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Synthesis and Screening of Fluoro Substituted Pyrazolyl Benzoxazoles

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ABSTRACT

A series of 3-Formylchromone **1** was reacted with 1-(4-(4-fluorophenyl)thiazol-2-yl)hydrazine **2** to get (1-(4-(4-fluorophenyl)thiazol-2-yl)-1*H*-pyrazol-4-yl)(2-hydroxyphenyl) methanone **3** which on reaction with hydroxylamine hydrochloride given methanone oxime **4** and **4** on treatment with $POCl_3$ formed 2-(1-(4-(4-fluorophenyl)thiazol-2-yl)-1*H*-pyrazol-4-yl)benzo[*d*]oxazole **5**. The structures of synthesized compounds were confirmed by spectral analysis further they were screened for their biological activity.

Key words: 3-Formylchromones, Methanone, Oxime, Benzoxazole, Spectral analysis, Biological activity.

INTRODUCTION

3-Formylchromones give several versatile condensation reactions as they contain 3-electrophilic centers in the molecule[1] which can be converted into various biological active compounds. 3-Formylchromones achieved by the most stable method through the application of Vilsmeir Haack reaction[1, 2] from 2-hydroxyacetophenone. It has an instantaneous aldehyde group and undergoes Knovengel condensation reaction and gives several important synthetic compounds. Different researchers were studying the condensation reactions of various nucleophiles with 3-formylchromones. 2-Hydroxyacetophenones are good precursors for several applications, which were synthesized by Fries rearrangement by known procedure[3].

Pyrazole nucleus based compounds exhibits focus on medicinal and agriculture chemistry because they found vast scope for biological activities like antitumor and anti-HCV agents[4], hepatoprotective[5], antidiabetic6, anticancer[6], cytotoxic[7], herbicidal[8] and fungicidal[9] activities.

Fluorinated moieties have been found unique properties in synthesizing the compounds in the drug world.

Methanones are effective inhibitors of FLT3-ITD kinase in vitro and stimulate apoptosis in PKC412 sensitive and resistant cell lines[10]. Many of them are also shown extensive band of bioactivities such as antimycobacterial[11], antipsychotic[12], antioxidant[13], antifeedant[13], they are effective inducer of apoptosis[14]. Oximes are being extensively used as an important intermediate in synthesizing the new heterocycles. Oximes shows acaricidal[15], insecticidal[16], antiviral (TMV)[17] and antimicrobial[18, 19] activities. Benzo-fused bicyclic hetero ring structure possess tempting pharmacological activities. Substituted benzoxazole derivatives show anti-HIV[20], antitubercular[21], anticonvulsant[22] and antiproliferative[23] activities. Benzoxazole is an antiallergic compound which inhibits the release of mediators of allergic reaction. Benzoxazole also shows two fold 5-Lipoxygenase and Cycloxygenase inhibitors with anti-inflammatory action[24].

Due to the extensive applications and biological activities allied with fluorine, pyrazole, benzoxazoles and the utility of oximes as an important intermediate provoked us to synthesize the variously substituted fluorine containing benzoxazole derivatives.

Biological activities

Antimicrobial activity

13 synthesized compounds were evaluated for their antibacterial activity against the bacteria *E. coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* using standard drugs like Gentamycin and Nystatin. The activities were studied by turbidity method using DMSO as a solvent. The Inhibition zones were measured in mm. The same compounds were also tested for fungal activities against the fungus *Candida sp.* using the same standard drugs in the same solvent as for antibacterial activities. The used concentration was 1mg/1000mm. At this concentration no activity was observed.

EXPERIMENTAL

The Physical constant of all the synthesized compounds were measured in open capillary tubes in paraffin liquid and are uncorrected. Purity of all synthesized compounds was checked by TLC. The IR spectral study was recorded on a Perkin-Elmer (spectrum on a FT-IR) spectrometer. The ^{1}H NMR was studied on a BRUKER AVANCE II 400 MHz NMR Spectrometer in $CDCl_3$ and DMSO as a solvent, chemical shift (δ) were expressed in ppm (scale) downfield from TMS and coupling constant (J) are expressed in hertz (Hz). Mass spectra were recorded on Waters, Q-TOF MICROMASS (LC-MS). TLC was performed on precoated silica plates, which was experiencing under UV illumination. All the synthesized compounds gave an adequate elemental analysis.

(1-(4-(4-Fluorophenyl)thiazol-2-yl)-1*H*-pyrazol-4-yl)(2-hydroxyphenyl)methanone

3-Formylchromone (0.02 mole) was dissolved in ethanol with 1-(4-(4-fluorophenyl) thiazol-2-yl) hydrazine (0.02 mole). The reaction mixture was reflux for 30 min to get analogous hydrazone. To the same reaction mixture 22 moles of KOH were added and heating was sustained for a further 6 hr. After finishing point of the reaction the contents were cooled to room temperature and poured into crushed ice. The ensuing solution was neutralized by means of conc. HCl. The solid obtained was separated by filtration and crystallized from ethanol. Compounds synthesized by the above reaction procedure are listed in **Table 1**.

(3a)

IR (cm^{-1}): 3229 (-OH stretching), 3180 (Ar C-H stretching), 1620 (>C=O stretching), 1538 (-C=N stretching of pyrazole), 656 (C-S stretching); ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 6.8 (d, 1H, J= 8.6 Hz), 7.0-7.4 (m, 4H), 7.17 (dd, 1H, J= 2.8 Hz), 7.44 (d, 1H, J= 2.8 Hz), 7.6 (s, 1H), 7.8 (s, 1H), 10.2 (s, 1H, -OH proton); MS: m/z 380.05 (M^+).

(3b)

IR (cm^{-1}): 3138 (-OH stretching), 3112 (Ar C-H stretching), 1627 (>C=O stretching), 1546 (-C=N stretching of pyrazole), 676 (C-S stretching); ^{1}H NMR ($CDCl_3$): δ 7.02 (m, 2H, J= 8.4Hz), 7.2 (t, 2H, J= 2Hz), 7.5 (t, 1H), 7.7 (dd, 1H), 7.9 (s, 1H), 8.05 (m, 2H, J= 2.2Hz), 8.2 (s, 1H), 8.9 (s, 1H), 10.9 (s, 1H, -OH proton); MS: m/z 364.1 (M^+)

(3c)

IR (cm^{-1}): 3282 (-OH stretching), 3189 (Ar C-H stretching), 1640 (>C=O stretching), 1588 (-C=N stretching of pyrazole), 696 (C-S stretching), 548

(C-Br stretching); ^{1}H NMR (DMSO): δ 6.9 (d, 1H), 7.2 (t, 1H, J= 8.8 Hz), 7.56 (d, 1H, J= 2.5 Hz), 7.58 (s, 1H), 7.9 (s, 1H), 7.91-8.0 (m, 2H), 8.2 (s, 1H), 8.9 (s, 1H), 10.6 (s, 1H, -OH proton); MS: m/z 444.88 (M^+).

(1-(4-(4-Fluorophenyl)thiazol-2-yl)-1*H*-pyrazol-4-yl)(2-hydroxyphenyl)methanone oxime

(1-(2-(4-Fluorophenyl) thiazol-5-yl)-1*H*-pyrazol-4-yl) (2-hydroxyphenyl) methanone (0.05 mol) was dissolved in 15 mL ethanol. To this 10 mL 40% KOH was added with steady stirring at 10^{0}C & equimolar hydroxylamine hydrochloride was added. Further stirring was continued at room temperature for 3-4 hr. Then reaction combination was poured into crushed ice and acidified with acetic acid. The product obtained was separated by filtration and crystallized from ethanol to furnish the pure (1-(2-(4-fluorophenyl) thiazol-5-yl)-1H-pyrazol-4-yl)(2-hydroxyphenyl) methanone oxime. The compounds synthesized by above method are listed in **Table 1**.

(4a)

IR (cm^{-1}): 3143 (Ar-OH stretching), 3112 (N-OH stretching), 2933 (Ar C-H stretching), 1531 (-C=N stretching), 632 (C-S stretching); ^{1}H NMR ($CDCl_3$)**:** δ 2.2 (s, 3H), 6.8 (d, 1H), 7.0-7.1 (m, 4H), 7.7-7.9 (m, 4H), 8.8 (s, 1H), 9.6 (s, 1H phenolic –OH proton), 11.7 (s, 1H oxime –N-OH proton); MS: m/z 395.1 (M^+).

(4b)

IR (cm^{-1}): 3123 (Ar-OH stretching), 3101 (N-OH stretching), 2911 (Ar C-H stretching), 1551 (-C=N stretching), 623 (C-S stretching); ^{1}H NMR ($CDCl_3$)**:** δ 6.8 (t, 1H), 6.9 (d, 1H), 7.2 to 7.3 (m, 4H), 7.8 (d, 2H, J= 5.2Hz), 7.9 (m, 2H, J= 5.4Hz), 8.2 (s, 1H), 8.8 (s, 1H, N-OH proton), 9.8 (s, 1H, Ar-OH proton); MS: m/z 371 (M^+).

Table 1: Characterization table of synthesized compounds

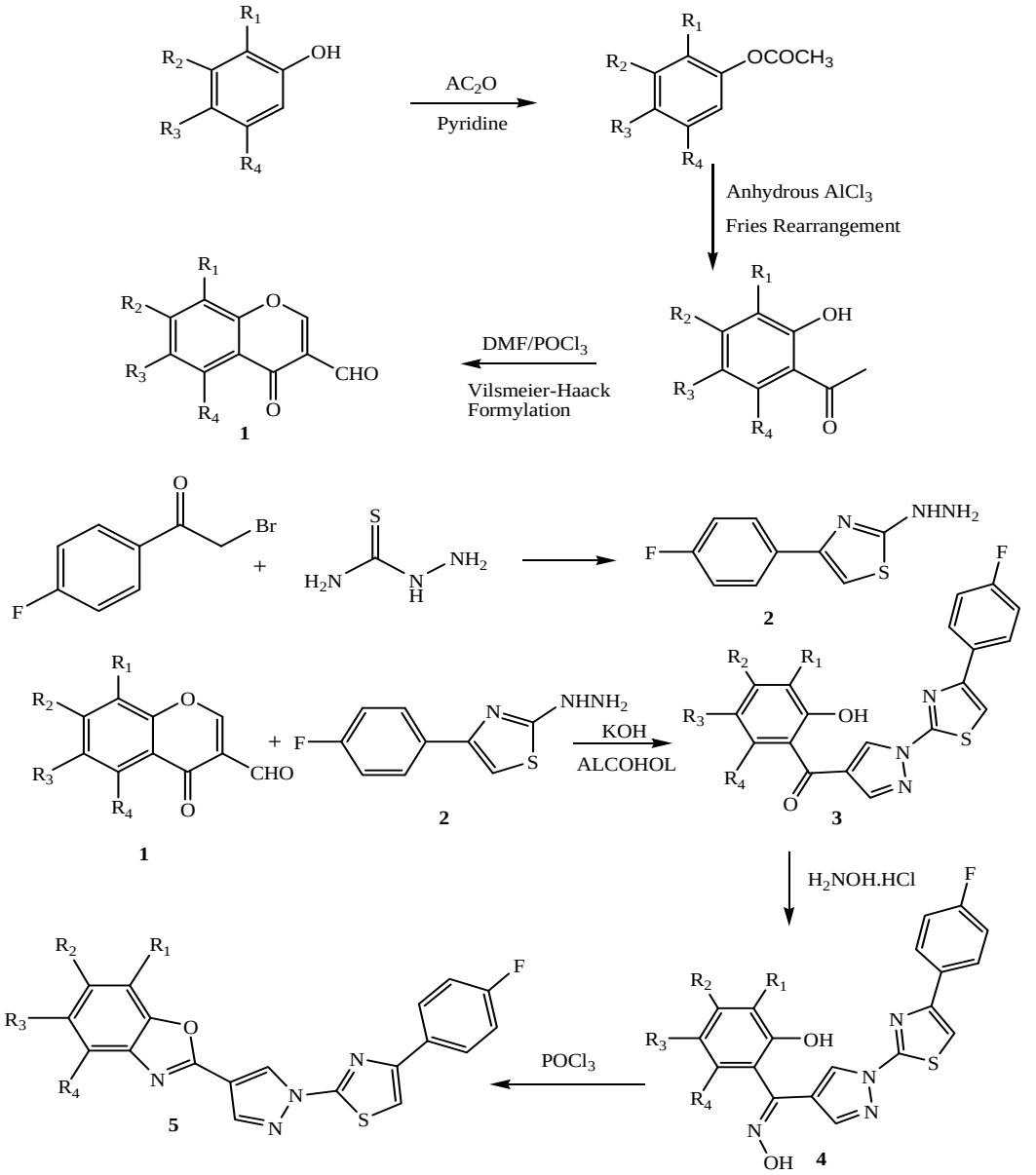
Compound No.	R_1	R_2	R_3	R_4	M.P. (^{0}C)	Yield (%)
3a	H	H	Me	H	181-185	82
3b	H	H	H	H	130-140	75
3c	H	H	Br	H	148	79
3d	H	Me	H	H	158	69
3e	Cl	H	Cl	H	125-130	69
3f	H	H	Cl	H	165-170	82
3g	H	Me	Cl	H	190	71
3h	H	H	Et	H	104	78
3i	H	Me	H	Me	110-112	80
4a	H	H	Me	H	220	66
4b	H	H	H	H	178	68
4c	H	H	Br	H	212-214	65
4d	H	Me	H	H	205	49
4e	Cl	H	Cl	H	168	70
4f	H	H	Cl	H	140-145	68
4g	H	Me	Cl	H	200-204	45
4h	H	H	Et	H	180	58
5a	H	H	Me	H	204-210	80
5b	H	H	H	H	180	86
5c	H	H	Br	H	185-190	90
5d	H	Me	H	H	186	89
5e	Cl	H	Cl	H	185	68
5f	H	H	Cl	H	240	75
5g	H	Me	Cl	H	178-180	72
5h	H	H	Et	H	130-140	65

(4c)

IR (cm^{-1}): 3144 (Ar-OH stretching), 3105 (N-OH stretching), 2919 (Ar C-H stretching), 1556 (-C=N stretching), 621 (C-S stretching) 539 (C-Br stretching); ^1H NMR (DMSO): δ 6.9 (d, 1H, J= 8.72 Hz),7.3 (t,2H, J= 8.72 Hz), 7.37 (m, 1H), 7.4 (d, 1H, J= 2 Hz), 7.8 (m, 2H), 8.0 (t, 2H, J=8.2 Hz), 8.8 (s, 1H), 10.12 (s, 1H, Ar-OH proton,), 12.06 (s, 1H, N-OH proton). MS: m/z 395.1 (M^+).

2-(1-(4-(4-Fluorophenyl)thiazol-2-yl)-1*H*-pyrazol-4-yl)benzo[*d*]oxazole

(1-(4-(4-Fluorophenyl)thiazol-2-yl)-1*H*-pyrazol-4-yl)(2-hydroxyphenyl)methanone oxime (0.05 mol) was dissolved in $POCl_3$ (15 mL) and refluxed for 3 hr. Then reaction combination was poured into crushed ice and neutralized the content by adding up sodium acetate, 2-(1-(4-(4-fluorophenyl)thiazol-2-yl)-1*H*-pyrazol-4-yl) benzo [*d*] oxazole obtained was separated by filtration, washed carefully with cold stream and crystallized from ethanol



Scheme 1:

to get the clean compounds. The synthesized compounds are listed in **Table-1**.

(5a)

IR (cm^{-1}): 1636 (Ar –C=C- stretching), 1574 (-C=N stretch of benzoxazole), 1529 (-C=N stretch of pyrazole), 1244 (-C-O-C- stretching), 612 (-C-S stretching); ^{1}H NMR (DMSO): δ 2.4 (s, 3H), 7.10 - 7.49 (m, 6H), 7.85 - 7.88 (m, 2H), 8.32 (s, 1H), 9.04 (s, 1H); MS: m/z 377 (M^+).

(5b)

IR (cm^{-1}): 1641(Ar –C=C- stretching), 1593 (-C=N stretch of benzoxazole), 1539 (-C=N stretch of pyrazole), 1233 (-C-O-C- stretching), 608 (-C-S stretching); ^{1}H NMR (DMSO)**:** δ 7.1 (t,2H), 7.3 (m, 3H), 7.5 (m, 1H), 7.7 (m, 1H), 7.8 (dd, 2H), 8.3 (s, 1H), 9.1(s, 1H). MS: m/z: 363 (M^+).

(5c)

IR (cm^{-1}): 1642 (Ar –C=C- stretching), 1601 (-C=N stretch of benzoxazole), 1540 (-C=N stretch of pyrazole), 1230 (-C-O-C- stretching), 647 (-C-S stretching), 568 (C-Br stretching); ^{1}H NMR (DMSO): δ 7.3 (t, 2H, J= 8.6Hz), 7.6 (d, 1H), 7.7 (d, 1H, J= 8.6Hz), 8.0 (d, 2H, J= 5.9Hz), 8.1 (t, 2H, J= 5.6Hz), 8.5 (s, 1H), 9.3 (s, 1H). MS: m/z 441 (M^+).

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