Syntheses and Biological Activities of Potent Potassium Channel Openers Derived from (±)-2-Oxo-1-pyridin-3-yl-cyclohexanecarbothioic Acid Methylamide: New Potassium Channel Openers

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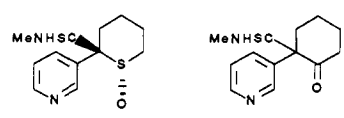
The syntheses and biological activities of (±)-2-(cyanomethylene)-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (6) and *trans*-(±)-2-(cyanomethyl)-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (14) derived from (±)-2-oxo-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (4) are reported. Compounds were tested for antagonism of potassium-induced contraction of de-endothelialized rat aorta. The effects of modification of 6 and 14 on *in vitro* K^+-channel opening activity are presented. These new series of potassium channel openers so derived are best exemplified by (±)-2-[2-(phenylsulfanyl)ethylidene]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (**13d**, RP 66266) and *trans*-(±)-2-[2-[(phenylsulfonyl)amino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (**25a**, RP 66784), which have IC_{90} values of 3 and 0.3 nM, respectively. The potency of the most active compounds indicates a possible interaction at an extra binding site. The compounds described herein are potential antihypertensive and antianginal agents.

Recently there has been a growing interest in the therapeutic potential of substances that open potassium channels,[1] especially those that act on the ATP-dependent channel.[2,3] The conductance of these channels is thought to be regulated by changes in the intracellular concentration of ATP, and it was proposed that opening of this channel hyperpolarized the smooth muscle plasmalemma toward the K^+ equilibrium potential, thereby reducing the probability of opening voltage-gated Ca^{2+} channels. This action would prevent depolarization-induced Ca^{2+} entry and the consequent contraction of the smooth muscle cell. Although nicorandil and pinacidil were the first compounds demonstrated to act on K_{ATP} channels,[3] cromakalim[4] is generally regarded as the archetypal potassium channel opener and until recently most of the newer potassium channel openers described have arisen by modification of cromakalim.[5a-f]

We recently described the synthesis and biological activity of a new class of potassium channel opener RP 49356 and analogues,[6] from which the (-)-enantiomer RP 52891 (aprikalim) was selected for development as an antihypertensive and antianginal agent. Here we describe the synthesis and biological activity of a new class of potassium channel openers derived from (±)-2-oxo-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (4).[7]

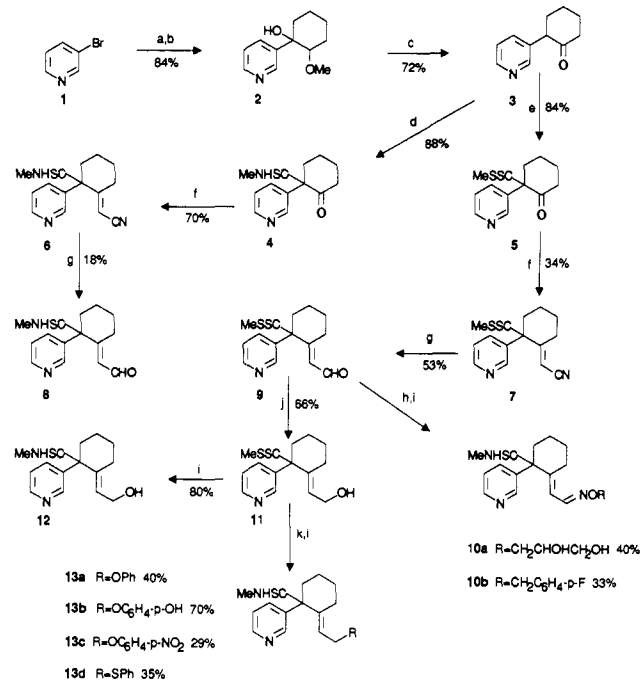


Aprikalim 4

Chemistry

The 3-pyridylcyclohexanone thioamide 4 and dithioester 5 are readily prepared from commercially available materials[7] as shown in Scheme I. Lithiation of 1 and reaction with 2-methoxycyclohexanone gave 2 in good yield. Treatment of 2 with concentrated sulfuric acid resulted in the high yield conversion to 3. Acylation of 3 with methyl isothiocyanate gave the thioamide 4 as previously described;[7] alternatively acylation of 3 with carbon disulfide followed by treatment with methyl iodide gave the dithioester 5. Compounds 4 and 5 served as starting materials for the synthesis of the substituted (±)-2-methylene-1-pyridin-3-ylcyclohexanecarbothioic acid methylamides listed in Table I. Reaction of 4 and 5 in the Wadsworth-Emmons modification of the Wittig reaction with diethyl (cyanomethyl)phosphonate[8] gave the α,β-

Scheme I[a]



[a] Reagents: (a) ^{n}BuLi, Et_2O, -60 °C; (b) 2-methoxycyclohexanone; (c) concentrated H_2SO_4 then NaOH; (d) KOBu^t, DMF, MeNCS, -30 °C; (e) KOBu^t, THF, CS_2, -30 °C then MeI; (f) NaH, diethyl (cyanomethyl)phosphonate, THF; (g) DIBAL, toluene, -20 °C; (h) requisite hydroxylamine, Δ; (i) 33% $MeNH_2$ in EtOH, THF; (j) $NaBH_4$, MeOH; (k) requisite phenol, Mitsunobu procedure.

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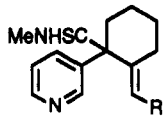
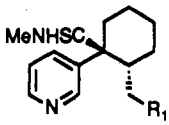
Table I. Substituted Methylene-1-pyridin-3-yl-cyclohexanecarbothioic Acid Methylamides



compd	R	relaxn of rat aorta; 20 mmol K^+ IC_{90}, μM[a]
aprikalim		0.4
6	CN	10
8	CHO	8–10
10a	CH=NOCH$_2$CHOHCH$_2$OH	3
10b	CH=NOCH$_2$-C$_6$H$_4$-*p*-F	0.1
12	CH$_2$OH	10–30
13a	CH$_2$OPh	0.065
13b	CH$_2$O-C$_6$H$_4$-*p*-OH	0.3
13c	CH$_2$O-C$_6$H$_4$-*p*-NO$_2$	0.1
13d	CH$_2$SPh	0.003

[a] Number of determinations ≥2.

Table II. Substituted *trans*-(±)-Methyl-1-pyridin-3-yl-cyclohexanecarbothioic Acid Methylamides



compd	R_1	relaxn of rat aorta; 20 mmol K^+ IC_{90}, μM[a]
14	CN	0.3
15	CH$_2$NH$_2$	10
16	CO$_2$Me	0.3
20	CH$_2$OH	1.7
21a	CH$_2$OCOCH$_3$	0.03
21b	CH$_2$OCOPh	0.03
21c	CH$_2$OCO-C$_6$H$_4$-*p*-F	0.1
22	CH=NOCH$_2$Ph	0.03
23	CH$_2$NHPh	0.003
24a	CH=CHPh	0.1
24b	CH=CH-C$_6$H$_4$-*p*-F	0.01

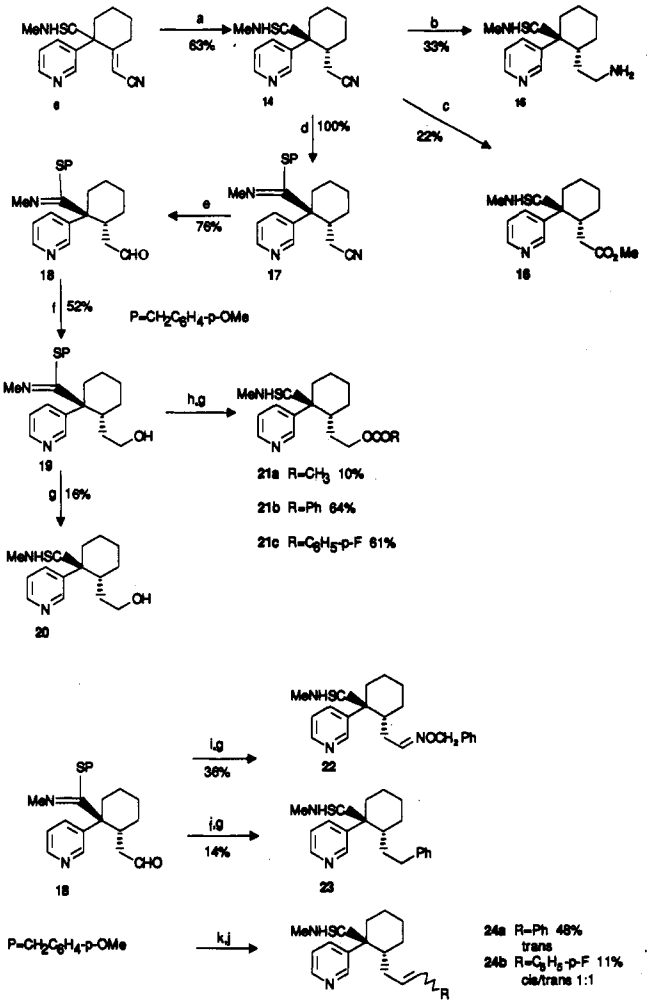
[a] Number of determinations ≥2.

unsaturated nitriles **6** and **7**, respectively. Reduction of **6** to the aldehyde **8** proceeded in low yield due to an intramolecular cyclization side reaction, the chemistry of which will be described elsewhere. To negate the inherent nucleophilicity of the thioamide group in **4**, reactions were carried out on the dithioester **5**, and conversion to the requisite carbothioic acid methylamide was performed in the final step as indicated in Scheme I.

Reduction of the nitrile **7** to the aldehyde **9** was accomplished using diisobutylaluminium hydride.[9] Reaction of **9** with the requisite hydroxylamine hydrochloride[10] followed by conversion to the thioamide gave the oximes **10a,b**. Further reduction of aldehyde **9** to the alcohol **11** was performed with sodium borohydride,[11] and reaction of **11** with ethanolic methylamine gave the thioamide **12**. Conversion of **11** to compounds **13a–d** was achieved using the Mitsunobu procedure[12] followed by treatment with ethanolic methylamine. Compounds **6–13d** are listed in Table I.

Compound **6** also served as the starting material for the synthesis of new 2-substituted *trans*-(±)-methyl-1-pyridin-3-ylcyclohexanecarbothioic acid methylamides shown in Table II. Reduction of the unsaturated nitrile **6** with lithium aluminium hydride at room temperature gave the *trans* nitrile **14** as shown in Scheme II. Complexation of the lithium aluminium hydride with the thioamide followed by delivery of hydride from the same face as the thioamide may explain the formation of the *trans* product. No *cis* product or reduction products of the nitrile group were observed under these conditions. The *trans* geometry was unambiguously established by X-ray crystallographic analysis of the derived ester **21c**.[13] Figure 1 depicts the X-ray structure of **21c**. Further reduction of **14** with lithium aluminium hydride in tetrahydrofuran at reflux gave the amine **15**. Treatment of **14** with gaseous hydrogen chloride in methanol produced the ester **16**.

Scheme II[a]



[a] Reagents: (a) LAH, THF, 25 °C, 10 min; (b) LAH, THF, reflux, 1 h; (c) Et_2O, HCl(g), MeOH; (d) 4-methoxybenzyl chloride, KOBu^t, THF; (e) DIBAL, −30 °C, CH_2Cl_2; (f) $NaBH_4$, MeOH, −20 °C; (g) TFA, anisole, 0 °C; (h) acid chloride, CH_2Cl_2, DMAP, 0 °C; (i) oxime hydrochloride, Δ; (j) aniline, reflux, toluene then $NaBH_3CN$, MeOH; (k) Wittig reagent, LDA, THF.

It was necessary to protect the thioamide group in **14** during further manipulations due to its inherent nucleophilicity causing side reactions. Treatment of **14** with 4-methoxybenzyl chloride/potassium *tert*-butoxide gave the protected thioamide **17**. Reduction of **17** with diisobutylaluminium hydride gave the aldehyde **18**, which upon further reduction with sodium borohydride gave the alcohol **19**. Deprotection of **19** using trifluoroacetic acid in anisole at 0 °C gave the alcohol **20**. Reaction of **19** with the appropriate acid chloride followed by similar thioamide deprotection yielded the esters **21a–c**.

Reaction of the aldehyde **18** with *O*-benzylhydroxylamine hydrochloride[10] followed by deprotection gave a 1:1 ratio of the *syn*/*anti*-oximes **22** as outlined in Scheme II. Reductive amination of **18** with aniline and sodium

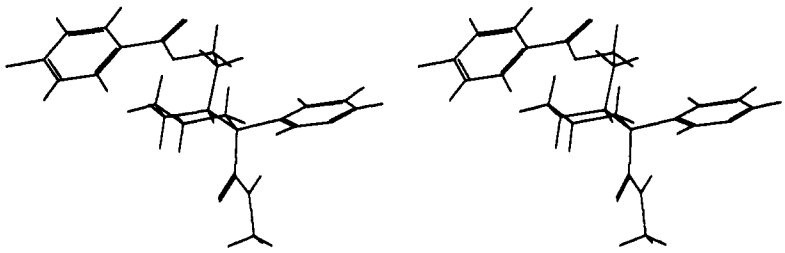
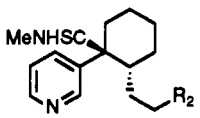


Figure 1. Stereoplot of the X-ray structure of **21c**.

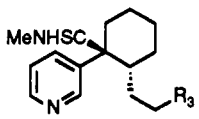
Table III. Substituted *trans*-(±)-2-Ethyl-1-pyridin-3-yl-cyclohexanecarbothioic Acid Methylamides



compd	R_2	relaxn of rat aorta; 20 mmol K^+ IC_{90}, μM[a]
25a	$NHSO_2Ph$	0.0003
25b	$NHSO_2Me$	0.17
25c	$NHSO_2$-C_6H_4-*p*-F	0.007
25d	$NHSO_2$-2-thienyl	0.001
25e	$NHSO_2$-3-pyridyl	0.003
25f	$NHSO_2$-C_6H_4-*p*-Cl	0.03
25g	$NHSO_2$-C_6H_4-*p*-NO_2	0.3
25h	$NHSO_2$-C_6H_4-*p*-OMe	0.3
25i	$NHSO_2$-C_6H_3-3,4-F_2	0.01

[a] Number of determinations ≥2.

Table IV. Substituted *trans*-(±)-2-Ethyl-1-pyridin-3-yl-cyclohexanecarbothioic Acid Methylamides



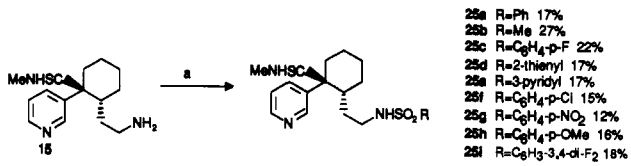
compd	R_3	relaxn of rat aorta; 20 mmol K^+ IC_{90}, μM[a]
26a	NHCOPh	0.3
26b	NHCO-C_6H_4-*p*-F	0.5
26c	$NHCOCH_2Ph$	0.3
26d	$NHCOCH_3$	0.13
26e	NHCO^{i}Pr	0.3
27a	NHC(=NSO_2Me)NHMe	0.03
27b	NHC(=NSO_2Ph)NHMe	0.3
28	N(–$COCH_2OCH_2CO$–)	0.1

[a] Number of determinations ≥2.

cyanoborohydride followed by thioamide deprotection gave **23**. Horner–Wittig chemistry on **18** using diethyl benzylphosphonate followed by deprotection gave exclusively the *trans* product **24a** (J = 16 Hz). Reaction of **18** with 4-fluorobenzylphosphonium chloride under typical Wittig conditions and subsequent removal of the protecting group resulted in a 1:1 *cis*:*trans* mixture of **24b** (J_{cis} = 12 Hz, J_{trans} = 16 Hz).

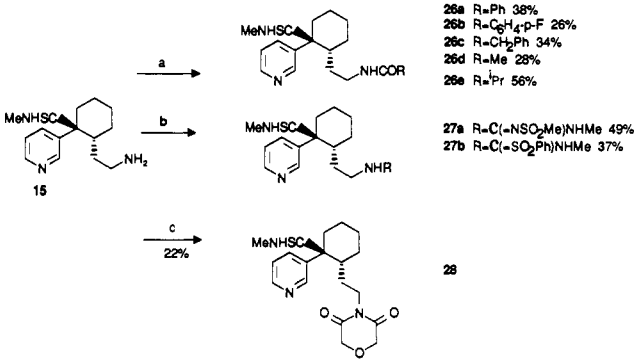
The amine **15** served as a useful intermediate for the reaction with various electrophiles to form the compounds listed in Tables III and IV. Treatment of **15** with the appropriate sulfonyl chloride in dichloromethane containing triethylamine, resulted in the formation of compounds **25a–i** as indicated in Scheme III. Reaction of the amine **15** with the requisite acid chloride gave amides **26a–e** as shown in Scheme IV. Treatment of **15** with *N*-[bis(methylsulfonyl)methylene]benzenesulfonamide or *N*-[bis(methylsulfonyl)methylene]methanesulfonamide followed by ethanolic methylamine gave compounds **27a,b**.

Scheme III[a]



[a] Reagents: (a) requisite sulfonyl chloride, CH_2Cl_2, Et_3N.

Scheme IV[a]



[a] Reagents: (a) requisite acid chloride, base; (b) $RSO_2N{=}C(SMe)_2$, EtOH, Δ followed by $MeNH_2$ in EtOH; (c) diglycollic anhydride, toluene, 1,2-dichlorobenzene, reflux.

Reaction of **15** with diglycollic anhydride yielded **28**. Compounds **26–28** are listed in Table IV.

Results and Discussion

The vasorelaxant activity tests were adapted from those described by Winslow[14] and Karaki[15] for differentiating vasorelaxant activity. The biological evaluation of compounds in vitro is based upon the ability of K^+ channel openers to relax de-endothelialised rat aortic strips toned with 20 mM but not with 60 mM KCl. A compound was considered active if it possessed an $IC_{90} < 30$ μM. As smooth muscle relaxants acting by different mechanisms may also relax 20 mM KCl induced tone, the activity of a compound was attributed to K^+ channel opening only if its action was reversed by glibenclamide, a blocker of ATP-regulated K^+ channels.[16]

During the research leading to aprikalim, it was established that a 3-substituted pyridine together with a *trans* relationship of the thioamide to the sulfoxide was essential for good activity.[6] Modeling and X-ray studies on aprikalim[6] have shown that in the *trans* geometry the thioamide and sulfoxide oxygen are axial and this is thought to be a requisite for activity. The keto compound **4** was synthesized to mimic the sulfoxide moiety of aprikalim retaining the thioamide and 3-substituted pyridine groups. This would remove one chiral center, give more synthetically accessible compounds, and also examine the effect of changing the geometry at the center bearing the oxygen atom. Aprikalim was active in vitro

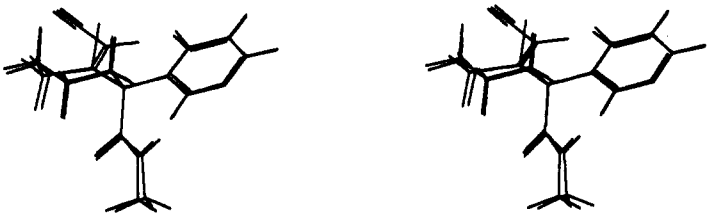


Figure 2. Stereoplot of **6** superimposed on Aprikalim.

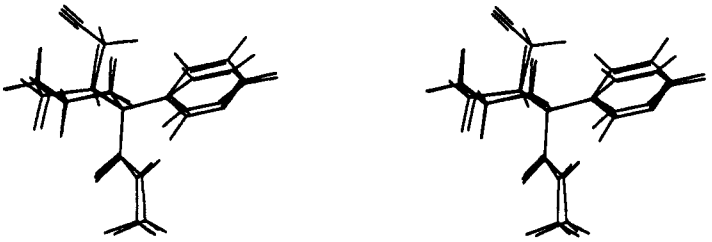


Figure 3. Stereoplot of **14** superimposed on Aprikalim.

with an IC_{90} = 400 nM and the ketone **4** has an IC_{90} = 800 nM, when racemic. Cyanomethenylation of **4** gave the α,β-unsaturated nitrile **6**, which resulted in reduced activity (IC_{90} = 10 μM). Reduced activities were also observed with **8**, **10a**, and **12** as compared to the parent keto compound **4**. The superimposition of MOPAC/AM1[17] low-energy conformers of aprikalim (from the X-ray structure) and **6** is depicted in Figure 2. This shows the difference in the geometry of the center which bears the sulfoxide oxygen of aprikalim and the cyanomethylene group in **6** and how this difference affects the spacial positioning of these groups and thus their potential interactive regions. Introduction of an aromatic nucleus by functionalization of the aldehyde **9** and alcohol **11** led to increased activity. This is indicated by the 2-hydroxyethylidene derivative **12** being weakly active and the 2-phenoxyethylidene **13a** being a potent compound (IC_{90} = 65 nM). Some loss of activity by para substitution of the aromatic nucleus was observed for **13b** and **13c**. The most potent compound in this series is the 2-(phenylsulfanyl)ethylidene analogue **13d** with an IC_{90} = 3 nM. The large increase in activity observed upon introduction of an aromatic nucleus may indicate the occupation of an extra binding site.

Changing the sp^2 geometry at C-2 of the substituted cyclohexane to sp^3 via reduction of the unsaturated nitrile **6** (IC_{90} = 10 μM) to the *trans* cyanomethyl derivative **14** led to increased activity (IC_{90} = 300 nM). If both the thioamide and the cyanomethyl side chain are axial, then the increased activity could be due to improved targeting of the cyanomethyl analogous to the sulfoxide oxygen of aprikalim, although this sp^2 to sp^3 change of geometry also favorably affects the equilibrium of the thioamide group between axial and equatorial positions toward the axial conformation.[6] Figure 3 shows the superimposition of a low-energy conformation of **14** with the X-ray conformation of aprikalim. The cyanomethyl side chain of **14** is now orientated similarly to the sulfoxide oxygen of aprikalim. Increased activity is also observed for the 2-hydroxyethyl compound **20** when compared to the 2-hydroxyethylidene derivative **12**. Further functionalization of **14** and **20** and introduction of an aromatic nucleus into the side chain has led to increased activity, as was observed in the unsaturated series above. The esters **21b,c**, oxime **22**, amine **23**, and the stryenes **24a,b** are all potent potassium channel openers. The most potent compound in this series is the amino phenylethyl derivative **23** with an IC_{90} = 3 nM. The effect of functionalization of the ethylamine **15** on activity is shown in Tables III and IV. The (sulfonylamino)ethyl derivatives **25a–i** are active, with the highest potency residing in the aromatic (sulfonylamino)ethyl derivatives **25a**, **25c**, and **25d** with IC_{90} values of 0.3, 7, and 1 nM, respectively. In general, para substitution in the aromatic sulfonamides led to compounds of reduced activity. The amides **26a–e** and derivatives **27a**, **27b**, and **28** are much less active than the sulfonamides. This could be due to the amide carbonyl having sp^2 geometry and the sulfonamide sulfonyl being sp^3 affecting the potential interaction regions of both the oxygen and aromatic groups. Hence the aromatic groups in the sulfonamides might be able to occupy space inaccessible by the aromatic groups of the benzamides so as to contribute to extra binding, and thus to the increased potency found in this series.

Summary

The synthesis of (±)-2-(cyanomethylene)-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide **6** has led to the discovery of a new series of potassium channel openers. Removal of the unsaturation from the above series and chemical modification has led to further more potent compounds. A trend of increased activity when C-2 of the cyclohexane nucleus is sp^3 substituted was found, indicative of the directional and conformational influences of this position. Introduction of aromatic functionality into the side chains in all series gives a large increase in potency, indicating a possible interaction at an extra binding site. The most potent compound synthesized was *trans*-(±)-2-[2-[(phenylsulfonyl)amino]ethyl]-1-pyridin-3-ylcyclohexane carbothioic acid methylamide (**25a**), with an IC_{90} of 0.3 nM. These compounds are being further investigated for hypotensive in vivo activity.

Experimental Section

Melting points were determined using an Electrothermal or a Reichert-Kofler apparatus and are uncorrected. Spectroscopic data for all compounds were recorded on Varian XL-200 and VXR 400 (NMR) instruments and were consistent with assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within 0.4% of the theoretical values. NMR data are reported in ppm downfield relative to external TMS (0 ppm) as standard. Concentration refers to

evaporation under aspirator vacuum using a Büchi rotary evaporator. Precoated silica gel 60 F_{254} plates with a layer thickness of 0.25 mm from E. Merck, Darmstadt, Germany, were used for thin-layer chromatography. Preparative column chromatography was performed using medium-pressure "flash" chromatography. The stationary phase used was "Sorbsil" (Crosfield) silica gel, mesh size 40–60 μm supplied by Rhône-Poulenc. All organic solutions were dried over magnesium sulfate. Yields are not optimized. All compounds are racemic.

Molecular Modeling. Graphical display and manipulation was performed using the Chem-X suite of programs[18] running on a VAX 3500 and an Evans and Sutherland PS390 graphics station. Conformational analysis was initially carried out using the default Chem-X force field; the structures were constructed from fragments whose geometry had been fully optimized by MOPAC/AM1 (QCPE 455, version 5.0)[17] calculations and MOPAC/AM1 derived charges were used. All potential low energy structures were further minimized using MOPAC/AM1 using criteria for terminating the optimization defined by the PRECISE keyword; further systematic conformational analysis was then performed on these structures using Chem-X in order to identify any further potential minima. X-ray crystal structures were also subjected to a MOPAC/AM1 calculation to remove any crystal packing effects before comparisons with other structures were made.

2-Oxo-1-pyridin-3-ylcyclohexanecarbodithioic Acid Methyl Ester (5). A solution of 2-pyridin-3-ylcyclohexanone (20 g, 0.11 mol) in dry THF (200 mL) at −40 °C was treated with potassium *tert*-butoxide (16.7 g, 0.14 mol). After 15 min at −40 °C the mixture was treated with carbon disulfide (10 mL, 0.165 mol). The mixture was warmed to 25 °C over 30 min. After 30 min at 25 °C the mixture was treated with methyl iodide (10.3 mL, 0.165 mol). After 12 h at 25 °C the mixture was diluted with ethyl acetate (500 mL) followed by water (500 mL). The organic phase was collected, dried, and filtered. Concentration in vacuo followed by flash chromatography eluting with EtOAc/hexane (30:70) gave **5**: yield 24.7 g (84%); mp 133–135 °C; NMR ($CDCl_3$) δ 1.66–2.14 (c, 4 H), 2.38–2.62 (c, 2 H), 2.62 (s, 3 H), 2.78–3.00 (c, 1 H), 3.38–3.58 (m, 1 H) , 7.24–7.34 (m, 1 H), 7.66–7.78 (m, 1 H), 8.52–9.00 (m, 1 H), 9.00–9.06 (m, 1 H). Anal. ($C_{13}H_{15}NOS_2$) C, H, N, S.

2-(Cyanomethylene)-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (6). A solution of diethyl (cyanomethyl)phosphonate (215 mg, 1.2 mmol) at room temperature in dry THF (20 mL) was treated with a 60% oil dispersion of NaH (40 mg, 1 mmol). After 15 min at room temperature 4 (245 mg, 1 mmol) was added and the resulting solution stirred for 3 h at room temperature; EtOAc (50 mL) and water (50 mL) were then added to the reaction mixture. The layers were separated, and the organic layer was washed with water (50 mL). The organic extract was dried and concentrated in vacuo to give a crude gum. Purification was by flash chromatography eluting with EtOAc/hexane (1:1) to give a colorless gum; trituration with ether gave a white solid, **6**: yield 190 mg (70%); mp 182–183 °C; NMR ($CDCl_3$) δ 1.47–1.78 (c, 4 H), 1.78–2.00 (c, 2 H), 2.20–2.38 (m, 1 H), 2.46–2.64 (m, 1 H), 2.82–2.96 (m, 1 H), 3.06–3.24 (m, 1 H), 3.22–3.26 (d, 3 H), 4.94 (s, 1 H), 7.26–7.36 (m, 1 H), 7.48–7.64 (m, 2 H), 8.48–8.52 (m, 1 H), 8.52–8.58 (m, 1 H). Anal. ($C_{15}H_{17}N_3S$) C, H, N.

2-(Cyanomethylene)-1-pyridin-3-ylcyclohexanecarbodithioic Acid Methyl Ester (7). A solution of diethyl cyanomethylphosphonate (18.2 g, 0.1 mol) in dry THF (200 mL) at 25 °C was treated with sodium hydride (4.5 g of a 60% oil dispersion). After 30 min at room temperature the mixture was treated with **5** (24.7 g, 0.93 mol) in dry THF (100 mL). After 3 h at reflux the mixture was cooled to room temperature over 30 min, diluted with EtOAc (500 mL), and washed with water (500 mL). The organic layer was collected and dried; concentration in vacuo afforded a crude oil which was purified by flash chromatography eluting with EtOAc/hexane (25:75) to give an orange gum, **7**: yield 7.4 g (39% corrected); NMR ($CDCl_3$) δ 0.78–1.02 (m, 1 H), 1.58–1.94 (c, 4 H), 2.26–2.38 (m, 1 H), 2.62 (s, 3 H), 2.78–2.90 (m, 1 H), 3.14–3.28 (m, 1 H), 5.02 (s, 1 H), 7.26–7.38 (m, 1 H), 7.62–7.70 (m, 1 H), 8.56–8.64 (m, 2 H). Anal. ($C_{15}H_{16}N_2S_2$) C, H, N.

2-(2-Oxoethylidene)-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (8). A solution of **6** (1.3 g, 4.8 mmol) in CH_2Cl_2 (30 mL) was cooled to −20 °C and treated with a 1 M solution of DIBAL in toluene (10.6 mL, 10.6 mmol). The mixture was allowed to warm to room temperature over 2 h, and CH_2Cl_2 (50 mL) was then added to the reaction mixture followed by an aqueous solution of Rochelle salt (50 mL). The organic layer was washed with aqueous Rochelle solution (50 mL), separated, and dried. Concentration in vacuo gave a crude gum which was purified by flash chromatography eluting with EtOAc/hexane (4:1) to give a white foam, **8**: yield 230 mg (18%); NMR ($CDCl_3$) δ 1.64–1.82 (c, 2 H), 1.82–2.04 (c, 2 H), 2.30–2.46 (m, 1 H), 2.46–2.70 (m, 1 H), 3.10–3.20 (c, 2 H), 3.20–3.28 (d, 3 H), 5.66–5.72 (d, 1 H), 7.28–7.36 (m, 1 H), 7.36–7.48 (br s, 1 H), 7.52–7.60 (m, 1 H), 8.48–8.52 (m, 1 H), 8.52–8.58 (m, 1 H), 10.06–10.12 (d, 1 H). Anal. ($C_{15}H_{18}N_2OS$) C, H, N.

2-(2-Oxoethylidene)-1-pyridin-3-ylcyclohexanecarbodithioic Acid Methyl Ester (9). A solution of **7** (7.2 g, 25 mmol) in CH_2Cl_2 (200 mL) at −20 °C was treated with a 1 M solution of DIBAL in toluene (50 mL, 0.05 mol). The mixture was allowed to warm to room temperature over 3 h and was diluted with CH_2Cl_2 (200 mL) and then washed with Rochelle solution (200 mL). The organic phase was filtered through Celite, dried, and concentrated in vacuo. The residue was purified by flash chromatography eluting with EtOAc/hexane (30:70) to give an orange gum, **9**: yield 3.17 g (53%); NMR ($CDCl_3$) δ 0.78–1.02 (c, 1 H), 1.56–1.94 (c, 4 H), 2.44–2.62 (m, 1 H), 2.64 (s, 3 H), 2.86–3.06 (m, 1 H), 3.12–3.34 (m, 1 H), 5.70–5.78 (d, 1 H), 7.24–7.36 (m, 1 H), 7.62–7.70 (m, 1 H), 8.50–8.64 (m, 2 H), 10.08–10.14 (d, 2 H). Anal. ($C_{15}H_{17}NOS_2$) C, H, N.

***Syn/anti*-2-[2-[(2,3-Dihydroxypropoxy)imino]ethylidene]-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (10a).** A solution of **9** was heated at reflux in dry toluene (5 mL) and dry pyridine (5 mL) with 2,3-dihydroxypropoxyamine hydrochloride (112 mg) for 3 h. The mixture was cooled and concentrated in vacuo. The residue was treated with water (10 mL), extracted with CH_2Cl_2 (10 mL), separated, and dried. Evaporation gave a brown oil which was purified by flash chromatography eluting with EtOAc/methanol (95:5) to give a gum, **10a**: yield 50 mg (40%); NMR ($CDCl_3$) δ 1.4–2.6 (m, 7 H), 2.6 (d, 3 H), 3.2 (d, 1 H), 3.6 (dd, 1 H), 3.7 (dd, 1 H), 4.0 (m, 1 H), 4.1 (m, 2 H), 5.7 (d, 1 H), 7.3 (q, 1 H), 7.6 (br s, 1 H), 8.2 (d, 1 H), 8.5 (q, 1 H). Anal. ($C_{18}H_{25}N_3O_3S \cdot 0.5H_2O$) C, H, N, S.

***Syn/anti*-2-[2-[[(4-Fluorobenzyl)oxy]imino]ethylidene]-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (10b).** A solution of *syn/anti*-2-[2-[[(4-fluorobenzyl)oxyimino]-ethylidene]-1-pyridin-3-yl-cyclohexane carbodithioic acid methyl ester (200 mg) in dry THF (5 mL) at room temperature was treated with a 33% ethanolic solution of methylamine (1 mL). The solution was stirred for 48 h and concentrated in vacuo and the residue purified by flash chromatography eluting with EtOAc/hexane (1:4) to give a white solid, **10b**: yield 130 mg (33%); mp 69–70 C; NMR (CDCl) δ 1.4–2.4 (m, 6 H), 2.65–2.9 (m, 1 H), 3.15–3.20 (m, 1 H), 3.3 (dd, 3 H), 5.0 (d, 2 H), 5.65 and 6.2 (d, 1 H), 7.0–7.2 (m, 2 H), 7.2–7.4 (m, 3 H), 7.6 (m, 1 H), 7.65 (br s, 1 H), 8.2 (d, 1 H), 8.5 (br s, 2 H). Anal. ($C_{22}H_{24}FN_3OS$) C: calcd, 66.5; found, 66.0; H, N.

2-(Hydroxyethylidene)-1-pyridin-3-ylcyclohexanecarbodithioic Acid Methyl Ester (11). A solution of **9** (890 mg, 3 mmol) in MeOH (20 mL) at room temperature was treated with $NaBH_4$ (127 mg, 3.36 mmol). After 30 min at room temperature the solution was treated with EtOAc (50 mL), and water (20 mL) was added dropwise. The organic layer was dried, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with EtOAc/hexane (70:30) afforded an orange solid, **11**: yield 590 mg (66%); mp 139–140 °C; NMR ($CDCl_3$) δ 1.46–1.80 (c, 5 H), 1.84–1.98 (br s, 1 H), 2.30–2.50 (c, 4 H), 2.60 (s, 3 H), 3.02–3.20 (m, 1 H), 4.28–4.34 (d, 3 H), 5.28–5.36 (t, 1 H), 7.22–7.30 (m, 1 H), 7.62–7.70 (m, 1 H), 8.46–8.52 (dd, 1 H), 8.58–8.62 (m, 1 H). Anal. ($C_{15}H_{19}NOS_2$) C, H, N.

2-(2-Hydroxyethylidene)-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (12). A solution of **9** (120 mg, 0.41 mmol) in THF (5 mL) was treated with a solution of 33% methylamine in ethanol (5 mL). After standing for 15 h at room temperature the mixture was diluted with EtOAc (40 mL) and washed with water (50 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo, and the residue was purified by flash chromatography eluting with EtOAc/MeOH (98:2) to

give a gum. Solidification with Et_2O/hexane afforded a white solid, **12**: yield 90 mg (80%); mp 172–173 °C; NMR ($CDCl_3$/CD_3SOCD_3) δ 1.28–1.54 (m, 1 H), 1.56–1.88 (c, 4 H), 1.98–2.26 (m, 1 H), 2.58–2.72 (m, 1 H), 3.00–3.18 (m, 1 H), 3.18–3.24 (d, 3 H), 3.94–4.08 (dd, 1 H), 4.18–4.32 (dd, 1 H), 5.00–5.10 (t, 1 H), 6.30–6.90 (br s, 1 H), 7.16–7.24 (m, 1 H), 7.50–7.58 (m, 1 H), 8.24–8.34 (m, 2 H), 8.50–8.62 (br s, 1 H). Anal. ($C_{15}H_{20}N_2OS$) C, H, N.

2-(2-Phenoxyethylidene)-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (13a). To a solution of Ph_3P (1.13 g, 4.3 mmol) in dry THF (10 mL) at 0–5 °C, was added diisopropyl azodicarboxylate (0.84 mL, 4.3 mmol). After 5 min a creamy suspension formed, and to this were added **11** (630 mg, 2.15 mmol) and phenol (405 mg, 4.3 mmol) in THF (10 mL). After stirring for 5 min at 0–5 °C the mixture was diluted with EtOAc (50 mL) and washed with water (50 mL). The organic layer was dried and the solvent removed in vacuo. Purification by flash chromatography eluting with EtOAc/hexane (20:80) gave 2-(3-pyridyl)-2-[(methylthio)(thiocarbonyl)]-1-(2-phenoxyethylidene)cyclohexane as a yellow gum 750 mg (94%). This was dissolved in THF (10 mL) and treated with a solution of 33% methylamine in ethanol (10 mL). After 2 h at room temperature the solution was concentrated in vacuo and the residue purified by flash chromatography eluting with EtOAc/hexane (1:1) to give a white solid, **13a**: yield 300 mg (40%); mp 121–122 °C; NMR ($CDCl_3$) δ 1.38–1.58 (m, 1 H), 1.60–2.00 (c, 5 H), 2.06–2.24 (m, 1 H), 2.66–2.80 (m, 1 H), 3.10–3.18 (d, 3 H), 4.50–4.58 (dd, 1 H), 4.64–4.76 (dd, 1 H), 6.18–6.26 (t, 1 H), 6.78–6.86 (dd, 1 H), 6.90–7.02 (t, 1 H), 7.18–7.34 (m, 3 H), 7.46–7.52 (m, 1 H), 7.66–7.86 (br s, 1 H), 8.44–8.48 (m, 2 H). Anal. ($C_{21}H_{24}N_2OS$) C, H, N.

By proceeding by a method similar to that described above, compounds **13b–d** were synthesized.

2-[2-(4-Hydroxyphenoxy)ethylidene]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (13b): white solid; yield 1.28 g (70%); mp 82–88 °C; NMR ($CDCl_3$) δ 1.18–2.02 (c, 5 H), 2.04–2.22 (m, 1 H), 2.66–2.82 (m, 1 H), 3.14–3.24 (m, 1 H), 3.18–3.24 (d, 3 H), 4.26–4.54 (dd, 1 H), 4.58–4.72 (dd, 1 H), 5.16–5.24 (t, 1 H), 6.68–6.84 (m, 4 H), 7.28–7.36 (m, 1 H), 7.56–7.62 (m, 1 H), 7.78–7.88 (br s, 1 H), 8.46–8.54 (m, 2 H). Anal. ($C_{21}H_{24}N_2O_2S$) C, H, N: calcd, 7.6; found, 6.6.

2-[2-(4-Nitrophenoxy)ethylidene]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (13c): white solid; yield 110 mg (29%); mp 201–202 °C; NMR ($CDCl_3$) δ 1.42–2.0 (c, 4 H), 2.0–2.30 (m, 2 H), 2.56–2.70 (dt, 1 H), 3.08–3.24 (m, 1 H), 3.22–3.26 (d, 3 H), 4.62–4.80 (m, 2 H), 5.26–5.34 (t, 1 H), 6.86–6.98 (m, 2 H), 7.22–7.32 (m, 2 H), 7.52–7.60 (m, 1 H), 7.62–7.78 (br s, 1 H), 8.14–8.24 (m, 2 H), 8.46–8.56 (m, 2 H). Anal. ($C_{21}H_{23}N_3O_3S$) C, H, N.

2-[2-(Phenylsulfanyl)ethylidene]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (13d): cream paste; yield 100 mg (35%); NMR ($CDCl_3$) δ 1.20–1.44 (m, 1 H), 1.50–1.90 (m, 4 H), 1.98–2.12 (dt, 1 H), 2.58–2.70 (m, 1 H), 3.02–3.14 (m, 1 H), 3.06–3.14 (d, 3 H), 3.44–3.56 (dd, 1 H), 3.66–3.78 (dd, 1 H), 5.00–5.18 (t, 1 H), 7.12–7.40 (m, 7 H), 7.48–7.66 (br s, 1 H), 8.36–8.38 (d, 1 H), 8.42–8.48 (dd, 1 H). Anal. ($C_{21}H_{24}N_2S_2 \cdot 0.5H_2O$) C, H, N.

***trans*-2-(Cyanomethyl)-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (14).** A suspension of LAH (135 mg, 3.54 mmol) in dry THF solution (10 mL) at room temperature was treated dropwise with a THF solution of **6** (960 mg, 3.54 mmol). The mixture was stirred at room temperature for 10 min, and water (5 mL) was then added dropwise followed by EtOAc (50 mL). The mixture was washed with an aqueous solution of Rochelle salt (50 mL) and the organic layer dried. Concentration in vacuo yielded an oil which was purified by flash chromatography eluting with EtOAc; trituration with ether/hexane gave a white solid, **14**: yield 610 mg (63%); mp 177–178 °C; NMR ($CDCl_3$) δ 1.38–2.6 (c, 10 H), 3.08–3.14 (d, 3 H), 3.64–3.80 (m, 1 H), 7.28–7.36 (m, 1 H), 7.48–7.68 (br s, 1 H), 7.72–8.00 (m, 1 H), 8.52–8.60 (m, 1 H). Anal. ($C_{15}H_{19}N_3S$) C, H, N.

***trans*-2-(2-Aminoethyl)-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (15).** A solution of **14** in dry THF (30 mL) was added dropwise at room temperature to a stirred suspension of LAH (1.25 g, 33 mmol) in dry THF (75 mL). The mixture was heated at reflux for 1 h, cooled, and treated with Rochelle salt solution (20 mL) and EtOAc (50 mL). The organic layer was dried and concentrated in vacuo to give a yellow oil which was triturated with Et_2O to give a yellow solid **15**: yield 2 g (33%); mp 66–74 °C; NMR ($CDCl_3$) δ 1.0–1.1 (m, 1 H), 1.4–1.8 (m, 4 H), 2.0 (m, 1 H), 2.1 (m, 1 H), 2.5 (m, 2 H), 2.7 (m, 4 H), 3.1 (d, 3 H), 3.15–3.3 (m, 2 H), 7.25 (q, 1 H), 7.9 (dt, 1 H), 8.4 (dd, 1 H), 8.7 (d, 1 H). Anal. ($C_{15}H_{23}N_3S$) C, H, N.

***trans*-[2-[Methyl(thiocarbamoyl)]-2-pyridin-3-ylcyclohexyl]acetic Acid Methyl Ester (16).** A solution of **14** (1 g, 3.66 mmol) in Et_2O (20 mL) and MeOH (20 mL) was treated with gaseous HCl until the solution was saturated. The mixture was allowed to stand at room temperature for 24 h. The mixture was then treated with water (10 mL) and adjusted to pH 12 by addition of 5% (w/v) NaOH. The basified mixture was extracted with EtOAc (100 mL). The organic layer was dried and concentrated in vacuo to yield a colorless gum which was purified by flash chromatography eluting with EtOAc to afford a white solid, **16**: yield 150 mg (22%); mp 158–159 °C; NMR ($CDCl_3$) δ 1.40–1.60 (c, 3 H), 1.68–1.76 (m, 2 H), 1.88–2.0 (c, 2 H), 2.08–2.16 (m, 1 H), 2.28–2.35 (dd, 1 H), 2.68–2.70 (m, 1 H), 3.12–3.16 (d, 3 H), 3.60 (s, 3 H), 3.68–3.75 (m, 1 H), 7.25–7.30 (dd, 1 H), 7.78–7.86 (br, 1 H), 7.94–7.98 (dt, 1 H), 8.48–8.52 (dd, 1 H), 8.58–8.62 (d, 1 H). Anal. ($C_{16}H_{22}N_2O_2S$) C, H, N.

***trans*-2-[2-[[(4-Methoxybenzyl)sulfanyl](methylimino)methyl]-2-pyridin-3-ylcyclohexyl]ethanol (19).** To a suspension of **14** (1 g, 3.7 mmol) in dry THF (20 mL) at room temperature was added portionwise potassium *tert*-butoxide (405 mg, 3.7 mmol). After 20 min the resulting clear solution was cooled to −20 °C and treated with 4-methoxybenzyl chloride (0.5 mL, 3.7 mmol). The solution was stirred at −20 °C for 10 min and at room temperature for a further 2 h. The mixture was concentrated in vacuo, treated with EtOAc (50 mL), and washed with water (20 mL). The organic extract was dried, concentrated in vacuo, and purified by flash chromatography eluting with EtOAc to give a colorless gum, **17**: yield 2.5 g (100%); NMR ($CDCl_3$) δ 1.2 (tt, 1 H), 1.4 (m, 1 H), 1.6 (br d, 1 H), 1.8 (m, 4 H), 2.1–2.3 (m, 2 H), 2.8 (d, 1 H), 3.15 (d, 1 H), 3.25 (d, 1 H), 3.6 (s, 3 H), 3.7 (d, 1 H), 3.75 (s, 3 H), 6.7 (m, 4 H), 7.3 (q, 1 H), 7.6 (dt, 1 H), 8.55 (dd, 1 H), 8.6 (d, 1 H). A solution of **17** (2 g, 5.1 mmol) in CH_2Cl_2 (60 mL) at −20 °C was treated dropwise with a solution of DIBAL (10.2 mL of a 1 M solution in CH_2Cl_2, 10.2 mmol). The mixture was stirred at −20 °C for 1 h and then at room temperature for 3 h. The mixture was washed with Rochelle salt solution (50 mL) and the organic layer was dried. Concentration in vacuo and purification by flash chromatography eluting with EtOAc gave a colorless gum **18**: yield 1 g (76%); NMR ($CDCl_3$) δ 1.2 (dt, 1 H), 1.4 (m, 2 H), 1.5 (m, 1 H), 1.7 (m, 2 H), 1.75 (dt, 1 H), 2.1 (m, 1 H), 2.3 (m, 1 H), 2.8 (br d, 1 H), 3.15 (d, 1 H), 3.6 (br s, 1 H), 3.65 (s, 3 H), 3.7 (d, 1 H), 3.75 (s, 3 H), 6.7 (q, 4 H), 7.25 (q, 1 H), 7.6 (dt, 1 H), 8.5 (dd, 1 H), 8.65 (d, 1 H), 9.2 (s, 1 H). A mixture of **18** (1 g, 2.52 mmol) and aluminium isopropoxide (1.03 g, 5.04 mmol) in 2-propanol (50 mL) was heated at reflux for 5 h. After cooling, the solution was concentrated in vacuo and the residue dissolved in CH_2Cl_2 (50 mL) and washed with Rochelle salt solution (20 mL). The organic layer was dried and concentrated in vacuo to give a cream solid. Recrystallization from EtOAc gave a white solid, **19**: yield 0.5 g (52%); mp 145–146 °C; NMR ($CDCl_3$) δ 1.0 (m, 1 H), 1.2–1.4 (m, 2 H), 1.4–1.55 (m, 3 H), 1.7–1.8 (br, 1 H), 1.9 (dt, 1 H), 2.0 (m, 1 H), 2.7 (d, 1 H), 2.85 (br d, 1 H), 3.1 (d, 1 H), 3.4 (m, 1 H), 3.55 (m, 1 H), 3.6 (s, 1 H), 3.7 (d, 1 H), 3.75 (s, 3 H), 6.7 (m, 3 H), 7.25 (m, 1 H), 7.65 (dd, 1 H), 8.5 (dd, 1 H), 8.65 (d, 1 H). Anal. ($C_{23}H_{30}N_2O_2S$) C, H, N, S.

***trans*-2-(2-Hydroxyethyl)-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (20).** The alcohol **19** (500 mg, 1.25 mmol) was added to 98% formic acid (10 mL) and stirred at 0–5 °C for 0.5 h and warmed to room temperature. The solution was concentrated in vacuo to give a yellow oil which was purified by flash chromatography eluting with EtOAc/MeOH (95:5) to give a white solid, **20**: yield 60 mg (17%); mp 199–200 °C; NMR ($CDCl_3$) δ 1.4 (m, 1 H), 1.5–1.7 (m, 6 H), 2.0 (m, 1 H), 2.2 (m, 1 H), 2.6 (q, 1 H), 3.05 (m, 1 H), 3.1 (d, 1 H), 3.5–3.7 (m, 1 H), 7.3 (q, 1 H), 7.4 (br s, 1 H), 8.4 (d, 1 H), 8.5 (dd, 1 H), 8.7 (d, 1 H). Anal. ($C_{15}H_{22}N_2OS$) C, H, N, S.

***trans*-4-Fluorobenzoic Acid 2-[2-[methyl(thiocarbamoyl)]-2-pyridin-3-ylcyclohexyl]ethyl Ester (21c).** A solution of **19** (800 mg, 2 mmol) in CH_2Cl_2 (20 mL) at 0 °C was treated with DMAP (300 mg, 2.4 mmol) followed by 4-fluorobenzoyl

chloride (380 mg, 2.4 mmol). The mixture was stirred at room temperature for 1 h and then diluted with CH_2Cl_2 (50 mL). The mixture was washed with water (50 mL) and brine (50 mL). The organic layer was dried and concentrated in vacuo; purification by flash chromatography eluting with EtOAc/hexane (50:50) gave 4-fluorobenzoic acid 2-[2-[[(4-methoxybenzyl)sulfanyl](methylimino)methyl]-2-pyridin-3-ylcyclohexyl]ethyl ester as a colorless gum (820 mg, 79%). This product (760 mg, 1.46 mmol) was treated with an ice-cold solution of anisole (1 mL) in TFA (8 mL) at 0 °C for 15 min followed by basification to pH 12 (NaOH, 25% w/v). The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic layer was dried and concentrated in vacuo. Solidification with Et_2O/hexane followed by recrystallization from EtOAc/hexane gave a white solid, **21c**: yield 450 mg (77%); mp 205–206 °C; NMR ($CDCl_3$) δ 1.34–1.56 (c, 4 H), 1.60–1.77 (c, 3 H), 2.04–2.12 (m, 1 H), 2.12–2.24 (m, 1 H), 3.05–3.12 (d, 3 H), 4.12–4.19 (m, 1 H), 4.25–4.33 (m, 1 H), 7.08–7.15 (t, 2 H), 7.16–7.22 (dd, 1 H), 7.92–7.96 (dt, 1 H), 8.0–8.06 (m, 1 H), 8.06–8.16 (br s, 1 H), 8.48–8.52 (dd, 1 H), 8.67–8.72 (d, 1 H). Anal. ($C_{22}H_{25}FN_2O_2S$) C, H, N.

***trans*-Acetic Acid 2-[2-[Methyl(thiocarbamoyl)]-2-pyridin-3-ylcyclohexyl]ethyl Ester (21a).** Proceeding by a similar method as described for **21c** but using the appropriate quantity of acetyl chloride gave a white solid, **21a**: yield 30 mg (10%); mp 139–140 °C; NMR ($CDCl_3$) δ 1.20–1.34 (m, 2 H), 1.35–1.70 (c, 5 H), 2.02 (s, 3 H), 1.94–2.16 (m, 2 H), 2.60–2.74 (m, 1 H), 3.08–3.14 (d, 3 H), 3.10–3.20 (m, 1 H), 3.86–3.95 (m, 1 H), 4.04–4.10 (m, 1 H), 7.25–7.32 (dd, 1 H), 7.68–7.78 (br s, 1 H), 7.92–7.98 (dd, 1 H), 8.48–8.52 (dd, 1 H), 8.58–8.62 (d, 1 H). Anal. ($C_{17}H_{24}N_2O_2S$) C, H, N.

***trans*-Benzoic Acid 2-[2-[Methyl(thiocarbamoyl)]-2-pyridin-3-ylcyclohexyl]ethyl Ester (21b).** Following a similar method to that described above but using the appropriate quantity of benzoyl chloride gave a white solid, **21b**: yield 150 mg (64%); mp 179–180 °C; NMR ($CDCl_3$) δ 1.35–1.84 (c, 7 H), 2.04–2.26 (m, 2 H), 2.54–2.70 (m, 1 H), 3.08–3.14 (d, 3 H), 3.20–3.36 (m, 1 H), 4.10–4.38 (m, 2 H), 7.16–7.24 (dd, 1 H), 7.38–7.62 (c, 4 H), 7.90–8.06 (c, 3 H), 7.46–7.52 (dd, 2 H), 7.62–7.66 (d, 1 H). Anal. ($C_{22}H_{26}N_2O_2S$) C, H, N.

***trans-syn/anti*-2-[2-[(Benzyloxy)imino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (22).** A solution of **18** (700 mg, 1.77 mmol) in dry toluene (40 mL) was treated with *O*-benzylhydroxylamine hydrochloride (282 mg, 1.77 mmol). The mixture was heated at reflux for 30 min and then cooled to room temperature; EtOAc (100 mL) was then added and the mixture washed with water (100 mL) and brine (100 mL). The organic layer was dried and concentrated in vacuo, and the resulting gum was triturated with Et_2O/hexane to give a white solid, **22**: yield 240 mg (36%); mp 158–160 °C; NMR ($CDCl_3$) δ 1.35–1.88 (c, 4 H), 2.05–2.20 (m, 2 H), 2.48–2.50 (m, 2 H), 3.05–3.12 (d, 3 H), 3.28–3.38 (m, 1 H), 4.96–5.04 (d, 2 H), 6.55–6.59/7.14–7.18 (2dd, 1 H), 7.20–7.40 (c, 7 H), 7.85–7.92 (m, 1 H), 8.46–8.54 (m, 1 H), 8.62–8.66 (m, 1 H). Anal. ($C_{22}H_{27}N_3OS$) C, H, N: calcd, 11.0; found, 11.8.

***trans*-2-[2-(Phenylamino)ethyl]-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (23).** To a solution of **18** (2.68 g, 6.77 mmol) in dry toluene (50 mL) was added aniline (0.76 g, 8.12 mmol) and the mixture was heated at reflux for 2 h under Dean and Stark conditions. The solvent was removed in vacuo, and the residue was dissolved in MeOH (30 mL), cooled to 0 °C, and treated with $NaBH_3CN$ (345 mg, 5.5 mmol), and the mixture was stirred at 0 °C for 30 min. The reaction was diluted with EtOAc (50 mL) and washed with water (50 mL). The organic layer was dried and concentrated in vacuo. Purification by flash chromatography eluting with EtOAc gave 4-[2-[2-[[(4-methoxybenzyl)sulfanyl](methylimino)methyl]-2-pyridin-3-ylcyclohexyl]ethyl]phenylamine as an orange gum 600 mg (20%). Treatment of this gum as described for **21c** followed by trituration with hexane gave a white solid, **23**: yield 14%; mp 177–179 °C; NMR ($CDCl_3$) δ 1.35–1.45 (m, 1 H), 1.45–1.70 (c, 7 H), 2.02–2.10 (m, 1 H), 2.14–2.20 (m, 1 H), 2.58–2.65 (m, 1 H), 2.97–3.05 (m, 1 H), 2.98–3.12 (d, 3 H), 3.10–3.18 (m, 1 H), 3.70–3.90 (br s, 1 H), 6.48–6.52 (d, 2 H), 6.46–6.68 (t, 1 H), 7.10–7.15 (m, 2 H), 7.13–7.17 (dd, 1 H), 7.85–7.88 (m, 1 H), 8.48–8.52 (dd, 1 H), 8.65–8.67 (d, 1 H). Anal. ($C_{21}H_{27}N_3S$) C, H, N.

***trans*-2-(3-Phenylallyl)-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (24a).** To a solution of diethyl benzylphosphonate (0.46 g, 2 mmol) in dry THF (5 mL) at 0 °C was added LDA (2.5 mL of a 1 M THF solution). To the stirred solution at 0 °C was added **18** (0.8 g, 2 mmol). After standing at ambient temperature for 16 h, the reaction was quenched with water (3 mL), diluted with EtOAc (25 mL), and washed with water (30 mL). The organic layer was dried and the solvent removed in vacuo. Purification by flash chromatography eluting with EtOAc/cyclohexane (1:1) gave an oil. Treatment of this oil as previously described for **21c**, followed by recrystallization from EtOAc/hexane gave a white solid, **24a**: yield 0.29 g (48%); mp 142–144 °C; NMR ($CDCl_3$) δ 1.40–2.22 (c, 9 H), 2.60–2.66 (m, 1 H), 3.12 (d, 3 H), 3.25–3.34 (m, 1 H), 6.02–6.10 (m, 1 H), 6.02–6.06 (d, 1 H, J = 16 Hz), 7.16–7.22 (m, 1 H), 7.25–7.35 (c, 5 H), 7.48–7.54 (br s, 1 H), 7.94–7.98 (m, 1 H), 8.48–8.52 (dd, 1 H), 8.58–8.70 (d, 1 H). Anal. ($C_{22}H_{26}N_2S$) C, H, N, S.

***cis/trans*-2-[3-(4-Fluorophenyl)allyl]-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (24b).** To a suspension of (4-fluorobenzyl)triphenylphosphonium chloride (1.06 g, 2.6 mmol) in dry THF (15 mL) at −78 °C was added LDA (2.5 mL of a 1.93 M solution in hexanes). The orange solution was stirred at −40 °C for 30 min and was then treated dropwise with **18** (1 g, 2.6 mmol) in dry THF (5 mL). The solution was allowed to stand at ambient temperature for 48 h. The mixture was diluted with EtOAc (50 mL) and washed with water (50 mL). The organic layer was dried and concentrated. Purification by flash chromatography eluting with EtOAc/hexane (30:70) gave *cis/trans*-[[2-[3-(4-fluorophenyl)allyl]-1-pyridin-3-ylcyclohexyl][(4-methoxyphenyl)sulfanyl]methylene]methylamine as a colorless gum (220 mg, 17%). Treatment of this gum as previously described for **21c** followed by recrystallization from EtOAc/hexane gave a white solid, **24b**: yield 90 mg (66%); mp 134–135 °C; NMR ($CDCl_3$) δ 1.30–1.94 (c, 4 H), 1.98–2.34 (c, 4 H), 2.52–2.64 (m, 1 H), 3.06–3.08 (d, 1.5 H), 3.14–3.24 (m, 1 H), 5.52–5.58 (m, 0.5 H), 5.94–6.02 (m, 0.5 H), 6.17–6.21 (d, 0.5 H, J = 16 Hz), 6.36–6.39 (d, 0.5 H, J = 12 Hz), 6.92–6.98 (m, 3 H), 7.02–7.06 (m, 1 H), 7.17–7.22 (dd, 0.5 H), 7.24–7.28 (m, 1 H), 7.26–7.31 (dd, 0.5 H), 7.32–7.42 (br s, 1 H), 7.84–7.88 (m, 0.5 H), 7.94–7.98 (m, 0.5 H), 8.46–8.48 (dd, 0.5 H), 8.50–8.52 (dd, 0.5 H), 8.64–8.66 (d, 0.5 H), 8.60–8.72 (d, 0.5 H). Anal. ($C_{22}H_{25}FN_2S$) C, H, N.

***trans*-2-[2-[(Phenylsulfonyl)amino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (25a).** A solution of **15** (0.5 g, 1.8 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with Et_3N (0.25 mL, 1.8 mmol) and benzenesulfonyl chloride (0.22 mL, 1.8 mmol). The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature over a further 1 h. The solution was treated with water (30 mL) and extracted with CH_2Cl_2 (30 mL). The organic layer was washed with water (30 mL), dried, and concentrated in vacuo. Purification by flash chromatography eluting with EtOAc/MeOH (95:5) gave a white solid, **25a**: yield 130 mg (17%); mp 109–110 °C; NMR ($CDCl_3$) δ 1.25–1.55 (m, 6 H), 1.80 (m, 1 H), 2.10–2.20 (m, 2 H), 2.50 (m, 1 H), 2.80 (m, 2 H), 3.0 (m, 1 H), 3.10 (d, 3 H), 4.90 (br t, 1 H), 7.20 (br s, 1 H), 7.30 (q, 1 H), 7.50–7.60 (m, 3 H), 7.80 (dt, 1 H), 8.50 (dd, 1 H), 8.60 (d, 1 H). Anal. ($C_{21}H_{27}N_3O_2S_2$) C, H, N.

By following a similar experimental procedure to that described above but replacing benzenesulfonyl chloride with the appropriate sulfonyl chloride, the following were prepared.

***trans*-2-(2-[(Methylsulfonyl)amino]ethyl)-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (25b)**: white solid; yield 170 mg (27%); mp 90–91 °C; NMR ($CDCl_3$) δ 1.3–1.4 (m, 1 H), 1.4–1.7 (m, 6 H), 1.9–2.05 (m, 1 H), 2.1–2.2 (m, 1 H), 2.6–2.7 (m, 1 H), 2.9 (s, 3 H), 3.0–3.1 (m, 2 H), 3.1 (d, 3 H), 3.2 (m, 1 H), 4.8 (br t, 1 H), 7.3 (q, 1 H), 7.5 (br s, 1 H), 7.85 (dt, 1 H), 8.5 (dd, 1 H), 8.65 (d, 1 H). Anal. ($C_{16}H_{25}N_3O_2S_2$) C, H, N: calcd, 11.8; found, 11.1.

***trans*-2-[2-[[(4-Fluorophenyl)sulfonyl]amino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (25c)**: white solid; yield 170 mg (22%); mp 64–66 °C; NMR ($CDCl_3$) δ 1.2–1.9 (m, 7 H), 2.1 (m, 1 H), 2.55 (m, 1 H), 2.7–3.0 (m, 4 H), 3.1 (d, 3 H), 5.2 (br t, 1 H), 7.1–7.3 (m, 3 H), 7.4 (br s 1 H), 7.7–7.9 (m, 3 H), 8.4 (dd, 1 H), 8.6 (d, 1 H). Anal. ($C_{21}H_{26}FN_3O_2S_2$) C, H, N: calcd, 9.6; found, 9.1.

***trans*-1-Pyridin-3-yl-2-[2-[(thiophene-3-ylsulfonyl)amino]ethyl]cyclohexanecarbothioic acid methylamide (25d)**:

white solid; yield 130 mg (17%); mp 96–98 °C; NMR ($CDCl_3$) δ 1.3–1.6 (m, 7 H), 1.8–1.9 (m, 1 H), 2.1–2.15 (m, 1 H), 2.5–2.6 (m, 1 H), 2.8–2.9 (m, 1 H), 2.9–3.0 (m, 1 H), 3.0–3.1 (m, 1 H), 3.1 (d, 3 H), 5.15 (br t, 1 H), 7.1 (dd, 1 H), 7.3 (q, 1 H), 7.32 (br s, 1 H), 7.6 (m, 2 H), 7.8 (dt, 1 H), 8.5 (dd, 1 H), 8.65 (dd, 1 H). Anal. ($C_{19}H_{25}N_3O_2S_3$) C, H, N, S.

***trans*-2-[2-[(Pyridin-3-ylsulfonyl)amino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (25e)**: white solid; yield 130 mg (17%); mp 101–102 °C; NMR ($CDCl_3$) δ 1.3–1.6 (m, 7 H), 1.8–1.9 (m, 1 H), 2.1–2.15 (m, 1 H), 2.5–2.6 (m, 1 H), 2.8–2.9 (m, 2 H), 3.05 (m, 1 H), 3.1 (d, 3 H), 5.9 (br t, 1 H), 7.3 (q, 1 H), 7.45 (q, 1 H), 7.5 (br s, 1 H), 7.8 (dt, 1 H), 8.15 (dt, 1 H), 8.4 (dd, 1 H), 8.6 (d, 1 H), 8.8 (dd, 1 H), 9.0 (d, 1 H). Anal. ($C_{20}H_{26}N_4O_2S_2 \cdot 0.5H_2O$) C, H, N.

***trans*-2-[2-[[(4-Chlorophenyl)sulfonyl]amino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (25f)**: white solid; yield 120 mg (15%); mp 106–107 °C; NMR ($CDCl_3$) δ 1.3–1.6 (m, 7 H), 1.8 (m, 1 H), 2.1–2.2 (m, 1 H), 2.5–2.55 (m, 1 H), 2.75–2.9 (m, 2 H), 2.95–3.05 (m, 1 H), 3.1 (d, 3 H), 5.1 (br s, 1 H), 7.25 (br s, 1 H), 7.3 (q, 1 H), 7.5 (d, 2 H), 7.8 (m, 3 H), 8.5 (dd, 1 H), 8.65 (d, 1 H). Anal. ($C_{21}H_{26}ClN_3O_2S_2$) C, H, N, S.

***trans*-2-[2-[[(4-Nitrophenyl)sulfonyl]amino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (25g)**: white solid; yield 100 mg (12%); mp 108–109 °C; NMR ($CDCl_3$) δ 1.2–1.9 (m, 8 H), 2.0–2.2 (m, 1 H), 2.4–2.6 (m, 1 H), 2.7–3.0 (m, 3 H), 3.1 (d, 3 H), 5.8 (br t, 1 H), 7.2–7.4 (m, 2 H), 7.8 (d, 1 H), 8.0 (d, 2 H), 8.4 (dd, 3 H), 8.6 (d, 1 H). Anal. ($C_{21}H_{26}N_4O_4S_2$) C, H, N, S.

***trans*-2-[2-[[(4-Methoxyphenyl)sulfonyl]amino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (25h)**: white solid; yield 130 mg (16%); mp 95–96 °C; NMR ($CDCl_3$) δ 1.25–1.6 (m, 7 H), 1.8 (m, 1 H), 2.05–2.15 (m, 1 H), 2.52–2.6 (m, 1 H), 2.8–2.9 (m, 2 H), 2.9–3.0 (m, 1 H), 3.1 (d, 3 H), 3.9 (s, 3 H), 4.85 (br t, 1 H), 7.0 (d, 2 H), 7.25–7.35 (m, 3 H), 7.8 (d, 2 H), 8.5 (dd, 1 H), 8.6 (d, 1 H). Anal. ($C_{22}H_{29}N_3O_3S_2$) C, H, N, S.

***trans*-2-[2-[[(3,4-Difluorophenyl)sulfonyl]amino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide (25i)**: white solid; yield 150 mg (18%); mp 90–91 °C; NMR ($CDCl_3$) δ 1.2–1.6 (m, 6 H), 1.6–2.0 (m, 3 H), 2.0–2.2 (m, 1 H), 2.4–2.6 (m, 1 H), 2.7–3.1 (m, 2 H), 3.1 (d, 3 H), 5.5 (t, 1 H), 7.2–7.4 (m, 2 H), 7.6–7.8 (m, 2 H), 8.45 (dd, 1 H), 8.6 (d, 1 H). Anal. ($C_{21}H_{25}F_2N_3O_2S_2$) C, H, N, S.

***trans*-*N*-[2-[2-[Methyl(thiocarbamoyl)]-2-pyridin-3-ylcyclohexyl]ethyl]benzamide (26a)**. To a solution of **15** (500 mg, 1.8 mmol) in dry pyridine (2 mL) at 0 °C was added dropwise benzoyl chloride (0.12 mL, 1.8 mmol). After stirring for 1 h at 0 °C the solution was allowed to warm to room temperature. The solvent was concentrated in vacuo, the residue dissolved in EtOAc (20 mL), and the solution washed with water (2 × 20 mL). The organic layer was dried and the solvent concentrated in vacuo. Purification by flash chromatography eluting with EtOAc/MeOH (9:1) gave a white solid, **26a**: yield 290 mg (38%); mp 97–99 °C; NMR ($CDCl_3$) δ 1.32–1.44 (m, 1 H), 1.44–1.70 (m, 6 H), 1.94–2.00 (m, 1 H), 2.22–2.28 (m, 1 H), 2.52–2.60 (m, 1 H), 2.95–3.02 (m, 1 H), 3.08–3.12 (d, 3 H), 3.30–3.40 (m, 1 H), 3.54–3.62 (m, 1 H), 6.72–6.75 (br s, 1 H), 7.08–7.16 (br s, 1 H), 7.28–7.32 (dd, 1 H), 7.44–7.52 (m, 3 H), 7.82–7.88 (m, 3 H), 8.55–8.58 (dd, 1 H), 8.70–8.72 (d, 1 H). Anal. ($C_{22}H_{27}N_3OS \cdot 0.5EtOAc$) C, H, N, S.

By following a similar method to that described for **26a** but replacing benzoyl chloride with the appropriate acid chloride, the following were prepared.

***trans*-4-Fluoro-*N*-[2-[2-[methyl(thiocarbamoyl)]-2-pyridin-3-ylcyclohexyl]ethyl]benzamide (26b)**: white solid; yield 190 mg (26%); mp 97–98 °C; NMR ($CDCl_3$) δ 1.25–1.74 (c, 7 H), 1.90–1.98 (m, 1 H), 2.24–2.32 (m, 1 H), 2.50–2.58 (m, 1 H), 2.92–3.00 (t, 1 H), 3.08–3.12 (d, 3 H), 3.30–3.40 (m, 1 H), 3.52–3.60 (m, 1 H), 6.78–6.86 (br s, 1 H), 7.04–7.12 (br s, 1 H), 7.12–7.17 (t, 2 H), 7.30–7.36 (dd, 1 H), 7.82–7.86 (m, 1 H), 7.86–7.94 (m, 2 H), 8.56–8.60 (dd, 1 H), 8.72–8.74 (d, 1 H). Anal. ($C_{22}H_{26}FN_3OS$) C, H, N, S.

***trans*-*N*-[2-[2-[Methyl(thiocarbamoyl)]-2-pyridin-3-ylcyclohexyl]ethyl]-2-phenylacetamide (26c)**: white solid; yield 490 mg (34%); mp 105–108 °C; NMR ($CDCl_3$) δ 1.20–1.30 (m, 1 H), 1.35–1.55 (c, 6 H), 1.85–1.94 (m, 1 H), 2.08–2.16 (m, 1 H), 2.54–2.62 (m, 1 H), 2.80–2.88 (m, 1 H), 3.05–3.09 (d, 3 H), 3.04–3.12 (m, 1 H), 3.22–3.32 (m, 1 H), 3.54–3.56 (s, 2 H), 7.22–7.26 (dd, 1 H), 7.26–7.42 (c, 6 H), 7.75–7.79 (m, 1 H), 8.48–8.50 (dd, 1 H), 8.58–8.60 (d, 1 H). Anal. ($C_{23}H_{29}N_3OS$) C, H, N.

***trans*-*N*-[2-[2-[Methyl(thiocarbamoyl)]-2-pyridin-3-ylcyclohexyl]ethyl]acetamide (26d)**: white solid; yield 320 mg (28%); mp 86–90 °C; NMR ($CDCl_3$) δ 1.34–1.64 (c, 7 H), 1.88–1.96 (m, 1 H), 1.96 (s, 3 H), 2.15–2.23 (m, 1 H), 2.58–2.66 (m, 1 H), 2.82–2.90 (m, 1 H), 3.02–3.10 (m, 1 H), 3.08–3.12 (s, 3 H), 3.30–3.38 (m, 1 H), 5.98–6.06 (br s, 1 H), 7.30–7.34 (dd, 1 H), 7.34–7.44 (br s, 1 H), 7.82–7.86 (m, 1 H), 8.52–8.54 (dd, 1 H), 8.66–8.68 (d, 1 H). Anal. ($C_{17}H_{25}N_3OS \cdot 0.5H_2O$) C, H, N: calcd, 12.8; found, 12.1; S.

***trans*-*N*-[2-[2-[Methyl(thiocarbamoyl)]-2-pyridin-3-ylcyclohexyl]ethyl]isobutyramide (26e)**: white solid; yield 200 mg (56%); mp 94–95 °C; NMR ($CDCl_3$) δ 1.15–1.18 (t, 6 H), 1.34–1.65 (c, 7 H), 1.90–1.98 (m, 1 H), 2.18–2.25 (m, 1 H), 2.54–2.62 (m, 1 H), 2.84–3.02 (m, 1 H), 3.04–3.15 (m, 1 H), 3.08–3.12 (d, 3 H), 3.30–3.40 (m, 1 H), 5.88–5.96 (br s, 1 H), 7.18–7.26 (br s, 1 H), 7.28–7.34 (dd, 1 H), 7.82–7.86 (m, 1 H), 8.54–8.56 (dd, 1 H), 8.68–9.00 (d, 1 H). Anal. ($C_{19}H_{29}N_3OS$) C, H, N: calcd, 11.3; found, 12.0.

***trans*-2-[2-[[(Methylsulfonyl)imino](methylamino)methyl]amino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (27a)**. A mixture of **15** (500 mg, 1.8 mmol) and *N*-[bis(methylsulfonyl)methylene]methanesulfonamide (360 mg, 1.8 mmol) in EtOH (10 mL) was heated at reflux for 6 h. The mixture was cooled to room temperature and concentrated. Purification by flash chromatography eluting with EtOAc/MeOH (95:5) gave *trans*-2-[2-[[[(methanesulfonyl)imino](methylsulfanyl)methyl]amino]ethyl]-1-pyridin-3-ylcyclohexane carbothioic acid methylamide (220 mg, 29%) as a white solid; mp 74–75 °C. Anal. C, H, N. This was dissolved in EtOH (5 mL) and treated with a 33% solution of methylamine in EtOH (1 mL) and the solution heated at reflux for 5 h. After cooling, the solution was concentrated in vacuo and the residue purified by flash chromatography eluting with EtOAc/MeOH (95:5) to give a white solid, **27a**: yield 100 mg (49%); mp 125–126 °C; NMR ($CDCl_3$) δ 1.3–1.7 (m, 7 H), 1.75 (m, 1 H), 2.15 (m, 1 H), 2.6 (m, 1 H), 2.9 (d, 3 H), 2.95 (m, 1 H), 2.96 (s, 3 H), 3.1 (d, 3 H), 3.25 (m, 2 H), 7.33 (q, 1 H), 7.4 (br s, 1 H), 7.8 (dt, 1 H), 8.55 (dd, 1 H), 8.65 (d, 1 H). Anal. ($C_{18}H_{29}N_5O_2S_2 \cdot 0.5H_2O$) C, H, N: calcd, 16.6; found, 15.9; S.

***trans*-2-[2-[[[(Phenylsulfonyl)imino](methylamino)methyl]amino]ethyl]-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (27b)**. Using the same method as described for **27a** but reacting **15** with *N*-[bis(methylsulfonyl)methylene]benzenesulfonamide gave a white solid, **27b**: yield 100 mg (37%); mp 163–164 °C; NMR ($CDCl_3$) δ 1.0–1.6 (m, 5 H), 1.6 (m, 1 H), 1.8–2.0 (m, 2 H), 2.8 (t, 3 H), 2.9–3.0 (m, 2 H), 3.05 (t, 3 H), 3.1–3.2 (m, 2 H), 7.2 (q, 1 H), 7.4 (m, 3 H), 7.8 (d, 3 H), 8.4 (d, 1 H), 8.6 (d, 1 H), 8.8 (br s, 1 H). Anal. ($C_{23}H_{31}N_5O_2S_2$) C: calcd, 58.3; found, 57.7; H, N, S.

***trans*-2-[2-(3,5-Dioxomorpholin-4-yl)ethyl]-1-pyridin-3-ylcyclohexanecarbothioic Acid Methylamide (28)**. To a solution of **15** (1 g, 3.6 mmol) in toluene (20 mL) and 1,2-dichlorobenzene (5 mL) was added 90% diglycollic anhydride (928 mg, 7.2 mmol) and the solution heated at reflux for 3 h. The mixture was cooled to room temperature, decanted, concentrated in vacuo, and purified by flash chromatography eluting with EtOAc/MeOH (95:5) to give a white solid, **28**: yield 290 mg (22%); mp 181–183 °C; NMR ($CDCl_3$) δ 1.4–1.6 (m, 8 H), 2.0–2.2 (m, 2 H), 2.6–2.7 (m, 1 H), 3.1 (d, 3 H), 3.7 (m, 1 H), 3.8 (m, 1 H), 4.35 (s, 4 H), 7.3 (br s, 1 H), 7.4 (q, 1 H), 7.95 (d, 1 H), 8.55 (dd, 1 H), 8.6 (d, 1 H). Anal. ($C_{19}H_{25}N_3O_3S$) C, H, N.

In Vitro Potassium Channel Opening Activity. Male Sprague–Dawley rats (200–300 g) were sacrificed and the thoracic aorta removed, cleaned of extraneous fat, and cut into four rings. Each ring was cut into transverse strips and gently rubbed to remove endothelium. The strips of tissue were placed in 20-mL water-jacketed organ baths containing Krebs bicarbonate buffer maintained at 37 °C and gassed with 95% O_2/5% CO_2. Tissues were attached to force displacement transducers and isometric contractions recorded. Aortae were equilibrated for 90 min under a resting tension of 2 g. Tissue preparations were exposed to 20 mmol KCl. When the maximum mechanical effect had devel-

oped, the ability of test compounds to relax the tissues was examined using a cumulative dose–response protocol. As soon as the maximum inhibitory effect of a given concentration of compound had been produced, tissues were exposed to a further concentration of relaxant. To determine whether the relaxants identified were opening an ATP-sensitive K^+ channel, the ability of 5 μM glibenclamide, a blocker of this channel, to reverse relaxation was assessed. Drug activity is expressed as IC_{90} values, that is the concentration of drug producing a 90% reduction in maximum contraction produced by 20 mmol KCl. The Krebs bicarbonate buffer solution had the following composition (mmol): NaCl, 118; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 1.2; $CaCl_2$, 2.5; KH_2PO_4, 1.2; $NaHCO_3$, 1.2; glucose, 10.1. All drugs were dissolved in DMSO.

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