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SYNTHESIS AND ANTIMICROBIAL ANALYSIS OF SUBSTITUTED 2-(5-(3-(2,4-DIFLUOROPHENYL)-1-(4-FLUOROPHENYL)-1H-PYRAZOL-4-YL)-4,5-DIHYDROISOXAZOL-3-YL)PHENOL

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ABSTRACT
Isoxazolines are known as the dihydro derivatives of Isoxazoles. They are also beneficial as intermediates for the preparation of a broad variety of biologically active natural products. The newly prepared compounds were screened for their antimicrobial and antifungal activity against Gram-ve and Gram +ve microorganisms. Moderate activity was shown by some compounds against standard drugs.

Keywords: *Isoxazolines, antimicrobial agents, 2-(5-(3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-4,5-dihydroisoxazol-3-yl)phenol.*

INTRODUCTION

Isoxazolines areuseful as antiseptic, in tuberculosis, antiviral, for fungal treatment, herbicidal, kills insects and antidepressant agents [1-5].Isoxazolines are also known to be the dihydro derivatives of Isoxazoles. Isoxazolines are important part of a molecular structure responsible particularly in several pharmacologically significant drug molecules. They are also beneficial as intermediates for the preparation of a broad variety of biologically active natural products [6]. These derivatives have played animportant role in the theoreticaldevelopment of heterocyclic chemistry and also useful in organic synthesis [7].

Heterocyclic compounds containing nitrogen and oxygen have acknowledgedextensiveconsideration due to their widespreadarray of pharmacological activity. Isoxazolines denote one of the active classes of compounds keeping a variedrange of biological activities. Isoxazolines have been testified to possess antidiabetic [8], diuretic [9], analgesic [10], anthelmintic [11], hypolipaemic [12] and antimicrobial activity, antioxidant, cytotoxicity [13]. In recent years, this heterocycle has received considerable attention due to the biological significance.

Isoxazolines are very useful heterocycles in medicinal andorganicchemistry. Organic chemists use Isoxazoline rings forsynthetic preparation toaddress complex molecular designs. Valdecoxib, Leflunomide, Isocarboxazid, Micafungin and Oxacillin are the examplesof drugs to confirm the pharmaceutical approval of such heterocyclic systems. Whenappropriatelymade within a minor molecule, these supports have been frequentlyconsidered asstable amide replacements. Hence, novel synthetic practices to make theseheterocycles with variations of exchanges are extremelyanticipated.

EXPERIMENTAL

A General procedure for the synthesis of 4-chloro-2-(5-(3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-4, 5-dihydroisoxazol-3-yl)-5-methylphenol (2f):

Compound **1f** (0.01mol) was dissolved in 15 ml ethanol. To this reaction mixture, 0.02 mol of hydroxyl amine hydrochloride added. After dissolution process, freshly fused anhydrous sodium acetate (3.0g) was added to this solution. Contents were heated under mild reflux for 7 hr and then cooled to room temperature. The progress of the reaction was monitored by Thin Layer Chromatography. Cold water (50ml) was slowly added to the flask and separated product was filtered, washed with cold water for several times and crystallized from methanol to obtain purified isoxazoline. The compounds **2(a-g)** were prepared by following the general procedure. Physical data are recorded in **Table 1**. and Antimicrobial data given in **Table 2** Their structures have been confirmed by IR, ^{1}HNMR and Mass spectra.

IR (2f) (cm^{-1}): 964(C-Cl), 1101(Ar-F), 1265(C-O), 1515(Ar C=C), 1598(C=N), 2925(Ar-CH_3), 3134(O-H).

^{1}H NMR (2f) (DMSO) δ ppm: 2.2769 (s, 3H, CH_3), 3.620-3.716 (dd, -CH_2-, *J*=9.1Hz & 9.1 Hz)

3.805-3.940(dd, -CH_2-, *J*=10.0Hz &10.4 Hz), 5.6158-5.6420(t, 1H,-CH-, *J*=9.1 Hz & 8.6 Hz),6.6332 (s, 1H, Ar-H), 6.8451-6.8522(m, 2H, Ar-H), 6.9035-7.3188(m, 1H, Ar-H), 7.3294-7.4348(m, 3H, Ar-H), 7.5051-7.6352(m, 2H, Ar-H), 8.6798 (s, 1H, Pyrazole-H), 10.20 (s, 1H, Ar-OH).

ES-MS (2f) (m/z):484.43 (M+1), 486.41(M+3)

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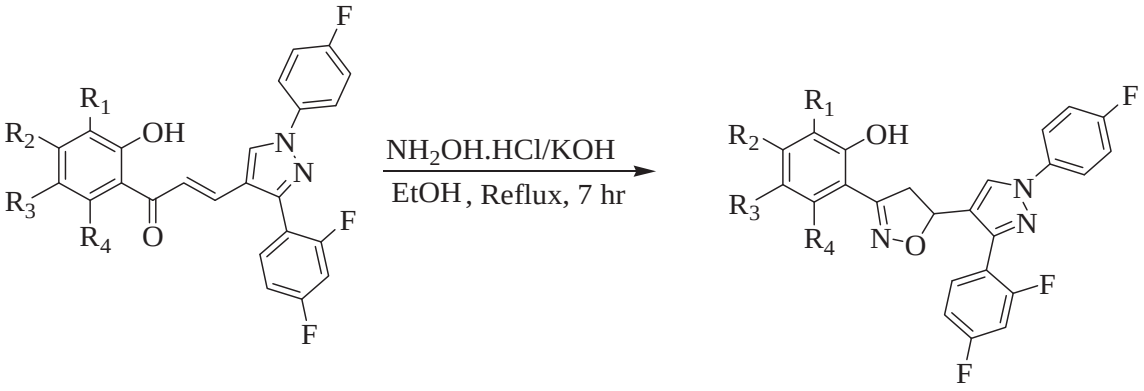
Scheme



1(a-g) **2(a-g)**

Scheme-1: Synthesis of various substituted 2-(5-(3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-4,5-dihydroisoxazol-3-yl)phenol

Table-1: Physical data of compounds 2(a-g)

Comp.	R_1	R_2	R_3	M.P. (^oC)	Yield (%)
2a	H	H	H	118-120	70
2b	H	H	CH_3	156-158	69
2c	H	H	Cl	110-112	72
2d	Cl	H	Cl	120-122	67
2e	H	H	F	134-136	65
2f	H	CH_3	Cl	90-92	70
2g	H	H	Br	160-162	72

RESULTS AND DISCUSSION

Antimicrobial activity:-Compounds **2(a-g)** were screened for their in vitro antimicrobial activity against Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853), Staphylococcus aureus (ATCC 25923) using Gentamycin as a reference standard drug by paper disc diffusion method. Antifungal activity was evaluated against Candida sp. using Nystatin as standard drug. All the tests were evaluated at 100 µg/ml concentration

Table-2: In-*vitro* antimicrobial activity of various substituted 2-(5-(3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-4, 5-dihydroisoxazol-3-yl) phenol 2(a-g).
Disc Diffusion Method

Sr. No.	Compound No.	Inhibition Zone Diameter (mm)			
		***E. coli* ATCC25922**	***Pseudomonas aeruginosa* ATCC27853**	***Staphylococcus aureus* ATCC 25923**	***Candida sp.***
1.	2a	No zone	No zone	No zone	No zone
2.	2b	No zone	No zone	No zone	No zone
3.	2c	No zone	No zone	No zone	No zone
4.	2d	No zone	No zone	No zone	No zone
5.	2e	No zone	No zone	No zone	No zone
6.	2f	No zone	No zone	No zone	No zone
7.	2g	No zone	No zone	No zone	No zone
8.	Gentamycin	20	20	24	--------
9.	Tetracyclin	20	No zone	25	--------
10.	Ketoconazole	--------	--------	--------	23

CONCLUSION

All the synthesized compounds were screened for antimicrobial activity. All the compounds screened showed no antibacterial and antifungal activity comparable with that of standard drug tested.

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