MICROWAVE ASSISTED, SOLVENT FREE SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF 3-ALKYL-5-CHLOROSULPHONYL-1,2-BENZISOXAZOLES AND THEIR DERIVATIVES

Shivaji Jadhav[1, 2]*, Sayyed Hussain[1], Megha Rai[2] and Mazahar Farooqui[2, 3]

1. Sir Sayyed College, Aurangabad 431001 (M S).India
2. Dr. Rafiq Zakaria College for Women, Aurangabad.(M.S).India
3. Post Graduate and Research Centre, Maulana Azad College, Aurangabad.(M.S).India

***E-mail: simshivv_48@yahoo.com**

ABSTRACT:

Most of the diseases in the current scenario are found to be infections caused by microbes like bacteria, fungi etc. many antibiotics have been discovered till date for treatment of such diseases but most of them associated with super-infection development of resistance, destruction of normal non-pathogenic bacterial flora and selectivity toxicity like aplastic anaemia, kidney damage etc. The present study based upon preparation of antibiotics with high potency, specificity and less toxicity. Benzisoaxazol are widely distributed in nature and they have been shown to have very interesting pharmacological activities like antibacterial. Hence in the present study the mixture of chlorosulphonic acid and 3-alkyl-benzisoxazole irradiated under ultrasonic irradiation for short time period (8-10 min.) at room temperature to get 3-alkyl-5-chloro sulphonyl-1,2-benzisoxazoles. All 3-alkyl-5-chloro sulphonyl-1,2-benzisoxazoles. All synthesized compounds are characterized by spectral analysis like IR, NMR and elemental analysis and also screened for antibacterial activity.

Keywords: Microwave, Benzisoaxazol, solvent-free, antibacterial.

INTRODUCTION:

Heterocyclic compounds promote the life on earth[1]. These are widely distributed in natureand essential to life as they play important roles. Heterocyclic ring systems containing ‘S’heteroatom exhibited chemotherapeutic, antituberculosis and other medicinal uses. A numberof benzisoxazoles show physiological activity and have been tested forpharmacological uses.

The derivatives of 6-acetamidobenzisoxazole-3-acetic acid have been reported to havetuberculostatic activity[2]. Compounds belonging to 3-aminobenzisoxazole series have beenshown to possess sedative and analgesic properties[3]. Some compounds have been found topossesstrypanocidal activity[4]. 4,5,6,7-Tetrahydro derivatives were tested as analeptics[5]. Somederivatives of napthisoxazolylphosphotioate have been used as acricides, insecticides andlarvicides[6]. In the year 1972, Sounder[7] concluded that 3-phenyl-5-methyl-1,2-benzisoxazolederivatives were anti-inflammatory at 25 to 500 mg dose. Nishimura and others[8] synthesized anumber of compounds having amidoxime substituent at 3-position and observedantidepressant, hypotensive and α-DOPA synergistic activities. The antifungal and antibacterial activities were observed by Thakkar and coworkers[9,10] in the nitro substitutedandformyl substituted 1,2-benzisoxazoles. Some of the 5-nitro derivatives show inhibitory

action on phytophathogenic bacteria. Freedom and Jules[11] observed C.N.S. depressant effect and sedative effect in benzothiapyranoisoxasoles. Various methods are reported in literature for the synthesis of isoxazoles. Some of the important methods are given below -

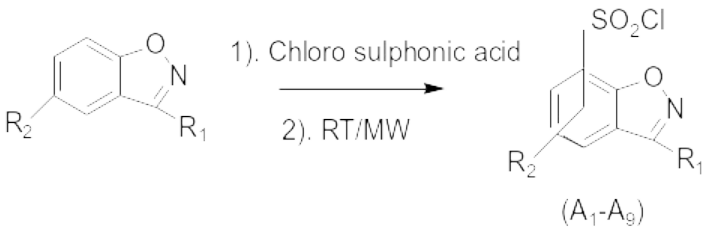
1. From O-halogeno-benzoyl compounds and hydroxyl amine.
2. From O-nitrobenzoyl compounds and hydroxylamine hydrochloride.
3. From other O-substituted benzoyl compounds and hydroxylamine.
4. From O-hydroxybenzoyl derivative.
5. Miscellaneous (a) By hydrolysis of O-hydroxybenzalazides(b) By bromination.
6. Closure of bond between 1-7a and 3-3a of 1,2-benzisoxazole and
7. Cyclising O-hydroxy benzoyl derivatives with pyridine.

It has been observed that neither cyclisation nor the methods mentioned above gives good yields and they are even tedious and time consuming. Thus, present work has been selected to synthesize benzisoxazole derivatives by using Microwave oven and also characterize them by means of IR,1H NMR and elemental analysis to overcome above difficulties.

In the biological investigation, the compound were screened for antibacterial activity against*Bascillussubtilis*(gram positive) and *Klebsiella* (gram negative) bacteria by employing the food poison technique at 250 and 100 ppm.

EXPERIMENTAL: General procedure for the preparation of 3-alkyl-5-chloro-sulphonyl-1,2-Benzisoxazoles: The chlorosulphonic acid (0.1 mol) was taken into flask and it was cooled. Then the3-alkyl-benzisoxazole (0.01mol) was added portion wise to the cooled chlorosulphonic acid and mixed properly with glass rod and then irradiated in a microwave oven for the appropriate period of times as mentioned in table-1 at 450 watt. The progress of reaction was monitored by TLC [n-Hexane: EA (80:20)]. After completion of the reaction, reaction mixture cooled and poured on crushed ice. It was stirred and solid separated was collected, washed with sodium bicarbonatesolution and distilled water. It was crystallized from aqueous acetone which givescompounds **(A1 – A9)**.

Reaction Scheme:



(A_1-A_9)

Where, R1 = Methyl, Ethyl, Propyl &R2 = H, Methyl.

Melting points were determined in open capillary tube and are uncorrected. The purity of test compounds were determined by TLC on protected SiO2 gel (HF254 200 mesh) on aluminium plates (E. Merck). A single spot was obtained on TLC, which confirmed the purity of substituted benzisoxazoles and yield was calculated (w/w).

The time of reaction, melting points, percentage yields and elemental analysis (% of sulphur) of thesynthesized compounds are given in **Table 1**

Table 1: Physical data and elemental analysis of compounds (A1 -A9)

Comp.	R_1	R_2	MW	Time in Min	MP (°C)	Yield (%) (w/w)	Sulphur (%)	
							Found	Calculated
A1	Methyl	5-Methyl	450	15	125	60	13.80	13.82
A2	Methyl	7-Methyl	450	15	110	57	12.99	13.03
A3	Methyl	H	450	10	133	74	12.98	13.03
A4	Ethyl	5-Methyl	450	15	108	61	13.04	13.07
A5	Ethyl	7-Methyl	450	15	95	65	12.26	12.38
A6	Ethyl	H	450	20	103	50	11.99	12.33
A7	Propyl	5-Methyl	450	20	132	54	12.34	12.32
A8	Propyl	7-Methyl	450	15	120	59	12.00	11.71
A9	Propyl	H	450	12	150	71	11.71	11.68

IR spectra:

Infra red spectra of these compounds were taken in nujol mull using Perkin-Elmer infracord. The compounds show characteristic absorption of benzisoxazoles molecules. The bands at 1540 cm–1, 1210 cm–1, 910 – 820 cm–1, and 1630 cm–1 are due to –C = N–, N–O– C,isoxazole ring stretching and –C = C– of phenyl ring of isoxazole respectively. Theabsorption bands at 1150 cm–1 and 1270 – 1315 cm–1 are characteristics of S = O symmetricand symmetric stretching.

1H NMR Spectra: The NMR spectra of few representative compounds were studied in TFAA onVarian T-60 spectrophotometer using TMS as an internal standard.

(A4): 3-ethyl-5-chlorosulphonyl-1,2-benzisoxazole:

1.4 – 1.8 δ(t, 3H, CH_2-CH_3)

3.1 – 3.6 δ(q, 2H, CH_2-CH_3)

7.8 – 8.2 δ(d, J = 8 Hz, 1Ha aromatic)

8.3 – 8.6 δ(dd, J = 8 and 2 Hz, 1Hb aromatic)

8.6 – 8.85 δ(d, J = 1.5 Hz, 1HC aromatic)

(A2): 3,5-dimethyl-5-chlorosulphonyl-1,2-benzisoxazole:

2.6 δ(S, 3H, 5-CH_3)

2.8 δ(S, 3H, 3-CH_3)

7.8 – 7.9 δ(d, J = 2 Hz, 1Ha aromatic)

8 – 8.1 δ(d, J = 1.5 Hz, 1Hb aromatic)

(A6): 3-ethyl-7-methyl-5-chlorosulphonyl -1,2-bensizoxazole:

1.5 – 1.8 δ(t, 3H, CH_2-CH_3)

2.8 δ(S, 3H, CH_3)

3.1 – 3.5 δ(q, 2H, CH_2-CH_3)

8.1 – 8.2 δ(d, J = 1.5 Hz, 1Ha aromatic)

8.4 – 8.5 δ(d, J = 1.5 Hz, 1Hb aromatic)

Biological evaluation (Antibacterial screening):

The randomly selected synthesized compounds were screened for antibacterial activity against*Bacillus subtilis* (gram positive) and *Klebsiella* (gram negative) bacteria by employing thefood poison technique at 250 and 100 ppm. The substituted benzisoxazoles showed moreactivity at higher concentrations. Results are given in **Table 2.**

Table 2: Antibacterial screening of compounds (A1, A2, A4, A6and A7):

Comp.	R_1	R_2	*Bacillus subtilis*		*Klebsiella pneum.*	
			250 ppm	100 ppm	250 ppm	100 ppm
A1	Methyl	5-Methyl	++	+	--	--
A2	Methyl	7-Methyl	++	+	--	--
A4	Ethyl	5-Methyl	++	+	--	--
A6	Ethyl	H	++	+	--	--

A7	Propyl	5-Methyl	+	--	--	-

RESULTS AND DISCUSSION:

The microwave assisted, solvent free synthesized 3-alkyl-5-chlorosulphonyl-1,2-benzisoxazoles and their derivativesexhibited significant to moderate antibacterialactivity. In the present work, substituted benzoxazole and chlorosulphonic acid were used askey raw material.Compounds (A1-A9) have been characterized on the basis of satisfactory analytical and spectral data.

CONCLUSION:

Synthesized 3-alkyl-5-chlorosulphonyl-1,2-benzisoxazole and their derivatives form an important class of heterocyclic compounds with diverse medicinal uses.

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