Synthesis and Characterization of New Biologically Active 2-(1,3-Disubstituted pyrazolyl)chromones and Corresponding Pyrimidine, Thiopyrimidine, Pyrazolyl Derivatives

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A series of 2-(1-methyl-3-*n*-propylpyrazol-5-yl)-chromones with interesting *Phosphodiesterase* IV inhibitition activities were synthesized. Different derivatives of the titled compounds like aminopyrimidine, thiopyrimidine, pyrazolyl were synthesized and their *Phosphodiesterase* IV inhibitition activities were checked.

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Introduction.

Molecules with heteroatom rings are widely distributed in nature. Indeed a number of heterocyclic compounds like chromones, pyrazoles, pyrimidines exhibit a variety of important biological activities. The chemistry of chromones and its derivatives has been studied for over a century or more, due to their diverse biological activities [1]. Biological activities associated with this nucleus are antibacterial, antifungal, anticholesterenic, antidiabetics, antiallergic, diuretics *etc* [2-4]. Chromones having heterocyclic substituents at 2-position and 3-position have been reported to possess coronary-dilatory activity, muscular relaxation effect and antimicrobial activities [5-11].

Chromones with pyridyl, furyl and quinolyl substituents at 2-position have been tested for antitumor activity, in particular 6-chloro-2-(2-quinolyl)chromone was found to be active against sarcoma-180 [12-13]. 2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-3-chlorochromones reported by us earlier were found to be associated with excellent antibacterial and antifungal activities [14]. Like other heterocyclic compounds, pyrazoles also exhibit a wide range of biological activities and pyrazole chemistry has been the focus of high attention for more than three decades due to versatile biological activities of pyrazole derivatives appearing as antimicrobial, anti-inflammatory, antihistaminic, antidepressant, anticonvulsant agents [15-20]. Therefore in continuation of our efforts to synthesize biologically active heterocyclic compounds herein we report some novel 2-(1,3-disubstituted pyrazolyl)chromones, which exhibited good *phosphodiesterase* IV inhibition activity.

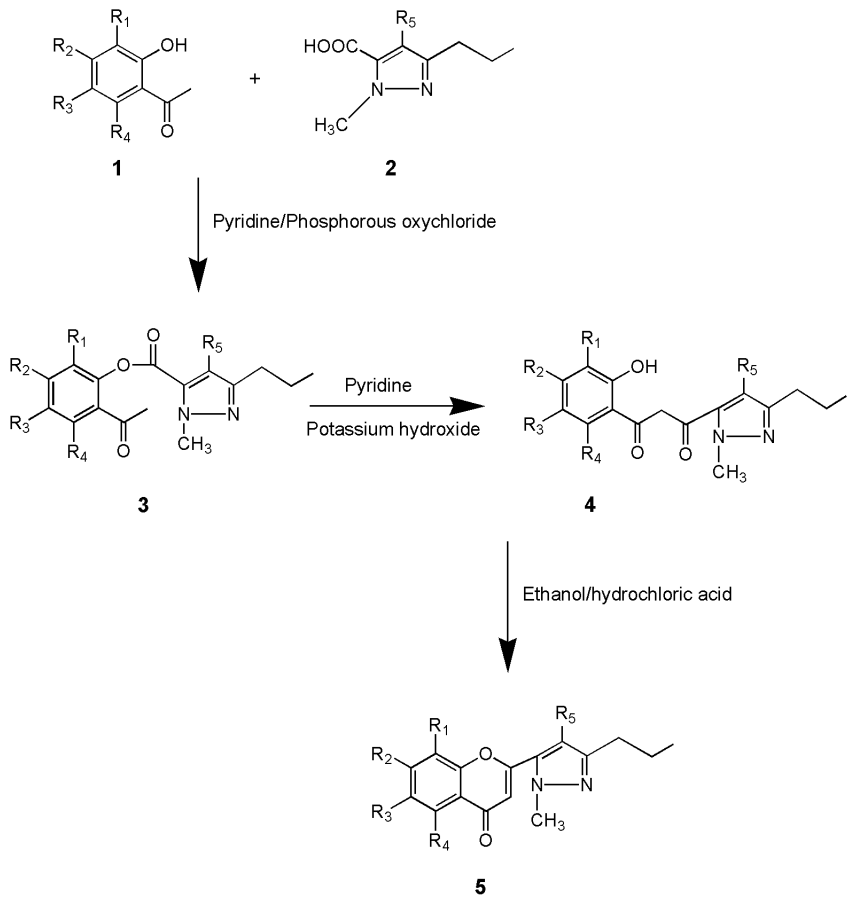
The chemistry of pyrimidines and its derivatives has been studied for their diverse biological activities like antibacterial, antiviral, antitumor, antihypertensive and antiinflamatory activities [21-28]. Therefore it was thought worthwhile to prepare some new derivatives like aminopyrimidines, thiopyrimidines and pyrazolyl, by the reaction of 2-(1,3-disubstituted pyrazolyl)chromones with guanidine hydrochloride, thiourea and hydrazine hydrate respectively.

Results and Discussion.

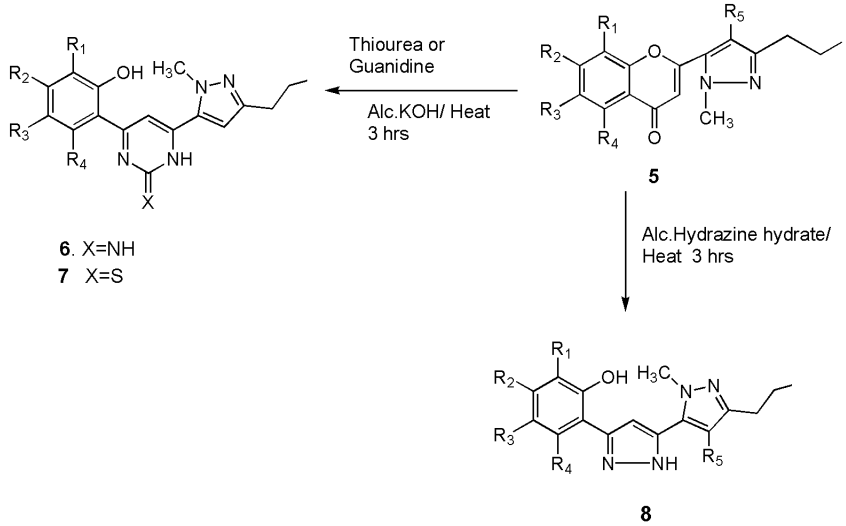
In the present work 2-hydroxy acetophenones **1** were treated with 1-methyl-3-propylpyrazole-5-carboxylic acid **2** in the presence of phosphorous oxychloride and pyridine to afford the corresponding esters **3**. 1-Methyl-3-propyl-pyrazole-5-carboxylic acid **2** is a well-known intermediate for the preparation of sildenafil citrate and can be easily made in two steps from 3-propyl pyrazole-5-carboxylic acid ethyl ester [29]. Compounds **3** were then reacted with a strong base like potassium hydroxide in presence of pyridine as per the well-known Baker-Venkatraman transformation resulting in 1-(2-hydroxyphenyl)-3-(1-methyl-3-propyl-1*H*-5-pyrazolyl)-1,3-propanediones **4**. Compounds **4** then underwent cyclization by refluxing in ethanol with a catalytic amount of hydrochloric acid to afford 2-(1-methyl-3-propyl-1*H*-5-pyrazolyl)-4H-4-chromenone **5** (Scheme 1). The physical and analytical data for compounds **3**, **4** and **5** are reported in Table 1, Table 2, Table 3 and Table 4.

The structures of **3**, **4** and **5** were evidenced by their spectra (mass, IR, ^{1}H NMR). For example, the infra red spectra (cm^{-1}) of **3** shows a strong absorption band at 1760-1740 cm^{-1} for -O-CO- group and the ^{1}H NMR spectrum shows a sharp singlet at around 2.5 δ for CO-CH_3 (see Table 2). The infra red spectra of **4** shows a strong and characteristic band for 1,3-diketone linkage at 1640-1560 cm^{-1}. The ^{1}H NMR of **4** shows disappearance of a singlet at around 2.55 δ (corresponding to CO-CH_3) but it shows two singlets for two protons each which are water-d$_2$ exchangeable, corresponding to Ph-O*H* and enol form of the 1,3-diketone (as it observed for all diketones at δ 11.7 and δ 15.90) (Table 3). The formation of the titled chromone **5** is also confirmed by ^{1}H NMR as it shows a singlet at δ 6.57 (corresponding to pyran ring proton). It is also observed that both the signals for –OH protons disappeared as they are used in the cyclization process (see Table 4).

Scheme 1



Scheme 2



6. X=NH
7 X=S

Compound **5** on reaction respectively with guanidine hydrochloride and thiourea in the presence of potassium hydroxide in ethanol gives 6-[2-imino-6-(1-methyl-3-propyl-1*H*5-pyrazolyl)-1,2-dihydro-4-pyrimidinyl]phenol **6** and 4-(2-hydroxyphenyl)-6-(1-methyl-3-propyl-1*H*-5-pyrazolyl)-1,2-dihydro-2-pyrimidinethione **7** (Scheme 2). Compound **5** on reaction with hydrazine hydrate gives 2-[5-(1-methyl-3-propyl-1*H*5-pyrazolyl)-1*H*3-pyrazolyl]

phenol **8**. The physical and analytical data for compounds **6**, **7**, and **8** are reported in Table 1, Table 5, Table 6, and Table 7.

The structures of **6**, **7** and **8** were evidenced by their spectra (mass, IR, and ^{1}H NMR spectra). For example, IR spectra of **6**, **7** and **8** reveal NH and OH bands in the regions 3300-3400 cm^{-1} and the absence of a carbonyl band in the region of 1680-1650 cm^{-1}, which is present in starting material **5**. In addition to this IR spectra of **7** shows the thioketone band in the region 1270-1190 cm^{-1}.

Table 1

Substitution					Compd.	Yield	M.P.	Compd.	Yield	M.P.	Compd.	Yield	M.P.
R_1	R_2	R_3	R_4	R_5	No.	(%)	(0 °C)	No.	(%)	(0 °C)	No.	(%)	(0 °C)
Cl	H	H	H	H	**3a**	57	63-64	**4a**	78	105-108	**5a**	76	126-128
Cl	H	Cl	H	H	**3b**	58	96-98	**4b**	80	135-139	**5b**	83	145-148
H	H	Cl	H	H	**3c**	55	70-71	**4c**	73	109-111	**5c**	81	119-123
Me	H	Me	H	H	**3d**	54	66-68	**4d**	75	119-122	**5d**	77	142-147
H	H	Br	H	H	**3e**	52	74-77	**4e**	70	110-114	**5e**	79	120-124
H	H	Me	H	NO_2	**3f**	56	95-98	**4f**	76	129-133	**5f**	70	114-116
Me	H	Me	H	NO_2	**3g**	58	85-87	**4g**	79	146-149	**5g**	72	126-130
H	Me	H	Me	NO_2	**3h**	54	82-86	**4h**	78	142-145	**5h**	74	113-118
Cl	H	Cl	H	NO_2	**3i**	59	93-97	**4i**	75	165-169	**5i**	79	127-131
H	H	Cl	H	NO_2	**3j**	55	77-81	**4j**	72	120-124	**5j**	77	110-112
H	Me	Cl	H	NO_2	**3k**	58	103-105	**4k**	80	131-134	**5k**	80	139-143
H	H	Et	H	H	**3l**	48	46-48	**4l**	54	70-72	**5l**	50	75-77
H	H	F	H	H	**3m**	51	67-70	**4m**	61	103-107	**5m**	60	112-115
Cl	H	Cl	H	H	**6b**	49	231-235	**7b**	44	244-248	**8b**	54	171-175
H	H	Cl	H	H	**6c**	45	214-218	**7c**	47	220-224	**--**	--	--
Me	H	Me	H	H	**6d**	48	225-229	**--**	--	--	**--**	--	--
H	H	Br	H	H	**--**	--	--	**7e**	43	252-255	**--**	--	--
H	H	Me	H	NO_2	**--**	--	--	**--**	--	--	**8f**	50	150-153
Me	H	Me	H	NO_2	**--**	--	--	**7g**	50	229-233	**8g**	49	138-142
H	H	Cl	H	NO_2	**--**	--	--	**7j**	47	234-238	**--**	--	--
H	Me	Cl	H	NO_2	**--**	--	--	**--**	--	--	**8k**	52	156-160
H	H	Et	H	H	**6l**	46	166-169	**--**	--	--			
H	H	F	H	H	**6m**	51	227-232	**--**	--	--	**8m**	55	166-170

Table 2

Compounds **3a-m**

Compd No.	IR (cm^{-1})	Spectral Data ^{1}H NMR δ (ppm)	Mass M+	Elemental analysis (Calcd%) found% C	H	N
3a	1746	7.81(d,1H,Ar-H)7.48(dd,1H,Ar-H)7.34(d,1H,Ar-H)	321	59.87	5.33	8.70
	1686	6.84(s,1H,Py-H)4.12(s,3H,N-CH_3)$_2$.61(t,2H,CH_2)		(59.91)	(5.34)	(8.73)
	1254	2.55(s,3H,$COCH_3$)1.71(m,2H,CH_2)0.99(t,3H,CH_3)				
3b	1751	7.85(s,2H,Ar-H)6.84(s,1H,Py-H)4.16(s,3H,N-CH_3)	355	53.98	4.53	7.87
	1682	2.85(t,2H,CH_2)2.56(s,3H,$COCH_3$)		(54.10)	(4.54)	(7.89)
	1216	1.75(m,2H,CH_2)1.00(t,3H,CH_3)				
3c	1743	7.80(d,1H,Ar-H)7.52(dd,1H,Ar-H)7.34(d,1H,Ar-H)	321	59.87	5.36	8.76
	1676	6.86(s,1H,Py-H)4.13(s,3H,N-CH_3)2.63(t,2H,CH_2)		(59.91)	(5.34)	(8.73)
	1260	2.56(s,3H,$COCH_3$)1.70(m,2H,CH_2)0.99(t,3H,CH_3)				
3d	1740	7.69(s,1H,Ar-H)7.30(s,1H,Ar-H)6.80(s,1H,Py-H)	314	68.72	7.02	8.89
	1675	4.14(s,3H,N-CH_3)2.88(t,2H,CH_2)2.56(s,3H,$COCH_3$)		(68.77)	(7.05)	(8.91)
	1220	2.42(s,3H,CH_3)$_2$.36(s,3H,CH_3)1.77(m,2H,CH_2)0.99(t,3H,CH_3)				
3e	1752	7.83(d,1H,Ar-H)7.54(dd,1H,Ar-H)7.36(d,1H,Ar-H)6.84(s,1H,Py-H)	365	52.68	4.69	7.69
	1692	4.11(s,3H,N-CH_3)2.66(t,2H,CH_2)2.57(s,3H,$COCH_3$)		(52.62)	(4.69)	(7.67)
	1259	1.72(m,2H,CH_2)0.99(t,3H,CH_3)				
3f	1749	7.83(s,1H,Ar-H)7.60(d,1H,Ar-H)7.34(d,1H,Ar-H)	345	59.33	5.56	12.20
	1679	4.14(s,3H,N-CH_3)2.89(t,2H,CH_2)2.58(s,3H,$COCH_3$)		(59.12)	(5.55)	(12.17)
	1230	2.38(s,3H,CH_3)1.76(p,2H,CH_2)1.02(t,3H,CH_3)				
3g	1748	7.82(s,1H,Ar-H)7.35(s,1H,Ar-H)4.11(s,3H,N-CH_3)	359	60.28	5.87	11.65
	1679	2.89(t,2H,CH_2)2.57(s,3H,$COCH_3$)2.45(s,3H,CH_3)		(60.16)	(5.89)	(11.69)
	1245	2.37(s,3H,CH_3)1.77(m,2H,CH_2)1.02(t,3H,CH_3)				
3h	1751	7.84(s,1H,Ar-H)7.37(s,1H,Ar-H)4.15(s,3H,N-CH_3)	359	59.99	5.91	11.71
	1676	2.90(t,2H,CH_2)2.56(s,3H,$COCH_3$)2.44(s,3H,CH_3)		(60.16)	(5.89)	(11.69)
	1232	2.38(s,3H,CH_3)1.76(m,2H,CH_2)1.02(t,3H,CH_3)				

Table 2 (continued)

Compd No.	IR (cm^{-1})	Spectral Data ^1H NMR δ (ppm)	Mass M+	Elemental analysis (Calcd%) found% C	H	N
3i	1747	7.85(s,2H,Ar-H)4.16(s,3H,N-CH_3)	400	47.84	3.79	10.53
	1694	2.85(t,2H,CH_2)2.56(s,3H,$COCH_3$)		(48.02)	(3.78)	(10.50)
	1228	1.75(m,2H,CH_2)1.00(t,3H,CH_3)				
3j	1758	7.85(d,1H,Ar-H)7.60(dd,1H,Ar-H)7.34(d,1H,Ar-H)	366	52.45	4.39	11.51
	1694	4.14(s,3H,N-CH_3)2.89(t,2H,CH_2)2.58(s,3H,$COCH_3$)		(52.54)	(4.41)	(11.49)
	1251	1.76(p,2H,CH_2)1.02(t,3H,CH_3)				
3k	1761	7.86(s,1H,Ar-H)7.27(s,1H,Ar-H)4.15(s,3H,N-CH_3)	380	53.92	4.79	11.08
	1689	2.90(t,2H,CH_2)2.56(s,3H,$COCH_3$)2.47(s,3H,CH_3)		(53.76)	(4.78)	(11.06)
	1254	1.76(p,2H,CH_2)1.02(t,3H,CH_3)				
3l	1742	7.79(s,1H,Ar-H)7.57(d,1H,Ar-H)7.31(d,1H,Ar-H)	314	68.51	7.03	8.89
	1678	4.14(s,3H,N-CH_3)2.78-2.67(m,4H,CH_2)2.58(s,3H,$COCH_3$)		(68.77)	(7.05)	(8.91)
	1223					
3m	1745	7.75(d,1H,Ar-H)7.50(dd,1H,Ar-H)7.31(d,1H,Ar-H)6.86(s,1H,Py-H)	304	63.07	5.62	9.19
	1677	4.13(s,3H,N-CH_3)2.63(t,2H,CH_2)2.56(s,3H,$COCH_3$)		(63.15)	(5.63)	(9.21)
	1227	1.70(m,2H,CH_2)0.99(t,3H,CH_3)				

Table 3

Compounds **4a-k**

Comp. No.	IR (cm^{-1})	Spectral Data ^1H NMR δ (ppm)	Mass M+	Elemental analysis (Calcd%) found% C	H	N
4a	3440	15.96(br s,1H,OH)11.67(s,1H,enolicOH)7.66(d,1H,Ar-H)	321	60.02	5.36	8.75
	1630	7.40(dd,1H,Ar-H)6.94(d,1H,Ar-H)6.61(s,1H,CH_2=O)6.52(s,1H,Py-H)		(59.91)	(5.34)	(8.73)
	1282	4.13(s,3H,N-CH_3)2.64(t,2H,CH_2)1.69(m,2H,CH_2)0.99(s,3H,CH_3)				
4b	3398	15.90(br s,1H,OH)11.53(s,1H,enolicOH)7.58(d,1H,Ar-H)	355	54.01	4.52	7.90
	1610	7.52(d,1H,Ar-H)6.58(s,1H,CH_2=O)6.48(s,1H,Py-H)		(54.10)	(4.54)	(7.89)
	1260	3.96(s,3H,N-CH_3)2.92(t,2H,CH_2)1.73(m,2H,CH_2)1.02(s,3H,CH_3)				
4c	3428	15.96(br s,1H,OH)11.67(s,1H,enolicOH)7.6(s,1H,Ar-H)	321	59.82	5.35	8.75
	1618	7.37(d,1H,Ar-H)6.92(d,1H,Ar-H)6.63(s,1H,CH_2=O)6.52(s,1H,Py-H)		(59.91)	(5.34)	(8.73)
	1266	4.14(s,3H,N-CH_3)2.60(t,2H,CH_2)1.68(m,2H,CH_2)0.99(s,3H,CH_3)				
4d	3398	16.03(s,1H,OH)11.90(s,1H,enolicOH)7.30(s,1H,Ar-H)	314	68.83	7.03	8.93
	1589	7.18(s,1H,Ar-H)6.60(s,2H,CH_2=O,Py-H)2.30(s,3H,CH_3)2.24(s,3H,CH_3)		(68.77)	(7.05)	(8.91)
	1282	4.14(s,3H,N-CH_3)2.60(t,2H,CH_2)1.71(m,2H,CH_2)0.99(s,3H,CH_3)				
4e	3421	15.98(br s,1H,OH)11.73(s,1H,enolicOH)7.76(s,1H,Ar-H)	365	52.57	4.67	7.65
	1568	7.54(d,1H,Ar-H)6.89(d,1H,Ar-H)6.66(s,1H,CH_2=O)6.54(s,1H,Py-H)		(52.62)	(4.69)	(7.67)
	676	4.15(s,3H,N-CH_3)2.62(t,2H,CH_2)1.69(m,2H,CH_2)0.99(s,3H,CH_3)				
4f	3434	15.10(s,1H,OH)11.55(s,1H,enolicOH)7.24(s,1H,Ar-H)7.21(d,1H,Ar-H)	345	59.21	5.57	12.14
	1628	6.92(d,1H,Ar-H)6.61(s,1H,CH_2=O)3.95(s,3H,N-CH_3)		(59.12)	(5.55)	(12.17)
	1277	2.91(t,2H,CH_2)2.31(s,3H,CH_3)1.73(m,2H,CH_2)1.01(s,3H,CH_3)				
4g	3431	15.90(s,1H,OH)11.87(s,1H,enolicOH)7.24(s,1H,Ar-H)	359	60.30	5.91	11.67
	1631	7.21(s,1H,Ar-H)6.61(s,1H,CH_2=O)2.31(s,3H,CH_3)2.23(s,3H,CH_3)		(60.16)	(5.89)	(11.69)
	1288	3.95(s,3H,N-CH_3)2.91(t,2H,CH_2)1.73(m,2H,CH_2)1.01(s,3H,CH_3)				
4h	3430	15.89(s,1H,OH)11.87(s,1H,enolicOH)7.24(s,1H,Ar-H)	359	60.04	5.88	11.68
	1632	7.21(s,1H,Ar-H)6.61(s,1H,CH_2=O)2.31(s,3H,CH_3)2.23(s,3H,CH_3)		(60.16)	(5.89)	(11.69)
	1288	3.95(s,3H,N-CH_3)2.91(t,2H,CH_2)1.73(m,2H,CH_2)1.01(s,3H,CH_3)				
4i	3401	16.02(br s,1H,OH)12.11(s,1H,enolicOH)7.58(d,1H,Ar-H)	400	48.03	3.79	10.51
	1610	7.52(d,1H,Ar-H)6.58(s,1H,CH_2=O)		(48.02)	(3.78)	(10.50)
	798	3.96(s,3H,N-CH_3)2.92(t,2H,CH_2)1.73(m,2H,CH_2)1.02(s,3H,CH_3)				
4j	3421	15.96(br s,1H,OH)11.67(s,1H,enolicOH)7.66(s,1H,Ar-H)	366	52.65	4.40	11.47
	1667	7.39(d,1H,Ar-H)6.99(s,1H,Ar-H)6.66(s,1H,CH_2=O)		(52.54)	(4.41)	(11.49)
	1365	4.12(s,3H,N-CH_3)2.86(t,2H,CH_2)1.74(m,2H,CH_2)1.02(s,3H,CH_3)				
4k	3432	15.89(s,1H,OH)11.87(s,1H,enolicOH)7.61(s,1H,Ar-H)7.50(s,1H,Ar-H)	380	53.87	4.76	11.09
	1640	4.11(s,3H,N-CH_3)2.90(t,2H,CH_2)2.47(s,3H,CH_3)		(53.76)	(4.78)	(11.06)
	1365	1.76(m,2H,CH_2)1.02(t,3H,CH_3)				
4l	3431	14.90(s,1H,OH)11.50(s,1H,enolicOH)7.24(s,1H,Ar-H)7.21(d,1H,Ar-H)	314	68.59	7.06	8.93
	1632	6.89(d,1H,Ar-H)6.59(s,1H,CH_2=O)2.88-2.70(t,4H,CH_2)		(68.77)	(7.05)	(8.91)
	1271	1.76(p,2H,CH_2)1.16(t,3H,CH_3)1.01(t,3H,CH_3)				
4m	3436	15.80(br s,1H,OH)11.62(s,1H,enolicOH)7.59(s,1H,Ar-H)	304	63.26	5.65	9.22
	1627	7.39(d,1H,Ar-H)6.92(d,1H,Ar-H)6.63(s,1H,CH_2=O)6.52(s,1H,Py-H)		(63.15)	(5.63)	(9.21)
	1256	4.14(s,3H,N-CH_3)2.60(t,2H,CH_2)1.68(m,2H,CH_2)0.99(s,3H,CH_3)				

Table 4
Componds **5a-k**

Compd No.	IR (cm^{-1})	Spectral Data ^1H NMR δ (ppm)	Mass M+	Elemental analysis (Calcd%) found C	H	N
5a	1654	8.19(d,1H,Ar-H)7.67(dd,1H,Ar-H)7.5(d,1H,Ar-H)	303	63.52	4.98	9.24
	1461	6.6(s,1H,py) 6.55(s,1H,cr)4.13(s,3H,N-CH_3)		(63.47)	(4.99)	(9.25)
	1271	2.6(t,2H,CH_2)1.7(m,2H,CH_2) 0.99(t,3H,CH_3)				
5b	1654	8.09(d,1H,Ar-H)7.74d,1H,Ar-H)6.58(s,1H,cr)	337	56.86	4.16	8.32
	1462	4.10(s,1H,N-CH_3) 2.65(t,2H,CH_2)1.76(m,2H,CH_2)		(56.99)	(4.18)	(8.31)
	1272	0.99(t,3H,CH_3)				
5c	1658	8.16(d,1H,Ar-H)7.62(dd,1H,Ar-H)7.46(d,1H,Ar-H)	303	63.58	4.97	9.27
	1451	6.57(s,1H,py) 6.53(s,1H,cr)4.11(s,3H,N-CH_3)		(63.47)	(4.99)	(9.25)
	1265	2.6(t,2H,CH_2)1.7(m,2H,CH_2)0.98(t,3H,CH_3)				
5d	1655	7.85(s,1H,Ar-H)7.37(s,1H,Ar-H)6.59(s,1H,py)6.53(s,1H,cr)	296	73.02	6.82	9.47
	1456	4.16(s,3H,N-CH_3)2.62(t,2H,CH_2)2.51(s,3H,CH_3)		(72.95)	(6.80)	(9.45)
	1270	2.42(s,3H,CH_3)1.72(m,2H,CH_2)0.99(t,3H,CH_3)				
5e	1658	8.35(d,1H,Ar-H)7.8(dd,1H,Ar-H)7.4(d,1H,Ar-H)	347	55.23	4.33	8.06
	1451	6.6(s,1H,py) 6.55(s,1H,cr)4.1(s,3H,N-CH_3)		(55.35)	(4.35)	(8.07)
	1266	2.6(t,2H,CH_2)1.7(m,2H,CH_2) 0.99(t,3H,CH_3)				
5f	1647	8.04(s,1H,Ar-H)7.56(d,1H,Ar-H)7.35(d,1H,Ar-H)	327	62.33	5.24	12.81
	1459	6.53(s,1H,cr)3.91(s,3H,N-CH_3)2.97(t,2H,CH_2)		(62.38)	(5.23)	(12.84)
	1355	2.49(s,3H,CH_3)1.76(m,2H,CH_2)1.05(t,3H,CH_3)				
5g	1646	7.89(s,1H,Ar-H)7.36(s,1H,Ar-H)6.55(s,1H,cr)	341	63.29	5.62	12.30
	1461	3.96(s,3H,N-CH_3)2.95(t,2H,CH_2)2.43(s,3H,CH_3)		(63.33)	(5.61)	(12.31)
	1359	2.37(s,3H,CH_3)1.76(m,2H,CH_2)1.05(t,3H,CH_3)				
5h	1647	7.88(s,1H,Ar-H)7.4(s,1H,Ar-H)6.53(s,1H,cr)	341	63.41	5.60	12.33
	1460	3.93(s,3H,N-CH_3)2.97(t,2H,CH_2)2.44(s,3H,CH_3)		(63.33)	(5.61)	(12.31)
	1360	2.39(s,3H,CH_3)1.8(m,2H,CH_2)1.05(t,3H,CH_3)				
5i	1672	8.1(d,1H,Ar-H)7.75(d,1H,Ar-H)6.6(s,1H,cr)	382	50.36	3.44	11.00
	1458	3.95(s,1H,N-CH_3) 2.96(t,2H,CH_2)1.79(m,2H,CH_2)		(50.28)	(3.43)	(10.99)
	1362	1.04(t,3H,CH_3)				
5j	1668	8.13(d,1H,Ar-H)7.74(dd,1H,Ar-H)	348	55.19	4.05	12.10
	1457	7.48(d,1H,Ar-H) 6.53(s,1H,cr)4.11(s,3H,N-CH_3)		(55.26)	(4.06)	(12.08)
	1351	2.6(t,2H,CH_2)1.7(m,2H,CH_2)0.98(t,3H,CH_3)				
5k	1653	8.12(s,1H,Ar-H)7.62(s,1H,Ar-H)	362	55.78	4.63	11.58
	1456	6.53(s,1H,cr)4.11(s,3H,N-CH_3)		(56.44)	(4.46)	(11.61)
	1344	2.6(t,2H,CH_2)1.7(m,2H,CH_2) 1.02(t,3H,CH_3)				
5l	1649	8.04(s,1H,Ar-H)7.56(d,1H,Ar-H)7.35(d,1H,Ar-H)	296	72.78	6.82	9.43
	1457	6.58(s,1H,py)6.53(s,1H,cr)4.10(s,3H,N-CH_3)		(72.95)	(6.80)	(9.45)
	1278	2.67(m,4H,CH_2)1.76(m,2H,CH_2)1.16(t,3H,CH_3)0.99(t,3H,CH_3)				
5m	1659	8.14(d,1H,Ar-H)7.62(dd,1H,Ar-H)7.46(d,1H,Ar-H)	286	67.27	5.30	9.80
	1454	6.55(s,1H,py) 6.51(s,1H,cr)4.11(s,3H,N-CH_3)		(67.12)	(5.28)	(9.78)
	1268	2.62(t,2H,CH_2)1.74(m,2H,CH_2)0.98(t,3H,CH_3)				

Table 5
Compounds **6b-m**

Compd. No.	IR (cm^{-1})	Spectral Data ^1H NMR δ (ppm)	Mass M+	Elemental analysis (Calcd %) found% C	H	N
6b	3429	12.89(s,1H,OH) 8.34-6.98(4H,Ar-H& py)	378	(53.90)	(4.54)	(18.53)
	1623	4.11(s,3H,NCH_3) 2.57(t,2H,CH_2)		(53.98)	(4.53)	(18.51)
	1523	1.65(m,2H,CH_2) 0.95(t,3H,CH_3)				
6c	3433	11.84(s,1H,OH) 8.14-6.94(5H,Ar-H& py)	343	59.21	5.26	20.31
	1644	4.05(s,3H,NCH_3) 2.50(t,2H,CH_2)		(59.39)	(5.28)	(20.37)
	1470	1.63(m,2H,CH_2) 0.92(t,3H,CH_3)				
6d	3441	12.84(s,1H,OH) 7.90-6.9(4H,Ar-H& py)	337	67.65	6.88	20.77
	1619	4.04(s,3H,NCH_3) 2.53(t,2H,CH_2)$_2$.49(s,3H,Me)		(67.63)	(6.87)	(20.76)
	1515	2.41(s,3H,Me)1.61(m,2H,CH_2)0.93(t,3H,Me)				
6l	3431	13.67(s,1H,OH) 7.94-6.80(5H,Ar-H& py)	337	67.46	6.85	20.78
	1638	4.17(s,3H,NCH_3)2.64-2.49(m,4H,CH_2)		(67.63)	(6.87)	(20.76)
	1582	1.64(m,2H,CH_2)1.20(t,3H,CH_3) 0.94(t,3H,CH_3)				
6m	3410	14.18(s,1H,OH) 7.94-6.90(5H,Ar-H& py)	327	62.51	5.52	21.33
	1576	4.16(s,3H,NCH_3) 2.64(t,2H,CH_2)		(62.37)	(5.54)	(21.39)
	1519	1.64(m,2H,CH_2) 0.95(t,3H,CH_3)				

Table 6
Compounds **7b-j**

Compd. No.	IR (cm^{-1})	Spectral Data ^1H NMR δ (ppm)	Mass M+	Elemental analysis (Calcd%) found % C	H	N
7b	3429	13.26(s,1H,OH)8.39(d,1H,Ar-H)	395	51.75	4.06	14.13
	1576	8.30(d,1H,Ar-H) 7.73(s,1H,py)		(51.65)	(4.08)	(14.17)
	1257	7.24(s,1H,py)4.12(s,3H,CH_3)$_2$.53(t,2H,CH_2) 1.64(m,2H,CH_2)0.93(t,3H,CH_3)				
7c	3433	12.3(s,1H,OH)8.22(d,1H,Ar-H)	360	56.53	4.76	15.50
	1571	7.7-7.0(4H,Ar-H&py) 4.11(s,3H,CH_3)		(56.58)	(4.75)	(15.53)
	1237	2.52(t,2H,CH_2) 1.6(m,2H,CH_2)0.93(t,3H,CH_3)				
7e	3400	11.96(s,1H,OH)8.17(s,1H,Ar-H)	405	50.39	4.21	13.86
	1574	7.6-6.9(m,3H,Ar-H&py) 4.10(s,3H,CH_3)		(50.38)	(4.23)	(13.82)
	1263	2.54(t,2H,CH_2) 1.63(m,2H,CH_2)0.96(t,3H,CH_3)				
7g	3398	13.00(s,1H,OH)7.56(s,1H,Ar-H)	399	57.03	5.32	17.50
	1574	7.08(s,1H,ArH)7.26(s,1H,py)		(57.13)	(5.30)	(17.53)
	1218	3.93(s,3H,CH_3)2.93(t,2H,CH_2)2.43(S,3H,CH_3) 2.38(S,3H,CH_3)1.73(m,2H,CH_2)1.02(t,3H,CH_3)				
7j	3409	12.00(s,1H,OH)8.17(d,1H,Ar-H)	389	52.46	4.13	17.95
	1597	7.6-7.5(m,2H,Ar-H) 7.23(s,1H,py)		(52.43)	(4.14)	(17.98)
	1228	4.10(s,3H,CH_3)2.54(t,2H,CH_2) 1.63(m,2H,CH_2)0.96(t,3H,CH_3)				

Table 7
Compounds **8b-m**

Compd. No.	IR (cm^{-1})	Spectral Data ^1H NMR δ (ppm)	Mass M+	Elemental analysis (Calcd%) found % C	H	N
8b	3419	11.13(s,1H,NH)10.33(s,1H,OH)	351	54.80	4.58	15.98
	1525	7.51(d,1H,Ar-H) 7.35(d,1H,ArH)		(54.71)	(4.59)	(15.95)
	1439	6.80(s,1H,py)6.32(s,1H,py) 3.99(s,3H,CH_3)2.63(t,2H,CH_2) 1.69(m,2H,CH_2)1.00(t,3H,CH_3)				
8f	3370	11.73(s,1H,OH)7.23(s,1H,ArH)	341	59.74	5.63	20.49
	1527	7.17(d,1H,Ar-H) 6.96(d,1H,ArH)		(59.81)	(5.61)	(20.52)
	1445	6.39(s,1H,py)3.99(s,3H,CH_3) 2.61(t,2H,CH_2)2.41(s,3H,CH_3) 1.67(m,2H,CH_2)0.99(t,3H,CH_3)				
8g	3408	12.10(s,1H,OH)7.61(s,1H,Ar-H)	355	61.04	5.94	19.67
	1503	7.06(s,1H,ArH)6.56(s,1H,py)		(60.83)	(5.96)	(19.71)
	1463	3.93(s,3H,CH_3)2.93(t,2H,CH_2) 2.50(s,3H,CH_3) 2.43(s,3H,CH_3) 1.73(m,2H,CH_2)1.02(t,3H,CH_3)				
8k	3411	12.46(s,1H,OH)8.21(s,1H,Ar-H)	376	54.27	4.85	18.53
	1542	7.26(s,1H,ArH)6.51(s,1H,py)		(54.33)	(4.83)	(18.64)
	1456	3.91(s,3H,CH_3)2.97(t,2H,CH_2) 1.76(m,2H,CH_2)1.04(t,3H,CH_3)				
8m	3380	10.43(s,1H,NH)10.23(s,1H,OH)	300	64.03	5.68	18.70
	1551	7.30(s,1H,Ar-H) 6.96(d,2H,ArH)		(63.99)	(5.71)	(18.66)
	1471	6.76(s,1H,py)6.31(s,1H,py) 3.97(s,3H,CH_3)2.62(t,2H,CH_2) 1.68(m,2H,CH_2)0.99(t,3H,CH_3)				

The ^1H NMR spectrum of **6** and **7** shows characteristic signal at around δ 7.23 assignable to the pyrimidine ring proton and a signal at around δ 11.9 assignable to OH the proton. The ^1H NMR spectrum of **8** shows, in addition to a signal at around δ 11.9 assignable to OH proton, characteristic signals at around δ 6.56 assignable to the N-methylated pyrazole ring proton and δ 6.3 assignable to the middle pyrazole ring proton. Their mass spectra also show the expected molecular ion peaks (see Tables 5, 6 and 7).

Biological Activity.

The selected compounds from **5, 6, 7** and **8** were tested for *Phosphodiesterase* IV inhibitory activity, which corresponds to antiallergic, antiasthamatic activities. *Phosphodiesterase* IV enzyme converts [^3H] cAMP to the

Table 8

Phosphodiesterase IV inhibition
(*in vitro*-radiometric assay)

Compd No	Conc.	% inhibition
5a	1μM	27.19
5c	1μM	65.81
5d	1μM	34.35
5e	1μM	9.00
5f	1μM	9.40
5g	1μM	19.71
5h	1μM	10.22
5i	1μM	44.39
5k	1μM	12.75
6m	1μM	16.60
7b	1μM	0.47
8b	1μM	5.18
8k	1μM	14.03
8m	1μM	20.08
Rolipram	2μM	70.51
Cilomilast	75nM	53.98

corresponding [^{3}H] 5'-AMP in proportion to the amount of *Phosphodiesterase* IV present. The [^{3}H] 5'-AMP then was quantitatively converted to free [^{3}H] adenosine and phosphate by the action of snake venom 5'-nucleotidase hence the amount of [^{3}H] adenosine librated is proportional to *Phosphodiesterase* IV activity [30].

From the results shown in Table 8 it can be concluded that methyl substitution in the aromatic ring (ring A) of the titled compound shows less *Phosphodiesterase* IV inhibition while chlorine substitution (ring A) shows good *Phosphodiesterase* IV inhibition. Derivatives of the titled compounds are not showing any significant *Phosphodiesterase* IV inhibition.

EXPERIMENTAL

All the recorded melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Perkin-Elmer FT spectrophotometer in potassium bromide disc. ^{1}H NMR spectra were recorded on Varian 300 MHz spectrophotometer in dimethyl sufoxide-d_6 as a solvent and trimethyl silane as an internal standard (chemical shifts in δ values). Mass spectra were obtained uising a Finnigan mass spectrometer. Elemental analysis was obtained on a Perkin-Elmer 2400 microanalyser. The structures of all compounds were assigned on the basis of IR, NMR, mass spectra, and elemental analysis.

General Procedure.

2-Acetyl-6-chlorophenyl-1-methyl-3-propyl-1*H*-5-pyrazolecarboxylate (**3a**).

A mixture of **1** (R_1=Cl 0.01 mole) and **2** (R_5=H, 0.01 mole) was dissolved in 10 ml dry pyridine and the contents were cooled to 0 °C in ice bath. To this reaction mixture (0.01 mole) of phosphorous oxychloride was added maintaining the temperature below 5 °C. After complete addition of phosphorous oxychloride, the reaction mixture was kept overnight and then poured over crushed ice. Resulting product was separated by filtration and washed with cold 1% sodium hydroxide solution followed by water. Product was crystallized with ethanol to afford pure compound **3a**. Compounds **3b-m** were synthesized similarly. Characterization data of these compounds is given in the Table 2.

1-(3-Chloro-2-hydroxyphenyl)-3-(1-methyl-3-propyl-1*H*-5-pyrazolyl)-1,3-propanediones (**4a**).

Compound **3a** (0.005 mole) was taken in 15 ml dry pyridine and to this reaction mixture excess (2 g) of powdered potassium hydroxide was added with constant stirring. After complete addition of potassium hydroxide, the reaction mixture was stirred at room temperature for 3 hours. Then the contents were poured into crushed ice and acidified with acetic acid. The resulting product was separated by filtration and crystallized from ethanol to afford pure compound **4a**. Compounds **4b-m** were synthesized similarly. Characterization data of these compounds is given in the Table 3.

8-Chloro-2-(1-methyl-3-propyl-1*H*-5-pyrazolyl)-4*H*-4-chromenone (**5a**).

Compound **4a** was taken in 10 ml ethanol and to this 1 ml concentrated hydrochloric acid was added. Reaction mixture was then heated under reflux for 1 hr. After completion of reaction, the mass was cooled and poured into crushed ice. The resulting product was separated by filtration and crystallized from ethanol to afford pure compounds **5a**. Compounds **5b-m** were synthesized similarly. Characterization data of these compounds is given in the Table **4**.

4-Chloro-6-[2-imino-6-(1-methyl-3-propyl-1*H*5-pyrazolyl)-1,2-dihydro-4-pyrimidinyl]phenol (**6c**).

Compound **5c** (0.003 mole) was taken in 10 ml ethanol. Contents were cooled to 10 °C and to this reaction mixture (0.004 mole) of guanidine hydrochloride and potassium hydroxide (0.005 mole) was added. Reaction mixture was stirred for 15 minutes and then heated under reflux for 3 hr. Reaction mixture was then cooled and poured into crushed ice and neutralized with acetic acid. Resulting product was separated by filtration and crystallized with ethanol to afford pure compounds **6c**. Compounds **6b**, **6d**, **6l** and **6m** were synthesized similarly. Characterization data of these compounds is given in the Table 5.

4-(3,5-Dichloro-2-hydroxyphenyl)-6-(1-methyl-3-propyl-1*H*-5-pyrazolyl)-1,2-dihydro-2-pyrimidinethione (**7b**).

A mixture of **5b** (0.003 mole) and (0.005 mole) of thiourea was dissolved in 10 ml ethanol. To this reaction mixture potassium hydroxide (0.005 mole) was added. Then reaction mixture was heated under reflux for 3 hr. After completion of heating, the reaction mixture was cooled to room temperature and then poured over crushed ice and neutralized with acetic acid. Resulting product was separated by filtration and crystallized with ethanol to afford pure compounds **7b**. Compounds **7c**, **7e, 7g** and **7j** were synthesized similarly. Characterization data of these compounds is given in the Table **6**.

2,4-Dichloro-2-[5-(1-methyl-3-propyl-1*H*5-pyrazolyl)-1*H*3-pyrazolyl]phenol (**8b**).

A mixture of **5b** (0.003 mole) and (0.005 mole) of hydrazine hydrate was dissolved in 10 ml ethanol. Reaction mixture was then refluxed for 3 hr. After completion of heating, the reaction mixture was cooled to room temperature and then poured over crushed ice and neutralized with acetic acid. Resulting product was separated by filtration and crystallized with ethanol to afford

pure compounds **8b**. Compounds **8f, 8g, 8k** and **8m** were synthesized similarly. Characterization data of these compounds is given in the Table 7.

Phosphodiesterase IV Inhibition Assay.

The assay was performed at 34 ° C in a 200 µL total reaction mixture. The reaction mixture contained 25 mM of tris buffer, 10 mM $MgCl_2$, 1 µM cAMP (cold) and [^{3}H] cAMP (0.1 µCi); stock solutions of the compounds to be investigated were prepared in dimethyl sulfoxide in concentrations such that the dimethyl sulfoxide content in the test samples did not exceed 0.05% by volume to avoid affecting the *Phosphodiesterase* IV activity. Compounds were then added in the reaction mixture (25 µL/tube). The assay was initiated by addition of enzyme mix (75 µL) and the mixture was incubated for 20 minutes at 34 °C. The reaction was stopped by boiling the tubes for 2 min at 100 °C in a water bath. After cooling on ice for 5 minutes and addition of 50 µg 5'-nucleotidase snake venom from *Crotalus atrox* incubation was carried out again for 20 min at 34 °C. The unreacted substrate was separated from (^{3}H) adenosine by addition of Dowex AG 1X-8 (400 µL), which was pre equilibrated in (1:1) water:ethanol. Reaction mixture was then thoroughly mixed, placed on ice for 15 minutes, vortexed and centrifuged at 14,000 rpm for 2 mins. After centrifugation, a sample of the supernatant (150µL) was taken and added in 24 well optiplates containing scinillant (1 mL) and mixed well. The samples in the plates were then determined for radioactivity in a Top Counter and the *Phosphodiesterase* IV activity was calculated. *Phosphodiesterase* IV enzyme was present in quantities that yield <30% total hydrolysis of substrate (linear assay conditions). Rolipram and Cilomilast were used as a standard in all assays. Results are summarized in Table 8.

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