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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of phenyl thiazole hydrazones and their activity against glycation of proteins

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Abstract Phenyl thiazole hydrazone derivatives **1**–**21** have been synthesized and screened for their in vitro antiglycation activity. Hydrazones **1**–**21** displayed assorted antiglycation activities having IC_{50} values in the range of 187.61 ± 1.12–886.98 ± 5.29 μM as compared to standard rutin (IC_{50} = 269.07 ± 3.79 μM). Compounds **5** (IC_{50} = 187.61 ± 1.12 μM), **3** (IC_{50} = 191.92 ± 3.08 μM), **4** (IC_{50} = 193.77 ± 3.06 μM), **6** (IC_{50} = 217.90 ± 2.48 μM), **15** (IC_{50} = 221.98 ± 2.34 μM), **2** (IC_{50} = 226.59 ± 1.19 μM), **21** (IC_{50} = 229.67 ± 1.95 μM), **18** (IC_{50} = 231.09 ± 0.38 μM), **12** (IC_{50} = 242.94 ± 2.05 μM), and **1** (IC_{50} = 264.22 ± 5.60 μM), respectively, showed excellent antiglycation activities superior to standard rutin. Compound **17** (IC_{50} = 269.94 ± 1.11 μM) demonstrated a comparable activity to the standard. Compounds **7**, **8**, **9**, **10**, **11**, **13**, **14**, and **16** exhibited weaker activities than standard. However, compounds **19** and **20** showed no activity. When evaluated for cytotoxicity against rat fibroblast cell line (3T3 cell line), all compounds were found to be non-toxic in cellular model.

Keywords Schiff bases · Phenyl thiazole hydrazones · Antiglycation · AGEPs · Glycation of protein

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Introduction

Hydrazones are heteroatomic compounds bearing azomethine moiety (–C=N–) and also known as Schiff bases which are generally prepared by condensation of active carbonyl groups and primary amines. Schiff bases are recognized due to their biological and pharmacological properties and showed potent activities against bacteria, fungi, cancer, and viruses (Bharti *et al.*, 2010; Pandey *et al.*, 2012). Hydrazones from aliphatic aldehydes are comparatively unstable and are readily polymerized (Campbell *et al.*, 1944). As far as aromatic aldehydes are concerned, they have an effective conjugation system and stability (Mohamed *et al.*, 2011; Brewster, 1924; Munir *et al.*, 1985). Hydrazones have outstanding properties due to their structural similarities with different naturally occurring bioactive molecules. Simple and easy synthesis and the synthetic flexibility are useful features of hydrazones to design and synthesize new bioactive compounds (Mustapha *et al.*, 2011). Hydrazones have also been used as basic units of certain dyes, and few of them are used as liquid crystals. In addition, hydrazones have come into view to be a significant intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or carbonyl group of the hydrazones (Vennilaa *et al.*, 2012; Amanullah *et al.*, 2011; Kadhum, 2011; AL-Garawi *et al.*, 2012). At pH 5, hydrazone undergoes rapid hydrolysis that increases its solubility in

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water which also amplifies the antitumor activity of hydrazones toward ascetic tumor (Sidambaram *et al.*, 2011; Patil *et al.*, 2011). In eukaryotic cells, hydrazones also play vital role in transamination of transaminases which is found in mitochondria and cytosol. All the transaminases posses the prosthetic group, i.e., pyridoxal phosphate, which is non-covalently linked to enzyme protein (Mahmud *et al.*, 2012). Many industrial and biologically active compounds utilize hydrazones as a substrate for cycloaddition, ring closure, and replacement reaction (Musharraf *et al.*, 2012). The benzoylhydrazones reported for antileishmanial (Taha *et al.*, 2013a, b) and antioxidant activities (Anouar *et al.*, 2013; Taha *et al.*, 2013a, b; Khan *et al.*, 2012a, b). The chemical reaction between sugar aldehydes and proteins known as non-enzymatic glycation is one of the key molecular basis of diabetic complications due to hyperglycemia (Elhassan *et al.*, 2012). Hyperglycemia and hyperlipidemia are two important characteristics of type 2 diabetes, an endocrine disorder-based disease. In modern medicine, no satisfactory effective therapy is still available to cure type 2 diabetes (Perez-Gutierrez *et al.*, 2010). Glycation is a non-enzymatic condensation reaction between reducing sugars and amino groups of proteins that rearranges to stable Amadori product (Monnier *et al.*, 2008). The ultimate effect of glycation is generation of high molecular weight protein aggregates and other fluorescent entities, referred to AGEs (advanced glycation end products). Some AGEs such as carboxymethyllysine (CML) and pentosidine have become highly useful biomarkers of glycoxidative damages (Kazeem *et al.*, 2012). It has been proposed that the discovery of inhibitors of the glycation cascade should offer a promising therapeutic approach for the prevention of diabetic and its related pathogenic complications (Wu *et al.*, 2009).

In recent past, we have reported several new classes of synthetic and natural products as antiglycating agents (Khan *et al.*, 2009, 2011a, b, 2012a, b, 2013a, b; Taha *et al.*, 2014). Considering previous reports on the hypoglycemic activities of benzothiazoles (Khan *et al.*, 2011a, b), we envisaged that due to structure similarities of phenyl thiazoles with benzothiazoles might stimulate their hypoglycemic activities. Therefore, a library of phenyl thiazoles **1**–**21** has been synthesized and screened for antiglycation potential. The observed results established that our initial hypothesis was correct. We discovered the potent antiglycation compounds.

Results and discussion

Chemistry

A library of phenyl thiazoles hydrazones (**1**–**21**) was generated by the condensation of 4-hydrazino-4-phenyl thiazole with varyingly substituted aromatic aldehydes and acetophenone in the presence of catalytic amount of acetic acid in refluxing ethanol. After completion of reaction, it was allowed to cool to room temperature, a precipitate formation was occurred. Recrystallization from methanol or ethanol afforded pure products in good yields (Scheme 1). The structures of phenyl thiazoles hydrazones (**1**–**21**) were deduced by NMR and EI MS spectroscopic techniques. Elemental analysis results were also found to be in good agreement with the calculated values.

Antiglycation activity

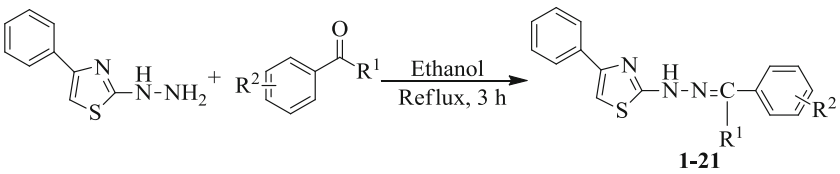
Antiglycation compounds may serve as practical lead compounds for the progress of new antidiabetic drugs that will probably not only reduce the glycation process but also help to eliminate glycation-induced oxidative stress (Taha *et al.*, 2014). As described earlier that the current study was carried out due to close structural resemblance of phenyl thiazole with benzothiazole which were found to be antiglycating agents, we synthesized a library of phenyl thiazole hydrazones (**1**–**21**) and evaluated their antiglycation potential. The experimental outcome indicates that our initial supposition accurately drives the results (Table 1).

A careful look on the structures of the molecules used in this study suggests that the antiglycation activity of compounds **1**–**21** depends upon R^1 substitution at the azomethine (C=N) residue or substitution at the phenyl ring attached to it. Only those compounds were found to be active where the R^1 is a proton. Compounds **19** and **20** have methyl group as R^1 found to be completely inactive. However, all other compounds having proton showed strong to weak antiglycation potential.

Phenyl thiazole hydrazone derivatives **1**–**21** displayed diversified antiglycation activities and showed IC_{50} values between 187.61 ± 1.12–886.98 ± 5.29 μM, if compared with standard rutin (IC_{50} = 269.07 ± 3.79 μM). Compounds **5** (IC_{50} = 187.61 ± 1.12 μM), **3** (IC_{50} = 191.92 ± 3.08 μM), **4** ((IC_{50} = 193.77 ± 3.06 μM), **6** ((IC_{50} = 217.90 ± 2.48 μM), **15** ((IC_{50} = 221.98 ± 2.34 μM), **2** ((IC_{50} = 226.59 ± 1.19 μM), **21** (IC_{50} = 229.67 ± 1.95 μM), **18** (IC_{50} = 231.09 ± 0.38 μM), **12** (IC_{50} = 242.94 ± 2.05 μM), and **1** (IC_{50} = 264.22 ± 5.60 μM), respectively, were found to be superior in activities as compared to standard rutin. Compound **17** (IC_{50} = 269.94 ± 1.11 μM) displayed a comparable activity to the standard. Compounds **7**, **8**, **9**, **10**, **11**, **13**, **14**, and **16** exhibited weaker activities than standard. However, all compounds were evaluated for cytotoxicity against rat fibroblast cell line (3T3 cell line) and were found to be non-toxic in cellular model.

Structure–activity relationship disclosed that the activity of compounds **1**–**18** and **21** mainly depends upon the substitution at the phenyl ring. Compound **5** (IC_{50} =

Scheme 1 Synthesis of phenyl thiazole hydrazones (**1–21**)



187.61 ± 1.12 μM) which has an *ortho* nitro residue is found to be the active most compound among all tested compounds. Compounds **6** (IC_{50} = 217.90 ± 2.48 μM) and **7** (IC_{50} = 437.81 ± 5.37 μM) have *meta* and *para* nitro group, respectively, and found to be weakly active as compared to compound **5** due to slight change in position of nitro group, suggesting that for a better antiglycation, the nitro group must be at the *ortho* position of phenyl ring. If we compare the activity of compounds **6** and **12** ((IC_{50} = 242.9 ± 2.05 μM), then it reveals that decrease in activity of compound **12** may be due to the presence of a chloro group at *ortho* position of phenyl ring.

Hydroxy-substituted phenyl ring containing compounds **3** (IC_{50} = 191.92 ± 3.08 μM), **4** (IC_{50} = 193.77 ± 3.06 μM), **15** (IC_{50} = 221.98 ± 2.34 μM), and **2** (IC_{50} = 226.59 ± 1.19 μM) demonstrated excellent activity. The activity difference in this type of compounds is also due to position of hydroxy group at phenyl ring. Compound **3** displayed an equivalent activity to compound **4,** suggesting that number of hydroxy does not influence the activity; it is the position which affects the activity. This fact is clearly proved by the comparable activities; however, compound **15** contains an additional hydroxy group. Compound **14** (IC_{50} = 321.13 ± 1.84 μM) showed a decreased activity due the obvious reason of positional difference of hydroxy group.

Compounds **1** (IC_{50} = 264.22 ± 5.60 μM), **17** (IC_{50} = 269.94 ± 1.11 μM), having hydroxy group as well as methoxy and **18** (IC_{50} = 231.09 ± 0.38 μM) having dimethoxy, the activity pattern follows by positions of hydroxy and methoxy suitable for interaction with sugar. Same way ethoxy substitution at para position as in compound **16** (IC_{50} = 488.19 ± 2.11 μM), also follows the same pattern.

In chloro-containing compounds, the positional isomer follows the nitro and hydroxy residues pattern.

Materials and methods

General experimental

NMR analyses were performed on Avance Bruker AM 300–500 MHz Instrument; CHN analysis was done with Carlo Erba Strumentazion-Mod-1106, Italy. Electron impact mass spectra (EI MS) were experimented on a Finnigan MAT-311A, Germany. Thin-layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms developed were visualized by UV at 254 and 365 nm.

Antiglycation assay

Bovine serum albumin-methylglyoxal glycation model

We performed the antiglycation assay according to the following procedure described with some modification. Reaction mixture contained 20 μL test sample, 50 μL BSA (10 mg/mL), 50 μL MGO (14 mM), and 80 μL phosphate buffer (100 mM; pH 7.4) containing NaN_3 (3 mM) as a antimicrobial agent. The reaction mixture was incubated for 9 days at 37 °C. Each sample was run in triplicate. Antiglycation effect of test sample was monitored by measuring the specific fluorescence (excitation, 330 nm; emission, 420 nm) against DMSO-treated control through a microtitre plate spectrofluorometer (Spectra Max, Molecular Devices, CA, USA). The IC_{50} values of compounds were calculated by using the EZ-Fit Enzyme kinetics software program (Perrella Scientific Inc. Amherst, MA, USA). Rutin was used as a positive control (IC_{50} = 269.07 ± 3.79 μM).

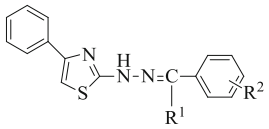
The percentage inhibition of each test compound was determined by the formula given below:

$$\% \text{ Inhibition} = (1 - \text{Fluorescence of test sample} / \text{Fluorescence of the control}) \times 100$$

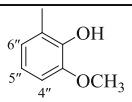
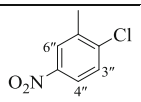
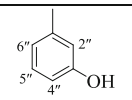
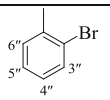
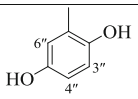
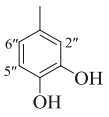
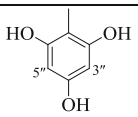
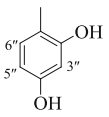
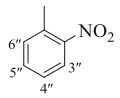
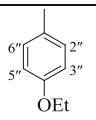
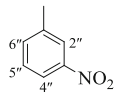
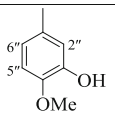
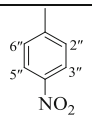
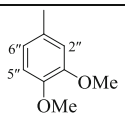
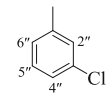
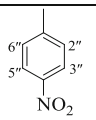
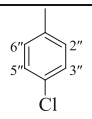
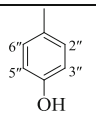
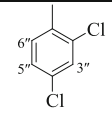
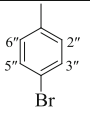
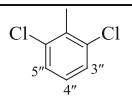
Cytotoxicity evaluation on rat fibroblast 3T3 cell lines

Rat fibroblast 3T3 cells were used in this assay. Briefly the 3T3-adherent cells (2×10^5 cells/mL) were cultured overnight in CO_2 environment in 96-well plate (at 37° C). Supernatant was removed, and 50 μL of various concentration of test compounds (100–12.5 μg/mL), 150 μL of DMEM medium (supplemented with penicillin (100 units/mL), 5 % (v/v) fetal bovine serum, and streptomycin (100 μg/mL) were added to each well, and further incubation was carried out for 72 h. After incubation, the culture medium was aspirated and 50 μL (2 mg/mL in PBS) of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide) solution was added to each well. This reaction mixture was

Table 1 In vitro antiglycation activity of phenyl thiazoles hydrazones **1–21**



1-21

Comp. No	R^1	R^2	$IC_{50} \pm SEM^a$ (μM)	Comp. No.	R^1	R^2	$IC_{50} \pm SEM^a$ (μM)
1	H		264.22 ± 5.6	**12**	H		242.94 ± 2.05
2	H		226.59 ± 1.19	**13**	H		886.98 ± 5.29
3	H		191.92 ± 3.08	**14**	H		321.13 ± 1.84
4	H		193.77 ± 3.06	**15**	H		221.98 ± 2.34
5	H		187.61 ± 1.12	**16**	H		488.19 ± 2.11
6	H		217.90 ± 2.48	**17**	H		269.94 ± 1.11
7	H		437.81 ± 5.37	**18**	H		231.09 ± 0.38
8	H		327.99 ± 5.91	**19**	CH_3		NA[b]
9	H		493.26 ± 1.51	**20**	CH_3		NA[b]
10	H		278.42 ± 2.17	**21**	H		229.67 ± 1.95
11	H		321.47 ± 3.87	**Rutin[b]**	-	-	269.07 ± 3.79

[a] SEM is the standard error of mean

[b] Rutin is standard for antiglycation activity

then further incubated for 4 h. After 4 h, the MTT solution was aspirated and cells were washed with phosphate-buffered saline. Finally, DMSO (100 µL) was added to dissolve the MTT-formazan adduct, formed by the action of mitochondrial dehydrogenase. The reaction plate was agitated at room temperature for 15 min, and then, absorbance was measured at 540 nm by using microplate reader (Spectra Max Plus 384, Molecular Devices, CA, USA) (Dimas *et al.,* 1998). The percent viability was calculated as the relative ratio of optical densities.

Statistical analysis

All experiments were performed in microplate reader (SpectraMax M2, Molecular Devices, CA, USA). Results are presented as mean ± SEM from three experiments. The obtained results were analyzed by SoftMaxPro 4.8, MS Excel and GraphPad Prism-5.0, software package. IC_{50} values were determined by using EZ-FIT, Enzyme kinetics software (Perrella Scientific, Inc., USA).

General procedure for the synthesis of hydrazones **1**–**21**

Commercially available 2-hydrazino-4-phenyl thiazole reacted with various aromatic aldehydes in absolute ethanol or methanol in the presence of catalytic amount of acetic acid which afforded compounds **1**–**21** in significant yields (Scheme 1). In a typical reaction, 2-hydrazino-4-phenyl thiazole (1 mmol) was reacted with different substituted aromatic aldehydes (1 mmol) in ethanol under reflux for 3 h. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was allowed to cool to room temperature. The solvent was evaporated by vacuum. The crude product was recrystallized in ethanol which afforded pure thiazole hydrazones derivatives **1**–**21** in significant yields.

*(E)-2-Methoxy-6-((2-(4-phenylthiazol-2-yl)hydrazono)methyl) phenol (**1**)* Yield: (81 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.01 (s, 1H, H–NH), 7.84 (d, 2H, J = 7.2 Hz, H-2′,6′), 7.68 (s, 1H, CH=NAr), 7.60 (d, 1H, J = 7.2 Hz, H-6″), 7.46 (d, 1H, J = 7.6 Hz, H-4″), 7.45–7.38 (m, 2H, H-4′,H-5″), 7.34 (s, 1H, H-5), 7.30 (t, 2H, J = 7.2 Hz, H-3′,5′), 3.81 (s, 1H, H–OH), 3.30 (s, 3H, –OCH_3); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.4 (C, C-2), 150.2 (C, C-2″), 150.0 (C, C-4), 149.2 (C, C-3″), 143.1 (C=N), 133.1 (C, C-1′), 129.2 (CH, C-3′, C-5′), 128.6 (CH, C-4′), 127.4 (CH, C-2′, C-6′), 124.3 (CH, C-6″), 119.2 (CH, C-1″), 116.4 (CH, C-5″), 115.20 (CH, C-4″), 105.1 (CH, C-5), 56.4 (CH_3, OCH_3); EI MS: *m/z* (rel. abund. %), 325 (M^+, 96.2), 308 (100), 176 (100), 134 (93.1), 104 (14.7). Anal. Calcd for $C_{17}H_{15}N_3O_2S$; (325.09); C, 62.75; H, 4.65; N, 12.91; O, 9.83; S, 9.85; Found; C, 62.73; H, 4.63; N, 12.89; O, 9.85; S, 9.83.

*(E)-3-((2-(4-Phenylthiazol-2-yl)hydrazono)methyl)phenol (**2**)* Yield: (87 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.10 (s, 1H, H–NH), 9.57 (s, 1H, –OH), 7.92 (s, 1H, CH=NAr), 7.84 (d, 2H, J = 7.2 Hz, H-2′,6′), 7.39 (t, 2H, J = 7.8 Hz, H-3′,5′), 7.31–7.26 (m, 1H, H-5 and H-4′), 7.21 (t, 1H, J = 7.8 Hz, H-5″), 7.09 (s, 1H, H-2″), 7.02 (d, 1H, J = 7.2 Hz, H-4″), 6.76 (d, 1H, J = 8.1 Hz, H-6″); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.6 (C, C-2), 158.4 (C, C-3″), 150.5 (C, C-4), 143.4 (C=N), 138.5 (CH, C-1″), 133.3 (C, C-1′), 129.8 (CH, C-5″), 129.1 (CH, C-3′, C-5′), 128.4 (CH, C-4′), 127.1 (CH, C-2′, C-6′), 121.2 (CH, C-6″), 118.8 (CH, C-4″), 115.4 (CH, C-2″), 105.4 (CH, C-5); EI MS: *m/z* (rel. abund. %), 295 (M^+, 100), 176 (100), 134 (100), 104 (47.1), 77 (43.9); 65 (39.3). Anal. Calcd for $C_{16}H_{13}N_3OS$; (295.36); C, 65.06; H, 4.44; N, 14.23; O, 5.42; S, 10.86; Found; C, 65.04; H, 4.46; N, 14.25; O, 5.44; S, 10.84.

*(E)-2-((2-(4-Phenylthiazol-2-yl)hydrazono)methyl)benzene-1, 4-diol (**3**)* Yield: (87 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.06 (s, 1H, NH), 9.35 (s, 1H, –OH), 8.90 (s, 1H, –OH), 8.23 (s, 1H, CH = NAr), 7.84 (d, 2H, J = 7.5 Hz, H-2′,6′), 7.39 (t, 2H, J = 7.5 Hz, H-3′,5′), 7.30–7.26 (m, 1H, H-4′), 7.30 (s, 1H, H-5), 7.04 (d, 1H, J = 2.4 Hz, H-6″), 6.721–6.615 (m, 2H, H-3″, H-4″); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.2 (C, C-2), 154.2 (C, C-2″), 152.1 (C, C-5″), 150.1 (C, C-4), 143.8 (C = N), 132.9 (C, C-1′), 129.5 (CH, C-3′, C-5′), 128.1 (CH, C-4′), 126.8 (CH, C-2′, C-6′), 121.2 (C, C-1″), 120.0 (CH, C-3″), 118.8 (CH, C-4″), 116.2 (CH, C-6″), 105.8 (CH, C-5); EI MS: *m/z* (rel. abund. %), 311 (M^+, 30.7), 294 (45.2), 176 (100), 134 (76.3). Anal. Calcd for $C_{16}H_{13}N_3O_2S$; (311.07); C, 61.72; H, 4.21; N, 13.50; O, 10.28; S, 10.30; Found; C, 61.74; H, 4.23; N, 13.48; O, 10.30; S, 10.28.

*(E)-2-((2-(4-Phenylthiazol-2-yl)hydrazono)methyl)benzene-1,3,5-triol (**4**)* Yield: (87 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.41 (s, 1H, H-3″,5″), 9.76 (s, 1H, H–NH), 8.44 (s, 1H, CH=NAr), 7.83 (d, 2H, J = 7.2 Hz, H-2′,6′), 7.39 (t, 2H, J = 7.2 Hz, H-3′,5′), 7.31–7.27 (m, 2H, H-4′, H-5); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.3 (C, C-2), 164.2 (C, C-2″, C-6″), 163.8 (C, C-4″), 149.8 (C, C-4), 144.1 (C=N), 133.3 (C, C-1′), 129.2 (CH, C-3′, C-5′), 128.3 (CH, C-4′), 127.8 (CH, C-2′, C-6′), 106.5 (C, C-1″), 104.8 (CH, C-5), 96.1 (CH, C-3″, C-5″); EI MS: *m/z* (rel. abund. %), 327 (M^+, 2.8), 309 (100), 161 (282.7), 134 (25.7). Anal. Calcd for $C_{16}H_{13}N_3O_3S$; (327.07); C, 58.70; H, 4.00; N, 12.84; O, 14.66; S, 9.80; Found; C, 58.68; H, 3.98; N, 12.86; O, 14.64; S, 8.98.

*(E)-2-(2-(2-Nitrobenzylidene)hydrazinyl)-4-phenylthiazole (**5**)* Yield: (87 %); ^{1}H-NMR (400 MHz, DMSO-d_6): δ

12.54 (s, 1H, H–NH), 8.41(s, 1H, CH=NAr), 8.04–8.02 (m, 2H, H-3″, 6″), 8.02 (d, 2H, J = 8 Hz, H-2′,6′), 7.65 (t, 1H, J = 7.6 Hz, H-4″), 7.48 (t, 2H, J = 7.2 Hz, H-5″), 7.38 (t, 1H, J = 7.2 Hz, H-3′,5′), 7.39 (s, 1H, H-5); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 172.1 (C, C-2), 150.9 (C, C-4), 148.2 (C, C-2″), 142.8 (C=N), 136.1 (C, C-5″), 133.4 (C, C-1′), 132.3 (CH, C-4″), 130.8 (CH, C-6″), 130.4 (CH, C-3′, C-5′), 129.4 (CH, C-4′), 129.2 (C, C-1″), 128.2 (CH, C-2′, C-6′), 123.2 (CH, C-3″), 105.7 (CH, C-5); EI MS: *m/z* (rel. abund. %), 324 (M^+, 58.5), 176 (100), 134 (100), 102 (36), 77 (21); 65 (8.4). Anal. Calcd for $C_{16}H_{12}N_4O_2S$; (324.36); C, 59.25; H, 3.73; N, 17.27; O, 9.87; S, 9.89; Found; C, 59.27; H, 3.75; N, 17.25; O, 9.85; S, 9.91.

(E)-2-(2-(3-Nitrobenzylidene)hydrazinyl)-4-phenylthiazole ***(6)*** Yield: (89 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.47 (s, 1H, H–NH), 8.46 (s, 1H, CH=NAr), 8.19 (dd, 1H, $J_{1'',2''}$ = 2 Hz, $J_{1'',3''}$ = 8 Hz, H-3″), 8.19 (s, 1H, H-2″), 8.08 (d, 1H, J = 8 Hz, H-6″), 7.85 (d, 2H, J = 7.6 Hz, H-2′,6′), 7.71 (t, 1H, J = 7.6 Hz, H-5″), 7.40 (t, 2H, J = 7.6 Hz, H-3′,5′), 7.38 (s, 1H, H-5), 7.30 (t, 1H, J = 7.2 Hz, H-4′); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 172.2 (C, C-2), 150.5 (C, C-4), 148.2 (C, C-3″), 143.1 (C=N), 134.9 (C, C-1″), 133.4 (C, C-1′), 132.3 (CH, C-6″), 130.2 (CH, C-3′, C-5′), 130.1 (CH, C-5″), 129.1 (CH, C-4′), 128.1 (CH, C-2′, C-6′), 126.8 (CH, C-4″), 121.4 (CH, C-2″), 105.3 (CH, C-5); EI MS: *m/z* (rel. abund. %), 324 (M^+, 35.1), 176 (100), 134 (89.9), 104 (12.3), 77 (19); 63 (5). Anal. Calcd for $C_{16}H_{12}N_4O_2S$; (324.36); C, 59.25; H, 3.73; N, 17.27; O, 9.87; S, 9.89; Found; C, 59.27; H, 3.75; N, 17.25; O, 9.85; S, 9.91.

(E)-2-(2-(4-Nitrobenzylidene)hydrazinyl)-4-phenylthiazole ***(7)*** Yield: (91 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.47 (s, 1H, H-NH), 8.21 (d, 2H, J = 8.8 Hz, H-2′,6′), 7.79 (d, 2H, J = 7.6 Hz, H-3″,5″), 7.66 (d, 2H, J = 8.8 Hz, H-2″,6″), 7.26 (s, 1H, CH = NAr), 7.40 (t, 2H, J = 7.6 Hz, H-3′, 5′), 7.33-7.31 (m, 1H, H-4′), 6.92 (s, 1H, H-5); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.9 (C, C-2), 150.6 (C, C-4″), 150.5 (C, C-4), 143.1 (C=N), 140.1 (C, C-1″), 133.1 (C, C-1′), 129.3 (CH, C-3′, C-5′), 128.9 (CH, C-4′), 127.2 (CH, C-2′, C-6′), 124.4 (CH, C-2″, C-6″), 124.1 (C, C-3″, C-5″), 105.1 (CH, C-5); EI MS: *m/z* (rel. abund. %), 324 (M^+, 90.6), 176 (100), 134 (65.2), 104 (7.7), 77 (6.2); 44 (24.9). Anal. Calcd for $C_{16}H_{12}N_4O_2S$; (324.36); C, 59.25; H, 3.73; N, 17.27; O, 9.87; S, 9.89; Found; C, 59.23; H, 3.71; N, 17.23; O, 9.89; S, 9.87.

(E)-2-(2-(3-Chlorobenzylidene)hydrazinyl)-4-phenylthiazole ***(8)*** Yield: (85 %); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.28 (s, 1H, H–NH), 8.01 (s, 1H, CH=NAr), 7.84 (d, 2H, J = 7.2 Hz, H-2′,6′), 7.68 (s, 1H, H-2″), 7.60 (d, 1H, J = 7.2 Hz, H-4″), 7.47–7.42 (m, 3H, H-3′,5′,5″), 7.39 (d, 1H, J = 7.6 Hz, H-6″), 7.34 (s, 1H, H-5), 7.29 (t, 1H, J = 7.6 Hz, H-4′); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.8 (C, C-2), 150.1 (C, C-4), 143.4 (C=N), 134.2 (C, C-3″), 133.1 (C, C-1′), 131.4 (CH, C-4″), 130.2 (CH, C-3′, C-5′), 130.1 (CH, C-5″), 128.9 (CH, C-4′), 127.5 (CH, C-6″), 127.3 (CH, C-2′, C-6′), 127.2 (CH, C-2″), 121.1 (C, C-1″), 105.2 (CH, C-5); EI MS: *m/z* (rel. abund. %), 313 (M^+, 25.1), 233 (91.3), 191 (100), 174 (70.3), 134 (93.6); 91(40.3), 43 (40.8). Anal. Calcd for $C_{16}H_{12}ClN_3S$; (313.04); C, 61.24; H, 3.85; Cl, 11.30; N, 13.39; S, 10.22; Found; C, 61.22; H, 3.87; Cl, 11.28; N, 13.41; S, 10.20.

(E)-2-(2-(4-Chlorobenzylidene)hydrazinyl)-4-phenylthiazole ***(9)*** Yield: (79 %); ^{1}H-NMR (300 M Hz, DMSO-d_6): δ 12.25 (s, 1H, H–NH), 8.01 (s, 1H, CH=NAr), 7.84 (d, 2H, J = 7.5 Hz, H-2′,6′), 7.66 (d, 2H, J = 8.7 Hz, H-2″,6″), 7.48 (d, 2H, J = 8.4 Hz, H-3″,5″) 7.40 (t, 2H, J = 7.2 Hz, H-3′,5′), 7.31 (t, 1H, J = 7.8 Hz, H-4′), 7.26 (s, 1H, H-5); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.8 (C, C-2), 150.4 (C, C-4), 143.5 (C=N), 136.8 (CH, C-4″), 135.1 (C, C-1″), 133.1 (C, C-1′), 130.4 (C, C-2″, C-6″), 129.5 (CH, C-3′, C-5′), 129.1 (C, C-3″, C-5″), 128.9 (CH, C-4′), 127.7 (CH, C-2′, C-6′), 105.3 (CH, C-5); EI MS: *m/z* (rel. abund. %), 311 (M^+, 23.0), 294 (7.9), 176 (100), 134 (66.3). Anal. Calcd for $C_{16}H_{12}ClN_3S$; (313.04); C, 61.24; H, 3.85; Cl, 11.30; N, 13.39; S, 10.22; Found; C, 61.26; H, 3.83; Cl, 11.28; N, 13.37; S, 10.24.

(E)-2-(2-(2,4-Dichlorobenzylidene)hydrazinyl)-4-phenylthiazole ***(10)*** Yield: (76 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.47 (s, 1H, H–NH), 8.26 (s, 1H, CH=NAr), 7.84 (d, 2H, J = 7.2 Hz, H-2′,6′), 7.56 (s, 1H, H-3″), 7.53 (s, 1H, H-5), 7.42–7.29 (m, 5H, H-3′,5′,4′, 5″,6″); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.8 (C, C-2), 150.1 (C, C-4), 143.5 (C=N), 133.1 (C, C-1′), 131.2 (C, C-2″), 129.6 (CH, C-3′, C-5′), 129.4 (CH, C-3″), 129.2 (CH, C-6″), 128.8 (CH, C-4′), 128.5 (C, C-4″), 127.7 (CH, C-2′, C-6′), 127.1 (CH, C-5″), 121.1 (C, C-1″), 105.2 (CH, C-5); EI MS: *m/z* (rel. abund. %), 347 (M^+, 3.37), 176 (100), 134 (92.1), 45 (28.5). Anal. Calcd for $C_{16}H_{11}Cl_2N_3S$; (347.01); C, 55.18; H, 3.18; Cl, 20.36; N, 12.07; S, 9.21; Found; C, 55.16; H, 3.16; Cl, 20.34; N, 12.05; S, 9.23.

(*E*)-2-(2-(2,6-Dichlorobenzylidene)hydrazinyl)-4-phenyl thiazole (*11*) Yield: (88 %); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.20 (s, 1H, H–NH), 8.26 (s, 1H, CH=NAr), 7.85 (d, 2H, J = 7.2 Hz, H-2′,6′), 7.54 (d, 2H, J = 8.4 Hz, H-3″,5″), 7.42–7.36 (m, 3H, H-3′,5′,4″), 7.32 (s, 1H, H-5), 7.32-7.29 (m, 3H, H-4′); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.6 (C, C-2), 150.1 (C, C-4), 143.2 (C = N), 133.8 (C, C-2″, C-6″), 133.1 (C, C-1′), 130.2 (C, C-1″), 129.4 (CH, C-3′, C-5′), 129.2 (CH, C-4″), 128.9 (CH, C-4′), 128.4 (CH, C-3″, C-5″), 127.4 (CH, C-2′, C-6′), 105.0 (CH, C-5); EI MS: *m/z* (rel. abund. %), 348 (M^+,1.2), 176 (100), 148 (71.6), 89 (1.5). Anal. Calcd for $C_{16}H_{11}Cl_2N_3S$; (347.01);

C, 55.18; H, 3.18; Cl, 20.36; N, 12.07; S, 9.21; Found; C, 55.16; H, 3.16; Cl, 20.34; N, 12.05; S, 9.23.

(E)-2-(2-(2-Chloro-5-nitrobenzylidene)hydrazinyl)-4-phenylthiazole (***12***) Yield: (89 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 11.88 (s, 1H, H–NH), 8.62 (d, 1H, J = 2.7 Hz, H-6″), 8.38 (s, 1H, CH=NAr), 8.16 (dd, 1H, $J_{1'',2''}$ = 3, $J_{1'',3''}$ = 9 Hz, H-4″), 7.86 (d, 2H, J = 7.2 Hz, H-2′,6′), 7.81 (d, 1H, J = 8.7 Hz, H-3″), 7.41 (t, 2H, J = 8.4 Hz, H-3′,5′), 7.41 (s, 1H, H-5), 7.32 (t, 1H, J = 7.2 Hz, H-4′); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.9 (C, C-2), 150.4 (C, C-4), 146.3 (C, C-5″), 143.5 (C = N), 140.1 (C, C-2″), 134.1 (C, C-1″), 133.2 (C, C-1′), 129.8 (CH, C-4″), 129.1 (CH, C-3′, C-5′), 128.9 (CH, C-4′), 128.3 (CH, C-3″), 127.4 (CH, C-2′, C-6′), 124.1 (CH, C-6″), 105.2 (CH, C-5); EI MS: *m/z* (rel. abund. %), 358 (M^+, 22.4), 176 (88.3), 134 (100), 77 (18); 45 (5.7). Anal. Calcd for $C_{16}H_{11}ClN_4OS$; (347.01); C, 53.56; H, 3.09; Cl, 9.88; N, 15.61; O, 8.92; S, 8.94; Found; C, 53.58; H, 3.11; Cl, 9.90; N, 15.59; O, 8.90; S, 9.23.

(E)-2-(2-(2-Bromobenzylidene)hydrazinyl)-4-phenylthiazole (***13***) Yield: (78 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.30 (s, 1H, H–NH), 8.51 (s, 1H, CH=NAr), 8.03 (dd, 1H, $J_{1'',2''}$ = 1.5, $J_{1'',3''}$ = 6.3 Hz, H-3″), 7.89 (d, 2H, J = 7.5 Hz, H-2′,6′), 7.64 (dd, 1H, $J_{1'',2''}$ = 0.9, $J_{1'',3''}$ = 8.1 Hz, H-5″), 7.45 (t, 1H, J = 7.5 Hz,H-4″), 7.22 (s, 1H, H-5), 7.40–7.25 (m, 4H, H-3′,4′,5′,6″); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.8 (C, C-2), 150.1 (C, C-4), 143.4 (C = N), 135.6 (C, C-1″), 133.1 (C, C-1′), 132.6 (CH, C-3″), 130.4 (CH, C-4″), 129.3 (CH, C-3′, C-5′), 128.8 (CH, C-4′), 127.9 (CH, C-5″), 127.6 (CH, C-2′, C-6′), 127.3 (CH, C-6″), 121.5 (C, C-2″), 105.1 (CH, C-5); EI MS: *m/z* (rel. abund. %), 358 (M^+, 29), 176 (100), 134 (89.9), 104 (26.2), 89, (24.1), 77 (14.9). Anal. Calcd for $C_{16}H_{12}BrN_3S$; (356.99); C, 53.64; H, 3.38; Br, 22.30; N, 11.73; S, 8.95; Found; C, 53.66; H, 3.40; Br, 33.28; N, 11.71; S, 8.97.

(E)-4-((2-(4-Phenylthiazol-2-yl)hydrazono)methyl)benzene-1,2-diol (***14***) Yield: (78 %); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H, H–NH), 9.22 (s, 2H, –OH), 7.84 (s, 1H, CH=NAr), 7.83 (d, 2H, J = 6.6 Hz, H-2′,6′), 7.39 (t, 2H, J = 7.2 Hz, H-3′,5′), 7.30–7.26 (m, 1H, H-4′), 7.26 (s, 1H, H-5), 7.13 (s, 1H, H-2″), 6.84 (s, 1H, H-5″), 6.74 (d, 1H, J = 8.1 Hz, H-6″); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.5 (C, C-2), 150.3 (C, C-4), 149.8 (C, C-4″), 146.2 (C, C-3″), 143.3 (C=N), 133.1 (C, C-1′), 131.2 (C, C-1″), 129.4 (CH, C-3′, C-5′), 128.9 (CH, C-4′), 127.3 (CH, C-2′, C-6′), 123.1 (CH, C-6″), 117.3 (CH, C-5″), 116.2 (CH, C-2″),105.2 (CH, C-5); EI MS: *m/z* (rel. abund. %), 311 (M^+, 46.9), 309(18.6), 176 (100), 134 (70.2). Anal. Calcd for $C_{16}H_{13}N_3O_2S$; (311.07); C, 61.72; H, 4.21; N, 13.50; O, 10.28; S, 10.30; Found; C, 61.74; H, 4.23; N, 13.48; O, 10.30; S, 10.28.

(E)-4-((2-(4-Phenylthiazol-2-yl)hydrazono)methyl)benzene-1,3-diol (***15***) Yield: (88 %); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H, H–NH), 10.14 (s, 2H, –OH), 8.19 (s, 1H, CH = NAr), 7.83 (d, 2H, J = 7.2 Hz, H-2′,6′), 7.39 (t, 2H, J = 7.6 Hz, H-3′,5′), 7.39 (s, 1H, H-3″), 7.30–7.25 (m, 2H, H-4′,6″), 6.32 (d, 1H, J = 6.8 Hz, 5″), 6.31 (s, 1H, H-5); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.9 (C, C-2), 162.4 (C, C-4″), 162.3 (C, C-2″), 150.1 (C, C-4), 143.5 (C=N), 133.6 (CH, C-6″), 133.1 (C, C-1′), 130.1 (CH, C-3′, C-5′), 128.9 (CH, C-4′), 127.1 (CH, C-2′, C-6′), 111.2 (C, C-1″), 108.3 (CH, C-5″), 103.6 (CH, C-3″), 105.3 (CH, C-5); EI MS: *m/z* (rel. abund. %), 311 (M^+, 23.0), 176 (100), 134 (66.3). Anal. Calcd for $C_{16}H_{13}N_3O_2S$; (311.07); C, 61.72; H, 4.21; N, 13.50; O, 10.28; S, 10.30; Found; C, 61.74; H, 4.23; N, 13.48; O, 10.30; S, 10.28.

(E)-2-(2-(4-Ethoxybenzylidene)hydrazinyl)-4-phenylthiazole (***16***) Yield: (85 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.16 (s, 1H, H–NH), 7.71 (t, 2H, J = 8.4 Hz, H-3′,5′), 7.62 (d, 2H, J = 8.7 Hz, H-2′,6′), 7.54–7.37 (m, 4H, H-4′, 2″, 6″ and CH=NAr), 6.92 (d, 2H, J = 8.7 Hz, H-3″, 5″), 6.70 (s, 1H, H-5), 4.11 (q, 2H, J = 6.9 Hz, –CH_2), 1.43 (t, 3H, J = 6.9 Hz, –CH_3); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.5 (C, C-2), 130.2 (CH, C-2″, C-6″), 114.7 (CH, C-3″, C-5″), 150.1 (C, C-4), 143.3 (C=N), 133.1 (C, C-1′), 129.1 (CH, C-3′, C-5′), 128.5 (CH, C-4′), 127.4 (CH, C-2′, C-6′), 125.2 (C, C-1″), 161.8 (C, C-4″), 105.1 (CH, C-5), 64.5 (CH_2, –OCH_2), 14.8 (CH_3, –OCH_2CH_3); EI MS: *m/z* (rel. abund. %), 323 (M^+, 80.6), 176 (100), 134 (54.5). Anal. Calcd for $C_{18}H_{17}N_3OS$; (323.11); C, 66.85; H, 5.30; N, 12.99; O, 4.95; S, 9.91; Found; C, 66.87; H, 5.28; N, 13.01; O, 4.93; S, 9.92.

(E)-2-Methoxy-5-((2-(4-phenylthiazol-2-yl)hydrazono)methyl)phenol (***17***) Yield: (88 %); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.92 (s, 1H, H–NH), 9.23 (s, 2H, –OH), 7.88 (s, 1H, CH=NAr), 7.83 (d, 2H, J = 7.5 Hz, H-2′,6′), 7.39 (t, 2H, J = 7.2 Hz, H-3′,5′), 7.30–7.27 (m, 1H, H-4′), 7.28 (s, 1H, H-5), 6.96 (d, 1H, J = 8.1 Hz, 5″), 3.79 (s, 3H, –OCH_3); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.5 (C, C-2), 152.3 (C, C-4″), 150.5 (C, C-4), 147.2 (C, C-3″), 143.2 (C=N), 133.1 (C, C-1′), 131.0 (C, C-1″), 129.3 (CH, C-3′, C-5′), 128.7 (CH, C-4′), 127.4 (CH, C-2′, C-6′), 122.7 (CH, C-6″), 116.0 (CH, C-2″), 112.1 (CH, C-5″), 105.2 (CH, C-5), 56.1 (CH_3, –OCH_3); EI MS: *m/z* (rel. abund. %), 325 (M^+, 30.3), 176 (100), 134 (23.3). Anal. Calcd for $C_{17}H_{15}N_3O_2S$; (325.09); C, 62.75; H, 4.65; N, 12.91; O, 9.83; S, 9.85; Found; C, 62.73; H, 4.67; N, 1289; O, 9.81; S, 9.87.

(E)-2-(2-(3,4-Dimethoxybenzylidene)hydrazinyl)-4-phenylthiazole (***18***) Yield: (85 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.10 (s, 1H, H–NH), 7.81 (d, 2H, $J_{2',6'}$ = 7.2 Hz, H-2′,6′), 7.52 (s, 1H, CH=NAr), 7.38 (t, 2H, J = 7.2 Hz,

H-3′,5′), 7.29 (d, 1H, $J = 7.2$ Hz, 5″), 7.20 (s, 1H, H-2″), 6.92 (d, 1H, $J = 8.1$ Hz, H-6″), 6.85 (s, 1H, H-5), 6.82 (t, 1H, $J = 8.4$ Hz, H-4′), 3.92 (s, 1H, $–OCH_3$), 3.89 (s, 1H, $–OCH_3$); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.6 (C, C-2), 152.1 (C, C-4″), 150.1 (C, C-4), 150.0 (C, C-3″), 143.1 (C=N), 132.9 (C, C-1′), 130.5 (C, C-1″), 129.1 (CH, C-3′, C-5′), 128.9 (CH, C-4′), 127.4 (CH, C-2′, C-6′), 122.4 (CH, C-6″), 111.5 (CH, C-2″), 109.1 (CH, C-5″), 105.1 (CH, C-5), 56.0 (CH_3, $–OCH_3$), 56.0 (CH_3, $–OCH_3$); EI MS: *m/z* (rel. abund. %), 339 (M^+, 24.7), 176 (100), 134 (23.0). Anal. Calcd for $C_{18}H_{17}N_3O_2S$; (339.10); C, 63.70; H, 5.05; N, 12.38; O, 9.43; S, 9.45; Found; C, 63.68; H, 5.03; N, 12.40; O, 9.45; S, 9.43.

*(E)-2-(2-(1-(4-Nitrophenyl)ethylidene)hydrazinyl)-4-phenylthiazole (**19**)* Yield: (81 %); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.20 (s, 1H, H–NH), 8.24 (d, 2H, $J = 8.8$ Hz, H-2′,6′), 7.92 (d, 2H, $J = 9.2$ Hz, H-3″,5″), 7.78 (d, 2H, $J = 7.2$ Hz, H-2″,6″), 7.39 (t, 2H, $J = 7.2$ Hz, H-3′,5′), 7.32–7.24 (m, 1H, H-4′), 6.94 (s, 1H, H-5); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.5 (C, C-2), 150.1 (C, C-4″), 150.0 (C, C-4), 143.5 (C, C-1″), 143.3 (C=N), 133.1 (C, C-1′), 129.4 (CH, C-3′, C-5′), 128.8 (CH, C-4′), 127.6 (CH, C-2′, C-6′), 127.5 (CH, C-2″, C-6″), 127.1 (CH, C-3″, C-5″), 105.1 (CH, C-5); EI MS: *m/z* (rel. abund. %), 323 (M^+, 80.6), 176 (100), 134 (54.5). Anal. Calcd for $C_{17}H_{14}N_4O_2S$; (338.08); C, 60.34; H, 4.17; N, 16.56; O, 9.46; S, 9.48; Found; C, 60.32; H, 4.15; N, 16.58; O, 9.48; S, 9.50.

*(E)-4-(1-(2-(4-Phenylthiazol-2-yl)hydrazono)ethyl)phenol (**20**)* Yield: (85 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.56 (d, 2H, $J = 7.8$ Hz, H-2′,6′), 7.87 (d, 2H, $J = 8.7$ Hz, H-2″,6″), 7.58-7.51 (m, 3H, H-3′, 4′, 5′), 6.89 (s, 1H, H-5), 6.87 (d, 2H, $J = 8.7$ Hz, H-3″,5″), 2.57 (s, 3H, $–CH_3$); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.5 (C, C-2), 160.9 (C, C-4″), 150.1 (C, C-4), 143.5 (C=N), 133.1 (C, C-1′), 130.2 (C, C-1″), 129.2 (CH, C-2″, C-6″), 129.1 (CH, C-3′, C-5′), 128.5 (CH, C-4′), 127.4 (CH, C-2′, C-6′), 116.1 (CH, C-3″, C-5″), 105.1 (CH, C-5); EI MS: *m/z* (rel. abund. %), 309 (M^+, 100), 176 (7.9), 134 (65.4). Anal. Calcd for $C_{17}H_{15}N_3OS$; (309.09); C, 66.00; H, 4.89; N, 13.58; O, 5.17; S, 10.36; Found; C, 58.98; H, 4.91; N, 13.46; O, 5.15; S, 10.30.

*(E)-2-(2-(4-Bromobenzylidene)hydrazinyl)-4-phenylthiazole (**21**)* Yield: (81 %); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10,10(s, 1H, H–NH), δ 7.78 (d, 2H, $J = 7.2$ Hz, H-2′,6′), 7.47 (s, 1H, CH=NAr), 7.45–7.41 (m, 2H, –CH and 4′), 7.373 (d, 1H, $J = 7.2$ Hz, H-6″), 7.31–7.27 (dd, 1H, $J_{1,2} = 2.4$ Hz, $J_{1,3} = 8.8$ Hz, H-4″), 6.84 (t, 2H, $J = 8.8$ Hz, H-3′,5′), 6.76 (d, 1H, $J = 2.4$ Hz, H-3); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 171.5 (C, C-2), 150.1 (C, C-4), 143.3 (C=N), 133.1 (C, C-1′), 132.5 (C, C-1″), 131.5 (CH, C-3″, C-5″), 129.1 (CH, C-3′, C-5′), 128.5 (CH, C-4′), 128.4 (CH, C-2″, C-6″), 127.4 (CH, C-2′, C-6′), 125.3 (C, C-4″), 105.2 (CH, C-5); EI MS: *m/z* (rel. abund. %), 338 (M^+,90.6), 176 (100), 134 (65.2), 104 (7.7), 77 (6.2); 44 (24.9). Anal. Calcd for $C_{16}H_{12}BrN_3S$; (356.99); C, 53.64; H, 3.38; Br, 22.30; N, 11.73; S, 8.95; Found; C, 53.66; H, 3.40; Br, 33.28; N, 11.71; S, 8.97.

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