Pergamon

Tetrahedron Letters 42 (2001) 8911–8913

TETRAHEDRON LETTERS

A convenient synthesis of 4-aminomethyl-4,5,6,7-tetrahydro-1,3-benzothiazole arginine side-chain mimetics

Petra Marinko, Jože Kastelic, Aleš Krbavčič and Danijel Kikelj*

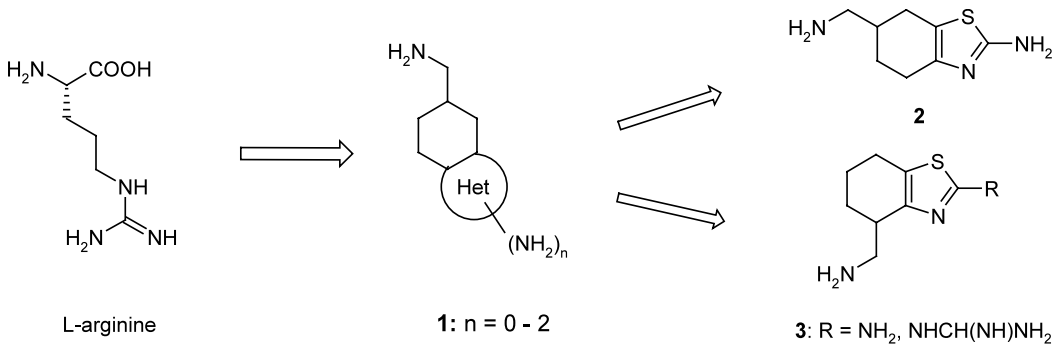
University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, 1000 Ljubljana, Slovenia

Received 29 August 2001; revised 2 October 2001; accepted 12 October 2001

Abstract—A convenient synthesis of novel 4-aminomethyl-4,5,6,7-tetrahydro-1,3-benzothiazole arginine side-chain mimetics designed for incorporation into thrombin inhibitors is reported.

During the last 3 years there has been a growing interest in heterocyclic arginine mimetics, comprising heterocyclic amines and aza-heterocycles as synthons for the preparation of trypsin-like serine protease inhibitors.[1] The reduced basicity of these heterocyclic compounds and the rigidity of the heterocyclic ring as compared to the guanidinoalkyl side-chain of arginine contribute to the increased bioavailability and selectivity of thrombin inhibitors containing heterocyclic arginine mimetics.[2–4] These peptidomimetic building blocks generally possess an amino group by which they are coupled to the rest of the inhibitor molecule by an amide bond. It has been demonstrated several times that a methylene linker between the heterocycle and the amino group, allowing substantial conformational freedom of the heterocycle, is crucial for the design of potent thrombin inhibitors.[5–7]

Recently, we have reported a general synthetic approach to the aminomethyl substituted heterobicyclic arginine side-chain mimetic **1**, which, through a synthetic strategy based on *N*-[(4-oxocyclohexyl)-methyl]acetamide as the key intermediate, provided compounds bearing an aminomethyl group at the *meta*/*para* position relative to the ring junction, including 5-aminomethyl-4,5,6,7-tetrahydroisoindole, 5-aminomethyl-4,5,6,7-tetrahydroindazole, 6-aminomethyl-4,5,6,7-tetrahydro-1,3-benzothiazole and 6-aminomethyl-5,6,7,8-tetrahydroquinazoline derivatives.[8,9] Among them, 6-(aminomethyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine (**2**) was shown to be one of the most promising arginine side-chain mimetics providing potent and selective thrombin inhibitors.[10] In order to optimize interactions of the P1 part of the inhibitors with the S1 pocket of thrombin, modification



Keywords: arginine mimetics; peptidomimetics; 4-aminomethyl-4,5,6,7-tetrahydro-1,3-benzothiazole derivatives.

* Corresponding author. Tel.: +386-1-476-9561; fax: +386-1-425-8031; e-mail: danijel.kikelj@ffa.uni-lj.si

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01939-6

of the arginine mimicking part of the inhibitor molecule by a different point of attachment of the aminomethyl group seemed to be a logical choice.

We report here a synthetic strategy leading to novel 4-aminomethyl-4,5,6,7-tetrahydro-1,3-benzothiazole arginine side-chain mimetics **3** which were designed as building blocks for the preparation of thrombin inhibitors.

Starting from commercially available ethyl 2-oxocyclohexanecarboxylate (**4**), bromination with bromine in diethyl ether afforded the 3-bromo derivative **5**[11] (Scheme 1). In the next step, a classical Hantzsch thiazole synthesis[12a] applying thiourea or amidinothiourea as an S–C–N synthon afforded fused thiazoles **6a**[13a,b] and **6b**.[20] Reduction of the esters **6a** and **6b** with lithium aluminum hydride and subsequent tosylation with *p*-toluenesulfonyl chloride in pyridine afforded tosylates **8a** and **8b**. In the case of the 2-amino derivative **7a**, in addition to the tosylate **8a**, the *N*-tosyl derivative was obtained as a by-product in 25% yield.[14] Nucleophilic substitution of tosylates **8a** and **8b** with sodium azide in *N*,*N*-dimethylformamide produced the azides **9a** and **9b**. Catalytic hydrogenation of the azide **9b** using 10% palladium on charcoal as a catalyst afforded the arginine side-chain mimetic **3b**.[18,21] In contrast, when the azide **9a** was subjected to reduction under various conditions (hydrogenation over palladium on charcoal,[15] reduction with tin(II) chloride[16]), the reaction was not successful due to formation of numerous by-products. Therefore, a direct substitution of the tosylate **8a** in liquid ammonia was attempted and this successfully produced the target arginine side-chain mimetic **3a** in 40% yield.[19,21]

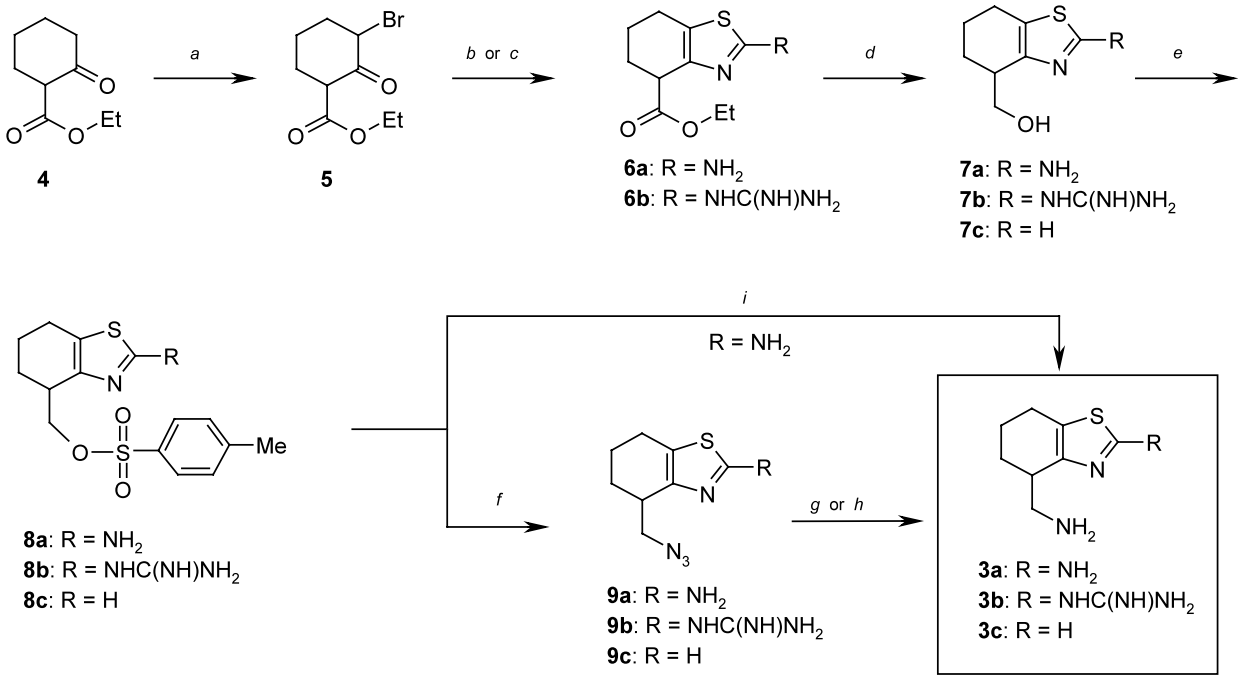
Interestingly, reduction of **6b** to **7b** with lithium aluminum hydride was accompanied by deguanylation yielding 4,5,6,7-tetrahydro-1,3-benzothiazol-4-ylmethanamine (**7c**) in 36% yield and by scission of an N–C bond in the guanidino group giving **7a** in 45% yield.[17] Although deaminations of similar substituted 1,3-thiazol-2-amines are known, according to the literature they are performed by reduction with sodium in liquid ammonia or mercury(II) oxide and generally give a mixture of products.[12b] By reducing the excess of lithium aluminum hydride from 1.6 to 1.3 equiv., the formation of **7a** and **7c** was completely suppressed and **7b** was obtained in 72% yield.

For conversion of **7c** to arginine side-chain mimetic **3c**,[21] the same strategy as described above for the synthesis of **3a** and **3b** was applied.

In conclusion, we have developed a straightforward synthetic pathway to novel 4-(aminomethyl)-4,5,6,7-tetrahydro-1,3-benzothiazole arginine side-chain mimetics bearing either an amino group or a guanidino residue at carbon 2. They were used as synthons for the preparation of non-covalent thrombin inhibitors which will be reported elsewhere.

Acknowledgements

This work was financially supported by the Ministry of Science and Technology of the Republic of Slovenia. The authors wish to thank Dr. Anthony R. Byrne for critical reading of the manuscript.



Scheme 1. (a) Br_2, ether, rt, 2 h, 98%; (b) H_2NCSNH_2, abs. EtOH, rt, 16 h, 98%; (c) $H_2NCSNHC(=NH)NH_2$, DMF, rt, 16 h, 73%; (d) $LiAlH_4$, THF, ice bath then reflux, 16 h, 31–72%; (e) TsCl, pyridine, rt, 16 h, 34–62%; (f) NaN_3, DMF, reflux, 3 h, 65–77%; (g) $SnCl_2 \cdot 2H_2O$, MeOH, rt, 16 h, 15%; (h) H_2, Pd/C, MeOH, 55%; (i) liq. NH_3, abs. EtOH, 50°C, 16 h, 40%.

References

1. Peterlin-Mašič, L.; Kikelj, D. *Tetrahedron* **2001**, *57*, 7073–7105.
2. Rewinkel, J. B. M.; Adang, A. E. P. *Curr. Pharm. Design* **1999**, *5*, 1043–1075.
3. Steinmetzer, T.; Hauptmann, J.; Stürzebecher, J. *Exp. Opin. Invest. Drugs* **2001**, *10*, 845–864.
4. Coburn, C. A. *Exp. Opin. Ther. Pat.* **2001**, *11*, 721–738.
5. Feng, D. M.; Gardell, S. J.; Lewis, S. D.; Bock, M. G.; Chen, Z.; Freidinger, R. M.; Naylor-Olsen, A. M.; Ramjit, H. G.; Woltmann, R.; Baskin, E. P.; Lynch, J. J.; Lucas, R.; Shafer, J. A.; Dancheck, K. B.; Chen, I.-W.; Maso, S. S.; Krueger, J. A.; Hare, T. A.; Mulichak, A. M.; Vacca, J. P. *J. Med. Chem.* **1997**, *40*, 3726–3733.
6. Wiley, M. R.; Lepore, S. D. PCT Int. Appl. WO 0,027,199, 2000; *Chem. Abstr.* **2000**, *132*, 347944.
7. Sanderson, P. E.; Lyle, T.; Dorsey, B.; Stanton, M. G.; Naylor-Olsen, A. M. PCT Int. Appl. WO 0,026,210, 2000; *Chem. Abstr.* **2000**, *132*, 334472.
8. Peterlin-Mašič, L.; Kikelj, D. *Tetrahedron Lett.* **2000**, *41*, 5589–5592.
9. Peterlin-Mašič, L.; Jurca, A.; Marinko, P.; Jančar, A.; Kikelj, D. *Tetrahedron*, accepted for publication.
10. Kikelj, D.; Peterlin-Mašič, L.; Marinko P.; Breznik, M.; Stegnar, M.; Trampuš-Bakija, A.; Fortuna, M. Patent Appl. PCT/GB01/01997 (04.05.2001).
11. Maillard, J.; Delaunay, P.; Langlois, M.; Portevin, B.; Legeai, J.; Benharkate, M. *Eur. J. Med. Chem.* **1984**, *19*, 457–460.
12. (a) Liebscher, J. In *Houben-Weyl*: *Methoden der Organischen Chemie*; Schaumann, E., Ed.; Georg Thieme: Stuttgart, 1994; Vol. E8b/Part 2, pp. 23–110; (b) Liebscher, J. In *Houben-Weyl*: *Methoden der Organischen Chemie*; Schaumann, E., Ed.; Georg Thieme: Stuttgart, 1994; Vol. E8b/Part 2, pp. 217–220.
13. Compound **6a** has been previously prepared by a modified procedure described in two patents. See: (a) Wei, P. H. L. US Patent 3,859,280, 1975; *Chem. Abstr.* **1975**, *82*, 140120; (b) Caprathe, B. W.; Jaen, J. C.; Wise, L. D. US Patent 4,988,699, 1991; *Chem. Abstr.* **1991**, *115*, 8786.
14. The *O*-tosyl (R_f=0.36; mp 131–134°C) and the *N*-tosyl (R_f=0.27; mp 73–76°C) derivatives were separated by column chromatography on silica gel using CH_2Cl_2/MeOH (20:1) as eluant and fully characterized by NMR, IR, mass spectrometry and CHN analysis.
15. Hydrogenation was carried out in methanol using 10% Pd/C as a catalyst at room temperature and normal pressure or in abs. ethanol at 90°C and 9 bar.
16. Maiti, S. N.; Singh, M. P.; Micetich, R. G. *Tetrahedron Lett.* **1986**, *27*, 1423–1424.
17. Compounds **7a** (R_f=0.27; mp 62–65°C), **7b** (R_f=0.00; mp 81–85°C) and **7c** (R_f=0.47; yellow oil; previously described in Ref. 11) were separated by column chromatography on silica gel using $CHCl_3$/MeOH (9:1) as eluant and fully characterized by NMR, IR, mass spectrometry and CHN analysis.
18. Compound **3b**: yield 55%, yellow solid; mp 149–153°C; IR (KBr): ν 3347, 2928, 1606, 1547, 1451, 1255, 967, 735 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.55–1.70 (m, 2H, CH_2), 1.75–1.87 (m, 2H, CH_2), 2.40–2.55 (m, 3H, CH, CH_2), 2.89–2.97 (AX part of an ABX system, J_{AB}= 11.50 Hz, J_{AX}=3.20 Hz, 1H, CH_2-N), 6.72 (br s, 4H, NHC(NH)NH_2); ^1H NMR (300 MHz, $CDCl_3$): δ 1.50–1.70 (m, 2H, CH_2), 1.87–2.01 (m, 2H, CH_2), 2.58–2.67 (m, 2H, CH_2), 2.68–2.79 (m, 1H, CH), 2.90–2.98 (ABX system, 2H, J_{AB}=18.08 Hz, J_{AX}=5.27 Hz, J_{BX}=6.41 Hz, CH_2-N); MS (70 eV, EI): m/z (%) 225 (M^+, 20), 196 (100). Anal. calcd for $C_9H_{15}N_5S\cdot0.5H_2O$: C, 46.13; H, 6.88; N, 29.89. Found: C, 46.52; H, 6.99; N, 29.76%.
19. Compound **3a**: yield 40%, brownish solid; mp 89–92°C; IR (NaCl): ν 3310, 2933, 1623, 1524, 1311, 1111 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.43–1.68 (m, 2H, CH_2), 1.71–1.88 (m, 2H, CH_2), 2.35–2.48 (m, 2H, CH_2), 2.52–2.60 (m, 2H, 2×CH), 2.75–2.85 (AX part of an ABX system, J_{AB}=12.25 Hz, J_{AX}=4.70 Hz, 1H, CH_2-N), 3.05 (br s, NH_2+H_2O), 6.60 (br s, 2H, NH_2); MS (70 eV, FAB): m/z (%) 184 (MH^+, 100); HRMS calcd for $C_8H_{13}N_3S$: 183.083019. Found: 183.083650.
20. Ethyl 2-{[amino(imino)methyl]amino}-4,5,6,7-tetrahydro-1,3-benzothiazole-4-carboxylate hydrobromide (**6b**): To a solution of compound **5** (19.2 g, 77 mmol) in 40 mL of anhydrous DMF was added 2-imino-4-thiobiuret (10.0 g, 85 mmol). After being stirred at room temperature for 12 h, the solvent was removed in vacuo. The resulting oily residue was treated with ether, and the precipitate dried in vacuo over P_2O_5 giving 19.6 g (73%) of the title compound as a white solid, mp 190–193°C; IR (KBr): ν 3298, 3174, 2868, 1717, 1675, 1606, 1510, 1377, 1297, 1185, 1087, 1012, 930, 703, 613 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.19 (t, 3H, J=7.16 Hz, CH_3), 1.72–1.90 (m, 2H, CH_2), 1.94–2.08 (m, 2H, CH_2), 2.65–2.74 (m, 2H, CH_2), 3.69–3.78 (m, 1H, CH), 4.11 (q, 2H, J=7.16 Hz, C$\underline{H}_2$-OH), 8.17 (br s, 5H, NHC(NH)NH_3^+); MS (70 eV, EI): m/z (%) 268 [$(M-HBr)^+$, 100]; Anal. (free base) calcd for $C_{11}H_{16}N_4O_2S\cdot0.75H_2O$: C, 46.86; H, 6.26; N, 19.87. Found: C, 47.33; H, 6.25; N, 19.48%.
21. The target compounds were obtained as racemates.