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Synthesis, biological evaluation and docking analysis of 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones as potential cyclooxygenase-2 (COX-2) inhibitors

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ABSTRACT

As a part of our continued efforts to discover new COX inhibitors, a series of 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones were synthesized and evaluated for in vitro COX inhibitory potential. Within this series, seven compounds (**3a–d**, **3h**, **3k** and **3q**) were identified as potential and selective COX-2 inhibitors (COX-2 IC_{50}'s in 1.79–4.35 μM range; COX-2 selectivity index (SI) = 6.8–16.7 range). Compound **3b** emerged as most potent (COX-2 IC_{50} = 1.79 μM; COX-1 IC_{50} >30 μM) and selective COX-2 inhibitor (SI >16.7). Further, compound **3b** displayed superior anti-inflammatory activity (59.86% inhibition of edema at 5 h) in comparison to celecoxib (51.44% inhibition of edema at 5 h) in carrageenan-induced rat paw edema assay. Structure–activity relationship studies suggested that *N*-phenyl ring substituted with *p*-CF_3 substituent (**3b**, **3k** and **3q**) leads to more selective inhibition of COX-2. To corroborate obtained experimental biological data, molecular docking study was carried out which revealed that compound **3b** showed stronger binding interaction with COX-2 as compared to COX-1.

Cyclooxygenase (COX) or prostaglandin endoperoxide synthase (PGHS), catalyzes the conversion of arachidonic acid to inflammatory mediators such as prostaglandins (PGs), prostacyclins and thromboxanes. COX exists in mainly two isoforms: COX-1 and COX-2.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs), widely used for relief of fever, pain and inflammation, act by inhibiting COX catalyzed biosynthesis of inflammatory mediators.[1,2] However, the therapeutic use of classical NSAIDs is associated with well-known side effects at the gastrointestinal level (mucosal damage, bleeding)[3] and, less frequently, at the renal level.[4] Two decades after the discovery of COX isoforms, it was recognized that selective inhibition of COX-2 might be endowed with improved anti-inflammatory properties and reduced gastrointestinal toxicity profiles than classical NSAIDs. Overall, these selective COX-2 inhibitors (coxibs) have fulfilled the hope of possessing reduced risk in gastrointestinal events, but unfortunately cardiovascular concerns regarding the use of these agents have emerged that led to the withdrawal of rofecoxib (Vioxx) and valdecoxib (Bextra) from the market in 2004 and 2005, respectively.[5] Ongoing safety concerns pertaining to the use of non-selective NSAIDs have spurred development of coxibs with improved safety profile.

Coumarin and its derivatives have engrossed substantial attention from organic and medicinal chemists over the last few years as they exhibit multiple biological activities[6–9] especially anti-inflammatory and antioxidant activities.[10,11] Naturally occurring coumarins like esculetin, fraxetin, daphnetin and other related coumarin derivatives have gained recognition as inhibitors of not only lipoxygenase and cyclooxygenase enzymes, but also of the neutrophil-dependent superoxide anion generation.[9] Pyrazole is a nitrogenous five-membered heterocyclic component of the drugs and has been well explored as anti-inflammatory,[12,13] antiviral,[14] antimalarial,[15] HIV-reverse transcriptase inhibitors,[16] and antitumor agent.[17] A perusal of literature has presented pyrazole derivatives as selective COX-2 and COX-1 inhibitors and their clinical applications as NSAIDs. Among the highly marketed COX-2 inhibitors, celecoxib that comprises pyrazole nucleus is the only COX-2 inhibitor available in the USA. Some other examples of pyrazole derivatives as NSAIDs are mefobutazone, ramifenazone, famprofazone.[18,19] Therefore, both coumarins and pyrazoles possess worthy and imperative bioactivities, which render them useful lead molecules for development of COX inhibitors. Moreover, many reports have witnessed excellent anti-inflammatory activity of coumarin derivatives containing pyrazole as heterocyclic ring.[20–22] In view of these observations and in continuation of our research programme to discover new COX inhibitors,[23,24] we report herein

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the synthesis and biological evaluation of new 3-methyl-1-phenyl-chromeno[4,3-*c*]pyrazol-4(1*H*)-ones as potential COX-2 inhibitors.

The methodology used to synthesize the target compounds (**3a–s**) is outlined in Scheme 1. In general, classical Knoevenagel condensation of commercially available salicylaldehydes and ethyl acetoacetate was followed to prepare 3-acetylcoumarins (**1a–d**). They were then treated with various substituted phenylhydrazines to prepare 3-[1-(phenylhydrazono)-ethyl]-chromen-2-ones (**2a–s**), followed by our recently reported strategy of potassium carbonate mediated cyclization[25] of **2** to furnish final compounds (**3a–s**) in excellent yields (Table 1).

All the prepared chromenopyrazoles (**3a–s**) were evaluated[23] for their ability to inhibit COX-1 and COX-2 using an ovine COX-1/COX-2 assay kit (Catalog No. 560101, Cayman Chemicals Inc., Ann Arbor, MI, USA) and results obtained are presented in Table 2. Of the tested compounds, seven compounds (**3a–d**, **3h**, **3k** and **3q**) displayed selective inhibition of COX-2. The study was further extended to determine IC_{50} values of these compounds. Celecoxib exhibited IC_{50} value of >30 and 0.15 μM against COX-1 and COX-2, respectively, indicating that celecoxib is selective COX-2 inhibitor. Compound **3b** demonstrated highest COX-2 inhibition (IC_{50} = 1.79 μM), followed by **3h** (IC_{50} = 2.36 μM) and **3c** (IC_{50} = 2.43 μM). From structure activity relationship (SAR), it was observed that substitution of *N*-phenyl ring with electron withdrawing groups (**3b–d**, **3h**, **3k** and **3q**) increased COX-2 selectivity, whereas electron donating groups (**3f**, **3o** and **3r**) had a reverse effect (Fig. 1). Within halogens, relative profile for selective inhibition of COX-2 was found to be *p*-CF_3 (**3b**) > *p*-F (**3h**) > *p*-Cl (**3c**) > *p*-Br (**3d**). This observation highlighted the significance of CF_3 group as a pharmacophoric feature for selective COX-2 inhibition, which is also evidenced from literature.[26–28] It was also noticed that methoxy group at C-7 (**3k** and **3n**) led to dramatic decrease in COX-2 activity, whereas chloro substitution at C-8 (**3q**) had a little effect.

Seven compounds (**3a–d**, **3h**, **3k** and **3q**) that displayed potent COX-2 inhibition in vitro were further evaluated for anti-inflammatory activity in carrageenan-induced rat paw edema assay, described by Winter et al.[29] Carrageenan-induced edema is a non-specific inflammation resulting from a complex of diverse mediators. This assay has been used for investigating new anti-inflammatory agents, since it reliably predicts the anti-inflammatory efficacy of the NSAIDs.[23] Compounds were tested at a dose of 150 μmol/kg and results obtained are summarized in Table 3. Of the seven compounds, four (**3b**, **3c**, **3h** and **3q**) were found to possess potent anti-inflammatory activity with percentage inhibition of edema ranging from 49.43 to 59.86 at 5 h, while the reference drug, celecoxib at the same dose demonstrated 51.44% inhibition at 5 h. Considering the fact that carrageenan-induced paw edema assay is a biphasic event and during the second phase (between 2 h and 5 h), it detects compounds that are anti-inflammatory agents as a result of inhibition of prostaglandin amplification.[30] It was observed that all the examined compounds inhibited development of second phase of edema. This could be attributed to their ability to bind cyclooxygenase (COX), an enzyme responsible for the biosynthesis of prostaglandins.

Table 1
Compounds and their yield

Compound	R^1	R^2	Ar	Yield[a]
3a	H	H	C_6H_5	95
3b	H	H	4-CF_3-C_6H_4	90
3c	H	H	4-Cl-C_6H_4	93
3d	H	H	4-Br-C_6H_4	95
3e	H	H	2,4-$(Cl)_2$-C_6H_3	90
3f	H	H	2,5-$(CH_3)_2C_6H_3$	89
3g	H	H	2-CF_3-C_6H_4	91
3h	H	H	4-F-C_6H_4	92
3i	OCH_3	H	C_6H_5	98
3j	OCH_3	H	2-CF_3-C_6H_4	92
3k	OCH_3	H	4-CF_3-C_6H_4	96
3l	OCH_3	H	4-Cl-C_6H_4	95
3m	OCH_3	H	4-Br-C_6H_4	96
3n	OCH_3	H	4-F-C_6H_4	90
3o	OCH_3	H	2,5-$(CH_3)_2C_6H_3$	88
3p	H	Cl	C_6H_5	85
3q	H	Cl	4-CF_3-C_6H_4	88
3r	H	Cl	2,5-$(CH_3)_2C_6H_3$	82
3s	H	Br	C_6H_5	83

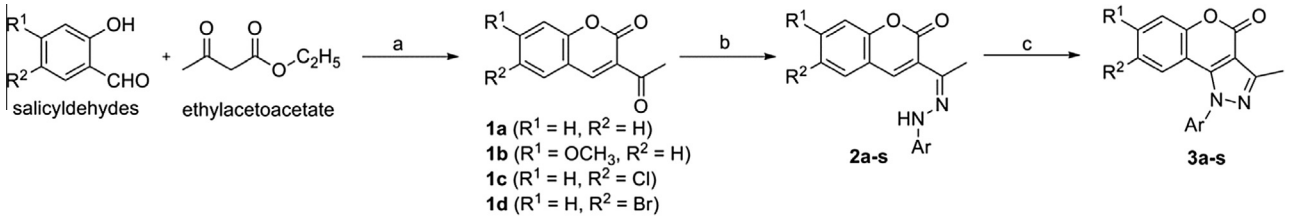
[a] Isolated yields.

Table 2
COX-1 and COX-2 enzyme inhibitory activity of chromenopyrazole derivatives

Compound	COX inhibition at 30 μM[a]		(IC_{50}, μM)		SI[b]
	COX-1	COX-2	COX-1	COX-2	
3a	48.07 ± 0.78	87.44 ± 1.29	>30	2.63	>11.4
3b	34.26 ± 0.27	94.29 ± 0.78	>30	1.79	>16.7
3c	43.74 ± 0.37	92.73 ± 1.21	>30	2.43	>12.3
3d	47.51 ± 2.11	88.57 ± 0.21	>30	3.65	>8.2
3e	30.54 ± 0.87	61.34 ± 1.78	ND	ND	ND
3f	21.33 ± 1.24	60.31 ± 0.46	ND	ND	ND
3g	34.58 ± 2.19	51.98 ± 2.10	ND	ND	ND
3h	28.28 ± 1.13	93.83 ± 0.60	>30	2.36	>12.7
3i	43.23 ± 0.48	78.34 ± 0.23	ND	ND	ND
3j	38.25 ± 0.14	53.84 ± 0.40	ND	ND	ND
3k	33.22 ± 1.09	87.76 ± 1.49	>30	4.35	>6.8
3l	34.81 ± 0.53	69.14 ± 2.43	ND	ND	ND
3m	27.3 ± 0.73	74.72 ± 1.21	ND	ND	ND
3n	34.82 ± 2.47	61.21 ± 0.98	ND	ND	ND
3o	39.5 ± 1.17	53.2 ± 1.35	ND	ND	ND
3p	43.75 ± 0.79	78.51 ± 1.08	ND	ND	ND
3q	33.17 ± 1.62	90.17 ± 0.68	>30	2.58	>11.6
3r	39.25 ± 1.45	56.5 ± 1.33	ND	ND	ND
3s	54.23 ± 0.52	65.12 ± 0.94	ND	ND	ND
Indomethacin[c]	98.23 ± 0.33	50.99 ± 0.34	0.18	ND	ND
Celecoxib[c]	13.01 ± 0.63	95.57 ± 0.48	ND	0.15	ND

ND—not determined.
[a] Values are expressed as mean ± SEM (n = 3).
[b] Selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).
[c] Positive control used.

To gain insight into the plausible mode of interaction of compounds within COX-1 and COX-2 enzyme, molecular docking study was performed using GOLD program. All compounds docked successfully into the active sites of COX-1 and COX-2 enzyme. In general, the compounds displayed higher gold fitness score against



Scheme 1. Reagent and conditions: (a) Piperidine, rt, 20 min; (b) $ArNHNH_2$, EtOH, reflux, 5 h; (c) K_2CO_3, acetone, reflux, 24 h.

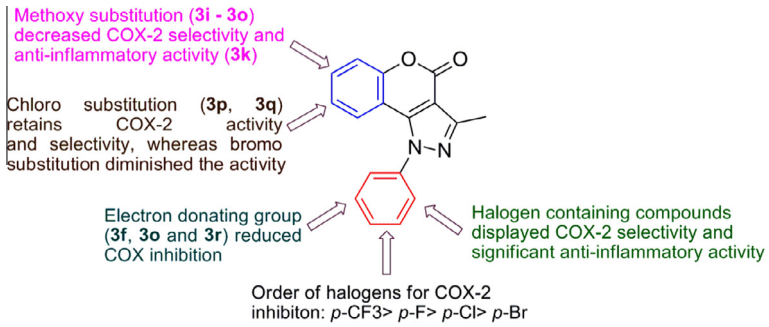


Figure 1. Structure activity relationship of chromenopyrazole derivatives.

Table 3
In vivo anti-inflammatory activity of chromenopyrazole derivatives in carrageenan-induced rat paw edema assay at dose 150 μmol/kg

Compound	Anti-inflammatory activity		
	% Inhibition after 1 h ± SEM	% Inhibition after 3 h ± SEM	% Inhibition after 5 h ± SEM
3a	19.33 ± 3.06**	30.09 ± 4.42***	38.23 ± 2.86***
3b	27.63 ± 4.78***	40.36 ± 2.84***	59.86 ± 2.26***
3c	21.34 ± 1.84***	35.18 ± 2.10***	49.43 ± 1.13***
3d	14.22 ± 2.10*	27.76 ± 3.44***	36.96 ± 4.10***
3h	24.57 ± 1.80***	39.75 ± 1.02***	55.60 ± 1.22***
3k	21.70 ± 2.40***	32.23 ± 3.03***	43.71 ± 2.51***
3q	23.33 ± 4.47***	36.09 ± 3.40***	57.81 ± 2.72***
Celecoxib	24.38 ± 2.29***	38.82 ± 2.92***	51.44 ± 2.68***

The results are expressed as mean ± SEM ($n = 5$). Significance was calculated by using one-way ANOVA with Dunnet's *t*-test. The difference in results were considered significant when $p < 0.05$ versus control.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

COX-2 in comparison to COX-1, which suggested favorable binding interactions of chromenopyrazoles in the COX-2 active site (Table 4). The most potent compound **3b** was found to dock into the active site of COX-2, wherein oxygen atom of C=O and, α-pyrone ring showed H-bond interactions with Tyr355 (C=O...HO = 2.04 Å, O...HO = 2.20 Å). In addition, the C=O group of **3b** was positioned towards the side-pocket lined by the residues Ser353, Arg513 and Tyr355. The trifluoromethyl group occupied hydrophobic side-pocket surrounded by the residues Phe381, Leu384, Tyr385 and Trp387 (Fig. 2A2). These residues displayed hydrophobic interactions with the trifluoromethyl group, with a maximum distance cutoff of 4.00 Å. It was observed that insertion of trifluoromethyl group into the side-pocket of COX-2 is assisted by one carbon chain which might be a reason for observed high COX-2 selectivity with this group, as compared to other halogens. In contrast, the docked pose of compound **3b** was found to be in inverse conformation in the COX-1 active site, wherein C=O formed a hydrogen bond with Ser530 (C=O...HO = 2.4 Å). The trifluoromethyl group was surrounded by residues Arg120 and Tyr355 (Fig. 2A1). The docking analysis of celecoxib was also

Table 4
Gold fitness scores of chromenopyrazoles and HBs formed with amino acid residues of COX-1 and COX-2

Compound	Gold fitness score COX-1	Residue involved in H-bond interaction with COX-1	Gold fitness score COX-2	Residue involved in H-bond interaction with COX-2
3a	40.96	Ser530	48.55	Tyr355
3b	36.17	Ser530	48.83	Tyr355
3c	39.70	Ser530	48.81	Tyr355
3d	42.60	Ser530	48.63	Tyr355
3e	36.17	Tyr355	40.57	Tyr355
3f	19.82	Tyr355	42.76	Tyr355
3g	20.20	Tyr385, Ser530	33.46	Tyr355
3h	36.45	Ser530	49.44	Tyr355
3i	36.51	Ser530	44.21	Tyr355
3j	26.48	Ser530	30.22	Tyr355
3k	28.13	Tyr355	44.76	Tyr355
3l	31.33	Tyr355	43.52	Tyr355
3m	27.11	Tyr355	47.54	Tyr355
3n	37.83	Ser530	40.51	Tyr355
3o	37.39	Tyr355	40.91	Tyr355
3p	35.37	Ser530	43.23	Tyr355
3q	34.70	Ser530	49.27	Tyr355
3r	39.21	Ser530	41.73	Tyr355
3s	38.59	Ser530	40.31	Tyr355
Celecoxib	32.21	Ser530, Tyr385	56.86	His90, Gln192, Leu352, Tyr355

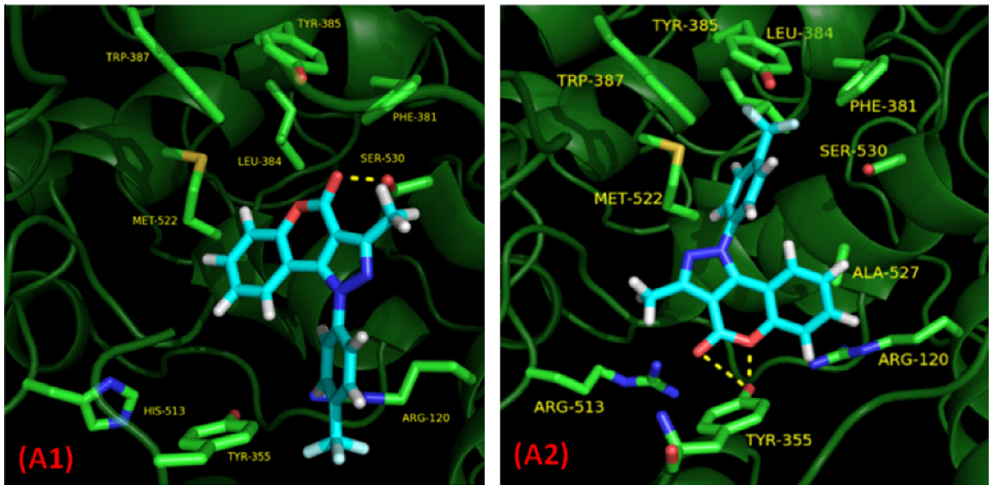


Figure 2. Docking pose of compound **3b** at the active site of COX-1 (A1) and COX-2 (A2), respectively.

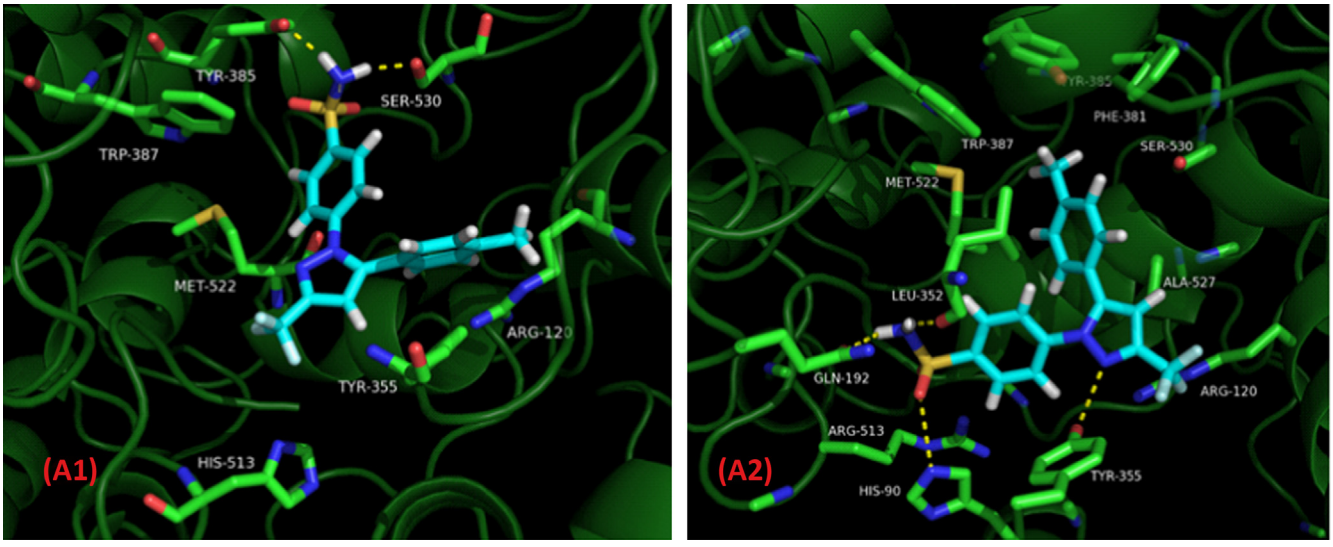


Figure 3. Docking pose of Celecoxib at the active site of COX-1 (A1) and COX-2 (A2), respectively.

performed for comparison. The compound **3b** occupy the same binding sites as that of celecoxib in COX-1 and COX-2 structure. In COX-1 active site, NH_2 of sulfonamide group in celecoxib was involved in hydrogen bonding with Tyr385 (O...HN = 2.0 Å) and Ser530 (O...HN = 2.0 Å, Fig. 3A1). In COX-2 structure, the oxygen atom and NH_2 of sulfonamide group in celecoxib forms three hydrogen bond with His90 (S=O...HN = 3.0 Å), Gln192 (C=O...HN = 2.4 Å) and Leu352 (C=O...HN = 2.1 Å), respectively. The nitrogen atom of pyrazole forms hydrogen bond with Tyr355 (N...HO = 3.0 Å, Fig. 3A2), same residue was also involved in hydrogen bonding with compound **3b**. Overall, docking analysis significantly indicated that the interaction of ligands with residue Tyr355 is important for directing COX-2 selectivity, which is also in agreement with our recent study.[23]

In conclusion nineteen 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-one derivatives were synthesized and evaluated for COX-1 and COX-2 inhibition. Compound **3b** exhibited potent COX-2 inhibition (IC_{50} = 1.79 μM) and selectivity (SI >16.7). Seven compounds (**3a–d**, **3h**, **3k** and **3q)** that displayed significant COX-2 inhibition, were tested for anti-inflammatory activity. Compound **3b** was identified as the most potent anti-inflammatory agent. Molecular docking studies further helped in understanding the binding orientation of ligands at the active site of enzyme and substantiated the observed COX-2 inhibition in vitro. The SAR study showed that appropriately substituted chromenopyrazoles have the necessary structural features to provide potent and selective inhibition of the COX-2 isozyme, and to exhibit excellent anti-inflammatory activity.

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Supplementary data

Supplementary data (Full experimental details, mp, ^{1}H, ^{13}C NMR and HRMS data have been incorporated in the supporting information.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.08.050.

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