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Review

Current perspective of TACE inhibitors: A review

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ABSTRACT

Rheumatoid Arthritis (RA) is one of the most common autoimmune inflammatory conditions, affecting approximately 1% of the adult population worldwide. TNF-α is a pleitropic, pro-inflammatory cytokine which plays a pivotal role in the origin and progression of RA and other immune mediated disorders. The success of anti-TNF-α biological agents proved that inhibition of TNF-α could result in effective control of RA. Since the discovery of anti-TNF-α biologicals, much efforts have gone into developing an orally bioavailable small size TNF-α antagonist. One of the ways to block TNF-α in biological fluids is to inhibit TNF-α converting enzyme (TACE). This target has been validated in preclinical trials using TACE inhibitors. But, even after more than a decade no single TACE inhibitor has passed the Phase II clinical trials. Very recently, it has been shown that TACE inhibitors could also be used for inhibition of pathogenic EGFR signaling in cancer. Hence, TACE inhibitors could perform a dual role, in curing not only RA but also certain cancerous conditions. Developments in the field have prompted us to review the research work on TACE inhibitors, especially their structure activity relationships and molecular modeling studies.

Contents

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] Transcription of TNF-α gene is regulated in a complex manner and

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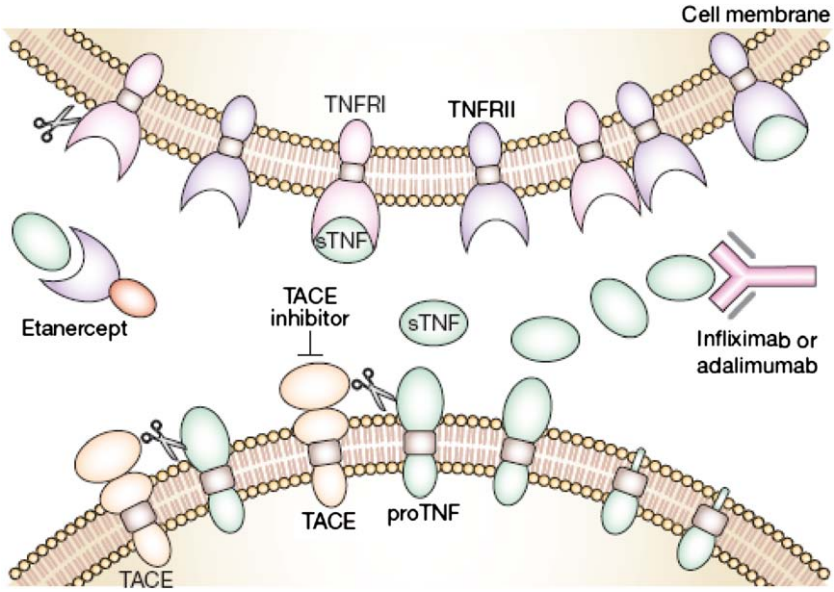


Figure 1. The graphical mode of action of anti-TNF biological agents and TACE inhibitors.[22]

there are multiple transcription factors like NF-κB, AP-1, NFIL-6, and NFAT. The p38 MAPK signaling pathway also plays a critical role in the production of TNF-α.[3,4]

The biological responses to TNF-α are mediated through two distinct receptors; namely TNF-R1 and TNF-R2. Both of these receptors are transmembrane glycoproteins. Although their extracellular domains share structural and functional homology, their intracellular domains are distinct. TNF-R1 is constitutively expressed in most tissues while TNF-R2 is typically found in cells of immune system. It has been experimentally proved that under physiological conditions, signaling through TNF-R1 seems to be primarily responsible for pro-inflammatory properties of TNF-α.[5] Though much information is not available about TNF-R2, it has been speculated that it acts as ligand passer, at least in some cells.[6]

Over-expression of TNF-α is responsible for a number of pathological conditions like Crohn's disease, ulcerative colitis,[3] diabetes,[7] multiple sclerosis,[8] atherosclerosis[9] and stroke.[10] Additionally there exists compelling evidence 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.[11–17] The major effects shown by TNF-α are listed below. It:

- Releases vasodialatory molecules, for example, bradykinin, histamine, prostacyclin;
- Stimulates bone resorption;
- Inhibits bone collagen synthesis;
- Stimulates matrix metalloproteinase release, which in turn plays an important role in the destruction of connective tissue;
- Acts as osteoclast activating factor;
- Stimulates production of COX and PGE2;
- Produces reactive oxygen species (ROS) which in turn causes tissue destruction;
- Induces neutrophil production by ROS;
- Causes neoangiogenesis which leads to the formation of pannus tissue;
- Induces production of other pro-inflammatory cytokines, for example, IL-1, IL-6, IL-8, GM-CSF, etc.

After the role of TNF-α was elucidated clearly in RA, efforts have been made to develop inhibitors of TNF-α, and three protein-based drugs have been approved by USFDA for their use in the treatment of RA.[18]

Etanercept is genetically engineered version of Tumor Necrosis Factor Receptor-2 (TNF-R2) that binds and inactivates TNF-α, preempting its role in RA. Infliximab (Mouse-human chimeric anti-human TNF-α antibody) and Adalimumab (Human anti-human TNF-α antibody) have also been approved for the treatment of RA.[19,4] These TNF-α blockers are effective for the treatment of RA and show significant, documentable improvement in signs, symptoms and laboratory parameters within 8–12 weeks.[20]

Success of these biological agents proved that inhibition of TNF-α would result in effective control of RA. Despite marked activity of the biological agents that neutralize TNF-α, from the stand point of ease of administration, reduced cost of treatment, patient compliance and potential for more precise control of TNF-α level, an orally administered, selective small molecule inhibitor of TNF-α would be desirable.[3,21] Attempts to disable TNF-α function are targeted at different levels. TNF-α can be inhibited at two stages:[21,22]

(i) *Inhibition of pro-TNF-α processing*: TNF-α is produced in the body from its precursor form, pro-TNF-α. Pro-TNF-α is proteolytically cleaved by a zinc metalloproteinase, called TNF-α converting enzyme (TACE), to the active and soluble form, s-TNF-α. Inhibition of this enzyme would automatically reduce the amount of active TNF-α in the blood.

(ii) *Inhibition of pro-TNF-α synthesis*: Inhibition of pro-TNF-α synthesis could be achieved by using Nuclear Factor (NF)- κB inhibitors, phosphodiesterase (PDE) inhibitors, and thalidomide analogs. It is seen that NF-κB and PDE, especially PDE4, are involved in the production of TNF-α. Thalidomide and its analogs also inhibit TNF-α production in the body by some unknown mechanism.

It is hypothesized that small size orally bioavailable TACE inhibitors would have the potential to effectively treat RA and other inflammatory diseases by limiting the levels of soluble—TNF-α.[3,23–25] 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.[26] Based on this hypothesis, several research groups world wide are actively pursuing for development of small molecule orally bioavailable TACE inhibitors.[27]

The graphical mode of action of anti-TNF biological agents and TACE inhibitors are shown in Figure 1.[22]

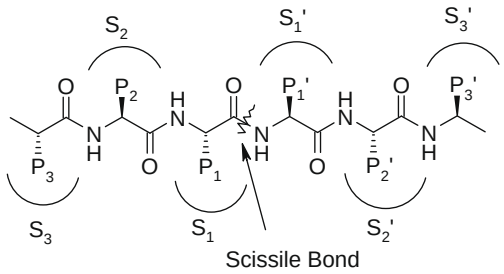


Figure 2. Standard nomenclature for substrate inhibitor residues and their corresponding binding sites[31] in the enzyme.

2. TNF-α converting enzyme (TACE)

TNF-α is produced in the body as pro-TNF-α, the inactive form of the cytokine as 233 aa membrane anchored precursor. It is transformed into the active and soluble form by limited proteolysis at the Ala76 and Val77 bond. The proteinase responsible for this cleavage, called TACE, has been cloned by two research groups at the same time.[28,29]

TACE (ADAM17, CD156b, EC 3.4.24) belongs to the ADAM (a disintegrin and metalloproteinase domain) family of proteinases that belongs to the super-family of metzincin. There are 39 distinct ADAM family members mentioned in public databases.[30] The structure of TACE closely resembles that of ADAM family members.

All proteinases bind their substrate in a groove or cleft, wherein amide bond hydrolysis occurs. Amino acid side chain of substrate occupies enzyme sub-sites in the groove, designated as S3, S2, S1, S1′, S2′ and S3′ that bind to corresponding substrate/inhibitor residues P3, P2, P1, P1′, P2′ and P3′ with respect to the cleavable amide bond as shown in Figure 2.[31]

2.1. Structure of TACE

TACE is a type I transmembrane protein, synthesized as zymogen. It contains a pro-domain, catalytic domain, a disintegrin and cysteine-rich region, a transmembrane segment and a cytoplasmic tail. The pro-domain is considered to act as an inhibitor of the proteinase activity. The free cysteine residue present in the pro-domain coordinates with the zinc in the active site of TACE and thus prevents its activity. Pro-domain removal is therefore regarded as pre-requisite for TACE activity.[32]

The potential furin cleavage site localized between pro- and the catalytic domain is responsible for the generation of the active TACE by removal of the pro-domain by furin.[33]

The catalytic domain contains the zinc-binding motif which is involved in co-ordinating zinc with histidine residue and creating the active site of the enzyme. The crystal structure of the catalytic domain is well documented in literature.[23]

The catalytic site of TACE has the oblate ellipsoid shape, central to a highly twisted 5-stranded β-pleated sheet (strands sI–sV, as shown in red color in Fig. 3) flanked on its convex side by α-helices hB and hB2 and on its concave side by helices hA and hC. β-Strands sII and sIII are linked by a large 'multiple-turn loop', a long 'intermediate' α-helix (hB), and an adjacent short α-helix (hB2), all arranged on 'top' of the β-sheet and thus fully shielding its central part from bulk water. The multiple-turn loop is bulged-out at two sites, giving rise to a 'spur-like' and an 'acidic' protuberance (visible in Fig. 3 on top of the molecule). The sIII–sIV linker terminates in a short 'bulge' before entering the 'edge' strand sIV, the only antiparallel β-strand. The sIV–sV connecting segment is dissected into two large 'ear-like' surface loops, the first one nestling to the main molecular body (giving rise to the 'blue' surface, center left in Fig. 3), and a long β-hairpin loop (sIVa–sIVb) projecting from the molecular surface (upper left in

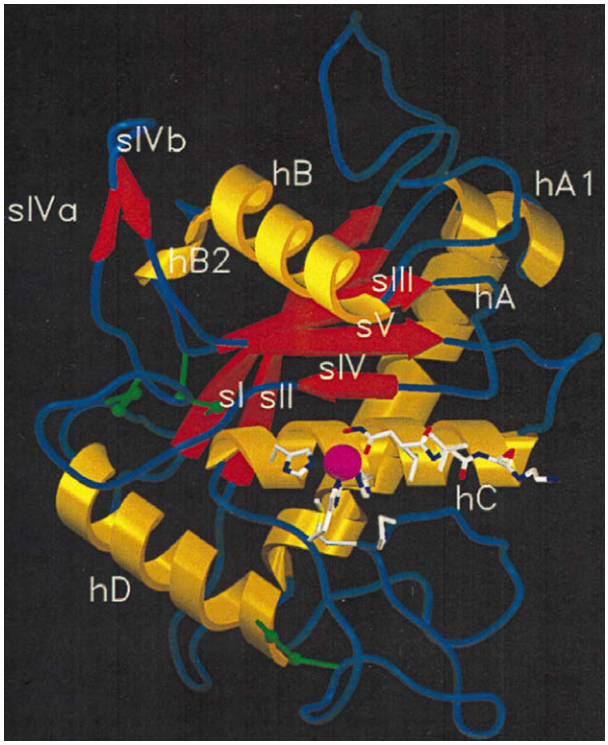


Figure 3. Ribbon diagram of TACE catalytic domain. The chain starts and ends on the lower and upper left backside, respectively. The three disulfides are shown as green connections and the catalytic zinc is shown as a pink sphere. His405, His 409, His415, Met435, Pro437 and the inhibitor (white) are shown with their full structures.[34]

Fig. 3). A bulged-out loop links sV with the 'active-site helix' hC, which is located in the center of the molecule and stops abruptly at the strictly conserved Gly412. At this point, the chain kinks down to build the lower sub-domain.[34]

Analysis of the amino acid sequence of TACE indicates the presence of an EGF-like domain and a crambin-like domain, unique to TACE, within the cysteine-rich domain. The cysteine-rich domain is responsible for the substrate recognition and also for the process of TACE maturation.[35]

The cytoplasmic tail of TACE contains potential sites for interaction with Src-homology-2 and Src-homology-3 and a potential tyrosine phosphorylation site as well as potential MAPK phosphorylation site.[36]

2.2. Functions of TACE

The role of TACE in shedding TNF has been confirmed by in vitro experiments. Both, T-cells and monocytes derived from 'TACE$^{\Delta Zn/\Delta Zn}$' transgenic mice are deficient in releasing TNF.[28] Most of the 'TACE$^{\Delta Zn/\Delta Zn}$' mice show developmental defects, such as failure of eyelids to fuse and specific hair and skin defects observed in the embryos closely resembling the defects characteristics for the TGF-α deficiency. Moreover, it has been shown that the release of TGF-α from the cell membrane of 'TACE$^{\Delta Zn/\Delta Zn}$' cells is inhibited. It proves that TACE is responsible for the release of the active form of TGF-α.[37]

Not only TGF-α, TACE is responsible for the shedding of a number of proteins, such as, L-Selectin, TNF-R2, Amyloid Precursor Protein (APP) and TypeII Interleukin (IL-1) receptor. But it has also been shown that TACE is not a universal sheddase.[38]

Hence, the question arises what makes a given protein a TACE substrate. The sequences obtained in various substrates are highly variable. Moreover, the structure of the substrate-binding cleft of

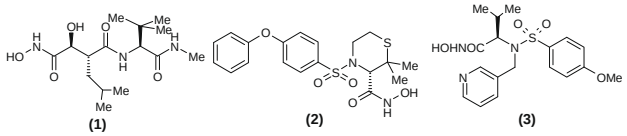
the enzyme does not suggest a strong interaction. It has been suggested that interactions distant to the cleavage site are required and also in some cases the substrate and the enzyme both have to anchor to a membrane.[38]

2.3. Regulation of TACE

The regulation of TACE activity is poorly understood. It has been observed that the shedding rate of TACE increases within minutes of addition of cell activators like phorbol ester. Inhibitors of Mitogen Activated Protein Kinase (MAPK) cascade block the increase in shedding rate in a number of cases where TACE is a primary sheddase.[39] However, the mechanism of action of MAPK cascade is not clear. Interestingly, a small protein, Tissue Inhibitor of Metalloproteinase (TIMP-3), that inhibits most matrix metalloproteinases,[40] also inhibits TACE, but whether TIMP-3 acts as a physiological regulator of the enzyme is unknown.

3. TACE and MMP

As the structure of catalytic site of TACE and matrix metalloproteinase (MMP) are same and also both are zinc endopeptidases, some previously identified MMP inhibitors were found to inhibit TACE as well, for example, marimastat (**1**), prinomastat (**2**), and CGS 27023A (**3**). But they failed in clinical trials as they showed dose-limiting musculoskeletal side effects.[41–43] Though the exact reason for this side effect is unknown, according to some researchers the efficacy of these molecules is due to their ability to inhibit TACE, but their ability to inhibit MMP-1 and/or MMP-14 is the cause for their toxicity.[44,45]

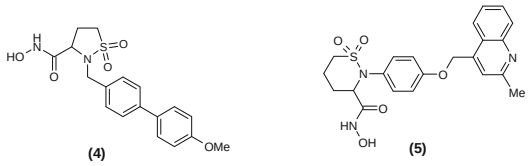


Hence, according to some researchers, it is desirable to develop selective TACE inhibitors devoid of any MMP activity.[26,46] Some others argue that compounds that are active against TACE as well as MMPs may be more efficacious than a selective TACE inhibitor only, as MMPs are also over-expressed in RA. Various research groups world-over are engaged in developing a dual TACE and MMP-13 inhibitor which does not inhibit MMP-1.[47–49] On the other hand, TACE and MMPs are involved in various normal physiological processes, and hence selective inhibitors may present fewer side effects. The optimal MMP selectivity profile for a TACE inhibitor in the treatment of RA is still unknown.[50,51]

Because of the structural similarities between TACE and MMPs, identification of selective TACE inhibitors proved elusive until recently. The difference in the shape and size of the S1′ pocket of TACE and MMPs might be exploited to design selective TACE inhibitors devoid of any MMP activity.[52,53]

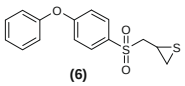
It is quite evident that the S1′ pocket [right hand side of the zinc atom (pink color) corresponding to P1′, P2′ and P3′ residues of the substrate] of TACE is larger and narrower than MMPs as shown in Figure 4A and B.

Bristol–Myers–Squibb reported a sulfonamide hydroxamate (**4**) as MMP inhibitor which lacked TACE inhibitory activity. This compound has Ki value of 3.8, 46.7 and 55 nM for MMP-2, 9 and 13, respectively, while the IC_{50} value for TACE is >1000 nM.[54]



To convert a non-selective MMP inhibitor into a selective TACE inhibitor, the same group of scientists, replaced the 4-methoxyphenyl group of **4** with a quinolinyl moiety. It was argued that the quinolinyl moiety would fit into the larger S1′ pocket of TACE while it would clash with the smaller S1′ pocket of MMPs. Introduction of the quinolinyl group and small changes in the structure of the molecule (**4**) provided compound (**5**), which had IC_{50} value of 3.7 nM for TACE and the compound was more than 1000-fold more selective for TACE over MMP-1, 2, 9 and 13.[55]

Solomon et al. found that the molecule, SB-3CT (**6**), showed different binding affinity for MMP-2 and TACE. Although there exists high three-dimensional structural similarity among the active sites of TACE and MMPs, the TACE conformational structure around the catalytic zinc ion and the total effective charge on this metal ion is very different from that of MMPs. They also discovered that active site of TACE was more polar than MMPs. Hence, they argued that the differences in electronic, structural and kinetic behavior observed between TACE and MMPs, might allow designing of specific inhibitors of TACE.[56]



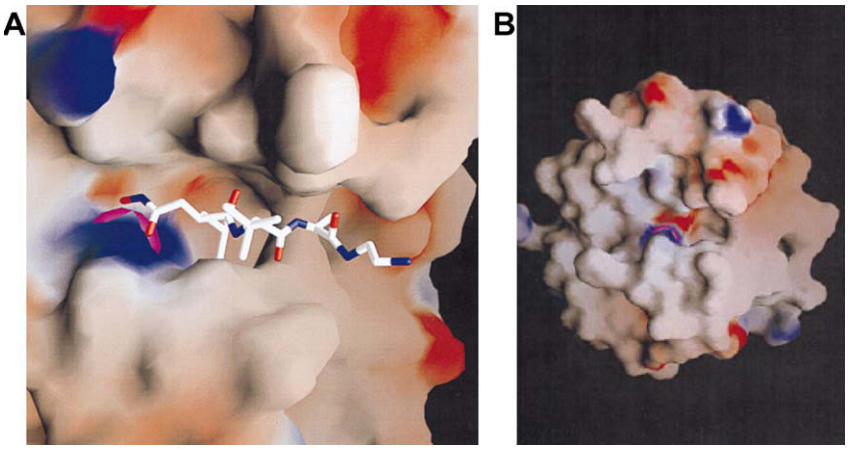


Figure 4. Solid surface representations of the catalytic domains of TACE (A) and MMP-3 (B).[34]

Lukacova et al. compared extensively the binding sites of TACE and MMPs. According to them, specificity for TACE in comparison to MMPs can be achieved by placing a negatively part of the charged ligand at the bottom of S2 sub-site and also at the entrance of S1′ sub-site.[57]

Zhao et al. analyzed and compared the properties of catalytic domains of TACE, MMP-1, MMP-2, MMP-3 and MMP-9. They reported that the conformations and molecular surface hydrophobicity of all of them are very similar although there were substantial differences in electrostatic potentials of catalytic domain.[58]

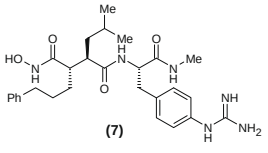
4. TACE inhibitors

4.1. Succinate-based dual TACE and MMP inhibitors

As previously stated, the early MMP inhibitors were also TACE inhibitors, like marimastat (**1**), prinomastat (**2**), CGS 27023A (**3**), etc. All of them showed good activity against TACE. The IC_{50} values of marimastat and prinomastat against TACE were found to be 3.8 nM and 22 nM respectively.[59] These are used as the lead molecules in the designing of newer TACE inhibitors.

Compound (**7**), developed by Daiichi Fine Chemical Co has a phenyl guanidine group to enhance its water solubility. Its IC_{50} value for inhibition of TNF-α synthesis in LPS stimulated THP1 cells is 130 nM. This compound is also an inhibitor of MMP-1 (IC_{50} = 6 nM) and MMP-13 (IC_{50} = 0.1 nM).[60]

PKF-242-484 (**8**) and PKF-241-466 (**9**) developed by Novartis are broad spectrum TACE inhibitors. In human peripheral blood mononuclear cells the IC_{50} values of PKF-242-484 (**8**) and PKF-241-466 (**9**) for TACE are 56 and 141 nM, respectively. They are also potent inhibitors of MMP-1 and MMP-2. These compounds were found to be effective in various models of lung inflammation.[61,62]



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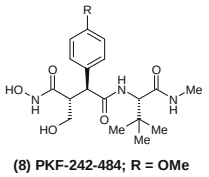
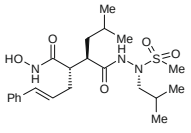


(8) PKF-242-484; R = OMe

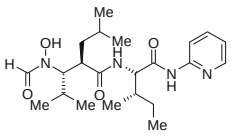
(9) PKF-241-466; R = Me



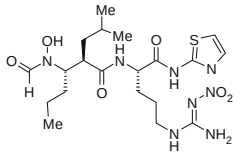
(10) Ro-32-7315

Ro-32-7315 (**10**) has around 100-fold higher selectivity for TACE over most of the MMPs. Structurally, it has the same succinate hydroxamic acid motif of MMP inhibitors with P2′ amino acid replaced by a hydrazide group. It has shown excellent potency against TACE in in vitro model (IC_{50} = 3 nM), but its oral bioavailability was found to be very poor and hence its development was stopped.[63,64]

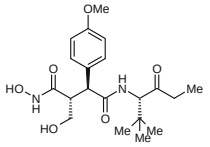
N-Hydroxyformamide analogs of succinate hydroxamates have also afforded potent inhibitors of TACE, like GW-3333 (**11**) and GW-4459 (**12**). They have shown IC_{50} values of 40 and 4.3 nM in cell-free TACE. Both the compounds are broad spectrum TACE/MMP inhibitors. GW-3333 was shown to be exceptionally potent (EC_{50} = 1 mg/Kg, po) and long lasting ($T_{1/2}$ > 12 h) in rat LPS model. The only problem with this compound (**11**) was its poor oral bioavailability. Hence, an elaborate series based on this compound was developed and studied by scientists at Glaxo Smith Kline Inc. to obtain a molecule with same or increased potency possessing oral bioavailability. But none of the molecules of this series showed good oral absorption.[65–67]



(11) GW3333



(12) GW-4459



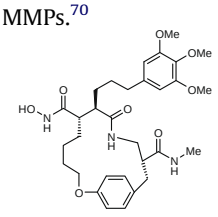
(13)

Kottrisch et al. have synthesized some β-arylsuccinic acid hydroxamates as dual TACE and MMP inhibitors. The best compound (**13**) of the series shows inhibition of TACE, MMP-1, MMP-2, MMP-3 at nanomolar levels. Oral administration of **13** to rats inhibits LPS-induced plasma TNF levels with an ED_{50} of 1 mg/kg.[68]

4.2. Macrocyclic inhibitors

In this type of compounds the P1′ and P2′ groups of succinate TACE inhibitors are joined together to form a cycle. The reason for the synthesis of the cyclic system was to reduce the potency of the compounds towards MMP-1.[69]

Trimethoxyphenyl group has been used as P1′ moiety in the construction of macrocyclic hydoxamate TACE inhibitor (**14**). Glycine *N*-methylamide P3′ analog SL-422 (**15**) TNF-α in human whole blood at a concentration of 0.22 μM. It was observed that longer P1′ group would reduce the potency of the compounds. However, this compound is a broad spectrum inhibitor of TACE.[70] Dramatic improvement in potency was seen in the macrocyclic carbamate compound, SP057 (**16**). The terminal glycine residue of (**15**) is extremely important for the in vivo activity of the compound as its deletion from the structure reduces its oral bioavailability. Compounds (**15**) and (**16**) both have short half-lives and moderate bioavailability in dogs. When the P1′ group, that is, isopropyl group of (**16**) was replaced with biphenyl moiety, the resulting compound (**17**) possessed the same TACE inhibitory potency, but interestingly this change increased its selectivity for TACE. Compound (**17**) was more than 100-fold more selective towards TACE over most of the MMPs.[70]



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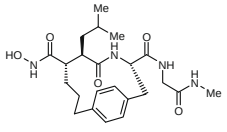
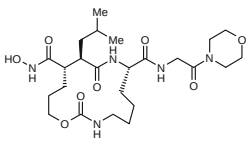
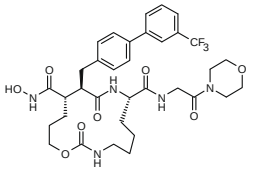


(15) SL-422



(16) SP-057



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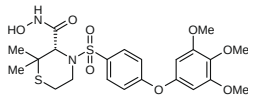
4.3. Sulfonamide Inhibitotrs

Some sulfonamide hydroxamates bearing novel P1′ groups are also reported as TACE inhibitors. Compound (**18**) having a trimethoxyphenyl group as P1′ moiety is a potent TACE inhibitor. Its IC_{50} value is reported to be 550 nM in THP1 cells.[61]



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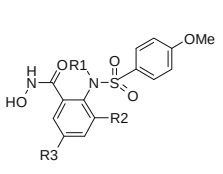
Some aryl hydroxamates were also reported as TACE/MMP inhibitors. The aryl groups were either isolated or fused. Among all of these groups, anthranilate derivatives (**19**) showed most promising in vitro TACE inhibitory activity.[71] The SAR reveals that presence of halogens at R_3 is extremely important for TACE inhibitory activity. Removal of halogen at R_3 decreases the activity toward TACE dramatically by six times. Replacement of bromo group at this position by methyl group decreases the activity by two times. The most potent compound of the series has bromo group at R_3 and methyl groups both at R_1 and R_2. The IC_{50} values of the best compound of the series against TACE and MMP-13 are 32 and 11 nM; while against MMP-1 it is 114 nM. It has also been observed that although this series of compounds showed very good in vitro activity, they were not active in in vivo models because of their low oral bioavailability.[72]



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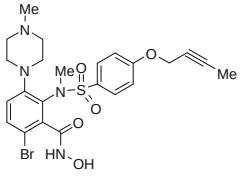
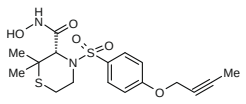


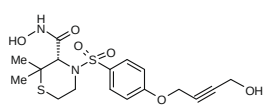
(20)

Researchers have sought further improvement in activity, selectivity and pharmacokinetic profile of anthranilate TACE inhibitors. The fact that S1′ site of TACE is narrower and longer than that of the MMPs,[52] has been utilized in the designing of selective TACE inhibitors. It was postulated that a carbon–carbon triple bond attached to a $–O–CH_2–$ group would fit perfectly with the S1′ site of TACE, while it would not allow effective binding with MMPs.[72] Several new molecules were synthesized based on the above theory and screened for their TACE as well as MMP inhibitory activity. The most potent and selective compound (**20**) has butynyloxy group at P1′. Its IC_{50} value for TACE is equal to 25 nM. It is more than 10 times more selective toward TACE over MMP-13 and almost 500 times more selective over MMP-1.[73] The oral activity of (**20**) was improved due to the attachment of basic piperazine moiety at 3-position.[74] Compound (**20**) has shown 100% inhibition of TNF-α in mouse (50 mg/Kg) after 1 hour of oral dosing.[75]

Levin et al. have explored thiomorpholine hydroxamates, bearing butynyloxy moiety at P1′ site. Among the compounds developed, the most promising was TMI-1 (**21**).[76,77] This compound is currently in the Phase-II of clinical trials. This is one of the best dual acting compounds discovered so far. Its IC_{50} values for TACE, MMP-1, MMP-2 and MMP-13 are 8.4, 6.6, 4.7 and 3.0 nM, respectively. This compound has also shown high activity in various in vivo models.[51,77] Apratastat, commonly known as TMI-05 (**22**) developed by this group is a broad spectrum TACE inhibitor. It is also a thiomorpholine derivative, like TMI-1 (**21**). The P1′ group is slightly different from that of TMI-1 (**21**). In the structure of this compound (**22**) free hydroxyl group is present. The compound has excellent in vitro activity against TACE. Its IC_{50} value is 0.44 μM. It also showed in vivo activity in mouse collagen induced arthritis model.[78] Though the compound (**22**) did not show any side effects in Phase I clinical trials, it was withdrawn from the Phase II of clinical trials due to lack of efficacy.[79]

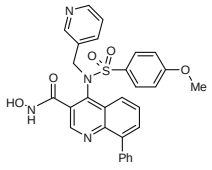


(21) TMI-1



(22) Apratastat or TMI-05

Quinoline hydroxamates are all moderately acting TACE inhibitors. In fact, they are selective inhibitors of MMP-13 over MMP-1 and TACE. The most potent quinoline derivative (**23**) has IC_{50} value of 120 nM towards TACE while its IC_{50} value for MMP-13 is only 4 nM.[80]



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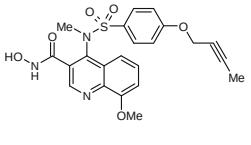
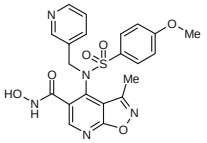


(24)

The concept of attaching butynyloxy group at P1′ site to make the molecule selective TACE inhibitor was extended to the quinoline moiety as well. It was found that compound (**24**) was more than 7 times more potent towards TACE. It has IC_{50} value of 17 nM toward TACE and has 50 times higher selectivity over MMP-1.[80]

Some heteroaryl-fused pyridinehydroxamates were also developed as moderately acting TACE inhibitors. The in vitro studies revealed that this class of compounds actually selectively inhibits MMP-13 over TACE. Compound (**25**) is 15 times more potent towards MMP-13 over TACE (IC_{50} values for MMP-13 and TACE are 10 and 147 nM, respectively).[80]



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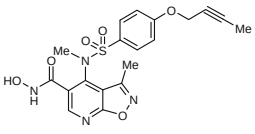
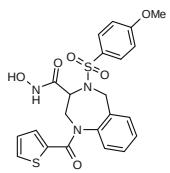


(26)

Some heteroaryl-fused pyridine derivatives were synthesized with butynyloxy group at P1′. The best compound (**26**) of the series shows IC_{50} value equal to 6 nM and about 10 times more potency towards TACE over MMP-13. It inhibited 95% production of TNF-α in mouse model at a dose of 100 mg/kg after 1 h of oral dosing.[75]

Some analogs of benzodiazepines were synthesized as dual TACE and MMP inhibitors. The compound having thiophene nucleus at N1 of benzodiazepine moiety (**27**) showed most potent in vitro activity. The compound is a broad spectrum inhibitor; it inhibited MMP-1, MMP-2, MMP-9, MMP-13 and TACE in nanomolar range.[81]



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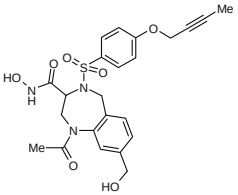
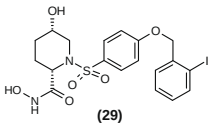


(28)

Incorporation of butynyloxy group at P1′ of the benzodiazepine analogs did not produce a selective TACE inhibitor. The best compound (**28**) in the series has IC_{50} value of 12 nM for TACE and 20 nM for MMP-13. This compound was found to be more than 40 times more selective towards TACE over MMP-1.[82]

It was also reported that substituted benzylic ether as P1′ group can also produce good TACE inhibitors. One of these active compounds is (**29**), which has IC_{50} value equal to 110 μM.[83] The 2-position of the terminal phenyl group of 5-hydroxy pipecolic acid has to be substituted with alkyl or halo group for the TACE inhibitory activity.



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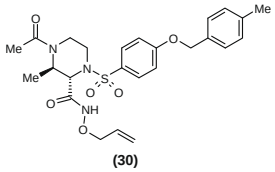
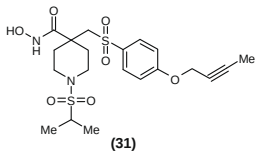


(30)

Letavic et al. have developed a piperizine-based dual inhibitor of TACE and MMP-13 which possessed minimal MMP-1 activity. The best compound (**30**) of the series has IC_{50} values of 1, 3 and 1600 against TACE, MMP-13 and MMP-1, respectively. Although this compound has shown moderate in vivo activity (ED_{50} = 17 mg/kg), may be due to short half-life of the compound in rat, search for a better compound in terms of activity, both in vivo and in vitro, still continues.[84]

Researchers at Wyeth Research Lab reported some 4,4-piperidine-β-sulfone hydroxamates bearing butynyloxy group at P1′ site as TACE inhibitors. The compounds were not only excellent TACE inhibitors, but also showed selectivity over MMPs 1, 2, 9 and 13. The best compound (**31**) has IC_{50} value equal to 1.5 nM against TACE. This compound showed 150 times more selectivity towards TACE over MMP-13 and 230 times over MMP-2.[85–87]



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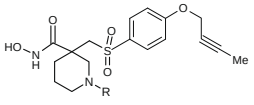
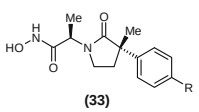


(32)

The Wyeth group also prepared some 3,3-piperidine-β-sulfone hydroxamate (**32**) bearing butynyloxy group at P1′ site as TACE inhibitors. Though the compounds of this series show low nanomolar inhibition of TACE in in vitro assay, they are intrinsically less potent than the 4,4-piperidine-β-sulfone hydroxamates.[88]

4.4. γ-Lactam inhibitors

Scientists at Bristol–Myers–Squibb have designed and developed γ-lactam hydroxamates (**33**) as selective TACE inhibitors. Docking studies of this series of compounds have revealed that hydroxamate group binds with zinc atom present in the active site of TACE as a bidentate ligand. The aromatic moiety of the molecule occupies the S1′ site of the enzyme. The oxygen atom of the pyrrlidinone ring forms hydrogen bond with Val163 and Leu164. The methyl group near the hydoxamate interacts with a small hydrophobic pocket of the enzyme, known as S2′ site.



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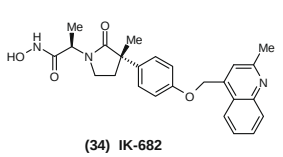


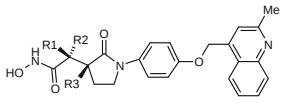
(34) IK-682

As the S1′ site of TACE is larger than most of the MMPs, it has been seen that more the bulk of the P1′ group the higher is the potency as well as selectivity of the molecule towards TACE over MMPs. Hence, the molecule possessing isobutyl group at R is 250 times less potent than the compound having benzyloxy group (IC_{50} values are 1000 nM and 4 nM, respectively). It has also been observed that at this position there should be an ether linkage present in the molecule; the molecule having biphenyl moiety at R has IC_{50} value of 13,000 nM, while that of the molecule having phenoxy group the value is 185 nM. Monosubstitution of the phenyl group did not improve the selectivity or potency of the compounds towards TACE. But the effect of disubstitution was dramatic. The compound possessing 3,5-bis-triflurometyl benzyloxy group at R showed IC_{50} value of 2 nM. This compound is found to be more than 1000 times more selective for TACE over MMP-1, MMP-2 and MMP-9.

Although, these compounds were highly active in vitro, but, they were found to possess low to moderate activity in human whole blood assay. The reason for the low activity was their high protein binding. Some of these compounds were found to be so highly protein bound that less than 1% of them were available as free fraction (e.g., **33**, R = 3,5-di-methoxybenzyloxy). To increase the free fraction, many polar bioisosteres of benzyloxy group were tried. Several pyridyl and quinolinyl derivatives were synthesized and their activity and selectivity profiles were checked. It was observed that the compound (**34**), IK-682, possessing (2-methylquinolin-4-yl)methoxy as R is the molecule of choice.[52]

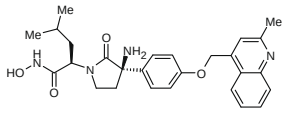
Its in vitro IC_{50} value is equal to 1 nM and in whole blood assay its IC_{50} value is 0.35 μM. It is at least 1000 times more selective towards TACE over most of the MMPs. Its free fraction in human serum is relatively high (3.6%). The compound was found to be 32% bioavailable in dog and 41% in rat.[52]

To broaden the TACE inhibitory portfolio, researchers at Bristol–Myers–Squibb have designed and synthesized *N*-hydroxy-2-(2-oxo-3-pyrrolidinyl)acetamide scaffold (**35**) as selective TACE inhibitors. As the (2-methyl-4-quinolinyl)methoxy P1′ group was already optimized for potency and selectivity, this group was retained. It has been observed that any other group than hydrogen at R2 clashes with the backbone of the protein; whereas R1 group is projected towards the solvent hence it is expected to tolerate variations. The compound having methyl groups at R3 and hydrogen atoms at R1 and R2, is an excellent inhibitor of TACE (IC_{50} value is equal to 1 nM). But its IC_{50} value in whole blood assay is poor (IC_{50} = 1.57 μM). The compound possessing Boc protected amino group at R1 and hydrogen atoms at R2 and R3 shows sub-micromolar inhibition in whole blood assay (IC_{50} = 0.42 nM). The compound is 700-fold more selective for TACE over MMP-1 and about 300-fold more selective over MMP-2 and MMP-9.[89]



(35)

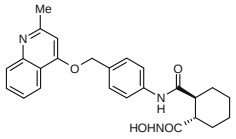
Another excellent selective TACE inhibitor (**36**), known as DPC-333 or BMS-561392 has been developed at Bristol–Myers–Squibb. In vitro IC_{50} value of the compound (**36**) is 0.20 nM and in whole blood assay it is 90 nM. It is more than 100-fold selective against TACE over MMPs. After oral administration to mice, the compound inhibited soluble TNF production following LPS challenge with an ED_{50} value of 6 mg/kg. This compound has shown good (54%) bioavailability in dogs and reasonable bioavailability in rats (16%). In Phase I of clinical studies, it was observed that the compound was well tolerated among healthy human volunteers at a dose range of 15–530 mg. It was also noted that the half-life of the molecule in humans was 3–6 h.[90,91] Though the compound showed excellent potency and selectivity toward TACE over MMPs, it caused hepatotoxicity. Hence, it was withdrawn from Phase II clinical trials.[22]



(36) BMS-561392 or DPC-333

4.5. Succinate-based selective TACE inhibitors

Researchers at Bristol–Myers–Squibb prepared some succinate hydroxamates as selective TACE inhibitors. They identified that compound (**37**) is a nanomolar range inhibitor of TACE in vitro with excellent selectivity (IC_{50} = 8 nM; almost 5000-fold more selective over MMPs). But, the compound showed very poor whole blood assay (IC_{50} > 50 μM) indicating that the compound would be inactive in vivo.[54]



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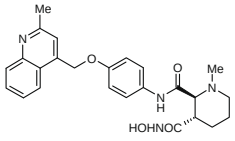
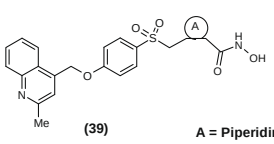


(38) IM-491

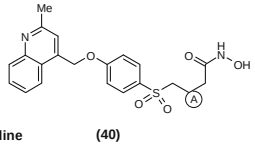
Next aim of the scientists of Bristol–Myers–Squibb was to improve the in vivo activity of compound (**37**). After suitable modification of the P1′ group and the cyclohexyl ring, the compound (**38**) was obtained. Although its in vitro TACE inhibitory activity (IC_{50} = 6.2 nM) was in the same range as that of the lead compound (**37**), the in vivo (Whole blood assay IC_{50} = 0.020 μM) activity increased many fold. This compound (**38**), also known as IM-491, has around 2000-fold higher selectivity over most of the MMPs.[92] Although the compound, IM-491, (**38**) has shown very promising in vitro and in vivo activities and very good bioavailability, unfortunately it was found to be not suitable for development in the preclinical trials because of the mutagenic property of 4-(2-methylquinolin-4-ylmethoxy)aniline moiety.[93,94]

Hence, Xue et al. replaced the amide functionality of IM-491 (**38**) with a sulfonyl group. Two series of compounds, α,β-cyclic (**39**) and β,β-cyclic γ-sulfonyl hydroxamates (**40**) were synthesized.[93] Though all the synthesized compounds showed very good in vitro activities, these were shown to be less potent than IM-491 (**38**) in whole blood assay. The best compound (**41**) of these two series showed in vitro IC_{50} value of 1 nM and IC_{50} value for whole blood assay 180 nM. The compound is more than 2000 times more selective for TACE over MMP-1, 2, 9 and 13.[93]



(39)

A = Piperidine/Pyrrolidine



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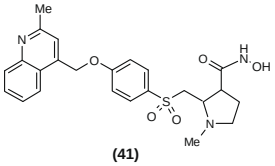
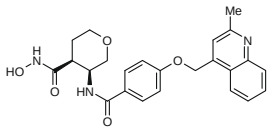


(41)

4.6. β-Benzamido TACE inhibitors

To overcome the toxicity of IM-491 (**38**), scientists at Bristol–Myers–Squibb examined the possibility of reversing the central amide moiety to obtain a series of β-benzamidohydroxamates. This change could serve two purposes; it could eliminate the toxicity problems of 4-(2-methylquinolin-4-ylmethoxy)aniline moiety present in IM-491 (**38**), and the new series of compounds could have the same binding interactions with TACE as that of IM-491 (**38**).[94]

After synthesizing and evaluating the biological activities of various derivatives of β-benzamidohydroxamates, it was found that compound (**42**) was a very potent and selective TACE inhibitor. The in vitro IC_{50} value of the compound (**42**) is less than 1 nM and in whole blood assay it is 130 nM. The compound was found to be more than 30,000-fold more selective for TACE over MMP-1, 2, 13, 14, 15 and 16. This compound has shown much better bioavailability in rats (58%) and shown oral ED_{50} value equal to 3.0 mg/kg in rats.[94]



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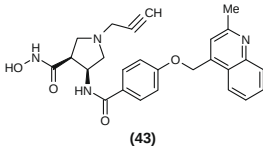
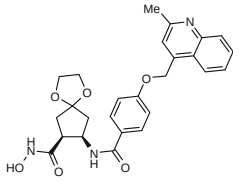


(43)

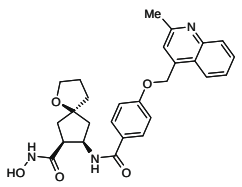
In search for a more potent and selective TACE inhibitor, the same group of researchers evaluated various 5-membered carbocyles and heterocycles in place of tetrahydropyran ring of (**42**). The best compound (**43**) of the series possesses in vitro IC_{50} value equal to 0.14 nM and whole blood assay IC_{50} value equal to 109 nM. The compound is more than 1000-fold more selective for TACE over MMP-1, 2, 7, 8, 9, 10, 13, 14 and 15. Although the oral bioavailability of the compound in rat is a modest 25%, the ED_{50} value is 3.3 mg/kg.[95]

In quest for a better molecule, scientists at Bristol–Myers–Squibb synthesized and biologically evaluated the 1,3-dioxalane moiety at 4-position of β-benzamidohydroxamic acid scaffold to arrive at compound (**44**). This change decreased the IC_{50} value in whole blood assay dramatically to 24 nM. But the molecule was not chosen for development because of its acid sensitive nature. Hence, one oxygen of the dioxalone species was changed to carbon and compounds (**45**) and (**46**) were synthesized and screened for their TACE inhibitory activities.



(44)

It was observed that both of the compounds (**45**) and (**46**) have comparable activities; the IC_{50} value of (**45**) in whole blood assay is 108 nM and that of (**46**) is 143 nM. Both the compounds showed more than 2000-fold higher selectivity for TACE over MMP-1, 2 and 9. The oral bioavailabilities for (**45**) and (**46**) are 31% and 35%, respectively, in dogs.[96]



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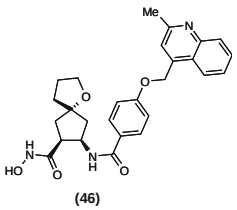
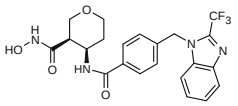


(46)

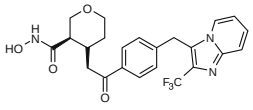
To obtain a more potent and selective TACE inhibitor, researchers at Bristol–Myers–Squibb changed the 4-(2-methylquinolinylmethoxy)phenyl P1′ group to 2-substituted benzimidazolemethylphenyl group in β-benzamidohydroxamic acid scaffold. After biological evaluation of a number of synthesized compounds, it was observed that compound (**47**) showed IC_{50} value of 1.4 nM. This compound is

found to have more than 10,000-fold higher selectivity for TACE over MMP-1, 2, 3, 7, 8, 9, 10, 13, 14, 15 and 16. Also, it is 8000-fold more selective over MMP-12. The compound (**46**) has half-life of about 5 h and oral bioavailability of 99% in dogs.[97]



(47)

As it is known that P1′ group of TACE inhibitors, which occupies the S1′ site of the enzyme, is the most critical determinant for TACE selectivity, researchers at Bristol–Myers–Squibb wanted to optimize the P1′ group in compounds of the class of β-benzamidohydroxamic acids. The compounds possessing indole and benzofuran ring as P1′ groups did not show good selectivity over MMP-12 (only 75-fold). The trifluromethyl analog of imidazopyridine P1′ group of compound (**48**) showed good selectivity over most of the MMPs, but it was found to be inactive in vivo because of its poor oral absorption. Interestingly, the trifluromethyl analog of pyrazolopyridine P1′ group (**49**) showed not only very good selectivity over all MMPs but its whole blood assay IC_{50} value was found to be equal to 171 nM. The compound (**49**) showed oral bioavalibility of more than 90% in rats.[98]



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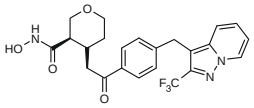
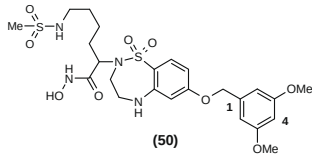


(49)

4.7. Benzothiadiazepine inhibitors

Scientists at Bristol–Myers–Squibb also designed and developed some benzothiadiazepine derivatives as selective TACE inhibitors. Most of the compounds of this class not only showed very good in vitro inhibition of TACE but were also more selective over MMP-1, 2 and 9. The most potent compound (**50**) of the series showed Ki value of 5 nM and over 75-fold higher selectivity over MMPs. Most of the compounds of this series were inactive in whole blood assay indicating that these compounds might not be active in vivo.[99]



(50)

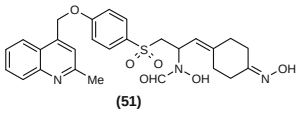
4.8. Non-hydroxamate TACE inhibitors

It is a well known fact that hydroxamic acids are the most potent motif for zinc binding. It is postulated that the oxygen of the carbonyl group and the hydroxyl group both share their lone pairs with the zinc atom in the enzyme and thus forms a five-membered stable cyclic system. At the same time, the hydrogen atom of the hydroxyl group forms hydrogen bond with the oxygen atom of Glu406 of TACE[100] as shown in Figure 5.

As hydroxamic acid is an excellent zinc binding motif, most of the TACE and MMP inhibitors, reported in the literature, rely on hydroxamate or reverse hydroxamate moieties as the zinc binding ligands. However, there are many a problems with the compounds possessing hydroxamic acid group. Often, the bioavailabilities of these molecules are very low because of very high renal clearance. They also carry potential metabolic liabilities. Hydroxamic acids undergo O-glucuronidation and hydsrolysis in vivo to give corresponding acid and toxic hydroxylamine.[46,101,102] Hence, researchers all over the world are interested to develop non-hydroxamate TACE inhibitors.[27]

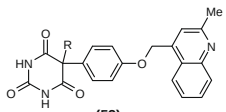
To overcome the problems associated with hydroxamates scientists have replaced hydroxamic acid moiety by *N*-formyl-*N*-hydroxyamino (reverse hydroxamte) moiety.

Kamei et al. have developed compound (**51**) bearing 4-(2-methylquinolin-4-ylmethoxy)phenyl group as the P1′ group. The compound shows IC_{50} value equal to 2.0 nM and is more than 20,000 times more selective for TACE over MMP-2, 9 and 13.[46]



(51)

Bristol–Myers–Squibb group replaced the hydroxamate moiety with 5-phenylpyrimidine-2,4,6-trione. As 4-(2-methylquinolin-4-ylmethoxy)phenyl moiety was previously designed for selective TACE inhibitory activity, this group was kept intact in the molecule. Compound (**52**) possessing methyl group at R showed IC_{50} values of 1.0 μM indicated that pyrimidinetrione is an effective zinc binding motif. To increase the potency of the molecule further, different aliphatic and aromatic moieties as R group were introduced in the molecule. It was found that introduction of piperazine group at R increased the potency of the compound. Compound (**53**) showed sub-micromolar inhibition of TACE (IC_{50} = 0.091 μM).[103]



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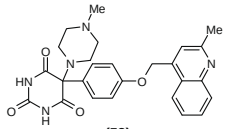


(53)

To further increase the potency of the pyrimidinetrione derivatives against TACE, the same group of scientists introduced a spacer in between pyrimidine and benzene rings. Several modifications were tried and the best compound of the series was found to be **54** which had IC_{50} value equal to 0.026 μM. The compound also showed good selectivity over most of the MMPs (almost 200-fold), but, it was found to be inactive in whole blood assay (IC_{50} > 50 μM).[104] Various other groups were tried at 5-position of pyrimidine nucleus in order to increase the potency of the molecule in whole blood assay. But, none of the compounds in this series were found to be effective in that particular assay indicating that this series of compounds, although very potent in vitro, might be inactive in vivo.[104]

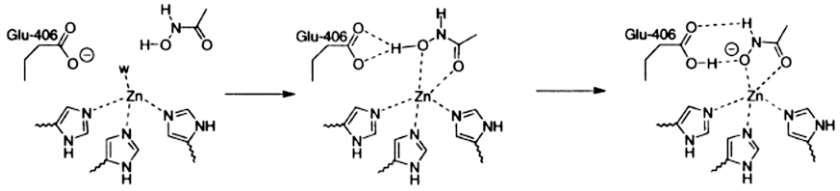
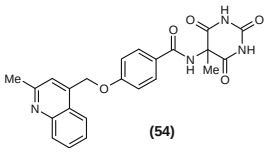
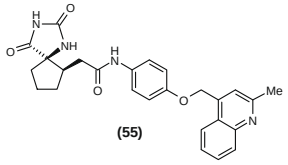


Figure 5. Interaction of zinc atom of TACE with hydroxamate moiety of inhibitor.



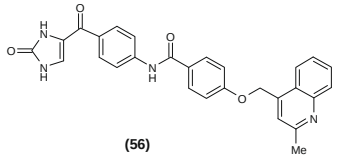
(54)

Bristol–Myers–Squibb researchers also examined hydantion as zinc binding ligand. Molecular modeling analysis revealed that although hydantoin moiety is a good zinc binding motif, it is intrinsically less potent than hydroxamic acid.[105] Compound (**55**) shows IC_{50} value equal to 11 nM against TACE and is found to be more selective for TACE by at least 200-fold over most of the MMPs. It has been observed that the stereochemistry of the hydantoin ring plays a very critical role in the potency of the compound, as a wrong stereochemistry would not project the quinolinyl P1′ group into the S1′ pocket of the enzyme. Hence, the above compound in (5*R*,6*S*)-*trans* form shows IC_{50} value of 11 nM, while in (5*S*,6*R*)-*trans* form its IC_{50} value becomes 900 nM.[106]



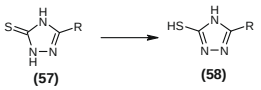
(55)

The same group of researchers at Bristol–Myers–Squibb also developed triazolone and imidazolone ring systems as potential zinc binding groups. The P1′ group, namely 4-[(2-methyl-4-quinolinyl)methoxy]benzoyl, selected on the basis of activity and selectivity for hydantoin derivatives was kept as such in these compounds as well. Compounds possessing triazolone and imidazolone rings were found to be active, hence it was argued that these two ring systems could also be regarded as zinc binding ligands. All the compounds synthesized so, showed very good selectivity for TACE over MMPs. Hence, the choice of the P1′ group gave the best results. The most potent compound (**56**) of the series has IC_{50} value equal to 9 nM. The compound is at least 350-fold more selective for TACE over MMP-2, 3, 7, 12 and 13.[107]



(56)

The group at Bristol–Myers–Squibb also tested 1,3,4-triazole-2-thione scaffold (**57**) as non-hydroxamate zinc binding ligand. The molecular modeling studies showed that the thiocarbonyl group interact with zinc in the active site of the enzyme. One of the NH groups of thiourea moiety can tautomerize to thiol (**58**) thus making a strong hydrogen bond with the active site Glu406.[108] The most potent compound (**59**) of the series was reported to have IC_{50} value equal to 1.5 nM and it possessed more than 3000-fold higher selectivity for TACE over MMPs.[108]



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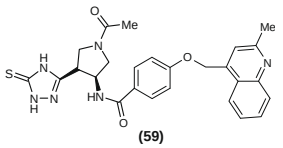
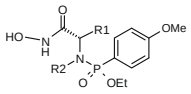


(59)

Although molecular modeling studies suggested that triazolethiones had less number of interactions (i.e., two) than hydroxamates,[105] they were found to be potent and selective TACE inhibitors. Moreover, triazolethiones appear to have intrinsically better potency than substituted 5-phenylpyrimidine-2,4,6-triones, hydantoins and triazolones, discussed above.[108]

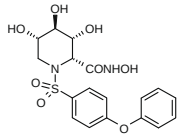
4.9. Miscellaneous TACE inhibitors

Sawa et al. have designed and synthesized phosphonamide derivatives as TACE inhibitors. It has been shown that the compound (**60**) possessing isobutyl group at R1 and hydrogen at R2 is the most selective TACE inhibitor in the series. This compound also showed promising TACE inhibition. Its IC_{50} value is 76 nM. It has also been reported that the *S*-configaration at carbon attached to nitrogen favors strong binding of the hydroxamate group with the zinc atom present in the enzyme.[109]



(60)

Moriyama et al. have synthesized some azasugar based TACE and MMP inhibitors. These compounds possess improved water solubility than most of the reported TACE and MMP inhibitors due to the presence of azasugar in the molecule, hence, they have better bioavailability. It was reported that the stereochemistry of 2, 3, 4 and 5 position of the azasugar scaffold is crucial for the selectivity profile of these compounds. The best compound (**61**) of the series has Ki values of 2.3 nM and 0.061 nM for TACE and MMP-9, respectively.[110,111]



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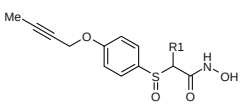
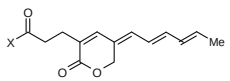


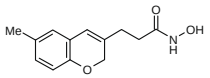
(62)

Venkatasen et al. have synthesized a series of 4-alkynyloxyphenyl sulfanyl—sulfinyl—and sulfonyalkyl hydroxamates (**62**). Their SAR revealed that the oxidation state of sulfur atom decides their selectivity. The sulfanyl and sulfonyl derivatives are predominantly MMP inhibitors with little or no TACE inhibitory activity while the sulfinyl derivatives are selective TACE inhibitors. The compound possessing *n*-hexyl group at R1 is the most potent TACE inhibitor. Its IC_{50} value for TACE is 4 nM. Although this compound showed good in vitro activity, its in vivo activity was not encouraging. Replacement of 4-piperidine ring at R1 instead of *n*-hexyl group increases the cellular potency of the compound to a minor degree.[50]

Gelastatin (**63**) and its hydroxamate (**64**) were prepared from the known methyl ester of gelastatin by Park et al. Both the compounds inhibited TACE as well as MMPs. The hydroxamate (**64**) was more active. Its IC_{50} values for the enzymes were found to be 0.028, 0.006 and 0.023 μM for TACE, MMP-2 and MMP-9, respectively.[112]



(63) X = OH
(64) X = NHOH

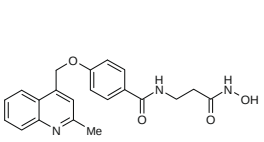


(65)

The same research group has also developed chromen-based TACE inhibitors. They synthesized these chromen analogs as these showed similar docking pattern as that of gelastatins. The most active compound (**65**) in the series has IC_{50} value of 0.06 μM. This compound was found to be 4 times more selective for TACE over MMP-2 and 50 times more selective over MMP-9.[113]

Scientists at Bristol–Myers–Squibb observed that compound (**66**) was an effective and selective TACE inhibitor with IC_{50} value of 1 nM. But this compound is ineffective in inhibiting TACE in

human whole blood. The oxygen of the central amide group of (**66**) forms two hyderogen bonds with Gly163 and Leu164 of the protein backbone of TACE apart from the binding of hydroxamate moiety to the zinc atom.[114]



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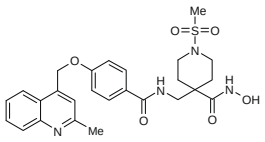

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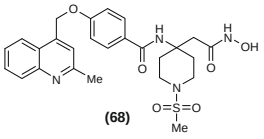
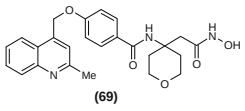


(68)

In an effort to develop TACE inhibitors which are active both in vitro as well as in whole blood assay, several series of cyclic β-aminohydroxamates were designed and synthesized. The α,α-cyclic series was developed to improve in vivo stability of hydroxamate moiety through steric hindrance. The most potent compound (**67**) of the series has IC_{50} value equal to 1.9 nM.[114]

The β,β-cyclic β-aminohydroxamic acid analogs were also synthesized. Piperidine ring was selected as the central cyclic group. Various functional groups were substituted at the nitrogen atom of the piperidine ring. It was observed that compound (**68**) had IC_{50} value of 1 nM. In addition to that, the compound was shown to have more than 5000 times higher selectivity over MMP-1 and 13.[114] But, it was observed that the compound (**69**) containing tetrahydropyran ring instead of piperidine ring was more bioavailable than (**68**). The oral bioavalibity of (**69**) in dog was found to be 79%.[114]



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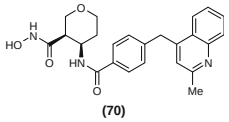
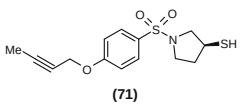


(70)

Although (2-methyl-4-quinolinyl)methoxyphenyl P1′ group is the critical determinant of selectivity for TACE to other MMPs,[45] a new P1′ group was sought after by the researchers at Bristol–Myers–Squibb. It was observed that for β-aminohydroxamic acid analogs the two atom linker between phenyl and 2-methyl quinoline ring could be shortened by eliminating the oxygen atom, but not the methylene group. Based on this observation, the (2-methyl-4-quinolinyl)methoxyphenyl group was replaced by 4-(2-methylquinolin-4-ylmethyl)phenyl group. The compound (**70**) bearing the new P1′ group has IC_{50} value equal to 1 nM.[115]

The fact that the S1′ site of TACE is larger and narrower than MMPs, has been exploited by many a researchers to design and develop selective TACE inhibitors. Another approach utilized the use of a non-hydroxamate zinc binding group.[116] Govind Rao et al. have applied a combination of these two approaches to develop selective TACE inhibitors. The designed molecules possess butynyloxy group, which would interact with the S1′ site of TACE; also thiol group is used as the zinc binding motif. One (**71**) of the potent compounds of the series has Ki value equal to 28 nM. This compound was shown to possess 200-fold higher selectivity for TACE over MMP-2 and MMP-7 while as much as 40-fold selectivity over MMP-8 and MMP-13.[117] The same group has also developed some thiol containing aryl sulfone as selective TACE inhibitors. It has been shown that in this series of compounds, replacement of butynyloxy tail of P1′ group with bytynylamino group produces more potent TACE inhibitors. The most potent compound (**72**) of the series has Ki value of 2 nM.[118]



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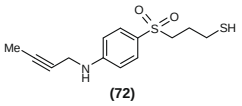
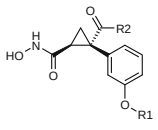


(72)

Zhu et al. synthesized some phenylcyclopropyl (**73**) and benzylcyclopropyl (**74**) hydroxamates as TACE inhibitors. Both of the series produced potent and selective TACE inhibitors. It has been seen that these two series of compounds showed different binding modes to TACE. The phenylcyclopropyl series of compounds (**73**) bind to the prime site in the catalytic site of TACE while benzylcyclopropyl series of compounds (**74**) bind to the non-prime site. By molecular modeling studies it has been proved that benzylcyclopropyl series of compounds (**74**) form extensive hydrogen bonds with the backbone of TACE. The only difference among the two series of compounds biologically was in the selectivity profile of the inhibitors over MMPs. The first series of compounds (**73**) produced molecules that were highly selective for TACE; the compounds were shown to be more than 2000 times more selective for TACE over MMP-1, 2, 7, 14 while, about 1500 times more selective over MMP- 3. The second series of compounds (**74**) were 9000-times more selective over MMP-1, but only 20 and 40 times more selective over MMP-3 and 7, respectively.[119]



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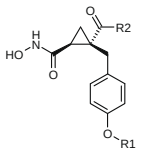

(74)

5. In-silico studies of TACE inhibitors

Structure-based drug designing is a rapidly growing area in medicinal chemistry in which many successes have occurred in recent years.[120] Crystal structures of proteins are the most common source of structural information for drug design since of proteins high resolution structures available. The method is useful for proteins that range in size from a few amino acids to 998 kDa.[121] Till date several crystal structures for TACE, co-crystallized with different inhibitors are available in the PDB databank; the details are given in Table 1.

X-ray crystal structure of TACE-IK-682 (Figs. 6 and 7) clearly reveals that the compound is embedded in the catalytic site of the enzyme. The hydroxamic acid moiety of IK-682 (**33**) interacts with the zinc atom present in the active site of TACE and coordinates with the carboxylate of Glu406 and the carbonyl oxygen of Gly349. The carbonyl group of pyrrolidinone ring is responsible for formation of a hydrogen bond with the amide nitrogen of Leu348 and Gly349. The methyl group on the pyrrolidinone ring is in van der Waals contact with the carbonyl oxygen of Gly346. The phenyl group of IK-682 (**33**) forms an aromatic stacking with the imidazole group of His405.[125]

Literature reveals that efforts are also made for designing of potent TACE inhibitors using ligand based approaches. 3D-QSAR studies for benzothiadiazepine hydroxamate class of TACE inhibitors reported from our laboratory revealed the significance of hydrophobic and hydrogen bond donor fields apart from electrostatic and steric field contributions for the TACE inhibitory activitities of these compounds.

The interaction study (Figs. 8 and 9) of the most active compound (**50**)[99] of benzothiadiazepine series with the active site of crystal structure of TACE reveals that apart from bonding with the oxygen of hydroxamic acid there is a strong bonding of SO_2Me group present in the compound (**50**) and zinc; this could be one of

Table 1
List of crystal structures available in PDB for TACE co-crystallized with various ligands

S. No	PDB Code	Resolution (Å)	Co-crystallized ligand	Release date	Reference
1	1BKC	2.00	3,*N*-(D,L-[2-(Hydroxyaminocarbonyl)methyl]-4-methylpentanoyl)-L-3-*t*-butylglycyl-L-alanine	22.06.1999	34
2	1ZXC	2.28	(3*S*)-4-{[4-(But-2-ynyloxy)phenyl]sulfonyl}-*N*-hydroxy-2,2-dimethylthiomorpholine-3-carboxamide	27.09.2005	122
3	2A8H	2.30	(3*S*)-4-[4-(4-Aminobut-2-ynoxy)phenyl]sulfonyl-*N*-hydroxy-2,2-dimethyl-thiomorpholine-3-carboxamide	27.02.2006	76
4	2DDF	1.70	3,*N*-(D,L-[2-(Hydroxyaminocarbonyl)methyl]-4-methylpentanoyl)l-3-(*t*-butyl)glycyl-L-alanine	14.03.2006	123
5	2FV9	2.02	*N*-[(2*R*)-2-Benzyl-4-(hydroxyamino)-4-oxobutanoyl]-L-isoleucyl-L-leucine	14.03.2006	123
6	2I47	1.90	4-({[4-(But-2-yn-1-yloxy)phenyl]sulfonyl} methyl)-1-[(3,5-dimethylisoxazol-4-yl)sulfonyl]-*N*-hydroxypiperidine-4-carboxamide	12.05.2006	124
7	2FV5	2.10	(2*R*)-*N*-Hydroxy-2-[(3*S*)-3-methyl-3-{4-[(2-methylquinolin-4-yl)methoxy]phenyl}-2-oxopyrrolidin-1-yl]propanamide	04.07.2006	125
8	2OI0	2.00	(3*S*)-1-{[4-(But-2-yn-1-yloxy)phenyl]sulfonyl}pyrrolidine-3-thiol	27.11.2007	117
9	3B92	2.00	3-{[4-(But-2-yn-1-yloxy)phenyl]sulfonyl}propane-1-thiol	18.121.2007	118

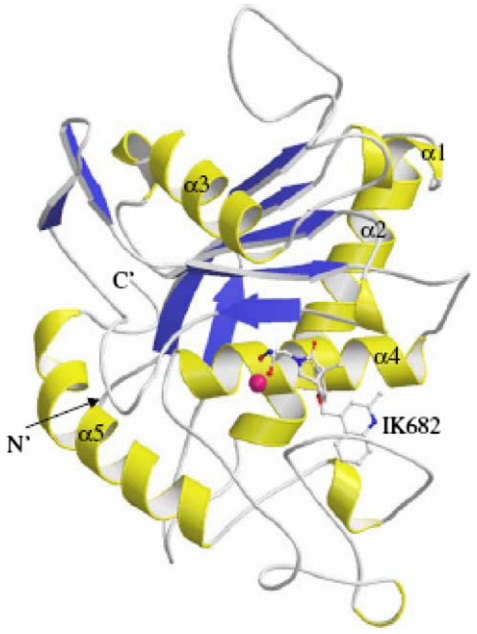

Figure 6. Crystal structure of catalytic site of TACE with IK 682.[125]

the reason why this compound is the most active one in the series. It was also predicted that an aliphatic substitution (*n*-butyl or *n*-pentyl) at 4-position of 3,5-dimethoxy phenyl ring of **50** could improve the TACE inhibitory activity.[126]

A plausible and predictive 3D-QSAR model[127] has also been developed for constrained β-aminohydroxamic acids as potent and selective TACE inhibitors[114,115] employing comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) techniques. It was observed that electrostatic field contributions for this series of compounds was more important than the steric contributions, unlike the benzothiadiazepine hydroxamate class of TACE inhibitors. External validation of CoMFA model was done by predicting the activity of IK-682 (**34**), a well known TACE inhibitor. The predicted activity (pIC_{50} = 8.991) was found to be very close to the experimentally determined value (pIC_{50} = 9.00).

The green contours in Figure 10 represent regions of high steric tolerance (80% contribution), while the yellow contours represent regions of low steric tolerance (20% contribution). The increase in the positive charges on atoms in the molecule was favored in blue regions (80% contribution) while increase in negative charge (20% contribution) favored in red regions (Fig. 11). The steric contours of CoMFA show a green contour enclosing the quinoline ring of the template structure. This indicates that the bulky group here would increase the TACE inhibitory activity. The steric contour map of CoMFA also shows a large contour enclosing the piperidine ring of the template molecule where bulkier substitutions are expected to increase the activity. The steric contour map also shows yellow contour near quinoline ring where bulky substituents are not tolerated. The electrostatic contours of CoMFA (Fig. 11) show red contours surrounding the central benzamide ring of the template molecule wherein high electron density is expected to increase the activity. The electrostatic contour shows blue polyhedron in the vicinity of central phenyl ring wherein low electron density is expected to increase activity.

Sheppeck et al. have reported the interaction study of various classes of non-hydroxamate TACE inhibitors and hydroxamate TACE inhibitors.[105] In their report, it was suggested that hydroxamic acid forms two hydrogen bonds with Glu406 and Gly349 of TACE apart from a bidentate ligation of the hydroxyl and carbonyl oxygen to the zinc atom. The interaction of non-hydroxamate zinc binding groups with the TACE active site differ from those of the hydroxamate ones because they ligate Zn in monodentate fashion and hydrogen bond the same residues but in a fundamentally different way. In case of pyrimidinetriones, only two hydrogen bonds are observed, one with the NH of Leu348 and the carbonyl at the 4-position of pyrimidinetrione and the other one with the Glu406 acid and the C2 carbonyl of the pyrimidinetrione. The hydantoins bind to the catalytic site of TACE in monodentate fashion.

There is an urgent need for developing common pharmacophore for TACE inhibitors so that the designing of various chemical classes of TACE inhibitors could be rationalized. Though Sheppeck et al. have reported that they have developed a pharmacophore model,[105] but the basic pharmacophore has not been disclosed. For developing the pharmacophore model, only binding of the inhibitors with the prime site of TACE should not be considered, as molecules binding with the non-prime site of the enzyme were shown to be potent inhibitors of TACE.[116] Efforts are being made in our laboratory for developing a common pharmacophore for different TACE inhibitors.

Modeling and QSAR studies of existing TACE inhibitors could help in developing a more potent and selective TACE inhibitor with lesser side effects and better pharmacokinetic properties.

6. Conclusions

Since the success of anti-TNF biological agents, much efforts have gone into developing a small molecule, orally bioavailable TNF-α inhibitor. One of the ways to block TNF actions in the body is to inhibit TACE. This target has been validated in preclinical trials for the treatment of RA. Many compounds belonging to different chemical classes have been synthesized as selective TACE

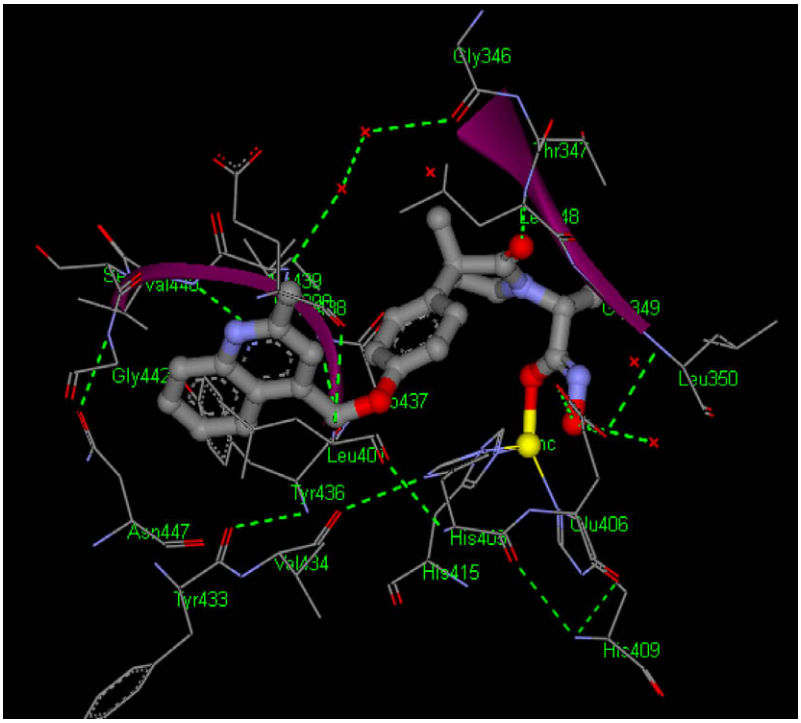

Figure 7. Interaction of IK682 with TACE active site. The inhibitor is shown in ball-and-stick rendering. Hydrogen bonds are shown as dashed lines and zinc is shown in yellow color. The figure has been constructed using the coordinates deposited in the Protein Data Bank (Accession Code 2FV5).[125]

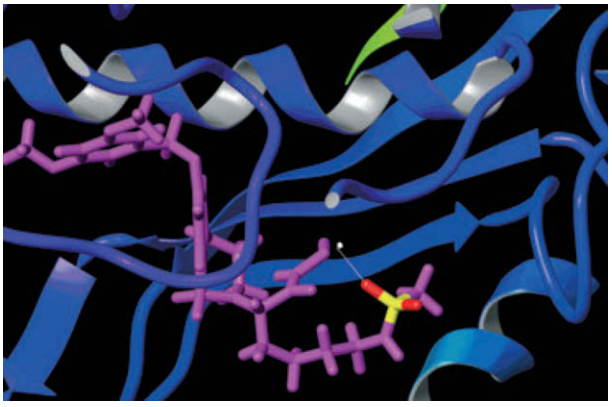

Figure 8. Interaction of active site Zn2+ ion (shown in white color) with oxygen red color) of SO_2Me group of template compound (50) has shown in violet color except for oxygen (red) and sulfur (yellow).[126]

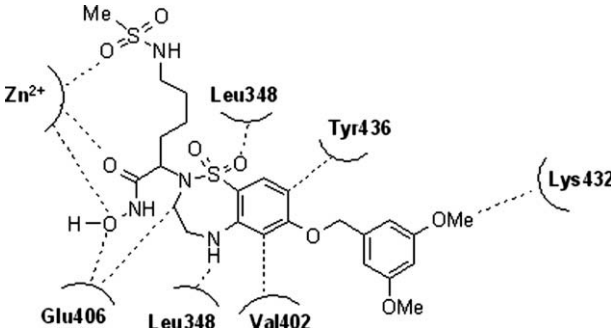

Figure 9. Interaction of active site of TACE with the template compound (50).[126]

inhibitors. Two molecules namely, TMI-05 (**22**) and BMS-561392 (**36**) have been withdrawn from Phase II clinical trials because of

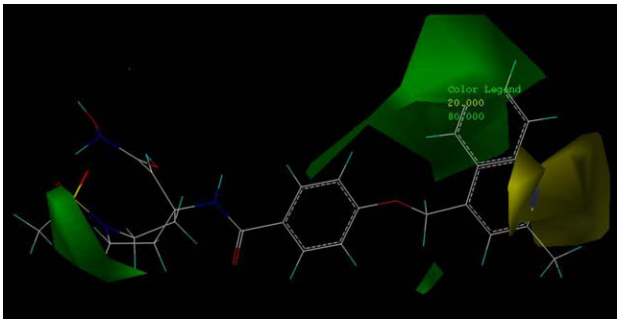

Figure 10. The CoMFA steric STDEV*COEFF contour plots of active compound (**68**).[127]

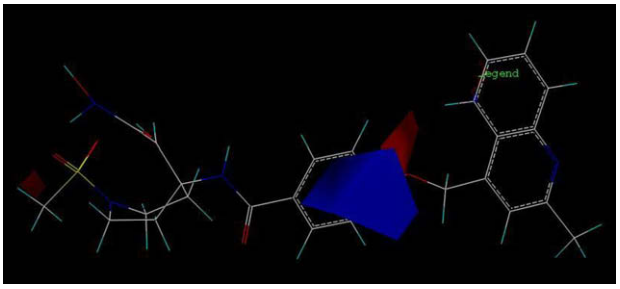

Figure 11. The CoMFA electrostatic STDEV*COEFF contour plots of active compound (**68**).[127]

lack of efficacy and hepatotoxicity, respectively. Although there is a growing concern among scientific fraternity whether a TACE inhibitor would show a favorable pharmacological profile and can be recommended for treating RA; there are many promising TACE inhibitors in the preclinical studies. Hence, it is too early to

rule out TACE inhibition as a cure for RA. This review aims at providing a bird's eyeview to readers about the developments in designing more potent and selective novel TACE inhibitors.

Recently, TACE has also been implicated in cancer.[128] It has been shown that TACE is a druggable target which could be used for inhibition of pathogenic EGFR signaling in cancer. Hence, a new TACE inhibitor, namely INCB 3619 is being studied clinically as an anticancer agent.[129,130] Some older TACE inhibitors are also being studied for their anticancer activity. This new finding has boosted the development of TACE inhibitors as anti-neoplastic agents as well.

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