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SYNTHESIS OF MOLECULES BASED ON 2-NAPTHYL-1,3,4-OXADIAZOLE SCAFFOLD AND EVALUATION OF THEIR ANTIMICROBIAL ACTION

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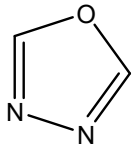
ABSTRACT

In the present work new antimicrobial agents based on 1,3,4- oxadiazole nucleus were synthesized and evaluated. All the compounds were obtained in 64-71% yields using the reaction conditions. The compounds exhibited the peaks of aromatic C=C stretching, C-H stretching, C-N and C=N stretching and C-O stretching. The compounds were evaluated for anti-microbial potential using cup and plate method against gram positive (*Bacilus subtilis* and *Staphylococcus aureus*) and gram negative bacteria (*Escherichia coli* and *Pseudomonas aeuroginosa*). Compounds containing nitro group (5**b, 5c & 5d**) were found to be the most potent against all the pathogenic bacteria. The presence of NH_2 and OH groups at para position was more effective than that at ortho position in the compounds.

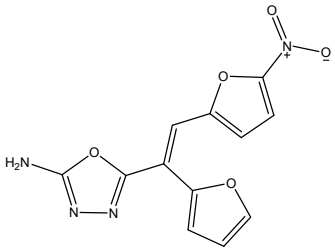
Keywords: Oxadiazole, antimicrobial, zone of inhibition, hydrazide, aromatic acid

INTRODUCTION

1,3,4-oxadiazole (**1**) derivatives are associated with many therapeutic fields and some have also been found to be potent antiviral **[1]**, antibacterials **[2]** & antifungal **[3]**. Furamizole (**2**), Nesapidil (**3**), Tiodazosin (**4**) are a few currently used clinical products based on oxadiazole nucleus **[4]**. The oxadiazoles have activity against a broad range of microorganisms including both fungi & bacteria. Newer synthesized derivatives of heterocycles may possess the capability to be a breakthrough and lead molecule for the treatment of bacterial resistance.



(**1**)



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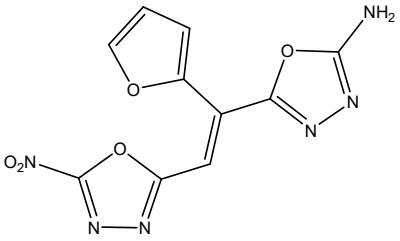

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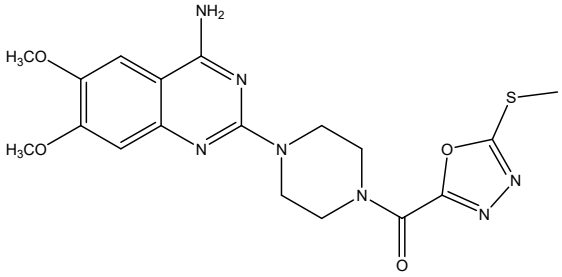
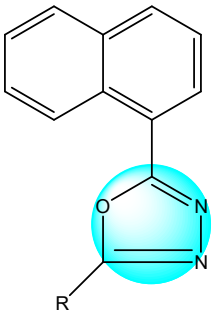


(**4**)

Structure activity relationship studies have shown that the 2-position and 5-position are extremely important site of molecular modification, playing a dominant role in determining the pharmacological activities of 1, 3, 4-oxadiazole derivatives.

Oxadiazoles have been known to exert good antimicrobial potential and have been recently widely researched for several other pharmacological actions. The objective of the current work was to synthesize some novel derivatives bearing oxadiazole to assess their anti microbial potential.

In light of the importance of the oxadiazole derivatives as antibacterial and anti fungal agents we planned to carry out the synthesis of some new derivatives (5) based on the oxadiazole scaffold utilizing naphthoic acid as starting material and evaluate them for antimicrobial activity.

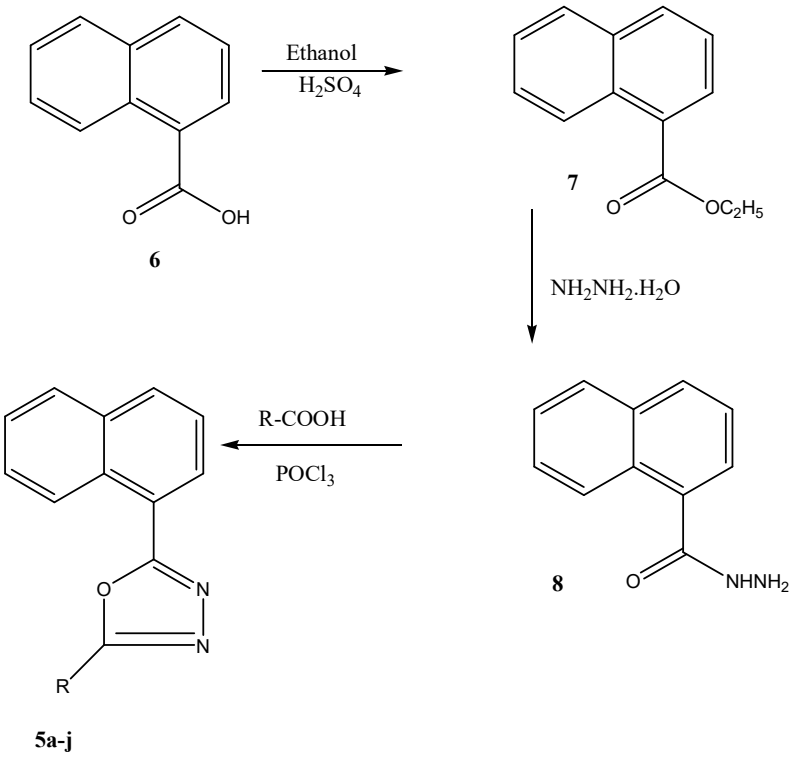


(**5**)

MATERIAL AND METHODS

All reagents and chemicals used were of synthesis grade, and purchased from CDH, Avra Chemicals and Oxford Chemicals and were used without further purification. Melting point are uncorrected and determined by open capillary technique. Precoated silica gel TLC plates were used to monitor the progress of the reaction. The structure of all the compounds was confirmed by IR, NMR and Mass spectral studies. The physicochemical properties like color, solubility and melting point were determined using previously reported methods **[5-7]**.

The scheme for the synthesis of the oxadiazole derivatives was adapted from the procedures reported by Mishra *et al* **[8]** and the scheme is depicted in **Figure 1**.



R = phenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 4-hydroxypenyl, 2-hydroxyphenyl,1-methoxyphenyl 1-naphthyl, 2-aminophenyl, 4-aminophenyl

Synthesis of ethyl 1-naphthoate, 7

0.1 moles of 1-naphthoic acid (**6**) was dissolved in 25 ml ethanol and the mixture was refluxed for 5h in presence of 5 drops of concentrated H_2SO_4. On cooling, a solid separated which was filtered and recrystallised using ethanol to give the carboethyoxy derivative of naphthoic acid **7**. Completion of the reaction was monitored by TLC.

Synthesis of 1-naphthohydrazide, 8

The hydrazide derivative of the naphthoic acid was synthesized by the reaction of **7** by hydrazine hydrate in presence of ethanol with catalytic amount of concentrated sulfuric acid. To 0.1 mole of product **7** dissolved in 20 ml ethanol, 0.1 mole of hydrazine hydrate was added. To the mixture, catalytic amount of concentrated sulfuric acid was added. The mixture was refluxed until the completion of the reaction (approximately 2 hours). On cooling, a solid separated, which was recrystallized from ethanol to give the product **8**.

General method for synthesis of 2-(naphthalene-1-yl)-1,3,4-oxadiazole, 5a-j

Product **8** (0.001 mol) and the aromatic acid (0.001 mol) were dissolved in phosphorus oxychloride and refluxed for 20 h. The reaction mixture was slowly poured over crushed ice and allowed to stand overnight. The solid that precipitated was filtered, washed with water, dried and recrystallized from ethanol to obtain compounds **5a-j.**

2-(naphthalen-1-yl)-5-phenyl-1,3,4-oxadiazole, 5a

Yellow powder with 71% yield; 221-223°C m.p. ^{1}H-NMR ($CDCl_3$): δ 7.179-7.971 (Ar-H); IR (cm^{-1}): 3084 (C-H), 2924 (C-C), 1599 (C=N), 1341 (C-N); m/z 272.3 (M^+)

2-(naphthalen-1-yl)-5-(2-nitrophenyl)-1,3,4-oxadiazole, 5b

Yellow powder with 69% yield; 229-232°C m.p. ^{1}H-NMR ($CDCl_3$): δ 8.001-8.025 (H adjacent to NO_2), 6.833-7.902 (Ar-H); IR (cm^{-1}): 3082 (C-H), 1751 (C-C), 1687 (C=N), 1597 (N-O), 1341 (C-N); m/z 317.3 (M^+)

2-(naphthalen-1-yl)-5-(3-nitrophenyl)-1,3,4-oxadiazole, 5c

Yellow powder with 65% yield; 235-236°C m.p. ^{1}H-NMR ($CDCl_3$): δ 8.003-8.031 (H adjacent to NO_2), 6.815-7.917 (Ar-H); IR (cm^{-1}): 3173 (C-H), 2602 (C-C), 1654 (C=N), 1599 (N-O), 1397 (C-N); m/z 317.3 (M^+)

2-(naphthalen-1-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole, 5d

Yellow powder with 66% yield; 230-232°C m.p. ^{1}H-NMR ($CDCl_3$): δ 8.001-8.025 (H adjacent to NO_2), 6.833-7.902 (Ar-H); IR (cm^{-1}): 3121 (C-H), 2602 (C-C), 1654 (C=N), 1588 (N-O), 1322 (C-N); m/z 317.3 (M^+)

2-(5-(naphthalen-1-yl)-1,3,4-oxadiazol-2-yl)phenol, 5e

Brown powder with 69% yield; 220-222°C m.p. ^{1}H-NMR ($CDCl_3$): δ 6.872-7.912 (Ar-H), 6.768-6.825 (H adjacent to OH), 4.996 (H of hydroxy); IR (cm^{-1}): 3431 (O-H), 3165 (C-H), 2599 (C-C), 1654 (C=N), 1323 (C-N); m/z 288.3 (M^+)

4-(5-(naphthalen-1-yl)-1,3,4-oxadiazol-2-yl)phenol, 5f

Yellow powder with 64% yield; 221-223°C m.p. ^{1}H-NMR ($CDCl_3$): δ 6.872-7.902 (Ar-H), 6.791-6.822 (H adjacent to OH), 4.969 (H of hydroxy); IR (cm^{-1}): 3422 (O-H), 3172 (C-H), 2634 (C-C), 1665 (C=N), 1325 (C-N); m/z 288.3 (M^+)

2-(5-(naphthalen-1-yl)-1,3,4-oxadiazol-2-yl)benzenamine, 5g

Brown powder with 67% yield; 236-238°C m.p. ^{1}H-NMR ($CDCl_3$): δ 6.906-7.902 (Ar-H), 6.833-6.872 (H adjacent to NH_2), 4.063 (H of NH_2); IR (cm^{-1}): 3240 (N-H), 3113 (C-H), 2943 (C-C), 1649 (C=N), 1396 (C-N); m/z 287.3 (M^+)

4-(5-(naphthalen-1-yl)-1,3,4-oxadiazol-2-yl)benzenamine, 5h

Brown powder with 68% yield; 235-237°C m.p. ^{1}H-NMR ($CDCl_3$): δ 6.912-7.911 (Ar-H), 6.827-6.841 (H adjacent to NH_2), 4.067 (H of NH_2); IR (cm^{-1}): 3242 (N-H), 3119 (C-H), 2979 (C-C), 1645 (C=N), 1398 (C-N); m/z 287.3 (M^+)

2-(4-methoxyphenyl)-5-(naphthalen-1-yl)-1,3,4-oxadiazole, 5i

Brown powder with 65% yield; 241-242°C m.p. ^{1}H-NMR ($CDCl_3$): δ 6.833-7.902 (Ar-H), 3.771 (H of OCH_3); IR (cm^{-1}): 3145 (C-H), 3045 (C-C), 1623 (C=N), 1397 (C-N); m/z 302.3 (M^+)

2,5-di(naphthalen-1-yl)-1,3,4-oxadiazole, 5j

Brown powder with 67% yield; 265-266°C m.p. ^{1}H-NMR ($CDCl_3$): δ 7.179-7.971 (Ar-H); IR (cm^{-1}): 3084 (C-H), 2924 (C-C), 1683 (C=N), 1341 (C-N); m/z 322.3 (M^+)

Antimicrobial Screening

Microorganisms tested

MTCC strains of *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* were used in the present investigation.

The lyophilized cultures were revived by adding 0.3 mL of nutrient broth to the culture ampoules to obtain a suspension of the bacteria. Revival of the fungal culture was done using 0.3 mL of water.

Ready to use nutrient agar powder was used for preparing the nutrient agar medium.Agar plates were prepared by pouring the sterilized medium into sterilized petridishes suitably marked and labeled. The plates were allowed to solidify in the laminar flow bench and stored packed for culturing with microbes and antimicrobial screening.

Antimicrobial screening

About 3 mm thick pre-poured nutrient agar plates were inoculated with a few drops of the bacterial suspension by swabbing on the surface of agar. The antimicrobial action was screened using disc diffusion method [9]. All the synthesized compounds were dissolved in DMSO to obtain 1mg/mL, 1.5 mg/mL and 2mg/mL solutions of each. Wells were bored into the agar plate at equal distances using cork borer (10mm) and 200µL of the compounds were placed in each hole. The plates were incubated for 24h

at 37 ± 0.1°C to allow for microbial growth. The zone of inhibition in each plate was measured in millimeters and the average diameter of the zone of inhibitions was calculated.

RESULTS AND DISCUSSION

All the compounds were yellowish to brown in colour and were obtained in 64-71% yields using the reaction conditions. The compounds were slightly soluble in water, and chloroform and soluble in methanol. The synthesis of the 1,3,4-oxadiazole derivatives was carried out in three steps involving initial esterification of naphthoic acid followed by its hydrazination and finally converting the hydrazide to oxadiazole via cyclization in presence of aromatic acid. All the compounds exhibited the peaks of aromatic C=C stretching, C-H stretching, C-N and C=N stretching and C-O stretching. The occurrence of absorption bands for C-O and C=N may occur at the same frequency. The ^{1}HNMR spectra of all the compounds exhibited chemical shifts of aromatic hydrogen. They also exhibited chemical shift arising due to the presence of –OH, OCH_3 and NH protons. The mass spectra of the compounds were examined for the presence of molecular ion peak or the isotopic peaks to confirm the formation of the compounds.

All the synthesized compounds (**5a-j**) showed dose dependent antimicrobial action against gram positive and gram negative bacteria (Table 1, Figure 1). Compounds containing nitro group (**5b, 5c & 5d**) were found to be the most potent against all the pathogenic bacteria whereas the unsubstituted compounds (5**a, 5j**) inhibited the bacterial growth very poorly. The presence of NH_2 and OH groups at para position (**5f, 5h**) was more effective than that at ortho position (**5e, 5g**) in the compounds.

It was also evident that the compounds were more active against the gram positive bacteria as compared to the gram negative bacterial.

Table 1: Zone of inhibition of 5a-j against gram positive and gram negative bacteria

Compound Code	Zone of Inhibition (mm)*											
	B. subtilis			*S. auerus*			*E.coli*			*P. aeruginosa*		
	1	1.5	2	1	1.5	2	1	1.5	2	1	1.5	2
5a	4	6	7	4	7	10	6	8	12	7	10	13
5b	13	18	20	12	19	22	11	16	18	10	16	19
5c	11	17	19	11	17	20	10	15	18	9	17	19
5d	15	20	25	14	20	26	13	18	20	14	19	21
5e	6	8	12	6	10	13	11	14	23	10	15	23
5f	11	17	18	11	17	18	10	15	17	9	15	16
5g	7	13	16	8	13	16	5	10	14	7	13	15
5h	11	17	19	11	17	20	10	15	18	9	17	19
5i	7	15	17	8	14	17	6	11	15	7	14	16
5j	7	9	12	6	7	10	5	8	11	7	9	13
Ciprofloxacin	15	21	33	13	22	27	15	23	35	16	22	36

*** Below 12 mm – poor activity; 13-18 mm – moderate activity & above 18 mm – good activity**

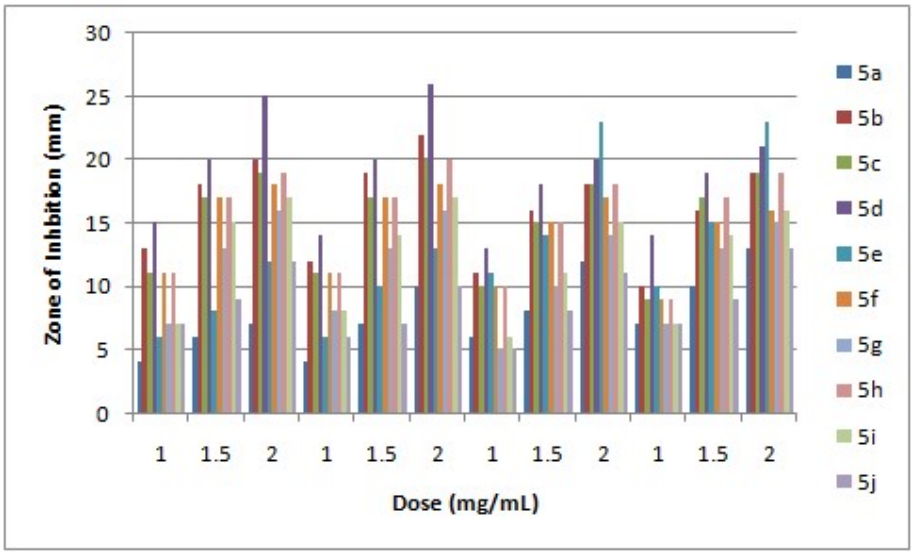


Figure 1: Comparative zone of inhibitions of 5a-j against gram positive and gram negative bacteria

CONCLUSION

The objective of the present investigation was to develop newer antimicrobial molecules based on 1,3,4-oxadiazole nucleus. It was accomplished by converting the carboxyl group of 1- naphthoic acid to hydrazide followed by the reaction with carboxylic acid to convert the hydrazide to substituted oxadiazole. The synthesized compounds presented anti microbial action against gram positive and gram negative bacteria activity comparable to that of the standard drug.

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