Bioorganic & Medicinal Chemistry 17 (2009) 3604–3617

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Studies on novel 2-imidazolidinones and tetrahydropyrimidin-2(1*H*)-ones as potential TACE inhibitors: Design, synthesis, molecular modeling, and preliminary biological evaluation

Shirshendu DasGupta, Prashant R. Murumkar, Rajani Giridhar, Mange Ram Yadav *

Pharmacy Department, Faculty of Technology and Engineering, Kalabhavan, The M. S. University of Baroda, Vadodara 390 001, Gujarat, India

ARTICLE INFO

Article history:
Received 14 January 2009
Revised 31 March 2009
Accepted 1 April 2009
Available online 8 April 2009

Keywords:
2-Imidazolidinones
Tetrahydropyrimidin-2(1*H*)-ones
TACE
TACE inhibitors
Molecular modeling

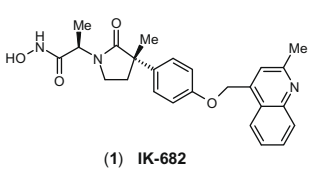
ABSTRACT

Compounds belonging to the class of 2-imidazolidinones and tetrahydropyrimidin-2(1*H*)-ones were synthesized and evaluated for their TACE inhibitory activity. Most of the compounds showed very good TACE inhibitory activity. Docking study clearly indicates importance of the P1′ group of the inhibitor for the TACE inhibitory activity. This work proves that these two classes of molecules could be used as potential leads for the development of TACE inhibitors.

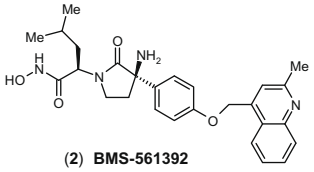
1. Introduction

Tumor Necrosis Factor (TNF)-α is a pleitropic, pro-inflammatory cytokine produced by monocytes, macrophages, neutrophils, T cells, mast cells, epithelial cells, osteoblasts, and dendritic cells.[1,2] Over expression of TNF-α is responsible for a number of pathological conditions such as Crohn's disease, ulcerative colitis,[3] diabetes,[4] multiple sclerosis,[5] and atherosclerosis.[6] In addition to this, there are compelling data to support the fact that TNF-α plays a pivotal role in the origin and progression of Rheumatoid Arthritis (RA) and other immune-mediated disorders.[7–13] It has been hypothesized that orally bioavailable small molecule TACE inhibitors would have the potential to effectively treat RA by limiting the levels of soluble TNF-α.[3,14] It has also been demonstrated that inhibition of TACE by small molecular weight orally bioavailable drugs would be more effective than the biological agents in blocking downstream cytokine production.[15] Based on this hypothesis, several research groups world-wide are actively pursuing for orally bioavailable small size TACE inhibitors.[16] Recently, Kenny et al. have shown that TACE inhibitors might be useful for treating certain types of cancers.[17,18]

Work is in progress in this laboratory on designing and synthesis of novel potential TACE inhibitors.[19,20] It became evident from survey of the literature that IK-682 (1) and BMS-561392 (2) the two γ-lactamhydroxamates, are potent and selective TACE inhibitors.



(1) IK-682



(2) BMS-561392

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 groups in this series of compounds:[21,22]

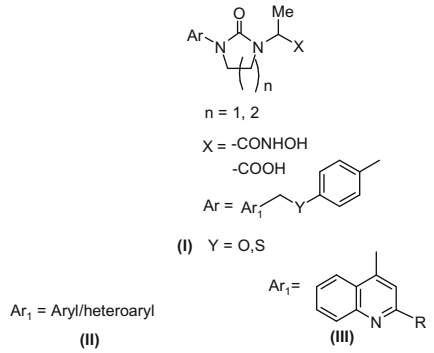
1. The aromatic moiety, that is, quinoline nucleus here, occupies the S1′ site of the enzyme. The choice of aromatic moiety is of prime importance as this is not only responsible for the selectivity over MMPs but can also be modified suitably so that the compound can become active in vivo,
2. The oxygen atom of the pyrrolidinone ring forms hydrogen bonds with Leu348 and Gly349,
3. The methyl group of IK-682 (**1**) and the isobutyl group of BMS-561392 (**2**) 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.

Taking the above-described 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

* Corresponding author. Tel.: +91 02645 2434187; fax: +91 0265 2418927.
E-mail address: mryadav11@yahoo.co.in (M.R. Yadav).

0968-0896/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2009.04.003

imidazolidinone ring structure in the designed compounds (**I**; n = 1). This change would not only remove the asymmetric environment but could also change the overall electron density in the ring. For the aryl group it was thought of having aryl/heteroaryl-substituted phenyl ether/thioether (**II**).



It has been reported that during the development of IK-682 (**1**) and BMS-561392 (**2**) inclusion of 4-quinolinyl group for the substituent 'Ar_1' not only enhanced selectivity of the compounds for TACE but also improved their potency.[19] Hence, it was decided to incorporate 4-quinolinyl moiety (**III**) in some of the compounds for the 'Ar_1' group. The R group was varied in the quinolinyl moiety to observe the effect of size of substituents in this position.

In order to see the effect of ring size, six-membered ring (**I**; 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 (**1**) 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, although hydroxamates have been reported to pose toxicity problems due to their conversion to toxic hydroxylamine. Though 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.

2. Results and discussions

2.1. Chemistry

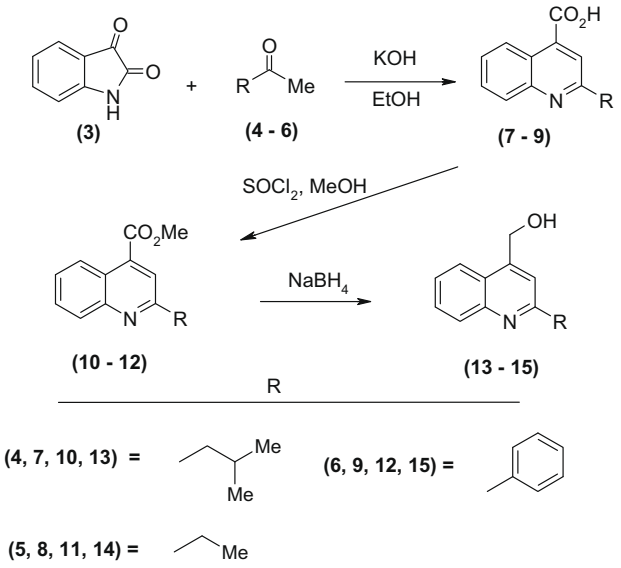
In order to synthesize the proposed molecules, various arylamines and isocyanates were required as the starting chemicals or intermediates. Some of the amines were available commercially while others were synthesized in the laboratory. Considering the instability of isocyanates (**B**), these were prepared afresh whenever required.

2.1.1. Synthesis of arylamines

The arylamines used for reacting isocyanates were ether/thioether-substituted arylamines. Their preparation involved the synthesis of different intermediates which are discussed under different headings.

The 2-substituted quinolin-4-yl-methanols (**13**–**15**) synthesized from isatin (**3**) in a three-step process is depicted in Scheme 1. In the first step, isatin was reacted with ketones (**4**–**6**) in the presence of a strong base like potassium hydroxide in ethanol to form 2-substituted quinoline-4-carboxylic acid as per the reported procedure.[23] These acids (**7**–**9**) were converted to esters (**10**–**12**) and the esters were reduced to obtain the desired 2-substituted quinolin-4-yl-methanols (**13**–**15**).

For the synthesis of required arylamines, the alcohols [synthesized as shown in Scheme 1 (**13**–**15**) and alcohols available



Scheme 1.

commercially (**16**–**19**)] were converted into chloro derivatives (**20**–**26**) (Scheme 2) by thionyl chloride treatment in excellent yields (more than 85%). Conversion of the alcohols into the chloro derivatives was monitored by TLC and the products so obtained were used as such for next step without characterization. The chloro compounds (**20**–**26**) were then reacted with 4-nitrophenol (**27**) in the presence of anhydrous potassium carbonate in DMF at 80–90 °C to prepare the nitro derivatives (**28**–**34**). These nitro compounds (**28**–**34**) were then treated with iron and aqueous sodium chloride in methanol to obtain the desired ether-substituted amino compounds (**35**–**41**) as per Scheme 2. This reaction took around 11–13 h to complete for all of the compounds. This was a longer time than expected, probably due to the poor solubility of the nitro compounds in methanol.

2.1.2. Synthesis of thioether substituted phenylamine

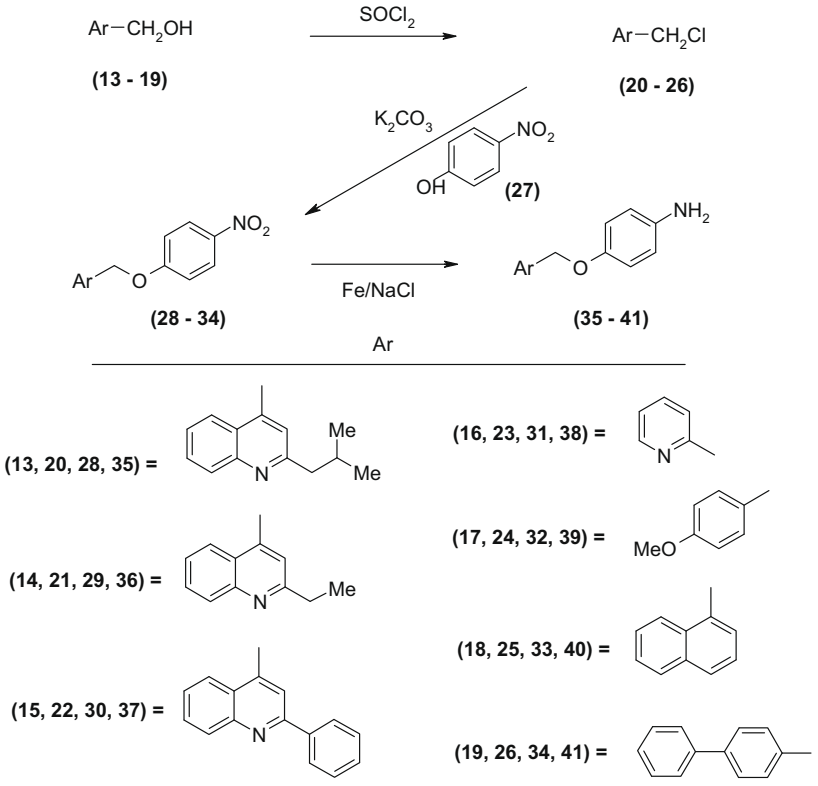
1-(4-Aminothiophenoxymethyl)-4-methoxybenzene (**43**) was synthesized from 4-methoxybenzyl chloride (**17**) and 4-aminothiophenol (**42**) in the presence of potassium carbonate as base as per Scheme 3. The isolated compound was purified by column chromatography on neutral alumina.

2.1.3. Synthesis of isocyanates

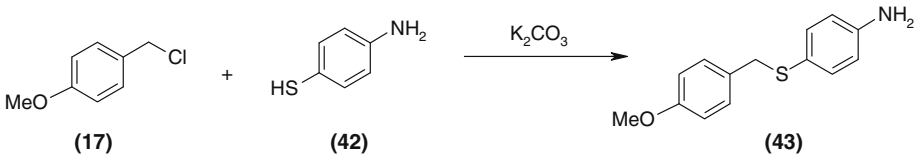
Isocyanates (**46**) were prepared in a two-step process[24] according to Scheme 4. The isocyanates are unstable at rt, sensitive to light and moisture, and lachrymatory in nature. Hence, no efforts were made to isolate or purify isocyanates (**46**). These isocyanates were prepared afresh and used immediately for the next step. It was observed that even if stored in a tightly closed amber colored vial at −5 °C, they were unsuitable for synthetic purposes after a week. The toluene solutions of isocynates were used for further reactions in the next step. It was assumed that the yields of isocyanates were quantitative for the calculation purposes.

2.1.4. Synthesis of target compounds (I)

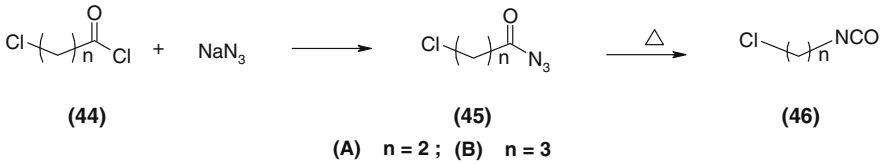
The aromatic amines [prepared as shown in Schemes 2 and 3 (**35**–**41**, **43**) and those available commercially (**47**, **48**)] were converted to 2-imidazolidinone derivatives (**60**–**69**) via urea derivatives (**49**–**59**) by reported method.[25,26] In the next step, 2-imidazolidinone derivatives (**60**–**69**) were converted to ester derivatives (**70**–**79**) using ethyl 2-bromopropionate in the presence of sodium hydride. In order to have zinc binding ligands in



Scheme 2.



Scheme 3.



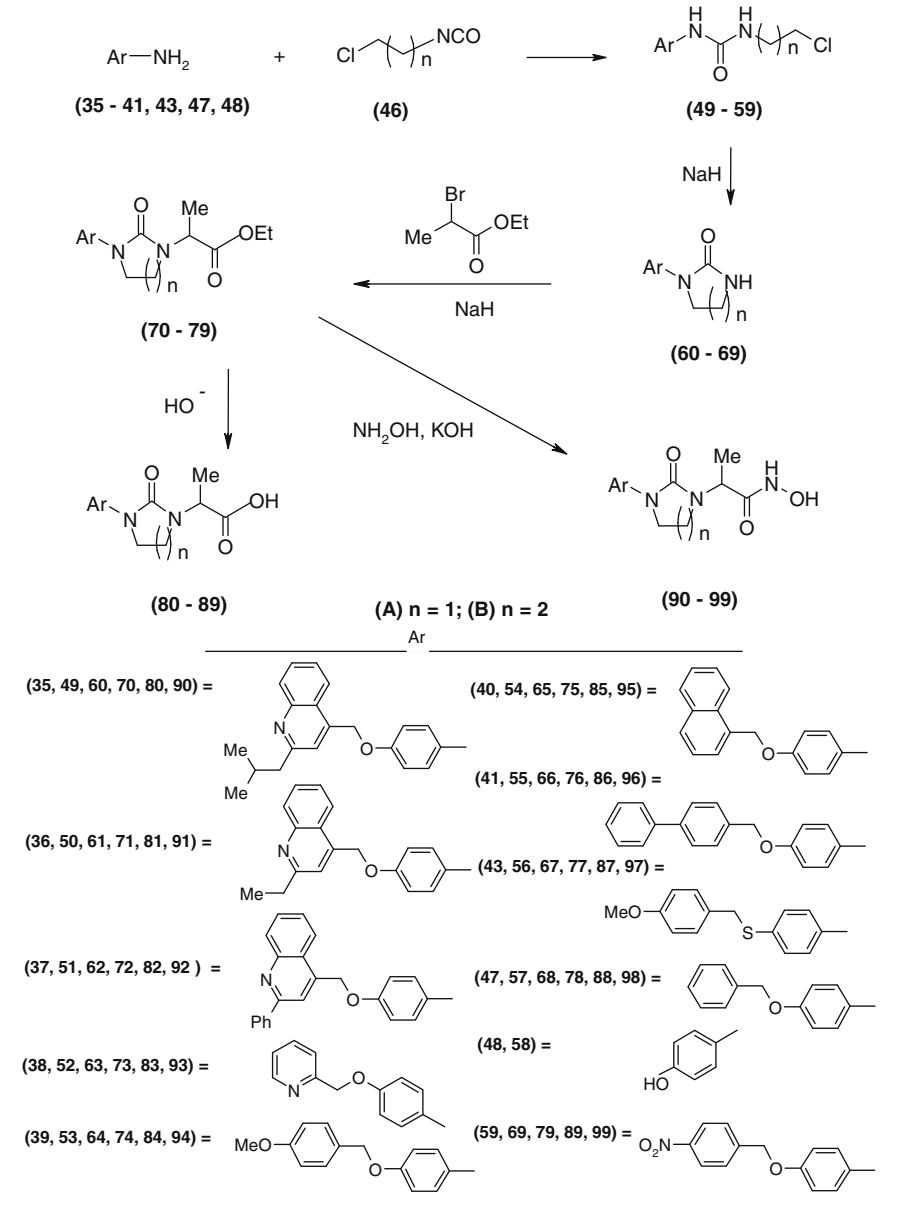
Scheme 4.

the targeted molecules, it was proposed to prepare carboxylic acid derivatives. To achieve this, esters (**70**–**79**) were hydrolyzed in basic medium to prepare the corresponding acids (**80**–**89**). Lithium hydroxide or sodium hydroxide was used as the base in aqueous medium in this reaction. To prepare hydroxamates (**90**–**99**) as zinc binding ligands esters (**70**–**79**) were reacted with hydroxylamine hydrochloride in basic conditions. The synthesis of the target compounds is shown in Scheme 5. As shown in Scheme 6, compound (**58A**) is treated with 4-nitrobenzyl bromide (**100**) in the presence of potassium carbonate in DMF to provide compound (**59A**).

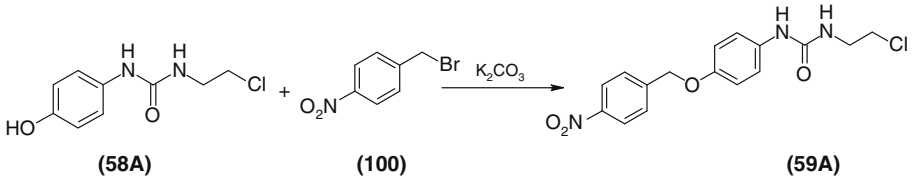
2.2. Biological activity and molecular modeling studies

In vitro biological studies were performed to evaluate the TACE inhibitory activities of the synthesized final compounds. Human monocytic acute leukemia (THP-1) cells were used for expressing TNF converting enzyme. The cells were grown and cell lysate was prepared according to the reported procedure.[27] This cell lysate was stored at −70 °C and was used as the source of TACE in the enzyme inhibition studies as and when required in a span of seven days.

To assess the TACE inhibitory activity of the synthesized compounds, InnozymeTM TACE activity ELISA kit was procured from Calbiochem, USA (Catalog No. CBA042). The method followed for the assay was as given in the protocol supplied by the manufacturer.[28] The kit contained 96-well plate and the wells were precoated with a monoclonal antibody specific for human TACE that captured the enzyme from the cell lysate. The diluted cell lysate was added to the wells and incubated for 1 h at 25 °C. After the enzyme was attached to the antibody, the wells were washed to discard the unbound enzyme, and inhibitors (synthesized compounds dissolved in DMSO) were added to the designated wells.



Scheme 5.



Scheme 6.

In one of the wells no inhibitor was added, which was regarded as blank and in one of the wells TAPI-1, a well known TACE inhibitor, was added. The wells were again incubated for 2 h at 25 °C. In the presence of an inhibitor, the enzyme would bind to it leading to a decreased concentration of the free enzyme. Upon addition of an internal fluorescent substrate (MCA-KPLGL-Dpa-AR-NH_2), the free enzyme would cleave the scissile amide bond of the substrate. Fluorescence intensity of the cleaved product, MCA-KPLG was measured at an excitation wavelength of 355 nm and emission wavelength of 405 nm. The fluorescence intensity is indirectly related to the inhibitory activity of the test compounds. The inhibitory activity of a test compound in a particular concentration was calculated from the following equation:

$$\%\text{Inhibition} = [1 - (\text{Fluorescence intensity of test} / \text{Fluorescence intensity of blank})] \times 100$$

Table 1
Activity of the compounds along with their docking score

Sr. No.	Compound ID	G-Score		% Inhibition at 0.1 μM/L*
		R-Isomer	*S*-Isomer	
1	80A	−7.75	−7.79	47
2	80B	−8.98	−7.67	20
3	81A	−8.48	−8.13	49
4	82A	−6.67	−6.83	30
5	82B	−5.43	−5.72	31
6	83A	−7.08	−7.08	28
7	83B	−8.53	−8.52	35
8	86A	−7.84	−7.52	30
9	86B	−7.25	−7.41	28
10	87A	−7.36	−9.97	40
11	90A	−10.01	−8.35	60
12	91A	−10.83	−12.51	62
13	91B	−7.56	−9.54	34
14	93A	−12.65	−11.85	50
15	93B	−10.47	−8.28	37
16	94A	−11.10	−12.31	38
17	94B	−8.76	−8.27	18
18	95A	−8.64	−7.99	36
19	95B	−11.13	−8.82	40
20	97A	−9.29	−9.97	42
21	98A	−9.49	−9.26	39
22	98B	−10.35	−8.42	28
23	99A	−12.04	−9.32	40
24	TAPI-1	−8.89		28
25	IK-682	−9.39		—

* Each value is an average of three determinations, and the standard errors for all determinations are less than 10%.

The blank well contains solvent (DMSO) and the substrate.

The TACE inhibitory activity of only some of the selected compounds was performed and the data are given in Table 1. TAPI-1, a well-known inhibitor of TACE and MMP,[29] was used as the positive control in the study.

From the activity data, the structure-activity relationship of this series of compounds has been derived. It was noted that the five-membered 2-imidazolidinone ring was more favored in the central part of the molecule rather than the six-membered tetrahydropyrimidin-2(1*H*)-one ring. TACE inhibition was found to be 62% for compound (**91A**) at 0.1 μM concentration while the inhibition was only 34% for compound (**91B**) in the same concentration. Similarly, TACE inhibition was found out to be 47% for compound (**80A**) and it was only 20% for compound (**80B**). In the same manner, compound (**93A**) showed an inhibition of 50% while compound (**93B**) showed 37%. The same observation was noted for compounds (**94A**) and (**94B**) as well. Compound (**94A**) showed an inhibition of 38% in comparison to compound (**94B**) which showed only 18% inhibition. Compounds (**98A**) and (**98B**) showed 39% and 28% inhibition of TACE, respectively, at 0.1 μM concentration.

Compound (**83B**) bearing carboxylic acid as the zinc binding group shows activity in the same range in comparison to compound (**93B**) at 0.1 μM concentration (35% and 37%, respectively). Compound (**87A**) having carboxylate moiety shows 40% inhibition of the enzyme, while compound (**97A**) having hydroxamate moiety shows 42% inhibition at 0.1 μM concentration. In these cases, it was observed that the hydroxamates were marginally more active than the corresponding carboxylates. Compound (**83A**) bearing carboxylate moiety showed 28% inhibition at 0.1 μM concentration while compound (**93A**), having hydroxamate moiety showed 50% inhibition in the same concentration. Similarly, it was noted from the activities of compounds (**81A**) and (**91A**) that the hydroxamates were more active than carboxylates (49% and 62% inhibition, respectively). The same observation was also made from the activities of compounds (**80A**) and (**90A**) (TACE inhibitory activities were 47% and 60%, respectively). From these observations, it could be concluded that although compounds bearing carboxylates as the zinc binding groups are active, hydroxamate has higher inhibitory activity over the previous carboxylate moiety.

Compound (**97A**) having thioether linkage at P1′ position is more active than compound (**94A**) bearing ether linkage in the same position, at 0.1 μM concentration (42% inhibition by **97A** in comparison to 38% inhibition by **94A**). Both the compounds have same structures except for this change. This fact might be considered while designing new TACE inhibitors in future.

The overall activity pattern of the compounds clearly shows that heterocyclic quinolinyl or pyridinyl rings at P1′ position is a preferred ring system than simple phenyl or substituted phenyl rings. It has also been indicated from the above activity data that ethyl group is the group of choice at 2-position of quinolinyl ring. The phenyl ring at this position is not favored from the SAR point-of-view. From the compounds tested, **91A** has shown the highest activity (62% inhibition). Compound (**90A**) which has shown 60% inhibition of TACE is also a very promising compound.

All the synthesized compounds were energy minimized and docked in the active site of human TACE. Binding interactions of only a few are discussed here. As all the synthesized compounds are racemic mixtures, docking study was carried out for both the isomers. Binding score differences between *R* and *S* isomers were found to be marginal for majority of the docked compounds. However, most of the compounds having *R*-configuration showed better G-score than *S*-isomers (Table 1). In compound IK-682, *R*-isomer is also the active form. Compound **93A** is the highest ranked compound with *R*-isomer, whereas compound **91A** with *S*-isomer showed higher binding score (G-score −12.51) (Table 1). During the binding studies it was observed that the conformation of methyl group in the side chain in the molecules of both the series changes as the aryl/heteroaryl substituents are varied. The binding interaction of 2-{3-[4-(2-ethyl-4-quinolinylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}-*N*-hydroxypropionamide (**91A**, 62% TACE inhibitory activity) was studied within the TACE binding site by docking studies. P1′ group of 91A (2-ethyl-4-quinolinyl)methoxy is oriented toward larger S1′ pocket of the TACE (Fig. 1) interacting with active site (Glu398, Leu348, Leu350, Ala439, Val440, Lys432, and Leu401). Central phenyl ring interacts with His405, Tyr436 as shown in Figure 2A. Catalytic zinc bonds with oxygen of NHOH group along with carbonyl group of imidazolidin ring. Glu406 and Leu348 residues interact with methylene group of imidazolidin ring. Carbonyl group of CONHOH bonds with the His405 and Leu350. This interaction study clearly reveals that compound **91A** perfectly interacts with the catalytic active site and also P1′ group orients toward S1′ pocket giving excellent TACE inhibitory activity along with best docking score (Gscore −12.51) (Table 1). Binding

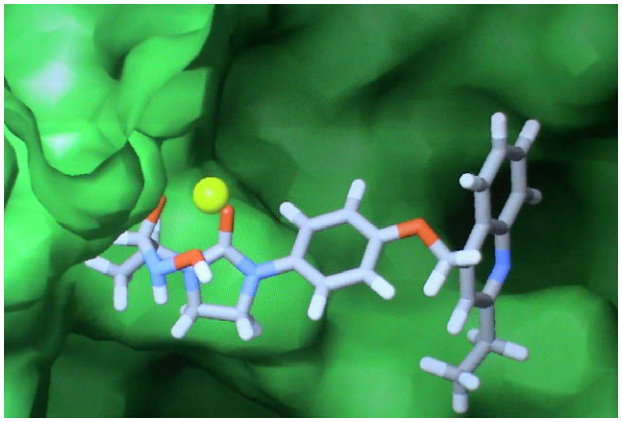


Figure 1. Positioning of the P1′ group of compound (ball and stick) 2-{3-[4-(2-ethyl-4-quinolinylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}-*N*-hydroxypropionamide (**91A**) in the active site of TACE.

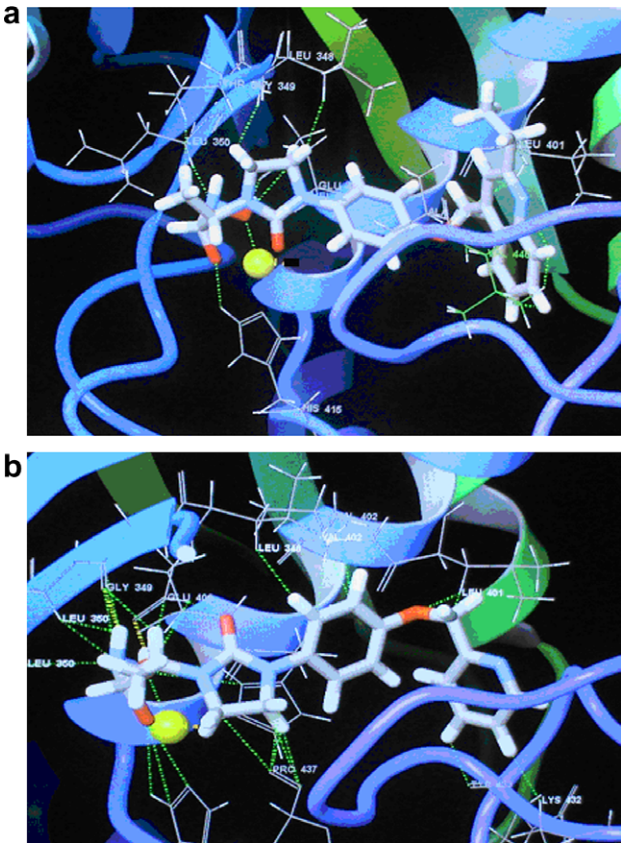


Figure 2. Docking of compounds (ball and stick) in the active site of TACE (a) 2-{3-[4-(2-ethyl-4-quinolinylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}-*N*-hydroxypropionamide (**91A**) and (b) *N*-hydroxy-2-{2-oxo-3-[4-(2-pyridinylmethoxy) phenyl]-1-imidazolidinyl}propionamide (**93A**). Interactions are shown as dashed lines and zinc is shown in yellow color.

mode of *N*-hydroxy-2-{2-oxo-3-[4-(2-pyridinylmethoxy)phenyl]-1-imidazolidinyl}propionamide (**93A**, 50% TACE inhibitory activity) was also examined (Fig. 2b). Leu401, Lys432, and Tyr433 residues interact with pyridinylmethoxy as shown in Figure 2b. Central phenyl ring interacts with Leu348 and Val402 residues. Imidazolidin ring is engaged with Glu406 residue through interaction with oxygen of carbonyl group and both the methylene groups interact with Pro437 residue. Oxygen of the NHOH group interacts with His405 and Glu406 residues along with the zinc. Nitrogen of NHOH is engaged with His415, Gly349, and Leu350 residues as shown in Figure 2b. Thus, compound **93A interacts** with all the amino acid residues which are the part of the active sites such as Zn, Glu406, Leu350, Gly439, His405, His415, Leu348, and Lys432. This might be a reason for showing good inhibitory activity and having highest ranked Glide score (−12.65) (Table 1).

From the interaction study of compound (**83A**) (Fig. 3), it is observed that the carboxylate end of the compound interacts with TACE almost in a similar manner as the hydroxamate groups of compound (**91A**, **93A**). But the P1′ group of the molecule interacts with Leu401 only. No other part of the compound interacts with the active site residues of S1′ site of TACE, unlike compound (**91A**, **93A**). Moreover, the orientation of P1′ group of (**83A**) is not aligned toward the S1′ pocket of the enzyme (Fig. 3). This might explain the poor docking score as well as biological activity of (**83A**). This proves that the orientation of the P1′ group is one of the most important factors for the biological activity of TACE inhibitors, particularly in imidazolidin-2-ones and tetrahydropyrimidin-2(1*H*)-ones scaffold-containing compounds. For all the compounds docking score was found to be in good correlation with the biological activity data.

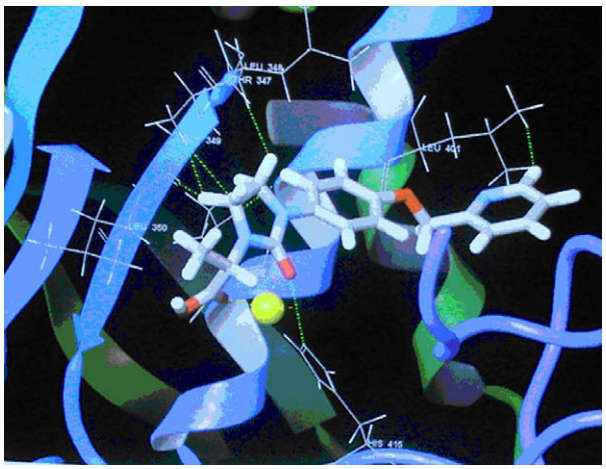


Figure 3. Docking of compound **83A** (ball and stick) in the active site of TACE.

3. Experimental

3.1. Chemistry

3.1.1. General procedure for the synthesis of 2-substituted quinolin-4-carboxylic acids (11–13)

Isatin (**3**) (13 mmol) was suspended in ethanol (9 mL). Potassium hydroxide (65 mmol) was added to the above suspension and stirred for 5 min. Ketones (**4**–**6**) (26 mmol) were added to the above mixture and the reaction mixture was placed in a microwave reactor with the given conditions (Power, 300 W; Temp., 100 °C; run time, 1.00 min; hold time, 5.00 min; stirrer speed, high). After the reaction was over, the reaction mixture was removed from the reactor and ethanol was completely removed from the reaction mixture under vacuum. The semi-solid mass thus obtained was dissolved in ice-water (20 mL). The aqueous layer was acidified with concd HCl up to pH 4. The precipitated material was filtered and dried in oven. The crude product thus obtained was purified by crystallization from methanol to afford off-white solid.

3.1.1.1. 2-Isobutylquinoline-4-carboxylic acid (7). Yield: 42.0%, R_f = 0.60 (50% EtOAc in *n*-hexane), mp 188–189 °C. (Lit.[23] 187–189 °C).

3.1.1.2. 2-Ethylquinoline-4-carboxylic acid (8). Yield: 62.2%, R_f = 0.51 (50% EtOAc in *n*-hexane), mp 225–227 °C, IR (KBr, cm^{-1}): 3412, 1660, 1610, 1315, 1238, 854, 769, PMR (DMSO-d_6): δ 7.93–7.95 (m, 1H), 7.76–7.78 (m, 1H), 7.64–7.68 (m, 1H), 7.51–7.55 (m, 2H), 3.01–3.04 (q, 2H, J = 7.72 Hz), 1.37–1.41 (t, 3H, J = 7.62 Hz).

3.1.1.3. 2-Phenylquinoline-4-carboxylic acid (9). Yield: 64.4%, R_f = 0.18 (30% EtOAc in *n*-hexane), mp 209–210 °C (Lit.[23] 210–12 °C).

3.1.2. General procedure for the synthesis of methyl 2-substituted quinolin-4-carboxylate (10–12)

2-Substituted quinoline-4-carboxylic acids (**7**–**9**) (5.4 mmol) were dissolved in methanol (10 mL) and cooled to 0–5 °C. Thionyl chloride (8.2 mmol) was added drop-wise to the above solution under stirring. After the addition was over, the reaction mixture was refluxed for 2 h. Excess methanol and thionyl chloride were removed from the reaction mixture, which was poured into saturated solution of sodium bicarbonate (50 mL). The aqueous layer was extracted with chloroform (3 × 20 mL); the combined organic layer was dried over anhydrous sodium sulfate and recovered to get the title compound as off-white solid (0.97 g, 74.2%). Mp 46–48 °C.

3.1.2.1. Methyl 2-isobutylquinoline-4-carboxylate (10). Yield: 74.2%, R_f = 0.82 (30% EtOAc in *n*-hexane), mp 46–48 °C, IR (KBr, cm^{-1}): 2956, 1724, 1591, 1508, 1433, 1246, 1147, 1022, 800.

3.1.2.2. Methyl 2-ethylquinoline-4-carboxylate (11). Yield: 65.9%, R_f = 0.52 (30% EtOAc in *n*-hexane).

3.1.2.3. Methyl 2-phenylquinoline-4-carboxylate (12). Yield: 84.9%, R_f = 0.79 (30% EtOAc in *n*-hexane), mp 68–70 °C, PMR ($CDCl_3$): δ 8.73–8.75 (m, 1H), 8.40 (s, 1H), 8.18–8.23 (m, 3H), 7.74–7.78 (m, 1H), 7.59–7.64 (m, 1H), 7.50–7.56 (m, 2H), 7.46–7.49 (m, 1H), 4.06 (s, 3H).

3.1.3. General procedure for the synthesis of methyl 2-substituted quinolin-4-methanol (13–15)

Methyl 2-substituted quinoline-4-carboxylates (**10**–**12**) (2.1 mmol) were dissolved in methanol (15 mL) and cooled to 0–5 °C. Sodium borohydride (21 mmol) was added in fractions to the above solution under stirring in such a manner that the temperature of the reaction mixture did not rise above 10 °C. The reaction mixture was stirred overnight at rt (about 35 °C). Methanol was recovered from the reaction mixture and cold water (10 mL) was added to it. The solid so precipitated was filtered and dried to get the desired compound as white solid.

3.1.3.1. 4-Hydroxymethyl-2-isobutylquinoline (13). Yield: 99.7%, R_f = 0.27 (30% EtOAc in *n*-hexane), mp 85–88 °C, PMR ($CDCl_3$): δ 8.06–8.09 (m, 1H), 7.89–7.91 (m, 1H), 7.64–7.66 (m, 1H), 7.47–7.51 (m, 1H), 7.41 (s, 1H), 5.20 (s, 2H), 2.80–2.82 (d, 2H), 2.16–2.23 (m, 1H), 0.94–0.96 (d, 6H).

3.1.3.2. 2-Ethyl-4-hydroxymethylquinoline (14). Yield: 93.8%, R_f = 0.15 (50% EtOAc in *n*-hexane), mp 113–114 °C, IR (KBr, cm^{-1}): 3124, 2968, 1604, 1566, 1446, 1134, 1089, 883, 754, PMR ($CDCl_3$): δ 8.06–8.08 (m, 1H), 7.89–7.91 (m, 1H), 7.66–7.70 (m, 1H), 7.52–7.58 (m, 1H), 7.46 (s, 1H), 5.21 (s, 2H), 2.96–3.02 (q, 2H, J = 7.64 Hz), 1.37–1.41 (t, 3H, J = 7.66 Hz).

3.1.3.3. 4-Hydroxymethyl-2-phenylquinoline (15). Yield: 93.2%, R_f = 0.65 (30% EtOAc in *n*-hexane), mp 102–104 °C, PMR ($CDCl_3$): δ 8.17–8.21 (m, 3H), 8.10 (s, 1H), 7.95–7.97 (m, 1H), 7.69–7.74 (m, 1H), 7.50–7.56 (m, 3H), 7.43–7.48 (m, 1H), 5.21 (s, 2H), 4.90 (br s, 1H).

3.1.4. General procedure for the synthesis of 1-aryl chloromethanol (20–26)

1-Aryl methanols (**13**–**19**) (28.5 mmol) were dissolved in dry chloroform (20 mL) and cooled to 5 °C. Thionyl chloride (42.8 mmol) was added to this solution at such a rate that the temperature of the reaction mixture did not rise above 10 °C. After the addition was over, the temperature of the reaction mixture was allowed to rise to rt (30 °C) and stirred further for about 30 min. The reaction mixture was basified to pH 8 by slow and careful addition of saturated sodium bicarbonate solution, extracted with chloroform (3 × 30 mL); the combined organic layer was washed with water (3 × 20 mL), dried over anhydrous sodium sulfate, and the solvent removed to get the title product as an oil (3.8 g, 85.2%).

3.1.4.1. 4-Chloromethyl-2-isobutylquinoline (20). Yield: 71.4%, R_f = 0.83 (30% EtOAc in *n*-hexane).

3.1.4.2. 4-Chloromethyl-2-ethylquinoline (21). Yield: 96.1%, R_f = 0.53 (30% EtOAc in *n*-hexane).

3.1.4.3. 4-Chloromethyl-2-phenylquinoline (22). Yield: 92.9%, R_f = 0.84 (30% EtOAc in *n*-hexane), mp 82–85 °C.

3.1.4.4. 2-Chloromethylpyridine (23). Yield: 90.9%, R_f = 0.77 (30% EtOAc in *n*-hexane).

3.1.4.5. 4-Methoxybenzyl chloride (24). Yield: 85.2%, R_f = 0.60 (30% EtOAc in *n*-hexane).

3.1.4.6. 1-Chloromethylnapthalene (25). Yield: 98.4%, R_f = 0.62 (10% EtOAc in *n*-hexane).

3.1.4.7. 4-Chloromethylbiphenyl (26). Yield: 77.9%, R_f 0.83 (30% EtOAc in *n*-hexane), mp 73–76 °C. (Lit.[30] 71–73 °C).

3.1.5. General procedure for the synthesis of nitro derivatives (28–34)

4-Nitrophenol (**27**) (38 mmol) was dissolved in dry DMF (10.5 mL). Anhydrous potassium carbonate (63 mmol) was added to the above solution under stirring followed by 1-aryl chloromethanol (**20**–**26**) (31.5 mmol). The reaction mixture was heated to 80 °C for 4 h and poured into ice-water (250 mL) under stirring. The solid so separated was filtered and washed with cold methanol (30 mL) to afford pure desired compound as white solids.

3.1.5.1. 2-Isobutyl-4-(4-nitrophenoxymethyl)quinoline (28). Yield: 61.7%, R_f = 0.67 (30% EtOAc in *n*-hexane), mp 95–97 °C, PMR ($CDCl_3$): δ 8.23–8.25 (d, 2H), 8.12–8.14 (m, 1H), 7.90–7.92 (m, 1H), 7.72–7.76 (m, 1H), 7.54–7.58 (m, 1H), 7.38 (s, 1H), 7.10–7.12 (d, 2H), 5.62 (s, 2H), 2.84–2.86 (d, 2H), 2.22–2.28 (m, 1H), 0.95–0.97 (d, 6H).

3.1.5.2. 2-Ethyl-4-(4-nitrophenoxymethyl)quinoline (29). Yield: 55.9%, R_f = 0.56 (30% EtOAc in *n*-hexane), mp 145–148 °C, IR (KBr, cm^{-1}): 1604, 1502, 1446, 1338, 1267, 1172, 1109, 846, 754, PMR (DMSO-d_6): δ 8.23–8.25 (d, 2H, J = 8.84 Hz), 7.98–8.07 (m, 2H), 7.70–7.75 (m, 1H), 7.55–7.59 (m, 1H), 7.50 (s, 1H), 7.21–7.23 (d, 2H, J = 8.88 Hz), 5.67 (s, 2H), 2.98–3.03 (q, 2H, J = 7.51 Hz), 1.37–1.41 (t, 3H, J = 7.50 Hz).

3.1.5.3. 2-Phenyl-4-(4-nitrophenoxymethyl)quinoline (30). Yield: 71.3%, R_f = 0.83 (50% EtOAc in *n*-hexane), mp 155–157 °C, PMR ($CDCl_3$): δ 8.25–8.28 (m, 3H), 8.14–8.16 (m, 2H), 8.00 (s, 1H), 7.95–7.97 (m, 1H), 7.77–7.81 (m, 1H), 7.59–7.61 (m, 1H), 7.48–7.56 (m, 3H), 7.14–7.16 (d, 2H), 5.69 (s, 2H).

3.1.5.4. 2-(4-Nitrophenoxymethyl)pyridine (31). Yield: 54.3%, R_f = 0.43 (30% EtOAc in *n*-hexane), mp 138–140 °C, PMR ($CDCl_3$): δ 8.62–8.63 (m, 1H), 8.19–8.23 (d, 2H), 7.72–7.77 (m, 1H), 7.47–7.49 (m, 1H), 7.26–7.29 (m, 1H), 7.04–7.08 (d, 2H), 5.30 (s, 2H).

3.1.5.5. 1-(4-Nitrophenoxymethyl)-4-methoxybenzene (32). Yield: 87.0%, R_f = 0.53 (30% EtOAc in *n*-hexane), mp 102–104 °C, IR (KBr, cm^{-1}): 2926, 1591, 1516, 1454, 1336, 1249, 1176, 1028.

3.1.5.6. 1-(4-Nitrophenoxymethyl)naphthalene (33). Yield: 99.1%, R_f = 0.68 (30% EtOAc in *n*-hexane), mp 142–145 °C, PMR (DMSO-d_6): δ 8.22–8.24 (d, 2H), 8.01–8.03 (m, 1H), 7.89–7.94 (m, 2H), 7.59–7.63 (m, 1H), 7.48–7.58 (m, 3H), 7.15–7.18 (d, 2H), 5.62 (s, 2H).

3.1.5.7. 4-(4-Nitrophenoxymethyl)biphenyl (34). Yield: 50.3%, R_f = 0.74(30% EtOAc in *n*-hexane), mp 158–160 °C, IR (KBr, cm^{-1}): 3072, 1587, 1512, 1491, 1384, 1338, 1251, 1170, 1109, 955.

3.1.6. General procedure for the synthesis of amino derivatives (35–41)

To the refluxing solutions of nitro derivatives (**28**–**34**) (17.1 mmol) in methanol (700 mL), iron powder (17.1 mmol) and saturated solution of sodium chloride (17.1 mmol) were added every 30 min in fractions. The reaction was complete after 11 h.

The reaction mixture was filtered through filtering aid (hyflosupercel) to remove iron powder. The filtrate so obtained was evaporated under vacuum and saturated sodium bicarbonate solution was added (until the pH was about 8) to the reaction mass. The slurry was extracted with chloroform (4 × 50 mL); the combined organic layer was dried over anhydrous sodium sulfate and the solvent removed to get the desired compound.

3.1.6.1. 4-(2-Isobutyl-4-quinolinylmethoxy)aniline (35). Yield: 80.3%, R_f = 0.28 (30% EtOAc in *n*-hexane), mp 78–80 °C, IR (KBr, cm^{-1}): 3390, 3323, 2955, 1608, 1512, 1232, 1182, 1018, 813, 748.

3.1.6.2. 4-(2-Ethyl-4-quinolinylmethoxy)aniline (36). Yield: 83.2%, R_f = 0.30 (30% EtOAc in *n*-hexane).

3.1.6.3. 4-(2-Phenyl-4-quinolinylmethoxy)aniline (37). Yield: 72.3%, R_f = 0.50 (50% EtOAc in *n*-hexane), mp 128–131 °C, IR (KBr, cm^{-1}): 3423, 3331, 1604, 1514, 1238, 1078, 815, 769.

3.1.6.4. 4-(2-Pyridinylmethoxy)aniline (38). Yield: 76.9%, R_f = 0.27 (50% EtOAc in *n*-hexane).

3.1.6.5. 4-(4-Methoxybenzyloxy)aniline (39). Yield: 100%, R_f = 0.37 (50% EtOAc in *n*-hexane), mp 97–99 °C, IR (KBr, cm^{-1}): 3419, 3346, 3010, 1610, 1510, 1249, 1178, 1028.

3.1.6.6. 1-(4-Aminophenoxymethyl)naphthalene (40). Yield: 97.3%, R_f = 0.23 (30% EtOAc in *n*-hexane), mp 78–81 °C.

3.1.6.7. 4-(4-Aminophenoxymethyl)biphenyl (41). Yield: 96.1%, R_f = 0.53 (50% EtOAc in *n*-hexane), mp 132–135 °C, IR (KBr, cm^{-1}): 3460, 3385, 1240, 1182, 1020, 848.

3.1.7. Preparation of 1-(4-aminothiophenoxymethyl)-4-methoxybenzene (43)

4-Aminothiophenol (**42**) (1.1 g, 8.7 mmol) was dissolved in dry DMF (3 mL). Potassium carbonate (1.2 g, 17 mmol) was added to the above solution under stirring followed by 4-methoxybenzyl chloride (**17**) (1.5 g, 9.6 mmol). The reaction mixture was stirred at rt (around 35 °C) for 1 h, poured into ice-water (100 mL) under stirring, and extracted with chloroform (3 × 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and the solvent removed under vacuum to get a sticky compound. The crude compound thus obtained was purified by column chromatography over neutral alumina using 10–25% ethyl acetate in *n*-hexane as eluant to afford the desired product as off-white solid. Yield: 48.9%, R_f = 0.42 (50% EtOAc in *n*-hexane), mp 78–80 °C, PMR ($CDCl_3$): δ 7.09–7.25 (m, 4H), 6.76–6.79 (m, 2H), 6.51–6.57 (m, 2H), 4.23 (s, 2H), 3.77 (s, 3H), 3.68 (br s, 2H).

3.1.8. General procedure for the synthesis of urea derivatives (49–59)

Aniline derivatives (**35**–**41**, **43**, **47**, **48**) (6.6 mmol) were dissolved in dry benzene (7 mL). Isocyanate (**46**) (7.0 mmol) was added to the above solution under stirring. The reaction mixture was stirred for 30 min. The precipitated material was filtered and dried to get the desired compound as white solid.

3.1.8.1. 1-(2-Chloroethyl)-3-[4-(2-isobutyl-4-quinolinylmethoxy)phenyl]urea (49A). Yield: 89.7%, R_f = 0.86 (80% EtOAc in *n*-hexane), mp 130–131 °C, IR (KBr, cm^{-1}): 3325, 2956, 1641, 1602, 1510, 1236, 1172, 1018, 827, 763, PMR ($CDCl_3$): δ 8.11–8.13 (m, 1H), 7.91–7.93 (m, 1H), 7.69–7.73 (m, 1H), 7.51–7.55 (m, 1H), 7.41 (s, 1H), 7.22–7.26 (m, 2H), 6.97–7.0 (m, 2H), 6.77 (br s, 1H), 5.47 (s, 2H), 5.38–5.41 (t, 1H), 3.62–3.65 (m, 2H), 3.55–3.59 (m, 2H), 2.84–2.86 (d, 2H), 2.17–2.21 (m, 1H), 0.94–0.96 (d, 6H).

3.1.8.2. 1-(3-Chloropropyl)-3-[4-(2-isobutyl-4-quinolinylmethoxy)phenyl]urea (49B). Yield: 89.7%, R_f = 0.48 (50% EtOAc in *n*-hexane), mp 115–116 °C, IR (KBr, cm^{-1}): 3358, 3292, 2955, 1637, 1600, 1510, 1236, 1170, 1070, 842, 761, PMR (DMSO-d_6): δ 8.14–8.15 (m, 1H), 8.00–8.03 (m, 2H), 7.68–7.72 (m, 1H), 7.52 (s, 1H), 7.45 (br s, 1H), 7.32–7.34 (d, 2H, J = 8.96 Hz), 6.93–6.95 (d, 2H, J = 8.80 Hz), 6.09–6.12 (t, 1H), 5.48 (s, 2H), 3.61–3.65 (m, 2H), 3.29–3.33 (m, 2H), 2.81–2.83 (d, 2H), 2.19–2.23 (m, 1H), 1.92–1.99 (m, 2H), 0.95–0.96 (d, 6H).

3.1.8.3. 1-(2-Chloroethyl)-3-[4-(2-ethyl-4-quinolinylmethoxy)-phenyl]urea (50A). Yield: 65.2%, R_f = 0.32 (50% EtOAc in *n*-hexane), mp 148 °C (dec.), IR (KBr, cm^{-1}): 3329, 2964, 1633, 1610, 1508, 1251, 1170, 1020, 833, 759, PMR (DMSO-d_6): δ 8.20–8.22 (m, 1H), 8.08–8.10 (m, 1H), 7.98–8.00 (m, 1H), 7.70–7.74 (m, 1H), 7.52–7.59 (m, 2H), 7.32–7.36 (d, 2H), 6.94–6.98 (d, 2H), 6.24–6.27 (t, 1H), 5.49 (s, 2H), 3.62–3.65 (m, 2H), 3.52–3.56 (m, 2H), 2.99–3.05 (q, 2H, J = 7.61 Hz), 1.37–1.41 (t, 3H, J = 7.62 Hz).

3.1.8.4. 1-(3-Chloropropyl)-3-[4-(2-ethyl-4-quinolinylmethoxy)phenyl]urea (50B). Yield: 70.1%, R_f = 0. 34 (50% EtOAc in *n*-hexane), mp 130–132 °C, IR (KBr, cm^{-1}): 3313, 1635, 1606, 1508, 1244, 1172, 1020, 756.

3.1.8.5. 1-(2-Chloroethyl)-3-[4-(2-phenyl-4-quinolinylmethoxy)phenyl]urea (51A). Yield: 78.2%, R_f = 0.35 (50% EtOAc in *n*-hexane), mp 168–170 °C, PMR ($CDCl_3$): δ 8.24–8.26 (m, 1H), 8.15–8.17 (m, 2H), 8.07 (s, 1H), 8.01–8.03 (m, 1H), 7.75–7.80 (m, 3H), 7.58–7.60 (m, 1H), 7.46–7.56 (m, 3H), 7.35–7.37 (m, 2H), 6.24–6.26 (t, 1H), 5.45 (s, 2H), 3.63–3.65 (m, 2H), 3.52–3.56 (m, 2H).

3.1.8.6. 1-(3-Chloropropyl)-3-[4-(2-phenyl-4-quinolinylmethoxy)phenyl]urea (51B). Yield: 86.9%, R_f = 0.22 (50% EtOAc in *n*-hexane), mp 170–172 °C, IR (KBr, cm^{-1}): 3316, 2985, 1640, 1592, 1281, 1252, 1052, 835, PMR ($CDCl_3$): δ 8.16–8.19 (m, 2H), 7.98–8.06 (m, 3H), 7.73–7.77 (m, 1H), 7.44–7.60 (m, 4H), 7.32–7.36 (d, 2H), 6.96–6.99 (d, 2H), 5.98–6.01 (t, 1H), 5.55 (s, 2H), 3.61–3.64 (m, 2H), 3.32–3.37 (m, 2H), 1.94–2.01 (m, 2H).

3.1.8.7. 1-(2-Chloroethyl)-3-[4-(2-pyridinylmethoxy)phenyl]urea (52A). Yield: 84.1%, R_f = 0.25 (50% EtOAc in *n*-hexane), mp 145–146 °C, PMR ($CDCl_3$): δ 8.57–8.59 (m, 1H), 8.09–8.11 (m, 1H), 7.72–7.76 (m, 1H), 7.51–7.53 (m, 1H), 7.24–7.32 (m, 3H), 6.86–6.90 (m, 2H), 6.19–6.21 (t, 1H), 5.15 (s, 2H), 3.62–3.65 (m, 2H), 3.51–3.56 (m, 2H).

3.1.8.8. 1-(3-Chloropropyl)-3-[4-(2-pyridinylmethoxy)phenyl]urea (52B). Yield: 76.5%, R_f = 0.64 (EtOAc), mp 133–134 °C, IR (KBr, cm^{-1}): 3312, 2980, 1648, 1596, 1282, 1252, 1048, 827, PMR ($CDCl_3$): δ 8.49–8.59 (m, 1H), 7.69–7.74 (m, 1H), 7.49–7.51 (m, 1H), 7.22–7.25 (m, 1H), 7.15–7.19 (d, 2H), 6.92–6.95 (d, 2H), 6.51 (br s, 1H), 5.17 (s, 2H), 5.01–5.03 (t, 1H), 3.55–3.58 (m, 2H), 3.34–3.39 (m, 2H), 1.94–2.00 (m, 2H).

3.1.8.9. 1-(2-Chloroethyl)-3-[4-(4-methoxybenzyloxy)phenyl]urea (53A). Yield: 67.6%, R_f = 0.32 (50% EtOAc in *n*-hexane), mp 135–138 °C, IR (KBr, cm^{-1}): 3292, 2958, 1653, 1599, 1508, 1242, 1178, 1006, 827.

3.1.8.10. 1-(3-Chloropropyl)-3-[4-(4-methoxybenzyloxy) phenyl]-urea (53B). Yield: 65.2%, R_f = 0.69 (70% EtOAc in *n*-hexane), mp 134–136 °C, IR (KBr, cm^{-1}): 3317, 1635, 1518, 1242, 1178, 1031, 825.

3.1.8.11. 1-(2-Chloroethyl)-3-[4-(1-naphthylmethoxy)phenyl]urea (54A). Yield: 65.6%, R_f = 0.41 (50% EtOAc in *n*-hexane), mp 150–151 °C, PMR (DMSO-d_6): δ 8.04–8.06 (m, 2H), 7.84–7.90 (m, 2H), 7.51–7.57 (m, 3H), 7.46–7.50 (m, 1H), 7.31–7.35 (m, 2H), 6.93–6.99 (m, 2H), 6.15–6.18 (t, 1H) 5.44 (s, 2H), 3.64–3.66 (m, 2H), 3.53–3.57 (m, 2H).

3.1.8.12. 1-(3-Chloropropyl)-3-[4-(1-naphthylmethoxy) phenyl] urea (54B). Yield: 73.3%, R_f = 0.14 (30% EtOAc in *n*-hexane), mp 143–145 °C, IR (KBr, cm^{-1}): 3309, 1639, 1510, 1249, 1224, 1024, 794.

3.1.8.13. 1-[4-(4-Biphenylmethoxy)phenyl]-3-(2-chloroethyl) urea (55A). Yield: 64.8%, R_f = 0.41 (50% EtOAc in *n*-hexane), mp 190–192 °C, IR (KBr, cm^{-1}): 3309, 3034, 1639, 1573, 1512, 1236, 1174, 1041, 825, 754.

3.1.8.14. 1-[4-(4-Biphenylmethoxy)phenyl]-3-(3-chloropropyl) urea (55B). Yield: 79.8%, R_f = 0.61 (50% EtOAc in *n*-hexane), mp 145–148 °C.

3.1.8.15. 1-(2-Chloroethyl)-3-[4-(4-methoxythiobenzyloxy) phenyl]urea (56A). Yield: 76.0%, R_f = 0.43 (50% EtOAc in *n*-hexane), mp 158–159 °C, IR (KBr, cm^{-1}): 3304, 1637, 1604, 1514, 1253, 1033, 819, 744.

3.1.8.16. 1-(4-Benzyloxyphenyl)-3-(2-chloroethyl)urea (57A). Yield: 52.5%, R_f = 0.50 (50% EtOAc in *n*-hexane), mp 168–170 °C, IR (KBr, cm^{-1}): 3310, 1639, 1600, 1508, 1382, 1236, 1006, PMR (DMSO-d_6): δ 8.46 (br s, 1H), 7.40–7.44 (m, 2H), 7.36–7.38 (m, 2H), 7.31–7.33 (m, 1H), 7.27–7.29 (m, 2H), 6.88–6.90 (m, 2H), 6.29–6.33 (t, 1H), 5.03 (s, 2H), 3.62–3.65 (m, 2H), 3.35–3.41 (m, 2H).

3.1.8.17. 1-(4-Benzyloxyphenyl)-3-(3-chloropropyl)urea (57B). Yield: 94.2%, R_f = 0.59 (50% EtOAc in *n*-hexane), mp 155–156 °C, IR (KBr, cm^{-1}): 3310, 2982, 1638, 1598, 1288, 1248, 1036, 831.

3.1.8.18. 1-(2-Chloroethyl)-3-(4-hydroxyphenyl)urea (58A). Yield: 87.6%, R_f = 0.68 (EtOAc), mp 135–137 °C, IR (KBr, cm^{-1}): 3307, 3031, 1635, 1585, 1508, 1465, 1238, 835.

3.1.8.19. 1-(2-Chloroethyl)-3-[4-(4-nitrobenzyloxy)phenyl]urea (59A). Yield: 62.2%, R_f = 0.31 (50% EtOAc in *n*-hexane), mp 191–193 °C, IR (KBr, cm^{-1}): 3301, 1629, 1595, 1527, 1515, 1452, 1344, 1244, 1174, 1109, 1047, 835, 736, PMR ($CDCl_3$): δ 8.20–8.23 (d, 2H), 8.15 (br s, 1H), 7.61–7.64 (d, 2H), 7.30–7.32 (d, 2H), 6.85–6.87 (d, 2H), 6.22–6.24 (t, 1H), 5.14 (s, 2H), 3.62–3.65 (m, 2H), 3.51–3.55 (m, 2H).

3.1.9. General procedure for the synthesis of cyclic urea derivatives (60–69)

Linear urea derivatives (**49**–**59**) (2.3 mmol) were dissolved in dry THF (10 mL) and cooled to 0–5 °C. Sodium hydride (4.6 mmol) was added to the above solution in fractions at such a rate that the temperature of the reaction mixture did not rise above 10 °C. After the addition was over the reaction mixture was stirred at rt (about 30 °C) for 1 h. The reaction mixture was poured into ice-water (150 mL) and the solid so appeared was filtered and dried to get the title compound as solid.

3.1.9.1. 1-[4-(2-Isobutyl-4-quinolinylmethoxy)phenyl]imidazolidin-2-one (60A). Yield: 52.0%, R_f = 0.39 (70% EtOAc in *n*-hexane), mp 154–155 °C, IR (KBr, cm^{-1}): 3242, 2955, 1685, 1606, 1516, 1292, 1240, 1024, 827, PMR (DMSO-d_6): δ 8.00–8.04 (m, 2H), 7.80 (s, 1H), 7.69–7.73 (m, 1H), 7.54–7.57 (m, 1H), 7.44–7.48 (m, 2H), 7.01–7.03 (m, 2H), 6.44 (br s, 1H), 5.51 (s, 2H), 3.85–3.89 (m, 2H), 3.48–3.50 (m, 2H), 2.82–2.84 (d, 2H), 2.14–2.21 (m, 1H), 0.95–0.97 (d, 6H).

3.1.9.2. 1-[4-(2-Isobutyl-4-quinolinylmethoxy)phenyl]tetrahydropyrimidin-2(1*H*)-one (60B). Yield: 58.8%, R_f = 0.25 (EtOAc), mp 139–140 °C, IR (KBr, cm^{-1}): 3225, 2978, 1671, 1498, 1438, 1241, 1182, 1045, 835, PMR (DMSO-d_6): δ 8.07–8.09 (m, 1H), 7.95–7.98 (m, 1H), 7.69–7.73 (m, 1H), 7.52–7.56 (m, 2H), 7.48 (s, 1H), 7.23–7.25 (m, 1H), 7.00–7.06 (m, 2H), 5.56 (s, 2H), 3.83–3.87 (m, 2H), 3.63–3.66 (m, 1H), 3.40–3.41 (m, 1H), 2.84–2.85 (d, 2H), 2.15–2.23 (m, 2H), 2.06–2.09 (m, 2H), 0.95–0.97 (d, 6H).

3.1.9.3. 1-[4-(2-Ethyl-4-quinolinylmethoxy)phenyl]imidazolidin-2-one (61A). Yield: 82.3%, R_f = 0.17 (50% EtOAc in *n*-hexane), mp 159–161 °C, IR (KBr, cm^{-1}): 3209, 2964, 1701, 1512, 1487, 1267, 1188, 1022, 825.

3.1.9.4. 1-[4-(2-Ethyl-4-quinolinylmethoxy)phenyl]tetrahydropyrimidin-2(1*H*)-one (61B). Yield: 86.6%, R_f = 0.1 (EtOAc), mp 189–190 °C, IR (KBr, cm^{-1}): 3213, 1658, 1606, 1508, 1244, 1224, 1174, 885, 835, 759.

3.1.9.5. 1-[4-(2-Phenyl-4-quinolinylmethoxy)phenyl]imidazolidin-2-one (62A). Yield: 84.3%, R_f = 0.48 (EtOAc), mp 159–161 °C, PMR ($CDCl_3$): δ 8.22–8.24 (m, 1H), 8.15–8.17 (m, 2H), 8.04 (s, 1H), 7.97–7.99 (m, 1H), 7.74–7.78 (m, 1H), 7.44–7.60 (m, 6H), 7.03–7.07 (m, 2H), 5.57 (s, 2H), 4.72 (br s, 1H), 3.89–3.93 (m, 2H), 3.54–3.58 (m, 2H).

3.1.9.6. 1-[4-(2-Phenyl-4-quinolinylmethoxy)phenyl]tetrahydropyrimidin-2(1*H*)-one (62B). Yield: 100%, R_f = 0.33 (10% MeOH in CHCl3), mp 200–201 °C, IR (KBr, cm^{-1}): 3223, 2987, 1670, 1494, 1444, 1249, 1179, 1039, 837, PMR (DMSO-d_6): δ 8.17–8.19 (m, 3H), 8.08–8.06 (m, 1H), 8.02–8.04 (m, 1H), 7.75–7.78 (m, 1H), 7.45–7.61 (m, 4H), 7.24–7.26 (d, 2H), 7.05–7.07 (d, 2H), 5.78 (br s, 1H), 5.59 (s, 2H), 3.63–3.66 (m, 2H), 3.37–3.41 (m, 2H), 2.04–2.09 (m, 2H).

3.1.9.7. 1-[4-(2-Pyridinylmethoxy)phenyl]imidazolidin-2-one (63A). Yield: 81.1%, R_f = 0.13 (50% EtOAc in *n*-hexane), mp 184–185 °C, PMR ($CDCl_3$): δ 8.58–8.60 (m, 1H), 7.68–7.72 (m, 1H), 7.50–7.52 (m, 1H), 7.40–7.44 (m, 2H), 7.20–7.23 (m, 1H), 6.95–6.99 (m, 2H), 5.19 (s, 2H), 4.95 (br s, 1H), 3.87–3.91 (m, 2H), 3.53–3.57 (m, 2H).

3.1.9.8. 1-[4-(2-Pyridinylmethoxy)phenyl]tetrahydropyrimidin-2(1*H*)-one (63B). Yield: 56.1%, R_f = 0.57 (EtOAc), mp 211–212 °C, IR (KBr, cm^{-1}): 3223, 2987, 1670, 1494, 1444, 1249, 1179, 1039, 837, PMR (DMSO-d_6): δ 8.58–8.59 (m, 1H), 7.68–7.73 (m, 1H), 7.50–7.52 (m, 1H), 7.18–7.23 (m, 3H), 6.94–6.97 (m, 2H), 5.19 (s, 2H), 4.87 (br s, 1H), 3.62–3.65 (m, 2H), 3.40–3.43 (m, 2H), 2.04–2.17 (m, 2H).

3.1.9.9. 1-[4-(4-Methoxybenzyloxy)phenyl]imidazolidin-2-one (64A). Yield: 72.9%, R_f = 0.64 (70% EtOAc in *n*-hexane), mp 192–193 °C, IR (KBr, cm^{-1}): 3265, 2912, 1681, 1516, 1246, 1020, 827, PMR (DMSO-d_6): δ 7.91 (br s, 1H), 7.40–7.46 (m, 2H), 7.33–7.38 (m, 2H), 7.21–7.23 (m, 1H), 6.85–6.93 (m, 3H), 4.96 (s, 2H), 3.74–3.84 (m, 5H), 3.30–3.35 (m, 2H).

3.1.9.10. 1-[4-(4-Methoxybenzyloxy)phenyl]tetrahydropyrimidin-2(1*H*)-one (64B). Yield: 80.1%, R_f = 0.64 (70% EtOAc in *n*-hexane), mp 218–220 °C, IR (KBr, cm^{-1}): 3217, 2955, 1647, 1585, 1510, 1244, 1174, 1030, 827, 810, PMR (DMSO-d_6): δ 7.33–7.35 (d, 2H), 7.14–7.16 (d, 2H), 6.88–6.90 (m, 4H), 6.27 (br s, 1H), 4.96 (s, 2H), 3.79 (s, 3H), 3.58–3.61 (m, 2H), 3.30–3.330 (m, 2H), 2.00–2.02 (m, 2H).

3.1.9.11. 1-[4-(1-Naphthylmethoxy)phenyl]imidazolidin-2-one (65A). Yield: 98.1%, R_f = 0.64 (70% EtOAc in *n*-hexane), mp 190–191 °C, PMR ($CDCl_3$): δ 8.04–8.07 (m, 1H), 7.87–7.91 (m, 2H), 7.59–7.61 (m, 1H), 7.52–7.55 (m, 2H), 7.44–7.49 (m, 3H), 6.99–7.02 (m, 2H), 6.29 (br s, 1H), 5.46 (s, 2H), 3.85–3.89 (m, 2H), 3.49–3.53 (m, 2H).

3.1.9.12. 1-[4-(1-Naphthylmethoxy)phenyl]tetrahydropyrimidin-2(1*H*)-one (65B). Yield: 83.7%, R_f =0.54 (70% EtOAc in *n*-hexane), mp 214–217 °C, PMR (DMSO-d_6): δ 8.02–8.04 (m, 1H), 7.85–7.91 (m, 2H), 7.69–7.71 (m, 1H), 7.54–7.59 (m, 2H), 7.50–7.52 (m, 1H), 7.20–7.24 (m, 2H), 6.98–7.02 (m, 2H), 5.92 (br s, 1H), 5.47 (s, 2H), 3.61–3.65 (m, 2H), 3.36–3.40 (m, 2H), 2.03–2.09 (m, 2H).

3.1.9.13. 1-[4-(4-Biphenylmethoxy)phenyl]imidazolidin-2-one (66A). Yield: 98.0%, R_f = 0.17 (50% EtOAc in *n*-hexane), mp 262–263 °C, IR (KBr, cm^{-1}): 3257, 2924, 1681, 1516, 1246, 1153, 1016, 825.

3.1.9.14. 1-[4-(4-Biphenylmethoxy)phenyl]tetrahydropyrimidin-2(1*H*)-one (66B). Yield: 83.8%, R_f = 0.17 (EtOAc), mp 248–250 °C, IR (KBr, cm^{-1}): 3221, 1645, 1510, 1242, 1224, 1033, 829, 758, 698.

3.1.9.15. 1-[4-(4-Methoxythiobenzyloxy)phenyl]imidazolidin-2-one (67A). Yield: 100%, R_f = 0.14 (50% EtOAc in *n*-hexane), mp 190–193 °C, IR (KBr, cm^{-1}): 3265, 2924, 1685, 1608, 1500, 1483, 1251, 1151, 1031, 835, 812.

3.1.9.16. 1-(4-Benzyloxyphenyl)imidazolidin-2-one (68A). Yield: 99.3%, R_f = 0.24 (50% EtOAc in *n*-hexane), mp 216–219 °C, IR (KBr, cm^{-1}): 3259, 1681, 1514, 1245, 1150, 1004, 827, PMR ($CDCl_3$): δ 7.40–7.48 (m, 4H), 7.35–7.39 (m, 2H), 7.29–7.33 (m, 1H), 6.91–6.94 (m, 2H), 6.29 (br s, 1H), 5.04 (s, 2H), 3.83–3.89 (m, 2H), 3.47–3.53 (m, 2H).

3.1.9.17. 1-(4-Benzyloxyphenyl)tetrahydropyrimidin-2(1*H*)-one (68B). Yield: 93.5%, R_f = 0.53 (70% EtOAc in *n*-hexane), mp 230–231 °C, IR (KBr, cm^{-1}): 3222, 2979, 1666, 1490, 1448, 1248, 1178, 1036, 833, PMR (DMSO-d_6): δ 7.35–7.42 (m, 4H), 7.28–7.32 (m, 1H), 7.16–7.19 (d, 2H, J = 8.84 Hz), 6.89–6.93 (d, 2H, J = 8.88 Hz), 6.01 (br s, 1H), 5.04 (s, 2H), 3.60–3.63 (m, 2H), 3.34–3.37 (m, 2H), 2.01–2.07 (m, 2H).

3.1.9.18. 1-[4-(4-Nitrobenzyloxy)phenyl]imidazolidin-2-one (69A). Yield: 85.2%, R_f = 0.37 (EtOAc), mp 200–201 °C, IR (KBr, cm^{-1}): 3273, 2929, 1693, 1583, 1514, 1433, 1350, 1257, 1232, 1186, 1051, 827.

3.1.10. General procedure for the synthesis of ester derivatives (70–79)

Imidazolidin-2-ones (**60**–**69**) (2.5 mmol) were dissolved in dry THF (10 mL) and cooled to 0–5 °C. Sodium hydride (0.34 g, 7.5 mmol) was added at this temperature to the reaction mixture. The reaction mixture was refluxed for 2 h. Ethyl 2-bromopropionate (5.0 mmol) was added to the reaction mixture drop-wise and it was further refluxed for 2 h. The reaction mixture was allowed to cool to rt and poured into ice-water (100 mL). The aqueous solution was extracted with chloroform (4 × 25 mL); the combined organic layer was dried over anhydrous sodium sulfate and the solvent removed to get crude oily product. The crude product thus obtained was purified by column chromatography over silica gel using ethyl acetate in *n*-hexane as eluant to afford the desired compound.

3.1.10.1. Ethyl 2-{3-[4-(2-isobutyl-4-quinolinylmethoxy)phenyl]-2-oxo-1-imidazo- lidinyl}propionate (70A). Yield: 48.5%, R_f = 0.39 (50% EtOAc in *n*-hexane), mp 122–123 °C, IR (KBr, cm^{-1}): 2953, 1739, 1689, 1518, 1278, 1245, 1182, 1076, 831, 769.

3.1.10.2. Ethyl 2-{3-[4-(2-isobutyl-4-quinolinylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionate (70B). Yield: 79.7%, R_f = 0.38 (50% EtOAc in *n*-hexane), mp 78–80 °C.

3.1.10.3. Ethyl 2-{3-[4-(2-ethyl-4-quinolinylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}propionate (71A). Yield: 56%, R_f = 0.53 (50% EtOAc in *n*-hexane), IR (KBr, cm^{-1}): 2926, 1739, 1701, 1518, 1437, 1280, 1242, 1180, 1020, 835, 763.

3.1.10.4. Ethyl 2-{3-[4-(2-ethyl-4-quinolinylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionate (71B). Yield: 65.1%, R_f = 0.29 (50% EtOAc in *n*-hexane).

3.1.10.5. Ethyl 2-{2-oxo-3-[4-(2-phenyl-4-quinolinmethoxy)phenyl]-1-imidazolidinyl}propionate (72A). Yield: 61%, R_f =0.32 (30% EtOAc in *n*-hexane).

3.1.10.6. Ethyl 2-{3-[4-(2-phenyl-4-quinolinylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionate (72B). Yield: 56.6%, R_f = 0.42 (EtOAc).

3.1.10.7. Ethyl 2-{2-oxo-3-[4-(2-pyridinylmethoxy)phenyl]-1-imidazolidinyl}propionate (73A). Yield: 58.9%, R_f = 0.28 (50% EtOAc in *n*-hexane), mp 80–83 °C, PMR ($CDCl_3$): δ 8.56–8.60 (m, 1H), 7.68–7.72 (m, 1H), 7.50–7.52 (m, 1H), 7.42–7.46 (m, 2H), 7.20–7.22 (m, 1H), 6.94–6.98 (m, 2H), 5.19 (s, 2H), 4.69–4.75 (q, 1H, J = 7.51 Hz), 4.16–4.21 (m, 2H), 3.76–3.86 (m, 2H), 3.61–3.68 (m, 1H), 3.48–3.54 (m, 1H), 1.45–1.47 (d, 3H, J = 7.48 Hz), 1.25–1.29 (t, 3H).

3.1.10.8. Ethyl 2-{3-[4-(2-pyridinylmethoxy)phenyl]-2(1H)-oxotetrahydro-1-pyrimi- dinyl}propionate (73B). Yield: 82.2%, R_f = 0.17 (50% EtOAc in *n*-hexane).

3.1.10.9. Ethyl 2-{3-[4-(4-methoxybenzyloxy)phenyl]-2-oxo-1-imidazolidinyl}propionate (74A). Yield: 64.2%, R_f =0.55 (50% EtOAc in *n*-hexane).

3.1.10.10. Ethyl 2-{3-[4-(4-methoxybenzyloxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionate (74B). Yield: 56.7%, R_f = 0.21 (30% EtOAc in *n*-hexane), IR (KBr, cm^{-1}): 2955, 1737, 1645, 1514, 1249, 1180, 1026, 829, 756.

3.1.10.11. Ethyl 2-{3-[4-(1-naphthylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}propionate (75A). Yield: 58%, R_f = 0.31 (30% EtOAc in *n*-hexane).

3.1.10.12. Ethyl 2-{3-[4-(1-naphthylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionate (75B). Yield: 61.7%, R_f = 0.55 (50% EtOAc in *n*-hexane), PMR ($CDCl_3$): δ 7.94–7.97 (m, 1H), 7.80–7.83 (m, 1H), 7.63–7.71(m, 1H), 7.45–7.52 (m, 2H), 7.25–7.31 (m, 1H), 7.13–7.18 (m, 2H), 6.95–6.98 (m, 1H), 6.75–6.78 (m, 2H), 5.39 (s, 2H), 4.45–4.49 (q, 1H), 4.07–4.15 (m, 2H), 3.57–3.60 (m, 2H), 3.30–3.34 (m, 2H), 2.05–2.13 (m, 2H), 1.36–1.38 (d, 3H), 1.19–1.22 (t, 3H).

3.1.10.13. Ethyl 2-{3-[4-(4-biphenylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}propionate (76A). Yield: 55.8%, R_f = 0.63 (50% EtOAc in *n*-hexane), mp 163–164 °C, IR (KBr, cm^{-1}): 2982, 1739, 1689, 1514, 1278, 1242, 1182, 1014, 825, 744.

3.1.10.14. Ethyl 2-{3-[4-(4-biphenylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrim- idinyl}propionate (76B). Yield: 83.2%, R_f = 0.39 (50% EtOAc in *n*-hexane), mp 119–120 °C, IR (KBr, cm^{-1}): 2966, 1735, 1645, 1508, 1240, 1188, 1016, 840, 765.

3.1.10.15. Ethyl 2-{3-[4-(4-methoxythiobenzyloxy)phenyl]-2-oxo-1-imidazolidinyl}propionate (77A). Yield: 60.4%, R_f = 0.49 (50% EtOAc in *n*-hexane), mp 90–95 °C, IR (KBr, cm^{-1}): 2924, 1732, 1701, 1514, 1273, 1199, 1031, 842, 754.

3.1.10.16. Ethyl 2-[3-(4-benzyloxyphenyl)-2-oxo-1-imidazolidinyl]propionate (78A). Yield: 53.3%, R_f = 0.82 (50% EtOAc in *n*-hexane), mp 102–104 °C, IR (KBr, cm^{-1}): 2985, 1732, 1685, 1519, 1438, 1280, 1242, 1008, 831, 738, PMR ($CDCl_3$): δ 7.45–7.48 (m, 4H), 7.41–7.42 (m, 2H), 7.33–7.35 (m, 1H), 6.95–6.99 (m, 2H), 5.06 (s, 2H), 4.71–4.77 (q, 1H, *J* = 7.50 Hz), 4.18–4.24 (m, 2H), 3.82–3.88 (m, 2H), 3.66–3.70 (m, 1H), 3.51–3.56 (m, 1H), 1.47–1.49 (d, 3H, *J* = 7.60 Hz), 1.28–1.31 (t, 3H).

3.1.10.17. Ethyl 2-[3-(4-benzyloxyphenyl)-2(1*H*)-oxotetrahydro-1-pyrimidinyl]propionate (78B). Yield: 52.3%, R_f = 0.66 (50% EtOAc in *n*-hexane).

3.1.10.18. Ethyl 2-{3-[4-(4-nitrobenzyloxy)phenyl]-2-oxo-1-imidazolidinyl}pro- pionate (79A). Yield: 80.7%, R_f = 0.47 (50% EtOAc in *n*-hexane), mp 126–128 °C, IR (KBr, cm^{-1}): 2923, 1732, 1693, 1514, 1487, 1352, 1272, 1197, 1047, 835, 738.

3.1.11. General procedure for the synthesis of acids (80–89)

Ester derivatives (**70**–**79**) (0.7 mmol) were dissolved in methanol (5 mL). Sodium hydroxide (1.4 mmol) or lithium hydroxide (3.5 mmol) was dissolved in distilled water (5 mL) and the solution was added to the above reaction mixture drop-wise with stirring at rt for 2 h. Methanol was recovered from the reaction mixture and ice-water (20 mL) was added to it. The reaction mixture was acidified with concd HCl (5 mL). The solid so appeared was filtered and dried. The crude product so obtained was crystallized from methanol to afford the desired compound.

3.1.11.1. 2-{3-[4-(2-Isobutyl-4-quinolinylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}propionic acid (80A). Yield: 69.9%, R_f = 0.55 (70% EtOAc in *n*-hexane), mp 192–195 °C, IR (KBr, cm^{-1}): 3483, 2981, 1748, 1652, 1512, 1487, 1248, 1075, 827, 750, PMR (DMSO-d_6): δ 8.02–8.04 (m, 1H), 7.78–7.82 (m, 1H), 7.62–7.66 (m, 1H), 7.57 (s, 1H), 7.43–7.52 (m, 3H), 7.01–7.04 (m, 2H), 5.56 (s, 2H), 4.64–4.70 (q, 1H, *J* = 7.50 Hz), 3.82–3.90 (m, 2H), 3.68–3.72 (m, 1H), 3.52–3.56 (m, 1H), 2.90–2.99 (m, 2H), 2.24–2.28 (m, 1H), 1.47–1.49 (d, 3H, *J* = 7.52 Hz), 0.98–1.00 (d, 6H), MS (*m*/*z*): 470.0 $(M+Na)^+$, 447.9 $(M+H)^+$.

3.1.11.2. 2-{3-[4-(2-Isobutyl-4-quinolinylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionic acid (80B). Yield: 54.2%, R_f = 0.22 (EtOAc), mp 129–131 °C, IR (KBr, cm^{-1}): 3445, 2980, 1734, 1652, 1436, 1242, 1178, 1026, 830, PMR ($CDCl_3$): δ 8.11–8.13 (m, 1H), 7.91–7.93 (m, 1H), 7.68–7.72 (m, 1H), 7.55–7.52 (m, 1H), 7.41 (s, 1H), 7.20–7.22 (d, 2H, *J* = 8.84 Hz), 7.01–7.03 (d, 2H, *J* = 8.84 Hz), 5.50 (s, 2H), 4.71–4.74 (q, 1H, *J* = 7.24 Hz), 3.64–3.67 (m, 2H), 3.41–3.44 (m, 2H), 2.84–2.86 (d, 2H), 2.14–2.22 (m, 3H), 1.51–1.53 (d, 3H, *J* = 7.28 Hz), 0.95–0.97 (d, 6H). Anal. Calcd for $C_{22}H_{31}N_3O_4$: C, 70.26, H, 6.77, N, 9.10. Found: C, 69.92, H, 6.93, N, 9.23.

3.1.11.3. 2-{3-[4-(2-Ethyl-4-quinolinylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}propionic acid (81A). Yield: 89.5%, R_f = 0.50 (70% EtOAc in *n*-hexane), mp 214–215 °C, IR (KBr, cm^{-1}): 3446, 1730, 1637, 1514, 1485, 1442, 1242, 831, 746, PMR (DMSO-d_6): δ 8.25–8.27 (m, 1H), 7.99–8.03 (m, 2H), 7.84–7.88 (m, 1H), 7.67 (s, 1H), 7.51–7.55 (m, 2H), 7.08–7.11 (m, 2H), 5.74 (s, 2H), 4.58–4.62 (q, 1H, *J* = 7.58 Hz), 3.81–3.91 (m, 2H), 3.65–3.71 (m, 1H), 3.51–3.58 (m, 1H), 3.42–3.46 (q, 2H, *J* = 7.61 Hz), 1.52–1.55 (t, 3H, *J* = 7.60 Hz), 1.46–1.48 (d, 3H, *J* = 7.52 Hz). Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72, H, 6.01, N, 10.02. Found: C, 68.44, H, 6.41, N, 10.13.

3.1.11.4. 2-{3-[4-(2-Ethyl-4-quinolinylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionic acid (81B). Yield: 73.7%, R_f = 0.12 (EtOAc), mp 182–183 °C, IR (KBr, cm^{-1}): 3448, 1723, 1652, 1506, 1436, 1248, 1182, 1036, 835, PMR (DMSO-d_6): δ 8.03–8.05 (m, 1H), 7.67–7.71 (m, 2H), 7.54–7.56 (m, 1H), 7.45–7.49 (m, 2H), 7.23–7.26 (m, 1H), 6.90–7.03 (m, 2H), 5.34 (s, 2H), 4.75–4.79 (q, 1H), 3.48–3.51 (m, 2H), 3.37–3.42 (q, 2H), 3.26–3.23 (m, 2H), 1.93–2.03 (m, 2H), 1.52–1.54 (t, 3*H*),1.32–1.36 (t, 3H). Anal. Calcd for $C_{29}H_{27}N_3O_4$: C, 69.27, H, 6.28, N, 9.69. Found: C, 69.04, H, 6.73, N, 9.47.

3.1.11.5. 2-{3-[4-(2-Phenyl-4-quinolinylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}propionic acid (82A). Yield: 71.3%, R_f = 0.22 (EtOAc), mp 120–122 °C, IR (KBr, cm^{-1}): 3442, 2980, 1751, 1652, 1512, 1419, 1237, 1181, 1076, 836, 756, PMR ($CDCl_3$): δ 8.36–8.38 (m, 2H), 8.15–8.17 (m, 2H), 8.05 (s, 1H), 7.97–7.99 (m, 1H), 7.76–7.80 (m, 2H), 7.46–7.55 (m, 4H), 7.02–7.06 (m, 2H), 5.57 (s, 2H), 4.66–4.71 (q, 1H), 3.81–3.86 (m, 2H), 3.60–3.66 (m, 1H), 3.50–3.55 (m, 1H), 1.49–1.51 (d, 3H), MS (*m*/*z*): 490.1 $(M+Na)^+$, 468.1 $(M+H)^+$, 422.1 $(M-COOH)^+$.

3.1.11.6. 2-{3-[4-(2-Phenyl-4-quinolinylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionic acid (82B). Yield: 86.0%, R_f = 0.22 (10% MeOH in $CHCl_3$), mp 124–127 °C, IR (KBr, cm^{-1}): 3412, 2937, 1734, 1639, 1602, 1508, 1444, 1298, 1182, 1028, 771, PMR (DMSO-d_6): δ 8.17–8.23 (m, 2H), 8.10 (s, 1H), 8.04–8.06 (m, 1H), 7.80–7.86 (m, 2H), 7.61–7.65 (m, 1H), 7.46–7.56 (m, 3H), 7.22–7.24 (d, 2H, *J* = 8.88 Hz), 7.04–7.06 (d, 2H, *J* = 8.92 Hz), 5.60 (s, 2H), 5.02–5.08 (q, 1H, *J* = 7.29 Hz), 3.64–3.67 (m, 2H), 3.42–3.46 (m, 2H), 2.06–2.12 (m, 2H), 1.42–1.44 (d, 3H, *J* = 7.40 Hz). Anal. Calcd for $C_{29}H_{27}N_3O_4$: C, 72.33, H, 5.65, N, 8.73. Found: C, 72.46, H, 5.87, N, 9.02.

3.1.11.7. 2-{2-Oxo-3-[4-(2-pyridinylmethoxy)phenyl]-1-imidazolidinyl}propionic acid (83A). Yield: 73.3%, R_f = 0.35 (70% EtOAc in *n*-hexane), mp 179–180 °C, IR (KBr, cm^{-1}): 3444, 2980, 1752, 1652, 1506, 1436, 1250, 1134, 1027, 813, 744, PMR (DMSO-d_6): δ 8.57–8.58 (m, 1H), 7.71–7.75 (m, 1H), 7.51–7.52 (m, 1H), 7.42–7.46 (m, 2H), 7.23–7.26 (m, 1H), 6.93–6.96 (m, 2H), 5.17 (s, 2H), 4.60–4.65 (q, 1H, *J* = 7.39 Hz), 3.77–3.85 (m, 2H), 3.65–3.68 (m, 1H), 3.50–3.54 (m, 1H), 1.45–1.47 (d, 3H, *J* = 7.48 Hz). Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33, H, 5.61, N, 12.31. Found: C, 63.84, H, 5.98, N, 12.01.

3.1.11.8. 2-{3-[4-(2-Pyridinylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionic acid (83B). Yield: 84.5%, R_f = 0.27 (80% EtOAc in *n*-hexane), mp 183–185 °C, IR (KBr, cm^{-1}): 3446, 2984, 1730, 1652, 1502, 1436, 1249, 1178, 1021, 826, 758, PMR (DMSO-d_6): δ 8.57–8.58 (m, 1H), 7.69–7.72 (m, 1H), 7.50–7.52 (m, 1H), 7.24–7.27 (m, 1H), 7.16–7.18 (d, 2H, *J* = 8.88 Hz), 6.91–6.94 (d, 2H, *J* = 8.96 Hz), 5.17 (s, 2H), 5.03–5.08 (q, 1H, *J* = 7.41 Hz), 3.62–3.65 (m, 2H), 3.40–3.45 (m, 2H), 2.00–2.08 (m, 2H), 1.42–1.43 (d, 3H, *J* = 7.40 Hz), MS (*m*/*z*): 394.0 $(M+K)^+$, 378.0 $(M+Na)^+$, 355.8 $(M+H)^+$, 309.7 $(M-COOH)^+$.

3.1.11.9. 2-{3-[4-(4-Methoxybenzyloxy)phenyl]-2-oxo-1-imidazolidinyl}propionic acid (84A). Yield: 77.2%, R_f = 0.14 (50% EtOAc in *n*-hexane), mp 159–160 °C, IR (KBr, cm^{-1}): 2900, 1749, 1658, 1490, 1444, 1282, 1244, 1180, 1008, 873, 752, PMR (DMSO-

d_6): δ 7.42–7.45 (m, 2H), 7.32–7.35 (m, 2H), 6.88–6.94 (m, 4H), 4.95 (s, 2H), 4.60–4.63 (q, 1H, *J* = 7.52 Hz), 3.80–3.86 (m, 5H), 3.65–3.69 (m, 1H), 3.51–3.55 (m, 1H), 1.45–1.47 (d, 3H, *J* = 7.48 Hz). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85, H, 5.99, N, 7.56. Found: C, 65.10, H, 6.29, N, 7.12.

3.1.11.10. 2-{3-[4-(4-Methoxybenzyloxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidi- nyl}propionic acid (84B). Yield: 81.4%, R_f = 0.61 (70% EtOAc in *n*-hexane), mp 184–186 °C, IR (KBr, cm^{-1}): 3446, 2954, 1737, 1685, 1517, 1450, 1251, 1174, 1029, 833, 744, PMR (DMSO-d_6): δ 7.33–7.35 (d, 2H), 7.14–7.16 (d, 2H), 6.88–6.91 (m, 4H), 4.96–5.01 (m, 3H), 3.80 (s, 3H), 3.60–3.65 (m, 2H), 3.40–3.43 (m, 2H), 2.09–2.17 (m, 2H), 1.40–1.42 (d, 3H), MS (*m*/*z*): 407.0 $(M+Na)^+$, 384.8 $(M+H)^+$.

3.1.11.11. 2-{3-[4-(1-Naphthylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}propionic acid (85A). Yield: 54.9%, R_f = 0.41 (70% EtOAc in *n*-hexane), mp 187–190 °C, IR (KBr, cm^{-1}): 2926, 1728, 1635, 1510, 1446, 1276, 1170, 835, 756, PMR ($CDCl_3$): δ 8.05–8.07 (m, 1H), 7.84–7.91 (m, 2H), 7.59–7.60 (m, 1H), 7.54–7.57 (m, 2H), 7.45–7.53 (m, 3H), 7.00–7.03 (m, 2H), 5.47 (s, 2H), 4.62–4.66 (q, 1H, *J* = 7.52 Hz), 3.78–3.88 (m, 2H), 3.65–3.71 (m, 1H), 3.50–3.56 (m, 1H), 1.47–1.48 (d, 3H, *J* = 7.48 Hz), MS (*m*/*z*): 412.8 $(M+Na)^+$, 390.9 $(M+H)^+$.

3.1.11.12. 2-{3-[4-(1-Naphthylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionic acid (85B). Yield: 54.9%, R_f = 0.73 (EtOAc), mp 207–209 °C, IR (KBr, cm^{-1}): 2985, 1737, 1643, 1502, 1444, 1296, 1180, 1024, 835, 777, PMR (DMSO-d_6): δ 8.02–8.05 (m, 1H), 7.85–7.91 (m, 2H), 7.55–7.61 (m, 2H), 7.45–7.52 (m, 2H), 7.20–7.22 (d, 2H, *J* = 8.92 Hz), 6.99–7.01 (d, 2H, *J* = 8.88 Hz), 5.47 (s, 2H), 5.04–5.08 (q, 1H, *J* = 7.44 Hz), 3.62–3.65 (m, 2H), 3.40–3.45 (m, 2H), 2.11–2.18 (m, 2H), 1.43–1.44 (d, 3H, *J* = 7.40 Hz), MS (*m*/*z*): 343.0 $(M+K)^+$, 427.0 $(M+Na)^+$, 404.9 $(M+H)^+$.

3.1.11.13. 2-{3-[4-(4-Biphenylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}propionic acid (86A). Yield: 80.1%, R_f = 0.24 (EtOAc), mp 249–251 °C, IR (KBr, cm^{-1}): 3446, 2982, 1734, 1652, 1512, 1456, 1241, 1014, 826, 746, PMR (DMSO-d_6): δ 7.56–7.61 (m, 4H), 7.42–7.50 (m, 6H), 7.32–7.36 (m, 1H), 6.93–6.96 (m, 2H), 5.07 (s, 2H), 4.56–4.60 (q, 1H, *J* = 7.44 Hz), 3.76–3.83 (m, 2H), 3.65–3.67 (m, 1H), 3.49–3.50 (m, 1H), 1.43–1.45 (d, 3H, *J* = 7.44 Hz), Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.10, H, 5.81, N, 6.73. Found: C, 71.92, H, 6.12, N, 6.56.

3.1.11.14. 2-{3-[4-(4-Biphenylmethoxy)phenyl]-2(1*H*)-oxotetra hydro-1-pyrimidinyl}propionic acid (86B). Yield: 69.8%, R_f = 0.26 (EtOAc), mp 204–205 °C, IR (KBr, cm^{-1}): 2981, 1743, 1641, 1446, 1242, 1180, 1026, 765, PMR (DMSO-d_6): δ 7.58–7.61 (m, 4H), 7.49–7.51 (m, 2H), 7.42–7.46 (m, 2H), 7.33–7.38 (m, 1H), 7.18–7.20 (m, 2H), 6.96–6.94 (m, 2H), 5.06–5.10 (m, 3H), 3.63–3.66 (m, 2H), 3.38–3.44 (m, 2H), 2.10–2.19 (m, 2H), 1.44–1.46 (d, 3H), Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54, H, 6.09, N, 6.51. Found: C, 72.26, H, 6.27, N, 6.74.

3.1.11.15. 2-{3-[4-(4-Methoxythiobenzyloxy)phenyl]-2-oxo-1-imidazolidinyl}propionic acid (87A). Yield: 44.4%, R_f = 0.61 (EtOAc), mp 156–158 °C, PMR ($CDCl_3$): δ 7.42–7.44 (d, 2H, *J* = 8.28 Hz), 7.26–7.28 (d, 2H, *J* = 8.36 Hz), 7.12–7.14 (d, 2H, *J* = 8.36 Hz), 6.78–6.80 (d, 2H, *J* = 8.32 Hz), 4.68–4.72 (q, 1H, J = 6.84 Hz), 3.99 (s, 2H), 3.80–3.84 (m, 2H), 3.77 (s, 3H), 3.62–3.66 (m, 1H), 3.51–3.55 (m, 1H), 1.50–1.52 (d, 3H, J = 6.72 Hz), MS (*m*/*z*): 409.3 $(M+Na)^+$, 387.1 $(M+H)^+$, 341.1 $(M-COOH)^+$.

3.1.11.16. 2-[3-(4-Benzyloxyphenyl)-2-oxo-1-imidazolidinyl]propionic acid (88A). Yield: 97.8%, R_f = 0.24 (70% EtOAc in *n*-hexane), mp 214–217 °C, IR (KBr, cm^{-1}): 2916, 1751, 1666, 1492, 1450, 1282, 1255, 1184, 1053, 819, 734, PMR ($CDCl_3$): δ 7.43–7.58 (m, 4H), 7.36–7.41 (m, 2H), 7.31–7.33 (m, 1H), 7.03–7.06 (m, 2H), 5.04 (s, 2H), 4.62–4.68 (q, 1H, *J* = 7.48 Hz), 3.90–3.98 (m, 2H), 3.62–3.66 (m, 1H), 3.54–3.58 (m, 1H), 1.51–1.53 (d, 3H, *J* = 7.48 Hz). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05, H, 5.92, N, 8.23. Found: C, 66.86, H, 6.13, N, 8.12.

3.1.11.17. 2-[3-(4-Benzyloxyphenyl)-2(1*H*)-oxotetrahydro-1-pyrimidinyl]propionic acid (88B). Yield: 56.5%, R_f = 0.64 (70% EtOAc in *n*-hexane), mp 207–209 °C, IR (KBr, cm^{-1}): 2981, 1743, 1643, 1566, 1446, 1298, 1174, 1026, 831, 754, PMR (DMSO-d_6): δ 7.38–7.43 (m, 4H), 7.30–7.33 (m, 1H), 7.15–7.18 (d, 2H, *J* = 8.96 Hz), 6.90–6.92 (d, 2H, *J* = 8.92 Hz), 5.03–5.05 (m, 3H), 3.62–3.65 (m, 2H), 3.37–3.42 (m, 2H), 2.09–2.15 (m, 2H), 1.41–1.43 (d, 3H). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.70, H, 6.25, N, 7.90. Found: C, 67.55, H, 6.46, N, 7.59.

3.1.11.18. 2-{3-[4-(4-Nitrobenzyloxy)phenyl]-2-oxo-1-imidazolidinyl}propionic acid (89A). Yield: 54.0%, R_f = 0.67 (EtOAc), mp 167–169 °C, IR (KBr, cm^{-1}): 2923, 1724, 1695, 1515, 1483, 1433, 1352, 1251, 1110, 839, 734, PMR ($CDCl_3$): δ 8.22–8.24 (d, 2H), 7.61–7.66 (d, 2H), 7.46–7.48 (d, 2H), 6.92–6.94 (d, 2H), 5.16 (s, 2H), 4.64–4.69 (q, 1H, *J* = 7.49 Hz), 3.80–3.88 (m, 2H), 3.73–3.78 (m, 1H), 3.49–3.55 (m, 1H), 1.46–1.48 (d, 3H, *J* = 7.52 Hz). Anal. Calcd for $C_{19}H_{19}N_3O_6$: C, 59.22, H, 4.97, N, 10.90. Found: C, 58.94, H, 5.24, N, 10.64.

3.1.12. General procedure for the synthesis of hydroxamic acids (90–99)

Hydroxylamine hydrochloride (75 mmol) was suspended in dry methanol (10 mL). Potassium hydroxide (77 mmol) was dissolved in methanol (10 mL) and added to the above suspension. The reaction mixture was stirred at rt (around 35 °C) for 30 min. Ester derivatives [(**70–79**) (0.7 mmol)] were added to the above reaction mixture and it was stirred at rt for 3 h. Ice-water (15 mL) was added to the reaction mixture. The reaction mixture was cooled below 0 °C and concd HCl was added drop-wise until the pH was around 6 and it was further stirred for 30 min. The aqueous layer was extracted with chloroform (3 × 20 mL); the combined organic layer was dried over anhydrous sodium sulfate and the solvent removed to afford an oily product. The oil thus obtained was triturated with ether to obtain the desired product.

3.1.12.1. *N*-Hydroxy-2-{3-[4-(2-isobutyl-4-quinolinylmethoxy)-phenyl]-2-oxo-1-imidazolidinyl}propionamide (90A). Yield: 62.2%, R_f = 0.24 (EtOAc), mp 190–192 °C, IR (KBr, cm^{-1}): 3440, 2985, 1684, 1623, 1506, 1456, 1241, 1076, 827, PMR ($CDCl_3$): δ 8.17–8.19 (m, 1H), 7.92–7.94 (m, 1H), 7.70–7.73 (m, 1H), 7.52–7.55 (m, 1H), 7.39–7.45 (m, 3H), 6.98–7.02 (m, 2H), 5.49 (s, 2H), 4.71–4.68 (q, 1H, *J* = 7.28 Hz), 3.88–3.92 (m, 1H), 3.80–3.84 (m, 1H, 3.67–3.70 (m, 1H), 3.52–3.57 (m, 1H), 2.86–2.87 (d, 2H, *J* = 6.48 Hz), 2.16–2.21 (m, 1H), 1.50–1.52 (d, 3H, *J* = 7.32 Hz), 0.95–0.96 (d, 6H). Anal. Calcd for $C_{26}H_{30}N_4O_4$: C, 67.51, H, 6.54, N, 12.11. Found: C, 67.16, H, 6.97, N, 12.28.

3.1.12.2. *N*-Hydroxy-2-{3-[4-(2-isobutyl-4-quinolinylmethoxy)-phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionamide) (90B). Yield: 57.5%, R_f = 0.22 (EtOAc), mp 116–118 °C, PMR (DMSO-d_6): δ 8.11–8.13 (m, 1H), 7.89–7.91 (m, 1H), 7.68–7.72 (m, 1H), 7.49–7.53 (m, 1H), 7.40 (s, 1H), 7.18–7.20 (d, 2H), 6.97–6.99 (d, 2H), 5.45 (s, 2H), 4.69–4.73 (q, 1H), 3.60–3.63 (m, 2H), 3.36–3.40 (m, 2H), 2.83–2.85 (d, 2H), 2.09–2.231 (m, 3H), 1.46–1.47 (d, 3H), 0.94–0.96 (d, 6H). Anal. Calcd for $C_{27}H_{32}N_4O_4$: C, 68.05, H, 6.77, N, 11.76. Found: C, 67.85, H, 7.01, N, 11.42.

3.1.12.3. 2-{3-[4-(2-Ethyl-4-quinolinylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}-*N*-hydroxypropionamide (91A). Yield: 65.6%, R_f = 0.25 (EtOAc), mp 130 °C, IR (KBr, cm^{-1}): 3444, 2972, 1684,

1506, 1387, 1254, 1018, 825, PMR (DMSO-d_6): δ 8.04–8.06 (m, 1H), 7.94–7.96 (m, 1H), 7.68–7.72 (m, 1H), 7.48–7.54 (m, 4H), 7.00–7.21 (m, 2H), 5.47 (s, 2H), 4.53–4.57 (q, 1H), 3.81–3.77 (m, 2H), 3.65–3.68 (m, 2H), 2.96–3.01 (q, 2H), 1.36–1.40 (m, 6H). Anal. Calcd for $C_{24}H_{26}N_4O_4$: C, 66.34, H, 6.03, N, 12.89. Found: C, 65.98, H, 6.28, N, 12.69.

3.1.12.4. *N*-Hydroxy-2-{3-[4-(2-ethyl-4-quinolinylmethoxy)-phenyl]-2(1*H*)-oxotetra-hydro-1-pyrimidinyl}propionamide (91B). Yield: 56.1%, R_f = 0.17 (EtOAc), mp 179–180 °C, PMR (DMSO-d_6): δ 10.47 (br s, 1H), 8.78 (br s, 1H), 8.24–8.26 (m, 1H), 8.03–8.07 (m, 2H), 7.88–7.91 (m, 1H), 7.42 (s, 1H), 7.26–7.28 (d, 2H), 7.06–7.08 (d, 2H), 5.75 (s, 2H), 5.06–5.11 (q, 1H, J = 7.40 Hz), 3.66–3.69 (m, 2H), 3.49–3.55 (m, 2H), 3.37–3.40 (m, 2H), 2.11–2.21 (m, 2H), 1.55–1.58 (t, 3H), 1.43–1.45 (d, 3H, J = 7.40 Hz), MS (m/z): 449.4 $(M+H)^+$, 434.1 $(M-14)^+$, 388.1 $(M-CONHOH)^+$.

3.1.12.5. *N*-Hydroxy-2-{3-[4-(2-phenyl-4-quinolinylmethoxy) phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionamide (92B). Yield: 60.5%, R_f = 0.17 (10% MeOH in $CHCl_3$), mp 132–134 °C, IR (KBr, cm^{-1}): 3414, 3203, 2937, 1680, 1602, 1508, 1444, 1238, 1182, 1028, 771, PMR (DMSO-d_6): δ 8.17–8.19 (m, 2H), 8.08 (s, 1H), 8.03–8.05 (m, 2H), 7.75–7.79 (m, 1H), 7.58–7.62 (m, 1H), 7.52–7.55 (m, 2H), 7.45–7.49 (m, 1H), 7.22–7.25 (d, 2H, J = 8.88 Hz), 7.04–7.07 (d, 2H, J = 8.96 Hz), 5.60 (s, 2H), 5.03–5.06 (q, 1H), 3.62–3.68 (m, 2H), 3.39–3.46 (m, 2H), 2.07–2.16 (m, 2H), 1.37–1.39 (d, 3H). Anal. Calcd for $C_{29}H_{28}N_4O_4$: C, 70.15, H, 5.63, N, 11.28. Found: C, 69.93, H, 5.89, N, 11.03.

3.1.12.6. *N*-Hydroxy-2-{2-oxo-3-[4-(2-pyridinylmethoxy)phenyl]-1-imidazolidinyl}propionamide (93A). Yield: 67.4%, R_f = 0.12 (70% EtOAc in *n*-hexane), mp 170–171 °C, IR (KBr, cm^{-1}): 3448, 1684, 1615, 1517, 1436, 1248, 1056, 827, 749, PMR ($CDCl_3$): δ 8.58–8.59 (m, 1H), 7.71–7.75 (m, 1H), 7.51–7.53 (m, 1H), 7.41–7.44 (m, 2H), 7.23–7.26 (m, 1H), 6.94–6.96 (m, 2H), 5.17 (s, 2H), 4.61–4.65 (q, 1H), 3.77–3.90 (m, 2H), 3.64–3.68 (m, 1H), 3.51–3.55 (m, 1H), 1.45–1.47 (d, 3H), MS (m/z): 374.1 $(M+NH_4)^+$, 341.9 $(M-14)^+$, 296.4 $(M-CONHOH)^+$.

3.1.12.7. *N*-Hydroxy-2-{3-[4-(2-pyridinylmethoxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionamide (93B). Yield: 67.4%, R_f = 0.12 (70% EtOAc in *n*-hexane), mp 175–178 °C, IR (KBr, cm^{-1}): 3446, 1652, 1250, 1177, 1052, 827, 744, PMR (DMSO-d_6): δ 8.56–8.57 (m, 1H), 7.72–7.76 (m, 1H), 7.49–7.51 (m, 1H), 7.25–7.28 (m, 1H), 7.15–7.17 (d, 2H, J = 8.36 Hz), 6.92–6.94 (d, 2H, J = 8.36 Hz), 5.14 (s, 2H), 4.96–4.99 (q, 1H, J = 7.44 Hz), 3.61–3.70 (m, 2H), 3.37–3.48 (m, 2H), 2.05–2.15 (m, 2H), 1.41–1.43 (d, 3H, J = 7.40 Hz), MS (m/z): 393.0 $(M+Na)^+$, 378.7 $(M-14+Na)^+$, 369.7 $(M-H)^+$, 355.8 $(M-14)^+$, 310.1 $(M-CONHOH)^+$.

3.1.12.8. *N*-Hydroxy-2-{3-[4-(4-methoxybenzyloxy)phenyl]-2-oxo-1-imidazolidinyl}propionamide (94A). Yield: 57.0%, R_f = 0.68 (70% EtOAc in *n*-hexane), mp 147–148 °C, IR (KBr, cm^{-1}): 3448, 2985, 1695, 1506, 1456, 1245, 1175, 1007, 826, PMR (DMSO-d_6): δ 7.41–7.45 (m, 2H), 7.33–7.35 (m, 2H), 6.89–6.94 (m, 4H), 4.96 (s, 2H), 4.63–4.66 (q, 1H, J = 7.48 Hz), 3.79–3.82 (m, 5H), 3.65–3.69 (m, 1H), 3.48–3.52 (m, 1H), 1.46–1.48 (d, 3H, J = 7.56 Hz), MS (m/z): 403.1 $(M+NH_4)^+$, 371.1 $(M-14)^+$, 325.1 $(M-CONHOH)^+$.

3.1.12.9. *N*-Hydroxy-2-{3-[4-(4-methoxybenzyloxy)phenyl]-2(1*H*)-oxotetrahydro-1-pyrimidinyl}propionamide (94B). Yield: 60.9%, R_f = 0.68 (70% EtOAc in *n*-hexane), mp 169–170 °C, IR (KBr, cm^{-1}): 3446, 1652, 1616, 1456, 1263, 1177, 1028, 827, 749, PMR (DMSO-d_6): δ 7.33–7.35 (d, 2H), 7.15–7.17 (d, 2H), 6.89–6.91 (m, 4H), 5.01–5.05 (q, 1H, J = 7.40 Hz), 4.96 (s, 2H), 3.81 (s, 3H), 3.62–3.65 (m, 2H), 3.47–3.40 (m, 2H), 2.10–2.16 (m, 2H), 1.42–1.44 (d, 3H, J = 7.36 Hz), MS (m/z): 407.0 $(M-14+Na)^+$, 398.9 $(M-H)^+$.

3.1.12.10. *N*-Hydroxy-2-{3-[4-(1-naphthylmethoxy)phenyl]-2-oxo-1-imidazolidinyl}propionamide (95A). Yield: 58.9%, R_f = 0.73 (EtOAc), mp 172–173 °C, IR (KBr, cm^{-1}): 3446, 1684, 1506, 1277, 1232, 996, PMR (DMSO-d_6): δ 8.03–8.05 (m, 1H), 7.83–7.89 (m, 2H), 7.43–7.58 (m, 6H), 6.98–7.01 (m, 2H), 5.44 (s, 2H), 4.57–4.61 (q, 1H), 3.80–3.83 (m, 2H), 3.64–3.68 (m, 2H), 1.44–1.45 (d, 3H), MS (m/z): 428.6 $(M+Na)^+$, 404.8 $(M-H)^+$, 391.0 $(M-14)^+$, 344.8 $(M-CONHOH)^+$.

3.1.12.11. *N*-Hydroxy-2-{3-[4-(1-naphthylmethoxy)phenyl]-2-(1*H*)-oxotetrahydro-1-pyrimidinyl}propionamide (95B). Yield: 52.5%, R_f = 0.72 (EtOAc), mp 202–203 °C, IR (KBr, cm^{-1}): 3440, 2991, 1652, 1508, 1436, 1296, 1221, 1169, 835, 750, PMR ($CDCl_3$): δ 8.02–8.04 (m, 1H), 7.85–7.91 (m, 1H), 7.58–7.60 (m, 2H), 7.52–7.55 (m, 2H), 7.50–7.46 (m, 1H), 7.20–7.22 (d, 2H, J = 8.84 Hz), 7.00–7.02 (d, 2H, J = 8.88 Hz), 5.47 (s, 2H), 5.07–5.13 (q, 1H, J = 7.39 Hz), 3.65–3.72 (m, 2H), 3.36–3.45 (m, 2H), 2.17–2.21 (m, 1H), 2.07–2.12 (m, 1H), 1.44–1.45 (d, 3H, J = 7.44 Hz), MS (m/z): 442.9 $(M+Na)^+$, 427.0 $(M-14+Na)^+$, 418.9 $(M-H)^+$, 404.9 $(M-14)^+$, 358.8 $(M-CONHOH)^+$.

3.1.12.12. 2-{3-[4-(4-Biphenylmethoxy)phenyl]-2-oxo-1-imidazolidin}-*N*-hydoxypropionamide (96A). Yield: 55.0%, R_f = 0.25 (EtOAc), mp 242–243 °C, IR (KBr, cm^{-1}): 3493, 1684, 1506, 1484, 1277, 1242, 1014, 826, PMR (DMSO-d_6): δ 7.59–7.62 (m, 4H), 7.49–7.51 (m, 2H), 7.42–7.47 (m, 4H), 7.33–7.36 (m,1H), 6.95–6.97 (d, 2H), 5.09 (s, 2H), 4.62–4.66 (q, 1H, J = 7.48 Hz), 3.79–3.86 (m, 2H), 3.66–3.68 (m, 1H), 3.52–3.56 (m, 1H), 1.46–1.48 (d, 3H, J = 7.48 Hz). Anal. Calcd for $C_{25}H_{25}N_3O_4$: C, 69.59, H, 5.84, N, 9.74. Found: C, 69.07, H, 6.03, N, 9.59.

3.1.12.13. 2-{3-[4-(4-Biphenylmethoxy)phenyl]-2(1H)-oxotetrahydro-1-pyrimidinyl}-*N*-hydroxypropionamide (96B). Yield: 69.7%, R_f = 0.16 (EtOAc), mp 233–235 °C, IR (KBr, cm^{-1}): 1643, 1581, 1242, 1172, 1029, 839, 732, PMR (DMSO-d_6): δ 10.09 (br s, 1H), 8.61 (br s, 1H), 7.63–7.58 (m, 4H), 7.49–7.51 (m, 2H), 7.42–7.46 (m, 2H), 7.33–7.37 (m, 1H), 7.17–7.20 (d, 2H), 6.92–6.97 (d, 2H), 5.10 (s, 2H), 4.99–4.95 (q, 1H, J = 7.20 Hz), 3.60–3.63 (m, 2H), 3.39–3.45 (m, 2H), 2.06–2.16 (m, 2H), 1.38–1.37 (d, 3H, J = 7.24 Hz), MS (m/z): 484.2 $(M+K)^+$, 473.2 $(M+Na)^+$, 431.1 $(M-14)^+$, 413.1 $(M-NHOH)^+$, 385.1 $(M-CONHOH)^+$.

3.1.12.14. *N*-Hydroxy-2-{3-[4-(4-methoxythiobenzyloxy)phenyl]-2-oxo-1-imidazolidinyl}propionamide (97A). Yield: 63.7%, R_f = 0.40 (EtOAc), mp 112–114 °C, PMR (DMSO-d_6): δ 7.52–7.55 (d, 2H, J = 8.76 Hz), 7.33–7.35 (d, 2H, J = 8.80 Hz), 7.21–7.23 (d, 2H, J = 8.52 Hz), 6.85–6.87 (d, 2H, J = 8.56 Hz), 4.65–4.69 (q, 1H, J = 7.40 Hz), 4.06 (s, 2H), 3.94–3.96 (m, 1H), 3.83–3.86 (m, 4H), 3.75–3.78 (m, 1H), 3.61–3.64 (m, 1H), 1.49–1.51 (d, 3H, J =7.36 Hz). Anal. Calcd for $C_{20}H_{23}N_3O_4S$: C, 59.83, H, 5.77, N, 10.47. Found: C, 59.48, H, 6.01, N, 10.29.

3.1.12.15. 2-[3-(3-Benzyloxyphenyl)-2-oxo-1-imidazolidinyl]-*N*-hydroxypropionamide (98A). Yield: 77.8%, R_f = 0.30 (EtOAc), mp 208–211 °C, IR (KBr, cm^{-1}): 3197, 2995, 1664, 1517, 1485, 1260, 1039, 735, PMR ($CDCl_3$): δ 10.70 (br s, 1H), 8.90 (br s, 1H), 7.48–7.52 (m, 4H), 7.42–7.46 (m, 2H), 7.35–7.39 (m, 1H), 7.02–7.04 (m, 2H), 4.35–4.40 (q, 1H, J = 7.08 Hz), 3.78–3.87 (m, 2H), 3.62–3.68 (m, 1H), 3.51–3.58 (m, 1H), 1.32–1.34 (d, 3H, J = 7.16 Hz). Anal. Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21, H, 5.96, N, 11.82. Found: C, 64.03, H, 6.13, N, 11.67.

3.1.12.16. *N*-Hydroxy-2-{3-[4-benzyloxyphenyl]-2(1H)-oxotetrahydro-1-pyrimidinyl}propionamide (98B). Yield: 67.6%,

R_f = 0.34 (70% EtOAc in *n*-hexane), mp 175–177 °C, IR (KBr, cm^{-1}): 3059, 1693, 1566, 1508, 1444, 1242, 1174, 1026, 831, 752, PMR (DMSO-d_6): δ 7.31–7.42 (m, 5H), 7.15–7.18 (m, 2H), 6.90–6.92 (m, 2H), 5.03 (s, 2H), 4.38–4.42 (m, 1H), 3.59–3.62 (m, 2H), 3.39–3.41 (m, 2H), 2.07–2.17 (m, 2H), 1.40–1.43 (m, 3H). Anal. Calcd for $C_{20}H_{23}N_3O_4$: C, 65.03, H, 6.27, N, 11.37. Found: C, 65.54, H, 6.68, N, 11.12.

3.1.12.17. *N*-Hydroxy-2-{3-[3-(4-nitrobenzyloxy)phenyl]-2-oxo-1-imidazolidinyl}propionamide (99A). Yield: 62.5%, R_f = 0.42 (70% EtOAc in *n*-hexane), mp 128–129 °C, IR (KBr, cm^{-1}): 3232, 2923, 1670, 1515, 1483, 1436, 1346, 1249, 1058, 827, PMR ($CDCl_3$): δ 10.60 (br s, 1H), 8.80 (br s, 1H), 8.23–8.25 (d, 2H), 7.68–7.70 (d, 2H), 7.44–7.46 (d, 2H), 6.97–7.00 (d, 2H), 5.23 (s, 2H), 4.26–4.30 (q, 1H, J = 7.16 Hz), 3.70–3.77 (m, 2H), 3.54–3.60 (m, 2H), 1.25-1.27 (d, 3H, J = 7.20 Hz). Anal. Calcd for $C_{19}H_{20}N_4O_6$: C, 57.00, H, 5.03, N, 13.99. Found: C, 56.87, H, 5.98, N, 14.16.

3.2. Molecular modeling (docking studies)

All the molecular modeling studies reported herein were performed on a Silicon Graphics Fuel Workstation running on the IRIX 6.5 operating system using SYBYL 6.9 molecular modeling software from Tripos, Inc., USA[31] and GLIDE from Schrödinger Inc., USA.[32,33] All compounds used for docking were built from the fragments in the SYBYL database. Each structure was fully geometry optimized using the standard Tripos force field with a distance-dependent dielectric function until a root mean square deviation (rms) of 0.01 kcal/mol Å was achieved. Conformational search was carried out using MULTISEARCH option in SYBYL 6.9. The lowest energy conformer thus obtained was further minimized using the Tripos force field and was subsequently used in docking. The crystal structure of human TACE (pdb code: 2FV5) obtained from the Protein Data Bank (USA) was refined to remove water molecules. The bond orders and formal charges were adjusted prior to docking. Docking was performed using GLIDE software according to their previously reported protocol.[32,33]

3.3. Biological screening

The method followed for the assay was as given in the protocol supplied by the manufacturer.[28] The compounds were weighed accurately in a micro-balance and dissolved in DMSO. They were further diluted to prepare the desired concentrations. The desired number of strips containing wells from the InnozymeTM TACE activity kit was removed and the remaining strips were resealed in the foil pouch for further use. The wells were washed well with wash buffer provided along with the kit for two times and then the residual liquid was wiped off with paper towel. The pure enzyme (Control) provided along with the kit was diluted (1:50) with sample buffer provided in the kit as per the protocol. Cell lysate was also diluted (1:50) with sample buffer. 100 μL of control and cell lysate was added to all the wells and covered with a plate sealer which was provided along with the kit. It was then incubated at 25 °C for 1 h. The wells were again washed with wash buffer for five times to remove any deposited material on the wells. The test inhibitors (100 μL) were added to the designated wells and incubated for 2 h at 25 °C. 20 μL of diluted substrate (diluted with assay buffer provided along with the kit, 1:10,000) was then added to each well and then the wells were incubated at 37 °C for 4 h. They were allowed to come to rt and the fluorescence was recorded on spectrofluorimetric ELISA reader.

4. Conclusion

In this work, novel 2-imidazolidinones and tetrahydropyrimidin-2-(1*H*)-ones were synthesized and evaluated for their TACE inhibitory activity. Most of the synthesized compounds showed moderate to high TACE inhibitory activity. This work has provided some important leads in the form of compounds (**80A**, **81A**, **93A**, **90A,** and **91A**) as potential TACE inhibitors. Biological activity data are in accordance with the modeling study. Docking study clearly reveals the importance of the P1′ group for the TACE inhibitory activity of these classes of compounds.

Acknowledgment

Two of the authors, S.D.G. and P.R.M., are thankful to All India Council for Technical Education (A.I.C.T.E), Government of India, New Delhi, India, for the award of National Doctoral Fellowship.

References and notes

1. Tracey, K. J.; Cerami, A. *Ann. Rev. Med.* **1994**, *45*, 491.
2. Goldfeld, A. E.; Strominger, J. L.; Doyle, C. *J. Exp. Med.* **1991**, *174*, 73.
3. Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **1999**, *42*, 2295.
4. Hotamisligil, G.; Arner, P.; Caro, J.; Atkinson, R.; Spiegelman, B. *J. Clin. Invest.* **1995**, *95*, 2409.
5. Selmaj, K.; Raine, C.; Cannella, B.; Brosnon, C. *J. Clin. Invest.* **1991**, *87*, 949.
6. Rus, H.; Niculescu, F.; Vlaicu, R. *Atherosclerosis* **1991**, *89*, 247.
7. Oppenheim, J. J.; Feldmann, M. In *Cytokine Reference*; Oppenheim, J. J., Feldmann, M., Eds.; Academic Press: New York, 2001; pp 3–20.
8. Feldmann, M.; Brennan, F. M.; Maini, R. N. *Ann. Rev. Immunol.* **1996**, *14*, 397.
9. Odeh, M. *Clin. Immunol. Immunpathol.* **1997**, *83*, 103.
10. Bertolini, D. R.; Nedwin, G. E.; Bringman, T. S.; Smith, D. D.; Mundy, G. R. *Nature* **1986**, *319*, 516.
11. Sakalatvala, J. *Nature* **1986**, *319*, 547.
12. Papadakis, K. A.; Targan, S. R. *Annu. Rev. Med.* **2000**, *51*, 289.
13. Tracey, D.; Klareskog, L.; Sasso, E. H.; Salfeld, J. G.; Tak, P. P. *Pharmcol. Ther.* **2008**, *117*, 244.
14. Nelson, F. C.; Zask, A. *Exp. Opin. Invest. Drugs* **1999**, *8*, 383.
15. Newton, R. C.; Solomon, K. A.; Covington, M. B.; Deccico, C. P.; Haley, P. J.; Friedeman, S. M.; Vaddi, K. *Ann. Rheum. Dis.* **2001**, *60*, 25.
16. Dasupta, S.; Murumkar, P. R.; Giridhar, R.; Yadav, M. R. *Bioorg. Med. Chem.* **2009**, *17*, 444.
17. Kenny, P. A.; Bissell, M. J. *J. Clin. Invest.* **2007**, *117*, 337.
18. Kenny, P. A. *Expert Opin. Ther. Targets* **2007**, *11*, 1287.
19. Murumkar, P. R.; Giridhar, R.; Yadav, M. R. *Chem. Biol. Drug Des.* **2008**, *71*, 363.
20. Murumkar, P. R.; Dasgupta, S.; Zambre, V.; Giridhar, R.; Yadav, M. R. Chem. *Biol. Drug Des.* **2009**, *73*, 97.
21. Duan, J. J. W.; Chen, L.; Wasserman, Z. R.; Lu, Z.; Liu, R. Q.; Covington, M. B.; Qian, M.; Hardman, K. D.; Magolda, R. L.; Newton, R. C.; Christ, D. D.; Wexler, R. R.; Decicco, C. P. *J. Med. Chem.* **2002**, *45*, 4954.
22. Niu, X.; Umland, S.; Ingram, R.; Beyer, B. M.; Liu, Y. H.; Sun, J.; Lundell, D.; Orth, P. *Arch. Biochem. Biophys.* **2006**, *451*, 43.
23. ElAshray, E. S. H.; Ramadan, E. S.; Hamid, H. A.; Hagar, M. *Synth. Commun.* **2005**, *35*, 2243.
24. Gorbatenko, V. I.; Samarai, L. I. *Synthesis* **1980**, *2*, 85.
25. Shia, K. S.; Li, W. T.; Chang, C. M.; Hsu, M. C.; Chern, J. H.; Leong, M. K.; Tseng, S. N.; Lee, C. C.; Lee, Y. C.; Chen, S. J.; Peng, K. C.; Tseng, H. Y.; Chang, Y. L.; Tai, C. L.; Shin, S. R. *J. Med. Chem.* **2002**, *45*, 1644.
26. Chern, J. H.; Chang, C. S.; Tai, C. L.; Lee, Y. C.; Lee, C. C.; Kang, I. J.; Lee, C. Y.; Shin, S. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4206.
27. Kirkegaard, T.; Pedersen, G.; Saermark, T.; Brynskov, J. *Clin. Exp. Immunol.* **2004**, *135*, 146.
28. www.merckbiosciences.com/product/CBA042, User Protocol CBA042 Rev.
29. Crowe, P. D.; Walter, B. N.; Mohler, K. M.; Evans, C. O.; BVlack, R. A.; Ware, C. F. *J. Exp. Med.* **1995**, *181*, 1205.
30. Aldrich Research Chemical Catalog, **2000**, 1299.
31. SYBYL Molecular modeling system, version 6.9, Tripos, Inc., St. Louis, USA, 2003.
32. Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelly, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. *J. Med. Chem.* **2004**, *47*, 1739.
33. Clark, M.; Crammer, R. D.; van Opdenbosh, N. *J. Comput. Chem.* **1989**, *10*, 982.