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One-pot multicomponent synthesis of novel 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives and evaluation of their cytotoxic activity

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Abstract A series of novel 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives (**4a–l**) were synthesized via one-pot multicomponent reaction of 5-substituted salicylaldehydes (**1a–c**), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**) and 2-hydrazinyl-4-arylthiazoles (**3a–d**) in acetonitrile using a catalytic amount of piperidine under reflux conditions. This multicomponent approach has advantages such as reduced reaction time and a high product yield percentage when compared with corresponding multistep approaches. All the synthesized compounds were evaluated for their cytotoxic activity against Hep G2 (hepatocellular liver carcinoma) and MCF-7 (breast cancer) cell lines and compared with the standard drug Doxorubicin. Among all the compounds, compounds **4d** against Hep G2, **4k** against MCF-7 and **4e** against both Hep G2 & MCF-7 showed excellent cytotoxic activity.

Keywords One-pot multicomponent reaction · 1-thiazolyl-5-coumarin-3-yl-pyrazole · Cytotoxic activity

Introduction

Cancer is a worldwide death causing disease. Although, clinically, many chemotherapeutic anticancer drugs are available, they cause several undesirable side effects to the patients such as reduced bioavailability, toxicity and drug-

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resistance [1, 2]. Hence it is a challenging research area for the medicinal chemists to discover newer and safer anticancer agents that have excellent cytotoxicity to cancer cells [3]. On the other hand, the development of a multicomponent approach is of considerable current interest in the field of organic synthesis. The concept of multicomponent reactions (MCRs) performing more than one transformation in a single vessel simplifies the work-up procedure, avoids unstable separation of intermediates, and produces a good product yield via the increased efficiency of the desired conversion [4, 5]. MCRs have advantages over stepwise reactions in the above-mentioned aspects and permit rapid access to combinatorial libraries of complex organic molecules, enabling efficient lead structure identification and optimal drug discovery.

Pyrazole scaffolds have attracted significant interest in medicinal chemistry over the past few decades. Several pyrazole derivatives possess a wide range of biological activities such as anticancer [6], antimicrobial [7], antiviral [8], antitubercular [9], antioxidant [10], anti-inflammatory [11], antidepressant and anticonvulsant [12] activities. Pyrazole scaffolds are not only independent, along with other heterocycles like thiazole and coumarins, but also possess marked biological activities [13–18]. Thiazoles and coumarins also portray an important role in medicinal and pharmaceutical chemistry due to their versatile biological applications, such as antimicrobial [19, 20], anticancer [21, 22], antitumor [23, 24], antiulcer [25, 26], antiviral [27, 28], antioxidant [29, 30], anticonvulsant [31, 32] and antihypertensive [33, 34] activities.

In view of the above-mentioned biological importance, especially the anticancer activity of pyrazoles, thiazoles and coumarins, as well as several advantages of multicomponent reactions for the synthesis of the above two or three moieties incorporating hybrid molecules [35, 36], here we report efficient one-pot multicomponent synthesis of 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives as new compounds having pyrazole, thiazole and coumarin moieties in a single frame. These compounds were evaluated for their anticancer activity.

Results and discussion

In continuation of our interest regarding synthesis of various biologically active novel heterocycles [37, 38], we designed synthesis of novel 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives. To analyze the synthetic route, the model reaction was carried out for the synthesis of product **4a** by using salicylaldehyde (**1a**), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**) and 2-hydrazinyl-4-arylthiazoles (**3a**) in acetonitrile with a catalytic amount of piperidine under reflux conditions. This model reaction was carried out in multistep as well as single step (one-pot multicomponent reaction involving sequential addition of reactants) approaches and the reaction time and percentage of yield for product **4a** were calculated. In the multistep reaction, first salicylaldehyde (**1a**) reacted with 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**) in acetonitrile with a catalytic amount of piperidine under reflux conditions for 30 min to furnish the intermediate 3-acetoacetylcoumarin (**6**) at a 78-% yield. In the second step, the resulting intermediate **6** reacted with 2-hydrazinyl-4-phenylthiazole (**3a**) in

Table 1 Synthesis of 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives (**4a–l**)

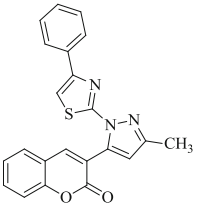
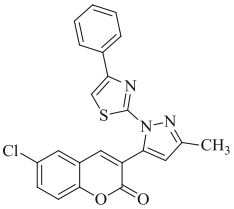
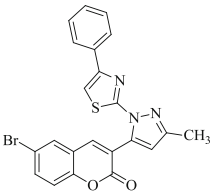
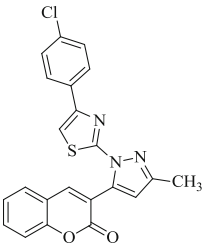
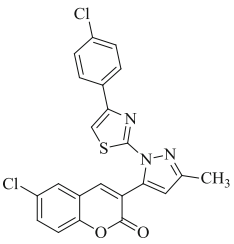
Entry[a]	Product	Time (h)	Yield[b] (%)
1	 **4a**	2	88
2	 **4b**	3	87
3	 **4c**	3	92
4	 **4d**	3.5	85
5	 **4e**	3	87

Table 1 continued

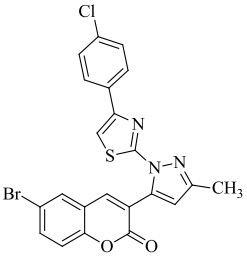
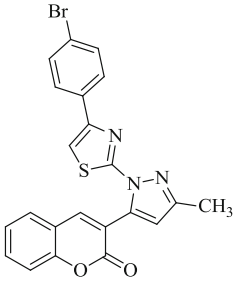
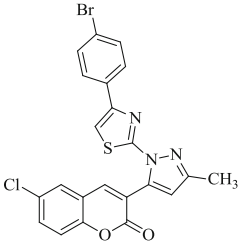
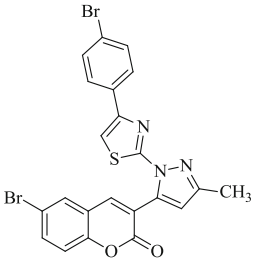
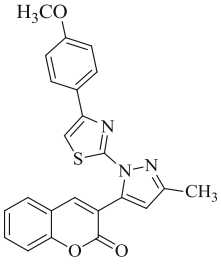
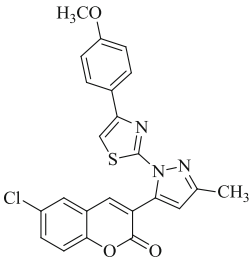
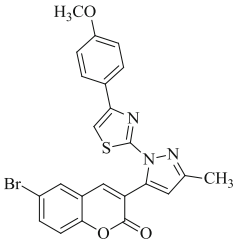
Entry[a]	Product	Time (h)	Yield[b] (%)
6	 **4f**	2.5	90
7	 **4g**	2	92
8	 **4h**	3	88
9	 **4i**	2	92

Table 1 continued

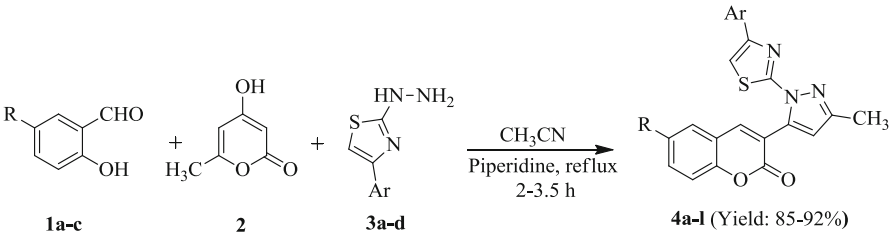
Entry[a]	Product	Time (h)	Yield[b] (%)
10	 **4j**	2	89
11	 **4k**	2.5	88
12	 **4l**	2	91

[a] *Reaction condition* Salicylaldehyde derivative (**1a–c**, 1 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**, 1 mmol), 2-hydrazinyl-4-arylthiazoles (**3a–d**, 1 mmol), acetonitrile (5 mL), piperidine (Cat.), reflux, 2–3.5 h

[b] Isolated yields

All the synthesized compounds were confirmed by their analytical and spectral (IR, ^{1}HNMR, ^{13}CNMR and mass) studies

acetonitrile under reflux conditions for 2 h, affording the product **4a** at 65 % yield. When the same reaction was carried out in a multicomponent approach we observed a decreased reaction time (2 h), and the product yield increased (88 %). Hence, we carried out the one-pot multicomponent reactions involving sequential addition of salicylaldehyde derivatives (**1a–c**), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**) and 2-hydrazinyl-4-arylthiazoles (**3a–d**) for the synthesis of 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives (**4a–l**; Table 1). A schematic representation and plausible mechanism for the formation of the products are shown in Scheme 1 and 2,



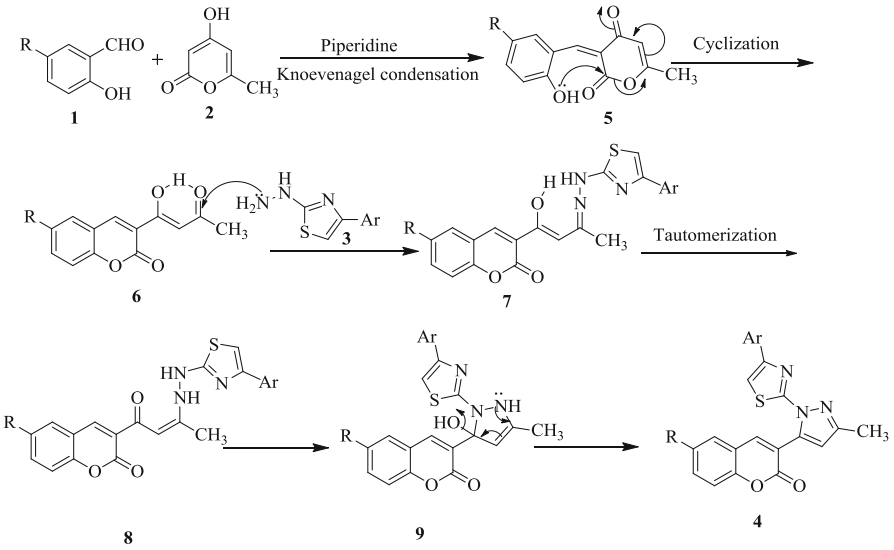
1a-c **2** **3a-d** **4a-l** (Yield: 85-92%)

1a: R = H
1b: R = Cl
1c: R = Br

3a: Ar = C_6H_5
3b: Ar = 4-ClC_6H_4
3c: Ar = 4-BrC_6H_4
3d: Ar = 4-$OCH_3C_6H_4$

4a: R = H; Ar = C_6H_5
4b: R = Cl; Ar = C_6H_5
4c: R = Br; Ar = C_6H_5
4d: R = H; Ar = 4-ClC_6H_4
4e: R = Cl; Ar = 4-ClC_6H_4
4f: R = Br; Ar = 4-ClC_6H_4
4g: R = H; Ar = 4-BrC_6H_4
4h: R = Cl; Ar = 4-BrC_6H_4
4i: R = Br; Ar = 4-BrC_6H_4
4j: R = H; Ar = 4-$OCH_3C_6H_4$
4k: R = Cl; Ar = 4-$OCH_3C_6H_4$
4l: R = Br; Ar = 4-$OCH_3C_6H_4$

Scheme 1 Synthesis of 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives



Scheme 2 Plausible mechanism for the synthesis of 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives

respectively. The starting compounds 2-hydrazinyl-4-arylthiazoles (**3a–d**) were obtained according to the literature procedure [39].

Cytotoxic activity

The cellular viability of the synthesized compounds (**4a–l**) against MCF-7 (breast cancer) and Hep-G2 (hepatocellular liver carcinoma) cell lines determined by an MTT-microcultured tetrazolium assay following the reported protocol [40–42].

Table 2 Cytotoxicity of 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives (**4a–l**)

S. no	Product	Hep-G2	MCF-7
1	4a	4.21 ± 0.03	9.04 ± 0.02
2	4b	6.14 ± 0.06	8.72 ± 0.04
3	4c	9.62 ± 0.08	9.35 ± 0.04
4	4d	3.74 ± 0.02	6.92 ± 0.03
5	4e	3.06 ± 0.01	4.42 ± 0.02
6	4f	11.24 ± 0.21	6.04 ± 0.04
7	4g	21.68 ± 0.32	15.26 ± 0.18
8	4h	18.42 ± 0.20	31.54 ± 0.38
9	4i	43.17 ± 0.36	29.24 ± 0.27
10	4j	4.87 ± 0.02	7.20 ± 0.03
11	4k	3.25 ± 0.01	4.03 ± 0.02
12	4l	6.16 ± 0.03	13.23 ± 0.05
13	Doxorubicin	3.01	1.08

Activity data (Table 2) revealed that all the compounds show good to moderate activity against both Hep-G2 and MCF-7 cancer cell lines in the range of IC_{50} 3.06–43.17 μM and 4.03–31.54, respectively, compared to standard drug Doxorubicin (IC_{50} = half maximal inhibitory concentration). Among all the compounds, compounds **4d** (IC_{50} 3.74 μM), **4e** (IC_{50} 3.06 μM) and **4k** (IC_{50} 3.25 μM) exhibited prominent activity against Hep-G2 compared to Doxorubicin (IC_{50} 3.01 μM). In the case of MCF-7 cell line compounds, **4e** (IC_{50} 4.42 μM) and **4k** (IC_{50} 4.03 μM) showed better activity than the remaining compounds and as compared to Doxorubicin (IC_{50} 1.08 μM). The remaining compounds were moderately active against both tested cell lines.

Conclusion

In conclusion, we synthesized a novel series of 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives by a one-pot multicomponent approach and evaluated them for their cytotoxicity. Compounds **4d** against Hep-G2, **4k** against MCF-7 and **4e** against Hep-G2 & MCF-7 showed excellent cytotoxicity. These synthetic methods and cytotoxicity evaluation may help develop the fields of synthetic organics and medicine.

Experimental section

Materials

All reagents and solvents were purchased from Aldrich/Merck and used without further purifications. Melting points were determined in open capillaries using a

Stuart SMP30 apparatus and are uncorrected. The progress of the reactions as well as purity of compounds was monitored by thin layer chromatography (TLC) with F_{254} silica-gel pre-coated sheets using hexane/ethyl acetate 8/2 as an eluent; ultraviolet (UV) light and iodine vapours were used for detection. Infrared (IR) spectra were recorded on a Perkin-Elmer 100S spectrometer utilizing potassium bromide (KBr) pellets. Proton nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, on a Bruker-400 MHz instrument using deuterated dimethyl sulfoxide (DMSO-d_6 as the solvent and trimethylsilane (TMS) as the internal standard. Elemental analyses were performed on a Carlo-Erba model EA1108 analytical unit and the values are ±0.4 % of the theoretical values. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

General procedure for the synthesis of 1-thiazolyl-5-coumarin-3-yl-pyrazole derivatives ***(4a–l)***

A mixture of salicylaldeyde derivatives (**1a**–**c**, 1 mmol) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**, 0.126 g, 1 mmol) in acetonitrile (5 mL) with a catalytical amount of piperidine were stirred on a magnetic stirrer for 30–60 min under reflux conditions. After solid separation in the reaction mixture, 2-hydrazinyl-4-arylthiazoles (**3a**–**d**, 1 mmol) was added and the solution was stirred an additional 1.5–2 h at the same temperature. After completion of the reaction (monitored by TLC), separated solid was filtered and washed with excess acetonitrile and dried. The dried compound was recrystallized from ethanol, affording the analytically pure products.

Protocol for the MTT-microcultured tetrazolium assay

MCF-7 and HepG-2 cells were plated into a 96-well plate at a density of 1×10^4 cells/well. Cells were grown overnight in the full medium and then switched to the low serum media. DMSO was used as a control. After 48 h of treatment with different concentrations of test compounds, the cells were incubated with MTT (2.5 mg/mL) in the CO_2 chamber for 2 h. The medium was then removed and 100 μL of DMSO was added to each well to dissolve formazan crystals. After thorough mixing, the plates were read at 570 nm for optical density, which is directly correlated with cell quantity. The results are represented as percentage of cytotoxicity/viability. All the experiments were carried out in triplicates. The IC_{50} values were calculated from the percentage of cytotoxicity and compared with the reference drug Doxorubicin. The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50 % inhibition of cell viability.

Spectral data

3-(3-Methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-yl)-2H-chromen-2-one **(4a)** White solid; mp. 199–201 °C; IR (KBr, cm^{-1}) υ_{max}: 1712 (C=O), 1602 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (*s*, 3H), 7.03 (*s*, 1H), 7.17 (*d*, 1H, $J = 8.0$ Hz), 7.36–7.45 (*m*, 2H), 7.50–7.58 (*m*, 1H), 7.67–7.70 (*m*, 2H), 7.80 (*d*, 1H, $J = 6.4$ Hz),

7.93 (*d*, 2H, $J = 7.6$ Hz), 8.05 (*s*, 1H), 8.31 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.6, 112.4, 113.2, 120.4, 124.8, 125.5, 127.5, 129.3, 131.2, 131.4, 133.8, 141.0, 147.1, 148.9, 159.6; Mass (ESI) *m/z*: 385 $[M]^+$; Anal. Calcd. for $C_{22}H_{15}N_3O_2S$: C, 68.55; H, 3.92; N, 10.90. Found: C, 68.73; H, 3.78; N, 10.78.

6-Chloro-3-(3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-yl)-2H-chromen-2-one **(4b)** Brown solid; mp. 213–215 °C; IR (KBr, cm^{-1}) υ_{max}: 1718 (C=O), 1600 (C=N), 820 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (*s*, 3H), 7.20 (*s*, 1H), 7.38–7.44 (*m*, 2H), 7.50–7.58 (*m*, 1H), 7.68–7.72 (*m*, 1H), 7.8 (*d*, 1H, $J = 8.8$ Hz), 7.85–7.87 (*m*, 1H), 7.93 (*d*, 2H, $J = 8.0$ Hz), 8.06 (*s*, 1H), 8.34 (*s*, 1H); Mass (ESI) *m/z*: 421 $[M + 2]^+$; Anal. Calcd. for $C_{22}H_{14}ClN_3O_2S$: C, 62.93; H, 3.36; N, 10.01. Found: C, 63.17; H, 3.19; N, 9.87.

6-Bromo-3-(3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-yl)-2H-chromen-2-one **(4c)** White solid; mp. 205–206 °C; IR (KBr, cm^{-1}) υ_{max}: 1717 (C=O), 1606 (C=N), 735 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (*s*, 3H), 7.25 (*s*, 1H), 7.27–7.45 (*m*, 2H), 7.50–7.58 (*m*, 1H), 7.69 (*t*, 1H, $J = 7.2$ Hz), 7.69–7.87 (*m*, 2H), 7.93 (*d*, 2H, $J = 8.0$ Hz), 8.06 (*s*, 1H), 8.34 (*s*, 1H); Mass (ESI) *m/z*: 464 $[M+]^+$; Anal. Calcd. for $C_{22}H_{14}BrN_3O_2S$: C, 56.91; H, 3.04; N, 9.05. Found: C, 57.16; H, 3.24; N, 8.89.

3-(1-(4-(4-Chlorophenyl)thiazol-2-yl)-3-methyl-1H-pyrazol-5-yl)-2H-chromen-2-one **(4d)** Brown solid; mp. 230–232 °C; IR (KBr, cm^{-1}) υ_{max}: 1720 (C=O), 1604 (C=N), 820 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (*s*, 3H), 7.21 (*s*, 1H), 7.37–7.45 (*m*, 1H), 7.50–7.58 (*m*, 2H), 7.68–7.76 (*m*, 2H), 7.85–7.87 (*m*, 1H), 7.93 (*d*, 2H, $J = 7.6$ Hz), 8.06 (*s*, 1H), 8.34 (*s*, 1H); Mass (ESI) *m/z*: 420 $[M+H]^+$; Anal. Calcd. for $C_{22}H_{14}ClN_3O_2S$: C, 62.93; H, 3.36; N, 10.01. Found: C, 63.18; H, 3.21; N, 9.80.

6-Chloro-3-(1-(4-(4-chlorophenyl)thiazol-2-yl)-3-methyl-1H-pyrazol-5-yl)-2H-chromen-2-one **(4e)** White solid; mp. 232–234 °C; IR (KBr, cm^{-1}) υ_{max}: 1716 (C=O), 1611 (C=N), 827 (C–Cl);^{1}H NMR (400 MHz, DMSO-d_6): δ ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (*s*, 3H), 7.37–7.44 (*m*, 1H), 7.46–7.58 (*m*, 2H), 7.69–7.73 (*m*, 1H), 7.86–7.88 (*m*, 1H), 7.94 (*d*, 1H, $J = 7.6$ Hz), 8.08 (*d*, 2H, $J = 8.0$ Hz), 8.25 (*s*, 1H), 8.35 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.6, 109.4, 113.4, 113.7, 124.0, 126.2, 128.5, 128.7, 128.8, 129.6, 131.9, 139.3, 150.0, 150.1, 158.9; Mass (ESI) *m/z*: 455 $[M+H]^+$; Anal. Calcd. for $C_{22}H_{13}Cl_2N_3O_2S$: C, 58.16; H, 2.88; N, 9.25. Found: C, 58.32; H, 3.04; N, 9.07.

6-Bromo-3-(1-(4-(4-chlorophenyl)thiazol-2-yl)-3-methyl-1H-pyrazol-5-yl)-2H-chromen-2-one **(4f)** Brown solid; mp. 217–219 °C; IR (KBr, cm^{-1}) υ_{max}: 1717 (C=O), 1609 (C=N), 827 (C–Cl), 742 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (*s*, 3H), 7.34–7.44 (*m*, 1H), 7.46–7.58 (*m*, 2H), 7.68–7.71 (*m*, 1H), 7.85–7.90 (*m*, 1H), 7.94 (*d*, 2H, $J = 7.6$ Hz), 8.08 (*s*, 1H), 8.35 (*s*, 1H); Mass (ESI) *m/z*: 498 $[M]^+$; Anal. Calcd. for $C_{22}H_{13}BrClN_3O_2S$: C, 52.98; H, 2.63; N, 8.42. Found: C, 54.41; H, 2.83; N, 8.28.

3-(1-(4-(4-Bromophenyl)thiazol-2-yl)-3-methyl-1H-pyrazol-5-yl)-2H-chromen-2-one **(4g)** Brown; mp. 208–210 °C; IR (KBr, cm^{-1}) υ_{max}: 1722 (C=O), 1601 (C=N), 741

(C–Br);^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (*s*, 3H), 7.36–7.44 (*m*, 2H), 7.45–7.64 (*m*, 2H), 7.69–7.73 (*m*, 1H), 7.73–7.87 (*m*, 2H), 7.94 (*d*, 2H, J = 7.6 Hz), 8.09 (*s*, 1H), 8.35 (*s*, 1H); Mass (ESI) *m/z*: 464 $[M]^+$; Anal. Calcd. for $C_{22}H_{14}BrN_3O_2S$: C, 56.91; H, 3.04; N, 9.05. Found: C, 57.20; H, 3.22; N, 8.86.

3-(1-(4-(4-Bromophenyl)thiazol-2-yl)-3-methyl-1H-pyrazol-5-yl)-6-chloro-2H-chromen-2-one **(4h)** Brown solid; mp. 222–224 °C; IR (KBr, cm^{-1}) υ_{max}: 1716 (C=O), 1612 (C=N), 833 (C–Cl) 735 (C–Br);^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (*s*, 3H), 7.39–7.76 (*m*, 3H), 7.69 (*t*, 1H, J = 7.2 Hz), 7.86 (*d*, 1H, J = 7.6 Hz), 7.92 (*d*, 1H, J = 7.2 Hz), 7.98 (*d*, 2H, J = 7.6 Hz), 8.00 (*s*, 1H), 8.35 (*s*, 1H); Mass (ESI) *m/z*: 498 $[M]^+$; Anal. Calcd. for $C_{22}H_{13}ClBrN_3O_2S$: C, 52.98; H, 2.63; N, 8.42. Found: C, 53.22; H, 2.80; N, 8.28.

6-Bromo-3-(1-(4-(4-bromophenyl)thiazol-2-yl)-3-methyl-1H-pyrazol-5-yl)-2H-chromen-2-one **(4i)** Brown solid; mp. 195–197 °C; IR (KBr, cm^{-1}) υ_{max}: 1719 (C=O), 1610 (C=N), 744 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34 (*s*, 3H), 6.69 (*s*, 1H), 7.44 (*d*, 2H, J = 8.8 Hz), 7.50 (*d*, 2H, J = 8.8 Hz), 7.63 (*d*, 1H, J = 8.8 Hz), 7.89 (*t*, 2H, J = 8.0 Hz), 8.05 (*s*, 1H), 8.20 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.6, 109.2, 109.8, 110.3, 111.3, 116.9, 117.8, 119.9, 121.3, 126.9, 127.2, 130.3, 131.2, 131.5, 132.5, 134.7, 136.5, 139.9, 150.4, 151.6, 152.4; Mass (ESI) *m/z*: 543 $[M]^+$; Anal. Calcd. for $C_{22}H_{13}Br_2N_3O_2S$: C, 48.64; H, 2.41; N, 7.74. Found: C, 50.03; H, 2.63; N, 7.55.

3-(1-(4-(4-Methoxyphenyl)thiazol-2-yl)-3-methyl-1H-pyrazol-5-yl)-2H-chromen-2-one **(4j)** Brown solid; mp. 177–179 °C; IR (KBr, cm^{-1}) υ_{max}: 1717 (C=O), 1607 (C=N), 1154 (C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (*s*, 3H), 3.76 (*s*, 3H), 6.94 (*s*, 1H), 7.38–7.45 (*m*, 1H), 7.50–7.58 (*m*, 2H), 7.71 (*t*, 2H, J = 7.6 Hz), 7.80 (*d*, 2H, J = 6,4 Hz), 7.92 (*t*, 1H, J = 8.0 Hz), 8.05 (*s*, 1H), 8.34 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.7, 55.1, 110.5, 112.4, 113.1, 113.2, 116.4, 121.4, 125.5, 126.0, 128.4, 128.6, 129.0, 130.0, 132.8, 133.5, 141.1, 151.8, 158.6, 159.6; Mass (ESI) *m/z*: 415 $[M]^+$; Anal. Calcd. for $C_{23}H_{17}N_3O_3S$: C, 66.49; H, 4.12; N, 10.11. Found: C, 66.71; H, 4.00; N, 9.89.

6-Chloro-3-(1-(4-(4-methoxyphenyl)thiazol-2-yl)-3-methyl-1H-pyrazol-5-yl)-2H-chromen-2-one **(4k)** Brown solid; mp. 203–205 °C; IR (KBr, cm^{-1}) υ_{max}: 1722 (C=O), 1611 (C=N), 1148 (C–O–C), 832 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (*s*, 3H), 3.67 (*s*, 3H), 7.37–7.44 (*m*, 1H), 7.46–7.58 (*m*, 2H), 7.71 (*t*, 1H, J = 7.8 Hz), 7.86 (*d*, 1H, J = 7.6 Hz), 7.94 (*d*, 1H, J = 8.4 Hz), 8.12 (*d*, 2H, J = 7.6 Hz), 8.14 (*s*, 1H), 8.35 (*s*, 1H); Mass (ESI) *m/z*: 451 $[M + 2]^+$; Anal. Calcd. for $C_{23}H_{16}ClN_3O_3S$: C, 61.40; H, 3.58; N, 9.34. Found: C, 61.57; H, 3.76; N, 9.06.

6-Bromo-3-(1-(4-(4-methoxyphenyl)thiazol-2-yl)-3-methyl-1H-pyrazol-5-yl)-2H-chromen-2-one **(4l)** Brown solid; mp. 192–194 °C; IR (KBr, cm^{-1}) υ_{max}: IR (KBr, cm^{-1}) υ_{max}: 1718 (C=O), 1601 (C=N), 1134 (C–O–C), 727 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (*s*, 3H), 3.78 (*s*, 3H), 7.39–7.55 (*m*, 1H), 7.57–7.72 (*m*, 2H), 7.81 (*s*, 1H), 7.80 (*d*, 1H, J = 6.4 Hz),7.95 (*d*, 1H, J = 7.6 Hz), 8.10 (*d*, 2H, J = 7.6 Hz), 8.21 (*d*, 1H, J = 8.0 Hz), 8.33 (*s*, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.6, 54.9,

106.5, 112.1, 112.4, 116.1, 122.2, 124.0, 126.3, 128.9, 129.8, 134.4, 137.1, 137.5, 151.9, 155.3, 157.6; Mass (ESI) *m/z*: 494 $[M]^+$; Anal. Calcd. for $C_{23}H_{16}BrN_3O_3S$: C, 55.88; H, 3.26; N, 8.50. Found: C, 56.16; H, 3.14; N, 8.32.

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