Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 15 (2005) 1641–1645

# Synthesis and SAR of diazepine and thiazepine TACE and MMP inhibitors

Arie Zask,[a,*] Joshua Kaplan,[a] XueMei Du,[a] Gloria MacEwan,[a] Vincent Sandanayaka,[a] Nancy Eudy,[a] Jeremy Levin,[a] Guixian Jin,[a] Jun Xu,[a] Terri Cummons,[b] Dauphine Barone,[c] Semiramis Ayral-Kaloustian[a] and Jerauld Skotnicki[a]

[a]*Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, USA*
[b]*Wyeth Research, PO Box CN 8000, Princeton, NJ 08543, USA*
[c]*Amgen, Seattle, WA 98101, USA*

Received 11 November 2004; revised 19 January 2005; accepted 21 January 2005

**Abstract**—Potent and selective TACE and MMP inhibitors utilizing the diazepine and thiazepine ring systems were synthesized and evaluated for biological activity in in vitro and in vivo models of TNF-α release. Oral activity in the mouse LPS model of TNF-α release was seen. Efficacy in the mouse collagen induced arthritis model was achieved with diazepine **20**.


Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that is believed to play a role in the etiology of rheumatoid arthritis (RA), Crohn's disease and other disease states.[1] Small molecule mediators of TNF-α action are important targets for the treatment of these inflammatory diseases. Enbrel™, a soluble TNF receptor-Fc dimer, modulates TNF-α by interacting with both the 26 kDa membrane-bound form of TNF-α and 17 kDa soluble TNF-α and is a highly effective RA therapy.[2] An alternative paradigm for affecting TNF-α levels is via the inhibition of TNF-α converting enzyme (TACE/ADAM-17), the enzyme primarily responsible for the shedding of membrane-bound TNF-α to provide its soluble form.[3] A number of small molecule TACE inhibitors possessing excellent enzyme and cellular potency have recently been disclosed having diverse selectivity profiles versus TACE and the MMPs.[4] Since a variety of MMPs have been found to be overexpressed in RA synovial tissue and have been implicated in the destruction of cartilage in RA joints, the optimal TACE/MMP selectivity profile for a drug to treat rheumatoid arthritis is at present unresolved.[5] In addition, several MMP inhibitors have been reported to exhibit a musculoskeletal syndrome as a side effect, however the cause of this toxicity (e.g. inhibition of MMP-1, MMP-14 or sheddases) is unclear.[4b]

Molecular modeling studies of the TACE X-ray crystal structure[6] indicated that an acetylenic P1′ group could fit in the tunnel connecting the S1′ and S3′ pockets.[7] The butynyloxy P1′ group has been found to be effective for increasing potency versus the TACE enzyme in a cell-free assay, and in LPS-stimulated THP-1 cells for anthranilic acid-based and benzodiazepine-based sulfonamide hydroxamic acids (Fig. 1).[7,8] The butynyloxy group has also been found to enhance the MMP-1 selectivity of these compounds. More recent work on the incorporation of polar groups onto the benzodiazepine scaffold, to enhance aqueous solubility and in vivo activity, has also been described.[9] As in the benzodiazepines, the diazepine and thiazepine ring systems constrains the butynyloxy P1′ group relative to the hydroxamic acid. However, removal of the phenyl ring decreases the

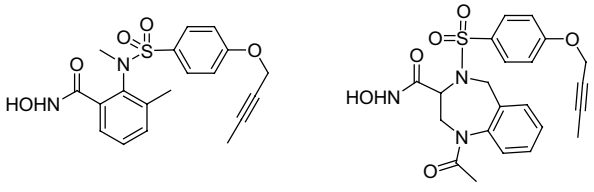



**Figure 1.** Butynyloxy TACE/MMP inhibitors.

* Corresponding author. Fax: +1 845 602 5561; e-mail: zaska@wyeth.com

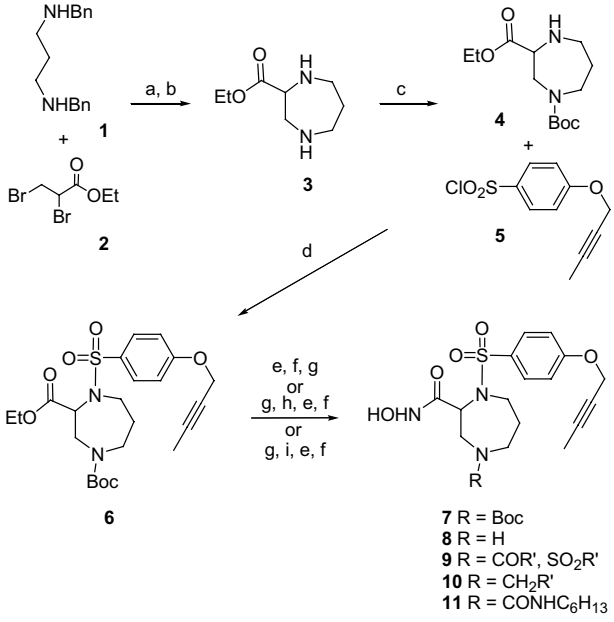
0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.01.053

lipophilicity of the system, increases the basicity of the ring nitrogen in the diazepines and changes the conformation of the seven membered ring. Through the use of the two possible 1,4-diazepine isomers, the location (relative to the hydroxamic acid) of the basic nitrogens, as well as the substituents attached to them can be altered, providing an opportunity to explore the tolerances of the enzyme for interactions with these groups, as well as their effects on cellular and in vivo activity. Similarly, the two isomeric 1,4-thiazepines were synthesized and the effects of the sulfur and sulfone moieties on activity were evaluated.

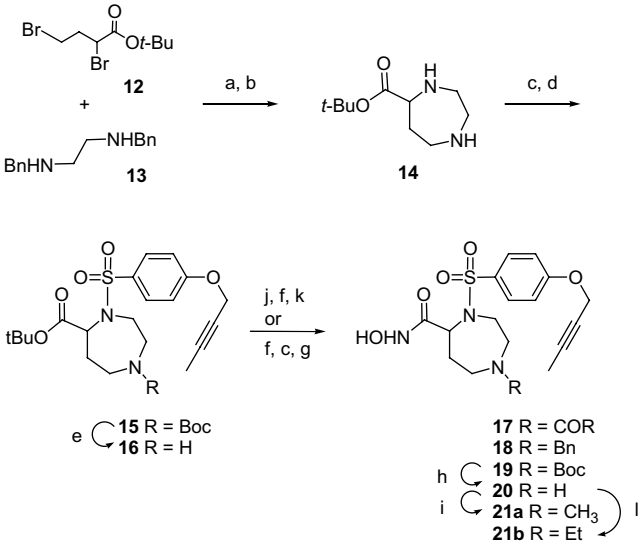
The 1,4-diazepine-2-carboxylate ring system was prepared by treating *N*,*N*′-dibenzyl-1,3-propanediamine (**1**) and ethyl 2,3-dibromopropionate (**2**) with triethylamine in benzene (Scheme 1).[10] The benzyl protecting groups were removed by catalytic hydrogenolysis using 10% Pd/C to give **3**. Selective protection of the more basic and sterically accessible amine using $Boc_2O$ gave **4**. Sulfonylation of **4** with 4-(2-butynyloxy)benzenesulfonyl chloride (**5**) gave **6**. Saponification of the ethyl ester in **6** with NaOH gave the corresponding carboxylic acid, which was converted to the hydroxamic acid (**7**) by treatment with hydroxylamine in the presence of EDC and HOBT. Subsequent removal of the Boc protecting group with HCl gave **8**. Alternatively, removal of the Boc group in **6** with HCl released the basic amine, which could then be *N*-acylated, *N*-sulfonylated or *N*-alkylated by treatment with acyl chlorides, sulfonyl chlorides or alkyl halides, respectively. *N*-Acylation could also be effected by coupling the free nitrogen with a carboxylic acid in the presence of EDC and HOBT. Treatment of the basic amine with cyclohexyl isocyanate in the presence of Hunig's base gave the corresponding urea. Conversion of the ester to a hydroxamic acid as described above gave compounds **9**–**11**.

The isomeric 1,4-diazepine-5-carboxylate scaffold was synthesized in an analogous way by treating 2,4-dibromo-butyric acid *tert*-butyl ester (**12**) and *N*,*N*′-dibenzyl-1,2-ethanediamine (**13**) with $Et_3N$ in $CH_2Cl_2$ (Scheme 2). The benzyl protecting groups were removed by catalytic hydrogenolysis using 10% Pd/C to give **14**. Selective protection of the more accessible nitrogen by treatment with $Boc_2O$ followed by sulfonylation with **5** gave **15**. Selective removal of the *N*-Boc group by treatment of **15** with HCl in dioxane gave **16**, whose free amine group could be acylated or alkylated. Subsequent removal of the *t*-butyl group using TFA in $CH_2Cl_2$ gave the corresponding carboxylic acid, which was converted to the hydroxamic acid by treatment with oxalyl chloride and hydroxylamine to provide **17** and **18**. Alternatively, treatment of **15** with TFA in $CH_2Cl_2$ removed both protecting groups. The nitrogen was then Boc protected as above and the carboxylic acid was converted to the hydroxamic acid to give **19**. Removal of the Boc group with HCl in dioxane gave **20**, which could be selectively alkylated on the ring nitrogen with $CH_3I$ and $Et_3N$ to give **21a**. Alternatively, treatment of **20** with HOAc and $NaBH_4$ gave the *N*-ethyl analog **21b**.

The isomeric 1,4-thiazepine-3-carboxylic acid scaffold was constructed beginning with D-cysteine (Scheme 3). Sequential treatment with 3-bromo-propan-1-ol and **5**, followed by conversion of the carboxylic acid to the *t*-butyl ester gave **22**. Cyclization by treatment with $PPh_3$ and diethyl azodicarboxylate gave **23**. Deprotection of the ester by treatment with TFA and conversion to the hydroxamic acid gave **24**. Oxidation of **24** with peracetic acid gave the sulfone **25**. In a similar fashion, the 1,4-thiazepine-5-carboxylic acid scaffold was




**Scheme 1.** Reagents and conditions (a) $Et_3N$, PhH; (b) $H_2$, 10% Pd/C; (c) $Boc_2O$, dioxane, NaOH (aq.); (d) pyridine; (e) NaOH; (f) EDC/HOBT/$NH_2OH$; (g) HCl; (h) RCOCl or $RSO_2Cl$ or RX, *i*-$Pr_2NEt$ or $RCO_2H$/EDC/HOBT; (i) $C_6H_{13}NCO$, *i*-$Pr_2NEt$.




**Scheme 2.** Reagents and conditions (a) $Et_3N$, $CH_2Cl_2$; (b) $H_2$, 10% Pd/C; (c) $Boc_2O$, dioxane, NaOH (aq.); (d) **5**, $Et_3N$, DMAP; (e) 4 N HCl/dioxane; (f) TFA, $CH_2Cl_2$; (g) EDC, HOBT, $NH_2OH$, DMF; (h) 2 N HCl/dioxane; (i) $CH_3I$, $Et_3N$, MeOH; (j) RCOCl or BnBr, $Et_3N$, $CH_2Cl_2$; (k) $(COCl)_2$, DMF, $NH_2OH$; (l) HOAc, $NaBH_4$.