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A novel facile solid-phase strategy for the synthesis of *N*,*N*′,*N*″-substituted guanidines

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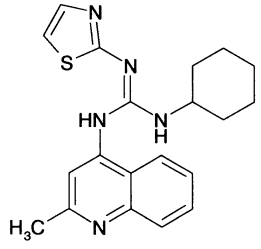
Abstract—A new facile solid-phase synthesis of *N*,*N*′,*N*″-substituted guanidines from an immobilised amine component is described. The resin-bound amine was reacted with di-(2-pyridyl)thionocarbonate to generate the isothiocyanate which was treated with aryl/alkyl amines to yield the corresponding resin-bound thiourea. Desulfurisation of the thiourea was readily achieved by treatment with triphenylphosphine dichloride, and further reaction with aryl/alkyl amines followed by acidic cleavage with trifluoroacetic acid yielded *N*,*N*′,*N*″-substituted guanidines of excellent purity and in good yield.

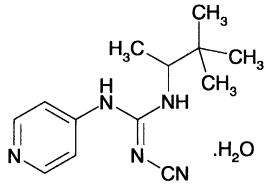
1. Introduction

Medicinal chemistry over the last decade has continued to adopt the ideology of solid supported synthesis,[1] and the application of parallel synthesis together with high throughput screening is considered an important tool in accelerating the lead discovery process.

Libraries of compounds can be prepared and screened rapidly, thus enabling structure–activity relationships to be assigned over a very short time period. Parallel synthesis has been adapted to numerous classes of compounds;[2] guanidines are an example of such a class. The guanidine moiety continues to invoke the curiosity of medicinal chemists, timegadine (**1**)[3] which has analgesic properties and pinacidil (**2**)[4] a successful antihypertensive being examples that stimulate the continued interest (Fig. 1).



Timegadine (**1**)



Pinacidil (**2**)

Figure 1.

The preparation of substituted guanidines on solid support has been described; activated thioureas,[5] azide formation[6] and the use of other highly toxic reagents[7] have been employed. Automated parallel synthesis, which was our aim throughout this study, requires robust chemistry and the employment of relatively non-toxic reagents. We therefore decided to investigate a new, mild and facile strategy for the formation of structurally diverse *N*,*N*′,*N*″-substituted guanidines **3** (Fig. 2). In a previous study we have shown the use of triphenylphosphine dichloride for the desulfurisation of acyl thiosemicarbazides in the formation of 1,3,4-oxadiazoles on solid support.[8]

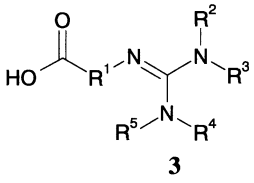


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Figure 2.

Traditional solution-phase literature reports have also suggested the use of triphenylphosphine/carbon tetrachloride for the extrusion of sulfur from thioureas.[9] Herein we report the results of our study of the application of triphenylphosphine dichloride to the removal of sulfur from thioureas, and thence to a new mild solid-phase strategy for the synthesis of *N*,*N*′,*N*″-substituted guanidines.

2. Results and discussion

The strategy developed is outlined in Scheme 1, and the various stages are discussed later. Optimisation of the

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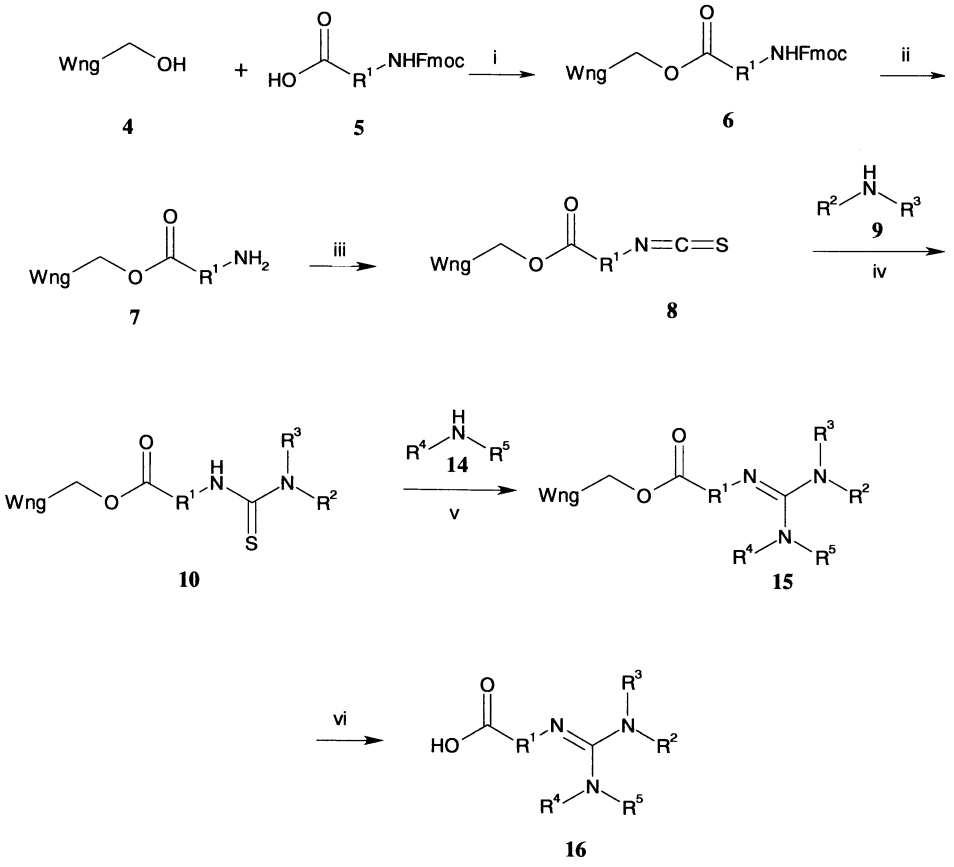
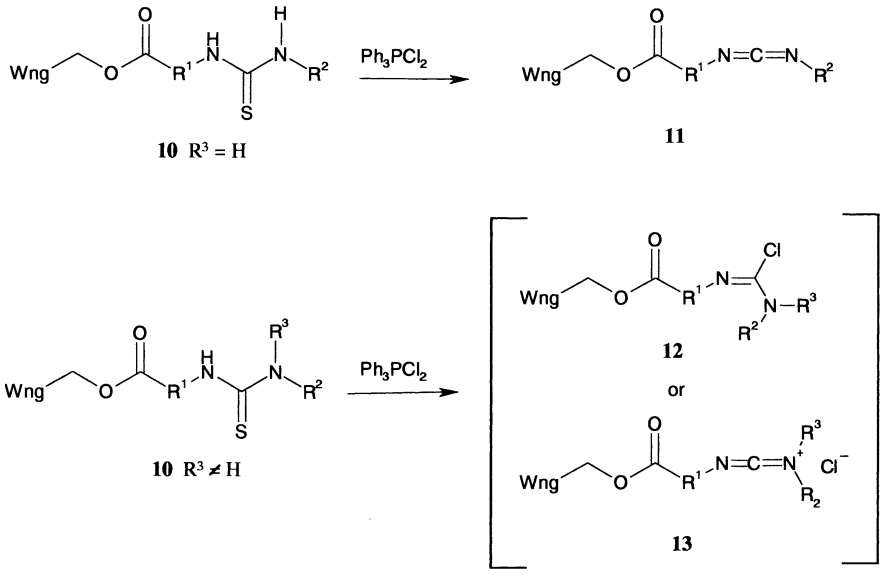


Scheme 1. *Reagents and conditions*: (i) (a) DIC, DMAP, DMF/DCM (1:1 v/v), 20°C, 16 h; (b) 5% Ac_2O, NMP/DIPEA (5:1 v/v), 20°C, 20 min; (ii) piperidine/NMP (1:4 v/v), 20°C, 20 min; (iii) DPT, DCM, 20°C, 3 h; (iv) NMP, 20°C, 16 h; (v) (a) Ph_3P, C_2Cl_6, dry THF, 20°C, 4 h; (b) dry NMP, 20°C, 16 h; (vi) TFA/DCM (1:1 v/v), 20°C, 2 h.

procedure was monitored throughout by cleavage of material from small portions (5–10 mg) of the intermediate resins followed by HPLC, MS and NMR analysis. Commercial Wang resin **4** was first loaded with Fmoc-protected amino acid **5** employing *N*,*N*′-diisopropylcarbodiimide (DIC) in the presence of catalytic *N*,*N*-dimethylaminopyridine (DMAP). Previous in-house work incorporating Wang resin has indicated sometimes incomplete esterification (loading) of the first residue, therefore as a general procedure the resin is 'capped' with acetic anhydride.

The supported Fmoc-protected amino acid **6** was deprotected by treatment with 20% piperidine in 1-methyl-2-pyrrolidone (NMP). The resin-bound primary amine **7** was then reacted with di-(2-pyridyl)thionocarbonate (DPT) to yield the corresponding immobilised isothiocyanate **8**. This isothiocyanate was quantitatively transformed into the substituted thioureas **10** via nucleophilic addition with a range of primary alkyl, secondary alkyl and aryl amines. Desulfurisation was achieved by treatment of immobilised thioureas **10** with a freshly prepared solution of triphenylphosphine dichloride made by the treatment of triphenylphosphine with hexachloroethane in dry tetrahydrofuran (THF). Traditional solution-phase literature reports indicate that when R^3=H the corresponding carbodiimide **11** is generated.[9] It can be suggested that when $R^3 \neq$H, an immobilised carbimidoyl chloride **12** or the equivalent charged resin bound carbodiimide salt **13** can be formed (Scheme 2). To address this issue a number of high-resolution magic angle spinning NMR experiments were performed, the results of which were unfortunately inconclusive. On the other hand, a recent report suggested that the application of triphenylphosphine/carbon tetrachloride/triethylamine in the solid-phase did not yield the immobilised carbodiimide as expected.[10] We also found that the addition of triethylamine hindered the formation of the carbodiimides **11**, however, exclusion of triethylamine yielded the carbodiimides quantitatively without the premature acid-mediated cleavage of the intermediate. A second nucleophilic insertion reaction was then carried out on the resin bound carbodiimide or carbodiimide equivalent. This could be achieved with a range of primary alkyl, secondary alkyl and aryl amines **14** in dry NMP. Initial attempts employing dimethylsulphoxide (DMSO) dried over molecular sieves yielded typically 0–15% of the corresponding urea by-product, the more reactive amines yielding the least by-product. This can possibly be attributed to the hygroscopic properties of DMSO. Cleavage of the *N*,*N*′,*N*″-substituted guanidines **15** from the polystyrene support was accomplished by treatment with 50% trifluoroacetic acid (TFA) in DCM. A small library of six *N*,*N*′,*N*″-substituted guanidines **16** was synthesised to validate this strategy; R^1 throughout was held constant as (p-$CH_2(C_6H_4)CH_2$) to exemplify the method. Attempts to incorporate α-aminoacids as R^1 failed, the resin-bound substituted thioureas formed when α-aminoacids were used reacted through an intramolecular cyclisation and simultaneous cleavage to form thiohydantoins. For clarity



Scheme 2.

structures of the synthesised examples are depicted as free bases in one of their possible tautomeric forms (Fig. 3). The purity and yields of the *N*,*N*′,*N*″-substituted guanidines are given in Table 1. Guanidines **16a** and **16d** are identical, but the latter was synthesised by the reverse sequence of amine insertion.

Compounds **16a**, **16c** and **16d** show that the strategy described is applicable for the inclusion of secondary amines and aryl amines in both R^2 and R^3, hence the strategy can be described as a 'robust' solid-phase strategy. The high purity of *N*,*N*′,*N*″-substituted guanidines can be attributed to the key step throughout the synthesis strategy, sulfur

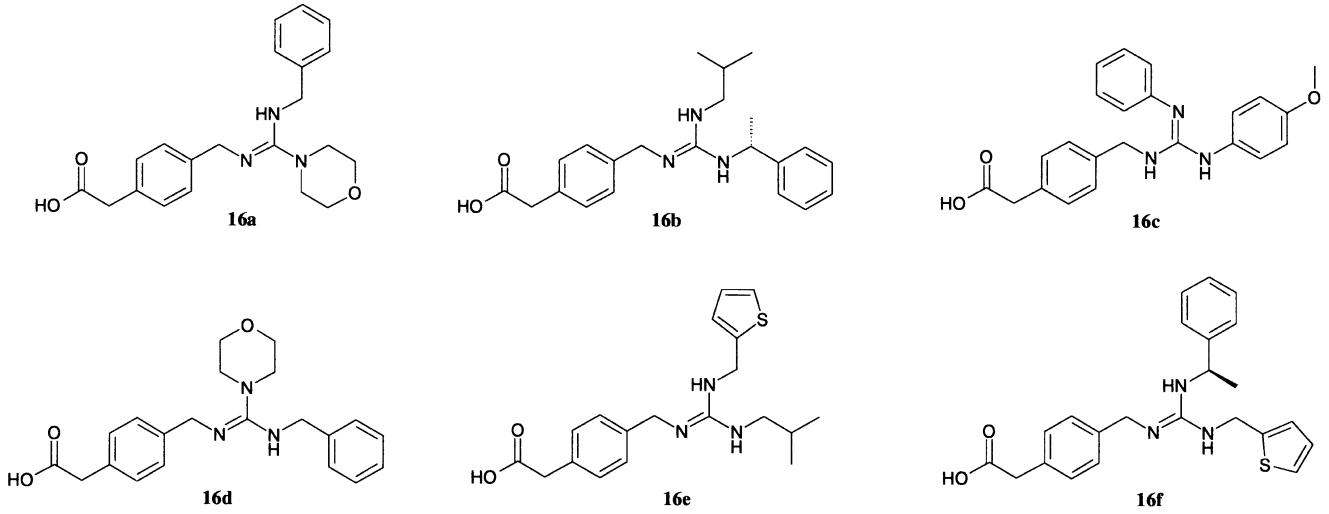


Figure 3. Structure of representative *N*,*N*′,*N*″-substituted guanidines synthesised.

Table 1. Purity and yield of representative *N*,*N*′,*N*″-substituted guanidines. Purity given is calculated from ELS peak integration, yields are derived from concentrations determined by NMR studies and the original loading of the Wang resin

Compound	Purity (%)	Yield (%)	M_w	*m*/*z* $[M+H]^+$
16a	>99	55	367	368.2
16b	>99	62	367	368.2
16c	94	39	389	390.1
16d	99	62	367	368.2
16e	99	35	359	360.1
16f	99	66	407	408.1

extrusion from immobilised substituted thioureas, which was almost quantitatively achieved at room temperature with the mild reagent triphenylphosphine dichloride prepared from triphenylphosphine and hexachloroethane in tetrahydrofuran.

3. Conclusion

Described in this paper is a new facile and robust synthesis strategy for the formation of *N*,*N*′,*N*″-substituted

guanidines. Commercial Wang resin was employed as the anchor for the attachment of protected non-α-aminoacids to yield the resin-bound R^1 synthon. DPT quantitatively transformed the de-protected amines to the corresponding isothiocyanates in relatively short reaction times. Incorporation of primary, secondary and aryl amines as the HNR^2R^3 and HNR^4R^5 synthons in the guanidine strategy yielded the *N*,*N*′,*N*″-substituted guanidines in good yield and purity. The application of this strategy employing large pools of amines has facilitated the synthesis of large combinatorial libraries of *N*,*N*′,*N*″-substituted guanidines.

4. Experimental

4.1. General

All reactions were performed in standard glassware or Teflon apparatus suitable for solid-phase synthesis. Starting materials and reagents were commercially available and used without further purification. 4-Alkoxybenzyl alcohol resin (Wang®, 200–400 mesh, polystyrene–divinylbenzene 1%) was purchased from BACHEM, Switzerland. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX300 spectrometer. Chemical shifts (δ ppm) are relative to TMS as internal standard. Multiplicities are indicated as s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet and coupling constants are quoted in Hertz (*J* values). IR spectra were recorded on a FT/IR Perkin–Elmer spectrometer, model Spectrum one. Electrospray (ES) mass spectra and LCMS analyses were recorded on a PE Sciex API 3000 instrument equipped with an HP1100 HPLC equipped with binary pump, column compartment, diode array detector, single quadrupole mass spectrometer detector and a C18 column (Waters Xterra MS C-18×3 mm) at 40°C with a flow rate of 1.0 mL/min. Two mobile phases (mobile phase A, 100% water, 0.01% TFA; mobile phase B, 100% acetonitrile, 0.01% TFA) were employed to run a gradient condition from 10 to 100% B in 7.5 min with UV detection at 210 nm and MS scanning range from 100–1000 amu. An injection volume of 1 μL was used.

4.2. General procedure for the preparation of *N*,*N*′,*N*″-substituted guanidines (16)

Coupling of Fmoc protected aminoacid (**6**). Fmoc-4-aminomethylphenylacetic acid (6.21 g, 16.05 mmol) in DCM/DMF (30 mL, 1:1 v/v) was added to pre-swollen Wang resin (3 g, 3.21 mmol) and DIC (2.5 mL, 16.05 mmol) in DCM/DMF (10 mL, 1:1 v/v) was added followed by DMAP (20 mg, 0.16 mmol). The mixture was shaken for 18 h. Excess reagents were removed by filtration and the resin was washed using the following solvents: DMF (3×), DCM (5×). Acetic anhydride (2 mL) in NMP/DIPEA (38 mL, 7:3 v/v) was added and the mixture shaken for 15 min before filtration and washing using the following solvents: NMP (3×), DCM (5×), MeOH (2×). The resin was dried in vacuo overnight at 40°C. A sample (10 mg) of resin **6** was removed and shaken with trifluoroacetic acid/DCM (0.5 mL, 1:1 v/v) for 1 h. The liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. MS (ES) *m*/*z* 410 $[M+Na]^+$

Formation of isothiocyanate (**8**). Resin **6** (200 mg, 0.214 mmol) in NMP/piperidine (2 mL, 4:1 v/v) was shaken for 20 min. The resin was filtered before washing with NMP (3×), DCM (3×). DPT (497 mg, 2.14 mmol) in DCM (3 mL) was added and the mixture was shaken for 5 h. The excess reagents were removed by filtration before the resin was washed with DCM (2×), NMP (3×), DCM (3×).

Formation of substituted thioureas (**10**). Typical procedure: benzylamine (229 mg, 2.14 mmol) in NMP (3 mL) was added to pre-swollen resin **8**, the mixture was shaken for 16 h before excess reagents were removed by filtration. The resin was washed with NMP (3×), DCM (3×), MeOH (3×). A sample (10 mg) of resin **10** was removed and shaken with trifluoroacetic acid/DCM (0.5 mL, 1:1 v/v) for 1 h. The liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. MS (ES) *m*/*z* 315 $[M+H]^+$

Sulfur extrusion. Triphenylphosphine (561 mg, 2.14 mmol) was added to a solution of hexachloroethane (505 mg, 2.14 mmol) in dry THF (3 mL) and the solution was agitated for 5 min before addition to resin **10**, pre-swollen in dry THF. The mixture was shaken for 5 h, excess reagents were removed by filtration and the resin was washed with dry THF (5×).

Formation of guanidines (**15**) *and resin cleavage*. Typical procedure: Morpholine (187 mg, 2.14 mmol) in dry NMP (3 mL) was added to resin **11** and the mixture was shaken for 16 h. Filtration removed the excess reagents from the resin that was subsequently washed with NMP (3×), DCM (10×). Trifluoroacetic acid (1.5 mL) in DCM (1.5 mL) was added to the resin and the mixture was shaken for 2 h before the liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. The residue was re-dissolved in acetonitrile (5 mL). A sample (500 μL, ca. 21 μmol) was removed and concentrated in vacuo for NMR concentration studies and LC–MS analysis. The residual crude products were purified by preparative HPLC to yield the representative compounds **16**, isolated as the trifluoroacetate salts.

4.2.1. (4-{[(*N*-Benzylmorpholine-4-carboximidoyl)amino]-methyl}phenyl)acetic acid (16a). White solid: $[\alpha]_D^{21}=+4.8$; ν_{max} (KBr) 3255, 1678, 1618, 1201, 1132, 1022, 952, 833, 800, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=3.39 (t, *J*=4.5 Hz, 4H, NCH_2 morpholine), 3.57 (s, 2H, $C(O)CH_2$), 3.65 (t, *J*=4.5 Hz, 4H, OCH_2 morpholine), 4.42 (m, 4H, $PhCH_2NH$), 7.17–7.25 (m, 6H, ArH), 7.31–7.38 (m, 3H, ArH), 8.44 (m, 2H, $2CH_2NH$); ^{13}C NMR (DMSO-d_6): δ=40.2 ($C(O)CH_2$), 46.7, 47.0 ($PhCH_2NH$), 47.8 (NCH_2 morpholine), 65.5 (OCH_2 morpholine), 126.9–129.5, 134.4, 135.2, 136.9 (ArC), 158.2 (NHCNH), 172.4 ($C(O)CH_2$). Calcd for $C_{21}H_{26}N_3O_3\cdot C_2F_3O_2\cdot 0.2C_2F_3HO_2$: C, 55.73; H, 5.24; N, 8.33. Found: C, 55.77; H, 5.18; N, 8.22.

4.2.2. {4-[*N*′-Isobutyl-*N*″-(1-phenylethyl)guanidino-methyl]-phenyl}acetic acid (16b). White solid: ν_{max} (KBr) 3281, 1678, 1628, 1201, 1133, 1022, 952, 831, 800, 766, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=0.63 (d, *J*=6.7 Hz, 3H, CH_3CHCH_3), 0.64 (d, *J*=6.4 Hz, 3H, CH_3CHCH_3), 1.46 (d, *J*=6.8 Hz, 3H, CH_3CHPh), 1.60–1.69 (m, 1H, $CH_2CH(CH_3)_2$), 2.91–3.13 (m, 2H, $NHCH_2CH$), 3.55 (s, 2H, $C(O)CH_2$), 4.41 (dd, *J*=16.2,

5.6 Hz, 1H, PhCH_2NH), 4.57 (dd, J=16.2, 5.6 Hz, 1H, PhCH_2NH), 4.95 (m, 1H, CH_3CHPh), 7.06–7.09 (m, 2H, ArH), 7.18–7.33 (m, 7H, ArH), 7.48 (t, J=5.6 Hz, 1H, PhCH_2NH), 7.67 (d, J=7.5 Hz, 1H, NHCHPh), 8.07 (t, J=6.0 Hz, 1H, NHCH_2CH); ^{13}C NMR (DMSO-d_6): δ=19.3 (CH_3CHCH_3), 22.6 (CH_3CHPh), 27.4 ($CH_2CH(CH_3)_2$), 40.2 (C(O)CH_2), 43.5 (PhCH_2NH), 48.1 (NHCH_2CH), 50.6 (CH_3CHPh), 125.7–129.2, 134.0, 135.5, 139.2, 142.5 (ArC), 153.5 (NHCNH), 172.4 (C(O)CH_2). Calcd for $C_{22}H_{30}N_3O_2\cdot C_2F_3O_2\cdot 0.33H_2O$: C, 59.13; H, 6.34; N, 8.62. Found: C, 59.26; H, 6.31; N, 8.61.

4.2.3. {4-[*N′*-(4-Methoxyphenyl)-*N″*-phenylguanidinomethyl]-phenyl}acetic acid (16c). White solid: ν_{max} (KBr) 2976, 1683, 1628, 1512, 1203, 1021, 950, 829, 800, 758, 719 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=3.58 (s, 2H, C(O)CH_2), 3.73 (s, 3H, OCH_3), 4.51 (d, J=5.6 Hz, 2H, PhCH_2NH), 6.92–6.96 (m, 2H, ArH), 7.13–7.39 (m, 11H, ArH), 8.66 (m, 1H, CH_2NH), 9.93 (bs, 2H, NHPh); ^{13}C NMR (DMSO-d_6): δ=40.2 (C(O)CH_2), 45.1 (PhCH_2NH), 55.2 (OCH_3), 114.5, 123.6–129.5, 134.2, 135.0, 136.2, (ArC), 153.3 (NHCNH), 172.4 (C(O)CH_2). Calcd for $C_{23}H_{24}N_3O_3\cdot C_2F_3O_2\cdot 0.5H_2O$: C, 58.59; H, 4.92; N, 8.20. Found: C, 58.34; H, 4.91; N, 8.14.

4.2.4. (4-{[(*N*-Benzyl-morpholine-4-carboximidoyl)amino]-methyl}phenyl)acetic acid (16d). (Identical with **16a**, but prepared by the inverse sequence of insertion reactions with the amines). White solid: ν_{max} (KBr) 3234, 1678, 1611, 1201, 1114, 1016, 950, 831, 800, 721 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=3.39 (t, J=4.1 Hz, 4H, NCH_2 morpholine), 3.57 (s, 2H, C(O)CH_2), 3.65 (t, J=4.5 Hz, 4H, OCH_2 morpholine), 4.42 (m, 4H, PhCH_2NH), 7.17–7.37 (m, 9H, ArH), 8.44 (m, 2H, 2CH_2NH); ^{13}C NMR (DMSO-d_6): δ=40.2 (C(O)CH_2), 46.7, 47.0 (PhCH_2NH), 47.8 (NCH_2 morpholine), 65.5 (OCH_2 morpholine), 126.9–129.5, 134.4, 135.2, 136.9 (ArC), 158.2 (NHCNH), 172.4 (C(O)CH_2). Calcd for $C_{21}H_{26}N_3O_3\cdot C_2F_3O_2\cdot 0.67H_2O$: C, 55.98; H, 5.58; N, 8.51. Found: C, 56.04; H, 5.45; N, 8.32.

4.2.5. [4-(*N′*-Isobutyl-*N″*-thiophen-2-ylmethylguanidinomethyl)phenyl]acetic acid (16e). White solid: ν_{max} (KBr) 3247, 1678, 1618, 1201, 1133, 1023, 952, 832, 799, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=0.73 (d, J=6.4 Hz, 6H, CH_3CHCH_3), 1.67–1.81 (m, 1H, $CH_2CH(CH_3)_2$), 2.99 (m, 1H, NHCH_2CH), 3.54 (s, 2H, C(O)CH_2), 4.44 (d, J=5.6 Hz, 2H, PhCH_2NH), 4.67 (d, 2H, J=5.6 Hz, NHCH_2), 6.98 (m, 2H, thienyl-H), 7.10 (d, J=7.9 Hz, 2H, ArH), 7.14 (d, J=7.9 Hz, 2H, ArH), 7.47 (t, J=2.6 Hz, 1H, thienyl-H), 7.67 (t, J=6.0 Hz, 1H, NHCH_2CH), 8.16 (t, J=5.6 Hz, 1H, PhCH_2NH), 8.23 (t, J=6.0 Hz, 1H, NHCH_2); ^{13}C NMR (DMSO-d_6): δ=19.4 (CH_3CHCH_3), 27.3 ($CH_2CH(CH_3)_2$), 39.7 ($NHCH_2$), 40.2 (C(O)CH_2), 43.5 (PhCH_2NH), 48.1 (NHCH_2CH), 125.5–129.3, 134.1, 135.2, 140.2, (ArC, thienyl-C), 153.7 (NHCNH), 172.4 (C(O)CH_2). Calcd for $C_{19}H_{26}N_3O_2S\cdot C_2F_3O_2$: C, 53.27; H, 5.53; N, 8.87. Found: C, 53.50; H, 5.59; N, 8.77.

4.2.6. {4-[*N′*-(1-Phenylethyl)-*N″*-thiophen-2-ylmethylguanidinomethyl]phenyl}acetic acid (16f). White solid: $[\alpha]_D^{21}$=−76.2; ν_{max} (KBr) 3280, 1678, 1630, 1202, 1132, 1021, 952, 832, 800, 767, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.44 (d, J=6.8 Hz, 3H, CH_3CHPh), 3.54 (s, 2H, C(O)CH_2), 4.38 (dd, J=16.2, 5.3 Hz, 1H, PhCH_2NH), 4.52 (dd, J=16.2, 5.6 Hz, 1H, PhCH_2NH), 4.63 (dd, J=16.6, 6.0 Hz, 1H, NHCH_2), 4.78 (dd, J=16.6, 5.6 Hz, 1H, NHCH_2), 4.88–4.95 (m, 1H, CH_3CHPh), 6.81 (d, J=3.0 Hz, 1H, thienyl-H), 6.89–6.96 (m, 3H, ArH, thienyl-H), 7.10–7.14 (m, 4H, ArH), 7.25–7.28 (m, 3H, ArH), 7.44 (dd, J=1.1, 3.8 Hz, 1H, thienyl-H), 7.85 (d, J=7.1 Hz, 1H, NHCHPh), 8.20 (t, J=5.6 Hz, 1H, PhCH_2NH), 8.29 (t, J=5.1 Hz, 1H, NHCH_2); ^{13}C NMR (DMSO-d_6): δ=22.5 (CH_3CHPh), 39.7 ($NHCH_2$), 40.2 (C(O)CH_2), 43.7 (PhCH_2NH), 50.6 (CH_3CHPh), 125.5–129.2, 134.0, 135.1, 140.0, 142.2 (ArC, thienyl-C), 153.4 (NHCNH), 172.4 (C(O)CH_2). Calcd for $C_{23}H_{26}N_3O_2S\cdot C_2F_3O_2\cdot 0.5H_2O$: C, 56.60; H, 5.13; N, 7.92. Found: C, 56.76; H, 4.99; N, 7.85.

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