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

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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 occurring 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.
1. Introduction

Among the compounds containing multiple nitrogen atoms, whose importance in the field of medicinal chemistry and smart materials is well known,\textsuperscript{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,\textsuperscript{3} a novel structural skeleton of 1H-pyridazino[4,5-b]indol-4(5H)-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.\textsuperscript{4-14} Moreover, various 5H-pyridazino[4,5-b]indole derivatives show promising in-vitro inhibitory activities against PI3Ka, significant anti-proliferative effects in various cell types\textsuperscript{15,16} and antimicrobial activity.\textsuperscript{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.\textsuperscript{18} Furthermore, the title ring system became interesting in the context of an ongoing program.
in search of new and selective inhibitors of copper-containing amine oxidases.\textsuperscript{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,\textsuperscript{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-6H-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.\textsuperscript{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-methylcellitin (elliptinium),\textsuperscript{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.\textsuperscript{26} Typical representatives of this type of ellipticine analogs are the drug candidates retelliptine\textsuperscript{26} and pazelliptine.\textsuperscript{27,28} Several new representatives of this ring system (3-azaellipticines) of type 4a were described by Haider et al.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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,\textsuperscript{33} I will report herein its reactions and biological importance.

![Figure 1. Some biologically active compounds.](image-url)
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.\(^{34-37}\)

![Scheme 1. Thionation of pyridazino[4,5-b]indol-4-one derivatives 6.](image)

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)-5H-pyridazino[4,5-b]indole derivatives 9.

![Scheme 2. Alkylation of 3,5-dihydro-4H-pyridazino[4,5-b]indole-4-thione 7.](image)

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.

Similarly, alklylation of 6 \((R^1 = R = H)\) with a set of alkylation 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-pyridazo[4,5-b]indol-3-
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(4H)-one 22 by the action of hydrazine hydrate (Scheme 5).

![Scheme 5](image)


Alkylation of 20 (R¹ = PhCH₂O, R = H) with aryl, phenylalkyl, or (dialkylamino)alkyl halides in the presence of sodium carbonate gave the 3,5-disubstituted derivatives 23.¹¹,¹²

![Scheme 6](image)

**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](image)

**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-1H-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
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-1H-pyrazino[4,5-b]indol-1-one 25.](image)

Also, 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 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-1H-pyrazino[4,5-b]indol-1-one 25 with epichlorohydrin.](image)
The regioselective\textsuperscript{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 regioselectively with sodium azide in aqueous dioxane analogously to a known procedure.\textsuperscript{42}

\begin{center}
\textbf{Scheme 10.} Ring opening of 30 with various nitrogen nucleophiles.
\end{center}

In continuation to previous work,\textsuperscript{41} El-Kashef et al\textsuperscript{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).

\begin{center}
\textbf{Scheme 11.} Interaction of pyridazinone 36 with 2-diethylaminoethyl chloride hydrochloride.
\end{center}
2.3 Addition

2.3.1. Michael addition. Sarhan et al.\(^3\) announced that, the Michael addition of nucleophile 20 (R\(^1\) = H, R = H) to acrylonitrile as the Michael acceptor in ethanol containing Et\(_3\)N yielded the Michael adduct 39 in excellent yield (Scheme 12).

![Scheme 12. Michael addition of nucleophile 20.](image)

2.4 Acetylation

Acetylation of pyridazino[4,5-b]indoles 40 (R = CH\(_3\), R\(^1\) = C\(_6\)H\(_5\)) 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.\(^4\) 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.](image)

2.5 Chlorination of pyridazinoindoles

2.5.1. Nucleophilic substitution reaction (S\(_{N2}\)). In 2015, treatment\(^1\) 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-5H-pyridazino[4,5-b]indoles 48,\(^4\) which underwent a nucleophilic substitution with furfuryl mercaptan to give the desired intermediates 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).
**Scheme 16.** Synthesis of compound 52 and sulfoxides 53.

The pyridazinones $20^{36,49,50}$ were subjected to chlorination with $\text{POCl}_3$ to obtain the corresponding 4-chloro-$5H$-pyridazino[4,5-$b$]indoles 54 which on reaction with hydrazine hydrate in the presence of $\text{K}_2\text{CO}_3$ 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 $\text{POCl}_3$.

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 $\text{POCl}_3$ 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 $\text{POCl}_3$ furnished the chloro derivatives 61-63.
Scheme 18. Synthesis of the 1,4-dichloro-5H-pyridazino[4,5-b]indole 56.


2.6 Reactions of chloropyridazinoindoles
It was described that 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, 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).
Scheme 20. Reactions of chloro compound 61 with some nitrogen nucleophiles.

Also, hydrazinolysis\(^{\text{41}}\) 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.
It was reported that\textsuperscript{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\textsuperscript{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.
In 2008, Haider et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{25,26} The final hydrolysis step, affording the new pyridazinone 85, succeeded by heating the chloropyridazine 84 in acetic acid.\textsuperscript{27}

El-Kashef et al\textsuperscript{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\textsuperscript{20} by catalytic hydrogenation of 62. The same result was obtained when the thione 76\textsuperscript{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).


The mechanism was suggested by the authors, 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).
Scheme 27. The suggested mechanism of catalytic hydrogenation of 62.

In 2008, El-Gendy et al.\(^{57}\) found that the 4-Chloro-substituted-5H-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-5H-pyridazino[4,5-b]indoles 92 and 93. Mannich condensation\(^{58}\) of 5-chloro-3H-pyridazino[4,5-b]indol-4(5H)-one 89 with 4-ethylpiperazine and formaldehyde in ethanol gave 8-chloro-3-((4-ethylpiperazin-1-yl)methyl)-3H-pyridazino[4,5-b]indol-4(5H)-one 94.


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.
Reaction of the chloro derivative 56 with amines (imidazole, aniline and morpholine) gave the disubstituted derivatives 97, while reaction with 90% hydrazine hydrate furnished 1-chloro-4-hydrazino-5H-pyridazino[4,5-b]indole 98. The chlorine atom was easily removed by reduction with NaBH₄ and compound 99 was obtained.

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

2.7 Amidation of diesters

It was reported 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 5H-pyridazino[4,5-b]indole-1,4-dicarboxylate 100 with 4 equivalents some amines in presence of MgCl₂ 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-dimethylethylene diamine was used.

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

Various attemptes were done to remove the carbomethoxy group from compound 101. These dealkoxycarbonylations were successfully performed by refluxing the appropriate compound 101 in DMF with
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.\(^{57}\)

\[
\text{CO}_2\text{Me} \quad \text{LiI, DMF, reflux.} \rightarrow \quad \text{CO}_2\text{Me}
\]

\[
\begin{array}{c}
\text{101} \\
\text{RR}_1 = (\text{CH}_2)_4
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{103}
\end{array}
\]

**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.

\[
\text{CO}_2\text{Me} \quad \text{R'} \quad \text{AlMe}_3 \rightarrow \quad \text{CO}_2\text{Me}
\]

\[
\begin{array}{c}
\text{100a-c} \\
a, \text{R'} = \text{Ts} \\
b, \text{R'} = \text{Bn} \\
c, \text{R'} = \text{SO}_2\text{Ph}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{104a-c} \\
a, \text{R'} = \text{Ts} \quad \text{R} = \text{CH}_3 \quad 90\% \\
b, \text{R'} = \text{Bn} \quad \text{R} = \text{CH}_3 \quad 73\% \\
c, \text{R'} = \text{SO}_2\text{Ph} \quad \text{R} = \text{H} \quad 93\%
\end{array}
\]

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

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

2.8.1. Formation of triazo-lo-and tetrazolo pyridazino[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).

\[
\text{105} \quad \text{Br} \quad \text{H}_3\text{C} \quad \text{Br} \quad \text{H}_3\text{C} \quad \text{Br} \quad \text{H}_3\text{C}
\]

\[
\text{105} \quad \text{HCl/MeOH, Reflux} \rightarrow \quad \text{106}
\]

**Scheme 34.** Reaction of 1,2,4-triazole-3-thione 105 with 4’-bromoacetophenone.
In 2004, it was reported\(^\text{21}\) 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.](image)

Also, the same author mentioned that\(^\text{21}\) 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.

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-11H-1,2,4-triazolo[3,4-c] pyridazino[4,5-b]indole 112.53

Scheme 37. Synthesis of 3-carbazoyl-6-hydrazino-11H-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 NaNO2/HCl gave the corresponding pyrazolo, triazolo, and tetrazolo derivatives 113-11560,64 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
Scheme 38. Synthesis of pyrazolo, triazolo, and tetrazolo derivatives 113-115.

It was reported that, 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. Reaction of the chloro derivative 113 with hydrazine hydrate or methyl hydrazine afforded the hydrazino derivatives 123.
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. 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. 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.

Scheme 41. Reactions of 4-(3,5-dimethyl-1H-pyrazol-1-yl)-1-hydrazineyl-5H-pyridazino[4,5-b]indole 123 with some reagents.
Interaction\textsuperscript{35,49,66} of hydrazino derivatives 8 with formic acid, acetic acid,\textsuperscript{34} benzoyl chloride, or nitrous acid yielded triazolo and tetrazolo derivatives 127 or 128, respectively, while treatment\textsuperscript{35,67} of 8 with aldehydes and ketones gave the hydrazones 129 (Scheme 42).

![Scheme 42. Reactions of hydrazino derivatives 8.](image)

Hiremath \textit{et al.}\textsuperscript{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-\textit{b}]indoles 130.](image)

Reaction of hydrazino derivative\textsuperscript{70} 8 (R\textsuperscript{1}= OCH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}, R =H) with acetyl acetone or acetyl acetone furnished the corresponding pyridazinoindole derivatives 131, 132, respectively.
Scheme 44. Reaction of hydrazino derivative 8 with 1,3- and 1,4-diketones.

Monge et al.\textsuperscript{68} described that 4-hydrazino-7,8-dimethoxy-5H-pyridazino[4,5-b]indole 8 (R\textsuperscript{1} = R\textsuperscript{2} = OCH\textsubscript{3}, R= H) was prepared analogously to a previously reported method\textsuperscript{35} by reaction of ethyl-5,6-dimethoxy-2-indolecarboxylate via formylation and hydrazinolysis to give the pyridazinindolone which underwent thionation with P\textsubscript{2}S\textsubscript{5} and subsequent hydrazinolysis to give the hydrazino derivative 8, which upon reaction\textsuperscript{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,\textsuperscript{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,\textsuperscript{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.\textsuperscript{55}

Treatment\(^\text{14}\) 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.\(^\text{14}\)

Scheme 47. Reactions of 1-amino-3,5-dihydro-4\(H\)-pyridazino[4,5-b]indol-4-ones with aldehydes and chloroacetyl chloride 139.
2.9 [4+2] cycloaddition process

Reaction\textsuperscript{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.\textsuperscript{71}

![Scheme 48. [4+2] cycloaddition reaction of pyridazine 143.](image)

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.\textsuperscript{72} the methyl ester 147 in 70% yield.\textsuperscript{71}

![Scheme 49. [4+2] cycloaddition reaction of pyridazine 143 with the acyclic enamine.](image)

2.10 Nitration

Nitration of the pyridazino[4,5-b]indole 148 in a mixture of H\textsubscript{2}SO\textsubscript{4} and HNO\textsubscript{3} gave the 8-nitro derivative 149 which was reduced to amino derivative 150.\textsuperscript{73}
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.\textsuperscript{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\textsuperscript{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 \( \mu \)g/mL) against *Bacillus subtilis*, which was the most sensitive microorganism to the tested compounds.

3.2. Pharmacological activity

Recently, it was reported that,\textsuperscript{3} the 1H-pyridazino[4,5-b]indol-4(5H)-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.\textsuperscript{3} Furthermore, it was found that,\textsuperscript{37} 4-(alkylthio)-5H-pyridazino[4,5-b]indole derivatives 9 exhibited the most promising cytotoxicity toward MCF-7 cells with an IC50 value of 12 \( \mu \)M. 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
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.

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

It was mentioned that, the synthesis of 8-methoxy-1-methyl-3,5-dihydro-4H-pyridazino[4,5-b]indol-4-one I and pyridazin-3(2H)-one analogs as DYRK1A inhibitors and potent pyridazinindole ligand for PET imaging of TSPO in cancer 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-4H-pyridazino[4,5-b]indole-1-acetamide II (SSR180575) as a promising probe for molecular imaging of glioma.

A series 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 the 7-chloro-N,N-dimethyl-5-[11C]methyl-4-oxo-3-phenyl-3,5-dihydro-4H-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.
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 \(\text{V}\) act as platelet aggregation inhibitors and/or antihypertensives. The 1,2,3,4-tetrazolopyridazino[4,5-b]indoles \(\text{VI}\) are known to be of interest as drugs.\(^ {70}\)

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 TBX\(_2\). 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 \(\text{VII, VIII}\) have blood platelet aggregation-inhibiting activity and particularly inhibit arachidonic acid induced platelet aggregation.

\(\text{V, R = H, alkyl, alkoxy, aryloxy, OH, aryl} \)
\(\text{R}^1 = \text{H, NH}_2, \text{NR}^1\text{R}^2 = \text{N, O, N} \)
\(\text{R}^2 = \text{Ph, H} \)
\(\text{R}^3 = \text{H, alkyl, acyl, aryl.} \)

\(\text{VI, R = OCH}_3 \)
\(\text{R}^3 = \text{H} \)

\(\text{VII R = H, CH}_3 \)
\(\text{R}^1 = \text{H, CH}_3, \text{C}_6\text{H}_5, \text{p-Cl-C}_6\text{H}_4 \)

\(\text{VIII R = H, CH}_3 \)
\(\text{R}^1 = \text{Cl, H, N}_3, \text{NHNH}_2, \text{piperidino, etc. } \)
\(\text{X = CH, CCH}_3, \text{CC}_6\text{H}_5, \text{N} \)
Pharmacological studies in vitro using human blood and in vivo in rats and guinea pigs were done by Monge et al., 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-hydrazinopyridazino[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 TXB2.

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 [R1R7 = O; R2 = R5 = R6 = R8 = H; R3 = Ac; R4 = CH3(CH2)8] was also tested ex vivo against guinea pig platelets.

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

Furthermore, the 3,4-dihydro-4-oxo-5H-pyridazino[4,5-b]indole XIV and 3,4-dihydro-4-oxo-8-benzyloxy-5H-pyridazino[4,5-b]indole XV inhibited ADP-, arachidonate-, and PGH2- induced platelet aggregation. The 1-hydroxy derivative XVI, 8-hydroxy derivative XVII and the 1-methyl derivative XVIII inhibited only ADP-induced aggregation.
It was reported that the pyridazino[4,5-b]indole derivatives XIX act as platelet aggregation inhibitors or antihypertensives. Furthermore, the 11H-1,2,4-triazolo[4’,3’:2,3]pyridazino[4,5-b]indoles XX and 11H-1,2,3,4-tetrazolo[4’,3’:2,3]-pyridazino[4,5-b]indoles XXI are useful as antihypertensives. Also the 4-hydrazino-5H-pyridazino[4,5-b]indoles XXII and XXIII exhibited antihypertensive activity (also in dogs), while the pyridazino[4,5-b]indoles XXIV act as antihypertensives and antiarrhythmics. A series of 4-hydrazino-5H-pyridazino[4,5-b]indoles XXII and their potential metabolites, 3,4-dihydro-4-oxo-5H-pyridazino[4,5-b]indoles, 1-oxopyridazino[4,5-b]indole derivatives and 11H-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.

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

3.3.1. Congestive heart failure (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. The traditional treatment of CHF has been based on the use of cardiac glycosides, diuretics, and vasodilators, either
separately or in combination. However, the pronounced toxic effects and the narrow therapeutic index of cardiac glycosides\textsuperscript{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.\textsuperscript{92} Several new positive inotropic agents\textsuperscript{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\textsuperscript{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.

![Chemical structures](image)

\[116, \quad 117, \quad 122, \text{R = substituted amines}\]

\[3.3.2. \text{Arterial hypertension}\] is a high prevalence health problem in industrialized countries, despite the vast number of antihypertensive drugs available. It was reported\textsuperscript{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.

![Chemical structure](image)

\[124 \quad \text{(A80a, CAS 135561-93-2)}\]

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-acetoxo-5-methyl-pyridazino[4,5-b]indole XXVII were found to be the best inhibitors in this series.\textsuperscript{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 \textit{in vitro}.\textsuperscript{95}
8-Alkoxy- and 8,9-benzo-3H-pyrazidino[4,5-b]indol-4-one derivatives XXIX and XXX were synthesized as serotonin antagonists.\textsuperscript{11} The 3,5-disubstituted pyrazidino[4,5-b]indole XXIX showed antiinflammatory\textsuperscript{12} and antihistaminic activity.\textsuperscript{12}

3.3.3. Human Immune deficiency Virus (HIV-1) pyrazidino[4,5-b]indole derivatives\textsuperscript{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\textsubscript{HIV}-infected HT41acZ-1 cells.\textsuperscript{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.\textsuperscript{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 pyrazidino[4,5-b]indoles XXXI-XXXVI have been described.\textsuperscript{14}

3.3.4. Vasodilators\textsuperscript{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 pyrazidino[4,5-b]indoles have a vasodilating effect.\textsuperscript{101,102} The new pyrazidino[4,5-b]indole\textsuperscript{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\textsuperscript+-induced and norepinephrine-induced contraction. DF-100 caused dose-independent relaxation of contractions produced by 80 mM K\textsuperscript{+}. Moreover, DF-100 significantly inhibited the CaCl\textsubscript{2} dose response in high K\textsuperscript{+} depolarizing medium. DF-100 inhibited the
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), 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-methylhydrazinopyridazino[4,5-b]indoles are a new chemical entity which exerts a hypotensive and antihypertensive activity, possibly attributable to vasodilator activity via interference with Ca²⁺ influx and release from intracellular stores.

Pyridazino[4,5-b]indoles 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. Some pyridazino[4,5-b] indoles (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, 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.
References

   https://doi.org/10.1039/D0RA01378A

   https://doi.org/10.3390/molecules25081909

   https://doi.org/10.1016/j.antiviral.2023.105607

   https://doi.org/10.1016/j.arabjc.2022.103756

   https://doi.org/10.3390/cryst13071036

   https://doi.org/10.1016/0223-5234(91)90202-X


   https://doi.org/10.1002/adsc.202101401

   https://doi.org/10.1002/chin.198747233

    https://doi.org/10.1002/chin.198033236


   https://doi.org/10.1016/0223-5234(95)88316-4

   https://doi.org/10.1016/j.ejmech.2012.09.001

   https://doi.org/10.1016/j.cclet.2007.07.027

   http://doi.org/10.3906/kim-1210-22

   https://doi.org/10.1007/s00044-015-1473-y
https://doi.org/10.2174/0929867043365305

https://doi.org/10.3998/ark.5550190.0004.e19

https://doi.org/10.3390/91000849

https://doi.org/10.3998/ark.5550190.0009.703

https://doi.org/10.1016/S0099-9598(08)60169-8

https://doi.org/10.1517/13543776.6.12.1285

https://doi.org/10.1016/0014-2964(78)90180-9

https://doi.org/10.1021/jm00185a012

https://doi.org/10.1039/P197900001706

https://doi.org/10.1021/jc00389a012

https://doi.org/10.3987/COM-98-8217

https://doi.org/10.3987/com-99-8695

https://doi.org/10.1126/science.162.3858.1086

https://doi.org/10.1039/p199100002757

https://doi.org/10.24820/ark.5550190.p011.949

https://doi.org/10.1021/jp100711222

https://doi.org/10.1021/jm00389a012

https://doi.org/10.1021/jp100711222

https://doi.org/10.3390/cryst12030353

https://doi.org/10.1039/d0ra02798g.
   https://doi.org/10.1055-s-2002-35569
   https://doi.org/10.1186/s13065-020-00682-6
   https://doi.org/10.1016/S0040-4039(01)01678-1
   https://doi.org/10.1016/0223-5234(91)90202-X
   https://doi.org/10.1002/jps.2600820519
   https://doi.org/10.1002/chin.198919225
   https://doi.org/10.1016/0223-5234(88)90098-0
   https://doi.org/10.1002/ardp.19953281002
   https://doi.org/10.3987/com-94-6726
   https://doi.org/10.1002/jhet.5570280430
   https://doi.org/10.1007/bf00945606
   https://doi.org/10.1016/j.bmcl.2014.09.017
   http://dx.doi.org/10.1016/j.bmcl.2014.07.091
   http://dx.doi.org/10.1007/s00259-010-1628-5


90. Smith, W. M., Am. J. Cardiol., 1985, 55, 3A.


https://doi.org/10.1002/jps.2600700533

https://doi.org/10.1016/0014-2999(92)90482-j


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