Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

https://doi.org/10.36673/AJRCPS.2023.v11.i02.A07

DESIGNED BIO ACTIVE SYNTHESIS OF SOME 1, 3, 4-OXADIAZOLES

N. Krishnarao*[1], B. Gandhi[1], B. Priyanka[1], M. Divya[1]

[1*]Department of Organic Chemistry, PRISM PG and DG College (Affiliated by Andhra University), Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

In present study, the synthesis of novel series of 2-phenyl-5-(pyridin-3-yl)-1, 3, 4-oxadiazole. These derivatives were obtained from Nicotinoyl hydrazide with substituted aromatic aldehydes in gridding process. The Nicotinoyl hydrazide can be synthesized by Nicotinoyl chloride with hydrazine hydrate in ethanol at reflux thionyl chloride in presence of DCM at 5-10^{o}C. The chemical structures of newly synthesized compounds were confirmed by IR, 1HNMR, 13CNMR, Mass spectral techniques and nitrogen (%) analyses. All these synthesized compounds were investigated for their antibacterial activities against bacterial strains i.e. *S.aureus, B. subtilis, E.coli and P. aeruginosa*.

KEYWORDS

Nicotinic acid, Nicotinylacylhydride, I_2, 2-phenyl-5-(pyridin-3-yl)-1, 3, 4-oxadiazole and Antimicrobial.

Author for Correspondence:

Krishna Rao N,

Department of Organic Chemistry,

PRISM PG and DG College (Affiliated by Andhra University), Visakhapatnam,

Andhra Pradesh, India.

Email: naallakrishnarao@gmail.com

INTRODUCTON

The world is presently experiencing the challenges of augmented microbial resistance development against usually available antimicrobial agents. Owing to this challenge of such resistance, there is always a need of search for classes of novel antibacterial agents. Nitrogen and oxygen containing five-memberted 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.

1, 3, 4-oxadiazoles is a well known important heterocycles both in synthetic as well as medicinal chemistry due to its simple synthesis and a wide range of biological activities. The common synthetic method for these compounds is cyclodehydration of diacylhydrazines and their derivatives with dehydrates such as phosphorous oxychloride, trifluoroacetic anhydride, thionyl chloride polyphosphoric acid and also reaction between the properly substituted acid hydrazide, carbon disulfide. 1, 3, 4 oxadiazoles and their derivatives constitutes as important class of organic compounds which have attracted much attention due to diverse biological activity as antimicrobial[1], antibacterial[2], antifungal[3], antiviral[4], antituberculosis[5], anti-diabetic[6], anticonvulsant[7], antioxidants[8], anti-inflammatory[9], anticancer[10] etc.

MATERIAL AND METHODS

General

All chemical compounds, solvents, reagents here used were analytical grade and they were procured from Merck and Aldrich Company. Melting points of all newly synthesized derivatives were determined in open capillary tubes on an electro Agarwal thermal apparatus and are uncorrected. The purity of the compounds was examined by thin layer chromatography on silica gel coated aluminum plate chromatography (TLC) using n-hexane / EtOAc (2:1) as an eluent. Infrared spectra (FT-IR) of products were recorded in potassium bromide (KBr) pellets using shimidzo 400 spectrometer. ^{1}H NMR and ^{13}CNMR spectra of compounds were recorded on a Brucker AMX 400 MHz spectrometer in $CDCl_3$ as a solvent using tetra methyl silane (TMS) as an internal standard. Chemical shifts and coupling constants are reported in δ and Hz respectively.

Experimental

The general procedure of Nicotinoyl chloride

Take dry and clean four necks RBF. The starting material niconicacid in dissolved in MDC and Thionyl chloride added drop wise in above solution into RBF at 5-100C and also fitted on the magnetic stirrer possesses hot plate. The reaction mixture continuous carried the reaction for 2 hrs at 400^{o}C. The progress of the reaction monitored by the TLC (EtOAc: n-hexane = 6:4). After completion of the consumed all reactants, cooled the reaction mixture at RT. The crude neutralized with as saturated solution of sodium bicarbonate and poured in ethyl acetate. The separated the organic layer and washed with water and separated the ethyl acetate layer. An organic layer can be distilled off under vacuums and solid compound obtained.

Characterization of Nicotinoyl chloride[2]

Yield: 90%, White solid, m.p. (°C): 185; IR (KBr, νmax, cm-1): 3045 (=C-H aromatic), 2978 and 2917 (-C-H aliphatic), 1608 and 1545 (C=C aromatic), 1H NMR (400 MHz, CDCl3) δppm: 8.475 (s, 1H, Pyridine), 8.310 (d, J=8.0Hz, 1H, Pyridine), 7.824 (d, J=7.4Hz, 1H, pyridine), 7.495 (s, 1H, pyridine), 13C NMR (100 MHz, CDCl3) δppm: 149.22, 145.65, 135.24, 133.04, 129.12, LCMS (m/z): 143.21(M+2); Molecular formulae: C_6H_4CNO. Elemental Analysis: Calculated: C- 50.91; H- 2.85; N- 9.90; Obtained: C-50.84; H-2.83; N- 9.68.

General Procedure for synthesis of Nicotinicacyl hydrazide (5a-5f)

Take dry and clean four necks 50mL RBF. The starting material Nicotinoyl chloride in dissolved in ethanol in a 50mL RBF. The hydrazine hydride added to drop wise above solution at RT and also fitted on the magnetic stirrer possesses hot plate and reaction continued at 70^{o}C. The reaction mixture continuous carried the reaction for 5 hrs at same temperature. The progress of the reaction monitored by the TLC (EtOAc: n-hexane = 7:3). After completion of the consumed all reactants, cooled the reaction mixture at RT. The crude neutralized with as saturated solution of sodium bicarbonate and poured in ethyl acetate. The separated the organic layer and washed with water and separated the ethyl acetate layer. An organic layer can be

distilled off under vacuums and solid compound obtained.

General Procedure for synthesis of phenyl-5-(pyridin-3-yl)-1, 3, 4-oxadiazolederivatives

Take dry and clean four necks RBF. The mixture Nicotinicacyl hydrazide and substituted aromatic aldehydes taken in a mortar. The molecular iodine added to the above mixtuture and grinding with piston and after completion of grinding and also arrangement fitted on the magnetic stirrer and containing hot plate. The reaction mixture continuous carried the reaction for 5 hrs at 70^{o}C .The progress of the reaction monitored by the TLC (EtOAc: n-hexane = 7:3). After completion of the consumed all reactants, cooled the reaction mixture at RT. The crude neutralized with as saturated solution of sodium bicarbonate and poured in ethyl acetate. The separated the organic layer and washed with water and separated the ethyl acetate layer. An organic layer can be distilled off under vacuums and solid compound obtained.

Characterization of phenyl-5-(pyridin-3-yl)-1, 3, 4-oxadiazole

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

Colourless, yields-77%. ^{1}HNMR (400Mz, $CDCl_3$) ppm: 8.846 (s, 1H, Pyridine), 8.592 (m, J=6.8Hz, 1H, Pyridine), 8.215 (d, J=7.6Hz, 1H, Pyridine), 7.792-7.525 (m, 5H, Ar-H), 7.498 (d, J=8.0Hz, 2H, Pyridine). ^{13}CNMR (100MHz, CDCl3) ppm: 166.74, 164.62, 148.56, 145.92, 134.62, 131.28, 129.73, 128.68, 126.56, 125.62. LCMS (m/z): 322.22(M+H). Molecular formulae: C13H9N$_3$O. Elemental Analysis: Calculated C-69.96, H- 4.06, N- 18.82. Obtained: C- 69.87, H- 4.04, N-18.91.

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

Colourless, yields-77%. 1HNMR (400Mz, CDCl3) ppm: 9.625 (s, 1H, -OH), 8.962 (s, 1H, Pyridine), 8.567 (d, J=7.6Hz, 1H, Pyridine), 8.126 (d, J=8.4Hz, 1H, Pyridine), 7.584 (t, J=7.6Hz, Pyridine), 7.425-7.267 (m, 4H, Ar-H). ^{13}CNMR (100MHz, CDCl3) ppm: 167.62, 164.35, 155.85, 150.27, 146.92, 135.62, 129.92, 128.84, 125.62, 118.65. LCMS (m/z): 240.27(M+H). Molecular formulae: C13H9N2O2. Elemental Analysis: Calculated C-65.27, H- 3.79, N-17.56. Obtained: C-65.18, H-3.77, N-17.25.

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

Colourless, yields-77%. 1HNMR (400Mz, CDCl3) ppm: 8.962 (s, 1H, Pyridine), 8.626(d, J=7.4Hz, 1H, Pyridine), 8.256 (d, J=8.0Hz, 1H, Pyridine), 7.926-7.722 (m, 2H, Ar-H), 7.568 (t.J=8.8Hz, 2H, Pyridine), 7.126-7.036 (m, 2H, Ar-H), 3.696 (s, 3H, -OCH_3). ^{13}CNMR (100MHz, CDCl3) ppm: 167.56, 164.32, 158.26, 150.36, 147.26, 133.96, 129.09, 124.62, 123.97, 119.76, 118.42, 116.37, 54.82. LCMS (m/z): 322.22(M+H). Molecular formulae: $C_{18}H_{15}N_3OS$.

2-(pyridin-3-yl)-5-(3, 4, 5-trimethoxyphenyl)-1, 3, 4-oxadiazole

Colourless, yields-77%. 1HNMR (400Mz, CDCl3) ppm: 8.712 (s, 1H, Pyridine), 8.567 (d, J=8.0Hz, 1H, Pyridine), 8.0135 (d, J=7.2Hz, 1H, Pyridine), 7.567 (t, J=8.8Hz, 2H, Pyridine), 7.292 (d. J=7.6Hz, 2H, Ar-H), 3.782 (s, 6H, OCH_3), 3.612 (s, 3H, OCH_3). ^{13}CNMR (100MHz, CDCl3) ppm: 166.62, 164.66, 151.62, 147.26, 145.32, 143.22, 134.09, 127.69, 124.62, 58.72, 55.63. LCMS (m/z): 314.36(M+H). Molecular formulae: C16H$_{15}$N$_3$O4, .Elemental Analysis: Calculated C-61.34, H-4.83, N-13.41. Obtained: C- 61.26, H-4.81, N-13.49.

2-(4-chlorophenyl)-5-(pyridin-3-yl)-1, 3, 4-oxadiazole:

Colourless, yields-77%. ^{1}HNMR (400Mz, $CDCl_3$) ppm: 8.846 (s, 1H, Pyridine), 8.596 (d, J=7.6Hz, 1H, Pyridine), 8.216 (d, J=8.1Hz, 1H, Pyridine), 7.742-7.532 (m, 4H, Ar-H), 7.496 (t, J=8.0Hz, 2H, Pyridine). ^{13}CNMR (100MHz, $CDCl_3$) ppm: 167.86, 165.24, 151.76, 149.62, 134.62, 132.76, 129.33, 128.62, 128.11, 127.35. LCMS (m/z): 259.44 (M+H). Molecular formulae: $C_{13}H8N_3OCl$, Elemental Analysis: Calculated C-60.60, H- 3.13, N-16.31. Obtained: C-60.510, H-3.11, N-16.39.

4-(5-(pyridin-3-yl)-1, 3, 4-oxadiazol-2-yl) benzonitrile

Colourless, yields-77%. ^{1}HNMR (400Mz, $CDCl_3$) ppm: 8.842 (s, 1H, Pyridine), 8.512 (d, J=9.0Hz, 1H, Pyridine), 8.256 (d, J=7.8Hz, 1H, Pyridine), 7.912-7.742 (m, 4H, Ar-H), 7.525 (t, J=8.0Hz, 2H, Ar-H). ^{13}CNMR (100MHz, $CDCl_3$) ppm: 167.62, 165.26, 151.62, 149.24, 147.66, 130.72, 129.28, 128.66, 125.24, 125.76, 119.72. LCMS (m/z):

247.33(M+H). Molecular formulae: $C_{14}H8N4O$, Elemental Analysis: Calculated C-67.74, H-3.25, N-22.57. Obtained: C- 67.65, H-3.23, N-22.65.

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

Colourless, yields-77%. 1HNMR (400Mz, CDCl3) ppm: 8.872 (s, 1H, Pyridine), 8.582 (d, J=8.0Hz, 1H, Pyridine), 8.326 (d, J=7.2Hz, 1H, Pyridine), 7.921-7.762 (m, 4H, Ar-H), 7.534 (t, J=8.0Hz, 2H, Pyridine). ^{13}CNMR (100MHz, $CDCl_3$) ppm: 167.96, 165.66, 151.66, 149.77, 145.72, 135.64, 134.12, 130.62, 130.75, 128.55, 125.62. LCMS (m/z): 269.36 (M+H). Molecular formulae: $C_{13}H_8N_4O_3$, .Elemental Analysis: Calculated C-58.21, H-3.01, N-20.89. Obtained: C-58.15, H-, 3.00, N-20.96.

RESULTS AND DISCUSSION

Chemistry

The present work reports efficient multistage approach for the synthesis of 1, 3, 4- oxadiazoles derivatives 5a-5f. This synthesis very simple and easiest method for preparation of phenyl-5-(pyridin-3-yl)-1, 3, 4-oxadiazole. This preparation followed by the synthesis of novel series of 2-phenyl-5-(pyridin-3-yl)-1, 3, 4-oxadiazole .These derivatives were obtained from Nicotinoyl hydrazide with substituted aromatic aldehydes in gridding process. The Nicotinoyl hydrazide can be synthesized by Nicotinoyl chloride with hydrazine hydrate in ethanol at reflux thionyl chloride in presence of DCM at 5-10^{o}C (Scheme No.).

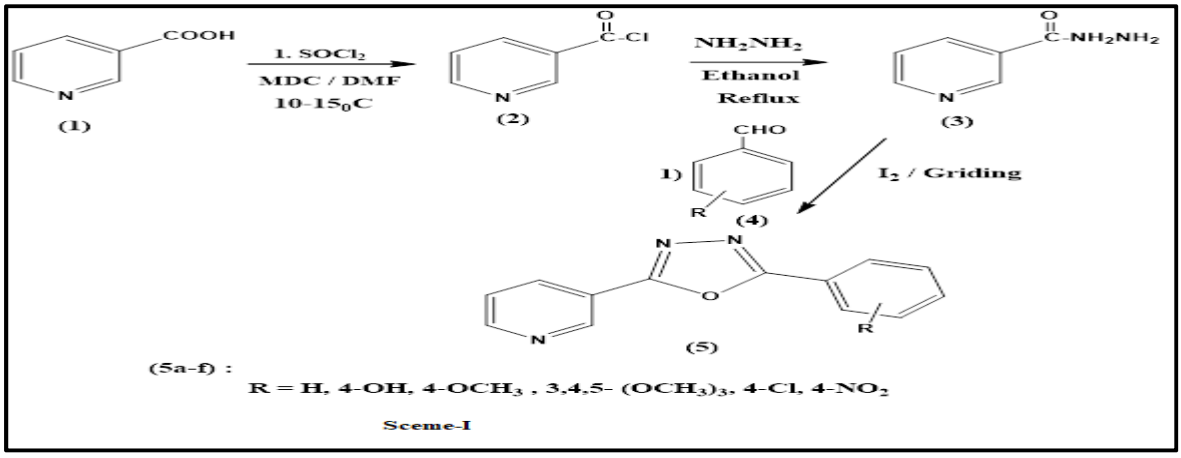
The structures of the titled compounds were characterized by ^{1}HNMR, ^{13}C NMR, mass spectral and elemental analyses. Similarly, its 1H NMR spectrum showed singlets at δ 8.961 of the pyridine protons and hydroxyl protons appeared at 9.625. The mass spectrum of 322.22 (M+H) and molecular formulae: $C_{13}H_9N_3O$ of compound 5a.

Oxadiazoles derivatives were screened for their in-vitro antibacterial and antifungal activities following micro broth dilution method. Antibacterial activity was screened against gram-positive (*Bacillus subtilis and Staphylococcus aureus*) and gram-negative (*Escherichia coli and P. aeruginosa*) microorganisms. Antifungal activity was screened against Aspergillus Niger and C.albicans microorganisms. The standard drugs used for this study were Streptomycin was used for antibacterial screening. Ketonozole was used for antifungal screening. The standard strains used for screening of antibacterial and antifungal activities were procured from the Culture collection and geneank (MTCC), Chandigarh, India. Mueller Hinton Broth was used as a nutrient medium for bacteria and Sabouraud dextrose Broth for fungal growth. Inoculums size for test strain was adjusted to 108 CFU/mL by comparing the turbidity. The results were recorded in the form of primary and secondary evaluation. The stock solution (2000µg/mL) of the compounds under investigation and standard drugs were prepared by successive twofold dilution.

In primary screening, 1000, 500 and 250µg/mL concentrations of the compounds were used. The compounds found to be active in this primary screening were further examination. In secondary screening, 200, 100, 50, 25, 12.5 and 6.25µg/mL concentrations were used. The inoculated wells were incubated overnight at 37 °C in a humid atmosphere. The highest dilution exhibiting complete inhibition was considered as a minimum inhibition concentration (MIC). The MIC values revealed that the synthesized compounds showed moderate to good inhibition. Compounds 5d, 5e exhibited good excellent activities against bacterial strains. The MIC values of antifungal activity shown that compound 5c and 5c exhibited good activity against all fungal strain. Antimicrobial activity of compounds (5a-5f) is listed in Table No.1.

Table No.1: Antimicrobial activity of compounds (5a-5f)

S.No	Entry	Antibacterial MIC (µg/mL)				Antifungal MIC (µg/mL)	
	Strains	*B. subtilis*	*S. aureus*	*P. aeruginosa*	*E. coli*	*A. Niger*	*C. Albicans*
1	5a	08	09	06	07	05	07
2	5b	18	16	17	16	12	13
3	5c	19	16	17	15	13	14
4	5d	21	20	22	21	17	16
5	5e	19	20	21	19	16	18
6	5f	08	07	05	03	18	19
7	Streptomycin	25	25	25	25	-	-
8	Ketonozole	-	-	-	-	22	22
9	DMSO						



Biological activities antibacterial and antifungal activities

CONCLUSION

In the present study, it is reported that the synthesized 1, 3, 4-oxadiazoles are developed from nicotinic acid hydrazides through simple synthetic approaches to search newer antimicrobial agents. For this, antimicrobial evaluation against different bacterial and fungal strains using disc diffusion method was studied. The antimicrobial compounds (5a-5f) were subjected to assess drug-like properties. The results of this microbiological assay have been further investigated in order to explore the mode of action of these outstanding antimicrobial agents along with toxicity studies. In conclusion, it is possible that auxiliary modifications in these bioactive compounds shall be of great effort to improved the selective antimicrobial agents.

ACKNOWLEDGEMENT

We would like to acknowledge PRISM PG and DG College, Visakhapatnam for providing us laboratory facility to carry out project work.

CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

BIBLIOGRAPHY

1. Jadhav R P. Synthesis and biological evaluation of a series of 1, 4-disubstituted 1, 2, 3-triazole derivatives as possible antimicrobial agents, *J Saudi Chem Soc,* 21(2), 2017, 152-159.
2. Kiranmehtha. Synthesis, characterization and *in vitro* antibacterial evaluation of oxadiazole derivatives, *SUSTJ,* 1(1), 2017, 27-35.

3. Sudeeshkumar, Gururaja R. Synthesis and biological properties of some novel 1, 3, 4-oxadiazole with quinolone moiety, *Der Pharma Chemica,* 9(15), 2017, 68-71.
4. Kavitha S. Biological aspects of 1, 3, 4-oxadiazole derivatives, *Asian J Pharm and Clin Res, 7*(4), 2014, 11-20.
5. Islam M. Synthesis and antimicrobial activity of some novel oxadiazole derivatives, *Acta Pol Pharma,* 64(4), 2008, 441-447.
6. Kavitha S. Synthesis, characterization and biological evaluation of novel 2, 5 substituted -1, 3, 4 oxadiazole derivatives, *Saudi Pharm J,* 25(3), 2017, 337-345.
7. Prasanna Kumar B N. Synthesis of N-[{5-Aryl-1, 3, 4- oxadiazole-2-yl} methyl] -4-methoxy aniline derivatives and their anticonvulsant activity, *J Chem,* 2013, 2013, 1-7.
8. Rabie A M. Design, synthesis and biological evaluation of novel 5-substituted-2-(3, 4, 5-trihydroxyphenyl)-1, 3, 4-oxidiazoles as potent antioxidants, *Am J Org Chem,* 6(2), 2016, 54-80.
9. Mohd Amir. Synthesis of Some 1, 3, 4-oxadiazole derivatives as potential anti-inflammatory agents, *Indian Journal of Chemistry,* 46B(6), 2007, 1014-1019.
10. Ahsan M J. Synthesis, Anticancer and molecular docking studies of 2-(4-chlorophenyl)-5-aryl-1, 3, 4 oxadiazole analogues, *Medicinal Chemistry,* 3(4), 2013, 294-297.
11. Zhu J, Bienayme H. Multi component reactions, *John Wiley and Sons,* 2006, 484.
12. Cappucino J G, Sherman N. Microbiology: A laboratory manual, *Addison Wesley Longman, New York, NY, USA,* 4th Edition, 1999.
13. Pharmacopoeia of India (The Indian Pharmacopoeia), *Controller 1 of Publications, New Delhi, India,* 1985, 858.
14. Patil S G *et al*. Synthesis and anticonvulsant, antimicrobial activity of some bis-1, 3, 4-oxadiazole and bis-1, 2, 4- triazole derivatives from sebacic acid, *Ind. J. Heterocyclic, Chem,* 17(1), 2007, 37-40.

Please cite this article in press as: Krishna Rao N *et al*. Designed bio active synthesis of some 1, 3, 4-oxadiazoles, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences,* 11(2), 2023, 42-47.