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Method for the Solid-Phase Parallel Synthesis of a 6-Alkylamino-2-(functionalized-aminomethyl)-2*H*-1-benzopyran Library

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A 2000-member library of benzopyran analogues was prepared by using a solid-phase synthesis protocol. Polymer-bound 6-alkylaminobenzopyrans **7** were synthesized as part of a first generation diversification step by employing reactions of a variety of alkyl halides with the amine **6**. Transformations of the resin-bound intermediates **8** formed in this manner by reactions with acid halides, sulfonyl chlorides, and isocyanates leads to introduction of the second level of diversification found in the series of 6-alkylamino-2-(functionalized-aminomethyl)-2-methyl-2*H*-1-benzopyran analogues **11** and **12**.

Introduction

Solid-phase combinatorial chemistry has become a powerful technique in the drug discovery process for generating large numbers of small organic molecules.[1] Heterocyclic compounds, a variety of which have been synthesized on solid supports, provide useful scaffolds on which pharmacophores can be arranged to yield potent and selective drugs.[2] As a part of an ongoing drug discovery program,[3] we needed to develop a facile and rapid solid-phase parallel synthesis methodology for constructing a small-molecule library based on a substituted benzopyran framework[3a,f] that has shown a broad spectrum of biological activities.[4] An earlier search, employing high-throughput screening, has demonstrated that 2,6-disubstituted 2-methyl-2*H*-1-benzopyrans (**1**) are modestly potent 5-lipoxygenase (5-LO) inhibitors.[5] In an effort to develop more active 5-LO inhibitors in this series, we have prepared benzopyrans containing functional groups at the 2-position (Figure 1) by using solid-phase techniques.[3a] Below, we describe the results of a more recent effort, aimed at the optimization of 5-LO inhibition activity, that has led to the design, parallel synthesis, and evaluation of a novel 6-alkylamino-2-(functionalized-aminomethyl)benzopyran library (**3**).

Results and Discussion

The overall synthetic strategy used to prepare the target benzopyran analogues **11** and **12** is outlined in Scheme 1. The Fmoc-protected benzopyran **5** was prepared from 2-dimethoxymethyl-2-methyl-2*H*-1-benzopyran **13**[6] employing solution-phase methods (Scheme 2). Removal of the acetal group in **13** by treatment with 50% trifluoroacetic acid (TFA) in DCM gives 2-formylbenzopyran, which is treated with methylamine hydrochloride and $NaBH(OAc)_3$ in the presence of triethylamine (TEA) to give the corresponding amine **14**. Protection of the amine in **14** by reaction with the Fmoc-Cl in the presence of TEA in DCM, followed by reduction of the nitro group with iron (Fe) at reflux in the presence of 20% $AcOH/H_2O$ in ethanol, yields the desired substance **5**.

In the solid-phase, parallel synthesis methodology, the backbone amide linker (BAL) resin[7] **4** was selected as the polymer support on the basis of the recognition that the secondary amine group in the product of its reductive amination reaction with **5** can be readily alkylated by various alkyl halides. Moreover, the target small molecules are easily removed from the support through cleavage of the benzylic amine bond by using dilute TFA without simultaneous production of by-products. In the first step of the sequence (Scheme 1), 6-aminobenzopyran resin **6** is prepared from the BAL resin **4** by reaction with 6-aminobenzopyran **5** under reductive amination conditions ($NaBH(OAc)_3$ in DMF containing 1% acetic acid).[3a,d,8] The outcome of this process was confirmed by monitoring the disappearance of the aldehyde carbonyl band in the ATR−FTIR spectra of a single bead of the resin at 1678 cm^{-1} and the appearance of Fmoc carbamate band at 1702 cm^{-1} (Figure 2B).

In the first-generation diversification step, resin **6**, containing a secondary amine group, is reacted with alkyl halides in the presence of diisopropylethylamine (DIEA) in DCM at room temperature. For second-generation diversification, resins **8** containing a secondary amino group were prepared by reaction of resins **7** with 20% piperidine in DMF at room temperature. The progress of these processes was monitored by the disappearance of the carbamate band of the Fmoc group at 1702 cm^{-1}.

Functionalization of the secondary amine groups in **8** is promoted by reaction with various electrophiles, including

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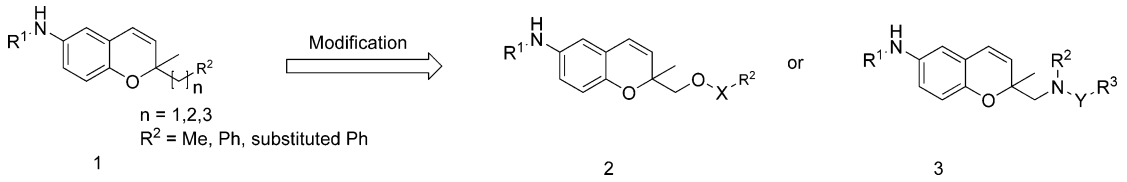
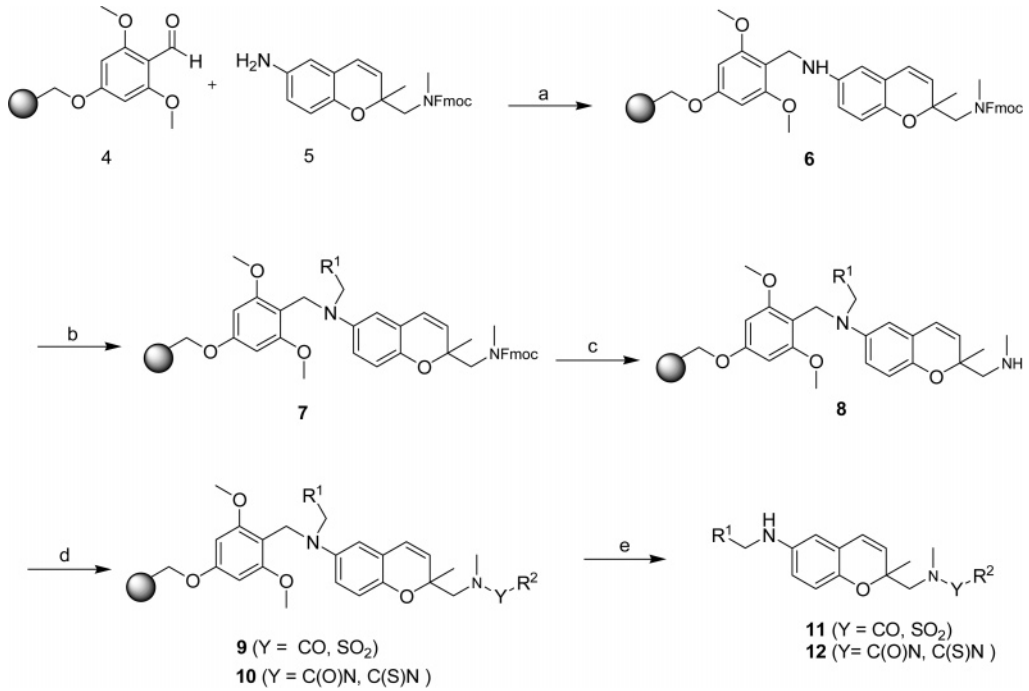


Figure 1. 2-Functionalized derivatives of benzopyrans.

Scheme 1. Solid-Phase Synthesis of 6-Alkylamino-2-(functionalized-aminomethyl)benzopyran Library[a]



[a] Reagents and conditions: (a) $NaBH(OAc)_3$, 1% AcOH/DMF, rt, 24 h; (b) alkyl halides, DIEA, DCM, rt, 12 h; (c) 20% piperidine, DMF, rt, 3 h; (d) electrophiles (acid chlorides, sulfonyl chlorides, isocyanates, and isothiocyanates), DMF, rt, 12 h; (e) 20% TFA, DCM, rt, 3 h.

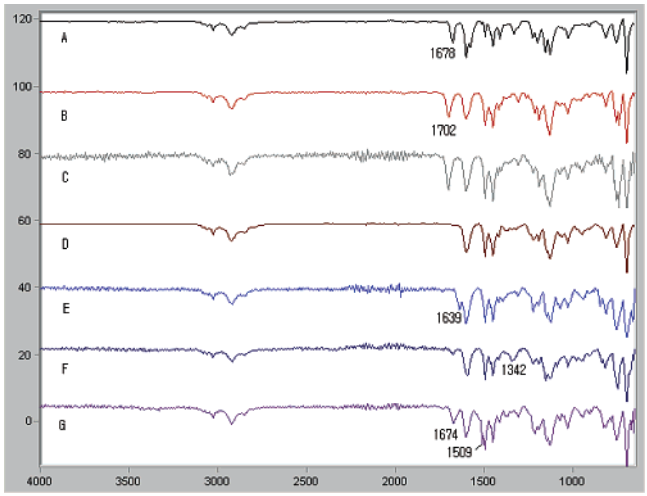


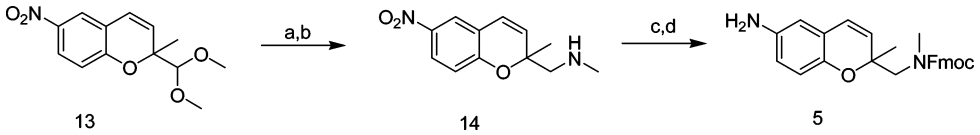
Figure 2. ATR−FTIR spectra on single beads of benzopyran resins **4** (A), **6** (B), **7** (C), **8** (D), **9a** (E), **10n** (F), and **11a** (H).

acid chlorides, sulfonyl chlorides, and isocyanates (in the presence of TEA as a base in DMF). This leads to the generation of the respective amide, sulfonamide, and urea derivatives. The progress of these processes was monitored by using a chloranil-based amine test and by monitoring the appearance of new bands (amide **9a**, 1639 cm^{-1}; sulfonamide **10n**, 1342 cm^{-1}; urea **11a**, 1674, 1509 cm^{-1}) in the ATR−FTIR spectra (Figure 2C, D). Further confirmation of product formation was accomplished by treatment of resins **9** and **10** with 20% TFA in DCM for 3 h and characterization of the liberated products **11** and **12**, respectively (Table 1 and 2).

Having established a flexible method for solid-phase synthesis of 6-alkylamino-2-(functionalized-aminomethyl)-2*H*-1-benzopyrans, our attention next turned to the evaluation of the potential drug properties of members of this family. In general, the goal of a drug discovery process is to synthesize chemical entities that are orally bioavailable; i.e., they possess physiological properties that allow them to be absorbed into the gastrointestinal system. Lipinski's Rule[9] and similar formulations[10] served as guidelines for an estimation of the physicochemical properties of the 2000-member 6-alkylamino-2-(functionalized-aminomethyl)-2*H*-1-benzopyran library calculated using Accord for Excel functions.[11] Of particular interest were the key bioavailability parameters molecular weight, lipophilicity, number of hydrogen bond donors and acceptors, number of rotatable bonds, and polar surface area. In Chart 1 are shown the results of these bioavailability calculations, performed on the library we have constructed. As can be seen by viewing the data, all of the key parameters for members of the constructed library fall in the range of those predicted to be reasonable drugs by using the commonly known rules.[9,10]

In conclusion, we have developed a novel solid-phase synthesis method for the preparation of 2,6-difuctionalized 2*H*-1-benzopyran analogues. Various polymer-bound 6-alkyl-

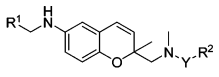
Scheme 2. Preparation of 6-Aminobenzopyran Motif[a]



13 14 5

[a] Reagents and conditions: (a) 50% Tfa/DCM, rt, 6 h; (b) $MeNH_2$·HCl, Tea, $NaBH(OAc)_3$, Dcm, rt, 12 h; (c) Fmoc-Cl, Tea, Dcm, rt, 6 h; (d) Fe, 20% AcOH/H_2O, EtOH, reflux, 2 h.

Table 1. Characterization of 6-Alkylamino-2-(functionalized -aminomethyl)-2*H*-1-benzopyrans **11**

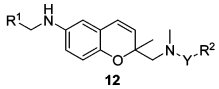


11

Entry	R^1	Y	R^2	Yield (%)[a]	Purity (%)[b]	Entry	R^1	Y	R^2	Yield (%)[a]	Purity (%)[b]
11a	Ph	CO		59	>99	**11n**	3-ClPh	SO_2	Ph	72	98
11b	Ph	CO	*c*-Pr	50	>99	**11o**	3-ClPh	SO_2	*n*-Pro	74	95
11c	3-MeOPh	CO		55	94	**11p**	3-ClPh	SO_2		61	96
11d	3-MeOPh	CO	4-*tert*-BuPh	61	>99	**11q**	3-ClPh	SO_2	4-MePh	70	94
11e	3-MeOPh	CO	Ph	78	96	**11r**		SO_2	Ph	64	98
11f	4-FPh	CO	Bu	82	96	**11s**		SO_2	Bn	86	98
11g	4-FPh	CO	*c*-Pro	66	>99	**11t**		SO_2	4-FPh	49	>99
11h	4-FPh	CO	Ph	80	98	**11u**		SO_2	4-MeOPh	79	99
11i	4-FPh	CO	4-*tert*-BuPh	76	98	**11v**		SO_2	4-*tert*-BuPh	75	99
11j	4-O_2NPh	CO	4-MeOPh	51	98	**11w**		SO_2		60	97
11k	4-O_2NPh	CO		69	98	**11x**		SO_2	4-FPh	57	97
11l		CO	Ph	63	99	**11y**		SO_2	4-MeOPh	76	96
11m		CO	4-FPh	70	92	**11z**		SO_2	*n*-Pro	68	92

[a] Five-step overall yield from the resin **4** (loading capacity of the resin **4** is 0.91 mmol/g). [b] Purity of final product was analyzed by LC/MS after passing the crude product through a silica gel cartridge.

Table 2. Characterization of 6-Alkylamino-2-(functionalized-aminomethyl)-2*H*-1-benzopyrans **11**



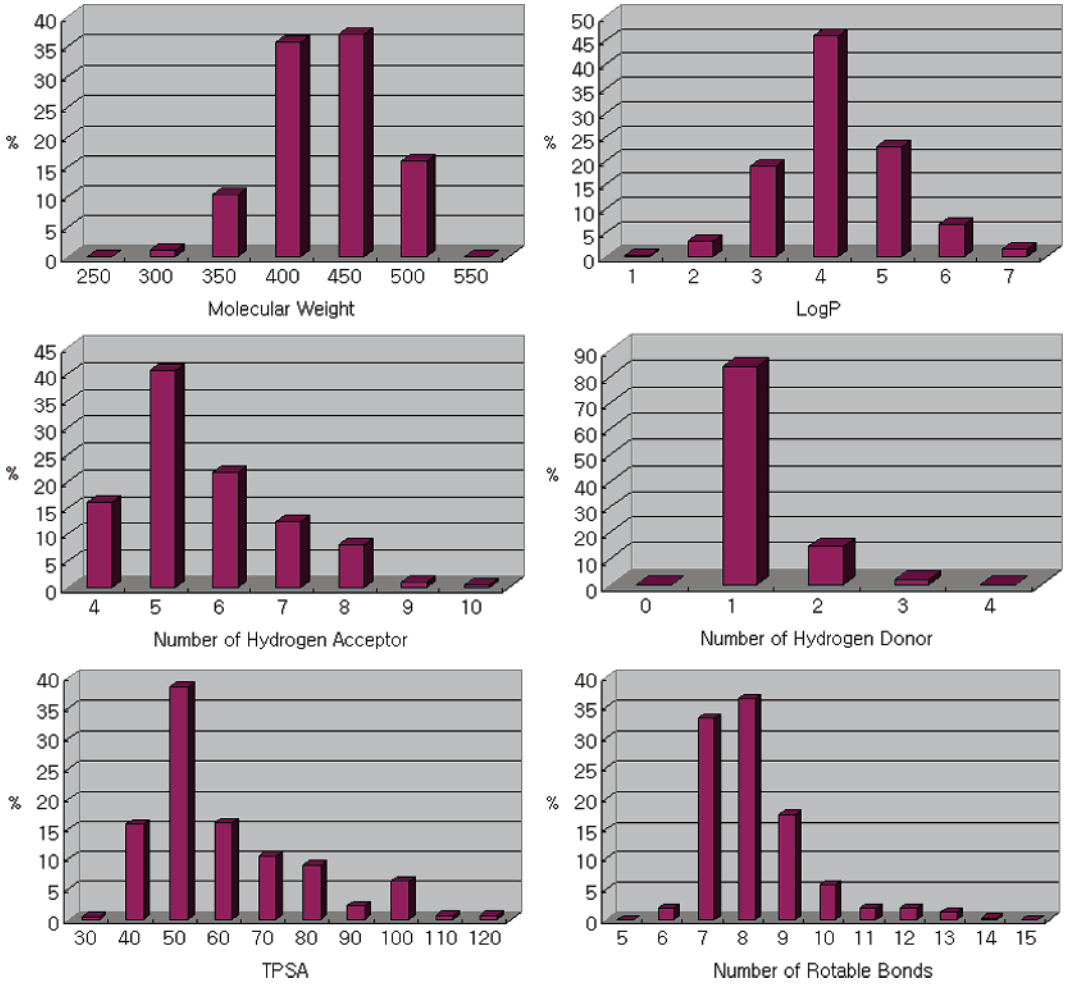
12

Entry	R^1	Y	R^2	Yield (%)[a]	Purity (%)[b]	Entry	R^1	Y	R^2	Yield (%)[a]	Purity (%)[b]
12a	Ph	C(O)NH	Bu	78	97	**12n**	4-FPh	C(O)NH	4-MeOPh	71	98
12b	Ph	C(O)NH	2-ClPh	74	95	**12o**	4-FPh	C(O)NH	*c*-Hex	63	98
12c	Ph	C(O)NH	4-FPh	80	>99	**12p**	4-FPh	C(O)NH		77	>99
12d	Ph	C(O)NH	4-O_2NPh	75	99	**12q**	4-F_3CPh	C(O)NH	Bu	70	98
12e	Ph	C(O)NH	4-MePh	70	98	**12r**	4-F_3CPh	C(O)NH	2-ClPh	68	94
12f	4-MePh	C(O)NH		69	>99	**12s**	4-F_3CPh	C(O)NH	2,6-diMePh	71	>99
12g	4-MePh	C(O)NH	*c*-Hex	65	98	**12t**	4-F_3CPh	C(O)NH	4-MeOPh	59	>99
12h	4-MePh	C(O)NH	4-FPh	66	>99	**12u**	4-F_3CPh	C(O)NH	4-FPh	80	>99
12i	4-MePh	C(O)NH	4-MeOPh	48	>99	**12v**	4-F_3CPh	C(S)NH	4-O_2NPh	74	95
12j	4-MePh	C(O)NH	2,6-diMePh	76	>99	**12w**	4-F_3CPh	C(S)NH	Ph	66	78
12k	4-FPh	C(O)NH	Bn	77	>99	**12x**	4-FPh	C(S)NH	4-O_2NPh	68	96
12l	4-FPh	C(O)NH	2-ClPh	75	96	**12y**	4-FPh	C(S)NH	Ph	57	93
12m	4-FPh	C(O)NH	4-EtPh	69	98	**12z**	4-MePh	C(S)NH	Ph	67	97

[a] Five-step overall yield from the resin **4** (loading capacity of the resin **4** is 0.91 mmol/g). [b] Purity of final product was checked by LC/MS through a short-path silica gel column.

aminobenzopyrans **7** were prepared by reacting alkyl halides with the amine precursor **6**. Transformations of the resin-bound intermediates **8** by reactions with acid halides, sulfonyl chlorides, and isocyanates were then used to introduce a second level of diversity found in the series of 2,6-difunctionalized 2-methyl-2*H*-1-benzopyran analogues **11**

Chart 1. Calculated Physicochemical Properties of the Constructed Library

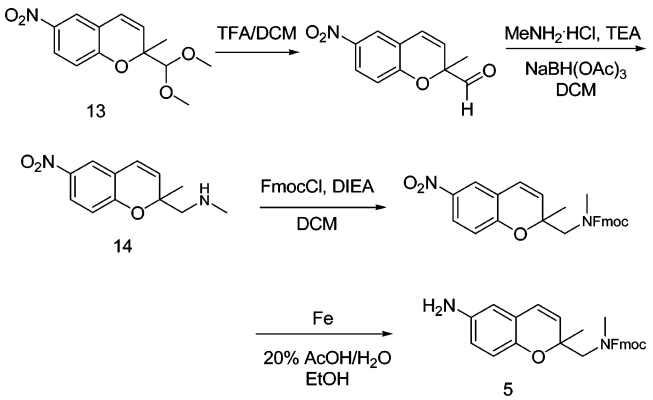


and **12** that are liberated from the polymer. Finally, the calculated physicochemical properties of members of the constructed library fall within druglike ranges.

Experimental Section

Materials and Methods. The resin and all reagents were obtained from commercial suppliers and used without further purification. Reactions, filtration, and washings were carried out on a Quest210 synthesizer and a MiniBlock. Crude products were purified by parallel chromatography using a silica cartridge. All of the intermediate resins were monitored by ATR−FTIR. The structures of the final products were confirmed by ^{1}H NMR and ^{13}C NMR. LC/MS data were recorded on a Waters ZQ electrospray mass spectrometer (EI) equipped with PDA (200−600-nm) detection using an XTerra MS column (C_{18}, 5 μm, 4.6 × 100 mm). HRMS data were recorded on Micromass Auto Spec MS.

Procedure for the Synthesis of Amine 14. To compound **13** (50 g, 0.188 mol) was added 50% TFA/DCM solution, and the mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo to eliminate the excess TFA. The residue was diluted with DCM and washed with saturated aqueous $NaHCO_3$ solution and brine. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give the crude product. A methylamine hydrochloride (15.2 g, 0.226 mol) and TEA



(39.3 mL, 0.282 mol) were added to a solution of the crude product in DCM, and then $NaBH(OAc)_3$ (59.8 g, 0.282 mol) was added, and the mixture was stirred at room temperature for 12 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution and brine. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated to give the crude product. The crude residue was purified by column chromatography ($MeOH/CH_2Cl_2$, 1:19 v/v) to yield methyl-(2-methyl-6-nitro-2*H*-chromen-2-ylmethyl)amine **14** (41.5 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (dd, 1H, J = 8.9 Hz, 2.7 Hz), 7.88 (d, 1H, J = 2.7 Hz), 6.82 (d, 1H, J = 8.9 Hz), 6.46 (d, 1H, J = 10.0 Hz), 5.78 (d, 1H, J = 10.0 Hz), 2.88 (d, 1H, J = 12.5 Hz), 2.78 (d, 1H, J = 12.5 Hz), 2.48 (s, 3H), 1.43 (s, 3H). MS (ESI) m/z 235 $(M + H)^+$.

Procedure for the Synthesis of Amine 5. To a solution of the amine **14** (40 g, 0.171 mol) in DCM was added FmocCl (44.2 g, 0.171 mol) and DIEA (26.5 mL, 0.205 mol), and the mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (*n*-hexane/EtOAc, 4:1 v/v) to give the Fmoc-protected amine in 77% yield (30.8 g, 0.132 mol). To a solution of Fmoc-protected amine (30 g, 0.128 mol) in ethanol (300 mL) was added Fe (30 g) and 20% AcOH/H_2O (50 mL), and the mixture was refluxed for 2 h. The reaction mixture was filtered off and washed with EtOAc, and the combined filtrates were concentrated in vacuo. The organic residue was diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$ solution and brine. The organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc, 1:1 v/v) to give the compound **5** in 91% yield (49.7 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76−7.73 (m, 2H), 7.57−7.54 (m, 2H), 7.39−7.36 (m, 2H), 7.32−7.28 (m, 2H), 6.59 and 6.47 (2d, 1H, 1:0.7, J = 8.4 Hz), 6.46 and 6.41 (m, 1H, 1:0.7), 6.32 and 6.26 (m, 1H, 1:0.7), 6.27 and 6.09 (d, 1H, 1:0.7, J = 9.9 Hz), 5.60 and 4.90 (d, 1H, 1:0.7, J = 9.9 Hz), 4.55 and 4.36 (m, 2H, 0.7:1), 4.25−4.20 (m, 1H), 3.54 and 3.07 (d, 1H, 1:0.7, J = 14.7), 3.45 and 2.96 (d, 1H, 1:0.7, J = 14.7 Hz), 3.25 (brs, 2H), 3.00 and 2.85 (s, 1H, 1:0.7, 3H), 1.35 and 0.93 (s, 3H, 1:0.7). MS (ESI) m/z 427 $(M + H)^+$.

Procedure for the Preparation of Polymer-Bound 6-Aminobenzopyran 6. To a suspension of BAL resin **4** (1.0 g, 0.91 mmol, loading 0.91 mmol/g) in DMF (20 mL) containing 1% acetic acid were added successively 6-aminobenzopyran **5** (0.78 g, 1.82 mmol) and $NaBH(OAc)_3$ (0.58 g, 2.73 mmol). The suspension was shaken for 24 h at room temperature under N_2. The 6-aminobenzopyran resin **6** was filtered; washed with DMF (×2), DCM (×2), and MeOH (×2); and dried under high vacuum. FTIR (cm^{-1}): 1702, 1599, 1489, 1477, 1128.

Representative Procedure for the First-Generation Diversification Step 7a. To a suspension of resin **6** (1.0 g, 0.91 mmol, loading 0.91 mmol/g) in DMF were added benzylbromide (0.54 mL, 4.55 mmol) and DIEA (0.475 mL, 2.73 mmol). The suspension was shaken for 24 h at room temperature under N_2. The desired resin **7a** was filtered; washed with DMF (×2), DCM (×2), and MeOH (×2); and dried under high vacuum. FTIR (cm^{-1}): 1697, 1601, 1489, 1447, 1124.

Representative Procedure for the Fmoc Deprotection of Resin 7. Resin **7** (1.0 g, 0.91 mmol) was treated with 20% peperidine in DMF at room temperature for 3 h; washed with DMF (×2), DCM (×2), and MeOH (×2); and dried under high vacuum. FTIR (cm^{-1}): 1604, 1489, 1447, 1124.

Representative Procedure for the Second-Generation Diversification Step 9a. To a suspension of resin **8a** (1.0 g, 0.91 mmol) in DMF were added 2-thiophencarbonyl chloride (0.046 mL, 0.45 mmol) and TEA (0.063 mL, 0.45 mmol). The suspension was shaken for 12 h at room temperature under N_2. The desired resin **9a** was filtered; washed with DMF (×2), DCM (×2), and MeOH (×2); and dried under high vacuum. FTIR (cm^{-1}): 1592, 1493, 1452, 1342, 1151.

Representative Procedure for the Cleavage Step from the Second Generated Resins 9. Thiophene-2-carboxylic Acid [6-Benzylamino-2-methyl-2*H*-chromen-2-ylmethyl]-methylamide (11a). Resin **9a** (100 mg, 0.091mmol) was treated with 3 mL of cleavage cocktail (TFA/DCM; 1:4). After the mixture was shaken at room temperature for 3 h, the resin was filtered off and washed with DCM (3 mL × 2). The combined filtrates were evaporated to yield thiophene-2-carboxylic acid [6-benzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]methylamide **11a** (21.7 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (m, 1H), 7.36−7.24 (m, 6H), 7.01 (m, 1H), 6.63 (d, 1H, J = 8.5 Hz), 6.45 (m, 1H), 6.33−6.30 (m, 2H), 5.66 (m, 1H), 4.26 (s, 2H), 3.86 (d, 1H, J = 13.6 Hz), 3.71 (d, 1H, J = 13.6 Hz), 3.34 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 144.2, 142.7, 139.6, 138.1, 129.5, 129.1, 128.6, 128.4, 128.2, 127.5, 127.2, 126.7, 124.4, 121.4, 116.5, 113.8, 111.1, 80.1, 55.1, 49.1, 40.2, 24.2. LC/MS (ESI) m/z 405 $(M + H)^+$.

Cyclopropanecarboxylic Acid (6-Benzylamino-2-methyl-2*H*-chromen-2-ylmethyl)methylamide (11b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41−7.36 and 7.32−7.28 (m, 5H, 3.5:1), 6.67−6.65 (m, 1H), 6.49−6.46 (m, 1H), 6.36−6.31 (m, 2H), 5.63−5.59 (d, 1H, 3:1, J = 9.8 Hz), 4.30 (s, 2H), 3.69−3.61 (m, 2H), 3.26 and 3.05 (s, 3H, 3:1), 1.81 and 1.77 (m, 1H, 1:3), 1.47 and 1.37 (s, 3H, 1:3), 1.00−0.96 (m, 2H), 0.80−0.76 (m, 2H). LC/MS (ESI) m/z 363 $(M + H)^+$.

Thiophene-2-carboxylic Acid [6-(3-Methoxybenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]methylamide (11c). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, 1H, J = 4.9 Hz), 7.32−7.24 (m, 2H), 7.03−7.02 (m, 1H), 6.96−6.92 (m, 2H), 6.80 (m, 1H), 6.64 (d, 1H, J = 8.5 Hz), 6.46−6.45 (m, 1H), 6.33−6.31 (m, 2H), 5.67 (br, 1H), 4.24 (s, 2H), 3.88−3.83 (m, 1H), 3.79 (s, 3H), 3.76−3.72 (m, 1H), 3.29 (s, 3H), 1.42 (s, 3H). LC/MS (ESI) m/z 435 $(M + H)^+$.

4-*tert*-Butyl-*N*-[6-(3-methoxybenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-*N*-methylbenzamide (11d). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, 2H, J = 8.2 Hz), 7.29−7.23 (m, 4H), 6.96−6.93 (m, 2H), 6.82−6.80 (m, 1H), 6.61 (d, 1H, J = 8.5 Hz), 6.45−6.44 (m, 1H), 6.35−6.33 (m, 2H), 5.71 (d, 1H, J = 9.9 Hz), 4.24 (s, 2H), 3.92 (d, 1H, J = 14.1 Hz), 3.75 (s, 3H), 3.65 (d, 1H, J = 14.1 Hz), 3.04 (s, 3H), 1.45 (s, 3H), 1.31 (s, 9H). LC/MS (ESI) m/z 485 $(M + H)^+$. HRMS (EI): $[M]^+$ calcd for $C_{31}H_{36}N_2O_3$, 484.2726; found, 484.2723.

***N*-[6-(3-Methoxybenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-*N*-methylbenzamide (11e).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.33 (m, 5H), 7.26−7.23 (m, 1H), 6.95−6.92 (m, 2H), 6.82−6.80 (m, 1H), 6.61 (d, 1H, J = 8.5 Hz), 6.44−6.42 (m, 1H), 6.36−6.34 (m, 2H), 5.72 (d, 1H, J = 9.9 Hz), 4.24 (s, 2H), 3.94−3.91 (m, 1H), 3.78 (s, 3H), 3.65 (d, 1H, J = 14.1 Hz), 3.01 (s, 3H), 1.46 (s, 3H). LC/MS (ESI) m/z 429 $(M + H)^+$.

Pentanoic Acid [6-(4-Fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]methylamide (11f). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.31 (m, 2H), 7.03−7.00 (m, 2H), 6.60 (d, 1H, J = 8.5 Hz), 6.42 (dd, 1H, J = 8.5 Hz, J = 2.4 Hz), 6.30 (d, 1H, J = 2.4 Hz), 6.28 (d, 1H, J = 9.9 Hz), 5.63 (d, 1H, J = 9.9 Hz), 3.68 (d, 1H, J = 14.3 Hz), 3.53

(d, 1H, $J = 14.3$ Hz), 3.05 (s, 3H), 2.30−2.28 (m, 2H), 1.61−1.58 (m, 2H), 1.39−1.33 (m, 5H), 0.92 (t, 3H, $J = 7.3$ Hz). LC/MS (ESI) *m/z* 397 $(M + H)^+$.

Cyclopropanecarboxylic Acid [6-(4-Fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]methylamide (11g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.31 (m, 2H), 7.03−7.00 (m, 2H), 6.62 (d, 1H, $J = 8.5$ Hz), 6.43 (dd, 1H, $J = 8.5$ Hz, $J = 2.4$ Hz), 6.31 (d, 1H, $J = 2.4$ Hz), 6.28 (d, 1H, $J = 9.9$ Hz), 5.61 (d, 1H, $J = 9.9$ Hz), 4.23 (s, 2H), 3.75−3.55 (br, 1H), 3.65 (d, 1H, $J = 14.3$ Hz), 3.58 (d, 1H, $J = 14.3$ Hz), 3.22 (s, 3H), 1.74−1.73 (m, 1H), 1.32 (s, 3H), 0.98−0.93 (m, 2H), 0.76−0.73 (m, 2H). LC/MS (ESI) *m/z* 381 $(M + H)^+$. HRMS (EI): $[M]^+$ calcd for $C_{23}H_{25}N_2O_2F_1$, 2380.1900; found, 380.1907.

***N*-[6-(4-Fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-*N*-methylbenzamide (11h).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.31 (m, 7H), 7.04−7.00 (m, 2H), 6.62 (d, 1H, $J = 8.5$ Hz), 6.43 (dd, 1H, $J = 8.5$ Hz, $J = 2.6$ Hz), 6.36−6.34 (m, 2H), 5.73 (d, 1H, $J = 9.9$ Hz), 4.24 (s, 2H), 3.94 (d, 1H, $J = 14.1$ Hz), 3.63 (d, 1H, $J = 14.1$ Hz), 3.01 (s, 3H), 1.46 (s, 3H). LC/MS (ESI) *m/z* 417 $(M + H)^+$.

4-*tert*-Butyl-*N*-[6-(4-fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-*N*-methylbenzamide (11i). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.25 (m, 6H), 7.04−7.00 (m, 2H), 6.62 (d, 1H, $J = 8.5$ Hz), 6.43−6.42 (m, 1H), 6.35−6.33 (m, 2H), 5.72 (d, 1H, $J = 9.9$ Hz), 3.93 (d, 2H, $J = 8.1$ Hz), 3.65 (d, 2H, $J = 8.1$ Hz), 3.04 (s, 3H), 1.45 (s, 3H), 1.31 (s, 9H). LC/MS (ESI) *m/z* 473 $(M + H)^+$.

4-Methoxy-*N*-methyl-*N*-[2-methyl-6-(4-nitrobenzylamino)-2*H*-chromen-2-ylmethyl]benzamide (11j). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (m, 2H), 7.54−7.51 (m, 2H), 7.31 (d, 2H, $J = 8.3$ Hz), 6.86 (d, 2H, $J = 8.3$ Hz), 6.61 (d, 1H, $J = 8.5$ Hz), 6.41−6.37 (m, 1H), 6.31−6.27 (m, 2H), 5.72 (d, 1H, $J = 9.5$ Hz), 4.41 (s, 2H), 3.99−3.92 (m, 2H), 3.82 (s, 3H), 3.62 (d, 1H, $J = 14.1$ Hz), 3.05 (s, 3H), 1.44 (s, 3H). LC/MS (ESI) *m/z* 474 $(M + H)^+$.

Thiophene-2-carboxylic Acid Methyl-[2-methyl-6-(4-nitrobenzylamino)-2*H*-chromen-2-ylmethyl]amide (11k). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21−8.18 (m, 2H), 7.53 (d, 2H, $J = 8.4$ Hz), 7.45 (d, 1H, $J = 4.5$ Hz), 7.31−7.30 (m, 1H), 7.03−7.01 (m, 1H), 6.62 (d, 1H, $J = 8.5$ Hz), 6.39 (dd, 1H, $J = 8.5$ Hz, $J = 2.7$ Hz), 6.30−6.25 (m, 2H), 5.68 (br, 1H), 4.01 (br, 1H), 3.88 (d, 1H, $J = 13.6$ Hz), 3.72−3.68 (m, 1H), 3.29 (s, 3H), 1.41 (s, 3H). LC/MS (ESI) *m/z* 450 $(M + H)^+$.

***N*-Methyl-*N*-{2-methyl-6-[(thiophen-2-ylmethyl)amino]-2*H*-chromen-2-ylmethyl}benzamide (11l).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.33 (m, 5H), 7.21−7.20 (m, 1H), 6.99−6.95 (m, 2H), 6.63 (d, 1H, $J = 8.5$ Hz), 6.39−6.35 (m, 2H), 5.73 (d, 1H, $J = 9.9$ Hz), 4.45 (s, 2H), 3.94 (d, 1H, $J = 14.1$ Hz), 3.64 (d, 1H, $J = 14.1$ Hz), 3.01 (s, 3H), 1.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 144.9, 142.0, 136.7, 129.5, 128.5, 128.3, 126.9, 126.8, 125.0, 124.6, 124.2, 116.5, 114.3, 111.6, 80.5, 54.3, 44.5, 40.2, 24.4. LC/MS (ESI) *m/z* 405 $(M + H)^+$.

4-Fluoro-*N*-methyl-*N*-{2-methyl-6-[(thiophen-2-ylmethyl)amino]-2*H*-chromen-2-ylmethyl}benzamide (11m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32−7.31 (m, 2H), 7.22−7.21 (m, 1H), 7.06−6.96 (m, 4H), 6.63 (d, 1H, $J = 8.5$ Hz), 6.50 (m, 1H), 6.39 (m, 2H), 5.71 (d, 1H, $J = 9.7$ Hz), 4.46 (s, 2H), 3.97 (d, 1H, $J = 14.2$ Hz), 3.59 (d, 1H, $J = 14.2$ Hz), 3.02 (s, 3H), 1.46 (s, 3H). LC/MS (ESI) *m/z* 423 $(M + H)^+$.

***N*-[6-(3-Chlorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-*N*-methylbenzenesulfonamide (11n).** ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78−7.73 (m, 2H), 7.61−7.44 (m, 3H), 7.34 (s, 1H), 7.26−7.23 (m, 3H), 6.57 (d, 1H, $J = 8.5$ Hz), 6.41−6.26 (m, 3H), 5.64 (d, 1H, $J = 9.8$ Hz), 4.24 (s, 2H), 3.23 (d, 1H, $J = 14.4$ Hz), 3.15 (d, 1H, $J = 14.4$ Hz), 2.87 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (125 MHz,$CDCl_3$): δ 144.2, 142.3, 141.7, 137.8, 134.5, 132.6, 129.9, 128.3, 127.5, 127.4, 127.3, 125.5, 124.7, 121.6, 116.7, 114.0, 111.2, 79.1, 55.7, 48.6, 37.0, 24.0. LC/MS (ESI) *m/z* 470 $(M + H)^+$.

Propane-1-sulfonic Acid [6-(3-Chlorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]methylamide (11o). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (s, 1H), 7.26−7.23 (m, 3H), 6.60 (d, 1H, $J = 8.6$ Hz), 6.42 (dd, 1H, $J = 8.5$ Hz, $J = 2.7$ Hz), 6.35 (d, 1H, $J = 9.8$ Hz), 6.30 (d, 1H, $J = 2.7$ Hz), 5.60 (d, 1H, $J = 9.8$ Hz), 4.26 (s, 2H), 3.37 (d, 1H, $J = 14.6$ Hz), 3.30 (d, 1H, $J = 14.6$ Hz), 3.00 (s, 3H), 2.92−2.88 (m, 2H), 1.81−1.77 (m, 2H), 1.43 (s, 3H), 1.01 (t, 3H, $J = 7.5$ Hz). LC/MS (ESI) *m/z* 435 $(M + H)^+$.

Thiophene-2-sulfonic Acid [6-(3-Chlorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]methylamide (11p). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, 1H, $J = 5.0$ Hz), 7.51 (m, 1H), 7.35 (m, 1H), 7.26−7.23 (m, 4H), 7.11−7.09 (m, 1H), 6.58 (d, 1H, $J = 8.6$ Hz), 6.40 (m, 1H), 6.35 (d, 1H, $J = 9.8$ Hz), 6.28 (d, 1H, $J = 2.8$ Hz), 5.63 (d, 1H, $J = 9.8$ Hz), 4.24 (s, 2H), 3.19 (d, 1H, $J = 14.3$ Hz), 3.14 (d, 1H, $J = 14.3$ Hz), 2.91 (s, 2H), 1.50 (s, 3H). LC/MS (ESI) *m/z* 476 $(M + H)^+$.

***N*-[6-(3-Chlorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-4,*N*-dimethylbenzenesulfonamide (11q).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, 2H, $J = 8.3$ Hz), 7.34 (s, 1H), 7.29−7.21 (m, 5H), 6.56 (d, 1H, $J = 8.6$ Hz), 6.38−6.32 (m, 2H), 6.25 (d, 1H, $J = 2.8$ Hz), 5.63 (d, 1H, $J = 9.8$ Hz), 4.23 (s, 2H), 3.18 (d, 1H, $J = 14.3$ Hz), 3.13 (d, 1H, $J = 14.3$ Hz), 2.84 (s, 3H), 2.40 (s, 3H), 1.50 (s, 3H). LC/MS (ESI) *m/z* 484 $(M + H)^+$.

***N*-Methyl-*N*-{2-methyl-6-[(5-methylthiophen-2-ylmethyl)-amino]-2*H*-chromen-2-ylmethyl}benzenesulfonamide (11r).** ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.79−7.72 (m, 2H), 7.60−7.43 (m, 3H), 6.78−6.73 (m, 1H), 6.60−6.55 (m, 2H), 6.34−6.32 (m, 2H), 5.64 (d, 1H, $J = 9.8$ Hz), 4.33 (s, 2H), 3.23 (d, 1H, $J = 14.3$ Hz), 3.14 (d, 1H, $J = 14.3$ Hz), 2.86 (s, 3H), 2.43 (s, 3H), 1.51 (s, 3H). LC/MS (ESI) *m/z* 455 $(M + H)^+$.

***N*-Methyl-*N*-{2-methyl-6-[(5-methylthiophen-2-ylmethyl)-amino]-2*H*-chromen-2-ylmethyl}-*C*-phenylmethanesulfonamide (11s).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (m, 5H), 6.76 (m, 1H), 6.59−6.57 (m, 2H), 6.45 (dd, 1H, $J = 8.5$ Hz, $J = 2.8$ Hz), 6.45−6.31 (m, 2H), 5.51 (d, 1H, $J = 9.9$ Hz), 4.33 (s, 2H), 4.22 (s, 2H), 3.12 (d, 1H, $J = 14.8$ Hz), 2.98 (d, 1H, $J = 14.8$ Hz), 2.88 (s, 3H), 2.43 (s, 3H), 1.33 (s, 3H). LC/MS (ESI) *m/z* 449 $(M + H)^+$.

4-Fluoro-*N*-methyl-*N*-{2-methyl-6-[(5-methylthiophen-2-ylmethyl)amino]-2*H*-chromen-2-ylmethyl}benzenesulfonamide (11t). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77−

7.74 (m, 2H), 7.18−7.15 (m, 2H), 6.75−6.74 (m, 1H), 6.58−6.57 (m, 2H), 6.45 (m, 1H), 6.37 (d, 1H, J = 9.8 Hz), 4.33 (s, 2H), 3.20 (d, 1H, J = 14.3 Hz), 3.15 (d, 1H, J = 14.3 Hz), 2.85 (s, 3H), 2.43 (s, 3H), 1.50 (s, 3H). LC/MS (ESI) m/z 473 $(M + H)^+$. HRMS (EI): $[M]^+$ calcd for $C_{24}H_{25}N_2O_3F_1S_2$, 472.1291; found, 472.1284.

4-Methoxy-*N*-methyl-*N*-{2-methyl-6-[(5-methylthiophen-2-ylmethyl)amino]-2*H*-chromen-2-ylmethyl}benzenesulfonamide (11u). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, 2H, J = 6.9 Hz), 6.95 (d, 2H, J = 6.9 Hz), 6.75 (d, 1H, J = 3.4 Hz), 6.59−6.56 (m, 2H), 6.44 (m, 1H), 6.36 (d, 1H, J = 9.8 Hz), 6.33 (d, 1H, J = 2.8 Hz), 5.64 (d, 1H, J = 9.8 Hz), 4.33 (s, 3H), 3.18 (d, 1H, J = 14.3 Hz), 3.12 (d, 1H, J = 14.3 Hz), 2.43 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (125 MHz,-$CDCl_3$): δ 162.8, 114.3, 142.2, 139.2, 129.5, 129.4, 128.3, 125.0, 124.7, 124.7, 121.6, 116.7, 114.4, 114.2, 111.5, 79.0, 55.7, 55.6, 44.5, 37.0, 23.9, 15.4. LC/MS (ESI) m/z 485 $(M + H)^+$. HRMS (EI): $[M]^+$ calcd for $C_{25}H_{28}N_2O_4S_2$, 484.1491; found, 484.1492.

4-*tert*-Butyl-*N*-methyl-*N*-{2-methyl-6-[(5-methylthiophen-2-ylmethyl)amino]-2*H*-chromen-2-ylmethyl}benzenesulfonamide (11v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, 2H, J = 8.5 Hz), 7.48 (d, 2H, J = 8.5 Hz), 6.74 (d, 1H, J = 3.2 Hz), 6.57 (m, 2H), 6.36 (d, 1H, J = 9.8 Hz), 6.33 (d, 1H, J = 2.8 Hz), 5.64 (d, 1H, J = 9.8 Hz), 4.32 (s, 2H), 3.21 (d, 1H, J = 14.3 Hz), 3.13 (d, 1H, J = 14.3 Hz), 2.42 (s, 3H), 1.52 (s, 3H), 1.33 (s, 9H). LC/MS (ESI) m/z 511 $(M + H)^+$.

Thiophene-2-sulfonic Acid Methyl-{2-methyl-6-[(pyridin-2-ylmethyl)amino]-2*H*-chromen-2-ylmethyl}amide (11w). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (d, 1H, J = 4.5 Hz), 7.64 (m, 1H), 7.55−7.50 (m, 2H), 7.33 (m, 1H), 7.15 (m, 1H), 7.08 (m, 1H), 6.59 (d, 1H, J = 2.8 Hz), 5.62 (d, 1H, J = 9.8 Hz), 4.38 (s, 2H), 3.19 (d, 1H, J = 14.8 Hz), 3.14 (d, 1H, J = 14.8 Hz), 2.91 (s, 3H), 1.50 (s, 3H). LC/MS (ESI) m/z 442 $(M + H)^+$.

4-Fluoro-*N*-methyl-*N*-{2-methyl-6-[(pyridin-2-ylmethyl)amino]-2*H*-chromen-2-ylmethyl}benzenesulfonamide (11x). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (m, 1H), 7.77−7.74 (m, 2H), 7.31 (d, 1H, J = 7.75 Hz), 7.18−7.14 (m, 3H), 6.57 (d, 1H, J = 8.5 Hz), 6.46−6.45 (m, 1H), 6.36 (d, 1H, J = 9.8 Hz), 6.34 (d, 1H, J = 2.5 Hz), 5.62 (d, 1H, J = 9.8 Hz), 4.37 (s, 2H), 3.21−3.17 (s, 3H), 2.87 (s, 3H), 1.49 (s, 3H). LC/MS (ESI) m/z 454 $(M + H)^+$.

4-Methoxy-*N*-methyl-*N*-{2-methyl-6-[(pyridin-2-ylmethyl)amino]-2*H*-chromen-2-ylmethyl}benzenesulfonamide (11y). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (d, 1H, J = 4.1 Hz), 7.69−7.64 (m, 3H), 7.32 (d,1H, J = 7.8 Hz), 7.24−7.20 (m, 1H), 6.95 (d, 2H, J = 6.9 Hz), 6.57 (d,1H, J = 8.6 Hz), 7.45 (m, 1H), 6.37−6.33 (m, 2H), 5.63 (d, 1H, J = 9.8 Hz), 4.38 (s, 2H), 3.84 (s, 2H), 3.18 (d,1H, J = 14.3 Hz), 3.13 (d, 1H, J = 14.3 Hz), 2.84 (s, 3H). LC/MS (ESI) m/z 466 $(M + H)^+$.

Propane-1-sulfonic Acid Methyl-{2-methyl-6-[(pyridin-2-ylmethyl)amino]-2*H*-chromen-2-ylmethyl}amide (11z). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, 1H, J = 4.4 Hz), 7.67−7.64 (m, 1H), 7.34 (d, 1H, J = 7.8 Hz), 7.21−7.18 (m, 1H), 6.61 (d, 1H, J = 8.6 Hz), 6.49 (dd, 1H, J = 8.6 Hz, J = 2.8 Hz), 6.38−6.35 (m, 2H), 5.59 (d, 1H, J = 9.9 Hz), 4.41 (s, 2H), 3.37 (d, 1H, J = 14.6 Hz), 3.30 (d, 1H, J = 14.6 Hz), 3.00 (s, 3H), 2.96−2.88 (m, 2H), 1.82−1.76 (m, 2H), 1.42 (s, 3H), 1.01 (t, 3H, J = 7.4 Hz). LC/MS (ESI) m/z 402 $(M + H)^+$.

1-(6-Benzylamino-2-methyl-2*H*-chromen-2-ylmethyl)-3-butyl-1-methylurea (12a). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.32 (m, 4H), 7.28−7.26 (m, 1H), 6.59 (d, 1H, J = 8.5 Hz), 6.47 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.36 (d, 1H, J = 2.7 Hz), 6.31 (d, 1H, J = 9.9 Hz), 5.62 (d, 1H, J = 9.9 Hz), 4.85 (br, 1H), 4.26 (s, 2H), 3.54 (d, 1H, J = 15.1 Hz), 3.43 (d, 1H, J = 15.1 Hz), 3.19−3.17 (m, 2H), 2.92 (s, 3H), 1.47−1.43 (m, 2H), 1.35−1.30 (m, 5H), 0.90 (t, 3H, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 144.0, 142.7, 139.6, 128.6, 128.4, 127.5, 127.2, 124.2, 121.4, 116.4, 113.7, 111.1, 80.4, 56.4, 49.1, 40.6, 36.6, 32.4, 23.7, 20.1, 13.9. LC/MS (ESI) m/z 494 $(M + H)^+$.

1-(6-Benzylamino-2-methyl-2*H*-chromen-2-ylmethyl)-3-(2-chlorophenyl)-1-methylurea (12b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21−8.19 (m, 1H), 7.37−7.22 (m, 8H), 6.93−6.92 (m, 1H), 6.66 (d, 1H, J = 8.5 Hz), 6.45 (d, 1H, J = 2.7 Hz), 6.36−6.34 (m, 2H), 5.65 (d, 1H, J = 9.9 Hz), 4.25 (s, 2H), 3.64 (d, 1H, J = 15.1 Hz), 3.60 (d, 1H, J = 15.1 Hz), 3.12 (s, 3H), 1.39 (s, 3H). LC/MS (ESI) m/z 448 $(M + H)^+$.

1-(6-Benzylamino-2-methyl-2*H*-chromen-2-ylmethyl)-3-(4-fluorophenyl)-1-methylurea (12c). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (br, 1H), 7.35−7.27 (m, 4H), 7.26−7.25 (m, 3H), 6.94 (t, 2H, J = 8.6 Hz), 6.66 (d, 1H, J = 8.5 Hz), 6.48−6.45 (m, 1H), 6.36−6.34 (m, 2H), 5.62 (d, 1H, J = 9.9 Hz), 4.27 (s, 2H), 3.61 (d, 1H, J = 15.5 Hz), 3.54 (d, 1H, J = 15.5 Hz), 3.06 (s, 3H), 1.37 (s, 3H). LC/MS (ESI) m/z 432 $(M + H)^+$.

1-(6-Benzylamino-2-methyl-2*H*-chromen-2-ylmethyl)-1-methyl-3-(4-nitrophenyl)urea (12d). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14−8.12 (m, 2H), 7.46 (d, 2H, J = 9.2 Hz), 7.36−7.33 (m, 4H), 7.29−7.25 (m, 1H), 6.68 (d, 1H, J = 8.5 Hz), 6.48 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.40 (d, 1H, J = 9.9 Hz), 6.37−6.36 (m, 1H), 5.63 (d, 1H, J = 9.9 Hz), 4.28 (s, 2H), 3.63 (d, 1H, J = 15.8 Hz), 3.58 (d, 1H, J = 15.8 Hz), 3.10 (s, 3H), 1.39 (s, 3H). LC/MS (ESI) m/z 459 $(M + H)^+$.

1-(6-Benzylamino-2-methyl-2*H*-chromen-2-ylmethyl)-1-methyl-3-*p*-tolylurea (12e). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.32 (m, 4H), 7.27−7.21 (m, 3H), 7.05 (d, 2H, J = 8.3 Hz), 6.67 (d, 1H, J = 8.5 Hz), 6.47−6.45 (m, 1H), 6.35−6.33 (m, 2H), 5.62 (d, 1H, J = 9.9 Hz), 4.26 (s, 2H), 3.61 (d, 1H, J = 15.5 Hz), 3.53 (d, 1H, J = 15.5 Hz), 3.05 (s, 3H), 2.27 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.0, 143.6, 143.1, 139.6, 137.0, 132.0, 129.3, 128.7, 127.9, 127.6, 127.3, 124.7, 121.4, 119.8, 116.5, 114.0, 11.2, 80.7, 57.7, 49.1, 37.3, 23.5, 20.8. LC/MS (ESI) m/z 428 $(M + H)^+$.

{3-Methyl-3-[2-methyl-6-(4-methylbenzylamino)-2*H*-chromen-2-ylmethyl]ureido}acetic Acid Ethyl Ester (12f). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25−7.24 (m, 2H), 7.14 (d, 2H, J = 7.8 Hz), 6.32 (d, 1H, J = 8.5 Hz), 6.43 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.33−6.31 (m, 2H), 5.60 (d, 1H, J = 9.9 Hz), 5.35 (br, 1H), 4.21−4.17 (m, 4H), 4.00−3.94

(m, 2H), 3.52−3.47 (m, 2H), 2.99 (s, 3H), 2.34 (s, 3H), 1.35 (s, 3H), 1.26 (t, 3H, J = 7.1 Hz). LC/MS (ESI) m/z 438 (M + H)$^+$.

3-Cyclohexyl-1-methyl-1-[2-methyl-6-(4-methylbenzylamino)-2*H*-chromen-2-ylmethyl]urea (12g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25−7.24 (m, 2H), 7.14 (d, 2H, J = 7.9 Hz), 6.59 (d, 1H, J = 8.5 Hz), 6.43 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.31−6.29 (m, 2H), 5.61 (d, 1H, J = 9.9 Hz), 4.80 (br, 1H), 4.21 (s, 2H), 3.59−3.58 (m, 1H), 3.51 (d, 1H, J = 15.1 Hz), 3.43 (d, 1H, J = 15.1 Hz), 2.92 (s, 3H), 2.34 (s, 3H), 1.93 (m, 2H), 1.68−1.65 (m, 2H), 1.57 (m, 1H), 1.36−1.33 (m, 5H), 1.15−1.06 (m, 3H). LC/MS (ESI) m/z 434 (M + H)$^+$.

3-(4-Fluorophenyl)-1-methyl-1-[2-methyl-6-(4-methylbenzylamino)-2*H*-chromen-2-ylmethyl]urea (12h). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (br, 1H), 7.27−7.24 (m, 4H), 7.15 (d, 2H, J = 7.9 Hz), 6.65 (d, 1H, J = 8.5 Hz), 6.47−6.45 (m, 1H), 6.37−6.33 (m, 2H), 5.62 (d, 1H, J = 9.9 Hz), 4.22 (s, 2H), 3.61 (d, 1H, J = 15.5 Hz), 3.53 (d, 1H, J = 15.5 Hz), 3.06 (s, 3H), 2.34 (s, 3H), 1.37 (s, 3H). LC/MS (ESI) m/z 446 (M + H)$^+$. HRMS (EI): [M]$^+$ calcd for $C_{27}H_{28}N_3O_2F_1$, 445.2166; found, 445.2169.

3-(4-Methoxyphenyl)-1-methyl-1-[2-methyl-6-(4-methylbenzylamino)-2*H*-chromen-2-ylmethyl]urea (12i). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25−7.22 (m, 5H), 7.15 (d, 2H, J = 7.8 Hz), 6.81 (d, 2H, J = 8.9 Hz), 6.65 (d, 1H, J = 8.5 Hz), 6.45 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.35−6.33 (m, 2H), 5.62 (d, 1H, J = 9.9 Hz), 4.22 (s, 2H), 3.76 (s, 3H), 3.61 (d, 1H, J = 15.5 Hz), 3.53 (d, 1H, J = 15.5 Hz), 3.05 (s, 3H), 2.33 (s, 3H), 1.37 (s, 3H). LC/MS (ESI) m/z 458 (M + H)$^+$.

3-(2,6-Dimethylphenyl)-1-methyl-1-[2-methyl-6-(4-methylbenzylamino)-2*H*-chromen-2-ylmethyl]urea (12j). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25−7.23 (m, 2H), 7.14 (d, 2H, J = 7.8 Hz), 7.03 (m, 3H), 6.61 (d, 1H, J = 8.5 Hz), 6.43 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.34 (m, 2H), 5.66 (d, 1H, J = 9.9 Hz), 4.21 (s, 2H), 3.72 (d, 1H, J = 15.1 Hz), 3.53 (d, 1H, J = 15.1 Hz), 3.09 (s, 3H), 2.33 (s, 3H), 2.19 (s, 6H), 1.37 (s, 3H). LC/MS (ESI) m/z 456 (M + H)$^+$.

3-Benzyl-1-[6-(4-fluorobenzylamino)-2-methyl-2*H*-chromen-2ylmethyl]-1-methylurea (32k). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32−7.23 (m, 7H), 7.00 (t, 2H, J = 8.7 Hz), 6.42 (m, 1H), 6.37−6.34 (m, 1H), 6.30−3.28 (m, 2H), 5.61 (d, 1H, J = 9.9 Hz), 5.25 (br, 1H), 4.40−4.38 (m, 2H), 4.21 (s, 2H), 3.58 (d, 1H, J = 15.1 Hz), 3.46 (d, 1H, J = 15.1 Hz), 2.95 (s, 3H), 1.34 (s, 3H). LC/MS (ESI) m/z 446 (M + H)$^+$. HRMS (EI): [M]$^+$ calcd for $C_{27}H_{19}N_3O_2F_1$, 445.2166; found, 445.2160.

3-(2-Chlorophenyl)-1-[6-(4-fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-1-methylurea (12l). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, 1H, J = 8.3 Hz), 7.40 (br, 1H), 7.33−7.30 (m, 3H), 7.25−7.22 (m, 1H), 7.02 (t, 2H, J = 8.6 Hz), 6.93 (m, 1H), 6.66 (d, 1H, J = 8.5 Hz), 6.43−6.41 (m, 1H), 6.35−6.31 (m, 2H), 5.65 (d, 1H, J = 9.9 Hz), 4.22 (s, 2H), 3.63−3.61 (m, 2H), 3.12 (s, 3H), 1.39 (s, 3H). LC/MS (ESI) m/z 466 (M + H)$^+$.

3-(4-Ethylphenyl)-1-[6-(4-fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-1-methylurea (12m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.30 (m, 2H), 7.25−7.23 (m, 2H), 7.08 (d, 2H, J = 8.3 Hz), 7.02 (t, 2H, J = 8.6 Hz), 6.67 (d, 1H, J = 8.5 Hz), 6.45 (m, 1H), 6.35−6.31 (m, 2H), 5.63 (d, 1H, J = 9.9 Hz), 4.23 (s, 2H), 3.61 (d, 1H, J = 15.4 Hz), 3.54 (d, 1H, J = 15.4 Hz), 3.06 (s, 3H), 2.58 (q, 2H, J = 7.6 Hz), 1.37 (s, 3H), 1.19 (t, 3H, J = 7.6 Hz). LC/MS (ESI) m/z 460 (M + H)$^+$.

1-[6-(4-Fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-3-(4-methoxyphenyl)-1-methylurea (12n). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.30 (m, 2H), 7.25−7.22 (m, 3H), 7.03−7.02 (m, 2H), 6.81 (d, 2H, J = 8.9 Hz), 6.66 (d, 1H, J = 8.5 Hz), 6.43 (m, 1H), 6.35−6.31 (m, 2H), 5.63 (d, 1H, J = 9.9 Hz), 4.23 (s, 2H), 3.76 (s, 3H), 3.61 (d, 1H, J = 15.5 Hz), 3.53 (d, 1H, J = 15.5 Hz), 3.05 (s, 3H), 1.37 (s, 3H). LC/MS (ESI) m/z 462 (M + H)$^+$.

3-Cyclohexyl-1-[6-(4-fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-1-methylurea (12o). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.31 (m, 2H), 7.03−7.00 (m, 2H), 6.59 (d, 1H, J = 8.5 Hz), 6.43−6.42 (m, 1H), 6.31−6.29 (m, 2H), 5.62 (d, 1H, J = 9.9 Hz), 4.79 (br, 1H), 4.23 (s, 1H), 3.59 (m, 1H), 3.51 (d, 1H, J = 15.1 Hz), 3.44 (d, 1H, J = 15.1 Hz), 2.92 (s, 3H), 1.93 (m, 2H), 1.67−1.65 (m, 2H), 1.57 (m, 1H), 1.37−1.33 (m, 5H), 1.14−1.06 (m, 3H). LC/MS (ESI) m/z 438 (M + H)$^+$.

{**3-[6-(4-Fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-3-methylureido}acetic Acid Ethyl Ester (12p).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.30 (m, 2H), 7.03−7.00 (m, 2H), 6.63 (d, 1H, J = 8.5 Hz), 6.42 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.32−6.30 (m, 2H), 5.61 (d, 1H, J = 9.9 Hz), 4.22−4.17 (m, 4H), 4.00−3.94 (m, 2H), 3.53−3.47 (m, 2H), 2.99 (s, 3H), 1.35 (s, 3H), 1.28−1.25 (m, 3H). LC/MS (ESI) m/z 442 (M + H)$^+$.

3-Butyl-1-methyl-1-[2-methyl-6-(4-trifluoromethylbenzylamino)-2*H*-chromen-2-ylmethyl]urea (12q). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, 2H, J = 8.1 Hz), 7.47 (d, 2H, J = 8.1 Hz), 6.58 (d, 1H, J = 8.5 Hz), 6.39 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.30−6.27 (m, 2H), 5.62 (d, 1H, J = 9.9 Hz), 4.83 (br, 1H), 4.34 (s, 2H), 3.91 (br, 1H), 3.53 (d, 1H, J = 15.1 Hz), 3.44 (d, 1H, J = 15.1 Hz), 3.20−3.16 (m, 2H), 2.93 (s, 3H), 1.47−1.42 (m, 2H), 1.36−1.30 (m, 5H), 0.90 (t, 3H, J = 7.3 Hz). LC/MS (ESI) m/z 462 (M + H)$^+$.

3-(2-Chlorophenyl)-1-methyl-1-[2-methyl-6-(4-trifluoromethylbenzylamino)-2*H*-chromen-2-ylmethyl]urea (12r). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, 1H, J = 8.3 Hz), 7.58 (d, 2H, J = 8.1 Hz), 7.47−7.45 (m, 3H), 7.31 (d, 1H, J = 8.0 Hz), 7.25−7.21 (m, 1H), 6.92 (m, 1H), 6.65 (d, 1H, J = 8.5 Hz), 6.38 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.32 (d, 1H, J = 9.9 Hz), 6.28−6.27 (m, 1H), 5.65 (d, 1H, J = 9.9 Hz), 4.33 (s, 2H), 3.87 (br, 1H), 3.64 (d, 1H, J = 15.5 Hz), 3.60 (d, 1H, J = 15.2 Hz), 3.11 (s, 3H), 1.39 (s, 3H). LC/MS (ESI) m/z 516 (M + H)$^+$.

3-(2,6-Dimethylphenyl)-1-methyl-1-[2-methyl-6-(4-trifluoromethylbenzylamino)-2*H*-chromen-2-ylmethyl]-urea (12s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, 2H, J = 8.1 Hz), 7.46 (d, 2H, J = 8.1 Hz), 7.02 (s, 3H), 6.60 (d, 1H, J = 8.5 Hz), 6.37 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.32−6.28 (m, 2H), 5.65 (d, 1H, J = 9.9 Hz), 4.32 (s, 2H), 3.91 (br, 1H), 3.71 (d, 1H, J = 15.1 Hz), 3.52 (d, 1H, J =

15.1 Hz), 3.08 (s, 2H), 2.18 (s, 6H), 1.36 (s, 3H). LC/MS (ESI) *m/z* 510 $(M + H)^+$.

3-(4-Methoxyphenyl)-1-methyl-1-[2-methyl-6-(4-trifluoromethylbenzylamino)-2*H*-chromen-2-ylmethyl]urea (12t). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, 2H, $J = 8.0$ Hz), 7.47 (d, 2H, $J = 8.0$ Hz), 7.25−7.21 (m, 3H), 6.80 (d, 2H, $J = 9.0$ Hz), 6.65 (d, 1H, $J = 8.5$ Hz), 6.41 (dd, 1H, $J = 8.5$ Hz, $J = 2.7$ Hz), 6.32 (d, 1H, $J = 9.9$ Hz), 6.29−6.28 (m, 1H), 5.63 (d, 1H, $J = 9.9$ Hz), 4.33 (s, 2H), 3.75 (s, 3H), 3.61 (d, 1H, $J = 15.5$ Hz), 3.53 (d, 1H, $J = 15.5$ Hz), 3.05 (s, 3H), 1.36 (s, 3H). LC/MS (ESI) *m/z* 512 $(M + H)^+$.

3-(4-Fluorophenyl)-1-methyl-1-[2-methyl-6-(4-trifluoromethylbenzylamino)-2*H*-chromen-2-ylmethyl]urea (12u). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, 2H, $J = 8.1$ Hz), 7.48 (m, 3H), 7.27−7.25 (m, 2H), 6.93 (t, 2H, $J = 8.7$ Hz), 6.65 (d, 1H, $J = 8.5$ Hz), 6.43 (m, 1H), 6.34 (d, 1H, $J = 9.9$ Hz), 6.30−6.29 (m, 1H), 5.63 (d, 1H, $J = 9.9$ Hz), 4.34 (s, 2H), 3.94 (br, 1H), 3.60 (d, 1H, $J = 15.5$ Hz), 3.54 (d, 1H, $J = 15.5$ Hz), 3.05 (s, 3H), 1.37 (s, 3H). LC/MS (ESI) *m/z* 500 $(M + H)^+$.

1-Methyl-1-[2-methyl-6-(4-trifluoromethylbenzylamino)-2*H*-chromen-2-ylmethyl]-3-(4-nitrophenyl)thiourea (12v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14−8.12 (m, 2H), 7.58 (d, 2H, $J = 8.1$ Hz), 7.47 (d, 2H, $J = 8.1$ Hz), 6.85−6.83 (m, 2H), 6.74 (d, 1H, $J = 8.5$ Hz), 6.70−6.69 (m, 1H), 6.48 (dd, 1H, $J = 8.5$ Hz, $J = 2.8$ Hz), 4.50 (d, 1H, $J = 9.9$ Hz), 4.37 (s, 2H), 3.67 (d, 1H, $J = 13.7$ Hz), 3.46 (d, 1H, $J = 13.7$ Hz), 3.21 (s, 3H), 3.02 (d, 1H, $J = 8.1$ Hz), 1.45 (s, 3H). LC/MS (ESI) *m/z* 559 $(M + H + 16)^+$.

1-Methyl-1-[2-methyl-6-(4-trifluoromethylbenzylamino)-2*H*-chromen-2-ylmethyl]-3-phenylthiourea (12w). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, 2H, $J = 8.1$ Hz), 7.47 (d, 2H, $J = 8.1$ Hz), 7.29−7.25 (m, 3H), 7.06−7.05 (m, 1H), 6.80−6.79 (m, 2H), 6.74−6.73 (m, 2H), 6.47−6.45 (m, 1H), 4.53 (d, 1H, $J = 8.9$ Hz), 4.37 (s, 2H), 3.67 (d, 1H, $J = 8.6$ Hz), 3.40 (d, 1H, $J = 8.6$ Hz), 3.20 (s, 3H), 2.82 (d, 1H, $J = 8.9$ Hz), 2.62 (br, 1H), 1.39 (s, 3H). LC/MS (ESI) *m/z* 514 $(M + H + 16)^+$.

1-[6-(4-Fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-1-methyl-3-(4-nitrophenyl)-thiourea (12x). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, 2H, $J = 8.9$ Hz), 7.33−7.31 (m, 2H), 6.84 (d, 2H, $J = 8.9$ Hz), 6.75 (d, 1H, $J = 8.5$ Hz), 6.70−6.69 (m, 1H), 6.63 (dd, 1H, $J = 8.5$ Hz, $J = 2.7$ Hz), 4.51 (d, 1H, $J = 8.0$ Hz), 4.26 (s, 2H), 3.68 (d, 1H, $J = 13.7$ Hz), 4.46 (d, 1H, $J = 13.7$ Hz), 3.21 (s, 3H), 3.03 (d, 1H, $J = 8.0$ Hz), 1.45 (s, 3H). LC/MS (ESI) *m/z* 509 $(M + H + 16)^+$. HRMS (EI): $[M]^+$ calcd for $C_{26}H_{25}N_4O_3F_1S_1$, 492.1631; found, 492.1628.

1-[6-(4-Fluorobenzylamino)-2-methyl-2*H*-chromen-2-ylmethyl]-1-methyl-3-phenylthiourea (12y). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.25 (m, 5H), 7.05−7.00 (m, 3H), 6.81−6.80 (m, 2H), 6.75−6.73 (m, 2H), 6.49 (m, 1H), 4.53 (d, 1H, $J = 8.8$ Hz), 4.25 (s, 2H), 3.68 (d, 1H, $J = 13.7$ Hz), 3.41 (d, 1H, $J = 13.7$ Hz), 3.20 (s, 1H), 2.83 (d, 1H, $J = 8.8$ Hz), 1.39 (s, 3H). LC/MS (ESI) *m/z* 464 $(M + H + 16)^+$.

1-Methyl-1-[2-methyl-6-(4-methylbenzylamino)-2*H*-chromen-2-ylmethyl]-3-phenylthiourea (12z). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30−7.23 (m, 5H), 7.15−7.13 (d, 2H, $J = 7.8$ Hz), 6.74 (d, 2H, $J = 8.6$ Hz), 6.50 (dd, 1H, $J = 8.5$ Hz, $J = 2.7$ Hz), 4.54 (d, 1H, $J = 8.8$ Hz), 3.67 (d, 1H, $J = 13.7$ Hz), 3.41 (d, 1H, $J = 13.7$ Hz), 3.20 (s, 3H), 2.84 (d, 1H, $J = 8.8$ Hz), 2.33 (s, 3H), 1.39 (s, 3H). LC/MS (ESI) *m/z* 461 $(M + H + 16)^+$. HRMS (EI): $[M]^+$ calcd for $C_{27}H_{29}N_3O_1S_1$, 443.2031; found, 443.2032.

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Supporting Information Available. General experimental procedures and analytical spectra (^{1}H NMR, ^{13}C NMR, and LC/MS) are given. This material is available free of charge via the Internet at http://pubs.acs.org

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