Pyrido[1,2-a]pyrimidin-4-ones: Ligand-based Design, Synthesis, and Evaluation as an Anti-inflammatory Agent

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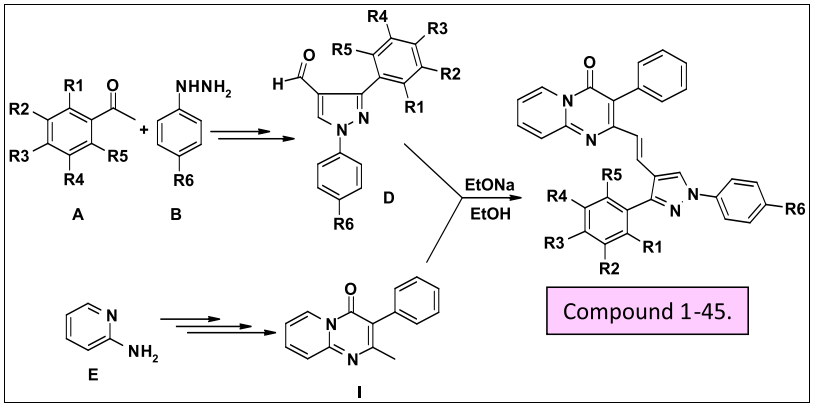
Received September 19, 2016
DOI 10.1002/jhet.2950
Published online 00 Month 2017 in Wiley Online Library (wileyonlinelibrary.com).



In the present study, a series of novel pyrido[1,2-a]pyrimidin-4-one derivatives (**1**–**45**) were synthesized, characterized, and evaluated for their anti-inflammatory activity. The structures of all newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, mass spectroscopy, and C, H, and N analyses. Preliminary these newly synthesized compounds were evaluated for their *in vitro* cyclooxygenase (COX)-2/COX-1 inhibitory activity. The celecoxib, a COX-2 inhibitor, was used as a reference standard drug. In this inhibitory study, compounds **42**, **43**, **44**, and **45** were found to have significant *in vitro* inhibitory profile as compared with the reference drug. These compounds were then subjected to their *in vivo* anti-inflammatory assay by using carrageenan-induced rat paw edema method in next level of screening. Later, these same compounds were tested for their ulcerogenic property. Based on these activity data, the compound **43** (*in vitro* COX-2 activity —IC_{50} = 0.4 μM, SI = 400, *in vivo* anti-inflammatory activity—72% inhibition after 3 h, and 0.38%—Ulcer index) was emerged as most promising anti-inflammatory agent with very low ulcerogenic action.

INTRODUCTION

Cyclooxygenases (COX) enzymes play an active role in the synthesis of prostaglandin (PG) H_2, which further involve in biosynthesis of PGs, prostacyclins, and thromboxanes [1]. There are two isoforms of COX, COX-1 and COX-2 [2,3]. COX-1, which plays role in housework activities, typically involves in the protection of gastric mucosa, platelets aggregation, and renal blood flow, while COX-2 is expressed in inflammation and pain [4]. Hence, the molecule that inhibits enzymatic activities of COX-2 has found to be a great therapeutic value. Traditional non-steroidal anti-inflammatory runners like ibuprofen, dichlofenac, and aspirin are non-selective; however, they exhibit superior selectivity for COX-1 than COX-2.

Fused pyrimidones are reported for their anti-inflammatory activity [5,6]. Particularly, pyrido[1,2-a] pyrimidinone and tetrahedron pyrido[1,2-a]pyrimidinone are well-known nucleus in drug discovery since they possess extensive range of biological activity along with anti-inflammatory property [7,8]. Moreover, marketed antipsychotic drugs Risperidone and Paliperidone comprise of tetrahedropyrido[1,2-a]pyrimidin-4-one pharmacophore [9].

The *trans-azo* derivative [10] and various naturally occurring *trans*-stilbenoids have been reported as COX inhibitors. As an example, resveratrol is a phytoalexin found in grapes skin and red wine displays moderate COX-1 inhibitory activity [11]. Also, the derivatives of resveratrol are documented for selective COX-2 inhibition [12].

Looking at the side effects of COX-1 inhibition like ulceration and GI irritation, superior selectivity toward COX-2 is a clinical need. Selective COX-2 inhibitors, especially the Coxibs, were highly appreciated initially.

Successively, cardiovascular adverse effects made them necessary for the alternative. So, the development of new scaffold for COX-2 inhibition is a challenge for medicinal chemist.

In continuation with our research activities [13–16], current research was targeted toward the design and synthesis of improved anti-inflammatory agent devoid of adverse effects. While designing, we boarded on molecular structure utilizing ligand-based drug design approach. Our interest was on pyrido[1,2-a]pyrimidin-4-one scaffold, *trans*-stilbene nuclei from *trans*-stilbenoids, and *N*-phenyl pyrazole moiety of celecoxib; therefore, these three moieties were combined together to get a novel hybrid heterocyclic molecule; in addition, we also gave premises to biologically active styryl quinazoline-4-one derivatives reported for their various biological activities [17,18] including their COX-2 inhibitory profile [19]. Hence, in our novel molecule, a phenyl ring was introduced at particular location of pyrimidin-4-one ring for the structural similarity with styryl quinazoline-4-ones (Fig. 1). Thus, a series of 45 molecules were synthesized and subjected for their *in vivo* COX-2 activity; later, selected compounds were tested for their *in vivo* anti-inflammatory activity and ulcerogenic liability.

RESULT AND DISCUSSIONS

Chemistry. The synthetic chemistry employed for the preparations of pyrido[1,2-a]pyrimidin-4-one derivatives (1–45) is outlined in scheme. In brief, the synthetic program started with preparation of different pyrazole aldehydes (**D**), one of the key precursor as shown in scheme according to the procedure reported in literature [20]. Here, commercially available different substituted acetophenones (**A**) were refluxed with commercially available various phenylhydrazines (**B**) in acidic medium by using ethanol as a solvent, to give corresponding imines (**C**). These imines (**C**) upon treatment with $POCl_3$ in DMF underwent cyclization to give different pyrazole aldehydes (**D**) in good yield as key precursors via Vilsmeier Haack reaction conditions (Fig. 1). Access to another important precursors for the preparation of pyrido[1,2-a]pyrimidin-4-one was achieved by following the process reported in literature [21]. 2-Amino pyridine (**E**) was treated with ethylacetoacetate (**F**) at reflux temperature in acetic acid to yield 2-methyl-pyrido[1,2-a]pyrimidin-4-one (**G**). This intermediate (**G**), when treated with iodine and ceric ammonium nitrate in acetonitrile at reflux temperature gave 3-iodo-2-methyl-pyrido[1,2-a]pyrimidin-4-one (**H**) in moderate to good yield. Finally, the requisite key precursor 2-methyl-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (**I**) was obtained by treating 3-iodo Intermediate (**H**) with coupling partner phenylboronic acid using palladium catalyzed Suzuki cross-coupling reaction conditions. The last step of this synthetic work was the preparation of the novel targeted compounds (**1**–**45**; Table 1), which involve the condensation of different pyrazole aldehydes (**D**) with 2-methyl-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (**I**) using sodium ethoxide at reflux temperature in ethanol. All the newly synthesized compounds were isolated in moderate to

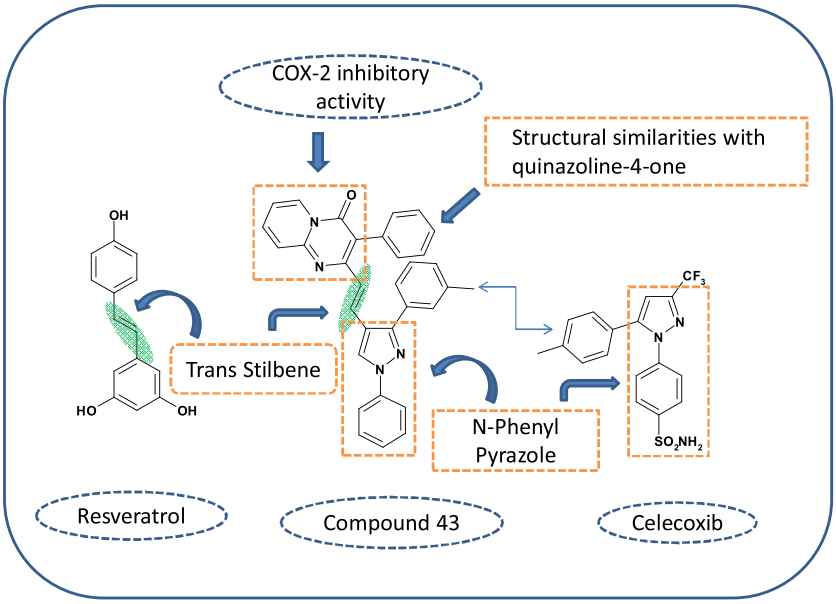
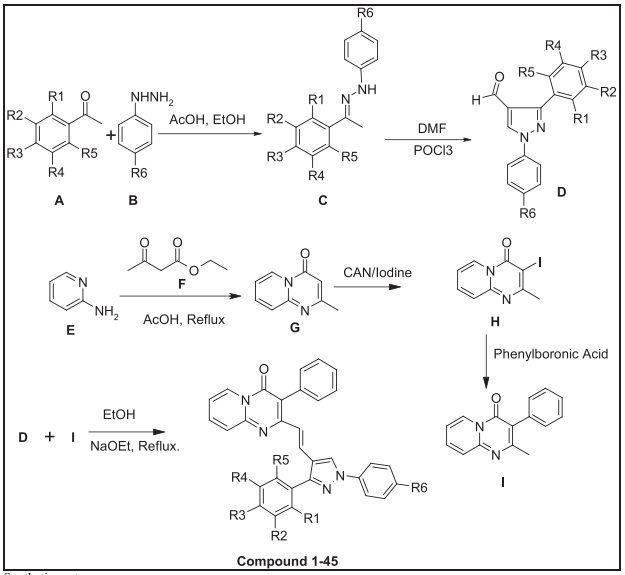


Figure 1. Pharmacophoric model. [Color figure can be viewed at wileyonlinelibrary.com]

good yield and were characterized by ES-MS, ^{1}H NMR spectral data, and elemental analysis. It was observed that the quantity required for ^{13}C NMR was not soluble in DMSO and MeOH, due to which it was difficult to run the ^{13}C NMR spectra and so, they are not included in the current report.



Synthetic route

COX-1/COX-2 inhibition study. The targeted compounds (**1**–**45**) were synthesized with methyl/methoxy variation across R_1–R_6 on the phenyl rings. After structural confirmation by spectroscopic techniques, the synthesized compounds were subjected to *in vitro* COX1/2 inhibition activity (Table 2).

The activity was judged by noticing reduction in PG production along with concerned enzymes in the presence of these compounds at various concentrations of 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8} M.

The compound (**1**) has shown satisfactory COX-2 inhibition activity (IC_{50} = 68 μM) even the selectivity was very poor (SI = 5.6). After encouraged from the preliminary results of compound **1**, we kept methoxy group at R_6 position and then one by one substitution (methyl/methoxy) across R_1–R_5 was introduced to get a set of six compounds (**2**–**7**), in which the compounds **2** and **4** have shown better selectivity (SI = 24.38 and 11.75, respectively), but taken as a whole, the inhibition was on inferior side. In order to improve the inhibition, next set of compounds **8**–**13** were synthesized, where compound **11** showed maximum potency (IC_{50} = 4 μM) with poor selectivity (SI = 13.33), while compound **13** has displayed highest selectivity index (SI = 114). However, both of these compounds were not as good as standard used for COX-2 inhibition.

Table 1

Substitution strategy for compounds $C_{1–45}$, $D_{1–45}$ and **1**–**45**.

ID	R_1	R_2	R_3	R_4	R_5	R_6
1	H	H	H	H	H	Me
2	OMe	H	H	H	H	OMe
3	H	OMe	H	H	H	OMe
4	H	H	OMe	H	H	OMe
5	Me	H	H	H	H	OMe
6	H	Me	H	H	H	OMe
7	H	H	Me	H	H	OMe
8	OMe	H	H	H	H	Me
9	H	OMe	H	H	H	Me
10	H	H	OMe	H	H	Me
11	Me	H	H	H	H	Me
12	H	Me	H	H	H	Me
13	H	H	Me	H	H	Me
14	OMe	OMe	H	H	H	OMe
15	OMe	H	OMe	H	H	OMe
16	OMe	H	H	OMe	H	OMe
17	OMe	H	H	H	OMe	OMe
18	OMe	Me	H	H	H	OMe
19	OMe	H	Me	H	H	OMe
20	OMe	H	H	Me	H	OMe
21	OMe	H	H	H	Me	OMe
22	Me	OMe	H	H	H	OMe
23	Me	H	OMe	H	H	OMe
24	Me	H	H	OMe	H	OMe
25	Me	H	H	H	OMe	OMe
26	Me	Me	H	H	H	OMe
27	Me	H	Me	H	H	OMe
28	Me	H	H	Me	H	OMe
29	Me	H	H	H	Me	OMe
30	OMe	OMe	H	H	H	Me
31	OMe	H	OMe	H	H	Me
32	OMe	H	H	OMe	H	Me
33	OMe	H	H	H	OMe	Me
34	OMe	Me	H	H	H	Me
35	OMe	H	Me	H	H	Me
36	OMe	H	H	Me	H	Me
37	OMe	H	H	H	Me	Me
38	Me	OMe	H	H	H	Me
39	Me	H	OMe	H	H	Me
40	Me	H	H	OMe	H	Me
41	Me	H	H	H	OMe	Me
42	Me	Me	H	H	H	Me
43	Me	H	Me	H	H	Me
44	Me	H	H	Me	H	Me
45	Me	H	H	H	Me	Me

For the further optimization, two different series of derivatives comprising compounds **14**–**21** and **22**–**29** (where R_6 was fixed by OCH_3 group) were synthesized. Unhappily, none of the compound from these series was potent; both the selectivity and COX-2 activity was insignificant, prompting us that OCH_3 group at R_6 might be responsible for poor potency.

By considering the above fact, we then explored the structure–activity relationship course and replaced R_6 by methyl group and methoxy group was shifted at R_1 position. These changes produce another set of compounds **30**–**37** where the methoxy group was shifted across R_2–R_5. Unfortunately, the previously mentioned

Table 2

IC_{50} (μM) for the compounds 1–45 (COX-1 and COX-2).

Sr. No	IC_{50} (μM)		Selectivity Index
	COX-1	COX-2	
1	12	68	5.6
2	2.42	59	24.38
3	8.4	78	9.28
4	5.7	67	11.75
5	1.7	18	10.58
6	17	85	5.0
7	1.2	7.6	6.33
8	2.9	67	23.1
9	6.7	42	6.26
10	0.9	108	120
11	0.3	4	13.33
12	67	51	0.76
13	1.4	49	35
14	16	68	4.25
15	4.9	99	20.2
16	6.8	12	1.76
17	15	84	5.6
18	6.0	91	15.1
19	12	65	5.41
20	19	134	7.01
21	4.2	144	34.28
22	9.0	50	5.55
23	6.0	43	7.16
24	8	65	8.12
25	3.4	67	19.70
26	7.8	84	10.76
27	4.4	14	3.18
28	3.2	67	21
29	12	68	5.66
30	15	34	2.25
31	5.6	67	12
32	6.7	59	8.80
33	3.9	45	11.53
34	4.6	40	9.8
35	4.0	45	11.2
36	7	65	9.2
37	9	59	6.55
38	3	34	11.3
39	0.08	9	150
40	15	65	4.33
41	3.9	47	12.05
42	0.01	0.52	40
43	0.001	0.4	400
44	0.01	0.63	63
45	0.002	0.67	335
Celecoxib	0.04	15	375

modification was unable to deliver the better potency for COX inhibition. Based on this result, we assumed that in order to get the improved inhibitory potency, methyl group might be essential at R_1 position. Accordingly, methoxy group was removed and another set of compounds **38**–**45** was synthesized with variation of methyl/methoxy at R_2–R_5. In this series, compound **39** displayed significant improvement in COX-2 inhibitory activity (IC_{50} = 9 μM) along with selectivity (SI = 150). From previously mentioned results, we confirmed that the presence of methyl group at R_1 position is essential for the potency. Further, we fixed R_1 position with methyl group and modifications were prepared and tested. Compounds **42**, **43**, **44**, and **45** showed decent COX-2 inhibition potency in all. However, compounds **42** and **44** have shown a poor selectivity ratio (SI = 40 and SI = 63). The compound **45** has displayed good potency (COX-2 IC_{50} = 0.67 μM), but selectivity (SI = 335) was less compared with standard celecoxib. Whereas compound **43** displayed as most active of all (COX-2 IC_{50} = 0.4 μM) with better inhibition than the standards used along with better selectivity ration (SI = 400) than celecoxib.

***In-vivo* anti-inflammatory activity.** The *in vivo* anti-inflammatory study was carried for active compounds **42**, **43**, **44**, and **45**. The experiment was performed as per the procedure previously described in literature [22]. Compound **42** showed only 31% inhibition after 3 h when compared with celecoxib (67% inhibition after 3 h). Compounds **44** and **45** with good COX-2 inhibition (COX-2 IC_{50} = 0.63 μM and 0.67 μM, respectively) displayed moderate *in vivo* profile (52% and 49% inhibitions, respectively, after 3 h). Derivative **43** with COX-2 IC_{50} = 0.40 μM and maximum selectivity (SI = 400) displayed decent *in vivo* profile with 72% of inhibition after 3 h. This result indicates that compound **43** was found superior than standard celecoxib (COX-2 IC_{50} = 15 μM, SI = 375, 67% inhibition after 3 h) (Table 3).

Ulcerogenicity. Compounds **42**, **43**, **44**, and **45** were subjected to ulcerogenic effect. The study was performed according to literature [23,24]. Compounds **42**, **43**, **44**, and **45** did not cause any gastric ulceration. Hence, gastric tolerance of these compounds was better than that of celecoxib. This result proves that these compounds are safe on gastric mucosa. The result is mentioned in Table 4.

Molecular docking studies on COX-1/2. In order to illustrate the binding interactions of most and least active compounds at the binding site of COX-1/2 isoenzyme, docking studies were performed with AUTODOCK VINA [25]. The solved X-ray crystal structures (COX-1, PDB: 3KK6; COX-2, PDB: 3LN1) of COX-1/2 isoenzyme with bound celecoxib, a COX-2 selective inhibitor, were used for docking studies. In brief, the docking protocol consisted of protein refinement where nonstandard residues were removed from crystal structure. To attain the native structure of enzyme, energy minimization was carried out in UCSF CHIMERA by using 10 000 steepest descent steps until gradient converses to 0.01 A^0. The 2D structures of compounds were transformed to 3D in Marvin sketch. The resulting 3D structures were optimized by using MM Universal force field in ARGUSLAB 4.0.1 with Broyden-Fletcher-Golfarb-Shanno search until the

Table 3

In vivo anti-inflammatory data for active compound.

	Change in rat paw volume (mL) after drug administration				*In vivo* anti-inflammatory inhibition (% Inhibition)		
ID	0 h	1 h	2 h	3 h	1 h	2 h	3 h
42	0.36 ± 0.04*	0.438 ± 0.03*	0.493 ± 0.03*	0.553 ± 0.05*	22	26	31
43	0.39 ± 0.03*	0.451 ± 0.04*	0.454 ± 0.04*	0.468 ± 0.07*	39	64.12	72.00
44	0.33 ± 0.04*	0.395 ± 0.05*	0.423 ± 0.08*	0.464 ± 0.02*	34.11	48.00	52.14
45	0.41 ± 0.01*	0.472 ± 0.06*	0.514 ± 0.05*	0.552 ± 0.05*	38.09	42.11	49.00
Control	0.31 ± 0.03*	0.41 ± 0.04*	0.49 ± 0.04*	0.59 ± 0.04*	—	—	—
Celecoxib	0.29 ± 0.10*	0.350 ± 0.01*	0.363 ± 0.10*	0.382 ± 0.08*	40	59	67

Data were analyzed by one-way ANOVA followed by Dunnet's test ($n = 6$). Dose levels–test compounds and celecoxib (25 mg/kg).
*$P < 0.05$ significant from control sample.

Table 4

Ulcerogenicity for active compound.

Compound	Dose mg/kg/day	Time in days	Ulcer index
42	25	4	0.25 ± 0.03**
43	25	4	0.38 ± 0.05**
44	25	4	0.22 ± 0.07**
45	25	4	0.29 ± 0.09**
Celecoxib	25	4	0.53 ± 0.22**
Control	CMC 1% w/v	4	----

Data were analyzed by one-way ANOVA followed by Dunnet's test ($n = 6$).
**$P < 0.01$ significant from control sample.

Table 5

Binding free energy output of AUTODOCK VINA.

	Binding free energy in Kcal/mol	
ID	COX-1	COX-2
2	−2.7	−3.2
5	−2.9	−3.9
6	−2.4	−3.2
7	−2.8	−4.1
8	−2.8	−3.2
11	−3	−4.1
13	−2.9	−3.2
15	−2.5	−3.1
17	−2.3	−3.1
18	−2.7	−3.1
20	−0.7	−3
21	−2.6	−3
26	−1.4	−3.2
28	−2.4	−3.2
38	−2.4	−3.3
39	−3.1	−4
42	−3.4	−4.5
43	−3.7	−4.6
44	−3.4	−4.3
45	−3.6	−4.3
cele	−3.2	−3.9

gradient converses to 0.001 kcal/mol/A^0. In AUTODOCK VINA run, grid box of size 14 × 14 × 14 A^0 with center −33.996, 43.834, and −6.086 for COX-1 and 32.522, −22.915, and −15.769 for COX-2 was chosen. Docking studies were validated by docking the celecoxib at the binding site. Docking produced the pose of celecoxib with root mean square deviation below 1° at the binding site of both proteins (Fig. S1 in the Supporting Information). From among the docking results, the results for 20 most active or least active compounds along with standard drugs are shown in Table 5.

The structural differences between COX-1 and COX-2 are due to two amino acid residues. Replacement of Ile517 in COX-1 by a hydrophobic smaller Val in COX-2 is the most important difference (Fig. S2). This modification in the COX-2 enzyme creates additional side pocket, which is a pre-requisite for COX-2 selectivity [26]. Further, the presence of His513 instead of Arg499 in the COX-1 enzyme also contributes toward COX-2 selectivity. In our docking studies, docked poses of most active compounds (42, 43, 44, and 45) were found to occupy the binding site of COX-2 iso-enzyme more favorably (Fig. 2). Phenyl-pyrido[1,2-a]pyrimidin-4-one ring occupies the hydrophobic cavity where CF_3 group of celecoxib interacts. As this cavity is made by most of the hydrophobic residues like val, it is evident that lager groups or rings could improve the COX-2 selectivity. The presence of CH_3 group (R_6) was found crucial in these most active compounds. The presence of OCH_3 group probably is too bulky to accommodate in the hydrophobic cavity surrounded by hydrophobic residues like Ala, Tyr, Gly, and Phe. Similarly, the substitution by OCH_3 on phenyl ring (R_1–R_5) is too bulky to accommodate third cavity where SO_2NH_2 group of celecoxib binds. In case of least active compounds (13, 20, and 21), the docked poses show that the bulky OCH_3 groups contribute toward the lower affinity to COX-2 binding site.

In case of docking with COX-1 iso-enzyme, it was found that the most active compounds (42, 43, 44, and 45) occupy the binding site but the phenyl-pyrido[1,2-a] pyrimidin-4-one ring could not occupy the cavity where CF_3 group of celecoxib binds. Here again, we found that

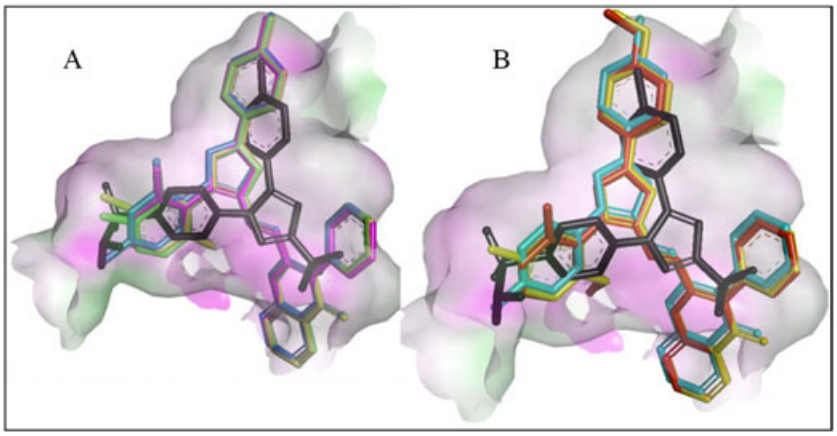


Figure 2. Docked poses of A: most active compounds (42, 43, 44, and 45) and B: least active compounds (13, 20, and 21) along with docked pose of celecoxib shown in black color. [Color figure can be viewed at wileyonlinelibrary.com]

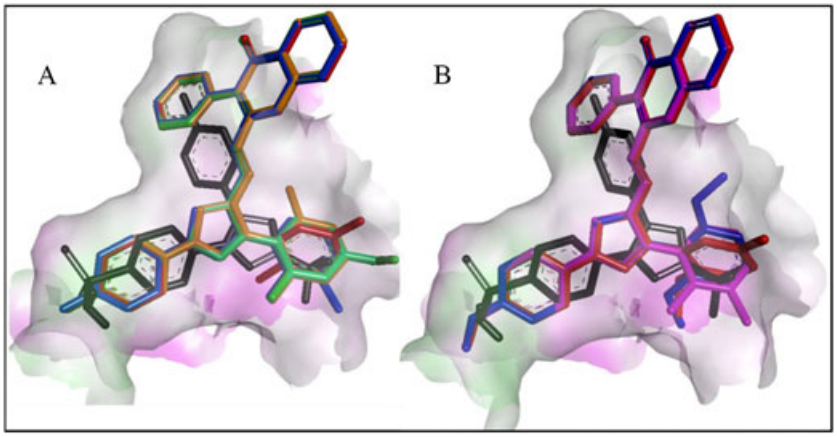


Figure 3. Docked poses of A: most active compounds (39, 42, 43, 44, and 45); B: least active compounds (17, 20, and 26) along with celecoxib shown in black color. [Color figure can be viewed at wileyonlinelibrary.com]

the OCH_3 substitution on phenyl ring (R_1–R_5) is too bulky to accommodate the cavity where $–CF_3$ group of celecoxib binds. Phenyl-pyrido[1,2-a]pyrimidin-4-one ring occupies the extended hydrophobic cavity surrounded by Ala, Tyr, Gly, and Phe. In case of least active compounds (17, 20, and 26), the presence of OCH_3 on phenyl ring was found unfavorable for binding (Fig. 3). Interactions of most active and least active compounds with COX-2 and COX-1 are given in Figures S3A, S3B, S4A, and S5B, respectively.

CONCLUSION

Present article deals with synthesis of pyrido[1,2-*a*] pyrimidin-4-ones derivatives as selective COX-2 inhibitors. Looking to *in vitro* assay (COX-1 and COX-2 inhibitions), compounds **42**, **43**, **44**, and **45** were potent candidates; however, compounds **43** and **45** were found very effective with respect to COX-2 selectivity. In addition, *in vivo* profile of **42** (31% inhibition after 3 h) was poor, while *in vivo* profiles for **44** and **45** (52.14 and 49% inhibition, respectively, after 3 h) were moderate. Whereas, the compound **43** (72% inhibition after 3 h) was emerged as a best anti-inflammatory agent and found superior than that of celecoxib. Additionally, **42**, **43**, **44**, and **45** demonstrated superior ulcerogenic index as compared with celecoxib. On the basis of these findings, compound **43** was identified as a lead candidate within current description.

EXPERMENTAL

Chemistry. The melting points of the synthesized compound were determined in open capillary tubes by using VMP-D melting point apparatus (Veego Instrument Corporation, Mumbai, India) and are uncorrected. The ^1H

NMR and ^{13}C NMR for the compound synthesized were recorded on Varian Mercury (Switzerland) plus 400 by using TMS as an internal standard and DMSO-d_6 solvent and chemical values are given δ scales. The spectra of mass were recorded on mass spectrometer (Acquity, Waters Corporation). Microanalyses were carried out on elementar (Vario Micro Cube, Germany). The follow-up of reactions was monitored by thin-layer chromatography (TLC) on silica gel-precoated aluminum sheets (Type 60, F254, Merck, Germany), and the spots were detected by exposer to UV lamp at λ 254 nm for 20–30 s. Necessary chemicals were ordered from Sigma-Aldrich and Spectrochem (INDIA). Commercial grade solvents were used without their purifications.

General procedure for synthesis of pyrazole aldehyde (D). A mixture of various acetophenones (1 mol) (**A**) and phenyl hydrazines (1 mol) (**B**) were heated in ethanol (10 volume of A) in presence of (3 mL) acetic acid at reflux temperature for 30 min. Resulting yellow solid product was separated by the filtration. This solid was washed by cold ethanol (20 mL) and was suck dried under vacuum. A mixture of *N,N*-dimethylformamide (2.5 mol), $POCl_3$ (2.5 mol), was stirred together at 0°C for 30 min.The previously mentioned solid was added to this reaction mixture at 0°C with constant stirring. The reaction mixture was then allowed to warm up to room temperature and stirred for 12–14 h. Reactions were monitored by TLC techniques; after completion of the reaction, reaction mixture was poured on crushed ice where upon the solid was separated. It was filtered and washed by saturated aqueous $NaHCO_3$ solution followed by water. The solid was crystalized from ethanol to get white crystalline product **D** in an average 70% yield.

Synthesis of 2-methyl-pyrido[1,2-a]pyrimidin-4-one (G). Ethyl acetoacetate **F** (39 g, 0.3 mol) was added to a stirred mixture of 2-aminopyridine **E** (92 g, 1.0 mol) and acetic acid (200 mL). The mixture was refluxed for 15 h. The reaction mixture was then cooled to room temperature, and acetic acid was removed to afford dark brown crude solid. It was dissolved in ethyl acetate (250 mL) and washed with saturated $NaHCO_3$ solution (200 mL × 2) followed by saturated brine solution (200 mL). Organic layer was dried over anhydrous Na_2SO_4, and solvent was concentrated under vacuum to afford the crude product. The crude was purified by column chromatography nby using silica (60–120) to give white solid of 2-methyl-pyrido[1,2-a]pyrimidin-4-one **G** (75 g, 49%). Conversion was monitored by TLC techniques. ^1H NMR (400 MHz, DMSO-d_6): δ ppm: 2.35 (s, 3H, pyrimidinone CH_3), 6.15 (s, 1H, pyrimidinone H), 7.01 (d, 1H, J = 8.05 Hz, ArH), 7.35–7.37 (m, 2H, ArH), 8.42 (d, 1H, J = 8.5 Hz, ArH near to nitrogen); ES-MS 161 (M + 1).

Synthesis of 2-methyl-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (I). A mixture of 2-methyl-pyrido [1,2-a]pyrimidin-4-one **G** (11.9 g, 0.05 mol), ceric ammonium nitrate (13.20 g, 0.024 mol), and iodine (3.78 g, 0.03 mol) in acetonitrile (100 mL) was stirred at 80°C for 5–6 h. Conversion was monitored by TLC; later, the heating was removed and reaction mixture was cooled to room temperature. Solvent was removed under reduced pressure; distilled water (80 mL) was added to residue and stirred it for 1 h at room temperature. Yellow solid (12 g) of 2-methyl-3-iodo-pyrido[1,2,a] pyrimidin-4-one **H** was obtained after filtration. ^1H NMR (400 MHz, DMSO-d_6): δ ppm: 2.37 (s, 3H, pyrimidinone CH_3), 7.09 (d, 1H, J = 8.0 Hz, ArH), 7.44–7.46 (m, 2H, ArH), 8.54 (d, J = 8.6 Hz, ArH); ES-MS 287.3 (M + 1).

Then **H** (3.8 g, 0.013 mol) was taken in toluene (125 mL), to that $Pd[(C_6H_5)_3P]_4$ (0.615 g, 0.00053 mol), and a solution of Na_2CO_3 (0.082 g, 0.00078 mol) in water (50 mL) were added. Further, a solution of phenylboronic acid (2.1 g, 0.017 mol) in ethanol (50 mL) was added and reaction mixture was stirred at refluxed for 2 h. After completion, the reaction was cooled and the solvent was removed under reduced pressure. The residue was partitioned in ethyl acetate (500 mL) and water (100 mL). The organic layer was washed by brine (100 mL) and was removed to afford crude product; it was then purified by column chromatography by using silica (60–120) and methanol chloroform as eluent to get yellow solid 2-methyl-3-phenyl-pyrido[1,2-a]pyrimidin-4-one **I** in 1.8 g (52%) yield. ^1H NMR (400 MHz, DMSO-d_6): δ ppm: 2.1 (s, 3H, pyrimidinone CH_3), 7.12 (d, J = 8.01 Hz, ArH), 7.32–7.40 (m, 4H, ArH), 8.10 (m, 2H, ArH), 8.78 (d, J = 8.2 Hz, ArH near to nitrogen); ES-MS 237 (M + 1).

General method for coupling of (D) and (I). Sodium ethoxide (2 mol) was added to a stirred mixture of 2-methyl-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (1 mol) and pyrazole aldehyde (1.5 mol) in ethanol (10 volume); reaction mixture was stirred at reflux for 13 h. Reaction mixture (transparent solution) was allowed to cool to room temperature. The product (precipitated solid) was obtained after filtration.

3-Phenyl-2-[2-(3-phenyl-1-p-tolyl-1H-pyrazol-4-yl)-vinyl]-pyrido[1,2-a]pyrimidin-4-one (1). Yield 67%; mp 198–200°C; ^1H NMR (400 MHz, DMSO-d_6): δ ppm: 2.20 (s, 3H, Ar-CH_3), 6.80 (d, J = 16 Hz, olefinic H near to pyrazole), 7.05 (d, 1H, J = 8.19 Hz, ArH), 7.20 (s, 1H, ArH), 7.30–7.45 (m, 6H ArH, and olefinic H near to pyrimidone ring), 7.46–7.60 (m, 3H, ArH), 7.80–7.85 (m, 2H, ArH), 8.00 (m, 1H, ArH), 8.20–8.29 (m, 3H, ArH), 8.30 (a, 1H, pyrazole ring H), 8.90 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.6 (Ar-CH_3), 108.6, 115.3, 121.3, 121.4, 125.3, 125.9, 129.2, 130.1, 131.2, 136.3, 137.1, 139.2, 146.1, 150.1, 150.5, 163.8; ES-MS m/z 481.3 [M + 1]. *Anal.* Calcd for $C_{32}H_{24}N_4O$.*Anal.* Calcd for $C_{32}H_{24}N_4O$ (480.5):

C, 79.98; H, 5.03; N, 11.66. Found C, 79.73; H, 5.29; N, 11.55.

2-{2-[1-(4-Methoxy-phenyl)-3-(2-methoxy-phenyl)-1H-pyrazol-4-yl]vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (2). Yield 61%; mp 212–214°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 3.95 (s, 3H, Ar-OCH_3), 3.99 (s, 3H, Ar-OCH_3), 6.70 (d, J = 16 Hz, Hz, 1H, olefinic H near to pyrazole ring), 7.00 (s, 1H, ArH), 7.24–7.60 (m, 8H, ArH, and olefinic H near to pyrimidinone), 7.80–8.00 (m, 5H, ArH), 8.15–8.22 (m, 3H, ArH), 8.32 (s, 1H, pyrazole ring H), 8.95 (s, 1H ArH). ^{13}C NMR (100 MHz, DMSO-d_6): 53.8 (Ar-OCH_3), 54.2 (Ar-OCH_3), 104.6, 117.2, 119.1 (olefinic C near to pyrazole ring), 120.3, 121.3, 121.9. 123.4. 126.2. 129.2, 136.1, 139.1, 154.3, 155.1, 164.2; ES-MS m/z 527.60 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O_3$ (526.5): C, 75.27; H, 4.98; N, 10.64. Found C, 75.16; H, 5.09; N, 11.06.

2-{2-[1-(4-Methoxy-phenyl)-3-(3-methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (3). Yield 77%; mp 211–213°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 3.97 (s, 3H, Ar-OCH_3), 3.99 (s, 3H, Ar-OCH_3), 6.80 (d, 1H, J = 16 Hz, olefinic H near to pyrazole ring), 7.00 (s, 1H, ArH), 7.24–7.60 (m, 8H, ArH, and olefinic H near to pyrimidinone), 7.80–8.00 (m, 4H, ArH), 8.21–8.29 (m, 3H, ArH), 8.33 (s, 1H, pyrazole ring H), 8.95 (s, 1H ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 54.6 (Ar-OCH_3), 55.1(Ar-OCH_3), 103.9, 116.3, 118.9, 120.1, 121.9, 123.2. 124.2, 127.3, 129.1, 131.9, 136.6, 139.1, 143.1, 149.1, 150.2, 154.2, 163.1(C═O); ES-MS *m/z* 527.60 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O_3$ (526.5): C, 75.27; H, 4.98; N, 10.64. Found C, 75.76; H, 4.76; N, 11.09.

2-{2-[1,3-Bis-(4-methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (4). Yield 62%; mp 234–236°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 3.93 (s, 3H, Ar-OCH_3), 3.95 (s, 3H Ar-OCH_3), 6.65 (d, 1H, J = 16 Hz, olefinic H near to pyrazole), 7.20 (s, 1H, ArH), 7.25–7.35 (m, 6H, ArH, and olefinic H near pyrimidinone), 7.65–8.00 (m, 6H, ArH), 8.20–8.28 (m, 3H, ArH), 8.37 (s, 1H, pyrazole ring H), 9.00 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 54. 6(Ar-OCH_3), 55.1(Ar-OCH_3), 108.2, 115.8, 118.2, 121.3, 121.9, 123.4, 123.9, 126.3, 129.2, 129.9, 131.4, 136.2, 139.2, 145.9, 150.2, 151.7, 159.2, 163.7 (C═O); ES-MS *m/z* 527.60 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O_3$ (526.5): C, 75.27; H, 4.98; N, 10.64. Found C, 75.12; H, 5.17; N, 11.09.

2-{2-[1-(4-Methoxy-phenyl)-3-o-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (5). Yield 71%; mp 215–217°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.34 (s, 3H, Ar-CH_3), 3.99 (s, 3H, Ar-Ar-OCH_3), 6.69 (d, 1H, J = 15.7 Hz, olefinic H near to pyrazole ring), 7.05–7.23 (m, 6H, ArH), 7.30–7.40 (m, 4H, ArH and olefinic H near to pyrimidinone), 7.45–7.70 (m, 3H, ArH), 7.80–8.00 (m, 4H. ArH), 8.22 (s, 1H, pyrazole ring H) 8.99 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21 (Ar-CH_3), 55 (Ar-OCH_3), 107.2, 117.8, 119.3, 120.1, 121.5, 121.9, 123.4, 123.9, 126.3, 129.2, 129.9, 131.4, 136.2, 139.2, 145.9, 150.2, 158.3, 164.8(C═O); ES-MS *m/z* 511.3 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O_2$. (510.3): C, 77.64; H, 5.13; N, 10.97. Found C, 78.01; H, 5.09; N, 11.18.

2-{2-[1-(4-Methoxy-phenyl)-3-m-tolyl]-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (6). Yield 55%; mp 210–212°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.34 (s, 3H, Ar-CH_3), 3.98 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, J = 16 Hz, olefinic H near to pyrazole), 7.20–7.30 (m, 6H, ArH), 7.45–7.65 (m, 4H, ArH, and olefinic H near to pyrimidinone), 7.80–8.00 (m, 3H, ArH), 8.23 (s, 1H, pyrazole ring H), 8.99 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 22.2 (Ar-CH_3), 56.3 (Ar-OCH_3), 105.2, 114.3, 118.3, 119.3, 121.6, 121.9, 123.4, 123.5, 126.4, 129.1, 129.2, 131.5, 134.2, 136.2, 139.2, 145.9, 148.3, 150.2, 158.3, 164.1(C═O); ES-MS *m/z* 511.3 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O_2$. (510.3): C, 77.64; H, 5.13; N, 10.97. Found C, 77.99; H, 5.03; N, 11.08.

2-{2-[1-(4-Methoxy-phenyl)-3-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (7). Yield 49%; mp 237–239°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.32 (s, 3H, Ar-CH_3), 3.91 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, J = 16 Hz, olefinic H near to pyrazole ring), 7.00 (d, 1H, J = 7.01 Hz, ArH), 7.21–7.45 (m, 4H, ArH, and olefinic H near to pyrimidinone), 7.60–7.70 (m, 3H, ArH), 7.80–8.00 (m, 3H, ArH), 8.00–8.12 (m, 4H, ArH), 8.21 (s, 1H, pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 22.4 (Ar-CH_3), 54.3 (Ar-OCH_3), 107.2, 116.3, 117.3, 119.4, 121.1, 121.9, 123.5, 123.9, 126.1, 129.1, 130.1, 131.5, 134.2, 136.2, 139.2, 145.9, 148.3, 150.2, 158.3, 164.1(C═O); ES-MS *m/z* 511.3 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O_2$. (510.3): C, 77.64; H, 5.13; N, 10.97. Found C, 77.88; H, 5.23; N, 11.08.

2-{2-[3-(2-Methoxy-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (8). Yield 64%; mp 214–216°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.34 (s, 3H, Ar-CH_3), 3.95 (s, 3H, Ar-OCH_3), 6.88 (d, 1H, J = 16 Hz, olefinic H near to pyrazole ring), 7.05–7.10 (m, 3H, ArH), 7.40–7.48 (m, 6H, ArH, and olefinic H near to pyrimidinone), 7.50 (d, 1H, J = 7.93 Hz, ArH), 7.58–7.75 (m, 2H, ArH), 7.89–8.00 (m, 4H, ArH), 8.23 (s, 1H, pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 22.9 (Ar-CH_3), 56.4, (Ar-OCH_3), 106.2, 117.1, 119.4, 120.1, 121.2, 121.9, 123.7, 124.9, 126.1, 129.1, 130.3, 131.5, 133.2, 136.4, 139.8, 144.5, 149.2, 150.9, 157.3, 163.2 (C═O); ES-MS *m/z* 511.3 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O_2$. (510.3): C, 77.64; H, 5.13; N, 10.97. Found C, 77.79; H, 5.35; N, 10.65.

2-{2-[3-(3-Methoxy-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (9). Yield 55%; mp 231–233°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.32 (s, 3H, Ar-CH_3), 3.95 (s, 3H, Ar-OCH_3), 6.69 (d, 1H, 16 Hz, olefinic H near to pyrazole), 7.10–7.30 (m, 6H, ArH), 7.34–7.45 (m, 4H, ArH, and olefinic H near to

pyrimidinone), 7.60–7.79 (m, 3H, ArH), 7.85–8.05 (m, 4H, ArH), 8.32 (s, 1H, pyrazole ring H), 8.90 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9 (Ar-CH_3), 56.1 (Ar-OCH_3), 106.4, 116.9, 119.1, 120.6, 121.4, 121.8, 123.9, 124.2, 126.4, 129.1, 130.9, 131.8, 133.2, 135.6, 139.2, 145.1, 149.3, 151.4, 157.2, 163.4 (C═O); ES-MS *m*/*z* 511.3 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O_2$. (510.3): C, 77.64; H, 5.13; N, 10.97. Found C, 77.80; H, 5.23; N, 11.03.

2-{2-[3-(4-Methoxy-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (10). Yield 54%; mp 212–213°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.37 (s, 3H, Ar-CH_3), 3.95 (s, 3H, Ar-OCH_3), 6.60 (d. 1H, 16 Hz, olefinic H near to pyrazole), 7.10–7.23 (m, 4H, ArH), 7.34–7.42 (m, 5H, ArH, and olefinic H near to pyrimidinone), 7.65–7.77 (m, 3H, ArH), 7.80–8.00 (m, 3H, ArH), 8.04–8.12 (m, 3H, ArH), 8.33 (s, 1H, pyrazole ring H), 8.99 (s. 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 22.1 (Ar-CH_3), 56.1, (Ar-OCH_3), 106.0, 117.4, 118.4, 120.2, 121.4, 121.6, 122.4, 124.1, 125.8, 129.1, 130.3, 131.4, 133.4, 136.1, 139.4, 144.7, 149.4, 151.2, 157.8, 163.6 (C═O); ES-MS *m*/*z* 511.3 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O_2$ (510.3): C, 77.64; H, 5.13; N, 10.97. Found C, 77.99; H, 5.07; N, 11.00.

3-phenyl-2-[2–3-o-toly1–1-p-tolyl-1H-pyrazol-4-yl)vinyl]-pyrido[1,2-a]pyrimidin-4-one (11). Yield 68%; mp 233–235°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.37 (s, 3H, Ar-CH_3), 2.40 (s, 3H, Ar-CH_3), 6.99 (d, 1H, *J* = 16 Hz, olefinic H near to pyrazole), 7.05–7.10 (m, 3H, ArH), 7.28–7.35 (m, 4H, ArH), 7.45–7.65 (m, 5H, olefinic H near to pyrimidinone, and ArH), 7.98–8.04 (m, 4H, ArH), 8.32 (s, 1H, pyrazole ring H), 9.00 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 22.9 (Ar-CH_3), 23.2 (Ar-CH_3), 104.2, 116.1, 119.4, 120.3, 120.4, 121.2, 121.5, 123.2, 124.7, 126.1, 126.9, 127.2, 129.4, 130.3, 131.5, 133.2, 136.1, 139.1, 144.5, 149.2, 150.9, 163.8 (C═O); ES-MS *m*/*z* 495.3 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O$. (494.60): C, 80.14; H, 5.30; N, 11.33. Found C, 80.23; H, 5.08; N, 11.09.

3-phenyl-2-[2–3-m-toly1–1-p-tolyl-1H-pyrazol-4-yl)vinyl]-pyrido[1,2-a]pyrimidin-4-one (12). Yield 74%; mp 234–236°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.31 (s, 3H, Ar-CH_3), 2.38 (s, 3H, Ar-CH_3), 6.49 (d, 1H, *J* = 16 Hz, olefinic H near to pyrazole ring), 7.03–7.09 (m, 3H, ArH), 7.37–7.61 (m, 5H, ArH and olefinic H near to pyrimidinone), 7.99–8.05 (m, 3H, ArH), 8.31 (s, 1H, pyrazole ring H), 9.05–9.15 (m, 3H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 22.9 (Ar-CH_3), 23.2 (Ar-CH_3), 105.9, 117.1, 119.8, 120.4, 120.9, 121.2, 122.8, 123.7, 124.5, 125.6, 126.9, 127.8, 128.9, 129.1, 130.3, 131.5, 133.5, 135.3, 135.9, 136.1, 138.3, 144.5, 149.2, 150.1, 162.9 (C═O); ES-MS *m*/*z* 495.3 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O$. (494.60): C, 80.14; H, 5.30; N, 11.33. Found C, 79.99; H, 5.08; N, 11.23.

2-[2-(1,3-Di-p-toly1–1H-pyrazol-4-yl)vinyl]-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (13). Yield 53%; mp 235–237°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.27 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Ar-CH_3), 6.58 (d, 1H, *J* = 16 Hz, olefinic H near to pyrazole ring), 7.00–7.10 (m, 2H, ArH), 7.22–7.34 (m, 4H, ArH), 7.42 (d, 1H, *J* = 16 Hz, olefinic H near to pyrimidinone), 7.50–7.70 (m, 4H, ArH), 7.78–8.00 (m, 4H, ArH), 8.12–8.20 (m, 3H, ArH), 8.32 (s, 1H, pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 22.1 (Ar-CH_3), 23.8 (Ar-CH_3), 107.1, 117.6, 119.1, 120.3, 120.9, 121.2, 121.4, 122.8, 123.9, 124.2, 125.9, 126.4, 127.9, 128.9, 129.5, 130.6, 131.7, 132.4, 133.9, 134.8, 135.3, 135.9, 136.1, 138.3, 144.6, 149.7, 150.7, 162.5 (C═O); ES-MS *m*/*z* 495.3 [M + 1]. *Anal.* Calcd for $C_{33}H_{26}N_4O$. (494.60): C, 80.14; H, 5.30; N, 11.33. Found C, 80.23; H, 5.08; N, 11.01.

2-{2-[3-(2,3-Dimethoxy-phenyl)-1-(4-methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (14). Yield 46%; mp 224–227°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.68 (s, 3H, Ar-OCH_3), 3.95 (s, 3H, Ar-OCH_3), 3.98 (s, 3H, Ar-OCH_3), 6.77 (d, 1H, *J* = 16.2 Hz, olefinic H near to pyrazole), 7.23–7.43 (m, 5H, olefinic H near to pyrazole and ArH), 7.49–8.01 (m, 4H, ArH), 8.12–8.23 (m, 5H, ArH), 8.32 (s, 1H, pyrazole ring H), 9.00 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 56.1 (Ar-OCH_3), 58.1 (Ar-OCH_3), 58.7 (Ar-OCH_3), 109.2, 118.6, 119.1, 120.5, 121.7, 122.9, 123.6, 124.5, 125.9, 126.4, 127.7, 128.7, 128.9, 130.1, 131.9, 132.8, 133.9, 134.8, 136.5, 138.1, 144.5, 149.9, 150.7, 158.1, 158.9, 162.9 (C═O); ES-MS *m*/*z* 557.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_4$. (556.60): C, 73.37; H, 5.03; N, 10.07. Found C, 73.23; H, 5.09; N, 10.22.

2-{2-[3-(2,4-Dimethoxy-phenyl)-1-(4-methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (15). Yield 53%; mp 235–237°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.62 (s, 3H, Ar-OCH_3), 3.90 (s, 3H, Ar-OCH_3), 3.96 (s, 3H, Ar-OCH_3), 6.30 (d, 1H, *J* = 16 Hz olefinic H near to pyrazole), 7.08 (d, 1H, *J* = 8.09 Hz, ArH), 7.41 (d, 1H, *J* = 15.8 Hz, olefinic H near to pyrimidinone), 7.42–7.80 (m, 6H, ArH), 7.93–8.03 (m, 2H, ArH), 8,21 (s, 1H, pyrazole H), 9.09–9.13 (m, 3H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 56.4 (Ar-OCH_3), 58.5 (Ar-OCH_3), 58.9 (Ar-OCH_3), 110.1, 120.1, 120.9, 121.9, 122.9, 123.8, 124.9, 125.8, 126.9, 127.6, 128.5, 129.1, 130.1, 131.9, 132.8, 133.9, 134.8, 136.1, 138.4, 144.7, 149.2, 151.4, 155.8, 157.3, 158.9, 163.9 (C═O); ES-MS *m*/*z* 557.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_4$. (556.60): C, 73.37; H, 5.03; N, 10.07. Found C, 73.23; H, 5.23; N, 10.22.

2-{2-[3-(2,5-Dimethoxy-phenyl)-1-(4-methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (16). Yield 56%; mp 239–241°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.62 (s, 3H, Ar-OCH_3), 3.90 (s, 3H,

Ar-OCH_3), 3.96 (s, 3H, Ar-OCH_3), 6.20 (d, 1H, J = 16.2 Hz, olefinic H near to pyrazole), 7..00 (d, 1H, J = 8.11 Hz, ArH), 7.05–7.10 (m, 4H, ArH), 7.38 (t, 2H, ArH), 7.45–7.65 (m, 6H, olefinic H near to pyrimidinone and ArH), 7.98–8.04 (m, 3H, ArH), 8.21 (s, 1H, pyrazole ring H). 9.05 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 56.2 (Ar-OCH_3), 56.4 (Ar-OCH_3), 57.4 (Ar-OCH_3), 109.3, 119.6, 120.1, 120.5, 121.7, 122.3, 122.9, 123.5, 124.7, 125.3, 126.7, 127.5, 128.9, 130.4, 131.9, 132.8, 133.7, 134.8, 136.3, 138.4, 144.4, 148.2, 151.2, 157.4, 158.2, 163.3 (C═O); ES-MS m/z 557.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_4$. (556.60): C, 73.37; H, 5.03; N, 10.07. Found C, 74.20; H, 5.63; N, 12.20.

2-{2-[3-(2,6-Dimethoxy-phenyl)-1-(4-methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (17). Yield 56%; mp 243–245°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.78(s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 3.96 (s, 3H, Ar-OCH_3), 6.67 (d, 1H, J = 16.3 Hz, olefinic H near to pyrazole), 7.25–7.56 (m, 8H, ArH and olefinic H near to pyrimidinone), 7.65 (m, 2H, ArH), 7.80–7.85 (m, 2H, ArH), 8.00 (d, 1H, J = 6.9 Hz, ArH), 8.20–8.33 (m, 4H, prazole ring H and ArH), 8.90 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 56.5 (Ar-OCH_3), 56.3 (Ar-OCH_3), 58.5 (Ar-OCH_3), 109.1, 119.1, 120.2, 120.9, 121.4, 122.8, 122.9, 123.5, 124.8, 125.7, 126.7, 127.2, 128.7, 130.9, 131.6, 132.3, 133.5, 134.5, 136.7, 138.1, 144.9, 149.1, 151.1, 157.1, 158.3, 163.5 (C═O); ES-MS m/z 557.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_4$. (556.60): C, 73.37; H, 5.03; N, 10.07. Found C, 73.80; H, 4.99; N, 10.00.

2-{2-[3-(2-Methoxy-3-methyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (18). Yield 49%; mp 229–231°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.34 (s, 3H, Ar-CH_3), 3.89 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.70 (d, 1H, J = 8.00 Hz, ArH), 7.24 (m, 4H, ArH), 7.42 (m, 4H, ArH), 7.62–7.80 (m, 5H, ArH), 8.20–8.35 (m, 4H, ArH), 9.00 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.1 (Ar-CH_3), 56.7 (Ar-OCH_3), 57.1 (Ar-OCH_3), 107.1, 117.2, 119.1, 120.1, 120.5, 120.9, 121.7, 122.3, 122.9, 123.5, 124.7, 125.3, 126.7, 127.5, 128.9, 130.4, 131.9, 132.8, 133.7, 134.8, 136.3, 138.4, 144.4, 148.2, 153.5, 157.1, 163.1 (C═O); ES-MS m/z 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.87; H, 5.08; N, 10.33.

2-{2-[3-(2-Methoxy-4-methyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-3-phenyl-pyrido[1,2-a] pyrimidin-4-one (19). Yield 53%; mp 219–222°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.34 (s, 3H, Ar-CH_3), 3.87 (s, 3H, Ar-OCH_3). 3.95 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, J = 16 Hz, olefinic H near to pyrazole), 7.25 (m, 4H, ArH), 7.34–7.40 (m, 4H, ArH and olefinic H near pyrimidinone), 7.65 (m, 2H, ArH), 7.82–8.00 (m, 4H, ArH), 8.22–8.30 (m, 3H, ArH and pyrazole ring H), 8.88 (s, 1H, ArH near to nitrogen). ^{13}C NMR (100 MHz, DMSO-d_6): 21.3 (Ar-CH_3), 56.7 (Ar-OCH_3), 58.1 (Ar-OCH_3), 107.13 117.4, 119.2, 120.7, 120.4, 120.6, 121.2, 121.4, 122.4, 122.9, 123.6, 124.2, 125.8, 126.1, 127.5, 128.3, 130.4, 131.2, 132.2, 133.4, 134.8, 136.9, 138.6, 144.8, 148.9, 153.5, 159.2, 163.6 (C═O); ES-MS m/z 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.49; H, 5.08; N, 10.00.

2-{2-[3-(2-Methoxy-5-methyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (20). Yield 78%; mp 204–206°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.37 (s, 3H, Ar-CH_3), 3.82 (s, 3H, Ar-OCH_3), 3.95 (s, 3H, Ar-OCH_3), 6.80 (d, 1H, J = 16 Hz, olefinic H near to pyrazole), 7.00 (m, 1H, ArH), 7.25–7.43 (m, 8H, ArH and olefinic H near to pyrimidinone), 7.60 (m, 1H, ArH), 7.72 (m, 2H, ArH), 8.00 (m, 2H, ArH), 8.20–8.30 (m, 3H, ArH and pyrazole ring H), 8.90 (s, 1H, ArH near to mitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9 (Ar-CH_3), 56.7 (Ar-OCH_3), 58.5 (Ar-OCH_3), 108.1 118.4, 119.8, 120.5, 120.9, 120.8, 121.7, 121.8, 122.2, 122.5, 123.7, 124.9, 125.3, 126.7, 127.8, 128.9, 130.5, 131.6, 132.0, 133.7, 134.9, 136.7, 138.9, 143.2, 148.7, 152.5, 157.9, 163.1 (C=O); ES-MS m/z 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.33; H, 5.20; N, 10.62.

2-{2-[3-(2-Methoxy-6-methyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (21). Yield 47%; mp 233–235°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.37 (s, 3H, Ar-CH_3), 3.95 (s, 3H, Ar-OCH_3), 3.99 (s, 3H, Ar-OCH_3), 6.80 (d, J = 16 Hz, 1H, olefinic H near to pyrazole), 7.00 (d, 1H, J = 7.88 Hz, ArH), 7.20–7.24 (m, 3H, ArH), 7.30–7.65 (m, 4H, ArH and olefinic H near to pyrimidinone), 7.80–8.00 (m, 5H, ArH), 8.20–8.35 (m, 4H, ArH and pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.3 (Ar-CH_3), 56.6 (Ar-OCH_3), 57.5 (Ar-OCH_3), 109.1 119.4, 120.1, 120.9, 121.3, 121.8, 122.2, 122.9, 123.9, 124.5, 125.8, 126.9, 127.1, 128.9, 130.9, 131.9, 132.4, 133.0, 134.9, 136.7, 138.9, 143.2, 148.7, 152.6, 157.1, 162.8 (C═O); ES-MS m/z 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.24; H, 5.08; N, 10.28.

2-{2-[3-(3-Methoxy-2-methyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (22). Yield 69%; mp 219–223°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.33 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 3.99 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, J = 16.1 Hz, olefinic H near to pyrazole), 7.00–7.20 (m, 3H, ArH), 7.24–7.35 (m, 3H, ArH), 7.40–7.60 (m, 3H, olefinic H near to pyrimidinones and ArH), 7.65–7.70 (m, 2H, ArH), 7.80–8.00 (m, 5H, ArH), 8.23 (s, 1H, pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 23.9 (Ar-CH_3), 56.9 (Ar-OCH_3), 57.9 (Ar-OCH_3), 106.3, 118.1, 120.7, 120.9, 121.9, 122.2, 122.9,

123.9, 124.8, 125.7, 126.9, 127.8, 129.1, 130.9, 131.9, 132.4, 133.0, 134.9, 136.1, 137.5, 138.9, 143.2, 148.7, 151.9, 157.8, 162.5 (C═O); ES-MS *m*/*z* 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 76.00; H, 5.09; N, 10.29.

2-{2-[3-(4-Methoxy-2-methyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-pyrido[1,2-a]pyrimidin-4-one (23). Yield 66%; mp 213–215°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.34 (s, 3H, Ar-CH_3), 3.89 (s, 3H, Ar-OCH_3), 3.97 (s, 3H, Ar-OCH_3), 670 (d, 1H, *J* = 16.2 Hz, olefinic H near to pyrazole), 7.20–7.35 (m, 3H, ArH), 7.40–7.55 (m, 4H, olefinic H near to pyrimidine and ArH), 7.70–8.00 (m, 4H, ArH), 8.00–8.20 (m, 6H, pyrazole ring H and ArH), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 23.8 (Ar-CH_3), 56.1 (Ar-OCH_3), 57.7 (Ar-OCH_3), 107.3, 118.5, 120.1, 120.9, 121.3, 122.5, 122.4, 123.6, 124.6, 125.9, 126.9, 127.6, 129.1, 130.7, 131.6, 132.7, 133.2, 134.5, 136.5, 137.7, 138.9, 142.4, 143.1, 148.5, 152.1, 157.8, 162.9 (C═O); ES-MS *m*/*z* 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.01; H, 5.27; N, 10.08.

2-{2-[3-(5-Methoxy-2-methyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-pyrido[1,2-a]pyrimidin-4-one (24). Yield 59%; mp 227–230°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.37 (s, 3H, Ar-CH_3), 3.82 (s, 3H, Ar-OCH_3), 3.95 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, *J* = 15.8 Hz, olefinic H near to pyrazole), 7.20–7.60 (m, 6H, olefinic H near to pyrimidinone and ArH), 7.65–8.00 (m, 5H, ArH), 8.20–8.30 (m, 6H, pyrazole ring H and ArH), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 23.1 (Ar-CH_3), 56.4 (Ar-OCH_3), 57.9 (Ar-OCH_3), 109.1, 118.1, 120.4, 120.8, 121.6, 122.7, 122.9, 123.4, 124.7, 125.2, 126.2, 127.1, 127.9, 130.7, 131.6, 132.7, 133.2, 134.4 136.1, 137.7, 138.3, 142.4, 143.1, 148.6, 152.9, 157.1, 163.2 (C═O); ES-MS *m*/*z* 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.24; H, 5.38; N, 10.29.

2-{2-[3-(6-Methoxy-2-methyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-pyrido[1,2-a]pyrimidin-4-one (25). Yield 56%; mp 244–246°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.33 (s, 3H, Ar-CH_3), 3.87 (s, 3H, Ar-OCH_3), 3.97 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, *J* = 16 Hz, olefinic H near to pyrazole), 7.05 (d, 1H, *J* = 7.89 Hz, ArH), 7.20–7.30 (m, 4H, ArH), 7.34–7.65 (m, 6H, olefinic H near to pyrimidinone and ArH), 7.80–8.00 (m, 3H, ArH), 8.20–8.34 (m, 3H, pyrazole ring H and ArH), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 23.9 (Ar-CH_3), 56.1 (Ar-OCH_3), 57.5 (Ar-OCH_3), 106.9, 117.8, 119.1, 120.7, 120.9, 121.8, 122.9, 122.8, 123.7, 124.1, 125.4, 126.1, 126.9, 127.9, 130.7, 131.6, 132.4, 133.7, 134.8 136.5, 137.9, 138.8, 142.8, 143.9, 148.9, 153.9, 157.7, 163.9 (C═O); ES-MS *m*/*z* 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.24; H, 5.29; N, 10.77.

2-{2-[3-(2,3-Dimethyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (26). Yield 59%; mp 218–221°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.33 (s, 3H, Ar-CH_3), 2.37 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, *J* = 15.5 Hz, olefinic H near to pyrazole), 7.05 (d, 1H, *J* = 8 Hz, ArH), 7.20–7.35 (m, 4H, ArH), 7.45–7.51 (m, 2H, olefinic H near to pyrimidinone and ArH), 7.80–7.85 (m, 3H, ArH), 8.00 (d, 1H, *J* = 6.89 Hz, ArH), 8.20–8.32 (m, 5H, pyrazole ring H and ArH), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.7 (Ar-CH_3),, 22.4 (Ar-CH_3), 56.6 (Ar-OCH_3), 107.9, 118.9, 119.6, 120.7, 120.9, 121.5, 122.9, 122.8, 123.4, 124.7, 125.8, 126.7, 126.2, 127.0, 130.1, 131.7, 132.1, 133.6, 133.9, 134.4 136.2, 137.5, 138.7, 142.8, 143.3, 148.2, 157.7, 163.1 (C═O); ES-MS *m*/*z* 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 77.87; H, 5.99; N, 10.80.

2-{2-[3-(2,4-Dimethyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (27). Yield 63%; mp 249–251°C; DMSO-d_6): δ ppm: 2.34 (s, 3H, Ar-CH_3), 2.38 (s, 3H, Ar-CH_3), 3.99 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, *J* = 16 Hz, olefinic H near to pyrazole), 7.10 (d, 1H, *J* = 7.09 Hz, ArH), 7.30–7.62 (m, 5H, olrfinic H near to pyrimidinone and ArH), 7.65–7.80 (m, 4H, ArH), 7.80–7.85 (m, 3H, ArH), 8.00 (d, 1H, *J* = 7.2 Hz, ArH), 8.20–8.22 (m, 2H, pyrazole ring H and ArH), 8.80 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9(Ar-CH_3),, 22.7 (Ar-CH_3), 56.9 (Ar-OCH_3), 106.5, 117.9, 119.6, 120.1, 120.4, 121.75, 122.8, 122.9, 123.4, 124.7, 125.8, 126.9, 127.2, 127.9, 130.1, 130.9, 131.7, 132.6, 133.8, 134.3, 134.9 136.1, 137.9, 138.7, 142.8, 143.1, 148.4, 157.7, 163.5 (C═O); ES-MS *m*/*z* 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 78.00; H, 5.09; N, 10.52.

2-{2-[3-(2,5-Dimethyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (28). Yield 57%; mp 219–221°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.31 (s, 3H, Ar-CH_3), 2.38 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, *J* = 16.2 Hz, olefinic H near to pyrazole), 7.05 (d, 1H, *J* = 7.65 Hz, ArH), 7.20–7.23 (m, 3H, ArH), 7.39–7.45 (m, 5H, ArH and olefinic H near to pyrimidinone), 7.50–7.65 (m, 4H, ArH), 7.80–8.00 (m, 3H, ArH), 8.22 (s. 1H, pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.1 (Ar-CH_3),, 22.9 (Ar-CH_3), 57.8 (Ar-OCH_3), 106.5, 117.7, 119.9, 120.7, 120.9, 121.7, 122.6, 122.9, 123.5, 124.7, 125.9, 126.3, 127.4, 127.9, 130.5, 130.9, 131.9, 132.8, 133.9, 134.5, 134.9 136.6, 137.9, 138.5, 142.9, 143.4, 148.6, 157.9, 163.9 (C═O); ES-MS *m*/*z* 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 77.09; H, 5.89; N, 10.55.

2-{2-[3-(2,6-Dimethyl-phenyl)-1-(4-Methoxy-phenyl)-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (29). Yield 66%; mp 212–214°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.33 (s, 3H, Ar-CH_3), 2.37 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.77 (d, 1H,

J = 8.22 Hz, ArH), 6.88–7.00 (m, 2H, olefinic H near to pyrazole and ArH), 7.20–7.34 (m, 4H, ArH), 7.40–7.60 (m, 3H, olefinic H near to pyrimidinone and ArH), 7.80–8.00 (m, 3H, ArH), 8.20–8.24 (m, 5H, pyrazole ring H and ArH), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.5 (Ar-CH_3),, 21.9 (Ar-CH_3), 54.6 (Ar-OCH_3), 106.7, 117.9, 119.9, 120.6, 120.9, 121.9, 122.7, 122.9, 123.9, 124.9, 125.5, 126.4, 127.8, 127.7, 130.6, 130.4, 131.9, 132.9, 133.9, 134.6, 134.9 136.4, 137.0, 138.6, 142.4, 143.7, 148.7, 157.9, 163.2 (C═O); ES-MS m/z 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 78.00; H, 5.41; N, 10.88.

2-{2-[3-(2,3-Dimethoxy-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (30). Yield 57%; mp 217–219°C ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.27 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, J = 16 Hz, olefinic H near to pyrazole), 7.00 (d, 1H, J = 8.22 Hz, ArH), 7.22–7.30 (m, 4H, ArH), 7.35–7.45 (m, 5H, olefinic H near to pyrimidinone and ArH), 7.60–8.00 (m, 4H, ArH), 8.20–8.30 (m, 3H, pyrazole ring H and ArH), 8.90 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9 (Ar-CH_3), 54.6 (Ar-OCH_3), 54.9 (Ar-OCH_3), 108.1, 118.3, 119.4, 120.2, 120.9, 121.5, 122.6, 122.9, 123.3, 124.4, 125.2, 126.3, 126.9, 127.1, 127.7, 130.4, 131.9, 132.5, 133.5, 134.2, 134.9 136.9, 137.0, 143.7, 148.7, 154.9, 157.9, 163.2 (C═O); ES-MS m/z 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.01; H, 4.88; N, 10.01.

2-{2-[3-(2,4-Dimethoxy-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (31). Yield 52%; mp 237–239°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.37 (s, 3H, Ar-CH_3), 3.95 (s, 3H, Ar-OCH_3), 3.99 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, J = 16 Hz, olefinic H near to pyrazole), 7.00–7.25 (m, 5H, ArH), 7.45–7.60 (m, 5H, olefinic H near to pyrimidinone ArH), 7.80–8.00 (m, 3H, ArH), 8.20–8.34 (m, 5H, pyrazole ring H and ArH), 8.90 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.1 (Ar-CH_3), 54.1 (Ar-OCH_3), 54.9 (Ar-OCH_3), 104.3, 116.3, 119.1, 120.2, 120.9, 121.7, 122.3, 122.9, 123.5, 124.3, 125.5, 126.2, 126.9, 127.1, 127.9, 130.8, 131.9, 132.5, 133.8, 134.7, 134.9 136.9, 137.2, 143.9, 148.9, 154.9, 157.0, 163.9 (C═O); ES-MS m/z 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.24; H, 5.09; N, 10.79.

2-{2-[3-(2,5-Dimethoxy-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (32). Yield 62%; mp 213–215°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.33 (s, 3H, Ar-CH_3), δ 3.97 (s, 3H, Ar-OCH_3), 3.99 (s, 3H, Ar-OCH_3), 6.70 (d, 1H, J = 15.4 Hz, olefinic H near to pyrazole), 7.23–7.45 (m, 5H, olefinic H near to pyrimidinone ArH), 7.55–7.60 (m, 5H, ArH), 7.80–8.00 (m, 4H, ArH), 8.20–8.34 (m, 3H, pyrazole ring H and ArH), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9 (Ar-CH_3), 54.8 (Ar-OCH_3), 55.9 (Ar-OCH_3), 104.6, 116.9, 120.2, 120.9, 121.7, 122.8, 122.9, 123.7, 124.4, 125.8, 126.5, 126.9, 127.1, 128.3, 130.8, 131.9, 132.8, 133.9, 134.9, 134.6, 136.7, 137.7, 143.9, 148.1, 154.9, 157.6, 163.1 (C═O); ES-MS m/z 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.01; H, 5.02; N, 10.27.

2-{2-[3-(2,6-Dimethoxy-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (33). Yield 64%; mp 228–230°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.32 (s, 3H, Ar-CH_3), 3.87 (s, 3H, Ar-OCH_3), 3.91 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, 16 Hz, olefinic H near to pyrazole), 7.00–7.20 (m, 2H, ArH), 7.34–7.45 (m, 5H, olefinic H near to pyrimidinone ArH), 7.55–7.65 (m, 3H, ArH), 7.70 (m, 2H, ArH), 7.80–7.82 (m, 2H, ArH), 8.00 (d, 1H, J = 7.09 Hz, ArH), 8.23 (s, 1H, pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.1 (Ar-CH_3), 54.1(Ar-OCH_3), 55.2 (Ar-OCH_3), 105.1, 117.9, 120.4, 120.9, 121.1, 122.9, 123.9, 124.8, 125.9, 126.7, 126.9, 127.5, 128.1, 130.4, 131.0, 132.7, 133.2, 134.0, 134.9, 136.7, 137.6, 143.6, 148.6, 154.9, 157.0, 163.5 (C═O); ES-MS m/z 541.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_3$. (540.6): C, 75.40; H, 5.21; N, 10.36. Found C, 75.01; H, 5.39; N, 10.87.

2-{2-[3-(2-Methoxy-3-Methyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (34). Yield 59%; mp 242–244°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.31 (s, 3H, Ar-CH_3), 2.38 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, J = 16.3 Hz, olefinic H near to pyrazole), 7.22–7.33 (m, 6H, ArH), 7.50–7.80 (m, 7H, olefinic H near to pyrimidinone and ArH), 7.98–8.22 (m, 4H, ArH and pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9 (Ar-CH_3), 23.1 (Ar-CH_3), 54.5 (Ar-OCH_3), 107.1, 117.3, 120.1, 120.9, 121.3, 122.8, 123.6, 124.5, 125.0, 126.9, 127.5, 128.4, 130.5, 131.0, 132.7, 133.1, 134.0, 134.9, 135.9, 136.1, 137.1, 143.1, 148.4, 157.2, 163.9 (C═O); ES-MS m/z 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 78.02; H, 5.39; N, 10.03.

2-{2-[3-(2-Methoxy-4-Methyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (35). Yield 67%; mp 234–236°C; mp^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.27 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, 16 Hz olefinic H near to pyrazole), 7.20–7.45 (m, 6H, ArH and olefinic H near to pyrimidinone), 7.60–7.85 (m, 4H, ArH), 8.00–8.22 (m, 6H, ArH and pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.2 (Ar-CH_3), 23.3 (Ar-CH_3), 54.6 (Ar-OCH_3), 107.5, 118.3, 120.5, 120.9, 121.7, 122.9, 123.9, 124.4, 125.6, 126.9, 127.4, 128.9, 130.7, 131.4, 132.6,

133.2, 134.1, 134.9, 135.9, 136.3, 137.5, 143.2, 148.2, 157.4, 163.9 (C═O); ES-MS *m/z* 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 77.88; H, 5.09; N, 10.50.

2-{2-[3-(2-Methoxy-5-Methyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (36). Yield 54%; mp 236–238°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.33 (s, 3H, Ar-CH_3), 2.37 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, *J* = 16 Hz, olefinic H near to pyrazole), 7.00–7.20 (m, 3H, ArH), 7.25–7.40 (m, 5H, ArH and olefinic H near to pyrimidinone), 7.45–7.60 (m, 6H, ArH), 7.80–8.00 (m, 2H, ArH), 8.24 (s, 1H, pyrazole ring H), 8.99 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9 (Ar-CH_3), 23.9 (Ar-CH_3), 54.1 (Ar-OCH_3), 105.9, 117.1, 120.1, 120.9, 121.7, 122.9, 123.2, 124.3, 125.1, 126.1, 127.5, 128.9, 130.1, 131.4, 132.3, 133.6, 134.4, 134.1, 135.2, 136.6, 137.7, 143.5, 148.6, 157.9, 163.2 (C═O); ES-MS *m/z* 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 77.74; H, 5.94; N, 10.17.

2-{2-[3-(2-Methoxy-6-Methyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (37). Yield 64%; mp 224–226 °C^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.38 (s, 3H, Ar-CH_3), 2.39 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, *J* = 15.8 Hz, Hz, ArH), 7.05 (d, 2H, ArH), 7.25–7.34 (m, 4H, ArH), 7.40–7.65 (m, 5H, olefinic H near to pyrimidinone and ArH), 7.80–7.90 (m, 3H, ArH), 8.00 (d, 1H, *J* = 7.05 Hz, ArH), 8.23 (s, 1H, pyrazole ring H), 8.99 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.1 (Ar-CH_3), 23.1 (Ar-CH_3), 54.2 (Ar-OCH_3), 105.2, 117.7, 120.6, 120.4, 121.2, 122.4, 123.4, 124.3, 125.9, 126.4, 127.6, 128.9, 130.5, 131.7, 132.4, 133.6, 134.2, 134.4, 135.2, 137.7, 143.5, 148.6, 157.9, 163.6 (C═O); ES-MS *m/z* 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 78.00; H, 5.49; N, 10.87.

2-{2-[3-(3-Methoxy-2-Methyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (38). Yield 68%; mp 222–224°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.31 (s, 3H, Ar-CH_3), δ 2.38 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, *J* = 16 Hz, ArH), 7.24–7.30 (m, 4H, ArH), 7.45–7.65 (m, 5H, olefinic H near to pyrimidinone and ArH), 7.70 (m, 1H, ArH), 7.80–8.10 (m, 6H, ArH), 8.23 (s, 1H, pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.2 (Ar-CH_3), 23.3 (Ar-CH_3), 54.1 (Ar-OCH_3), 106.1, 117.2, 120.5, 120.6, 121.1, 122.9, 123.2, 124.3, 125.1, 126.3, 127.8, 128.9, 130.5, 131.7, 132.3, 133.5, 134.1, 135.6, 136.6, 137.4, 143.9, 148.7, 157.1, 163.0 (C═O); ES-MS *m/z* 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 77.78; H, 5.88 N, 10.12.

2-{2-[3-(4-Methoxy-2-Methyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (39). Yield 54%; mp 217–219°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.27 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 6.60 (d, 1H, *J* = 15.3 Hz, olefinic H near to pyrazole), 7.00 (d, 1H, *J* = 8.05 Hz, ArH), 7.23–7.35 (m, 6H, ArH), 7.45–7.60 (m, 4H, olefinic H near to pyrimidinone and ArH); 7.80–7.89 (m, 5H, ArH), 8.22 (s, 1H, pyrazole ring H), 8.91 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.1 (Ar-CH_3), 23.2 (Ar-CH_3), 54.9 (Ar-OCH_3), 105.8, 117.2, 120.3, 120.8, 121.4, 122.2, 123.4, 124.4, 125.7, 126.2, 127.4, 128.6, 130.3, 131.9, 132.3, 133.5, 134.4, 134.1, 135.5, 136.7, 137.7, 143.6, 148.0, 157.9, 163.2 (C═O); ES-MS *m/z* 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 77.63; H, 5.40; N, 11.08.

2-{2-[3-(5-Methoxy-2-Methyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (40). Yield 59%; mp 214–216°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.33 (s, 3H, Ar-CH_3), 3.97 (s, 3H, Ar-OCH_3), 3.99 (s, 3H, Ar-OCH_3), 6.80 (d, 1H, *J* = 16.20 Hz, olefinic H near to pyrazole), 7.20–7.35 (m, 6H, ArH), 7.45–7.65 (m, 4H, olefinic H near to pyrimidinone and ArH), 7.80–8.00 (m, 6H, ArH), 8.22 (s, 1H, pyrazole ring H). 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.3 (Ar-CH_3), 23.1 (Ar-CH_3), 55.9 (Ar-OCH_3), 107.8, 118.2, 119.2, 120.8, 121.9, 122.6, 123.5, 124.7, 125.6, 126.1, 127.7, 128.8, 130.9, 131.4, 132.3, 133.6, 134.1, 135.7, 136.8, 137.9, 143.7, 148.9, 157.9, 162.9 (C═O); ES-MS *m/z* 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 78.01; H, 5.41; N, 10.82.

2-{2-[3-(6-Methoxy-2-Methyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (41). Yield 68%; mp 224–226°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.34 (s, 3H, Ar-CH_3), 2.38 (s, 3H, Ar-CH_3), 3.99 (s, 3H, Ar-OCH_3), 6.70 (d, 1H, *J* = 16 Hz, ArH), 7.00–7.35 (m, 7H, ArH), 7.45–7.65 (m, 5H, olefinic H near to pyrazole and ArH), 7.80–8.00 (m, 4H, ArH), 8.29 (s, 1H, pyrazole ring H), 8.99 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9 (Ar-CH_3), 23.8 (Ar-CH_3), 56.9 (Ar-OCH_3), 108.1, 117.9, 119.2, 120.1, 121.7, 122.1, 123.4, 124.1, 125.1, 126.3, 127.0, 128.5, 130.1, 131.5, 132.4, 133.5, 134.6, 135.4, 136.7, 137.0, 143.3, 148.6, 157.0, 164.1 (C═O); ES-MS *m/z* 525.6 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O_2$. (524.6): C, 77.84; H, 5.39; N, 10.68. Found C, 78.00; H, 4.99; N, 10.97.

2-{2-[3-(2,3-Dimethyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (42). Yield 53%; mp 238–240°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.30 (s, 3H, Ar-CH_3), 2.35–2.40 (d, 6H, 2 X Ar-CH_3), 6.65 (d, 1H, 16 Hz, olefinic H near to pyrazole), 7.20 (s, 1H, ArH), 7.25–7.35 (m, 6H, olefinic H near to pyrimidinone and ArH), 7.65–8.00 (m, 5H, ArH), 8.20–8.35 (m, 4H, pyrazole ring H and ArH), 9.00 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9 (Ar-CH_3), 22.3 (Ar-CH_3), 23.8 (Ar-CH_3), 106.5,

117.1, 119.1, 120.3, 121.1, 122.4, 123.8, 124.9, 125.2, 126.1, 127.1, 128.4, 130.4, 131.4, 132.2, 133.3, 134.5, 135.7, 136.1, 137.1, 143.2, 148.1, 164.1 (C═O); ES-MS *m*/*z* 509.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O$. (508.6): C, 80.29; H, 5.55; N, 11.02. Found C, 80.49; H, 5.40; N, 10.90.

2-{2-[3-(2,4-Dimethyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (43). Yield 55%; mp 212–214°C; ^{1}H NMR (400 MHz, DMSO-*d*6): δ ppm: 2.20 (s, 3H, Ar-CH_3), 2.25–2.37 (d, 6H, 2 X Ar-CH_3), 6.60 (d, 1H, 16 Hz, olefinic H near to pyrazole), 7.24–7.55 (m, 7H, olefinic H near to pyrimidinone ArH), 7.65–8.05 (m, 7H, ArH), 8.10–8.35 (m, 3H, pyrazole H and ArH), 9.00 (s, 1H, ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.2 (Ar-CH_3), 22.4 (Ar-CH_3), 23.9 (Ar-CH_3), 108.5, 117.3, 119.4, 120.1, 121.2, 122.6, 123.4, 124.1, 125.5, 126.5, 127.5, 128.8, 130.9, 131.8, 132.1, 133.6, 134.1, 135.9, 136.2, 137.7, 143.1, 148.5, 163.9 (C═O); ES-MS *m*/*z* 509.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O$. (508.6): C, 80.29; H, 5.55; N, 11.02. Found C, 80.23; H, 5.35; N, 11.39.

2-{2-[3-(2,5-Dimethyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (44). Yield 74%; mp 218–220°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.21 (s, 3H, Ar-CH_3), 2.39 (d, 3H, Ar-CH_3), 2.42 (s, 3H, Ar-CH_3), 6.80 (d, 1H, *J* = 16 Hz, olefinic H near to pyrazole), 7.00 (s, 1H, ArH), 7.24–7.60 (m, 10H, olefinic H near to pyrimidinone and ArH), 7.80–8.00 (m, 5H, ArH), 8.29 (s, 1H, pyrazole ring H), 8.95 (s, 1H ArH near to nitrogen); ^{13}C NMR (100 MHz, DMSO-d_6): 21.2 (Ar-CH_3), 22.5 (Ar-CH_3), 23.0 (Ar-CH_3), 107.6, 117.9, 119.1, 120.1, 121.6, 122.2, 123.5, 124.4, 125.5, 126.9, 127.1, 128.3, 130.8, 131.7, 132.4, 133.7, 134.2, 135.1, 136.1, 137.2, 143.4, 148.7, 163.2 (C═O); ES-MS *m*/*z* 509.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O$. (508.6): C, 80.29; H, 5.55; N, 11.02. Found C, 80.34; H, 5.60; N, 11.04.

2-{2-[3-(2,6-Dimethyl-phenyl)-1-p-tolyl-1H-pyrazol-4-yl]-vinyl}-3-phenyl-pyrido[1,2-a]pyrimidin-4-one (45). Yield 59%; mp 227–229°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 2.22 (s, 3H, Ar-CH_3), 2.35 (d, 3H, Ar-CH_3), 2.42 (s, 3H, Ar-CH_3), 6.60 (d, 1H, *J* = 16 Hz, olefinic H near to pyrazole), 7.22–7.55 (m, 7H, olefinic H near to pyrimidinone and ArH), 7.60–8.00 (m, 4H, ArH), 8.10–8.16 (m, 5H, ArH), 8.21 (s, 1H, pyrazole rng H), 8.95 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.6 (Ar-CH_3), 22.9 (Ar-CH_3), 23.0 (Ar-CH_3), 107.1, 117.29, 119.0, 120.1, 121.4, 122.1, 123.1, 124.1, 125.3, 126.9, 127.3, 128.1, 130.3, 131.4, 132.1, 133.4, 134.1, 135.3, 136.5, 137.8, 143.7, 148.9, 163.1 (C═O); ES-MS *m*/*z* 509.3 [M + 1]. *Anal.* Calcd for $C_{34}H_{28}N_4O$. (508.6): C, 80.29; H, 5.55; N, 11.02. Found C, 80.30; H, 5.84; N, 10.84.

Biology. ***COX-1/COX-2 inhibitory screening assay.*** The "COX inhibitor screening assay" kits with 96-well plates were used to carry *in vitro* COX-1/2 inhibitory performance of synthesized analogues. Ovine COX-1 and human recombinant COX-2 were used in this experiment. Each activity tube of the experiment kit was initially filled with 10 µL of heme, 10 µL of COX-1 and COX-2, and 950 µL of reaction buffer (0.1 M Tris-HCl, pH 8.0, comprising 5 mM EDTA and 2 mM phenol). Similarly, the inhibitory tubes were prepared by addition of all these material along with addition of inhibitory compound with final concertation of 100, 10, 0.1, 0.01, and 0.001 µM, so that the final volume of the tube was adjusted to 1 mL. The COX-1 and COX-2 inactivated enzyme tubes were obtained after keeping these tubes in boiling water for a few minutes. Once the tube incubated for 20 min at 37°C, the arachidonic acid was added in each tube and initiated the reaction, hence incubated the tubes for 2–3 min at 37°C. Afterward, the reaction was quenched by adding 1 M HCl (50 µL). The $SnCl_2$ (100 µL) was added to obtain PGF2a by the reduction of PGH2 thus formed. PG antiserum was added to quantify the PG generation in each tubes. As there is competition between PG and prostaglandin A conjugates (PG tracers) for the limited amount PG antiserum as the concertation of PG varies while the concentration of PG tracers held constant, the concertation of PG tracers binds to PG antiserum that is inversely proportional to the concentration of PG in the tube. This rabbit antiserum-P (either free or tracer) complex binds to a mouse monoclonal antirabbit antibody that has been previously attached to the tube. The plate is washed to remove any unbound reagents, and then Ellman's reagent (which contains the substrate to AChe) is added to the well. Typical yellow color was observed due to this enzymatic actiivity, which was strongly observed at 420 nm. The intensity of color was determined spectrophotometrically. The intensity of color is proportional to the amount of free PG traces bound to the tube, which is inversely proportional to the amount of free PG present in the tube during incubation process. When there is an absorption at 420 nm observed in 96-well plates, it indicates the presence of higher level of PG in the tubes, which in turn shows less inhibition of enzymes. These absorption values of different tubes confirm the COX inhibitory activities of synthesized compounds. With the help of GraphPad PRISM, the IC_{50} value (concentration of test compound responsible for 50% inhibition) of the test compound was determine by plotting dose–response inhibition curve.

In vivo anti-inflammatory activity study. Carrageenan-induced rat paw edema method was used to determine *in vivo* anti-inflammatory activities of selected compounds. In this experiment, three different sets of rats of either sex were prepared, one set for standard

compound, second set for control sample ,and third set for synthesized compounds. Inflammation was induced by injection of freshly prepared aqueous solution carrageenan (1.0% w/v, 0.1 mL) in subplanter region of right paw in each rat. Before injecting the carrageenan solution, the paw volumes of rat from all sets were measured with the help of digital plethysmometer (UGO BASIL, ITALY) and then again after 1, 2, and 3 h time point, the volumes of paw was measured. After treatments of the test compound, the reduction in paw volumes were expressed as oedema and % inhibitions were calculated as per following formula.

$$\% \text{ Inhibition} = \frac{(Vt - Vc)_{\text{control}} - (Vt - Vc)_{\text{tested compound}}}{(Vt - Vc)_{\text{control}} X\ 100}$$

Wherein Vt = Volumes of oedema at particular time and Vc = Volume oedema at zero time.

Data was analysed by one-way ANOVA followed by Dunnet's test (n=6).

Dose levels – Test compounds and celecoxib (25 mg/Kg).

Ulcerogenicity study. Albino rats of weight 150–200 g were taken for this study. These rats of either sex were divided into different groups (six in each group). Control group animals were administered only 1% carboxymethyl cellulose solution in water. Second group was administered with diclofenac sodium (25 mg/kg) daily for the period of 4 days. Third group were administered with synthesized (test) compound (25 mg/kg) for 4 days. Later, on the fifth day, pylorus was ligated. Prior to ligation, the animals were fasted for 24 h. After ligation, the stomach was removed and opened along with the greater curvature.

Acknowledgments. We acknowledge the management of Dr. Rafiq Zakaria College for Women and Maulana Azad College for their constant encouragement.

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