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A general synthetic approach to novel conformationally restricted arginine side chain mimetics

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Abstract—A general synthesis of several novel partially saturated, conformationally restricted heterobicyclic arginine side chain mimetics is described. These compounds are interesting peptidomimetic building blocks for incorporation into trypsin-like serine protease inhibitors.

1. Introduction

Trypsin-like serine proteases that are involved in many biological processes (e.g. blood coagulation) cleave a polypeptide chain after the basic amino acids arginine (**I**) and lysine. The basic side chains of these amino acids interact via hydrogen bonding and ionic interactions with an aspartic acid residue at the bottom of the S_1 pocket of the enzyme.[1,2] Arginine residue (**I**) or mimetics thereof are, consequently, common groups that have been incorporated into the P_1 position of many thrombin inhibitors.[3–8] It has been shown that bioavailability and selectivity of an inhibitor for specific serine-proteases can be conferred based on the structure and basicity of the moiety incorporated into the P_1 position.[3–8] 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, in addition possess reduced basicity.[9a] To this end, we designed and described in a preliminary communication[9b] several novel conformationally restricted heterocyclic arginine side chain mimetics, which were incorporated as isosteric replacements for the arginine moiety into tripeptidomimetic thrombin inhibitors.[10]

2. Results and discussion

In this paper we report a general synthesis of novel partially saturated, heterobicyclic arginine side chain mimetics **III** containing a five- or six-membered *N*-heterocyclic ring optionally substituted by amino or guanidino groups (Fig. 1). The cyclohexane ring, which mimics the arginine methylene side chain, introduces conformational rigidity into the molecule. These compounds are interesting mimetics of the arginine side chain, which can be easily functionalised via the nucleophilic aminomethyl group. When incorporated into potential tripeptidomimetic thrombin inhibitors, the bulky cyclohexane ring of **III** could confer selectivity for inhibition of thrombin vs trypsin. Additionally, the aminomethyl group bound to the cyclohexane ring of **III** gives to the inhibitors more

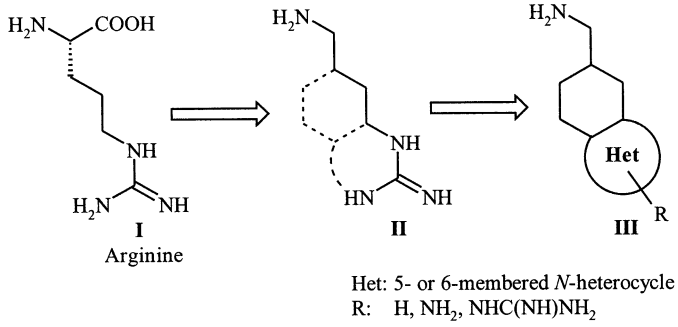

Figure 1.

Keywords: heterocycles; arginine mimetics; peptidomimetics; serine proteases; thrombin inhibitors.
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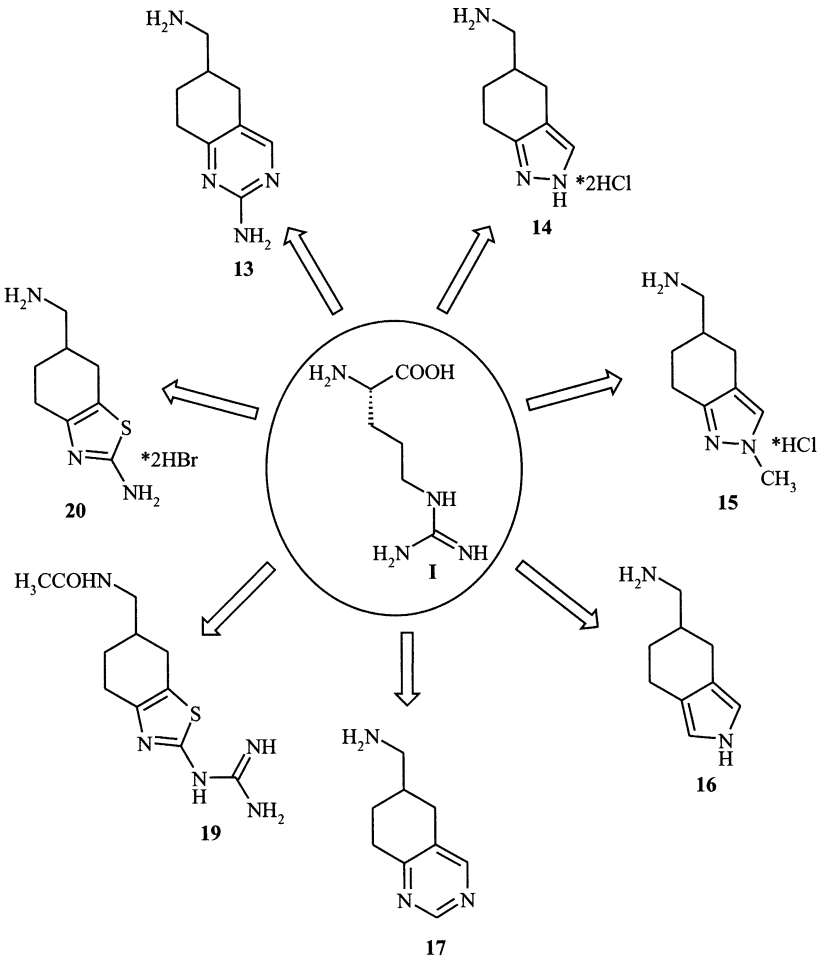


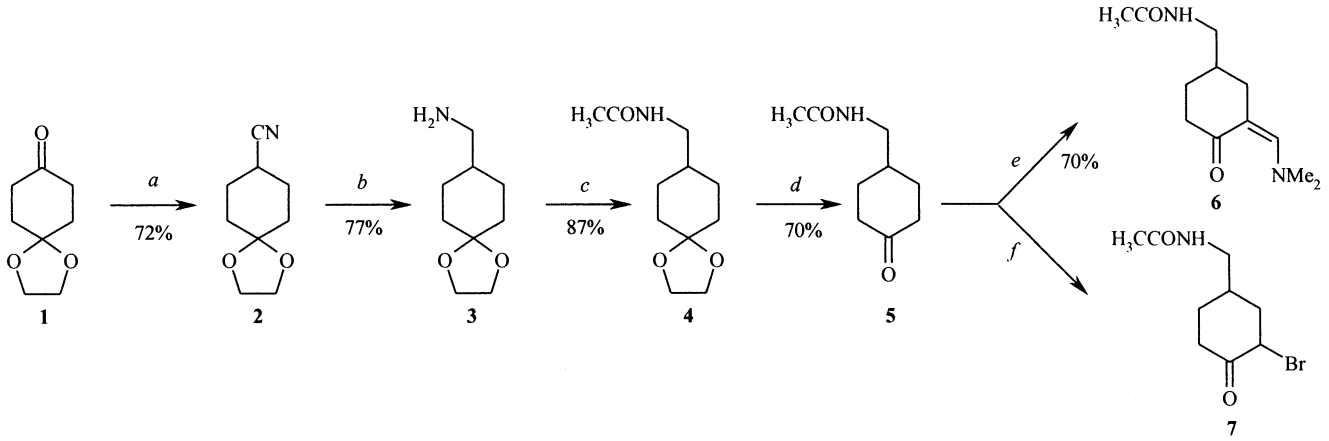
Scheme 1.

conformational freedom as compared to the inhibitors containing similar arginine side-chain mimetics with amino group bound directly to the cyclohexane ring.[11] Although several heterocyclic amines have recently been used as arginine mimetics,[12–15] partially saturated aminomethyl substituted heterobicycles **III** have not so far been described. A general synthetic approach to conformationally restricted heterocyclic arginine side chain mimetics with general structure **III** is, therefore, highly desirable.

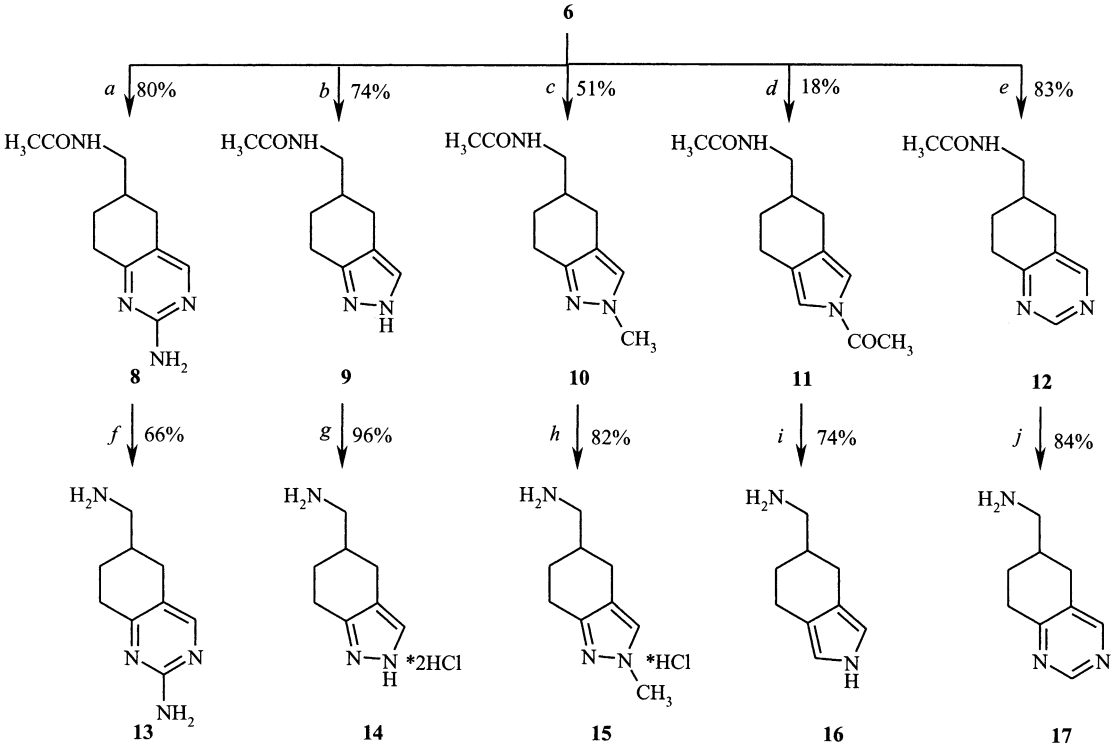
Different heterocyclic arginine side chain mimetics prepared as a part of this study are listed in Scheme 1. A general approach to afford arginine side chain mimetics **13**–**17**, **19** and **20** includes the synthesis of ketone **5**, which was transformed by condensation with dimethylformamide dimethyl acetal (DMFDMA) or by bromination to the key intermediates enamino ketone **6** or bromo ketone **7** (Scheme 2). Ketones **6** and **7** are useful intermediates for further transformations with different bifunctional nucleophiles into different heterocyclic compounds **III**. Enamino ketone **6** could be easily transformed by cyclocondensation with different nucleophiles and subsequent hydrolysis to the bicyclic heterocycles **13**–**17** (Scheme 3), whereas cyclocondensation of the bromo ketone **7** afforded bicyclic heterocycles **19** and **20** (Scheme 4).

The synthesis of enamino ketone **6** and bromo ketone **7** (Scheme 2) started with the preparation of 1,4-dioxaspiro [4.5]dec-8-ylmethanamine (**3**) by reductive cyanation of 1,4-cyclohexanedione monoethylene acetal (**1**) with tosylmethyl isocyanide and subsequent reduction of the nitrile **2** with lithium aluminum hydride.[16] After protecting the amino group of **3** by acetylation, cleavage of the 1,3-dioxolane ring with 90% formic acid gave *N*-[(4-oxocyclohexyl)methyl] acetamide (**5**). The ketone **5** was converted by condensation with DMFDMA[17] into novel enamino ketone **6** and by bromination into novel bromo ketone **7**, which were found as useful intermediates for further transformations into different heterocyclic compounds **III**.

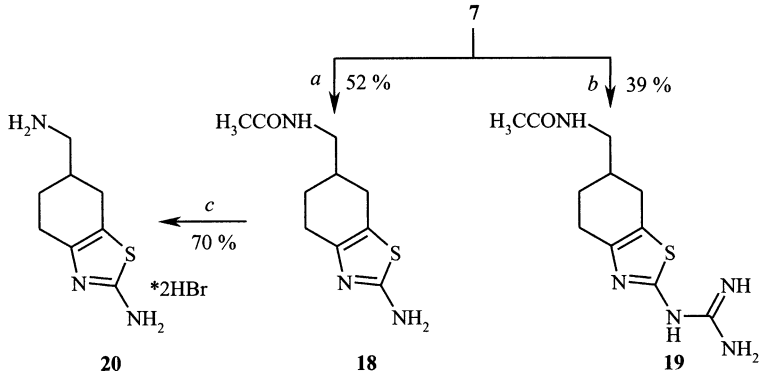
The preparation of arginine side chain mimetics **13**–**17** is depicted in Scheme 3. The reaction of the enamino ketone **6** with guanidine hydrochloride in the presence of sodium ethoxide in dry ethanol, followed by hydrolysis of the resulting tetrahydroquinazoline derivative **8** with aqueous sodium hydroxide in methanol gave 6-(aminomethyl)-5,6,7,8-tetrahydro-2-quinazolinamine (**13**) in 66% yield. Facile cyclocondensation of **6** with hydrazine hydrate or *N*-methylhydrazine in ethanol gave tetrahydroindazole derivative **9** in 74% yield and methyltetrahydroindazole derivative **10** in 51% yield, respectively. Final hydrolysis of acetamides **9** and **10** with 6 M hydrochloric acid gave 4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethanamine dihydrochloride (**14**) in 96%



Scheme 2. (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, Et_3N, toluene, reflux, 7 h; (f) Br_2, CH_2Cl_2, 40°C, 30 min.



Scheme 3. (a) Guanidine hydrochloride/NaOEt, abs. EtOH, reflux, 3 h; (b) $NH_2NH_2{\cdot}H_2O$, EtOH, rt, 16 h; (c) NH_2NHCH_3, EtOH, rt, 16 h; (d) (i) glycine, KOH, abs. EtOH, reflux, 2 h; (ii) Ac_2O, reflux, 1 h; (e) formamidine hydrochloride/NaOEt, abs. EtOH, reflux 4 h; (f), (i), (j) aq. NaOH, MeOH, reflux, 16 h; (g), (h) 6 M HCl, reflux, 6 h.



Scheme 4. (a) Thiourea, EtOH, reflux 2 h; (b) amidinothiourea, EtOH, reflux, 16 h; (c) 47% HBr, reflux, 16 h.

yield and 2-methyl-4,5,6,7-tetrahydro-2*H*-indazol-5-yl) methanamine hydrochloride (**15**) in 82% yield.

Base-catalyzed reaction of **6** with glycine, performed by analogy to a previously published procedure,[18] afforded a potassium-salt adduct, which on treatment with acetic anhydride was cyclized, decarboxylated, and acetylated to give the diamide **11**. After purification by column chromatography, the compound **11**, which eluted from the column in the later fractions, was obtained in low (18%) yield. Basic hydrolysis of **11** with aqueous sodium hydroxide in methanol produced 4,5,6,7-tetrahydro-2*H*-isoindol-5-yl-methanamine (**16**) in 74% yield. 6-(Aminomethyl)-5,6,7,8-tetrahydroquinazoline (**17**) was prepared by cyclocondensation of the enamino ketone **6** and formamidine hydrochloride in the presence of sodium ethoxide in dry ethanol and subsequent basic hydrolysis.

The condensation of the bromo ketone **7** with bifunctional nucleophiles leading to compounds **18**–**20** is shown in Scheme 4. The reaction of **7** with thiourea and amidinothiourea produced amino-substituted tetrahydrobenzothiazole **18** in 52% yield and guanidino-substituted tetrahydrobenzothiazole **19** in 39% yield, respectively. Deprotection of the acetamido group of **18** in 47% HBr under reflux yielded 6-(aminomethyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine (**20**) as a hydrobromide salt in 70% yield. Deprotection of the guanidino substituted tetrahydrobenzothiazole **19** by acid hydrolysis using aqueous hydrochloric or hydrobromic acid with several modifications of the reaction conditions, including time, solvent and concentration of acid, were unsuccessful, due to the destruction of the guanidino-substituted heterocycle as indicated by mass spectra and proton nuclear magnetic resonance.

3. Conclusion

To summarize, we have succeeded in preparing novel partially saturated, conformationally restricted heterobicyclic arginine side chain mimetics **13**–**17**, **19** and **20**. These compounds are interesting building blocks for incorporation into various serine protease inhibitors.

4. Experimental

4.1. General

Chemicals were purchased from Aldrich Chemical Co. and Fluka and used without further purification. THF was kept over sodium and distilled immediately prior to use. Analytical TLC was performed on Merck silica gel (60 F 254) plates (0.25 mm). Visualization was effected with ultraviolet light or any of the following reagents: ninhydrin and 2,4-dinitrophenylhydrazine. Column chromatography was carried out on Florisil® (particle size 100–200 mesh) and silica gel 60 (particle size 240–400 mesh). Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE DPX$_{300}$ spectrometer in $CDCl_3$ or DMSO solution with TMS as the internal standard. IR spectra were obtained on a Perkin–Elmer 1600 FT-IR spectrometer. Microanalyses were performed on a Perkin–Elmer C, H, N analyzer 240 C. Elemental analyses for C, H, N were within ±0.4% of the calculated values. Mass spectra were obtained using a VG-Analytical Autospec Q mass spectrometer.

4.1.1. 1,4-Dioxaspiro[4.5]decane-8-carbonitrile (2). To a cooled (−10°C) suspension of 1,4-cyclohexanedione monoethylene acetal (**1**) (15.0 g, 0.096 mol) and tosylmethylisocyanide (24.5 g, 0.125 mol) in DME (300 mL) containing abs. EtOH (10 mL) was added *t*-BuOK (25.0 g, 0.221 mol) portionwise over the course of 0.5 h so that the temperature was maintained at <5°C. After the addition was completed, the reaction was stirred for 1 h at 0°C and then for 2 h at rt. The mixture was concentrated to an orange-brown solid; water (100 mL) was added to the residue and extracted with Et_2O (5×70 mL). The combined extracts were washed with brine (3×50 mL) and dried (Na_2SO_4). Concentration under reduced pressure gave a yellow oil which was purified by distillation through a 10 cm Vigreux column to give **2** as a colourless oil: bp 95°C, 0.6 Torr; lit: 94–95°C, 1 Torr;[16] yield: 11.5 g (72%). IR (KBr): ν 3534, 2954, 2885, 2239, 1693, 1625, 1448, 1373, 1336, 1231, 1103, 1033, 936 cm^{-1}. MS (FAB): *m/z* (%) 168 (MH^+, 92), 154 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.57–1.67 (m, 2H, 7-H, 9-H), 1.79–1.90 (m, 2H, 7-H, 9-H), 1.90–2.04 (m, 4H, 6-H, 10-H), 2.61–2.70 (m, 1H, 8-H), 3.95 (s, 4H, 2-H, 3-H).

4.1.2. 1,4-Dioxaspiro[4.5]dec-8-ylmethanamine (3). To an ice-bath-cooled 1 M solution of $LiAlH_4$ in THF (141 mL, 0.141 mol), nitrile **2** (15.7 g, 0.094 mol) was added dropwise over 1 h. After the addition was complete, the solution was heated to reflux for 2 h and then stirred at rt for 12 h. The reaction mixture was quenched by careful sequential addition of H_2O (5.6 mL), 15% NaOH (5.6 mL), and H_2O (15.7 mL). The initial H_2O portion was diluted with THF to aid addition and moderate the quench. The resulting precipitate was collected by filtration. Concentration under reduced pressure and distillation of the resulting oil gave **3** as colourless oil: bp 72°C, 0.3 Torr; lit: 110–111°C, 3 Torr;[16] yield: 12.3 g (77%). IR (KBr): ν 3364, 2934, 1669, 1558, 1448, 1375, 1338, 1104, 1034, 929 cm^{-1}. MS (FAB): *m/z* (%) 172 (MH^+, 100). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.04 (br s, 2H, NH_2), 1.14–1.40 (m, 3H, 7-H, 8-H, 9-H), 1.46–1.59 (m, 2H, 7-H, 9-H), 1.71–1.80 (m, 4H, 6-H, 10-H), 2.55 (d, 2H, *J*=6.02 Hz, CH_2), 3.92 (s, 4H, 2-H, 3-H).

4.1.3. *N*-(1,4-Dioxaspiro[4.5]dec-8-ylmethyl)acetamide (4). A solution of 1,4-dioxaspiro[4.5]dec-8-ylmethylamine (**3**) (12.3 g, 0.072 mol) in an excess of acetic anhydride (70 mL) was stirred at rt for 1 h. The excess acetic anhydride was removed under reduced pressure. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×40 mL). The organic extracts were washed with brine (3×40 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give **4** as yellow oil; yield: 12.3 g (80%). IR (KBr): ν 3297, 3094, 2937, 2884, 1734, 1651, 1556, 1446, 1230, 1155, 1099, 1034, 915 cm^{-1}. MS (FAB): *m/z* (%) 214 (MH^+, 100). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.18–1.33 (m, 2H, 7-H, 9-H), 1.44–1.57 (m, 3H, 7-H, 8-H, 9-H), 1.68–1.78 (m, 4H, 6-H, 10-H), 1.97 (s, 3H, $COCH_3$), 3.12 (t, 2H, *J*=6.36 Hz, CH_2), 3.96 (s, 4H, 2-H,

3-H), 5.68 (br s, 1H, NH). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.92; N, 6.57. Found: C, 61.78; H, 8.87; N, 6.39.

4.1.4. *N*-[(4-Oxocyclohexyl)methyl]acetamide (5). A solution of *N*-(1,4-dioxaspiro[4.5]dec-8-ylmethyl)acetamide (**4**) (12.3 g, 0.058 mol) in 90% formic acid (120 mL) was stirred at rt for 16 h. The excess formic acid was removed under reduced pressure. Water (30 mL) and aq. $NaHCO_3$ (40 mL) were added, and the mixture was extracted with CH_2Cl_2 (5×30 mL). The organic extracts were washed with aq. NaCl (3×30 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give **5** as a white solid; yield: 7.5 g (77%); mp 51–54°C. IR (KBr): ν 3276, 3092, 2940, 1715, 1654, 1560, 1437, 1368, 1298, 1167, 1118, 998, 784, 610, 497 cm^{-1}. MS (EI): *m/z* (%) 169 (M^+, 45), 110 (100). ^1H NMR (300 MHz, $CDCl_3$): δ=1.35–1.51 (m, 2H, 2-H, 6-H), 2.01 (s, 3H, $COCH_3$), 2.02–2.11 (m, 3H, 1-H, 2-H, 6-H), 2.26–2.48 (m, 4H, 3-H, 5-H), 3.21 (t, 2H, *J*=6.41 Hz, 7-CH_2), 5.77 (br s, 1H, NH). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.91; H, 8.88; N, 8.28. Found: C, 63.85; H, 8.71; N, 8.02.

4.1.5. (±)-*N*-({3-[(Dimethylamino)methylidene]-4-oxocyclohexyl}methyl)acetamide (6). A solution of *N*-[(4-oxocyclohexyl)methyl]acetamide (**5**) (5.0 g, 0.03 mol), DMFDMA (35 mL, 0.26 mol), and Et_3N (0.6 mL) in toluene (160 mL) was distilled over a period of 2 h to about one-half the original volume. Toluene (80 mL) was then added to the residue, and the mixture was maintained just below the boiling point for 2 h. Distillation was continued to a volume one-half of the original during 1.5 h. Toluene (80 mL) was again added, and the process was repeated a third and fourth time. Volatiles were distilled, and the product was purified by column chromatography on 120 g of Florisil® using CH_2Cl_2/MeOH (95:5) as eluant to yield **6** as a yellow oil; yield: 4.5 g (66%). IR (KBr): ν 3278, 2929, 1637, 1540, 1420, 1333, 1202, 1128, 1010 cm^{-1}. MS (EI): *m/z* (%) 224 (M^+, 55), 152 (100). ^1H NMR (300 MHz, $CDCl_3$): δ=1.38–1.50 (m, 1H, 1-H), 1.73–1.83, 1.84–1.93 (2×m, 2H, 6-H), 2.01 (s, 3H, $COCH_3$), 2.01–2.35, 2.37–2.43, 2.45–2.49, 2.82–2.86, 2.87–2.91 (5×m, 4H, 2-H, 5-H), 3.09 (s, 6H, $N(CH_3)_2$), 3.11–3.20, 2.33–3.33 (2×m, 2H, 7-H), 5.85 (br s, 1H, NHCO), 7.49 (m, 1H, CH–methylidene). Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.29; H, 8.93; N, 12.50. Found: C, 63.95; H, 8.89; N, 12.39.

4.1.6. (±)-*N*-[(3-Bromo-4-oxocyclohexyl)methyl]acetamide (7). A freshly prepared solution of Br_2 (0.876 g, 5.5 mmol) in CH_2Cl_2 (19.0 mL) was added dropwise over a 1 h period, to a stirred solution of *N*-[(4-oxocyclohexyl)-methyl]acetamide (**5**) (0.930 g, 5.5 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was then refluxed for 1 h, the solvent was removed under reduced pressure to obtain a brown foam, which was used further without purification.

4.1.7. (±)-*N*-[(2-Amino-5,6,7,8-tetrahydro-6-quinazolinyl)-methyl]acetamide (8). To a solution of sodium ethoxide (0.1 g, 4.46 mmol) in abs. EtOH (20 mL), guanidine hydrochloride (0.43 g, 4.46 mmol) was added. After stirring for 0.5 h, a solution of *N*-({3-[(dimethylamino)methylidene]-4-oxocyclohexyl}methyl) acetamide (**6**) (1.0 g, 4.46 mmol) in abs. EtOH was added and the reaction mixture was refluxed under argon for 3 h. The separated solid was collected by filtration to give **8** as a white solid; yield: 0.75 g (76%); mp 205–208°C. IR (KBr): ν 3304, 3084, 2944, 2859, 1674, 1649, 1602, 1560, 1493, 1421, 1376, 1265, 1211, 1096, 960, 786 cm^{-1}. MS (EI): *m/z* (%) 220 (M^+, 34), 148 (100). ^1H NMR (300 MHz, $CDCl_3$): δ=1.41–1.55 (m, 1H, 6-H), 1.88–2.03 (m, 2H, 7-H), 2.04 (s, 3H, $COCH_3$), 2.26–2.34, 2.66–2.78 (2×m, 4H, 5-H, 8-H), 3.31 (t, 2H, *J*=6.78 Hz, CH_2), 4.83 (s, 2H, 2-NH_2), 5.60 (br s, 1H, NHCO), 8.02 (s, 1H, 4-H). Anal. Calcd for $C_{11}H_{16}N_4O$: C, 60.00; H, 7.27; N, 25.45. Found: C, 59.76; H, 7.06; N, 25.21.

4.1.8. (±)-*N*-(4,5,6,7-Tetrahydro-2*H*-indazol-5-ylmethyl)-acetamide (9). A solution of the enamino ketone **6** (1.0 g, 4.46 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.25 mL, 5.0 mmol) in MeOH (20 mL) was stirred at rt for 16 h. The solvent was evaporated and the product was purified by column chromatography on Florisil® using EtOAc/MeOH (2:1) as eluant to yield **9** as a white solid; yield: 0.56 g (65%); mp 129–132°C. IR (KBr): ν 3261, 2928, 1652, 1558, 1437, 1368, 1293, 1088, 1035, 962, 782, 605 cm^{-1}. MS (EI): *m/z* (%) 193 (M^+, 36), 121 (100). ^1H NMR (300 MHz, $CDCl_3$): δ=1.49–1.60 (m, 1H, 5-H), 1.89–1.95 (m, 2H, 6-H), 2.02 (s, 3H, $COCH_3$), 2.18–2.28, 2.58–2.89 (2×m, 4H, 4-H, 7-H), 3.22–3.40 (m, 2H, CH_2), 5.61 (br s, 1H, NHCO), 7.31 (s, 1H, 3-H), 10.0–14.0 (very broad s, 1H, NH). Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.18; H, 7.77; N, 21.76. Found: C, 61.88; H, 7.85; N, 21.44.

4.1.9. (±)-*N*-[(2-Methyl-4,5,6,7-tetrahydro-2*H*-indazol-5-yl)methyl]acetamide (10). A solution of the enamino ketone **6** (0.80 g, 3.57 mmol) and *N*-methylhydrazine (0.19 mL, 3.57 mmol) in MeOH (15 mL) was stirred at rt for 16 h. The solvent was evaporated, and the product was purified by column chromatography on Florisil® using CH_2Cl_2/MeOH (2:1) as eluant to yield **10** as a yellow solid; yield: 0.38 g (51%); mp 121–124°C. IR (KBr): ν 3323, 1641, 1540, 1476, 1378, 1279, 1181, 1014, 787 cm^{-1}. MS (EI): *m/z* (%) 207 (M^+, 56), 35 (100). ^1H NMR (300 MHz, $CDCl_3$): δ=1.42–1.55 (m, 1H, 5-H), 1.84–1.96 (m, 2H, 6-H), 1.99 (s, 3H, $COCH_3$), 2.13–2.24, 2.55–2.86 (2×m, 4H, 4-H, 7-H), 3.28 (t, 2H, *J*=6.4 Hz, CH_2), 3.81 (s, 3H, 2-CH_3), 5.77 (br s, 1H, NH), 7.03 (s, 1H, 3-H). Anal. Calcd for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.61; H, 8.45; N, 20.45.

4.1.10. (±)-*N*-[(2-Acetyl-4,5,6,7-tetrahydro-2*H*-isoindol-5-yl)methyl]acetamide (11). The compound was prepared in analogy to procedure described in Ref. 18. To a solution of glycine (0.74 g, 9.91 mmol), and KOH (0.56 g, 9.91 mmol) in abs. EtOH (33 mL) was added enamino ketone **6** (2.0 g, 9.91 mmol). The resulting mixture was heated under reflux for 2 h and then diluted with ether. The potassium salt was filtered off and treated with Ac_2O (33 mL). The solution was then refluxed for 1 h and the excess Ac_2O removed under reduced pressure. The residue was purified by column chromatography (Kieselgel 60, 0.40–0.063 mm, CH_2Cl_2/MeOH (9:1)) to obtain **11** as a yellow solid; yield: 0.41 g (18%); mp 90–93°C. IR (KBr): ν 3304, 2926, 1726, 1645, 1547, 1406, 1327, 1216, 1068, 940, 784, 621 cm^{-1}. MS (FAB): *m/z* (%) 235 (MH^+, 100). ^1H NMR (300 MHz, $CDCl_3$): δ=1.35–1.47 (m, 1H, 5-H), 1.82–1.96 (m, 2H, 6-H), 2.03 (s, 3H, $COCH_3$) 2.15–2.27, 2.50–2.58, 2.67–2.79 (3×m, 4H, 4-H, 7-H), 2.47 (s, 3H, 2-$COCH_3$), 3.21–3.38

(m, 2H, CH_2), 5.56 (br s, 1H, NHCO), 6.99 (br s, 2H, 1-H, 3-H). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.82; H, 7.60; N, 12.22.

4.1.11. (±)-*N*-[(5,6,7,8-tetrahydro-6-quinazolinyl)methyl]-acetamide (12). To a solution of sodium ethoxide (40 g, 1.74 mmol) in abs. EtOH (20 mL), formamidine hydrochloride (0.14 g, 1.74 mmol) was added. After stirring for 0.5 h, a solution of enamino ketone **6** (0.3 g, 1.34 mmol) in abs. EtOH was added and the reaction mixture was refluxed under argon for 4 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Kieselgel 60, 0.40–0.063 mm, CH_2Cl_2/MeOH (9:1)) to obtain **12** as a white solid; yield: 0.23 g (83%); mp 105–108°C. IR (KBr): ν 3283, 2920, 1693, 1558, 1458, 1401, 1306, 1046 cm^{-1}. MS (FAB): *m/z* (%) 206 (MH^+, 100). ^1H NMR (300 MHz, $CDCl_3$): δ=1.50–1.64 (m, 1H, 6-H), 1.97–2.14 (m, 2H, 7-H), 2.05 (s, 3H, $COCH_3$), 2.42–2.54, 2.82–3.07 (2×m, 4H, 5-H, 8-H), 3.34 (t, 2H, J=6.78 Hz, CH_2), 5.70 (br s, 1H, NHCO), 8.42 (s, 1H, 4-H), 8.95 (s, 1H, 2-H). Anal. Calcd for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.03; H, 7.22; N, 20.15.

4.1.12. (±)-6-(Aminomethyl)-5,6,7,8-tetrahydro-2-quinazolinamine (13). A solution of *N*-[(2-amino-5,6,7,8-tetrahydro-6-quinazolinyl)methyl]acetamide (**8**) (0.7 g, 3.18 mmol) and NaOH (15 g, 0.38 mol) in a mixture of H_2O (20 mL) and MeOH (30 mL) was refluxed for 16 h. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×20 mL). The organic extracts were washed with brine (3×20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give **13** as a white solid; yield: 0.34 g (60%); mp 152–155°C. IR(KBr): ν 3315, 3142, 2927, 2855, 1648, 1590, 1557, 1473, 1424, 1197, 964, 861, 808, 593, 501 cm^{-1}. MS (EI): *m/z* (%) 178 (M^+, 40), 161 (100). ^1H NMR (300 MHz, $CDCl_3$): δ=1.12–1.43 (br s, 2H, NH_2), 1.40–1.55 (m, 1H, 6-H), 1.68–1.82 (m, 1H, 7-H), 2.00–2.10 (m, 1H, 7-H), 2.22–2.33, 2.69–2.81 (2×m, 6H, 5-H, 8-H, CH_2), 4.85 (s, 2H, 2-NH_2), 8.03 (s, 1H, 4-H). Anal. Calcd for $C_9H_{14}N_4$: C, 60.67; H, 7.87; N, 31.46. Found: C, 60.35; H, 7.81; N, 31.25.

4.1.13. (±)-4,5,6,7-Tetrahydro-2*H*-indazol-5-ylmethanamine dihydrochloride (14). A solution of the amide **9** (0.43 g, 2.23 mmol) in 6 M HCl (25 mL) was heated under reflux for 6 h. It was then concentrated, and the product was crystallized from EtOH (10 mL) to yield **14** as a crystalline solid; yield: 0.48 g (96%); mp 289–292°C. IR (KBr): ν 3408, 2945, 1975, 1611, 1532, 1472, 1290, 1232, 858, 757, 644 cm^{-1}. MS (FAB): *m/z* (%) 152 (MH^+, 100). ^1H NMR (300 MHz, DMSO-d_6): δ=1.41–1.56 (m, 1H, 5-H), 1.97–2.08 (m, 2H, 6-H), 2.19–2.30, 2.57–2.79, (2×m, 4H, 4-H, 7-H), 2.80–2.87 (m, 2H, CH_2), 4.39 (br s, NH_3^++H_2O), 7.78 (d, 1H, J=2.64 Hz, 3-H), 8.23 (m, 1H, NH_2^+-exchange). Anal. Calcd for $C_8H_{15}Cl_2N_3$: C, 42.86; H, 6.70; N, 18.75. Found: C, 42.61; H, 6.68; N, 18.62.

4.1.14. (±)-2-Methyl-4,5,6,7-tetrahydro-2*H*-indazol-5-yl)methanamine hydrochloride (15). A solution of the amide **11** (0.25 g, 1.21 mmol) in 6 M HCl (18 mL) was heated under reflux for 6 h. It was then concentrated, and the product was crystallized from EtOH (10 mL) to yield **15** as a crystalline solid; yield: 0.20 g (82%); mp 195–197°C. IR (KBr): ν 3434, 2900, 1627, 1515, 1460, 1400, 1179, 1073, 1021, 923, 856, 807 cm^{-1}. MS (EI): *m/z* (%) 166 (M^+, 75), 148 (100). ^1H NMR (300 MHz, DMSO-d_6): δ=1.35–1.48 (m, 1H, 5-H), 1.89–2.03 (m, 2H, 6-H), 2.13–2.22, 2.56–2.63 (2×m, 4H, 4-H, 7-H), 2.75–2.85 (m, 2H, CH_2), 3.74 (s, 3H, 2-CH_3), 7.40 (s, 1H, 3-H), 8.03 (br s, 3H, NH_3^+). Anal. Calcd for $C_9H_{16}ClN_3$: C, 56.33; H, 8.34; N, 21.90. Found: C, 56.01; H, 8.16; N, 21.69.

4.1.15. (±)-4,5,6,7-Tetrahydro-2*H*-isoindol-5-ylmethanamine (16). A solution of the diamide **11** (42 mg, 0.179 mmol), NaOH (3.0 g), H_2O (3 mL), and MeOH (12 mL) was refluxed for 16 h. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4×20 mL). The organic extracts were washed with brine (3×20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to yield **16** as an orange solid; yield: 20 mg (74%); mp 87–90°C. IR (KBr): ν 3362, 2916, 1629, 1570, 1441, 1204, 1061, 922, 769, 601 cm^{-1}. MS (FAB): *m/z* (%) 151 (MH^+, 100). ^1H NMR (300 MHz, $CDCl_3$): δ=1.36–1.48 (m, 5-H, NH_2+H_2O), 1.69–1.79 (m, 1H, 6-H), 1.92–2.02 (m, 1H, 6-H), 2.18–2.28, 2.53–2.65, 2.70–2.86 (3×m, 6H, 4-H, 7-H, CH_2), 6.51 (s, 1H, CH), 6.52 (s, 1H, CH), 7.95 (m, 1H, NH-exchange). Anal. Calcd for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65. Found: C, 72.05; H, 9.32; N, 18.28.

4.1.16. (±)-6-(Aminomethyl)-5,6,7,8-tetrahydroquinazoline (17). A solution of *N*-[(5,6,7,8-tetrahydro-6-quinazolinyl)methyl]acetamide (**12**) (0.13 g, 0.63 mmol) and NaOH (9 g, 0.225 mol) in a mixture of H_2O (12 mL) and MeOH (18 mL) was refluxed for 16 h. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×20 mL). The organic extracts were washed with brine (3×20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give **17** as a white solid; yield: 84 mg (84%); mp 88–91°C. IR (KBr): ν 3350, 2928, 1580, 1454, 1396, 1324, 1164, 936, 730 cm^{-1}. MS (EI): *m/z* (%) 163 (M^+, 14), 134 (100). ^1H NMR (300 MHz, $CDCl_3$): δ=1.44 (br s, NH_2+H_2O), 1.48–1.61 (m, 1H, 6-H), 1.76–1.89 (m, 1H, 7-H), 2.06–2.17 (m, 1H, 7-H), 2.41–2.51 (dd, 1H, J=10.55 Hz, CH), 2.77 (d, 2H, J=6.78 Hz, CH_2), 2.84–3.06 (m, 3H, CH, CH_2), 8.42 (s, 1H, 4-CH), 8.93 (s, 1H, 2-CH). Anal. Calcd for $C_9H_{13}N_3$: C, 66.23; H, 8.03; N, 25.74. Found: C, 65.92; H, 7.91; N, 25.45.

4.1.17. (±)-*N*-[(2-Amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)methyl]acetamide (18). To a solution of bromo ketone **7** (0.992 g, 4.0 mmol) in abs. EtOH (20 mL) thiourea (0.396 g, 5.2 mmol) was added and the mixture was heated under reflux for 2 h. The solvent was removed under reduced pressure. Water (20 mL) was added to the residue, the solution was made alkaline with 1 M NaOH to pH 12 and the mixture extracted with EtOAc (3×10 mL). The organic extracts were washed with aq. NaCl (3×10 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The product was purified by column chromatography (Kieselgel 60, EtOAc/MeOH (7:1)) to obtain **18** as a slightly yellow solid; yield 0.38 g (52%); mp 187–189°C. IR (KBr): ν 3440, 3314, 3080, 2928, 1618, 1534, 1474, 1365, 1315, 1254, 1096, 707, 598 cm^{-1}. MS (FAB): *m/z* (%) 226 (MH^+, 100). ^1H NMR (300 MHz, DMSO-d_6): δ=1.29–1.43 (m, 1H, 6-H), 1.75–1.90 (m, 2H, 5-H), 1.82 (s, 3H, $COCH_3$), 2.08–2.20, 2.26–

2.44, 2.55–2.61 (3×m, 4H, 4-H, 7-H), 3.04 (t, 2H, J=6.41 Hz, CH_2), 6.57 (s, 2H, 2-NH_2), 7.86 (br t, 1H, NHCO). Anal. Calcd for $C_{10}H_{15}N_3OS$: C, 53.31; H, 6.71; N, 18.65. Found: C, 53.24; H, 6.76; N, 18.73.

4.1.18. (±)-*N*-[(2-{[Amino(imino)methyl]amino}-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)methyl]-acetamide (19). To a solution of bromoketone **7** (0.620 g, 2.5 mmol) in abs. EtOH (15 mL) amidinothiourea (0.385 g, 3.25 mmol) was added and the mixture was heated under reflux for 16 h. The solvent was removed under reduced pressure to give a slightly yellow foam. Water was added to the residue, the solution was made alkaline with 1 M NaOH to pH 12 and the mixture extracted with EtOAc (3×10 mL). The organic extracts were washed with aq. NaCl (3×10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give **19** as a slightly brown solid; yield 0.260 g (39%); mp 247–249°C. IR (KBr): ν 3375, 2919, 1652, 1610, 1540, 1452, 1362, 1265, 1198, 981, 743, 642 cm^{-1}. MS (EI): *m/z* (%) 183 (M^+, 22), 166 (100). ^1H NMR (300 MHz, DMSO-d_6): δ=1.37–1.51 (m, 1H, 6-H), 1.82 (s, 3H, $COCH_3$), 1.83–1.95 (m, 2H, 5-H), 2.24–2.36, 2.50–2.80 (2×m, 4H, 4-H, 7-H), 3.07 (t, 2H, J=6.40 Hz, CH_2), 7.96 (br t, 1H, NHCO), 8.11 (br s, 4H, NHC(NH)NH_2). Anal. Calcd for $C_{11}H_{17}N_5OS$: C, 49.42; H, 6.41; N, 26.20. Found: C, 49.27; H, 6.23; N, 25.98.

4.1.19. (±)-6-(Aminomethyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine dihydrobromide (20). A solution of **18** (100 mg, 0.44 mmol) in 47% aqueous hydrobromic acid (2 mL) was heated under reflux for 16 h. The excess HBr was removed under reduced pressure and acetone was added to the residue. The separated solid was collected by filtration to yield a slightly brown crystalline solid; yield: 0.056 g (70%); mp 326–328°C. IR (KBr): ν 3301, 2850, 1616, 1568, 1489, 1443, 1016, 907, 779, 701 cm^{-1}. MS (FAB): *m/z* (%) 268 (MH^+, 100). ^1H NMR (300 MHz, DMSO-d_6): δ=1.43–1.57 (m, 1H, 6-H), 1.91–2.02 (m, 1H, 5-H), 2.05–2.17 (m, 1H, 5-H), 2.24–2.36, 2.40–2.57, 2.58–2.71 (3×m, 4H, 4-H, 7-H), 2.86 (t, 2H, J=6.41 Hz, CH_2N), 7.91 (br s, 3H, NH_3^+), 9.16 (br s, 3H, NH_3^+). Anal. Calcd for $C_8H_{15}Br_2N_3S$: C, 27.80; H, 4.35; N, 12.17. Found: C, 27.68; H, 4.33; N, 11.93.

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