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Review

Recent advances in selective α_1-adrenoreceptor antagonists as antihypertensive agents

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Abstract—Hypertension is one of the most serious health problems of the modern world with a continuous rise in the number of patients. Selective α_1-adrenoreceptor antagonists though have many advantages and uses in the management of arterial hypertension, their lack of specificity at the level of α_1-adr subtypes leads to multiple side effects. Existence of multiple α_1-adr subtypes holds great promise for the discovery and development of more specific and selective drug molecules, targeting only one α_1-adr subtype at a time and thus relative freedom from side effects. Herein, the research done on the discovery and evaluation of a variety of chemically diverse structures as selective antagonists of α_1-adr and α_1-adr subtypes in recent years has been reviewed.

Contents

Keywords: Hypertension; Antihypertensive agents; α_1-Adrenergic receptor; α_1-adr subtypes; Selective α_1-adrenergic receptor antagonists.
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1. Introduction

In today's era of globalization, characterized by hurry, worry, and curry, the incidences of cardiovascular diseases are on the rise. Hypertension is a condition where the blood pressure is constantly higher than normal. This poses a serious health risk because it forces the heart to work extra hard. Constantly higher blood pressure can damage the coronary arteries, the brain, the kidneys, and the eyes. Hypertension is a major cause of strokes and heart attacks[1] (Fig. 1).

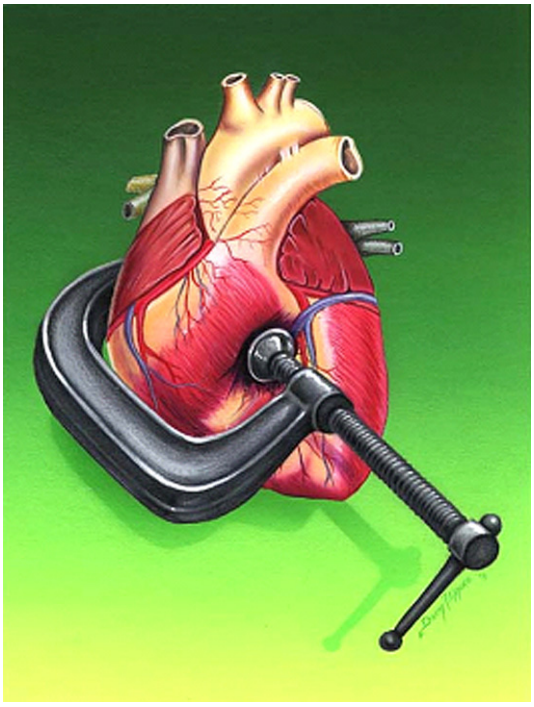


Figure 1. Heart under pressure.

1.1. Hypertension and its types

Hypertension is defined conventionally as blood pressure $\geqslant$140/90 mm. The Joint National Committee, The World Health Organization, as well as, International Hypertension Society's Subcommittee have published their own definitions of classification of blood pressure.[2,3]

(1) *Primary hypertension*
Despite many years of active research, there is no single major factor that can be attributed to primary hypertension. There is a natural progression of the disease which suggests that an early elevation in blood volume and cardiac output might initiate subsequent changes in systemic vasculature (increased resistance).
Though the specific cause for this type is unknown, almost 90% of the total hypertension cases are of this type. It is also called as 'essential or idiopathic' hypertension.
(2) *Secondary hypertension*
There are many known conditions that can cause secondary hypertension also known as 'inessential hypertension'. Regardless of the cause, arterial pressure becomes elevated either due to increase in cardiac output or increase in systemic vascular resistance or both. When cardiac output is elevated, it is generally due to either increased neurohumoral activation of the heart or increased blood volume.
The cause may be any of these: renal artery disease, eclampsia of pregnancy or pheochromocytoma. Only around 10% of the total cases belong to this category (Table 1).

1.2. Control of blood pressure

Blood pressure in its simplest term is the force of pumping of heart action, working against the resistance provided by the blood vessels. Body has a special 'blood pressure system'. The purpose of this system is to main-

Table 1. Definition (classification) of blood pressure by the Word Health Organization/International Society of Hypertension[4]

Category	Systolic blood pressure (SBP) (mm Hg)	Diastolic blood pressure (DBP) (mm Hg)
Normotension	<140	<90
Mild hypertension	140–180	90–95
Subgroup: borderline	140–160	90–95
Moderate and severe hypertension	⩾180	⩾105
Isolated and systolic hypertension	⩾140	<90
Subgroup: borderline	140–160	<90

'<' = less than; '>' = more than; '⩾' = more than or equal; '⩽' = less than or equal.

tain blood flow to all the tissues of the body at rest or during movements[4,5] (Fig. 2).

The Figure 3 and Table 2 depict the delicate coordination between cardiovascular system and the sympathetic nervous system involving some important organs like kidneys, brain, adrenals, and heart, to regulate the blood pressure. Genetic and environmental factors cause imbalance in this and cause hypertension.

1.3. Causes and pathological risks of uncontrolled hypertension

High blood pressure is a potential risk factor for cardiovascular diseases, independent of the presence or absence of other risk factors, for example, smoking, diabetes, and/or hypercholesterolemia. The other factors such as genetics, age, sex, race, diet, and environmental factors. (e.g., stress and physical activity), also play important role in elevation of the blood pressure. Herein, Table 3 denotes the pathological risks of uncontrolled, untreated hypertension to various organs and circulatory system.[8,9]

1.4. Antihypertensive drugs

1.4.1. History and classification. The discovery of most of our current antihypertensive drugs did not involve the target design of molecules to modify a blood pressure control system. Most of the drugs have evolved out through conventional synthesis and biological evaluation processes based on QSAR studies.[10] The currently used antihypertensive drugs are classified into seven broad categories (Table 4).

2. The α-adrenergic receptors and subtypes

The α-adr receptors play a pivotal role in the regulation of a variety of physiological processes, particularly within the cardiovascular system (Table 5) The past two decades have seen a renaissance of interest in α-adrs, their physiological relevance, classification, and second messenger system. Indepth knowledge arising from their research is leading towards development of agonists and antagonists, highly selective for the various subtypes of α-adr and with possible therapeutic values and lesser side effects.[11]

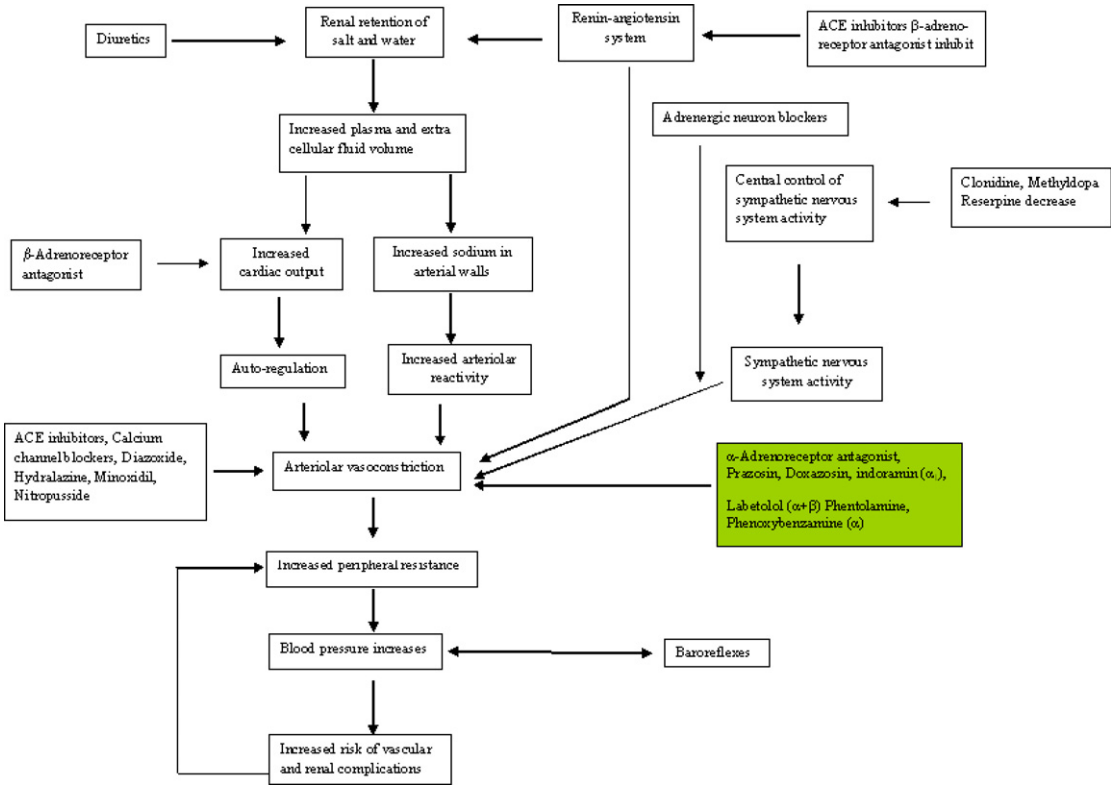


Figure 2. Body's blood pressure modulating system.

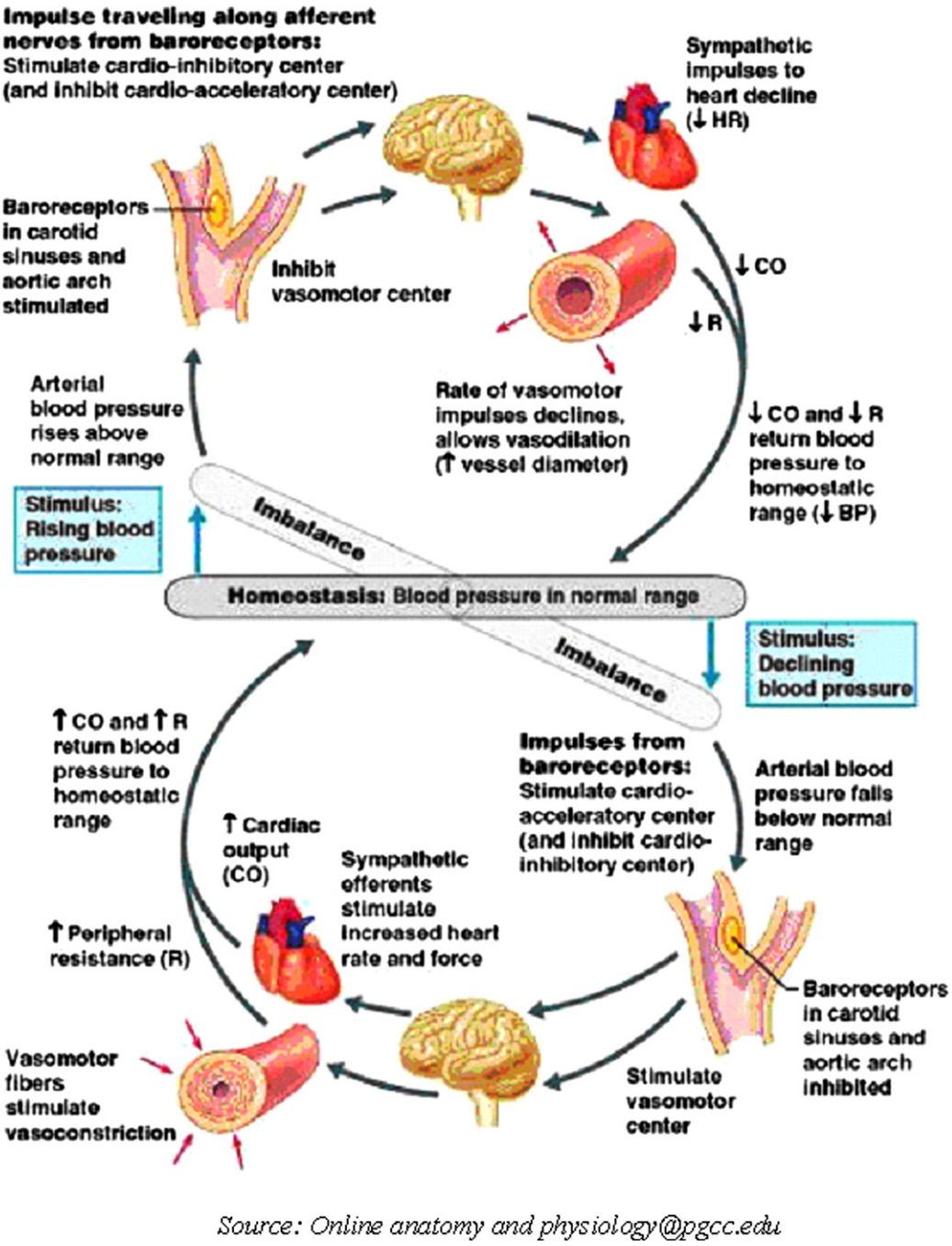


Figure 3. The interplay between cardiovascular organ system to regulate 'normal' blood pressure and the genetic and environmental factors that lead to hypertension.[6]

The main subtypes of α-adrs are α_1 and α_2.

The α_1- and α_2-adrs are located in the vascular smooth muscle cell membrane, and upon stimulation by appropriate agonists they mediate vasoconstriction. The occurrence of α_1/α_2-adrs throughout the vascular bed is not uniform. Table 6 summarizes which α-adr subtype mediates vasoconstrictions in different vascular beds in different mammalian species.

The simultaneous occurrence of both receptor subtypes on vascular smooth muscles makes it conceivable that α_1- and α_2-adrs can contribute to the maintenance of peripheral arterial tone and may play an important role in the increased peripheral resistance seen in hypertension. Drugs acting as selective antagonists at various post-junctional α_1-adrs are now frequently used in the therapy of high blood pressure, prazosin being the most common drug. However, the possibility of orthostatic hypotension after the onset of prazosin (first dose effect) has to be recognized.[38] Effectiveness of prazosin in the chronic therapy of hypertension is partially due to its lack of affinity for α_2-adr, or very high α_1-/α_2-adr selectivity index.

Table 2. Cellular sites of blood pressure control[7]

Organ/tissue	Cell type	Cellular response	BP Effect
Blood vessels (including renal coronary, mesentric and cerebral)	Smooth muscle cells	Contract and release endothelin	↓Resistance Hypertrophy
	Endothelial cells	Release NO↑	↓Resistance
	Interstitial cells (fibroblasts)	Collagen synthesis	↑Resistance
	Circulating blood cells (platelets)	Aggregate and release cytokines	↓↑Resistance ↓↑ Capillary permeability
Kidneys	Afferent/arterioles	Contract	↓↑GFR
	Mesangial	Contract	↓↑GFR
		Release gravin factors	Hypertrophy (↓↑GFR)
	Glomerular cells	Rennin release	↑Ang II synthesis (↑resistance)
	Tubular cells	Na^+, H_2O transport	↓↑Plasma volume
Adrenals	Zona glomerulosa cells	Release aldosterone	↑Na^+ reabsorption (↑volume)
	Medullary chromophin cells	Catecholamine release	↑Resistance, ↑CO
Heart	Myocytes	Contract	↑Flow
		Hypertrophy	↓↑Resistance
	Non-myocytes	Collagen synthesis	↑Resistance
Sympathetic nerves	Post-ganglionic cells	Norepinephrine release	↑Resistance, ↑CO
Brain	Neurohypophysis	AVP release	↑Na reabsorption, (↑volume)
	Neurones (medulla, hypothalamus, cerebral cortex)	↓↑Firing rate, transmitter release	↓↑Sympathetic outflow

GFR, glomerular filtration rate; CO, cardiac output; ↑, increase; ↓, decrease.

Table 3. Pathological risks of uncontrolled hypertension

Target organ	Clinical manifestations
Brain	Strokes (cerebral vascular accidents), transient cerebral ischemia
Heart	Acute myocardial infarction, sudden coronary death, accelerated ischemic heart disease (angina, arrhythmias), congestive heart failure
Kidney	Renal failure
Blood vessels	Aortic aneurysm (fusiform, dissecting), atherothrombotic obstruction and atenosis, ocular fundus damage (spasms to papilloedema), peripheral vascular disease

In contrast to the α_1-adr, the post-junctional vascular α_2-adr receptors have not been established yet as a target for antihypertensive therapy, though there is some evidence suggestive of some role of α_2-adrs in the pathogenesis and maintenance of hypertension.[39]

3. The α_1-adrenergic receptor subtypes

3.1. Introduction and discovery

Shortly after the division of adrenoreceptor into two major subtypes α_1- and α_2-adrenoceptors, evidence

Table 4. Classes of currently established drugs for the treatment of hypertension

Class	Chemical	Examples of drugs
Diuretics	Thiazide type	Chlorothiazide, chlorthalidone, Bendroflumethiazide, Trichlormethiazide
	Potassium sparing type	Spironolactone, Amiloride, Triamterene
	Loop type	Furosemide, Ethacrynic acid, Bumetanide, Torasemide
β-Blockers	Non-selective (β_1/β_2)	Propranolol, Timolol, Nadolol, Pindolol, Cartetolol
	Selective β_1	Atenolol, Betaxolol, Metaprolol, Acebutolol, Tozalol
ACE inhibitors		Captopril, Enalapril, Lisinopril, Fosinopril, Ramipril
Ca^{2+} blockers	Dihydropyridine	Nifedipine, Nicardipine, Felodipine, Amlodipine
	Phenyalkylamines Verapamil, Gallopumil	
	Benzothiazepines	Diltiazem
α_1-Adr antagonists		Prazosin, Doxazosin, Terazosin, Labetolol
α_1-Adr agonists		Clonidine, Guanafexine, Guanabenz
Miscellaneous		α-Methyldopa, Euronal blockers (Bretilium, Guanethidine) Rauwolfia and its alkaloids, (Reserpine, Deserpine, Rauwolfia whole root) Ganglionic blockers (Guanadrel, Mecamylamine, Hexamethonium) Non-specific vasodilators (Hydralazine, Nitroprusside, Diazoxide, Minoxidil)

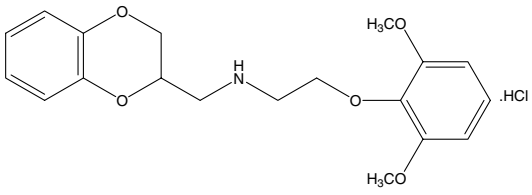
Table 5. Distribution, location and function of α_1- and α_2-adr

Type	Organ/tissue	Activation effects
α_1	Blood vessels (postsynaptic)	Contraction
	Smooth muscle (postsynaptic)	Contraction
	Heart (postsynaptic)	Positive inotropy/chronotropy
	Eyes (postsynaptic)	Mydriasis, ocular hypertension
	Liver (postsynaptic)	Glycogen phosphorylase activation
	CNS (postsynaptic)	Stimulation, inhibition of baroreceptor afferent inputs
	Sympathetic neurons (presynaptic)	Inhibition of noradrenaline release
α_2	Sympathetic, cholinergic and serotonergic neurons (presynaptic)	Inhibition of noradrenaline, acetylcholine, and serotonin release
	CNS (postsynaptic)	Hypotension, bradycardia
	Sympathetic ganglia	Hyperpolarization
	Somadendrites in CNS	Inhibition of firing
	Platelets	Aggregation
	Fat cells	Inhibition of lipolysis
	Pancreatic islets	Inhibition of insulin secretion
	Blood vessels (postsynaptic)	Contraction
	Intestinal epithelial cells	Inhibition of intestinal secretion

Table 6. Distribution of α_1-adr in various vascular beds

Vascular bed	Species	α_1-Adr in subtype	Ref.
Whole animal (blood pressure)	Anesthetized dog	$\alpha_1 + \alpha_2$	12
	Pithed dog	$\alpha_1 + \alpha_2$	13
	Conscious dog	$\alpha_1 + \alpha_2$	14
	Anesthetized cat	$\alpha_1 + \alpha_2$	15
	Pithed cat	$\alpha_1 + \alpha_2$	16
	Pithed rat	$\alpha_1 + \alpha_2$	17
	Pithed rabbit	$\alpha_1 + \alpha_2$	18
	Conscious rabbit	$\alpha_1 + \alpha_2$	19
Venous capacitance vessels	Pithed rat	$\alpha_1 + \alpha_2$	16
	Pithed cat	α_1	16
	Anesthetized dog	α_1	20
	Conscious dog	$\alpha_1 + \alpha_2$	14
	Anesthetized dog	$\alpha_1 + \alpha_2$	21
Coronary circulation	Anesthetized dog	$\alpha_1 + \alpha_2$	22
	Isolated guinea pig heart	$\alpha_1 + \alpha_2$	23
Mesenteric circulation	Pithed rat	$\alpha_1 + \alpha_2$	24
	Anesthetized dog	$\alpha_1 + \alpha_2$	25
	Anesthetized cat	$\alpha_1 + \alpha_2$	26
Renal vasculature	Anesthetized cat	α_1	27
	Pithed rat	α_1	28
	Anesthetized cat	α_1	26
	Anesthetized dog	α_1	29
	Anesthetized rabbit	$\alpha_1 + \alpha_2$	30
	Human (hypertensive)	$\alpha_1 + \alpha_2$	31
Pulmonary circulation	Anesthetized dog	$\alpha_1 + \alpha_2$	32
	Anesthetized cat	$\alpha_1 + \alpha_2$	33
Muscular	Anesthetized dog (femoral)	$\alpha_1 + \alpha_2$	29
	Anesthetized cat (femoral)	$\alpha_1 + \alpha_2$	34
	Anesthetized rabbit	$\alpha_1 + \alpha_2$	35
	Anesthetized rat (hindquarters)	$\alpha_1 + \alpha_2$	36
	Human (forearm)	$\alpha_1 + \alpha_2$	37

began to emerge that was inconsistent with a single vascular α-adr. The initial sub-classification of α-adrs into α_{1A} and α_{1B} subtypes was determined by receptor-binding experiments, using the competitive antagonist WB-4101 and the alkylating agent chloroethylclonidine (CEC). Whereas the α_{1A}-subtype displayed a moderate affinity for WB-4101 and was CEC-insensitive, α_{1B}-adr exhibited a low affinity for WB-4101, but was sensitive to CEC. Following the initial cloning of the hamster α_{1B}-adr, two additional cDNAs were cloned.[40,41]



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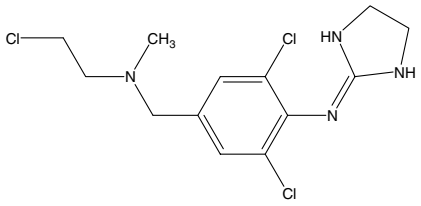


Chloroethylchlonidine

The α_{1A}-adr is the predominant receptor, causing vasoconstriction in many vascular beds, including the following arteries: mammary, mesenteric, splenic, hepatic, omental, renal, pulmonary, and epicardial coronary. It is also the predominant subtype in the *vena cava* and the saphenous and pulmonary veins. Together with the α_{1B} receptor subtype, it promotes cardiac growth and structure. The α_{1B} receptor subtype is the most abundant type in the heart, whereas the α_{1D} receptor subtype is the predominant receptor, causing vasoconstriction in the aorta. There is evidence to support the idea that α_{1B} receptors mediate behaviors such as reaction to novelty and exploration and are involved in behaviorial sensitization and in the vulnerability to addiction[42] (Table 7). The characteristics of the α_1-adr subtypes are tabulated (Table 8).

Table 7. Subtypes of α_1-adr (tissue localization and other dominant effects)

Subtype	Gene location in human chromosome	Tissue localization	Subtype dominant effects
α_{1A}	8	Heart, liver, cerebellum, cerebral cortex, prostate, lung, vas deferens, blood vessels	Predominant receptors causing contraction of smooth muscle including vaso constriction in arteries and veins
α_{1B}	5	Kidney, spleen, lung, cerebral cortex, blood vessels	Most abundant subtype in heart, with1A promotes cardiac growth structure
α_{1D}	20	Platelets, cerebral cortex, prostate, hippocampus	Predominant receptor causing vaso constriction in the aorta and coronary arteries

Table 8. Summary of α_1-adr subtype characteristics

	α_{1A}	α_{1B}	α_{1D}
Previous names	α_{1A}, α_{1B}	α_{1B}	α_{1A}, $\alpha_{1A/D}$
Functional response(s)	Rat vas deferens contraction, rat renal artery contraction, rat caudal artery contraction, rat isolated perfused kidney vasoconstriction control of blood pressure	Rat spleen contraction, role in rat tail contraction, control of blood pressure	Rat aorta contraction, control of blood pressure (hypertension)
Ligand-binding assay	Rabbit liver, rat submandibular gland	Rat liver and spleen, transfected CHO and HEK 239 cells	Rat aorta, transfected CHO and HEK 239 cells
Non-selective agonists	Phenylephrine, cirazoline, methoxamine	phenylephrine, cirazoline, methoxamine	Phenylephrine, cirazoline, methoxamine
Selective agonists	A61603, oxymetazoline	None	None
Non-selective antagonists	Prazosin	Prazosin	Prazosin
Selective antagonists	For example, 5-methylurapidil, RS 17053	L-765, 314	BMY7378
Potency order	Noradrenaline $\geqslant$ adrenline	Noradrenaline = adrenalin	noradrenaline > adrenalin
Receptor distribution	Brain, prostate, vas deferens, heart, blood vessels	Spleen, kidney, brain, heart, blood vessels	Brain, rat aorta, blood vessels
Tissue function(s)	Smooth muscle and myocardial contraction	Smooth muscle contraction	Smooth muscle contraction
Sensitivity to CEC	+/−	+++	++
Second messenger system(s)	Activation of $Gq_{/11}$, increase in PI turnover with elevation of $[Ca^{2+}]_i$, activation of voltage-gated Ca^{2+} channels		
Notes	A61603 also displays high affinity at α_2-adrenoreceptor subtypes; there are four known isoforms	CEC also affects other receptors	The rat aorta appears to contain other α_1-adrenoreceptor subtypes

CEC, chloroethylclonidine; PI, phosphoinositol; CHO, Chinese hamster ovary; HEK 203, human embryonic kidney cells.

3.2. Significance of receptor subtypes

As the diversity and selectivity increases, it is evident that multiple subtypes of receptors exist within many previously defined classes. Molecular cloning has further accelerated discovery of novel receptor subtypes and their expression as recombinant proteins has facilitated discovery of subtype-selective drugs. When selective ligands are not known, the receptors are more commonly referred to as isoforms rather than as subtypes. Receptor subtypes may display different mechanisms of signal output. The α_{1A},- α_{1B}-, and α_{1D}-adr isoforms differ little in their biochemical properties, although their tissue distribution is distinct[43] (Table 9).

Table 9. Subtypes of α_1 and α_2 adrenergic receptors[43]

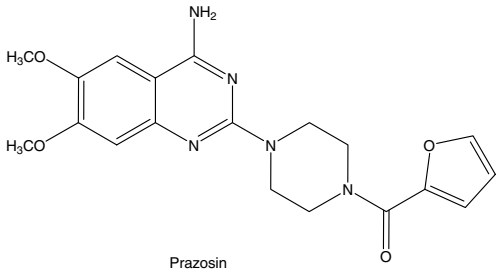
Sub type	Selective agonists	Selective antagonists	Tissue localization	Biological effect
α_{1A}	Not available yet	5-Methylurapidil (+)-Niguldipine	Heart, Liver, *Vas deferens*	Increased force and rate of contraction Glycogenolysis, Gluconeogenesis Contraction
α_{1B}	Not available yet	Not available	Kidney, spleen, aorta, lung, cerebral cortex	Smooth muscle contraction
α_{1D}	Not available yet	Not available	Aorta, cerebral cortex, prostate, hippocampus	Smooth muscle contraction

Additional α_1-adr subtypes have been proposed, these are namely α_{1L}, α_{1H}, and α_{1N} based on their affinity of prazosin namely, α_{1H} ($K_b < 1$ nM) > α_{1L} ($K_b > 2$ nM) $\geqslant$ α_{1N} ($K_b > 2$ nM). However, α_{1N}-adr has higher affinity for yohimbine ($K_b < 100$ nM) compared to α_{1L}-adr ($K_b > 300$ nm). However, clear cut location of these subtypes is yet to be confirmed.

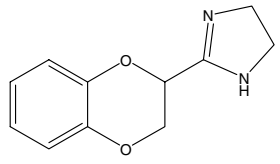
3.3. α_1-Adrenergic receptor antagonists

3.3.1. Introduction. The discovery of prazosin followed the investigation of the blood pressure lowering effect of 4-aminoquinazolines. The candidate compound prazosin is the 4-aminoquinazoline, which lowered blood pressure involving a component of sympathetic inhibition at the peripheral site or central sites. Unlike previous α-blockers such as phentolamine, prazosin has significantly less cardio-stimulatory effects. Such difference can now be explained on the basis of α-adr subtype.

Prazosin is the prototype of an α_1-adr receptor antagonist and idozoxan is the prototype of α_2-adr antagonists. Prazosin selectively blocks postsynaptic α_1-adr while having no effect on presynaptic α_2-adr, responsible for the inhibition of norepinephrine release from sympathetic nerve.[44]



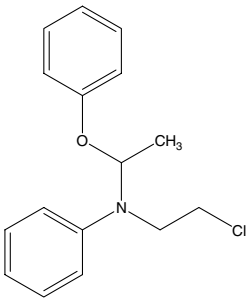
Prazosin



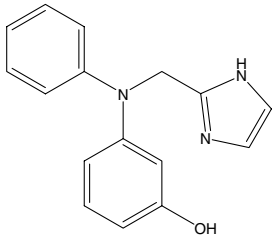
Idozoxan

Phentolamine, by contrast non-selectively inhibits both α_1- and α_2-adrs resulting in a greater activation of sympathetic nerves.

3.3.2. Chemistry. The first series of adrenergic blocking agents that acted at what was later designated 'α-receptor' were the haloalkylamines, represented by phenoxybenzamine. These compounds were related to nitrogen mustards and cyclized to form reactive ethylinimonium intermediates. In addition to α-adr blockade, these agents also inhibited response to serotonin, histamine, and acetylcholine. Phenoxybenzamine was used by oral and IV administration, but was limited by marked hypotension and reflex tachycardia.

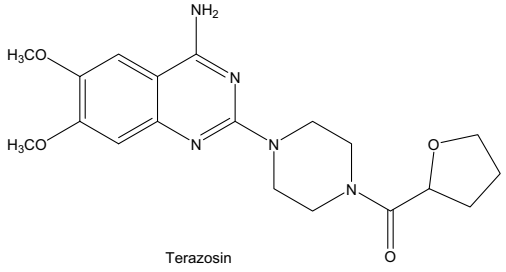


Phenoxybenzamine

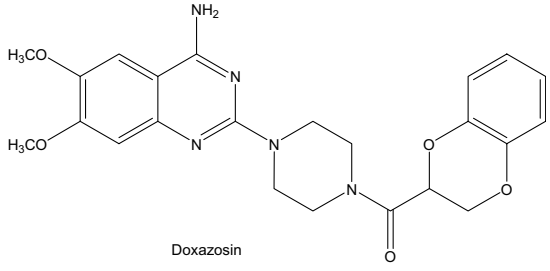


Phentolamine

The next important development came from a series of 2-substitutedimidazolines observed to have histamine like depressed activity, From these studies came phentolamine which was shown to reverse the pressor response to epinephrine. Phentolamine is still being used in the management of hypertensive emergencies, but its use is limited by orthostatic hypotension and reflex cardiac stimulation. Although many other molecules have subsequently shown to have sympatholytic or adrenolytic activity, prazosin was the first α-blocker suitable for chronic oral treatment of essential hypertension. Prazosin was chosen from a series of dimethoxyquinazolines for its potency and duration of action, 2-furoylpiperazine was preferred over simpler ester or the simple dimethylamine substituent. The duration of the half-life of prazosin is approximately 3 h. Simple saturation of furan rings is terazosin with increased lipid solubility and with a half-life of approximately 12 h. Further increase in half-life (reduced metabolism) was accomplished with doxazosin, which contains a bulky replacement of furan ring.[45]



Terazosin



Doxazosin

3.3.3. Uses and applications.

3.3.3.1. Comparative efficacy. The use of α_1-adr blockers for the treatment of hypertension has been limited due to concerns that they are less effective than other antihypertensive drugs and that tolerance develops with continued use. Monotherapy with an α_1-blocker has been effective in controlling blood pressure in 50–60% of

patients. The 7th report of the Joint National Committee on the detection, evaluation, and treatment of hypertension[46] has given a list of various 14 categories of oral antihypertensive drugs considered suitable for the initial treatment of hypertension. One of these categories is the α_1-blockers, which includes doxazosin, prazosin, and terazosin.

Tolerance did occur when α_1-blockers were used as after-load reducers in patients with CHF. However, tolerance does not develop to the antihypertensive effects and patients treated with α_1-blockers have demonstrated continued blood pressure control for several years. Like the ACE inhibitors and Ca^{2+} channel blockers, α_1-adr blockers have not been studied in large, randomized clinical trials for the prevention of hypertension related complications. Their ability to prevent strokes, coronary heart disease events, or the progression of renal disease is known.[47]

3.3.3.2. Comparative safety. Postural hypotension (usually most significant after the first dose of the drug and occasionally resulting in syncope) is the most significant side effect of the α_1-blockers. 'First dose syncope' was a common problem when large initial doses of prazosin (2 mg) were used. The incidence of first dose hypotension reported with terazosin and doxazosin is lower (<2%) reflecting a more gradual onset of their hypotensive effect and the use of lower initial doses. Postural hypotension can be minimized by starting with low doses (see table for recommended initial doses of each drug), increasing the dose gradually (minimum of 3 days between dosage titrations), and administering the drug at bedtime. Dizziness, headache, and fatigue are the most common side effects associated with the α_1-blockers.

3.3.3.3. Role in hypertension. The α_1-adr blockers can be used for the initial treatment of HT (and may be preferred in patients with BPH, that is, benign prostatic hypertrophy). However, they probably have a larger role in combination with other antihypertensive drugs when diuretics and β-blockers cannot be used.[47]

3.4. Demerits of currently used adrenoceptor antagonists

The discovery and development of especially, prazosin and its congeners, terazosin, trimazosin, doxazosin, etc., bearing a very high index of α_1-/α_2-adr affinity have triggered off a renaissance of interest in α_1-adr antagonist drugs. Also, they have many advantages like dictating both resistance and capacitance of blood vessels. They are widely used for the management of arterial hypertension. However, their lack of specificity at the level of α_1-adrenoreceptor subtypes leads to multiple side effects.

Existence of multiple α_1-adr subtypes holds great promise for the discovery and development of more specific selective drug molecules, targeting only one α_1-adr subtype and free from side effects. Thus, today medicinal chemists worldwide are involved in design and synthesis of very specific α_1-adr subtype antagonists. Herein, in the forthcoming sections an attempt has been made to review the literature on the research done on the discovery and evaluation of a variety of chemically diverse structures as selective antagonists of α_1-adr and α_1-adr subtypes in recent years.

4. Recent advances in α_1-adrenoceptor antagonists

The effort to design agents as selective antagonist for each of the three α_1-adr subtypes has been an area of active research. Therapeutically α_{1A}-adr antagonists might be useful in the treatment of benign prostatic hyperplasia (BPH).[48–53]

Recently, a role for the α_{1B}-adr subtype in the regulation of blood pressure has been advanced,[54] whereas a potential therapeutic use for the α_{1D}-adr subtype has not been firmly established. Yet they may have a role in the control of blood pressure because of their involvement in the contraction of a variety of vessels.[55] Furthermore, the α_{1D}-adr is predominant in the detrusor muscle and is upregulated in the detrusor of obstructed rats.[56] This suggests a relevant role also for this subtype, in the control of the symptoms associated with BPH. Although the collection of α_1-adr antagonists presented in this section covers a range of structural types, all the compounds possess a central basic center flanked on at least one side by aromatic systems. The presence of a protonated form of the molecule, at physiological pH appears to be a vital feature for α_1-adr antagonists. However, the precise profile in terms of subtype selectivity is heavily dependent on the nature of the basic center, the substitution of the aromatic rings, and the spatial orientation of the groups. The following overview separates the agents into structural classes defined by the basic center and discusses briefly how α_1-adr subtype selectivity varies within each series.

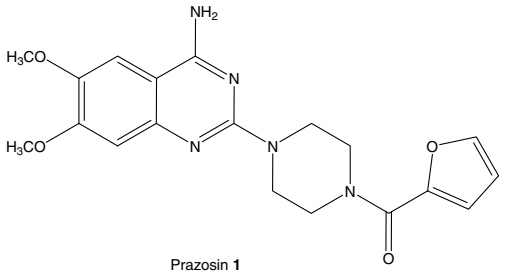
The different agents discussed are as follows:

4.1. 2,4-Diamino-6,7-dimethoxyquinazolines
4.2. 1,4-Benzodioxans and related compounds
4.3. Dihydropyridines and dihydropyrimidines
4.4. Fused pyrimidindiones
4.5. Pyridazinone derivatives
4.6. Imidazolines and fused imidazolines
4.7. *N*-Arylindoles
4.8. *N*-Aryl and *N*-heteroaryl piperazine derivatives
4.9. Miscellaneous compounds

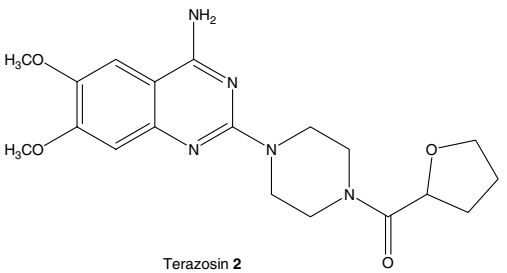
4.1. 2,4-Diamino-6,7-dimethoxyquinazolines

4.1.1. Introduction. This is the most effective and clinically used class of selective α_1-adr antagonists as antihypertensive agents. These derivatives have a very high index of α_1-/α_2-adr affinity that triggered off a renaissance of interest in the treatment of hypertension using these drugs.[57] As a logical approach for the effective management of arterial hypertension, prazosin, and its analogues such as

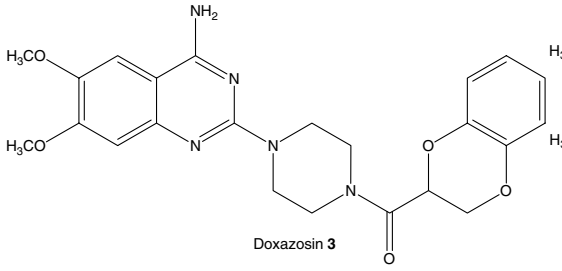
terazosin **2**,[58] doxazosin **3**,[59] tiodazosin **4**,[60] bunazosin **5**,[61] afluzosin **6**,[62] and trimazosin **7**[63] are employed clinically, as they are vasodilators with strong action in the arteriolar vascular bed. Further, they have many advantages like dictating both resistance and capacitance of blood vessels, favorable hemodynamic effects, virtual absence of reflux tachycardia, and maintenance of renal blood flow and glomerular filtration rate with intact auto regulation of noradrenaline due to non-blockade of presynaptic α_2-adr. They also have favorable effects on the lipid profile, carbohydrate metabolism, and insulin resistance. These drugs are also useful in the treatment of Congestive Heart Disease (CHD), Variant or Prinzmetal's Angina, Raynauds disease, etc. However, there is a need of developing more specific analogues with specific affinities to receptor subtypes to remove their side effects.[57]



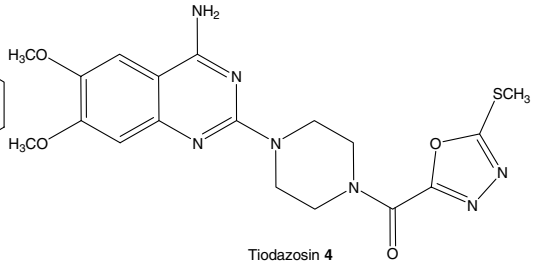
Prazosin **1**



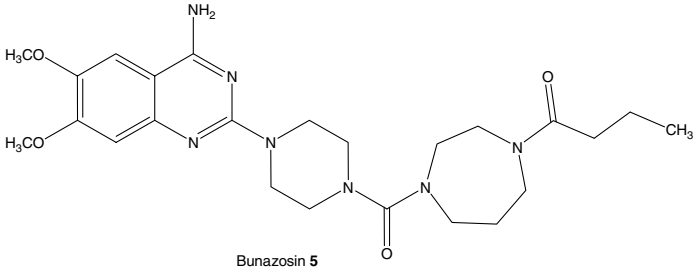
Terazosin **2**



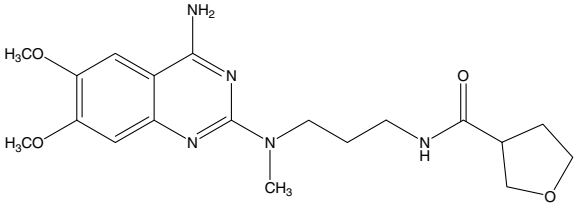
Doxazosin **3**



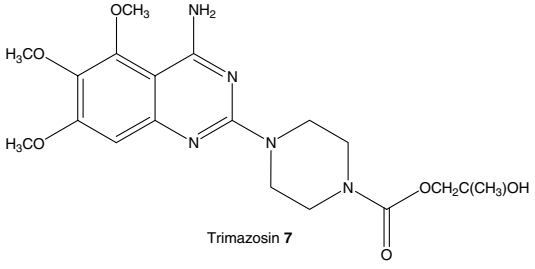
Tiodazosin **4**



Bunazosin **5**



Alfuzosin **6**

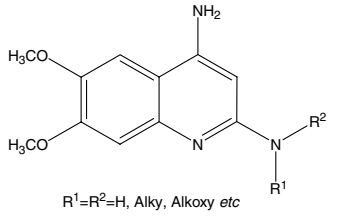


Trimazosin **7**

Though they are used widely for the management of arterial hypertension, their lack of specificity at the level of α_1-adr subtype leads to multiple side effects, which includes postural hypotension, syncope and first dose phenomena. The existence of multiple α_1-adr subtypes holds promise for the discovery and development of more specific selective drug molecules targeting only one receptor subtype and making them free from side effects.[57] Toward this aim wide ranging modifications have been reported on the basic structure.

The structure–activity relationship (SAR) studies on the prazosin analogues reveal some important points of modifications as seen from the various literature reports, which are discussed herein chronologically. The 4-amino group is an integrally essential part for the α_1-adr antagonist activity of this class of compounds (Fig. 4).

4.1.2. Modifications made in/on the pyrimidine ring of 4-amino-6,7-dimethoxyquinazoline nucleus. The 2,4-diaminoquinazoline ring though seems to be very essential for the α_1-adr receptor antagonist activity, the bioisosteric replacement of quinazoline with quinoline moiety, as seen in compounds **8** and **9** without adversely affecting their activities indicates that the N_1 atom of the quinazoline is essential for the activity, while the N_3 can be replaced.[64]



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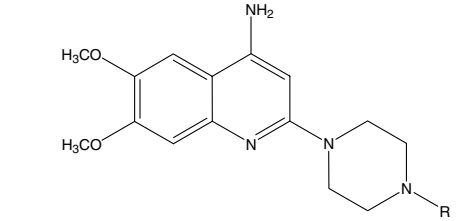


9

Active

The lack of activity in the isoquinoline analogues **10** and **11** even at higher doses, further substantiates the importance of the N_1 atom for the activity.[65]

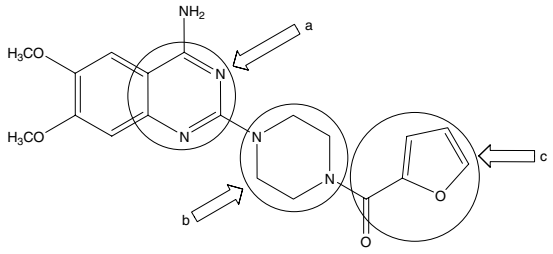
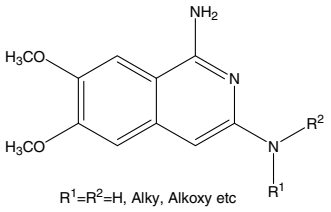


Figure 4. Points of modifications in the 2,4-diamino-6,7-dimethoxyquinazoline nucleus.



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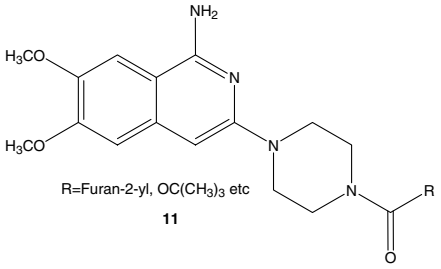
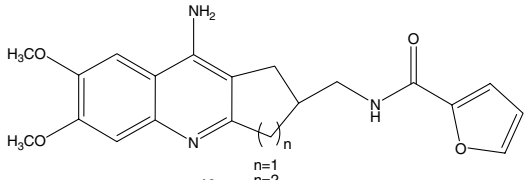


11

Inactive

With the aim of improving the selectivity profile at α_1-adr, in a study, prazosin was further modified affording a series of derivatives, in which the N_1 atom is present, often included in a different cyclic system. Modification of the quinazoline system into a tetrahydroacridine ring **12** was thus carried out. This structural modification, in addition to preserving the basicity of N_1, could force the N_1 and the furan moiety to assume a reciprocal arrangement, similar to that of prazosin in one of its low-energy confirmations. Moreover, since the N_3 function is not essential for the α_1-adr affinity, it was thought that its removal should not negatively affect activity of these tetrahydroacridine derivatives at α_1-adr. These derivatives **12** and **13** had the liner fusion of cyclopentane, cyclohexane, and cycloheptane rings to the 4-aminoquinazoline ring system, **12** ($n = 1, 2, 3$).[66] However, the whole series of derivatives resulted to be less potent at all α_1-adr subtypes, relative to the prototype.[67]



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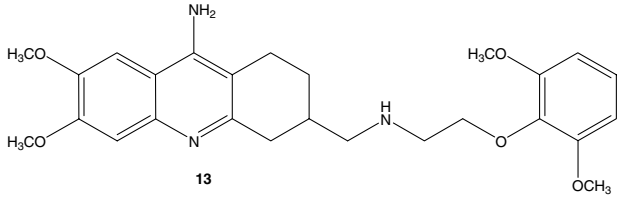
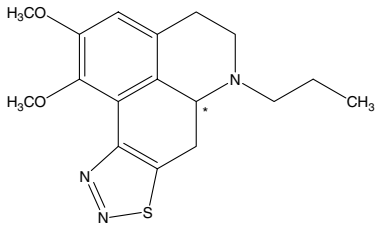


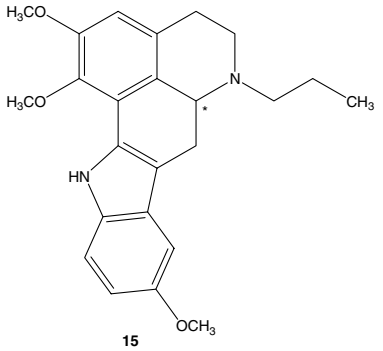
13

Another closely related series **14** was synthesized. Ligand-based design (pharmacophore development) methods have been used to design this novel 1,2,3-thiadiazole ring D analogues of the aporphine system. Synthesis and design of these compounds as a ligand on cloned and expressed human α_1-adr have been studied. Low-binding affinity for most of the derivatives was found, possibly due to an unfavorable electrostatic potential distribution.

The ring D thiadiazole analogue **14** of the aporphine system had very low affinity for the α_1-adr, whereas the ring D indole analogue **15** showed high affinity for the α_1-adr subtypes comparable to aporphine.[68]



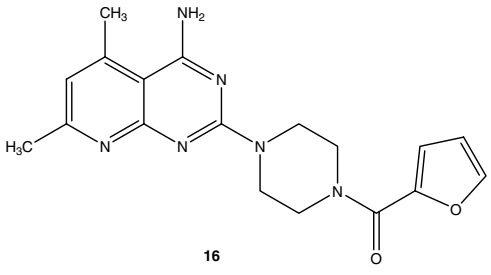
14



15

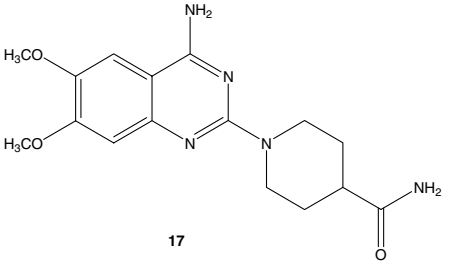
It is worth mentioning that the 6,7-dimethoxy groups of the parent prazosin structure are extremely essential for the selective α_1-adr antagonist activity. This can be seen in all the above discussed modifications like compounds **1**–**15** wherein these two methoxy groups were preserved.

However, there is a report indicating the replacement of the dimethoxybenzene with dimethylpyridine ring. Thus, a series of 4-amino-5,7-dimethyl-2-(substituted)amino-pyrimidines was designed using structure-based approach, to study the importance of the dimethoxybenzene ring for selective α_1-adr antagonist activity. Some of the synthesized compounds exhibited significant α_1-adr antagonistic activity. Compound **16** exhibited in vivo activity ($pA_2 = 7.8$) comparable to that of the standard drug prazosin ($pA_2 = 8.0$). Further, it was found more potent than prazosin when screened by the in vivo method (lowering of blood pressure of spontaneously hypertensive rats). This study revealed that the replacement of the dimethoxybenzene ring of prazosin by a bioisosteric pyridine ring did not affect the α_1-adr antagonistic activity.[69]

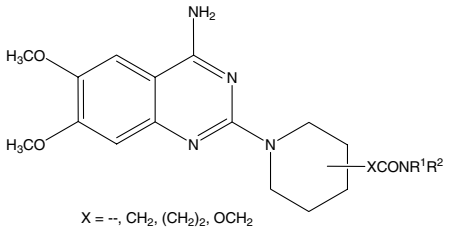


16

4.1.3. Modifications involving the 2-piperazinyl ring. 4.1.3.1. Replacement of the 2-piperazine ring. In many cases the piperazine ring at the 2-position has been replaced by its 4-deaza analogue, the piperidine ring system bearing a carboxamide moiety on its 4th position. It has been observed that the increase or decrease in the activity is rather related to the substitutions on this 4-carboxamido moiety. Thus, while the primary carboxamide in **17** was active even in nanomolar range, improvement in potency was observed by both alkyl and cycloalkyl substituents. However, shifting the position of the carboxamide function to the 3rd position was detrimental, leading to 13- to 100-fold decrease in the activity as seen in compound **18**.[70]



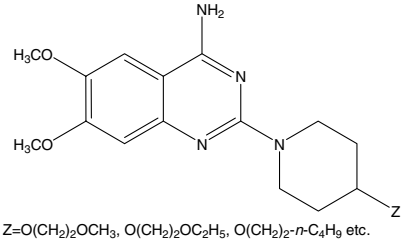
17



X = --, CH_2, $(CH_2)_2$, OCH_2

18

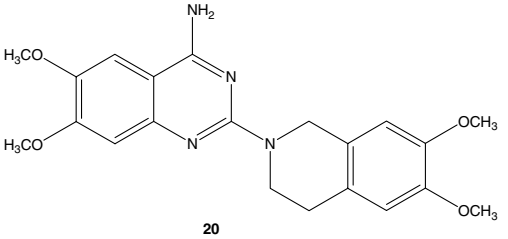
Interestingly, replacement of this carboxamido system with ethylenedioxyalkyl groups as seen in the series of compounds **19**, led to an increase in the α_1-adr affinity and potency compared to prazosin.[71]



Z=$O(CH_2)_2OCH_3$, $O(CH_2)_2OC_2H_5$, $O(CH_2)_2$-*n*-C_4H_9 etc.

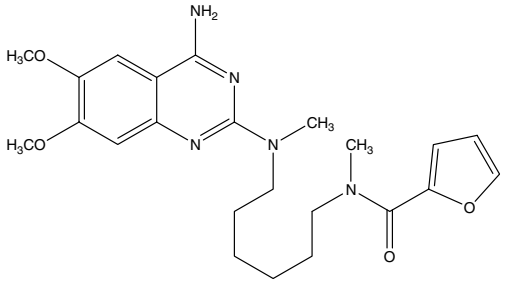
19

Replacement of piperazine ring with isoquinoline ring as in **20** was also tried. The compound was found to be a very potent α_1-adr antagonist.[72]



20

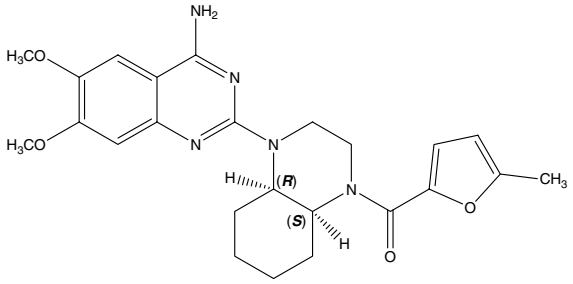
4.1.3.2. Modifications involving ring opening, ring expansion or C-substitution of the 2-piperazinyl ring. Studies reported by Italian workers[73] have indicated that compound **21**, bearing a 1,6-hexamethylenediamine moiety, was the most active of the series, being more potent than prazosin in both in vivo and in vitro evaluations. From these results is advanced the hypothesis that the α_1-adr incorporates a lipophilic area, located between the binding sites for the quinazoline and the furan ring of prazosin, w!hich is able to accommodate optimally a 1,6-disubstituted hexane moiety. However, compound **21** gives only limited information on the size and possible stereochemical requirements of this lipophilic area, because its polyethylene chain is very flexible and can assume many conformations.



21

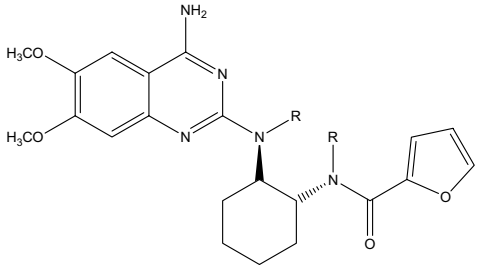
A series of compounds were designed in which the polymethylene chain at the position 2 is incorporated partially or completely into a constrained structure. It was thought that this structural modification would afford the compounds in which the quinazoline and furan rings appear in a position quite similar to that of prazosin, hopefully to give information on the size and spatial orientation of the lipophilic pocket. 1,2-Cyclohexanediamines **22**, mono- and di-substitutedpiperazines **23**, decahydroquinoxalines **24**, and related compounds were studied. Insertion of alkane chain of **21** into a decahydroquinoxaline nucleus increased the selectivity and affinity for α_1-adr. The selectivity of α_1-adr is strictly related to the presence of a piperazine ring, especially when its flexibility is further reduced by replacing it by a *cis*-decahydroquinoxaline moiety. The quinoxalinyl derivative cyclazosin **24** proved not only a potent and selective α_1-adr antagonist, but also to be an effective antihypertensive agent.[74]

In a recent study on cyclazosin analogues, substituents were introduced at position 5 of its 2-furoyl moiety, as well as, its replacement with classical isosteric rings was investigated. The 5-methylfuryl derivative (+)-**25**, [(+)-metcyclazosin], improved the pharmacological properties of the progenitor, displaying a competitive antagonism, and an 11-fold increased selectivity for α_{1B} over α_{1A}, while maintaining a similar selectivity for the α_{1B}-adr relative to the α_{1D}-adr.[75]



(+) Metcyclazosin **25**

Another approach was to incorporate new structural elements into the piperazine subunit. Moderate α_{1B} selectivity was induced by incorporating an (*s*)-*tert*-butylcarboxamido group at the C_3 of the piperazine moiety, as in compound **26**. One plausible explanation for this is that the 3-carboxamido group can form a hydrogen bond with a binding site within the α_{1B}-receptors. Another possibility is that a steric discrimination could be established. This explanation is consistent with the α_{1B}-selectivity observed for the (+)-enantiomer of cyclazosin, which bears a bulky substitution on the piperazine core ring.[76]



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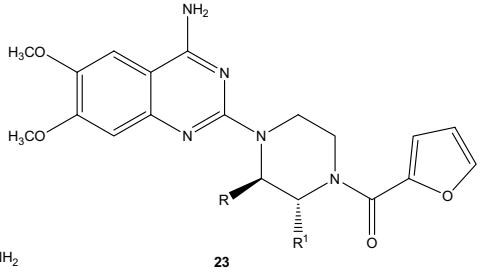

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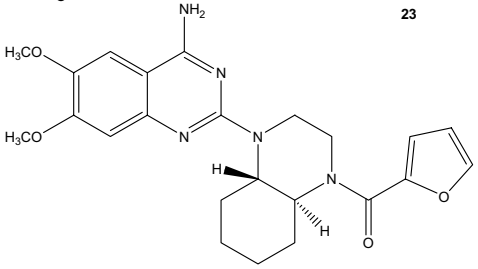
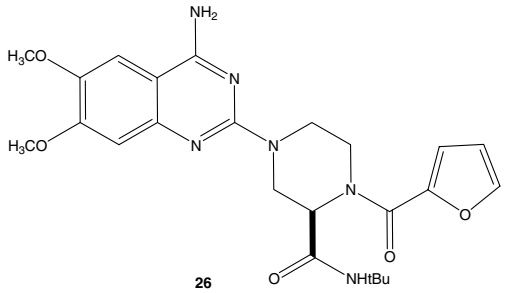


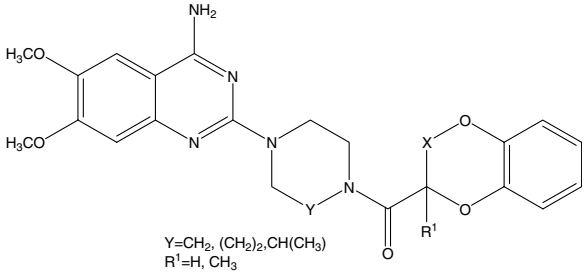
Cyclazosin **24**



26

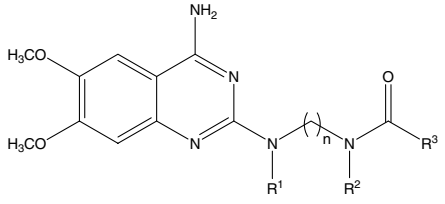
Many derivatives of doxazosin **3** were synthesized in which the 1,4-benzodioxan moiety was explored with the aims to preserve the α_1-adr affinity and selectivity, and to prolong the duration of antihypertensive activity, so that only a single dose/day may be sufficient in an adult. Most of the members of this series displayed high (ca. 10^{-9} nM) affinity for α_1 receptors and no compound showed any significant activity (>10^{-6} nM) at α_2 sites. Some of the important observations based on the modifications tried in a series of compounds, **27** and results obtained thereof are as follows:

(a) Mono-substitution on the aromatic ring of **27** with 8-methoxy, 8-methyl, or 7-acetyl groups preserved high α_1-adr activity, while there were only small reductions in potency with the 6-methoxy and 6-acetyl isomers. Larger substituents or di-substitutions were also well tolerated. These results suggested considerable scope for the modification of the aromatic moiety but, unexpectedly, the mono or dichloro derivatives were some 11-fold less active than doxazosin.
(b) Introduction of methyl groups into the 1,4-benzodioxan system at the 2- or 3-positions gave compounds essentially equipotent with doxazosin.
(c) Expansion of benzodioxan or piperazine ring was also acceptable, but the 3-methylpiperazino derivative had slightly reduced activity. A 24-h control of blood pressure is achieved after single daily dosing (0.5 mg/kg, po) and an extended plasma half-life (4.7 h) over prazosin (2.8 h) is consistent with improved duration of antihypertensive activity[77,78] with some of the compounds of this series.



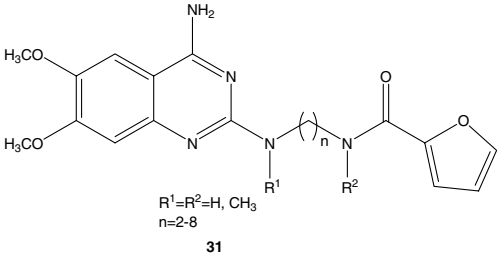
27

4.1.3.3. Complete opening of the piperazine ring. It is observed that intact piperazine ring at position 2 is not essential for the activity. Based on this, the synthesis and biological activity of some *N*-[(acylamino)alkyl]-6,7-dimethoxy-2,4-quinazoline diamines was carried out and it was found that the anti-hypertensive properties of these new molecules appear to strongly depend on the length of the alkylamine chain, the size, and nature of the R^1, R^2, and R^3 substituents. Maximum activity was observed in compounds having a propyl chain between the two nitrogen atoms and having R^1 as a methyl group, R^2 as a hydrogen atom or a methyl group and R^3 as an unsubstituted aromatic or heterocyclic/alicyclic ring such as furan, tetrahydrofuran, or cyclopentane. Compounds **28**–**30** were found to be the most potent derivatives as anti-hypertensive agents form this study.[79]



28: n=3,R^1=CH_3, R^2=H, R^3=C_6H_5
29: n=3,R^1=CH_3, R^2=H, R^3=tetrahydro-2-furyl
30: n=3,R^1=CH_3, R^2=H, R^3=Cyclopentyl

Further, the compounds of the type **31** bearing a secondary and tertiary nitrogen atom in the polyethylenediamine chain were found to be highly selective toward α_1-antagonists.[73]

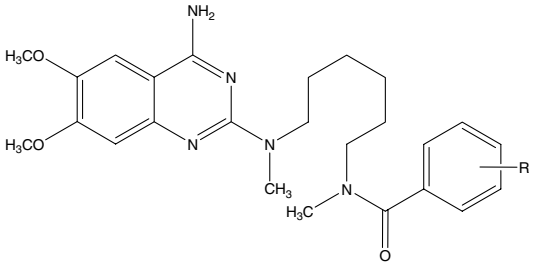


31

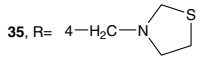
Since cyclazosin **24** incorporates a decahydroquinoxaline in a *cis* relationship, which is responsible for the high affinity for α_1-adr and bears two chiral centers in a different position relative to terazosin, it was thought to investigate whether the enantiomers might be able to discriminate among α_1-adr subtypes. This study demonstrated that the replacement of the piperazine ring of prazosin with a *cis*-decahydroquinoxaline moiety affording (+)-**24** does not affect the affinity for α_1-adr, while it significantly decreases the affinity for α_1 (α_{1B}-adr subtypes) in comparison to prazosin. The overall result of this structural modification is a significant improvement in selectivity toward the α_{1B}-adr. Thus, (+)-cyclazosin [(+)-**24**] emerges as a valuable tool for the characterization of α_1-adr subtypes owing to its unprecedented selectivity for α_{1B}-adr, associated with high potency.[80]

The simultaneous replacement of both piperazine and furan ring of prazosin gave **32**, which resulted in a potent, selective α_{1B}-adr antagonist (85- and 15-fold more

potent than prazosin, at the α_{1A} and α_{1D}-adr subtypes, respectively). Insertion of a substitution in the benzene ring of the **32** affected, according to the type and the position of the substituents, affinity and selectivity for α_1-adr. Consequently, the insertion of appropriate substituents in the phenyl ring of **32** may represent the basis of designing new selective ligands for α_1-adr subtypes. Interestingly, the finding that polyamines **33**–**35** bearing a 1,6-hexanediamine moiety, retained high affinity for α_1-adr subtypes, suggests that the substituents did not give rise to negative interactions with the receptor.[81]

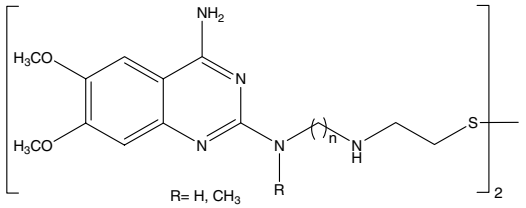


32, R=H; **33**, R=2-$CH_2NH(CH_2)_6$-NH_2; **34**, R=3-$CH_2N(CH_3)(CH_2)_6NHCH_3$



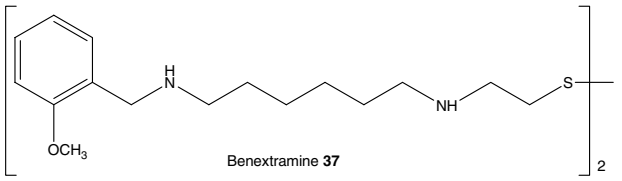
35, R=

Tetramine disulfides derivatives **36** were designed by combining the structural features of benextramine **37**, an irreversible α_1-/α_2-adr antagonist and prazosin. Some compounds showed up to 11-fold selectivity for α_{1B}-adr in contrast to both prazosin and benextramine, which are not selective for the α_{1B} and α_{1A}-subtypes, respectively. Surprisingly, none of the hybrid tetramine disulfides, unlike benextramine, irreversibly inhibited α_1-adr (actually found 5- to 80-fold lower than prazosin).[82]



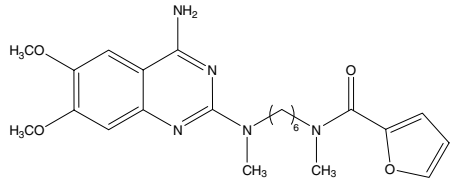
R= H, CH_3
n= 4-6, 8, 10, 12

36

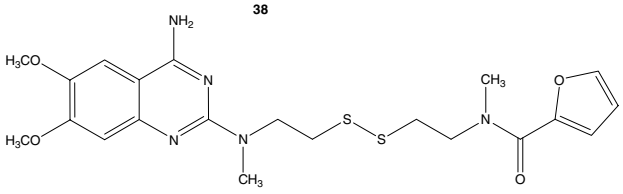


Benextramine **37**

A novel series of quinazolines related to prazosin and its two open chain amino analogue, **38** was synthesized and evaluated for antagonistic activity on α_1-adr subtypes. The cystamine bearing quinazoline **39** (cystazosin) of this series has a reversed affinity profile relative to (+)-cyclazosin, owing to its higher affinity for α_{1D}-adr and a significantly lower affinity for the α_{1A} and α_{1B} subtypes. Cystazosin **39** displays a much better specificity profile since it has a lower affinity for D_2 and 5-HT_{1A} receptors.[83]

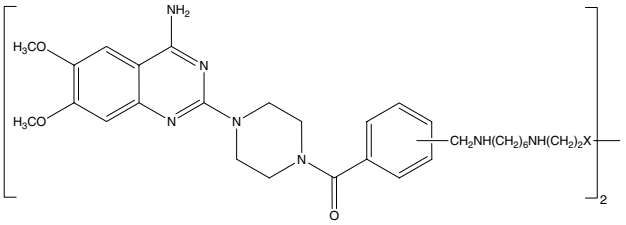


38

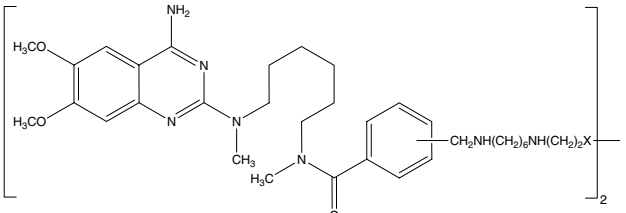


Cystazosin **39**

Hybrid tetramine disulfides **40** were synthesized by combining the structural features of prazosin and benextramine. Their biological profiles at α_1-adr subtypes were assessed on isolated rats *vas deferens* (α_{1A}), spleen (α_{1B}), and aorta (α_{1D}). To verify the role of the disulfide moiety on the interactions with α_1-adr subtypes, the carbon analogues **41** were also included in this study. All quinazolines lacking the disulfide bridge behaved, like prazosin, as competitive antagonists, whereas all polyamine disulfides **40** displayed a non-homogeneous mechanism of inhibition of three subtypes, like benextramine, as non-competitive antagonists at the α_{1A} and α_{1B} subtypes, while being competitive antagonists at the α_{1D}. On the other hand, polyamines **42** emerged as promising molecules for the characterization of α_1-adr subtypes, owing to their receptor subtype selectivity.[84]



40, X=S
41, X=CH_2

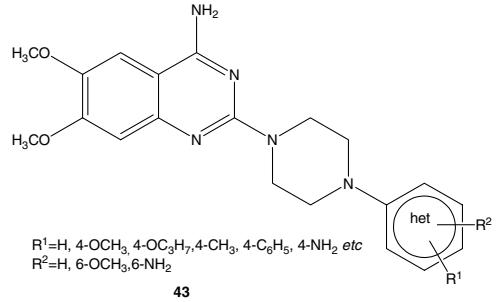


X=S, CH_2

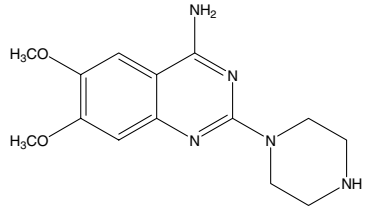
42

4.1.4. Modifications involving the replacement of the furoyl moiety. In order to clarify further the importance and the function of the furoyl π system, the synthesis and pharmacological properties of a series of 2-(4-heterocyclylpiperazin-1-yl)quinazolines **43** are reported.[85] For these compounds, the carbonyl moiety was replaced by a heteroaromatic π system, which also allows the influence of dipole direction to be probed. In addition, modification of heterocyclic substitution permits optimization of hydrophobic interaction. Results demonstrate that the heteroaryl moieties in this series provide effective replacement for the carbonyl function present in

prazosin. The similar potency shown by these isomeric derivatives with prazosin suggests that neither the magnitude nor the direction of heteroaryl or carbonyl dipoles has any particular influence on α_1-adr interactions. However, activity results that the unsubstituted 2-piperazin-1-yl quinazoline **44** has an increase in α_1-binding affinity of at least 100-fold confirm that appropriate substituents in this area of the quinazoline nucleus can have a profound effect on receptor affinity.

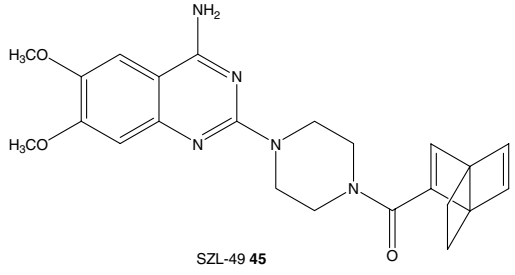


43



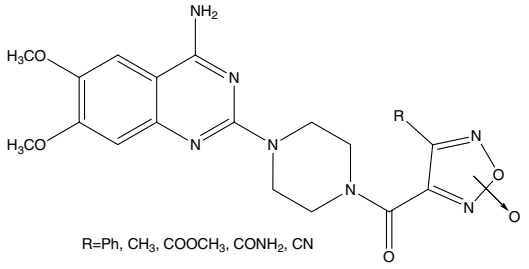
44

A new series of prazosin analogues comprising *N*-acyl derivatives of *N*′-(4-amino-6,7-dimethoxyquinazolinyl)piperazine **44** was prepared and the nature of their binding to α_1-adr was investigated. A very high affinity and irreversible binding was observed with the bicyclo[2.2.2]octa-2,5-dien-2-ylcarbonyl derivative, SZL-49 **45**.[86]

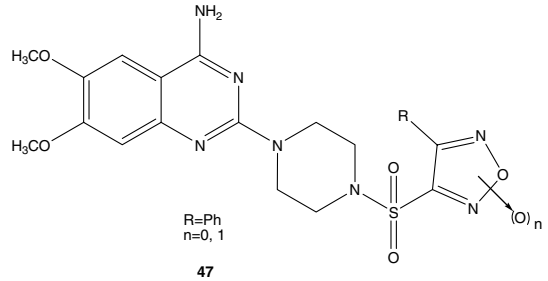


SZL-49 **45**

Recent results have shown that furoxan derivatives are able to activate the soluble guanylate cyclase by releasing nitric oxide under the action of thiol co-factors. Since NO is involved in many bioregulatory processes, the furoxan system could be used in the designing of a variety of hybrid molecules. Synthesis of furoxan analogues of prazosin, in which the phenyl (or methyl) furoxanylcarbonyl system was substituted for the 2-furonylcarbonyl moiety was carried out with the aim to develop new vasodilators, capable of displaying NO-dependant effect on the micro and macrovascular systems, mixed with the α_1-adr antagonist activities. When the vasodilating activities of these compounds were assessed on the epididymal portion of rat *vas deferens*, the results showed that all the hybrid compounds were strongly or completely biased toward α_1-antagonist properties.[87] Later on, the design and synthesis of prazosin analogues **46** and **47** were undertaken. Both series of compounds exhibited same potency. This supports the working hypothesis that the sulfonemethylene group could be used as a bio-isosteric moiety of the amide function in the design of new analogues. These derivatives display antagonistic activity similar to that of prazosin and NO-vasodilating properties near to that of sodium nitroprusside. On the whole, these results show that the substituted furoxan ring is a very flexible system in the designing of hybrids in which a NO-dependant activity can be mixed with mutually complementary biological activity.[88]

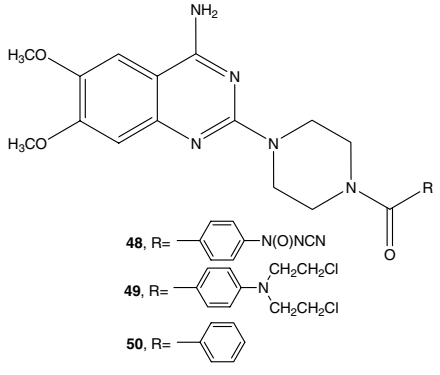


46

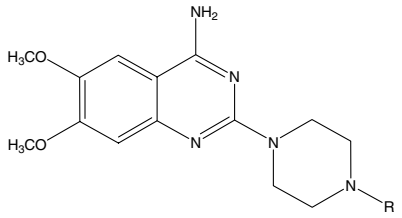


47

Studies with a series of tetramine disulfides related to benextramine suggest that in the surface of α_1-adr, a thiol group, able to irreversibly react with the disulfide moiety of the drug, is present.[89] On this basis design of a new series of compounds, **48** and **49**, as potential irreversible α_1-antagonists structurally related to prazosin was made. When benzoyl moiety is substituted for the 2-furoyl structure, the resulting molecule **50** retains high affinity and selectivity for the α_1 receptor.[90]

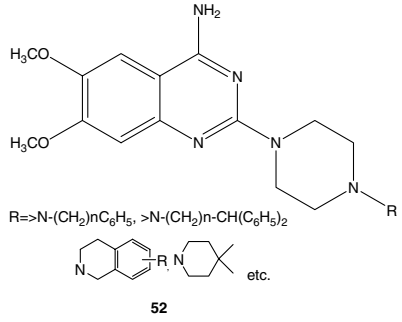


A novel series of piperazine and non-piperazine derivatives of 2,4-diamino-6,7-dimethoxyquinazoline, **51** and **52** were synthesized and evaluated for their binding affinities toward α_1-adrenergic receptors.[91] Of the various compounds synthesized and evaluated, **51** showed moderate selectivity toward α_{1B}-adr subtype, whereas compound **52** showed in vivo potency close to that of prazosin.[92]



R=COR',COAr, CO(CH$_2$)nCOR', CO(CH$_2$)n-OAr
R'=alkyl, Ar=disubstituted aryl

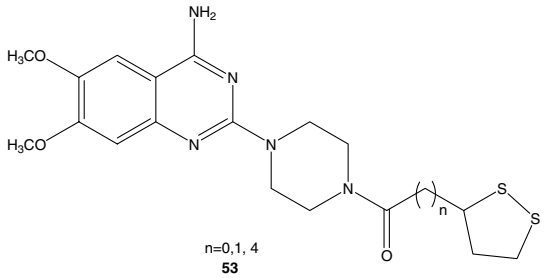
51



R=>N-(CH$_2$)nC$_6$H$_5$, >N-(CH$_2$)n-CH(C$_6$H$_5$)$_2$

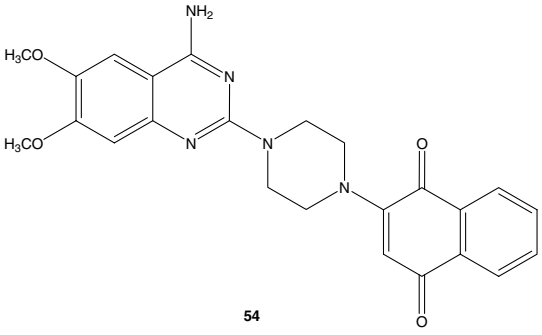
52

To combine in the same molecule, the α_1-adr blocking and antioxidant properties, compounds **53** and **54** were designed and synthesized. All compounds were effective α_1-adr antagonists and were tested by both functional and binding assays. In addition, these compounds also displayed significant capacity to inhibit intracellular oxidative stress, as well as, potent antiproliferative activity in lymph node carcinoma of prostate cells. While in compounds **53** the furoyl moiety of prozosin was replaced with the lipoyl fragment of lipoic acid and its homologs, in compound, **54**, it was replaced with 1,4-naphthoquinone.[93]



n=0,1, 4

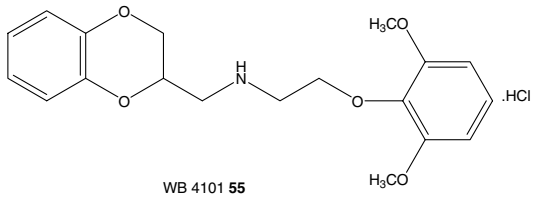
53



54

4.2. 1,4-Benzodioxans and related compounds

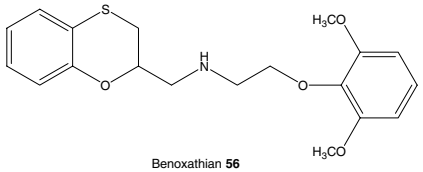
Benzodioxans represent one of the oldest and best known class of α-adr antagonists, which involve chemical structures incorporating a 1,4-benzodioxan-2-yl moiety as the main structural feature responsible for the α_1-adr antagonist activity. Compound, WB 4101 **55**, (*N*-[2-(2,6-dimethoxyphenoxy)ethyl]-2,3-dihydro-1,4-benzodioxan-2-methanamine), is the prototype of α_1-adr antagonists bearing a benzodioxan moiety. Several investigations have been devoted to improving both affinity and selectivity of these compounds. Both the benzodioxan-2-yl and (2,6-dimethoxyphenoxy)ethylamino moieties are reported to be essential for the activity. As a result, a variety of analogues have been studied involving modifications at the benzodioxan ring, the amine function, or the (2,6-dimethoxyphenoxy)ethyl moiety.[94,95]



WB 4101 **55**

The following points of modifications have been explored on the basis of the structure–activity relationships of 1,4-benzodioxan-related compounds. These points are discussed in subsequent sections, with respect to compound **55** (see Fig. 5).

4.2.1. Modifications done on the 1,4-benzodioxan and phenoxy ring systems. Replacement of ring oxygen at position 4 of the benzodioxan ring of WB 4101 with sulfur atom as in the benoxathian **56**, did not modify the biological profile, but rather gave a potent and highly selective α_1-adr antagonist.[96,97]



Benoxathian **56**

The various structural modifications performed on the benzodioxan ring system include replacement of hydrogens at 2- or 3-position with a variety of substituents.[98] Insertion of a phenyl ring at position 3 having a *trans* relationship with the side chain at 2, afforded phenodioxan **57**, (*trans*-*N*-[2-(2,6-dimethoxyphenoxy)ethyl]-2,3-dihydro-3-phenyl-1,4- benzodioxan-2-methanamine). Although, this compound was less active than the parent compound (five times less potent), it was over three orders of magnitude more potent than the *cis* isomer at the α_1-adr. How-

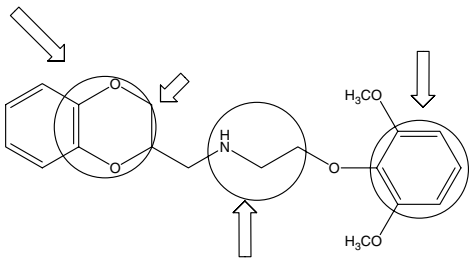
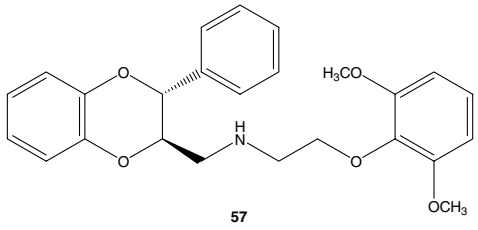


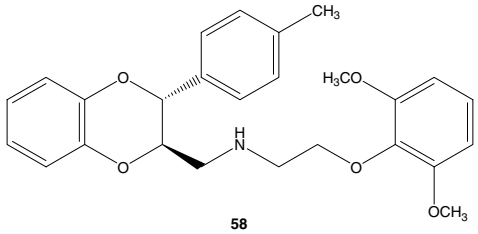
Figure 5. Points of modifications in the 1,4-benzodioxan nucleus.

ever, the insertion of phenyl ring at the position 3 of **55** is highly detrimental toward the α_2-adr activity either in *trans* or *cis* relation with respect to the side chain at position 2. This derivative, namely, phenodioxan was considered as the most potent derivative for the selective α_1-adr subtype in the benzodioxan series.[99]



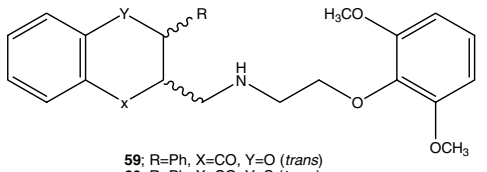
57

Further, replacement of the 3-phenyl group of **57** by methyl, isopropyl, cyclohexyl, or *p*-substitutedphenyl groups either in *cis* or *trans* relationship relative to the side chain at position 2 led to compounds though having better α_1/α_2 selectivity, but except for the derivative bearing the *p*-methylphenyl substitution at position 3, none of them showed selectivity for the α_1-adr subtype. These results imply that the 3-substitution endows a significant role in the modulation of selectivity for α_1-adr subtypes. These findings led to the development of mephendioxan **58**, a *p*-tolyl analogue of phendioxan. This work has demonstrated that the insertion of a *trans* aryl substituent at position 3 of **57** increases the affinity and selectivity for α_{1A}-adr, while significantly decreasing the affinity for α_2-adr, 5-HT_{1A} and D_2, receptors in comparison to the prototype.[100] Furthermore, it has been shown that the affinity and selectivity for α_{1A}-adr resides predominantly in the enantiomer, (−)-mephendioxan [(−)-**58**].[101]

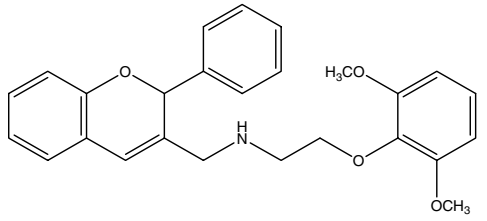


58

By taking as a starting point, prototype **55** (WB-4101), subtle variations at positions 1 and 4 have been made to assess how affinity and selectivity for α_1-adr receptor subtype can be markedly affected by making following changes in the prototype structure **55**: (a) by inserting carbonyl group at 4 as in **59**, (b) by replacing the oxygen atom at position 1 by a carbonyl group and at 4 by a sulfur atom, as in **60** or a methylene group, as in **61**, (c) by replacing the oxygen atom at position 4 by a methylene group affording **62** and **63**, and (d) by replacing the oxymethylene moiety by a vinyl group as in compound **64**. These modifications however, did not improve the biological profile of these molecules with some exception of compound **59**. But all these compounds have same selectivity profile at the α_1-adr. Compound **59** is more selective to α_{1A}-adr subtype than to the α_{1B} and α_{1D}-adr subtypes. Compound **60** and **61** shows significant decrease in affinity for all the three α_1-adr subtypes. The affinity for α_{1A}-adr further dropped in case of compound **64** compared to compounds **59**–**63**, indicating the importance of oxygen or carbonyl at position 1 in these compounds. Compound **64** however, retained high affinity for 5-HT_{1A} receptors.[102]

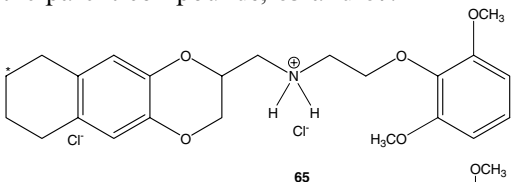


59; R=Ph, X=CO, Y=O (*trans*)
60; R=Ph, X=CO, Y=S (*trans*)
61; R=Ph, X=CO, Y=CH_2 (*trans*)
62; R=Ph, X=O, Y=CH_2 (*cis*)
63; R=Ph, X=O, Y=CH_2 (*trans*)

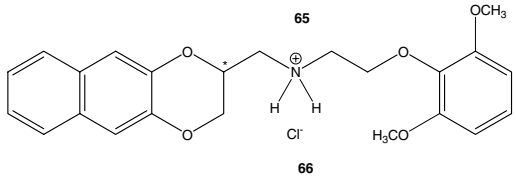


64

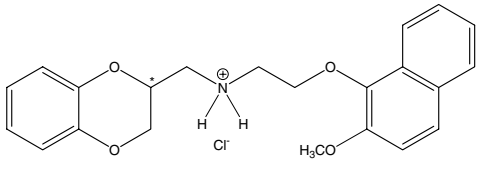
Further modifications in WB 4101, to optimize the activity by fusion of cyclohexane as in **65** or an additional benzene ring as in **66** with benzodioxan or additional benzene ring fused to the phenoxy moiety as in **67**, were tried and evaluated for the possible significant modulations in activity and selectivity.[103] Thus, through a planned short sequence of modifications, consisting of introducing an additional or fused benzene or cyclohexane ring into the benzodioxan or the phenoxy portion of WB 4101 enantiomers and finally hybridizing two of these modifications, led to the identification of a new, potent, highly specific α_{1A}-adr antagonist, (*S*)-**68**, in which a tetrahydronaphthodioxane and a 2-methoxy-1-naphthoxy residue were used. This new α_{1A}-adr antagonist, (*S*)-**68,** hybridizes the high antagonistic affinity of both the parent compounds, **65** and **67**.[104]



65



66



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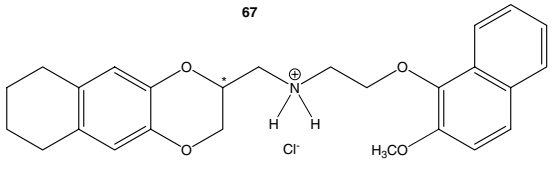
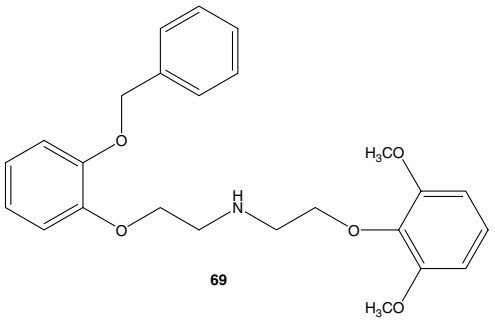


68

4.2.2. Opening of the 1,4-dioxan ring system. Opening the dioxan ring of **55** through the cleavage of C_2 and C_3 bonds gave **69**, which was a very potent ligand at α_1-adr, while retaining the affinity for 5-HT_{1A} receptors (although the affinity for the latter was 22- to 174-fold lower than that for the former one). This structural modification also resulted in an inversion of the selectivity profile, as **69**, was more potent at α_{1D}-adr than at α_{1A} and α_{1B}-adr subtypes.[102] Quaglia et al.[105] studied the antitumor activity of these open chain analogues of **55** due to their selectivity toward α_{1D}-adr. All the compounds of this series showed greater affinity for α_{1D}-adr particularly the 4-chlorophenylmethoxy derivative **70**, which had more significant α_{1D}-selectivity and a higher lipophilic character with respect to doxazosin.



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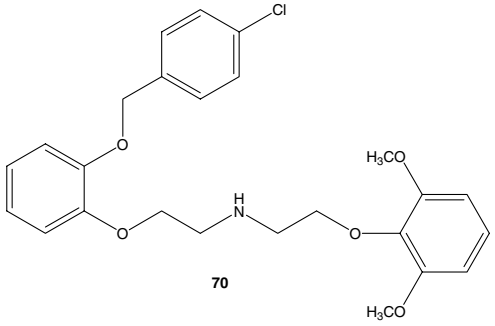
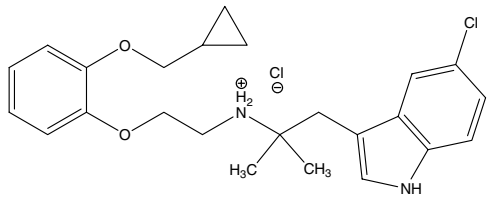


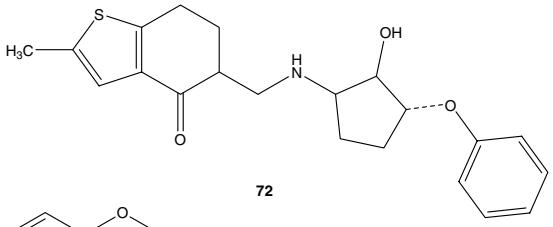
70

Pharmacological properties of a novel, selective α_1-adr antagonist, *N*-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro-α,α-dimethyl-1*H*-indole-3-ethanaminehydrochloride **71** (RS-17053) was studied and it was found to be a potent and selective α_1-adr antagonist. The low affinity of RS-17053 in antagonizing contractions of human lower urinary tract tissues to norepinephrine provides strong evidence against pharmacological identity of this α_1-adr subtype with the cloned and native α_1-adr. In this regard, RS-17053 is not singular, as several other α_1-adr antagonists (prazosin, WB 4101, S-(+)-niguldipine, and SNAP 5089) also distinguish between the two adrenoceptors. It is clear that the three fully defined α_1-adr subtypes do not describe satisfactorily the functional data in the human lower uterine tract, supporting the notion that the α_{1L}-adr exists as a distinct pharmacological entity.[106]



RS-17053 **71**

4.2.3. Modifications in the side chain. A series of WB 4101 **55** related benzodioxans were synthesized by replacing the ethylene chain separating the amine and the phenoxy units of **55** with a cyclopentanol moiety, a feature of 6,7-dihydro-5-[(*cis*-2-hydroxy-*trans*-3-phenoxycyclopentyl)amino]methyl-2- methyl-2-methylbenzo[*b*]thiophen-4-(5*H*)-one, **72**, that was reported to display an intriguing selectivity profile at α_1-adr. Replacement of 6,7-dihydro-2-methylbenzo[*b*]thiophen-4(5*H*)-one unit of **72** with benzodioxan moiety of **57**, led to the potent α_1-adr antagonist, **73**, which displayed a significant affinity toward the α_{1D}-adr. The stereochemistry of cyclopentane unit had a greater influence on the affinity than that of the benzodioxan moiety. Interestingly enough, a 1-*R* configuration conferred higher affinity at α_1-adr, whereas 1-*S* configuration produced higher affinity for 5-HT_{1A} receptors, indicating that the two receptors systems have different stereochemical requirements.[107]



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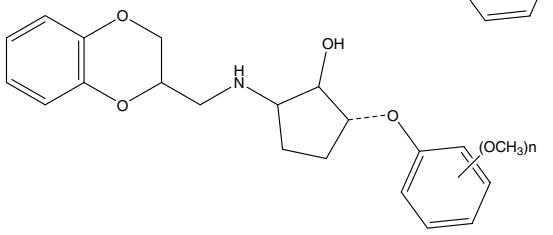
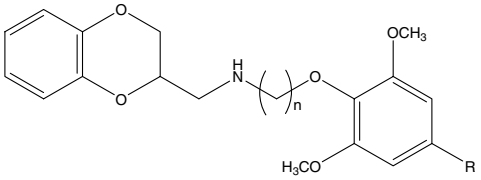


73

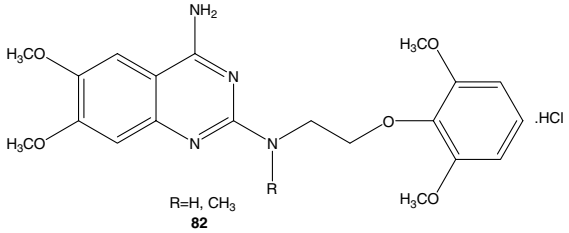
A series of WB 4101 **55** related benzodioxans, **74**–**81,** has been synthesized by replacing the phenoxymethyl moiety of **55,** with an *N*-alkylpiperazine bearing a cyclic substituent (a substituted or unsubstituted phenyl group, a pyridine or pyridazinone ring, or a furoyl moiety) at the second hydrogen atom. The binding profile of these compounds has been assessed by radioligand receptor-binding assays at α_1 and α_2-adr, in comparison to prazosin and rauwolscine, respectively. It was observed that the 4-methoxyphenyl derivatives had lower α_1-adr affinities than **55.** The 2-fluorophenyl derivatives were even lesser active than their methoxy counterparts.[108]



74=R=4-$CH_3OC_6H_4$; n=2
75=R=4-$CH_3OC_6H_4$; n=3
76=R=2-FC_6H_4; n=2
77=R=2-FC_6H_4; n=3
78=R=2-CH_3-4-Cl-pyridazin-3(2*H*)-one-5-yl; n=2
79=R=2-CH_3-4-Cl-pyridazin-3(2*H*)-one-5-yl; n=2 n=3
80=R=2-Furoyl; n=2
81=R=2-Furoyl; n=3

Among various α_1-adr antagonists, both prazosin and WB 4101 have shown good affinity for α_1-adr and have a prominent role in characterization of the receptors. Many structure–activity relationships have been studied. It was therefore thought of interest by some workers to

synthesize and evaluate the combination structures of prazosin and the benzodioxane WB 4101, as the hybrid of their integral structural features, as in **82**–**86**. All the compounds exhibited a marked selectivity toward α_1-adr. Furthermore, their potency at α_1-adr ranged within three orders of magnitude, whereas activity at α_2-adr did not vary dramatically. It is concluded that structural changes markedly affecting the binding at α_1-site do not affect α_2-sites. All these molecules obtained as hybrids of **55** and prazosin are significantly weaker antagonists than the parent compounds. Although, this might indicate that **55** and prazosin bind at unrelated sites, the possibility that they recognize the identical site cannot be excluded since the decreased activity observed for hybrid compounds simply reflect their decrease in affinity for such a site.[109]



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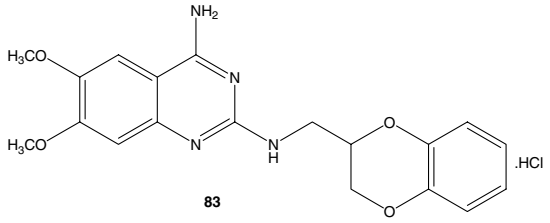

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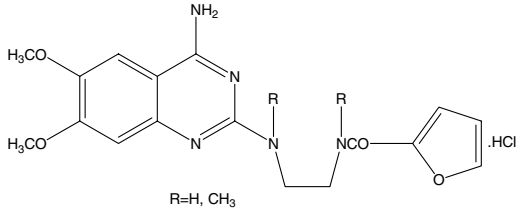

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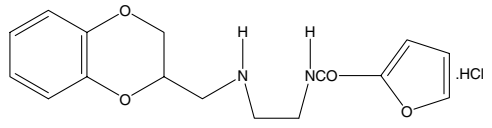

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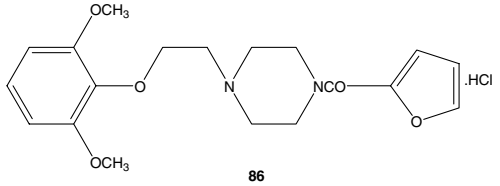
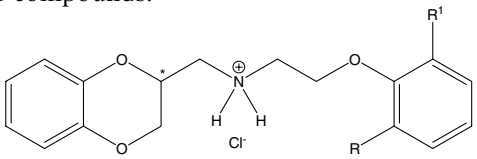


86

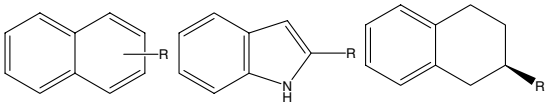
4.2.4. Modifications in the 2,6-dimethoxyphenoxyalkyl ring system. A number of *ortho*-disubstituted analogues of 2-[(2-phenoxyethyl)aminomethyl]-1,4-benzodioxan were designed and synthesized in both the enantiomeric forms and tested in binding assays on the same receptors. The affinity values of the new compounds, **87**, were compared with those of the enantiomers of WB 4101 and of the *ortho*-monosubstituted derivatives, suggesting some distinctive aspects of the interaction of the phenoxy moiety, in particular with the α_{1A}-adr and the 5-HT_{1A} receptors of the monosubstituted and the disubstituted compounds.[110]



R=R^1=F, Cl, *t*-Bu, OCH_3, CH_3, C_2H_5, CH_2CH_2Cl, *i*-Pr etc

87

4.2.5. Replacement of 1,4-benzodioxan ring system with other fused ring systems. To evaluate a possible role of π electrons, the dehydrodioxan ring of **55** was replaced by a phenyl ring as in **88**. Since, the indole system is present in the structure of some α_1-adr antagonists as in Indoramin,[111] the combination of the indole moiety with **55** as in **89** was also studied. Further, the 1,4-benzodioxane ring of **55** was also replaced with tetrahydronaphthalene, as in **90**. Low activity of all these compounds **88**–**90**, indicates that the 1,4-benzodioxane ring system is an integral pharmacophore for the activity, and rings like naphthalene, indole, tetrahydronaphthalene may have unfit planarity with the α_1-adrs.[112]



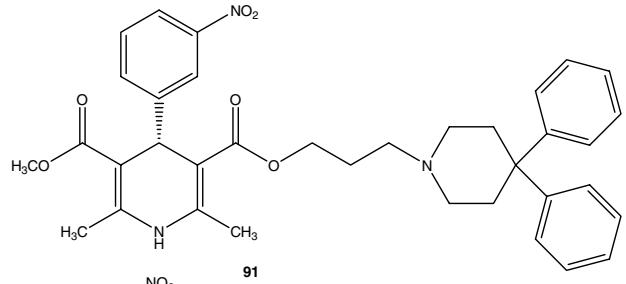
R=$CH_2NH(CH_2)_2O$-2,6-$(CH_3O)_2C_6H_3$

88 **89** **90**

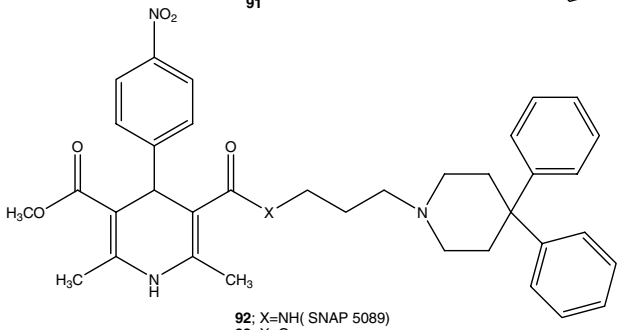
4.3. Dihydropyridines and dihydropyrimidines

4.3.1. Derivatives from dihydropyridine nucleus. In contrast to the prazosin analogues, the 1,4-dihydropyridine, (*S*)-(+)-niguldipine **91** exhibits 340- to 630-fold selectivity in binding to the cloned human α_{1A}-adr relative to the α_{1B}-adr and α_{1D}-adrs.[113] (*R*)-(−)-Niguldipine was 29-fold less potent at the α_{1A}-adr than its enantiomer and also less subtype selective. The main agent appearing within the dihydropyridine class of compounds is SNAP 5089 **92**, which is closely related to niguldipine a known Ca^{2+} channel blocker. Some of these compounds have been used to treat BPH and found to cause undesired side effects, such as dizziness and asthenia. These side effects may be due to cross-reaction of these compounds at α_{1B} and α_{1D}-adrs. Analogues of **91** were synthesized with the aim of achieving greater selectivity and affinity for the human α_{1A}-adr and reducing Ca^{2+} channel affinity. The affinity of 4-(nitrophenyl)-1,4-dihydropyridines for the L-type Ca^{2+} channel is known to depend on the position of the nitro group. 4-Nitrosubstitution is detrimental for the Ca^{2+} channel blocking activity as compared to 3-nitro and 2-nitro substitutions. Compound **93** (X = O) exhibited a 54-fold reduction in potency relative to **91** as an antagonist of the L-type Ca^{2+} channel. Notably, **92** maintained high affinity and subtype selectivity of 630-, 1500-, and 1500-fold in

binding to the α_{1A}-adr relative to the α_{1A}, α_{1B}-adrs, and the L-type Ca^{2+} channel, respectively. This compound was also >1000-fold selective in binding to the human α_{1A}-adr relative to the cloned human α_{2A}, α_{2B}, and α_{2C}-adrs. The enantiomers of **92** were separated by HPLC on a chiral column. The (−)-enantiomer proved to be more active at the α_{1A}-adr, but less active at the L-type Ca^{2+} channel than the (+)-enantiomer.[114]

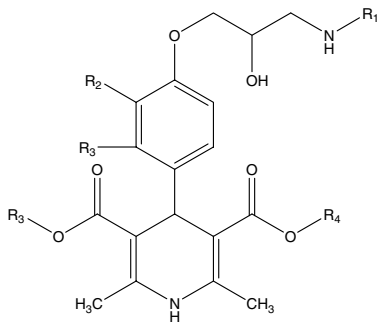


91



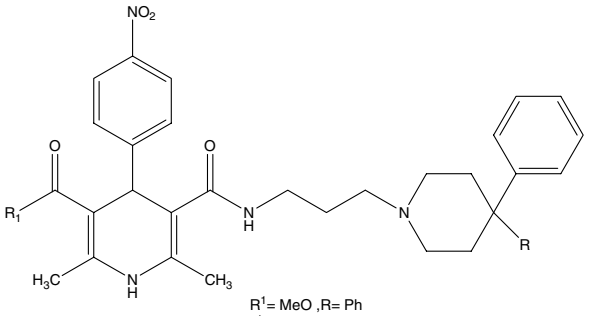
92; X=NH(SNAP 5089)
93; X=O

A new series of dihydropyridine derivatives, bearing oxypropanolamine moiety on phenyl ring at the 4-position of the dihydropyridine base, was prepared. These compounds were evaluated for inotropic, chronotropic, and aorta contractility that are associated with Ca^{2+} channel and adrenergic antagonist activities. Derivatives with oxypropanolamine side chain on their 4-phenyl ring associated α/β-adr blocking activities created a new family of calcium entry and the third generation β-adr blockers. It was concluded that compounds **94**–**96** showed not only markedly high calcium-antagonistic activity, but also the highest antihypertensive effect. Compound **95** was selected for further pharmacological and pre-clinical evaluation studies.[115]



94=R_1=*t*-butyl, R_2=OCH_3, R_3=H, R_4=CH_3
95=R_1=guaiacoxyethyl, R_2=OCH_3, R_3=H, R_4=CH_3
96=R_1=guaiacoxyethyl, R_2=H, R_3=Cl, R_4=C_2H_5

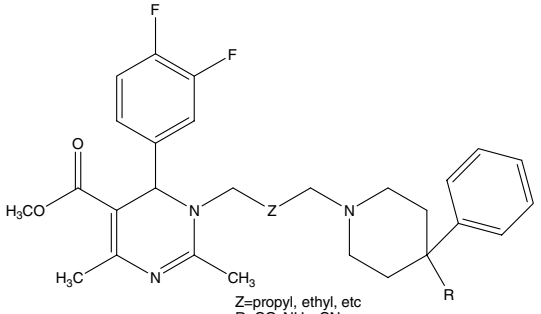
Some other dihydropyridinyldicarboxylate amides and esters, **97** as α-adr blockers have been reported, but they showed poor oral bioavailability in rats (5%).[116]



R^1= MeO ,R= Ph
R^1=NH_2, R=CO_2CH_3

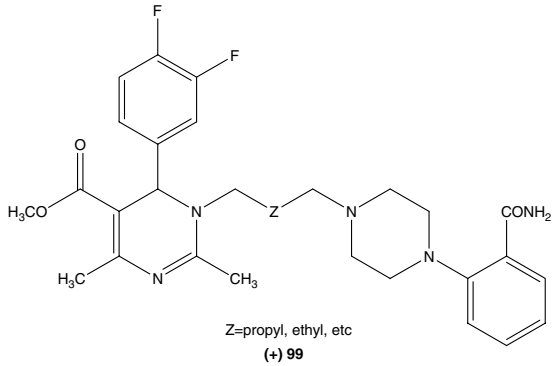
97

4.3.2. Derivatives from dihydropyrimidine nucleus. In an effort to optimize the pharmacokinetic parameters by replacing the dihydropyridine moiety with a dihydropyrimidine template, a number of dihydropyrimidines **98** and **99** showed good binding affinity (>300-fold) and selectivity for α_{1A}-adr over α_{1B}, α_{1D}, and α_2-adrs. Most of the compounds displayed negligible affinity for rat L-type Ca^{2+} channel. A number of modifications on the dihydropyrimidine template, linker chain, and piperidine or piperazine side chains are well tolerated. Although, all these modifications yielded compounds with good binding affinity and selectivity for α_{1A} receptors, their pharmacokinetic profile was found to be poor with low bioavailability and short plasma half-lifes.[117]



Z=propyl, ethyl, etc
R=CO_2NH_2, CN

(+) 98

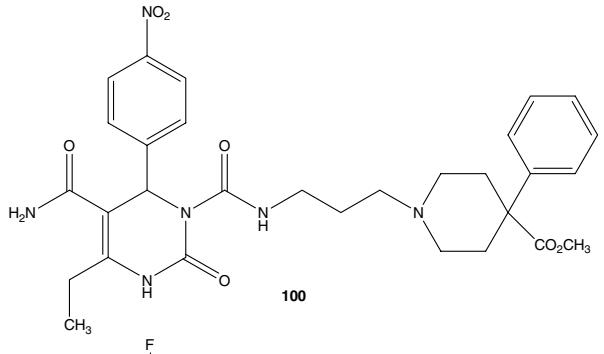


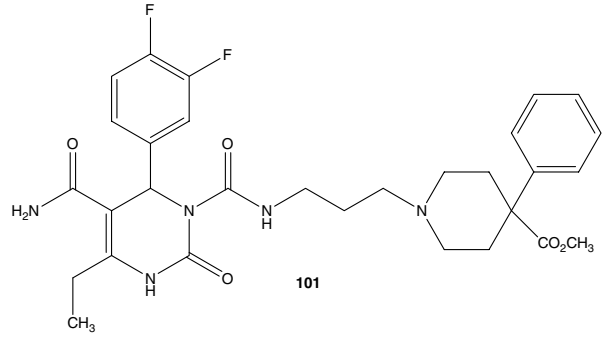
Z=propyl, ethyl, etc

(+) 99

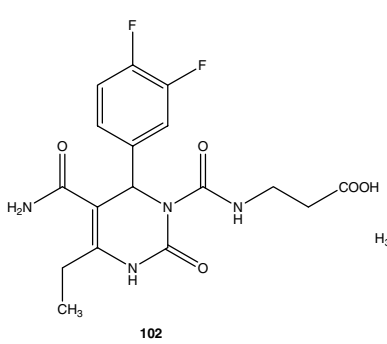
4.3.3. Derivatives from dihydropyrimidinones. It is possible that the poor pharmacokinetic profile of **97** may be due to a rapid conversion of the dihydropyridine moiety into pyridine moiety by oxidative metabolism. Thus, it

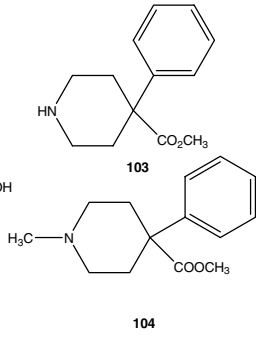
was suggested that a dihydropyrimidinone in place of dihydropyrimidine nucleus would not undergo such oxidative metabolism and therefore, might exhibit a better pharmacokinetic profile. Thus, new compounds **100** and **101** were synthesized. These compounds showed good binding affinity and subtype selectivity for α_{1A}-adr. On the basis of the lack of cardiovascular effects and the superior pharmacodynamic profiles of these α_{1A}-selective compounds in the animal models, it was proposed that they could offer a significant improvement over the current treatments of BPH.[118]



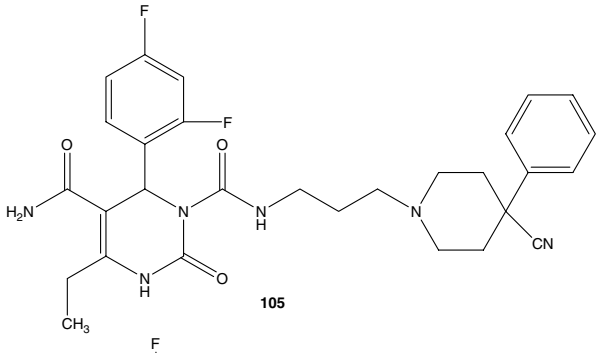


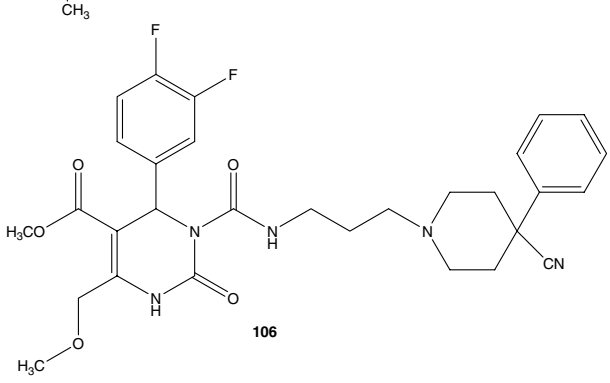
Study of the metabolites of compound **101** revealed **102** and **103** as two major metabolites. Compound **102** was found to be devoid of α_{1A}-antagonistic activity and showed negligible cross-reactivity at several other G-protein coupled receptors and the L-type Ca^{2+} channel.



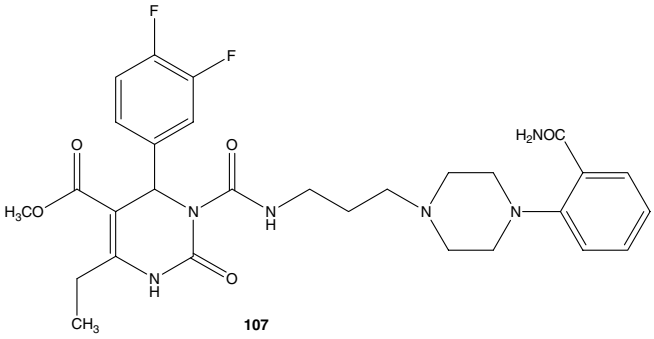


Metabolite **103**, however, was found to be a μ-opioid agonist and is a close analogue of the μ-opioid agonist meperidine **104**.[119] Since this may lead to opioid liabilities on chronic administration of **101**, modifications were sought. Thus, by modifying the linker to minimize the formation of 4-methoxycarbonyl-4-phenylpiperidine and replacement of the piperidine portion of **101** with other piperidines that do not have the μ-opioid agonist activity were thought. Various approaches to modify the linker chain resulted in several compounds with good α_{1A}-binding affinity and selectivity, but they did not significantly affect the *N*-dealkylation and the formation of **102**. However, compounds (+) **105** and (+) **106** showed excellent selectivity over α_{1B} and α_{1D}-adrs along with good selectivity over several recombinant human G-protein coupled receptors.[120]



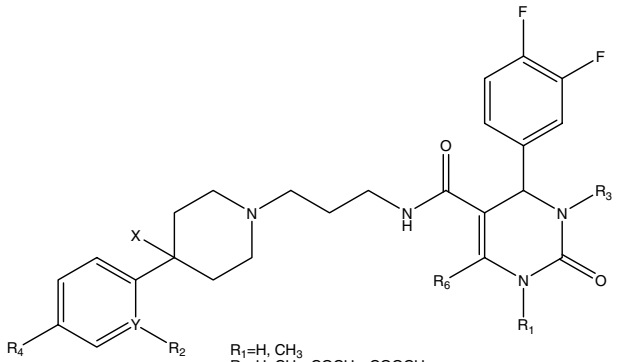


Working on similar goals, new derivatives of dihydropyrimidinones containing substituted 4-phenylpiperazines were synthesized. Judicious alterations based on the steric and electronic nature of the substituents on the phenyl ring of the 4-phenylpiperazines led to the identification of 2-carboxamidophenylpiperazine moiety as a preferred side chain subunit having much weaker binding affinity at the opioid receptors. Compound (+)-**107** was identified as a lead compound with a binding and functional profile comparable to the standard.[121]



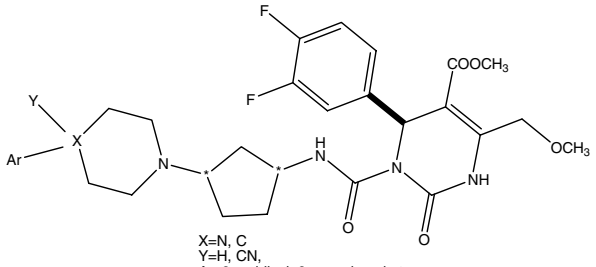
The α_{1A}-adr antagonistic activity of a series of dihydropyrimidinones C_5 amides **180** is analyzed through Fujita-Ban and Hansch approach. The role of different substituents on the activity of these analogues is explored and SAR developed. Both approaches predict

that more hydrophobic X-substituents and the phenyl or 2-cyanophenyl substituents at the 4-position of the piperidine ring are beneficial in raising the α_{1A}-adr antagonistic activity of the compounds. Similarly, the presence of fluorine at R_4 further helped in increasing the activity. Hydrogen and methyl substituents at R_1 and R_3 are more favorable for the activity. Similarly, hydrogen or methyl ester substituents at R_6 position enhanced the activity.[122]



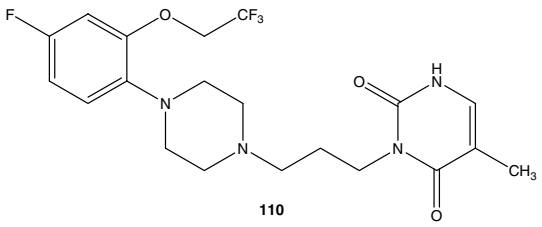
108

Replacement of the linker chain with more constrained 1,3-substituted cyclopentanes was done. This thinking was mainly influenced by the fact that, constraining a flexible section of an enzyme inhibitor or receptor antagonist, often results in enhanced binding affinity due to reduced entropic penalties on binding, when the constraint mimics the bioactive conformation. It was found that the potency of compounds **109** was similar to that of the open chain analogues. Also the receptor can tolerate various stereochemical orientations, as many different conformations were found to be active. The best configuration for the overall potency and α_{1A}-adr subtype selectively is (*R*, *R*) stereochemistry in these compounds.[123]

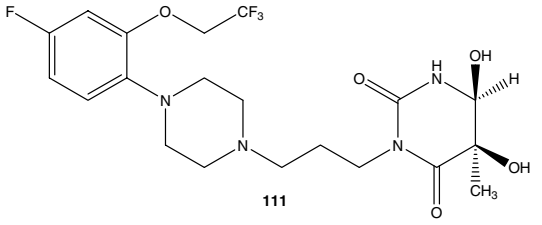


109

Some more replacements for the arylpiperazinyl group have also been worked out, affording compounds with better affinity and selectivity profile for α_{1A}-adr subtype. A series of 3-(4-arylpiperazin-1-ylalkyl)uracil antagonists was prepared and tested for *in vitro* affinity. Two compounds **110** and **111** are found to possess high uroselectivity.[124]



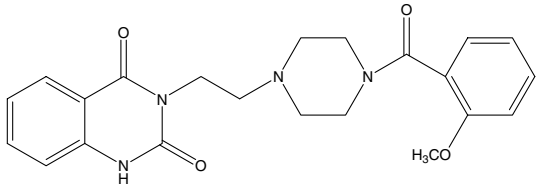
110



111

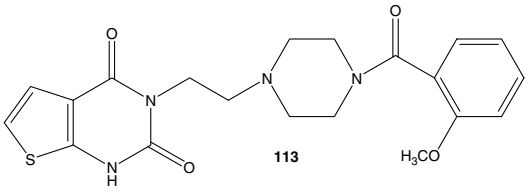
4.4. Fused pyrimidindiones

The prototype of this type of compounds expressed by the general structure, Figure 6, has been the quinazoline-2,4-dione derivative, SGB 1534 **112** which has exhibited potent α_1-adr activity.[125] The above structure has been based on the reports on the various analogues of **112,** synthesized and evaluated by number of workers till date. Various points of modifications in this general structure are shown in Figure 6.



SGB 1534 **112**

The quinazoline-2,4-dione part has been replaced with a variety of heterocycles like thienopyrimidine-2,4-diones as in **113**, which has exhibited effective α_1-adr blocking properties.[126]



113

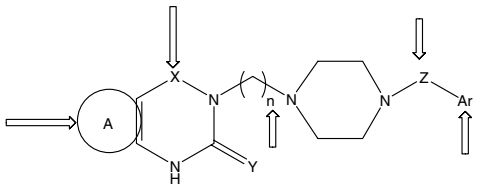
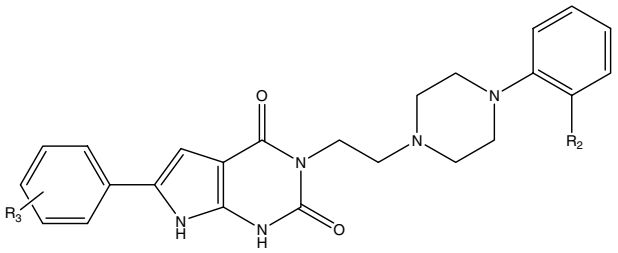


Figure 6. Points of modifications in pyrimidindiones.

A new series of selective and high-affinity α_1-adr ligands, characterized by a 1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione system, was synthesized. Compounds, **114–116,** displayed affinity in the nanomolar range for α_1-adr. These compounds showed their ability to address properly α_1-adr selectivity, over 5-HT_{1A}, D_1, and D_2 dopaminergic receptors. In particular, compound **116**, endowed with affinity in the nanomolar range for the α_1-adr, showed the best profile in terms of selectivity toward other tested receptors and in functional assays, a preference for the α_{1D} with respect to α_{1A} and α_{1B}-adr of one order of magnitude.[127]

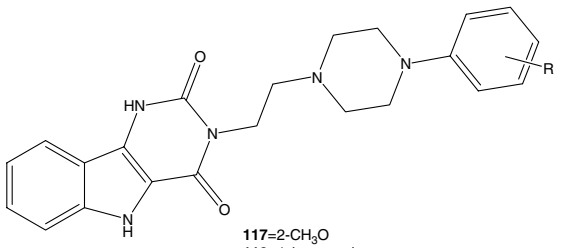


114=R_3=2-CH_3, R_2=Cl
115=R_3=2-OCH_3, R_2=Cl
116=R_3=4-Cl, R_2=Cl

On similar lines a tricyclic 3-substitutedpyrimido[5,4-*b*]-indole-2,4-dione system has also been coupled by the means of an alkyl chain to the phenyl piperazine moiety to develop selective α_1-adr ligands. In this series, compound **117** has emerged as the most interesting candidate showing high affinity and selectivity for α_1-adr on rat cortical membranes over α_2-adr, β_2-adr, and 5-HT_{1A} receptors.

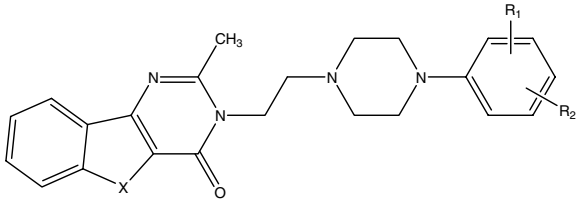
The most interesting feature of these molecules which seemed necessary for the receptor binding was the presence of a phenyl ring on *N*-4 atom of the piperazine moiety of the side chain. In all the above compounds, **112–119**, presence of a *o*-methoxy substitution on the phenyl or benzoyl moiety attached to the 4th position of the piperazine increased the affinity to the α_1-adr, 10 folds. On the other hand, *p*-substitution at these positions drastically reduced the activity.[128]

In the compounds of the series of the pyrimido[5,4-*b*]indole derivatives **117**, the compounds **118** and **119**, bearing 4-*iso*-propyl and 4-*tert*-butyl substituents, respectively, when tested in the binding assays on the three human cloned α_1-adr (α_{1A}, α_{1B}, and α_{1D}) subtypes, exhibited very good α_{1D}-adr selectivity.[129]



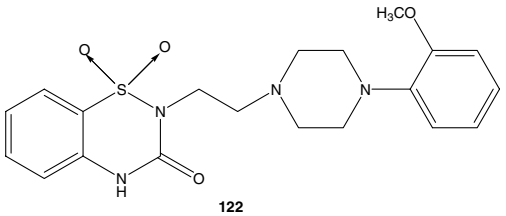
117=2-CH_3O
118=4-*iso*-propyl
119=4-*tert*-butyl

A number of new pyrimido[5,4-*b*]indole and benzothieno[3,2-*d*]pyrimidine derivatives were synthesized and evaluated for their binding and functional properties at α_1-adr receptor subtypes. In binding assays on human cloned receptors, some new compounds such as **120** and **121** showed very high affinity and a slight preference for the α_{1D}-adr subtype. In addition, functional tests in isolated rat tissues evidenced that new compounds act as potent α_1-adr antagonists.[130]



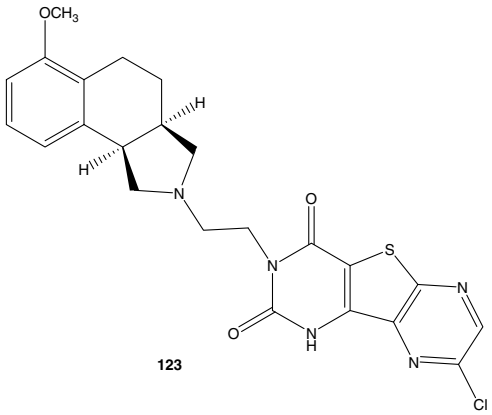
120=X=NH; R_1 =2-CH_3O; R_2= 5-Cl
121=X=S; R_1 =2-CH_3O; R_2= H

Replacement of the aminocarbonyl (C=O) at position 4 of SGB 1534 **112** with a sulfonyl group (SO_2) resulted in 2-[[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide **122.** The compound exhibited very potent antihypertensive activity.[131]



122

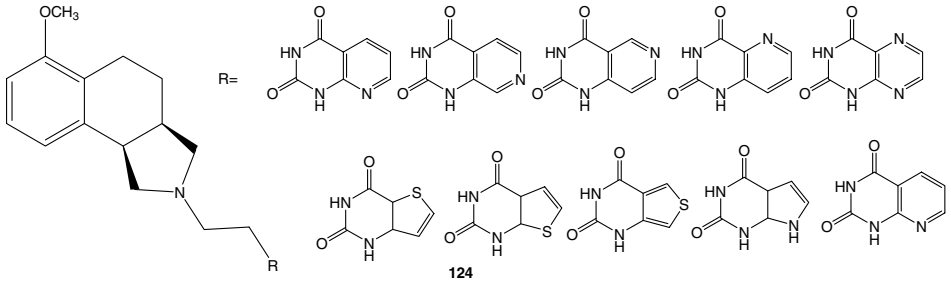
There are also some reports on the examples in which modifications are affected by replacing the aryl piperazinyl moiety of the general structure of Figure 6 with heterocyclic ring systems, especially the tricyclic substituted-hexahydro[*e*]isoindole nucleus. Compound **123** is a good example of such series that has led to potential selective α_1-adr antagonists that could be useful for the symptomatic treatment of benign prostatic hyperplasia (BHP).[53,132]



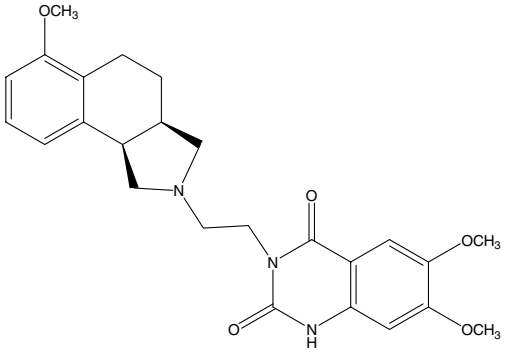
123

Further, modifications in this series involving replacement of tricyclic pyrazinothienopyrimidine-2,4-dione part with various azaquinazoline-2,4-diones, diazaquinazolin-2,4-diones, pyrrolopyrimidine-2,4-diones, and

various thienopyrimidine-2,4-diones gave a diverse series of compounds **124.** The dimethoxyquinazolin-2,4-dione has also been used to replace the tricyclic pyrazinothienopyrimidine-2,4-dione part as in **125**. Compound **125** was found to be the most potent, with highest degree of selectivity in the radioligand-binding assays (57-fold). The overall conclusion from the various modifications discussed above as compounds **123**–**125** is that, the selectivity is only manifested with the quinazolinediones of which the 6,7-dimethoxyquinazolinediones are the best.[133]

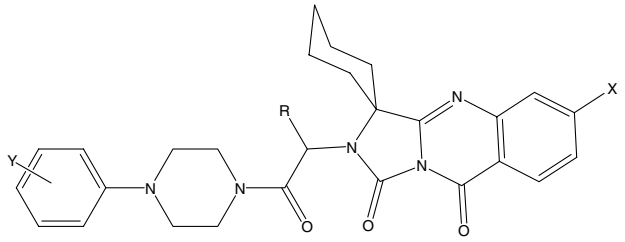


124



125

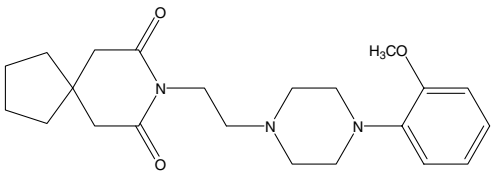
In an interesting study, which is based upon the molecular modeling simulations of the fitting values and conformational energy values of the best-fitted conformers to both α_1-adr agonist and α_1-adr antagonist hypotheses, a series of new imidazo[5,1-*b*]quinazoline derivatives **126** was synthesized. For the best α_1-adr antagonist activity the phenyl ring attached to the piperazine ring must be unsubstituted. Substitutions like *o*-methoxy or *p*-fluoro at this phenyl ring increased the agonistic activity for α_1-adr. Branching of the linker carbonyl group was also found to be detrimental for the α_1-adr affinity.[134]



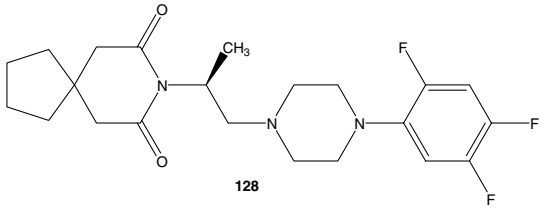
Y=H, 2 or 4-F, 2-OCH_3
R=H, CH_3
X=H, Cl

126

In a somewhat related type of compounds, very interesting novel derivatives of types **127** and **128** have been prepared in which, though the arylpiperazinylethylamino moiety is kept intact, the fused pyrimidine-2,4-dione moiety has been replaced with azaspirodecanediones and azaspiroundecanediones. The compounds act as selective α_{1D}-adr antagonists with high affinity. However, their affinity toward serotonin 5-HT_{1A} and dopamine D_2 and D_3 receptors is found to be slightly decreased. In the above compounds, compound **128** bearing a trifluoro substitution on the phenyl ring had high affinity for α_{1D}-adr, but reduced affinity for 5-HT_{1A} and D_2 receptors. Further, in this compound, the placement of β-methyl group on the linker decreases the binding affinity.[135–139]



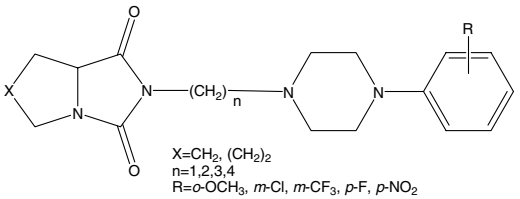
127



128

On similar lines, like the azaspirodecandiones, bicyclohydantoin moiety has also been tried and a series of compounds **129** with affinity for 5-HT_{1A} and α_1-adr receptors was synthesized and subjected to the

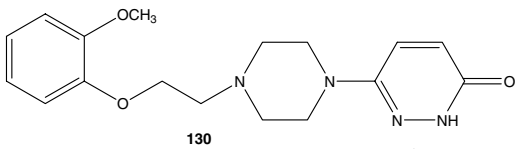
3D QSAR study to get the insight into the structural requirements that are responsible for 5-HT_{1A} and α_1-adr selectivity. It was concluded that the hydantoin moiety and the side chain length modulate not only the affinity, but also the selectivity for the receptors.[140]



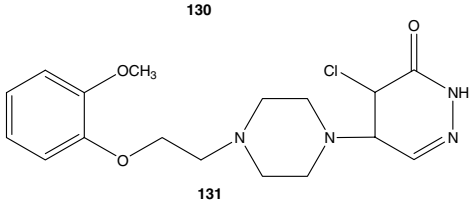
129

4.5. Pyridazinone derivatives

The literature search reveals pyridazinones as a class of compounds with a potential for selective α_1-adr antagonist activity. The pyridazinone derivatives **130** and **131** have been reported as biologically active antihypertensives.[141,142]

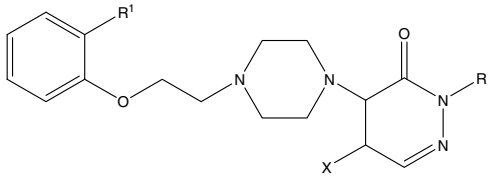


130



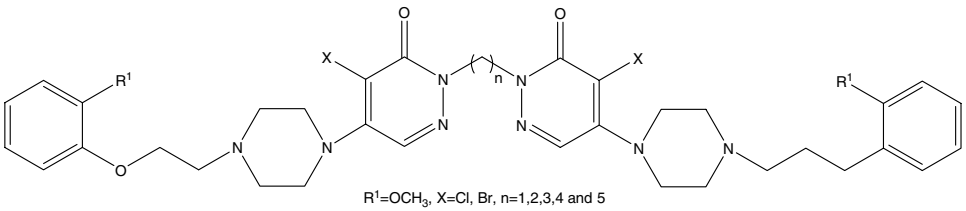
131

Further, derivatives of the 3(2*H*)-pyridazinone nucleus have been synthesized showing a planar aromatic region and a chain with basic nitrogen.[143] Through further modifications on these moieties, the compounds, 4-[4-(phenoxyethyl)-1-piperazinyl-3(2*H*)-pyridazinones **132** and alkane-bridge dimers of 4-, 5- and 6-[4-(phenoxyethyl)-1-piperazinyl]-3(2*H*)-pyridazinones **133** were synthesized. While, they all exhibited good affinity toward α_1-adr, few of them were found to have good selectivity. The dimers **134** and **135** are particularly interesting as there though slightly low in activity than the starting monomers, show high selectivity ratio for the receptors ($\alpha_1/\alpha_2 > 100$), respectively.[144]



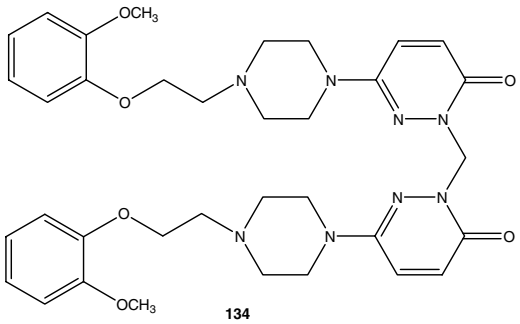
R^1=OCH_3, H, R=H, CH_3, X=Cl, Br

132

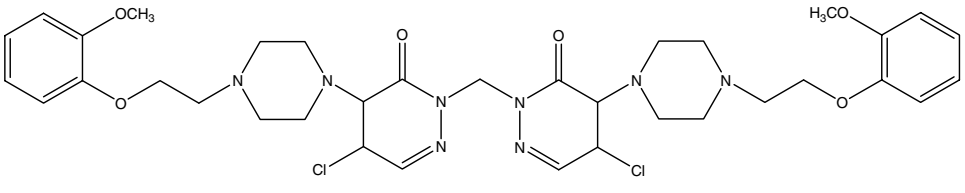


R^1=OCH_3, X=Cl, Br, n=1,2,3,4 and 5

133

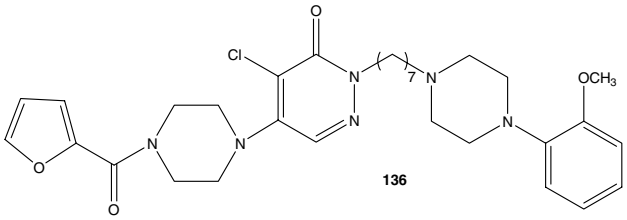


134



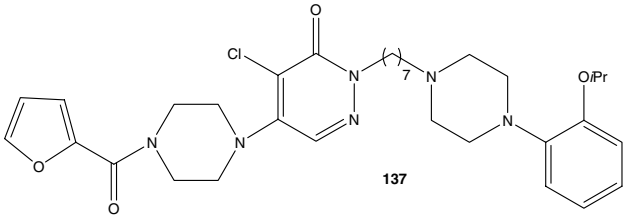
135

Barbaro et al.,[145] in order to increase the selectivity of these compounds, developed a three dimensional model of the pharmacophoric features responsible for the α_1-adr antagonistic activity. They demonstrated some very important features for the affinity and selectivity for the α_1-adr with respect to α_2-adr. They showed that the methoxy group at the *o*- position of the phenylpiperazine moiety led to the best α_1-affinity and selectivity profile. Also the polymethylene chain linking the arylpiperazine moiety to the pyridazinone ring is a critical structural feature in determining the affinity and selectivity profile of the compounds. In fact, the alkyl moiety serves as a spacer to bring both the pyridazinone and the arylpiperazine moiety to the optimal distance to interact with a hydrogen bond donor and a hydrophobic pocket of the putative receptor, respectively. The gradual increase in affinity was obtained by lengthening the chain from two to seven-carbon atoms. On this basis, a new series of pyridazin-3(2*H*)-one derivatives was evaluated for its in vitro affinity toward both α_1 and α_2-adr. Compound **136** showed a very high selective affinity for α_1-adr, which was 274 times more than that for α_2-adr.



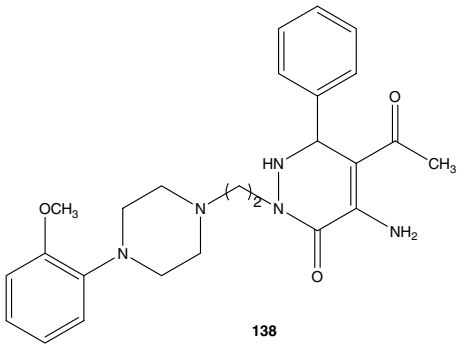
136

The effect of a methoxy substitution at the *o*-position was studied and it was found that the bulkier alkoxy substitution at this position increased the affinity by 4- to 5-folds. The optimum activity was obtained in compound **137** bearing an *iso*-propoxy substitution.[146]



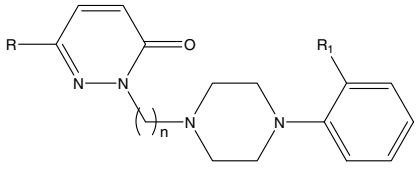
137

4,5-Disubstituted-6-phenylpyridazinones, having an arylpiperazinylalkyl side chain at position 2, carrying an ethylenic spacer between the protonated arylpiperazine and the pyridazinone **138** showed slight α_{1D}/α_{1A}, high α_{1D}/α_{1B}, and very high α_{1A}/5-HT_{1A} and α_{1D}/5-HT_{1A} selectivities.[147]



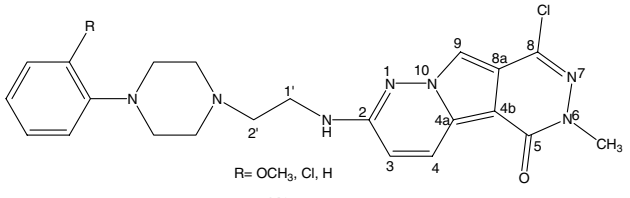
138

Using a rational design approach, a series of novel N_1-aryl-N_2-alkyl (pyridazinonyl)piperazines, bearing a benzimidazolyl or imidazolyl substituent on the pyridazinone moiety, have been synthesized and evaluated for α_1-adr affinity and blocking activities A 1.1 nM affinity toward α_1-adr was found for compound **139**, the most active of this series.[148]



139= R=1-benzimidazolyl or imidazolyl; R_1=OCH_3

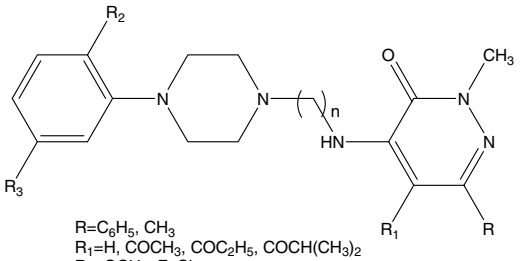
The importance of the substituents on the pyridazinone ring was further studied by synthesizing a series of derivatives having arylpiperazinylalkyl chain at different positions of the ring. A novel series of 8-chloro-substitutedarylpiperazinylethylamino-6-methylpyrrolo[1,2-*b*:3,4-*d*']dipyridazin-5(6*H*)-ones, **140**, was synthesized and evaluated. Most of the synthesized compounds showed high potency on all the assays and some selectivity for α_{1A} and α_{1D}-adr subtypes.[149]



140

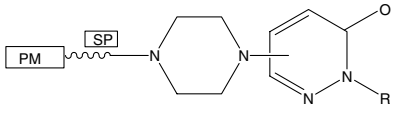
Same workers have employed new QSAR models for designing a series of compounds **141** characterized by *N*-phenylpiperazinylalkylamino moiety linked to the substituted pyridazinones. The newly synthesized compounds were evaluated for the binding affinities toward the α_{1A}, α_{1B}, and α_{1D}-adr cloned subtypes as well as the

5-HT_{1A} receptors. This study indicated that substitutions in the positions 5 and/or 6 of the pyridazinone ring as well as in the positions 2′ and 5′ of the phenyl ring together with the length of the linker are responsible for modulating the ligand α_1-adr-binding affinities and α_{1A}-adr/5-HT_{1A} selectivities.[150]

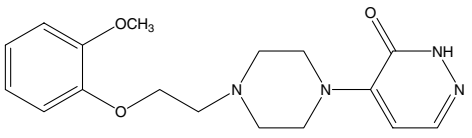


141

A novel series of piperazine derivatives of general structure **142** has been prepared. These compounds were evaluated for their α_1-adr activity. In this class of compounds, the *N*-1 piperazine nitrogen has been directly linked to the 4-, 5-, or 6-positions of the pyridazinone ring and the *N*-4 nitrogen, by a suitable spacer (SP), to various α_1-adr pharmacophore moieties (PM) such as 1,4-benzodioxanyl, 2-methoxyphenyl, or phenoxyethyl groups. Comparative molecular field analysis of these pyridazinone containing derivatives has been studied. To validate the predicted capability of the partial least squares (PLS) model, compound **143** was evaluated for biological activity whose the lowest energy conformer had a predicted pK_b of 6.56, which has slightly higher than the observed pK_b of 6.18.[151]

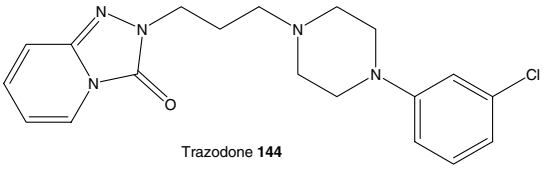


142

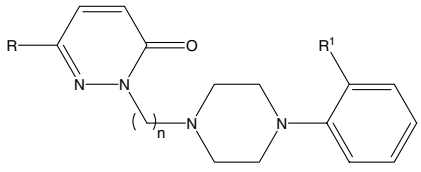


143

In order to increase the affinity and selectivity for α_1-adr and its subtypes, new series of compounds containing benzimidazolylpyridazinone, an indolylpyridazinone, or imidazolylpyridazinone moieties were prepared by modifying the structure of trazodone **144**. The SAR studies of these compounds, suggested that the presence of a methoxy group at the *o*-position of the phenylpiperazine moiety led to the best α_1-adr affinity and selectivity profile. Lengthening of the spacer chain to three- or four-carbon atoms afforded compounds with an increased affinity toward α_1- and α_2-adrs. Further, elongation of the spacer to five- and six-carbon atoms led to slight decrease in the activity. These experimental results suggested that the long alkyl spacer, mainly based on its conformational flexibility, could assume a size and shape that influences the affinity (and selectivity) of compounds to α_1 and α_2-adrs. SAR considerations also led to the hypothesis that a heterocyclic terminal fragment bigger than an aromatic five-membered ring is required for best activity. In fact, compounds bearing a benzimidazole or an indole group are all characterized by higher affinity with respect to the corresponding imidazole derivatives, suggesting that the size of the terminal heterocyclic ring is able to affect the biological properties of such compounds. The number of nitrogen atoms on the heterocyclic ring is an additional element leading to a variation in affinity with indole derivatives. Compounds **145**–**147** were found to be the most active in this study.[152]



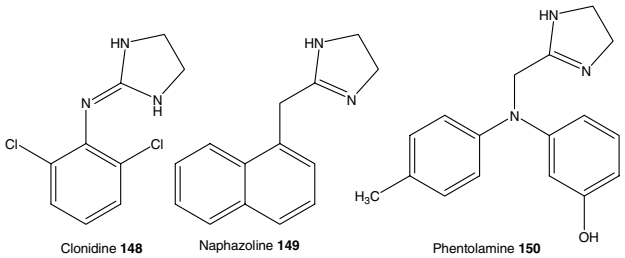
Trazodone **144**

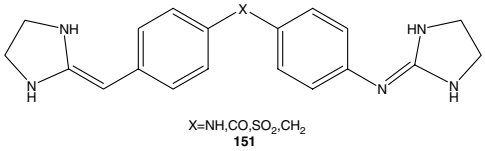


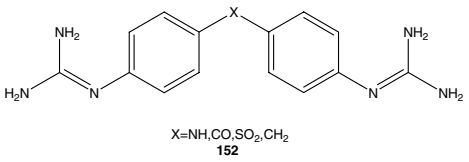
145=R=1-benzimidazolyl, n=4, R^1=OCH_3
146=R=1-imidazolyl, n=7, R^1=Cl
147=R=1-indolyl, n=4, R^1=OCH_3

4.6. Imidazolines and fused imidazolines

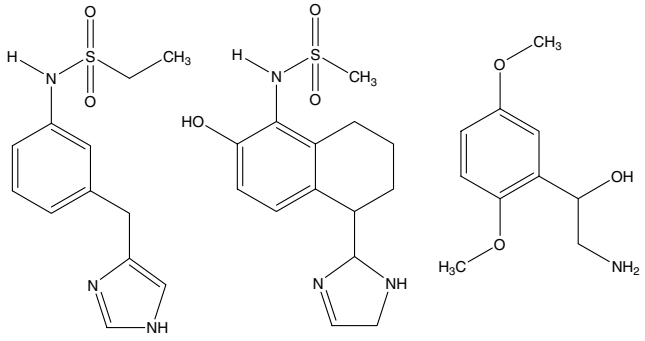
4.6.1. Imidazoline derivatives. Since a long time imidazoline derivatives have been considered as one of the major class of drugs interacting with α-adr receptors. Compounds like clonidine **148** and naphazoline **149**, which contain a 2-iminoimidazoline or an imidazoline ring, respectively, show α_1- and α_2-adr antagonist activities.[153] Furthermore, specifically phentolamine **150**, which contains an imidazoline ring, is a well known α_1-adr antagonist.[154] It has been shown that the 2-aminoimidazoline resembles guanidine, not only in its geometrical parameters, but also at the electronic levels and both can be considered as excellent isosteres of each other. In other words, 2-aminoimidazoline can be considered as the masked or restricted guanidine.[155] Based on these facts a series of derivatives containing the guanidine or the 2-aminoimidazoline groups were synthesized. The bis-imidazolinenaminophenyl **151** and bis-guanidinediphenyl **152** derivatives when synthesized and evaluated showed slight antagonistic activity for α_1-adr.[156]

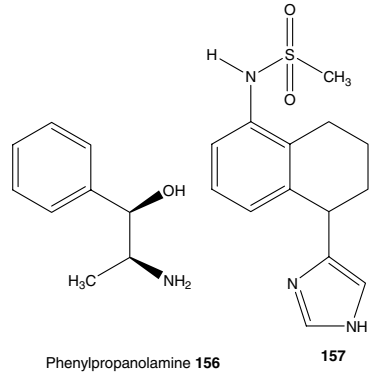






A report describes *N*-[3-(1*H*-imidazol-4-ylmethyl)-phenyl]ethanesulfonamide (ABT-866, **153**) as a novel α_1-adr agent having the unique profile of α_{1A}-adr (rabbit urethra, $EC_{50} = 0.60\ \mu M$) agonism with α_{1A} (rat spleen, $pA_2 = 5.4$) and α_{1D} (rat aorta, $pA_2 = 6.2$) antagonism. An in vivo dog model showed **153** to be more selective for the urethra over the vasculature than A-61603 **154**, ST-1059 **155** (the active metabolite of midodrine), and phenylpropanolamine **156**.[157]

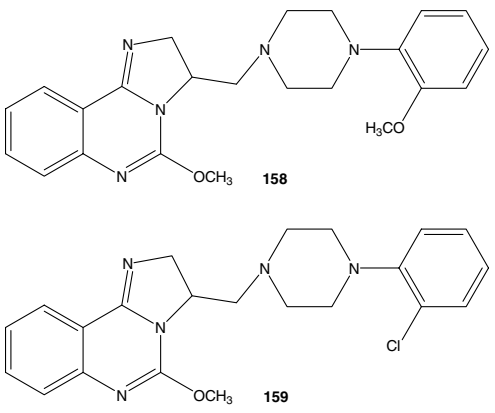




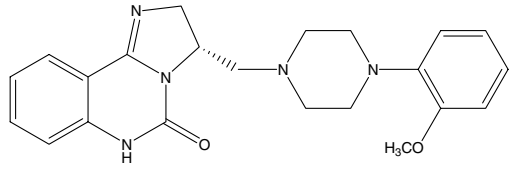
Further, compared to phenylephrine, ABT-866 also demonstrates intrinsic activity at the α_{1A}-adr subtype present in the rabbit urethra ($pD_2 = 6.22$, with 80% of the phenylephrine response), reduced intrinsic activity at the α_{1B}-adr subtype in the rat spleen ($pD_2 = 6.16$, with 11% of the phenylephrine response) and no intrinsic activity at the rat aorta α_1-adr subtype. ABT-866 also demonstrated antagonism at the rat spleen α_{1B}-adr. ($pA_2 = 5.39 \pm 0.08$, slope $= 1.20 \pm 0.12$) and the rat aorta α_{1D}-adr ($pA_2 = 6.18 \pm 0.09$, slope $= 0.96 \pm 0.13$).[158]

The same group has performed the structure–activity studies on the α_{1A}-adr selective agonist *N*-[5-(1*H*-imidazol-4-yl)-5,6,7,8-tetrahydro-1-naphthalenyl]methane sulfonamide **157** and its analogues. The compounds were evaluated for binding activity at the α_{1A}, α_{1B}, α_{1D}, α_{2A}, and α_{2B}-adr subtypes. Functional activities in tissues containing the α_{1A} (rabbit urethra), α_{1B} (rat spleen), α_{1D}, (rat aorta), and α_{2A} (rat prostatic *vas deferens*) were also evaluated. A dog *in vivo* model simultaneously measuring intraurethral pressure (IUP) and mean arterial pressure (MAP) was used to assess the uroselectivity of the compounds. Many of the compounds that were highly selective in vitro for the α_{1A}-adr subtype, were also more uroselective in vivo for increasing IUP over MAP. Correlation of the α-adr-binding affinities (pKi) as well as functional agonist (D_2) with MAP and IUP was generated. Of these, the best correlations were observed for functional α_{1A}-adr activity (constriction of rabbit urethra) versus MAP ((r^2) 0.70) and IUP ((r^2) 0.82).[159]

4.6.2. Fused imidazolines. The conformationally restricted analogues of SGB 1534 **112** have been synthesized to check their selectivity for α_{1A}-adr. The most important structural feature of these molecules that seems to be necessary is the presence of *o*-substitution on the phenyl ring at the *N*-4 position of the piperazine moiety of the side chain attached to the 2- or 3-positions of the 2,3-dihydroimidazo[1,2-*c*]quinazoline ring system. Compounds **158** and **159** are the most potent compounds of this series and show better affinity than those of prazosin and SGB 1534.[160]



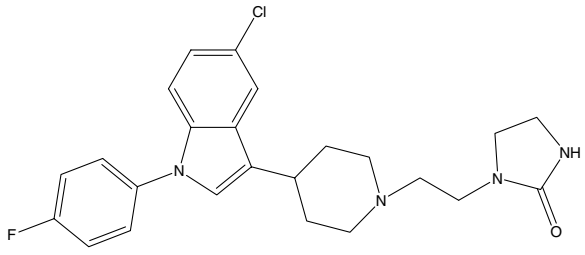
Similarly, the replacement of the 4-carbonyl (C=O) at position 4 by the imidazoline as in the SGB 1534 derivative **160**, of which the *S*-form, (*S*)-(−)-**160**, is more active than the *R*-form as a selective α_1-adr antagonist. It was found to be most potent in reducing mean arterial blood pressure.[161]



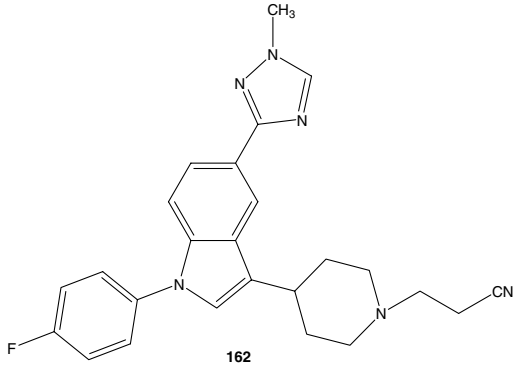
(*S*)-(-)-**160**

4.7. *N*-Arylindoles

The phenylindole nucleus of sertindole **161**, an atypical antipsychotic drug, has shown to be a promising template for the development of the centrally acting α_1-adr antagonists. Replacement of the 5-chloro atom in sertindole with polar substituents such as carbamoyl and aminomethyl groups afforded a new class of selective α_1-adr antagonists. The replacement of the 5-chloro atom in sertindole with heteroaromatic substituents such as azoles, pyridines, and pyrimidines has yielded several highly selective α_1-adr antagonists. Tetrazoles were found to be the optimal heteroaromatics with respect to the overall selectivity. Considering selectivity for α_{1A}-receptors with respect to the D_2, D_3, D_4, and serotonin 5-HT_{2A} and 5-HT_{2C} receptors, the optimal activity was shown by the triazoles. Compound **161** has the affinities of 0.99, 3.2, and 9.0 nM for α_{1A}, α_{1B}, and α_{1D}-adr subtypes.[162]

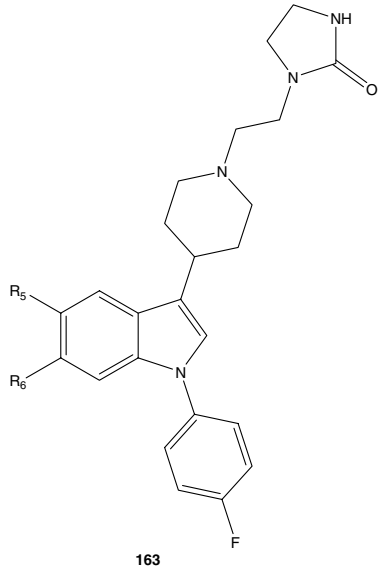


Sertindole **161**



162

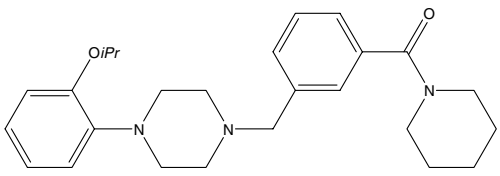
Receptor-binding affinities for the α_1-adr subtypes α_{1A}, α_{1B}, and α_{1D} for a series of 39 α_1-adr antagonists **163** derived from the antipsychotic sertindole are reported and the SAR of the compounds with respect to affinity for the α_{1A}, α_{1B}, and α_{1D}-adr subtypes, as well as, affinity obtained by an α_1-adr assay (rat brain membranes) was investigated using a 3D QSAR approach based on the GRID/GOLPE methodology. Good statistics (r^2 = 0. 91–0.96; q^2 = 0.65–0.73) were obtained with the combination of the water (OH_2) and methyl (C3) probes. The α_{1A}-adr receptor seems to be more tolerant to large substituents in the area between the indole 5- and 6-positions compared to the α_{1B} and α_{1D}-adr receptor subtypes. There seems to be minor differences in the position of areas in the α_{1B}-adr receptor compared to α_{1A} and α_{1D} receptors, where electrostatic interaction between the molecules and the receptor (OH_2 probe) contributes to increased affinity.[163]



163

4.8. *N*-Aryl and *N*-heteroaryl piperazine derivatives

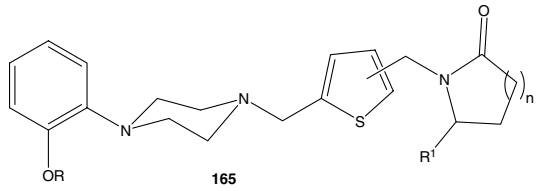
Synthesis and activity of **164** (RWJ-37796), an arylpiperazine derivative, which binds with high affinity (K_i < 4 nM) to 5-HT_{1A} and α_{1A}-adr receptors, have been reported.[164] Compound **164** has an octanol–water partition coefficient (log *P*) of 4.00 (experimentally determined), and is predicted to have fair blood–brain barrier penetration. It has high affinities (K_i <4 nM) for D_2, D_3, 5-HT_{1A}, and α_1-adr receptors and weaker affinities for 5-HT_2 (165 nM), 5-HT_{1B} (2880 nM), and α_2-adr (17 nM) sites. α_1-Adr binding has been broken into α_{1A}-adr (0.20 nM) and α_{1B}-adr (47 nM) components by competition experiments with the α_{1A}-adr ligand, WB 4101.



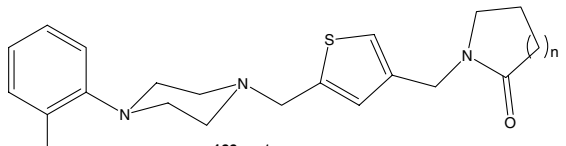
RWJ 37796 **164**

Screening of a chemical library against α_1-adr in a radioligand-binding assay has led to the discovery of a new series of compounds with the general structure of **165**. Further, modifications in the structure of these compounds was done with an aim to improve their affinity and selectivity, keeping in mind that the 1-(2-alkoxyaryl)piperazine moiety was necessary for its potency and selectivity. In this series, almost no selectivity was

seen between α_{1A} and α_{1D}-adr, though selectivity between the subtypes α_{1A} and α_{1B}-adr was good (>125-fold). However, by changing the substitution pattern from 2,5-disubstituted to 2,4-disubstituted thiophene, the affinity was retained and selectivity was enhanced. Compounds **166**–**168** are highly potent against α_{1A}-adr and very selective for them than other subtypes.[165]

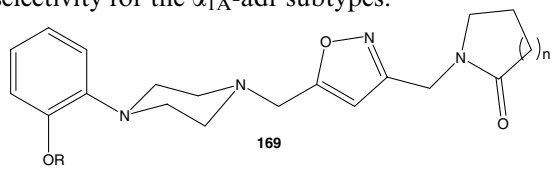


165

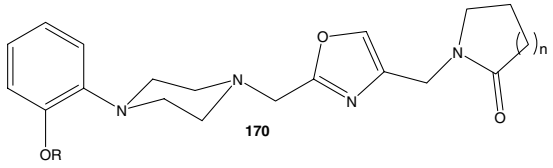


166: n=1
167: n=2
168: n=2

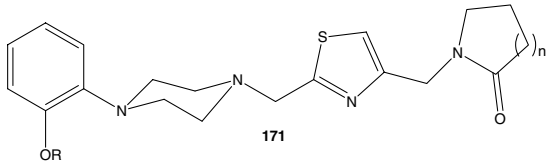
A new series, in which the thiophene ring was replaced by other five-membered heterocyclic ring systems like isoxazole as in compound **169**, oxazole as in compound **170**, and thiazole as in **171**, was synthesized and evaluated for α_1-adr subtypes binding affinities. Binding affinities of these derivatives clearly indicate that these heterocyclic ring systems were not well tolerated for the potency, as well as selectivity for the α_{1A}-adr subtypes.[166]



169

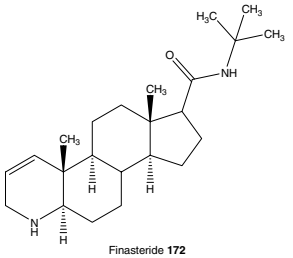


170

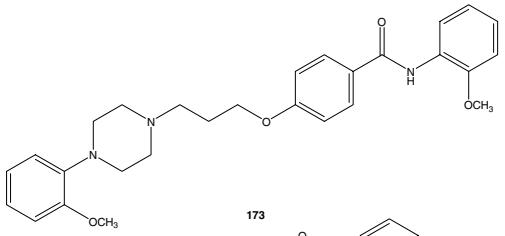


171

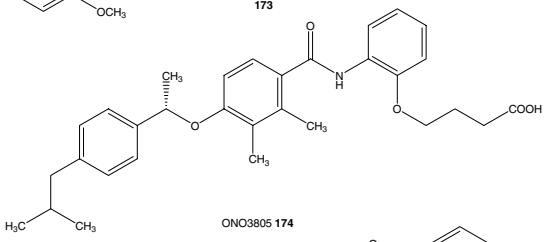
Dihydrotestosterone has been established as a dominant factor of prostatic growth. Research on inhibitors of steroid 5α-reductase (5α-R), an enzyme which converts testosterone to the more potent dihydrotestosterone, has been carried out. It is known that finasteride **172**, a 5 α-R inhibitor, is approved for BPH treatment.[167,168] Some dual acting compounds with α_1-adr antagonistic action and steroidal 5-α reductase (5α-R) inhibitory activity were developed. From the earlier study,[169] compound **173** shows α_1-adr receptor antagonistic activity, which seems to be very close to ONO3805 **174** that has been reported as a non-steroidal 5α-R inhibitor. The methoxy group of **173** was replaced with the 4-carboxypropyl group of **174** to yield a new series of compounds **175**. The biological evaluation results of these compounds show that lengthening of the spacer chain increased the 5α-R inhibitory activity, whereas no difference was observed for the α_1-adr antagonistic activity. The introduction of a phenyl group markedly increased both α_1 and 5α-R inhibitory activities. As the alkyl substituent at this position becomes larger the α_1-antagonistic activity decreases, while 5α-R inhibitory activity increases.[170]



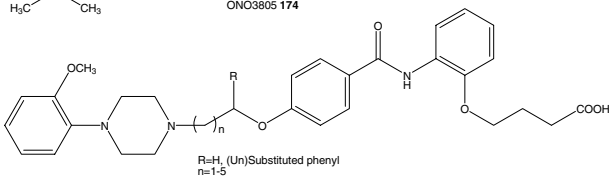
Finasteride **172**



173



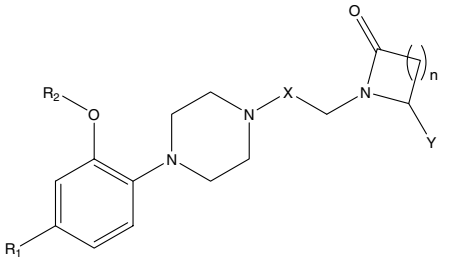
ONO3805 **174**



R=H, (Un)Substituted phenyl
n=1-5

175

In order to gain insight into the structural principles governing subtype selectivity, 3D QSAR studies have been performed on a set of arylpiperazines, **176**, for the α_{1A}-adr receptor antagonistic activity by using a logico-structural-based approach for the pharmacophore mapping. The resulting models exhibited good r^2 (0.80) values.[171]

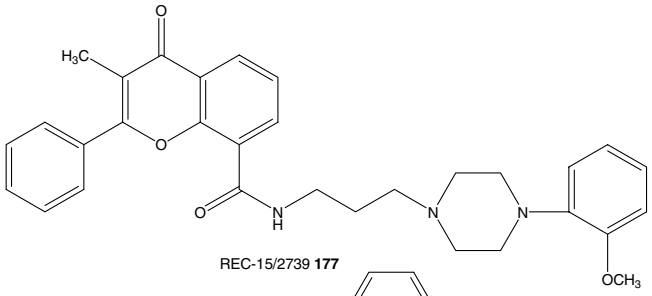


R_1=H, F
R_2=CH_3, *i*-pr, CH_2CF_2
X=$C_2H_4N(CH_3)CO$, $(CH_2)_3NHCO$, C_2H_4NHCO, $(CH_2)_2OCO$ *etc*
Y=H, $COOC_2H_5$
n=2, 3, 4

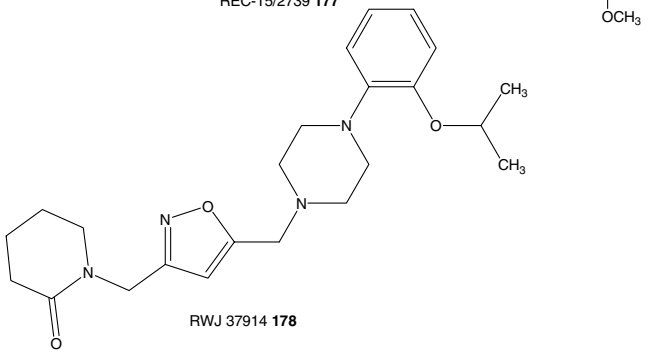
176

Development of REC 15/2739 **177** as potential α_1-adr antagonist opened up another new avenue.[172] Hybridization of **177** with the first generation lead RWJ

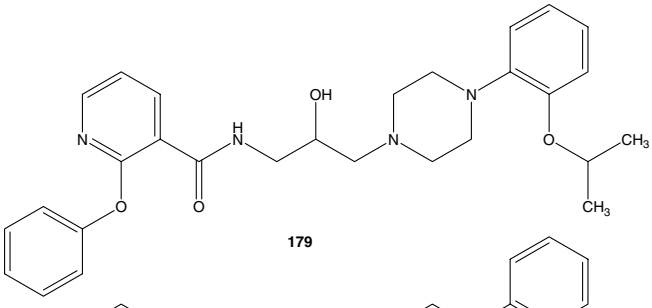
37914 **178** then led to the discovery of second generation leads in which the (*o*-isopropoxyphenyl)piperazine moiety was fixed. Hydroxy group was also introduced to modify the pharmacokinetic properties of the molecules. From these compounds, **177** and **178**, compound **179** was found, which exhibited improved binding affinity (11-fold) and maintained good selectivity at the α_{1A}-adr than the first generation lead.[173] To improve the selectivity and binding affinity for α_{1A}-adr, the hydroxyl enantiomers of **179** were explored along with substitution on phenoxy ring. The *S*-hydroxy derivative **180** displayed higher selectivity in inhibiting rat prostrate contraction than rat aorta contraction and also exhibited a modest improvement of uroselectivity.[174]



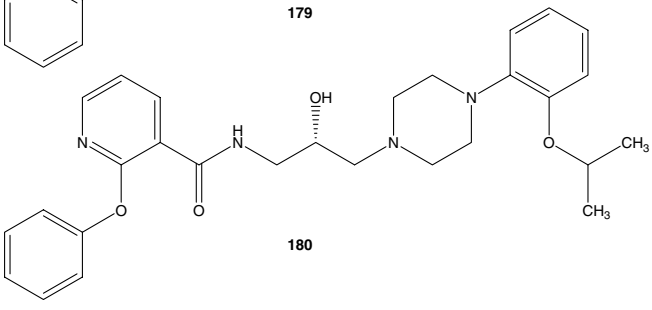
REC-15/2739 **177**



RWJ 37914 **178**

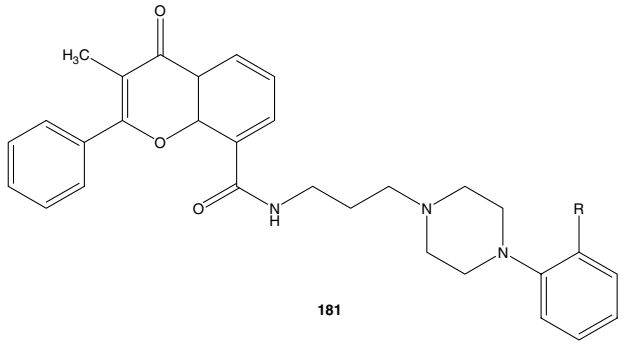


179

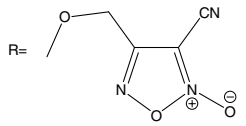


180

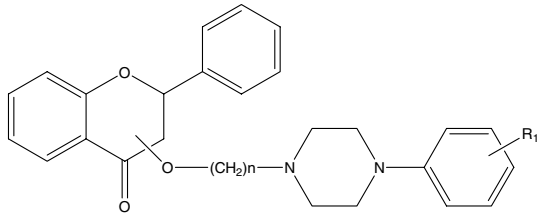
Further, modifications in REC 15/2739 **176** with nitrooxy and furoxan NO-donor moieties yielded new NO-donor α_1-antagonists **181**. All these compounds were found to be potent and selective ligands for human cloned α_1-antagonists subtype.[175]



181

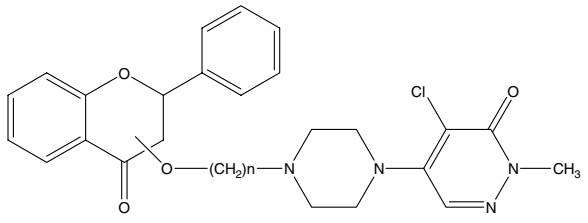


A new class of piperazine derivatives (**182**–**184**) was designed, synthesized, and biologically tested for the α_1-adr antagonistic activity. The new compounds are characterized by a flavone system linked through an ethoxy or propoxy spacer to a phenyl- or pyridazinone-piperazine moiety. Biological data showed an interesting profile for the phenylpiperazine subclass which was found to have a nanomolar affinity toward α_1-adr and less pronounced affinity for α_2-adr and the 5-HT_{1A} serotoninergic receptors.[176]



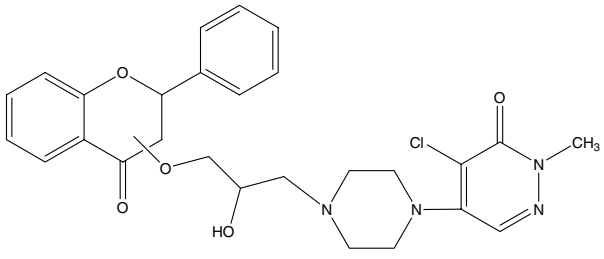
n=2,3
R_1=OCH_3, O*i*Pr
Substitution pattern=3,6,7

182



Substitution pattern=3,6,7

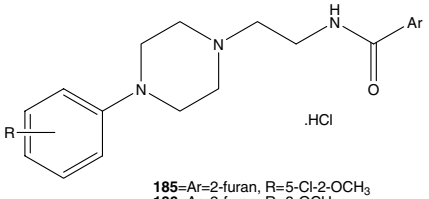
183



Substitution pattern=6,7

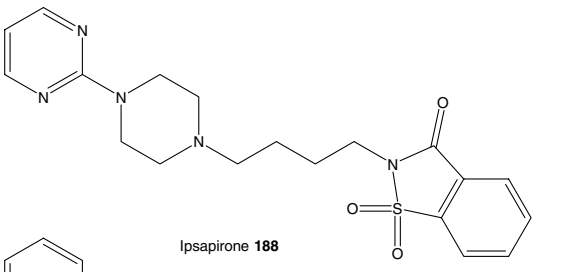
184

A new series of phenylpiperazines were designed and synthesized based on the pharmacophore for uro-selective α_1-adr antagonists and 3D chemical database searching. These compounds were evaluated for their α_1-adr antagonistic activities and the result showed that three compounds, **185**–**187**, displayed high α_1-adr antagonistic pA_2 of 8.56, 8.56 and 9.12, respectively. All three compounds have similar or better α_1-adr antagonistic activities comparable with those of prazosin.[177]

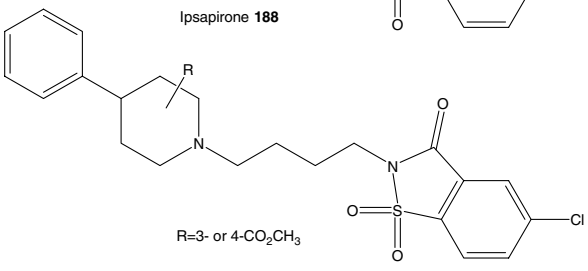


185=Ar=2-furan, R=5-Cl-2-OCH_3
186=Ar=2-furan, R=3-OCH_3
187=Ar=2-furan, R=2-OCH_3

Isapirone **188**, an anti-anxiety agent, has been shown to have modest affinity for α_1-receptors. In order to increase its affinity for the α_1-adrs, its piperazine subunit was replaced with a variety of piperidines. Thus, replacing the *N*-(2-pyrimidinyl)piperazine present in spirone with a 4-carboxymethyl-4-phenylpiperidine moiety led to a modest improvement in the α_{1A}-binding affinity and enhanced the α_{1A}-receptor subtype selectivity. Relocation of the carboxyalkyl group to the 3-position caused a variety of stereochemically dependent results. The (±)-*cis* 3-carbethoxy-4-phenylpiperidine derivative **189** was substantially more potent and more selective than its corresponding *trans* isomer. Upon separation, the (−)-*cis* isomer proved to be more active and selective than the (+)-*cis* isomer.[178]



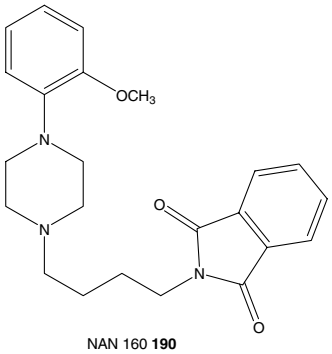
Ipsapirone **188**



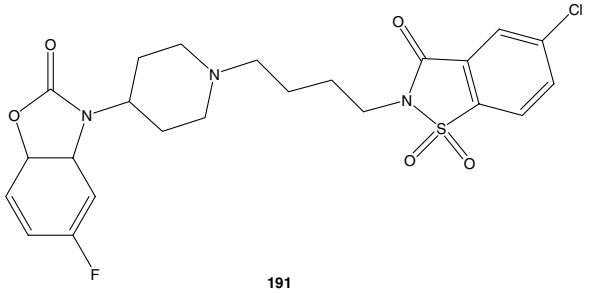
R=3- or 4-CO_2CH_3

189

Considering NAN 190 **190**,[179] a known 5-HT_{1A} and α_1-adr ligand, as a template, a new series of selective α_1-adr antagonists has been developed. Replacing the phthalimide group with a 1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (saccharin) ring system afforded better selectivity against α_{1B}-adr. Further, when the benzoxazolone ring was substituted with fluorine at the 6-position, it led to an increase in potency and similar selectivity for α_{1A}-adr over α_{1B}-adr and α_{1D}-adr. Substitutions at 5 and 6-position of the saccharin ring were found to afford potent α_{1A}-adr antagonists. Compound **191** represents a class of novel α_{1A}-adr antagonists with high affinity and selectivity.[180]

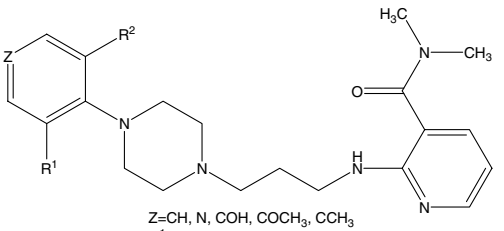


NAN 160 **190**



191

Elworthy et al.[181] added to the SAR for arylpiperazinyl derivatives as α_1-antagonists. They developed compounds **192** and showed that greater the size of a single *ortho* moiety, greater the affinity and selectivity is achieved. However, the optimum substituents are lower alkyl, alkylalkoxy or heterocyclics. Presence of electron withdrawing groups, regardless of size, led to loss of affinity. The aryloxy analogues afforded compounds with lower affinity, but the subtype selectivity was retained. *ortho*-Substitution of the (aryloxy)ethylamine led to the desired antagonistic properties as also realized in the arylpiperazine series. Substitution of the amide group with methyl groups increased affinity and improved the subtype selectivity. The dimethyl substitution was found to be optimal for affinity and selectivity.

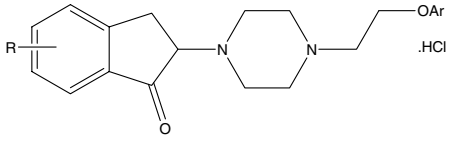


Z=CH, N, COH, $COCH_3$, CCH_3
R^1=H, CH_3
R^2=H, CN, alkoxy, alkyl, 2-oxozolo, SCH_3 etc

192

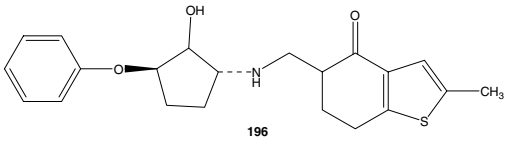
4.9. Miscellaneous compounds

A novel series of 1-indanone α_1-adr antagonists was designed and synthesized based on a 3D-pharmacophore model. Their in vitro α_1-adr antagonist activity assay showed that three compounds **193**–**195** had similar or improved α_1-adr antagonistic activities relative to the positive control prazosin. Based on these results, a 3D QSAR study was performed using a self-organizing molecular field analysis (SOMFA) method to provide insight for the future development of α_1-adr antagonists.[182]



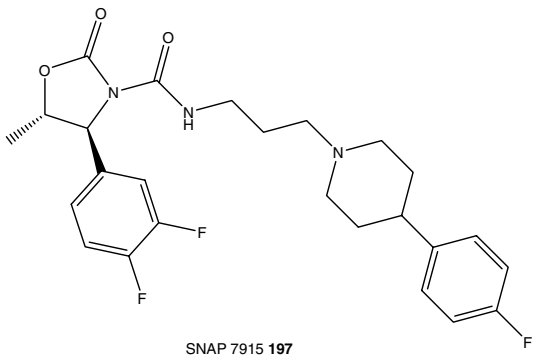
193 =R= 6-methoxy, Ar= 1-naphthyl
194=5,6-dimethoxy, phenyl
195=5,6-dimethoxy, 4-*t*-butylphenyl

It has been reported that certain aminothiopheneamines act as α_1-adr receptor antagonists. This fact led to the discovery of a compound **196** and its stereoisomers. It was found that it has a unique mechanism of action that combines DA_1 receptor agonistic activity with vasodilation produced by selective α_1-adr receptor blocked.[183]



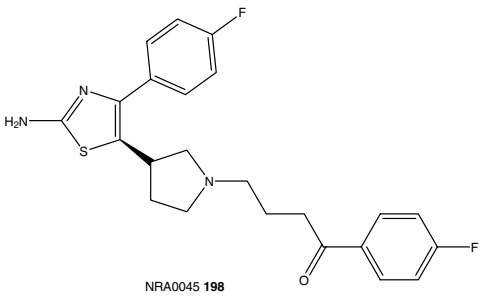
196

An oxazolidinone derivative, SNAP 7915 **197**, showed sub nanomolar (0.17 nM) binding affinity for the recombinant human α_{1A}-adr and greater than 700-fold selectivity over α_{1A}- and α_{1D}-adr in competitive-binding assays. Compound **197** did not show significant affinity for the rat L-type Ca^{2+} channel and a number of G-protein coupled receptors such as α_2-adrenergic, histamine, and serotonin receptors. It exhibited significantly improved oral bioavailability and plasma half-life compared to dihydropyrimidinone analogues.[184]



SNAP 7915 **197**

A novel thiazole derivative (*R*)-(1)-2-amino-4-(4-fluorophenyl)-5-[1-[4-(4-fluorophenyl)-4- oxobutyl]pyrrolidin-3-yl]thiazole **198** (NRA 0045) was found to possess high affinities for the human cloned dopamine $D_{4.2}$, $D_{4.4}$, and $D_{4.7}$ receptors, with K_i values of 2.54, 0.55, and 0.54 nM, respectively. NRA 0045 is approximately 91-fold more potent at the dopamine $D_{4.2}$ receptor, compared with human cloned dopamine D_{2L} receptor. NRA 0045 also has high affinities for the serotonin (5-HT_{2A}) receptor (K_i = 1.92 nM) and α_1-adr (K_i = 1.4 nM).[185]

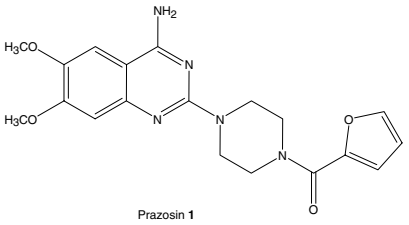


NRA0045 **198**

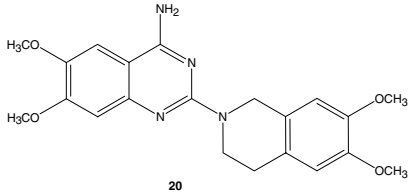
A quantitative structure–activity relationship (QSAR) study[186] of a wide series of structurally diverse α_1-adr antagonists was performed using the CODESSA (comprehensive descriptors for structural and statistical analysis) technique. Size and shape descriptors were considered in the attempt of using information relevant to α_1 receptors subtype interactions. In the series of antagonists considered in this study, subtypes of analogues identified were the constituents of extensively investigated classes of ligands, such as quinazolines, *N*-arylpiperazines, imidazolines, phenylalkylamines, benzodioxanes, and indoles, 1,4-dihydropyridines, the ligands chosen were superimposed, by a rigid fit procedure, minimizing the rms deviations with respect to three dummy atom pairs. The volumes of the resulting supermolecules were computed and redundant constituents were successively eliminated for each α-adr subtype ligand class. The overall three-dimensional shape of the supermolecules with respect to each receptor subtype α_{1A}, α_{1B}, and α_{1D} was obtained.

Thus, to model the pharmacological α_1-adr subtype binding affinities, compounds **1**, **20**, **55** **91**, **200**, **201**, and **205** were used for the α_{1A} supermolecule, whereas compounds **24**, **199**, and **204** were used for the α_{1B} supermolecule. For the α_{1D} supermolecule, compounds **1**, **199**, **202**, **203**, and **204** were selected. Very good predictions were obtained for the α_1-adr subtypes, pertaining to the structural requirements of the ligands for the binding affinity, functional activity and in vitro and in vivo selectivities at various α_1-adr subtypes.

A new three-dimensional computational approach for lead evolution, based on multiple pharmacophore hypotheses is described.[187] The ensemble hypothesis has been used to search virtual chemical libraries to identify compounds for the synthesis. This model is very



Prazosin **1**



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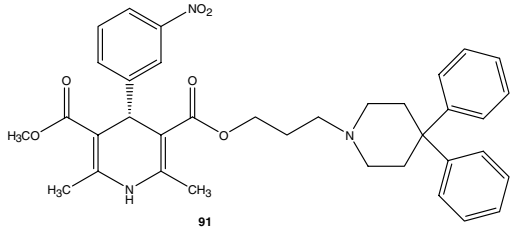
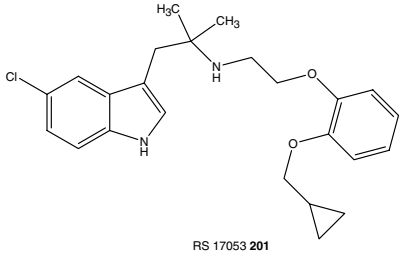
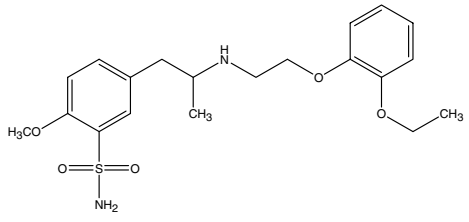


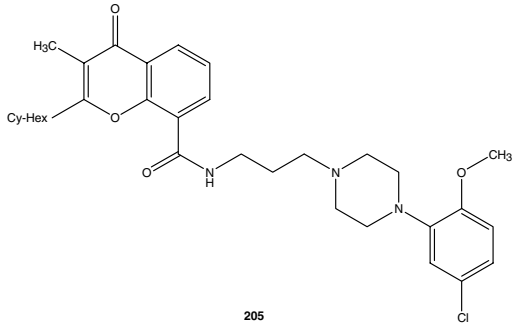
91



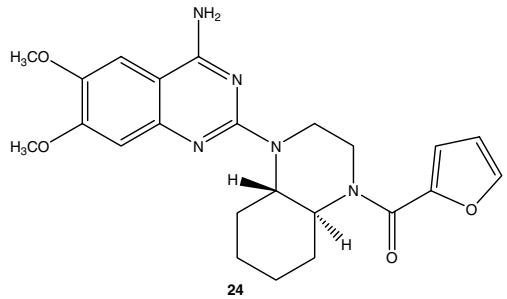
RS 17053 **201**



Tamsulosin **200**



205



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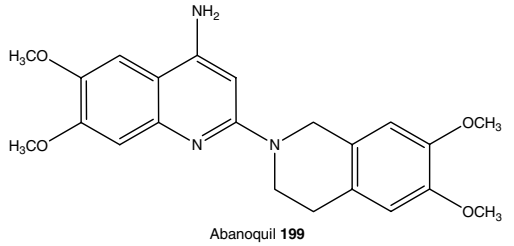
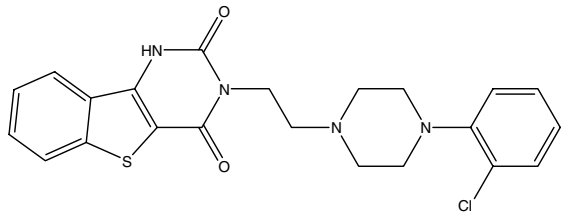
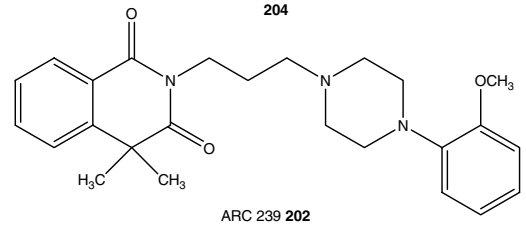


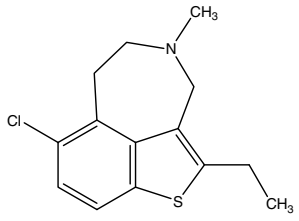
Abanoquil **199**



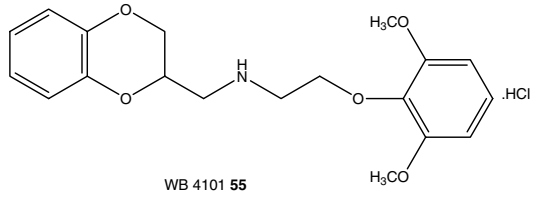
204



ARC 239 **202**



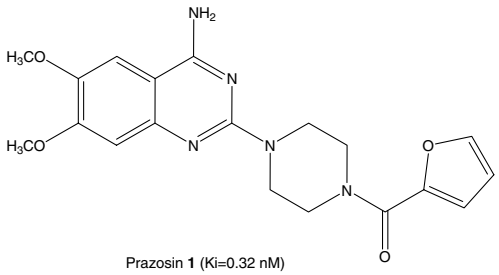
SKF 106686 **203**



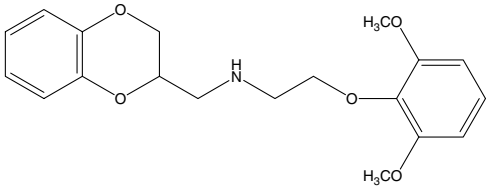
WB 4101 **55**

rapid, allowing very large virtual libraries of the order of a million compounds to be filtered efficiently. By applying this method to α_1-adr ligands, it has been demonstrated that lead evolution from heterocyclic α_1-adr ligands to highly dissimilar active *N*-substituted glycine compounds is possible.

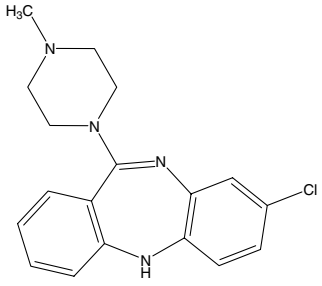
Thus, from the known heterocyclic α1-adr ligands prazosin **1**, compound **55**, clozapine **206** and haloperidol **207**, novel *N*-substituted glycine ligands have been proposed from the library as structures **208**–**210**.



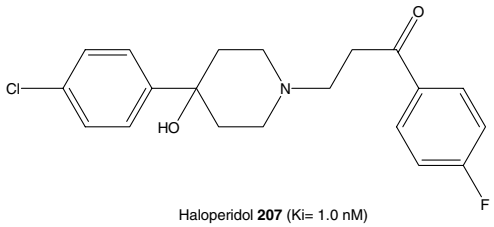
Prazosin **1** (Ki=0.32 nM)



55 (Ki=0.54 nM)



Clozapine **206** (Ki= 1.4 nM)



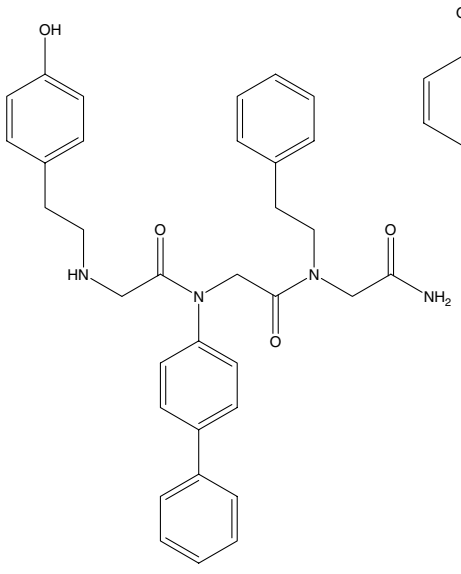
Haloperidol **207** (Ki= 1.0 nM)

5. Pharmacological evaluation of selective α_1-adrenoceptor subtypes antagonist activity

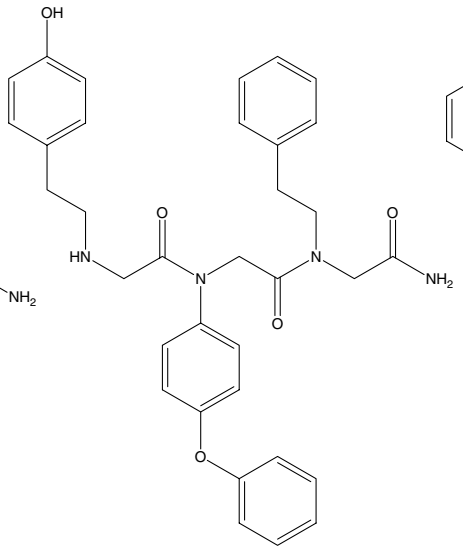
There are a few reports available in the literature for the evaluation of test compounds (ligands) for the selective antagonist activity against specific adr subtypes. Evaluation of selective α_{1A}-adr antagonists activity is done using prostatic *vas deferens* of rat.[188] Another report describes rat hippocampal membranes pretreated with CEC as the model.[189] Phenylepherine treated splited spleen of Sprague–Dawley rats has been used as the model for the evaluation of α_{1B}-adr antagonist activity.[190] The same report describes the use of thoracic aorta of rats for evaluation of α_{1D}-adr antagonist activity. Recombinant mice lacking α_{1D}-adr have also been used as a model along with normal mice to evaluate α_{1D}-adr antagonist activity.[191] Oshita et al.,[192] have evaluated the α_{1L}-adr antagonist activity using NE-induced contraction of rabbit aorta pretreated with CEC as the model.

6. Summary and conclusion

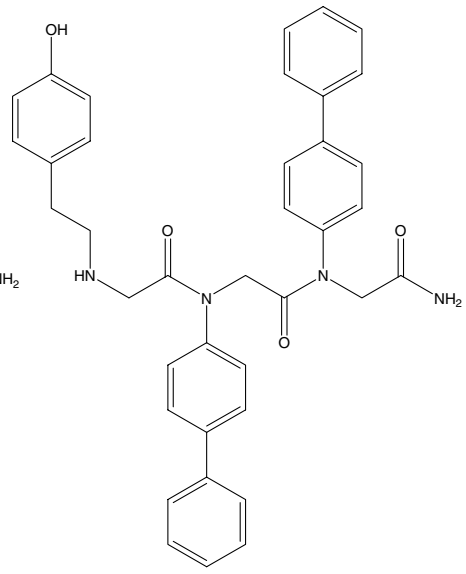
A brief introduction of hypertension, its causes, risks, and drugs currently used for its treatment and control is given. The role of α_1-adr, their subtypes, their physiological roles and distribution are discussed. The subtypes of α_1-adrs, namely, α_{1A}, α_{1B}, and α_{1D} in particular have been discussed with respect to their characteristics, structures, distribution, and significance. With a preliminary discussion on selective α_1-adr antagonists pertaining to their chemistry, uses, and application in hypertension, safety, merits, and demerits, the main focus has been laid on the advances in the past one decade in the field of drug design and discovery involving the synthesis and evaluation of novel α_1-adr antagonists, particularly selective toward α_1-adr subtypes.



208 (Ki = 0.32 nM)



209 (Ki = 140 nM)



210 (Ki = 310 nM)

Existence of multiple α_1-adr subtypes holds great promise for the discovery and development of more specific selective drug molecules, targeting only one α_1-adr subtype and free from side effects. Thus, today medicinal chemists worldwide are involved in design and synthesis of very specific α_1-adr subtype antagonists. A review of the literature on the research done on the discovery and evaluation of a variety of chemically diverse structures as selective antagonists of α_1-adr and α_1-adr subtypes in recent years, has been presented.

The various molecules designed, synthesized, and evaluated so far have been broadly classified into nine different categories: 2,4-diamino-6,7-dimethoxyquinazolines, 1, 4-benzodioxans, dihydropyridines and dihydropyrimidines, fused pyrimidindiones, pyridazinones, imidazolines, *N*-arylindoles, *N*-aryl and *N*-heteroaryl piperazines, and miscellaneous compounds.

The collection of α_1-adr antagonists presented in this review covers a range of structural types, of which all the compounds possess a central basic center flanked on at least one side by aromatic systems. The presence of a protonated form of the molecule, at physiological pH appears to be a vital feature for α_1-adr antagonists. However, the precise profile in terms of subtype selectivity is heavily dependent on the nature of the basic center, the substitution of the aromatic rings, and the spatial orientation of the groups. This overview separates the agents into structural classes defined by the basic center and discusses briefly how α_1-adr subtype selectivity varies within each series.

With synthetic tools of drug design and evaluation (e.g., radio ligand assays), it is expected that medicinal chemists will soon be able to discover very specific and selective antagonists for α_{1A}, α_{1B}, and α_{1D}-adr subtypes, which shall be very specific in action and have relatively negligible side effects.

Acknowledgments

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