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Synthesis of new benzo[*b*]thieno fused ring systems via transition metal-mediated cyclisations

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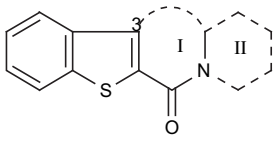
ABSTRACT

The compact synthesis of a new ring fused benzo[*b*]thieno derivative with an embedded nine-membered ring system via ring closing metathesis methodology is described. The preparation of the novel 11*H*-benzo[*b*]thieno[2,3-*c*]pyrrolo[2,3-*a*]indol-11-one via palladium-mediated oxidative cyclisation of benzo[*b*]thien-2-oyl indole derivatives is also reported.

1. Introduction

Compounds based on the benzo[*b*]thiophene nucleus continue to attract significant attention in view of the range of biological activities they display. Recent examples include benzo[*b*]thiophene derivatives as anabolic agents for the potential treatment of osteoporosis,[1] or as anti-inflammatory agents,[2] together with histone deacetylase inhibitors,[3] novel antibacterial and antibiotic resistance inhibitors[4] and antimalarial agents.[5] Ring fused analogues also show interesting properties as in the recent example of anti-tumour benzo[*b*]thienonaphthyridinones derived from benzo[*b*]thiophene-2-carboxamides.[6] As part of a program targeted at potential antimicrobial (antibacterial and antiplasmodial) agents with novel structures, we became interested in compounds based on the generic structure **1** in which was embedded the benzo[*b*]thiophene-2-carboxamidic structural motif. Earlier work had established very weak antibacterial activity in compounds of type **2** (R, R_1, R_2=H, F, Br, OCH_3, CH_3).[7] In order to modify conformational flexibility and explore SAR relationships further, it was planned to incorporate the amide nitrogen as part of a ring system I or II, or as part of both rings I and II as shown in the general structure 1. In the context of the latter design objective, and with a view to potential synthetic accessibility, we targeted the semi-constrained nine-membered ring (ring I) derivative **10** (Scheme 2), with ring II being part of a tetrahydroisoquinoline moiety, together with the tightly constrained analogue **13** (Scheme 3), with rings I and II both being five-membered. The syntheses of **10** and **13** are now reported in this paper.



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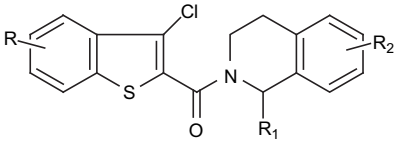

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2. Results and discussion

In the syntheses of both **10** and **13**, the overall strategy involved, in part, a common starting material **3**, and completion of ring I in the penultimate step by a Ru-mediated ring closing metathesis (RCM) reaction or a Pd-promoted oxidative cyclisation reaction,

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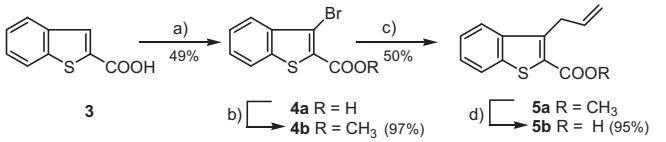
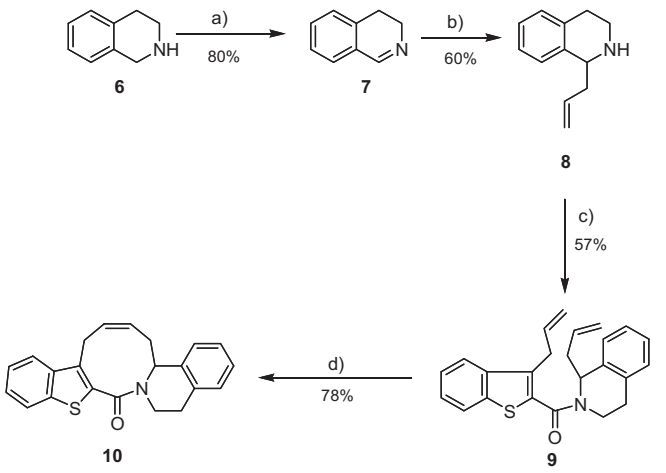
respectively. The highly versatile ring closing metathesis procedure has been applied successfully[8] to nine-membered ring formation but not, as far as we are aware, with bis-ring fused systems as in **10**. The precursor required for the RCM was the di-allyl substituted benzo[*b*]thiophene-isoquinoline **9** and this was conveniently accessed in turn from commercially available benzo[*b*]thiophene-2-carboxylic acid (**3**) (Scheme 1) and 1,2,3,4-tetrahydroisoquinoline (**6**) (Scheme 2).



Scheme 1. (a) (i) CH_3COOH, CH_3COONa, (ii) Br_2, 55 °C; (b) (i) MeOH, H_2SO_4; (c) (i) CH_2=$CHCH_2SnBu_3$, Ph_3P, $PdCl_2$, DMF, 90–100 °C/sealed tube; (d) (i) 2% LiOH, THF, (ii) 1 M HCl.



Scheme 2. (a) (i) NBS, DCM, 5 h, (ii) distillation; (b) **7** (i) Zn powder, THF, (ii) CH_2=$CHCH_2Br$, 2 days rt; (c) (i) **5b**, DCC, HOBt, DMF; (d) (i) Grubbs' first generation catalyst (polymer supported), DCM, 12 h reflux.

Regiospecific electrophilic bromination of **3** gave the known 3-bromo derivative **4a** in moderate yield, and after protection of the carboxylic acid as the methyl ester **4b**, a Stille coupling with allyl tributylstannane gave **5a**. Alkaline hydrolysis followed by acidification then afforded the allylated acid **5b** (Scheme 1) required for coupling with the amine **8** (Scheme 2).

In a separate reaction stream, the 1-allyl-tetrahydroisoquinoline **9** could be obtained in good yield in a two step process involving oxidation of **6** to the dihydroisoquinoline **7** on reaction[9a] with NBS, followed by an organozinc-mediated nucleophilic addition[10] of the allyl group at C1 to give **8**[9b] in moderate yield (Scheme 2). This amine **8** was then smoothly converted to the amide **9** on reaction with the carboxylic acid **5b** in the presence of dicyclohexylcarbodiimide and HOBt. With the di-allyl substituted amide **9** in hand, successful ring closing metathesis using Grubbs' first generation Ru catalyst (with the polymer bound or the homogeneous catalyst) then realised the target fused nine-membered ring derivative **10** in good yield. Both the polymer supported Grubbs' first generation catalyst and the homogeneous version gave similar yields but ease of work-up was an advantage with the former catalyst. The structure of **10**, which is the first representative of a new heterocyclic ring system, was secured on the basis of the ^1H and ^{13}C NMR and MS data. From the ^1H NMR it appeared that only one diastereomer was present with the coupling constant for the vicinal alkenyl protons suggesting the (*Z*)-configuration for the nine-membered ring olefinic bond. Preliminary computational studies using AM1 minimisation[11] suggested that the (*Z*) arrangement of the olefinic double bond in the ring was about 5 kcal mol^{-1} more stable than its (*E*) counterpart. This appears to be due in part to the steric strain induced on the tertiary carbon adjacent to the amide nitrogen. In the case of the (*E*)-isomer there is a larger deviation from tetrahedral geometry for this carbon than there is in the corresponding carbon for the *Z*-isomer. This feature, and the overall structure of **10**, was confirmed by a single crystal X-ray study.

The X-ray structure determination of **10** indicated that one formula unit (a single molecule), devoid of crystallographic symmetry, comprised the asymmetric unit of the structure (Fig.1). The geometries of the two peripheral benzo[*b*]thiophene and tetrahydroisoquinoline ring systems and the lactam and olefinic components were as expected. Torsion angles in the bonds around the nine-membered ring were as follows (carbon atom numbers only): 2–3, 3-N(4), N(4)-11, 11–12, 12–13, 13–14, 14–15, 15–16, 2–16: −52.1(4) −2.4(3), 107.5(2), −37.3(3), −57.6(4), −5.9(4), 99.2(3), −34.7(4), 8.2(5), while those in the fused NC_5 ring were: N(4)-5, 5–6, 6-6A, 6A–10A, 10A-11, N(4)-11: −67.5(2), 46.3(3), −15.3(3), −0.2(3), −15.8(3), 50.2(2); O(3), 2–3-N(4)-5, 13–12–11–10a and S-2–3-O(3) were −4.4(3), 177.3(2), −159.4(2), −40.2(3)°. The C(13)–C(14) double bond length was 1.319(4) Å. The dihedral angle between the peripheral C_8S and C_6 planes was 78.70(8)° and between those and the C.C:C.C plane 80.3(1) and 54.0(1)°. The X-ray derived structure closely matched the local AM1 minimum structure for the (*Z*)-isomer (Supplementary data).

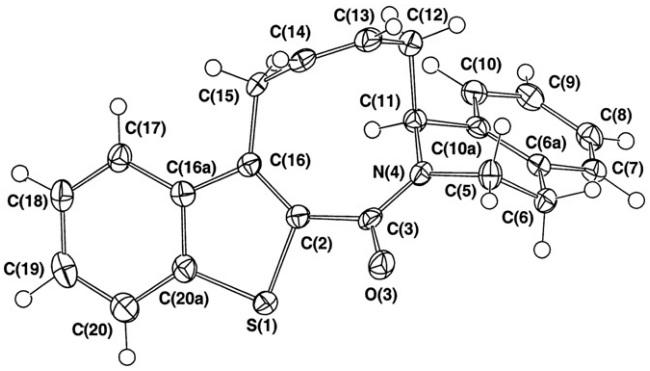
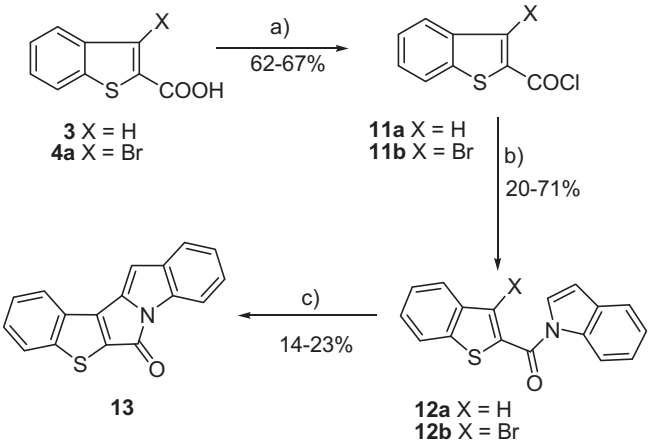


Fig. 1. Molecular projection of **10**; 50% probability amplitude displacement ellipsoids are shown for the non-hydrogen atoms and hydrogen atoms have arbitrary radii of 0.1 Å. Non-systematic numbering is used.

In the synthesis of the other more conformationally constrained target molecule **13**, Pd-mediated oxidative cyclisation[12] of the amide precursors **12a** and **12b** was investigated (Scheme 3). In this approach the amide **12a**, which was readily accessed from the carboxylic acid **3** via its acid chloride **11a** and indole, was heated



Scheme 3. (a) (i) $SOCl_2$, pyridine, toluene; (b) (i) NaH, DMF, (ii) indole; (c) (i) $Pd(OAc)_2$, glacial HOAc, heat.

with palladium(II) acetate in glacial acetic acid. It was anticipated that oxidative cyclisation should proceed to complete the five-membered fused ring and indeed this was the case with the fused lactam **13** being obtained although in low yield (14%). Some improvement in the yield of **13** was realised (23%) when the bromo analogue **12b** (obtained from **4a** via **11b** and indole) was heated in acetic acid with palladium(II) acetate. Yields in this cyclisation reaction were presumably compromised by competitive palladation at the C5 position in the cyclised product **13** thus providing scope for other reaction pathways.[13]

The compound **13**, with the three contiguous five-membered rings, also represents a new condensed heterocyclic ring system. An AM1 local minimum-derived molecular model (results not shown) confirmed that, as expected, **13** was highly planar, and, consistent with the extensive π-electron delocalisation possible, this compound is a deep orange-red colour. In the ^{1}H NMR spectrum the signal for the indolic H5 proton was assigned to a singlet at δ 6.57, while a signal at δ 162.9 in the ^{13}C NMR was consistent with the presence of the lactam.

Studies on the antimicrobial activity of **10** and some other lactams will be reported separately.

3. Conclusions

Compact syntheses of two new condensed benzo[*b*]thiophene-fused heterocyclic ring skeletons containing a central lactam moiety as part of a nine- or five-membered ring were achieved. The lactam nitrogen was part of a reduced isoquinoline or an indole ring system. Both synthetic routes used the same benzo[*b*]thiophene-2-carboxylic acid as one of the starting materials and a common strategy of penultimate lactam ring formation via Ru- or Pd-mediated cyclisations through C–C bond formation. The routes described should be amenable to further generalisation to substituted derivatives and analogues of these polycyclic systems of potential chemical and biological interest.

4. Experimental

4.1. General

The melting point (mp) determinations were recorded on a Reichert melting point apparatus and are reported uncorrected. Unless otherwise stated, proton NMR spectra were acquired on a Varian Unity 300 NMR spectrometer running at 299.5 MHz at 298 K. Chemical shifts are quoted in δ values in parts per million shift relative to TMS. Coupling constants (*J*) are reported in hertz, with signal multiplicity designated as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), quintet (qn), sextet (sx), multiplet (m) and broad (b). Unless otherwise stated, ^{13}C NMR spectra were acquired on a Varian Unity 300 NMR spectrometer running at 74.99 MHz at 298 K. Completely proton decoupled spectra were recorded. Low-resolution chemical ionization (isobutane, CI^+) mass spectroscopy (LRMS) was obtained on a Shimadzu CC-17A gas chromatograph equipped with a QP-5000 mass spectrometer and CI-50 chemical ionization controller. The direct probe insertion method was used to acquire data. High-resolution mass spectra (HRMS) (methane CI^+ and EI^+) were determined on a VG Autospec spectrometer using PFK (Perfluorokerosene) as the reference. UV spectra (solvent corrected) were recorded on Shimadzu 2401-PC-UV–vis spectrophotometer. IR spectra were recorded on neat solids using a Thermo Avatar 360 FTIR instrument.

Column chromatography was performed using silica gel 60 (230–400 mesh, Merck). Reactions were monitored with thin layer chromatography (0.25 mm aluminium backed silica gel plates) using analytical grade solvents and R_f values were determined using these plates. Chromatographic solvent mixtures refer to volume ratios. Column chromatography was performed with the indicated solvents freshly distilled over molecular sieves (4 Å). Where indicated, preparative plate chromatography for separating smaller quantities of isolates was performed using pre-made silica plates with aluminium backing (0.2 mm thickness) supplied by Merck. Visualization of the separated bands on preparative TLC plates was done using short and long-wavelength UV light.

Organic solvent extracts were dried over anhydrous Na_2SO_4 and solvents were removed in vacuo by a Büchi rotary evaporator. Petroleum spirit (pet. spirit) refers to the boiling point range 40–60 °C. The carboxylic acid (**3**) and the 1,2,3,4-tetrahydroisoquinoline (**6**) were obtained from Aldrich and were used as received.

4.2. Activation of zinc powder and syntheses

Zinc powder (4.0 g, 62.6 mmol) was suspended in 0.1 M HCl (15 mL) and stirred at room temperature for 1 min. The mixture was then vacuum filtered and the solid washed successively with distilled water (20 mL), ethanol (20 mL) and finally diethyl ether (25 mL). The zinc powder was then dried under vacuum and stored in a vacuum desiccator over silica gel.

*4.2.1. 3-Bromobenzo[b]thiophene-2-carboxylic acid (**4a**).* Bromine (2.48 g, 31.4 mmol) was added dropwise to a solution of the carboxylic acid **3** (1.0 g, 5.61 mmol), and anhydrous sodium acetate (1.0 g, 12.1 mmol) in glacial acetic acid (35 mL). The reaction mixture was stirred at 55 °C under a reflux condenser in a nitrogen atmosphere over 24 h. The mixture was poured into ice water and the resulting precipitate filtered under reduced pressure and then washed with distilled water (3×25 mL) followed by cold ethanol (25 mL) to afford a colourless solid. The product was then oven-dried for 10 min and recrystallised from hot acetone to afford **4a** (0.70 g, 49%) as colourless needles. Mp 280–283 °C (lit.[14] mp 278–279 °C). ^{1}H NMR (CD_3COCD_3, 300 MHz): δ 7.58–7.67 (m, 2H, Ar–H5 and H6), 7.99–8.05 (m, 2H, ArH4 and H7); ^{13}C NMR: δ 115.2 (C3), 122.8 (C7), 125.5 (C5), 125.8 (C6), 128.3 (C2), 138.7 (C3a), 139.4 (C7) and 161.9 (C=O). MS (CI^+), *m*/*z* 257, 259 [MH^{+1}, ^{79}Br, ^{81}Br].

*4.2.2. Methyl 3-bromobenzo[b]thiophene-2-carboxylate (**4b**).* The acid **4a** (1.0 g, 3.89 mmol) was converted to its methyl ester derivative **4b** by heating it at reflux in methanol (15 mL) and a catalytic amount of concentrated sulfuric acid overnight. Compound **4b**[15] was obtained as a white solid (0.9 g, 90%). MS (EI^+), *m*/*z* 270, 272 [$M^{+\bullet}$, ^{79}Br, ^{81}Br].

*4.2.3. Methyl 3-allylbenzo[b]thiophene-2-carboxylate (**5a**).* A glass high-pressure tube was flushed with nitrogen and a mixture of palladium(II) chloride (0.1 g, 0.85 mmol) and triphenylphosphine (0.23 g, 0.87 mmol) added, and to this mixture was then added the methyl ester **4b** (0.5 g, 1.85 mmol) in anhydrous DMF (15 mL) and stirring continued. Allyl tributylstannane (0.6 mL) was then injected into the reaction mixture and the tube sealed. The mixture was heated at 90 °C with stirring for 2 h, and then at 100 °C for 36 h. The reaction mixture was then cooled to room temperature and the solvent evaporated under reduced pressure to give a yellow oil. The oil was then purified via column chromatography (10% ethyl acetate/pet. spirit) to give **5a** (0.21 g, 50%) as a yellow oil. R_f 0.7 (10% ethyl acetate/pet. spirit). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.91 (s, 3H, CH_3), 4.15 (d, *J*=4.2 Hz, 2H, H1′), 5.04–5.13 (m, 2H, H3′), 5.97–6.06 (m, 1H, H2′), 7.46 (m, 2H, ArH–H5 and H6), 7.85 (m, 2H, ArH–H4 and H7). ^{13}C NMR: δ 31.6 (C1′), 52.4 (CH_3), 116.2 (C3′), 122.9 (C7), 124.1 (C4), 124.7 (C5), 124.8 (C6), 127.4 (C2), 135.4 (C2′), 140.9 (C3b), 142.7 (C3a) and 163.6 (C=O). MS (CI^+) *m*/*z* 233 [MH^{+1}]; HRMS (CI) found: 232.0555 (1.0 ppm), required: 232.0558 for $C_{13}H_{12}O_2S$.

*4.2.4. 3-Allylbenzo[b]thiophene-2-carboxylic acid (**5b**).* A mixture of **5a** (0.17 g, 0.73 mmol) and 2% aqueous LiOH (10 mL) in

tetrahydrofuran (15 mL) was heated at reflux for 3 h. The reaction mixture was then cooled to room temperature and the solvent was concentrated under reduced pressure. The residue was then acidified with 1 M HCl at 5–10 °C (ice bath). The precipitate was vacuum filtered, washed with distilled water (20 mL) and then dried under vacuum to give **5b** (0.14 g, 93%) as a colourless solid. ^{1}H NMR (CD_3COCD_3, 300 MHz): δ 4.13 (d, J=4.2 Hz, 2H, H1′), 4.97; 5.14 (m, 2H, H3′), 5.96; 6.05 (m, 1H, H2′), 7.52 (m, 2H, ArH–H5 and H6), 7.97 (dd, J=3.45, 5.26 Hz, 2H, ArH–H4 and H7). ^{13}C NMR: δ 31.6 (C1′), 116.2 (C3′), 122.9 (C7), 124.1 (C4), 124.7 (C5), 124.8 (C6), 127.4 (C2), 135.4 (C2′), 140.9 (C3b), 142.7 (C3a) and 163.6 (C=O). MS (CI^+) m/z 219 [MH^{+1}].

*4.2.5. 3,4-Dihydroisoquinoline (**7**).* The tetrahydroisoquinoline **6** (3.0 g, 22.6 mmol) was dissolved in DCM (50 mL) under nitrogen. To this stirred solution, *N*-bromosuccinimide (4.41 g, 24.8 mmol) was gradually added over 20 min. The mixture was stirred at room temperature for 1.5 h. Sodium hydroxide solution (15 mL, 30%) was added and stirring was continued for 1 h. Distilled water (20 mL) was added to the mixture, and stirred for a further 15 min. The two phases were separated and the aqueous phase washed with DCM (20 mL). The combined organic phases were washed with water (25 mL) and extracted with 2 M hydrochloric acid (2×30 mL, 15 mL). Combined aqueous extracts were washed with DCM (25 mL) and basified to pH 11 with concentrated aqueous ammonia solution, to afford a yellow oil, which was back extracted with DCM (20 mL, 2×15 mL), dried and the solvent evaporated under reduced pressure. The yellow oil was distilled under reduced pressure on a Kugelrohr distillation apparatus and the imine **7**[16] collected at 140 °C between 50 and 70 mbar as a colourless oil (2.32 g, 79%), which turned pale yellow on standing. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.71 (t, J=7.8 Hz, 2H, H4), 3.74 (t, J=6.6 Hz, 2H, H3), 7.12 (d, J=7.5 Hz, 1H, H8), 7.21–7.34 (m, 3H, H5, H6 and H7) and 8.31 (s, 1H, H1). ^{13}C NMR: δ 25.2 (C4), 47.5 (C3), 127.2 (C7), 127.3 (C5), 128.6 (C8), 131.2 (C6), 136.4 (C8a) and 160.4 (C1). MS (CI^+), m/z 132 [MH^{+1}].

*4.2.6. 1-Allyl-1,2,3,4-tetrahydroisoquinoline (**8**).* Allyl bromide (1.83 g, 15.3 mmol) was added to a stirred suspension of activated zinc powder (1.00 g, 15.4 mmol) in dry tetrahydrofuran (20 mL) under nitrogen. The mixture was cooled to 0 °C then **7** (2.00 g, 15.0 mmol) in dry tetrahydrofuran (30 mL) was added slowly and stirring maintained for 2 days. Saturated sodium bicarbonate solution (25 mL) was then added and the mixture stirred for 15 min before being filtered through Celite. The organic solvent was removed under reduced pressure and the resulting aqueous mixture extracted with DCM (1×25 mL, 1×10 mL). The combined organic extracts were extracted with 2 M hydrochloric acid (2×25 mL). Combined aqueous portions were washed with DCM (25 mL), basified with concentrated aqueous ammonia solution to pH 11 on an ice bath, and then back extracted with DCM (2×25 mL, 1×15 mL). The combined organic extract was dried, and solvent evaporated under reduced pressure to afford the 1-allylated tetrahydroisoquinoline **8**[9b] as a pale yellow oil (1.55 g, 59%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.63; 2.49 (m, 2H, H1′), 2.69 (qn, J=1.72 Hz, 2H, H4), 2.93 (qn, J=4.05 Hz, 2H, H3), 5.15 (m, 2H, H3′), 5.81 (m, 1H, H2′), 4.03 (t, J=4.5 Hz, 1H, H1), 7.05–7.16 (m, H5, H6, H7 and H8). ^{13}C NMR: δ 30.2 (C4), 40.9 (C3), 41.3 (C2′), 55.3 (C1), 118.1 (C3′), 126.0 (C7), 126.2 (C5), 129.5 (C5 and C8), 135.6 (C1′), 135.9 (C8a), and 138.9 (C4a). MS (CI^+), m/z 174 [MH^{+1}].

*4.2.7. (1-Allyl-1,2,3,4-tetrahydroisoquinolin-2-yl)(3-allylbenzo[b] thien-2-yl)methanone (**9**).* The isoquinoline **8** (0.11 g, 0.063 mmol) was added to a cooled mixture (ice bath) of **5b** (0.14 g, 0.61 mmol), 1,3-dicyclohexylcarbodiimide (0.13 g, 0.63 mmol), and 1-hydroxybenzotriazole (0.10 g, 0.74 mmol) in dry DMF (10 mL). The mixture was stirred at room temperature under nitrogen (24 h). The precipitated dicyclohexylurea was removed by vacuum filtration. The solvent was then evaporated under reduced pressure to give an oily residue, which was then taken up in ethyl acetate (20 mL) and filtered to remove further dicyclohexylurea. The filtrate was then washed with distilled water (40 mL), dried and the solvent evaporated to give a yellow oil. The oil was further purified via column chromatography (20% ethyl acetate/pet. spirit) to give **9** (0.10 g, 55%) as a clear oil. R_f 0.6 (20% ethyl acetate/pet. spirit). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.70; 2.95 (m, 2H, H1″ allyl THIQ; tetrahydroisoquinoline), 3.50; 3.66 (m, 2H, H4′), 3.66–3.88 (m, H3′ and H1″ allyl BTP; benzo[*b*]thiophene), 4.85–5.18 (m, 5H, 2× H3″ (CH_2) and H1′), 5.91–6.02 (m, 2H, 2× H2″), 7.11–7.36 (m, 4H, ArH THIQ), 7.42 (m, 2H, ArH–H5 and H6), 7.79 (m, 2H, ArH–H4 and H7). ^{13}C NMR: δ 29.8 (C4′), 31.7 (C1″, allyl BTP), 41.5 (C1″, allyl THIQ), 41.8 (C3′), 52.2 (C1′), 116.6 (C3″, THIQ), 118.1 (C3″, BTP), 122.7 (C7), 123.3 (C4), 124.7 (C6), 125.5 (C5), 127.0 (C5′), 135.0 (C2′, THIQ), 135.4 (C2), 136.6 (C2′, BTP) and 164.7 (C=O). MS (CI^+), 374 [MH^{+1}]; 332 ($C_{21}H_{18}NOS^+$).

*4.2.8. 5,8,16,17-Tetrahydroazonino[3,4-b]benzo[b] thieno[3,2-a] isoquinolin-14(4bH)-one (**10**).* Dry DCM (10 mL) was added to a mixture of **9**, (0.1 g, 0.26 mmol) and polymer supported Grubbs' first generation catalyst (0.15 g) under nitrogen and the mixture heated at reflux for 12 h. The reaction mixture was then cooled to room temperature and then filtered to recover the catalyst. The filtrate was evaporated under reduced pressure to afford a clear oil, which solidified rapidly. The crude product was further purified via column chromatography (30% ethyl acetate/pet. spirit) to give a colourless solid, which was recrystallised from ethanol to give **10** (0.07 g, 78%) as a highly crystalline solid. *Note*: A similar reaction was also attempted using the homogeneous Grubbs' first generation catalyst to give **10** (0.18 g, 75%) as a crystalline solid after chromatography and re-crystallisation from ethanol. Mp 233–235 °C. R_f 0.4 (30% ethyl acetate/pet. spirit). ν_{max} 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.73–2.86 (m, 4H, H5 and H16), 3.64–3.88 (m, 2H, H17); 4.10 (q, J=13.8 Hz, 2H, H8), 5.02 (t, J=6.6 Hz, 1H, H15a), 5.99 (q, J=3.3 Hz, 1H, H7), 6.17 (q, J=10.3 Hz, 1H, H6), 6.92–7.16 (m, 4H, ArH–H1–H4), 7.46 (m, 2H, ArH–H5 and H6), 7.82 (dd, J=3.45, 5.3 Hz, 2H, ArH–H4 and H7). ^{13}C NMR: δ 27.9 (C8), 28.2 (C17), 36.2 (C5) 36.7 (C16), 59.0 (4b), 122.8 (C9 and C12), 125.8–127.1 (C1–C3, C10 and C11), 129.4 (C7), 130.2 (C6), 133.2 (C13a), 138.0 (C4a), 138.9 (C17a), 140.0 (C8a) and 164.3 (C=O). MS (CI^+), 346 [MH^{+1}]; HRMS (CI) found: 345.1183 (1.3 ppm), required: 345.1187 for $C_{22}H_{19}NOS$ [M].

*4.2.9. Benzo[b]thiophene-2-carbonyl chloride (**11a**).* Thionyl chloride (0.81 mL, 11.1 mmol) was added to a solution of benzo[*b*] thiophene-2-carboxylic acid **3** (0.4 g, 2.24 mmol), in pyridine (0.3 mL, 1.8 mmol) and toluene (15 mL, 14.1 mmol) at reflux. The reaction mixture was quenched in ice water and the toluene evaporated in vacuo. The acid chloride was extracted with distilled DCM (2×25 mL, 2×10 mL) and the combined organic extracts washed with distilled water (2×20 mL) and dried. The solvent was evaporated under reduced pressure to give a brown residue, which was purified using flash chromatography with DCM as the eluent to yield **11a**[17] (0.27 g, 61%) as a colourless solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50 (m, 2H), 7.91 (m, 2H), 8.27 (s, 1H). ^{13}C NMR: δ 123.1 (C3), 125.9 (C7), 126.9 (C4), 128.9 (C5 and C6), 136.1 (C2), 138.3 (C3a), 144.3 (C7) and 161.9 (C=O). MS (CI^+), m/z 197, 199 [MH^{+1}, ^{35}Cl, ^{37}Cl].

*4.2.10. 3-Bromobenzo[b]thiophene-2-carbonyl chloride (**11b**).* In the same manner as that reported for **11a**, reaction of **4a** (0.60 g, 2.33 mmol) yielded **11b** (0.43 g, 67%) after chromatography (DCM) as a colourless solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58–7.67 (m, 2H, ArH–H5 and H6), 7.99–8.05 (m, 2H, ArH–H4 and H7). ^{13}C NMR:

δ 115.2 (C3), 122.8 (C7), 125.5 (C5), 125.8 (C6), 128.3 (C2), 138.7 (C3a), 139.4 (C7), and 161.9 (C=O). MS (CI^+), *m/z* 273, 275, 277 [MH^{+1}, Cl, Br].

*4.2.11. (Benzo[b]thien-2-yl)(1H-indol-1-yl)methanone (**12a**).* Anhydrous DMF (10 mL) was syringed in to a flask containing sodium hydride (0.082 g, 3.51 mmol) under nitrogen and the solution cooled to 5 °C (ice bath) with stirring. Indole (0.16 g, 1.36) dissolved in dry DMF (10 mL) was then added and stirring maintained for 45 min between 0 and 5 °C. The reaction mixture was then warmed to room temperature and stirring continued for a further 45 min after which time the mixture was cooled to −60 °C (liquid nitrogen/chloroform). The acid chloride **11a** (0.27 g, 1.37 mmol) dissolved in dry DMF (15 mL) was then added slowly and the mixture warmed to room temperature and stirring maintained over 12 h. After all the substrate had reacted, the solvent was concentrated in vacuo to give a brown solid residue. Distilled water (20 mL) was added to the flask containing the residue and the mixture stirred for 1 h, after which time it was extracted with DCM (2×25 mL). The aqueous layer was washed once with DCM (15 mL). The combined organic solvents were then dried and evaporated to give a brown oil, which solidified rapidly. The solid was purified by column chromatography (40% ethyl acetate/hexane) to give **12a** (0.27 g, 71%) as a brown crystalline solid. Mp 44–47 °C. R_f 0.8 (40% ethyl acetate/hexane). ν_{max} 1662 cm^{-1} (CO). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.71 (d, *J*=3.6 Hz, 1H, H3), 7.28 (d, *J*=15.6 Hz, 1H, H2), 7.33–7.46 (m, 4H, H5; H6, H5′; H6′), 7.74 (d, *J*=3.9 Hz, 1H, H4), 7.90 (s, 1H, H3′), 7.93 (dd, *J*=3.45, 5.3 Hz, 2H, ArH–H4 and H7), 8.44 (dd, *J*=1.2, 2.6 Hz, 1H, H7). ^{13}C NMR: δ 102.8 (C3), 111.2 (C7), 120.0 (C4), 120.9 (C6), 121.2 (C3′), 122.2–125.5 (C5, C6, C4′-C7′), 125.8 (C2), 130.4 (C3a) and 138.7 (C7a). MS (CI^+), 278 [MH^{+1}]; 161 ($C_9H_5OS^+$).

*4.2.12. (3-Bromobenzo[b]thien-2-yl)(1H-indol-1-yl) methanone (**12b**).* In the same manner as that reported for **12a**, reaction of the bromo substituted acid chloride **11b** (0.60 g, 2.33 mmol) and indole (0.34 g, 2.90 mmol) yielded **12b** after chromatography (40% ethyl acetate/hexane) as a brown solid (0.20 g, 45%). R_f 0.6 (10% ethyl acetate/hexane). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.71 (d, *J*=3.6 Hz, 1H, H3), 7.26 (d, *J*=15.6 Hz, 1H, H2), 7.33–7.44 (m, 4H, H5; H6, H5′; H6′), 7.74 (d, *J*=3.9 Hz, 1H, H4), 7.93 (dd, *J*=3.45, 5.26 Hz, 2H, ArH–H4 and H7), 8.44 (dd, *J*=1.2, 2.5 Hz, 1H, H7). ^{13}C NMR: δ 102.6 (C3), 111.3 (C7), 120.0 (C4), 120.9 (C6), 122.2–125.5 (C5, C6, C4′-C7′), 125.8 (C2), 130.2 (C3a), 138.7 (C7a) and 164.3 (C=O). MS (CI^+), *m/z* 356, 358 [MH^{+1}, ^{79}Br, ^{81}Br], 239,241 [$C_9H_4BrOS^+$, ^{79}Br, ^{81}Br].

*4.2.13. 11H-Benzo[b]thieno[2,3-c]pyrrolo[2,3-a]indol-11-one (**13**) from the amide **12a**.* To a mixture of **12a** (0.22 g, 0.79 mmol) and palladium(II) acetate (0.17 g, 0.75 mmol) was added glacial acetic acid (70 mL) and the mixture heated to 100 °C with continuous stirring under nitrogen for 7 h. The reaction mixture was cooled to room temperature and solvent evaporated under reduced pressure to give a black residue. The crude residue was dissolved in DCM (15 mL) and vacuum filtered through Celite to remove suspended palladium(0) particles. After solvent evaporation, the impure solid was purified by chromatography (40% ethyl acetate/hexane) to give **13** (0.03 g, 14%) as a deep orange coloured solid. The product was further purified by multi-development preparative TLC (20% ethyl acetate/hexane) to give **13** (6.6 mg). Mp 188–190 °C. R_f 0.8 (30% ethyl acetate/hexane). ν_{max} 1714 cm^{-1} (CO). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.57 (s, 1H, H5), 7.00–7.17 (m, 2H, H2 and H3), 7.25–7.55 (m, 3H, H1, H7 and H8), 7.72 (d, *J*=3.9 Hz, 1H, H4), 8.06 (m, 2H, H6 and H9). ^{13}C NMR: δ 102.1 (C5), 111.4 (C1), 119.6 (C2), 121.7 (C3 and C9), 124.7–124.9 (C5a, C7 and C8), 128.0 (C4a) 135.2 (C12a) and 162.9 (C=O) MS (CI^+), *m/z* 276 [MH^{+1}]; HRMS (CI) found: 276.0484 (0.3 ppm), required: 276.0483 for $C_{17}H_{10}NOS$.

*4.2.14. 11H-Benzo[b]thieno[2,3-c]pyrrolo[2,3-a]indol-11-one (**13**) from the bromoamide **12b**.* In the same manner as that described for **12a** above, **12b** (0.20 g, 0.75 mmol) was reacted with palladium(II) acetate in glacial acetic acid to form **13**, which was isolated after chromatography as a deep orange coloured solid (0.05 g, 23%).

4.3. Single crystal X-ray structure determination of (10)

A full sphere of CCD/area-detector diffractometer data was measured (Bruker AXS instrument; monochromatic Mo Kα radiation; ω-scans; λ=0.7107$_3$ Å; $2\theta_{max}$=58°; *T* ca. 150 K) yielding 15,200 reflections, these merging to 4146 unique (R_{int}=0.062) after 'empirical'/multiscan absorption correction (proprietary software; μ_{Mo}=0.21 mm; specimen: 0.11×0.10×0.04 mm; '$T_{min/max}$=0.90), which were used in the full matrix least squares refinement on F^2 (neutral atom complex scattering factors; SHELXL program;[18] reflection weights $(\sigma^2(F_o^2)+(0.040P^2)+1.78P)^{-1}$ $(P=(F_o^2+2F_c^2)/3)$); 2681 with $I>2\sigma(I)$ were considered 'observed'.

Residuals at convergence were *R*1=0.060, *wR*2=0.14; *S*=1.02. $|\Delta\rho_{max}|$=0.41 e $Å^{-3}$. CCDC798767.

Crystal data: $C_{22}H_{19}NOS$, M_r=345.4. Monoclinic, space group $P2_1/n$ (C_{2h}^5 No. 14 (variant)), *a*=13.515(3), *b*=8.1116(16), *c*=16.273(4) Å, β=111.684(3)°, *V*=1657.7(6) $Å^3$. D_c (*Z*=4)=1.38$_4$ g cm^{-3}.

4.4. Molecular modelling

The modelling studies were performed using AM1[11] running on the computer program Spartan'02 (Wavefunction Inc., 2002).

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Supplementary data

The minimum energy conformation model of compound **10**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.093.

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