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Rapid Synthesis of *N*-Alkyl-2-imino-2*H*-chromene-3-carboxamides Catalyzed by a Keplerate-type Giant Nanoporous Isopolyoxomolybdate

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Among the six-membered oxygen-containing heterocycles, chromene derivatives have received considerable attention due to their biological and pharmacological properties, such as anticancer,[1,2] antibacterial,[3] antihypertensive,[4] antiviral,[5] antimalarial,[6] anti-leishmanial,[7] anti-HIV,[8] anticonvulsant,[9] and antifungal[10] activities. Certain derivatives of chromenes induce apoptosis in cancer cell lines.[11,12] They have also been widely employed as cosmetics,[13] pigments,[13] and potent biodegradable agrochemicals,[14] and are found in natural alkaloids, tocopherols, flavonoids, and anthocyanins.[15] A number of compounds with the chromene moiety are known as potential inhibitors of notum pectinacetylesterase,[16] hMAO,[17] aldose reductase,[18] dihydrofolate reductase,[19] TNF-α,[20] and acetylcholinesterase.[21]

Functionalized 2-iminochromenes have been a subject of increasing interest. A number of these compounds are used as protein tyrosine kinase (PTK) inhibitors,[22,23] as well as anti-Alzheimer,[24] antimicrobial,[25] anticancer,[26] and cytotoxic[27] agents. These compounds are important intermediates in chemical synthesis.[28–31] In spite of these properties, a closer look at the literature disclosed that there are few reports on the synthesis of 2-iminochromenes. The classic method for the synthesis of these compounds is the reaction of salicylaldehydes with active methylene compounds prompted by catalysts such as potassium phthalimide,[32] $NaHCO_3$ or Na_2CO_3,[30] polyethylene polyamine functionalized polyacrylonitrile fiber,[33] and piperidine in the presence[34] or absence[35] of microwave irradiation. Although each of these individual methods has its own merits, some suffer from limitations such as unsatisfactory yields, long reaction times, and the use of relatively expensive catalysts. These findings make further improvements for the synthesis of these compounds essential.

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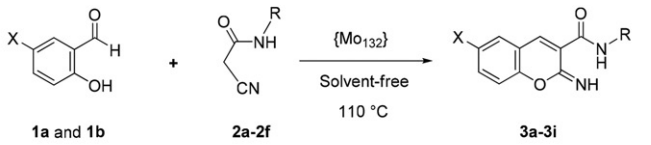


1a and **1b** **2a-2f** **3a-3i**

1a) X = H, **1b)** X = Br, **2a)** R = CH_2Ph, **2b)** R = n-Bu, **2c)** R = CH_2CH_2Ph, **2d)** R = Cyclohexyl, **2e)** R = Me, **2f)** R = Octyl, **3a)** X = H, R = CH_2Ph, **3b)** X = Br, R = n-Bu, **3c)** X = H, R = n-Bu, **3d)** X = Br, R = CH_2CH_2Ph, **3e)** X = H, R = CH_2CH_2Ph, **3f)** X = Br, R = Cyclohexyl, **3g)** X = H, R = Cyclohexyl, **3h)** X = H, R = Me, **3i)** X = H, R = Octyl

Scheme 1. $\{Mo_{132}\}$ catalyzed synthesis of *N*-alkyl-2-imino-2*H*-chromene-3-carboxamides.

Recently, $(NH_4)_{42}[Mo^{VI}_{72}Mo^{V}_{60}O_{372}(CH_3COO)_{30}(H_2O)_{72}]$, a Keplerate-type giant-ball nanoporous isopolyoxomolybdate denoted as $\{Mo_{132}\}$, firstly synthesized and characterized by Muller and co-workers,[36] was used in our group as a catalyst for a series of organic transformations. This new reusable catalyst performed well and showed a high level of catalytic activity in the synthesis of 1,2,4,5-tetrasubstituted imidazoles,[37] 1,8-dioxo-octahydroxanthenes,[38] 1,8-dioxodecahydroacridines,[38] polyhydroquinolines,[39] dihydropyrano[3,2-*c*]chromenes,[40] and biscoumarins.[41]

Based on these precedents and in extension of our previous work on the development of new environmentally friendly methods for the synthesis of organic compounds using reusable catalysts,[42–48] we report here the application of $\{Mo_{132}\}$ as catalyst in the synthesis of *N*-alkyl-2-imino-2*H*-chromene-3-carboxamides **3a-3i.** This is done by reaction of salicylaldehydes **1a** and **1b** with *N*-alkyl-2-cyanoacetamides **2a-2f** using $\{Mo_{132}\}$ as a reusable catalyst under solvent-free conditions (*Scheme 1*).

Compounds **2a-2f** were prepared according to earlier methods.[34,49,50] A pilot reaction was tested using salicylaldehyde **1a** (1 mmol) with *N*-benzyl-2-cyanoacetamide **2a** (1 mmol) in the presence of $\{Mo_{132}\}$ in different sets of reaction conditions. A summary of the optimization experiments is provided in *Table 1*. The advantages of performing organic reactions under solvent-free conditions prompted us to study the efficiency of $\{Mo_{132}\}$ in the model reaction under solvent-free conditions with different catalyst amounts and temperatures. We were pleased to see that the reaction was efficiently catalyzed by $\{Mo_{132}\}$ under solvent-free conditions at elevated temperature leading to a high yield of product **3a**. It is evident that the best result was obtained by the application of 0.05 g of $\{Mo_{132}\}$ at 110 °C (*Entry 13*). Higher amounts of the catalyst and higher temperatures slightly reduced the yield of the product (*Entries 14,15*). To prove the necessity of the catalyst, a blank reaction was also tested at 110 °C under solvent-free conditions. Low yield of the product **3a** was obtained after 120 min (*Entry 1*). Subsequently, the reaction was performed in the presence of 0.05 g of the catalyst in different solvents including H_2O, MeOH, EtOH, $CHCl_3$, and CH_3CN; all gave good yields of the product but none as high as under solvent-free conditions. Therefore, all subsequent reactions were carried out using 0.05 g of the catalyst at 110 °C under solvent-free conditions.

Our results are shown in *Table 2*. As can be seen, all reactions proceed very cleanly to give the corresponding **3a-3i** in high yields over short reaction times, and no undesirable side-products were observed, showing the high catalytic activity of $\{Mo_{132}\}$.

The structure of the products **3a-3i** was deduced from their spectral and microanalytical data. In the ^1H NMR spectra of all compounds **3a-3i**, a splitting between the

Table 1
Optimization of Reaction Parameters for the Synthesis of Compound **3a** Catalyzed by $\{Mo_{132}\}$*

Entry	Catalyst (g)	Solvent	T (°C)	Time (min)	Isolated Yield (%)
1	———	———	110	120	27
2	0.02	———	80	50	69
3	0.02	———	100	50	72
4	0.02	———	110	40	78
5	0.03	———	80	30	77
6	0.03	———	100	30	81
7	0.03	———	110	25	85
8	0.04	———	80	20	84
9	0.04	———	100	15	86
10	0.04	———	110	15	90
11	0.05	———	80	15	87
12	0.05	———	100	15	91
13	0.05	———	110	12	98
14	0.05	———	120	15	95
15	0.06		110	15	96
16	0.05	H_2O	Reflux	45	82
17	0.05	MeOH	Reflux	30	80
18	0.05	EtOH	Reflux	20	84
19	0.05	$CHCl_3$	Reflux	60	75
20	0.05	CH_3CN	Reflux	50	78

*Reaction conditions: salicylaldehyde 1**a** (1 mmol) and N-benzyl-2-cyanoacetamide 2**a** (1mmol).

Table 2
Synthesis of *N*-alkyl-2-imino-2*H*-chromene-3-carboxamides **3a-3i** Catalysed by $\{Mo_{132}\}$

Entry	X	R	Product	Time (min)	Isolated Yield (%)	mp (°C)	lit. mp (°C)
1	H	CH_2Ph	**3a**	12	98	133-135	133 [34]
2	Br	*n*-Bu	**3b**	5	83	152-154	New Compound
3	H	*n*-Bu	**3c**	10	90	165-168	New Compound
4	Br	CH_2CH_2Ph	**3d**	8	90	155-157	New Compound
5	H	CH_2CH_2Ph	**3e**	7	92	138-139	New Compound
6	Br	Cyclohexyl	**3f**	10	90	201-203	207-209 [30]
7	H	Cyclohexyl	**3g**	10	85	170-172	172-174 [28]
8	H	Me	**3h**	10	89	160-163	Not reported [31]
9	H	Octyl	**3i**	15	91	68-70	New Compound

*Reaction conditions: an salicylaldehyde 1**a** or 1**b** (1 mmol), N-alkyl-2-cyanoacetamide 2**a-2f** (1 mmol), $\{Mo_{132}\}$ (0.05 g), 110 °C, solvent-free.

amidic NH group with its vicinal proton(s) can be observed. Such splitting is expected when the proton exchange in the NH group is slow. For example, as shown in the expanded views of the ^{1}H NMR spectrum of compound **3b** in $CDCl_3$ (*Figure 1*), an

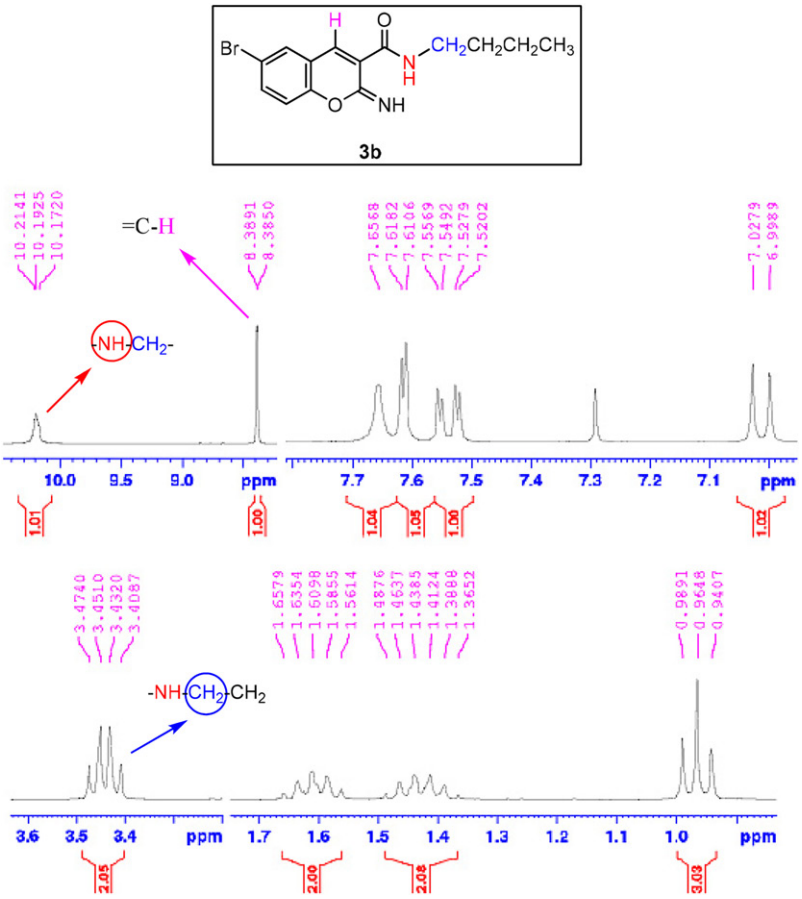
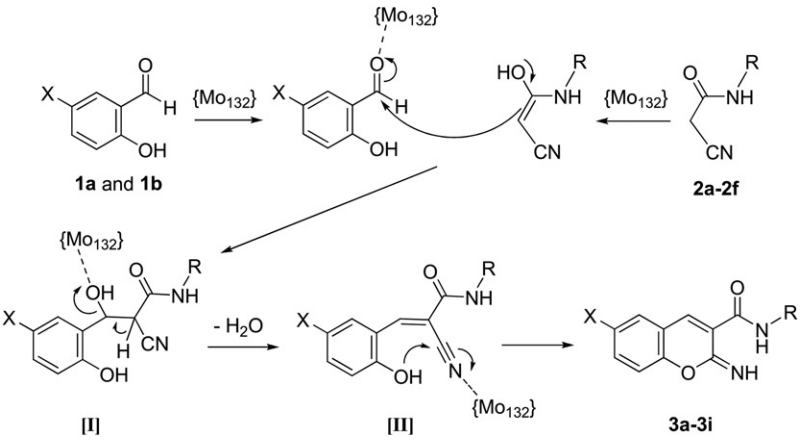


Figure 1. Expanded views of the ^{1}H NMR spectrum of compound **3b** in $CDCl_3$.

A_2X splitting pattern for the -NH-CH_2- group is seen in which the NH appears as a broadened triplet at $\delta = 10.19$ ppm. However, since the methylene group in -NH-CH_2- can be also split with another vicinal methylene group (-NH-CH_2-CH_2-), it appears as quartet at $\delta = 3.44$ ppm, as expected. The methine group in the pyran ring is also seen as a doublet at $\delta = 8.38$ ppm with the coupling constant $J = 1.2$ Hz as the result of a five-bond zig-zag coupling. Long-range couplings across five bonds are rare,[51,52] but can be observed under favorable circumstances in rigid conformations. These signals along with other signals including a triplet, a sextet and a quintet at $\delta = 0.96$, 1.42, and 1.61 ppm, respectively, for the $CH_3CH_2CH_2$- group, a broadened singlet at δ 7.66 ppm for the = NH group as well as the characteristic signals for aromatic protons indicated the formation of compound **3b**. The IR spectrum of compound **3b** showed the NH and C = O absorption bands at 3319, 3193, and 1676 cm^{-1}, respectively. Moreover, the ^{13}C NMR spectrum and elemental analysis data are consistent with the assigned structure **3b** with molecular formula $C_{14}H_{15}BrN_2O_2$ (See Experimental Section).

The recovery and catalytic activity of recycled {Mo_{132}} was also investigated using the same model reaction. Upon completion of the first run, the reaction mixture was cooled to room temperature and hot ethanol was added. The catalyst was collected by



Scheme 2. Plausible mechanism for the formation of compounds **3a-3i**.

filtration and washed with a small portion of hot ethanol and subsequently dried at 60 °C under vacuum for 1 h before being reused in a similar reaction. The catalyst could be used at least four times without significant reduction in its activity (98, 97, 95, and 95% yields for first to fourth use, respectively).

A mechanistic rationalization for this reaction is provided in *Scheme 2*. On the basis of our previous reports,[37,40,41] it is reasonable to assume that several accessible Mo sites and NH_4 groups in $\{Mo_{132}\}$ could act as Lewis acid and Brönsted acid centers, respectively, and therefore promote the necessary reactions. The catalyst would play a significant role in increasing the electrophilic character of the electrophiles in the reaction. As shown, the intermediate **II** is readily formed *in situ* by Knoevenagel condensation of activated salicylaldehydes **1a** and **1b** with corresponding *N*-alkyl-2-cyanoacetamides **2a-2f**, in enolic form, *via* the intermediate **I**. Finally, cyclization of the intermediate **II** gave the products **3a-3i**. Under these conditions, however, attempts to isolate the proposed intermediates failed even after careful monitoring of the reactions.

In conclusion, we report here the synthesis of *N*-alkyl-2-imino-2*H*-chromene-3-carboxamides **3a-3i** by reaction of salicylaldehydes **1a** or **1b** with *N*-alkyl-2-cyanoacetamides **2a-2f** using $\{Mo_{132}\}$ as a reusable catalyst. The reactions occur under solvent-free conditions and furnish the expected products in high yields over short reaction times. This property combined with ease of recovery and catalyst reusability makes this method an economic, benign and waste-free chemical process for the synthesis of *N*-alkyl-2-imino-2*H*-chromene-3-carboxamides.

Experimental Section

N-Alkyl-2-cyanoacetamides **2a-2f** were prepared according to the literature procedures.[34,49,50] All reagents chemicals were available commercially from Merck and Aldrich, and used without purification. Melting points were determined using a Stuart SMP3 melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a Tensor 27 Bruker spectrophotometer. The ^{1}H and ^{13}C NMR spectra were determined using Bruker 300 FT spectrometer at 300 and 75 MHz frequencies for ^{1}H and ^{13}C, respectively, in $CDCl_3$ as the solvent with TMS as the internal reference.

Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer. The catalyst $\{Mo_{132}\}$ was prepared as previously reported.[36–41]

General Procedure for the Synthesis of N-Alkyl-2-imino-2H-chromene-3-carboxamides (3a-3i) Catalyzed by {Mo$_{132}$}

A mixture of a salicylaldehyde (**1a** or **1b**, 1 mmol), *N*-alkyl-2-cyanoacetamides (**2a-2f**, 1 mmol), and $\{Mo_{132}\}$ (0.05 g) was heated in an oil bath at 110 °C for 5-15 min. After completion of the reaction, monitored by TLC on silica gel (*n*-hexane-ethyl acetate, 3:2), the mixture was cooled to room temperature and hot ethanol (10 ml) was added. The catalyst was collected by filtration and washed with a small portion of hot ethanol (5 ml). The combined filtrate was concentrated by half and allowed to stand at room temperature. The precipitated solid was collected by filtration, and recrystallized from 96% ethanol to give compounds **3a-3i** in high yields (see *Table 2*).

Larger Scale Preparation of 3a

A mixture of salicylaldehyde (**1a**, 1.8 g, 15 mmol), *N*-benzyl-2-cyanoacetamide (**2a**, 2.6 g, 15 mmol), and $\{Mo_{132}\}$ (0.75 g) was heated in an oil bath at 110 °C for 12 min. After completion of the reaction, monitored by TLC on silica gel (*n*-hexane-ethyl acetate, 3:2), the mixture was cooled to room temperature and hot ethanol (150 ml) was added. The catalyst was collected by filtration and washed with a small portion of hot ethanol (75 ml). The combined filtrate was concentrated by half and allowed to stand at room temperature. The precipitated solid was collected by filtration, and recrystallized from ethanol to give compound **3a** in 98% yield (see *Table 2*).

N-Benzyl-2-imino-2H-chromene-3-carboxamide (3a)

FT-IR: υ 3307 (NH), 3214 (NH), 1673 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.68 (d, 2H, $J = 5.6$ Hz, CH_2), 7.14 (d, 1H, $J = 8.2$ Hz, H_{Ar}), 7.22 (t, 1H, $J = 7.5$ Hz, H_{Ar}), 7.30-7.55 (m, 7H, H_{Ar}), 7.58 (s br., 1H, =NH), 8.53 (s, 1H, pyran CH), 10.74 (s br., 1H, -CO-NH).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.61; H, 5.19; N, 9.92.

6-Bromo-N-butyl-2-imino-2H-chromene-3-carboxamide (3b)

FT-IR: υ 3319 (NH), 3193 (NH), 1676 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, 3H, $J = 7.2$ Hz, CH_3), 1.42 (sex, 2H, $J = 7.2$ Hz, CH_2), 1.61 (quin, 2H, $J = 7.2$ Hz, CH_2), 3.44 (q, 2H, $J = 6.9$ Hz, NCH_2), 7.00 (d, 1H, $J = 8.7$ Hz, H_{Ar}), 7.53 (dd, 1H, $J = 8.7$, 2.3 Hz, H_{Ar}), 7.61 (d, 1H, $J = 2.3$ Hz, H_{Ar}), 7.66 (s br., 1H, =NH), 8.38 (d, 1H, $J = 1.2$ Hz, pyran CH with a long range coupling), 10.19 (s br., 1H, -CO-NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 20.3, 31.4, 39.6, 116.4, 116.9, 120.6, 121.7, 131.5, 135.0, 139.9, 152.6, 156.9, 161.6.

Anal. Calcd. for $C_{14}H_{15}BrN_2O_2$: C, 52.03; H, 4.68; N, 8.67. Found: C, 52.24; H, 4.53; N, 8.49.

N-Butyl-2-imino-2H-chromene-3-carboxamide (3c)

FT-IR: υ 3317 (NH), 3192 (NH), 1677 (C = O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, 3H, $J = 7.2$ Hz, CH_3), 1.44 (sex, 2H, $J = 7.2$ Hz, CH_2), 1.63 (quin, 2H, $J = 7.2$ Hz, CH_2), 3.46 (q, 2H, $J = 6.9$ Hz, NCH_2), 7.14 (d, 1H, $J = 8.2$ Hz, H_{Ar}), 7.22 (t, 1H, $J = 7.5$ Hz, H_{Ar}), 7.45-7.54 (m, 2H, H_{Ar}), 7.57 (s br., 1H, =NH), 8.49 (s, 1H, pyran CH), 10.28 (s br., 1H, -CO-NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 20.3, 31.4, 39.5, 115.2, 116.5, 124.0, 125.2, 132.4, 133.9, 141.3, 153.8, 157.6, 161.4.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.60; H, 6.77; N, 11.28.

6-Bromo-2-imino-N-(2-phenyl)ethyl-2H-chromene-3-carboxamide (3d)

FT-IR: υ 3309 (NH), 3217 (NH), 1670 (C = O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (t, 2H, $J = 7.2$ Hz, CH_2), 3.71 (q, 2H, $J = 7.3$ Hz, NCH_2), 7.02 (d, 1H, $J = 8.7$ Hz, H_{Ar}), 7.22-7.37 (m, 5H, H_{Ar}), 7.55 (dd, 1H, $J = 8.7$, 2.3 Hz, H_{Ar}), 7.61 (s br., 1H, =NH), 7.63 (d, 1H, $J = 2.3$ Hz, H_{Ar}), 8.40 (s, 1H, pyran CH), 10.29 (s br., 1H, -CO-NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.7, 41.4, 116.4, 116.9, 120.6, 121.6, 126.4, 128.5, 128.9, 131.5, 135.1, 139.2, 140.0, 152.6, 156.7, 161.7.

Anal. Calcd. for $C_{18}H_{15}BrN_2O_2$: C, 58.24; H, 4.07; N, 7.55. Found: C, 58.48; H, 3.92; N, 7.67.

2-Imino-N-(2-phenyl)ethyl-2H-chromene-3-carboxamide (3e)

FT-IR: υ 3283 (NH), 3190 (NH), 1673 (C = O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (t, 2H, $J = 7.2$ Hz, CH_2), 3.72 (q, 2H, $J = 7.4$ Hz, NCH_2), 7.13 (d, 1H, $J = 8.2$ Hz, H_{Ar}), 7.17-7.37 (m, 6H, H_{Ar}), 7.44-7.52 (m, 2H, H_{Ar}), 7.53 (s br., 1H, =NH), 8.48 (s, 1H, pyran CH), 10.40 (s br., 1H, -CO-NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.7, 41.4, 115.2, 118.9, 120.5, 124.1, 126.4, 128.5, 128.9, 129.5, 132.5, 139.3, 141.5, 153.8, 157.5, 162.3.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.71; H, 5.70; N, 9.72.

6-Bromo-N-cyclohexyl-2-imino-2H-chromene-3-carboxamide (3f)

FT-IR: υ 3316 (NH), 3185 (NH), 1676 (C = O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25-2.02 (m, 10H, $5CH_2$ in cyclohexyl), 3.92-4.05 (m, 1H, CH in cyclohexyl), 7.02 (d, 1H, $J = 8.7$ Hz, H_{Ar}), 7.54 (dd, 1H, $J = 8.7$, 2.3 Hz, H_{Ar}), 7.62 (d, 1H, $J = 2.3$ Hz, H_{Ar}), 7.66 (s br., 1H, =NH), 8.39 (s, 1H, pyran CH), 10.21 (d, 1H, $J = 7.2$ Hz, -CO-NH).

Anal. Calcd. for $C_{16}H_{17}BrN_2O_2$: C, 55.03; H, 4.91; N, 8.02. Found: C, 54.85; H, 4.79; N, 8.28.

N-Cyclohexyl-2-imino-2H-chromene-3-carboxamide (3g)

FT-IR: υ 3293 (NH), 3209 (NH), 1698 (C = O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17-1.94 (m, 10H, $5CH_2$ in cyclohexyl), 3.84-3.97 (m, 1H, CH in cyclohexyl), 7.04 (d, 1H, $J = 8.2$ Hz, H_{Ar}), 7.11 (td, 1H, $J = 7.5$, 0.9 Hz, H_{Ar}), 7.34-7.44 (m, 2H, H_{Ar}), 7.48

(s br., 1H, =NH), 8.39 (d, 1H, $J = 1.05$ Hz, pyran CH with a long range coupling), 10.20 (d, 1H, $J = 6.4$ Hz, -CO-NH).

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.28; H, 6.55; N, 10.19.

2-Imino-N-methyl-2H-chromene-3-carboxamide (3h)

FT-IR: υ 3309 (NH), 3191 (NH), 1673 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.05 (d, 3H, $J = 5.6$ Hz, NCH_3), 7.38-7.76 (m, 5H, H_{Ar} and = NH), 8.80 (br., 1H, -CO-NH), 8.95 (s, 1H, pyran CH).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.60; H, 5.11; N, 13.63.

2-Imino-N-octyl-2H-chromene-3-carboxamide (3i)

FT-IR: υ 3249 (NH), 3187 (NH), 1669 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.80-1.70 (m, 15H, $(CH_2)_6CH_3$), 3.35-3.55 (m, 2H, CH_2), 7.13 (d, 1H, $J = 7.5$ Hz, H_{Ar}), 7.20 (t, 1H, $J = 7.1$ Hz, H_{Ar}), 7.42-7.54 (m, 2H, H_{Ar}), 7.58 (s br., 1H, =NH), 8.48 (s, 1H, pyran CH), 10.27 (s br., 1H, -CO-NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.7, 27.1, 29.2, 29.3 (two carbons at 29.28 and 29.34), 31.8, 39.9, 115.2, 119.0, 120.6, 124.1, 129.5, 132.5, 141.4, 153.8, 157.8, 162.1.

Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.69; H, 7.94; N, 9.49.

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