Available online on 30.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-18, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited

Open Access Research Article

Biological Evaluation of Novel Synthesized 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives

Sanwar Mal Solet, Neetesh Kumar Sharma*, Dr. Raghvendra Singh Bhadauria

[1] PhD Scholar, Sun Rise University, Alwar, Rajasthan, India

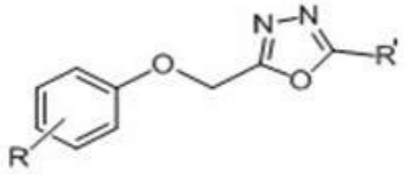
[2] Associate Professor (Pharmaceutical Chemistry), Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bhatinda, Punjab, India

[3] Principal at Shrinathji Institute of Pharmacy, Nathdwara, Rajasthan, India

ABSTRACT

Synthesis of a series of various 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives (7a-7v) have been done previously. These novel synthesized derivatives (7a-7v) have been tested for their antibacterial activity against Gram +ve *S. aureus* and Gram -ve *E. Coli* bacterias by broth dilution method. A comparative study has been done for all derivatives. Based on the visual turbidity, the MIC of the evaluated molecules has been studied, the evaluation concentration was used single therefore, the exact MIC could not determined and results are represented in less than and more than based on growth of microorganism. To get more exact MIC of the tested molecules need to be evaluated at low concentration. Further testing for all compounds at lower concentrations is required to compare their activity with standard Streptomycin at its MIC to get exact MIC the synthesized compounds.

Previously novel synthesized derivatives are; 2-(phenoxymethyl)-5-phenyl-1, 3, 4-oxadiazole (7a), 4-(5-(phenoxymethyl)-1, 3, 4-oxadiazol-2-yl)aniline (7b), 3-(5-(phenoxymethyl)-1, 3, 4-oxadiazol-2-yl) aniline (7c), 2-(5-(phenoxymethyl)-1, 3, 4-oxadiazol-2-yl)phenol (7d), 2, 4-dinitro-6-(5-(phenoxymethyl)-1, 3, 4-oxadiazol-2-yl)phenol (7e), 2-(4-(methylthio)benzyl)-5-(phenoxymethyl)-1,3,4-oxadiazole (7f), 2-((2, 4-dichlorophenoxy) methyl)-5-phenyl-1,3,4-oxadiazole (7g), 4-(5-((2, 4-dichlorophenoxy) methyl)-1,3,4-oxadiazol-2-yl)aniline (7h), 3-(5-((2, 4-dichlorophenoxy) methyl)-1,3,4-oxadiazol-2-yl)aniline (7i), 2-(5-((2, 4-dichlorophenoxy) methyl)-1, 3, 4-oxadiazol-2-yl)phenol (7j), 2-(5-((2, 4-dichlorophenoxy) methyl)-1,3,4-oxadiazol-2-yl)-4,6-dinitrophenol (7k), 2-((2,4-dichlorophenoxy) methyl)-5-(4-(methylthio)benzyl)-1,3,4-oxadiazole (7l), (Z)-2-((2, 4-dichlorophenoxy) methyl)-5-styryl-1,3,4-oxadiazole (7m), (S)-4-(2-(5-((2,4-dichlorophenoxy) methyl)-1, 3, 4-oxadiazol-2-yl)propyl)phenol (7n), 2-((4-nitrophenoxy) methyl)-5-phenyl-1, 3, 4-oxadiazole (7o), 4-(5-((4-nitrophenoxy)methyl)-1,3,4-oxadiazol-2-yl)aniline (7p), 3-(5-((4-nitrophenoxy)methyl)-1,3,4-oxadiazol-2-yl)aniline (7q), 2-(5-((4-nitrophenoxy)methyl)-1,3,4-oxadiazol-2-yl)phenol (7r), 2, 4-dinitro-6-(5-((4-nitrophenoxy)methyl)-1,3,4-oxadiazol-2-yl)phenol (7s), 2-(4-(methylthio) benzyl)-5-((4-nitrophenoxy) methyl)-1,3,4-oxadiazole (7t), (Z)-2-((4-nitrophenoxy)methyl)-5-styryl-1,3,4-oxadiazole (7u) and 5-((2, 4-dichlorophenoxy) methyl)-1,3,4-oxadiazole-2-thiol (7v).



7a-v

Article Info: Received 27 June 2019; Review Completed 17 Aug 2019; Accepted 23 Aug 2019; Available online 30 Aug 2019

Cite this article as:

Solet SM, Sharma NK, Bhadauria RS, Biological Evaluation of Novel Synthesized 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives, Journal of Drug Delivery and Therapeutics. 2019; 9(4-A):573-576 **http://dx.doi.org/10.22270/jddt.v9i4-A.3522**

***Address for Correspondence:**

Neetesh Kumar Sharma, Associate Professor (Pharmaceutical Chemistry), Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bhatinda, Punjab, India

Table 1: Various derivatives of 2,5-disubstituted-1,3,4-oxadiazole derivatives (7a-7v)

Sr. No.	Compound	R	R'
1	7a	-H	$-C_6H_5$
2	7b	-H	$4-NH_2C_6H_5-$
3	7c	-H	$3-NH_2C_6H_5-$
4	7d	-H	$2-OHC_6H_5-$
5	7e	-H	2- OH-3,5-dinitroC_6H_5-
6	7f	-H	$1-CH_2-4-SCH_3C_6H_5-$
7	7g	Chloro at position 2 and 4	$-C_6H_5$
8	7h	Chloro at position 2 and 4	$4-NH_2C_6H_5-$
9	7i	Chloro at position 2 and 4	$3-NH_2C_6H_5-$
10	7j	Chloro at position 2 and 4	$2-OHC_6H_5-$
11	7k	Chloro at position 2 and 4	2- OH-3,5-dinitroC_6H_5-
12	7l	Chloro at position 2 and 4	$1-CH_2-4-SCH_3C_6H_5-$
13	7m	Chloro at position 2 and 4	$C_6H_5CH=CH-$
14	7n	Chloro at position 2 and 4	$4-OHC_6H_5CH_2(NH_2)-$
15	7o	Nitro group at position 4	$-C_6H_5$
16	7p	Nitro group at position 4	$4-NH_2C_6H_5-$
17	7q	Nitro group at position 4	$3-NH_2C_6H_5-$
18	7r	Nitro group at position 4	$2-OHC_6H_5-$
19	7s	Nitro group at position 4	2- OH-3,5-dinitroC_6H_5-
20	7t	Nitro group at position 4	$1-CH_2-4-SCH_3C_6H_5-$
21	7u	Nitro group at position 4	$C_6H_5CH=CH-$
22	7v	Chloro at position 2 and 4	-SH

1. INTRODUCTION

All synthesized derivatives (7a-7v) were subjected to antimicrobial evaluation against *Escherichia coli* and *S. aureus* microorganism using broth dilution method keeping appropriate positive and negative controls simultaneously.

Infection: Infection is the invasion of an organism's body tissues by disease causing agents, there multiplication, and the reaction of host tissues to the infectious agents and the toxins they produce[1,2].

Anti-infectives: This term is used to describe any medicine that is capable of inhibiting the spread of an infectious organism or by killing the infectious organism[3].

Role of 1,3,4-Oxadiazole moiety in modern drug discovery.

A broad range of substituted 1,3,4-oxadiazoles have ramarkable attention in the field of drug discovery because of their large spectrum of pharmacological activities. Oxadiazoles have been kept at a specific place in the field of medicinal chemistry due to its wide range of activities[4].

1,3,4-oxadiazole derivatives show anticonvulsant[5], antimicrobial activity[6], insecticide[7], anti-tubercular activity[8], anti-inflammatory activity[9], cardiovascular activity[10], antialzheimers activity[11], anti-tumor agents[12], antidiabetes[13] and spasmolytic activity[14].

2. EXPERIMENTAL

2.1 Anti-microbial testing

Activity of anti-infective agents may be demonstrated under suitable conditions by their inhibitory effect on microorganisms. The anti-microbial activity of the synthesized compounds was carried out by standard procedure using broth dilution method and minimum inhibitory concentration was determined by visual comparison with the negative control tubes.

Detailed test procedure:

2.1.1 Stock Solutions of test compounds and standard drug

Compounds were taken as test samples along with a standard Streptomycin sample. Weight taken in the range of 8-20 mg of each test compound and was dissolved in 1 ml of DMSO. For preparing stock solution of Streptomycin, 10 mg of Streptomycin was dissolved in 1 ml of water.

2.1.2 Test organism

The organisms employed in the *in vitro* testing of the compounds were *Escherichia coli* and *S. aureus*. All the cultures were maintained on nutrient broth agar (Microbiology grade, CDH Pvt. Ltd. New Delhi.) medium by periodic sub culturing.

2.1.3 Preparation of Innoculum

Procedure for the preparation of innoculum for both the strains was same. The innoculum was prepared from a 24-hours old growth of organism on nutrient broth agar slant. To the agar slant, saline solution was added to obtain O.D value of 0.1 on photoelectric optical colorimeter. 0.5ml of this solution was further diluted to 20ml with use of saline.

2.1.4 Preparation of Medium

1.3 gms of nutrient broth (Microbiology grade, CDH Pvt. Ltd. New Delhi.) was dissolved in 100 ml of sterile distilled water.

2.1.5 Addition of drug, innoculum solution to medium

From diluted innoculum solution prepared, 100µl was added to separate test tube each containing 0.9ml of medium. 25 µl solution of test stock solution was added in four separate test tube containing 0.9ml of medium with 100 µl innoculum. The tests were carried out in duplicate. Apart from putting the controls of standard drug (Streptomycin), controls with dimethylsulphoxide (DMSO) were used. DMSO (positive control) is DMSO inoculated with organisms and dimethylsulphoxide (negative control) is plain DMSO. For

incubation, test tubes were kept in incubator at 35°C for 24 hours.

2.1.6 Observations

At the end of incubation period, the results were interpreted by comparison with negative control. The lowest concentration of test compound which showed inhibitory effect on growth on visual distinction was taken as minimum inhibitory concentration (MIC) and visual turbidity was consider for MIC of the test molecules; standard drug and DMSO positive and negative control visual turbidity were recorded.

The synthesized derivatives were tested for antimicrobial activity against *Escherichia coli* and *S. aureus* microorganism using broth dilution method keeping appropriate positive and negative controls simultaneously.

Visual turbidity of evaluated compounds is given in **Table 2**

Table 2: Visual turbidity of evaluated compounds

Sr. No.	Mol. ID	*E.coli* Visual turbidity	*S. aureus* Visual turbidity	Sr. No.	Mol. ID	*E.coli* Visual turbidity	*S. aureus* Visual turbidity
1	**7a**	_	_	13	**7m**	–	–
2	**7b**	_	_	14	**7n**	+	+
3	**7c**	_	_	15	**7o**	–	–
4	**7d**	_	_	16	**7p**	+	–
5	**7e**	_	_	17	**7q**	–	+
6	**7f**	_	_	18	**7r**	–	–
7	**7g**	_	_	19	**7s**	+	–
8	**7h**	_	_	20	**7t**	–	–
9	**7i**	_	_	21	**7u**	+	–
10	**7j**	_	_	22	**7v**	–	–
11	**7k**	+	+	23	**Streptomycin**	_	_
12	**7l**	+	_	_	**Positive**	++	++

- =No Turbidity (No bacterial growth), + = Turbidity (Bacterial growth)

Based on the visual turbidity, the MIC of the evaluated molecules is given in **Table 3** the evaluation concentration was used single therefore, the exact MIC could not determined and results are represented in less than and more than based on growth of microorganism. To get more exact MIC of the tested molecules need to be evaluated at low concentration.

The evaluation results of the single concentration is tabulated in **Table 3**

Table 3: Testing result of evaluated compounds

Sr. No.	Comp-ound	*E. coli* (µg/ml)	*S. aureus* (µg/ml)	Sr. No.	Comp-ound	*E. coli* (µg/ml)	*S. aureus* (µg/ml)
1	**7a**	< 600	< 600	13	**7m**	< 450	< 450
2	**7b**	< 450	< 450	14	**7n**	> 500	> 500
3	**7c**	< 500	< 500	15	**7o**	**< 25**	**< 25**
4	**7d**	< 425	< 425	16	**7p**	> 450	< 450
5	**7e**	< 350	< 350	17	**7q**	< 375	> 375
6	**7f**	< 500	< 500	18	**7r**	< 325	< 325
7	**7g**	< 325	< 325	19	**7s**	> 475	< 475
8	**7h**	< 375	< 375	20	**7t**	< 850	< 850
9	**7i**	< 375	< 375	21	**7u**	> 300	< 300
10	**7j**	< 450	< 450	22	**7v**	< 450	< 450
11	**7k**	> 750	> 750	23	**Strepto-mycin**	< 450	< 450
12	**7l**	> 450	< 450	_	_	_	_

3. RESULTS AND DISCUSSION

Most of the tested molecules showed bacterial growth inhibition at tested concentration. The compounds (**7e**, **7g**, **7h**, **7i** and **7u**) exhibited bacterial growth inhibition at concentration of less than 400µg/ml against both microorganisms. Compounds (**7o**) showed growth of inhibition at 25µg/ml against both microorganisms. Further testing for all compounds at lower concentrations is required to compare their activity with standard Streptomycin at its MIC to get exact MIC the synthesized compounds.

4. REFERENCES

1. Definition of "Infection" from several medical dictionaries, retrieved on 03, April, 2012.
2. "Utilizing antibiotics agents effectively will preserve present day medication". News Ghana; 21, November, 2015.
3. Plattener J., Chiron C. Cancer and Infectious diseases. *Annual Reports in Medicinal Chemistry*, A. M. Doherty, Editor, ElseveirAcademic press, NewYork, 2003, 38, 163-172.
4. Somani RR, Shirodkar PY Oxadiazole: A biologically important heterocycle. Chem Inform, 2011, 42.
5. Zarghi A, Faizi M, Shafaghi B, Ahadian A, Khojastehpoor HR, et al., Design and synthesis of new 2-substituted-5-(2-benzylthiophenyl)-1,3,4- oxadiazoles as benzodiazepine receptor agonists. Bioorg Med Chem Letters, 2005, 15, 3126-3129.
6. Sahin G, Palaska E, Ekizoglu M, Ozalp M Synthesis and antimicrobial activity of some 1, 3, 4-oxadiazole derivatives. II Farmaco, 2002, 57, 539-542.
7. Cao S, Qian X, Song G, Huang Q Syntheses and insecticidal activity of new 2-(5-(trifluoromethyl) pyridyloxymethyl)-1, 3, 4-oxadiazoles. Journal of Fluorine Chemistry, 2002, 117, 63-66.
8. Dewangan D, Pandey A, Sivakumar T, Rajavel R, Dubey RD. Synthesis of some novel 2, 5-disubstituted 1, 3, 4-oxadiazole and its analgesic, antiinflammatory, anti-bacterial and anti-tubercular activity. Int J Chem Tech Res, 2010, 2, 1397-1412.
9. Bansal S, Bala M, Suthar SK, Choudhary S, Bhattacharya S, et al. Design and synthesis of novel 2-phenyl-5-(1, 3-diphenyl-1H-pyrazol-4-yl)-1, 3, 4-oxadiazoles as selective COX-2 inhibitors with potent anti-inflammatory activity. European Journal of Medicinal Chemistry, 2014, 80, 167-174.
10. Malhotra V, Pathak SR, Nath R, Mukherjee D, Shanker K. Substituted imidazole derivatives as novel cardiovascular agents. Bioorg Med Chem Letters, 2011, 21, 936-939.
11. Saitoh M, Kunitomo J, Kimura E, Hayase Y, Kobayashi H, et al. Design, synthesis and structure–activity relationships of 1, 3, 4-oxadiazole derivatives as novel inhibitors of glycogen synthase kinase-3β. Bioorg Med Chem, 2009, 17, 2017-2029.
12. Sun J, Li M-H, Qian S-S, Guo F-J, Dang X-F, et al. Synthesis and antitumor activity of 1,3,4-oxadiazole possessing 1,4-benzodioxan moiety as a novel class of potent methionine aminopeptidase type II inhibitors. Bioorg Med Chem Letters, 2013, 23, 2876-2879.
13. He Y-W, Cao L-H, Zhang J-B, Wang D-Z, Aisa HA. Synthesis and bioactivity of 5-(1-aryl-1H-tetrazol-5-ylsulfanylmethyl)-N-xylopyranosyl-1, 3, 4-oxa (thia) diazol-2-amines. Carbohydrate research, 2011, 346, 551-559.
14. Neetu Bharatiya CPG Green And Efficient Microwave One Pot Synthetic Approach to N-Phenyl Piperazinyl-1,3,4-Oxadiazole Derivatives and Evaluation of Their Antioxidant and Anti Inlammatory Activity. Indian Journal of Applied Research, 2014, 4, 88-90.

JDDT