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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ANALYSIS OF VARIOUS SUBSTITUTED 2-(3-(3-BROMOTHIOPHEN-2-YL)-1-PHENYL-1*H*-PYRAZOL-4-YL)-4*H*-CHROMEN-4-ONE

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We have developed a protocol for the synthesis of some novel chromones from various chalcones by using I_2 in DMSO. All the products were characterized by IR, NMR and Mass spectral data. In addition to this newly synthesized compounds have been screened for their antimicrobial activity against Gram +ve and Gram –ve microorganisms. Some of the compounds show moderate antimicrobial activity.

Keywords: chalcones, chromones, antimicrobial, Gram +ve and Gram –ve microorganisms.

Introduction:

Heterocyclic Compounds shows broad spectrum of biological activity. Among all heterocyclic compounds Chromones shows interesting possibilities in exploring their more pharmacological and biocidal potentials. As the chromones are the part of the flavonoid family, they are widely spread in the nature[i]. These compounds have been reported to shows multiple biological activities for example antifungal[ii,iii], antibacterial, antioxidant[iv], anti-HIV[v] and anticancer[i].

Molecules containing the chromone structure get considerable attention in the literatures recently, due to its biological and physiological activities including antifungal, antimycobacterial, antimicrobial, anticonvulsant, mushroom tyrosinase inhibition activities, intermediates to various products of fine chemical industries[vi].

In heterocyclic compounds, pyrazole annulated compounds are known as a stimulating unit in pharmaceuticals[vii], pyrazoles and its derivatives, a class of well known nitrogen heterocycles, due to their diverse biological activities, occupy a leading position in medicinal and pesticide chemistry[viii]. They have been known to exhibit antimicrobial, anti-inflammatory, analgesic, antidepressant, anticancer, anti-tubercular, anticonvulsant, antihyperglycemic, antipyretic, antihelmintic, antioxidant and herbicidal properties[ix].

The reactivity of chalcone and their derivatives are important intermediates in organic synthesis. On account of their impressive biological properties such as anticancer, psychopharmacological, anti HIV, etc. this nucleus has remained in the mainstay as evergreen medicinal scaffold from which potential drug candidates can be projected [x-xii].

Experimental

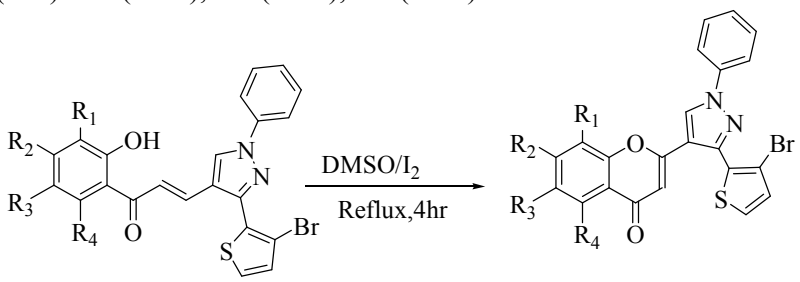
All the chemicals which are necessary for the synthesis of the compounds were purchased from Sigma Aldrich and SD Fine chemicals. Melting points of all synthesized compounds were recorded in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded in DMSO-d_6 on Bruker Avance II 400 MHz NMR Spectrophotometer and TMS as an internal standard, Using FT-IR Spectrophotometer Model RZX (Perkin Elmer) the infra-red spectra were recorded as potassium bromide disk. By using electro-spray method (ES) mass spectra were recorded on Macromass mass spectrophotometer (Waters). Using TLC silica gel coated plates obtained from Merck as stationary phase and solvent mixture of hexane/ethyl acetate (80:20) as mobile phase, purity of the all synthesized compounds were checked.

General experimental procedure

General experimental Procedure for the synthesis of (*E*) 2-(3-(3-bromothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-chromen-4-one (2c): (0.5 gm) of chalcone **1c** was dissolved in 20 ml of DMSO. To this reaction mixture catalytic amount of iodine (I_2) was added and heated in an oil bath for 4 hr at 120^{o}C. After completion of reaction (monitored by TLC), reaction mass was left overnight. 20 ml cold water was slowly added to the flask, while adding, product was separated and the separated product was filtered, washed with water then by dil. sodium thiosulphate solution for a number of times. Again washed with water, dried under vacuum and crystallized from ethanol. The physical data of the compounds **2(a-h)** is recorded in **Table 1**.Structures of synthesized compounds have been confirmed by ^{1}HNMR, Mass and IR spectra.

IR (2a) (cm^{-1}): 1039(Ar-Br), 1271(C-O), 1539(C=N), 1560(Ar-C=C), 1606(C=C), 1692(C=O).
^{1}H NMR (2a) (DMSO-d_6) δ ppm: 6.520 (s,1H,Chromone-H), 6.722-6.761 (d,2H,Ar-H, *J* =15.6 Hz),7.215-7.321 (m,5H,Ar-H), 7.391-7.530 (m,4H,Ar-H), 7.825(s,1H,Pyrazole-H).
ES-MS (2a) (m/z): 449(M+1), 450(M+2), 451(M+3)
IR (2b) (cm^{-1}): 1055(Ar-Br), 1260(C-O), 1528(C=N), 1571(Ar-C=C), 1622(C=C), 1660(C=O).
^{1}H NMR (2b) (DMSO-d_6) δ ppm: 2.3299-2.521(s,3H), 6.625 (s,1H,Chromone-H), 6.971-7.001(d,2H,Ar-H,*J*=12Hz),7.298-7.351 (m,5H,Ar-H), 7.356-7.398 (m,3H,Ar-H), 7.992(s,1H,Pyrazole-H).
ES-MS (2b) (m/z): 463(M+1), 464(M+2), 465(M+3)
IR (2c) (cm^{-1}): 726(C-Cl), 1051(Ar-Br), 1263(C-O), 1533(C=N), 1556(Ar-C=C), 1600(C=C), 1647(C=O).
^{1}H NMR (2c) (DMSO-d_6) δ ppm: 6.577 (s,1H,Chromone-H), 7.200-7.222 (d,2H,Ar-H, *J* =8.8 Hz),7.437-7.452 (d,2H,Ar-H,J=5.64Hz), 7.5211-7.449 (m,4H,Ar-H), 7.825-7.976(m,2H,Ar-H),7.995(s,1H,Pyrazole-H).
ES-MS (2c) (m/z): 483(M+1), 483(M+3), 487(M+5)
IR (2d) (cm^{-1}): 735(C-Cl), 1055(Ar-Br), 1259(C-O), 1530(C=N), 1553(Ar-C=C), 1602(C=C), 1690(C=O).
^{1}H NMR (2d) (DMSO-d_6) δ ppm: 6.616 (s,1H,Chromone-H), 6.981-7.025 (d,2H,Ar-H, *J* =17.6 Hz),7.358-7.412 (m,5H,Ar-H), 7.419-7.438 (d,2H,Ar-H, J=7.6Hz), 7.912 (s,1H,Pyrazole-H).

ES-MS (2d) (m/z): 517 (M+1), 518(M+2), 519(M+3), 520(M+4)
IR (2e) (cm^{-1}): 1020(Ar-F), 1071(Ar-Br), 1265(C-O), 1551(C=N), 1591(Ar-C=C), 1595(C=C), 1665(C=O).
^{1}H NMR (2e) (DMSO-d_6) δ ppm: 6.701 (s,1H,Chromone-H), 6.825-6.860 (d,2H,Ar-H, *J* =3.2 Hz),7.321-7.398 (m,5H,Ar-H), 7.401-7.498 (dd,3H,Ar-H,J=7.8 & 3.6Hz), 7.901 (s,1H,Pyrazole-H).
ES-MS (2e) (m/z): 467(M+1), 468(M+2), 468(M+3)
IR (2f) (cm^{-1}): 728(C-Cl), 1051(Ar-Br), 1140(C-O), 1552(C=N), 1582(Ar-C=C), 1586(C=C), 1691(C=O).
^{1}H NMR (2f) (DMSO-d_6) δ ppm: 2.342(s,3H), 6.756 (s,1H,Chromone-H), 6.829-6.865 (d,2H,Ar-H, *J* =14.4 Hz),6.925-7.298 (m,5H,Ar-H), 7.346-7.398 (d,2H,Ar-H, J=20.8Hz), 7.995(s,1H,Pyrazole-H).
ES-MS (2f) (m/z): 497(M+1), 498(M+2), 499(M+3),500(M+4)
IR (2g) (cm^{-1}): 1091(Ar-Br), 1254 (C-O), 1540(C=N), 1549(Ar-C=C), 1586(C=C), 1650(C=O).
^{1}H NMR (2g) (DMSO-d_6) δ ppm: 6.692 (s,1H,Chromone-H), 6.925-6.969 (d,2H,Ar-H, *J* =17.6 Hz),7.292-7.7351 (m,5H,Ar-H), 7.360-7.425 (m,3H,Ar-H), 8.002(s,1H,Pyrazole-H).
ES-MS (2g) (m/z): 527(M+1), 528(M+2), 529(M+3), 530(M+4)
IR (2h) (cm^{-1}): 1005(Ar-Br), 1132(C-O), 1540(C=N), 1560(Ar-C=C), 1580(C=C), 1696(C=O).
^{1}H NMR (2h) (DMSO-d_6) δ ppm: 2.392(s,6H), 6.712 (s,1H,Chromone-H), 6.921-6.958 (d,2H,Ar-H, *J* =14.8 Hz),7.125-7.298 (m,5H,Ar-H), 7.321-7.341 (d,2H,Ar-H,J=8Hz), 7.942(s,1H,Pyrazole-H).
ES-MS (2h) (m/z): 477(M+1), 478(M+2), 479(M+3)



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

Scheme 1: Synthesis of various (*E*) 2-(3-(3-bromothiophen-2-yl)-1-phenyl-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. (^{o}C)	Yield (%)
2a	**H**	**H**	**H**	196-198	69
2b	**H**	**H**	**CH_3**	200-202	72
2c	**H**	**H**	**Cl**	228-230	82
2d	**Cl**	**H**	**Cl**	222-224	81
2e	**H**	**H**	**F**	230-232	71
2f	**H**	**CH_3**	**Cl**	198-200	79
2g	**H**	**H**	**Br**	216-218	76
2h	**CH_3**	**H**	**CH_3**	202-204	80

Result and Discussion

All derivatives of chromones were synthesized successfully in reasonable to good yields. On the basis of melting point range, IR, ^{1}H NMR, Mass spectral analysis, all newly synthesized compounds were identified and were screened for antimicrobial activity using disc diffusion method.

Antimicrobial activity: By using paper disc diffusion method, Compounds **2(a-h)** were screened for their in vitro antimicrobial activity against *Staphylococcus aureus (ATCC 25923), Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853),* Gentamycin as a reference standard drug. Also antifungal activity was screened against *Candida sp.* using Nystatin as standard drug. All the tests were evaluated at 100 µg/ml concentration. Muller Hinton agar was the culture media. At 37^{o}C, the region of inhibition was measured in mm after 24 hr of incubation. Microbial data for compounds 2(a-h) are summarized below in **Table 2.**

Table 2: Antimicrobial Analysis Data

Sr. No.	Comp.No.	*Escherichia coli (ATCC 25922)*	*Pseudomonas aeruginosa (ATCC 27853)*	*Staphylococcus aureus (ATCC 25923)*	*Candida sp.*
1	2a	6	3.6	5.4	5
2	2b	9	7	8.4	7.4
3	2c	-	-	4.6	5.8
4	2d	5.6	7	1	9
5	2e	8	-	4.6	5.5
6	2f	8	8.6	-	-
7	2g	10	8	2.5	9
8	2h	3.6	-	-	4
9	Gentamycin	28 mm	23 mm	32 mm	--
10	Nystatin	--	--	--	23 mm

Conclusion

In conclusion, starting from chalcone we have successfully synthesized chromones. These newly synthesized compounds were screened against Candida sp. and Gram positive as well as Gram negative bacterial strains. The synthesized compounds shown moderate activity as compared to standard drug. The obtained data during the present work shows a good agreement between the experimental and computed spectral data.

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