http://dx.doi.org/10.5012/bkcs.2012.33.1.128

Solid-phase Parallel Synthesis of a Novel *N*-[Alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted Amide and Amine Drug-like Libraries

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Received November 1, 2011, Accepted November 11, 2011

We report the solid-phase library construction of 222 number of a novel *N*-[alkyl sulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide **1A** and amine **1B** derivatives. The polymer-bound *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide **9** and amine **10** derivatives were obtained by first diversity generation with various acid chlorides and alkyl halides. Further reactions on the resins **9** and **10** with substituted sulfonyl chlorides produced the desired *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide **1A** and amine **1B** analogues.

Key Words : Spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl derivatives, Solid-phase parallel synthesis, Drug-like benzopyran core skeleton

Introduction

Heterocyclic compounds provide scaffolds on which pharmacophores can be arranged to yield potent and selective drugs, and a variety of heterocycles have been synthesized on solid support.[1] As a part of our research on drug discovery program, we needed to develop a facile and rapid solid-phase parallel synthesis for construction of the drug-like small molecules using heterocycles.[2] Especially, we were interested in constructing the variously substituted benzopyran library because of their broad biological activities.[3] Over several years, we have investigated many structural classes of 5-LO inhibitors with the aim of identifying orally active 5-LO (5-lipoxygenase) target as *anti*-inflammatory inhibitors. As the results, we found out a novel 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2*H*-1-benzopyran hit compound (one representative lead compound is KRH-102140 with the 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2*H*-1-benzopyran and showed good *in vitro* activity at 0.16 μm IC_{50} value)[4a] toward 5-LO target.[4] However, we didn't find out much improved hit compound by optimization process of KRH-102140 core skeleton derivatives. Therefore, our concern focused on the development of a spiro-benzopyran core skeleton to improve more active benzopyran derivatives then the KRH-2140 as shown Figure 1. As the results, herein, we report a solid-phase parallel synthesis of a novel *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide **1A** and amine **1B** derivatives that relies on BAL linker and present an chemical properties using a in silico screening.

Results and Discussion

As shown in the Scheme 1, the strategy we have developed, backbone amide linker (BAL) resin[5] **2** was selected as the polymer support since the secondary amino group, resulting from reductive amination, should be highly reactive with various alkyl halides and acid chlorides. Moreover, the final products should be readily cleaved from the support by using dilute TFA solutions.[6] In the first step of the sequence, *N*-[ethylcarbamate-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]amine resin **4** was prepared by reaction of BAL resin **2** with *N*-[ethylcarbamate-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]amine[7] **3** under reductive amination conditions ($NaBH(OAc)_3$ in DMF containing 1% acetic acid).[8] The success of this process was confirmed by the disappearance of the aldehyde carbonyl band in the ATR-FTIR (Attanuated Total Reflection-FTIR) spectrum at 1677 cm^{-1} and the appearance of the carbamate band at 1694 cm^{-1}.

In the first generation diversification step, the secondary

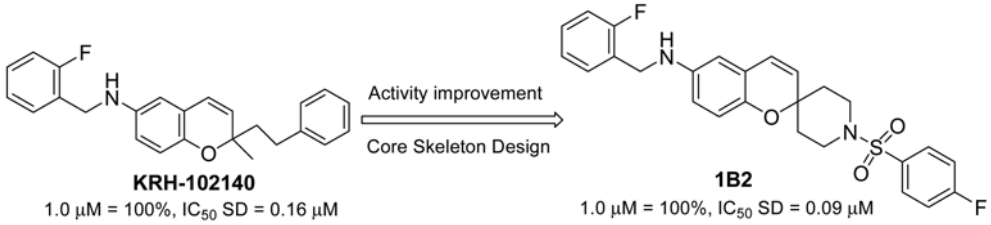


Figure 1. Design strategy for the *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] amine **1** core skeleton to improve chemical properties.

amine group in *N*-[ethylcarbamate-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]amine resin **4** was transformed into the 6-substituted amide and amine groups in *N*-[ethylcarbamate-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]substituted amide resin **5** or amine resin **6** by reactions with acid chlorides or alkyl halides in the presence of DBU (1,8-diazabicylclo[5,4,0]undec-7ene) or LiO^{t}Bu (litium-*tert*-butoxide) in DMF solution, respectively. The progress of these reactions was assessed by the appearance of characteristic bands in the ATR-FTIR spectrum (amide **5**: 1650 cm^{-1}, amine **6**: disappearance NH band about 3200 cm^{-1}). For the purpose of second generation diversity, the carbamate deprotection of the 6-substituted amide resin **5** and the 6-substituted amine resin **6** were carried out to yield the piperidines **5** and **6** by hydrolysis reaction by hydrolysis reaction in the presence of NaOH under the condition of *n*-butanol and 1,4-dioxane mixture solvent at room temperature. And then, functionalization of the secondary piperidine amine group on the resins **7** and **8** were promoted by reactions with various sulfonyl chlorides to generate respective *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide resin **9** and substituted amine resin **10** in the presence of Et_3N in DMF. Finally, the resins **9** and **10** were treated with 20% TFA in CH_2Cl_2 for 3 h to yield the desired drug-like *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide **1A** and amine **1B** derivatives. The five-step overall yields was shown in Table 1 and 2. In the Table 1, our concern focused on the introduction of various amide substituents R_1 groups on the 6-amine position of *N*-[ethylcarbamate-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]amine resin **4** with acid chlorides, such as electron donating group **1A2**, withdrawing group **1A3**. And also, we have successful proceeded various sulfonyl substituents R_3 groups on the 6-substituted amide resin **7** with various sulfonyl chlorides. Finally, we could obtained the desired drug-like *N*-[alkyl sulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide derivatives **1A** from the 6-substituted amide resin **9** with high five-step overall yields. Next, as shown in the Table 2, we tried to find out good reaction condition to introduce amine substituents R_2 on the 6-position of *N*-[ethylcarbamate-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]amine resin **4**. The LiO^{t}Bu base condition gave to the substituted amine derivatives, such as alkyl or benzyl functional groups on the *N*-[ethylcarbamate-spiro-(2*H*-1-benzopyran-2,4-piperidine)-6-yl]amine resin **4** with various alkyl halides.

The introduction of sulfonyl groups into the secondary piperidine amine group on resin **8** was proceeded under mild base condition after deprotection of the carbamate-protected

Table 1. Preparation of *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide derivatives **1A**

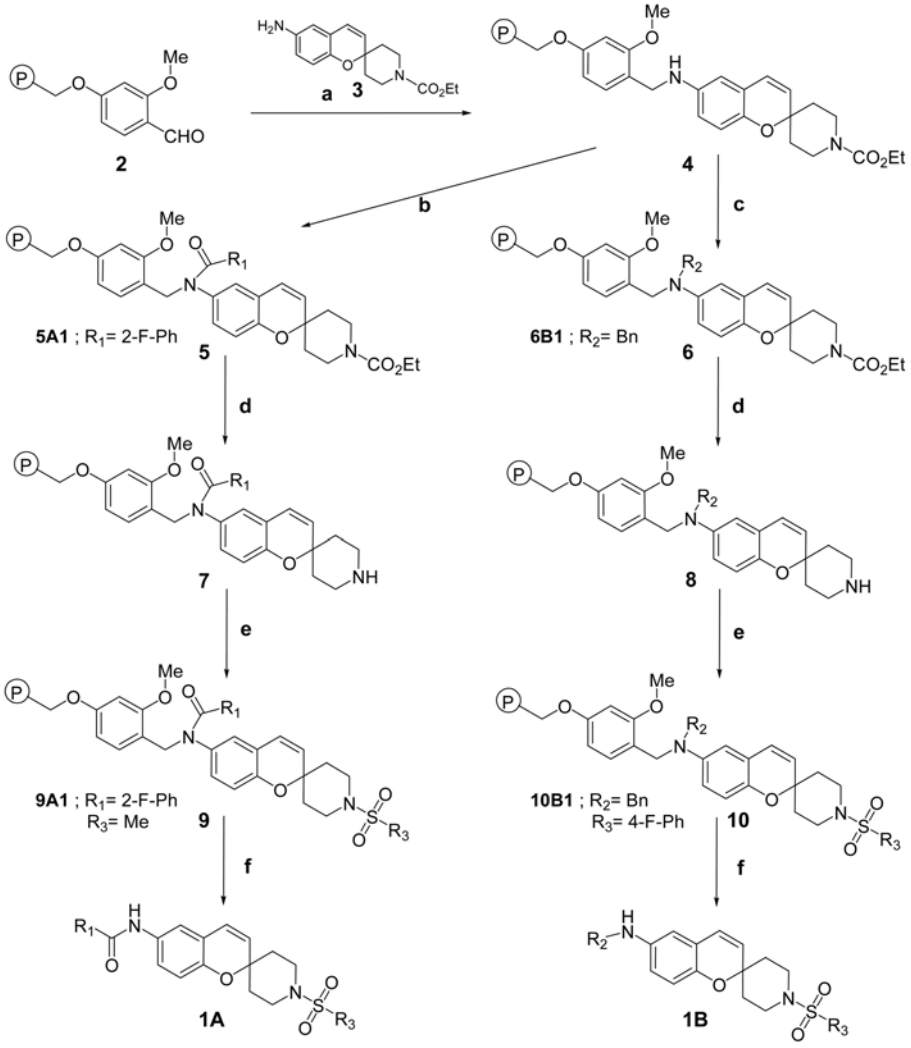
Products	R_1	R_3	Yield (%)[a]
1A1	2-F-Ph	Me	47
1A2	3-MeO-Ph	Me	38
1A3	3-NO_2-Ph	Me	45
1A4	Cyclo-Hexyl	Me	34
1A5	2-Cl-Ph	*i*-Propyl	46
1A6	2-CF_3-Ph	*i*-Propyl	42
1A7	4-CN-Ph	*i*-Propyl	41
1A8	4-MeO-Ph	*i*-Propyl	30
1A9	2-F-Ph	4-F-Ph	53
1A10	4-MeO-Ph	4-F-Ph	38
1A 11	4-Ph-Ph	4-F-Ph	32
1A12	Cyclo-Hexyl	4-F-Ph	35
1A13	2-Furanyl	4-F-Ph	27
1A14	2-F-Ph	4-MeO-Ph	41
1A15	4-NO_2-Ph	4-MeO-Ph	35
1A16	4-Ph-Ph	4-MeO-Ph	23
1A17	Cyclo-Hexyl	4-MeO-Ph	73
1A18	2-Furanyl	4-MeO-Ph	21
1A19	2-CF_3-Ph	4-Me-Ph	43
1A20	4-NO_2-Ph	4-Me-Ph	28
1A21	4-MeO-Ph	4-Me-Ph	51
1A22	4-Ph-Ph	4-Me-Ph	24
1A23	2-F-Ph	2-Thiophenyl	27
1A24	2-Cl-Ph	2-Thiophenyl	28
1A25	4-NO_2-Ph	2-Thiophenyl	23

[a]Five-step overall yield from the resin **2** (loading capacity of the resin **2** is 0.5 mmol/g).

Table 2. Preparation of *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amine derivatives **1B**

Products	R_2	R_3	Yield (%)[a]
1B1	Bn	4-F-Ph	34
1B2	2-F-Bn	4-F-Ph	45
1B3	3-F-Bn	4-F-Ph	32
1B4	4-F-Bn	4-F-Ph	47
1B5	3-Cl-Bn	4-F-Ph	34
1B6	4-Cl-Bn	4-F-Ph	41
1B7	2-NO_2-Bn	4-F-Ph	40
1B8	4-NO_2-Bn	4-F-Ph	37
1B9	4-CN-Bn	4-F-Ph	39
1B10	2-MeO-Bn	4-F-Ph	33
1B11	4-MeO-Bn	4-F-Ph	35
1B12	2-Pyridinomethyl	4-F-Ph	29
1B13	4-Pyridinomethyl	4-F-Ph	26
1B14	*n*-Propyl	4-F-Ph	29
1B15	*i*-Butyl	4-F-Ph	28
1B16	2-Thiophenemethyl	4-F-Ph	25
1B17	2-F-Bn	4-Cl-Ph	46
1B18	4-F-Bn	4-Cl-Ph	49
1B19	2-F-Bn	4-NO_2-Ph	43
1B20	4-F-Bn	4-NO_2-Ph	44
1B21	2-F-Bn	4-MeO-Ph	42
1B22	4-F-Bn	4-MeO-Ph	49
1B23	2-F-Bn	2-Thiophenyl	29
1B24	4-F-Bn	2-Thiophenyl	30
1B25	2-F-Bn	*n*-Propyl	39

[a]Five-step overall yield from the resin **2** (loading capacity of the resin **2** is 0.5 mmol/g).



Scheme 1. (a) $NaBH(OAc)_3$, 1% AcOH/DMF, rt, 24 h; (b) acid chloride, DBU, DMAP, DMF, 40 °C, 24 h; (c) alkyl halide, LiO^{t}Bu, DMF, 40 °C, 24 h; (d) NaOH (5.0 eq), *n*-butanol/1,4-dioxane, v/v, 1/3, rt, 8 h; (e) R_3-SO_2-Cl, Et_3N, DMF, rt, 12 h; (f) TFA/CH_2Cl_2, 1/4, rt, 3 h.

resin **6**. And the cleavage of the *N*-[alkylsulfonamido-spiro-(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amine resin **10** gave the desired drug-like *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amine derivatives **1B** under same reaction condition of the amide generation reaction **1A**. At this point, our effort was focused on the generation of fluorine substituent as R_1, R_2 and R_3 groups since the most of fluorine substituted derivatives appeared to show much higher inhibition activity toward 5-LO (5-lipoxygenase) in cell base assay.

The effort described above has led to the development of a novel solid-phase parallel synthetic strategy for the preparation of a broad *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide **1A** and amine **1B** libraries. Having established a flexible method for solid phase synthesis of *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide and amine derivatives, 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 which are orally bioavailable; *i.e.* they possess physiological properties that allow them to be absorbed into the gastrointestinal system. Lipinski's Rule[10] and similar formulations[11] served as guidelines for an estimation of the physicochemical properties of the synthesized 222 member *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide **1A** and amine **1B** library, which was calculated using Accord for Excel functions.[12] Of particular interest were the key bioavailability parameters such as molecular weight, lipophilicity, number of hydrogen bond donors and acceptors, number of rotatable bonds, and polar surface area. 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 values for reasonable drugs by using the commonly known Lipinski's rule of 5.

In summary, we constructed of 222 number of a novel *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-

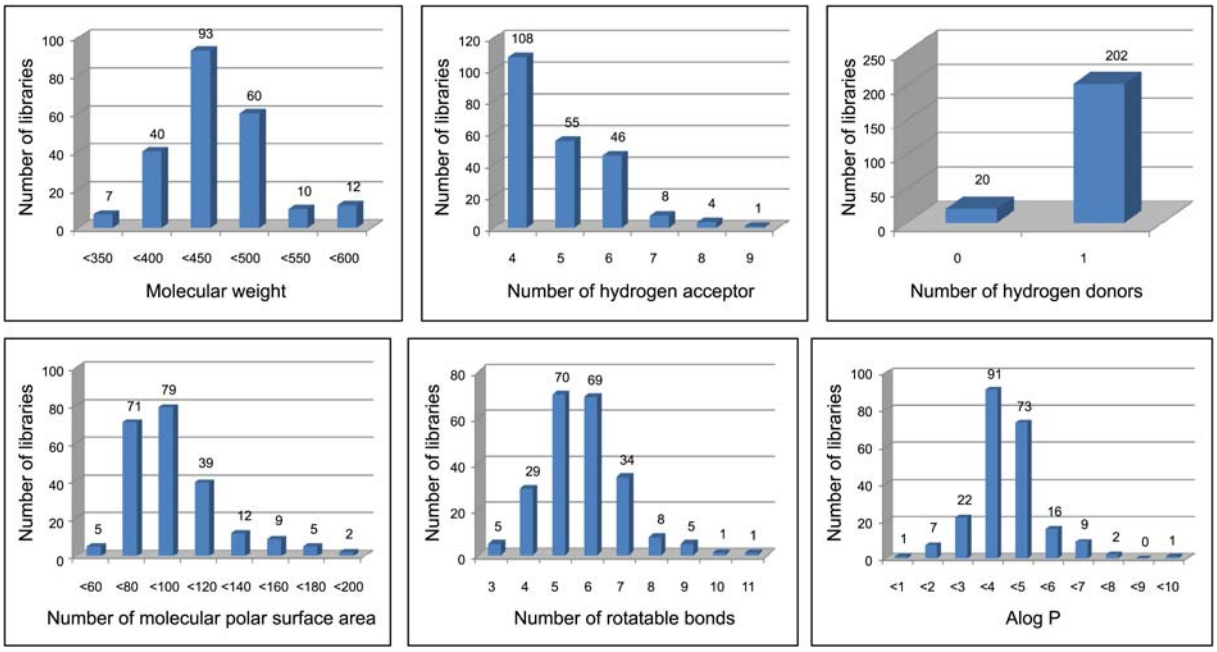


Chart 1. Represent calculated physicochemical properties of the 222 number of *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amide **9** and amine **10** derivatives.

6-yl] substituted amide **1A** and amine **1B** derivatives by solid-phase parallel synthesis with high five-step overall yields. The primary biological tests toward 5-LO targets were conducted to develop *anti*-inflammatory inhibitors. And then we found out several good hit compounds for 5-LO inhibitors, which result was applied to the Korean patent.[9] In the next plan, the selected hit *N*-[alkylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] substituted amine **1B** compounds will be subjected to *in vivo* and pharmacology analysis for the development of a novel *anti*-inflammatory drugs underlying the 5-LO mechanistic target to discovery new *anti*-inflammatory drug.

Experimental Section

General Procedures. All chemicals were reagent grade and used as purchased. Reactions were monitored by TLC analysis using Merck silica gel 60 F-254 thin layer plates. Flash column chromatography was carried out on Merck silica gel 60 (230-400 mesh). The crude products were purified by parallel chromatography using Quad3^{TM}. ^{1}H NMR spectra were recorded in d units relative to deuterated solvent as an internal reference using a Bruker 300 or 500 MHz NMR instrument. LC-MS analysis was performed on an ESI mass spectrometer with PDA detection. LC-MS area % purities of all products were determined by LC peak area analysis (XTerraMS C_{18} column, 4.6 mm × 100 mm; PDA detector at 200-400 nm; gradient, 5-95% CH_3CN/H_2O).

Preparation of Key Intermediate Polymer-bound *N*-[ethylcarbamate-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]amine 4. To a suspension of BAL resin **2** (1.0 g, 0.5 mmol, loading capacity 0.5 mmol/g) in DMF (10 mL) containing 1% acetic acid were added successively *N*-[ethylcarbamate-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] amine **3** (0.47 mg, 1.6 mmol) and $NaBH(OAc)_3$ (0.34 g, 1.6 mmol). The suspension was shaken for 24 h at room temperature under N_2 gas. The suspension was filtered and the precipitate containing the *N*-[ethylcarbamate-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] amine resin **4** was washed with DMF (× 2), DCM (× 2), and MeOH (× 2), and dried under high vacuum. FTIR (cm^{-1}): 1694.

Representative Procedure for the First Diversification Step, Formation of the *N*-[1'-methyl sulfonamido-spiro-(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-fluorophenyl Amide Resin 5A1. To a suspension of resin **4** (1.0 g, 0.5 mmol, loading capacity 0.5 mmol/g) in DMF were added 2-flurobezoyl chloride (237.8 mg, 1.5 mmol) and DBU (228.4 mg, 1.5 mmol) with cat. DMAP. The suspension was shaken for 24 h at 40 °C under N_2 gas. The suspension was filtered and the precipitate containing the 6-(2-fluorophenyl) amide resin **5A1** was washed with DMF (× 2), DCM (× 2), and MeOH (× 2), and dried under high vacuum.

Representative Procedure for the Carbamate Deprotection Step, Formation of the 6-(2-fluorophenyl) Amide Resin 7A1. To a suspension of resin **5A1** (1.0 g, 0.5 mmol, loading capacity 0.5 mmol/g) in *n*-butanol and 1,4-dioxane (1:3) mixture solvent were added NaOH (100 mg, 2.5 mmol). The suspension was shaken for 8 h at room temperature. The suspension was filtered and the precipitate containing 6-(2-fluorophenyl)amide carbamate deprotected resin **7A1** was washed with DMF (× 2), DCM (× 2), and MeOH (× 2), and dried under high vacuum.

Representative Procedure for the Second Diversification Step, Formation of the *N*-methyl sulfonyl-6-(2-fluorophenyl) Amide Resin 9A1. To a suspension of resin **7A1** (1.0 g, 0.5 mmol, loading capacity 0.5 mmol/g) in DMF

solvent were added methyl sulfonyl chloride (171.8 mg, 1.5 mmol) and Et_3N (506.0 mg, 2.5 mmol). The suspension was shaken for 12 h at room temperature. The suspension was filtered and the precipitate containing *N*-methanesulfonyl-6-(2-fluorophenyl) amide resin **9A1** was washed with DMF (× 2), DCM (× 2), and MeOH (× 2), and dried under high vacuum.

Representative Procedure for Cleavage of Resin 9A1, Preparation of *N*-[methyl sulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-fluorophenyl Amide 1A1. *N*-methanesulfonyl-6-(2-fluorophenyl) amide resin **9A1** (200 mg, 0.1 mmol) was treated with 2 mL 1:4 TFA/DCM. After being shaken at room temperature for 3 h, the mixture was filtered and the precipitate containing resin washed with DCM (3 mL × 2). The combined filtrates were concentrated in vacuous to yield *N*-[1'-methane sulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-fluorophenyl amide **1A1** (10.4 mg, five-step overall yields, 47%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (m, 1H), 8.20 (m, 1H), 7.50 (m, 1H), 7.44 (d, 1H, *J* = 2.5 Hz), 7.32 (m, 2H), 7.20 (m, 1H), 6.84 (d, 1H, *J* = 8.6 Hz), 6.44 (d, 1H, *J* = 9.7 Hz), 5.59 (d, 1H, *J* = 9.7 Hz), 3.64-3.62 (m, 2H), 3.16 (m, 2H), 2.85 (s, 3H), 2.17-2.14 (m, 2H), 1.78 (m, 2H); LC/MS (ESI) *m/z* 417 $(M+H)^+$.

***N*-[Methylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-3-methoxy Phenyl Amide 1A2.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, 2H, *J* = 6.8 Hz, *J* = 2.1 Hz), 7.61 (s, 1H, NH), 7.40 (d, 1H, *J* = 2.5 Hz), 7.27 (dd, 1H, *J* = 8.6 Hz, *J* = 2.1 Hz), 6.83 (d, 1H, *J* = 8.6 Hz), 6.43 (d, 1H, *J* = 9.7 Hz), 5.58 (d, 1H, *J* = 9.7 Hz), 3.88 (s, 3H), 3.64-3.62 (m, 2H), 3.16 (m, 2H), 2.84 (s, 3H), 2.17-2.14 (m, 2H), 1.78 (m, 2H).

***N*-[Methylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-3-nitrophenyl Amide 1A3.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, 2H, *J* = 8.6 Hz), 8.02 (d, 2H, *J* = 8.6 Hz), 7.62 (s, 1H, NH), 7.40 (d, 1H, *J* = 2.5 Hz), 7.27 (dd, 2H, *J* = 8.6 Hz, *J* = 2.5 Hz), 6.83 (d, 1H, *J* = 8.6 Hz), 6.43 (d, 1H, *J* = 9.7 Hz), 5.61 (d, 1H, *J* = 9.7 Hz), 3.64-3.62 (m, 2H), 3.17 (m, 2H), 2.85 (s, 3H), 2.17-2.14 (m, 2H), 1.78 (m, 2H).

***N*-[Methylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-cyclohexyl Amide 1A4.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, 1H, *J* = 2.7 Hz), 7.20 (dd, 1H, *J* = 8.5 Hz, *J* = 2.7 Hz), 6.95 (s, 1H, NH), 6.77 (d, 1H, *J* = 8.5 Hz), 6.39 (d, 1H, *J* = 9.8 Hz), 5.55 (d, 1H, *J* = 9.8 Hz), 3.58 (m, 2H), 3.14 (m, 2H), 2.83 (s, 3H), 2.12 (m, 2H), 1.80 (m, 2H), 1.78 (m, 3H), 1.56-1.54 (m, 4H), 1.28-1.25 (m, 4H).

***N*-[Methylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-chlorophenyl Amide 1A5.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.75 (d, 1H, *J* = 8.6 Hz), 7.44-7.37 (m, 3H), 7.30-7.28 (m, 1H), 6.84 (d, 1H, *J* = 8.6 Hz), 6.42 (d, 1H, *J* = 9.8 Hz), 5.59 (d, 1H, *J* = 9.8 Hz), 3.65 (m, 2H), 3.38 (m, 1H), 3.21 (m, 1H), 2.07 (m, 2H), 1.75 (m, 2H), 1.37 (d, 6H, *J* = 6.8 Hz).

***N*-[*i*-Propylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-trifluoro Methylphenyl Amide 1A6.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, 1H, *J* = 7.7 Hz), 7.63 (m, 2H), 7.59 (s, 1H), 7.41 (m, 1H), 7.36 (d, 1H, *J* = 2.6 Hz), 7.22 (dd, 1H, *J* = 8.6 Hz, *J* = 2.6), 6.82 (d, 1H, *J* = 8.6 Hz), 6.41 (d, 1H, *J* = 9.8 Hz), 5.58 (d, 1H, *J* = 9.8 Hz), 3.64 (m, 2H), 3.37 (m, 1H), 3.20 (m, 1H), 2.06 (m, 2H), 1.77 (m, 2H), 1.35 (d, 6H, *J* = 6.8 Hz).

***N*-[*i*-Propylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-4-cyanophenyl Amide 1A7.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, 1H, *J* = 7.7 Hz), 7.63 (m, 2H), 7.59 (s, 1H), 7.41 (m, 1H), 7.36 (d, 1H, *J* = 2.6 Hz), 7.22 (dd, 1H, *J* = 8.6 Hz, *J* = 2.6), 6.82 (d, 1H, *J* = 8.6 Hz), 6.41 (d, 1H, *J* = 9.8 Hz), 5.58 (d, 1H, *J* = 9.8 Hz), 3.64 (m, 2H), 3.37 (m, 1H), 3.20 (m, 1H), 2.06 (m, 2H), 1.77 (m, 2H), 1.35 (d, 6H, *J* = 6.8 Hz).

***N*-[*i*-Propylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-4-methoxy Phenyl Amide 1A8.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.61 (dd, 1H, *J* = 3.7 Hz, *J* = 1.0), 7.53 (dd, 1H, *J* = 5.0 Hz, *J* = 1.1), 7.36 (d, 1H, *J* = 2.5 Hz), 7.11 (dd, 1H, *J* = 4.9 Hz, *J* = 3.8), 6.81 (d, 1H, *J* = 8.6 Hz), 6.38 (d, 1H, *J* = 9.8 Hz), 5.57 (d, 1H, *J* = 9.8 Hz), 3.64 (m, 2H), 3.38 (m, 1H), 3.21 (m, 1H), 2.07 (m, 2H), 1.75 (m, 2H), 1.37 (d, 6H, *J* = 6.8 Hz).

***N*-[(4-Fluorophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-fluorophenyl Amide 1A9.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (m, 1H), 8.16 (m, 1H), 7.82 (m, 2H), 7.56 (m, 1H), 7.34-7.22 (m, 6H), 6.64 (d, 1H, *J* = 8.6 Hz), 6.40 (d, 1H, *J* = 9.8 Hz), 5.54 (d, 1H, *J* = 9.8 Hz), 3.60 (m, 2H), 2.81 (m, 2H), 2.09 (m, 2H), 1.78 (m, 2H).

***N*-[(4-Fluorophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-4-methoxyphenyl Amide 1A10.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84-7.80 (m, 4H), 7.25 (m, 3H), 7.19 (d, 1H, *J* = 8.6 Hz), 6.96 (d, 2H, *J* = 8.9 Hz), 6.63 (d, 1H, *J* = 8.6 Hz), 6.39 (d, 1H, *J* = 9.8 Hz), 5.53 (d, 1H, *J* = 9.8 Hz), 3.87 (s, 3H), 3.59 (m, 2H), 2.81 (m, 2H), 2.09 (m, 2H), 1.79 (m, 2H).

***N*-[(4-Fluorophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-4-phenyl-phenyl Amide 1A11.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.71-7.63 (m, 5H), 7.48-7.42 (m, 4H), 7.25 (m, 4H), 6.65 (d, 1H, *J* = 8.6 Hz), 6.40 (d, 1H, *J* = 9.8 Hz), 5.54 (d, 1H, *J* = 9.8 Hz), 3.60 (m, 2H), 2.81 (m, 2H), 2.10 (m, 2H), 1.78 (m, 2H).

***N*-[(4-Fluorophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-cyclohexyl Amide 1A12.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.25 (m, 2H), 7.06 (m, 2H), 6.57 (d, 1H, *J* = 8.6 Hz), 6.34 (d, 1H, *J* = 9.8 Hz), 5.50 (d, 1H, *J* = 9.8 Hz), 3.57 (m, 2H), 2.79 (m, 2H), 2.18 (m, 1H), 2.06 (m, 2H), 1.92 (m, 2H), 1.83-1.75 (m, 5H), 1.50 (m, 2H), 1.27 (m, 3H).

***N*-[(4-Fluorophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-furanyl Phenyl Amide 1A13.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.58 (dd, 1H, *J* = 3.7 Hz, *J* = 0.8 Hz), 7.53 (dd, 1H, *J* = 3.7 Hz, *J* = 2.6 Hz), 7.35 (d, 1H, *J* = 2.6 Hz), 7.25 (m, 2H), 7.20 (dd, 1H, *J* = 8.6 Hz, *J* = 2.6 Hz), 7.12 (d, 1H, *J* = 2.6 Hz), 6.63 (d, 1H, *J* = 8.6 Hz), 6.38 (d, 1H, *J* = 9.8 Hz), 5.53 (d, 1H, *J* = 9.8 Hz), 3.59 (m, 2H), 2.81 (m, 2H), 2.08 (m, 2H), 1.78 (m, 2H).

***N*-[(4-Methoxyphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-fluorophenyl Amide 1A14.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, 1H), 8.15 (m, 1H),

7.74 (dd, 2H, J = 6.9 Hz, J = 1.9 Hz), 7.42 (m, 1H), 7.30 (m, 1H), 7.25 (m, 1H), 7.11 (m, 1H), 7.03 (dd, 2H, J = 6.9 Hz, J = 1.9 Hz), 6.63 (d, 2H, J = 8.6 Hz), 6.38 (d, 2H, J = 9.6 Hz), 5.53 (d, 2H, J = 9.6 Hz), 3.91 (s, 3H), 3.56 (m, 2H), 2.80 (m, 2H), 2.07 (m, 2H), 1.77 (m, 2H).

***N*-[(4-Methoxyphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-4-nitrophenyl Amide 1A15.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, 2H, J = 8.5 Hz), 8.00 (d, 2H, J = 8.6 Hz), 7.74 (d, 2H, J = 8.5 Hz), 7.67 (s, 1H, NH), 7.36 (d, 1H, J = 2.5 Hz), 7.22 (dd, 1H, J = 8.5 Hz, J = 2.5 Hz), 7.03 (d, 2H, J = 8.6 Hz), 6.67 (d, 1H, J = 8.5 Hz), 6.39 (d, 1H, J = 9.8 Hz), 5.56 (d, 1H, J = 9.8 Hz), 3.91 (s, 3H), 3.59-3.56 (m, 2H), 2.83-2.78 (m, 2H), 2.09-2.05 (m, 2H), 1.82-1.76 (m, 2H).

***N*-[(4-Methoxyphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-4-phenyl-phenyl Amide 1A16.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, 2H, J = 8.3 Hz), 7.74 (d, 2H, J = 1.1 Hz), 7.70 (d, 2H, J = 8.3 Hz), 7.69 (s, 1H, NH), 7.64-7.62 (m, 2H), 7.48-7.46 (m, 2H), 7.41 (m, 1H), 7.40 (d, 1H, J = 2.3 Hz), 7.25 (dd, 1H, J = 8.6 Hz, J = 2.3 Hz), 7.04 (d, 2H, J = 8.7 Hz), 6.66 (d, 1H, J = 8.6 Hz), 6.40 (d, 1H, J = 9.8 Hz), 5.55 (d, 1H, J = 9.8 Hz), 3.92 (s, 3H), 3.58-3.56 (m, 2H), 2.84-2.78 (m, 2H), 2.10-2.05 (m, 2H), 1.81-1.76 (m, 2H).

***N*-[(4-Methoxyphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] cyclohexyl amide 1A17.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, 2H, J = 7.2 Hz, J = 1.8 Hz), 7.28 (d, 1H, J = 2.4 Hz), 7.08 (dd, 1H, J = 8.7 Hz, J = 2.4 Hz), 7.03 (dd, 2H, J = 7.2 Hz, J = 1.8 Hz), 6.57 (d, 1H, J = 8.7 Hz), 6.33 (d, 1H, J = 9.8 Hz), 5.50 (d, 1H, J = 9.8 Hz), 3.91 (s, 3H), 3.54 (m, 2H), 2.78 (m, 2H), 2.20 (m, 1H), 2.04 (m, 2H), 1.92 (m, 2H), 1.83-1.74 (m, 4H), 1.50 (m, 2H), 1.26 (m, 4H).

***N*-[(4-Methoxyphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-furanyl amide 1A18.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, 2H, J = 8.9 Hz), 7.58 (d, 1H, J = 1.1 Hz), 7.53 (dd, 1H, J = 5.0 Hz, J = 1.1 Hz), 7.52 (s, 1H, NH), 7.32 (d, 1H, J = 2.5 Hz), 7.19 (dd, 1H, J = 8.6 Hz, J = 2.5 Hz), 7.12 (d, 1H, J = 5.0 Hz), 7.03 (d, 2H, J = 8.9 Hz), 6.63 (d, 1H, J = 8.6 Hz), 6.37 (d, 1H, J = 9.8 Hz), 5.53(d, 1H, J = 9.8 Hz), 3.92 (s, 3H), 3.58-3.55 (m, 2H), 2.82-2.77 (m, 2H), 2.09-2.06 (m, 2H), 1.80-1.74 (m, 2H).

***N*-[(4-Methylphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-trifluoromethylphenyl amide 1A19.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75-7.59 (m, 5H), 7.38-7.32 (m, 4H), 7.16 (dd, 1H, J = 8.6 Hz, J = 2.6 Hz), 6.63 (d, 1H, J = 8.6 Hz), 6.38 (d, 1H, J = 9.8 Hz), 5.54 (d, 1H, J = 9.8 Hz), 3.57 (m, 2H), 2.80 (m, 2H), 2.48 (s, 3H), 2.07 (m, 2H), 1.78 (m, 2H).

***N*-[(4-Methylphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-4-nitro phenyl amide 1A20.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, 2H, J = 8.7 Hz), 8.00 (d, 2H, J = 8.7 Hz), 7.74 (s, 1H, NH), 7.68 (d, 2H, J = 8.2 Hz), 7.37-7.35 (m, 3H), 7.23 (dd, 1H, J = 8.6 Hz, J = 2.6 Hz), 6.65 (d, 1H, J = 8.6 Hz), 6.38 (d, 1H, J = 9.8 Hz), 5.55 (d, 1H, J = 9.8 Hz), 3.59-3.57 (m, 2H), 2.84-2.79 (m, 2H), 2.48 (s, 3H), 2.09-2.05 (m, 1H), 1.81-1.76 (m, 2H).

***N*-[(4-Methylphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-4-methoxyphenyl amide 1A21.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, 2H, J = 7.0 Hz, J = 1.7 Hz), 7.68 (d, 2H, J = 8.2 Hz), 7.62 (s, 1H), 7.36 (d, 2H, J = 8.2 Hz), 7.35 (d, 1H, J = 2.5 Hz), 7.20 (dd, 1H, J = 8.6 Hz, J = 2.5 Hz), 6.96 (dd, 2H, J = 7.0 Hz, J = 1.7 Hz), 6.62 (d, 1H, J = 8.6 Hz), 6.37 (d, 1H, J = 9.8 Hz), 5.52 (d, 1H, J = 9.8 Hz), 3.87 (s, 3H), 3.57 (m, 2H), 2.81 (m, 2H), 2.48 (s, 3H), 2.07 (m, 2H), 1.76 (m, 2H).

***N*-[(4-Methylphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-4-phenyl-phenyl amide 1A22.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, 2H, J = 8.4 Hz), 7.75 (s, 1H, NH), 7.70-7.61 (m, 4H), 7.48 (m, 3H), 7.40-7.36 (m, 5H), 7.25 (dd, 1H, J = 8.6 Hz, J = 2.6 Hz), 6.63 (d, 2H, J = 8.6 Hz), 6.38 (d, 1H, J = 9.8 Hz), 5.53 (d, 1H, J = 9.8 Hz), 3.59-3.56 (m, 2H), 2.83-2.78 (m, 2H), 2.48 (s, 3H), 2.09-2.06 (m, 2H), 1.80-1.74 (m, 2H).

***N*-[(2-Thiophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-fluoro-phenyl Amide 1A23.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (m, 1H), 8.15 (m, 1H), 7.66 (dd, 1H, J = 5.0 Hz, J = 1.3 Hz), 7.58 (dd, 1H, J = 3.8 Hz, J = 1.3 Hz), 7.49 (m, 1H), 7.41 (d, 1H, J = 2.5 Hz), 7.31-7.26 (m, 1H), 7.19 (m, 2H), 6.66 (d, 1H, J = 8.6 Hz), 6.40 (d, 1H, J = 9.8 Hz), 5.55 (d, 1H, J = 9.8 Hz), 3.63-3.60 (m, 2H), 2.92-2.87 (m, 2H), 2.13-2.11 (m, 2H), 1.84-1.77 (m, 2H).

***N*-[(2-Thiophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-2-chloro Phenyl Amide 1A24.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H, NH), 7.74 (d, 1H, J = 2.3 Hz), 7.45-7.38 (m, 4H), 7.29 (dd, 1H, J = 8.6 Hz, J = 2.3 Hz), 6.84 (d, 1H, J = 8.6 Hz), 6.43 (d, 1H, J = 9.8 Hz), 5.59 (d, 1H, J = 9.8 Hz), 3.61 (m, 2H), 3.25 (m, 2H), 2.95-2.88 (m, 2H), 2.10 (m, 2H), 1.89-1.84 (m, 2H), 1.76 (m, 2H), 1.09 (t, 3H, J = 7.5 Hz).

***N*-[(2-Thiophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-4-nitro Phenyl Amide 1A25.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, 2H, J = 8.7 Hz), 8.01 (d, 2H, J = 8.7 Hz), 7.67 (dd, 1H, J = 5.0 Hz, J = 1.3 Hz), 7.59 (dd, 1H, J = 3.8 Hz, J = 1.3 Hz), 7.36 (d, 1H, J = 2.5 Hz), 7.26 (dd, 1H, J = 8.6 Hz, J = 2.5 Hz), 7.20 (dd, 1H, J = 5.0 Hz, J = 3.8 Hz), 6.69 (d, 1H, J = 8.6 Hz), 6.41 (d, 1H, J = 9.8 Hz), 5.58 (d, 1H, J = 9.8 Hz), 3.64-3.62 (m, 2H), 2.93-2.88 (m, 2H), 2.14-2.11 (m, 2H), 1.85-1.82 (m, 2H).

Representative Procedure for the First Diversification Step, Formation of the *N*-[4-fluorophenylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] Benzyl Amine Resin 6B1. To a suspension of resin **4** (1.0 g, 0.5 mmol, loading capacity 0.5 mmol/g) in DMF were added benzyl chloride (189.9 mg, 1.5 mmol) and LiO^tBu (120.7 mg, 1.5 mmol). The suspension was shaken for 24 h at 40 °C under N_2 gas. The suspension was filtered and the precipitate containing the 6-benzyl substituted amine resin **6B1** was washed with DMF (× 2), DCM (× 2), and MeOH (× 2), and dried under high vacuum.

Representative Procedure for the Carbamate Deprotection Step, Formation of the 6-Benzyl Substituted Amine Piperidine Carbamate Deprotected Resin 8B1. To a suspension of resin **6B1** (1.0 g, 0.5 mmol, loading capacity

0.5 mmol/g) in *n*-butanol and 1,4-dioxane (1:3) mixture solvent were added NaOH (100 mg, 2.5 mmol). The suspension was shaken for 8 h at room temperature. The suspension was filtered and the precipitate containing 6-benzyl amine carbamate deprotected resin **8B1** was washed with DMF (× 2), DCM (× 2), and MeOH (× 2), and dried under high vacuum.

Representative Procedure for the Second Diversification Step, Formation of the Spiro-*N*-(4-fluorophenyl)-sulfonamido-6-benzyl amine resin 10B1. To a suspension of resin **8B1** (1.0 g, 0.5 mmol, loading capacity 0.5 mmol/g) in DMF solvent were added methyl sulfonyl chloride (171.8 mg, 1.5 mmol) and Et_3N (506.0 mg, 2.5 mmol). The suspension was shaken for 12 h at room temperature. The suspension was filtered and the precipitate containing *N*-(4-fluorophenyl)sulfonamido-6-benzyl amine resin **10B1** was washed with DMF (× 2), DCM (× 2), and MeOH (× 2), and dried under high vacuum.

Representative Procedure for Cleavage of Resin 10B1, Preparation of *N*-[4-Fluorophenyl sulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl] benzyl amine 1B1. *N*-4-fluorophenyl sulfonamido-6-substituted benzyl amide resin **10B1** (200 mg, 0.1 mmol) was treated with 2 mL 1:4 TFA/DCM. After being shaken at room temperature for 3 h, the mixture was filtered and the precipitate containing resin washed with DCM (3 mL × 2). The combined filtrates were concentrated *in vacuo* to yield *N*-[4-fluorophenylsulfonamido-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-benzyl amine **1B1** (10.4 mg, five-step overall yields, 34%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.34-7.22 (m, 7H), 6.48 (d, 1H, *J* = 8.5 Hz), 6.38 (dd, 1H, *J* = 8.5 Hz, *J* = 2.7 Hz), 6.30 (m, 2H), 5.48 (d, 1H, *J* = 9.8 Hz), 4.24 (s, 2H), 3.56 (m, 2H), 2.78 (m, 2H), 2.05 (m, 2H), 1.72 (m, 2H); LC/MS (ESI) *m/z* 463 $(M+H)^+$.

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(2-fluorobenzyl) amine 1B2.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.35 (m, 1H), 7.23 (m, 3H), 7.08 (m, 2H), 6.48 (d, 1H, *J* = 8.5 Hz), 6.40 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.32 (d, 1H, *J* = 2.8 Hz), 6.30 (d, 1H, *J* = 9.8 Hz), 5.48 (d, 1H, *J* = 9.8 Hz), 4.31 (s, 2H), 3.56 (m, 2H), 2.77 (m, 2H), 2.05 (m, 2H), 1.72 (m, 2H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(3-fluorobenzyl) amine 1B3.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.28-7.22 (m, 3H), 7.11 (d, 1H, *J* = 7.6 Hz), 7.07 (m, 1H), 6.97 (m, 1H), 6.47 (d, 1H, *J* = 8.5 Hz), 6.35 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.29 (d, 1H, *J* = 9.8 Hz), 6.28 (d, 1H, *J* = 2.8 Hz), 5.48 (d, 1H, *J* = 9.8 Hz), 4.26 (s, 2H), 3.57 (m, 2H), 2.77 (m, 2H), 2.06 (m, 2H), 1.73 (m, 2H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(4-fluorobenzyl) amine 1B4.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.30 (m, 2H), 7.24 (m, 2H), 7.00 (m, 2H), 6.49 (d, 1H, *J* = 8.5 Hz), 6.38 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.29 (m, 2H), 5.49 (d, 1H, *J* = 9.8 Hz), 4.21 (s, 2H), 3.56 (m, 2H), 2.78 (m, 2H), 2.06 (m, 2H), 1.73 (m, 2H).

***N*-[(4-Fluorophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(3-chloro benzyl) amine 1B5.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.34 (s, 1H), 7.23 (m, 5H), 6.47 (d, 1H, *J* = 8.5 Hz), 6.35 (dd, 1H, *J* = 8.5 Hz, *J* = 2.7 Hz), 6.29 (d, 1H, *J* = 9.8 Hz), 6.27 (d, 1H, *J* = 2.7 Hz), 5.49 (d, 1H, *J* = 9.8 Hz), 4.24 (s, 2H), 3.57 (m, 2H), 2.77 (m, 2H), 2.06 (m, 2H), 1.73 (m, 2H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(4-chloro benzyl) amine 1B6.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.30-7.22 (m, 6H), 6.47 (d, 1H, *J* = 8.5 Hz), 6.34 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.27 (m, 2H), 5.48 (d, 1H, *J* = 9.8 Hz), 4.22 (s, 2H), 3.56 (m, 2H), 2.77 (m, 2H), 2.06 (m, 2H), 1.73 (m, 2H).

***N*-[(4-Fluorophenyl sulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(2-nitro benzyl) amine 1B7.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (m, 1H), 7.80 (m, 2H), 7.63 (m, 1H), 7.56 (m, 1H), 7.40 (m, 1H), 7.24 (m, 2H), 6.46 (d, 1H, *J* = 8.5 Hz), 6.32 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.26 (d, 1H, *J* = 9.8 Hz), 6.23 (d, 1H, *J* = 2.8 Hz), 5.48 (d, 1H, *J* = 9.8 Hz), 4.63 (s, 2H), 3.56 (m, 2H), 2.77 (m, 2H), 2.05 (m, 2H), 1.72 (m, 2H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(4-nitro benzyl) amine 1B8.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, 2H, *J* = 8.4 Hz), 7.80 (m, 2H), 7.50 (d, 2H, *J* = 8.4 Hz), 7.25 (m, 2H), 6.47 (d, 1H, *J* = 8.5 Hz), 6.32 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.26 (d, 1H, *J* = 9.8 Hz), 6.23 (d, 1H, *J* = 2.8 Hz), 5.49 (d, 1H, *J* = 9.8 Hz), 4.39 (s, 2H), 3.56 (m, 2H), 2.77 (m, 2H), 2.05 (m, 2H), 1.73 (m, 2H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidin)-6-yl]-(4-cyano benzyl) amine 1B9.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.61 (d, 2H, *J* = 8.2 Hz), 7.45 (d, 2H, *J* = 8.2 Hz), 7.24 (m, 2H), 6.47 (d, 1H, *J* = 8.5 Hz), 6.31 (dd, 1H, *J* = 8.5 Hz, *J* = 2.7 Hz), 6.27 (d, 1H, *J* = 9.8 Hz), 6.23 (d, 1H, *J* = 2.7 Hz), 5.49 (d, 1H, *J* = 9.8 Hz), 4.34 (s, 2H), 3.56 (m, 2H), 2.78 (m, 2H), 2.05 (m, 2H), 1.74 (m, 2H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(2-methoxybenzyl) amine 1B10.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.24 (m, 4H), 6.88 (m, 2H), 6.46 (d, 1H, *J* = 8.5 Hz), 6.40 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.33 (d, 1H, *J* = 2.8 Hz), 6.30 (d, 1H, *J* = 9.8 Hz), 5.47 (d, 1H, *J* = 9.8 Hz), 4.24 (s, 2H), 3.85 (s, 3H), 3.56 (m, 2H), 2.77 (m, 2H), 2.05 (m, 2H), 1.72 (m, 2H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(4-methoxybenzyl) amine 1B11.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.25 (m, 4H), 6.86 (dd, 2H, *J* = 8.7 Hz, *J* = 1.9 Hz), 6.48 (d, 1H, *J* = 8.5 Hz), 6.38 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.30 (m, 2H), 5.48 (d, 1H, J = 9.8 Hz), 4.16 (s, 2H), 3.79 (s, 3H), 3.56 (m, 2H), 2.78 (m, 2H), 2.06 (m, 2H), 1.72 (m, 2H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(2-pyridinomethyl) amine 1B12.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61(d, 1H, *J* = 4.8 Hz), 7.82-7.79 (m, 2H), 7.70 (m, 1H), 7.39 (d, 1H, *J* = 7.8 Hz), 7.27-7.23 (m, 3H), 6.48 (d, 1H, *J* = 8.5 Hz), 6.43 (dd, 1H, *J* = 8.5 Hz, *J* = 2.7 Hz), 6.34 (d, 1H, *J* = 2.7 Hz), 6.30 (d, 1H, *J* = 9.8 Hz), 5.48 (d, 1H, *J* = 9.8 Hz), 4.44 (s, 2H), 3.58-3.55 (m,

2H), 2.80-2.75 (m, 2H), 2.07-2.04 (m, 2H), 1.76-1.69 (m, 2H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(4-pyridinomethyl) amine 1B13.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, 2H, *J* = 5.7 Hz), 7.82-7.79 (m, 2H), 7.34 (d, 2H, *J* = 5.7 Hz), 7.25-7.22 (m, 2H), 6.47 (d, 1H, *J* = 8.5 Hz), 6.30 (dd, 1H, *J* = 8.5 Hz, *J* = 2.7 Hz), 6.26 (d, 1H, *J* = 9.8 Hz), 6.22 (d, 1H, *J* = 2.7 Hz), 5.49 (d, 1H, *J* = 9.8 Hz), 4.33 (s, 2H), 3.58-3.56 (m, 2H), 2.80-2.75 (m, 2H), 2.07-2.04 (m, 2H), 1.76-1.70 (m, 2H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(*n*-propyl) amine 1B14.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.24 (m, 2H), 6.49 (d, 1H, *J* = 8.5 Hz), 6.39 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.32 (m, 2H), 5.49 (d, 1H, *J* = 9.8 Hz), 3.57 (m, 2H), 3.00 (t, 2H, *J* = 7.2 Hz), 2.78 (m, 2H), 2.06 (m, 2H), 1.73 (m, 2H), 1.60 (m, 2H), 0.97 (t, 3H, *J* = 7.4 Hz).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(*i*-butyl) amine 1B15.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.25 (m, 2H), 6.48 (d, 1H, *J* = 8.5 Hz), 6.35-6.30 (m, 3H), 5.49 (d, 1H, *J* = 9.8 Hz), 3.57 (m, 2H), 2.85 (d, 2H, *J* = 6.8 Hz), 2.78 (m, 2H), 2.06 (m, 2H), 1.80 (m, 1H), 1.73 (m, 2H), 0.96 (s, 3H), 0.95 (s, 3H).

***N*-[(4-Fluorophenylsulfonamide)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(2-thiphenemethyl) amine 1B16.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.25 (m, 2H), 7.19 (dd, 1H, *J* = 5.0 Hz, *J* = 1.0 Hz), 6.97 (d, 1H, *J* = 1.0 Hz), 6.95 (d, 1H, *J* = 5.0 Hz), 6.48 (d, 1H, *J* = 8.5 Hz), 6.43 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.35 (d, 1H, *J* = 2.8 Hz), 6.31 (d, 1H, *J* = 9.8 Hz), 5.49 (d, 1H, *J* = 9.8 Hz), 4.43 (s, 2H), 3.57 (m, 2H), 2.78 (m, 2H), 2.06 (m, 2H), 1.73 (m, 2H).

***N*-[(4-Chlorophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(2-fluorobenzyl) amine 1B17.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, 2H, *J* = 6.8 Hz, *J* = 1.8 Hz), 7.54 (dd, 2H, *J* = 6.8 Hz, *J* = 1.8 Hz), 7.34 (m, 1H), 7.26 (m, 1H), 7.08-7.06 (m, 2H), 6.49 (d, 1H, *J* = 8.5 Hz), 6.39 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.31 (d, 1H, *J* = 2.8 Hz), 6.30 (d, 1H, *J* = 9.7 Hz), 5.48 (d, 1H, *J* = 9.7 Hz), 4.32 (s, 2H), 3.58-3.56 (m, 2H), 2.81-2.76 (m, 2H), 2.07-2.05 (m, 2H), 1.75-1.69 (m, 2H).

***N*-[(4-Chlorophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(4-fluorobenzyl) amine 1B18.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, 2H, *J* = 6.8 Hz, *J* = 1.8 Hz), 7.54 (dd, 2H, *J* = 6.8 Hz, *J* = 1.8 Hz), 7.31-7.29 (m, 2H), 7.03-6.99 (m, 2H), 6.50 (d, 1H, *J* = 8.5 Hz), 6.39 (dd, 2H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.31-6.29 (m, 2H), 5.49 (d, 1H, *J* = 9.7 Hz), 4.21 (s, 2H), 3.58-3.56 (m, 2H), 2.81-2.76 (m, 2H), 2.07-2.05 (m, 2H), 1.76-1.70 (m, 2H).

***N*-[(4-Nitrophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(2-fluoro benzyl) amine 1B19.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, 2H, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.97 (dd, 2H, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.40 (m, 1H), 7.26 (m, 1H), 7.10-7.04 (m, 2H), 6.47 (dd, 2H, *J* = 8.5 Hz), 6.46 (d, 2H, *J* = 8.5 Hz), 6.38 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.31 (d, 1H, *J* = 3.2 Hz), 6.30 (d, 1H, *J* = 9.7 Hz), 5.48 (d, 1H, *J* = 9.7 Hz), 4.31 (s, 2H), 3.65-3.63 (m, 2H), 2.86-2.80 (m, 2H), 2.10-2.07 (m, 2H), 1.76-1.70 (m, 2H).

***N*-[(4-Nitrophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(4-fluoro benzyl) amine 1B20.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, 2H, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.97 (dd, 2H, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.31-7.26 (m, 2H), 7.02-6.99 (m, 2H), 6.48-6.46 (d, 1H, *J* = 8.5 Hz), 6.36 (dd, 2H, *J* = 2.8 Hz), 6.30-6.29 (m, 2H), 5.48 (d, 1H, *J* = 9.7 Hz), 4.21 (s, 2H), 3.65-3.63 (m, 2H), 2.86-2.81 (m, 2H), 2.10-2.07 (m, 2H), 1.77-1.70 (m, 2H).

***N*-[(4-Methoxyphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(2-fluorobenzyl) amine 1B21.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, 2H, *J* = 6.9 Hz, *J* = 2.1 Hz), 7.78 (m, 1H), 7.24 (m, 1H), 7.07 (m, 2H), 7.02 (dd, 2H, *J* = 6.9 Hz, *J* = 2.1 Hz), 6.48 (d, 1H, *J* = 9.8 Hz), 6.39 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.31 (d, 1H, *J* = 2.8 Hz), 6.29 (d, 1H, *J* = 9.8 Hz), 5.48 (d, 1H, *J* = 9.8 Hz), 4.31 (s, 2H), 3.90 (s, 3H), 3.53 (m, 2H), 2.77 (m, 2H), 2.04 (m, 2H), 1.72 (m, 2H).

***N*-[(4-Methoxyphenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(4-fluorobenzyl) amine 1B22.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, 2H, *J* = 6.9 Hz, *J* = 2.1 Hz), 7.30 (m, 2H), 7.03-6.99 (m, 4H), 6.48 (d, 1H, *J* = 8.5 Hz), 6.37 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.28 (m, 2H), 5.49 (d, 1H, *J* = 9.8 Hz), 4.21 (s, 2H), 3.90 (s, 3H), 3.53 (m, 2H), 2.77 (m, 2H), 2.04 (m, 2H), 1.73 (m, 2H).

***N*-[(2-Thiophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(2-fluoro benzyl) amine 1B23.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, 1H, *J* = 5.0 Hz, *J* = 1.3 Hz), 7.56 (dd, 1H, *J* = 3.8 Hz, *J* = 1.3 Hz), 7.33 (m, 1H), 7.25 (m, 1H), 7.17 (dd, 1H, *J* = 5.0 Hz, *J* = 3.8 Hz), 7.08 (m, 2H), 6.50 (d, 1H, *J* = 8.5 Hz), 6.41 (dd, 1H, *J* = 8.5 Hz, *J* = 2.4 Hz), 6.32 (d, 1H, *J* = 2.4 Hz), 6.30 (d, 1H, *J* = 9.8 Hz), 5.49 (d, 1H, *J* = 9.8 Hz), 4.32 (s, 2H), 3.59-3.57 (m, 2H), 2.89-2.84 (m, 2H), 2.09-2.07 (m, 2H), 1.78-1.72 (m, 2H).

***N*-[(2-Thiophenylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(4-fluoro benzyl) amine 1B24.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, 1H, *J* = 5.0 Hz, *J* = 1.3 Hz), 7.56 (dd, 1H, *J* = 3.7 Hz, *J* = 1.3 Hz), 7.30 (m, 2H), 7.17 (dd, 1H, *J* = 5.0 Hz, *J* = 3.7 Hz), 7.01 (m, 2H), 6.50 (d, 1H, *J* = 8.5 Hz), 6.36 (dd, 1H, *J* = 8.5 Hz, *J* = 2.8 Hz), 6.31 (d, 1H, *J* = 9.8 Hz), 6.29 (d, 1H, *J* = 2.8 Hz), 5.50 (d, 1H, *J* = 9.8 Hz), 4.23 (s, 2H), 3.58 (m, 2H), 2.86 (m, 2H), 2.08 (m, 2H), 1.75 (m, 2H).

***N*-[(*n*-Propylsulfonamido)-spiro(2*H*-1-benzopyran-2,4-piperidine)-6-yl]-(2-fluoro benzyl) amine 1B25.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 1H), 7.26 (m, 1H), 7.10-7.08 (m, 2H), 6.68 (d, 1H, *J* = 8.5 Hz), 6.46 (dd, 1H, *J* = 8.5 Hz, *J* = 2.7 Hz), 6.35 (d, 1H, *J* = 2.7 Hz), 6.32 (d, 1H, *J* = 9.8 Hz), 5.52 (d, 1H, *J* = 9.8 Hz), 4.34 (s, 2H), 3.61-3.58 (m, 2H), 3.26-3.21 (m, 2H), 2.93-2.90 (m, 2H), 2.10-2.07 (m, 2H), 1.90-1.85 (m, 2H), 1.70 (m, 2H), 1.08 (t, 3H, *J* = 7.5 Hz).

Acknowledgments. This research was supported by a grant (CBM34-B1000-01-00-01) from the Center for Biological Modulators of the 21st Century Frontier R&D and the National R&D Program for Cancer Control (grant number 1020050), and the Ministry of Knowledge and Economy, Korea.

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