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Research Article

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Synthesis and Characterization of some biologically active 2, 5-Substituted Oxadiazoles

Wanale S. G.[1*], Pachling S. P.[2] and Hangirgekar S. P.[1]

[1]School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded (MS) 431606 INDIA
[2]P. G. Department of Chemistry, N. S. B. College, Nanded (MS) 431602 INDIA

ABSTRACT

Present paper reports the synthesis of four new biologically active 2, 5-substituted oxadiazoles by oxidative cyclization of the semicarbazones obtained from the reaction of semicarbazides with corresponding aromatic aldehydes. The structures of target oxadiazoles were confirmed by elemental, IR, NMR and LCMS data. These compounds were screened for their antifungal activity and found active.

Keywords: synthesis, oxidative cyclisation, oxadiazoles, antibacterial activity, MIC.

INTRODUCTION

1,3,4-oxadiazoles are biologically versatile compounds displaying a variety of biological effects[1-3]. The extensive use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry, established this moiety as a member of the privileged structures class. The 2,5-substituted derivatives have been known to posses anti-inflammatory[4], antifungal[5], Cardiovascular[6], antimicrobial[7], herbicidal[8], hypoglycaemic[9], hypotension[10], antiviral[11], and anti-tumour activities[12].

In the present investigation we report on the synthesis of new members (AOYP, ODDP, PIOA and PYOA) of this applicably important type of compounds from aroylhydrazones and hydrazides using oxidative cyclization routes as ligands (Figure 1).

EXPERIMENTAL SECTION

Materials

All reagents were of commercial analytical quality and have been used without further purification. Elemental analyses were done using CHNS Analyzer at I.R.M.R.A. Pune. The electronic spectra of the ligands and metal complexes in ethanol were recorded on Shimadzu-61 UV-Visible spectrometer in the region 200-700 nm. IR spectra were recorded in KBr pellets with a Perkin Elmer spectrometer at Chandigarh, in the range 400–4000 cm^{-1}. ^{1}HNMR and ^{13}CNMR spectra of ligands were recorded at SAIF Punjab University, Chandigarh in DMSO solvent using TMS as an internal standard and in $CDCl_3$ respectively.

1,3,4-oxadiazole derivatives were screened for antimicrobial activity by using the well diffusion method reported in the literature by Perez et al[13].

General procedure of Synthesis of 2, 5-substituted oxadiazoles: (AOYP, PIOA and PYOA)
An ethanolic solution (25 ml) of aldehyde (10 mmol) was added with stirring to an aqueous solution (40 ml) of a mixture of semicarbazide hydrochloride (10.2 mmol) and sodium acetate (10.3 mmol). The mixture was warmed on a water bath for 5-10 min and allowed to cool in ice water. The semicarbazone crystals were filtered off, washed

with cold water, dried and recrystallised with ethanol. The obtained semicabazone (0.01M) and sodium acetate (0.02 M) were dissolved in 30-40 ml of glacial acetic acid taken in a round bottom flask equipped with separating funnel for addition of bromine. Bromine (7 ml in 5 ml glacial acetic acid) was added slowly to it, while stirring magnetically. After half an hour stirring, the solution was poured on crushed ice. The resulting solid was separated, dried and recrystallised from ethonal. In case of PIOA, further acetylation of the cyclised product was carried out to obtain the target molecule.

Procedure of Synthesis of ODDP:

Salicylic acid (0.01 mol) and hydrazine dihydrochloride (0.01 mol) was dissolved in 25 ml (15 ml ethanol + 10 ml water) solution in a two neck round bottom flask equipped with separating funnel and refluxed for 15 min. After 15 min, ethanolic solution (5 ml) of salicylaldehyde (0.01 mol) was added slowly to the hydrazine derivative in the flask, while stirring magnetically. After 10-15 min the mixture was cooled, the solid semicarbazone was filtered, dried and recrystallised from ethanol. The oxidative cyclisation of the obtained semicarbazone with bromine in acetic acid by the above mentioned general procedure yielded the target molecule.

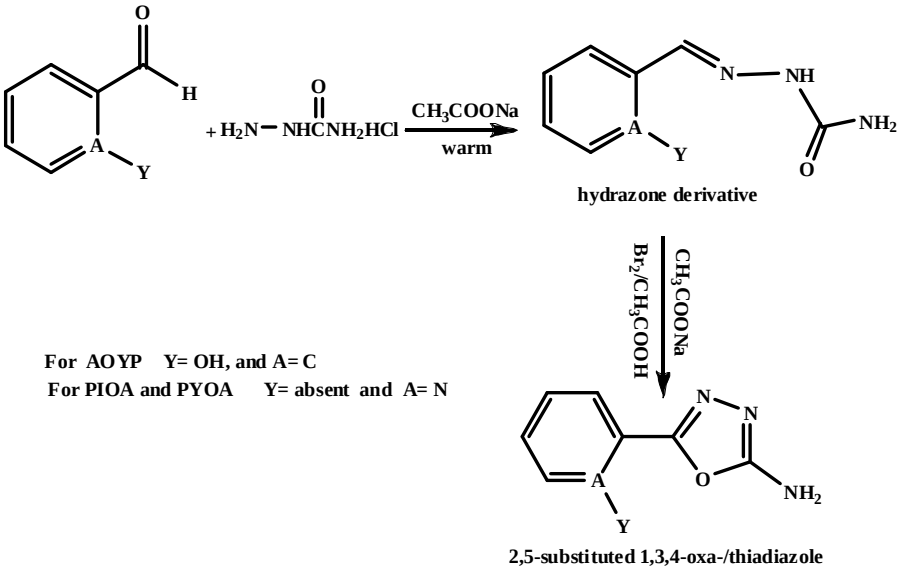

Figure 1. Synthesis of 2, 5-substituted 1, 3, 4-oxadiazole derivatives

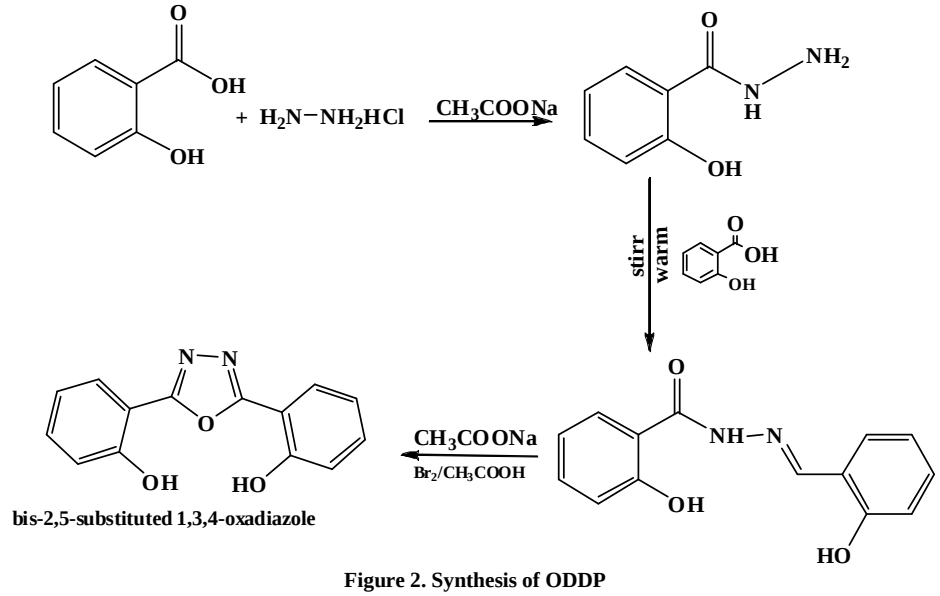

Figure 2. Synthesis of ODDP

The physical and analytical data of the synthesized title compounds (Figure 3) are given as follows.

***2-(5-amino-1,3,4-oxadiazol-2-yl) phenol* (AOYP):** m.p. 137°C, molecular formula ($C_8H_7N_3O_2$), molecular weight 177, recrystallization solvent ethanol, yield 92%, elemental analysis (%)calculated H(3.98), C(54.24), N(23.72), found H(4.02), C(55.23), N(23.80). IR cm^{-1}: 3382(OH), 3273-3251(NH_2), 1597(C=N). 1255(Phenolic C-O), 1013(C-O-C). ^{1}H NMR (DMSO-d_6) ppm: 12.14 (2H,s, Ar-NH_2), 7.35-7.75 (4H,m,Ar-H), 5.21 (1H,s,OH).

2,2'-(1,3,4-oxadiazole-2,5-diyl) diphenol **(ODDP):** m.p. 133°C, molecular formula ($C_{14}H_{10}N_2O_3$), molecular weight 254, recrystallization solvent ethanol, yield 78%, elemental analysis: (%)calculated H(3.96), C(66.14), N(11.02) found H(4.12), C(66.56), N(11.57). IR cm^{-1}: 3203(OH), 3273-3251(NH_2), 1605(C=N), 1265(Phenolic C-O), 1012(C-O-C). ^{1}H NMR (DMSO-d_6) ppm: 6.98-7.69 (8H,m,Ar-H), 5.31(2H,s,OH).

N-(5-Pyridin-2-yl)-1,3,4-oxadiazol-2-yl) acetamide **(PIOA):** m. p. 136°C, molecular formula ($C_9H_8N_4O_2$), molecular weight 204, recrystallization solvent ethanol, yield 80%, elemental analysis: (%)calculated H(3.95), C(52.94), N(27.44) found H(4.23), C(52.60), N(27.89). IR cm^{-1}: 3260(NH), 1690(C=O), 1596(C=N), 1044(C-O-C). ^{1}H NMR (DMSO-d_6) ppm: 9.92 (1H,s,NH), 7.34-8.72(4H,m,Ar-H), 2.38(3H,s,CH_3).

5-(1H-pyrrol-2-yl)-1,3,4-oxadiazol-2-amine **(PYOA):** m.p. 130°C, molecular formula ($C_6H_6N_4O$), molecular weight 150, recrystallization solvent ethanol, yield 81%, elemental analysis: (%)calculated H(4.03), C(48.00), N(37.32) found H(4.80), C(48.37), N(37.03). IR cm^{-1}: 3232-3188(NH_2), 3134(NH-pyrole), 1613(C=N), 1035(C-O-C). ^{1}H NMR (DMSO-d_6) ppm: 10.92 (2H,s, Ar-NH_2), 8.63(1H,s, NH-pyrole), 6.28-6.96 (3H,m,Ar-H).

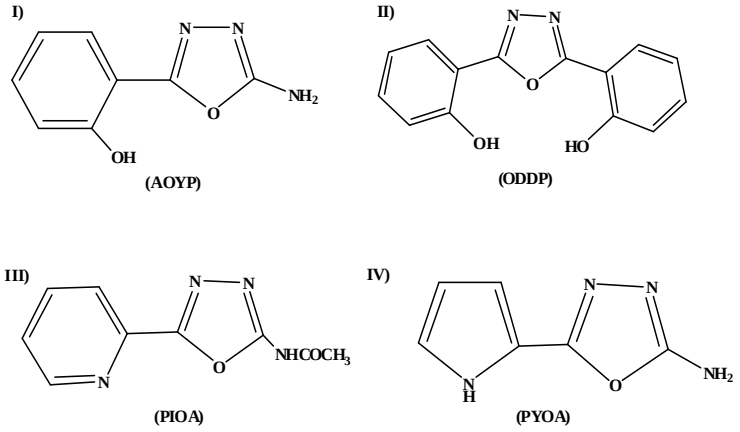

Figure 3. Structures of synthesized oxadiazoles

RESULTS AND DISCUSSION

All compounds were in conformity with the structure envisaged by spectral data (UV, IR, H1 NMR, Mass and Elemental analysis). In LCMS analysis, all the synthesized molecules showed molecular ion (M+) peak characteristic of their molecular weight which confirms their formation. The structures of the synthesized compounds were elucidated from the results obtained from various characterizations, i.e. UV (Table-1), IR, H^1 NMR, C^{13} NMR and Elemental analysis. The TLC of these synthesized compounds was done by using silica gel G glass plates and petroleum ether:ethyl acetate mixture (8:2) as developing solvent.

Electronic spectra of Ligands:

It can be seen from the data that solution spectrum of the ligands shows three bands lying in the region 210-217 *nm*, 245-264 *nm* and 295-310 *nm* of which first two bands may be assigned to $\pi \rightarrow \pi^*$ transition of benzenoid system and third band assigned to the $n \rightarrow \pi^*$ transition[4]. The observed λ_{max} are listed in table-1and a selected UV spectra is represented as figure- 4.

Table 1: Electronic Spectral Data

Compound	λ_1	λ_2	λ_3
AOYP	211 nm	260 nm	300 nm
ODDP	210 nm	254 nm	299 nm
PIOA	212 nm	248 nm	310 nm
PYOA	217 nm	245 nm	298 nm

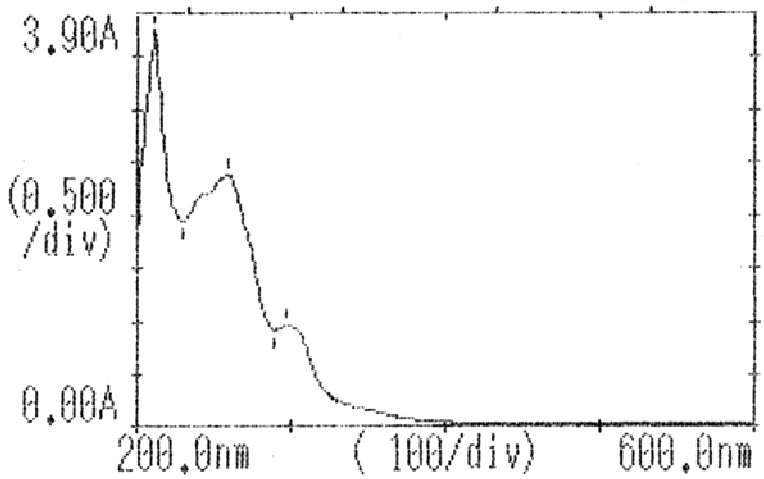

Figure 4: Electronic spectrum of AOYP

Antimicrobial Activity

Bacterial strains used in the study were clinical isolates of *Staphylococcus aureus*, *Escherechia coli*, *Proteus mirabilis*, and *Pseudomonas aeroginosa*, all of them were collected from Pharmacy College, Nanded, Maharashtra.

Table 2: The antimicrobial activity of 1, 3, 4-oxadiazole derivatives against various types of bacteria.
Screening results (Zone of inhibition in mm)

Compound (4 mg/ml)	Zone of inhibition in mm			
	S. aureus	*E. coli*	*P. mirabilis*	*P. aeroginosa*
AOYP	08	12	11	07
ODDP	07	11	12	09
PIOA	09	14	11	13
PYOA	09	13	15	12
Ciprofloxacin	27	36	32	29

Table 3: MIC Determination of 1, 3, 4-oxa-/thiadiazole derivatives and their complexes (for *P. mirabilis*)

Conc. (µg/mL)	AOYP	ODDP	PIOA	PYOA
4 x 10^3	-ve	-ve	-ve	-ve
2 x 10^3	-ve	-ve	-ve	-ve
1x 10^3	-ve	-ve	-ve	-ve
500	**+ve**	-ve	-ve	-ve
250	+ve	-ve	**+ve**	-ve
125	+ve	**+ve**	+ve	-ve
62.5	+ve	+ve	+ve	**+ve**
31.25	+ve	+ve	+ve	+ve
15.62	+ve	+ve	+ve	+ve
7.81	+ve	+ve	+ve	+ve
3.90	+ve	+ve	+ve	+ve
1.95	+ve	+ve	+ve	+ve
0.97	+ve	+ve	+ve	+ve
P.C.	+ve	+ve	+ve	+ve
S.C.	-ve	-ve	-ve	-ve

**Positive Control, **Sterility Control, Bacterial growth (+ve or –ve)*

All the 1,3,4-oxadiazole derivatives and its complexes were screened for for their in vitro antimicrobial activity by using the well diffusion method reported in the literature by Perez et al [13]. Three colonies of bacteria were transferred to sterile tubes each containing 5 ml of Tryptic Soy Broth. Turbidity of the bacterial suspensions was adjusted to reach an optical density equivalent to a 0.5 McFarland standard to give a bacterial suspension of 10^8 cfu/ml. Mueller-Hinton agar plates were inoculated by streaking bacterial swabs over the entire surface of the plates. Plates were allowed to dry at room temperature. Six millimetre wells were punched in the plates. Ciprofloxacin was used as a standard drug. All the compounds were dissolved in dimethyl sulfoxide. Fifty microliters of 4 mg/ml solutions of each of the 1,3,4-oxadiazole derivatives and their complexes were added into duplicate wells. Plates were allowed to stand at room temperature to let the tested derivative diffuse into the agar, and afterwards, they were incubated at 37^o C for 18 to 24 hours. Plates were examined for bacterial growth inhibition and zones of inhibition were measured in millimetres.

Determination of Minimum Inhibitory Concentration (MIC) [14]
MIC was determined by Broth dilution method. Drugs with inhibitory zones against the above mentioned bacterial strains were used in this part. Two-fold serial dilutions were prepared from the drugs in Tryptic Soy Broth. Duplicate tubes of each dilution were inoculated with $5x10^5$ of the bacterial strains. All tubes were incubated at 37^o C for 18 to 24 hours. The highest dilution of the drug that resulted in inhibition of bacterial growth was considered as the MIC.

Antimicrobial assessment
It can be seen from the screening results (Table-2) that the PIOA and PYOA showed better activity than others. The results also reveal that amongst the synthesised compounds, the PYOA and PIOA showed highest comparative activities especially against *P. mirabilis* and *E. coli* respectively. The zones of inhibition varied from 07 mm to 15 mm for the analytes. PYOA showed the highest zone of inhibition, it was about 15 mm, and its effect, on an average is at least half than that of the standard.

MIC
Owing to the better activity of PIOA and PYOA against *P. mirabilis*, the MIC tests of them were selectively screened for *P. mirabilis*. The results obtained from it are summarized in Table 2. As shown in Table-3, MIC of AOYP is at least two fold higher than the MIC of PYOA. MIC for the selected title compounds was determined by dilution of the different derivatives to various concentrations and compared with a standard (Ciprofloxacin, Cipla Ltd. Mumbai, India).

CONCLUSION

The proposed derivatives of oxadiazoles i.e. 2,5-substituted 1,3,4-oxadiazoles (AOYP, ODDP, PIOA and PYOA) were synthesized successfully. All the compounds were characterised using elemental, IR, NMR and LCMS studies and were evaluated for antibacterial activity. The compounds were found to have good activity against gram negative bacteria compared to that with gram positive bacteria. Among all the active compounds, PYOA showed good activity.

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