The Synthesis of Two Combinatorial Libraries Using a 4-(2'-Thienyl)-Pyrrole Template

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The synthesis of the novel biaryl compound, 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1) by Suzuki-Miyaura coupling conditions is reported. Compound 1 was subsequently used as a combinatorial template in the parallel solution-phase synthesis of an amine and imine compound library. The amine library was produced using reductive amination conditions and purification was achieved by a liquid-liquid partition followed by silica chromatography to afford 10 amine analogues. The imine library consisted of 5 compounds, which were synthesised using volatile primary amines that allowed purification by evaporation. The synthesis of the novel and related biaryl carbaldehyde, *tert*-butyl-2-(5'-formyl-1*H*-pyrrol-3'-yl)-1*H*-pyrrole-1-carboxylate (2) is also reported.

Introduction

The past decade has seen combinatorial chemistry emerge as a powerful research tool for the pharmaceutical industry with the synthesised libraries generally being designed around a core structure or template. A number of publications have recently been reported in which the template has been based on a known natural product.^[1-10] The main advantage with these new designs is the structural diversity associated with the known natural product, which can include unique stereochemical and/or carbon-carbon/carbon-heteroatom arrangements. With the natural product based template serving as a framework for the organisation of substituents in space, even greater structural diversity can be achieved through the use of combinatorial chemistry.^[11]

We recently reported the use of a tambjamine natural product template in the generation of an enamine library using parallel solution-phase synthesis.^[12] In our continuing interest in five-membered biaryl compounds, we attempted to synthesise a number of structures related to the tambjamine template, 4-methoxy-2-(1*H*-pyrrol-2'-yl)-1*H*-pyrrole-5-carbaldehyde (3). These new carbaldehyde templates were to be of a similar molecular weight (M_w) to 3 (i.e. 190 Da) so that the resulting combinatorial libraries would contain compounds with M_w 's less than 500 Da. This weight restriction is desirable since it has been reported that compounds which satisfy this criteria generally have better bioavailability.^[13] Alternate biaryl systems to 3 were required so that the generated libraries would contain compounds with different spatial characteristics to the previously synthesised tambjamine combinatorial library (Figure 1). We report here the synthesis of two novel biaryl carbaldehydes (1 and 2) and the subsequent generation of two combinatorial libraries using 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1) as the template.

Results and Discussion

Synthesis of the Biaryl Carbaldehydes

The synthesis of both biaryl carbaldehydes (1 and 2) was achieved using Suzuki-Miyaura coupling conditions^[14] that used *tetrakis*(triphenylphosphine)palladium (0) [(Ph₃P)₄Pd(0)], 1,2-dimethoxyethane (DME)/H₂O, sodium carbonate (Na₂CO₃), and the previously synthesised 4-bromo-1*H*-pyrrole-2-carbaldehyde.^[15,16] The commercially available 2-thiophene boronic acid and the readily synthesised 1-(*tert*-butoxycarbonyl)-1*H*-pyrrol-2-ylboronic acid^[17] were the boronic acid derivatives used for the synthesis of compounds 1 and 2, respectively (Scheme 1). Chromatographic purification of the individual reaction mixtures afforded pure 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1) and *tert*-butyl-2-(5'-formyl-1*H*-pyrrol-3'-yl)-1*H*-pyrrole-1-carboxylate (2) in yields of 78% and 23%, respectively. To the best of our knowledge this is the first reported synthesis for both compounds 1 and 2. Full one-dimensional (1D) and two-dimensional (2D) nuclear magnetic resonance (NMR) spectroscopy combined with negative-ion high-resolution electrospray mass spectrometry [(-)-HRESMS] analysis was used to structurally elucidate both of these biaryl compounds. Due to yield considerations, 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1) was chosen for the synthesis of the new combinatorial libraries.

Synthesis of the Amine Combinatorial Library

The reductive amination reaction is among the most useful and important tools in the synthesis of different amines. While a large number of reducing reagents exist for this particular chemical transformation, sodium triacetoxy borohydride [NaBH(OAc)₃] has become the reducing agent of choice due to its mild and selective properties. This borohydride reagent has been reported in the *direct* reductive aminations of aliphatic and cyclic ketones, and aliphatic and aromatic aldehydes, using a wide variety of primary (1°) and secondary (2°) amines.^[18,19]

We initially performed three separate, *direct* reductive amination reactions using 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1), NaBH(OAc)₃ and morpholine in a variety of solvents, which included 1,2-dichloroethane (DCE), tetrahydrofuran (THF) and acetonitrile (CH₃CN). Following basic work-up, the reaction mixtures were all chromatographed on silica packed solid phase extraction (SPE) cartridges and afforded pure 4-{[4-(2'-thienyl)-1*H*-pyrrol-2-yl]methyl} morpholine (4) in a range of yields (Scheme 2). DCE was chosen as the solvent for all further reactions due to yield considerations and its compatibility with the basic work-up protocol, which involved partitioning the reaction mixture between aqueous sodium hydrogen carbonate (NaHCO₃) and dichloromethane (DCM) (Scheme 2). This optimised *direct* reductive amination method was used for the generation of the amine combinatorial library. Ten parallel reactions were performed simultaneously using five 1° amines and five 2° amines. Basic work-up and purification on silica packed SPE cartridges resulted in ten amines (4-13), which were structurally elucidated and analysed for purity using ¹H and pulse-field gradient two-dimensional correlation spectroscopy (gCOSY) NMR spectroscopy and both positive- and negative-ion low-resolution electrospray mass spectrometry [(±)-LRESMS]. Yields were calculated based on the weight of each compound (Figure 1). Liquid chromatography/mass spectrometry (LC/MS) studies were performed on the synthesised tertiary (3°) amines with the chromatograms displaying a single peak that corresponded to the relevant *m/z* ion for each analogue. The 3° amine (4) was fully characterised by 1D and 2D NMR spectroscopy and (+)-HRESMS.

Of the 10 amines synthesised, 9 were obtained in yields greater than 57%. However, the reaction involving *n*-butylamine did not work using the standard reaction conditions. ¹H NMR and LRESMS analysis of the reaction mix after work-up showed the presence of only minute quantities of the desired amine (9), along with the biaryl carbaldehyde (1) and another compound that was tentatively assigned to the imine, 14. Synthesis of *N*-{(*E*)-[4-(2'-thienyl)-1*H*-pyrrol-2-yl]methylidene}-

1-butanamine (14) by reacting 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1) in DCE with *n*-butylamine, confirmed that the side-product was the proposed imine (Scheme 3).

With the knowledge that the reductive amination using *n*-butylamine was relatively slow, compared with all the other amines used for the library production, an *indirect* reductive amination reaction was attempted. NaBH(OAc)₃ was added to the synthesised imine (14) in dry DCE and the reaction mixture was stirred at room temperature for 4 h (Scheme 4). Silica chromatography on the reaction mixture yielded the dialkylated amine, *N,N*-bis{[4-(2-thienyl)-1*H*-pyrrol-2-yl]methyl}-1-butanamine (15) and the monoalkylated amine, *N*-{[4-(2-thienyl)-1*H*-pyrrol-2-yl]methyl}-1-butanamine (9). The presence of the dialkylated amine (15) suggested that the reduction of 14 was very slow and as a result, the small amount of produced monoalkylated amine (9) had sufficient time to either react with the aldehyde (1), produced by hydrolysis of the imine (14), or the imine (14) itself, to produce the dialkylated amine (15). The problem of dialkylation when performing reductive aminations using certain aldehydes and 1° amines has been reported in the literature, and this problem is usually rectified by adopting a stepwise procedure involving imine formation followed by the reduction using sodium borohydride (NaBH₄) in an alcoholic solvent.^[18] This protocol was applied, with the initial synthesis of *N*-{(E)-[4'-(2"-thienyl)-1*H*-pyrrol-2'-yl]methylidene}-1-butanamine (14) and the subsequent reduction using NaBH₄ in ethanol (EtOH) at room temperature. After basic work-up only the pure monoalkylated amine (9) was obtained (Scheme 4). It has also been reported that acetic acid (AcOH) acts as a catalyst in *direct* reductive amination reactions,^[18] hence this acid was added to 4-(2-thienyl)-1*H*-pyrrole-2-carbaldehyde (1), NaBH(OAc)₃ and *n*-butylamine in DCE and stirred at room temperature for 4 h. Following basic work-up, *N*-{[4'-(2"-thienyl)-1*H*-pyrrol-2'-yl]methyl}-1-butanamine (9) was identified as the major product. A minute quantity of the dialkylated product (15) was also identified by NMR analysis. Integration of the ¹H NMR spectrum was used to determine the relative ratio of the mono to dialkylated amine, which was calculated to be 11:1. Although the *indirect* reductive amination method produced the higher quality product, the *direct*

method, which is more amenable to combinatorial solution-phase synthesis, proved to be acceptable for library generation although the product quality was slightly compromised.

Closer inspection of the ^1H NMR spectra for all the synthesised 2° amines (10-13) identified the distinctive proton resonance at $\sim\delta$ 6.14 which was indicative of the dialkylated species. Once again integration of the ^1H NMR spectrum provided the relative ratio of the mono to dialkylated amine for each sample. The quantity of the dialkylated amine in each sample varied between 3.4% and 6.3% (Table 1).

All the amines (4, 5, 6-13) proved to be stable if stored dry at 0 °C. Stability studies were performed in which small amounts of each amine were left in deuterated dimethyl sulfoxide ($\text{DMSO-}d_6$) at room temperature for several months. After 3 months the samples were analysed by ^1H NMR spectroscopy and it was determined that all the 2° amines (9-13) had fully decomposed, while the 3° amines (4-8) had only partially degraded. While no definitive decomposition product was identified in any of samples, the presence of many downfield ^1H NMR signals between δ 6.0 and δ 8.0 suggested the formation of polymeric material.

Synthesis of an Imine Combinatorial Library

Due to the successful synthesis of *N*-{(E)-[4'-(2"-thienyl)-1*H*-pyrrol-2'-yl]methylidene}-1-butanamine (14), a small series of related imines were synthesised by solution-phase parallel chemistry and stability studies were performed. The reaction conditions involved stirring anhydrous DCE, 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1) and the relevant 1° amine at room temperature for 4 h. Removal of the excess volatile 1° amine by evaporation under nitrogen (N_2) yielded the individual pure imine.

The imines (14, 16-19) were structurally elucidated by ^1H and gCOSY NMR analysis combined with (+)-LRESMS. *N*-{(*E*)-[4'-(2''-thienyl)-1*H*-pyrrol-2'-yl]methylidene}-1-butanamine (14) was fully characterised by 1D and 2D NMR spectroscopy and (+)-HRESMS.

All the synthesised imines (14, 16-19) proved to be unstable even when stored dry at 0 °C. After 3 months in storage the imines were analysed by ^1H NMR spectroscopy and it was determined that all the samples had started to decompose. The major decomposition product was the starting material, 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1), which was identified by the salient ^1H chemical shift at δ 9.50. Integration of the ^1H NMR spectra resulted in the calculation of the relative ratio of the aldehyde (1) to the imine for each sample (Table 2).

Conclusion

The model template, 4-(2-thienyl)-1*H*-pyrrole-2-carbaldehyde (1) was successfully synthesised and subsequently used in the generation of an amine and imine combinatorial library. Each of the libraries were produced using solution-phase parallel combinatorial chemistry and the resulting individual compounds were analysed for purity and characterised by ^1H /gCOSY NMR spectroscopy combined with LC/MS and LRESMS. Stability studies were performed on both the amine and imine combinatorial libraries. The synthesis of the novel biaryl carbaldehyde, *tert*-butyl-2-(5-formyl-1*H*-pyrrol-3-yl)-1*H*-pyrrole-1-carboxylate (2) using Suzuki-Miyaura coupling conditions was also achieved. Biological activities for all stable synthesised compounds will be evaluated and reported at a later date.

Experimental

General

NMR spectra were recorded on a Varian 500 or 600 MHz Unity INOVA at 499.923 or 599.926 MHz for ^1H , and 124.981 or 149.982 for ^{13}C . The 500 MHz spectrometer was equipped with a SMS autosampler. The ^1H and ^{13}C chemical shifts are reported in parts per million relative to the reference solvent peaks at δ 2.49 and 39.51 ppm for $\text{DMSO-}d_6$, and δ 7.26 and 77.00 ppm for deuterated chloroform (CDCl_3). Standard parameters were used for the 1D and 2D NMR spectra obtained, which included ^1H , ^{13}C , gCOSY, pulse-field gradient homonuclear single quantum coherence (gHSQC), and pulse-field gradient heteronuclear multiple bond coherence (gHMBC) experiments. HRESMS were recorded on a Bruker BioAPEX 47e mass spectrometer equipped with a Bradford CT 06405 electrospray ion source. LRESMS and LC/MS were recorded on a Fisons VG platform mass spectrometer connected to a Waters Alliance HT 2790 system equipped with a PDA detector. LC/MS samples were injected from a 96 well microtitre plate onto a Waters HPLC Symmetry column $3.5\ \mu\text{m}$ C_8 ($2.1\ \text{mm} \times 50\ \text{mm}$) with a 1:10 splitter attached. A linear gradient from 50% CH_3CN /1.0% aqueous trifluoroacetic acid (TFA) to 100% CH_3CN in 3 min at a flowrate of 0.4 mL/min was used for each sample injection. Infrared (IR) and ultraviolet (UV) spectra were recorded on a Perkin-Elmer 1725X spectrophotometer and a GBC UV/Vis 916 spectrophotometer respectively. Melting points were determined using a Gallenkamp melting point apparatus and were uncorrected. SPE cartridges ($10\ \text{mm} \times 20\ \text{mm}$) were packed with Alltech Davisil $30\text{--}40\ \mu\text{m}$ $60\ \text{\AA}$ silica ($\sim 200\ \text{mg}$). All chromatographic solvents were Merck Omnisolv grade and the H_2O used was Millipore Milli-Q PF filtered. All synthetic reagents were obtained from Sigma-Aldrich and used without further purification. Combinatorial chemistry reactions were performed using dry N_2 and Wheaton V-Vials (1 mL) and V-stirrers. Size-exclusion chromatography was performed on Pharmacia Biotech Sephadex LH-20 with the glass column ($45\ \text{mm} \times 350\ \text{mm}$) connected to a Waters 486 Tunable Absorbance Detector and

Waters Fraction Collector. A lab-made droplet counter-current chromatogram (total volume, 800 ml) equipped with an Alltech 301 MPLC pump was used for DCCC. A Gilson 204 fraction collector was used for the DCCC work.

4-(2'-thienyl)-1H-pyrrole-2-carbaldehyde (1).

2-Thiophene boronic acid (384 mg, 3.0 mmol), 4-bromo-1*H*-pyrrole-2-carbaldehyde (352 mg, 2.0 mmol),^[15,16] (Ph₃P)₄Pd(0) (116 mg, 0.1 mmol, 5% mol) and Na₂CO₃ (532 mg, 5.0 mmol) were added to a two-necked round bottom flask (50 mL) charged with argon (Ar). Anhydrous DME (8 mL) and degassed H₂O (2 mL) were added and the solution was heated at 85 °C for 16 h. After evaporation of the solvent *in vacuo* the residue was partitioned between H₂O (25 mL) and DCM (2 × 25 mL). The organic layer was evaporated to dryness and chromatographed on a silica flash column (40 mm × 20 mm) using 100% DCM as the eluent. This fraction was chromatographed on a Sephadex LH-20 column run at a flowrate of 8 mL/min with 50% methanol (MeOH)/50% DCM as the eluent and yielded one fraction that was recrystallised using 100% DCM to afford pure 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1, 277 mg, 78% yield) as fine orange plates. Mp 183-185 °C. UV (MeOH) λ_{max} 265 (ε 20 000), 324 nm (ε 9 000). IR ν_{max} (NaCl) 3200-3600, 2094, 1648, 1446, 1384, 1356, 1133 cm⁻¹. ¹H NMR (DMSO-*d*₆, 500 MHz) δ 7.03, 1H, dd, *J* 5.4, 3.6 Hz, H3; 7.19, 1H, dd, *J* 3.0, 1.2 Hz, H10; 7.23, 1H, d, *J* 3.6 Hz, H4; 7.33, 1H, d, *J* 5.4 Hz, H2; 7.54, 1H, dd, *J* 2.0, 1.2 Hz, H7; 9.50, 1H, s, H11; 12.87, 1H, br s, 8-NH. ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 116.6, C10; 120.2, C6; 122.1, C4; 123.0, C2; 123.6, C7; 127.8, C3; 133.2, C9; 137.3, C5; 179.4 C11. (-)-LRESMS *m/z* 176 (100%) [M-H]⁻. (-)-HRESMS *m/z* 176.0174 (calc. for C₉H₆N₁O₁S₁ [M-H]⁻ 176.0176, Δ -1.1 ppm).

Tert-butyl-2-(5'-formyl-1H-pyrrol-3'-yl)-1H-pyrrole-1-carboxylate (2).

1-(*Tert*-butoxycarbonyl)-1*H*-pyrrol-2-ylboronic acid (105 mg, 0.5 mmol),^[17] 4-bromo-1*H*-pyrrole-2-carbaldehyde (88 mg, 0.5 mmol),^[15,16] (Ph₃P)₄Pd(0) (58 mg, 0.05 mmol) and Na₂CO₃ (133 mg, 1.25 mmol) were added to a two-necked round bottom flask (50 mL) charged with Ar. DME (10 mL) and degassed H₂O (2 mL) were added and the solution was heated at 100 °C for 16 h. After evaporation of the solvent *in vacuo* the residue was partitioned with the solvent system 1:2:4:2 H₂O:MeOH:ethyl acetate (EtOAc):hexanes (50 mL). The upper phase was dried *in vacuo* and further purified using DCCC with a solvent system of 1:2:4:2 H₂O:MeOH:EtOAc:hexanes run in the ascending mode at 0.8 mL/min. This yielded pure *tert*-butyl-2-(5-formyl-1*H*-pyrrol-3-yl)-1*H*-pyrrole-1-carboxylate (2, 30 mg, 23% yield) as a stable red-orange oil. UV (MeOH) λ_{max} 232 (ϵ 9 000), 265 (ϵ 12 000), 296 nm (sh, ϵ 9 000). IR ν_{max} (NaCl) 3200-3400, 2108, 1734, 1648, 1507, 1456, 1394, 1370, 1322, 1256, 1140, 1079, 1052, 1007, 911, 843 cm⁻¹. ¹H NMR (CDCl₃, 600 MHz) δ 1.51, 9H, s, H15; 6.20, 1H, m, H4; 6.20, 1H, m, H3; 7.06, 1H, dd, *J* 3.0, 1.8 Hz, H10; 7.27, 1H, ddd, *J* 3.0, 1.8, 1.2 Hz, H7; 7.30, 1H, dd, *J* 3.6, 1.8 Hz, H2; 9.51, 1H, d, *J* 1.2 Hz, H11; 9.80, 1H, br s, 8-NH. ¹³C NMR (CDCl₃, 150 MHz) δ 27.9, 3C, C15; 83.7, C14; 110.6, C3; 114.1, C4; 119.4, C6; 122.1, C10; 122.4, C2; 126.2, C7; 128.2, C5; 132.1, C9; 149.2, C12; 179.4, C11. (-)-LRESMS *m/z* 259 (100%) [M-H]⁻. (-)-HRESMS *m/z* 259.1091 (calc. for C₁₄H₁₅N₂O₃ [M-H]⁻ 259.1088, Δ +1.2 ppm).

General Procedure for Amine Synthesis

The relevant amine (68 μ mol) was added to a solution of 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1, 6 mg, 34 μ mol) and NaBH(OAc)₃ (14 mg, 68 μ mol) in anhydrous DCE (500 μ L) and the reaction was stirred at room temperature for 4 h. The solution was partitioned between DCM (1.5

mL) and 1N NaHCO₃ (3 × 2 mL). The organic phase was chromatographed on a silica packed SPE cartridge using a gradient from 100% DCM to 10% MeOH/90% DCM in 5% stepwise elutions. The resulting fractions were analysed by silica thin layer chromatography (TLC), in order to identify the fraction containing the pure amine.

4-([4'-(2''-Thienyl)-1H-pyrrol-2-yl]methyl) morpholine (4). Yellow-brown oil, 7.4 mg (88% yield). UV (MeOH) $\lambda_{\max}$ 232 (ϵ 9 000), 289 nm (ϵ 7 000). IR $\nu_{\max}$ (NaCl) 3400-3200, 2960, 2855, 1708, 1650, 1573, 1453, 1349, 1270, 1181, 1112, 1005, 911, 862, 670 cm⁻¹. ¹H NMR (DMSO-*d*₆, 600 MHz) δ 2.34, 4H, m, H13; 3.38, 2H, s, H11; 3.55, 4H, t, *J* 4.8 Hz, H14; 6.12, 1H, dd, *J* 2.4, 1.8 Hz, H10; 6.94, 1H, dd, *J* 2.4, 1.8 Hz, H7; 6.94, 1H, dd, *J* 4.8, 3.0 Hz, H3; 7.00, 1H, dd, *J* 3.0, 1.2 Hz, H4; 7.17, 1H, dd, *J* 4.8, 1.2 Hz, H2; 10.83, 1H, br s, 8-NH. ¹³C NMR (DMSO-*d*₆, 150 MHz) δ 52.8, 2C, C13; 54.7, C11; 66.1, 2C, C14; 106.0, C10; 114.3, C7; 117.4, C6; 120.1, C4; 121.1, C2; 127.5, C3; 128.7, C9; 139.8, C5. (+)-LRESMS *m/z* 162 (100%) [M-C₄H₈N₁O₁]⁺ and 249 (5%) [M+H, C₁₃H₁₇N₂O₁S₁]⁺. (-)-LRESMS *m/z* 247 (100%) [M-H, C₁₃H₁₅N₂O₁S₁]⁻. (-)-HRESMS *m/z* 247.0909 (calc. for C₁₃H₁₅N₂O₁S₁ [M-H]⁻ 247.0910, Δ -0.4 ppm). (+)-LC/MS retention time for [M+H, C₁₃H₁₇N₂O₁S₁]¹⁺, 1.20-1.65 min.

N-benzyl-N-methyl[4-(2'-thienyl)-1H-pyrrol-2-yl]methanamine (5). Yellow-brown oil, 5.7 mg (59% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 2.05, 3H, s, H18; 3.45, 2H, s, H13; 3.47, 2H, s, H11; 6.15, 1H, dd, *J* 2.5, 2.0 Hz, H10; 6.95, 1H, dd, *J* 5.0, 3.5 Hz, H3; 6.97, 1H, dd, *J* 2.5, 2.0 Hz, H7; 7.02, 1H, dd, *J* 3.5, 1.0 Hz, H4; 7.17, 1H, dd, *J* 5.0, 1.0 Hz, H2; 7.23, 1H, dddd, *J* 7.0, 7.0, 1.5, 1.5 Hz, H17; 7.29-7.34, 4H, m, H15, H16; 10.82, 1H, br s, 8-NH. (+)-LRESMS *m/z* 122 (100%) [(M-(C₉H₇N₁S₁)+H]⁺, 162 (95%) [M-C₈H₁₀N₁]⁺ and 283 (10%) [M+H, C₁₇H₁₉N₂S₁]⁺. (+)-LC/MS retention time for [M+H, C₁₇H₁₉N₂S₁]⁺, 1.40-1.80 min.

1-Ethyl-4-([4'-(2''-thienyl)-1H-pyrrol-2'-yl]methyl)piperazine (6). Pale yellow solid, 6.9 mg (74% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 0.96, 3H, t, *J* 7.0 Hz, H17; 2.27, 2H, q, *J* 7.0 Hz, H16; 2.34, 8H, br s, H13, H14; 3.58, 2H, s, H11; 6.10, 1H, dd, *J* 2.0, 2.0 Hz, H10; 6.92, 1H, dd, *J* 2.5, 2.0 Hz, H7; 6.94, 1H, dd, *J* 5.0, 3.5 Hz, H3; 7.00, 1H, dd, *J* 3.5, 1.0 Hz, H4; 7.17, 1H, dd, *J* 5.0, 1.0 Hz, H2; 10.80, 1H, br s, 8-NH. (+)-LRESMS *m/z* 162 (100%) [M-C₆H₁₃N₂]⁺ and 276 (50%) [M+H, C₁₅H₂₂N₃S₁]⁺. (+)-LC/MS retention time for [M+H, C₁₅H₂₂N₃S₁]⁺, 1.05-1.60 min.

4-([4'-(2''-Thienyl)-1H-pyrrol-2'-yl]methyl)thiomorpholine (7). Pale brown oil, 7.2 mg (81% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 2.60, 8H, m, H13, H14; 3.41, 2H, s, H11; 6.12, 1H, s, H10; 6.95, 1H, s H7; 6.96, 1H, dd, *J* 4.5, 2.5 Hz, H3; 7.02, 1H, d, *J* 2.5 Hz, H4; 7.19, 1H, d, *J* 4.5 Hz, H2; 10.82, 1H, br s, 8-NH. (+)-LRESMS *m/z* 162 (100%) [(M-C₄H₈N₁S₁)]⁺ and 265 (5%) [M+H, C₁₃H₁₇N₂S₂]⁺. (+)-LC/MS retention time for [M+H, C₁₃H₁₇N₂S₂]⁺, 1.25-1.65 min.

1-Acetyl-4-([4'-(2''-thienyl)-1H-pyrrol-2'-yl]methyl)piperazine (8). Yellow-brown oil, 5.6 mg (57% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.96, 3H, s, H17; 2.28^a, 2H, t, *J* 5.0 Hz, H13; 2.34^a, 2H, t, *J* 5.0 Hz, H13; 3.39, 4H, m, H14; 3.42, 2H, s, H11; 6.12, 1H, dd, *J* 2.0, 2.0 Hz, H10; 6.95, 1H, m, H7; 6.95, 1H, dd, *J* 5.0, 3.5 Hz, H3; 7.01, 1H, dd, *J* 3.5, 1.0 Hz, H4; 7.17, 1H, dd, *J* 5.0, 1.0 Hz, H2; 10.85, 1H, br s, 8-NH. (+)-LRESMS *m/z* 162 (100%) [(M-C₆H₁₁N₂O₁)]⁺ and 290 (5%) [M+H, C₁₅H₁₉N₃S₁O₁]⁺. (+)-LC/MS retention time for [M+H, C₁₅H₁₉N₃S₁O₁]⁺, 1.10-1.70 min.

^aSignals are interchangeable and are due to a 1:1 mix of amide bond rotamers.

2-Methoxy-N-([4'-(2''-thienyl)-1H-pyrrol-2'-yl]methyl)ethanamine (10). Yellow-brown oil, 4.9 mg (61% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 2.63, 2H, t, *J* 6.0 Hz, H13; 3.22, 3H, s, H16; 3.37,

2H, t, *J* 6.0 Hz, H14; 3.60, 2H, s, H11; 6.09, 1H, dd, *J* 2.0, 2.0 Hz, H10; 6.92, 1H, dd, *J* 2.0, 2.0 Hz, H7; 6.94, 1H, dd, *J* 5.0, 3.5 Hz, H3; 6.98, 1H, dd, *J* 3.5, 1.0 Hz, H4; 7.16, 1H, dd, *J* 5.0, 1.0 Hz, H2; 10.74, 1H, br s, 8-NH. (+)-LRESMS *m/z* 162 (100%) [M-C₃H₈N₁O₁]⁺, 237 (5%) [M+H, C₁₂H₁₇N₂O₁S₁]⁺ and 398* (2%) [M+H, C₂₁H₂₅N₃O₁S₁]⁺.

*Due to dialkylated compound.

2-(4'-Morpholinyl)-N-{[4''-(2'''-thienyl)-1H-pyrrol-2''-yl]methyl}ethanamine (11). Yellow-brown oil, 6.1 mg (62% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 2.30, 4H, br t, *J* 5.0 Hz, H16; 2.35, 2H, t, *J* 6.5 Hz, H14; 2.57, 2H, t, *J* 6.5 Hz, H13; 3.54, 4H, t, *J* 5.0 Hz, H17; 3.59, 2H, s, H11; 6.09, 1H, dd, *J* 2.0, 2.0 Hz, H10; 6.92, 1H, dd, *J* 2.5, 2.0 Hz, H7; 6.94, 1H, dd, *J* 5.5, 3.5 Hz, H3; 6.98, 1H, dd, *J* 3.5, 1.0 Hz, H4; 7.16, 1H, dd, *J* 5.5, 1.0 Hz, H2; 10.77, 1H, br s, 8-NH. (+)-LRESMS *m/z* 162 (100%) [M-C₆H₁₃N₂O₁]⁺, 292 (30%) [M+H, C₁₅H₂₂N₃O₁S₁]⁺ and 453* (5%) [M+H, C₂₄H₂₉N₄O₁S₂]⁺.

*Due to dialkylated compound.

N-(2-chlorobenzyl)[4'-(2''-thienyl)-1H-pyrrol-2'-yl]methanamine (12). Yellow-brown oil, 6.5 mg (63% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) 3.65, 2H, s, H11; 3.76, 2H, s, H13; 6.14, 1H, dd, *J* 2.0, 2.0 Hz, H10; 6.94, 1H, m, H7; 6.94, 1H, dd, *J* 5.0, 3.5 Hz, H3; 6.99, 1H, dd, *J* 3.5, 1.0 Hz, H4; 7.17, 1H, dd, *J* 5.0, 1.0 Hz, H2; 7.26, 1H, ddd, *J* 7.5, 8.0, 1.0 Hz, H18; 7.33, 1H, ddd, *J* 7.5, 8.0, 1.0 Hz, H17; 7.40, 1H, dd, *J* 8.0, 1.0 Hz, H16; 7.56, 1H, dd, *J* 8.0, 1.0 Hz, H19; 10.78, 1H, br s, 8-NH. (+)-LRESMS *m/z* 162 (100%) [M-C₇H₇N₁Cl₁]⁺, 303 (5%) [M+H, C₁₆H₁₆N₂S₁³⁵Cl₁]⁺, 305 (2%) [M+H, C₁₆H₁₆N₂S₁³⁷Cl₁]⁺, 464* (1%) [M+H, C₂₅H₂₃N₃S₂³⁵Cl₁]⁺ and 466* (< 1%) [M+H, C₂₅H₂₃N₃S₂³⁷Cl₁]⁺.

*Due to dialkylated compound.

1-[3'-([4''-(2'''-Thienyl)-1H-pyrrol-2''-yl]methyl)amino]propyl]-2-pyrrolidinone (13): Yellow-brown oil, 6.0 mg (58% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.57, 2H, tt, *J* 7.5, 7.0 Hz, H14;

1.88, 2H, tt, *J* 8.0, 7.5 Hz, H19; 2.17, 2H, t, *J* 8.0 Hz, H18; 2.44, 2H, t, *J* 7.0 Hz, H13; 3.19, 2H, t, *J* 7.5 Hz, H15; 3.29, 2H, t, *J* 7.5 Hz, H20; 3.58, 2H, s, H11; 6.09, 1H, dd, *J* 2.0, 2.0 Hz, H10; 6.92, 1H, dd, *J* 2.0, 2.0 Hz, H7; 6.94, 1H, dd, *J* 5.0, 3.5 Hz, H3; 6.98, 1H, dd, *J* 3.5, 1.0 Hz, H4; 7.17, 1H, dd, *J* 5.0, 1.0 Hz, H2; 10.71, 1H, br s, 8-NH. (+)-LRESMS *m/z* 143 (65%) [M-(C₉H₇N₁S₁)+H]⁺, 304 (10%) [M+H, C₁₆H₂₂N₃S₁O₁]⁺ and 465* (2%) [M+H, C₂₅H₂₉N₄S₂O₁]⁺.

*Due to dialkylated compound.

Synthesis of 9 and 15 using the Indirect Reductive Amination with NaBH(OAc)₃ in DCE

N-butylamine (31 μL, 340 μmol) was added to 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1, 6 mg, 34 μmol) in anhydrous DCE (500 μL) and the reaction was stirred at room temperature for 4 h. The excess amine and DCE were evaporated to dryness then resuspended in dry DCE and NaBH(OAc)₃ (28 mg, 132 μmol) was added. This solution was stirred at room temperature for 4 h. The solution was partitioned between DCM (1.5 mL) and 1N NaHCO₃ (3 × 2 mL). The organic phase was chromatographed on a silica packed SPE cartridge using a gradient from 100% DCM to 10% MeOH/90% DCM in 5% stepwise elutions. Pure *N*-{[4'-(2"-thienyl)-1*H*-pyrrol-2'-yl]methyl}-1-butanamine (9, 2.3 mg, 29% yield) eluted with the 10% MeOH/90% DCM wash, while the earlier 5% MeOH/95% DCM wash yield pure *N,N*-bis{[4'-(2"-thienyl)-1*H*-pyrrol-2'-yl]methyl}-1-butanamine (15, 3.2 mg, 24% yield) as a stable yellow oil. UV (MeOH) λ_{max} 204 (ε 19 000), 228 nm (sh, ε 13 000), 285 nm (ε 12 000). IR ν_{max} (NaCl) 3300-3000, 2958, 2871, 1654, 1559, 1457, 1301, 1119, 1023, 893, 840, 805, 691, 652 cm⁻¹. ¹H NMR (DMSO-*d*₆, 500 MHz) δ 0.80, 3H, t, *J* 7.5 Hz, H16; 1.23, 2H, tq, *J* 7.5, 7.5 Hz, H15; 1.41, 2H, tt, *J* 7.5, 7.5 Hz, H14; 2.32, 2H, t, *J* 7.5 Hz, H13; 3.50, 4H, s, H11; 6.15, 2H, s, H10; 6.95, 2H, dd, *J* 5.0, 3.5 Hz, H3; 6.98, 2H, dd, *J* 2.0, 2.0 Hz, H7; 7.01, 2H, dd, *J* 3.5, 1.0 Hz, H4; 7.17, 2H, dd, *J* 5.0, 1.0 Hz, H2; 10.71, 2H, br s, 8-NH. ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 13.9, C16;

20.0, C15; 28.4, C14; 50.1, 2C, C11; 51.8, C13; 105.2, 2C, C10; 114.1, 2C, C7; 117.3, 2C, C6; 120.0, 2C, C4; 121.0, 2C, C2; 127.5, 2C, C3; 130.2, 2C, C9; 140.0, 2C, C5. (+)-LRESMS m/z 162 (100%) $[M-C_{13}H_{17}N_2S_1]^+$, 235 (5%) $[M-(C_9H_7N_1S_1)+H]^+$ and 396 (5%) $[M+H, C_{22}H_{26}N_3S_2]^+$. (-)-HRESMS m/z 394.1411 (calc. for $C_{22}H_{24}N_3S_2$ $[M-H]^-$ 394.1417, Δ -1.5 ppm).

Synthesis of 9 using the Indirect Reductive Amination with NaBH₄ in EtOH.

N-butylamine (31 μ L, 340 μ mol) was added to 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1, 6 mg, 34 μ mol) in anhydrous DCE (500 μ L) and the reaction was stirred at room temperature for 4 h. The organic solvent was evaporated to dryness and NaBH₄ (2.6 mg, 68 μ mol) in 99% EtOH (500 μ L) was added and the mixture was stirred at room temperature for 1 h. The solution was partitioned between DCM (1.5 mL) and 1N NaHCO₃ (3 $\times$ 2 mL). The organic phase was evaporated to yield pure *N*-{[4'-(2''-thienyl)-1*H*-pyrrol-2'-yl]methyl}-1-butanamine (9, 7.8 mg, 98% yield) as a pale yellow oil. UV (MeOH) λ_{max} 205 (ϵ 28 000), 231 nm (sh, ϵ 23 000), 289 nm (ϵ 23 000). IR ν_{max} (NaCl) 3300-2900, 2957, 2870, 1689, 1590, 1548, 1432, 1361, 1301, 1264, 1119, 1080, 1047, 1022, 892, 840, 804, 735, 690 cm⁻¹. ¹H NMR (DMSO-*d*₆, 500 MHz) δ 0.85, 3H, t, *J* 7.0 Hz, H16; 1.30, 2H, tq, *J* 7.0, 7.5 Hz, H15; 1.38, 2H, tt, *J* 7.0, 7.5 Hz, H14; 2.46, 2H, t, *J* 7.0 Hz, H13; 3.57, 2H, s, H11; 6.08, 1H, s, H10; 6.91, 1H, s H7; 6.94, 1H, dd, *J* 5.0, 3.5 Hz, H3; 6.98, 1H, dd, *J* 3.5, 1.0 Hz, H4; 7.16, 1H, dd, *J* 5.0, 1.0 Hz, H2; 10.72, 1H, br s, 8-NH. ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 13.8, C16; 19.9, C15; 31.6, C14; 48.2, C13; 45.7, C11; 104.2, C10; 113.7, C7; 117.1, C6; 119.9, C4; 121.0, C2; 127.5, C3; 132.5, C9; 140.1, C5. (+)-LRESMS m/z 162 (100%) $[M-C_4H_{10}N_1]^+$ and 235 (5%) $[M+H, C_{13}H_{19}N_2S_1]^+$. (-)-HRESMS m/z 233.1115 (calc. for $C_{13}H_{17}N_2S_1$ $[M-H]^-$ 233.1118, Δ -1.3 ppm).

Synthesis of 9 Using a Direct Reductive Amination Method with AcOH.

AcOH (4.0 μ L, 68 μ mol), *n*-butylamine (6.2 μ L, 68 μ mol) and NaBH(OAc)₃ (14 mg, 68 μ mol) were added to 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1, 6 mg, 34 μ mol) in anhydrous DCE (500 μ L) and the reaction was stirred at room temperature for 4 h. The solution was partitioned between DCM (1.5 mL) and 1N NaHCO₃ (3 $\times$ 2 mL). The organic phase was evaporated to dryness to yield a 1:11 mix of *N,N*-bis{[4-(2-thienyl)-1*H*-pyrrol-2-yl]methyl}-1-butanamine (15) and *N*-{[4'-(2''-thienyl)-1*H*-pyrrol-2'-yl]methyl}-1-butanamine (9).

General Procedure for Imine Synthesis

The relevant primary amine (339 μ mol) was added to 4-(2'-thienyl)-1*H*-pyrrole-2-carbaldehyde (1, 6 mg, 33.9 μ mol) in anhydrous DCE (500 μ L) and the reaction was stirred at room temperature for 4 h. The DCE was evaporated under N₂ then DCM (1 mL) was added and evaporated. This resuspension and evaporation process was repeated twice, to yield the pure imine.

N-{(E)-[4'-(2''-Thienyl)-1*H*-pyrrol-2'-yl]methylidene}-1-butanamine (14). Pale yellow oil, 7.7 mg (97% yield). UV (MeOH) λ_{max} 202 (ϵ 3 000), 259 (ϵ 2 000), 297 nm (ϵ 2 000). IR ν_{max} (NaCl) 3200-3000, 2957, 2929, 2871, 1641, 1453, 1397, 1138, 1080, 1020, 973, 893, 841, 809, 690 cm⁻¹. ¹H NMR (DMSO-*d*₆, 500 MHz) δ 0.89, 3H, t, *J* 7.0 Hz, H16; 1.31, 2H, tq, *J* 7.0, 7.0 Hz, H15; 1.56, 2H, tt, *J* 7.0, 7.0 Hz, H14; 3.47, 2H, t, *J* 7.0 Hz, H13; 6.64, 1H, d, *J* 1.0 Hz, H10; 6.98, 1H, dd, *J* 5.0, 3.5 Hz, H3; 7.11, 1H, dd, *J* 3.5, 1.0 Hz, H4; 7.15, 1H, d, *J* 1.0 Hz, H7; 7.25, 1H, dd, *J* 5.0, 1.0 Hz, H2; 8.06, 1H, s, H11; 11.53, 1H, br s, 8-NH. ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 13.7, C16; 19.8, C15; 32.8, C14; 59.9, C13; 110.4, C10; 118.7, 2C, C6, C7; 121.0, C4; 122.0, C2; 127.7, C3; 130.9, C9; 138.6, C5; 151.2, C11. (+)-LRESMS *m/z* 150 (55%) [(M-C₅H₉N₁)+H]⁺, 177 (10%) [(M-C₄H₈)+H]⁺ and 233

(100%) $[M+H, C_{13}H_{17}N_2S_1]^+$. (+)-HRESMS m/z 233.1105 (calc. for $C_{13}H_{17}N_2S_1 [M+H]^+$ 233.1107, Δ - 0.9 ppm).

N-{(E)-[4'-(2''-Thienyl)-1H-pyrrol-2'-yl]methylidene}-1-propanamine (16). Pale yellow oil, 5.4 mg (73% yield). 1H NMR (DMSO- d_6 , 500 MHz) δ 0.88, 3H, t, J 7.5 Hz, H15; 1.60, 2H, tq, J 7.0, 7.5 Hz, H14; 3.44, 1H, t, J 7.0 Hz, H13; 6.65, 1H, d, J 1.5 Hz, H10; 6.99, 1H, dd, J 5.0, 3.5 Hz, H3; 7.12, 1H, dd, J 3.5, 1.0 Hz, H4; 7.15, 1H, d, J 1.5 Hz, H7; 7.25, 1H, dd, J 5.0, 1.0 Hz, H2; 8.06, 1H, s, H11; 11.54, 1H, br s, 8-NH. (+)-LRESMS m/z 150 (90%) $[(M-C_4H_7N_1)+H]^+$, 177 (15%) $[(M-C_3H_6)+H]^+$ and 219 (100%) $[M+H, C_{13}H_{17}N_2S_1]^+$.

N-{(E)-[4'-(2''-thienyl)-1H-pyrrol-2'-yl]methylidene}-2-butanamine (17). Pale yellow oil, 6.2 mg (78% yield). 1H NMR (DMSO- d_6 , 500 MHz) δ 0.79, 3H, t, J 7.8 Hz, H15; 1.15, 3H, d, J 6.0 Hz, H16; 1.50, 2H, m, H14; 3.11, 1H, tq, J 6.0, 6.0 Hz, H13; 6.64, 1H, d, J 1.2 Hz, H10; 6.98, 1H, dd, J 5.4, 3.6 Hz, H3; 7.11, 1H, dd, J 3.6, 0.6 Hz, H4; 7.15, 1H, d, J 1.2 Hz, H7; 7.24, 1H, dd, J 5.4, 0.6 Hz, H2; 8.05, 1H, s, H11; 11.51, 1H, br s, 8-NH. (+)-LRESMS m/z 150 (40%) $[(M-C_5H_9N_1)+H]^+$, 177 (70%) $[(M-C_4H_8)+H]^+$ and 233 (100%) $[M+H, C_{13}H_{17}N_2S_1]^+$.

N-{(E)-2-methoxyethyl}-N-{(E)-[4'-(2''-thienyl)-1H-pyrrol-2'-yl]methylidene}amine (18). Pale yellow oil, 7.0 mg (89% yield). 1H NMR (DMSO- d_6 , 500 MHz) δ 3.24, 3H, s, H16; 3.55, 2H, t, J 5.4 Hz, H14; 3.63, 2H, t, J 5.4 Hz, H13; 6.66, 1H, d, J 1.2 Hz, H10; 6.99, 1H, dd, J 5.4, 3.6 Hz, H3; 7.12, 1H, dd, J 3.6, 0.6 Hz, H4; 7.16, 1H, d, J 1.2 Hz, H7; 7.25, 1H, dd, J 5.4, 0.6 Hz, H2; 8.05, 1H, s, H11; 11.57, 1H, br s, 8-NH. (+)-LRESMS m/z 150 (75%) $[(M-C_4H_7N_1O_1)+H]^+$, 177 (15%) $[(M-C_3H_6O_1)+H]^+$ and 235 (100%) $[M+H, C_{12}H_{15}N_2O_1S_1]^+$.

N-{(E)-[4'-(2''-thienyl)-1H-pyrrol-2'-yl]methylidene}-2-propanamine (19). Pale yellow oil, 6.7 mg (91% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ 1.16, 6H, t, J 6.5 Hz, H14; 3.44, 1H, qq, J 6.5, 6.5 Hz, H13; 6.63, 1H, d, J 1.0 Hz, H10; 6.98, 1H, dd, J 5.0, 3.5 Hz, H3; 7.11, 1H, dd, J 3.5, 1.0 Hz, H4; 7.14, 1H, d, J 1.0 Hz, H7; 7.24, 1H, dd, J 5.0, 1.0 Hz, H2; 8.08, 1H, s, H11; 11.50, 1H, br s, 8-NH. (+)-LRESMS m/z 150 (60%) [(M-C₄H₇N₁)+H]⁺, 177 (50%) [(M-C₃H₆)+H]⁺ and 219 (100%) [M+H, C₁₂H₁₅N₂S₁]⁺.

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Table 1. Relative ratio of mono to dialkylated amine for samples (10-13).

Sample	monoalkylated:dialkylated
(10)	23:1
(11)	28:1
(12)	15:1
(13)	25:1

Table 2. Relative ratio of imine to aldehyde for samples (14, 16-19).

Sample	imine:aldehyde
(14)	12:1
(16)	4:1
(17)	2:1
(18)	4:1
(19)	2:1

Scheme 1^a

^aReagents and conditions.

(i) $(\text{Ph}_3\text{P})_4\text{Pd}(0)$, Na_2CO_3 , DME: H_2O (4:1), 85 °C, 16 h, Ar (1, 78%).

(ii) $(\text{Ph}_3\text{P})_4\text{Pd}(0)$, Na_2CO_3 , DME: H_2O (4:1), 100 °C, 16 h, Ar (2, 23%).

Scheme 2^a

^aReagents and conditions.

(i) DCE, $\text{NaBH}(\text{OAc})_3$, rt, 4 h, N_2 (4, 88%).

(ii) THF, $\text{NaBH}(\text{OAc})_3$, rt, 4 h, N_2 (4, 65%).

(iii) CH_3CN , $\text{NaBH}(\text{OAc})_3$, rt, 4 h, N_2 (4, 79%).

Scheme 3^a

^aReagents and conditions.

(i) DCE, rt, 4 h, N_2 (14, 97%).

Scheme 4^a

^aReagents and conditions.

(i) DCE, $\text{NaBH}(\text{OAc})_3$, rt, 4 h, N_2 (9, 29%; 15, 24%).

(ii) EtOH, NaBH_4 , rt, 1 h, N_2 (9, 98%).

Figure 1. The biaryl carbaldehyde templates (1-3).

Figure 2. The synthesised amine library.

Figure 3. The synthesised imine library.