A Platinum Open Access Journal for Organic Chemistry

Review

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2023** (i) 202211949

Synthetic strategies of pyridazino[4,5-b]indoles

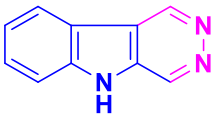
Abdel-Rahman A. H. Farghaly

Department of Chemistry, Faculty of Science, Jazan University, Jazan- Saudi Arabia
Email: farghaly431@gmail.com

Received 12-18-2022 **Accepted** 01-31-2023 **Published on line** 03-08-2023

Abstract

Pyridazino[4,5-*b*]indole is an important class of heterocyclic compounds with numerous applications in the field of medicinal chemistry. This review summarizes the synthetic methods of pyridazino[4,5-*b*]indoles published during the period from 1962 to 2022. In this review, we have discussed different methods for the synthesis of pyridazino[4,5-*b*]indole from various starting materials and the difficulties that scientists faced during the preparation process. We focus on the recent developments in synthetic methods of the pyridazino [4,5-*b*]indoles.

Pyridazino[4,5-*b*]indoles	Biological importance of pyridazino[4,5-*b*]indoles
 • Pyridazino[4,5-*b*]indole ring system has been known for several decades and various biological activity has been reported for a large number of its derivatives.	✓ As anxiolytic ✓ *As* antihypertensive ✓ As thromboxane A2 synthetase inhibitors ✓ As antihistaminic ✓ As *HIV-1* reverse transcriptase inhibitors ✓ As antiarrhythmics ✓ As phosphatidylinositol 3-kinase (PI3K) inhibitors ✓ As blood platelet aggregation inhibitors

Keywords: Pyridazino[4,5-*b*]indole, synthetic methods, Vilsmeier's reaction, hydrazinolysis

Table of Contents

1. Introduction

Pyridazino[4,5-*b*]indole's nucleus contains two heterocyclic cores that interact with many receptors and are important to biological and metabolic processes within the body.[1–4] Because of their bioisosterism with γ- and β-carboline, these two heterocyclic compounds have a wide range of uses in medicinal chemistry.

Pyridazino[4,5-*b*]indole derivatives have therapeutic effects as they act as thromboxane A2 synthetase inhibitors,[5] phosphatidylinositol 3-kinase (PI3K) inhibitors,[6] and they have antimicrobial and antiproliferative effects in different cell types.[7] Also, they have inhibitory effects against cancer cells such as human neuroblastoma IMR-32 cell lines (Figure 1), hepatocellular carcinoma Huh-7, human primary glioblastoma U-87, prostate carcinoma PC3, colorectal adenocarcinoma Caco2, breast cancer cells MDA-MB-231, colorectal carcinoma HCT-116, one normal cell line (fibroblasts), lung carcinoid NCI-H727, and MCF 7; additionally, they inhibit enzymes in cancer cells.[8–12] Moreover, pyridazino[4,5-b]indole derivatives provide powerful therapeutic effects for different diseases related to acute and chronic inflammation,[13] neuroinflammation, and neoplastic progression.[14]

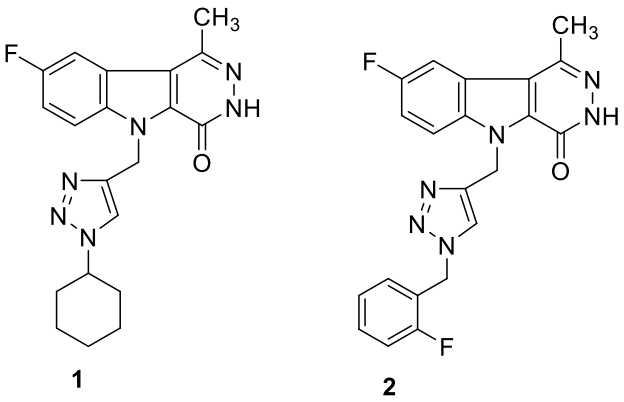


Figure 1. Bioactive pyridazino[4,5-*b*]indole derivatives.

Pyridazino[4,5-*b*]indole-derived drug molecules have been used in the treatment of a number of diseases such as *neurological disorders,*[15] *congestive heart failure (CHF),*[16] *human immune deficiency virus (HIV-1),*[17] *arterial hypertension*[18] for many years and can be regarded as interesting compounds from a pharmaceutical point of view. Nevertheless, as with other classes of pharmaceutically used compounds, there is continuing interest in the systematic variation of the chemical structure of such agents in order to investigate the possibility of further optimization of their pharmacological and pharmacokinetic profiles as well as discovering new uses. For instance, 1-hydrazino-4-(3,5-dimethyl-1-pyrazolyl)pyridazino[4,5-*b*]indole (A80a) can be used for treatment of *hypertension* as a new structural analog of the well-known antihypertensive agents, dihydralazine (Nepresol®),[19] and hydralazine (Apresoline®).[20]

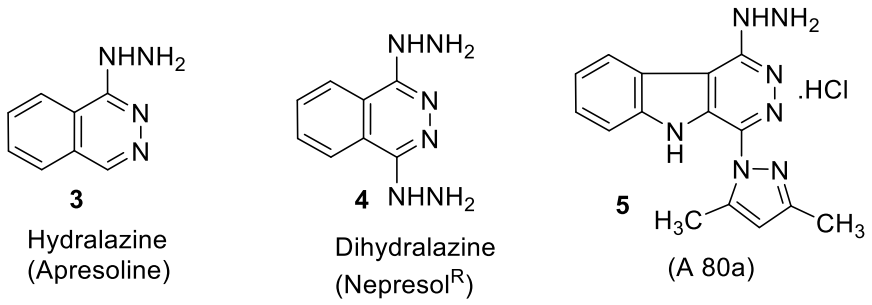


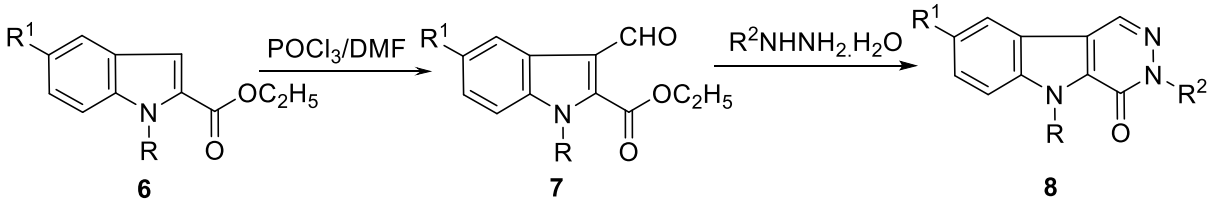
Figure 2. Some well-known antihypertensive agents.

2. Synthesis of Pyridazino[4,5-*b*]indoles

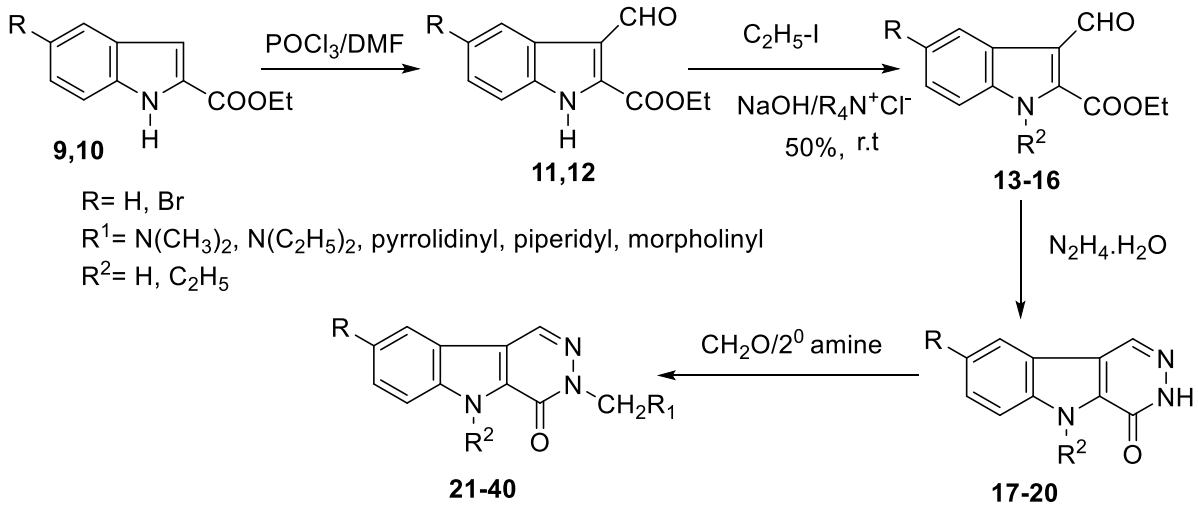
2.1. From ethyl indole-2-carboxylates. It was reported[21,22] that the ethyl indole-2-carboxylates **6**[12,23-25] were treated with DMF and $POCl_3$ according to Vilsmeier's reaction, affording **7**[12,23,25,26] in high yield. Reaction of **7** with hydrazine hydrate and/or substituted hydrazines in ethanol under reflux gives pyridazino[4,5-*b*] indol-4-ones **8**[12,23,26,27] (Scheme 1).

El-Gendy *et al.* found that,[28] formylation of compounds **9** and **10** with $POCl_3$ in DMF in a similar way described previously (James and Synder 1959) giving 2-ethoxycarbonyl-3-formylindole **11, 12**. Alkylation of the latter compounds with ethyl iodide by phase–transfer catalysis (Barco et al., 1976), using benzyltriethylammonium chloride as catalyst and 50% of NaOH in benzene gave the corresponding 2-

ethoxycarbonyl-1-ethyl-3-formylindoles **13,14**. Heating of **13-16** with hydrazine hydrate under reflux gave 5*H*-pyridazino[4,5-*b*]indoles **17-20.** Reaction of **17-20** with formalin and appropriate secondary amines by heating under reflux in ethanol containing drops of acetic acid gave the Mannich bases **21-40** (Scheme 2).



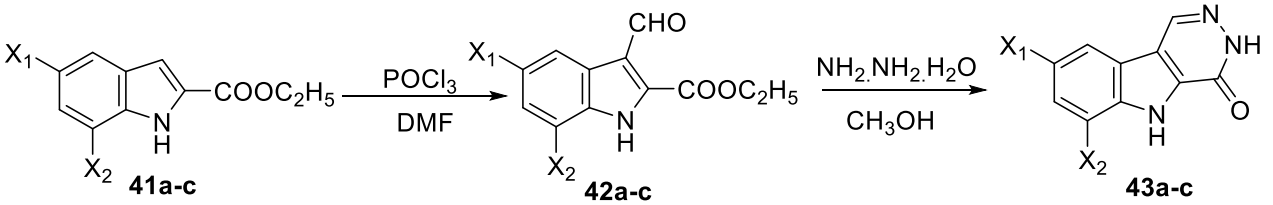
Scheme 1. Synthesis of pyridazino[4,5-*b*]indol-4-ones **8**.



Compd. No.	R	R^1	R^2	Compd. No.	R	R^1	R^2
21	H	$N(CH_3)_2$	H	**31**	Br	$N(CH_3)_2$	Et
22	H	$N(CH_2CH_3)_2$	H	**32**	Br	$N(CH_2CH_3)_2$	Et
23	H	pyrrolidinyl	H	**33**	Br	pyrrolidinyl	Et
24	H	piperidyl	H	**34**	Br	piperidyl	Et
25	H	morpholinyl	H	**35**	Br	morpholinyl	Et
26	H	$N(CH_3)_2$	H	**36**	Br	$N(CH_3)_2$	Et
27	H	$N(CH_2CH_3)_2$	H	**37**	Br	$N(CH_2CH_3)_2$	Et
28	H	pyrrolidinyl	H	**38**	Br	pyrrolidinyl	Et
29	H	piperidyl	H	**39**	Br	piperidyl	Et
30	H	morpholinyl	H	**40**	Br	morpholinyl	Et

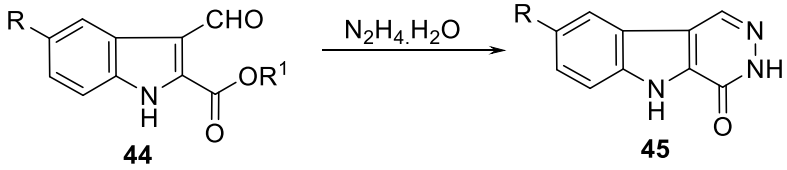
Scheme 2. Synthesis of Mannich bases **21-40**.

In continuation to the previous work,[29] El-Gendy *et al.* found that the reaction of compounds **41a-c** with $POCl_3$/DMF gave 3-formyl-substituted-1H-indole-2-carboxylic acid ethyl esters **42a-c**. The substituted-3H-pyridazino[4,5-*b*]indol-4(5H)-ones **43a-c** were prepared by boiling **10a-c** with hydrazine hydrate for six hours with 80% yield; under microwave irradiation, only 3 min were required to reach better yields (Scheme 3).



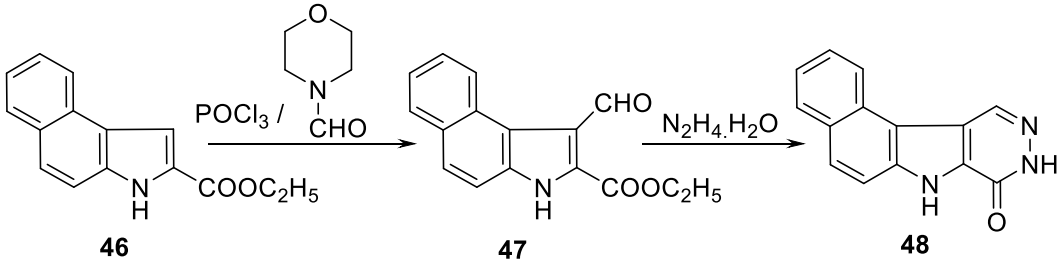
Scheme 3. Synthesis of substituted-3*H*-pyridazino[4,5-*b*]indol-4(5H)-ones **43a-c**.

Hiremath *et al.*[30] described that the 4-oxo-*5H*-pyridazino[4,5-*b*]indoles **45** were obtained from 3-formylindole-2-carboxylates **44** by reaction with hydrazine hydrate (Scheme 4).



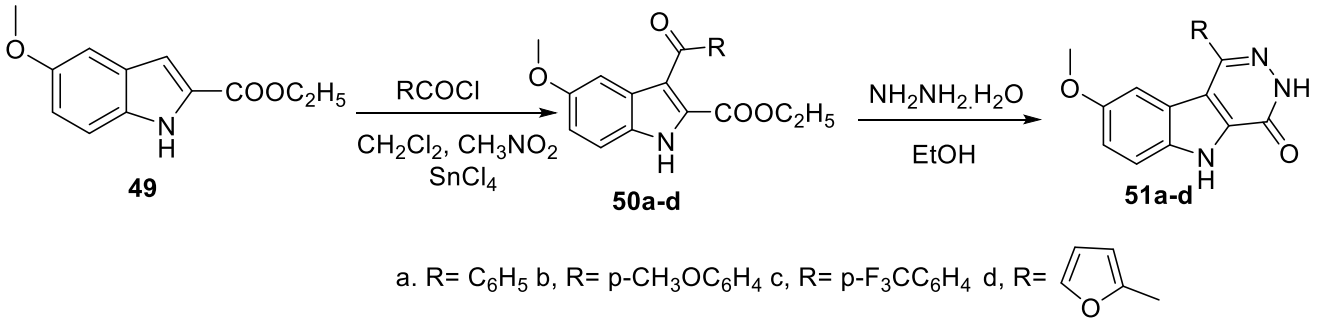
Scheme 4. Hydrazinolysis of 3-formylindole-2-carboxylates **44**.

Namirski *et al.*[31,32] found that reaction of ethyl-4,5-benzindole-2-carboxylate **46** with $POCl_3$ and *N*-formylmorpholine in dioxane gave ethyl 4,5-benzo-3-formylindole-2-carboxylate **47** which reacted with hydrazine hydrate in *N,N*-dimethylformamide (DMF) to give the corresponding 8,9-benzo-3*H*-pyridazino[4,5-*b*] indole **48** (Scheme 5).



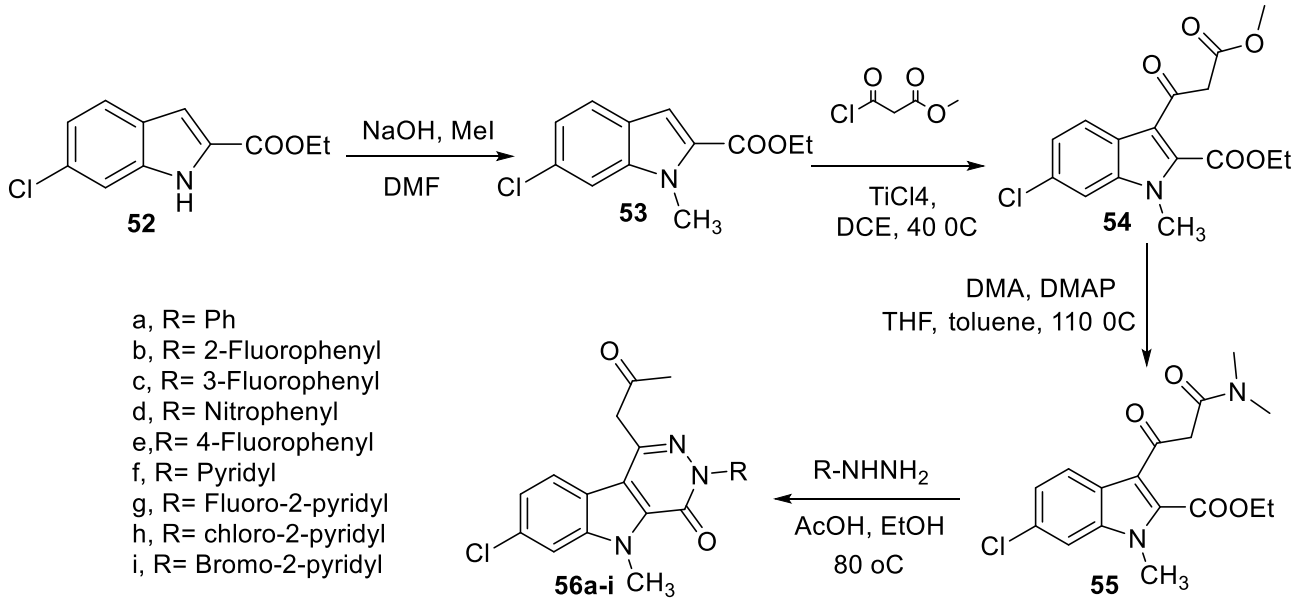
Scheme 5. Synthesis of 8,9-benzo-3*H*-pyridazino[4,5-*b*]indole **58**.

In 2014, it was reported that,[33] the Friedel–Crafts acylation of the ethyl 5-methoxy-*1H*-indole-2-carboxylate **49** with a wide variety of acid chlorides in the presence of tin(IV) chloride in methylene chloride-nitromethane gave the corresponding indole derivatives **50a-d** which were cyclized with hydrazine hydrate in ethanolic solution to afford the expected pyridazino[4,5-*b*]indol-4-ones **51a-d** (Scheme 6).



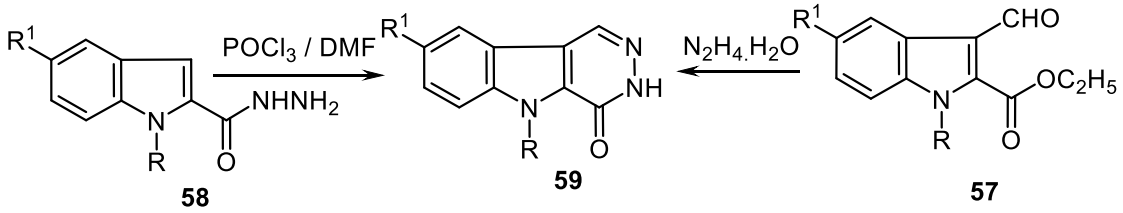
Scheme 6. Friedel–Crafts acylation of the ethyl 5-methoxy-*1H*-indole-2-carboxylate **51.**

Also, Cheung *et al.*[34] mentioned that, the deprotonation of the commercially available indole **52**, with sodium hydride in DMF, followed by treatment with methyl iodide, gave the desired N-methylated intermediate **53**. Acylation of **53** at C3 was achieved using $TiCl_4$ and methyl 3-chloro-3-oxopropanoate in dichloroethane at 40 °C for 15 h, which gave keto diester **54**. The necessary *N,N*-dimethylamide moiety at C1 **55** was achieved through displacement of the methoxy group of **54** with dimethylamine in toluene and THF in a sealed tube at 110 °C for 15 h. Final condensation with phenylhydrazine (R= phenyl) gave the lead compound **56**. To date, this stands as the shortest reported synthesis of this particular TSPO ligand. Diversification at the N3 position of 8 was achieved through condensation of key intermediate **55** with a series of monosubstituted aryl hydrazines (31–50%). The hydrazines chosen focused upon variation of the endogenous N^3-phenyl ring, with particular attention towards preliminary SAR and functional groups amenable to PET ligand development, namely the presence of a fluorine atom and groups that would facilitate radiolabeling with ^{18}F through an ipso-type substitution. The groups explored included: a substituted phenyl ring (2-, 3-, 4-positions) (**56b-e**); a 2-pyridyl ring **56f**; a substituted 2-pyridyl ring (**56g-h**) (Scheme 7).



Scheme 7. Condensation of key intermediate **55** with a series of monosubstituted aryl hydrazines.

2.2. From 2-indolecarbohydrazides. In 2009, it was described[35,36] that the 5*H*-pyridazino[4,5-*b*]indoles **59**[37] can be prepared by boiling ethyl 3-formylindole-2-carboxylates **57** with hydrazine hydrate or by direct formylation[38] of the corresponding 2-indolecarbohydrazides **58** with DMF/$POCl_3$ (Scheme 8).

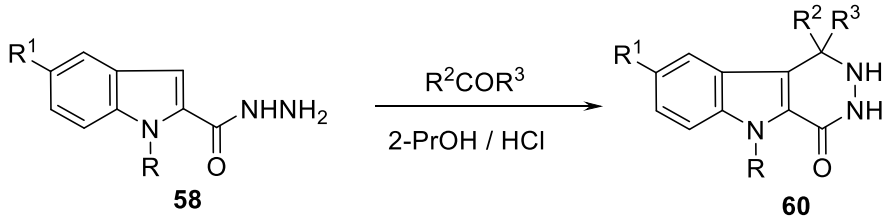


Lit.[36],R^1= Cl, R = H, CH_3, $CH_2C_6H_5$

Lit.[35] ,R^1= H, R = CH_2Ph

Scheme 8. Formylation of the corresponding 2-indolecarbohydrazides **58.**

In a similar fashion, treatment of the hydrazides **58** with aldhydes or ketones in isopropyl alcohol in the presence of HCl effected cyclization into the pyridazinone derivatives **60** in good yield[39] (Scheme 9).



R = H, CH_3

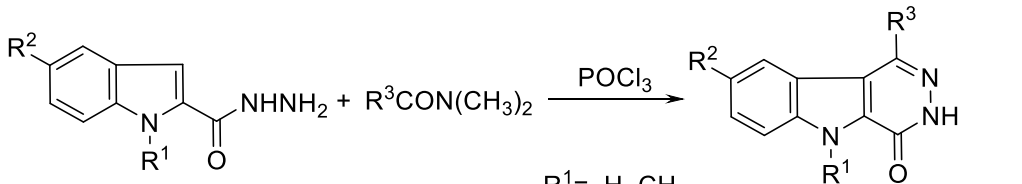
R_1 = H, $C_6H_5CH_2O$, C_2H_5O

R^2= H, CH_3

R^3= C_6H_5

Scheme 9. Treatment of the hydrazides **58** with aldehydes and ketones.

A simple preparation for 4-oxo-3,4-dihydro-*5H*-pyridazino[4,5-*b*]indoles **61** was achieved by cyclocondensation of the 2-indolecarbohydrazides **58** with *N,N*-dimethylamides and $POCl_3$[40](Scheme 10).



58 a) R^1 = R^2 = H

b) R^1 = CH_3, R^2 = $C_6H_5CH_2O$

R^1= H, CH_3

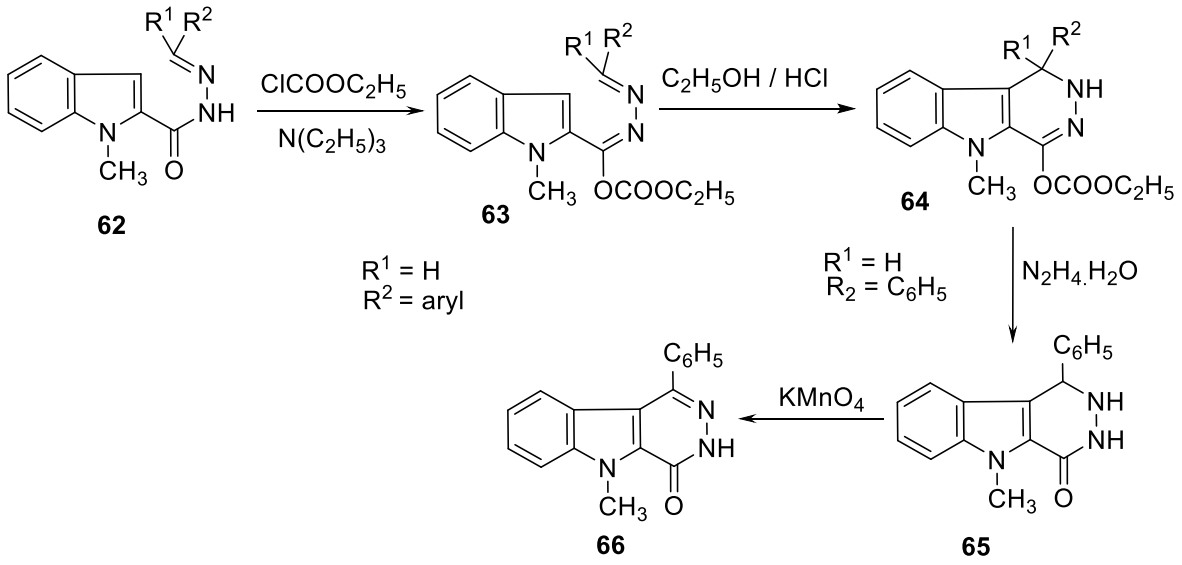
R^2= H, $PhCH_2O$

R^3 = H,CH_3, CH_3CH_2, n-C_3H_7, 4-ClC_6H_4

Scheme 10. Cyclocondensation of the 2-indolecarbohydrazides **58**.

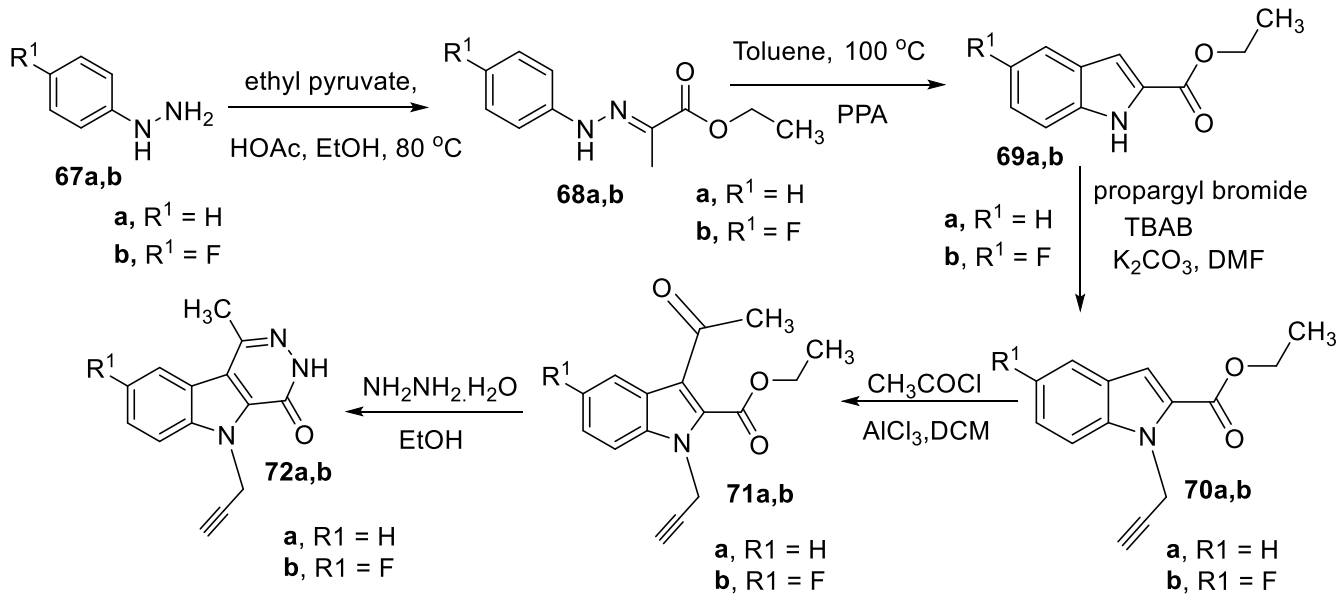
2.3. From intramolecular cyclization of (*N*-methylindole)carbohydrazones. Intramolecular cyclization of compound **63** in EtOH-HCl and subsequent removal of the ethoxycarbonyl group with $NH_2NH_2{\cdot}H_2O$ gave the

1,2,3,4-tetrahydro-4-oxo-*5H*-pyridazino[4,5-*b*]indole **65**. Oxidation of **65** with potassium permanganate gave **66** quantitatively[12,39,41] (Scheme 11).



Scheme 11. Synthesis of 5-methyl-1-phenyl-3,5-dihydro-4H-pyridazino[4,5-b]indol-4-one **66.**

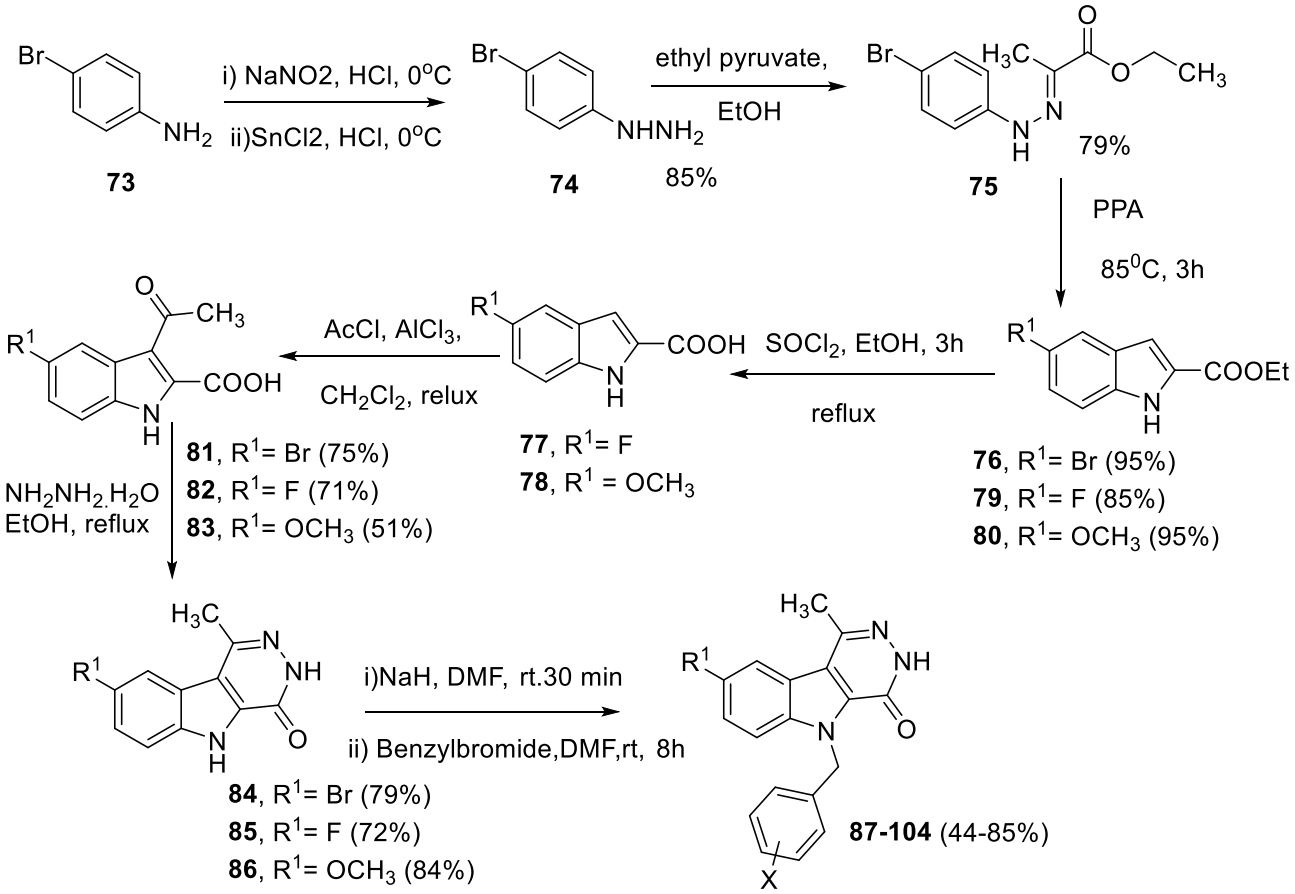
2.4. From phenylhydrazine. In 2016, Panathur *et al.*[42] reported that, the basic indole moiety was built by precise and proficient three-step synthesis following Fischer indole synthetic protocol (Humphrey and Kuethe, 2006) as given in Scheme 12. Alkylation of the indole-2-carboxylic ester intermediate **69** with propargyl bromide gave alkylated compound **70**. The intermediate **70** was then acylated at position 3 by following Friedel–Craft acylation protocol using $AlCl_3$ as the Lewis acid catalyst to give the acetyl derivative **71**. The indole-fused pyridazinone ring system **72** was then constructed by refluxing intermediate **71** with hydrazine hydrate in ethanol (Scheme 12).



Scheme 12. Synthesis of indole-fused pyridazinone ring system **76a,b.**

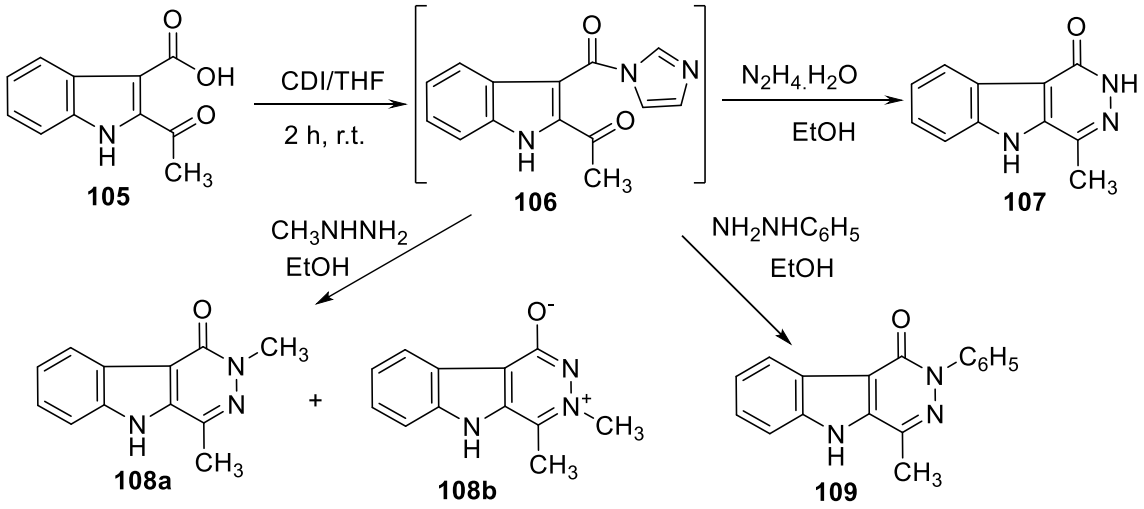
In 2012, It was reported that,[43] the synthetic pathway to obtain the 5-benzylated compounds is shown in Scheme 13. Key intermediates ethyl indole-2-carboxylates **76, 79, 80** can be prepared by intramolecular cyclization of the corresponding ethyl pyruvate 4-bromophenylhydrazone **78** in polyphosphoric acid (PPA) as a catalyst, according to Fischer's indole synthesis or by esterification of commercially 5-fluoro **77** and 5-methoxyindol-2-carboxylic acids **78**. Friedel Crafts acylation using aluminium trichloride and acetyl chloride gave indoles **81** and **82** with good yields. Moderate yield obtained for compounds **83** was due to the effect of the electron-donating methoxy group which activates the benzene ring and orients electrophilic attacks in ortho position. Condensation of hydrazine provided 4-oxo-3,4-dihydro-5H-pyridazino[4,5-*b*]indoles **84-86**. Finally, and as expected, treatment of these compounds with sodium hydride and 3- or 4-substituted benzyl bromides afforded the target molecules **87-104**.

Compd. No	R^1	X	Compd. No	R^1	X
87	Br	4-NO_2	**96**	F	3-CN
88	Br	3-NO_2	**97**	F	4-OMe
89	Br	4-CN	**98**	F	3-OMe
90	Br	3-CN	**99**	OMe	4-NO_2
91	Br	4-OMe	**100**	OMe	3-NO_2
92	Br	3-OMe	**101**	OMe	4-CN
93	F	4-NO_2	**102**	OMe	3-CN
94	F	3-NO_2	**103**	OMe	4-OMe
95	F	4-CN	**104**	OMe	3-OMe



Scheme 13. Synthesis of 8-subsituted-5-benzyl-1-methyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-one **87-104**.

2.5. From 2-acetylindole-3-carboxylic acid. Haider *et al.*[44] had done a modification on the procedure of preparation of pyridazino[4,5-*b*]indole **107** which was reported previously by Zhungietu *et al*.[45] by condensation of 2-acetylindole-3-carboxylic acid **105** with hydrazine hydrate at elevated temperature. This reaction, however, suffers from poorly reproducible yields which reflect the high decarboxylation tendency of the starting material, causing a significant side reaction (formation of 2-acetylindole or its hydrazone, respectively). It could substantially improve this step by first transforming the keto acid **105** into a suitable activated derivative under mild conditions and subsequent treatment of this intermediate with hydrazine hydrate. For this purpose, the imidazolide **107** was found to be a good choice, as it can be easily prepared in an inert solvent at room temperature by treatment of **105** with 1,1'-carbonyldiimidazole (CDI), and without isolation this compound smoothly undergoes hydrazinolysis to afford the pyridazinone **107.** Also monosubstituted hydrazines can be employed in the cyclization reaction with **107** to afford the 2-substituted products **108a** and **109**, although yields are somewhat lower and, in the case of methylhydrazine, formation of small amounts of an isomeric side product **108b** was observed (Scheme 14).

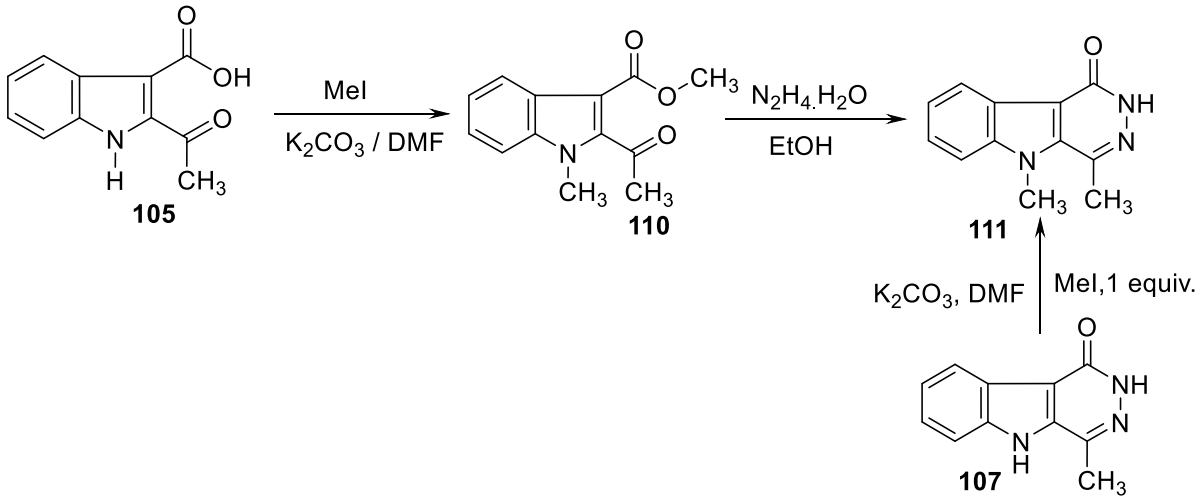


Scheme 14. Reaction of 1-(3-(1H-imidazole-1-carbonyl)-1H-indol-2-yl)ethan-1-one **106** with hydrazine hydrate.

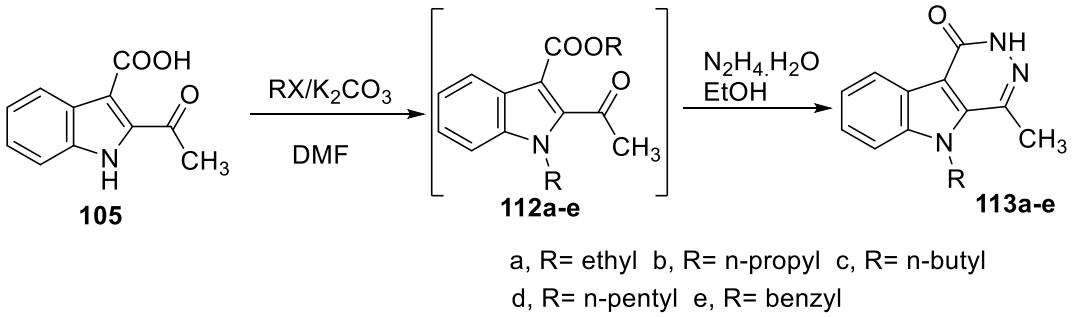
However[7] treatment of the 2-acetyl indole-3-carboxylate **105** with methyl iodide in DMF and potassium carbonate afforded *N*-methyl-2-acetyl indole-3-carboxylate **110.** Hydrazinolysis of the later compound **110** with hydrazine hydrate in boiling ethanol gave the corresponding 4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one **111.** Alternatively, reaction of the *N*-unsubstituted pyridazinoindole **107**[44] with an equimolar amount of methyl iodide in dry DMF in the presence of potassium carbonate afforded only the corresponding pyridazino[4,5-*b*]indole **111** (Scheme 15).

In 2008, Haider *et al.* reported that[25] the introduction of the desired alkyl residues at the indole nitrogen is preferentially accomplished before the pyridazinone unit is formed. Thus, the reaction of 2-acetylindole-3-carboxylic acid[46] **105** with a larger excess of alkylating agent (generally an alkyl iodide, with the exception of benzyl bromide) can be safely employed, effecting N-alkylation and esterification of the carboxylic group at the same time. The resulting ester **112** functionality, in turn, offers the additional advantage of facilitating the subsequent ring-closure reaction with hydrazine, because free carboxylic acids of this type have been known to undergo concurrent decarboxylation very easily.[47] Although also this procedure gives only low to moderate yields, the sequence can be carried out very conveniently in a one-pot manner and opens a simple and short

access to compounds of type **113** which are free of any contamination by 2,5-disubstituted derivatives (Scheme 16).

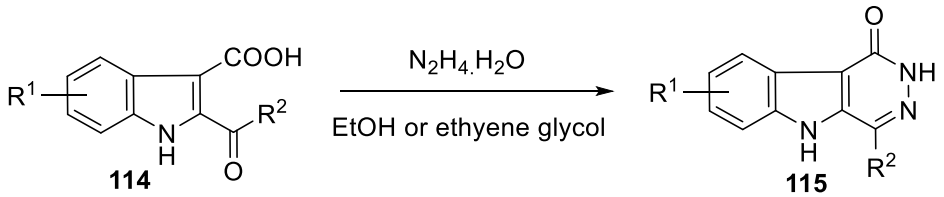


Scheme 15. Synthesis of 4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one **(111).**



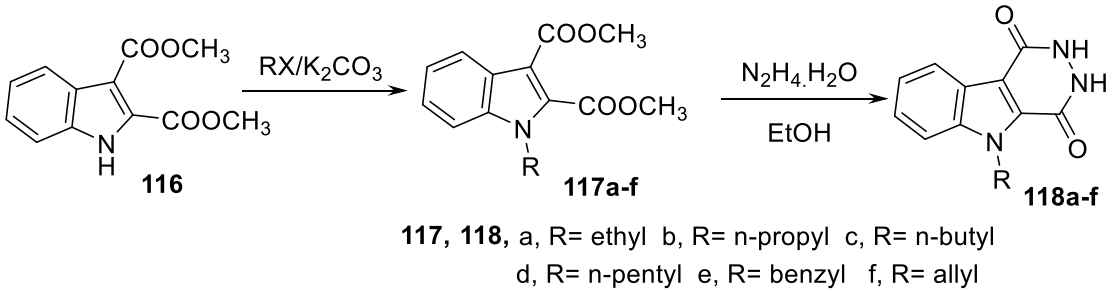
Scheme 16. Synthesis of 4,5-dimethyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-ones **113**.

In 1982, Zhungietu *et al.*[45] described that the 5*H*-pyridazino[4,5-*b*]indol-1-ones **115** were prepared by heating 2-acetylindole-3-carboxylic acids or 2-aroylindole-3-carboxylic acids **114** with hydrazine hydrate in ethylene glycol or ethanol (Scheme 17).



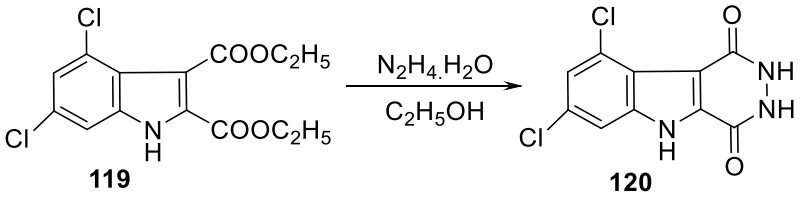
Scheme 17. Synthesis of 5*H*-pyridazino[4,5-*b*]indol-1-ones **115**.

2.6. From dimethyl indole-2,3-dicarboxylate. *N*-Alkylation[25] of dimethyl indole-2,3-dicarboxylate **116**[48] with an excess of the appropriate alkyl iodide (or benzyl bromide or allyl bromide, respectively) in the presence of potassium carbonate in dimethylformamide solution afforded the intermediate *N*-alkyl esters **117a-f** which was reacted with hydrazine hydrate to give the 5-alkyl-substituted 1,4-dihydroxypyridazino[4,5-*b*]indole derivatives **118a-f** in satisfactory yields (Scheme 18).



Scheme 18. Synthesis of 5-alkyl-substituted 1,4-dihydroxypyridazino[4,5-*b*]indole derivatives **118a-f.**

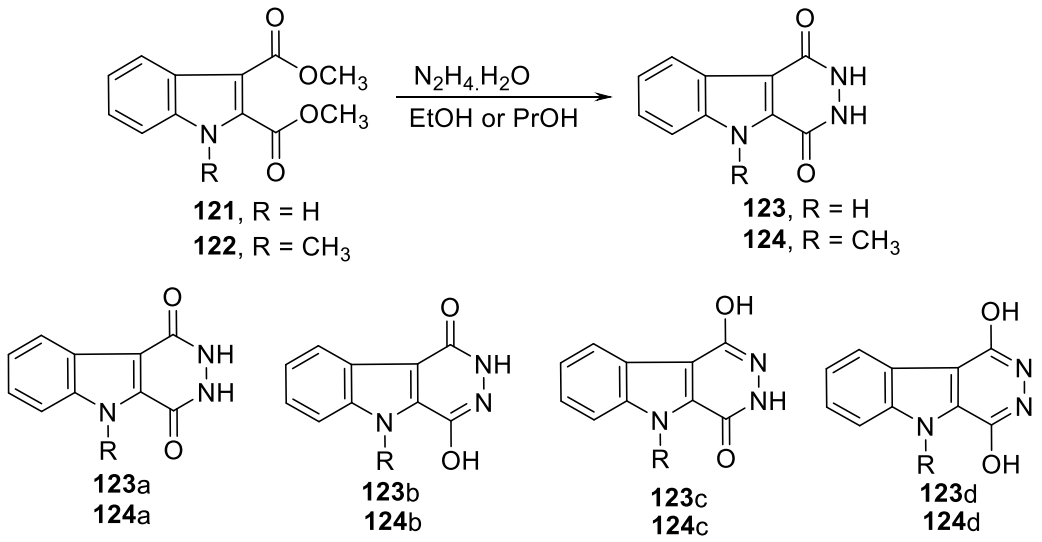
Reaction of diethyl 4,6-dichloroindole-2,3-dicarboxylate **119** with hydrazine hydrate in refluxing ethanol afforded the 7,9-dichloropyridazino[4,5-*b*]indole-1,4-dione derivative **120** in 70% yield[15] (Scheme 19).



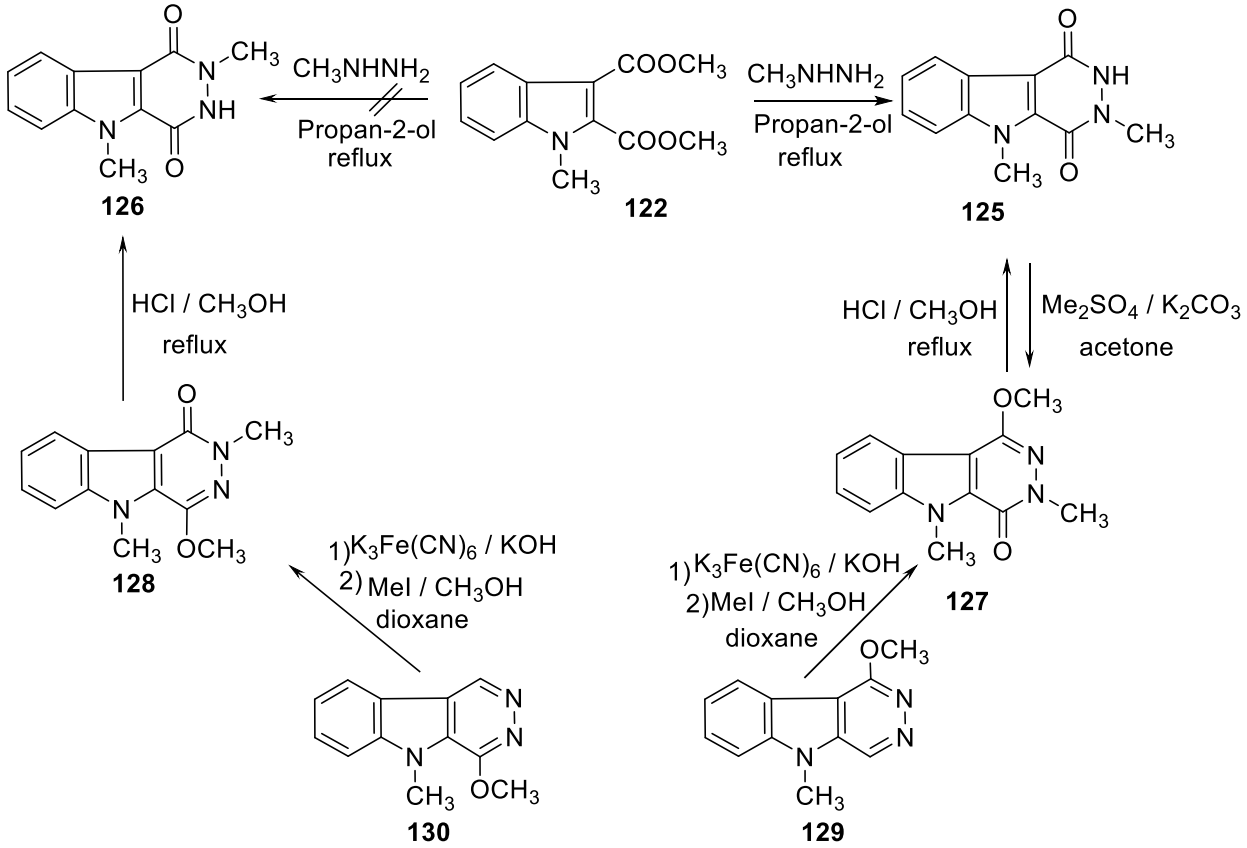
Scheme 19. Synthesis of 7,9-dichloropyridazino[4,5-*b*]indole-1,4-dione derivative **120**.

In continuation of some previous work, the tautomeric ratio for 1,2,3,4-tetrahydro-1,4-dioxo-*5H*-pyridazino[4,5-*b*]indole **123** was investigated.[49] Unlike the tautomeric pyridazine-3,6-dione system which has three possible tautomeric forms,[33] the 1,4-dioxygenated pyridazinoindole can exist not only in the dioxo form **123a** and the dihydroxy form **123d**, but there is also the possibility of two non-equivalent mono-hydroxy mono-oxo forms **123b** and **123c**. The 5-H and 5-methyl pyridazino[4,5-*b*]indoles **123** and **124** were prepared by reaction of dimethyl indole-2,3-dicarboxylate **121**[49,34] or dimethyl 1-methylindole-2,3-dicarboxylate **122**[34,49,50] with hydrazine hydrate in refluxing ethanol or propanol in good yields[49] (Scheme 20).

It is noteworthy[49] that the reaction of dimethyl 1-methylindole-2,3-dicarboxylate **122** with methyl hydrazine is regiospecific and produces 3,5-dimethylpyridazino[4,5-*b*]indole **125** and not the 2,5-dimethyl isomer **124**. This observation reflects the greater susceptibility of the 2-methoxycarbonyl group to nucleophilic attack, compared with the 3-ester. In an alternative approach, the pyridazinoindole derivatives **125** and **126** could be obtained via solvolysis of the corresponding methoxy derivatives **127** and **128**, which were prepared from the known[51] 1-methoxy-5-methylpyridazino[4,5-*b*]indole and the 4-methoxy derivative **129** and **130** respectively (Scheme 21).

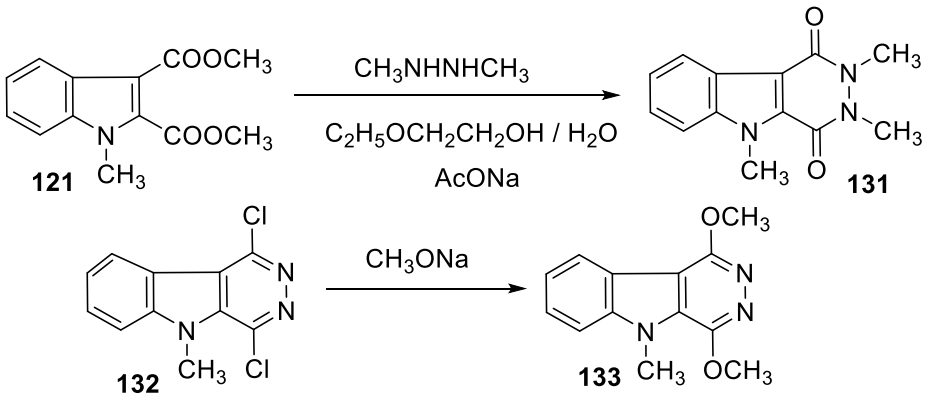


Scheme 20. Synthesis and tautomeric forms of 5-alkyl-2,3-dihydro-1H-pyridazino[4,5-*b*]indole-1,4(5H)-dione **123, 124.**



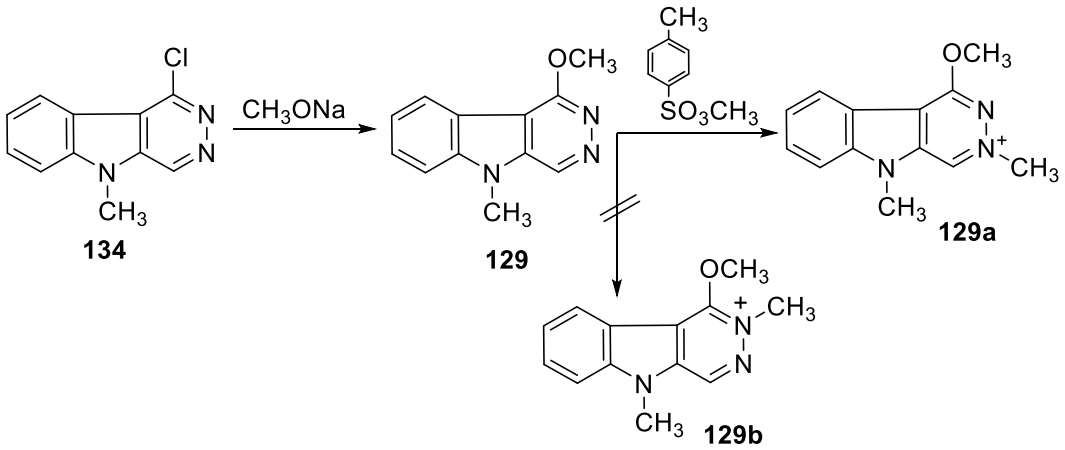
Scheme 21. Regiospecific hydrazinolysis of dimethyl 1-methylindole-2,3-dicarboxylate **122**.

The preparation of 2,3,5-trimethyl-*5H*-pyridazino]4,5-*b*]indole **131** has been achieved by reaction of the dimethyl 1-methylindole-2,3-dicarboxylate **121** with 1,2-dimethylhydrazine in refluxing 2-ethoxyethanol-water mixture (1:1),[49] whereas the fixed dimethoxy derivative **133** was prepared by treatment of the dichloro derivative **132** with sodium methoxide[49] (Scheme 22).



Scheme 22. Synthesis of 2,3,5-trimethyl-*5H*-pyridazino]4,5-*b*]indole **131** and 1,4-dimethoxy derivative **133**.

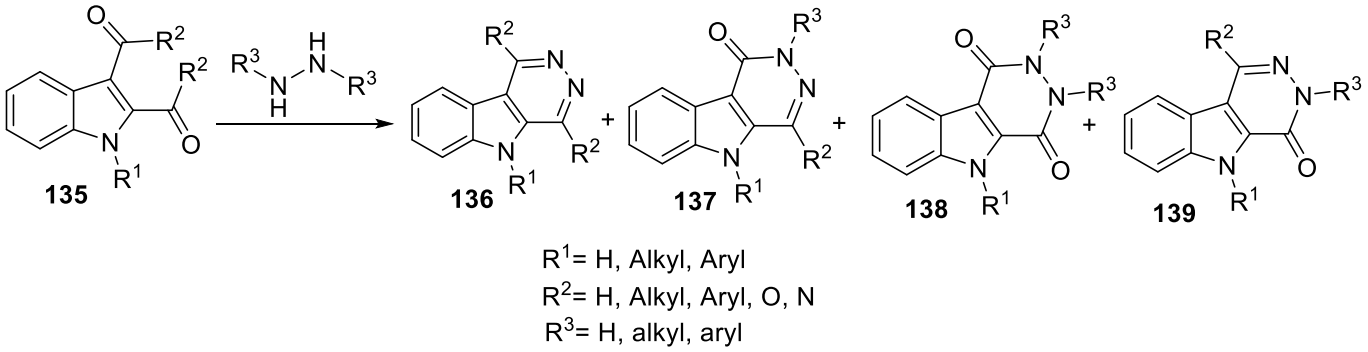
The preparation of 1-methoxy-5-methylpyridazino[4,5-*b*]indole **129** has been achieved by nucleophilic reaction of the corresponding 1-chloro derivative **134** with sodium methoxide,[49] but all attempts to synthesize a 5-unsubstitued analog by an analogous procedure failed.[51] The reaction of **129** with methyl toluene-4-sulfonate furnished the 3,5-dimethylpyridazino[4,5-*b*]indolium salt **129a**, and not the 2,5-dimethyl derivative **129b**, and all attempts to prepare the 2,5-dimethylpyridazinoindolium salt **129b** *via* alternative routes failed (Scheme 23).



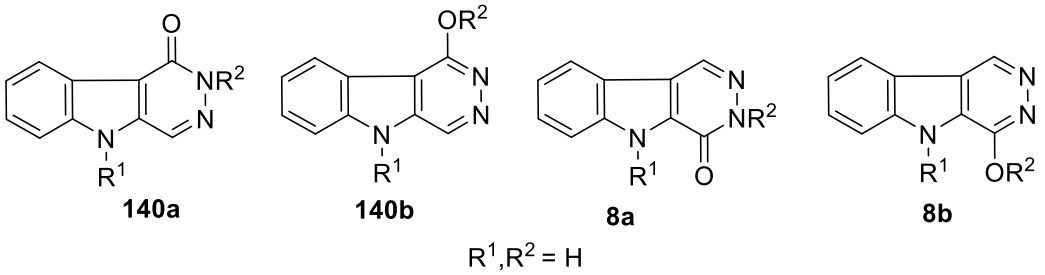
Scheme 23. Synthesis of 1-methoxy-5-methylpyridazino[4,5-*b*]indole **129**.

In 2013 it was reported that,[12] the pyridazino[4,5-*b*]indoles **136-139** are mostly prepared from 2,3-dicarbonylindoles **135** in the presence of hydrazine and its derivatives. This method allows the obtaining of a large variety of pyridazino[4,5-*b*]indoles in a one-pot procedure from 2,3-dicarbonylindoles **135** depending on the substitutions of hydrazines and indoles (Scheme 24).

In continuation[51] of studies of extended heterocyclic systems[52] and fused ring pyridazinones,[53] the tautomeric equilibrium position for 2,5-dihydro-1H-pyridazino[4,5-b]indol-1-one **140a** and 3,5-dihydro-4H-pyridazino[4,5-b]indol-4-one **8a** was investigated. Vigorous conditions[51] were required for the conversion of the appropriate 2-formylindol-3-carboxylic esters 2,5-dihydro-1H-pyridazino[4,5-b]indol-1-one **140a** and its 2- and 5-methyl derivatives, and the hydrazones were isolable under relatively mild conditions (Scheme 25).

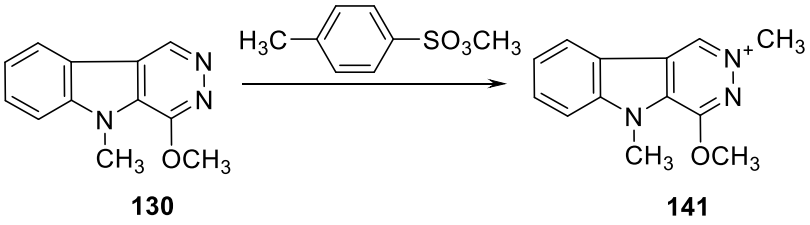


Scheme 24. Synthesis of pyridazino[4,5-*b*]indoles **136-139**.



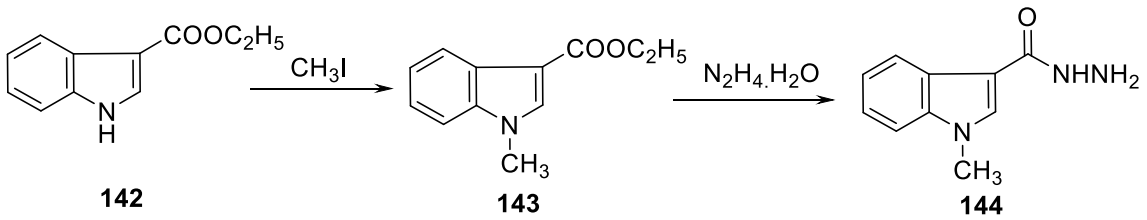
Scheme 25. The tautomeric equilibrium of pyridazino[4,5-*b*]indoles **8** and **140**.

The tautomeric 4-oxo/4-hydroxy pyridazino[4,5-*b*]indole derivatives **8a,b** and its 3-and 5-methylated derivatives were obtained by standard procedures from 3-formylindole-2-carboxylic esters (Scheme26).[51] The 4-methoxy-5-methyl derivative **130** was prepared in a manner analogous to that used for the corresponding 1-methoxy isomer **129** which was converted into the 2-methylpyridazino-indolium salt **141** upon reaction with methyl toluene-4-sulfonate.



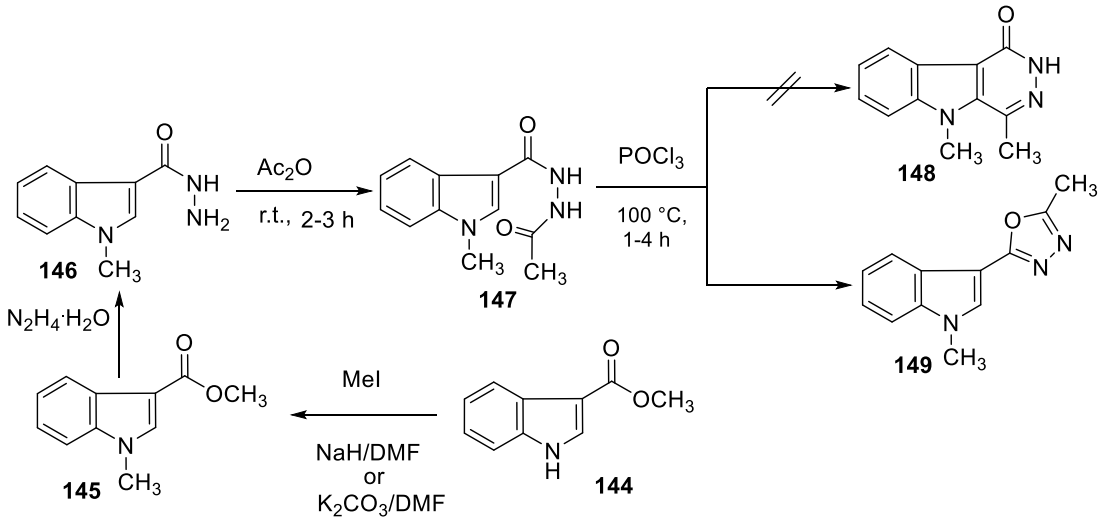
Scheme 26. Synthesis of the 2-methylpyridazino-indolium salt **141**.

2.7. From acetyl indole-3-carbohydrazide. It was reported that methylation of **142** with methyl iodide gave ethyl *N*-methylindole-3-carboxylate **143**, which was reacted with hydrazine hydrate to afford the corresponding hydrazide **144**[54] (Scheme 27).



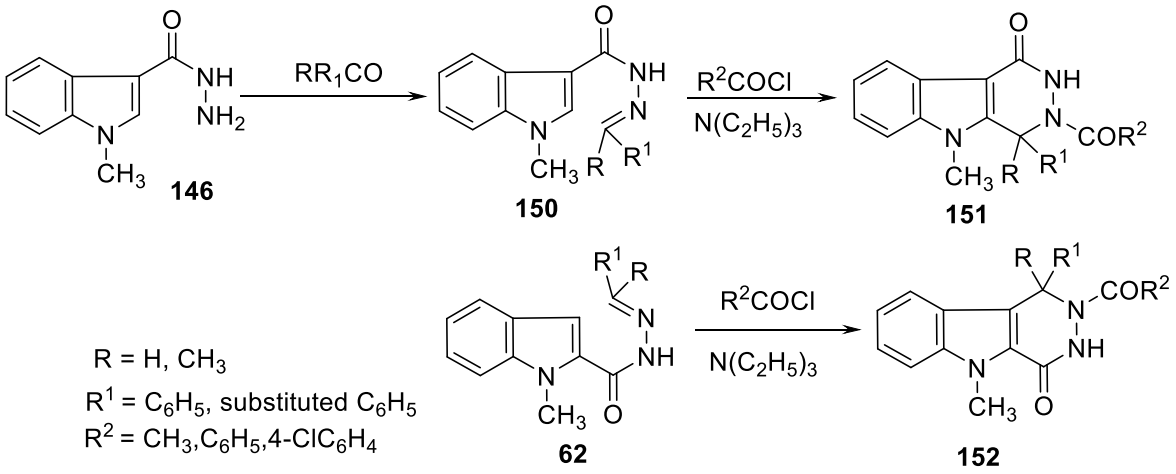
Scheme 27. Synthesis of corresponding hydrazide **144**.

In 2016, Farghaly *et al* reported that,[7] an attempts were done to prepare the 4,5-dimethyl-2,5-dihydro-*1H*-pyridazino[4,5-*b*]indol-1-one **148** by the reaction of methyl indole-3-carboxylate **144** with methyl iodide in dry DMF in the presence of sodium hydride affords the N-methylated ester **145** in 81% yield. hydrazinolysis of the later compound **145** gave the corresponding hydrazide **146** which was reacted with acetic anhydride at room temperature for 2-3 hours giving the mono acetyl derivative **147** in a good yield (72%). Treatment of **147** with $POCl_3$ under various conditions (at room temperature or at 100 °C for 1-4 hours) did not give the corresponding pyridazinone **148** but afforded the oxadiazole derivative **149** in 77% yield (Scheme 28).



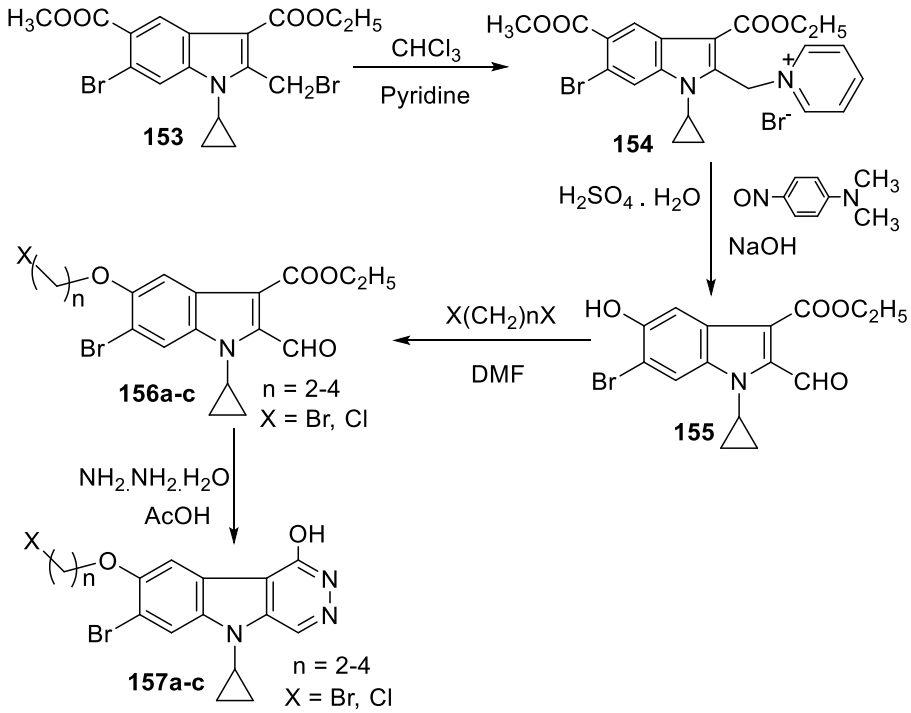
Scheme 28. Attempts to prepare Synthesis of 4,5-dimethyl-2,5-dihydro-1H-pyridazino[4,5-*b*]indol-1-one **148**.

Reaction of **146** with aldehydes or ketones gave the hydrazone derivatives **150**, cyclization of the latter compounds and 2-indolecarbohydrazones **62** with acid chlorides and triethylamine in ethyl acetate or chloroform as solvent afforded 1-oxo- and 4-oxo-1,2,3,4-tetrahydro-*5H*-pyridazino[4,5-*b*]indole derivatives **151**[12] and **152**[39,54] (Scheme 29).



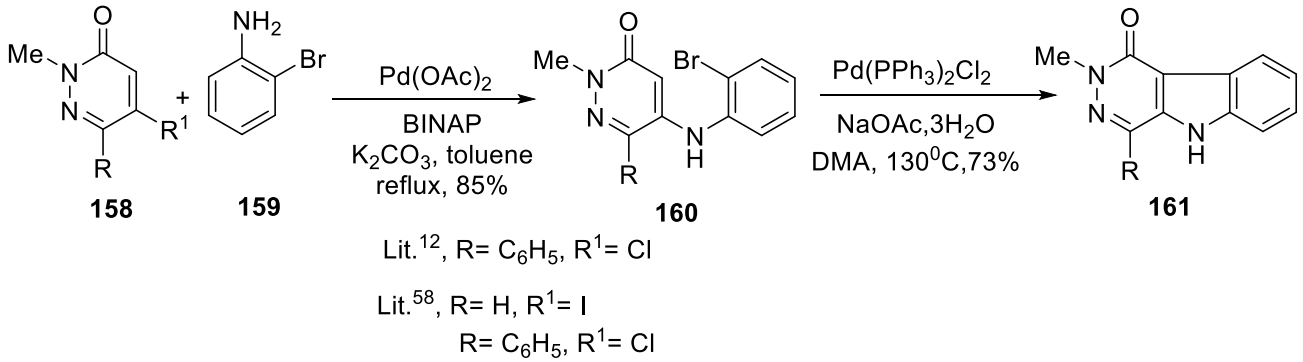
Scheme 29. Synthesis of 1-oxo- and 4-oxo-1,2,3,4-tetrahydro-*5H*-pyridazino[4,5-*b*]indole derivatives **151**,**152**.

2.8. From 3-ethyl 5-methyl 6-bromo-2-(bromomethyl)-1-cyclopropyl-1*H*-indole-3,5-dicarboxylate. In 2015, It was mentioned that,[55-57] the starting material, ethyl 5-acetoxy-6-bromo-2-bromomethyl-1-cyclopropylindole-3-carboxylate **153**, was synthesized according to the method reported previously.[56] Reaction of compound **153** with pyridine in trichloromethane afforded nearly pure hyamine **154** in good yield. Treatment of **154** with the freshly prepared *p*-nitrosodimethylaniline hydrochloride in the presence of sodium hydroxide aqueous solution in ethanol afforded the oxidized intermediate α-substituted nitrone, which was used in the next step without further purification. Subsequent hydrolysis reaction of nitrone intermediate in sulfuric acid aqueous solution gave rise to intermediate **155**.[57] Compound **155** was *O*-alkylated with 1-bromo-3-chloropropane/dichloroethane/1,4-dibromobutane in the presence of potassium carbonate in *N,N*-dimethyl formamide (DMF) to provide compounds **156a-c**. Cyclization of latter compounds with an excess amount of 80% hydrazine hydrate gave compounds **157a-c** (Scheme 30).



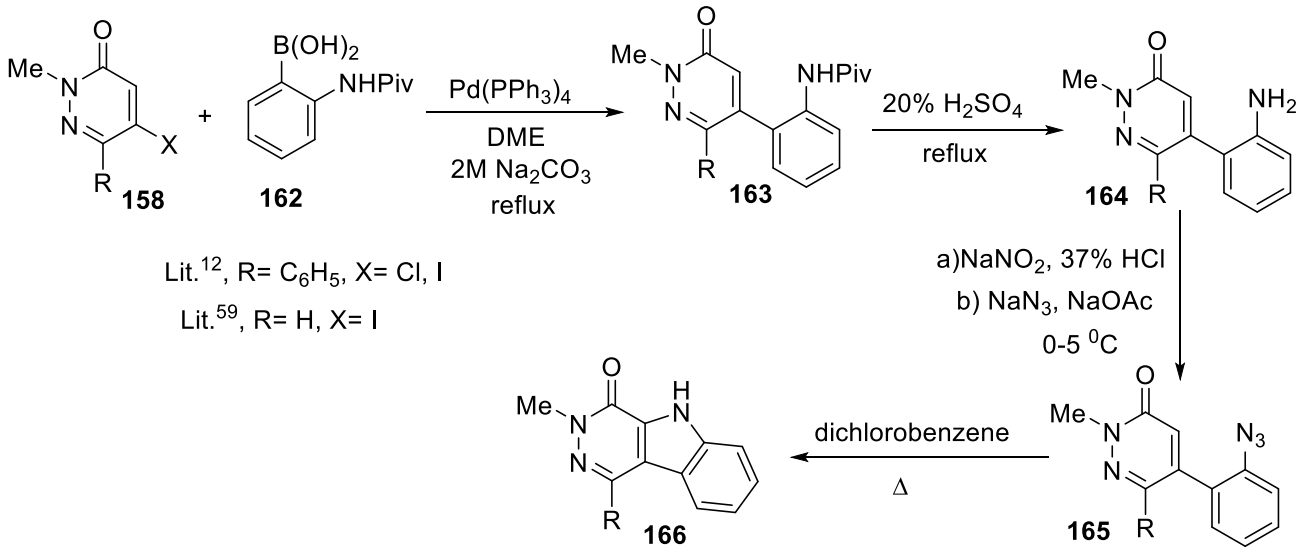
Scheme 30. Synthesis of 7-bromo-8-(halomethoxy)-5-cyclopropyl-5*H*-pyridazino[4,5-*b*]indol-1-ol **157.**

2.9. From palladium-mediated coupling reactions. It was reported that,[12,58] the palladium-mediated coupling reactions are widely used to form C–C and C–N bonds in organic compounds including heterocycles under mild conditions with high efficiencies.[18] Thus, Buchwald–Hartwig amination of 2-methyl-5-halopyridazin-3(2*H*)-one **158** with 2-bromoaniline **159** afforded the corresponding 5-[(2-bromophenyl) amino]-2-methylpyridazin-3(2*H*)-one **160.** The Pd(0)-catalyzed Heck coupling reaction was utilized for compound **160** to give 2-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one **161** (Scheme 31).[14]



Scheme 31. Pd(0)-catalyzed Heck coupling reaction of compound **160**.

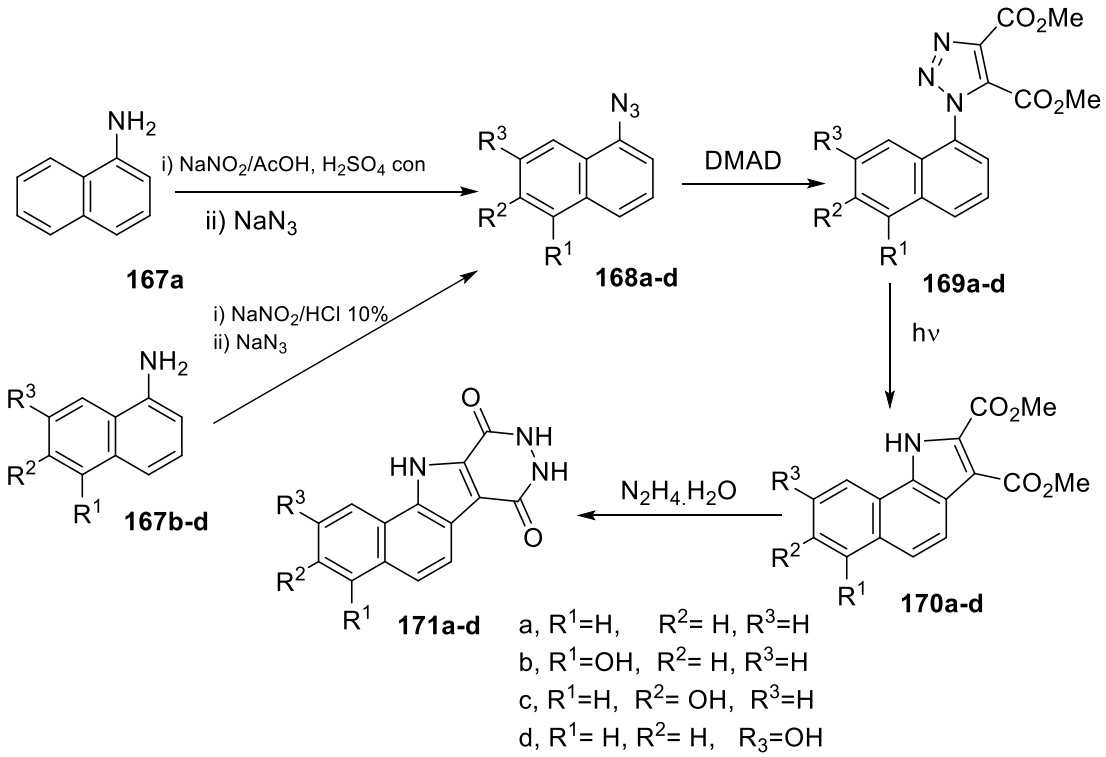
2.10. From azide derivatives. In 2013, it was reported that,[12,58] Suzuki cross-coupling reaction of 5-halo-2-methyl-6-phenylpyridazin-3(2*H*)-one **158** with *o*-pivaloylaminophenyl boronic acid **162** furnished the corresponding arylated 5-pivaloylaminophenyl derivative **163**, which was transformed into amine form **164** after elimination of pivaloyl protection.[59,60] Ring closure of nitrene intermediate generated *in situ* from azide **165** yielded pyridazino[4,5-*b*]indole **166** as a single product (Scheme 32).[61,15]



Scheme 32. Ring closure of azide **165** to pyridazino[4,5-*b*]indole **166**.

In 2001, Kurumi *et al.* reported that,[62] treatment of naphthylamine derivatives **167a-d** with sodium nitrite in a mixture of AcOH/H_2SO_4 and sodium azide gave the corresponding 1-azidonaphthalene **168a-d**. Consequently compounds **168b**-**d** were used in the next step without further purification. The reactions of

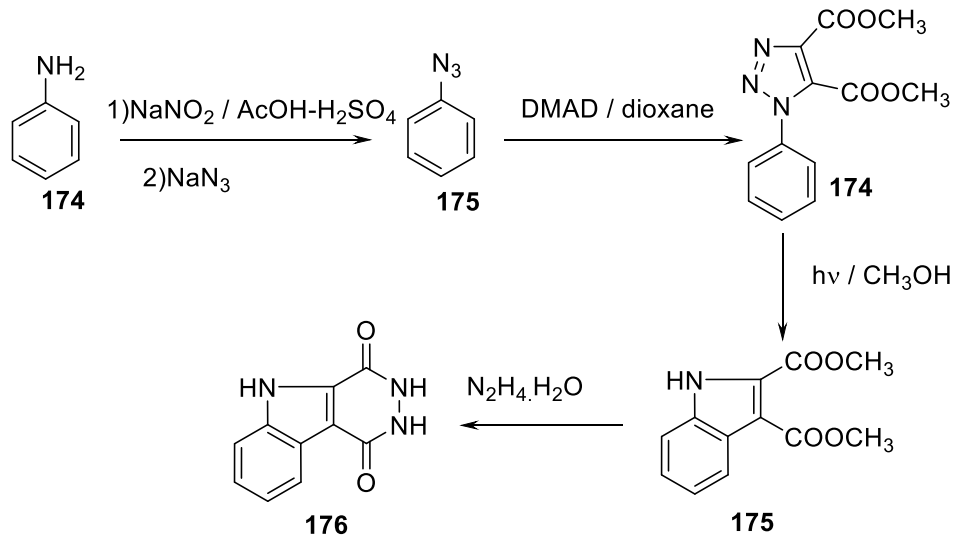
compounds **168a-d** with dimethyl acetylenedicarboxylate (DMAD) at room temperature for 10 days in the dark afforded the corresponding triazoles **169a-d**. These triazoles **169a-d** were transformed into the corresponding dimethyl 1*H*-benz[*g*]indole-2,3-carboxylates **170a-d** *via* photocyclization using a 500-watt mercury high pressure lamp by the method of Nagawa *et al*.[63,64] Compounds **170a-d** were converted to the corresponding benzopyridazinoindoles **171a-d** by reaction with hydrazine hydrate. These reactions proceeded by using a large excess of hydrazine hydrate and heating at reflux (Scheme 33).



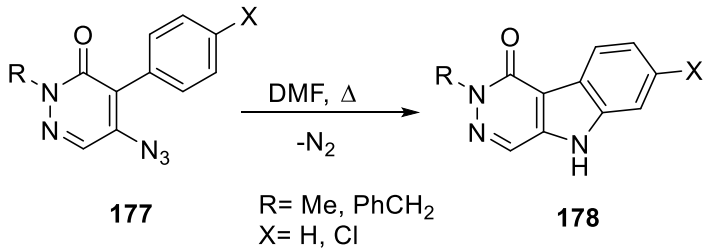
Scheme 33. Synthesis of benzopyridazinoindoles **171a-d**

In the year 2000, it was found[59] that pyridazino[4,5-*b*]indoles can be prepared by reaction of aniline **172** with sodium nitrite in a mixture of AcOH/H_2SO_4 and sodium azide according to Forster *et al.*[63] This method gave the azido compound **173** which reacted with dimethyl acetylenedicarboxylate (DMAD) to afford the 4,5-dicarboxylate derivative **174**. This compound was transformed into indole-2,3-dicarboxylate **175** by photocyclization reaction followed by loss of nitrogen.[64] Treatment of later compound **175** with hydrazine hydrate afforded the corresponding pyridazinoindole derivative **176** (Scheme 34).

In 2006, Haider *et al.*[72] reported that the 5-azido-4-arylpyridazin-3(2*H*)-ones **177**, which are easily available from 4,5-dihalopyridazin-3(2*H*)-ones in few steps, were found to undergo in high yields a thermally induced cyclization into pyridazino[4,5-*b*]indole derivatives **178** ("aza-carbolinones") by formation of the N-5/C-5 a bond *via* a nitrene insertion process. This new method is complementary to a previously reported pathway in which the C-4a/N-5 bond of the ring system is formed (Scheme 35).

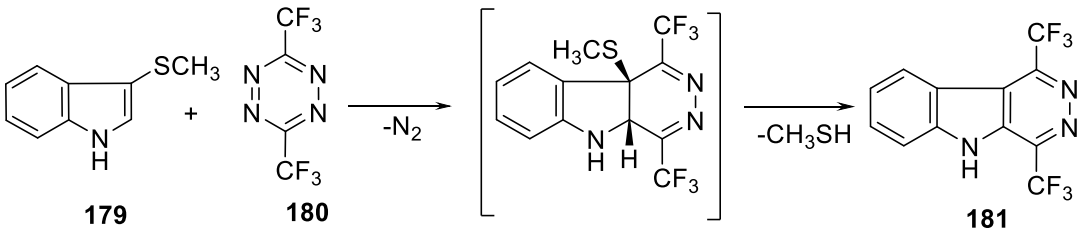


Scheme 34. Synthesis of 2,3-dihydro-1H-pyridazino[4,5-b]indole-1,4(5H)-dione **176**.



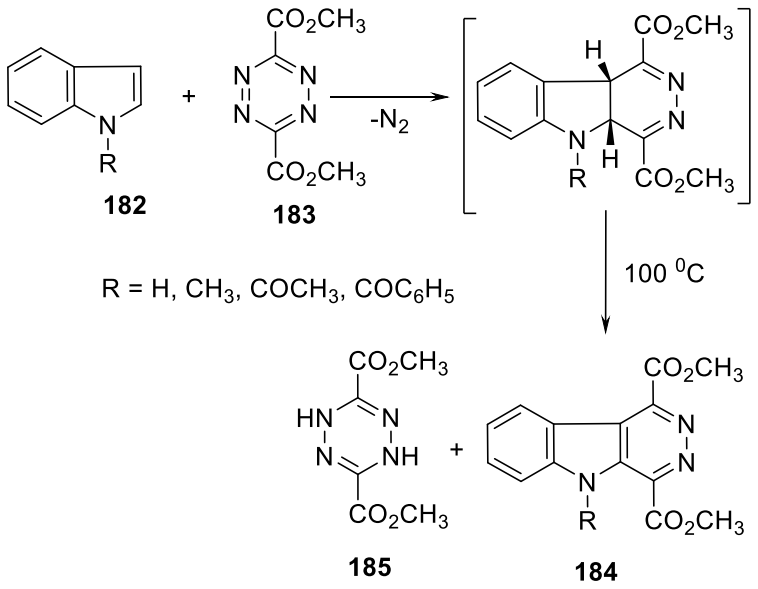
Scheme 35. Synthesis of pyridazino[4,5-*b*]indole derivatives **178**.

2.11. From [4+2] cycloaddition reaction of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine with indole. The isolation of 1,4-bis(trifluoromethyl)pyridazino[4,5-*b*]indole **181**[12] as a reaction product from a cycloaddition/cycloreversion process starting from indole and 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine[65] **180** has been described by Seitz and Mohr.[66] A more efficient synthesis of **181** was reported by Haider *et al.*[67] Thus, tetrazine **180** was reacted with an equimolar amount of readily available 3-methylthioindole[68,42] **179** in refluxing toluene to afford after spontaneous elimination of molecular nitrogen and methanethiol the tricyclic compound **181** (Scheme 36).



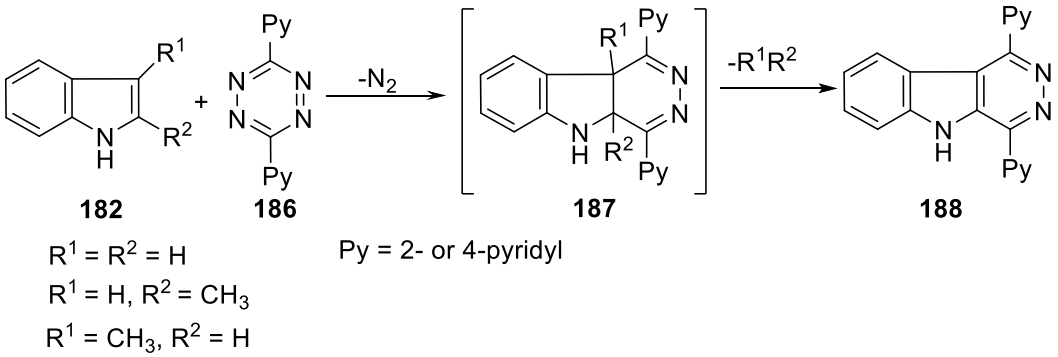
Scheme 36. Synthesis of 1,4-bis(trifluoromethyl)-5H-pyridazino[4,5-*b*]indole **181**.

Benson *et al.*[5,69,70] reported that pyridazino[4,5-*b*]indoles can be prepared via an inverse-electron-demand Diels-Alder reaction. Treatment of indole derivatives **182** acting as dienophiles with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **183** effects a [4+2] cycloaddition reaction to give the corresponding 5*H*-pyridazino[4,5-*b*]indole **184** and as a side product the dihydrotetrazine **185** (Scheme 37).



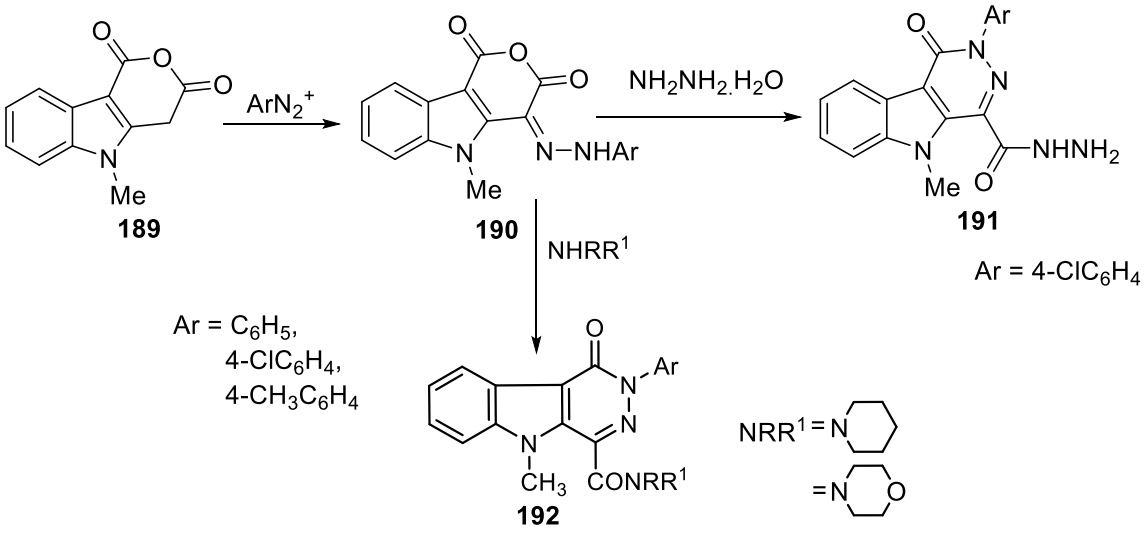
Scheme 37. An inverse-electron-demand Diels-Alder reaction to prepare pyridazino[4,5-*b*]indole **184**.

Takahashi *et al.*[71] described that the cycloaddition of 1,2,3,4-tetrazines **186** with indoles **182**, followed by elimination of nitrogen gave the corresponding 5*H*-pyridazino[4,5-*b*]indoles **188** (Scheme 38).



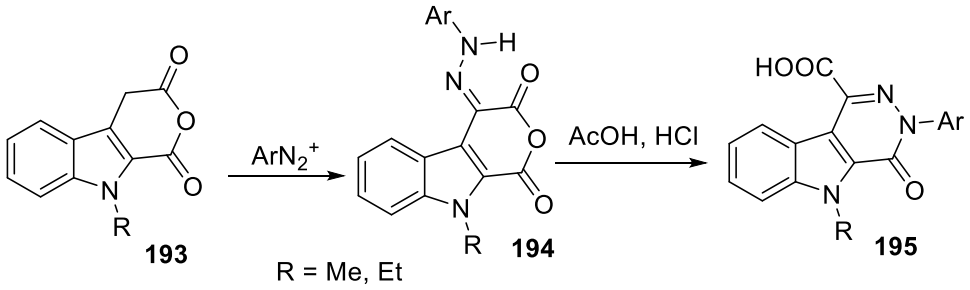
Scheme 38. Synthesis of 5*H*-pyridazino[4,5-*b*]indoles **188**.

Furthermore,[12,73] treatment of aryl diazonium salts with pyrano[4,3-*b*]indole-1,3(4*H*,5*H*)-diones **189** and subsequent cyclization of intermediate **190** gave pyridazino[4,5-*b*] indoles **191** (Scheme 39) whereas reaction of the α-hydrazono anhydrides with piperidine or morpholine in xylene gave the amide derivatives **192**.[73]



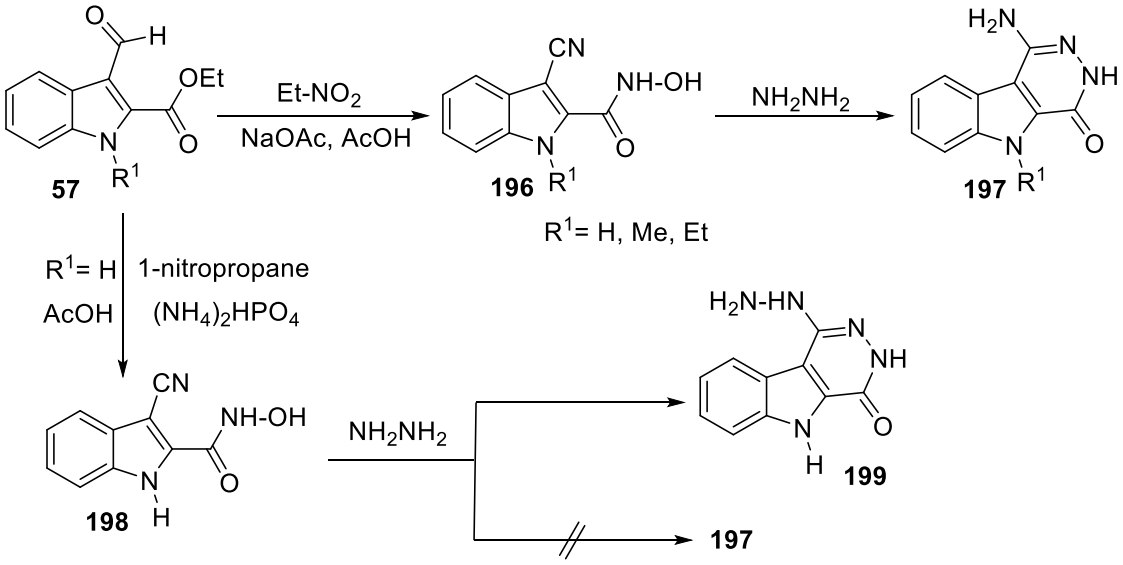
Scheme 39. Ring opening and cyclization of intermediate **190**.

Similarly,[12] treatment of 9-alkyl-4,9-dihydropyrano[3,4-b]indole-1,3-dione **193** with aryldiazonium salts gave the corresponding α-hydrazono anhydrides **194**, which was reacted with a mixture of acetic acid and HCl to afford the corresponding pyridazino[4,5-*b*]indole **195** (Scheme 40).



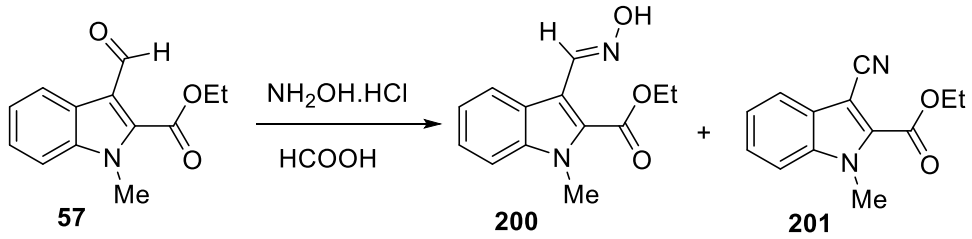
Scheme 40. Reaction of 4,9-dihydropyrano[3,4-b]indole-1,3-dione **194** with AcOH/HCl.

2.12. From ethyl 3-cyano-1*H*-indole-2-carboxylates. Also, it was reported that,[12] the interaction of formyl indoles **61** with an in situ hydroxylamine-producing buffer consisting of acetic acid, sodium acetate and nitroethane[48] afforded the corresponding ethyl 3-cyano-1*H*-indole-2-carboxylates **196** which were subsequently treated with hydrazine to obtain 1-amino-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indoles **197**. The 3-cyanoindole **198** was also prepared as reported previously[77] by treatment of indole-3-carboxaldehyde with another buffer consisting of diammonium hydrogen phosphate, acetic acid, and 1-nitropropane. By the treatment of 3-formyl-1*H*-indole-2-carboxylate **57** with this high boiling buffer gave 3-cyano-1H-indole-2-hyroxamic acid **198**. The reaction of **198** with unsubstituted hydrazine gave 3,4-dihydro-1-hydrazino-4-oxo-5*H*-pyridazino[4,5-*b*]indole **199** and did not give the expected **197**, Compound **199** was reformed from hydroxamic acid derivative **198** in several other attempts under the same conditions (Scheme 41).



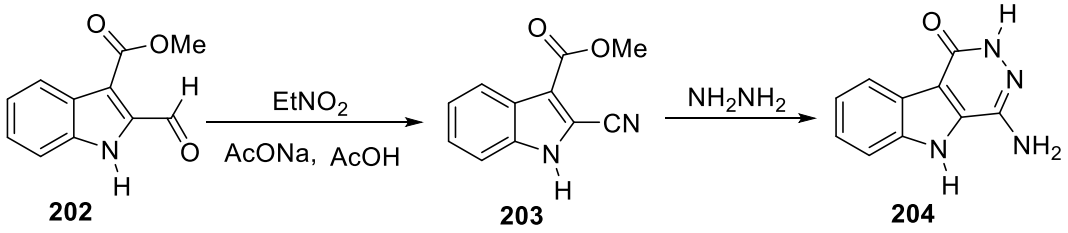
Scheme 41. Synthesis of 3,4-dihydro-1-hydrazino-4-oxo-5*H*-pyridazino[4,5-*b*]indole **197.**

In continuation to same studies another approach[12] to introduce cyano functionality is the treatment of formyl functionalized indoles with hydroxylamine in formic acid. Nevertheless, reaction of **57** with hydroxylamine resulted in the formation of 2 different products, ethyl 3-(*N* -hydroxyiminomethyl)-1-methyl-1*H*-indole-2-carboxylate **200** and ethyl 3-cyano-1-methyl-1*H*-indole-2-carboxylate **201**, in moderate yields (Scheme 42).



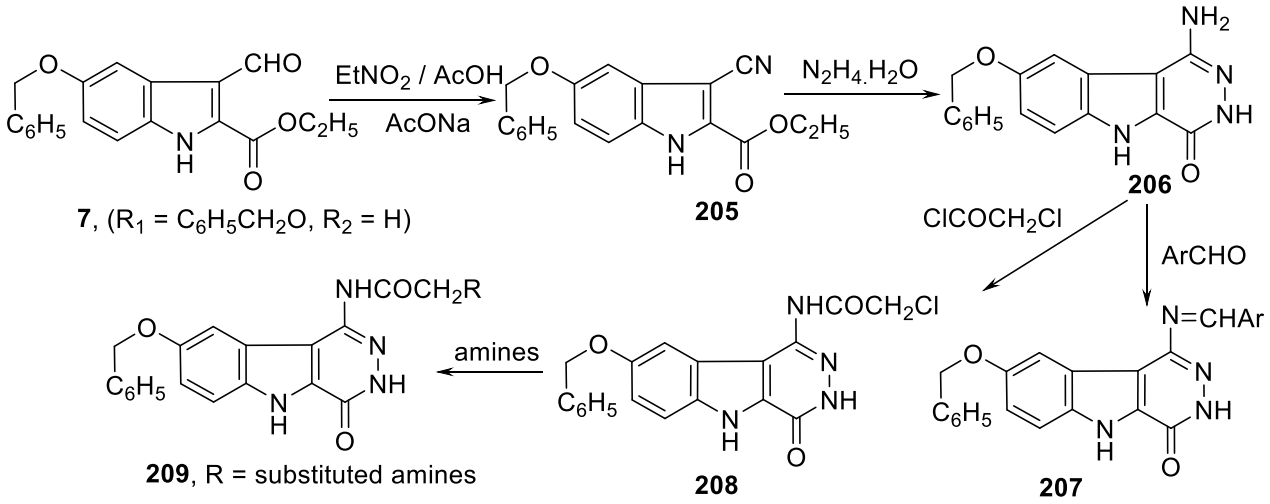
Scheme 42. Preparation of ethyl 3-cyano-1-methyl-1*H*-indole-2-carboxylate **201**.

On the other hand, the 4-amino-1,2-dihydro-1-oxo-5*H*-pyridazino[4,5-*b*]indole **204**[12] (Scheme 43) was obtained in 45% yield from the cyclization of hydrazine and methyl 2-cyano-1*H*-indole-3-carboxylates **203**, which were prepared from corresponding 2-formylindole **202** by treatment with nitroethane buffer.[75]



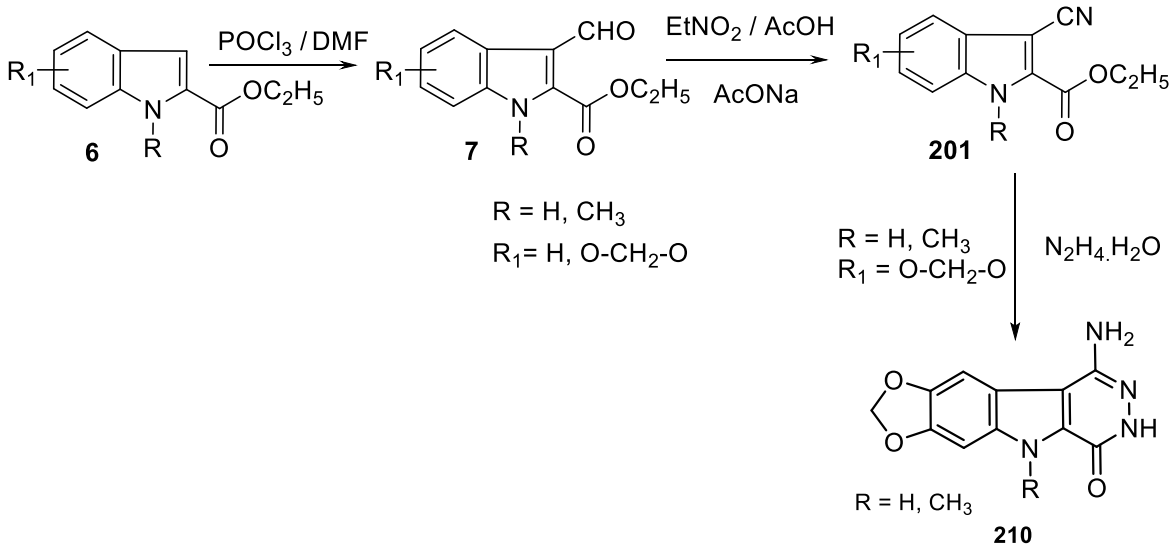
Scheme 43. Synthesis of 4-amino-1,2-dihydro-1-oxo-5*H*-pyridazino[4,5-*b*]indole **204**.

Treatment[21] of **7** (R^1 = $PhCH_2O$, R^2 = H) with nitroethane in an acetic acid/sodium acetate solution produces the cyano derivative **205**, which was reacted with 90% hydrazine hydrate to give 1-amino-8-benzyloxy-3,4-dihydropyridazino[4,5-*b*]indol-4-one **206**.[21] Reaction of the amino compound **206** with different aldehydes in the absence of a solvent gives a series of imines **207** in low yields, except in the case of 4-OHC_6H_5CHO.[21] Treating **206** with chloroacetyl chloride under reflux leads to the corresponding amide derivative **208**, which was reacted with different amines affording the 1-acetamido-8-benzyloxy-3,4-dihydropyridazino[4,5-*b*]indol-4-one derivatives **209** (Scheme 44).



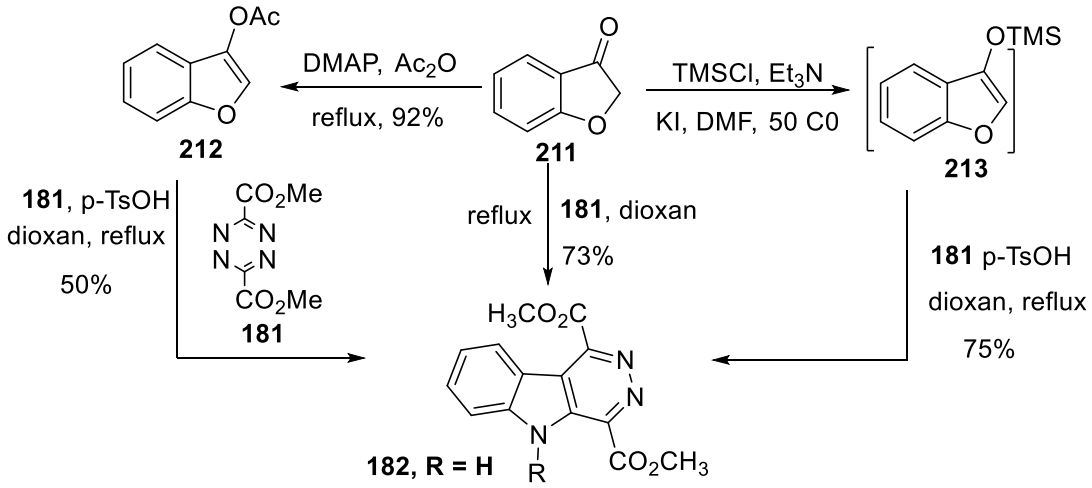
Scheme 44. Synthesis of 1-amino-8-benzyloxy-3,4-dihydropyridazino[4,5-*b*]indol-4-one **206**.

Monge *et al.*[17] reported that 3-formylindole-2-carboxylates **7** were obtained from the corresponding indoles **6** by Vilsmeier-Haack formylation with $POCl_3$ and *N,N*-dimethylformamide (DMF). Nitrile derivatives[17] **201** were synthesized by the reaction of the formyl compound **7** with nitroethane in an acetic acid/sodium acetate medium.[76] Pyridazino[4,5-*b*]indoles[17] **210** were synthesized by reaction of compound **201** (R = O-CH_2-O) with hydrazine hydrate (Scheme 45).



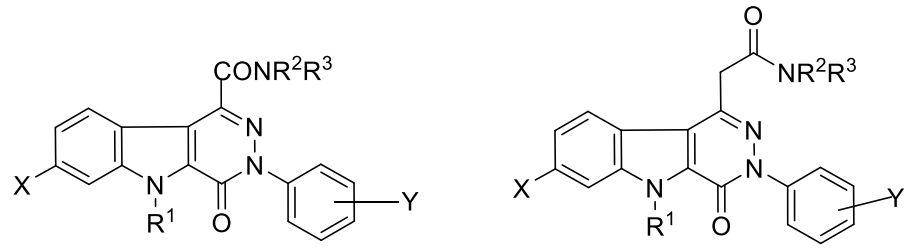
Scheme 45. Synthesis of [1,3]dioxolo[4,5-*f*]pyridazino[4,5-*b*]indol-6-one **210**.

2.13. From Diels–Alder reaction. In 2002, it was mentioned that,[68] the Diels–Alder reaction of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine to a 3-coumaranone system[77] was used in the synthesis of compound **182**. Thus, treatment of coumaranone **211** with acetic anhydride in presence of 4-dimethylaminopyridine (DMAP) under reflux gave 3-acetate-benzo[*b*]furan **212** which was reacted with tetrazine **181** in presence of (*p*-TsOH) to give the corresponding pyridazinoindole derivative **182.** Also, reaction of coumaranone **211** with trimethylsilyl chloride in DMF/Et_3N gave the 3-trimethylsilyl derivative **213** which was reacted directly with tetrazine **181** in presence of (*p*-TsOH) to afford the pyridazinoindole compound **184**. Furthermore, coumaranone **211** was reacted directly with tetrazine **181** to give pyridazinoindole **182** (Scheme 46).



Scheme 46. Synthesis of dimethyl 5-methyl-5*H*-pyridazino[4,5-*b*]indole-1,4-dicarboxylate **182**.

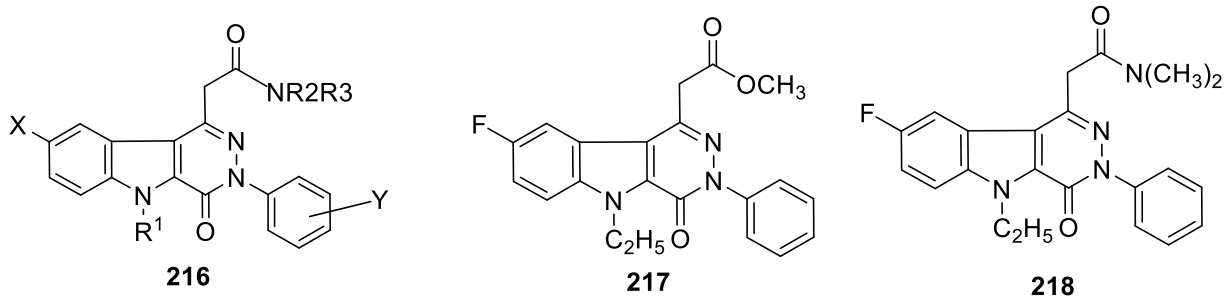
Marguet *et al.*[78] prepared the 4-oxo-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indole-1-carboxamide derivatives **214**. The pyridazinone derivatives **215** had been prepared according to the literaturet[79] (Scheme 47).



Scheme 47. Synthesis of 4-oxo-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indole-1-carboxamide **214**.

Evanno *et al.*[80] described the preparation of 4-oxo-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indole-1-acetamide derivatives as displayed below **216**. For instance, ethyl 5-fluoro-1*H*-indole-2-carboxylate underwent a sequence of *N*-ethylation, acylation by $(COCl_2)_2$ in the 3-position, methanolysis, and cyclization with phenylhydrazine to give the pyridazinoindole intermediate **217**. The latter compound underwent reduction of

the ester with $NaBH_4$ to an alcohol, which was converted into a bromide, and then to a nitrile, which was hydrolyzed to an acid and then amidated, to give compound **218** (Scheme 48).



216, X = H, halo, CH_3, OCH_3, or $OCH_2C_6H_5$
Y = H, 1 or 2 halo atoms, CH_3, OH, OCH_3, or NO_2
R^1= H or C1-C4 alkyl
R^2,R^3 = H or C1-C4 alkyl or CH_2CH_3 or
NR^2,R^3 = azetidinyl, pyrrolidinyl, 3-ethoxypyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or 1,3-thiazolidinyl

Scheme 48. Synthesis of pyridazino[4,5-*b*]indole derivatives **216-218**.

3. Conclusions

Pyridazino[4,5-*b*]indoles are structurally interesting molecules having several biological applications. Hence, development of various synthetic methodologies to synthesize interesting pyridazino[4,5-*b*]indoles have attracted particular attention of synthetic chemists as well as medicinal and material chemists. Ethyl indole-2-carboxylates often plays an important role in the synthesis of different pyridazino[4,5-*b*]indole derivatives. The reactions and applications of pyridazino[4,5-*b*]indoles will be submitted for publication in the next future.

Acknowledgements

I want to thank Professor Hussein El-Kashef, Department of Chemistry, Faculty of Sciences, Assiut University, Egypt and Professor Norbert Haider, Department of Pharmaceutical Sciences, Faculty of Life Sciences, University of Vienna, Austria, for their continuous support to me.

References

1. Bruel, A.; Bénéteau, R.; Chabanne, M.; Lozach, O.; Le Guevel, R.; Ravache, M.; Bénédetti, H.; Meijer, L.; Logé, C.; Robert, J. M. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 5037. https://doi.org/10.1016/j.bmcl.2014.09.017.
2. Martins, P.; Jesus, J.; Santos, S.; Raposo, L.R.; Roma-Rodrigues, C.; Baptista, P.V.; Fernandes, A.R. *Molecules* **2015**, *20*, 16852.

https://doi.org/10.3390/molecules200916852
3. Afzal, O.; Kumar, S.; Haider, M.R.; Ali, M.R.; Kumar, R.; Jaggi, M.; Bawa, S. *Eur. J. Med. Chem.* **2015**, *97*, 871. https://doi.org/10.1016/j.ejmech.2014.07.044
4. Sravanthi, T.; Manju, S. *Eur. J. Pharm. Sci*. **2016**, 91, 1. https://doi.org/10.1016/j.ejps.2016.05.025
5. Panathur, N.; Gokhale, N.; Dalimba, U.; Venkat Koushik, P.; Yogeeswari, P.; Sriram, D. *Med. Chem. Res*. **2016**, *25*, 135. https://doi.org/10.1007/s00044-015-1473-y
6. Bruel, A.; Logé, C.; De Tauzia, M.-L.; Ravache, M.; Le Guevel, R.; Guillouzo, C.; Lohier, J.-F.; Santos, J.S.O.; Lozach, O.; Meijer, L.; et al. *Eur. J. Med. Chem.* **2012**, *57*, 225. https://doi.org/10.1016/j.ejmech.2012.09.001
7. Radini, I.; El-Kashef, H.; Haider, N.; Farghaly, A.-R. *Arkivoc* **2016**, *V*, 101. http://dx.doi.org/10.3998/ark.5550190.p009.763
8. Wróbel, A.; Drozdowska, D. *Curr. Med. Chem*. **2021**, *28*, 910–939. https://doi.org/10.2174/0929867326666191016151018
9. Raimondi, M.V.; Randazzo, O.; La Franca, M.; Barone, G.; Vignoni, E.; Rossi, D.; Collina, S. *Molecules* **2019**, *24*, 1140. https://doi.org/10.3390/molecules24061140
10. Jendele, L.; Krivak, R.; Skoda, P.; Novotny, M.; Hoksza, D. *Nucleic Acids Res*. **2019**, *47*, W345–W349. https://doi.org/10.1093/nar/gkz424
11. Vin, V.; Leducq, N.; Bono, F.; Herbert, J.M. *Res. Commun*. **2003**, *310*, 785–790. https://doi.org/10.1016/j.bbrc.2003.09.079
12. Avan, I.; Güven, A.; Güven, K. *Turk. J. Chem*. **2013**, *37*, 271–291. https://doi.org/10.3906/kim-1210-22
13. Vasir, J.K.; Labhasetwar, V. *Technol. Cancer Res*. *Treat*. **2005**, *4*, 363–374. https://doi.org/10.1177/153303460500400405
14. Salama, E.E.. *BMC Chem*. **2020**, *14*, 30. https://doi.org/10.1186/s13065-020-00682-6
15. Bare, T. M.; Resch, J. F.; Jackson, P. F., EP 512817, 1992; *Chem. Abstr*. **1993**, *118*, 101975.
16. Sircar, I.; Steffen, R. P.; Bobowski, G.; Burke, S. F.; Newton, R. S.; Weishaar, R. E.; Bristol, J. A; Evans, D. B. *J. Med. Chem*. **1989**, *32*, 342. https://doi.org/10.1021/jm00122a011
17. Font, M.; Monge, A.; Curatero, A.; Euorriaga, A.; Martínez-Irujo, J.-J.; Alberdi, E.; Santiago, E.; Prieto, I.; Lasarte, J. J.; Sarobe, P.; Borráts, F., *Eur. J. Med. Chem*., **1995**, *30*, 963. https://doi.org/10.1016/0223-5234(96)88316-4
18. Frechilla, D.; Bernedo, E.; Castiella, E.; Lasheras, B.; Cenarruzabeitia, E.; Monge, A.; Aldana, I.; Alvarez, T.; Losa, M. J.; Font, M., *Eur. J. Pharmacol*. **1992**, *219*, 409. https://doi.org/10.1016/0014-2999(92)90482-J
19. Lopez-de Cerain, A.; Garcia, E.; Gullon, A.; Alvarez, T.; Losa, M. J.; Monge, A., *Arzneim.-Frosch*., **1994**, *44*, 310.
20. Monge, A.; Aldana, I.; Alvarez, T.; Losa, M. J.; Font, M.; Cenarruzabeitia, E.; Lasheras, B.; Frechilla, D.; Castiella, E.; Fernandez-Alvarez, E., *Eur. J. Med. Chem*., **1991**, *26*, 655. https://doi.org/10.1016/0223-5234(91)90202-X

21. Monge, A.; Navarro, M.-E.; Font, M.; Santiago, E.; Alberdi, E.; Martínez-Irujo, J.-J. *Arch. Pharm*. (Weinheim, Ger.) **1995**, *328*, 689. https://doi.org/10.1002/ardp.19953281002
22. Monge Vega, A.; Font Arellano, M.; Aldana Moraza, I., ES 552101, **1987**; *Chem. Abstr.*, **1988**, *109*, 92975.
23. Monge Vega, A.; Aldana, I.; Parrado, P.; Font, M.; Fernandez Alvarez, E., *J. Pharm. Sci.* **1982,** *71*, 1406. https://doi.org/10.1002/jps.2600711224
24. Remers, W. A. in *'Indoles'*, Houlihan, W. J., ed.; Wiley, New York, **1979**; Part 3, p. 357.
25. Haider, N.; Wobus, A. *Arkivoc* **2008,** (vii), 16.
26. Monge, A.; Parrado, P.; Font, M.; Fernandez-Alvarez, E., *J. Med. Chem.,* **1987**, *30*, 1029. https://doi.org/10.1021/jm00389a012
27. Salama, E. E.; Althobaiti, I. O.; Haukka M.; Boraei A. T. A. *Crystals* **2022**, *12*, 353. https://doi.org/10.3390/cryst12030353
28. El-Gendy, A. A.; El-Banna, H. A. *Arch. Pharm. Res.* **2001**, *24*, 21. https://doi.org/10.1007/BF02976488
29. El-Gendy, A. A.; Said, M. M.; Ghareb, N.; Mostafa, Y. M.; El-Ashry, E.-S.H. *Arch. Pharm. Chem. Life Sci*. **2008**, *341*, 294. http://dx.doi.org/10.1002/ardp.200700161
30. Hiremath, S. P.; Ullagaddi, A.; Shivaramayya, K.; Purohit, M. G., *Indian J. Heterocycl. Chem.,* **1994,** *3*, 145; *Chem. Abstr.*, **1994**, *121*, 83093. https://doi.org/10.1002/chin.198901148
31. Nantka-Namirski, P.; Ozdowska, Z., PL 65774, **1972**; *Chem. Abstr.*, **1972**, *77*, 140114.
32. Nantka-Namirski, P.; Ozdowska, Z., *Acta Pol. Pharm.*, **1972,** *29*, 7; *Chem. Abstr.*, **1972**, *77*, 101504.
33. Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P., *Adv. Heterocycl. Chem.,* Suppl. 1, **1976**.
34. Acheson, R. M.; Vernon, J. M., *J. Chem. Soc.,* **1962**, 1148. https://doi.org/10.1039/jr9620001148
35. Said, M. M.; Ghareb, N.; Pierre, H.; El-Gendy, A. A. *Egypt. J. Biomed. Sci***. 2009,** *30,* 1.
36. El-Gendy, A. A.; Abou-Sier, A. H., *Egypt. J. Pharm. Sci.*, **1993,** *34*, 207; *Chem. Abstr.*, **1993**, *122*, 239634.
37. Monge, A.; Angacio, A.; Fernandez-Alvarez, E. *J. Med. Chem.,* **1978**, *13*, 573. https://doi.org/10.1021/jm00114a010
38. Monge Vega, A.; Font Arellano, M.; Aldana Moraza, I., ES 543463, **1986**; *Chem. Abstr.*, **1988**, *108*, 186756. https://doi.org/10.1002/jps.2600711224
39. Monge-Vega, A.; Palop, J. A.; Martinez, M. T.; Fernandez-Alvarez, E., *J. Heterocycl. Chem.*, **1980,** *17*, 249. https://doi.org/10.1002/chin.198033236
40. Monge, A.; Aldana, I.; Lezamiz, I.; Fernandez-Alvarez, E., *Synthesis*, **1984**, 160. https://doi.org/10.1055/s-1984-30765
41. Monge, A.; Palop, J. A.; Tabar, P.; Fernandez-Alvarez, E., *J. Heterocycl. Chem*., **1984,** *21*, 397. https://doi.org/10.1002/chin.198449219
42. Harris, N. L. R., *Tetrahedron Lett.,* **1969**, 4465. https://doi.org/10.1016/s0040-4039(01)88725-6
43. Bruel, A.; Logé, C.; De Tauzia, M.-L.; Ravache, M.; Le Guevel, R.; Guillouzo, C.; Lohier, J.-F.; Santos, J.S.O.; Lozach, O.; Meijer, L.; et al. *Eur. J. Med. Chem.* **2012**, *57*, 225.

https://doi.org/10.1016/j.ejmech.2012.09.001
44. El-Kashef, H.; Farghaly, A. A. H.; Floriani, S.; Haider, N. *Arkivoc* **2003**, (*xiv*), 198. https://doi.org/10.3998/ark.5550190.0004.e19
45. Zhungietu, G. I.; Zorin, L. M.; Gorgos, V. I.; Rekhter, M. A., *Chem. Heterocycl. Compd. (Engl. Transl.)*, **1982,** *18*, 811. https://doi.org/10.1007/bf00506584
46. Gorgos, V. I.; Zorin, L. M.; Zhungietu, G. I.; Rekhter, M. A. *Chem. Heterocycl. Compd.* **1983**, *19*, 1179. https://doi.org/10.1007/bf00506584
47. Black, D. St. C.; Wong, L. C. H. *J. Chem. Soc., Chem. Comm.* **1980**, 200. https://doi.org/10.1039/c39800000200
48. Gribble, G.W. in 'The Alkaloids', Vol. 39, A. Brossi, ed.; *Academic Press, New York*, **1990**, 239. https://doi.org/10.1016/S0099-9598(08)60169-8
49. Guven, A.; Jones, R. A., *Tetrahedron*, **1993,** *49*, 1145. https://doi.org/10.1016/s0040-4020(01)81802-0
50. Reif, G., *Chem. Ber.,* **1909,** *42*, 3036. https://doi.org/10.1002/cber.19090420322
51. Guven, A.; Jones, R. A., *J. Chem. Res., Synop.*, **1993**, 362.
52. Voro, T. N., Ph. D. Thesis, University of East Anglia, **1990**; Dida, F. W. B., Ph. D. Thesis, University of East Anglia, **1991**.
53. Acar, F.; Badesha, S. S.; Flitsch, W.; Gözogul, R.; Inel, O.; Inel, S.; Jones, R. A.; Ögretir, C.; Rustidge, D. C.; *Chim. Acta Turc*., **1981**, *9*, 225; Inel, S.; Jones, R. A.; Ögretir, C. *Tetrahedron*, **1984**, *20*, 3979. https://doi.org/10.1016/0040-4020(84)85076-0
54. Monge Vega, A.; Palop, J. A.; Gracia Casanova, I.; Fernandez-Alvarez, E., *An. R. Acad. Farm.*, **1982,** *48*, 213; *Chem. Abstr.*, **1983**, *98*, 34554. https://doi.org/10.1002/chin.198212282
55. Xin, Z.; Limei W.; Jiyue, S.; Ping, G. *Chem. Res. Chin*. *Univ*., **2015**, *31*, 372. https://doi.org/10.1007/s40242-015-4435-5.
56. Li, R. D.; Zhai, X.; Zhao, Y. F., Yu, Sh.; Gong, P. *Arch. Pharm. Chem. Life Sci*. **2007**, *340*, 424. https://doi.org/10.1002/ardp.200700078.
57. Li, R. D.; Zhai, X.; Zhao, Y. F., Yu, Sh.; Gong, P. *Chin Chem. Lett.* **2007**, *18*, 1191. https://doi.org/10.1016/j.cclet.2007.07.027.
58. Dajka-Halász, B.; Monsieurs, K.; Éliás, O.; Károlyházy, L.; Tapolcsányi, P.; Maes, B. U. W.; Riedl, Z.; Hajós, G.; Dommisse, R. A.; Lemière, G. L. F.; Košmrlj, J.; Mátyus, P., *Tetrahedron* **2004,** *60*, 2283. https://doi.org/10.1016/j.tet.2004.01.024
59. Kurumi, M.; Sasaki, K.; Takata, H.; Nakayama, T. *Heterocycles* **2000**, *53*, 2809. https://doi.org/10.3987/com-00-9049
60. Huntress, E. H.; Hearon, W. M. *J. Am. Chem. Soc.* **1941**, *63*, 2762. https://doi.org/10.1021/ja01855a075
61. Krajsovszky, G.; Matyus, P.; Riedl, Z.; Csanyi, D.; Hajos, G. *Heterocycles* **2001**, *55*, 1105. https://doi.org/10.3987/com-01-9200
62. Kurumi, M.; Sasaki, K.; Takata, H.; Nakayama, T. *J. Heterocycl Chem*. **2001***, 38*, 629. https://doi.org/10.1002/jhet.5570380313
63. Y. Nagawa, M. Goto, K. Honda and H. Nakanishi, *Bull. Chem. Soc. Jpn*. **1989**, *62*, 3109. https://doi.org/10.1246/bcsj.62.3109

64. Y. Nagawa, K. Honda and H. Nakanishi, *Heterocycles*, **1999**, *51*, 1093. https://doi.org/10.3987/com-98-8467
65. Barlow, M. G.; Haszeldine, R. N.; Pickett, J. A., *J. Chem. Soc. Perkin Trans*. *1,* **1978**, 378. https://doi.org/10.1039/p19780000378
66. Seitz, G.; Mohr, R., *Che.-Ztg.* **1987,** *111*, 81. https://doi.org/10.1002/chin.198732085
67. Haider, N.; Wanko, R., *Heterocycles*, **1994,** *38*, 1805. https://doi.org/10.3987/com-94-6726
68. Gassman, P. G.; Van Bergan, T. J., *J. Am. Chem. Soc.* **1973,** *95*, 591. https://doi.org/10.1021/ja00783a049
69. Gonzalez-Gomez, J. C., Uriarte , E. *Synlett*, **2002**, *12*, 2059. https://doi.org/10.1055/s-2002-35569.
70. Benson, S. C.; Palabrica, C. A.; Snyder, J. K., *J. Org. Chem.*, **1987,** *52*, 4610. https://doi.org/10.1021/jo00229a034
71. Takahashi, M.; Ishida, H.; Kohmoto, M., *Bull. Chem. Soc. Jpn.* **1976,** *49*, 1725. https://doi.org/10.1246/bcsj.49.1725
72. Haider, N.; Wobus, A. J. H. *Heterocycles* **2006**, *68*, 2549. https://doi.org/10.3987/COM-06-10879
73. Monge, A.; Palop, J. A.; Goni, T.; Fernandez-Alvarez, E., *J. Heterocycl. Chem.*, **1986,** *23*, 141. https://doi.org/10.1002/chin.198639245
74. Ohashi, M.; Oki, T., Expert. Opin. Ther. Pat., **1996**, *6*, 1285. https://doi.org/10.1517/13543776.6.12.1285
75. Juret, P.; Tanguy, A.; Girard, A.; LeTalaer, J. Y.; Abbatucci, J. S.; Dat-Xuong N.; Le Pecq, J. B.; Paoletti, C., *Eur. J. Cancer*, **1978**, *14*, 205. https://doi.org/10.1016/0014-2964(78)90180-9
76. Blater, H. M.; Lukaszewski, H.; Stevens, G.; *J. Am. Chem. Soc.*, **1961**, *83*, 2203. https://doi.org/10.1021/ja01470a043
77. González-Gómez, J. C.; Santana, L.; Uriarte, E. *Synthesis* **2002**, 43. https://doi.org/10.1055/s-2002-19292
78. Marguet, F.; Froissant, J.; Bartsch-Li, R.; Marabout, B.; Sevrin, M.; WO 0044751, *Chem. Abstr.* **2000**, *133*, 150566.
79. Ferazaz, B.; Benavides, J.; Marguret, F.; Froissant, J.; Marabout, B.; Evanno,Y.; Sevrin M.; Janiak, P., WO 0044384, *Chem. Abstr.*, **2000**, *133*, 144945.
80. Evanno, Y.; Dubois, L.; Sevrin, M.; Marguet, F.; Froissant, J.; Bartsch, R.; Gille, C.; WO 9906406, *Chem. Abstr.*, **1999**, *130*, 168385.

Authors' Biographies

Abdel-Rahman Farghaly, is professor of Organic Chemistry at Department of Chemistry, Faculty of Science, Assiut University, Egypt. He has received his B.Sc. (1989) and M.Sc. (1994) in Organic Chemistry at faculty of Science, Assiut University and completed his Ph. D through Chanel Scholarship between University of Assiut and University of Vienna (2001). His Ph.D. thesis has been performed in the Department of Drug and Natural Product Synthesis, Faculty of Life Sciences, University of Vienna, Vienna- Austria in the period from 15/10/1999 to 15/10/2001. He is interested in the field of Medicinal Chemistry, especially in the synthesis of new compounds focusing on a particular heterocyclic ring system which appears of considerable pharmaceutical interest and total synthesis of natural products. He has a practical placement and training assignment at the University of Nice-Sophia Antipolis, Department of Chemistry, Laboratory Falvour- France, Synthesis and interactions during the period from 02- 31/5/2005. He completed a postdoctoral fellowship at Department of Chemistry, Sogang University, in total synthesis of natural products and medicinal chemistry laboratory, 1 Shinsoo-dong, Mapo-Gu, Seoul 121-742. Korea, from 12/05/2006 to 11/ 03/2007, sponsored by KOSEF. He had two postdoctoral fellowships at Department of Chemistry, laboratoire des Molécules Bioactives et des Arômes, CNRS, UMR 6001, Université de Nice-Sophia Antipolis, 06108 Nice Cedex 2, France during the period from 16/10/2007 to 12/12/2007 and from 09/06/2008 to 31/08/2008.

