Imidazoline Receptor and Imidazolidine Derivatives
อิมิดาโซลีนรีเซพเตอร์และอนุพันธ์อิมิดาโซลิดีน

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อิมิดาโซลีนรีเซพเตอร์เป็นรีเซพเตอร์ชนิดใหม่ที่จัดอยู่ในกลุ่ม non-adrenergic binding site ทำให้มีการศึกษารีเซพเตอร์เหล่านี้เพื่อใช้ในการรักษาโรคความดันโลหิตสูงโดยไม่มีผลข้างเคียงทำให้คนไข้หลับ ได้มีการสังเคราะห์และศึกษาฤทธิ์ทางเภสัชวิทยาของอนุพันธ์อิมิดาโซลีดีนหลายชนิด พบว่าสารเหล่านี้มีผลลดความดันในลูกตามากกว่าการลดความดันโลหิต การศึกษาความสัมพันธ์ระหว่างสูตรโครงสร้างและการออกฤทธิ์ พบว่าวงแหวนอิมิดาโซลมีความจำเป็นต่อการจับกับรีเซพเตอร์ โดยหมู่ที่เกาะกับวงแหวนอิมิดาโซลมีความสำคัญต่อฤทธิ์การลดความดันในลูกตา ดังนั้นจึงสามารถพัฒนาอนุพันธ์อิมิดาโซลิดีนเหล่านี้ไปใช้เป็นยารักษาโรคต้อหิน

คำสำคัญ : อิมิดาโซลีน อิมิดาโซลิดีน รีเซพเตอร์

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Imidazoline receptors are new receptors, which are classified as non-adrenergic binding sites. These receptors provide a new concept in treating hypertensive without the sedative side effect. Many imidazolidine derivatives were synthesized and studied for their pharmacological activities. These compounds reduce pressure in the ocular tissue instead of the circulatory system. Structure activity relationship studies revealed that imidazole ring is essential for binding to the receptors and the side chain attached to the imidazole ring is important for the lowering intra-ocular pressure properties. Therefore, the imidazolidine derivatives can be useful as effective agents for treating glaucoma.

Key words : imidazoline, imidazolidine, receptor

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Introduction

α Adrenoceptors have many important physiological functions in humans. They are classified as α_1 and α_2 adrenoceptors based on the drug selectivities. α_1 receptors are predominately located at postsynaptic while α_2 receptors are distributed both at pre- and postsynaptic neurons. The distribution, localization and function of these receptors are shown in tables 1 and 2 (Williams *et al.*, 1989). It is obviously known that the stimulation or inhibition of α adrenoceptors has tremendous effects on blood pressure.

Table 1 Distribution, Localization and Function of α_1 Adrenoceptors

Organ/tissue (location)	Activation causes
Blood vessels (postsynaptic)	Contraction
Smooth muscle (postsynaptic)	Contraction
Heart (postsynaptic)	Positive inotropy/chronotropy (negative chronotropy)
Eye (postsynaptic)	Mydriasis, ocular hypertension
Liver (postsynaptic)	Glycogen phosphorylase activation
CNS (postsynaptic)	Stimulation; inhibition of baroreceptor afferent inputs
Sympathetic neurons (presynaptic?)	Inhibition of norepinephrine release (?)

Table 2 Distribution, Localization and Function of α_2 Adrenoceptors

Organ/tissue (location)	Activation causes
Sympathetic, cholinergic, and serotonergic neurons (presynaptic)	Inhibition of norepinephrine, acetylcholine and serotonin release
CNS (postsynaptic)	Hypotension, bradycardia
CNS (presynaptic?)	Sedation/behavioral depression, analgesia/ psychotropic activity, endocrinologic effects
Sympathetic ganglia	Hyperpolarization
Somadendrites in CNS	Inhibition of firing
Blood vessels (postsynaptic)	Contraction
Platelets	Aggregation
Fat cells	Inhibition of lipolysis
Pancreatic islets	Inhibition of insulin secretion
Eye	Ocular hypotension
Intestinal epithelial cells	Inhibition of intestinal secretions

Figure 1 demonstrates the pre- and postsynaptic α adrenoceptors in adrenergic synapses. Stimulation of sympathetic neuron causes the exocytotic releasing of norepinephrine (NE) from storage vesicle which interacts with postsynaptic α receptor (α_1) producing vasoconstriction. In contrast, the interaction of NE with presynaptic α receptors (α_2) will give the negative feedback effect providing the inhibition of NE releasing. The centrally postsynaptic α_2 also contributes to lowering the blood pressure. From these physiological roles, many drugs have been developed to mimic the agonist or antagonist action on α adrenoceptors in order to relieve the hypertensive symptoms in the patients.

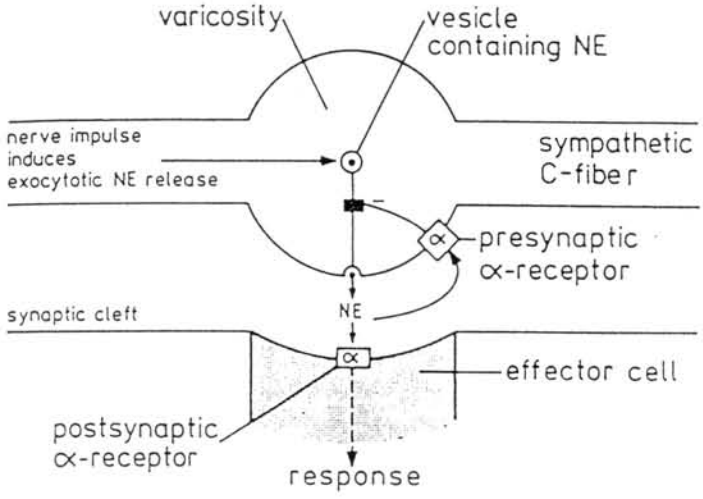


Figure 1 Localization of pre- and postsynaptic α adrenoceptor in adrenergic synapse
(Williams *et al.*, 1989)

Imidazoline receptors

Clonidine, an imidazole, is clinically useful antihypertensive agent which lowers arterial blood pressure by action within the central nervous system. It also produces sedative side effects in patients. Clonidine elicits the action as an α_2 adrenoceptor agonist at the rostal ventrolateral medulla (RVL) (Gomez *et al.*, 1991). However, there is evidences that clonidine lowers blood pressure not only by interacting with α_2 adrenergic receptors but a non-adrenergic binding site, i.e. imidazoline receptor (Gomez *et al.*, 1991; Lubie *et al.*, 1985; van Zweten *et al.*, 1986; Weerasuriya *et al.*, 1984). Many researchers have extensively studied this new receptor, some of them are discussed here.

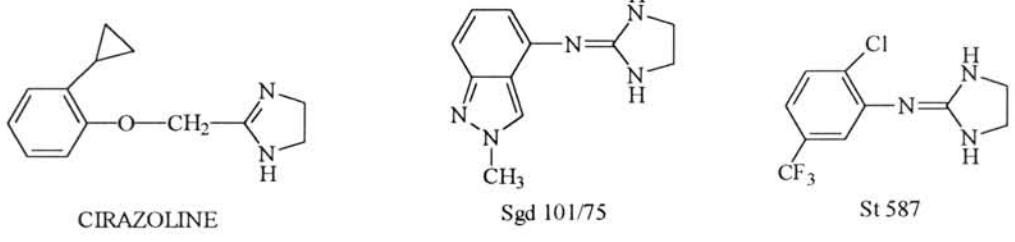
A. Observations from Division of Neurobiology and Neuroscience, Cornell University Medical College

1. Cirazoline (Figure 2), α_2 antagonist imidazole, gave clonidine-like vasodepressor response when microinjected into RVL (Gomez *et al.*, 1991).

2. Rilmenidine (structure not shown), oxazolidine analog of clonidine, can be used as an effective antihypertensive agent in animal and man (Gomez *et al.*, 1991; Lubie *et al.*, 1985; VanZweten *et al.*, 1986; Weerasuriya *et al.*, 1984). It produces less sedative side effect than clonidine (Vlahakos *et al.*, 1985).

3. SKF 86466 (Figure 3), highly selective α_2 antagonist, did not block the effects of clonidine and rilmenidine (Hieble *et al.*, 1986; Ernsberger *et al.*, 1990). However, idazoxan (Figure 3) prevented rilmenidine's lower blood pressure action (Gomez *et al.*, 1991).

From this study it can be concluded that rilmenidine acts at RVL region containing receptors which differs from α_2 adrenoreceptors. The α_2 antagonist, SKF 86466 and idazoxan bind at distinct receptors. Further studies also showed that a lower dose of rilmenidine binds to imidazole receptors in the RVL while occupying a few α_2 adrenoceptor in the frontal cortex (Gomez *et al.*, 1991). This explains the less severe sedative side effect compares to clonidine.



CIRAZOLINE Sgd 101/75 St 587

Figure 2 Structures of selective α_1 adrenoceptor agonists

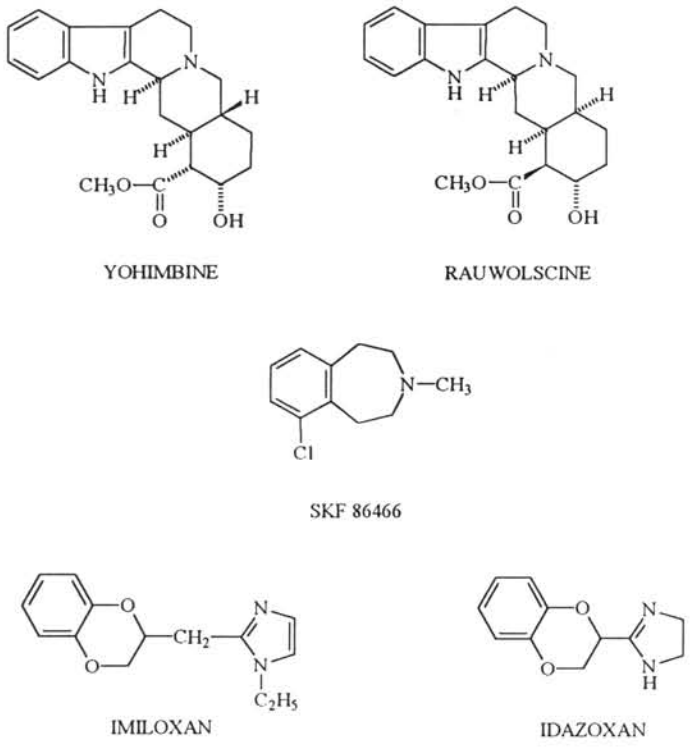


Figure 3 Structures of selective α_2 adrenoceptor antagonists (various chemical features)
(Williams *et al.*, 1989)

B. Observations from laboratorire de Pharmacologie Cardiovasculaire et Renale, Faculte de Medicine, Universite Louis Pasteur, France (Tibirica *et al.*, 1991)

1. Idazoxan (Figure 3) antagonized the hypotensive effects of clonidine and neuronal inhibition in the nucleus reticularis lateralis (NRL) but did not inhibit at the locus coeruleus (LC) in rat. Conversely, yohimbine, a classical α_2 antagonist, had no effect in NRL but it did show neuronal inhibition in LC region.

2. Azepexoale (structure not shown), an oxazoline-azepine, lowered blood pressure that could be antagonized by α adrenergic antagonists.

3. Rilmenidine (structure not shown), a new centrally acting antihypertensive drug structurally related to clonidine, stimulated the imidazoline-specific receptors in NRL producing the hypotensive response which was antagonized by idazoxan more than yohimbine.

4. SKF 86466 (Figure 3) did not reverse action of rilmenidine.

5. Injection of imidazolines in cat NRL lowered arterial pressure while phenylethylamine and α-methylmoradrenaline could not reduce the arterial pressure.

These discoveries suggest that there are two different pharmacological action mechanisms for the hypotensive (imidazoline-specific) and sedative (adrenergic) effect of clonidine-type drugs. In rat brain, NRL region is responded to the site of the hypotensive action while LC region is involved in the sedative effect of these drugs (Tibirica *et al.*, 1991). Binding studies also demonstrated the existence of a population of imidazoline-specific receptors in the brainstem of animal and man (Ernsberger *et al.*, 1987). Azepexole centrally lowers blood pressure by distinct mechanisms and sites from clonidine and rilmenidine. This molecule lacks the imidazole moiety, therefore shows the low affinity for the imidazoline binding sites. From observation 5, the imidazole ring is an essential feature to the induction of hypotension in rat brain region.

C. Observations from Institut fur Pharmacologie und Toxikologie der Rheinishen Friedrich-Wilhelmus-Universitat Bonn and Pharmakologisches Institut der Universitat Essen Federal Republic of German (Molderings *et al.*, 1991)

1. The α_2 adrenoceptor blocking imidazolines tolazoline, BDF 6100, [2-(2-imidazoline 2-ylamino)-isoindoline] (Figure 4), and BDF 7572 (4,7-dichloro-derivative of BDF 6100) (Figure 5) increased the electrical-evoked ^{3}H-noradrenaline overflow. The concentration-response curves were bell-shaped.

2. In contrast, moxonidine, clonidine, agonidine and BDF 7579 [4-chloro-(2-isoindolinyl)-guanidine] inhibited the evoked ^{3}H-noraddrenaline overflow. The concentration-response curves for noradrenaline were inhibited by rauwolscine.

3. In the presence of rauwolscine (Figure 3) the inhibitory effect was also observed with the α_2 adrenoceptor blocking imidazolines tolazoline, BDF 6100 and ST 587 [2-(2-chloro-5-trifluoromethylphenylimino)-imidazoline] (Figure 2); the potency was as follow: aganodine (Figure 5) > BDF 7579 (Figure 5) > BDF 7572 > BDF 6100 > clonidine > ST 587 > moxonidine > tolazoline.

These studies were done on rabbit pulmonary artery and the results suggest that imidazoline receptors mediating inhibition of noradrenaline release exist on the sympathetic nerve of this artery. The new receptor is an allosteric site of the presynaptic α_2 adrenoceptor.

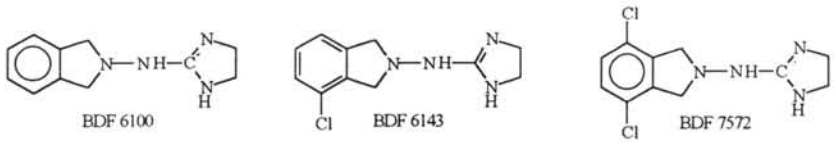


Figure 4 Structures of selective α_2 adrenoceptor antagonists (aminoimidazoline substitute isoindoline derivatives) (Williams et al., 1989)

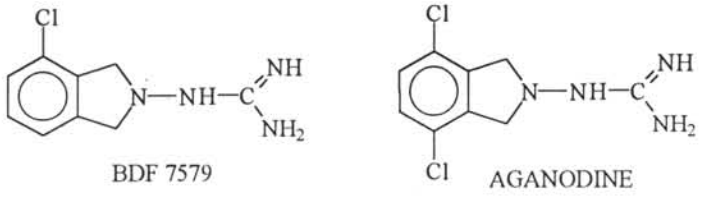


Figure 5 Structures of selective α_2 adrenoceptor antagonists (guanidine substitute isoindoline derivatives) (Molderings *et al.*, 1991)

New imidazoline derivatives

The existence of imidazoline receptors produces a new concept in the synthesis of antihypertension agents. However, the specific structures which fit this receptor have not been well characterized. The mechanism of new imidazoline derivatives are still based on the action at the β or α adrenoceptors.

A. Pharmacology

The novel imidazolidine analogues (compound 3-6) shown in Figure 6 were synthesized and found to be useful for glaucoma instead of general antihypertensive action. Glaucoma is delineated by the increasing of intraocular pressure (IOP) due to the excessive production of aqueous humor. The chronic high pressure cause the damage to optic disc at the juncture of the optic nerve and the retina following by the irreversible blindness (Gilman *et al.*, 1980).

Glaucoma is generally treated by cholinergic drugs or anticholinesterase agents (AchE inhibitors) such as physostigmine and neostigmine, which cause miosis and reduce the tension in the eye by facilitating outflow of aqueous humor. However, these agents especially the long acting AchE inhibitors, decamerium and echothiophate produce some unwanted side effects. They precipitate the risk of cataract (Gilman *et al.*, 1980). In

addition, blurred vision, headache and various allergic reactions are minor side effects found in long term drug users.

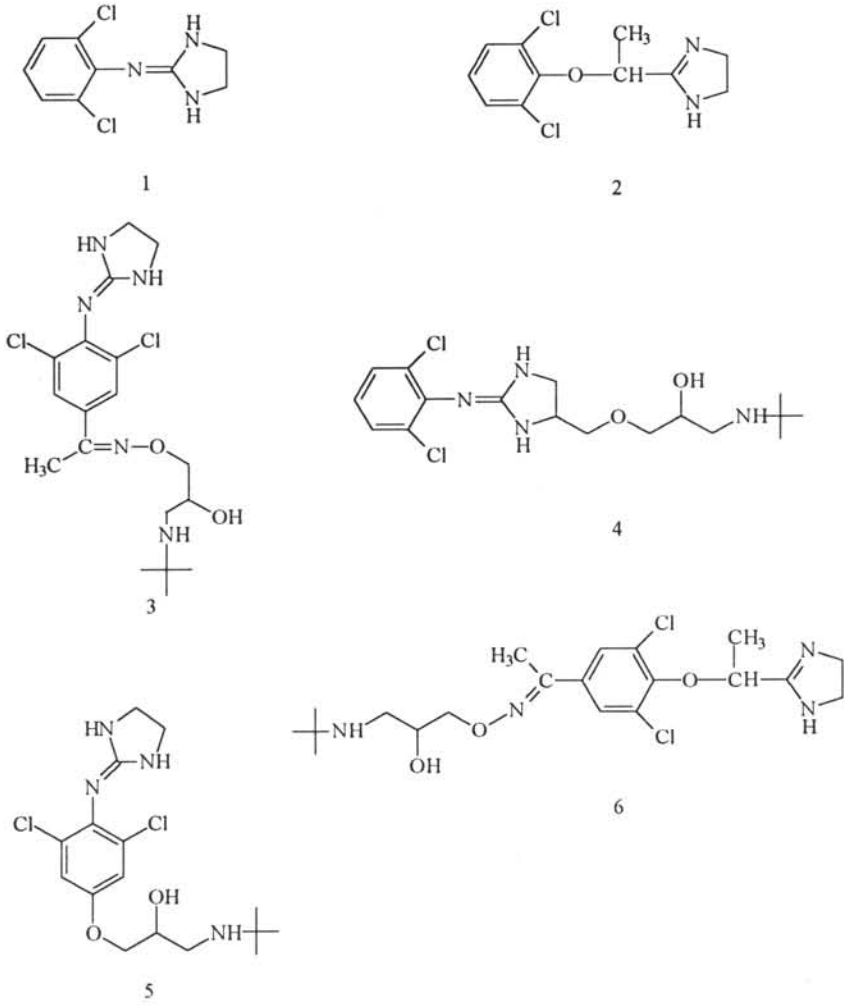
In order to avoid these drawbacks, adrenergic drugs are studied for the ophthalmic properties. The receptors in ciliary body of eye tissues which response to the controlling of aqueous humor are mostly α_2 and β_2 type (Huber *et al.*, 1991; Ralli, 1975; Allen and Langham, 1976; Krieglstein *et al.*, 1987; Jumblatt and Liu, 1987). Prazosin, a selective antagonist at α_1 receptors, can lower intraocular pressure in animal model but it also obstructs the outflow of the aqueous humor which decreases its potential for clinical usefulness (Huber *et al.*, 1991).

The imidazolidine derivatives are a class of agents which possess β-adrenergic antagonist and α-adrenergic agonist properties (Huber *et al.*, 1991). The effects of reducing the aqueous humor formation and decreasing resistance to aqueous humor outflow were demonstrated in α-chymotrypsin-induced ocular hypertension in rabbit. These two effects result in lowering intraocular pressure which make these new imidazoline derivatives a potential medical management for glaucoma patients with minimum side effects compare to cholinergic drugs or AchE inhibitors.

B. Structure-Activity Relationships

Clonidine can decrease aqueous humor flow through its effect on α-adrenergic receptors in the ciliary body (Huber *et al.*, 1991). The imidazolidine analogues based on clonidine (1) and lofexidine (2) are designed by attaching a β-side chain either on the 4-position of the aromatic ring or on the imdazole ring 14 and expected to have the lowering effect of intraocular pressure.

The effects of compounds 3-6 on reducing intraocular pressure are shown in Figure 7. A 0.5 % solution of 3 produced a gradual and sustained fall in IOP. Maximum effect (-31.5 %) occurred at 3 h. Maximum IOP decrease was -21.5 % with compound 4, -22.0 % with compound 5 and -20.1 % with 6. Compound (+) -3 and (-) -3 have a maximum IOP decrease of, respectively, -23.5 % and -22.7 % after 3 h (Huber *et al.*, 1991).



1 = Clonidine

2 = Lofexidine

3 = 3,5-Dichloro-4-(2-imidazolidinylideneamino) acetophenone O-[3-(tert-Butylamino)-2-hydroxypropyl] oxime

4 = 2-[(2,6-Dichlorophenyl) imino-4-[[[3-(tert-butylamino)-2-hydroxykpropyl] oxy] methyl] imidazolidine

5 = 2-[2,6-Dichloro-4-[3-(tert-butylamino)-2-hydroxypropoxy] phenyl] imino] imidaxolidine=-

6 = 2-[1-[2,6-Dichloro-4-[1-[[3-tert-butylamino)-2-hydroxypropoxy] imino] ethyl] phenoxy] ethyl]-2-imidaxoline

Figure 6 Structures of imidazolidine derivatives (Huber *et al.*, 1991)

Compounds 3-6 have no α_1 adrenergic activity as clonidine on rat aorta but still have α_2 adrenomimetic properties on guinea pig vas deferens. Only 4 and 6 showed β blocking properties. Compound 4 containing a β side chain attached to the imidazolidine ring is the best α_2 agonist and β_1 antagonist among the others but it has no β_2 antagonist action. It reduces IOP similar to 5 and 6, thus varying adrenergic activities do not effect the lowering IOP action in 3-6.

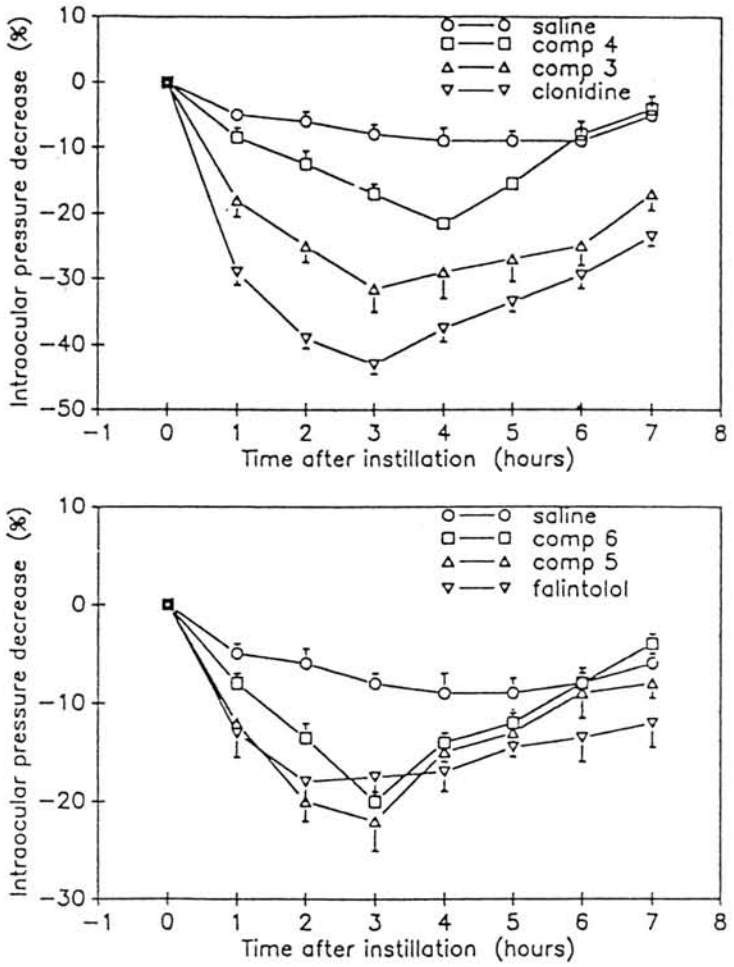


Figure 7 Effects of saline, 3, 4 and clonidine (top) and effect of saline, 5, 6, and falintolol (bottom) on the time course of the IOP in rabbits with α-chymotrypsin-induced ocular hypertension (Huber *et al.*, 1991)

Conclusions

The discovery of imidazole receptor revealed a potential new conception treating hypertension in order to separate the antihypertensive action and the sedative side effects. The imidazole ring is the necessary moiety for the receptor. However, the imidazolidine analogues developed so far are found to act at adrenergic receptors (α and β receptors). They provide the reduction of pressure in the ocular tissue instead of the circulatory system. The side chain attached to the imidazole ring is important for the lowering IOP properties, it can be either propanolamine oxime or oxypropanolamine moiety. Compound 3 containing the former side chain is slightly more potent than the other analogues. The success of synthesis of these imidazolidine derivatives might generate a unique series of effective ocular antihypertensive agent.

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