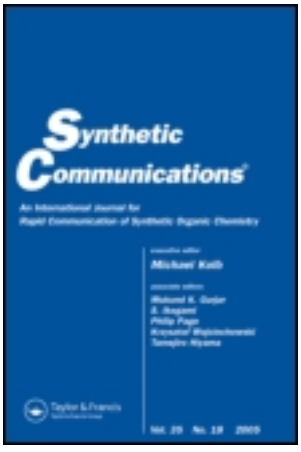

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Ketopiperazines: Conformationally Constrained Peptidomimetic of Arginine Amides

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Abstract: We have synthesized guanidine-containing ketopiperazines designed to be conformational mimics of peptidomimetic arginine amides. *D*-Allylglycine was converted by an efficient approach to give enantiopure ketopiperazines in which the *trans* stereochemistry of the C-substituents resulted from stereospecific enolate alkylation.

Keywords: Arginine, ketopiperazines, peptidomimetics

INTRODUCTION

It has long been recognized that biologically active peptides possess significant potential for drug development.[1] However, major limitations in developing peptide drugs arise from their susceptibility to protease degradation, poor transportability through cell membranes, and their high

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hydrophilicity leading to rapid clearance from plasma.[2,3] We have been involved in research to identify effective peptidomimetics that overcome these drawbacks yet maintain their conformational properties, which may lead to therapeutic utility.

One such approach has been to test the hypothesis that an arginine peptide conformation **A** can be maintained by constraining the amide groups within a piperazine ring, as shown in **B** (Figure 1).

To help design these mimics, a conformational analysis was performed on the arginine scaffold using a Monte Carlo approach with the Merck Molecular Force Field (MMFF) force field implemented in Spartan.[4] This search generated seven low-energy conformations, which were further treated using *ab initio* quantum mechanical calculations to determine the equilibrium geometry. Target compound **1** was also subjected to a Monte Carlo search in which 25 low-energy conformers were found to exist with strain energies within 10 kcal/mol of the minimum energy. These 25 conformers were entered into a database that was subsequently flexibly superimposed using FlexS[5,6] onto the seven conformers obtained for the arginine scaffold. The result indicates that the proposed scaffold allows three substituents to maintain a spatial orientation similar to that found in the unconstrained arginine scaffold. On this basis we initiated our synthetic efforts toward such a peptidomimetic scaffold of arginine.

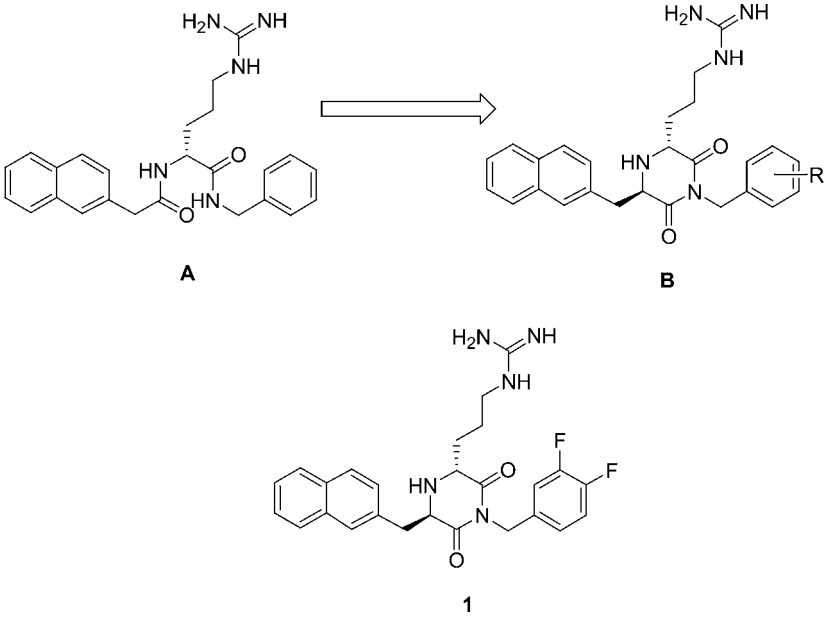
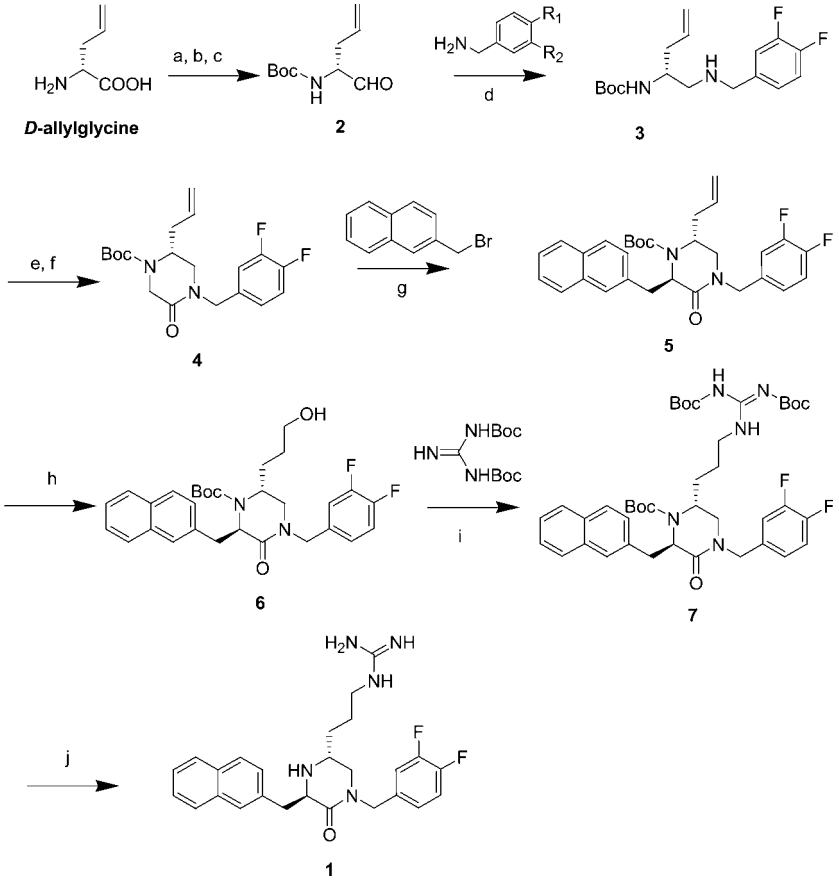


Figure 1. Ketopiperazine—a constrained argine mimic.

RESULT AND DISCUSSION

Our synthesis of ketopiperazines is outlined in Scheme 1. Commercially available *D*-allylglycine was protected as an *N*-Boc derivative, which was subsequently converted to the corresponding aldehyde **2** by $LiAlH_4$ reduction of the Weinreb amide.[7] Following the procedure of Dinsmore et al.,[8] the aldehyde **2** was reductively aminated with 3,4-difluorobenzylamine to give secondary amines **3** in excellent yield. Key intermediate ketopiperazine ring compound **4** was produced by chloroacetylation, followed by base-mediated



Scheme 1. Reagents and conditions: (a) Boc_2O, Et_3N, MeOH, rt, 79%; (b) $ClCO_2CH_3$, NMM, MeNH(OMe), CH_2Cl_2-THF; (c) $LiAlH_4$, Et_2O, -45 to $-5^{\circ}C$, 2 h, 65% for two steps; (d) $NaBH(OAc)_3$, 4Å MS, $ClCH_2CH_2Cl$, rt, 24 h, 90%; (e) $ClCH_2COCl$, $NaHCO_3$, EtOAc-H_2O, 0°C, 30 min; (f) Cs_2CO_3, DMF, 65°C, 2 h, 93%; (g) LiHMDS, THF, $-78^{\circ}C$, 2 h, 69%; (h) 9-BBN, THF, rt, 3 h, then H_2O_2/NaOH, 78%; (i) PPh_3, DIAD, THF, rt, 2 h, 90%; (j) CF_3COOH, CH_2Cl_2, 100%.

cyclization in high yield.[8] In the chloroacetylation step, it was essential to completely remove excess chloroacetyl chloride by repeated washes of the reaction mixture with aqueous $NaHCO_3$ to avoid by-product formation in the cyclization step. Alkylation of compound **4** with 2-(bromomethyl)-naphthalene using LiHMDS at $-78^{\circ}C$ gave the disubstituted products **5** with high *trans* diastereoselectivity.[8]

To introduce elements of the guanidine side chain, hydroboration–oxidation of the allyl terminus in **5** afforded alcohol **6** in good yield.[9] Mitsunobu reaction of **6** with *N*,*N*′-Bis-Boc-guanidine provided the corresponding guanidine **7** in high yield.[10] Treatment of **7** with TFA resulted in Boc deprotection in quantitative yield. Thus, the synthesis of target compound **1** was achieved in 23% overall yield from *D*-allylglycine.

In conclusion, a ketopiperazine scaffold for arginine peptidomimetics was designed based on computer modeling using conformation analysis and synthesized starting from optically active allylglycine in an efficient manner. The synthetic approach we have established should have potential for the generation of analogs with substituent variations around the ketopiperazine ring, which are useful in pharmaceutical research.

EXPERIMENTAL

All melting points are uncorrected. ^1H NMR spectra were determined in the solvent indicated at 400 MHz. Mass spectra were recorded by using APCI or API-ES mode. Flash chromatography was performed with 40–63-μm silica gel.

{1-[(3,4-Difluorobenzylamino)-methyl]-but-3-enyl}-carbamic Acid *tert*-Butyl Ester (3)

To a solution of aldehyde **2** (342 mg, 1.72 mmol, prepared by the reported procedure[7]) and 3,4-difluorobenzylamine (224 mg, 1.89 mmol) in 4 mL of 1,2-dichloroethane at 0°C was added 4A molecular sieves (0.45 g), followed by addition of sodium triacetoxyborohydride (537 mg, 2.41 mmol). The reaction mixture was then stirred at room temperature for 14 h. The mixture was diluted with EtOAc and washed with aqueous sodium bicarbonate solution and brine, and then dried over $MgSO_4$. The solvent was removed under the reduced pressure, and the residue was purified by flash chromatography to give the pure product **3** as colorless oil (505 mg, 90%).

MS (API-ES, positive): m/z 327.2 [M + H]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20–7.15 (m, 1H), 7.11–7.03 (m, 2H), 5.81–5.71 (m, 1H), 5.10 (d, $J = 18.7$ Hz, 1H), 5.08 (d, $J = 9.9$ Hz, 1H), 4.64 (br, 1H), 3.78, 3.72 (AB, $J = 13.5$ Hz, 2H), 3.80–3.71 (m, 1H), 2.70–2.61 (m, 2H), 2.28–2.23 (m, 2H), 1.45 (s, 9H).

2-Allyl-4-(3,4-difluorobenzyl)-5-oxo-piperazine-1-carboxylic Acid *tert*-Butyl Ester (4)

Chloroacetylchloride (80 mg, 1.0 mmol) and saturated aqueous sodium bicarbonate solution (1 mL) were added to a solution of **3** (163 mg, 0.5 mmol) in EtOAc (1 mL) at 0°C. The resulting mixture was stirred at this temperature for 20 min and diluted with EtOAc (20 mL). The organic layer was washed with water and aqueous sodium bicarbonate, and then dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was dried in vacuum to give colorless oil (202 mg, 100%), which is directly used in the next step without further purification.

Cs_2CO_3 (326 mg, 1.0 mmol) was added to this intermediate solution in dry DMF (2 mL). The resulting mixture was gently heated to 65°C and stirred at this temperature for 2 h. The mixture was cooled to room temperature and diluted with a mixed solvent EtOAc–hexanes (90 : 10). The mixture was washed with water and brine, and then dried over Na_2SO_4. The solvent was removed in vacuum, and the residue was purified by flash chromatography to give compound **4** as colorless oil (170 mg, 93%).

MS (API-ES, positive): m/z 389.2 [M + Na]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–7.10 (m, 2H), 7.04–7.01 (m, 1H), 5.65–5.56 (m, 1H), 5.01 (d, $J = 10.1$ Hz, 1H), 4.87 (d, $J = 16.9$ Hz, 1H), 4.75 (d, $J = 14.5$ Hz, 1H), 4.41–4.31 (m, 3H), 3.82 (d, $J = 18.8$ Hz, 1H), 3.50 (dd, $J = 4.5$ Hz, 12.3 Hz, 1H), 3.07 (d, $J = 12.2$ Hz, 1H), 2.33–2.26 (m, 1H), 2.16–2.05 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 28.6 (3C), 34.8, 45.2, 48.3, 49.6 (2C), 81.2, 117.8, 118.0, 118.8, 124.9, 125.0, 133.8, 148.8, 152.3, 154.0, 166.0. HRMS: calcd. for $C_{15}H_{17}F_2N_2O_3$ [M + H-^{t}Bu] m/z 311.1207; found 311.1216.

6-Allyl-4-(3,4-difluorobenzyl)-2-naphthalen-2-ylmethyl-3-oxo-piperazine-1-carboxylic Acid *tert*-Butyl Ester (5)

Lithium bis(trimethylsilyl)amide (1M in THF, 0.51 mL, 0.51 mmol) was added dropwise to a solution of **4** (170 mg, 0.46 mmol) in THF (1 mL) at −78°C. The mixture was stirred under argon at −78°C for 20 min, and then a solution of 2-(bromomethyl)-naphthalene (122 mg, 0.55 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at −78°C for 2 h and then quenched by addition of saturated ammonium chloride aqueous solution (2 mL). The mixture was allowed to warm to room temperature and partitioned with EtOAc and saturated aqueous sodium bicarbonate solution. The organic layer was separated and washed with brine, and then dried over $MgSO_4$. The solvent was removed in vacuum, and the residue was purified by flash chromatography to give the pure compound **5** as white solid (161 mg, 69%).

Mp: 112–113°C. MS (API-ES, positive): m/z 507.2 [M + H]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.80 (m, 1H), 7.73–7.68 (m, 2H), 7.51–7.47

(m, 3H), 7.18 (d, $J = 8.0$ Hz, 1H), 7.04–6.98 (m, 2H), 6.84 (br, 1H), 5.37–5.32 (m, 1H), 4.87 (d, $J = 10.1$ Hz, 1H), 4.69 (dd, $J = 3.0$ Hz, 5.5 Hz, 1H), 4.59 (d, $J = 16.9$ Hz, 1H), 4.48 (br, 1H), 4.17–4.10 (m, 1H), 3.81–3.57 (m, 2H), 3.31 (dd, $J = 3.0$ Hz, 13.6 Hz, 1H), 2.58–2.48 (m, 1H), 2.32–2.19 (m, 1H), 1.92–1.84 (m, 2H), 1.59 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 28.8 (3C), 35.8, 39.9, 45.1, 49.9, 50.8, 59.2, 81.4, 117.5, 117.8, 118.3, 118.5, 125.5, 126.1, 126.5, 127.9, 128.0, 128.7, 129.0, 132.7, 133.4, 133.5, 133.6, 134.2, 148.8, 152.1, 154.1, 169.0. HRMS: calcd. for $C_{30}H_{33}F_2N_2O_3$ [M + H] m/z 507.2459; found 507.2477.

4-(3,4-Difluorobenzyl)-6-(3-hydroxy-propyl)-2-naphthalen-2-ylmethyl-3-oxo-piperazine-1-carboxylic Acid *tert*-Butyl Ester (6)

A solution of compound **5** (320 mg, 0.64 mmol) in THF (4 mL) was added dropwise to a 9-BBN solution (0.5M in THF, 1.5 mL, 0.77 mmol) at 0°C. The mixture was stirred at room temperature for 3 h and then cooled to 0°C again. An aqueous solution of 3M NaOH (4.8 mL) was added, followed by dropwise addition a solution of H_2O_2 (30%, 4.8 mL). The resulting mixture was stirred at room temperature overnight. The mixture was extracted with EtOAc. The combined extacts were washed with water and brine, and then dried over MgSO4. The solvent was removed in vacuum, and the residue was purified by flash chromatography to give the pure compound **6** as white foam (261 mg, 78%).

Mp: 135–137°C. MS (API-ES, positive): m/z 525.2 [M + H]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.81 (m, 1H), 7.75–7.70 (m, 2H), 7.52–7.47 (m, 3H), 7.18 (dd, $J = 1.3$ Hz, 8.3 Hz, 1H), 7.04–6.98 (m, 2H), 6.83 (br, 1H), 4.75 (d, $J = 13.7$ Hz, 1H), 4.66 (dd, $J = 3.2$ Hz, 5.5 Hz, 1H), 3.86 (d, $J = 14.3$ Hz, 1H), 3.88–3.57 (m, 2H), 3.43 (br, 2H), 3.30 (dd, $J = 3.0$ Hz, 13.6 Hz, 1H), 2.51–2.47 (m, H), 1.94–1.86 (m, 1H), 1.57 (s, 9H), 1.52–1.48 (m, 2H), 1.07–0.93 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 26.6, 28.0, 28.8 (3C), 38.7, 45.1, 49.7, 50.3, 59.2, 62.1, 81.6, 117.6, 117.8, 118.2, 118.4, 125.4, 126.1, 126.5, 127.9, 128.0, 128.6, 129.0, 132.8, 133.6, 134.5, 149.0, 152.1, 154.5, 169.0. HRMS: calcd. for $C_{30}H_{35}F_2N_2O_4$ [M + H] m/z 525.2565; found 525.2587.

Mitsunobu Reaction of Compound 6 with N,N′-Bis-Boc-guanidine

Triphenylphosphine (173 mg, 0.66 mmol) and 1,3-bis(*tert*-butoxycarbonyl)-guanidine (257 mg, 0.99 mmol) were added to a solution of compound **6** (173 mg, 0.33 mmol) in THF (4 mL) at 0°C, followed by dropwise addition of diisopropyl azodicarboxylate (133 mg, 0.66 mmol). The resulting mixture was stirred at room temperature for 2 h. Then the mixture was diluted with EtOAc, washed with water and brine, and then dried over $MgSO_4$. The

solvent was removed in vacuum, and the residue was purified by flash chromatography to give the pure compound **7** as white foam (227 mg, 90%).

Mp: 102–103°C. MS (API-ES, positive): m/z 766.4 [M + H]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (br, 1H), 9.12 (br, 1H), 7.81–7.79 (m, 1H), 7.73–7.69 (m, 2H), 7.53–7.46 (m, 3H), 7.20 (d, $J = 8.2$ Hz, 1H), 7.15–7.05 (m, 1H), 6.98 (dd, $J = 6.0$ Hz, 16.0 Hz, 1H), 6.87 (br, 1H), 4.65 (dd, $J = 3.2$ Hz, 5.6 Hz, 1H), 4.67–4.64 (m, 1H), 4.00–3.51 (m, 5H), 3.31 (dd, $J = 3.0$ Hz, 13.5 Hz, 1H), 3.05–2.80 (m, 1H), 2.09–1.95 (m, 1H), 1.60–1.10 (m, 4H), 1.57 (s, 9H), 1.48 (s, 9H), 1.30 (s, 9H). HRMS: calcd. for $C_{41}H_{54}F_2N_5O_7$ [M + H] m/z 766.3991; found 766.3961.

N-{3-(3,4-Difluorobenzyl)-6-naphthalen-2-ylmethyl-5-oxo-piperazin-2-yl]-propyl}-guanidine (1)

Trifluoroacetic acid (1 mL) was added dropwise to a solution of compound **7** (50 mg, 0.065 mmol) in CH_2Cl_2 (1 mL) at 0°C. The mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure, and the residue was treated with dried toluene. Removal of solvent provided compound **1** as white foam (TFA salt: 45 mg, 100%).

Mp: 185–186 °C. MS (API-ES, positive): m/z 466.2 [M + H]; ^{1}H NMR (400 MHz, CD_3OD): δ 7.86–7.80 (m, 4H), 7.50–7.46 (m, 3H), 7.26–7.19 (m, 2H), 7.11 (br, 1H), 4.70, 4.54 (AB, $J = 14.7$ Hz, 2H), 4.06 (br, 1H), 3.40 (d, $J = 5.4$ Hz, 2H), 3.29 (d, $J = 10.7$ Hz, 1H), 3.14 (d, $J = 12.2$ Hz, 1H), 3.16–3.07 (m, 3H), 1.57–1.26 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 27.7, 29.8, 39.4, 43.8, 50.8, 51.6, 53.5, 59.6, 120.6, 120.9, 121.0, 121.3, 127.9, 130.0, 130.5, 131.1, 131.2, 132.4, 132.6, 135.8, 136.3, 137.0, 152.0, 155.5, 160.7, 168.0. HRMS: $C_{26}H_{30}F_2N_5O$ [M + H] m/z 466.2418; found 466.2423.

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