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Stereoselective Synthesis of Hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] Scaffolds through an Intramolecular Prins Cascade Process

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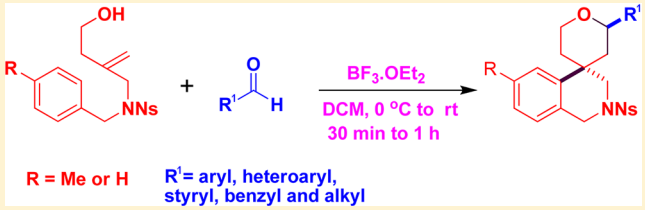
Supporting Information

ABSTRACT: A novel tandem cyclization strategy has been developed for the synthesis of hexahydro-1*H*-spiro-[isoquinoline-4,4′-pyran] derivatives through the condensation of 3-((benzylamino)methyl)but-3-en-1-ol with aldehydes using $BF_3{\cdot}OEt_2$. The reaction proceeds in a highly stereoselective manner, leading to a single diastereoisomer. This approach is a simple and efficient alternative for the synthesis of pharmacologically important spiroisoquinoline scaffolds.



The design and synthesis of spirocycles has received considerable attention among the scientific community due to their diverse molecular architecture and a wide range of biological activities. They are key components of various natural products[1] and molecules displaying potent biological activities.[2] Moreover, the inherent rigidity of these structures makes them ideal for the construction of chiral ligands such as the spirobisoxozoline, spinol, sprix, spirop, and spinol-derived phosphoric acids, which have been used successfully for various enantioselective transformations.[3] Owing to their complex structure and well-defined three-dimensional spatial arrangement, they exhibit specific action with biological receptors and enzymes.[4] The above properties make them attractive synthetic targets.[5] In particular, the spiroisoquinoline and its derivatives are known to exhibit a broad spectrum of biological activities such as antiarrhythmic, antidepressant, stimulant effect on respiration, analgesic, and cardiotonic behavior (Figure 1).[6]

Furthermore, tetrahydroisoquinolines are privileged structures in medicinal chemistry and are prevalent in a large number of therapeutic agents[7] and naturally occurring molecules.[8] However, a few methods are reported for the synthesis of spirohexahydroisoquinoline derivatives;[9] hence there is a great demand for the development of novel synthetic strategies for the stereoselective construction of spirocycles.

The "Prins cyclization" has been extensively used as a powerful strategy for the stereoselective construction of the tetrahydropyran ring, which is often found in many natural products as a core structure.[10] In particular, an intramolecular Prins cyclization is a versatile strategy for the stereoselective synthesis of fused and bridged heterocycles.[11,12] Though this strategy has been effectively applied to the synthesis of biologically active molecules,[13] the utility of this tandem process has not yet been explored for the synthesis of spiroisoquinoline derivatives from a readily accessible *N*-benzyl-tethered homoallylic alcohol.

Following our interest in Prins and its related cyclizations,[14,15] we herein report a novel strategy for the synthesis of hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] derivatives through a cascade of Prins/Friedel−Craft reaction. The requisite **4** homoallyl alcohol was prepared as shown in Scheme 1. Conjugated aldehyde **1**, which was prepared using the literature procedure,[16] was reduced under Luche reduction conditions to produce the allyl alcohol **2**. Coupling of allyl alcohol **2** with *N*-nosyl benzylamine under Mitsunobu conditions followed by desilylation with TBAF gave the desired homoallyl alcohol **4**.

As shown in Table 1, we performed the reaction of 3-((benzylamino)methyl)but-3-en-1-ol **4a** with benzaldehyde in the presence of various Lewis and Bronsted acids in different solvents at different temperatures. Lewis acids such as $In(OTf)_3$, $Sc(OTf)_3$, $TiCl_4$, and $SnCl_4$ gave the product in low to moderate yields. Interestingly, the use of 1.2 equiv of $BF_3{\cdot}OEt_2$ gave product in 95% yield with excellent selectivity. Though the reaction proceeds at 0 °C, it requires a long reaction time for completion. In addition, TMSOTf was also found to be equally effective for this conversion. On the other hand, Bronsted acids such as *p*-toluenesulfonic acid and camphorsulfonic acid were ineffective even after prolonged reaction time and at elevated temperature. Among all the acids tested, $BF_3{\cdot}OEt_2$ gave the best results in terms of time and conversion. It was observed that the reaction becomes sluggish when decreasing the amount of Lewis acid. Of various solvents, DCM was found to be the best for this conversion.

The reaction was further investigated using various aldehydes having diverse electronic effects on the aromatic ring. In most cases, the products were obtained in good yields and high purity without any side products. It is noteworthy to mention that a wide range of functional groups are well-tolerated under these reaction conditions (Table 2). The substituents present on the aromatic ring had a little effect on the conversion. It was observed that aromatic aldehydes

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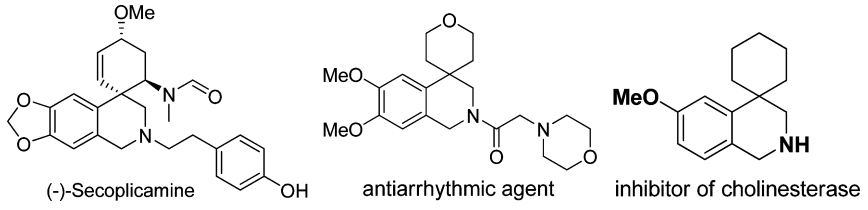


Figure 1. Representative examples of biologically active spirotetrahydroisoquinolines.

Scheme 1. Preparation of Starting Material 4

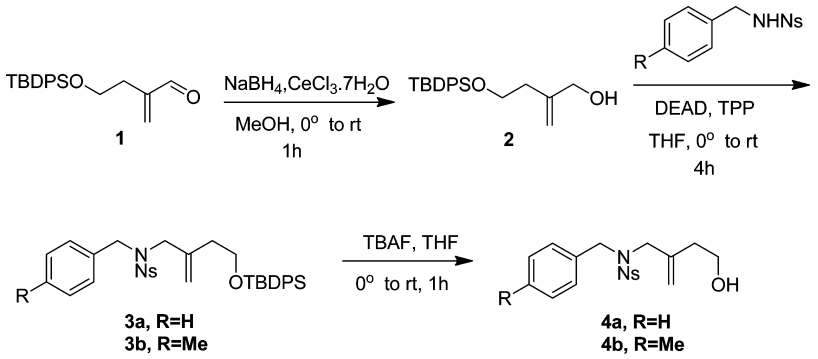
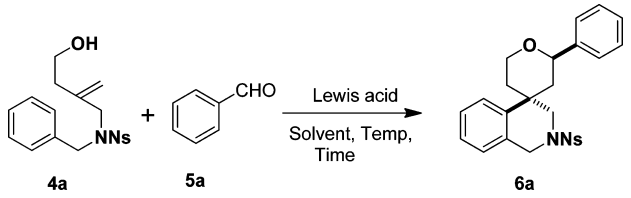


Table 1. Optimization of the Reaction Conditions

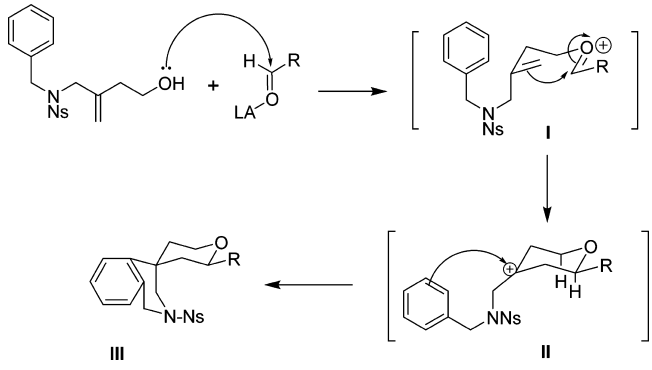


entry	Lewis/Bronsted acid	equiv	solvent	temp (°C)	time (h)	yield (%)[a]
a	*p*-TSA	1	DCE	80	15	20
b	CSA	1	DCE	80	16	15
c	$In(OTf)_3$	1	DCM	rt	16	60
d	$Sc(OTf)_3$	1	DCM	rt	10	65
e	$SnCl_4$	1	DCM	0	10	40
f	$TiCl_4$	1	DCM	0	10	50
g	$InCl_3$	1	DCM	0	10	45
h	$BF_3{\cdot}OEt_2$	1.2	DCM	0	8	80
i	$BF_3{\cdot}OEt_2$	1.2	DCM	rt	1	95
j	$BF_3{\cdot}OEt_2$	1.2	THF	rt	10	20
k	$BF_3{\cdot}OEt_2$	1.2	benzene	rt	10	35
l	$BF_3{\cdot}OEt_2$	1.2	AcCN	rt	10	
m	TMSOTf	1.2	DCM	rt	2	90

[a]Yield refers to pure products after column chromatography.

bearing either electron-donating or electron-withdrawing substituents gave the products in relatively lower yields than the corresponding halogenated or alkyl-substituted aromatic aldehydes. Furthermore, this method works well even with acid-sensitive substrates such as phenyl acetaldehyde and cinnamaldehyde (Table 2, entries j and l) and sterically hindered 1-naphthaldehyde (Table 2, entry i). The scope of this method is also demonstrated by performing the reaction with aliphatic aldehydes (Table 2, entries k and x) and heterocyclic aldehyde, such as thiophene-2-carboxaldehyde (Table 2, entry e). The stereochemistry of **6b** was ascertained based on X-ray crystallography.[17]

Scheme 2. Plausible Reaction Mechanism



On the basis of our previous works on Prins and related cyclizations, we proposed a plausible reaction mechanism in Scheme 2. We assume that the reaction proceeds through the formation of oxocarbenium ion **I**, which is formed from the condensation of aldehyde with *N*-benzyl-tethered homoallylic alcohol under acidic conditions. The resulting oxocarbenium ion is attacked by an internal olefin leading to the formation of a tertiary carbocation **II**, which is subsequently trapped by a tethered aryl ring leading to the formation of a spiropyrano-hexahydroisoquinoline **III** as depicted in Scheme 2. The observed diastereoselectivity is assumed to originate from a favorable trapping of the carbocation from a less hindered equatorial side in order to overcome unfavorable 1,3-diaxial interactions.

In summary, we have developed a novel bicyclization strategy for the synthesis of hexahydro-1*H*-spiroisoquinoline-4,4′-pyran derivatives through the coupling of 3-((benzylamino)methyl)-but-3-en-1-ol with aldehydes. This method is highly diastereoselective, affording the corresponding spiroisoquinolines in good to excellent yields. This methodology provides a direct access to pharmaceutically interesting spirocycles, which are reported to show potent antiarrhythmic activity, CNS activity,

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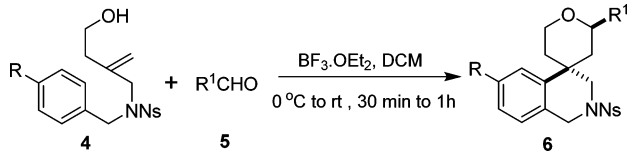
Table 2. Preparation of Hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] Scaffolds through a Prins Cascade Process



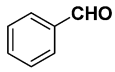
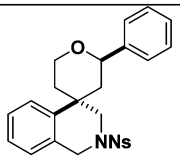
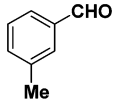
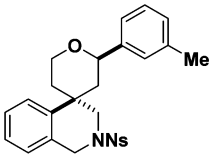
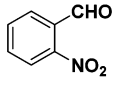
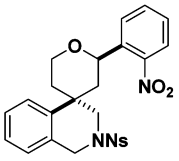
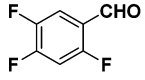
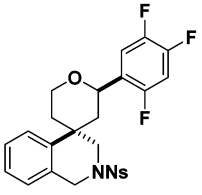
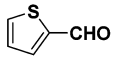
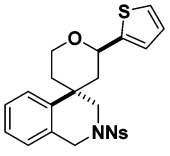
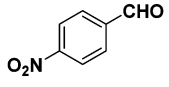
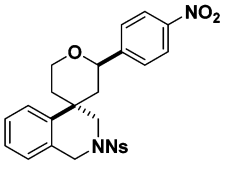
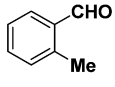
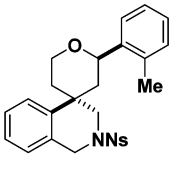
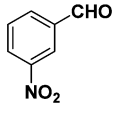
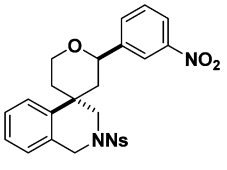
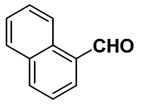
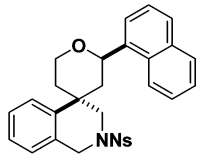
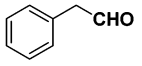
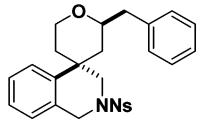
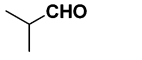
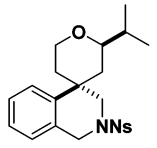
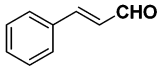
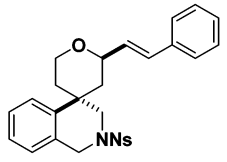
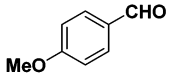
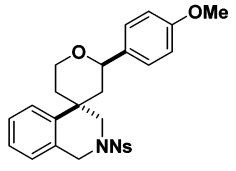
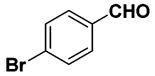
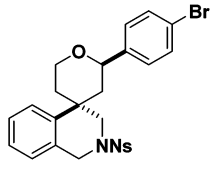
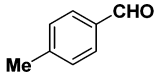
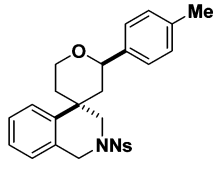
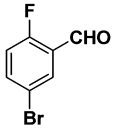
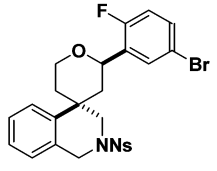
Entry	Aldehyde (**5**)	Product (**6**)	Yield(%)[a]
a			95
b			92
c			85
d			94
e			75
f			85
g			95
h			88
i			90
j			80
k			75
l			88
m			80
n			98
o			96
p			90

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Table 2. continued

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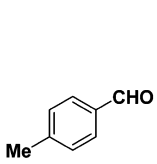
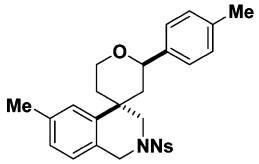
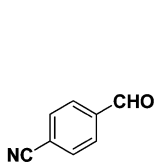
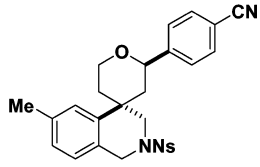
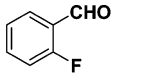
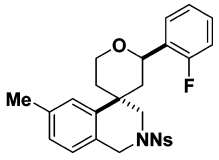
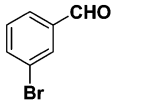
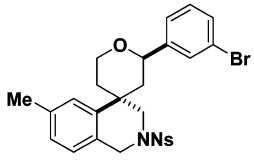
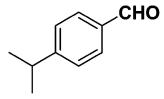
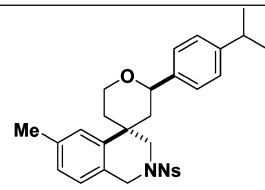
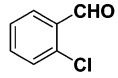
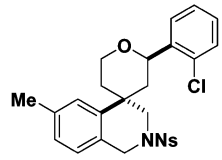
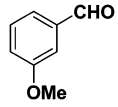
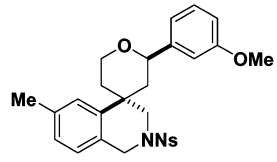
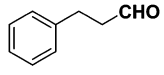
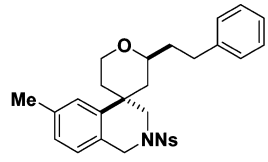
q			93
r			97
s			98
t			94
u			95
v			94
w			82
x			80

[a]Yields refer to the pure products after column chromatography.

stimulant effect on respiration, analgesic activity, and cardiotonic behavior.

EXPERIMENTAL SECTION

General. All solvents were dried according to standard literature procedures. Reactions were performed in oven-dried round-bottom flasks, and the flasks were fitted with rubber septa; the reactions were conducted under a nitrogen atmosphere. Glass syringes were used to transfer solvents. Crude products were purified by column chromatography on silica gel 60−120 or 100−200 mesh. Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapors and/or by exposure to methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on a rotary evaporator at 35−40 °C. IR spectra were recorded on a FT-IR spectrometer. ^{1}H and ^{13}C NMR (proton-decoupled) spectra were recorded in $CDCl_3$ solvent on 200, 300, 400, or 500 MHz NMR spectrometers. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (J) are quoted in hertz (Hz). Mass spectra were recorded on a mass spectrometer by electrospray ionization (ESI) or an atmospheric pressure chemical ionization (APCI) technique.

Typical Procedure for Prins Spirocyclization. To a mixture of *N*-benzyl-*N*-(4-hydroxy-2-methylenebutyl)-2-nitrobenzenesulfonamide (0.25 mmol) and benzaldehyde (0.3 mmol) in anhydrous DCM (5 mL) was added $BF_3{\cdot}OEt_2$ (1.2 equiv) at 0 °C. The resulting mixture was warmed to rt and allowed to stir at the same temperature for the specified time (Table 2). After completion of the reaction, the reaction mixture was partitioned between $NaHCO_3$ solution (5 mL) and dichloromethane (2 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The resulting crude product was purified by silica gel column chromatography (100−200 mesh) using an ethyl acetate/hexane gradient mixture to afford the pure product **6a** (Table 2, entry a).

2-(2-Nitrophenylsulfonyl)-2′-phenyl-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6a): White solid; yield 110 mg, 95%; mp 170−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−8.09 (m, 1H), 7.78−7.72 (m, 2H), 7.69−7.65 (m, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.41−7.36 (m, 2H), 7.34−7.30 (m, 2H), 7.28−7.21 (m, 2H), 7.18 (t, J = 7.1 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 4.74 (dd, J = 2.7, 10.6 Hz, 1H), 4.53 (ABq, J = 15.1 Hz, 2H), 4.14 (dd, J = 4.5, 12.3 Hz, 1H), 4.01−3.94 (m, 2H), 3.67 (d, J = 12.9 Hz, 1H), 2.31 (td, J = 5.1, 13.5 Hz, 1H), 2.05−1.94 (m, 2H), 1.69 (d, J = 13.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 142.3, 141.1, 133.8, 131.6, 131.1, 130.8, 128.2, 127.4, 127.3, 126.6, 126.2, 125.8, 125.5, 124.1, 74.9, 64.0, 49.1, 47.9, 43.1, 37.5, 34.2; MS-ESI m/z 465.0 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{25}H_{24}O_5N_2NaS$ $[M + Na]^+$ 487.1287, found 487.1292.

2-(2-Nitrophenylsulfonyl)-2′-*m*-tolyl-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6b): White solid; yield 109 mg, 92%; mp 169−171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15−8.07 (m, 1H), 7.80−7.72 (m, 2H), 7.70−7.63 (m, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.30−7.13 (m, 5H), 7.10−7.02 (m, 2H), 4.70 (dd, J = 5.2, 8.3 Hz, 1H), 4.53 (ABq, J = 15.1 Hz, 2H), 4.14 (dd, J = 4.5, 12.0 Hz, 1H), 4.02−3.89 (m, 2H), 3.70 (d, J = 12.8 Hz, 1H), 2.34 (s, 3H), 2.32−2.23 (m, 1H), 2.03−1.95 (m, 2H), 1.70 (d, J = 13.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 142.2, 141.2, 137.9, 133.8, 131.6, 131.2, 130.9, 130.8, 128.1, 128.1, 127.4, 126.6, 126.2, 125.9, 124.1, 122.7, 75.0, 64.1, 49.2, 47.9, 43.0, 37.6, 34.4, 21.4; MS-ESI m/z 479 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{26}H_{26}O_5N_2NaS$ $[M + Na]^+$ 501.1457, found 501.1457.

2′-(2-Nitrophenyl)-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6c): White solid; yield 108 mg, 85%; mp 105−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11−8.08 (m, 1H), 7.99−7.91 (m, 2H), 7.81−7.74 (m, 2H), 7.71−7.66 (m, 2H), 7.46−7.41 (m, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.25−7.17 (m, 2H), 7.09 (d, J = 7.3 Hz, 1H), 5.32 (d, J = 10.2 Hz, 1H), 4.78 (d, J = 15.1 Hz, 1H), 4.63 (d, J = 12.9 Hz, 1H), 4.31 (d, J = 15.1 Hz, 1H), 4.14 (dd, J = 4.8, 12.8 Hz, 1H), 4.06 (td, J = 2.2, 12.3 Hz, 1H), 3.20

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(d, J = 12.3 Hz, 1H), 2.22−2.16 (m, 1H), 2.09−2.03 (m, 1H), 2.01−1.94 (m, 2H); ^{13}C NMR δ (125 MHz, $CDCl_3$): 148.7, 146.9, 140.8, 138.2, 133.8, 133.7, 131.6, 130.8, 130.6, 128.0, 127.9, 127.4, 126.6, 126.3, 125.8, 124.4, 124.1, 71.2, 64.6, 48.8, 48.2, 42.1, 37.8, 34.9; MS-ESI m/z 532.0 $[M + Na]^+$; HRMS (Orbitrap ESI) calcd for $C_{25}H_{23}O_7N_3NaS$ $[M + Na]^+$ 532.1143, found 532.1144.

2-(2-Nitrophenylsulfonyl)-2′-(2,4,5-trifluorophenyl)-2,2′,3,-3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6d): White solid; yield 121 mg, 94%; mp 190−192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13−8.09 (m, 1H), 7.79−7.75 (m, 1H), 7.69−7.65 (m, 1H), 7.43−7.36 (m, 2H), 7.28−7.24 (m, 1H), 7.20 (td, J = 1.0, 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.89−6.83 (m, 1H), 4.94 (dd, J = 4.1, 9.3 Hz, 1H), 4.51 (ABq, J = 15.1 Hz, 2H), 4.12 (dd, J = 4.4, 12.3 Hz, 1H), 3.99 (td, J = 2.1, 12.6 Hz, 1H), 3.94 (d, J = 12.9 Hz, 1H), 3.71 (d, J = 12.9 Hz, 1H), 2.19 (td, J = 5.3, 13.5 Hz, 1H), 2.00−1.92 (m, 2H), 1.80 (d, J = 14.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 154.9, 153.0, 150.1, 150.0, 149.9, 148.6, 148.1, 148.0, 147.9, 146.0, 145.9, 140.8, 133.9, 131.6, 130.9, 127.5, 126.7, 126.3, 125.8, 124.2, 115.3, 115.2, 115.1, 105.4, 105.2, 108.1, 105.0, 68.4, 64.2, 48.9, 47.9, 41.5, 37.4, 34.4; MS-ESI m/z 519 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{25}H_{22}O_5N_2F_3S$ $[M + Na]^+$ 519.1199Found: 519.1199.

2-(2-Nitrophenylsulfonyl)-2′-(thiophen-2-yl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6e): White solid; yield 88 mg, 75%; mp 150−152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−8.08 (m, 1H), 7.77−7.72 (m, 2H), 7.68−7.64 (m, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.30−7.27 (m, 1H), 7.24 (dd, J = 1.3, 5.0 Hz, 1H), 7.21 (td, J = 1.2, 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.97−6.93 (m, 2H), 4.95 (dd, J = 2.1, 11.4 Hz, 1H), 4.53 (ABq, J = 15.2 Hz, 2H), 4.11 (dd, J = 4.1, 12.3 Hz, 1H), 3.98 (td, J = 2.1, 12.6 Hz, 1H), 3.84 (d, J = 13.1 Hz, 1H), 3.74 (d, J = 13.1 Hz, 1H), 2.27 (td, J = 5.3, 13.7 Hz, 1H), 2.22−2.16 (m, 1H), 2.13−2.09 (m, 1H), 1.72 (dd, J = 1.5, 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 145.3, 140.9, 133.9, 131.6, 131.1, 130.9, 127.6, 126.7, 126.4, 126.3, 125.9, 124.5, 124.2, 123.5, 71.1, 64.2, 49.1, 47.9, 42.5, 37.5, 34.2; MS-ESI m/z 471 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{23}H_{22}O_5N_2NaS_2$ $[M + Na]^+$ 493.0861, found 493.0863.

2′-(4-Nitrophenyl)-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6f): White solid; yield 108 mg, 85%; mp 105−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19−8.16 (m, 2H), 8.14−8.11 (m, 1H), 7.80−7.76 (m, 2H), 7.72−7.68 (m, 1H), 7.58−7.55 (m, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.28−7.24 (m, 1H), 7.20 (td, J = 1.0, 7.4 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 4.90 (dd, J = 1.8, 11.5 Hz, 1H), 4.68 (d, J = 15.1 Hz, 1H), 4.42 (d, J = 15.2 Hz, 1H), 4.30 (d, J = 13.1 Hz, 1H), 4.20 (dd, J = 4.2, 12.3 Hz, 1H), 3.99 (td, J = 2.1, 12.6 Hz, 1H), 3.40 (d, J = 13.1 Hz, 1H), 2.44 (td, J = 5.3, 13.8 Hz, 1H), 2.20−2.15 (m, 1H), 1.80−1.73 (m, 1H), 1.64 (dd, J = 1.5, 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 148.4, 147.0, 140.7, 133.9, 131.7, 131.3, 130.9, 127.6, 126.8, 126.3, 126.2, 125.7, 124.2, 123.5, 74.1, 64.0, 49.0, 48.0, 43.3, 37.4, 33.7; MS-ESI m/z 510.0 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{25}H_{23}O_7N_3NaS$ $[M + Na]^+$ 532.1156, found 532.1157.

2-(2-Nitrophenylsulfonyl)-2′-*o*-tolyl-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6g): White solid; yield 113 mg, 95%; mp 105−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11−8.07 (m, 1H), 7.77−7.73 (m, 2H), 7.67−7.63 (m, 1H), 7.52 (d, J = q7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.28−7.05 (m, 6H), 4.92 (dd, J = 1.9, 11.2 Hz, 1H), 4.48−5.24 (m, 2H), 4.17−4.11 (m, 1H), 4.00 (td, J = 1.9, 12.6 Hz, 1H), 3.84 (s, 2H), 2.38 (s, 3H), 2.27 (td, J = 5.3, 13.8 Hz, 1H), 2.05−1.99 (m, 1H), 1.95−1.90 (m, 1H), 1.75 (dd, J = 1.3, 14.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 141.2, 140.3, 134.5, 133.9, 131.5, 130.9, 130.7, 130.4, 130.2, 127.5, 127.1, 126.6, 126.2, 126.1, 125.9, 125.2, 124.1, 71.9, 64.2, 49.2, 48.5, 41.6, 37.6, 34.7, 19.0; MS-ESI m/z 479 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{26}H_{26}O_5N_2NaS$ $[M + Na]^+$ 501.1454, found 501.1456.

2′-(3-Nitrophenyl)-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6h): White solid; yield 112 mg, 88%; mp 105−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.3−8.21(m, 1H), 8.15−8.08 (m, 2H), 7.81−7.76 (m, 2H), 7.72−7.67 (m, 2H), 7.48 (t, J = 7.9 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.29−7.24 (m, 1H), 7.20 (t, J = 7.0 Hz, 1H), 7.08 (d, J = 7.4 Hz, 1H), 4.87 (d, J = 10.3 Hz, 1H), 4.65 (d, J = 15.1 Hz, 1H), 4.45 (d, J = 15.2 Hz, 1H), 4.23−4.17 (m, 2H), 4.0 (td, J = 1.6, 12.6 Hz, 1H), 3.49 (d, J = 13.1 Hz, 1H), 2.42 (td, J = 5.3, 13.7 Hz, 1H), 2.15 (d, J = 14.1 Hz, 1H), 1.87−1.80 (m, 1H), 1.67 (d, J = 13.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 148.3, 144.7, 140.8, 133.9, 132.0, 131.7, 131.3, 130.9, 129.1,127.6, 126.8, 126.3, 125.8, 124.2, 122.2, 120.5, 73.8, 64.0, 49.0, 48.0, 43.2, 37.5, 33.8; MS-ESI m/z 510 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{25}H_{23}O_7N_3NaS$ $[M + Na]^+$ 532.1151, found 532.1152.

2′-(Naphthalen-1-yl)-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6i): White solid; yield 115 mg, 90%; mp 120−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 8.5 Hz, 1H), 8.15−8.11 (m, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.74−7.68 (m, 3H), 7.67−7.63 (m, 1H), 7.55−7.51 (m, 1H), 7.49−7.43 (m, 3H), 7.24 (t, J = 7.1 Hz, 1H), 7.17 (td, J = 1.0, 7.6 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 5.47 (dd, J = 1.6, 11.2 Hz, 1H), 4.52 (ABq, J = 15.2 Hz, 2H), 4.25 (dd, J = 5.3, 12.3 Hz, 1H), 4.17−4.10 (m, 2H), 3.84 (d, J = 12.6 Hz, 1H), 2.39 (td, J = 5.4, 13.4 Hz, 1H), 2.25−2.20 (m, 1H), 2.17−2.11 (m, 1H), 1.80 (dd, J = 1.3, 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 141.0, 138.0, 133.9, 133.5, 131.5, 131.0, 130.5, 130.1, 128.6, 127.8, 127.4, 126.6, 126.2, 126.0, 125.8, 125.4, 125.3, 124.1, 123.3, 122.6, 72.0, 64.4, 47.3, 47.9, 42.2, 37.8, 34.6; MS-ESI m/z 515 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{29}H_{26}$ O_5N_2NaS $[M + Na]^+$ 537.1454, found 537.1452.

2′-Benzyl-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6j): White solid; yield 96 mg, 80%; mp 65−67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05−8.01 (m, 1H), 7.75−7.70 (m, 2H), 7.66−7.62 (m, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.31−7.17 (m, 7H), 7.05 (d, J = 7.6 Hz, 1H), 4.45 (ABq, J = 15.5 Hz, 2H), 3.97−3.85 (m, 2H), 3.80−3.69 (m, 2H), 3.55 (d, J = 12.9 Hz, 1H), 2.91 (dd, J = 7.1, 13.8 Hz, 1H), 2.68 (dd, J = 5.6, 14.0 Hz, 1H), 2.10 (td, J = 5.1, 13.4 Hz, 1H), 1.85−1.78 (m, 1H), 1.72−1.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 141.4, 138.1, 133.8, 131.5, 131.0, 130.8, 129.3, 128.2, 127.4, 126.5, 126.2, 126.1, 125.9, 124.1, 73.5, 63.7, 49.2, 47.9, 42.8, 40.5, 37.2, 34.6; MS-ESI m/z 479 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{26}H_{27}O_5N_2S$ $[M + H]^+$ 479.1636, found 479.1635.

2′-Isopropyl-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6k): Viscous liquid; yield 80 mg, 75%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10−8.04 (m, 1H), 7.77−7.72 (m, 2H), 7.67−7.63 (m, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.30−7.25 (m, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H), 4.49 (ABq, J = 15.1 Hz, 2H), 3.96 (dd, J = 4.5, 12.2 Hz, 1H), 3.78−3.69 (m, 2H), 3.62 (d, J = 12.8 Hz, 1H), 3.33−3.27 (m, 2H), 2.12 (td, J = 5.1, 13.4 Hz, 1H), 1.80−1.57 (m, 4H), 0.97 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 141.7, 133.8, 131.6, 131.0, 130.8, 127.4, 126.4, 126.1, 125.9, 124.1, 77.7, 63.7, 49.4, 47.9, 37.7, 37.0, 34.8, 33.2, 18.4, 18.1; MS-ESI m/z 431 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{22}H_{26}O_5N_2NaS$ $[M + Na]^+$ 453.1454, found 453.1455.

(*E*)-2-(2-Nitrophenylsulfonyl)-2′-styryl-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6l): White solid; yield 104 mg, 88%; mp 95−97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−8.08 (m, 1H), 7.78−7.73 (m, 2H), 7.68−7.65 (m, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.38−7.35 (m, 2H), 7.32−7.27 (m, 3H), 7.24−7.18 (m, 2H), 7.08 (d, J = 7.6 Hz, 1H), 6.63 (d, J = 16 Hz, 1H), 6.17 (dd, J = 5.6, 16.0 Hz, 1H), 4.52 (ABq, J = 15.4 Hz, 2H), 4.36−4.30 (m, 1H), 4.05 (dd, J = 4.2, 12.3 Hz, 1H), 3.90 (td, J = 1.9, 12.6 Hz, 1H), 3.80 (d, J = 12.9 Hz, 1H), 3.72 (d, J = 12.9 Hz, 1H), 2.20 (td, J = 5.3, 13.7 Hz, 1H), 1.98−1.84 (m, 2H), 1.69 (dd, J = 1.3, 14.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 141.2, 136.7, 133.8, 131.6, 131.1, 130.9, 130.3, 129.6, 128.4, 127.5, 126.6, 126.4, 126.2, 125.9, 124.1, 73.1, 63.6, 49.1, 47.9, 40.9, 37.2, 34.4; MS-ESI m/z 491 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{27}H_{26}O_5N_2NaS$ $[M + Na]^+$ 513.1456, found 513.1457.

2′-(4-Methoxyphenyl)-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6m): White solid; yield 99 mg, 80%; mp 81−83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14−8.07 (m, 1H), 7.79−7.71 (m, 2H), 7.70−7.63 (m, 1H),

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7.46 (d, J = 7.7 Hz, 1H), 7.35−7.14 (m, 4H), 7.07 (d, J = 7.3 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 4.68 (dd, J = 5.0, 8.5 Hz, 1H), 4.52 (ABq, J = 15.1 Hz, 2H), 4.16−4.07 (m, 1H), 4.02−3.9 (m, 2H), 3.79 (s, 3H), 3.70 (t, J = 13.0 Hz, 1H), 2.29 (td, J = 5.2, 13.2 Hz, 1H), 2.02−1.93 (m, 2H), 1.69 (d, J = 13.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 148.5, 141.3, 134.5, 133.8, 131.6, 131.2, 130.9, 127.5, 126.9, 126.6, 126.2, 125.9, 124.2, 113.6, 74.6, 64.1, 55.2, 49.2, 48.0, 42.9, 37.6, 34.3; MS-ESI m/z 494.1 $[M + Na]^+$; HRMS (Orbitrap ESI) calcd for $C_{26}H_{27}O_6N_2S$ $[M + H]^+$ 495.1588, found 495.1587.

2′-(4-Bromophenyl)-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6n): White solid; yield 132 mg, 98%; mp 92−94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−8.09 (m, 1H), 7.78−7.74 (m, 2H), 7.70−7.66 (m, 1H), 7.45−7.41 (m, 3H), 7.28−7.24 (m, 3H), 7.19 (td, J = 1.2, 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 4.72 (dd, J = 1.8, 11.5 Hz, 1H), 4.60 (d, J = 15.1 Hz, 1H), 4.45 (d, J = 15.1 Hz, 1H), 4.17−4.11 (m, 2H), 4.09 (d, J = 12.8 Hz, 1H), 3.96 (td, J = 2.2, 12.6 Hz, 1H), 3.55 (d, J = 13.1 Hz, 1H), 2.34 (td, J = 5.3, 14.0 Hz, 1H), 2.06−2.01 (m, 1H), 1.89−1.83 (m, 1H), 1.66 (dd, J = 1.3, 14.0 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 141.5, 141.0, 133.8, 131.6, 131.3, 130.9, 130.8, 127.5, 127.3, 126.7, 126.2, 125.8, 124.2, 121.0, 74.3, 64.0, 49.1, 47.9, 43.2, 37.5, 34.1; MS-ESI m/z 543.0 $[M + H]^+$; HRMS (Orbitrap ESI) $C_{25}H_{24}O_5N_2BrS$ $[M + H]^+$ 543.0591, found 543.0591.

2-(2-Nitrophenylsulfonyl)-2′-p-tolyl-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6o): White solid; yield 114 mg, 96% ; mp 165−167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−8.09 (m, 1H), 7.77−7.73 (m, 2H), 7.69−7.65 (m, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.29−7.23 (m, 3H), 7.18 (t, J = 7.3 Hz, 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.07 (d, J = 7.6 Hz, 1H), 4.69 (dd, J = 3.5, 10.2 Hz, 1H), 4.52 (ABq, J = 15.1 Hz, 2H), 4.12 (dd, J = 5.0, 12.3 Hz, 1H), 4.00−3.90 (m, 2H), 3.72 (d, J = 12.9 Hz, 1H), 2.32 (s, 3H), 2.31−2.24 (m, 2H), 2.05−1.94 (m, 2H); ^{13}C NMR δ (125 MHz, $CDCl_3$): 148.5, 141.2, 139.3, 136.9, 133.8, 131.6, 131.2, 130.9, 128.9, 127.4, 126.5, 126.2, 125.9, 125.5, 124.1, 74.8, 64.1, 49.2, 47.9, 43.0, 37.6, 34.4, 21.0; MS-ESI m/z 479.0 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{26}H_{26}O_5N_2NaS$ $[M + Na]^+$ 501.1453, found 501.1455.

2′-(4-Bromo-2-fluorophenyl)-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6p): White solid; yield 126 mg, 90%; mp 115−117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−8.09 (m, 1H), 7.78−7.74 (m, 1H), 7.71−7.65 (m, 2H), 7.42 (d, J = 7.9 Hz, 1H), 7.35−7.32 (m, 1H), 7.28−7.24 (m, 2H), 7.19 (td, J = 1.0, 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.9−6.86 (m, 1H), 4.97 (dd, J = 2.5, 10.9 Hz, 1H), 4.57 (d, J = 15.1 Hz, 1H), 4.46 (d, J = 15.1 Hz, 1H), 4.13 (dd, J = 4.1, 12.3 Hz, 1H), 4.03−3.96 (m, 2H), 3.66 (d, J = 12.8 Hz, 1H), 2.18 (td, J = 5.3, 13.5 Hz, 1H), 2.05−1.93 (m, 2H), 1.82 (dd, J = 1.3, 14.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 156.5, 148.5, 140.7, 133.9, 131.9, 131.6, 131.5, 131.4, 130.9, 130.8, 130.0, 127.5, 126.7, 126.2, 125.8, 124.1, 117.0, 116.9, 116.8, 116.7, 68.7, 64.2, 48.9, 47.9, 41.4, 37.4, 31.4; MS-ESI m/z 563 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{25}H_{23}O_5N_2BrFS$ $[M + H]^+$ 561.0489, found 561.0490.

6-Methyl-2-(2-nitrophenylsulfonyl)-2′-*p*-tolyl-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6q): White solid; yield 114 mg, 93%; mp 108−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13−8.06 (m, 1H), 7.78−7.71 (m, 2H), 7.70−7.63 (m, 1H), 7.31−7.21 (m, 3H), 7.13 (dd, J = 7.7 Hz, 2H), 7.03−6.92 (m, 2H), 4.69 (dd, J = 3.5, 10 Hz, 1H), 4.48 (ABq, J = 15.6 Hz, 2H), 4.12 (dd, J = 4.5, 12.2 Hz, 1H), 4.01−3.94 (m, 1H), 3.88 (d, J = 13.0 Hz, 1H), 3.71 (d, J = 13.0 Hz, 1H), 2.37−2.20 (m, 7H), 2.05−1.89 (m, 2H), 1.68 (d, J = 14.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 141.0, 139.4, 137.0, 136.9, 133.8, 131.6, 131.2, 130.9, 128.9, 127.8, 127.4, 126.3, 126.1, 125.5, 124.1, 74.7, 64.1, 49.2, 47.8, 43.1, 37.5, 34.4, 21.2, 21.0; MS-ESI m/z 493 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{27}H_{29}O_5N_2S$ $[M + H]^+$ 493.17951, found 493.17952.

4-(6-Methyl-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran]-2′-yl)benzonitrile (6r): White solid; yield 122 mg, 97%; mp 120−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−8.08 (m, 1H), 7.80−7.75 (m, 2H), 7.71−7.66 (m, 1H), 7.63−7.59 (m, 2H), 7.54−7.49 (m, 2H), 7.22−7.19 (m, 1H), 7.03−6.94 (m, 2H), 4.84 (d, J = 10.3 Hz, 1H), 4.62 (d, J = 14.9 Hz, 1H), 4.37 (d, J = 14.9 Hz, 1H), 4.24 (d, J = 13.1 Hz, 1H), 4.18 (dd, J = 4.5, 12.2 Hz, 1H), 3.97 (td, J = 1.5, 12.5 Hz, 1H), 3.38 (d, J = 13.1 Hz, 1H), 2.42 (td, J = 5.3, 13.5 Hz, 1H), 2.31 (s, 3H), 2.12 (d, J = 14.1 Hz, 1H), 1.75 (t, J = 12.3 Hz, 1H), 1.61 (d, J = 14.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 147.9, 140.6, 137.1, 133.9, 132.0, 131.7, 131.3, 130.8, 127.8, 127.6, 126.1, 124.2, 118.9, 110.8, 74.2, 64.0, 49.0, 47.8, 43.3, 37.3, 33.7, 21.2; MS-ESI m/z 504 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{27}H_{26}O_5N_3S$ $[M + H]^+$ 504.1593, found 504.1592.

2′-(2-Fluorophenyl)-6-methyl-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6s): White solid; yield 121 mg, 98%; mp 116−118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−8.08 (m, 1H), 7.78−7.72 (m, 2H), 7.68−7.64 (m, 1H), 7.57 (td, J = 1.6, 7.4 Hz, 1H), 7.68−7.64 (m, 1H), 7.57 (td, J = 1.6, 7.4 Hz, 1H), 7.26−7.20 (m, 2H), 7.16 (td, J = 1.0, 7.4 Hz, 1H), 7.02−6.95 (m, 3H), 5.0 (d, J = 11.4 Hz, 1H), 4.56 (d, J = 14.9 Hz, 1H), 4.39 (d, J = 14.9 Hz, 1H), 4.15−4.07 (m, 2H), 4.0 (td, J = 1.9, 12.5 Hz, 1H), 3.57 (d, J = 12.8 Hz, 1H), 2.31 (s, 3H), 2.19−2.08 (m, 2H), 1.91 (d, J = 14.0 Hz, 1H), 1.83 (dd, J = 1.5, 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ160.9, 157.6, 148.6, 140.8, 137.0, 133.8, 131.6, 131.0, 130.8, 129.6, 129.5, 128.8, 128.7, 127.9, 127.5, 127.0, 126.3, 126.1, 124.1, 115.2, 114.9, 69.2, 64.3, 49.0, 47.8, 41.5, 37.4, 34.6, 21.2; MS-ESI m/z 497 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{26}H_{26}O_5N_2FS$ $[M + H]^+$ 497.1539, found 497.1538.

2′-(3-Bromophenyl)-6-methyl-2-((2-nitrophenyl)sulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6t): White solid; yield 130 mg, 94%; mp 102−104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14−8.06 (m, 1H), 7.81−7.72 (m, 2H), 7.71−7.64 (m, 1H), 7.58−7.54 (m, 1H), 7.37 (d, J = 7.9, 1H), 7.33−7.14 (m, 3H), 7.05−6.91 (m, 2H), 4.71 (d, J = 10.3 Hz, 1H), 4.49 (ABq, J = 14.9 Hz, 2H), 4.14 (dd, J = 4.7, 11.8 Hz, 1H), 4.07−3.89 (m, 2H), 3.56 (d, J = 13.0 Hz, 1H), 2.39−2.25 (m, 4H), 2.02 (d, J = 15.1 Hz, 1H), 1.93−1.82 (m, 1H), 1.66 (d, J = 13.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 144.7, 140.7, 137.1, 133.8, 131.6, 131.2, 130.8, 130.3, 129.8, 128.4, 127.7, 127.5, 126.2, 126.1, 124.3, 124.1, 122.3, 74.1, 64.0, 49.1, 47.8, 43.1, 37.4, 34.0, 21.2; MS-ESI m/z 557 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{26}H_{26}O_5N_2BrS$ $[M + H]^+$ 557.0746, found 557.0745.

2′-(4-Isopropylphenyl)-6-methyl-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6u): White solid; yield 123 mg, 95%; mp 90−92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15−8.05 (m, 1H), 7.79−7.71 (m, 2H), 7.70−7.63 (m, 1H), 7.35−7.15 (m, 5H), 7.02−6.92 (m, 2H), 4.69 (dd, J = 2.4, 10.5 Hz, 1H), 4.55−4.42 (m, 2H), 4.12 (dd, J = 4.7, 12.0 Hz, 1H), 3.97 (d, J = 12.4 Hz, 1H), 3.88 (d, J = 13.1 Hz, 1H), 3.72 (d, J = 13.0 Hz, 1H), 2.88 (heptate, 6.7 Hz, 1H), 2.31 (s, 3H), 2.29−2.17 (m, 1H), 2.08−1.91 (m, 2H), 1.68 (d, J = 14.1 Hz, 1H), 1.22 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 148.0, 141.0, 139.7, 137.0, 133.8, 131.6, 131.2, 130.9, 127.8, 127.4, 126.3, 126.1, 125.6, 124.1, 74.8, 64.1, 49.2, 47.8, 42.9, 37.5, 34.4, 33.8, 23.9, 21.3; MS-ESI m/z 521 $[M + H]^+$; HRMS (Orbitrap ESI) calcd for $C_{29}H_{33}O_5N_2S$ $[M + H]^+$ 521.2101, found 521.2102.

2′-(2-Chlorophenyl)-6-methyl-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6v): White solid; yield 120 mg, 94%; mp 105−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−8.07 (m, 1H), 7.77−7.72 (m, 2H), 7.68−7.64 (m, 2H), 7.35−7.28 (m, 2H), 7.22−7.17 (m, 2H), 7.01−6.94 (m, 2H), 5.05 (dd, J = 3.0, 10.3 Hz, 1H), 4.63 (d, J = 14.9 Hz, 1H), 4.37 (d, J = 12.8 Hz, 1H), 4.31 (d, J = 14.8 Hz, 1H), 4.16−4.10 (m, 1H), 4.03 (td, J = 2.2, 12.5 Hz, 1H), 3.36 (d, J = 12.8 Hz, 1H), 2.30 (s, 3H), 2.09−1.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 140.8, 140.1, 137.0, 133.8, 131.5, 131.2, 130.9, 130.8, 129.1, 128.3, 127.8, 127.5, 127.1, 126.8, 126.3, 126.1, 124.1, 71.9, 64.4, 48.9, 47.9, 41.1, 37.6, 34.9, 21.2; MS-ESI m/z 513 $[M + Na]^+$; HRMS (Orbitrap ESI) calcd for $C_{26}H_{26}O_5N_2SCl$ $[M + H]^+$ 513.12475 Found: 513.12478.

2′-(3-Methoxyphenyl)-6-methyl-2-(2-nitrophenylsulfonyl)-2,2′,3,3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6w): White solid; yield 104 mg, 82%; mp 81−83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14−8.07 (m, 1H), 7.79−7.72 (m, 2H), 7.70−7.64 (m, 1H), 7.25−7.20 (m, 2H), 7.02−6.92 (m, 4H), 6.79 (dd, J = 1.5,

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8.3 Hz, 1H), 4.71 (dd, J = 5.2, 8.3 Hz, 1H), 4.49 (ABq, J = 15.1 Hz, 2H), 4.18−4.09 (m, 1H), 4.01−3.88 (m, 2H), 3.82 (s, 3H), 3.68 (d, J = 12.8 Hz, 1H), 2.32 (s, 3H), 2.29−2.22 (m, 1H), 2.06−1.94 (m, 2H), 1.68 (d, J = 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 148.5, 144.1, 140.9, 137.0, 133.8, 131.6, 131.2, 130.8, 129.2, 127.8, 127.4, 126.3, 126.1, 124.1, 117.9, 112.9, 110.9, 74.8, 64.1, 55.2, 49.2, 47.8, 43.1, 37.4, 34.3, 21.2; MS-ESI m/z 531 $[M + Na]^+$; HRMS (Orbitrap ESI) calcd for $C_{27}H_{29}O_6N_2S$ $[M + H]^+$ 509.1742, found 509.1741.

6-Methyl-2-(2-nitrophenylsulfonyl)-2′-phenethyl-2,2′,3,-3′,5′,6′-hexahydro-1*H*-spiro[isoquinoline-4,4′-pyran] (6x): White solid; yield 101 mg, 80%; mp 70−72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05−8.02 (m, 1H), 7.76−7.62 (m, 1H), 7.32−7.16 (m, 6H), 7.01 (d, J = 7.7 Hz, 1H), 6.96 (d, J = 7.7 Hz, 1H), 4.49−4.41 (m, 2H), 3.98 (dd, J = 4.4, 12.3 Hz, 1H), 3.77 (td, J = 1.9, 12.6 Hz, 1H), 3.69−3.58 (m, 3H), 2.85−2.78 (m, 1H), 2.70−2.62 (m, 1H), 2.34 (s, 3H), 2.12 (td, J = 5.1, 13.4 Hz, 1H), 1.88−1.77 (m, 2H), 1.73−1.63 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 142.1, 141.2, 137.0, 133.7, 131.5, 131.0, 130.8, 128.3, 128.2, 127.8, 127.4, 126.3, 126.1, 125.6, 124.1, 72.2, 63.7, 49.4, 47.8, 40.8, 38.3, 37.1, 34.8, 31.7, 21.3; MS-ESI m/z 529 $[M + Na]^+$; HRMS (Orbitrap ESI) calcd for $C_{28}H_{31}O_5N_2S$ $[M + H]^+$ 507.1952, found 507.1951.

■ ASSOCIATED CONTENT

Supporting Information

X-ray data for compound **6b** as CIF files. Copies of ^{1}H and ^{13}C NMR spectra of products (**6a−x** and starting materials **3a**, **3b**, **4a**, and **4b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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