Bioorganic & Medicinal Chemistry Letters 18 (2008) 5249–5251

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Design and synthesis of a series of *meta* aniline-based LFA-1 ICAM inhibitors

Kevin M. Guckian *, Edward Yin-Shiang Lin, Laura Silvian, Jessica E. Friedman, Donovan Chin, Daniel M. Scott

Biogen Idec, 14 Cambridge Center, Cambridge, MA 02142, USA

ARTICLE INFO

Article history:
Received 28 July 2008
Revised 14 August 2008
Accepted 18 August 2008
Available online 22 August 2008

Keywords:
LFA-1
ICAM
i-Domain
LFA-1/ICAM inhibitors

ABSTRACT

A series of *meta*-substituted anilines were designed and synthesized to inhibit the interaction of LFA-1 with ICAM for the treatment of autoimmune disease. Design of these molecules was performed by utilizing a co-crystal structure for structure-based drug design. The resulting molecules were found to be potent and to possess favorable pharmaceutical properties.

LFA-1 (Leukocyte function-associated antigen-1) is a cell surface adhesion protein expressed on all leukocytes. The counter receptors for LFA-1 are ICAMs 1, 2, and 3 (intracellular adhesion molecule). The interaction of LFA-1 with the ICAM family of receptors is necessary for extravasation of leukocytes from the blood to the site of inflammation. Disruption of the LFA-1/ICAM interaction should lead to decreased leukocyte migration to sites of inflammation and has become an important target in the treatment of autoimmune disease.[1–3] Raptiva®, an antibody that disrupts that LFA-1/ICAM interaction was approved in 2003 for the treatment of autoimmune disease.[4]

The LFA-1/ICAM interaction can be disrupted at the site of LFA-1/ICAM interaction, the metal-ion-dependent adhesion site (MIDAS), or through binding to an allosteric site (I domain allosteric site, IDAS) on LFA-1 that causes it to adopt a conformation that cannot bind to ICAM.[5] Binding to the MIDAS site has been successfully achieved through peptide and peptidomimetic strategies by researchers at Genentech.[6] Our strategy focused on the allosteric site through modification of a series of molecules originally described by Abbott laboratories.[7–13] Herein, we describe the discovery of a series of potent inhibitors of the LFA-1/ICAM interaction by utilizing a structure-based drug design approach.

The scaffold (Fig. 1) we chose for further investigation consists of three rings designated A, B, and C. SAR studies (unpublished results) showed the B bis-trifluoromethyl C morpholino rings in these positions to be a highly preferred substitution and was chosen for further analoging. Utilizing a co-crystal structure (unpublished results) with the B–C combination described above, a series of molecules were docked to investigate substitution on

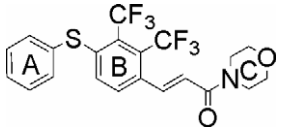
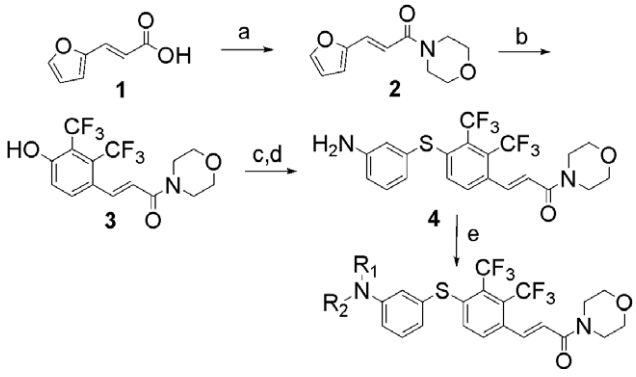


Figure 1. Scaffold targeted for further optimization.



Scheme 1. Synthetic scheme for the production of compound 4 and derivatives. (a) Morpholine, HATU, DIPEA, rt o/n; (b) bis-trifluoromethylacetylene, DCE, −78 to 115 °C o/n then borontrifluoride diethyl etherate, DCE; (c) DCM, pyridine, triflic anhydride 0–rt; (d) potassium *t*-butoxide, 3-aminothiophenol 78 °C; (e) ketone or aldehyde, triacetoxyborohydride, acetic acid, DCE.

* Corresponding author.
E-mail address: kevin.guckian@biogenidec.com (K.M. Guckian).

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.08.061

the A-ring. Based on docking into X-ray co-crystal structures, the *meta*-substituted aniline seemed to be in an optimal position to form a hydrogen bond to the carbonyl oxygen of Glu 284 in the A ring pocket and was chosen for analog synthesis.

Synthesis of the target molecule occurred in four steps starting from commercially available (*E*)-3-(furan-2-yl)acrylic acid (Scheme 1). The acid (**1**) was first coupled to morpholine using HATU and DIPEA then bis-trifluoromethylacetylene was added at −78 °C and heated in a high pressure reactor to 115 °C overnight to affect the Diels Alder reaction.[14,15] The intermediate was then concentrated and a rearrangement ensued upon addition of boron trifluoride diethyl etherate and heating. The phenol (**3**) was then activated as the triflate, which was displaced by the anion of 3-aminothiophenol to give compound **4**.

Compound **4** showed good inhibition of the LFA-1/ICAM interaction with an IC_{50} of 2.0 nM. It was further profiled and was found to have 27% oral availability with a 4.5-h half-life when dosed at 1 mg/kg in rat. Furthermore, a co-crystal structure with LFA-1 was obtained that confirmed the design hypothesis of hydrogen bond formation between the aniline N–H of compound **4** and the carbonyl oxygen of Glu 284 (Fig. 2). To further optimize this compound a series of *meta*-aniline analogs was investigated.

We first looked at simple alkyl and cycloalkyl substitution on the aniline. These compounds were synthesized by reacting the parent aniline dissolved in dichloroethane with the corresponding aldehyde or ketone in the presence of triacetoxyborohydride and acetic acid (Scheme 1). Compounds **5** and **6** were synthesized by an alternate route in the same reaction by addition of methyl iodide to a solution containing potassium carbonate and DMF.

N-Methyl and *N*,*N*-dimethyl aniline were synthesized to investigate the importance of the hydrogen bond to Glu 284. (A 5-fold loss of potency was found going from mono-methyl to di-methyl consistent with the binding hypothesis.) Several other substitutions were investigated and a selected subset are shown in Table 1. To summarize, addition of unsubstituted cycloalkyls (**7–9**) results in a loss in potency relative to the unsubstituted aniline. Upon introduction of polar functionality in the 4 position of the ring, most of the binding affinity is restored (**10–14**). Of note are the *trans* and *cis* isomers of the 1,4 cyclohexyl carboxylic acid (**10** and **11**). The *cis* isomer (**11**) was found to be 3-fold more potent than the unsubstituted aniline and 4-fold more potent than the *trans* isomer (**10**). Furthermore the ester mixture of *cis* and *trans* isomers (**12**) was found to lose between one and two orders of magnitude in potency when compared to the corresponding acids (**10** and **11**). Addition of a methylene between the aniline nitrogen and the cyclohexane ring to give compounds **15** and **16** resulted in a slight loss in potency when compared to compound **11**. Further investigation of compound **11** showed the molecule to have 13% oral bioavailability in rats with a short half-life of 1.8 h and clearance of 8.3 ml/min/kg when dosed at 1 mpk.

The most potent series of molecules was found when N-alkylated piperidines were introduced onto the aniline nitrogen (Table

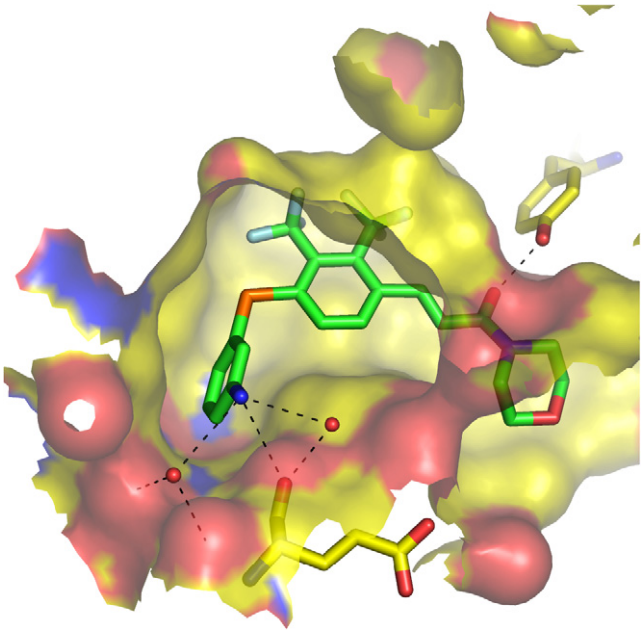
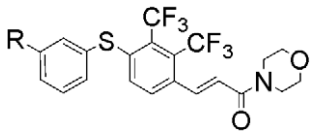
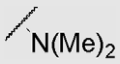
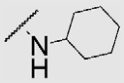
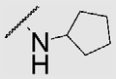
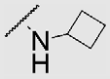
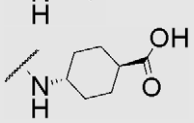
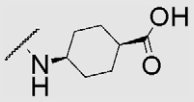
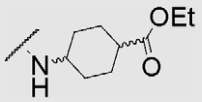
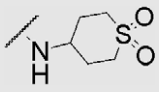
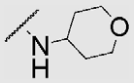
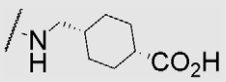
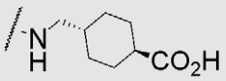


Figure 2. Co-crystal structure of compound **4** bound within the LFA-1 I domain. RCSB file name (3BQM).

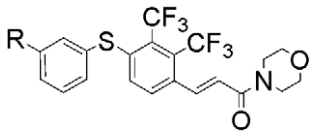
Table 1
Alkyl substitution[a]

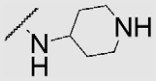
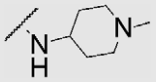
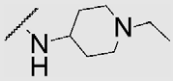
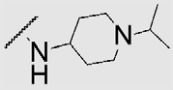
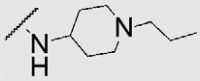
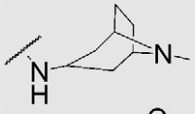
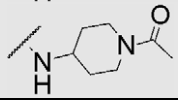


Compound	R	LFA-1/ICAM1-IG IC_{50} (nM)
4		1.7
5		4.4
6		23
7		28
8		45
9		19
10		2.4
11		0.5
12		45
13		6.0
14		5.4
15		3.2
16		1.4

[a] Assay was performed as described in Ref. 9.

Table 2
Piperdine substitution[a]



Compound	R	LFA-1/ICAM1-IG IC_{50} (nM)
17		1.4
18		0.5
19		1.4
20		0.35
21		0.9
22		0.94
23		7.0

[a] Assay was performed as described in Ref. 9.

2). Both large and small alkyl groups were well tolerated, but acetyl substitution (**23**) resulted in a loss in potency. Interestingly, the tropinone derivative (**22**) is very potent, demonstrating the large size of the A ring pocket. In general, molecules in this subseries were orally available; for example compound **20** was found to have 32% oral bioavailibility and a 7-h half-life when dosed at 1 mpk in rats.

In addition to the alkyl and cycloalkyl substitutions discussed above, several other functionalities were investigated. A sulfonamide series was designed to increase the acidity of the aniline N–H and make it a better H-bond acceptor. However, sulfonamide substitution led to equipotent or less potent compounds and the PK properties of these compounds were poor relative to that seen with many of the alkyl-substituted compounds. In addition, urea, thiourea, amide, and carbamate substitutions were investigated. None were found to contain the properties seen by the alkyl-substituted piperidines or *cis*-cyclohexanecarboxylic acid substitution (unpublished results).

To summarize we have designed a series of potent *meta*-substituted aniline containing LFA-1/ICAM inhibitors. Several molecules within this class contain good pharmaceutical properties and are currently subject to further evaluation.

References and notes

1. Giblin, P. A.; Lemieux, R. M. *Curr. Pharm. Des.* **2006**, *12*, 2771.
2. Staunton, D. E.; Lupher, M. L.; Liddington, R.; Gallatin, W. M. *Adv. Immun.* **2006**, *91*, 111.
3. Shimaoka, M.; Springer, T. A. *Curr. Top. Med. Chem.* **2004**, *4*, 1485.
4. Gottlieb, A.; Krueger, J. G.; Bright, R.; Ling, M.; Lebwohl, M.; Kang, S.; Feldman, S.; Spellman, M.; Wittkowski, K.; Ochs, H. D.; Jardieu, P.; Bauer, R.; White, M.; Dedrick, R.; Garovoy, M. *J. Am. Acad. Dermatol.* **2000**, *42*, 428.
5. Luo, B.-H.; Carman, C. V.; Springer, T. A. *Ann. Rev. Immun.* **2007**, *25*, 619.
6. Gadek, T. R.; Burdick, D. J.; McDowell, R. S.; Stanley, M. S.; Marsters, J. C., Jr.; Paris, K. J.; Oare, D. A.; Reynolds, M. E.; Ladner, C.; Zioncheck, K. A.; Lee, W. P.; Gribling, P.; Dennis, M. S.; Skelton, N. J.; Tumas, D. B.; Clark, K. R.; Keating, S. M.; Beresini, M. H.; Tilley, J. W.; Presta, L. G.; Bodary, S. C. *Science* **2002**, *295*, 1086.
7. Winn, M.; Reilly, E. B.; Liu, G.; Huth, J. R.; Jae, H.-S.; Freeman, J.; Pei, Z.; Xin, Z.; Lynch, J.; Kester, J.; von Geldern, T. W.; Leitza, S.; DeVries, P.; Dickinson, R.; Mussatto, D.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 4393.
8. Pei, Z.; Xin, Z.; Liu, G.; Li, Y.; Reilly, E. B.; Lubbers, N. L.; Huth, J. R.; Link, J. T.; von Geldern, T. W.; Cox, B. F.; Leitza, S.; Gao, Y.; Marsh, K. C.; DeVries, P.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 2913.
9. Liu, G.; Link, J. T.; Pei, Z.; Reilly, E. B.; Leitza, S.; Nguyen, B.; Marsh, K. C.; Okasinski, G. F.; von Geldern, T. W.; Ormes, M. *J. Med. Chem.* **2000**, *43*, 4025.
10. Zhu, G.-D.; Arendsen, D. L.; Gunawardana, I. W.; Boyd, S. A.; Stewart, A. O.; Fry, D. G.; Cool, B. L.; Kifle, L.; Schaefer, V.; Meuth, J.; Marsh, K. C.; Kempf-Grote, A. J.; Kilgannon, P.; Gallatin, W. M.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 3469.
11. Liu, G.; Huth, J. R.; Olejniczak, E. T.; Mendoza, R.; DeVries, P.; Leitza, S.; Reilly, E. B.; Okasinski, G. F.; Fesik, S. W.; von Geldern, T. W. *J. Med. Chem.* **2001**, *44*, 1202.
12. Stewart, A. O.; Bhatia, P. A.; McCarty, C. M.; Patel, M. V.; Staeger, M. A.; Arendsen, D. L.; Gunawardana, I. W.; Melcher, L. M.; Zhu, G.-D.; Boyd, S. A.; Fry, D. G.; Cool, B. L.; Kifle, L.; Lartey, K.; Marsh, K. C.; Kempf-Grote, A. J.; Kilgannon, P.; Wisdom, W.; Meyer, J.; Gallatin, W. M.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 988.
13. Link, J. T.; Sorensen, B.; Liu, G.; Pei, Z.; Reilly, E. B.; Leitza, S.; Okasinski, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 973.
14. Zhu, G.-D.; Staeger, M. A.; Boyd, S. A. *Org. Lett.* **2000**, *2*, 3345.
15. Barlow, M. G.; Suliman, N. N. E.; Tipping, A. E. *J. Fluor. Chem.* **1995**, *70*, 95.