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p-Hydroxybenzaldehyde as a Precursor for Some New Thiazoles: Green Synthesis Antibacterial evaluation, ADMET and DFT Studies

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Abstract

Green synthetic approach of new thiazoles **4-7** and thiazolidinones **8** based on *p*-hydroxybenzaldehyde derivatives through the reaction with different hydrazonyl halides. Optimization for synthetic procedure was operated to detect the suitable conditions for the synthesis, which demonstrated that the best synthetic way is to use dioxane - chitosan (5 x 10^{-3} mol) to catalyze the reaction. Bacterial inhibition growth assessment was performed against different bacterial species revealing better suppression activity with good minimal concentration values. The most active antibacterial candidate **4d** was applied for theoretical study (DFT) by the B3LYP/6–311G++(d,p) set of functions to obtain its suitable geometrical optimized structure besides its Molecular electronic potential (MEP). Also, the DFT method at B3LYP/6-311++G (d,p) basis set was applied to detect the energy and energy gap for the orbitals (HOMO and LUMO) for compound **4d**. The ADME study was performed for compound **4d** using Swiss ADME program revealing excellent pharmaceutical and chemical descriptors. The Osiris methodology for the newly synthesized compounds revealed moderate hazards and toxicity.

Keywords: Chitosan; DFT; *p*-hydroxy benzaldehyde; hydrazonoyl halide; green chemistry; Osiris methodology; Swiss ADME; thiazoles; thiazolidinones.

1. Introduction

In recent years, green chemistry has drawn a lot of attention because of its potential to minimize waste, chemical hazards, pollution, and human risks. Catalysts are crucial for organic synthesis because they speed up reaction times and produce high quantities of needed material [1]. The development of the liquid phase reliant reactions is an important area of research, due to the ease of collecting, separating, and recycling catalysts, this study is crucial for creating cleaner and more efficient systems [2,3]. Chitosan, a naturally found polymer sourced from many units of saccharides, attracted considerable interest in the area of organic synthesis [4]. Cost-effectiveness, water soluble, ability to modify, stability, biodegradability and other advantages are just some of the numerous benefits of chitosan [5-8]. A major hazard to global health, bacterial infections are linked to a persistent rise in mortality rates [9,10], such that the creation of new antibiotics is imperative. The development of antibiotic drugs increasingly depends on heterocyclic scaffolds that include nitrogen [11-14]. The strong medicinal potential of the thiazole scaffold has drawn a lot of attention, that has contributed to the design and creation of many compounds containing thiazoles that display a variety of pharmacological characteristics, with a particular focus on antibacterial activity [15-19]. It has been stated that the thiazole derivatives **I** and **II** demonstrated antibacterial effectiveness versus *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*St. aureus*) with MIC value equals 19.53-78.125 µg/L [20]. Also, the thiazole derivative **III** was indicated to have antibacterial effects against different strains, especially against vancomycin-resistant *Enterococcus faecalis* (*E. faecalis*) with MIC ≤0.125 µg/mL besides, it prevented biofilm development of *Pseudomonas aeruginosa* (*P. aeruginosa*) and *St. aureus* at sub-MIC doses [21]. The thiazole derivative **IV** showed MIC = 12.5 µg/mL with outstanding suppression toward *St. aureus* [22]. Involving green synthesis approaches in synthesis of thiazoles was a major concern of many researchers. For example, Shinde et al [23] adopted synthesis of eight diverse thiazoles using green synthetic capabilities of polyethylene glycol and sulfamic acid were evaluated, and their bacterial growth suppression effects against *E. coli*, *P. aeruginosa*, and *St. aureus* were tested revealing significant bacterial suppression effectiveness against *St. aureus*. Additionally, Chitosan-mediated synthesis of the thiazole **V** and **VI** by catalysing the reaction of carbothioamide derivative with various hydrazonoyl halides was managed which further were assessed against bacterial strains revealing better growth inhibition revealing excellent MIC values in *E. coli*, *P. aeruginosa*, *St. aureus* and *Streptococcus pneumonia* (*St. pneumonia*) [24], as shown in Figure 1.

These biological traits, along with the findings mentioned earlier, have driven us to develop new heterocyclic compounds featuring thiazole and thiazolidinone groups, which have demonstrated the ability to improve pharmacological properties, particularly as antibacterial agents, additionally, building upon our scientific reports [25-44]. The article involved preparation of four groups of thiazoles; 4a-f, 5a-f, 6a,b and 7a,b and thiazolidines 8a-d which all comprising *p*-hydroxybenzaldehyde derivatives and that is demonstrated in Figure 2, adopting green synthesis protocol using chitosan as a mediated catalyst. The majority of the reported compounds were checked versus various bacterial types, demonstrating inhibition of bacterial growth.

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Furthermore, The most stable optimized structure for the most active biological candidate, compound 4d, was determined by theoretical DFT study by B3LYP method with 6-311++G(d,p) sets. In addition, the MEP, HOMO and LUMO orbitals were also calculated. In addition to the ADME calculations by Swiss ADME together with Osiris methodology were done revealing safe physicochemical and pharmaceutical characters for all the new compounds.

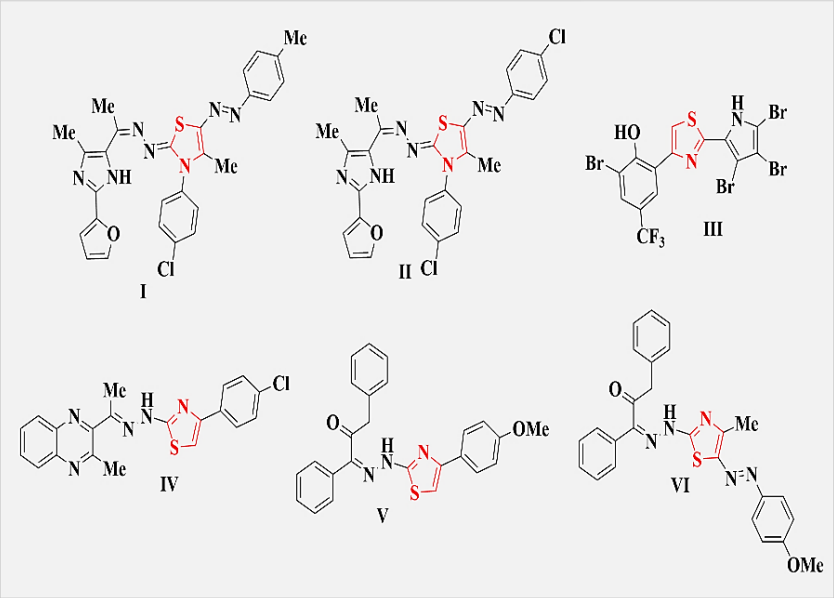


Fig. 1 Reported thiazoles with antibacterial activity (**I-IV**) and thiazoles synthesized by chitosan mediated reaction (**V-VI**).

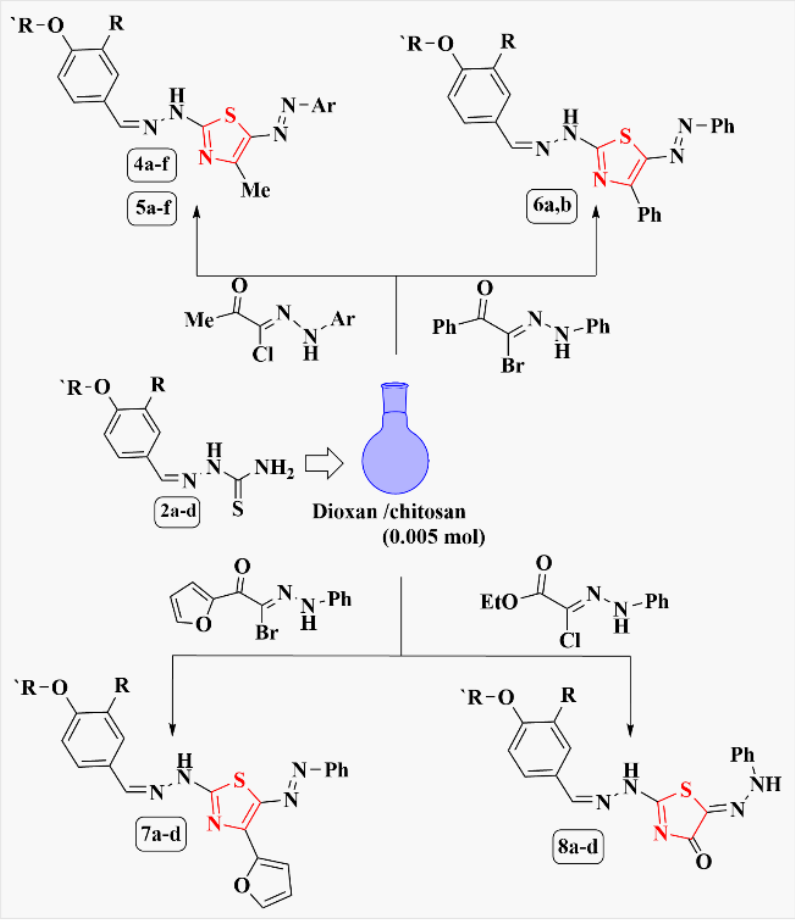


Fig. 2 Synthetic strategy for the synthesis of thiazoles and thiazolidinones: **4a-f**, **5a-f**, **6a,b**, **7a,b** and **8a-d**.

2. Materials and Methods

Measurements

Melting points were measured in (°C) using Kleinfeld device are unadjusted. IR spectra were obtained as KBr pellets using a Nicolet 205 spectrophotometer. Mass spectra were acquired using a Shimadzu device (70 eV). The ^{1}H-NMR (500 MHz) spectra and ^{13}C-NMR spectra (75 MHz) were recorded on a Varian EM spectrometer, using DMSO-d^6 as solvent and Tetramethyl silane as a reference. The analyses were conducted at the Microanalytic center of Cairo University. The antibacterial studies were conducted at the Microanalytic center of Cairo University. The compounds **2a-d**, **3a-c**, and hydrazonyl halides were made following the described procedure [45-51].

Synthetic procedure for 4

Compounds **2a,b** (1 x 10^{-2} mol) added with the acetyl hydrazonyl halide derivatives **3a-c** (1 x 10^{-2} mol) in dioxan (10 ml) including chitosan (5 x 10^{-3} mol) and heated to reflux for 2 hour furnishing yellowish orange or red solids. Filtration was used to collect the produced crystals, which were subsequently cleaned with ethanol and recrystallized from dioxan.

4-((2-(4-Methyl-5-(phenyldiazenyl)thiazol-2-yl) hydrazineylidene)methyl)phenol (4a)

Reddish orange, 87%, m.p 226-228ºC, υ/cm^{-1}= 3311 (broad, OH and NH); δ^{1}_{H} = 2.24 (s, 3H, CH_3), 6.87 (d, 2H, *J* = 8.1 Hz, ArH), 7.10-7.13 (m, 3H, ArH), 7.23 (d, 2H, *J* = 8.1 Hz, ArH), 7.70 (d, 2H, *J* = 8.4 Hz, ArH), 8.53 (s, 1H, =CH), 10.18 (s, 1H, NH), 10.44 (s, 1H, OH); δ^{13}_{C} = 114.7, 116.4, 125.5, 130.2, 130.8, 131.6, 138.0, 141.7, 160.2, 161.3, 172.0, 178.0; Elemental anal. for $C_{17}H_{15}N_5OS$ (337.4): Calc.: C, 60.52; H, 4.48; N, 20.76; S, 9.50%, Found: C, 60.73; H, 4.67; N, 20.48; S, 9.34%.

4-((2-(4-Methyl-5-(p-tolyldiazenyl)thiazol-2-yl) hydrazineylidene)methyl)phenol (4b)

Yellowish orange, 80%, m.p 260-262ºC, υ/cm^{-1}= 3289 (broad, OH and NH); δ^{1}_{H} = 2.26 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.89 (d, 2H, *J* = 8.0 Hz, ArH), 7.38 (d, 2H, *J* = 7.5 Hz, ArH), 7.51-7.62 (m, 4H, ArH), 8.54 (s, 1H, =CH), 9.68 (s, 1H, NH), 10.43 (s, 1H, OH); Elemental anal. for $C_{18}H_{17}N_5OS$ (351.4): Calc.: C, 61.52; H, 4.88; N, 19.9; S, 9.12%, Found: C, 61.74; H, 5.11; N, 20.04; S, 9.01%.

4-((2-(5-((4-Chlorophenyl)diazenyl)-4-methylthiazol -2-yl)hydrazineylidene) methyl)phenol (4c)

Yellowish orange, 79%, m.p 248-250ºC, υ/cm^{-1}= 3401 (OH), 3388 (NH); δ^{1}_{H} = 2.41 (s, 3H, CH_3), 6.73 (d, 2H, *J* = 7.15 Hz, ArH), 7.19 (d, 2H, *J* = 7.5 Hz, ArH), 7.38-7.51 (m, 4H, ArH), 8.45 (s, 1H, =CH), 9.81 (s, 1H, NH), 10.18 (s, 1H, OH); Elemental anal. for $C_{17}H_{14}ClN_5OS$ (371.8): Calc.: C, 54.91; H, 3.80; N, 18.83; S, 8.62%, Found: C, 55.11; H, 3.94; N, 18.66; S, 8.34%.

2-Methoxy-4-((2-(4-methyl-5-(phenyldiazenyl) thiazol-2-yl) hydrazineylidene)methyl)phenol (4d)

Yellowish orange, 88%, m.p 230-232ºC, υ/cm^{-1}= 3260 (broad, OH and NH); δ^{1}_{H} = 2.47 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.87 (d, 2H, *J* = 8.1 Hz, ArH), 6.95 (m, 1H, ArH), 7.30-7.33 (m, 4H, ArH), 7.41 (m, 1H, ArH), 8.50 (s, 1H, =CH), 9.82 (s, 1H, NH), 10.53 (s, 1H, OH); δ^{13}_{C} = 16.9, 56.2, 111.7, 114.7, 116.3, 122.6, 123.8, 125.8, 129.7, 138.6, 144.0, 148.5, 151.0, 160.8; Elemental anal. for $C_{18}H_{17}N_5O_2S$ (367.4): Calc.: C, 58.84; H, 4.66; N, 19.06; S, 8.73%, Found: C, 58.71; H, 4.84; N, 19.24; S, 8.68%.

2-Methoxy-4-(2-(4-methyl-5-(p-tolyldiazenyl) thiazol-2-yl)hydrazineylidene)methylphenol (4e)

Yellowish orange, 78%, m.p 240-242ºC, υ/cm^{-1}= 3278 (broad, OH and NH); δ^{1}_{H} = 2.26 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.88 (d, 1H, *J* = 7.8 Hz, ArH), 7.12 (d, 1H, *J* = 7.8 Hz, ArH), 7.24-7.34 (m, H, ArH), 7.43 (s, 1H, ArH), 8.52 (s, 1H, =CH), 9.81 (s, 1H, NH), 10.48 (s, 1H, OH); Elemental anal. for $C_{19}H_{19}N_5O_2S$ (381.4): Calc.: C, 59.83; H, 5.02; N, 18.36; S, 8.40%, Found: C, 58.74; H, 5.13; N, 18.41; S, 7.98%.

4-((2-(5-((4-Chlorophenyl)diazenyl)-4-methylthiazol -2-yl)hydrazineylidene)methyl)-2-methoxyphenol (4f)

Reddish orange, 75%, m.p 254-256ºC, υ/cm^{-1}= 3321 (OH), 3281 (NH); δ^{1}_{H} = 2.47 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.86-7.41 (m, 7H, ArH), 8.51 (s, 1H, =CH), 9.83 (s, 1H, NH), 10.60 (s, 1H, OH); Elemental anal. for $C_{18}H_{16}ClN_5O_2S$ (401.8): Calc.: C, 53.80; H, 4.01; N, 17.43; S, 7.98%, Found: C, 53.91; H, 4.38; N, 17.61; S, 8.01%.

Synthetic procedure for 5

Compounds **2c,d** (1 x 10^{-2} mol) mixed with the acetyl hydrazonyl halide derivatives **3a-c** (1 x 10^{-2} mol) in dioxan (10 ml) with chitosan (5 x 10^{-3} mol) and refluxed for 1 hour furnishing yellowish orange or red solids. The resultant crystals were filtered out, cleaned with ethanol, and then recrystallized from dioxan.

4-((2-(4-Methyl-5-(phenyldiazenyl)thiazol-2-yl) hydrazineylidene)methyl)phenyl benzoate (5a)

Reddish orange, 66%, m.p 262-264ºC, υ/cm^{-1}= 3249 (NH) and 1735 (CO); δ^{1}_{H} = 2.47 (s, 3H, CH_3), 6.95-6.98 (m, 1H, ArH), 7.29-7.35 (m, 4H, ArH), 7.45 (d, 2H, *J* = 8.55 Hz, ArH), 7.59-7.62 (m, 2H, ArH), 7.73-7.76 (m, 1H, ArH), 7.95 (d, 2H, *J* = 8.1 Hz, ArH), 8.12 (d, 2H, *J* = 7.15 Hz, ArH), 8.70 (s, 1H, =CH), 10.62 (s, 1H, NH); δ^{13}_{C} = 17.0, 114.8, 123.2, 129.2, 129.5, 129.8, 130.0, 130.3, 132.2, 134.7, 138.3, 153.5, 159.6, 164.9, 179.1; m/ȥ = 441 (8.4%), 419 (6.8%), 406 (10.1%), 393 (14%), 381 (19.3%), 375 (10.5%), 360 (24.6%), 331 (13.7%), 322 (17.7%), 299 (25.8%), 292 (12.3%), 277 (10.6%), 268 (11.8%), 262 (18.7%), 258 (10.2%), 204 (89%), 189 (26.5%), 170 (24.6%), 154 (15.3%), 138 (30.8%), 99 (11.8%), 56 (91%); Elemental anal. for $C_{24}H_{19}N_5O_2S$ (441.5): Calc.: C, 65.29; H, 4.34; N, 15.86; S, 7.26%, Found: C, 65.33; H, 4.47; N, 16.01; S, 7.01%.

4-((2-(4-Methyl-5-(p-tolyldiazenyl)thiazol-2-yl)hydrazineylidene)methyl)phenyl benzoate (5b)

Reddish orange, 70%, m.p 253-255ºC, υ/cm^{-1}= 3338 (NH) and 1730 (CO); δ^{1}_{H} = 2.23 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.38 (d, 2H, *J* = 8.0 Hz, ArH), 7.44-7.64 (m, 9H, ArH), 8.09 (d, 2H, *J* = 7.5 Hz, ArH), 8.38 (s, 1H, =CH), 10.59 (s, 1H, NH); Elemental anal. for $C_{25}H_{21}N_5O_2S$ (455.5): Calc.: C, 65.92; H, 4.65; N, 15.37; S, 7.04%, Found: C, 66.12; H, 4.73; N, 15.21; S, 6.82%.

4-((2-(5-((4-Chlorophenyl)diazenyl)-4-methyl thiazol-2-yl)hydrazineylidene)methyl)phenyl benzoate (5c)

Reddish orange, 51%, m.p 235-238ºC, υ/cm^{-1}= 3317 (NH) and 1727 (CO); δ^{1}_{H} = 2.46 (s, 3H, CH_3), 7.21 (d, 2H, *J* = 7.5 Hz, ArH), 7.38-7.42 (m, 4H, ArH), 7.61-7.74 (m, 5H, ArH), 8.14 (d, 2H, *J* = 8.0 Hz, ArH), 8.54 (s, 1H, =CH), 10.81 (s, 1H, NH); Elemental anal. for $C_{24}H_{18}ClN_5O_2S$ (475.9): Calc.: C, 60.57; H, 3.81; N, 14.71; S, 6.74%, Found: C, 60.64; H, 4.11; N, 14.64; S, 6.71%.

2-Methoxy-4-(2-(4-methyl-5-(phenyldiazenyl)thiazol -2-yl)hydrazineylidene)methylphenyl benzoate (5d)

Reddish orange, 70%, m.p 275-277ºC, υ/cm^{-1}= 3251 (NH), 1719 (CO); δ^{1}_{H} = 2.25 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.11 (d, 2H, *J* = 8.4 Hz, ArH), 7.25 (d, 2H, *J* = 8.1 Hz, ArH), 7.40 (d, 1H, *J* = 8.1 Hz, ArH), 7.56-7.65 (m, 5H, ArH), 7.74-7.78 (m, 1H, ArH), 8.12 (d, 2H, *J* = 7.5 Hz, ArH), 8.68 (s, 1H, =CH), 10.59 (s, 1H, NH); Elemental anal. for $C_{25}H_{21}N_5O_3S$ (471.5): Calc.: C, 63.68; H, 4.49; N, 14.85; S, 6.80%, Found: C, 63.82; H, 4.61; N, 14.54; S, 6.73%.

2-Methoxy-4-((2-(4-methyl-5-(p-tolyldiazenyl) thiazol-2-yl)hydrazineylidene)methyl)phenyl benzoate (5e)

Reddish orange, 65%, m.p 240-242ºC, υ/cm^{-1}= 3318 (NH), 1723 (CO); δ^{1}_{H} = 2.22 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.11-7.40 (m, 2H, ArH), 7.54-7.62 (m, 3H, ArH), 7.72-7.75 (m, 1H, ArH), 8.10 (d, 2H, *J* = 7.15 Hz, ArH), 8.65 (s, 1H, =CH), 10.59 (s, 1H, NH); δ^{13}_{C} = 17.0, 20.9, 56.5, 112.8, 114.8, 121.5, 124.1, 128.9, 129.5, 130.2, 130.4, 133.5, 134.7, 141.6, 151.8, 159.7, 164.3, 173.6, 178.7; Elemental anal. for $C_{26}H_{23}N_5O_3S$ (485.5): Calc.: C, 64.31; H, 4.77; N, 14.42; S, 6.60%, Found: C, 64.56; H, 4.83; N, 14.11; S, 5.89%.

4-(2-(5-(4-Chlorophenyldiazenyl)-4-methylthiazol-2-yl)hydrazineylidene)methyl-2-methoxyphenyl benzoate (5f)

Reddish orange, 58%, m.p 268-270ºC, IR: υ/cm^{-1}= 3265 (NH) and 1715 (CO); δ^{1}_{H} = 2.47 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.35-7.40 (m, 4H, ArH), 7.53-7.62 (m, 5H, ArH), 7.73-7.75 (m, 1H, ArH), 8.10 (d, 2H, *J* = 7.5 Hz, ArH), 8.66 (s, 1H, =CH), 10.71 (s, 1H, NH); δ^{13}_{C} = 16.9, 56.5, 112.8, 116.2, 116.3, 121.5, 121.6, 124.2, 128.9, 129.6, 130.4, 133.4, 134.7, 139.0, 142.4, 151.8, 160.2, 164.3; m/ȥ = 505 (2.2%), 465 (6%), 452 (2.0%), 440 (2.4%), 418 (4.0%), 396 (34.2%), 389 (63.2%), 378 (3.3%), 350 (3.4%), 329 (24.0%), 303 (22.4%), 292 (2.6%), 280 (45.6%), 251 (20.6%), 248 (24.0%), 245 (32.0%), 236 (13.7%), 221 (43.5%), 213 (28.8%), 201 (4.1%), 191 (34.75), 186 (35.6 %), 181 (12.4%), 176 (24.6%), 159 (100%), 155 (84.7%), 144 (26.6%), 138 (57.4%), 112 (55.5%), 58 (37.8%). Elemental anal. for $C_{25}H_{20}ClN_5O_3S$ (505.9): Calc.: C, 59.35; H, 3.98; N, 13.84; S, 6.34%, Found: C, 59.22; H, 4.01; N, 13.72; S, 6.42%.

Synthetic procedure *for 6*

Compounds **2c,d** (1 x 10^{-2} mol) mixed with diphenylacetohydrazonoyl bromide (1 x 10^{-2} mol) in dioxan (10 ml) containing chitosan (5 x 10^{-3} mol) and refluxed for 1 hour furnishing yellowish orange or red solids. After being collected by filtering and cleaned with ethanol, the produced crystals were recrystallized from dioxan.

4-((2-(4-Phenyl-5-(phenyldiazenyl)thiazol-2-yl)hydrazineylidene)methyl)phenyl benzoate (6a)

Yellowish orange, 63%, m.p 265-267ºC, υ/cm^{-1}= 3345 (NH) and 1719 (CO); δ^{1}_{H} = 7.23-7.50 (m, 9H, ArH), 7.56-7.72 (m, 5H, ArH), 7.76-8.11 (m, 5H, ArH), 8.28 (s, 1H, =CH), 10.83 (s, 1H, NH); Elemental anal. for $C_{29}H_{21}N_5O_2S$ (503.5): Calc.: C, 69.17; H, 4.20; N, 13.91; S, 6.37%, Found: C, 69.45; H, 4.42; N, 13.87; S, 6.27%.

2-Methoxy-4-((2-(4-phenyl-5-(phenyldiazenyl) thiazol-2-yl)hydrazineylidene)methyl)phenyl benzoate (6b)

Yellowish orange, 53%, m.p 265-267ºC, υ/cm^{-1}= 3280 (NH) and 1698 (CO); δ^{1}_{H} = 3.84 (s, 3H, OCH_3), 7.19-7.36 (m, 9H, ArH), 7.51-7.66 (m, 4H, ArH), 7.71-7.84 (m, 5H, ArH), 8.31 (s, 1H, =CH), 10.67 (s, 1H, NH); Elemental anal. for $C_{30}H_{23}N_5O_3S$ (533.6): Calc.: C, 67.53; H, 4.34; N, 13.12; S, 6.01%, Found: C, 67.64; H, 4.51; N, 13.28; S, 5.98%.

Synthetic procedure for 7

Compounds **2c,d** (1 x 10^{-2} mol) mixed with furanyl-*N*-phenylacetohydrazonoyl chloride (1 x 10^{-2} mol) in dioxan (10 ml) comprising chitosan (5 x 10^{-3} mol) and heated to reflux for 1 hour furnishing yellowish orange or red solids. The generated crystals were recovered using filtration, washed with ethanol, and then recrystallized from dioxan.

4-((2-(4-(Furan-2-yl)-5-(phenyldiazenyl)thiazol-2-yl)hydrazineylidene)methyl) phenyl benzoate (7a)

Reddish brown, 58%, m.p 248-250ºC, υ/cm^{-1}= 3317 (NH) and 1721 (CO); δ^{1}_{H} = 6.83-6.88 (m, 5H, ArH), 7.01- 7.66 (m, 7H, ArH), 7.69-7.91 (m, 5H, ArH), 8.31 (s, 1H, =CH), 10.83 (s, 1H, ArH); Elemental anal. for $C_{27}H_{19}N_5O_3S$ (493.5): Calc.: C, 65.71; H, 3.88; N, 14.19; S, 6.50%, Found: C, 65.84; H, 3.91; N, 13.89; S, 6.32%.

4-((2-(4-(Furan-2-yl)-5-(phenyldiazenyl)thiazol-2-yl)hydrazineylidene)methyl)-2-methoxyphenyl benzoate (7b)

Reddish brown, 64%, m.p 250-252ºC, υ/cm^{-1}= 3387 (NH) and 1701 (CO); δ^{1}_{H} = 3.83 (s, 3H, OCH_3), 6.83-8.28 (m, 17H, ArH), 10.71 (s, 1H, NH); Elemental anal. for $C_{28}H_{21}N_5O_4S$ (523.5): Calc.: C, 64.23; H, 4.04; N, 13.38; S, 6.12%, Found: C, 64.34; H, 4.14; N, 13.43; S, 6.43%.

Synthetic procedure for 8

In a round flask, compounds **2a-d** (1 x 10^{-2} mol) with ethyl 2-chloro-2-(2-phenylhydrazineylidene)acetate (1 x 10^{-2} mol) in dioxan solution (10 ml) and chitosan (5 x 10^{-3} mol) were heated for 6 hours. The generated crystals were recovered using filtration, washed with ethanol, and then recrystallized from dioxan.

2-(2-(4-Hydroxybenzylidene)hydrazineyl)-5-(2-phenylhydrazineylidene)thiazol-4(5H)-one (8a)

Yellowish orange, 68%, m.p 268-270ºC, υ/cm^{-1}= 3426-3388 (NH) and 1688 (CO); δ^{1}_{H} = 6.81 (d, 2H, J = 7.8 Hz, ArH), 7.11-7.41 (m, 5H, ArH), 7.68 (d, 2H, J = 7.8 Hz, ArH, ArH), 8.28 (s, 1H, =CH), 9.63 (s, 1H, NH), 10.36 (s, 1H, NH), 11.80 (s, 1H, OH); Elemental anal. for $C_{16}H_{13}N_5O_2S$ (339.3): Calc.: C, 56.63; H, 3.86; N, 20.64; S, 9.45 %, Found: C, 56.32; H, 4.52; N, 20.67; S, 9.18%.

2-(2-(4-Hydroxy-3-methoxybenzylidene) hydrazineyl)-5-(2-phenylhydrazineylidene)thiazol-4(5H)-one (8b)

Yellowish orange, 75%, m.p 255-257ºC, υ/cm^{-1}= 3418-3387 (NH) and 1716 (CO); δ^{1}_{H} = 3.84 (s, 3H, OCH_3), 6.87-6.96 (m, 3H, ArH), 7.28-7.37 (m, 7H, ArH), 8.39 (s, 1H, =CH), 9.69 (s, 1H, NH), 10.38 (s, 1H, NH), 12.41 (s, 1H, OH); δ^{13}_{C} = 55.7, 113.8, 115.7, 121.6, 122.4, 124.8, 125.3, 129.2, 143.8, 147.5, 147.9, 149.9, 155.1, 155.3, 157.8, 163.5, 168.1; Elemental anal. for $C_{17}H_{15}N_5O_3S$ (369.3): Calc.: C, 55.28; H, 4.09; N, 18.96; S, 8.68 %, Found: C, 55.01; H, 4.76; N, 18.74; S, 8.42%.

4-((2-(4-Oxo-5-(2-phenylhydrazineylidene)-4,5-dihydrothiazol-2-yl)hydrazineylidene)methyl)phenyl benzoate (8c)

Yellowish brown, 54%, m.p 270-272ºC, υ/cm^{-1}= 3366 (NH) and 1700 (CO); δ^{1}_{H} = 7.11-7.38 (m, 7H, ArH), 7.58-7.61 (m, 3H, ArH), 7.78 (d, 2H, *J* = 8.1 Hz, ArH), 8.01 (d, 2H, *J* = 7.8 Hz, ArH), 8.36 (s, 1H, =CH), 9.81 (s, 1H, NH), 10.34 (s, 1H, NH); Elemental anal. for $C_{23}H_{17}N_5O_3S$ (443.4): Calc.: C, 62.29; H, 3.86; N, 15.79; S, 7.23 %, Found: C, 62.65; H, 4.51 N, 15.62; S, 6.83%.

2-Methoxy-4-((2-(4-oxo-5-(2-phenylhydrazineylidene)-4,5-dihydrothiazol-2-yl)hydrazineylidene) methyl)phenyl benzoate (8d)

Yellowish orange, 60%, m.p 266-268ºC, υ/cm^{-1}= 3411 (NH) and 1697 (CO); δ^{1}_{H} = 3.84 (s, 3H, OCH_3), 7.08-7.24 (m, 3H, ArH), 7.31 (d, 2H, *J* = 8.1 Hz, ArH), 7.35 (d, 2H, *J* = 8.1 Hz, ArH), 7.51-7.71 (m, 5H, ArH), 8.14 (d, 2H, *J* = 7.8 Hz, ArH), 8.41 (s, 1H, =CH), 9.76 (s, 1H, NH), 10.51 (s, 1H, NH); Elemental anal. for $C_{24}H_{19}N_5O_4S$ (473.5): Calc.: C, 60.88; H, 4.04; N, 14.79; S, 6.77 %, Found: C, 62.81; H, 4.72; N, 15.09; S, 7.01%.

Biological activity

Antibacterial investigation through Agar-diffusion method [52]

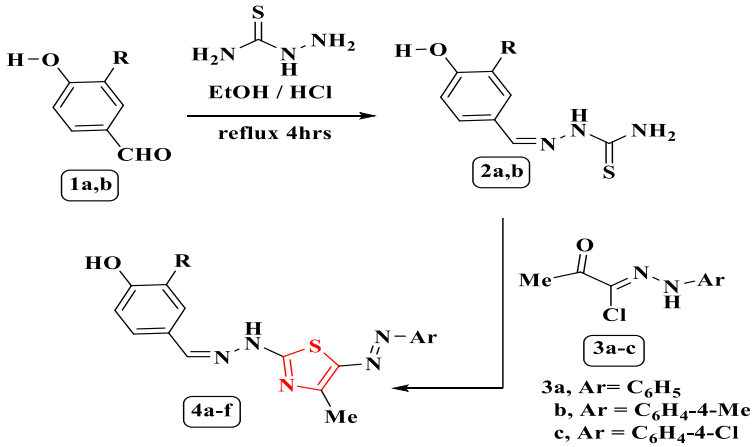
The antibacterial activity of the produced compounds was assessed utilizing the agar-based well diffusion technique. All substances were tested in vitro for antibacterial activity against a variety of bacterial strains using nutrient agar media. DMSO was used as the solvent reference. The compounds were tested against specific types of bacteria and fungi at a 15 mg/ml dosage. The sanitized media has been placed in sanitized Petri dishes (20-25 ml each) and allowed to harden at room temperature. The McFarland 0.5 standard solution (1.5 x 10^5 CFU mL-1) was used to establish a microbiological suspension in sterile saline. The transparency was calibrated to OD = 0.13 using a spectrophotometer at 625 nm. Ideally, within 15 minutes of changing the turbidity of the inoculum solution, a sterile cotton swab should be soaked in the changed suspension and dispersed over the dry agar surface, then allowed to dry for 15 minutes with the lid on. A sterile borer was used to construct 6-mm-diameter wells in the solidified material. A micropipette was employed to add 1 x 10^2 µL of the tested compound solution into each well. The plates were incubated at 37°C for 24 hours to determine antibacterial activity. This experiment was repeated three times, and inhibition zones were recorded in millimeters.

Minimum Inhibition Concentration (MIC) [53]

For each species, three to five particular colonies were selected over the new agar plate and transferred to a tube with 3-4 ml of sterile broth. The suspension of bacterial species was properly mixed before incubating at 35-37°C for 2-6 hours. The bacterial suspension's clarity must equal or exceed that of a McFarland Standard 0.5. Then, 1 mg of the tested compound (antimicrobial agent) was dissolved in 1 ml of DMSO, and a two-fold consecutive dilution was done using broth medium. A constant volume of the produced bacteria inoculum was added to each tube and cultured at 37°C for 16-20 hours. The MIC is defined as the minimal concentration of the antimicrobial agent that precludes observable development in the tested isolate, as viewed without the use of instruments.

3. Results and Discussion

The reaction of *p*-hydroxybenzaldehyde and *p*-hydroxy-*o*-methoxybenzaldehyde **1a,b** with thiosemicarbazide obtained the corresponding thiosemicarbazones **2a,b**. Moreover, **2a,b** and acetyl hydrazonyl halide derivatives **3a-c** reacted together to give the corresponding thiazoles **4a-f** (Scheme 1). Next, the synthesis of the target 4-(2-(4-methyl-5-(phenyldiazenyl)thiazol-2-yl)hydrazineylidene) methylphenol **4a** was utilized as a template reaction to achieve the ideal reaction conditions. The prior product was created through monitoring the reaction between the precursors **2a** and **3a**, different reaction conditions were used to discover the proper medium for the prior reaction from the point of solvents and catalyst (Table 1). The first trail for the synthesis, ethanol and triethyl amine (TEA) mixture were used for synthesis of **4a** in 8 hrs with 65% yields (Table 1, Input 1). Next, different solvents were used to furnish **4a** in different yield% (Input 2-4). Employing chitosan as a sustainable catalyst in place of TEA to facilitate the reaction with solvents: ethanol and dioxane yielding **4a** in outstanding yields. (Table 1, See Inputs 5-6) with short time reflux. In addition, the synthesis of **4a** utilizing dioxane as a solvent and chitosan as a catalyst proved to be the most effective method, yielding 87% in just 2 hours (Input 6). The synthesis of thiazoles **4a-f** was achieved by reacting **2a,b** with acetyl hydrazonyl halide derivatives **3a-c** in a dioxane solution, using a catalytic amount of chitosan (5 x 10^{-3} mole), resulting in excellent yields within 2 hours. Adjusting the catalyst quantity for performing the synthesis of **4a** revealed that the optimal molar amount of chitosan is 5 x 10^{-3} mole, resulting in the highest yield of **4a** (Table 2). IR spectrum of **4d**, as a representative example for the series, has a broad band at wavenumber = 3260 cm^{-1} for hydroxyl and imino group. The ^{1}H NMR spectrum of **4d** displayed two singlet signals at chemical shift = 2.47 and 3.82 ppm for methyl and methoxy protons, repetitively, besides two singlet signals at chemical shift = 9.82 and 10.53 ppm for imino and hydroxy protons, in succession. Also, it exposed one doublet signal at chemical shift = 6.87 ppm with *J* coupling constant equals 8.1 Hz, and a singlet signal at chemical shift = 8.50 ppm for aryl proton. Furthermore, the ^{1}H NMR spectrum of **4d** displayed a multiplet signals at chemical shift = 7.30-7.40 ppm for aryl protons. The ^{13}C NMR of **4d** proclaimed signals at chemical shift = 16.9, 56.2, 111.7, 114.7, 116.3, 122.6, 123.8, 125.8, 129.7, 138.6, 144.0, 148.5, 151.0 and 160.8 ppm (Scheme 1).



4a, R = H, R`= H, R_1= C_6H_5
b, R = H, R`= H, R_1= C_6H_4-4-Me
c, R = H, R`= H, R_1= C_6H_4-4-Cl
d, R = OMe, R`= H, R_1= C_6H_5
e, R = OMe, R`= H, R_1= C_6H_4-4-Me
f, R = OMe, R`= H, R_1= C_6H_4-4-Cl

Scheme 1 Synthetic scheme for synthesis of **4a-f**.

Table 1. Adjustment of Reaction variables for designing of the desired thiazole **4a**

Input	Reaction medium (solvent / catalyst)	Yield%	Duration of reaction (hr)
1	Ethanol / TEA	65	8
2	$CHCl_3$ / TEA	64	3
3	Dioxane / TEA	71	6
4	DMF / TEA	69	8
5	Ethanol / Chitosan	80	5
6	Dioxane / Chitosan	87	2
7	DMF / Chitosan	66	6

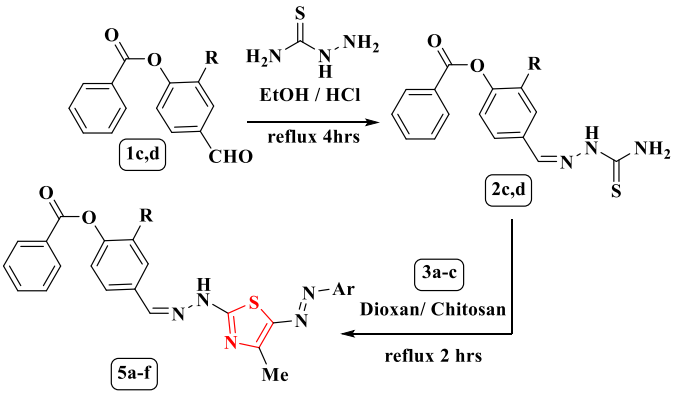
* 1 mL of TEA was utilized to facilitate the reactions in Inputs 1-4, 5 x 10^{-3} mole of chitosan were employed to facilitate the reaction in Inputs 5-7.

Table 2. Adjustment of catalyst`s molar ratio for the synthesis of the target thiazole **4a**

Input	Solvent	Catalyst* Conc.Mol%	Yield %	Time (hr)
1	dioxane	1 x 10^{-2}	70	3
2	dioxane	5 x 10^{-3}	87	2
3	dioxane	2.5 x 10^{-3}	68	3
4	dioxane	1 x 10^{-4}	71	3

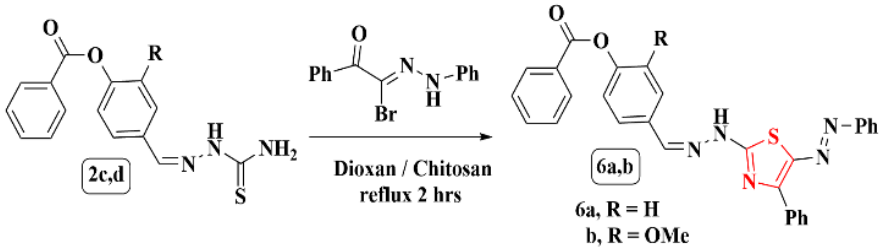
*****Catalyst used is chitosan, Solvent used is dioxane.

Similarly, the thiosemicarbazones **2c,d** reacted with acetyl hydrazonyl halide derivatives **3a-c** to deliver the corresponding thiazoles **5a-f** (Scheme 2). The reaction conditions were investigated to identify the optimal setting for synthesizing **5a**. The ideal synthesis conditions involve employing dioxane as the solvent and chitosan (5 x 10^{-3} mole) as a catalyst. The IR spectrum of **5e** disclosed bands at wavenumbers equal 3400 and 1700 cm^{-1} for imino and carbonyl functions, correspondingly. The ^{1}H NMR spectrum of **5e** proclaimed three singlet signals at the upstream region with chemical shift equal 2.25 and 2.58 ppm for two methyl protons and 3.85 ppm for methoxy protons, besides, doublet signals at chemical shift = 7.11, 7.25, 7.40, 7.74 and 8.12 ppm with *J* coupling constant equal 8.4, 8.1 and 7.5 Hz, each signal in sequence. Also, it uncovered multiple signals at chemical shift = 7.56-7.65 ppm for aryl protons, together with two singlet signals at chemical shift = 8.68 and 10.59 ppm for vinylic proton and imino protons, individually. The ^{13}C NMR spectrum of **5e** appeared characteristic signals at δ = 17.0, 20.9 and 56.5 ppm for two methyl and methoxy carbons, each in order of that, besides other expected signals.



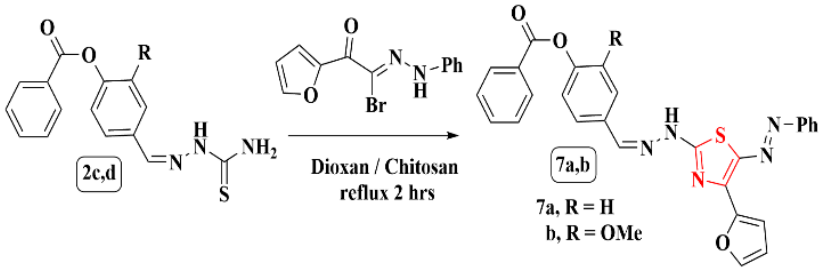
Scheme 2 The reaction of **2c,d** with hydrazonyl halides **3a-c** to afford the respective thiazoles **5a-f**.

Furthermore, the reaction of **2c,d** with diphenylacetohydrazonoyl bromide delivered the corresponding thiazoles **6a,b** (Scheme 3). In the same way, various reaction conditions were performed to identify the most efficient method for the preparation. The compound **6a** served as a representative case for determining optimal reaction conditions, and after completing the experiments, compound **6a** was successfully obtained in 2 hours with a yield of 90% using dioxane as the solvent and chitosan (5 x 10^{-3} mole) as the catalyst, which proved to be the best method for synthesizing the other compounds in the series. The IR spectrum of **6a** flourished bands at wavenumbers equal 3389 cm^{-1} for imino group and 1665 cm^{-1} for carbonyl group. The ^{1}H NMR spectrum for **6a** disclosed a singlet signal at chemical shift = 10.65 ppm for NH proton besides two doublet signals at chemical shift = 6.88 ppm (*J* coupling constant = 7.8 Hz) and 7.12 ppm (*J* coupling constant = 8.1 Hz). Also, its ^{1}H NMR spectrum posted multiplet signals at chemical shift = 7.31-7.77 and 7.91-8.01 ppm for aryl protons.



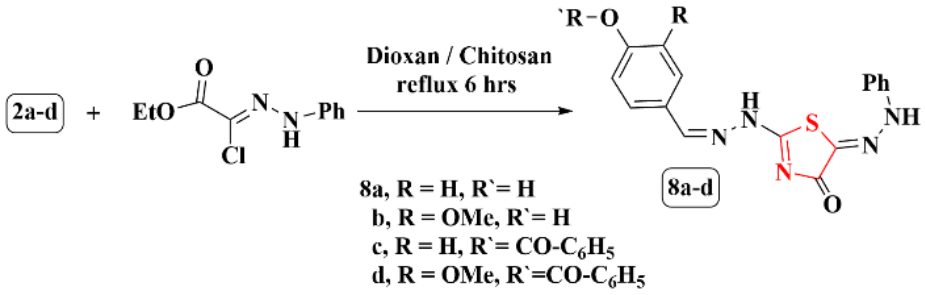
Scheme 3 The reaction of **2c,d** with diphenylaceto-hydrazonoyl bromide gave **6a,b**.

Moreover, the reaction of **2c,d** with furanyl-*N*-phenylacetohydrazonoyl chloride accomplished the corresponding thiazoles **7a,b** (Scheme 4). Similarly, different reaction conditions were conducted to find the best ease method for the preparation. The IR spectrum of **7b** displayed a broad band at wavenumber = 3340 cm^{-1} for imino group and a sharp band at wavenumber = 1711 cm^{-1} for carbonyl group. The ^1H NMR spectrum of **7b** produced two singlet signals at chemical shift = 3.86 ppm for methoxy protons and 8.59 ppm for vinylic protons, besides a singlet signal at chemical shift = 11.00 ppm for imino proton. In addition, its ^1H NMR spectrum unveiled multiplet signals at chemical shift = 6.85-7.64 ppm for aryl protons together with two doublet signals at chemical shift = 7.74 ppm (*J* coupling = 7.2 Hz) and 8.12 ppm (*J* coupling constant = 6.9 Hz).



Scheme 4. The reaction of **2c,d** with furanyl-*N*-phenylacetohydrazonoyl chloride gave **7a,b**.

Finally, the reaction of thiosemicarbazones **2a-d** with ethyl 2-chloro-2-(2-phenylhydrazineylidene)acetate afforded the corresponding thiazolidinones **8a-d** (Scheme 5). The synthesis of compound **8b** was evaluated under various reaction conditions to identify a simpler method for its preparation, with the dioxane/chitosan (5 x 10^{-3} mole) condition proving to be the most effective (yield% = 75%, 6 hrs). The IR spectrum of **8b** has a broad band at wavenumber = 3418-3387 cm^{-1} for imino group and a band at wavenumber = 1716 cm^{-1} due to carbonyl group. The ^1H NMR spectrum showed a singlet signal at chemical shift = 3.84 ppm for methoxy protons besides, three singlet signals at chemical shift = 12.41, 10.38 and 9.69 ppm for hydroxyl and imino protons, in order of that. Also, its ^1H NMR spectrum revealed multiplet signals at chemical shift = 6.87-6.96 and 7.28-7.37 ppm assigned to aryl protons. The ^{13}C NMR spectrum showed characteristic signals at chemical shift = 55.7, 113.8, 115.7, 121.6, 122.4, 124.8, 125.3, 129.2, 143.8, 147.5, 147.9, 149.9, 155.1, 155.3, 157.8, 163.5 and 168.1 ppm.



Scheme 5. The formation of **8a-d** through the reaction of **2a-d** with ethyl 2-chloro-2-(2-phenylhydrazineylidene)acetate.

Biology

***In Vitro* antibacterial activity evaluation by agar diffusion method**

The newly created thiazoles and thiazolidinones were evaluated for their antibacterial capabilities using the agar well diffusion technique against different types of bacteria [52]. The obtained results are shown in Table 3. Initially, the compounds studied showed low to moderate effectiveness against the strains. Among the tested compounds, compound **4d** proclaimed the strongest activity among the tested compounds especially against *E. coli* with IZD equals 23 ± 1 mm compared to the standard antibiotic gentamicin which has IZD value equals 27 ± 0.1 mm. Besides, compound **4d** exhibited antibacterial activity against *A. baumannii* with IZD equals 10 ± 1 mm. The compound **4f** revealed strong bacterial growth inhibition against *K. pneumonia* with IZD: 28 ± 1 mm, which is quite potent like the used antibiotic gentamicin (IZD equals 29 ± 0.5 mm) besides it revealed strong activity against *E. coli* with IZD equals 20 ± 1 mm. Similarly, compound **5f** unveiled strong antibacterial activity towards *K. pneumonia* with IZD: 23 ± 1 mm. Notably, compound **5d** was the only compound that exhibited bacterial growth inhibition

towards *St. aureus* and *St. mutans* with IZD: 20 ± 1 and 22 ± 1 mm, respectively. In general, nearly all of the tested substances demonstrated considerable to moderate antibacterial activity toward Gram-negative bacteria, particularly *E. coli* and *A. baumannii* (Table 3). The newly synthesized products that exhibited the highest antibacterial activity were subsequently assessed to ascertain their minimum inhibitory concentration (MIC) values [53] against all Gram-negative and Gram-positive bacterial strains, showing MIC values between 62.5 and 500 µg/L. Among the compounds being evaluated, compound **4d** showed an MIC value of 62.5 µg/L against *E. coli*, while gentamicin exhibited an MIC of 31.25 µg/L. The MIC values for the other tested compounds are presented in Table 4.

Computational studies

Optimization By DFT and MEP

The most antibacterial active compound **4d**, was further subjected to theoretical studies using Gaussian 09W [54] besides GaussView 6.0 [55] to calculate the optimized structure`s parameters and its molecular electronic potential (MEP) for indicating its active sites for reactions. The DFT calculation was done using the B3LYP/6–311G ++ (d,p) level of theory. The **4d**`s optimized structure was shown in Figure 3, the dipole moment for **4d** was calculated to be 4.5156 Debye. The MEP of compound **4d** changed from -7.513 eV (dark red region) to 7.513 eV (dark blue region) as displayed in Figure 4. It is demonstrated that the location of nucleophilic reactivity is revealed by the blue color area and the location of electrophilic reactivity is revealed by the red color region. From the calculations obtained, the area with negative potential is concentrated at the azo group at N31 and N32 as noted in the optimized structure (Fig.3). While, the positive regions are concentrated at OH group [O41 and H42] (Fig.4).

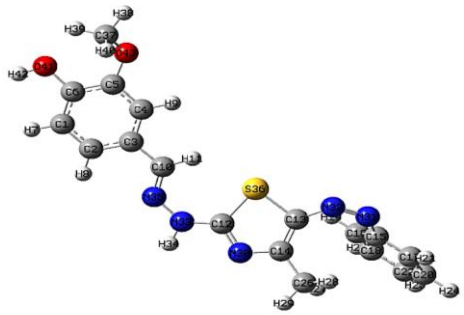


Fig. 3 The **4d**`s most stable geometric configuration obtained by DFT/B3LYP/6-311++G(d,p) level of theory.

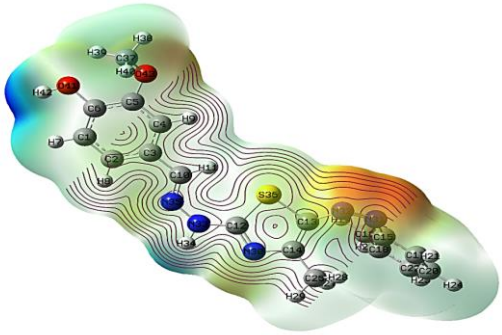


Fig. 4 The MEP of **4d** with contour. MEP of **4d** changed from -7.513 eV (dark red region) to 7.513 eV (dark blue region).

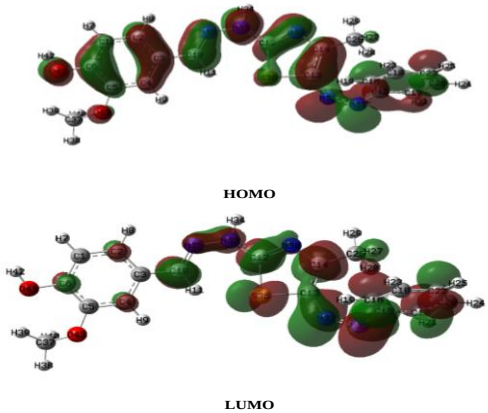


Fig. 5 The HOMO and LUMO orbitals of compound **4d**.

Table 3. Showing IZD (mm) of the examined compounds in the tested bacteria.

Cpd.No.	*E. coli*	*K. pneumonia*	*A. baumannii*	*St. aureus*	*St. mutans*
	IZD				
4b	-	-	19 ± 1	-	-
4d	23 ± 1	-	10 ± 1	-	-
4f	20 ± 1	28 ± 1	10 ± 1	-	-
5b	18 ± 1	-	-	-	-
5d	15 ± 1	-	-	20 ± 1	22 ± 1
5f	19 ± 1	23 ± 1	-	-	-
6b	20 ± 1.2	-	-	-	-
7a	-	15 ± 1	-	-	-
7b	-	-	11 ± 1	-	-
8a	-	-	11 ± 1	-	-

*****Gentamicin IZD in *E. coli* = 27 ± 0.1 mm and in *K. pneumonia* = 29 ± 0.5 mm. Tigecycline IZD in *A.baumannii* = 23 ± 0.4 mm. Ampicillin MIC in *St. aureus* = 29 ± 0.2 mm and *St. mutans* = 22 ± 0.1 mm.

Table 4. Indicating the MIC values of the evaluated compounds. * MIC quantified in µg/L.

Cpd. No.	*E. coli*	*K. pneumonia*	*A. baumannii*	*St. aureus*	*St. mutans*
	MIC				
4b	-	-	125	-	-
4d	62.5	-	-	-	-
4f	125	-	-	-	-
5b	500	-	-	-	-
5d	500	-	-	125	-
5f	500	-	-	-	-
7a	-	500	-	-	-
7b	-	-	125	-	-
8a	-	-	500	-	-

*****Gentamicin MIC in *E. coli* = 31.25 µg/L, and in *K. pneumonia* = 62.5 µg/L. Tigecycline MIC in *A. baumannii* = 31.25 µg/L. Ampicillin MIC in *St. aureus* and *St. mutans* = 62.5 µg/L.

HOMO and LUMO Energies

Applying the DFT calculation at B3LYP/6-311++G(d,p) level of theory to calculate the energy and energy gap for The frontier molecular orbitals (HOMO and LUMO) gave an account about the chemical properties and reactivity of compound **4d** (Fig. 5). The energy gap between HOMO and LUMO indicates the kinetic stability and reactivity of the compounds. A smaller gap between the energies of HOMO and LUMO in a compound indicates its greater reactivity [56,57]. For the compound **4d**, the HOMO energy is
-5.4542 eV, the LUMO energy is -2.6018 eV, and the energy gap (△E) is -2.8524 eV. The electronegativity parameter (χ) indicates how well atoms in a molecule can attract bond electrons [58]. When the electronegativity value is high, the attraction of bonding electrons is high and the molecule's reactivity is low [59]. The electronegativity of **4d** (χ) = - 4.028 eV. Assessing the chemical hardness (η) and chemical softness (σ) indicates the extent of the polarization and softness characteristics of molecules, respectively. Rigid molecules struggle to easily donate electrons to an acceptor that stabilizes the active site, resulting in them being less reactive compared to soft molecules [60]. The compound **4d** exhibits reduced hardness (η = 1.4262 eV) and increased softness (σ = 0.7011 eV^{-1}), enhancing its compatibility with biological activity.

Toxicity potential *in silico* via Osiris program.

The newly synthesized thiazoles and thiazolidinones were examined to their pharmaceutical properties using the Osiris methodology, [61] with the results presented in Table S1 (see supplemental file). Findings differed among the compounds, but the general conclusion showed moderately safe as drug candidates. Compounds **4a-f** and **5a-f** admitted high risk in causing tumors and moderate risk leading to mutagenicity. Similarly, compounds **6a,b** and **7a,b** showed high risk in resulting tumors and moderate risk leading to mutagenicity, irritancy and reproductive problems. The physicochemical properties of rest of compounds displayed Table S1 (see supplemental file). The drug score for the series **8a-d** is the highest among the newly synthesized compounds, it ranges from 0.24 to 0.45. The topological polar surface area (TPSA) value for the compounds was lower than 140.0 Å (ranging from 110.4 Å to 139.0 Å, respectively).

Swiss ADME predictions of 4d

The most antibacterial active candidate **4d** was subjected for more *in silico* studies using Swiss ADME free application [http://www.swissadme.ch]. The acronym ADME stands for absorption, distribution, metabolism, and excretion, and it is primarily utilized in areas like pharmacology and pharmacokinetics. The four-letter acronym represents descriptors that measure

the interaction of a specific drug within the body over time. This defines the drug's suitability and ultimately its medicinal chemical properties by basing these evaluations on pharmacokinetics, physicochemical traits, lipophilicity, and solubility.

The Absorption factor pertains to the method through which a compound enters a tissue, typically via the bloodstream, often through (intestinal absorption) via mucous membranes in the digestive system before being absorbed by the intended cells. For that the compound`s solubility is an important factor that affects its absorption. From the revealed data, the water solubility of **4d** found to be insoluble. The compound **4d** is found to be low gastrointestinal absorption, as its lipophilicity properties equals 3.87 so it isn`t absorbed by mucous. Besides, Absorption critically determines how the compound can be administrated; either by oral intravenously or by inhalation administration. Substances that have low absorption when ingested must be given through less preferable methods, such as intravenously or via inhalation, which means that compound **4d** cannot be taken orally because of its poor gastrointestinal absorption. Absorption critically determines the compound's bioavailability. Bioavailability indicates the degree to which a substance or medication is fully accessible to its targeted biological site. A bioavailability score of ≥ 0.55 is deemed optimal and is efficiently absorbed by the
body [62], making compound **4d** an ideal drug from the perspective of absorption.

The Distribution factor refers to the reversible movement of a compound from one compartment to another. Distribution can pose a significant challenge at certain natural barriers such as the blood–brain barrier. As noted from the obtained data, the TPSA for **4d** is 119.7 $Å^2$ and its molecular weight is lower than 500 g/mol. The compound **4d** revealed no penetration through BBB.

The Metabolism factor defines the breakdown of the drug as once the compound enters the body it starts to be broken down into metabolites. The compounds **4d** are no cytochrome P450 inhibitor except **6c** which leads to drug-drug interactions.

According to Drug-likeness rules, compound **4d** obeyed all the rules; Lipinski, Veber, Ghose and Egan rules it flourished no violation. The compound **4d** has MW = 367.42 g/mol, numbers H-bond acceptors = 6, numbers H-bond donors = 2 and Clog P = 2.49, thus it obeys all the terms of Lipinski rule. The Veber rule requires number of rotatable bonds less than 10 and TPSA < 140, for that compound **4d** revealed 6 rotatable bonds and TPSA equals 119.70 $Å^2$. For Ghose rule, the most important term is the molar refractivity (MR) which must be higher than 40 and lower than 130. The MR of **4d** equals 103.09. All the other rules have the same terms of the rules previously mentioned. The medicinal chemical descriptors revealed that compound **4d** can cause pains and brenk. Compound **4d** exhibited two lead-likeness violations. The synthetic accessibility for a compound was stated that the value equals 1 for synthetic accessibility means it is very easy to obtain while the value equals 10 means it is very difficult to obtain. The synthetic accessibility for **4d** is 3.60.

Table 5 Data obtained from Osiris property software.

	Solubility	***Drug-likeness***	***Drug score***	***TPSA***
4a	-5.6	-4.69	0.06	110.4
4b	-5.61	-4.39	0.05	119.7
4c	-7.36	-3.87	0.04	116.5
4d	-7.38	-2.59	0.04	125.7
4e	-5.94	-5.61	0.08	110.4
4f	-5.96	-5.26	0.08	119.7
5a	-7.71	-4.82	0.05	116.5
5b	-7.72	-3.47	0.05	125.7
5c	-6.33	-3.49	0.06	110.4
5d	-6.35	-3.18	0.06	119.7
5e	-8.1	-2.78	0.04	116.5
5f	-8.12	-1.49	0.04	125.7
6a	-8.77	-3.53	0.03	116.5
6b	-8.79	-2.28	0.03	125.7
7a	-8.12	-3.71	0.02	129.6
7b	-8.14	-2.45	0.02	138.9
8a	-3.54	3.64	0.45	123.7
8b	-3.56	3.87	0.45	132.9
8c	-5.3	4.15	0.25	129.8
8d	-5.32	5.33	0.24	139.0

Conclusion

Green synthesis of new thiazoles and thiazolidinones based on *p*-hydroxybenzaldehyde derivatives through the reaction with different hydrazonyl halides and ethyl 2-chloro-2-(2-phenylhydrazineylidene)acetate. Optimization protocols were implemented to identify the ideal conditions for synthesis, revealing that the most effective method involves using dioxane as a solvent and chitosan as a catalyst (5 x 10^{-3} mol). The antibacterial study was conducted against various gram-negative and gram-positive bacteria revealing better inhibition activity with good minimum inhibition concentration (MIC) for some compounds. The most effective antibacterial candidate **4d** was subjected for DFT study by the B3LYP/6–311G++(d,p) level to obtain its suitable geometrical optimized structure besides its MEP. Also, the DFT method at B3LYP/6-311++G(d,p) level was done to compute the energy and energy gap for the frontier molecular orbitals (HOMO and LUMO) for compound **4d**. The ADME

study was performed for compound **4d** using Swiss ADME program revealing excellent pharmaceutical and chemical descriptors. The *in-silico* studies by Osiris methodology of recently created compounds showed moderate risks and toxicity.

Conflict of Interest

The authors state that there is no conflict of interest.

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