Synthesis and Biological Evaluation of Some Heterocyclic Compounds from Salicylic Acid Hydrazide[1]

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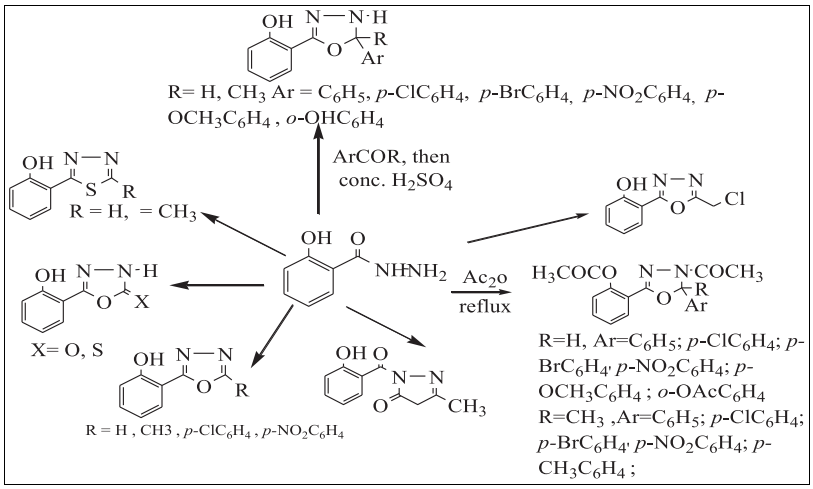

Different heterocyclic compounds were prepared starting from 2-hydroxy benzohydrazide; for example, cyclization of hydrazide hydrazone **3** derived from 2-hydroxybenzohydrazide **2** with acetic anhydride or concentrated sulfuric acid gave 1,3,4-oxadiazole derivatives **4–5**. On the other hand, direct cyclization of 2-hydroxy benzohydrazide **2** with one carbon cyclizing agent gave a new derivative of 1,3,4-oxadiazole **7–11**. Heating of hydrazide hydrazone **3** with thioglycolic acid in pyridine gave thiazolidinone **12**. When 2-hydroxy benzohydrazide **2** reacted with aliphatic carboxylic acids such as formic acid or acetic acid, it gave the corresponding *N*-formyl or *N*-acetyl derivatives **6**. Subsequent cyclization of **6** using phosphorous pentasulphide in pyridine gave 1,3,4-thiadiazoles **13**. Cyclization of 2-hydroxy benzohydrazide with ethyl acetoacetate gives pyrazolone derivative **14**. Finally, when an ethanolic solution of acid hydrazide **2** was treated with ammonium thiocyanate in 35% HCl, it gave the thiosemicarbazide **15**. Subsequent treatment of **15** with concentrated sulfuric acid or 10% sodium hydroxide gave 5-amino-1,3,4-thiadiazole **16** and 1,2,4-triazole **17,** respectively. The structures of all newly isolated compounds were confirmed using ^{1}H NMR, IR spectra, and elemental analyses. The antimicrobial activities for all isolated compounds were examined against different microorganisms.

INTRODUCTION

Hydrazides and related compounds have been described as useful building blocks for the assembly of various heterocyclic rings [2,3]. A large number of aliphatic, alicyclic, aromatic, and heterocyclic carbohydrazides are reported to present a plethora of biological activities [4–17]. In recent years, Hydrazides have received much attention because of their biological activities as tuberculostatic [18], antibacterial agent [19], antitumor agent [20], and anticancer agent [21]. In view of their high reactivity, hydrazides are also important starting materials and intermediates in the synthesis of hydrazones and heterocyclic compounds [22–26]. Oxadiazole moiety and its various derivatives were studied frequently in the past few decades and found to be potent in various pharmacological and pathological conditions [27]. Literature reveals that 1,3,4-oxadiazole is a highly privileged structure, the derivatives of which exhibit a wide range of biological activities including antibacterial [28], antitubercular [29], vasodialatory [30], antifungal [31], cytotoxic [32–34], hypolipidemic [35], anticancer [36], and ulcerogenic [37] activities. 1, 3, 4-Oxadiazole derivatives have been found to possess broad spectrum antimicrobial activity and therefore are useful substructures for further molecular exploration [38].

RESULTS AND DISCUSSION

2-Hydroxybenzohydrazide **2** was prepared in good yield for heterocyclic compounds synthesis by heating methyl salicylate with hydrazine hydrate in 95% ethanol [39,40]. The synthetic routes to our prepared compounds **2–17** are shown in Schemes 1, 2, and 3.

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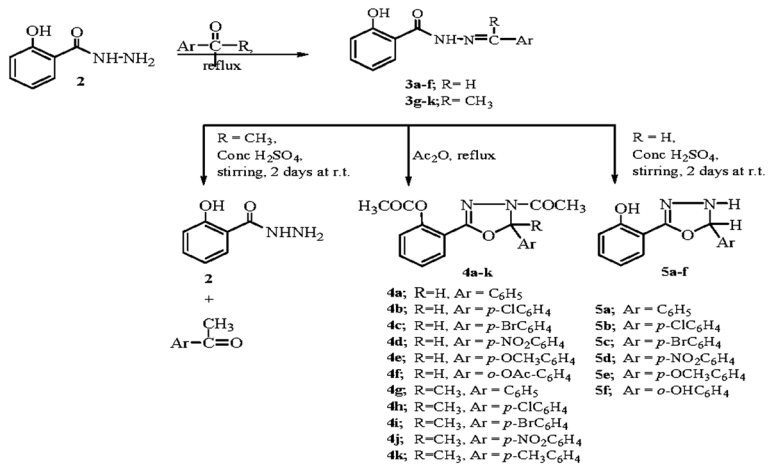
Synthesis of 1,3,4-oxadiazole derivatives. In this work, oxadiazole ring annulations were performed by two different routes. The first route required cyclization of hydrazide hydrazone **3** derived from 2-hydroxybenzohydrazide **2** using either acetic anhydride or concentrated sulfuric acid (Scheme 1).

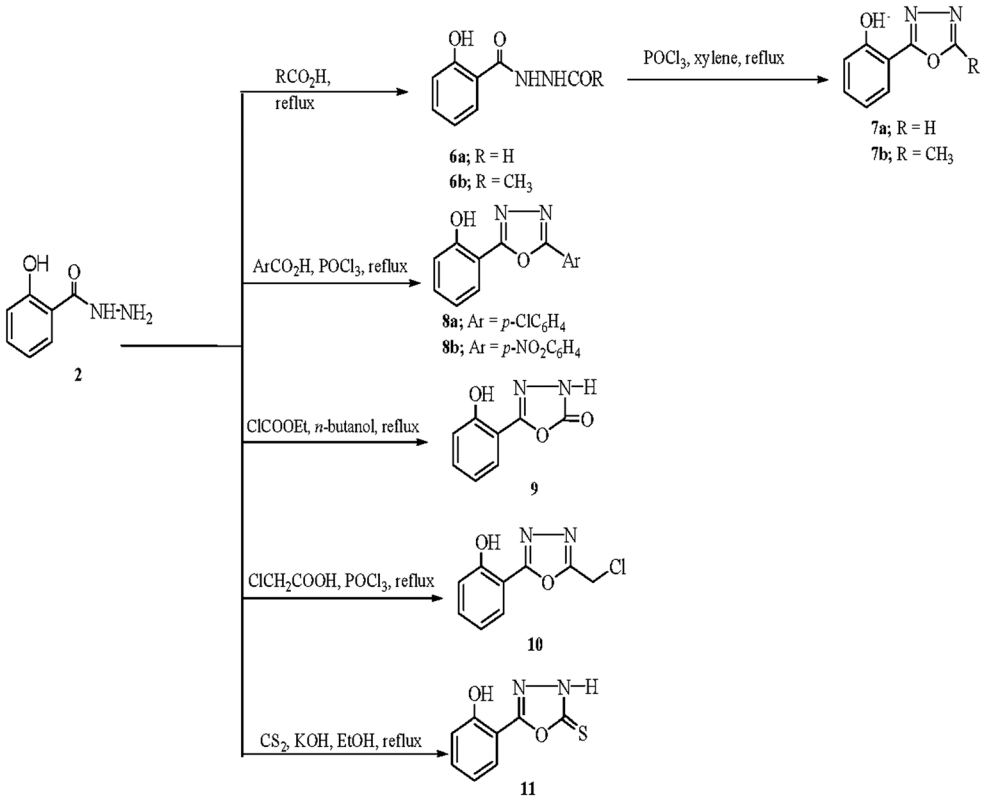
The second one required cyclization of 2-hydroxybenzohydrazide **2** with one carbon cyclizing agent such as aliphatic carboxylic acids, aromatic carboxylic acids, ethyl chloroformate, chloroacetic acid, and carbon disulphide (Scheme 2).

Synthesis of 1, 3, 4-oxadiazoles from hydrazide hydrazones. Hydrazide hydrazones **3a-k** were prepared in good yields by acid catalyzed condensation of 2-hydroxybenzohydrazide **2** with the appropriate benzaldehyde or acetophenone derivatives (Scheme 1).

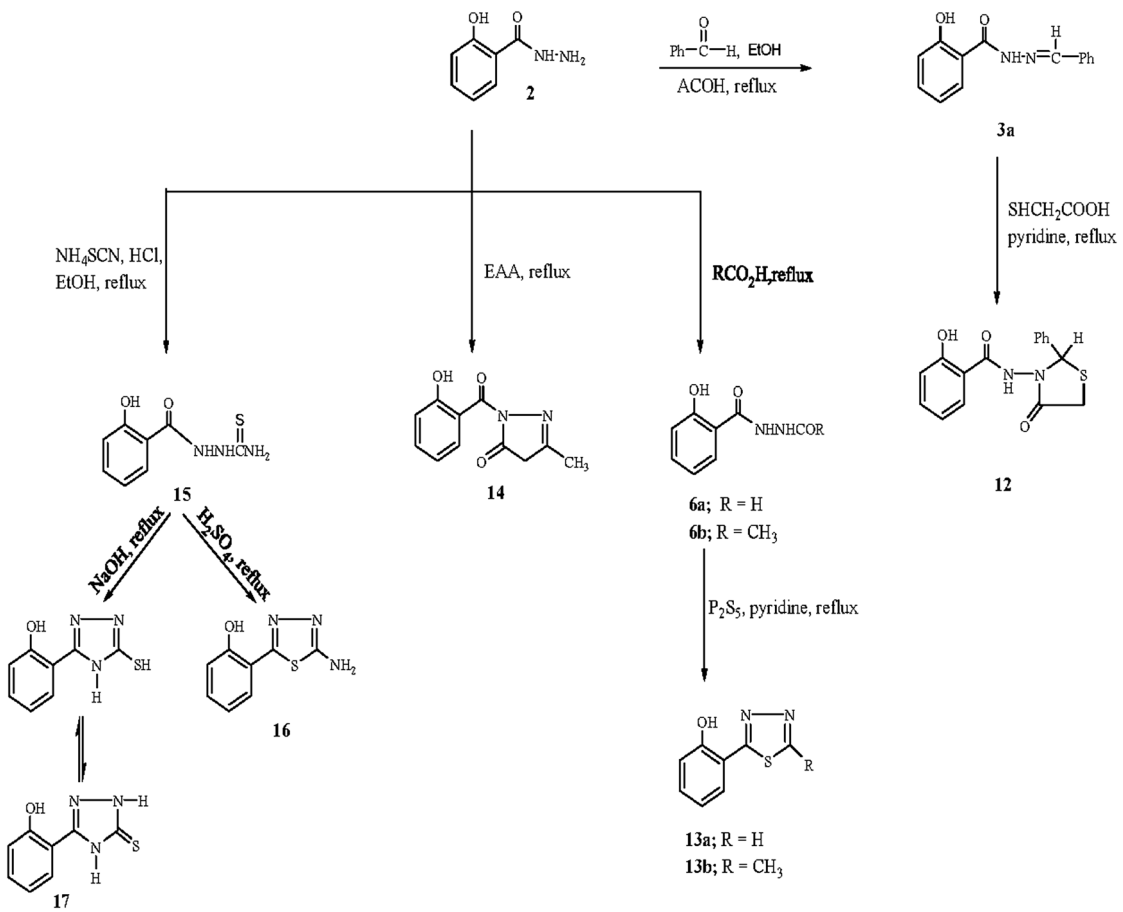
Scheme 1



Scheme 2

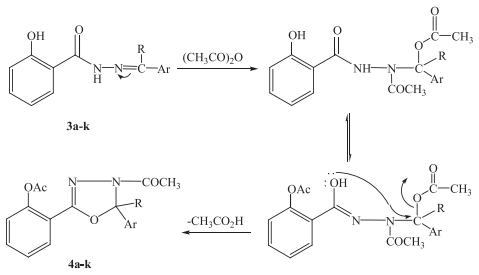


Scheme 3



The structures of the isolated compounds were supported by spectral methods. The IR of benzaldehyde hydrazones (R = H) **3a-f** and acetophenone hydrazones (R = CH_3) **3 g-k** showed the characteristic bands for C=C at 1528–1579, C=N at 1600–1620, C=O at 1630–1642, secondary amine (NH) at 3196–3280, and phenolic OH at 3310–3467 cm^{-1}, respectively. The ^1H NMR spectra of **3a-k** showed the presence of two exchangeable singlets characteristic for NH and phenolic OH protons. The aromatic protons of **3a-k** appeared as a multiplet at $\delta = 6.88–8.28$ ppm characteristic for the aromatic protons. The azomethine proton (CH=N) of **3a-f** appeared as a singlet at 8.39–8.65 ppm. In the case of acetophenone hydrazones **3 g-k**, the ^1H NMR spectra revealed the presence of a singlet equivalent to three protons intensity for methyl group attached to the azomethine group (CH_3–C=N) at 2.26–2.34 ppm. The cyclization reaction of the hydrazide hydrazone with acetic anhydride to N-acetyl oxadiazole has been well discussed [41–44]. Herein in the same context, treatment of **3a-k** with acetic anhydride produced N-acetyl oxadiazole derivatives **4a-k** in good yields (Mechanism 1). The reaction would be initiated by nucleophilic addition of acetic anhydride at the azomethine carbon of the carbazone moiety followed by tautomerization, subsequent nucleophilic attack by the unshared electron over the oxygen atom of the hydroxyl group at the benzylic carbon, and loss of acetic acid afford the desired products.

Mechanism 1

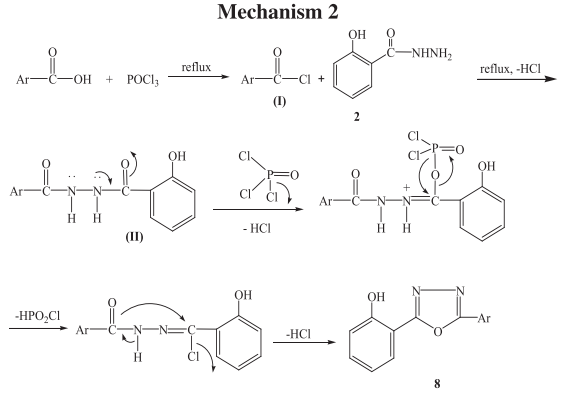


The structures of **4a-k** were supported by spectral methods. The IR spectra revealed the absence of OH and NH bands characteristic for the starting hydrazide hydrazones, and instead they showed the characteristic bands for amide carbonyl and ester carbonyl groups at 1656–1670 and 1733–1776 cm^{-1}, respectively. The ^1H NMR spectra of

4a-k revealed the following signals: a singlet at δ = 2.12–2.88 ppm characteristic for the N–$COCH_3$ protons, another singlet at δ = 2.28–2.97 ppm characteristic for the O-acetyl protons attached to phenyl group (Ph–O–$COCH_3$), and a multiplet at δ = 6.97–8.23 ppm characteristic for the aromatic protons. In the case of **4a-f**, C_2-H of the 1,3,4-oxadiazole ring appeared as a singlet at the deshielding area δ = 6.87–7.12 ppm, while the methyl protons attached to C_2 of the 1,3,4-oxadiazole ring for **4 g-k** appeared as a singlet at δ = 2.22–2.56 ppm. On the other hand, when benzaldehyde hydrazone derivatives (R = H) **3a-f** were stirred for 2 days with concentrated sulfuric acid [45] at room temperature, they underwent cyclization reaction to give 2,3-dihydro-5-(2-hydroxyphenyl)-2-aryl-1,3,4-oxadiazoles **5a-f** (Scheme 1). It is noteworthy that treatment of acetophenone hydrazone derivatives (R = CH_3) **3 g-k** with concentrated sulfuric acid and subsequent neutralization using 10% Na_2CO_3 resulted in formation of the starting 2-hydroxybenzohydrazide **2** and acetophenone derivatives. The structure of 2,3-dihydro-oxadiazole **5a-f** was supported by spectral methods. The IR spectra of **5a-f** revealed the characteristic bands for C=C at 1537–1602, C=N at 1606–1625, NH at 3250–3380, and phenolic OH at 3440–3480 cm^{-1}. The ^1H NMR spectra showed the presence of two exchangeable singlet at δ = 8.66–11.79 ppm and at δ = 8.72–11.89 ppm characteristic for the NH and OH protons, respectively. The C_2-H of the 2,3-dihydro-oxadiazole **5a-f** appeared as a singlet and the aromatic protons appeared as a multiplet at δ = 6.94–8.62 ppm.

Synthesis of 1,3,4-oxadiazoles from 2-hydroxybenzohydrazide. Through previous studies, it has been reported that treatment of some hydrazides with formic acid [46,47] gave 1-formyl-2-acyl hydrazine, the synthesized 1-formyl derivatives were converted to 2-substituted-1,3,4-oxadiazoles by their reaction with phosphorous oxychloride. Likewise, our study showed that the reaction of 2-hydroxybenzohydrazide **2** with either formic acid or acetic acid gave N-formyl or N-acetyl derivative **6a-b** (Scheme 2) and that subsequent dehydrative cyclization of **6a-b** using phosphorous oxychloride gave **7a-b**. The IR spectra of **6a-b** showed the characteristic bands for C=C at 1578–1609, NH–CO–Ph at 1634–1649, NH–CO–R (R = H, CH_3) at 1671–1684, and OH stretching vibration band at 3304–3415 cm^{-1}, while the ^1H NMR spectra showed three exchangeable hydrogens at 10.15–10.34 ppm, 10.50–10.59 ppm and 11.79–11.88 ppm characteristic for NHCOR, *o*–OH–Ph–CO–N*H* and phenolic OH, respectively. The aromatic ring protons of **6a-b** appeared at 6.90–8.12 ppm. In the case of **6a**, the formyl proton (O=C–H) appeared as a singlet at 8.13 ppm. The high chemical shift value for the formyl proton of **6a** was attributed to strong deshielding effect by the electronegative nitrogen atom and anisotropic effect of carbonyl group [48,49]. The ^1H NMR spectra of **6b** showed another singlet at δ = 1.94 ppm of three protons intensity due to incorporation of acetyl group ($COCH_3$). On the other hand, the IR spectra of the 1,3,4-oxadiazoles **7a-b** indicated the presence of stretching vibration bands for C–O–C at 1265–1288, C=C at 1503–1568, C=N at 1609–1640, and OH at 3411–3439 cm^{-1}. The IR spectra of **7a-b** lacked the presence of primary and secondary amine stretching vibration bands characteristic of the starting 2-hydroxybenzohydrazide **2**. The ^1H NMR spectra of **7a-b** showed an exchangeable singlet of one proton intensity at 10.36–10.88 ppm for the phenolic OH group and a multiplet of four protons intensity at 6.91–7.93 ppm for the hydroxyphenyl aromatic protons. The oxadiazole C_5-H of **7a** appeared as a singlet at 6.71 ppm, while the methyl protons attached to position five at the oxadiazole ring in **7b** appeared as a singlet of three protons intensity at 2.83 ppm. One pot cyclization reaction to 1,3,4-oxadiazole derivative was performed by refluxing acid hydrazide, aromatic carboxylic acid, and phosphorous oxychloride [50]. Therefore, when a mixture of 2-hydroxybenzohydrazide **2**, *p*-substituted benzoic acid and phosphorous oxychloride was heated under reflux, it gave 2-(2-hydroxyphenyl)-5-aryl-1,3,4-oxadiazole **8a-b**. According to mechanism **2**, the intermediate diaroyl hydrazine (**II**) will be formed through the reaction of acid chloride (**I**) with acid hydrazide **2**. The reaction proceeds through an ordinary nucleophilic substitution by the electron pair of N-2 atom of the hydrazide to the acid chloride carbonyl group. Finally, cyclodehydration process of the intermediate (**II**) will take place by its reaction with phosphorous oxychloride, which acts as a chlorinating and dehydrating agent to give oxadiazole **8**.

Mechanism 2



The structure of **8a-b** was confirmed by elemental analyses and spectral methods. The IR spectra for **8a-b** do not reveal the characteristic stretching vibration bands of the primary and secondary amine group at the starting hydrazide **2**, but it reveals the OH stretching vibration band at 3133–3290 cm^{-1}. The ^1H NMR spectra of **8a-b** showed a broad exchangeable singlet at 10.38–12.07 ppm characteristic for phenolic proton (OH), while the aromatic protons appeared as a multiplet at 6.71–8.39 ppm.

5-(2-Hydroxyphenyl)-1,3,4-oxadiazol-(3H)-2-one **9** was synthesized through the reaction of the acid hydrazide **2** with ethyl chloroformate under reflux in *n*-butanol. The IR spectrum of **9** showed absorption bands at 1562 (C=C), 1608 (C=N), 1640 (C=O), 3094 (NH), and 3448 cm^{-1} (OH). The ^1H NMR spectrum of **9** showed a multiplet at δ = 6.92–7.89 ppm characteristic for four aromatic protons and two exchangeable singlets at 10.88 ppm and 11.80 ppm characteristic for NH and OH protons, respectively. These data are in agreement with the proposed structure for compound **9**.

5-Chloromethyl-2-(2-hydroxyphenyl)-1,3,4-oxadiazole **10** was prepared by condensation of acid hydrazide **2** with chloroacetic acid using phosphorous oxychloride as cyclising agent [51]. The most characteristic IR bands of 2-hydroxybenzohydrazide **2** appeared at 1597 for C=C, 3270 cm^{-1} for NH_2 and NH, which disappeared in the spectrum of compound **10** with new bands that appeared at 1239 and 1626 cm^{-1} because of C–O–C and C=N stretching vibrations, respectively. The ^1H NMR spectrum of compound **10** showed a singlet at δ = 5.09 ppm because of CH_2–Cl protons, a multiplet at δ = 6.95–7.74 ppm because of aromatic protons, and an exchangeable singlet equivalent to one proton intensity at δ = 10.35 ppm because of OH proton. These data confirmed the conversion of acid hydrazide **2** to 1, 3, 4-oxadiazole derivative **10**. When hydrazide **2** was reacted with carbon disulphide in ethanolic KOH, it gave the corresponding 5-(2-hydroxyphenyl)-1,3,4-oxadiazole-2(3H)-thione **11** in good yield. The absence of the characteristic weak SH stretching band at 2550–2600 cm^{-1} and the appearance of strong C=S stretching band at 1180 cm^{-1} in the IR spectrum of compound **11** confirmed its thione form and excluded the tautomeric thiol structure [52–54]. The IR spectrum of **11** showed also bands at 1266 cm^{-1} (C–O–C stretching of oxadiazole ring), 1576 cm^{-1} (C=C), 1613 cm^{-1} (C=N), 3204 cm^{-1}(NH), and 3333 cm^{-1}(OH). The ^1H NMR spectrum revealed the presence of the two exchangeable singlets at 10.43 ppm and 14.61 ppm characteristic for the oxadiazolyl NH proton and phenolic proton, respectively. The ^1H NMR spectrum showed also a multiplet at 6.93–7.62 ppm equivalent to four aromatic protons.

Synthesis of thiazolidinone, 1,3,4-thiadiazoles, pyrazole and 1,2,4-triazole. In this part, we are interested in the synthesis of different types of heterocyclic compounds to show the importance of 2-hydroxybenzohydrazide in heterocyclic synthesis. The synthetic pathways for our prepared compounds are outlined in Scheme 3. For example, condensation of hydrazone **3a** with thioglycolic acid in dry pyridine gave thiazolidinone derivative **12**. The IR spectrum of **12** lacked the presence of C=N stretching vibration band at the starting hydrazone **3a**. The IR spectrum of the starting hydrazone **3a** showed C=O band at 1630 cm^{-1}. A new strong band at 1699 cm^{-1} in the IR spectrum of **12** provided firm support for ring closure. The most significant evidence for the reaction was the presence of two doublets (dd, 2H, C_5-H of thiazolidine ring, J = 16 and 16 Hz) at δ = 3.79 ppm and 3.93 ppm in the ^1H NMR spectrum of **12** [55]. Geminal splitting was explained by the presence of chiral carbon at C_2 of the thiazolidine ring, which resulted in two diastereotopic hydrogens at C_5-H of the thiazolidine ring. Moreover, the ^1H NMR spectrum of **12** showed a singlet at 6.03 ppm because of C_2-H of the thiazolidine ring. When N-formyl- or N-acetyl-2-hydroxybenzohydrazide **6a-b** was heated under reflux with phosphorous pentasulphide in pyridine, it gave 1,3,4-thiadiazole derivative **13a-b**. The structure of **13** was assigned on the basis of its IR, ^1H NMR, and elemental analysis. The IR spectra of **13** do not reveal the presence of C=O at the starting **6**, but it showed C=N stretching vibration bands at 1624–1630 cm^{-1}. Furthermore, the IR spectra of **13** lacked the presence of two stretching vibration bands for the two secondary amino groups at the starting compound **6**. The ^1H NMR spectra of **13a-b** lacked the presence of two exchangeable singlets characteristic for two amino groups (2 NH) at the starting compound **6**. The IR spectrum of compound **15** revealed the appearance of a new absorption band for C=S. Stretching vibration at 1236 cm^{-1} confirmed a thiosemicarbazide formation [56]. The most significant evidence for the reaction was the presence of four exchangeable singlets expressed NH_2 protons overlapped with aromatic hydrogens at δ = 6.87–7.78 ppm, two NH protons at 9.40 ppm and 10.51 ppm, and OH proton at 11.85 ppm in the ^1H NMR spectrum of **15**. The thiosemicarbazide **15** was converted to 1,3,4-thiadiazole **16** and 1,2,4-triazole **17** by its reaction with concentrated sulfuric acid [57] and 2 N sodium hydroxide [58] solution, respectively. The structures of 1,3,4-thiadiazole **16** and 1,2,4-triazole **17** were confirmed by spectral methods. The IR spectra of **16** showed a new strong absorption band at 1633 cm^{-1} (C=N), and it lacked the presence of C=S and C=O stretching vibration bands in the starting thiosemicarbazide **15**.

The ^1H NMR spectrum of **16** revealed the existence of two exchangeable singlets at δ = 9.25 ppm (NH_2) and 11.75 ppm (OH) instead of four exchangeable singlets characteristic for the starting thiosemicarbazide **15**. In the case of **17**, we have observed that extensive thiol–thione tautomerism exists. In DMSO-d_6 solution, the ^1H NMR spectrum of **17** showed an exchangeable singlet at δ = 13.67 ppm, whereas IR (KBr) spectra of triazole **17** in a solid state indicated a strong absorption band for C=S stretching vibration at 1242 cm^{-1}. It has been reported that the crystal structures of **17**-like compounds correspond to

Table 1

Antimicrobial activities of all the synthesized compounds.

Compounds numbers	MIC in μg/mL and inhibition zone (A in mm) for different organisms					
	Staphylococcus aureus		*Candida albicans*		*Escherichia coli*	
	A	MIC	A	MIC	A	MIC
3a	8	—	13	—	10	—
3b	8	—	15	—	10	—
3c	8	—	15	—	10	—
3d	8	—	15	—	10	—
3e	8	—	13	—	10	—
3f	8	—	13	—	10	—
3 g	8	—	15	—	10	—
3 h	8	—	15	—	10	—
3i	8	—	13	—	10	—
3j	8	—	15	—	10	—
3 k	8	—	13	—	10	—
4a	8	—	25	125	10	—
4b	8	—	15	—	10	—
4c	8	—	15	—	10	—
4d	8	—	15	—	10	—
4e	8	—	15	—	10	—
4f	8	—	15	—	10	—
4 g	8	—	15	—	10	—
4 h	8	—	15	—	10	—
4i	8	—	15	—	10	—
4j	8	—	15	—	10	—
4 k	8	—	15	—	10	—
5a	8	—	15	—	10	—
5b	8	—	15	—	10	—
5c	8	—	15	—	10	—
5d	8	—	15	—	10	—
5e	8	—	15	—	10	—
5f	8	—	15	—	10	—
6a	8	—	18	—	10	—
6b	8	—	15	—	10	—
7a	8	—	15	—	10	—
7b	8	—	15	—	10	—
8a	8	—	15	—	10	—
8b	8	—	15	—	10	—
9	20	62.50	27	62.5	16	62.5
10	11	31.25	30	62.5	10	—
11	8	—	15	—	10	—
12	8	—	15	—	10	—
13a	8	—	15	—	10	—
13b	8	—	15	—	10	—
14	8	—	15	—	10	—
15	15	62.50	20	31.5	10	—
16	8	—	15	—	10	—
17	15	62.50	23	62.5	10	—
Imipenem	30	—	30	—	26	—
DMF	8	—	13	—	10	—

MIC, minimum inhibitory concentration.

the thione form [59,60], but they showed thiol–thione tautomerism in solution.

Antimicrobial activity. A drug is considered to have bacteriostatic or fugistatic activity when it inhibits the growth of bacteria or fungi, respectively, and bactericidal or fungicidal when it kills the bacteria or fungi. Literature survey reveals that the synthesis and evaluation of antimicrobial activity of various heterocyclic compounds have been carried out. Prompted by these observations, the antimicrobial activity of the synthesized compounds was evaluated. All of our compounds were tested for antimicrobial activity against three test organisms: *Staphylococcus aureus* ATCC6538P, *Escherichia coli* ATCC8739 and *Candida albicans* ATCC2091 using Imipenem (10 μg/ disc) as standard drug. The agar well-

diffusion method [61,62] was used for studying the potential activities of these compounds. Minimum inhibitory concentration (MIC) values for the individual compounds that showed inhibition zones >10 were determined by means of the agar well-diffusion method in DMF. The results of antimicrobial activities of our synthesized compounds against *S. aureus and C. albicans* are shown in Table 1 as zone of inhibition (mm) and minimum inhibitory concentration, MIC (μg/mL). The investigation of antimicrobial screening revealed that compound **9** showed significant activity against *E. coli*, whereas the others had no remarkable activity on this strain. Moreover, compound **9** was found to be more active than the others against *S. aureus* and showed moderate activity against *C. albicans*; on the other hand, compound **10** was found to be more active than the others against *C. albicans*, with low significant activity against *S. aureus*. This depends on the different substituents at C-5 position of the oxadiazole ring of both compounds **9**,**10** (−C=O,-CH_2Cl), respectively. Compounds **15**,**17** showed activity against *S. aureus* and *C. albica*ns. Compound **4a** showed activity towards *C. albicans* in the same range with compounds **9**, **15**, **17**, whereas it showed no activity against *S. aureus*.

From the aforementioned results, it can be concluded that the trend of activity against *S. aureus* was observed as follows: **9 > 15=17 > 10,** while **4a** showed no activity, and the trend of activity against *C. albicans* observed was as follows: **10 > 9 > 4a > 17 > 15**.

CONCLUSIONS

Many heterocyclic compounds were prepared starting from 2-hydroxybenzohydrazide and its corresponding hydrazide–hydrazones. The isolated compounds were examined against different microorganisms; structure–activity relationship (SAR) plays an important role in the study of the activities of synthesized compounds. The antimicrobial activities for oxadiazoles depend on substituents at C_5 of the oxadiazole ring.

EXPERIMENTAL

Melting points were taken in open capillary tubes using an Electrothermal apparatus 9100 (Rochford, UK), and they were uncorrected. Elemental microanalyses were performed at the Regional Center for Mycology and Biotechnology, Al-Azhar University, Egypt, using an elemental analyzer Euro EA 3000 (Italy). IR spectra were recorded using potassium bromide disk on a Perkin Elmer Spectrum RXI/FT-IR System (Faculty of Pharmacy, Alexandria University, Egypt) and on a Bruker FT-IR spectrometer Model: Tensor 37 and expressed in wave number (υ_{max}) cm^{-1} (Faculty of Science, Alexandria University, Egypt). The ^{1}H-NMR spectra were measured in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulphoxide (DMSO-d_6) on a Jeol EAC 500 MHz FT-NMR spectrophotometer (Faculty of Science, Alexandria University, Egypt) and on a Bruker AVANCE III Nano Bay 400 MHz FT-NMR spectrophotometer (Faculty of Pharmacy, Cairo University, Egypt) and on a Varian Mercury VX-300 MHz spectrophotometer (Faculty of Science, Cairo University, Egypt). Chemical shifts were recorded in δ as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. Reaction progresses were monitored by thin layer chromatography (TLC) using Macherey-Nagel Alugram Sil G/UV_{254} silica gel plates, and chloroform or chloroform-ethanol (9:1) or (19:1) was used as an eluting system to examine compound purity and reaction completion. The spots were visualized using Vilber Lourmet ultraviolet lamp at 254 = ג and 266 nm or using iodine vapor.

General procedure for preparation of 2-hydroxybenzohydrazide (2). A mixture of methyl salicylate **1** (10 m*M*) and hydrazine hydrate (20 m*M*) was heated under reflux in 50 mL of 95% ethanol for 15 h, then the reaction mixture was concentrated and poured onto crushed ice. The separated crude solid was filtered off, washed successively with water, dried and recrystallized from ethanol to give **2** as colorless needles. The yield of **2** was 77%, m.p. 142–144°C and IR as reported previously in literature [39,40].

General procedure for preparation of hydrazones (3a–k). A mixture of the appropriate 2-hydroxybenzohydrazide **2** (10 m*M*), benzaldehyde, or acetophenone derivatives (10 m*M*) in absolute ethanol (10 mL) and a few drops of acetic acid was refluxed for 5–9 h, the reaction mixture was left to attain room temperature, and the solid matter that separated was filtered off and recrystallized from ethanol to give hydrazones **3a-k**.

***N*-(Phenylmethylidene)-2-hydroxybenzohydrazide (3a).** Compound **3a** was obtained in 88% yield as colorless needles by recrystallization from ethanol, m.p. 244–245°C; IR (KBr): (C=C) 1564, (C=N) 1620, (C=O) 1630, (NH) 3237, (OH) 3450 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz,) δ: 3.32 (s, 1H, NH), 6.94–6.99 (m, 2H, Ar-H), 7.43–7.49 (m, 4H, Ar-H), 7.75–7.77 (m, 2H, Ar-H), 7.88–7.91 (m, 1H, Ar-H), 8.47 (s, 1H, C*H*=N), 11.85 (s, 1H, OH); Anal. calcd. For $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.00; N, 11.67. Found: C, 70.01; H, 4.96; N, 11.63.

***N*-[(4-Chlorophenyl)methylidene]-2-hydroxybenzohydrazide (3b).** Compound **3b** was isolated as colorless crystals in 83% yield by recrystallization from ethanol, m.p. 259–261°C; IR (KBr) : (C=C) 1528, (C=N) 1606, (C=O) 1632, (NH) 3280, (OH) 3452 cm^{-1}; ^{1}H NMR (DMSO-*d* , 500 MHz,) δ: 6.94–7.91 (m, 9H, Ar-H and NH), 8.47 (s, 1H, C*H*=N), 11.86 (s, 1H, OH); Anal. calcd. For $C_{14}H_{11}N_2O_2Cl$: C, 61.09; H, 4.00; N, 10.18; Cl, 13.09. Found: C, 61.12; H, 3.97; N, 10.15; Cl, 13.13.

***N*-[(4-Bromophenyl)methylidene]-2-hydroxybenzohydrazide (3c).** Compound **3c** was obtained in a good yield (87%) as colorless crystals by recrystallization from ethanol, m.p. 243–244°C; IR (KBr): (C=C) 1554, (C=N) 1600, (C=O) 1630, (NH) 3250, (OH) 3441 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ: 6.92–6.95 (m, 2H, Ar-H), 7.40 (m, 1H, Ar-H), 7.62–7.67 (m, 4H, Ar-H), 7.83 (m, 1H, Ar-H), 8.39 (s, 1H, C*H*=N), 11.85 (s, 2H, OH and NH, D_2O exch); Anal. calcd. For $C_{14}H_{11}N_2O_2Br$: C, 52.66; H, 3.45; N, 8.78; Br, 25.08. Found: C, 52.63; H, 3.44; N, 8.74; Br, 25.01.

***N*-[(4-Nitrophenyl)methylidene]-2-hydroxybenzohydrazide (3d).** Compound **3d** was obtained as colorless crystals in 88% yield by recrystallization from ethanol, m.p. 278–279°C; IR (KBr) : (C=C) 1550, (C=N) 1620, (C=O) 1633, (NH) 3251, (OH) 3460 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 3.52 (s, 1H, NH, D_2O exch), 6.93–6.97 (m, 2H, Ar-H), 7.82 (m, 1H, Ar-H), 7.96 (m, 1H, Ar-H), 7.97 (m, 2H, Ar-H), 8.26–8.28 (m, 2H, Ar-H), 8.51 (s, 1H, C*H*=N), 12.02 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.86; N, 14.74. Found: C, 58.94; H, 3.88; N, 14.76.

***N*-[(4-Methoxyphenyl)methylidene]-2-hydroxybenzohydrazide (3e).** Compound **3e** was isolated as colorless crystals in 86% yield by recrystallization from ethanol, m.p. 218–220°C; IR (KBr) : (C=C) 1549, (C=N) 1609, (C=O) 1633, (NH) 3251, (OH) 3441 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.26 (s, 3H, CH_3), 3.52 (s, 1H, NH, D_2O exch), 6.93–6.96 (m, 2H, Ar-H), 7.41 (m, 1H, Ar-H), 7.95–7.97 (m, 3H, Ar-H), 8.26–8.28 (m, 2H, Ar-H), 8.51 (s, 1H, C*H*=N), 12.03 (s,1H, OH, D_2O exch); Anal. calcd. For $C_{15}H_{14}N_2O_3$: C, 66.67; H, 5.19; N, 10.37 Found C, 66.63; H, 5.19; N, 10.36.

***N*-[(2-Hydroxyphenyl)methylidene]-2-hydroxybenzohydrazide (3f).** Compound **3f** was obtained as colorless crystals in a good yield (89%) by recrystallization from ethanol m.p. 273–274°C; IR (KBr) : (C=C) 1555, (C=N) 1616, (C=O) 1635, (NH) 3196, (OH) 3438 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 3.51(s, 1H, NH), 6.88–7.86 (m, 8H, Ar-H), 8.65 (s, 1H, C*H*=N), 11.22 (s, 1H, OH), 12.02 (s, 1H, OH); Anal. calcd. For $C_{14}H_{12}N_2O_3$: C, 65.63; H, 4.69; N, 10.94. Found: C, 65.61; H, 4.66; N, 10.91.

***N*-(Phenylethylidene)-2-hydroxybenzohydrazide (3g).** Compound **3g** was obtained as colorless crystals in 80% yield by recrystallization from ethanol, m.p. 201–202°C; IR (KBr): (C=C) 1547, (C=N) 1607, (C=O) 1639, (NH) 3276, (OH) 3464 cm^{-1}; ^1H NMR (DMSO-*d* , 400 MHz) δ: 2.29 (s, 3H, C*H*$_3$–C=N), 6.96–7.03 (m, 2H, Ar-H), 7.40–7.44 (m, 4H, Ar-H), 7.84–8.00 (m, 3H, Ar-H), 11.11 (s, 1H, NH, D_2O exch), 11.77 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found: C, 70.99; H, 5.49; N, 11.14.

***N*-[(4-Chlorophenyl)ethylidene]-2-hydroxybenzohydrazide (3h).** Compound **3h** was isolated as colorless crystals in 78% yield by recrystallization from ethanol, m.p. 245–246°C; IR (KBr): (C=C) 1557, (C=N) 1604, (C=O) 1642, (NH) 3276, (OH) 3440 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 2.29 (s, 3H, C*H*$_3$–C=N), 6.96–7.00 (m, 2H, Ar-H), 7.47–7.49 (m, 3H, Ar-H), 7.84–7.85 (m, 3H, Ar-H), 11.32 (s, 1H, NH, D_2O exch), 11.76 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_{15}H_{13}N_2O_2Cl$: C, 62.28; H, 4.50; N, 9.69; Cl, 12.30. Found: C, 62.31; H, 4.55; N, 9.65; Cl, 12.26.

***N*-[(4-Bromophenyl)ethylidene]-2-hydroxybenzohydrazide (3i).** Compound **3i** was obtained as colorless crystals in 77% yield by recrystallization from ethanol, m.p. 253–255°C; IR (KBr): (C=C) 1543, (C=N) 1605, (C=O) 1640, (NH) 3205, (OH) 3310 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 2.26 (s, 3H C*H*$_3$–C=N), 6.94–7.00 (m, 2H, Ar-H), 7.37–7.96(m, 6H, Ar-H), 11.34 (s, 1H, NH, D_2O exch), 11.88 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_{15}H_{13}N_2O_2Br$: C, 54.05; H, 3.90; N, 8.41; Br, 24.02. Found: C, 54.01; H, 3.84; N, 8.44; Br, 24.07.

***N*-[(4-Nitrophenyl)ethylidene]-2-hydroxybenzohydrazide (3j).** Compound **3j** was obtained as colorless crystals in a good yield (79%) by recrystallization from ethanol, m.p. 265–266°C; IR (KBr): (C=C) 1553, (C=N) 1606, (C=O) 1638, (NH) 3270, (OH) 3460 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 2.34 (s, 3H, C*H*$_3$–C=N), 6.96–7.00 (m, 2H, Ar-H), 7.40 (m, 1H, Ar-H), 8.05–8.07 (m, 3H, Ar-H), 8.23–8.25 (m, 2H, Ar-H), 11.08 (s, 1H, NH, D_2O exch), 11.46 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.35; N, 14.05. Found: C, 60.23; H, 4.37; N, 14.02.

***N*-[(4-Methylphenyl)ethylidene]-2-hydroxybenzohydrazide (3k).** Compound **3k** was obtained as colorless crystals in 75% yield by recrystallization from ethanol, m.p. 231–233°C; IR (KBr): (C=C) 1579, (C=N) 1606, (C=O) 1636, (NH) 3275, (OH) 3467 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 2.28 (s, 6H, C*H*$_3$–C=N and C*H*$_3$–Ph), 6.96–7.99 (m, 8H, Ar-H), 11.27 (s, 1H, NH), 11.78 (s, 1H, OH); Anal. calcd. For $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.69; H, 5.97; N, 10.41.

General procedure for the preparation of 3-*N*-acetyl-5-[2-acetoxy-phenyl]-2-aryl-2,3-dihydro-1,3,4-oxadiazole derivatives and 3-*N*-acetyl-5-[2-acetoxyphenyl]-2-methyl-2-aryl-2,3-dihydro-1,3,4-oxadiazole derivatives (4a–k). A mixture of hydrazone derivatives **3a-k** (2 m*M*) and acetic anhydride (10 mL) was heated under reflux for 7–9 h. After cooling, the reaction mixture was poured onto crushed ice water with vigorous stirring. The formed precipitate was collected by filtration and recrystallized from ethanol to give **4** as colorless needles.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-phenyl-2,3-dihydro-1,3,4-oxadiazole (4a).** Oxadiazole **4a** was obtained in 77% yield, m.p. 112–114°C; IR (KBr): (C–O–C) 1202, (C=C) 1530, (C=N) 1620, (amide C=O) 1661, (ester C=O) 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.12 (s, 3H, N–CO–CH_3), 2.47 (s, 3H, O–CO–CH_3), 7.02 (s, 1H, C_2-H of oxadiazole), 7.25–7.61 (m, 6H, Ar-H), 8.10–8.14 (m, 3H,

Ar-H); Anal. calcd. For $C_{18}H_{16}N_2O_4$: C, 66.67; H, 4.94; N, 8.64. Found: C, 66.64; H, 4.96; N, 8.60.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-(4-chlorophenyl)-2,3-dihydro-1, 3,4-oxadiazole (4b)**. Oxadiazole **4b** was obtained in 79% yield, m.p. 134–137°C; IR (KBr): (C–O–C) 1193, (C=C) 1557, (C=N) 1626, (amide C=O) 1661, (ester C=O) 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.46 (s, 3H, N–CO–CH_3), 2.56 (s, 3H, O–CO–CH_3), 7.12 (s, 1H, C_2-H of oxadiazole), 7.26–7.62 (m, 5H, Ar-H), 8.04–8.10 (m, 3H, Ar-H); Anal. calcd. For $C_{18}H_{15}N_2O_4Cl$: C, 60.17; H, 4.18; N, 7.80; Cl, 10.03. Found: C, 60.21; H, 4.25; N, 7.88; Cl, 9.98.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-(4-bromophenyl)-2,3-dihydro-1,3,4-oxadiazole (4c)**. Oxadiazole **4c** was obtained in 74% yield, m.p. 133–135°C; IR (KBr): (C–O–C) 1192, (C=C) 1542, (C=N) 1605, (amide C=O) 1661, (ester C=O) 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.29 (s, 3H, N–CO–CH_3), 2.32 (s, 3H, O–CO–CH_3), 6.95 (s, 1H, 53.60; H, 3.72; N, 6.95; Br, 19.85. Found: C, 53.69; H, 3.68; N, 7.03; Br; 19.91.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-(4-nitrophenyl)-2,3-dihydro-1,3,4-oxadiazole (4d)**. Compound **4d** was obtained in 89% yield, m.p. 171–174°C; IR (KBr): (C–O–C) 1192, (C=C) 1542, (C=N) 1599, (amide C=O) 1656, (ester C=O) 1766 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.33 (s, 3H, N–CO–CH_3), 2.35 (s, 3H, O–CO–CH_3), 7.07 (s, 1H, C_2-H of oxadiazole), 7.17–8.34 (m, 8H, Ar-H); Anal. calcd. For $C_{18}H_{15}N_3O_6$: C, 58.54; H, 4.07; N, 11.38. Found: C, 58.50; H, 4.12; N, 11.41.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-(4-methoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole (4e)**. Oxadiazole **4e** was obtained in 82% yield, m.p. 139–141°C; IR (KBr): (C–O–C) 1190, (C=C) 1514, (C=N) 1613, (amide C=O) 1664, (ester C=O) 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.46 (s, 3H,N–CO–CH_3), 2.54 (s, 3H, O–CO–CH_3), 3.88(s, 3H, CH_3), 6.87 (s, 1H, C_2-H of oxadiazole), 7.02–7.57 (m, 5H, Ar-H), 8.03–8.05 (m, 3H, Ar-H); Anal. calcd. For $C_{19}H_{18}N_2O_5$: C, 64.41; H, 5.08; N, 7.91. Found: C, 64.45; H, 5.11; N, 7.95.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-(2-acetoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole (4f)**. Oxadiazole **4f** was obtained in 89% yield, m.p. 164°C; IR (KBr): (C–O–C) 1198, (C=C) 1513, (C=N) 1605, (amide C=O) 1659, (ester C=O) 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.14 (s, 3H, N–CO–CH_3), 2.43 (s, 6H, O–CO–CH_3), 7.10 (s, 1H, C_2-H of oxadiazole), 7.25–7.58 (m, 6H, Ar-H), 8.06–8.07 (m, 2H, Ar-H); Anal. calcd. For $C_{20}H_{18}N_2O_6$: C, 62.83; H, 4.71; N, 7.33. Found: C, 62.86; H, 4.76; N, 7.36.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-methyl-2-phenyl-2, 3-dihydro-1, 3, 4-oxadiazole (4g)**. Compound **4g** was obtained in 63% yield, m.p. 126–128°C; IR (KBr): (C–O–C) 1188, (C=C) 1600, (C=N) 1634, (amide C=O) 1670, (ester C=O) 1776 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.22–2.23 (s, 3H, C_2-CH_3 of oxadiazole), 2.28 (s, 6H, N–CO–CH_3 and O–CO–CH_3), 7.33–7.88 (m, 9H, Ar-H); Anal. calcd. For $C_{19}H_{18}N_2O_4$: C, 67.46; H, 5.33; N, 8.28. Found: C, 67.52; H, 5.37; N, 8.29.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-methyl-2-(4-chlorophenyl)-2,3-dihydro-1,3,4-oxadiazole (4h)**. Oxadiazole **4h** was obtained in 89% yield, m.p. 139°C; IR (KBr): (C–O–C) 1188, (C=C) 1602, (C=N) 1634, (amide C=O) 1669, (ester C=O) 1776 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.23 (s, 3H, C_2-CH_3 of oxadiazole), 2.29 (s, 6H, N–CO–CH_3 and O–CO–CH_3), 7.14–7.47 (m, 7H, Ar-H), 7.49 (m, 1H, Ar-H); Anal. calcd. For $C_{19}H_{17}N_2O_4Cl$: C, 61.13; H, 4.56; N, 7.51; Cl, 9.65. Found: C, 61.19; H, 4.60; N, 7.52; Cl, 9.71.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-methyl-2-(4-bromophenyl)-2 ,3-dihydro-1,3,4-oxadiazole (4i)**. Oxadiazole **4i** was obtained in 92% yield, m.p. 115–117°C; IR (KBr): (C–O–C) 1187, (C=C) 1608, (C=N) 1633, (amide C=O) 1669, (ester C=O) 1776 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.23 (s, 3H, C_2-CH_3 of oxadiazole), 2.29 (s, 6H, N–CO–CH_3 and O–CO–CH_3), 7.16–7.50 (m, 7H, Ar-H), 7.51 (m, 1H, Ar-H); Anal. calcd. For $C_{19}H_{17}N_2O_4Br$: C, 54.68; H, 4.08; N, 6.71; Br, 19.18. Found: C, 54.66; H, 4.11; N, 6.73; Br, 19.21.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-methyl-2-(4-nitrophenyl)-2,3 -dihydro-1,3,4-oxadiazole (4j)**. Oxadiazole **4j** was obtained in 90% yield, m.p. 121–123°C; IR (KBr): (C–O–C) 1193, (C=C) 1606, (C=N) 1634, (amide C=O) 1663, (ester C=O) 1770 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.28 (s, 3H, C_2-CH_3 of oxadiazole), 2.29 (s, 3H, N–CO–CH_3), 2.30 (s, 3H, O–CO–CH_3), 7.16–7.75 (m, 6H, Ar-H), 8.22–8.23 (m, 2H, Ar-H); Anal. calcd. For $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.44; N, 10.97. Found: C, 59.57; H, 4.39; N, 10.94.

***3-N*-Acetyl-5-[2-acetoxyphenyl]-2-methyl-2-(4-methylphenyl)-2,3-dihydro-1,3,4-oxadiazole (4k)**. Oxadiazole **4 k** was obtained in 69% yield, m.p. 112–114°C; IR (KBr): (C–O–C) 1188, (C=C) 1591, (C=N) 1633, (amide C=O) 1670, (ester C=O) 1775 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.48 (s, 3H, CH_3–Ph), 2.56 (s, 3H, C_2–CH_3 of oxadiazole), 2.88 (s, 3H, N–CO–CH_3), 2.97 (s, 3H, O–CO–CH_3), 6.97 (m, 2H, Ar-H), 7.25 (m, 2H, Ar-H), 7.57 (m, 1H, Ar-H), 7.59 (m, 2H, Ar-H), 7.78–7.80 (m, 1H, Ar-H); Anal. calcd. For $C_{20}H_{20}N_2O_4$: C, 68.18; H, 5.68; N, 7.95. Found: C, 68.21; H, 5.71; N, 7.94.

General procedure for the synthesis of 2,3-dihydro-5-(2-hydroxy-phenyl)-2-aryl-1,3,4-oxadiazoles (5a–f). In a conical flask, a mixture of N-[phenylmethylidene]-2-hydroxybenzohydrazide derivatives **3a-f** (2 m*M*) and 10 mL of concentrated H_2SO was stirred at room temperature for 2 days. The formed mixture was treated with 50 mL cold H_2O, and the formed solid matter was filtered off, washed with 10% Na_2CO (50 mL), and recrystallized from ethanol/chloroform to give 5 as yellow crystals.

2,3-Dihydro-5-(2-hydroxyphenyl)-2-phenyl-1,3,4-oxadiazole (5a). Compound **5a** was obtained in 79% yield, m.p. 203–204°C; IR (KBr): (C–O–C) 1215, (C=C) 1537,

(C=N) 1606, (NH) 3284, (OH) 3459 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.48–7.91 (m, 10 H, Ar-H and C_2-H of oxadiazole), 8.72 (s, 2H, OH, NH); Anal. calcd. For $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.00; N, 11.67. Found: C, 70.06; H, 4.97; N, 11.64.

2,3-Dihydro-5-(2-hydroxyphenyl)-2-(4-chlorophenyl)-1,3,4-oxadiazole (5b). Compound **5b** was obtained in 68% yield, m. p. 178–179°C; IR (KBr): (C–O–C) 1207, (C=C) 1589, (C=N) 1622, (NH) 3255, (OH) 3480 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 6.94–8.46 (m, 9H, Ar-H and C_2-H of oxadiazole), 11.79 (s, 1H, NH), 11.89 (s, 1H, OH); Anal. calcd. For $C_{14}H_{11}N_2O_2Cl$: C, 61.09; H, 4.00; N, 10.18; Cl, 13.09. Found: C, 61.11; H, 4.03; N, 10.21; Cl, 13.06.

2,3-Dihydro-5-(2-hydroxyphenyl)-2-(4-bromophenyl)-1,3,4-oxadiazole (5c). Compound **5c** was obtained in 77% yield, m.p. 218–219°C; IR (KBr): (C–O–C) 1207, (C=C) 1585, (C=N) 1625, (NH) 3250, (OH) 3440 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 7.38–7.80 (m, 9H, Ar-H and C_2-H of oxadiazole), 8.66 (s, 1H, NH, D_2O exch), 9.95 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_{14}H_{11}N_2O_2Br$: C, 52.66; H, 3.45; N, 8.78; Br, 25.08. Found: C, 52.66; H, 3.44; N, 8.74; Br, 25.11.

2,3-Dihydro-5-(2-hydroxyphenyl)-2-(4-nitrophenyl)-1,3,4-oxadiazole (5d). Compound **5d** was obtained in 69% yield, m. p. 210–212°C; IR (KBr): (C–O–C) 1207, (C=C) 1572, (C=N) 1619, (NH) 3264, (OH) 3460 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 7.67–8.61 (m, 9H, Ar-H and C_2-H of oxadiazole), 9.80 (s, 1H, NH), 11.45 (s, 1H, OH); Anal. calcd. For $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.86; N, 14.74. Found: C, 58.98; H, 3.89; N, 14.77.

2,3-Dihydro-5-(2-hydroxyphenyl)-2-(4-methoxyphenyl)-1,3,4-oxadiazole (5e). Compound **5e** was obtained in 83% yield, m.p. 171–173°C; IR (KBr): (C–O–C) 1215, (C=C) 1602, (C=N) 1623, (NH) 3345, (OH) 3462 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 3.84 (s, 3H, CH_3), 6.94–8.62 (m, 9H, Ar-H and C_2-H of oxadiazole), 10.08 (s, 1H, NH), 11.78 (s, 1H, OH); Anal. calcd. For $C_{15}H_{14}N_2O_3$: C, 66.67; H, 5.19; N, 10.37. Found: C, 66.63; H, 5.17; N, 10.34.

2,3-Dihydro-5-(2-hydroxyphenyl)-2-(2-hydroxyphenyl)-1,3,4-oxadiazole (5f). Compound **5f** was obtained in 81% yield, m.p. 184–87°C; IR (KBr): (C–O–C) 1201, (C=C) 1573, (C=N) 1624, (NH) 3380, (OH) 3465 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.96–7.34 (m, 9H, Ar-H and C_2-H of oxadiazole), 8.70 (s, 1H, NH, D_2O exch), 11.40 (s, 1H, OH, D_2O exch), 11.96 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_{14}H_{12}N_2O_3$: C, 65.63; H, 4.69; N, 10.94. Found: C, 65.62; H, 4.71; N, 10.91.

General procedure for preparation of *N*-formyl 2-hydroxybenzohydrazide and *N*-acetyl-2-hydroxybenzohydrazide (6a–b). A mixture of 2-hydroxybenzohydrazide **2** (5 m*M*) in 15 mL formic acid or acetic acid was heated under reflux for 25 h, and the reaction mixture was evaporated under reduced pressure. The formed solid matter was treated with 25 mL cold water, filtered off, and recrystallized from ethanol to give **6** as colorless needles.

***N*-Formyl-2-hydroxybenzohydrazide (6a).** Compound **6a** was obtained in 68% yield, m.p. 184–187°C; IR (KBr): (C=C) 1609, (N*H*–CO–Ar) 1649, (N*H*–COH) 1684, (NH) 3120, (NH) 3268, (OH) 3304 cm^{-1}; ^1H NMR (DMSO-*d* , 300 MHz) δ: 6.91–7.01 (m, 2H, Ar-H), 7.41–7.47 (m, 1H, Ar-H), 7.81–8.12 (m, 1H, Ar-H), 8.13 (s, 1H, H–C=O), 10.34 (s, 1H, N*H*–CHO), 10.59 (s, 1H, *o*–OH–Ph–CO–N*H*); 11.79 (s, 1H, OH); Anal. calcd. For $C_8H_8N_2O_3$: C, 53.33; H, 4.44; N, 15.56. Found: C, 53.31; H, 4.42; N, 15.60.

***N*-Acetyl-2-hydroxybenzohydrazide (6b).** Compound **6b** was obtained in 73% yield, m.p. 175–176°C; IR (KBr): (C=C) 1578, (N*H*–CO–Ar) 1634, (N*H*–$COCH_3$) 1671, (NH) 3198, (NH) 3320, (OH) 3415 cm^{-1}; ^1H NMR (DMSO-*d* , 300 MHz) δ: 1.94 (s, 3H, CH_3–C=O), 6.90–6.97 (m, 2H, Ar-H), 7.40–7.46 (m, 1H, Ar-H), 7.86–7.89 (m, 1H, Ar-H), 10.15 (s, 1H, N*H*–$COCH_3$, D_2O exch), 10.50 (s, 1H, *o*–OH–Ph–CO–N*H*, D_2O exch), 11.88 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_9H_{10}N_2O_3$: C, 55.67; H, 5.15; N, 14.43. Found: C, 55.69; H, 5.19; N, 14.47.

General procedure for the preparation of 2-(2-hydroxyphenyl)-1,3,4-oxadiazole and 2-(2-hydroxyphenyl)-5-methyl-1,3,4-oxadiazole (7a–b). To a solution of *N*-formyl-2-hydroxybenzohydrazide **6a** or N-acetyl-2-hydroxybenzo-hydrazide **6b** (10 m*M*) in xylene (150 mL), phosphorous oxychloride (10 m*M*) was added. The mixture was heated under reflux for 16 h, the solvent was evaporated under reduced pressure, and the residue was recrystallized form ethanol to give **7** as colorless needles.

2-(2-Hydroxyphenyl)-1,3,4-oxadiazole (7a). Compound **7a** was obtained in 65% yield, m.p. 136–138°C; IR (KBr) : (C–O–C) 1265, (C=C) 1568, (C=N) 1609, (OH) 3411 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.71 (s, 1H, C_5-H of oxadiazole), 6.91–7.01 (m, 2H, Ar-H), 7.49–7.54 (m, 1H, Ar-H), 7.91–7.93 (m, 1H, Ar-H), 10.36 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_8H_6N_2O_2$: C, 59.26; H, 3.70; N, 17.28. Found: C, 59.28; H, 3.66; N, 17.25.

2-(2-Hydroxyphenyl)-5-methyl-1,3,4-oxadiazole (7b). Compound **7b** was obtained in 61% yield, m.p. 120–123°C; IR (KBr): (C–O–C) 1288, (C=C) 1503, (C=N) 1640, (OH) 3439 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.83 (s, 3H, CH_3), 6.92–6.97 (m, 2H, Ar-H), 7.43 (m, 1H, Ar-H), 7.90–7.91 (m, 1H, Ar-H), 10.88 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_9H_8N_2O_2$: C, 61.36; H, 4.55; N, 15.91. Found: C, 61.34; H, 4.59; N, 15.96.

General procedure for the preparation of 2-(2-hydroxyphenyl)-5-aryl-1,3,4-oxadiazole (8a–b). A mixture of 2-hydroxybenzohydrazide **2** (10 m*M*), aromatic acid (10 m*M*) and phosphorous oxychloride (10 m*M*) was heated under

reflux for 18–22 h; the reaction mixture was left to cool at room temperature and then slowly poured onto crushed ice (50 g) and kept overnight. The separated solid mass was filtered, dried, and purified by recrystallization from ethanol to give **8** as colorless needles.

2-(2-Hydroxyphenyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (8a). Compound **8a** was obtained in 75% yield, m.p. 163–165°C; IR (KBr): (C–O–C) 1231, (C=C) 1558, (C=N) 1608, (OH) 3133 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.71–6.72 (m, 2H, Ar-H), 6.90–6.91 (m, 2H, Ar-H), 6.93 (m, 2H, Ar-H), 7.52–7.53 (m, 1H, Ar-H), 7.85–8.27 (m, 1H, Ar-H), 12.08 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_{14}H_9N_2O_2Cl$: C, 61.54; H, 3.97; N, 10.26; Cl, 13.19. Found: C, 61.65; H, 4.03; N, 10.31.

2-(2-Hydroxyphenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (8b). Compound **8b** was obtained in 74% yield, m.p. 215°C; IR (KBr): (C–O–C) 1232, (C=C) 1556, (C=N) 1606, (OH) 3290 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 6.99–7.07 (m, 2H, Ar-H), 7.44 (m, 1H, Ar-H), 7.88 (m, 1H, Ar-H), 8.26–8.39 (m, 4H, Ar-H), 10.38 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_{14}H_9N_3O_4$: C, 59.36; H, 3.18; N, 14.84. Found: C, 59.39; H, 3.21; N, 14.87.

5-(2-Hydroxyphenyl)-1,3,4-oxadiazol-(3H)-2-one (9). A mixture of 2-hydroxybenzohydrazide **2** (5 m*M*), ethyl chloroformate (5 m*M*), and *n*-butanol (20 mL) was heated under reflux for 20 h, and the reaction mixture was kept to cool at room temperature. The formed solid matter was filtered, washed with water, dried, and recrystallized from ethanol to give **9** as colorless needles in 75% yield, m.p. 303–305°C; IR (KBr): (C–O–C) 1249, (C=C) 1562, (C=N) 1608, (C=O) 1640, (NH) 3094, (OH) 3448 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 6.92–6.97 (m, 2H, Ar-H), 7.42 (m, 1H, Ar-H), 7.88–7.89 (m, 1H, Ar-H), 10.88 (s, 1H, NH, D_2O exch), 11.80 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_8H_6N_2O_3$: C, 53.93; H, 3.37; N, 15.73. Found: C, 53.91; H, 3.39; N, 15.77.

5-Chloromethyl-2-(2-hydroxyphenyl)-1,3,4-oxadiazole (10). A mixture of 2-hydroxybenzohydrazide **2** (5 m*M*), chloroacetic acid (5 m*M*), and 10 mL phosphorous oxychloride was heated under reflux on a water bath for 10 h. The reaction mixture was cooled and poured onto crushed ice (50 g) with continuous stirring. The solid mass that separated was neutralized with (30 mL) sodium carbonate solution (10%), filtrated, washed well with water, dried, and recrystallized from ethanol to give **10** as colorless needles in 88% yield, m.p. 110°C; IR (KBr): (C–O–C) 1239, (C=C) 1589, (C=N) 1626, (OH) 3458 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ: 5.09 (s, 2H, CH_2), 6.95–7.05 (m, 2H, Ar-H), 7.42 (m, 1H, Ar-H), 7.72–7.74 (m, 1H, Ar-H), 10.35 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_9H_7N_2O_2Cl$: C, 51.18; H, 3.32; N, 13.27; Cl, 17.06. Found: C, 51.18; H, 3.36; N, 13.29; Cl, 17.11.

5-(2-Hydroxyphenyl)-1,3,4-oxadiazole-2-(3H)-thione (11). A mixture of 2-hydroxybenzohydrazide **2** (10 m*M*), potassium hydroxide (10 m*M*), and carbon disulphide (10 mL) in (50 mL) of 95% ethanol was heated under reflux for 12 h, and the formed mixture was concentrated and cooled to attain room temperature then acidified with dilute HCl (10 mL). The solid mass that separated out was recrystallized from ethanol to give **11** as colorless needles in 81% yield, m.p. 186–188°C; IR (KBr): (C=S) 1180, (C–O–C) 1266, (C=C) 1576, (C=N) 1613, (NH) 3204, (OH) 3333 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 6.9–7.02 (m, 2H, Ar-H), 7.40 (m, 1H, Ar-H), 7.61–7.62 (m, 1H, Ar-H), 10.43 (s, 1H, NH, D_2O exch), 14.61 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_8H_6N_2O_2S$: C, 49.48; H, 3.09; N, 14.43; S, 16.49. Found: C, 49.47; H, 3.11; N, 14.46; S, 16.52.

***N*-[2-Phenyl-4-oxo-1,3-thiazolidine-3-yl]-2-hydroxybenzamide (12).** A mixture of the appropriate N-(phenylmethylidene)-2-hydroxybenzohydrazide **3a** (10 m*M*) and thioglycolic acid (10 m*M*) in dry pyridine (10 mL) was heated under reflux for 16 h and left to attain room temperature. The reaction mixture was poured onto cold dilute HCl (15 mL), the residue that formed was filtered off and recrystallized from ethanol to give **12** as colorless needles, yield 92%, m.p. 165–167°C; IR (KBr): (C=C) 1600, (C=O) 1646, (C=O of thiazolidine ring) 1699, (NH) 3253, (OH) 3441 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.79 and 3.92 (dd, 2H, C_5-H of thiazolidine ring, J = 16 and 16 Hz), 6.03 (s, 1H, C_2-H of thiazolidin ring), 6.71–6.73 (m, 2H, Ar-H), 7.25–7.40 (m, 7H, Ar-H), 9.35 (s, 1H, NH), 11.15 (s, 1H, OH); Anal. calcd. For $C_{16}H_{14}N_2O_3S$: C, 61.15; H, 4.46; N, 8.92; S, 10.19. Found: C, 61.13; H, 4.41; N, 8.89; S, 10.22.

General procedure for preparation of 2-(2-hydroxyphenyl)-1,3,4 thiadiazole and 2-(2-hydroxyphenyl)-5-methyl-1,3,4-thiadiazole (13a–b). A solution of N-formyl-2-hydroxybenzohydrazide and N-acetyl-2-hydroxybenzohydrazide **6a-b** (10 m*M*) in pyridine (20 mL) was treated with phosphorous pentasulphide (10 m*M*). The mixture was heated under reflux for about 20 h, the solvent was evaporated, and the residue that separated was washed successively with water, dried, and recrystallized form ethanol to give **13**

2-(2-Hydroxyphenyl)-1,3,4-thiadiazole (13a). 1,3,4-Thiadiazole derivative **13a** was obtained in good yield (71%), m.p. 223–226°C; IR (KBr): (C=C) 1594, (C=N) 1624, (OH) 3463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.73 (s, 1H, C_5-H of thiadiazole), 6.93–6.95 (m, 2H, Ar-H), 7.24–7.30 (m, 1H, Ar-H), 7.75–7.77 (m, 1H, Ar-H), 10.46 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_8H_6N_2OS$: C, 53.93; H, 3.37; N, 15.73; S, 17.98. Found: C, 54.02; H, 3.35; N, 15.68; S, 18.04.

2-(2-Hydroxyphenyl)-5-methyl-1,3,4-thiadiazole (13b). 1,-3,4-Thiadiazole derivative **13b** was obtained in 70% yield, m.p. 188–189°C; IR (KBr): (C=C) 1588, (C=N) 1630, (OH) 3461 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.81–2.83 (s, 3H, CH_3), 6.92 (m, 1H, Ar-H), 7.08–7.10 (m, 1H, Ar-H),

7.43–7.44 (m, 2H, Ar-H), 10.94 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_9H_8N_2OS$: C, 56.25; H, 4.17; N, 14.58; S, 16.67. Found: C, 56.23; H, 4.19; N, 14.55; S, 16.69.

1-(2-Hydroxybenzoyl)-3-methyl-1H-pyrazol-5(4H)-one (14). A mixture of 2-hydroxybenzohydrazide **2** (5 m*M*) and ethyl acetoacetate (5 m*M*) was heated under reflux for 25 h. The formed mixture was left to cool at room temperature; the solid that separated out was filtered off, dried, and recrystallized from ethanol to give **14** as colorless needles in 75% yield, m.p. 118–120°C, and IR is identical to that published in literature [56].

1-(2-Hydroxybenzoyl)-3-thiosemicarbazide (15). A mixture of 2-hydroxybenzohydrazide **2** (2 m*M*), excess amount of ammonium thiocyanate (6 m*M*), hydrochloric acid (8 mL, 35%) in absolute ethanol (50 mL) was heated under reflux for 22 h. The formed mixture was evaporated under reduced pressure, and the residue that separated out was poured on crushed ice (20 g) with continuous stirring. The solid that formed was filtered, dried, and recrystallized from ethanol to give **15** as colorless needles in 86% yield, m.p. 189–190°C; IR (KBr): (C=S) 1236, (C=C) 1540, (C=O) 1655, (NH_2) 3199, (NH) 3304, (OH) 3388 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ: 6.87–7.78 (m, 6H, Ar-H and NH_2, D_2O exch), 9.40 (s, 1H, NH, D_2O exch), 10.51 (s, 1H, NH, D_2O exch), 11.85 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_8H_9N_3O_2S$: C, 45.50; H, 4.27; N, 19.91; S, 15.17. Found: C, 45.49; H, 4.28; N, 19.88; S, 15.14.

5-Amino-2-(2-hydroxyphenyl)-1,3,4-thiadiazole (16). A mixture of 1-(2-hydroxybenzoyl)-3-thiosemicarbazide **15** (5 m*M*) was treated with concentrated sulfuric acid (10 mL). The mixture was heated on a water bath at 90°C with stirring for 2 h, cooled, then poured onto ice water (30 g) and neutralized with cold concentrated ammonium hydroxide solution (60 mL). The formed precipitate was filtered, washed with cold water, dried, and recrystallized from ethanol to give **16** as colorless needles. The yield of **16** was 81%, m.p. 118–119°C; IR (KBr): (C=C) 1601, (C=N) 1633, (NH) 2918, (NH) 2957, (OH) 3433 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 6.95–8.17 (m, 4H, Ar-H), 9.25 (s, 2H, NH_2, D_2O exch), 11.75 (s, 1H, OH, D_2O exch); Anal. calcd. For $C_8H_7N_3OS$: C, 49.74; H, 3.63; N, 21.76; S, 16.58. Found: C, 49.71; H, 3.61; N, 21.77; S, 16.62.

4H-5-(2-Hydroxyphenyl)-1,2,4-triazole-3-thiol (17). A mixture of 1-(2-hydroxybenzoyl)-3-thiosemicarbazide **15** (1 m*M*) and (10%) sodium hydroxide solution (15 mL) was heated under reflux for 3 h. The formed mixture was cooled acidified by 10% hydrochloric acid (8 mL). The formed solid matter was filtered and recrystallized from ethanol to give **17** as colorless needles in 83% yield, m.p. 282–285°C; IR (KBr) : (C=S) 1242, (C=C) 1566, (C=N) 1621, (NH) 3194, (OH) 3443 cm^{-1}; ^1H NMR (DMSO-*d* , 500 MHz) δ: 6.89–6.97 (m, 2H, Ar-H), 7.31 (m, 1H, Ar-H), 7.60–7.61 (m, 1H, Ar-H), 10.20 (s, 1H, NH, D_2O exch), 13.19 (s, 1H, OH, D_2O exch), 13.67 (s, 1H, SH, D_2O exch); Anal. calcd. For $C_8H_7N_3OS$: C, 49.74; H, 3.63; N, 21.76; S, 16.58. Found: C, 49.73; H, 3.60; N, 21.78; S, 16.52.

Determination of antimicrobial activity. Cultures of three different microorganisms, namely *E. coli*, *S. aureus*, and *C. albicans*, were used to investigate the antimicrobial activities of all synthesized compounds. The antimicrobial activities were assayed biologically using diffusion plate technique. The experiments were carried out by pouring spore suspension 10^6 colon-forming units (CFU) per mL of the test strain to 75 mL of nutrient agar medium at 45°C, mixed well and then poured into a 15 cm sterile metallic *Petri* plate. The medium was allowed to solidify, and 8 mm wells were dug with a sterile metallic borer, then a DMF solution of the test sample (1 mL) at 1 mg/mL was added to the respective wells. DMF was served as negative control, and the standard antimicrobial drug Imipenam is used as positive control. The layer was allowed to set for 30 min and incubated at optimum incubation temperature 28 ± 2°C. Test organism growth may be affected by the inhibitory action of the test compound, and so, a clear zone around the disc appeared as an indication of the inhibition of the test organism growth. The size of clearing zone is proportional to the inhibitory action of the test compound. Measurements were considered after 72 h for fungi and 24 h for bacteria.

Preparation of different concentrations for the tested compounds. All the synthesized compounds were dissolved separately to prepare a stock solution containing 1000 µg/mL of DMF, and so, 10 mg of different synthesized compounds was dissolved in 10 mL of the DMF; thus, 1 mL of the resulted solution gives 1000 µg/mL. Dilution was conducted by adding 1 mL of the aforementioned solution to 1 mL of DMF to give half concentration of the first solution. Successive concentrations like 250, 125, and 62.5 µg/mL were prepared in a similar manner. The tubes were mixed well after each addition, and all the tubes were inoculated with one loopful of one test organism. The process was repeated with a different test organism. Both a positive control and a negative control were also prepared to confirm the nutritive property and sterility, respectively, of the prepared medium. The tubes were incubated at 25°C for 48 h, and the presence or absence of growth organisms was observed after incubation.

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