Synthesis, *in vitro* Antiproliferative and Anti-HIV Activity of New Derivatives of 2-Piperazino-1,3-benzo[*d*]thiazoles

Yaseen A. Al-Soud[a], Haitham H. Al-Sa'doni[a], Sadeekah O. W. Saber[a], Reem H. M. Al-Shaneek[a], Najim A. Al-Masoudi[b], R. Loddo[c], and P. La Colla[c]

[a] Department of Chemistry, College of Science, University of Al al-Bayt, Al-Mafraq, Jordan
[b] Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq
[c] Department of Biomedical Sciences and Technologies, University of Cagliari, Cittadella Universitaria, 09042 Monserrato (CA), Italy

Reprint requests to Prof. N. A. Al-Masoudi. E-mail: najim.al-masoudi@gmx.de

Z. Naturforsch. **2010**, *65b,* 1372 – 1380; received May 28, 2010

A series of *N*-{2-oxo-2-[4-(1,3-benzothiazol-2-yl)piperazin-1-yl]}-(het)arenecarboxamides **4a** – **l**, sulfonamide derivatives **8a** – **i** as well as benzothiazole-containing N^1-(2-oxoethyl)-N^1-arylthioureas **9a** – **c** have been synthesized. Compounds **4a** – **l** and **9a** were evaluated, *in vitro*, for their antiproliferative activity against a large panel of human tumor-derived cell lines. Compounds **4l** and **9a** were the most potent analogs in this series, showing remarkable effects on human splenic B-lymphoblastoid cells (WIL-2NS) and human acute B-lymphoblastic leukemia (CCRF-SB) cell lines (**4l**: CC_{50} = 5.1 and 7.3 μM, respectively), and compound **5** against CCRF-SB cell lines with CC_{50} = 2.3 μM. These compounds are leading candidates for further development. Compounds **6** – **7a** – **i** were screened as inhibitors against HIV-1 and HIV-2, and no activity has been witnessed.

Key words: Antiproliferative Activity, Anti-HIV Activity, Benzothiazole, Aryl Isothiocyanate, Amide, Thiourea Derivatives

Introduction

Several benzothiadiazoles have shown selective antiproliferative activity, especially the phenyl-substituted benzothiazoles [1 – 3]. Substituted 2-(4-aminophenyl)benzothiazoles were developed and comprised a novel class of antitumor-active compounds, especially against sensitive breast tumor cell lines, *e. g.*, MCF-7 and MDA 468, and extended to certain colon, lung, melanoma, renal, and ovarian tumor cell lines [4 – 7]. Pyrimidobenzothiazole and benzothiazoloquinoline derivatives [5], imidazobenzothiazoles [8], polymerized benzothiazoles [9, 10] as well as several derivatives of substituted benzothiazoles [11] showed remarkable antitumor activity against malignant cell lines.

Some (arylamino)benzothiazoles, such as 2-(4-amino-3-methylphenyl)-benzothiazole [12, 13], 2-(4-aminophenyl)-benzothiazole [14, 15], the fluoro analog (5F 203) [16 – 19] and 2-(3,4-dimethoxyphenyl)-5-fluoro-benzothiazole (**1**) [20] are considered as potent ligands for the arylhydrocarbon receptor (AhR) which translocates with the drug to cell nuclei (Fig. 1). A further class of benzothiazoles, *e. g.* 4-(benzothiazol-2-yl)-4-hydroxycyclohexa-2,5-dienone [21], have been synthesized and exhibited potent antitumor activity against renal and colon cancer cell lines with prodrug Phortress [22], and human mammary tumor xenografs [23], and is currently under pharmacological investigation in phase I clinical trial in the UK. Yoshida *et al.* [24] have synthesized a highly potent benzothiazole derivative bearing an amido substituent that displays excellent *in vivo* inhibitory effect on tumor growth. Recently, Racane *et al.* [25] have described the synthesis of bis-disubstituted amidinobenzothiazoles as potential anti-HIV agents.

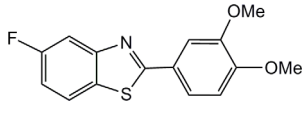
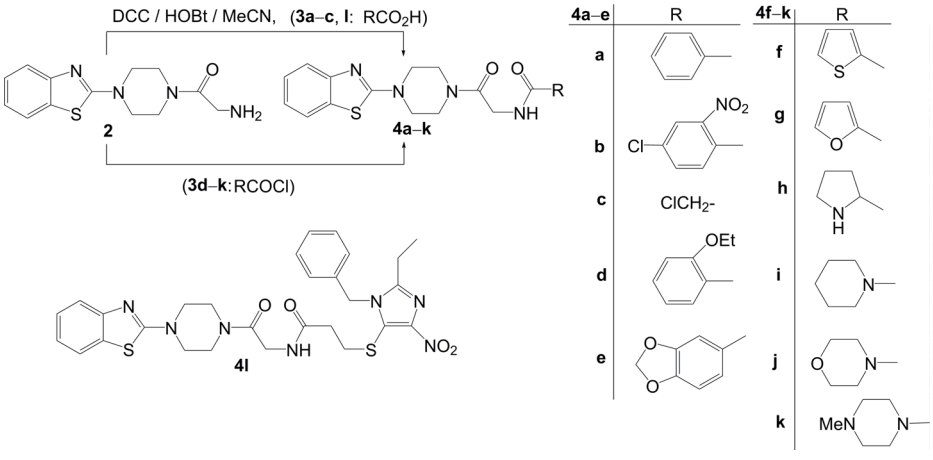


Fig. 1. 2-(3,4-Dimethoxyphenyl)-5-fluoro-1,3-benzothiazole (DMFB, **1**).

In continuation of our research on the synthesis and biological evaluation of benzothiazole analogs [26 – 29], we report here the synthesis and antiproliferative and anti-HIV evaluation of new benzothiazole derivatives bearing 2-(piperazin-1-yl)-2-oxoethyl-benzamide, sulfonamide and thiourea functions.

0932–0776 / 10 / 1100–1372 $ 06.00



Scheme 1.

Results and Discussion

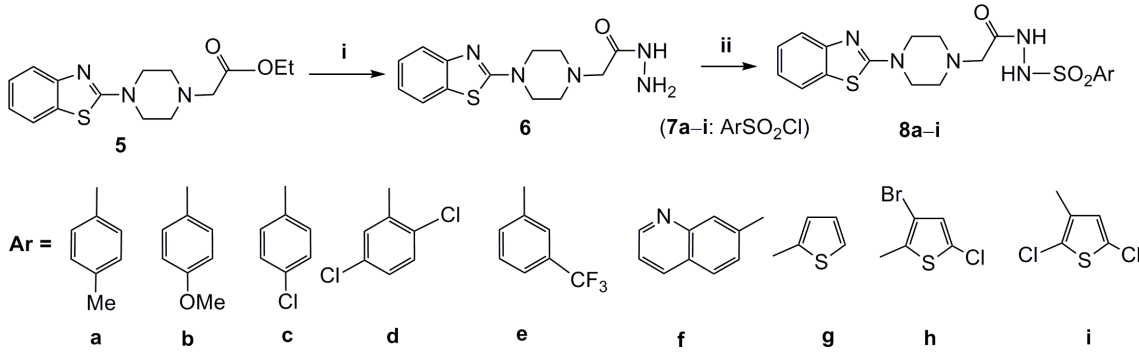
Synthesis

In the present work, amine **2**, prepared previously in our laboratory, has been selected for the synthesis of new potentially active substituted amide derivatives. Two methods have been employed in the preparation of the corresponding amide derivatives from the reaction of **2** with the appropriate carboxylic acid **3a**–**l** (Scheme 1). The first method includes the preparation of amides **4a**–**c**, **l** (23–38 % yield), by treatment of **2** with the benzoic acids **3a**–**c** or 3-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-ylthio)propanoic [30] acid, using 1-hydroxybenzotriazole (HOBt) [31, 32] and *N*,*N*′-dicyclohexylcarbodiimide (DCC)[33] as coupling reagents. The second method proceeded by preparation of the amides **4d**–**k** in 57–90 % yield, from treatment of **2** with the carboxylic acid chlorides **3d**–**k** in the presence of Et_3N.

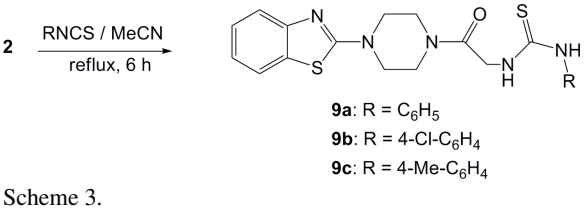
The structures of the newly synthesized compounds **4a**–**k** are in agreement with the ^{1}H NMR, ^{13}C NMR, and mass spectra. In the ^{1}H NMR spectra, the piperazine protons showed a similar pattern in the region δ = 4.10–3.13 ppm for all compounds. The singlets in the region δ = 4.43–3.94 ppm were assigned to CH_2NH protons. The ^{13}C NMR spectra of **4a**–**l** contained similar resonance signals for the piperazine and benzothiazole carbon atoms. CH_2NH carbon signals were observed in the region δ = 41.9–41.0 ppm. Compound **4l** was selected for further NMR studies. In the gradient-selected HMBC spectrum [34] of **4l**, the CH_2NH methylene protons at δ_H = 4.11 ppm showed a $^3J_{C,H}$ coupling to the carbonyl carbon atom ($C_{CH_2CH_2S}$ = O, δ_C = 169.1 ppm) as well as a $^2J_{C,H}$ coupling to the carbonyl carbon atom $C_{Npiperazine}$ =O, (δ_C = 166.0 ppm). Furthermore, the $C_{CH_2CH_2S}$ = O carbon atom showed two couplings: a $^3J_{C,H}$ coupling with the CH_2CH_2S protons at δ_H = 3.20 ppm, and a $^2J_{C,H}$ coupling with the CH_2CH_2S protons at δ_H = 2.55 ppm. C-4 of the imidazole moiety (δ_C = 148.3 ppm) showed a $^3J_{C,H}$ coupling to the CH_2CH_2S protons (δ_H = 3.20 ppm).

Next, our target was the synthesis of *N*-{2-oxo-2-[4-(1,3-benzothiazol-2-yl)piperazin-1-yl]}-(het)arenesulfonamides aiming to evaluate their HIV-inhibiting potential. Thus, the hydrazide **6** was prepared (84 %) by treatment of the ester **5** with hydrazine hydrate. Treatment of **6** with the arenesulfonyl chlorides **7a**–**i** afforded the corresponding sulfonamides **8a**–**i** in 39–96 % yield (Scheme 2).

The structures of **6** and **8a**–**i** were assigned on the basis of their ^{1}H NMR, ^{13}C NMR, and mass spectra. In the former the multiplets at higher field (δ = 8.56–7.04 ppm) were attributed to the aryl protons. The methylene protons of the piperazine moiety appeared as multiplets in the region δ = 3.69–2.42 ppm. The ^{13}C NMR spectra of **6** and **8a**–**i** were fully assigned (*cf.* Experimental Section), while compound **8b** was selected for a detailed ^{13}C NMR analysis. The spectrum showed signals at δ = 169.9–167.9 ppm and δ = 168.5–164.0 ppm which were assigned to C=N and C=O, respectively. The $CO\mathit{CH}_2$ resonances were observed in the region δ = 60.8–59.9 ppm, and the piperazine carbon atoms resonated in the regions δ = 53.3–51.4 ppm and δ = 48.5–47.2 ppm. The aromatic carbon atoms were observed in the region δ = 144.9–114.5 ppm.



Scheme 2. Reagents and conditions: i) EtOH, $NH_2NH_2 \cdot H_2O$, reflux, 8 h; ii) $CHCl_3$, **7a – i**, Et_3N, r. t., 20 – 24 h.



Scheme 3.

Compounds **9a – c**, combining a benzothiazole, a piperazinecarbonyl and a thiourea residue were also prepared. Thus, treatment of **2** with phenyl, 4-chloro- or 4-methylphenyl isothiocyanate afforded the thiourea derivatives **9a – c** in 61, 69, and 59 % yield, respectively (Scheme 3). The assignment of proton and carbon atoms of the benzothiazole and piperazine rings were deduced from comparison with those of **4a – k**. The CH_2NS protons resonated together with the piperazine protons in the region $\delta = 3.49 - 3.31$ ppm as multiplets. In the ^{13}C NMR spectra of **9a – c**, the C=S carbon signals appeared at higher field (δ = 181.3, 181.6, and 180.0 ppm, respectively), while the resonances at δ = 167.5, 167.9, and 167.7 ppm were assigned to $C^2_{benzothiazol}$, respectively. $C_{Npiperazine}$ = O carbons appeared at δ = 164.3, 164.7, and 164.1 ppm, respectively, and $C^4_{benzothiazol}$ carbons resonated at δ = 149.2, 149.0, and 149.1 ppm, respectively. The CH_2NS carbon atoms appeared together with the piperazine carbons in the region $\delta = 48.5 - 43.1$ ppm. The signals of aromatic carbon atoms were assigned.

In vitro antiproliferative activity

Compounds **4a – l** and **9a** were selected for the antiproliferative activity screening and tested *in vitro* against a panel of tumor cell lines consisting of CD4 human T-cells containing integrated leukaemia, human acute T-lymphoblastic leukaemia (CCRF-CEM), and human splenic B-lymphoblastoid cells (WIL-2NS), human acute B-lymphoblastic leukaemia (CCRF-SB), human skin melanoma (SK-MEL-28), human breast adenocarcinoma (MCF-7), human lung squamous carcinoma (SK-MES-1), human hepatocellular carcinoma (Hep-G2), human prostate carcinoma (DU-145), human foreskin fibroblast (CRL7065), and human lung fibroblast (MRC-5). The microculture tetrazolium assay (MTT) method [35] was used for estimation of the *in vitro* tumor-inhibiting activity of the tested compounds. The cell lines of tumor subpanels were incubated within five concentrations (0.01 – 100 mmol L^{-1}) of each tested compound for 48 h. For comparative purposes, we evaluated the cytotoxic activities of the compounds relative to Doxorubicin. The compounds were dissolved in DMSO at 100 mmol L^{-1} and then diluted in culture.

All compounds were inactive except **4l** which showed activity against human splenic B-lymphoblastoid cells (WIL-2NS) and human acute B-lymphoblastic leukemia (CCRF-SB) cell lines with CC_{50} = 5.1 and 7.3 μM, respectively. Compound **9a** exhibited activity against CCRF-SB cell lines with CC_{50} = 2.3 μM. In conclusion, introduction of a thiourea residue in the backbones of **9a** generally enhanced the activity of the benzothiazole derivatives in comparison to the activity of other analogs **4a – l**.

In vitro anti-HIV assay

Compounds **5 – 8a – i** were evaluated for their *in vitro* anti-HIV activity by using the IIIB strain for HIV-1 and the ROD strain for HIV-2 in human T-lymphocyte (MT-4) cells, and the results are sum-

Table 1. *In vitro* anti-HIV-1[a] and HIV-2[b] of some new benzothiazole derivatives.

Compound	Virus strain	EC_{50} ($\mu g\,mL^{-1}$)[c]	CC_{50} ($\mu g\,mL^{-1}$)[d]	SI[e]
5	III_B	> 95.98	95.98	< 1
	ROD	> 95.98	95.98	< 1
6	III_B	> 74.58	74.58	< 1
	ROD	> 74.58	74.58	< 1
8a	III_B	> 53.38	53.38	< 1
	ROD	> 53.38	53.38	< 1
8b	III_B	> 62.45	62.45	< 1
	ROD	> 62.45	62.45	< 1
8c	III_B	> 55.50	55.50	< 1
	ROD	> 55.50	55.50	< 1
8d	III_B	> 58.55	58.55	< 1
	ROD	> 58.55	58.55	< 1
8e	III_B	> 31.85	31.85	< 1
	ROD	> 31.85	31.85	< 1
8f	III_B	> 60.65	60.65	3.5
	ROD	> 60.65	60.65	2.1
8g	III_B	> 113.75	113.75	< 1
	ROD	> 113.75	113.75	< 1
8i	III_B	> 57.28	57.58	< 1
	ROD	> 57.28	57.28	< 1
8h	III_B	> 19.87	> 19.87	< 1
	ROD	> 19.87	19.87	< 1
Nevirapine	III_B	0.050	> 4.00	> 80
	ROD	> 4.00	> 4.00	< 1

[a] Anti-HIV-1 activity measured with strain III_B; [b] anti-HIV-2 activity measured with strain ROD; [c] compound concentration required to achieve 50 % protection of MT-4 cells from the HIV-1 and 2-induced cytopathogenic effect; [d] compound concentration that reduces the viability of mock-infected MT-4 cells by 50 %; [e] SI: selectivity index (CC_{50}/EC_{50}).

marized in Table 1. Cytotoxicity induced by these compounds was also measured in MT-4 cells parallel with the antiviral activity. The results are summarized in Table 1, in which the data for Nevirapine (BOE/BIRG587) [36] are included for comparison purposes. None of the new benthiazoles derivatives were found to inhibit HIV-1 and HIV-2 replication *in vitro* at EC_{50} lower than the CC_{50} in comparison to Nevirapine. In conclusion, the reported data showed no selective anti-HIV activity.

Conclusion

In summary, *in vitro* screening led to the identification of *N*-[2-(4-benzothiazol-2-yl-piperazin-1-yl)-2-oxoethyl]-3-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-ylthio)propanamide (**4l**) and 1-(2-(4-(benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl)-3-phenylthiourea (**9a**) as new antitumor candidates, which are promising agents for further structural modification and pharmacological evaluation.

Experimental Section

General

Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (Büchi Labortechnik AG, Switzerland). Microanalytical data were obtained with a Euro Vector EA 3000 Elemental apparatus. NMR spectra were recorded on 300 MHz (^1H) spectrometers with TMS as internal standard and on 75 MHz (^{13}C) spectrometers (Bruker, Germany) with TMS as internal standard and on the δ scale in ppm. Mass spectra were recorded at 70 eV on EI (Shimadzu QP5050A). Silica gel (0.040 – 0.063 mm) used for column chromatography and analytical silica gel TLC plates 60 F_{254} were purchased from Merck.

*General procedure for the preparation of N-[2-(4-(benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]benzamides **4a – l***

Method A. (Synthesis of **4a – c**, **l**). To a cold solution of **2** (400 mg, 1.50 mmol) in dry MeCN (25 mL) was added the appropriate carboxylic acid **3a – c**, **l** (1.50 mmol) followed by the addition of HOBt (1.50 mmol) and DCC (1.50 mmol). The mixture was stirred at 0 °C for 1 h, at 5 °C for 1 h, and then at 23 °C for 16 h. The mixture was filtered to remove DCU, and the filtrate was evaporated to dryness. The residue was partitioned successively between EtOAc and 5 % $NaHCO_3$, 1 M HCl and water. The organic layer was dried (Na_2SO_4), filtered and evaporate to dryness. The residue was purified by thin-layer chromatography, using $CHCl_3$-MeOH (9 : 1) as eluent to give the desired product.

Method B. (Synthesis of **4d – k**). To a solution of **2** (400 mg, 1.50 mmol) in $CHCl_3$ (50 mL) was added the appropriate carboxylic chloride **3** (1.50 mmol) followed by a few drops of Et_3N, and the mixture was stirred at 23 °C for 24 h. The mixture was partitioned with water (50 mL), and the organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by TLC, using $CHCl_3$-MeOH (9 : 1) as eluent, to give the pure product.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-benzamide (**4a**)*

From **3a** (183 mg). Yield: 52 mg (38 %), m. p. 215 – 220 °C (dec.), colorless powder. – ^1H NMR ($CDCl_3$): δ = 7.91 – 7.12 (m, 10H, NH + Ar-H); 4.32 (s, 2H, CH_2NH); 3.94 – 3.62 (m, 8H, piperazine-H). – ^{13}C NMR ($CDCl_3$): δ = 168.1 ($C^2_{benzothiazol}$); 167.2 ($C_{arom.}$ =O); 166.9 ($C_{Npiperazine}$ =O); 151.0 ($C^4_{benzothiazol}$); 133.7, 131.7, 128.6, 128.6, 127.1, 126.6, 126.4, 122.5, 122.3, 120.9, 119.3, 119.1 ($C_{arom.}$); 48.4, 48.1, 43.8, 41.7 ($C_{piperazine}$); 41.3 (CH_2NH). – MS (EI): *m/z* = 380 $[M]^+$. – $C_{20}H_{20}N_4OS$: calcd. C 63.14, H 5.30, N 14.73; found C 62.97, H 5.31, N 14.52.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-4-chloro-3-nitro-benzamide (**4b**)*

From **3b** (302 mg). Yield: 115 mg (23 %), m. p. 189 – 193 °C (dec.), yellow powder. – ^{1}H NMR ([D$_6$]DMSO): δ = 8.10 (br s., 1H, NH); 8.58 – 6.94 (m, 7H, Ar-H); 4.36 (s, 2H, CH_2NH); 3.73 – 3.41 (m, 8H, piperazine-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 164.1 ($C^2_{benzothiazol}$); 162.7 ($C_{arom.}$ =O); 161.5 ($C_{Npiperazine}$ =O); 151.1 ($C^4_{benzothiazol}$); 146.7 ($C_{arom.}$-NO_2); 134.3, 133.1, 130.1, 130.0, 129.9, 126.5, 121.7, 121.6, 119.5 ($C_{arom.}$), 48.4, 47.9, 42.8, 42.2 ($C_{piperazine}$); 41.9 (CH_2NH). – MS (EI): *m/z* = 459 [M]$^+$. – $C_{20}H_{18}ClN_5O_4S$: calcd. C 52.23, H 3.94, N 15.23; found C 52.01, H 4.01, N 15.56.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-2-chloroacetamide (**4c**)*

From **3c** (142 mg). Yield: 58 mg (32 %), m. p. 176 – 180 °C (dec.), yellow powder. – ^{1}H NMR ([D$_6$]DMSO): δ 7.71 – 7.11 (m, NH +4H, Ar-H); 4.20 (s, 2H, CH_2Cl); 3.94 (s, 2H, CH_2NH); 3.92 – 3.60 (m, 8H, piperazine-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 169.1 ($C^2_{benzothiazol}$); 166.2 (C_{CH_2Cl} =O); 163.5 ($C_{Npiperazine}$ =O); 152.1 ($C^4_{benzothiazol}$); 131.4, 129.3, 128.6, 122.5, 121.2, 119.8 ($C_{arom.}$); 48.7, 46.9, 42.3, 41.9 ($C_{piperazine}$); 41.1 (CH_2NH); 40.5 (CH_2Cl). – MS (EI): *m/z* = 352 [M]$^+$. – $C_{15}H_{17}ClN_4O_2S$: calcd. C 51.06, H 4.86, N 15.88; found C 51.31, H 4.85, N 15.66.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-2-ethoxybenzamide (**4d**)*

From **3d** (276 mg). Yield: 242 mg (57 %), m. p. 168 – 171 °C (dec.), colorless powder. – ^{1}H NMR ($CDCl_3$): δ = 9.11 (br s., 1H, NH); 8.20 – 6.92 (m, 8H, Ar-H); 4.35 (s, 2H, CH_2NH); 4.31 (q, *J* = 7.0 Hz , 2H, CH_2O); 3.82 – 3.51 (m, 8H, piperazine-H); 1.60 (t, *J* = 7.6 Hz, 3H, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 168.2 ($C^2_{benzothiazol}$); 167.2 ($C_{arom.}$ =O); 165.1 ($C_{Npiperazine}$ =O); 157.4 ($C^4_{benzothiazol}$); 135.1, 133.9, 133.1, 132.1, 126.4, 122.3, 121.1, 121.1, 119.3, 112.6, 112.2 ($C_{arom.}$); 65.7 (CH_2O); 49.1, 48.4, 43.9, 42.2 ($C_{piperazine}$); 41.5 (CH_2NH); 14.6 (CH_3). – MS (EI): *m/z* = 424 [M]$^+$. – $C_{22}H_{24}N_4O_3S$: calcd. C 62.24, H 5.70, N 13.20; found C 61.97, H 5.78, N 12.99.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-benzo[1,3]dioxole-5-carboxamide (**4e**)*

From **3e** (277 mg). Yield: 312 mg (74 %), m. p. 188 – 192 °C (dec.), colorless powder. – ^{1}H NMR ($CDCl_3$): δ = 7.42 – 6.81 (m, NH +7H, Ar-H); 4.40 (s, 2H, CH_2NH); 4.03 – 3.44 (m, 8H, piperazine-H). – ^{13}C NMR ($CDCl_3$): δ = 170.5 ($C^2_{benzothiazol}$); 168.1 ($C_{arom.}$ =O); 161.0 ($C_{Npiperazine}$ =O); 151.8 ($C^4_{benzothiazol}$ + $C_{arom.}OCH_2O$); 130.8, 130.0, 126.5, 125.9, 122.3, 120.9, 120.1, 119.1 ($C_{arom.}$); 97.9 (OCH_2O); 48.4, 47.9 42.8, 42.6 ($C_{piperazine}$); 41.5 (CH_2NH). – MS (EI): *m/z* = 424 [M]$^+$. – $C_{21}H_{20}N_4O_4S$: calcd. C 59.42, H 4.75, N 13.20; found C 59.23, H 4.72, N 13.56.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]thiophen-2-carboxamide (**4f**)*

From **3f** (220 mg). Yield: 240 mg (78 %), m. p. 217 – 222 °C (dec.), colorless powder. – ^{1}H NMR ($CDCl_3$): δ = 7.90 (br s, 1H, NH), 7.71 – 7.02 (m, 7H, Ar-H); 4.43 (s, 2H, CH_2NH); 3.90 – 3.51 (m, 8H, piperazine-H). – ^{13}C NMR ($CDCl_3$): δ = 168.3 ($C^2_{benzothiazol}$); 165.2 ($C_{Npiperazine}$ =O); 161.5 ($C_{thiophen}$ =O); 152.1 ($C^4_{benzothiazol}$); 134.7, 133.4, 129.5, 128.0, 127.0, 126.5, 122.5, 121.0, 119.1 ($C_{arom.}$+ $C_{thiophen}$); 48.6, 47.7, 44.2, 41.2 ($C_{piperazine}$); 41.0 (CH_2NH). – MS (EI): *m/z* = 386 [M]$^+$. $C_{18}H_{18}N_4O_2S_2$: calcd. C 55.94, H 4.64, N 14.50; found C 56.21, H 4.80, N 14.78.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-furan-2-carboxamide (**4g**)*

From **3g** (196 mg). Yield: 110 mg (82 %), m. p. 275 – 278 °C (dec.), colorless powder. – ^{1}H NMR ($CDCl_3$): δ = 7.61 – 6.40 (m, 8H, NH +Ar-H); 4.20 (s, 2H, CH_2NH); 3.92 – 3.60 (m, 8H, piperazine-H). – ^{13}C NMR ($CDCl_3$): δ = 168.1 ($C^2_{benzothiazol}$); 166.8 ($C_{Npiperazine}$ =O); 158.2 (C_{furan} =O); 147.6 ($C^4_{benzothiazol}$); 147.5, 144.5 (C^2_{furan} + C^5_{furan}); 126.5, 122.2, 121.1, 121.0, 119.5, 114.5, 112.1 ($C_{arom.}$ + C_{furan}); 48.4, 48.2, 43.8, 41.5 ($C_{piperazine}$); 41.0 (CH_2NH). – MS (EI): *m/z* = 370 [M]$^+$. – $C_{18}H_{18}N_4O_3S$: calcd. C 58.36, H 4.90, N 15.12; found C 58.09, H 4.88, N 15.10.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-pyrrolidin-1-carboxamide (**4h**)*

From **3h** (204 mg). Yield: 247 mg (90 %), m. p. 141 – 144 °C (dec.), colorless powder. – ^{1}H NMR ($CDCl_3$): δ = 7.72 – 7.10 (m, 4H, NH +Ar-H); 4.32 (s, 2H, CH_2NH); 3.91 – 3.44 (m, 16H, piperazine-H + pyrrolidin-H). – ^{13}C NMR ($CDCl_3$): δ = 170.5 ($C_{pyrrolidin}$ =O); 168.2 ($C^2_{benzothiazol}$); 164.2 ($C_{Npiperazine}$ =O); 150.9 ($C^4_{benzothiazol}$); 129.9, 128.8, 128.6, 122.4, 120.9, 119.3 ($C_{arom.}$); 59.9 ($C^2_{pyrrolidin}$); 48.6, 48.5, 47.9, 47.8 ($C_{piperazine}$); 42.8 ($C^5_{pyrrolidin}$); 41.5, (CH_2NH); 31.9, 25.1 ($C^3_{pyrrolidin}$ + $C^4_{pyrrolidin}$). – MS (EI): *m/z* = 373 [M]$^+$. – $C_{18}H_{23}N_5O_2S$: calcd. C 57.89, H 6.21, N 18.75; found C 57.74, H 6.48, N 18.82.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-piperidin-1-carboxamide (**4i**)*

From **3i** (221 mg). Yield: 278 mg (90 %), m. p. 119 – 122 °C (dec.), colorless powder. – ^{1}H NMR ($CDCl_3$): δ = 7.76 – 7.14 (m, 4H, Ar-H); 4.81 (br s, 1H, NH), 3.95 (s, 2H,

CH_2NH); 4.10 – 3.13 (m, 12H, piperazine-H + piperidin-H), 1.63 (m, 6H, piperidin-H). – ^{13}C NMR ($CDCl_3$): δ = 167.0 ($C^2_{benzothiazol}$); 163.0 ($C_{Npiperazine}$ =O); 156.0 ($C_{piperidin}$ =O); 125.5, 121.9, 121.1, 120.0, 118.3, 117.5 ($C_{arom.}$); 48.2, 48.0 46.6, 45.2, 41.5 ($C_{piperazine}$ + $C^2_{piperidin}$+ $C^6_{piperidin}$); 41.0 (CH_2NH); 24.7, 23.5, 23.5 ($C^3_{piperidin}$+ $C^4_{piperidin}$ + $C^5_{piperidin}$). – MS (EI): *m/z* = 387 $[M]^+$. – $C_{19}H_{25}N_5O_2S$: calcd. C 58.89, H 6.50, N 18.07; found C 58.70, H 6.75, N 17.80.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-morpholin-4-carboxamide (**4j**)*

From **3j** (224 mg). Yield: 268 mg (85 %), m. p. 130 – 133 °C (dec.), colorless powder. – ^1H NMR ($CDCl_3$): δ = 8.22 (br s, 1H, NH); 7.81 – 7.10 (m, 4H, Ar-H); 4.31 (s, 2H, CH_2NH); 4.05 – 3.42 (m, 16H, piperazine-H + morpholine-H). – ^{13}C NMR ($CDCl_3$): δ = 170.5 ($C^2_{benzothiazol}$); 168.2 ($C_{Npiperazine}$ =O); 156.8 ($C_{morpholine}$ =O); 130.5, 128.8, 126.4, 122.4, 120.9, 119.5 ($C_{arom.}$); 66.6 ($C^2_{morpholin}$ + $C^6_{morpholin}$); 59.9, 48.4, 47.8, 42.8 ($C^3_{morpholine}$+ $C^5_{morpholine}$+ $C_{piperazine}$); 41.6 (CH_2NH). – MS (EI): *m/z* = 389 $[M]^+$. – $C_{18}H_{23}N_5O_3S$: calcd. C 55.51, H 5.95, N 17.98; found C 55.78, H 6.13, N 18.13.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-4-methyl-piperazin-1-carboxamide (**4k**)*

From **3k** (243 mg). Yield: 283 mg (80 %), m. p. 194 – 197 °C (dec.), colorless powder. – ^1H NMR ($CDCl_3$): δ = 7.72 – 7.11 (m, 4H, Ar-H); 4.82 (br s, 1H, NH); 4.30 (s, 2H, CH_2C=O); 4.02 – 3.22 (m, 16H, piperazine-H); 2.61 (s, 3H, NCH_3). – ^{13}C NMR ($CDCl_3$): δ = 170.5 ($C^2_{benzothiazol}$); 168.2 ($C_{Npiperazine}$ =O); 156.8 ($C_{Me-piperazine}$ =O); 130.4, 128.8, 126.5, 122.2, 120.9, 119.4 ($C_{arom.}$); 59.9 ($C^3_{Me\text{-}piperazine}$ + $C^5_{Me\text{-}piperazine}$); 48.5, 48.3, 47.9, 47.8, 42.9 ($C_{piperazine}$ + $C^2_{Me\text{-}piperazine}$ + $C^6_{Me\text{-}piperazine}$); 41.4 ($CH_2NH$); 40.9 ($NCH_3$). – MS (EI): *m/z* = 402 $[M]^+$. – $C_{19}H_{26}N_6O_2S$: calcd. C 56.69, H 6.51, N 20.88; found C 56.77, H 6.58, N 20.83.

*N-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-3-(1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-ylthio)propanamide (**4l**)*

From 3-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-ylthio) propanoic acid (**3l**) (503 mg). Yield: 248 mg (23 %), m. p. 120 – 123 °C (dec.), colorless powder. – ^1H NMR ([D_6]DMSO): δ = 7.80 – 6.92 (m, 9H, Ar-H); 6.27 (br s., 1H, NH); 5.42 (s, 2H, PhCH_2); 4.11 (s, 2H, CH_2NH); 3.91 – 3.60 (m, 8H, piperazine-H); 3.20 (m, 2H, CH_2CH_2S), 2.72 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 2.55 (m, 2H, CH_2CH_2S), 1.31 (t, 3H, CH_2CH_3). – ^{13}C NMR ([D_6]DMSO): δ = 169.1 ($C_{CH_2CH_2S}$ =O); 167.0 ($C^2_{benzothiazol}$); 166.0 ($C_{Npiperazine}$ =O); 156.8 ($C^2_{imidazol}$); 149.8, 148.3 ($C^4_{imidazol}$ + $C^5_{imidazol}$); 134.0, 128.3, 128.3, 127.2, 127.2, 126.2, 125.2, 125.1, 125.0, 123.5, 122.3, 120.1, 117.5 ($C_{arom.}$); 47.8, 46.9, 42.9, 41.6 ($C_{piperazine}$); 40.2 (CH_2NH); 31.2 (PhCH_2); 24.8, 23.9 (CH_2CH_2S); 20.3 (CH_2CH_3); 10.2 (CH_2CH_3). – MS (EI): *m/z* = 593 $[M]^+$. – $C_{28}H_{31}N_7O_4S_2$: calcd. C 56.64, H 5.26, N 16.51; found C 56.38, H 5.37, N 16.45.

*Preparation of (4-benzothiazol-2-yl-piperazin-1-yl)acetic acid hydrazide (**6**)*

A mixture of **5** (3.20 g, 10.0 mmol) and hydrazine hydrate (5.0 g, 10 mmol) in EtOH (25 mL) was heated under reflux for 8 h. On cooling, the solid hydrazide **6** was collected and recrystallized from EtOH (2.58 g, 84 %), m. p. 187 – 189 °C (dec.), yellow powder. – ^1H NMR ($CDCl_3$): δ = 8.21 (br s., 1H, NH); 7.63 – 7.10 (m, 4H); 4.49 (br s., 2H, NH_2); 3.18 (s, 2H, CH_2C=O); 3.70 – 2.67 (m, 8H, piperazine-H). – ^{13}C NMR ($CDCl_3$): δ = 169.9 (C=N); 168.5 (C=O); 152.5 (C-3a); 130.7, 126.1, 121.6, 120.9, 119.2 (Ar); 60.6 (CH_2C=O); 52.9, 48.3 ($C_{piperazine}$). – MS (FAB): *m/z* = 307 $[M+H]^+$. – $C_{14}H_{21}N_5OS$: calcd. C 54.70, H 6.89, N 22.78; found C 54.87, H 6.66, N 22.91.

*General procedure for the preparation of 2-[4-(1,3-benzothiazol-2-yl)piperazin-1-yl]-N′-(arylsulfonyl)acetohydrazides **8a – i***

A solution of **6** (1.0 mmol) and arylsulfonyl chlorides **7** (1.0 mmol) in $CHCl_3$ (50 mL) containing Et_3N (0.1 mL, 1.0 mmol) was stirred at 23 °C for 22 h. The solvent was evaporated to dryness, and the residue was purified by thin layer chromatography, using $CHCl_3$-MeOH (15 : 1) as eluent to give the desired product which was purified by recrystallization from EtOH.

*2-[4-(1,3-Benzothiazol-2-yl)piperazin-1-yl]-N′-[(4-methylphenyl)sulfonyl]acetohydrazide (**8a**)*

From **7a** (0.19 g). Yield: 0.22 g (50 %), m. p. 234 – 236 °C (dec.), colorless powder. – ^1H NMR ([D_6]DMSO): δ = 10.01 (br s., 2H, NH); 7.78 – 7.04 (m, 8H); 3.32 (s, 2H, CH_2C=O); 2.50 – 2.42 (m, 8H, piperazine-H); 2.35 (s, 3H, CH_3). – ^{13}C NMR ([D_6]DMSO): δ = 168.0 (C=N); 167.3 (C=O); 152.4 (C-3a); 143.3, 135.9, 130.4, 129.2, 127.8, 125.9, 121.2, 121.1, 118.5 (Ar); 59.1 (CH_2C=O); 51.8, 47.2 ($C_{piperazine}$); 21.0 (CH_3). – MS (FAB): *m/z* = 446 $[M+H]^+$. – $C_{20}H_{23}N_5O_3S_2$: calcd. C 53.91, H 5.20, N 15.72; found C 54.10, H 5.16, N 15.75.

*2-[4-(1,3-Benzothiazol-2-yl)piperazin-1-yl]-N′-[(4-methoxyphenyl)sulfonyl]acetohydrazide (**8b**)*

From **7b** (0.21 g). Yield: 0.18 g (39 %), m. p. 232 – 234 °C (dec.), colorless powder. – ^1H NMR ([D_6]DMSO): δ = 9.99

(br s., 2H, NH); 7.77 – 7.05 (m, 8H); 3.81 (s, 3H, OCH_3); 2.96 (s, 2H, CH_2C=O); 2.58 – 2.43 (m, 8H, piperazine-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 168.5 (C=N); 167.9 (C=O); 163.2, 152.9 (C-3a); 130.9, 130.8, 130.6, 126.4, 121.7, 121.6, 119.4, 114.5 (Ar); 59.2 (CH_2C=O); 56.1 (OCH_3); 51.8, 48.3 ($C_{piperazine}$). – MS (FAB): *m/z* = 462 $[M+H]^+$. – $C_{20}H_{23}N_5O_4S_2$: calcd. C 52.04, H 5.02, N 15.17; found C 52.27, H 5.12, N 15.48.

*2-[4-(1,3-Benzothiazol-2-yl)piperazin-1-yl]-N′-[(4-chlorophenyl)sulfonyl]acetohydrazide (**8c**)*

From **7c** (0.21 g). Yield: 0.19 g (41 %), m. p. 232 – 234 °C (dec.), colorless powder. – ^{1}H NMR ([D$_6$]DMSO): δ = 10.12 (br s., 2H, NHNH); 7.82 – 7.07 (m, 8H); 2.97 (s, 2H, CH_2C=O); 3.53 – 2.45 (m, 8H, piperazine-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 168.5 (C=N); 168.1 (C=O); 152.9 (C-3a); 138.4, 138.3, 130.9, 130.2, 129.4, 126.4, 121.7, 121.6, 119.0 (Ar); 59.1 (CH_2C=O); 51.9, 48.3 ($C_{piperazine}$). – MS (FAB): *m/z* = 465/467 $[M+H]^+$. – $C_{19}H_{20}ClN_5O_3S_2$: calcd. C 48.97, H 4.33, N 15.03; found C 49.15, H 4.39, N 15.06.

*2-[4-(1,3-Benzothiazol-2-yl)piperazin-1-yl]-N′-[(2,5-dichlorophenyl)sulfonyl]acetohydrazide (**7d**)*

From **7d** (0.25 g). Yield: 0.45 g (90 %), m. p. 207 – 209 °C (dec.), colorless powder. – ^{1}H NMR ([D$_6$]DMSO): δ = 10.15 (br s., 2H, NH); 7.93 – 7.07 (m, 7H, Ar-H); 3.02 (s, 2H, CH_2C=O); 3.54 – 2.50 (m, 8H, piperazine-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 168.6 (C=N), 168.5 (C=O); 152.9 (C-3a); 139.1, 134.5, 134.0, 132.0, 131.4, 130.9, 130.8, 126.4, 121.7, 121.6, 119.1 (Ar); 59.0 (CH_2C=O); 51.8, 48.2 ($C_{piperazine}$). – MS (FAB): *m/z* = 500/502 $[M+H]^+$. – $C_{19}H_{19}Cl_2N_5O_3S_2$: calcd. C 45.60, H 3.83, N 13.99; found C 45.80, H 4.05, N 14.23.

*2-[4-(1,3-Benzothiazol-2-yl)piperazin-1-yl]-N′-{[(3-trifluoromethyl)phenyl]sulfonyl}acetohydrazide (**8e**)*

From **7e** (0.25 g). Yield: 0.48 g (96 %), m. p. 201 – 203 °C (dec.), colorless powder. – ^{1}H NMR ([D$_6$]DMSO): δ = 10.21 (br s., 2H, NH); 8.12 – 7.04 (m, 8H); 2.96 (s, 2H, CH_2C=O); 3.51 – 2.43 (m, 8H, piperazine-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 168.5 (C=N); 168.3 (C=O); 152.9 (C-3a); 140.8, 132.3, 130.9, 130.2, 129.7 (CF_3), 126.4, 124.8, 121.7, 121.6, 119.0 (Ar); 59.1 (CH_2C=O); 51.8, 48.2 ($C_{piperazine}$). – MS (FAB): *m/z* = 499 $[M+H]^+$. – $C_{20}H_{20}F_3N_5O_3S_2$: calcd. C 48.09, H 4.04, N 14.02; found C 45.28, H 4.17, N 14.24.

*2-[4-(1,3-Benzothiazol-2-yl)piperazin-1-yl]-N′-[(quinolin-8-yl)sulfonyl]acetohydrazide (**8f**)*

From **7f** (0.23 g). Yield: 0.23 g (47 %), m. p. 128 – 130 °C (dec.), colorless powder. – ^{1}H NMR ([D$_6$]DMSO): δ = 9.14 (br s., 2H, NH); 8.56 – 7.04 (m, 10H, Ar-H); 2.98 (s, 2H, CH_2C=O); 3.50 – 2.44 (m, 8H, piperazine-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 167.9 (C=N); 167.7 (C=O); 152.3 (C-3a); 151.3, 143.0, 137.1, 136.4, 134.1, 131.0, 130.3, 128.5, 125.9, 125.4, 122.53, 121.2, 121.1, 118.5 (Ar); 59.1 (CH_2C=O); 51.4, 47.7 ($C_{piperazine}$). – MS (FAB): *m/z* = 482 $[M+H]^+$. – $C_{22}H_{22}N_6O_3S_2$: calcd. C 54.75, H 4.60, N 17.41; found C 55.03, H 4.84, N 17.45.

*2-[4-(1,3-Benzothiazol-2-yl)piperazin-1-yl]-N′-(2-thienylsulfonyl)acetohydrazide (**8g**)*

From **7g** (0.18 g). Yield: 0.293 g (67 %), m. p. 222 – 224 °C (dec.), colorless powder. – ^{1}H NMR ([D$_6$]DMSO): δ = 10.09 (br s., 2H, NH); 7.96 – 7.04 (m, 7H, Ar-H); 3.01 (s, 2H, CH_2C=O); 3.56 – 2.50 (m, 8H, piperazine-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 168.5 (C=N); 168.1 (C=O); 152.9 (C-3a); 139.6, 134.4, 133.8, 130.9, 128.0, 126.4, 121.7, 121.6, 119.0 (Ar); 59.2 (CH_2C=O); 51.9, 48.4 ($C_{piperazine}$). – MS (FAB): *m/z* = 437 $[M+H]^+$. – $C_{17}H_{19}N_5O_3S_3$: calcd. C 46.66, H 4.38, N 16.01; found C 46.93, H 4.47, N 16.17.

*2-[4-(1,3-Benzothiazol-2-yl)piperazin-1-yl]-N′-[(3-bromo-5-chloro-2-thienyl)sulfonyl] acetohydrazide (**8h**)*

From **7h** (0.3 g). Yield: 0.31 g (56 %), m. p. 166 – 168 °C (dec.), colorless powder. – ^{1}H NMR ([D$_6$]DMSO): δ = 9.05 (br s., 2H, NH); 7.77 – 7.06 (m, 5H, Ar-H); 2.90 (s, 2H, CH_2C=O); 3.59 – 2.52 (m, 8H, piperazine-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 168.5 (C=N); 164.0 (C=O); 152.9 (C-3a); 131.4, 130.9, 129.6, 126.4, 126.4, 121.7, 121.6, 119.1, 119.0 (Ar); 60.8 (CH_2C=O); 52.3, 48.5 ($C_{piperazinee}$). – MS (FAB): *m/z* = 550/552 $[M+H]^+$. – $C_{17}H_{17}BrClN_5O_3S_3$: calcd. C 37.06, H 3.11, N 12.71; found C 37.26, H 3.27, N 12.96.

*2-[4-(1,3-Benzothiazol-2-yl)piperazin-1-yl]-N′-[(2,5-dichloro-3-thienyl)sulfonyl]aceto-hydrazide (**8i**)*

From **7i** (0.25 g). Yield: 0.45 g (89 %), m. p. 176 – 178 °C (dec.), colorless powder. – ^{1}H NMR ([D$_6$]DMSO): δ = 9.04 (br s., 2H, NH); 7.79 – 7.06 (m, 5H, Ar-H); 3.35 (s, 2H, CH_2C=O); 3.69 – 3.29 (m, 8H, piperazine-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 168.5 (C=N); 164.2 (C=O); 152.9 (C-3a); 144.9, 130.9, 129.2, 126.4, 126.4, 123.2, 121.7, 121.6, 119.0 (Ar); 60.6 (CH_2C=O); 52.2, 48.5 ($C_{piperazine}$). – MS (FAB): *m/z* = 506/504 $[M+H]^+$. – $C_{17}H_{17}Cl_2N_5O_3S_3$: calcd. C 40.32, H 3.38, N 13.83; found C 40.17, H 3.59, N 14.03.

*General procedure for the preparation of 1-[2-(4-(benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-3-arylthioureas **9a – c***

To a stirred solution of **2** (400 mg, 1.50 mmol) in MeCN (15 mL) was added aryl isothiocyanate (1.63 mmol), and the mixture was heated under reflux for 6 h. The precipitate was filtered and then washed with ether to give a crude product.

This was purified by column chromatography (SiO_2) using $CHCl_3$-MeOH (19 : 1) as eluent to give the desired thiourea derivatives.

*1-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-3-phenylthiourea (**9a**)*

From phenyl isothiocyanate (220 mg). Yield: 0.34 g (61 %); m. p. 160 – 163 °C. – ^{1}H NMR ([D$_6$]DMSO): δ = 7.89 – 6.41 (m, 9H, Ar-H); 4.52 (br s, 1H, NH); 3.49 – 3.36 (m, 10H, piperazine-H + CH_2NS). – ^{13}C NMR ([D$_6$]DMSO): δ = 181.3 (C=S); 167.5 ($C^2_{benzothiazol}$); 164.3 ($C_{N\text{-}piperazine}$ =O); 149.2 ($C^4_{benzothiazol}$); 136.3, 128.6, 126.2, 125.2, 125.1, 125.0, 123.8, 121.8 ($C_{arom.}$); 47.9, 47.5, 43.3, 43.1 ($C_{piperazine}$ + CH_2NH). – MS (FAB): *m/z* = 372 $[M+H]^+$. – $C_{18}H_{19}N_4OS_2$: calcd. C 58.19, H 5.16, N 15.08; found C 57.93, H 5.02, N 14.88.

*1-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]3-(4-chlorophenyl)-thiourea (**9b**)*

From 4-chlorophenyl isothiocyanate (276 mg). Yield: 0.44 g (61 %); m. p. 172 – 174 °C. – ^{1}H NMR ([D$_6$]DMSO): δ = 8.21 – 6.43 (m, 8H, Ar-H); 3.49 – 3.35 (m, 10H, piperazine-H + CH_2NS). – ^{13}C NMR ([D$_6$]DMSO): δ = 181.6 (C=S); 167.9 ($C^2_{benzothiazol}$); 164.7 ($C_{N\text{-}piperazine}$ =O); 149.0 ($C^4_{benzothiazol}$); 135.2, 129.1, 126.8, 125.3, 125.0, 124.8, 121.9 ($C_{arom.}$); 48.4, 48.5, 44.1, 43.7 ($C_{piperazine}$ + CH_2NH). – MS (FAB): *m/z* = 446/448 $[M+H]^+$. – $C_{20}H_{20}ClN_5OS_2$: calcd. C 53.86, H 4.52, N 15.70; found C 53.67, H 4.39, N 15.41.

*1-[2-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-oxoethyl]-3-(4-methylphenyl)-thiourea (**9c**)*

From 4-methylphenyl isothiocyanate (238 mg). Yield: 0.41 g (59 %); m. p. 150 – 152 °C. – ^{1}H NMR ([D$_6$]DMSO): δ = 8.20 – 6.38 (m, 8H, Ar-H); 3.41 – 3.31 (m, 10H, piperazine-H + CH_2NS). – ^{13}C NMR ([D$_6$]DMSO): δ = 181.0 (C=S); 167.7 ($C^2_{benzothiazol}$); 164.1 ($C_{N\text{-}piperazine}$ = O); 149.1 ($C^4_{benzothiazol}$); 133.9, 130.1, 129.1, 126.2, 125.0, 123.2, 121.6 ($C_{arom.}$); 48.1, 48.3, 44.2, 43.8 ($C_{piperazine}$ + CH_2NH); 24.1 (*Me*-Ph). – MS (FAB): *m/z* = 426 $[M+H]^+$. – $C_{21}H_{23}N_5OS_2$: calcd. C 59.27, H 5.45, N 16.46; found C 59.01, H 5.40, N 16.12.

Cytotoxicity assays

Cell cultures were seeded at 1×10^5 cells mL^{-1} in 96 multiwall plates in specific media supplemented (5 %) with 10 % FCS and antibiotics, then incubated at 37 °C in a humidified CO_2 atmosphere in the absence or presence of serial dilutions of test compounds. Cell viability was determined after 96 h at 37 °C by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) method. Compounds were dissolved in DMSO at 100 mM and then diluted into the culture medium.

Acknowledgements

We thank Dr. G. Gosselin, Laboratoires Idenix Sarl, Montpellier cedex 4 (France), for helping in the antitumor screening and Prof. C. Pannecouque, Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium, for the anti-HIV screening.

[1] T. D. Bradshaw, M.-S. Chua, H. L. Browne, V. Trapani, E. A. Sauville, M. F. G. Stevens, *Br. J. Cancer* **2002**, *86*, 1348 – 1354.
[2] I. Hutchinson, S. A. Jennings, B. R. Vishnuvajjala, A. D. Westwell, M. F. G. Stevens, *J. Med. Chem.* **2002**, *45*, 744 – 747.
[3] C. O. Leong, M. Suggitt, D. J. Swaine, M. C. Bibby, M. F. G. Stevens, T. D. Bradshaw, *Mol. Cancer Ther.* **2004**, *3*, 1565 – 1575.
[4] D.-F. Shi, T. D. Bradshaw, S. Wrigley, C. J. McCall, P. Lelieveld, I. Fichtner, M. F. G. Stevens, *J. Med. Chem.* **1996**, *39*, 375 – 3384.
[5] T. D. Bradshaw, S. Wrigley, R. J. Schultz, K. D. Paull, M. F. G. Stevens, *Br. J. Cancer* **1998**, *77*, 745 – 752.
[6] T. D. Bradshaw, D.-F. Shi, R. J. Schultz, K. D. Paull, L. Kelland, A. Wilson, C. Garner, H. H. Fiebig, S. Wrigley, M. F. G. Stevens, *Br. J. Cancer* **1998**, *77*, 421 – 429.
[7] E. Kashiyama, I. Hutchinson, M.-S. Chua, S. F. Stinson, L. R. Phillips, G. Kaur, E. A. Sausville, T. D. Bradshaw, A. D. Westwell, M. F. G. Stevens, *J. Med. Chem.* **1999**, *42*, 4172 – 4184, and refs. cited therein.
[8] A. Rana, N. Siddiqui, S. A. Khan, *Indian J. Pharm. Sci.* **2007**, *69*, 10 – 17.
[9] G. Trapani, M. Franco, A. Latrofa, A. Reho, G. Liso, *Eur. J. Pharm. Sci.* **2001**, *14*, 209 – 216.
[10] K. J. Watson, D. R. Anderson, S. T. Nguyen, *Macromolecules* **2001**, *34*, 3507 – 3509.
[11] I. Caleta, M. Grdisa, D. Mrvos-Sermek, M. Cetina, V. K. Trali-Kulenovi, G. Paveli, G. Karminski-Zamola, *Farmaco* **2004**, *59*, 297 – 305.
[12] A. I. Loaiza-Pérez, V. Trapni, V. Patel, C. Hose, S. S. Singh, J. B. Trepel, M. F. G. Stevens, T. D. Bradshaw, E. A. Sauville, *Mol. Pharmacol.* **2002**, *61*, 13 – 19.
[13] A. Monks, E. Harris, C. Hose, J. Connelly, E. A. Sausville, *Mol. Pharmacol.* **2003**, *63*, 766 – 772.
[14] T. D. Bradshaw, M. C. Bibby, J. A. Double, I. Fichtner, P. A. Cooper, M. C. Alley, S. Donohue, S. F. Stinson, J. E. Tomaszewjski, E. A. Sausville, M. F. G. Stevens, *Mol. Cancer Ther.* **2002**, *1*, 239 – 246.

[15] V. Trapani, V. Patel, C.-O. Leong, H. P. Ciolino, G. C. Yeh, C. Hose, J. B. Trepel, M. F. G. Stevens, E. A. Sausville, A. I. Loaiza-Pérez, *Br. J. Cancer* **2003**, *8*, 599 – 605.

[16] C. O. Leong, M. Gaskell, E. A. Martin, R. T. Heydon, P. B. Farmer, M. C. Bibby, P. A. Cooper, J. A. Double, T. D. Bradshaw, M. F. G. Stevens, *Br. J. Cancer* **2003**, *88*, 470 – 477.

[17] C. D. Hose, M. Hollingshead, E. A. Sausville, A. Monks, *Mol. Cancer Ther.* **2003**, *2*, 1265 – 1972.

[18] E. Brantley, S. Antony, G. Kohlhagen, L. Meng, K. Agama, S. F. Stinson, E. A. Sausville, Y. Pommier, *Cancer Chemother. Pharmacol*. **2006**, *58*, 62 – 72.

[19] E. Brantley, V. Trapani, M. C. Alley, C. D. Hose, T. D. Bradshaw, M. F. G. Stevens, E. A. Sausville, S. F. Stinson, *Drug Metab. Dispos.* **2004**, *32*, 1392 – 13401.

[20] G. Mortimer, G. Wells, J.-P. Grochard, E. L. Stone, T. D. Bradshaw, M. F. G. Stevens, A. D. Westwell, *J. Med. Chem.* **2006**, *49*, 179 – 185.

[21] G. Wells, J. M. Berry, T. D. Bradshaw, A. M. Burger, A. Seaton, B. Wang, A. D. Westwell, M. F. G. Stevens, *J. Med. Chem.* **2003**, *46*, 532 – 541.

[22] T. D. Bradshaw, A. D. Westwell, *Curr. Med. Chem.* **2004**, *11*, 1009 – 1021.

[23] I. Fichtner, A. Monks, C. Hose, M. F. G. Stevens, T. D. Bradshaw, *Breast cancer treat.* **2004**, *87*, 97 – 107.

[24] M. Yoshida, I. Hayakawa, N. Hayashi, T. Agatsuma, Y. Oda, F. Tanzawa, S. Iwasaki, K. Koyama, H. Furukawa, S. Kurakata, Y. Sugano, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3328 – 3333.

[25] L. Racane, V. Tralic-Kulenovic, L. Fiser-Jakic, D. W. Boykin, G. Karminski-Zamola, *Heterocycles* **2001**, *55*, 2085 – 2098.

[26] Y. A. Al-Soud, H. Al-Sa'doni, H. A. S. Amajaour, N. A. Al-Masoudi, *Z. Naturforsch*. **2007**, *62b*, 523 – 528.

[27] Y. A. Al-Soud, H. H. Al-Sa'doni, H. A. S. Amjaour, K. S. M. Salih, M. S. Mubarak, N. A. Al-Masoudi, I. H. Jaber, *Z. Naturforsch.* **2008**, *63b*, 83 – 89.

[28] T. Akhtar, S. Hameed, N. A. Al-Masoudi, *Acta Pharm.* **2008**, *58*, 135 – 149.

[29] Y. A. Al-Soud, H. Al-Sa'doni, B. Saeed, I. Jaber, M. O. Beni-Khalid, N. A. Al-Masoudi, T. Abdul-kadir, P. La Colla, B. Bursonera, T. Sanna, R. Loddo, *Arkivoc* **2008**, *x*, 225 – 238.

[30] Y. A. Al-Soud, N. A. Al-Masoudi, E. De Clercq, C. Panneccoque, *Heteroatom Chem.* **2007**, *18*, 333 – 340.

[31] S. Davis, A. K. Mohammed, *J. Chem. Soc., Perkin Trans.* **1981**, *1*, 2982 – 2990, and refs. cited therein.

[32] W. König, R. Geiger, *Chem. Ber.* **1970**, *103* 788 – 798.

[33] R. M. Pennington, R. R. Fischer, *J. Biol. Chem.* **1981**, *256* 8963 – 8969.

[34] W. Willker, D. Leibfritz, W. Kerssebaum, W. Bermel, *Mag. Reson. Chem.* **1993**, *31*, 287 – 297.

[35] M. C. Alley, D. A. Scudiero, A. Monks, M. L. Hursey, M. J. Czerwinski, D. L. Fine, B. J. Abbott, L. G. Mayo, R. H. Schoemaker, M. R. Boyd, *Cancer Res*. **1988**, *48*, 589 – 601.

[36] K. D. Hargrave, J. R. Proudfoot, K. G. Grozinger, E. Cullen, S. R. Kapadia, U. R. Patel, V. U. Fuchs, S. C. Mauldin, J. Vitous, M. L. Behnke, J. M. Klunder, K. Pal, J. W. Skiles, D. W. McNeil, J. M. Rose, G. C. Chow, M. T. Skoog, J. C. Wu, G. Schmidt, W. W. Engel, W. G. Eberlein, T. D. Saboe, S. J. Campbell, A. S. Rosenthal, J. Adam, *J. Med. Chem.* **1991**, *34*, 2231 – 2241.