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REVIEW ARTICLE

Antihypertensive activity of indole and indazole analogues: A review

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Abstract Heterocyclic compounds occupy an important position in chemistry because of their wide range of uses in drug design, photochemistry, agrochemicals, and other fields. Indole and indazole scaffolds are available from natural and synthetic sources, and molecules containing these scaffolds have been shown to have various biological effects, including anti-inflammatory, antibacterial, antiviral, antifungal, analgesic, anticancer, antioxidant, anticonvulsant, antidepressant, and antihypertensive activities. Indole and indazole molecules bind to receptors with high affinity, and thus are useful for the study of bioactive compounds involved in multiple pathways. In this review, we highlight the antihypertensive activity and the mechanisms of action of indole and indazole derivatives. In addition, structure–activity relationship studies of the antihypertensive effect are presented.

Contents

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1. Introduction

Hypertension is often referred to as the "silent killer" because most people are unaware that they are affected by hypertension. Hypertension is regarded as one of the most important risk factors for cardiovascular illnesses, affects approximately one billion people globally, and is closely related to congestive heart exhaustion, stroke, and coronary heart disease. As per WHO hypertension report 2019, about 1.13 billion people globally have hypertension (Britannica encyclopedia, 2021, Bai et al., 2018, Gilyarevskiy, 2017, Höcht et al., 2019, Kishi and Fujii, 2019, Kucan et al., 2018, Perez et al., 2015). Reducing hypertension can decrease cardiovascular illness complications and mortality. Recently, the adjustment of vasomotor tension and the theory of central antihypertensive medicines have been widely investigated (Burnier et al., 2019, Bialy et al., 2018, Garkani-Nejad and Poshteh-Shirani, 2013, Tamargo et al., 2015). The vasodilating effects of the third generation β-adrenolytics are produced via diverse mechanisms, for instance, α_1-blockade, α_2-adrenoceptor agonistic action, β_2-agonistic action, NO release, antioxidant action, and calcium (Ca^{2+}) blockade, Krasavin, 2015, Zeng et al., 2016, Liu et al., 2021). Despite the availability of many antihypertensive drugs, it is often necessary to combine several of these drugs for the effective treatment of hypertension.

Nitrogen-containing heterocycles are important pharmacological structures that are present in many commercial medicines. Heterocyclic chemistry is a branch of organic chemistry that plays a pivotal role in the construction of synthetic molecules. Indole and indazole are considered to be important heterocyclic moieties because of the diverse biological activities of compounds containing these structures, and are useful molecules in drug discovery. Indole and indazole are aromatic heterocyclic organic compounds, with the chemical formulae C_8H_7N and $C_7H_6N_2$, respectively, which have a bicyclic structure consisting of a benzene ring fused with a pyrrole or pyrazole ring, respectively. Indole and indazole derivatives can have biological activity, for example, anti-malarial, anti-HIV, antifungal, antibacterial, anti-convulsion, anticancer, anti-inflammatory, antihypertensive, and anti-diabetic activity (Aingh et al., 2017, Ates-Alagoz et al., 2005, Ali et al., 2013, Cerecetto et al., 2005, Chu et al., 2017, Dong et al., 2018, Dousson et al., 2016, El-Ayoubi et al., 2002, Garg et al., 2019, Stec et al., 2016, Zhang et al., 2017, Pérez-Villanueva et al., 2018, Sun et al., 2017, Kim et al., 2013, Zhao et al., 2013, Praveen et al., 2011). Thus, the discovery of new indolyl and indazolyl derivatives is of interest.

To date, few reviews have reported the synthesis, medicinal use, and SAR of indole and indazole derivatives in terms of antihypertensive activity. Therefore, in this review, we summarize the various synthetic routes for indole- and indazole-based analogues with a focus on analogues with antihypertensive activity and present information from SAR studies. We believe that this review will provide substantial guidance for further research on drugs to alleviate hypertension. Information was compiled on the synthesis, and antihypertensive activity from *in vitro* and *in vivo* studies, of various indole and indazole derivatives from various research publications obtained from searching scientific databases (e.g., PubMed and ScienceDirect) focused on the period 1980–2021.

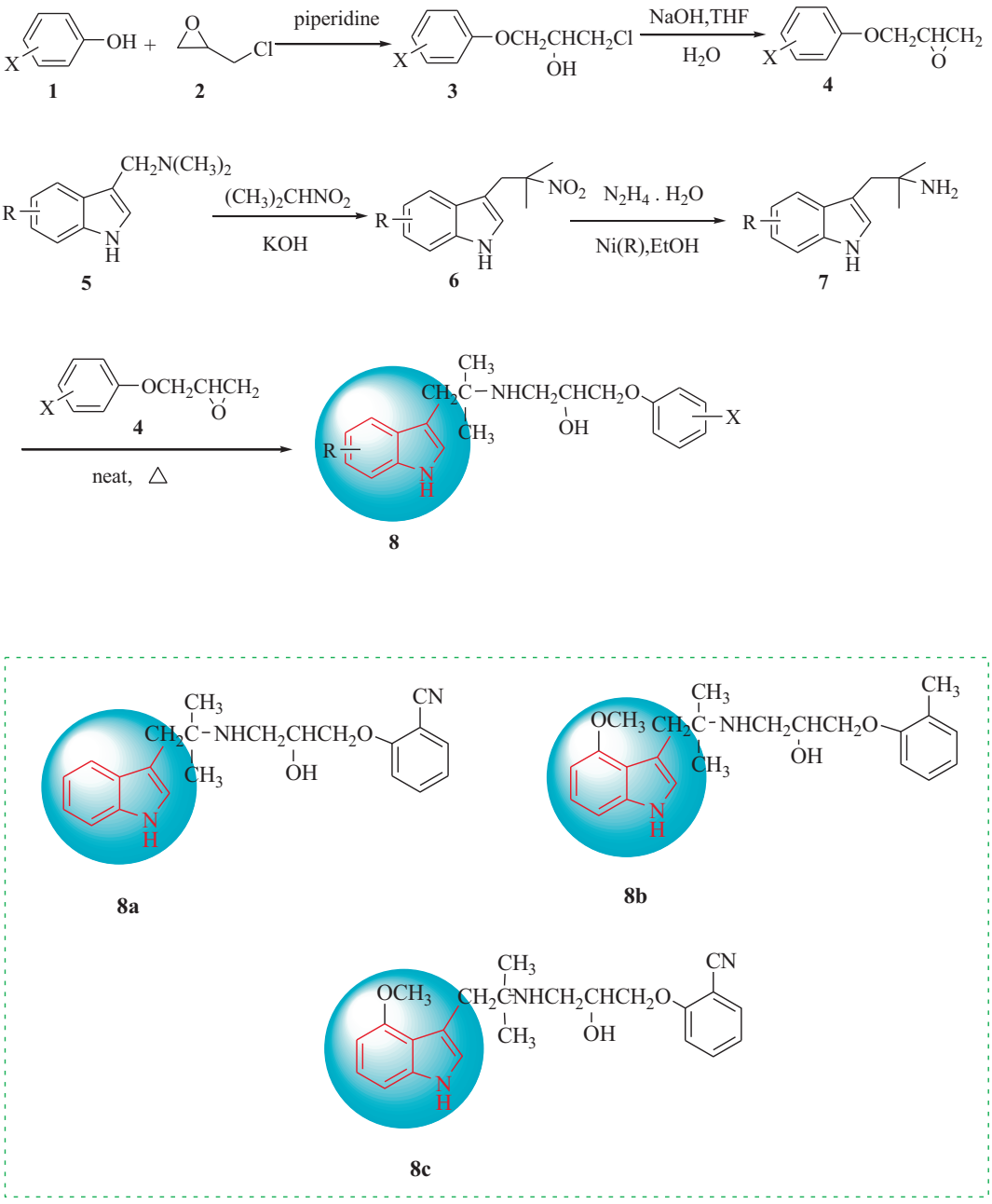
2. Synthetic strategies and SAR studies of the antihypertensive activity

Indole analogues are known as "privileged structures" that can bind to a variety of high affinity receptors. Indole and indazole derivatives have been demonstrated to have antihypertensive effects (Kornicka et al., 2017, Klioze and Ehrgott, 1979, Lavrado et al., 2010, Ozaki, 1989, Shi et al., 1992, Song et al., 2000, Bunch et al., 2004, Horton et al., 2013, Rajan et al., 2018, Singh, T.P. and Singh, O.M, 2018). This review describes the synthesis and *in vivo*, and *in vitro* studies of various indole and indazole derivatives.

2.1. Analogues containing an indole skeleton

Kreighbaum et al. (Kreighbaum et al., 1980) a adopted a three-step process to synthesize 25 phenoxypropanolamine-bearing indole analogues. First, epichlorohydrin (2) reacted with a substituted phenol in piperidine (1) to obtain the intermediate (3), which was transformed to an epoxide (4) under conditions of NaOH and tetrahydrofuran. Then, 2-nitropropane and a substituted gramine (5) were refluxed with KOH to provide 3-(2-methyl-2-nitropropyl)-1*H*-indole (6) and the amine derivatives (indolyl *tert*-butylamines) (7) were obtained using Raney nickel and hydrazine hydrate. Ultimately, the indolyl *tert*-butylamine was refluxed with the epoxide (4) to form the final target compound (8), as shown in Scheme 1. The generated analogues were assessed for antihypertensive activity *in vivo* from the vasodilating effect at a dosage of 100 $mL{\cdot}kg^{-1}$ orally administered (*p.o.*) and 2 $mL{\cdot}kg^{-1}$ intravenous injection (*i.v.*) in rats with ganglion block and SHR, respectively. Compound **8a** displayed a remarkable antihypertensive activity in SHR and compounds **8b** and **8c** substituted with 2-methyl and 2-cyano groups, respectively, on the benzene ring of the phenylpropanolamine moiety, and indoles with 5-methoxy substitution exhibited better vasodilation properties than the other synthesized compounds (Fig. 1).

Monge Vega et al. (Monge Vega et al., 1982) prepared a series of compounds, compounds 12a-12d and 13a-13d in Fig, 1, and assessed the antihypertensive properties. Compounds 9 were reacted with hydrazine hydrate to undergo cyclization to form compounds 10. Then, under basic conditions, P_2S_5 was used to transform the keto group into a thioketone (11). And then, the derivatives (12) were obtained with hydrazine hydrate. Finally, the derivatives 12 underwent cyclization with substituted formaldehyde form the target derivatives 13 as shown in Scheme 2. The changes in the arterial pressure in SHR were measured after intraperitoneal injection (*i.p*) of 1, 2, and 5 $mL{\cdot}kg^{-1}$ and oral administration of



Scheme 1 Synthesis of 25-indole derivatives of phenoxypropanolamines.

2.5 mL·kg^{-1} of the synthesized compounds. Administration of compounds **12a** and **12b** resulted in a marked decrease in the arterial pressure. The most active compounds **12c** and **12d** were assessed in desoxycorticosterone-saline rats (2 mL·kg^{-1} and 5 mL·kg^{-1}, *i.p*), the results showed that**12c** and **12d** remarkably decreased the arterial blood pressure. Compounds 13 exhibiting antihypertensive effects do not necessarily have a hydrazine group, indicating that the hydrazine is not necessary for antihypertensive activity (Fig. 1).

Kim et al. produced compounds 17 and assessed their antihypertensive activity (Kim et al., 1983). Compounds 14 were acylated with methacryloyl chloride to obtain substituted ethyl 1-acryloyl-indoline-2-carboxylated derivatives 15, which were hydrolyzed to give 1-acryloyl-indoline-2-carboxylic acids (16) under basic conditions. The subsequent treatment of the 1-acryloyl indoline-2-carboxylic acids (16) with thiobenzoic acid provided the substituted 1-(3-mercaptopropanoyl)indoline-2-carboxylic acid derivatives (17) (predominant product 70%), as shown in Scheme 3. Among the compounds **17**, compound **17b** (*S, S*) displayed the greatest activity with $IC_{50} = 3.7 \times 10^{-9}$ M, which is three times the activity of captopril. Compared with captopril, the hydrophobicity of **17b** (*S, S*) was increased, which indicated that there is a hydrophobic group in the active site of ACE. Compound **17b** (*S, S*) showed oral antihypertensive activity in spontaneously hypertensive rats that was 27 times greater than captopril. The benzoyl **17a** (*S, S*) was 24 times more potent than captopril. The considerable antihypertensive activity shown by **17a** and **17b** indicated that as well as

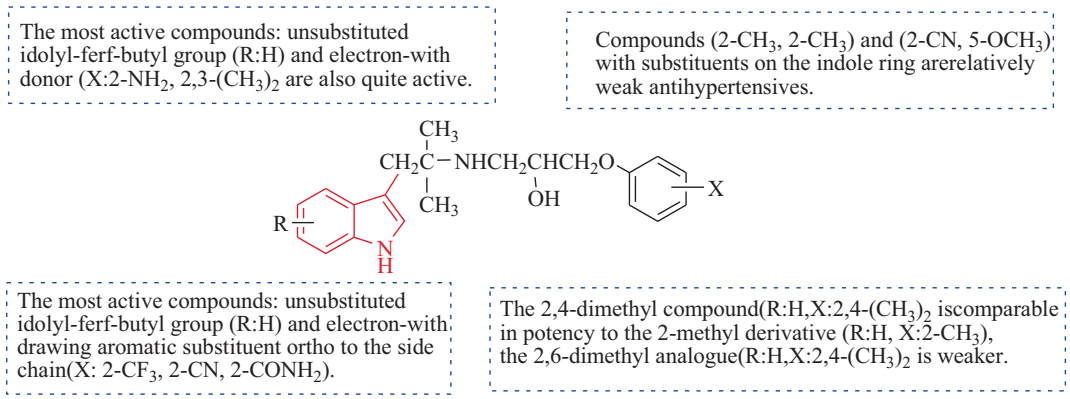
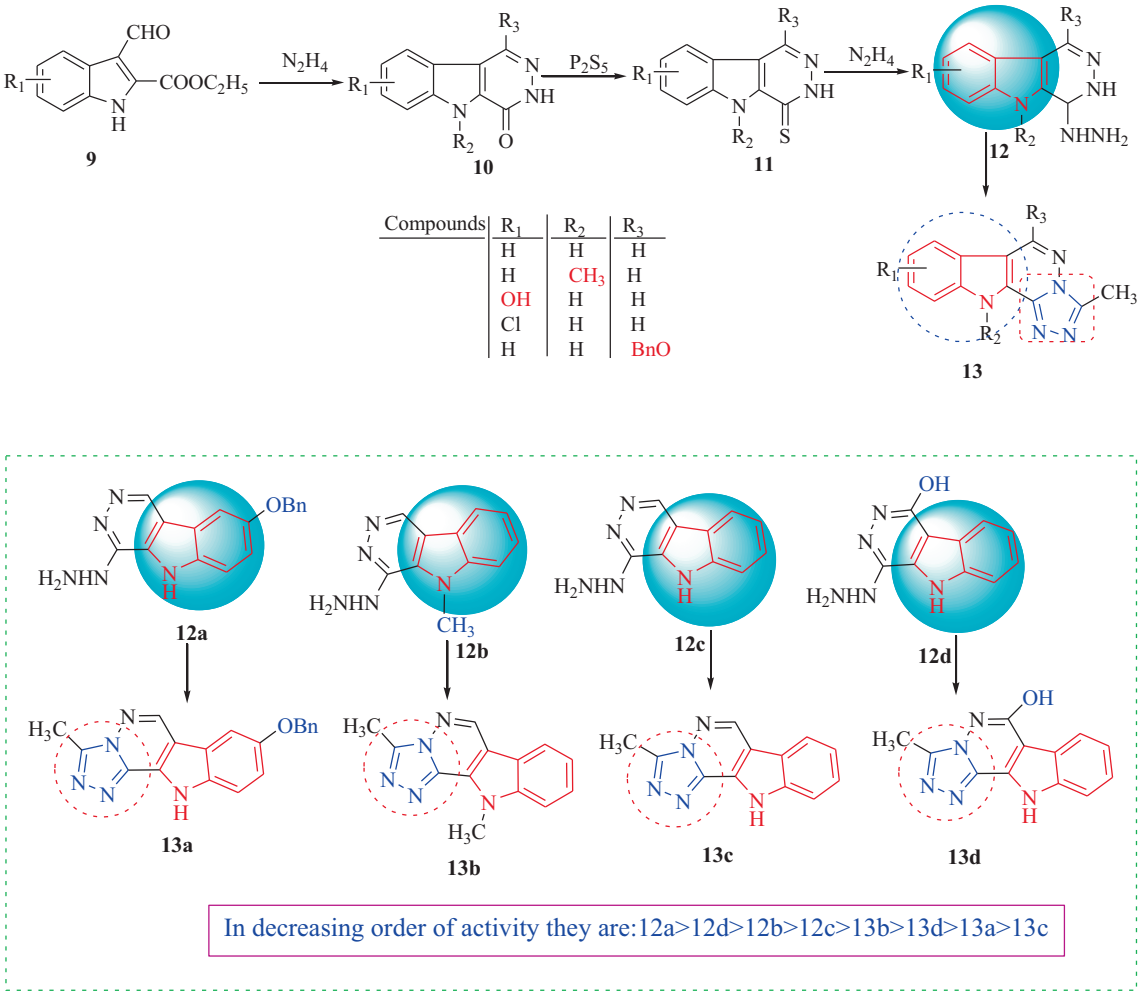


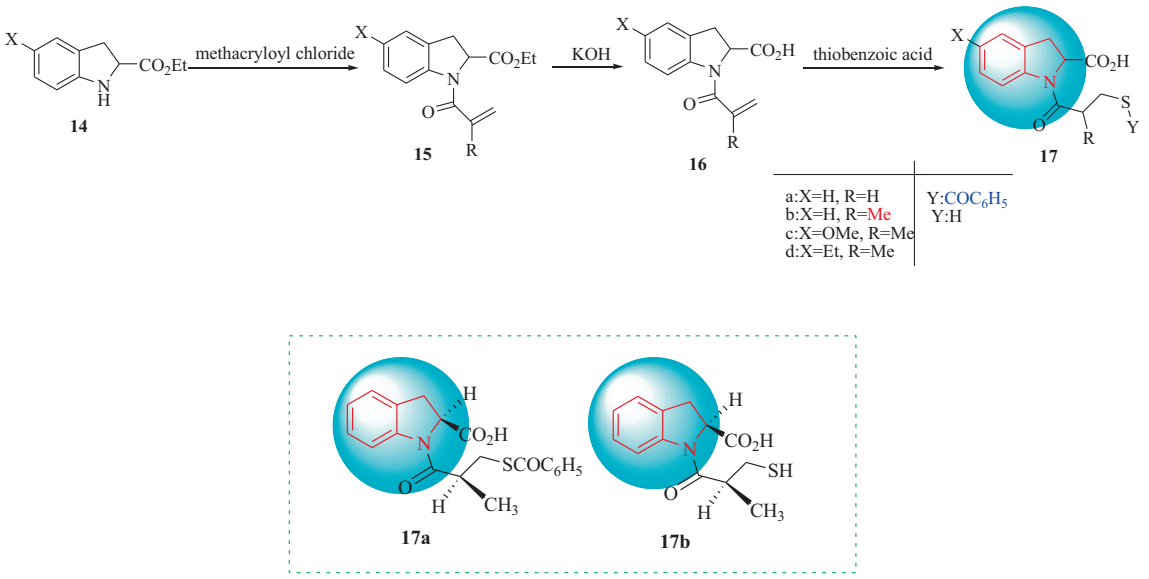
Fig. 1 The SAR of the antihypertensive activity of phenoxypropanolamine-bearing indole analogues.



Scheme 2 Synthetic route of pyridazino[4,5-*b*]indole derivatives.

peripheral ACE inhibitory activity, other antihypertensive mechanisms may also be involved (Fig. 2).

In 1986, Asselin et al. (Asselin et al., 1986) prepared and appraised the antihypertensive activity of compounds **25**, as shown in Scheme 4. First, the condensation of l-acetylindoline (18) with chloroacetyl chloride provided a 93% yield of the 5-chloroacetyl compound 19 in 1,2-dichloroethane. Then, the 5-chloroacetyl compound (19) was reacted with dibenzylamine to obtain a dibenzylamino ketone compound 20, which was reduced with $NaBH_4$ to obtain an amino ethanol compound 21. Further reaction with cuprous potassium cyanide and cyanide gave the nitrile compound 22. The nitrile compound 22 was reacted with NaOH to provide the 7-cyanoindoline compound 23. Hydrolysis of the



Scheme 3 Synthesis of 1-(3-mercaptopropanoyl)indoline-2-carboxylic acids.

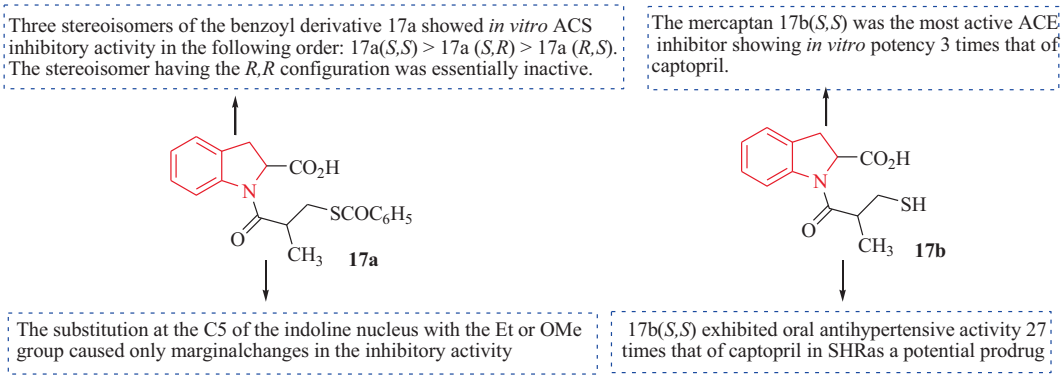
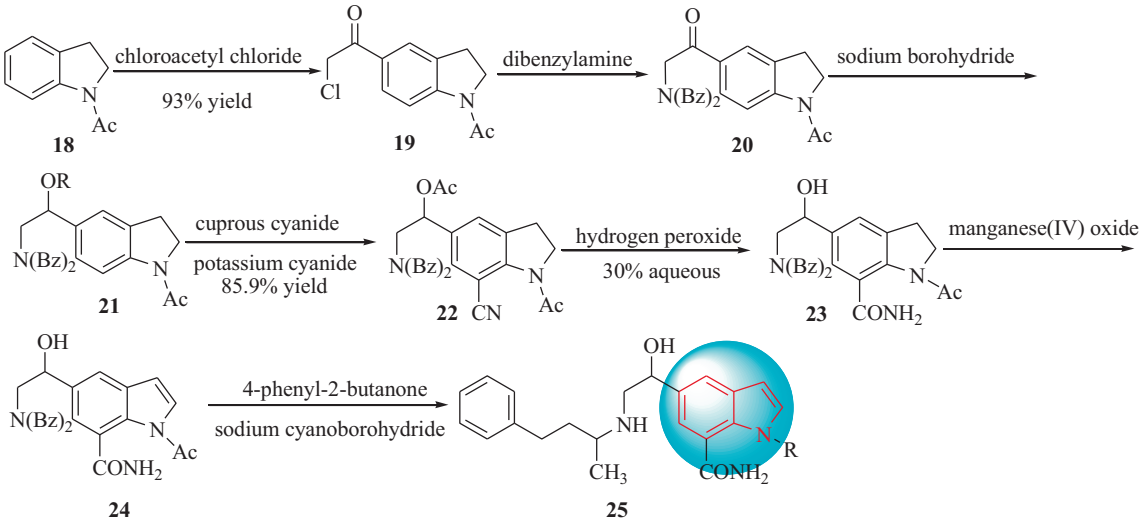


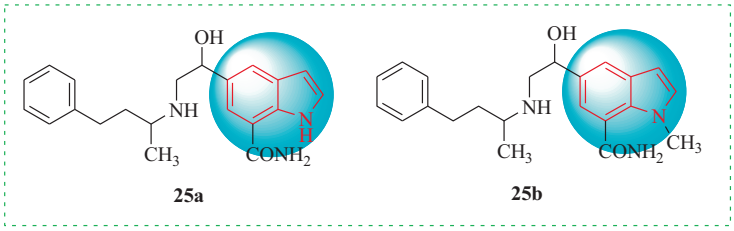
Fig. 2 The SAR of the antihypertensive activity of indoline-2-carboxylic acid derivatives.

cyano group to prepare the carboxamide group (23) was effected by mixing NaOH in hydrogen peroxide. The indole-7-carboxamide (24) was obtained using manganese (IV) oxide. The compounds **24** were reacted under conditions of sodium cyanoborohydride to give the target compounds **25a** and **25b**. Compounds **25a** and **25b** could reduce blood pressure in SHR with an ED_{50} value of 5 $mL{\cdot}kg^{-1}$ (*p.o*) (Table 1). Isolated tissue studies of **25a** and **25b** indicated that these compounds were non-selective β-adrenergic receptor antagonists. Additionally, **25a** and **25b** showed significant β-adrenoceptor intrinsic sympathomimetic effects. The β-adrenergic receptor antagonist and agonist actions of **25a** and **25b** were generated though the formation of a hydrogen bond with the receptor.

In 1987, Monge et al. (Monge et al., 1987) designed and prepared 5*H*-pyridazino[4,6-*b*]indole derivatives 31, as illustrated in Scheme 5. The target products were synthesized starting from derivatives 26 that were reacted under conditions of $POCl_3$ and DMF to give derivatives 27, which is the Vilsmeier-Haack reaction. Derivatives 28 were obtained from derivatives **27** treated with 90 % hydrazine hydrate, followed by reaction with phosphorus pentasulfide and pyridine to provide derivatives 29. The derivatives 29 were mixed and reacted with hydrazine hydrate to afford derivatives 30. Finally, derivatives 31 were obtained by reaction of derivatives 28 with boiling acetic acid or formic acid, and nitrosation ($NaNO_2$/H^+). Table 2 shows the effect of *i.v.* administration at a dosage of 1 $mg{\cdot}kg^{-1}$ *i.p* of compounds 30a-30c on the systolic blood pressure in rats over time. The compounds decreased the blood pressure in the order **30c** > hydralazine = **30a** > **30b**. The increasing order of stimulation was observed: hydralazine = **30a** = **30b** ≪ **30c** and at a higher dose **30b** = **30a** ≪ **30c** in a dose of 1 $mg{\cdot}kg^{-1}$ *i.p*. But derivatives **31** displayed weakly effects. And then, the LD_{50} values for **30a**, **30b**, **30c** are about 2.2–2.5 times less toxic than for hydralazine. The acute toxicity in mice for **30a** is 225 ± 12 $mg{\cdot}kg^{-1}$. All the above-reported results suggest that **30a** is a potentially promising antihypertensive agent.

In 1990, Squadrito et al. (Squadrito et al., 1990) explored the effect of compound 32 (Fig. 3) on the systolic blood pressure in rats with spontaneous hypertension and Grollman hypertension. Administration of 32 markedly reduced the systolic blood pressure in model of hypertension at a dosage of 100 $mL{\cdot}kg^{-1}$ by p.o. gavage for 10 days. In addition, 32 partially inhibited the development of hypertension, when admin-





Scheme 4 Synthetic route of 1*H*-indole-7-carboxamide **25a** and **25b**.

Table 1 *In vitro* antagonist and intrinsic sympathomimetic activity of **25a**, **25b**.

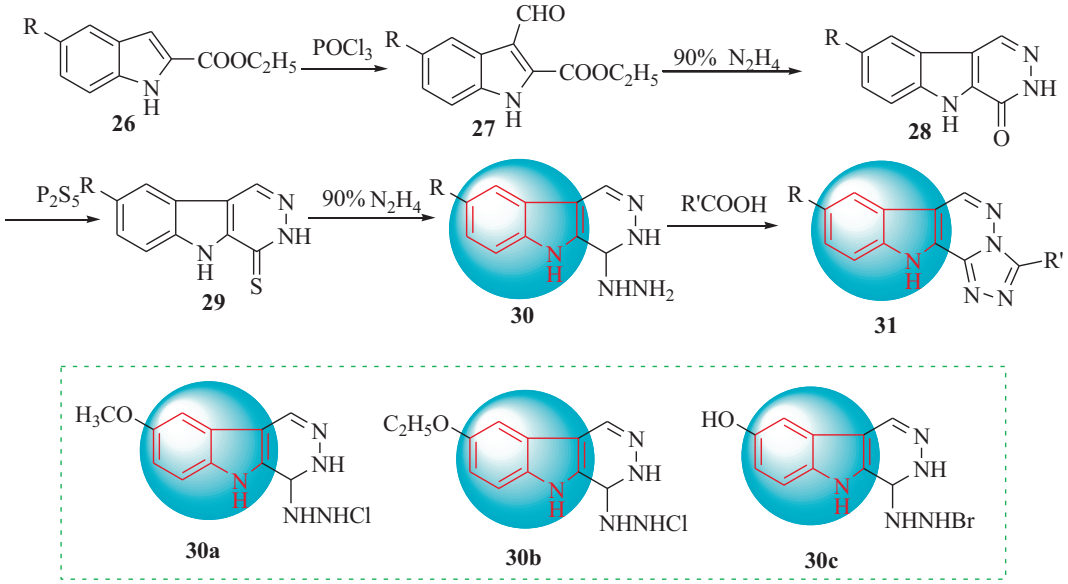
Compound	Receptor pA_2 values[a]			
	β_1	β_2	α_1	α_2
25a	7.4 ± 0.1[b]	7.3 ± 0.2	6.6 ± 0.1	5.4 ± 0.2
25b	< 6.0	< 5.0	6.2 ± 0.04	< 5.0
	β_1-ISA[c]		β_2-ISA[d]	
	% change[e]	concn M	% relaxation	concn M
25a	17.0 ± 2.4[f]	1×10^{-6}	89.0 ± 6.1[g]	3×10^{-7}
25b	2.7 ± 1.4	1×10^{-6}	34.6 ± 5.3	1×10^{-5}

[a] Data are expressed as pA_2 ± SEM from multiple observations from the number of tissues indicated in parentheses. [b] pA2 = -logK_p, K_p was derived by using the method of Kaumann and Blinks. [c] Positive chronotropic effect on guinea pig right atria. [d] Relaxant effect against a $PGF_{2\alpha}$-contracted guinea pig trachea. [e] Percentage increase from basal spontaneous beating rate. [d] Relative to maximum relaxation induced by salbutamol (1×10^{-6} M). [g] Equivalent to 18.6% of maximum response to isoproterenol (1×10^{-6} M).

istered daily to 5-week-old SHR for 7 weeks. Administration of 32 also enhanced the levels of tryptophan and 5-HIAA in the diencephalon and cortex. The brain stem serotonin content in SHR was also increased by treatment with 32. These results indicated that 32 can reduce the blood pressure in dissimilar rat models of hypertension.

In 1991, Todd and Fitton (Todd, Fitton, 1991) reported that perindopril (**33**), a prodrug, was a long-acting ACE inhibitor (Fig. 3). Compound **33** is a lipophilic small molecule with an indole ring. **33** is used to control blood pressure in patients with mild to moderate the basic hypertension, at dose of 4–8 mg once daily. In addition, the study showed that **33** may be a useful alternative to other ACE inhibitors for the treatment of all types of hypertension (Alfakih and Hall, 2006, Ghiadoni, 2011, De leeuw, 2011).

In 2001, EI-Gendy et al. (EI-Gendy et al., 2001) synthesized two series of Mannich bases derivatives **34** and **38** and tested the antihypertensive effects (Scheme 6). 2-Ethoxycarbonylindoles 26 were reacted with formaldehyde and the appropriate secondary amines to give derivatives 34 by heating under reflux in ethanol containing drops of acetic acid. The formylation of derivatives 26 with $POCl_3$ and DMF gave 2-ethoxycarbonyl-3-formylindoles (35). The alkylation of derivatives 35 with ethyl iodide was carried out using



Scheme 5 Synthesis of 5*H*-pyridazino[4,6-*b*]indole derivatives.

Table 2 Antihypertensive activities of **30a-30c** in SHR.

Compound	Percentage falls in systolic blood pressure, directly measured on carotid[a]											
	Dose mg/kg	Control	Minutes									
			5	10	15	30	45	60	75	90	120	180	240
30a	1	250	30	-	36	40	-	60	54	-	40	36	30
30b	1	220	16	18	20	32	36	41	32	25	*[b]	*	*
30c	1	225		44	60	56	56	67	56	56	*	*	*
Hydralazine	1	250	40	48	48	52	60	20	*	*	250	40	48

([a]Iv (vehicle normal saline) on the jugular vein. [b](*) no significant values ($p \leqq 5\%$).

benzyltriethylammonium chloride as catalyst to give 2-ethoxy carbonyl-l-ethyl-3-formylindoles (36) in 50% NaOH/benzene. Heating of derivatives 36 with hydrazine hydrate provided 5*H*-pyridazino[4,5-*b*]indoles (37). Refluxing of 37 with formalin and the appropriate secondary amine supplied the *N*-Mannich bases (38) in ethanol. The synthesized compounds were administered *i.p.* at a dosage of 40 mg·kg^{-1}. Blood pressure measurements were taken at 10, 30, 60, 120, 180, and 240 min after injection (Table 3). **34a**, **34b**, **34c** and **34d** significantly reduced the blood pressure. Nevertheless, derivatives **38** did not display diminished the blood pressure. Three anaesthetized dogs weighing 12–16 kg were injected with 35 mg·kg^{-1} pentobarbital sodium and administered compound **34b**. Compound **34b** at a dose of 40 mg·kg^{-1}, significantly decreased the systolic blood pressure from 70 ± 10 to 120 ± 10 mmHg with a LD_{50} value of 180 mg·kg^{-1}, and displayed antihypertensive activity.

In 2003, the derivatives **44** were synthesized, as shown in Scheme 7. The starting aminoester (39) was reacted with triethylorthoesters to afford the intermediate iminoethers (40). The intermediate tricyclic alcohols (41) were obtained from the iminoethers (40) with 3-amino-1-propanol or 2-ethanolamine. By reaction with $SOCl_2$, the tricyclic alcohols (41) were transformed into alkyl chloride hydrochlorides (42). The final products (44) were obtained at 140 °C with 1-(2-ethoxy-phenyl)piperazine or 1-(2-methoxyphenyl) piperazine (43). The target compounds 44 and 46 were examined in binding experiments with three cloned human α_1-AR subtypes and the antihypertensive effects were evaluated (Romeo et al., 2003). Most of the compounds displayed selective affinity. Compounds **46a** and **46b** displayed moderate affinities for α_{1D}-AR [(pK_i) 7.45 and 7.70, respectively] with no measurable affinity for α_{1A}-AR, α_{1B}-AR subtypes, when tested for binding experiments on the 3 human cloned. In addition, among compounds **44a-44 g**, **44a** and **44b** showed the highest affinity (pK_i = 9.14 and 9.39), a slight selectivity for the α_{1D}-AR (Table 4). The SAR of based on fitting a pharmacophore model for α_{1D}-AR of the antihypertensive is discussed in Fig. 4 (Romeo et al., 2014).

In 2006, a series of new pyrimido[5,4-*b*]indole and [1] benzothieno[3,2-*d*]pyrimidine derivatives was prepared, as shown in Scheme 8. 3-Amino-2-ethoxycarbonylbenzo[*b*]thiophene (47) was reacted with 1,1,1-triethoxyethane to provide the ethyl-3-(1-ethoxyethylideneamino)benzo[*b*]thiophene-2-carboxylate (48). Then, derivatives 49 was obtained with 2-ethanolamine, in which was converted to derivatives 50 in thionyl chloride and toluene. Finally, the target compounds (51) were obtained with 1-(2-methoxyphenyl)piperazine (50)

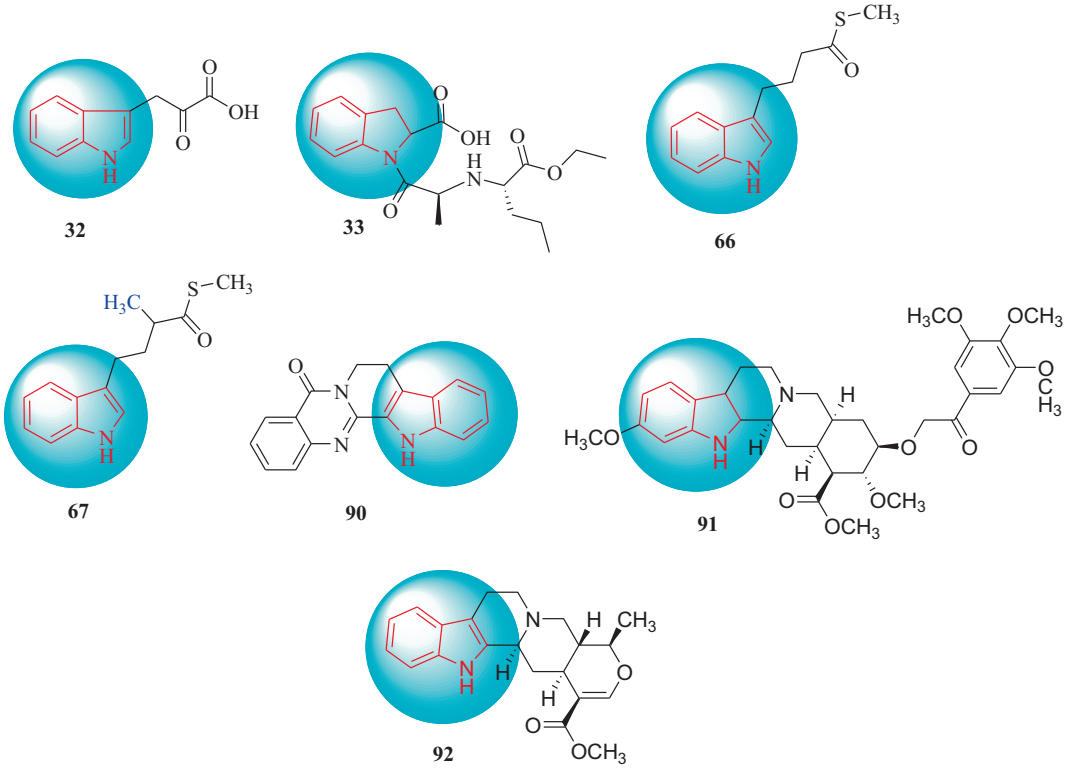
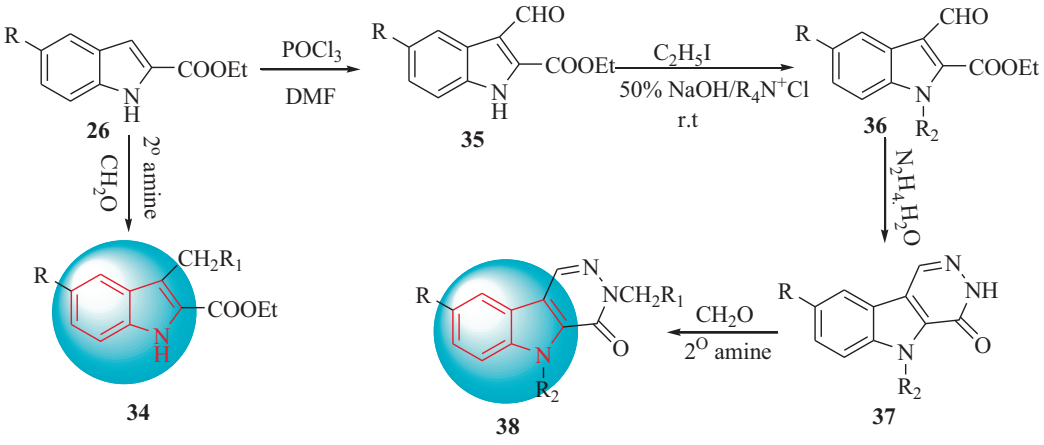
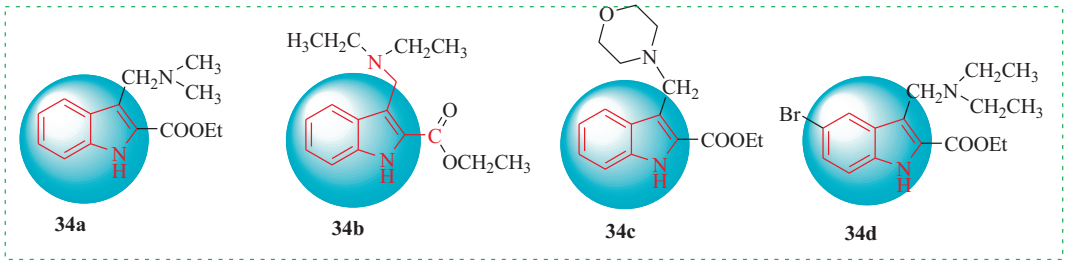


Fig. 3 Chemical structure of indole derivatives **32**, **33**, **66**, **67**, **90–92**.



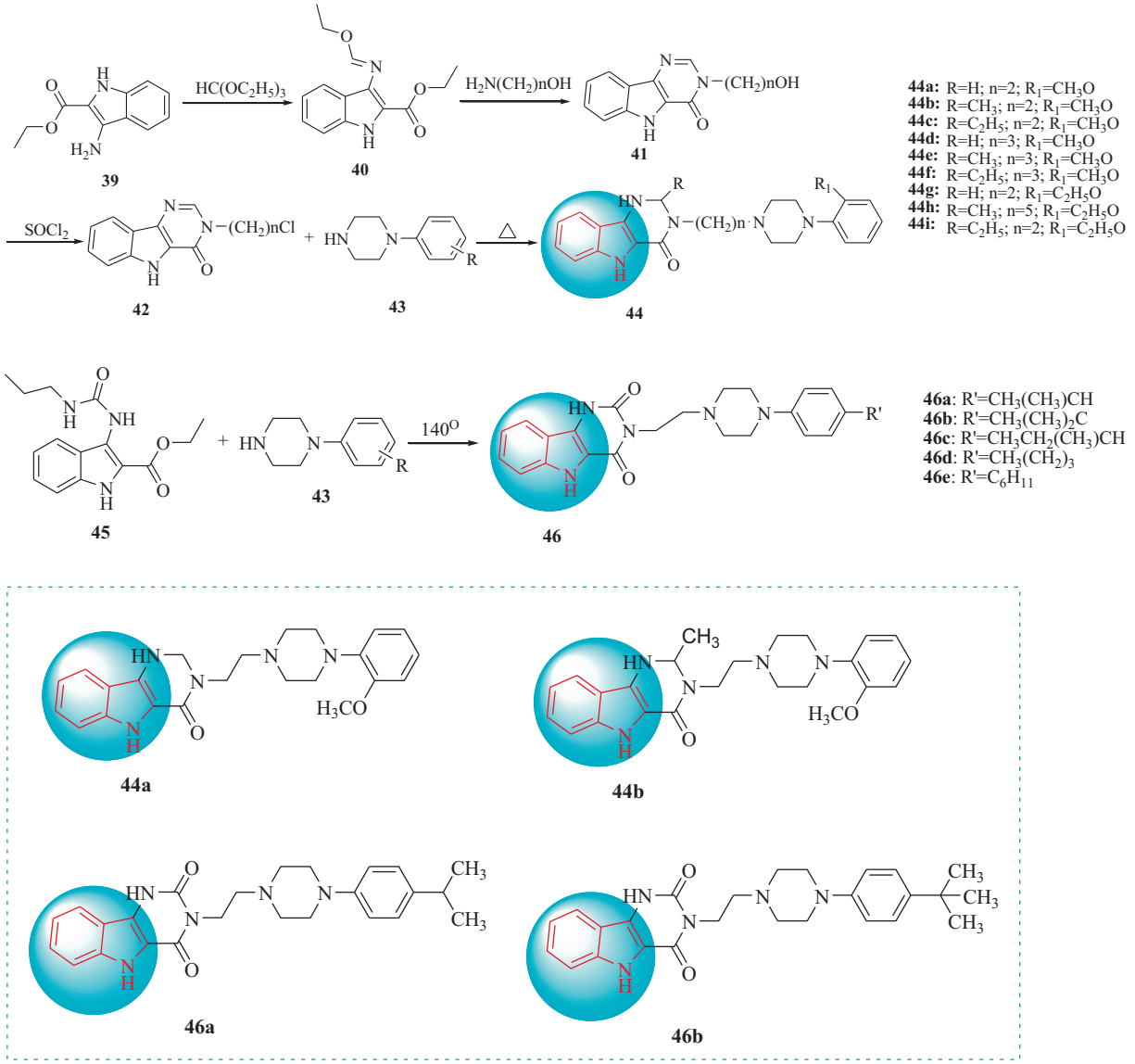


Scheme 6 Synthesis of indole analogues **34** and **38**.

Table 3 Antihypertensive effect in normotensive anesthetized rat after *i.p.* injection of 40 mg·kg^{-1}.

Compound	Control mean ± SEM	Systolic arterial blood pressure (mmHg)					
		10 min	30 min	60 min	120 min	180 min	240 min
34a	119 ± 8	80 ± 11*	72 ± 11*	75 ± 12*	75 ± 12*	84 ± 10*	85 ± 11*
34b	138 ± 4	63 ± 8*	69 ± 9*	61 ± 8*	69 ± 8*	66 ± 9*	73 ± 10*
34c	137 ± 4	90 ± 11*	99 ± 10*	86 ± 11*	84 ± 10*	92 ± 12*	88 ± 9*
34d	116 ± 8	87 ± 9*	80 ± 8*	83 ± 9*	83 ± 10*	91 ± 10*	92 ± 8*
vehicle	117 ± 1	115 ± 3	117 ± 2	115 ± 2	116 ± 2	114 ± 2	117 ± 2

*Indicates statistically significant changes with respect to the vehicle treated control group, $P < 0.05$.



Scheme 7 Synthesis of pyrimido[5,4-*b*]indol-4(5*H*)-one with piperazin.

by heating at 140 °C. The synthesized compounds were assessed in binding experiments using human α_1-AR, α_{1B}-AR, and α_{1D}-AR subtypes expressed in HEK293 cells with [^{125}I] BE2254 as a radioligand (Romeo et al., 2006). Among them, **51b** with 3,4-disubstituted chloro groups showed modest affinity. Compound **51a** with a 2-methoxy and a 5-chloro group showed high affinity for the α_{1D}-AR subtype (pK_i = 9.78). The 2-methoxy derivative **51c** exhibited high affinity for the α_{1D}-AR subtype (pK_i = 9.40). The effects of compounds **51a-51d** were investigated in α_1-AR subtypes from

Table 4 Binding properties of 5*H*-pyrimido[5,4-*b*]indole derivatives.

Compound	pK_i (M) or [% of inhibition at 1 μM][a]		
	α_{1A}-AR	α_{1B}-AR	α_{1D}-AR[b]
44a[c]	8.85 ± 0.08	7.86 ± 0.11	9.14 ± 0.08 (9.46)
44b[d]	8.52 ± 0.03	7.68 ± 0.05	9.39 ± 0.19 (9.38)
44 c[c]	7.31 ± 0.13	6.61 ± 0.05	8.16 ± 0.10 (8.43)
44d[c]	7.78 ± 0.17	6.79 ± 0.04	7.79 ± 0.12 (7.74)
44e	8.31 ± 0.14	7.57 ± 0.08	8.59 ± 0.16
44f[c]	7.97 ± 0.11	7.56 ± 0.12	7.90 ± 0.11 (7.82)
44g[d]	8.01 ± 0.03	7.21 ± 0.07	8.22 ± 0.12 (7.70)
46a[d]	4.89 ± 0.18	5.02 ± 0.13	7.45 ± 0.14 (5.36)
46b[c]	[8 ± 3]	[2 ± 4]	7.70 ± 0.08 (6.77)
46 c[c]	[26 ± 4]	[4 ± 3]	7.22 ± 0.014 (7.43)
46d[c]	[19 ± 6]	[6 ± 5]	6.61 ± 0.07 (6.96)
46e[c]	[7 ± 2]	[18 ± 5]	[3 ± 2] (6.74)

[a] Each value is the mean ± SE for data from three different experiments conducted in duplicate. [b] Estimated and predicted affinity values calculated by Catalyst for the training set and test set, respectively, are reported in parentheses. [c] Compound used to build the training set. [d] Compound used to build the test set.

isolated rat spleen (α_{1B}-AR), prostate vas deferens (α_{1A}-AR), and thoracic aorta (α_{1D}-AR) (Table 5). In addition, compounds **51a** and **51c** displayed high affinity and a slight selectivity for the α_{1D}-AR in binding experiments in human cloned receptors. The SAR of indole and pyrimidine derivatives for α_{1D}-AR of the antihypertensive is discussed in Fig. 5.

Bell et al. (Bell et al., 2007) synthesized a new compound **57**. Compound **57** was made in a five-step synthesis, as shown in Scheme 9. Benzyl-1*H*-indol-7-yl-carbamate (53) was made by hydrogenation of the commercially available **52** followed by reaction with $BnCO_2Cl$ to give the protected amino indole. Then, under acidic conditions, **55** was condensed with **53** to obtain **54**. Finally, after deprotection, chiral resolution of the obtained aniline 56, mesylation, and recrystallization, the product **57** was obtained. Compound **57** was shown to be an effective, selective, and orally active MR antagonist. Compound **32** was a high affinity (hMR K_i) 0.494 (0.23 nM), and functional antagonist (hMR K_b) 19 (12.8 nM), which had moderate efficacy *in vivo*. In salt-containing, mononephrectomized in Sprague–Dawley rats, after 14 days (*p.o.*, qd) administration of **57** at a dose of 3 mpk, resulted in a decrease in blood pressure, which was further decreased to 1 at 30 mpk. Interestingly, addition of the *ortho*-F in **57** resulted in a remarkable effect (Bell et al., 2004).

Zhou et al. (Zhou et al., 2010) reported the compounds *rhynchophylline* (**58**) and *isorhynchophylline* (**59**) from the Chinese herb *Uncaria* (Fig. 6). Compound **58** displayed antihypertensive effects, including a reduction in blood pressure with eventually, a return to normal blood pressure (Zhang et al., 1978, Sun et al., 1996, Song et al., 2000). Compound **59** at a dosage of 10 or 20 $mg{\cdot}kg^{-1}$ by the duodenum resulted in hypotensive activity at 10 and 20 min after administration, and the effectiveness continued for at least 3 h. Compound **59** at doses from 10 to 20 $mg{\cdot}kg^{-1}$ (*i.v.*) decreased the blood pressure of hypertensive rats and the cardiac rate of anesthetized dogs (Zhou, J.Y. and Zhou, S.W., 2012).

Indapamide (compound **60**) contains an indole ring and is a sulfonamide diuretic (Fig. 6). Experimental data showed that **60** had a vasodilating action. Clinical investigations have shown that straightforward vascular actions contributed to the antihypertensive effects of **60** (Neglia et al., 2011, Ambrosioni et al., 1998). Compound **60** is a strongly lipophilic molecule that can reduce *trans*-membrane calcium influx as well as lead to vascular dilation. Therefore, several of the hypotensive actions of **60** may be concerned with calcium antagonist-like activity (Waeber et al., 2012).

In 2014, Zhu et al. (Zhu et al., 2014) synthesized a sequence of indole derivatives **65** (Scheme 10). The derivatives **63** were obtained after reaction of derivatives **61** with compound 62 in the presence of K_2CO_3, and hydrolysis with aqueous NaOH. The derivatives **63** were reacted with 2-fluorobenzonitrile and K_2CO_3 to give derivatives 64. The final target compounds (**65**) were acquired after hydrolysis of derivatives **64** in NaOH. The *in vitro* effects on angiotensin II, as well as *in vivo* antihypertensive effects, were assessed for indole derivatives **65** (Table 6). Radioligand binding assays indicated that **65c** showed affinity for the angiotensin II type 1 receptor

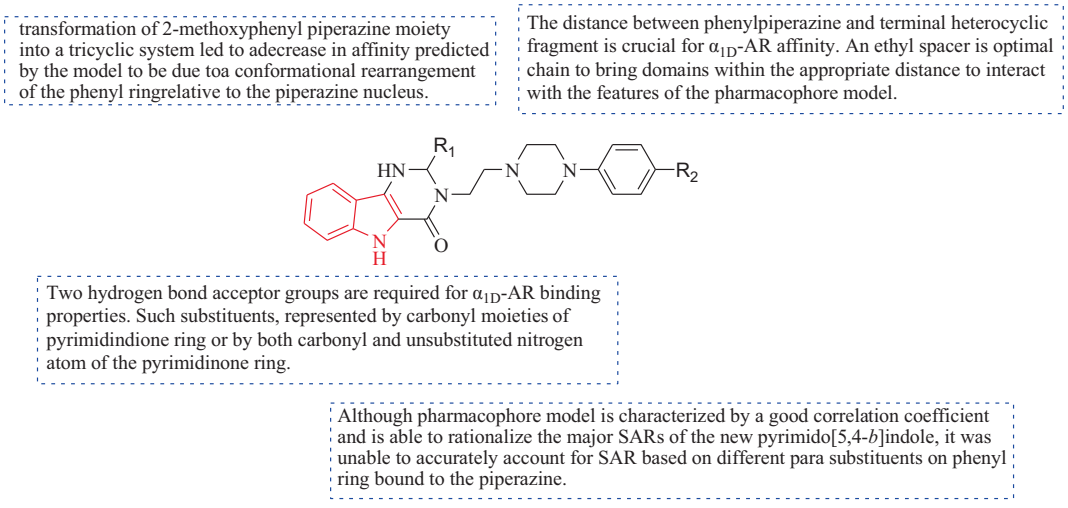
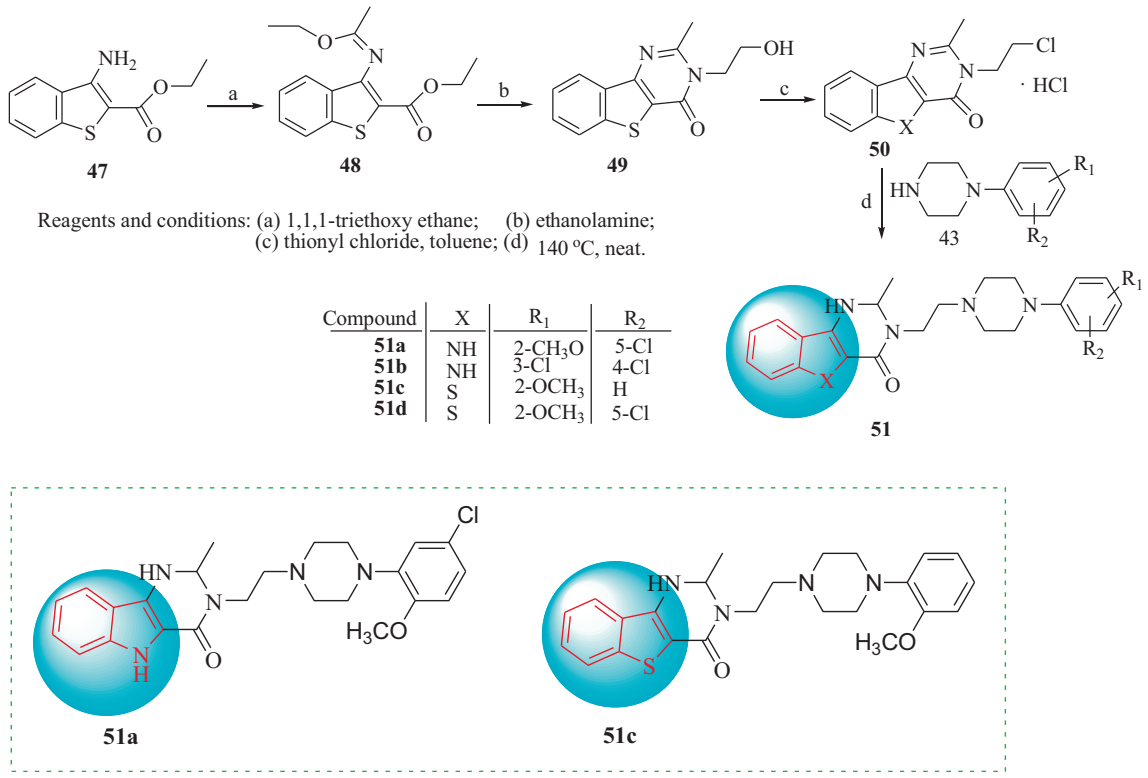


Fig. 4 The SAR of based on fitting a pharmacophore model for α_{1D}-AR of the antihypertensive.



Scheme 8 Synthetic route of indole derivatives **51**.

Table 5 Antagonist potency, pK_i[a], pK_b values of indole derivatives at α_1-AR.

Compounds	pK_i[a] (M)		
	α_{1A}-AR	α_{1B}-AR	α_{1D}-AR
51a	8.88 ± 0.04	8.35 ± 0.04	9.78 ± 0.03
51b	7.52 ± 0.13	7.08 ± 0.07	8.13 ± 0.05
51c	8.83 ± 0.03	7.76 ± 0.03	9.40 ± 0.05
51d	8.46 ± 0.05	7.76 ± 0.03	9.08 ± 0.05
		pK_b[b](M)	
51a	7.60 ± 0.19	8.68 ± 0.07	8.39 ± 0.07
51b	8.65 ± 0.09	7.63 ± 0.14	8.98 ± 0.01
51c	7.52 ± 0.14	8.91 ± 0.09	7.57 ± 0.06

[a] Each value is the mean ± SE for data from three different experiments conducted in duplicate.

[b] pK_b values were calculated according to van Rossum at a single concentration. Each concentration was investigated at least four times.

(IC_{50} = 1.03 ± 0.26 nM). In SHR and renal hypertensive rats, administration of **65c** led to a prominent reduction in the mean blood pressure in a dose-dependent manner. The best responses were reductions in the mean blood pressure of 30 and 41 mmHg in the 5 and 10 mg·kg^{-1} (*p.o.*) groups, respectively, and the remarkable antihypertensive activity continued for > 24 h. In addition, **65c** was more effective antihypertensive agent compared with losartan. Accordingly, **65c** may be a potentially useful antihypertensive drug. The SAR of 5-nitro benzimidazole with 1,4-disubsituted or 1,5-disubsituted indole derivatives of the antihypertensive is discussed in Fig. 7.

In 2014, the indole sulfur-containing alkaloids, *N-demethylglypetelotine* (**66**) and *glypetelotine* (**67**) (Fig. 3), were extracted from the foliage of *Glycosmis petelotii*. The ability of the two compounds to relax aortic rings, and the effect on the L-type Ba^{2+} current [$I_{Ba(L)}$] in a single muscle cell isolated from the tail artery were evaluated. Compounds **66** and **67** reduced phenylephrine-triggered shrinkage of the aortic ring (IC_{50} = 50 and 20 μM, respectively). In addition, **66** and **67** did not affect calcium ion delivery from the sarcoplasmic reticulum induced by phenylephrine. The antispasmodic effect of **67** decreased with membrane depolarization. At K^+ concentrations of 60 mM, **66** and **67** reduced the shrinkage caused by the accumulation of Ca^{2+} in a concentration-dependent manner; the inhibition was inversely proportional to the Ca^{2+} concentration. Compound **67** reduced the $I_{Ba(L)}$ value, and impacted the $I_{Ba(L)}$ kinetics. Therefore, **67** was determined to be new type of vasodilator that can antagonize L-type Ca^{2+} channels (Cuong et al., 2014).

In 2015, Zhu and colleagues (Zhu et al., 2015) designed an analogue of indoloquinolizidine that had antihypertensive activity. The synthetic route is shown in Scheme 11. Condensation between compound 68 in the presence of DIC and DPTS gave compound 69. Removal of the Boc group of compound 69 under acidic conditions resulted in the target **70**. Compound **70** had a significant influence on the contractile response of thoracic aorta rings in male SD rats (IC_{50} = 1.129 × 10^{-9}) and reduced the SBP and HR of SHR. Mechanism studies indicated that **70** induced vasodilation in endothelium-dependent and independent manners. L-NAME (1 × 10^{-6} mol·L^{-1}) and ODQ (1 × 10^{-6} mol·L^{-1}) inhibited the relaxation of the endothelium of intact aortic rings induced by **70**. In addition, compound **70** inhibited intracellular Ca^{2+} release

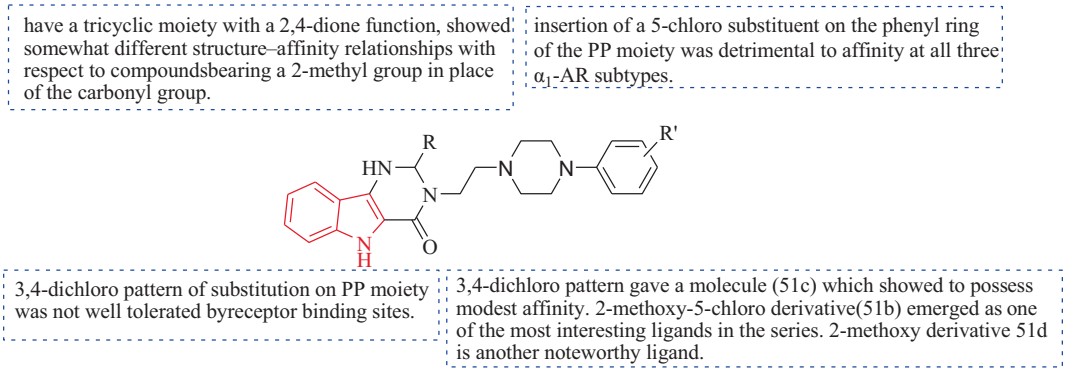
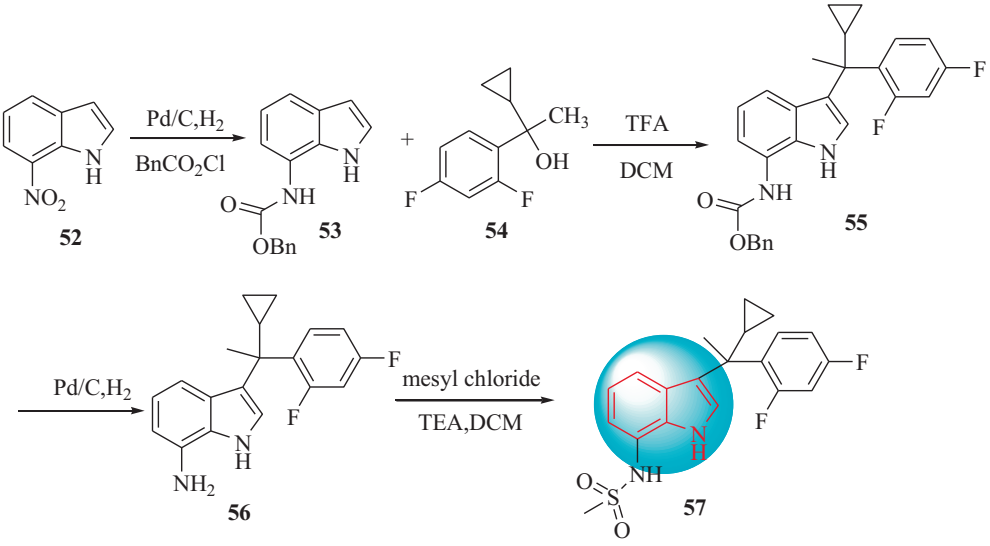


Fig. 5 The SAR of pyrimido[5,4-*b*]indole and [1]benzothieno[3,2-*d*]pyrimidine for α_{1D}-AR.



Scheme 9 Synthetic route of compound **57**.

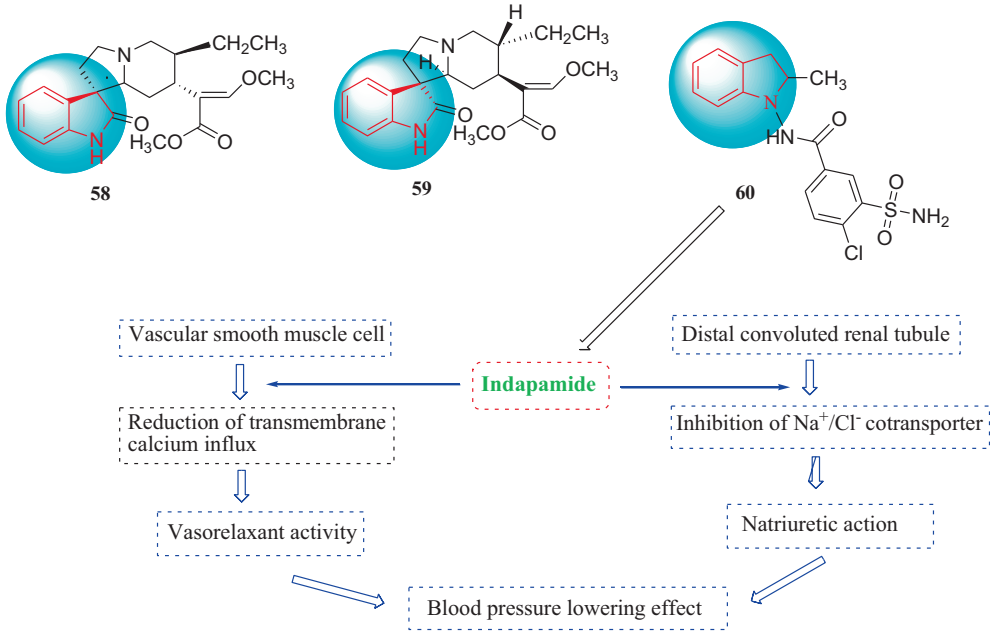
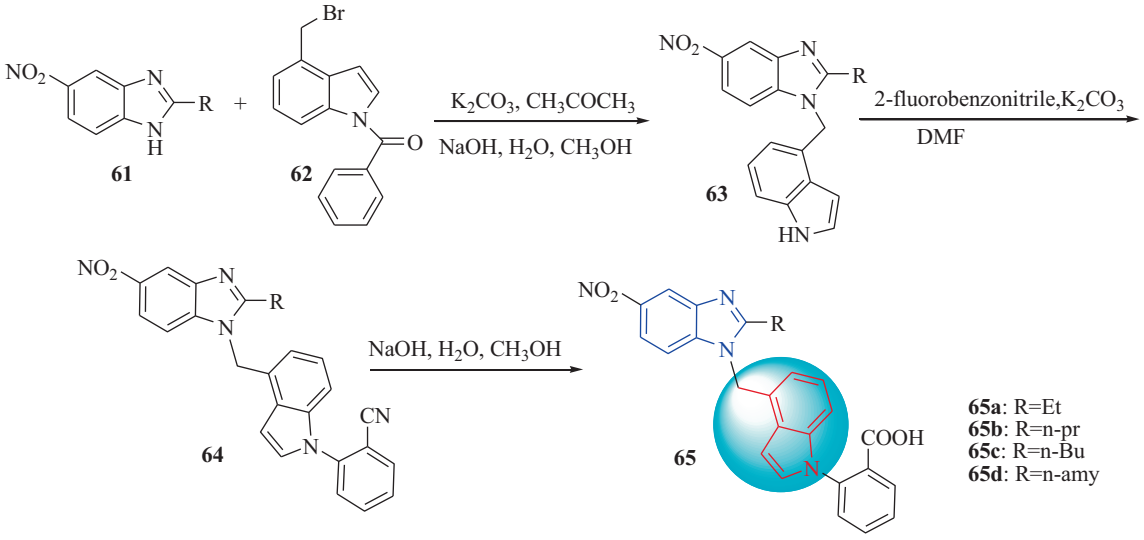


Fig. 6 The chemical structures of indole derivatives **58**–**60** and the mechanisms of **60**.



Scheme 10 Synthetic route of derivatives **65**.

Table 6 IC_{50} and K_i value of the indole derivatives **65**.

Compounds	IC_{50} ± SEM (nM)	K_i(nM)
65a	4.12 ± 1.15	3.04 ± 1.17
65b	5.43 ± 0.27	4.23 ± 0.47
65c	1.03 ± 0.26	0.97 ± 0.43
65d	15.74 ± 0.32	13.42 ± 2.78

and blocked Ca^{2+} influx through L-type Ca^{2+} channels, while not influencing K^+ channels (Fig. 3).

Sączewski et al. (Sączewski et al., 2012, Sączewski et al., 2016) developed the series of the derivatives **73**. The derivatives **73** were prepared from the corresponding indoles (**71**) and compound **72** in sodium hydride and anhydrous THF, as outlined in Scheme 12. Then, the target indole analogues were evaluated in α_1-adrenoceptor and α_2-adrenoceptor binding assays and via radioligand binding *in vitro*. The nature and position of the substituents affected the affinity of the compounds for the α_1-AR and α_2-AR, that is, 7-Cl > 7-Br > 7-CH_3 > 7-F for the α_1-AR and 7-Cl > 7-F > 7-CH_3 > 7-Br for the α_2-AR. Clonidine-based antihypertensive drugs have been shown to bind to the imidazoline I_1 and I_2 receptors. Compounds **3a**, **73c** and **73e** displayed good antihypertensive effects.

Bednarski et al. (Bednarski et al., 2016) synthesized the series of indole derivatives 76 (Scheme 13). Compound **74** was obtained through a nucleophilic substitution using 4-hydroxyindole and epichlorohydrin in NaOH. Next, through

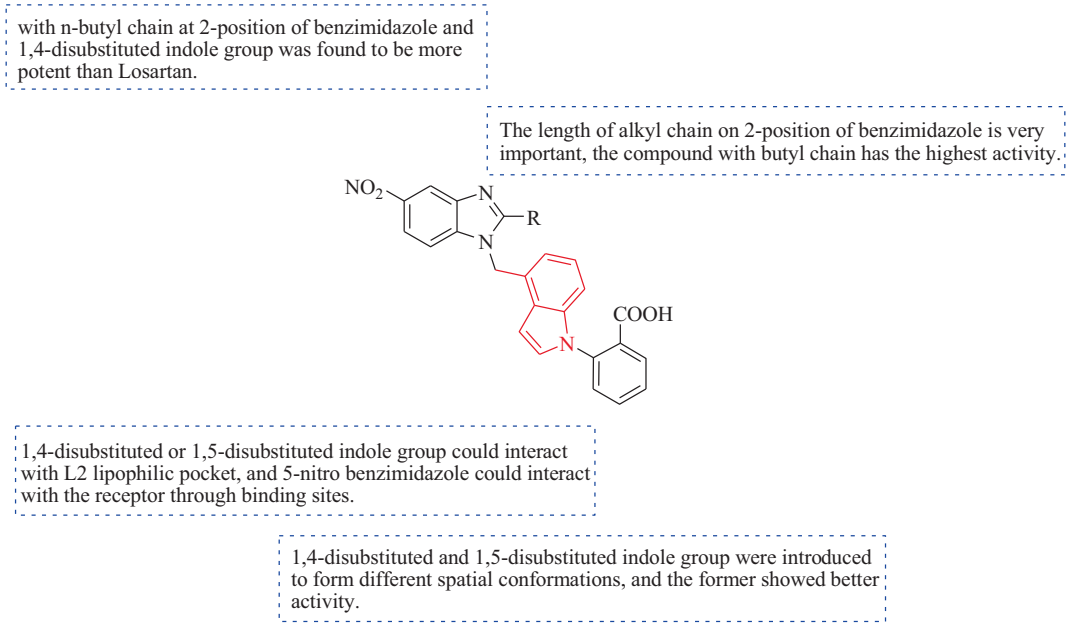
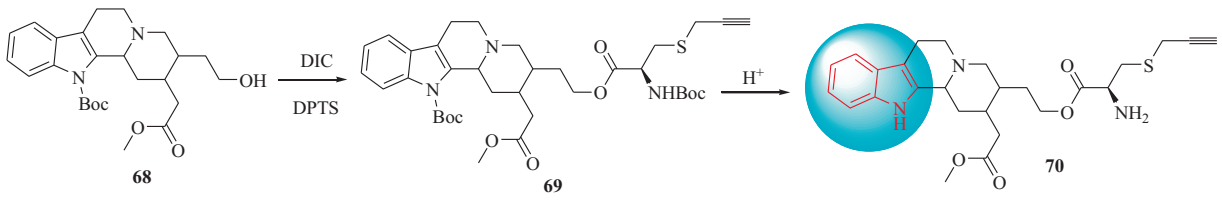
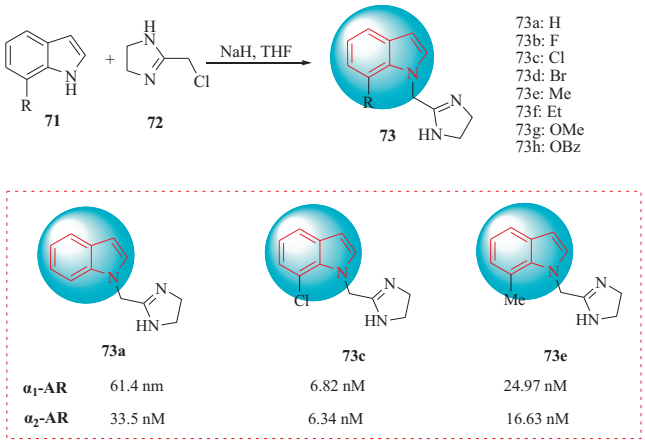


Fig. 7 The SAR of 5-nitro benzimidazole with indole derivatives of the antihypertensive.



Scheme 11 Synthesis of indoloquinolizidine **70**.

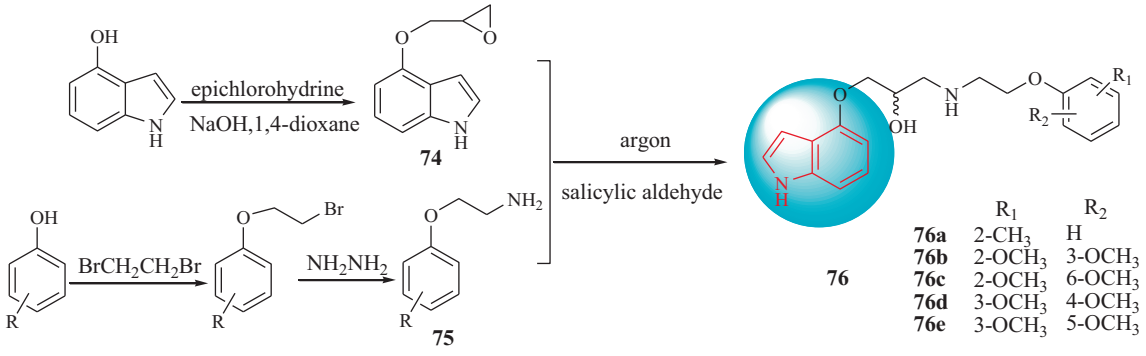


Scheme 12 Synthesis of imidazol containing indole derivatives 73.

Gabriel synthesis, the Manske modification was used with the appropriate alkyl halide to obtain substituted 2-phenoxyethylamine derivatives (75). Finally, **74** and the substituted 2-phenoxyethanamine derivatives (75) were reacted in salicylic aldehyde to obtain the target compounds **76**. The hypotensive effect of the compounds was measured after intravenous administration to anesthetized rats with normal blood pressure. In addition, the hypotensive effect of indole derivatives under study was measured after intravenous administration to anesthetized rats with normal blood pressure. Compounds **76a**, **76b**, **76d**, and **76e** exhibited a high correlation of hypotensive activity of spatial configuration. As hypertensive agent, the most active is enantiomer *S*, while the *R*-enantiomer is 2–32 times weaker. The hypotensive activity probably results from adrenoceptor blockade (α_1 in arteries and β_1 in heart), and found the difference only in affinity of enantiomers to β_1-not α_1-adrenoceptor in radioligand binding studies. Compound **76a** in the form of a racemic mixture decreased systolic and diastolic blood pressure at a dose of 0.25–1.0 mg·kg^{-1}; hypotensive activity occurred 30 min after intravenous administration of 0.25 mg·kg^{-1}. The compounds containing methyl and dimethoxy groups and their enantiomers showed α_1-adrenolytic and β_1-adrenolytic activity, and had anti-hypertensive pharmacological effects. The most active hypertensive agents were the *S*-enantiomers. The docking analysis is shown in Fig. 8.

In 2016, Zhu et al. (Zhu et al., 2016a) synthesized a series of 5-oxo-1,2,4-oxadiazole analogues with 1,4-disubsituted or 1,5-disubsituted indoles, and studied the pharmacological actions as AT_1 antagonists. The preparation of compounds is shown in Scheme 14. The disubstituted indole analogues **77** were obtained from the reaction of 2-(4 or 5-chloromethyl-1*H*-indol-1-yl)benzonitrile with compound **78**. The obtained products were oxidized to obtain the carboxylic acid compounds **79**, which were treated with methyl iodide to generate the methyl benzoate compounds **80**. Then, **80** were reacted with hydroxylamine hydrochloride to obtain the *N*-hydroxyformamidine compounds **81**. CDI was used to cyclize the formamidines (82) through a condensation reaction to obtain the target compounds 83. Table 7 shows the evaluation of the *in vitro* AII antagonistic activity of **83a-83d** and the *in vivo* antihypertensive effects. Compounds **83a-83d** exhibited obvious antagonism of the AT_1 receptor with similar activity to losartan. Compound **82a** with a 1,4-disubsituted indole group (IC_{50} = 5.01 ± 1.67 nM) displayed a strong anti-hypertensive effect in SHR. The maximum response of compound **82a** (10 mg·kg^{-1}*p.o.*) was to lower the average blood pressure by 30 mmHg. The antihypertensive effect of **82a** lasted for > 24 h.

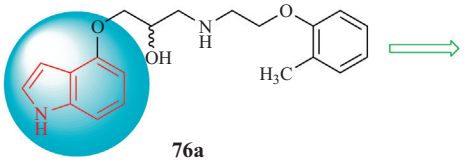
Kornicka et al. (Kornicka et al., 2017) designed a sequence of 1-((imidazolidine-2-yl)imino)-1*H*-indole analogues (Scheme 15). 1-Amino-1*H*-indoles (84) were reacted with *N*-



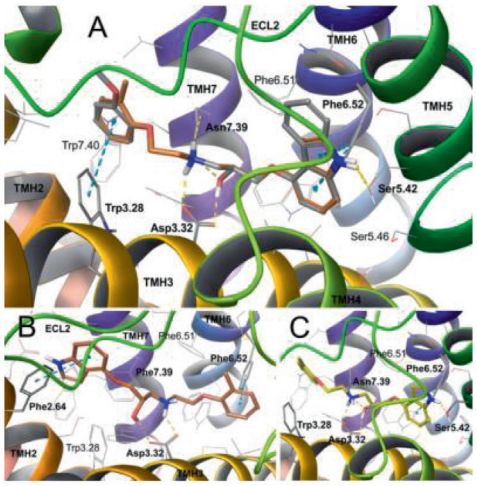
Scheme 13 Synthesis of indole including phenoxy and ethylaminopropan-2-ol derivatives.

hydrogen bond between protonated nitrogen atom of ligand and carboxyl group of Asp3.32, supported by H-bond interaction between hydroxyl group substituted in alkyl linker of ligand . CH–π contact between aromatic moiety and Phe6.52.For β_1 receptor, ligand's basic nitrogen was capable of forming additional interaction of H-bond nature with Asn7.39, which form aromatic CH–π interaction between substituted phenoxyethanamine and Trp3.28 (Fig. 2A).

The central fragment of the *R*-enantiomer formed H-bond with Asp3.32, no specific interaction of 2-methylphenoxyethanamine (Fig. 2C). Both enantiomers bound to deeper receptor cavity in same manner, forming CH–π contact between Phe6.52 and 1*H*-indol-4-yloxy moiety, served H-bond donor to Ser5.42 (Fig. 2A and C).

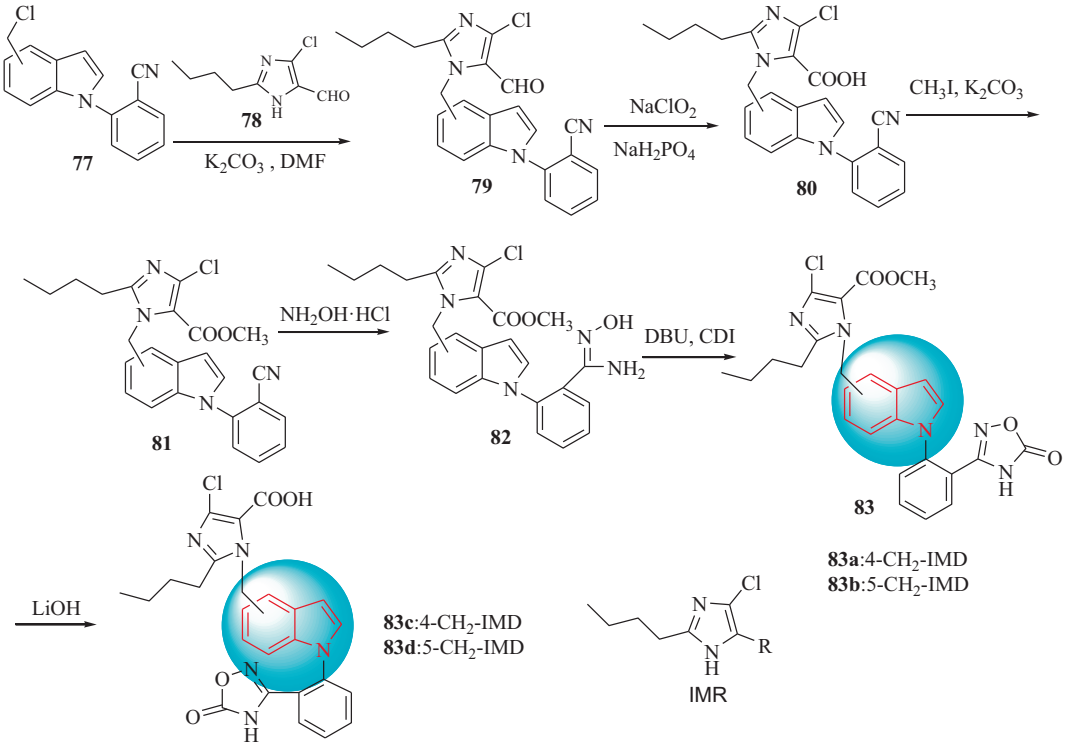


76a



In α_{1A}-receptor-ligand complex, amine and hydroxy groups of 76a formed H-bonds to Asp3.32, present Phe7.39 residue enforced molecule to take reversed pose in the binding site. 1*H*-indol-4-yloxy moiety attached to longer 1-aminopropan-2-ol linker caused less steric clashes with bulky phenyl side residue of Phe7.39 than 2-methylphenoxyethanamine fragment did. 1*H*-indol-4-yloxy moiety interacted with Phe2.64 (CH–π stacking), while 2-methylphenoxy residue formed similar aromatic interaction with Phe6.52 (Fig. 2B).

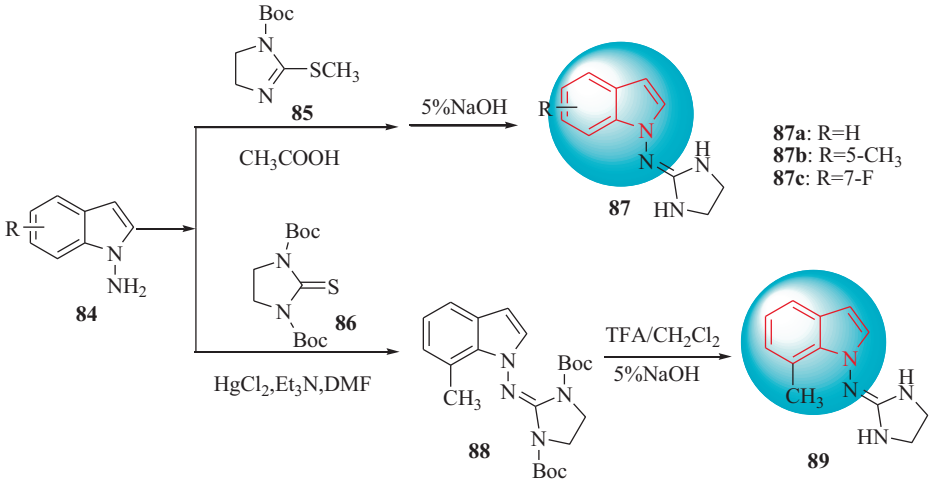
Fig. 8 The predicted binding mode of *S*-enantiomer (eutomer) of 76a (orange), displayed together with reference carvedilol molecule (gray). (A) *R*-enantiomer (distomer, yellow); (B) in site of adrenergic β_1-receptor. *S*-enantiomer of 76a docked in site of α1A-receptor;(C) Amino acid residues engaged in ligand binding are displayed as sticks, whereas crucial residues, e.g., forming H-bonds (dotted yellow lines) or π-π/CH-π stacking interactions (dotted cyan lines) are represented as thick sticks.



Scheme 14 Synthetic route of indole derivatives **83**.

Table 7 IC_{50} and K_i value of indole derivatives **83a-83d**, losartan, and irbesartan.

Compounds	R	IC_{50} (nM)	K_i (nM)
83a	4-CH_2-	5.01 ± 1.67	3.63 ± 1.21
83b	4-CH_2-	9.40 ± 2.12	6.81 ± 1.54
83c	5-CH_2-	8.95 ± 1.39	6.48 ± 1.00
83d	5-CH_2-	6.67 ± 2.12	4.83 ± 1.54
losartan	/	10.51 ± 2.19	7.61 ± 1.59
lrbesartan	/	1.30 ± 0.06	0.94 ± 0.04



Scheme 15 Synthetic route of indole derivatives **87** and **89**.

Table 8 Binding affinity data for the indole derivatives **87a-87c** and **89**.

Compounds	Binding affinities [a] Selectivity ratio					
	α_1K_i (nM)[b]	α_2 K_i (nM)[b]	I_1 IC_{50}(nM)[c]	I_2K_i (nM)[b]	α_1/α_2	I_1/α_2
87a	70.2	5.33	6930	1840	13	1300
87b	118	16.5	159,000	354	7	9636
87c	167	12	15,230	1087	14	1269
89	166	12.1	7152	2536	13.7	591.6

[a] Values given are means ± SEM of three or four independent experiments. [b] K_i affinity values for α_1-ARs, α_2ARs, and I_2 imidazoline binding sites were assessed by measuring the ability of derivatives to compete with [^{3}H]prazosin, [^{3}H]RX821002 or [^{3}H]2BFI binding to rat brain membranes. [c] Molar concentration of derivatives that displaces 50% of specifically bound [^{3}H]clonidine in rat kidney membranes in the presence of rauwolscine (I_1 imidazoline binding sites)

Boc-2-methylthio-4,5-dihydro-1*H*-imidazole (85) in acetic acid to obtain, after deprotection of the formed intermediates, and then, under alkaline conditions to give the target free indoles analogues 87. In the presence of $HgCl_2$, compounds 84 and 86 bind to *N, N'*-bis-boc-imidazolidine-2-thione (88), then reacted to give the Boc-protected intermediate and the protecting groups were cleaved with TFA and CH_2Cl_2 to give compound **89** (Mundla et al., 2000, Sączewski et al., 2011, Dardonville et al., 2000). The indole analogs 87 and 89 were evaluated for selective α_1 and α_2 adrenoceptor affinity though radioligand binding assays *in vitro* (Table 8). The indole analogs 87 and 89 displayed high receptor binding affinity for the α_2-AR with varying selectivity towards the α_2-AR vs I_1 binding positions (I_1/α_2 selectivity ratios: 592–9636). The biggest difference in affinity between the α_2-AR and I_1-imidazoline receptor was shown for the unsubstituted compound **87a**, compared with the 5-CH_3-, 7-F, and 7-CH_3 substituted compounds **87b**, **87c** and **89**, respectively (I_1/α_2 selectivity ratios of 1300, 9636, 1269, and 591.6, respectively). The 7-fluoro analogue **87c** (10 μg/kg *i.v.*) displayed the most obvious anti-blood pressure effect and bradycardia activity (Fig. 9).

In 2019, Tian et al. (Tian et al., 2019) isolated *rutaecarpine* (**90**) from *Evodiarutaecarpa* (Wu Zhu Yu, Family: Rutaceae) (Fig. 3), which is a potential clinical candidate for the treatment of hypertension. Compound **55** reduced the right ventricular systolic and mean pulmonary artery pressure induced in PHR by monocrotaline. In addition, compound **90** also reduced the systolic blood pressure of the right ventricle. In

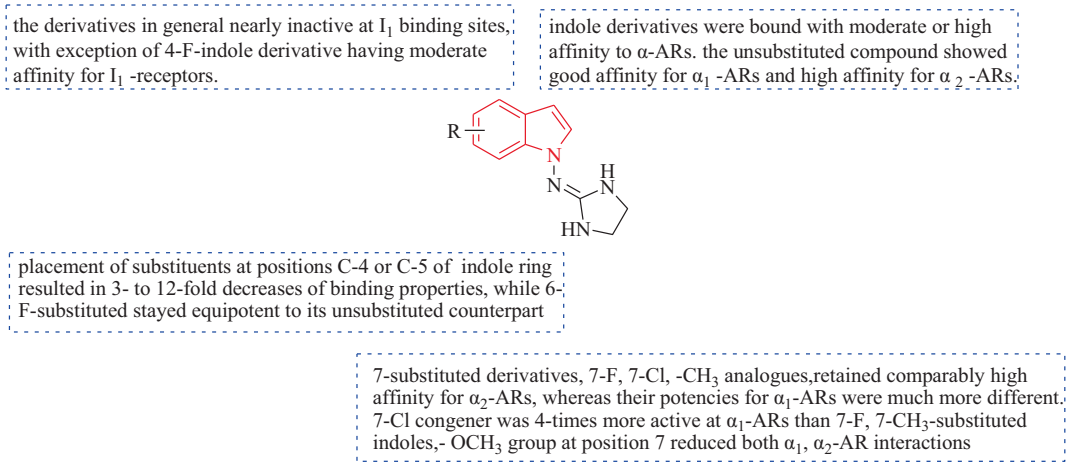
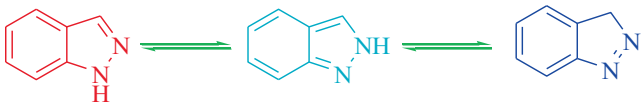


Fig. 9 The SAR of indole analogues is discussed.



1*H*-indazole 2*H*-indazole 3*H*-indazole

Fig. 10 The chemical structure of tautomers of indazole.

a hypertensive rat model, **90** showed anti-hypertensive effects after 2-kidney and 1-clip surgical operation. Rutaecarpine, as an inhibitor of Ang-II type I receptors, significantly reduced systolic blood pressure and Ang-II secretion in a dose-dependent way (Deng et al., 2004, Li et al., 2014, Li et al., 2016, Ding et al., 2008, Jia and Hu, 2010, Qin et al., 2007).

In 2021, Irshad and Khatoon (Irshad and Khatoon, 2021) reported two antihypertensive monoterpenoid indole alkaloids in *Rauvolfia* species from northern India (91 and 92) (Fig. 3). The monoterpenoid indole alkaloids **91** and **92** are the major phytochemicals reported from plants and are well known for their potential antihypertensive activity (Leão et al., 2017, Shamon and Perez, 2016, Douglas, 2015, Dey, A. and Dey, J.N., 2011).

2.2. Analogues containing an indazole skeleton

Benzene and pyrazole rings are fused to obtain an aromatic heterocyclic molecule called an indazole, which has three tautomeric constructions (Fig. 10). A 1*H*-Indazole and analogues

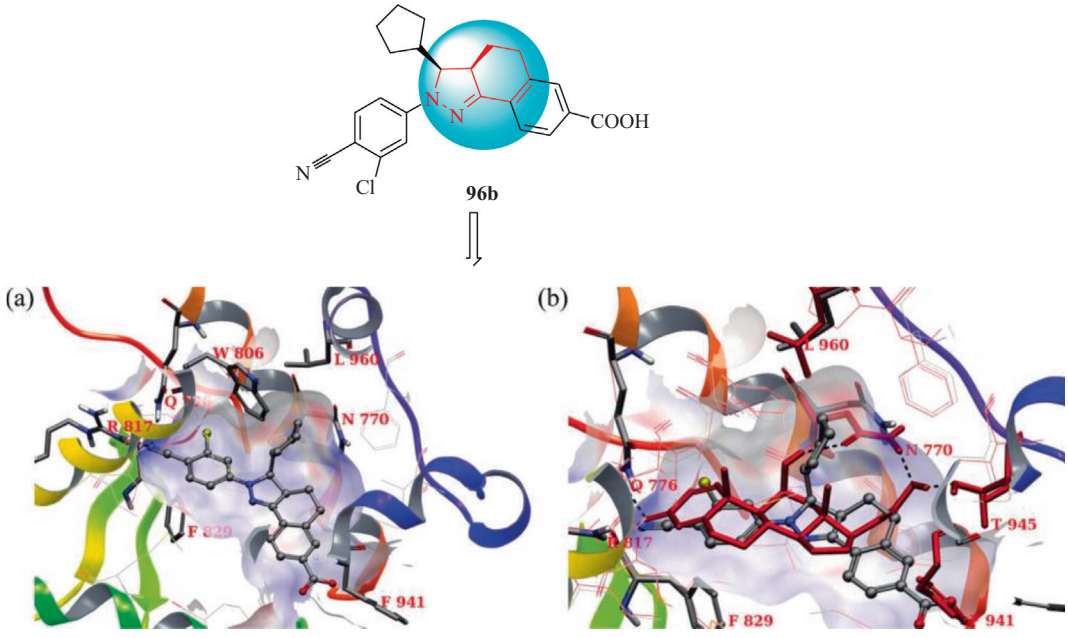
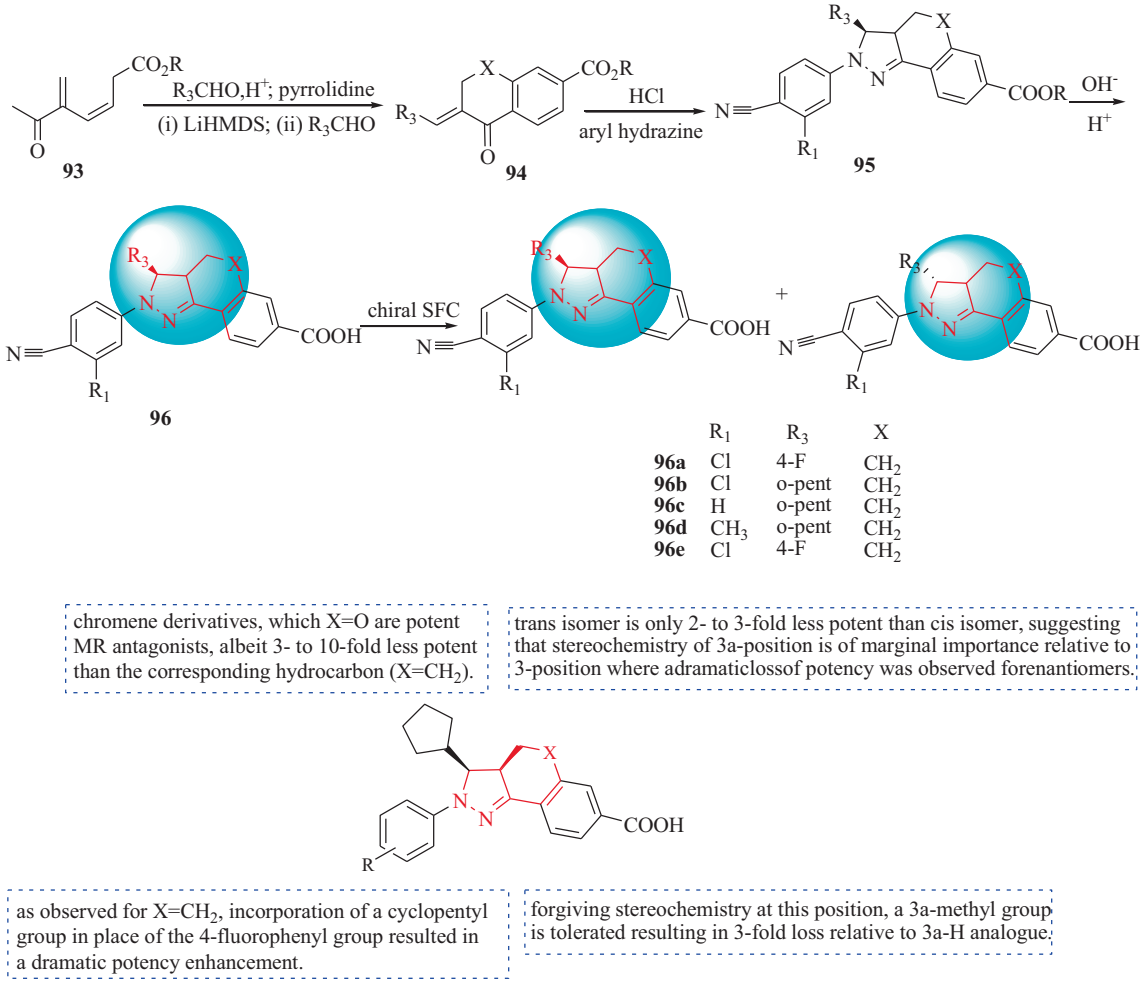


Fig. 11 Induced-fit model of **96b** din MR: (a) ball and stick, showing residues L960 (helix12), F941 (helix11), N770 (helix 3), Q776 and R817 (ketosteroid recognition), and F829, tube; (b) overlay of native crystal MR/corticosterone crystal structure 2A3I(red)with the 56-MR induced-fit model.



Scheme 16 Synthesis and SAR of pyrazoline derivatives **96**.

Table 9 NHR selectivity of pyrazoline carboxylic acids **94b-94d**.

Compounds	MR IC_{50} nM	AR IC_{50} nM	GR IC_{50} nM	PR IC_{50} nM	ER IC_{50}
96b	38	> 10000	> 10000	3180	n.d.
96c	9	> 8910	> 10000	416	> 10000
96d	26	> 10000	> 10000	1880	n.d.

are the most thermodynamically stable of these tautomers (Kuhn et al., 2014, Ali et al., 2013).

In 2010, Meyers et al. discovered a new type of non-steroidal pyrazoline antagonists of the MR receptor for the potential treatment of nephropathy and hypertension (Meyers et al., 2010). A sequence of conformationally confined pyrazolines was prepared (Scheme 16). The cyclic ketones derivatives **93** were reacted with an alkyl or aryl aldehyde to obtain the flavone analogues **94**. Then, condensation with aryl hydrazine analogues gave the pyrazoline derivatives **93** predominantly as the cis diastereomers. The final pyrazolines derivatives **96** were produced via ethyl ester hydrolysis. The target compounds were resolved by chiral supercritical fluid chromatography. Compounds **96c-96d** were potent MR antagonists with selectivity over other nuclear receptors (Table 9). The SAR of pyrazoline analogues of the antihypertensive is discussed in Scheme 16. Compound **96b** had four times the functional productivity (MR binding IC_{50} = 2.7 nM). In the same way, the binding affinity of **96b** for the PR was two times the functional PR strength. The binding affinity of **96b** for the MR was 115 times that for the PR, which was compared with spironolactone (MR binding IC_{50} = 8.1 nM vs. PR binding IC_{50} = 2440 nM; 301-fold) and eplerenone (MR binding IC_{50} = 138 nM vs. PR binding IC_{50} > 10000 nM; > 72-fold). To identify the potential binding mode of the pyrazoline of **96b**, the 1.95 Å MR/corticosterone X-ray crystal structure 2A3I (Bledsoe et al., 2005, Li et al., 2005) was used to prepare induced fit models with **96b**. The N_1 cyanophenyl group was in the A-ring pocket and formed hydrogen bonds with R817 and Q776, which mimicked the A-ring 3-carbonyl group of corticosterone in this model (Sun et al., 2006; Bohl et al., 2008). The dangling cyclopentyl group forces the L960 side chain into

97
Selective α_2–agonist
α_2K_i =14 nM
I_1K_i =54500 nM

98
non-selective α_2/I_1–agonist
α_2K_i =53 nM
I_1K_i =387 nM

Fig. 12 The structure of the new hypotensive imidazolines.

a higher energy conformation and displaces the N770 side chain from its normal position, disrupting the hydrogen bond network stabilized by the 11β -hydroxyl group of corticosterone. This feature might be an important component of these pyrazoline antagonistic MR, namely the formation of hydrogen bonds between ligands and N770 in helix 3 and T945 in helix 10. In addition, the ligand carboxylate replaces the side chains of L848, especially F941, opening the pathway to the solvent under helix 11. Compound **96b** was selected as a clinical candidate for the treatment of diabetic nephropathy because of its promising *in vitro* potency and selectivity, *in vivo* potency, pharmacokinetic properties, and preclinical safety profile, and is currently undergoing clinical research (Fig. 11).

In 2013, Wróblewska et al. (Wróblewska et al., 2013) described the synthesis of two imidazoline compounds: marsanidine (**97**) and 7-methylmarsanidine (**98**). Compound **97**, with a selectivity ratio α_2/I_1 of 3879, was a highly selective α_2-adrenergic receptor ligand. Compound **98**, with a selectivity ratio α_2/I_1 of 7.2, was a mixed α_2-adrenergic receptor/imidazoline I_1 receptor agonist. Intravenous injection of **97** and **98** induced a reduction in the heart rate and blood pressure and resulted in antihypertensive effects in Wistar rats. The hypotensive activity of the imidazolines was mediated not only by a decrease in renal sympathetic nerve activity and direct actions on peripheral receptors but also by activating central α_2 and/or I_1 receptors (Fig. 12). Compound **98** was significantly more effective as an antihypertensive agent than **97**, which may be because of its moderate affinity for the I_1-imidazoline receptor.

Table 10 Selectivity profile of **99** in the panel assay of 13 other kinases.

Enzymes	IC_{50} value (nM)
Rho kinase 2 (ROCK2)	0.02
Rho kinase 1 (ROCK1)	0.1
AKT1	> 10
Cyclin-dependent kinase 1 (CDK1)	> 10
IκB kinase (IKKβ)	> 10
c-Jun *N*-terminal kinase 1 (JNK1)	> 10
LIM kinase 1 (LIMK1)	> 10
Mitogen- and stress-activated protein kinase 1 (MSK1)	> 10
Protein kinase A (PKA)	> 10
Protein kinase Cη(PKCη)	> 10
Polo-like kinase 1 (PLK1)	> 10
p38*a* Mitogen-activated protein kinase (p38*a*)	> 10
p70S6 Kinase (S6K)	9.8
p90 Ribosomal S6 kinase 1(RSK1)	9.2
Serum- and glucocorticoid-induced protein kinase (SGK)	> 10

In 2013, the Rho kinase inhibitor **99** was discovered and investigated in biochemical, tissue, animal, and cellular experiments. Compound **99** demonstrated inhibition of the kinase activity of Rho kinase 1 and Rho kinase 2 *in vitro*. In analysis of a panel of 13 kinases, compound **99** showed high selectivity for Rho kinase (Table 10) and as a selective Rho kinase inhibitor, **99** was 10 times more effective than fasudil in inhibiting the activity of Rho kinase. In a study of isolated vascular tissues, **99** exerted a vasodilator effect on phenylephrine or 5-hydroxytriphenylamine-induced contractions in a concentration-dependent manner. The administration of **99** resulted in a significant dose-dependent decrease in the blood pressure of spontaneously hypertensive rats. In addition, **99** blocked the formation of stress fibers and cell hypertrophy induced by angiotensin II in rat heart-derived H9C2 cells. These results showed that **99** can reduce the pathophysiological effects of Rho kinase, such as cell hypertrophy, stress fiber formation, and hypertension, and that **99** was a highly selective and effective Rho kinase inhibitor (Oh et al., 2013). The crystal structures of seven AGC family kinases, mitogen, Rho kinase 2, Rho kinase 1, stress-activated protein kinase 1, protein kinase Cη, p90 ribosomal S6 kinase 1, and protein kinase A and glucocorticoid- and serum-induced protein kinases were combined (Fig. 13A) to investigate the selectivity of **99** in molecular modeling studies, and identify the residues involved in the binding in the active site. The piperazine portion of **99** tended to interact with the Asp176 of Rho kinase 2, thereby enhancing the activity of the compound (Fig. 13C). The Met172 residue in the hinge region of Rho kinase 2 clearly interacted with **99** as shown in Fig. 13B. Additionally, the long fatty chain containing the Gly107 residue of the serum- and

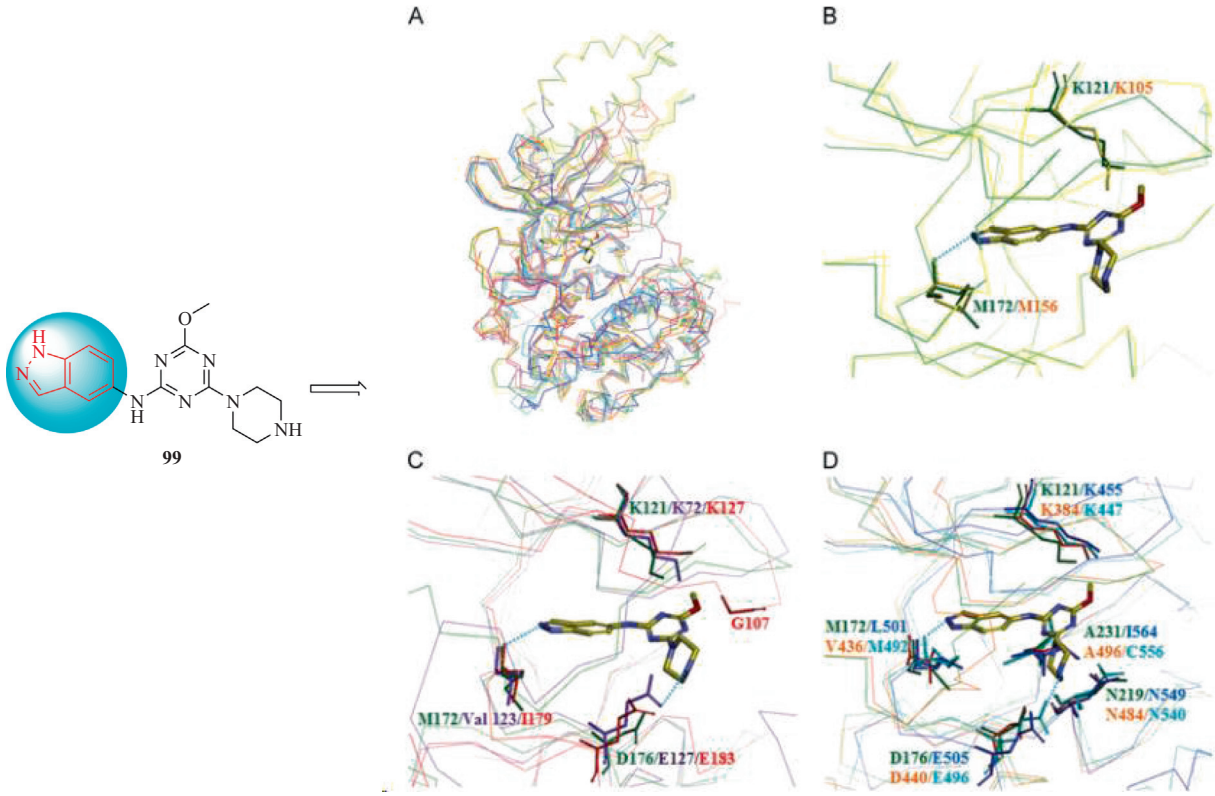


Fig. 13 Modeling of **99** with Rho kinase 2 (pdb entry; 2H9V) and Rho kinase 1 (pdb entry: 3NCZ), mitogen- and stress-activated protein kinase 1 (pdb entry: 3KN5), protein kinase A (pdb entry: 3POO), protein kinase Cη (pdb entry: 3TXO), p90 ribosomal S6 kinase 1 (pdb entry: 2WNT), and serum- and glucocorticoid-induced protein kinase (pdb entry: 3HDM).

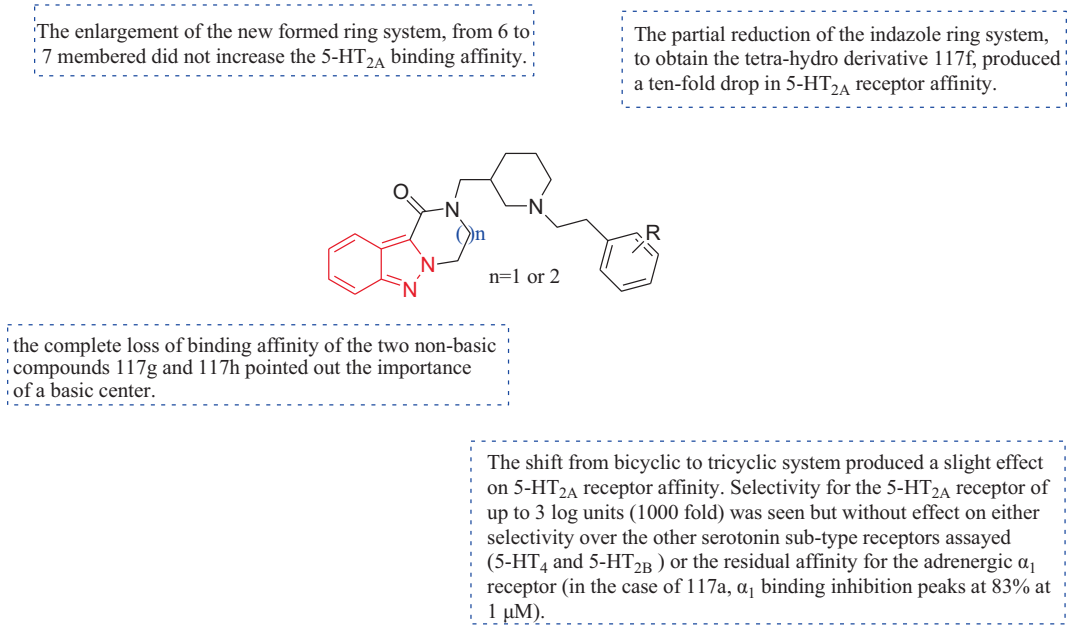
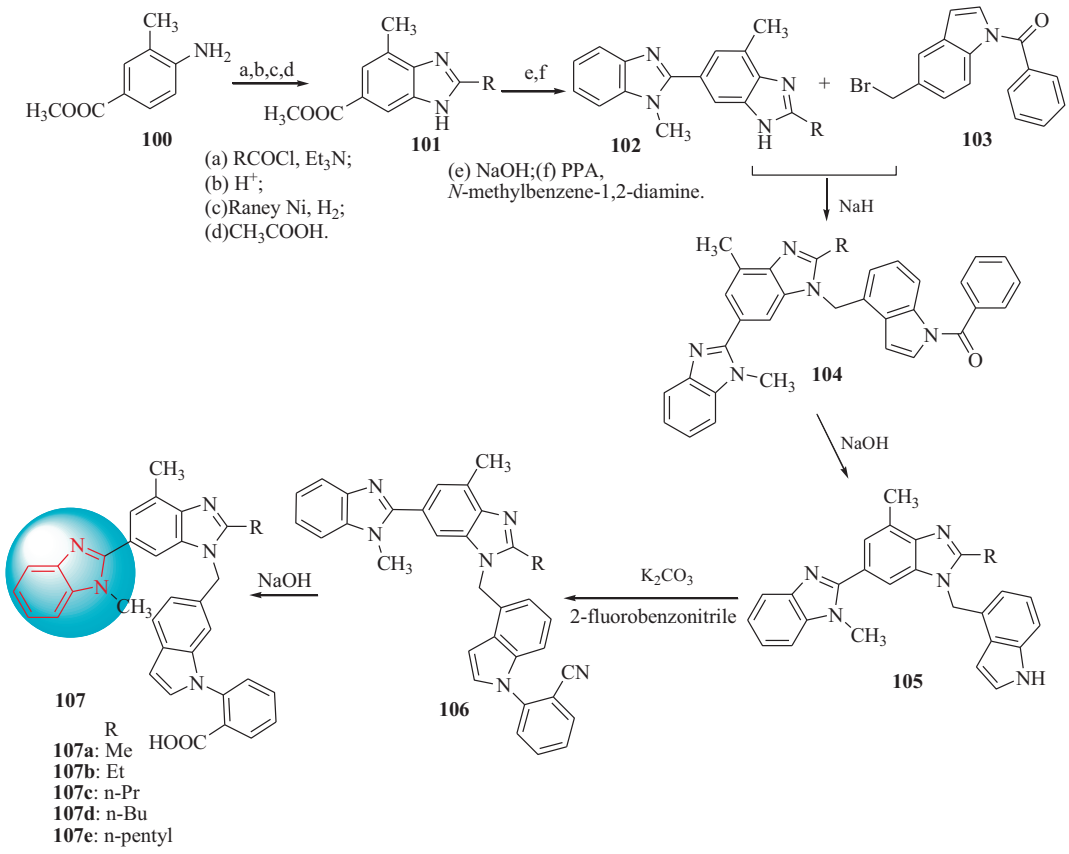
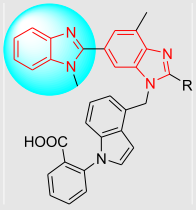


Fig. 14 The SAR of indazol-1(2*H*)-one derivatives of the antihypertensive.



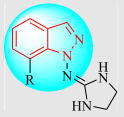
Scheme 17 Synthesis of *N*-phenyl indole derivatives 107.

Table 11 IC_{50} and K_i value of the tested compounds **107a-107e**.



Compounds	R	IC_{50} ± SEM (nM)	K_i (nM)
107a	Me	7.46 ± 0.16	4.66 ± 0.78
107b	Et	1.83 ± 0.19	1.14 ± 0.23
107c	n-Pr	0.36 ± 0.18	0.23 ± 0.17
107d	n-Bu	2.61 ± 0.26	1.63 ± 0.19
107e	n-pentyl	11.30 ± 5.89	7.06 ± 4.14
losartan	–	20.09 ± 0.11	13.06 ± 0.07
telmisartan	–	3.80 ± 0.22	2.75 ± 0.17

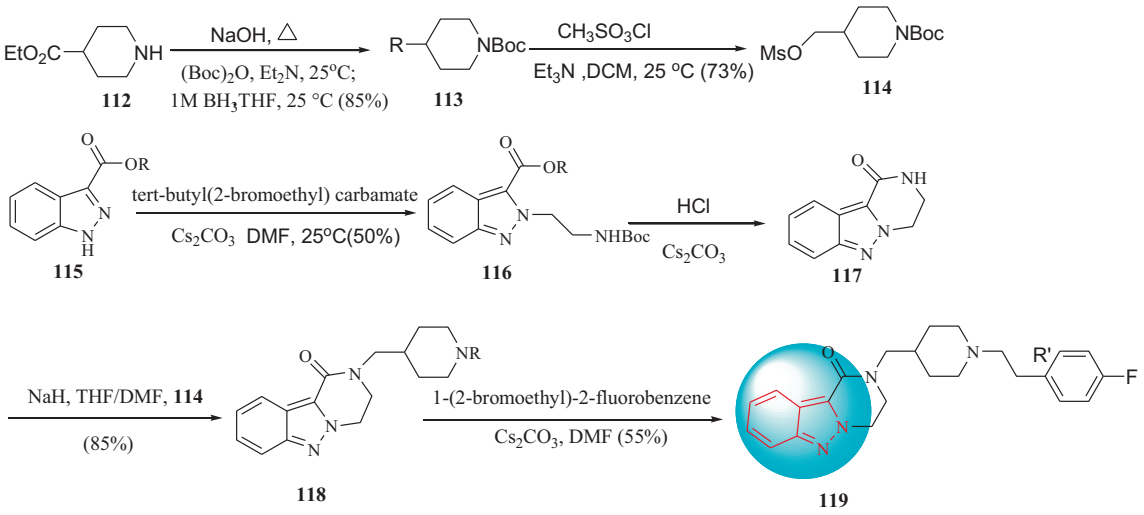
Table 12 The tested compounds affinity data to α2 adreno and I1 imidazoline receptor.



Compounds	R	$\alpha_2 K_i$ (nM)	I_i (nM)	α_2 / I_i
108	–	14.05	54,500	3879
109	7-CH_3	53.5	387	7.23
110	7-Cl	30.3	46,800	1544
111	7-F	30.9	7740	250

glucocorticoid-induced protein kinases, and the long fatty chain of the protein kinase A Glu183 collided with the methoxy group of **99**. In p90 ribosomal S6 kinase 1 and protein kinase Cη, there was steric hindrance between the extended Lys447 and Lys384 residues, respectively, and the **99** methoxy group, which may have caused the low binding to these receptors (Fig. 13D).

In 2016 (Zhu et al., 2016b), the synthesis of derivatives **107** was outlined in Schemes 17. Substituted benzimidazoles derivatives 100 were obtained with methyl 4-amino-3-methylbenzoate (100) in DCM with alkyl acid chloride, nitrated with concentrated nitric acid, hydrogenated with hydrogen, and cyclized in acetic acid. The bisbenzimidazole (102) were obtained to react with benzimidazoles (101) in NaOH, cyclization with *N*-methylbenzene-1,2-diamine in the presence of polyphosphorous acid (PPA). The derivatives 104 were obtained with 5-bromomethyl-1*H*-indol-1-phenylmethanone (105) in NaH, then derivatives 104 in



Scheme 18 Synthetic route of indazol derivatives **119**.

Table 13 Functional activity of 119 on serotonin 2A, adrenergic α1A, α1B, α1D, α2B and α2C.

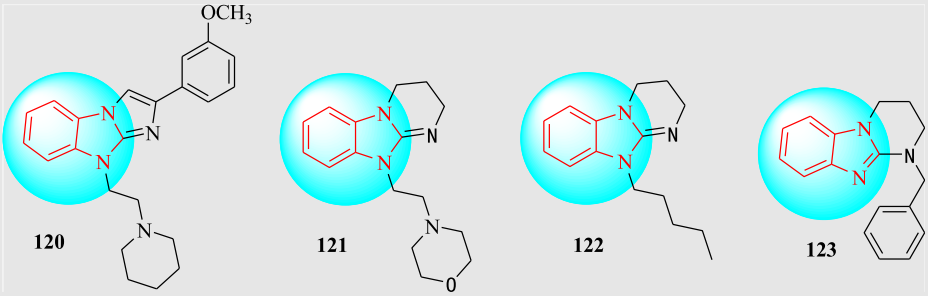
Receptor	IC_{50} nM	K_b nM	Functional activity
5-HT_{2A}	18	4	antagonist
α1A	1500	190	antagonist
α1B	220	24	antagonist
α1D	910	260	antagonist
α2B	67,000	8800	antagonist
α2C	3600	1700	antagonist

NaOH to derivatives 105. The compounds 105 were alkylated with 2-fluorobenzonitrile to obtain benzonitrile (106) after deprotection of the benzoyl group, finally, hydrolyzed to derivatives **107** with NaOH in methanol. Compounds **107** were evaluated as angiotensin II receptor antagonists *in vivo* and *in vitro* (Table 11). According to the results of radioligand binding analysis, several benzimidazole derivatives displayed high-affinity binding to the angiotensin II type 1 receptor, in the same order of magnitude as telmisartan. Compound **107c** reduced the MBP in a dose-dependent manner in spontaneously hypertensive rats. The maximum response was a reduction of 53 mmHg in MBP when **107c** was administered orally at a dose of 5 mg•kg^{-1}, and the MBP was reduced by 64 mmHg when the dose was 10 mg•kg^{-1}. The antihypertensive effect lasted > 24 h, which was comparable to telmisartan and losartan. These results indicated that **107c** was worthy of further research for application as an active and long-lasting antihypertensive agent.

In 2014, Boblewski et al. (Boblewski et al., 2014) synthesized indazole derivatives that exerted promising actions on the heart rate and blood pressure in Wistar rats. In 2017, Boblewski et al. (Boblewski et al., 2017) evaluated **108**–**111** that had different affinities to the α_2-adrenorecptor and to the I_1 imidazoline receptor (Table 12). Among them, **108** showed the lowest affinity for the α_2-adrenoreceptor and the highest affinity for the I_1 receptor. The effects of **108**–**111** on the blood pressure, heart rate, and diuresis were compared. Male Wistar rats received the tested compounds at two doses: 10 and 100 μg•kg^{-1} *i.v.* The MAP, ECG, and HR were recorded continuously. Compounds **108**–**111** caused a profound decrease in the MAP. Compound **111** at a dose of 100 μg•kg^{-1}. caused the strongest drop in the MAP. The weakest and the shortest duration of effect were observed after administration. The HR was reduced after administration of each compound and the greatest effect was observed after **110** was administered at a dose of 100 μg•kg^{-1}. The weakest and the shortest duration of effect was observed after **108** administration. These data suggested that a methyl substituent at the 7-position of the indazole ring was the most effective substitution for improving the hypotensive effects of the synthesized imidazolidine derivatives.

In 2018, a series of 3,4-dihydropyrazino[1,2-*b*]indazol-1(2*H*)-one derivatives were synthesized by Furlotti et al. (Furlotti et al., 2018), as outlined in Scheme 18. The preparation of the piperidine 114 was obtained: (a) the *N*-protection and the subsequent basic hydrolysis (NaOH) of the aminoester 112 to the acid intermediate, then the direct reduction of intermediate to primary alcohol 113; (c) the conversion of the hydroxyl moiety to a better leaving group. The tricyclic initial scaffold 117 was obtained through the deprotection and the ring closure of the intermediate 116, which, in turn, was prepared starting from the simple indazole-3-carboxylic acid 115 upon esterification and subsequent *N*-alkylation. The derivatives 118 were obtained with 117 under NaOH, then derivatives 18 reacted with 1-(2-bromoethyl)-2-fluorobenzene under Cs_2CO_3 to give the target compound 119. Then, 3,4-dihydropyrazino[1,2-*b*]indazol-1(2*H*)-one derivatives be studied as a potential ocular hypotensive compound. Compound **119** acted on two receptors (serotonin 2A, 5-HT_{2A}, and adrenergic α_1) related to the regulation of aqueous humor fluid dynamics as a potential ocular hypotensive agent (Table 13). Compound **119**, which was a potent 5-HT_{2A} antagonist (IC_{50} = 18 nM), was > 100 times more selective for 5-HT_{2A} than other serotonin subtype receptors, and had a positive effect on the α_1 receptors (IC_{50} values ranging from 220 nM to 1.5 μM). In addition, compared with the clinically

Table 14 Comparative IOP lowering effect of 120–123.



Compounds	%	Max IOP decrease from baseline (%)	Max IOP decrease from control	Duration of action	AUC
Timolol	0.5	20.00	12.50	5 ± 0.0	7.25 ± 0.66
120	0.1	27.91	26.21	4 ± 1.00	16.3 ± 4.04[a]
	0.2	31.83	31.83	5 ± 2.89	20.3 ± 2.10 [a]
	0.4	30.22	30.22	4 ± 0.58	13.0 ± 6.91 [a]
121	0.1	20.00	21.73	5 ± 0.00	13.1 ± 2.90 [a]
	0.2	27.70	27.70	5 ± 0.58	16.5 ± 2.90 [a]
	0.4	31.13	27.91	5 ± 0.58	17.9 ± 3.70 [a]
122	0.1	29.19	29.19	5 ± 0.58	18.8 ± 2.20 [a]
	0.2	30.00	27.06	4 ± 0.58	17.2 ± 1.70 [a]
	0.4	31.91	28.87	5 ± 0.58	18.5 ± 2.00 [a]
123	0.1	19.53	19.53	5 ± 0.58	14.1 ± 1.80 [a]
	0.2	23.24	21.43	5 ± 0.58	16.0 ± 3.20 [a]
	0.4	25.54	17.92	5 ± 0.58	10.4 ± 4.40

[a] significant difference compared to Timolol 0.5% (p-Value ≦0.05).

used reference compound timolol, compound **119** showed a greater ability to lower the intraocular pressure *in vivo* when administered topically (Fig. 14).

To find new hypotensive drug candidates, imidazo[1,2-*a*] benzimidazole and pyrimido[1,2-*a*] benzimidazole derivatives were screened (Marcus et al., 2018). The compound were studied in rats with normal blood pressure, and a rebound tonometer was employed to estimate the IOP. Compounds **120**–**123** were administered by a single drop, at 0.1%, 0.2%, and 0.4% concentrations (Table 14). Compounds**120-123** reduced the IOP in ocular normotensive rats. A relationship between the ability to lower intraocular pressure and the ability to lower blood pressure has been shown. According to pharmacophore analysis, pyrimido[1,2-*a*]benzimidazole is a better scaffold than imidazo[1,2-*a*]benzimidazole to provide compounds with a high intraocular pressure reduction effect. The key features for high intraocular pressure reducing activity were phenylalkyl and methoxyphenyl fragments, as well as non-conjugated six-membered heterocycles.

3. Conclusions

Hypertension is an important risk factor for cardiovascular complications. The treatment of hypertension is fundamental for the prevention of cardiovascular events. Effective methods for designing drug-like molecules include fragment-based drug discovery. The indole and indazole scaffolds are widely present in many biomolecules and medical products. This review describes the synthesis and antihypertensive bioactivity of indole and indazole analogues. It has been reported that indole- and indazole-substituted derivatives have antihypertensive activity. Interestingly, most of the indole and indazole derivatives were identified by scaffold hopping strategies or screening approaches. The review focused on the antihypertensive effects of recently developed indole and indazole derivatives effected via several targets. Analysis of the structural characteristics revealed that (I) the N_1 indole nitrogen atom has biological significance because of its hydrogen bond donor and acceptor properties; (II) the pyrrole ring of the indole skeleton can form hydrogen bonds with amino acid residues in the hinge region of enzymes, acting as a hydrogen bond donor or acceptor, which can result in inhibitory actions. The phenyl moiety of indole contributes to good hydrophobic gated interactions; and (III) the indazole supplies a coordination site for metals. The π-π and dipolar interactions between the indazole fragment and nitrogenous bases can heighten the antihypertensive activity. The information provided in this review regarding the activities of indole and indazole derivatives will assist in the design of new compounds with improved biological properties and lead to the development of novel synthetic strategies. These advancements may lead to the development of indole and indazole derivatives for clinical use in the eradication and control of various diseases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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