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ORIGINAL RESEARCH

Synthesis, characterization and their anticonvulsant, anti-inflammatory studies of some novel chromeno oxadiazoles

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Abstract In this study, a series of new 1,2,4-oxadiazole derivatives containing 3,4-dihydro-2*H*-chromen-2-amine moiety were synthesized by efficient microwave reaction of 2-amino-*N*′-hydroxychroman-3-carboxamidine and suitable aldehyde. Structures of all the synthesized compounds were confirmed by spectral studies and C, H, N analyses. Newly synthesized compounds were screened for their anticonvulsant and anti-inflammatory properties. Few of the compounds exhibited excellent anticonvulsant activity as compared to the standard drug Diazepam. Also compounds have exhibited moderate anti-inflammatory activity as compared to the standard drug Diclofenac sodium.

Keywords Chromeno oxadiazole · Anticonvulsant activity · Anti-inflammatory activity

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Introduction

Nitrogen–oxygen containing heterocycles are of synthetic interest because they constitute an important class of natural and synthetic products, many of which exhibit useful biological activities (Vu *et al*., 1999). The interest in five-membered systems containing one oxygen and two nitrogen atoms (positions 1, 2, and 4) stems from the occurrence of saturated and partially saturated 1,2,4-oxadiazoles in biologically active compounds and natural products (Orlek *et al*., 1991; Ankersen *et al*., 1997).

1,2,4-Oxadiazoles have recently received considerable attention by synthetic chemists as heterocyclic amide and ester bioisosteres. Bioisosteric replacement of the amide moiety represents an area that is currently a center of focus because of its implications in peptide chemistry and the development of peptidomimetics (Kaboudin and Navaee, 2003; Andersen *et al*., 1994). Furthermore, derivatives containing 1,2,4-oxadiazole ring systems have been employed as antirhinovirals, tyrosine kinase inhibitors, serotoninergic (5-HT3) antagonists, dopamine receptor (D4) ligands, anti-inflammatory agents, antitumor agents, monoamine oxidase inhibitors, coronary artery dilators, anesthetic agents, muscle relaxants, antischistosomal agents, and aldose reductase inhibitors (Caliendo *et al*., 2001). In our recent paper (Isloor *et al*., 2010), 1,2,4-oxadiazole derivatives have showed significant antimicrobial properties.

Compounds comprising a coumarin (2-oxo-2*H*-1-benzopyran) backbone have a wide range of biological activities (Kalluraya *et al*., 2000, 2001). Thus, among the natural and synthetic coumarin derivatives, there are compounds possessing antimicrobial (Isloor *et al*., 2010; Maxwell, 1993), antitumor (Dexeus *et al*., 1990), anti-HIV (Zembower *et al*., 1997), and other (Maxwell, 1993) activities. Combination of chromene and oxadiazoles may further enhance the

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biological activity. Keeping in view of these observations and in continuation of our research on biologically active heterocycles, we hereby report the synthesis of some novel 1,2,4-oxadiazoles containing 3,4-dihydro-2*H*-chromen-2-amine containing moieties and their pharmacological evaluation.

Chemistry

The general strategy used for the synthesis of **3**,(1,2,4-oxadiazol-3-yl)-3,4-dihydro-2*H*-chromen-2-amine is outlined in Scheme 1. Compound **1** was prepared by following the reported procedure (Evdokimov *et al*., 2007). Subsequent reduction of **1** using sodium borohydride in alcohol medium gave compound **2** in high yield. Amidoxime **3** was prepared by treating compound **2** with hydroxylamine hydrochloride in the presence of base. Further, 1,2,4-oxadiazole was prepared by using method reported in (Adib *et al*., 2006). The structure of **4a** was confirmed based on the elemental analyses and spectral data. The efficiency of the first reaction prompted us to extend this procedure to synthesize series of compounds (**4a**–**n**) using microwave reactor (Scheme 1).

Pharmacology

Anticonvulsant activity

Male albino mice weighting 25–35 g were used for pharmacological study. Animals were allowed free access to food and water except during the experiment (Singh *et al*., 1978; Srivastava *et al*., 1979) and housed at controlled room temperature with 12 h light and 12 h dark cycle. Animals were placed individually in glass cylinder (25 cm width, 25 cm length) and allowed to habituate for 30 min before the drug administration. For induction of convulsions, pentylenetetrazole (PTZ, Sigma, 80 mg/kg) was injected intraperitoneally. Immediately after PTZ injection, each animal was placed into the cylinder and its behavior was observed directly. PTZ solution was prepared by dissolving in distilled water and the test compounds were suspended in carboxymethylcellulose sodium (CMC 1 %) and tween 80 (5 %). The test compounds (25 mg/kg) were injected orally to groups of 06 mice 30 min before PTZ injection. PTZ-induced convulsions and mortality were evaluated for 30 min after drug injection based on seizure latency of tonic–clonic convulsions. Control groups received vehicle including water with CMC/tween 80. The anticonvulsant activity of the compounds was compared with diazepam as standard anticonvulsant at the dose of 2 mg/kg, by injecting intraperitoneally. As per the acute toxicity study (OECD 425), the dose of 25 mg/kg bw has been selected.

Anti-inflammatory activity

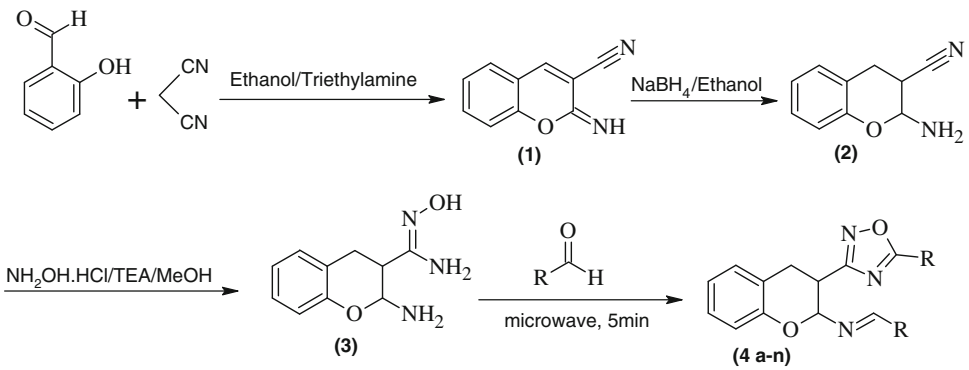
Screening of anti-inflammatory drugs by carrageenan-induced paw edema method (Maria et al., 2008; Hu et al., 2008)

Edema was induced in the left hind paw of Wistar rats (200–250 g) by the sub-plantar injection of 0.1 mL of 1 % carrageenan in distilled water. Both sexes were used. Each group composed of 6 animals. The animals which were bred in our laboratory were housed under standard conditions and received a diet of commercial food pellets and water ad libitum during the maintenance but they were entirely fasted during the experiment period. Our studies were conducted in accordance with recognized guidelines on animal experimentation.

The test compounds were given intraperitoneally 30 min after carrageenan injection. The difference in the paw volume of the injected and the control were compared for each animal and expressed as the difference of final paw volume to initial paw volume.

Statistical analysis

All experimental groups were composed of 6 animals. Data obtained from animal experiments were expressed as



Scheme 1 Synthetic route for the chromeno oxadiazoles

mean ± standard error (SEM). The statistical significance of difference between groups were assessed by means of analysis of variance (ANOVA) followed by Dunnet's test.

Result and discussion

Formation of 3,4-dihydro-2*H*-chromen-2-amine 1,2,4-oxadiazole derivatives was confirmed by recording their IR, ^{1}H NMR and mass spectra. IR spectrum of oxadiazole **4a** showed absorption at 3,006 cm^{-1} which is due to the aromatic stretching. An absorption band at 1,699 cm^{-1} is due to the C=N group, band at 1,057 cm^{-1} is due to stretching of oxadiazole. The ^{1}H NMR spectrum of **4a** showed multiplet in the region of δ, 7.03–7.14, δ, 7.5 is due to aromatic proton. The mass spectrum of **4a** showed molecular ion peak at *m/z* 450 and 452 which is in agreement with the molecular formula $C_{24}H_{17}C_{l2}N_3O_2$. Similarly, the spectral values for all the compounds and C, H, N analyses are given in the "Experimental".

Anti-inflammatory activity screening was carried out by paw edema method using Wistar rats. Anti-inflammatory activity revealed that the most of the tested compounds were moderately active. Compounds **4a**, **4g**, **4k**, and **4n** have showed % inhibition of 37, 40.9, 42.5, and 37.0, as compared to the standard drug Diclofenac sodium, which showed percentage of inhibition at 80.7. However, remaining compounds have showed poor anti-inflammatory activity. The presence of chromene ring in association with oxadiazole and other substitutions has accounted for the anti-inflammatory activity. The results of the anti-inflammatory studies have been presented in Table 1.

Further anticonvulsant activity of test compounds revealed that most of the tested compounds showed excellent anticonvulsant activity against the male albino mice. Eight of the tested compounds, namely **4a**, **4b**, **4c**, **4d**, **4e**, **4g**, **4l**, and **4m** have showed 100 % protection as compared to the standard drug Diazepam. All these molecules have chromene ring along with oxadiazoles with different substitutions, which has accounted for their significant anticonvulsant activity. Similarly, compounds **4h** and **4k** have showed moderate anticonvulsant activity. The results have been presented in Table 2.

Conclusion

A series of novel chromeno oxadiazoles were synthesized by microwave reaction in reasonably good yield. They were characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry, IR studies, and elemental analyses. Few of the selected compounds were screened for their possible anticonvulsant and anti-inflammatory studies using Diazepam and Diclofenac sodium as standards, respectively. Few of the tested compounds exhibited excellent anticonvulsant activity as compared to the standard drug Diazepam. Also compounds have exhibited moderate anti-inflammatory activity as compared to the standard drug Diclofenac sodium.

From the anticonvulsant study, it was clear that most of the compounds showed percentage inhibition of 100 % as compared to the standard drug. The presence of the chromene ring in association with the oxadizole has accounted for the biological activity.

Experimental

Melting points were determined by open capillary method and were uncorrected. The IR spectra (In KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded on a Perkin–Elmer EM 300 MHz

Table 1 Anti-inflammatory activity of test compounds by Carrageenan-induced paw odema test

Treatment	Dose (mg/kg)	Initial paw volume (ml) (b)	Paw volume after 3 h (ml) (a)	Edema volume (a − b)	Percentage inhibition
Control	Vehicle	0.93 ± 0.01	2.20 ± 0.04	1.27 ± 0.02	
Diclofenac	10	0.80 ± 0.04	1.05 ± 0.02	0.25 ± 0.04	80.4**
4a	20	0.93 ± 0.08	1.73 ± 0.01	0.80 ± 0.09	37.0
4b	20	1.00 ± 0.04	1.93 ± 0.06	0.93 ± 0.02	26.8
4c	20	0.93 ± 0.01	1.85 ± 0.08	0.92 ± 0.01	27.5
4d	20	0.83 ± 0.09	1.70 ± 0.02	0.87 ± 0.04	31.5
4f	20	0.93 ± 0.02	1.90 ± 0.04	0.97 ± 0.08	23.6
4g	20	0.85 ± 0.09	1.60 ± 0.09	0.75 ± 0.04	40.9*
4k	20	0.90 ± 0.04	1.63 ± 0.01	0.73 ± 0.02	42.5*
4m	20	0.80 ± 0.01	1.85 ± 0.04	1.05 ± 0.08	17.3
4n	20	0.98 ± 0.09	1.78 ± 0.02	0.80 ± 0.01	37.0

* $p < 0.05$, ** $p < 0.01$ compared to control

Table 2 Anticonvulsant studies: PTZ-induced convulsions

Treatment	Dose (mg/kg)	No. of animals used	No. of animals survived	Onset of clonic convulsions (s)	Mortality (%)	(%) Protection
Control	–	06	00	61	100	0
Standard (Diazepam)	02	06	06	Absent	0	100
4a	25	06	06	226	0	100
4b	25	06	06	218	0	100
4c	25	06	06	325	0	100
4d	25	06	06	158	0	100
4e	25	06	06	101	0	100
4g	25	06	06	60	0	100
4h	25	06	04	128	33.3	66.6
4k	25	06	04	80	33.3	66.6
4l	25	06	06	104	0	100
4m	25	06	06	201	0	100

* $p < 0.05$, ** $p < 0.01$ compared to control

spectrometer using TMS as internal standard. The mass spectra were recorded on a JEOL JMS-D 300 spectrometer operating at 70 eV. Purity of the compounds was checked by TLC silica-coated plates obtained from Merck.

Preparation of 2-amino-*N*′-hydroxychroman-3-carboxamidine (**3**)

To stirred solution of 2-amino-3,4-dihydro-2*H*-chromene-3-carbonitrile **2** (10 g, 0.05 mol) in methanol (100 mL) was added hydroxylamine hydrochloride (7.8 g, 0.1 mol), and triethylamine (6.9 g, 0.06 mol) at 0 °C. Reaction mixture was heated to reflux for 8 h, mass analysis of reaction mixture confirms completion of reaction. Reaction mixture was cooled to room temperature, diluted with water (100 mL), solid separated was filtered, dried to get pure compound as yellow solid. Yield 11.4 g, 96 %, m.p: 187–190 °C, IR (cm^{-1}); 3416 (O–H), 3386 (N–H), 3003 (C–H), 1699 (C=N), 1284 (C–O). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.5 (m, 2H, CH_2), 3.5 (m, 1H, CH), 4.8 (m, 1H, CH), 5.9 (bs, 2H, NH_2), 7.18–7.21 (m, 1H, Ar–H), 7.24–7.29 (m, 1H, Ar–H), 7.55–7.61 (m, 2H, Ar–H), 9.63 (s, 2H, NH_2). MS: $m/z = 208.1$ (M+1). Anal. calcd. for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.95; H, 6.38; N, 22.33 %.

General procedure for the synthesis of 3-(1,2,4-oxadiazol-3-yl)-3,4-dihydro-2*H*-chromen-2-amine derivatives (**4a**–**n**)

A mixture of 2-amino-*N*′-hydroxychroman-3-carboxamidine **3** (2.4 mmol) and aldehyde (6 mmol) were irradiated in microwave for 5 min. The completion of reaction was monitored by TLC and mass analysis of crude reaction mixture. The reaction mixture was diluted with diethyl ether to get desired compound as a solid, which was recrystalised using ethanol.

*N-(2-chlorobenzylidene)-3-(5-(2-chlorophenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-2-amine (**4a**)*

Yield 85 %, m.p:150–152 °C, IR (cm^{-1}) 3006 (C–H), 1699 (C=N), 1284 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.59 (m, 2H, CH_2), 3.3 (m, 1H, CH), 4.8 (m, 1H, CH), 6.31 (d, 1H, Ar–H, $J = 8$ Hz), 6.76–6.80 (m, 1H, Ar–H), 6.88 (d, 1H, Ar–H, $J = 8$ Hz), 6.96 (m, 1H, Ar–H), 7.03–7.14 (m, 3H, Ar–H), 7.15 (m, 2H, Ar–H), 7.34–7.29 (m, 1H, Ar–H), 7.58–7.61 (m, 2H, Ar–H), 8.97 (s, 1H, CH). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 176.2, 173.2, 159.5, 155.6, 141.3, 137.8, 135.0, 134.8, 133.5, 131.2, 129.4, 129.1, 128.8, 128.4, 127.5, 126.7, 124.5, 120.5, 98.2, 47.4, 28.3. MS: $m/z = 450$ (M+1), 452 (M+2). Anal. calcd. for $C_{24}H_{17}C_{l2}N_3O_2$: C, 64.01; H, 3.81; N, 9.33. Found: C, 64.11; H, 3.91; N, 9.38.

*N-(4-chlorobenzylidene)-3-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-2-amine (**4b**)*

Yield 88 %, m.p:145–147 °C, IR (cm^{-1}) 3013 (C–H), 1689 (C=N), 1413 (C=C), 1284 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.58 (m, 2H, CH_2), 3.3 (m, 1H, CH), 4.8 (m, 1H, CH), 6.69 (m, 1H, Ar–H), 6.91 (d, 1H, Ar–H, $J = 7.6$ Hz), 7.0 (t, 1H, Ar–H, $J = 7.6$ Hz), 7.19 (d, 1H, Ar–H, $J = 7.6$ Hz), 7.47–7.50 (m, 4H, Ar–H), 7.8 (d, 2H, Ar–H, $J = 8.4$ Hz), 7.90 (d, 2H, Ar–H, $J = 9.2$ Hz), 8.97

(s, 1H, CH). MS: $m/z = 450$ (M+1), 452 (M+2). Anal. calcd. for $C_{24}H_{17}C_{l2}N_3O_2$: C, 64.01; H, 3.81; N, 9.33. Found: C, 64.08; H, 3.84; N, 9.34.

*N-(2-hydroxybenzylidene)-3-(5-(2-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-2-amine (**4c**)*

Yield 90 %, m.p:130–132 °C, IR (cm^{-1}) 3002 (C–H), 1656 (C=N), 1470 (C=C), 1350 (C–N), 1284 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.90 (m, 1H, CH_2), 3.07 (m, 1H, CH_2), 3.68 (m, 1H, CH), 4.96 (m, 1H, CH), 6.73 (t, 1H, Ar–H, $J = 7.6$ Hz), 6.80 (d, 1H, Ar–H, $J = 8$ Hz), 6.96–7.05 (m, 5H, Ar–H), 7.15 (d, 1H, Ar–H, $J = 7.8$ Hz), 7.44–7.53 (m, 2H, Ar–H), 7.54–7.55 (m, 1H, Ar–H), 7.60–7.62 (m, 1H, Ar–H), 9.0 (s, 1H, CH), 9.07 (bs, 1H, –OH). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 176.2, 173.2, 159.5, 155.6, 141.3, 137.8, 135.0, 134.8, 133.5, 131.2, 129.4, 129.1, 128.8, 128.4, 127.5, 126.7, 124.5, 120.5, 98.2, 48.0.4, 28.3. MS: $m/z = 414.1$ (M+1). Anal. calcd. for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N, 10.16. Found: C, 69.75; H, 4.53; N, 10.14.

*N-(3,4-dimethoxybenzylidene)-3,4-dihydro-3-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2H-chromen-2-amine (**4d**)*

Yield 93 %, m.p: 141–143 °C, IR (cm^{-1}) 3012 (C–H), 1658 (C=N), 1440 (C=C), 1346 (C–N), 1293 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.59 (m, 1H, CH_2), 2.79 (m, 1H, CH_2), 3.5 (m, 1H, CH), 3.84 (s, 6H, 2–OCH_3), 4.9 (m, 1H, CH), 6.65–6.75 (m, 3H, Ar–H), 6.98–7.11 (m, 4H, Ar–H),7.47–7.56 (m, 3H, Ar–H), 9.02 (s, 1H, CH). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 176.1, 172.7, 161.8, 156.2, 154.5, 153.8, 153.5, 153.1, 133.8, 131.0, 128.2, 126.3, 124.1, 122.0, 121.5, 121.8, 120.8, 118.2, 117.8, 116.2, 115.3, 97.1, 57.3, 47.8, 27.3. MS: $m/z = 502.2$ (M+1). Anal. calcd. for $C_{28}H_{27}N_3O_6$: C, 67.05; H, 5.43; N, 8.38. Found: C, 67.12; H, 5.38; N, 8.38.

*N-(4-fluorobenzylidene)-3-(5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-2-amine (**4e**)*

Yield 93 %, m.p: 154–157 °C, IR (cm^{-1}) 3010 (C–H), 1654 (C=N), 1432 (C=C), 1340 (C–F), 1284 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.58 (m, 2H, CH_2), 3.3 (m, 1H, CH), 4.8 (m, 1H, CH), 6.69 (m, 1H, Ar–H), 6.91 (d, 1H, Ar–H, $J = 7.6$ Hz), 7.0 (t, 1H, Ar–H, $J = 7.6$ Hz), 7.19–7.29 (m, 5H, Ar–H), 7.47–7.50 (m, 4H, Ar–H), 8.97 (s, 1H, CH). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 175.9, 172.8, 166.2, 162.9, 161.4, 156.6, 136.5, 131.1, 130.2, 129.3, 128.0, 126.7, 122.6, 117.3, 116.0, 115.5, 97.6, 47.7, 27.9. MS: $m/z = 418$ (M+1). Anal. calcd. for $C_{24}H_{17}F_2N_3O_2$: C, 69.06; H, 4.11; N, 10.07. Found: C, 69.02; H, 4.13; N, 9.97.

*3,4-Dihydro-N-(3-phenylallylidene)-3-(5-styryl-1,2,4-oxadiazol-3-yl)-2H-chromen-2-amine (**4f**)*

Yield 78 %, m.p: 160–162 °C, IR (cm^{-1}) 2996 (C–H), 1656 (C=N), 1478 (C=C), 1352 (C–N), 1281 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.88 (m, 1H, CH_2), 3.01 (m, 1H, CH_2), 3.68 (m, 1H, CH), 4.46 (m, 1H, CH), 5.8 (m, 1H,CH), 6.70 (m, 2H, Ar–H, CH), 6.84–6.99 (m, 3H, Ar–H,CH), 7.15–7.30 (m, 10H, Ar–H), 8.5 (s, 1H, CH). MS: $m/z = 434.2$ (M+1). Anal. calcd. for $C_{28}H_{23}N_3O_2$: C, 77.58; H, 5.35; N, 9.69. Found: C, 77.55; H, 5.36; N, 9.59.

*N-(3-nitrobenzylidene)-3,4-dihydro-3-(5-(3-nitrophenyl)-1,2,4-oxadiazol-3-yl)-2H-chromen-2-amine (**4g**)*

Yield 87 %, m.p: 168–170 °C, IR (cm^{-1}) 3012 (C–H), 1648 (C=N), 1537 (N–O), 1358 (N–O), 1490 (C=C), 1330 (C–N), 1274 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.60 (m, 1H, CH_2), 3.17 (m, 1H, CH_2), 3.58 (m, 1H, CH), 5.06 (m, 1H, CH), 6.76 (t, 1H, Ar–H, $J = 7.6$ Hz), 6.85 (d, 1H, Ar–H, $J = 8$ Hz), 6.96–7.25 (m, 5H, Ar–H), 7.35 (d, 1H, Ar–H, $J = 7.8$ Hz), 7.44–7.53 (m, 2H, Ar–H), 7.54–7.55 (m, 1H, Ar–H), 7.60–7.62 (m, 1H, Ar–H), 9.1 (s, 1H, CH). MS: $m/z = 472.2$ (M+1). Anal. calcd. for $C_{24}H_{17}N_5O_6$: C, 61.15; H, 3.63; N, 14.86. Found: C, 61.08; H, 3.65; N, 14.81.

*N-(5-bromo-2-fluorobenzylidene)-3-(5-(5-bromo-2-fluorophenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-2-amine (**4h**)*

Yield 93 %, m.p: 134–136 °C, IR (cm^{-1}) 2996 (C–H), 1664 (C=N), 1419 (C=C), 1328 (C–F), 1276 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.52 (m, 1H, CH_2), 3.2 (m, 1H, CH), 3.8 (m, 1H, CH), 4.84 (m, 1H, CH), 6.34 (m, 1H, Ar–H), 6.47 (m, 1H, Ar–H), 6.80 (t, 1H, Ar–H, $J = 7.2$ Hz), 6.88–6.96 (m, 2H, Ar–H), 7.02–7.15 (m, 5H, Ar–H), 8.91 (s, 1H, CH). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 176.5, 173.8, 160.9, 159.7, 158.4, 155.6, 136.2, 135.0, 134.9, 133.7, 129.9, 128.1, 127.3, 126.8, 126.5, 122.6, 122.0, 121.5, 121.2, 117.1, 97.9, 47.5, 27.3. MS: $m/z = 476$ (M+1). Anal. calcd. for $C_{24}H_{15}Br_2F_2N_3O_2$: C, 50.11; H, 2.63; N, 7.3. Found: C, 50.17; H, 2.55; N, 7.28.

*N-benzylidene-3,4-dihydro-3-(5-phenyl-1,2,4-oxadiazol-3-yl)-2H-chromen-2-amine (**4i**)*

Yield 95 %, m.p: 140–142 °C, IR (cm^{-1}) 3000 (C–H), 1699 (C=N), 1284 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.59 (m, 2H, CH_2), 3.2 (m, 1H, CH), 4.7 (m, 1H, CH), 6.31 (d, 1H, Ar–H, $J = 8$ Hz), 6.76–6.80 (m, 1H, Ar–H), 6.88 (d, 1H, Ar–H, $J = 8$ Hz), 6.96 (m, 1H, Ar–H),

7.03–7.14 (m, 5H, Ar–H), 7.15 (m, 2H, Ar–H), 7.34–7.39 (m, 1H, Ar–H), 7.58–7.61 (m, 2H, Ar–H), 8.92 (s, 1H, CH). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 176.2, 172.8, 150.9, 155.8, 140.3, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 126.0, 121.5, 116.2, 98.0, 47.4, 27.2. MS: $m/z = 382.2$ (M+1). Anal. calcd. for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.59; H, 5.02; N, 11.12.

*3,4-Dihydro-3-(5-(thiophen-2-yl)-1,2,4-oxadiazol-3-yl)-N-((thiophen-2-yl)methylene)-2H-chromen-2-amine (**4j**)*

Yield 73 %, m.p: 126–128 °C, IR (cm^{-1}) 2990 (C–H), 1675 (C=N), 1286 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.51 (m, 2H, CH_2), 3.0 (m, 1H, CH), 4.2 (m, 1H, CH), 6.76–6.80 (m, 2H, Ar–H), 6.88–6.98 (m, 3H, Ar–H,), 6.96 (m, 2H, Ar–H), 7.13–7.24 (m, 3H, Ar–H), 8.92 (s, 1H, CH). MS: $m/z = 394.2$ (M+1). Anal. calcd. for $C_{20}H_{15}N_3O_2S_2$: C, 61.05; H, 3.84; N, 10.68. Found: C, 61.25; H, 3.80; N, 10.69.

*N-(4-hydroxy-3-methoxybenzylidene)-3-(5-(4-hydroxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-2-amine (**4k**)*

Yield 85 %, m.p: 172–174 °C, IR (cm^{-1}) 2994 (C–H), 1660 (C=N), 1420 (C=C), 1328 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.48 (m, 1H, CH_2), 2.96 (m, 1H, CH), 3.88 (m, 1H, CH),3.93 (s, 6H, CH_3), 4.94 (m, 1H, CH), 6.65 (m, 1H, Ar–H), 6.77 (m, 2H, Ar–H), 6.80–6.90 (m, 3H, Ar–H), 6.98–7.06 (m, 2H, Ar–H), 7.15–7.24 (m, 2H, Ar–H), 8.91 (s, 1H, CH), 9.6 (bs, 1H, –OH). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 176.2, 173.2, 161.5, 156.1, 153.4, 149.7, 148.8, 129.4, 128.1, 126.0, 124.1, 123.2, 123.0, 120.5, 118.4, 117.8, 116.1, 115.5, 98.1, 47.9, 27.3. MS: $m/z = 474.1$ (M+1). Anal. calcd. for $C_{26}H_{23}N_3O_6$: C, 65.95; H, 4.90; N, 8.87. Found: C, 65.99; H, 4.80; N, 8.97.

*N-(4-bromobenzylidene)-3-(5-(4-bromophenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-2-amine (**4l**)*

Yield 94 %, m.p: 151–154 °C, IR (cm^{-1}) 3015 (C–H), 1689 (C=N), 1412 (C=C), 1290 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.56 (m, 2H, CH_2), 3.32 (m, 1H, CH), 4.9 (m, 1H, CH), 6.71 (m, 1H, Ar–H), 6.91 (d, 1H, Ar–H, $J = 7.6$ Hz), 7.0 (t, 1H, Ar–H, $J = 7.6$ Hz), 7.19 (d, 1H, Ar–H, $J = 7.6$ Hz), 7.47–7.50 (m, 4H, Ar–H), 7.8 (d, 2H, Ar–H, $J = 8.4$ Hz), 7.90 (d, 2H, Ar–H, $J = 9.2$ Hz), 8.93 (s, 1H, CH). MS: $m/z = 540$ (M+1), 542 (M+2). Anal. calcd. for $C_{24}H_{17}Br_2N_3O_2$: C, 53.46; H, 3.18; N, 7.79. Found: C, 53.41; H, 3.12; N, 7.84.

*3,4-Dihydro-3-(5-(thiazol-2-yl)-1,2,4-oxadiazol-3-yl)-N-((thiazol-2-yl) methylene)-2H-chromen-2-amine (**4m**)*

Yield 70 %, m.p: 136–138 °C, IR (cm^{-1}) 2994 (C–H), 1680 (C=N), 1283 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.56 (m, 2H, CH_2), 3.15 (m, 1H, CH), 4.28 (m, 1H, CH), 6.61 (d, 1H, Ar–H, $J = 8$ Hz), 6.76–6.80 (m, 1H, Ar–H), 6.88 (d, 1H, Ar–H, $J = 8$ Hz), 6.96 (m, 1H, Ar–H), 7.34–7.42 (m, 2H, Ar–H),8.24–8.16 (m, 2H, Ar–H), 9.2 (s, 1H, CH). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 173.2, 165.7, 158.9, 157.6, 155.6, 143.8, 131.2, 127.4, 126.0, 121.5, 119.8, 115.5, 97.8, 47.6, 27.3. MS: $m/z = 394.2$ (M+1). Anal. calcd. for $C_{18}H_{13}N_5O_2S_2$: C, 54.67; H, 3.31; N, 17.71. Found: C, 54.66; H, 3.38; N, 17.63.

*N-(4-fluoro-3-phenoxybenzylidene)-3-(5-(4-fluoro-3-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-2-amine (**4n**)*

Yield 91 %, m.p: 158–161 °C, IR (cm^{-1}) 3010 (C–H), 1688 (C=N), 1289 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.59 (m, 2H, CH_2), 3.2 (m, 1H, CH), 4.7 (m, 1H, CH), 6.31 (d, 1H, Ar–H, $J = 8$ Hz), 6.76–6.80 (m, 1H, Ar–H), 6.88 (d, 1H, Ar–H, $J = 8$ Hz), 6.96 (m, 1H, Ar–H), 7.03–7.14 (m, 5H, Ar–H), 7.15 (m, 3H, Ar–H), 7.34–7.39 (m, 4H, Ar–H), 7.58–7.61 (m, 4H, Ar–H), 8.92 (s, 1H, CH). MS: $m/z = 382.2$ (M+1). Anal. calcd. for $C_{36}H_{25}F_2N_3O_4$: C, 71.87; H, 4.19; N, 6.98. Found: C, 71.80; H, 4.23; N, 6.70.

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