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Design and synthesis of 6,7-dimethoxyquinazoline analogs as multi-targeted ligands for α_1- and AII-receptors antagonism

M. R. Yadav *, P. P. Naik, H. P. Gandhi, B. S. Chauhan, R. Giridhar

Pharmacy Department, Faculty of Tech. & Engg., The M.S. University of Baroda, Vadodara 390001, Gujarat, India

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ABSTRACT

Multiple-targeted ligands can have certain advantages for the management of hypertension which has multiple controls. Molecules with dual bioactivities are available in literature for treating metabolic disorders like diabetes, hypertension and hypercholesterolemia. After scrutinizing the SAR of prazosin-type α_1-blockers and AII-antagonists it was planned to develop dual α_1- and AII-antagonists. Five series of quinazoline derivatives were synthesized and evaluated as dual α_1- and AII-antagonists on rat aortic strips for the blockade of known α_1- and AII-agonist mediated contractions. Many compounds showed balanced activity on both the receptors but compound (**22**) was found to be the most active derivative having higher antagonistic activity on both the receptors. In the in vivo experiments the chosen compound (**22**) was slightly less active than prazosin but was found to be equipotent to losartan. These findings shed a new light on the structural requirements for both α_1- as well as AII-receptor antagonists.

It is increasingly being recognized that a balanced modulation of multiple targets can provide a superior therapeutic efficiency in comparison to targeting a single enzyme/receptor in a diseased state.[1] There is no single drug treatment of hypertension due to differences in etiology, risk factors and body constitution of individuals.[2] It requires a combination therapy as a single drug of any class of antihypertensives proves ineffective.[3,4] The conventional treatment of hypertension involves combination of drugs from such categories of drugs as diuretics, α_1-adrenergic receptor antagonists, β-blockers, calcium channel blockers, ACE inhibitors, AII-receptor antagonists etc.

Compared to drug combinations, there are certain advantages associated with a multiple-targeted ligand as a therapeutic agent, such as more predictable pharmacokinetic and pharmacodynamic relationship and improved patient compliance as a consequence of administration of a single drug at a time. It is interesting to note that of the known multiple targeted (multi-action) drugs only a few have been designed to act on the intended targets. Rest others have been serendipitously discovered wherein the modes of action of the drugs were elucidated retrospectively to be multiple targeted. Increase in the number of publications on the designing and development of multiple targeted molecules in recent times is an indication of developing interest in the field.[5–7] Rational designing approaches, in which structural features of selected ligands are combined into one single entity, have produced new ligands that act on a variety of targets. A key challenge in the designing of such multiple-targeted ligands is attaining a balanced activity at each target of interest while achieving a higher selectivity and a suitable pharmacokinetic profile simultaneously.[8] The so called dual acting drugs (dimeric ligands) are designed by joining together the pharmacophores by a cleavable/noncleavable linker or more commonly by overlapping the pharmacophores of two drugs into a single chemical entity by taking advantage of common structural features of two or more classes of drugs. To integrate the pharmacophores of two drugs common structural features of both of the drugs are overlapped.

There are numerous examples of hybrid molecules wherein dual bioactivities have been packed into a single chemical entity. Glitazones (insulin sensitizers) and fibrates (lipid lowering agents) act through PPARγ and PPARα receptors respectively. The aryloxazole (**1**) is a combination of thiazolidinedione derivative (**2**) and fenofibric acid[9] (**3**). A dual acting hybrid sulphonamide (**4**) was obtained by linking propranolol, a β-blocker with mefruside, a diuretic.[10] In prizidilol (**5**), hydralazine a well known vasodilator was integrated with a pharmacophoric group responsible for β-blocking activity to afford a dual acting drug.[11]

* Corresponding author. Tel.: +91 265 2434187; fax: +91 265 2418927.
E-mail address: mryadav11@yahoo.co.in (M.R. Yadav).

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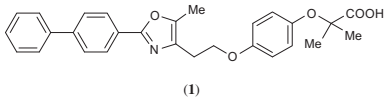
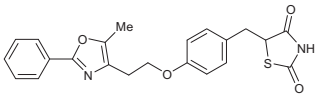


(1)



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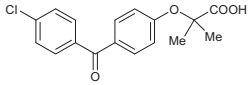

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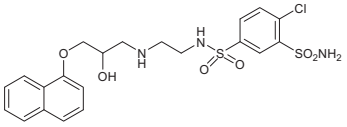

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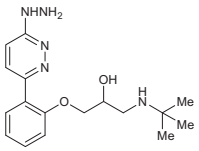
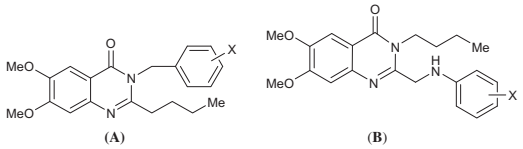


(5)

Several experimental and clinical studies have pointed towards the linked action of RAAS (renin angiotensin aldosterone system) and SNS (sympathetic nervous system) in the homeostatic control of cardiovascular functions.[12,13] Evidences show that these two systems interact mutually with each other to effect their cardiovascular regulatory roles.[14,15] Stimulation of SNS results into vasoconstriction and increased inotropic and chronotropic effects of heart while stimulation of RAAS results in increased production of active hormone angiotensin II (AII) which raises blood pressure. The RAAS–SNS interactions have physiological as well as pathophysiological relevance; a reciprocal reinforcement of the favorable as well as unfavorable cardiovascular, renal, metabolic and reflex effects of the two systems have been reported in a variety of cardiovascular conditions like hypertension.[15–17] SNS and RAAS become important targets in order to control the blood pressure as both of the systems work in coordination. Simultaneous blockade of both the systems should prove to be beneficial in the management of hypertension. Two important targets belonging to the RAAS–SNS systems are the α_1- and AII receptors.

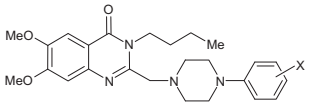
α_1-adrenergic receptor blocking agents and AII receptor antagonists both are important classes of antihypertensive drugs. A wide variety of chemical structures[18] possess α_1-adrenoceptor blocking activity. Similar observations have been made for AII receptor antagonists.[19] After studying the structure activity relationships of both the classes of drugs minutely, it became evident that the drug binding sites of both the receptors could accommodate wide structural variations in the active molecules. And if that presumption was correct, then designing of dual acting α_1 and AII antagonists should not be a distant dream.

Prazosin (**6**), an important α_1-blocker was chosen as the lead molecule. Not many structural changes have been carried out in prazosin type of α_1-blockers except for some variations in the side chain at position-2 of the quinazoline ring system. On the other hand, by considering losartan (**7**) as the lead molecule of AII antagonists, it was noted that too many structural changes have been performed to obtain potent AII antagonists, like replacement of imidazole nucleus with other heterocyclicring systems, replacement of the biphenylmethyl side chain with smaller and bigger groupings, and replacement of tetrazole moiety with other acidic groups. So, it was planned to design hybrid structures by employing 6,7-dimethoxyquinazoline ring skeleton as the common structural motif for α_1 as well as AII antagonism and attaching various types of side chains at its 2-and/or 3-positions. The main obstacle in the selection of the side chain was the nature of the side chain grouping—whether the attached side chain should have acidic functionality or a basic one because prazosin-type of α_1-blockers contained basic groupings in the side chain while all reported AII antagonists had an acidic functionality in the side chain. It was envisaged to make a try with all the three types of functional groups, acidic, basic as well as neutral in the attached side chain for designing of the compounds. Assuming a high degree of structural tolerance for antagonistic activity by both the receptors, the given five types (**A**–**E**) of compounds were designed:



(A)

(B)



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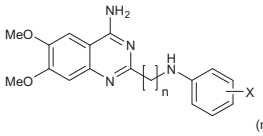

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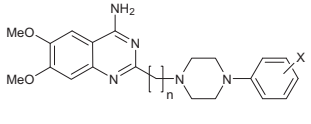
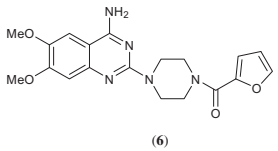


(E)

Work was initiated for the preparation of series **A** compounds. For synthetic convenience, compounds with neutral groups like CH_3, OCH_3, Cl, Br, NO_2, CN etc. at different positions of the phenyl ring were prepared first. Compounds so synthesized (Scheme 1) were screened for obtaining preliminary biological data. The results of this preliminary biological screening were a bit shocking to us. Surprisingly, all of the screened compounds showed dual antagonism to the phenylephrine and AII responses in the in vivo normotensive rat model; although the level of antagonism was low to moderate in comparison to prazosin and losartan, the two prototype lead antagonists. In vitro experimentation on isolated rat aortic strip could not be performed for these neutral compounds due to their solubility problem in aqueous solutions. These results forced us to have a relook at the mechanism of antihypertensive actions of both prazosin and losartan. When neutral molecules without any characteristic side chains could show dual α_1- and AII-receptor antagonism, was it possible for prazosin and losartan also to show dual antagonism at both the receptors? pA_2 value determinations of both of the standard lead molecules confirmed the correctness of our assumption of wide structural tolerance by both the receptors in their active spaces—prazosin exhibited potent dual antagonism at α_1- (pA_2 8.91) as well as AII-receptors (pA_2 8.26) (Table 1) while losartan was found to be a potent antagonist at AII-receptor (pA_2 8.08) but a poor (pA_2 5.46) one at α_1-receptor when evaluated on rat aortic strip using phenylephrine and AII as agonists.[20]



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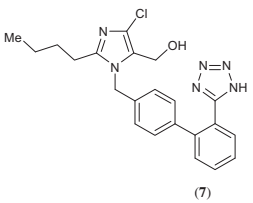

(7)