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Arkivoc **2023**, (i) 202312084

Pyridazino[4,5-b]indoles II. Reactions and biological importance

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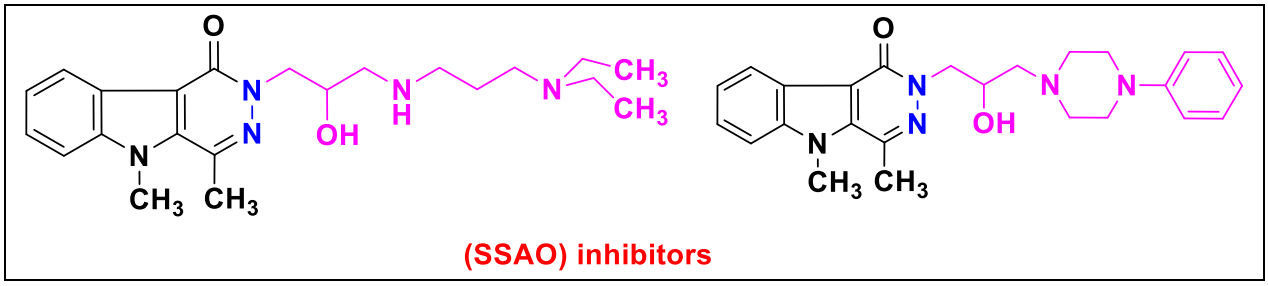
Received 09-14-2023 **Accepted** 11-06-2023 **Published on line** 11-28-2023

Abstract

The nucleus of pyridazino[4,5-*b*]indoles contains two heterocyclic moieties that interact with many receptors. They are an important class of heterocyclic compounds with diverse applications in the field of medicinal chemistry. This review summarizes the reactions and biological importance of pyridazino[4,5-*b*] indoles during the period from 1962 to 2023. The reactions involve chlorination, hydrazinolysis, functionalization of pyridazino[4,5-*b*]indoles at positions 1, 2, or 5 and others dealing with reactions occuring at positions 1 and 3. This review article will include the latest advances on the applications of the pyridazino[4,5-*b*]indoles.



Keywords: Pyridazino[4,5-*b*]indole, reactions, aza-carbolines and biological importance.

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1. Introduction

Among the compounds containing multiple nitrogen atoms, whose importance in the field of medicinal chemistry and smart materials is well known,[1,2] it is worth mentioning the pyridazino[4,5-*b*]indol-4-ones, which are a class of heterocycles containing a fused tricyclic containing pyridazine and indole moieties. Recently,[3] a novel structural skeleton of 1*H*-pyridazino[4,5-*b*]indol-4(5*H*)-one discovered to be a potent anti-ZIKV inhibitor with very low cytotoxicity. ZFD-10's anti-ZIKV potency is independent of cell lines and ZFD-10 mainly targets the post-entry stages of the ZIKV life cycle.

The pyridazino[4,5-*b*]indole scaffold has attracted particular attention due to its bio-isosterism with β-carboline as well as γ-carboline, as the core structure of a wide variety of bio-active compounds.[4-14] Moreover, various 5*H*-pyridazino[4,5-*b*]indole derivatives show promising *in-vitro* inhibitory activities against PI3Ka, significant anti-proliferative effects in various cell types[15,16] and antimicrobial activity.[17] Recently, it was reported that some pyridazino[4,5-*b*]indole derivatives containing alkyl-, benzyl- and phenacyl-substituted 1,2,3-triazolylmethyl units exhibit potent cancer cell growth inhibition activity at low micromolar concentrations.[18] Furthermore, the title ring system became interesting in the context of an ongoing program

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in search of new and selective inhibitors of copper-containing amine oxidases.[19] During the past few years, we have investigated the synthesis and biological activity of various new representatives of this “aza-carboline" ring system, mainly focusing on potential antitumor agents,[20-22] encouraged by the pharmaceutical importance of these ring systems.

Related to this tricyclic ring system is the tetracyclic system, pyrido[4,3-*b*]carbazole, which also contains an indole ring and a π-deficient hetarene (a pyridine, in this case), but here they are separated by an additional benzene ring. The discovery of the pronounced *antitumor* activity of the alkaloid *ellipticine* (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) about forty years ago has stimulated considerable efforts to modify this natural compound to find congeners with a superior pharmaceutical profile.[23,24] In order to overcome some limitations, such as low water solubility or cardiovascular side effects in the therapeutic use of *ellipticine* and early congeners, a number of analogs has been synthesized and evaluated so far. Besides quaternization of the pyridine ring atom, like in the case of 9-hydroxy-2-methylellipticinium acetate (*elliptinium*),[25] the introduction of a basic side chain into position 1 of the tetracyclic system can affect the desired solubility enhancement and it has been shown that such a (*N,N*-dialkylamino)alkylamino substructure significantly enhances the molecule’s affinity to the phosphate backbone of DNA.[26] Typical representatives of this type of *ellipticine* analogs are the drug candidates *retelliptine*[26] and *pazelliptine*[27,28] Several new representatives of this ring system (3-*azaellipticines*) of type **4a** were described by Haider *et al.*[29,30]

Other condensed ring systems incorporating an indole structure as well as a π-deficient hetarene are the carbolines. For instance, the seeds of *Peganum harmala* (Zygophyllaceae family) has been used as a spice and an intoxicant. Some harmala bases have been shown to elicit hallucinogenic effects in humans.[31] The tricyclic system, pyrido[3,4-*b*]indole, is the main structural feature of such compounds. Interestingly, it was described that pyrido[4,3-*b*]indoles bearing a basic side chain in position 1 and a methyl group in position 4 possess antitumor activity. In particular, the γ-carboline derivatives **4b** display potent biological activity in various systems,[32] thus proving that the tetracyclic structure of ellipticine-type antineoplastic agents can be reduced to a tricyclic skeleton without loss of activity. A more detailed discussion will be given in section 3.2.

Based on these findings mentioned above and in continuation of previous work on the synthetic strategies of pyridazino[4,5-*b*]indole which has been published recently,[33] I will report herein its reactions and biological importance.

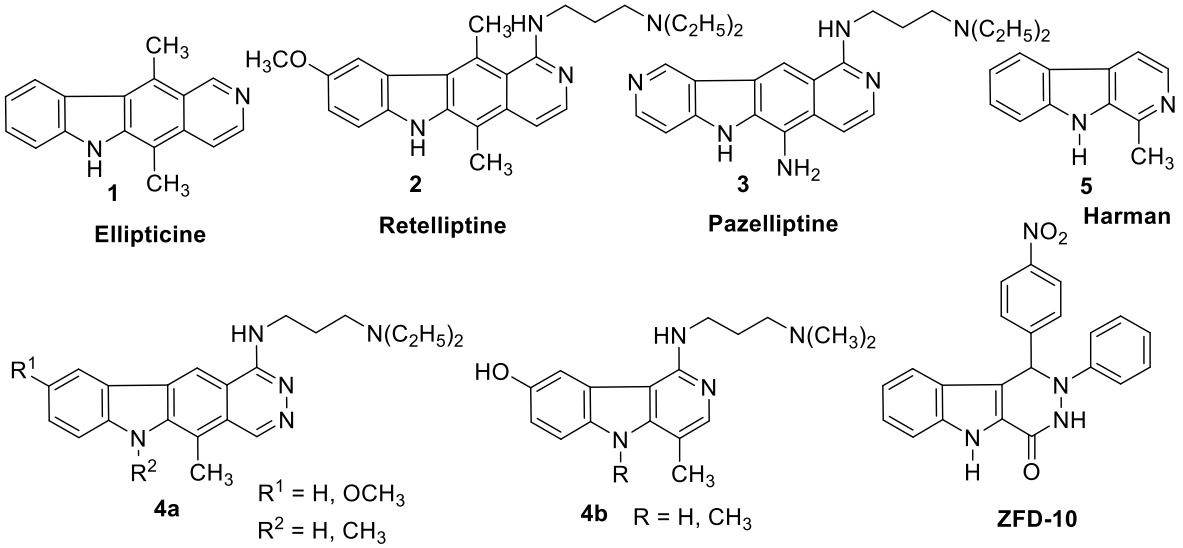

Figure 1. Some biologically active compounds.

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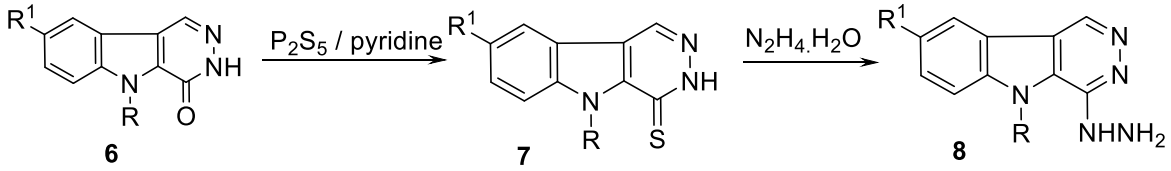
2. Reactions of pyridazino[4,5-*b*]indoles

2.1 Thionation

Pyridazino[4,5-*b*]indol-4-one derivatives **6** were reacted with excess P_2S_5 in pyridine as a solvent to afford the corresponding thioxo derivatives **7**. Treatment of thiones **7** with boiling 90 % hydrazine hydrate gave 4-hydrazino-8-benzyloxypyridazino[4,5-*b*]indoles **8** in good yield. [34-37]



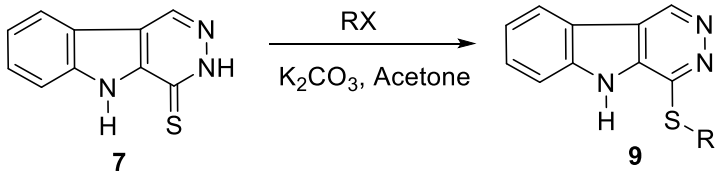
6 **7** **8**

Lit.[36,38],R1 = H, CH_3O, C_2H_5O, $C_6H_5CH_2O$
R = H, CH_3
Lit.[40],R1 = H, alkyl, alkoxy, aryloxy, OH, aryl
R = H, alkyl, acyl, aroyl
Lit.[41],R1= R = H

Scheme 1. Thionation of pyridazino[4,5-*b*]indol-4-one derivatives **6**.

2.2 Alkylation

Alkylation of the thione **7** (R^1 =R = H) with benzyl bromide, allyl bromide and ethyl chloroacetate was achieved in the presence of potassium carbonate and acetone[37] to afford the 4-(alkylthio)-5*H*-pyridazino[4,5-*b*]indole derivatives **9**.



7 **9**

R^1= R= H R= $CH_2C_6H_5$, $CH_2CH{=}CH_2$, CH_2COOEt

Scheme 2. Alkylation of 3,5-dihydro-4*H*-pyridazino[4,5-*b*]indole-4-thione **7**.

Recently, it was reported that[38] the interaction of **6** (R^1= R= H) with ethyl chloroacetate using K_2CO_3 in acetone afforded a mixture containing the monoester product **10**, while its interaction with ethyl chloroacetate using KOH/DMSO afforded the bis(ester) product **11**. Hydrazinolysis of the monoester **10** gave the monohydrazide **12**, whereas hydrazinolysis of the bis(ester) **11** afforded the bis-hydrazide **13**.

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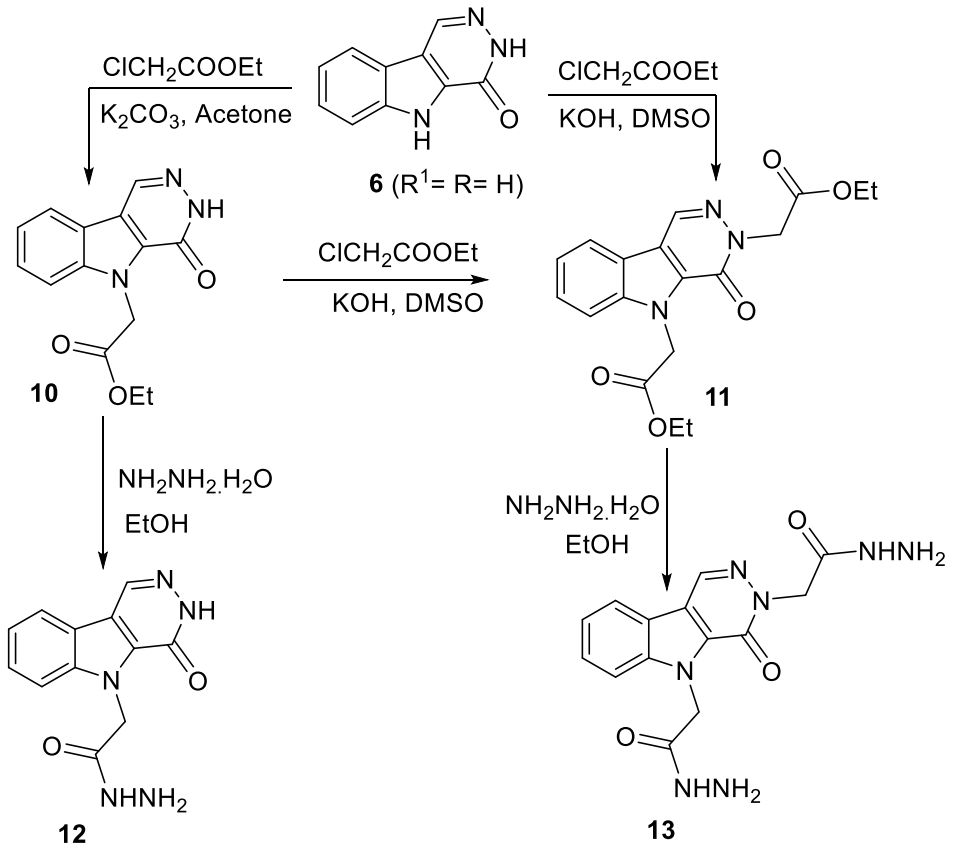
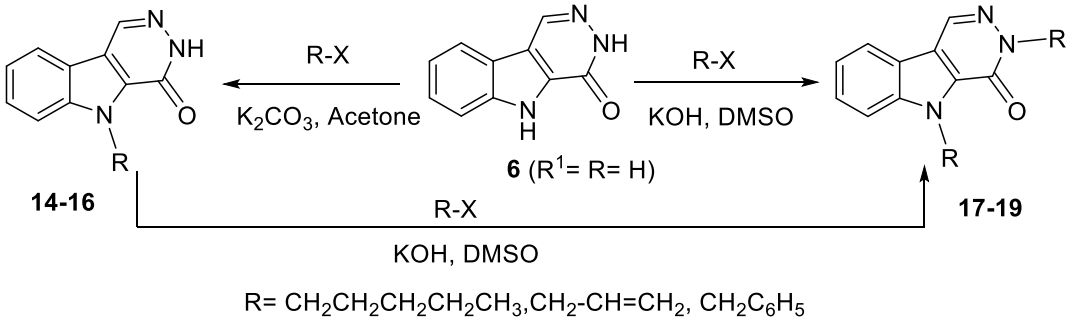


Scheme 3. Alkylation of 3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-one **6.**

Similarly,[38] alkylation of **6** (R^1= R= H) with a set of alkylating agents, namely amyl bromide, allyl bromide and benzyl bromide in the presence of K_2CO_3 in acetone afforded a mixture of two products, which were separated by column chromatography and identified to include alkylation at the indole nitrogen **14-16** and alkylation at both indole and pyridazine nitrogens **17-19**. The bis(alkylated) products **17-19** were selectively obtained in excellent yields either from **6** or from the respective monoalkylated products **14-16** using KOH as a base in dimethyl sulfoxide as a solvent (Scheme 4).



Scheme 4. Synthesis of the bis(alkylated) products **17-19.**

Reaction of compound[39] **20** (R^1= H, R= CH_2Ph**)** was reacted with ethyl 2-bromoacetate in DMF with a catalytic amount of triethylamine to yield ethyl 2-(5-benzyl-4-oxo-4,5-dihydro-3H-pyridazino[4,5-*b*]indol-3-

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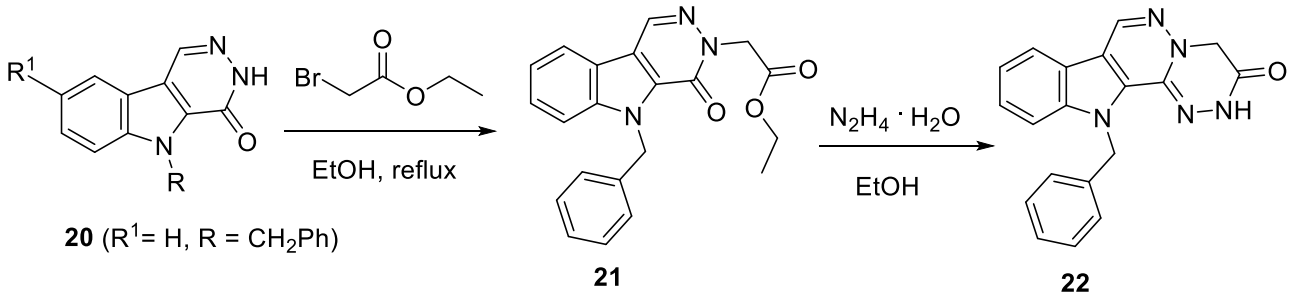
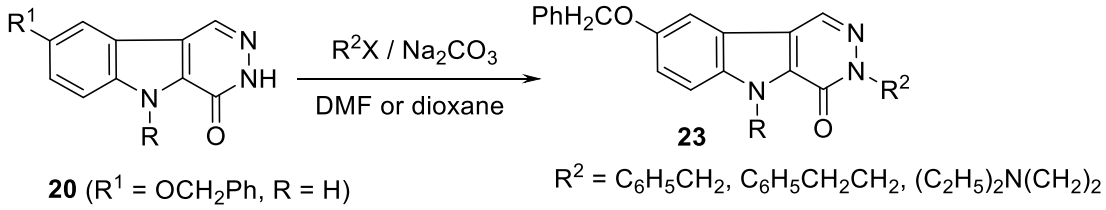
yl)acetate **21**. The latter **21** was cyclized to 12-benzyl-2,12-dihydro-[1,2,4]triazino[4',3':2,3]pyridazino[4,5-*b*] indol-3(4*H*)-one **22** by the action of hydrazine hydrate (Scheme 5).



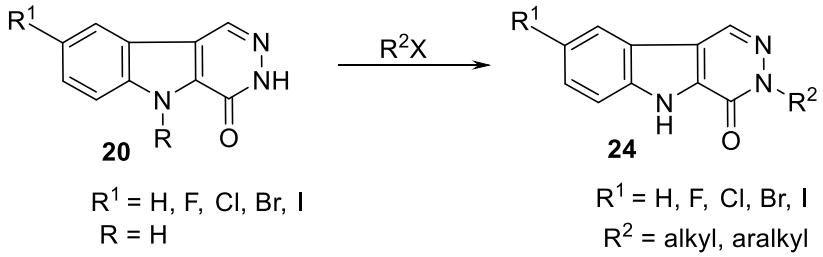
Scheme 5. Synthesis of 12-benzyl-2,12-dihydro-[1,2,4]triazino[4',3':2,3]pyridazino[4,5-b]indol-3(4*H*)-one **22.**

Alkylation of **20** (R^1 = $PhCH_2O$, R = H) with aroyl, phenylalkyl, or (dialkylamino)alkyl halides in the presence of sodium carbonate gave the 3,5-disubstituted derivatives **23**.[11,12]



Scheme 6. Synthesis of the 3,5-disubstituted pyridazino[4,5-*b*]indole derivatives **23**.

Venkateswar *et al*.[40] reported that the 3-substituted 4-oxo-*5H*-pyridazino[4,5-*b*]indoles **24** were prepared by reaction of **20** with alkyl or aralkyl halides.



Scheme 7. Synthesis of 3-substituted 4-oxo-*5H*-pyridazino[4,5-*b*]indoles **24**.

Raddini *et al*[41] described that, the introduction of a variety of different alkyl groups into position 2 of 4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**25**) appeared interesting from a pharmaceutical point of view. Thus, **25** was allowed to react with some alkylating agents such as benzyl chloride, 2-diethylaminoethyl chloride, or 4-(2-chloroethyl)morpholine. The reactions were performed in dry DMF in the presence of potassium carbonate to afford the corresponding pyridazinoindole derivatives **26**, **27**, and **28** as colorless solids in yields of 49–55%. The hydrochloride **29** was obtained in 60% yield by dissolving the free

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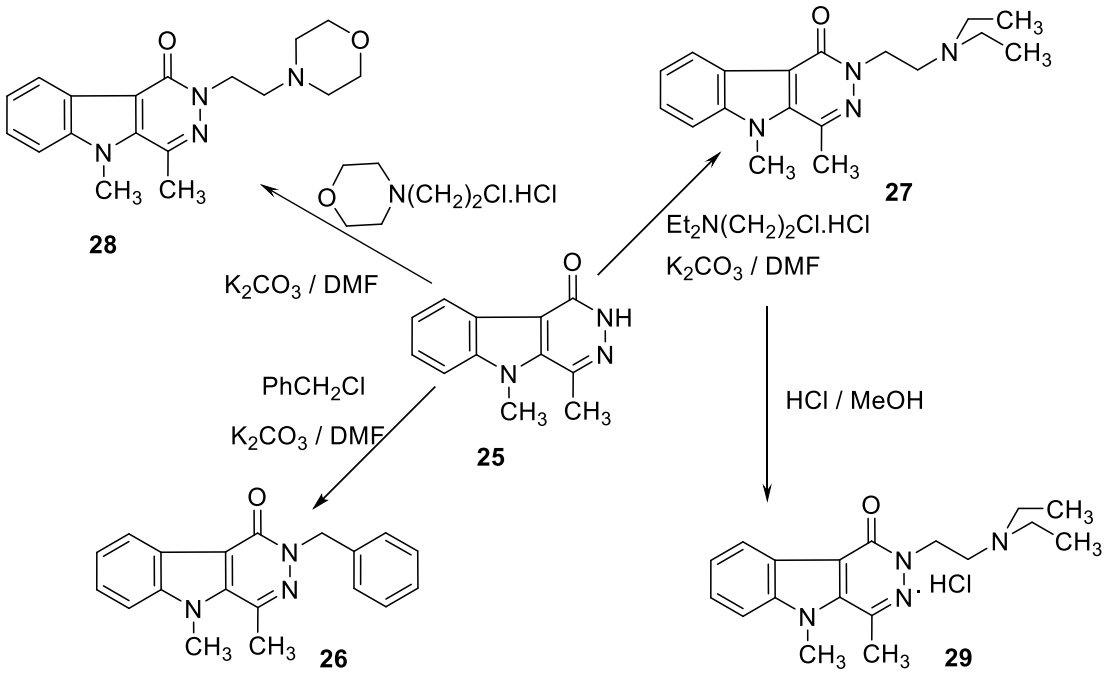
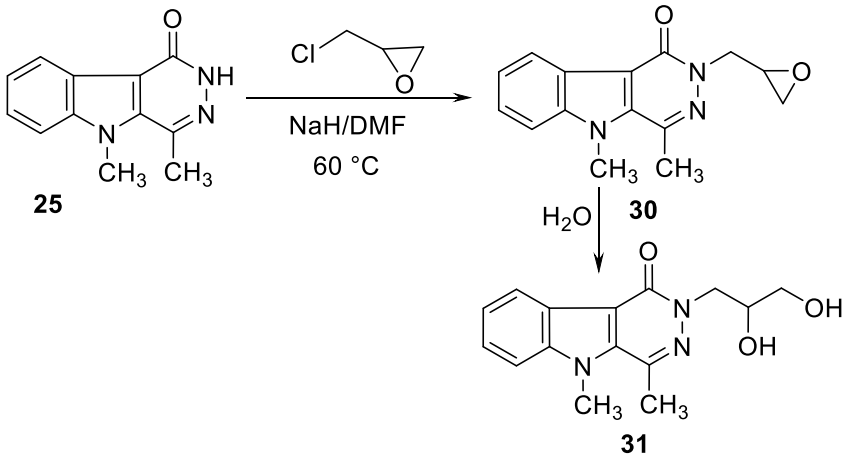
base **27** (which is difficult to recrystallize) in methanolic hydrogen chloride (freshly prepared from acetyl chloride and methanol (Scheme 8).



Scheme 8. Alkylation of 4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one **25**.

Also,[41] the high reactivity of epoxides and their usefulness for further functionalization reactions prompted the authors to synthesize and investigate the epoxide **30**, which was prepared by treatment of the pyridazinone **25** with an excess of epichlorohydrin in the presence of sodium hydride in dry DMF solution at 60 °C (Scheme 9). Under these conditions, the epoxide **30** was formed in high yield and in sufficient purity for further transformations, i.e. ring-opening reactions with nitrogen nucleophiles. The same author[41] mentioned that, during work-up of **30**, contact with water must be reduced to a minimum, otherwise the sensitive epoxide ring undergoes hydrolysis. In this manner, the dihydroxypropyl derivative **31** was obtained in 25% yield.



Scheme 9. Reaction of 4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one **25** with epichlorohydrin.

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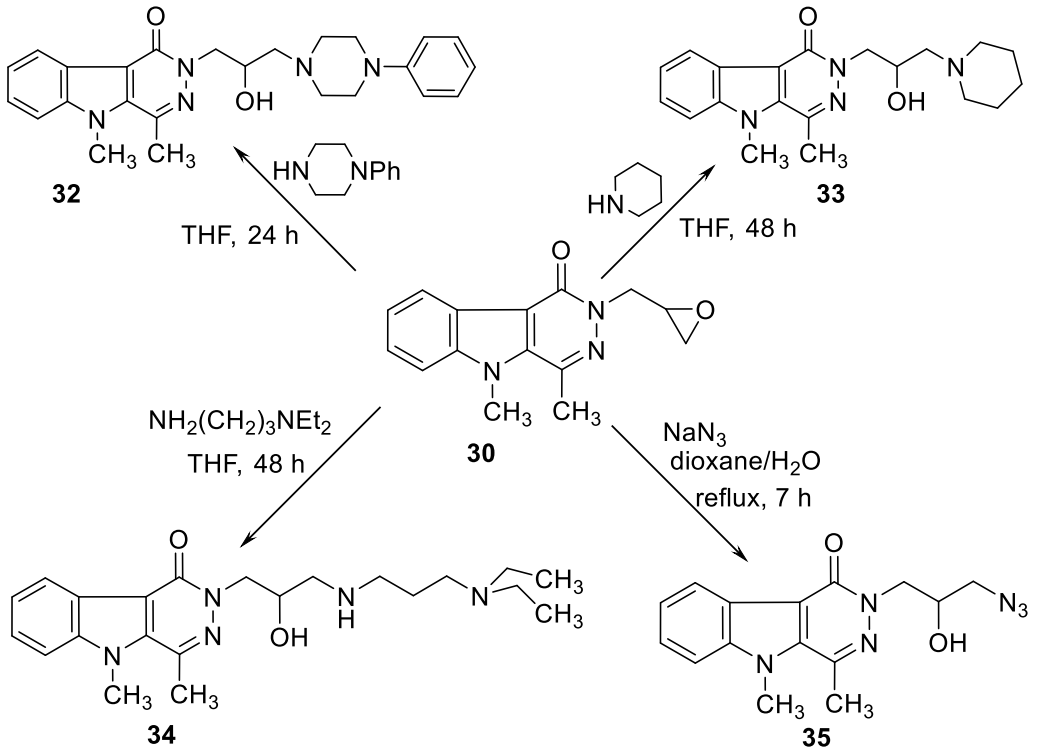
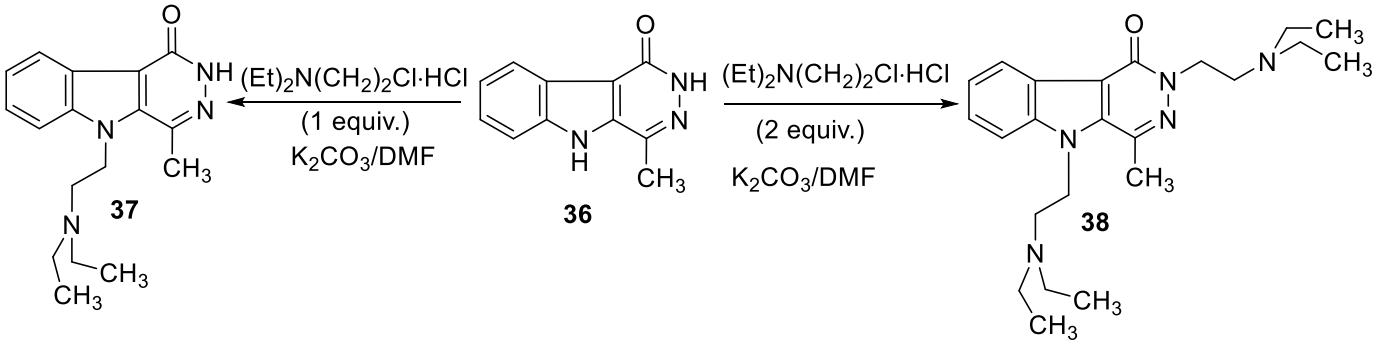
The regioselective[41] ring opening of **30** with various nitrogen nucleophiles was anticipated to afford a series of new amino alcohols that might exhibit interesting pharmacological properties (Scheme 10). Thus, opening of the oxirane ring of **30** with primary or secondary amines was performed in tetrahydrofuran to afford the corresponding amino alcohols **32-34** in 49-80% yield. The reactions were carried out using three molar equivalents of the nucleophilic reagent (*N*-phenylpiperazine, piperidine, or 3-diethylamino-1-propylamine, respectively). For the synthesis of the azido alcohol **35**, the epoxide was opened regioselectivity with sodium azide in aqueous dioxane analogously to a known procedure.[42]



Scheme 10. Ring opening of **30** with various nitrogen nucleophiles.

In continuation to previous work,[41] El-Kashef *et al*[20] reported that alkylation of the condensed pyridazinone **36** preferentially takes place at the indole nitrogen. Thus, reaction of **36** with one equivalent of 2-diethylaminoethyl chloride hydrochloride in dimethylformamide solution in the presence of potassium carbonate gives the 5-substituted product **37** in moderate yield, whereas employment of two equivalents of the alkylating agent affords the 2,5-disubstituted compound **38** (Scheme 11).



Scheme 11. Interaction of pyridazinone **36** with 2-diethylaminoethyl chloride hydrochloride.

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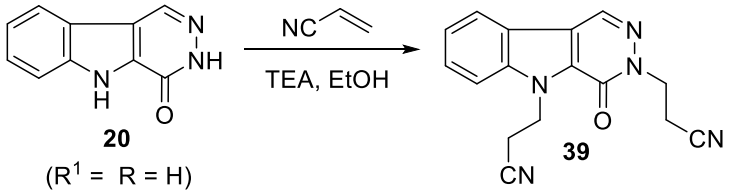
2.3 Addition

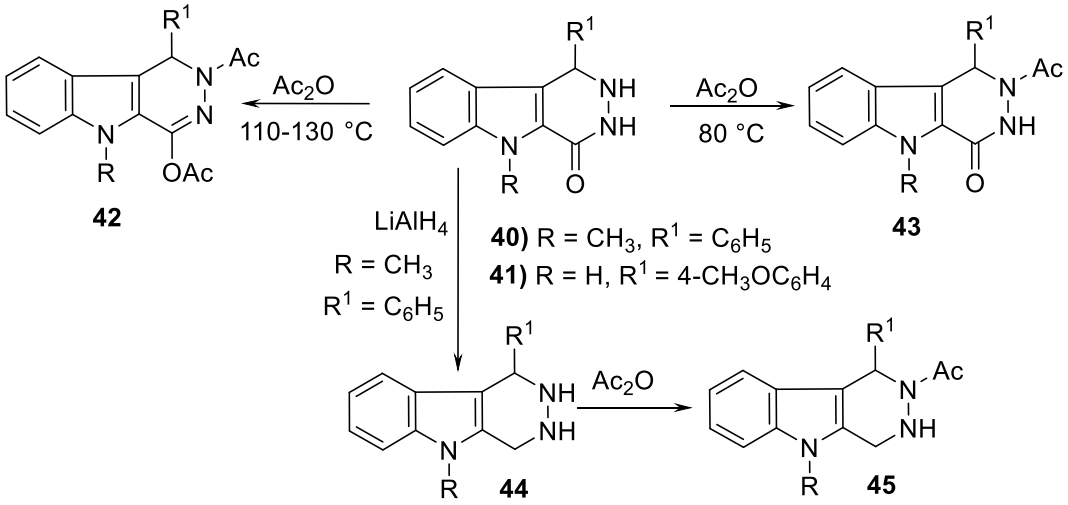
2.3.1. Michael addition. Sarhan *et al*[38] announced that, the Michael addition of nucleophile **20** (R^1 = H, R = H) to acrylonitrile as the Michael acceptor in ethanol containing Et_3N yielded the Michael adduct **39** in excellent yield (Scheme 12).



Scheme 12. Michael addition of nucleophile **20**.

2.4 Acetylation

Acetylation of pyridazino[4,5-*b*]indoles **40** (R= CH_3, R^1= C_6H_5) and **41** with acetic anhydride at 110-130°C afforded 2-acetyl-4-acetoxypyridazinoindole derivatives **42**, whereas the acetylation at 80°C gave 2-acetyl derivatives **43**.[43] Reduction of **40** by $LiAlH_4$, followed by acetylation of the resulted intermediate **44** gave compound **45** in good yield.



Scheme 13. Acetylation of pyridazino[4,5-*b*]indoles **40** and **41**.

2.5 Chlorination of pyridazinoindoles

2.5.1. Nucleophilic substitution reaction (S_N2). In 2015, treatment[16,44,45] of the hydroxyl compounds **46** with $POCl_3$ afforded the corresponding chlorinated products **47**. S_N2 reactions of chloride in the intermediates **47** with the appropriate anilines furnished 1-anilino-5*H*-pyridazino[4,5-*b*]indoles **48**,[46] which underwent a nucleophilic substitution with furfuryl mercaptan to give the desired intermediates **49**.

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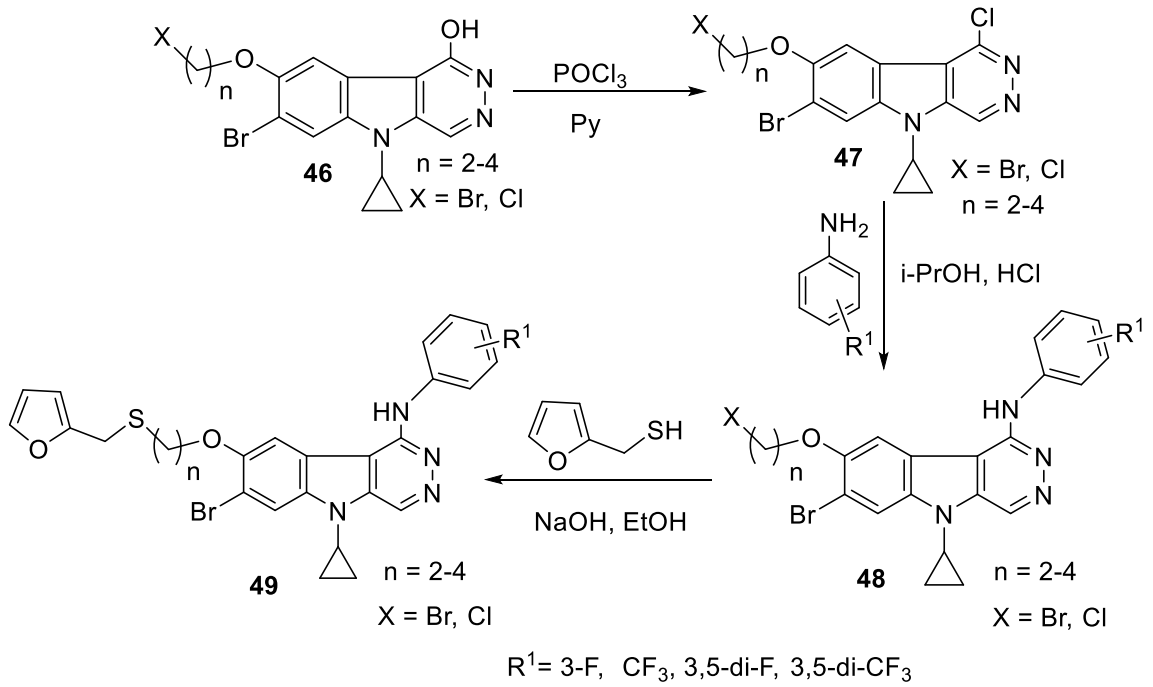
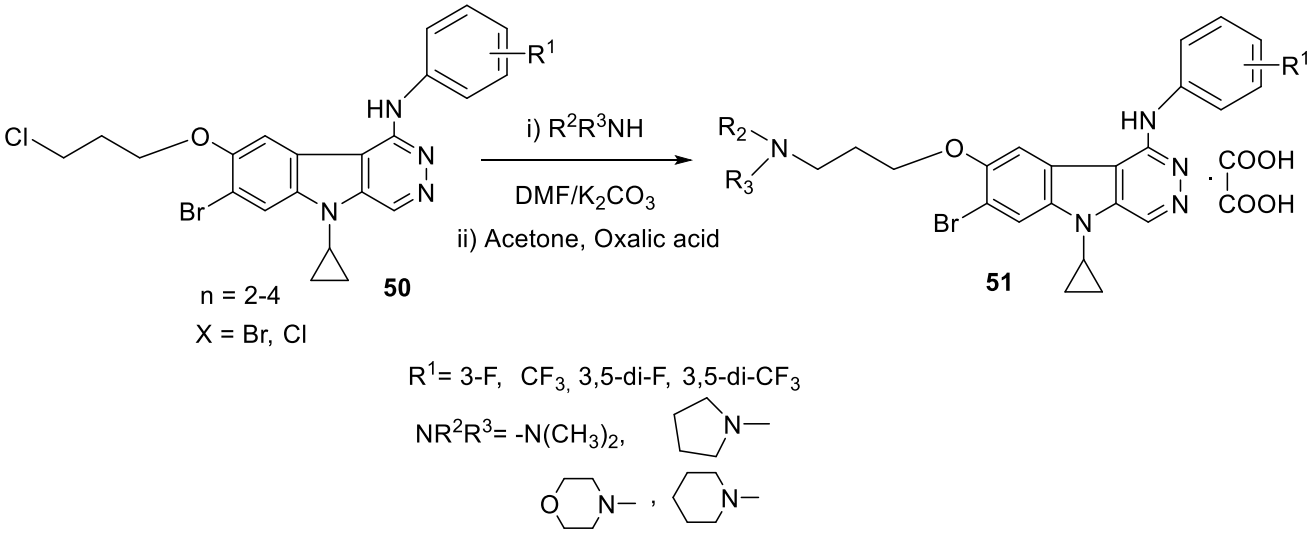


Scheme 14. Synthesis of 7-bromo-5-cyclopropyl-8-(((furan-2-ylmethyl)thio)methoxy)-*N*-phenyl-5*H*-pyridazino-[4,5-*b*]indol-1-amine derivatives **49**.

Moreover[45], the reaction of **50** with the appropriate secondary amines in dimethylformamide afforded the corresponding target compounds **51** as the oxalate (Scheme 15).



Scheme 15. Reaction of chloro derivative **50** with appropriate secondary amines.

Furthermore, the regioselective Mannich reactions[44,45] at 5-position of furyl group of intermediates **49** with the appropriate secondary amines in glacial acetic acid afforded the target compounds **52**. In addition, an alternative monoxidation of thioether derivatives **52** by means of sodium perborate in glacial acetic acid yielded the corresponding sulfoxides **53**[48] (Scheme 16).

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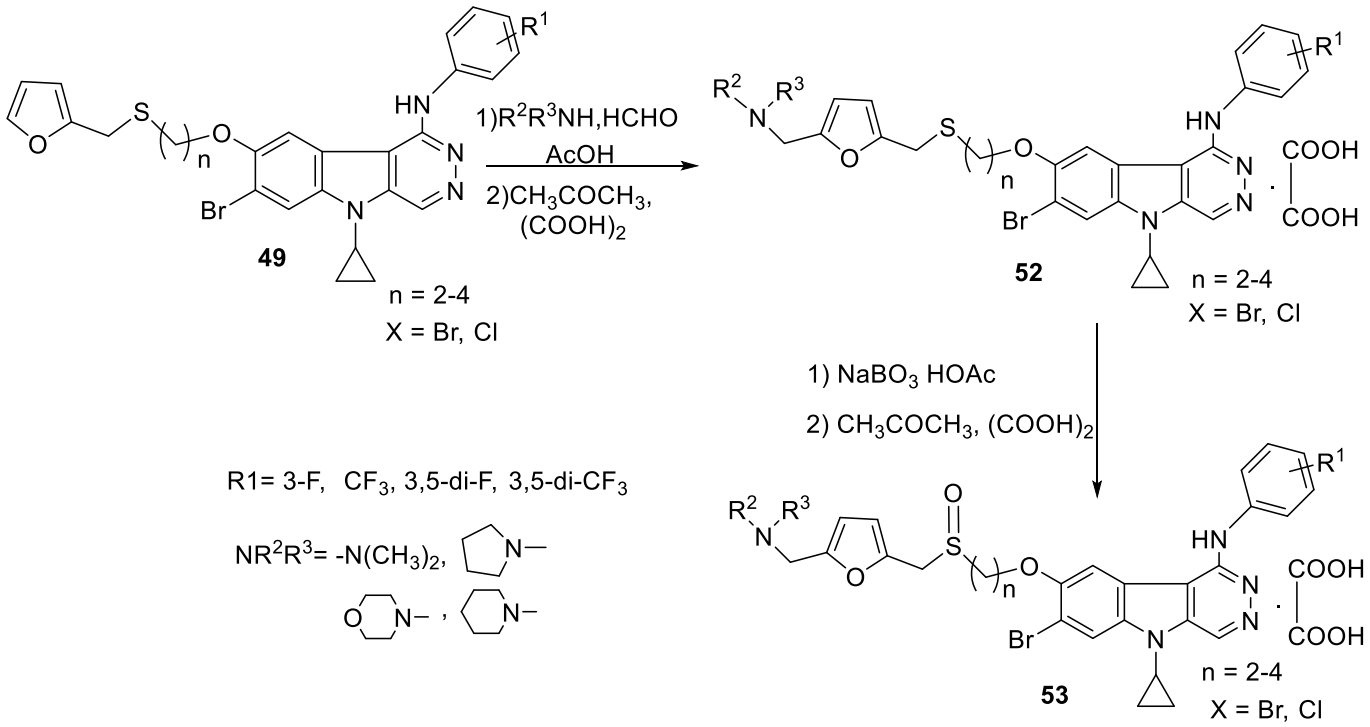
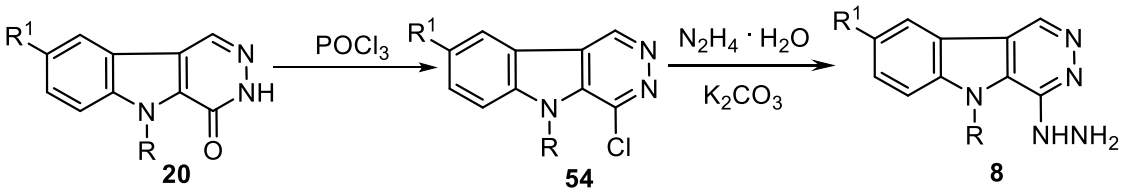


Scheme 16. Synthesis of compound **52** and sulfoxides **53.**

The pyridazinones **20**[36,49,50] were subjected to chlorination with $POCl_3$ to obtain the corresponding 4-chloro-*5H*-pyridazino[4,5-*b*]indoles **54** which on reaction with hydrazine hydrate in the presence of K_2CO_3 afforded 4-hydrazino-*5H*-pyridazino[4,5-*b*]indoles **8**.[51]



Scheme 17. Hydrazinolysis of 4-chloro-*5H*-pyridazino[4,5-*b*]indoles **54**.

Monge *et al.*[52,53] and Diels *et al.*[54] reported that the pyridazino[4,5-*b*]indole **56** (Scheme 18) was prepared by treatment of **55** with $POCl_3$.

It was reported that,[55] the synthesis of 1-aryl-4-hydrazino-*5H*-pyridazino[4,5-*b*]indoles **59** has been achieved by reaction of **57** with $POCl_3$ to afford the corresponding chloro derivative **58**, which underwent hydrazinolysis with hydrazine hydrate to give the hydrazine compound **59**. Treatment[20,41,56] of the pyridazinone derivatives **25**, **36** and **60** with $POCl_3$ furnished the chloro derivatives **61-63**.

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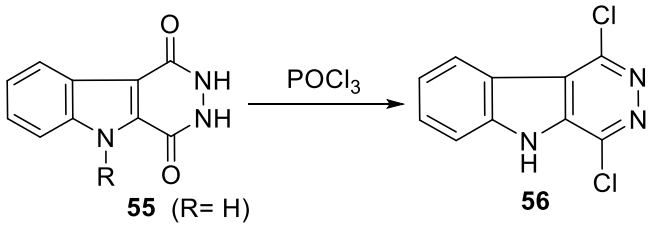
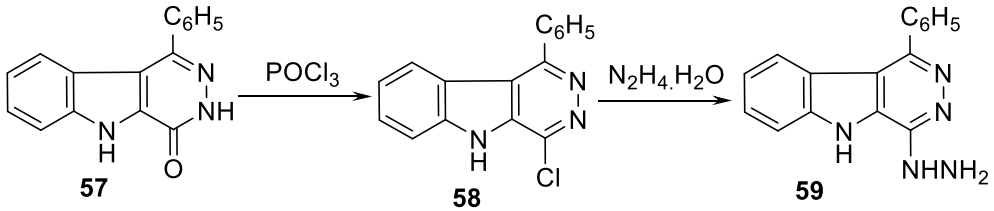
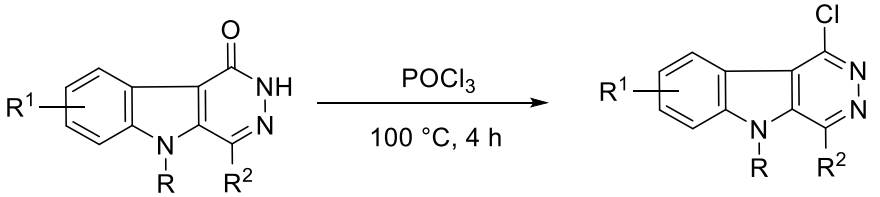


Scheme 18. Synthesis of the 1,4-dichloro-*5H*-pyridazino[4,5-*b*]indole **56**.





Lit.[41] **25**, R^1= H, R= CH_3, R^2= CH_3
Lit.[20] **36**, R^1= H, R= H, R^2= CH_3
Lit.[55,56,] **60,** R^1= H, Br, Cl, OCH_3, CH_3, R= H, R^2 = CH_3, C_6H_5, substituted C_6H_5

Lit.[41] **61,** (R^1= H, R= R^2= CH_3)
Lit.[20] **62**, R^1= H, R= H, R^2= CH_3
Lit.[55,56] **63,** R^1 = H, Br, Cl, OCH_3, CH_3, R= H, R^2 = CH_3, C_6H_5, substituted C_6H_5

Scheme 19. Synthesis of chloro derivatives **61-63**.

2.6 Reactions of chloropyridazinoindoles

It was described that[41] the chlorine atom of the chlorine derivative **61** is labile and could be easily substituted by nitrogen nucleophiles such as 3-diethylaminopropylamine and benzylamine in the absence of a solvent, giving the corresponding pyridazinoindoles **64** and **65**, respectively (Scheme 20).

Moreover,[41] reaction of the chloro derivative **61** with sodium azide in dry DMF gave the tetrazolo compound **66** in 82% yield, whereas its reaction with thiourea, followed by saponification with sodium hydroxide and subsequent acidification afforded the corresponding thione **67** (Scheme 21).

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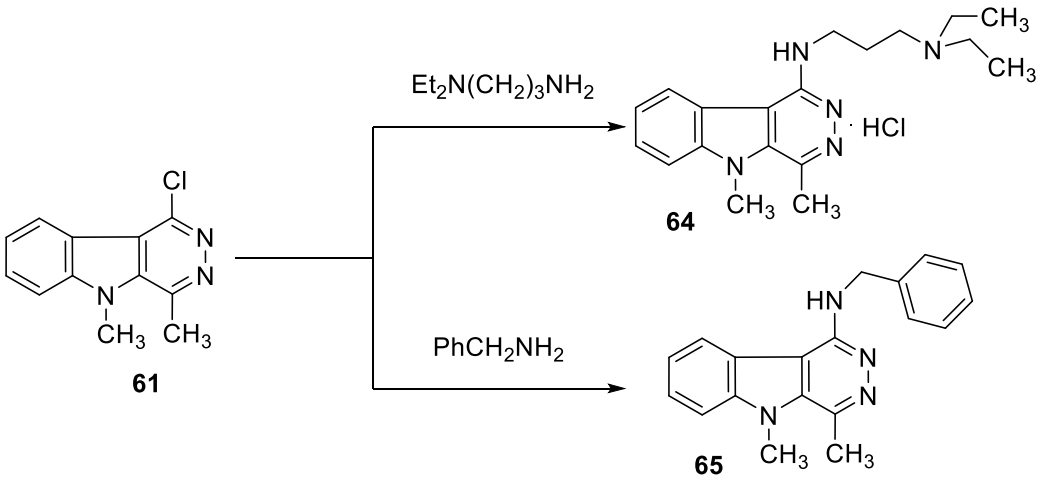
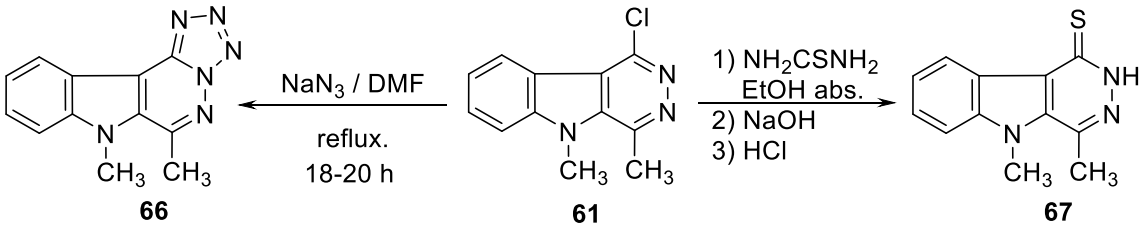
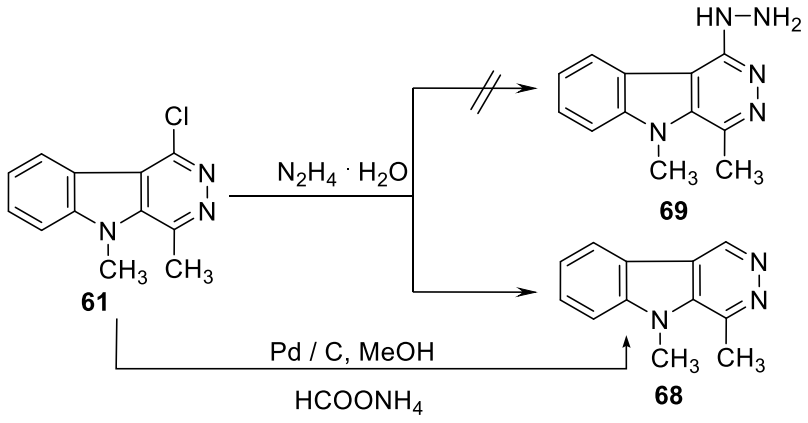


Scheme 20. Reactions of chloro compound **61** with some nitrogen nucleophiles.



Scheme 21. Synthesis of tetrazolo compound **66** and thione derivative **67.**

Also, hydrazinolysis[41] of **61** resulted in dechlorination giving **68** rather than the corresponding hydrazino derivative **69** (Scheme 22). The formation of **68** can be attributed to an oxidative dehydrazination reaction of the unstable hydrazino compound **69** in the presence of aerial oxygen. The 1-unsubstituted pyridazine **68** could be prepared alternatively by catalytic transfer hydrogenation of **61** using ammonium formate as the hydrogen source and Pd/C as a catalyst in refluxing methanol.



Scheme 22. Hydrazinolysis of **61** and formation of the 1-unsubstituted pyridazine **68.**

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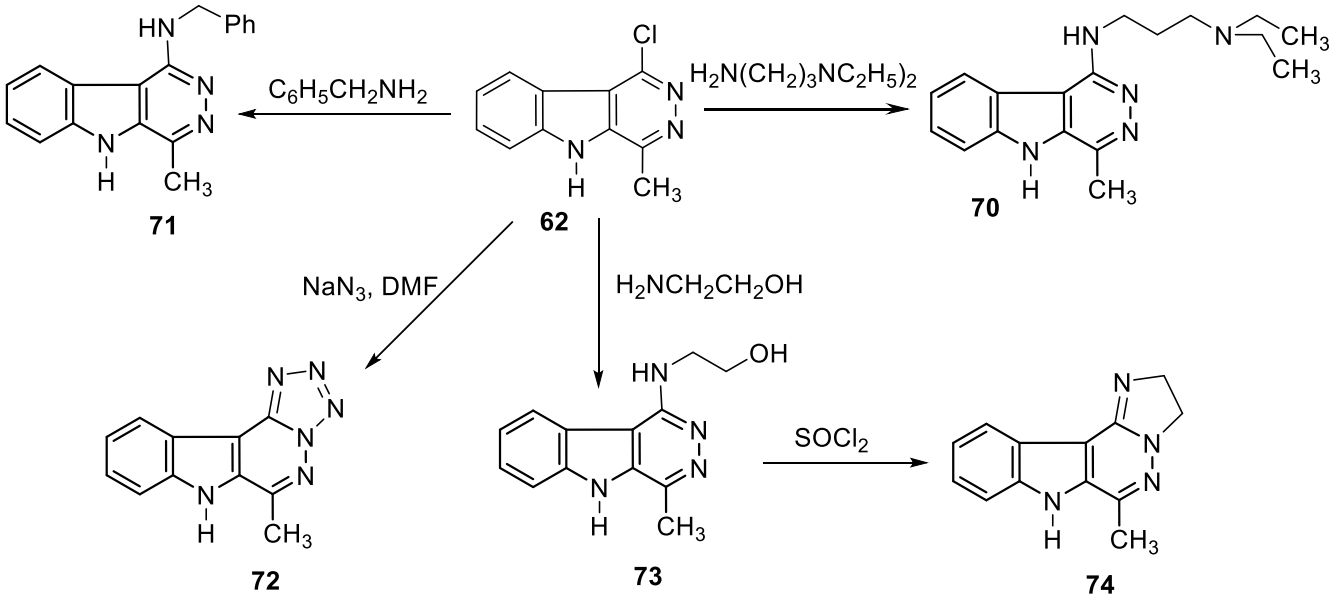
It was reported that[20] the chloro derivative **61** seems to be remarkably inert towards nucleophilic attack. Obviously, this lack of reactivity is mainly caused by considerable steric shielding of the chloro function by the 9-H atom at the benzene ring, in addition to electronic factors (annulation of an electron-rich indole system onto the chloropyridazine moiety). Nucleophilic substitution of the chloro function in **61** with amines requires relatively harsh conditions, e. g. heating in a high-boiling amine in the absence of a solvent. By this method, the benzylamino compound **71** could be obtained in good yield. Likewise, the potential anticancer agent **70**, bearing a 3-(diethylamino)propylamino side chain as well as the hydroxyethylamino derivative **73** were prepared, albeit in lower yields owing to work-up losses and some decomposition during the substitution reaction. The alcohol **73**, when heated in thionyl chloride, is transformed into the corresponding chloro derivative which spontaneously cyclizes into the imidazo[2',1':6,1]pyridazino[4,5-*b*]indole **74** (obtained as the hydrochloride), which represents a new ring system. Another representative of a hitherto unknown ring system, the tetrazolo[5',1':6,1]pyridazino[4,5-*b*]indole **72**, was prepared from **61** in a single step by refluxing with excess sodium azide in dimethylformamide solution.



Scheme 23. Reaction of chloro derivative **61** with some nucleophiles.

Also, it was mentioned that[20] an attempt to convert the pyridazinone **36** into the corresponding thione by refluxing with phosphorus pentasulfide in pyridine gave only a very low yield of the desired compound **76**, whereas employment of Lawesson's reagent met with a complete failure. However, reaction of the chloropyridazine **62** with thiourea in ethanol, followed by alkaline hydrolysis of an intermediate isothiourea derivative **75** was found to afford the pyridazinethione **76** (Scheme 24). Expectedly, reaction of this compound with alkylating agents takes place at the sulfur atom exclusively, as demonstrated by the transformation of **75** into the alkylsulfanyl compounds **77-79**, which are obtained by treatment of the thione with methyl iodide, diethylaminoethyl chloride, or ethyl bromoacetate, respectively, in ethanolic solution in the presence of a weak base (sodium acetate). In contrast to the sluggish nucleophilic displacement reactions with the chloropyridazine **62**, reductive dehalogenation takes place very smoothly when **62** is subjected to catalytic transfer hydrogenation in refluxing methanol, employing ammonium formate as the hydrogen source and palladium on carbon as the catalyst. Thus, the 1-unsubstituted tricycle **80** which represents an aza isostere of the natural product, *harmane*, is obtained.

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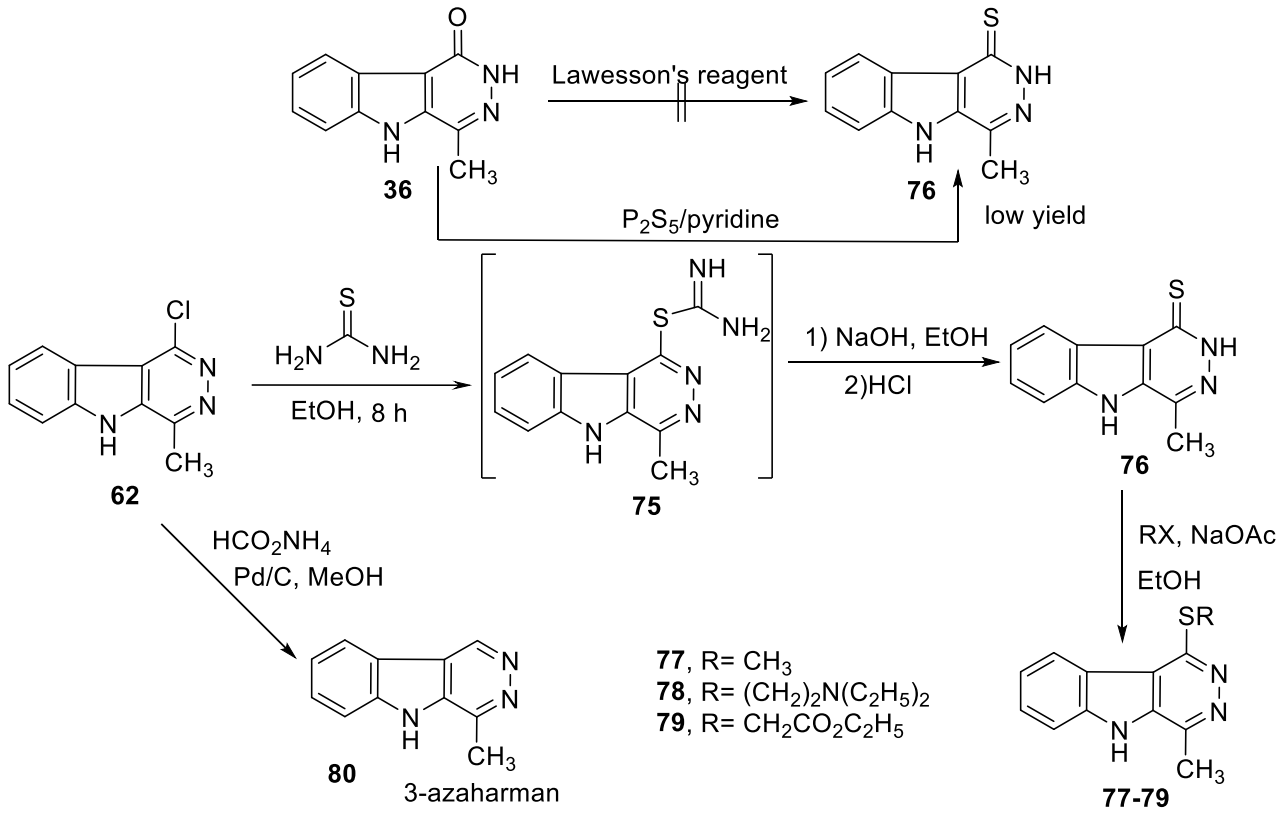

Scheme 24. Reactions of thione **76** with some alkylating agents.

In 2008, Haider *et al*[22] reported that heating of pyridazinedione **81** with phosphorus oxychloride smoothly afforded the dichloro compound **82** in 82% yield. Hydrazinolysis of the latter compound with hydrazine hydrate gave a monohydrazino-monochloro product **83** regioselectivity. An analogous transformation of the 5- unsubstituted dichloro congener, leading to a 1-chloro-4-hydrazino compound, had been previously reported by Monge and coworkers.[24] In the case of Haider *et al,* the regioselectivity of this substitution was found to be completely reversed, leading to the 4-chloro-1-hydrazino derivative **83** exclusively. Obviously, steric shielding of the 4-position by the adjacent *N*-alkyl residue is responsible for the observed preferential attack of the nucleophile at C-1 rather than at C-4 (as in Monge's 5-unsubstituted compound). The transformation of **83** into **84** was accomplished by treatment with mercuric oxide in aqueous suspension in analogy to previous protocols.[25,26] The final hydrolysis step, affording the new pyridazinone **85**, succeeded by heating the chloropyridazine **84** in acetic acid.[27]

El-Kashef *et al*[21] mentioned that the initial attempts to transform the chloropyridazine **62** into the required 1-hydrazino compound **86** by heating with excess hydrazine hydrate failed and after complete consumption of the starting material (48 hours), the 1-unsubstituted tricycle **80** was isolated in 50% yield as the sole reaction product. This compound **80** had been prepared previously[20] by catalytic hydrogenation of **62**. The same result was obtained when the thione **76**[20] was employed as a substrate for hydrazinolysis: in this case **86** was obtained. When the chloro compound **62** was refluxed in hydrazine hydrate under argon, a nearly quantitative yield of the hydrazino product **86** was obtained (Scheme 26).

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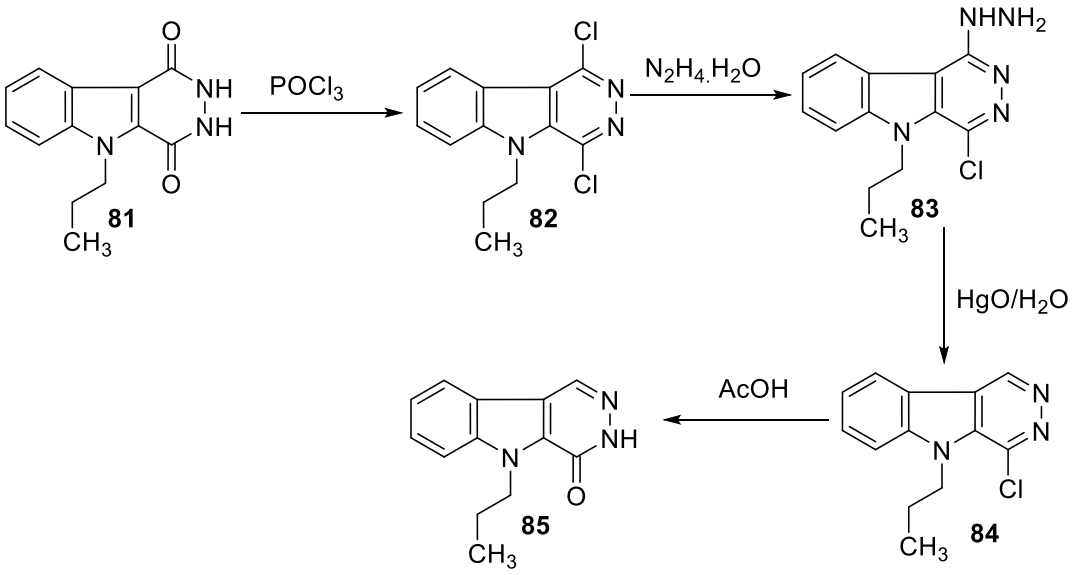
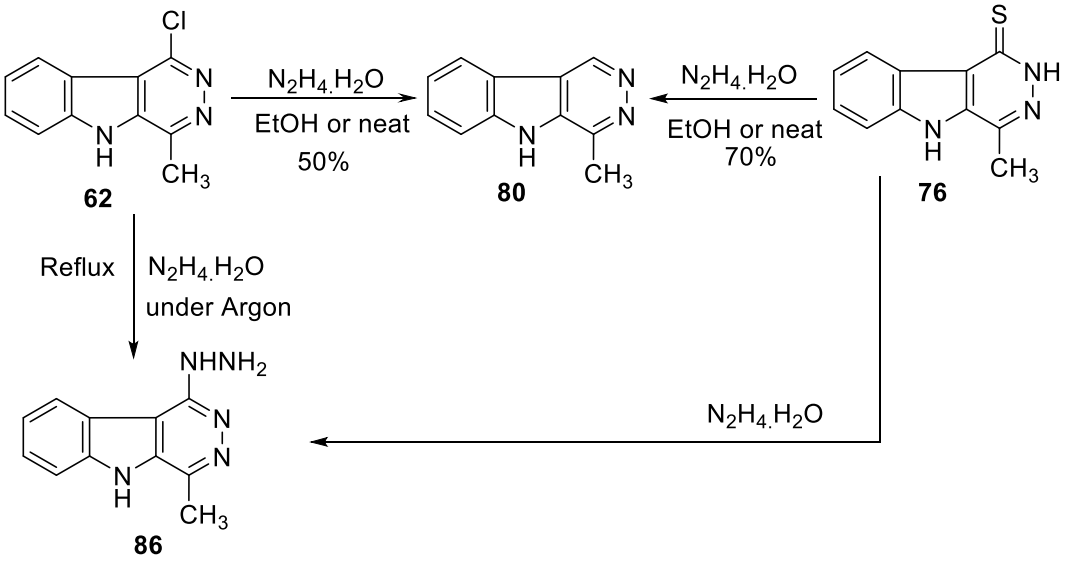


Scheme 25. Synthesis of 5-propyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-one **85**.



Scheme 26. Catalytic hydrogenation of 1-chloro-4-methyl-5*H*-pyridazino[4,5-*b*]indole **62.**

The mechanism was suggested by the authors,[21] thus the initially formed hydrazinopyridazine **86** is very susceptible towards oxidation by air oxygen, and thus undergoes oxidative dehydrazination under the conditions required for nucleophilic displacement of the leaving group at the 1 position. As a mechanism of the observed transformation, they proposed a dehydrogenation of the N–N bond of the hydrazino function into a diazene structure, followed by spontaneous loss of molecular nitrogen to give substituted pyridazinoindole derivative **80** (Scheme 27).

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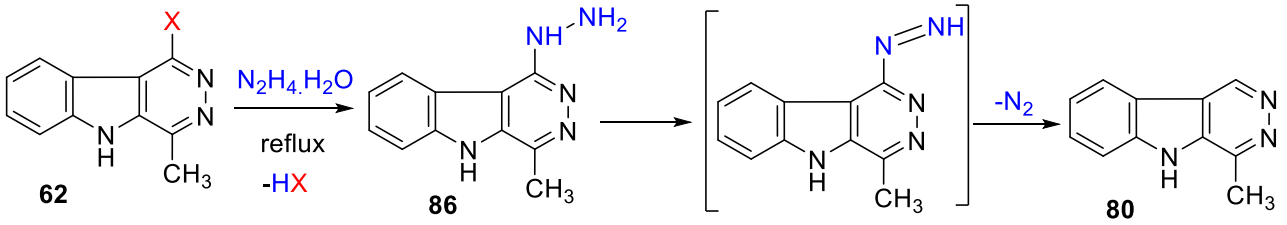
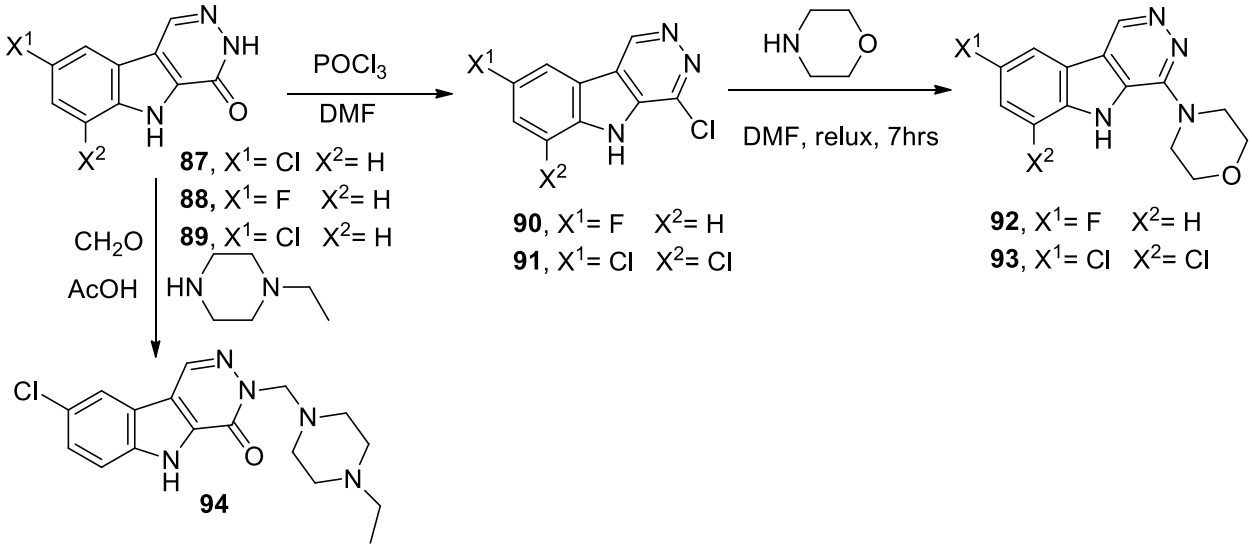


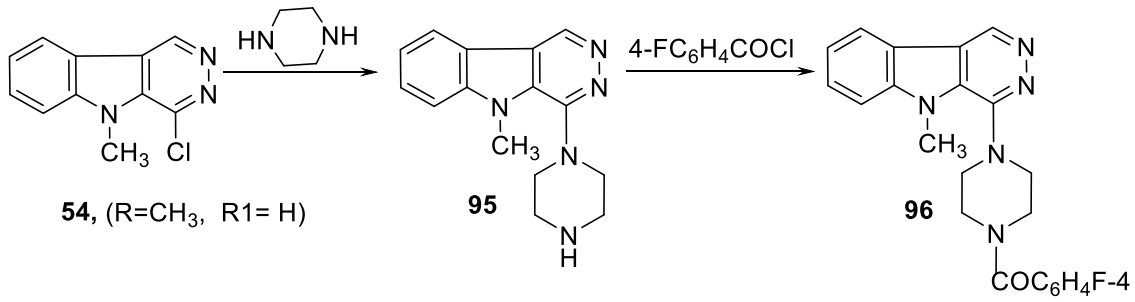
Scheme 27. The suggested mechanism of catalytic hydrogenation of **62.**

In 2008, El-Gendy *et al*[57] found that the 4-Chloro-substituted-5*H*-pyridazino[4,5-b]indoles **90** and **91** were prepared by boiling **87** and **88** with $POCl_3$ for 10 h; their reaction with morpholine in DMF[37] led to the formation of 4-morpholino- substituted-5*H*-pyridazino[4,5-b]indoles **92** and **93**. Mannich condensation[58] of 5-chloro-3H-pyridazino[4,5-*b]*indol-4(5*H*)-one **89** with 4-ethylpiperazine and formaldehyde in ethanol gave 8-chloro-3-((4-ethylpiperazin-1-yl)methyl)-3*H*-pyridazino[4,5-*b*]indol-4(5*H*)-one **94**.



Scheme 28. Mannich condensation of 5-chloro-3*H*-pyridazino[4,5-*b*]indol-4(5*H*)-one **89**.

Amination of the chloro derivative **54** (R^1 = H, R = CH_3) with piperazine, followed by acylation with 4-fluorobenzoyl chloride gave the pyridazinoindole compound **96**.[59]



Scheme 29. Synthesis of pyridazinoindole compound **96**.

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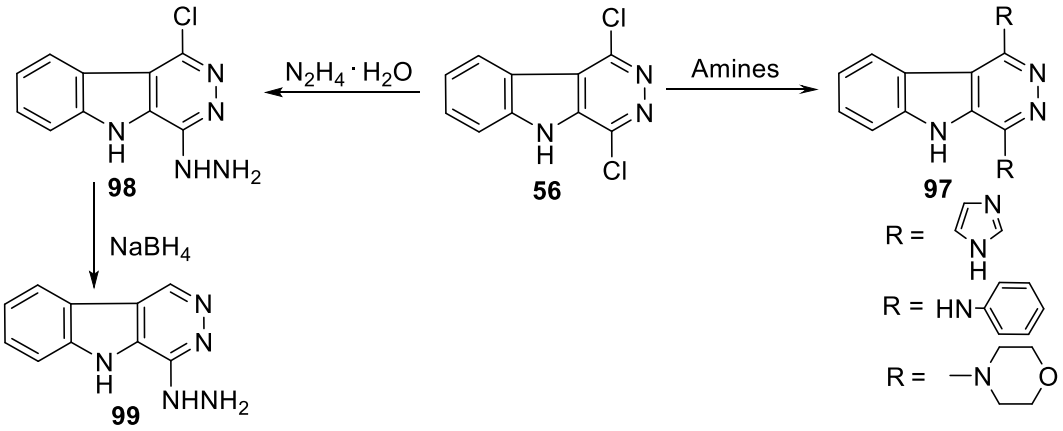
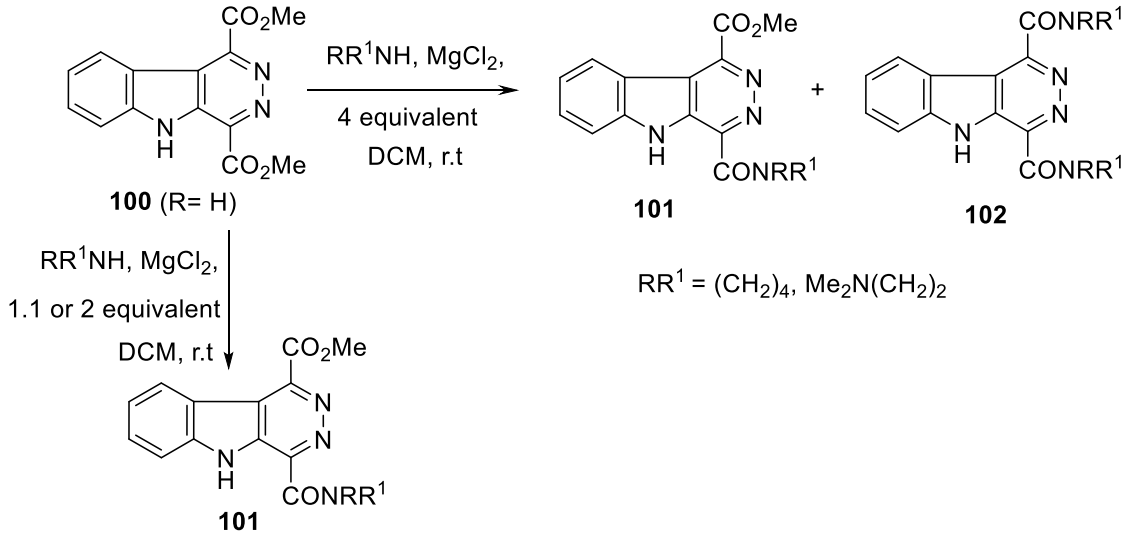
Reaction of the chloro derivative **56** with amines (imidazole, aniline and morpholine[60]) gave the disubstituted derivatives **97**[52], while reaction with 90% hydrazine hydrate furnished 1-chloro-4-hydrazino-*5H*-pyridazino[4,5-*b*]indole **98**.[53,54] the chlorine atom was easily removed by reduction with $NaBH_4$ and compound **99** was obtained.



Scheme 30. Reaction of chloro derivative **56** with amines.

2.7 Amidation of diesters

It was reported[61] that the direct mild amidation of diester **100** with 1.1 or 2 equivalents of amine occurred regioselectivity at C-4 to afford the corresponding monocarboxamides. Thus, the reaction of dimethyl 5*H*-pyridazino[4,5-*b*]indole-1,4-dicarboxylate **100** with 4 equivalents some amines in presence of $MgCl_2$ in dichloromethane at room temperature, It is worth noting that in the case of reaction with pyrrolidine, C-4 amidation occurred giving the corresponding monocarboxamide derivative **101** and the bisamides **102** were obtained when the primary *N*,*N*-dimethylethylenediamine was used.



Scheme 31. Regioselective amidation of diester **100** with 1.1 or 2 and 4 equivalents of amine.

Various attemptes[61] were done to remove the carbomethoxy group from compound **101**. These dealkoxycarbonylations were successfully performed by refluxing the appropriate compound **101** in DMF with

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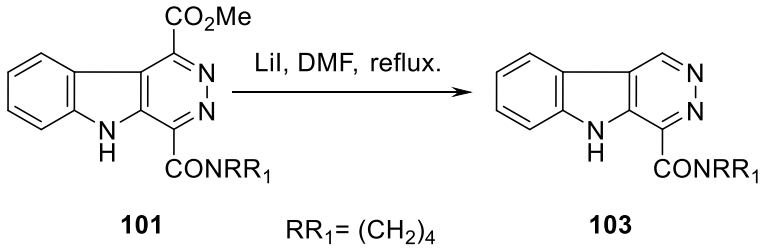
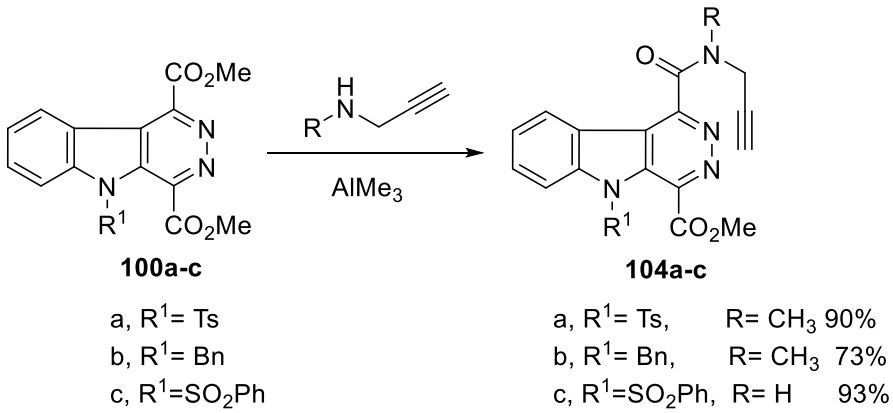
LiI. to afford the corresponding **103**. These mild conditions can easily be applied to other, more complex molecules and avoid the tedious classical procedure of ester hydrolysis followed by thermal decarboxylation.[57]



Scheme 32. Dealkoxycarbonylations of compound **101** in DMF with LiI.

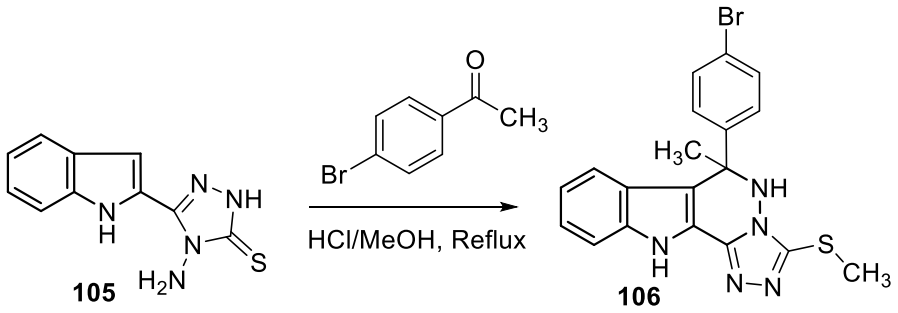
It was reported that, the Weinreb amidation[63] of **100a-c** with *N*-methylpropargylamine hydrochloride salt occurred exclusively on the C1 ester to give the monoamides **104a-c** respectively.



Scheme 33. Weinreb amidation of dimethyl 5-substitued-5*H*-pyridazino[4,5-*b*]indole-1,4-dicarboxylate **100.**

2.8 Reactions of hydrazino pyridazino[4,5-*b*]indoles

2.8.1. Formation of triazolo-and tetrazolopyridazino[4,5-*b*]indoles. Recently, it was reported that[3] the reaction of 1,2,4-triazole-3-thione **105** with 4'-bromoacetophenone in methanol and the presence of concentrated HCl as an acid catalyst afforded 1,2,4-triazolo [4',3':2,3]pyridazino[4,5-*b*]indole **106** in good yield (Scheme 34).



Scheme 34. Reaction of 1,2,4-triazole-3-thione **105** with 4'-bromoacetophenone.

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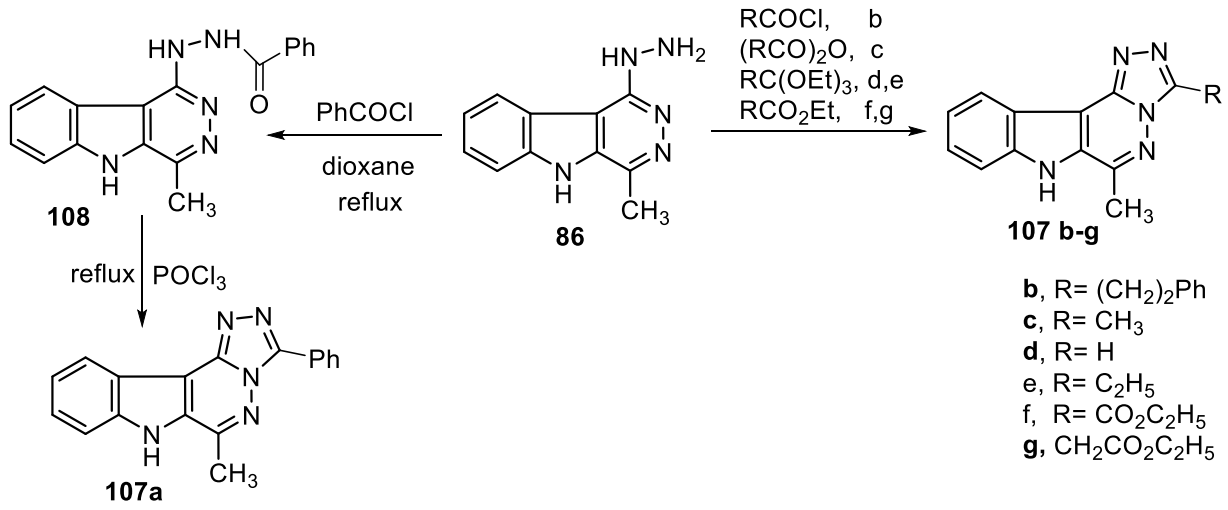
In 2004, it was reported that[21] treatment of **86** with benzoyl chloride in refluxing dioxane afforded the benzhydrazide **108** as a stable derivative. The open-chain structure of **108**, which was isolated as the hydrochloride can be smoothly dehydrated by heating in phosphorus oxychloride, affording the fused triazole **107a** in high yield. When phenylpropionyl chloride is employed in the reaction with **86**, the initially formed hydrazide cyclizes spontaneously into the phenethyl-substituted triazole **107b**. In a similar fashion, heating of **86** in excess acetic anhydride gives **107c**. For the synthesis of the 3-unsubstituted and the 3-ethyl congeners **107d** and **107e**, heating of the hydrazine **86** in the appropriate ortho ester (triethyl orthoformate or triethyl orthopropionate, respectively), was found to be a suitable method. Also, with high-boiling carboxylic acid esters, analogous cyclocondensations can be affected, as exemplified by the one-step preparation of the esters **107f** and **107g** from **86**, using diethyl oxalate or diethyl malonate, respectively.



Scheme 35. Synthesis of triazolopyridazino[4,5-*b*]indoles **107.**

Also, the same author mentioned that[21] another new type of [1,2,4]-triazolo[4',3':1,6]pyridazino[4,5-*b*] indoles was made available by reacting the hydrazine **86** with carbon-dioxide-type building blocks (Scheme 36). Heating of **86** with 1,1'-carbonyldiimidazole (CDI) in dry dioxane smoothly gave the fused triazolone **108**, whereas the corresponding tetracyclic thione **109** was obtained in satisfactory yield on treatment of **86** with carbon disulfide in ethanolic potassium hydroxide. Expectedly, alkylation of the latter compound was found to take place preferentially at the sulfur atom. Thus, the two alkylsulfanyl derivatives **110a,b**, featuring a basic side chain at position 3 of the condensed system were prepared from **109** by reaction with the respective alkyl chloride in ethanolic solution in the presence of sodium acetate.

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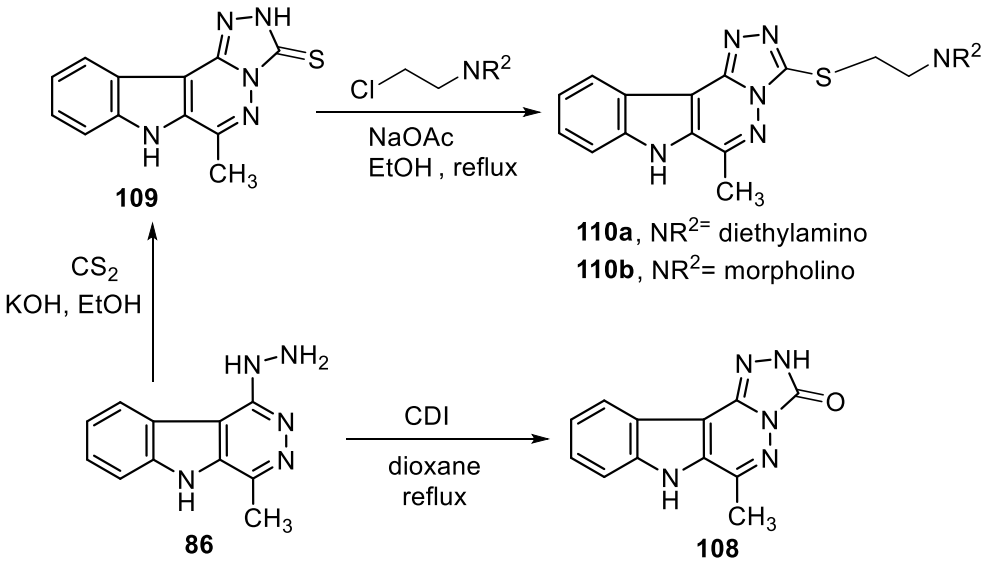
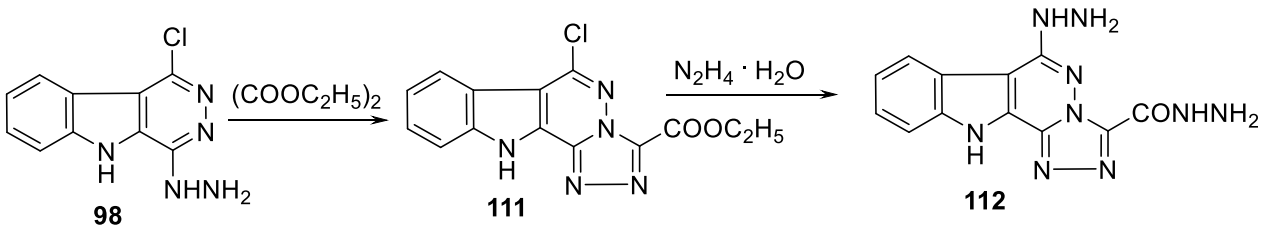


Scheme 36. Synthesis of new type of [1,2,4]-triazolo[4',3':1,6]pyridazino[4,5-*b*] indoles **108-110**.

Reaction of the hydrazino derivative **98** with diethyl oxalate gave the triazolo derivative **111**, which upon treatment with 90% hydrazine hydrate gave 3-carbazoyl-6-hydrazino-11*H*-1,2,4-triazolo[3,4-*c*] pyridazino[4,5-*b*]indole **112**.[53]



Scheme 37. Synthesis of 3-carbazoyl-6-hydrazino-11*H*-1,2,4-triazolo[3,4-*c*]pyridazino[4,5-*b*]indole **112**.

Reaction of the hydrazino compound **98** with acetyl acetone, formic acid, acetic acid, or $NaNO_2$/HCl gave the corresponding pyrazolo, triazolo, and tetrazolo derivatives **113-115**[60,64] respectively. Reaction of compounds **114** and **115** with imidazole afforded the imidazolyl derivatives **116** and **117**, respectively.[52] Treatment of the hydrazino derivative **98** with aldehydes and ketones afforded the hydrazones **118a,b.**[60]

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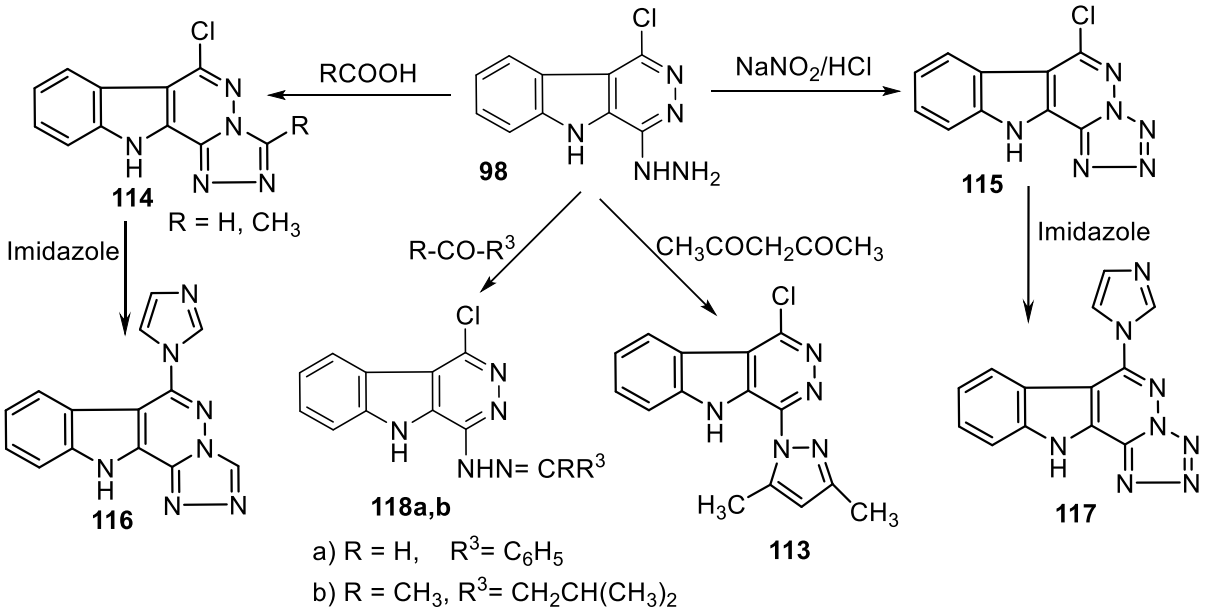
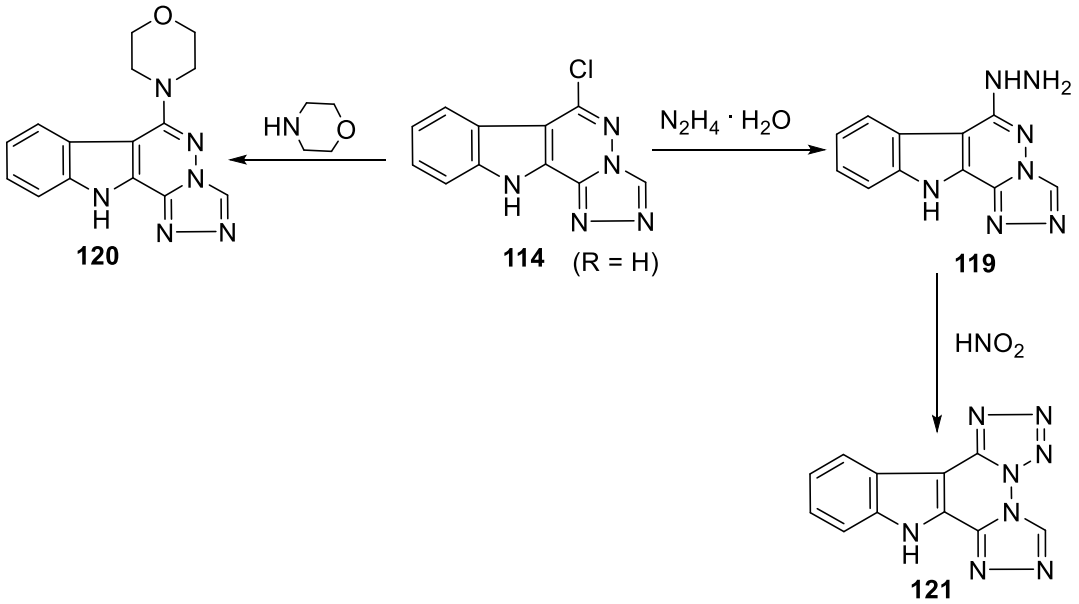


Scheme 38. Synthesis of pyrazolo, triazolo, and tetrazolo derivatives **113-115**.

It was reported that,[60] the treatment of chloro derivative **114** (R = H) with hydrazine hydrate or morpholine gave the corresponding pyridazinoindole derivatives **119**, **120**. The tetrazolo compound **121** was formed by reaction of the hydrazino compound **119** with nitrous acid.



Scheme 39. Reactions of the chloro derivative **115** with hydrazine hydrate or morpholine.

Interaction of the chloro derivative **113** with amines, namely imidazole, aniline, morpholine, piperidine, 4-(4′-methoxyphenyl)piperazine), 4-methylpiperazine, 4-(2′-ethoxyphenyl)piperazine, 4-(2′-methoxyphenyl) piperazine, and 4-(4′-fluorophenyl)-piperazine furnished pyridazinoindole derivatives **122**.[52,53] Reaction of the chloro derivative **113** with hydrazine hydrate or methyl hydrazine afforded the hydrazino derivatives **123**.[53,64]

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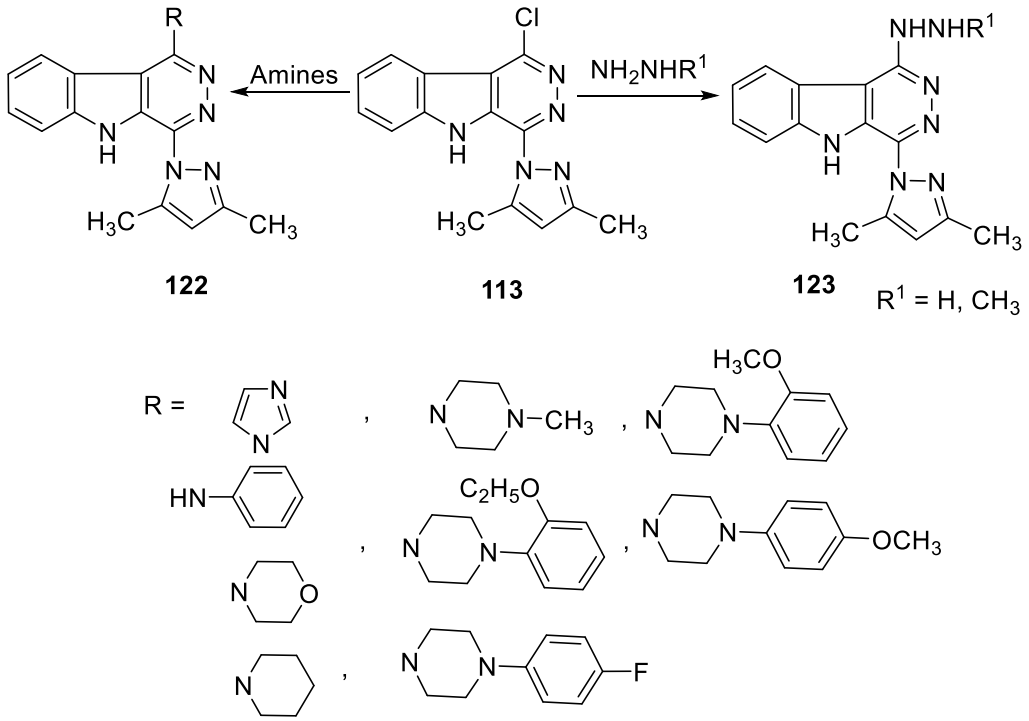
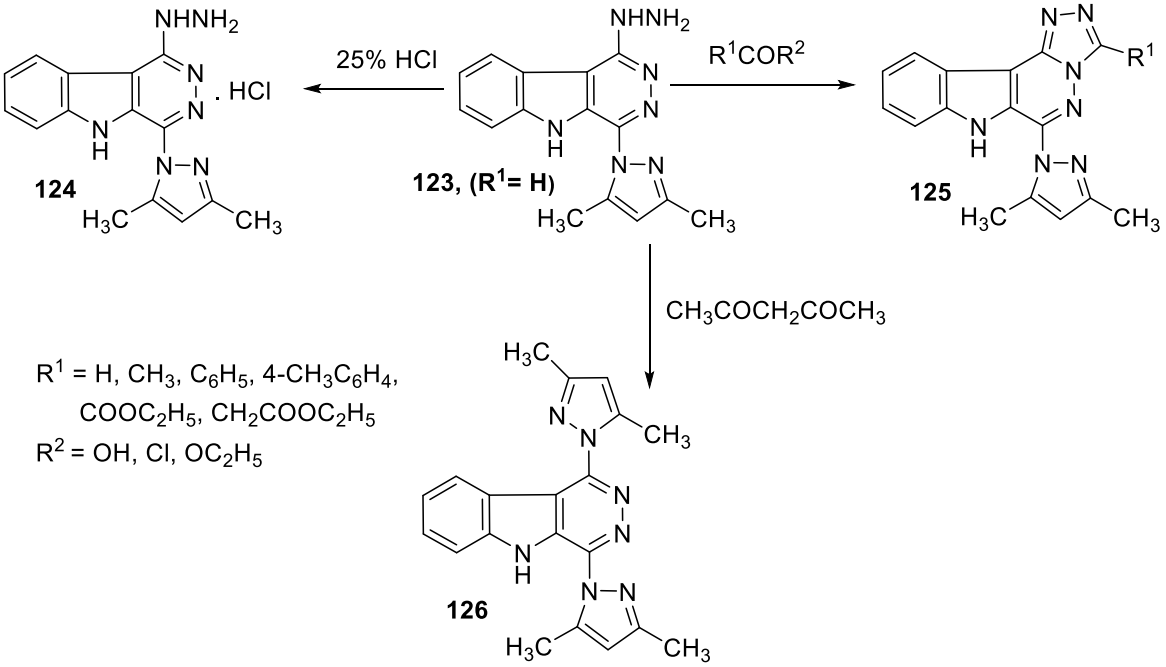


Scheme 40. Interaction of the chloro derivative **113** with amines.

Treatment of **123** (R^1 = H) with 25% hydrochloric acid yielded the hydrazino-pyridazino[4,5-*b*]indole hydrochloride **124** in 90% yield.[53] Condensation with formic acid, acetic acid, benzoyl chloride, 4´-methylbenzoylchloride, diethyloxalate, or diethyl malonate gave the 6-(3,5-dimethyl-1-pyrazolyl)-*5H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indoles **125**.[69] Similarly, treatment of the hydrazino derivative **123** (R^1 = H) with acetylacetone as a reagent and solvent under reflux gave the 1,4-bis(3,5-dimethyl-1-pyrazolyl)-*5H*-pyridazino[4,5-*b*]indole **126**.[53]



Scheme 41. Reactions of 4-(3,5-dimethyl-1*H*-pyrazol-1-yl)-1-hydrazineyl-5*H*-pyridazino[4,5-*b*]indole **123** with some reagents.

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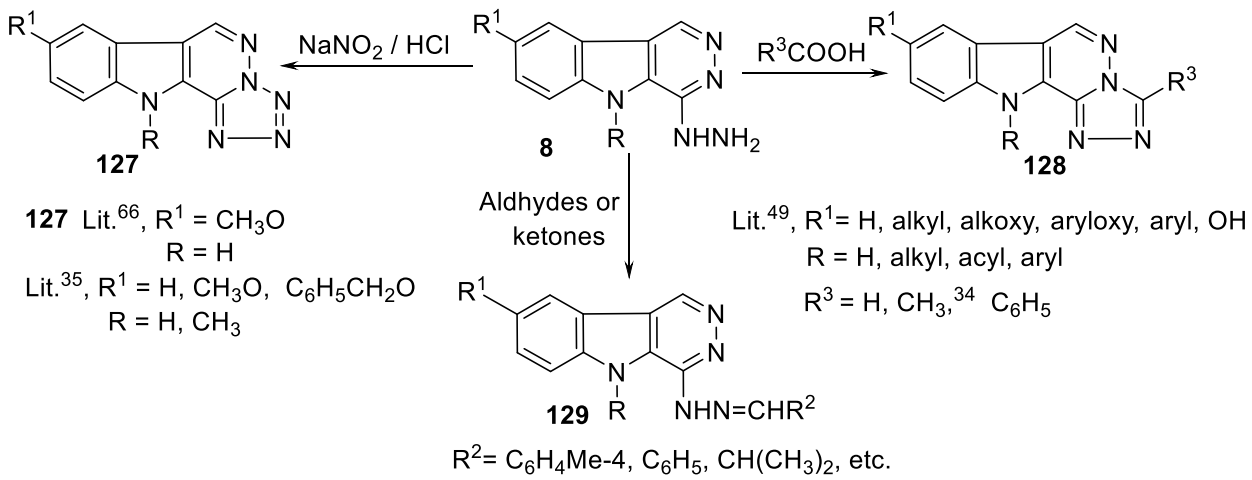
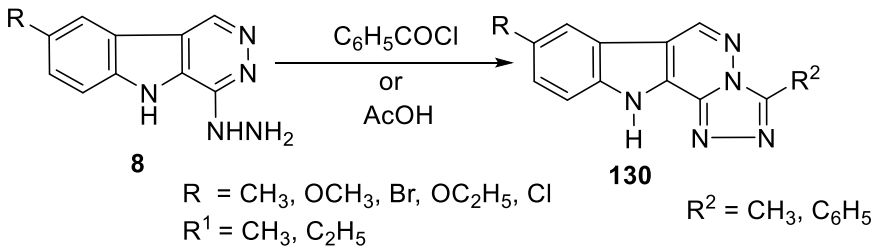
Interaction[35,49,66] of hydrazino derivatives **8** with formic acid, acetic acid,[34] benzoyl chloride, or nitrous acid yielded triazolo and tetrazolo derivatives **127** or **128**, respectively, while treatment[35,67] of **8** with aldehydes and ketones gave the hydrazones **129** (Scheme 42).



Scheme 42. Reactions of hydrazino derivatives **8**.

Hiremath *et al.*[50] described the hydrazino compound **8** were treated with acetic acid or benzoyl chloride to yield the desired compounds **130**.



Scheme 43. Synthesis of triazolopyridazino[4,5-*b*]indoles **130**.

Reaction of hydrazino derivative[70] **8** (R^1= $OCH_2C_6H_5$, R =H) with acetonyl acetone or acetyl acetone furnished the corresponding pyridazinoindole derivatives **131**, **132,** respectively.

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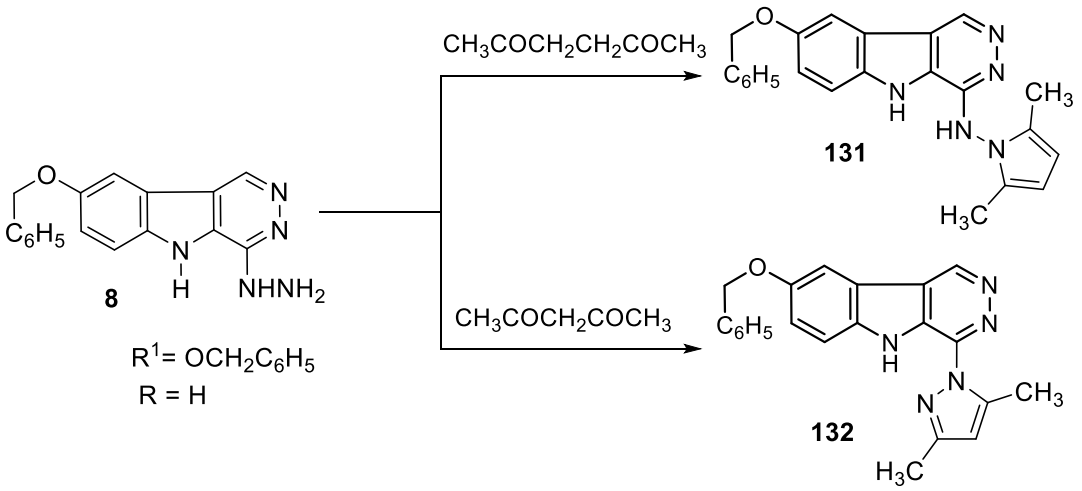
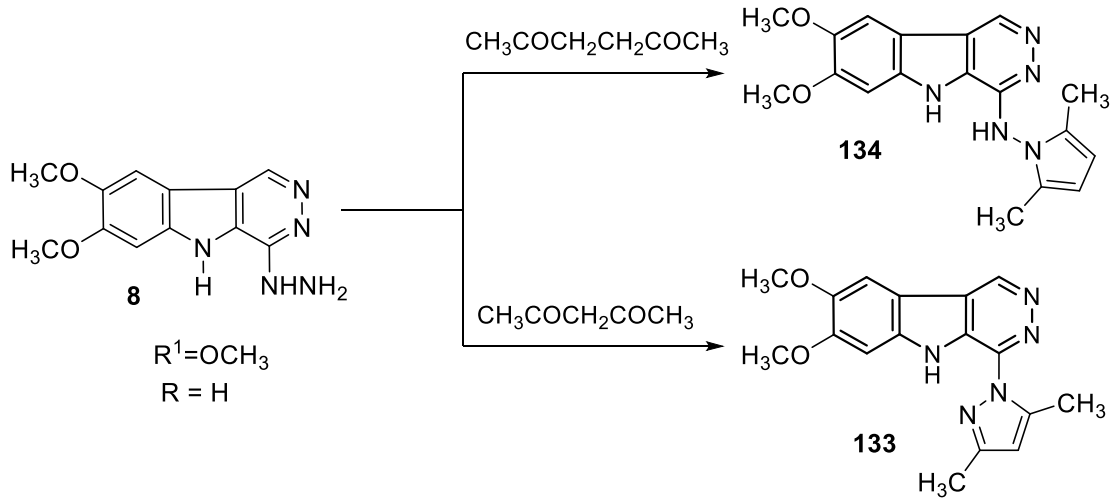


Scheme 44. Reaction of hydrazino derivative **8** with 1,3- and 1,4-diketones.

Monge *et al.*[68] described that 4-hydrazino-7,8-dimethoxy-*5H*-pyridazino[4,5-*b*]indole **8** (R^1 = R^2 = OCH_3, R= H) was prepared analogously to a previously reported method[35] by reaction of ethyl-5,6-dimethoxy-2-indolecarboxylate via formylation and hydrazinolysis to give the pyridazinoindolone which underwent thionation with P_2S_5 and subsequent hydrazinolysis to give the hydrazino derivative **8**, which upon reaction[69] with acetyl acetone or acetonylacetone gave the pyrazolo and pyrrolo derivatives **133** and **134** respectively.



Scheme 45. Reaction of hydrazino derivative **8** with 1,3-and 1,4-diketones.

On the other hand,[69] treatment of the hydrazino compound **8** with formic acid, ethyl orthoformate, or sodium nitrite in the presence of hydrochloric acid afforded the triazolo and tetrazolo derivatives **135** and **136**, respectively,[69] whereas its reaction with aldehydes gave the corresponding hydrazone derivatives **137**. The hydrazino derivative **59** was reacted with benzaldehyde to give the hydrazones **138**.[55]

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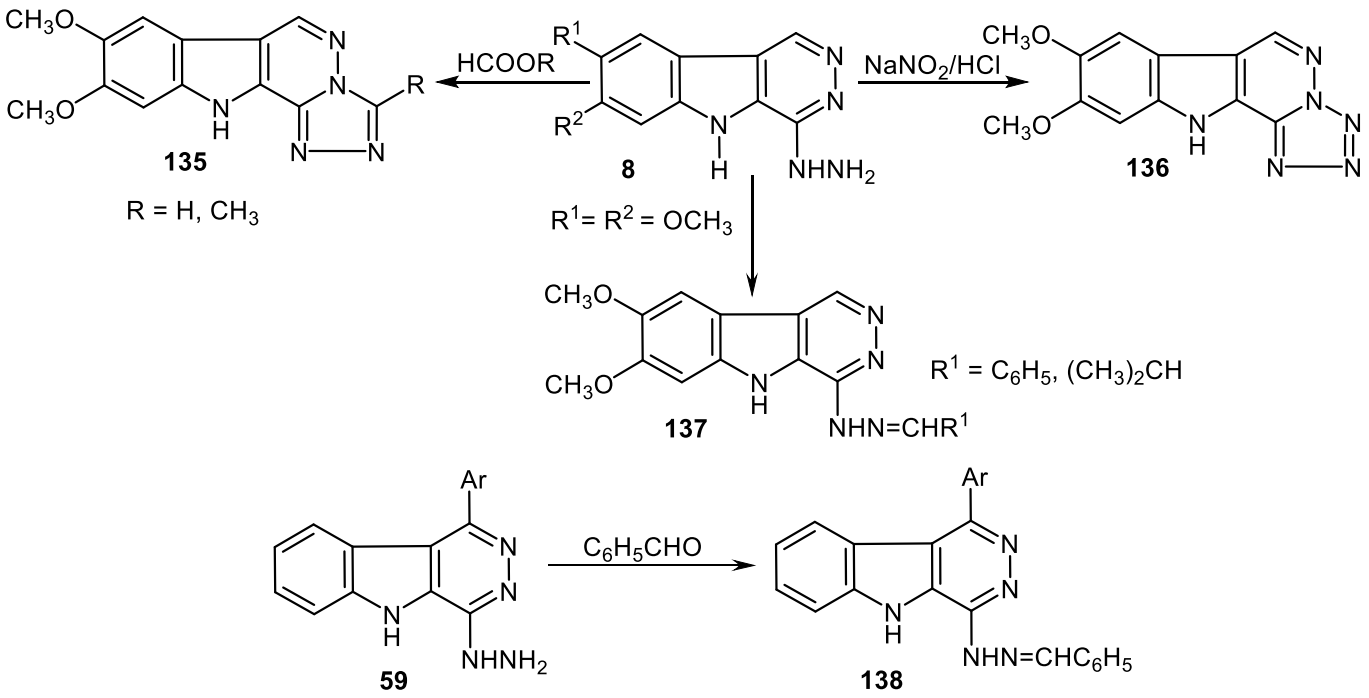
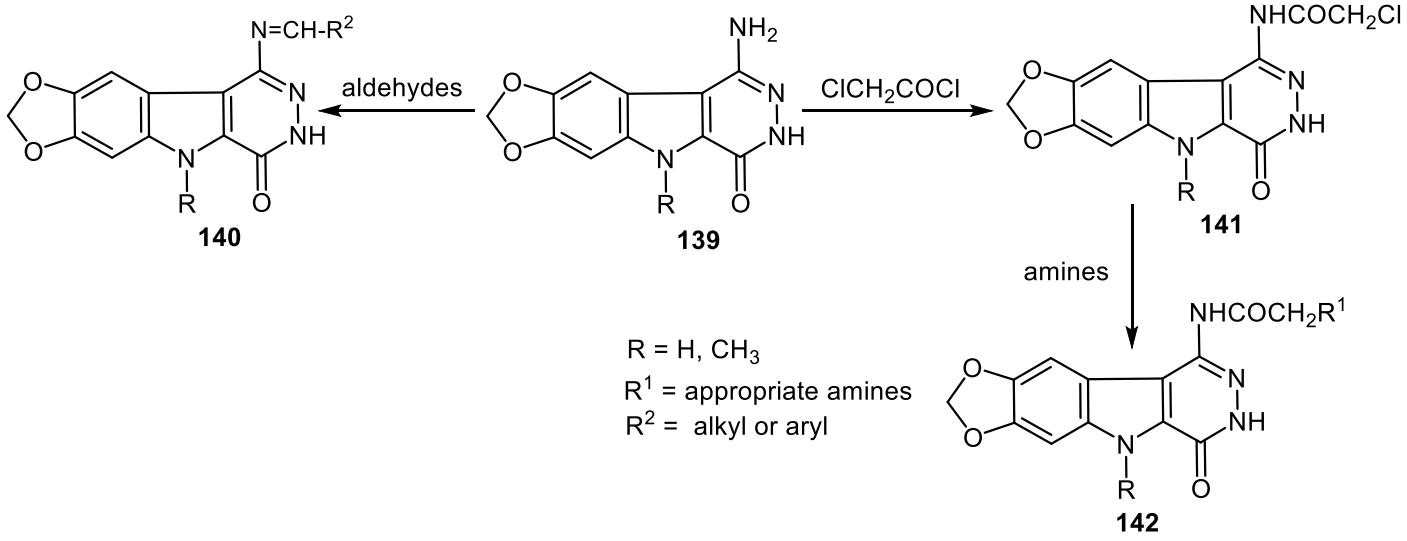


Scheme 46. Synthesis of triazolo-and tetrazolopyridazino[4,5-*b*]indoles **135** and **136**.

Treatment[14 of] 1-amino-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-ones **139** with aldehydes afforded the imino derivatives **140**. Reaction of **139** with chloroacetyl chloride gave the corresponding 1-chloroacetamido-3,4-dihydro-7,8-methylenedioxy pyridazino[4,5-*b*]indol-4-one **141**. Treatment of the latter compound **141** with amines furnished 1-acetamido-3,5-dihydro-7,8-methylenedioxy-4*H*-pyridazino[4,5-*b*]indol-4-ones **142**.[14]



Scheme 47. Reactions of 1-amino-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-ones with aldehydes and chloroacetyl chloride **139**.

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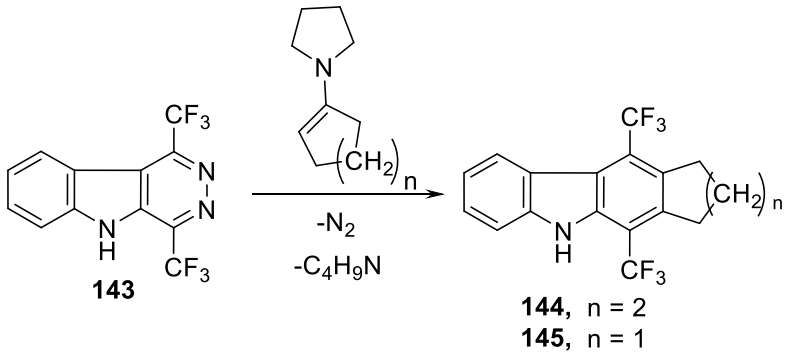
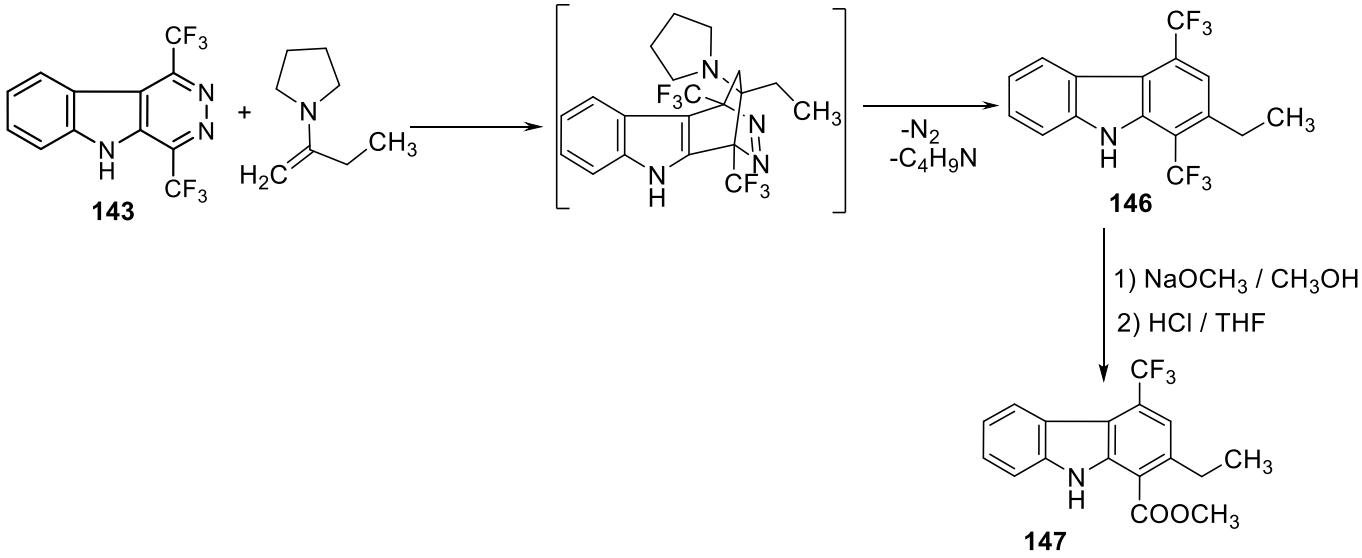
2.9 [4+2] cycloaddition process

Reaction[71] of compound **143** with an excess of a cyclohexanone-derived enamine in 1,4-dioxane/acetonitrile gave the expected tetracyclic product, 6,11-bis(trifluoromethyl)-7,8,9,10-tetrahydrobenzo[*b*]carbazole **144** in 21% yield (Scheme 48). However, heating of the pyridazine **143** with the more reactive five-membered enamine, 1-pyrrolidino-1-cyclopentene in 1,4-dioxane solution for 5 days afforded the cyclopenta[*b*]carbazole derivative **145** in 69 % yield.[71]



Scheme 48. [4+2] cycloaddition reaction of pyridazine **143**.

Refluxing **143** with the acyclic enamine, 2-pyrrolidino-1-butene, according to a [4+2] cycloaddition process gave the 2-ethylcarbazole **146**, which on heating with sodium methoxide/methanol in an autoclave afforded after subsequent acidic hydrolysis of an intermediate ortho ester (in analogy to lit.[72] the methyl ester **147** in 70 % yield.[71]



Scheme 49. [4+2] cycloaddition reaction of pyridazine **143** with the acyclic enamine.

2.10 Nitration

Nitration of the pyridazino[4,5-*b*]indole **148** in a mixture of H_2SO_4 and HNO_3 gave the 8-nitro derivative **149** which was reduced to amino derivative **150.**[73]

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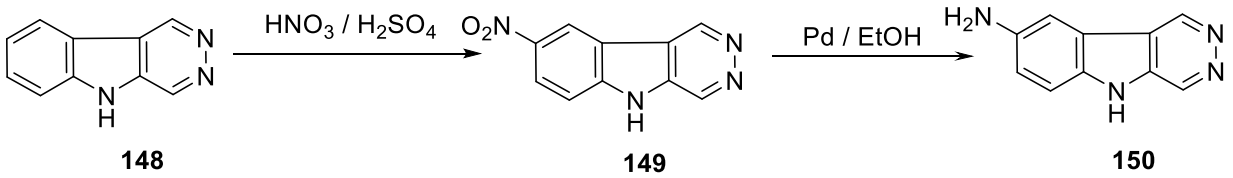
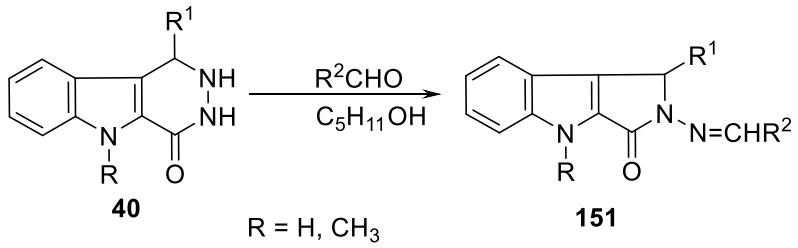


Scheme 50. Synthesis of amino derivative **150**.

Isomerization of pyridazino[4,5-*b*]indoles has been achieved by boiling **40** with aromatic aldehydes, affording the pyrrolo[3,4-*b*]indoles **151**.[74]

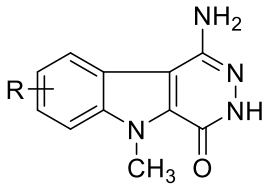


Scheme 51. Synthesis of pyrrolo[3,4-*b*]indoles **151**.

3. Biological importance of pyridazino[4,5-*b*]indoles

3.1. Antimicrobial activity

In 2013, it was reported that[17] the pyridazino[4,5-b]indole derivatives showed significant antimicrobial activities against the variety of selected bacteria and a fungus. For instance, compound **139** (R= H) exhibited a moderate MIC value (15.6 *µ*g/mL) against *Bacillus subtilis*, which was the most sensitive microorganism to the tested compounds.



139, R = H

3.2. Pharmacological activity

Recently, It was reported that,[3] the 1*H*-pyridazino[4,5-b]indol-4(5*H*)-one (ZFD-10) was firstly synthesized and discovered to be an anti-viral agent against anti-ZIKV inhibitor with very low cytotoxicity. The authors claimed that this compound was able to inhibit the ZIKV NS5 RdRp enzyme and confirmed this using an RNA polymerase assay.[3] Furthermore, it was found that,[37] 4-(alkylthio)-5*H*-pyridazino[4,5-*b*]indole derivatives **9** exhibited the most promising cytotoxicity toward MCF-7 cells with an IC50 value of 12 µM. Moreover, it exhibited promising inhibition activity toward EGFR and its downstream PI3K–AKT pathway, which suggests that it is a multitarget compound. Additionally, it increased apoptosis 47.98-fold in MCF-7 cells and increased

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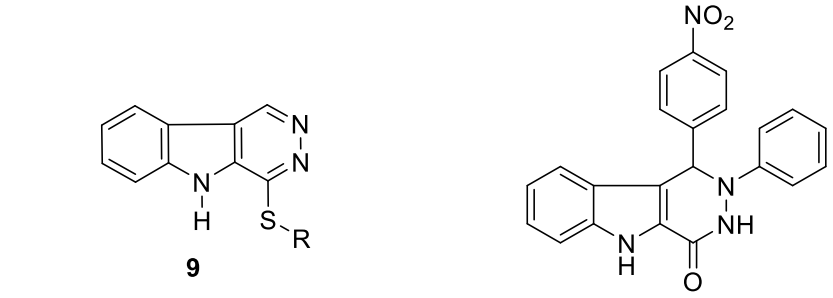
total apoptosis by 38.87%. Hence, compound **9** is recommended to be as an anti-breast cancer chemotherapeutic due to its effects on the EGFR-PI3K-AKT pathway.

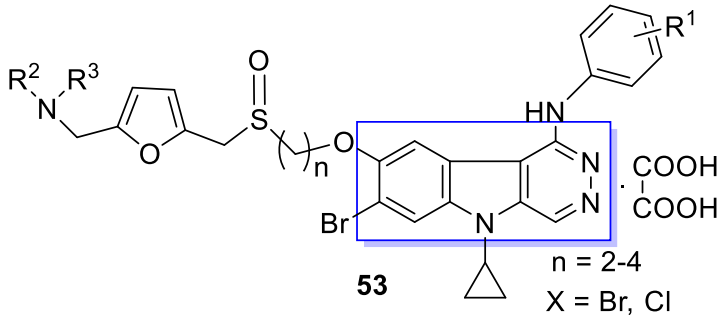


9

R = CH_2-CH=CH_2, $CH_2C_6H_5$, CH_2COOEt

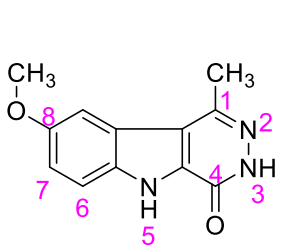
ZFD-10

In 2015 It was reported[44] that a series of novel tricyclic 5*H*-pyridazino[4,5-*b*] indoles **53** were found to be as potent antitumor agents and antiproliferative activities.[45]



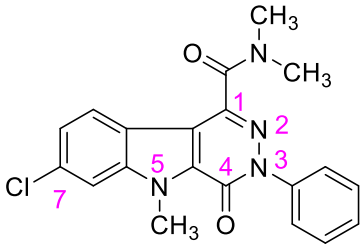
53

It was mentioned that,[75] the synthesis of 8-methoxy-1-methyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-one **I** and pyridazin-3(2H)-one analogs as DYRK1A inhibitors and potent pyridazinoindole ligand for PET imaging of TSPO in cancer.[76] whereas, it was reported that, a novel synthesis of the translocator protein (TSPO) ligand 7-chloro-N,N,5-trimethyl-4-oxo-3-phenyl-3,5-dihydro-4*H*-pyridazino[4,5-b]indole-1-acetamide **II** (SSR180575) as a promising probe for molecular imaging of glioma.[76]



DYRK1A (IC50 = 5 μM)

I



SSR180575

II

A series[15] of novel 5-benzylated 4-oxo-3,4-dihydro-5H-pyridazino[4,5-*b*]indoles **III** exhibited also significant anti-proliferative effects in various human cancer cell lines including those resulting in activation of the PI3K pathway. While,[77] the 7-chloro-*N,N*-dimethyl-5-[^{11}C]methyl-4-oxo-3-phenyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indole-1-acetamide **IV** is the first PET radioligand for the TSPO based on an indole acetamide scaffold designed for imaging neuroinflammation in animal models and in the clinic.

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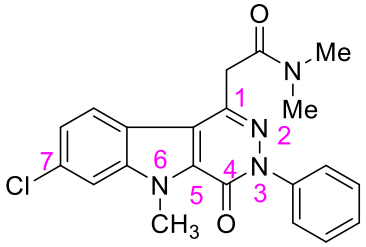
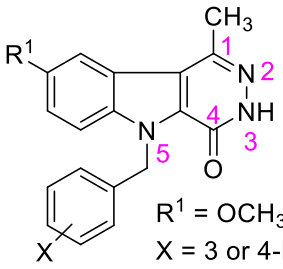


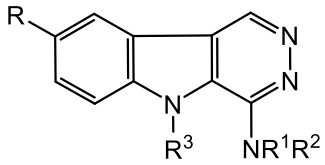
III

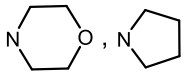


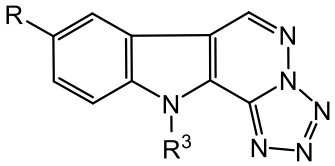
R^1 = OCH_3, F, Br
X = 3 or 4-NO_2, CN, OCH_3

IV

It was described that pyridazino[4,5-*b*]indole derivatives have neurotrophic activity,[78] moreover they can be used for treating diseases and disorders related to the peripheral benzodiazepine receptor[103] and diseases related to GABA-ergic transmission disorders.[79] It was reported[36] that the pyridazino[4,5-*b*]indoles **V** act as *platelet aggregation inhibitors* and/or *antihypertensives.* The 1,2,3,4-tetrazolopyridazino[4,5-*b*]indoles **VI** are known to be of interest as drugs.[70]

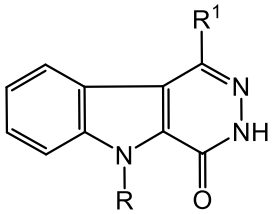


V, R = H, alkyl, alkoxy, aryloxy, OH, aryl
R^1 = H, NH_2 , NR^1R^2 = 
R^2 = Ph, H
R^3 = H,alkyl, acyl, aroyl.

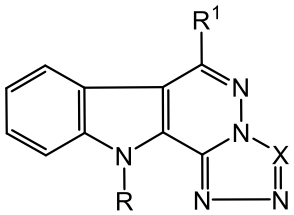


VI, R = OCH_3
R^3 = H

Antithrombotic drugs which prevent platelet aggregation by inhibition of platelet cyclooxygenase have been widely studied,[69] the foremost example being acetylsalicylic acid. However, a more efficient approach may be the selective inhibition of thromboxane A_2 (TXA_2) synthetase, which under physiological conditions is rapidly hydrolysed to TXB_2. In addition, the inhibition of the production of TXA_2 may increase the production of the vasodilator*, prostacyclin* (PC). Pyridazino[4,5-*b*]indole derivatives[9,35,68,69,80] exerted antihypertensive activity and can act as inhibitors of thromboxane synthetase. The new *thromboxane* A_2 synthetase inhibitors[84] of type **VII, VIII** have *blood platelet aggregation-inhibiting* activity and particularly inhibit arachidonic acid induced *platelet aggregation*.



VII R = H, CH_3
R^1 = H, CH_3, C_6H_5, p-Cl-C_6H_4



VIII R = H, CH_3
R^1 = Cl, H, N_3, $NHNH_2$, piperidino, etc.....
X = CH, CCH_3, CC_6H_5, N

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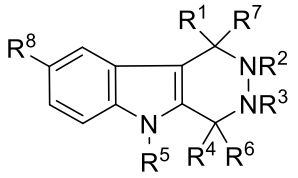
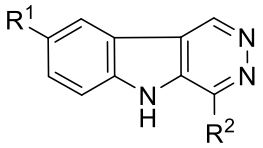
Pharmacological studies *in vitro* using human blood and *in vivo* in rats and guinea pigs were done by Monge *et al*.,[82] and it was found that also the 4-hydrazinopyridazino[4,5-*b*]indoles **IX** were selective inhibitors of thromboxane synthetase. On the other hand, 8-methoxy-4-hydrazino[4,5-*b*]indole **IX** did not inhibit prostacyclin formation and shows promise as an antihypertensive agent which inhibits blood platelet aggregation by inhibiting the synthesis of TXB_2.

Moreover, the oxopyridazino[4,5-*b*]indoles **X** were tested in vitro for their ability to inhibit thromboxane synthetase in human, dog, and guinea pig blood plasma. The aggregation-inducing agents employed were arachidonic acid, ADP, and prostaglandin H2. The most active oxopyridazino[4,5-*b*]indole **X** [R^1R^7 = O; R^2 = R^5 = R^6 = R^8 = H; R^3 = Ac; R^4 = $CH_3(CH_2)_8$] was also tested *ex vivo* against guinea pig platelets.[83]



IX

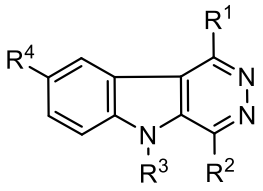


X

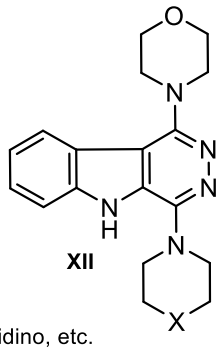
R^1 = CH_3O, C_2H_5O, Benzyloxy.
R^2 = OH, $NHNH_2$

IX R^1 = C_6H_5, 4-$CH_3C_6H_4$, 3,4-$CH_2O_2C_6H_3$; R^5 = H, CH_3
R^2 = H, Ac, Bz, R^6 = H,CH_3, C_2H_5, C_6H_5; R^4R^6= O
R^3 = H, Ac, R^7 = H, CH_3; R^1R^7 = O
R^4 = CH_3, C_6H_5, $C_6H_5(CH_2)_8$, R^8 = $C_6H_5CH_2O$, H

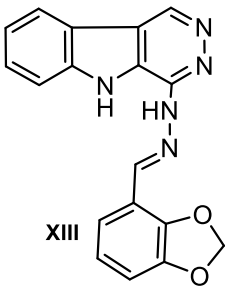
Also pyridazino[4,5-*b*]indoles **XI** were evaluated as inhibitors of human blood platelet aggregation and thromboxane synthetase, and the pyridazinoindoles **XII** and **XIII** were found to be selective inhibitors of thromboxane synthetase.[84]



XI



XII



XIII

XI R^1= H, Cl, N-piperidino, etc.
R^2 = H, $NHNH_2$, C_6H_5-NH, N-piperidino, etc.
R^3 = H, CH_3
R^4 = H, $C_6H_5CH_2O$

Furthermore, the 3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole **XIV** and 3,4-dihydro-4-oxo-8-benzyloxy-5*H*-pyridazino[4,5-*b*]indole **XV** inhibited ADP-, arachidonate-, and PGH_2- induced platelet aggregation.[85] The 1-hydroxy derivative **XVI**, 8-hydroxy derivative **XVII** and the 1-methyl derivative **XVIII** inhibited only ADP-induced aggregation.

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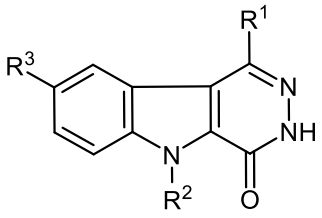


XIV, $R^1 = R^2 = R^3 = H$

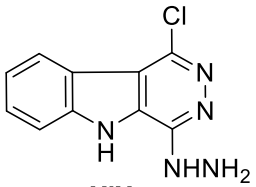
XV, $R^1 = R^2 = H$, $R^3 = C_6H_5CH_2O$

XVI, $R^1 = OH$, $R^2 = R^3 = H$

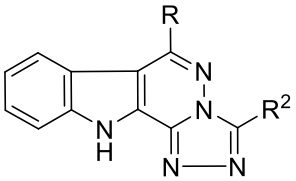
XVII, $R^1 = R^2 = H$, $R^3 = OH$

XVIII, $R^1 = CH_3$, $R^2 = R^3 = H$

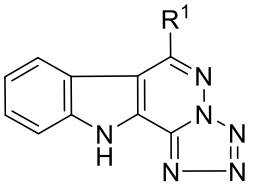
It was reported that the pyridazino[4,5-*b*]indole derivatives **XIX** act as platelet aggregation inhibitors or antihypertensives.[36,68] Furthermore, the 11*H*-1,2,4-triazolo[4′,3′:2,3]pyridazino[4,5-*b*]indoles **XX** and 11*H*-1,2,3,4-tetrazolo[4′,3′:2,3]-pyridazino[4,5-*b*]indoles **XXI** are useful as *antihypertensives*.[86] Also the 4-hydrazino-5*H*-pyridazino[4,5-*b*]indoles **XXII** and **XXIII** exhibited *antihypertensive* activity[87] (also in dogs[88]), while the pyridazino[4,5-*b*]indoles **XXIV** act as a*ntihypertensives*[59] and *antiarrhythmics.*[59] A series[34] of 4-hydrazino-5*H*-pyridazino[4,5-*b*]indoles **XXII** and their potential metabolites, 3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indoles, 1-oxopyridazino[4,5-*b*]indole derivatives[89] and 11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indoles showed *antihypertensive* activity in spontaneously hypertensive rats at 25 mg/kg orally, the hydrazino derivative was the most active and the most toxic.



XIX



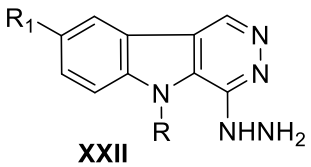
XX



XXI

R^1 = Cl, $NHNH_2$, morpholino, piperdino.

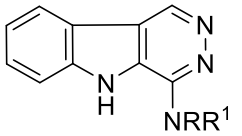
R = Cl, $NHNH_2$, morpholino, piperidino, $NHN{:}CHC_6H_5$, R^2 = H, CH_3, C_6H_5



XXII

R^1= OCH_3

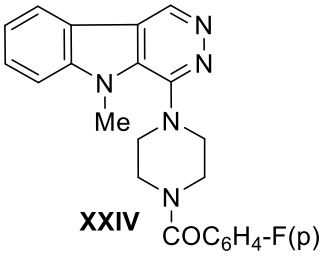
R = H



XXIII

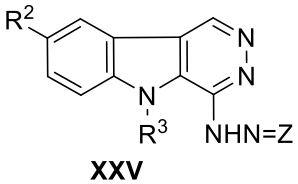
R = H, R^1= C_6H_5, $C_6H_5CH_2$

NRR^1 = piperidino, morpholino



XXIV

COC_6H_4-F(p)



XXV

R^3 = H, CH_3, R^2 = H, $C_6H_5CH_2O$

Z = H_2, alkylidene, CHC_6H_5,substituted benzylidene, $CCH_3C_6H_5$, etc.

3.3. The most common pharmacological importance of the pyridazino[4,5-*b*]indoles

3.3.1. Congestive heart failure[70] (CHF) is a clinical syndrome which occurs when the left ventricle is unable to provide an adequate output. It is an illness which affects millions of persons throughout the world and has a high death rate in spite of the efforts made in the therapeutic field over these past few years.[90] The traditional treatment of CHF has been based on the use of cardiac glycosides, diuretics, and vasodilators, either

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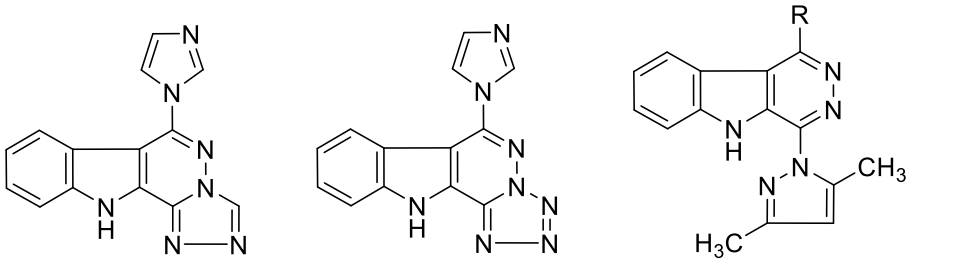
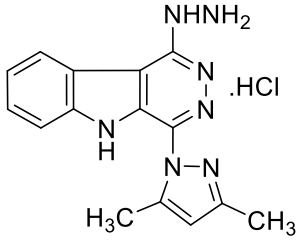
separately or in combination. However, the pronounced toxic effects and the narrow therapeutic index of cardiac glycosides[91] have promoted an extensive search for alternatives to the conventional therapy of this disease, especially for those cases in which conventional long-term treatment is not advisable, having reached a high degree of deterioration or hemodynamic instability, such as in the case of patients with severe CHF requiring a more aggressive therapy, usually intravenous administration of therapeutic agents.[92] Several new positive inotropic agents[52] are being developed for the clinical treatment of CHF. Some of these are selective inhibitors of the adenosine 3′,5-cyclic phosphate phosphodiesterase (cAMP-PDE-IV), present in the cardiac muscle. A second generation of cardiotonics is emerging with compounds that possess a good balance of inotropic and vasodilator activity as well as additional actions that will retard or even reverse the progression of the disease and prolong the life of the congestive heart failure patients. It was described[52] that some new compounds related to the pyridazino[4,5-*b*]indole structure such as compounds **116**, **117**, and **122** possess inotropic and vasodilatory activity and are of interest in the context of CHF.



116 **117** **122,** R = substituted amines

3.3.2. Arterial hypertension is a high prevalence health problem in industrialized countries, despite the vast number of antihypertensive drugs available. It was reported[93] that the 1-hydrazino-4-(3,5-dimethyl-1-pyrazolyl)pyridazino[4,5-*b*]indole **124** (A80a), a new structural analog of the well-known antihypertensive agent, *hydralazine*, shows antihypertensive activity in spontaneously hypertensive rats (SHR) and hypotensive activity in normotensive rats. The presence of antihypertensive activity may be due to a vasodilating effect which is mediated, in part, through interference with mobilization of intracellular calcium.



124 (A80a, CAS 135561-93-2)

Some pyridazino[4,5-*b*]indoles act as monoamine oxidase inhibitors, 3,4-dihydro-5-methyl-3-ethyl-4-oxopyridazino[4,5-*b*]indole **XXVI** and 1,2-dihydro-1-phenyl-4-acetoxy-5-methyl-pyridazino[4,5-*b*]indole **XXVII** were found to be the best inhibitors in this series.[94] Moreover, the 1,2,3,4-tetrahydro-1-aryl-4-oxo-5-methyl-8-ethoxypyridazino[4,5-*b*]indoles **XXVIII** were tested for inhibitory activity against calf liver mitochondrial monoamine oxidase *in vitro*.[95]

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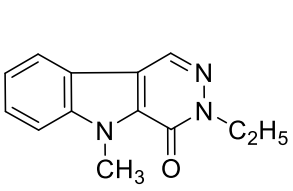
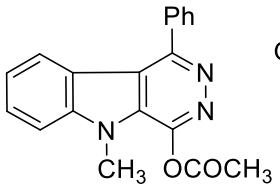
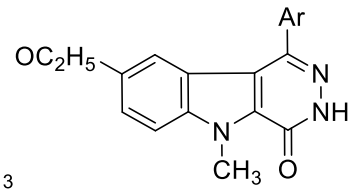


XXVI

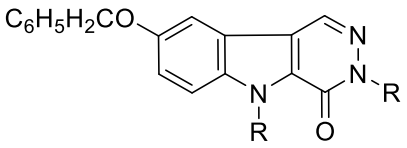


XXVII

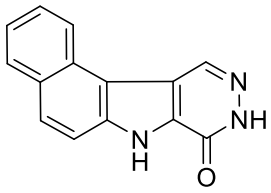


XXVIII, Ar = C_6H_5, 4-OHC_6H_4

8-Alkoxy- and 8,9-benzo-3*H*-pyridazino[4,5-*b*]indol-4-one derivatives **XXIX** and **XXX** were synthesized as *serotonin* antagonists.[11] The 3,5-disubstituted pyridazino[4,5-*b*]indole **XXIX** showed antiinflammatory[12] and antihistaminic activity.[12]

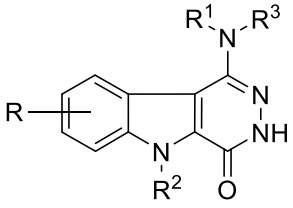


XXIX



XXX

3.3.3. Human Immune deficiency Virus (*HIV-1*) pyridazino[4,5-*b*]indole derivatives[14] were reported as inhibitors of HIV-1 reverse transcriptase (RT), the activity of these compounds as inhibitors of different types of *HIV-1* RT (wild type enzyme and mutant forms P236L, Y 181C and P236L/Y181C) was evaluated. The activity of the most active compounds was investigated in the syncytia reduction in vitro assay, in *HIV-1*$_{IIIB}$-infected HT41acZ-1 cells.[14] Within the wide range of the therapeutic targets involved in the understanding of the replication cycle of the *HIV-1* virus, the design of new nonnucleoside reverse transcriptase enzyme inhibitors continues to be an objective of great interest, especially if the problems of toxicity and resistance to the utilization of the anti-retrovirals are taken into account.[97-99] In an attempt to obtain new compounds that act as inhibitors of *HIV-1* reverse transcriptase *(HIV-1 RT)*, compounds with the general structure of the pyridazino[4,5-*b*]indoles **XXXI-XXXVI** have been described.[14]



XXXI, XXXII, R = H,-O-CH_2-O- , R^1, R^3= substituted amines
XXXIII, R^2 = H
XXXVI, R^2 = CH_3

3.3.4. Vasodilators[100] are another group of antihypertensive drugs which include compounds acting directly on the vascular smooth muscle, causing vasodilation and thus lowering blood pressure. The cellular mechanism of their action is not fully understood, though their hemodynamic and clinical effects are clear. Examples of this class of drugs include diazoxide, minoxidil, hydralazine and dihydralazine. Some pyridazino[4,5-*b*]indoles have a vasodilating effect,[101,102] The new pyridazino[4,5-*b*]indole[101] **XXXVII** (DF-100) is related to the well-known antihypertensive drug, dihydralazine. The inhibitory effects of DF-100 were investigated on the contractions in isolated aorta and portal vein. In rat aorta, DF-100 inhibited both K^+-induced and norepinephrine-induced contraction. DF-100 caused dose-independent relaxation of contractions produced by 80 mM K^+. Moreover, DF-100 significantly inhibited the $CaCl_2$ dose response in high K^+ depolarizing medium. DF-100 inhibited the

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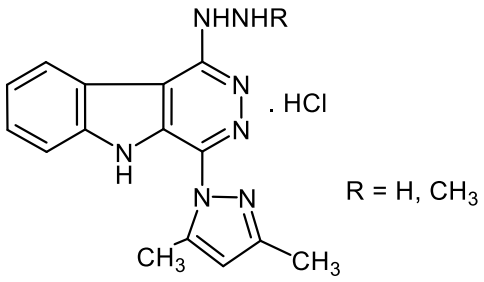
phasic contractile response to norepinephrine and the caffeine-induced response. In rat aortal vein, DF-100 inhibited the spontaneous rhythmic contractions. Also 1-methylhydrazinopyridazino[4,5-*b*]indole derivative showed potent and long lasting antihypertensive activity in spontaneous hypertensive rats (SHR),[102] the decrease in diastolic pressure was greater than the decrease in systolic pressure and cardiac frequency was not modified significantly. These results suggested that 1-methyhydrazinopyridazino[4,5-*b*]indoles are a new chemical entity which exerts a hypotensive and antihypertensive activity, possibly attributable to vasodilator activity via interference with Ca^{2+} influx and release from intracellular stores.



XXXVII (DF-100)

Pyridazino[4,5-*b*]indoles[70] gained some pharmaceutical attention, because of their *in vitro* activity as inhibitors of different phosphodiesterases isolated from dog cardiac tissue, dog aorta, and bovine platelets; the study of their activity as inhibitors of platelet aggregation was carried out with guinea pig whole blood, with ADP and arachidonic acid (AA) as pro-aggregants. Likewise compounds **20** and **24** have been studied as inhibitors of phosphodiesterases and inhibitors of platelet aggregation, and were found to be potent inodilators, with a complementary beneficial activity as inhibitors of aggregation, activities which could possibly be related to the inhibitors of PDEs and they showed cardiotonic activity.[65] Some pyridazino[4,5-*b*] indoles[52] (compounds **116, 117, 122**) showed potent inhibitory activity towards different PDEs isolated from dog heart, vasodilator activity by inhibition of different isoenzymes isolated from dog aorta and platelet antiaggregatory properties, by determining the values of inhibition of PDE isolated from human platelets and by studying their activity as inhibitors of platelet aggregation induced by adenosine diphosphate (ADP) and arachidonic acid (AA)) in guinea pig whole blood.

Conclusions

Pyridazino[4,5-*b*]indoles are structurally interesting molecules having several biological applications and play an important role in medicinal chemistry. For these reasons and in continuation to my previous work on the synthetic strategies of pyridazino[4,5-*b*]indoles which was reported recently,[33] I decided herein to do comprehensive study of its interactions and their importance in all aspects. In this review I discussed the different types of reactions used and its conditions, likewise thionation, alkylation, addition, Michael addition, (4+2) cycloaddition acetylation, chlorination of pyridazinoindoles, nucleophilic substitution reaction (S_N2), reactions of chloropyridazinoindoles, amidation of diesters, reactions of 1-hydrazino pyridazino[4,5-*b*]indoles, formation of triazo-and tetrazolopyridazino[4,5-*b*]indoles and nitration in addition to the comprehensive survey on the biological importance of these class of compounds.

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