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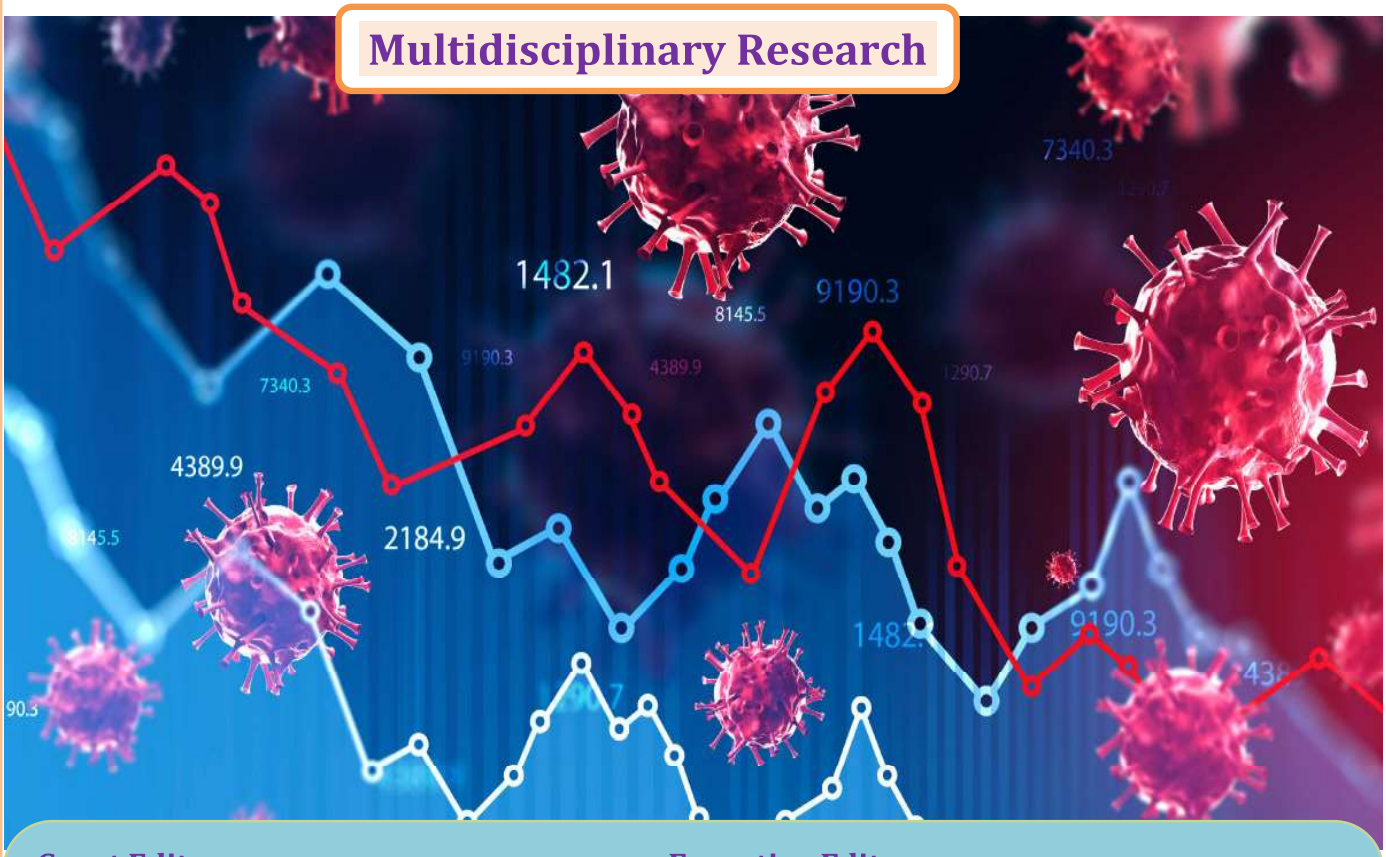

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Synthesis, Characterization and Antimicrobial Analysis of Some New Substituted Pyrazoles From Chromones

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Abstract:

Pyrazoles are one of the most commonly used organic moieties. Among various heterocyclic compounds, the medicinal importance of derivatives of pyrazoles is significant. Pyrazole derivatives have a lengthy history of application in pharmaceutical and agrochemicals industry as active pharmaceuticals and herbicides, due to their antiviral, anti-neoplastic, antibiotic and anti-inflammatory including other biological activities. Herein we report novel pyrazoles from chromone by using hydrazine hydrate. All synthesized pyrazoles derivatives were well characterized by spectral analysis and were screened for antimicrobial activity and they showed moderate activity.

Keywords: Pyrazoles, Chromones, hydrazine hydrate, antimicrobial, Gram +ve and Gram –ve microorganisms.

Introduction:

In 1883, the term pyrazole was introduced by Ludwig Knorr. Pyrazole refers to the class of simple organic aromatic ring compounds of the heterocyclic series which characterized by a 5-membered ring structure containing three carbon atoms and two nitrogen atoms in adjacent positions. Due to so composed and having pharmacological effects on humans, they are classified as alkaloids, while they are rare in nature. An efficient investigation of this class of heterocyclic compounds lead revealed that pyrazole bearing pharmacoactive agents play significant role in medicinal chemistry**.** The prevalence of pyrazole cores in biologically active molecules has stimulated the need for well-designed and efficient ways to make these heterocyclic lead[1].

Because of medicinal and pesticidal importance of nitrogen-linked heterocyclic compounds received considerable attention in recent times[2-4]. It is very well known that the study of pyrazole containing compounds are significant in pesticide chemistry and some of their derivatives which were broadly used because of their antibacterial[5], anti-inflammatory[6], antiviral[7], antitumor[8], fungicidal activities[9], herbicidal[10], insecticidal[11], molluscidal[12], Angiotensin-I-converting enzymes inhibitory[13], and ulcerogenic activity[14]. By founding the o-phthalimide nucleus, which incorporates a pyrazole ring, shows a huge number of biological activities, particularly herbicidal activities. In addition to that, many biological compounds contain a fluoro moiety, which indicates that this moiety may be important for huge number of biological activity[15].

The derivatives of pyrazole amide play an important role in development of medicine and pesticide due to their large spectrum of biological activity[16-21]. In recent years, considerable attention towords the study of synthesis and biological activity of pyrazole amide and its derivatives has been compensated[22].

Experimental:

For the synthesis of the compounds, all chemicals used were obtained especially from SD Fine chemicals and Sigma Aldrich. In liquid paraffin bath, melting points of synthesized compounds were recorded in open capillaries and which are uncorrected. The purity was checked of the synthesized compounds by using TLC, in which silica gel coated plates obtained from Merck as a stationary phase and solvent mixture of ethyl acetate and hexane as a mobile phase. Infrared spectra of synthesized compounds were recorded on Schimadzu-FT-IR Spectrophotometer using potassium bromide pellet technique and the absorption bands are expressed in cm^{-1}. ^1H NMR spectra of synthesized compounds were recorded on Varian 400 MHz and Mercury YH 300 MHz instrument in solvents DMSO-d_6, $CDCl_3$ and TMS as an internal standard, the chemical shift data were expressed as δ values relative to TMS and in hertz (Hz) coupling constants (*J*) were expressed. By using electro-spray method (ES), on Macromass mass spectrophotometer (Waters), mass spectra were recorded.

General procedure:

Compound **1c** (0.003 mol) was taken with 15 ml ethanol in 100 ml RBF. 1 ml hydrazine hydrate and 0.5 gm KOH were added in this reacting mixture and heated under reflux for about five hour. After completing of reaction (monitored by TLC), this contents were cooled to room temperature and then poured over crushed ice and acidified by using HCl. The obtained solid was separated by filtration and recrystallized in ethanol to get pure compound **2c**. The compounds **2(a-h)** were prepared following by the above explained procedure. In **Table 1,** physical data of these synthesized compounds are recorded. Synthesized compounds structures have been confirmed by IR, ^1H NMR and Mass spectra.

IR (2c) (cm^{-1}): 959(C-Cl), 1061 (Ar-Br), 1276(C-O), 1501(Ar C=C), 1598(C=N), 2979(N-H), 3065(O-H).

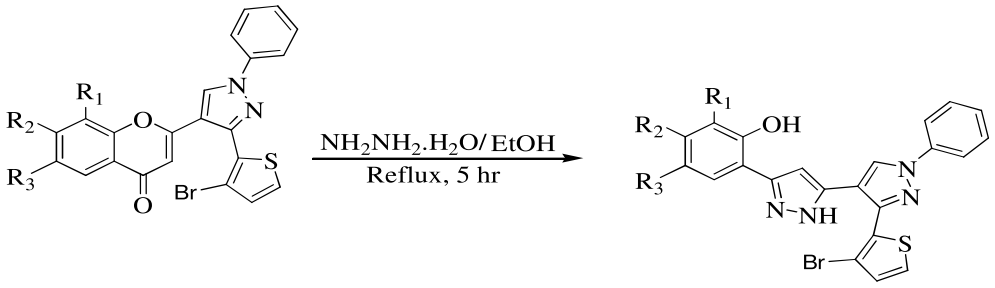
^1H NMR (2c) (DMSO) δ ppm: 6.9984 (s, 1H, Pyrazoline N-H), 7.1993-7.2998 (m, 2H, Ar-H), 7.3253-7.3987(m, 2H, Ar-H), 7.4128-7.4756 (m, 1H, Ar-H), 7.5745-7.7512(m, 2H, Ar-H), 7.7543-7.8147(m, 1H, Ar-H), 7.8425-7.9979(m, 2H, Ar-H), 8.8802 (s, 1H, Pyrazole-H), 10.8417 (s, 1H, Pyrazole-H), 13.4652 (s, 1H, Ar-OH).

ES-MS (2c) (m/z): 497.5(M+1), 499.5(M+3).

IR (2d) (cm^{-1}): 961(C-Cl), 1049(Ar-Br), 1281(C-O), 1499(Ar C=C), 1591(C=N), 2973(N-H), 3165(O-H).

^1H NMR (2d) (DMSO) δ ppm: 6.9854 (s, 1H, Pyrazoline N-H), 7.2145-7.2564(m, 1H, Ar-H), 7.3116-7.3514(m, 2H, Ar-H), 7.3984-7.4354 (m, 1H, Ar-H), 7.5684-7.6599(m, 2H, Ar-H), 7.7367-7.7994(m, 1H, Ar-H), 7.8371-7.8759(m, 2H, Ar-H), 8.9743 (s, 1H, Pyrazole-H), 10.9641 (s, 1H, Pyrazole-H), 13.0129 (s, 1H, Ar-OH).

ES-MS (2d) (m/z): 531(M+1), 533(M+3).



1(a-h) **2(a-h)**

Scheme 1: Synthesis of 2-(5-(3-(3-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-1H-pyrazol-3-yl)phenol

➢ **Table 1: Physical data of compounds 2(a-h)**

Comp.	R_3	R_2	R_1	M.P. (^oC)	Yield (%)
2a	H	H	H	158-160	80
2b	CH_3	H	H	144-146	69
2c	Cl	H	H	118-120	82
2d	Cl	H	Cl	196-198	69
2e	F	H	H	184-186	71
2f	Cl	CH_3	H	180-182	75
2g	Br	H	H	174-176	78
2h	CH_3	H	CH_3	192-194	67

Result and Discussion:

Eight new pyrazole derivatives have been synthesized successfully having good yields. The newly synthesized pyrazole derivatives have been confirmed using ^1H NMR, melting point range, Mass, IR spectral analysis. By using disc diffusion method, all newly synthesized compounds were screened for antimicrobial activity.

Antimicrobial activity:

Compounds **2(a-h)** were screened for their antimicrobial activity against Gram positive (*Enterobacter aerogenes, Salmonella abony, Salmonella typh, Pseudomonas aerogenosa, Escherichia coli, Shigella boydii)* and Gram negative pathogens(*Staphylococcus aureus, Megaterium Bacillus, Bacillus subtilis, Bacillus cereus*) by paper disc diffusion method using tetracyclin as a reference standard drug. By using Nystatin as standard drug, antifungal activity was screened against *Aspergillus niger, Saccharomyces cerevisiae, Candida albicans* at 100 µg/ml concentration. Culture media was Muller Hinton agar. In mm The zone of inhibition was measured, after the 24 hr of incubation at 37°C. Microbial data for 2(a-h) are summarized in

Table 2.

Table 2: Antimicrobial Analysis Data of 2(a-h)

	Bacterial pathogens										Fungal pathogen		
	Gram negative pathogen						Gram positive pathogen						
Compounds	*Salmonella typhi*	*Enterobacter*	*Escherichia coli*	*Pseudomonas*	*Salmonella abany*	*Shigella boydii*	*Bacillus subtilis*	*Bacillus Megateriu*	*Staphylococcus*	*Bacillus cereus*	*Candida albicans*	*Saccharomyces*	*Aspergillus niger*
2a	11	09	12	10	14	08	-	13	**07**	09	-	10	11
2b	09	08	13	16	15	-	08	12	10	-	11	-	09
2c	10	10	12	11	12	09	-	19	06	09	10	-	09
2d	-	11	10	13	08	07	08	14	14	-	15	07	08
2e	-	14	11	12	10	-	-	08	11	-	14	-	07
2f	15	-	12	15	17	11	10	12	12	-	15	07	19
2g	-	09	12	-	11	-	-	15	13	-	-	-	18
2h	11	-	12	09	15	11	09	13	10	-	11	09	14
DMSO	-	-	-	-	-	-	-	-	-	-	-	-	-
STND.	22	20	20	33	21	26	25	20	30	25	24	20	25

*Standard for bacterial pathogens-tetracyclin, for fungal pathogens-nystatin

Conclusion:

In conclusion, we have successfully synthesized pyrazole derivatives starting from Chromones, these newly synthesized pyrazoles derivatives were screened against Gram positive as well as Gram negative bacterial strains and these compounds shows moderate activity as compared to standard drug. The obtained data through the present work shows a good agreement between the experimental and computed spectral data.

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