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Synthesis of novel substituted 3-(4-((1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-ones: various approaches

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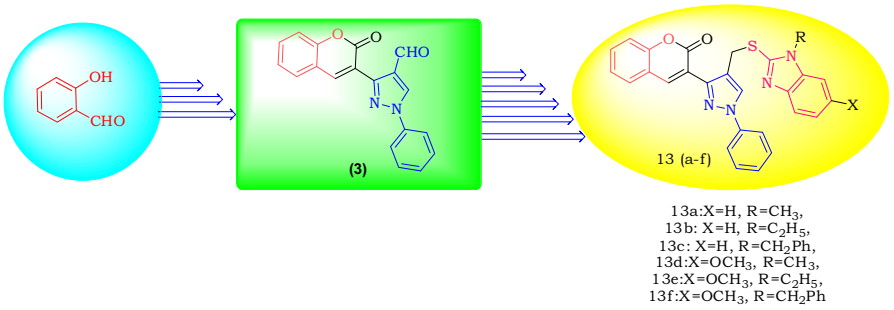
Abstract Considering benzimidazole as a privileged structure for developing probes of impressive pharmacological potentials, some new coumarin and pyrazole conjugates of benzimidazoles were synthesized with a sulphur linkage. Thus, 3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3**) was prepared starting from simple salicylaldehyde which has been used as an important synthon and incorporated in a series of structural manipulations to obtain various of pharmacophoric motif conjugates **9(a–b)** and **13(a–f)**, in fair yields. We have developed facile and stepwise methods for the synthesis of all these compounds in various approaches, which also involves sub-sequences. All synthesized compounds were well characterized by IR, ^{1}HNMR, ^{13}CNMR and mass spectra data.

Graphical Abstract



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Introduction

The class of coumarin compounds exhibit diversified biological activity, which have been recently reviewed by us [1]. Apart from these, other therapeutic properties of coumarin include histone deacetylase inhibition activity [2], free-radical scavenging activity [3] and immunomodulatory activity [4]. Beside these properties coumarin and its derivatives were found to show a variety of photophysical properties [5, 6].

Nitrogen-containing heterocycles are significant and play vital role in chemistry and biology. Pyrazoles are five-membered heterocyclic compounds with 1,2 diaza groups present in natural and synthetic heterocyclic compounds. Generally, pyrazoles are rarely found in nature due to difficulty in the formation of N–N bonds by living organisms [7]. Some drugs with a pyrazole nucleus include rimonabant, which is used in the treatment of obesity, fomepizole, which acts as an alcohol dehydrogenase, celecoxib, which exhibits anti-inflammatory activity. Various other pharmacological activities of pyrazole includes analgesic [8], antioxidant [9], anti-inflammatory [10], antimicrobial [11], anti-cancer [12], anticonvulsant [13], fungistatic [14]. Also, pyrazoles have exhibited diverse properties such as insecticidal [15], dyes [16], and fluorescence [17].

Benzimidazoles are also very important therapeutic agents in pharmaceutical chemistry where they exhibit various biological properties such as antihypertensive [18] (candesartan, talemisartan), antihelmentics [19, 20] (albendazole, mebendazole), antiviral [21], and anticancer [22]. Other applications of benzimidazoles include their use as organic ligands [23], fluorescent whitening dyes [24], functional materials [25], various photophysical properties [26], and photoelectric properties [27]. The most prominent activity of benzimidazoles is as proton pump inhibitors when linked with a sulphur atom, which is generally known as a prazole class [28] (Fig. 1).

Proton pump inhibitors are mainly used to treat symptoms of gastro-esophageal reflux disease and gastritis. They are also used to treat peptic ulcers (duodenal and gastric) and drug-induced ulcers, such as those associated with non-steroidal anti-inflammatory drugs, and to promote healing of erosive esophagitis, which can lead to scarring and narrowing of the esophagus (stricture), or to Barrett's esophagus, which is a risk factor for esophageal cancer [29].

In the design of new drugs, the concept of molecular hybridization is an attractive strategy [30]. The literature reports showed enhanced therapeutic activity when two pharmacophoric moieties of different bioactive substances produce a new hybrid compound compared to the individual components. Liu et al. [31] reported the anthelmintic activity of coumarin-benzimidazole hybrid derivatives. Arora et al. [32] reported the combined effect of hybrid scaffolds of coumarin-benzimidazoles with antioxidant and anti-inflammatory activities. The combined pharmacological effect of coumarin with a pyrazole ring as a potent antioxidant and antihyperglycemic agents has been described by Kenchappa et al. [33]. Synthesis, as well as antioxidant and anticancer activity of some new coumarin derivatives linked with pyrazole moiety has

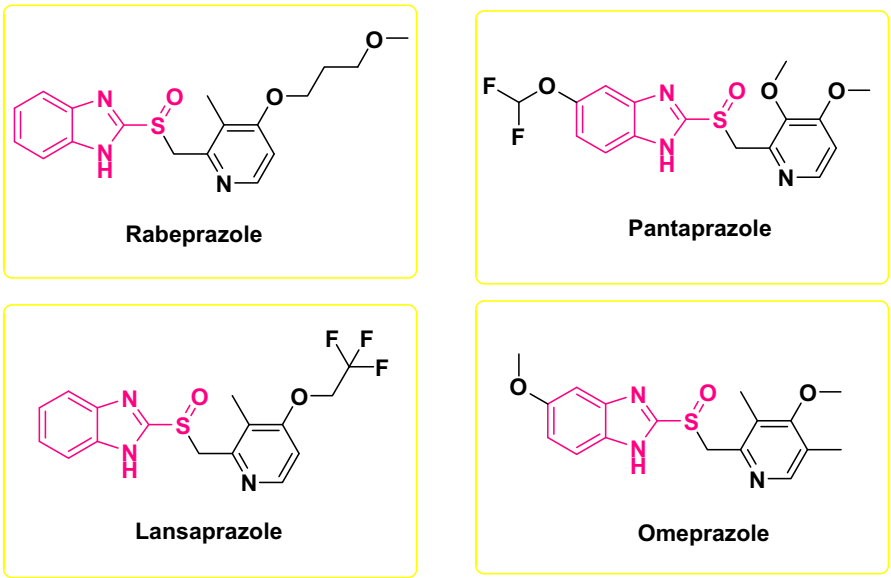


Fig. 1 Commercially available proton pump inhibitors

been reported by Khaled et al. [34]. Galal et al. [35] reported the synthesis and biological activity evaluation of novel pyrazole-benzimidazole conjugates as checkpoint kinase 2 (Chk2) inhibitors. Mahesh et al. [36] described the synthesis and antioxidant activity of some new *N*-alkylated pyrazole-containing benzimidazoles.

So, based on the mentioned literature precedence and in continuation of earlier work [37–40], it was considered worthwhile to prepare compounds bearing coumarin, pyrazole and benzimidazoles in a single framework with a sulphur linkage, which may act as potential anti-ulcer agents.

Experimental

General

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification. All the solvents were freshly dried and distilled before use. Melting points were measured in a hot sulphuric acid bath and are uncorrected. ^{1}HNMR and ^{13}CNMR spectra were acquired with a Bruker Avance DRX-400 instrument at 400 MHz in DMSO-*d*6 at room temperature. FT-IR spectra were recorded on a Perkin Elmer spectrometer. The development of the reactions and purity of the products were monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel aluminium sheets, visualized by UV light or iodine. All the synthesized compounds were dried under hot air oven.

General procedure for the preparation of 2 from 1 A mixture of **1** (5 mmol) and phenylhydrazine (5 mmol) and acetic acid (10 mL) was stirred at room temperature

for 10 min. Then, the mixture was poured into ice-cold water (30 mL). The separated solid was filtered, washed with aqueous acetic acid (1:1, 2 × 5 mL) and dried. The crude product was recrystallized from a suitable solvent to obtain pure **2**.

Yield = 1.29 g (93%); mp 186-188 °C; IR (KBr): 1717 cm^{-1} (strong, sharp, –CO of coumarin ring), 3380–3430 cm^{-1} (broad, medium, –NH group); ^{1}H-NMR (400 MHz, DMSO-d_6/TMS): δ 2.22 (s, 3H, –C**H**$_3$), 6.77–7.85 (m, 8H, Ar–**H**), 8.20 (s, 1H, Ar–**H**), 9.42 (s, 1H, –NH); HRMS calculated for $C_{17}H_{14}N_2O_2$ $[M+H]^+$: 279.1133, Found: 279.1131.

General procedure for synthesis of 3 from 2 Sample **2** (5 mM) was added to a cold solution of DMF (25 mL) and $POCl_3$ (5 mL) at 0–5 °C. The reaction mixture was stirred at RT for 2–3 h. After the completion of reaction, as indicated by the disappearance of starting materials on TLC, the mixture was poured into ice-cold water (30 mL). The separated solid was filtered, washed with water (2 × 15 mL) and dried to obtain crude **3.** Recrystallization from a suitable solvent gave pure **3.**

IR (KBr): 1716 cm^{-1} (strong, sharp, –CO of aldehyde group), 1731 cm^{-1} (strong, sharp, –CO of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 7.36–8.10 (m, 8H, Ar–**H**), 8.46 (s, 1H, Ar–**H**), 9.27 (s, 1H, Ar–**H**), 9.97 (s, 1H, –C**H**O); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 114.8, 119.3, 119.9, 120.1, 123.4, 124.8, 127.8, 129.7, 132.6, 138.5, 142.8, 143.3, 146.4, 147.3, 159.0, 185.4; HRMS Calculated for $C_{19}H_{12}N_2O_3$ $[M+H]^+$: 317.0926, Found: 317.0933.

General procedure for the synthesis of 4 from 2 A mixture of **2** (5 mM), DMF-DMA (5 mM) and dioxane (20 mL) was heated at 100 °C for about 4 h. The reaction was monitored by TLC analysis. After the completion of reaction, the mixture was cooled to RT and poured into ice-cold water (30 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from a suitable solvent to yield pure **4**.

IR (KBr): 1736 cm^{-1} (strong, sharp, –CO of coumarin ring); ^{1}H-NMR (400 MHz, DMSO-d_6/TMS): δ 6.76 (d, J = 8 Hz, 1H, Ar–**H**), 7.28–7.72 (m, 9H, Ar–**H**), 7.86 (d, 1H, Ar–**H**), 8.20 (s, 1H, Ar–H); ^{13}C-NMR (100 MHz, DMSO-d_6/TMS): 114.8, 119.3, 119.9, 120.1, 123.4, 124.8, 127.8, 129.7, 132.6, 138.5, 142.8, 143.3, 146.4, 147.3, 159.0; HRMS calculated for $C_{18}H_{12}N_2O_2$ $[M+H]^+$: 289.0977, Found: 289.0966.

General method for the synthesis of 3 from 4 Sample **4** (5 mM) to a cold mixture of DMF (25 mL) and $POCl_3$ (5 mL) in an ice-bath at 0–5 °C. Then the reaction mixture temperature was allowed to rise to RT and further to 55–60 °C in an oil-bath and maintained for 4–6 h. The completion of the reaction was checked by TLC for the disappearance of starting material. After completion of the reaction, the mixture was poured into ice-cold water (30 mL). The separated solid was filtered, washed with water (2 × 20 mL) and dried to obtain a crude product. The latter was recrystallized from a suitable solvent to obtain pure **3.**

Preparation of 5 from 3 A mixture of **3** (5 mM), $NaBH_4$ (5 mM) and THF (25 mL) was stirred at RT for a period of 2 h. After the completion of reaction as indicated by disappearance of **3** on TLC, the mixture was poured into ice-cold water (40 mL). The separated solid was filtered, washed with water (2 × 20 mL) and dried to obtain crude product, which was recrystallized from methanol to get pure **5**.

IR (KBr): 1725 cm^{-1} (strong, sharp, –CO of coumarin ring), 3310–3335 (broad, medium, –OH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 4.51 (d, J = 5.6 Hz, 2H, –C**H**$_2$), 4.95 (t, J = 8.2 Hz, 1H, O**H**), 7.31–7.89 (m, 9H, Ar–**H**), 8.33 (s, 1H, Ar–**H**), 8.47 (s, 1H, Ar–**H**); Ms: *m/z* 319 [M.$^+$+1].

Preparation of 6 from 5 A mixture of **5** (5 mM), $SOCl_2$ (5 mL) in benzene was refluxed on a water bath for about 1 h. Progress of the reaction was monitored on TLC. After completion of reaction as indicated by TLC, the mixture was cooled to RT and was distilled off, washed with hexane (2 × 20 mL) and dried to obtain crude **6**. The latter was recrystallized from chloroform to obtain pure **6**.

IR (KBr): 1718 cm^{-1} (strong, sharp, –CO of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 4.50 (s, 2H, –C**H**$_2$), 7.31–7.85 (m, 9H, Ar–**H**), 8.29 (s, 1H, Ar–**H**), 8.41 (s, 1H, Ar–**H**); Ms: *m/z* 337 [M.$^+$+ 1].

Preparation of 7 from 6 *O*-ethyl carbonodithioate (5 mM) was added to a solution of **6** (5 mM) in ethanol (20 mL), and the resulting mixture was refluxed in a water bath for about 2 h. The reaction was monitored by TLC analysis. After the completion of reaction, the mixture was cooled to RT and poured into ice-cold water (30 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from ethanol to yield pure **7**.

IR (KBr): 1238 cm^{-1} (strong, sharp, –C=S of thiocarbonyl ring), 1726 cm^{-1} (strong, sharp, –CO of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 1.18 (t, J = 7.6 Hz, 3H, –C**H**$_3$), 4.0 (s, 2H, –C**H**$_2$), 4.60 (q, 2H, OC**H**$_2$), 6.75–7.81 (m, 10H, Ar–**H**), 8.19 (s, 1H, Ar–**H**), 8.41 (s, 1H, Ar–**H**); Ms: *m/z* 423 [M.$^+$+1].

General method for the preparation of 9 from 7 by reaction with 8 A mixture of **7** (5 mM), **8** (5 mM) in ethanol was refluxed for a period of 3–4 h. After the completion of reaction, the mixture was cooled to RT and poured into ice-cold water. The separated solid was filtered and washed with water (2 × 30 mL) to obtain crude **9**. The crude product was recrystallized from suitable solvent to give pure **9**.

3-(4-(((1H-benzo[d]imidazol-2-yl)thio)methyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one 9a

IR (KBr): 1723 cm^{-1} (strong, sharp, –COof coumarin ring), 3405–3430 (broad, medium, –NH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 4.58 (s, 2H, –C**H**$_2$), 6.96–7.83 (m, 13H, Ar–**H**), 8.26 (s, 1H, Ar–**H**), 8.61 (s, 1H, Ar–**H**), 12.50 (s, 1H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 24.8, 109.4, 115.3, 116.8, 117.5, 120.8, 123.1, 127.0, 127.2, 128.0, 128.8, 129.1, 129.4, 129.5, 130.7, 135.2, 136.7, 139.2, 142.5, 144.4, 146.9, 155.0, 160.4; HRMS Calculated for $C_{26}H_{18}N_4O_2S$ $[M+H]^+$: 451.12587, Found: 451.12556.

3-(4-(((6-Methoxy-1H-benzo[d]imidazol-2-yl)thio)methyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one 9b

IR (KBr): 1714 cm^{-1} (strong, sharp, –COof coumarin ring), 3400–3434 (broad, medium, –NH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.66 (s, 2H, –C**H**$_2$), 4.52 (s, 3H, OCH_3), 6.57–7.84 (m, 12H, Ar–**H**), 8.21 (s, 1H, Ar–H), 8.60 (s, 1H, Ar–

H); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 26.1, 55.0, 109.8, 115.2, 116.3, 117.4, 121.2, 123.4, 127.2, 127.5, 128.1, 129.1, 129.6, 129.9, 130.1, 130.9, 135.3, 137.1, 139.4, 141.9, 144.2, 146.8, 155.1, 158.4; Ms: *m/z* 481 [M.$^+$+1].

General method for the preparation of 10 from 6 A mixture of **6** (5 mM), thiourea (5 mM) in ethanol was refluxed for 3 h in a water bath. After completion of the reaction as indicated by the disappearance of starting materials on TLC, the mixture was cooled to RT and poured into ice-cold water, and the separated solid was filtered to get crude **10**. The crude product was then recrystallized from acetonitrile to obtain pure **10**.

IR (KBr): 1724 cm^{-1} (strong, sharp, –COof coumarin ring), 2880–2930 (broad, medium, –SH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 4.52 (s, 2H, –C**H**$_2$), 7.32–7.96 (m, 9H, Ar–**H**), 8.34 (s, 1H, Ar–**H**), 8.46 (s, 1H, Ar–**H**); Ms: *m/z* 335 [M.$^+$+1].

General method for the preparation of 9 from 10 by reaction with 11 A mixture of **10** (5 mM), **11** (5 mM) in DMF (20 mL) containing K_2CO_3 (2 mM) and TBAB (2 mM) was stirred at RT for a period of 3–5 h. The reaction was monitored by TLC analysis. After the completion of reaction, the mixture was poured into ice-cold water (30 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from a suitable solvent to yield pure **9**.

General method for the preparation of 9 from 6 by reaction with 12 Sample **11** (5 mM) was added to a mixture of **6** (5 mM) in DMF (20 mL) containing K_2CO_3 (2 mM) and TBAB (2 mM), and the mixture stirred at RT for 3–5 h. The reaction was monitored by checking TLC. After completion of reaction, the mixture was poured into ice-cold water (30 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from a suitable solvent to yield pure **9**.

General method for the preparation of 13 from 9 A mixture of **9** (5 mM) in DMF (20 mL) containing K_2CO_3 (2 mM) and TBAB (2 mM), alkylating agent (DMS or DES or benzyl chloride) (5 mM) was added and stirred at RT for 3–5 h. The reaction was monitored by checking TLC. After completion of reaction, the mixture was cooled to RT and poured into ice-cold water (30 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from a suitable solvent to yield pure **13**.

3-(4-(((1-Methyl-1H-benzo[d]imidazol-2-yl)thio)methyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one (13a)

IR (KBr): 1718 cm^{-1} (strong, sharp, –COof coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.58 (s, 3H, –C**H**$_3$), 4.64 (s, 2H, –C**H**$_2$), 6.95–7.89 (m, 13H, Ar–**H**), 8.27 (s, 1H, Ar–**H**), 8.65 (s, 1H, Ar–**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 26.9, 30.3, 109.8, 116.5, 117.9, 118.9, 119.4, 119.8, 121.2, 121.8, 122.1, 125.2, 127.2, 129.3, 129.5, 130.1, 132.7, 137.0, 139.5, 143.0, 146.7, 151.2, 153.8, 159.8; Ms: *m/z* 465 [M.$^+$+1].

3-(4-(((1-Ethyl-1H-benzo[d]imidazol-2-yl)thio)methyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one (13b)

IR (KBr): 1718 cm^{-1} (strong, sharp, –COof coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 1.08 (t, J = 7.6 Hz, 3H, –C**H**$_3$), 3.94 (q, 3H, –C**H**$_2$), 4.62 (s, 2H, –C**H**$_2$), 6.90–7.87 (m, 13H, Ar–**H**), 8.22 (s, 1H, Ar–**H**), 8.60 (s, 1H, Ar–**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 14.2, 27.2, 30.8, 108.7, 116.7, 117.3, 117.9, 120.1, 121.2, 121.7, 121.9, 122.3, 125.6, 128.0, 129.7, 130.1, 130.5, 133.0, 137.2, 140.1, 142.9, 146.6, 150.9, 153.9, 160.4; Ms: *m/z* 478 [$M.^{+}$+1].

3-(4-(((1-Benzyl-1H-benzo[d]imidazol-2-yl)thio)methyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one (13c)

IR (KBr): 1727 cm^{-1} (strong, sharp, –COof coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.13 (s, 2H, –C**H**$_2$), 4.61 (s, 2H, –C**H**$_2$), 6.85–7.89 (m, 19H, Ar–**H**), 8.29 (s, 1H, Ar–**H**), 8.68 (s, 1H, Ar–**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 25.9, 49.0, 110.0, 115.2, 116.1, 118.0, 119.9, 120.9, 121.9, 123.0, 125.4, 125.7, 126.2, 127.6, 127.9, 128.3, 128.6, 129.3, 129.5, 134.2, 137.3, 138.9, 139.7, 140.0, 146.1, 152.6, 153.0, 161.9; Ms: *m/z* 541 [$M.^{+}$+1].

3-(4-(((6-Methoxy-1-methyl-1H-benzo[d]imidazol-2-yl)thio)methyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one (13d)

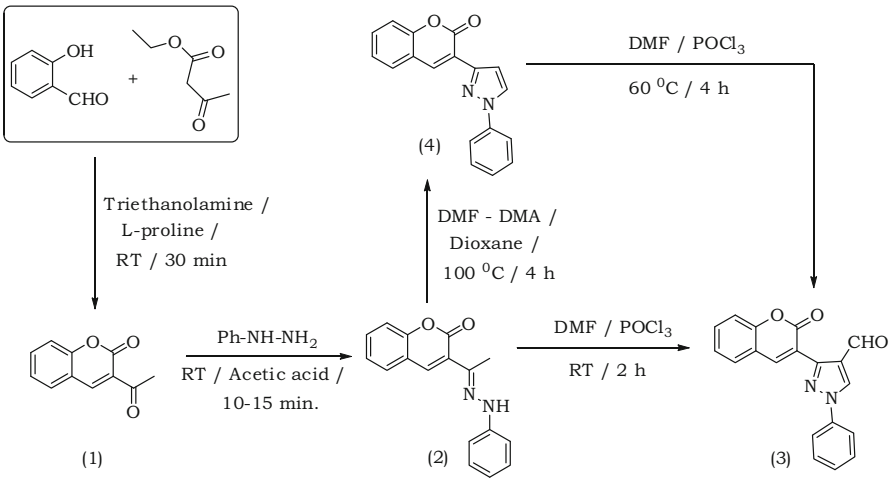
IR (KBr): 1723 cm^{-1} (strong, sharp, –COof coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.13 (s, 2H, –C**H**$_2$), 4.49 (s, 2H, –C**H**$_2$), 4.73 (s, 3H, –OC**H**$_3$), 6.98–7.83 (m, 12H, Ar–**H**), 8.32 (s, 1H, Ar–**H**), 8.65 (s, 1H, Ar–**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 27.2, 31.0, 55.8, 110.1, 115.8, 117.7, 119.1, 119.5, 119.9, 121.3, 121.9, 122.3, 124.9, 127.1, 129.0, 129.7, 130.3, 131.9, 137.3, 139.6, 143.2, 146.8, 151.5, 153.8, 158.2; Ms: *m/z* 495 [$M.^{+}$+1].

3-(4-(((1-Ethyl-6-methoxy-1H-benzo[d]imidazol-2-yl)thio)methyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one (13e)

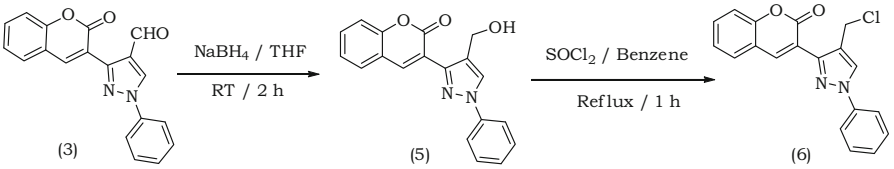
IR (KBr): 1726 cm^{-1} (strong, sharp, –COof coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 1.08 (t, J = 6.4 Hz, 3H, –C**H**$_3$), 3.94 (q, 3H, –C**H**$_2$), 4.46 (s, 2H, –C**H**$_2$), 4.71 (s, 2H, –OC**H**$_3$), 6.92–7.96 (m, 12H, Ar–**H**), 8.23 (s, 1H, Ar–**H**), 8.48 (s, 1H, Ar–**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 14.5, 27.7, 30.9, 55.4, 109.1, 116.4, 117.6, 117.9, 120.2, 121.4, 121.8, 122.9, 123.2, 125.8, 128.1, 129.6, 130.2, 130.8, 133.2, 137.3, 141.5, 143.7, 146.5, 151.2, 154.4, 158.4; Ms: *m/z* 509 [$M.^{+}$+1].

3-(4-(((1-Benzyl-6-methoxy-1H-benzo[d]imidazol-2-yl)thio)methyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one (13f)

IR (KBr): 1718 cm^{-1} (strong, sharp, –COof coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.13 (s, 2H, –C**H**$_2$), 4.43 (s, 2H, –C**H**$_2$), 4.69 (s, 3H, OC**H**$_3$), 6.81–7.93 (m, 18H, Ar–**H**), 8.31 (s, 1H, Ar–**H**), 8.64 (s, 1H, Ar–**H**); ^{13}C NMR



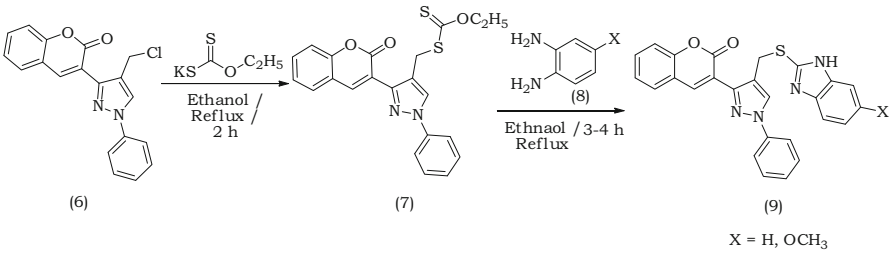
Scheme 1 Synthesis of 3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3**) in two different routes



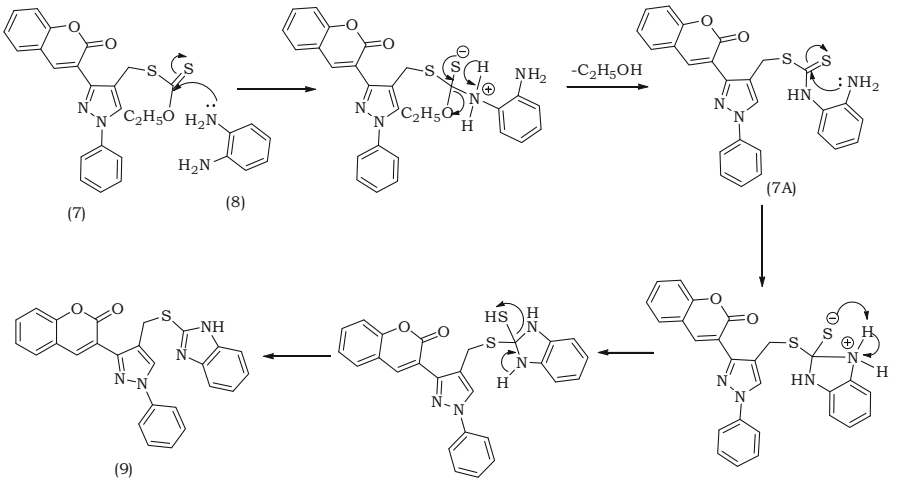
Scheme 2 Synthesis of 3-(4-(chloromethyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one (**6**)

(100 MHz, DMSO-d_6/TMS): 27.1, 49.1, 56.3, 109.6, 114.9, 115.8, 118.1, 120.2, 120.8, 122.0, 123.1, 124.9, 125.2, 126.4, 127.5, 128.0, 128.4, 128.8, 129.4, 129.8, 133.8, 137.1, 137.8, 139.6, 140.2, 145.6, 151.7, 153.2, 159.8; Ms: *m/z* 571 [$M.^{+}$+1].

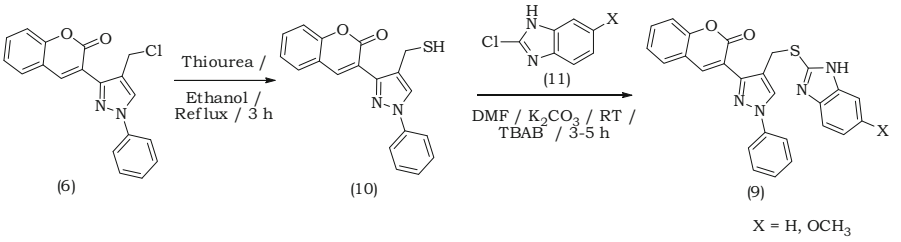
*General method for the preparation of **13** from **10** by reaction with **14*** A mixture of **10** (5 mM), **14** (5 mM) in DMF (20 mL) containing K_2CO_3 (2 mM) and TBAB (2 mM) was stirred at RT for a period of 3–5 h. The reaction was monitored by TLC analysis. After the completion of reaction, the mixture was poured into ice-cold



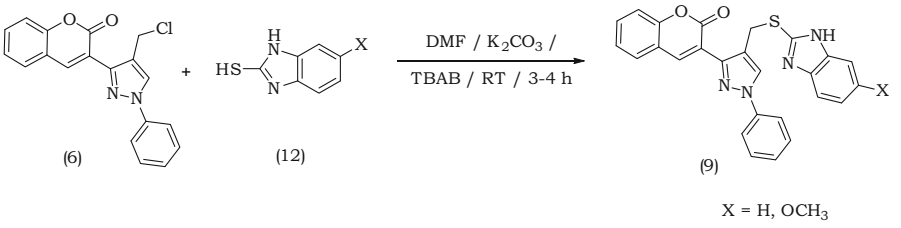
Scheme 3 Synthesis of substituted 3-(4-((1*H*-benzo[d]imidazol-2-ylthio)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-ones (**9**)



Scheme 4 Plausible mechanism for the formation of **9** from **7**



Scheme 5 Alternative synthesis of compounds **9** from **6**

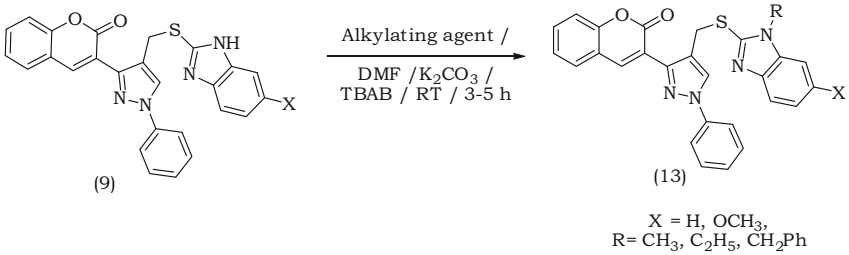


Scheme 6 Another alternative approach or the synthesis of 9 from 6

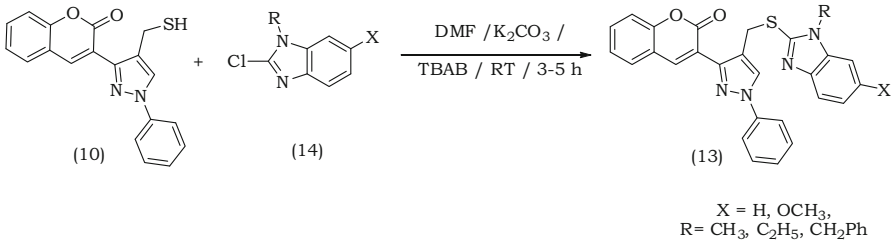
water (30 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from ethanol to yield pure **13**.

Table 1 Reaction conditions, yield and physical data of compounds **5, 6, 7, 9 (a–b)** and **10**

S. no.	Substrate-I	Substrate-II	Reaction condition	Product obtained	Yield (%)	Melting point (°C)
1	**3**	$NaBH_4$	RT/2 h	**5**	76	143–145
2	**5**	$SOCl_2$	Reflux/1 h	**6**	66	202–204
3	**6**	$KSC(S)OC_2H_5$	Reflux/2 h	**7**	61	88–90
4	**7**	**8a**: X=H	Reflux/3 h	**9a**: X=H	54	215–217
5	**7**	**8b**: X=OCH_3	Reflux/4 h	**9b**: X=OCH_3	50	234–236
6	**6**	Thiourea	Reflux/3 h	**10**	63	108–110
7	**10**	**11a**: X=H	RT/3 h	**9a**: X=H	78	215–217
8	**10**	**11b**: X=OCH_3	RT/5 h	**9b**: X=OCH_3	72	234–236
9	**6**	**12a**: X=H	RT/3 h	**9a**: X=H	77	215–217
10	**6**	**12b**: X=OCH_3	RT/4 h	**9b**: X=OCH_3	70	234–236



Scheme 7 Alkylation of **9** to obtain the corresponding compounds **13**



Scheme 8 Alternative synthesis of **13** from **10**

Results and discussion

Commercially available salicylaldehyde was treated with ethyl acetoacetate in triethanolamine containing a catalytic amount of *L*-proline at room temperature for 30 min to yield 3-acetyl-2*H*-chromen-2-one (**1**). This on reaction with phenylhydrazine in acetic acid at RT for 10-15 min resulted in the formation of (3-(1-(2-phenylhydrazono)ethyl)-2*H*-chromen-2-ones (**2**). Vilsmeier–Haack reaction of **2** at room temperature for 2 h gave the compound 3-(2-oxo-2*H*-chromen-3-yl)-1-

phenyl-1*H*-pyrazole-4-carbaldehydes (**3**). In another approach, **2** in treatment with DMF-DMA in dioxane at 100 °C for 4 h, resulted in the formation of 3-(1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one (**4**), which on Vilsmeier–Haack reaction gave **3**. This product was compared with the products prepared in earlier routes and were found to be identical in all respects with mp, mmp and co-TLC (Scheme 1).

Reduction of **3** with sodium borohydride in tetrahydrofuran (THF) at RT for 2 h resulted in the formation of 3-(4-(hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one (**5**). The latter was chlorinated with thionyl chloride in refluxing benzene for 1 h to afford 3-(4-(chloromethyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one (**6**) (Scheme 2).

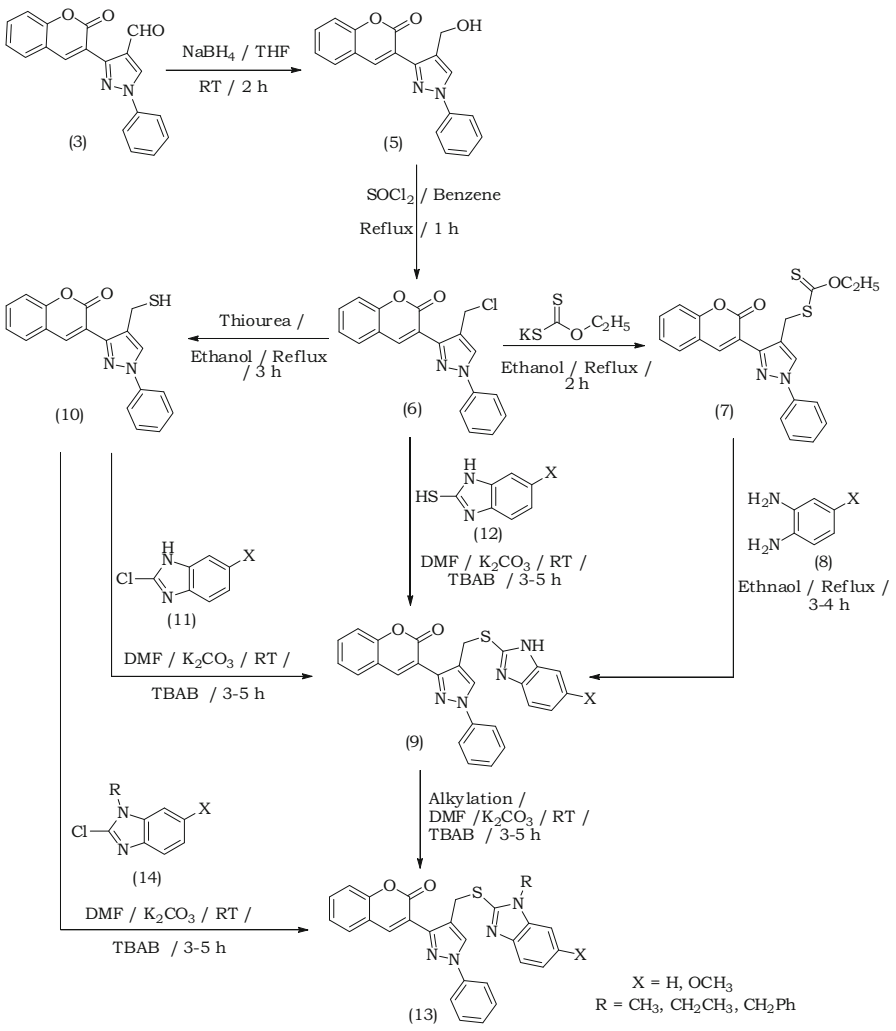
6 was treated with potassium *O*-ethyl carbonodithioate in ethanol under refluxing conditions for 2 h resulting in the formation of *O*-ethyl S-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methyl) carbonodithioate (**7**). *O*-ethyl carbonodithioate itself was obtained by the reaction of freshly prepared ethanolic KOH solution with CS_2 at 5–10 °C for 2 h. **7** when refluxed with o-phenylenediamine (**8**) in ethanol for 3–4 h gave 3-(4-(((1*H*-benzo[d]imidazol-2-yl)thio)-methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-ones (**9**), which were identified based on their spectral data (Scheme 3). (Please see the "Experimental" section.)

A plausible mechanism has been proposed for the formation of **9** from 7, and it seems to be as follows. The nucleophilic addition reaction of *o*-phenylenediamine (**8**) with the thiocarbonyl group of **7** initiates the process, followed by concomitant loss of ethanol to form **7A**. **7A** with another amine group again undergoes nucleophilic addition reaction with the thiocarbonyl group, subsequent cyclization to give **9** (Scheme 4).

Alternatively, **9** could also be prepared by the reaction of **6** with thiourea under refluxing ethanol for 3 h to yield 3-(4-(mercaptomethyl)-1-phenyl-1*H*-pyrazol-3-

Table 2 Reaction conditions, yield and physical data of compounds **13(a–f)** prepared from **9(a–b)** and **10**

S. no.	Substrate-I	Substrate-II	Reaction condition	Product obtained	Yield (%)	Melting point (°C)
1	**9a**: X=H	DMS	RT/3 h	**13a**: X=H, R=CH_3	76	184–186
2	**9a**: X=H	DES	RT/4 h	**13b**: X=H, R=C_2H_5	69	153–155
3	**9a**: X=H	$PhCH_2Cl$	RT/3½ h	**13c**: X=H, R=CH_2Ph	71	210–212
4	**9b**: X=OCH_3	DMS	RT/4 h	**13d**: X=OCH_3, R=CH_3	74	194–196
5	**9b**: X=OCH_3	DES	RT/5 h	**13e**: X=OCH_3, R=C_2H_5	70	205–207
6	**9b**: X=OCH_3	$PhCH_2Cl$	RT/4½ h	**13f**: X=OCH_3, R=CH_2Ph	75	233–235
7	**10**	**14a**: X=H, R=CH_3	RT/3½ h	**13a**: X=H, R=CH_3	71	184–186
8	**10**	**14b**: X=H, R=C_2H_5	RT/4 h	**13b**: X=H, R=C_2H_5	73	153–155
9	**10**	**14c**: X=H, R=CH_2Ph	RT/4½ h	**13c**: X=H, R=CH_2Ph	76	210–212
10	**10**	**14d**: X=OCH_3, R=CH_3	RT/5 h	**13d**: X=OCH_3, R=CH_3	69	194–196
11	**10**	**14e**: X=OCH_3, R=C_2H_5	RT/3½ h	**13e**: X=OCH_3, R=C_2H_5	72	205–207
12	**10**	**14f**: X=OCH_3, R=CH_2Ph	RT/4 h	**13f**: X=OCH_3, R=CH_2Ph	73	233–235



Scheme 9 Synthesis of title compounds (**13**) in various approaches

yl)-2*H*-chromen-2-one (**10**) followed by its reaction with 2-chlorobenzimidazoles (**11**) in DMF containing K_2CO_3 as base and tetra-n-butylammonium bromide (TBAB) as a phase transfer catalyst at RT for a period of 3–5 h (Scheme 5).

Also, the reaction of **6** with 2-thiobenzimidazole (**12**) in DMF containing K_2CO_3 and TBAB at RT for 3–4 h gave a product which was found to be identical with **9** in all respects, such as mp, mmp & co-TLC (Scheme 6). Here, the alkylation preferably occurs on SH group rather than NH, because the nucleophilicity of sulphur is more than that of nitrogen atom (Table 1).

9 on further alkylation with alkylating agents independently, with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride in DMF using K_2CO_3 as a base and TBAB as phase transfer catalyst at RT for 3–5 h gave the

corresponding *N*-alkylated products (**13**) (Scheme 7). The structures of all these products have been established on the basis of their spectral data. (Please see the experimental Section).

Alternatively, **13** could also be prepared by the reaction of **10** with *N*-alkylated-2-chloro-1*H*-benzo[d]imidazoles (**14**) in DMF containing TBAB, K_2CO_3 at RT for 3–5 h (Scheme 8). **13** were itself prepared by the alkylation of 2-chlorobenzimidazole (**11**) with each of the alkylating agent independently. Thus, the products obtained in this method were found to be identical with the ones obtained in the earlier sequence i.e., **9**→**13** (Table 2).

All the mentioned reactions are very nicely depicted in the summarizing Scheme 9.

Conclusion

In the present work, 3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (3) was prepared as a precursor in good yield in two different approaches. The reactivity of this compound was exploited in a series of synthetic transformations encompassing various condensation approaches for the synthesis of new coumarin-pyrazole-benzimidazole–pharmacophoric–motif probes with a sulphur linker. We have developed simple, stepwise and efficient protocols for the synthesis of title compounds in various approaches with sub-sequences. All these compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR and mass spectral data.

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