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# Fischer synthesis of isomeric thienopyrrole LHRH antagonists

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ABSTRACT

As part of a structure–activity exploration into LHRH antagonists, structures containing the thieno[2,3-*b*]pyrrole core were identified as potent antagonists. This letter describes the employment of the *Fischer* synthesis to access this thienopyrrole and isomeric final compounds.



## 1. Introduction

*Zoladex* is currently the standard for the treatment of hormone dependant prostrate cancer.[1] *Zoldex* is a decapeptidic agonist that binds to the gonadotropin-releasing hormone (GnRH) or leutenizing-hormone receptor (LHRH).[2] Agonism of the receptor produces a transient increase in the level of serum testosterone leading to tumour flare, which lasts for around one week before the receptors are down-regulated and the tumour starts to shrink.[3] We became interested in searching for a pure LHRH antagonist to avoid this flare effect. Recently, peptidic LHRH antagonists have achieved clinical success[4] and a series of orally active non-peptidic antagonists having good bioavailability have been discovered.[5]

In a previous paper, we communicated the identification and synthesis of a novel class of GnRH antagonists based on the thieno[2,3-*b*]pyrrole core (Scheme 1).[6] From the docking studies and the structure–activity relationships established,[6] we were positive the C-2 substituted thieno[2,3-*b*]pyrrole isomer was the most valid scaffold. However, in order to defend our claims, the remaining isomeric final compounds had to be synthesised and tested. Minimum energy representations of three of the isomers were overlayed with **1** to see what would be the best fit scenario. From Figure 1, the best 2D overlay with both stable conformers of **1** is observed with **3**. Although one can argue the closest fit scenario of **1** with **2** and **4** was far from ideal because the key lipophilic amide side chain, key for activity, clearly occupies a different zone in the receptor, we decided to engage their syntheses in order to confirm the hypothesis.

## 2. Results and discussion

In medicinal chemistry, thienopyrroles are important and common isosteric replacements of indoles.[7] Similarly, in synthesis, recognised routes towards thienopyrroles use ring construction methodology borrowed from indole pioneers such as *Fischer*,[8] *Larock*[9] and others.[10] We needed an efficient route to access large quantities of thieno[2,3-*b*]pyrrole skeleton **10**, a precursor affording two key diversity points to develop structure–activity relationships of the GnRH receptor. After quickly comparing the major options, we chose to focus our efforts on the *Fischer* synthesis of thienopyrroles, which would offer the quickest route to **10**, first reported by Binder et al. using a 10-fold excess of ketone in acetic acid at reflux.[11]

The synthesis of **1** started from ethyl thiophene-2-acetate. Alkylation with an excess of iodomethane in the presence of NaH afforded **5**. Regioselective nitration at C-2 using nitronium tetrafluoroborate followed by reduction to the amine by catalytic hydrogenation and protection of the resulting amine with di-*tert*-butyl dicarbonate (Boc-*O*-Boc) afforded **7**. The resulting carbamate **7** was deprotonated and successfully aminated with either *O*-(4-nitrobenzoyl)-hydroxylamine,[11] *O*-(2,4-dinitrophenyl)-hydroxylamine,[12] or *O*-(diphenylphosphinyl)-hydroxylamine.[13,14] There are no *Fischer* cyclisations[11,15] reported with λ-ketoalcohols. After extensive process

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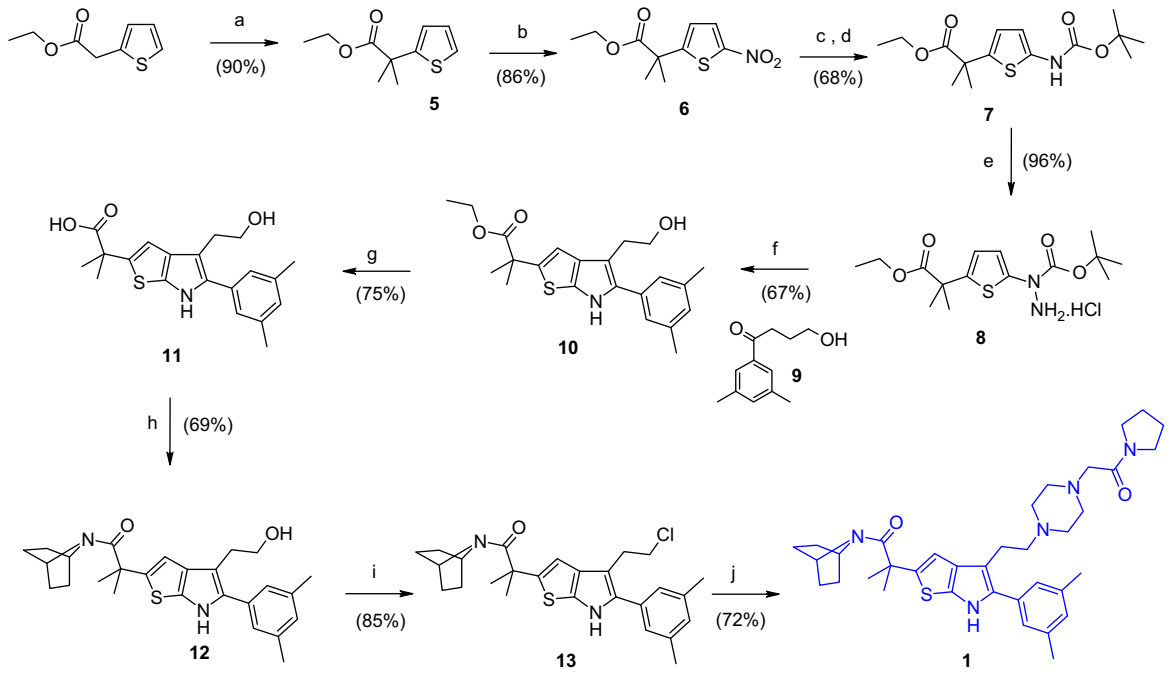



**Scheme 1.** Preparation of the [3,2-*b*]thieonpyrrole isomer. Conditions: (a) MeI, NaH, THF; (b) $NO_2BF_4$, DME, −55 °C to rt; (c) $H_2$, Pd–C, EtOH/EtOAc, rt, 5 h; (d) $(Boc)_2O$, THF, 70 °C; (e) NaH, *O*-(4-nitrobenzoyl)hydroxylamine, DMF, 0 °C to rt; (f) $ZnCl_2$, *s*-BuOH, 120 °C; (g) NaOH, EtOH, 60 °C; (h) 7-azanorbornane·HCl, DIPEA, HATU, DCM; (i) $SOCl_2$, cat. Py, DCM, 0 °C to rt; (j) *N*-(2-(1-piperazino)-acetyl)-pyrrolidine, DMF, 100 °C.

optimisation evaluating many common Bronsted and Lewis Acid catalysed conditions, we found the combination of a soft azaphilic Lewis acid, in zinc chloride in the presence of a hindered alcohol permitted cyclisation of **9** to afford a respectable 60–70% yield of the key hydroxy ester unit (**10**). Saponification of the ethyl ester followed by amide coupling under basic conditions with 7-azanorbonane,[16] made from *trans*-4-aminocyclohexanol in three steps without chromatography,[17] afforded the amide **12**. Transformation of the alcohol to the corresponding chloride was achieved using thionyl chloride and pyridine as the activating agent avoiding the using of DMF known to be responsible for the generation of unacceptable levels of the potent carcinogen, dimethylcarbamoyl chloride (DMCC).[18] Displacement of the chloride was achieved using an excess of the commercially available *N*-(2-(1-piperazino)-acetyl)-pyrrolidine to give the final compound **1** (Scheme 1).

We decided to retain the *Fischer* approach for the remaining five isomers. Consequently, in essence, the whole synthetic strategy relied upon accessing the appropriately substituted α- and β-hydrazinothiophenes. Literature precedent strongly suggested the use of bromine atoms as latent protecting groups for the reactive α-positions of the thiophene ring facilitating nitration at the least reactive β-positions.[19]

The synthesis of the C-3 substituted thieno[2,3-*b*]pyrrole isomer was straightforward using similar chemistry as previously described for the lead C-2 substituted thieno[2,3-*b*]pyrrole isomer. Carrying out the alkylation of the ester before nitrating proved key. The steric

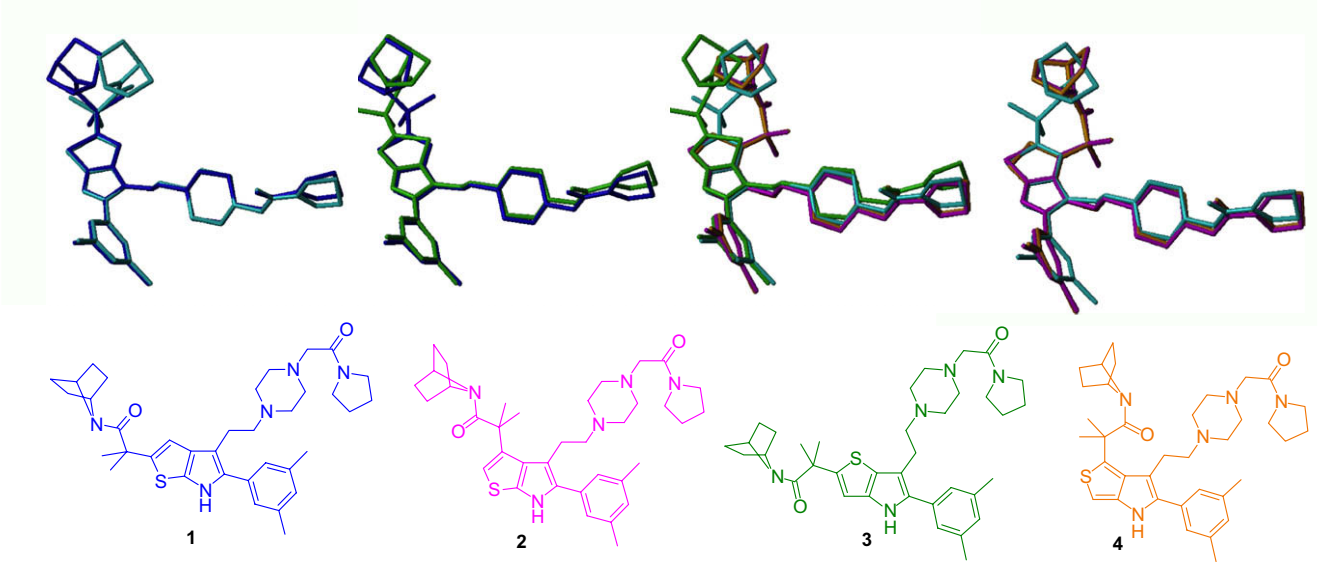
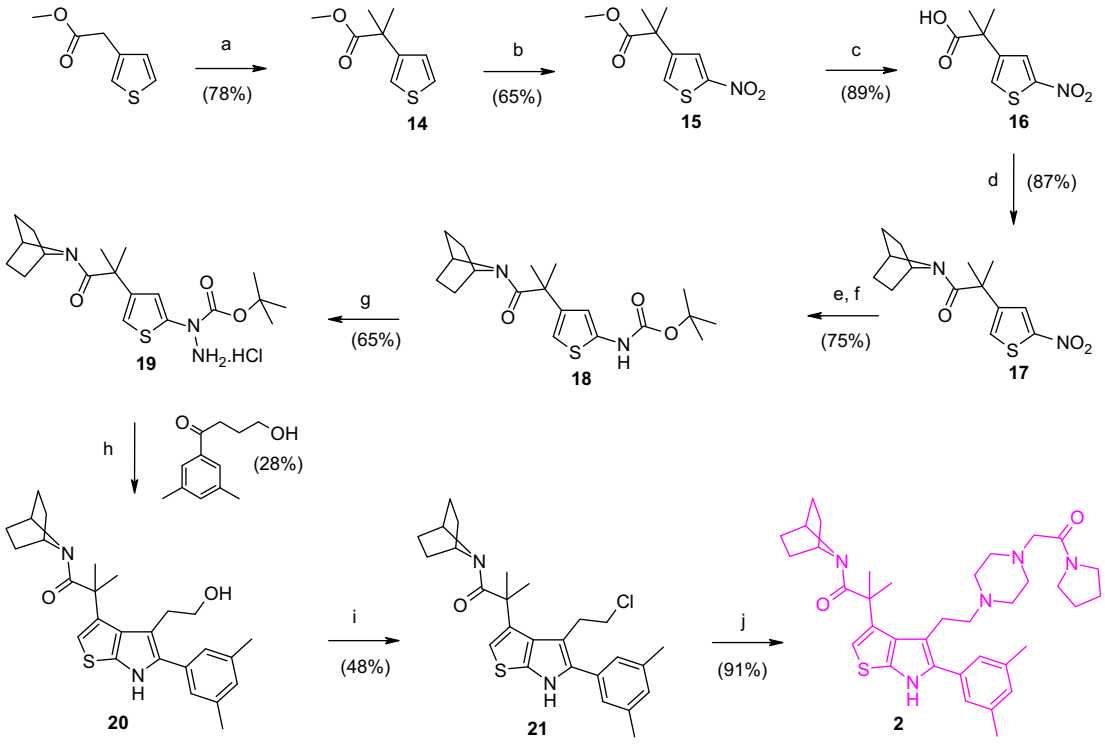
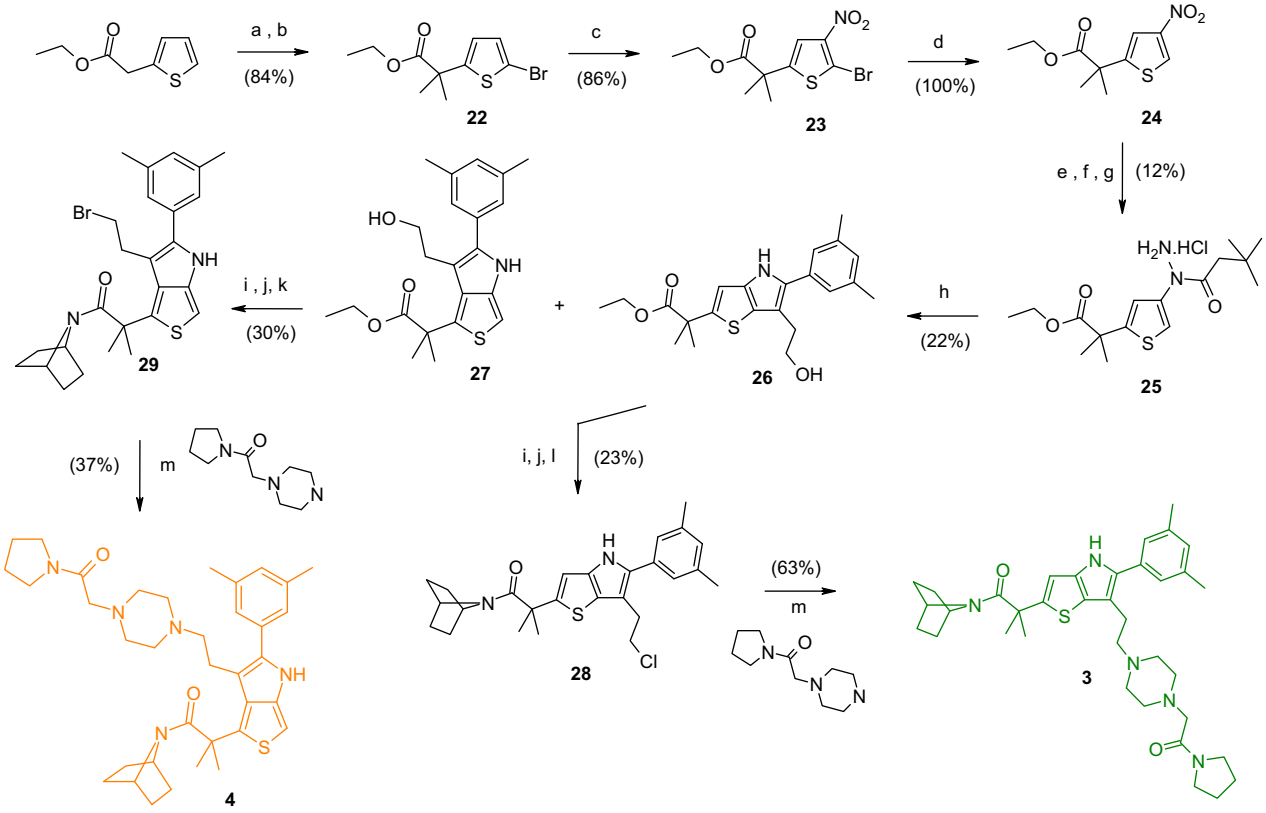



**Figure 1.** Minimum energy structural representations of *thienopyrrole isomers* **1** (blue), **2** (magenta), **3** (green) and **4** (orange); (a) overlay of the two stable conformers of **1**; (b) best fit overlay of **3** and **1** (conformer A); (c) best fit overlay of **2** and **4** with **1** (conformer B); (d) structural overlay of **1** (conformer B), **2**, **3** and **4**.




**Scheme 2.** Preparation of the [3,2-*b*]thienopyrrole isomer. Conditions: (a) MeI, NaH, THF; (b) $NO_2BF_4$, DME, −55 °C to rt; (c) NaOH, EtOH, 60 °C; (d) 7-azanorbornane·HCl, DIPEA, TBTU, DCM; (e) $H_2$, Pd–C, EtOH/EtOAc, rt, 5 h; (f) $(Boc)_2O$, THF, 70 °C; (g) NaH, *O*-(4-nitrobenzoyl)hydroxylamine, DMF, 0 °C to rt; (h) $ZnCl_2$, *s*-BuOH, 120 °C; (i) $SOCl_2$, cat. Py, DCM, 0 °C to rt; (j) *N*-(2-(1-piperazino)-acetyl)-pyrrolidine, DMF, 100 °C.



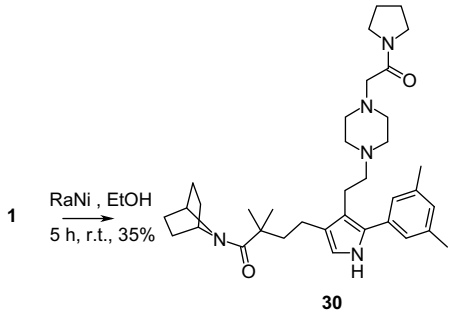

**Scheme 3.** Conditions: (a) MeI, NaH, THF; (b) NBS, THF, 0 °C to rt; (c) $NO_2BF_4$, DCM, 0 °C to rt; (d) (EtO)P(O)–H, TEA, 0 °C to rt; (e) $H_2$, Pd–C, EtOH/EtOAc, rt, 5 h; (f) $(Boc)_2O$, THF, 70 °C; (g) NaH, *O*-(4-nitrobenzoyl)hydroxylamine, DMF, 0 °C to rt; (h) $ZnCl_2$, *s*-BuOH, 120 °C; (i) NaOH, EtOH, 70 °C; (j) 7-azanorbornane·HCl, DIPEA, TBTU, DCM; (k) TPP, $CBr_4$, MeCN, 60 °C; (l) $SOCl_2$, cat. Py, DCM, 0 °C to rt; (m) *N*-(2-(1-piperazino)-acetyl)-pyrrolidine, DMF, 100 °C.

hindrance offered by the bulky pivalate side chain was sufficient to block entirely the other reactive α-position, affording **15** in excellent yield (Scheme 2). Transformation to the hydrazine was achieved using conditions already discussed. *Fischer* cyclisation of the resulting hydrazine was much more sluggish than with **9**. We postulate exposure of the reactive α-position during these harsh thermal conditions lead to degradation of the thiophene hydrazine intermediate before cyclisation. Nonetheless, the desired thieno[2,3-*b*]pyrrole **20** was isolated and transformed to **2** in acceptable yield using standard functional group chemistry (Scheme 2).

The thieno[3,2-*b*]pyrrole and [3,4-*b*]isomers were synthesised from the same thiophene hydrazine requiring the use of a bromine α-blocker. Bromination of ethyl 2-thiopheneacetate was carried out at room temperature affording a quantitative yield of the α-protected thiophene **22**. Nitration of **22** at C-3 with nitronium tetrafluoroborate in 50 volumes of dichloromethane afforded regioselectively **23** in excellent yield. The total regioselectivity could be explained by the positive mesomeric influence of the C-2–Br that stabilises the positive charge on sulfur resulting from electrophilic attack, despite the weakly positive inductive effect of the acetate at C-5. Many attempts (e.g., Zn, AcOH;[20] $H_2$, Pd–C[21]) were made aiming at a direct one-pot conversion of the 2-bromo-3-nitrothiophene (**23**) to the corresponding 3-aminothiophene but in all cases little or no product was observed. Splitting the reaction into two steps proved essential to access **25**. A rare employment of a stoichiometric quantity of diethylphosphonate anion permitted quantitative debromination of **23** to the corresponding C3-nitrothiophene **24**; subsequent reduction, protection and amination afforded the C-3 hydrazine **25** in acceptable overall yield. The use of the DEP anion for aromatic dehalogenations has been reported in the past on an activated thiophene example but using a 50-fold excess of diethylphosphonate and triethylamine.[22] As a synthetic tool for selective de-halogenations, we believe these conditions present a convenient alternative to more commonly used methodology. *Fischer* cyclisation afforded, in equal proportion, the two isomers **26** and **27** in poor yields. Transformation to final compounds **3** and **4** was achieved using standard functional group chemistry as already discussed. The only difference being in the case of the [3,4-*b*]isomer (**4**), whereby bromide **29** had to be prepared (TPP, $CBr_4$, MeCN, 60 °C) as alcohol **27** decomposed rapidly in the presence of thionyl chloride (Scheme 3).

Attempts to synthesise the remaining isomers having the ester side chain *ortho* to the hydrazine moiety by employing the *Fischer* process failed due to intramolecular cyclisation of the carbonyl function onto the hydrazine affording stable carbazates. Molecular-modelling studies suggested these isomers would be the least interesting to pursue so we abandoned their synthesis.

At the same time, we also managed to selectively desulfurise a selection of thieno[2,3-*b*]pyrrole final products to their pyrrole analogues using an excess of Raney® nickel in EtOH under nitrogen.[23] In fact, there is enough active hydrogen already on the catalyst to effect this reaction thus avoiding the necessity of putting the reaction mixture under high pressures of hydrogen (Scheme 4).




**Scheme 4.** Desuflurisation of thienopyrroles to pyrroles.

**Table 1**
Comparative in vitro assay of final compounds assessed in a competition assay for [$^{125}$I]-D-Trp$^6$ GnRH radioligand binding to rat and human receptors[24]

| Cpd | Rat (nM) | Human (nM) | Cell (nM) |
|---|---|---|---|
| **1** | 50 | 144 | 67 |
| **2** | 430 | 2260 | 675 |
| **3** | 287 | 1860 | 158 |
| **4** | 6090 | N/A | 73 |
| **30** | 99 | 263 | 403 |

The cell activity was determined by inhibition of GnRH-stimulated LH release in isolated primary pituitary cells.[25]

Selected in vitro results for the isomeric thienopyrrole isomers synthesised and the pyrrole analogue of **1** can be seen in Table 1. Our initial 2D overlay studies were backed up by the in vitro assay results. The best fit isomer (**3**) was the most active followed by the other [2,3-*b*]isomer (**2**) with the amide side chain at C-3. The [3,4-*b*]isomer (**4**) was completely inactive but the pyrrole analogue (**30**) had an acceptable activity and, having eliminated the sulfur atom, had much improved physical properties.

## 3. Conclusion

In conclusion, we have developed efficient syntheses of highly substituted thienopyrroles using optimised *Fischer* protocol for γ-ketoalcohols and shown that the C-2 substituted thieno[2,3-*b*]-pyrroles are probably the most active isomers in this class of GnRH antagonists.

## 4. Experimental

### 4.1. General methods

$^1$H NMR spectra were recorded on a BRUKER Biospin AVANCE 500 spectrometer. Chemical shifts are reported as $\delta$ values downfield from internal TMS in appropriate organic solutions. The purity and the structures of the products were confirmed by LCMS (254 nm) on a Waters 2690 photodiode array detector system using the following conditions: Column, Symmetry C-18; Solvent A, water 0.1% formic acid; Solvent B, $CH_3CN$; flow rate, 2.5 mL/min; run time, 4.5 min; gradient, from 0 to 100% solvent B; mass detector, micro mass ZMD. All strength measurements are carried out as follows: to a 2 mL vial, is added precisely ca. 10 mg of the compound and maleic acid (2 mg), the reference compound, and the resulting mixture is dissolved in a mixture of DMSO-$d_6$ (0.55 mL) and $CD_3COOD$ (five drops). The mixture can be warmed if necessary to obtain a complete dissolution. A proton spectrum is recorded with a long pulse delay (8 s) in order to obtain a quantitative measurement. Strength by $^1$H NMR is calculated using the formula below:

$$Strength = \frac{Ic \times wr \times Mc \times nHr}{Ir \times wc \times Mr \times nHc} \times PR$$

where: $I$=integration; $w$=weight; $M$=molecular weight; $n$=number of proton in the studied signal; $c$=compound; $r$=reference; $PR$=reference purity.

### 4.2. Preparation of the electrophilic aminating agents

#### 4.2.1. *O*-(4-Nitrobenzoyl)hydroxylamine

*4.2.1.1. tert-Butyl hydroxycarbamate.* To a stirred solution of hydroxylamine (50% v/v in water, 120 mL, 2.04 M) in methanol (250 mL) at −5 °C (acetone/ice), was added a solution of di-*tert*-butyl dicarbonate (200 g, 916 mmol) in methanol (1 L) over

a period of 1 h [CAUTION: EXOTHERMIC]. The resulting clear, colourless solution was allowed to warm to room temperature and stirred for a further 1 h. The methanol was removed by rotary evaporation and the resulting residue was chilled to 0 °C and the pH adjusted to 3 using a saturated aqueous solution of citric acid. The mixture was extracted with ethyl acetate (3×500 mL). The combined organic phases were washed with water (5×25 mL), dried over magnesium sulfate and concentrated to afford the crude product as a white crystalline solid. The solid was suspended in pentane, collected by filtration and dried to a constant weight under vacuum to afford *tert*-butyl hydroxycarbamate (89.1 g, 73%) as a white crystalline solid, which was used without further purification: $^1$H NMR (DMSO-$d_6$) $\delta$ 1.44 (s, 9H), 8.45 (s, 1H), 9.26 (br s, 1H); strength determined by $^1$H NMR (DMSO-$d_6$)=99%±3% w/w.

*4.2.1.2. tert-Butyl [(4-nitrobenzoyl)oxy]carbamate.* In two separate batches: to a stirred suspension of 4-nitrobenzoic acid (50.0 g, 300 mmol) and *tert*-butyl hydroxycarbmate (40.0 g, 300 mmol) in dichloromethane (2 L), was added dimethylaminopyridinium tosylate[26] and the suspension was cooled to −10 °C (acetone/ice). Diisopropylcarbodiimide (62.0 mL, 390 mmol) was added dropwise over a period of 1 h, ensuring that the internal temperature did not exceed −5 °C. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for a further 2 h. The resulting suspension was filtered, the filtrate was concentrated and the residue purified by flash chromatography on silica gel eluting with pure dichloromethane to afford the title compound as a white solid (59.5 g, 74%). $^1$H NMR (DMSO-$d_6$) $\delta$ 1.42 (s, 9H), 8.27 (d, $J$=8.8 Hz, 2H), 8.41 (d $J$=8.8 Hz, 2H).

*4.2.1.3. O-(4-Nitrobenzoyl)hydroxylamine hydrochloride.* To a stirred solution of *tert*-butyl [(4-nitrobenzoyl)oxy]carbamate (109 g, 408 mmol) dissolved in nitromethane (750 mL) was bubbled anhydrous hydrogen chloride gas for 30 min under mechanical agitation. After 2 h, the resulting thick, white precipitate was collected by filtration, washed with nitromethane (5×20 mL), diethyl ether (5×20 mL) and dried to a constant weight in a vacuum oven at 40 °C to afford the title compound (73.2 g, 82%) as a white solid. $^1$H NMR (DMSO-$d_6$) $\delta$ 7.15, 7.28, 7.40 (ammonium protons, 3H), 8.32 (d, $J$=8.7 Hz, 2H), 8.39 (d $J$=8.7 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 124.1, 131.1, 136.9, 150.4, 166.2.

*4.2.1.4. O-(4-Nitrobenzoyl)hydroxylamine.* To a stirred saturated aqueous solution of sodium hydrogen carbonate (825 mL) at 0–5 °C, was added portionwise solid *O*-(4-nitrobenzoyl)hydroxylamine hydrochloride (82.0 g, 376 mmol) over a period of 2 h. The solid changed physical form during the neutralisation process. After a further 2 h of agitation, the suspension was extracted with dichloromethane (3×500 mL). The combined organic phases were washed with water (5×25 mL), dried over magnesium sulfate and concentrated to afford *O*-(4-nitrobenzoyl)hydroxylamine (64.2 g, 93%) as an off-white solid. $^1$H NMR (DMSO-$d_6$) $\delta$ 6.14 (br s, 2H), 8.18 (d, $J$=9.0 Hz, 2H), 8.37 (d, $J$=9.0 Hz, 2H); strength determined by $^1$H NMR=99%±3% w/w.

*4.2.2. O-(2,4-Dinitrophenyl)hydroxylamine*

To a stirred solution of potassium hydroxide (5.6 g, 100 mmol) in EtOH (200 mL) at 0 °C, was added successively *tert*-butyl hydroxycarbamate (13.3 g, 100 mmol) and 2,4-dinitrofluorobenzene (18.7 g, 100 mmol). The reaction mixture was stirred at 0 °C for 3 h. Trifluoroacetic acid (30 mL) was added over a period of 10 min and the resulting solution was diluted with EtOAc (500 mL) and water (50 mL). The organic phase was washed with a saturated aqueous solution of brine (1×50 mL), dried over magnesium sulfate and concentrated to afford the crude product as a pale orange gum. The crude product was purified by flash chromatography on silica gel eluting with 5–25% ethyl acetate in petroleum ether. The solvent was evaporated to dryness to afford *O*-(2,4-dinitrophenyl)hydroxylamine (6.7 g, 34%) as an orange solid. $^1$H NMR ($CDCl_3$) $\delta$ 6.44 (br s, 2H), 8.06 (d, $J$=9.0 Hz, 1H), 8.43 (dd, $J$=9.0 Hz, $J'$=3.0 Hz, 2H), 8.82 (d, $J$=3.0 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 122.8, 123.5, 129.0, 134.1, 136.7, 163.2; strength determined by $^1$H NMR=94%±3% w/w.

*4.2.3. O-(Diphenylphosphinyl)hydroxylamine*

To a stirred 6.6 M aqueous solution of hydroxylamine hydrochloride (104 mL, 685 mmol) at 0 °C, was added a solution of sodium hydroxide (7.1 M, 82 mL, 580 mmol). 1,4-Dioxane (330 mL) was added and the solution was stirred at 0 °C for 20 min. A solution of diphenylphosphinic chloride (59.0 g, 250 mmol) in dioxane (250 mL) was added over a period of 5 min affording a white precipitate. The resulting suspension was stirred for 30 min and the solid was collected by filtration. The solid was subsequently suspended in a solution of sodium hydroxide (0.25 M, 250 mL) and stirred for a further 30 min. The white solid was collected by filtration, washed with water (5×20 mL) and dried to a constant weight in a vacuum oven at 40 °C to afford *O*-(diphenylphosphinyl)hydroxylamine (27.1 g, 47%) as a white solid. $^1$H NMR (DMSO-$d_6$) $\delta$ 6.16 (br s, 2H), 7.45 (m, 6H), 7.72 (m, 4H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 128.6 (d, $J^P$=12.4 Hz), 131.3 (d, $J^P$=9.7 Hz), 131.3 (d, $J^P$=2.2 Hz), 136.5 (d, $J^{P-C}$=133.6 Hz); strength determined by $^1$H NMR=91%±3% w/w.

## 4.3. Preparation of key building blocks

*4.3.1. 7-Azabicyclo[2.2.1]heptane or 7-azanorbornane·HCl*

*4.3.1.1. (trans-4-Hydroxycyclohexyl)-4-methylbenzene sulfonamide.* To a stirred suspension of *trans*-4-aminocyclohexanol (300 g, 1.98 mol) in isopropanol (3.5 L) at 0 °C was added triethylamine (1.1 L, 7.92 mol) followed by solid *p*-toluenesulfonyl chloride (377 g, 198 mmol) over a period of 30 min. The reaction mixture was heated at 60 °C for 2 h after which HPLC showed no remaining starting material. The resulting suspension was cooled to room temperature and the precipitate of triethylamine hydrochloride removed by filtration. The filtrate was evaporated to dryness on a rotary evaporator to afford a colourless oil, which was dissolved in ethyl acetate (3 L), washed with 0.5 N HCl (800 mL), water (1.5 L) and dried over $MgSO_4$. The solvent was evaporated on a rotary evaporator to afford *N*-(*trans*-4-hydroxycyclohexyl)-4-methylbenzenesulfonamide (456.5 g, 86%) a white crystalline solid: LCMS ($t_R$=2.02 min, purity=100%), ESI$^+$ $m/z$ 270.12 $(M+H)^+$; $^1$H NMR (DMSO-$d_6$) $\delta$ 0.95–1.20 (m, 4H), 1.52–1.61 (m, 2H), 1.64–1.73 (m, 2H), 2.40 (s, 3H), 2.79–2.90 (m, 1H), 3.20–3.43 (m partially hidden by $H_2O$, 1H), 4.47 (d, $J$=4.4 Hz, 1H), 7.38 (d, $J$=8.1 Hz, 2H), 7.53 (d, $J$=7.0 Hz, 1H), 7.68 (d, $J$=8.1 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.3, 31.3, 33.9, 52.0, 67.9, 126.6, 129.9, 139.6, 142.6.

*4.3.1.2. 7-[(4-Methylphenyl)sulfonyl]-7-azabicyclo[2.2.1]heptane.* To a stirred solution of *N*-(*trans*-4-hydroxycyclohexyl)-4-methylbenzenesulfonamide (600 g, 2.23 mol) in THF (2 L) at −10 °C in an ice/acetone bath, was added triphenylphosphine (700 g, 2.67 mol) followed by di-*tert*-butylazadicarboxylate (DTBAD) (564 g, 2.45 mmol) in THF (1.5 L) over a period of 1.5 h maintaining the internal temperature below 10 °C. The ice/acetone bath was removed and reaction mixture was allowed to warm to room temperature over a period of 1.5 h after which HPLC showed no remaining starting material. The reaction mixture was evaporated to dryness and the residue was crystallised from hot MeOH (2.8 L). The resulting crystalline suspension was cooled to 0 °C and the crystals collected by filtration, washed with cold MeOH (2×200 mL) and dried to a constant weight in a vacuum oven to

afford 7-[(4-methylphenyl)sulfonyl]-7-azabicyclo[2.2.1]-heptane (378.2 g, 68%) as a white crystalline solid routinely contaminated with approximately 10% (w/w) of triphenylphospine oxide: LCMS ($t_R$=2.87 min, purity=90%), ESI$^+$ *m/z* 252.23 (M−H)$^-$; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.31–1.38 (m, 4H), 1.51–1.57 (m, 4H), 2.43 (s, 3H), 4.10–4.14 (m, 2H), 7.39 (d, *J*=8.1 Hz, 2H), 7.75 (d, *J*=8.1 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.4, 29.9, 59.2, 127.6, 130.0, 137.8, 143.7.

*4.3.1.3. 7-Azabicyclo[2.2.1]heptane or 7-azanorbornane·HCl.* In two separate batches: to a stirred solution of 7-[(4-methylphenyl)-sulfonyl]-7-azabicyclo[2.2.1]heptane (380 g, 1.51 mol) in THF (3 L) at 0 °C was added solid pellets of lithium aluminium hydride (229.4 g, 6.04 mol) over a period of 2 h under a blanket of nitrogen. The resulting grey suspension was allowed to warm to room temperature and stirred for 4 days after which HPLC showed no remaining starting material. The reaction mixture was diluted with THF (1 L), cooled to 0 °C and solid sodium sulfate decahydrate was added over a period of 2 h with rapid agitation. When the effervescence had subsided, the resulting suspension was filtered and the filtrate acidified with gaseous HCl affording a thick white precipitate, which was collected by filtration, washed with THF (2×500 mL) and dried to a constant weight to afford 7-azabicyclo[2.2.1]heptane (batch 1: 86.8 g; 43%) (batch 2: 97.3 g; 49%) as a white solid. The filter cakes obtained from the first filtration were suspended in 6 N NaOH (400 mL) and filtered. The filtrate was extracted with diethyl ether (4 L). The organic layer was acidified with gaseous HCl affording a thick white precipitate, which was collected by filtration, washed with diethyl ether (2×500 mL) and dried to a constant weight in a vacuum oven at 40 °C to afford 7-azabicyclo[2.2.1]heptane·HCl (105.9 g) as a white solid. The total yield for the operation was 290 g (72%): $^1$H NMR (DMSO-$d_6$) $\delta$ 1.57 (m, 4H), 1.86 (m, 4H), 4.12 (m, 2H), 8.94 (br s, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 27.1, 57.6; strength determined by $^1$H NMR=97%±3% w/w.

*4.3.2. 1-(3,5-Dimethylphenyl)-4-hydroxybutan-1-one (**9**)*

To a stirred solution of 5-bromoxylene (128 mL, 910 mmol) in a mixture of THF (1 L) and diethyl ether (1 L) at −78 °C under argon, was added dropwise *n*-butyllithium (1.6 M, 569 mL, 910 mmol) while maintaining an internal temperature of <−65 °C. The resulting cloudy suspension was stirred for 1 h then added dropwise via cannular to a stirred solution of γ-butyrolactone (84.0 mL, 1.09 M) dissolved in THF (900 mL) at −78 °C. The resulting suspension was stirred at −78 °C for 2 h, treated with a saturated aqueous solution of ammonium chloride (800 mL), allowed to warm to room temperature and stirred overnight. The reaction mixture was decanted and the aqueous phase extracted with diethyl ether (2×500 mL). The organic phases were combined, washed with a saturated aqueous solution of brine (500 mL), dried over magnesium sulfate and concentrated to afford the title compound (161 g, 92%) as a clear, colourless oil, which was used without further purification: LCMS ($t_R$=2.73 min, purity=89%), ESI *m/z* no mass ion detected; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.71–1.79 (m, 2H), 2.33 (s, 6H), 3.01 (t, *J*=7.3 Hz, 2H), 3.42–3.47 (m, 2H), 4.49 (t, *J*=5.3 Hz, 1H), 7.26 (s, 1H), 7.57 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.3, 27.1, 35.5, 62.5, 126.0, 134.8, 137.0, 138.3, 201.1; strength determined by $^1$H NMR=60%±3% w/w.

### 4.4. Preparation of 2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole (1)

*4.4.1. Ethyl 2-methyl-2-(2-thienyl)propanoate (**5**)*

To a suspension of NaH (54 g, 1.35 mol) and 18-crown-6 in THF (2 L) stirred at ambient temperature under argon, was added ethyl thiophene-2-acetate (100 g, 0.588 mol) over a period of 30 min. After stirring overnight, the mixture was cooled at 0 °C and methyl iodide (80.0 mL, 1.29 mol) was added dropwise. The mixture was stirred at 18 °C for 3 h, poured into a saturated solution of $NH_4Cl$ (200 mL) and extracted with AcOEt (2 L). The organic phase was evaporated and purified by flash chromatography eluting with petroleum ether/ethyl acetate (95:5) to give ethyl 2-methyl-2-(2-thienyl)propanoate (104 g, 90%) as an oil: LCMS ($t_R$=3.84 min, purity=100%), ESI *m/z* no mass ion detected; $^1$H NMR ($CDCl_3$) $\delta$ 1.22 (t, *J*=7.5 Hz, 3H), 1.66 (s, 6H), 4.13 (q, *J*=7.5 Hz, 2H), 6.92–6.97 (m, 2H), 7.19 (dd, *J*=4.9 Hz, *J′*=1.1 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.4, 28.0, 45.1, 61.6, 124.0, 124.4, 126.9, 149.8, 175.7.

*4.4.2. Ethyl 2-methyl-2-(5-nitro-2-thienyl)propanoate (**6**)*

Nitronium tetrafluoroborate (77.9 g, 0.586 mol) was added at −55 °C to a stirred solution of **5** (105.6 g, 0.583 mol) in DME (1.5 L). The mixture was allowed to warm up to −10 °C over a period of 4 h. After extraction with ethyl acetate (2 L), the organic phase was washed with a saturated solution of sodium hydrogen carbonate (1×100 mL), water (2×100 mL), dried ($MgSO_4$), concentrated and purified by flash chromatography eluting with petroleum ether/AcOEt (95:5) to give **6** (121 g, 86%): LCMS ($t_R$=3.93 min, purity=100%), ESI *m/z* no mass ion detected; $^1$H NMR ($CDCl_3$) 1.25 (t, *J*=7.2 Hz, 3H), 1.67 (s, 6H), 4.14 (q, *J*=7.2 Hz, 2H), 6.93 (d, *J*=4.4 Hz, 1H), 7.78 (d, *J*=4.4 Hz, 1H).

*4.4.3. Ethyl 2-{5-[(tert-butoxycarbonyl)amino]-2-thienyl}-2-methylpropanoate (**7**)*

A suspension of **6** (101.7 g, 0.41 mol) and 10% Pd/C (15 g) in a mixture of ethanol (700 mL) and ethyl acetate (300 mL) was hydrogenated (5 bar) for 5 h. After removal of the catalyst by filtration through a pad of Celite, the residue was evaporated, re-dissolved in THF (900 mL), di-*tert*-butyl dicarbonate (100 g, 0.46 mol) was added and the mixture was refluxed for 16 h. After evaporation of the solvents, the resulting solid was triturated with petroleum ether (500 mL) and collected by filtration, dried to a constant weight to give **7** (87.3 g, 68%): LCMS ($t_R$=3.83 min, purity=100%), ESI$^+$ *m/z* 314.56 (M+H)$^+$, 258.50 (M−$^t$Bu)$^+$; $^1$H NMR ($CDCl_3$) 1.22 (t, *J*=7.1 Hz, 3H), 1.51 (s, 9H), 1.60 (s, 6H), 4.12 (q, *J*=7.1 Hz, 2H), 6.34 (d, *J*=3.9 Hz, 1H), 6.63 (d, *J*=3.9 Hz, 1H), 6.83 (br s, 1H).

*4.4.4. tert-Butyl 1-[5-(2-ethoxy-1,1-dimethyl-2-oxoethyl)-2-thienyl]hydrazine carboxylate hydrochloride (**8**)*

*Procedure A*. To a suspension of sodium hydride (60% dispersion in mineral oil, 44.6 g, 1.12 mol) in DMF (700 mL) at 10 °C, was added a solution of **7** (290 g, 930 mmol) in DMF (1 L) over a period of 5 min. The resulting orange suspension was allowed to warm to room temperature and stirred for 2 h. The resulting solution was cooled to −5 °C in an acetone/ice bath and a solution of *O*-(4-nitrobenzoyl)hydroxylamine (201 g, 1.02 mol) in DMF (1.4 L) was added over a period of 1 h. During this period additional DMF (1 L) was added to mobilise the thick precipitate, which formed. The resulting suspension was allowed to warm to room temperature and stirred overnight after which HPLC showed no remaining starting material. The suspension was poured into water (6 L) and extracted with diethyl ether (3×2 L). The organic extracts were combined and concentrated to approximately 3 L and washed with water (4×1.5 L), a saturated solution of brine (1 L), dried over magnesium sulfate and evaporated to dryness to afford the free base as an off-white solid in quantitative yield. To a stirred solution of the free base (300 g, 914 mmol) in diethyl ether (2.4 L) and heptane (1.2 L) at 0 °C, was added a 4.0 M solution of HCl in 1,4-dioxane (290 mL, 1.14 mol) over a period of 1 h. The resulting thick, white precipitate was collected by filtration, washed with a mixture of diethyl ether/heptane (1:1, 1 L) and dried to a constant weight to afford **8** (320 g, 96%) as a white solid: LCMS ($t_R$=3.67 min,

purity=100%), ESI$^+$ $m/z$ 329.10 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.23 (t, $J$=7.1 Hz, 3H), 1.56 (s, 9H), 1.61 (s, 6H), 4.13 (q, $J$=7.1 Hz, 2H), 4.51 (br s, 3H), 6.67 (d, $J$=4.0 Hz, 1H), 6.70 (br s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 14.3, 27.2, 28.2, 44.1, 61.0, 110.7, 121.9, 138.8, 146.7, 153.2, 175.0.

*Procedure B*. As above but using *O*-(diphenylphosphinyl)hydroxylamine (7.44 g, 35.1 mmol) as the aminating agent carried out on a 10 g (31.9 mmol) scale of input carbamate **7** to afford **8** (10.1 g, 87%) as a white solid.

*Procedure C*. e.g., *tert*-Butyl 1-[5-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-2-thienyl]hydrazine carboxylate.

To a stirred solution of *tert*-butyl [5-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-2-thienyl]carbamate (7.00 g, 20.7 mmol) in DMF (24 mL) at room temperature was added sodium hydride (60% dispersion in mineral oil, 1.00 g, 23.8 mmol) under argon. The resulting suspension was heated at 60 °C for 1 h, cooled to 0 °C and a solution of *O*-(2,4-dinitrophenyl)hydroxylamine (4.95 g, 24.8 mmol) in DMF (20 mL) was added over a period of 20 min. The reaction mixture was allowed to warm to room temperature and stirred for 3 h at room temperature after which LCMS showed complete consumption of the starting material. The reaction mixture was diluted with EtOAc (200 mL), washed with water (5×10 mL), dried over magnesium sulfate and purified by flash chromatography on silica gel eluting with 0–50% ethyl acetate in petroleum ether to afford the free base as an orange foam. The foam was taken up in $Et_2O$ (50 mL) and a 4.0 M solution of HCl in 1,4-dioxane (5.20 mL, 20.7 mmol) was added dropwise over a period of 1 h. The resulting thick, white precipitate was collected by filtration, washed with a mixture of diethyl ether/heptane (1:1, 10 mL) and dried to a constant weight to afford the title compound (6.34 g, 79%) as a white solid: LCMS ($t_R$=3.28 min, purity=95%), ESI$^+$ $m/z$ 354.59 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.56 (s, 9H), 1.68–1.74 (br m, 10H), 3.07 (br m, 2H), 3.45 (br m, 2H), 6.67 (d, $J$=4.0 Hz, 1H), 6.95 (d, $J$=4.0 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 23.1, 26.7, 28.2, 28.6, 44.6, 46.8, 47.8, 81.8, 110.7, 121.2, 140.5, 146.1, 153.2, 172.7.

#### 4.4.5. Ethyl 2-[5-(3,5-dimethylphenyl)-4-(2-hydroxyethyl)-6H-thieno[2,3-b]pyrrol-2-yl]-2-methylpropanoate (**10**)

To a stirred solution of **8** (141 g, 380 mmol) in 2-butanol (1.3 L) was added 1-(3,5-dimethylphenyl)-4-hydroxybutan-1-one (**9**, 104 g, 540 mmol) and zinc chloride (106 g, 770 mmol). The resulting suspension was heated at 120 °C for 8 h after which HPLC showed no remaining starting material. The resulting dark brown solution was evaporated to dryness on a rotary evaporator. The resulting dark brown residue was dissolved in DCM (100 mL), filtered and the filtrate was purified by flash chromatography eluting with DCM/ethyl acetate (9:1) to afford the title compound (**10**, 98 g, 67%) as a brown solid: LCMS ($t_R$=2.69 min, purity=98%), ESI$^+$ $m/z$ 386.52 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (t, $J$=7.3 Hz, 3H), 1.68 (s, 6H), 2.36 (s, 6H), 3.04 (t, $J$=6.6 Hz, 2H), 3.90–3.97 (m, 2H), 4.15 (q, $J$=7.3 Hz, 2H), 6.90 (s, 1H), 6.96 (s, 1H), 7.09 (s, 2H), 8.15 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.1, 21.5, 27.6, 29.4, 45.4, 61.3, 63.2, 109.3, 113.8, 125.5, 128.9, 131.5, 132.4, 133.3, 135.7, 138.5, 142.6, 175.6.

#### 4.4.6. 2-[5-(3,5-Dimethylphenyl)-4-(2-hydroxyethyl)-6H-thieno[2,3-b]pyrrol-2-yl]-2-methylpropanoic acid (**11**)

To a stirred solution of **10** (98.0 g, 254 mmol) was dissolved in ethanol (1.8 L) was added 1 N NaOH (1.27 L, 1.27 mol). The resulting solution was heated at 60 °C for 4 h after which HPLC showed no remaining starting material. The reaction mixture was cooled to room temperature and the ethanol was removed on a rotary evaporator. The resulting brown solution was cooled to 5 °C and concentrated HCl was added dropwise with rapid agitation decreasing the pH to 1. The resulting precipitate was collected by filtration, washed to a neutral pH with water (3×1 L) and dried to a constant weight in a vacuum oven at 50 °C to afford **11** (68.3 g, 75%) as a beige solid, which was used without further purification: LCMS ($t_R$=2.00 min, purity=93%), ESI$^+$ $m/z$ 358.16 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.52 (s, 6H), 2.31 (s, 6H), 2.85 (t, $J$=7.5 Hz, 2H), 3.61–3.69 (m, 2H), 4.67 (t, $J$=5.3 Hz, 1H), 6.86 (s, 1H), 6.91 (s, 1H), 7.10 (s, 2H), 11.29 (br s, 1H).

#### 4.4.7. 2-[2-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrol-4-yl]ethanol (**12**)

To a stirred solution of **11** (35.7 g, 100 mmol) and 7-azabicyclo[2.2.1]heptane·HCl (20.0 g, 150 mmol) in DCM (1 L) at 0 °C, was added DIPEA (70.0 mL, 400 mmol) and solid HATU (57.0 g, 150 mmol) over a period of 15 min. The reaction mixture was allowed to warm to room temperature and stirred for 2 h after which HPLC showed no remaining starting material. The reaction mixture was washed with a saturated aqueous solution of citric acid (350 mL), a saturated aqueous solution of sodium bicarbonate (350 mL) and water (3×350 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness on a rotary evaporator. The resulting oily residue was triturated with ethyl acetate (100 mL) and the resulting precipitate collected by filtration and dried to a constant weight in a vacuum oven at 40 °C to afford **12** (31.4 g, 69%) as a beige solid: LCMS ($t_R$=3.83 min, purity=100%), ESI$^+$ $m/z$ 437.22 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.34 (m, 4H), 1.51 (t, 1H, $J$=5.9 Hz), 1.66 (s, 6H), 1.70 (br s, 4H), 2.38 (s, 6H), 3.06 (t, 2H, $J$=6.6 Hz), 3.90–3.98 (m, 2H), 4.15 (br s, 1H), 4.75 (br s, 1H), 6.80 (s, 1H), 6.98 (s, 1H), 7.13 (s, 2H), 8.25 (br s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.5, 28.7, 29.4, 29.8, 30.2, 45.7, 54.3, 56.0, 62.1, 109.9, 113.6, 125.1, 128.1, 131.2, 131.3, 133.8, 134.1, 137.8, 142.8, 170.4.

#### 4.4.8. 2-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-4-(2-chloroethyl)-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole (**13**)

To a stirred solution of **12** (29.7 g, 68.1 mmol) in DCM (700 mL) and pyridine (1 mL) at 0 °C was added dropwise neat thionyl chloride (6.00 mL, 81.7 mmol). The mixture was allowed to warm to room temperature and stirred for a period of 2 h after which HPLC showed no remaining starting material. The reaction mixture was evaporated and purified by flash chromatography, eluting with methylene chloride/AcOEt (9:1) to give **13** as beige foam. The foam was triturated with diethyl ether (100 mL) and the resulting solid collected by filtration, washed with diethyl ether (2×50 mL) and dried to a constant weight in a vacuum oven at 40 °C to afford **13** as a white solid (26.5 g, 85%): LCMS ($t_R$=4.25 min, purity=100%), ESI$^+$ $m/z$ 455.24 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.32 (br s, 4H), 1.63 (s, 6H), 1.65 (br s, 4H), 2.36 (s, 6H), 3.22 (t, $J$=7.7 Hz, 2H), 3.72 (t, $J$=7.7 Hz, 2H), 4.13 (br s, 1H), 4.73 (br s, 1H), 6.76 (s, 1H), 6.98 (s, 1H), 7.06 (s, 2H), 8.18 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.4, 28.9, 29.3, 29.8, 30.0, 45.3, 45.8, 54.4, 56.1, 108.9, 113.7, 125.3, 128.4, 130.6, 131.5, 133.4, 134.6, 138.0, 143.2, 170.4.

#### 4.4.9. 2-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-6H-thieno[2,3-b]pyrrole (**1**)

A mixture of **13** (1.00 g, 2.20 mmol), *N*-(2-(1-piperazino)-acetyl)-pyrrolidine (1.30 g, 6.60 mmol) in DMF (5 mL) was heated at 110 °C for 3 h. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 2–5% of 7 N $NH_3$ in MeOH in methylene chloride to give, after trituration in ether/pentane (1:1, 20 mL), **1** (1.32 g, 98%) as a white solid: LCMS ($t_R$=2.21 min, purity=100%), ESI$^+$ $m/z$ 616.40; $^1$H NMR ($CDCl_3$) $\delta$ 1.29 (br s, 4H), 1.48 (br s, 4H), 1.51 (s, 6H), 1.69–1.79 (m, 2H), 1.79–1.88 (m, 2H), 2.31 (s, 6H), 2.48 (br s, 8H), 2.56 (br s, 2H), 2.79–2.89 (m, 2H), 3.07 (s, 2H), 3.26 (t, $J$=5.5 Hz, 2H), 3.45 (t, $J$=5.5 Hz, 2H), 4.13 (br s, 1H), 4.45 (br s, 1H), 6.79 (s, 1H), 6.91 (s, 1H), 7.09 (s, 2H), 11.26 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.0, 23.6, 25.6, 28.4, 28.9, 29.4,

45.2, 45.5, 52.6, 53.8, 55.4, 58.8, 60.7, 110.5, 113.1, 124.5, 127.6, 130.6, 130.9, 133.2, 137.4, 142.4, 167.2, 170.0, 171.9.

### 4.5. Preparation of 3-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole (2)

#### 4.5.1. Methyl 2-methyl-2-(3-thienyl)propanoate (**14**)

A solution of methyl 2-thiopheneacetate (20.0 g, 128 mmol) in DMA (100 mL) was added dropwise over 20 min to a stirred suspension of sodium hydride (60% dispersion, 12.2 g, 305 mmol) in DMA (100 mL) cooled to 0 °C under nitrogen. After the addition was complete, the reaction mixture was allowed to warm to 10 °C, stirred for further 1 h and re-chilled to −5 °C and methyl iodide (20 mL, 323 mmol) was added over a period of 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The DMA was evaporated under reduced pressure and the residue quenched with water/ice (500 mL) and acidified with 2 N HCl (50 mL). The mixture was then extracted with ethyl acetate (2×250 mL). The extracts were combined, washed with brine, dried and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/*iso*-hexane (9:1) to give **14** (16.0 g, 68%) as a colourless oil: LCMS ($t_R$=3.83 min, purity=100%), ESI$^-$ *m*/*z* 184.26 (M−H)$^-$; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.50 (s, 6H), 3.58 (s, 3H), 7.05 (m, 1H), 7.30 (m, 1H), 7.48 (m, 1H).

#### 4.5.2. Methyl 2-methyl-2-(5-nitro-3-thienyl)propanoate (**15**)

Nitronium tetrafluoroborate (8.00 g, 60.2 mmol) was added dropwise to a stirred solution of **14** (10.0 g, 54.3 mmol) in DME (200 mL) cooled to −50 °C under a nitrogen atmosphere. The reaction mixture was stirred for a further hour at −50 °C, a saturated solution of. sodium bicarbonate (100 mL) was added and the mixture allowed to warm to room temperature. The resulting mixture was further diluted with water (300 mL) and extracted with ethyl acetate (3×100 mL). The extracts were combined, dried and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/*iso*-hexane (2:8) to give **15** (7.62 g, 61%) as a yellow oil: LCMS ($t_R$=3.92 min, purity=100%), ESI *m*/*z* no mass ion detected; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.52 (s, 6H), 3.61 (s, 3H), 7.86 (d, *J*=1.4 Hz, 1H), 8.10 (d, *J*=1.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 26.7, 45.0, 53.1, 127.6, 128.4, 146.2, 152.4, 175.6.

#### 4.5.3. 2-Methyl-2-(5-nitro-3-thienyl)propanoic acid (**16**)

Sodium hydroxide (6.80 g, 17.0 mmol) in water (70 mL) was added to a solution of **15** (7.50 g, 32.8 mmol) in methanol (300 mL) and the mixture was stirred for 24 h at room temperature. The methanol was evaporated under reduced pressure, the residue diluted with water (200 mL) and acidified with 2 N HCl (20 mL). The resulting solution was extracted with ethyl acetate (3×100 mL), the extracts combined, dried over magnesium sulfate and evaporated to dryness to give **16** (7.01 g, 99%) as an orange solid: LCMS ($t_R$=2.94 min, purity=100%), ESI$^-$ *m*/*z* no mass ion detected; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.49 (s, 6H), 7.83 (d, *J*=1.4 Hz, 1H), 8.09 (d, *J*=1.4 Hz, 1H), 12.6 (br s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 26.3, 44.4, 129.5, 130.1, 146.6, 151.2, 176.5.

#### 4.5.4. 7-[2-Methyl-2-(5-nitro-3-thienyl)propanoyl]-7-azabicyclo[2.2.1]heptane (**17**)

EDCI (8.70 g, 45.4 mmol) was added to a stirred mixture of **16** (7.00 g, 32.6 mmol), 7-azanorborane·HCl (5.12 g, 38.5 mmol) and DMAP (21.3 g, 175 mmol) in dichloromethane (200 mL) under nitrogen. The reaction mixture was stirred for a further 18 h, washed with an aqueous solution of citric acid (1 M, 2×100 mL), dried over magnesium sulfate and evaporated to dryness to afford an orange residue. The residue was purified on a silica flash column eluting with ethyl acetate/*iso*-hexane (4:6) to give **17** (6.92 g, 72%) as a pale orange solid: LCMS ($t_R$=4.01 min, purity=100%), ESI$^+$ *m*/*z* 294.97 (M+H)$^+$; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.15–1.60 (m, 8H), 1.42 (s, 6H), 3.80–4.30 (br m, 2H), 7.80 (d, *J*=1.4 Hz, 1H), 7.94 (d, *J*=1.4 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 27.7, 29.1, 45.2, 54.8, 128.6, 129.6, 148.0, 151.5, 169.9.

#### 4.5.5. tert-Butyl {4-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-thienyl}carbamate (**18**)

A stirred suspension of **17** (4.50 g, 15.3 mmol) and 10% Pd–C (ca. 5 g) in EtOH/EtOAc (120 mL, 10:1) was exposed to 1.7 atm of hydrogen for 6 h after which HPLC indicated no remaining starting material. The catalyst was removed by filtration through a pad of Celite and the filtrate evaporated to dryness. The resulting solid was dissolved in THF and evaporated to dryness. The resulting solid was re-dissolved in THF (200 mL) and $Boc_2O$ (16.7 g, 76.5 mmol) was added and the resulting solution was heated to reflux overnight after which HPLC showed no remaining starting material. The solvent was removed and the resulting residue purified by flash chromatography on silica gel eluting with DCM/EtOAc (80:20) to afford **18** (4.20 g, 75%) as a white solid: LCMS ($t_R$=3.65 min, purity=100%), ESI$^+$ *m*/*z* 365.28 (M+H)$^+$, 309.25 (M−$^t$Bu)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.29 (br s, 4H), 1.51 (s, 9H), 1.60 (s, 6H), 1.64 (br s, 4H), 3.95 (br s, 1H), 4.69 (br s, 1H), 6.34 (d, *J*=1.5 Hz, 1H), 6.53 (d, *J*=1.5 Hz, 1H), 6.98 (br s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 27.7, 28.4, 28.6, 29.9, 44.7, 53.7, 55.7, 80.3, 109.1, 109.3, 141.7, 144.8, 152.7, 170.8.

#### 4.5.6. tert-Butyl 1-{4-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-thienyl}hydrazine carboxylate hydrochloride (**19**)

To a stirred solution of **18** (2.00 g, 5.50 mmol) in DMF (10 mL) at −10 °C was added solid NaH (60% dispersion in mineral oil, 0.264 g, 6.60 mmol) over a period of 5 min. The reaction mixture was stirred at room temperature for a further 20 min. The reaction mixture was cooled again to −10 °C and *O*-(4-nitrobenzoyl)hydroxylamine (1.10 g, 6.05 mmol) was added over a period of 5 min. The reaction mixture was allowed to warm to room temperature and stirred for a further 2 h after which HPLC showed no remaining starting material. Diethyl ether (100 mL) was added and the reaction mixture was washed with water (2×30 mL), dried ($MgSO_4$) and evaporated to dryness to afford an orange residue. The residue was dissolved in diethyl ether and the resulting solution was cooled to 0 °C. A 4 M solution of HCl in dioxane (1.38 mL, 5.50 mmol) was added over a period of 10 min and the resulting precipitate was collected by filtration, washed with diethyl ether (4×20 mL) and dried to a constant weight in a vacuum oven at 40 °C to afford **19** (1.50 g, 65%) as a white solid: LCMS ($t_R$=3.54 min, purity=97%), ESI$^+$ *m*/*z* 380.25 (M+H)$^+$, 280.27 (M−Boc)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.24–1.35 (m, 4H), 1.52 (s, 6H), 1.67 (s, 9H), 1.66 (br s, 4H), 4.36 (m, 2H), 5.72 (m, 3H), 7.72 (s, 1H), 7.15 (s, 1H).

#### 4.5.7. 2-[3-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrol-4-yl]ethanol (**20**)

To a stirred suspension of **19** (1.50 g, 3.61 mmol) and 1-(3,5-dimethylphenyl)-4-hydroxybutan-1-one (**9**, 1.04 g, 5.42 mmol) in butan-2-ol (3 mL), was added zinc chloride (0.74 g, 5.42 mmol) at room temperature. The resulting suspension was heated at 120 °C for 5 h after which HPLC showed no remaining hydrazine. The resulting dark brown solution was evaporated to dryness and the resulting brown residue was dissolved in DCM and purified by flash chromatography on silica gel eluting with DCM/EtOAc (50:50) to afford **20** (0.44 g, 28%) as a beige foam: LCMS ($t_R$=3.68 min, purity=99%), ESI$^+$ *m*/*z* 437.28 (M+H)$^+$; $^1$H NMR

($CDCl_3$) $\delta$ 1.19–1.31 (m, 2H), 1.31–1.42 (m, 2H), 1.66 (s, 6H), 1.74 (br s, 4H), 2.36 (s, 6H), 3.06–3.17 (m, 2H), 3.58–3.70 (m, 2H), 4.14–4.21 (m, 1H), 4.86–4.93 (m, 1H), 6.63 (s, 1H), 6.97 (s, 1H), 7.07 (s, 2H), 8.21 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.4, 27.8, 28.6, 29.1, 30.4, 44.7, 53.7, 55.2, 62.2, 110.0, 111.28, 125.1, 128.2, 129.3, 133.8, 134.5, 134.9, 137.8, 139.4, 171.0.

#### *4.5.8. 3-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-4-(2-chloroethyl)-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole*

To a stirred solution of **20** (0.30 g, 0.69 mmol) in DCM (20 mL) at −10 °C, was added thionyl chloride (0.246 g, 2.07 mmol) and 1 pasteur pipette drop of pyridine. The resulting dark brown solution was allowed to warm to room temperature and stirred for 5 h after which HPLC showed no remaining starting material. The reaction mixture was washed with a saturated solution of sodium bicarbonate (2×5 mL), water (2×5 mL), dried ($MgSO_4$) and evaporated to dryness to afford a brown residue. The residue was dissolved in DCM/THF (1 mL, 50:50) and purified by flash chromatography on silica gel eluting with pure DCM to afford **21** (0.150 g, 48%) as a white solid: LCMS ($t_R$=2.53 min, purity=100%), ESI$^+$ $m/z$ 456.07 $(M+H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.11–1.37 (m, 6H), 1.57–1.73 (m, 2H), 1.63 (s, 6H), 2.35 (s, 6H), 3.26–3.35 (m, 2H), 3.37–3.44 (m, 2H), 3.94 (br s, 1H), 4.78 (br s, 1H), 6.61 (s, 1H), 6.97 (s, 1H), 7.05 (s, 2H), 8.22 (br s, 1H).

#### *4.5.9. [2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-6H-thieno[2,3-b]pyrrole (**2**)*

To a stirred solution of **21** (0.150 g, 0.331 mmol) in DMF (0.5 mL) was added *N*-(2-(1-piperazino)-acetyl)-pyrrolidine (0.196 g, 0.933 mmol). The reaction mixture was heated at 100 °C for 3 h after which HPLC showed no remaining starting material. The reaction mixture was cooled to 5 °C and triturated with water (30 mL). The resulting precipitate was collected by filtration, slurry washed with water (3×10 mL) and dried to a constant weight in a vacuum oven at 40 °C to afford **2** (0.185 g, 91%) as a pale pink solid: LCMS ($t_R$=2.28 min, purity=100%), ESI$^+$ $m/z$ 616.41 $(M+H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.07–1.21 (m, 3H), 1.21–1.36 (m, 3H), 1.54–1.72 (m, 4H), 1.60 (s, 6H), 1.79–1.87 (m, 2H), 1.89–1.97 (m, 2H), 2.33 (s, 6H), 2.33–2.38 (m, 2H), 2.53 (br s, 8H), 2.99–3.05 (m, 2H), 3.09 (s, 2H), 3.43–3.50 (m, 2H), 3.87–3.91 (m, 1H), 4.72–4.77 (m, 1H), 6.57 (s, 1H), 6.93 (s, 1H), 7.06 (s, 2H), 8.19 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.4, 22.8, 24.0, 26.1, 27.8, 28.6, 30.4, 44.8, 45.8, 46.0, 52.8, 53.2, 53.8, 55.2, 59.1, 61.3, 111.3, 111.4, 124.8, 128.1, 129.2, 133.8, 134.3, 134.5, 137.7, 139.3, 167.7, 170.9.

### 4.6. Preparation of 2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6-{2-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-4*H*-thieno[3,2-*b*]pyrrole (3) and 4-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-3-{2-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1*H*-thieno[3,4-*b*]pyrrole (4)

#### *4.6.1. Ethyl 2-methyl-2-(2-thienyl)propanoate (**5**)*

To a suspension of NaH (54 g, 1.35 mol) and 18-crown-6 in THF (2 L) stirred at ambient temperature under argon, was added ethyl thiophene-2-acetate (100 g, 0.588 mol) over a period of 30 min. After stirring overnight, the mixture was cooled at 0 °C and methyl iodide (80.0 mL, 1.29 mol) was added dropwise. The mixture was stirred at 18 °C for 3 h, poured into a saturated solution of $NH_4Cl$ (200 mL) and extracted with AcOEt (2 L). The organic phase was evaporated and purified by flash chromatography eluting with petroleum ether/ethyl acetate (95:5) to give ethyl 2-methyl-2-(2-thienyl)propanoate (104 g, 90%) as an oil: LCMS ($t_R$=3.84 min, purity=100%), ESI $m/z$ no mass ion detected; $^1$H NMR ($CDCl_3$) $\delta$ 1.22 (t, $J$=7.5 Hz, 3H), 1.66 (s, 6H), 4.13 (q, $J$=7.5 Hz, 2H), 6.92–6.97 (m, 2H), 7.19 (dd, $J_1$=4.9 Hz, $J_2$=1.1 Hz, 1H).

#### *4.6.2. Ethyl 2-(5-bromo-2-thienyl)-2-methylpropanoate (**22**)*

To a stirred solution of **5** (50.0 g, 253 mmol) in THF (400 mL) at room temperature was added solid *N*-bromosuccinimide (49.4 g, 278 mmol) over a period of 10 min. The resulting solution was allowed to stir overnight after which HPLC showed no remaining starting material. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluting with petroleum ether/DCM (70:30) to afford **22** (65.2 g, 93%) as a yellow oil: LCMS ($t_R$=4.20 min, purity=100%) ESI $m/z$ no mass ion detected; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.17 (t, $J$=7.2 Hz, 3H), 1.56 (s, 6H), 4.10 (q, $J$=7.2 Hz, 2H), 6.86 (d, $J$=3.6 Hz, 1H), 7.09 (d, $J$=3.6 Hz, 1H).

#### *4.6.3. Ethyl 2-(5-bromo-4-nitro-2-thienyl)-2-methylpropanoate (**23**)*

To a stirred solution of **22** (71.3 g, 257.4 mmol) in DCM (3.5 L) at room temperature was added solid nitronium tetrafluoroborate (34.2 g, 257.4 mmol) over a period of 20 min. The resulting dark red suspension was stirred at room temperature for 2 h after which HPLC showed no remaining starting material. The reaction mixture was cooled to 0 °C and a saturated solution of sodium bicarbonate (400 mL) was added over a period of 5 min. The two phases were separated and the organic layer was washed with water (2×200 mL), dried ($MgSO_4$) and evaporated to dryness to afford **23** (71.0 g, 86%) as a orange oil, which was used without further purification: LCMS ($t_R$=4.10 min, purity=92%) ESI $m/z$, no mass ion detected; $^1$H NMR ($CDCl_3$) $\delta$ 1.27 (t, $J$=7.1 Hz, 3H), 1.63 (s, 6H), 4.19 (q, $J$=7.1 Hz, 2H), 7.42 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.4, 27.4, 45.8, 62.4, 114.4, 121.2, 154.1, 149.5, 174.2.

#### *4.6.4. Ethyl 2-methyl-2-(4-nitro-2-thienyl)propanoate (**24**)*

To a stirred solution of **23** (68.0 g, 211 mmol) in triethylamine (32.1 g, 317 mmol) at 0 °C was added dropwise diethylphosphonate (35.0 g, 253 mmol) over a period of 10 min. The reaction mixture was allowed to warm to room temperature and stirred for a further 2 h after which HPLC showed no remaining starting material. The reaction mixture was partitioned between diethyl ether (1 L) and a 1 N aqueous solution of HCl (100 mL). The organic extract was retained, washed with water (3×50 mL), dried ($MgSO_4$) and evaporated to dryness to afford an orange residue. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EtOAc (90:10) to afford **24** (51.3 g, 100%) as a yellow oil: LCMS ($t_R$=3.63 min, purity=100%) ESI $m/z$, no mass ion detected; $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (t, $J$=7.1 Hz, 3H), 1.67 (s, 6H), 4.17 (q, $J$=7.1 Hz, 2H), 7.51 (s, 1H), 8.19 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.4, 27.7, 45.5, 62.2, 119.5, 126.7, 148.0, 151.3, 174.5.

#### *4.6.5. Ethyl 2-{4-[(tert-butoxycarbonyl)amino]-2-thienyl}-2-methylpropanoate*

A stirred solution of **24** (50.0 g, 205.8 mmol) and 10% Pd–C (30 g) in EtOH/EtOAc (500 mL, 4:1) was exposed to 1.7 atm of hydrogen for 5 h after which HPLC indicated no remaining starting material. The catalyst was removed by filtration through a pad of Celite and the filtrate evaporated to dryness. The resulting solid was dissolved in THF and evaporated to dryness to remove any traces of EtOH. The resulting solid was re-dissolved in THF (20 mL), $(Boc)_2O$ (84.8 g, 411.6 mmol) was added and the resulting solution was heat to reflux overnight after which HPLC showed no remaining starting material. The solvent was removed and the resulting residue purified by flash chromatography on silica gel eluting with petroleum ether/EtOAc (90:10) to afford ethyl 2-{4-[(*tert*-butoxycarbonyl)amino]-2-thienyl}-2-methylpropanoate (20.2 g, 31.4%) as a white solid: LCMS ($t_R$=3.83 min, purity=94%), ESI$^+$ $m/z$ 314.26 $(M+H)^+$, 258.24

($M-{}^tBu)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.11 (t, 3H, $J$=7.1 Hz), 1.38 (s, 9H), 1.49 (s, 6H), 4.01 (q, 2H, $J$=7.1 Hz), 6.44 (br s, 1H), 6.68 (s, 1H), 6.91 (br s, 1H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 14.2, 27.3, 28.4, 44.5, 61.1, 79.3, 104.8, 118.5, 136.7, 147.4, 153.1, 174.5.

#### 4.6.6. *tert*-Butyl 1-[5-(2-ethoxy-1,1-dimethyl-2-oxoethyl)-3-thienyl]hydrazine carboxylate hydrochloride (**25**)

To a stirred solution of ethyl 2-{4-[(*tert*-butoxycarbonyl)amino]-2-thienyl}-2-methylpropanoate (10.0 g, 31.9 mmol) in DMF (150 mL) at −10 °C was added solid NaH (60% dispersion in mineral oil, 1.53 g, 38.3 mmol) over a period of 5 min. The reaction mixture was stirred at room temperature for 20 min. The reaction mixture was cooled again to −10 °C and solid *O*-(4-nitrobenzoyl)hydroxylamine (6.39 g, 35.1 mmol) was added over a period of 5 min. The reaction mixture was allowed to warm to room temperature and stirred for a further 2 h after which HPLC showed an acceptable reaction profile. Diethyl ether (300 mL) was added and the reaction mixture was washed with water (5×20 mL), dried ($MgSO_4$) and evaporated to dryness to afford an orange residue. The residue was dissolved in diethyl ether (150 mL) and pentane (50 mL) and the resulting solution was cooled to 0 °C. A 4 M solution of HCl in dioxane (7.98 mL, 31.9 mmol) was added over a period of 10 min to lower the pH of 1–2. The resulting precipitate was collected by filtration, washed with diethyl ether (4×20 mL) and dried to a constant weight in a vacuum oven at 40 °C to afford **25** (4.60 g, 40%) as a white solid: LCMS ($t_R$=3.83 min, purity=100%), $ESI^+$ $m/z$ 329.23 $(M+H)^+$, 270.23 $(M-{}^tBu)^+$, 229.24 $(M-Boc)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.21 (t, $J$=7.1 Hz, 3H), 1.52 (s, 9H), 1.69 (s, 6H), 4.12 (q, $J$=7.1 Hz, 2H), 7.18 (s, 1H), 7.36 (s, 1H).

#### 4.6.7. (Ethyl 2-[5-(3,5-dimethylphenyl)-6-(2-hydroxyethyl)-4H-thieno[3,2-b]pyrrol-2-yl]-2-methylpropanoate) (**26**) and (ethyl 2-[2-(3,5-dimethylphenyl)-3-(2-hydroxyethyl)-1H-thieno[3,4-b]pyrrol-4-yl]-2-methylpropanoate) (**27**)

To a stirred suspension of **25** (4.60 g, 12.6 mmol) and 1-(3,5-dimethylphenyl)-4-hydroxybutan-1-one (2.91 g, 15.2 mmol) in butan-2-ol (15 mL), was added zinc chloride (2.58 g, 19.0 mmol) at room temperature. The resulting suspension was heated at 110 °C for 5 h after which HPLC showed no remaining hydrazine. The resulting dark brown solution was evaporated to dryness and the resulting brown residue was dissolved in DMF and purified by preparative HPLC to afford **26** (0.547 g, 11%) and **27** (0.537 g, 11%), respectively, as pale brown oils: Data for **26**: LCMS ($t_R$=4.61 min, purity=100%), $ESI^+$ $m/z$ 386.10 $(M+H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.26 (t, $J$=7.1 Hz, 3H), 1.68 (s, 6H), 2.36 (s, 6H), 3.03 (t, $J$=6.4 Hz, 2H), 3.99 (t, $J$=6.4 Hz, 2H), 4.15 (q, $J$=7.1 Hz, 2H), 6.86 (s, 1H), 6.96 (s, 1H), 7.09 (s, 2H), 8.08 (br s, 1H); data for **27**: LCMS ($t_R$=4.34 min, purity=98%), $ESI^+$ $m/z$ 386.10 $(M+H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.23 (t, $J$=7.1 Hz, 3H), 1.67 (s, 6H), 2.36 (s, 6H), 3.13 (t, $J$=5.3 Hz, 2H), 3.97 (t, $J$=5.3 Hz, 2H), 4.13 (q, $J$=7.1 Hz, 2H), 6.85 (s, 1H), 6.89 (s, 1H), 7.12 (s, 2H), 8.88 (br s, 1H).

#### 4.6.8. 2-[5-(3,5-Dimethylphenyl)-6-(2-hydroxyethyl)-4H-thieno[3,2-b]pyrrol-2-yl]-2-methylpropanoic acid

To a stirred solution of **26** (0.507 g, 1.32 mmol) in EtOH (10 mL) was added a 1 N solution of NaOH (6.58 mL, 6.58 mmol). The resulting orange solution was heated at 70 °C for 4 h after which TLC (silica gel, DCM/EtOAc, 50:50) showed no remaining starting material. The EtOH was removed on a rotary evaporator and the remaining aqueous solution was cooled to 5 °C and acidified to pH 1 with concentrated HCl. The resulting precipitate was collected by filtration, washed with water (4×10 mL) and dried to a constant weight in a vacuum oven at 40 °C to afford 2-[5-(3,5-dimethylphenyl)-6-(2-hydroxyethyl)-4*H*-thieno[3,2-*b*]pyrrol-2-yl]-2-methylpropanoic acid (0.37 g, 79%) as a beige solid: LCMS ($t_R$=3.38 min, purity=89%), $ESI^+$ $m/z$ 358.21 $(M+H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.71 (s, 6H), 2.36 (s, 6H), 3.02 (t, $J$=6.4 Hz, 2H), 3.98 (t, $J$=6.4 Hz, 2H), 6.92 (s, 1H), 6.96 (s, 1H), 7.08 (s, 2H), 8.11 (br s, 1H).

#### 4.6.9. 2-[2-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4H-thieno[3,2-b]pyrrol-6-yl]ethanol

To a stirred solution of 2-[5-(3,5-dimethylphenyl)-6-(2-hydroxyethyl)-4*H*-thieno[3,2-*b*]pyrrol-2-yl]-2-methylpropanoic acid (0.371 g, 1.04 mmol), 7-azanorborane·HCl (0.207 g, 1.56 mmol) and DIPEA (0.423 g, 3.27 mmol) in DCM (10 mL) at 0 °C, was added solid TBTU (0.501 g, 1.56 mmol) over a period of 5 min. The resulting dark brown suspension was allowed to warm to room temperature and stirred for a further 1 h after which HPLC showed no remaining starting material. The resulting suspension was diluted with DCM (50 mL) and washed with water (10 mL), a saturated solution of citric acid (10 mL), a saturated solution of sodium bicarbonate (10 mL) and water (10 mL). The organic extract was dried ($MgSO_4$), concentrated and purified by flash chromatography on silica gel eluting with DCM/EtOAc (80:20) to afford 2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4*H*-thieno[3,2-*b*]pyrrol-6-yl]ethanol (0.203 g, 45%): LCMS ($t_R$=2.50 min, purity=100%), $ESI^+$ $m/z$ 437.22 $(M+H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.32 (br s, 4H), 1.63 (s, 6H), 1.71 (br s, 4H), 2.36 (s, 6H), 3.05 (t, $J$=6.2 Hz, 2H), 4.00 (t, $J$=6.2 Hz, 2H), 4.04 (br s, 1H), 4.74 (br s, 1H), 6.70 (s, 1H), 6.96 (s, 1H), 7.11 (s, 2H), 8.11 (br s, 1H).

#### 4.6.10. 2-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-6-(2-chloroethyl)-5-(3,5-dimethylphenyl)-4H-thieno[3,2-b]pyrrole (**28**)

To a stirred solution of 2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4*H*-thieno[3,2-*b*]-pyrrol-6-yl]ethanol (0.203 g, 0.47 mmol) in DCM (10 mL) at room temperature was added thionyl chloride (0.083 g, 0.699 mmol) and a pasteur pipette drop of pyridine. The resulting dark brown solution was stirred at room temperature for 3 h after which HPLC showed no remaining starting material. The solvent was evaporated and the residue was dissolved in DCM/THF (2 mL, 50:50) and purified by chromatography on silica gel eluting with pure DCM to afford **28** (0.146 g, 66%) as a green foam: LCMS ($t_R$=2.80 min, purity=96%), $ESI^+$ $m/z$ 456.07 $(M+H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.31 (br s, 4H), 1.63 (s, 6H), 1.69 (br s, 4H), 2.36 (s, 6H), 3.24 (t, $J$=7.7 Hz, 2H), 3.82 (t, $J$=7.7 Hz, 2H), 4.04 (br s, 1H), 4.74 (br s, 1H), 6.70 (s, 1H), 6.99 (s, 1H), 7.07 (s, 2H), 8.07 (br s, 1H).

#### 4.6.11. 2-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6-{2-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-4H-thieno[3,2-b]pyrrole (**3**)

To a stirred solution of **28** (0.142 g, 0.312 mmol) in DMF (2 mL) was added *N*-(2-(1-piperazino)-acetyl)-pyrrolidine (0.185 g, 0.936 mmol). The reaction mixture was heated at 100 °C for 5 h after which HPLC showed no remaining starting material. The reaction mixture was cooled to 5 °C and triturated with water (30 mL). The resulting precipitate was collected by filtration, dissolved in DCM (2 mL) and purified by chromatography on silica gel eluting with DCM/7 N $NH_3$ in MeOH (90:10) to afford **3** (0.120 g, 63%) as a beige foam: LCMS ($t_R$=2.29 min, purity=100%), $ESI^+$ $m/z$ 616.38 $(M+H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.31 (m, 4H), 1.62 (s, 6H), 1.68 (br s, 4H), 1.81–1.88 (m, 2H), 1.90–1.99 (m, 2H), 2.35 (s, 6H), 2.63 (br s, 8H), 2.73–2.80 (m, 2H), 2.93–3.00 (m, 2H), 3.13 (s, 2H), 3.45–3.53 (m, 4H), 4.04 (br s, 1H), 4.72 (br s, 1H), 6.68 (s, 1H), 6.94 (s, 1H), 7.06 (s, 2H), 8.02 (br s, 1H).

#### 4.6.12. 2-[2-(3,5-Dimethylphenyl)-3-(2-hydroxyethyl)-1H-thieno[3,4-b]pyrrol-4-yl]-2-methylpropanoic acid

To a stirred solution of **27** (0.550 g, 1.43 mmol) in EtOH (10 mL) was added a 1 N solution of NaOH (7.14 mL, 7.14 mmol). The resulting dark brown solution was heated at 70 °C for 3 h after which HPLC showed no remaining starting material. The EtOH was removed on a rotary evaporator and the remaining aqueous solution was cooled to 5 °C and acidified to pH 1 with concentrated HCl. The resulting

precipitate was collected by filtration, washed with water (4×10 mL) and dried to a constant weight in a vacuum oven at 40 °C to afford 2-[2-(3,5-dimethylphenyl)-3-(2-hydroxyethyl)-1*H*-thieno[3,4-*b*]pyrrol-4-yl]-2-methylpropanoic acid (0.40 g, 78%) as a pink solid, which was used without further purification: LCMS ($t_R$=2.53 min, purity=88%), ESI$^+$ *m*/*z* 358.22 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.70 (s, 6H), 2.36 (s, 6H), 3.12 (t, *J*=5.5 Hz, 2H), 3.96 (t, *J*=5.5 Hz, 2H), 6.89 (s, 1H), 6.91 (s, 1H), 7.11 (s, 2H), 8.92 (br s, 1H).

#### 4.6.13. 2-[4-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1H-thieno[3,4-b]pyrrol-3-yl]ethanol

To a stirred solution of 2-[2-(3,5-dimethylphenyl)-3-(2-hydroxyethyl)-1*H*-thieno[3,4-*b*]pyrrol-4-yl]-2-methylpropanoic acid (0.400 g, 1.12 mmol), 7-azanorborane·HCl (0.222 g, 1.68 mmol) and DIPEA (0.434 g, 3.36 mmol) in DCM (10 mL) at 0 °C, was added solid TBTU (0.539 g, 1.68 mmol) over a period of 5 min. The resulting dark brown suspension was allowed to warm to room temperature and stirred for a further 1 h after which HPLC showed no remaining starting material. The resulting suspension was diluted with DCM (50 mL) and washed with water (10 mL), a saturated solution of citric acid (10 mL), a saturated solution of sodium bicarbonate (10 mL) and water (10 mL). The organic extract was dried ($MgSO_4$), concentrated and purified by flash chromatography on silica gel eluting with DCM/EtOAc (80:20) to afford 2-[4-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-thieno[3,4-*b*]pyrrol-3-yl]ethanol (0.240 g, 49%): LCMS ($t_R$=3.86 min, purity=100%), ESI$^+$ *m*/*z* 437.23 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.31 (m, 4H), 1.63 (s, 6H), 1.71 (m, 4H), 2.37 (s, 6H), 3.16 (t, *J*=5.5 Hz, 2H), 4.00 (t, *J*=5.5 Hz, 2H), 4.09 (br s, 1H), 4.71 (br s, 1H), 6.68 (s, 1H), 6.90 (s, 1H), 7.14 (s, 2H), 8.97 (br s, 1H).

#### 4.6.14. 4-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-3-(2-bromoethyl)-2-(3,5-dimethylphenyl)-1H-thieno-[3,4-b]pyrrole (29)

To a stirred solution of 2-[4-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-thieno[3,4-*b*]pyrrol-3-yl]ethanol (0.240 g, 0.552 mmol) in MeCN (10 mL) at room temperature, were added triphenylphosphine (0.190 g, 0.718 mmol) and $CBr_4$ (0.201 g, 0.61 mmol). The reaction mixture was heated at 60 °C for 2 h after which HPLC showed no remaining starting material. The reaction mixture was cooled to room temperature and evaporated to dryness. The resulting solid was dissolved in DCM and purified by flash chromatography (silica gel, DCM) to afford **29** (0.20 g, 73%) as a yellow foam: LCMS ($t_R$=3.91 min, purity=99%), ESI$^+$ *m*/*z* 500.38 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.29 (m, 4H), 1.63 (s, 6H), 1.65 (m, 4H), 2.34 (s, 6H), 3.48 (t, *J*=7.0 Hz, 2H), 3.63 (t, *J*=7.0 Hz, 2H), 4.06 (br s, 1H), 4.72 (br s, 1H), 6.71 (s, 1H), 6.93 (s, 1H), 7.12 (s, 2H), 8.38 (br s, 1H).

#### 4.6.15. 4-[2-(7-Azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-3-{2-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1H-thieno[3,4-b]pyrrole (4)

To a stirred solution of **29** (0.150 g, 0.301 mmol) in DMF (2 mL) was added *N*-(2-(1-piperazino)-acetyl)-pyrrolidine (0.178 g, 0.904 mmol). The reaction mixture was heated at 100 °C for 2 h after which HPLC showed no remaining starting material. The reaction mixture was cooled to 5 °C and triturated with water (30 mL). The resulting precipitate was collected by filtration, dissolved in DCM and purified by chromatography on silica gel eluting with DCM/7 N $NH_3$ in MeOH (90:10) to afford **4** (0.068 g, 37%) as a beige foam: LCMS ($t_R$=2.53 min, purity=100%), ESI$^+$ *m*/*z* 616.35 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.29 (br s, 4H), 1.64 (s, 6H), 1.70 (br s, 4H), 1.82–1.91 (m, 2H), 1.93–2.01 (m, 2H), 2.37 (s, 6H), 2.69 (br s, 8H), 2.70–2.78 (m, 2H), 3.06–3.13 (m, 2H), 3.21 (s, 2H), 3.46–3.54 (m, 4H), 4.13 (br s, 1H), 4.72 (br s, 1H), 6.75 (s, 1H), 6.88 (s, 1H), 7.14 (s, 2H), 10.63 (br s, 1H).

### 4.7. 7-[4-(5-(3,5-Dimethylphenyl)-4-{2-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1*H*-pyrrol-3-yl)-2,2-dimethylbutanoyl]-7-azabicyclo[2.2.1]heptane (30)

To a stirred solution of **1** (0.30 g, 0.49 mmol) in EtOH (50 mL), was added fresh Raney® nickel (0.50 g) and the resulting suspension was stirred at room temperature for 3 days under nitrogen. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated and purified by flash chromatography eluting with DCM/7 N $NH_3$ in MeOH (95:5) to afford **30** (0.102 g, 35%) as a pale yellow foam: LCMS ($t_R$=2.29 min, purity=100%), ESI$^+$ *m*/*z* 588.36 (M+H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 1.29–1.40 (m, 6H), 1.49–1.42 (m, 4H), 1.76–1.95 (m, 12H), 2.32 (s, 6H), 2.42–2.59 (m, 10H), 2.75–2.79 (m, 2H), 3.11 (s, 2H), 3.46–3.50 (m, 4H), 4.66 (br s, 2H), 6.55 (s, 1H), 6.89 (s, 1H), 7.02 (s, 2H), 7.92 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 20.8, 21.4, 24.0, 26.1, 26.5, 29.4, 41.6, 42.8, 45.7, 46.0, 53.1, 55.4, 59.6, 61.2, 115.2, 116.5, 123.4, 124.2, 127.3, 128.2, 134.1, 137.6, 167.7.

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## Supplementary data

$^1$H and $^{13}$C NMR spectra of compounds **1**, **2**, **3**, **4** and **30** are available free of charge. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.007.

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decomposition 961 J/g). Second large exotherm from 211 °C, which was complete at 380 °C (heat of decomposition 2548 J/g); (c) *O*-(Diphenylphosphinyl)hydroxylamine; large, sharp exotherm from 94 °C. Exotherm complete at 140 °C, heat of decomposition 702 J/g. Heats of decomposition of >800 J/g generally indicates possible explosive properties (*Recommendations for the Transport of Dangerous Goods Manual on Tests and Criteria* 2003, 4th Edition, United Nations, Economic Commission for Europe); for a recent reference evaluating the stability of the mesitylene version see Mendiola, J.; Rincon, J. A.; Mateos, C.; Francisco Soriano, J.; de Frutos, O.; Niemeier, J. K.; Davis, E. M. *Org. Proc. Res. Dev.* **2009**, *13*, 263–267.

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25. Cell assay. Primary pituitary cells were isolated from >12 week-old female AP Han Wistar rats by enzymatic digestion. The suspended cells were cultivated for 4 days in 24-well tissue culture plates. On the assay day, the cells were washed and treated with a medium containing 10 nM GnRH (LHRH) and the test compounds at concentrations between 3 and 3000 nM in a final concentration of 0.1% DMSO. After a 4 h incubation period, the medium was removed and centrifuged. The supernatant was analysed for LH content using a EIA kit specific for rat LH (Amersham). The results are reported as an $IC_{50}$ value representing the antagonist concentration required to inhibit the GnRH-stimulated LHR release by 50%.
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