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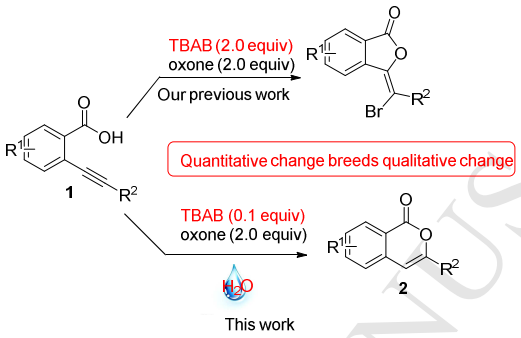

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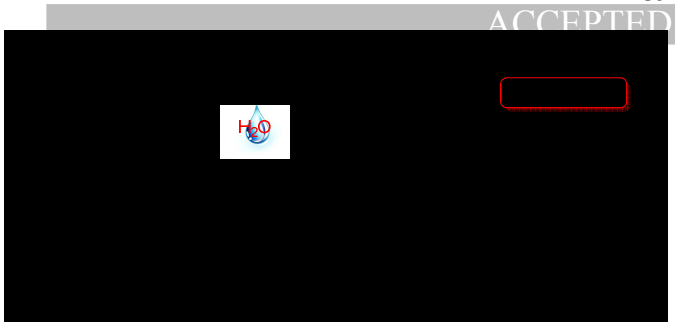
ABSTRACT

In this work, a regioselective synthesis of isocoumarins from 2-alkynylbenzoic acid is reported. The transformations proceed smoothly with good yields in water via a metal-free radical pathway. When catalytic TBAB is employed, the reaction provides various isocoumarin derivatives according to the structures of the corresponding precursors. It is believed that TBAB serves as a phase transfer catalyst and radical initiator in the reaction. Compared to previous methodologies, the synthetic procedure reported herein provides a more environmentally benign route for the synthesis of isocoumarins.

Alkyne-based chemistry has attracted increasing attention in the scientific community due to its versatility for the synthesis of diverse synthons and biologically useful architectures.[1] Although alkyne-based reactions provide a number of attractive applications, reaction efficiency and regioselectivity remain major issues which need to be addressed. Generally, the regioselectivity of a reaction is controlled by the nature of the substrate. Therefore, a series of dual-functionalized substrates bearing alkynyl and reactive groups at the *ortho* position of aromatic compounds have been used to investigate the regioselectivity of alkyne-based transformations, and have also been applied to the synthesis of various privileged skeletons under mild conditions.[2]

The isocoumarin skeleton represents an ubiquitous structural core present in a number of useful molecules and natural products.[3] For example, *Thunberginol A*, exhibiting a range of cytotoxicities, is a type of isocoumarin found in *Hydrangea macrophylla*. To date, tremendous effort has been devoted to the development of new synthetic ruotes for the preparation of isocoumarins due to their potential applications.[4-8] For example, Oliver et al. reported an 6-*endo-dig* electrophilic bromocyclization of 2-alkynylbenzoate in 1984 and found that the reaction specifically produces 4-bromoisocoumarin.[5] The ensuing decades witnessed intense interest in the studies of regioselectivie reactions. To date, the 6-*endo-dig* cyclization of 2-alkynylbenzoate is braodly recognized as an important transformation for the construction of the isocoumarin core.[6-8]

Furthermore, 2-alkynylbenzoic acid, an analogue of 2-alkynylbenzoate, has been found to produce isocoumarins with higher atom efficiency. Therefore, Larock et al. extensively studied the regioselective 6-*endo-dig* cyclization of 2-alkynylbenzoic acid with an aim to synthesize various isocoumarins in an efficient manner.[9] In contrast to 2-alkynylbenzoate,[5] the electrophilic cyclization of 2-alkynylbenzoic acid resulted in a mixture of both 5-*exo-dig* cyclization and 6-*endo-dig* cyclization products. Although the base-mediated cyclization of 2-alkynylbenzoic acid proceeds mainly in a 5-*exo-dig* fashion,[10] the development of an alternative approach for realising the regioselective cyclization of 2-alkynylbenzoic acid is still highly desired. Considering the importance of the isocoumarin core,[3] the regioselective cyclization of 2-alkynylbenzoic acids could be used to synthesize isocoumarin derivatives. Recently, the Gabriele [11] and Bourissou [12] groups proposed that using an ionic liquid as a solvent or transitional metals as Lewis acid catalysts, enabled a regioselective 6-*endo-dig* cyclization of 2-alkynylbenzoic acids for the synthesis of isocoumarins. However, most of the reported reactions provide products containing both 5-*exo-dig* and 6-*endo-dig* cyclization products. Very recently, our group developed a TBAB-mediated regioselective oxidative bromocyclization of 2-alkynylbenzoic acids for the synthesis 3-metheneisobenzofurans.[13e] In this work, we report a new strategy for the regioselective 6-*endo-dig* cyclization of 2-alkynylbenoic acids to afford isocoumarins.



Scheme 1 Proposed route for the synthesis of isocoumarins from 2-alkynylbenzoic acid

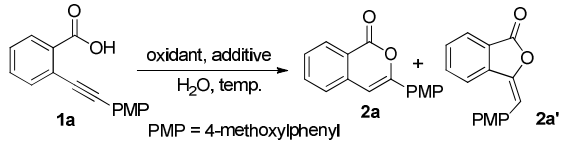
Over the past few years, our group has strived towards developing cleaner, safer and more economic methodologies for the regioselective transformation of alkynes.[13] For example, we recently reported a TBAB/oxone/water-promoted 2, 4-dibromohydration of 2-enynylbenzoate, suggesting that the regioselectivity of this reaction was attributed to the use of water as a solvent.[13a] We hypothesize that using water as a solvent in this reaction would modify the reaction pathway. Moreover, the expansion of the TBAB/oxone/water system to the reaction of 2-alkynylbenamides enabled the cyclization of 2-alkynylbenamides in a regioselective 5-*exo-dig* manner for the synthesis of isobenzofurans.[13b] Mechanistic studies suggest that the regioselective reaction proceeds via a radical pathway.

Additionally, we envisioned that the regioselective 6-*endo-dig* cyclization of 2-alkynylbenoic acids for the preparation of isocoumarins could be realized via a radical pathway using water as the solvent (Scheme 1). It is hypothesized that 2-alkynylbenzoic acid oxygen radical **A**, generated from oxidation of 2-alkynylbenzoic acid **1**, subsequently undergoes a regioselective 6-*endo-dig* cyclization to form isocoumarin radical **B**. Hydrogen abstraction of the isocoumarin radical B affords the final product **2** (Scheme 1). The projected transformation represents a more environmentally benign protocol for the synthesis of isocoumarins from 2-alkynylbenzoic acid via a regioselective 6-*endo-dig* radical cyclization. To verify the transformation as outlined in Scheme 1, optimization experiments were performed.

Oxone was first employed as an oxidant based on our previously reported works.[13] Encouragingly, the model reaction of 2-((4-methoxyphenyl)ethynyl)benzoic acid **1a** afforded the desired 6-*endo-dig* cyclization product isocoumarin **2a** in 43% isolated yield (entry 1, Table 1); the 5-*exo-dig* cyclization product, isobenzofuran **2a'**, was not observed. Compound **2a** was characterized using H-NMR, C-NMR and HRMS.[7a, 7d] The results are consistent with the assumption that regioselective 6-*endo-dig* cyclization of 2-alkynylbenzoic acid could be achieved in water through a radical pathway.

Inspired by this promising outcome, we next optimized other influential factors, the results of which are illustrated in Table 1. To improve the solubility of 2-alkynylbenzoic acid in water, various phase transfer catalysts (PTC) were studied (entries 2-4, Table 1). As expected, PTC was favourable to reaction efficiency. Reaction using sodium dodecyl sulfate gave rise to the desired product **2a** in a 62% yield (entry 2, Table 1), while TBAI, TBAB and TBAC provided **2a** in 71%, 78% and 66% yields, respectively (entries 3-5, Table 1). Conducting the reaction using TBAB and K_2CO_3 as a co-additive was unfavourable to the yield of **2a** and resulted in an increase in the yield of the side product **2a'** (entry 6, Table 1). Surprisingly, increasing the loading of TBAB altered the reaction pathway (entries 7-8, Table 1). In the presence of 2.0 equiv TBAB, the reaction only provided a trace amount of isocoumarin **2a**, while (*E*)-3-(bromo(4-methoxyphenyl)-methylene)-isobenzofuran-1(3*H*)-one **3a** (see Scheme S1 in ESI and Ref 13e) was obtained in a yield of 74% (entry 8, Table 1). Moreover, reducing either the loading of oxone or reaction temperature (entries 9-11, Table 1) did not improve the product yield. Compared to other oxidants, oxone was found to be the best choice (entry 12, Table 1).Use of other

Table 1 Initial studies for the reaction of regioselective 6-*endo-dig* cyclization of 2-alkynylbenzoic acid [a]



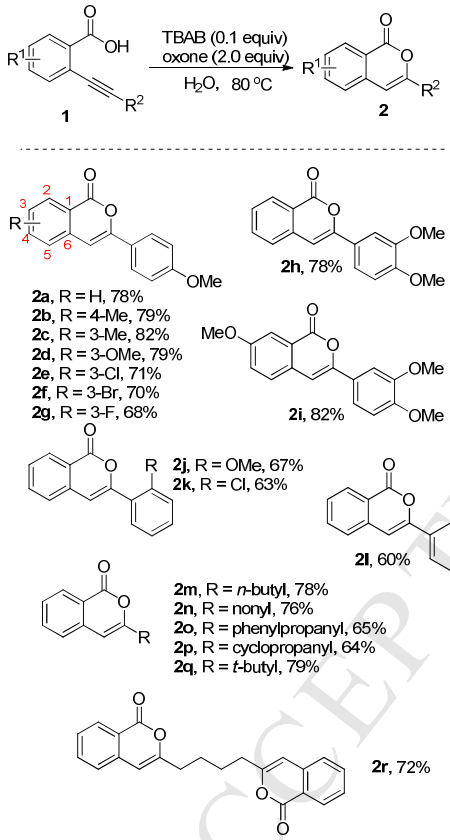
Entry	Additive (equiv)	Oxidant (equiv)	T (^oC)	Yield of **2a** (%)[a,b]
1	-	Oxone (2.0)	80	43
2	Sodium dodecyl sulfate (0.1)	Oxone (2.0)	80	62
3	Tetrabutyl ammonium iodide (0.1)	Oxone (2.0)	80	71
4	Tetrabutyl ammonium bromide (TBAB, 0.1)	Oxone (2.0)	80	78
5	Tetrabutylammonium chloride (TBAC, 0.1)	Oxone (2.0)	80	66
6[c]	TBAB (0.1)	Oxone (2.0)	80	19
7	TBAB (0.5)	Oxone (2.0)	80	40
8[d]	TBAB (2.0)	Oxone (2.0)	80	trace
9	TBAB (0.1)	Oxone (1.0)	80	64
10	TBAB (0.1)	Oxone (2.0)	50	36
11	TBAB (0.1)	Oxone (2.0)	rt	trace
12	TBAB (0.1)	$K_2S_2O_8$ (2.0)	80	48
13	KBr (0.1)	Oxone (2.0)	80	39
14	$ZnBr_2$ (0.05)	Oxone (2.0)	80	17
15	NBS (0.1)	Oxone (2.0)	80	11(77[e])
16[f]	TBAB (0.1)	Oxone (2.0)	80	79

[a]Isolated yield based on 2-alkynylbenzoi acid **1a**; [b]Standard conditions: 2-alknylbenzoic acid **1a** (0.2 mmol), additive (0.1 equiv), Oxone (2.0 equiv), solvent (2 mL), 80 ^oC, 8 h, under air; [c]2.0 equiv K_2CO_3 was added, and isobenzofuran **2a'** was obtained in 29% yield; [d] (*E*)-3-(bromo(4-methoxyphenyl)-methylene)isobenzofuran-1(3*H*)-one **3a** was afforded in 74% yield; [e] AIBN (15 mol%) was added; [f] THF/H_2O (v/v = 1:4, 2.0 mL) as the co-solvent. Oxone = $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.

bromo sources, including KBr, NaBr, and NBS, did not benefit the reaction (entries 13-15, Table 1). Furthermore, in order to verify the plausible radical pathway, we added AIBN (15 mol%) to the NBS conditions and found that the yield of the reaction increased (entry 15, Table 1). We have also implemented a co-solvent system consisting of THF/H_2O (v/v = 1:4), and a comparable yield was obtained (entry 16, Table 1). Therefore, the optimized conditions are 0.1 equiv of TBAB and 2.0 equiv of oxone in water, and conducting the reaction at a temperature of 80 ^oC.

After optimizing the conditions, we then explored the generality of the reaction . The results are outlined in Table 2. As shown in Table 2, a series of substituted isocoumarins were prepared in good yields. The substituent effects of R^1 were also investigated. The results reveal that electronic effects only have a slight impact on the yield of the desired product. For example, reaction with a substrate containing a 4-methyl group as R^1 afforded the desired isocoumarin **2b** in 79% yield, while a substrate bearing a 3-fluoro group gave the corresponding product **2g** in a 68% yield. Other substituents including methoxy, chloro, and bromo groups were compatible with the reaction conditions, leading to the corresponding products **2c**-**2f** in 70-82% yields.

Table 2 Generation of isocoumarins **2** through a regioselective 6-*endo-dig* radical cyclization of various 2-alkynylbenzoic acids [a]



[a] Isolated yield based on 2-alkynylbenzoic acid **1**.

Subsequently, we explored the tolerance of R^2 substituents. Encouragingly, R^2 substituents could be replaced by aryl, vinyl, and alkyl groups. The corresponding products **2h**-**2q** were obtained in 60-79% yields. For instance, reaction of a substrate bearing a 2-methoxylaryl substituent produced the desired isocoumarin **2j** in 67% yield, whereas a substrate bearing a 2-chloroaryl group gave the desired product with a slightly lower yield of 63%. Trimethoxyl-substituted isocoumarin **2i** was also obtained in 82% yield under the standard conditions. Interestingly, isocoumarin **2i** has a high structural similiarity with the natural product *Thunberginol A*. Additionally, 2-(cyclohex-1-en-1-ylethynyl)benzoic acid was also amenable to the reaction conditions, with the corresponding isocoumarin **2l** being prepared in 60% yield. The reactions of various alkyl group-linked substrates worked well, with the formation of a diverse range of isocoumarins **2m**-**2q** in good yields. Remarkably, the substrate 2,2'-(octa-1,7-diyne-1,8-diyl)dibenzoic acid is an efficient reaction partner, giving the corresponding isocoumarin **2r** in 72% yield.

To gain more insight into the mechanism, control experiments with TEMPO, BHT and 1,1-diphenylethene as radical scavengers were carried out (Scheme 2). The results show that the reaction is retarded drastically when radical scavengers are employed. However, none of the radical-trapped species were observed using mass spectroscopy. The control reaction involving the formation of brominated 1,1-diphenylethane product **4** provides unambiguous proof that the reaction proceeds via a radical pathway. Additionally, reaction using D_2O as a solvent produced the deuterized isocoumarin **2a-D** in 72% yield, which implied that the H atom at the C4 position in isocoumarin most likely originates from water.

In light of the above results, a plausible mechanism has been proposed, as shown in Scheme 2. The bromide is oxidized to a bromo radical.[14] Reaction of 2-alkynylbenzoic acid **1** with the bromo radical results in the conversion of the hydroxyl group to oxygen radical species **A**.[15] The oxygen radical species **A** undergoes a 6-*endo-dig* radical cyclization to form isocoumarin radical **B**. Hydrogen abstraction with water occurs on the isocoumarin radical **B**, providing the final isocoumarin **2**. In the presence of base, 2-alkynylbenzoic acid anion **C** undergoes a well known 5-*exo-dig* cyclization to produce isobenzofuran-1-one anion **D** [10]. Subsequently, the protonation of isobenzofuran-1-one anion **D** results in the formation of the corresponding product **2a'**.

In conclusion, we have developed a TBAB-catalyzed synthetic strategy towards the preparation of isocoumarins from various 2-alkynylbenzoic acids. The transformation proceeds smoothly in water. Mechanistic studies showed that the reaction proceeds in a regioselective manner via a metal-free radical pathway. For the synthesis of isocoumarins, it is believed that TBAB serves as a phase transfer catalyst and allows for the generation of a benzoic acid oxygen radical. Compared to previous methodologies, the synthetic procedure reported herein provides a more environmentally benign route for the preparation of isocoumarins.

Experimental Section

General procedure for the synthesis of compound 2:

2-alkynylbenzoic acid **1** (0.2 mmol), TBAB (0. 1 equiv), and Oxone (2.0 equiv) were added to a test tube, and then H_2O (2.0 mL) was added. The mixture was stirred at 80°C for 8 h, under air. After the disappearance of the substrate as indicated by TLC, the mixture was filtered and the resulting filtrate was extracted with DCM (3*2 mL). The organic layers were combined and dried over Na_2SO_4. Filtration, evaporation of the solvent and purification by flash column chromatography provided the desired product **2**.

Scheme 2 Control experiments and plausible mechanism

3-(4-methoxyphenyl)-1*H*-isochromen-1-one (**2a**) (yellow solid, 39.4 mg, 78%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.9 Hz, 2H), 7.68 (t, J = 7.6 Hz, 1H), 7.48 - 7.42 (m, 2H), 6.96 (d, J = 8.9 Hz, 2H), 6.82 (s, 1H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 161.0, 153.7, 137.9, 134.8, 129.6, 127.6, 126.8, 125.9, 124.5, 120.1, 114.2, 100.2, 55.4; IR (KBr): 3032, 2840, 1739, 1632, 1510, 1354, 1237, 1022, 925, 880, 792, 683 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}O_3^+$: 253.0859 (M^++H), found: 253.0856

3-(4-methoxyphenyl)-6-methyl-1*H*-isochromen-1-one (**2b**) (white solid, 42.1 mg, 79%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.27 - 7.16 (m, 2H), 6.93 (d, J = 8.3 Hz, 2H), 6.71 (s, 1H), 3.83 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 160.9, 153.6, 145.8, 137.9, 129.5, 129.0, 126.7, 125.6, 124.6, 117.7, 114.1, 100.1, 55.3, 21.9; IR (KBr): 3173, 2957, 1764, 1680, 1526, 1354, 1274, 1046, 816, 659 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}O_3^+$: 267.1016 (M^++H), found: 267.1021

3-(4-methoxyphenyl)-7-methyl-1*H*-isochromen-1-one (**2c**) (white solid, 43.7 mg, 82%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.76 (s, 1H), 3.83 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.8, 152.8, 137.9, 136.1, 135.4, 129.2, 126.6, 125.6, 124.6, 119.9, 114.1, 100.1, 55.3, 21.3; IR (KBr): 3121, 2914, 1747, 1688, 1581, 1373, 1254, 1059, 873, 798 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}O_3^+$: 267.1016 (M^++H), found: 267.1017

7-methoxy-3-(4-methoxyphenyl)-1*H*-isochromen-1-one (**2d**) (yellow solid, 44.6 mg, 79%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 2H), 7.69-7.67 (m, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 8.9 Hz, 2H), 6.77 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.7, 159.2, 151.8, 131.6, 131.3, 127.3, 126.4, 124.7, 121.1, 114.1, 109.8, 100.0, 55.7, 55.3; IR (KBr): 3172, 2924, 1760, 1680, 1585, 1379, 1259, 1059, 876, 636 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}O_4^+$: 283.0965 (M^++H), found: 283.0962

7-chloro-3-(4-methoxyphenyl)-1*H*-isochromen-1-one (**2e**) (yellow solid, 40.7 mg, 71%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 8.6 Hz, 2H), 6.77 (s, 1H), 3.85 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 161.2, 154.0, 136.2, 135.1, 133.2, 129.0, 127.1, 126.8, 124.0, 121.1, 114.2, 99.3, 55.4; IR (KBr): 3122, 2878, 1802, 1677, 1582, 1391, 1247, 1083, 833 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{12}ClO_3^+$: 287.0469 (M^++H), found: 287.0470

7-bromo-3-(4-methoxyphenyl)-1*H*-isochromen-1-one (**2f**) (yellow solid, 46.2 mg, 70%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.76-7.72 (m, 3H), 7.30 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 8.5 Hz, 2H), 6.74 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 161.1, 154.1, 137.8, 136.6, 132.0, 127.2, 126.8, 124.0, 121.3, 120.82, 114.2, 99.4, 55.4; IR (KBr): 3118, 2915, 1802, 1677, 1582, 1374, 1202, 1010, 853, 623 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{12}BrO_3^+$: 330.9964 (M^++H), found: 330.9976

7-fluoro-3-(4-methoxyphenyl)-1*H*-isochromen-1-one (**2g**) (white solid, 36.8 mg, 68%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.47 - 7.36 (m, 2H), 6.94 (d, J = 8.3 Hz, 2H), 6.78 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 161.5 (d, $^1J_{CF}$ = 248 Hz), 161.1, 153.1, 134.4, 127.9 (d, $^3J_{CF}$ = 8 Hz), 126.7, 124.1, 123.3 (d, $^2J_{CF}$ = 23 Hz), 121.5 (d, $^3J_{CF}$ = 8 Hz), 115.0 (d, $^2J_{CF}$ = 23 Hz), 114.2, 99.4, 55.4; IR (KBr): 3128, 2857, 1764, 1637, 1532, 1381, 1247, 1054, 771, 540 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{12}FO_3^+$: 271.0765 (M^++H), found: 271.0769

3-(3,4-dimethoxyphenyl)-1*H*-isochromen-1-one (**2h**) (blue solid, 44.0 mg, 78%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.2 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.45-7.41 (m, 3H), 7.34 (s, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.81 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 153.6, 150.6, 149.1, 137.8, 134.8, 129.6, 127.7, 125.7, 124.8, 120.1, 118.4, 111.1, 108.1, 100.5, 56.1, 56.0; IR (KBr): 3028, 2867, 1734, 1637, 1512, 1371, 1260, 788, 572 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}O_4^+$: 283.0965 (M^++H), found: 283.0965

3-(3,4-dimethoxyphenyl)-7-methoxy-1*H*-isochromen-1-one (**2i**) (blue solid, 51.2 mg, 82%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (m, 1H), 7.42 - 7.36 (m, 2H), 7.34-7.30 (m, 1H), 7.27 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.79 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 159.2, 151.7, 150.3, 149.1,

131.5, 127.3, 125.0, 124.7, 121.1, 118.0, 111.1, 109.9, 107.9, 100.3, 56.1, 55.9, 55.7; IR (KBr): 3020, 2872, 1735, 1655, 1381, 1265, 760, 552 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}O_5^+$: 313.1071 (M^++H), found: 313.1073

3-(2-methoxyphenyl)-1*H*-isochromen-1-one (**2j**) (yellow solid, 33.8 mg, 67%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 7.8 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.86 - 7.80 (m, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.50 - 7.39 (m, 2H), 7.04-7.00 (m, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 157.3, 150.6, 136.4, 135.3, 131.8, 131.1, 129.8, 129.0, 126.3, 122.3, 120.8, 120.3, 111.3, 103.8, 55.7; IR (KBr): 3010, 2892, 1744, 1650, 1380, 1264, 756 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}O_3^+$: 253.0859 (M^++H), found: 253.0871

3-(2-chlorophenyl)-1*H*-isochromen-1-one (**2k**) (white solid, 32.3 mg, 63%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 7.9 Hz, 1H), 7.77 - 7.67 (m, 2H), 7.52-7.48 (m, 3H), 7.37-7.33 (m, 2H), 6.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 151.4, 137.0, 134.9, 132.3, 131.6, 130.7, 130.6, 130.63, 129.6, 128.7, 127.0, 126.2, 120.6, 107.7; IR (KBr): 3074, 2920, 2872, 1740, 1625, 1600, 757, 560 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{10}ClO_2^+$: 257.0364 (M^++H), found: 257.0372

3-(cyclohex-1-en-1-yl)-1*H*-isochromen-1-one (**2l**) (yellow solid, 27.2 mg, 60%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 7.7 Hz, 1H), 7.67 - 7.61 (m, 1H), 7.42-7.38 (m, 2H), 6.83-6.79 (m, 1H), 6.36 (s, 1H), 2.31 - 2.23 (m, 4H), 1.80-1.73 (m, 2H), 1.67-1.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 154.3, 137.8, 134.6, 130.1, 129.5, 128.2, 127.5, 125.7, 120.6, 100.0, 25.6, 24.1, 22.3, 21.8; IR (KBr): 3083, 2930, 1682, 1625, 1553, 1280, 1220, 1111, 881 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{15}O_2^+$: 227.1067 (M^++H), found: 227.1066

3-butyl-1*H*-isochromen-1-one (**2m**) (yellow oil, 31.6 mg, 78%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 7.9 Hz, 1H), 7.67-7.63 (m, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 6.24 (s, 1H), 2.51 (t, J = 7.6 Hz, 2H), 1.72 - 1.64 (m, 2H), 1.44 - 1.34 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 158.3, 137.6, 134.7, 129.4, 127.5, 125.0, 120.1, 102.8, 33.2, 28.9, 22.1, 13.7; IR (KBr): 3120, 3080, 2925, 1650, 1575, 1381, 1250, 1011, 878 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}O_2^+$: 203.1067 (M^++H), found: 203.1073

3-decyl-1*H*-isochromen-1-one (**2n**) (yellow oil, 43.5 mg, 76%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 6.23 (s, 1H), 2.50 (t, J = 7.6 Hz, 2H), 1.73 - 1.63 (m, 2H), 1.30-1.20 (m, 14H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 158.3, 137.6, 134.6, 129.4, 127.5, 125.0, 120.1, 102.8, 33.5, 31.8, 29.5, 29.5, 29.3, 29.3, 29.0, 26.9, 22.6, 14.1; IR (KBr): 3122, 3083, 2930, 1625, 1578, 1380, 1252, 1006, 880 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{27}O_2^+$: 287.2006 (M^++H), found: 287.2013

3-(3-phenylpropyl)-1*H*-isochromen-1-one (**2o**) (white oil, 34.4 mg, 65%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 7.6 Hz, 1H), 7.68-7.63 (m, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.31-7.27 (m, 2H), 7.19 (d, J = 7.3 Hz, 3H), 6.24 (s, 1H), 2.70 (t, J = 7.4 Hz, 2H), 2.55 (t, J = 7.5 Hz, 2H), 2.10 - 2.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 157.7, 141.3, 137.5, 134.7, 129.5, 128.4, 128.4, 127.6, 126.0, 125.0, 120.1, 103.2, 35.1, 32.9, 28.4; IR (KBr): 3111, 2980, 1625, 1578, 1389, 1254, 1022, 773 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}O_2^+$: 265.1223 (M^++H), found: 265.1207

3-cyclopropyl-1*H*-isochromen-1-one (**2p**) (white solid, 23.8 mg, 64%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.9 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 6.30 (s, 1H), 1.82-1.74 (m, 1H), 1.10-1.03 (m, 2H), 0.96-0.89 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 158.4, 137.9, 134.7, 129.5, 127.1, 124.6, 119.9, 101.3, 13.8, 6.9; IR (KBr): 3120, 3005, 2920, 1644, 1580, 1378, 1026, 878 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{11}O_2^+$: 187.0754 (M^++H), found: 187.0751

3-(tert-butyl)-1*H*-isochromen-1-one (**2q**) (white solid, 32.0 mg, 79%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 6.30 (s, 1H), 1.32 (d, J = 1.0 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 163.0, 137.6, 134.6, 129.3, 127.6, 125.4, 120.1, 99.7, 35.6, 27.9; IR (KBr): 3180, 2975, 1625, 1580, 1381, 1250, 1002, 778 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}O_2^+$: 203.1067 (M^++H), found: 203.1067

3,3'-(butane-1,4-diyl)bis(1*H*-isochromen-1-one) (**2r**) (white solid, 49.9 mg, 72%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 6.26 (s, 1H), 2.55 (d, J = 6.4 Hz, 2H), 1.82 - 1.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 157.3, 137.4, 134.8, 129.4, 127.7, 125.1, 120.1, 103.3, 33.2, 26.2; IR (KBr): 3173, 2936, 1680, 1560, 1380, 1252, 1140, 775 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{19}O_4^+$: 347.1278 (M^++H), found: 347.1302

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