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Synthesis, Characterization, and Biological Evaluation of 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole and 3,6-diphenyl[1,2,4]triazole[3,4-][1,3,4]thiadiazole Derivatives

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ABSTRACT

A series of 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole 3(a-c) and 3,6-iphenyl[1,2,4]triazole[3,4-][1,3,4] thiadiazole 6(a-g) derivatives were synthesized. Compounds 3(a-c) were synthesized by the reaction of substituted benzohydrazide with different benzoic acids in the presence of $POCl_3$. Cyclocondensation of the SH and NH_2 groups of compound 5(a-b) with appropriate benzoic acid derivatives in the presence of phosphoryl chloride gave 3,6-diphenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives 6(a-g). The synthesized compounds were screened for their antimicrobial and antioxidant activities. Among the tested, compounds 6a and 6d displayed very good antibacterial activity. Compound 6a showed good antifungal activity against all the fungal strains. Compound 6g displayed good activity against Aspergillus flavus. Compounds 6a and 6d showed promising 2,2-diphenylpicrylhydrazyl radical scavenging activity.

Key words: *Oxadiazole, Triazole, Thiadiazole, Antimicrobial, Antioxidant.*

1. INTRODUCTION

Nitrogen and oxygen containing five-membered heterocycles are important bioactive agents, due to its vast pharmacological and industrial applications. Syntheses of such heterocyclic compounds are of pharmaceutical importance and foremost task for chemists. 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives are heterocyclic compounds which exhibit remarkable pharmacological activities. It has been known that the activity of azo linkage increases with the incorporation of the suitable heterocyclic moiety. Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical interest. 2,5-substituted diphenyl-1,3,4-oxadiazoles are associated with diverse biological activities by the virtue of -N=C-O- grouping. Tetrazole, thiadiazole, quinoline, and indole derivatives are well known for their significant biological activities. A large number of 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles has been reported to exhibit various biological activities. Examples of such compounds bearing the 1,2,4-triazole moieties are fluconazole, a powerful azole antifungal agents well as the potent antiviral N-nucleoside ribavirin. 1,3,4-thiadiazole analogs are associated with diverse biological activities probably by virtue of toxophoric -N=C-S-group.

Heterocyclic azo compounds are well known for their medicinal importance and are recognized for their use as antineoplastics [1], antidiabetics [2], antiseptics [3], anti-inflammatory, antibacterial [4,5], and other useful chemotherapeutic agents [6,7]. Azo dyes are used as hypnotic drugs for the nervous system in detecting cancer as chemotherapeutic agents and are involved in the structure of nucleic acids in living cells. Azo dyes are known to be involved in a number of biological reactions such as inhibition of DNA, RNA, protein synthesis, carcinogenesis, and nitrogen fixation [3,8]. Evans blue and Congo red are being studied as HIV inhibitors. This effect is believed to be caused by binding of azo dyes to both protease and reverse transcriptase of this virus [9]. 1,2,3-oxadiazoles can also act as HIV integrase inhibitors [10]. 1,3,4-oxadiazoles are five-membered heterocyclic compounds having significant position in synthetic and medicinal chemistry due to their wide array of biological activities such as antifungal [11], antimicrobial [12], anti-inflammatory, analgesic [13-15], hypolipidemic [16] antitubercular [17,18], anticonvulsant [19,20], cytotoxicity [21], and antioxidant agent [22,23]. The ability of 1,3,4-oxadiazole heterocyclic compounds to undergo various chemical reactions has made them important for molecule planning because of their privileged structure, which has an enormous biological potential. Two examples of compounds containing the 1,3,4-oxadiazole unit currently used

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in clinical medicine are raltegravir, an antiretroviral drug [24], and zibotentan an anticancer agent [25].

In view of biological importance of substituted 1,3,4-oxadiazole and thiadiazole derivatives, it was contemplated to synthesize and characterize substituted 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole derivatives 3(a-c) and 3,6-diphenyl[1,2,4] triazolo[3,4-b][1,3,4]thiadiazole derivatives 6(a-g) with a view to explore their potency as better chemotherapeutic agents. The newly synthesized compounds were screened for their antimicrobial and antioxidant activities.

2. EXPERIMENTAL

2.1. Materials and Methods

All the chemicals used were of analytical grade. Melting points were determined on a Bu¨chi Melting Point B-545 apparatus. A purity of the compounds was checked by TLC on Merck 60 F-254 silica gel plates with visualization by UV-light using ethyl acetate and n-hexane as solvent system.^{1}H-NMR spectra were recorded on Bruker (400 MHz) spectrometer instruments in DMSO-d_6 and chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were recorded on LC-MS Aglilent 1100 series with MSD (Ion trap) using 0.1% aqueous TFA in acetonitrile system on C18-BDS column for 10 min.

3. GENERAL PROCEDURE

3.1. Synthesis of 1,3,4-oxadiazole Derivatives 3(a-c)

To a mixture of equimolar 1 and substituted benzoic acid was added phosphorous oxychloride (10 vol) at 0°C. The contents were slowly heated to 115°C and maintained at that temperature for 16h under nitrogen. The reaction completion was monitored by TLC. After completion, the reaction mass was cooled to room temperature and poured into ice-cold water (250 ml). The product was extracted with ethyl acetate; the organic layer was washed with 10% sodium bicarbonate solution followed by water wash and saturated sodium chloride solution. The organic layer was dried over sodium sulfate and concentrated under vacuum to residue. The crude compounds were purified by flash chromatography using ethyl acetate and hexane as eluent.

2-(4-chloro-2-methylphenyl)-5-(2-methylphenyl)-1,3,4-oxadiazole (3a): Off white solid, Yield - 61%; m.p. 255-258.5°C; ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 2.71 (s, 6H), 7.28-7.97 (m, 7H, Ar-H); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 164.49, 163.66, 140.34, 138.56, 137.18, 131.88, 131.34, 131.20, 130.15, 128.98, 126.54, 122.85, 121.57, 22.7,22.2; MS(LCMS) 285.6[M+]: Mol. formula; $C_{16}H_{13}ClN_2O$.

2-(4-chloro-2-methylphenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (3b): Yellow solid, Yield - 64%, m.p.: 229-232°C; ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 2.69 (s, 3H), 7.42-8.76 (m, 7H, Ar-H); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 165.49, 164.74, 137.33, 134.12, 132.22, 131.56, 130.69, 130.67, 130.34,125.34, 125.22, 124.88, 123.18, 122.67, 22.29; MS(LCMS); m/z 316.6[M+]: Mol. formula; $C_{15}H_{10}ClN_3O_3$.

2-(4-chloro-2-methylphenyl)-5-[2-fluoro-5-(trifluoromethyl)phenyl]-1,3,4-oxadiazole (3c): Light brown solid, Yield - 67%; m.p.: 262-266.5°C; ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 2.67 (s, 3H), 7.43-8.09 (m, 6H, Ar-H); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.49, 160.74, 137.33, 133.12, 132.22, 131.55, 130.99, 130.77, 130.34, 125.34, 125.22, 124.88, 123.88, 122.67, 121.98, 22.21; MS(LCMS); m/z: 357.6[M+]: Mol. formula; $C_{16}H_9ClF_3N_2O$.

3.2. Synthesis of 4-amino-5-(2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (5a) or 4-amino-5-(5-chloro-2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (5b)

Hydrazine hydrate (45.38 mmol) was added to compound 4a or 4b (45.38 mmol) and the contents were refluxed for 2 h. After the reaction completion (checked by TLC), the reaction mixture was acidified with concentration HCl. The precipitate was filtered and dried under vacuum to obtain compound 5a or 5b.

4-amino-5-(2-methyl phenyl)-4*H*-1,2,4-triazole-3-thiol (5a): White solid, Yield - 87.7%, m.p.: 167-170°C; ^{1}H-NMR: 2.27 (s, 3H), 5.49 (bs, 2H), 7.18-7.37 (m, 4H, Ar-H), 14.25 (s, 1H); Mol formula: $C_9H_{10}N_4S$; MW: 206.3, $[m/z]^+$: 207.4.

3.3. General Procedure for the Synthesis of Thiadiazole Derivatives 6(a-g)

To a stirred solution of 1,2,4-triazole-3-thiol 5a/5b (4.84 mmol) in phosphoryl chloride (10 mL), was added benzoic acid (1 eq.) and the reaction mixture was refluxed about 10 h. The reaction was monitored by TLC, after the reaction completion, the mass was quenched with ice-water, and the product was extracted with ethyl acetate (2×75 mL). The organic layer was washed 10% sodium bicarbonate solution (50 mL) followed by water and saturated sodium chloride solution. The organic layer was treated with anhydrous sodium sulfate and concentrated under vacuum to afford title compounds. These compounds were purified by column chromatography using ethyl acetate and petroleum ether.

3-(2-methylphenyl)-6-(4-nitrophenyl)[1,2,4] triazolo[3,4-b][1,3,4]thiadiazole (6a): Off white solid, Yield - 83%; m.p. 126-129°C; IR (KBr, υ_{max}, cm^{-1}): 2925 (Ar-CH), 1595 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 2.49 (s, 3H), 7.28-7.99 (m, 7H, Ar-H); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 165.16, 164.30, 162.63, 154.79, 146.58,

137.81, 134.75, 134.66, 131.61, 130.86, 130.78, 129.85, 126.79,121.97, 116.38, 21.1; MS(LCMS): m/z 338.3[M+]: Mol. formula; $C_{16}H_{11}N_5O_2S$.

6-(2,6-Dimethylphenyl)-3-(2-methylphenyl)[1,2,4] triazole[3,4,b][1,3,4]thiadiazole (6b): White solid, Yield - 73%, m.p 152-154.5°C; H^1-NMR (400 MHz, DMSO-d_6, δ ppm) 2.26 (s, 6H), 2.41 (s, 3H), 7.26 -8.16 (m, 7H, Ar-H); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm), 168.0, 148.0, 143.3, 138.7, 138.2, 136.6, 134.2, 132.6, 130.9, 129.3, 126.3, 126.1, 21.8, 21.2; MS(LCMS): m/z320.3[M]: Mol. formula; $C_{18}H_{16}N_4S$.

6-(3-Bromo-5-iodophenyl)-3-(2methylphenyl) [1,2,4]triazole[3,4,b][1,3,4]thiadiazole (6c): Yellow solid, Yield - 76%; m.p 141-142°C; H^1-NMR (400 MHz, DMSO-d_6, δ ppm) 2.48 (s, 3H), 7.29-8.17 (m, 7H, Ar-H); C^{13}-NMR (400 MHz, DMSO-d_6, δ ppm) 165.16, 164.3, 162.6, 154.79, 146.5, 137.8, 134.7, 131.6, 129.8, 126.8, 125.07, 121.9, 121.7, 116.6, 116.38, 21.2. MS(LCMS), m/z497.0[M]: Mol. formula; $C_{16}H_{10}BrIN_4S$.

6-[2-Fluoro-5-(trifluoromethyl)phenyl]-3-(2-methylphenyl)[1,2,4]triazolo[3,4 b][1,3,4] thiadiazole (6d): Light brown solid, Yield - 89%; m.p. 126-129°C; ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 2.41 (s, 3H), 7.67-8.20 (m, 6H, Ar-H) 8.24 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 165.16, 164.30, 162.63, 154.79, 146.58, 137.81, 134.75, 134.66, 131.61, 130.86, 130.78, 129.85, 126.79, 121.97, 116.38, 21.10; MS(LCMS) m/z 379.2[M]: Mol. formula; $C_{17}H_{10}F_4N_4S$.

6-(2,6-dimethylphenyl)-3-(4-chloro-2-methylphenyl)[1,2,4]triazole[3,4,b][1,3,4] thiadiazole (6e): White solid, Yield - 75%, m.p 152-154.5°C; ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm) 2.26 (s, 6H), 2.41 (s, 3H), 7.26-8.16 (m, 6H, Ar-H); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm), 168.0, 148.0, 143.3, 138.7, 138.2, 136.6, 134.2, 132.6, 130.9, 129.3, 126.3, 126.1, 21.8, 21.2; MS(LCMS) m/z354.07[M+]: Mol. formula; $C_{18}H_{15}ClN_4S$.

6-(3-bromo-5-iodophenyl)-3-(4-chloro-2-methylphenyl)[1,2,4]triazole[3,4,b][1,3,4]: thiadiazole (6f): Brown solid, Yield - 70%; m.p 141-142°C; ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm), δ 2.48 (s, 3H), 7.65-8.36 (m, 6H, Ar-H); ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm), 168.0, 148.0, 143.3, 143.0, 138.2, 136.6, 135.6, 134.5, 134.2, 131.6, 129.3, 128.8, 126.3, 124.8, 96.6, 21.2; MS(LCMS): m/z 531.6[M+]: Mol. formula; $C_{16}H_9BrClIN_4S$.

6-(3-bromophenyl)-3-(4-chloro-2-methylphenyl) [1,2,4]triazole[3,4,b][1,3,4]thiadiazole (6g): White solid, Yield - 72%, m.p. 149-153°C; ^{1}H-NMR (400 MHz, DMSO-δ ppm), δ 2.45 (s, 3H), 7.61-8.25 (m, 7H, Ar-H): ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm) 165.16, 164.3, 162.6, 154.79, 146.5, 137.8, 134.7, 131.6, 129.8, 126.8, 125.07, 121.9, 121.7, 116.6, 116.38, 21.2, MS(LCMS) 405.7, [m/z]= 406[M+]: Mol. formula; $C_{16}H_{10}BrClN_4S$.

4. BIOLOGICAL ACTIVITY

4.1. Antimicrobial Activity

Antimicrobial activity of the synthesized compounds was tested against five bacterial strains using agar well diffusion method[xviii]. Dimethylsulfoxide (DMSO) was used as a solvent control. The bacterial cultures were inoculated on nutrient agar (Merck) and fungal culture was inoculated on Potato Dextrose agar media (20 mL). The test compounds were dissolved in DMSO to get a concentration of 12.79 M, and 100 µl of this sample was loaded into the wells of agar plates directly. Plates inoculated with the bacteria were incubated at 37°C for 24 h and the fungal culture was incubated at 25°C for 72 h. All determinations were done in triplicates. The streptomycin and fluconazole were used as standard drugs for antibacterial and antifungal activities, respectively.

4.2. Antioxidant Activity

4.2.1. Free radical scavenging activity by 2,2-diphenylpicrylhydrazyl (DPPH) method

Free radical-scavenging capacities of synthesized compounds were determined according to the reported procedure[xix]. The newly synthesized compounds at different concentrations (25-100 µmol/L) were added to each test tube and volume was made up to 4 ml using methanol. To this, 3 ml of 0.004% DPPH in methanol was added, and the mixtures were incubated at room temperature under the dark condition for 30 min. The absorbance was recorded at 517 nm using UV-Visible spectrophotometer (Shimadzu UV-1800, Japan). Butylated hydroxytoluene (BHT), dissolved in distilled water was used as a reference. A control sample was prepared using the same volume without any compound and BHT, 95% methanol served as blank. The test was performed in triplicate, and the results were averaged. Radical scavenging activity was calculated using the formula:

$$\% \text{ of radical scavenging activity} = [(A_{control} - A_{test})/A_{control}] \times 100$$

Where $A_{control}$ is the absorbance of the control sample (DPPH solution without test sample) and A_{test} is the absorbance of the test sample (DPPH solution + test compound).

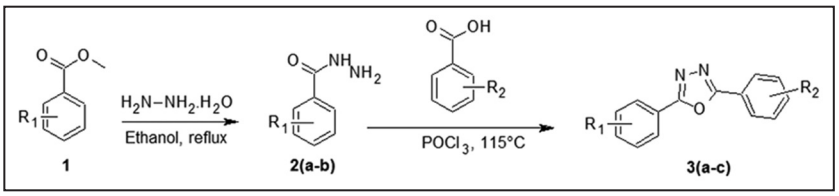
5. RESULTS AND DISCUSSION

5.1. Chemistry

The synthetic strategy for the synthesis of these series of compounds has been described in the Schemes 1 and 2. 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole 3(a-c) were synthesized by the reaction of 2-methylbenzohydrazide (2a) or 5-chloro-2-

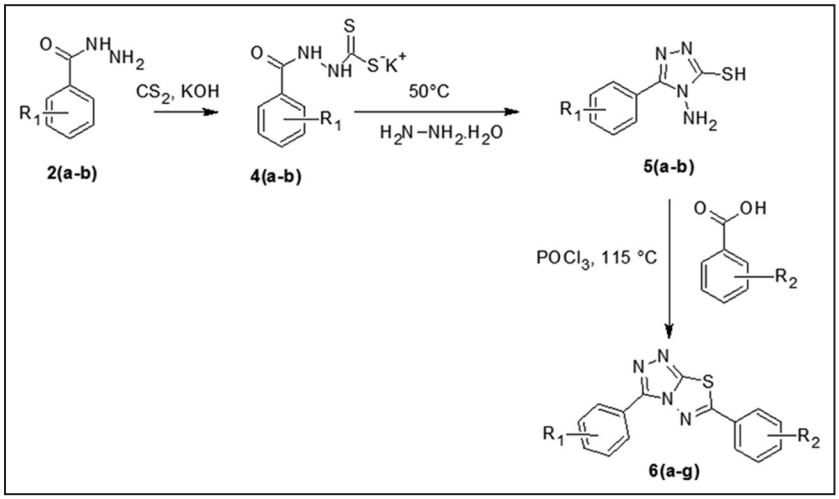
methylbenzohydrazide (2b) with different benzoic acids in the presence of phosphorous oxychloride. Aminothiols 5(a-b) were obtained from their corresponding potassium salts of 2-(2-methylbenzoyl) hydrazinecarbodithiol (4a)/2-(5-chloro-2-methylbenzoyl)hydrazinecarbodithiol (4b) by reacting with hydrazine hydrate. Further Cyclocondensation of the SH and NH_2 groups of aminothiols 5(a-b) with appropriate benzoic acid derivatives in the presence of phosphoryl chloride gave 3,6-diphenyl[1,2,4] triazolo[3,4-b][1,3,4]thiadiazole derivatives 6(a-g). The newly synthesized compounds were characterized by spectroscopic methods such as IR, NMR, and mass spectroscopic data.

The IR spectrum of compounds 2-(4-chloro-2-methylphenyl)-5-(2-methylphenyl)-1,3,4-oxadiazole (3a) exhibited a band at 1040/cm corresponding to C-F



Comp	R^1	R^2
19a	4-Cl,2-CH_3	2-CH_3
19b	4-Cl,2-CH_3	4-NO_2
19c	4-Cl,2-CH_3	5-F,2-CF_3

Scheme 1: Synthesis of 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole derivatives 3(a-c)



Comp.	R^1	R^2
19a	4-Cl,2-CH_3	2-CH_3
19b	4-Cl,2-CH_3	4-NO_2
19c	4-Cl,2-CH_3	5-F,2-CF_3
22a	2-CH_3	4-NO_2
22b	2-CH_3	2,6-CH_3
22c	2-CH_3	3-Br,5-I
22d	2-CH_3	5-F,2-CF3
22e	4-Cl,2-CH_3	2,6-CH_3
22f	4-Cl,2-CH_3	3-Br,5-I
22g	4-Cl,2-CH_3	3-Br

Scheme 2: Synthesis of 3,6-diphenyl[1,2,4]triazole[3,4-][1,3,4]thiadiazole derivatives 6(a-g)

stretching, 1606/cm corresponding to C=N stretching. ^{1}H-NMR displayed multiplet between 7.2-8.0 ppm corresponding to seven aromatic protons and a singlet at 2.7 ppm corresponding to six methyl protons. The IR spectrum of compound (6c) exhibited absorption band at 546/cm corresponding to C-Br stretching, 1021/cm corresponding to C-I stretching, 1595/cm corresponding to C=N stretching frequency. ^{1}H-NMR spectrum exhibited multiplet between 7.4 and 8.2 ppm corresponding to seven aromatic protons and a singlet at 2.67 ppm corresponding to three methyl protons. The ^{13}C-NMR spectra data were consistent with the assigned structure; triazole -C=N- carbon of 6c was observed at 154.79 ppm; thiadiazole -N=C=N-S carbon was observed at 165.16 ppm. Further, the mass spectrum of compound 6c showed a molecular ion peak M^{+} at m/z 497.

5.2. Antimicrobial Activity

The investigation of antibacterial screening revealed that the test compounds showed varying degree of activity against all the tested micro-organisms. Among the tested compounds 6a and 6d displayed very good activity with zone of inhibition 6-13 mm. compound 19b is inactive against all the tested bacterial strains. The rest of the compounds displayed less activity. The antibacterial activity results are tabulated in Table 1.

From antifungal activity results, it was found that the compounds 6a showed good antifungal activity against all the fungal strains. Compound 6g displayed good activity against *Aspergillus flavus*. Compounds 3b and 6g are inactive against the tested fungal strains. The antifungal activity results are tabulated in Table 2.

5.3. DPPH Radical Scavenging Activity

The investigation of (DPPH) radical scavenging activity of the newly synthesized compounds 6(a-g) revealed that compounds 6a and 6d which contains electron withdrawing group(s) on phenyl ring have shown promising antioxidant property when compared to standard. The remaining compounds displayed less

Table 1: Antibacterial activity data of compounds 3(a-c) and 6(a-g).

Compounds	*Escherichia coli*		*Bacillus substitus*		*Psedomonas aeruginosa*	
	1	**0.5**	**1**	**0.5**	**1**	**0.5**
3a	5.4±0.3	1.7±0.4	4.2±0.5	1.4±0.2	0	0
3b	0	0	0	0	0	0
3c	5.2±0.3	2.3±0.4	4.3±0.5	2.4±0.3	5.2±0.6	2.4±0.5
6a	10±0.1	8±0.2	13±0.2	10±0.1	8±0.1	6±0.2
6b	9±0.1	7±0.2	8±0.1	5±0.2	6±0.1	4±0.2
6c	4±0.1	1±0.1	4±0.2	2±0.2	3±0.2	0.2±00.1
6d	13±0.1	10±0.2	11±0.2	8±0.2	10±0.1	7±0.2
6e	5±0.1	3±0.2	4±0.1	3±0.2	6±0.1	3±0.2
6f	6±0.1	3±0.2	4±0.2	2±0.1	5±0.1	3±0.2
6g	3±0.2	2±0.1	5±0.1	3±0.2	4±0.2	2±0.1
Streptomycin	18±0.2	14±0.1	16±0.2	12±0.2	16±0.2	13±0.2

Table 2: Antifungal activity data of compounds 3(a-c) and 6(a-g) oxadiazole and thiadiazoles.

Compounds	*Aspergillus flavus*		*Chrysosporium keratinophilum*		*Candida albicans*	
	1	**0.5**	**1**	**0.5**	**1**	**0.5**
3a	4±0.3	3±0.5	4±0.5	2.5±0.2	0	0
3b	0	0	0	0	0	0
3c	5.2±0.3	2.3±0.4	4.3±0.5	2.4±0.3	5.2±0.6	2.4±0.5
6a	9±0.2	6±0.2	8±0.2	7±0.2	10±0.2	7±0.1
6b	4±0.2	2±0.2	4±0.1	1±0.1	5±0.1	2±0.2
6c	6±0.2	4±0.4	5±0.2	3±0.2	6±0.1	4±0.2
6d	6±0.1	5±0.2	7±0.2	6±0.1	8±0.2	7±0.2
6e	0	0	0	0	0	0
6f	5±0.1	3±0.2	3±0.1	2±0.1	4±0.2	1±0.1
6g	7±0.2	5±0.3	5±0.1	2±0.2	6±0.2	4±0.1
Fluconazole	14±0.2	10±0.1	16±0.2	14±0.2	23±0.2	20±0.2

Table 3: Scavenging effect of selected synthesized compounds on stable radical DPPH 6(a-g).

Compounds	DPPH assay in %
6a	64.6
6b	32.5
6c	39.7
6d	62.3
6e	16.1
6f	22.3
6g	58.7
BHT	94.3

DPPH: 1,1-diphenylpicrylhydrazyl,
BHT: Butylatedhydroxytoluene

activity. The DPPH radical scavenging activity results are tabulated in Table 3.

6. CONCLUSION

In the present investigation, we have synthesized series of 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole 3(a-c) and 3,6-iphenyl[1,2,4]triazole[3,4-][1,3,4]thiadiazole 6(a-g) derivatives were synthesized and screened for their antimicrobial and antioxidant activities. A some of the tested compounds showed very good biological activities.

7. ACKNOWLEDGMENT

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