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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDIES ON CERTAIN SUBSTITUTED ARYLAZO IMIDAZOLE CONTAINING OXADIAZOLES

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ABSTRACT

A series of novel substituted 1-[5-(2-methyl-5-nitro-4phenyl-imidazol-1yl methyl)-2-phenyl-(1,3,4)oxadiazol-3-yl]-ethanones have been synthesized. Formation of 1,3,4-oxadiazole ring was accomplished by the reaction of corresponding hydrazide with acetic anhydride. The structure determination of these compounds has been made on the basis of IR, ^{1}H NMR, and elemental analysis. All the compounds were screened for their antibacterial activity. The antimicrobial activity of title compounds were examined against two gram-negative (Staphylococcus aureus and Bacillus subtilis), two gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa) and antifungal activity was carried out against Candida albicans. The MIC values for the newly synthesized compounds have been assessed by serial dilution method All the compounds demonstrated potent antibacterial activity.

KEYWORDS: Imidazole, 1,3,4-Oxadiazole, Characterization, Antimicrobial activity

RESUMO

Uma série nova de etanonas substituídas, 1-{5-2(-metil-5-nitro-4-fenil(1,3,4)oxadiazol-3-il}-etanonas, foram sintetizadas. A formação do anel do 1,3,4-oxadiazol foi obtida através da reação da hidrazida correspondente com anhidrido acético. As estruturas dos compostos foi determinada usando técnicas de IV, RMN e análise elementar. Os compostos mostraram atividade antimicrobiana contra várias bactérias e Cândida albicans,

PALAVRAS CHAVE: Imidazol, 1,3,4-Oxadiazol, Atividade antimicrobians

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INTRODUCTION

N and O containing heterocylces have been reported to be associated with a wide range of biological activity. 1, 3, 4- Oxadiazoles are five membered ring compounds with two nitrogen atoms and one oxygen atoms. 1, 3, 4- Oxadiazoles are the class of compounds which have demonstrated immense biological activity due to the presence of –N=C-O- linkage. The wide spread use of 1, 3, 4- oxadiazole moiety as a scaffold in medicinal chemistry establishes it as an important bioactive class of heterocycles. Molecules containing 1, 3, 4-oxadiazoles moiety have shown broad spectrum of biological activities including antifungal[1], antibacterial[2], antiviral[3], anti tubercular[4], cytotoxic[5], anticancer[6], anti-inflamatory[7]. Hence 1, 3, 4-oxadiazole moiety serve as a versatile building block for experimental drug design.

On the other hand, imidazole moiety has occupied a unique place in the field of medicinal chemistry. Being a polar and ionisable aromatic compound, it improves pharmacokinetic characteristics of lead molecules. Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of diseases including antibacterial[8], antifungal[9], antitubercular[10], antiviral[11], anticancer[12] etc. Hence the incorporation of the imidazole nucleus is an important synthetic strategy in drug discovery.

From the above discussion it is evident that imidazole and 1,3,4- oxadiazoles have become important components of many pharmaceuticals. With a view to broaden the scope in chemotherapy and to integrate the high therapeutic characteristics of both these moieties, the authors have made an attempt to incorporate above mentioned moieties, in a single entity.

MATERIALS AND METHODS

The starting material 2-methyl-5-nitro-imidazole (1) employed in the preparation of hydrazide (3) was obtained as a gift sample from Arathi Drugs company, Mumbai. Ethyl chloroacetate was procured from Ranbaxy, India. All the reagents and chemicals used were analytical grade obtained from Merck, India.

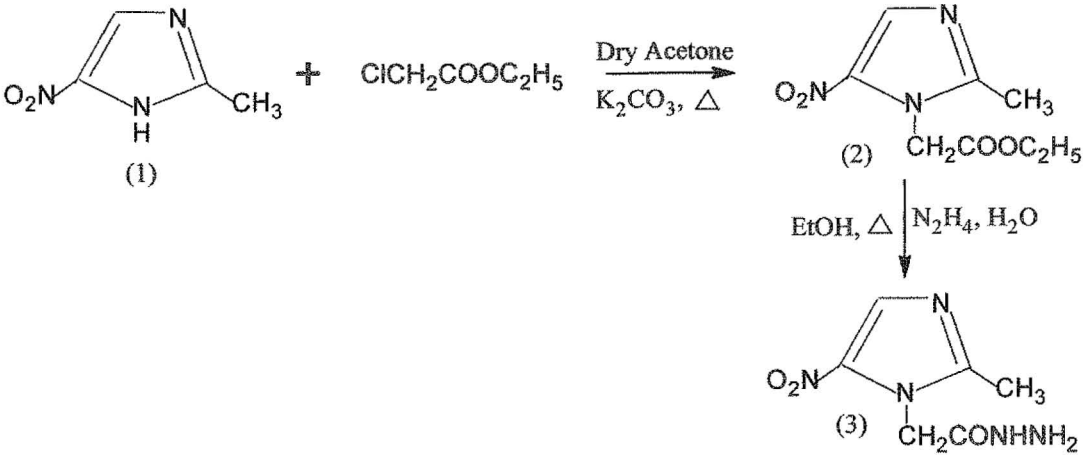
The melting points of the newly synthesized compounds were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 IR spectrophotometer in KBr pellet. The ^{1}H-NMR spectra were recorded on a Bruker AC 300F (200 MHz) NMR spectrometer using DMSO – d_6 as solvent and TMS as an internal standard. All chemical shift values are expressed in δ scale downfield from TMS. The purity of all the compounds was confirmed by TLC.

GENERAL PROCEDURES FOR THE SYNTHESIS

Synthesis of (2-Methyl-5-nitro-imidazole-1-yl)-acetic acid hydrazide[13]

The mixture of 1 (0.1 mol), ethylchloroacetate (0.1 mol) and potassium carbonate (0.2 mol) in dry acetone was refluxed for about 10 hours to get 2-methyl-5-nitro-1-imidazo-ethyl acetate (2). The reaction mixture was filtered and ester so obtained was recrystalised from ethanol.

A mixture of 2-methyl-5-nitro-1-imidazo-ethyl acetate (2) (0.5 mol) and hydrazine hydrate (0.5 mol) in ethanol (100 mL) was refluxed for 8 hours. The solutions was cooled, filtered and recrystallized from ethanol to get imidazole hydrazide (3). The two steps involved in the synthesis are shown in Scheme 1.



Scheme 1. Synthesis of (2-Methyl-5-nitro-imidazole-1-yl)-acetic acid hydrazide

GENERAL PROCEDURE FOR THE SYNTHESIS OF SUBSTITUTED 1-[5-(2-METHYL-5-NITRO-4PHENYL-IMIDAZOL-1YL METHYL)-2-PHENYL-(1,3,4)OXADIAZOL-3-YL]-ETHANONE (7).

Synthesis of [4-(4-substituted-phenyl azo)-2-methyl-5-nitro-imidazole-1-yl]-acetic acid hydrazide (5)

The required benzene azo diazonium chlorides (4 a-f) were synthesized according to literature methods[14-16].

To a mixture of sodium acetate (1.0 g) in 100 mL of aqueous alcohol (50%) and 2-methyl-5-nitro-1-imidazo-acethydrazide (0.1 mol) (3) in 50 mL of ethanol cooled to 0^0C, corresponding diazonium chloride (4) was added slowly to get reddish brown crystals. The crystals (5a–f) were filtered, washed with water and dried.

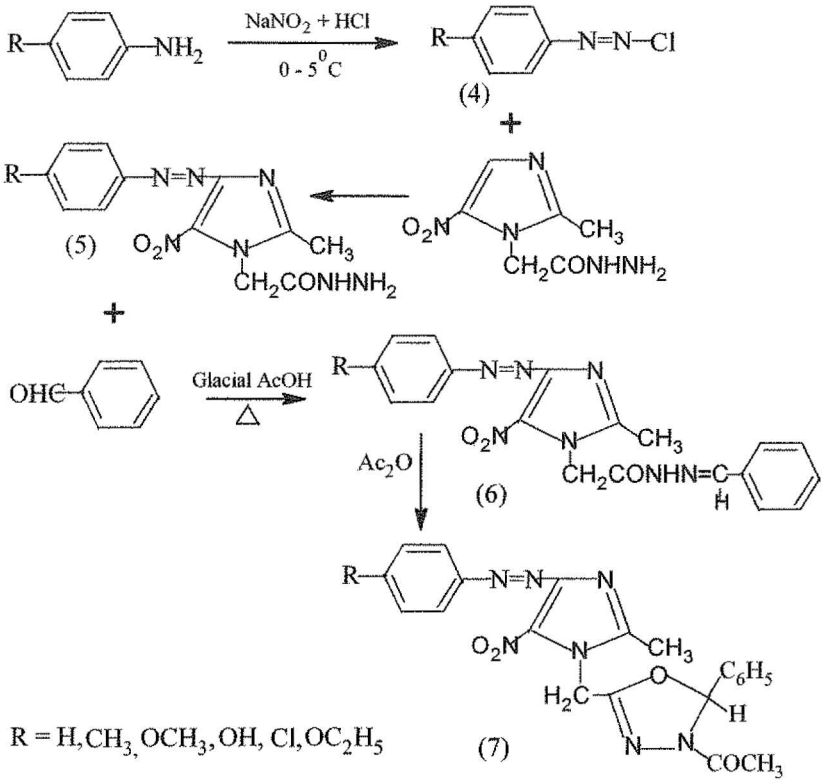
Synthesis of substituted (2-methyl-5-nitro-4-phenyl azo-imidazol-1-yl)-acetic acid benzylidene-hydrazide (6).

A mixture of 5 (0.1 mol) and benzaldehyde (0.1 mol) in glacial acetic acid (50 mL) was refluxed for one hour. The reaction mixture was cooled to room temperature and the contents were

poured into ice-cold water. The solid separated was filtered, dried and recrystallized from a mixture of ethanol-DMF to give **6a-f.**

Synthesis of substituted 1-[5-(2-methyl-5-nitro-4phenyl-imidazol-1yl methyl)-2-phenyl-(1,3,4)oxadiazol-3-yl]-ethanone (7).

A mixture of 6 (0.05 mol) and acetic anhydride (30 mL) was refluxed for 4 hours. The excess acetic anhydride was distilled off and the residue was poured into ice-cold water. The solid separated was filtered, dried and recrystallized from a mixture of ethanol-DMF. Different steps involved in the synthesis are shown in Scheme 2.



Scheme 2. Synthesis of substituted 1-[5-(2-methyl-5-nitro-4phenyl-imidazol-1yl methyl)-2-phenyl-(1,3,4)oxadiazol-3-yl]-ethanone

RESULTS AND DISCUSSION

The elemental and analysis data, spectral data and the respective assignments of **5** are given below.

Table 1. Characterization data of (2-methyl-5-nitro-4-phenylazo-imidazol-1-yl)-aceticacid hydrazide (5 a-f)

Compound No.	-R	Molecular formula	Yield (%) m.p. (^{0}c)	(Calculated) Found %			
				C	H	N	Cl
5a	H	$C_{12}H_{13}N_7O_3$	84 193-194	(47.52) 46.92	(4.32) 4.07	(32.33) 32.83	--
5b	CH_3	$C_{13}H_{15}N_7O_3$	68 207-209	(49.21 48.71	(4.76) 4.51	(30.90) 31.50	--
5c	OCH_3	$C_{13}H_{15}N_7O_4$	72 196-198	(46.85 46.15	(4.54) 4.29	(29.42) 29.92	--
5d	OH	$C_{12}H_{13}N_7O_4$	63 229-221	(45.14 44.64	(4.10) 3.85	(30.71) 31.31	--
5e	Cl	$C_{12}H_{12}ClN_7O_3$	76 236-238	(42.68 42.08	(3.58) 3.33	(29.03) 29.53	(10.50) 10.96
5f	OC_2H_5	$C_{14}H_{17}N_7O_4$	58 221-223	(48.41 47.71	(4.93) 4.68	(28.23) 28.83	--

IR (KBr) Spectral data (ν_{max} in cm^{-1})

5a: 3295 (NH), 3440 and 3420 (NH_2), 2932 (CH_3), 1665 (C=O), 1544 and 1355 (NO_2), 1625 (N=N), 3040 (C_6H_5)

5b: 3285 (NH), 3436 and 3416 (NH_2), 2930 (CH_3), 1655 (C=O), 1556 and 1310 (NO_2), 1620 (N=N), 3035 (C_6H_5)

5c: 3328 (NH), 3435 and 3415 (NH_2), 2934 (CH_3), 1668 (C=O), 154 and 1325 (NO_2), 1635 (N=N), 3031 (C_6H_5)

5d: 3292 (NH), 3434 and 3414 (NH_2), 2938 (CH_3), 1659 (C=O), 1545 and 1335 (NO_2), 1638 (N=N), 3038 (C_6H_5)

5e: 3306 (NH), 3432 and 3412 (NH_2), 2932 (CH_3), 1666 (C=O), 1540 and 1332 (NO_2), 1632 (N=N), 3033 (C_6H_5)

5f: 3275 (NH), 3416 and 3396 (NH_2), 2936 (CH_3), 1676 (C=O), 1546 and 1322 (NO_2), 1638 (N=N), 3029 (C_6H_5)

^{1}H NMR Spectral data

The ^{1}H NMR spectra (200MHz) of [4-(4-substituted-phenyl azo)-2-methyl-5-nitro-imidazole-1-yl]-acetic acid hydrazide : **5 a-f** : were recorded using DMSO-d_6 as a solvent and TMS as an internal standard. ^{1}H NMR spectrum of **5a** contains a signal due to the methyl group δ 1.35 integrating for 3 protons. The N-CH_2CO group protons came into resonance at δ 7.27. The aromatic protons of the phenyl group appeared as singlet at δ 7.52. The NH proton appeared as a broad singlet at δ 10.92, while the NH_2 proton appeared as singlet at δ 2.1.

^{1}H NMR (DMSO – d_6) Spectral data (δ in ppm)

5a: 1.35(s, 3H, CH_3), 7.27 (s, 2H, NCH_2), 10.92 (s, H, CONH), 2.10 (s, 2H, NH_2), 7.52 (s, 5H, C_6H_5)

5b: 1.30 (s, 3H, CH_3), 7.22 (s, 2H, NCH_2), 10.87 (s, H, CONH), 2.05 (s, 2H, NH_2), 7.25-7.35 (m, 4H, C_6H_4)

5c: 1.22 (s, 3H, CH_3), 3.65 (s, OCH_3), 7.32 (s, 2H, NCH_2), 10.97 (s, H, CONH), 2.20 (s, 2H, NH_2), 6.80-7.20 (m, 4H, C_6H_4)

5d: 1.18 (s, 3H, CH_3), 4.85 (s, H, OH), 7.42(s, 2H, NCH_2), 11.07 (s, H, CONH), 2.30 (s, 2H, NH_2), 6.90-7.30 (m, 4H, C_6H_4)

5e: 1.13 (s, 3H, CH_3), 7.47 (s, 2H, NCH_2), 11.12 (s, H, CONH), 2.35 (s, 2NH, NH_2), 6.95-7.35 (m, 4H, C_6H_4)

5f: 1.21 (s, 3H, CH_3), 3.90 (q, 2H, OCH_2), 1.30 (t, 3H, CH_3), 7.57 (s, 2H, NCH_2), 11.19 (s, H, CONH), 2.42 (s, 2H, NH_2), 7.02-7.42 (m, 4H, C_6H_4)

Table 2. Characterization data of (2-methyl-5-nitro-4-phenyl azo-imidazol-1-yl)-aceticacid benzylidene - hydrazide (6 a-f)

Compound No	-R	Molecular formula	Yield (%) m.p. (^{0}C)	(Calculated) Found %			
				C	H	N	Cl
6a	H	$C_{19}H_{17}N_7O_3$	72 212-215	(58.31) 57.71	(4.38) 4.06	(25.05) 25.65	--
6b	CH_3	$C_{20}H_{19}N_7O_3$	83 226-228	(59.25) 58.75	(4.72) 4.32	(24.18) 24.88	--
6c	OCH_3	$C_{20}H_{19}N_7O_4$	78 184-186	(57.00) 56.40	(4.54) 4.22	(23.27) 23.87	--
6d	OH	$C_{19}H_{17}N_7O_4$	75 204-206	(56.02) 55.52	(4.21) 3.81	(24.07) 24.77	--
6e	Cl	$C_{19}H_{16}Cl\ N_7O_3$	74 191-194	(53.59) 52.99	(3.79) 3.47	(23.03) 23.63	(8.33) 8.03
6f	OC_2H_5	$C_{21}H_{21}N_7\ O_4$	69 242-244	(57.92) 57.42	(4.86) 4.46	(22.52) 23.22	--

IR (KBr) Spectral data (ν_{max} in cm^{-1})

6a: 3285 (NH), 2927 (CH_3), 1675 (C=O), 1534 and 1390 (NO_2), 1615 (N=N), 3030 (C_6H_5), 1625 (C=N)

6b: 3275 (NH), 2925 (CH_3), 1665 (C=O), 1546 and 1350 (NO_2), 1595 (N=N), 3025 (C_6H_5), 1610 (C=N)

6c: 3318 (NH), 2934 (CH_3), 1668 (C=O), 1535 and 1335 (NO_2), 1615 (N=N), 3021 (C_6H_5), 1630 (C=N)

6d: 3282 (NH), 2938 (CH_3), 1659 (C=O), 1535 and 1365 (NO_2), 1623 (N=N), 3028 (C_6H_5), 1613 (C=N)

6e: 3303 (NH), 2927 (CH_3), 1690 (C=O), 1556 and 1398 (NO_2), 1620 (N=N), 3023 (C_6H_5), 1620 (C=N)

6f: 3265 (NH), 2936 (CH_3), 1676 (C=O), 1536 and 1312 (NO_2), 1630 (N=N), 3019 (C_6H_5), 1620(C=N)

^{1}H NMR spectral data

The ^{1}HNMR (200MHz) spectrum of 6a contains a singlet at δ 1.45 integrating for 3 protons. due to methyl group. The N-CH_2CO protons were appeared at δ 7.35. The aromatic protons of phenyl group directly attached to N=N group were noticed at δ7.56 and the other phenyl group linked to –N=CH- was observed at δ7.74. The NH proton has appeared as a broad singled at δ 10.96, while N=CH proton came into resonance at δ 11.2 as a singlet.

^{1}H NMR (DMSO – d_6) Spectral data (δ in ppm)

6a: 1.45(s, 3H, CH_3), 6.90 (s, 2H, NCH_2), 10.96 (s, H, CONH), 11.2 (s, H, N=CH), 7.33 (m, 5H), 7.56 (s, 5H)

6b:1.41 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.00 (s, 2H, NCH_2), 11.06 (s, H, CONH), 11.30 (s, H, N=CH), 7.43 (m, 5H) , 7.66 (s, 4H)

6c: 1.49 (s, 3H, CH_3), 3.75 (s, OCH_3), 7.10 (s, 2H, NCH_2), 11.16 (s, H, CONH), 11.40 (s, H, N=CH), 7.53 (m, 5H) , 7.40 (m, 4H)

6d: 1.52 (s, 3H, CH_3), 4.85 (s, H, OH), 7.20 (s, 2H, NCH_2), 11.26 (s, H, CONH), 11.30 (s, H, N=CH), 7.63 (m, 5H) , 7.86 (m, 4H)

6e: 1.58 (s, 3H, CH_3), 7.27 (s, 2H, NCH_2), 10.94 (s, H, CONH), 11.11 (s, H, N=CH), 7.74 (m, 4H, Ar-H), 7.5-7.7(m, 5H, Ar-H)

6f: 1.41 (s, 3H, CH_3), 7.25 (s, 2H, NCH_2), 11.01 (s, H, CONH), 11.05 (s, H, N=CH), 7.38 (m, 5H), 7.61 (m, 4H) 3.90 (q, 2H, OCH_2) 1.30 (t, 3H, CH_3)

Table 3. Characterization data of 1-[5-(2-methyl-5-nitro-4-phenyl azo-imidazol-1-yl)-2-phenyl-[1,3,4]oxadiazol-3-yl]-ethanone (7 a-f)

Compound No.	-R	Molecular formula	Yield (%) m.p. (0C)	(Calculated) Found %			
				C	H	N	Cl
7a	H	$C_{21}H_{19}N_7O_4$	86 201-204	(58.19) 57.59	(4.42) 4.06	(22.62) 23.12	--
7b	CH_3	$C_{22}H_{21}N_7O_4$	65 188-191	(59.05) 58.55	(4.73) 4.47	(21.91) 22.41	--
7c	OCH_3	$C_{22}H_{21}N_7O_5$	72 211-214	(57.02) 56.42	(4.57) 4.21	(21.16) 21.76	--
7d	OH	$C_{21}H_{19}N_7O_5$	66 216-218	(56.12) 55.62	(4.26) 4.00	(21.82) 28.32	--
7e	Cl	$C_{21}H_{18}ClN_7O_4$	71 222-224	(53.91) 53.31	(3.88) 3.52	(20.96) 21.56	(7.58) 7.38
7f	OC_2H_5	$C_{23}H_{23}N_7O_5$	72 208-211	(57.86) 57.36	(4.86) 4.60	(20.53) 20.03	--

IR (KBr) Spectral data (ν_{max} in cm^{-1})

7a: 1630 (N=N), 1556 and 1373 (NO_2), 2929 (CH_3), 1685 (C=O), 3034 (C_6H_5)

7b: 1625 (N=N), 1551 and 1305 (NO_2), 2927 (CH_3), 1650 (C=O), 3029 (C_6H_5)

7c: 1640 (N=N), 1540 and 1320 (NO_2), 2931 (CH_3), 1663 (C=O), 3025 (C_6H_5)

7d: 1643 (N=N), 1540 and 1330 (NO_2), 2935 (CH_3), 1654 (C=O), 3032 (C_6H_5)

7e: 1637 (N=N), 1535 and 1335 (NO_2), 2931 (CH_3), 1666 (C=O), 3025 (C_6H_5)

7f: 1643 (N=N), 1541 and 1317 (NO_2), 2933 (CH_3), 1675 (C=O), 3023 (C_6H_5)

^{1}H NMR spectral data

The ^{1}H NMR (200MHz) spectrum of 7a contains a singlet integrating for three protons of methyl group was observed at δ2.22. The singlet integrating for three protons of the acetyl group was observed at δ 2.46. The NCH_2 protons came into resonance at δ 5.26. The oxadiazole protons (5H) appeared as a singlet at δ 6.86. The aromatic protons were noticed at δ 7.3 and δ 7.5 as multiplets. The ^{1}H NMR data of 36a-f are presented below.

^{1}H NMR (DMSO – d_6) Spectral data (δ in ppm)

7a: 2.22(s, 3H, CH_3), 2.46 (s, 3H, $COCH_3$), 5.26 (s, 2H, NCH_2), 6.86 (Oxadiazole 5H proton), 7.30(m, 5H), 7.50 (s, 5H)

7b: 2.20 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.6 (s, 3H, $COCH_3$), 5.24 (s, 2H, NCH_2), 6.83 (s, Oxadiazole 5H proton), 7.26 (d, 2H, Ar-H), 7.83 (d, 2H, Ar-H)

7c: 2.18 (s, 3H, CH_3), 2.8 (s, 3H, $COCH_3$), 5.24 (s, 2H, NCH_2), 2.43 (s, OCH_3), 7.0 (s, Oxadiazole 5H proton), 7.2 (d, 2H, Ar-H), 7.5 (d, 2H, Ar-H), 7.7 (m, 5H, Ar-H)

7d: 2.12 (s, 3H, CH_3), 2.32(s, 3H, $COCH_3$), 5.18 (s, 2H, NCH_2), 6.73-7.13 (m, 4H), 7.43 (s, 5H), 4.80 (s, H, OH), 6.82(s, Oxadiazole 5H proton)

7e: 2.09 (s, 3H, CH_3), 2.29 (s, 3H, $COCH_3$), 5.15 (s, 2H, NCH_2), 6.70-7.10 (m, 4H), 7.40 (s, 5H), 6.83 (s, Oxadiazole 5H proton)

7f: 2.16 (s, 3H, CH_3), 2.36 (s, 3H, $COCH_3$), 5.22 (s, 2H, NCH_2), 6.77-7.17 (m, 4H), 7.47 (s, 5H), 3.90 (q, 2H, OCH_2), 1.30 (t, 3H, CH_3) 6.82 (s, Oxadiazole 5H proton)

Anti-microbial activity

The newly synthesized 1, 3, 4 – oxadiazoles were screened for antibacterial and antifungal activity. Antibacterial activity was carried out against four different pathogenic organisms, two of them were gram-negative namely *Staphylococcus aureus* and *Bacillus subtilis* and two of them were gram-negative namely *Escherichia coli* and *Pseudomonas aeruginosa.* Antifungal activity was carried out against *Candida albicans.* The MIC values for the newly synthesized compounds in the present investigation have been assessed by serial dilution method.

Table 4. Antibacterial and Antifungal activity data of compounds

Compd No.	Antibacterial activity (MIC in μg/mL)				Antifungal activity (MIC in μg/mL)
	S. aureus	*P.aeruginosa*	*E.coli*	*B.subtilis*	*C. albicans*
7a	0.25	0.25	0.25	0.50	0.20
7b	0.25	0.25	0.25	0.25	0.20
7c	0.40	0.25	0.25	0.40	0.20
7d	0.25	0.25	0.25	0.25	0.20
7e	0.25	0.25	0.25	0.50	0.20
7f	0.25	0.25	0.25	0.25	0.20
Standard Furacin	0.25	0.25	0.25	0.50	---
Standard Flucanazole	---	---	---	---	0.25
Control : (DMF)	---	---	---	---	---

It is evident from the Table 4 that all the compounds demonstrated significant antimicrobial activity and was comparable with that of the standards.

CONCLUSION

A series of 6 novel imidazole containing oxadiazoles were synthesized and characterized. The antimicrobial activity all the newly synthesized compounds was evaluated and reported. Form the present study, it can be concluded that by varying the substituents in the heterocycles, these compounds can be developed in to potential antimicrobial agents.

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