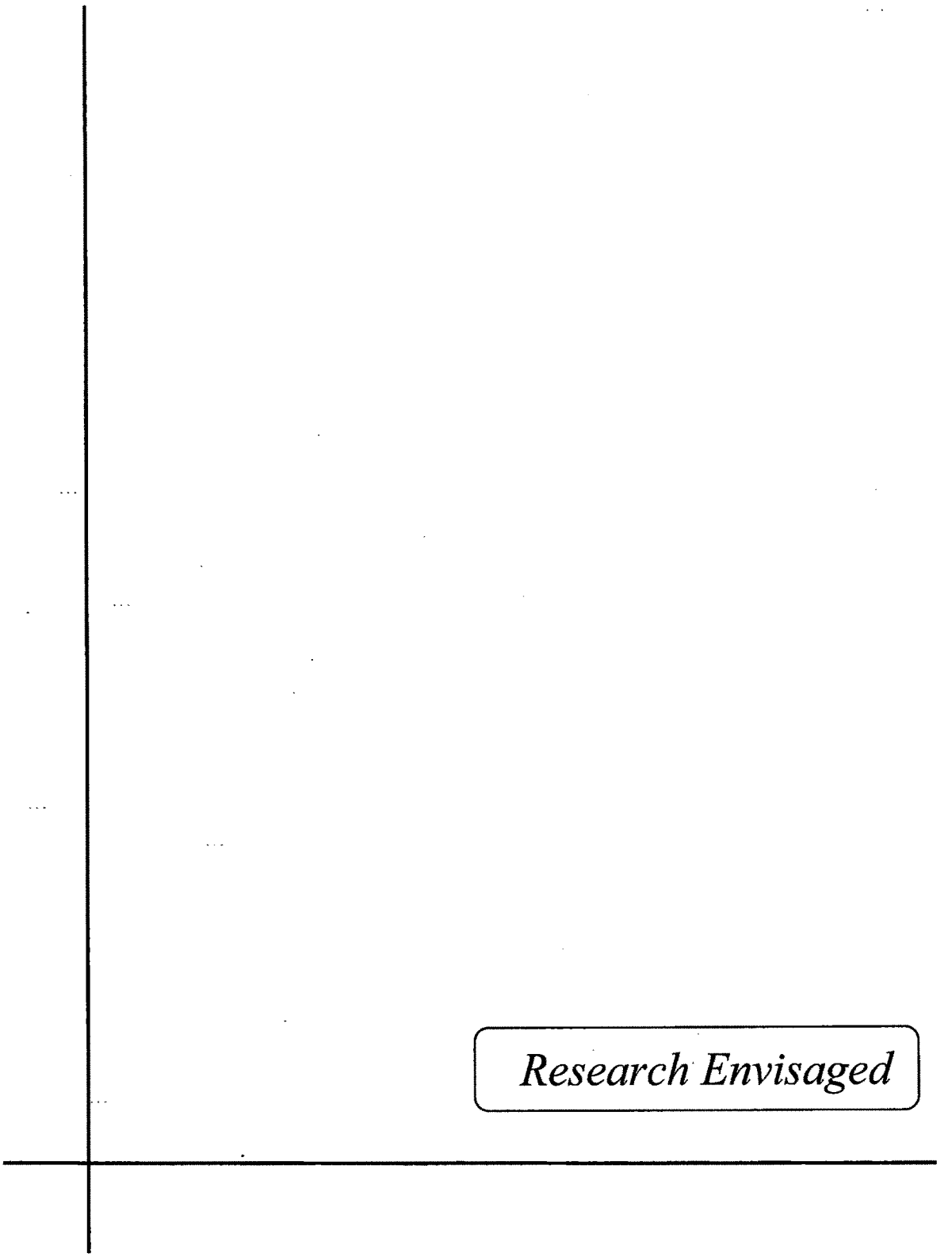

Research Envisaged

is a potent, long-acting and partially insurmountable antagonist. It inhibited the pressor effect of ang II at a dose 10 mg/kg (p.o.) for up to 20 hours.[367] Edmunds et al. reported a series of 5-substituted hydantoins as AT_1 antagonists. The most potent compound (**AT109**) of the series (3.8 nM, rabbit aorta) reduced the MABP of RHR by 40% at 30 mg/kg p.o. and by 25% at 10 mg/kg p.o. In addition, this compound (**AT109**) was efficacious in the salt-depleted normotensive monkey model decreasing blood pressure by 27% at 10 mg/kg (p.o.).[368]

Patients suffering from hypertension need multidrug therapy for effective control of blood pressure. Multidrug therapy poses certain pharmacokinetic problems. So it was planned to design and synthesize compounds bearing dual, α_1 and AT_1 receptor antagonistic properties.

A key challenge in the design of multiple target ligands is attaining a balanced activity at each target of interest while simultaneously achieving a higher selectivity and suitable pharmacokinetic profile. Rational designing approaches involve selection of structural features from selective ligands combined into one single entity to produce multiple targeted ligands. Dual antagonists have been designed by considering the two different approaches, screening and knowledge-based approaches as discussed earlier.

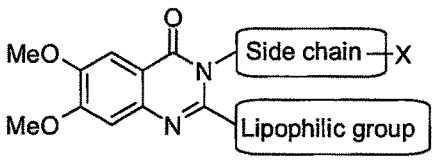
Knowledge–based approach was used for designing of dual α_1 and AT_1 antagonists. This approach is based on combining of frameworks and underlying pharmacophores of two drug molecules, each selective for one particular target of interest, into a single chemical entity possessing both of the activities of the parent molecules. The resulting dual acting ligands could have linked, fused or merged pharmacophores. In order to design dual α_1 and AT_1 antagonists, a thorough survey of literature for α_1 and AT_1 antagonists was performed as discussed earlier. The molecules were designed by considering the structure activity relationships of both categories of compounds. The following points emerged from the study of the structures of the α_1 antagonists:

- α_1 Antagonists could be categorized distinctly into two categories: prazosin and related compounds which bear quinazoline moiety, and phenoxybenzamine and phentolamine type of compounds which can not be clubbed under one chemical category.
- All quinazoline derivatives possessed 6,7-dimethoxyquinazoline ring which was reported to be essential for α_1 antagonistic activity.
- Substitution at C_2 position did not appear to be critical for activity.

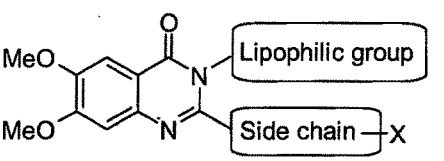
- Substitution at N_3 is not essential for activity.
- The amino function at 4-position is highly favorable for activity although it could be effectively substituted by keto function.

  Following generalizations could be made for AT_1 receptor antagonists:
- Imidazole ring in losartan could be easily substituted by other five- or six-membered heterocyclic rings or even by simple open chain moieties containing nitrogen.
- *n*.Alkyl groups in the heterocyclic ring give more active compounds but it is not an essential structural feature.
- A suitably placed hydrogen bond acceptor either in the heterocyclic ring or part of an open chain moiety provides active molecule.
- An aromatic ring system possessing an acidic functionality as a side chain is required for activity. A biphenylmethyl group containing an acidic tetrazole affords the most potent ang II antagonists however, various types of ring systems have been reported to provide active compounds.

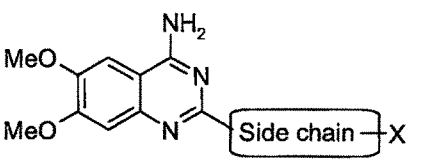
After studying the structural features of both of the classes of compounds it was felt that it should be possible to design dual α_1 and AT_1 receptor antagonists. It was envisaged to synthesize the following three categories of compounds:



(I)



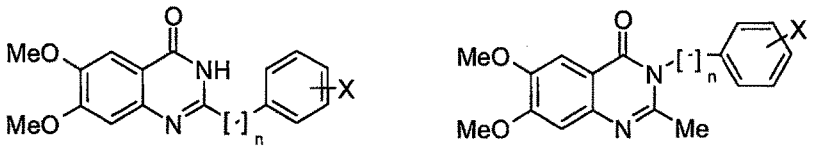
(II)



(III)

X = Neutral/acidic/basic groups

To explore the synthetic feasibility, preliminary work was started in this laboratory with the synthesis of simple 2/3-substituted phenyl-6,7-dimethoxyquinazoline-4(3*H*)-ones (**IV** and **V**) bearing neutral groups like methyl, halo, nitriles etc.

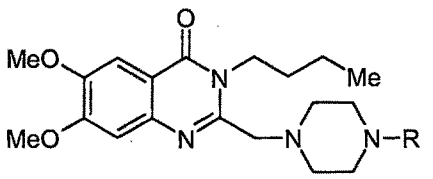


(IV) n = 0, 1 **(V)**

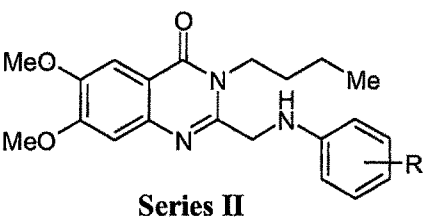
The synthesized compounds were evaluated for *in vivo* blockade of pressor response of phenylephrine (α_1) and ang II in rat model. To our astonishment, almost all of the synthesized compounds showed significantly good blockade of responses of both of the agonists. But, unfortunately, majority of these compounds showed poor aqueous solubility which could be because of their neutral character.

As all of the above evaluated compounds had 6,7-dimethoxyquinazoline motif, we got suspicious of the existence of the dual α_1 and AT_1 inhibiting activity even in a drug like prazosin, a well documented α_1 inhibitors. When prazosin was evaluated for its AT_1 antagonistic activity, it showed high AT_1 antagonistic activity. However, losartan, a clinically used AT_1 antagonist did not show any α_1 antagonistic activity.[369]

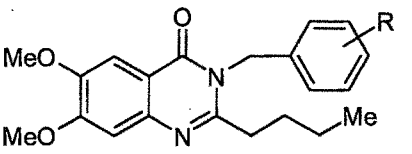
Encouraged by these results, it was planned by this investigation to synthesize compounds which could have better aqueous solubility and more structural variations. The following six series of compounds were aimed to be synthesized and their biological activity evaluated:



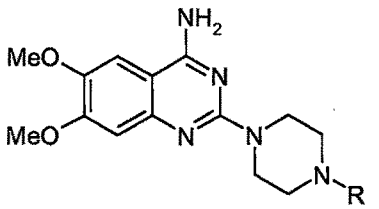
Series I



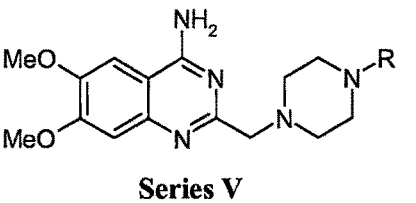
Series II



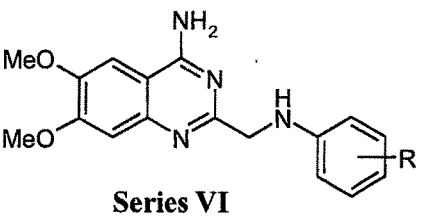
Series III



Series IV



Series V



Series VI