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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activity of coumarin pyrazole pyrimidine 2,4,6(1H,3H,5H)triones and thioxopyrimidine4,6(1H,5H)diones

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Abstract A series of 5-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (**4a–f**) and dihydro-5-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-thioxopyrimidine-4,6(1H,5H)-dione (**5a–f**) derivatives were synthesized by the condensation of 3-(2-oxo2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**3a–f**) with barbituric acid and thiobarbituric acid in acetic acid under microwave irradiation method. The newly synthesized compounds were evaluated for their antibacterial activity against *Bcillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeoginosa*, and *Klebsiella pneumoniae*. All the compounds were found to be moderately active against used microorganisms, whereas compounds (4d) and (4e) exhibited good anti-fungal activity against *Aspergillus niger*.

Keywords Antimicrobial activity · Barbituric acid · Coumarin · Microwave irradiation · Pyrazole · Thiobarbituric acid

Introduction

Bacterial resistance to antibiotics has increased worldwide in recent years. In order to combat this new problem, novel antibiotic compounds/substances need to be found which are effective (Francesca, 2011). In spite of the large number of antibiotics and chemotherapeutics available for medical use, the emergence of old and new antibiotic-resistant bacterial strains in the last decades indicates a substantial need for new classes of antibacterial agents (Chopra *et al.*, 2008). Pyrazole and Isoxazole derivatives exhibit various biological properties, viz., bacteriostatic, antidiabetic, analgesic, antioxident, anti-inflammatory, antimicrobial, and anticancer (Padmaja *et al.*, 2009; Patricia *et al.*, 2008; Padmaja *et al.*, 2011; Gadakh *et al.*, 2010; Diana *et al.*, 2007). It is also known that coumarin derivatives have wide range of biological and therapeutic properties (Jih *et al.*, 2011; Gnerre *et al.*, 2000; Khalid *et al.*, 2004; Manolov *et al.*,1995; Emmanuel-Giota *et al.*, 2001). Antimicrobial activity of coumarin derivatives is well documented in the literature (Smyth *et al.*, 2009; Kawase *et al.*, 2001). Thiobarbituric acid (TBA) and Barbituric acid (BA) derivatives are used as antibacterial, (Yan *et al.*, 2009) sedatives, (David *et al.*, 2007) antidiabetic, (Sandeep *et al.*, 2008) fungicides (Brouwer *et al.*, 1990; Brouwer *et al.*, 1991), and antiviral (Esanu *et al.*, 1985; Esanu *et al.*, 1986) agents. Recently, BA and TBA were reported as anti cancer agents (Singh *et al.*, 2009). Microwave-assisted organic reaction is a well-established technique for the synthesis of various heterocycles. All thermally driven reactions can be accelerated by microwave irradiation. Spectacular results, viz., shorter reaction time, experimental simplicity, selectivity of products, easy work up etc., were obtained, giving clear indication of the potentialities of this technique over conventional heating (Caddick, 1995; Verma, 1999; Mavandadi and Lidström, 2004.). In view of these facts, and as part of our ongoing studies in developing new anti microbial agents (Vijaya Laxmi *et al.*, 2011; Suresh *et al.*, 2011), it was envisaged to construct a system, which combines both these moieties in a single molecular frame work to explore the additive effect of antimicrobial activities. In this article, we wish to report microwave-assisted synthesis of pyrazolyl coumarin barbiturates and their antimicrobial activity.

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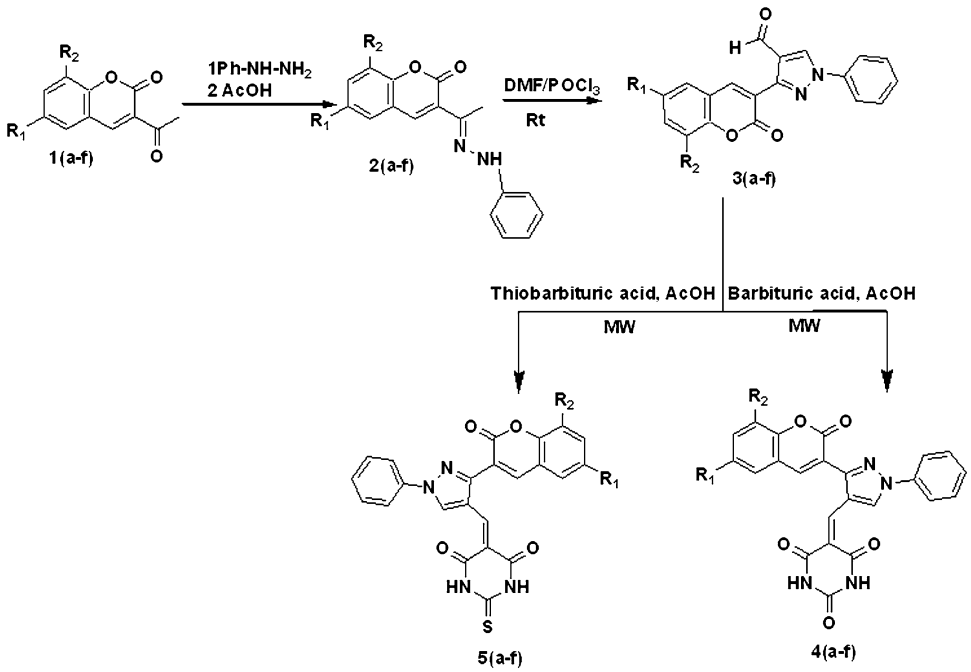
Scheme 1 Synthesis of compounds **4**(**a**–**f**) and **5**(**a**–**f**)



Results and discussion

Synthesis of coumarin pyrazole barbiturate derivatives **4**(**a**–**f**) and **5**(**a**–**f**) is outlined in Scheme 1, when 3-acetyl coumarins **1**(**a**–**f**) treated with phenyl hydrazine in methanolic acetic acid refluxed for half an hour afforded the compounds **2**(**a**–**f**) (Chodankar *et al.*, 1986). Vilsmeier formylation of these compounds **2**(**a**–**f**) at room temperature afforded the compounds **3**(**a**–**f**) in good yields; however, in literature the reaction was carried out at 80 °C poor yields were observed (Chodankar *et al.*, 1986; Selvi and Perumal, 2002a, b). Hence, we made a comparative study on vilsmeier formylation, at room temperature (method 1) and also at 80 °C (method 2) the results are depicted in Table 1, unexpectedly good yields were observed in method 1. Structures of the compounds were confirmed by ^{1}H NMR spectral data. Further Knoevenagel condensation (Thirupathi Reddy *et al.*, 2010) of aldehyde **3**(**a**–**f**) with BA and TBA on microwave irradiation, furnished the compounds **4**(**a**–**f**) and **5**(**a**–**f**) in good yields (Table 2). We did a comparative study on conventional and microwave irradiation method and observed excellent yields (75–85 %) in microwave irradiation method within a short period. All coumarin pyrazole barbiturate analogs provide satisfactory spectral data. (IR,^{1}H NMR,^{13}CNMR, and Mass spectra). In IR spectra, bands in the region 3,180–3,200 cm^{-1} attributed to NH group of the BA and TBA. Bands at 1,704 cm^{-1} obtained from the lactone ring of coumarin C=O, 1,667 and 1,733 cm^{-1} stretching frequencies were correspond to the C=O groups of BA. In thiobarbiturates, C=S stretching frequency was observed at 1,292 cm^{-1}. In

Table 1 Results of the synthesized compounds **3a–f**

Entry	Product	R_1	R_2	Yields at (80 °C)	Yield at r.t
1	**3a**	H	H	70	85
2	**3b**	Cl	H	72	88
3	**3c**	Cl	Cl	75	87
4	**3d**	Br	H	73	84
5	**3e**	Br	Br	72	82
6	**3f**	7,8 benzo		70	86

Table 2 Results of the synthesized compounds **4a–f**, **5a–f**

Entry	Product	R_1	R_2	Conventional method (h)	Yield (%)	Time (min)	Yield (%)
1	**4a**	H	H	7	35	5	85
2	**4b**	Cl	H	8	40	10	83
3	**4c**	Cl	Cl	8	50	10	85
4	**4d**	Br	H	6	40	10	80
5	**4e**	Br	Br	7	50	10	88
6	**4f**	7,8 benzo		5	60	5	82
7	**5a**	H	H	6	50	5	82
8	**5b**	Cl	H	7	40	10	75
9	**5c**	Cl	Cl	8	60	10	80
10	**5d**	Br	H	9	40	10	86
11	**5e**	Br	Br	10	50	10	80
12	**5f**	7,8 benzo		6	55	5	82

^{1}H NMR spectra, the absence of aldehyde proton signal at δ 9.93 and the presence of a signal at the range δ 9.7–9.8 (C=C–H) supports the formation of compounds **4**(**a**–**f**) and

5(**a**–**f**). The NH signals of BA were detected at 11.33–11.36 ppm range, while NH signal in TBA was observed at 11.3–12.47 ppm range. In both the series, aromatic protons appeared as multiplet in regular aromatic region at 7.2–8.5 ppm range. ^{13}C-NMR signal at δ 158.5–159.3 confirmed lactone carbonyl, signal at δ 162.6–162.8 ppm and 163.3–163.6 ppm assign the C=O groups in BA **4**(**a**–**f**), where as signal at 178.3 ppm attributed to C=S group **5**(**a**–**f**).

Biological activities

All the compounds **4**(**a**–**f**) and **5**(**a**–**f**) were evaluated for their in vitro antibacterial and antifungal activity (National Committee for Clinical Laboratory Standards, 1982; Linday, 1962).

Antibacterial activity

Determination of minimum inhibitory concentration (MIC) of synthetic compounds

The MIC was measured by broth dilution method (Villanova, 1984). A set of sterile test tubes with nutrient broth media were capped with cotton plugs (1–9). The test compound is dissolved in DMSO and a concentration of 100 μg/mL of the test compound was added to the first tube, which was serially diluted from 1 to 9. A fixed volume of 0.5 mL over night culture was added in all the test tubes and incubated at 37 °C for 24 h. After incubation period, the tubes were measured for turbidity using spectrophotometer; ciprofloxacin was used as a standard drug.

Antifungal activity

The ready-made Potato Dextrose Agar (PDA) medium (Himedia, 39 g) was suspended in distilled water (1,000 mL) and heated to boiling until it dissolved completely, the medium and petri dishes were autoclaved at pressure of 15 lb/inc^2 for 20 min. Agar cup bioassay was employed for testing antifungal activity. The medium was poured into sterile petri dishes under aseptic conditions in a laminar flow chamber. When the medium in the plates solidified, 0.5 mL of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in methanol and different concentrations were obtained (30 and 100 μg/mL). After inoculation, cups were scooped out with 6-mm sterile cork borer and the lids of the dishes were replaced. To each cup, different concentrations of test solutions (30,100 μg/mL) were added. Controls were maintained with Methanol and Fluconazole (30 μg/mL). The treated controls were kept at 27 °C for 48 h. Inhibition zones were measured and the diameter was calculated in mille meter. Three to four replicates were maintained for each treatment.

Antibacterial activity

All the compounds have shown moderate activity at MIC on 6 different bacterial strains. Results are summarized in (Table 3).

Table 3 In vitro antibacterial activity (MIC) values for compounds **4a–f**, **5a–f**

MIC (μg/mL)						
Compound	*B. subtilis*	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeroginosa*	*K. pneumoniae*
4a	300	300	300	300	150	150
4b	150	150	150	150	150	150
4c	300	300	300	300	150	150
4d	150	150	150	600	600	150
4e	150	150	150	150	150	300
4f	150	300	300	300	150	300
5a	300	150	150	600	300	150
5b	150	300	600	300	150	150
5c	300	150	300	600	300	150
5d	600	600	300	300	300	150
5e	150	150	300	150	150	150
5f	300	150	300	600	150	150
Ciprofloxacin	24	25	22	20	12.5	25

Table 4 In vitro antifungal activity (MIC) values for compounds **4d** and **4e**

Zone of inhibition (mm)		
Compound	*A. niger*	
	100 μg	150 μg
4d	14	20
4e	7	10
Fluconazole	30	

Antifungal activity

All the synthesized compounds were screened for In vitro antifungal activity; except compounds **4d** and **4e** remaining all the compounds were inactive. In both compounds (**4d**) and (**4e**), analog (**4d**) was found to be more potent against *Aspergillus niger*. Structure–activity relationship studies revealed that (Table 4) the presence of bromo at 6th position on coumarin (**4d**) enhanced the activity, while the activity is diminished when additional bromo group is introduced at 8th position on coumarin (**4e**). Hence, a new lead compound (**4d**) with antifungal activity encourages further optimization to develop more potent and effective analogs as antimycotic agents.

Experimental protocols

Chemistry

The barbituric acid and thiobarbituric acid with 98 % purity were purchased from Merck Company. All melting points were determined using a Quimis apparatus, Q-340s 13 model and are uncorrected. TLC was performed on 2.0 × 6.0 cm aluminum sheets covered with silica gel (Sorbent, 200-μm thickness) under ultraviolet radiation. Ethyl acetate:hexane (2:8) is used as a mobile phase. Infrared (IR) spectra were obtained using ABB spectrophotometer, FTLA 2000-100 model, using KBr pellets. ^{1}H NMR, was measured on a Brucker 300 MHz, spectrometer using DMSO as a solvent and TMS as internal standard; splitting patterns are as follows: s, singlet; d, doublet; and m, multiplet (Chemical shifts in δ *ppm*) mass spectra were recorded on a Jeol JMSD-300 spectrometer.

General procedure for the synthesis of 3-(2-oxo-2H-chromen-3-yl-)-1-phenyl-1H-pyrazole-4-carbaldehyde (3a–f) derivatives

To the cooled solution of DMF (1.0 mL,0.014 mol), $POCl_3$ (1.3 mL, 0.014 mol) was added drop wise for half an hour by maintaining the temperature at 0–5 °C. To this solution, derivatives of 3-[1-(phenyl-hydrazono)-ethyl]-chromen-2-one, 0.97 g (0.0035 mol) (**2a–f**), were added and the reaction mixture was stirred for 8–10 h at room temperature. Completion of the reaction was monitored by TLC, reaction mixture was poured into ice-cold water, and neutralized with 10 % NaOH solution. The crude product precipitated out was filtered, dried, and recrystallized from ethanol.

3-(2-Oxo-2H-chromen-3-yl-)-1-phenyl-1H-pyrazole-4-carbaldehyde (**3a**)

m.p.: 180–185 °C; ^{1}H-NMR (DMSO, δ, ppm): 7.42–8.47 (m, 10H), 9.25 (s, 1H), 9.93 (s, 1H). MS ESI: m+ 1 317 (100 %) for the M.F $C_{19}H_{12}N_2O_3$, M.Wt 316.

3-(6-Chloro-2-oxo-2H-chromen-3-1-phenyl-1H-pyrazole-4-carbaldehyde (**3b**)

m.p.: 190–195 °C; ^{1}H-NMR (DMSO, δ, ppm): 7.46–8.21 (m, 9H), 8.85 (s, 1H), 9.92 (s, 1H).

3-(6,8-Dichloro-2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**3c**)

m.p.: 175-180 °C; ^{1}H-NMR (DMSO, δ, ppm): 7.23-8.34 (m, 8H), 8.75 (s, 1H), 9.91 (s, 1H).

3-(6-Bromo-2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**3d**)

m.p.: 180–185 °C; ^{1}H-NMR (DMSO, δ, ppm): 7.3–8.45 (m, 9H), 8.92 (s, 1H), 9.89 (s, 1H).
^{13}C-NMR (DMSO, δ, ppm): 116.4, 118.5, 119.3, 120.6, 121, 123.4, 127.9, 129.7, 131, 132.7, 134.9, 138.5, 141.7, 147, 152.5, 158.8, 185.5.

3-(6,8-Dibromo-2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**3e**)

m.p.: 185–190 °C; ^{1}H-NMR (DMSO, δ, ppm): 7.39–8.26 (m, 8H), 8.279 (s, 1H), 9.92 (s, 1H).

3-(2-Oxo-2-H-benzo[g]chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**3f**)

m.p.: 220–225 °C; ^{1}H-NMR (DMSO, δ, ppm): 7.59–8.42 (m, 12H), 9.27 (s, 1H), 9.92 (s, 1H).

General procedure for the synthesis of 5-((3-(2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene) pyrimidine-2,4,6(1H,3H,5H)-trione derivatives (4a–f)

0.1 g (0.00031 mol) of derivatives of 3-(2-oxo-2H-chromen-3-yl-)-1-phenyl-1H-pyrazole-4-carbaldehyde (**3a–f**),

0.039 g (0.0003 mol) of BA and acetic acid (quantity) were finely mixed together. The reaction mixture was placed in a screw-capped vial and irradiated for 5–10 min in a domestic microwave oven at 300 W. On cooling, solid was separated out, which was filtered and recrystallized from ethanol.

5-((3-(2-Oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (**4a**)

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3231, 3089 (NH), 1732, 1704, 1667 (C=O), 1573 (C=N); ^{1}H-NMR (DMSO, δ, ppm): 7.44–8.5 (m, 10H), 9.27 (s, 1H), 9.77(s, 1H), 11.34 (s, 1H, NH), 11.36 (s, 1H, NH). ^{13}C-NMR (DMSO, δ, ppm): 113.1, 114.5, 116.7, 116.8, 118, 119.9, 122.7, 126.5, 128.3, 128.8, 129.1, 130.1, 134.6, 138.6, 141.8, 143.5, 150.3, 152.8, 154, 159.5, 162.8, 163.2. MS EIMS: m + 426. For the M.F $C_{23}H_{14}N_4O_5$, M.wt 426.

5-((3-(6-Chloro-2-oxo-2H-chromene-3-yl)-1phenyl1Hpyrazol4yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (**4b**)

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3280,3100 (NH), 1730, 1704, 1665 (C=O), 1573 (C=N); ^{1}H-NMR (DMSO, δ, ppm): 7.47–8.1 (m, 9H), 8.4 (s, 1H), 9.76 (s, 1H), 11.35 (s, 2H, 2NH).^{13}C-NMR (DMSO, δ, ppm): 114.5, 116.4, 118.3, 119.5, 120, 128, 128.1, 128.6, 129.9, 132.4, 134.5, 138.3, 143.2, 144, 150, 151.8, 152.3, 158.8, 162.5, 163.2. MS ESI: m+ 1 461. For the M.F $C_{23}H_{13}ClN_4O_5$, M.wt 460.

5-((3-(6,8-Dichloro-2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)pyrimidine2,4,6 (1H,3H,5H)-trione (**4c**)

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3279, 3920 (NH), 1733, 1702, 1662 (C=O), 1573 (C=N); ^{1}H-NMR (DMSO, δ, ppm): 7.2–8.1 (m, 8H), 8.4 (s, 1H), 9.77 (s, 1H) 11.34 (s, 1H, NH), 11.34 (s, 1H, NH). ^{13}C-NMR (DMSO, δ, ppm) 114.5, 116.4, 118.3, 119.5, 120, 128, 128.1, 128.6, 129.9, 132.4, 134.5, 138.3, 143.2, 144, 150, 151.8, 152.3, 158.8, 162.2, 162.3.MS HRMS: m+ 495, m+ 1 496. For the M.F $C_{23}H_{12}Cl_2N_4O_5$, M.wt 495.

5-((3-(6-Bromo-2-oxo-2H-chromene-3-yl)-1-phenyl1Hpyrazol4yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (**4d**)

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3298, 3160 (NH), 1732, 1704, 1665 (C=O), 1572 (C=N); ^{1}H-NMR (DMSO, δ, ppm): 7.38–8.6 (m, 9H), 9.2 (s, 1H), 9.68 (s, 1H), 11.34 (s, 1H, NH), 11.36 (s, 1H, NH). M S EIMS: 70 eV m+ 1 505. For the M.F $C_{23}H_{13}BrN_4O_5$, M.Wt 504. ^{13}C-NMR (DMSO, δ, ppm): 116.4, 118.5, 119.3, 120.6, 121, 123.4, 127.9, 129.7, 131, 132.7, 134.9, 138.5, 141.7, 147, 152.5, 158.8, 161.2, 162.3.MS EIMS: m+ 505. For the M.F $C_{23}H_{13}BrN_4O_5$, M.wt 505.

5-((3-(6,8-Dibromo-2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (**4e**)

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3283, 3102 (NH), 1733, 1704, 1667 (C=O), 1573 (C=N); ^{1}H-NMR (DMSO, δ, ppm): 7.47–8.26 (m, 8H), 8.42 (s, 1H), 9.76 (s, 1H), 11.35 (s, 2H, 2NH). ^{13}C-NMR (DMSO, δ, ppm): 110.2, 114.7, 116.5, 119.6, 120.8, 121.7, 128.2, 129.9, 130.7, 134.6, 137, 138.3, 143.5, 149.7, 150.1, 152.7, 158.2, 162.5, 163.3, 165.3. MS EIMS: m + 585. For the M.F $C_{23}H_{12}Br_2N_4O_5$, M.wt 585.

5-((3-(2-Oxo-2H-benzo[g]chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (**4f**)

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3270, 3089 (NH), 1730, 1701, 1665 (C=O), 1570 (C=N); ^{1}H-NMR (DMSO, δ, ppm): 7.49–8.7 (m, 12H), 9.27 (s,1H), 9.81 (s, 1H), 11.3 (s, 1H, NH), 11.3 (s, 1H, NH). ^{13}C-NMR (DMSO, δ, ppm): 113.1, 114.5, 116.7, 116.8, 118, 119.9, 122.7, 126.5, 128.3, 128.8, 129.1, 130.1, 134.6, 138.6, 141.8, 143.5, 150.3, 152.8, 154, 158.5, 162.8, 163.6.

General procedure for the synthesis of dihydro-5-((3-(2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)2-thioxopyrimidine4,6(1H,5H)-diones (5a–f).

Derivatives of 3-(2-oxo-2H-chromen-3-yl-)-1-phenyl-1H-pyrazole-4-carbaldehyde (**3a–f**) 0.1 g (0.00031 mol), TBA 0.0044 g (0.00031 mmol), and acetic acid were finely mixed together and placed in a screw-capped vial and irradiated for 5–10 min in a domestic microwave oven at 300 W power level. On cooling, solid was separated out, which was filtered and recrystallized from ethanol.

Dihydro-5-(-((3-(2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)2-thioxopyrimidine4,6 (1H,5H)-dione (**5a**).

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3229, 3093 (NH), 1732, 1704, (C=O), 1573 (C=N), 1292 (C=S); ^{1}H-NMR (DMSO, δ, ppm): 7.44–8.51 (m, 10H), 9.7 (s, 1H), 9.80 (s, 1H), 11.3 (s, 1H, NH), 12.45 (s, 1H, NH). ^{13}C-NMR (DMSO, δ, ppm)

116.3, 118.7, 119.6, 125, 129.2, 129.9, 133, 134.5, 134.8, 138.5, 138.4, 144.3, 144.4, 145.6, 150.1, 152.4, 153.7, 159.3, 160.4, 161.6, 162.6, 163.4, 178.3. MS ESI: m+ 1 443. For the M.F $C_{23}H_{14}N_4O_4S$, M.wt 442.

5-((3-(6-Chloro-2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-dihydro-thioxopyrimidine-4,6(1H,5H)-dione (**5b**)

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3260, 3082 (NH), 1730, 1705, (C=O), 1573 (C=N), 1294 (C=S); ^{1}H-NMR (DMSO, δ, ppm): 7.2–8.13 (m, 9H), 8.44 (s, 1H), 9.79 (s, 1H), 11.1 (s, 1H, NH), 11.3 (s, 1H, NH). ^{13}C-NMR (DMSO, δ, ppm) 114.5, 116.4, 118.3, 119.5, 120, 128, 128.1, 128.6, 129.9, 132.4, 134.5, 138.3, 143.2, 144, 150, 151.8, 152.3, 158.8, 162.5, 162.7, 178.2. MS EIMS: m+ 476. For the M.F $C_{23}H_{13}ClN_4O_4S$, M.wt 476.

5-((3-(6,8-Dichloro-2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-dihydro-thioxopyrimidine-4,6(1H,5H)-dione (**5c**)

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3294, 3092 (NH), 1733, 1707, (C=O), 1573 (C=N), 1296 (C=S); ^{1}H-NMR (DMSO, δ, ppm): 7.42–8.45 (m, 8H), 9.27 (s, 1H), 9.80 (s, 1H), δ = 12.46 (s, 1H, NH), δ = 12.47 (s, 1H, NH). ^{13}C-NMR (DMSO, δ, ppm): 114.7, 116.7, 118.3, 119.6, 119.9, 120, 128.1, 128.2, 129.9, 132.4, 138.2, 144.0, 144.3, 152.0, 152.3, 158.8, 160.3, 161.5, 178.3.

5-((3-(6-Bromo-2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-dihydro-thioxopyrimidine-4,6(1H,5H)-dione (**5d**).

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3300, 3190 (NH), 1733, 1705 (C=O), 1573 (C=N), 1292 (C=S); ^{1}H-NMR (DMSO, δ, ppm): 7.37–8.13 (m, 9H), 8.7 (s, 1H), 9.80 (s, 1H), 12.44 (s, 1H, NH), 12.45 (s, 1H, NH). ^{13}C-NMR (DMSO, δ, ppm): 116.4, 118.5, 119.3, 120.6, 121, 123.4, 127.9, 129.7, 131, 132.7, 134.9, 138.5, 141.7, 147, 152.5, 158.8, 161.2, 162.2, 178.2. MS ESI: m+ 519, m+ 1 520 For the M.F $C_{23}H_{13}BrN_4O_4S$, M.wt 519.

5-((3-(6,8-Dibromo-2-oxo-2H-chromene-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-dihydro-thioxopyrimidine-4,6(1H,5H)-dione (**5e**)

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3272, 3074 (NH), 1730, 1702 (C=O), 1571; (C=N), 1295 (C=S); ^{1}H-NMR (DMSO, δ, ppm): 7.25–8.14 (m, 8H), 8.4 (s, 1H), 9.79 (s, 1H), 11.1 (s, 1H, NH), 11.3 (s, 1H, NH). ^{13}C-NMR (DMSO, δ, ppm): 116.2, 117.7, 119.6, 122.6, 129.3, 129.9, 131.1, 133.7, 134.8, 135.2, 138.3, 139.4, 144, 152.2, 158, 158.8, 160.3, 161.6, 178.3. MS ESI: m+ 598. For the M.F $C_{23}H_{12}Br_2N_4O_4S$, M.wt 598.

Dihydro-5-((3-(2-oxo-benzo[g]chromene-3-yl)-1-phenyl-1H-pyrazol-4yl)methylene)thioxopyrimidine-4,6(1H,5H)-dione (**5f**)

m.p.: >300 °C; IR (KBr) (cm^{-1}): 3298, 3152 (NH), 1733, 1704 (C=O), 1570 (C=N), 1292 (C=S); ^{1}H-NMR (DMSO, δ, ppm): 7.51–8.7 (m, 12 H), 9.27 (s, 1H), 9.84 (s, 1H), 12.45 (s, 1H, NH), 12.46 (s, 1H, NH) ^{13}C-NMR (DMSO, δ, ppm): 112.9, 114.4, 116.5, 116.9, 117.7, 119.7, 122.5, 126.3, 128.2, 128.6, 128.9, 129.9, 130, 134.4, 134.7, 138.4, 141.7, 144.4, 152.8, 153.9, 159.3, 160.4, 161.6, 178.3. MS ESI: m+ 1 493. For the M.F $C_{27}H_{16}N_4O_4S$, M.wt 492.

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