

## Practical and Versatile Synthesis of Thioflavones from 2-Bromobenzoyl Chlorides

Jae In Lee\* and Jin Sun Choi

Department of Chemistry, College of Natural Science, Duksung Women's University, Seoul 132-714, Korea.

\*E-mail: jilee@duksung.ac.kr

(Received February 9, 2015; Accepted March 16, 2015)

**Key words:** Thioflavones, Acylation, 1,4-Addition, Cyclization

Thioflavones (2-phenyl-4*H*-benzothiopyran-4-ones) are thio analogues of flavones in which an oxygen atom is substituted with a sulfur atom and have drawn considerable interest because of their profound pharmacological activities. They exhibit antibacterial,<sup>1</sup> antimicrobial,<sup>2</sup> and anticancer effects<sup>3</sup> in human breast cancer cell lines and are useful inhibitors of human steroid sulfatase.<sup>4</sup> Thioflavone sulfur atoms are easily oxidized with *m*-CPBA<sup>5,6</sup> or dimethyldioxirane<sup>7</sup> in contrast with flavones and their 1-oxide derivatives show antitumor activities<sup>5</sup> and are potent inhibitors of cytomegalovirus protease.<sup>6</sup>

Thioflavones have been generally synthesized by Friedel-Crafts acylation of  $\beta$ -(arylthio)cinnamates, prepared by condensing ethyl benzoylacetates with arylthiols<sup>5b,8</sup> or by the 1,4-addition of sodium arylthiolates to aryl propiolates,<sup>9</sup> with hot polyphosphoric acid. However, when the cinnamyl ring is activated by methoxy substituents, this method induces competitive cyclization in the cinnamyl aromatic ring, rather than in the sulfur-bearing ring. The cyclization of *S*-protected ( $\alpha$ -sulfinyl)enones, prepared by condensing 2'-*tert*-butylthioacetophenones<sup>10</sup> or  $\alpha$ -(2-*S*-benzylbenzoyl) sulfoxide<sup>11</sup> and arylaldehydes, with iodine and formic acid, respectively, afforded thioflavones in multiple steps. Similarly, the condensation of polythiated *N*-carboalkoxyhydrazones<sup>12</sup> or acetoanilides<sup>13</sup> using excess LDA with methyl thiosalicylate afforded C-acylated mercaptohydrazones. These compounds then underwent hydrolysis/cyclodehydration with hydrochloric acid to give thioflavones under reflux.

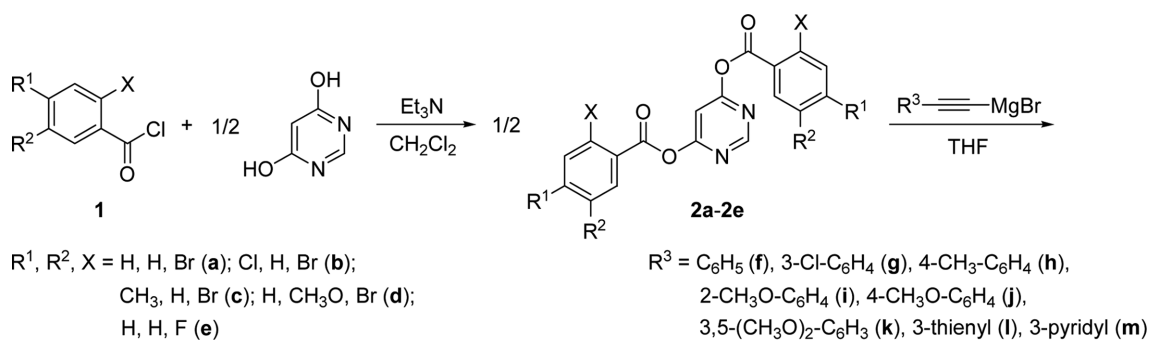
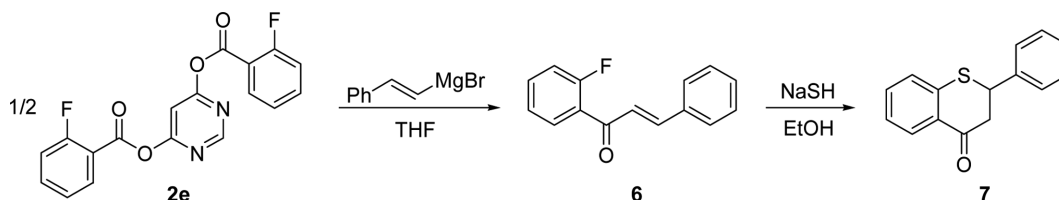
The Wittig-type cyclization of acylphosphoranes derived from *S*-aroyl thiosalicylic acids and triphenylphosphine,<sup>5</sup> *N*-phenyl(triphenylphosphoranylidene)ethanimine,<sup>14</sup> or (trimethylsilyl)methylenetriphenylphosphorane<sup>15</sup> also resulted in thioflavones. However, the separation of phenyl isocyanate and silylated ethers is often tedious. The addition/cyclization of 1-(*o*-haloheteroaryl)-3-phenylprop-2-yn-1-ones, which were prepared by coupling *o*-haloheteroaroyl chlorides with phenylacetylene using a Pd(OAc)<sub>2</sub> catalyst, with sodium

hydrosulfide in refluxing EtOH afforded heterocyclic analogues of thioflavones.<sup>16</sup> However, the yields of the coupling and addition/cyclization steps vary depending on heterocyclic group structures and the synthesis of thioflavones was not fully investigated. The coupling-addition-nucleophilic substitution of (hetero)aroyl chlorides, phenyl acetylenes, and sodium sulfide in consecutive one-pot reactions afforded (hetero)thioflavones in a microwave cavity in moderate yields.<sup>17</sup>

In a previous paper, we reported that thioflavones were synthesized by the cyclodehydration of 1-(2-mercaptophenyl)-3-phenyl-1,3-propanediones with H<sub>2</sub>SO<sub>4</sub> in CH<sub>3</sub>CN at room temperature.<sup>18a,b</sup> However, thioflavone derivatives with substituents on the condensed benzene ring were not prepared because the starting materials of substituted thiosalicylic acids were not readily accessible. Recently we reported that 3',4'-dimethoxythioflavone induced vasorelaxation through activation of epidermal growth factor (EGF) receptor in the endothelium.<sup>19</sup> As an extension of thioflavonoid synthesis, we describe a practical and versatile synthesis of thioflavones from 2-bromobenzoyl chlorides as potent drug candidates, including derivatives with chloro, methyl, or methoxy substituents on the condensed benzene ring.

4,6-Pyrimidyl di(2-halobenzoates) (**2a–2e**) were readily prepared by acylation of 2 equiv of **1** with 4,6-dihydroxypyrimidine in the presence of 2 equiv of triethylamine in methylene chloride at room temperature (Scheme 1). After evaporating methylene chloride, the mixture was dissolved in anhydrous THF and triethylamine hydrochloride was filtered off. The condensed residue was purified by short pathway silica gel (Davisil®, pH=7) column chromatography or recrystallization in 75% EtOAc/*n*-hexane to give **2** in 85–94% yields.

Successful synthesis of 2 equiv of 1-(2-bromophenyl)-3-(hetero)aryl-2-propyn-1-ones (**3**) was accomplished by reacting 1 equiv of **2** with 2 equiv of (hetero)arylethynylmagnesium bromides. The addition of 2 equiv of (hetero)arylethynyl-

Scheme 1. Synthesis of thioflavones **5**.Scheme 2. Synthesis of thioflavanone **7**.

magnesium bromides, generated from the reaction of (hetero)arylacetylenes and ethylmagnesium bromide in THF for 0.5 h at 0 °C, to a solution of **1** equiv of **2** in THF at 0 °C led to the formation of the precipitates. These intermediates were hydrolyzed with saturated  $\text{NH}_4\text{Cl}$  solution to give **3** in 78–89% yields. The reaction seemed to proceed *via* a 6-membered chelate. Side products such as the corresponding alcohols, due to the over-addition of (hetero)arylethynylmagnesium bromides to **3**, were not observable regardless of the steric hindrance of the 2-bromo group in **2**.

Benzothiopyran ring formation was achieved *via* the 1,4-addition of hydrosulfide anion and one-pot sequence of bromide substitution. The addition of **3** in EtOH to a suspended solution of sodium hydrosulfide hydrate in EtOH at room temperature rapidly afforded unsaturated thiolate adducts **4** which were detected by TLC as yellow spots. These intermediates subsequently underwent intramolecular nucleophilic substitution at reflux to give thioflavones **5** with the formation of sodium bromide precipitate. Cyclization of the corresponding thiolate adducts of 1-(2-bromo-4-chlorophenyl)-3-(hetero)aryl-2-propyn-1-ones (**3bj**, **3bl**) and 1-(2-bromo-5-methoxyphenyl)-3-aryl-2-propyn-1-ones (**3dg**, **3dk**) was completed in 1.5 h and 24 h, respectively,

indicating that the first step of thiolate addition in **4** is slow.

Similarly the synthesis of thioflavanone was briefly accomplished using 4,6-pyrimidyl di(2-fluorobenzoate) (**2e**). The addition of 2 equiv of styrylmagnesium bromide to a solution of **2e** in THF afforded 1-(2-fluorophenyl)-3-phenyl-2-propen-1-one (**6**) in 57% yield, which was subsequently treated with sodium hydrosulfide in EtOH for 7 h at 80 °C to give thioflavanone (**7**) in 88% yield (Scheme 2).

As shown in Table 1, various thioflavones were synthesized with overall high yields (56–71%) from starting material **1**. The reaction worked well with electron-withdrawing substituents, such as 7-chloro groups (**5bj**, **5bl**), and electron-donating substituents, such as 7-methyl (**5ch**, **5ci**, **5cm**) and 6-methoxy groups (**5dg**, **5dk**), in the condensed benzene rings. The reaction worked also well regardless of the type and position of electron-withdrawing groups (**5ag**, **5dg**) and electron-donating groups (**5aj**, **5bj**, **5ch**, **5ci**, **5dk**) of the 2-substituted phenyl rings under the present reaction conditions. Furthermore, this method was applicable for synthesizing of **5** containing heteroaromatic groups, such as 3-thienyl (**5bl**) and 3-pyridyl groups (**5cm**), in place of the 2-substituted phenyl group.

In conclusion, the present method offers practical and

**Table 1.** Synthesis of thioflavones **5** from alkynones **3**

Entry <b>5</b>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Isolated yields, % <sup>a</sup>
<b>af</b>	H	H	C <sub>6</sub> H <sub>5</sub>	80 (56)
<b>ag</b>	H	H	3-Cl-C <sub>6</sub> H <sub>4</sub>	83 (61)
<b>aj</b>	H	H	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	81 (63)
<b>bj</b>	Cl	H	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	85 (60)
<b>bl</b>	Cl	H	3-thienyl	87 (63)
<b>ch</b>	CH <sub>3</sub>	H	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	89 (71)
<b>ci</b>	CH <sub>3</sub>	H	2-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	80 (66)
<b>cm</b>	CH <sub>3</sub>	H	3-pyridyl	85 (62)
<b>dg</b>	H	CH <sub>3</sub> O	3-Cl-C <sub>6</sub> H <sub>4</sub>	83 (63)
<b>dk</b>	H	CH <sub>3</sub> O	3,5-(CH <sub>3</sub> O) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	83 (61)

<sup>a</sup>The numbers in parentheses indicate the overall yields of three steps from 2-bromobenzoyl chlorides **1**.

versatile synthesis of thioflavones from 2-bromobenzoyl chlorides. It has the advantages of providing (i) 2 equiv of alkynones **3** from 1 equiv of 4,6-pyrimidyl di(2-bromobenzoates) **2** (ii) versatile thioflavones with various substituents (iii) readily available starting materials (iv) high yields in each step. Therefore, this method can be widely utilized for the practical synthesis of thioflavone derivatives.

## EXPERIMENTAL

### Preparation of 4,6-pyrimidyl di(2-bromo-4-chlorobenzoate) (**2b**)

2-Bromo-4-chlorobenzoyl chloride (2.54 g, 10.0 mmol) was added to a suspended solution of 4,6-dihydroxypyrimidine (560 mg, 5.0 mmol) and triethylamine (1.40 mL, 10.0 mmol) in methylene chloride (40 mL) at room temperature. After stirring for 3 h, methylene chloride was evaporated *in vacuo*. The mixture was dissolved in anhydrous THF and triethylamine hydrochloride was filtered off. The residue was recrystallized twice in 75% EtOAc/*n*-hexane to give **2b** (2.32 g, 85%). mp 134–136 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.99 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 0.8 Hz, 2H), 7.47 (dd, *J*<sub>1</sub> = 8.5 Hz, *J*<sub>2</sub> = 0.8 Hz, 2H), 7.40 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.6, 161.1, 159.2, 140.4, 135.0, 133.6, 128.0, 127.1, 124.3, 105.4; FTIR (KBr) 1762 (C=O) cm<sup>-1</sup>.

### Preparation of 1-(2-bromo-4-chlorophenyl)-3-(4-methoxyphenyl)-2-propyn-1-one (**3bj**)

4-Methoxyphenylethynylmagnesium bromide, generated from 4-methoxyphenylacetylene (529 mg, 4.0 mmol) and ethylmagnesium bromide (1.0 M, 4.0 mL, 4.0 mmol) in THF (10 mL), was slowly added to a solution of **2b** (1.09 g, 2.0 mmol) in THF (15 mL) at 0 °C under argon atmosphere.

The mixture was stirred for 0.5 h at 0 °C and then quenched with saturated NH<sub>4</sub>Cl solution (5 mL). After evaporating THF, the mixture was poured into saturated NH<sub>4</sub>Cl solution (30 mL) and extracted with methylene chloride (3×20 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was recrystallized twice in 10% EtOAc/*n*-hexane to give **3bj** (1.16 g, 83%). mp 131–133 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.01 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 1.8 Hz, 1H), 7.60 (d, *J* = 8.9 Hz, 2H), 7.43 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 1.9 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 176.4, 162.0, 138.9, 136.1, 135.3, 134.6, 133.5, 127.7, 121.9, 114.5, 111.5, 96.1, 87.9, 55.5; FTIR (KBr) 2196 (C≡C), 1641 (C=O) cm<sup>-1</sup>; Ms *m/z* (%) 352 (M<sup>+</sup>+4, 21), 350 (M<sup>+</sup>+2, 85), 348 (M<sup>+</sup>, 67), 324 (13), 322 (54), 320 (42), 159 (100).

### Preparation of 7-chloro-4'-methoxythioflavone (**5bj**)

A solution of **3bj** (1.05 g, 3.0 mmol) in EtOH (20 mL) was added to a suspended solution of sodium hydrosulfide hydrate (60% dispersion in mineral oil, 336 mg, 3.6 mmol) in EtOH (15 mL) at room temperature. Stirring was continued at this temperature for 0.5 h and the resulting reddish solution was refluxed for 1.5 h more. After evaporating EtOH, the mixture was poured into saturated NH<sub>4</sub>Cl solution (30 mL) and extracted with methylene chloride (3×20 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was recrystallized twice in 10% EtOAc/*n*-hexane to give **5bj** (772 mg, 85%). mp 173–174 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.45 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 1.9 Hz, 1H), 7.63 (d, *J* = 8.9 Hz, 2H), 7.47 (dd, *J*<sub>1</sub> = 8.6 Hz, *J*<sub>2</sub> = 2.0 Hz, 1H), 7.16 (s, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 3.88 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 180.1, 162.0, 152.5, 138.9, 138.2, 130.1, 129.3, 128.4, 128.3 (overlapped), 125.7, 122.2, 114.7, 55.5; FTIR (KBr) 1625 (C=O) cm<sup>-1</sup>; Ms *m/z* (%) 304 (M<sup>+</sup>+2, 40), 302 (M<sup>+</sup>, 100), 276 (15), 274 (47), 261 (11), 259 (34), 132 (41).

**5af**, **5ag**, **5aj**, and **7**: All products were identified by means of mp, <sup>1</sup>H/<sup>13</sup>C NMR, FTIR, and mass spectrometry and consistent with the previous results.<sup>18a,c</sup>

**7-Chloro-3-thienyl-4H-1-benzothiopyran-4-one (5bl)**: mp 150–151 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.44 (d, *J* = 8.6 Hz, 1H), 7.77 (dd, *J*<sub>1</sub> = 2.9 Hz, *J*<sub>2</sub> = 1.4 Hz, 1H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.45–7.50 (m, 2H), 7.42 (dd, *J*<sub>1</sub> = 5.1 Hz, *J*<sub>2</sub> = 1.3 Hz, 1H), 7.21 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 180.2, 146.5, 138.5, 138.4, 137.3, 130.2, 129.4, 128.4, 127.8, 125.6, 125.3, 125.2, 122.1; FTIR (KBr) 1615 (C=O) cm<sup>-1</sup>; Ms *m/z* (%) 280 (M<sup>+</sup>+2, 41), 278 (M<sup>+</sup>, 98), 252 (41), 250 (100), 170 (47).

**7,4'-Dimethylthioflavone (5ch)**: mp 129 °C; <sup>1</sup>H NMR

(300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.42 (d,  $J = 8.3$  Hz, 1H), 7.58 (d,  $J = 8.2$  Hz, 2H), 7.43 (s, 1H), 7.34 (d,  $J = 8.3$  Hz, 1H), 7.29 (d,  $J = 8.0$  Hz, 2H), 7.19 (s, 1H), 2.47 (s, 3H), 2.42 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  180.8, 152.7, 142.4, 141.2, 137.9, 133.8, 129.9, 129.2, 128.8, 128.5, 126.8, 126.2, 122.9, 21.6, 21.4; FTIR (KBr) 1638 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; Ms  $m/z$  (%) 266 ( $\text{M}^+$ , 100), 238 (86), 150 (34), 121 (21).

**7-Methyl-2'-methoxythioflavone (5ci):** mp 118–119 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (d,  $J = 8.3$  Hz, 1H), 7.42–7.46 (m, 2H), 7.40 (s, 1H), 7.33 (d,  $J = 8.3$  Hz, 1H), 7.12 (s, 1H), 7.06 (d,  $J = 7.6$  Hz, 1H), 7.01 (d,  $J = 8.4$  Hz, 1H), 3.85 (s, 3H), 2.46 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  180.7, 156.5, 149.9, 142.2, 138.9, 131.5, 130.3, 129.1, 128.7, 128.4, 126.8, 125.9, 125.6, 120.9, 111.7, 55.8, 21.6; FTIR (KBr) 1620 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; Ms  $m/z$  (%) 282 ( $\text{M}^+$ , 100), 151 (72), 121 (25).

**7-Methyl-3-pyridyl-4H-1-benzothiopyran-4-one (5cm):** mp 154–155 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.94 (d,  $J = 1.9$  Hz, 1H), 8.75 (dd,  $J_1 = 4.8$  Hz,  $J_2 = 1.3$  Hz, 1H), 8.43 (d,  $J = 8.3$  Hz, 1H), 7.95–7.99 (m, 1H), 7.42–7.46 (m, 1H), 7.46 (s, 1H), 7.38 (d,  $J = 8.3$  Hz, 1H), 7.19 (s, 1H), 2.50 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  180.4, 151.6, 149.0, 147.7, 142.9, 137.3, 134.3, 132.7, 129.7, 128.6, 126.2, 124.3, 123.8, 123.2, 21.6; FTIR (KBr) 1636 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; Ms  $m/z$  (%) 253 ( $\text{M}^+$ , 100), 225 (74), 150 (29), 121 (24).

**6-Methoxy-3'-chlorothioflavone (5dg):** mp 189–190 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (d,  $J = 2.7$  Hz, 1H), 7.68 (s, 1H), 7.55–7.59 (m, 2H), 7.41–7.50 (m, 2H), 7.25–7.29 (m, 1H), 7.22 (s, 1H), 3.95 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  180.4, 159.7, 151.2, 138.4, 135.3, 132.3, 130.7, 130.5, 129.4, 127.8, 127.1, 125.2, 123.0, 122.4, 108.8, 55.8; FTIR (KBr) 1625 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; Ms  $m/z$  (%) 304 ( $\text{M}^+ + 2$ , 39), 302 ( $\text{M}^+$ , 100), 272 (28), 123 (20).

**6,3',5'-Trimethoxythioflavone (5dk):** mp 154–155 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (d,  $J = 2.8$  Hz, 1H), 7.56 (d,  $J = 8.8$  Hz, 1H), 7.24 (s, 1H), 7.26 (dd,  $J_1 = 8.5$  Hz,  $J_2 = 2.1$  Hz, 1H), 6.82 (d,  $J = 2.2$  Hz, 2H), 6.58 (t,  $J = 2.2$  Hz, 1H), 3.94 (s, 3H), 3.85 (s, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  180.5, 161.3, 159.6, 153.0, 138.6, 132.4, 129.7, 127.8, 122.6, 122.2, 108.9, 105.1, 102.7, 55.7, 55.6; FTIR (KBr) 1626 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; Ms  $m/z$  (%) 328 ( $\text{M}^+$ , 100), 298 (33), 123 (12).

## REFERENCES

- Nakazumi, H.; Ueyama, T.; Kitao, T. *J. Heterocycl. Chem.* **1984**, *21*, 193.
- Nakazumi, H.; Kobara, Y.; Kitao, T. *J. Heterocycl. Chem.* **1992**, *29*, 135.
- Choi, E. J.; Lee, J. I.; Kim, G.-H. *Int. J. Mol. Med.* **2012**, *29*, 252.
- (a) Nussbaumer, P.; Winiski, A. P.; Billich, A. *J. Med. Chem.* **2003**, *46*, 5091. (b) Horvath, A.; Nussbaumer, P.; Wolff, B.; Billich, A. *J. Med. Chem.* **2004**, *47*, 4268.
- (a) Holshouser, M. H.; Loeffler, L. J.; Hall, I. H. *J. Med. Chem.* **1981**, *24*, 853. (b) Wang, H.-K.; Bastow, K. F.; Cosentino, L. M.; Lee, K.-H. *J. Med. Chem.* **1996**, *39*, 1975.
- Dhanak, D.; Keenan, R. M.; Burton, G.; Kaura, A.; Darcy, M. G.; Shah, D. H.; Ridgers, L. H.; Breen, A.; Lavery, P.; Tew, D. G.; West, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3677.
- Patonay, T.; Adam, W.; Levai, A.; Kover, P.; Nemeth, M.; Peters, E.-M.; Peters, K. *J. Org. Chem.* **2001**, *66*, 2275.
- (a) Nakazumi, H.; Watanabe, S.; Kitaguchi, T.; Kitao, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 847. (b) Dekermendjian, K.; Kahnberg, P.; Witt, M.-R.; Sterner, O.; Nielsen, M.; Liljefors, T. *J. Med. Chem.* **1999**, *42*, 4343. (c) Sabatini, S.; Gosetto, F.; Manfroni, G.; Tabarrini, O.; Kaatz, G. W.; Patel, D.; Cecchetti, V. *J. Med. Chem.* **2011**, *54*, 5722.
- Wadworth, D. H.; Detty, M. R. *J. Org. Chem.* **1980**, *45*, 4611.
- Kobayashi, K.; Kobayashi, A.; Ezaki, K. *Heterocycles* **2012**, *85*, 1997.
- (a) Taylor, A. W.; Dean, D. K. *Tetrahedron Lett.* **1988**, *29*, 1845. (b) Kataoka, T.; Watanabe, S.; Mori, E.; Kadomoto, R.; Tanimura, S.; Kohno, M. *Bioorg. Med. Chem.* **2004**, *12*, 2397.
- (a) French, K. L.; Angel, A. J.; Williams, A. R.; Hurst, D. R.; Beam, C. F. *J. Heterocycl. Chem.* **1998**, *35*, 45. (b) Angel, A. J.; Finefrock, A. E.; French, K. L.; Hurst, D. R.; Williams, A. R.; Rampey, M. E.; Studer-Martinez, S. L.; Beam, C. F. *Can. J. Chem.* **1999**, *77*, 94.
- Metz, C. R.; Knight, J. D.; Pastine, S. J.; Pennington, W. T.; Beam, C. F. *J. Chem. Crystallogr.* **2010**, *40*, 536.
- (a) Kumar, P.; Rao, A. T.; Pandey, B. *J. Chem. Soc., Chem. Commun.* **1992**, 1580. (b) Kumar, P.; Rao, A. T.; Pandey, B. *Synth. Commun.* **1994**, *24*, 3297.
- Kumar, P.; Bodas, M. S. *Tetrahedron* **2001**, *57*, 9755.
- Fuchs, F. C.; Eller, G. A.; Holzer, W. *Molecules* **2009**, *14*, 3814.
- (a) Willy, B.; Muller, T. J. J. *Synlett* **2009**, 1255. (b) Willy, B.; Frank, W.; Muller, T. J. J. *Org. Biomol. Chem.* **2010**, *8*, 90.
- (a) Lee, J. I. *Bull. Korean Chem. Soc.* **2009**, *30*, 710. (b) Lee, J. I.; Kim, M. J. *Bull. Korean Chem. Soc.* **2011**, *32*, 1383. (c) Lee, J. I. *Bull. Korean Chem. Soc.* **2008**, *29*, 1263.
- Jang, E. J.; Seok, Y. M.; Lee, J. I.; Cho, H. M.; Sohn, U. D.; Kim, I. K. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2013**, *386*, 339.