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A general synthesis of novel conformationally restricted arginine side-chain mimetics

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Abstract

6-(Aminomethyl)-5,6,7,8-tetrahydro-2-quinazolinamine and 4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethanamine were synthesized as novel conformationally restricted arginine side-chain mimetics, designed for incorporation into trypsin-like serine protease inhibitors.

Keywords: arginine side-chain mimetics; serine proteases.

Trypsin-like serine proteases that cleave a polypeptide chain after the basic amino acids arginine (**1**) and lysine are involved in many physiological and pathophysiological processes, including digestion, blood coagulation, fibrinolysis and inflammation.[1] Thus, the specific inhibition of certain trypsin-like serine proteases, e.g. thrombin is a therapeutically important target.[2,3] Arginine residues or mimetics thereof are common groups that have been incorporated into the P_1 position of many thrombin inhibitors.[4–7] It has been shown that selectivity of an inhibitor for a particular serine protease can be conferred based upon the structural moiety incorporated in the P_1 position.[3] However, most of the inhibitors incorporating an arginine residue lack selectivity for the targeted serine protease. It is also generally accepted that highly basic moieties such as the guanidino or amidino groups are the main barriers to absorption of thrombin inhibitors after peroral application.[5,6] Thus, significant effort has been focused on the design and preparation of arginine mimetics and arginine side-chain mimetics that could confer selective inhibition for specific serine proteases and possess reduced basicity. With regard to this, we have designed and synthesized several novel conformationally restricted heterocyclic arginine side-chain mimetics, which were incorporated into tripeptidomimetic[6] thrombin inhibitors shown to inhibit human thrombin.[8]

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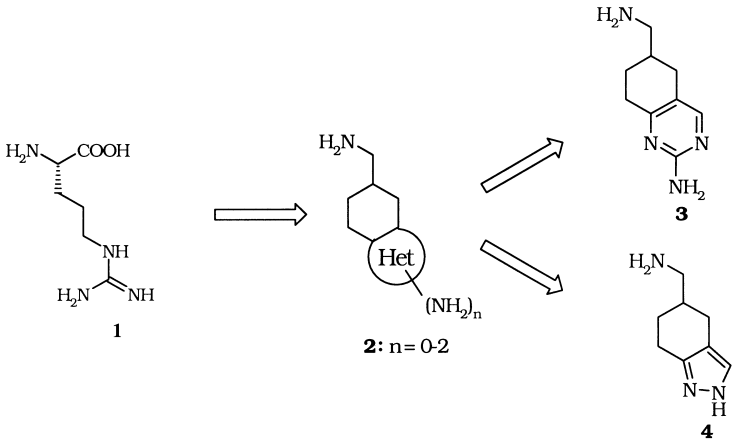
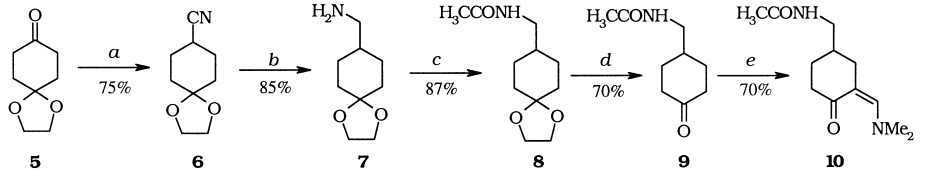


In this paper, we report a general synthesis of novel arginine side-chain mimetics **2** containing a five- or six-membered *N*-heterocyclic ring, optionally substituted by amino group(s) mimicking the guanidino moiety of arginine and a saturated cyclohexane ring mimicking the arginine trimethylene side chain. When incorporated into potential inhibitors, the bulky cyclohexane ring of **2** could confer selectivity for certain types of serine proteases. Additionally, the aminomethyl group bound to the cyclohexane ring of **2** could give to the inhibitors a substantial conformational freedom as compared to inhibitors comprising similar arginine side-chain mimetics in which the amino group is bound directly to the cyclohexane ring.[9]

At the beginning of our studies directed towards the design and synthesis of selective thrombin inhibitors we envisaged the hitherto unknown 6-(aminomethyl)-5,6,7,8-tetrahydro-2-quinazolinamine (**3**) and 4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethanamine (**4**) as interesting mimetics of the arginine side-chain, which would be easily functionalized via the nucleophilic aminomethyl group. Although several heterocyclic amines have recently been used as mimetics of arginine,[10–13] partially saturated aminomethyl-substituted bicyclic heterocycles **2** have not been described so far. Therefore, a general synthesis of arginine side-chain mimetics of the general structure **2** seemed highly desirable. A strategy originally designed by us to afford the arginine side-chain mimetics **3** and **4** included the synthesis of the novel enamino ketone **10** as the key intermediate (Scheme 1), which as a versatile synthon could be easily transformed by cyclocondensation and subsequent hydrolysis to the bicyclic compounds **3** and **4**.

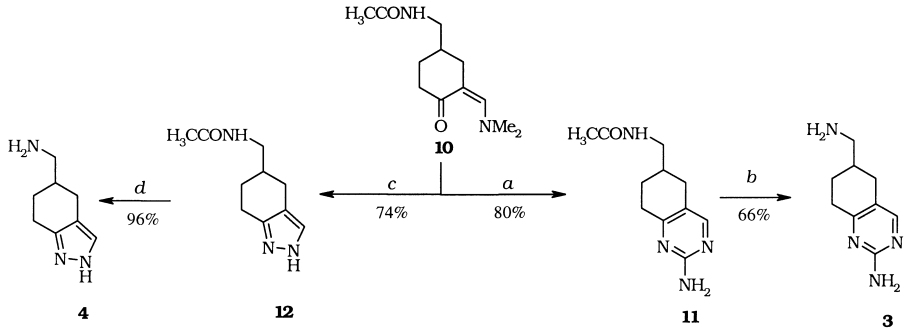


Scheme 1. (*a*) TOSMIC, *t*-BuOK/DME, 0°C, 1 h, then rt, 2 h; (*b*) $LiAlH_4$/THF, reflux, 2 h, then rt, 12 h; (*c*) Ac_2O, rt, 1 h; (*d*) 90% HCOOH, rt, 16 h; (*e*) DMFDMA, reflux, 16 h

Our synthesis started with the preparation of the known 1,4-dioxaspiro[4.5]dec-8-ylmethanamine (**7**) by reductive cyanation of 1,4-cyclohexanedione monoethylene acetal (**5**) with tosylmethyl isocyanide and subsequent reduction of the nitrile **6** with lithium aluminum hydride.[14] After

protecting the amino group of **7**, e.g. by acetylation,[15] cleavage of the 1,3-dioxolane ring with 90% formic acid gave *N*-[(4-oxocyclohexyl)methyl]acetamide (**9**). The ketone **9** was converted by condensation with dimethylformamide dimethyl acetal (DMFDMA)[16] into novel enamino ketone **10**[17] (Scheme 1), which is a useful intermediate for further transformations into different heterocyclic compounds **2**.

The reaction of the enamino ketone **10**, e.g. with guanidine hydrochloride in the presence of sodium ethoxide gave the tetrahydroquinazoline derivative **11**,[18] which, upon hydrolysis under basic conditions, produced the amine **3** (Scheme 2). Similarly, the enamino ketone **10** was smoothly transformed with hydrazine hydrate into the tetrahydroindazole derivative **12**,[19] which, after acid hydrolysis, provided 4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethanamine (**4**) (Scheme 2).



Scheme 2. (*a*) Guanidine hydrochloride/NaOEt, abs. EtOH, reflux, 3 h; (*b*) aq. NaOH, MeOH, reflux, 6 h; (*c*) $NH_2NH_2 \times H_2O$, rt, 16 h; (*d*) 6M HCl, reflux, 6 h

To summarize, we have succeeded in preparing 6-(aminomethyl)-5,6,7,8-tetrahydro-2-quinazolinamine (**3**) and 4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethanamine (**4**) as novel conformationally restricted arginine side-chain mimetics. These compounds are interesting peptidomimetic building blocks for incorporation into various serine protease inhibitors. Starting from the key intermediate, the novel enamino ketone **10**, the method is generally applicable for the synthesis of arginine side-chain mimetics **2**,[20] which are currently under investigation in our laboratory and will be reported in due course.

Acknowledgements

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17. Compound **10**: IR (KBr): ν 3278, 2929, 1637, 1540, 1420, 1333, 1202, 1128, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.38–1.50 (m, 1H, CH), 1.73–1.90 (m, 2H, CH_2), 2.01 (s, 3H, CH_3), 2.25–2.50 (m, 3H, CH_2, CH), 3.09 (s, 6H, 2×CH_3), 2.80–2.92 (m, 1H, CH), 3.11–3.23, 3.30–3.39 (2×m, 2H, CH_2NH), 5.75 (s br, 1H, NH), 7.49 (s, 1H, CH-methylidene); MS (70 eV, EI): m/z (%) 224 (M^+, 56), 152 (100). Anal. calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 63.95; H, 8.89; N, 12.39.
18. (±)-*N*-[(2-Amino-5,6,7,8-tetrahydro-6-quinazolinyl)methyl]acetamide (**11**): To a solution of sodium ethoxide (0.1 g, 4.46 mmol) in 20 ml of absolute ethanol, guanidine hydrochloride (0.43 g, 4.46 mmol) was added. After stirring for 30 min, a solution of *N*-{3-[(dimethylamino)methylidene]-4-oxocyclohexyl}methyl)acetamide (**10**) (1.0 g, 4.46 mmol) in absolute ethanol was added and the reaction mixture was refluxed under an argon atmosphere for 3 hours. The separated solid was collected by filtration to give 0.75 g (76%) of white solid; IR (KBr): ν 3304, 3084, 2944, 2859, 1674, 1649, 1602, 1560, 1493, 1421, 1376, 1265, 1211, 1096, 960, 786, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42–1.58 (m, 1H, CH), 1.88–2.08 (m, 2H, CH_2), 2.04 (s, 3H, CH_3), 2.25–2.38 (m, 1H, CH), 2.68–2.82 (m, 3H, CH_2, CH), 3.32 (t, 2H, J = 6.6 Hz, CH_2NH), 4.83 (s br, 2H, 2-NH_2), 5.60 (s br, 1H, NH), 8.00 (s, 1H, 4-CH); MS (70 eV, EI): m/z (%) 220 (M^+, 35), 148 (100). Anal. calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 59.76; H, 7.06; N, 25.21.
19. (±)-*N*-(4,5,6,7-Tetrahydro-2*H*-indazol-5-ylmethyl)acetamide (**12**): A solution of the enamino ketone **10** (1.0 g, 4.46 mmol) and NH_2NH_2×H_2O (0.25 ml, 5.0 mmol) in 20 ml of methanol was stirred at room temperature for 16 hours. The solvent was evaporated, and the product was purified by column chromatography on Florisil using ethyl acetate:methanol (2:1) as eluent to yield 0.56 g (65%) of **12**; IR (KBr): ν 3261, 2928, 1652, 1558, 1437, 1368, 1293, 1088, 1035, 962, 782, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.49–1.60 (m, 1H, CH), 2.02 (s, 3H, CH_3), 1.89–2.05 (m, 2H, CH_2), 2.18–2.28 (m, 1H, CH), 2.58–2.90 (m, 3H, CH_2, CH), 3.20–3.40 (m, 2H, CH_2NH), 3.51 (s, 1H, NH), 5.60 (s broad, 1H, *NH*), 7.31 (s, 1H, 3-CH); MS (70 eV, EI): m/z (%) 193 (M^+, 40), 121 (100). Anal. calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.74. Found: C, 61.88; H, 7.85; N, 21.44.
20. Compounds **3**, **4**, **10**, **11** and **12** were obtained as racemates; experiments directed towards the preparation of pure enantiomers of arginine side-chain mimetics **2** are in progress.