



Design, Synthesis and Biological Activity of Isoxazole Derivatives as Potent Medicinal Compound

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ABSTRACT:

Isoxazole, constituting an important family of five-membered heterocycles with one oxygen atom and one nitrogen atom at adjacent positions is of immense importance because of its wide spectrum of biological activities and therapeutic potential. It is, therefore, of prime importance that the development of new synthetic strategies and designing of new isoxazole derivatives should be based on the most recent knowledge emerging from the latest research. The present study comprises of design and synthesis of some newer derivatives by incorporating isoxazole nucleus in the pharmacophore and characterizing them physicochemically and by spectral means. In vitro tube dilution method was followed for their antimicrobial screening against bacteria: *S. aureus*, *B. cereus*, *E. coli*, *P. aeruginosa*, and two fungal strain: *Candida albicans* and *Aspergillus niger* respectively. The results indicated that compound 5a and 5f were found to be the most active antibacterial and antifungal agents respectively.

Keywords: heterocyclic compound, medicinal chemistry, isoxazole, antimicrobial

INTRODUCTION

In medicinal chemistry, the process by which drugs are discovered and designed is known as Drug Discovery. The process of drug discovery involves the identification of candidates, synthesis, characterization, screening and assays for therapeutic efficiency. [1] The drug discovery process increased in intensity because of the major screening and chemical synthetic effort in the pharmaceutical industry in worldwide industrialized countries. Despite understanding biological system and advance in technology, the drug discovery is still a long process with low rate of new therapeutic discovery. [2, 3]

Organic chemistry play an important role in modern science and has wide varieties applications in different fields since many research has been going on to synthesize new organic compounds and derivatives of naturally occurring ones. Heterocyclic chemistry research encompasses almost half of the organic chemistry research throughout the world. [4] A huge amount of bioactive organic compounds that contain heterocyclic frameworks play a vital role in medicinal field. [5]

Isoxazoles are unsaturated aromatic heterocyclic compounds that contains a ring with three carbon atoms and one oxygen atom. The isoxazole behavior can be modified by the effects of substituent at position 1 and one nitrogen atom at position 2 [6]. Isoxazoles exhibits broad spectrum of pharmacological and biological activities which include antifungal [7], anti-HIV [8], antinociceptive [9], anticancer [10], antithrombotic [11], GABA antagonist [12], antibacterial [13], immunomodulatory [14]. Keeping in view the above facts, we have designed some more isoxazole derivatives and evaluated them for the antimicrobial activity.

2.1 EXPERIMENTAL [15-18]

Synthesis of compound 5a[5-(4-Methoxynaphthalen-1-yl)-4-(3,4,5-triethoxyphenyl)]

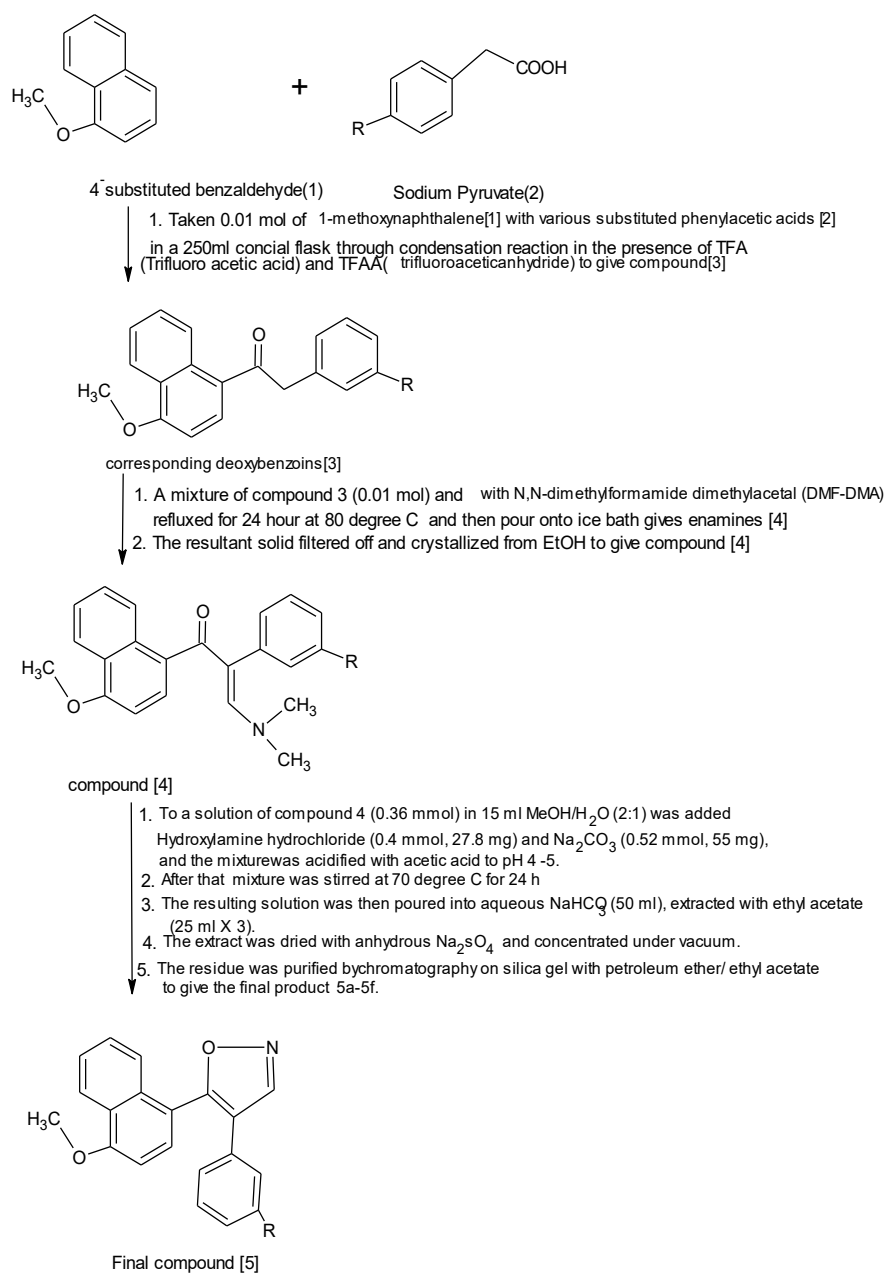
Isoxazole]

Step 1: Synthesis of corresponding benzoin[3]: Taken 20ml of 0.01 mol of 1-methoxy naphthalene[1] with 20ml of 0.01mol (3,4,5-triethoxyphenyl)acetic acid in a 250ml conical flask refluxed in the presence of 30ml 0.1mol Trifluoroacetic acid(TFA) and 20ml of 0.01mol of Trifluoroacetic anhydride(TFAA) to give corresponding benzoin compounds.[3]



Step 2: Synthesis of corresponding enamine[4]: A mixture of 10ml compound[3] (0.01 mol) reacted with mixture of 50ml of N,N-dimethylformamide and dimethyl acetal refluxed for 24h at 80 degree C. the mixture is then cooled and poured onto ice. The resultant solid filtered off and crystallized from EtOH to give corresponding benzoin compound. [4]

Step 3: Synthesis of compound 5a[5-(4-Methoxynaphthalen-1-yl)-4-(3,4,5-triethoxy phenyl) Isoxazole]: To a solution of compound [4] 0.36mol made in 15ml methanol and water in the ration 2:1 was added hydroxylamine hydrochloride(0.4mmol, 27.8mg) and sodium carbonate(0.52mmol, 55mg), the mixture was then acidified with acetic acid to made the pH between 4-5. The mixture was then stirred for 24hours at 70 degree C. The resulting solution was then poured into 50ml of aqueous sodium bicarbonate and then extracted with ethyl acetate(25ml X3). The extract was then dried with anhydrous sodium sulphite and concentrated under vacuum. The residue was then purified by chromatography on silica gel with petroleum ether/ethyl acetate solution to give the final compound 5a. Same procedure follow for other compounds.



Scheme 1: Synthesis of Isoxazole Derivatives



Table 1: List of compounds synthesized

Derivatives	R
5a	3,4,5- Tri ethoxy
5b	6-Cl-4- ethoxy
5c	6-Nitro-4-ethoxy
5d	3,5- dichloro
5e	3,5- difloro
5f	3,5- dibromo

Physical Property: The synthesized compound was first subjected to preliminary physical observation to assess its appearance, including its color, texture, and physical state (solid, liquid, or semi-solid). This step provided an initial indication of the nature of the product and any potential impurities. [19]

Melting Point: The melting point of the compound was then determined using a digital melting point apparatus. A small amount of the dried compound was placed in a capillary tube, and the temperature range at which the compound melted was recorded. A sharp melting point typically suggested a pure compound, while a broad range indicated possible impurities.

Solubility Study: Following this, the solubility of the compound was tested in various solvents such as distilled water, ethanol, methanol, chloroform, and dimethyl sulfoxide (DMSO). A small quantity of the compound was added to each solvent, and solubility was observed at room temperature, with gentle warming if necessary. [20]

Thin layer chromatography: The thin-layer chromatography (TLC) technique was employed to check the purity of the synthesized compound. A small amount of the sample was spotted on a TLC plate coated with silica gel, and the plate was developed in a suitable solvent system. The R_f value was calculated and compared with standard references or reaction precursors to assess purity and reaction completion.

- Stationary phase: silica gel-g
- Mobile phase: n-hexane-ethyl acetate: few drop of formic acid
- Detection: iodine chamber

Spectral analysis: Collectively, the data obtained from FTIR, NMR and MS, spectroscopy provided comprehensive structural elucidation of the synthesized compound. These complementary techniques not only confirmed the identity and purity of the compound but also verified that the desired synthesis pathway was successfully achieved. [21-22]

Antibacterial activity: The newly synthesized compounds were evaluated for their antibacterial activity against *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli* and *Pseudomonas aeruginosa* bacterial strains by the serial broth dilution method. Activity of each compound was compared with Gentamycin as standard. Serial dilutions of the drug in Nutrient broth were taken and their pH was adjusted to 7.2-7.4. Standardized suspension of the test bacterium was inoculated and incubated for 24 h at 37°C. The minimum inhibitory concentration (MIC) was noted by observing the lowest concentration of the drug at which there was no visible growth. Test compounds and standard drug Gentamycin were dissolved in 10% dimethyl sulfoxide (DMSO) to give a concentration of 2000 µg/ml. Nutrient Agar was poured into petri dish, excess of suspension was decanted and placing in incubator at 37°C for 24 hours. After specified time of incubation of solid slant culture, a loop full of grown culture was transferred into 5-6 ml of fresh nutrient broth. This was incubated at appropriate temperature of 35-37°C for 24 h (10^7 - 10^8 CFU/ml). From this 0.1 ml was withdrawn and was diluted to 10 ml with sterile water and this served as working inoculum for screening the newly synthesized compounds for their antibacterial activity. [23-25]

Antifungal activity: Newly prepared compounds were screened for their antifungal activity against *Candida albicans* and *Aspergillus niger*, in DMSO by serial broth dilution method. Activity of each compound was compared with Miconazole as standard. [26]



RESULTS AND DISCUSSION

Table 2: Chemical Properties of synthesized compounds (5a-5f)

Derivatives	Chemical Formula	M.W	Composition							M.P.(°C)
			C	H	N	O	Cl	F	Br	
5a	C ₂₆ H ₂₉ NO ₅	435.51	71.7%	6.71%	3.22%	18.37%	-	-	-	112°C
5b	C ₂₂ H ₂₀ NO ₃ Cl	381.85	69.20%	5.28%	3.67%	12.57%	9.28%	-	-	106°C
5c	C ₂₂ H ₂₀ N ₂ O ₅	392.40	67.34%	5.14%	7.14%	20.39%	-	-	-	121°C
5d	C ₂₀ H ₁₅ NO ₂ Cl ₂	372.24	64.53%	4.06%	3.76%	8.60%	19.05%	-	-	114°C
5e	C ₂₀ H ₁₅ NO ₂ F ₂	339.33	70.79%	4.46%	4.13%	9.43%	-	11.20%	-	108°C
5f	C ₂₀ H ₁₅ NO ₂ Br ₂	461.14	52.09%	3.28%	3.04%	6.94%	-	-	34.65%	166°C

Table 3: Physical and chemical properties of synthesized compound

Code	Chemical Formula	Colour	Rf value	% yield
5a	C ₂₆ H ₂₉ NO ₅	Pale yellow solid	0.68	82.30%
5b	C ₂₂ H ₂₀ NO ₃ Cl	yellow solid	0.76	75.30%
5c	C ₂₂ H ₂₀ N ₂ O ₅	Pale yellow solid crystals	0.76	76.40%
5d	C ₂₀ H ₁₅ NO ₂ Cl ₂	yellow solid	0.78	72.70%
5e	C ₂₀ H ₁₅ NO ₂ F ₂	Yellow solid,	0.82	81.20%
5f	C ₂₀ H ₁₅ NO ₂ Br ₂	Yellow solid,	0.75	82.98%

Table 4: Interpretation of FTIR spectra of synthesized compounds

S. NO.	Compd	Frequency (cm-1)
1	5a	3737, 3164, 2888, 1710, 1604, 1511, 1487, 1455, 1400, 1372, 1226, 1179, 1116, 1067, 1044, 968, 944, 811, 754, 624, 584, 516.
2	5b	3163, 2914, 2360, 1900, 1706, 1591, 1489, 1455, 1401, 1228, 1090, 1012, 945, 823, 754, 647, 587, 517.
3	5c	3282, 2952, 2835, 2360, 1718, 1604, 1511, 1487, 1457, 1374, 1303, 1249, 1173, 1031, 947, 828, 754, 634, 592
4	5d	3753, 3182, 2869, 2735, 1946, 1689, 1604, 1582, 1488, 1454, 1400, 1289, 1224, 1105, 1069, 1045, 973, 838, 752, 694, 622, 568, 508.
5	5f	3308, 3151, 1698, 1604, 1540, 1493, 1443, 1400, 1310, 1242, 1173, 1119, 1098, 1027, 923, 894, 864, 829, 786, 750, 688, 634, 598, 568, 501, 458.

Table 5: Interpretation of NMR spectra of synthesized compound

S. NO.	Compd	δ (ppm)
1	5a	9.475 (s, 1H, H-4 of coumarin), 9.020 (d, J=11.6Hz, 1H, H-5 of coumarin), 8.487–8.512 (m, 3H, H-6, H-7 & H-8 of coumarin), 6.878 – 6.908 (m, 3H, isoxazole & 2ArH), 7.230 (d, J=11.6Hz, 2H, 2ArH)
2	5b	8.336 (s, 1H, H-4 of coumarin), 7.844 (d, J=9.2Hz, 1H, H-5 of coumarin), 7.308–7.471 (m, 2H, H-6 & H-8 of coumarin), 7.583 (t, J=8.6Hz, 1H, H-7 of coumarin), 6.195 (s, 1H, isoxazole), 7.217 (d, J=9.6Hz, 2H, 2ArH), 6.666 (d, J=14Hz, 2H, 2ArH), 1.241 (s, 3H, –CH ₃)
3	5c	8.327 (s, 1H, H-4 of coumarin), 7.939 (d, J=12Hz, 1H, H-5 of coumarin), 7.352–7.381 (m, 2H, H-6 & H-8 of coumarin), 7.566 (t, J=5.8Hz, 1H, H-7 of coumarin), 6.358 (s, 1H, isoxazole), 7.150 (d, J=12Hz, 2H, 2ArH), 6.789 (d, J=6.8Hz, 2H, 2ArH), 1.233 (s, 3H, –OCH ₃)
4	5d	8.331 (s, 1H, H-4 of coumarin), 7.919 (d, J=10.8Hz, 1H, H-5 of coumarin), 7.326–7.412 (m, 2H, H-6 & H-8 of coumarin), 7.564 (t, J=15.2Hz, 1H, H-7 of coumarin), 6.625 (s, 1H, isoxazole), 7.159 (d, J=5.6Hz, 2H, 2ArH), 6.913 – 6.989 (m, 3H, 3ArH), 6.740 (d, J=5.2Hz, 2H, –CH=)
5	5f	7.781 (s, 1H, H-4 of coumarin), 7.956 (d, J=7.6Hz, 1H, H-5 of coumarin), 7.362–7.465 (m, 4H, H-6 & H-8 of coumarin & 2ArH), 7.624 (t, J=7.6Hz, 1H, H-7 of coumarin), 8.689 (s, 1H, Thiazole), 10.337 (s, 1H, –NH), 7.753 (d, J=8Hz, 2H, 2ArH), 7.005 (t, J=7.4Hz, 1H, 1ArH).

Antibacterial activity” The antibacterial activity of the newly synthesized compounds 5a-5f were reported as minimum inhibitory concentration (MIC) at the concentration range, 1.56-100 µg/ml against *S. aureus*, *B. cereus* (gram-positive bacteria) and *E. coli*, *P.*



aeruginosa (gram-negative bacteria) using Gentamycin as standard and the results are summarized in Table 3.7 The compounds 5a, and 5f exhibited highest activity against all tested bacteria. Compounds 5a and 5f showed comparatively good activity against S. aureus, Compound 5d showed moderate to good activity against B. cereus, Compounds 5c and 5e exhibited moderate to good activity against E. coli and Compounds 5d, 5e exhibited significant activity against P. aeruginosa.

Table 6: Minimum Inhibitory Concentration

Comp	Minimum Inhibitory Concentration			
	S. aureus	B. cereus	E. coli	P. aeruginosa
5A	6.25	6.25	6.25	12.5
5B	50	25	25	12.5
5C	25	25	12.5	50
5D	12.5	12.5	25	6.25
5E	50	25	12.5	25
5F	6.25	6.25	6.25	6.25
GENTAMICIN	1.56	1.56	1.56	1.56

MIC Values were evaluated at concentration range, 1.56-100 µg/mL.

Antifungal activity: The antifungal data of the synthesized compounds 5a-5f were reported as minimum inhibitory concentration (MIC) at the concentration range, 1.56-100 µg/ml against *Candida albicans* and *Aspergillus niger* using Miconazole as standard and the results are summarized in Table 3.8 The compounds 5a and 5f exhibited highest activity against all tested fungi. Compounds 5b and 5e showed good activity against *C. albicans* while Compound 5d exhibited moderate to good activity against *A. niger*. It was observed that the isoxazole derivatives having phenyl group (5a and 5b) and p-bromo phenyl group (5f) at position C-6 possess high activity. Replacement of these groups by o-bromo phenyl resulted in a decrease in antibacterial and antifungal activity.

Table 7: Minimum Inhibitory Concentration

Comp	Minimum Inhibitory Concentration	
	C. Albicans	A. Niger
5a	6.25	6.25
5b	12.5	25
5c	50	25
5d	25	12.50
5e	12.5	25
5f	6.25	6.25
Miconazole	1.56	1.56

MIC Values Were Evaluated At Concentration Range, 1.56-100 µg/mL

CONCLUSION

In conclusion, the present study successfully demonstrated the rational design and synthesis of a series of novel isoxazole derivatives, targeting their potential as medicinal agents. Isoxazole, a five-membered heterocyclic compound, has long been recognized for its significant pharmacological properties. By integrating different functional groups and optimizing the synthetic pathways, a diverse array of derivatives was achieved, exhibiting favorable yields and purity. The structural modifications were aimed at enhancing biological activity and improving physicochemical properties critical for drug development.

The design and synthesis of six isoxazoles derivatives were carried out. The structures of the compounds were confirmed on the basis of FTIR, ¹H NMR, ¹³C NMR and ESI-Mass spectrum. In the antimicrobial study using minimum inhibitory concentration, the compound 5a and 5f showed the highest antibacterial and antifungal activity among the synthesized compounds of isoxazole derivatives.

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