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Laboratory note

2,4-Disubstituted thiazoles II.* A novel class of antitumor agents, synthesis and biological evaluation

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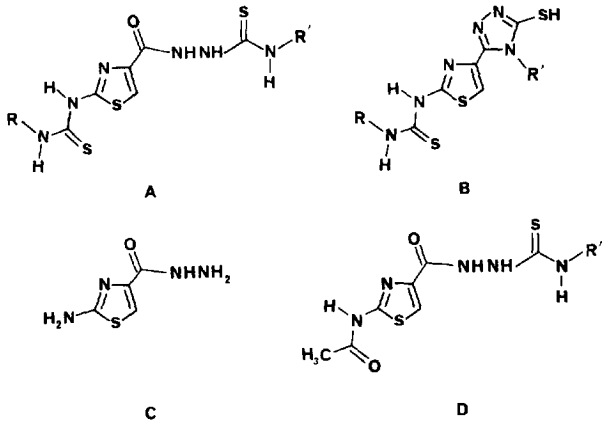
Summary — A series of 2,4-disubstituted thiazole derivatives bearing *N*-*n*-butyl or *N*-cyclohexylthioureido synthon at position 2 and *N*-substituted thiosemicarbazone moiety at position 4 have been synthesized and tested for antitumor activity using the National Cancer Institute's in-vitro-disease-oriented antitumor screen. All of the tested compounds showed antineoplastic activity at concentrations less than 100 μM. Compounds **7**, **9**, **15** and **17** in particular showed activity with GI_{50} (mean-graph midpoint) of 17.8, 8.5, 9.5 and 7.4 μM, respectively. The detailed syntheses, spectroscopic and biological data are discussed.

2,4-disubstituted thiazole / thioureido derivative / thiosemicarbazone / antitumor testing

Introduction

The antitumor activity of certain 2,4-disubstituted thiazole analogues was reported recently [1–3]. This class of compounds has the general structure **A** with a thioureido group at position 2 and a thiosemicarbazone moiety at position 4. Potato disc assay [4] was used to evaluate the antitumor activity of these compounds. Consequently, a tentative structure–activity relationship (SAR) [1] was obtained revealing the following. First, an amide moiety at position 4 of the thiazole ring is essential for activity; cyclization of the active thiosemicarbazones **A** with the loss of the amide function led to the inactive 1,2,4-triazolthiones **B**. Second, the NHCSNH-R (or R') group in **A** is essential for antitumor activity, as evidenced by structural comparison with its hydrazide precursor **C**. Third, the alkyl groups (R = R') on **A** have a significant contribution to the antitumor activity. Aliphatic alkyl derivatives are more potent than aromatic substitution and activity increases as the number of carbons increases (cyclohexyl > *n*-butyl > ethyl). Finally, the substitution at position 2 of the thiazole ring (thioureido as in **A** or acetamido as in **D**) showed no great influence on activity, which suggested that they act as an anchoring group to help the active moiety (4-amido function) attack the active site or enzyme(s) involved.



A **B** **C** **D**

R = R' = C_2H_5, *n*-C_4H_9, C_6H_{11}, C_6H_5.

The results obtained from our previous study showed that derivatives of **A** (R = R' = *n*-butyl or cyclohexyl) are among the most active compounds investigated. These two derivatives were used as lead compounds in the present study, and were further derivatized in the *N*-substituted thiosemicarbazone area to explore the scope and limitations of activity and to screen their cytotoxicity on human tumor cell lines. A new series of thiazole derivatives **A** was synthesized in which R on the 2-thioureido group is still either

*For Part I, see reference [1].

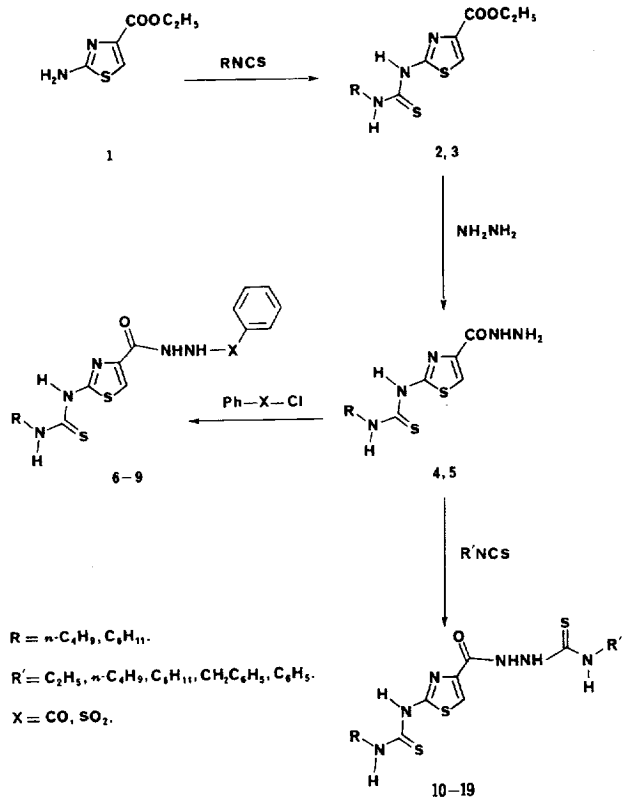
n-butyl or cyclohexyl, while the R' on the thiosemicarbazone moiety is varied from a 2 to 6 carbon chain, such as ethyl, *n*-butyl or cyclohexyl, representing aliphatic substitution, or benzyl or phenyl, representing aromatic substitution, to determine the effect of such a variation on antitumor activity.

Compounds containing an amide function such as bleomycin [5, 6], mitomycin [7] and streptozocin [8] are known antineoplastic agents. Recent literature reports discussed the anticancer potency of some sulphonamide analogues [9, 10]. Accordingly, the -NHCSNHR' function of the thiosemicarbazone moiety was replaced by -NHCOPh or -$NHSO_2$Ph to form *N*-aroylhydrazones or *N*-sulphonylhydrazones, respectively, in order to evaluate the influence of these two pharmacophores on the antitumor activity of the thiazole-4-thiosemicarbazone analogues. The anticancer testing was performed using the National Cancer Institute's (NCI) in-vitro-disease-oriented antitumor screen.

Chemistry

Ethyl 2-aminothiazole-4-carboxylate **1** was reacted with *n*-butyl or cyclohexyl isothiocyanates in pyridine to give the corresponding 2-thiourea derivatives **2** and **3** in 80 and 78% yields, respectively. Treatment of **2** or **3** with hydrazine hydrate yielded the acid hydrazides **4** or **5**, respectively, which were subsequently reacted with benzenesulphonyl chloride and benzoyl chloride in pyridine to give the sulphonyl hydrazones **6** and **8**, and the benzoyl hydrazones **7** and **9**, respectively.

The hydrazide function of **4** and **5** was further used to prepare the *N*-substituted thiosemicarbazone derivatives **10–19** by allowing them to react with a variety of isothiocyanate derivatives (ethyl, *n*-butyl, cyclohexyl, benzyl, phenyl) in refluxing ethanol (scheme 1, table I).



Scheme 1.

Biological investigation and discussion

The NCI's in-vitro-disease-oriented antitumor screen determines a test compound's effect on growth against a panel of approximately 60 human tumor cell lines [11, 12]. The antitumor screen usually involves the determination of the molar concentration that inhibits net cell growth to 50% (median growth inhibitory concentration, GI_{50}), the molar concentration which causes total inhibition of cell growth (total growth inhibitory concentration, TGI) and the molar concentration which causes 50% loss of initial cell level at the end of incubation period (median lethal concentration, LC_{50}) for each compound along with the full panel mean-graph midpoint concentrations (MG-MID) for all GI_{50}, TGI and LC_{50} values. Most of the tested compounds showed anticancer activity (GI_{50}, TGI and $LC_{50} \leq 100$ μM) against leukemia, non-small-cell lung, colon, central nervous system, melanoma, ovarian, renal, prostate and breast cancer subpanel cell lines (tables II and III).

Compounds **7**, **9**, **15** and **17** showed effective growth inhibition GI_{50} values (MG-MID) of 17.8, 8.5, 9.5 and 7.4 μM, cytostatic activity TGI values (MG-MID) of 47.9, 38.9, 40.7 and 30.2 μM, and cytotoxic activity LC_{50} values (MG-MID) of 83.2, 83.2, 83.2 and 74.1 μM, respectively. Compounds **6**, **8**, **13** and **18** showed GI_{50} values (MG-MID) of 33.1, 30.9, 35.5 and 33.9 μM, respectively; compounds **10**, **12**, **14** and **19** showed GI_{50} values (MG-MID) of 66.1, 85.1, 79.4 and 53.7 μM, respectively.

The ratio obtained by dividing the compound's full panel MG-MID (μM) by its individual subpanel MG-MID concentration (μM) is considered as an indication of the compound's selectivity [13]. Ratios between 3 and 6 refer to moderate selectivity, while ratios greater than 6 indicate selectivity towards the corre-

Table I. Recrystallization solvents, melting points, yield percentages and molecular formula of the synthesized compounds.

Compound	*R*	*R' or X*	*Solvent*	*Mp (°C)*	*Yield (%)*	*Molecular formula*
2	n-C_4H_9	–	iso-PrOH	106–107	80	$C_{11}H_{17}N_3O_2S_2$
3	n-C_6H_{11}	–	iso-PrOH	186–187	78	$C_{13}H_{19}N_3O_2S_2$
4	n-C_4H_9	–	n-BuOH	125–127	46	$C_9H_{15}N_5OS_2$
5	n-C_6H_{11}	–	iso-PrOH	201–205	58	$C_{11}H_{17}N_5OS_2$
6	n-C_4H_9	SO_2	DMF	196–197	78	$C_{15}H_{19}N_5O_3S_3$
7	n-C_4H_9	CO	AcOH	125–126	55	$C_{16}H_{19}N_5O_2S_2$
8	n-C_6H_{11}	SO_2	DMF	175–176	84	$C_{17}H_{21}N_5O_3S_3$
9	n-C_6H_{11}	CO	AcOH	112–113	90	$C_{18}H_{21}N_5O_2S_2$
10	n-C_4H_9	C_2H_5	EtOH	198–200	65	$C_{12}H_{20}N_6OS_3$
12	n-C_4H_9	C_6H_{11}	EtOH	189–190	50	$C_{16}H_{26}N_6OS_3$
13	n-C_4H_9	$C_6H_5CH_2$	EtOH/H_2O	219–220	82	$C_{17}H_{22}N_6OS_3$
14	n-C_4H_9	C_6H_5	EtOH/H_2O	243–244	70	$C_{16}H_{20}N_6OS_3$
15	n-C_6H_{11}	C_2H_5	EtOH	229–230	56	$C_{14}H_{22}N_6OS_3$
16	n-C_6H_{11}	n-C_4H_9	EtOH/H_2O	184–185	74	$C_{16}H_{26}N_6OS_3$
18	n-C_6H_{11}	$C_6H_5CH_2$	EtOH	139–140	80	$C_{19}H_{24}N_6OS_3$
19	n-C_6H_{11}	C_6H_5	EtOH/H_2O	164–165	85	$C_{18}H_{22}N_6OS_3$

Compounds **11** (R = R' = n-C_4H_9) and **17** (R = R' = C_6H_{11}) are cited in reference [1].

Table II. Median growth inhibitory concentration (GI_{50}, μM) of in vitro subpanel tumor cell lines.

Cancer cell line panel	***6***	***7***	***8***	***9***	***10***	***12***	***13***	***14***	***15***	***17***	***18***	***19***
Leukemia	40.1	40.9	47.2	5.0	65.4	62.8	26.9	>100	5.7	24.9	46.8	51.7
Non-small-cell lung	39.6	20.6	44.8	10.3	85.8	>100	54.2	87.3	36.3	31.0	42.5	75.4
Colon	30.1	14.2	29.0	7.2	66.8	90.4	35.5	90.4	20.0	18.1	33.1	45.6
CNS	34.5	21.4	31.6	23.9	78.5	97.9	31.1	76.6	14.9	6.9	37.7	74.4
Melanoma	24.8	15.7	25.0	12.4	79.8	95.4	30.0	73.6	7.2	6.4	28.3	54.5
Ovarian	32.3	13.6	38.3	6.7	82.6	79.5	55.0	>100	3.9	6.9	52.7	74.7
Renal	41.3	16.9	34.0	17.5	69.1	86.9	42.9	79.4	11.7	7.9	42.5	82.3
Prostate	32.3	17.5	30.7	13.3	86.8	>100	50.8	>100	14.8	12.9	48.2	81.2
Breast	39.9	16.0	26.5	10.1	75.0	96.3	37.8	84.5	8.5	9.4	32.6	50.4
MG-MID[a]	33.1	17.8	30.9	8.5	66.1	85.1	33.5	79.4	9.5	7.4	33.9	53.7

Data obtained from NCI's in-vitro-disease-oriented human tumor cell screen (see references [11–13] for detail). Compounds **11** and **16** were not tested; [a]GI_{50} (μM) full panel mean-graph midpoint.

Table III. Total growth inhibitory concentration (TGI, μM) of in vitro subpanel tumor cell lines.

Cancer cell line panel	***6***	***7***	***8***	***9***	***13***	***15***	***17***	***18***	***19***
Leukemia	>100	>100	>100	70.9	81.9[b]	83.8[b]	74.4	91.6[b]	>100
Non-small cell lung	>100	64.4	97.8[b]	39.2	>100	68.0	51.6	95.0[b]	>100
Colon	81.2	39.3	78.9	23.0	>100	35.6	38.1	76.3	>100
CNS	95.3[b]	76.7	85.0[b]	60.8	92.2[b]	41.4	25.3	89.6[b]	>100
Melanoma	61.0	32.3	59.8	31.0	93.5[b]	24.7	31.0	76.7	80.7
Ovarian	90.8[b]	49.6	86.6[b]	50.6	>100	52.7	25.4	>100	>100
Renal	87.8[b]	39.7	75.1	51.9	96.1[b]	49.6	33.5	94.2[b]	97.5
Prostate	96.6[b]	46.6	90.8[b]	50.1	>100	55.2	62.5	>100	>100
Breast	96.6[b]	45.2	62.0	44.2	94.2[b]	42.1	43.7	90.2[b]	>100
MG-MID[a]	83.2	47.9	75.9	38.9	93.3	40.7	30.2	85.1	95.6

Compounds **11** and **16** were not tested; compounds **10**, **12** and **14** showed TGI values >100 μM. [a]TGI (μM) full panel mean-graph midpoint. [b]Compounds showed LC_{50} (median lethal concentration) >100 μM.

sponding cell-line subpanel [13]. All of the active compounds in the present study (**7**, **9**, **15** and **17**) proved to be nonselective with broad spectrum antitumor activity against the nine tumor subpanels used with ratios of 0.2–1.7 for GI_{50} and 0.4–1.7 for TGI.

Structure–activity correlations of the obtained antitumor screening data revealed that the 2-cyclohexylthioureido derivatives **15** and **17** (R' = C_2H_5 and C_6H_{11}; GI_{50} (MG-MID) = 9.5 and 7.4 μM, respectively) are more active than their corresponding 2-*n*-butylthioureido compounds **10** and **12** (R' = C_2H_5 and C_6H_{11}; GI_{50} (MG-MID) = 66.1 and 85.1 μM, respectively). The introduction of either the benzyl or phenyl moiety to position 4 of the thiosemicarbazone group in both 2-cyclohexyl and 2-*n*-butylthioureido series gave compounds of almost equal activity as shown in **13** and **18** (R' = $C_6H_5CH_2$; GI_{50} (MG-MID) = 33.5 and 33.9 μM, respectively); and **14** and **19** (R' = C_6H_5; GI_{50} (MG-MID) = 79.4 and 53.7 μM, respectively). It is worth mentioning that even though the *n*-butyl and cyclohexyl groups have the same spacial distance (four carbons length), the 2-cyclohexylthioureido series is more active than the 2-*n*-butylthioureido derivatives possibly due to the increased cell membrane permeability, which supports our earlier findings [1].

Further interpretation of the obtained data showed that, within the cyclohexyl series, aliphatic substitution at the 4-thiosemicarbazone moiety, such as in **15** and **17** (GI_{50} (MG-MID) = 9.5 and 7.4 μM, respectively) increased the antitumor activity to more than threefold what was found for the aromatic substitution derivatives **18** and **19** (GI_{50} (MG-MID) = 33.9 and 53.7 μM, respectively).

Replacing the -NHCSNHR' of the 4-thiosemicarbazone moiety of **10–19** by the benzoylhydrazone group (-NHCOPh) led to the more active compound **9** with GI_{50} (MG-MID) = 8.5 μM, which is comparable to the activity of compound **17**. On the other hand, replacing the same moiety with sulphonylhydrazone synthon (-$NHSO_2Ph$, **6** and **8**) did not improve the antitumor potency. Benzoylhydrazones **7** and **9** (GI_{50} (MG-MID) = 17.8 and 8.5 μM, respectively) are found to be more active than the sulphonylhydrazone derivatives **6** and **8** (GI_{50} (MG-MID) = 33.1 and 30.9 μM, respectively). Further evidence emphasizing the enhanced activity of the 2-cyclohexylthioureido series over the 2-*n*-butylthioureido derivatives is obtained by comparing the activity of the 2-cyclohexylthioureido-4-benzoylhydrazone derivative **9** (GI_{50} (MG-MID) = 8.5 μM) with 2-*n*-butylthioureido-4-benzoylhydrazone derivative **7** (GI_{50} (MG-MID) = 17.8 μM); compound **9** is about twice as active as **7**.

In conclusion, our investigation revealed that the -$NHCOC_6H_5$ and -$NHCSNHC_6H_{11}$ moieties could replace each other without loss of antitumor activity, as shown from the obtained antitumor data of compounds **9** and **17**. Compounds **9** MG-MID = 8.5, 38.9 and 83.2 μM, **15**, MG-MID = 9.5, 40.7 and 83.2, and **17** MG-MID = 7.4, 30.2 and 74.1 μM, for GI_{50}, TGI and LC_{50}, respectively, are the most active members of this series, showing broad spectrum antitumor activity.

Experimental protocols

Melting points (°C, uncorrected) were recorded on a Electrothermal melting point apparatus. ^{1}H-NMR spectra were recorded on a Varian FT-80A, 80 MHz instrument, in DMSO-d_6 using TMS as an internal standard (chemical shift in δ ppm). Microanalytical data (C, H, N) agreed with the proposed structures within ±0.4% of the theoretical values. Thin layer chromatography (TLC) was performed on precoated silica-gel plates (60-F 254, 0.2 mm) manufactured by EM Sciences Inc; shortwave UV light (254 nm) was used to detect the UV-absorbing compounds.

Chemistry

*1-n-Butyl or 1-cyclohexyl-3-[4-(ethoxycarbonyl)thiazol-2-yl] thioureas **2** and **3***

A mixture of ethyl 2-aminothiazole-4-carboxylate (**1**, 0.01 mol, 1.7 g) and *n*-butyl or cyclohexyl isothiocyanate (0.01 mol) in pyridine (10 mL) was heated under reflux for 8 h; the solvent was then removed in vacuo. The obtained residue was flash chromatographed on silica using CH_2Cl_2. The purified compounds were then recrystallized. ^{1}H-NMR, **2**: δ 0.7–1.0 (m, 3H, $-N(CH_2)_3CH_3$), 1.2–1.8 (m, 7H, $-CH_2CH_3$ and $-NCH_2(CH_2)_2$), 3.2–3.5 (m, 2H, $-NCH_2$), 4.1 (q, 2H, $-CH_2CH_3$), 6.8 (brs, 2H, NH), 7.6 (s, 1H, thiazole-H). **3**: 1.2–2.3 (m, 13H, cyclohexyl-H and $-CH_2CH_3$), 3.2–3.4 (m. 1H, cyclohexyl-H), 4.2 (q, 2H, $-CH_2CH_3$), 6.2–6.4 (m, 1H, NH), 7.7 (s, 1H, thiazole-H), 8.2 (brs, 1H, NH).

*1-n-Butyl or 1-cyclohexyl-3-[4-(hydrazinocarbonyl)thiazol-2-yl]-thioureas **4** and **5***

A mixture of the thiourea derivatives **2** or **3** (0.01 mol) and hydrazine hydrate 85% (10 g, 0.2 mol) in ethanol (25 mL) was heated under reflux for 4 h; the solvent was then removed under reduced pressure and the moist solid obtained was isotroped twice with benzene (50 mL). The resulted solid was adsorbed to silica and column chromatographed using 20% EtOAc/CH_2Cl_2 to obtain an analytically pure sample. ^{1}H-NMR, **4**: δ 0.6–0.9 (m, 3H, $-N(CH_2)_3CH_3$), 1.2–1.6 (m, 4H, $-NCH_2(CH_2)_2$), 3.3–3.5 (m, 2H $-NCH_2$), 6.3 (brs, 2H, NH), 7.7 (s, 1H, thiazole-H), 8.2 (m, 1H, NH), 9.3 (brs, 2H, NH). **5**: 1.0–2.1 (m, 10H, cyclohexyl-H), 3.1–3.2 (m, 1H, cyclohexyl-H), 6.1–6.3 (m, 2H, NH), 7.7 (s, 1H, thiazole-H), 7.9 (brs, 1H, NH), 8.6 (m, 2H, NH).

*1-n-Butyl or 1-cyclohexyl-3-[4-(N-benzenesulphonyl or N-benzoyl hydrazinocarbonyl)thiazol-2-yl]thioureas **6–9***

A mixture of the hydrazide derivatives **4** or **5** (0.01 mol) and benzene sulphonyl chloride or benzoyl chloride (0.01 mol) in pyridine was stirred at room temperature for 10 h. Pyridine was then removed under reduced pressure, the gummy residue was washed with petroleum ether 60–80° and was loaded onto a silica-gel column, then eluted with CH_2Cl_2. The purified compounds were then recrystallized. ^{1}H-NMR, **6**: δ 0.7–1.0 (m, 3H, $-N(CH_2)_3CH_3$), 1.1–1.7 (m, 4H, $-NCH_2(CH_2)_2$), 3.2–3.4 (m, 2H, $-NCH_2$), 5.9 (br, m, 2H, NH), 7.4–7.8 (m, 6H, ArH and thiazole-H), 8.1 (brs, 1H, NH), 9.3 (brs, 1H, NH). **7**: 0.8–1.1 (m, 3H, $-N(CH_2)_3CH_3$), 1.2–1.7 (m, 4H, $-NCH_2(CH_2)_2$), 3.1–3.5 (m, 2H, $-NHCH_2$), 6.6 (brm, 2H, NH), 7.2–7.5 (m, 5H, ArH), 7.7 (s, 1H, thiazole-H), 8.3 (brm, 2H, NH). **8**: 1.1–2.1 (m, 10H, cyclohexyl-H), 3.0–3.3 (m, 1H, cyclohexyl-H), 5.9 (brs, 1H, NH), 6.2 (brs, 1H, NH), 7.2–8.0 (m, 7H, ArH; thiazole-H and NH), 8.5 (brs, 1H, NH). **9**: δ 1.0–2.1 (m, 10H, cyclohexyl-H), 3.1–3.3 (m, 1H, cyclohexyl-H), 4.5–5.2 (brm, 2H, NH), 7.1–8.2 (m, 8H, ArH; thiazole-H and NH).

*4-Alkyl or aryl-1-[2-(N-alkyl or N-arylthioureido)thiazol-4-carbonyl]thiosemicarbazides **10–19***

The acid hydrazide **4** or **5** (0.01 mol) was treated with alkyl or aryl isothiocyanate (0.015 mol) in ethanol (50 mL) and was heated under reflux for 4 h. The separated solid obtained upon cooling was filtered and washed with water. The obtained solids were then recrystallized. ^{1}H-NMR, **10**: δ 0.8–1.2 (m, 3H, $-N(CH_2)_3CH_3$), 1.3–1.7 (m, 7H, $-CH_2CH_3$ and $-NCH_2(CH_2)_2$), 3.1–3.5 (m, 2H, $-NCH_2$), 4.2 (m, 3H, $-CH_2CH_3$ and NH), 4.9 (m, 2H, NH), 6.5 (brs, 1H, NH), 7.4 (brs, 1H, NH), 7.8 (s, 1H, thiazole-H), **12**: δ 0.8–2.2 (m, 17H, $-N(CH_2)_3CH_3$, $-NCH_2(CH_2)$ and cyclohexyl-H), 3.0–3.6 (m, 4H, $-NCH_2$, cyclohexyl-H and NH), 5.1 (brs, 1H, NH), 6.7 (brs, 1H, NH), 7.6 (m, 3H, thiazole-H and NH). **13**: δ 0.9–1.1 (m, 3H, $-N(CH_2)_3CH_3$), 1.2–1.7 (m, 4H, $-NCH_2(CH_2)_2$), 3.2–3.6 (m, 2H, $-NCH_2$), 4.6 (m, 3H, $BnCH_2$ and NH), 5.4 (brm, 2H, NH), 7.3 (m, 6H, ArH and NH), 7.7 (s, 1H, thiazole-H), 8.2 (brs, 1H, NH). **14**: δ 0.8–1.1 (m, 3H, $-N(CH_2)_3CH_3$), 1.1–1.7 (m, 4H, $-NCH_2(CH_2)_2$), 3.1–3.5 (m, 2H, $-NCH_2$), 5.2 (brm, 2H, NH), 6.2 (brs, 1H, NH), 7.2 (s, 5H, ArH), 7.8 (s, 1H, thiazole-H), 8.3 (brm, 2H, NH). **15**: δ 1.0–2.1 (m, 13H, $-CH_2CH_3$ and cyclohexyl-H), 3.1–3.3 (m, 1H, cyclohexyl-H), 4.1–4.3 (m, 3H, $-CH_2CH_3$ and NH), 5.6 (brm, 2H, NH), 6.4 (brs, 1H, NH), 6.9 (brs, 1H, NH), 7.7 (s, 1H, thiazole-H). **16**: δ 0.9–2.3 (m, 17H, $-N(CH_2)_3CH_3$, $-NCH_2(CH_2)_2$ and cyclohexyl-H), 3.1–3.6 (m, 3H, $-NCH_2$ and cyclohexyl-H), 4.9 (brs, 1H, NH), 5.4 (brm, 2H, NH), 6.3 (brs, 1H, NH), 7.7 (s, 1H, thiazole-H), 8.1 (brs, 1H, NH). **18**: δ 1.1–2.2 (m, 10H, cyclohexyl-H), 3.0–3.4 (m, 1H, cyclohexyl-H), 4.4 (m, 3H, Bn CH_2 and NH), 6.4 (m, 2H, NH), 7.3 (m, 6H, ArH and NH), 7.6 (s, 1H, thiazole-H), 8.0 (brs, 1H, NH). **19**: δ 1.0–2.1 (m, 10H, cyclohexyl-H), 3.0–3.3 (m, 1H, NH), 6.5 (brs, 1H, NH), 7.3 (s, 5H, ArH), 7.7 (s, 1H, thiazole-H), 7.9 (m, 2H, NH).

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