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Synthesis and antimicrobial screening of (1-(2,4-dichlorophenyl)-1*H*-pyrazol-4yl (2-hydroxyphenyl) methanone and 2- (1-2,4-dichlorophenyl)-1*H*-pyrazol-4yl) benzo [d] oxazole

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ABSTRACT

3-Formylchromone 1 was treated with 2, 4-dichlorophenylhydrazine hydrochloride to get (1-(2,4-dichlorophenyl)-1*H*-pyrazol-4yl (2-hydroxyphenyl) methanone 2. Compound 2 on treatment with hydroxylamine hydrochloride gave the compound (1-(2,4-dichlorophenyl)-1*H*-pyrazol-4yl (2-hydroxyphenyl) oxime 3. Compound 3 on treatment with $POCl_3$ gave 2- (1-2,4-dichlorophenyl)-1*H*-pyrazol-4yl) benzo [d] oxazole 4. The structures of compounds have been established on the basis of spectral data. These compounds were screened for their antimicrobial activities.

Key words: 3-Formylchromone, antimicrobial activity, spectral data, compounds.

INTRODUCTION

3-Formylchromone is a versatile synthone[1] and can be converted into different heterocyclic compounds. 3-Formylchromone is used as a starting material for synthesis of different bioactive heterocycles due to the presence of three electrophilic centers in this molecule[2-4]. Condensation reactions of different nucleophiles with 3-formylchromone are studied by different workers[5-9]. Condensation products of these reactions showed significant biological activities.

Pyrazole chemistry has been the focus of high attention for more than three decades due to versatile biological activities of pyrazole derivatives. Pyrazole moiety containing compounds are associated with different biological activities like anti-inflammatory[10], hepatoprotective[11], antibacterial, antifungal[12], antitumor and antianginogenic[13-14].

Chlorinated aromatic compounds have found wide use as fungicides, insecticides, herbicides[15-16] and canabinoid antagonist[17].

Benzoxazole derivatives constitute an important class of compounds possessing divers types of biological activities including antitumor, antimicrobial and antiviral[18-20].

Activities associated with these nuclei prompted us to synthesize benzoxazole containing pyrazole nucleus and chlorine atoms.

In present work 3-formylchromone 1 on treatment with 2, 4-dichlorophenylhydrazine hydrochloride gave (1-(2,4-dichlorophenyl)-1*H*-pyrazol-4yl (2-hydroxyphenyl) methanone 2. Compound 2 on treatment with hydroxylamine hydrochloride afforded the compound (1-(2,4-dichlorophenyl)-1*H*-pyrazol-4yl (2-hydroxyphenyl) oxime 3. Compound 3 on treatment with $POCl_3$ gave 2- (1-2,4-dichlorophenyl)-1*H*-pyrazol-4yl) benzo [d] oxazole 4.Synthesized compounds were tested for their antimicrobial activities.

RESULTS AND DISCUSSION

3-Formylchromone 1 on treatment with 2, 4-dichlorophenyl-hydrazine hydrochloride afforded compound 2. Compound 2 showed characteristics IR absorption bands at 3077 and 1640 cm^{-1} due to –OH and –C=O functionality. ^1H NMR showed peaks at 11.88 δ due to – OH proton. The structure of compounds were also confirmed by ^{13}CNMR and mass spectrum.

Table 1: Characterization data of synthesized compounds

Compd No	R_1	R_2	R_3	M. P. (°C)	Yield (%)
2a	CH_3	H	H	80	68
2b	Cl	H	H	138	65
2c	F	H	H	127	62
2d	H	H	H	70	45
2e	Et	H	H	78	44
2f	H	CH_3	H	142	70
2g	Cl	H	Cl	190	55
2h	Cl	CH_3	H	142	50
2i	Br	H	H	117	50
2j	CH_3	H	CH_3	144	70
3a	CH_3	H	H	207	60
3b	Cl	H	H	204	64
3c	F	H	H	180	55
3d	H	H	H	80	45
3e	Et	H	H	155	40
3f	H	CH_3	H	197	60
3g	Cl	H	Cl	250	45
3h	Cl	CH_3	H	190	50
3i	Br	H	H	203	55
3j	CH_3	H	CH_3	212	65
4a	CH_3	H	H	149	55
4b	Cl	H	H	199	62
4c	F	H	H	195	50
4d	Cl	H	cL	208	40
4e	Br	H	H	204	45
4f	H	CH_3	H	146	60
4g	Cl	CH_3	H	209	48
4h	CH_3	H	CH_3	142	40

Compound 2 on treatment with hydroxylamine hydrochloride in KOH afforded compound 3. Compound 3 showed characteristics IR absorption bands 3178 cm^{-1} due to –OH group of phenol and oxime, formation of oxime was confirmed as the band at 1640 cm^{-1} gets disappeared. The structure of compounds 3 were also confirmed by ^{1}H NMR, $^{13}CNMR$ and mass spectrum.

Compound 3 on treatment with phosphorous oxychloride gets cyclised to compound 4. Cyclization was confirmed by IR spectra as the band at 3178 cm^{-1} gets disappeared. ^{1}H NMR showed disappearance of the peaks due to -OH proton at 11.60δ. The structure of compounds 3 were also confirmed by $^{13}CNMR$ and mass spectrum.

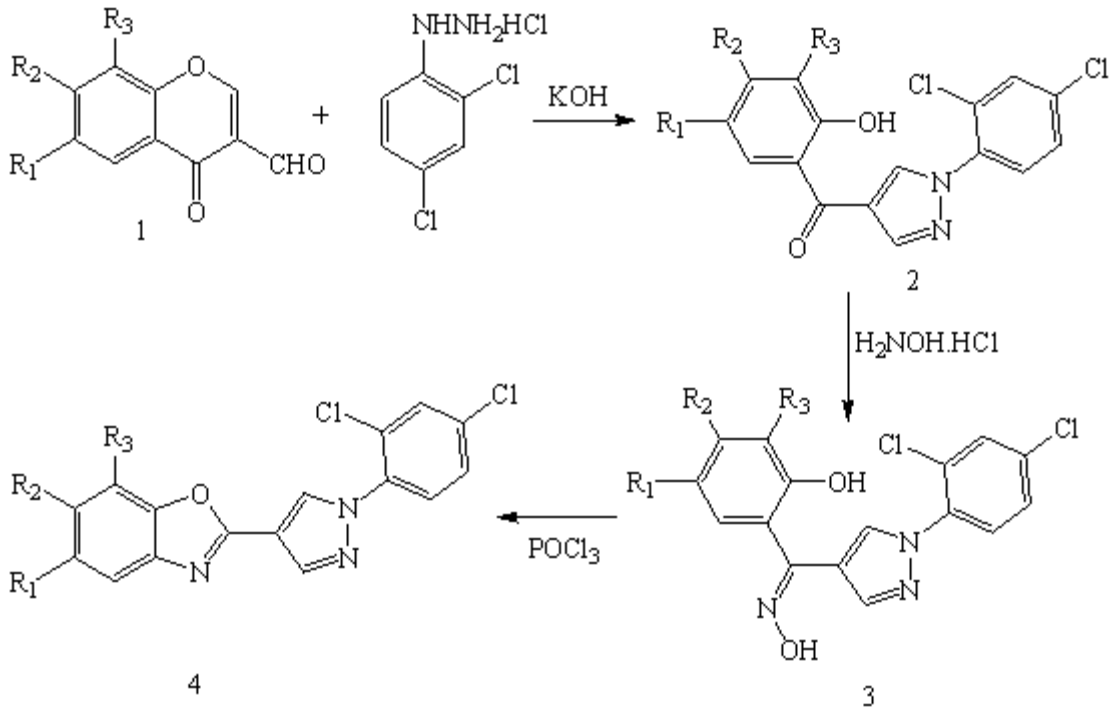
Antimicrobial activity

Some of the compounds 2 to 4 were screened for their antibacterial activities against the bacteria *E-coli*, *S-aureus*, *S-typhimurium* using standard antibiotic drug Cephalexine. The biological activities of these compounds have been evaluated by turbidity method DMSO was used as a solvent. MIC was determined after 48 hr or 72 hr incubation along with positive and negative controls at 37 ^{0}C and 30 ^{0}C respectively. Inhibition zones were measured in mm and results obtained are shown in Table 2. Most of the compounds showed moderate bactericidal activity against both bacteria.

These compounds were also tested for their fungicidal activity against *C-albicans*, *A-niger* using Fluconazole as *a* control and DMSO as a solvent. Most of the compounds showed moderate fungicidal activity against fungi. The results are shown in Table 2.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. Purity of the compounds was checked on TLC. IR spectra were recorded on a Perkin Elmer 1420 FT

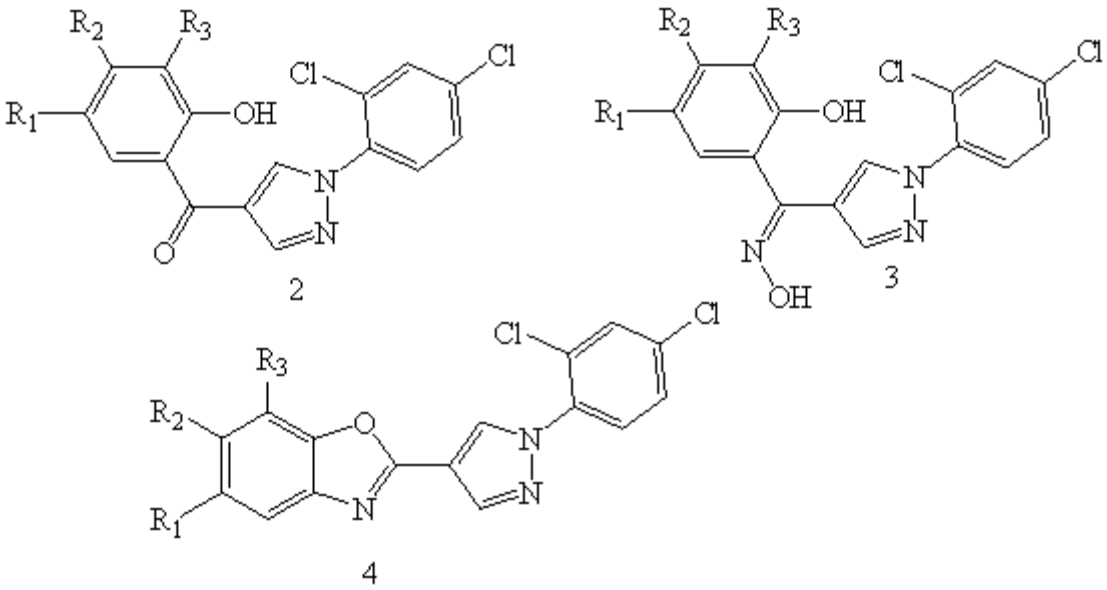


Scheme

Table 2: Antibacterial and antifungal activity of compounds (2-4)

Compd	Fungal model		Bacterial model		
	C. albicans	*A. niger*	*S. aureus*	*E. coli*	*S. typhimurium*
2a	-	-	-	14	-
2b	-	12	10	11	10
2c	11	14	10	11	-
2d	-	-	-	11	10
2e	11	10	11	12	-
2f	10	-	12	14	-
3a	-	-	12	11	14
3b	12	-	12	14	-
3c	15	10	11	12	-
3d	14	12	10	14	12
3e	10	10	11	13	-
4a	12	12	10	12	10
4b	14	10	12	13	-
4c	10	12	11	10	12
4f	11	11	14	11	-
4g	11	10	11	12	-
Fluconazole	24	20	NA	NA	NA
Cephalexine	NA	NA	28	20	23

N. A. : Not applicable



Graphical abstract

Synthesis and antimicrobial screening of (1-(2,4-dichlorophenyl)-1*H*-pyrazol-4yl (2-hydroxyphenyl) methanone and 2- (1-2,4-dichlorophenyl)-1*H*-pyrazol-4yl) benzo [d] oxazole.

spectrophotometer in KBr disc. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300 MHz spectrometer using DMSO-d_6 as a solvent and TMS as internal standard. Peak values are shown in δ (ppm). Mass spectra were recorded on a Finnigan mass spectrometer.

General procedure

(1-(2,4-Dichlorophenyl)-1*H*-pyrazol-4yl (2-hydroxyphenyl) methanone (2a-j)

3-Formylchromone 1 (0.001 mol) and 2, 4-dichlorophenyl-hydrazine hydrochloride (0.001 mol) were dissolved in ethanol. The content were refluxed for 20 min. Then reaction mixture was cooled at room temperature to afford hydrazone derivative. To this 1 gm KOH added to get clear solution and refluxed for 3 hr. Then reaction mixture was poured into crushed ice and acidified with conc. HCl. The product obtained was separated by filtration and crystallized from ethanol to afford pure compounds 2. The compounds synthesized by above method are listed in Table 1. 2f: IR (KBr) cm^{-1} : 3077 (OH), 1660 (C=O), 1601 (C=N), 1107 (Ar-Cl), 1221 (C-O); ^{1}H NMR (DMSO-d_6): 2.37 (s, 3H, Ar-CH_3), 6.80-7.95 (m, 6H, Ar-H), 8.29-8.80 (s, 2H, pyrazole), 11.88 (s, 1H, -OH); ^{13}CNMR: 190.23, 159.99, 146.10, 142.25, 136.31, 136.04, 136.42, 132.40, 131.02, 130.03, 129.60, 128.43, 122.73, 120.47, 119.52, 117.64, 21.32; Mass: (M^+); *m/z* 347 with isotopic peaks.

(1-(2,4-Dichlorophenyl)-1*H*-pyrazol-4yl (2-hydroxyphenyl) methanone oxime (4a-j)

The compound 2 (0.05 mol) was dissolved in ethanol (15 ml). To this 40% KOH (10 ml) was added with constant stirring at 10^{O}C and to this excess hydroxylamine hydrochloride was added in portion wise. Further stirring was continued at room temperature for 3-4 hr. Then reaction mixture was poured into crushed ice and acidified with acetic acid. The product obtained was separated by filtration and crystallized from aq. ethanol to afford the pure compounds 3. The compounds synthesized by above method are listed in Table 1. 3f: IR (KBr) cm^{-1} : 3178 (OH), 1621 (C=N), 1107 (Ar-Cl); ^{1}H NMR (DMSO-d_6): 2.30 (s, 3H, Ar-CH_3), 6.70-7.80 (m, 6H, Ar-H), 7.90-8.55 (s, 2H, pyrazole), 9.95 (s, 1H, -OH of oxime), 11.60 (s,1H, Ar-OH); ^{13}CNMR: 155.80, 147.44, 142.22, 139.61, 136.40, 134.03, 133.62, 130.26, 130.04, 129.24, 128.84, 128.41, 119.73, 119.63, 116.54, 114.82, 20.95; Mass: (M^+); *m/z* 362 with isotopic peaks.

2-(1-2,4-Dichlorophenyl)-1*H*-pyrazol-4yl) benzo [d] oxazole (4a-h)

The compound 3 (0.05 mol) was dissolved in $POCl_3$ (15 ml) and refluxed for 3 hr. Then reaction mixture was poured into crushed ice and neutralized the content by adding sodium acetate, the solid obtained was separated by filtration, washed thoroughly with cold water and crystallized from ethanol to afford the pure compounds 4. The compounds synthesized by above method are listed in Table-1. 4f: IR (KBr) cm^{-1}: 1590 (C=N of bezoxazole), 1534 (C=N of pyrazole), 1245 (C-O-C), 1104 (Ar-Cl); ^{1}H NMR (DMSO-d_6): 2.30 (s, 3H, Ar-CH_3), 7.22-7.98 (m, 6H, Ar-H), 8.45-9.00 (s, 2H, pyrazole); ^{13}CNMR: 140.17, 139.21, 137.21, 136.10, 135.02, 134.39, 133.16, 130.09, 129.59, 128.49, 125.84, 119.24, 118.69, 112.41, 111.52, 110.65, 21.25; Mass: (M^+); *m/z* 344 with isotopic peaks.

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