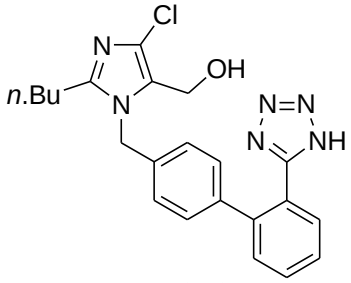
3. Aims and objectives

It has been proved that α_1- and AT_1-receptors work through SNS and RAS respectively, as the prime targets to set the elevated blood pressure to normal levels. Both these receptors could be targeted simultaneously for the better control of blood pressure. In order to attain balanced activity on the identified targets with selectivity for the desired targets and acceptable pharmacokinetic profile, designing of multiple target-directed ligands is a challenging task. It is a prerequisite to know about the pharmacophores in prototype compounds to design such type of molecules.

Knowledge-based approach was used for the designing of dual α_1 and AT_1 antagonists. This approach is based on combining of frameworks and underlying pharmacophores of two drug molecules, each selective for one particular target of interest, into a single chemical entity possessing both of the activities of the parent molecules. The resulting dual acting ligands could have linked, fused or merged pharmacophores. After an in depth study of literature, it was envisaged to fuse the selected pharmacophores of two compounds *i.e.* prazosin (acting on α_1-receptors) and losartan (acting on AT_1-receptors) into a single chemical entity to offer balanced activity on the desired targets. The following key points about both the receptors (α_1 and AT_1) were considered from the literature.

3.1 AT_1-receptor antagonists [prototype losartan (13)]

- Imidazole ring in losartan can be easily replaced by other five or six membered heterocyclic rings.
- N_1 function is essential.

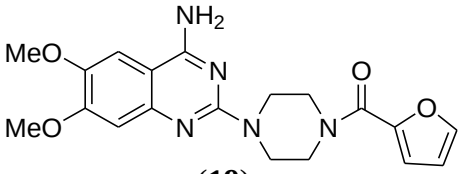


(13)

- Alkyl chain at 2nd position of imidazole ring gives more active compounds but it is not an essential structural requirement.
- A hydrogen bond acceptor either in the heterocyclic ring or as part of the open chain is required for active molecules.

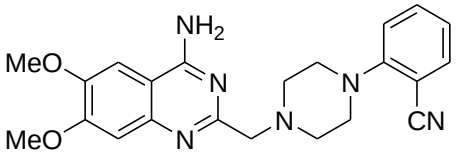
3.2 α_1-Receptor antagonists [prototype prazosin (19)]

- 4-Aminoquinazoline ring is an important pharmacophoric feature for α_1-antagonistic activity.
- N_1 function is essential for the activity.
- 2nd position of quinazoline ring can be easily substituted with heterocyclic or lipophilic moieties.
- Substitution at 3rd position is not essential for activity.
- Primary amino group at 4th position imparts greater activity than a keto group.



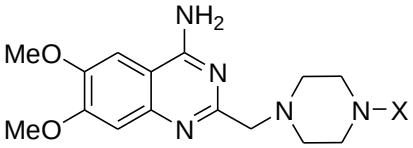
(**19**)

Earlier studies in our laboratory have revealed that integration of pharmacophoric features of the α_1- and AT_1- selective molecules resulted into new potent and dual acting chemical entities. Losartan (**13**) and prazosin (**19**) are the AT_1- and α_1-receptors antagonists respectively. Our group has tried to incorporate the structural features of both these drugs in order to obtain a hybrid molecule (**20**) as a potent antihypertensive agent with ability to bind to both the receptors synergistically. The designed compounds were synthesized and evaluated for their biological activities on both the earlier discussed receptors. In the *in vitro* evaluation some of these compounds were found to be active on both the discussed receptors.

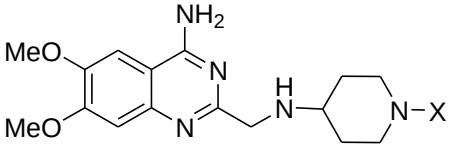


(**20**)

The outcome from our earlier work created an interest to work further in this direction. Encouraged by these results, it was planned to synthesize compounds which could have better aqueous solubility and more structural variations. The following seven series of compounds were planned to be synthesized and their biological activity evaluated through *in vivo* and *in vitro* experiments:



Series I



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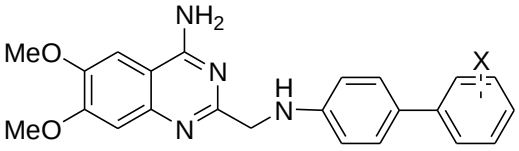

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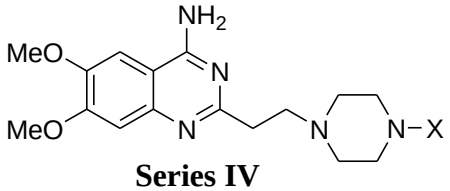

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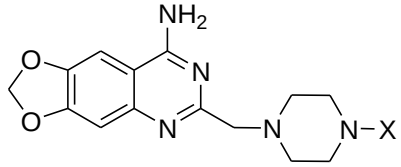

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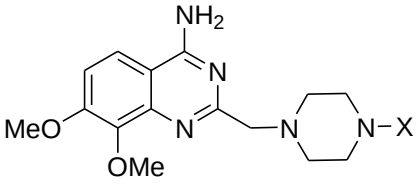

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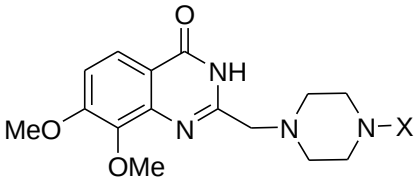

Series VII