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SYNTHESIS AND BIOLOGICAL SCREENING OF NOVEL PYRAZOLE AND ISOOXAZOLE DERIVATIVES

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ABSTRACT
A new series of 5-(4-(4-fluorophenylthio) phenyl)-4, 5-dihydro-3-phenyl-1H-pyrazoles and 5-(4-(4-fluorophenylthio) phenyl)-4,5-dihydro-3-phenyl isoxazoles have been prepared efficiently. In view of the vital role played by sulfur and fluorine in numerous pharmacological activities, we thought worthwhile to synthesize important pyrazole and isoxazole derivatives and investigate the biological activities. All the newly synthesized compounds have been screened for their in vitro antimicrobial activity.

Keywords: Pyrazole, Isoxazole and Antimicrobial.

INTRODUCTION

Nitrogen containing heterocyclic compounds constitutes largest and most varied family of organic compounds with wide range of biological activities. Five member heterocycles having nitrogen occupy a significant place in synthetic organic chemistry [1]. In particular, pyrazolines are very important five member heterocycles containing two nitrogen atoms at 1-2 position. Pyrazolines and its derivatives reported to possess anti-inflammatory [2], antimicrobial [3], antibacterial [4], and anticancer activities [5]. Differently substituted pyrazolines are reported to show analgesic [6] immunosuppressive [7], antidepressant [8], antitubercular [9], antiviral [10], cardiovascular [11] and antidiabetic activities [12].

Elucidation of physicochemical properties of pyrazolines enables new data which shows considerable importance in pyrazolines aromatic system. Pyrazolines are well known for their antipyretic [13], agrochemicals [14], herbicide [15] and insecticide properties [16].Pyrazolines also work as non-steroidal drugs [17]. Initially, Antipyrine the first pyrazolines used in the management of inflammation and pain [18]. Many pharmacological aspects of pyrazolines have been explored; sulfur containing pyrazolines reported antinociceptive activity [19].Some thiocarbamoyl pyrazolines has shows greater antiamoebic activity compared to commonly used drug metronidazole [20].Certain sulfur containing pyrazolines derivatives reported CNS activity [21]. Sulfur based pyrazolines derivatives e.g. 5-(4-chlorophenyl)-4,5-dihydro-1-(4-methoxyphenyl)-3-(thiophen-2-yl)-1H-pyrazole and 5-(4-chlorophenyl)-4,5-dihydro-3-(thiophen-2-yl)pyrazole-1-carbothioamide as monoamine oxidase (MAO) plays major role in body degradation. The mentioned pyrazolines derivatives showed good MAO inhibition activity through interaction with monoamine oxidase [22] Pyrazolines with fluorine and β-amino acyl group showed blood glucose lowering property and found to be inhibitors of DPP-IV at submicromolar concentration [23].

Isoxazolines, an important class of azoles received much attention in the field of medicinal chemistry as potential anticancer agents [24]. Functionalized isoxazoline exhibited promising antineoplastic properties [25]. Isoxazoline are active pharmacophore in several important molecules which are used as intermediates for the synthesis of a wide variety of bioactive natural products [26, 27]. Isoxazolines reported antimicrobial [28] analgesic [29], antidiabetic [30], antimalarial [31], diuretic [32], hypolipidemic [33], and antihelmintic activities [34].

EXPERIMENTAL

Material and Methods

Open capillaries in a paraffin bath have been used to determine the melting points of newly synthesized compounds. The progress of the reaction was monitored by using precoated plates of silica gel G254 supplied by Merck. Infrared (IR) spectra (KBr disc) were recorded on a FTIR-4100 spectrometer and the absorption bands are expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Bruker Advance II 400 MHz spectrometer using TMS as a reference standard. Macro mass spectrometer (Waters) by electro-spray method (ES) was used to record the mass spectra.

General procedure for the synthesis of substituted 5-(4-(4-fluorophenylthio)phenyl)-4,5-dihydro-3-phenyl-1*H*-pyrazole In an Round Bottom Flask compound **1a-h** (0.001mol) was dissolved in 5ml DMSO. To this reaction, mixture (0.002 mol, 0.20ml) of hydrazine hydrate was added and the mixture was refluxed. The progress of the reaction was monitored with the help of TLC. After the completion of reaction, the reaction

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mixture was slowly added to the flask and the separated product was filtered and washed with cold water. The final compound was purified by recrystallization from ethanol gives **2(a-h)**.

General procedure for the synthesis of substituted 5-(4-(4-fluorophenylthio)phenyl)-4,5-dihydro-3-phenylisoxazoles

Chalcones **1(a-h)** (1 mmol), hydroxylamine hydrochloride (3 mmol) and potassium hydroxide (3 mmol) were dissolved in absolute ethanol (10 mL). The mixture was refluxed for 4-5 hr. The progress of reaction was monitored by TLC (Ethyl acetate: Pet ether). After completion of the reaction, the mixture was poured on crushed ice and neutralized with 2N HCl. The precipitate was separated by filtration, washed with cold water, and crystallized from ethanol. The percentage yield and physical constants were recorded in **Table 1**.

2-(5-(4-((4-fluorophenyl)thio)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (2b)

^{1}H NMR (400 MHz, DMSO-d6, δppm): 2.32(s,3H,CH_3), 3.2 (dd, 1H, CH_2), 3.65 (dd, 1H, CH_2), 3.7(s,1H,CH), 7.0-7.32 (m, 12H, Ar-H and pyrazole-H),δ 11.50 (s, 1H, -OH);IR (KBr, cm-1): 3340 (N-H), 3156 (OH), 1480 and 1580 (Aromatic C=C); ES-MS: m/z: 378

2-(5-(4-((4-fluorophenyl)thio)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (2c)

^{1}H NMR (400 MHz, DMSO-d6, δppm):, 3.25 (dd, 1H, CH_2), 3.45 (dd, 1H, CH_2), 3.8(s,1H,CH), 6.9-7.5 (m, 13H, Ar-H and pyrazole-H),δ 11.45 (s, 1H, -OH)

IR (KBr, cm-1): 3332 (N-H), 3154 (OH), 1482 and 1588 (Aromatic C=C); ES-MS: m/z: 364

2, 4-dichloro-6-(5-(4-((4-fluorophenyl)thio)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (2g)

^{1}H NMR (400 MHz, DMSO-d6, δppm):, 3.1 (dd, 1H, CH_2), 3.55 (dd, 1H, CH_2), 7.01-7.42 (m, 11H, Ar-H and pyrazole-H),δ 11.63 (s, 1H, -OH);IR (KBr, cm-1): 3338 (N-H), 3153 (OH), 1487 and 1587 (Aromatic C=C); ES-MS: m/z: 432

2-(5-(4-((4-fluorophenyl) thio) phenyl)-4, 5-dihydroisoxazol-3-yl)phenol (3c)

^{1}H NMR (400 MHz, DMSO-d6, δppm):, 3.64 (dd, 1H, isoxazoline C_4-H), 3.90 (dd, 1H, isoxazoline C_4-H), 5.4 (t, 1H, isoxazoline CH), 6.84 to 7.74 (m,12H,Ar-H),δ 13.25 (s, 1H, -OH);IR (KBr, cm-1): 3460 (OH), 3060 (C-H), 1689(C=C), and 1489 (Aromatic C=N);

ES-MS: m/z: 367.2

4-chloro-2-(5-(4-((4-fluorophenyl) thio) phenyl)-4, 5-dihydroisoxazol-3-yl) phenol (3f)

^{1}H NMR (400 MHz, DMSO-d6, δppm):, 3.52 (dd, 1H, isoxazoline C_4-H), 3.80 (dd, 1H, isoxazoline C_4-H), 5.2 (t, 1H, isoxazoline CH), 6.90 to 7.72 (m,11H,Ar-H),δ 12.25 (s, 1H, -OH);IR (KBr, cm-1): 3465 (OH), 3065 (C-H), 1680(C=C), and 1480 (Aromatic C=N);

ES-MS: m/z: 399.1

2,4-dichloro-6-(5-(4-((4-fluorophenyl)thio)phenyl)-4,5-dihydroisoxazol-3-yl)phenol (3g)

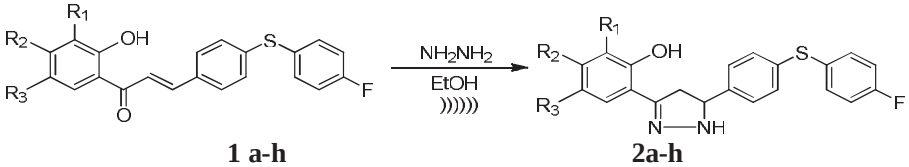
^{1}H NMR (400 MHz, DMSO-d6, δppm):, 3.42 (dd, 1H, isoxazoline C_4-H), 3.70 (dd, 1H, isoxazoline C_4-H), 5.2 (t, 1H, isoxazoline CH), 6.85 to 7.50 (m,10H,Ar-H),δ 12.25 (s, 1H, -OH);IR (KBr, cm-1): 3445 (OH), 3052 (C-H), 1675(C=C), and 1489 (Aromatic C=N);

ES-MS: m/z: 433.2

RESULTS AND DISCUSSION

Chemistry

The starting precursor's (E)-1-(2-hydroxyphenyl)-3-(4-(phenylthio)phenyl)prop-2en-1-ones **1a-h was** prepared using o-hydroxyacetophenone and 4-F(phenylthio)benzaldehyde ethanol. The mixture was irradiated under ultrasonication for 4-5 hr. The reaction of (E)-1-(2-hydroxyphenyl)-3-(4-(phenylthio) phenyl) prop-2en-1-ones **1a-h** with hydrazine hydrate in ethanol gave the target products **2a-h** (**Scheme 1**). Compound (E)-1-(2-hydroxyphenyl)-3-(4-(phenylthio) phenyl) prop-2en-1-ones **1a-h**, with hydroxylamine hydrochloride at reflux condition gave the target products **3a-h** (**Scheme 2**). Structural assignments to the newly synthesized compounds were based on their IR, ^{1}H-NMR, Mass spectral data.



1 a-h **2a-h**

Scheme-1: Synthesis of pyrazole 2a-h

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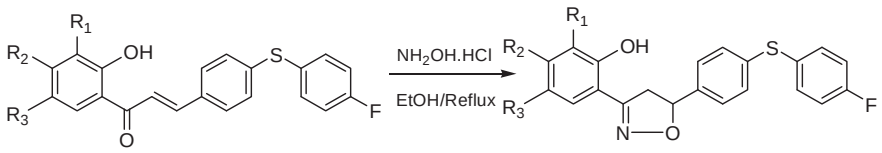

1a-h **3a-h**

Scheme-2: Synthesis of isoxazole 3a-h

Table-1: Physical data of compounds 2a-h and **3a-h**

Comp.	R_1	R_2	R_3	Yield (%)	M. P. (°C)
2a	H	CH_3	Cl	77	55-57
2b	H	H	CH_3	65	99-101
2c	H	H	H	72	120-122
2d	CH_3	H	CH_3	65	52-54
2e	H	H	F	64	56-58
2f	H	H	Cl	68	90-92
2g	Cl	H	Cl	74	148-150
2h	H	H	Br	72	140-142
3a	H	CH3	Cl	72	154-156
3b	H	H	CH3	70	145-147
3c	H	H	H	72	152-154
3d	CH3	H	CH3	69	142-144
3e	H	H	F	65	148-150
3f	H	H	Cl	67	98-100
3g	Cl	H	Cl	64	204-206
3h	H	H	Br	68	166-168

ANTIMICROBIAL ACTIVITY

Antimicrobial activity of all the synthesized compounds was determined by the well-diffusion method Two Gram-positive bacterial strains *E. coli* and *A. flavus* strains used to study and investigate the antimicrobial activities. The bacterial liquid cultures were prepared in fusion broth. All the newly synthesized compounds were dissolved in DMSO at concentration of 1 mg/mL. The antibacterial activity of DMSO was checked against the test organisms and was found to be nil. In Petri dishes, the molten nutrient agar was poured and allowed to solidify. The holes of 10 mm diameter were punched using a cork borer and completely filled with the test solutions. The culture plates were incubated for 24 hr at 36 °C. The inhibition zone around the holes in each plate was measured after 24 hr. The diameter of inhibition zone and minimal inhibitory concentrations (MICs) showed the antibacterial activity **Table 2**.

Table-2: In vitro antibacterial screening of compounds (**2a-h**) and (**3a-h**)

Compound	Inhibition zone (mm) (*Escherichia coli*)	Inhibition zone (mm) (*Aspergillus flavus*)
2a	Nil	Nil
2b	Nil	Nil
2c	Nil	Nil
2d	Nil	Nil
2e	02	Nil
2f	Nil	Nil
2g	Nil	Nil
2h	Nil	Nil
3a	Nil	Nil
3b	Nil	Nil
3c	Nil	Nil
3d	Nil	Nil
3e	Nil	Nil
3f	01	Nil
3h	Nil	Nil
Control (Solvent)	Nil	Nil

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The newly synthesized compounds **2a-h** and **3a-h** were evaluated for in-*vitro* antimicrobial activities. The preliminary screening data showed that among active compounds and exhibited moderate activity.

CONCLUSIONS

In conclusion, synthesis, and antibacterial activities of a novel series of 5-(4-(4-fluorophenylthio) phenyl)-4, 5-dihydro-3-phenyl-1*H*-pyrazole 2a-h, and 6a-h and 5-(4-(4-fluorophenylthio) phenyl)-4, 5-dihydro-3-phenylisoxazoles 3a-h, have been presented for the first time *via* synthetic procedure in good yield. In addition, compounds showed moderate activity, indicating the future scope for optimization.

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