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Novel benzothiazolyl urea and thiourea derivatives with potential cytotoxic and antimicrobial activities

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Abstract
A novel series of benzothiazole urea and thiourea derivatives was synthesized and evaluated for its *in vitro* cytotoxicity against MCF-7 breast cancer cells. The N^1-(benzothiazol-2-yl)-N^3-morpholinourea **3** displayed the highest cytotoxic activity in this series. A docked pose of **3** was obtained bound to G-quadruplex of human telomere DNA active site using the Molecular Operating Environment (MOE) module. Moreover, the synthesized compounds were screened for their antimicrobial activity against *Mycobacterium tuberculosis* $H_{37}R_v$, *E. coli*, *S. aureus* and *C. albicans*. Again, **3** showed the best activity against *M. tuberculosis* $H_{37}R_v$ while other compounds were equipotent with ampicillin against *S. aureus* and *E. coli*.

Keywords: *Benzothiazoles, cytotoxicity, antimycobacterial, antibacterial, G-quadruplex stabilization*

Introduction

Cancer remains one of the most pressing health problems facing the world with breast cancer causing the most mortality among women. In recent years, the search for novel anticancer agents identified telomerase inhibitors as an ideal treatment not only for breast cancer but also for other cancers as well [1,2]. This reverse transcriptase enzyme (telomerase) is responsible for the maintenance of telomere length in over 80% of all tumor cells rendering them with an almost infinite capacity to divide and to be immortalized. Thus, the inhibition of telomerase activity will result in the loss of the divisional ability of tumor cells. On the other hand, the fact that the telomerase enzyme is not expressed in normal somatic cells made telomerase inhibition an ideal target for anticancer drug design. Therefore, many research groups recently reported a variety of telomerase inhibitors ranging from HIV reverse transcriptase inhibitors, to G-quadruplex stabilizers or others [3–9].

Various benzothiazoles (eg. **I**) (Figure 1) [10–12] as well as the urea and thiourea derivatives [13–15] have been reported to possess potent anticancer activities. The combination the urea or thiourea derivatives with benzothiazoles lead to inhibitors of DNA topoisomerase [16,17] or HIV reverse transcriptase (eg. **II**) (Figure 1) [18,19].

As previously mentioned, stabilization of the quadruplex conformation of telomeres by small molecules has been shown to inhibit telomerase, resulting in cancer cell death and many research groups have reported a variety of G-quadruplex stabilizers (eg. **III**, **IV**) (Figure 2). [8,9].

Guided by this data, we suggested that benzothiazole urea and thiourea derivatives would possess anticancer activities possibly through inhibition of telomerase enzyme through G-quadruplex stabilization. To verify this hypothesis and as a continuation of our research program on the synthesis of novel anticancer agents [20], herein we report here the design and synthesis of benzothiazole urea and thiourea derivatives and their

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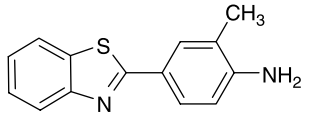
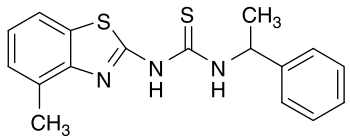


(I)



(II)

Figure 1. Some biologically active benzothiazoles: Antitumor agent (**I**) and HIV reverse transcriptase inhibitor (**II**).

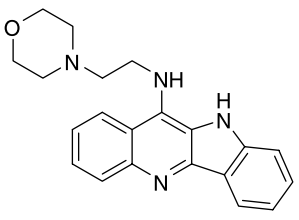
cytotoxic evaluation against MCF-7 breast cancer cells.

Furthermore, the pronounced antimicrobial activity of urea and thiourea as well as benzothiazole derivatives [21–25] encouraged us to study the effect of the synthesized compounds against a variety of microorganisms such as *Mycobacterium tuberculosis*, *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*.

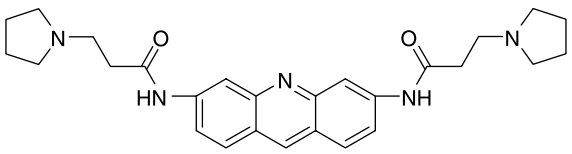
Materials and methods

Chemistry

Melting points were determined with an electrothermal apparatus (Stuart Scientific, England) and are uncorrected. Monitoring the chemical reactions and purity of the compounds was carried out using thin-layer chromatography (TLC) using silica gel 60 GF_{245} precoated sheets. Elemental analyses were performed on a "Analytischer Funktionstest vario EL Fab.-Nr. 11982027" (Germany). IR spectra were recorded as KBr disks on a Shimadzu-470 IR spectrophotometer (Japan). ^{1}H-NMR spectra were carried out on a Bruker Avance 500 MHz, (USA) relative to TMS as internal standard. ^{13}C-NMR spectra were recorded on a Bruker Avance at 125 MHz, (USA) using DMSO-d_6 as internal standard. EI-MS spectra were recorded on a JEOL JMS 600 mass spectrometer.



(III)



(IV)

Figure 2. Potent telomerase inhibitors through G-quadruplex stabilization.

*N-(Benzothiazol-2-yl)-1*H*-imidazole-1-carboxamide (2a)*. A solution of 1,1′-carbonyldiimidazole (50 mmol) and 2-aminobenzothiazole (50 mmol) in acetonitrile (125 mL) was stirred at room temperature for 20 h. The resulting precipitate was collected by filtration. Yield 50%, mp: 250–253°C. IR cm^{-1}: 3410-3235 (NH), 1650 (C=O), 1610 (C=N), 1457, 1370; ^{1}H NMR (DMSO-d_6), δ ppm: 6.95–6.98 (m, 3H, ArH), 7.15–7.18 (t, 1H, J = 8 Hz, ArH), 7.28–7.30 (d, 1H, J = 8 Hz, ArH), 7.43 (s, 1H, NH), 7.59–7.62 (m, 2H, ArH). Anal. calcd. for $C_{11}H_8N_4OS$: C, 54.09; H, 3.30; N, 22.94. Found: C, 53.91; H, 3.41; N, 23.07%.

*N-(Benzothiazol-2-yl)-1*H*-imidazole-1-carbothioamide (2b)*. As described for preparation of **2a** but using 1,1′-thiocarbonyldiimidazole instead of 1,1′-carbonyldiimidazole as reported [8,9]. Yield: 45%, mp: 210–212°C. IR cm^{-1}: 3451-3240 (NH), 1634, 1613(C=N), 1225 (C=S); ^{1}H NMR (DMSO-d_6), δ ppm: 6.93–6.98 (m, 1H, ArH), 7.15–7.18 (m, 3H, ArH), 7.28–7.30 (d, 1H, J = 8 Hz, ArH), 7.43 (s, 2H, NH), 7.59–7.61 (d, 1H, J = 8 Hz, ArH), 8.02 (s, 1H, ArH).

N-(Benzothiazol-2-yl)-N′-morpholinourea (3). A solution of **2a** (8 mmol) and N-aminomorpholine (8 mmol) in DMF (10 mL) was stirred at 100°C for 1.5 h, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The white precipitate obtained upon addition of cold water was collected and recrystallized from aqueous ethanol; Yield: 55%; mp: 262–265°C; IR cm^{-1}: 3450 & 3390 (NH), 1696 (C=O), 1607 (C=N), 1517, 1258, 1107; ^{1}H NMR (DMSO-d_6), δ ppm: 2.64–2.93 (dd, 4H, morphlino), 3.66–3.78 (dd, 4H, morphlino), 7.22–7.25 (t, 1H, J = 8 Hz, ArH), 7.36–7.39 (t, 1H, J = 8 Hz, ArH), 7.64–7.65(d, 1H, J = 8 Hz, ArH), 7.88–7.89 (d, 1H, J = 8 Hz, ArH), 8.65 (s, 1H, NH), 10.47(s, 1H, NH). ^{13}C NMR (DMSO-d_6), δ ppm: 56.00, 66.13, 120.37, 121.77, 123.33, 126.27, 174.35. EI-MS: m/z 278 $[M]^+$(14.3%), 279 $[M+1]^+$(3.4%), 176 (33.3%), 149 (100%), 101 (70.7%), Anal. calcd. for

$C_{12}H_{14}N_4O_2S.\ \frac{1}{2}H_2O$: C, 50.16; H, 5.26; N, 19.50. Found: C, 49.44; H, 4.91; N, 19.32%.

Ethyl{[(benzothiazol-2-ylamino)carbonyl]amino}acetate (4a). A mixture of **2a** (8 mmol), glycine ethyl ester hydrochloride (8 mmol) and Triethylamine (8 mmol) in DMF (10 mL) was stirred at 100°C for 1.5 h, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The white precipitate obtained upon addition of cold water was collected and recrystallized from ethanol; Yield: 60%; mp: 266–268°C; IR cm^{-1}: 3445 & 3390 (NH), 1726 (C=O, ester), 1695 (C=O, urea), 1625 (C=N), 1532, 1190; ^{1}H NMR (DMSO-d_6), δ ppm: 1.15–1.18 (t, 3H, J = 7 Hz, -CH_2CH_3), 3.92–3.93 (d, 2H, J = 5.7 Hz, -NHCH_2), 4.06–4.11 (q, 2H, J = 7 Hz, -CH_2CH_3), 7.10 (t, 1H, J = 5.7 Hz, -NHCH_2), 7.17–7.20 (t, 1H, J = 8 Hz, ArH), 7.31–7.34 (t, 1H, J = 8 Hz, ArH), 7.59–7.60 (d, 1H, J = 8 Hz, ArH), 7.83–7.84 (d, 1H, J = 8 Hz, ArH), 11.00 (s, 1H, NH). ^{13}C NMR (DMSO-d_6), δ ppm: 14.42, 41.84, 61.05, 121.75, 123.21, 126.26, 170.52. EI-MS: m/z 279 $[M]^+$(3.5%), 280 $[M+1]^+$(1.6%), 176 (43.4%), 149 (100%). Anal. calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04. Found: C, 51.10; H, 4.56; N, 14.92%.

Ethyl{[(benzothiazol-2-ylamino)thiocarbonyl]amino}acetate. (4b). Prepared as described for **4a** but starting from **2b**. Recrystallized from ethanol; Yield: 58%; mp: 148–150°C; IR cm^{-1}: 3470 & 3395 (NH), 1731 (C=O), 1634, 1613, 1544, 1506, 1211(C=S); ^{1}H NMR (DMSO-d_6), δ ppm: 1.16–1.19 (t, 3H, J = 7 Hz, -CH_2CH_3), 4.09–4.13 (q, 2H, J = 7 Hz, -CH_2CH_3), 4.35–4.36 (d, 2H, J = 5 Hz, -NHCH_2), 7.23–7.26 (t, 1H, J = 8 Hz, ArH), 7.37–7.40 (t, 1H, J = 8 Hz, ArH), 7.60–7.61 (d, 1H, J = 8 Hz, ArH), 7.85–7.87 (d, 1H, J = 8 Hz, ArH), 10.10 (bs, 1H, NH), 12.20 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6), δ ppm: 14.44, 46.17, 61.17, 122.25, 124.14, 126.83, 169.31. Anal. calcd. for $C_{12}H_{13}N_3O_2S_2$: C, 48.79; H, 4.44; N, 14.23. Found: C, 48.60; H, 3.98; N, 14.16%.

{[(Benzothiazol-2-ylamino)carbonyl]amino}acetic acid hydrazide (5a). A solution of **4a** (5 mmol) and hydrazine hydrate (10 mmol) in ethanol (10 mL) was refluxed for 2 h, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The white precipitate obtained was collected and recrystallized from aqueous ethanol; Yield: 85%; mp: 210–212°C; IR cm^{-1}: 3410 & 3250 (NH), 1696 (C=O, urea), 1675 (C=O, hydrazide), 1607 (C=N). ^{1}H NMR (DMSO-d_6), δ ppm: 3.76–3.77 (d, 2H, J = 5 Hz, -NHCH_2), 4.20–4.40 (bs, 2H, -NHNH_2), 7.04 (bs, 1H, NH), 7.15–7.18 (t, 1H; J = 8 Hz, ArH), 7.30–7.33 (t, 1H; J = 8 Hz, ArH), 7.57–7.59 (d, 1H, J = 8 Hz, ArH), 7.81–7.83 (d, 1H; J = 8 Hz, ArH), 9.20 (bs, 1H, NH), 10.80 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6), δ ppm: 41.70, 120.04, 121.71, 123.13, 126.22, 131.68, 149.29, 154.32, 160.14, 168.70. Anal. calcd. for $C_{10}H_{11}N_5O_2S$: C, 45.27; H, 4.18; N, 26.40. Found: C, 44.96; H, 4.08; N, 26.35%.

{[(Benzothiazol-2-ylamino)thiocarbonyl]amino}acetic acid hydrazide (5b). Prepared as described for **5a** but starting from **4b**. Recrystallized from aqueous ethanol; Yield: 80%; mp: 195–196°C; IR cm^{-1}: 3410 & 3230 (NH), 1654 (C=O), 1610 (C=N), 1466, 1368, 1228 (C=S). ^{1}H NMR (60 MHz, DMSO-d_6), δ ppm: 4.30–4.40 (d, 2H, J = 5 Hz,-NHCH_2), 4.50–4.70 (bs, 2H, -NHNH_2), 7.50–7.55 (s, 1H, NH), 7.60–8.50 (m, 4H, ArH), 9.20–9.30(bs, 1H, NH), 10.70–10.90 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6), δ ppm: 41.70, 120.04, 121.71, 123.13, 126.22, 131.68, 149.29, 154.32, 160.14, 168.70. Anal. calcd. for $C_{10}H_{11}N_5OS_2$: C, 45.27; H, 4.18; N, 26.40. Found: C, 44.96; H, 4.08; N, 26.35%.

1-({[(Benzothiazol-2-ylamino)carbonyl]amino}acetyl)-4-phenythiosemi- carbazide (6). A solution of **5a** (0.005 mmol) and phenyl isothiocyanate (0.005 mmol) in ethanol (10 mL) was refluxed for 2 h, the reaction mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The white precipitate obtained was collected and recrystallized from aqueous ethanol; Yield: 75%; mp: 197–198°C; IR cm^{-1}: 3390, 3275 (NH), 1703(C=O, urea), 1659 (C=O, hydrazide), 1540, 1206 (C=S). ^{1}H NMR (DMSO-d_6), δ ppm: 3.92–3.93 (d, 2H, J = 5 Hz, -NHCH_2), 7.09 (bs, 1H, NH), 7.14–7.20 (m, 3H, ArH), 7.30–7.34 (m, 3H, ArH), 7.40–7.42 (d, 1H, J = 8 Hz, ArH), 7.58–7.60 (d, 1H, J = 8 Hz, ArH), 7.81–7.82 (d, 1H, J = 8 Hz, ArH), 9.48 (bs, 1H, NH), 9.68 (s, 1H, NH), 10.26 (s, 1H, NH), 11.00 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{16}N_6O_2S_2$: C, 50.98; H, 4.03; N, 20.98. Found: C, 50.11; H, 3.60; N, 20.77%.

In vitro *cytotoxicity screening*

Human MCF-7 breast cancer cells were from ATCC (Manassas, VA, USA). MTT kit was obtained from Sigma (St. Louis, MO, USA).

Procedures. Human MCF-7 breast cancer cells were cultured in RPMI medium supplemented with 10% fetal calf serum and 1 μg/mL kanamycin at 37°C in 5% CO_2 in humidified air. *In vitro* cytotoxicity was

determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [26]. This assay measures the reduction of the tetrazolium salt to the formazan salt by mitochondrial dehydrogenases in living cells. After being cultured overnight to allow for cell attachment, the cells, plated in 96-well culture plates (3×10^3 cells/well), were incubated in the presence of different test compounds at 10, 100 μM for 96 h. The spectrophotometric absorbance of the formazan salt was measured at 580 nm using a microplate reader. Pirarubicin (Pharmacia-Upjohn) was used as a positive control. The cell survivals were calculated as percentages of the absorbency of treated cells over untreated controls.

Modeling studies

Computer-assisted simulated docking experiments were carried out under an MMFF94X force field on telemetric DNA G-quadruplex structures (PDB ID: 1L1H) using Chemical Computing Group's Molecular Operating Environment (moe-dock 2005) software, Montréal, Canada.

Methodology. The coordinates of the X-ray crystal structure of **IV** bound to the G-quadruplex were obtained from Protein Data Bank (PDBID: 1L1H). The ligand molecules were constructed using the builder module and were energy minimized. The active site of G-quadruplex was generated using the MOE-Alpha Site Finder, and then ligands were docked within this active site using the MOE-Dock. The lowest energy conformation was selected and the ligand interactions (hydrogen bonding and hydrophobic interaction) with G-quadruplex were determined.

Antimycobacterial assay

The primary antimycobacterial evaluation was performed at the National Hansen's Disease Programs (NHDP) TAACF facilities, Baton Rouge, LA, USA. The screening was conducted at a single concentration of 6.25 μg/mL against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA). Compounds exhibiting fluorescence were tested in the BACTEC 460-radiometric system [27]. Compounds effecting $<90\%$ inhibition in the primary screen were not evaluated further.

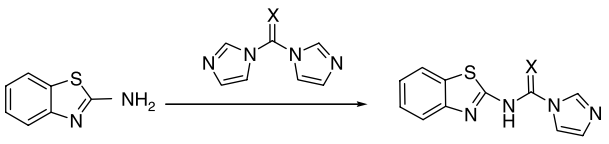
Antimicrobial assay

The microdilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) were used for the determination of antibacterial and antifungal activity [28]. The utilized test organisms were: *Escherichia coli* ATCC 25922 as an example of Gram-negative bacteria, *Staphylococcus aureus* ATCC 19433 as an example of Gram-Positive bacteria and *Candida albicans* as yeast-like fungi. Ampicillin trihydrate and clotrimazole were used as standard antibacterial and antifungal agents, respectively. Solutions of the test compounds, ampicillin trihydrate and clotrimazole were prepared in DMSO at a concentration of 1600 μg mL^{-1}. The two-fold dilutions of the compounds were prepared (800, 400,..6.25 μg mL^{-1}). The microorganism suspensions at 10^6 CFU mL^{-1} (Colony Forming Unit/mL) concentrations were inoculated to the corresponding wells. Plates were incubated at 36°C for 24 h to 48 h. The incubation chamber was kept sufficiently humid. At the end of the incubation period, the minimal inhibitory concentrations (MICs) were determined which were defined as the minimum concentrations of a compounds that visually inhibits the growth of tested microorganisms.

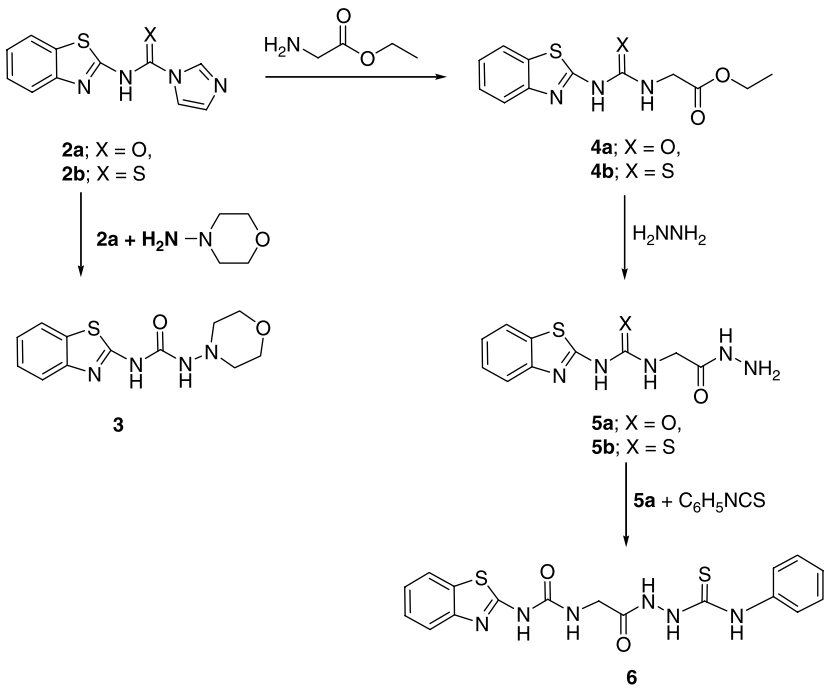
Results & discussion

Chemistry

Benzothiazolyl urea and thiourea derivatives **3–6** were prepared according to the procedure depicted in Schemes 1, 2. The precursors **2a** and **2b** were prepared by analogy with a previously reported method [18,19] by reaction of 2-aminobenzothiazole **1** with 1,1′-carbonyldiimidazole or 1,1′-thiocarbonyldiimidazole, respectively. Reaction of **2a** with N-aminomorpholine afforded **3** while reaction of **2a** and **2b** with ethyl glycinate yielded the esters **4a** and **4b**, respectively. When these esters reacted with hydrazine hydrate, the corresponding hydrazides **5a, 5b** were obtained (Scheme 1). Further reaction of the hydrazide **5a** with phenyl isothiocyanate yielded the thiosemicarbazide **6**. The identities of the compounds obtained were confirmed by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. The IR spectra of the synthesized compounds generally show the characteristic bands corresponding to the carbonyl and the thiocarbonyl functions, in addition to the NH moieties. The ^{1}H-NMR spectra of **1–6** showed the benzothiazole nucleus protons at the aromatic region and broad exchangeable singlets due to NH urea or



Scheme 1. The synthetic pathway of **2a, 2b.**



Scheme 2. The synthetic pathway of **3–6.**

thiourea protons. All other aromatic and aliphatic protons were observed in the expected regions.

Cytotoxicity study

Out of the synthesized benzothiazole derivatives, **2a**, **2b**, **3**, **4a**, **4b**, and **5a** were evaluated for their cytotoxic activity against MCF-7 (Breast cancer cell lines) using (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) MTT assay [26] with pirarubicin as a positive control. Compounds were tested at 100 μM and 10 μM concentrations and the culture was incubated for 96 h. The percent survival for each compound was reported as the percent of growth of the treated cells when compared to the untreated control cells. For each compound, the procedures were repeated four times and the mean value was calculated. As shown in Table I, at 100 μM, all the tested compounds reduced the growth of MCF-7 cell lines to the 32–75% range. On the other hand, at 10 μM, **3** was the most active compound reducing the growth of MCF-7 cells to 76%.

Table I. Primary *in vitro* growth inhibition assay results for compounds at 100 and 10 μM concentration.

	Growth percentage of MCF-7 breast cancer cells	
Compound	Mean ± S.E. at 100 μM	Mean ± S.E. at 10 μM
Control	100	100
2a	32.50 ± 0.44	96.90 ± 1.76
2b	38.79 ± 2.36	100.42 ± 1.63
3	39.81 ± 2.01	75.77 ± 2.14
4a	58.46 ± 1.55	121.02 ± 1.43
4b	78.53 ± 2.42	111.55 ± 2.64
5a	35.62 ± 1.36	96.32 ± 2.64
Pirarubicin	ND	1.14 ± 1.25

Docking of 3 with G-quadruplex of human telomere DNA

In an attempt to understand the reason for the observed cytotoxic activity of **3**, we performed a molecular modeling study using the Molecular Operating Environment (MOE) module.

A structural similarity between **3** and the reported G-quadruplex stabilizers (eg. **III**, **IV**) (Figure 2.), encouraged us to study a possible G-quadruplex stabilization action of **3**. To test this hypothesis, as a starting point, we used the crystal structure of **IV** with G-quadruplex (PDB ID: 1H1L) (Figure 3) [29]. Docking of the energy minimized conformation of **3** into the G-quadruplex of human telomere DNA (Figure 4) showed a very close pattern of binding to the G-quadruplex of human telomere DNA as that resulting from the crystal structure of **IV**. In both cases (**IV** and **3**) a hydrogen bond interaction can be observed between a carbonyl group of the ligand and the thiamine 1006 base. From this data, **3** may provide a starting point for the design of unique compounds with high affinity and selectivity for human telomeric DNA, leading to enhanced telomerase inhibition.

Antimycobacterial activity

Compounds **2–6** were tested for their primary antimycobacterial activity against *M. tuberculosis*

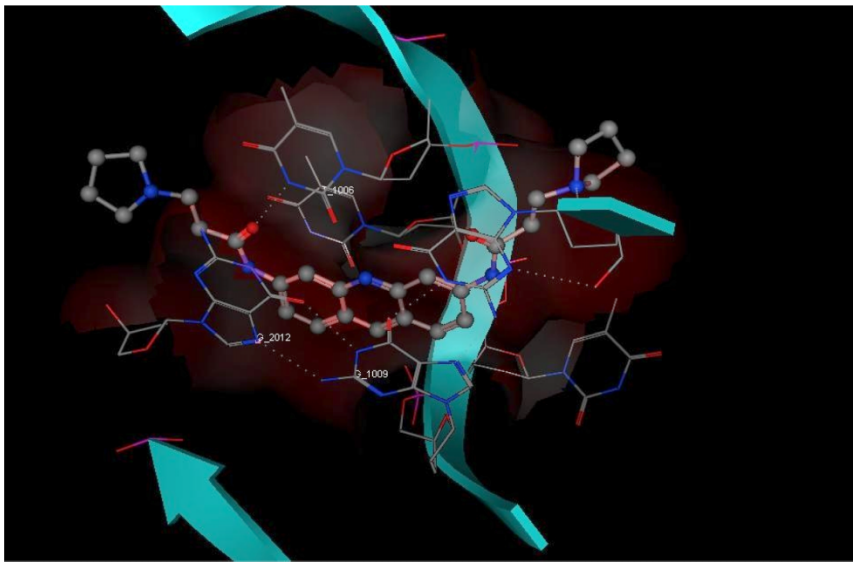


Figure 3. 3D View from a molecular modeling study, of the minimum-energy structure of the complex of **IV** docked in the G-quadruplex of human telomere DNA (PDB ID: 1H1L). White dashed lines depict hydrogen bond interactions. Viewed using Molecular Operating Environment (MOE) module. (See colour online)

$H_{37}R_v$ at a single concentration of 6.25 μg/mL [27]. As shown in Table II, the imidazole derivatives **2a**, **2b** were the least active in this series while there was no observed variations of the biological activities of the tested esters **4a**, **4b**, hydrazides **5a**, **5b** or the thiosemicarbazide derivative **6**. Again, **3** was the most effective in this series with a 37% growth inhibition. From the above results we can conclude that the benzothiazole urea or thiourea derivatives appear to be a useful scaffold for the antimycobacterial agents.

Antimicrobial activity

Compounds **2–6** were tested for their *in vitro* antimicrobial against *E. coli* ATCC 25922, *S. aureus* ATCC 19433, and *C. albicans* [28]. Ampicillin trihydrate and clotrimazole were used as standard

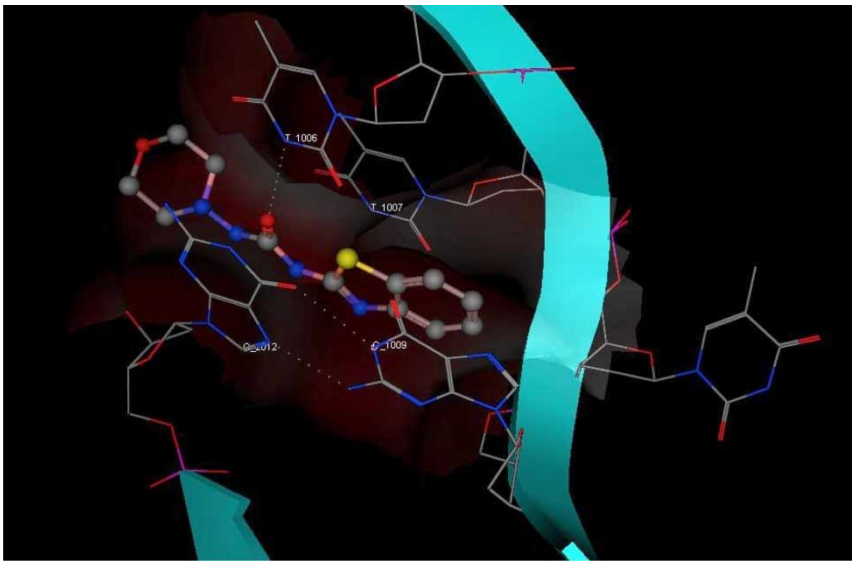


Figure 4. 3D View from a molecular modeling study, of the minimum-energy structure of the complex of **3** docked in the G-quadruplex of human telomere DNA (PDB ID: 1H1L). White dashed lines depict hydrogen bond interactions. Viewed using Molecular Operating Environment (MOE) module. (See colour online)

Table II. Antimycobacterial *in vitro* activity of test compounds.

Compound	TAACF ID[a]	% inhibition[b]
2a	299139	6
2b	299140	9
3	299141	37
4a	299143	19
4b	299144	18
5a	299145	17
5b	299146	18
6	299147	17
Ethionamide	–	89

[a]TAACF: Tuberculosis Antimicrobial Acquisition and Coordinating Facility.; [b]Growth inhibition of *Mycobacterium tuberculosis* $H_{37}R_v$ at a single concentration of 6.25 μg/mL

antibacterial and antifungal agents, respectively. As shown in Table III., the MIC values of the tested compounds are generally within the range of 12.5 to more than 200 μg mL^{-1} against all evaluated strains. Against *E. coli*, **6** showed similar activity to ampicillin, while the other compounds are only moderately active. Only **5b** showed similar activity against *S. aureus* as ampicillin. None of the tested compounds showed any activity against *C. albicans* when compared to clotrimazole. Further studies on these types of compounds are needed to find out a possible mechanism of action and will be the subject of future reports.

Conclusions

In conclusion, a series of benzothiazole urea and thiourea derivatives was synthesized as potential cytotoxic and antimicrobial agents. Compound **3** was the most effective against MCF-7 breast cancer cell lines and *Mycobacterium tuberculosis* $H_{37}R_v$ strain. On the other hand, **6** and **5b** were the most effective derivatives against *E. coli* and *S. aureus*, respectively.

Table III. Minimal inhibitory concentrations (MIC) in μg mL^{-1} of test compounds.

Compound	*E. coli*	*S. aureus*	*C. albicans*
2a	100	>200	>200
2b	50	>200	>200
3	100	100	>200
4a	>200	>200	>200
4b	>200	>200	>200
5a	100	>200	>200
5b	100	12.5	>200
6	25	50	>200
Ampicillin	25	12.5	—
Clotrimazole	—	—	12.5

(—) = not determined

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