Synthesis of Isothiocyanato-1-[1-(2-benzo[*b*]thienyl)cyclohexyl]piperidines, Potential Irreversible Ligands at the Dopamine Re-uptake Site

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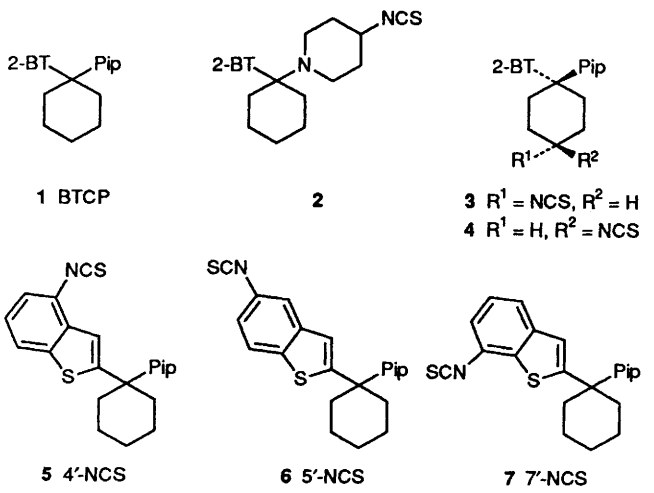
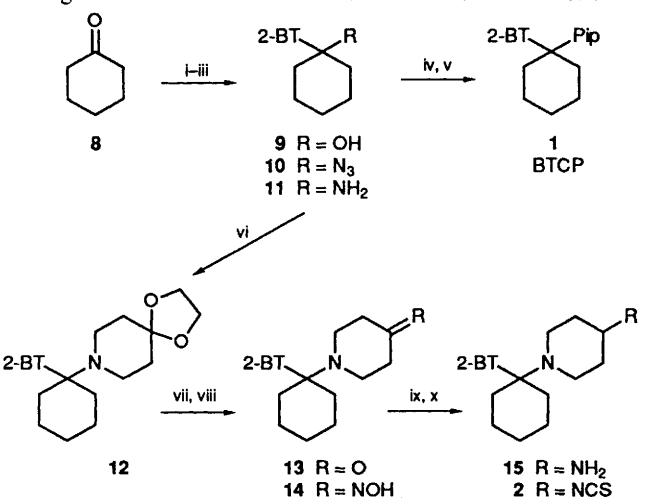
Isomeric isothiocyanate derivatives **2**–**7** of the potent dopamine re-uptake (DA) inhibitor 1-[1-(2-benzo[*b*]thienyl)cyclohexyl]piperidine (BTCP **1**) have been synthesized as potential irreversible ligands for this site. $NaNO_2$–CF_3CO_2H provided a mild procedure for mononitration of the benzo[*b*]thienyl ring of **1** as a route to aryl isothiocyanates **5**–**7**. Novel methodology, utilizing 3,3-ethylenedioxypentane-1,5-diol dimethanesulfonate ester is described for the synthesis of piperidone **13**, a precursor for 4-isothiocyanatopiperidine **2**. $NaBH_4$ or $LiAlH_4$ reduction of 4-(2-benzo[*b*]thienyl)-4-hydroxycyclohexanone **18** and 4-(2-benzo[*b*]thienyl)-4-(piperidino)cyclohexanone oxime **35** gives the corresponding *cis*-diol **21** and *cis*-cyclohexane-1,4-diamine **36** as the major isomers which have been investigated as precursors to the cyclohexane ring isothiocyanates **3** and **4**. Alternative routes to **3** and **4** are compared and their stereochemical outcome investigated.

Cocaine is a major drug of abuse resulting in a number of fatalities and hospital emergencies. This and related compounds exert their behavioural effects at the dopamine (DA) transport complex by markedly increasing extracellular dopamine levels as they are potent inhibitors of DA-reuptake into dopaminergic neurons in the brain.[1] Several other classes of compounds including disubstituted piperazines (BGR12909 and 12935),[2] 1-[1-(2-benzo[*b*]thienyl)cyclohexyl]piperidine **1** (BTCP)[3] and nomifensine[4] are known to interact at binding sites on the DA-reuptake site. Irreversible ligands have proven to be valuable tools in the determination of the structure and function of receptors (for a review, see ref. 5). We aimed, therefore, to synthesize potential irreversible ligands based upon the highly selective and potent DA-reuptake ligand, BTCP **1**.[3,6] The isothiocyanate (N=C=S) group, among others, has proven suitable in the development of a variety of irreversible ligands.[5] Here we report the synthesis and characterization of isomeric isothiocyanate (N=C=S) congeners **2**–**7** of BTCP. The NCS analogues were selected in such a way as to utilize all three ring systems of **1** in order to probe the BTCP binding site for a suitably located nucleophile.

The isothiocyanate **2** (Scheme 1) was obtained in eight steps starting with cyclohexanone **8**. Condensation of **8** with 2-benzo[*b*]thienyllithium[7] (quantitative) followed by HN_3 solvolysis,[8] $LiAlH_4$ reduction and coupling with 1,5-dibromopentane[8] furnished BTCP **1** in 71% yield. Synthesis of **1** has been previously described but no synthetic details given.[3] Compound **1** was used as a precursor for aryl isothiocyanate analogues **5**–**7** of BTCP (see Scheme 5). Condensation of primary amine **11** with 3,3-ethylenedioxypentane-1,5-diol dimethanesulfonate ester[9] (Scheme 1) afforded the intermediate ethylene ketal **12** in 89% yield which on acid hydrolysis (65% yield), oximation (quantitative) and $LiAlH_4$ reduction furnished the amine **15** in 90% yield. Treatment with thiophosgene ($CSCl_2$)[10] gave the isothiocyanate **2** in 81% yield. The IR spectrum of **2** exhibited a strong band at 2095 cm^{-1} characteristic of the NCS function.



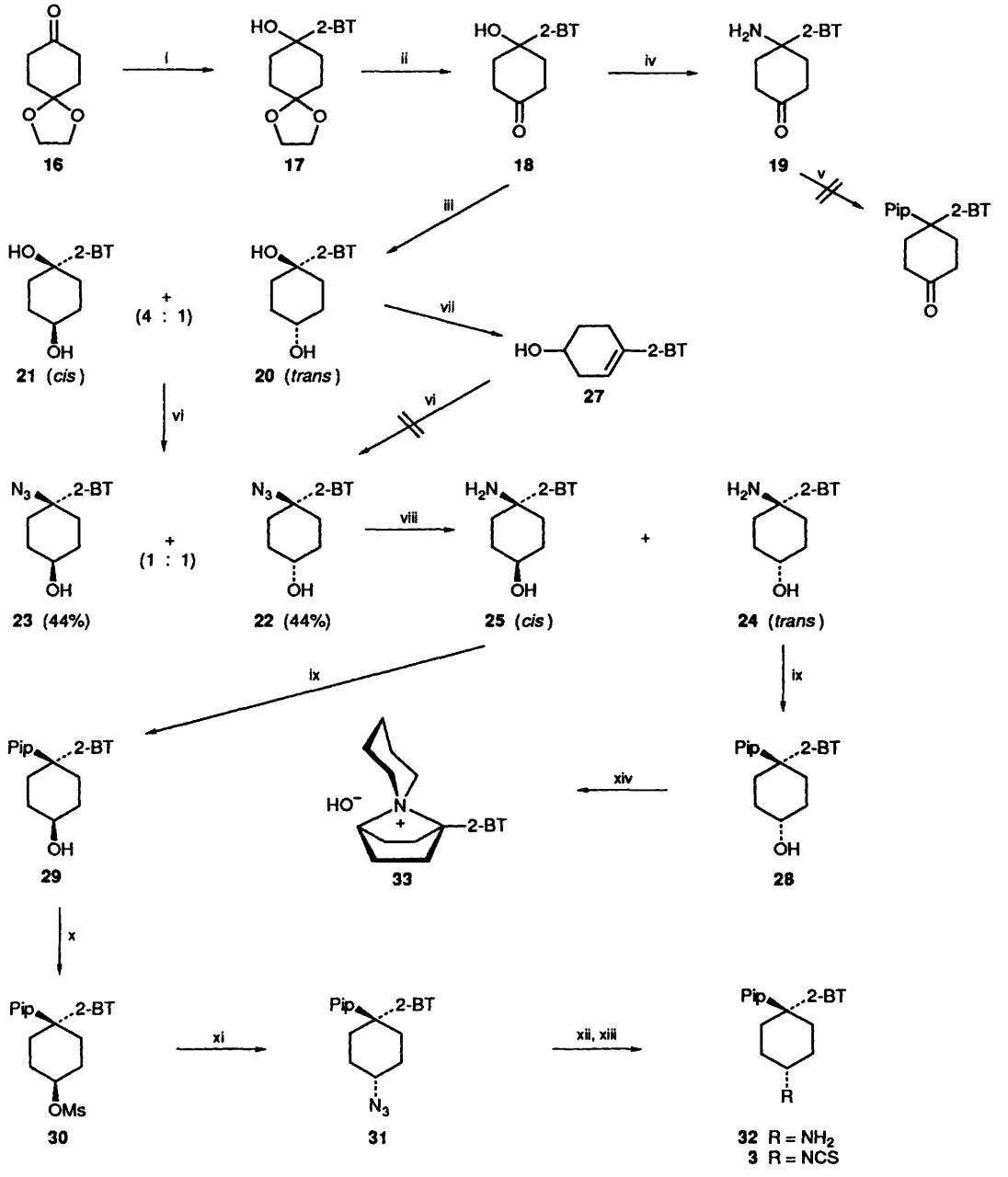
2-BT = 2-benzo[*b*]thienyl, Pip = piperidino



2-BT = 2-benzo[*b*]thienyl, Pip = piperidino

Scheme 1 i, 2-Benzo[*b*]thienyllithium, Et_2O; ii, NaN_3, CF_3CO_2H, $CHCl_3$; iii, $LiAlH_4$, Et_2O; iv, 1,5-dibromopentane, DMF, 60 °C; v, K_2CO_3; vi, 3,3-ethylenedioxypentane-1,5-diol dimethanesulfonate ester, K_2CO_3, DMF, 60 °C; vii, HCl (6 mol dm^{-3}), 60 °C; viii, NH_2OH·HCl, NaOAc, EtOH; ix, $LiAlH_4$, THF; x, $CSCl_2$, sat. aq. $NaHCO_3$, $CHCl_3$

Cyclohexyl isothiocyanate derivatives **3** and **4** were obtained starting from cyclohexanedione monoethylene ketal **16** (Schemes 2 and 4). Condensation with benzo[*b*]thienyllithium afforded the tertiary alcohol **17**[11] (Scheme 2) in quantitative



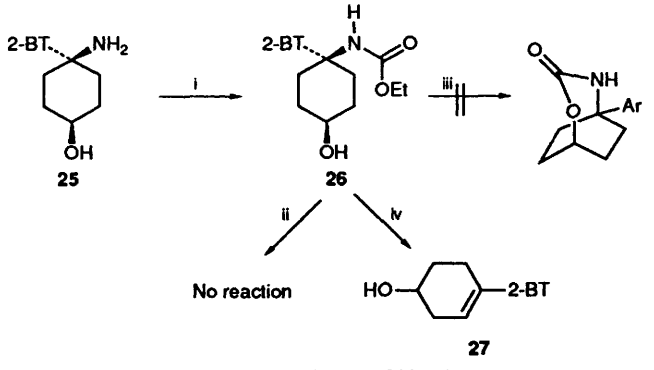
Scheme 2 i, 2-Benzo[*b*]thienyllithium, Et_2O; ii, AcOH, H_2O (4:1), 55 °C; iii, $NaBH_4$, MeOH, 0 °C; iv, NaN_3, CF_3CO_2H, $CHCl_3$; H_2, 10% Pd/C, HCl, EtOH; v, 1,5-dibromopentane, K_2CO_3, DMF, 55 °C, 7 d; vi, NaN_3, CF_3CO_2H, $CHCl_3$, 0 °C; vii, CF_3CO_2H, $CHCl_3$, 5 °C; viii, H_2, 10% Pd/C, MeOH; ix, 1,5-dibromopentane, K_2CO_3, DMF, 50 °C, 48 h; x, MsCl, Et_3N, THF; xi, NaN_3, DMF, 85 °C; xii, H_2, 10% Pd/C, HCl, MeOH; xiii, $CSCl_2$, sat. aq. $NaHCO_3$, $CHCl_3$; xiv (i) Ms_2O, Et_3N, $CHCl_3$, (ii) $CHCl_3$–aq. NaOH

yield which on hydrolysis with acetic acid–water (4:1) at 55 °C gave the ketone **18** in high yield; attempts to hydrolyse the ketal **17** using 88% formic acid at 20 °C or MeOH–aqueous HCl resulted in elimination of the benzylic hydroxy and a low yield of **18**. Treatment of **18** with HN_3 followed by catalytic hydrogenation afforded 75% overall (from **18**) yield of the amino ketone **19**. Examination of the base form of **19** by IR spectroscopy revealed a free keto group (1709 cm^{-1}). No hemiaminal formation was evident at room temperature. However, **19** proved unreactive towards 1,5-dibromopentane (several days reaction at 55 °C) presumably due to a dipolar interaction of the nitrogen lone-pair of electrons with the carbonyl group. This is in contrast to the facile reaction observed between **11** and 1,5-dibromopentane (Scheme 1). Synthesis of **3** and **4** *via* **19** was, therefore, not possible.

Reduction of **18** with $NaBH_4$ in MeOH (Scheme 2) resulted in a 1:4 mixture of the *trans*-**20** and *cis*-**21** diols. The proton α to the hydroxy group of the *trans*-diol **20** exhibited a relatively compact (*w* 17.8 Hz) multiplet centred at δ 4.08. The *cis*-diol **21** α-proton appeared as a broad (*w* 36 Hz) multiplet centred at δ 3.76 characteristic of an axial proton. Crystallization of this mixture of diols from MeOH afforded the pure *cis*-diol **21**. Treatment of either a mixture of **20** and **21** or pure **21** with NaN_3–CF_3CO_2H afforded a 1:1 mixture of the *trans*-azide **22** δ 4.02 (m, 1 H, C*H*OH) and the *cis*-azide **23** δ 3.72 (tt, 1 H, *J* 4.9 and 9.8 Hz, C*H*OH). A small amount (12% of product mixture) of the elimination product **27** (alkenic signal, a multiplet at δ 6.15) resulting from elimination of the benzylic hydroxy was also formed. The latter could be generated quantitatively by treatment of **20** and **21** with 1:1 CF_3CO_2H–

$CHCl_3$ at 5 °C (Scheme 2). Treatment of **27** with NaN_3–CF_3CO_2H in $CHCl_3$ either at 0 °C or at ambient temperature failed to give detectable amounts of the azides **22** and **23** suggesting that **27** is not an intermediate in the formation of **22** and **23** from **20** and **21**. The azides **22** and **23** were catalytically reduced to the amino alcohol mixture **24** and **25**, a small portion of which was chromatographically separated to give pure **25** identical with a reference sample prepared by a different method.[11]

In an attempt to define the *cis* or *trans* configuration of **25**, the carbamate **26** was generated in quantitative yield by reaction of the amine with EtOCOCl–$NaHCO_3$ (Scheme 3). Treatment of **26** with NaH–dimethylformamide (DMF), KOBu^t–tetrahydrofuran (THF) or overnight with boiling xylenes (137–144 °C) failed to give the corresponding cyclic carbamate. Pyrolysis of **26** at 250–270 °C for 10 min gave the cyclohexene **27** as the major product. These results suggested either a *trans* configuration or failure of the *cis* carbamate **26** to cyclize. The configuration of **25** was, however, unequivocally determined to be *cis* from single crystal X-ray analysis of **25** (Fig. 1, see later).



Scheme 3 i, EtOCOCl, $CHCl_3$, sat. aq. $NaHCO_3$; ii, boiling xylenes, reflux overnight; iii, NaH, DMF, 20 °C of Bu^{t}OK, THF, 20 °C; iv, 250→270 °C, neat, 10 min

The *trans*-hydroxy amine **24** exhibited a relatively narrow multiplet (1 H, *J* 3.8 Hz, C*H*OH) at δ 3.90 whereas the *cis*-hydroxyamine **25** gave a broader multiplet (tt, 1 H, *J* 4.6 and 9.3 Hz, C*H*OH) in its ^{1}H NMR spectrum. A mixture of **24** and **25** was treated with 1,5-dibromopentane–K_2CO_3 to give **28** and **29** (Scheme 2) which were readily separated chromatographically. Compound **29** was transformed *via* the methanesulfonate **30** to the isothiocyanate **3**. Similar treatment of **28** with $(MeSO)_2O$ in the presence of Et_3N resulted only in the unstable internally cyclized product **33** (isolated in $CHCl_3$ solution as its hydroxide salt) because of favourable (*trans*) geometry for internal displacement of $MeSO_3^-$ by the piperidine nitrogen atom.

Thus, in an alternative approach to the isothiocyanate **4** (Scheme 4), a mixture of **28** and **29** (1:1) was oxidized in high yield with dimethyl sulfoxide (DMSO)–$(COCl)_2$–Et_3N[12] to give the ketone **34**. The sequence of oximation and hydrogenation in acetic acid in the presence of PtO_2 afforded a 1:9 (^{1}H, NMR comparison) mixture of the desired amine **36** to the undesired *trans*-amine **32**. Adsorption of the piperidine ring nitrogen atom onto the catalyst surface and addition of hydrogen to the oxime C=N from the same face affords the *trans* isomer as the major product under these conditions. No significant reduction was observed under the same conditions when using 10% Pd/C instead of PtO_2, most likely a result of poisoning of the less active (than Pt) Pd/C catalyst by the benzothiophene sulfur atom. In contrast, reduction of **35** with an excess of $LiAlH_4$ at 0 °C afforded a 1:5 mixture of **32** and **36** which is comparable to the *cis*:*trans* ratio observed with

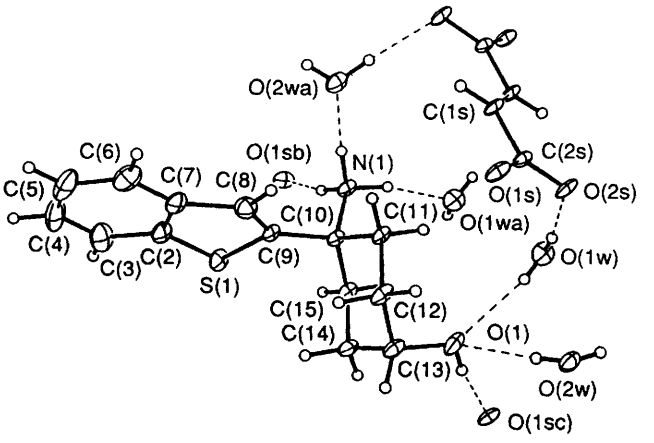
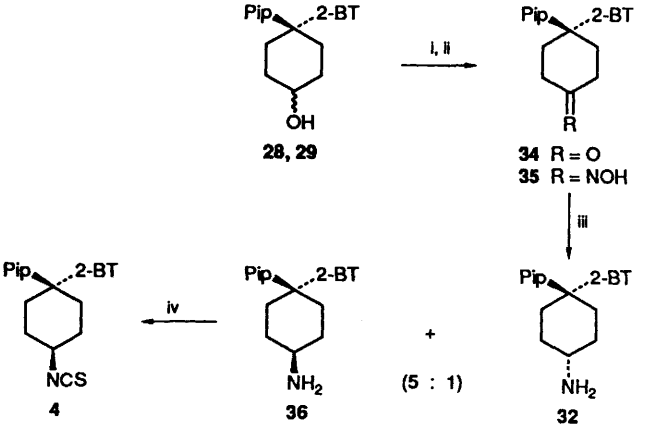


Fig. 1 The molecular structure and numbering scheme for the fumarate salt of **25**. Thermal ellipsoids are drawn at the 20% probability level. Dotted lines are hydrogen bonds and atoms [(O(1wa) and O(2wa)], O(1sb) and O(1sc) are symmetry related *via* $(x,y-1.0,z)$, $(x-0.5,-y-0.5,z)$ and $(x,y+1.0,z)$, respectively. The lower occupancy atoms in the disorder [(S(1′) and C(8′)] are not shown.



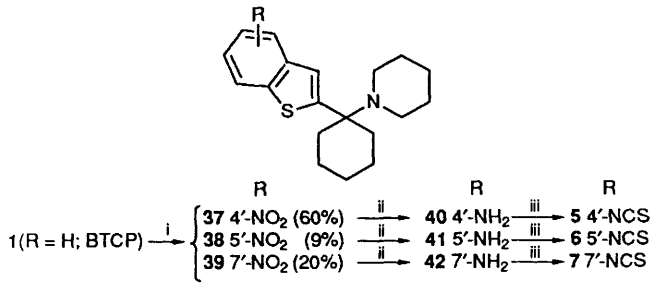
Scheme 4 i, DMSO–$(COCl)_2$, Et_3N, CH_2Cl_2, −78→20 °C; ii, NH_2OH·HCl, NaOAc, EtOH; iii, $LiAlH_4$, THF, 0 °C; iv, $CSCl_2$, sat. aq. $NaHCO_3$, $CHCl_3$

$NaBH_4$ reduction of ketone **18**. In both the case of the oxime **35** and the ketone **18**, access of the hydride reducing agent to both faces of the C=O/C=N is equally likely on steric grounds. However, the greater proportion of *cis* isomer formed suggests that product development control (in which the dominating factor is formation of a transition state in which the interactions between the complexed ketone oxygen or oxime nitrogen and the rest of the molecule are minimized) is the deciding factor for stereochemical outcome.

Target outcome **4** was obtained on treatment of the amine **36** with $CSCl_2$.[10]

Aryl isothiocyanate derivatives **5**–**7** were synthesized (Scheme 5) *via* nitration of **1** (Scheme 1). Initial attempts to nitrate **1** by treatment with HNO_3–H_2SO_4 gave an inseparable mixture. An improved procedure utilizing $NaNO_2$ in CF_3CO_2H[13] afforded mononitro derivatives **37** (60%), **38** (9%) and **39** (20%). Catalytic hydrogenation of **37** in the presence of 10% Pd/C proceeded slowly to give amine **40** in 96% yield which was transformed into **5**. Compounds **6** and **7** were similarly prepared from **38** and **39**.

Preliminary data indicates that compounds **5** and **6** are potent (equipotent to BTCP) displacers of [^{3}H]BTCP from dopamine reuptake sites in rat striatal membranes whereas **2**–**4**



Scheme 5 i, $NaNO_2$, CF_3CO_2H, 20 °C; ii, H_2, 10% Pd/C, EtOH; iii, $CSCl_2$, sat. aq. $NaHCO_3$ or K_2CO_3, $CHCl_3$

and **7** are considerably less efficaceous (IC_{50} > 1000 nmol dm^{-3}) in this effect.[14] The irreversible binding properties of **2**–**7** are currently under investigation.

Experimental

Materials.—Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were determined at Atlantic microlabs, Atlanta, Georgia, USA. Chemical ionization mass spectra (CIMS) were obtained using a Finnigan 1015 mass spectrometer. Electron ionization mass spectra (EIMS) and high resolution mass measurements (HRMS) were obtained using a VG-Micromass 7070F mass spectrometer. IR spectra were taken for $CHCl_3$ solutions of compounds using a Bio-Rad FTS-45 FTIR spectrometer. ^1H NMR spectra were recorded with a Varian XL-300 spectrometer; results are recorded as ppm downfield of the Me_4Si signal; *J* values are given in Hz. TLC was performed on 250 μm Analtech GHLF silica gel plates. TLC system A corresponds to concentrated aqueous NH_3–MeOH–$CHCl_3$ (1:9:90); B (0.5:4.5:95); C (0.2:1.8:98). TLC solvent system D refers to ethyl acetate–hexane (1:9); E (1:1). Ether refers to diethyl ether. Spectral data (NMR and IR) for all amines is reported for the free base.

1-(2-*Benzo*[b]*thienyl*)*cyclohexanol* **9**.—To a solution of benzo[*b*]thiophene (30.7 g, 229 mmol) in ether (200 cm^3) was added during 15 min, with cooling from a water-bath, a solution of butyllithium in hexane (2.5 mol dm^3; 101 cm^3, 252 mmol, 1.1 equiv.). The reaction mixture began to reflux gently during the addition. The solution was stirred for a further 2 h at 20 °C and then treated dropwise with cyclohexanone (26 cm^3, 252 mmol, 1.1 equiv.). The solution became warm and started to reflux during the addition of the cyclohexanone. Towards the end of the addition, a copious white precipitate of the lithium salt of **9** separated from the solution. When the addition was complete, the reaction mixture was poured into water (200 cm^3) and the aqueous layer was discarded. The organic layer was washed with saturated brine (100 cm^3) and evaporated to give the pure *alcohol* **9** as a crystalline solid (53.1 g, quantitative). Analytically pure material was obtained by crystallization of **9** from hexanes: m.p. 94–95 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3590, 3010, 2939, 2860, 1458, 1436, 1306, 1171, 1157 and 966; $\delta_H(CDCl_3)$ 7.80 (dd, *J* 1.2 and 8.0, 1 H), 7.70 (dd, *J* 1.6 and 7.0, 1 H), 7.30 (m, 2 H), 7.19 (s, 1 H), 1.99 (m, 4 H) and 1.58–1.86 (complex m, 6 H). CIMS [Found: 233 (MH^+). MH^+ calc. for $C_{14}H_{16}OS$: 233] (Found: C, 72.3: H, 7.0. $C_{14}H_{16}OS$ requires C, 72.37; H, 6.94%).

1-(2-*Benzo*[b]*thienyl*)*cyclohexylamine* **11**.—To a stirred solution of the alcohol **9** (61.9 g, 267 mmol) in alcohol-free $CHCl_3$ (260 cm^3) at 0 °C containing NaN_3 (52.0 g, 800 mmol, 3.0 equiv.) was added CF_3CO_2H (82 cm^3, 1.06 mol, 4.0 equiv.) and the solution was then stirred overnight at 20 °C. The reaction mixture was treated with water (200 cm^3) followed by an excess of concentrated aqueous ammonia solution. After thorough shaking of the mixture in a separatory funnel, the lower $CHCl_3$ layer was separated and the aqueous layer was extracted with further $CHCl_3$ (200 cm^3). The combined organic layer was washed with water (200 cm^3), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the crude azide **10** in quantitative yield: IR ($CHCl_3$)/cm^{-1} 2100 (v strong N_3 str).

The crude azide was dissolved in dry ether (400 cm^3) and treated dropwise at 20 °C with $LiAlH_4$ (1.0 mol dm^{-3}; 500 cm^3, 500 mmol) in THF at such a rate that a gentle reflux was maintained. The reaction mixture was stirred overnight under a nitrogen atmosphere when TLC (solvent system A) indicated the reaction to be complete. The reaction was quenched by dropwise addition of water (19 cm^3), 15% aqueous NaOH (19 cm^3) and finally water (57 cm^3). The precipitated aluminium salts were filtered off and the filter-cake was washed with ether (200 cm^3). The combined filtrate and washings were evaporated to a colourless oil which was dissolved in a solution of citric acid monohydrate (80 g) in water (500 cm^3). Copious crystallization of the citrate salt occurred on addition of the base. The aqueous suspension of citrate salt was washed with ether (3 × 500 cm^3) and the ether extract was discarded. The aqueous mixture was basified by the addition of an excess of concentrated aqueous ammonia, extracted with CH_2Cl_2 (3 × 300 cm^3) and the latter back-extracted with water (200 cm^3) and then evaporated to give the *amine* **11** as a colourless oil (40.7 g, 66%). **11**·HCl (EtOAc); m.p. 236–238 °C (decomp.); $\nu_{max}(CHCl_3)/cm^{-1}$ 3375w, 3300w, 3009, 2936, 2858, 1458, 1435, 911 and 829; $\delta_H(CDCl_3)$ 7.79 (d, *J* 7.7, 1 H), 7.69 (d, *J* 7.2, 1 H), 7.29 (m, 2 H), 7.16 (s, 1 H), 2.05 (m, 2 H), 1.76–1.88 (complex m, 2 H) and 1.34–1.75 (complex m, 8 H). EIMS [Found: 231 (M^+), 214 ($M^+ - NH_3$) and 188 ($M^+ - NH_3 - C_2H_6$). M^+ calc. for $C_{14}H_{17}NS$: 231] (Found: C, 62.7; H, 6.8; N, 5.2. $C_{14}H_{18}ClNS$ requires C, 62.79; H, 6.77; N, 5.23%).

1-[1-(2-*Benzo*[b]*thienyl*)*cyclohexyl*]*piperidine* (*BTCP*)[3] **1**.—The amine **11** (36.27 g, 157 mmol) in dry DMF (400 cm^3) was treated with 1,5-dibromopentane (36.10 g, 1.1 equiv.) and the reaction mixture was stirred and heated at 60 °C for 48 h. K_2CO_3 (23.9 g, 173 mmol, 1.1 equiv.) was added and the reaction mixture was heated and stirred at 60 °C for a further 24 h. TLC (solvent system A) indicated the reaction to be complete. The solution was cooled, quenched with cold water (1.2 dm^3) and extracted with ether (3 × 400 cm^3). The combined extracts were back-extracted with water (500 cm^3) and then the volume reduced to 500 cm^3 at the rotary evaporator. The ethereal solution of crude **1** was partitioned between 10% aqueous citric acid (1 dm^3) and ether (500 cm^3) and the organic extract was discarded. The aqueous acidic solution was washed with further ether (2 × 500 cm^3) and then basified by addition of an excess of aqueous ammonia. The basified solution was extracted with ether (3 × 300 cm^3) and the combined organic extracts were back-washed with water (500 cm^3), dried (Na_2SO_4), and evaporated to yield *BTCP* **1** (33.2 g, 71%) as a crystalline solid. Further purification was achieved by crystallization of the fumarate salt from MeOH–propan-2-ol; m.p. 187–188.5 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3008, 2936, 2856, 1741, 1433 and 1252; $\delta_H(CDCl_3)$ 7.79 (d, *J* 7.7, 1 H), 7.72 (d, *J* 7.2, 1 H), 7.29 (m, 2 H), 7.04 (s, 1 H), 2.43 (m, 4 H), 2.06 (m, 4 H), 1.76 (m, 2 H), 1.35–1.61 (complex m, 8 H) and 1.30 (m, 2 H). EIMS [Found: 299 (M^+), 256 ($M^+ - C_3H_7$) and 215 ($M^+ - C_5H_{11}N - H^+$). M^+ calc. for $C_{19}H_{25}NS$: 299]. HRMS [Found: 229.1724 (M^+). M^+ calc. for $C_{19}H_{25}NS$: 229.1708] (Found for **1**·fumarate: C, 66.35; H, 7.05; N, 3.35. $C_{23}H_{29}NO_4S$ requires C, 66.48; H, 7.03; N, 3.37%). **1** (propan-2-ol): m.p. 82–83 °C. **1**·HCl (EtOAc): m.p. 192–193 °C.

1-[1-(2-*Benzo*[b]*thienyl*)*cyclohexyl*]-4,4-*ethylenedioxypiperidine* **12**.—A mixture of amine **11** (base obtained from 3 g of

11·HCl salt by partitioning between aqueous ammonia and $CHCl_3$) (11.2 mmol) and 3,3-ethylenedioxypentane-1,5-diol dimethanesulfonate ester[9] (3.43 g, 10.8 mmol) in dry DMF (30 cm^3) was heated and stirred at 60 °C for 4 d and then treated with further dimethanesulfonate (3.43 g). The reaction was allowed to proceed for a further 2 d after which K_2CO_3 (3.2 g, 22.4 mmol, 2.0 equiv.) was added to the reaction mixture. TLC (solvent system A) indicated the reaction to be complete. The acetal (3.57 g, 89%) was isolated as for BTCP above. **12**·fumarate crystallized from hot ethanol (50 cm^3), m.p. 177–178 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3011, 2937, 2829, 1457, 1364, 1308, 1250, 1235, 1141, 1123, 1066 and 1038; $\delta_H(CDCl_3)$ 7.78 (d, *J* 7.6, 1 H), 7.70 (d, *J* 7.5, 1 H), 7.28 (m, 2 H), 7.05 (s, 1 H), 3.86 (s, 4 H), 2.56 (m, 4 H), 2.07 (m, 4 H), 1.71 (m, 4 H), 1.58 (m, 2 H) and 1.46 (m, 4 H). EIMS [Found: 357 (M^+). M^+ calc. for $C_{21}H_{27}NO_2S$: 357] (Found for **12**·fumarate: C, 63.0; H, 6.7; N, 3.1. $C_{25}H_{31}NO_6S$·0.33H_2O requires C, 62.60; H, 6.66; N, 2.92%).

1-[1-(2-*Benzo*[b]*thienyl*)*cyclohexyl*]-4-*piperidone* **13**.—The free base obtained from **12**·fumarate (1.42 g, 2.96 mmol) was dissoved in HCl (6 mol dm^{-3}; 100 cm^3) and the solution was heated at 60 °C for 2 h when TLC (solvent system B) indicated complete reaction. The reaction mixture was cooled and poured into 10% aqueous Na_2CO_3 (500 cm^3). The solution was extracted with $CHCl_3$ (3 × 100 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude *piperidone* **13** as an oil which gave **13**·HCl (propan-2-ol) (0.68 g, 66%); m.p. 189–190 °C (decomp.); $\nu_{max}(CHCl_3)/cm^{-1}$ 3005, 2940, 2858, 2817, 1711, 1602, 1119 and 1068; $\delta_H(CDCl_3)$ 7.78 (dd, *J* 1.2 and 7.9, 1 H), 7.72 (dd, *J* 1.6 and 6.8, 1 H), 7.30 (m, 2 H), 7.09 (s, 1 H), 2.80 (t, *J* 5.7, 4 H), 2.41 (t, *J* 5.7, 4 H), 2.14 (m, 4 H), 1.79 (m, 2 H) and 1.46–1.60 (complex m, 4 H); EIMS [Found: 313 (M^+). M^+ calc. for $C_{19}H_{23}NOS$: 313] (Found for **13**·HCl: C, 65.0; H, 6.95; N, 3.95. $C_{19}H_{24}ClNOS$ requires C, 65.22; H, 6.91; N, 4.00%).

1-[1-(2-*Benzo*[b]*thienyl*)*cyclohexyl*]-4-*piperidone Oxime* **14**.—A mixture of piperidone **13**·HCl (0.58 g, 1.66 mmol), NaOAc·3H_2O (0.58 g, 4.26 mmol, 2.57 equiv.) and H_2NOH·HCl (0.14 g, 2.01 mmol, 1.2 equiv.) in ethanol (22 cm^3) was stirred for 3 h at 20 °C when TLC (solvent system B) indicated complete reaction. The solvent was evaporated *in vacuo* and the residue was partitioned between 10% aqueous Na_2CO_3 (100 cm^3) and $CHCl_3$ (100 cm^3). The $CHCl_3$ extract was back-washed with water (50 cm^3) and then evaporated to give the *oxime* **14** (0.54 g, quantitative) as a colourless foam. **14**·HCl (propan-2-ol–EtOAc); m.p. 175–177 °C (decomp.); $\nu_{max}(CHCl_3)/cm^{-1}$ 3592, 3009, 2939, 2857, 2818, 1457, 1434, 1329, 1250, 1124, 994, 962 and 905; $\delta_H(CDCl_3)$ 7.77 (d, *J* 7.4, 1 H), 7.71 (dd, *J* 1.2 and 7.7, 1 H), 7.29 (m, 2 H), 7.07 (s, 1 H), 6.80 (br s, 1 H), 2.50–2.68 (complex m, 6 H), 2.30 (m, 2 H), 2.11 (m, 4 H), 1.78 (m, 2 H), 1.58 (m, 2 H) and 1.48 (m, 4 H). CIMS [Found: 329 (MH^+) and 311 (MH^+ − 18). MH^+ calc. for $C_{19}H_{24}N_2OS$: 329] (Found for **14**·HCl: C, 61.2; H, 7.0; N, 7.5. $C_{19}H_{25}ClN_2OS$·0.5H_2O requires C, 61.02; H, 7.01; N, 7.49%).

4-*Amino*-1-[1-(2-*benzo*[b]*thienyl*)*cyclohexyl*]-*piperidine* **15**.—The oxime **14** (base) (0.54 g, 1.65 mmol) in dry THF (10 cm^3) was added dropwise to a stirred solution of $LiAlH_4$ in THF (1.0 mol dm^3; 10 cm^3, 10 mmol) and the reaction mixture was stirred for 24 h at room temp.; TLC (solvent system A) indicated a trace of unchanged **14** remaining after this time. The product was isolated by standard methods to give the *amine* **15** as a crystalline solid (0.52 g, quantitative). **15** (propan-2-ol); m.p. 92–93 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3375w, 2937, 2856, 2809, 1576, 1259, 1074 and 870; $\delta_H(CDCl_3)$ 7.78 (d, *J* 7.6, 1 H), 7.72 (dd, *J* 1.3 and 7.9, 1 H), 7.29 (m, 2 H), 7.04 (s, 1 H), 3.00 (m, 2 H), 2.46 (m, 2 H), 2.06 (m, 4 H), 1.94 (m, 2 H), 1.76 (m, 4 H) and 1.24–1.54 (complex m, 8 H). CIMS [Found: 315 (MH^+) and 215 ($MH^+ - C_5H_{12}N_2$). MH^+ calc. for $C_{19}H_{26}N_2S$: 315] (Found: C, 72.6; H, 8.4; N, 8.96. $C_{19}H_{26}N_2S$ requires C, 72.57; H, 8.33; N, 8.91%).

1-[1-(2-*Benzo*[b]*thienyl*)*cyclohexyl*]-4-*isothiocyanato-piperidine* **2**.—To a rapidly stirred solution of the amine **15** (0.20 g, 0.637 mmol) in a mixture of saturated aqueous $NaHCO_3$ (10 cm^3) and $CHCl_3$ (10 cm^3) was added freshly redistilled $CSCl_2$ (58.3 mm^3, 0.71 mmol, 1.1 equiv.) in $CHCl_3$ (1.0 cm^3). TLC (solvent system B) indicated complete reaction after 10 min at 20 °C. The organic layer was separated, diluted to 50 cm^3 with $CHCl_3$, washed with saturated aqueous $NaHCO_3$ (10 cm^3) and water (10 cm^3) and evaporated to give the *product* **2** as a yellow oil (0.23 g, quantitative). **2**·HCl (0.202 g, 81%) (EtOAc), m.p. 170–171 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3008, 2938, 2857, 2813, 2095br vs (NCS str), 1456, 1364, 1254, 1128, 1075 and 964; $\delta_H(CDCl_3)$ 7.78 (d, *J* 7.5, 1 H), 7.72 (d, *J* 7.1, 1 H), 7.30 (m, 2 H), 7.05 (s, 1 H), 3.48 (m, 1 H), 2.87 (m, 2 H), 1.90–2.24 (complex m, 8 H), 1.64–1.86 (complex m, 4 H) and 1.47 (m, 4 H). CIMS [Found: 357 (MH^+) and 215 ($MH^+ - C_6H_{10}N_2S$). MH^+ calc. for $C_{20}H_{24}N_2S_2$:357] (Found: C, 60.4; H, 6.5; N, 7.0. $C_{20}H_{25}ClN_2S_2$·0.25H_2O requires C, 60.42; H, 6.47; N, 7.04%).

4-(2-*Benzo*[b]*thienyl*)-4-*hydroxycyclohexanone* **18**.—A stirred solution of the ketal **17** (for preparation, see ref. 11) (87.2 g, 301 mmol) in a mixture of acetic acid (800 cm^3) and water (200 cm^3) was heated for 2 h at 55 °C or until TLC (solvent system E) indicated the reaction to be complete. The reaction mixture was diluted to 2000 cm^3 with water and extracted with ether (2 × 700 cm^3). The combined organic extracts were washed with an excess of aqueous ammonia (500 cm^3) and water (500 cm^3), dried (Na_2SO_4) and evaporated to give **18** (quantitative) as a crystalline solid. Recrystallization from propan-2-ol gave *ketone* **18** (55.1 g, 74%), m.p. 150–151 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3587 (non H-bonded OH str), 3063, 3012, 2936, 2860, 1711vs, 1459, 1332, 1231 and 948; $\delta_H(CDCl_3)$ 7.82 (d, *J* 6.9, 1 H), 7.73 (d, *J* 6.8, 1 H), 7.34 (m, 2 H), 7.24 (s, 1 H), 2.91 (m, 2 H) and 2.42 (m, 6 H). CIMS [Found: 247 (MH^+). MH^+ calc. for $C_{14}H_{14}O_2S$: 247] (Found: C, 68.2; H, 5.75. $C_{14}H_{14}O_2S$ requires C, 68.27; H, 5.73%).

4-*Amino*-4-(2-*benzo*[b]*thienyl*)*cyclohexanone* **19**.—To a stirred mixture of the ketone **18** (7.00 g, 28.4 mmol) in hydrocarbon-stabilized $CHCl_3$ (200 cm^3) at 0 °C was added NaN_3 (3.70 g, 56.9 mmol, 2.0 equiv.) followed by CF_3CO_2H (9.73 cm^3, 126 mmol, 4.4 equiv.). After being stirred overnight at 20 °C, the reaction mixture was diluted to 500 cm^3 with $CHCl_3$, washed with 10% NaOH (200 cm^3) and water (200 cm^3), and evaporated to leave a semicrystalline mass; IR $(CHCl_3)/cm^{-1}$ 2120 (N_3 str), 1720 (C=O str) and 1230. No attempt was made to further purify or characterize this crude azide [4-azido-4-(2-benzo[*b*]thienyl)cyclohexanone]. The entire azide product was taken up in 95% ethanol (150 cm^3) and the solution was acidified by addition of concentrated HCl (5 cm^3). The reaction mixture was hydrogenated at 50 psi* for a total of 2.5 h when TLC analysis (solvent system A) indicated completion. The catalyst was removed by filtration through Celite and the filtrate was evaporated. The residue was dissolved in water (200 cm^3) and extracted with ether (2 × 200 cm^3). The aqueous layer was basified by addition of concentrated aqueous ammonia, extracted with CH_2Cl_2 (2 × 200 cm^3), the combined organic extracts were dried (Na_2SO_4), and evaporated to give crystalline *amine* **19** (5.2 g, 75% overall yield). **19**·HCl (EtOAc), m.p. 219–220 °C (decomp.); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392 (NH_2 str),

* (1 psi = 6.9 × 10^3 Pa).

3323 (NH_2 str), 3019, 2938, 2864, 1709, 1458, 1436, 1225, 1157 and 1130; $\delta_H(CDCl_3)$ 7.81 (dd, *J* 1.4 and 8, 1 H), 7.71 (dd, *J* 1.7 and 6.8, 1 H), 7.33 (m, 2 H), 7.21 (s, 1 H), 2.82 (m, 2 H), 2.35–2.48 (complex m, 4 H), 2.18–2.31 (complex m, 2 H) and 1.69 (br s, 2 H). CIMS [Found: 246 (MH^+). MH^+ calc. for $C_{14}H_{15}NOS$: 246] (Found: for **19**·HCl: C, 58.15; H, 5.8; N, 4.75. $C_{14}H_{16}ClNOS{\cdot}0.5H_2O$ requires C, 57.81; H, 5.89; N, 4.82%).

trans- *and* cis-1-(2-*Benzo*[b]*thienyl*)*cyclohexane*-1,4-*diols* **20** *and* **21**.—To a stirred suspension of the ketone **18** (28.0 g, 114 mmol) in anhydrous MeOH (500 cm^3) at 0 °C was added, rapidly, a freshly prepared solution of $NaBH_4$ (8.61 g, 228 mmol) in MeOH (250 cm^3). Examination of the reaction mixture by TLC (solvent system E) after 5 min indicated complete reaction. Acetone (50 cm^3) was added to destroy unchanged hydride and the solvent was evaporated under reduced pressure at < 40 °C. The residue was taken up in water (300 cm^3) and most of the inorganic salts were dissolved by addition of acetic acid (50 cm^3) (to pH 5). The aqueous mixture was extracted with $CHCl_3$ (3 × 300 cm^3). The combined organic extracts were washed with water (300 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to afford the product (6.5 g). The aqueous mixture was filtered and the filter-cake was washed well with 10% aqueous acetic acid (500 cm^3), to remove any inorganic salts, and water (100 cm^3), and pressed dry and dried overnight *in vacuo* (yield 21.2 g) (combined yield of mixed alcohols 27.7 g, 98%). The mixed diols appeared as a single spot on TLC (solvent system A), ^1H NMR analysis of the mixed diols **20** and **21** indicated a 1:4 mixture of the *trans*-diol **20** [$\delta_H(CDCl_3)$ 4.08 (m, *J* 2.6, 1 H, C*H*OH)] to *cis*-diol **21** [$\delta_H(CDCl_3)$ 3.76 (tt, *J* 4.9 and 9.9, 1 H, C*H*OH)]. Recrystallization of this mixture from hot MeOH (300 cm^3) afforded the pure *cis*-diol **21** (20.6 g), m.p. 201.5–202 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3591 (OH str), 3605 (OH str), 3008, 2943, 2864, 1602, 1458, 1436, 1306, 1053 and 957; $\delta_H(CDCl_3)$ 7.80 (dd, *J* 7.8 and 1.1, 1 H), 7.71 (dd, *J* 8.2 and 1.6, 1 H), 7.31 (m, 2 H), 7.20 (s, 1 H), 3.76 (tt, *J* 4.9 and 9.9 1 H, axial H, C*H*OH), 2.08–2.19 (complex m, 2 H), 2.02 (m, 2 H), 1.77–1.98 (complex m, 4 H) and 1.54 (br s, 2 H). EIMS [Found: 248 (M^+), 230 ($M^+ - H_2O$) and 210 ($M^+ - 2H_2O - H_2$). M^+ calc. for $C_{14}H_{16}O_2S$: 248] (Found: C, 67.6; H, 6.5. $C_{14}H_{16}O_2S$ requires C, 67.71; H, 6.49%). Evaporation of the mother liquor and recrystallization of the residue from propan-2-ol (100 cm^3) furnished a mixture of **20** and **21** (5.9 g).

trans- *and* cis-4-*Azido*-4-(2-*benzo*[b]*thienyl*)*cyclohexanols* **22** *and* **23**.—To a stirred suspension of the *cis*-diol **21** (19.5 g, 78.6 mmol) and NaN_3 (15.34 g, 236 mmol, 3.0 equiv.) at 0 °C in hydrocarbon-stabilized $CHCl_3$ (300 cm^3) was added, dropwise, CF_3CO_2H (24.23 cm^3, 315 mmol, 4.0 equiv.). The mixture was stirred at room temperature overnight and was then treated as for the synthesis of the azide **10** to give the crude azides (21.5 g, quantitative) as a crystalline solid. ^1H NMR analysis of the mixture indicated the presence of a 1:1 mixture of the *trans*-azide **22** [$\delta_H(CDCl_3)$ 4.02 (m, 1 H, C*H*OH)] and *cis*-azide **23** [$\delta_H(CDCl_3)$ 3.72 (tt, 1 H, *J* 4.9 and 9.8, C*H*OH)]. A small amount of alkenic product **27** (12% of product mixture) [$\delta_H(CDCl_3)$ 6.15 (dd, *J* 1.5 and 3.5, 1 H, alkenic-H)] was also formed; $\nu_{max}(CHCl_3)/cm^{-1}$ (mixture of **22** and **23**) 3611 (OH str), 2939, 2102vs (N_3 str). No attempt was made to purify further this mixture of azides; instead it was subjected immediately to catalytic hydrogenation as described below.

For purposes of assignment of configuration, however, a sample of the pure cis-*azide* **23** (0.42 g) was obtained by crystallization of 2.0 g of the above mixture from propan-2-ol (20 cm^3), m.p. 167–168 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3609 (OH str), 3010, 2942, 2865, 2103vs (N_3 str), 1458, 1436, 1249, 1157 and 1054; $\delta_H(CDCl_3)$ 7.82 (dd, *J* 6.2 and 3.3, 1 H), 7.75 (dd, *J* 7.1 and 2.5, 1 H), 7.35 (m, 2 H), 7.26 (s, 1 H), 3.72 (tt, 1 H, *J* 4.9 and 9.8, C*H*OH), 2.24–2.36 (complex m, 2 H), 1.90–2.07 (complex m, 4 H), 1.70–1.86 (complex m, 2 H) and 1.54 (br s, 1 H, OH). EIMS [Found: 273 (M^+) and 2.45 ($M^+ - N_2$). M^+ calc. for $C_{14}H_{15}N_3OS$: 273] (Found: C, 61.7; H, 5.55; N, 15.3. $C_{14}H_{15}N_3OS$ requires C, 61.52; H, 5.53; N, 15.37%). Catalytic hydrogenation of **23** in the presence of 10% Pd/C gave the amino alcohol **25** identical (by ^1H NMR) with an authentic sample of **25** of defined configuration; this established the configuration of **23** as *cis*.

4-(2-*Benzo*[b]*thienyl*)*cyclohex*-3-*enol* **27**.—To a stirred suspension of a 1:1 mixture of the alcohols **20** and **21** (2.00 g, 8.06 mmol) in hydrocarbon-stabilized $CHCl_3$ (20 cm^3) at 5 °C was added dropwise CF_3CO_2H (20 cm^3) at such a rate that the solution remained pale yellow and the temperature remained at 5 °C. The reaction mixture was stirred for a further 5 min at 5 °C after which TLC (solvent system E) indicated the reaction to be complete. The reaction mixture was poured into a mixture of 15% aqueous NaOH (150 cm^3) and crushed ice (150 g) and shaken. The lower $CHCl_3$ layer was separated and the aqueous layer was washed with $CHCl_3$ (150 cm^3). The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give **27** (1.85 g, quantitative) as a pale yellow crystalline solid. **27** (pale yellow laminate from propan-2-ol), m.p. 163–163.5 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3610, 2929, 2845, 1650, 1603, 1559, 1457, 1435 and 1066; $\delta_H(CDCl_3)$ 7.73 (dd, *J* 2.2 and 6.5, 1 H), 7.67 (dd, *J* 2.4 and 6.3, 1 H), 7.28 (m, 2 H), 7.13 (s, 1 H), 6.17 (m, 1 H, alkenic C*H*), 4.08 (m, 1 H, C*H*OH), 2.66–2.79 (m, 1 H), 2.52–2.67 (complex m, 2 H), 2.19–2.32 (m, 1 H), 2.04 (m, 1 H) and 1.85 (m, 1 H) (Found: C, 72.5; H, 6.2. $C_{14}H_{14}OS{\cdot}125H_2O$ requires C, 72.30; H, 6.18%).

trans- *and* cis-4-*Amino*-4-(2-*benzo*[b]*thienyl*)*cyclohexanols* **24** *and* **25**.—A mixture of azides **22** and **23** (1:1) (10 g, 36.6 mmol) in MeOH (500 cm^3) was catalytically reduced (1.00 g of 10% Pd/C, H_2, at 1 atm) to a mixture of amines **24** and **25** as described below for **32**. Analysis of the mixture by ^1H NMR spectroscopy indicated the presence of a 1:1 mixture of amino alcohols: *trans*-amino alcohol **24** exhibited a signal at $\delta_H(CDCl_3)$ 3.90 (m, 1 H, *J* 3.8, C*H*OH) whereas the *cis*-amino alcohol **25** exhibited $\delta_H(CDCl_3)$ 3.76 (tt, 1 H, *J* 4.6 and 9.3, C*H*OH) identical with that prepared previously.[11] No attempt was made to separate this mixture.

trans- *and* cis-4-(2-*Benzo*[b]*thienyl*)-4-*piperidinylcyclohexanols* **28** *and* **29**.—A mixture of amines **24** and **25** (1:1) (3.0 g, 12.1 mmol) was treated with 1,5-dibromopentane as described for BTCP to give the product mixture as a crystalline solid (quantitative). The mixture was separated by column chromatography on silica gel, eluting with EtOAc. The earlier fractions afforded **29** (1.1 g, 57%), m.p. (propan-2-ol) 154–155 °C (lit.,[11] 154–155 °C); $\delta_H(CDCl_3)$ 7.78 (d, *J* 7.6, 1 H), 7.72 (d, *J* 7.3, 1 H), 7.30 (m, 2 H), 7.03 (s, 1 H), 3.76 (m, 1 H, C*H*OH), 2.43 (m, 4 H), 1.71–1.93 (complex m, 4 H), 1.56 (m, 4 H) and 1.31 (m, 2 H) identical to that described previously.[11] The later fractions afforded **28** (1.1 g, 57%), m.p. (propan-2-ol) 188–189 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3610, 2936, 2859, 2808, 1457, 1433, 1245, 1156, 1057 and 985; $\delta_H(CDCl_3)$ 7.79 (d, *J* 7.4, 1 H), 7.73 (dd, *J* 1.7 and 7.9, 1 H), 7.30 (m, 2 H), 7.07 (s, 1 H), 3.83 (m, 1 H, C*H*OH), 2.31–2.51 (complex m, 6 H), 1.87–2.06 (complex m, 4 H), 1.40–1.65 (complex m, 6 H) and 1.24–1.35 (complex m, 2 H); CIMS [Found: 316 (MH^+). MH^+ calc. for $C_{19}H_{25}NOS$: 316] (Found: C, 72.1; H, 8.0, N, 4.46. $C_{19}H_{25}NOS$ requires C, 72.34; H, 7.99; N, 4.44%).

trans-1-[4-*Azido*-1-(2-*benzo*[b]*thienyl*)*cyclohexyl*]*piperidine* **31**.—A stirred mixture of compound **30** (prepared as previously described[11]) (0.60 g, 1.66 mmol) and NaN_3 (1.08g, 16.6 mmol,

10 equiv.) was heated at 85 °C overnight under an N_2 atmosphere. TLC (solvent system C) indicated reaction to be complete. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (100 cm^3) and extracted with ether (2 × 100 cm^3). The combined extract were back-washed with water (50 cm^3), dried (Na_2SO_4) and evaporated to give **31** (0.52 g, 93%). The crystalline *azide* **31** (0.42 g) was obtained from MeOH, m.p. 78–80 °C; ν_{max}(KBr)/cm^{-1} 2920, 2840, 2800, 2100s, 1455, 1260, 1125, 980, 960 and 740; δ_H($CDCl_3$) 7.79 (d, *J* 7.6, 1 H), 7.73 (d, *J* 7.2, 1 H), 7.05 (s, 1 H), 3.63 (m, 1 H), 2.43 (m, 4 H), 2.30 (m, 2 H), 2.03 (m, 4 H), 1.54 (m, 6 H) and 1.30 (m, 2 H). CIMS [Found: 341 (MH^+). MH^+ calc. for $C_{19}H_{24}N_4S$: 341] (Found: C, 66.95; H, 7.1; N, 16.4. $C_{19}H_{24}N_4S$ requires C, 67.02; H, 7.10; N, 16.45%).

trans-1-[4-*Amino*-1-(2-*benzo*[b]*thienyl*)*cyclohexyl*]-*piperidine* **32**.—The azide **31** (0.30 g, 0.88 mmol) in MeOH (20 cm^3) was treated with an excess of concentrated HCl (to pH 3), and then 10% Pd/C (30 mg) was added. The reaction mixture was stirred at atmospheric pressure under an H_2 atmosphere for 2 h and was then filtered through Celite. The filter-cake was washed with a little MeOH (20 cm^3). Evaporation of the filtrate under reduced pressure afforded the *amine dihydrochloride* **32**·HCl as a glassy residue (0.37 g, quantitative). Crystalline **32**·HCl (EtOAc), m.p. 190–193 °C; ν_{max}($CHCl_3$)/cm^{-1} 3700w, 3600w, 2935, 2858, 2810, 1601, 1581, 1469, 1432, 1250, 1156, 1102, 1072 and 897; δ_H($CDCl_3$) 7.79 (d, *J* 7.8, 1 H), 7.73 (dd, *J* 1.3 and 7.9, 1 H), 7.30 (m, 2 H), 7.07 (s, 1 H), 2.77 (m, 1 H), 2.47 (m, 6 H), 1.84 (m, 4 H), 1.55 (m, 4 H), 1.45 (m, 2 H) and 1.29 (m, 4 H). CIMS [Found: 315 (MH^+). MH^+ calc. for $C_{19}H_{26}N_2S$: 315] (Found for **32**·HCl: C, 55.7; H, 7.6: N, 6.7. $C_{19}H_{28}Cl_2N_2S$·1.25H_2O requires C, 55.66; H, 7.50; N, 6.83%).

trans-1-[1-(2-*Benzo*[b]*thienyl*)-4-*isothiocyanatocyclohexyl*]-*piperidine* **3**.—As described for the synthesis of **2** earlier starting with **32**·HCl (0.20 g, 0.517 mmol) gave the *isocyanate* **3** (182 mg, quantitative); **3**·HCl (EtOAc), m.p. 155 °C (decomp.); ν_{max}($CHCl_3$)/cm^{-1} 2936, 2809, 2116br *vs* (NCS str), 1433, 1364, 1322, 1156, 1130 and 955; δ_H($CDCl_3$) 7.81 (d, *J* 7.7, 1 H), 7.75 (d, *J* 7.2, 1 H), 7.32 (m, 2 H), 7.06 (s, 1 H), 3.93 (m, 1 H), 2.41 (m, 4 H), 2.18 (m, 6 H), 1.77 (m, 2 H), 1.46–1.60 (complex m, 4 H) and 1.30 (m, 2 H). CIMS [Found: 357 (MH^+). MH^+ calc. for $C_{20}H_{24}N_2S_2$: 357] (Found for **3**·HCl: C, 59.4; H, 6.7; N, 6.5. $C_{20}H_{25}ClN_2S_2$·0.5H_2O requires C, 59.75; H, 6.52; N, 6.96%).

1-(2-*Benzo*[b]*thienyl*)-*spiro*(7-*azabicyclo*[2.2.1]*heptane*-7,1′-*piperidin*-1′-*ium*) *Hydroxide* **33**.—To a stirred solution of *trans*-amino alcohol **28** (26.2 mg, 0.083 mmol) in dry $CHCl_3$ (1 cm^3) at room temp. was added a solution of methanesulfonic anhydride (21.7 mg, 0.12 mmol) in $CHCl_3$ (1 cm^3). Stirring was continued at room temp. No observable reaction was evident under these conditions even after 20 min (TLC, solvent system A). After this time, Et_3N (0.1 cm^3) was added in one portion. The reaction mixture was stirred at room temp. for 10 min when TLC (solvent system A) indicated complete conversion of the starting material into a polar (TLC, solvent system A, heavily iodine absorbing spot) product. The solvent was evaporated under reduced pressure and traces of Et_3N were removed by addition of and subsequent evaporation of $CHCl_3$ (3 × 5 cm^3). The residue proved to be mixture of **33** methanesulfonate and Et_3NH + methanesulfonate (^1H NMR). In order to separate this mixture of salts, the residue was dissolved in $CHCl_3$ (1 cm^3) and extracted with 15% aqueous NaOH (1 cm^3). The $CHCl_3$ layer was separated and evaporated under reduced pressure to give **33**·hydroxide (free from Et_3N) as an unstable white solid (26 mg, quantitative); δ_H($CDCl_3$) 8.04 (s, 1 H, ArH), 7.97 (d, *J* 5.9, 1 H, ArH), 7.85 (d, *J* 5.9, 1 H, ArH), 7.45 (m, 2 H, ArH), 4.77 (t, *J* 0 and 4.6, 1 H, N^+CH), 3.87 [m, 2 H, $N^+(CH_2)_2$], 2.97–3.13 (m, 2 H), 2.71–2.86 (m, 2 H), 2.52–2.68 (m, 2 H), 2.34–2.51 (m, 2 H), 1.84–1.22 (complex m, 6 H) and 1.18–1.44 (m, 2 H); δ_C($CDCl_3$) 140.2, 139.5, 131.4, 130.3, 126.5, 125.4, 122.1, 82.7, 65.5, 51.7, 39.5, 33.7, 26.6, 22.3 and 21.9. CIMS [Found: 298 (M^+, base peak). Calc. for $C_{19}H_{24}NS^+$): 298]. No attempt was made to further purify this material because of its instability.

1-(2-*Benzo*[b]*thienyl*)-N-*ethoxycarbonyl*-4-*hydroxycyclohexylamine* **26**.—To a stirred suspension of amine **25**·fumarate (0.30 g, 0.83 mmol) (for synthesis of this compound see ref. 11 or Scheme 2) in a mixture of saturated aqueous $NaHCO_3$ (10 cm^3) and $CHCl_3$ (10 cm^3) was added ethyl chloroformate (189 mm^3, 1.98 mmol, 2.4 equiv.). The reaction mixture was stirred at 20 °C overnight when TLC (EtOAc) indicated complete reaction. The $CHCl_3$ layer was separated and washed with 10% aqueous citric acid (10 cm^3), 10% aqueous NaOH (10 cm^3) and water (10 cm^3) and evaporated to give the *carbamate* **26** as an oil (0.26 g, quantitative) which crystallized with time (EtOAc–hexanes), m.p. 88–91 °C; ν_{max}($CHCl_3$)/cm^{-1} 3610 (carbamate NH), 3438 (OH), 3009, 2941, 2865, 1727s, 1501s, 1436, 1255, 1234, 1094 and 1052; δ_H($CDCl_3$) 7.75 (dd, *J* 1.2 and 8.0, 1 H), 7.68 (dd, *J* 1.6 and 6.8, 1 H), 7.28 (m, 2 H), 7.17 (s, 1 H), 5.03 (br s, 1 H), 4.05 (q, *J* 7.1, 2 H), 3.75 (m, 1 H), 2.58 (m, 2 H), 1.86–2.01 (complex m, 5 H) and 1.56–1.72 (complex m, 4 H). EIMS [Found: 319 (M^+), 273 ($M^+ - C_2H_6O$). Calc. for $C_{17}H_{21}NO_3S$: 319] (Found: C, 63.8; H, 6.7; N, 4.4. $C_{17}H_{21}NO_3S$ requires C, 63.92; H, 6.63; N, 4.39%).

Attempted Cyclization of cis-1-(2-*Benzo*[b]*thienyl*)-N-*ethoxycarbonyl*-4-*hydroxycyclohexylamine* **26**.—Attempts to cyclize **26** (Scheme 3) by treatment with NaH in DMF or Bu^{t}OK in THF were unsuccessful, preventing assignment of configuration based on this approach.

Heating of **26** (5 mg) for 24 h in boiling xylenes (b.p. 137–144 °C) under an argon atmosphere resulted only in unchanged starting material (^1H NMR).

Pyrrolysis of **26** (27 mg) at 250→270 °C during 10 min in a melting point tube followed by TLC (solvent system E) separation of the major product gave **27** (10.1 mg, 52%) as a pale yellow crystalline solid together with unchanged starting material (8 mg). This compound exhibited spectral data identical with those of **27** prepared by a different method (Scheme 2); δ_H($CDCl_3$) 7.74 (dd, *J* 2.2 and 6.3, 1 H), 7.67 (dd, *J* 2.3 and 6.3, 1 H), 7.28 (m, 2 H), 7.13 (s, 1 H), 6.17 (dd, *J* 1.5 and 3.5, 1 H, alkenic-H), 4.08 (m, 1 H), 2.52–2.81 (complex m, 3 H), 2.25 (m, 1 H), 2.04 (m, 1 H), 1.86 (m, 1 H) and 1.56 (br s, 1 H). HRMS [Found: 230.0758 (M^+). M^+ calc. for $C_{14}H_{14}OS$: 230.0765].

4-(2-*Benzo*[b]*thienyl*)-4-*piperidinocyclohexanone* **34**.—To a stirred solution of oxalyl chloride (2.1 cm^3, 24.4 mmol) in dry CH_2Cl_2 (20 cm^3) at −78 °C was added very slowly, dry dimethyl sulfoxide (3.5 cm^3, 36.7 mmol, 2.1 equiv.). The solution was stirred at −78 °C for 15 min, and then a solution of alcohols **28** and **29** (1:1) (5.5 g, 17.5 mmol) in dry CH_2Cl_2 (60 cm^3) was added dropwise. The reaction mixture was stirred at −78 °C for 15 min after which Et_3N (14.9 cm^3, 107 mmol, 6.1 equiv.) was added dropwise over 1 min. The reaction mixture was stirred for 5 min at −78 °C and then warmed to 20 °C with a water-bath. Analysis of the reaction mixture by TLC (solvent system E) indicated the disappearance of **28** and **29** and the formation of a major less polar product. The reaction mixture was poured into water (200 cm^3), extracted with ether (200 cm^3), and the aqueous layer was discarded. The ethereal layer was washed with water (2 × 100 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the ketone **34** (5.2 g, 82%) as a crystalline solid. **34** (propan-2-ol) m.p. 160–162 °C; ν_{max}($CHCl_3$)/ cm^{-1} 2974, 2936, 2850, 2811, 1707 (CO str), 1458, 1125

and 960; $\delta_H(CDCl_3)$ 7.80 (dd, *J* 1.5 and 7.8, 1 H), 7.75 (dd, *J* 1.8 and 8.0, 1 H), 7.32 (m, 2 H), 7.10 (s, 1 H), 2.72 (m, 4 H), 2.52 (m, 4 H), 2.36 (m, 1 H), 2.31 (m, 1 H), 2.09–2.24 (complex m, 2 H), 1.58 (complex m, 4 H) and 1.35 (complex m, 2 H). CIMS [Found: 314 (MH^+). MH^+ calc. for $C_{19}H_{23}NOS$: 314] (Found: C, 72.0; H, 7.4; N, 4.5. $C_{19}H_{23}NOS·0.25H_2O$ requires C, 71.77; H, 7.45; N, 4.41%).

4-(2-*Benzo*[b]*thienyl*)-4-*piperidinocyclohexanone Oxime* **35**.—Ketone **34** (2.2 g, 7.03 mmol) was converted into oxime **35** (2.3 g, quantitative) as described earlier for the oxime **14**. Crystalline *oxime* **35** (EtOAc–hexanes), m.p. 163–165 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3696 (oxime OH str), 3591 (oxime OH str), 2935, 1602, 1457, 1433, 1225, 1124, 958 and 902; $\delta_H(CDCl_3)$ 7.79 (dd, *J* 1.2 and 7.9, 1 H), 7.73 (dd, *J* 1.7 and 7.9, 1 H), 7.31 (m, 2 H), 7.07 (s, 1 H), 2.84–2.95 (complex m, 2 H), 2.42–2.65 (complex m, 6 H), 2.22–2.33 (complex m, 2 H), 1.89–2.05 (complex m, 4 H) and 1.24–1.38 (complex m, 4 H). CIMS [Found: 329 (MH^+). MH^+ calc. for $C_{19}H_{24}N_2OS$: 329] (Found: C, 67.6; H, 7.5; N, 8.3. $C_{19}H_{24}N_2OS·0.5H_2O$ requires C, 67.62; H, 7.47; N, 8.30%).

cis-1-[4-*Amino*-1-(2-*benzo*[b]*thienyl*)*cyclohexyl*]*piperidine* **36**.—To a rapidly stirred solution of $LiAlH_4$ in THF (1.0 mol dm^{-3}; 79 cm^3, 79 mmol) at 0 °C was added, dropwise, a solution of oxime **35** (2.6 g, 7.9 mmol) in THF (79 cm^3). The solution was stirred from 0 to >20 °C overnight after which TLC (solvent system A) indicated the reaction to be complete. Standard isolation and purification of the crude product by column chromatography on silica gel eluting with solvent system A gave the amines **36** (1.55 g, 62%) and **32** (0.31 g, 13%). Combined yield 1.86 g (75%). The amine **32** was identical (^1H NMR and TLC) with an authentic sample prepared earlier by a different route (see Scheme 2). The *amine* **36** was crystallized from cold propan-2-ol (10 cm^3), m.p. 145–146 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2935, 1580, 1457, 1433, 1128, 1071, 968 and 860; $\delta_H(CDCl_3)$ 7.78 (d, *J* 7.3, 1 H), 7.72 (dd, *J* 1.7 and 8.0, 1 H), 7.29 (m, 2 H), 7.02 (s, 1 H), 2.78 (m, 1 H, C*H*NH_2), 2.49 (m, 2 H), 2.42 (m, 4 H), 1.44–1.81 (complex m, 10 H) and 1.31 (m, 2 H). CIMS [Found: 315 (MH^+). MH^+ calc. for $C_{19}H_{26}N_2S$: 315] (Found: C, 72.5; H, 8.4; N, 8.9. $C_{19}H_{26}N_2S$ requires C, 72.57; H, 8.33; N, 8.91%).

cis-1-[1-(2-*Benzo*[b]*thienyl*)-4-*isothiocyanatocyclohexyl*]-*piperidine* **4**.—The method of preparation was as described earlier for the isothiocyanate **2** except starting with the amine **36** (0.50 g, 1.59 mmol), to give *isothiocyanate* **4** (quantitative) as a pale yellow crystalline solid (one spot on TLC, solvent system C). Recrystallization from propan-2-ol (20 cm^3) afforded **4** (0.54 g, 95%), m.p. 134–135 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2935, 2855, 2114vs (NCS str), 1602, 1457, 1433, 1368, 1320, 1155 and 964; $\delta_H(CDCl_3)$ 7.78 (d, *J* 7.3, 1 H), 7.72 (d, *J* 7.1, 1 H), 7.30 (m, 2 H), 7.01 (s, 1 H), 3.76 (m, 1 H, C*H*NCS), 2.42 (m, 6 H), 2.01–1.15 (complex m, 2 H), 1.80–1.94 (complex m, 4 H), 1.56 (m, 4 H) and 1.24–1.38 (complex m, 2 H). CIMS [Found: 357. MH^+ calc. for $C_{20}H_{24}N_2S_2$: 357] (Found: C, 67.3; H, 6.8; N, 7.9. $C_{20}H_{24}N_2S_2$ requires C, 67.37; H, 6.78; N, 7.86%).

1-{1-(4-*Nitro*-2-*benzo*[b]*thienyl*)*cyclohexyl*}*piperidine* **37**.—To a stirred solution of BTCP **1** (2.0 g, 6.7 mmol) in CF_3CO_2H (17.6 cm^3) was added $NaNO_2$ (1.39 g, 20.1 mmol, 3.0 equiv.) at 20 °C under a nitrogen atmosphere. The brown solution was stirred for 3 h when a deep orange–red colour developed. TLC (solvent system D) indicated complete reaction. The reaction mixture was poured into water (100 cm^3), excess of saturated $NaHCO_3$ added, and the mixture was extracted with $CHCl_3$ (100 cm^3). Fractionation of the product mixture by column chromatography on silica gel eluting with solvent system D gave the *nitro compound* **37** (1.38 g, 60%) as a yellow oil; **37**·fumarate (propan-2-ol), m.p. 184–185 °C (decomp.); $\nu_{max}(CHCl_3)/cm^{-1}$ 2980, 2937, 2856, 2806, 1601, 1525, 1500, 1444, 1348s, 1325s, 1294 and 966; $\delta_H(CDCl_3)$ 8.28 (d, *J* 7.9, 1 H), 8.06 (d, *J* 8.0, 1 H), 7.92 (s, 1 H), 7.37 (t, *J* 7.9, 1 H), 2.42 (m, 4 H), 2.08 (m, 4 H), 1.78 (m, 2 H), 1.37–1.64 (complex m, 8 H) and 1.31 (m, 2 H) (Found for **37**·fumarate: C, 59.8; H, 6.8; N, 5.6. $C_{23}H_{28}N_2O_6S·0.5H_2O$ requires C, 59.98; H, 6.97; N, 5.38%).

The 5-nitro isomer **38** (0.20 g, 9%) was obtained as a minor product; **38** (base) (EtOH), m.p. 128–129 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2937, 2857, 2805, 1525, 1500, 1443, 1340s, 1130 and 967; $\delta_H(CDCl_3)$ 8.71 (d, *J* 1.7, 1 H), 8.18 (dd, *J* 1.7 and 8.8, 1 H), 7.79 (d, *J* 8.8, 1 H), 7.15 (s, 1 H), 2.41 (m, 4 H), 1.96–2.18 (complex m, 4 H), 1.78 (m, 2 H) and 1.20–1.61 (complex m, 10 H) (Found: C, 66.15; H, 7.0; N, 8.1. $C_{19}H_{24}N_2O_2S$ requires C, 66.25; H, 7.02; N, 8.13%).

Similarly, the 7-nitro isomer **39** (0.46 g, 20%) was obtained as an unstable red oil, $\delta_H(CDCl_3)$ 8.34 (d, *J* 8.0, 1 H), 8.04 (d, *J* 8.0, 1 H), 7.49 (t, *J* 8.0, 1 H), 7.18 (s, 1 H), 2.46 (m, 4 H), 2.12 (m, 4 H), 1.81 (m, 2 H), 1.57 (m, 4 H), 1.47 (m, 4 H) and 1.33 (m, 2 H). No attempt was made to further purify this compound. HRMS [Found: 344.1561 (M^+). M^+ calc. for $C_{19}H_{24}N_2O_2S$: 344.1558].

The positions of nitration were ascertained by direct comparison of the aromatic splitting patterns and chemical shift values of **37**–**39** with each other and with those of the unsubstituted BTCP as well as from NOE experiments. Thus, as expected from charge distribution considerations, the 4′-nitro isomer **37** showed a strongly deshielded 3-H (δ 7.92) with respect to the unsubstituted BTCP 3-H (δ 7.04) and with respect to the alternative 7′-nitro isomer **39** which showed a signal for 3-H at δ 7.18 not much different from BTCP. No observable NOE difference was observed after irradiation of the singlet for 3-H [7.92 (s, 1 H)] in **37** on any of the other protons in the benzo[*b*]thienyl ring thus distinguishing it from the 7′-nitro isomer **39**. BTCP, with adjacent 4-H and 3-H protons showed a weak long-range interaction between 3-H [7.04 (s, 1 H)] and 4-H [7.79 (d, *J* 7.7, 1 H)] protons (NOESY). Similarly, a small interaction between 3-H [7.15 (s, 1 H)] and 4-H [8.71 (d, *J* 1.7, 1 H)] confirmed the 5-nitro substitution of **38**.

1-[1-(4-*Amino*-2-*benzo*[b]*thienyl*)*cyclohexyl*]*piperidine* **40**.—The nitro compound **37** (0.88 g, 2.56 mmol) in EtOH (100 cm^3) was catalytically hydrogenated (as described for the reduction of **31** to **32**) to give the *amine* **40** as an unstable crystalline solid (0.77 g, 96%); $\nu_{max}(film)/cm^{-1}$ 3449 (NH_2), 3357 (NH_2), 3220 (NH_2), 2930, 2851, 2801, 1618, 1573, 1468, 1344 and 1289; $\delta_H(CDCl_3)$ 7.61 (d, *J* 9.1, 1 H), 7.43 (m, 1 H), 7.30 (m, 1 H), 6.95 (s, 1 H), 4.31 (br s, 2 H), 2.50 (m, 4 H), 2.05–2.25 (complex m, 4 H) and 1.05–1.95 (complex m, 12 H). CIMS [Found: 230 ($MH^+ - C_5H_{11}N$). MH^+ calc. for $C_{19}H_{26}N_2S$: 315]. No attempt was made to further characterize or purify the amine **40** because of its lability.

1-[1-(4-*Isothiocyanato*-2-*benzo*[b]*thienyl*)*cyclohexyl*]-*piperidine* **5**.—The amine **40** (0.77 g, 2.72 mmol) was treated with $CSCl_2$ as for the isothiocyanate **2** to give the isothiocyanate **5** (0.86 g, 97%). Crystallization from EtOH gave **5** (0.68 g, 78%), m.p. 98–100 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2936, 2855, 2804, 2113vs (NCS str), 1562, 1512, 1455, 1421, 1293, 1155 and 971; $\delta_H(CDCl_3)$ 7.69 (d, *J* 7.3, 1 H), 7.15–7.24 (complex m, 3 H), 2.42 (m, 4 H), 2.07 (m, 4 H), 1.78 (m, 2 H), 1.38–1.60 (complex m, 8 H) and 1.24–1.38 (m, 2 H). CIMS [Found: 272 ($MH^+ - C_5H_{11}N$). MH^+ calc. for $C_{20}H_{24}N_2S_2$: 357] (Found: C, 67.44; H, 6.80; N, 7.80. $C_{20}H_{24}N_2S_2$ requires C, 67.37; H, 6.78; N, 7.86%).

1-[1-(5-*Isothiocyanato*-2-*benzo*[b]*thienyl*)*cyclohexyl*]-*piperidine* **6**.—The nitro isomer **38** (0.20 g, 0.58 mmol) was catalytically hydrogenated to the corresponding aniline as described above for the amine **40** and directly transformed into

Table 1 Atomic coordinates ($\times 10^4$)

Atom	x	y	z
S(1)	7 181(1)	97(3)	1 765(1)
C(2)	6 831(2)	−1 608(5)	1 095(2)
C(3)	6 076(3)	−1 352(7)	520(2)
C(4)	5 847(3)	−2 752(9)	7(2)
C(5)	6 310(3)	−4 386(8)	37(2)
C(6)	7 032(3)	−4 666(5)	601(2)
C(7)	7 305(2)	−3 278(4)	1 130(2)
C(8)	8 030(6)	−2 986(12)	1 801(4)
C(9)	8 047(2)	−1 447(3)	2 179(1)
C(10)	8 629(2)	−859(3)	2 922(1)
C(11)	9 570(2)	−1 897(4)	3 036(2)
C(12)	10 274(2)	−1 273(4)	2 444(2)
C(13)	10 448(2)	786(4)	2 487(2)
C(14)	9 521(2)	1 832(4)	2 366(2)
C(15)	8 815(2)	1 222(3)	2 957(2)
N(1)	8 054(2)	−1 340(3)	3 615(1)
O(1)	10 914(1)	1 195(3)	3 245(1)
S(1′)	8 184(2)	−3 755(5)	1 802(1)
C(8′)	7 343(11)	−660(22)	1 763(6)
C(1S)	10 157(2)	−5 291(3)	4 671(2)
C(2S)	11 074(2)	−4 685(3)	4 354(2)
O(1S)	11 263(1)	−5 299(3)	3 684(1)
O(2S)	11 589(1)	−3 592(3)	4 761(1)
O(1W)	8 991(2)	32(3)	5 010(1)
O(2W)	7 790(2)	4 875(3)	3 710(1)

the isothiocyanate **6** (0.19 g, 65% yield from **38**) as described above. **6**·fumarate (propan-2-ol), m.p. 220 °C (decomp.); ν_{max}(film)/cm^{-1} 2928, 2851, 2800, 2107vs (NCS str), 1600, 1257 and 1156; δ_H($CDCl_3$) 7.68 (s, 1 H), 7.66 (d, *J* 8.0, 1 H), 7.22 (dd, *J* 8.0 and 1.7, 1 H), 7.18 (s, 1 H) and 0.80–2.55 (complex m, 20 H). CIMS [Found: 357 (MH^+). MH^+ calc. for $C_{20}H_{24}S_2$: 357] HRMS [Found: 356.1370 (M^+). M^+ calc. for $C_{20}H_{24}S_2$: 356.1381].

1-[1-(7-*Isothiocyanato*-2-*benzo*[b]*thienyl*)*cyclohexyl*]-*piperidine* **7**.—The nitro isomer **39** (0.46 g, 1.34 mmol) was transformed into the isothiocyanate **7** (0.28 g, 59%) as described above for isothiocyanate **6**. **7**·fumarate (propan-2-ol), m.p. 177–178 °C (decomp.); ν_{max}(film)/cm^{-1} 2929, 2854, 2111vs (NCS str), 1603, 1451, 1257, 1170 and 1024; δ_H($CDCl_3$) 7.64 (d, *J* 7.9, 1 H), 7.29 (t, *J* 7.9, 1 H), 7.17 (d, *J* 7.9, 1 H), 7.09 (s, 1 H), 2.44 (m, 4 H), 2.09 (m, 4 H), 1.79 (m, 2 H) and 1.40–1.70 (complex m, 10 H). HRMS [Found: 356.1373 (M^+). M^+ calc. for $C_{20}H_{24}N_2S_2$: 356.1381] (Found for **7**·fumarate: C, 57.7; H, 6.25; N, 5.6. $C_{24}H_{28}N_2O_4S_2$·1.5H_2O requires C, 60.99; H, 5.97; N, 5.93).

Single Crystal X-Ray Diffraction of the Fumarate Salt of the Amine **25**.—$C_{14}H_{18}NOS$·2H_2O·0.5($C_4H_2O_4$), FW = 341.4, monoclinic space group *P*21/*a*, *a* = 14.196(2), *b* = 7.235(1), *c* = 16.835(2) Å, β = 93.78(1)°, *V* = 1725.3(4) Å^3, *Z* = 4, D_c = 1.314 mg mm^{-3}, λ(Cu-Kα) = 1.541 84 Å, μ = 1.836 mm^{-1}, *F*(000) = 728, *T* = 295 K.

A clear colourless 0.15 × 0.42 × 0.45 mm crystal, in the shape of an irregular plate, was used for data collection on an automated Siemens R3m/V diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from 25 centred reflections within $50 \leqslant 2\theta \leqslant 60°$. The data collection range of *hkl* was $-15 \leqslant h \leqslant 15$, $0 \leqslant k \leqslant 7$, $0 \leqslant l \leqslant 18$, with $[(\sin\theta)/\lambda]_{max}$ = 0.55. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to ±2.1% during the data collection. A set of 2216 reflections was collected in the $\theta/2\theta$ mode, with scan width $[2\theta(K_{\alpha 1}) - 1.0]$ to $[2\theta(K_{\alpha 2}) + 1.0]°$ and ω scan rate (a function of count rate) from 3.0° min^{-1} to 15.0° min^{-1}. There were 2216 unique reflections, and 2215 were observed with $F_o > 3\sigma(F_o)$. The structure was solved and refined with the aid of the SHELXTL system of programs.[15] A full-matrix least-squares refinement varied 273 parameters; atom coordinates are presented in Table 1. The H atoms for the benzo[*b*]thienyl were included using a riding model (coordinate shifts of C applied to attached H atoms, C–H distances set to 0.96 Å, and H angles idealized). Coordinates for all other H atoms were refined isotropically. Final residuals were R = 0.052 and R_w = 0.072 with final difference Fourier excursions of 28 and −0.24 e Å^{-3}.

The salt of amine **25** crystallized with the dianionic fumarate on a centre of symmetry. The asymmetric unit consists of the *cis*-benzo[*b*]thienylaminium cyclohexanol cation, half of the fumarate dianion and two water molecules bound by an extensive network of hydrogen bonding with the cations and dianion linked through hydrogen bonding to the water molecules. In the cation the planar benzo[*b*]thienyl rings are oriented *trans* to the hydroxy on the cyclohexane ring which adopts a chair conformation (Fig. 1). The orientation of the benzo[*b*]thienyl rings may be further defined by the S(1)–C(9)–C(10)–C(11) = −159.8(2)° torsion angle. In the crystal this fused ring system is disordered by 180° rotation about the bond to the cyclohexane ring with alternate positions for both S(1)[S(1′)], and C(8)[C(8′)] in an occupancy ratio of 63:37. Overall, bond distances and angles are normal with a C–S average of 1.740 Å. The C(8)–C(9) = 1.282(9) and C(9)–C(8′) = 1.312(14) Å distances are shorter in this ionic compound than the corresponding bond in a number of substituted benzothiophenes[16–18] (1.33 to 1.28 Å). Tables of bond distances and angles, and anisotropic thermal parameters are available on request from the Cambridge Crystallographic Data Centre.*

* See Instructions for Authors (1992), *J. Chem. Soc., Perkin Trans 1*, 1992, Issue 1.

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