Synthesis and Antibacterial Activity Studies of 8,9-Dihydro [7h] Benzo 1,2,4-Oxadiazoles and its Coumarin Derivatives

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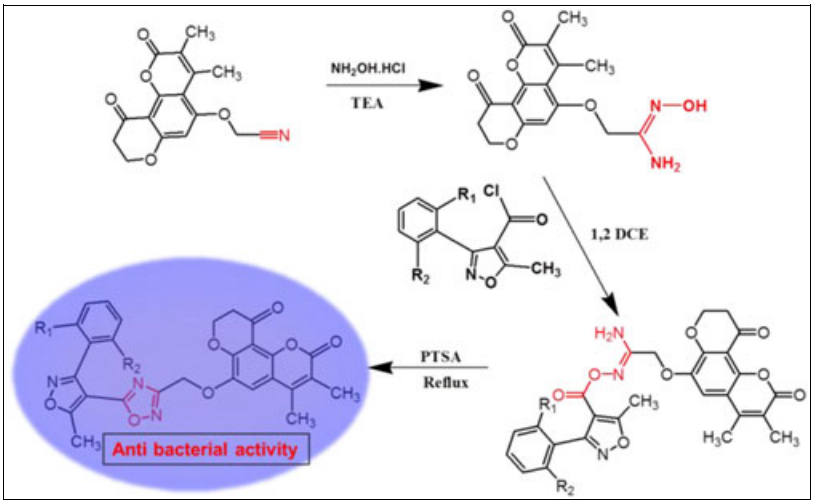


Synthesis, characterization, and antibacterial active studies of 12 coumarin derivatives were described in this study. Synthesis was achieved by the reaction of 4-carbonyl chloride with 1,2-dichloroethane as a solvent, in moderate to good yields. The structures of all the newly synthesized molecules were assigned by spectral data and elemental analysis. The synthesized compounds were screened for their antibacterial activities strains using paper disc method.

INTRODUCTION

Hetero-aromatic compounds have been attracting considerable attention [1] for the applications in the design of verity of biologically active molecules and also for unique physical properties. Design and synthesis of new hetero-aromatic compounds by more economical methods in desirable good yields is always of great interest in synthetic organic chemistry. Pyrazoles and its derivatives are well-known nitrogen containing heterocyclic compounds exhibits important applications such as antibacterial [2], antifungal [3], antiviral [4], antitubercular [5], antioxidant [6], antiandrogenic [7], antimicrobial [8], anti-inflammatory [9], and antitumor [10] activities. On the other hand, sulfonamides and their derivatives are extensively used in medicine because of their pharmacological properties such as antibacterial activity [11–15].

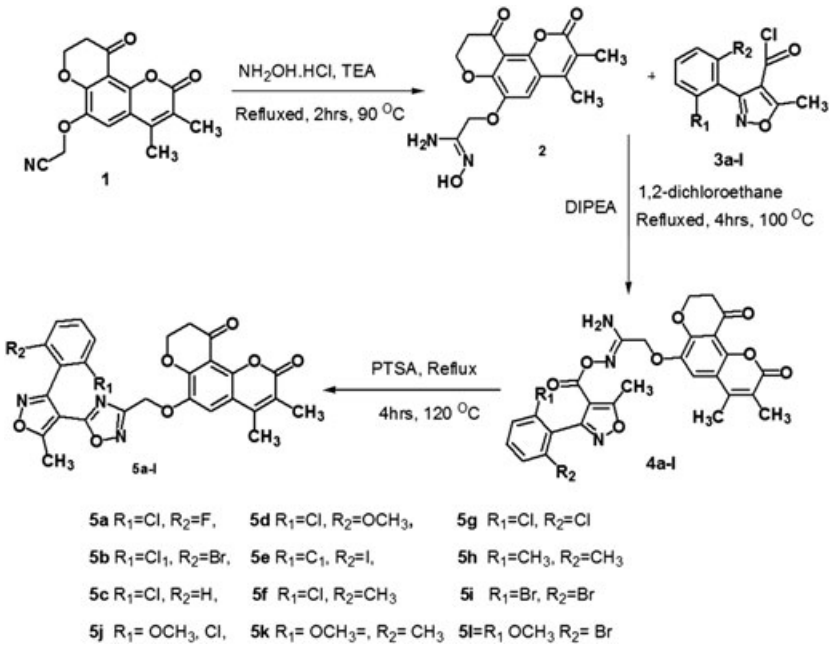
Recent review by Clapp *et al*. [16] demonstrated that the synthesis of majority of 1,2,4-oxadiazoles is encompassed by two major synthetic routes: (a) the condensation of amidoximes with carboxylic acid derivatives and (b) the dipolar cycloaddition of nitrile oxides to nitriles. Subsequently, Lin and co-workers [17] reported a new general method in which *N*′-acyl-dimethylamides react with hydroxylamine to form 3,5-disubstituted or 5-monosubstituted 1,2,4-oxadiazoles [18] in high yields. In this context, after reviewing both methods, we have chosen a method similar to Lin and co-workers [17], for the synthesis of coumarin derivatives (**5a–l**) by conventional synthesis method.

RESULTS AND DISCUSSION

We have successfully synthesized 12 novel coumarin derivatives (**5a–l**) in good yields via 8,9-dihydro [7h] benzo 2-(alkyl-2-oxo-2*H*-chromen-6-yloxy)-*N*′-hydroxyacetamidine (**4**) by employing the reaction conditions described in Scheme 1**.**

The compound 8,9-dihydro [7h] benzo 2-(3,4-dimethyl-2-oxo-2*H*-chromen-6-yloxy)acetonitrile (**1**) was dissolved in methanol, and hydroxyl amine hydrochloride was added to the reaction mixture. The whole reaction mixture was

Scheme 1. Reagents and conditions for the synthesis of title compounds (**5a–l**).



refluxed at 90°C for 2 h, in presence of triethylamine solvent to yield 8,9-dihydro [7h] benzo 2-(3,4-dimethyl-2-oxo-2*H*-chromen-6-yloxy)-*N*′-hydroxyacetamidine (**2**). In the ^{1}H-NMR:($CDCl_3$, 400 MHz) spectrum of compound **2** two singlet's at δ 7.27 and δ 7.24, which corresponds to 8-H and 5-H of coumarin moiety, remaining at δ 6.31 (s, 3-H), 4.52 (s, OCH_2), 2.51 (s, 4-CH_3), 2:28 (s, 7-CH_3). In the ^{13}C-NMR: ($CDCl_3$, 100 MHz): peaks at δ 160.0 (2′-C), 153.2 (C-2), 152.8 (C-6), 148.2 (C-4), 146.5 (C-8a), 132.6 (C-7), 118.1 (C-8), 117.2 (C-4a), 113.7 (C-3), 107.3 (C-5), 67.4 (I′-C), 18.0 (4-CH_3), and 16.1 (7-CH_3). Mass (ES): *m*/*z* $[M + H]^+$ peak at 263.4. Compound (**2**) and 3-aryl,5-methylisoxazole-4-carbonyl chloride (**3**) in 1,2-dichloroethane were refluxed at 100°C in the presence of N, N-Diisopropylethylamine (DIPEA) for 4 h, which yielded 8,9-dihydro [7h] benzo *N*′-(3-aryl)-5-methylisoxazole-4-carbonyloxy)-2-(4-methyl-2-oxo-2*H*-chromen-6-yloxy) acetimidamide (**4a–l**). The IR (KBr) spectrum of 8,9-dihydro [7h] benzo *N*′-(3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyloxy)-2-(3,4-dimethyl-2-oxo-2*H*-chromen-6-yloxy)acetimidamide (**4a**) showed two sharp peaks at 3491 and 3356 cm^{-1} because of symmetric and asymmetric stretching vibration, respectively, of NH_2; the absence of N─OH stretching of **2** and the newly formed ester carbonyl is observed at 1741 and 1701 cm^{-1} and is due to C═O of coumarin. In mass spectrum, $[M + H]^+$ appeared at *m*/*z* 500.3, confirming the presence of O-acylation.

The reaction conditions and reagents employed for the synthesis of title compounds are shown in Scheme 1. Synthesis of 8,9-dihydro [7h] benzo 6-[{5-(3-aryl)-5-methylisoxazol-4yl)-l,2,4-oxadiazol-3-yl}methoxy]-4-methyl-2*H*-chromen-2-ones (**5a–l**) were carried out by conventional method, and the yields were calculated. In simple conventional method, (**4a–l**) was refluxed at 120°C for 4 h in toluene with *p*-toluenesulfonic acid to give 8,9-dihydro [7h] benzo 6-[{5-(3-aryl)-5-methylisoxazol-4yl)-l,2,4-oxadiazol-3-yl}methoxy]-4-methyl-2*H*-chromen-2-ones (**5a–l**) in 52–72% of yields.

Antibacterial activity. All the newly synthesized compounds (**5a–l**) were screened for the antibacterial activity study using the paper disc method. Organisms *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive) were used for the study.

After solidification of media, petriplates inoculated with actively growing culture of *E. coli* and *S. aureus* separately as follows. Filter paper discs of 5 mm diameter were dipped in the test solution of different concentrations. After drying the disc, it was kept on Antibiotic med-3 agar in petriplates seeded with 1 mL bacterial culture of *E. coli* and *S. aureus* and incubated for 24 h at 37°C.

Antibacterial screening data showed that most of the compounds **5a–l** showed moderate to excellent activities against the used microorganisms (Table 1) compared with the reference drug (Chloramphenicol). These results suggested that the introduction of halogen substituent increased the hydrophobicity in synthesized compounds and leads to the increase of the antibacterial activity [19,20]. The present coumarin derivatives shown good antibacterial activity against the Gram-positive bacteria and very poor activity against Gram-negative bacteria, respectively, can be explained based on their cell outer

Table 1
Antibacterial activity of the coumarin oxadiazol derivatives (**5a–l**).

	Zone of inhibition (mm)[a]					
	Escherichia coli (MTCC 40) (Gram-negative) (Conc. μg/mL)			*Staphylococcus aureus* (MTCC 96) (Gram-positive) (Conc. μg/mL)		
Comp.	200	100	50	200	100	50
5a	15	11	5	17	12	5
5b	18	12	8	18	13	10
5c	27	20	19	29	21	19
5d	15	12	11	21	19	4
5e	22	11	6	22	18	7
5f	11	13	14	24	18	26
5g	28	24	20	31	29	24
5h	22	22	16	24	22	20
5i	20	12	18	20	12	21
5j	19	20	17	21	20	19
5k	20	22	19	20	19	17
5l	17	19	17	21	19	20
Chloramphenicol	31	30	21	33	30	23

[a]Average of triplicate.

layers [21]. Gram-positive bacteria have an ineffective and permeable outer barrier made of peptidoglycan layer, which is responsible for permeability of drug constituents. However, Gram-negative bacteria have an impermeable outer membrane to drug constituents, as cell wall contains multilayered peptidoglycan and phospholipid [22]. Among the compounds screened, **5c** and **5g** showed high activity. The observed antibacterial activity profile suggested that the presence of halogen functional group, like monosubstituted and disubstituted chlorine, enhanced the activity.

CONCLUSION

In summary, we successfully synthesized twelve 8,9-dihydro [7h] benzo 6-[{5-(3-aryl)-5-methylisoxazol-4yl)-l,2,4-oxadiazol-3-yl}methoxy]-4-methyl-2*H*-chromen-2-ones (**5a–l**) with the reaction of 4-carbonyl chloride with 1,2-dichloroethane as a solvent, in moderate to good yields. The structures of all the newly synthesized molecules were assigned by spectral data and elemental analysis. All the newly synthesized compounds were screened for their minimum inhibitory concentration (MIC) and zone of inhibition against two strains of bacteria: *E. coli* and *S. aureus,* using paper disc method. Most of the compounds have shown moderate to good antibacterial and antifungal properties with reference drug chloramphenicol. Whereas some compounds have shown promising antifungal properties, which were under progress for further used to determine minimum bactericidal concentration and minimal fungicidal concentration against some selected strains of bacteria and fungi.

EXPERIMENTAL

All the reagents were obtained commercially (SD fine, India) and used without further purification. Melting points were determined by open capillary method. The IR spectra (in KBr pellets) were recorded on a Perkin-Elmer Fourier transform infrared spectrophotometer. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100.6 MHz) were recorded on spectrometer Tetramethylsilane (TMS) as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument. The completion of the reaction was monitored by thin-layer chromatography on silica gel plates using a mixture of *n*-hexane and ethyl acetate solvent.

General procedure for the synthesis of 8,9-dihydro [7h] benzo *N′*-(3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyloxy)-2-(3,4-dimethyl-2-oxo-2*H*-chromen-6-yloxy)acetimidamide (*4a*). 8,9-Dihydro [7h] benzo 2-(4,7-dimethyl-2-oxo-2*H*-chromen-6-yloxy)-*N′*-hydroxyacetamidine (**2**) (l.0 g, 0.004 mol) and DIPEA (12 mL) were taken in 30 mL of 1,2-dichloroethane solvent. The reaction mixture was cooled to 10°C, and then 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride (**3a**) (1.2 g) was added in portions wise. Later the whole reaction mixture was refluxed for at 100°C for 4 h to yield 8,9-dihydro [7h] benzo *N′*-(3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyloxy)-2-(3,4-dimetyl-2-oxo-2*H*-chromen-6-yloxy) acetimidamide (**4a**). The crude product was purified by column chromatography with ethyl acetate/pet-ether (10:90).

IR (KBr) *v*: 3491 cm^{-1}, 3356 cm^{-1} (NH_2), 1741 cm^{-1} (C═O of ester), 1701 cm^{-1} (C═O of coumarin). Mass (ES): *m*/*z* 569 $[M + H]^+$.

General procedure for the synthesis of 8,9-dihydro [7h] benzo 6-((5-(3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2*H*-chromen-2-one (5a–l). The compound (**4a**) (1 g, 0.002 mol) was refluxed at 120°C for 4 h in 25 mL of toluene with catalytic amount of *p*-toluenesulfonic acid to yield 8,9-dihydro [7h] benzo 6-((5-(3-(2-chloro-6 fluorophenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl) methoxy)-4-methyl-2*H*-chromen-2-one (**5a**) in solid form. The crude solid product was purified by silica gel column chromatography with ethyl acetate/ether. The spectral data for **5a**, as follows, yield: 70%. IR (KBr) *v*: 1720 (C═O), 1568 (C═N), 1158 (C─O), 902 (N─O) cm^{-1}, ^{1}H-NMR: ($CDCl_3$, 400 MHz): δ 7.32 (dd, J = 5.8 Hz, J = 0.8 Hz), 7.26 (d, J = 6.2 Hz), 7.18 (dddd, J = 8.2 Hz, J = 0.8 Hz), 7.01–7.08 (m, 5-H, 7-H, 8-H), 6.22 (s, 3-H), 4.89 (s, OCH_2), 2.54 (s, CH_3), 2.36

(s, CH_3).^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 172.2, 168.4, 165.7, 161.8, 160.3, 158.4, 153.9, 151.4, 149.7, 148.0, 147.1, 132.3, 131.6, 130.7, 124.8, −118.7, 118.0, 115.7, 113.3, 104.8, 62.3, 18.4, and 14.6. Mass (ES): *m*/*z* = 551 $[M + H]^+$. M. P: 144°C.

Similar experimental procedure of **5a** was employed for all the remaining derivatives, **5b**–**5I** with yields between 52 and 72%.

8,9-Dihydro [7h] benzo 6-((5-(3-(2-chloro-6-bromophenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2H-chromen-2-one (5b). The spectral data for **5b**, as follows, yield: 72%. IR (KBr) *v*: 1716 (C═O), 1562 (C═N), 1161 (C─O), 906 (N─O) cm^{-1}. ^{1}H-NMR: ($CDCl_3$, 400 MHz): 7.35 (dd, J = 5.8 Hz, J = 1.2 Hz), 7.29 (d, J = 6.4 Hz), 7.23 (dddd, J = 7.6 Hz, J = 1.2 Hz), 6.96–7.08 (m, 5-H, 7-H, 8-H), 6.21 (s, 3-H), 4.91 (s, OCH_2), 2.61 (s, CH_3), 2.33 (s, CH_3). ^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 176.5, 167.3, 164.8, 161.3, 160.8, 159.8, 155.4, 153.0, 152.3, 151.0, 147.2, 134.9, 133.0, 131.9, 124.7, 118.8, 117.4, 115.8, 113.0, 102.2, 63.5, 20.8, and 18.2. Mass (ES): *m*/*z* = 612 $[M + H]^+$. M.P: 147°C,

8,9-Dihydro [7h] benzo 6-((5-(3-(2-chlorophenyl)-5-methylisoxazol-4-yl)-l, 2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2H-chromen-2-one (5c). The spectral data for **5c**, as follows, yield: 72%. IR (KBr) *v*: 1714 (C═O), 1571 (C═N), 1171 (C─O), 911 (N─O) cm^{-1}. ^{1}H-NMR: ($CDCl_3$, 400 MHz): 7.35 (dd, J = 5.6 Hz, J = 0.8 Hz), 7.32 (dd, J = 6.2 Hz, J = 0.8 Hz), 7.22–7.29 (m), 7.15–7.20 (m), 7.00–7.08 (m, 5-H, 7-H, 8-H), 6.32 (d, J = 0.8 Hz, 3-H), 4.89 (s, OCH_2), 2.54 (s, CH_3), 2.38 (d, J = 0.8 Hz, CH_3). ^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 167.3, 163.7, 161.8, 160.1, 156.2, 152.8, 150.7, 149.9, 147.3, 146.1, 133.3, 131.7, 130.9, 129.4, 124.8, 120.2, 117.8, 116.1, 102.8, 111.8, 60.2, 19.6, and 14.5. Mass (ES): *m*/*z* = 533 $[M + H]^+$. M.P: 151°C,

8,9-Dihydro [7h] benzo 6-((5-(3-(2-chloro-6-methoxyphenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2H-chromen-2-one (5d). The spectral data for **5d**, as follows, yield: 64%. IR (KBr) *v*: 1718 (C═O), 1653 (C═N), 1560 (C═C), 1166 (C─O), 902 (N─O) cm^{-1}. ^{1}H-NMR: ($CDCl_3$, 400 MHz): δ 7.37 (dd, J = 6.0 Hz, J = 0.8 Hz, H), 7.31 (d, J = 8 Hz), 7.13 (dddd, J = 8.4 Hz, J = 0.8 Hz), 7.08 (s, 8-H), 7.00 (s, 5-H), 6.23 (d, J = 0.8 Hz, 3-H), 4.67 (s, OCH_2), 2.86 (s, CH_3), 2.35 (d, J = 0.8 Hz, CH_3), 2.28 (s, 7-CH_3). ^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 174.1, 169.3, 166.7, 162.1, 161.0, 159.6, 154.3, 152.6, 151.9, 150.8, 148.5, 135.2, 133.3, 132.2, 125.5, 119.1, 118.0, 116.2, 114.4, 106.0, 61.7, 18.7, 16.6, and 13.3. Mass (ES): *m*/*z* = 563 $[M + H]^+$. M.P: 143°C,

8,9-Dihydro [7h] benzo 6-((5-(3-(2-chloro-6-iodophenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2H-chromen-2-one (5e). The spectral data for **5e**, as follows, yield: 66%. IR (KBr) *v*: 1721 (C═O), 1564 (C═N), 1165 (C─O), 909 (N─O) cm^{-1}. ^{1}H-NMR: ($CDCl_3$, 400 MHz): δ 12.9 (dd, J = 6.0 Hz, J = 1.2 Hz, H), 7.25 (d, J = 8 Hz), 7.13 (dddd, J = 7.6 Hz, J = 1.2 Hz), 7.06 (s, 8-H), 6.95 (s, 5-H), 6.25 (d, J = 0.8 Hz, 3-H), 5.20 (s, OCH_2), 2.66 (s, CH_3), 2.38 (d, J = 0.8 Hz, CH_3), 2.64 (s, 7-CH═). ^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 171.2, 168.2, 167.7, 161.3, 158.2, 153.4, 152.8, 150.8, 149.5, 147.3, 134.2, 133.8, 132.6, 130.1, 124.9, 120.3, 117.6, 114.2, 113.8, 108.2, 63.9, 20.2, 17.6, and 14.5. Mass (ES): *m*/*z* = 659 $[M + H]^+$. M.P: 149°C,

8,9-Dihydro [7h] benzo 6-((5-(3-(2-chloro-5-methylphenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2H-chromen-2-one (5f). The spectral data for **5f**, as follows, yield: 67%.IR (KBr) *v*: 1716 (C═O), 1561 (C═N), 1159 (C─O), 902 (N─O) cm^{-1}. ^{1}H-NMR: ($CDCl_3$, 400 MHz): δ 7.39 (dd, J = 6.0 Hz, J = 1.2 Hz), 7.33 (dd, J = 6.2 Hz, J = 1.2 Hz), 7.26–7.32 (m), 7.18–7.24 (m), 7.12 (s, 8-H), 6.98 (s, 5-H), 6.27 (s, 3-H), 5.12 (s, OCH_2), 2.68 (s, CH_3), 2.36 (s, CH_3), 2.31 (s, 7-CH_3). ^{13}C-NMR: ($CDCl_3$, 100 MHz): δ 169.1, 161.7, 160.3, 159.8, 151.8, 150.3, 148.7, 146.9, 145.2, 134.8, 132.8, 129.6, 128.4, 127.6, 122.2, 116.3, 115.5, 110.1, 109.6, 64.6, 22.0, 19.9, 15.8, and 12.7. Mass (ES): *m*/*z* = 547 $[M + H]^+$. M.P: 146°C,

8,9-Dihydro [7h] benzo 6-((5-(3-(2,6dichlolophenyl)-5-methylisoxazol-4-yl)-l, 2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2H-chromen-2-one (5g). The spectral data for **5g**, as follows, yield: 56%. IR (KBr) *v*: 1732 (C═O), 1578 (C═N), 1180 (C─O), 914 (N─O) cm^{-1}. ^{1}H-NMR: ($CDCl_3$, 400 MHz): δ 7.35 (dd, J = 6.2 Hz, J = 1.8 Hz), 7.30 (d, J = 8.2 Hz), 7.16–7.21 (m), 7.06 (s, 8-H), 7.00 (s, 5-H), 6.28 (s, 3-H), 4.88 (s, OCH_2), 2.79 (s, CH_3), 2.30 (s, CH_3). ^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 172.1, 168.3, 167.9, 163.4V, 162.7, 158.7, 155.5, 152.7, 150.6, 149.3, 147.0, 142.1, 137.4, 132.6, 129.7, 123.3, 120.0, 118.2, 114.1, 103.9, 54.2, 22.3, and 14.8. Mass (ES): *m*/*z* = 568 $[M + H]^+$. M.P: 138°C,

8,9-Dihydro [7h] benzo 6-((5-(3-(2,6-dimethylphenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2H-chromen-2-one (5h). The spectral data for **5h**, as follows, yield: 52%. IR (KBr) *v*: 1728 (C═O), 1578 (C═N), 1175 (C─O), 908 (N─O) cm^{-1}. ^{1}H-NMR: ($CDCl_3$, 400 MHz): δ 7.48 (dd, J = 5.8 Hz, J = 1.2 Hz), 7.37 (d, J = 7.2 Hz), 7.17 (dddd, J = 8.2 Hz, J = 1.2 Hz), 7.08 (s, 8-H), 7.05 (s, 5-H), 6.27 (d, J = 0.8 Hz, 3-H), 4.93 (s, OCH_2), 2.59 (s, CH_3), 2.34 (d, J = 0.8 Hz, 4-CH_3). ^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 170.3, 167.2, 166.6, .162.0, 157.2, 154.2, 150.9, 149.3, 147.8, 146.1, 138.2, 135.3, 133.4, 131.7, 129.2, 126.6, 120.2, 116.2, 112.1, 107.3, 68.1, 22.2, and 12.3. Mass (ES): *m*/*z* = 523 $[M + H]^+$. M.P: 128–131°C,

8,9-Dihydro [7h] benzo 6-((5-(3-(2,6-dibromophenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methoxy) -3,4-dimethyl-2H-chromen-2-one (5i). The spectral data for **5i**, as follows, yield: 58%. IR (KBr) *v*: 1717 (C═O), 1572 (C═N), 1166 (C─O), 903 (N─O) cm^{-1}. ^{1}H-NMR:

($CDCl_3$, 400 MHz): δ 7.42 (dd, J = 6.0 Hz, J = 0.8 Hz), 7.36 (dd, J = 6.0 Hz, J = 0.8 Hz), 7.28–7.34 (m), 7.20–7.26 (m), 7.09 (s, 8-H), 6.88 (s, 5-H), 6.21 (s, 3-H), 5.23 (s, OCH_2), 2.54 (s, CH_3), 238 (s, CH_3). ^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 165.8, 161.9, 160.3, 159.6, 156.7, 1513, 149.4, 148.1, 146.6, 1453, 140.0, 136.3, 132.4, 127.4, 126.1, 122.1, 119.9, 115.1, 113.0, 109.7, 593, 17.7, and 12.8. Mass (ES): m/z = 657 $[M + H]^+$. M.P: 136°C,

8,9-Dihydro [7h] benzo 6-((5-(3-(2-methoxy-6-chlorophenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2H-chromen-2-one (5j). The spectral data for **5j**, as follows, yield: 60%. IR (KBr) *v*: 1720 (C═O), 1653 (C═N), 1565 (C═C), 1170 (C─O), 905 (N─O) cm^{-1}. ^{1}H-NMR: ($CDCl_3$, 400 MHz): δ 7.35 (dd, J = 6.0 Hz, J = 0.8 Hz), 7.30 (d, J = 8 Hz), 7.15 (dddd, J = 8.4 Hz, J = 0.8 Hz), 7.08 (s, 8-H), 7.00 (s, 5-H), 6.25 (d, J = 0.8 Hz, 3-H), 4.65 (s, OCH_2), 2.25 (s, CH_3), 2.37 (d, J = 0.8 Hz, CH_3), 2.20 (s, 7-CH_3). ^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 174.1, 169.3, 165.7, 165.1, 163.0, 159.6, 155.3, 151.6, 151.9, 152.8, 148.5, 134.2, 132.3, 131.2, 120.5, 119.1, 118.0, 116.2, 114.4, 106.0, 61.7, 18.7, 15.6, and 13.3. Mass (ES): m/z = 581 $[M + H]^+$. M.P: 154°C,

8,9-Dihydro [7h] benzo 6-((5-(3-(2-methoxy-6-methylphenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2H-chromen-2-one (5k). The spectral data for **5k**, as follows, yield: 70%. IR (KBr) *v*: 1720 (C═O), 1655 (C═N), 1565 (C═C), 11656 (C─O), 910 (N─O) cm^{-1}. ^{1}H-NMR: ($CDCl_3$, 400 MHz): δ 7.35 (dd, J = 6.0 Hz, J = 0.8 Hz), 7.35 (d, J = 8 Hz), 7.15 (dddd, J = 8.4 Hz, J = 0.8 Hz), 7.08 (s, 8-H), 7.00 (s, 5-H), 6.23 (d, J = 0.8 Hz, 3-H), 4.67 (s, OCH_2), 2.86 (s, CH_3), 2.35 (d, J = 0.8 Hz, CH_3), 2.25 (s, 7-CH_3). ^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 175.1, 165.3, 164.7, 160.1, 161.0, 159.6, 155.3, 152.6, 152.9, 150.8, 145.5, 130.2, 133.3, 132.2, 125.5, 119.1, 118.0, 116.2, 114.4, 106.0, 61.7, 18.7, 15.6, and 14.3. Mass (ES): m/z = 561 $[M + H]^+$. M.P: 150°C,

8,9-Dihydro [7h] benzo 6-((5-(3-(2-methoxy-6-bromophenyl)-5-methylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methoxy)-3,4-dimethyl-2H-chromen-2-one (5l). The spectral data for **5l**, as follows, yield: 69%. IR (KBr) *v*: 1720 (C═O), 1655 (C═N), 1565 (C═C), 1170 (C─O), 905 (N─O) cm^{-1}. ^{1}H-NMR: ($CDCl_3$, 400 MHz): δ 7.35 (dd, J = 6.0 Hz, J = 0.8 Hz), 7.35 (d, J = 8 Hz), 7.15 (dddd, J = 8.4 Hz, J = 0.8 Hz), 7.10 (s, 8-H), 7.00 (s, 5-H), 6.25 (d, J = 0.8 Hz, 3-H), 4.55 (s, OCH_2), 2.86 (s, CH_3), 2.35 (d, J = 0.8 Hz, CH_3), 2.28 (s, 7-CH_3). ^{13}C-NMR: ($CDCl_3$, 100.6 MHz): δ 174.1, 169.3, 165.7, 165.1, 162.0, 155.6, 152.3, 152.6, 151.9, 150.8, 148.5, 137.2, 134.3, 132.2, 125.5, 119.1, 118.0, 115.2, 114.4, 106.0, 60.7, 18.7, 15.6, and 15.3. Mass (ES): m/z = 625 $[M + H]^+$. M.P: 145°C,

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