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Research Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW SERIES OF OXAZOLIDINEDIONE DERIVATIVES

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ABSTRACT

A new series of Oxazolidine-4,5-dione **1(e, f)** and Oxazolidine-2,4-dione **2(c, d)** were synthesized in presence of oxalylchloride, aminoacids and diethylcarbonate respectively. The purity of the synthesized compounds was confirmed by their physical constant and TLC. The structure of the synthesized compounds was confirmed by spectral data (FT-IR, ^{1}H NMR and Mass Spectroscopy). Antibacterial and Antifungal activity was carried out by broth micro dilution method & many of the compounds have show prominent anti-microbial activity.

Keywords: Oxazolidinedione, Amino Acids, Spectroscopy, Antibacterial Activity, Antifungal Activity, Antitubercular Activity,

INTRODUCTION

Heterocyclic compounds like polycyclic ring compounds, are usually known by non-systematic names[1]. In the family of heterocyclic compounds nitrogen and oxygen containing heterocyclic are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes[2].

Oxazole are five member heterocyclic compounds containing in their rings two hetero atoms, one of which is nitrogen and other is oxygen. Standard drugs used in some of the medicinally important derivatives containing oxazole are Trimethadione etc. which possess antiepileptic[3] properties.

Apart from this, oxazolidinone, oxazole benzyl esters, phenyl oxazolidine, spiroxazolidine possess different biological activities like antibacterial[4], anti-tuberculosis[5] cardiac activity[6] and muscarinic agonist[7].

Oxazolidine-2,4-diones are similar in general properties to the hydantoins[8] and may be prepared by analogous methods. Oxazolidine-2,4-diones are a class of biologically active compounds[9]. They are employed as anticonvulsants, particularly in the symptomatic treatment of absence seizures[8]. 3,5,5-Trimethyloxazolidine-2,4-dione (trimethadione) is the most active, but even 5-ethyl-3,5-dimethyloxazolidine-2,4-dione (paramethadione) and 3-allyl-5-methyloxazolidine-2,4-dione (malidone) display interesting therapeutic properties[10].

MATERIALS AND METHODS

All the reactions required anhydrous conditions were conducted in flame dried apparatus. Solvents and reagents were purified by standard methods. All AR grade chemicals are used for syntheis. Melting points were determined in open capillary tubes and are uncorrected. Purity of the compounds was checked by pre-coated TLC plate.

Synthesis

Synthesis of methyl ester of different aminoacids 1(a, b):

1mole of aminoacid was dissolve in methanol and treated with 1.5 mole of thionylchloride at 0°C. This cleared solution was treated with 1 mole of sodiumethoxide and refluxed. After compleation of reaction (reaction was monitored by TLC) excess of sodiumethoxide was filtered and solvent was evoprated[11].

Synthesis of chloroacetylchloride derivative of 1(c, d):

Methyl ester of **4(a-f)** (1 mol) was dissolved in DMF and cooled up to 0°C then chloroacetyl chloride (1mol) was added. Reaction stirred at mild heat and monitored by TLC. After completion of reaction DMF was evaporated residue was washed with ethanol then chloroform[12].

Synthesis of 2, 3-disubsstitude Oxazolidine-4,5-dione1(e, f):

Chloroacetyl chloride derivative of different aminoacids **1(c & d)** (1 mol) are dissolved in chloroform and oxaloylchloride (1mol) was added. Reaction was refluxed and monitored by TLC. After completion of reaction solution was concentrated

and dichloromethane was added[13]. To this solution charcoal was added and filtered. On addition of hexane to filtrate ppt. was obtained. Ppt. was dried and heated up to 5-10°C less than their melting point to get **1(e & f)**.

Synthesis of 2,4-Oxazolidinedione using diethyl carbonate.

Synthesis of different 2-hydroxy anilides 2(a, b):

Lactic acid (4ml) was treated with thanoylchloride (20 ml) and heat for 30 min. Then to this solution chloroform was added and equimolar amount of 4-substituted aniline (NH_3 in **2a**) dissolved in chloroform was added. Ppt. obtained was filtered and wash with chloroform[11].

Synthesis of different Oxazolidine-2,4-dione 2(c, d):

Sodium (1.05g) was dissolved in dry methyl alcohol (8-10 moles) in a three-necked flask. After the solution had cooled to 35°, the 2-hydroxy amide **2(a, b)** (1 mole) was added in solution in diethyl carbonate (1.16 moles) and when necessary, sufficient methyl alcohol (3-8 moles) to bring about complete solution of the amide. The resulting reaction mixture was then heated to the refluxing temperature (56-70°) until the reaction was completed (monitored by TLC). At the end of the reaction period the alcohol was distilled off, the cooled residue dissolved in water, and the solution extracted with ether to remove traces of unreacted starting material. On acidification of the aqueous layer, the oxazolidinedione separated. If the oxazolidinedione solidified the product was filtered off and dried. In the preparations involving low melting or water soluble derivatives, the acidified aqueous solution was extracted with isopropyl ether[14].

RESULTS AND DISCUSSION

Microbiological Screening:

Antibacterial Activity:

All the newly synthesized compounds were screened for the antibacterial activity by disc diffusion method and broth microdilution assay method. Ciprofloxacin and Norfloxacin were used as standard drug and activity of all newly synthesized compounds was measured against it.

The MIC values of synthesized compounds **1e, 1f, 2c & 2d** against different bacterial strains are shown in Table No.**1**

Antifungal Activity:

All the newly synthesized compounds were screened for the antifungal activity by disc diffusion method and broth micro dilution assay method. Fluconazole and Griseofulvin were used as standard drug and activity of all newly synthesized compounds was measured against it. MIC were measured and compared against Fluconazole and Griseofulvin.

The MIC values of synthesized compounds **1e, 1f, 2c & 2d** against different fungal strains are shown in Table No.**2**.

Anti-tubercular screening-Alamar blue dye using microplate alamar blue assay:

All the newly synthesized compounds were screened for the antitubercular activity against *Mycobacterium tuberculosis* H37RV by Alamar Blue Dye using Micro plate Alamar Blue Assay (MABA) method. Pyrazinamide and Streptomycin were used as standard drugs and activity of all the newly synthesized compounds was measured against them. The MIC was measured in µg/ml. Table No.**3** reveals the antitubercular activity (MIC) of newly synthesized compounds **1e, 1f, 2c & 2d.**

From biological evaluation it was found that 3-subistuted oxazole-4,5-dione having tryptophan amino acid at N_3 **(1f)** position was most active against all tested microorganism for antibacterial and antifungal activity. But when we replace tryptophan with glycine amino acid **(1e)**, all antibacterial and antifungal activity are lost. When we made substitution of electron donating group at C_5 **(2c & 2d)** position all antibacterial and antifungal activity are diminished. All compounds show resistant for antitubercular activity.

Table 1: Anti-bacterial MIC (µg/ml) values of the synthesized compounds.

Compounds	*Staphylococcus Aureus*	*Bacillus Subtilis*	*Klebsiella Pneumoniae*	*Escherichia coli*
1e	100	50	100	100
1f	0.8	0.8	0.8	0.8
2c	25	25	50	12.5
2d	25	25	50	12.5
Ciprofloxacin	**2**	**1**	**1**	**1**
Norfloxacin	**3**	**1**	**1**	**10**

Table 2: Anti-fungal MIC (µg/ml) values of the synthesized compounds.

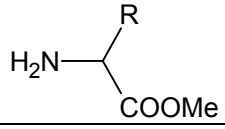
Compounds	*Candida Albicans*	*Candida neoformans*	*Aspergillus Niger*	*Aspergillus Flavus*
1e	100	50	100	50
1f	0.8	0.8	0.8	0.8
2c	50	25	12.5	25
2d	50	50	12.5	25
Fluconazole (30µg)	**16**	**16**	**8**	**8**
Griseofulvin	**500**	**500**	**100**	**100**

Table 3: Assay (MABA) method (MIC µg/ml).

Sl.No	Compounds	100	50	25	12.5	6.25	3.125	1.6	0.8
1	1e	S	R	R	R	R	R	R	R
2	1f	S	R	R	R	R	R	R	R
3	2c	S	R	R	R	R	R	R	R
4	2d	S	R	R	R	R	R	R	R

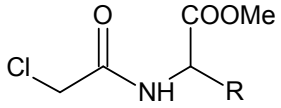
S – Sensitive, R – Resistant.
Standard values for the Anti-TB test which was performed.
Pyrazinamide- 3.125µg/ml, Streptomycin- 6.25µg/ml.

Table 4:.Physicochemical data of different amino acid esters 1(a,b).



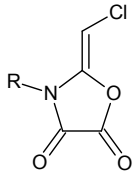
Comp. No.	R	Molecular Formula	Molecular Weight	MP (^oC)	Yield (%)	R_f^*	CHN analysis (%) Calculated (Found) C	H	N
1a	H	$C_3H_7O_2N$	89	176.2	80.71	0.63	40.44 (40.32)	7.92 (7.69)	15.72 (15.86)
1b	3-methylen Indole	$C_{13}H_{12}N_2O$	217	152-53	80.23	0.55	66.04 (66.35)	6.47 (6.06)	12.84 (12.45)

Table 5: Physicochemical data of different acetylchloride derivative of aminoacidesters 1(c, d).



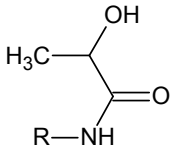
Comp. No.	R	Molecular Formula	Molecular Weight	MP (^oC)	Yield (%)	R_f^*	CHN analysis (%) Calculated (Found) C	H	N
1c	H	$C_5H_8O_3NCl$	89	176-77	80.71	0.72	36.27 (36.54)	4.87 (4.54)	8.46 (8.82)
1d	3-methylene Indole	$C_{15}H_{13}N_2O_2Cl$	217	152-53	80.23	0.65	57.05 (57.58)	5.13 (5.58)	9.50 (9.25)

Table 6: Physicochemical data of different oxazolidine-4, 5-dione (using aminoacid) 1(e,f).



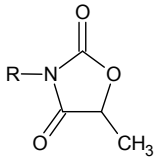
Comp. No.	R	Molecular Formula	Molecular Weight	mp (^oC)	Yield (%)	R_f^*	CHN analysis (%) Calculated (Found) C	H	N
1e	$C_3H_5O_2$	$C_7H_6NO_5Cl$	219	70-73	26.12	0.32	38.29 (38.58)	2.75 (2.42)	6.38 (6.92)
1f	methyl 2-amino-3-(indol-3-yl)propanoate	$C_{16}H_{13}N_2O_5Cl$	348	258-65	20.10	0.25	55.10 (55.52)	3.76 (3.09)	8.03 (7.69)

Table 7: Physicochemical data of different α-hydroxyl anilides 2(a, b).



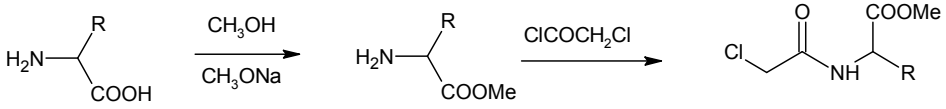
Comp. No.	R	Molecular Formula	Molecular Weight	mp (°C)	Yield (%)	R_f^*	CHN analysis (%) Calculated (Found) C	H	N
2c	H	$C_4H_5NO_3$	109	110-16	20.20	0.88	41.74 (41.48)	4.38 (4.85)	12.17 (12.52)
2d	4-BrC_6H_4	$C_{10}H_8NO_3Br$	256	150-52	22.30	0.52	44.47 (44.01)	2.99 (2.30)	5.19 (4.94)

Table 8: Physicochemical data of different oxazolidine-2, 4-dione (using diethyl carbonate) 2(c, d).



Comp. No.	R	Molecular Formula	Molecular Weight	mp (°C)	Yield (%)	R_f^*	CHN analysis (%) Calculated (Found) C	H	N
2a	H	$C_3H_7NO_2$	89	186-90	80.10	0.70	40.44 (40.04)	7.92 (7.48)	15.72 (15.26)
2b	4BrC_6H_4	$C_9H_{10}NO_2Br$	244	150-55	78.36	0.59	44.29 (43.05)	4.13 (3.85)	5.74 (5.23)

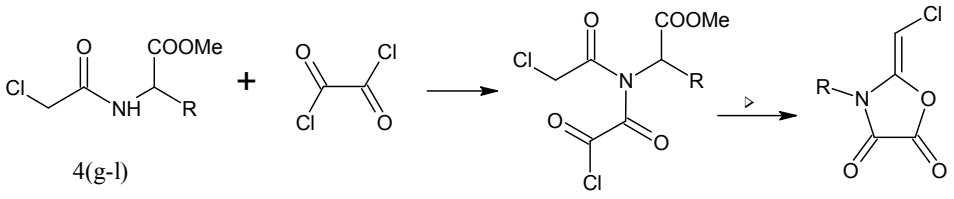
Step-I Synthesis of different acetylchloride derivative of aminoacids.



R = H (1a), 3-methylenindol (1b)

R = H (1c), 3-methylenindol (1d)

Step-II Synthesis of different oxazolidine-4,5-done using 1c, 1d.

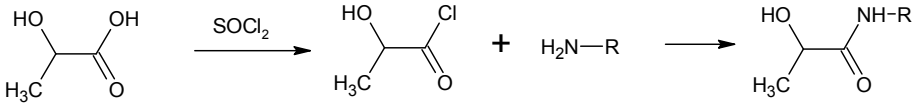


4(g-l)

R = $C_3H_5O_2$ (1e), methyy-2-amino-3-(indol-3-yl)propanoate (1f).

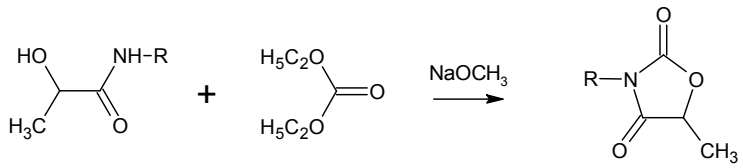
Scheme 1: Synthesis of 2, 3-disubsstitude Oxazolidine-4,5-dione using oxaloyl chloride and amino acids

Step-I Synthesis of different 2-hydroxy anilides .



R =H(2a),
4BrC_6H_5(2b).

Step-II Synthesis of different oxazolidine-2,4-dione.



R = H(2c), 4BrC_6H_4 (2d).

Scheme 2: Synthesis of 2,4-Oxazolidinedione using diethyl carbonate

CONCLUSION

Biological evaluation of selected compound shows that 3-subistuted oxazole-4,5-dione having tryptophan amino acid at position N_3 **(1f)** was most active against all tested microorganism for antibacterial and antifungal activity. On replacement of tryptophan with glycine amino acid **(1e)**, all antibacterial and antifungal activity was lost. When electron donating group were substituted at C_5 **(2c & 2d)**, antibacterial and antifungal activity were decreased. Compounds synthesized during our study were resistant to *Mycobacterium tuberculosis.*

REFERENCES

1. Introduction to Heterocyclic compound [Online]. 1997. [cited 2013 March 22]; [5 screens]. Available; URL:http://www.3rd1000.com/chem301/chem302a.htm.
2. Heda LC, Sharma R, Pareek C, Chaudhari PB. Synthesis and antimicrobial activity of some derivatives of 5-substituted indole dihydropyrimidines. Euro J Chem 2009;6:770-4.
3. Abraham DJ. Burger's medicinal chemistry and drug discovery. Vrginia: Wiley-interscience,A john wiley and sons,inc,publication; 6th ed. vol 6. p. 263-328.
4. Weon BI, Choi SH, Park JY, Choi SH, Finn J, Yoon SH. Discovery of torezolid as a novel 5-hydroxymethyl-oxazolidinone antibacterial agent. Euro J Med Chem 2011; 46: 1027-39.
5. Abraham DJ. Burger"s medicinal chemistry and drug discovery. Wiley-interscience,A john wiley and sons,inc.,publication, 6th ed. vol 6. p. 563-628.
6. Moraski GC, Chang M, Estrada AV, Franzblau SG, Mollmann U, Miller MJ. Stracture activity relationship of new anti tuberculosis agent derived from Oxazolin and oxazole benzyl esters. Euro J Med Chem 2010;45:1703-16.
7. Gudaprthi V, Bharathi K, Omprakash G. Synthesis,characterisation and cardiac activity of some novel 2,3 substituted-4-phenyl-1,3-oxazolidine derivatives. Asian J Chem 2011; 23;765-9.
8. Clark-lewis JW. 2,4-Oxazolidinediones. Chem Revs 1958; 58: 63-99.
9. Casadeia MA, Stefania C, Achille I. Electrochemical Studies on Haloamides. Part XII Electrosynthesis of Oxazolidine-2,4-diones. Tetrahedron 1995; 51(20): 5891-900.
10. Mercier, J. Anticonvulsant drugs in International encyclopedia of pharmacology and therapeutics. Mercier J, editor. Pergamon Press: Oxford 1973; 1: 213-5.
11. Brian S, Hannaford AJ, Smith PWG, Tatchell AR. Investigation and characterization of organic compound. In: Vogel's textbook of practical organic chemistry.5th ed. London: Longman scientific and technical, longman group UK limited; 1989; 1261-3.
12. Murugesana S, Gangulya S, Magab G. Synthesis, evaluation and molecular modeling studies of some novel tetrahydroisoquinoline derivatives targeted at the HIV-1 reverse transcriptase. Der Pharmacia Lettre 2011;3:317-32.
13. Spezia AJ, Smit LR. The reaction of oxalyl chloride with amides. II. oxazolidinediones and acyl isocyanates. J Org Chem 1963;28:1805–11.
14. Wallingford VH, Thorpe MA, Stoughton RW. Alkyl carbonates in synthetic chemistry. VI. Condensation with α-hydroxy amides. A new method for Preparing 2,4-Oxazolidinediones. J Am Chem Soc 1945; 67: 522–3.

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