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SYNTHESIS OF SOME 1,3-THIAZOLE CONTAINING 2,3-DIHYDROXY BENZYLIDENE AMINO MOIETY AS ANTITUMOR AGENTS

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ABSTRACT

2-[2,3-dihydroxybenzylidene)amino]-4-phenyl and/or (5-phenyl)-1,3-thiazole were obtaines via the cyclization of 2,3-dihydroxybenzaldehyde thiosemicarbazone (**1**) with phenacyl bromide under different conditions. Acetylation, alkylation, halogenation and condensation reactions of 2-[(2,3-dihydroxybenzylidene)amino]-5-phenyl-1,3-thiazole (**3**) yielded the corresponding triacetyl derivatives (**4**), N-alkyl derivatives (**5** and **6**), bromo derivatives (**7**) and arylidene derivatives (**9**). The structure of the 1,3-thiazole derivatives was confirmed by IR, NMR, MS spectra and elemental analyses. The antitumor activity of synthesized 1,3-thiazole derivatives were evaluated on human breast and liver cancer cell lines. As a result of the cell culture studies, all of the prepared compounds showed anticancer activity for breast and liver cancer cells. In conclusion, novel 1,3-thiazole derivatives might be potentially useful in the field of cancer treatment.

I) INTRODUCTION

1,3-thiazole derivatives play an important role in nature and have a diverse range of biological activities such as antitumor[1-3], anti-inflammatory[4,5], antiviral[6], and antimicrobial activity[7].

Thiazole compounds containing 1,3-thiazole amine moiety exhibit interesting biological activities depending on the substitution pattern at the thiazole ring[8]. Recently, *N*-substituted-

2-amino-1,3-thiazole research are unexpectedly became interesting and promising for oncology.

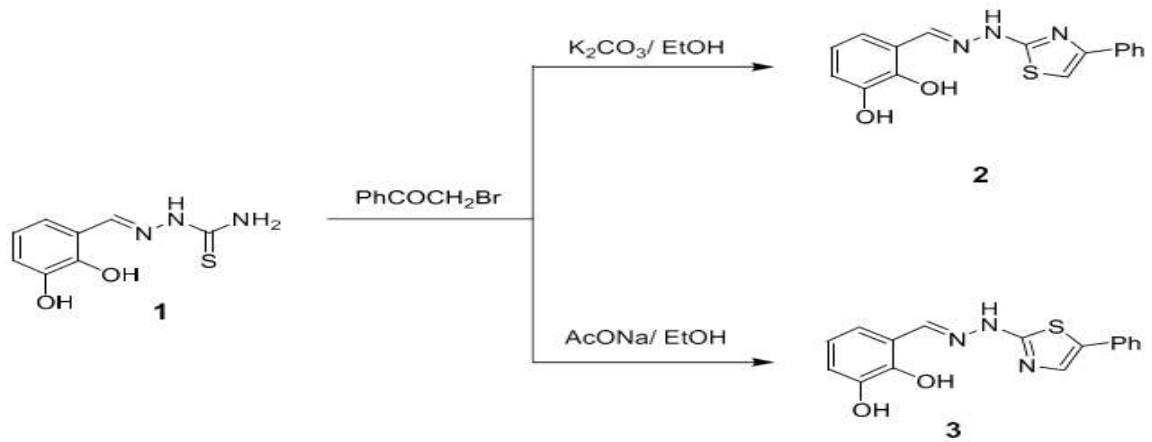
N-(2-chloro-6-methylphenyl)-2-[(6-(4-(2-hydroxy ethyl)-1-piperazinyl)]-2-methyl-4-pyrimidinyl]-amino)]-1,3-thiazole-5-carboxamid e is a novel multi-targeted kinase inhibitor recently approved in several countries for the treatment of chronic myelogenous leukaemia (CML) as well as philadelphia chromosome positive acute lymphocytic leukaemia (ALL).

Dasatinib exhibits greater potency than imatinib mesylate and inhibits the majority of kinase mutation in imatinib-resistant CML[9-12]. Unlike imatinib, which binds to the active form of the enzyme[13]. The ability to inhibit SRC family kinases such as Hck and Lyn, in addition to binding to the active conformation of Bcr-ABL, may both contribute to the effectiveness of dasatinib against imatinib-resistant tumors[14].

A literature survey shows that 1,3-thiazole derivatives as interesting in medicinal chemistry, we decided to explore the synthesis of these some novel 1,3-thiazole derivatives containing 2,3-dihydroxybenzylidene amino substituent.

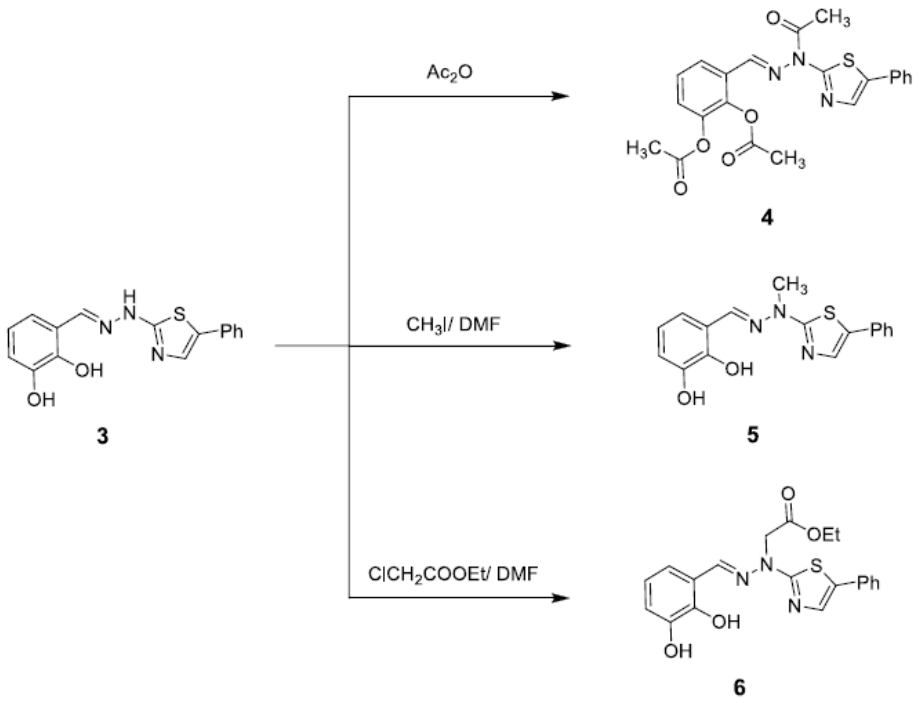
II) RESULTS AND DISCUSSION

Cyclization of 2,3-dihydroxybenzaldehyde thiosemicarbazone (**1**) with phenacyl bromide in the presence of anhydrous potassium carbonate afforded 2-[(2,3-dihydroxybenzylidene) amino]-4-phenyl-1,3-thiazole (**2**), while cyclization of carbazone (**1**) with phenacyl bromide in the presence of fused sodium acetate in ethanol led to the formation 2-[(2,3-dihydroxybenzylidene)amino]-5-phenyl-1,3-thiazole (**3, Scheme 1**).



Scheme 1: Formation of 1,3-thiazole derivatives **2** and **3**

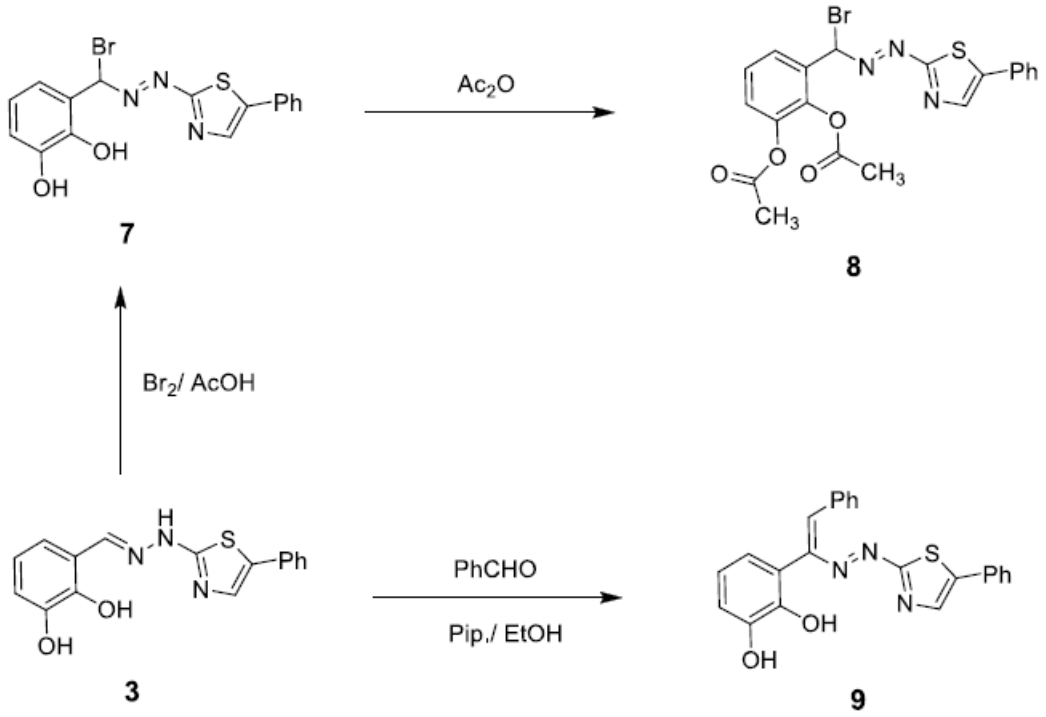
Acylation and alkylation of 2-substituted -5-phenyl-1,3-thiazole (**3**) with acetic anhydride, methyl iodide and ethyl chloroacetate in dimethyl formamide yielded the corresponding 2-(N-(2,3-diacetoxybenzylidene)-N-acetyl]-amino-5-phenyl-1,3-thiazole (4), 2-[N-(2,3-dihydroxybenzylidene)-N-methyl]-amino-5-phenyl-1,3-thiazole (5) and ethyl N-(5-phenyl thiazole-2-yl)-N-(2,3-dihydroxybenzylidene)amino acetate (**6**, **Scheme 2**).



Scheme 2: Acetylation and alkylation of 1,3-thiazole **(3)**

Halogenation of 2-[(2,3-dihydroxybenzylidene)amino]-5-phenyl-1,3-thiazole with bromine in glacial acetic acid at room temperature led to the formation of 2-[(2,3-dihydroxyphenyl-bromo)methyl] azo-5-phenyl-1,3-thiazole (**7**). The compound (**7**) was confirmed *via* its acetylation with acetic anhydride to give 2-[(2,3-diacetoxyphenyl-bromo)methyl]azo-5-phenyl-1,3-thiazole (**8, Scheme 3**).

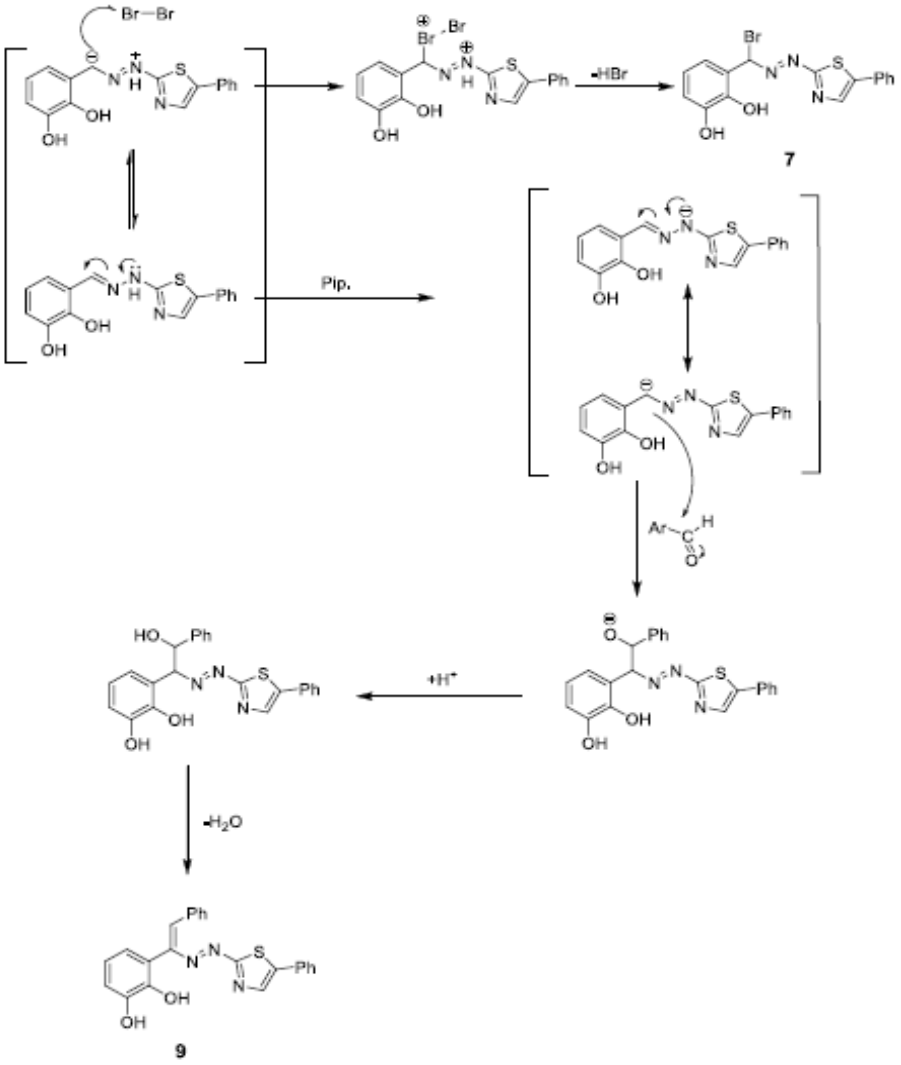
It was also reported that the condensation of thaizole derivatives (**3**) with benzaldehyde in ethanol and piperidine under reflux gave the corresponding 2-[(□-2,3-dihudroxyphenyl, □-phenyl)vinyl]azo-5-phenyl-1,3-thiazole (**9**, **Scheme 3**).



Scheme 3: Reactions of bromine and banzaldehyde with compound **(3)**

The formation of compound 7 and 9 indicate that the formation of carbon nucleophile in the compound 3. The carbon nucleophilic attack the bromine and the carbonyl group in benzaldehyde molecules followed by elimination of hydrogen bromide and water molecules as shown in **scheme 4**.

The ^{1}H-NMR spectra of compounds(**7**) and (**9**) showed the disappearance of two singlet signals for NH at δ 12.15 ppm and CH=N at δ 8.33 ppm, respectively. In addition, the ^{1}H-NMR spectra of compound (**7**) showed the presence of one chemical shift at δ 3.84 ppm, assigned to (CHBr) group. The ^{13}C-NMR spectra of compound **(7)** showed a new signal at δ 53.73 ppm due to the carbon of bromomethyl (CHBr) group.



Scheme 4: Suggested mechanism of formation for 1,3-thiazole derivatives **7** and **9**

II-2) Antitumor activity

All the synthesized 1,3-thiazole derivatives (2,3,7 and 9) were evaluated for their cytotoxicity against two different cancer cell lines MCF-7 (human breast cancer) and Hep-G2 (human liver cancer) by using the method of Skehan *et al* [15]. in the cell culture lab., Cancer Biology Department and Pharmacology Unit, National Cancer Institute, Cairo University, Cairo, Egypt. Doxorubicin was used as a reference standard. The inhibitory activity against breast cancer cells (MCF-7) and liver carcinoma cells (Hep-G2) was detected by using different concentration of the tested samples (50, 25, 12.5, 5.00 and 0.00 □g/ml) and surviving fraction (%) was determined by colorimetric method. The IC_{50} was calculated from **Table 1, 2**.

Table 1: Cytotoxixcity of some thiazole derivatives (2,3,7 and 7) against human breast cancer (MCF-7) cell lines.

Conc. (µg/ml)	2	3	7	9	Dox.
50.00	0.591	0.601	0.355	0.309	0.294
25.00	0.405	0.455	0.423	0.341	0.322
12.50	0.409	0.485	0.450	0.405	0.365
5.00	0.455	0.489	0.455	0.682	0.381
0.00	1.000	1.000	1.000	1.000	1.000

Table 2: Cytotoxixcity of some thiazole derivatives (2,3,7 and 7) against human hepatocellular carcinoma (Hep-G2) cell lines.

Conc. (µg/ml)	2	3	7	9	Dox.
50.00	0.52	0.55	0.268	0.400	0.314
25.00	0.380	0.395	0.34	0.360	0.319
12.50	0.380	0.401	0.48	0.400	0.388
5.00	0.468	0.501	0.600	0.548	0.507
0.00	1.000	1.000	1.000	1.000	1.000

The IC_{50} values of tested 1,3-thiazole derivatives are listed in **Table 3.**

Table 3: **IC_{50} (µg/ml) values of thiazole derivatives after 48 h continuous exposure of tumor cell lines compared with control.**

Compound No.	Tumor cell types	
	MCF-7	Hep-G2
2	4.48	4.50
3	4.63	4.72
7	4.49	10.60
9	10.0	7.50
Doxorubicin	3.83	5.18

The result showed in Table 3, compounds (**2)** and (**3**) were found to exhibit good cytotoxic activity against MCF-7 and Hep-G2 cell lines compared with standard doxorubicin drug. It was observed that compounds (**7)** displayed good activity on MCF-7 cells. In the case of MCF-7 cells, compound 9 showed a weak cytotoxicity compared with standard doxorubicin drug as control. Compound (**7**) and (**9**) showed a moderate inhibitory activity against Hep-G2 cells.

These data of 1,3-thiazole derivatives (**2**) and (**3**) in **Table 3** suggest that these compounds provide a good model for future design of potent antitumor agents for treatment of breast and liver cancers.

CONCLUSION

Some important 1,3-thiazole derivatives containing (2,3-dihydroxybenzylidene) amino substituent were designed and synthesized from cyclization of thiosemicarbazone derivatives (**1**) with phenacyl bromide under different conditions. Their structures were confirmed by IR, NMR and Mass spectra and elemental analysis. The primary bioassay showed some of them exhibited a good anticancer activities. Finally, the thiazole derivatives (**2** and **3**) can be suggested as potent candidates for breast and liver cancer drugs.

IV) Experimental IV-1) Instruments

Melting points were determined in open capillary on a melt-Temp. II Apparatus and were uncorrected. The IR spectra were recorded on a SHIMADZU FT-IR spectrometer as KBr pellets and the wave number are given in cm-1. The ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Brucker-400 spectrometer (400MHz). All chemical shifts are reported in δ (ppm) using TMS (tetramethylsilane) as internal standard. Mass spectra were obtained on a PROBE AGILENT MSD 5975 and TLC-MS: Xcalibur spectrometer operating at 70 eV. The microanalyses was performed on a Perkin Elmer 2400 series II CHN elemental analyzer.

IV-2) Syntheses

IV-2.1) 2-[(2,3-dihydroxybenzylidene)amino]-4-phenyl-1,3-thiazole (2)

A mixture of 2,3-dihydroxybenzaldehyde thiosemicarbazone (**1**, 0.01 mol) and anhydrous potassium carbonate (0.03 mol) in ethanol was heated for 30 min, then added phenacyl bromide (0.01 mol). The reaction mixture was heated under reflux for 4h, then cooled and poured into water, and neutralized with dilute hydrochloric acid (2%). The resulting solid was filtered off, washed with water, dried and purified by recrystallization from ethanol to give compound **2.** As pale yellow crystals, yield 71%, m.p.: 187 ^{o}C. IR (KBr): ν_{max} 3470-2970 (br. OH), 3215 (NH), 1625 (C=N), 1608, 1571 (C=C), 1153, 1053, 1031 (C-O) cm^{-1}**.** ^{1}H-NMR (DMSO-d_6): δ 6.70-7.87 (m, 9H, Ar-H and H-thiazole), 8.33 (s, 1H, CH=N), 9.44 (s, 1H, OH), 9.47 (s, 1H, OH), 12.15 (s, 1H, NH) ppm. ^{13}C-NMR (DMSO-d_6): δ 168.32 (S-C=N), 146.05, 145.21 (2x C-O), 141.41 (C=N), 135.00, 129.08, 128.06, 126.01, 120.90, 119.81, 117.75, 116.74, 103.66 (C-aromatic and thiazole ring) ppm. MS (m/z, **%):** 312 (M^{+}+1, 21.20), 311 (M^{+}, 78.20). Anal. Calcd. For $C_{16}H_{13}N_3O_2S$: C, 61.74; H, 4.18; N, 13.50. Found: C, 61,34; H, 4.01; N, 13.23.

IV-2.2) 2-[(2,3-dihydroxybenzylidene)amino]-5-phenyl-1,3-thiazoles (3)

A mixture of 2,3-dihydroxybenzaldehyde thiosemicarbazone (**1**, 0.01 mol) and phenacyl bromide (0.01 mol) and fused sodium acetate in ethanol (30 mL) was heated under reflux for 4h. The solid formed after cooling was filtered off, washed with ethanol and dried and purified by ethanol to give compound (**3)** as Pale yellow crystals, yield 76%, m.p.: 210 ^{o}C. IR (KBr): ν_{max} 3463-2900 (br. OH), 3243 (NH), 1624 (C=N), 1605, 1571 (C=C), 1149, 1058 (C-O)cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 6.71-7.83 (m, 9H, Ar-H and thiazole-H), 8.37 (s, 1H, CH=N), 9.43-4.64 (br. s, 2H, 2 x OH) ppm. ^{13}C-NMR (DMSO-d_6): δ 168.38 (S-C=N), 150.08, 146.07 (C-OH), 145.30 (C=N), 141.92, 134.55, 129.11, 128.78, 128.63, 128.39, 128.22, 126.08, 119.82, 117.69, 116.85, 103.80 (C-aromatic and thiazole ring) ppm. MS (m/z, %): 312 (M^++1, 23.10), 311 (M^+, 100), 295 (23.30), 294 (100), 293 (30.90), 261 (2.10), 260 (1.60), 252 (2.60), 250 (1.40), 191 (11.30), 190 (2.50), 189 (5.10), 178 (8.70), 177 (23.10), 176 (100), 175 (30.60), 163 (3.60), 162 (21.30), 152 (2.70), 150 (2.90), 149 (6.90), 148 (15.00), 147 (5.60), 137 (67.50), 136 (16.70), 135 (29.30), 134 (100), 133 (7.60), 122 (7.10), 121 (15.50), 118(13.90), 109 (11.80), 108 (13.30), 105 (13.40), 104 (26.90), 103 (12.90), 102(12.80), 91 (13.30), 90 (12.80), 89 (16.80), 82 (32.90), 81 (21.90), 80 (41.00), 79(20.70), 77 (40.90), 76 (12.80), 63 (13.00), 53 (12.00), 52 (12.80), 51 (17.90). Anal. Calcd. for $C_{16}H_{13}N_3O_2S$: C, 61.74; H, 4.18; N, 13.50. Found: C, 61,43; H, 3.98; N, 13.32.

IV-2.3) 2-[*N*-acetyl-*N*-[(2,3-diacetoxybenzylidene)amino]-5-phenyl-1,3-thiazole(4)

2-[(2,3-diacetoxyphenyl-bromomethyl)azo]-5-phenyl-1,3-thiazoles (8)

A solution of compounds **(3** and **7**, 0.01 mol) in acetic anhydride (30 mL) was heated under reflux for 2 h. The reaction mixture was cooled and poured into ice-water. The resultant solid was filtered off, washed with water, dried and recrystallized from benzene to give **4** and **8**.

Compound **4** as Colorless crystals, yield 67%, m.p.: 170 ^{0}C. IR (KBr): ν_{max} 1766, 1685 (C=O of ester and amide), 1605, 1577 (C=C), 1172, 1049, 1014 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.10 (s, 3H, $COCH_3$), 2.29 (s, 3H, $COCH_3$), 2.52 (s, 3H, $COCH_3$), 7.34-8.09 (m, 9H, Ar-H and thiazole-H), 9.09 (s, H, CH=N) ppm. MS (m/z, %): 437 (M^+, 15.20), 345 (M^+, 45.60). Anal. Calcd. for $C_{22}H_{19}N_3O_5S$: C, 60.41; H, 4.35; N, 9.61. Found: C, 60.16; H, 4.21; N, 9.44.

IV-2.4) 2-*N*-methyl-*N*-[(2,3-dihydroxybenzylidene)amino]-5-phenyl-1,3-thiazole (5)

Compound **8** as yellow crystals, yield: 62%, m.p. 167 ºC, IR (KBr): vmax 1782 (C=O), 1678 (C=N), 1605, 1581 (C=C), 1078, 1006 (C-O) cm-1. 1H-NMR (DMSO-*d6*): δ 2.30 (s, 3H, COCH3), 2.50 (s, 3H, COCH3), 3.88 (s, 1H, CHBr), 7.12-8.40 (m, 9H, Ar-H and thiazole-H) ppm. 13C-NMR (DMSO-*d6*): δ 172.47, 168.29, 162.95 (C=O, S-C=N), 152.64, 147.21(C-O), 140.56, 135.62, 132.23, 131.39, 129.92, 129.76, 129.65, 129.45, 129.03, 128.61, 117.85, 106.28 (C-aromatic and C-thiazol ring), 53.71 (CHBr), 21.52, 20.79, (2x COCH3) ppm. Anal. Calcd. for C20H16BrN3O4S: C, 50.74; H, 3.38; N, 8.88. Found: C, 50.45; H, 3.17; N, 8.62.

Ethyl *N*-(5-phenylthiazol-2-yl), *N*-(2,3-dihydroxybenzylidene)amino acetate (6)

A solution of compound **3** (0.1 mol) and alkyl halides (namely, iodomethane and ethyl chloroacetate, 0.01 mol) in dimethyl formamide (30 mL) was heated under reflux for 4 h. the reaction mixture was cooled and poured into ice-water (50 mL) and neutralized with dilute hydrochloric acid (2 mol/L). The resulting solid was filtered to isolate compound **(5)** and **(6)**.

Compound **5** as yellow crystals, yield: 61%, m.p. 155 ºC, IR (KBr): ν_{max} 3510-2880 (br. OH), 1634 (C=N), 1600, 1581 (C=C), 1111, 1056, 1028 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 3.78 (s, 3H, N-CH_3), 6.83-7.95 (m, 9H, Ar-H and thiazole-H), 8.13 (s, 1H, CH=N), 9.39 - 9.52 (br. s, 2H, 2x OH) ppm. ^{13}C-NMR (DMSO-d_6): δ 169.56 (S-C=N), 150.78, 146.59 (C-O), 145.15 (C=N), 137.24, 134.99, 130.21, 130.04, 129.45, 129.05, 128.89, 128.67, 121.10, 119.86, 117.99, 116.75, 105.75 (C-aromatic and thiazole ring), 32.88 (N-CH_3) ppm. Anal. Calcd. for $C_{17}H_{115}N_3O_2S$: C, 62.77; H, 4.61; N, 12.92. Found: C, 62.46; H, 4.41; N, 12.71.

IV-2.5) 2-[(2,3-dihydroxyphenyl-bromomethyl)azo]-5-phenyl-1,3-thiazole (7)

Compound (**6)** as colorless, yield: 61%, m.p. 145 ºC, IR (KBr): ν_{max} 3550-2350 (br. OH), 1739 (C=O of ester), 1624 (C=N), 1605, 1577 (C=C), 1211, 1157, 1028 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.24 (t, 3H, CH_3), 4.20 (q, 2H, OCH_2), 5.4 (s, 2H, NCH_2CO), 6.88-7.99 (m, 9H, Ar-H and thiazole-H), 8.44 (s, 1H, CH=N) ppm. Anal. Calcd for $C_{20}H_{19}N_3O_4S$: C, 60.45; H, 4.78; N, 10.58. Found: C, 60.16; H, 4.47; N, 10.33.

A solution of compounds **3** (0.01 mol), in glacial acetic acid (25 mL) was added a solution from bromine in glacial acetic acid (0.01 mol) *dropwise* with stirring at room temperature for 30 min. The reaction mixture was stirred at room temperature for 2 h., then poured into ice-water. The solid formed was filtered off, washed with water, dried and purified by

recrystallization from ethanol to give compound (**7)** as pale yellow crystals yield: 72%, m.p. 163 ºC, IR (KBr): v_{max} 3550-2650 (br. OH), 1678 (N=N), 1625 (C=N), 1600, 1550 (C=C), 1195, 1168, 1072 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 3.84 (s, 1H, CHBr), 6.91-8.01 (m, 9H,Ar-H and thiazole-H), 9.15 (br. s, 1H, OH), 9.51 (br. s, 1H, OH) ppm. ^{13}C-NMR (DMSO-d_6): δ 168.11, 166.53 (S-C=N), 156.26, 152.64 (C-O), 140.55, 132.51, 132.23, 131.89, 129.91, 129.77, 129.55, 129.05, 128.61, 116.24, 112.8, 110.86 (C-aromatic and thiazole ring), 53.73 (CHBr) ppm. Anal. Calcd for $C_{16}H_{12}BrN_3O_2S$: C, 49.36; H, 3.08; N, 10.80. Found: C, 49.19; H, 2.97; N, 10.58.

IV-2.6) 2-[(α-2,3-dihydroxyphenyl-β-phenyl)vinyl]azo-5-phenyl-1,3-thiazole (20)

A mixture of compound **3** (0.01 mol), benzaldehyde (0.01 mol) and piperidine (1mL) was fused on a hot plate at 120^0C for 1h. the reaction mixture was added ethanol (30 mL)and reflux for 2h. cooled and neutralized with dilute hydrochloric acid (2%). The resulting product was filtered off, washed with water, dried and recrystallized from ethanol to give compound **9** as red crystals yield: 71%, m.p. 178 ºC, IR (KBr): v_{max} 3490-2570 (br. OH), 1604, 1562 (C=C), 1180, 1072, 1026 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 6.85-7.88 (m, 14H, Ar-H and thiazole-H), 8.93 (s, 1H, H-olefinic) ppm. Anal. Calcd for $C_{23}H_{19}N_3O_3S$: C, 66.19; H, 4.55; N, 10.07. Found: C, 65.97; H, 4.22; N, 9.87.

IV-3) measurement of potential cytotoxicity for 1,3-thiazole by SRB assay

Two different human cancer cell lines were obtained from national cancer institute, Cairo, Egypt. cells were plated in 96 multi well plate (104 cells/well) for 24 h before treatment with the tested compounds to allow attachment of the cell to the well of the plate. Different concentration of the compounds under test (5.00, 12.50, 25.00 and 50.00 µg/ml) were added to the cell monolayer triplicate wells were prepared from each individual dose. monolayer cells were incubated with the test compounds for 48 h at 37 ºc and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed and stained with sulforhodamine-B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tri EDTA buffer. Color intensity was measured in ELISA reader. The relation between surviving fraction and compound concentration is plated to get the survival curve of each tumor cell line after the specified compound.

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