Synthesis and Antimicrobial Screening of Some Novel 2-(5-(4-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenols Incorporated by Triazole Moiety

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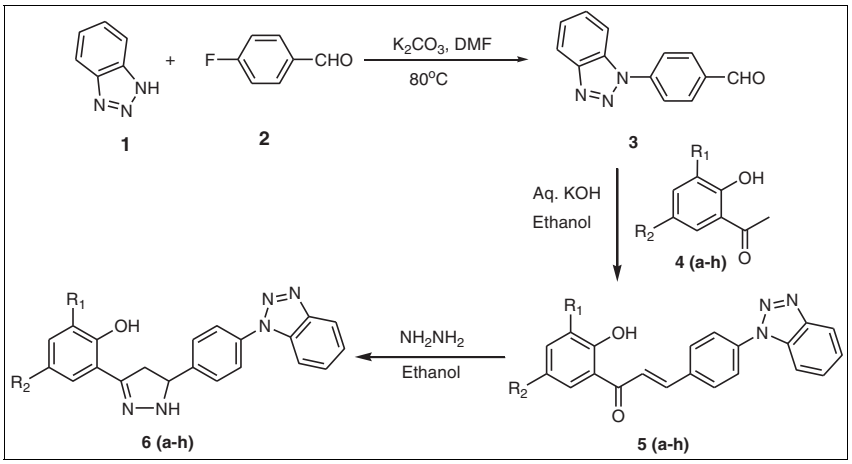

A novel series of 2-(5-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenols derivative has been synthesized from (*E*)-3-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-ones in ethanol and hydrazine hydrate under reflux condition. The synthesized compounds were screened for antibacterial activity against Gram-positive bacteria viz *Staphylococcus aureus* and *Bacillus subtilis* and Gram-negative bacteria viz *Escherichia coli* and *Salmonella typhi*, respectively. Some of the tested compounds showed significant antimicrobial activity. IR, ^{1}H NMR, mass spectral data, and elemental analysis elucidated the structures of all the newly synthesized compounds.

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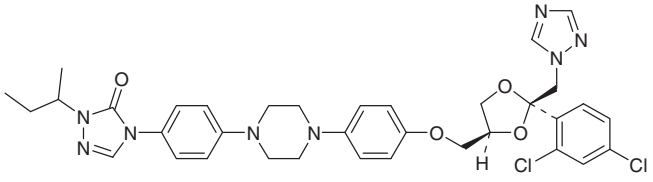
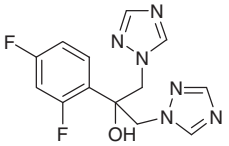
INTRODUCTION

Azoles are found widely in natural sources and there are several drugs available that contain azole ring. Triazoles are important five-membered heterocyclic rings. Triazoles are basically of three types, that is, 1,2,3-triazole; 1,2,4-triazole; and 1,2,3-benzotriazole. The 1*H*-1,2,4-triazoles are considered interesting heterocycles because they possess important pharmacological activities such as antifungal and antiviral. Examples of antifungal drugs [1,2] are fluconazole [3,4], itraconazole [5], ravuconazole [6], voriconazole [7–9], ICI 153066 [10], and posaconazole [11]. The action of these compounds is based on the inhibition of biosynthesis of ergosterol, the major steroid in fungal membranes, by blocking 14-α-demethylation, which occurs with accumulation of 14-α-methyl steroids and disruption of the fungal membranes [12–14]. Fluconazole causes second bronchial arch anomalies in mice [15].



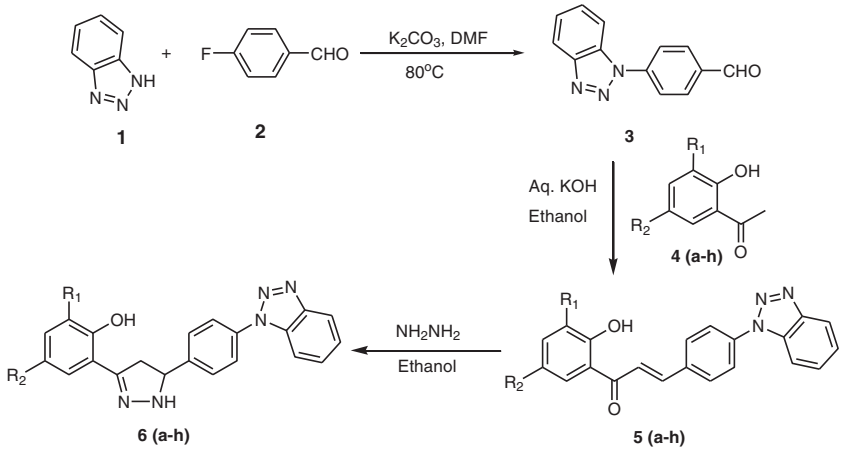
1.Itraconazole.



2.Fluconazole

2-Pyrazoline ring system has attracted significant interest in organic and medicinal chemistry over the past few decades. Scaffolds containing the 2-pyrazoline (4, 5-dihydropyrazole) heterocyclic have demonstrated a wide range of biological activities, including anticancer activity through the inhibition of kinesin spindle protein [16], CB1 receptor antagonism for obesity [17], monoamine oxidase inhibition for depression [18], and a host of

Scheme 1. Synthesis of chalcones and pyrazolines.



other antibacterial and antiviral agents [19]. Some of the pyrazoline derivatives are reported to possess antidiabetic and antidepressant properties [20]. Pyrazoline derivatives find applications as dyestuffs, analytical reagents, and agrochemicals [21]. Also the pyrazoline derivatives possess pronounced anti-inflammatory activity [22–24].

Therefore, in view of these important biological activities of both the scaffolds, and in continuation of our research program [25–29], we report the synthesis of some new 1*H*-1,2,4-triazoles-incorporated pyrazolines derivatives from the chalcones and tested the antibacterial and antifungal activities of the new resulting compounds, which have been found to possess an interesting profile of pharmacological activity, against representative Gram-negative and Gram-positive bacteria and fungi.

RESULT AND DISCUSSION

Chemistry. The synthetic route for the preparation of 2-(5-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenol is shown in Scheme 1. 1*H*-Benzo[*d*][1,2,3]triazole (**1**) treated with 4-flurobenzaldehyde (**2**) in DMF and K_2CO_3 at 80°C to yield 4-(phenylthio) benzal4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)benzaldehyde (**3**). The 4-(phenylthio)benzal4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)benzaldehyde (**3**) was subjected to base-catalyzed Claisen–Schmidt condensation reaction [30] with appropriate *o*-hydroxy acetophenones (**4a–h**) generating (*E*)-1-(2-hydroxyphenyl)-3-(4-(phenylthio)phenyl)prop-2-en-1-one(*E*)-3-(4-(1*H*-enzo[*d*][1,2,3]triazol-1-yl)phenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (**5a–h**). 2-(5-(4-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenol (**6a–h**) was prepared by the oxidative cyclization of corresponding (*E*)-1-(2-hydroxyphenyl)-3-(4-(phenylthio) phenyl)prop-2-en-1-one(*E*)-3-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**5a–h**) in ethanol and hydrazine hydrate under reflux condition.

The purity of compounds was checked by TLC. Analytical and spectral data (IR, ^{1}H NMR, mass, and elemental analysis) of the newly synthesized compounds were in full agreement with the proposed structure. The structure of **5a** is interpreted from spectroscopic data. The IR spectrum of **5a** showed a characteristic absorption band at 3334 and 1676 cm^{-1} due to -OH and C═O stretching. Its ^{1}H NMR spectrum exhibits presence of olefinic protons as a doublet at $\delta = 7.9$ and 8.2 regions with a mutual coupling constant value ($J = 15.6$ and 15.6 Hz). These observed coupling constant values indicate the presence of *E*-configuration from the structure and the remaining aromatic protons appear at their respective positions. The phenolic -OH is highly deshielded and appears at $\delta = 12.40$ ppm. Mass spectrum of (*E*)-1-(2-hydroxyphenyl)-3-(4-(phenylthio)phenyl)prop-2-en-1-one(*E*)-3-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one showed (M^+) peak at 342 and (M^-) peak at 340. The IR spectra of prepared **6a** revealed the absorption band at 3238 cm^{-1} due to -OH stretching and also exhibited C═N stretching vibrations in the region 1522 cm^{-1}, and compound **6a** showed an additional absorption band at 3058 cm^{-1} characteristic for pyrazole NH. In ^{1}H NMR spectra of compounds **6a** showed three multiplets at δ 3.06, 3.67 and 4.97 ppm that resulted from the AMX pattern displayed by two diastereotopic protons at C-4 (H_a and H_b) and one proton (H_c) at C-5. One singlet proton at 11.13 ppm due to -OH and the rest of the aromatic proton appear at their respective position and exhibit one doublet at 7.99 ppm due to NH. Mass spectrum of preparation 2-(5-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl) phenol showed (M^+) peak at 356.2 and (M^-) at 354.2.

CONCLUSION

In summary, we have synthesized a series of benzotriazole-incorporated novel (*E*)-1-(2-hydroxyphenyl)-3-(4-(phenylthio) phenyl)prop-2-en-1-one(*E*)-3-(4-(1*H*-benzo[*d*][1,2,3]

triazol-1-yl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one and 2-(5-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol derivatives, and their antimicrobial activities have been evaluated. All the compounds demostrated potent inhibition against all the tested strains. The importance of such work lies in the possibility that the new compounds might be more efficacious drugs against bacteria, which could be helpful in designing more potent antibacterial agent for therapeutic use. The structure of the synthesized compounds was confirmed with their spectral data.

EXPERIMENTAL

The melting points of all synthesized compounds were determined in open capillary tubes and are uncorrected. The purity of all compounds was checked by TLC. IR spectra were recorded on Jasco FT-IR-4100 in KBr disk (Tokyo, Japan). ^{1}H NMR spectra were recorded on a Varian As 400 MHz spectrometer in $CDCl_3$/DMSO-d_6 (Palo Alto, CA); chemical shifts (δ) are in parts per million (ppm) relative to TMS and coupling constant (*J*) are expressed in hertz (Hz). Mass spectra were recorded on a Macro mass spectrometer (Waters, Milford, MA) by electro-spray method (ES). Elemental analysis was performed on Perkin-Elmer EAL-240 elemental analyzer (Waltham, MA).

Synthesis of 4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl) benzaldehyde (3). 1,2,3-Benzotriazole (**1**) was dissolved in DMF (1.0 g, 8.4 mmol). To this solution, K_2CO_3 (2.3 g, 16.8 mmol) was added and heated at 80°C with stirring. After 30 min. (1 mL, 8.4 mmol) 4-fluorobenzaldehyde (**2**) was added and heating continued for 8–10 h. On completion of reaction, the reaction mixture was cooled and added dropwise to ice water. The separated product (**3**) was filtered and dried. The product obtained was pure and used further without any purification.

General procedure for the synthesis of (*E*)-1-(2-hydroxyphenyl)-3-(4-(phenylthio) phenyl)prop-2-en-1-one(*E*)-3-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (5a–h). An aqueous solution of KOH (0.410 g, 2.8 mmol) was added to a suspension of 1-(2-hydroxyphenyl) ethanone (**4g**) (0.500 g, 1.4 mmol) and 4-(1*H*-benzo[*d*][1,2,3] triazol-1-yl)benzaldehyde (**3**) (0.326 g, 1.4 mmol) in 10 mL ethanol–water mixture. The mixture was stirred at room temperature for overnight. The mixture was poured into water and acidified with HCl (2 *M*) till pH = 4. The solid product (**6g**) separated out was filtered off and crystallized from ethanol. The compounds (**6a–h**) were prepared by following the aforementioned procedure. Their structures have been confirmed by mass, IR, and ^{1}H NMR spectra (Table 1).

(E)-1-(2-Hydroxyphenyl)-3-(4-(phenylthio) phenyl)prop-2-en-1-one(E)-3-(4-(1H-benzo[d][1,2,3]triazol-1-yl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (5a). IR (KBr) cm^{-1}: 3334 (OH), 1676 (C═O), 1524 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.004–7.041 (m, 2H, aromatic); 7.521–7.600 (m, 2H, aromatic); 7.676–7.712 (m, 1H, aromatic); 7.933–7.972 (d, *J* = 15.6 Hz, 1H, ethylenic); 8.245–8.284 (d, *J* = 15.6 Hz, 1H, ethylenic); 8.006–8.038 (m, 3H, aromatic); 8.153–8.199 (m, 3H, aromatic); 8.284–8.306 (dd, 1H, aromatic); 12.40 (s, 1H, -OH); EC–MS: 342 (M^+), 340 (M^-); *Anal*. Calcd. for C, 73.90; H, 4.40; N, 12.32; Found: C, 73.86; H, 4.45; N, 12.35.

Table 1

Physical data of the compounds (**5a–h**) and (**6a–h**).

Compound	R_1	R_2	Yield (%)	mp (°C)
5a	H	H	74	134–136
5b	H	Cl	72	137–139
5c	CH_3	CH_3	60	155–157
5d	Cl	Cl	63	156–158
5e	H	CH_3	65	148–150
5f	H	Br	70	169–171
5g	CH_3	Cl	64	158–160
5h	H	F	68	132–134
6a	H	H	67	143–145
6b	H	Cl	65	146–148
6c	CH_3	CH_3	50	165–167
6d	Cl	Cl	61	172–174
6e	H	CH_3	53	160–162
6f	H	Br	64	184–186
6g	CH_3	Cl	58	149–151
6h	H	F	66	139–141

(E)-3-(4-(1H-Benzo[d][1,2,3]triazol-1-yl)phenyl)-1-(5-chloro-2-hydroxyphenyl)prop-2-en-1-one (5b). IR (KBr) cm^{-1}: 3330 (OH), 1672 (C═O), 1520 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.000–7.043 (m, 2H, aromatic); 7.5213–7.620 (m, 1H, aromatic); 7.686–7.712 (m, 1H, aromatic); 7.942–7.979 (d, *J* = 15.4 Hz, 1H, ethylenic); 8.345–8.384 (d, *J* = 15.5 Hz, 1H, ethylenic); 8.006–8.038 (m, 3H, aromatic); 8.163–8.169 (m, 3H, aromatic); 8.294–8.316 (dd, 1H, aromatic); 12.35 (s, 1H, -OH); EC–MS: 376.3 (M^+), 374.21 (M^1); *Anal*. Calcd. for C, 67.20; H, 3.73; N, 11.2; Found: C, 67.21; H, 3.76; N, 11.24.

(E)-3-(4-(1H-Benzo[d][1,2,3]triazol-1-yl)phenyl)-1-(2-hydroxy-3,5-dimethylphenyl)prop-2-en-1-one (5c). IR (KBr) cm^{-1}: 3340 (OH), 1679 (C═O), 1528 (C═C).; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.924–6.939 (d, 1H, aromatic); 7.224–7.260 (d, 1H, aromatic); 7.943–7.972 (d, *J* = 15.5 Hz, 1H, ethylenic); 8.325–8.374 (d, *J* = 15.4 Hz, 1H, ethylenic); 8.106–8.138 (m, 4H, aromatic); 8.353–8.399 (m, 4H, aromatic); 12.42 (s, 1H, -OH); EC–MS: 370.25 (M^+), 368.43 (M^-); *Anal*. Calcd. for C, 74.8; H, 4.88; N, 11.38; Found: C, 74.82; H, 4.89; N, 11.40.

(E)-3-(4-(1H-Benzo[d][1,2,3]triazol-1-yl)phenyl)-1-(3,5-dichloro-2-hydroxyphenyl)prop-2-en-1-one (5d). IR (KBr) cm^{-1}: 3344 (OH), 1671 (C═O), 1530 (C═C).; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.314–7.341 (d, 1H, aromatic); 7.561–7.6010 (d, 1H, aromatic); 7.776–7.742 (m, 4H, aromatic); 7.943–7.979 (d, *J* = 15.6 Hz, 1H, ethylenic); 8.445–8.464 (d, *J* = 15.6 Hz, 1H, ethylenic); 8.253–8.299 (m, 4H, aromatic); 8.284–8.306 (dd, 1H, aromatic); 12.38 (s, 1H, -OH); EC–MS: 410.1 (M^+); *Anal*. Calcd. for C, 61.61; H, 3.42; N, 10.27; Found: C, 61.60; H, 3.44; N, 10.26.

General procedure for the synthesis of 2-(5-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (6a–h). Chalcone (**5g**) (0.1 g, 0.29 mmol) was dissolved in 2 mL of ethanol. To this reaction mixture, hydrazine hydrate (0.014 mL, 2.9 mmol) was added. The reaction mass was heated at reflux for 4 h. After completion of reaction (checked by TLC), reaction mixture was cooled to room temperature. At the end, 10 mL cold water was slowly added to the flask, and the separated product (**6g**) was filtered and washed with cold water and crystallized

from ethanol. The compounds (**6a–h**) were prepared by following the aforementioned procedure. Their structures have been confirmed by mass, IR, and H^1NMR spectra.

2-(5-(4-(1H-Benzo[d][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (6a). IR (KBr) cm^{-1}: 3238(OH), 3058 (NH), 1522 (C═N); 1118 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.06–3.13 (m, 1H, C_4 Pyrazoline); 3.67–3.74 (m, 1H, C_4 Pyrazoline); 4.97–5.03 (m, 1H, chiral Pyrazoline); 6.87–6.92 (m, 2H, aromatic); 7.20–7.93 (m, 8H, aromatic); 8.16–8.19 (d, J = 12 Hz, 2H, aromatic); 7.99–8.00 (d, 1H, NH); 11.13 (s, 1H, -OH); EC–MS: 356.2 (M^+) and 354.2 (M^-); *Anal*. Calcd. for C, 70.98; H, 4.78; N, 19.71; Found: C, 70.95; H, 4.80; N, 19.78.

2-(5-(4-(1H-Benzo[d][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4-chlorophenol (6b). IR (KBr) cm^{-1}: 3242 (OH), 3052 (NH), 1527 (C═N); 1128 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.16–3.19 (m, 1H, C_4 Pyrazoline); 3.70–3.748 (m, 1H, C_4 Pyrazoline); 4.99–5.00 (m, 1H, chiral Pyrazoline); 6.90–6.96 (m, 2H, aromatic); 7.25–7.97 (m, 7H, aromatic); 8.18–8.20 (d, J = 12.1 Hz, 2H, aromatic); 8.00–8.10 (d, 1H, NH); 11. 45 (s, 1H, -OH); EC–MS: 380.4 (M^+) and 378.3 (M^-); *Anal*. Calcd. for C, 64.78; H, 4.11; N, 17.99; Found: C, 64.75; H, 4.13; N, 17.97.

2-(5-(4-(1H-Benzo[d][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4,6-dimethylphenol (6c). IR (KBr) cm^{-1}: 3234 (OH), 3061 (NH), 1526 (C═N); 1124 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.09–3.14 (m, 1H, C_4 Pyrazoline); 3.69–3.77 (m, 1H, C_4 Pyrazoline); 4.99–5.05 (m, 1H, chiral Pyrazoline); 6.94–6.97 (m, 2H, aromatic); 7.50–7.98 (m, 8H, aromatic); 8.26–8.29 (d, J = 12.4 Hz, 2H, aromatic); 8.00–8.12 (d, 1H, NH); 11.1343 (s, 1H, -OH); EC–MS: 356.2 (M^+) and 354.2 (M^-); *Anal*. Calcd. for C, 72.75; H, 5.23; N, 18.32; Found: C, 72.74; H, 5.24; N, 18.31.

2-(5-(4-(1H-benzo[d][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4,6-dichlorophenol (6d). IR (KBr) cm^{-1}: 32342 (OH), 3063 (NH), 1531 (C═N); 1127 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.19–3.21 (m, 1H, C_4 Pyrazoline); 3.71–3.74 (m, 1H, C_4 Pyrazoline); 4.99–5.07 (m, 1H, chiral Pyrazoline); 6.94–6.98 (d, 1H, aromatic); 7.50–7.98 (m, 8H, aromatic); 8.36–8.39 (d, J = 12.2 Hz, 1H, aromatic); 8.00–8.12 (d, 1H, NH); 11.1343 (s, 1H, -OH); EC–MS: 424.1 (M^+); *Anal*. Calcd. for C, 59.57; H, 3.54; N, 16.55; Found: C, 59.59; H, 3.55; N, 16.57.

Biological assay. Some of the synthesized compounds were screened for *in vitro* antibacterial activities against Gram-positive and Gram-negative bacteria. In Gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis* were used and in Gram-negative *Escherichia coli* and *Salmonella typhi* were used against standard tetracyclin and ampicillin. The antibacterial activities were carried out on nutrient agar with standard composition and by standard procedure of paper disk method [31]. Petri dishes and necessary glasswares were sterilized in hot air oven (190°C, 45 min). The nutrient agar and saline (0.82% NaCl) were sterilized in autoclave (121°C, 15 psi, 20 min). Inoculum was prepared in sterile saline, and optical density of all pathogens was adjusted to 0.10 at 625 nm on Chemito Spectrascan UV 2600 spectrophotometer (Mumbai, India), which is equivalent to 0.5 McFarland standards. The nutrient agar plates were prepared by pour plate method [32]. The sensitivity of the compounds was tested by disk diffusion method (paper disk method). All the bacterial cells were cultured in nutrient plates and the compounds to be tested were dissolved in DMSO solvent and were soaked on paper disks. The disks were placed into the plates and incubated at 37°C for 24 h. The diameter in millimeter of zone of inhibition around each disk was measured by scale, and the observed data of antimicrobial activity of compounds and the standard drugs are given in Table 2. Among all the compounds screened, **5e**, **5f**, **6d**, **6f**, and **6g** showed good antibacterial activity against Gram-positive

Table 2

Antimicrobial activity of compounds (**5a–h**) and (**6a–h**).

	Gram-positive		Gram-negative	
Entry	*Staphylococcus aureus*	*Bacillus subtilis*	*Escherichia coli*	*Salmonella typhi*
5a	18	20	18	14
5b	20	25	21	27
5c	—	—	—	—
5d	21	21	18	28
5e	29	28	17	23
5f	27	19	15	20
5g	22	20	19	29
5h	22	20	19	13
6a	20	22	16	18
6b	—	—	31	27
6c	—	—	—	—
6d	21	26	26	23
6e	22	21	33	24
6f	30	26	25	22
6g	25	—	15	12
6h	19	22	30	—
Ampicillin	35	30	34	31
Tetracyclin	32	33	38	35

bacteria, and compounds **5b**, **5d**, **5g**, **6b**, **6d**, and **6e** showed good activity against Gram-negative bacteria as comparable with that of standard drug tested. So the result of all preliminary studies indicated that the substituted (*E*)-1-(2-hydroxyphenyl)-3-(4-(phenylthio) phenyl)prop-2-en-1-one(*E*)-3-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl) phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one and 2-(5-(4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl) phenol moiety represent a new class of pharmacophore for broad spectrum antimicrobial activity.

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