Synthesis of 1,4-Benzodiazepine-1-carbothioamides, Bicyclic Analogues of the TIBO-type Anti-HIV Agents

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A series of *N'*-substituted 1,4-benzodiazepine-1-carbothioamides **2a-j** were prepared by reacting the precursor 1,4-benzodiazepine **11** with the corresponding *N*-substituted isothiocyanates **2a-i** or with sodium thiocyanate-trifluoroacetic acid (**2j**). Despite the structural ressemblance of these molecules with the potent TIBO-type anti-HIV compound R82150, **2a-j** displayed no anti-HIV activity *in vitro*.

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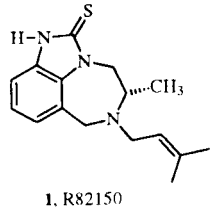
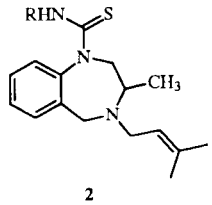
Introduction.

Although several nucleoside analogues such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxyinosine (DDI) and 2',3'-dideoxycytidine (DDC) display potent anti-HIV (human immunodeficiency virus, the causative agent of AIDS) activity [1], the limited clinical effectiveness of this class of molecules, together with the toxicities and resistance associated with their long-term use, has led to the development of a number of non-nucleoside anti-HIV compounds [2], among them the TIBO derivatives (for example, R82150, **1**) [3].



1, R82150



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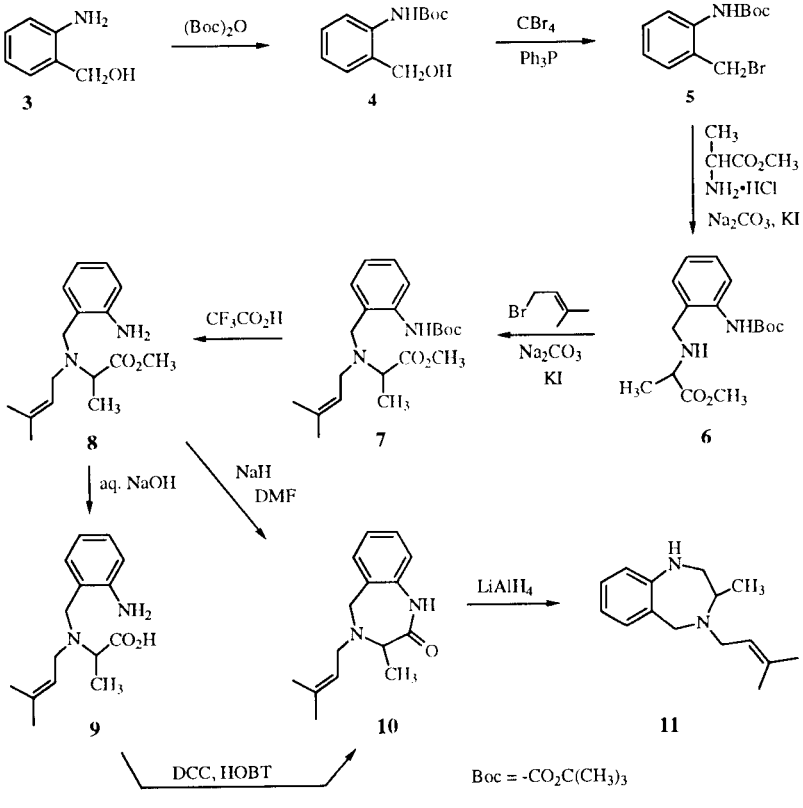
While the structure-activity relationships of TIBO-type molecules have been well studied [4,5], the necessity of maintaining their tricyclic nucleus to ensure anti-HIV activity has received little attention. Recently, Townsend and coworkers [6] have synthesized benzimidazole derivatives possessing all the important structural features of TIBO except the benzodiazepine ring. These molecules

Scheme 1



3 **4** **5** **6** **7** **8** **9** **10** **11**

displayed only modest anti-HIV activity, however, and probably by an altogether different mechanism than TIBO derivatives. We have now investigated the synthesis and anti-HIV activity of a series of benzodiazepine-1-carbothioamides **2**, structural equivalents of R82150 (**1**) in which the C10a-N1 bond has been suppressed [7].

Results and Discussion.

A good strategy for the efficient synthesis of the various derivatives of **2** would require that the variable portion of the molecule (the R group) be introduced in the last step. To this end, it was judged that the benzodiazepine **11** (Scheme 1) would serve as a convenient intermediate since the R group of **2** could be modified simply by reacting **11** with the appropriate, generally commercial *N*-substituted isothiocyanates.

The starting material chosen for the preparation of **11** was 2-aminobenzyl alcohol **3**. Treatment of this material with di-*tert*-butyl dicarbonate [8] gave the *N*-Boc protected derivative **4**. The bulkiness of the Boc group prevents intramolecular attack of the carbonyl function of **4** by the hydroxyl group and formation of a cyclic carbamate [9]. The hydroxyl group of **4** was subsequently transformed into the bromide **5** by the action of carbon tetrabromide and triphenylphosphine in ether [10]. Alkylation of the amine function of L-alanine with bromide **5** in the presence of sodium carbonate and potassium iodide then yielded compound **6**. A small percentage of dialkylated product was also formed in this reaction. The same reaction conditions (sodium carbonate and potassium iodide in DMF) were used to alkylate the secondary amine function of **6** with 4-bromo-2-methyl-2-butene, affording **7** in almost quantitative yield.

After removal of the Boc blocking group of **7** with trifluoroacetic acid, the resulting free amine derivative **8** was cyclized to give the 1,4-benzodiazepin-2-one **10** using two different methods. Thus, hydrolysis of the ester function of **8** with aqueous sodium hydroxide in methanol furnished, as principal product, the carboxylic acid **9**. A small amount of the desired benzodiazepine **10** was also isolated from the reaction mixture. Treatment of **9** with dicyclohexylcarbodiimide and 1-hydroxybenzotriazole then furnished **10**, albeit in modest overall yield (42% from **8**). The isolation of a minor amount of cyclized product **10** when **8** was treated with aqueous base prompted us to attempt cyclization of **8** under anhydrous basic conditions. When **8** was treated with sodium hydride in DMF [11], benzodiazepine **10** was effectively formed in good yield (66%).

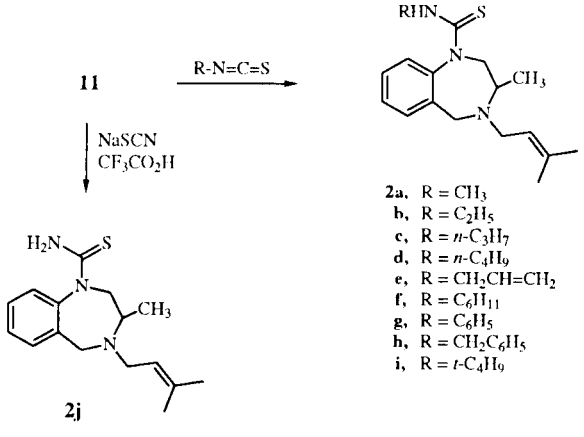
Finally, the required precursor **11** was obtained by lithium aluminum hydride reduction of the carboxamide group of **10**. By refluxing an ethanolic solution of **11** in the presence of an alkyl or aryl isothiocyanate (RN=C=S) [12], the corresponding *N*-substituted 1-carbothioamides **2a-h** were then formed in generally high yields (Scheme 2).

In the case of the *N*-*tert*-butyl derivative **2i**, the reaction necessitated 3 days of heating at 100° in neat *N*-*tert*-butyl isothiocyanate in order to form any appreciable quantity of product. The slowness of this reaction is most likely the result of steric hindrance [13]. The unsubstituted carbothioamide analogue **2j** was prepared by reaction of **11** with sodium thiocyanate and trifluoroacetic acid in toluene according to a methodology developed by Loev and coworkers [14].

Anti-HIV Activity.

Compounds **2a-j** were tested *in vitro* for their ability to inhibit HIV-1 in CEM-cl 13 cells. None of the compounds were active at doses up to 20 μg/ml. From this and other work [5,6], it may be concluded that the potent anti-HIV activity of TIBO derivatives requires an intact tricyclic structure.

Scheme 2



EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. The ^1H nmr spectra were determined on a Bruker WP200 MHz or WP250 MHz instrument. Chemical shifts are given as δ values with reference to tetramethylsilane as an internal standard. Electron impact mass spectra were recorded on an AEI MS-50 spectrometer. FAB spectra and high-resolution mass spectra (hrms) were recorded on a Kratos MS80RF instrument. Thin layer chromatography (tlc) and preparative tlc were performed on Merck silica gel 60 plates or neutral type E alumina plates with fluorescent indicator. The plates were visualized with uv light (254 nm) and, for tlc, with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230-240 mesh) at medium pressure (200 mbar). All solvents were distilled and stored over 4 Å molecular sieves before use. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

2-(*tert*-Butyloxycarbonyl)aminobenzyl Alcohol (**4**).

A mixture of 2-aminobenzyl alcohol (**3**, 3.69 g, 30 mmoles) and di-*tert*-butyl dicarbonate (6.54 g, 30 mmoles) in 1,2-dichloroethane (75 ml) was refluxed for 2.5 hours. More di-*tert*-butyl dicarbonate (2.5 g, 11.5 mmoles) was added to the reaction mixture at this point and reflux was continued for 1.5 hours. The solvent was then removed under reduced pressure, leaving compound **4** which could be used without further purification in the following step. An analytical sample of **4** (an oil) was obtained by purification on silica gel using dichloromethane-ethyl acetate (95:5) as developer; ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.52 (s, 9H, 3 x CH_3,), 2.31 (t, 1H, J = 6.0 Hz, exchangeable with deuterium oxide, OH), 4.67 (d, 2H, CH_2), 7.01 (t, 1H, ArH), 7.14 (d, 1H, ArH), 7.26 (t, 1H, ArH), 7.65 (br s, 1H, exchangeable with deuterium oxide, NH), 7.90 (d, 1H, ArH); ms: 223 (M^+).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.57; H, 7.62; N, 6.28. Found: C, 64.32; H, 7.50; N, 6.55.

2-(*tert*-Butyloxycarbonyl)aminobenzyl Bromide (**5**).

A solution of compound **4** (6.7 g, 30 mmoles) and carbon tetrabromide (17.4 g, 30 mmoles) in anhydrous diethyl ether (120 ml) was treated with triphenylphosphine (11.1 g, 42 mmoles). The reaction mixture was stirred for 30 minutes at room temperature and the precipitate which formed was removed by filtration and washed with ether. The filtrate and washings were combined, the solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel (dichloromethane-heptane 1:1) yielding compound **5** as a red oil (70% from **3**); ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.54 (s, 9H, 3 x CH_3), 4.49 (s, 2H, CH_2), 6.71 (br s, 1H, exchangeable with deuterium oxide, NH), 7.04 (t, 1H, ArH), 7.24-7.36 (m, 2H, ArH), 7.82 (d, 1H, ArH).

Methyl-2-{[2-(*tert*-Butyloxycarbonylamino)benzyl]amino}-propanoate (**6**).

A suspension of compound **5** (7.55 g, 25 mmoles), L-alanine methyl ester hydrochloride (3.9 g, 37.5 mmoles), sodium carbonate (4.0 g, 37.5 mmoles) and potassium iodide (4.15 g, 27.5 mmoles) in anhydrous DMF (250 ml) was stirred under an atmosphere of nitrogen at room temperature for 15 hours. The solvent was then removed under reduced pressure and the residue was partitioned between dichloromethane and water. The organic extract was dried over sodium sulfate, the solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel using first dichloromethane-heptane (1:1) as developer followed by dichloromethane. Compound **6** was thus obtained as an oil in 74% yield; ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.34 (d, 3H, J = 7.0 Hz, $CHCH_3$), 1.53 (s, 9H, 3 x CH_3), 1.91 (s, 1H, exchangeable with deuterium oxide, NH), 3.36 (q, 1H, $CHCH_3$), 3.65 (d, 1H, J_{gem} = 12.7 Hz, CH_aH_b), 3.76 (s, 3H, OCH_3), 3.87 (d, 1H, CH_aH_b), 6.93 (t, 1H, ArH), 7.05 (d, 1H, ArH), 7.23 (t, 1H, ArH), 7.97 (d, 1H, ArH), 9.38 (br s, 1H, exchangeable with deuterium oxide, NH); ms: 308 (M^+).

Anal. Calcd. for $C_{16}H_{24}N_2O_4$: C, 62.34; H, 7.79; N, 9.09. Found: C, 62.15; H, 7.76; N, 9.34.

Methyl 2-{[2-(*tert*-Butyloxycarbonylamino)benzyl](3-methyl-2-butenyl)amino}propanoate (**7**).

A mixture of amine **6** (4.9 g, 15.1 mmoles), sodium carbonate (3.15 g, 30 mmoles), potassium iodide (3.75 g, 22.6 mmoles) and 4-bromo-2-methyl-2-butene (3.4 ml, 30 mmoles) in anhydrous DMF (150 ml) was stirred under a nitrogen atmosphere at room temperature for 20 hours. The solvent was then removed under reduced pressure and the residue was partitioned between dichloromethane and water. The organic fraction was dried over sodium sulfate, the solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel (dichloromethane-heptane 8:2), yielding compound **7** (85%); ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.31 (d, 3H, J = 7.0 Hz, $CHCH_3$), 1.55 (s, 9H, 3 x CH_3), 1.64 (s, 3H, =C-CH_3), 1.75 (s, 3H, =C-CH_3), 3.11 (m, 2H, CH_2CH=), 3.52 (q, 1H, $CHCH_3$), 3.73 (s, 3H, OCH_3), 3.74 (d, 1H, J_{gem} = 13.4 Hz, CH_aH_b), 3.77 (d, 1H, CH_aH_b), 5.27 (dd, 1H, J = 6.9 Hz, CH_2CH=), 6.90 (t, 1H, ArH), 7.06 (d, 1H, ArH), 7.25 (t, 1H, ArH), 7.99 (d, 1H, ArH), 9.57 (br s, 1H, exchangeable with deuterium oxide, NH); ms: 376 (M^+).

Anal. Calcd. for $C_{21}H_{32}N_2O_4$: C, 67.02; H, 8.51; N, 7.45. Found: C, 66.81; H, 8.33; N, 7.47.

Methyl 2-[(2-Aminobenzyl)(3-methyl-2-butenyl)amino]propanoate (**8**).

A solution of compound **7** (2.8 g, 7.5 mmoles) in trifluoroacetic acid (50 ml) was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure, the residue was taken up in dichloromethane (20 ml) and the solution was washed with 10% aqueous ammonium hydroxide (10 ml). The aqueous fraction was extracted with dichloromethane (10 ml), the combined organic extracts were dried over sodium sulfate and the solvents were evaporated *in vacuo*. The resulting crude product was purified by chromatography on silica gel using first dichloromethane-heptane (3:1) as developer followed by dichloromethane, providing amine **8** as an oil in 91% yield; ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.28 (d, 3H, J = 7.0 Hz, $CHCH_3$), 1.61 (s, 3H, =CCH_3), 1.71 (s, 3H, =C-CH_3), 3.09 (d, 2H, J = 6.3 Hz, CH_2CH=), 3.57 (q, 1H, $CHCH_3$), 3.69 (s, 5H, OCH_3 and $PhCH_2$), 4.67 (br s, 2H, exchangeable with deuterium oxide, NH_2), 5.18 (t, 1H, CH_2CH=), 6.58-6.66 (m, 2H, ArH), 6.94-7.05 (m, 2H, ArH); ms: 276 (M^+).

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.57; H, 8.70; N, 10.14. Found: C, 69.55; H, 8.61; N, 10.04.

3-Methyl-4-(3-methyl-2-butenyl)-3,4-dihydro-1*H*,5*H*-1,4-benzodiazepin-2-one (**10**).

Procedure A.

A mixture of compound **8** (120 mg, 0.46 mmole) and sodium hydroxide (18.3 mg, 0.46 mmole) in methanol-water (2.2 ml of a 3:1 mixture) was stirred overnight at room temperature. The reaction mixture was neutralized with acetic acid and concentrated under reduced pressure. The residue was partitioned between dichloromethane-methanol (9:1) and water. The organic phase was dried over sodium sulfate, the solvents were removed under reduced pressure and the crude product was purified by preparative tlc on silica gel (dichloromethane-methanol 95:5). The minor, higher Rf compound, obtained in 10% yield, was identified as **10**, mp 101-102° (hexane); ^{1}H nmr (250 MHz, deuteriochloroform): δ 1.36 (d, 3H, J = 6.8 Hz, $CHCH_3$), 1.57 (s, 3H, =C-CH_3), 1.75 (s, 3H, =C-CH_3), 3.15 (m, 2H, CH_2CH=), 3.53 (q, 1H, $CHCH_3$), 3.86 (d, 1H, J_{gem} = 14.6 Hz, $PhCH_aH_b$), 3.91 (d, 1H, $PhCH_aH_b$), 5.26 (t, 1H, J = 6.8 Hz, CH_2CH=), 7.01-7.30 (m, 4H, ArH), 8.77 (br s, 1H, exchangeable with deuterium oxide, NH); ms: 244 (M^+).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.77; H, 8.20; N, 11.48. Found: C, 73.58; H, 8.05; N, 11.36.

The major, lower Rf product, carboxylic acid **9**, was obtained in 61% yield; ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.45 (d, 3H, J = 7.5 Hz, CHCH_3), 1.60 (s, 3H, =CCH_3), 1.75 (s, 3H, =CCH_3), 3.43 (oct, 2H, J_{gem} = 13.7 Hz, J_{vic} = 6.3 Hz, CH_2CH=), 3.75 (m, 1H, CHCH$_3$), 3.78 (d, 1H, J_{gem} = 13.1 Hz, PhCH_aH$_b$), 4.12 (d, 1H, PhCH$_a$$H_b$), 5.24 (t, 1H, J = 6.3 Hz, CH$_2$CH=), 6.02 (br s, 3H, exchangeable with deuterium oxide, OH, NH$_2$), 6.67 (m, 2H, ArH), 7.01 (d, 1H, ArH), 7.13 (t, 1H, ArH); ms: (FAB) 263 (M$^+$ + 1).

A solution of compound **9** (69 mg, 0.26 mmole) and 1-hydroxybenzotriazole monohydrate (76 mg, 0.52 mmole) in anhydrous pyridine (2 x 3 ml) was evaporated under reduced pressure in order to co-evaporate water of hydration. The residue was dissolved in anhydrous tetrahydrofuran (2 ml) and dicyclohexylcarbodiimide (61 mg, 0.3 mmole) was added to the solution. The reaction mixture was stirred at room temperature for 5 hours and the solid which formed was removed by filtration. The filtrate was concentrated under reduced pressure and the crude product was purified by preparative tlc on silica gel (dichloromethane-methanol 93:7) affording compound **10** (68%) identical in all respects to that isolated above.

Procedure B.

To a solution of amine **8** (654 mg, 2.37 mmoles) in anhydrous DMF (12 ml) was added sodium hydride (142 mg, 3.55 mmoles; 60% oil dispersion). The reaction mixture was stirred under a nitrogen atmosphere at room temperature overnight. It was then cooled to 0°, water (0.5 ml) was added and the solvents were removed under reduced pressure. The residue was partitioned between dichloromethane and water, the organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure, yielding crude **10**. The latter was purified by chromatography on silica gel (dichloromethane-methanol 99:1) affording pure **10** (66%), identical in all respects to that prepared above.

2,3,4,5-Tetrahydro-3-methyl-4-(3-methyl-2-butenyl)-1*H*-1,4-benzodiazepine (**11**).

To a solution of **10** (1.16 g, 4.75 mmoles) in anhydrous tetrahydrofuran (50 ml) was added lithium aluminum hydride (0.9 g, 23.8 mmoles). The mixture was refluxed under a nitrogen atmosphere for 4 hours, then cooled and carefully quenched with water. The precipitate was removed by filtration, the filtrate was diluted with dichloromethane (200 ml) and washed with water. The organic phase was dried over sodium sulfate and the solvents were removed under vacuum. The resulting crude product was purified by chromatography on silica gel (dichloromethane-methanol 95:5), yielding compound **11** (97%), mp 52-53° (ethyl acetate); ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.27 (d, 3H, J = 6.4 Hz, CHCH_3), 1.49 (s, 3H, =CCH_3), 1.75 (s, 3H, =CCH_3), 2.98-3.20 (m, 5H, CHCH$_3$, CH_2CH=, NHCH_2), 3.74 (d superimposed on br s, 2H, J_{gem} = 15.0 Hz, partly exchangeable with deuterium oxide, PhCH_aH$_b$, NH), 4.23 (d, 1H, PhCH$_a$$H_b$), 5.30 (t, 1H, CH$_2CH$=), 6.70 (d, 1H, ArH), 6.80 (t, 1H, ArH), 6.99-7.08 (m, 2H, ArH); ms: 230 (M$^+$).

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.26; H, 9.57; N, 12.17. Found: C, 78.04; H, 9.73; N, 12.13.

General Procedure for the Preparation of the *N'*-Substituted Thiourea Derivatives **2a-2h**.

A solution of **11** and the corresponding isothiocyanate (RNCS) (2.2 equivalents) in 95% ethanol (5 ml/mmole) was refluxed overnight. The solvent and unreacted isothiocyanate were removed *in vacuo* and the resulting crude product was purified by preparative tlc on silica gel using dichloromethane-methanol (96:4) as developer.

In this manner, the following compounds were prepared:

N,3-Dimethyl-4-(3-methyl-2-butenyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbothioamide (**2a**).

This compound was obtained from **11** and methyl isothiocyanate in 88% yield as an oil; ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.19 (d, 3H, J = 6.0 Hz, CHCH_3), 1.45 (s, 3H, =C-CH$_3$), 1.76 (s, 3H, =C-CH$_3$), 2.74 (m, 1H, collapses to a d when CH$_2$CH= is irradiated, $J_{a,b}$ = 13.6 Hz, CH_aH$_b$CH=), 3.02 (m, 2H, CH$_a$$H_b$CH=, NH), 3.06 (d, 3H, J = 4.4 Hz, NCH$_3$), 3.55 (m, 1H, CHCH$_3$), 3.79 (d, 1H, $J_{a,b}$ = 14.0 Hz, ArCH_aH$_b$), 3.88 (d, 1H, ArCH$_a$$H_b$), 5.23 (m, 2H, CH$_2CH$=, NC$H_aH_b$CH), 5.54 (m, 1H, NCH$_a$$H_b$CH), 7.19-7.38 (m, 4H, ArH).

Calcd. for $C_{17}H_{25}N_3S$: 303.1766; hrms Found: 303.1771.

N-Ethyl-3-methyl-4-(3-methyl-2-butenyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbothioamide (**2b**).

This compound was obtained from **11** and ethyl isothiocyanate in 91% yield as an oil; ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.09 (t, 3H, J = 7.2 Hz, CH$_2$CH_3), 1.19 (d, 3H, J = 6.1 Hz, CHCH_3), 1.46 (s, 3H, =C-CH$_3$), 1.76 (s, 3H, =C-CH$_3$), 2.75 (m, 1H, collapses to a d when CH$_2$CH= is irradiated, $J_{a,b}$ = 13.7 Hz, CH_aH$_b$CH=), 3.02 (m, 2H, CH$_a$$H_b$CH=, NH), 3.53-3.73 (m, 3H, CHCH$_3$, NCH_2CH$_3$), 3.77 (d, 1H, $J_{a,b}$ = 14.3 Hz, ArCH_aH$_b$), 3.89 (d, 1H, ArCH$_a$$H_b$), 5.20 (m, 2H, CH$_2CH$=, NC$H_aH_b$CH), 5.45 (m, 1H, NCH$_a$$H_b$CH), 7.19-7.37 (m, 4H, ArH).

Calcd. for $C_{18}H_{27}N_3S$: 317.1926; hrms Found: 317.1918.

3-Methyl-4-(3-methyl-2-butenyl)-*N*-*n*-propyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbothioamide (**2c**).

This compound was obtained from **11** and *n*-propyl isothiocyanate in 95% yield as an oil; ^{1}H nmr (250 MHz, deuteriochloroform): δ 0.83 (t, 3H, J = 7.3 Hz, CH$_2$CH_3), 1.18 (d, 3H, J = 5.7 Hz, CHCH_3), 1.49 (m, 2H, CH_2CH$_3$), 1.46 (s, 3H, =C-CH$_3$), 1.76 (s, 3H, =C-CH$_3$), 2.74 (m, 1H, collapses to a d when CH$_2$CH= is irradiated, $J_{a,b}$ = 13.5 Hz, CH_aH$_b$CH=), 2.98 (m, 2H, CH$_a$$H_b$CH=, NH), 3.43-3.63 (m, 3H, CHCH$_3$, NCH_2CH$_2$), 3.78 (d, 1H, $J_{a,b}$ = 14.6 Hz, ArCH_aH$_b$), 3.88 (d, 1H, ArCH$_a$$H_b$), 5.23 (m, 2H, CH$_2CH$=, NC$H_aH_b$CH), 5.49 (m, 1H, NCH$_a$$H_b$CH), 7.19-7.36 (m, 4H, ArH).

Calcd. for $C_{19}H_{29}N_3S$: 331.2082. hrms Found: 331.2090.

N-*n*-Butyl-3-methyl-4-(3-methyl-2-butenyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbothioamide (**2d**).

This compound was obtained from **11** and *n*-butyl isothiocyanate in 66% yield as a solid which was crystallized from ethyl acetate, mp 84-85°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 0.87 (t, 3H, J = 7.0 Hz, CH$_2$CH_3), 1.18-1.37 (m, 7H, CHCH_3, CH_2CH_2), 1.45 (s, 3H, =C-CH$_3$), 1.76 (s, 3H, =C-CH$_3$), 2.74 (m, 1H, collapses to a d when CH$_2$CH= is irradiated, $J_{a,b}$ = 14.1 Hz, CH_aH$_b$CH=), 3.02 (m, 2H, CH$_a$$H_b$CH=, NH), 3.51-3.72 (m, 3H, CHCH$_3$, NCH_2CH$_2$), 3.77 (d, 1H, $J_{a,b}$ = 14.7 Hz, ArCH_aH$_b$), 3.88 (d, 1H, ArCH$_a$$H_b$), 5.23 (m, 2H, CH$_2CH$=, NC$H_aH_b$CH), 5.44 (m, 1H, NCH$_a$$H_b$CH), 7.18-7.33 (m, 4H, ArH).

Anal. Calcd. for $C_{20}H_{31}N_3S$: C, 69.57; H, 8.99; N, 12.17; S, 9.28. Found: C, 69.48; H, 9.18; N, 12.03; S, 9.28.

N-Allyl-3-methyl-4-(3-methyl-2-butenyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbothioamide (**2e**).

This compound was obtained from **11** and allyl isothiocyanate in 66% yield as an oil; ^{1}H nmr (250 MHz, deuteriochloroform): δ 1.19 (d, 3H, J = 6.3 Hz, CHCH_3), 1.46 (s, 3H, =C-CH_3), 1.76 (s, 3H, =C-CH_3), 2.74 (m, 1H, collapses to a d when CH_2C*H*= is irradiated, $J_{a,b}$ = 13.7 Hz, CH_aH$_b$CH=), 2.95 (br s, 1H, NH), 3.03 (m, 1H, CH$_a$$H_b$CH=), 3.57 (m, 1H, C*H*CH$_3$), 3.79 (d, 1H, $J_{a,b}$ = 14.4 Hz, ArCH_aH$_b$), 3.90 (d, 1H, ArCH$_a$$H_b$), 4.16 (m, 1H, $J_{a,b}$ = 15.6 Hz, CH_aH$_b$CH=CH$_2$), 4.36 (m, 1H, CH$_a$$H_b$CH=CH$_2$), 5.06 (m, 2H, J_{cis} = 9.4 Hz, J_{trans} = 19.5 Hz, CH$_2$CH=CH$_2$), 5.22 (m, 2H, C*H*=C(CH$_3$)$_2$, NCH_aH$_b$CH), 5.54 (m, 1H, NCH$_a$$H_b$CH), 5.80 (m, 1H, C*H*=CH$_2$), 7.22-7.37 (m, 4H, ArH).

Calcd. for $C_{19}H_{27}N_3S$: 329.1926; hrms Found: 329.1910.

N-Cyclohexyl-3-methyl-4-(3-methyl-2-butenyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbothioamide (**2f**).

This compound was obtained from **11** and cyclohexyl isothiocyanate in 80% yield as a solid which was crystallized from ethyl acetate, mp 86-87°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 0.91-2.04 (m, 10H, cyclohexyl CH$_2$), 1.18 (d, 3H, J = 6.1 Hz, CHCH_3), 1.45 (s, 3H, =CCH_3), 1.76 (s, 3H, =CCH_3), 2.76 (m, 1H, collapses to a d when CH_2C*H*= is irradiated, $J_{a,b}$ = 13.4 Hz, CH_aH$_b$CH=), 3.02 (m, 2H, CH$_a$$H_b$CH=, NH), 3.54 (m, 1H, C*H*CH$_3$), 3.74 (d, 1H, $J_{a,b}$ = 14.4 Hz, ArCH_aH$_b$), 3.88 (d, 1H, ArCH$_a$$H_b$), 4.29 (m, 1H, NHC*H*), 5.20 (m, 2H, CH$_2$C*H*=, NCH_aH$_b$CH), 5.34 (m, 1H, NCH$_a$$H_b$CH), 7.16-7.33 (m, 4H, ArH); ms: 371 (M$^+$).

Anal. Calcd. for $C_{22}H_{33}N_3S$: C, 71.16; H, 8.89; N, 11.32; S, 8.63. Found: C, 71.21; H, 9.01; N, 11.11; S, 8.70.

3-Methyl-4-(3-methyl-2-butenyl)-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbothioamide (**2g**).

This compound was obtained from **11** and phenyl isothiocyanate in 88% yield as a solid which was crystallized from ethyl acetate, mp 74-76°; ^{1}H nmr (250 MHz, deuteriochloroform): δ 1.22 (d, 3H, J = 6.0 Hz, CHCH_3), 1.48 (s, 3H, =CCH_3), 1.78 (s, 3H, =CCH_3), 2.79 (m, 1H, collapses to a d when CH$_2$C*H* is irradiated, $J_{a,b}$ = 13.2 Hz, CH_aH$_b$CH=), 3.07 (m, 2H, CH$_a$$H_b$CH=, NH), 3.65 (m, 1H, C*H*CH$_3$), 3.93 (br s, 2H, ArCH_2), 5.29 (m, 3H, CH$_2$C*H*=, NCH_2CH), 7.11-7.36 (m, 9H, ArH); ms: 365 (M$^+$).

Anal. Calcd. for $C_{22}H_{27}N_3S$: C, 72.33; H, 7.40; N, 11.51; S, 8.77. Found: C, 72.45; H, 7.38; N, 11.23; S, 8.75.

N-Benzyl-3-methyl-4-(3-methyl-2-butenyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbothioamide (**2h**).

This compound was obtained from **11** and benzyl isothiocyanate in 76% yield as a solid which was crystallized from ethyl acetate, mp 93-94°; ^{1}H nmr (250 MHz, deuteriochloroform): δ 1.20 (d, 3H, J = 6.3 Hz, CHCH_3), 1.46 (s, 3H, =CCH_3), 1.76 (s, 3H, =CCH_3), 2.74 (m, 1H, collapses to a d when CH$_2$C*H*= is irradiated, $J_{a,b}$ = 13.6 Hz, CH_aH$_b$CH=), 3.03 (m, 2H, CH$_a$$H_b$CH=, NH), 3.61 (m, 1H, C*H*CH$_3$), 3.81 (d, 1H, $J_{a,b}$ = 14.4 Hz, ArCH_aH$_b$), 3.89 (d, 1H, ArCH$_a$$H_b$), 4.78 (q, 1H, $J_{a,b}$ = 14.9 Hz, $J_{CH,NH}$ = 4.8 Hz, NHCH_aH$_b$), 4.89 (q, 1H, NHCH$_a$$H_b$), 5.23 (m, 2H, CH$_2$C*H*=, NC$H_aH_b$CH), 5.78 (m, 1H, NCH$_a$$H_b$CH), 7.25 (m, 9H, ArH); ms: 379 (M$^+$).

Anal. Calcd. for $C_{23}H_{29}N_3S$: C, 72.82; H, 7.65; N, 11.08; S, 8.44. Found: C, 72.80; H, 7.82; N, 11.10; S, 8.56.

N-tert-Butyl-3-methyl-4-(3-methyl-2-butenyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbothioamide (**2i**).

A solution of **11** (34 mg, 0.15 mmole) in *tert*-butyl isothiocyanate (0.5 ml, 4 mmoles) was heated at 100° for 3 days. The solvent was removed under reduced pressure and the crude product was purified by preparative tlc on silica gel using dichloromethane-methanol (97:3) as developer. Compound **2i** was obtained as an oil in 12% yield; ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.20 (d, 3H, CHCH_3), 1.42 (s, 9H, C(CH_3)$_3$), 1.45 (s, 3H, =CCH_3), 1.76 (s, 3H, =CCH_3), 2.77 (m, 1H, collapses to a d when CH_2C*H*= is irradiated, $J_{a,b}$ = 12.8 Hz, CH_aH$_b$CH=), 3.00 (m, 2H, CH$_a$$H_b$CH=, NH), 3.50 (m, 1H, C*H*CH$_3$), 3.68-3.94 (m, 2H, ArCH_2), 5.24 (m, 2H, CH$_2$C*H*=, NCH_aH$_b$CH), 5.45 (m, 1H, NCH$_a$$H_b$CH), 7.16-7.37 (m, 4H, ArH); ms: 345 (M$^+$).

Anal. Calcd. for $C_{20}H_{31}N_3S$: C, 69.56; H, 8.99; N, 12.17; S, 9.28. Found: C, 69.30; H, 9.05; N, 12.12; S, 9.52.

3-Methyl-4-(3-methyl-2-butenyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbothioamide (**2j**).

To a mixture of **11** (70 mg, 0.3 mmole) and sodium thiocyanate (97 mg, 1.2 mmoles) in anhydrous toluene (0.6 ml) was added trifluoroacetic acid (60 µl, 0.9 mmole). The reaction mixture was allowed to stir overnight at room temperature under nitrogen and it was then heated at 100° for 2 hours. The solvent was removed by pipette and the residual solid was partitioned between dichloromethane and water. The organic phase was separated, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by preparative tlc using dichloromethane-methanol (98:2) as developer, affording **2j** in 13% yield, mp 132-133° (from ethyl acetate); ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.21 (d, 3H, J = 6.8 Hz, CHCH_3), 1.45 (s, 3H, =CCH_3), 1.77 (s, 3H, =CCH_3), 2.70 (dd, 1H, $J_{a,b}$ = 13.6 Hz, J_{vic} = 8.0 Hz, CH_aH$_b$CH=), 3.01-3.09 (m, 3H, CH$_a$$H_b$CH=, NC$H_2$CH), 3.64 (m, 1H, C*H*CH$_3$), 3.88 (d, 1H, $J_{a,b}$ = 14.8 Hz, ArCH_aH$_b$), 3.91 (d, 1H, ArCH$_a$$H_b$), 5.24 (m, 1H, CH$_2$C*H*=), 5.81 (br s, 2H, NH$_2$), 7.28-7.40 (m, 4H, ArH); ms: 289 (M$^+$).

Anal. Calcd. for $C_{16}H_{23}N_3S$: C, 66.44; H, 7.96; N, 14.53; S, 11.07. Found: C, 66.38; H, 7.71; N, 14.52; S, 11.00.

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