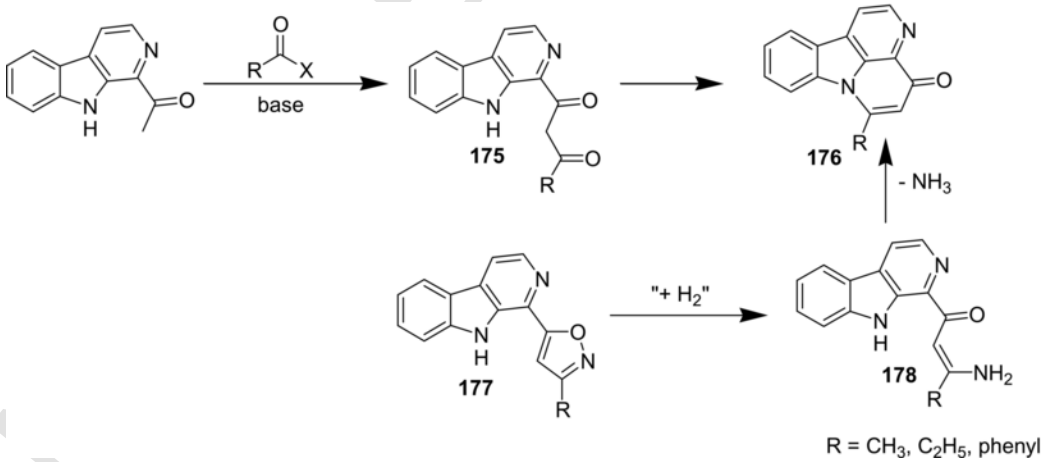
3.3.2 Other systems with nitrogen as the only ring heteroatom

Gold-catalyzed reactions between allenes and nitrogen nucleophiles are important C—N.

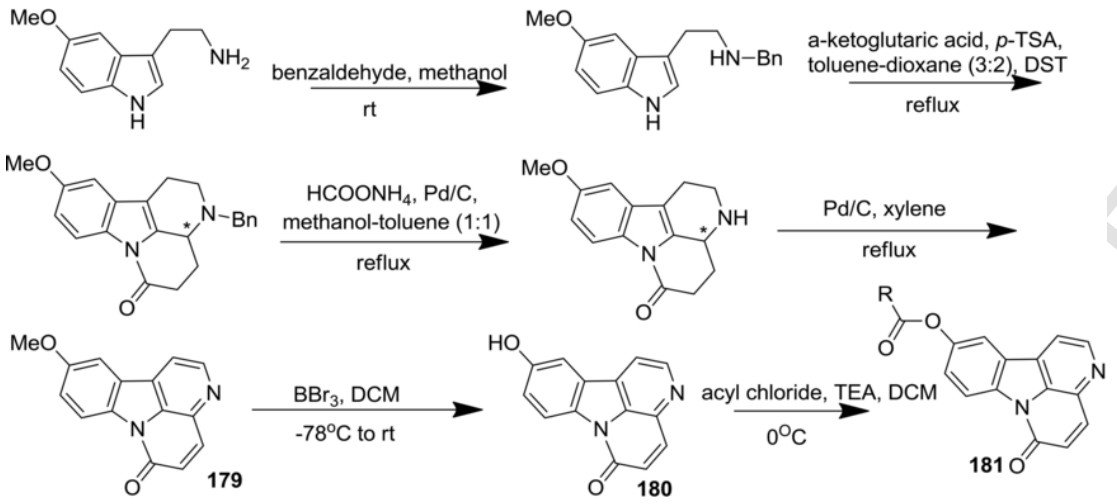
bond-forming processes. To explore the reactivity of aminoallene-tethered indolizidines towards hydroamination, compound **182** was selected as a model substrate. Catalyst screening led to the identification of [IPrAuSbF$_6$] as the most suitable promoter because adduct **183**



Scheme 57



Scheme 58



R = C_6H_5, 2-pyridyl, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_4$, 4-$CH_3OC_6H_4$, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 2-$CF_3C_6H_4$, 3-$CF_3C_6H_4$, 4-$CF_3C_6H_4$, 1-naphthyl, 2-naphthyl, CH_3, C_2H_5, $CH_3(CH_2)_2$, $CH_3(CH_2)_3$, $CH_3(CH_2)_4$, $CH_3(CH_2)_{10}$

Scheme 59

was obtained in 62–88% yields during 12–48 h at room temperature[72] (Eq. 8).

(8)

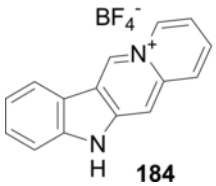
R = Me, Bn, Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, PMP = 4-$MeOC_6H_4$

4 Fused tricyclic heterocycles with a 6:6 ring junction heteroatom

4.1 Linearly fused systems

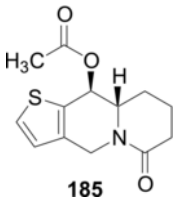
4.1.1 One heteroatom per ring

As for pyrroloquinolizinium salts, there are data only in one source[73] which is dedicated to the quantum studies of compound **184**. The lowest singlet and triplet excited states of quinolizinium salt **184** were characterized in the absence and in the presence of DNA.[73]



The structure of compound **185** was determined.[74] It is a chiral molecule with two stereogenic centers. Its absolute configuration was derived from the synthesis and confirmed by X-ray diffraction analysis. The expected stereochemistry of atoms *C*5 and *C*6 was confirmed to be *S*. The central 6-membered rings are not planar and adopt a half-chair conformation. A calculation of least-squares planes showed that these rings are puckered in such a manner that the five atoms *C*1, *C*2, *C*3, *C*5 and *N*1 (second ring: *N*1, *C*6, *C*7, *C*10 and *C*11)

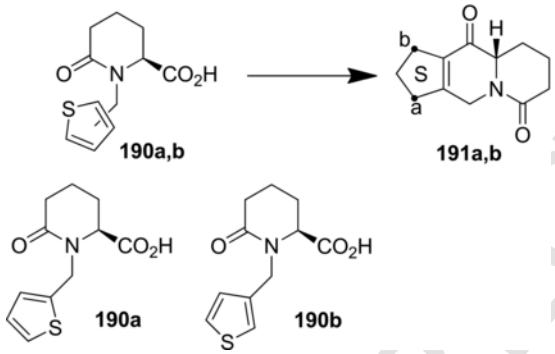
are planar, while atoms *C*4 (*C*5) are deviated from these planes with the out-of-plane displacement of 0.582 (3) Å and 0,666 (2) Å in the second ring, respectively. Dihedral angle between the planes of the two rings is 40.0 (1)°. Crystal structure is stabilized by C—H ··· O hydrogen interactions.[74]



185

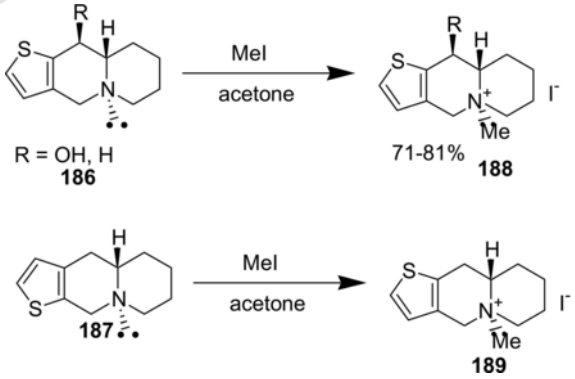
The synthetic routes for preparation of thienoquinolizinium iodides **188** and **189** is shown in **Scheme 60** by treatment of the respective substrates **186** and **187** with methyl iodide in dry acetone.[75] These products are antibacterial agents with the most sensitive microorganism being Gram-positive bacterium *S. epidermidis*. Compound **187** shows the best antifungal activity although *C. albicans* is resistant to all tested derivatives. The highest biological activity is observed for structures that are present in the saturated quinolizidine skeleton as found in the natural occurring plant alkaloid cryptoleurine.[75]

Cyclization reaction of carboxylic acid **190a** in the presence of $AlCl_3$ as catalyst, initially at 10–40 °C, then 0–40 °C for 2 h after the addition of the catalyst, furnished the tricyclic product **191a** in 32% yield. Similarly, the keto-lactam **191b** was obtained from carboxylic acid **190b** in a yield up to 42% (Eq. **9**).[76]

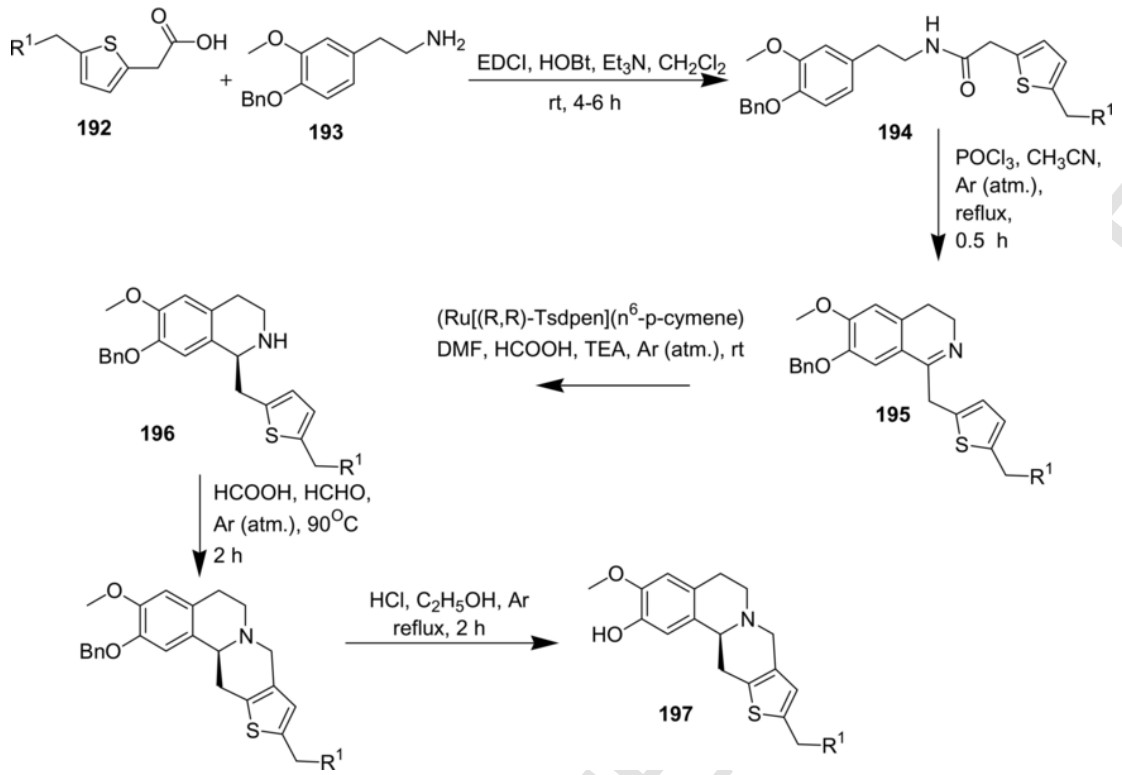


(9)

The general synthetic route to compounds **197** is described in **Scheme 61**. Condensation of **192** with 4-benzyloxy-3-methoxyphenylethylamine **193** furnished amides **194** in good yields. Treatment of amides **194** with phosphoryl trichloride yielded the corresponding imines **195** the asymmetrical reduction of which in the presence of Noyori's catalyst (Ru-(II)-complex) afforded chiral amines **196**. The target products **197** were obtained in good yield and with good enantiomeric purity via the Pictet-Spengler reaction followed by deprotection.[77]



Scheme 60

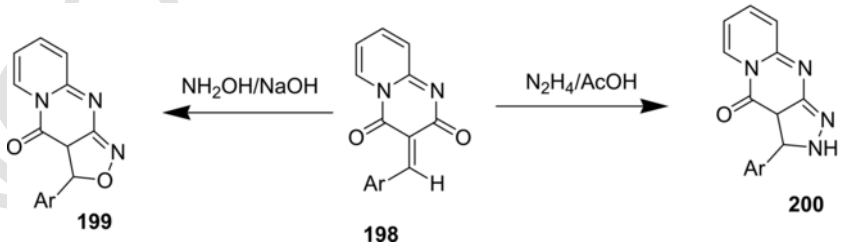


Scheme 61

4.1.2 Systems with more than one heteroatom per ring

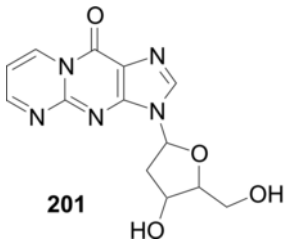
The chalcones **198** were allowed to react with hydroxylamine and hydrazine hydrate under different conditions to give cyclized products, 3-(aryl)-3*H*-isoxazole[3,4-*d*]pyrido[1,2-*a*]pyrimidin-4-(3a*H*)-one **199** and 3-(aryl)-3,3a-dihydropyrazolo[3,4-*d*]pyrido[1,2-*a*]pyrimidin-4-(2*H*)-one **200** (Scheme 62).[78]

The in vivo metabolism and elimination of the endogenous DNA adduct M_1dG {3-(2-Deoxy-D-erythropentofuranosyl)pyrimido[1,2-*r*]purin-10(3H)-one}, compound **201**, were studied by accelerator mass spectrometry. Results of the oxidative metabolism study of M_1dG suggest that metabolism and alternate routes of elimination may contribute to the complexity of DNA adduct analysis in biological matrixes.[79] The DNA synthesis by human DNA polymerase on templates containing a pyrimidopurinone deoxyguanosine adduct **201**



Scheme 62

was studied.[80]



201

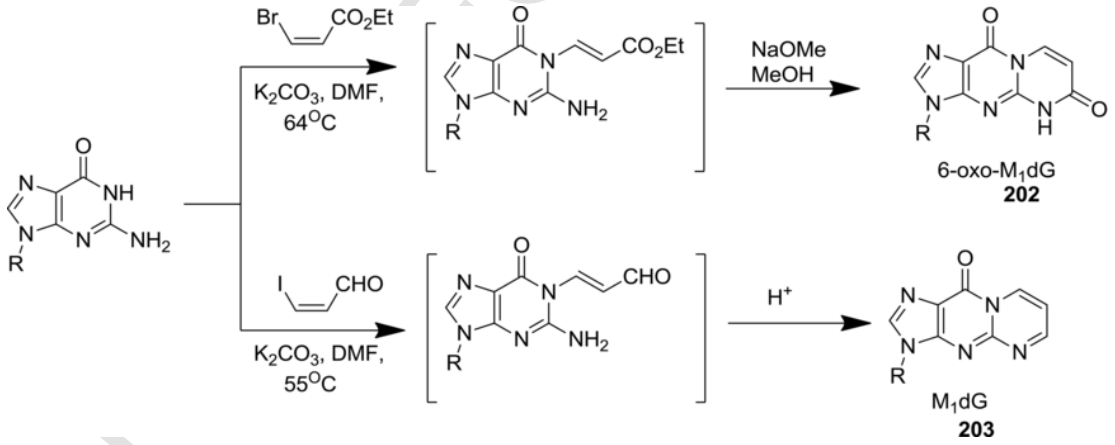
Selective alkylation of dG at the *N*1-position can often be achieved by forming the *N*1-anion. This reactivity was utilized in the synthesis of 6-oxo-M_1dG **202** by alkylating dG with commercially available ethyl *cis*-3-bromoacrylate through an addition-elimination pathway to afford *N*1-(3-carboxyethyl-1-propenyl)-dG (**Scheme 63**). Subsequent treatment of this intermediate product with sodium methoxide in methanol provided 6-oxo-M_1dG **202**. This strategy was extended to the synthesis of the homologue M_1dG **203** by using 3-iodoacrolein as the electrophile. 3-Iodoacrolein was condensed with dG as described above and after neutralization with dilute acetic acid, M_1dG **203** was obtained in 50% isolated yield (**Scheme 63**).[81]

Relative reactivities including ring-opening reactions of **204–206** were studied. Hydrolytic ring-opening of **204** occurs by reversible addition of hydroxide to form the anion of **205**. At pH's below neutrality, the anion of **205** is protonated and rapidly cyclizes to a hydroxypropeno intermediate **206** that slowly undergoes dehydration to **204** (**Scheme 64**).[82]

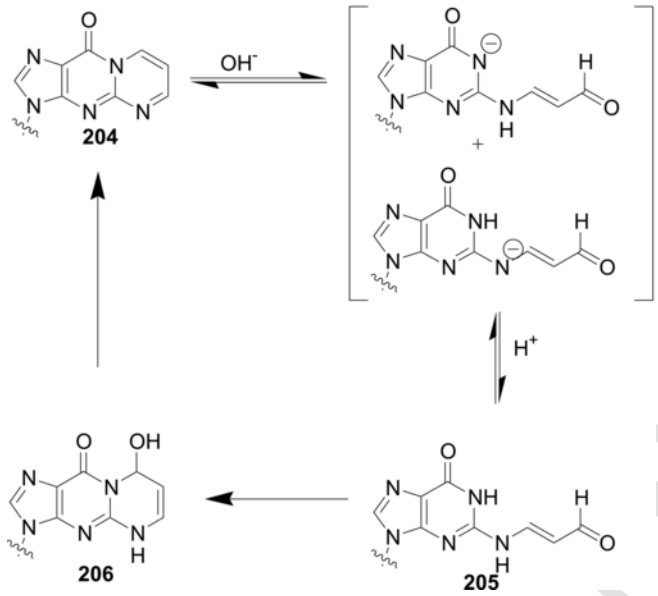
4.2 Angularly fused systems

4.2.1 Pyrroloquinazolines including natural products

Five new hexacyclic monoterpenoid indole alkaloids, rauvovertine A(1) **207**, 17-*epi*-rauvovertine A(2) **208**, rauvovertine B(3) **209**, 17-*epi*-rauvovertine B(4) **210** and rauvovertine C(5) **211** were isolated from the stems of *Rauvolfia verticillata*.[83] The structures of **207–211** were established by spectroscopic analysis and with the aid of molecular modeling. The new alkaloids were evaluated for

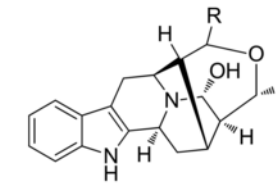


Scheme 63

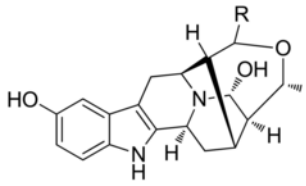


Scheme 64

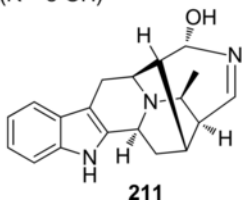
their cytotoxicity *in vitro* against human tumor HL-60, SMMC-7721, A-549, MCF-7 and SW-480 cell lines.[83]



207 (R = a-OH), **208** (R = e-OH)

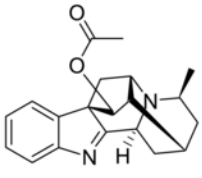


209 (R = a-OH), **210** (R = e-OH)

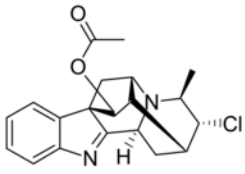


211

Analysis of the leaves of *R. yunnanensis* yielded five new indole alkaloids, rauvoloids **212–216**, together with two known alkaloids, raucaffrinoline **217** and perakine **218**.[84]



212



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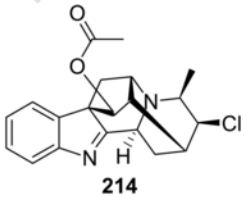

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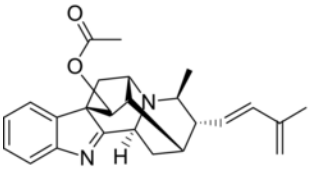
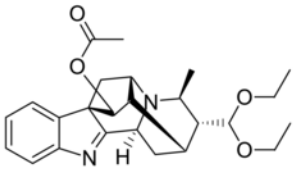


215



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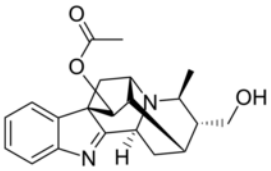
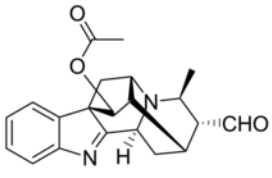


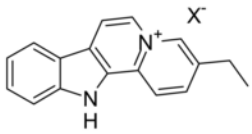
217



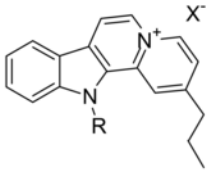
218

In addition to the already reported nukuhivensiums **219** and **220**, other indole alkaloids were isolated from the bark of the plant *Rauvolfia nukuhivensis*, growing in the Marquesas archipelago, including flavopereirine **221**.[85] Alkaloids **222**, **223** and **224** are desacethylakuammiline, 10-methoxydesacethylakuammiline and 10-methoxyakuammiline, respectively, isolated from *Rhazya stricta* and

Catharanthus roseustissue cultures.[86]

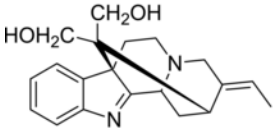


Flavopereirine **221**

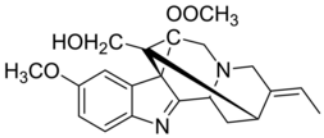


Nukuhivensium (R = H) **219**

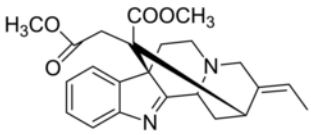
N_{12}-Methylnukuhivensium (R = CH_3) **220**



222

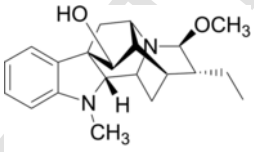


223



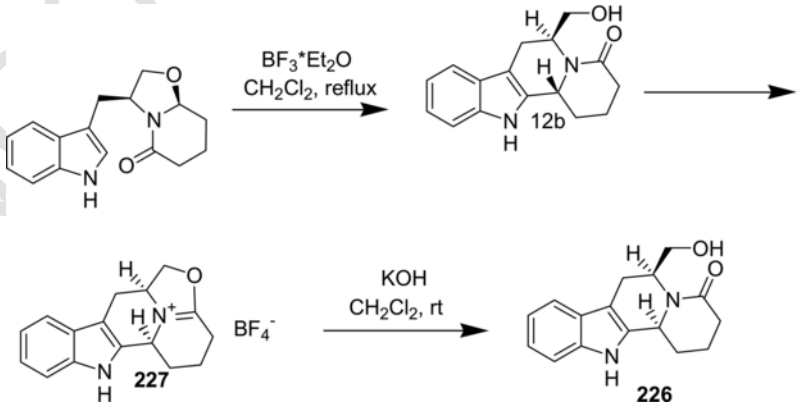
224

A new ajmaline-type alkaloid, 21-*O*-methylisoajmaline **225**, was isolated from the roots of *Rauvolfia serpentina*. Its structure was elucidated by spectroscopic data analysis and comparison with literature data.[87]



225

The reaction conditions for the preparation of indolo[2,3-*a*]quinolizidines **226** were studied. It was demonstrated that the isomerization of the kinetic *trans*-*H*-6/*H*-12b isomer to the *cis*-*H*-6/*H*-12b isomer upon treatment with $BF_3{\cdot}Et_2O$ involves the formation of an intermediate oxazolinium salt **227** (**Scheme 65**).[88]



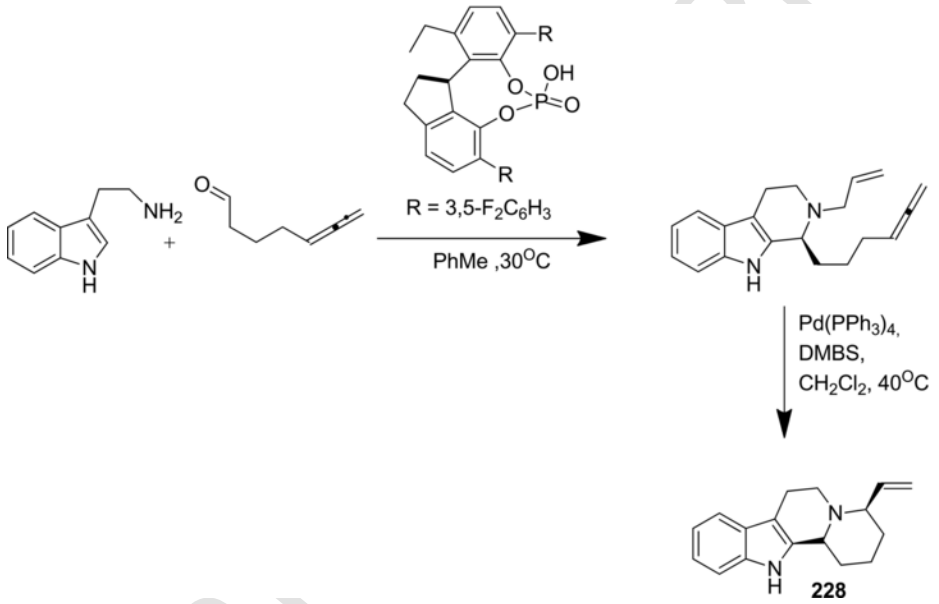
Scheme 65

The palladium-catalyzed tandem deprotection/cyclization reaction of enantio-enriched *N*-allyl-tetrahydro-β-carbolines substituted with an allene was studied.[89] Tetrahydro-β-carboline undergoes a cyclization on the allene function via the intermediary of a π-allylPd(II) derivative. This reaction furnishes a chiral indole tetracycle **228** substituted with a vinyl function (**Scheme 66**).

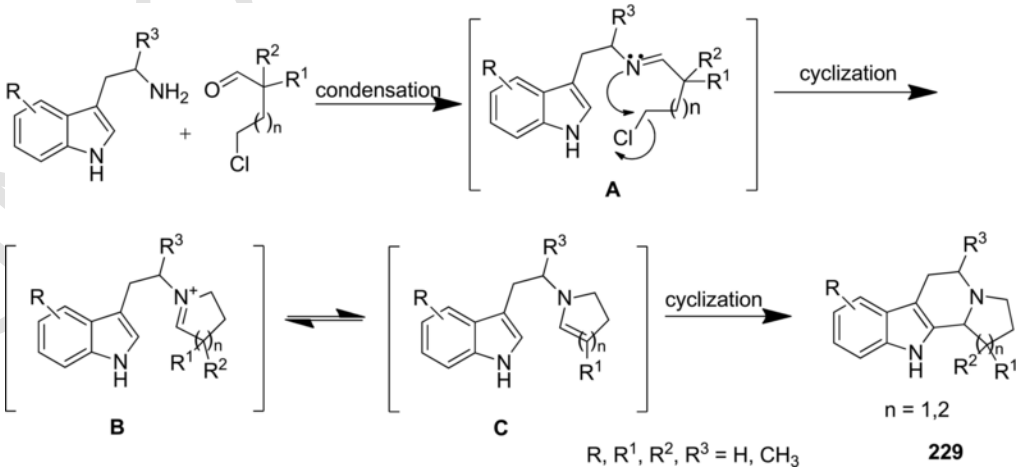
Synthesis of indole derivatives **229** from tryptamine derivatives and halo aldehydes was studied (**Scheme 67**). It was found that the reaction proceeds through the intermediary of **A**, **B** and **C** by heating the mixture in acetonitrile in the presence of trifluoroacetic acid at 90 °C for 12 h.[90]

A synthetic route to structurally diverse tetrahydroindolo[2,3-*a*]quinolizines **230** was developed using an imino-Diels-Alder reaction as the key step, leading to a compound library of more than 500 members (**Scheme 68**). The synthesis was successfully conducted on a multigram scale.[91]

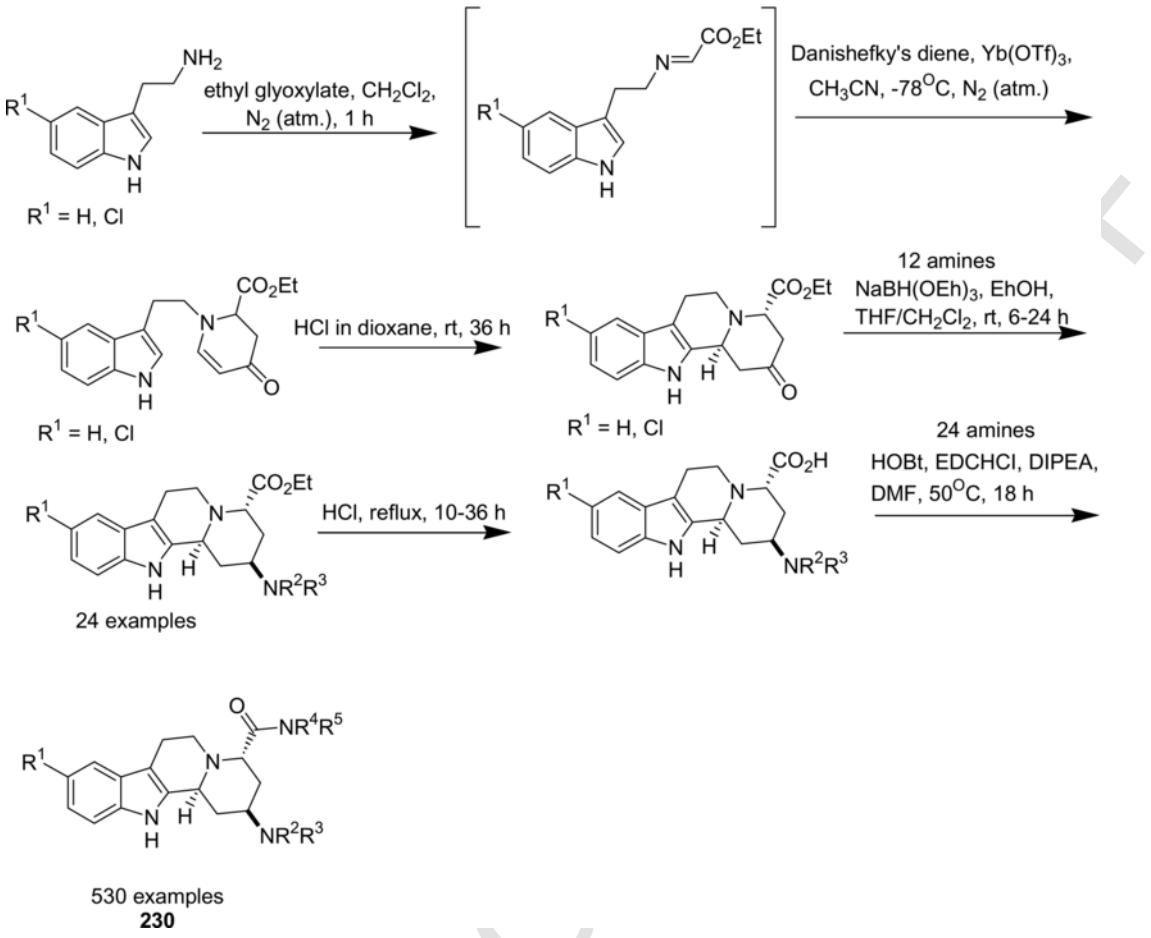
Hydrogenation reaction of *anti*-isomer **231** followed by removal of chiral auxiliary with sodium methoxide in methanol gave the 1-hydroxylactam **232** in 80% yield (**Scheme 69**). The chiral auxiliary 8-phenylmenthol was recovered in 85% yield and continuously used without loss of induction. Then, reduction of the carbonyl group of **232** with freshly prepared aluminum hydride solution (AlH_3) in tetrahydrofuran afforded **233** in 96% yield. Next, the inversion of configuration of the (*R*)-hydroxy moiety in **233** to give **234** was achieved using the Mitsunobu reaction. Treatment of **234** with chloroacetyl chloride in the presence of potassium carbonate in a highly diluted solution in *N,N*-dimethylformamide furnished compound **235** in 58% yield.[92]



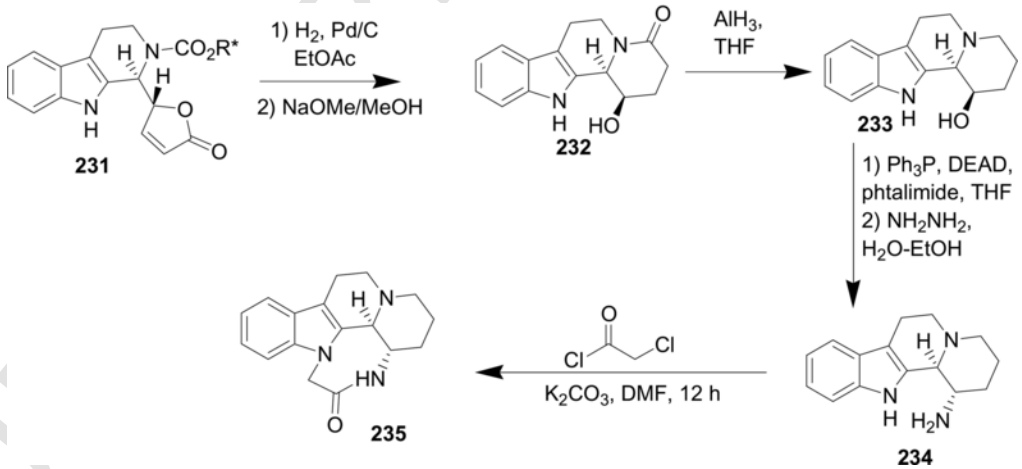
Scheme 66



Scheme 67



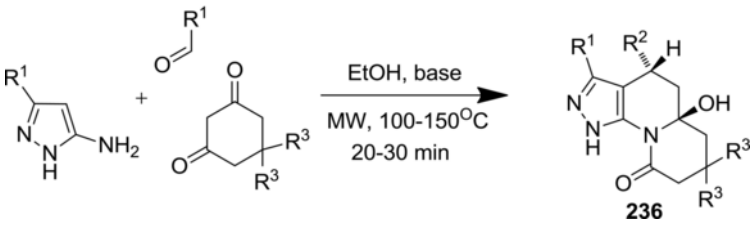
Scheme 68



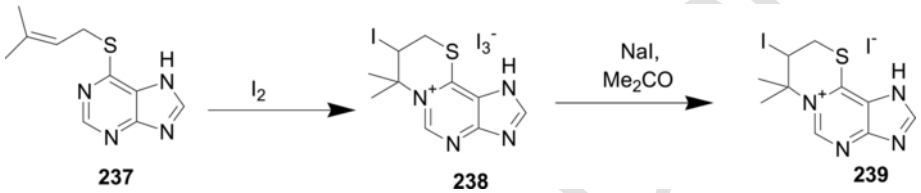
Scheme 69

4.2.2 Pyrazoloquinolizines

An efficient synthesis of 5a-hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-ones **236** based on the three-component condensation of 5-aminopyrazoles, aromatic aldehydes, and cyclic 1,3-diketones is described.[93] The multicomponent reaction is performed under strongly basic conditions applying controlled microwave heating in a sealed vessel. It involves an unusual base-mediated ring-opening/recyclization of the cyclic 1,3-diketone moiety (Eq. **10**). A similar synthetic approach was described in Ref. **94**.

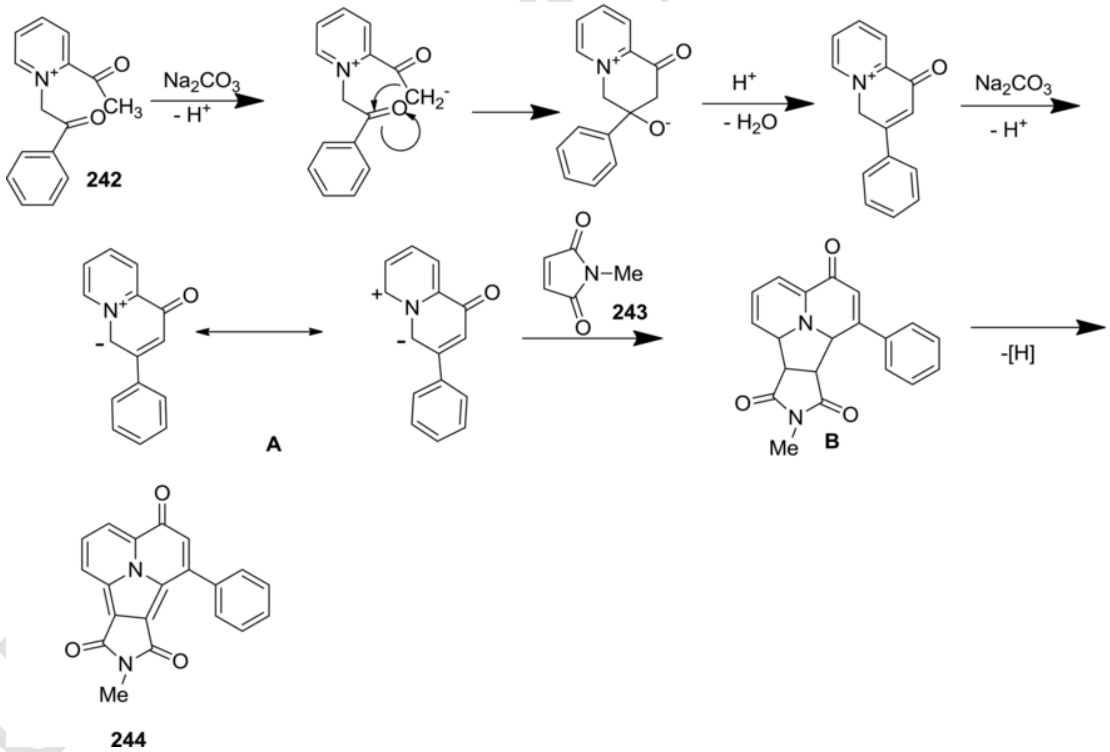


236 (10)



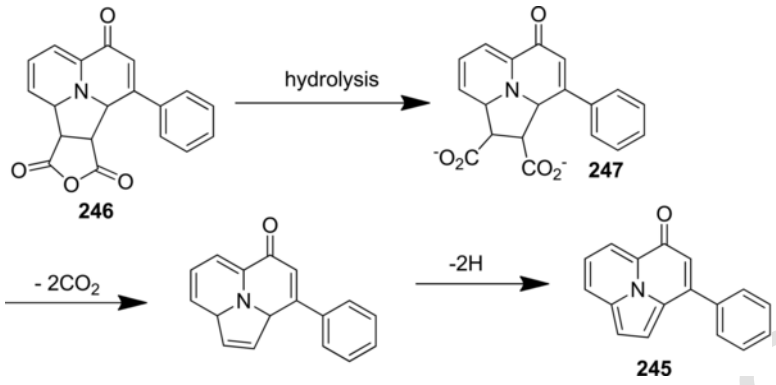
237 **238** **239**

Scheme 70

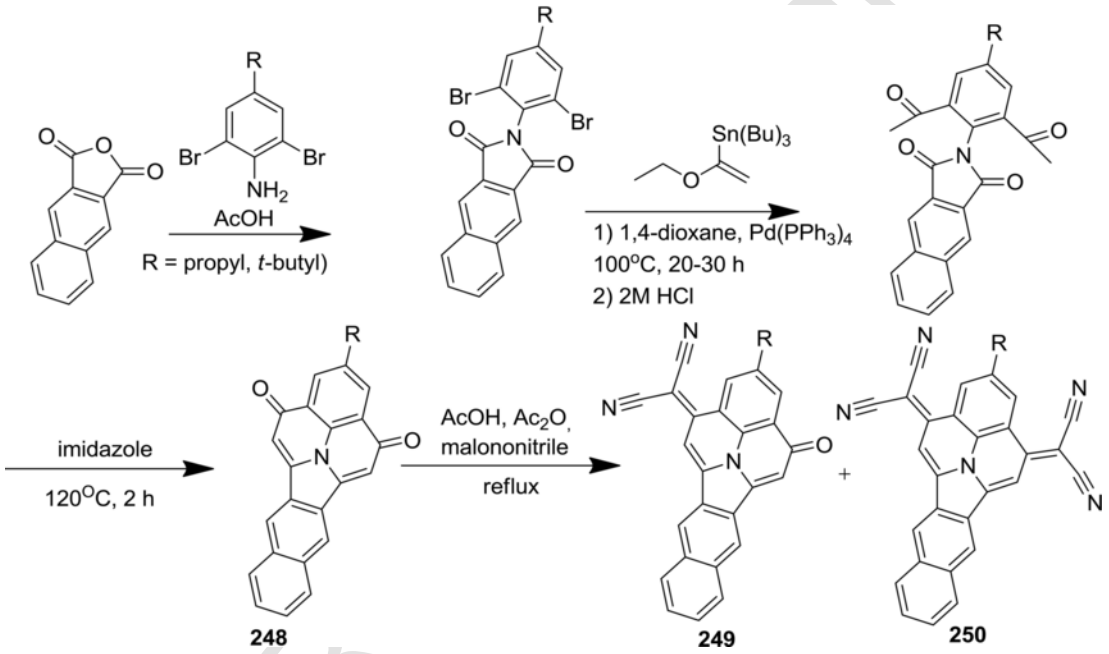


242 **A** **243** **B** **244**

Scheme 71



Scheme 72

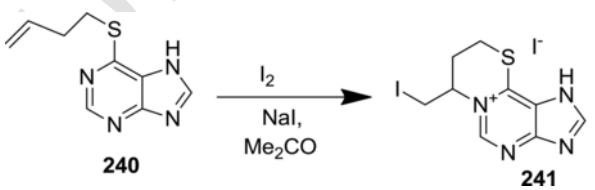


Scheme 73

4.2.3 Thiazino[2,3-i]purines

The reaction of prenyl sulfide **237** with iodine at a 1:2 ratio in acetic acid is a regiospecific process of annulation to 8-iodo-7,7-dimethyl-1,7,8,9-tetrahydro[1,3]thiazino[2,3-i]-purinium triiodide **238**. The intermediate product **238** was allowed to react with sodium iodide in acetone to form a yellow 8-iodo-7,7-dimethyl-1,7,8,9-tetrahydro[1,3]thiazino[2,3-*i*]purinium iodide **239** (Scheme 70).[95]

The reaction of butenyl sulfide **240** with iodine in acetic acid gives 7-(iodomethyl)-1,7,8,9-tetrahydro-[1,3]thiazino[2,3-*i*]purinium triiodide as a dark precipitate. The latter reacts with NaI in acetone a light yellow 7-(iodomethyl)-1,7,8,9-tetrahydro[1,3]thiazino-[2,3-i]purinium iodide **241** (Eq. 11).[95]



(11)

5 Cycl[3.3.2]azines and related systems

Reaction of the 2-acetyl-*N*-phenacyl pyridinium salt **242** with *N*-methylmaleimide **243** under the typical reaction conditions for a [3 + 2] cycloaddition of a pyridinium ylide with alkene in DMF at 90 °C in the presence of sodium carbonate and an oxidant gave product **244** in 80% yield. In this reaction, the 1-oxoquinolizinium ylide **A** generated in situ from **242** undergoes a 1,3-dipolar cycloaddition with **243** to give the primary cycloadduct **B**, which is then dehydrogenated to give product **244** (**Scheme 71**).[96]

Product **245** was proposed to be formed by hydrolysis of the primary cycloadduct **246** and the oxidative bisdecarboxylation of dicarboxylate **247** followed by dehydrogenation (**Scheme 72**).[96]

Diketocycl[3,3,2]azine **248** (**Scheme 73**) reveals pronounced colorant properties. A series of π-extended cycl[3,3,2]azines **248** bearing additional carbonyl groups were synthesized via aldol condensations. Two strong electron acceptor molecules **249** and **250** with low-lying LUMO energy levels of − 3.99 and − 3.95 eV, respectively, were obtained. Organic thin-film transistors (TFTs) based on the cyanated cyclazine derivatives **250** were fabricated by vapor deposition, exhibiting extraordinarily stable *n*-type semiconductor character under ambient conditions with high electron mobility.[97]

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