JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00531 • Publication Date (Web): 29 Mar 2018

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

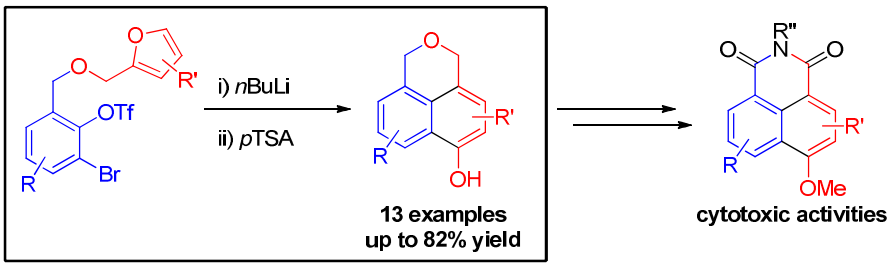
Intramolecular Aryne-Furan Cycloadditions for the Synthesis of Anticancer Naphthalimides

Sébastien Prévost,[†, ‡] Ambre Dezaire,[§] Alexandre Escargueil[§]*

[†] Laboratoire de Synthèse Organique, CNRS, Ecole Polytechnique, ENSTA ParisTech, UMR 7652, Université Paris-Saclay, 828 Bd des Maréchaux, 91128 Palaiseau, France

[‡] Museum National d'Histoire Naturelle, CNRS, UMR 7245 MCAM, Sorbonne Universités, 57 rue Cuvier (CP 54), 75005 Paris, France

[§] Sorbonne Université, INSERM, Laboratory of Cancer Biology and Therapeutics, Centre de Recherche Saint-Antoine, CRSA, F-75012 Paris, France



Abstract

An intramolecular aryne Diels-Alder reaction with a furan moiety was applied to the synthesis of dihydrobenzo[*de*]isochromenes as intermediates towards naphthalimides. After oxidation, this method offers an efficient approach for the synthesis of substituted naphthalimides, which showed potent cytotoxic activity against HT-29 human cancer cell line.

Naphthalimides and naphthalic anhydrides are important skeleton in chemistry.[1] They are present in natural products and many bioactive compounds such as the antitumor agent amonafide (Figure 1).[2] These compounds exhibit a lot of biological properties including antitumor activities as a result of their DNA-intercalating properties,[3] activity against the malaria parasite *Plasmodium falciparum*[4] as well as antiviral properties.[5] Naphthalimides are also used as fluorescent probes for several applications such as cytochrome P450 1A, glutathione or metal detection.[6] Moreover their absorption and emission behavior is highly dependent on their substitution pattern.[7] Due to these fascinating properties, the synthesis of new naphthalimide derivatives is of great interest in order to modify their biological and physiochemical properties.

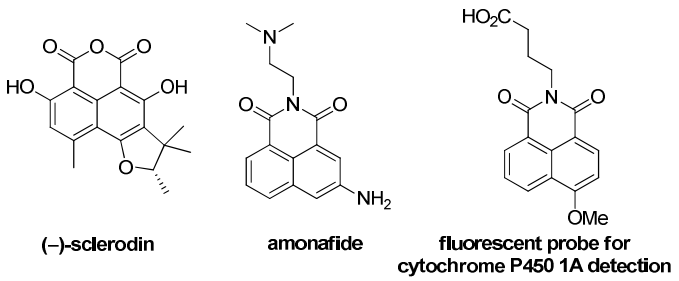


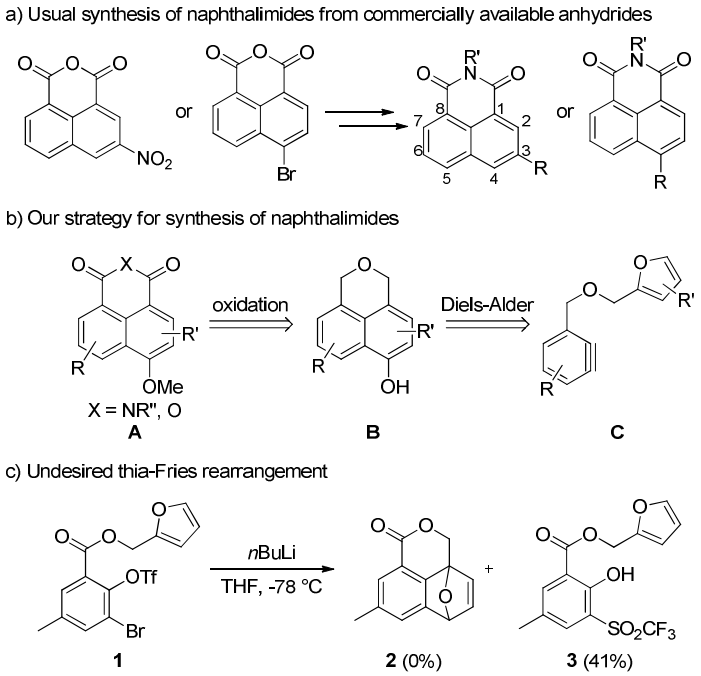
Figure 1. *Natural product and active compounds exhibiting naphthalic anhydride or naphthalimide moieties*

Despite all these applications, no general method has been developed to synthesize the naphthalimide core allowing access to a wide range of substitutions. Most of the known naphthalimides are only substituted in position 3 or 4 because their syntheses are realized from commercially available anhydrides (Scheme 1a). Regarding this lack of diversity, we were keen to develop a new versatile method to synthesize dihydrobenzo[*de*]isochromene intermediates, in order to have a rapid access to substituted naphthalimides and to evaluate their anticarcinogenic properties.

Our synthetic strategy was based on an intramolecular aryne Diels-Alder reaction with a furan substituent to generate directly the tricyclic core of the molecule (Scheme 1b).

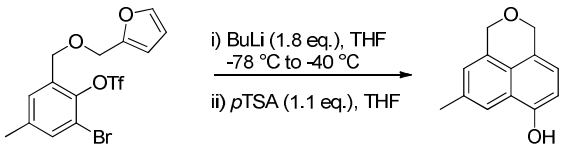
Arynes are indeed well-known to react with furans through [4+2] cycloaddition and to generate a naphthol, after acid-promoted opening of the oxa-bridged product.[8] However, the regioselectivity of this reaction is substrate dependent.[9] In our strategy, the intramolecular character of the reaction would solve the regioselectivity issue and allow an easy access to the dihydrobenzoisochromene tricylic core.[10] Preliminary experiments on the Diels-Alder reaction were attempted on aryne precursor **1** linked to the furan partner through an ester bond, but desired Diels-Alder product **2** was not observed. Only sulfone **3**, resulting of a thia-Fries rearrangement, could be isolated in 41% yield (Scheme 1c).[11] This led us to modify the strategy, replacing the ester linker by a benzylic ether between the aryne and the furan partner. The intramolecular Diels-Alder reaction was therefore expected to furnish dihydrobenzoisochromenol **B** after oxabridge opening, while benzylic oxidation was foreseen in order to install the anhydride moiety, as shown in scheme 1.

Scheme 1. *Synthetic Strategy towards Naphthalimides*



At the outset, we focused our attention on the Diels-Alder reaction of bromo compound **4a** (Table 1) which can be easily synthesized from 5-methylsalicylic acid. First, the aryne was generated with *n*BuLi (1.8 eq.) in THF (0.1 M) at −78 °C. After completion of the Diels-Alder reaction, the reaction was quenched and the residue was treated with *p*-toluenesulfonic acid to obtain naphthol **5a** in 60% overall yield from **4a** (Table 1, entry 1). The optimization work proved the reaction concentration to be crucial, with a 77% yield achieved when the Diels-Alder reaction was carried out at 0.01 M (Table 1, entry 3). Finally, the use of *s*BuLi to form the benzyne moiety did not show any improvement of the reaction (Table 1, entry 4).

Table 1. *Optimisation of the Intramolecular Diels-Alder Reaction*[a]



4a **5a**

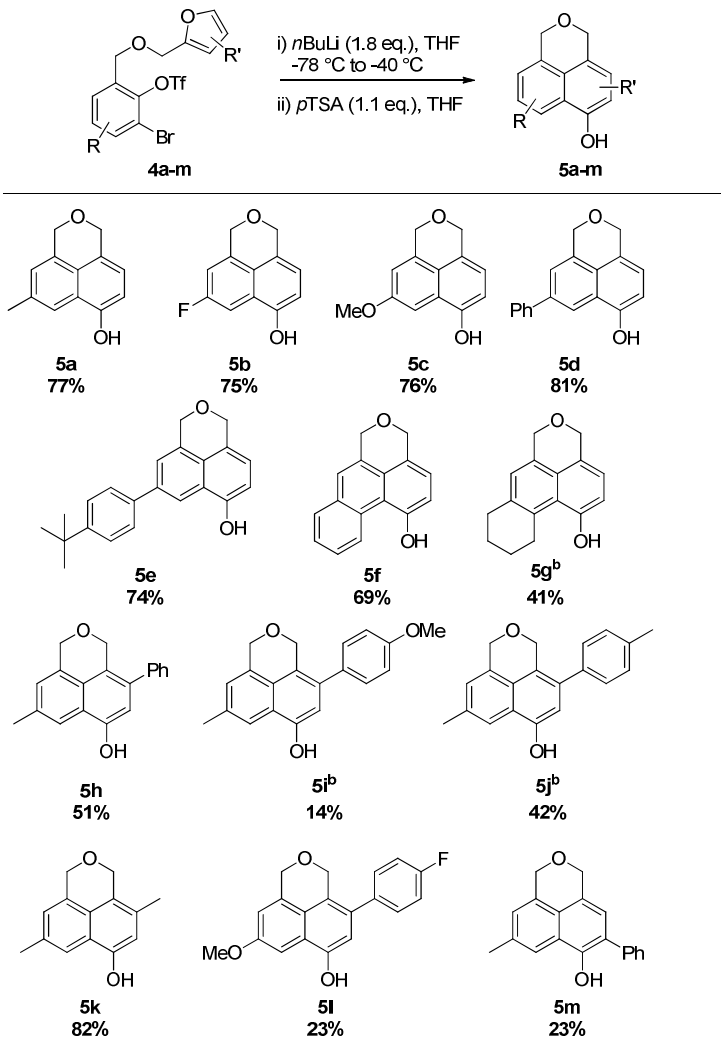
Entry	BuLi	C (mol.L^{-1})[b]	Yield (%)[c]
1	*n*BuLi	0.1	60
2	*n*BuLi	0.3	64
3	*n*BuLi	0.01	77
4	*s*BuLi	0.01	71

[a]Reactions were carried out on 0.25 mmol scale. [b]Concentration of the Diels-Alder step. [c]Isolated yield.

With the optimized conditions in hand, we next investigated the substrate scope of this intramolecular Diels-Alder reaction as shown in Scheme 2. Starting materials **4a-m** were easily prepared by triflation of phenols **13a-m**, obtained in two steps from benzylic alcohols **12a-g**. First, dihydrobenzoisochromenols substituted in position 6 with an alkyl, fluorine, methoxy or aryl group (**5a-e**) were synthesized in good yields from *o*-bromoaryl triflates **4a-e**. The transformation was also compatible with more substituted products such as **5f** and **5g**, although a higher concentration (0.05M) was required for this last substrate. Interestingly, the

Diels-Alder reaction was also possible with substrates substituted on the furan moiety, giving access to all possible substitutions on dihydrobenzoisochromenols. Indeed, products **5h-l**, substituted in position 2 with an aryl or an alkyl group, were obtained in moderate to good yields. In certain cases (**5i-j**), the reaction was carried out at higher concentration in order to achieve full conversion. Finally, dihydrobenzoisochromenol **5m**, substituted in position 3, 4 and 6 was synthesized despite a moderate yield.

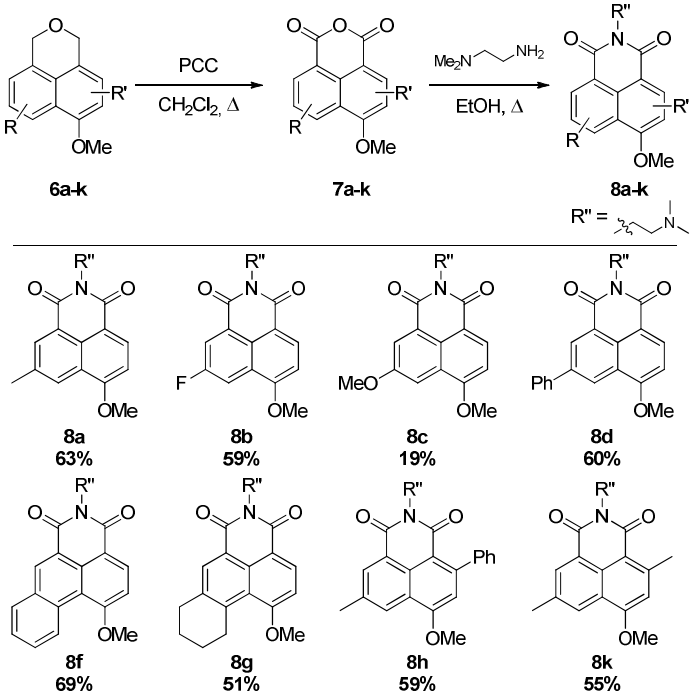
Scheme 2. *Scope of the Intramolecular Diels-Alder Reaction*[a]



[a]Reaction conditions: i) **4** (0.25 mmol), *n*BuLi (0.45 mmol), THF (25 mL), -78 °C to -40 °C; ii) *p*TSA (0.275 mmol), THF (1.65 mL), r.t. [b]step i) was carried out at 0.05M.

Then, we turned our attention to the double benzylic oxidation step in order to generate naphthalic anhydrides. Dihydrobenzoisochromenols **5a-k** were first methylated to obtain dihydrobenzoisochromenes **6a-k** with good yield (66-98%) and several oxidizing reagent were screened.[12] Pyridinium chlorochromate (PCC) in dichloromethane at 60 °C was found to directly convert dihydrobenzoisochromenes **6a-k** to corresponding anhydrides **7a-k** in good yields (32-86%; a lost was observed for **7c** during the purification step due to a very poor solubility). Interestingly, a lactone was exclusively formed when dichloro-dicyanobenzoquinone (DDQ) was used as oxidant.[13] Finally, anhydrides **7a-k** were converted to naphthalimides **8a-k** using *N*,*N*-dimethylethylenediamine as primary amine (Scheme 3).

Scheme 3. *Synthesis of the Naphthalimide Products*[a]



[a]Yields refer to the two steps.

Due to the known anticarcinogenic activity of naphthalimides, compounds **8a-k** were evaluated against the human colon carcinoma HT-29 cell line (Table 2). All the synthesized

products showed promising results, exhibiting a much higher activity, between 0.066 and 0.640 μM, than the reference compound amonafide (4.67 μM).[3d] In particular, naphthalimide **8f** was the most active with an IC_{50} value of 66 nM, showing that the presence of an extended aromatic character was beneficial to the cytotoxicity. On the other hand, the presence of a phenyl ring in position 2 occasioned a drop in activity (compound **8h**). In comparison, naphthalimides were also tested on normal immortalized fibroblastic AB943 cells, displaying lower activity against these normal cells, in the range of 0.463-2.4 μM.

Table 2. *Biological Evaluation of Naphtalimides 8a-k*[a]

Compounds	HT-29 cell line	AB943 cell line
8a	0.286 ± 0.026	1.5 ± 0.3
8b	0.148 ± 0.031	0.810 ± 0.058
8c	0.233 ± 0.080	1.0 ± 0.5
8d	0.466 ± 0.068	0.760 ± 0.114
8f	0.066 ± 0.011	0.463 ± 0.055
8g	0.448 ± 0.068	2.4 ± 0.1
8h	5.0 ± 1	4.6 ± 0.4
8k	0.640 ± 0.135	2.4 ± 0.5
amonafide	4.67	NT

[a]IC_{50} (μM, mean ± SEM)

In conclusion, we have developed a new method to synthesize dihydrobenzoisochromenols based on an intramolecular aryne Diels-Alder reaction with furans. This reaction proceeds efficiently with diverse substitutions and represents a powerful way to have access to a wide variety of naphthalimides. These compounds were biologically evaluated and showed significant cytotoxic activities, which may be related to their ability to intercalate DNA. Further applications involving their fluorescence properties in chemical biology will be explored.

Experimental Section

Materials and methods

All reactions were carried out in oven-dried vessels under an atmosphere of argon and in anhydrous solvents. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by TLC on Merck silica gel 60-F_{254} aluminium sheets (ref.1.05554.0001), using UV absorption then vanillin-H_2SO_4 (1% vanillin in ethanol + 2% H_2SO_4) or basic permanganate (1% $KMnO_4$ + 15% Na_2CO_3 in water) as staining system. The products were purified by silica gel column chromatography (Geduran silica gel Si 60, 40-63 μm). Petroleum ether refers to 40/60 petroleum ether. NMR spectra were recorded on a Bruker 400 MHz Avance III spectrometer. Proton chemical shifts are reported in ppm (δ) with the solvent resonance employed as the internal standard ($CDCl_3$ δ 7.26, DMSO-d_6 δ 2.50). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, Q = quintuplet, h = heptuplet, m = multiplet, br = broad), coupling constants (Hz) and integration. Carbon chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$ δ 77.16, DMSO-d_6 δ 39.52). High resolution mass spectra (HR-MS) were measured on an ESI-QTOF mass spectrometer (Applied Biosystem QSTAR Pulsar-I spectrometer) or by positive electron impact on a double-focusing high-resolution mass spectrometer (JEOL JMS-GCmate II mass spectrometer). Infrared spectra were recorded on a Perkin Elmer Spectrum two FTIR spectrometer. Melting points were measured on a Büchi B-545 apparatus. Alcohols **12a-d** and **12f-g** were synthesized according to literature.[14]

Preparation of benzyl alcohol 12e

methyl 4'-(*tert*-butyl)-4-hydroxy-[1,1'-biphenyl]-3-carboxylate (10):

To a solution of methyl 2-hydroxy-5-iodobenzoate (2 g, 7.19 mmol, 1 eq.) and 4-*tert*-butylphenylboronic acid (1.408 g, 7.91 mmol, 1.1 eq.) in dioxane (44 mL) was added potassium carbonate (2.982 g, 21.58 mmol, 3 eq.) in H_2O (14.4 mL). The mixture was purged with argon during 20 min. Then, $Pd_2(dba)_3$ (198 mg, 0.22 mmol, 0.03 eq.) and triphenylphosphine (226 mg, 0.86 mmol, 0.12 eq.) were added, the mixture was purged with argon during 10 min and stirred under reflux overnight. The solvent was removed under vacuum and EtOAc (40 mL) was added. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, Petroleum Ether/CH_2Cl_2 7:3) to obtain **10** (1.076 g, 3.78 mmol, 53% yield) as a white solid.

R_f = 0.40 (Petroleum Ether/CH_2Cl_2, 6:4). M_p = 95 °C. ν_{max} (neat): 3256, 2949, 1675, 1484, 1178, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 10.75 (s, 1H), 8.06 (d, *J* = 2.4 Hz, 1H), 7.70 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.52-7.43 (m, 4H), 7.05 (d, *J* = 8.6 Hz, 1H), 3.98 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 170.7, 160.9, 150.2, 137.1, 134.5, 132.5, 128.2, 126.4 (2C), 125.9 (2C), 118.1, 112.6, 52.5, 34.7, 31.5 (3C). HRMS (*m/z*) calcd for $C_{18}H_{20}O_3$ [M^+] 284.1412, found 284.1407.

methyl 5-bromo-4'-(*tert*-butyl)-4-hydroxy-[1,1'-biphenyl]-3-carboxylate (11):

To a solution of phenol **10** (1.052 g, 3.70 mmol, 1 eq.) in MeOH (27 mL) was added dropwise a solution of bromine (220 µL, 4.18 mmol, 1.13 eq.) in MeOH (8.6 mL). The mixture was stirred at r.t. during 1 h 30 min. A saturated aqueous solution of $NaHCO_3$ was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic

layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, Petroleum Ether/CH_2Cl_2 7:3) to obtain **11** (436 mg, 1.20 mmol, 32% yield) as a white solid.

R_f = 0.46 (Petroleum Ether/CH_2Cl_2, 6:4). M_p = 104 °C. ν_{max} (neat): 2957, 1679, 1441, 1244, 793 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 11.42 (s, 1H), 8.04 (d, *J* = 2.2 Hz, 1H), 7.97 (d, *J* = 2.2 Hz, 1H), 7.46 (s, 4H), 4.00 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 170.4, 157.3, 150.8, 137.5, 135.9, 133.5, 127.4, 126.4 (2C), 126.1 (2C), 113.6, 111.7, 53.0, 34.7, 31.5 (3C). HRMS (*m/z*) calcd for $C_{18}H_{19}BrO_3$ [M^+] 362.0518, found 362.0529.

3-bromo-4'-(*tert*-butyl)-5-(hydroxymethyl)-[1,1'-biphenyl]-4-ol (12e):

To a suspension of $LiAlH_4$ (88 mg, 2.32 mmol, 2 eq.) in anhydrous THF (1.6 mL) was added a solution of ester **11** (426 mg, 1.16 mmol, 1 eq.) in anhydrous THF (4 mL) at 0 °C. The mixture was stirred at r.t. during 18 h. At 0 °C, a saturated aqueous solution of NH_4Cl was added and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, Petroleum Ether/AcOEt 85:15) to obtain **12e** (272 mg, 0.82 mmol, 70% yield) as a pale yellow solid.

R_f = 0.40 (Petroleum Ether/AcOEt, 75:25). M_p = 97 °C. ν_{max} (neat): 3322, 2961, 1476, 831 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.66 (d, *J* = 2.2 Hz, 1H), 7.44 (s, 4H), 7.36 (d, *J* = 2.2 Hz, 1H), 6.70 (br s, 6.70, 1H), 4.86 (s, 2H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 150.5, 150.5, 136.6, 134.9, 130.3, 127.4, 126.5 (2C), 126.5, 126.0 (2C), 111.1, 63.4, 34.7, 31.5 (3C). HRMS (*m/z*) calcd for $C_{17}H_{19}BrO_2$ [M^+] 334.0568, found 334.0570.

General procedure for the synthesis of phenols 13

To an ice-cooled solution of benzyl alcohol **12** (1 eq.) in anhydrous chloroform (0.44 M) was added dropwise phosphorus tribromide (0.5 eq.). The reaction mixture was stirred at r.t. for 3 h. The reaction mixture was then cooled to 0 °C and H_2O was added carefully. The layers were separated and the aqueous layer was extracted twice with chloroform. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum.

To a NaH (3.9 eq., 60% in mineral oil) suspension in anhydrous THF (0.48 M related to bromo derivative) was added furfuryl alcohol (3 eq., dissolved in a small amount of anhydrous THF if it is a solid). The reaction mixture was stirred at r.t. for 4 h. Then, the previous bromo derivative (1 eq.) in anhydrous THF (0.48 M) was added dropwise. The reaction mixture was stirred for 16 h under reflux. The reaction mixture was then cooled to 0 °C and 1% aqueous HCl was added carefully. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, Cyclohexane/Et_2O).

2-bromo-6-((furan-2-ylmethoxy)methyl)-4-methylphenol (13a):

Prepared from 7.65 mmol of 2-bromo-6-(hydroxymethyl)-4-methylphenol **12a** to afford 1.653 g (5.56 mmol, 73% yield) of **13a** as a colorless oil.

R_f = 0.32 (Cyclohexane/Et_2O, 9:1). ν_{max} (film): 3368, 2918, 1742, 1483, 1234, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.46-7.41 (m, 1H), 7.28-7.23 (m, 1H), 6.96 (s, 1H), 6.92-6.88 (m, 1H), 6.39-6.33 (m, 2H), 4.64 (s, 2H), 4.55 (s, 2H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 150.7, 149.6, 143.4, 132.6, 130.8, 128.8, 123.8, 110.5, 110.3, 110.2, 69.6, 64.3, 20.3. HRMS (*m/z*) calcd for $C_{13}H_{13}{}^{79}BrO_3Na$ [MNa^+] 318.9946, found 318.9944.

2-bromo-4-fluoro-6-((furan-2-ylmethoxy)methyl)phenol (13b):

Prepared from 1 mmol of 2-bromo-4-fluoro-6-(hydroxymethyl)phenol **12b** to afford 208 mg (0.69 mmol, 69% yield) of **13b** as a colorless oil.

R_f = 0.35 (Cyclohexane /Et_2O, 9:1). ν_{max} (neat): 3343, 1478, 1150, 779 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.47-7.43 (m, 1H), 7.18 (dd, *J* = 7.7, 3.0 Hz, 1H), 6.91 (s, 1H), 6.89 (dd, *J* = 8.3, 3.0 Hz, 1H), 6.40-6.35 (m, 2H), 4.64 (s, 2H), 4.56 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -122.4 (s, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 156.0 (d, *J* = 242.3 Hz), 150.5, 148.2 (d, *J* = 2.7 Hz), 143.5, 125.1 (d, *J* = 7.4 Hz), 118.8 (d, *J* = 25.7 Hz), 114.6 (d, *J* = 23.4 Hz), 110.6, 110.4, 110.2 (d, J = 10.1 Hz), 69.0 (d, *J* = 1.5 Hz), 64.5. HRMS (*m/z*) calcd for $C_{12}H_{10}{}^{79}BrFO_3Na$ [MNa^+] 322.9695, found 322.9698.

2-bromo-6-((furan-2-ylmethoxy)methyl)-4-methoxyphenol (13c):

Prepared from 2.57 mmol of 2-bromo-6-(hydroxymethyl)-4-methoxyphenol **12c** to afford 439 mg (1.40 mmol, 55% yield) of **13c** as a colorless oil.

R_f = 0.27 (Cyclohexane /Et_2O, 9:1). ν_{max} (neat): 3359, 1480, 1044, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.46-7.42 (m, 1H), 7.00 (d, *J* = 3.0 Hz, 1H), 6.71 (d, *J* = 3.0 Hz, 1H), 6.69 (s, 1H), 6.39-6.34 (m, 2H), 4.64 (s, 2H), 4.55 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 153.3, 150.7, 145.9, 143.4, 124.7, 117.2, 114.3, 110.5, 110.5, 110.3, 69.5, 64.3, 56.1. HRMS (*m/z*) calcd for $C_{13}H_{13}{}^{79}BrO_4Na$ [MNa^+] 334.9895, found 334.9903.

3-bromo-5-((furan-2-ylmethoxy)methyl)-[1,1'-biphenyl]-4-ol (13d):

Prepared from 1 mmol of 3-bromo-5-(hydroxymethyl)-[1,1'-biphenyl]-4-ol **12d** to afford 226 mg (0.63 mmol, 63% yield) of **13d** as a pale yellow oil.

R_f = 0.32 (Cyclohexane /Et_2O, 9:1). ν_{max} (neat): 3334, 1471, 1053, 761 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.68 (d, *J* = 2.2 Hz, 1H), 7.54-7.48 (m, 2H), 7.47-38 (m, 3H), 7.36-7.29

(m, 2H), 7.25 (s, 1H), 6.41-6.35 (m, 2H), 4.75 (s, 2H), 4.60 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.4, 150.6, 143.5, 139.5, 134.7, 130.9, 129.0 (2C), 127.4, 126.8 (2C), 126.8, 124.4, 111.1, 110.6, 110.4, 69.8, 64.4. HRMS (*m/z*) calcd for $C_{18}H_{16}{}^{79}BrO_3$ [MH^+] 359.0283, found 359.0278.

3-bromo-4'-(*tert*-butyl)-5-((furan-2-ylmethoxy)methyl)-[1,1'-biphenyl]-4-ol (13e):

Prepared from 0.80 mmol of 3-bromo-4'-(*tert*-butyl)-5-(hydroxymethyl)-[1,1'-biphenyl]-4-ol **12e** to afford 133 mg (0.32 mmol, 40% yield) of **13e** as a pale yellow oil.

R_f = 0.51 (Petroleum Ether/Et_2O, 75:25). ν_{max} (neat): 3356, 2961, 1477, 831, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.69 (d, *J* = 2.2 Hz, 1H), 7.48-7.42 (m, 5H), 7.32 (d, *J* = 2.2 Hz, 1H), 7.28 (br s, 1H), 6.40 (d, *J* = 3.1 Hz, 1H), 6.38 (dd, *J* = 3.1, 1.8 Hz, 1H), 4.75 (s, 2H), 4.60 (s, 2H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.2, 150.6, 150.4, 143.5, 136.6, 134.5, 130.8, 126.6, 126.5 (2C), 125.9 (2C), 124.2, 111.1, 110.6, 110.4, 69.8, 64.3, 34.6, 31.5 (3C). HRMS (*m/z*) calcd for $C_{22}H_{23}{}^{79}BrO_3$ [M^+] 414.0831, found 414.0845.

1-bromo-3-((furan-2-ylmethoxy)methyl)naphthalen-2-ol (13f):

Prepared from 5.24 mmol of 1-bromo-3-(hydroxymethyl)naphthalen-2-ol **12f** to afford 198 mg (0.59 mmol, 11% yield) of **13f** as a yellow oil.

R_f = 0.25 (Cyclohexane /Et_2O, 9:1). ν_{max} (neat): 3497, 1452, 1403, 1148 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.08 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.69 (s, 1H), 7.55 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.46 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.38 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.15 (s, 1H), 6.42-6.35 (m, 2H), 4.84 (s, 2H), 4.62 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 150.9, 150.0, 143.4, 132.5, 129.2, 128.2, 127.8, 127.6, 125.6, 125.6, 124.4, 110.5, 110.3, 106.8, 69.4, 64.4. HRMS (*m/z*) calcd for $C_{16}H_{14}{}^{79}BrO_3$ [MH^+] 333.0126, found 333.0131.

1-bromo-3-((furan-2-ylmethoxy)methyl)-5,6,7,8-tetrahydronaphthalen-2-ol (13g):

Prepared from 2.78 mmol of 1-bromo-3-(hydroxymethyl)-5,6,7,8-tetrahydronaphthalen-2-ol **12g** to afford 356 mg (1.06 mmol, 38% yield) of **13g** as a colorless oil.

R_f = 0.33 (Cyclohexane /Et_2O, 9:1). ν_{max} (neat): 3319, 2925, 1469, 1045, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.43 (dd, *J* = 1.4, 1.2 Hz, 1H), 6.87 (s, 1H), 6.77 (s, 1H), 6.39-6.33 (m, 2H), 4.63 (s, 2H), 4.54 (s, 2H), 2.70 (dt, *J* = 11.6, 6.4 Hz, 4H), 1.85-1.76 (m, 2H), 1.76-1.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.1, 149.4, 143.2, 137.0, 130.6, 128.5, 121.2, 113.7, 110.5, 110.0, 69.1, 64.1, 30.5, 29.4, 23.3, 22.9. HRMS (*m/z*) calcd for $C_{16}H_{18}{}^{79}BrO_3$ [MH^+] 337.0439, found 337.0442.

2-bromo-4-methyl-6-(((3-phenylfuran-2-yl)methoxy)methyl)phenol (13h):

Prepared from 1 mmol of 2-bromo-6-(hydroxymethyl)-4-methylphenol **12a** to afford 269 mg (0.72 mmol, 72% yield) of **13h** as a yellow oil.

R_f = 0.37 (Pentane/Et_2O, 9:1). ν_{max} (neat): 3350, 1481, 1053, 743, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.48 (d, *J* = 1.9 Hz, 1H), 7.46-7.37 (m, 4H), 7.36-7.29 (m, 1H), 7.28-7.24 (m, 1H), 6.88 (s, 1H), 6.84 (d, *J* = 1.3 Hz, 1H), 6.59 (d, *J* = 1.9 Hz, 1H), 4.66 (s, 2H), 4.63 (s, 2H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 149.6, 146.6, 142.8, 133.0, 132.7, 130.8, 129.1, 128.9 (2C), 128.1 (2C), 127.4, 126.5, 123.9, 111.6, 110.3, 69.6, 63.0, 20.3. HRMS (*m/z*) calcd for $C_{19}H_{17}{}^{79}BrO_3Na$ [MNa^+] 395.0259, found 395.0261.

2-bromo-6-(((3-(4-methoxyphenyl)furan-2-yl)methoxy)methyl)-4-methylphenol (13i):

Prepared from 1 mmol of 2-bromo-6-(hydroxymethyl)-4-methylphenol **12a** to afford 215 mg (0.53 mmol, 53% yield) of **13i** as a colorless oil.

R_f = 0.30 (Pentane/Et_2O, 9:1). ν_{max} (neat): 3361, 1516, 1247, 1033, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.45 (d, *J* = 1.8 Hz, 1H), 7.39-7.32 (m, 2H), 7.26 (s, 1H), 6.98-6.94 (m,

1H), 6.94-6.91 (m, 2H), 6.83 (d, J = 1.1 Hz, 1H), 6.55 (d, J = 1.8 Hz, 1H), 4.66 (s, 2H), 4.61 (s, 2H), 3.84 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 159.0, 149.6, 146.0, 142.6, 132.6, 130.7, 129.2 (2C), 129.1, 126.2, 125.4, 123.9, 114.3 (2C), 111.6, 110.2, 69.5, 63.0, 55.4, 20.2. HRMS (*m/z*) calcd for $C_{20}H_{19}{}^{79}BrO_4Na$ [MNa^+] 425.0364, found 425.0357.

2-bromo-4-methyl-6-(((3-(*p*-tolyl)furan-2-yl)methoxy)methyl)phenol (13j):

Prepared from 0.53 mmol of 2-bromo-6-(hydroxymethyl)-4-methylphenol **12a** to afford 117 mg (0.30 mmol, 57% yield) of **13j** as a yellow oil.

R_f = 0.45 (Petroleum Ether/Et_2O, 85:15). ν_{max} (neat): 3362, 2920, 1483, 1051, 821 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.46 (d, J = 1.8 Hz, 1H), 7.35-7.29 (m, 2H), 7.25 (d, J = 1.6 Hz, 1H), 7.23-7.18 (m, 2H), 6.94 (br s, 1H), 6.83-6.79 (m, 1H), 6.56 (d, J = 1.8 Hz, 1H), 4.65 (s, 2H), 4.62 (s, 2H), 2.38 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 149.8, 146.4, 142.8, 137.3, 132.8, 130.8, 130.1, 129.7 (2C), 129.2, 128.1 (2C), 126.6, 124.0, 111.7, 110.4, 69.7, 63.1, 21.4, 20.4. HRMS (*m/z*) calcd for $C_{12}H_{11}O$ [M-$C_8H_8BrO_2^+$] 171.0805, found 171.0804; calcd for $C_8H_7{}^{79}BrO$ [M-$C_{12}H_{11}O_2^+$] 197.9675, found 197.9669.

2-bromo-4-methyl-6-(((3-methylfuran-2-yl)methoxy)methyl)phenol (13k):

Prepared from 1.35 mmol of 2-bromo-6-(hydroxymethyl)-4-methylphenol **12a** to afford 345 mg (1.11 mmol, 82% yield) of **13k** as a pale yellow oil.

R_f = 0.19 (Petroleum Ether/Et_2O, 95:5). ν_{max} (neat): 3351, 2922, 1483, 1053, 743 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.34 (d, J = 1.8 Hz, 1H), 7.25 (d, J = 1.6 Hz, 1H), 7.17 (s, 1H), 6.89-6.85 (m, 1H), 6.23 (d, J = 1.8 Hz, 1H), 4.62 (s, 2H), 4.51 (s, 2H), 2.24 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 149.8, 146.2, 142.4, 132.7, 130.7, 128.6, 123.8, 120.1, 113.1, 110.3, 70.0, 62.1, 20.3, 10.0. HRMS (*m/z*) calcd for C_6H_7O [M-$C_8H_8BrO_2^+$] 95.0492, found 95.0493; calcd for $C_8H_7{}^{79}BrO$ [M-$C_{12}H_{11}O_2^+$] 197.9675, found 197.9672.

2-bromo-6-(((3-(4-fluorophenyl)furan-2-yl)methoxy)methyl)-4-methoxyphenol (13l):

Prepared from 0.70 mmol of 2-bromo-6-(hydroxymethyl)-4-methoxyphenol **12c** to afford 146 mg (0.36 mmol, 51% yield) of **13l** as a yellow solid.

R_f = 0.43 (Petroleum Ether/Et_2O, 7:3). M_P = 78 °C. ν_{max} (neat): 3385, 1515, 1481, 1224, 1046, 838 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.46 (d, *J* = 1.9 Hz, 1H), 7.43-7.35 (m, 2H), 7.13-7.04 (m, 2H), 7.00 (d, *J* = 3.0 Hz, 1H), 6.69 (d, *J* = 3.0 Hz, 1H), 6.54 (d, *J* = 1.9 Hz, 1H), 6.53 (br s, 1H), 4.66 (s, 2H), 4.59 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.3 (d, *J* = 246.7 Hz), 153.3, 146.6, 145.8, 142.9, 129.7 (d, *J* = 8.0 Hz, 2C), 129.0 (d, *J* = 3.5 Hz), 125.6, 124.7, 116.4 (d, *J* = 139.0 Hz, 2C), 115.9, 114.7, 111.5, 110.5, 69.5, 63.0, 56.0. HRMS (*m/z*) calcd for $C_{11}H_8FO$ [M-$C_8H_8BrO_3^+$] 175.0554, found 175.0556; calcd for $C_8H_8{}^{79}BrO_2$ [M-$C_{11}H_8FO_2^+$] 213.9624, found 213.9613.

2-bromo-4-methyl-6-(((4-phenylfuran-2-yl)methoxy)methyl)phenol (13m):

Prepared from 0.61 mmol of 2-bromo-6-(hydroxymethyl)-4-methylphenol **12a** to afford 178 mg (0.48 mmol, 78% yield) of **13m** as a pale yellow solid.

R_f = 0.23 (Petroleum Ether/Et_2O, 9:1). M_P = 69 °C. ν_{max} (neat): 3361, 1483, 1135, 757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.72 (d, *J* = 0.9 Hz, 1H), 7.50-7.43 (m, 2H), 7.41-7.34 (m, 2H), 7.31-7.24 (m, 1H), 7.17 (s, 1H), 6.95-6.91 (m, 1H), 6.90 (s, 1H), 6.68 (s, 1H), 4.68 (s, 2H), 4.58 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.9, 149.6, 139.1, 132.7, 132.2, 130.9, 129.0 (2C), 128.9, 127.4, 127.3, 125.9 (2C), 123.8, 110.3, 109.4, 69.6, 64.4, 20.3. HRMS (*m/z*) calcd for $C_{19}H_{17}{}^{79}BrO_3$ [M^+] 372.0361, found 372.0361.

General procedure for the synthesis of bromo-triflates 4

To an ice-cooled solution of phenol **13** (1 eq.) and pyridine (1.8 eq.) in anhydrous CH_2Cl_2 (0.17 M) was added triflic anhydride (1.2 eq.). The reaction mixture was stirred for 1

h at r.t. The reaction mixture was then cooled to 0 °C and 1% aqueous HCl was added carefully. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, Cyclohexane/Et_2O).

2-bromo-6-((furan-2-ylmethoxy)methyl)-4-methylphenyl trifluoromethanesulfonate (4a):

Prepared from 5.46 mmol of 2-bromo-6-((furan-2-ylmethoxy)methyl)-4-methylphenol **13a** to afford 1.924 g (4.48 mmol, 82% yield) of **4a** as a colorless oil.

R_f = 0.46 (Cyclohexane /Et_2O, 95:5). ν_{max} (film): 2922, 1416, 1215, 866 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.45-7.42 (m, 1H), 7.42-7.39 (m, 1H), 7.38-7.33 (m, 1H), 6.39-6.33 (m, 2H), 4.63 (s, 2H), 4.54 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.1, 143.2, 141.7, 140.1, 134.2, 133.7, 129.9, 118.7 (q, J = 320.8 Hz), 115.9, 110.5, 110.1, 66.4, 64.8, 20.8. HRMS (*m/z*) calcd for $C_{14}H_{12}{}^{79}BrF_3O_5SNa$ [MNa^+] 450.9439, found 450.9433.

2-bromo-4-fluoro-6-((furan-2-ylmethoxy)methyl)phenyl trifluoromethanesulfonate (4b):

Prepared from 0.65 mmol of 2-bromo-4-fluoro-6-((furan-2-ylmethoxy)methyl)phenol **13b** to afford 248 mg (0.57 mmol, 88% yield) of **4b** as a colorless oil.

R_f = 0.65 (Cyclohexane /Et_2O, 9:1). ν_{max} (neat): 2915, 1412, 1211, 1134, 863 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.43 (dd, J = 1.8, 0.9 Hz, 1H), 7.37-7.30 (m, 2H), 6.39-6.33 (m, 2H), 4.65 (s, 2H), 4.56 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -72.1 (s, 3F), -109.9 (s, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 161.3 (d, J = 253.6 Hz), 150.7, 143.4, 139.6 (d, J = 3.5 Hz), 136.7 (d, J = 8.6 Hz), 120.7 (d, J = 26.6 Hz), 118.7 (q, J = 320.8 Hz), 117.1, 115.9 (d, J =

24.7 Hz), 110.6, 110.4, 66.0, 64.9. HRMS (*m/z*) calcd for $C_{13}H_9{}^{79}BrF_4O_5SNa$ [MNa^+] 454.9188, found 454.9192.

2-bromo-6-((furan-2-ylmethoxy)methyl)-4-methoxyphenyl trifluoromethanesulfonate (4c):

Prepared from 1.28 mmol of 2-bromo-6-((furan-2-ylmethoxy)methyl)-4-methoxyphenol **13c** to afford 478 mg (1.07 mmol, 84% yield) of **4c** as a colorless oil.

R_f = 0.28 (Cyclohexane /Et_2O, 95:5). ν_{max} (neat): 2943, 1407, 1206, 859 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.42 (d, *J* = 0.7 Hz, 1H), 7.12-7.06 (m, 2H), 6.38-6.33 (m, 2H), 4.64 (s, 2H), 4.53 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 159.3, 151.0, 143.3, 137.2, 135.2, 119.0, 118.7 (q, *J* = 320.6 Hz), 116.8, 113.9, 110.5, 110.2, 66.4, 64.7, 56.1. HRMS (*m/z*) calcd for $C_{14}H_{12}{}^{79}BrF_3O_6SNa$ [MNa^+] 466.9388, found 466.9396.

3-bromo-5-((furan-2-ylmethoxy)methyl)-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate (4d):

Prepared from 0.52 mmol of 3-bromo-5-((furan-2-ylmethoxy)methyl)-[1,1'-biphenyl]-4-ol **13d** to afford 202 mg (0.41 mmol, 79% yield) of **4d** as a colorless oil.

R_f = 0.64 (Cyclohexane /Et_2O, 9:1). ν_{max} (neat): 1409, 1207, 1132, 859 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.82-7.79 (m, 1H), 7.79-7.75 (m, 1H), 7.59-7.53 (m, 2H), 7.50-7.37 (m, 4H), 6.40-6.33 (m, 2H), 4.73 (s, 2H), 4.58 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.0, 143.3, 142.9, 142.9, 138.2, 134.5, 132.2, 129.2 (2C), 128.7, 127.8, 127.3 (2C), 118.7 (q, *J* = 320.9 Hz), 116.6, 110.5, 110.2, 66.5, 64.8. HRMS (*m/z*) calcd for $C_{19}H_{15}{}^{79}BrF_3O_5S$ [MH^+] 490.9776, found 490.9772.

3-bromo-4'-(*tert*-butyl)-5-((furan-2-ylmethoxy)methyl)-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate (4e):

Prepared from 0.31 mmol of 3-bromo-4'-(*tert*-butyl)-5-((furan-2-ylmethoxy)methyl)-[1,1'-biphenyl]-4-ol **13e** to afford 153 mg (0.28 mmol, 90% yield) of **4e** as a pale yellow oil.

R_f = 0.45 (Petroleum Ether/Et_2O, 95:5). ν_{max} (neat): 2963, 1412, 1209, 1133, 861 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.80 (d, *J* = 2.3 Hz, 1H), 7.77 (d, *J* = 2.3 Hz, 1H), 7.55-7.46 (m, 4H), 7.43 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.39 (d, *J* = 3.2 Hz, 1H), 6.37 (dd, *J* = 3.2, 1.8 Hz, 1H), 4.73 (s, 2H), 4.58 (s, 2H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.9, 151.0, 143.3, 142.8, 142.7, 135.3, 134.4, 132.0, 127.6, 127.0 (2C), 126.1 (2C), 118.7 (q, *J* = 320.7 Hz), 116.6, 110.5, 110.2, 66.5, 64.8, 34.8, 31.4 (3C). HRMS (*m/z*) calcd for $C_{23}H_{22}{}^{79}BrF_3O_5S$ [M^+] 546.0323, found 546.0299.

1-bromo-3-((furan-2-ylmethoxy)methyl)naphthalen-2-yl trifluoromethanesulfonate (4f):

Prepared from 0.59 mmol of 1-bromo-3-((furan-2-ylmethoxy)methyl)naphthalen-2-ol **13f** to afford 192 mg (0.41 mmol, 70% yield) of **4f** as a white solid.

R_f = 0.44 (Cyclohexane /Et_2O, 9:1). M_p = 52 °C. ν_{max} (film): 2906, 1408, 1223, 895, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.29 (d, *J* = 8.4 Hz, 1H), 8.06 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.66 (ddd, *J* = 7.8, 6.9, 0.8 Hz, 1H), 7.63-7.56 (m, 1H), 7.44 (d, *J* = 0.8 Hz, 1H), 6.44-6.35 (m, 2H), 4.84 (s, 2H), 4.63 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.2, 143.3, 142.7, 133.0, 132.3, 130.7, 129.1, 128.6, 128.5, 128.1, 127.9, 118.8 (q, *J* = 321.2 Hz), 117.0, 110.5, 110.2, 67.1, 64.8. HRMS (*m/z*) calcd for $C_{17}H_{13}{}^{79}BrF_3O_5S$ [MH^+] 464.9619, found 464.9615.

1-bromo-3-((furan-2-ylmethoxy)methyl)-5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate (4g):

Prepared from 0.96 mmol of 1-bromo-3-((furan-2-ylmethoxy)methyl)-5,6,7,8-tetrahydronaphthalen-2-ol **13g** to afford 386 mg (0.82 mmol, 85% yield) of **4g** as a colorless oil.

R_f = 0.37 (Cyclohexane /CH_2Cl_2, 8:2). ν_{max} (neat): 2936, 1406, 1204, 1132, 857 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.44-7.40 (m, 1H), 7.27 (s, 1H), 6.38-6.33 (m, 2H), 4.62 (s, 2H), 4.52 (s, 2H), 2.82-2.71 (m, 4H), 1.88-1.79 (m, 2H), 1.79-1.70 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.2, 143.2, 141.8, 139.8, 139.1, 130.2, 129.5, 119.1, 118.7 (q, J = 320.7 Hz), 110.5, 110.0, 66.5, 64.6, 30.9, 30.0, 23.0, 22.3. HRMS (*m/z*) calcd for $C_{17}H_{17}{}^{79}BrF_3O_5S$ [MH^+] 468.9932, found 468.9922.

2-bromo-4-methyl-6-(((3-phenylfuran-2-yl)methoxy)methyl)phenyl trifluoromethanesulfonate (4h):

Prepared from 0.55 mmol of 2-bromo-4-methyl-6-(((3-phenylfuran-2-yl)methoxy)methyl)phenol **13h** to afford 215 mg (0.43 mmol, 77% yield) of **4h** as a yellow oil.

R_f = 0.46 (Cyclohexane /CH_2Cl_2, 8:2). ν_{max} (neat): 1408, 1206, 1132, 860 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.49-7.44 (m, 3H), 7.44-7.37 (m, 3H), 7.36-7.29 (m, 2H), 6.59 (d, J = 1.9 Hz, 1H), 4.68 (s, 2H), 4.63 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 146.9, 142.7, 141.7, 140.1, 134.2, 133.7, 133.0, 130.0, 128.9 (2C), 128.1 (2C), 127.4, 126.4, 118.7 (q, J = 320.3 Hz), 115.9, 111.5, 66.6, 63.6, 20.9. HRMS (*m/z*) calcd for $C_{20}H_{16}{}^{79}BrF_3O_5SNa$ [MNa^+] 526.9752, found 526.9750.

2-bromo-6-(((3-(4-methoxyphenyl)furan-2-yl)methoxy)methyl)-4-methylphenyl trifluoromethanesulfonate (4i):

Prepared from 0.48 mmol of 2-bromo-6-(((3-(4-methoxyphenyl)furan-2-yl)methoxy)methyl)-4-methylphenol **13i** to afford 188 mg (0.35 mmol, 73% yield) of **4i** as a colorless oil.

R_f = 0.30 (Cyclohexane /CH_2Cl_2, 8:2). ν_{max} (neat): 1517, 1409, 1208, 862 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.43 (d, *J* = 1.8 Hz, 1H), 7.42-7.35 (m, 3H), 7.35-7.31 (m, 1H), 6.97-6.91 (m, 2H), 6.54 (d, *J* = 1.8 Hz, 1H), 4.67 (s, 2H), 4.60 (s, 2H), 3.84 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 159.1, 146.3, 142.5, 141.7, 140.1, 134.2, 133.8, 130.0, 129.2 (2C), 126.0, 125.5, 118.7 (q, *J* = 322.0 Hz), 115.9, 114.3 (2C), 111.5, 66.6, 63.6, 55.4, 20.8. HRMS (*m/z*) calcd for $C_{21}H_{18}{}^{79}BrF_3O_6SNa$ [MNa^+] 556.9857, found 556.9857.

2-bromo-4-methyl-6-(((3-(*p*-tolyl)furan-2-yl)methoxy)methyl)phenyl trifluoromethanesulfonate (4j):

Prepared from 0.29 mmol of 2-bromo-4-methyl-6-(((3-(*p*-tolyl)furan-2-yl)methoxy)methyl)phenol **13j** to afford 136 mg (0.26 mmol, 90% yield) of **4j** as a yellow oil.

R_f = 0.47 (Petroleum Ether/Et_2O, 9:1). ν_{max} (neat): 2924, 1412, 1211, 1135, 866 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.44 (d, *J* = 1.8 Hz, 1H), 7.42-7.38 (m, 1H), 7.37-7.29 (m, 3H), 7.24-7.18 (m, 2H), 6.56 (d, *J* = 1.8 Hz, 1H), 4.67 (s, 2H), 4.61 (s, 2H), 2.39 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 146.6, 142.6, 141.7, 140.1, 137.2, 134.2, 133.7, 130.1, 130.0, 129.6 (2C), 127.9 (2C), 126.3, 118.7 (q, *J* = 320.8 Hz), 115.9, 111.6, 66.5, 63.6, 21.3, 20.9. HRMS (*m/z*) calcd for $C_{21}H_{18}{}^{79}BrF_3O_5S$ [M^+] 518.0010, found 518.0004.

2-bromo-4-methyl-6-(((3-methylfuran-2-yl)methoxy)methyl)phenyl trifluoromethanesulfonate (4k):

Prepared from 1.03 mmol of 2-bromo-4-methyl-6-(((3-methylfuran-2-yl)methoxy)methyl)phenol **13k** to afford 335 mg (0.76 mmol, 73% yield) of **4k** as a pale yellow oil.

R_f = 0.26 (Petroleum Ether/CH_2Cl_2, 9:1). ν_{max} (neat): 1411, 1208, 1134, 864 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.42-7.38 (m, 1H), 7.37-7.34 (m, 1H), 7.33 (d, J = 1.8 Hz, 1H), 6.22 (d, J = 1.8 Hz, 1H), 4.60 (s, 2H), 4.51 (s, 2H), 2.35 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 146.6, 142.3, 141.6, 140.1, 134.1, 133.9, 129.8, 119.9, 118.7 (q, J = 320.8 Hz), 115.8, 113.1, 66.2, 62.7, 20.9, 9.9. HRMS (*m/z*) calcd for $C_{15}H_{14}{}^{79}BrF_3O_5S^+$ [M^+] 441.9697, found 441.9686.

2-bromo-6-(((3-(4-fluorophenyl)furan-2-yl)methoxy)methyl)-4-methoxyphenyl trifluoromethanesulfonate (4l):

Prepared from 0.35 mmol of 2-bromo-6-(((3-(4-fluorophenyl)furan-2-yl)methoxy)methyl)-4-methoxyphenol **13l** to afford 164 mg (0.30 mmol, 87% yield) of **4l** as a yellow oil.

R_f = 0.53 (Petroluem Ether/Et_2O, 7:3). ν_{max} (neat): 2923, 1410, 1212, 864 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.44 (d, J = 1.8 Hz, 1H), 7.44-7.37 (m, 2H), 7.14-7.04 (m, 4H), 6.54 (d, J = 1.8 Hz, 1H), 4.67 (s, 2H), 4.58 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.3 (d, J = 246.6 Hz), 159.3, 146.8, 142.7, 137.2, 135.0, 129.7 (d, J = 8.0 Hz, 2C), 129.0 (d, J = 3.5 Hz), 125.5, 119.0, 118.7 (q, J = 320.6 Hz), 116.9, 115.7, 115.0 (d, J = 183.6 Hz, 2C), 111.5, 66.6, 63.4, 56.1. HRMS (*m/z*) calcd for $C_{20}H_{15}{}^{79}BrF_4O_6S$ [M^+] 537.9709, found 537.9704.

2-bromo-4-methyl-6-(((4-phenylfuran-2-yl)methoxy)methyl)phenyl trifluoromethanesulfonate (4m):

Prepared from 0.44 mmol of 2-bromo-4-methyl-6-(((4-phenylfuran-2-yl)methoxy)methyl)phenol **13m** to afford 221 mg (0.44 mmol, 99% yield) of **4m** as a pale yellow oil.

R_f = 0.41 (Petroleum Ether/Et_2O, 9:1). ν_{max} (neat): 1409, 1207, 1131, 861 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.71 (d, *J* = 0.9 Hz, 1H), 7.51-7.44 (m, 2H), 7.43-7.41 (m, 1H), 7.41-7.34 (m, 3H), 7.31-7.24 (m, 1H), 6.68 (s, 1H), 4.69 (s, 2H), 4.57 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 152.2, 141.7, 140.2, 139.0, 134.3, 133.7, 132.3, 130.0, 129.0 (2C), 127.4, 127.3, 126.0 (2C), 118.7 (q, *J* = 320.9 Hz), 115.9, 109.3, 66.7, 65.0, 20.9. HRMS (*m/z*) calcd for $C_{20}H_{16}{}^{79}BrF_3O_5S$ [M^+] 503.9854, found 503.9850.

General procedure for the intramolecular Diels-Alder reaction

To a solution of **4** (0.25 mmol, 1 eq.) in anhydrous THF (25 or 5 mL) was added dropwise *n*BuLi (180 µL, 0.45 mmol, 2.5 M in hexanes, 1.8 eq.) at -78 °C. The reaction mixture was warmed to -40 °C in 1 h and, then, a saturated aqueous solution of NH_4Cl was added dropwise. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4 and concentrated under vacuum.

The crude was dissolved in THF (1.65 mL) and *p*TSA (47 mg, 0.275 mmol, 1.1 eq.) was added. The reaction mixture was stirred at r.t. for 30 min and a saturated aqueous solution of $NaHCO_3$ was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H_2O, and brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, Cyclohexane/Et_2O).

8-methyl-1,3-dihydrobenzo[*de*]isochromen-6-ol (5a):

Prepared from 0.25 mmol of 2-bromo-6-((furan-2-ylmethoxy)methyl)-4-methylphenyl trifluoromethanesulfonate **4a** (C = 0.01 M) to afford 39 mg (0.19 mmol, 77% yield) of **5a** as a white solid.

R_f = 0.37 (Cyclohexane /Et_2O, 6:4). M_P = 176 °C. ν_{max} (film): 3264, 1591, 1071, 818 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.80 (s, 1H), 7.04 (s, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 7.4 Hz, 1H), 5.32 (s, 1H), 5.02 (s, 2H), 5.00 (s, 2H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 150.0, 135.0, 132.5, 126.3, 125.1, 124.1, 123.0, 119.4, 119.2, 108.5, 69.5, 69.4, 22.2. HRMS (*m/z*) calcd for $C_{13}H_{13}O_2$ [MH^+] 201.0916, found 201.0904.

8-fluoro-1,3-dihydrobenzo[*de*]isochromen-6-ol (5b):

Prepared from 0.25 mmol of 2-bromo-4-fluoro-6-((furan-2-ylmethoxy)methyl)phenyl trifluoromethanesulfonate **4b** (C = 0.01 M) to afford 38 mg (0.19 mmol, 75% yield) of **5b** as a white solid.

R_f = 0.27 (Cyclohexane /Et_2O, 7:3). M_P = 168 °C. ν_{max} (film): 3304, 1605, 1522, 1254, 864 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.66 (dd, *J* = 10.6, 2.5 Hz, 1H), 6.99 (ddd, *J* = 8.5, 2.5, 1.2 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 5.31 (s, 1H), 5.02 (s, 2H), 4.99 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -113.9 (s, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 160.3 (d, *J* = 245.8 Hz), 150.1 (d, *J* = 5.2 Hz), 135.8 (d, *J* = 8.3 Hz), 125.3, 125.3 (d, *J* = 1.8 Hz), 125.1 (d, *J* = 2.9 Hz), 119.4 (d, *J* = 2.2 Hz), 111.3 (d, *J* = 25.7 Hz), 109.4, 104.5 (d, *J* = 22.7 Hz), 69.3, 69.0 (d, *J* = 2.2 Hz). HRMS (*m/z*) calcd for $C_{12}H_{10}FO_2$ [MH^+] 205.0665, found 205.0655.

8-methoxy-1,3-dihydrobenzo[*de*]isochromen-6-ol (5c):

Prepared from 0.25 mmol of 2-bromo-6-((furan-2-ylmethoxy)methyl)-4-methoxyphenyl trifluoromethanesulfonate **4c** (C = 0.01 M) to afford 41 mg (0.19 mmol, 76% yield) of **5c** as a white solid.

R_f = 0.17 (Cyclohexane /Et_2O, 7:3). M_P = 132 °C. ν_{max} (neat): 3247, 1590, 1251, 1211, 816 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.33 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 1.2 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 5.70 (br s, 1H), 5.01 (s, 2H), 4.99 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 157.3, 149.7, 134.3, 125.3, 125.0, 123.6, 117.8, 113.6, 109.1, 98.9, 69.4, 69.2, 55.5. HRMS (*m/z*) calcd for $C_{13}H_{13}O_3$ [MH^+] 217.0865, found 217.0855.

8-phenyl-1,3-dihydrobenzo[*de*]isochromen-6-ol (5d):

Prepared from 0.25 mmol of 3-bromo-5-((furan-2-ylmethoxy)methyl)-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate **4d** (C = 0.01 M) to afford 53 mg (0.20 mmol, 81% yield) of **5d** as a white solid.

R_f = 0.20 (Cyclohexane /Et_2O, 75:25). M_P = 182 °C. ν_{max} (neat): 3208, 1587, 1393, 1064, 815, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.26 (d, *J* = 1.5 Hz, 1H), 7.76-7.69 (m, 2H), 7.51-7.44 (m, 3H), 7.41-7.34 (m, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 5.41 (s, 1H), 5.11 (s, 2H), 5.04 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 150.8, 141.3, 138.0, 133.2, 129.0 (2C), 127.6 (2C), 127.6, 127.2, 125.1, 124.3, 120.5, 120.2, 118.6, 108.9, 69.5, 69.5. HRMS (*m/z*) calcd for $C_{18}H_{15}O_2$ [MH^+] 263.1072, found 263.1062.

8-(4-(*tert*-butyl)phenyl)-1,3-dihydrobenzo[*de*]isochromen-6-ol (5e):

Prepared from 0.25 mmol of 3-bromo-4'-(*tert*-butyl)-5-((furan-2-ylmethoxy)methyl)-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate **4e** (C = 0.01 M) to afford 59 mg (0.185 mmol, 74% yield) of **5e** as a white solid.

R_f = 0.24 (Petroleum Ether/Et_2O, 75:25). M_P = 193 °C. ν_{max} (neat): 3323, 2959, 1588, 1211, 833 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ_H = 10.11 (s, 1H), 8.21 (d, *J* = 1.5 Hz, 1H), 7.74-7.65 (m, 2H), 7.55 (d, *J* = 1.5 Hz, 1H), 7.54-7.46 (m, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 5.02 (s, 2H), 4.92 (s, 2H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ_C = 152.2, 149.9, 137.5, 135.9, 133.4, 126.7, 126.5 (2C), 125.8 (2C), 124.2, 122.9, 120.6, 119.4, 117.6, 108.2, 68.4, 68.3, 34.3, 31.1 (3C). HRMS (*m/z*) calcd for $C_{22}H_{22}O_2$ [M^+] 318.1620, found 318.1608.

4,6-dihydrodibenzo[*de,g*]isochromen-1-ol (5f):

Prepared from 0.25 mmol of 1-bromo-3-((furan-2-ylmethoxy)methyl)naphthalen-2-yl trifluoromethanesulfonate **4f** (C = 0.01 M) to afford 41 mg (0.17 mmol, 69% yield) of **5f** as a white solid.

R_f = 0.21 (Cyclohexane/Et_2O, 7:3). M_P = 221 °C. ν_{max} (film): 3428, 1686, 1578, 1397, 1088, 754 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ_H = 10.59 (s, 1H), 9.74-9.68 (m, 1H), 7.91-7.84 (m, 1H), 7.63-7.54 (m, 2H), 7.53 (s, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 4.99 (s, 2H), 4.98 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ_C = 155.2, 131.3, 130.3, 129.8, 128.2, 127.8, 127.5, 126.0, 125.9, 123.6, 122.6, 121.2, 118.1, 112.7, 68.8 (2C). HRMS (*m/z*) calcd for $C_{16}H_{13}O_2$ [MH^+] 237.0916, found 237.0910.

4,6,8,9,10,11-hexahydrodibenzo[*de,g*]isochromen-1-ol (5g):

Prepared from 0.25 mmol of 1-bromo-3-((furan-2-ylmethoxy)methyl)-5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate **4g** (C = 0.05 M) to afford 25 mg (0.10 mmol, 41% yield) of **5g** as a white solid.

R_f = 0.30 (Cyclohexane /Et_2O, 8:2). M_P = 125 °C. ν_{max} (neat): 3180, 2926, 1577, 1417, 1023, 818 cm^{-1}. ^1H NMR (400 MHz, DMSO-*d*6) δ_H = 9.65 (s, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.84 (s, 1H), 6.75 (s, *J* = 7.7 Hz, 1H), 4.84 (s, 4H), 3.49-3.40 (m, 2H), 2.85-2.76 (m, 2H), 1.79-1.66 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ_C = 154.4, 132.4, 131.8, 129.0, 127.6, 123.3, 122.9, 122.9, 120.0, 109.7, 68.8, 68.5, 30.6, 29.3, 23.5, 22.0. HRMS (*m/z*) calcd for $C_{16}H_{17}O_2$ [MH^+] 241.1229, found 241.1220.

8-methyl-4-phenyl-1,3-dihydrobenzo[*de*]isochromen-6-ol (5h):

Prepared from 0.25 mmol of 2-bromo-4-methyl-6-(((3-phenylfuran-2-yl)methoxy)methyl)phenyl trifluoromethanesulfonate **4h** (C = 0.01 M) to afford 35 mg (0.13 mmol, 51% yield) of **5h** as a white solid.

R_f = 0.28 (Cyclohexane /Et_2O, 85:15). M_P = 178 °C. ν_{max} (neat): 3201, 1597, 1402, 913, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.83 (s, 1H), 7.46-7.32 (m, 3H), 7.31-7.25 (m, 2H), 7.07 (s, 1H), 6.72 (s, 1H), 5.55 (br s, 1H), 5.02 (s, 2H), 4.98 (s, 2H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 149.7, 140.2, 134.8, 134.1, 132.8, 129.2 (2C), 128.4 (2C), 127.4, 126.5, 123.5, 123.5, 121.8, 119.5, 110.9, 69.6, 68.4, 22.1. HRMS (*m/z*) calcd for $C_{19}H_{17}O_2$ [MH^+] 277.1229, found 277.1226.

4-(4-methoxyphenyl)-8-methyl-1,3-dihydrobenzo[*de*]isochromen-6-ol (5i):

Prepared from 0.25 mmol of 2-bromo-6-(((3-(4-methoxyphenyl)furan-2-yl)methoxy)methyl)-4-methylphenyl trifluoromethanesulfonate **4i** (C = 0.05 M) to afford 11 mg (0.04 mmol, 14% yield) of **5i** as a white solid.

R_f = 0.13 (Cyclohexane /Et_2O, 85:15). M_P = 172 °C. ν_{max} (neat): 3191, 1606, 1509, 834 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.82 (s, 1H), 7.26-7.21 (m, 2H), 7.06 (s, 1H), 6.99-6.94 (m, 2H), 6.74 (s, 1H), 5.36 (s, 1H), 5.01 (s, 2H), 4.98 (s, 2H), 3.87 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 159.0, 149.6, 134.7, 133.7, 132.9, 132.6, 130.3 (2C), 126.6, 123.4, 123.4, 121.9, 119.4, 113.9 (2C), 111.1, 69.6, 68.5, 55.5, 22.1. HRMS (*m/z*) calcd for $C_{20}H_{19}O_3$ [MH^+] 307.1334, found 307.1328.

8-methyl-4-(*p*-tolyl)-1,3-dihydrobenzo[*de*]isochromen-6-ol (5j):

Prepared from 0.25 mmol of 2-bromo-4-methyl-6-(((3-(*p*-tolyl)furan-2-yl)methoxy)methyl)phenyl trifluoromethanesulfonate **4j** (C = 0.05 M) to afford 30 mg (0.11 mmol, 42% yield) of **5j** as a white solid.

R_f = 0.24 (Petroleum Ether/Et_2O, 7:3). M_P = 180 °C. ν_{max} (neat): 3304, 2919, 1602, 1405, 1215, 822 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.83 (s, 1H), 7.27-7.17 (m, 4H), 7.06 (s, 1H), 6.74 (s, 1H), 5.39 (br s, 1H), 5.01 (s, 2H), 4.99 (s, 2H), 2.52 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 149.6, 137.2, 137.1, 134.7, 134.0, 132.8, 129.2 (2C), 129.1 (2C), 126.6, 123.4, 123.4, 121.8, 119.4, 111.0, 69.6, 68.5, 22.1, 21.4. HRMS (*m/z*) calcd for $C_{20}H_{18}O_2$ [M^+] 290.1307, found 290.1315.

4,8-dimethyl-1,3-dihydrobenzo[*de*]isochromen-6-ol (5k):

Prepared from 0.25 mmol of 2-bromo-4-methyl-6-(((3-methylfuran-2-yl)methoxy)methyl)phenyl trifluoromethanesulfonate **4k** (C = 0.01 M) to afford 44 mg (0.21 mmol, 82% yield) of **5k** as a white solid.

R_f = 0.21 (Petroleum Ether/Et_2O, 8:2). M_P = 233°C. ν_{max} (neat): 3264, 2917, 2849, 1591, 1406, 1213, 1061, 843 cm^{-1}. ^1H NMR (400 MHz, DMSO-*d*6) δ_H = 9.80 (s, 1H), 7.69 (s, 1H), 7.01 (s, 1H), 6.63 (s, 1H), 4.88 (s, 2H), 4.86 (s, 2H), 2.41 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ_C = 150.9, 132.2, 131.7, 128.1, 126.0, 122.6, 122.3, 119.7, 119.5, 111.0, 67.9, 66.3, 21.5, 17.8. HRMS (*m/z*) calcd for $C_{14}H_{14}O_2$ [M^+] 214.0994, found 214.0984.

4-(4-fluorophenyl)-8-methoxy-1,3-dihydrobenzo[*de*]isochromen-6-ol (5l):

Prepared from 0.25 mmol of 2-bromo-6-(((3-(4-fluorophenyl)furan-2-yl)methoxy)methyl)-4-methoxyphenyl trifluoromethanesulfonate **4l** (C = 0.01 M) to afford 18 mg (0.06 mmol, 23% yield) of **5l** as a white solid.

R_f = 0.29 (Petroleum Ether/Et_2O, 6:4). M_P = 153 °C. ν_{max} (neat): 3419, 2924, 1604, 1510, 1221, 1158, 841 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.35 (d, *J* = 2.5 Hz, 1H), 7.30-7.22 (m, 2H), 7.16-7.08 (m, 2H), 6.93-6.88 (m, 1H), 6.72 (s, 1H), 5.28 (br s, 1H), 4.99 (s, 2H), 4.92 (s, 2H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.3 (d, *J* = 246.4 Hz), 157.3, 149.3, 136.1 (d, *J* = 3.1 Hz), 134.9, 131.5, 130.8 (d, *J* = 8.0 Hz, 2C), 125.2 (d, *J* = 116.3 Hz), 123.8, 122.2, 115.3, 114.8 (d, *J* = 146.8 Hz, 2C), 111.3, 98.9, 69.4, 68.2, 55.6. HRMS (*m/z*) calcd for $C_{19}H_{15}FO_3$ [M^+] 310.1005, found 310.0991.

8-methyl-5-phenyl-1,3-dihydrobenzo[*de*]isochromen-6-ol (5m):

Prepared from 0.25 mmol of 2-bromo-4-methyl-6-(((4-phenylfuran-2-yl)methoxy)methyl)phenyl trifluoromethanesulfonate **4m** (C = 0.01 M) to afford 16 mg (0.21 mmol, 23% yield) of **5m** as a white solid.

R_f = 0.51 (Petroleum Ether/Et_2O, 7:3). M_P = 126°C. ν_{max} (neat): 3412, 2918, 1581, 1184, 1088, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.92 (s, 1H), 7.58-7.49 (m, 4H), 7.47-7.40 (m, 1H), 7.06 (s, 1H), 6.99 (s, 1H), 5.72 (br s, 1H), 5.04 (s, 2H), 5.02 (s, 2H), 2.53 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 146.3, 137.5, 135.4, 132.4, 129.7 (2C), 129.5 (2C), 128.1, 125.8, 124.7, 124.0, 123.0, 121.2, 121.0, 120.2, 69.4, 69.3, 22.2. HRMS (*m/z*) calcd for $C_{19}H_{16}O_2$ [M^+] 276.1150, found 276.1137.

General procedure for the synthesis of dihydrobenzo[*de*]isochromene 6

To a solution of naphthol **5** (1 eq.) in anhydrous DMF (0.26 M) was added potassium carbonate (3 eq.) and methyl iodide (1.5 eq.). The reaction mixture was stirred at r.t. overnight. EtOAc (15 mL) and H_2O (15 mL) were added. The layers were separated and the organic layer was washed with H_2O (15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, Cyclohexane/Et_2O).

7-methoxy-5-methyl-1,3-dihydrobenzo[*de*]isochromene (6a):

Prepared from 0.56 mmol of 8-methyl-1,3-dihydrobenzo[*de*]isochromen-6-ol **5a** to afford 100 mg (0.47 mmol, 83% yield) of **6a** as a white solid.

R_f = 0.57 (Cyclohexane /Et_2O, 6:4). M_P = 136 °C. ν_{max} (film): 2965, 1587, 1451, 1217, 1086, 1049, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.90 (s, 1H), 7.04 (s, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 5.01 (s, 2H), 5.00 (s, 2H), 3.99 (s, 3H), 2.51 (s, 3H). ^{13}C

NMR (101 MHz, $CDCl_3$) δ_C = 154.1, 134.9, 132.3, 126.0, 125.3, 124.6, 122.9, 119.8, 119.1, 103.7, 69.5, 69.4, 55.6, 22.2. HRMS (*m/z*) calcd for $C_{14}H_{15}O_2$ [MH^+] 215.1072, found 215.1059.

5-fluoro-7-methoxy-1,3-dihydrobenzo[*de*]isochromene (6b):

Prepared from 0.19 mmol of 8-fluoro-1,3-dihydrobenzo[*de*]isochromen-6-ol **5b** to afford 41 mg (0.19 mmol, 98% yield) of **6b** as a white solid.

R_f = 0.29 (Cyclohexane /Et_2O, 9:1). M_P = 93 °C. ν_{max} (film): 2963, 2853, 1601, 1518, 1476, 1213, 922 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.71 (dd, *J* = 10.7, 2.5 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.97 (ddd, *J* = 8.4, 2.4, 1.1 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 5.01 (s, 2H), 4.98 (s, 2H), 3.97 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -114.2 (s, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 160.3 (d, *J* = 245.5 Hz), 154.1 (d, *J* = 5.1 Hz), 135.6 (d, *J* = 8.2 Hz), 126.3 (d, *J* = 9.3 Hz), 124.8, 124.7 (d, *J* = 1.5 Hz), 119.3 (d, *J* = 3.0 Hz), 111.1 (d, *J* = 26.3 Hz), 104.8 (d, *J* = 22.6 Hz), 104.6, 69.2, 69.0 (d, *J* = 2.2 Hz), 55.6. HRMS (*m/z*) calcd for $C_{13}H_{12}FO_2$ [MH^+] 219.0821, found 219.0813.

5,7-dimethoxy-1,3-dihydrobenzo[*de*]isochromene (6c):

Prepared from 0.66 mmol of 8-methoxy-1,3-dihydrobenzo[*de*]isochromen-6-ol **5c** to afford 134 mg (0.58 mmol, 88% yield) of **6c** as a white solid.

R_f = 0.32 (Cyclohexane/Et_2O, 95:5). M_P = 118 °C. ν_{max} (neat): 2936, 1590, 1253, 1071, 814 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.40 (s, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.86 (s, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 4.99 (s, 2H), 4.98 (s, 2H), 3.99 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 157.4, 153.6, 134.4, 126.4, 124.8, 123.2, 117.7, 113.4, 104.4, 99.2, 69.4, 69.2, 55.6, 55.5. HRMS (*m/z*) calcd for $C_{14}H_{15}O_3$ [MH^+] 231.1021, found 231.1013.

7-methoxy-5-phenyl-1,3-dihydrobenzo[*de*]isochromene (6d):

Prepared from 0.18 mmol of 8-phenyl-1,3-dihydrobenzo[*de*]isochromen-6-ol **5d** to afford 48 mg (0.17 mmol, 96% yield) of **6d** as a white solid.

R_f = 0.55 (Cyclohexane/Et_2O, 8:2). M_P = 116 °C. ν_{max} (neat): 2945, 1585, 1453, 1254, 1214, 763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.36 (d, *J* = 1.7 Hz, 1H), 7.77-7.71 (m, 2H), 7.52-7.44 (m, 3H), 7.41-7.35 (m, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 5.11 (s, 2H), 5.04 (s, 2H), 4.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 154.8, 141.5, 138.9, 133.1, 128.9 (2C), 127.6 (2C), 127.4, 127.0, 125.4, 124.5, 120.5, 120.2, 119.0, 104.0, 69.5, 69.4, 55.7. HRMS (*m/z*) calcd for $C_{19}H_{17}O_2$ [MH^+] 277.1229, found 277.1220.

1-methoxy-4,6-dihydrodibenzo[*de,g*]isochromene (6f):

Prepared from 0.14 mmol of 4,6-dihydrodibenzo[*de,g*]isochromen-1-ol **5f** to afford 25 mg (0.10 mmol, 70% yield) of **6f** as a white solid.

R_f = 0.17 (Cyclohexane /Et_2O, 95:5). M_P = 129 °C. ν_{max} (film): 2818, 1684, 1508, 1248, 1099, 812 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 9.65 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.83 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.66-7.55 (m, 2H), 7.45 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 5.10 (s, 2H), 5.08 (s, 2H), 4.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 158.0, 132.1, 130.0 (2C), 128.7, 128.2, 128.0, 126.4, 126.2, 125.3, 122.3, 122.2, 120.7, 108.2, 70.1, 70.0, 55.9. HRMS (*m/z*) calcd for $C_{17}H_{15}O_2$ [MH^+] 251.1072, found 251.1067.

1-methoxy-4,6,8,9,10,11-hexahydrodibenzo[*de,g*]isochromene (6g):

Prepared from 0.13 mmol of 4,6,8,9,10,11-hexahydrodibenzo[*de,g*]isochromen-1-ol **5g** to afford 22 mg (0.09 mmol, 68% yield) of **6g** as a white solid.

R_f = 0.37 (Cyclohexane /Et_2O, 95:5). M_P = 102 °C. ν_{max} (neat): 2925, 2828, 1575, 1454, 1216, 1097, 805 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.00 (d, *J* = 7.7 Hz, 1H), 6.87 (s, 1H), 6.76

(d, J = 7.7 Hz, 1H), 4.97 (s, 2H), 4.97 (s, 2H), 3.89 (s, 3H), 3.52-3.39 (m, 2H), 2.96-2.83 (m, 2H), 1.90-1.73 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 157.4, 134.1, 132.8, 129.1, 127.7, 125.1, 124.9, 123.7, 119.7, 105.9, 69.9, 69.6, 55.6, 31.5, 30.1, 24.2, 22.5. HRMS (*m/z*) calcd for $C_{17}H_{19}O_2$ [MH^+] 255.1385, found 255.1378.

6-methoxy-8-methyl-4-phenyl-1,3-dihydrobenzo[*de*]isochromene (6h):

Prepared from 0.09 mmol of 8-methyl-4-phenyl-1,3-dihydrobenzo[*de*]isochromen-6-ol **5h** to afford 17 mg (0.06 mmol, 66% yield) of **6h** as a white solid.

R_f = 0.42 (Petroleum Ether/Et_2O, 85:15). M_P = 126 °C. ν_{max} (neat): 2920, 1596, 1444, 1219, 1087, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.94 (s, 1H), 7.51-7.43 (m, 2H), 7.43-7.34 (m, 3H), 7.08 (s, 1H), 6.75 (s, 1H), 5.02 (s, 2H), 4.98 (s, 2H), 4.00 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 153.7, 140.8, 134.8, 133.8, 132.7, 129.3 (2C), 128.5 (2C), 127.4, 126.2, 124.7, 123.5, 121.4, 119.8, 106.4, 69.6, 68.3, 55.7, 22.1. HRMS (*m/z*) calcd for $C_{20}H_{18}O_2$ [M^+] 290.1307, found 290.1315.

6-methoxy-4,8-dimethyl-1,3-dihydrobenzo[*de*]isochromene (6k):

Prepared from 0.20 mmol of 8-methyl-4-methyl-1,3-dihydrobenzo[*de*]isochromen-6-ol **5k** to afford 33 mg (0.14 mmol, 72% yield) of **6k** as a white solid.

R_f = 0.46 (Petroleum Ether/Et_2O, 85:15). M_P = 142 °C. ν_{max} (neat): 2951, 2810, 1589, 1436, 1119, 837 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.85 (s, 1H), 7.01 (s, 1H), 6.59 (s, 1H), 5.00 (s, 2H), 4.96 (s, 2H), 3.98 (s, 3H), 2.48 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 153.5, 133.8, 131.7, 128.0, 126.2, 123.8, 122.9, 121.3, 119.7, 107.3, 69.1, 67.3, 55.6, 22.0, 18.6. HRMS (*m/z*) calcd for $C_{15}H_{16}O_2$ [M^+] 228.1150, found 228.1149.

General procedure for the synthesis of naphthalic anhydrides 7

To a solution of **6** (0.06 mmol, 1 eq.) in CH_2Cl_2 (605 µL) was added PCC (65 mg, 0.3 mmol, 5 eq.) and the reaction mixture was stirred at 60 °C for 24 h. The reaction was checked by TLC and, if it was not completed, more PCC (13 mg, 1 eq.) was added. After completion of the reaction, the mixture was filtrated on silica with CH_2Cl_2 and concentrated under vacuum. (*Due to very poor solubility of the naphthalic anhydrides in all solvents, some ^{13}C NMR were not recorded)*

7-methoxy-5-methylbenzo[*de*]isochromene-1,3-dione (7a):

Prepared from 0.06 mmol of 7-methoxy-5-methyl-1,3-dihydrobenzo[*de*]isochromene **6a** to afford 9 mg (0.04 mmol, 63% yield) of **7a** as a pale yellow solid.

R_f = 0.47 (CH_2Cl_2). M_P = 264 °C. ν_{max} (film): 2924, 1765, 1736, 1574, 1341, 1252, 1059, 976 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.51 (d, *J* = 8.3 Hz, 1H), 8.45 (s, 1H), 8.43 (s, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 4.15 (s, 3H), 2.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 161.5, 160.7, 137.0 (2C), 135.5, 135.0, 130.3, 129.6, 124.1, 118.7, 110.8, 106.0, 56.6, 21.9. HRMS (*m/z*) calcd for $C_{14}H_{11}O_4$ [MH^+] 243.0657, found 243.0644.

5-fluoro-7-methoxybenzo[*de*]isochromene-1,3-dione (7b):

Prepared from 0.06 mmol of 5-fluoro-7-methoxy-1,3-dihydrobenzo[*de*]isochromene **6b** to afford 11 mg (0.04 mmol, 76% yield) of **7b** as a pale yellow solid.

R_f = 0.59 (CH_2Cl_2). M_P = 213 °C. ν_{max} (film): 1775, 1740, 1586, 1254, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.56 (d, *J* = 8.3 Hz, 1H), 8.35 (dd, *J* = 7.9, 2.4 Hz, 1H), 8.27 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 4.17 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -110.4 (s, 1F). HRMS (*m/z*) calcd for $C_{13}H_8FO_4$ [MH^+] 247.0407, found 247.0388.

5,7-dimethoxybenzo[*de*]isochromene-1,3-dione (7c):

Prepared from 0.06 mmol of 5,7-dimethoxy-1,3-dihydrobenzo[*de*]isochromene **6c** to afford 5 mg (0.02 mmol, 32% yield) of **7c** as a yellow solid.

R_f = 0.48 (CH_2Cl_2). M_P = 271 °C. ν_{max} (neat): 1765, 1732, 1579, 1248, 1008, 796 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.44 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 2.7 Hz, 1H), 7.94 (d, *J* = 2.7 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 4.16 (s, 3H), 4.02 (s, 3H). HRMS (*m/z*) calcd for $C_{14}H_{11}O_5$ [MH^+] 259.0606, found 259.0599.

7-methoxy-5-phenylbenzo[*de*]isochromene-1,3-dione (7d):

Prepared from 0.06 mmol of 7-methoxy-5-phenyl-1,3-dihydrobenzo[*de*]isochromene **6d** to afford 13 mg (0.04 mmol, 71% yield) of **7d** as a white solid.

R_f = 0.64 (CH_2Cl_2). M_P = 273 °C. ν_{max} (neat): 1760, 1725, 1567, 1248, 1075, 998 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.89 (s, 1H), 8.84 (s, 1H), 8.58 (d, *J* = 8.3 Hz, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59-7.51 (m, 2H), 7.50-7.43 (m, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 4.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.1, 161.5, 139.9 (2C), 138.9, 135.7, 133.1, 130.9, 129.4 (2C), 128.7, 127.8, 127.6 (2C), 124.4, 119.4, 110.9, 106.3, 56.7. HRMS (*m/z*) calcd for $C_{19}H_{13}O_4$ [MH^+] 305.0814, found 305.0806.

1-methoxydibenzo[*de,g*]isochromene-4,6-dione (7f):

Prepared from 0.06 mmol of 1-methoxy-4,6-dihydrodibenzo[*de,g*]isochromene **6f** to afford 14 mg (0.05 mmol, 86% yield) of **7f** as a pale yellow solid.

R_f = 0.44 (CH_2Cl_2). M_P = > 290°C. ν_{max} (film): 1763, 1721, 1620, 1570, 1271, 1098, 1022 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 9.63 (d, *J* = 8.6 Hz, 1H), 9.06 (s, 1H), 8.67 (d, *J* = 8.6 Hz, 1H), 8.16 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.91 (ddd, *J* = 7.0, 1.6, 1.5 Hz, 1H), 7.81-7.75 (m, 1H),

7.42 (d, J = 8.6 Hz, 1H), 4.31 (s, 3H). HRMS (*m/z*) calcd for $C_{17}H_{11}O_4$ [MH^+] 279.0657, found 279.0648.

1-methoxy-8,9,10,11-tetrahydrodibenzo[*de,g*]isochromene-4,6-dione (7g):

Prepared from 0.06 mmol of 1-methoxy-4,6,8,9,10,11-hexahydrodibenzo[*de,g*]isochromene **6g** to afford 11 mg (0.04 mmol, 64% yield) of **7g** as a pale yellow solid.

R_f = 0.60 (CH_2Cl_2). M_P = 235 °C. ν_{max} (neat): 2950, 1759, 1716, 1563, 1250, 1016, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.48 (d, J = 8.4 Hz, 1H), 8.31 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 4.09 (s, 3H), 3.58-3.47 (m, 2H), 3.08-2.97 (m, 2H), 1.94-1.79 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.7, 161.8, 145.2, 136.7 (2C), 136.5, 134.7, 131.9, 123.7, 115.6, 111.0, 107.3, 56.2, 31.3, 31.1, 23.4, 21.8. HRMS (*m/z*) calcd for $C_{17}H_{15}O_4$ [MH^+] 283.0970, found 283.0965.

6-methoxy-8-methyl-4-phenylbenzo[*de*]isochromene-1,3-dione (7h):

Prepared from 0.06 mmol of 6-methoxy-8-methyl-4-phenyl-1,3-dihydrobenzo[*de*]isochromene **6h** to afford 12 mg (0.04 mmol, 61% yield) of **7h** as a pale yellow solid.

R_f = 0.43 (CH_2Cl_2). M_P = 253 °C. ν_{max} (neat): 2918, 1757, 1720, 1582, 1231, 975, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.50 (s, 1H), 8.45 (s, 1H), 7.56-7.35 (m, 5H), 6.89 (s, 1H), 4.12 (s, 3H), 2.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 161.9, 159.8, 158.8, 151.9, 141.0, 136.7, 135.8, 131.1, 129.5, 128.4 (2C), 128.4, 128.2 (2C), 123.7, 118.9, 110.3, 107.7, 56.6, 21.7. HRMS (*m/z*) calcd for $C_{20}H_{14}O_4$ [M^+] 318.0892, found 318.0904.

6-methoxy-4,8-dimethylbenzo[*de*]isochromene-1,3-dione (7k):

Prepared from 0.06 mmol of 6-methoxy-8-methyl-4-phenyl-1,3-dihydrobenzo[*de*]isochromene **6k** to afford 10 mg (0.04 mmol, 65% yield) of **7k** as a yellow solid.

R_f = 0.31 (CH_2Cl_2). M_P = 277 °C. ν_{max} (neat): 2921, 1726, 1579, 1258, 1113, 980 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.43 (d, *J* = 1.7 Hz, 1H), 8.37 (dd, *J* = 1.7, 0.9 Hz, 1H), 6.86 (s, 1H), 4.13 (s, 3H), 2.95 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.0, 160.1, 159.8, 151.1, 135.8, 135.3, 131.3, 129.5, 123.2, 118.1, 110.4, 108.2, 56.4, 24.3, 21.6. HRMS (*m/z*) calcd for $C_{15}H_{12}O_4$ [M^+] 256.0736, found 256.0724.

General procedure for the synthesis of naphthalimides 8

To a suspension of **7** (1 eq.) in EtOH (0.46 M) was added *N*,*N*-dimethylethylenediamine (2 eq.) and the reaction mixture was stirred for 2 h under reflux. The reaction mixture was directly purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 95:5).

2-(2-(dimethylamino)ethyl)-7-methoxy-5-methyl-1*H*-benzo[*de*]isoquinoline-1,3(*2H*)-dione (8a):

Prepared from 0.04 mmol of 7-methoxy-5-methylbenzo[*de*]isochromene-1,3-dione **7a** to afford 12 mg (0.04 mmol, 100% yield) of **8a** as a yellow solid.

R_f = 0.36 (CH_2Cl_2/MeOH 9:1). M_P = 198 °C. ν_{max} (film): 2918, 2766, 1701, 1648, 1273, 804 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.46 (d, *J* = 8.3 Hz, 1H), 8.42 (d, *J* = 1.2 Hz, 1H), 8.31 (s, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 4.33 (t, *J* = 7.1 Hz, 2H), 4.10 (s, 3H), 2.70 (t, *J* = 7.1 Hz, 2H), 2.61 (s, 3H), 2.40 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.8, 164.2, 160.5, 136.3, 133.4, 132.6, 128.0, 127.9, 123.8, 122.3, 115.1, 105.3, 57.1, 56.3, 45.7 (2C), 37.9, 21.9. HRMS (*m/z*) calcd for $C_{18}H_{20}N_2O_3$ [MH^+] 313.1552, found 313.1544.

2-(2-(dimethylamino)ethyl)-5-fluoro-7-methoxy-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (8b):

Prepared from 0.05 mmol of 5-fluoro-7-methoxybenzo[*de*]isochromene-1,3-dione **7b** to afford 12 mg (0.04 mmol, 78% yield) of **8b** as a pale yellow solid.

R_f = 0.54 (CH_2Cl_2/MeOH 9:1). M_P = 148 °C. ν_{max} (film): 2764, 1708, 1659, 1589, 1352, 1261, 808 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.49 (d, *J* = 8.2 Hz, 1H), 8.30 (dd, *J* = 8.5, 2.6 Hz, 1H), 8.14 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 4.30 (t, *J* = 7.0 Hz, 2H), 4.11 (s, 3H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.36 (s, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -111.8 (s, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 163.6 (d, *J* = 2.9 Hz), 162.9 (d, *J* = 182 Hz), 160.3 (d, *J* = 5.2 Hz), 159.5, 132.8 (d, *J* = 2.2 Hz), 126.6, 125.1, 125.0, 120.8 (d, *J* = 26.4 Hz), 115.3, 113.2 (d, *J* = 23.4 Hz), 106.0, 57.1, 56.4, 45.8 (2C), 38.2. HRMS (*m/z*) calcd for $C_{17}H_{18}FN_2O_3$ [MH^+] 317.1301, found 317.1292.

2-(2-(dimethylamino)ethyl)-5,7-dimethoxy-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (8c):

Prepared from 0.04 mmol of 5,7-dimethoxybenzo[*de*]isochromene-1,3-dione **7c** to afford 8 mg (0.02 mmol, 59% yield) of **8c** as a yellow solid.

R_f = 0.37 (CH_2Cl_2/MeOH 9:1). M_P = 190 °C. ν_{max} (neat): 2944, 2760, 1692, 1580, 1266, 1069, 800 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.38 (d, *J* = 8.2 Hz, 1H), 8.22 (d, *J* = 2.6 Hz, 1H), 7.84 (d, *J* = 2.6 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 4.32 (t, *J* = 7.0 Hz, 2H), 4.11 (s, 3H), 3.99 (s, 3H), 2.68 (t, *J* = 7.0 Hz, 2H), 2.39 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.4, 164.2, 159.8, 158.0, 130.9, 125.1, 124.9, 124.0, 122.5, 115.2, 108.5, 105.6, 57.0, 56.2, 56.0, 45.7 (2C), 38.0. HRMS (*m/z*) calcd for $C_{18}H_{21}N_2O_4$ [MH^+] 329.1501, found 329.1490.

2-(2-(dimethylamino)ethyl)-7-methoxy-5-phenyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (8d):

Prepared from 0.06 mmol of 7-methoxy-5-phenylbenzo[*de*]isochromene-1,3-dione **7d** to afford 19 mg (0.05 mmol, 85% yield) of **8d** as a pale yellow solid.

R_f = 0.46 (CH_2Cl_2/MeOH 9:1). M_P = 155 °C. ν_{max} (neat): 2774, 1694, 1652, 1570, 1230, 805 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.84 (d, *J* = 1.6 Hz, 1H), 8.71 (d, *J* = 1.6 Hz, 1H), 8.50 (d, *J* = 8.2 Hz, 1H), 7.80-7.72 (m, 2H), 7.56-7.47 (m, 2H), 7.46-7.38 (m, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 4.33 (t, *J* = 6.9 Hz, 2H), 4.12 (s, 3H), 2.68 (t, *J* = 6.9 Hz, 2H), 2.38 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.7, 164.0, 161.1, 139.6, 139.1, 133.3, 131.0, 129.2 (2C), 128.6, 128.3, 127.5 (2C), 126.2, 124.1, 123.0, 115.1, 105.6, 57.1, 56.3, 45.8 (2C), 38.1. HRMS (*m/z*) calcd for $C_{23}H_{23}N_2O_3$ [MH^+] 375.1709, found 375.1698.

5-(2-(dimethylamino)ethyl)-1-methoxy-4*H*-dibenzo[*de,g*]isoquinoline-4,6(5*H*)-dione (8f):

Prepared from 0.04 mmol of 1-methoxydibenzo[*de,g*]isochromene-4,6-dione **7f** to afford 11 mg (0.03 mmol, 80% yield) of **8f** as a pale yellow solid.

R_f = 0.44 (CH_2Cl_2/MeOH 9:1). M_P = 194 °C. ν_{max} (film): 2930, 2758, 1694, 1636, 1238, 814 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 9.56 (d, *J* = 8.6 Hz, 1H), 8.96 (s, 1H), 8.60 (d, *J* = 8.6 Hz, 1H), 8.09 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.81 (ddd, *J* = 7.0, 1.6, 1.5 Hz, 1H), 7.73-7.66 (m, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 4.35 (t, *J* = 7.0 Hz, 2H), 4.24 (s, 3H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.40 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.6, 164.4, 163.5, 136.4, 132.3, 131.6, 131.3, 131.3, 130.5, 129.4, 128.5, 127.3, 120.6, 118.9, 115.7, 109.0, 57.1, 56.3, 45.8 (2C), 38.2. HRMS (*m/z*) calcd for $C_{21}H_{21}N_2O_3$ [MH^+] 349.1552, found 349.1538.

5-(2-(dimethylamino)ethyl)-1-methoxy-8,9,10,11-tetrahydro-4*H*-dibenzo[*de,g*]isoquinoline-4,6(5*H*)-dione (8g):

Prepared from 0.04 mmol of 1-methoxy-8,9,10,11-tetrahydrodibenzo[*de,g*]isochromene-4,6-dione **7g** to afford 11 mg (0.03 mmol, 80% yield) of **8g** as a yellow solid.

R_f = 0.34 (CH_2Cl_2/MeOH 9:1). M_P = 160 °C. ν_{max} (neat): 2927, 2764, 1686, 1644, 1567, 1394, 805, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.48 (d, *J* = 8.3 Hz, 1H), 8.31 (s, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 4.32 (t, *J* = 7.0 Hz, 2H), 4.04 (s, 3H), 3.54-3.44 (m, 2H), 3.06-2.96 (m, 2H), 2.70 (t, *J* = 7.0 Hz, 2H), 2.40 (s, 6H), 1.92-1.78 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.9, 164.4, 163.7, 143.2, 135.9, 134.5, 132.4, 129.7, 123.4, 119.6, 115.4, 106.7, 57.0, 55.9, 45.7 (2C), 37.8, 31.3, 30.9, 23.6, 22.0. HRMS (*m/z*) calcd for $C_{21}H_{25}N_2O_3$ [MH^+] 353.1865, found 353.1856.

2-(2-(dimethylamino)ethyl)-6-methoxy-8-methyl-4-phenyl-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (8h):

Prepared from 0.04 mmol of 6-methoxy-8-methyl-4-phenylbenzo[*de*]isochromene-1,3-dione **7h** to afford 15 mg (0.03 mmol, 96% yield) of **8h** as a pale yellow solid.

R_f = 0.32 (CH_2Cl_2/MeOH 9:1). M_P = 217 °C. ν_{max} (neat): 2921, 1691, 1650, 1582, 1374 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.52 (d, *J* = 1.8 Hz, 1H), 8.37 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.52-7.42 (m, 3H), 7.41-7.36 (m, 2H), 6.79 (s, 1H), 4.22 (t, *J* = 7.0 Hz, 2H), 4.07 (s, 3H), 2.66-2.55 (m, 2H), 2.64 (s, 3H), 2.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.6, 163.2, 158.7, 149.5, 143.0, 136.1, 133.9, 128.7, 128.2 (2C), 128.0 (2C), 127.9, 127.6, 123.5, 122.6, 112.0, 110.2, 56.9, 56.3, 45.6 (2C), 37.7, 21.8. HRMS (*m/z*) calcd for $C_{24}H_{24}N_2O_3$ [M^+] 388.1787, found 388.1790.

2-(2-(dimethylamino)ethyl)-6-methoxy-4,8-dimethyl-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (8k):

Prepared from 0.05 mmol of 6-methoxy-4,8-dimethylbenzo[*de*]isochromene-1,3-dione **7k** to afford 15 mg (0.05 mmol, 94% yield) of **8k** as a pale yellow solid.

R_f = 0.15 (CH_2Cl_2/MeOH 95:5). M_P = 220 °C. ν_{max} (neat): 2924, 1686, 1650, 1378, 1215 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.45 (d, *J* = 1.7 Hz, 1H), 8.34-8.28 (m, 1H), 6.79 (s, 1H), 4.37 (t, *J* = 6.9 Hz, 2H), 4.09 (s, 3H), 2.96 (s, 3H), 2.79 (t, *J* = 6.9 Hz, 2H), 2.59 (s, 3H), 2.49 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.6, 164.4, 159.1, 148.8, 135.2, 133.5, 128.9, 128.0, 123.0, 121.7, 112.3, 110.4, 56.7, 56.1, 45.3 (2C), 37.2, 24.9, 21.6. HRMS (*m/z*) calcd for $C_{19}H_{22}N_2O_3$ [M^+] 326.1630, found 326.1620.

7-methoxy-5-methylbenzo[*de*]isochromen-1(3H)-one (14):

To a solution of 7-methoxy-5-methyl-1,3-dihydrobenzo[*de*]isochromene **6a** (160 mg, 0.75 mmol, 1 eq.) in CH_2Cl_2 (16 mL) was added water (134 µL, 7.5 mmol, 10 eq.) and 2,3-dichloro-5,6-dicyanobenzoquinone (508 mg, 2.24 mmol, 3 eq.). The mixture was stirred during 30 min and a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, Cy/Et_2O 1:1) and lactone **14** was obtained as a white solid (145 mg, 85% yield).

R_f = 0.23 (Cyclohexane/Et_2O 1:1). M_P = 184 °C. ν_{max} (neat): 2922, 1702, 1580, 1226, 1043 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.28 (d, *J* = 8.2 Hz, 1H), 7.93 (s, 1H), 7.19 (s, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 5.72 (s, 2H), 4.07 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.7, 159.7, 135.9, 130.5, 128.0, 127.1, 124.3, 124.0, 120.5, 112.7, 104.9, 70.1, 56.0, 22.1. HRMS (*m/z*) calcd for $C_{14}H_{12}O_3$ [M^+] 228.0786, found 228.0780.

Biological Evaluation

The cytotoxicity was determined by the MTT assay (Methylthiazolyldiphenyl-tetrazolium bromide). Cells were seeded in 96-well tissue culture plates and incubated overnight. Fibroblasts were seeded at 2500 cells per well and colorectal carcinoma HT-29 cells at 1000 cells per well. The exponentially growing cells were then exposed to different drug concentrations for 4-5 doubling times. Cellular viability was determined by exposing cells to the MTT tetrazolium salt for 3 h at 37 °C, and the formation of formazan was measured at 570 nm by a microplate reader. The concentration inhibiting cell growth by 50 % compared with untreated controls was determined from the curves plotting survival as a function of dose. All values are averages of at least two experiments each done in duplicate +/- SD.

Author Information

Corresponding Author

* E-mail: sebastien.prevost@ensta-paristech.fr

Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. NMR spectra (PDF).

Acknowledgments

We thank the MNHN (especially the ATM “SYBIOF”), ENSTA ParisTech, the Ecole Polytechnique and the CNRS for financial support. The NMR spectrometer used in this study

was funded jointly by the *Région Ile-de-France*, the MNHN and the CNRS. We also acknowledge the platform for immortalization of human cells from the Institut de Myologie for providing immortalized human fibroblasts.

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