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$TiCl_4$-Mediated Synthesis of 3,4-Hetero-Disubstituted Isocoumarins by Means of Isocyanide Insertion Reactions

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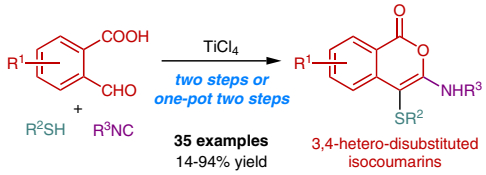

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Abstract The isocyanide insertion into sulfanyl-phthalides under Lewis acid conditions is reported with full details. This sequential three-component reaction affords a new straightforward and highly convenient method for the preparation of 3-amino-4-sulfanyl isocoumarins, the potential of which is still unexplored.

Key words isocyanides, isocoumarins, thio-Passerini reaction, thiocarbonyl surrogates

Isocoumarins constitute a family of synthetic or naturally occurring molecules that demonstrate an exceptionally wide array of biological activities and, for more than half a century, have been the cornerstone of many organic and pharmaceutical chemistry research programs.[1,2] Among this class, several 3,4-disubstituted isocoumarins including oospolactone, polygolide and cephalosol have exhibited interesting antifungal, anti-inflammatory and antimicrobial activities.[3] Furthermore, some 4-chloro-substituted analogues are very potent protease inhibitors with potential applications in Alzheimer's disease, while various 3-amino-4-aryl derivatives have demonstrated encouraging anti-cholesteremic and anti-arteriosclerotic activities (Figure 1).[4]

As a consequence, the development of new synthetic routes to 3,4-disubstituted isocoumarin scaffolds has become a very active field of research.[2–7] Whereas the vast majority of the reported methods rely on the use of internal alkynes by means of transition-metal-catalyzed or electrophilic annulation reactions,[1d,5,6] the regioselective incorporation of heteroatoms on position 3 and/or 4 still remains a significant challenge.

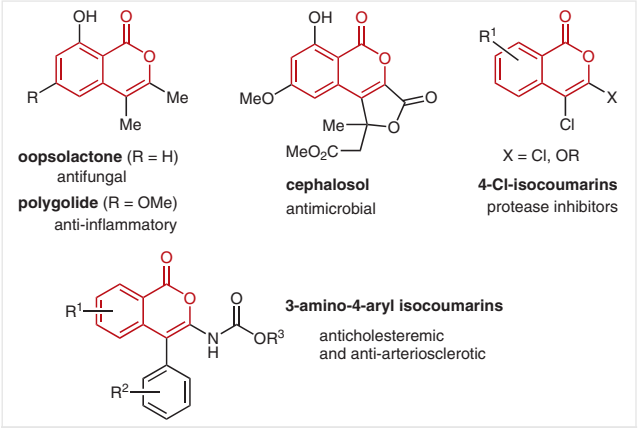
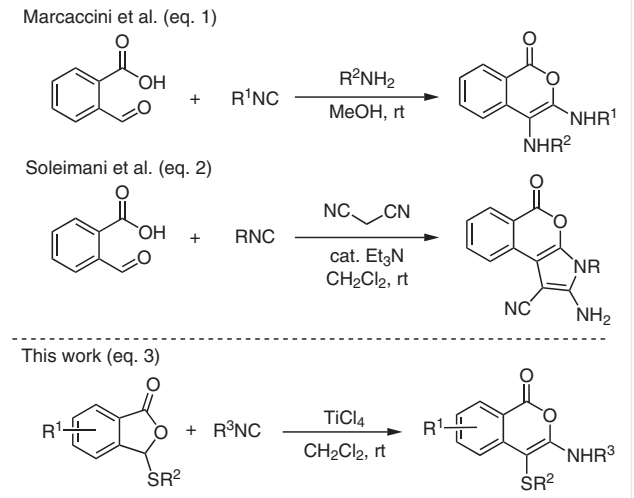


Figure 1 Representative biologically active 3,4-disubstituted isocoumarins

In this area, isocyanide-based insertion reactions have emerged as particularly promising strategies.[8,9] In 2010, Marcaccini et al. reported that, starting from 2-formylbenzoic acid, an isonitrile and an amine, various 3,4-diaminoisocoumarins could be obtained (Scheme 1, eq. 1).[8a] Later, by replacing the amine partner with malononitrile, Soleimani et al. were able to extend this work to the synthesis of 3,4-pyrazolo-isocoumarins (Scheme 1, eq. 2).[8b]

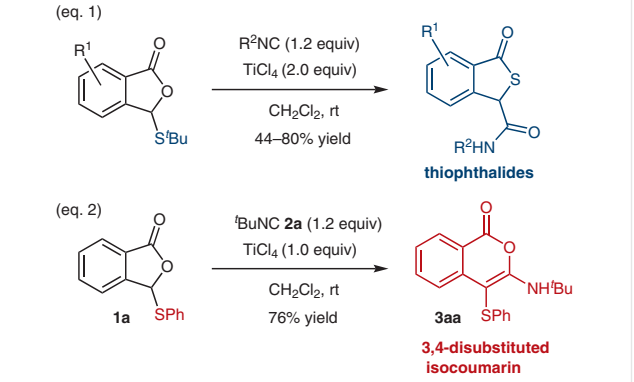
In continuation of our interest in isocyanide chemistry,[10] we recently reported the preparation of various thiophthalides by a formal thio-Passerini reaction.[11] During this work, we incidentally discovered that, in specific cases, valuable 3-amino-4-sulfanyl isocoumarins could be obtained (Scheme 1, eq. 3). We report herein with full details

this regioselective method for access to 3,4-hetero-disubstituted isocoumarins, starting from sulfanyl-phthalides or directly from 2-formylbenzoic acids.



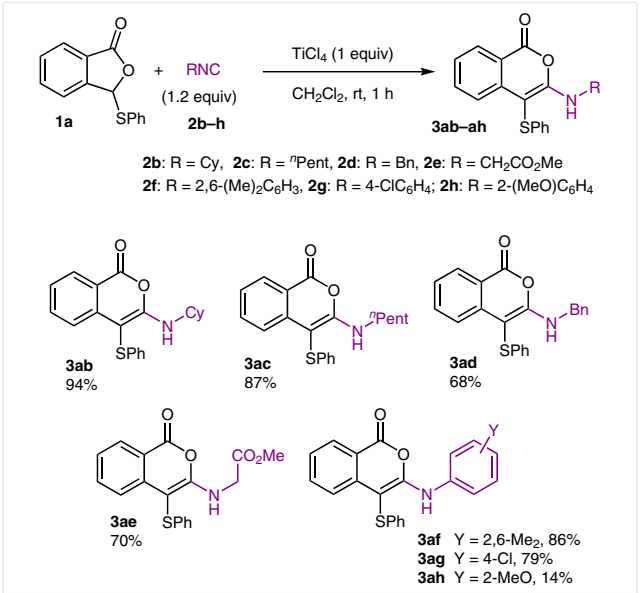
Scheme 1 State of the art and the aim of this work

We previously reported that, upon reaction with isonitriles and $TiCl_4$ at room temperature, 3-(*tert*-butylsulfanyl)-phthalides allowed the formation of a variety of thiophthalides in respectable yields (Scheme 2, eq. 1).[11] During the related optimization studies, we alternatively witnessed an interesting reactivity dichotomy when 3-phenylsulfanyl-phthalide (**1a**) was employed. Indeed, with *tert*-butyl isocyanide (**2a**), this particular substrate in which solely the *S*-substitution changes led cleanly to the 3-amino-4-sulfanyl isocoumarin **3aa** in a good 76% yield (Scheme 2, eq. 2). While, to the best of our knowledge, the preparation of such heterocyclic scaffolds has been scarcely studied,[7g,h] the potential of an original synthetic access to these 3,4-hetero-disubstituted isocoumarins encouraged us to study the scope and limitations of this novel transformation.



Scheme 2 Divergent synthesis of thiophthalides and 3,4-disubstituted isocoumarin **3aa**

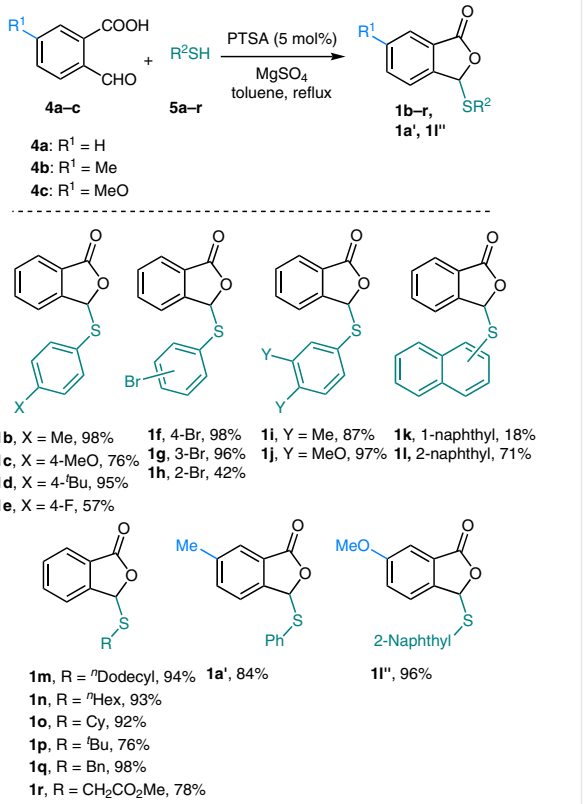
For this purpose, in dichloromethane at room temperature, 3-phenylsulfanyl-phthalide (**1a**) was initially submitted to a variety of isocyanides **2b–h** (1.2 equiv) and $TiCl_4$ (1.0 equiv) (Scheme 3). To our delight, the desired isocyanide insertion reaction took place regardless of the aliphatic or aromatic nature of the isocyanide engaged in the process. Accordingly, secondary alkyl as well as primary alkyl isocyanides **2b–e** afforded the desired 3,4-disubstituted isocoumarins **3ab–ae** with up to 94% yield, while aromatic isocyanides **2f** and **2g** afforded **3af** and **3ag** in 86% and 79% yield, respectively. As a probable consequence of competitive polymerization processes, the use of electron-rich 2-methoxyphenyl isocyanide **2h** only afforded a 14% yield of **3ah**.



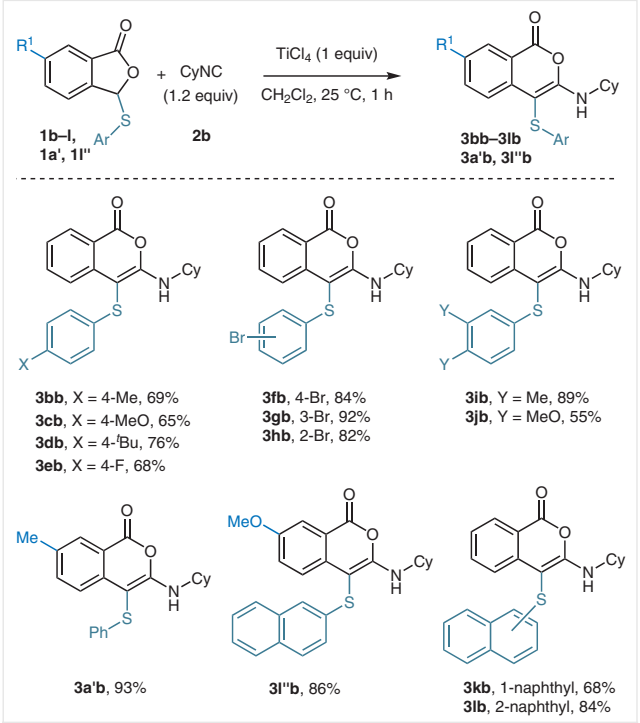
Scheme 3 Scope of various isocyanides in the $TiCl_4$-promoted isocyanide insertion reaction into sulfanyl-phthalide **1a**

We next studied the impact of the sulfur atom substitution on the overall efficiency of the isocyanide insertion process. A large panel of diversely functionalized sulfanyl-phthalides was prepared according to a straightforward protocol in which 2-formylbenzoic acids **4a–c** and various thiols **5a–r** were refluxed in toluene in the presence of $MgSO_4$ (Scheme 4). Pleasingly, this method proved to be quite robust and allowed the required sulfanyl-phthalides **1b–r**, **1a′** and **1l″** to be obtained in good to excellent yields (42–98%), apart from in the case of 1-naphthyl-substituted compound **1k** (18% yield).

Submitting *S*-aryl substituted sulfanyl-phthalides to the isocyanide-insertion conditions afforded the desired isocoumarin derivatives in good to excellent yields (Scheme 5). The substitution on the aromatic core poorly influences the efficiency of the reaction as electron-donating groups such as methoxy or alkyl give yields similar to those obtained



Scheme 4 Preparation of a wide variety of sulfanyl-phthalides **1**



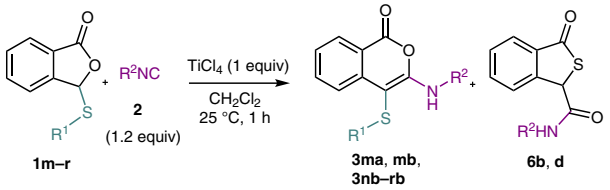
Scheme 5 Evaluation of the scope of the reaction starting from various *S*-aryl-substituted sulfanyl-phthalides and cyclohexylisocyanide (CyNC)

with electron-withdrawing groups such as halogen atoms. The *ortho*, *meta* or *para* position of the substituent seemed to have no effect on the reaction as isocoumarins **3fb–hb** were obtained in almost identical yields.

The scope was next examined for *S*-alkyl-substituted phthalides. Depending on the nature of the starting thiol, different results were observed. Primary thiols with long aliphatic chains gave the expected isocoumarins in good yields (Table 1, entries 1–3). However, secondary or benzylic thiols afforded the desired products along with substantial amounts (16–32%) of the corresponding thiophthalides **6** (Table 1, entries 5–7). We surmised that such outcomes could be rationalized by the ability of the *S*-substituent to stabilize the formed carbocation to allow the final 1,5-acyl transfer (Scheme 6). This hypothesis was further confirmed by the formation of **6b** as the major product in 70% isolated yield when using *tert*-butyl thiol (Table 1, entry 8).

These experimental results led us to propose a plausible mechanistic path for the isocoumarin synthesis (Scheme 6). The complexation of the Lewis acid with the starting sulfanyl-phthalide **1** induces the formation of the thiocarbenium intermediate **A**, which is electrophilic enough to promote nucleophilic addition of the isocyanide. The resulting nitrilium species **B** is then trapped intramolecularly to give **C**. After tautomerization, the latter evolves toward the pyrylium

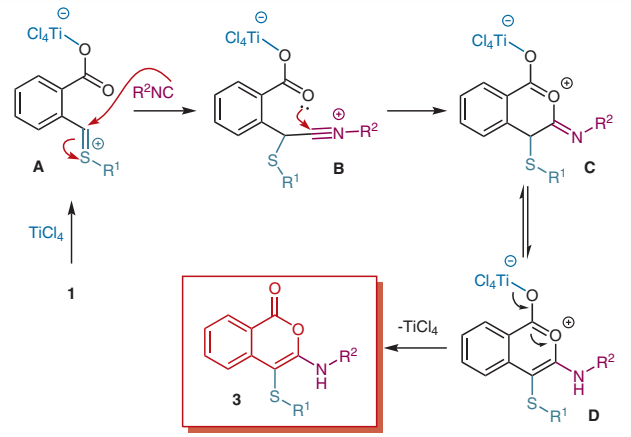
Table 1 Evaluation of *S*-Alkyl-Substituted Sulfanyl-phthalides



Entry	Phthalide **1** (R^1)	Isocyanide **2** (R^2)	Isocoumarin **3** (yield)[a]	Thiophthalide **6** (yield)[a]
1	**1m** (nDodecyl)	**2b** (Cy)	**3mb** (93%)	–[b]
2	**1m** (nDodecyl)	**2a** (tBu)	**3ma** (50%)[c]	–[b]
3	**1n** (nHex)	**2b** (Cy)	**3nb** (93%)	–[b]
4	**1r** (CH_2CO_2Me)	**2b** (Cy)	**3rb** (24%)	–[b]
5	**1o** (Cy)	**2b** (Cy)	**3ob** (68%)	**6b** (32%)
6	**1o** (Cy)	**2d** (Bn)	**3od** (55%)	**6d** (29%)
7	**1q** (Bn)	**2b** (Cy)	**3qb** (70%)	**6b** (16%)
8	**1p** (tBu)	**2b** (Cy)	**3pb** (16%)	**6b** (70%)

[a] Yield of isolated product.
[b] Not detected by ^{1}H NMR spectroscopy of the crude reaction mixture.
[c] Partial deprotection of isocoumarin **3ma** was additionally observed (**3ma'**, R^2 = H, 12%).

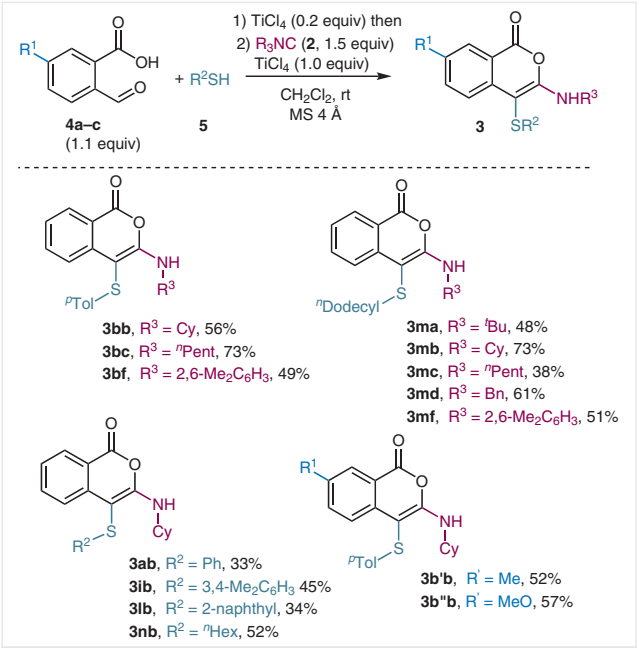
D, which is most probably responsible for the intense dark-blue color of the reaction mixture. Indeed, when adding water at the end of the reaction, the color vanishes and the expected isocoumarin **3** is formed. This hypothesis is rather consistent with the need for a stoichiometric amount of Lewis acid as the pyrylium species **D** is still linked to one molecule of $TiCl_4$. In the case of more labile R^1 substituents, intermediate **C** could evolve through the loss of this group and competitive 1,5-acyl transfer from *O* to *S*, which would give the corresponding thiophthalide **6**.



Scheme 6 A plausible mechanistic pathway

We envisioned developing a one-pot procedure for the formation of 3-amino-4-sulfanyl isocoumarins **3** starting directly from 2-formylbenzoic acids **4** and thiols **5**. Unfortunately, all our attempts at a multicomponent version of the reaction failed. The sulfanyl-phthalides **1** were thus preformed at room temperature by mixing the 2-formylbenzoic acid **4** with the thiol **5** in the presence of catalytic amounts of the Lewis acid and 4 Å molecular sieves. After one hour, a slight excess of isocyanide **2** was added to the reaction mixture along with one equivalent of $TiCl_4$. Under these optimized conditions, the desired 3,4-disubstituted isocoumarins **3** were isolated in good yields in all the cases examined (Scheme 7). Albeit sequential, this method allows a convenient and efficient synthesis of 4-amino-3-thio-substituted isocoumarins **3** avoiding the tedious isolation of sulfanyl-phthalides **1**.

To conclude, we have developed an original access to a large variety of interesting 3,4-hetero-disubstituted isocoumarin derivatives starting from easily accessible 2-formylbenzoic acids, thiols and isocyanides. This straightforward and operationally simple process enables the synthesis of isocoumarins with different substitution patterns. In addition, this method constitutes a new tool to explore the untapped potential of 3-amino-4-sulfanyl isocoumarins which, in addition to potentially possessing biological activities, display notable fluorescence properties (see the Supporting Information for further details).



Scheme 7 One-pot synthesis of 3,4-disubstituted isocoumarins starting from 2-formylbenzoic acids

All reactions were performed under an argon atmosphere and the reagents were ordered from commercial suppliers and used without further purification. Solvents were distilled or purified on activated alumina columns before use. Isocyanides **2f–h** and substituted 2-formylbenzoic acids **4b** and **4c** were prepared according to literature procedures.[8d,12] The preparation and characterization of compounds **1a**, **1m**, **1o**, **1p**, **3aa**, **3ab**, **3ad**, **3af**, **3ma**, **3mb** and **3ob** have previously been reported.[11] Column chromatography was accomplished using Acros Silica gel 60 (40–63 μm). Melting points were obtained using a Kofler bench apparatus. ^1H, ^{13}C and ^{19}F NMR spectra were obtained using Bruker AVANCE 300 or 400 spectrometers with $CDCl_3$ as the solvent. High-resolution mass spectrometry was performed using a Jed JMS-GCmate II instrument.

General Procedure A

To a stirred solution of 2-formylbenzoic acid **4a–c** (1.1 mmol), *p*-toluenesulfonic acid (8 mg) and $MgSO_4$ (2.0 g) in anhyd toluene (5 mL) was added the appropriate thiol **5** (1.0 mmol). The mixture was heated at reflux for 3 h before being cooled to room temperature and filtered through a small pad of silica. After washing with toluene (3 × 20 mL), the solvent was removed under reduced pressure to afford essentially pure racemic 3-sulfanyl-phthalide **1** or, if needed, the residue was submitted to purification by silica gel flash column chromatography.

General Procedure B

To a screw-cap vial under an argon atmosphere were sequentially added thiophthalide **1** (100 mg, 1 equiv), isocyanide **2** (1.2 equiv), CH_2Cl_2 (5 mL) and $TiCl_4$ (1 M in CH_2Cl_2, 1 equiv). The resulting mixture was stirred at room temperature for 1 h before dropwise addition of saturated aqueous $NaHCO_3$ (10 mL). After separation of the organic phase, the aqueous layer was extracted with CH_2Cl_2 (4 × 15 mL) and the combined organic extracts washed with H_2O (40 mL) and brine (40 mL) before being dried over $MgSO_4$. After filtration and evaporation of the solvents under reduced pressure, the crude material was purified by flash column chromatography on silica gel to afford the desired isocoumarin derivative **3**.

General Procedure C

To a screw-cap vial under an argon atmosphere were sequentially added the 2-carboxybenzaldehyde **4** (1.10 mmol, 1.1 equiv), the appropriate thiol **5** (1.00 mmol, 1.0 equiv), CH_2Cl_2 (5 mL), activated 4 Å MS (2.00 g) and $TiCl_4$ (200 µL, 1 M in CH_2Cl_2, 0.2 equiv). After stirring the resulting mixture at room temperature for 1 h, isocyanide **2** (1.50 mmol, 1.5 equiv) and $TiCl_4$ (1.00 mL, 1 M in CH_2Cl_2, 1 equiv) were sequentially added. After 1 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and the organic layer was separated. The aqueous phase was then extracted with CH_2Cl_2 (4 × 20 mL) and the combined organic extracts washed with H_2O (50 mL) and brine (50 mL) before being dried over $MgSO_4$. After filtration and evaporation of the solvents under reduced pressure, the crude material was purified by flash column chromatography on silica gel to afford the desired isocoumarin derivative **3**.

(*R*/*S*)-3-(*p*-Tolylthio)isobenzofuran-1(3*H*)-one (1b)

Starting from phthalaldehydic acid (**4a**) (165 mg, 1.1 mmol) and 4-methylbenzenethiol (**5b**) (124 mg, 1 mmol) and following the general procedure A, **1b** was obtained as a white solid (251 mg, 98% yield); mp 126–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.62 (m, 3 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.39–7.33 (m, 2 H), 7.05 (d, *J* = 7.9 Hz, 2 H), 6.66 (s, 1 H), 2.29 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.3, 146.4, 139.4, 134.3 (2 C), 130.0, 129.9, 126.4, 125.5, 123.5, 86.8, 21.3.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{15}H_{12}O_2S$: 256.0558; found: 256.0556.

(*R*/*S*)-3-[(4-Methoxyphenyl)thio]isobenzofuran-1(3*H*)-one (1c)

Starting from phthalaldehydic acid (**4a**) (400 mg, 2.7 mmol, 1.1 equiv) and 4-methoxythiophenol (**5c**) (300 µL, 2.4 mmol, 1 equiv) and following the general procedure A, **1c** was obtained as a white solid (498 mg, 76% yield); mp 112–114 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.6 Hz, 1 H), 7.71–7.66 (m, 1 H), 7.63 (dd, *J* = 7.5, 0.7 Hz, 1 H), 7.49–7.44 (m, 1 H), 7.39–7.32 (m, 2 H), 6.75–6.71 (m, 2 H), 6.60 (s, 1 H), 3.74 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 160.6, 146.3, 136.7, 134.1, 129.8, 126.2, 125.3, 123.3, 119.5, 114.4, 86.7, 55.2.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{15}H_{12}O_3S$: 272.0507; found: 272.0508.

(*R*/*S*)-3-(4-*tert*-Butylphenylthio)isobenzofuran-1(3*H*)-one (1d)

Starting from phthalaldehydic acid (**4a**) (165 mg, 1.1 mmol) and 4-*tert*-butylbenzenethiol (**5d**) (168 µL, 1 mmol) and following the general procedure A, **1d** was obtained as a white solid (284 mg, 95% yield); mp 102–104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.7 Hz, 1 H), 7.65–7.40 (m, 2 H), 7.46–7.34 (m, 3 H), 7.24–7.19 (m, 2 H), 6.61 (s, 1 H), 1.19 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.3, 152.5, 146.3, 134.3, 133.7, 130.0, 127.1, 126.4, 126.2, 125.5, 123.5, 87.0, 34.7, 31.3.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{18}H_{18}O_2S$: 298.1028; found: 298.1033.

(*R*/*S*)-3-[(4-Fluorophenyl)thio]isobenzofuran-1(3*H*)-one (1e)

Starting from phthalaldehydic acid (**4a**) (500 mg, 3.3 mmol, 1.1 equiv) and 4-fluorothiophenol (**5e**) (320 µL, 3 mmol, 1 equiv) and following the general procedure A, **1e** was obtained as a white solid (443 mg, 57% yield); mp 112–114 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.6 Hz, 1 H), 7.71 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.64 (dd, *J* = 7.7, 1.0 Hz, 1 H), 7.50 (t, *J* = 7.4 Hz, 1 H), 7.48–7.42 (m, 2 H), 6.96–6.91 (m, 2 H), 6.65 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 163.4 (d, J_{C-F} =250.2 Hz), 146.0, 136.7 (d, J_{C-F} = 8.7 Hz), 134.3, 130.0, 126.2, 125.5, 124.6 (d, J_{C-F} = 3.4 Hz), 123.3, 116.2 (d, J_{C-F} = 22.0 Hz), 86.3.

^{19}F NMR (300 MHz, $CDCl_3$): δ = –111.2.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{14}H_9FO_2S$: 260.0307; found: 260.0315.

(*R*/*S*)-3-(4-Bromophenylthio)isobenzofuran-1(3*H*)-one (1f)

Starting from phthalaldehydic acid (**4a**) (165 mg, 1.1 mmol) and 4-bromobenzenethiol (**5f**) (189 mg, 1 mmol) and following the general procedure A, **1f** was obtained as a white solid (313 mg, 98% yield); mp 142–144 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.6 Hz, 1 H), 7.75–7.67 (m, 1 H), 7.64 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.42–7.32 (m, 4 H), 6.68 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 146.0, 135.4, 134.5, 132.4, 130.3, 129.4, 126.4, 125.7, 123.8, 123.4, 86.1.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{14}H_9BrO_2S$: 319.9507; found: 319.9507.

(*R*/*S*)-3-(3-Bromophenylthio)isobenzofuran-1(3*H*)-one (1g)

Starting from phthalaldehydic acid (**4a**) (165 mg, 1.1 mmol) and 3-bromobenzenethiol (**5g**) (118 µL, 1 mmol) and following the general procedure A, **1g** was obtained as a white solid (308 mg, 96% yield); mp 114–116 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.7 Hz, 1 H), 7.72 (td, *J* = 7.6, 1.0 Hz, 1 H), 7.67–7.60 (m, 2 H), 7.53 (t, *J* = 7.5 Hz, 1 H), 7.49–7.36 (m, 2 H), 7.14 (t, *J* = 7.9 Hz, 1 H), 6.72 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.9, 145.7, 135.6, 134.5, 132.9, 131.9, 131.8, 130.5, 130.4, 126.2, 125.6, 123.5, 122.7, 86.1.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{14}H_9BrO_2S$: 319.9507; found: 319.9508.

(*R*/*S*)-3-(2-Bromophenylthio)isobenzofuran-1(3*H*)-one (1h)

Starting from phthalaldehydic acid (**4a**) (165 mg, 1.1 mmol) and 2-bromobenzenethiol (**5h**) (120 µL, 1 mmol) and following the general procedure A, **1h** was obtained after crystallization from hexane/toluene (5:1) as a white solid (134 mg, 42% yield); mp 132–134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.6 Hz, 1 H), 7.83–7.69 (m, 3 H), 7.64–7.53 (m, 2 H), 7.33 (td, *J* = 7.7, 1.4 Hz, 1 H), 7.25–7.15 (m, 1 H), 6.83 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 145.6, 134.6, 133.7, 133.52, 133.46, 130.5, 129.8, 128.4, 126.4, 126.3, 125.8, 123.8, 85.7.

HRMS (ESI): *m*/*z* $[M^•]^+$ (^{79}Br) and $[M^•]^+$ (^{81}Br) calcd for $C_{14}H_9BrO_2S$: 319.9507 and 321.9507; found: 319.9509 and 321.9599.

(*R*/*S*)-3-(3,4-Dimethylphenylthio)isobenzofuran-1(3*H*)-one (1i)

Starting from phthalaldehydic acid (**4a**) (165 mg, 1.1 mmol) and 3,4-dimethylbenzenethiol (**5i**) (135 µL, 1.0 mmol) and following the general procedure A, **1i** was obtained as a white solid (234 mg, 87% yield); mp 130–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.54 (m, 3 H), 7.41 (t, *J* = 7.4 Hz, 1 H), 7.21–7.11 (m, 2 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 6.57 (s, 1 H), 2.11 (t, *J* = 4.5 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.3, 146.3, 137.9, 137.6, 135.1, 134.3, 131.5, 130.3, 130.0, 126.9, 126.3, 125.4, 123.5, 87.0, 19.6 (2 C).

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{16}H_{14}O_2S$: 270.0715; found: 270.0719.

(*R*/*S*)-3-[(3,4-Dimethoxyphenyl)thio]isobenzofuran-1(3*H*)-one (1j)

Starting from phthalaldehydic acid (**4a**) (200 mg, 1.3 mmol) and 3,4-dimethoxythiophenol (**5j**) (173 µL, 1.2 mmol) and following the general procedure A, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (7:3) as eluent gave **1j** as a white solid (351 mg, 97% yield); mp 119–121 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.7 Hz, 1 H), 7.72–7.62 (m, 2 H), 7.50–7.44 (m, 1 H), 7.03 (dd, *J* = 8.3, 2.1 Hz, 1 H), 6.89 (d, *J* = 2.1 Hz, 1 H), 6.70 (d, *J* = 8.3 Hz, 1 H), 6.65 (s, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 150.2, 148.7, 146.4, 134.1, 129.8, 128.4, 126.3, 125.4, 123.3, 119.6, 117.7, 111.1, 86.6, 56.0, 55.8.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{16}H_{14}O_4S$: 302.0613; found: 302.0618.

(*R*/*S*)-3-(Naphthalen-1-ylthio)isobenzofuran-1(3*H*)-one (1k)

Starting from phthalaldehydic acid (**4a**) (500 mg, 3.3 mmol) and naphthalene-1-thiol (**5k**) (420 µL, 3.0 mmol) and following the general procedure A, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (9:1) as eluent gave **1k** as a white solid (161 mg, 18% yield); mp 103–105 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 8.4 Hz, 1 H), 7.92 (d, *J* = 7.2 Hz, 1 H), 7.86–7.77 (m, 3 H), 7.74–7.71 (m, 1 H), 7.69–7.59 (m, 2 H), 7.57–7.38 (m, 3 H), 6.74 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 146.0, 134.1, 134.0, 133.9, 130.1, 130.0, 128.5, 128.0, 127.0, 126.4, 126.1, 125.5, 125.4, 125.3, 123.4, 86.8.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{18}H_{12}O_2S$: 292.0558; found: 292.0560.

(*R*/*S*)-3-(Naphthalen-2-ylthio)isobenzofuran-1(3*H*)-one (1l)

Starting from phthalaldehydic acid (**4a**) (165 mg, 1.1 mmol) and naphthalene-2-thiol (**5l**) (160.2 mg, 1.0 mmol) and following the general procedure A, **1l** was obtained as a white solid (208 mg, 71% yield); mp 120–122 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 1.3 Hz, 1 H), 7.80–7.66 (m, 6 H), 7.57–7.44 (m, 4 H), 6.77 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.2, 146.0, 134.4, 133.4, 133.0, 132.9, 130.1, 130.0, 128.8, 128.0, 127.8, 127.7, 126.9, 126.8, 126.2, 125.5, 123.5, 86.7.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{18}H_{12}O_2S$: 292.0558; found: 292.0568.

(*R*/*S*)-3-(Hexylthio)isobenzofuran-1(3*H*)-one (1n)

Starting from phthalaldehydic acid (**4a**) (165 mg, 1.1 mmol) and hexane-1-thiol (**5n**) (141 µL, 1.0 mmol) and following the general procedure A, **1n** was obtained as a colorless oil (233 mg, 93% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.5 Hz, 1 H), 7.65 (dd, *J* = 10.9, 4.1 Hz, 1 H), 7.56–7.43 (m, 2 H), 6.53 (s, 1 H), 2.69–2.44 (m, 2 H), 1.64–1.47 (m, 2 H), 1.40–1.10 (m, 6 H), 0.81 (dd, *J* = 6.8, 5.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 146.8, 134.3, 129.9, 126.2, 125.4, 123.1, 85.0, 31.2, 30.7, 29.5, 28.3, 22.4, 13.9.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{14}H_{18}O_2S$: 250.1028; found: 250.1023.

(*R*/*S*)-3-(Benzylthio)isobenzofuran-1(3*H*)-one (1q)

Starting from phthalaldehydic acid (**4a**) (165 mg, 1.1 mmol) and phenylmethanethiol (**5q**) (118 µL, 1.0 mmol) and following the general procedure A, **1q** was obtained as a white solid (252 mg, 98% yield); mp 83–85 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.6 Hz, 1 H), 7.57 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.46 (dd, *J* = 10.9, 4.0 Hz, 1 H), 7.38 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.29–7.14 (m, 5 H), 6.32 (s, 1 H), 3.93 (d, *J* = 13.2 Hz, 1 H), 3.74 (d, *J* = 13.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 146.5, 136.5, 134.3, 130.0, 129.2, 128.7, 127.5, 126.3, 125.6, 123.0, 83.3, 35.0.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{15}H_{12}O_2S$: 256.0558; found: 256.0570.

(*R*/*S*)-Methyl 2-(3-Oxo-1,3-dihydroisobenzofuran-1-ylthio)acetate (1r)

Starting from phthalaldehydic acid (**4a**) (165 mg, 1.1 mmol) and methyl 2-mercaptoacetate (**5r**) (91 µL, 1.0 mmol) and following the general procedure A, **1q** was obtained as colorless oil (186 mg, 78% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.0 Hz, 1 H), 7.69 (t, *J* = 7.5 Hz, 1 H), 7.54 (t, *J* = 7.2 Hz, 2 H), 6.71 (s, 1 H), 3.67 (d, *J* = 1.9 Hz, 3 H), 3.46 (dd, *J* = 15.4, 1.9 Hz, 1 H), 3.25 (d, *J* = 15.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 168.9, 145.8, 134.5, 130.3, 126.3, 125.7, 123.2, 83.5, 52.7, 31.6.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{11}H_{10}O_4S$: 238.0300; found: 238.0310.

(*R*/*S*)-6-Methyl-3-(phenylthio)isobenzofuran-1(3*H*)-one (1a′)

Starting from 2-formyl-5-methylbenzoic acid (**4b**) (271 mg, 1.65 mmol) and thiophenol (**5a**) (154 µL, 1.5 mmol) and following the general procedure A, **1a′** was obtained as a white solid (321 mg, 84% yield); mp 128–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.37 (m, 5 H), 7.21–7.13 (m, 3 H), 6.58 (s, 1 H), 2.33 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 143.5, 140.6, 135.5, 133.5, 130.8, 129.1, 128.8, 126.5, 125.4, 123.1, 86.5, 21.4.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{15}H_{12}O_2S$: 256.0558; found: 256.0563.

(*R*/*S*)-6-Methoxy-3-(naphthalen-2-ylthio)isobenzofuran-1(3*H*)-one (1l″)

Starting from 2-formyl-5-methoxybenzoic acid (**4c**) (297 mg, 1.65 mmol) and naphthalene-2-thiol (**5l**) (240 mg, 1.5 mmol) and following the general procedure A, **1l″** was obtained as a white solid (466 mg, 96% yield); mp 130–132 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 1.2 Hz, 1 H), 7.84–7.70 (m, 3 H), 7.60–7.45 (m, 4 H), 7.27–7.18 (m, 2 H), 6.74 (s, 1 H), 3.80 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2, 161.4, 138.2, 133.5, 132.9, 132.7, 129.9, 128.7, 128.5, 127.8, 127.7, 126.9, 126.7, 124.3, 123.1, 107.4, 86.8, 55.8.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{19}H_{14}O_3S$: 322.0664; found: 322.0662.

3-(Pentylamino)-4-(phenylthio)-1*H*-isochromen-1-one (3ac)

Starting from 3-(phenylthio)isobenzofuran-1(3*H*)-one (**1a**) (100 mg, 0.41 mmol), 1-isocyanopentane (**2c**) (63 µL, 0.50 mmol), $TiCl_4$ (410 µL, 1 M in CH_2Cl_2, 0.41 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3ac** as a yellow solid (121 mg, 87% yield); mp 102–104 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–7.96 (m, 1 H), 7.50 (dd, *J* = 8.2, 0.5 Hz, 1 H), 7.45–7.35 (m, 1 H), 7.16–6.96 (m, 6 H), 5.73 (t, *J* = 5.9 Hz, 1 H), 3.31 (m, 2 H), 1.52–1.40 (m, 2 H), 1.25–1.11 (m, 4 H), 0.76 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 159.7, 142.3, 136.1, 135.6, 130.0, 129.2, 125.6, 125.5, 123.2, 121.9, 114.9, 75.5, 42.0, 29.9, 28.8, 22.4, 14.0.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{20}H_{21}NO_2S$: 339.1293; found: 339.1306.

Methyl 2-[1-Oxo-4-(phenylthio)-1*H*-isochromen-3-ylamino]acetate (3ae)

Starting from 3-(phenylthio)isobenzofuran-1(3*H*)-one (**1a**) (50 mg, 0.21 mmol), methyl 2-isocyanoacetate (**2e**) (23 µL, 0.25 mmol), $TiCl_4$ (210 µL, 1 M in CH_2Cl_2, 0.21 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3ae** as a pale yellow solid (49.3 mg, 70% yield); mp 136–138 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17–8.11 (m, 1 H), 7.68–7.63 (m, 1 H), 7.60–7.50 (m, 1 H), 7.25–7.09 (m, 6 H), 6.23 (t, *J* = 5.8 Hz, 1 H), 4.20 (d, *J* = 6.0 Hz, 2 H), 3.76 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 160.1, 158.6, 141.7, 135.8, 130.1, 129.3, 125.8 (2 C), 124.0, 122.4, 115.6, 78.0, 52.6, 43.3.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{18}H_{15}NO_4S$: 341.0722; found: 341.0710.

3-(4-Chlorophenylamino)-4-(phenylthio)-1*H*-isochromen-1-one (3ag)

Starting from 3-(phenylthio)isobenzofuran-1(3*H*)-one (**1a**) (100 mg, 0.41 mmol), 4-chlorophenylisocyanide (**2g**) (68.5 mg, 0.50 mmol), $TiCl_4$ (410 µL, 1 M in CH_2Cl_2, 0.41 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3ag** as a yellow solid (123 mg, 79% yield); mp 130–132 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 8.0, 0.9 Hz, 1 H), 7.62 (d, *J* = 8.3 Hz, 2 H), 7.55–7.40 (m, 1 H), 7.24–7.02 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 156.1, 141.0, 136.0, 135.9, 135.2, 130.3, 129.58, 129.53, 129.48, 126.2, 125.8, 124.8, 123.0, 122.1, 116.4, 80.0.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{21}H_{14}ClNO_2S$: 379.0434; found: 379.0452.

3-(2-Methoxyphenylamino)-4-(phenylthio)-1*H*-isochromen-1-one (3ah)

Starting from 3-(phenylthio)isobenzofuran-1(3*H*)-one (**1a**) (100 mg, 0.41 mmol), 2-methoxyphenylisocyanide (**2h**) (66.3 mg, 0.50 mmol), $TiCl_4$ (410 µL, 1 M in CH_2Cl_2, 0.41 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3ah** as a yellow solid (21.9 mg, 14% yield); mp 100–102 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46 (s, 1 H), 8.24–8.19 (m, 1 H), 7.97–7.92 (m, 1 H), 7.81–7.76 (m, 1 H), 7.65–7.60 (m, 1 H), 7.31–7.14 (m, 6 H), 7.10–7.00 (m, 2 H), 6.92–6.87 (m, 1 H), 3.83 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.9, 156.7, 149.0, 141.7, 135.8, 130.2, 129.3, 127.4, 126.4, 126.0, 124.3, 123.7, 122.9, 121.5, 119.7, 116.0, 110.7, 80.4, 56.1.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{22}H_{17}NO_3S$: 375.0929; found: 375.0929.

3-(Cyclohexylamino)-4-(*p*-tolylthio)-1*H*-isochromen-1-one (3bb)

Starting from 3-(*p*-tolylthio)isobenzofuran-1(3*H*)-one (**1b**) (100 mg, 0.39 mmol), cyclohexylisocyanide (**2b**) (58 µL, 0.47 mmol), $TiCl_4$ (390 µL, 1 M in CH_2Cl_2, 0.39 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (9:1) as eluent gave **3bb** as a yellow solid (98 mg, 69% yield). Starting from 4-methylbenzenethiol (**5b**) (1.0 mmol) and following general procedure C, **3bb** was obtained as a white solid (204 mg, 56% yield); mp 142–144 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.9 Hz, 1 H), 7.60 (d, *J* = 8.1 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 7.07–6.98 (m, 4 H), 5.72 (d, *J* = 8.4 Hz, 1 H), 3.92–3.69 (m, 1 H), 2.27 (s, 3 H), 1.99–1.96 (m, 2 H), 1.77–1.53 (m, 3 H), 1.38–1.34 (m, 2 H), 1.27–1.14 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 159.0, 142.2, 135.4, 135.3, 132.3, 129.9, 125.5, 123.0, 121.9, 114.8, 76.2, 50.6, 33.7, 25.3, 24.6, 20.8.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{22}H_{23}NO_2S$: 365.1449; found: 365.1442.

3-(Cyclohexylamino)-4-[(4-methoxyphenyl)thio]-1*H*-isochromen-1-one (3cb)

Starting from 3-[(4-methoxyphenyl)thio]isobenzofuran-1(3*H*)-one (**1c**) (100 mg, 0.37 mmol), cyclohexylisocyanide (**2b**) (55 µL, 0.44 mmol), $TiCl_4$ (370 µL, 1 M in CH_2Cl_2, 0.37 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (95:5) as eluent gave **3cb** as a yellow solid (91 mg, 65% yield); mp 135–137 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.70–7.59 (m, 1 H), 7.60–7.47 (m, 1 H), 7.46–7.33 (m, 1 H), 7.16–7.06 (m, 2 H), 6.87–6.77 (m, 2 H), 5.75 (d, *J* = 8.5 Hz, 1 H), 3.81–3.80 (m, 1 H), 3.75 (s, 3 H), 1.98 (d, *J* = 12.1 Hz, 2 H), 1.74–1.60 (m, 3 H), 1.43–1.35 (m, 2 H), 1.28–1.16 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 158.2, 142.3, 135.5, 132.7, 129.9, 127.5, 126.6, 123.0, 122.0, 114.9, 114.6, 55.4, 50.6, 33.8, 25.4, 24.6.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{22}H_{23}NO_3S$: 381.1399; found: 381.1393.

4-{[4-(*tert*-Butyl)phenyl]thio}-3-(cyclohexylamino)-1*H*-isochromen-1-one (3db)

Starting from 3-(4-*tert*-butylphenylthio)isobenzofuran-1(3*H*)-one (**1d**) (100 mg, 0.34 mmol), cyclohexylisocyanide (**2b**) (50 µL, 0.40 mmol), $TiCl_4$ (340 µL, 1 M in CH_2Cl_2, 0.34 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (95:5) as eluent gave **3db** as a yellow solid (105 mg, 76% yield); mp 109–111 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.63 (dd, *J* = 8.2, 0.5 Hz, 1 H), 7.55–7.45 (m, 1 H), 7.27–7.23 (m, 2 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 5.72 (d, *J* = 8.5 Hz, 1 H), 3.91–3.74 (m, 1 H), 2.02–1.92 (m, 2 H), 1.74–1.68 (m, 2 H), 1.64–1.57 (m, 1 H), 1.45–1.34 (m, 2 H), 1.27 (s, 9 H), 1.24–1.15 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 159.0, 148.7, 142.3, 135.5, 132.4, 129.9, 126.2, 125.3, 123.0, 122.1, 114.8, 76.3, 50.6, 34.4, 33.7, 31.2, 25.3, 24.6.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{25}H_{29}NO_2S$: 407.1919; found: 407.1933.

3-(Cyclohexylamino)-4-[(4-fluorophenyl)thio]-1*H*-isochromen-1-one (3eb)

Starting from 3-[(4-fluorophenyl)thio]isobenzofuran-1(3*H*)-one (**1e**) (100 mg, 0.38 mmol), cyclohexylisocyanide (**2b**) (57 µl, 0.46 mmol), $TiCl_4$ (380 µL, 1 M in CH_2Cl_2, 0.38 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (9:1) as eluent gave **3eb** as a yellow solid (96 mg, 68% yield); mp 140–142 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18–8.04 (m, 1 H), 7.61–7.56 (m, 1 H), 7.55–7.51 (m, 1 H), 7.15–7.12 (m, 1 H), 7.11–7.05 (m, 2 H), 6.98–6.90 (m, 2 H), 5.69 (d, *J* = 8.4 Hz, 1 H), 3.87–3.74 (m, 1 H), 1.97 (dd, *J* = 12.6, 3.5 Hz, 2 H), 1.74–1.66 (m, 2 H), 1.65–1.58 (m, 1 H), 1.46–1.35 (m, 2 H), 1.26–1.15 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2 (d, J_{C-F} = 244.0 Hz), 160.4, 159.1, 142.0, 135.6, 130.9 (d, J_{C-F} = 3.1 Hz), 130.0, 127.1 (d, J_{C-F} = 7.8 Hz), 123.2, 121.7, 116.3 (d, J_{C-F} = 22.1 Hz), 114.9, 76.1, 50.6, 33.7, 25.3, 24.6.

^{19}F NMR (300 MHz, $CDCl_3$): δ = –117.1.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{21}H_{20}FNO_2S$: 369.1199; found: 369.1207.

4-(4-Bromophenylthio)-3-(cyclohexylamino)-1*H*-isochromen-1-one (3fb)

Starting from 3-(4-bromophenylthio)isobenzofuran-1(3*H*)-one (**1f**) (100 mg, 0.31 mmol), cyclohexylisocyanide (**2b**) (47 µL, 0.37 mmol), $TiCl_4$ (310 µL, 1 M in CH_2Cl_2, 0.31 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3fb** as a yellow solid (113 mg, 84% yield); mp 150–152 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16–8.05 (m, 1 H), 7.55–7.49 (m, 2 H), 7.35–7.28 (m, 2 H), 7.16–7.09 (m, 1 H), 7.00–6.92 (m, 2 H), 5.66 (d, *J* = 8.5 Hz, 1 H), 3.90–3.72 (m, 1 H), 2.03–1.91 (m, 2 H), 1.77–1.55 (m, 3 H), 1.48–1.11 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 159.3, 141.9, 135.7, 135.4, 132.2, 130.1, 127.0, 123.3, 121.8, 119.2, 115.0, 75.1, 50.8, 33.8, 25.4, 24.7.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{21}H_{20}BrNO_2S$: 429.0398; found: 429.0411.

4-(3-Bromophenylthio)-3-(cyclohexylamino)-1*H*-isochromen-1-one (3gb)

Starting from 3-(3-bromophenylthio)isobenzofuran-1(3*H*)-one (**1g**) (100 mg, 0.31 mmol), cyclohexylisocyanide (**2b**) (46 µL, 0.37 mmol), $TiCl_4$ (310 µL, 1 M in CH_2Cl_2, 0.31 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3gb** as a yellow solid (123 mg, 92% yield); mp 108–110 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 7.9 Hz, 1 H), 7.64–7.50 (m, 2 H), 7.28–7.21 (m, 2 H), 7.20–7.04 (m, 2 H), 7.04–6.95 (m, 1 H), 5.62 (d, *J* = 8.6 Hz, 1 H), 3.91–3.75 (m, 1 H), 2.00–1.95 (m, 2 H), 1.78–1.57 (m, 3 H), 1.50–1.31 (m, 2 H), 1.31–1.13 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 159.2, 141.8, 138.5, 135.7, 130.5, 130.1, 128.6, 127.9, 123.7, 123.3, 123.2, 121.7, 114.9, 74.6, 50.7, 33.7, 25.3, 24.6.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{21}H_{20}BrNO_2S$: 429.0398; found: 429.0409.

4-(2-Bromophenylthio)-3-(cyclohexylamino)-1*H*-isochromen-1-one (3hb)

Starting from 3-(2-bromophenylthio)isobenzofuran-1(3*H*)-one (**1h**) (100 mg, 0.31 mmol), cyclohexylisocyanide (**2b**) (47 µL, 0.37 mmol), $TiCl_4$ (310 µL, 1 M in CH_2Cl_2, 0.31 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3hb** as a yellow crystalline solid (110 mg, 82% yield); mp 148–150 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16–8.10 (m, 1 H), 7.53 (m, 3 H), 7.18–7.06 (m, 2 H), 7.03–6.95 (m, 1 H), 6.74 (dd, *J* = 7.9, 1.6 Hz, 1 H), 5.62 (d, *J* = 8.5 Hz, 1 H), 3.89–3.75 (m, 1 H), 1.96 (dd, *J* = 12.2, 3.1 Hz, 2 H), 1.78–1.56 (m, 3 H), 1.42–1.13 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 159.3, 141.9, 136.8, 135.7, 133.2, 130.1, 128.0, 126.7, 125.5, 123.4, 121.9, 121.0, 115.1, 74.9, 50.9, 33.8, 25.4, 24.8.

HRMS (ESI): *m*/*z* $[M^•]^+$ (^{79}Br) and $[M^•]^+$ (^{81}Br) calcd for $C_{21}H_{20}BrNO_2S$: 429.0398 and 431.0398; found: 429.0407 and 431.0359.

3-(Cyclohexylamino)-4-[(3,4-dimethylphenyl)thio]-1*H*-isochromen-1-one (3ib)

Starting from 3-(3,4-dimethylphenylthio)isobenzofuran-1(3*H*)-one (**1i**) (100 mg, 0.37 mmol), cyclohexylisocyanide (**2b**) (55 µL, 0.44 mmol), $TiCl_4$ (370 µL, 1 M in CH_2Cl_2, 0.37 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (95:5) as eluent gave **3ib** as a yellow solid (125 mg, 89% yield). Starting from 3,4-dimethylbenzenethiol (**5i**) (1.0 mmol) and following general procedure C, **3ib** was obtained as a yellow solid (169 mg, 45% yield); mp 128–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19–8.06 (m, 1 H), 7.63 (d, *J* = 8.1 Hz, 1 H), 7.55–7.46 (m, 1 H), 7.16–7.07 (m, 1 H), 6.97 (dd, *J* = 11.9, 4.7 Hz, 2 H), 6.85 (dd, *J* = 7.9, 1.9 Hz, 1 H), 5.76 (d, *J* = 8.5 Hz, 1 H), 3.91–3.77 (m, 1 H), 2.19 (s, 6 H), 2.00 (dd, *J* = 12.2, 3.0 Hz, 2 H), 1.79–1.57 (m, 3 H), 1.51–1.14 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 159.1, 142.4, 137.6, 135.5, 134.2, 132.6, 130.4, 129.9, 126.9, 123.0 (2 C), 122.1, 115.0, 76.5, 50.7, 33.8, 25.4, 24.7, 19.8, 19.2.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{23}H_{25}NO_2S$: 379.1606; found: 379.1601.

3-(Cyclohexylamino)-4-[(3,4-dimethoxyphenyl)thio]-1*H*-isochromen-1-one (3jb)

Starting from 3-(3,4-dimethoxyphenylthio)isobenzofuran-1(3*H*)-one (**1j**) (100 mg, 0.33 mmol), cyclohexylisocyanide (**2b**) (49 µL, 0.40 mmol), $TiCl_4$ (330 µL, 1 M in CH_2Cl_2, 0.33 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (8:2) as eluent gave **3jb** as a yellow pasty residue (75 mg, 55% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (dd, *J* = 7.9, 1.0 Hz, 1 H), 7.63 (d, *J* = 7.9 Hz, 1 H), 7.53 (m, 1 H), 7.12 (m, 1 H), 6.73 (d, *J* = 8.4 Hz, 1 H), 6.72 (d, *J* = 2.1 Hz, 1 H), 6.64 (dd, *J* = 8.4, 2.1 Hz, 1 H), 5.75 (d, *J* = 8.6 Hz, 1 H), 3.86–3.81 (m, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 2.02–1.94 (m, 2 H), 1.76–1.67 (m, 2 H), 1.66–1.58 (m, 1 H), 1.49–1.32 (m, 2 H), 1.30–1.12 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 159.0, 149.5, 147.6, 142.2, 135.5, 129.9, 127.0, 123.1, 121.9, 118.0, 114.8, 112.0, 109.6, 77.0, 56.0, 55.9, 50.6, 33.7, 25.3, 24.6.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{23}H_{25}NO_4S$: 411.1504; found: 411.1515.

3-(Cyclohexylamino)-7-methyl-4-(phenylthio)-1*H*-isochromen-1-one (3a′b)

Starting from 6-methyl-3-(phenylthio)isobenzofuran-1(3*H*)-one (**1a′**) (100 mg, 0.39 mmol), cyclohexylisocyanide (**2b**) (58 µL, 0.47 mmol), $TiCl_4$ (390 µL, 1 M in CH_2Cl_2, 0.39 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (99:1) as eluent gave **3a′b** as a yellow crystalline solid (132 mg, 93% yield); mp 126–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.50 (d, *J* = 8.3 Hz, 1 H), 7.35 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.28–7.17 (m, 2 H), 7.11 (dd, *J* = 7.2, 5.4 Hz, 3 H), 5.60 (d, *J* = 8.5 Hz, 1 H), 3.81 (qd, *J* = 10.2, 5.1 Hz, 1 H), 2.35 (s, 3 H), 1.97 (dd, *J* = 12.4, 3.1 Hz, 2 H), 1.76–1.55 (m, 3 H), 1.48–1.08 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9, 158.8, 139.9, 137.2, 136.3, 133.1, 129.6, 129.3, 125.6, 125.5, 122.2, 115.0, 75.9, 50.8, 33.9, 25.5, 24.8, 20.9.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{22}H_{23}NO_2S$: 365.1449; found: 365.1461.

3-(Cyclohexylamino)-7-methoxy-4-(naphthalen-2-ylthio)-1*H*-isochromen-1-one (3l″b)

Starting from 6-methoxy-3-(naphthalen-2-ylthio)isobenzofuran-1(3*H*)-one (**1l″**) (100 mg, 0.31 mmol), cyclohexylisocyanide (**2a**) (46 µL, 0.37 mmol), $TiCl_4$ (310 µL, 1 M in CH_2Cl_2, 0.31 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (99:1) as eluent gave **3l″b** as a yellow solid (114 mg, 86% yield); mp 132–134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 11.8, 8.0 Hz, 2 H), 7.58–7.44 (m, 3 H), 7.41–7.26 (m, 3 H), 7.17 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.06 (dd, *J* = 9.0, 2.7 Hz, 1 H), 5.49 (d, *J* = 8.6 Hz, 1 H), 3.83–3.63 (m, 4 H), 1.89 (dd, *J* = 12.3, 3.2 Hz, 2 H), 1.68–1.43 (m, 3 H), 1.40–0.96 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 158.3, 156.3, 136.4, 134.0, 133.7, 131.8, 129.0, 127.9, 127.0, 126.8, 126.0, 125.6, 124.1, 124.0, 123.2, 115.7, 110.0, 76.0, 55.8, 50.9, 33.9, 25.5, 24.8.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{26}H_{25}NO_3S$: 431.1555; found: 431.1572.

3-(Cyclohexylamino)-4-(naphthalen-1-ylthio)-1*H*-isochromen-1-one (3kb)

Starting from 3-(naphthalen-2-ylthio)isobenzofuran-1(3*H*)-one (**1k**) (90 mg, 0.31 mmol), cyclohexylisocyanide (**2b**) (46 µl, 0.37 mmol), $TiCl_4$ (310 µL, 1 M in CH_2Cl_2, 0.31 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (95:5) as eluent gave **3kb** as a yellow solid (80 mg, 68% yield); mp 135–137 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 8.4 Hz, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 7.89 (d, *J* = 7.6 Hz, 1 H), 7.66–7.60 (m, 2 H), 7.59–7.53 (m, 2 H), 7.51–7.44 (m, 1 H), 7.28–7.24 (m, 1 H), 7.16–7.11 (m, 1 H), 6.96 (d, *J* = 7.4 Hz, 1 H), 5.67 (d, *J* = 8.5 Hz, 1 H), 3.89–3.78 (m, 1 H), 2.01–1.91 (m, 2 H), 1.73–1.64 (m, 2 H), 1.63–1.56 (m, 1 H), 1.43–1.32 (m, 2 H), 1.22–1.08 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 159.2, 142.1, 135.6, 134.0, 132.3, 130.9, 130.0, 128.7, 126.3, 126.2, 125.9, 125.6, 123.5, 123.2, 122.0, 121.0, 115.1, 74.0, 50.7, 33.7, 25.3, 24.6.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{25}H_{23}NO_2S$: 401.1449; found: 401.1450.

3-(Cyclohexylamino)-4-(naphthalen-2-ylthio)-1*H*-isochromen-1-one (3lb)

Starting from 3-(naphthalen-2-ylthio)isobenzofuran-1(3*H*)-one (**1l**) (100 mg, 0.34 mmol), cyclohexylisocyanide (**2b**) (51 µL, 0.41 mmol), $TiCl_4$ (340 µL, 1 M in CH_2Cl_2, 0.34 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3lb** as a yellow solid (115 mg, 84% yield). Starting from naphthalene-2-thiol (**5l**) (1.0 mmol) and following general procedure C, **3lb** was obtained as a yellow solid (137 mg, 34% yield); mp 134–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.61 (dd, *J* = 13.4, 8.2 Hz, 2 H), 7.51 (d, *J* = 8.6 Hz, 2 H), 7.39–7.22 (m, 4 H), 7.15 (dd, *J* = 8.6, 1.9 Hz, 1 H), 7.02–6.95 (m, 1 H), 5.64 (d, *J* = 8.5 Hz, 1 H), 3.77–3.65 (m, 1 H), 1.90–1.80 (m, 2 H), 1.61–1.41 (m, 3 H), 1.33–0.92 (m, 5 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.7, 159.2, 142.2, 135.6, 133.9, 133.4, 131.7, 130.0, 128.9, 127.8, 126.9, 126.7, 125.5, 124.0, 123.2, 123.0, 122.0, 115.0, 75.7, 50.7, 33.7, 25.3, 24.7.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{25}H_{23}NO_2S$: 401.1449; found: 401.1463.

3-(Cyclohexylamino)-4-(hexylthio)-1*H*-isochromen-1-one (3nb)

Starting from 3-(hexylthio)isobenzofuran-1(3*H*)-one (**1n**) (100 mg, 0.40 mmol), cyclohexylisocyanide (**2b**) (60 µL, 0.48 mmol), $TiCl_4$ (400 µL, 1 M in CH_2Cl_2, 0.4 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3nb** as a yellow solid (133.8 mg, 93% yield). Starting from hexane-1-thiol (**5n**) (1.0 mmol) and following general procedure C, **3nb** was obtained as a yellow solid (187 mg, 52% yield); mp 58–60 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.05 (m, 1 H), 7.79–7.71 (m, 1 H), 7.60–7.55 (m, 1 H), 7.12–7.07 (m, 1 H), 5.81 (d, *J* = 8.6 Hz, 1 H), 3.86–3.69 (m, 1 H), 2.57–2.48 (m, 2 H), 2.07–1.95 (m, 2 H), 1.82–1.15 (m, 16 H), 0.86 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9, 158.6, 142.8, 135.3, 130.1, 122.7, 122.0, 115.0, 78.9, 50.6, 34.8, 34.0, 31.5, 29.8, 28.7, 25.6, 24.8, 22.6, 14.1.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{21}H_{29}NO_2S$: 359.1919; found: 359.1929.

4-(*tert*-Butylthio)-3-(cyclohexylamino)-1*H*-isochromen-1-one (3pb)

Starting from 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one (**1p**) (100 mg, 0.45 mmol), cyclohexylisocyanide (**2b**) (67 µL, 0.54 mmol), $TiCl_4$ (450 µL, 1 M in CH_2Cl_2, 0.45 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3pb** as a yellow sticky gum (23.7 mg, 16% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.03 (m, 1 H), 7.87–7.82 (m, 1 H), 7.60–7.40 (m, 1 H), 7.10–7.04 (m, 1 H), 5.98 (d, *J* = 8.5 Hz, 1 H), 3.87–3.71 (m, 1 H), 2.00 (d, *J* = 4.1 Hz, 2 H), 1.77–1.61 (m, 4 H), 1.54–1.18 (m, 13 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9, 159.9, 144.3, 134.9, 129.8, 123.2, 122.6, 114.6, 50.6, 49.9, 34.2, 33.9, 31.5, 25.6, 24.9.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{19}H_{25}NO_2S$: 331.1606; found: 331.1617.

Methyl 2-[3-(Cyclohexylamino)-1-oxo-1*H*-isochromen-4-ylthio]acetate (3rb)

Starting from methyl 2-(3-oxo-1,3-dihydroisobenzofuran-1-ylthio)acetate (**1r**) (100 mg, 0.42 mmol), cyclohexylisocyanide (**2b**) (63 µL, 0.50 mmol), $TiCl_4$ (420 µL, 1 M in CH_2Cl_2, 0.42 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3rb** as an orange viscous liquid (34.6 mg, 24% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.04 (m, 1 H), 7.72–7.69 (m, 1 H), 7.65–7.50 (m, 1 H), 7.14–7.07 (m, 1 H), 6.28 (d, *J* = 8.3 Hz, 1 H), 3.85–3.70 (m, 1 H), 3.64 (s, 3 H), 3.29 (s, 2 H), 2.06–1.95 (m, 2 H), 1.84–1.72 (m, 2 H), 1.65 (dd, *J* = 9.1, 3.4 Hz, 1 H), 1.52–1.17 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 160.7, 159.3, 142.4, 135.5, 130.3, 122.9, 121.5, 114.9, 52.7, 50.8, 36.8, 33.8, 25.6, 24.9.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{18}H_{21}NO_4S$: 347.1191; found: 347.1176.

3-(Benzylamino)-4-(cyclohexylthio)-1*H*-isochromen-1-one (3od)

Starting from 3-(cyclohexylthio)isobenzofuran-1(3*H*)-one (**1o**) (100 mg, 0.40 mmol), benzylisocyanide (**2d**) (59 µL, 0.48 mmol), $TiCl_4$ (400 µL, 1 M in CH_2Cl_2, 0.40 mmol) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3od** as a yellow solid (81 mg, 55% yield); mp 128–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 8.0, 0.9 Hz, 1 H), 7.71 (d, *J* = 8.2 Hz, 1 H), 7.53–7.40 (m, 1 H), 7.30–7.15 (m, 5 H), 7.10–7.02 (m, 1 H), 6.14 (t, *J* = 6.2 Hz, 1 H), 4.50 (d, *J* = 6.3 Hz, 2 H), 2.69–2.57 (m, 1 H), 1.83–1.72 (m, 2 H), 1.67–1.38 (m, 3 H), 1.29–1.00 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 158.9, 143.0, 138.3, 135.2, 130.0, 128.9, 127.8, 127.7, 123.1, 122.6, 115.3, 79.2, 47.1, 46.0, 33.6, 26.2, 25.7.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{22}H_{23}NO_2S$: 365.1449; found: 365.1450.

4-(Benzylthio)-3-(cyclohexylamino)-1*H*-isochromen-1-one (3qb)

Starting from 3-(benzylthio)isobenzofuran-1(3*H*)-one (**1q**) (100 mg, 0.39 mmol), cyclohexylisocyanide (**2b**) (58 µL, 0.47 mmol), $TiCl_4$ (390µL, 1 M in CH_2Cl_2, 1.0 equiv) and following the general procedure B, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (98:2) as eluent gave **3qb** as a yellow sticky gum (100 mg, 70% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.05 (m, 1 H), 7.75–7.69 (m, 1 H), 7.52–7.65 (m, 1 H), 7.25–7.17 (m, 3 H), 7.14–7.04 (m, 3 H), 5.41 (d, *J* = 8.3 Hz, 1 H), 3.67 (s, 2 H), 3.57–3.44 (m, 1 H), 1.75–1.50 (m, 5 H), 1.39–0.84 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 159.2, 142.6, 138.5, 135.4, 130.1, 128.9, 128.6, 127.2, 122.7, 121.7, 114.8, 77.1, 50.3, 38.6, 33.6, 25.5, 24.7.

HRMS (APPI): *m*/*z* $[M^•]^+$ calcd for $C_{22}H_{23}NO_2S$: 365.1449; found: 365.1436.

3-(Pentylamino)-4-(*p*-tolylthio)-1*H*-isochromen-1-one (3bc)

Starting from 2-carboxybenzaldehyde (**4a**) (165 mg, 1.1 mmol), 4-methylbenzenethiol (**5b**) (124 mg, 1.0 mmol), 1-pentylisocyanide (**2c**) (189 mg, 1.5 mmol), $TiCl_4$ (1.2 mL, 1 M in CH_2Cl_2, 1.2 mmol) and following the general procedure C, then purification of the crude material by flash column chromatography on silica gel using petroleum ether/ethyl acetate (95:5) as eluent gave **3bc** as a yellow pasty residue (257 mg, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 7.53 (dd, *J* = 11.4, 3.9 Hz, 1 H), 7.13 (dd, *J* = 11.0, 4.0 Hz, 1 H), 7.03 (q, *J* = 8.0 Hz, 4 H), 5.81 (t, *J* = 5.8 Hz, 1 H), 3.41 (dd, *J* = 13.5, 6.7 Hz, 2 H), 2.27 (s, 3 H), 1.61–1.51 (m, 2 H), 1.33–1.24 (m, 4 H), 0.87 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.5, 159.5, 142.3, 135.6, 135.4, 132.4, 130.0, 129.9 (2 C), 125.4 (2 C), 123.1, 121.9, 114.8, 75.9, 41.9, 29.9, 28.8, 22.3, 20.9, 13.9.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{21}H_{23}NO_2S$: 353.1449; found: 353.1448.

3-[(2,6-Dimethylphenyl)amino]-4-(*p*-tolylthio)-1*H*-isochromen-1-one (3bf)

Starting from 2-carboxybenzaldehyde (**4a**) (165 mg, 1.1 mmol), 4-methylbenzenethiol (**5b**) (124 mg, 1.0 mmol), 2,6-dimethylphenylisocyanide (**2f**) (197 mg, 1.5 mmol), $TiCl_4$ (1.2 mL, 1 M in CH_2Cl_2, 1.2 mmol) and following the general procedure C, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (8:2) as eluent gave **3bf** as a yellow solid (190 mg, 49% yield); mp 135–141 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.78–7.72 (m, 1 H), 7.65–7.55 (m, 1 H), 7.24–7.15 (m, 2 H), 7.13–7.06 (m, 7 H), 2.30 (s, 3 H), 2.20 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 158.0, 141.9, 136.1, 135.69, 135.65, 133.6, 133.1, 132.0, 130.3, 130.1, 128.5, 128.2, 127.5, 125.7, 123.7, 122.2, 115.6, 20.9, 18.4.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{24}H_{21}NO_2S$: 387.1293; found: 387.1286.

4-(Dodecylthio)-3-(pentylamino)-1*H*-isochromen-1-one (3mc)

Starting from 2-carboxybenzaldehyde (**4a**) (165 mg, 1.1 mmol), dodecane-1-thiol (**5m**) (240 µL, 1.0 mmol), pentylisocyanide (**2c**) (189 µL, 1.5 mmol), $TiCl_4$ (1.2 mL, 1 M in CH_2Cl_2, 1.2 mmol) and following the general procedure C, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (99:1) as eluent gave **3mc** as a yellow sticky gum (163 mg, 38% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.01 (m, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 7.60–7.50 (m, 1 H), 7.12–7.05 (m, 1 H), 5.90 (t, *J* = 6.0 Hz, 1 H), 3.40 (dd, *J* = 13.3, 6.9 Hz, 2 H), 2.55–2.47 (m, 2 H), 1.65–1.40 (m, 4 H), 1.40–1.17 (m, 22 H), 0.95–0.80 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 159.1, 142.7, 135.2, 130.0, 122.7, 122.0, 115.0, 78.8, 41.9, 34.7, 32.0, 30.1, 29.8, 29.7 (3 C), 29.6, 29.4, 29.3, 29.0 (2 C), 22.7, 22.4, 14.1, 14.0.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{26}H_{41}NO_2S$: 431.2858; found: 431.2849.

3-(Benzylamino)-4-(dodecylthio)-1*H*-isochromen-1-one (3md)

Starting from 2-carboxybenzaldehyde (**4a**) (165 mg, 1.1 mmol), 1-dodecanethiol (**5m**) (241 µL, 1.0 mmol), benzylisocyanide (**2d**) (183 µL, 1.5 mmol), $TiCl_4$ (1.2 mL, 1 M in CH_2Cl_2, 1.2 mmol) and following the general procedure C, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (9:1) as eluent gave **3md** as a yellow pasty residue (277 mg, 61% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (dd, *J* = 8.0, 0.9 Hz, 1 H), 7.81–7.76 (m, 1 H), 7.65–7.55 (m, 1 H), 7.38–7.33 (m, 4 H), 7.34–7.28 (m, 1 H), 7.20–7.10 (m, 1 H), 6.18 (t, *J* = 6.2 Hz, 1 H), 4.61 (d, *J* = 6.2 Hz, 2 H), 2.51 (t, *J* = 7.4 Hz, 2 H), 1.55–1.42 (m, 2 H), 1.24 (d, *J* = 8.4 Hz, 18 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 158.4, 142.4, 138.2, 135.3, 130.0, 128.8 (2 C), 127.7, 127.6 (2 C), 123.1, 122.1, 115.3, 79.8, 45.9, 34.7, 31.9, 29.7, 29.6 (2 C), 29.6, 29.5, 29.3, 29.2, 29.0, 22.7, 14.1.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{28}H_{37}NO_2S$: 451.2545; found: 451.2544.

3-(2,6-Dimethylphenylamino)-4-(dodecylthio)-1*H*-isochromen-1-one (3mf)

Starting from 2-carboxybenzaldehyde (**4a**) (165 mg, 1.1 mmol), dodecane-1-thiol (**5m**) (240 µL, 1.0 mmol), 2,6-dimethylphenylisocyanide (**2f**) (197 mg, 1.5 mmol), $TiCl_4$ (1.2 mL, 1 M in CH_2Cl_2, 1.2 mmol) and following the general procedure C, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (99:1) as eluent gave **3mf** as a pasty orange solid (236 mg, 51% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17–8.06 (m, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.67 (s, 1 H), 7.34 (s, 1 H), 7.22–7.13 (m, 4 H), 2.77–2.67 (m, 2 H), 2.33 (s, 6 H), 1.77–1.65 (m, 2 H), 1.51–1.23 (m, 18 H), 0.93 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 157.4, 142.2, 136.1, 135.3, 134.2, 130.1, 128.5, 127.3, 123.3, 122.2, 115.8, 79.9, 34.8, 32.0, 30.1, 29.7 (3 C), 29.5, 29.4, 29.3, 29.1, 22.7, 18.6, 14.2.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{29}H_{39}NO_2S$: 465.2702; found: 465.2710.

3-(Cyclohexylamino)-7-methyl-4-(*p*-tolylthio)-1*H*-isochromen-1-one (3b′b)

Starting from 2-formyl-5-methylbenzoic acid (**4b**) (100 mg, 0.61 mmol), 4-methylbenzenethiol (**5b**) (69.0 mg, 0.55 mmol), cyclohexylisocyanide (**2b**) (103 µL, 0.83 mmol), $TiCl_4$ (665 µL, 1 M in CH_2Cl_2, 0.665 mmol) and following the general procedure C, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (99:1) as eluent gave **3b′b** as a yellow crystalline solid (109.1 mg, 52% yield); mp 138–140 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.51 (d, *J* = 8.3 Hz, 1 H), 7.34 (dd, *J* = 8.3, 1.6 Hz, 1 H), 7.07–6.97 (m, 4 H), 5.63 (d, *J* = 8.5 Hz, 1 H), 3.87–3.72 (m, 1 H), 2.31 (d, *J* = 23.5 Hz, 6 H), 1.97 (dd, *J* = 12.3, 3.0 Hz, 2 H), 1.77–1.55 (m, 3 H), 1.48–1.12 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9, 158.7, 140.0, 137.1, 135.4, 133.0, 132.7, 130.0, 129.5, 125.7, 122.2, 115.0, 76.5, 50.8, 33.9, 25.5, 24.8, 21.0, 20.9.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{23}H_{25}NO_2S$: 379.1606; found: 379.1595.

3-(Cyclohexylamino)-7-methoxy-4-(*p*-tolylthio)-1*H*-isochromen-1-one (3b″b)

Starting from 2-formyl-5-methoxybenzoic acid (**4c**) (100 mg, 0.55 mmol), 4-methylbenzenethiol (**5b**) (63.0 mg, 0.50 mmol), cyclohexylisocyanide (**2b**) (94 µL, 0.75 mmol), $TiCl_4$ (600 µL, 1 M in CH_2Cl_2, 0.6 mmol) and following the general procedure C, then purification of the crude material by flash column chromatography on silica gel using cyclohexane/ethyl acetate (99:1) as eluent gave **3b″b** as a yellow solid (112.3 mg, 57% yield); mp 118–120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.45 (m, 2 H), 7.15 (dd, *J* = 8.9, 2.8 Hz, 1 H), 7.08–6.95 (m, 4 H), 5.57 (d, *J* = 8.6 Hz, 1 H), 3.87–3.71 (m, 4 H), 2.26 (s, 3 H), 2.04–1.91 (m, 2 H), 1.75–1.55 (m, 3 H), 1.48–1.09 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 158.1, 156.1, 136.4, 135.4, 132.6, 129.9, 125.9, 125.6, 123.9, 115.5, 109.8, 76.6, 55.7, 50.8, 33.9, 25.5, 24.7, 20.9.

HRMS (ESI): *m*/*z* $[M^•]^+$ calcd for $C_{23}H_{25}NO_3S$: 395.1555; found: 395.1557.

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Supporting Information

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