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Design, Synthesis, and Anticancer Evaluation of Some Novel Thiourea, Carbamimidothioic Acid, Oxazole, Oxazolidine, and 2-Amino-1-Phenylpropyl-2-Chloroacetate Derived from L-Norephedrine[1]

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Abstract—A novel series of thiourea, carbamimidothioic acid, 4, 5-dihydrooxazole-2-thiol, oxazolidine-2-thine, and 2-amino-1-phenylpropyl-2-chloroacetate derivatives was designed and synthesized using 2-amino-1-phenylpropan-1-ol (L-norephedrine) as a strategic starting material. The structures of the newly synthesized compounds were established by elemental analyses, IR, and ^{1}H NMR and ^{13}C NMR spectral data. The compounds were evaluated for their in vitro anticancer activity against various cancer cell lines. The corresponding acetamide, carbamimidothioic acid, and 2-2-amino-1-phenylpropyl-2-chloroacetate derivatives showed almost the same activity as the standard drug doxorubicin against human breast cancer cell line (MCF-7). Also, the acetamide and 2-thioxoimidazolidin-4-one derivatives exhibited higher activity than the reference drug doxorubicin against human colon cancer cell line (HCT 116).

Keywords: *thiourea carbamimidothioic acid, oxazole, oxazolidine, 2-amino-1-phenylpropyl-2-chloroacetate, anticancer activity*

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INTRODUCTION

According to the World Health Organization, cancer is a foremost health tricky. More than 7 million deaths are reported worldwide annually [1, 2]. Because of limitation of surgery and radiotherapy in curing cancer, chemotherapy is of increasing importance [1, 2]. Therefore, identification of novel potent, selective, and less toxic anticancer agents remains one of the most pressing health problems. Thioureas are sulfur and nitrogen-containing compounds that have proved to be promising in drug research in recent years [3–8]. Some carbamimidothioic acid derivatives possess valuable antibacterial and anticancer activities [9–12]. Most of these compounds include heterocyclic rings, such as oxazole and oxazolidine. It is well known that oxazoles and oxazolidines find applications in the fields of medicine and industry [13–16]. Oxazole and oxazolidine nuclei have also been incorporated into a wide variety of therapeutically important molecules to transform them into better drugs. Thioureas can be used in control of plant pathogens, such as *Penicillum expansum* and *Fusarium oxysporum* [17]. 1,3-Dialkyl or diarylthioureas exhibit significant antifungal activity against *Pyricularia oryzae* and *Drechslera oryzae* [18]. It has been reported that thiourea, oxazole, and oxazolidine derivatives show potent anticancer activity [19, 20]. Crank et al. [21, 22] reported for the first time the antifungal activity of 2-aminooxazole thiourea derivatives against *Botrytis cinerea*. In this work, a series of new thiourea, carbamimidothioic acid, oxazole, oxazolidine, and 2-amino-1-phenylpropyl-2-chloroacetate derivatives bearing biologically active moieties were prepared and evaluated for their anticancer activity against three human cancer cell lines.

RESULTS AND DISCUSSION

2-Amino-1-phenylpropan-1-ol (L-norephedrine) (**I**) was reacted with *p*-chlorophenylisothiocyanate(**II**) to give three novel compounds: 1-(4-chlorophenyl)-3-(1-hydroxy-1-phenylpropan-2-yl)thiourea (**III**), 4-methyl-5-phenyl-4,5-dihydrooxazole-2-thiol (**V**), and its isomer 4-methyl-5-phenyloxazolidine-2-

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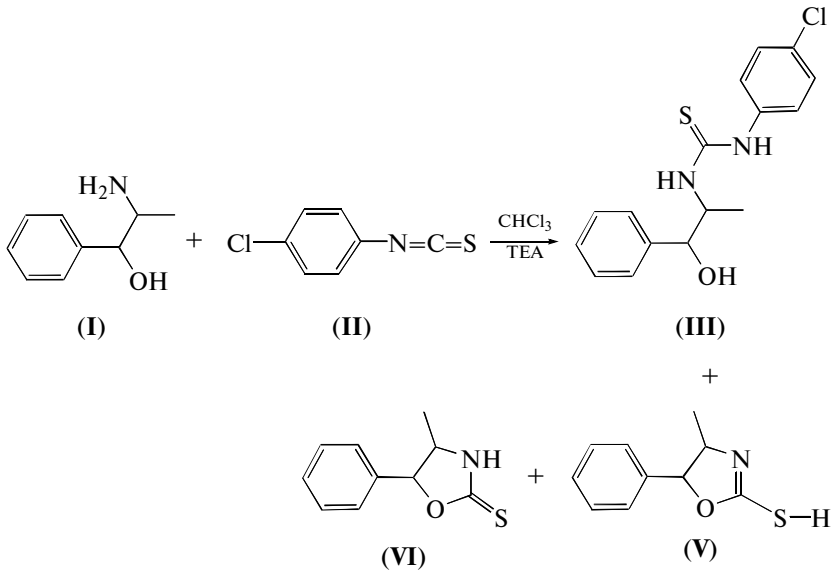
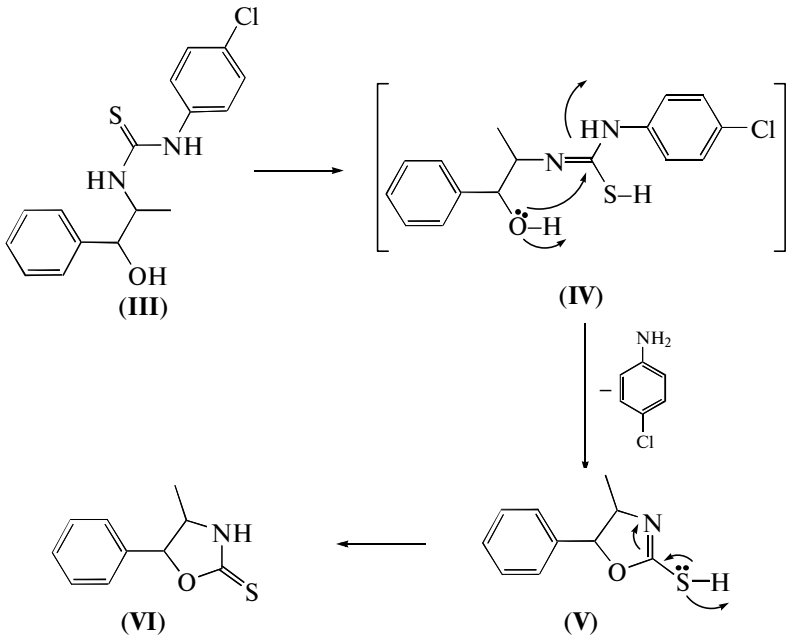
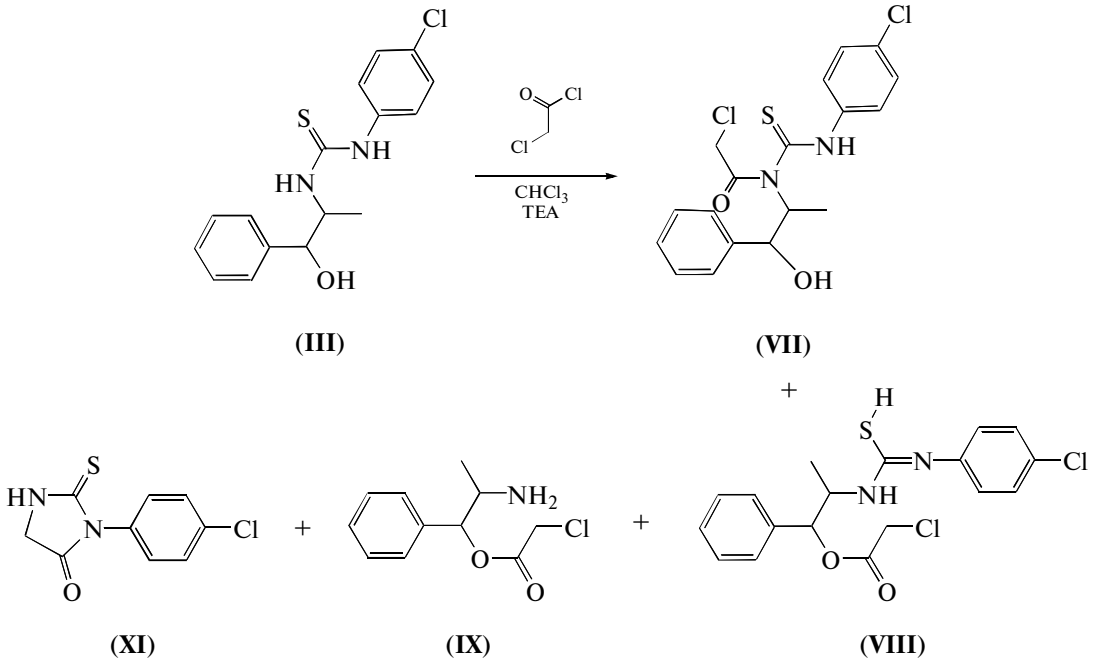
thione (**VI**) (Scheme 1). Compounds (**V**) and (**VI**) were formed via intermediate (**IV**) (Scheme 2). The structures of compounds (**III**), (**V**), and (**VI**) were established on the basis of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. IR spectra of compounds (**V**) and (**VI**) revealed the absence of OH and C–Cl bands and the presence of bands at 3100, 3068 cm^{-1} (CH arom.) and 2942, 2835, 2956, and 2876 cm^{-1} (CH aliph.), respectively. The main difference between the two compounds was the presence of C=N band at 1612 cm^{-1} in compound (**V**) replaced by C=S band at 1271 cm^{-1} in compound (**VI**). The ^{1}H NMR spectra of compounds (**V**) and (**VI**) showed closely related peaks for CH_3, CH–N and CH–O protons and five aromatic protons. The main difference was in the singlet at δ_H 7.61 assigned for S<u>H</u> together with the ^{13}C NMR signal at δ_C 155.52 assigned for <u>C</u>=N function in compound (**V**). Compound (**VI**) showed singlet at δ_H 10.26 assigned for N<u>H</u> together with the ^{13}C NMR signal at δ_C 187.91 assigned for <u>C</u>=S function. Both compounds showed the same M^+ at 193 *m/z*, however, in compound (**VI**) the molecular ion was the base peak due to the stability of the ion thioxo group at position 2 comparing with the much less stable keto-enol thiol (mercapto) group. Reaction of compound (**III**) with chloroacetyl chloride in chloroform in the presence of triethylamine as a catalyst afforded four novel compounds: 2-chloro-*N*-(4-chlorophenylcarbamothioyl)-*N*-(1-hydroxy-1-phenylpropan-2-yl)acetamide (**VII**), *N*-(1-(2-chloroacetoxy)-1-phenylpropan-2-yl)-*N*′-(4-chlorophenyl)carbamimidothioic acid (**VIII**), 2-amino-1-phenylpropyl-2-chloroacetate (**IX**), and 3-(4-chlorophenyl)-2-thioxoimidazolidin-4-one (**XI**) (Schemes 3–5). The structures of compounds (**VII**), (**VIII**), (**IX**), and (**XI**) were established on the basis of microanalyses, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. Compounds (**VII**) and (**VIII**) showed the same M^+ at 397 *m/z* indicating their isomeric nature and the addition of $ClCH_2C{=}O$ to (**III**). IR spectrum of compound (**VIII**) showed clear absence of OH band. Besides ^{1}H NMR signals of L-norephedrine and 4-chlorophenyl moieties, compound (**VII**) showed singlet at δ_H 3.73 assigned for CH_2Cl group. The disappearance of the NH signal of L-norephedrine indicated the site of acylation at this position. Signals of the CH_2Cl–C=O moiety appeared at δ_C 31.83 and 155.72 ppm in the ^{13}C NMR. The ^{1}H NMR spectrum of compounds (**VIII**) revealed the presence of singlet at δ_H 3.76 assigned for CH_2Cl group and the disappearance of OH signal and the shift of the C<u>H</u>–OH proton to δ_H 5.02 indicating that the acylation occurred at the OH group. The signals for CH_2Cl–C=O moiety appeared at δ_C 33.97 and 166.91 ppm in the ^{13}C NMR spectrum. Another significant features of the ^{1}H and ^{13}C NMR spectra of compound (**VIII**) were the singlet at δ_H 10.32 assigned for SH proton and replacement of C=S signal with C=N signal at δ_C 164.79 ppm. The ^{1}H NMR spectrum of compound (**IX**) showed signals characteristic of L-norephedrine. However, the absence of OH signal and the downfield shift of the C<u>H</u>–OH to δ_H 5.02, together with the CH_2Cl singlet at δ_H 3.57, indicated that the OH group was acylated. The ^{13}C NMR spectrum of compound (**IX**) showed all signals of L-norephedrine and CH_2Cl signal at δ_C 31.62 ppm. The M^+ at 227 *m/z* was in complete agreement with the proposed structure. The ^{1}H NMR spectrum of compound (**XI**) indicated the complete absence of L-norephedrine signals. The two doublets at δ_H 7.33 and 7.59, $J = 8$, each integrated for 2H, were assigned for the *p*-substituted aromatic ring. The singlet at δ_H 3.69 integrated for 2H, together with corresponding ^{13}C NMR signal at δ_C 44.45 ppm was assigned to the NH–<u>CH_2</u>–C=O moiety. The signals at δ_C 168.51 and 178.78 ppm were assigned ftoor C=O and C=S carbons, respectively.



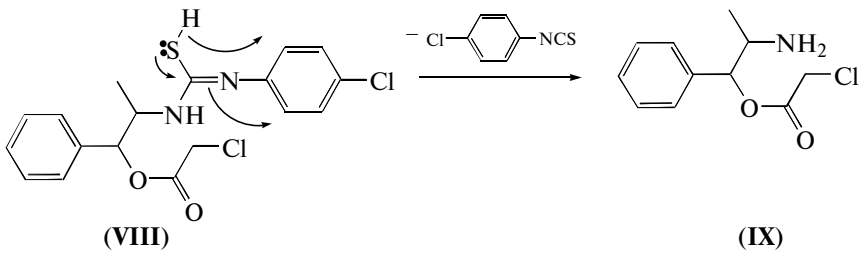
Scheme 1. Formation of compounds (**III**), (**V**), and (**VI**).



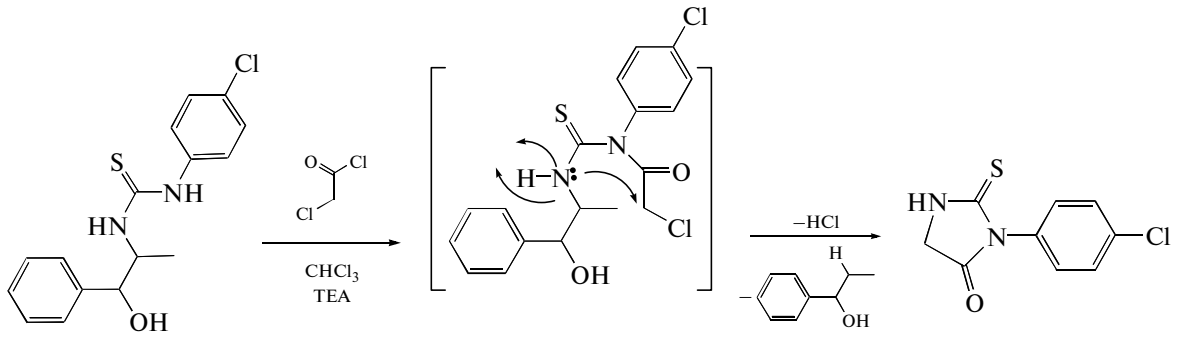
Scheme 2. Postulated mechanisms of the formation of compounds (**V**) and (**VI**).



Scheme 3. Formation of compounds (**VII**)–(**IX**), and (**XI**).



Scheme 4. Postulated mechanism for the formation of compound (**IX**).



(III) **(X)** **(XI)**

Scheme 5. Postulated mechanism for the formation of compound (**XI**).

In Vitro Anticancer Activity

The newly synthesized compounds were evaluated for their in vitro cytotoxic activity against human breast (MCF-7), liver (HepG2), and colon (HCT 116) cancer cell lines. The clinically used drug doxorubicin, one of the most effective anticancer agents, was used as a reference drug in the current study. The obtained IC_{50} values are presented in the table indicating the in vitro anticancer activity of the tested compounds compared to the reference drug. It was found in the negative control that the solvent had no effect on the cells since the surviving fraction was 100%. Compounds (**VII**) and (**IX**) were the most potent with IC_{50} of 3.60 μg/mL and exhibited higher cytotoxic activities as compared with effect of the reference drug doxorubicin on HCT116 cells. The thiourea derivatives carrying *N*-acetyl chloride moiety (**VII**), carbamimidothioic acid (**VIII**) having a biologically active thiol (SH) group, 2-amino-1-phenylpropyl-2-chloroacetate (**IX**) were nearly as active as the reference drug doxorubicin against the breast cancer cell line MCF-7. In addition, compounds (**V**) and (**VI**) revealed a moderate activity against breast cancer cell line. All the tested compounds showed lower activity than the positive control doxorubicin against the liver cancer cell line HepG2. Compounds (**VII**) and (**IX**) exhibited no activity against the liver cancer cell line. The structure–activity relationship indicated that the addition of thiourea to 4-chloroaniline with free OH group was proved to be effective in the case of compound (**VII**) showing a slight increase in the activity (IC_{50} 5.50 μg/mL). On the contrary, the activity of compound (**VIII**) decreased to 5.60 μg/mL when the free OH group was substituted by the *O*-acetyl chloride group. However, additional in vitro and in vivo biological experiments are required in order to explore the possibility of utilization of these promising compounds in practice.

In vitro anticancer screening of the newly synthesized compounds against human breast (MCF-7), liver (HEPG2), and colon (HCT 116) cancer cell lines

Compound	IC_{50}, μg/mL		
	MCF-7	HepG2	HCT116
Doxorubicin	5.40	2.97	5.26
(III)	34.00	17.20	10.40
(V)	19.00	9.60	7.60
(VI)	19.00	35.00	29.2
(VII)	5.50	NA	3.60
(VIII)	5.60	6.20	7.20
(IX)	5.60	NA	3.60

NA: Not active.

EXPERIMENTAL

General

Melting points (uncorrected) were determined in an open capillary on a Gallen Kamp melting point apparatus (Sanyo Gallen Kamp, UK). Precoated silica gel plates (Kieselgel 0.25 mm, 60 F254, Merck, Germany) were used for thin layer chromatography. A developing solvent system of chloroform–methanol (8 : 2) was used; the spots were detected by ultraviolet light. IR spectra (ν, cm^{-1}; KBr disc) were recorded using a Perkin Elmer FT-IR spectrophotometer (USA). NMR spectra were recorded on a NMR spectrophotometer (Bruker AXS Inc., Switzerland) operating at 500 MHz for ^1H and 125.76 MHz for ^{13}C NMR. Chemical shifts are expressed in ppm relative to TMS as an internal standard using DMSO-d_6 as a solvent. Elemental analyses were done on a model 2400 CHNSO analyzer (Perkin Elmer); all the values were within ±0.4% of theoretical values. All reagents used were of AR grade. The starting 2-amino-1-phenylpropan-1-ol (**I**) was purchased from Sigma (USA) and was directly used for preparation of the target compounds.

1-(4-Chlorophenyl)-3-(1-hydroxy-1-phenylpropan-2-yl) thiourea (III), 4-methyl-5-phenyl-4, 5-dihydrooxazole-2-thiol (V) and isomeric 4-methyl-5-phenyloxazolidine-2-thione (VI). A mixture of 2-amino-

1-phenylpropan-1-ol (L-norephedrine) (**I**) (151 mg, 1 mmol) and 4-chlorophenyl isothiocyanate (**II**) (170 mg, 1 mmol) in chloroform (10 mL) containing 3 drops of triethylamine was stirred at room temperature for 3 h. The mixture was fractionated over silica gel column (2 mm i.d., 30 g) using dichloromethane as an eluent. Fractions of 50 mL were collected and screened by TLC and similar fractions were pooled. Fractions 3–7 afforded 230 mg of compound (**III**). Fractions 11–17 were further purified on silica gel by PTLC using CH_2Cl_2–MeOH (95 : 5) as a developing system to afford 23 mg of compound (**V**) and 29 mg of compound (**VI**). (**III**): yield 82%; mp semi-solid. IR: 3473 (OH), 3374, 3265 (2NH), 3096 (CH arom.), 2946, 2853 (CH aliph.), 1268 (C=S), 754 (C–Cl); ^{1}H NMR: H 0.94 (d, J = 6.5 Hz, 3H, CH_3 of L-norephedrine), 4.78 (bs, NH–CH–CH_3 of L-norephedrine), 4.93 (bs, 1H, CH–OH), 7.26–7.42 (m, 9H, aromatic), 7.83 (d, J = 7.8 Hz, 1H, NH of L-norephedrine), 9.74 (s, NH of 4-chlorophenyl); ^{13}C NMR: C 12.47, 54.98, 73.03, 124.04–128.28 (10), 138.49, 143.22, 179.38; MS, m/z (%): 320 (10, M^+), 303 (11), 193 (24), 148 (18), 128 (100). Calcd. for $C_{16}H_{17}ClN_2OS$ (320): C, 59.90; H, 5.34; N, 8.73. Found: C, 59.67; H, 5.09; N, 8.46. (**V**): yield 8%; mp semi-solid. IR: 3100 (CH arom.), 2942, 2835 (CH aliph.), 1612 (C=N); ^{1}H NMR: H 0.68 (d, J = 6.7 Hz, 3H, CH3 of L-norephedrine), 4.41 (bs, NH-CH-CH_3 of L-norephedrine), 5.67 (d, J = 8.7 Hz, 1H, CH–O), 7.27–7.40 (m, 5H, aromatic), 7.61 (s, SH); ^{13}C NMR: C 17.60, 51.62, 82.07, 126.41–128.75 (5), 137.58, 155.52; MS, m/z (%): 193 (4, M^+), 180 (56), 140 (33), 138 (99), 132 (88), 117 (37), 105 (47), 91(100). Calcd. for $C_{10}H_{11}NOS$ (193): C, 62.15; H, 5.74; N, 7.25. Found: C, 62.43; H, 5.49; N, 7.66. (**VI**): yield 10%; mp semi-solid. IR: 3186 (NH) 3068 (CH arom.), 2956, 2876 (CH aliph.), 1271 (C=S); ^{1}H NMR: H 0.65 (d, J = 6.5 Hz, 3H, CH_3 of L-norephedrine), 4.42 (q, J = 2 Hz, NH–CH–NH–CH–CH_3 of L-norephedrine), 6.00 (d, J = 9 Hz, 1H, CH–O), 7.26–7.45 (m, 5H, aromatic), 10.26 (s, NH); ^{13}C NMR: C 16.56, 55.37, 85.34, 126.60–128.92 (5), 135.33, 187.91; MS, m/z (%): 193 (100, M^+), 150 (36), 132 (70), 117 (51), 105 (40), 91(100). Calcd. for $C_{10}H_{11}NOS$ (193): C, 62.15; H, 5.74; N, 7.25. Found: C, 61.82; H, 6.07; N, 7.55.

2-Chloro-*N*-(4-chlorophenylcarbamothioyl)-*N*-(1-hydroxy-1-phenylpr-opan-2-yl)acetamide (VII), *N*-(1-(2-chloroacetoxy)-1-phenylpropan-2-yl)-*N'*-(4-chlorophenyl)carbamimidothioic acid (VIII), 2-amino-1-phenylpropyl-2-chloro-acetate (IX), and 3-(4-chlorophenyl)-2-thioxoimidazolidin-4-one (XI). A mixture of (**III**) (160 mg, 0.5 mmol) and chloroacetylchloride (56.5 mg, 0.5 mmol) in chloroform (10 mL) containing 3 drops of triethylamine was stirred for 10 min. The mixture was fractionated on a silica gel column (2 mm i.d., 30 g) eluted with dichloromethane. Fractions of 50 mL were collected and screened by TLC; similar fractions were pooled. Fraction 2 afforded 11 mg of (**XI**). Fractions 5–7 afforded 48 mg of (**VII**). Fractions 10–14 afforded 50 mg of (**VIII**). Fractions 19–20 afforded 12 mg of (**IX**). (**VII**): yield 40%; mp 131.6°C; IR: 3427 (OH), 3244 (NH), 3088 (CH arom.), 2966, 2863 (CH aliph.), 1687 (C=O), 1257 (C=S), 733 (C–Cl); ^{1}H NMR: H 1.61 (d, J = 6.9 Hz, 3H, CH_3 of L-norephedrine), 3.73 (s, 2H, CH_2Cl), 4.64 (t, J = 7.0 Hz, NH–CH–CH_3 of L-norephedrine), 5.11 (bs, 1H, CH–OH), 5.79 (d, J = 6.5 Hz, 1H, CH–OH), 6.72 (bs, 1H aromatic), 7.26–7.42 (m, 8H, aromatic), 9.61 (s, NH of 4-chlorophenyl); ^{13}C NMR: C 13.95, 31.83, 56.17, 72.42, 122.39–129.19 (10), 142.52, 147.03, 155.72, 171.98; MS, m/z (%): 411 (8, M^+), 334 (31), 284 (7), 275 (19), 259 (24), 176 (54), 77 (100). Calcd. for $C_{19}H_{20}Cl_2N_2O_2S$ (411): C, 55.48; H, 4.90; N, 6.81. Found: C, 55.18; H, 5.17; N, 6.51. (**VIII**): yield 41%; mp 168.9°C; IR: 3286 (NH), 3065 (CH arom.), 2937, 2853 (CH aliph.), 1694 (C=O), 1599 (C=N), 733 (C–Cl); ^{1}H NMR: H 0.96 (d, J = 6.5 Hz, 3H, CH_3 of L-norephedrine), 3.76 (s, 2H, CH_2Cl), 4.32 (bq, J = 5.4 Hz, NH–CH–CH_3 of L-norephedrine), 5.02 (d, J = 6.4 Hz, 1H, CH–OH), 7.34–7.63 (m, 9H, aromatic), 8.56 (d, J = 6.9 Hz, 1H, NH of L-norephedrine), 10.32 (s, 1H, SH); ^{13}C NMR: C 17.53, 33.97, 52.52, 65.83, 120.53–128.65 (10), 137.91, 138.47, 164.79, 166.91; MS, m/z (%): 397 (7, M^+), 396 (10), 271 (18), 201 (55), 153 (12), 127 (100), 125 (62), 99 (16), 91 (27). Calcd. for $C_{18}H_{18}Cl_2N_2O_2S$ (411): C, 54.41; H, 4.57; N, 7.05. Found: C, 54.73; H, 4.19; N, 6.79. (**IX**): yield 10%; mp 151°C; IR: 3370, 3295 (NH_2), 3072 (CH arom.), 2959, 2845 (CH aliph.), 1688 (C=O), 851 (C–Cl); ^{1}H NMR: H 1.26 (d, J = 6.4 Hz, 3H, CH_3 of L-norephedrine), 3.57 (s, 2H, CH_2Cl), 4.78 (bs, 1H, NH–CH–CH_3 of L-norephedrine), 5.02 (bs, 1H, CH–OH), 6.75 (s, 2H, NH_2), 7.16–7.44 (m, 5H, aromatic); ^{13}C NMR: C 9.90, 31.62, 57.14, 73.77, 121.50–128.38 (5), 140.49, 170.94; MS, m/z (%): 227 (100, M^+), 153 (7), 133 (10), 110 (7), 77 (11). Calcd. for $C_{11}H_{14}ClNO_2$ (227): C, 58.03; H, 6.20; N, 6.15. Found: C, 58.31; H, 6.47; N, 5.78. (**XI**): yield 9%; mp semi-solid; IR: 3389 (NH), 3099 (CH arom.), 2951, 2836 (CH aliph.), 1699 (C=O), 1266 (C=S), 773 (C–Cl); ^{1}H NMR: H 3.69 (s, 2H, NH–CH_2–C=O), 7.33 (d, J = 8, 2H), 7.59 (d, J = 8, 2H); –^{13}C NMR: C 44.45, 122.52 (2X), 129.86 (3X), 132.85, 168.51, 178.78; MS, m/z (%): 226 (10, M^+), 201 (26), 154 (8), 129 (32), 127 (100), 99 (23). Calcd. for $C_9H_7ClN_2OS$ (226): C, 47.69; H, 3.11; N, 12.36. Found: C, 47.44; H, 2.84; N, 12.69.

In Vitro Anticancer Activity

In vitro cytotoxic activity of the novel synthesized compounds was measured using the sulforhodamine B stain (SRB) assay and the method of Skehan et al. [23]. The human tumor breast cancer cell line MCF-7,

human colon cancer cell line HCT 116, and human liver cancer cell line HEPG2 (obtained from National Cancer Institute, Cairo, Egypt) were maintained at 37°C in 5%-CO_2 as subconfluent monolayers in 80 cm^3 culture flasks (Nunclon) and were subcultured once or twice weekly in Dulbecco's modification of Eagle's medium (Flow) supplemented with 5% heat-inactivated fetal calf serum (FCS) and 1 mM L-glutamine. During experiments, 50 μg/mL gentamicin was added to the culture medium. Passage levels were in the range of 5–20 according to the original receipt. Cells were harvested from exponential phase cultures by trypsinization, counted, and plated in 96-well flat-bottomed microliter plates (Greiner Labortechnik, Germany) (100 μL cell suspension containing 10^4 cells per well). Following plating and a 24-h recovery to allow cells to resume exponential growth, 100 μL culture medium or culture medium containing the drug was added to the wells. Test compounds were dissolved in DMSO as a 0.1 mol L^{-1} stock solution (the final concentration of DMSO in culture medium was less than 0.1%) and diluted with phosphate buffered saline (PBS) to form 10 mmol L^{-1} stock solution. Different concentrations of each of the test compounds (5, 12, 25, and 50 μmol L^{-1}) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37°Cin an atmosphere of 5%-CO_2. Forty eight hours after drug addition, the cells were fixed with 50% trichloroacetic acid at 4°C (50 μL/well) for 1 h, washed with 1% acetic acid, and stained for 30 min with 50 μL of 0.4% (m/V) SRB dissolved in 1% acetic acid. Excess unbound dye was removed by four washes with 1% acetic acid and attached stain was recovered with Tris-EDTA buffer. Color intensity was measured using an enzyme-linked immunosorbent assay ELISA reader. Optical density was read at 510 nm. The relation between the surviving fraction and drug concentration was plotted to get the survival curve for MCF-7, HCT 116, and HEPG2 cell lines after specified time [23]. The molar concentration required for 50% inhibition of cell viability (IC_{50}) was preliminarily calculated from the constructed dose–response curve using Prism software (Graphpad, Inc., USA) and the results are given in the table.

CONCLUSIONS

A novel thiourea, carbamimidothioic acid, oxazole, oxazolidine, and 2-amino-1-phenylpropyl-2-chloroacetate hybrids were synthesized and their in vitro anticancer activities were evaluated on three human tumor cancer cell lines. Among the compounds tested, three candidates, i.e. thioureido derivative (**VII**) carrying *N*-chloroacetyl chloride moiety, carbamimidothioic acid (**VIII**) bearing *O*-chloroacetyl chloride moiety, and 2-amino-1-phenylpropyl-2-chloroacetate (**IX**) are nearly as active as the reference drug doxorubicin against breast cancer cell line, while compounds (**VII**) and (**IX**) exhibited higher activity than the reference drug doxorubicin against human colon cancer cell line HCT 116. The active compounds could be considered as promising templates for further development of more potent anticancer agents.

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