



# Synthesis and Biological activity of 1,3-Thiazolylidenehydrazinylidene ethylpyridiniumbromide monohydrate, 1,3-Thiazolylidenehydraziniumbromide and 1,3-Thiazolylidenehydrazine derivatives

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## ABSTRACT

1,3-Thiazolylidenehydrazinylidene ethylpyridinium bromide monohydrate, 1,3-thiazolylidenehydrazinium bromide and 1,3-thiazolylidenehydrazine derivatives were synthesized by heterocyclization of 2-(1-substituted ethylidene)hydrazinecarbothioamides, characterized and screened for their anti-bacterial activities. **3h** showed the highest inhibitory effect against all types of bacterial compared to Moxifloxacin. The structures of synthesized compounds were established by spectroscopic (IR, <sup>1</sup>H, <sup>13</sup>C-NMR, Mass) and X-ray analyses.

## Keywords

Substituted ethylidenehydrazinecarbothioamides, 1-aryl-2-bromoethanones, 1,3-thiazolylidene-hydrazine derivatives and their salts, anti-bacterial activity.

## Academic Discipline And Sub-Disciplines

Chemistry

## SUBJECT CLASSIFICATION

Organic Synthesis

## TYPE (METHOD/APPROACH)

Cycloaddition elimination reactions

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## INTRODUCTION

Compounds possessing Schiff bases are well known for their pharmacological properties as antifungal, anti-cancer and anti-viral agents [1,2].

Thiosemicarbazones reacted with cyclization reagents such as dichloroacetone, ethylchloroacetate, ethyl-1,2-chloroacetoacetate and 2-bromoacetophenone to give substituted (benzylidenehydrazono)thiazoles [3-6].

A NBS-mediated sequential one-pot synthesis of multi-functionalized thiazoles from 1,3-dicarbonyl compounds and mercaptonitrile salts has been developed under mild conditions [7].

The occurrence of thiazole ring system in numerous biologically active molecules have recognized and possess wide ranges of biological properties such as antioxidant [8], antibacterial drugs [9-11], fungicidal treatment [3,12], anti-inflammatory [13-16], anticonvulsant [17], and anti-HIV [18-20]. 2-Aminothiazole was used as inhibitors of human cancer and Alzheimer's disease [21-24].

The most frequently used synthetic method of generating thiazoles is the Hantzsch process [25], in which  $\alpha$ -haloketone is condensed with thioamides. Several methods for the synthesis of tri- substituted thiazoles have been reported [26-29].

N-substituted pyridinium salts are widely used in organic synthesis [30-32], and have much attention in the field of non-linear optics (NLO) [30,31,33] as well as antibacterial and antifungal activities [34].

In view of these, it was thought of interest to combine both pharmacophoric moieties 1,3-thiazole and aromatic compounds (with donating and withdrawing groups) as well as heterocyclic ring (such as pyridine).

A series of substituted 1,3-thiazole derivatives were synthesized and evaluated for their antibacterial activity.

## RESULTS AND DISCUSSION

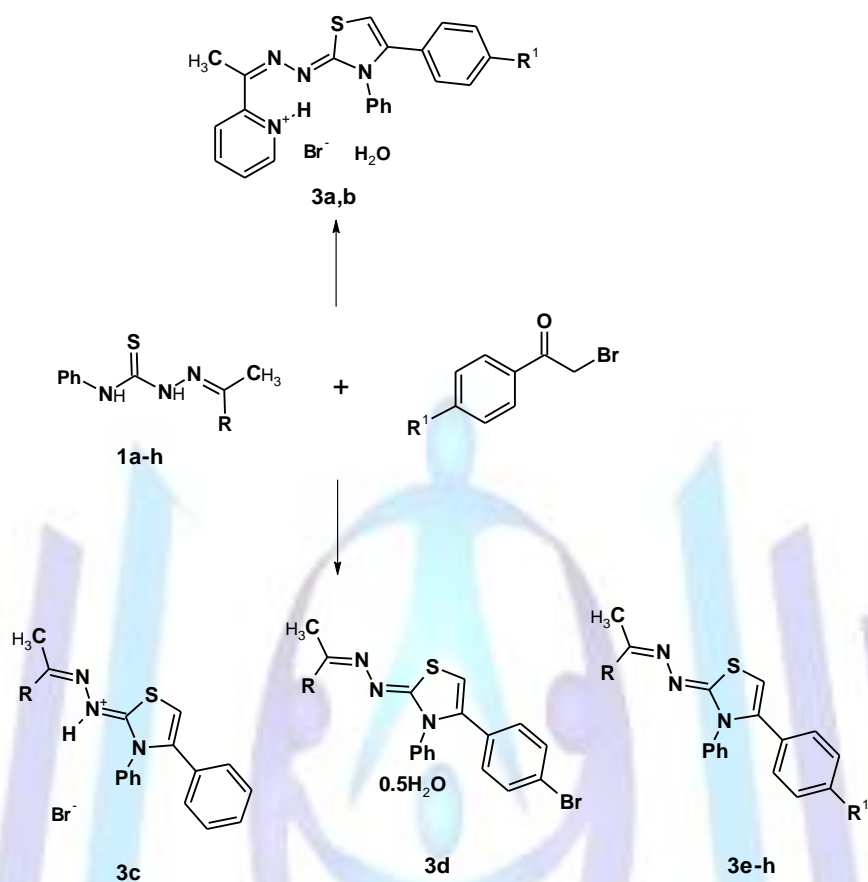
Our investigation was performed by reacting 2-(1-substituted-ethylidenehydrazinecarbothioamides **1a-h** with 1-aryl-2-bromoethanones **2a,b** in refluxing ethanol/ piperidine, the general synthetic pathway was depicted in (Scheme 1). [(3,4-Diaryl-1,3-thiazolylidene)(hydrazineylid-ene)]ethyl-pyridinium bromide monohydrates (**3a,b**), (3,4-diaryl-1,3-thiazolylidene)ethylidenehydrazinium bromides (**3c,d**) and (3,4-diaryl-1,3-thiazolylidene)hydrazines (**3e-h**) were obtained in (80-89%) yields as three different types of thiazole products from the reaction of **1a-h** with **2a,b**.

A detailed interpretation of IR bands of **3a** is discussed. The IR spectrum of **3a** shows a broad band at  $3361\text{cm}^{-1}$  which can be attributed to NH. The (N-N) stretching band in thiazole derivative **3a** observed at  $1567\text{cm}^{-1}$ . The IR of **3a** revealed strong band at  $1619\text{cm}^{-1}$  due to (C=N), the (C-S-C) band was observed at  $767\text{cm}^{-1}$  [6]. A broad band at  $3448$  due to the OH of  $\text{H}_2\text{O}$  molecule.

The  $^1\text{H}$  NMR of **3a** chosen as prototype showed that the pyridine-nitrogen still had a proton and pyr-NH resonance at 9.17 ppm, four proton multiplets at 8.20-8.28 due to pyridine-CH, two singlets at 2.32 and 6.42 because the proton of  $\text{CH}_3$  and thiazole-CH, respectively. A broad signal at 1.6 ppm due to OH of one molecule of  $\text{H}_2\text{O}$ . Multiplets at 7.12-7.78 accounting for ten aromatic protons.

The  $^{13}\text{C}$  NMR spectrum of **3a** supported the  $^1\text{H}$  NMR spectroscopic data by the distinctive appearance of carbon signals representing acyclic C=N at  $\delta_{\text{H}}=157.22$  ppm, thiazole C2, C4 resonate at 168.12 and 148.55 ppm, respectively and thiazole-CH at 104.06. Furthermore, in the  $^{13}\text{C}$  NMR of **3a,b**, the pyridine-C2 is downfield shifted 148.55-147.12. The mass spectrometry fragmentation of **3a** was studied under electron ionization. Loss of ( $\text{HBr}+\text{H}_2\text{O}$ ) giving rise to the ion  $m/z = 363$ . The resulting fragment ions undergo loss of 104 a.m.u. [ $\text{C}_6\text{H}_5\text{-C}(\text{CH}_3)$ ], and 135 a.m.u. ( $\text{Ph-N=C=S}$ ).

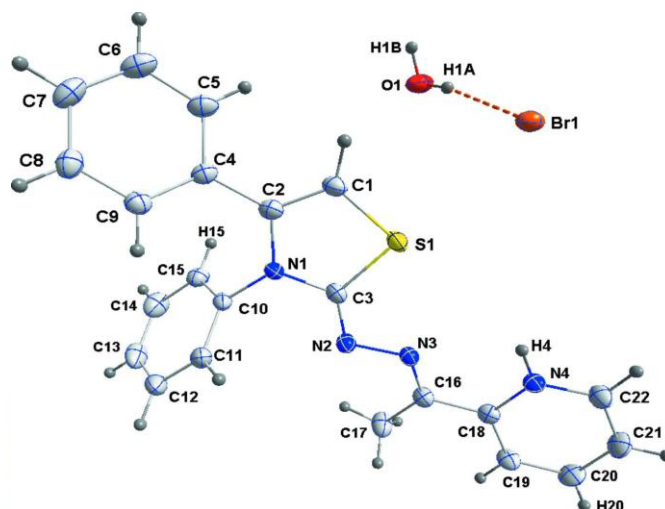
Scheme 1



<b>1a-h</b> and <b>3a-h</b>	<b>a</b>	<b>b</b>	<b>c</b>	<b>d</b>	<b>e</b>	<b>f</b>	<b>g</b>	<b>h</b>
<b>R</b>								
<b>R<sup>1</sup></b>	H	Br	H	Br	H	Br	H	Br

The molecular structure of **3a** was established by single crystal X-ray analysis (Fig. 1) [35]. The dihedral angle between S1/N1C1-C3 thiazolylidene and N4/C18-C22 pyridinium rings is 14.73 C(3) $\sigma$  while that between the phenyl groups C4-C9 and C10-C15 and the mean plane of the thiazolylidene ring are 34.69 (13) and 64.27 (13) $^\circ$ , respectively.

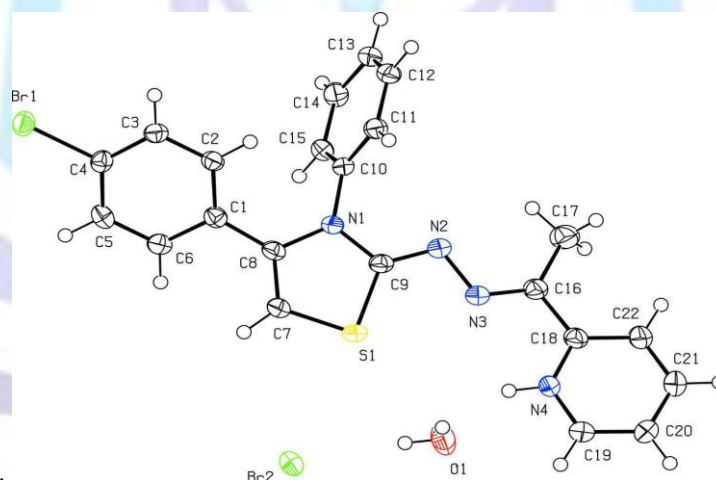
Fig. 1. Molecular conformation of 3a with 50% probability displacement ellipsoids



In the crystal zigzag chains of alternating bromide ions and water molecules associated through O-H....Br interactions run in channels approximately parallel to the b axis [35].

On the other hand, 2-(((1E)-1-{2-[(2E)-4-(4-bromo-phenyl)-3-phenyl-2,3-dihydro-1,3-thiazol-2-ylidene]hydr-azine-1-ylidene)ethyl}-pyridinium bromide monohydrate formed during the reaction of **1b** with **2b**. In the crystal structure of the title hydrated salt  $C_{22}H_{18}BrN_4S^+ \cdot Br^- \cdot H_2O$  the N4/C18-C22, C1-C6 and C10-C15 aromatic rings make dihedral angles of 14.20 (12), 34.29 (10) and 68.75 (11) $^\circ$ , respectively with the (S1/N1/C7-C9) thiazole ring (Fig. 2) [36].

Fig. 2. The crystal structure of the hydrated salt  $C_{22}H_{18}BrN_4S^+ \cdot Br^- \cdot H_2O$  (**3b**).



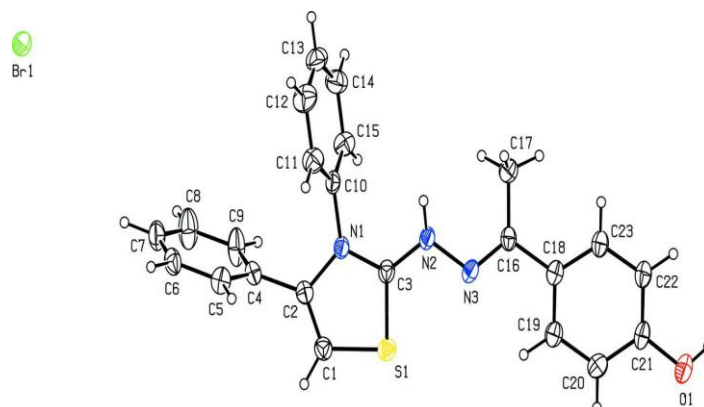
The elemental analyses and mass spectra of **3c,d** clearly revealed that the products were formed by the addition of one molecule of **1c,d** to one molecule of **2a,b** with elimination one molecule of  $H_2O$ . The IR spectrum of **3c** showed absorption of phenolic-OH and NH at 3423 and 3332  $cm^{-1}$ , two strong bands at 1612, 1564 due to C=N vibrations and (N-N) stretching, respectively.

The  $^1H$  NMR spectrum of **3c**, two broad signals at 9.51 and 9.20 ppm due to phenolic-OH, and hydrazinium-NH respectively. In the  $^{13}C$  NMR spectrum of **3c** signals at  $\delta C = 157.10$ , 168.53 and 148.79 ppm were assigned to acyclic C=N, thiazole-C2 and thiazole-C4, respectively. The following additional remarks are necessary: The  $^1H$  NMR spectrum of **3c** shows the presence of one singlet at  $\delta H = 2.31$  ppm due to  $CH_3$ , multiplets at 6.84-7.77 due to aromatic protons. The  $^{13}C$  NMR shows the  $CH_3$  group at 14.15 and thiazole-CH at 102.83 ppm.

The single crystal X-ray structure analysis of (Z)-1-[(2E)-3,4-diphenyl-2,3-dihydro-1,3-thiazol-2-ylidene]-2-[1-(4-hydroxyphenyl)ethylidene]hydrazinium bromide (**3c**) confirmed that, the dihydrothiazole ring [r.m.s. deviation = 0.015 Å] is twisted with respect to each of C- and N-bound phenyl rings and the hydroxy benzene ring, making dihedral angles of 76.0

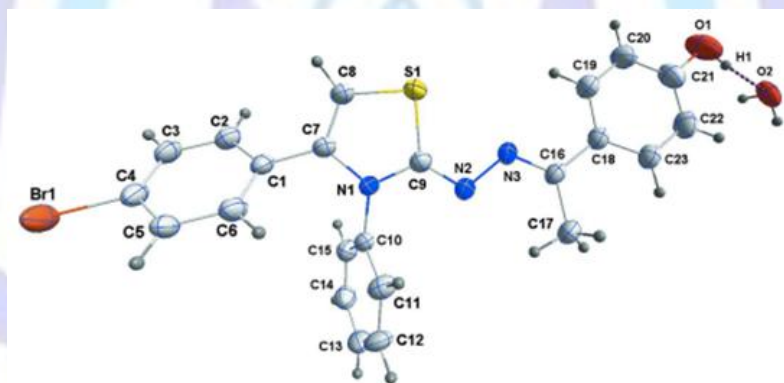
(2), 71.2 (2) and 9.8 (2)<sup>0</sup>, respectively (Fig. 3) [37]. In the crystal inversion related molecules are linked by association of the bromide ions with the cations via N-H...Br and O-H...Br hydrogen-bonding interactions [37].

Fig. 3. Single crystal x-ray structure of **3c**



Substitution the *p*-hydrogen atom of benzene ring attached to thiazole-C4 by bromide afforded the title compound **3d**. For further elucidation the structure of **3d**, the single crystal X-ray diffraction has carried out and showed that the bromo-phenyl, phenyl and phenol rings make dihedral angles of 46.5 (1), 66.78 (8) and 15.4 (2), respectively, with the mean squares plane of the thiazolidene ring. In the crystal, the lattice water molecule is hydrogen bonded to the phenol group and makes a weaker O—H...N connection (Fig. 4) [38].

Fig. 4 Crystal structure of **3d**



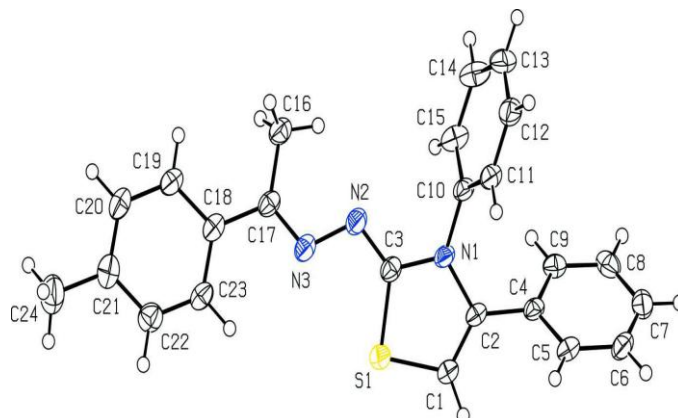
The structures of the third type of the products containing compounds **3e-h** were assigned using spectroscopic tools such as IR, NMR (<sup>1</sup>H-, <sup>13</sup>C) and mass spectrometry as well as single crystal X-ray analyses.

The mass spectrometry and elemental analyses confirm the molecular masses and molecular composition of **3e-h**, which obtained from reacting one molecule of **1e-h** and one molecule of **2a,b** via loss a molecule of H<sub>2</sub>O and another of HBr.

The <sup>1</sup>H NMR spectra of **3e-h** showed the presence of two singlets with the ratio 3:1 at 2.27-2.38 and 6.17-6.21 to CH<sub>3</sub> and thiazole-CH, respectively, in addition to aromatic protons. The <sup>1</sup>H NMR of **3e,f** clearly indicated the presence of extra CH<sub>3</sub> centered at 2.35-2.58 ppm. The presence of thiazole-CH was also proved by <sup>13</sup>C-DEPT NMR spectrum, exhibiting positive signals at 101.72-103.14 ppm. Signals at 168.51-169.67 and 148.86-149.12 were observed due to thiazole-C2 and thiazole-C4.

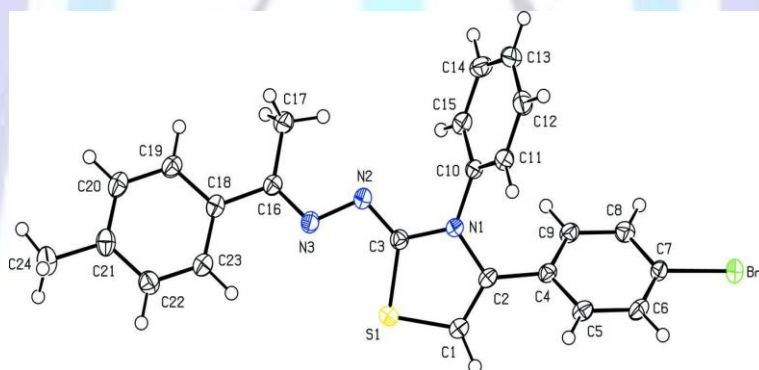
In (1*Z*,2*E*)-1-(3,4-diphenyl-2,3-dihydro-1,3-thiazol-2-ylidene)-2-(1-*p*-tolylrthylidene)hydrazine (**3e**), the thiazole ring makes dihedral angles of 52.03 (6), 62.63 (6) and 12.35 (6)<sup>0</sup>, respectively, with two phenyl rings and the benzene ring (Fig. 5) [39].

Fig. 5. Molecular structure of 3e



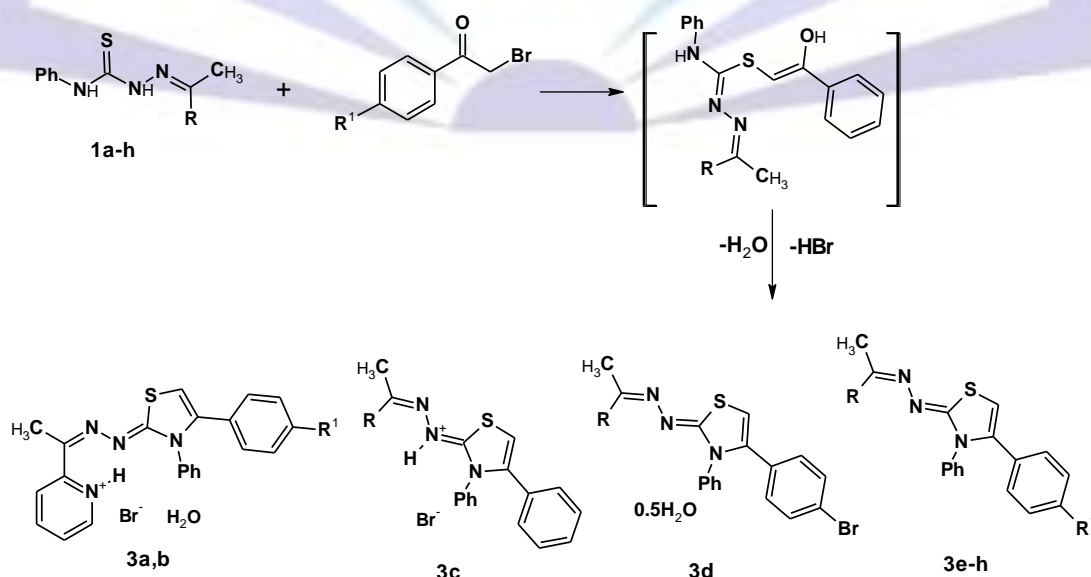
Moreover, in (2E)-4-(4-bromophenyl)-2-((2Z)-(1-(4-methylphenyl)ethylidene)hydrazinylidene)-3-phenyl-2,3-dihydro-1,3-thiazole (**3f**), the dihydrothiazole ring is approximately planar with a maximum deviation of 0.08 (2) Å, and is twisted with respect to the 4-bromophenyl ring, the phenyl ring and methyl phenyl ring, making dihedral angles of 47.96 (8), 59.52 (9) and 16.96 (9)<sup>o</sup>, respectively (Fig. 6) [40].

Fig. 6. Perspective view of 3f showing the planarity of thiazole ring



A rationale for the formation of compounds **3a-h** as depicted in (Scheme 2) via the formation of intermediate **4a-h** followed by elimination a molecule of HBr and another of H<sub>2</sub>O.

Scheme 2





## Conclusion

In summary, we have described the synthesis for four types of thiazolyliidenhydrazine derivatives via heterocyclization of 2-(1-substituted ethylidene)hydrazinecarbothio-amides by the reaction with 1-aryl-2-bromoethanones. The first type of products is substituted 1,3-thiazolylidene-hydrazonylidene ethylpyridinium bromide monohydrate, whereas substituted 1,3-thiazolyliidenhydrazinium bromide is the second type of products. The third, is the hemihydrate of 1,3-thiazolyliidenhydrazine derivatives in addition to the derivatives of 1,3-thiazolyliidenhydrazine as the fourth type. Among all types of 1,3-thiazolyliidenhydrazines, **3h** showed the highest inhibitory effect against all gram positive and gram negative bacterial strains compared to the standard broad spectrum antibiotic Moxifloxacin.

## Experimental

Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus (Weiss-Gallenkamp, Loughborough, UK) and are uncorrected. Infrared spectra ( $\text{u/cm}^{-1}$ ) were recorded from potassium bromide disks with a Shimadzu 408 (Shimadzu Corporation, Kyoto, Japan).  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra (400 MHz for  $^1\text{H}$ , 100 MHz for  $^{13}\text{C}$ ) were observed in  $\text{CDCl}_3$  on DELTA2-NMR spectrometer (DELTA2, Manchester Metropolitan University, United Kingdom) with tetramethylsilane as the internal standard. The  $^{13}\text{C}$ -NMR signals were assigned with the aid of DEPT 135/90 experiments. Mass spectra (70 eV, electron impact mode) were recorded on Finnegan MAT 312 (Germany) instrument. X-ray diffractions were measured using Bruker SMART APEX CCD diffractometer with Graphite monochromator and fine-focus scaled tube as a Radiation source. Thin layer chromatography (TLC) was performed on analytical Merck 9385 Silica aluminium sheets (Kieselgel 60) with Pf 254 indicator, TLC's were viewed at  $\lambda_{\text{max}} = 254 \text{ nm}$ . Elemental analyses were carried out at Microanalytical Center, Cairo University, Egypt.

## Starting Materials

2-(1-Substituted ethylidene)hydrazinecarbothioamides **1a-h** were prepared by condensation 4-phenylthiosemicarbazide with the appropriate ketones according to the published procedures [41,42]. 1-Aryl-2-bromoethanones (**2a,b**) were prepared according to Nobuta and Salama [43,44]. Anti-bacterial activity has been carried out at Botany Department, Sohag University.

## Products

### Synthesis of 1,3-thiazolyliidenhydrazinyliiden pyridinium salts and 1,3-thiazolyliidenhydrazine derivatives 3a-h

#### General procedure

A mixture of (1 mmol) 2-(1-substituted ethylidene)hydrazine-carbothioamides **1a-h** and (1 mmol) of 1-aryl-2-bromoethanones (**2a,h**) in absolute ethanol (30 ml) was refluxed for 6-8 h, then cooled to room temperature. A yellow solid precipitated, it was filtered and washed with a small amount of ethanol and recrystallized from ethanol to afford good quality crystals.

**2-((1E)-1-{2-[(2Z)-3,4-Diphenyl-2,3-dihydro-1,3-thiazol-2-ylidene]hydrazine-1-ylidene}ethyl)pyridin-1-ium bromide monohydrate (3a)**. Yellow crystals (ethanol), m.p. 234-236 °C (0.38 g, 81%), IR (KBr) = 3361 (Pyr- $^+\text{NH}$ ), 1619 (C=N), 1567 (N-N) stretching.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta_{\text{H}} = 1.61$  (br, 2H,  $\text{H}_2\text{O}$ ), 2.32 (s, 3H,  $\text{CH}_3$ ), 6.42 (s, 1H, thiazole-CH), 7.12-7.23 (m, 2H, Ar-H), 7.24-7.26 (m, 4H, Ar-H), 7.28-7.33 (m, 4H, Ar-H), 8.20-8.28 (m, 4H, pyr-H), 9.17 (br, 1H, pyr- $^+\text{NH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta_{\text{C}} = 14.17$  ( $\text{CH}_3$ ), 104.06 (thiazole-CH), 123.24, 123.51, 128.26, 128.39, 128.50, 128.94 (Ar-CH), 130.41, 130.80 (pyridine-CH), 131.05, 137.08 (Ar-C), 141.20, 141.63 (pyridine-CH), 146.37 (pyridine-C), 148.55 (thiazole-C4), 157.22 (acyclic C=N), 168.12 (thiazole-C2). Ms. m/z (%) 363 ( $\text{M}^+$ -HBr+ $\text{H}_2\text{O}$ ), 23, 263 (10), 236 (18), 135 (27), 104 (76), 77 (100). Anal. Calcd for  $\text{C}_{22}\text{H}_{21}\text{BrN}_4\text{O}_5$  (469.40), C, 56.29; H, 4.51; Br, 17.02; N, 11.94; S, 6.83. Found C, 56.17; H, 4.61; Br, 16.88; N, 12.11, S, 6.94.

**2-((1E)-1-{2-[(2Z)-4-(4-Bromophenyl)-3-phenyl-2,3-dihydro-1,3-thiazol-2-ylidene]hydrazin-1-ylidene}ethyl)pyridine-1-iumbromide monohydrate (3b)**. Yellow crystals (ethanol), m.p. 248-250 °C (0.47g, 68%), IR (KBr) = 3346 (pyr- $^+\text{NH}$ ), 1614 (C=N), 1576 (N-N) stretching.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta_{\text{H}} = 1.63$  (br, 2H,  $\text{H}_2\text{O}$ ), 2.49 (s, 3H,  $\text{CH}_3$ ), 6.41 (s, 1H, thiazole-CH), 6.97-6.99 (m, 2H, Ar-H), 7.27-7.34 (m, 4H, Ar-H), 7.36-7.37 (m, 3H, Ar-H), 8.23-8.25 (m, 4H, pyr-H), 9.10 (br, 1H, pyr- $^+\text{NH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta_{\text{C}} = 14.12$  ( $\text{CH}_3$ ), 103.12 (thiazole-CH), 122.82, 123.56, 128.23, 129.12, 129.92 (Ar-CH), 130.94, 131.27 (pyridine-CH), 128.14, 131.77, 141.03 (Ar-C), 141.63, 141.94 (pyridine-CH), 147.12 (Pyridine-C), 149.11 (thiazole-C4), 156.38 (acyclic C=N), 168.51 (thiazole-C2). MS. m/z (%) 466-468 ( $\text{M}^+$ -HBr+ $\text{H}_2\text{O}$ ), 15, 343 (16), 315 (28), 135 (43), 105 (81), 77 (100). Anal. Calcd for  $\text{C}_{22}\text{H}_{20}\text{Br}_2\text{N}_4\text{O}_5$  (548.29), C, 48.19; H, 3.68; Br, 29.15; N, 10.22; S, 5.85. Found C, 48.33; H, 3.74; Br, 28.96; N, 10.37; S, 5.69.

**(Z)-1-[(2E)-3,4-Diphenyl-2,3-dihydro-1,3-thiazol-2-ylidene]-2-[1-(4-hydroxyphenyl)ethylidene]hydrazinium bromide (3c)**. Yellow crystals (ethanol), mp 260-262 °C (0.705 g, 85%), IR (KBr) = 3423 (OH), 3332 (hydrazinium  $\text{NH}^+$ ), 1616 (C=N), 1595 (Ar C=C), 1564 (N-N) stretching.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta_{\text{H}} = 2.31$  (s, 3H,  $\text{CH}_3$ ), 6.3 (s, 1H, thiazole-CH), 6.84-6.99 (m, 3H, Ar-H), 7.11-7.18 (m, 3H, Ar-H), 7.20-7.29 (m, 3H, Ar-H), 7.33-7.55 (m, 2H, Ar-H), 7.75-7.77 (m, 2H, Ar-H) 9.51 (br, 1H, CH), 9.20 (br, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta_{\text{C}} = 14.15$  ( $\text{CH}_3$ ), 101.83 (thiazole-CH), 122.88, 125.26, 125.54, 126.27, 127.12, 127.88, 128.21 (Ar-CH) 124.16, 131.22, 133.12, 142.14 (Ar-C), 148.79 (thiazole-C4), 157.10 (acyclic C=N), 161.05 (Ar-C-CH), 168.53 (thiazole-C2). Ms. m/z (%) 385 ( $\text{M}^+$ -HBr, 11), 370 (10), 238 (13), 180 (12), 135 (21), 105



(24), 91 (45), 77 (100). *Anal. Calcd for* C<sub>23</sub>H<sub>20</sub>BrN<sub>3</sub>OS (466.39), C, 59.23; H, 4.32; Br, 17.13; N, 9.01; S, 6.88. Found C, 59.37, H, 4.21; Br, 16.95; N, 8.87; S, 6.94.

**4-((1E)-1-((2Z)-2-[4-(4-bromophenyl)-3-phenyl-2,3-dihydro-1,3-thiazol-2-ylidene]hydrazin-1-ylidene)ethyl)phenol hemihydrate (3d).** Yellow crystals (ethanol), mp 274-276 °C (0.454 g, 83%), IR (KBr) (OH), (hydrazinium, \*NH), (C=N), (Ar-C=C), (N-N) stretching. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ<sub>H</sub> = 2.33 (s, 3H, CH<sub>3</sub>), 6.21 (s, 1H, thiazole-CH), 6.81-6.94 (m, 3H, Ar-H), 7.15-7.21 (m, 3H, Ar-H), 7.22-7.30 (m, 3H, Ar-H), 7.45-7.61 (m, 2H, Ar-H), 7.79-7.82 (m, 2H, Ar-H) 9.63 (br, 1H, CH), 9.28 (br, 1H, NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ<sub>C</sub> = 14.43 (CH<sub>3</sub>), 102.15 (thiazole-CH), 123.11, 124.76, 125.84, 126.32, 127.10, 127.73, 128.31 (Ar-CH) 124.14, 130.55, 132.87, 141.81 (Ar-C), 149.19 (thiazole-C4), 158.12 (acyclic C=N), 160.85 (Ar-C-CH), 169.23 (thiazole-C2).

**(1Z2E)-1-(3,4-Diphenyl-2,3-dihydro-1,3-thiazol-2-ylidene)-2-(1-p-tolylethylidene)hydrazine (3e).** Yellow crystals (ethanol), m.p. 232-234 °C (0.31 g, 80%), IR (KBr) = 3060 (Ar-CH), 1629 (C=N), 1594 (Ar-C=C), 1567 (N-N) stretching. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 2.38 (s, 3H, CH<sub>3</sub>), 2.58 (s, 3H, CH<sub>3</sub>), 6.21 (s, 1H, thiazole-CH), 7.08- 7.10 (m, 3H, Ar-H), 7.17-7.19 (m, 4H, Ar-H), 7.24-7.26 (m, 4H, Ar-H), 7.43-7.45 (m, 3H, Ar-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ<sub>C</sub> = 14.31 (CH<sub>3</sub>), 103.14 (thiazole-CH), 127.08, 128.11, 128.57, 128.77, 128.94, 129.15, 129.56, 129.79 (Ar-CH), 130.84, 131.42, 132.16 (Ar-C), 142.11 (Ar-C-N), 149.11 (thiazole-C4), 157.62 (acyclic=N), 168.51 (Thiazole-C2). Ms, m/z (%) 383 (M<sup>+</sup>, 265, 368 (14), 265 (32), 248 (16), 237 (18), 135 (41), 118 (58), 91 (100), 77 (86). *Anal. Calcd for* C<sub>24</sub>H<sub>21</sub>N<sub>3</sub>S (383.51), C, 75.16; H, 5.52; N, 10.96; S, 8.36. Found C, 74.47; H, 5.41; N, 11.14; S, 8.51.

**(2E)-4-(4-Bromophenyl)-2-((2Z)-[1-(4-methylphenyl)-ethylidene]hydrazinylidene)-3-phenyl-2,3-dihydro-1,3-thiazole (3f).** Yellow crystals (ethanol), m.p. 220-222 °C (0.38 g, 83%), IR (KBr) = 3063 (Ar-CH), 1612 (C=N), 1600 (Ar-C=C), 1564 (N-N) stretching. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ<sub>H</sub> = 2.27 (s, 3H, CH<sub>3</sub>), 2.35 (s, 3H, CH<sub>3</sub>), 6.16 (s, 1H, thiazole-CH), 6.98-7.00 (m, 2H, Ar-CH), 7.73- 7.76 (m, 3H, Ar-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ<sub>C</sub> = 14.84 (CH<sub>3</sub>), 21.30 (CH<sub>3</sub>), 102.29 (thiazole-CH), 126.27, 127.48, 128.25, 128.75, 128.87, 129.51, 129.73 (Ar-H), 124.63, 131.46, 132.16, 132.36, 141.83 (Ar-C), 148.86 (thiazole-CH), 157.52 (acyclic C=N), 168.52 (thiazole-C2). MS, m/z (%) 461/463 (M<sup>+</sup>, 21), 381 (16), 135 (20), 118 (93), 41 (81), 77 (100). *Anal. Calcd for* C<sub>24</sub>H<sub>20</sub>BrN<sub>3</sub>OS (462.40) C, 62.34; H, 4.36; Br, 17.28; N, 9.09; S, 6.93. Found C, 62.19; H, 4.45; Br, 17.41; N, 8.92; S, 7.11.

**(E)-2-((E)-[1-(4-Chlorophenyl)ethylidene]hydrazono)-3,4-diphenyl-2,3-dihydrothiazole (3g).** Yellow crystals (ethanol), mp. 176-178 °C (0.36 g, 89%), IR (KBr) = 3048 (Ar-CH), 1603 (C=N), 1590 (Ar-C=C), 1569 (N-N) stretching. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ<sub>H</sub> = 2.30 (s, 3H, CH<sub>3</sub>), 6.17 (s, 1H, thiazole-CH), 7.11-7.13 (m, 2H, Ar-H), 7.19-7.21 (m, 4H, Ar-H), 7.24-7.26 (m, 4H, Ar-H), 7.29-7.32 (m, 2H, Ar-H), 7.78-7.80 (m, 2H, Ar-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ<sub>C</sub> = 14.68 (CH<sub>3</sub>), 101.72 (thiazole-CH), 127.45, 127.59, 128.26, 128.34, 128.39, 128.41, 128.68, 128.83 (Ar-CH), 131.34, 131.89, 132.42, 141.66 (Ar-C), 149.12 (thiazole-C4), 157.68 (acyclic C=N), 169.67 (thiazole-C2). Ms, m/z (%) 403/405 (M<sup>+</sup>, 26), 388 (14), 367 (15), 260 (23), 232 (19), 167 (62), 135 (49), 91 (100), 77 (92). *Anal. Calcd for* C<sub>23</sub>H<sub>18</sub>ClN<sub>3</sub>S (403.93) C, 68.39, H, 4.49, Cl, 8.78; S, 7.94. Found C, 68.53; H, 4.37; Cl, 8.62; S, 8.12.

**(E)-4-(4-Bromophenyl)-2-((E)-[1-(4-Chlorophenyl)-ethylidene]hydrazono)-3-phenyl-2,3-dihydrothiazole (3h).** Yellow crystal (ethanol), m.p. 186-188 °C (0.392 g, 81%), IR (KBr) = 3076 (Ar-CH), 1605 (C=N), 1585 (Ar-C=C), 1562 (N-N) stretching. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ<sub>H</sub> = 2.29 (s, 3H, CH<sub>3</sub>), 6.19 (s, 1H, thiazole-CH), 6.97-6.99 (m, 2H, Ar-H), 7.25-7.29 (m, 4H, Ar-H), 7.31-7.35 (m, 4H, Ar-H), 7.77-7.81 (m, 3H, Ar-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ<sub>C</sub> = 14.59 (CH<sub>3</sub>), 102.50 (thiazole-CH), 127.50, 127.55, 128.22, 128.29, 128.76, 129.12, 129.52 (Ar-CH), 130.13, 131.47, 131.76, 132.14, 141.26 (Ar-C), 149.11 (thiazole-C4), 155.97 (acyclic C=N), 169.26 (thiazole C2) Ms, m/z (%) 481/485 (M<sup>+</sup>, 14), 445/447 (26), 430 (11), 401 (25), 342 (11), 167 (10), 139 (32), 135 (41), 91 (82), 77 (100). *Anal. Calcd for* C<sub>23</sub>H<sub>17</sub>BrClN<sub>3</sub>S (482.82) C, 57.21; H, 3.55; Br, 16.55; Cl, 7.34; N, 8.70; S, 6.64. Found, C, 57.07; H, 3.62; Br, 16.69; Cl, 7.28; N, 8.56; S, 6.76.

#### Anti-bacterial Activity

The synthesized compounds **3a-h** were dissolved in DMSO. In order to ensure that the solvent had no effect on bacterial growth or enzymatic activity, negative control tests were performed using DMSO at the same concentrations.

The inhibitory effect of tested compounds **3a-h** on the in vitro growth of four different types of bacteria *Bacillus cereus* and *Micrococcus lutes* as gram positive bacteria (+ve) and *Pseudomonas aureginosa* and *Serratia marcescens* as gram negative bacteria (-ve) was evaluated using agar diffusion method (cup and plate method) [45-48]. All plates were incubated at 37±0.5 °C for 24 h. The inhibition zone of active compounds was measured in cm scale. The results shown in table 1 revealed that compounds **3h** and **3f** showed the highest inhibitory effect against the two types of bacteria at the three used concentrations, while compounds **3d** and **3e**, showed moderate activity compared to the standard Moxifloxacin as a broad spectrum antibiotic. Compound **3h** exhibited the highest inhibitory effect against the gram positive *Bacillus cereus* at high concentration while **3c** showed high inhibition zone against the gram positive bacteria *Micrococcus lutes* at low concentration. On the other hand, compounds **3a-c**, **3e** and **3g** showed no bactericidal activity against the gram negative bacterial *Pseudomonas aureginosa* (table 1).





Table 1: Anti-bacterial activity of compounds 3a-h

Bacteria		Compd	3a	3b	3c	3d	3e	3f	3g	3h	Moxifloxacin
		Conc. [ppm]									
Gm- Bacteria	<i>Pseudomonas aeruginosa</i>	10000	-	-	-	0.4	-	-	-	0.8	1.4
		30000	-	-	-	0.7	-	0.2	-	1.0	1.5
		50000	-	-	-	0.7	-	0.4	-	1.1	1.4
	<i>Serratia marcescens</i>	10000	-	0.1	-	0.3	1.1	1.3	0.5	1.5	1.5
		30000	-	0.2	-	0.6	1.4	1.4	0.7	1.7	1.6
		50000	-	0.2	-	0.6	1.7	1.6	0.9	1.8	1.6
Gm+ Bacteria	<i>Bacillus cereus</i>	10000	-	0.2	1.0	1.1	1.6	1.2	1.0	1.6	1.6
		30000	-	0.2	1.2	1.5	1.5	1.7	0.8	1.8	1.8
		50000	-	0.4	1.4	1.4	1.4	1.7	0.6	1.8	1.8
	<i>Micrococcus lutes</i>	10000	0.2	0.5	1.5	1.0	1.3	1.1	0.1	0.9	0.8
		30000	0.3	0.6	1.3	1.3	1.2	1.0	0.1	1.1	1.0
		50000	0.4	0.8	1.1	1.2	1.1	0.9	0.1	1.1	1.1

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### Author' biography with Photo



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