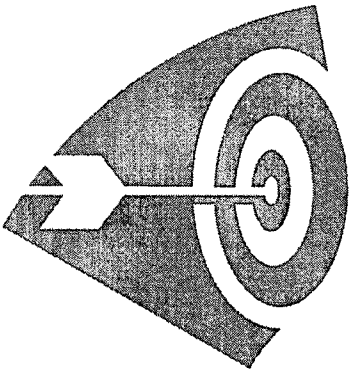
CHAPTER-2



Research Envisaged

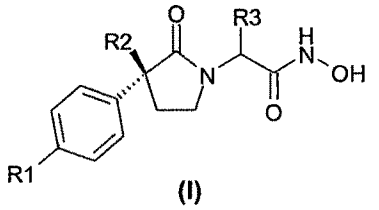
2 RESEARCH ENVISAGED

Arthritis, a life style disease, was once considered to be the disease of Western countries. With growing affluence more and more people are falling prey to this disease in India as well. Though arthritis does not cause morbidity, it severely affects the quality of life of the patient[4]. Researchers till date could not identify the exact cause of the disease, but there are enough evidences to show that arthritis is an autoimmune disease. For a long time, there was no cure for this disease. All the drugs treated the disease symptomatically; none of them cured the underlying causes of the disease. It was proved beyond doubt that TNF-α plays a pivotal role in the origin and progression of the disease[26,27]. Scientists all over the world have been trying to develop TNF-α inhibitors, and they have been successful in developing TNF-α-targeted biological agents (TNF-α antibody and TNF receptor) that proved to be effective in treating the disease[40]. Although these agents are used successfully in treating the disease, a small molecular weight, orally bioavailable TNF inhibitor as a drug has been sought after due to obvious reasons[41]. One of the ways of excluding TNF--α from the biological system is to block TACE, the enzyme responsible for maturation of inactive form of TNF[42].

So far, most of the clinical interest in TACE has remained concentrated on arthritis, but recently reported preclinical studies in a variety of tumor model systems have revealed that inhibition of TACE also inhibits pathogenic EGFR signaling in cancer. Hence it was speculated that TACE inhibitors might cure cancer as well[141].

As is evident from the literature survey, MMP inhibitors possess some degree of TACE inhibitory activity and vice-versa. Although the optimal MMP activity profile of a TACE inhibitor in the treatment of RA remains unknown[73,74], it is desirable to develop selective TACE inhibitors which are devoid of MMP activity[41]. It was envisaged in this project to develop potential selective TACE inhibitors.

It became evident from the survey of literature that γ-lactamhydroxamates (I) are the most potent and selective TACE inhibitors. Two compounds of the series

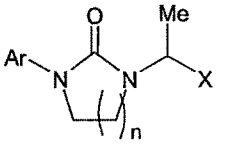


(I)

namely, IK-682 (33I) and BMS-561392 (35I) have shown high binding for TACE in molecular modeling studies. These compounds have also shown high selectivity for TACE over a number of MMPs[75, 112].

In order to identify the structural requirements of γ-lactamhydroxamates as selective TACE inhibitors, molecular modeling studies have been performed. These studies revealed four binding grouping in this series of compounds[140]:

1. The aromatic moiety occupies the S1' site of the enzyme. The choice of aromatic moiety is of prime importance as this not only is responsible for the selectivity over MMPs but can also be modified suitably so that the compound can be active *in vivo*,
2. The oxygen atom of the pyrrolidinone ring forms a hydrogen bond with Leu348 and Gly349,
3. The methyl group of IK-682 (33I) and the isobutyl group of BMS-561392 (35I) occupy the small hydrophobic pocket known as S2', and
4. The hydroxamic acid forms a stable five membered ring with the zinc atom, present in the catalytic site of the enzyme.



(II)

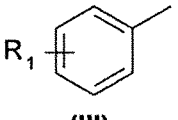
n = 1, 2

X = -CONHOH

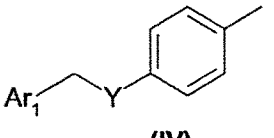
-COOH

$-CH_2SH$

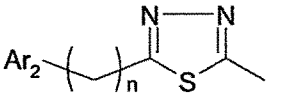
Ar



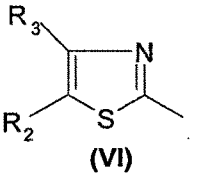
(III)



(IV)



(V)



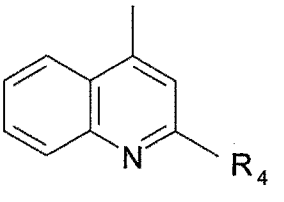
(VI)

Taking the above discussed four TACE binding groups of γ-lactamhydroxamates into consideration, it was planned to replace the asymmetric carbon of γ-lactam with achiral nitrogen to offer imidazolidinone ring structure in the designed compounds (II; n = 1). This change would not only remove the asymmetric environment but would also change the overall electron density in the ring. For the

aryl group it was thought of having substituted phenyl (**III**), substituted phenyl ether/thioether (**IV**), 1,3,4-thiadiazole (**V**) or 1,3-thiazole rings (**VI**).

It is known that S1' site of TACE is larger than that of MMPs and this fact has been exploited in designing of selective TACE inhibitors[65,75-77]. It was planned to incorporate large aromatic moieties for the group 'Ar' to increase selectivity for TACE over MMPs.

During the development of IK-682 (**33I**) and BMS-561392 (**35I**) it was observed that inclusion of 4-quinolinyl group for the substituent 'Ar_1' not only enhanced selectivity of the compounds for TACE but also improved their potency. Hence some of the compounds were designed to have 4-quinolinyl (**VII**) for the 'Ar_1' grouping. The R_4 group was incorporated in the quinolinyl moiety to observe the effect



(VII)

of bulk size in this position.

In order to see the effect of ring size, six-membered ring (**II; n = 2**) was also incorporated in place of five-membered imidazolidinone ring. For binding to the S2' site of TACE, methyl group of IK-682 (**33I**) was retained in the designed compounds.

A zinc binding motif was required in the designed molecules as group 'X'. The most effective zinc binding motif known till date is hydroxamate. Hence, it was envisaged to incorporate hydroxamic acid in the designed molecules. In some of the compounds hydroxamic acid was replaced with thiol, as thiol is also a strong ligand for zinc ions and hydroxamates have reports of poor bioavailability of the molecules. Hydroxamates have also been reported to pose toxicity problems due to their conversion to toxic hydroxylamine[125]. Thiol grouping can offer an additional advantage of higher selectivity for the enzyme, TACE[138,139]. Although carboxylate is not that good a ligand for zinc ions but due to its non-controversial nature it was thought of retaining this grouping in some of the molecules.

It was envisaged to synthesize the above designed compounds and to evaluate them biologically for their enzyme binding affinity for TACE through *in vitro* studies.

The work carried out in the direction of achieving the proposed targets has been discussed under the 'Results and Discussion' section.