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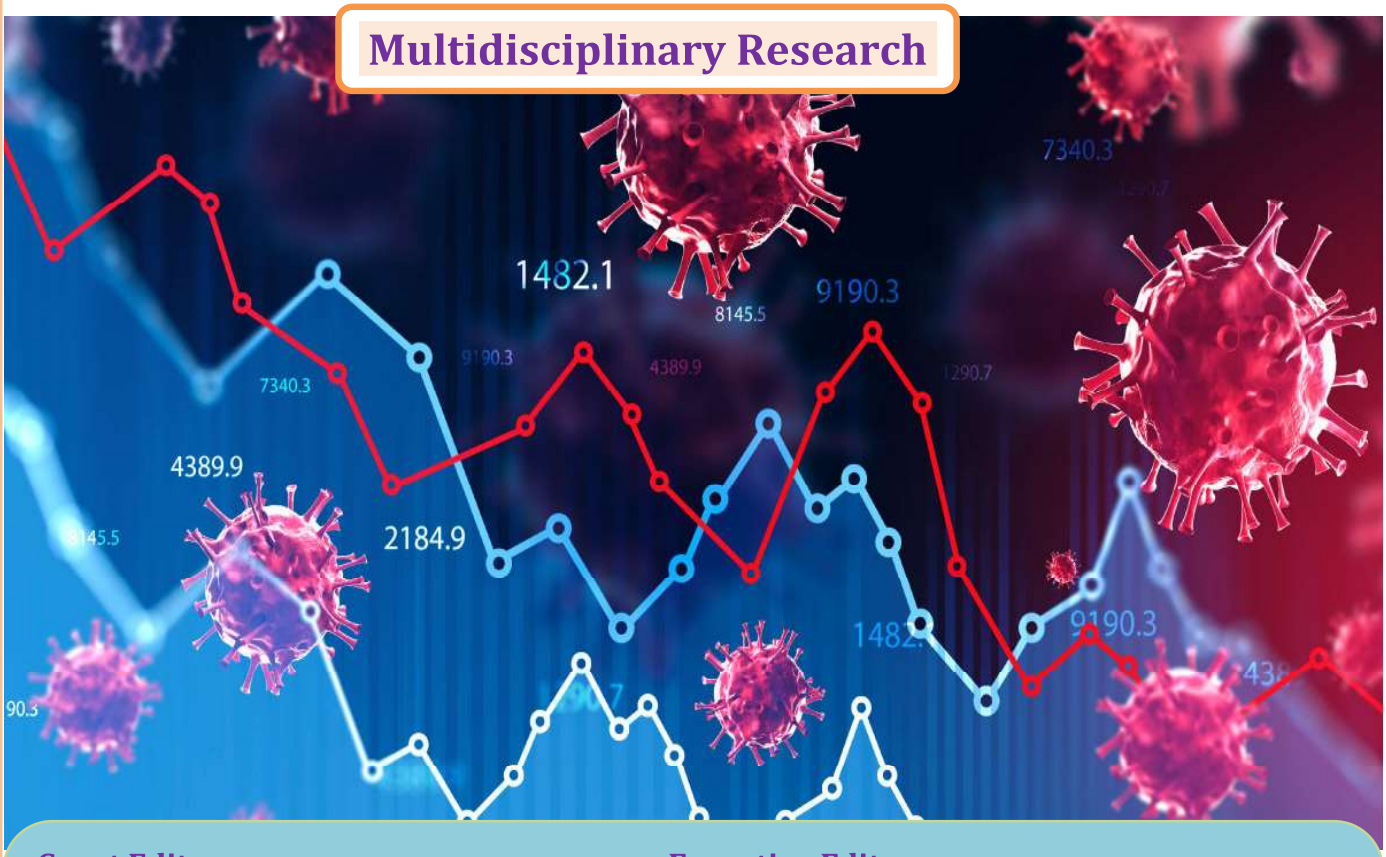

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Synthesis and Antimicrobial Screening of Novel Pyrazole Substituted Chlorochromones

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Abstract: -

The title compounds Chlorochromones were prepared by the reaction of Chalcones with Cuprous chloride by oxidative cyclization under reflux condition. The synthesized compounds were characterized by Spectral analysis like IR, ^{1}HNMR and Mass Spectra.Antibacterial and antifungal screening of newly prepared compounds was carried out.

Keywords: -Chlorochromones, chromones

Introduction: -

Heterocyclic compounds are widely distributed in natural products and comprise a huge number of biologically active compounds. A wide range of medical applications such as anti-inflammatory, antiviral, anti-HIV, antibacterial,anticancer, antimalarial, antidepressants, antipsychotics,anaesthetics, and steroids have shown by fluorinated compounds [1, 2]. Introducing fluorineatoms into drugs can also alter the rate and route of drug metabolism [1], and stereoelectronic factors associated with the fluorine atom can lead to changes in the biological action of molecules in comparison to its hydroxyl or hydrogen analogues [3]. The substitution of fluorine for hydrogen can lead to changes in the mechanism of the drug as well as enzyme inhibition [3]. The small size of the fluorine atom, the enhanced lipophilicity it imparts to the molecules, and the electronegativity of the atom often result in improved therapeutic drugs [2]. As part of an ongoing study on fluorinated pharmaceutical compounds, we have chosen to explore the antibacterial and antifungal effects of fluorinated chlorochromones.

Some of the chromones, especially those having heterocyclic substituents at C-2 and C-3 positions have good pharmacological activities *viz.* coronary spasmolytic and bronchodilatory activities useful in the treatment of asthma [4-8]. The synthesis of 3-substituted chromones appears worthy of study because they are important natural products like isoflavones and in medicines such as ipriflavone, an antiosteoporosis drug [9].Gill *et al.* [10] have reported the synthesis and antimicrobial screening of chlorochromones bearing pyrazoles.

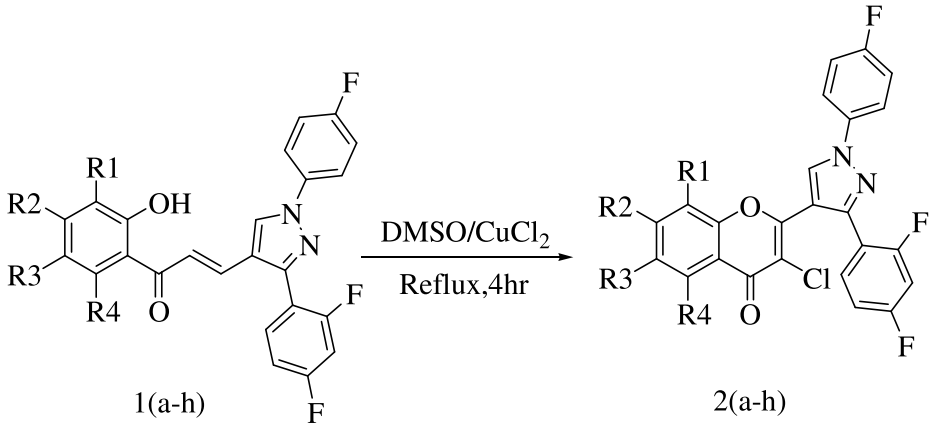
Experimental:

General Procedure for the synthesis of 3, 6-dichloro-2-(3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-4*H*-chromen-4-one(2c): (0.25 gm, 0.0007 mmole) of chalcone **1c** was dissolved in 15 mL of DMSO. To this reaction mixture catalytic amount of cuprous chloride ($CuCl_2$) was added. The reaction mixture was heated in an oil bath for 4 hr at 120^{o}C. After completion of reaction (monitored by TLC) reaction mass was left overnight. 10 mL cold water was slowly added to the flask and the separated product was filtered, washed with water followed by dil. HCl for several times. It was again washed with water, dried under vacuum and crystallized from ethanol to afford **2c**. The physical data of the compounds **2(a-h)** is recorded in **Table 1**.Their structures have been confirmed by ^{1}H NMR, Mass and IR spectra.

IR (2c) (cm^{-1}): 715(C-Cl), 1217(C-F), 1597, 1612(C=C), 1653(C=O).

^{1}H NMR (2c) ($CDCl_3$)δ ppm: 6.944-6.954(d, 1H, Ar-H, *J*=3.6Hz), 7.001-7.013(d, 1H, Ar-H, *J*=3.6Hz), 7.251-7.270(d, 1H, Ar-H, *J*=7.6Hz), 7.383-7.420(m, 1H, Ar-H),7.506-7.545(m, 1H, Ar-H), 7.618-7.624(d, 1H, Ar-H, *J*=2.4Hz),7.650-7.657(d, 1H, Ar-H, *J*=2.8Hz),7.768-7.785(m, 2H, Ar-H),8.256-8.262(d, 1H, Ar-H, *J*=2.4Hz),8.581(s, 1H, Pyrazole-H).

ES-MS (2c) (m/z): 487(M+1), 489(M+3), 491(M+5).



Scheme1

Scheme1- Synthesis of various substituted 3-chloro-2-(3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-4*H*-chromen-4-one

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

Comp.	R_1	R_2	R_3	M.P. (°C)	Yield (%)
2a	H	H	H	140-142	44
2b	H	H	CH_3	170-172	74
2c	H	H	Cl	166-168	66
2d	Cl	H	Cl	120-122	72
2e	H	H	F	240-242	56
2f	H	CH_3	Cl	146-148	72
2g	H	H	Br	254-256	74
2h	CH_3	H	CH_3	188-190	68

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)* usingCiprofloxacin as a reference standard drug by paper disc diffusion method. Antifungal activity was evaluatedagainst *Candida sp.* using fluconazole as standard drug. All the tests were evaluated at 100 µg/ml concentration.The culture media was Muller Hinton agar. The zone of inhibition was measured in mm after 24 hr ofincubation at 37°C.Microbial data for corresponding compounds is summarized in **Table 2.**

Table 2: Antimicrobial Analysis Data

Sr. No.	Compound No.	Inhibition Zone Diameter (mm)					
		Candida sp.	S. aureus	S.albus	Klebsiella	Candida sp.	S. aureus
1.	2a	5	-	7	-	6	-
2.	2b	-	10	-	-	8	-

3.	2c	7	10	-	-	12	-
4.	2d	-	-	-	13	8	-
5.	2e	-	10	9	11	11	-
6.	2f	-	9	8	13	11	-
7.	2g	11	14	-	14	10	-
8.	2h	12	13	-	14	10	-
9.	Control	8	3	3	6	8	10
10.	Ciprofloxacin	---	20	22	22	21	23
11.	Fluconazole	---	20	22	22	21	23

Conclusion:

The novel synthesized compounds were tested against Gram positive and Gram negative bacterialstrains. As well as they were tested against Candida species. From the results it is concluded that, compounds 2g-2h exhibited moderate anti-microbial activity. The other compounds have shown goodactivity compared to standard drug.

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