Scientific paper

Synthesis, Characterization and Biological Activity of Some Dithiourea Derivatives

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Abstract

Novel dithiourea derivatives have been designed as HIV-1 protease inhibitors using Autodock 4.2, synthesized and characterized by spectroscopic methods and microanalysis. 1-(3-Bromobenzoyl)-3-[2-({[(3-bromophenyl)formamido]methanethioyl}amino)phenyl]thiourea (**10**) and 3-benzoyl-1-{[(phenylformamido)methanethioyl]amino}thiourea (**12**) gave a percentage viability of 17.9 ± 5.6% and 11.2 ± 0.9% against *Trypanosoma brucei*. Single crystal X-ray diffraction analysis of 1-benzoyl-3-(5-methyl-2-{[(phenylformamido)methanethioyl]amino}phenyl)thiourea (**1**), 3-benzoyl-1-(2-{[(phenylformamido)methanethioyl]amino}ethyl)thiourea (**11**), 3-benzoyl-1-{[(phenylformamido)methanethioyl]amino}thiourea (**12**) and 3-benzoyl-1-(4-{[(phenylformamido)methanethioyl]amino}butyl)thiourea (**14**) have been presented. 1-(3-Bromobenzoyl)-3-[2-({[(3-bromophenyl)formamido]methanethioyl}amino)phenyl]thiourea (**10**) gave a percentage inhibition of 97.03 ± 0.37% against HIV-1 protease enzyme at a concentration of 100 μM.

Keywords: Dithiourea, cytotoxicity; HIV-1 protease inhibition; *plasmodium falciparum* activity; *trypanosoma brucei* activity

1. Introduction

Thiourea derivatives have been synthesized by a variety of methods.[1–8] A solvent-free three-component one-pot reaction between 2,6-diaminopyridine or 1,2-diaminobenzene and NH₄SCN with subsequent addition of an aroyl chloride gave bis-1-(aroyl)-3-(aryl)thioureas in excellent yields. The thiocyanate derivatives were first synthesized and then used to prepare the thiourea derivatives.[1] Benzoyl chloride has been reacted with ammonium thiocyanate in CH_2Cl_2 solution under solid–liquid phase transfer catalysis, using polyethylene glycol-400 as the catalyst, to give the corresponding benzoyl isothiocyanate.

Dropwise addition of a solution of 1,4-butylenediamine in CH_2Cl_2 yielded 3,3'-dibenzoyl-1,1'-(butane-1,4-diyl)dithiourea,[2] while 3,3-bis(4-nitrophenyl)-1,10-(*para*-phenylene)dithiourea has been prepared by the reaction of (*para*-nitro)benzoyl isothiocyanate with *para*-phenylenediamine in CH_2Cl_2 using polyethylene glycol-400 as a phase transfer catalyst.[3] This reaction has been carried out using 1,6-hexyldiamine as the source diamine to give *N,N*-(1,6-hexamethylene)-bis(benzoylthiourea).[4] Thiocarbonohydrazide has been converted into 1-aminothiocarbamoyl-4-aroyl-3-thiosemicarbazides and 1,5-bis(aroylthiocarbamoy1)thiocarbonohydrazides by the addition
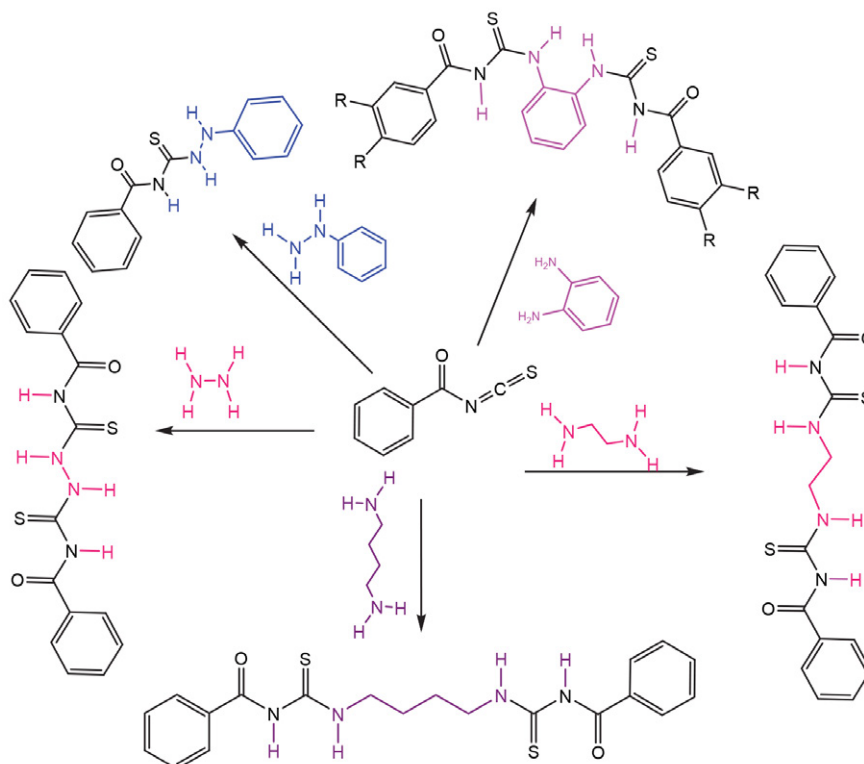
of one or two equivalents of aroyl isothiocyanate, respectively. 1-Phenyl- or 1-benzylidene-thiocarbonohydrazide and aroyl isothiocyanates gave the appropriate mono-adduct analogues. 1-Aminothiocarbamoyl-4-benzoyl-3-thiosemicarbazide is cyclised to 3-mercapto-5-phenyl-1,2,4-triazole in alkaline medium, and to 2-benzamido-5-mercapto-1,3,4-thiadiazole in acid media; the action of alkyl halides on the appropriate alcohol yields 2-benzamido-5-alkylthio-l,3,4-thiadiazoles.[5]

The reaction of benzoyl isothiocyanate with *ortho*-phenylenediamine has been done in acetone using potassium thiocyanate as a thiocyanate source.[6] Urea attacks the benzoyl isothiocyanate on one end of the molecule. Potassium thiocyanate in acetone has been reacted with benzoyl chloride at 50 °C.[7] 1,2-Diaminoethane, 1,3-diaminopropane or 1,4-diaminobutane dissolved in acetone were added and stirred at room temperature for 2 h.[8]

2. Results and Discussion

2. 1. Synthesis and Spectroscopic Characterization

The phenyl thiourea derivatives are formed by the attack of the thione carbon of the starting benzoyl isothiocyanate by the two amino groups of the other starting molecule. Scheme 1 gives the synthetic pathway for the synthesis of the diamine derivatives.
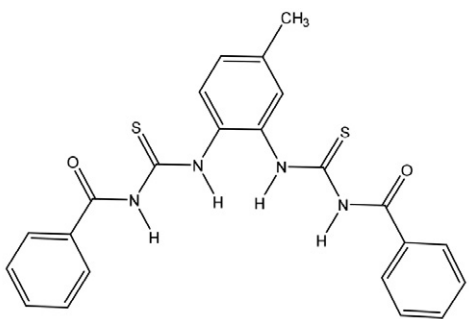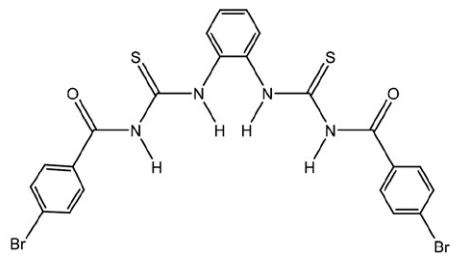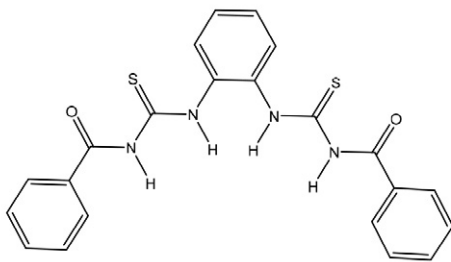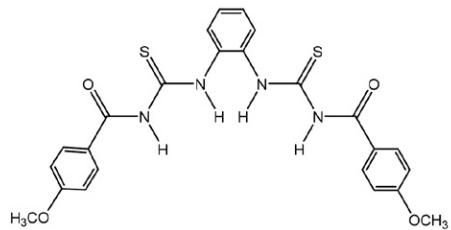
Spectroscopic characterization. The dithiourea derivatives were obtained by the reaction of ammonium thiocyanate with the respective benzoyl chloride in acetone and heating under reflux for 2 h to yield the benzoyl isothiocyanate derivatives. The addition of the diamines and further heating under reflux for 3 h gave the final products **1**–**14**. The ^{1}H NMR gave signals between δ 14.24 and 11.24 ppm for the NH proton of the amide. Table 1 gives the structures of all the synthesized compounds and their yields.

Aromatic protons gave signals between δ 11.72 and 7.01 ppm. In the ^{13}C NMR the thione signal was observed between δ 180.8 and 171.5 ppm whilst the carbonyl occurred between δ 168.3 and 161.0 ppm. Signals for aromatic carbons were observed between δ 159.0 and 113.3 ppm. The IR gave signals for the N–H stretching between 3440 and 3071 cm^{-1}, whilst the aliphatic C–H stretching occurred between 2993 and 2727 cm^{-1}. The C=S stretching was observed between 1683 and 1670 cm^{-1}, with the carbonyl stretching occurring between 1687 and 1640 cm^{-1} and the C=C stretching observed between 1597 and 1506 cm^{-1}.

Crystal structures of compounds 1, 11, 12 and 14. Compounds **1**, **11**, **12** and **14** were recrystallized from DMSO/toluene (1:1). Compound **1** was obtained as white crystals, whilst compounds **11** and **12** were obtained as brown and light brown crystals, respectively. Compound **14** recrystallized from DMSO/toluene (1:3) as a light brown solid. The crystallographic data, selected bond
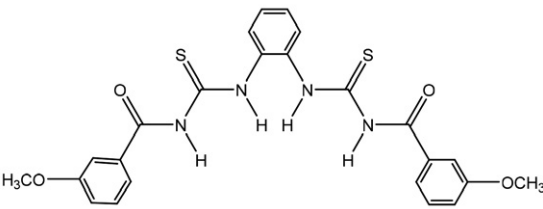

Scheme 1. Synthesis of phenylthiourea compounds and other diamine derivatives.

Table 1. List of synthesized compounds and their yields.

Compound	Structure	Yield (%)
1		78.0
2		78.0
3		74.7
4		70.7
5		73.0
6		76.4

Compound	Structure	Yield (%)
7		72.2
8		77.1
9		75.3
10		80.0
11		70.9
12		71.8
13		71.6
14		80.8

lengths and bond angles for the crystal structures of compounds **1**, **11**, **12** and **14** are provided in Tables 2 and 3. The ORTEP diagrams for compounds **1**, **11**, **12** and **14** are presented in Figures 1, 2, 3 and 4. Compounds **1**, **11** and **14** crystallized in the monoclinic space group *P*2₁/*c*, while compound **12** crystallized in the monoclinic space group

Table 2. Crystallographic data and structure refinement summary for compounds **1**, **11**, **12** and **14**.

Property	1	11	12	14
Formula	$C_{23}H_{20}N_4O_2S_2$	$C_{18}H_{18}N_4O_2S_2$	$C_{16}H_{14}N_4O_2S_2$, 2(C_2H_6OS)	$C_{20}H_{22}N_4O_2S_2$
CCDC Number	1448382	1919730	1919731	1919732
Formula weight	448.57	386.50	514.73	414.56
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P2_1/c$
a [Å]	10.8288(4)	11.2036(13)	6.3738(2)	5.9962(2)
b [Å]	17.8575(7)	7.1780(8)	15.3854(5)	23.2946(10)
c [Å]	22.6276(9)	11.0901(13)	12.6585(4)	7.1680(3)
α [°]	90	90	90	90
β [°]	92.581(2)	100.783(5)	93.448(1)	103.777(2)
γ [°]	90	90	90	90
V [Å³]	4371.2(3)	876.11(18)	1239.09(7)	972.42(7)
Z	8	2	2	2
D_{calc} [g/cm³]	1.363	1.465	1.380	1.416
Mu(MoKa) [/mm]	0.272	0.325	0.417	0.298
$F(000)$	1872	404	540	436
Crystal size [mm]	0.23 × 0.32 × 0.54	0.14 × 0.22 × 0.25	0.15 × 0.27 × 0.33	0.06 × 0.47 × 0.58
Temperature [K]	200	200	200	200
Tot., unique data, R(int)	40580, 10903, 0.028	2175, 2175, 0.000	11663, 3088, 0.020	13405, 2402, 0.020
Observed data [$I > 2.0\,\sigma(I)$]	7835	1986	2596	2022
N_{ref}	10903	2175	3088	2402
N_{par}	616	128	155	135
R, wR_2, S	0.0605, 0.1408, 1.08	0.1277, 0.4138, 1.17	0.0298, 0.0821, 1.03	0.0339, 0.0931, 1.06
Min. and max. resd. dens. [e/Å³]	−0.63, 0.71	−1.59, 1.64	−0.27, 0.33	−0.20, 0.32

Table 3. Selected bond lengths (Å) and bond angles (°) for compounds **1**, **11**, **12** and **14**.

	Bond Distances (Å)						
	1		**11**		**12**		**14**
S21–C22	1.667(1)	S1–C2	1.662(1)	S1–C2	1.668(1)	S1–C2	1.673(1)
S11–C12	1.667(1)	O1–C1	1.218(1)	O1–C1	1.225(2)	O1–C1	1.223(2)
O21–C21	1.230(1)	C1–C11	1.492(1)	N1–C1	1.382(2)	N1–C1	1.374(2)
O11–C11	1.224(1)	N1–C2	1.405(1)	N1–C2	1.383(2)	N2–C2	1.321(2)
N21–C22	1.399(1)	N1–C1	1.371(1)	N2–N2_a	1.373(2)	N2–C3	1.461(2)
N22–C22	1.332(1)	C3–C3_a	1.522(1)	N2–C2	1.332(2)	N1–C2	1.390(2)
N22–C221	1.421(3)	N2–C2	1.325(2)	S2–O2	1.508(1)	C3–C4	1.521(2)
N23–C23	1.335(4)	N2–C3	1.454(2)	N2–C2	1.332(2)	C4–C4_a	1.522(2)

	Bond Angles (°)						
	1		**11**		**12**		**14**
N21–C22–N22	114.5(2)	C1–N1–C2	128.6(1)	O2–S2–C4	106.2(1)	C1–N1–C2	129.3(1)
S21–C22–N22	127.6(2)	C2–N2–C3	123.3(1)	O2–S2–C3	105.6(1)	C2–N2–C3	122.3(1)
O11–C11–N11	122.4(2)	O1–C1–N1	122.4(1)	N2_a–N2–C2	119.6(1)	O1–C1–C11	122.1(1)
N21–C21–C211	117.6(2)	S1–C2–N2	126.0(1)	N1–C1–C11	115.1(1)	N1–C2–N2	117.8(1)
N11–C12–N12	114.7(2)	S1–C2–N1	118.4(1)	N1–C2–N2	116.1(1)	S1–C2–N2	124.7(1)
S22–C23–N24	118.2(2)	N1–C1–C11	115.3(1)	S1–C2–N1	121.2(1)	N2–C3–C4	112.4(1)
S22–C23–N23	126.0(2)	O1–C1–C11	122.3(1)	C3–S2–C4	97.1(1)	S1–C2–N1	117.5(1)
O22–C24–N24	122.7(3)	N1–C2–N2	115.6(1)	C1–N1–C2	126.5(1)	N1–C1–C11	115.4(1)
O22–C24–C231	121.4(3)	N2–C3–C3_a	111.1(1)	O1–C1–N1	122.9(1)	O1–C1–N1	122.5(1)
O11–C11–C111	122.4(2)	C1–C11–C12	123.5(1)	O1–C1–C11	122.0(1)	C1–C11–C12	117.5(1)
O21–C21–C211	120.7(2)	C1–C11–C16	116.6(1)	S1–C2–N2	122. 8(1)	C1–C11–C16	123.7(1)

$P2_1/n$. In compound **1** the bond distances O21–C21 and O11–C11 are 1.230(1) Å and 1.224(1) Å which are consistent with carbonyls,[9] whilst the bond distances of S21–C22 and S11–C12 which are 1.667(1) Å and 1.667(1) Å are typical of thiones.[10] The bond angles of S21–C22–N22 and O11–C11–N11 are 127.6(2)° and 122.4(2)° respectively this confirms that the carbon atoms are sp² hybridized. The bond distances of S1–C2 and O1–C1 in compound **11** are 1.662(1) Å and 1.218(1) Å for a thione and a carbonyl, respectively. The bond distance of C3–C3_a is

1.522(1) Å which is consistent with a carbon-carbon single bond.[11] The bond angles of S1–C2–N2 and S1–C2–N1 are 126.0(1)° and 118.4(1)° confirming that the carbon is sp² hybridized, whilst the bond angle of N2–C3–C3_a which is 111.1(1)° confirms the carbon is sp³ hybridized. In compound **12** the bond distance S1–C2 which was 1.668(1) Å was consistent with a thione, whilst the carbonyl O1–C1 bond legth was 1.225(2) Å. The N2–N2_a bond distance was 1.373(2) Å. The bond angles of O1–C1–N1 and O1–C1–C11 were 122.9(1)° and 122.0(1)°,
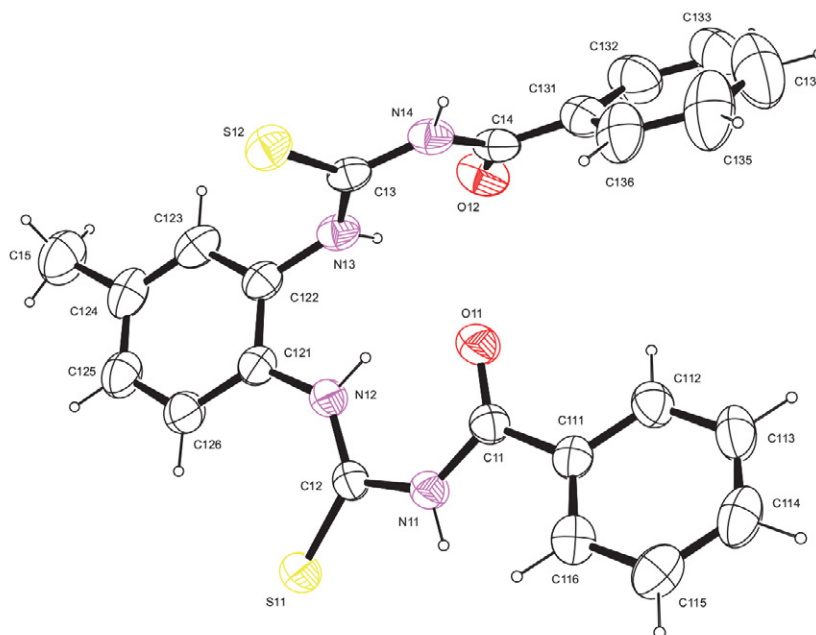

Figure 1. An ORTEP view of 1-benzoyl-3-(5-methyl-2-{[(phenylformamido)methanethioyl]amino}phenyl)thiourea (**1**) showing 50% probability displacement ellipsoids and the atom labelling.
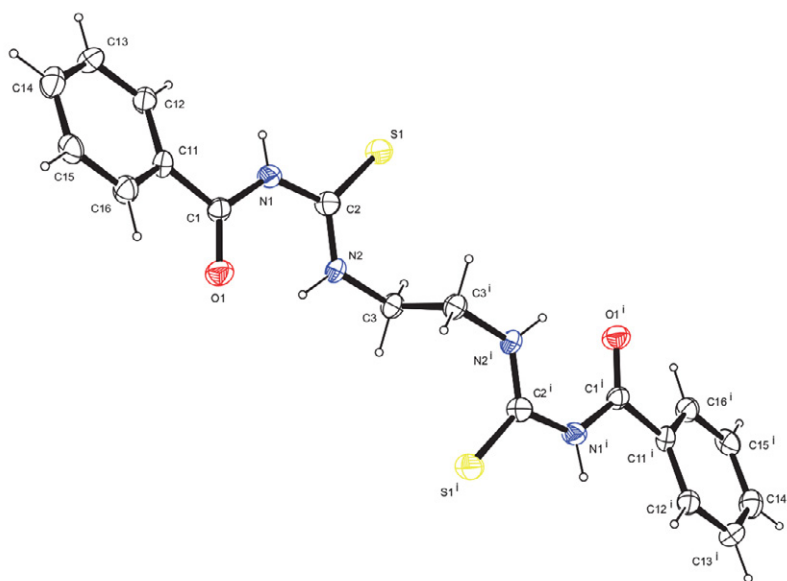

Figure 2. An ORTEP view of 3-benzoyl-1-(2-{[(phenylformamido)methanethioyl]amino}ethyl)thiourea (**11**) showing 50% probability displacement ellipsoids and the atom labelling.

respectively, confirming that the carbon atom involved is sp² hybridized.

In compound **14** the carbonyl O1–C1 bond length was 1.223(2) Å, whilst the thione S1–C2 was 1.673(1) Å. The bond angles of O1–C1–C11, N1–C2–N2 and S1–C2–N2 in compound **14** were 122.1(1)°, 117.8(1)° and 124.7(1)° which is characteristic of sp² hybridized carbon.

The crystal structure of compound **11** was reported at 293 K,[12] but this work gives the crystal structure at 200 K. Both measurements gave a monoclinic space group $P2_1/c$ with two molecules in the unit cell. The cell parameters obtained at 273 K were slightly higher than the measurement at 200 K.

The crystal structure of compound **12** has been reported at 273 K,[13] whilst this work presents the crystal structure at 200 K. Both measurements gave a monoclinic space group $P2_1/n$ with two molecules in the unit cell and each molecule bonded to two molecules of dimethylsulfox-
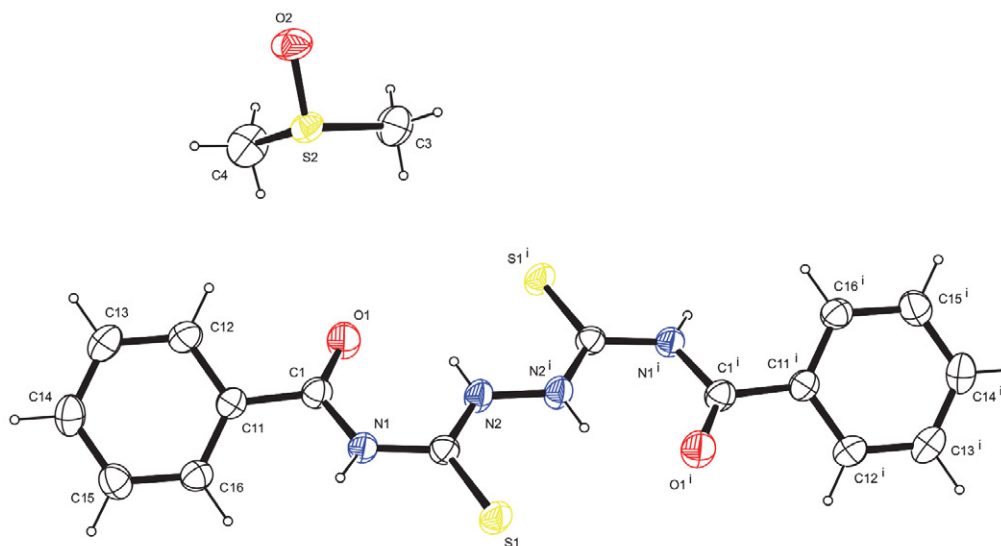

Figure 3. An ORTEP view of 3-benzoyl-1{[(phenylformido)methanethioyl]amino}thiourea dimethyl sulfoxide (**12**) showing 50% probability displacement ellipsoids and the atom labelling.
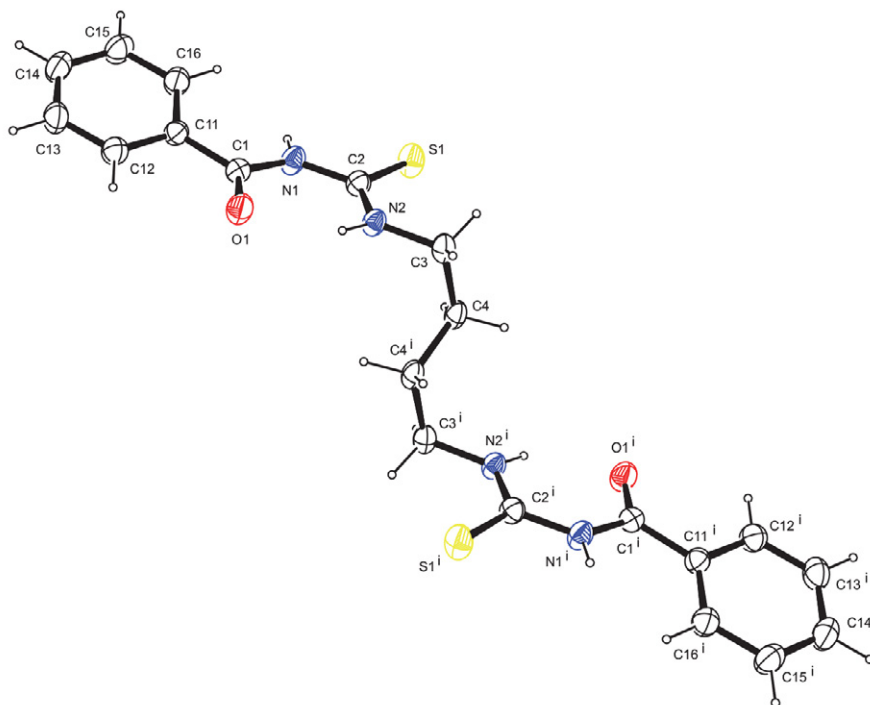

Figure 4. An ORTEP view of 3-benzoyl-1-(4-{[(phenylformamido)methanethioyl]amino}butyl)thiourea (**14**) showing 50% probability displacement ellipsoids and atom labelling.

ide. The cell parameters for the determination at 273 K gave consistently higher values than the measurement at 200 K. The measurement at 273 K gave a lower density (1.347 g cm^{-3}) than the measurement at 200 K (1.380 g cm^{-3})

The crystal structure of compound **14** has been reported at 298 K,[2] whilst this work reports the crystal structure at 200 K. Both measurements gave a monoclinic space group $P2_1/c$ with two molecules in the unit cell. The cell parameters for the determination at 298 K gave consistently higher values than the measurement at 200 K. The measurement at 298 K gave a lower density (1.380 g cm^{-3}) than the measurement at 200 K (1.416 g cm^{-3})

3. Biological Studies

The compounds were tested for their cytotoxicity using Hela cells, and tested against HIV-1 protease with ritonavir as a positive control and *Plasmodium falciparum* strain 3D7 (20 µM) with chloroquine as a positive control. The compounds were also tested for their activity against *Trypanosoma brucei* (20 µM) with pentamidine as a positive control.

Cytotoxicity tests. The graph (Figure 5) and table (Table 4) below give the % HeLa cell viability obtained for each tested compound (**1–12**). Compounds **1** and **12** were found to be cytotoxic against Hela cells whilst all the other compounds were found to be non-cytotoxic.

HIV-1 protease activity. Table 5 and Figure 6 give the HIV-1 screening results for the diamine derivatives of benzoyl isothiocyanate and their *in silico* results. The

Table 4. % HeLa cell viability obtained for the compounds **1–12**.

Compound	% Viability
1	42.48
2	68.62
3	67.55
4	67.67
5	75.44
6	91.16
7	99.55
8	72.61
9	63.29
10	65.97
11	71.01
12	49.73

screening of the compounds **1–14** was completed at 100 µM and 10 µM of inhibitor and ritonavir, respectively. The predicted inhibition constant for compound **1** (4-methyldithiourea) was 0.19 µM whilst the HIV-1 assay gave a % inhibition of 17.69 ± 9.61%, compound **2** (unsubstituted) gave a predicted inhibition constant of 0.13 µM and a percentage inhibition of 10.30 ± 6.12%. For compound **3** (4-nitro derivative) a predicted inhibition constant of 0.47 µM and a percentage inhibition of 31.03 ± 0.42% were obtained whilst compound **5** (3-nitro derivative) gave predicted inhibition constant of 0.11 µM and a percentage inhibition of 32.68 ± 11.03%. Though the predicted inhibition constant of the 3-nitro derivative seems to be better than that of the 4-nitro, the percentage inhibition for both compounds are not too different, due to their interaction with solvent molecules which does not greatly change
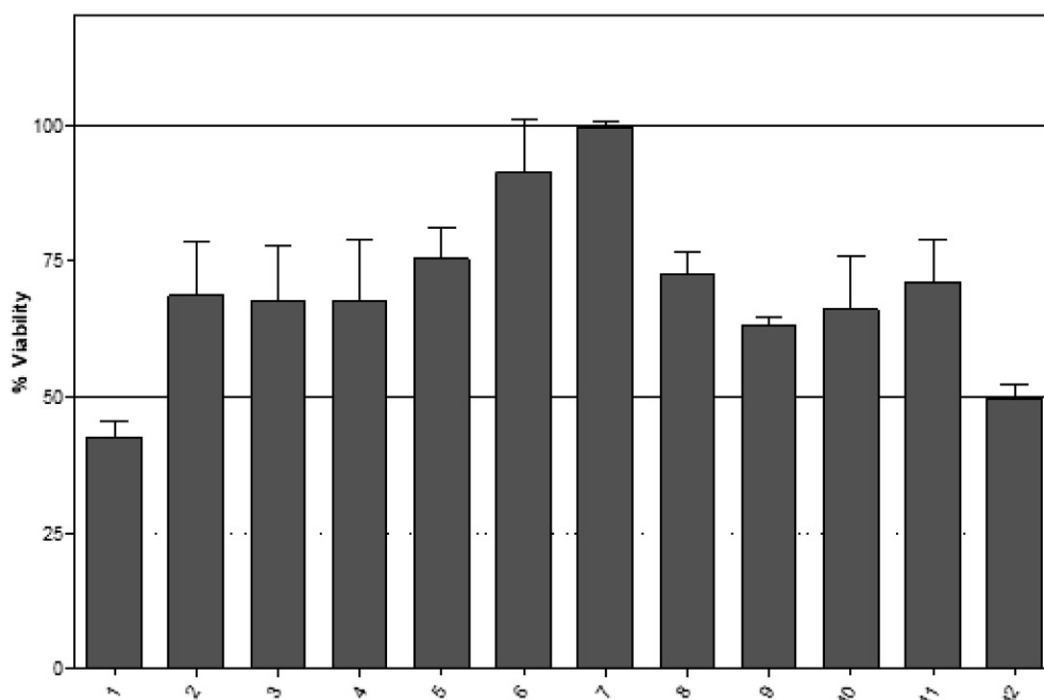

Figure 5. % HeLa cell viability ± SD obtained for compounds **1–12**.

their orientations in the active site. Compounds **4** (4-chloro derivative), **6** (3-methoxy derivative) and **8** (4-methoxy derivative) showed no activity in the HIV-1 protease assay with the predicted inhibition constants of 0.21, 1.90 and 0.81 µM, suggesting that in solution the methoxy substituent on the dithiourea makes the whole molecule inactive against HIV-1 protease at a concentration of 100 µM whilst a chloro substitution at position 4 makes the molecule ineffective at inhibiting HIV-1 protease because the chloro group interacts with the surrounding groups that interfere with its ability to fit well into the active site for effective inhibition of the protease. When the chloro group is attached at position 3, such as in compound **9** (3-chloro derivative), it gave a predicted inhibition constant of 0.06 µM which was the best predicted inhibition constant from the set and a percentage inhibition of 1.78 ± 11% confirming that the chloro group undergoes too much interaction with polar groups in solution hence the substantial departure from the predicted inhibition. Compound **7** (4-bromo derivative) gave predicted inhibition constant of 0.12 µM and a percentage inhibition of 29.62 ± 4.10% whilst compound **10** (3-bromo derivative) gave predicted inhibition constant of 0.095 µM and a percentage inhibition of 97.03 ± 0.37%. Compound **10** gave the best percentage inhibition of all the compounds. In these class of compounds, a bromo substituent at position 3 gives the best percentage inhibition among this class of compounds. The size of the bromo group allows the substituent to fit the active site for effective binding to the aspartate groups and the bridging water molecules in the active site. The other diamine derivatives gave lower predicted inhibition constants than those with the phenyl backbone. In the computation, the lack of rigidity in these molecules accounts for their lower predicted inhibition constants even though their protease
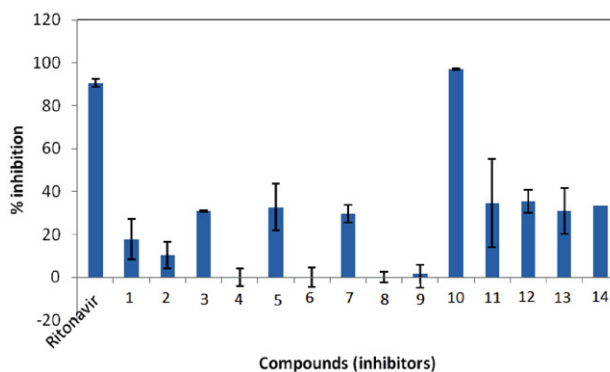

Figure 6. HIV-1 protease screening results illustrating percentage inhibition of selected diamine derivatives of benzoyl isothiocyanate (100 µM) and ritonavir (10 µM) relative to untreated control. Error bars represent standard deviation of *n* = 3.

% inhibition is comparable to the *ortho*-phenylenediamine derivatives. Compound **11** (ethanediamine derivative) gave predicted inhibition constant of 19.98 µM and a percentage inhibition of 34.53 ± 20.69%. Compound **12** (hydrazine derivative) gave predicted inhibition constant of 10.98 µM and a percentage inhibition of 35.49 ± 5.24%. Compound **13** (phenylhydrazine derivative) gave predicted inhibition constant of 0.25 µM and a percentage inhibition of 30.80 ± 10.61%. Compound **14** (butyldiamine derivative) gave predicted inhibition constant of 10.98 µM and a percentage inhibition of 33.18 ± 0.16%.

Figure 7 gives the 2D representation of compound **10** in the protease active site. The presence of a polar group on this class of compounds improves the extent of interaction at the active site both in the docking studies and the bioassays making this class of compounds active against the protease.

Table 5. HIV-1 protease screening results of the screened **1–14** diamine derivatives of benzoyl isothiocyanate.

| Compound	Fluorescence	% Activity relative to untreated control	% Inhibition relative to untreated control	*In silico* results K_i (µM)
Ritonavir	36.24	9.34	90.66 ± 1.88	Unsuccessful
1	186.01	82.31	17.69 ± 9.61	0.19
2	202.70	89.70	10.30 ± 6.12	0.13
3	155.85	68.97	31.03 ± 0.42	0.47
4	402.60	103.79	0 ± 4.10	0.21
5	152.13	67.32	32.68 ± 11.03	0.11
6	243.51	107.76	0 ± 4.60	1.90
7	159.05	70.38	29.62 ± 4.10	0.12
8	446.80	115.18	0 ± 2.43	0.81
9	381.00	98.22	1.78 ± 11	0.06
10	11.522	2.97	97.03 ± 0.37	0.095
11	147.94	65.4	34.53 ± 20.69	19.98
12	145.79	64.52	35.49 ± 5.24	10.98
13	268.44	69.20	30.80 ± 10.61	0.25
14	151.00	66.82	33.18 ± 0.16	1.34
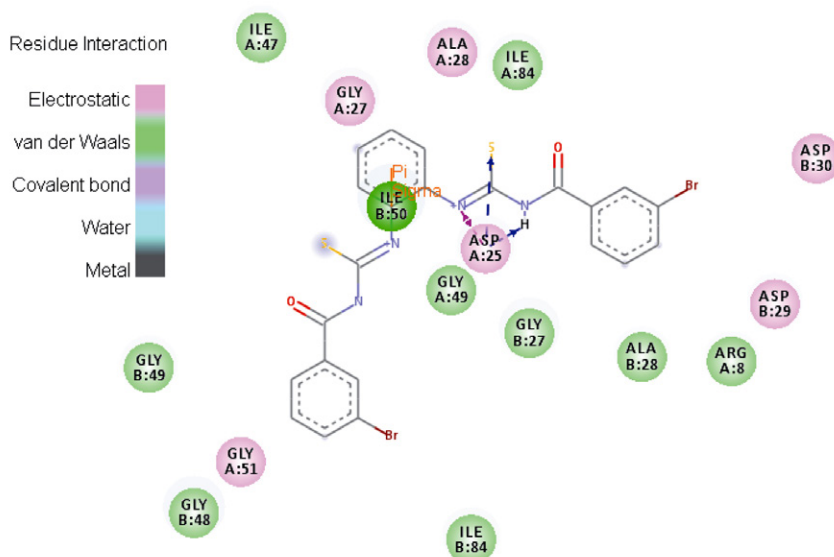
Figure 7. 2D representation of 1-(3-bromobenzoyl)-3-[2-({[(3-bromophenyl)formamido]methanethioyl}amino)phenyl]thiourea (**10**) in the HIV-1 protease binding site.

Anti-malaria test. The bar graph (Figure 8) and table (Table 6) below show the percentage parasite (*Plasmodium falciparum* strain 3D7) viability ± SD obtained after a 48 h incubation with 20 μM of the individual compounds **1–12**. The anti-malaria test showed varying degrees of activity, with compound **6** giving the best percentage viability of 57.2 ± 1.3, whilst compound **11** was the least active with a percentage viability of 98.0 ± 13.4. Chloroquine was used as the standard in the antimalarial test.

Trypanosoma brucei **activity.** The graph (Figure 9) and table (Table 7) below show the residual percentage parasite (*Trypanosoma brucei*) viability obtained after a 48 h incubation with 20 μM of the individual compounds **1–12**. Compounds **10** and **12** gave very good activity with percentage viability of 17.9 ± 5.6% and 11.2 ± 0.9%, re-

Table 6. Percentage parasite *(Plasmodium falciparum* strain 3D7) viability ± SD obtained for the compounds **1–12**.

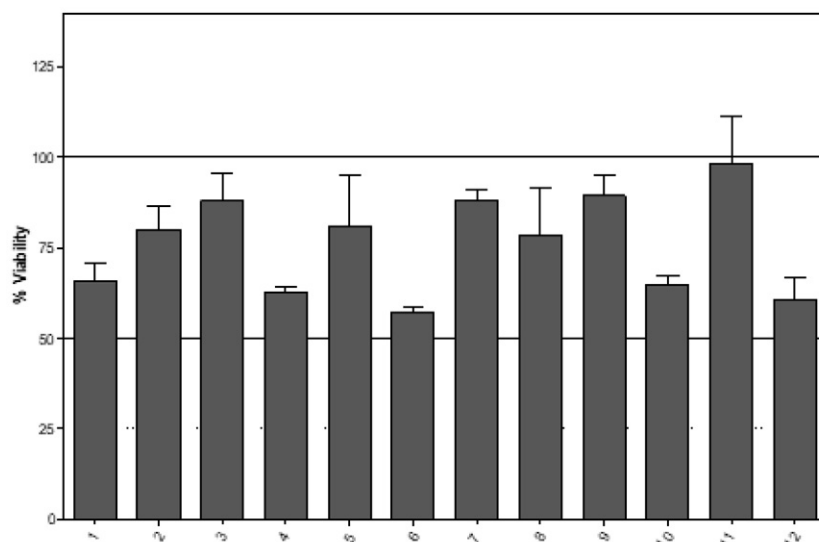| Compound	Viability %
1	65.9 ± 5.0
2	80.0 ± 6.5
3	87.8 ± 7.9
4	62.6 ± 1.8
5	80.9 ± 14.2
6	57.2 ± 1.3
7	88.1 ± 3.1
8	78.2 ± 13.2
9	89.2 ± 5.9
10	64.9 ± 2.2
11	98.0 ± 13.4
12	60.6 ± 6.3

Figure 8. Percentage parasite *(Plasmodium falciparum* strain 3D7) viability ± SD obtained for compounds **1–12**.
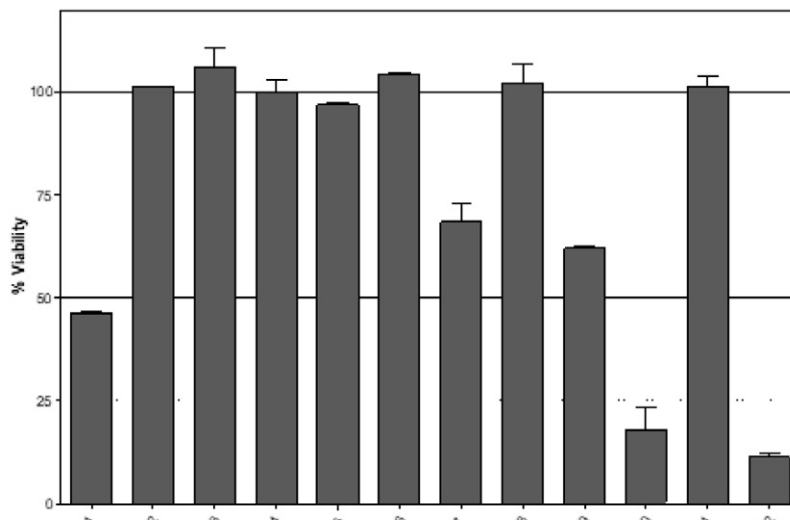
Figure 9. The residual percentage parasite (*Trypanosoma brucei*) viability ± SD obtained for compounds **1**–**12**.

spectively whilst the least active was compound **3** with a percentage viability 106.1 ± 4.5%. Pentamidine was used as the standard.

Table 7. Percentage parasite (*Trypanosoma brucei*) viability ± SD obtained for the compounds **1**–**12**.

Compound at 20 µM	Viability %
1	46.4 ± 0.4
2	101.2 ± 0.1
3	106.1 ± 4.5
4	100.1 ± 3.0
5	96.9 ± 0.5
6	104.2 ± 0.5
7	68.4 ± 4.3
8	102.2 ± 4.7
9	62.0 ± 0.6
10	17.9 ± 5.6
11	101.3 ± 2.7
12	11.2 ± 0.9

4. Experimental

Chemicals and instrumentation. Analytical grade reagents and solvents for synthesis and analysis which included 3-chlorobenzoyl chloride, 4-chlorobenzoyl chloride, 4-methoxybenzoyl chloride, 3-methoxybenzoyl chloride, 3-bromobenzoyl chloride, 4-bromobenzoyl chloride, 4-nitrobenzoyl chloride, 3-nitrobenzoyl chloride, *ortho*-phenylenediamine, 4-methyl-*ortho*-phenylenediamine, 2-(2-aminophenyl)benzimidazole ethylene diamine, hydrazine hydrate and ammonium thiocyanate were obtained from Sigma Aldrich (USA), whilst benzoyl chloride, toluene and acetone were obtained from Merck Chemicals (SA). The chemicals were used as received (*i.e.* without further purification). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AV 400 MHz spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C, using deuterated dimethyl sulfoxide as the solvent and tetramethylsilane as the internal standard. Chemical shifts are expressed in ppm. Structural assignments of resonances have been performed with the help of 2D NMR gradient experiments (^{1}H–^{1}H COSY). FT-IR spectra were recorded on a Bruker Platinum ATR Spectrophotometer Tensor 27 and the data were processed using OPUS. Elemental analyses were performed using a Vario Elementar Microcube ELIII. Melting points were obtained using a Stuart Lasec SMP30 melting point apparatus and are reported uncorrected, whilst the mass spectra were determined using an Agilent 7890A GC System connected to a 5975C VL-MSC with electron impact as the ionization mode and detection by a triple-axis detector.

General method for the synthesis of dithiourea derivatives. The dithiourea derivatives were prepared by dissolving ammonium thiocyanate (0.04 mol, 3.05 g) in 80 mL of acetone, the respective benzoyl chloride (0.04 mol) was then added and heated under reflux at 100–120 °C for 2 h. The benzoyl isothiocyanate derivative (0.04 mol) obtained was filtered, 4-methyl-*ortho*-phenylenediamine, *ortho*-phenylenediamine, ethylenediamine or hydrazine hydrate (0.04 mol) was added to the filtrate and refluxed at 100–120 °C for 3 h.

1-Benzoyl-3-(5-methyl-2-{[(phenylformamido)methanethioyl]amino}phenyl)thiourea (1). The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a brown solid. M.p. 172–173 °C. Yield 78.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H, NH), 12.41 (s, 1H, NH), 11.72 (d, 2H, *J* = 8.0 Hz, NH), 7.90 (d, 4H, *J* = 8.0 Hz), 7.77 (m, 1H, *J* = 8.4 Hz), 7.73 (s, 1H), 7.64 (t, 2H, *J* = 7.2 Hz), 7.49 (t, 4H, *J* = 7.6 Hz), 7.22 (d, 1H, *J* = 8.0 Hz), 2.31 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.40 (C=S), 168.3 (C=O), 136.8 (C), 133.2 (C), 133.1 (C), 130.9

(CH), 128.5 (CH), 128.3 (CH), 127.7 (CH), 126.9 (CH), 126.5 (CH), 20.7 (CH$_3$). IR ν_{max} 3186 (N–H), 2981 (C–H), 1670 (C=S), 1593 (C=O), 1512 (C=C), 1487 (C–N) cm^{-1}. Anal. calcd. for C$_{23}$H$_{20}$N$_4$O$_2$S$_2$: C 61.59; H, 4.49; N, 12.49; S, 14.30. Found: C 61.65; H, 4.54; N, 12.56; S, 14.46. LRMS (*m/z*, M+) found for C$_{23}$H$_{20}$N$_4$O$_2$S$_2$: 448.40, expected mass: 448.56.

1-Benzoyl-3-(2-{[(phenylformamido)methanethioyl] amino}phenyl)thiourea (2). The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a light brown solid. M.p. 174–176 °C. Yield 78.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (s, 1H), 8.10 (d, 2H), 7.94 (d, 2H), 7.71 (m, 2H), 7.65 (m, 4H), 7.48 (m, 2H), 7.42 (m, 2H), 7.11 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3 (C=O), 166.4 (C=O), 144.2 (C), 131.8 (C), 130.7 (CH), 129.2 (CH), 128.8 (CH), 128.5 (CH), 124.4(CH) 113.5 (CH). IR ν_{max} 3327 (N–H), 3262 (N–H), 3134 (N–H), 1673 (C=S), 1643 (C=O), 1596 (C=C), 1514 (C=C), 1486 (C-N), 1337 cm^{-1}. Anal. calcd. for C$_{22}$H$_{18}$N$_2$O$_2$S$_2$: C, 60.81; H, 4.18; N, 12.89; S, 14.76. Found: C, 60.56; H, 4.28; N, 12.78; S, 14.52. LRMS (*m/z*, M+) found for C$_{22}$H$_{18}$N$_4$O$_2$S$_2$: 434.45, expected mass: 434.53.

1-(4-Nitrobenzoyl)-3-[2-({[(4-nitrophenyl)formamido] methanthioyl]amino}phenyl]thiourea (3). The mother liquor was allowed to stand overnight in a fume hood. The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a yellow solid. M.p. 202–204 °C Yield 74.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 2H, NH), 12.13 (s, 2H, NH), 833 (d, 4H, *J* = 8.0 Hz), 8.09 (d, 4H, *J* = 8.0 Hz), 7.93 (m, 2H), 7.42 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.1 (C=S), 161.0 (C=O), 149.7 (C), 138.1 (C), 133.3 (C), 130.20 (CH), 127.3 (CH), 126.8 (CH), 123.2 (CH). IR ν_{max} 3200 (N–H), 3071 (N–H), 1683 (C=S), 1662 (C=O), 1508 (C=C), 1484 (C–N) cm^{-1}. Anal. calcd. for C$_{22}$H$_{16}$N$_6$O$_6$S$_2$: C, 50.38; H, 3.07; N, 16.02; S, 12.23. Found: C, 50.49; H, 3.11; N, 16.17; S, 12.36. LRMS (*m/z*, M+) found for C$_{22}$H$_{16}$N$_6$O$_6$S$_2$: 524.20, expected mass: 524.53.

1-(4-Chlorobenzoyl)-3-[2-({[(4-chlorophenyl)forma-mido]methanethioyl}amino)phenyl thiourea (4). The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a yellow solid. M.p. 173–175 °C. Yield 70.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (m, 2H), 7.93 (d, 2H, *J* = 7.6 Hz), 7.89 (d, 2H, *J* = 7.6 Hz), 7.81 (br, 2H), 7.65 (br, 2H), 7.55 (t, 2H, *J* = 8.0 Hz), 7.50 (t, 2H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.8 (C), 132.1 (CH), 125.9 (CH), 124.0 (CH), 119.6 (CH). IR ν_{max} 3038 (N–H), 1640 (C=O), 1578 (C=C), 1555 (C=C), 1476 (C–N), 1447 (C–N) cm^{-1}. Anal. calcd. for C$_{22}$H$_{16}$Cl$_2$N$_4$O$_2$S$_2$: C, 52.49; H, 3.20; N, 11.13; S, 12.74. Found: C, 52.56; H, 3.26; N, 11.22; S, 12.85. LRMS (*m/z*, M+) found for C$_{22}$H$_{16}$Cl$_2$N$_4$O$_2$S$_2$: 503.20, expected mass: 503.42.

1-(3-Nitrobenzoyl)-3-[2-({[(3-nitrophenyl)formamido] methane}amino)phenyl] thourea (5). The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a yellow solid. M.p. 201–203 °C. Yield 73.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 2H, NH), 12.18 (s, 2H, NH), 8.65 (s, 2H), 8.48 (d, 2H, *J* = 8.0 Hz), 8.31 (d, 2H, *J* = 8.0 Hz), 7.96 (m, 2H), 7.78 (dd, 2H, *J* = 8 Hz), 7.44 (t, 2H, *J* = 4.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.2 (C=S), 166.4 (C=O), 147.3 (C), 135.1 (C), 133.7 (C), 133.3 (CH), 130.1 (CH), 127.4 (CH), 127.2 (CH), 126.6 (CH), 123.5 (CH). IR ν_{max} 3351 (N–H), 3204 (N–H), 1687 (C=O), 1515 (C=C) cm^{-1}. Anal. calcd. for C$_{22}$H$_{16}$N$_6$O$_6$S: C, 50.38; H, 3.07; N, 16.02; S, 12.23. Found: C, 50.24; H, 3.20; N, 16.18; S, 12.19. LRMS (*m/z*, M$^+$) found for C$_{22}$H$_{16}$N$_6$O$_6$S: 524.60, expected mass: 524.53.

1-(3-Methoxybenzoyl)-3-[2-({[(3-methoxyphenyl)for-mamido]methanethioyl}amino)phenyl] thiourea (6). The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a white solid. M.p. 164–166 °C. Yield 76.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 2H), 11.69 (s, 2H), 7.92 (m, 2H), 7.50 (d, 2H, *J* = 7.6 Hz), 7.45 (s, 2H), 7.41 (t, 4H, *J* = 8 Hz), 7.21 (d, 2H, *J* = 8.8 Hz), 3.77 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.4 (C=S), 168.1 (C=O), 159.0 (C), 133.4 (C), 129.8 (C), 127.1 (CH), 126.6 (CH), 120.8 (CH), 119.3 (CH), 113.3 (CH), 55.5 (CH$_3$). IR ν_{max} 3326 (N–H), 3184 (N–H), 3003 (N–H), 1663 (C=O), 1597 (C=C), 1506 (C=C), 1464 (C–N) cm^{-1}. Anal. calcd. for C$_{24}$H$_{22}$N$_4$O$_4$S$_2$: C, 58.28; H, 4.48; N, 11.33; S, 12.97. Found: C, 58.12; H, 4.29; N, 11.42; S, 12.86. LRMS (*m/z*, M$^+$) found for C$_{24}$H$_{22}$N$_4$O$_4$S$_2$: 494.35, expected mass: 494.59.

1-(4-Bromobenzoyl)-3-[2-({[(4-bromophenyl)forma-mido]methanethioyl}amino)phenyl] thiourea (7). The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a white solid. M.p. 205–207 °C. Yield 72.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 2H), 11.82 (s, 2H), 7.91 (m, 2H), 7.81 (d, 4H, *J* = 8.0 Hz), 7.73 (d, 4H, *J* = 7.6 Hz), 7.40 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.5 (C=S), 167.4 (C=O), 133.6 (C), 131.4 (CH) 131.2 (C), 130.6 (CH), 127.2 (CH), 127.1 (C), 126.7 (CH). IR ν_{max} 3140 (N–H), 2993 (C–H), 1681 (C=O), 1585 (C=C), 1517 (C=C), 1429 (C–N) cm^{-1}. Anal. calcd. for C$_{22}$H$_{16}$Br$_2$N$_4$O$_2$S$_2$: C, 44.61; H, 2.72; N, 9.46; S, 10.83. Found: C, 44.70; H, 2.65; N, 9.40; S, 10.76. LRMS (*m/z*, M$^+$) found for C$_{22}$H$_{16}$Br$_2$N$_4$O$_2$S$_2$: 592.20, expected mass: 592.33.

1-(4-Methoxybenzoyl)-3-[2-({[(4-methoxylphenyl)for-mamido]methanethioyl}amino)phenyl] thiourea (8). The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a white solid. M.p. 206–208 °C. Yield 77.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 2H, NH), 11.48 (s, 2H, NH), 7.92 (m, 6H), 7.38 (m, 2H, *J* = 3.6, 5.6 Hz), 7.01 (d, 4H, *J* = 8.8 Hz), 3.82 (s, 6H). ^{13}C NMR

(100 MHz, DMSO-d_6) δ 180.8 (C=S), 167.5 (C=O), 163.2 (C), 133.3 (C), 131.0 (CH), 126.9 (CH), 123.9 (CH), 113.71 (CH), 55.8 (CH$_3$). IR ν$_{max}$ 3404 (N–H), 3278 (N–H), 3001 (N–H), 2961 (C–H), 2837 (C–H), 1653 (C=O), 1594 (C=C), 1525 (C=C), 1489 (C–N) cm^{-1}. Anal. calcd. for C$_{24}$H$_{22}$N$_4$O$_4$S$_2$: C, 58.26; H, 4.48; N, 11.33; S, 12.97. Found: C, 58.13; H, 4.37; N, 11.29; S, 13.03. LRMS (*m/z*, M$^+$) found for C$_{24}$H$_{22}$N$_4$O$_4$S$_2$: 494.20, expected mass: 494.59.

1-(3-Chlorobenzoyl)-3-[2-({[(3-chlorophenyl)formamido]methanethioyl}amino)phenyl] thiourea (9). The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a light brown solid. M.p. 143–145 °C. Yield 75.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (br, 2H), 11.88 (s, 2H, NH), 8.04 (m, 1H), 7.91 (d, 3H, *J* = 12.8 Hz), 7.83 (d, 2H, *J* = 7.6 Hz), 7.70 (d, 2H, *J* = 8.0 Hz), 7.52 (m, 2H, *J* = 8.0, 7.2 Hz), 7.41 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.4 (C=S), 167.0 (C=O), 134.3 (C), 133.2 (C), 132.8 (CH), 130.5 (CH), 128.5 (CH), 127.3 (CH), 127.1 (CH), 126.7 (CH). IR ν$_{max}$ 3440 (N–H), 3166 (N–H), 2971 (C–H), 1668 (C=O), 1593 (C=C), 1510 (C=C), 1471 (C–N), 1459 (C–N) cm^{-1}. Anal. calcd. for C$_{22}$H$_{16}$Cl$_2$N$_4$O$_2$S$_2$: C, 52.49; H, 3.20; N, 11.13; S, 12.74. Found: C, 52.31; H, 3.29; N, 11.22; S, 12.86. LRMS (*m/z*, M$^+$) found for C$_{22}$H$_{16}$Cl$_2$N$_4$O$_2$S$_2$: 503.35, expected mass: 503.42.

1-(3-Bromobenzoyl)-3-[2-({[(3-bromophenyl)formamido]methanethioyl}amino)phenyl] thiourea (10). The mother liquor was allowed to stand overnight in a fume hood. The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a light yellow solid. M.p. 191–193 °C. Yield 80.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 2H), 11.75 (s, 2H), 7.93 (s, 2H), 7.89 (m, 2H), 7.79 (d, 4H, *J* = 7.6 Hz), 7.44 (d, 2H, *J* = 8 Hz), 7.41 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.65 (C=S), 167.74 (C=O), 136.3 (C), 134.5 (CH), 133.8 (C), 131.5 (CH), 131.2 (CH), 127.9 (CH), 126.9 (CH), 122.1 (CH). IR ν$_{max}$ 3389 (N–H), 3176 (N–H), 3016 (N–H), 1662 (C=O), 1595 (C=C), 1563 (C=C), 1456 (C–N) cm^{-1}. Anal. calcd. for C$_{22}$H$_{16}$Br$_2$N$_4$O$_2$S$_2$: C, 44.61; H, 2.72; N, 9.46; S, 10.83. Found: C, 44.75; H, 2.68; N, 9.39; S, 10.70. LRMS (*m/z*, M$^+$) found for C$_{22}$H$_{16}$Br$_2$N$_4$O$_2$S$_2$: 592.10, expected mass: 592.33.

3-Benzoyl-1-(2-{[(phenylformamido)methanethioyl]amino}ethyl)thiourea (11). The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a light brown solid. M.p. 220–222 °C. Yield 70.85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 2H), 7.91 (d, 4H, *J* = 7.6 Hz), 7.61 (t, 2H, *J* = 7.2 Hz), 7.51 (t, 4H, *J* = 7.6 Hz), 3.09 (s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.8 (C=S), 167.3 (C=O), 132.9 (C), 132.2 (CH), 128.5 (CH) 43.4 (CH$_2$). IR ν$_{max}$ 3420 (N–H), 3229(N–H), 3047 (N–H), 1664 (C=O), 1579 (C=C), 1507 (C=C), 1448 (C–N) cm^{-1}. Anal. calcd. for C$_{18}$H$_{18}$N$_4$O$_2$S$_2$: C, 55.94; H, 4.69; N, 14.50;

S, 16.59. Found: C, 56.03; H, 4.74; N, 14.42; S, 16.63. LRMS (*m/z*, M$^+$) found for C$_{18}$H$_{18}$N$_4$O$_2$S$_2$: 386.30, expected mass: 386.49.

3-Benzoyl-1{[(phenylformido)methanethioyl]amino}thiourea (12). The product obtained was filtered and recrystallized from DMSO/toluene (1:1) as a white solid. M.p. 345–346 °C. Yield 71.8%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.24 (s, 1H, NH), 12.12 (s, 1H, NH), 8.13 (d, 2H, *J* = 8.0 Hz), 8.01 (d, 2H, *J* = 8.0 Hz), 7. 94 (d, 1H, *J* = 8.0 Hz), 7.65 (m, 1H), 7.55 (t, 3H, *J* = 8.0 Hz), 7.50 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.5 (C=O), 168.3 (C=S), 167.3 (C=O), 165.0 (C=O), 156.0 (C), 150.2 (C), 134.2 (CH), 132.8 (CH), 131.6 (CH), 131.2 (CH), 130.7 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 125.4 (CH). IR ν$_{max}$ 2988 (C–H), 2911 (C–H), 1670 (C=O), 1658 (C=O), 1536 (C=C), 1489 (C–N), 1424 (C–N) cm^{-1}. Anal. calcd. for C$_{16}$H$_{14}$N$_4$O$_2$S$_2$: C, 53.61; H, 3.94; N, 15.63; S, 17.89. Found: C, 53.73; H, 4.02; N, 15.60; S, 17.78. LRMS (*m/z*, M$^+$) found for C$_{16}$H$_{14}$N$_4$O$_2$S$_2$: 358.36, expected mass: 358.44.

3-Benzoyl-1-(phenylamino)thiourea (13). The product recrystallized from DMSO/toluene (1:1) as a white solid. M.p. 242–244 °C. Yield 71.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (m, 2H), 7.44 (m, 2H), 7.37 (m, 5H), 7.34 (s, 1H), 7.19 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.9 (C=O), 149.6 (C), 136.8 (C), 129.9 (CH), 129.4 (CH), 129.3 (CH), 128.7 (CH), 126.6 (CH), 125.1 (CH). IR ν$_{max}$ 3070 (N–H), 3018 (N–H), 2727 (C–H), 1591 (C=O), 1561 (C=O), 1499 (C–N), 1475 (C–N) cm^{-1}. Anal. calcd. for C$_{14}$H$_{13}$N$_3$OS: C, 62.31; H, 5.19; N, 14.42; S, 13.86. Found: C, 62.31; H, 5.19; N, 14.42; S, 13.86. LRMS (*m/z*, M$^+$) found for C$_{14}$H$_{13}$N$_3$OS: 271.80, expected mass: 271.97.

3-Benzoyl-1-(4-{[(phenylformamido)methanethioyl]amino}butyl)thiourea (14). The product was filtered and recrystallized from DMSO/toluene (1:1) as a light brown solid. M.p. 159–161 °C. Yield 80.8%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.24 (s, 1H, NH), 10.94 (br, 1H, NH), 7.90 (d, 2H, *J* = 8.0 Hz,), 7.62 (t, 1H, *J* = 7.2, 7.6 Hz), 7.48 (t, 2H, *J* = 7.6 Hz), 3.76 (m, 4H), 2.51, (br, 2H, NH), 2.06 (t, 2H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.2 (C=S), 167.7 (C=O), 132.9 (C), 132.2 (CH), 128.4 (CH), 128.3 (CH), 42.6 (CH$_2$), 26.7 (CH$_2$). IR ν$_{max}$ 3405 (N–H), 3217 (N–H), 2929 (C–H), 1666 (C=O), 1511 (C=C), 1432 (C–N) cm^{-1}. Anal. calcd. for C$_{20}$H$_{22}$N$_4$O$_2$S$_2$: C, 57.95; H, 5.35; N, 13.32; S, 15.47. Found: C, 57.87; H, 5.42; N, 13.45; S, 15.36. LRMS (*m/z*, M$^+$) found for C$_{20}$H$_{22}$N$_2$O$_2$S$_2$: 414.70. Expected mass: 414.54.

X-ray crystal structure determination. X-ray diffraction analyses of **1**, **11**, **12** and **14** were performed at 200 K using a Bruker Kappa Apex II diffractometer with monochromated Mo Kα radiation (λ = 0.71073 Å). APEXII[14] was

used for data collection and[15] for cell refinement and data reduction. The structures were solved by direct methods using SHELXS-2013,[14] and refined by least-squares procedures using SHELXL-2013,[15] with SHELXLE,[14] as a graphical interface. All non-hydrogen atoms were refined anisotropically. Carbon-bound H atoms were placed in calculated positions (C–H 0.95 Å for aromatic carbon atoms and C–H 0.99 Å for methylene groups) and were included in the refinement in the riding model approximation, with U_{iso}(H) set to $1.2U_{eq}$(C). The H atoms of the methyl groups were allowed to rotate with a fixed angle around the C–C bond to best fit the experimental electron density (HFIX 137 in the SHELX program suite[15]) with U_{iso}(H) set to $1.5U_{eq}$(C). Nitrogen-bound H atoms were located on a difference Fourier map and refined freely. Data were corrected for absorption effects using the numerical method implemented in SADABS.[16]

5. Conclusions

The work involved the design and synthesis of dithiourea derivatives for HIV-1 protease inhibitors using Autodock 4.2, the compounds were characterized by spectroscopic techniques and microanalysis. 1-(3-Bromobenzoyl)-3-[2-({[(3-bromophenyl)formamido]methanethioyl} amino)phenyl]thiourea (**10**) and 3-benzoyl-1-{[(phenylformido)methanethioyl]amino}thiourea (**12**) gave a percentage viability of 17.9 ± 5.6% and 11.2 ± 0.9% against *Trypanosoma brucei*. The single crystal X-ray diffraction analysis of 1-benzoyl-3-(5-methyl-2-{[(phenylformamido)methanethioyl]amino}phenyl)thiourea (**1**), 3-benzoyl-1-(2-{[(phenylformamido)methanethioyl]amino}ethyl)thiourea (**11**), 3-benzoyl-1{[(phenylformido)methanethioyl]amino} thiourea (**12**) and 3-benzoyl-1-(4-{[(phenylformamido) methanethioyl]amino}butyl)thiourea (**14**) have been presented. 1-(3-Bromobenzoyl)-3-[2-({[(3-bromophenyl)formamido]methanethioyl}amino)phenyl]thiourea (**10**) gave a percentage inhibition of 97.03 ± 0.37% against HIV-1 protease enzyme at a concentration of 100 μM.

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Supplementary Information

Supplementary data associated with this article can be found in the online version. CCDC numbers 1448382, 1919730, 1919731 and 1919732 contain the crystal structures associated with this article.

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Povzetek

Izvedli smo načrtovanje (s pomočjo Autodock 4.2) in sintezo novih ditiosečninskih derivatov kot inhibitorjev HIV-1 proteaze. Nove spojine smo karakterizirali s spektroskopskimi metodami in z mikroanalizo. Spojini 1-(3-bromoben-zoil)-3-[2-({[(3-bromofenil)formamido]metantioil}amino)fenil]tiosečnina (**10**) in 3-ben(**12**) sta dali 17.9 ± 5.6% in 11.2 ± 0.9% sposobnost preživetja za genske difrakcijske analize monokristalov spojin 1-benzoil-3-(5-metil-2-{[(fenil-formamido)metantioil]amino}fenil)tiosečnine (**1**), 3-benzoil-1-(2-{[(fenilformamido)metantioil]amino}etil)tiosoč-nine (**11**), 3-benzoil-1-{[(fenilformamido)metantioil]amino}tiosečnine (**12**) and 3-benzoil-1-(4-{[(fenilformamido) metantioil]amino}butil)tiosečnine (**14**). Za spojino 1-(3-bromobenzoil)-3-[2-({[(3-bromofenil)formamido]metantioil} amino)fenil]tiosečnina (**10**) smo izmerili odstotno inhibicijo 97.03 ± 0.37% proti encimu HIV-1 proteaza pri koncen-traciji 100 μM.