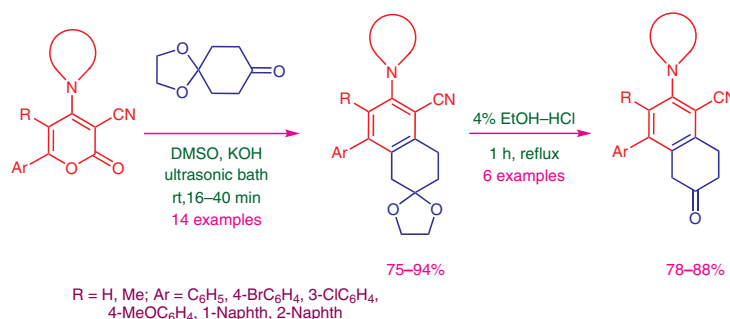


# A Metal-Free Approach for the Synthesis of 2-Tetralones via Carbanion-Induced Ring Transformation of 2H-Pyran-2-ones

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**Abstract** A metal-free, ultrasound-assisted approach for the synthesis of highly functionalized 2-tetralones in high yields is described. The process involves ring transformation of 2H-pyran-2-ones with the spirocyclic ketone 1,4-cyclohexandione monoethylene ketal to yield spirocyclic ketals and subsequent acid-mediated hydrolysis. This protocol is free from any organometallic reagents, is economical and tolerates a wide range of functional groups.

**Key words** 2-tetralones, 2H-pyran-2-ones, ring transformation reactions, 1,4-cyclohexanedione monoethylene ketal, spirocyclic ketals

Tetralone-cored systems have been identified as important synthetic intermediates in organic<sup>1,2</sup> and medicinal chemistry.<sup>3-6</sup> Among all aromatic bicyclic ketones, 2-tetralones constitute a significant class of building blocks due to their versatile reactivity. They are important starting materials for the synthesis of various biologically active synthetic<sup>7</sup> and naturally occurring compounds.<sup>8</sup> Moreover, these scaffolds are potential precursors for the synthesis of different drug molecules such as nepinalone,<sup>9</sup> treprostinil,<sup>10</sup> idarubicin,<sup>11</sup> ( $\pm$ )-daunomycinone<sup>12</sup> and rotigotine.<sup>13</sup> In addition, 2-tetralones have been used as key substrates for the construction of merocyanine dyes<sup>14</sup> and some fluorescent polycyclic compounds.<sup>15</sup>

Over the years, numerous synthetic methodologies have been employed for the preparation of 2-tetralones. In 2009, Hon and Devulapally<sup>16</sup> developed the titanium(IV)-mediated synthesis of 2-tetralones by intramolecular cyclization of 4-methoxy-5-arylethyl-1,3-dioxolan-2-ones. Subsequently, the same group reported a new synthetic route to obtain a variety of substituted 2-tetralone derivatives via cyclization of 4-aryl-2-hydroxybutanal diethyl acetals using TiCl<sub>4</sub> as the promoter.<sup>17</sup> In 2013, Flowers and co-workers<sup>18</sup>

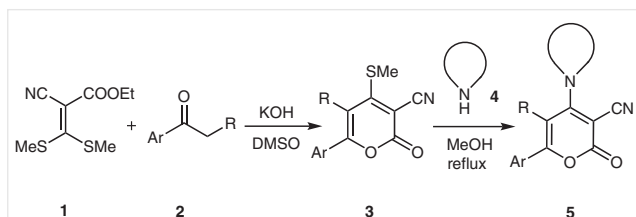
developed a Ce(IV)-mediated approach for the intramolecular cyclization of  $\beta$ -dicarbonyl compounds to functionalized  $\beta$ -tetralones. In 2015, the intramolecular hydroarylation/isomerization of propargyl alcohols leading to a diverse array of 2-tetralones was reported using Bi(OTf)<sub>3</sub> as the catalyst.<sup>19</sup> Furthermore, Lei and co-workers<sup>20</sup> synthesized similar systems by the oxidation of  $\beta$ -alkyl styrenes using a combination of Fukuzumi's catalyst with cobaloxime. Recently, the Au-catalyzed oxidation of terminal alkynes in the presence of 2,6-dichloropyridine 1-oxide was used to achieve the synthesis of similar compounds.<sup>21</sup>

However, most of the available methods are associated with limitations such as the use of toxic metals, prolonged reaction times, poor yields and harsh reaction conditions. Thus, this prompted us to develop an efficient, simple and economical synthetic protocol to produce 2-tetralones that would overcome the drawbacks of existing approaches.

2H-Pyran-2-ones are of great interest as they are versatile synthons for the construction of functionally crowded benzenes,<sup>22</sup> polyarylbenzenes<sup>23</sup> and nitrogen-<sup>24</sup> and oxygen-containing<sup>25</sup> heterocyclic compounds, all of which find wide-scale application in biological and materials chemistry. 2-oxo-2H-pyran-3-carbonitriles possess three electrophilic centers: C-2, C-4, C-6, and the latter is highly prone to nucleophilic attack because of the extended conjugation and presence of a cyano group at position 3 of the pyran ring.

The synthesis of substrates **3** was achieved by the reaction of ketene dithioacetal **1** with various substituted aryl ketones **2** in DMSO using KOH as the base.<sup>22b,23b,e,26</sup> The methylsulfanyl group of 2-pyranones **3** is a good leaving group which can be easily replaced by several cyclic secondary amines **4** under refluxing conditions in methanol for 6–8 hours to yield compounds **5** (Scheme 1). The parent precursor ketene dithioacetal **1** was synthesized by the re-

action of ethyl cyanoacetate, carbon disulfide and dimethyl sulfate in the presence of sodium methoxide as the base in absolute methanol.<sup>23e,26</sup>

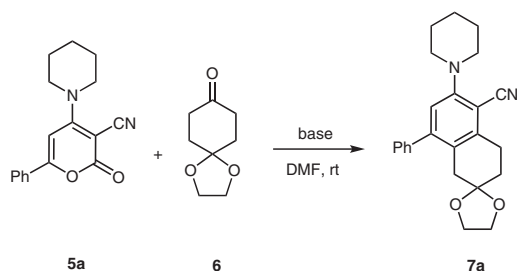


**Scheme 1** Synthesis of 2*H*-pyran-2-one precursors **3** and **5**

Herein, we report a new synthetic route for the preparation of highly functionalized spirocyclic ketals **7a–n** via carbanion-induced ring transformation of 2*H*-pyran-2-ones **5a–n** with 1,4-cyclohexanedione monoethylene ketal **6** at room temperature in an ultrasonic bath. Subsequent acid-mediated hydrolysis of ketals **7a–n** yields 2-tetralones **11a–f** in high yields. This protocol is free from any organometallic reagents and transition-metal catalysts and tolerates a wide range of functional groups.

Initially, our efforts were directed to find an appropriate base for the ring transformation of substrate **5a** with spirocyclic ketone **6** in DMF and the results are shown in Table 1. To begin with, potassium hydroxide was used as the base and the corresponding product **7a** was isolated in 73% yield (Table 1, entry 1).

**Table 1** Optimization of the Base for the Synthesis of Spirocyclic Ketal **7a** by the Ring Transformation of 2*H*-Pyran-2-one **5a** with Ketone **6**



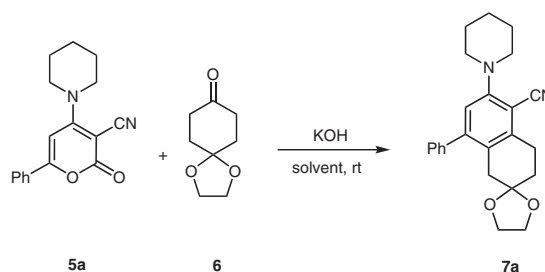
Entry	Base	Time (h)	Yield (%)
1	KOH	11	73
2	NaOH	14	60
3	Et <sub>3</sub> N	17	10
4	K <sub>2</sub> CO <sub>3</sub>	24	–
5	KO <sup>t</sup> Bu	8	69
6	NaH	9	71

The same ring transformation reaction was attempted with sodium hydroxide and the desired product **7a** was obtained in 60% yield (Table 1, entry 2). Reaction product **7a**

was obtained in only 10% yield when Et<sub>3</sub>N was used as the base (Table 1, entry 3), whereas no product formation was observed in the presence of potassium carbonate and starting materials were recovered (Table 1, entry 4). Finally, the reaction was also studied with KO<sup>t</sup>Bu and NaH and the desired product **7a** was isolated in 69% and 71% yields, respectively (Table 1, entries 5 and 6).

Next, our efforts were directed to examine the solvent effect on the ring transformation of lactone **5a** with spirocyclic ketone **6**. The reaction was performed in a number of polar and non-polar solvents and the results are listed in Table 2. Initially, the reaction was carried out in DMF and the desired product **7a** was isolated in 73% yield (Table 2, entry 1). An improved yield of 77% of the ring-transformed product **7a** was obtained when the reaction was carried out in the dipolar aprotic solvent DMSO (Table 2, entry 2). The same reaction was performed in chloroform and the reaction product **7a** was isolated in only 20% yield along with unreacted starting materials (Table 2, entry 3). Further, the reaction was carried out in the polar protic solvent ethanol, but the desired product **7a** was not observed and starting materials were recovered (Table 2, entry 4). The reaction was also tested in THF and diethyl ether, with the reaction product **7a** being isolated in 27% and 10% yields, respectively, along with unreacted starting materials (Table 2, entries 5 and 6).

**Table 2** Optimization of the Solvent for the Synthesis of Spirocyclic Ketal **7a** by the Ring Transformation of 2*H*-Pyran-2-one **5a** with Ketone **6**



Entry	Solvent	Time	Yield (%)
1	DMF	11 h	73
2	DMSO	10 h	77
3	CHCl <sub>3</sub>	14 h	20
4	EtOH	24 h	–
5	THF	14 h	27
6	Et <sub>2</sub> O	16 h	10
7 <sup>a</sup>	DMSO	16 min	84

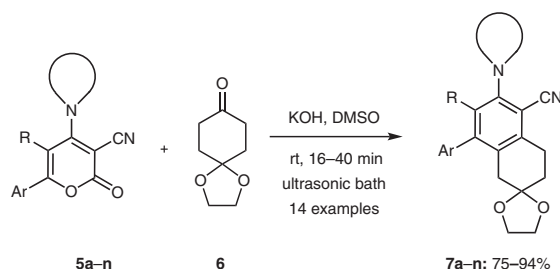
<sup>a</sup> The ring transformation reaction was performed in an ultrasonic bath.

Furthermore, our efforts were focused on reducing the reaction time for this ring transformation. Nowadays, ultrasound-assisted organic synthesis is a highly efficient and

attractive green technique, widely used as alternative energy source in many organic reactions.<sup>27–34</sup> Hence we carried out the same reaction of 2*H*-pyran-2-one **5a** with spirocyclic ketone **6** under ultrasound irradiation at room temperature. Surprisingly, the reaction was complete in just 16 minutes and the ring-transformation product **7a** was obtained in 84% yield (Table 2, entry 7). Thus, the optimized conditions for the synthesis of spirocyclic ketals **7** are: 2*H*-pyran-2-ones **5**, spirocyclic ketone **6**, powdered KOH (1.2 equiv), DMSO, ultrasound irradiation, room temperature.

Having optimized the conditions, we next examined the scope of different substrates in this ring transformation reaction (Table 3). Thus, lactones **5a–j** were successfully converted into the corresponding spirocyclic ketals **7a–j** in yields of 75–94% (Table 3, entries 1–10). Interestingly, the reaction worked smoothly with bulky 6-naphthyl-2*H*-pyran-2-ones **5g–j** and the desired products **7g–j** were obtained in 75–82% yields (Table 3, entries 7–10). Additionally, highly congested 6-aryl-5-methyl-2*H*-pyran-2-ones **5k–n** were successfully converted into fully functionalized spirocyclic ketals **7k–n** in good yields under the optimized reaction conditions (Table 3, entries 11–14). Notably, various electron-donating and electron-withdrawing substituents

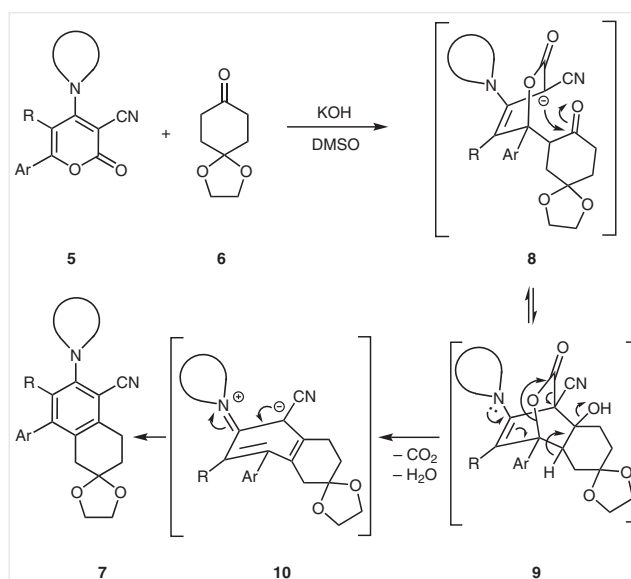
**Table 3** Synthesis of Spirocyclic Ketals **7a–n** by the Ring Transformation of 2*H*-Pyran-2-ones **5a–n** with Spirocyclic Ketone **6**



Entry	Ar	R	Amine	Product	Time (min)	Yield (%)
1	C <sub>6</sub> H <sub>5</sub>	H	piperidine	<b>7a</b>	16	84
2	C <sub>6</sub> H <sub>5</sub>	H	<i>N</i> -phenylpiperazine	<b>7b</b>	25	87
3	4-BrC <sub>6</sub> H <sub>4</sub>	H	piperidine	<b>7c</b>	18	94
4	4-BrC <sub>6</sub> H <sub>4</sub>	H	<i>N</i> -phenylpiperazine	<b>7d</b>	27	90
5	4-MeOC <sub>6</sub> H <sub>4</sub>	H	piperidine	<b>7e</b>	19	76
6	4-MeOC <sub>6</sub> H <sub>4</sub>	H	<i>N</i> -phenylpiperazine	<b>7f</b>	24	78
7	1-naphthyl	H	piperidine	<b>7g</b>	26	82
8	1-naphthyl	H	<i>N</i> -phenylpiperazine	<b>7h</b>	38	79
9	2-naphthyl	H	piperidine	<b>7i</b>	32	80
10	2-naphthyl	H	<i>N</i> -phenylpiperazine	<b>7j</b>	40	75
11	C <sub>6</sub> H <sub>5</sub>	Me	piperidine	<b>7k</b>	27	77
12	3-ClC <sub>6</sub> H <sub>4</sub>	Me	piperidine	<b>7l</b>	30	80
13	3-ClC <sub>6</sub> H <sub>4</sub>	Me	<i>N</i> -phenylpiperazine	<b>7m</b>	35	82
14	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	<i>N</i> -phenylpiperazine	<b>7n</b>	37	75

on the phenyl ring in substrates **5** were successfully tolerated. Moreover, it was observed that ring-transformed products **7** were obtained in higher yields from substrates **5** having electron-withdrawing substituents on the phenyl ring (Table 3, entries 3 and 4). All the synthesized compounds were characterized by spectroscopic analysis.

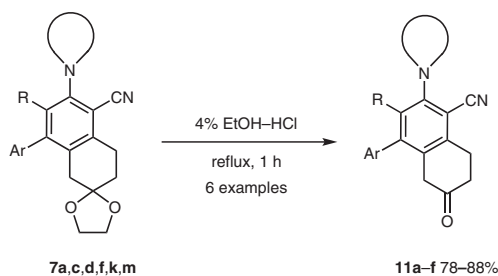
On the basis of available literature,<sup>22,23</sup> a proposed mechanism for the ring transformation of lactones **5** into the corresponding ketals **7** is depicted in Scheme 2. The reaction is initiated by nucleophilic attack of the carbanion generated from ketone **6** under basic conditions at C6 of 2*H*-pyran-2-one **5** to give intermediate **8**, subsequent intramolecular cyclization of which yields the intermediate **9**. Finally, intermediate **9** undergoes decarboxylation and dehydration to furnish the spirocyclic ketal product **7**.



**Scheme 2** Proposed mechanism for the synthesis of spirocyclic ketals **7** by the ring transformation of 2*H*-pyran-2-ones **5** with ketone **6**

Furthermore, spirocyclic ketals **7a–f** were hydrolyzed with 4% ethanolic HCl under refluxing conditions to give highly substituted 2-tetralones **11a–f** in 78–88% yields (Table 4, entries 1–6).<sup>35</sup> All the synthesized compounds were characterized by spectroscopic analysis.

In summary, we have achieved a metal-free approach for the ultrasound-assisted synthesis of highly functionalized spirocyclic ketals **7a–n** through carbanion-induced ring transformation of 2-pyranones **5a–n** with 1,4-cyclohexanedione monoethylene ketal **6**. Several examples of the spirocyclic ketal products **7** were converted into 2-tetralones **11a–f** via ketal cleavage using 4% ethanolic HCl. The present synthetic route is inexpensive, is free from organometallic reagents, involves an easy work-up procedure

**Table 4** Synthesis of Functionalized 2-Tetralones **11a–f** by Acidic Hydrolysis of Ketals **7a–f**

Entry	Ar	R	Amine	Product	Yield (%)
1	C <sub>6</sub> H <sub>5</sub>	H	piperidine	<b>11a</b>	78
2	4-BrC <sub>6</sub> H <sub>4</sub>	H	piperidine	<b>11b</b>	81
3	4-BrC <sub>6</sub> H <sub>4</sub>	H	<i>N</i> -phenylpiperazine	<b>11c</b>	83
4	4-MeOC <sub>6</sub> H <sub>4</sub>	H	<i>N</i> -phenylpiperazine	<b>11d</b>	88
5	C <sub>6</sub> H <sub>5</sub>	Me	piperidine	<b>11e</b>	80
6	3-ClC <sub>6</sub> H <sub>4</sub>	Me	<i>N</i> -phenylpiperazine	<b>11f</b>	84

and does not require harsh reaction conditions. Studies on the further application of this approach are currently in progress.

All experiments were performed without using an inert atmosphere. Dimethyl sulfoxide and other solvents were purchased from Avra Synthesis Pvt. Ltd. All other purchased chemicals were used without further purification. All reactions were monitored by thin-layer chromatography (TLC) performed on Merck KGaA pre-coated sheets of silica gel 60. Column chromatography was performed with silica gel or neutral alumina (Avra synthesis, 100–125 mesh). Eluting solvents are indicated in the text. Melting points were measured with a REMI DDMS 2545 melting point apparatus. IR spectra were recorded on a Thermo Scientific Nicolet Nexus 470FT-IR spectrophotometer and band positions are reported in reciprocal centimeters. Samples were prepared as KBr pellets. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on an AV-400 Bruker spectrometer. Deuterated chloroform (CDCl<sub>3</sub>) was used as the solvent and tetramethylsilane (Me<sub>4</sub>Si) as an internal standard. Mass spectra (*m/z*) were recorded under electron impact (EI), electrospray (ES) or chemical ionization (CI). CHN analysis was performed using an Elementar VarioMICRO Select 15162036 Analyzer.

#### Ethyl 2-Cyano-3,3-dimethylsulfanylacrylate (**1**)<sup>23e</sup>

Ethyl cyano acetate (11.3 mL, 100.0 mmol) was added dropwise over a period of 15 min to an ice-cold solution of sodium methoxide, freshly prepared in situ by dissolving sodium metal (3.44 g, 150.0 mmol) in absolute MeOH (40 mL) at 0 °C. The resulting white-colored precipitate was stirred vigorously for another 15 min followed by the dropwise addition of carbon disulfide (6.4 mL, 100.0 mmol) at 20 °C to give a yellow-colored liquid. Next, dimethyl sulfate (23.6 mL, 248 mmol) was added slowly over a period of 30 min. The resulting yellow semi-solid material was stirred for another 15 min and excess

MeOH was removed under high vacuum. Finally, the reaction mixture was poured onto crushed ice with constant stirring and the precipitate thus obtained was filtered, washed with cold H<sub>2</sub>O, dried and recrystallized from EtOAc/hexane (1:4) to give yellow, crystalline compound **1**.<sup>23e</sup>

#### 6-Aryl-4-methylsulfanyl-2-oxo-2H-pyran-3-carbonitriles **3a–n**; General Procedure<sup>23e,26</sup>

A mixture of ethyl 2-cyano-3,3-dimethylsulfanylacrylate (**1**) (2.17 g, 10.0 mmol, 1.0 equiv), aryl ketone **2** (12 mmol, 1.2 equiv) and powdered KOH (0.84 g, 15 mmol, 1.5 equiv) in dry DMSO was stirred at room temperature for 14–18 h. On completion of the reaction, the mixture was poured into ice-cold H<sub>2</sub>O with constant stirring. The residue thus obtained was removed by filtration and purified by silica gel chromatography using CHCl<sub>3</sub> as the eluent. The isolated products were characterized as 6-aryl-4-methylsulfanyl-2-oxo-2H-pyran-3-carbonitriles **3a–n** by spectroscopic analysis. The NMR data was found to correlate with those reported in the literature.<sup>23e,26</sup>

#### 6-Aryl-4-amino-2-oxo-2H-pyran-3-carbonitriles **5a–n**; General Procedure<sup>23e,26</sup>

A mixture of 6-aryl-4-methylsulfanyl-2-oxo-2H-pyran-3-carbonitrile **3a–n** (1.0 mmol, 1.0 equiv) and secondary amine **4** (1.2 mmol, 1.2 equiv) was refluxed in MeOH for 6–8 h. The course of the reaction was monitored by TLC. On completion, the reaction mixture was cooled, filtered and the remaining solid rinsed with MeOH (2 × 5 mL) to give products **5a–n**.<sup>23e,26</sup>

#### Functionalized Spirocyclic Ketals **7a–n**; General Procedure

A mixture of 2H-pyran-2-one **5a–n** (1.0 mmol, 1.0 equiv), 1,4-cyclohexanedione monoethylene ketal **6** (1.2 mmol, 1.2 equiv) and powdered KOH (1.2 mmol) in dry DMSO (3.0 mL) was irradiated in an ultrasonic bath for 16–40 min at room temperature. The progress of the reaction was monitored by TLC. On completion of the reaction, ice-cold H<sub>2</sub>O (10 mL) was added and the mixture was neutralized with dilute HCl. After that, the reaction mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under vacuum. The obtained crude residue was purified through a neutral alumina column using EtOAc/hexane (1:4) as the eluent. Finally, the isolated ketals **7a–n** were characterized by spectroscopic analysis.

#### 8-Phenyl-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (**7a**)

Yield: 0.315 g, 0.841 mmol (84%); white solid; mp 165–167 °C; *R<sub>f</sub>* = 0.5 (EtOAc/hexane, 1:4).

IR (KBr): 2214 cm<sup>-1</sup> (CN) cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.44–1.53 (m, 2 H, CH<sub>2</sub>), 1.62–1.74 (m, 4 H, 2 CH<sub>2</sub>), 1.91 (t, *J* = 6.8 Hz, 2 H, CH<sub>2</sub>), 2.63 (s, 2 H, CH<sub>2</sub>), 2.97–3.07 (m, 4 H, 2 NCH<sub>2</sub>), 3.14 (t, *J* = 6.8 Hz, 2 H, CH<sub>2</sub>), 3.78–3.92 (m, 4 H, 2 OCH<sub>2</sub>), 6.66 (s, 1 H, ArH), 7.13–7.20 (m, 2 H, ArH), 7.25–7.39 (m, 3 H, ArH).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 24.1, 26.2, 27.9, 30.8, 37.6, 53.4, 64.5, 105.4, 107.9, 117.5, 118.4, 126.1, 127.6, 128.4, 128.6, 140.5, 140.7, 147.3, 155.7.

GC-MS: *m/z* = 375 [M + 1]<sup>+</sup>.

Anal. Calcd for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.62; H, 6.81; N, 7.34.

**8-Phenyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7b)**

Yield: 0.393 g, 0.871 mmol (87%); yellow solid; mp 170–173 °C;  $R_f$  = 0.5 (EtOAc/hexane, 1:4).

IR (KBr): 2218 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.88–1.99 (m, 2 H,  $\text{CH}_2$ ), 2.65 (s, 2 H,  $\text{CH}_2$ ), 3.04–3.41 (m, 10 H, 4  $\text{NCH}_2$  +  $\text{CH}_2$ ), 3.75–3.98 (m, 4 H, 2  $\text{OCH}_2$ ), 6.71 (s, 1 H, ArH), 6.76–6.93 (m, 3 H, ArH), 7.12–7.24 (m, 4 H, ArH), 7.28–7.40 (m, 3 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.0, 30.8, 37.6, 49.6, 51.8, 64.5, 105.6, 107.8, 116.4, 118.3, 120.0, 121.8, 127.2, 127.8, 128.4, 128.6, 129.2, 130.4, 140.3, 141.2, 151.2, 154.2.

GC–MS:  $m/z$  = 452 [ $\text{M} + 1$ ]\*.

Anal. Calcd for  $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_2$ : C, 77.13; H, 6.47; N, 9.31. Found: C, 76.82; H, 6.07; N, 9.10.

**8-(4-Bromophenyl)-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7c)**

Yield: 0.426 g, 0.940 mmol (94%); white solid; mp 179–183 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 2211 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.44–1.59 (m, 2 H,  $\text{CH}_2$ ), 1.62–1.74 (m, 4 H, 2  $\text{CH}_2$ ), 1.90 (t,  $J$  = 7.0 Hz, 2 H,  $\text{CH}_2$ ), 2.59 (s, 2 H,  $\text{CH}_2$ ), 2.98–3.07 (m, 4 H, 2  $\text{NCH}_2$ ), 3.13 (t,  $J$  = 6.8 Hz, 2 H,  $\text{CH}_2$ ), 3.79–3.93 (m, 4 H, 2  $\text{OCH}_2$ ), 6.62 (s, 1 H, ArH), 7.04 (d,  $J$  = 8.0 Hz, 2 H, ArH), 7.47 (d,  $J$  = 8.4 Hz, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 24.1, 26.2, 27.9, 30.8, 37.6, 53.4, 64.6, 105.6, 107.8, 117.3, 118.1, 121.9, 125.9, 130.3, 131.6, 139.4, 140.9, 145.9, 155.7.

GC–MS:  $m/z$  = 453 [ $\text{M} + 1$ ]\*.

Anal. Calcd for  $\text{C}_{24}\text{H}_{25}\text{BrN}_2\text{O}_2$ : C, 63.58; H, 5.56; N, 6.18. Found: C, 63.30; H, 5.21; N, 6.01.

**8-(4-Bromophenyl)-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7d)**

Yield: 0.477 g, 0.900 mmol (90%); yellow solid; mp 178–181 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 2213 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.85–1.98 (m, 2 H,  $\text{CH}_2$ ), 2.62 (s, 2 H,  $\text{CH}_2$ ), 3.08–3.38 (m, 10 H, 4  $\text{NCH}_2$  +  $\text{CH}_2$ ), 3.76–3.96 (m, 4 H, 2  $\text{OCH}_2$ ), 6.68 (s, 1 H, ArH), 6.75–6.95 (m, 3 H, ArH), 7.01–7.12 (m, 2 H, ArH), 7.14–7.27 (m, 2 H, ArH), 7.44–7.55 (m, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.0, 30.8, 37.7, 49.5, 51.8, 64.6, 105.8, 107.7, 116.4, 117.1, 118.0, 120.1, 122.1, 126.9, 129.2, 130.3, 131.7, 139.1, 141.4, 146.2, 151.2, 154.3.

GC–MS:  $m/z$  = 530 [ $\text{M} + 1$ ]\*.

Anal. Calcd for  $\text{C}_{29}\text{H}_{28}\text{BrN}_3\text{O}_2$ : C, 65.66; H, 5.32; N, 7.92. Found: C, 65.29; H, 5.06; N, 7.58.

**8-(4-Methoxyphenyl)-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7e)**

Yield: 0.307 g, 0.760 mmol (76%); white solid, mp 170–173 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 2216 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.43–1.54 (m, 2 H,  $\text{CH}_2$ ), 1.62–1.74 (m, 4 H, 2  $\text{CH}_2$ ), 1.90 (t,  $J$  = 6.8 Hz, 2 H,  $\text{CH}_2$ ), 2.65 (s, 2 H,  $\text{CH}_2$ ), 2.96–3.05 (m, 4 H, 2  $\text{NCH}_2$ ), 3.12 (t,  $J$  = 6.8 Hz, 2 H,  $\text{CH}_2$ ), 3.77 (s, 3 H,  $\text{OCH}_3$ ), 3.78–3.92 (m, 4 H, 2  $\text{OCH}_2$ ), 6.65 (s, 1 H, ArH), 6.87 (d,  $J$  = 8.8 Hz, 2 H, ArH), 7.10 (d,  $J$  = 8.8 Hz, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 24.1, 26.2, 27.9, 30.9, 37.7, 53.5, 55.4, 64.5, 105.1, 107.9, 113.8, 117.5, 118.5, 126.3, 129.8, 132.8, 140.7, 147.0, 155.7, 159.1.

GC–MS:  $m/z$  = 405 [ $\text{M} + 1$ ]\*.

Anal. Calcd for  $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_3$ : C, 74.23; H, 6.98; N, 6.93. Found: C, 73.92; H, 6.73; N, 6.76.

**8-(4-Methoxyphenyl)-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7f)**

Yield: 0.376 g, 0.780 mmol (78%); yellow solid; mp 186–188 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 2219 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.93 (t,  $J$  = 6.8 Hz, 2 H,  $\text{CH}_2$ ), 2.68 (s, 2 H,  $\text{CH}_2$ ), 3.15 (t,  $J$  = 6.8 Hz, 2 H,  $\text{CH}_2$ ), 3.23–3.40 (m, 8 H, 4  $\text{NCH}_2$ ), 3.78 (s, 3 H,  $\text{OCH}_3$ ), 3.80–3.93 (m, 4 H, 2  $\text{OCH}_2$ ), 6.73 (s, 1 H, ArH), 6.89 (d,  $J$  = 8.4 Hz, 3 H, ArH), 6.99 (d,  $J$  = 8.0 Hz, 2 H, ArH), 7.12 (d,  $J$  = 8.4 Hz, 2 H, ArH), 7.24 (t,  $J$  = 7.8 Hz, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.0, 30.8, 37.8, 50.3, 51.5, 55.4, 64.6, 105.3, 107.8, 113.9, 117.0, 117.3, 118.6, 121.2, 127.6, 129.3, 129.8, 132.5, 141.1, 147.4, 150.1, 154.0, 159.3.

GC–MS:  $m/z$  = 482 [ $\text{M} + 1$ ]\*.

Anal. Calcd for  $\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_3$ : C, 74.82; H, 6.49; N, 8.73. Found: C, 74.38; H, 6.28; N, 8.35.

**8-(Naphthalen-1-yl)-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7g)**

Yield: 0.348 g, 0.820 mmol (82%); white solid; mp 140–143 °C;  $R_f$  = 0.5 (EtOAc/hexane, 1:4).

IR (KBr): 2213 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.40–1.76 (m, 6 H, 3  $\text{CH}_2$ ), 1.89 (s, 2 H,  $\text{CH}_2$ ), 2.26–2.48 (m, 2 H,  $\text{CH}_2$ ), 2.93–3.28 (m, 6 H, 2  $\text{NCH}_2$  +  $\text{CH}_2$ ), 3.57–3.88 (m, 4 H, 2  $\text{OCH}_2$ ), 6.71 (s, 1 H, ArH), 7.12–7.50 (m, 5 H, ArH), 7.74–7.88 (m, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 24.1, 26.2, 28.0, 30.9, 36.7, 53.4, 64.4, 105.6, 107.8, 117.5, 118.9, 125.4, 125.5, 126.1, 126.5, 127.6, 128.1, 128.4, 131.2, 133.5, 138.2, 140.6, 145.8, 155.7.

GC–MS:  $m/z$  = 425 [ $\text{M} + 1$ ]\*.

Anal. Calcd for  $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_2$ : C, 79.22; H, 6.65; N, 6.60. Found: C, 78.92; H, 6.53; N, 6.27.

**8-(Naphthalen-1-yl)-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7h)**

Yield: 0.396 g, 0.790 mmol (79%); yellow solid; mp 195–197 °C;  $R_f$  = 0.5 (EtOAc/hexane, 1:4).

IR (KBr): 2211 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.83–2.09 (m, 2 H,  $\text{CH}_2$ ), 2.29–2.49 (m, 2 H,  $\text{CH}_2$ ), 3.12–3.38 (m, 10 H, 4  $\text{NCH}_2$  +  $\text{CH}_2$ ), 3.58–3.89 (m, 4 H, 2  $\text{OCH}_2$ ), 6.73–6.95 (m, 4 H, ArH), 7.12–7.27 (m, 3 H, ArH), 7.28–7.51 (m, 4 H, ArH), 7.76–7.89 (m, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.0, 30.9, 36.8, 49.6, 51.8, 64.5, 105.8, 107.7, 116.4, 117.3, 118.8, 120.1, 125.4, 125.5, 126.1, 126.2, 126.6, 128.3, 128.5, 128.6, 129.2, 131.1, 133.6, 137.9, 140.9, 146.1, 151.1, 154.2.

GC-MS:  $m/z$  = 502 [M + 1] $^+$ .

Anal. Calcd for  $\text{C}_{33}\text{H}_{31}\text{N}_3\text{O}_2$ : C, 79.01; H, 6.23; N, 8.38. Found: C, 78.69; H, 6.03; N, 8.13.

**8-(Naphthalen-2-yl)-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7i)**

Yield: 0.339 g, 0.800 mmol (80%); yellow solid; mp 203–206 °C;  $R_f$  = 0.5 (EtOAc/hexane, 1:4).

IR (KBr): 2210 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.42–1.78 (m, 6 H, 3  $\text{CH}_2$ ), 1.86–2.00 (m, 2 H,  $\text{CH}_2$ ), 2.67 (s, 2 H,  $\text{CH}_2$ ), 2.96–3.23 (m, 6 H, 2  $\text{NCH}_2$  +  $\text{CH}_2$ ), 3.69–3.93 (m, 4 H, 2  $\text{OCH}_2$ ), 6.75 (s, 1 H, ArH), 7.24–7.34 (m, 1 H, ArH), 7.39–7.51 (m, 2 H, ArH), 7.58–7.67 (m, 1 H, ArH), 7.72–7.87 (m, 3 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 24.1, 26.2, 28.0, 30.9, 37.7, 53.5, 64.5, 105.4, 107.9, 117.5, 118.6, 126.3, 126.4, 126.5, 126.7, 127.5, 127.8, 127.9, 128.1, 132.6, 133.2, 138.0, 140.8, 147.2, 155.8.

GC-MS:  $m/z$  = 425 [M + 1] $^+$ .

Anal. Calcd for  $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_2$ : C, 79.22; H, 6.65; N, 6.60. Found: C, 79.03; H, 6.23; N, 6.49.

**8-(Naphthalen-2-yl)-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7j)**

Yield: 0.376 g, 0.750 mmol (75%); yellow solid; mp 200–203 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 2219 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.88–1.99 (m, 2 H,  $\text{CH}_2$ ), 2.69 (s, 2 H,  $\text{CH}_2$ ), 3.10–3.42 (m, 10 H, 4  $\text{NCH}_2$  +  $\text{CH}_2$ ), 3.71–3.92 (m, 4 H, 2  $\text{OCH}_2$ ), 6.75–6.93 (m, 4 H, ArH), 7.14–7.25 (m, 3 H, ArH), 7.41–7.50 (m, 2 H, ArH), 7.60–7.67 (m, 1 H, ArH), 7.73–7.86 (m, 3 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.0, 30.9, 37.8, 49.6, 51.9, 64.5, 105.6, 107.8, 116.4, 117.2, 118.4, 120.0, 126.5, 126.6, 127.4, 127.5, 127.8, 128.1, 129.2, 132.7, 133.2, 137.8, 141.3, 147.5, 151.2, 154.2.

GC-MS:  $m/z$  = 502 [M + 1] $^+$ .

Anal. Calcd for  $\text{C}_{33}\text{H}_{31}\text{N}_3\text{O}_2$ : C, 79.01; H, 6.23; N, 8.38. Found: C, 78.69; H, 6.08; N, 8.08.

**7-Methyl-8-phenyl-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7k)**

Yield: 0.298 g, 0.770 mmol (77%); white solid; mp 158–163 °C;  $R_f$  = 0.5 (EtOAc/hexane, 1:4).

IR (KBr): 2220 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.29–1.89 (m, 11 H,  $\text{CH}_3$  + 4  $\text{CH}_2$ ), 2.38 (s, 2 H,  $\text{CH}_2$ ), 2.78–3.38 (m, 6 H,  $\text{CH}_2$  + 2  $\text{NCH}_2$ ), 3.61–3.91 (m, 4 H, 2  $\text{OCH}_2$ ), 6.88–7.00 (m, 2 H, ArH), 7.21–7.40 (m, 3 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.0, 24.2, 26.9, 27.4, 30.7, 38.4, 51.8, 64.5, 107.8, 109.0, 118.0, 127.2, 128.2, 128.9, 129.7, 133.4, 137.4, 139.9, 147.8, 153.3.

GC-MS:  $m/z$  = 389 [M + 1] $^+$ .

Anal. Calcd for  $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_2$ : C, 77.29; H, 7.26; N, 7.21. Found: C, 76.95; H, 7.04; N, 6.78.

**8-(3-Chlorophenyl)-7-methyl-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7l)**

Yield: 0.338 g, 0.800 mmol (80%); white solid; mp 171–174 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 2210 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.46–1.67 (m, 6 H, 3  $\text{CH}_2$ ), 1.79–1.91 (m, 5 H,  $\text{CH}_3$  +  $\text{CH}_2$ ), 2.37 (s, 2 H,  $\text{CH}_2$ ), 2.89–3.33 (m, 6 H,  $\text{CH}_2$  + 2  $\text{NCH}_2$ ), 3.76–3.93 (m, 4 H, 2  $\text{OCH}_2$ ), 6.84–6.91 (m, 1 H, ArH), 6.99 (s, 1 H, ArH), 7.26–7.33 (m, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.1, 24.2, 26.9, 27.4, 30.6, 38.5, 51.8, 64.5, 107.7, 109.4, 117.8, 126.6, 127.6, 128.4, 129.4, 130.3, 133.2, 134.8, 137.6, 141.7, 146.2, 153.4.

GC-MS:  $m/z$  = 423 [M + 1] $^+$ .

Anal. Calcd for  $\text{C}_{25}\text{H}_{27}\text{ClN}_2\text{O}_2$ : C, 70.99; H, 6.43; N, 6.62. Found: C, 70.71; H, 6.07; N, 6.45.

**8-(3-Chlorophenyl)-7-methyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7m)**

Yield: 0.410 g, 0.820 mmol (82%); yellow solid; mp 163–166 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 2219 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.81–1.95 (m, 5 H,  $\text{CH}_3$  +  $\text{CH}_2$ ), 2.39 (s, 2 H,  $\text{CH}_2$ ), 2.94–3.56 (m, 10 H,  $\text{CH}_2$  + 4  $\text{NCH}_2$ ), 3.77–3.95 (m, 4 H, 2  $\text{OCH}_2$ ), 6.80 (t,  $J$  = 7.2 Hz, 1 H, ArH), 6.85–6.95 (m, 3 H, ArH), 6.99 (s, 1 H, ArH), 7.16–7.25 (m, 2 H, ArH), 7.27–7.35 (m, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.4, 27.4, 30.6, 38.5, 50.4, 50.5, 64.5, 107.6, 110.3, 116.6, 117.5, 119.9, 126.5, 127.7, 128.4, 129.1, 130.4, 130.5, 133.3, 134.9, 138.1, 141.4, 146.4, 151.6, 151.7.

GC-MS:  $m/z$  = 501 [M + 1] $^+$ .

Anal. Calcd for  $\text{C}_{30}\text{H}_{30}\text{ClN}_2\text{O}_2$ : C, 72.06; H, 6.05; N, 8.40. Found: C, 71.73; H, 5.93; N, 8.09.

**8-(4-Methoxyphenyl)-7-methyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-[1,3]dioxolane]-5-carbonitrile (7n)**

Yield: 0.371 g, 0.750 mmol (75%); yellow solid; mp 207–210 °C;  $R_f$  = 0.3 (EtOAc/hexane, 1:4).

IR (KBr): 2218 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.82–1.95 (m, 5 H,  $\text{CH}_3$  +  $\text{CH}_2$ ), 2.42 (s, 2 H,  $\text{CH}_2$ ), 3.04–3.60 (m, 10 H,  $\text{CH}_2$  + 4  $\text{NCH}_2$ ), 3.78 (s, 3 H,  $\text{OCH}_3$ ), 3.80–3.91 (m, 4 H, 2  $\text{OCH}_2$ ), 6.79 (t,  $J$  = 7.4 Hz, 1 H, ArH), 6.84–6.96 (m, 6 H, ArH), 7.15–7.25 (m, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.4, 27.5, 30.7, 38.6, 50.5, 50.6, 55.3, 64.5, 107.8, 109.8, 114.4, 116.6, 117.7, 120.1, 129.1, 129.3, 131.2, 131.8, 133.9, 137.7, 147.9, 151.5, 151.6, 158.8.

GC-MS:  $m/z$  = 496 [M + 1] $^+$ .

Anal. Calcd for  $\text{C}_{31}\text{H}_{33}\text{N}_3\text{O}_3$ : C, 75.13; H, 6.71; N, 8.48. Found: C, 74.82; H, 6.40; N, 8.32.

**Functionalized 2-Tetralones 11a–f; General Procedure<sup>35</sup>**

A solution of spirocyclic ketal **7a–f** (0.25 mmol) in 4% ethanolic HCl (5 mL) was refluxed for 1 h. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was cooled to room temperature and the solvent was evaporated under high vacuum. The reaction mixture was diluted with  $\text{H}_2\text{O}$  (5 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ),

filtered and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography using EtOAc/hexane (1:4) as the eluent to give tetralones **11a–f**.

**6-Oxo-4-phenyl-2-(piperidin-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitrile (11a)**

Yield: 0.064 g, 0.195 mmol (78%); white solid; mp 165–167 °C;  $R_f$  = 0.5 (EtOAc/hexane, 1:4).

IR (KBr): 1719 (CO), 2221 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.47–1.62 (m, 2 H,  $\text{CH}_2$ ), 1.64–1.78 (m, 4 H, 2  $\text{CH}_2$ ), 2.49 (t,  $J$  = 6.6 Hz, 2 H,  $\text{CH}_2$ ), 3.04–3.13 (m, 4 H, 2  $\text{NCH}_2$ ), 3.28 (t,  $J$  = 6.8 Hz, 2 H,  $\text{CH}_2$ ), 3.36 (s, 2 H,  $\text{CH}_2$ ), 6.76 (s, 1 H, ArH), 7.10–7.18 (m, 2 H, ArH), 7.28–7.40 (m, 3 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 24.0, 26.1, 27.5, 37.0, 42.4, 53.4, 104.8, 117.3, 118.8, 124.3, 128.0, 128.6, 128.7, 139.4, 142.2, 146.5, 155.8, 209.3.

GC–MS:  $m/z$  = 331  $[\text{M} + 1]^+$ .

Anal. Calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}$ : C, 79.97; H, 6.71; N, 8.48. Found: C, 79.64; H, 6.45; N, 8.35.

**4-(4-Bromophenyl)-6-oxo-2-(piperidin-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitrile (11b)**

Yield: 0.082 g, 0.202 mmol (81%); white solid; mp 180–183 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 1720 (CO), 2223 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.47–1.60 (m, 2 H,  $\text{CH}_2$ ), 1.65–1.77 (m, 4 H, 2  $\text{CH}_2$ ), 2.49 (t,  $J$  = 6.8 Hz, 2 H,  $\text{CH}_2$ ), 3.04–3.12 (m, 4 H, 2  $\text{NCH}_2$ ), 3.28 (t,  $J$  = 6.8 Hz, 2 H,  $\text{CH}_2$ ), 3.32 (s, 2 H,  $\text{CH}_2$ ), 6.71 (s, 1 H, ArH), 7.02 (d,  $J$  = 8.4 Hz, 2 H, ArH), 7.49 (d,  $J$  = 8.4 Hz, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 24.0, 26.1, 27.5, 36.9, 42.3, 53.4, 105.1, 117.2, 118.6, 122.4, 124.0, 130.4, 131.8, 138.2, 142.5, 145.2, 155.9, 208.9.

GC–MS:  $m/z$  = 409  $[\text{M} + 1]^+$ .

Anal. Calcd for  $\text{C}_{22}\text{H}_{21}\text{BrN}_2\text{O}$ : C, 64.55; H, 5.17; N, 6.84. Found: C, 64.35; H, 4.79; N, 6.53.

**4-(4-Bromophenyl)-6-oxo-2-(4-phenylpiperazin-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitrile (11c)**

Yield: 0.101 g, 0.207 mmol (83%); white solid; mp 189–192 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 1718 (CO), 2220 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.51 (t,  $J$  = 6.8 Hz, 2 H,  $\text{CH}_2$ ), 3.22–3.41 (m, 12 H, 4  $\text{NCH}_2$  + 2  $\text{CH}_2$ ), 6.77 (s, 1 H, ArH), 6.82 (t,  $J$  = 7.4 Hz, 1 H, ArH), 6.90 (d,  $J$  = 8.4 Hz, 2 H, ArH), 7.03 (d,  $J$  = 8.4 Hz, 2 H, ArH), 7.22 (t,  $J$  = 8.4 Hz, 2 H, ArH), 7.51 (d,  $J$  = 8.4 Hz, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 27.5, 36.8, 42.3, 49.5, 51.8, 105.3, 116.5, 116.9, 118.6, 120.3, 122.6, 125.2, 129.2, 130.4, 131.9, 137.9, 142.8, 145.4, 151.0, 154.5, 208.5.

GC–MS:  $m/z$  = 487  $[\text{M} + 1]^+$ .

Anal. Calcd for  $\text{C}_{27}\text{H}_{24}\text{BrN}_3\text{O}$ : C, 66.67; H, 4.97; N, 8.64. Found: C, 66.29; H, 4.81; N, 8.37.

**4-(4-Methoxyphenyl)-6-oxo-2-(4-phenylpiperazin-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitrile (11d)**

Yield: 0.096 g, 0.220 mmol (88%); white solid, mp 180–183 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 1716 (CO), 2221 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.44–2.55 (m, 2 H,  $\text{CH}_2$ ), 3.19–3.46 (m, 12 H, 4  $\text{NCH}_2$  + 2  $\text{CH}_2$ ), 3.79 (s, 3 H,  $\text{OCH}_3$ ), 6.77–6.86 (m, 2 H, ArH), 6.87–6.96 (m, 4 H, ArH), 7.05–7.13 (m, 2 H, ArH), 7.16–7.26 (m, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 27.6, 36.9, 42.4, 49.6, 51.8, 55.5, 104.7, 107.7, 114.1, 116.5, 117.1, 118.9, 120.2, 125.5, 129.2, 130.0, 131.4, 142.6, 146.5, 154.4, 159.6, 208.9.

GC–MS:  $m/z$  = 438  $[\text{M} + 1]^+$ .

Anal. Calcd for  $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_2$ : C, 76.86; H, 6.22; N, 9.60. Found: C, 76.41; H, 5.89; N, 9.37.

**3-Methyl-6-oxo-4-phenyl-2-(piperidin-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitrile (11e)**

Yield: 0.071 g, 0.206 mmol (80%); white solid; mp 122–125 °C;  $R_f$  = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 1717 (CO), 2219 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.44–1.73 (m, 6 H, 3  $\text{CH}_2$ ), 1.89 (s, 3 H,  $\text{CH}_3$ ), 2.49 (t,  $J$  = 6.8 Hz, 2 H,  $\text{CH}_2$ ), 2.92–3.39 (m, 8 H, 2  $\text{CH}_2$  + 2  $\text{NCH}_2$ ), 6.89–7.00 (m, 2 H, ArH), 7.26–7.41 (m, 3 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.4, 24.2, 26.8, 27.0, 37.4, 43.0, 51.9, 108.4, 117.9, 127.7, 128.2 (3 C), 129.0, 134.3, 138.5, 138.9, 147.2, 153.6, 209.2.

GC–MS:  $m/z$  = 345  $[\text{M} + 1]^+$ .

Anal. Calcd for  $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}$ : C, 80.20; H, 7.02; N, 8.13. Found: C, 79.91; H, 6.88; N, 7.75.

**4-(3-Chlorophenyl)-3-methyl-6-oxo-2-(4-phenylpiperazin-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitrile (11f)**

Yield: 0.077 g, 0.169 mmol (84%); white solid; mp 171–174 °C;  $R_f$  = 0.3 (EtOAc/hexane, 1:4).

IR (KBr): 1720 (CO), 2222 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.96 (s, 3 H,  $\text{CH}_3$ ), 2.47–2.56 (m, 2 H,  $\text{CH}_2$ ), 3.04–3.64 (m, 12 H, 2  $\text{CH}_2$  + 4  $\text{NCH}_2$ ), 6.82 (t,  $J$  = 7.2 Hz, 1 H, ArH), 6.84–6.89 (m, 1 H, ArH), 6.90–6.96 (m, 2 H, ArH), 6.97–7.01 (m, 1 H, ArH), 7.16–7.26 (m, 2 H, ArH), 7.28–7.37 (m, 2 H, ArH).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.7, 27.1, 37.2, 42.9, 50.5, 50.6, 109.6, 116.7, 117.3, 120.1, 126.5, 128.1, 128.4, 129.0, 129.1, 130.5, 134.3, 135.1, 138.9, 140.4, 145.8, 151.6, 152.0, 208.5.

GC–MS:  $m/z$  = 456  $[\text{M} + 1]^+$ .

Anal. Calcd for  $\text{C}_{28}\text{H}_{26}\text{ClN}_3\text{O}$ : C, 73.75; H, 5.75; N, 9.22. Found: C, 73.34; H, 5.49; N, 9.09.

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## Supporting Information

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