Pyrazino[1,2-a]Indoles

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Contributor: Olivier Provot

The pyrazino[1,2-a]indole unit is a tricyclic aromatic nucleus combining an indole and a pyrazine linked by the N5 and C9a atoms. The Synthesis and Biological Activities of Pyrazino[1,2-a]Indole and Pyrazino[1,2-a]Indol-1-One Derivatives is presented.

Keywords: pyrazinoindole ; pyrazinoindolone ; cyclization ; catalysis ; biological activity

1. Introduction

The pyrazino[1,2-*a*]indole unit is a tricyclic aromatic nucleus combining an indole and a pyrazine linked by the N5 and C9a atoms (**Figure 1**).

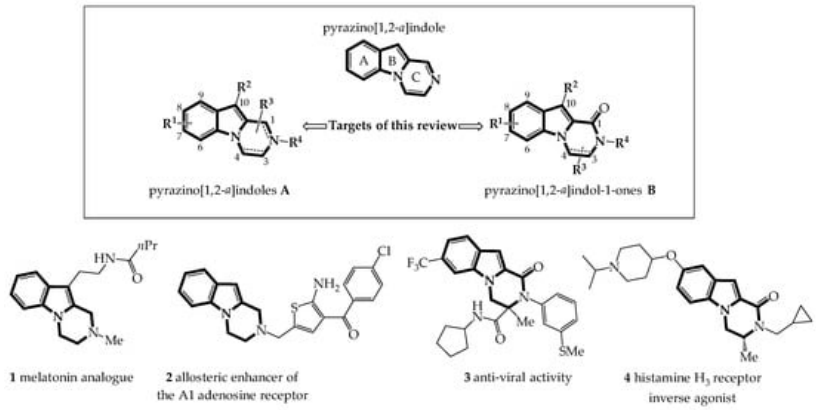
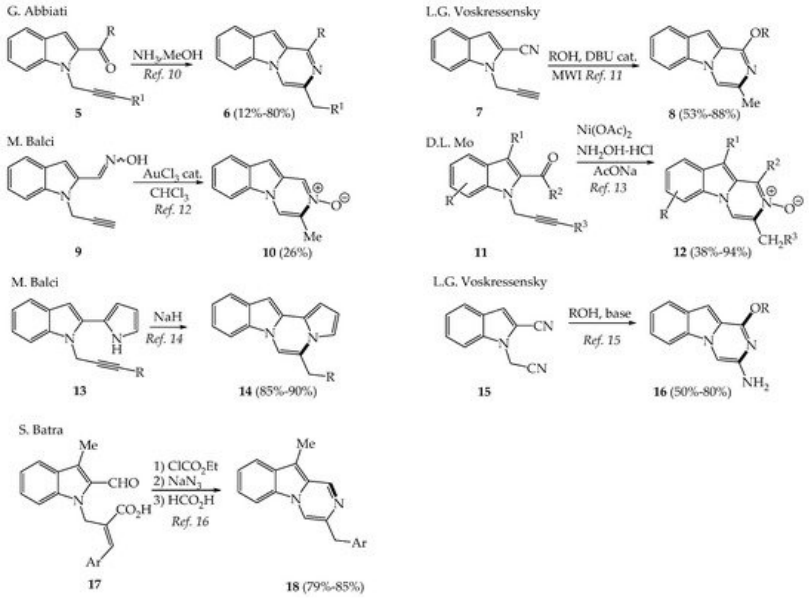


Figure 1. Targets of this review and selection of biologically active tetrahydro-pyrazino[1,2-*a*]indoles **1a**, **2a** and dihydro-pyrazino[1,2-*a*]indol-1-ones **3a**, **4a**.

The access to this substituted aromatic nucleus has been well studied since 1997 by the chemist community from a synthetic point of view and for its potential in medicinal chemistry [1][2]. In parallel, structural modifications of the pyrazino[1,2-*a*]indole nucleus showed that (3,4-dihydro)pyrazino[1,2-*a*]indoles (type A) and (3,4-dihydro)-pyrazino[1,2-*a*]indol-1-ones (type B) were efficient pharmacophores used in a variety of diseases. To illustrate, 3,4-dihydropyrazinoindoles **1** [3] and **2** [4] (type A) have been showed to be effective at melatonin and adenosine receptors, while 3,4-dihydropyrazinoindol-1-ones **3** [5] and **4** [6] (type B) have been studied for their anti-viral and anti-allergenic activities, respectively.

2. Recent Synthetic Approaches to Variously Substituted Pyrazinoindoles and 3,4-Dihydropyrazinoindoles

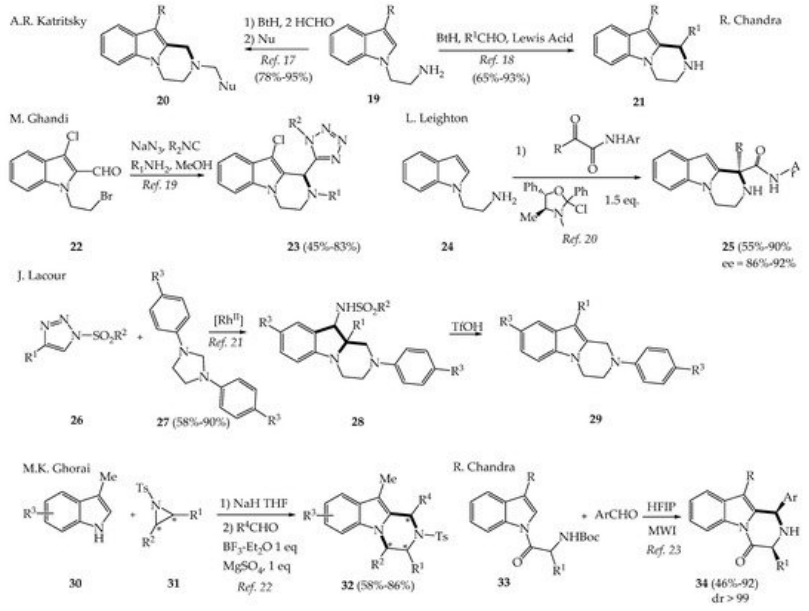
The creation of the pyrazino[1,2-*a*]indole nucleus was mainly achieved by cyclizing indole having various groups (CHO, ketone, imine, nitrile, etc.) on C2 with a nucleophile linked to the indole nitrogen atom, thus creating the pyrazino C-ring (Scheme 1). For example, 2-substituted-1-(prop-2-yn-1-yl)-1*H*-indoles **5**, **7**, **9**, **11**, **13** transformed into pyrazinoindoles **6**, **8**, **10**, **12** and **14** respectively by intramolecular cyclization using NH_3 in MeOH, [7][8] DBU under microwave irradiation, [9] $AuCl_3$ [10] as triple bond activator, $Ni(OAc)_2$ in the presence of hydroxylamine [11] or NaH in DMF [12].



Scheme 1. Synthesis of pyrazinoindoles.

The C-ring of the pyrazino[1,2-*a*]indole system has been also built by alcoholate promoted cyclization of indolodinitrile compound **15** [13] and by Curtius reaction using Morita–Baylis–Hillman derivatives **17** [14] with good to excellent yields.

The synthesis of variously substituted pyrazinoindoles having a saturated C-ring has been more studied than that of their aromatic counterparts, probably because these compounds offer more functional diversity such as diastereoselective accesses, but mainly because they have shown superior efficacy in medicinal chemistry. Among the simplest reactions described to prepare these compounds was the one proposed by Katritzky, who used a cycloaddition reaction between a *N*-ethylamine-indole **19** and formaldehyde in the presence of benzotriazole (Bt) (Scheme 2). A subsequent nucleophilic substitution reaction of the benzotriazole gives rise to various *N*-substituted pyrazinoindoles **20** [15]. *N*-ethylamine-indoles **19** also reacted, in a complementary approach, with aldehydes and Bt in the presence of Lewis acids to give C1-substituted pyrazinoindoles **21** [16].



Scheme 2. Synthesis of 1,2,3,4-tetrahydro-pyrazinoindoles.

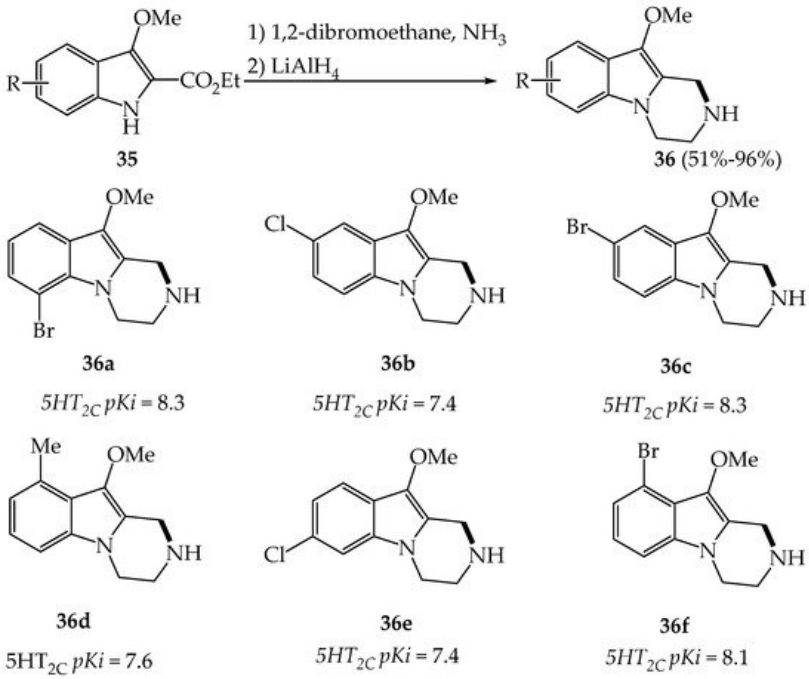
A Ugi-azide four component approach was recently published to prepare a series of *N*-substituted pyrazinoindoles **23** having on C1 a substituted tetrazole ring [17]. Leighton et al. proposed highly enantioselective iso-Pictet–Spengler reactions using the condensation of 2-(1*H*-indol-1-yl)ethanamine **24** with a variety of α-ketoamides, followed by the addition of a commercially available chiral silicon Lewis acid (L*) to give 1,1-disubstituted-tetrahydropyrazino[1,2-*a*]indoles **25** with good yields (55–90%) and high enantioselectivity (ee = 86–96%) [18]. Guinchard et al. also reported an Au(I)-catalyzed Pictet–Spengler reaction to prepare a variety of complex heterocyclic compounds including tetrahydro-pyrazinoindoles with good yields ranging from 43 to 93% [19]. In 2021, Lacour et al. reported that *N*-sulfonyltriazoles **26** and imidazolines **27** reacted under rhodium catalysis to give a variety of hexahydro-pyrazinoindoles **28** with excellent

yields easily transformed in tetrahydropyrazinoindoles **29** after a welcome rearrangement in triflic acid TfOH [20]. Ghorai et al. reported in 2018 of an elegant synthesis of 1,3-disubstituted 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **32** with excellent stereoselectivity (de, ee >99%) via base-mediated ring opening of chiral aziridines **31** with skatoles **30** followed by BF_3-OEt_2 catalyzed Pictet–Spengler reaction [21]. Chandra group reported synthesis of di-substituted pyrazinoindol-4-ones **34** with an excellent diastereoselectivity (>99%) via a Pictet–Spengler reaction by mixing 3-substituted-*N*-acylindoles **33** and aromatic aldehydes in the presence of hexafluoroisopropanol (HFIP) under microwave irradiation [22].

3. Biologically Active Pyrazino[1,2-a]indoles

3.1. Neuropsychiatric Properties

Bos et al., in a program dedicated to the discovery of novel drugs for the treatment of neuropsychiatric disorders, synthesized a variety of pyrazino[1,2-*a*]indoles **36a–f** which were found as partial agonist ligands at the $5HT_{2C}$ receptor (Scheme 3) [23].



Scheme 3. Synthesis of tetrahydro-pyrazinoindoles **36** and their binding data at the $5HT_{2C}$ receptor subtype.

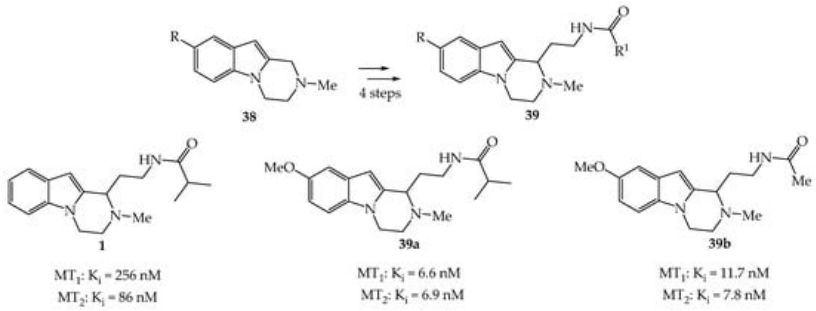
Pyrazinoindole derivatives **36a–f** were prepared according to a *N*-alkylation/cyclization/reduction sequence of indoles **35** having an ester function on C2 [23]. Pyrazinoindoles **36** were found to be partial agonists at the $5HT_{2C}$ receptor subtype binding with a higher affinity than for $5HT_{2A}$ receptors. Best affinities for $5HT_{2C}$ receptor were observed for 10-methoxy-pyrazinoindoles having on 6, 7, 8 or 9-position of the A-ring bulky atoms (F < Me < Cl < Br). In animals, **36d** showed a 30-fold selectivity for $5HT_{2C}$ receptors compared to $5HT_{2A}$ receptors and an only 3-fold selectivity compared to $5HT_{1A}$ receptors. In vivo results (rats and monkeys) also demonstrated that pyrazinoindole **36d** had a promising therapeutic potential for the treatment of various psychiatric disorders, such as obsessive-compulsive disorders, panic anxiety or depression.

Imidazoline receptors exist in two forms, I_1 and I_2, for which there are very few ligands that are selective for one of the two forms. As a result, it is very difficult to assign a well-defined role to them even though I_2 receptors have been described as involved in a variety of CNS disorders. Tetrahydro-pyrazinoindoles **37a–c** were evaluated by Glennon group for their potential as I_2 imidazoline receptor ligands [24] due to their resemblance to β-carbolines [25] and imidazo-pyridoindoles (**Figure 2**) [26].

Figure 2. Tetrahydro-pyrazinoindoles **37** and their binding data at I_2 and α-adrenergic receptors.

Remarkably, 8-methoxypyrazinoindole **37c** binds to I_2 receptors with high affinity (*Ki* = 6.2 nM) and has a 1500-fold selectivity for I_2 receptors compared to α2-adrenergic receptors (*Ki* = 9550 nM) and a 1000-fold selectivity for I_1 receptors. A similar high selectivity for **37c** was also observed towards I_2 receptors compared to serotonin $5HT_{2A}$ and $5HT_{2C}$ receptors.

Zlotos et al. synthesized a series of C1-substituted tetrahydro-pyrazinoindoles **1** and **39** as novel potent melatoninergic ligands from **38** in 4 steps (Scheme 4) [3].

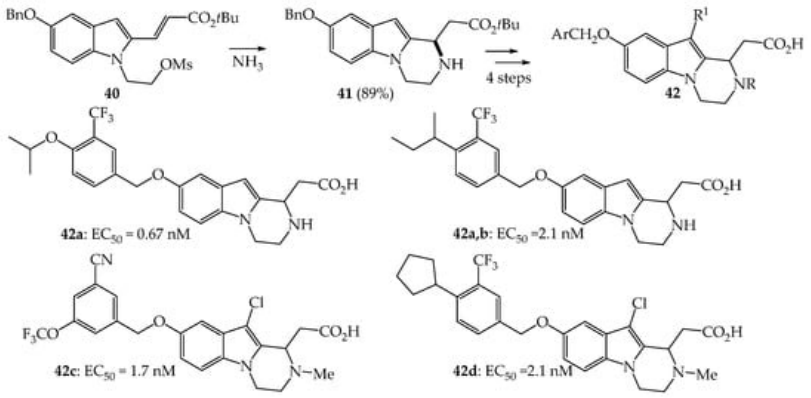


Scheme 4. Synthesis of tetrahydro-pyrazinoindoles **1** and **39**.

The affinity of pyrazinoindoles **1**, **39a**,**b** for human MT1 and MT2 melatonin receptors in Chinese Hamster Ovary (CHO) cells was measured by competition binding analysis using 2-[^{125}I]-iodomelatonin. The most active compound **39a** was found to be an interesting ligand for MT1 and MT2 receptors with excellent affinity, but with no subtype selectivity (MT1: Ki = 6.6 nM; MT2: Ki = 6.9 nM, respectively). This tetrahydro-pyrazinoindole compound was found to be a partial agonist at MT_1 receptors and possessed no intrinsic activity at MT_2 receptors. It is noteworthy that the treatment of pyrazinoindole 7 (R = H) with MeI gave the corresponding *N*-dimethyliodonium salt which was found to displace [^{3}H]-cytisine from the nicotinic binding sites on rat cerebral cortex and was revealed to be a nicotinic agonist ligand [27].

3.2. Auto-Immune Properties

Among the C1-substituted pyrazinoindoles, we can cite the work of Buzard et al. who prepared a series of C3-tetrahydro-pyrazinoindoles **42** from the same precursor **41** resulting from an intramolecular Michael reaction carried out on mesylate **40** in the presence of NH_3 (Scheme 5) [28]. In a previous work, Buzard et al. showed that some cyclopenta[*b*]indoles were very potent agonists of the sphingosine 1-phosphate ($S1P_1$) receptor that could be used for the treatment of certain autoimmune diseases [29]. Due to the structural resemblance to these indoles, a series of tricyclic analogues (pyridoindoles, oxazinoindoles and pyrazinoindoles) were designed, synthesized, and evaluated. Pyridoindoles proved to be the most promising compounds in this series of fused-indole compounds, even if pyrazinoindoles **42a–d**, prepared from **41** in four steps (*N*-Boc protection, *O*-debenzylation, *O*-functionalization with various benzyl chlorides and *t*-Butylester hydrolysis) showed interesting activities as $S1P_1$ receptor agonists with nanomolar EC_{50} values. For the treatment of autoimmune disease as rheumatoid arthritis, Hill et al. synthesized a pyrazinoindole derivative having on C10 a substituted maleimide nucleus which was unfortunately found to be poorly active as protein kinase C inhibitor (IC_{50} = 540 nM) [30].



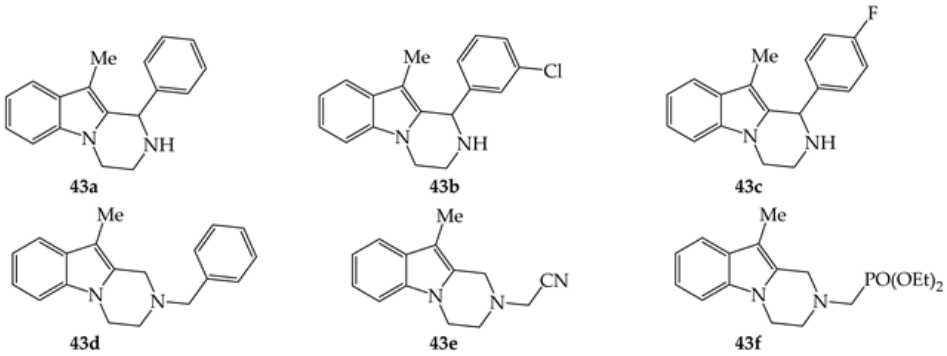
Scheme 5. Synthesis of tetrahydro-pyrazinoindole **41** and human $S1P_1$ cAMP EC_{50} values of derivatives **42a–d**.

3.3. Anti-Bacterial and Anti-Fungal Properties

A series of 15 pyrazinoindoles **43** were prepared according to Refs. [15][16] (see Scheme 2) by Verma group and evaluated for their anti-bacterial properties (**Table 1**) [31]. The in vitro antibacterial activity was evaluated by disc diffusion assay

(DDA) using pathogenic strains of *Staphylococcus aureus*, *Salmonella typhi*, *Streptomyces thermonitrificans*, *Pseudomonas aeruginosa* and *Escherichia coli*. It was demonstrated that **43a** was only active on *P. aeruginosa* and, similarly, a significant activity on *P. aeruginosa* and *S. thermonitrificans* was noticed with **43b**. Pyrazinoindoles **43c–e** were found to be active against all tested strains but with a relatively modest efficacy when compared with gentamycin. From these results, it seems that the presence of substituents on the nitrogen atom of pyrazinoindoles is deleterious for a satisfactory anti-bacterial activity. Pyrazinoindoles having an aromatic C-ring were not active against all tested strains.

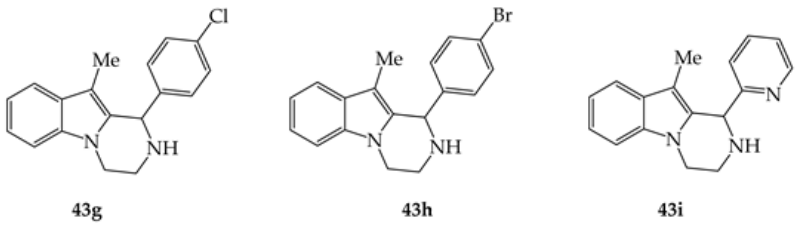
Table 1. Anti-bacterial properties of tetrahydro-pyrazinoindoles **43a–f**.



Cpnd	DDA Minimum Inhibitory Concentrations (μg/disc)			
	S. aureus	*S. typhi*	*P. aeruginosa*	*S. thermonitrificans*
43a	-	-	3.75	-
43b	-	-	15	3.75
43c	30	30	30	7.5
43d	15	60	60	60
43e	15	30	60	30
43f	-	-	60	60
Gentamycin	1	1	0.5	1

Tetrahydro-pyrazinoindoles **43** were also evaluated for their anti-fungal activity against *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus. niger* and *Candida albicans* (**Table 2**) [32]. The anti-*Aspergillus* activity was evaluated by disc diffusion assay (DDA) and the anti-*Candida* activity was investigated by microbroth dilution assay. The more active tetrahydro-pyrazinoindoles **43** presented in **Table 2** displayed a mild to moderate anti-fungal activity, even if these pyrazinoindoles were found to be, in vitro, less cytotoxic than Amphotericin B when used at high concentrations. SARs with compounds **43** were similar for both anti-bacterial and anti-fungal activities.

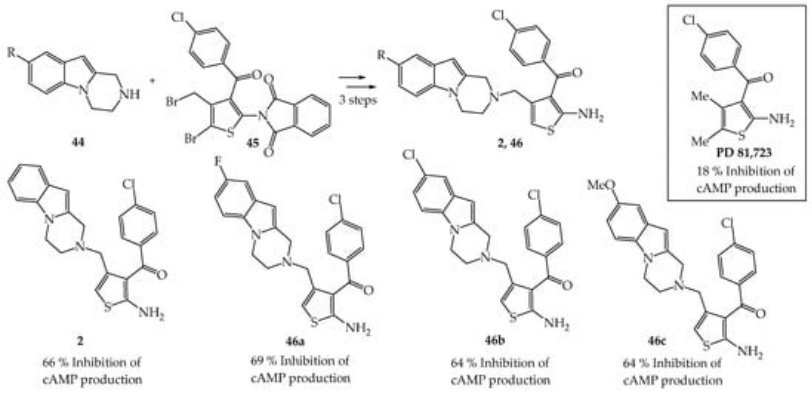
Table 2. Anti-fungal properties of tetrahydro-pyrazinoindoles **43g–l** and **43c**.



Cpnd	DDA Minimum Inhibitory Concentrations (µg/disc)			
	A. flavus	*A. fumigatus*	*A. niger*	*C. albicans*
43g	11.7	5.8	11.7	15.6
43h	47	23	47	62.5
43i	187	94	187	125
43c	47	47	47	125
Gentamycin	1	1	0.5	1

3.4. Anti-Arrhythmic, Anti-Lipolytic, Neuro- and Cardio-Protective Properties

In a program dedicated to the discovery of ligands able to activate the A_1AR adenosine receptor, Romagnoli et al. proposed some derivatizations on PD81,723, an allosteric modulator acting at the A_1AR receptor, enhancing the functional effects of adenosine receptor subtype (Scheme 6) [4].

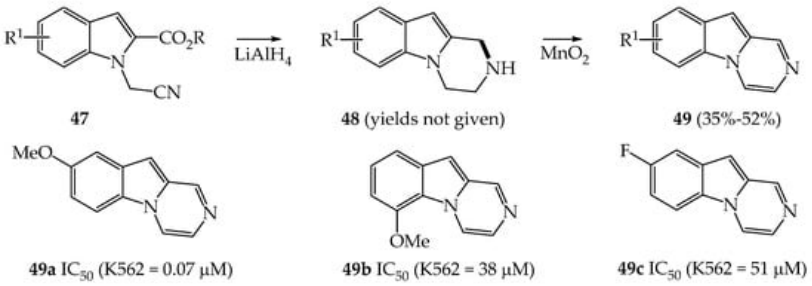


Scheme 6. Synthesis of tetrahydro-pyrazinoindoles **2**, **46a–c** and effect in cAMP assay in hA_1CHO cells.

Thus, pyrazinoindoles **2**, **46a–d** were synthesized from dibromothiophene **45** and 8-substituted pyrazinoindoles **44** in 3 steps (S_N2 reaction, debromination, phthalimide hydrolysis). Pyrazinoindoles **2**, **46a–c** were next evaluated in a functional assay for their ability to inhibit forskolin stimulated cAMP production via the hA_1-AR in intact Chinese hamster ovary (CHO) cells. The four pyrazinoindoles **2**, **46a–c** were found to be significantly more active than the reference PD 81,723. The best compound 8-fluorated pyrazinoindole **46a** inhibited the percentage of cAMP production by 69% vs. 18% for PD 81,723. It was also shown that these derivatives significantly inhibited antagonist binding at the hA_1AR, hA_2AR or hA_3AR receptors.

3.5. Anti-Cancer Properties

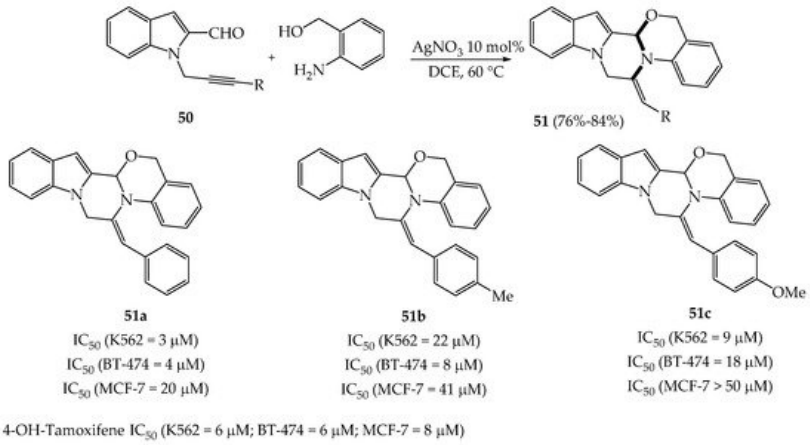
Romagnoli et al. studied in 2009 the antiproliferative properties of a series of pyrazinoindoles **17** which were prepared from the reduction/cyclization of *N*-cyanomethyl derivatives **47** followed by an oxidation reaction using MnO_2 (Scheme 7) [33].



Scheme 7. Synthesis and anti-cancer properties of a selection of pyrazinoindoles **49a–c**.

It was shown that pyrazinoindole **49a** was the more cytotoxic derivative against human leukemia K562 cancer cells with a promising IC_{50} value of 0.07 µM. However, this strong cytotoxicity was not observed in other cell lines such as murine leukemia (L1210), murine mammary carcinoma (FM3A), human T-lymphoblastoid (Molt/4 and CEM) and human cervical carcinoma (HeLa) cells with IC_{50} values superior to 20 µM.

In view of preparing pyrazinoindoles **51** as anti-cancer agents, Kumar et al. mixed *N*-propargyl indoles **50** having an aldehyde function on C2 with (2-aminophenyl)methanol derivatives in the presence of a catalytic amount of $AgNO_3$ (Scheme 8) [34]. After the reaction of δ-alkynyl aldehydes and nucleophilic anilines, the alcohol function adds on the imine thus creating a second bond (C-O). The third bond creation (C-N) of this process occurs with the nitrogen atom of the imine which reacts with the alkyne triple bond activated by $AgNO_3$ in a 6-*exo*-*dig* manner (76–84%).



Scheme 8. Synthesis of pyrazinoindoles **51** and their IC_{50} values against three human cancer cell lines.

Pyrazinoindoles **51** were next evaluated against 3 cancer cell lines (K562 leukemia cells, BT-474 human breast cells; MCF-7 breast cancer cells). As it can be seen in Scheme 8, the more cytotoxic compound was **51a** against K562 and BT-474 cancer cells. This pyrazinoindole was significantly more active than 4OH-tamoxifene, used as reference compound, against K562 and BT-474 cells but displayed a lower IC_{50} value against MCF-7 cancer cells. This result is interesting as **51a** exhibited maximum cytotoxicity in p53-deficient cell lines K562 and BT-474 cells but not in p53 wildtype MCF-7 cells. It would certainly be interesting to perform SARs on these structures and to evaluate them on a panel of human cancer lines resistant to the usual treatments.

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