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Efficient Synthesis of Novel Therapeutic Agent Possessing Sulfonamide Oxothiazolidine Moiety

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ABSTRACT

A convenient method of synthesizing sulphonamide compounds possessing oxothiazolidine moiety is described, which has been carried out in excellent isolated yields. The physicochemical characterization was unambiguously confirmed by the usual spectroscopic methods. 1HNMR, 13CNMR, IR and the microbial screening revealed excellent positive effects.

Keywords : Oxothiazolidine - Sulfonamide Moieties, Therapeutic Agent (Anticonvulsant).

I. INTRODUCTION

The sulfonamides possessing SO_2, NH_2 in their structures are excellent chemotherapeutic agents which are found to be active against certain gram positive and gram negative cocci, certain gram negative bacilli and protozoa's. Besides being cheap and safe antibacterials, an effort has been made to determine their mechanism of action. This has given a tremendous impetus to investigate other antimetabolites of therapeutic interests. Oxozolidinones containing sulfonamide moiety have attracted obvious attention due to their significant biological properties and their role as pharmacophores[1]. These heterocyclic compounds were used as antibacterials[2], inhibitors of monoamine oxidase[3], cytokine modulators [4], sigma receptors [5], pschyotropics[6], antiallergic agents[7], antibiotics[8], as intermediates in the synthesis of renin inhibitors[9], β-lactam and macrolide antibiotics[10], immune suppressants[11] , in addition to many other applications [12,13].

As these sulfonamide moiety enhances the activity of certain antibacterial agents especially against both gram-positive and gram-negative [14-16] certain sulfoxides[17], sulfonamide[18], cyclic sulfonamide[19] with oxazolidine derivates[20] have been successfully reported [21,22].

Thus, as part of our ongoing research work, aimed at the synthesis of novel products with potential antibacterial activities, the present study took birth by synthesizing new compound with sulfonamide and oxothiazolidine moieties.

II. MATERIALS AND METHODS

All chemicals and solvents were purchased from common business sources and were used as received with none more purification. All reactions were monitored by TLC on silica percolated glass plates and developed by spraying with ninhydrin. Nucleon nuclear magnetic resonance spectra were recorded on a Brucker spectrometer at 400 MHz. Chemical shifts were reported in δ units (ppm) with TMS as reference (δ0.00) and coupling constants in Hertz, multiplicity is additionally indicated. Carbon nuclear magnetic resonance spectra were recorded on a Brucker Varian VMS and Brucker Avance II+ 500 MHz spectrometers at 100 MHz. Infrared spectra were recorded on a shimadzu FT-IR-8000 spectrometer. Melting points

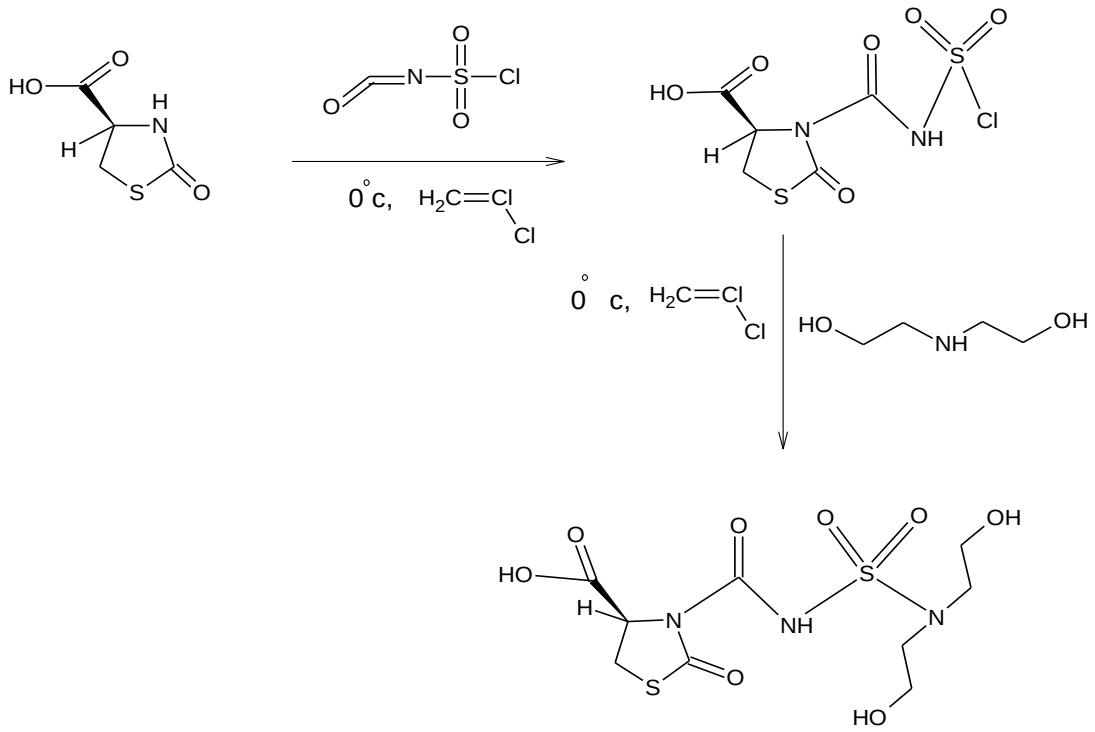
were determined in open capillary tubes and elemental analysis by usual standard procedures [23]. Magnetic data by using gouy balance and microwave appliance (Samsung-Model-MW73AD) was used.

III. PROCEDURES

Ligand-IPOCA:

A solution of 2-oxothioazolidine 4-carboxylic acid (0.01) in anhydrous CH_2Cl_2(5ml) was added to a stirring solution of chlorosulfonyl isocyanate (CSI)(0.01M) in 5 ml of anhydrous CH_2Cl_2 at 0°c dropwise over a period of 30 min. The resulting solution was transferred to a solution of 2,2-imminodiethanol (0.01M) in CH_2Cl_2(5 ml).

The solution was magnetically stirred at 0°c for 2 hrs and washed with a mixture of H_2O and HCl (0.1N). The organic layer was filtered and concentrated. The residue was purified by silica gel chromatography to give the obtained sulfonamides in good yield (81%).



Scheme 1: Synthesis of 2-2-(iminodiethano)-N-(N-phenylsulphamoyal)- oxothiazoline-4-carboxlic acid.

Complexes

For this, L-M ratio was confirmed by conductometric titrations using monovariation method on systronics conductivity meter using dip type electrode. Conductometric titrations supported 2:1(L: M) ratio, further supported by Job's method of continuous variation [24] modified by Turner and Anderson [25].

The metal complexes were prepared by microwave radiations using solutions of the ligand and metal salts (2:1) for about 6 min. Solid crystalline products appeared.

Antibacterial Screening

Above synthesized ligand and its metal complexes were screened against bacteria, E.Coli and B.Subtilis using streptomycin as standard by filter paper disc method [26] at various concentrations using nutrient agar as medium. Sterlized filter paper of 5 mm diameter were soaked in solutions of different concentrations of test samples and introduced on nutrient agar plates, which were incubated for 48hrs at 35°c.

IV. RESULTS AND DISCUSSION

(a) **Physical Parameters (IPOCA):** White amorphous state (81%), M.P~137°c, solubility in ethanol.

(b) **Spectral:**

(i) IR(KBr cm^{-1}): (OH ethanolic)3440,(C=O)1755, (C-OH) 3200,(C-H) 1800, (S-C=O) 2120, (N-C=O) 1650, (C-NH-S) 3330, (S=O) 1340.

(ii)^{1}HNMR(400 MH_3,$CDCl_3$): δ (C-N-H-S) 2.2ppm, (C-CH_2-S) 2.7ppm, (C-C-H) 0.9ppm, (OH-C=O) 11.6ppm.

(iii)^{13}CNMR(100MH_3,$CDCl_3$): δ(ppm) (C=O) 179ppm, (C-OH) 162ppm, (C-CH-N) 142ppm, (C-C-C) 47ppm, (C-C-S) 55ppm, (S-CO-N) 57, (N-CO-N) 2210ppm, (C-N-C) 60ppm.

V. COMPLEXES

1. **Physical parameters (Fe(II), Ni(II), Co(II) complexes**: Coloured compounds with satisfactory yield. Elemental analysis data, formula weights and melting points are given in table1.
2. **Magnetic moment**: Susceptibility parameters reveal their paramagnetic nature.
3. **Molar conductance**: Values are in the range of 9.5-14$\Omega^{-1}cm^2$ mol^{-1} suggesting their non-electrolytic nature [27].

Table1 : Physiochemical and analytical data of IPOCA and complexes.

L/C	Elemental Analysis %Found (Calc)						Colour	M.P.°c	Yield%	μ_{eff} (BM)
	C	H	N	O	S	M				
IPOCA	33.23 (32.25)	04.61 (04.53)	12.90 (12.40)	39.38 (38.20)	09.80 (09.70)	-	White	137	81	
IPOCA-Fe	28.42 (27.86)	03.68 (03.50)	11.05 (10.90)	33.68 (33.16)	08.42 (08.13)	14.73 (14.56)	Peach	185	67	5.20
IPOCA-Ni	28.27 (27.80)	3.66 (03.45)	10.99 (10.79)	33.50 (33.10)	8.37 (08.10)	15.18 (14.45)	Light green	208	58	2.94
IPOCA-Co	28.19 (27.60)	3.65 (03.33)	10.96 (10.74)	33.42 (33.02)	8.35 (08.04)	15.40 (14.20)	Bluish green	215	60	4.63

4. **Electronic Spectra and Magnetic Measurements :** Electronic spectral measurements were used for assigning the stereochemistry of metal ions in the complexes. Bands at 11300cm^{-1} for $^5T_{2g}\rightarrow{}^5E_g(G)$ and 19300 cm^{-1} to charge transfer and μ(BM) as 5.20 BM supports an octahedral environment in Fe(II)[28], whereas for Ni(II)-10250,16900 and 25300 cm^{-1} supports transitions[29] in allignment with 2.94B as magnet moment for its octahedral stereochemistry.

   Two prominent bands at 18500 and 22500cm^{-1} for $^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$ &$^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$ transitions are in fair agreement with an octahedral geometry,supported by 4.63B.M[30].
5. **Infrared spectra:**_(OH ethanolic)3440,(C=O)1755, (C-OH) 3200,(C-H) 1800, (S-C=O) 2120, (N-C=O) 1650, (C-NH-S) 3330, (S=O) 1340, (M-S) 210-260, (M-N) 520-600.
6. **^{1}HNMR:** δ (C-N-H-S) 2.2ppm, (C-CH_2-S) 2.7ppm, (C-C-H) 0.9ppm, (OH-C=O) 11.6ppm.
7. **^{13}CNMR:**δ(ppm) (C=O) 179ppm, (C-OH) 162ppm, (C-CH-N) 142ppm, (C-C-C) 47ppm, (C-C-S) 55ppm, (S-CO-N) 57, (N-CO-N) 2210ppm, (C-N-C) 60ppm.
8. **Antibacterial Activity**: The antibacterial screening of the synthesized compound IPOCA and its

metal complexes (table2), reveals that the activity zones were also visible for IPOCA but for complexes significant values were obtained which supports that chelation increases the activity[31].

Table 2 : Antibacterial screening data of IPOCA and its complexes.

Compound/ Complexes	Antibacterial zone of inhibition(mm)	
	E.Coli	B.Sebtilis
IPOCA	16.12	14.18
IPOCA-Fe(II)	28.20	20.30
IPOCA-Ni(II)	19.24	15.11
IPOCA-Co(II)	25.30	18.10
Streptomycine	18.00	16.00

VI. MECHANISM OF ACTION

Chemically it (IPOCA) can be classified as an antiseizure drug. The mechanism by which it exerts its antiseizure effect is unknown, although it is believed that the drug can block sodium and T-type calcium channels, which leads to the suppression of neuronal hypersynchronization(i.e. seizure- form activity). It is also known to be a weak carbonic anhydrase inhibitor, similar to the anticonvulsant property.

VII. VII. PHARMACOKINETICS

Absoption: Variable, yet relatively rapid rate of absorption with a time to peak concentration of 2.8-3.9 hours was absorbed in albino rats.

VIII. CONCLUSION

In nut shell a convenient and efficient route for the synthesis of novel sulfonamide oxothiazolidine chiral compound by carbamoylation followed by sulfamoylation was studied with no side reactions and with satisfactory isolation of the product. Significant antibacterial parameters can decide its use as a therapeutic agent[32-34].

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