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Design, Synthesis and Evaluation of Newer Diaryl Ether Analogues Integrated with 1, 3, 4 Oxadiazole Core

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ABSTRACT

In this study, we describe the design and synthesis of diaryl ether analogs that incorporated 1,3,4 oxadiazole functionality to improve their biological activity. A series of 1-(2-(3-Phenoxyphenyl)-5-((substituted-amino aryl)methyl)-1,3,4-oxadiazol-3(2*H*)-yl) ethanone have been synthesized in good yields and characterized by IR, NMR, mass spectral analysis. Compounds were evaluated for their preliminary in vitro antibacterial activity against some Gram-positive, Gram-negative bacteria as well for antifungal activity and also screened for antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ strain. Some compounds showed potential antibacterial and antitubercular activities.

INTRODUCTION

There are numerous frequently found substructures of many biological important in natural products [1-3]. These substructures have the great impact on life science. Either as single heterocyclic derivatives or infusion with the others is emerging as the most explored center to obtain clinically significant compounds. It is well known in the literature that nitrogen and oxygen containing compounds are essentially used in medicine for the treatment of different kinds of fungal and bacterial infections along with the treatment of gastric ulcer, cancer, etc. Schiff bases are the precursors of countless versatile organic processes for the production of intermediates/products and in making the carbon-nitrogen linkage. Five-membered heterocyclic compounds show various types of biological activities. A diphenyl ether nucleus is an important unit found in several synthetic and natural agents possessing a wide range of pharmacological activities such as Vancomycin and Riccardin [4]. Triclosan has broad-spectrum antimicrobial activity against a variety of Gram-positive and Gram-negative bacteria [5] and continuous studies have been focused on it [6]. A series of heterocycle substituted diphenyl ether derivatives and all the compounds showed good antitubercular activity against *Mycobacterium tuberculosis strain H37Rv* [7]. Diaryl amide skeleton is also a class of privileged structure with a broad range of biological activities such as antiviral [8], anti-inflammatory [9], analgesic [10], antibacterial [11], melanin synthesis inhibitor [12], and S1P4 antagonist [13]. Recently in a high throughput screening for inhibitors of *M. tuberculosis* $H_{37}Rv$ for several diaryl amides [14] have been studied. The oxadiazoles are classified into four different groups [15] depending on the position of nitrogen and oxygen atoms in the ring. These are 1:2:3-oxadiazole, 1:2:5 oxadiazole, 1:2:4 oxadiazole and 1:3:4 oxadiazole. [1,3,4]-oxadiazoles: The 2,5-disubstituted [1,3,4] oxadiazoles are heterocyclic compounds [16] which serve both as biomimetic and reactive pharmacophores. A wide variety of substituted 1,3,4-oxadiazoles have attracted considerable attention in the field of drug discovery because of their wide range of pharmacological activities. Oxadiazoles have occupied a specific place in the field of medicinal chemistry due to its wide range of activities [17]. As a part of our continuous search for potential bioactive molecules, the pharmacological potency of 1,3,4-oxadiazole, as well as diaryl ether analogs, has prompt us to synthesize the newer hybrid compounds in a single molecular framework, a series of hybrid compounds were synthesized and screened for in vitro-biological activity. Therefore, this work deals with the synthesis of a series of 1-(2-(3-phenoxyphenyl)-5-((substituted-amino aryl) methyl)-1,3,4-oxadiazol-3(2*H*)-yl) ethanone.

MATERIALS AND METHODS:

Chemistry protocols:

All the reagents were of commercial grade and were used without purification. Reaction progress was checked by TLC. Melting points were determined with the open capillary method on a Buchi apparatus and are uncorrected. IR spectra were recorded on a Nicolet 5700 FT-IR instrument as KBr disc. ^{1}H NMR spectra were recorded on Bruker 400 MHz Spectrometer using $CDCl_3$ and DMSO-d6 as solvents and TMS as an internal standard. All chemical shifts were reported as δ values (ppm). Mass spectra were recorded using Agilent GCMS.

Biology protocols:

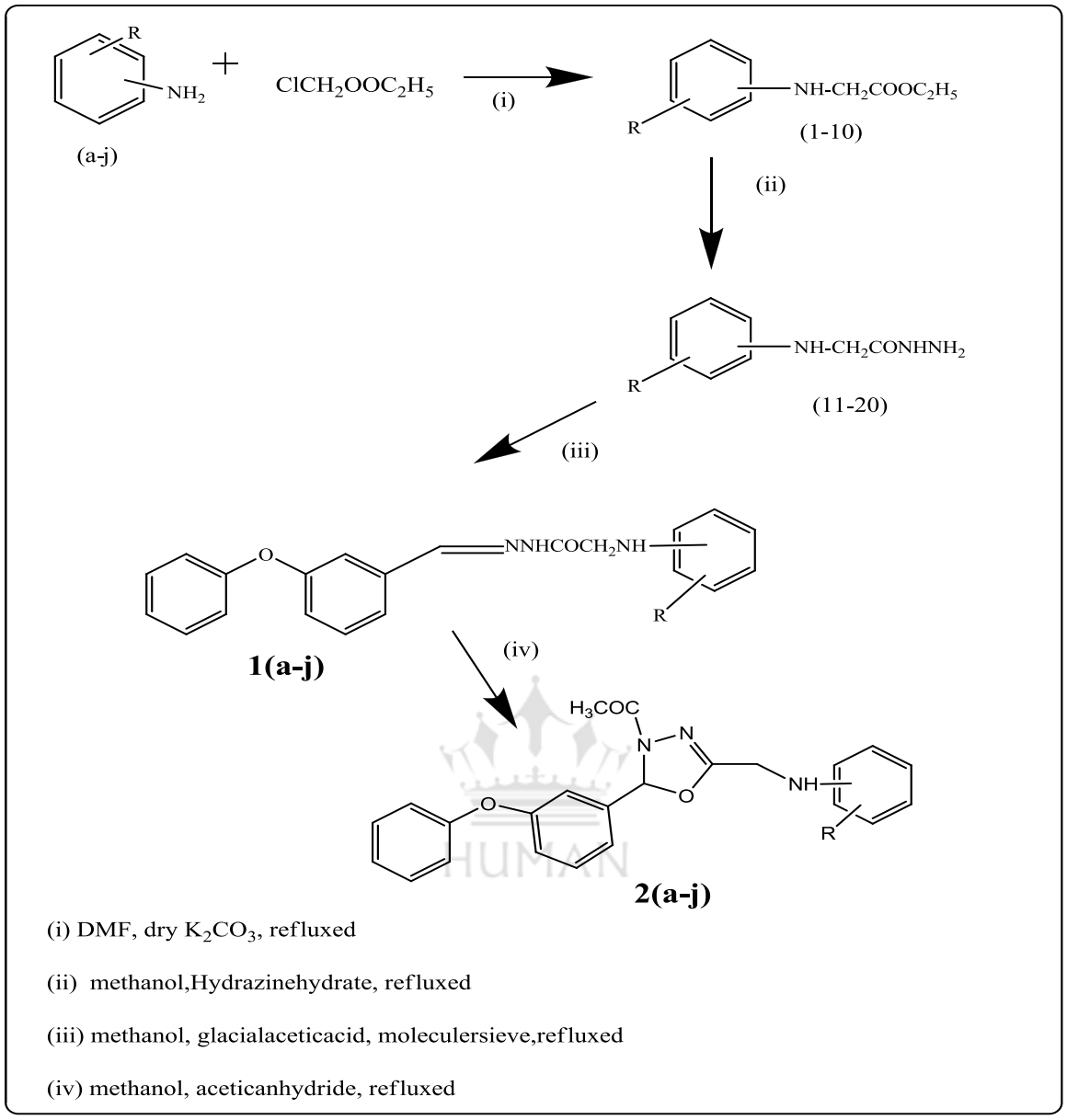
Antimicrobial activity

The broth dilution method was used for in vitro antibacterial activity. The synthesized compounds 2(a-j) were screened against the bacterial strain. The minimum inhibitory concentration MIC-100µM, 250µM was carried out using microdilution susceptibility method and compared with standard drugs Ampicillin, chloramphenicol, ciprofloxacin, and nystatin. Alternatively, newly synthesized derivatives were tested as potential antifungal agents with MIC-100µM, 500µM against reference drug Nystatin, Griseofulvin.

In vitro anti-mycobacterial activity

All the derivatives were screened for *in vitro* anti-mycobacterial activity by MABA method; MIC (99 % inhibition at 50µM); against Strain: *Mycobacterium tuberculosis* H37Rv with Test Concentration: 100µg/ml in DMSO.

Scheme:



General procedure

Synthesis of A (1-10): ethyl-2-(substituted-arylamino)acetate.

To a solution of aromatic amine (0.1mol) in dry DMF (25 ml), anhydrous potassium carbonate (2.5mol) and ethyl chloroacetate (1.25mol) were added at r.t. The resultant mixture was stirred at 80^{o}C for 15-17 hrs. The reaction was monitored by TLC on silica gel using mobile phase ethyl acetate: toluene (3:7 v/v). After the completion of the reaction cooled to room temperature and poured the reaction mixture to a large amount of water with stirring.

The solid separated was filtered, washed with an excess of water and dried. The crude product was purified by recrystallization from methanol with good yield m.p. 186^{o}C.

Synthesis of B (11-20): 2-(substituted-arylamino) acetohydrazide.

To a solution of ethyl-2-(substituted-arylamino)acetate (0.05mol) in methanol (30 ml), added hydrazine hydrate (0.1 mol) at r.t. The reaction mixture was refluxed on a water bath for 10-12 h. The reaction was monitored by TLC on silica gel using ethyl acetate: toluene (2:8 v/v). After the completion of the reaction, the solvent was evaporated under reduced pressure and the crude solid was washed with water and recrystallized from acetone to give 2-(4-chlorophenylamino) acetohydrazide with a good yield m.p. 198^{o}C.

Synthesis of (Z)-2-(substituted-arylamino)-N'-(3-phenoxybenzylidene) acetohydrazide: 1(a-j).

To a stirred solution of 2-(substituted-arylamino) acetohydrazide (1.0mol) in methanol (30 ml) was added *m*-phenoxybenzaldehyde (1.5mol) and few drops of glacial acetic acid. The reaction mixture was refluxed on a water bath for 6-8 h. The reaction was monitored by TLC on silica gel using methanol: dichloromethane (1:9 v/v). The solvent was evaporated under reduced pressure and the crude was poured onto ice-water; filtered and dried. The crude solid recrystallized inappropriate alcohol to give the yellow color product of (Z)-2-(substituted-arylamino)-N'-(3-phenoxybenzylidene) acetohydrazide with a good yield.

Synthesis of 1-(2-(3-Phenoxyphenyl)-5-((substituted-amino aryl) methyl)-1,3,4-oxadiazol-3(2*H*)-yl) ethanone: 2(a-j)

A mixture of (Z)-2-(substituted-arylamino)-N'-(3-phenoxybenzylidene) acetohydrazide (1mol) and acetic anhydride (15ml) was heated under reflux for 4h. The reaction progress was monitored by TLC toluene: methanol (7:3 v/v) as a mobile phase. After completion of reaction cooled it to attain the room temperature, excess acetic anhydride was decomposed by water and the mixture was stirred for further 30 min. The separated product was filtered, washed with water, dried and recrystallized in an appropriate solvent to give the product.

Results of desired products

Comp.	Ar- substituted amino aryl	% yield	M.P Range (±5) °C
2a	4,6-dimethoxypyrimidin-2-amine	60	225
2b	Piperazine	65	238
2c	p-toluidine	55	215
2d	4-amino-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one	75	232
2e	4-chloroaniline	60	257
2f	5-chloro-2-methylamine	62	245
2g	phenylethylamine	55	194
2h	1H-1,2,3-triazole	60	210
2i	5-methylbenzo[d]thiazol-2-amine	60	205
2j	5-methylthiazol-2-amine	64	220

Spectral Data

2a:1-(5-((4,6-dimethoxypyrimidin-2-ylamino)methyl)-2-(3-phenoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone.

IR (KBr): NH at 3039cm^{-1}, C=O at 1723cm^{-1}; **^{1}HNMR**: 7.01-7.43(m, 9H, Ar-H), 6.8(s, 1H, -CH-oxadiazole), 5.8(s, 1H, -CH-pyrimidine), 4.3(s, 1H, -NH-Ar), 3.8(s, 6H, -OCH_3-pyrimidine), 3.4(s, 2H, -CH_2-Ar), 2.3(s, 3H, -CH_3-oxadiazole); ^{13}CMR: 174.2(C_4,C_6-pyridine), 170.7($COCH_3$), 163.2(C_2-oxadiazole), 159(C-O-C,diarylether), 156.3(C_2-pyrimidine), 116.5-142.5(Ar-C), 82.4(C_5-oxadizole), 75.17(C_5,-pyrimidine), 56.8(-OCH_3-pyrimidine), 53.8(-CH2-Ar), 49.97(C_2, C_6-piperazine), 26.2(-CH_3-oxadiazole), **MS** (EI) *m*/*z*: 449 (M^+).

2b: 1-(2-(3-Phenoxyphenyl)-5-(piperazin-1-ylmethyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone.

IR (KBr): NH at 3045cm^{-1}, C=O at 1710cm^{-1}; **^{1}HNMR** (δ ppm): 7.11-7.48(m, 9H, Ar-H), 6.66(s, 1H, -CH-oxadiazole), 2.78(m, 4H, -CH_2-piperazine), 2.62(s, 2H, -CH_2-Ar), 2.58(m, 4H, --CH_2-piperazine), 2.38(s, 3H, -CH3CO-oxadiazole), 1.86(s, 1H, -NH-piperazine) ; **^{13}CMR**: 174.7($COCH_3$), 168.2(C_2-oxadiazole), 160(C-O-C,diarylether), 116.5-142.5(Ar-C), 86.4(C_5-oxadizole), 55.17(C_3, C_5,-piperazine), 53.8(-CH2-Ar), 49.97(C_2, C_6-piperazine), 25.2(-CH_3-oxadiazole), **MS** (EI) *m*/*z*: 380 (M^+), 381 (M + 1).

2c: **1-(2-(3-Phenoxyphenyl)-5-((p-tolylamino)methyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone.**

IR (KBr): NH at 3110cm^{-1}, C=O at 1690cm^{-1}; **^{1}HNMR**: 6.87-7.48(m, 13H, Ar-H), 6.58(s, 1H, -CH-oxadiazole), 4.1(s, 1H, -NH-Ar), 3.38(s, 2H, -CH_2-Ar), 2.4(s, 3H, -CH_3), 2.1(s, 3H, -CH_3CO-oxadiazole);**^{13}CMR**: 178.7($COCH_3$), 168.2(C_2-oxadiazole), 156(C-O-C,diarylether), 114.5-137.5(Ar-C), 88.4(C5-oxadizole), 55.17(-CH2-NH), 20.3(-CH_3-oxadiazole).MS(EI) *m*/*z*: 401 (M^+).

2d:4-((4-Acetyl-5-(3-phenoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methylamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one.

IR (KBr): NH at 3060cm^{-1}, C=O at 1745cm^{-1}; **^{1}HNMR**: 6.87-7.98(m, 14H, Ar-H), 6.58(s, 1H, -CH-oxadiazole), 2.89(s, 3H, -CH3-pyrazolidinone), 2.78(s, 2H, -CH_2-Ar), 2.4(s, 3H, -CH_3), 2.1(s, 3H, -CH_3CO-oxadiazole), 1.89(s, 1H, -NH-Ar); **^{13}CMR**: 172.7($COCH_3$), 169.8(-C=O, pyrazolidinone),165.2(C_2-oxadiazole),156(C-O-C,diarylether),138.2(C5-pyrazolidinone), 118.2(C4-pyrazolidinone), 114.5-137.5(Ar-C), 86.4(C5-oxadizole), 52.17(-CH2-NH), 41.3(-N-CH3-pyrazolidinone),27.3(-CH_3-oxadiazole),24.6(-CH3-pyrazolidinone);**MS(EI)** *m*/*z*: 498 (M^+).

2e:1-(5-((4-Chlorophenylamino)methyl)-2-(3-phenoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl) ethanone.

IR (KBr): NH at 3083cm^{-1}, C=O at 1673cm^{-1}; **^{1}HNMR** (δ ppm): 6.87-7.48(m, 13H, Ar-H), 6.38(s, 1H, -CH-oxadiazole), 4.2(s, 1H, -NH-Ar), 3.28(s, 2H, -CH_2-Ar), 2.18(s, 3H, -CH_3CO-oxadiazole); **^{13}CMR:** 168.7($COCH_3$), 166.2(C_2-oxadiazole), 160(C-O-C,diaryether), 116.5-148.5(Ar-C), 87.4(C_5-oxadizole), 53.8(-CH2-Ar), 24.2(-CH_3-oxadiazole), **MS** (EI) *m*/*z*: 422 (M^+), 424 (M + 2)

2f:1-(5-((5-Chloro-2-methylphenylamino)methyl)-2-(3-phenoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone.

IR (KBr): NH at 3125cm^{-1}, C=O at 1720cm^{-1}; **^{1}HNMR** (δ ppm): 6.98-7.78(m, 14H, Ar-H), 6.68(s, 1H, -CH-oxadiazole), 4.1(s, 1H, -NH-CH_2), 3.58(s, 2H, -CH_2-Ar), 2.68(s, 2H, -CH_3-Ar), 2.18(s, 3H, -CH_3CO-oxadiazole),); **^{13}CMR**: 169.7($COCH_3$), 165.2(C_2-oxadiazole), 159(C-O-C,diarylether), 116.5-142.5(Ar-C), 84.4(C_5-oxadizole), 53.8 (-CH_2-NH), 29.2(-CH_3-oxadiazole),26.5(-CH_3-Ar); **MS** (EI) *m*/*z*: 436 (M^+), 438(M + 1)

2g:1-(5-((benzylamino)methyl)-2-(3-phenoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone.

IR (KBr): NH at 3060cm^{-1}, C=O at 1740cm^{-1}; **^{1}HNMR**(δ ppm): 7.13-7.78(m,14H,Ar-H), 6.58(s,1H,-CH-oxadiazole), 3.58(s,2H,-CH_2-Ar), 2.68(s,2H,-CH_2-NH), 2.18(s,3H,-CH_3CO-oxadiazole), 1.97(s,1H,-NH-CH_2); **^{13}CMR**:165.7($COCH_3$), 160.2(C_2-oxadiazole), 158(C-O-C,diarylether), 116.5-142.5(Ar-C), 85.4(C_5-oxadizole), 53.8(-CH_2-Ar), 49.87(-CH_2-NH), 26.2(-CH_3-oxadiazole), **MS** (EI) *m/z*: 401 (M^+), 402(M + 1).

2h:1-(5-((1H-1,2,3-triazol-1-yl)methyl)-2-(3-phenoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl) ethanone.

IR (KBr): NH at 3125cm^{-1}, C=O at 1698cm^{-1}; **^{1}HNMR** (δ ppm): 7.78(d,1H, triazole), 7.68(d,1H, triazole),7.13-7.58(m, 9H, Ar-H), 6.68(s, 1H, CH-oxadiazole), 4.86(s, 2H, -CH_2-Ar), 2.12(s,3H,-CH_3CO-oxadiazole); **^{13}CMR**: 167.7($COCH_3$), 163.2(C_2-oxadiazole), 136.5(C_4-triazole), 158(C-O-Cdiarylether), 126.8(C_5-triazole),116.5-142.5(Ar-C), 85.4(C_5-oxadizole), 53.8(-CH_2-Ar), 26.2(-CH_3-oxadiazole), **MS** (EI) *m/z*: 363(M^+).

2i:1-(5-((5-Methylbenzo[d]thiazol-2-ylamino)methyl)-2-(3-phenoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone.

IR (KBr): NH at 3132cm^{-1}, C=O at 1743cm^{-1}; **^{1}HNMR** (δ ppm): 7.13-8.06 (m, 12H, Ar-H), 6.78(s, 1H, -CH-oxadiazole), 4.2(s, 1H, NH-Ar), 3.38(s, 2H, -CH_2-Ar), 2.68(s, 3H, -CH_3-Ar), 2.28(s, 3H, -CH_3CO-oxadiazole); **^{13}CMR**: 172.4(C_2-benzothiazole), 166.7($COCH_3$), 162.2(C_2-oxadiazole), 159(C-O-C,diarylether), 116.5-142.5(Ar-C), 84.4(C_5-oxadizole), 53.8(-CH2-NH), 26.2(-CH_3-oxadiazole), 23.8(-CH3-Ar); **MS** (EI) *m/z*: 459 (M^+), 460 (M + 1).

2j:1-(5-((5-Methylthiazol-2-ylamino)methyl)-2-(3-phenoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone.

IR (KBr): NH at 3135cm^{-1}, C=O at 1745cm^{-1}; **^{1}HNMR (δ ppm)**: 7.03-7.68 (m, 9H, Ar-H), 6.87(s, -CH, thiazole), 6.58(s, 1H, -CH-oxadiazole), 4.1(s, 1H, -NH-Ar), 3.48(s, 2H, -CH_2-Ar), 2.48(s, 3H, -CH_3-thiazole), 2.24(s, 3H, -CH_3CO-oxadiazole); **^{13}CMR**: 170.7($COCH_3$), 166.4(C_2-thiazole), 162.2(C_2-oxadiazole), 157(C-O-C,diarylether), 138.6(C4-thiazole), 116.5-142.5(Ar-C), 122.8(C5-thiazole), 83.4(C_5-oxadizole), 53.8(-CH2-NH), 26.2(-CH_3-oxadiazole), 22.2(-CH_3-thiazole); **MS** (EI) *m/z*: 408(M^+).

In vitro antimicrobial activity:

Table-2

Code	ANTIBACTERIAL ACTIVITY(MIC)				ANTIFUNGAL ACTIVITY(MIC)		
	Gram-negative		Gram-positive				
	E.coli	*P.aeruginosa*	*S.aureus*	*S.pynogenus*	*C.abicans*	*A.niger*	*A.clavatvs*
	MTC 442	MTC 441	MTCC 96	MTC 443	MTCC 227	MTCC 282	MTCC 1323
	Microgram/ml				Microgram/ml		
2a	200	250	125	200	1000	1000	1000
2b	200	125	125	100	500	1000	1000
2c	250	200	200	250	1000	500	1000
2d	100	200	250	250	1000	>1000	>1000
2e	100	62.5	200	200	500	>1000	>1000
2f	100	250	250	200	250	1000	1000
2g	200	100	200	100	250	500	500
2h	125	250	100	200	500	500	500
2i	200	200	100	200	500	1000	1000
2j	100	125	200	200	500	>1000	>1000
Gentamycin	0.05	1	0.25	0.5			
Ampicillin	100	100	250	100			
Chloramphenicol	50	50	50	50			
Ciprofloxacin	25	25	50	50			
Norfloxacin	10	10	10	10			
Nystatin	-	-	-	-	100	100	100
Griseofulvin	-	-	-	-	500	100	100

In vitro- antimycobacterial activity

Table-3

Sample Id	% Inh at conc.50µg/ml
2a	35
2b	56
2c	25
2d	9
2e	62
2f	23
2g	13
2h	92
2i	13
2j	5
Rifampicin	100
Isoniazid	100

RESULTS AND DISCUSSION

Chemistry:

2,3-dihydro-1,3,4-oxadiazole derivatives 2(a-j) obtained from hydrazones 1(a-j) via intra cyclization with acetic anhydride. IR spectra of 2c had characteristics as they showed NH stretching bands at 3019 cm^{-1}, C=O bands at 1732.9 cm^{-1} which were attributed to the C=O stretching of the acetyl group. 2a gave the singlet at δ 6.8 in the ^{1}H NMR spectra which were attributed to the -O-CHR-N resonance of the oxadiazole ring and two singlets at δ 3.8 and δ 2.3 were assigned to -OCH_3-pyrimidine ring and acetyl -CH_3 of oxadiazole ring. The formation of the oxadiazole was further supported by the ^{13}C NMR data of compounds 2c. ^{13}C NMR spectra -OCHR-N-was observed at δ 88.4 after cyclization of oxadiazole ring. In the ^{13}C NMR spectrum of 2c, this signal was observed at δ 88.4 due to the sp3 hybridization. Further evidence for the formation of 2,3-dihydro-1,3,4-oxadiazole 2a was obtained by recording the mass spectra. The mass spectrum of compound 2a showed a molecular ion peak at m/z 449.

Biology

The minimum inhibitory concentrations (MIC: 100 µM, 250 µM) of **2(a-j)** were screened against different strains. Results revealed (Table-2) that some of the newly synthesized, some compounds with MIC: 100µM, 250µM comparable to the reference drugs Ampicillin, Chloramphenicol. Compounds **2d,2e,2f,2j** showed promising inhibition against *E-COLI* while **2e,2g** show activity against *P.AERUGINOSA*.Compound **2b,2g**, and **2d,2f** show potency against *S.PYNOGENUS* and *S.AUREUS* respectively. Remaining compounds displayed moderate to least activity against both bacteria. Alternatively, newly synthesized derivatives were tested as potential antifungal agents. Compounds **2b,2e,2h,2i,2j** exhibited potency with (MIC; 500µM) against *C. albicans*, similar to that of reference drug Griseofulvin.

In vitro antimycobacterial activity

From preliminary examination results displayed in (Table-3) of the antimycobacterial activity of **2(a-j)** compound **2h** found to be an active (99 % inhibition at 50µM) against *M. tuberculosis.* Whereas compound **2e** showed encouraging activity with 62 % inhibition at 50µM while rest of the compound is not active in the preliminary examination.

CONCLUSION

The synthesized new series of diaryl ether enclosed with 1,3,4 oxadiazole core exhibited promising to moderate in vitro antibacterial activity against both pathogens strain. The present work reveals that comp **2h** is the potent motif for antimycobacterial activity. The present study leads to further research in the area of anti-tuberculosis to construct diaryl ether analogs clubbed with heterocycles.

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