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# Fused thia-heterocycles *via* isothiocyanates. Part I. Facile synthesis of some new 1-benzothiopyran-4-one derivatives

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**Abstract:** A selected set of new 4*H*-benzothiopyran-4-one derivatives **6a–h** has been prepared by a one-pot reaction involving deprotonated methyl 3-oxo-3-(2',4',5'-trichlorophenyl)propanoate **5** and the appropriate aryl or alkyl isothiocyanate. 2,4,5-Trichloroacetophenone **4**, required for the synthesis of **5**, is successfully prepared by Friedel–Craft's acylation of 1,2,4-trichlorobenzene in 82% yield. The structures of the new compounds **5** and **6a–h** are based on microanalytical and spectral (NMR, MS(EI), and HRMS) data.

**Keywords:** 1,2,4-trichlorobenzene; 4-oxo-1-benzothiopyrans; Friedel–Craft's acylation; isothiocyanates; methyl 3-oxo-3-(2',4',5'-trichlorophenyl)propanoate.

## 1 Introduction

The 4-oxo-1-benzothiopyran (thiochromone) ring system **1a** [1–3] gains continued interest as a sulfur analog of the naturally occurring chromone nucleus **1b** (Fig. 1) [4, 5]. Several derivatives of **1a** were reported to possess remarkable biological activities and regain pharmacological interest. Notable examples include **2a** [6] which showed *in vitro* inhibitory potency against HIV ( $ED_{50} = 0.65 \mu\text{M}$ ), **2b** [7] and related analogs [8] acting as antitumor agents, and the anti-inflammatory analgesic agent **3** (Fig. 1) [9]. Meanwhile, certain other derivatives act as potential anti-malarials [10], photoactive pesticides [11], and selective inhibitors of the v-abl tyrosine protein kinase [12].

General synthetic routes to **1a** utilize suitably-substituted thiophenol as the sulfur atom source, and

annulating the thiopyranone entity thereupon [1–3]. Examples include various thiophenols (represented, in their cyclocondensation with  $\beta$ -keto esters [13–15] or propiolates [16, 9], early favored methods), employment of thiosalicylic acid [17–20], methyl thiosalicylate [21–23],  $\beta$ -(2-chloroaryl) thioacetanilides [24], thioisatins [25], while related routes utilize potassium *O*-ethylxanthate [26] or carbon disulfide [27] as the source of sulfur atom.

During the past decades, isothiocyanates have been employed as attractive synthons in the construction of various heterocyclic systems, and the subject has been reviewed [28]. Herein, we wish to report on the synthesis and properties of some new 1-benzothiopyran-4-ones (**6a–g**) utilizing aryl/alkyl isothiocyanates (as the source of the sulfur atom) as depicted in Scheme 1 (*vide infra*).

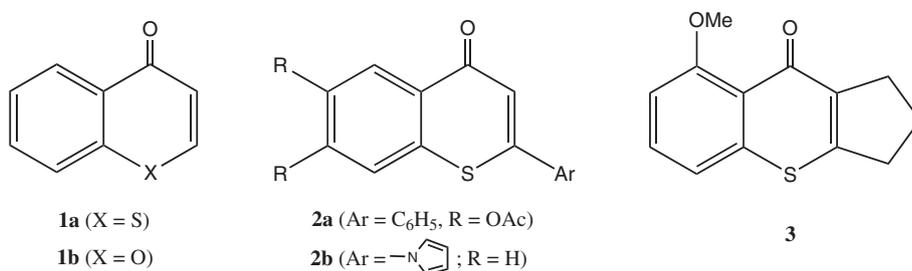
## 2 Results and discussion

### 2.1 Chemistry

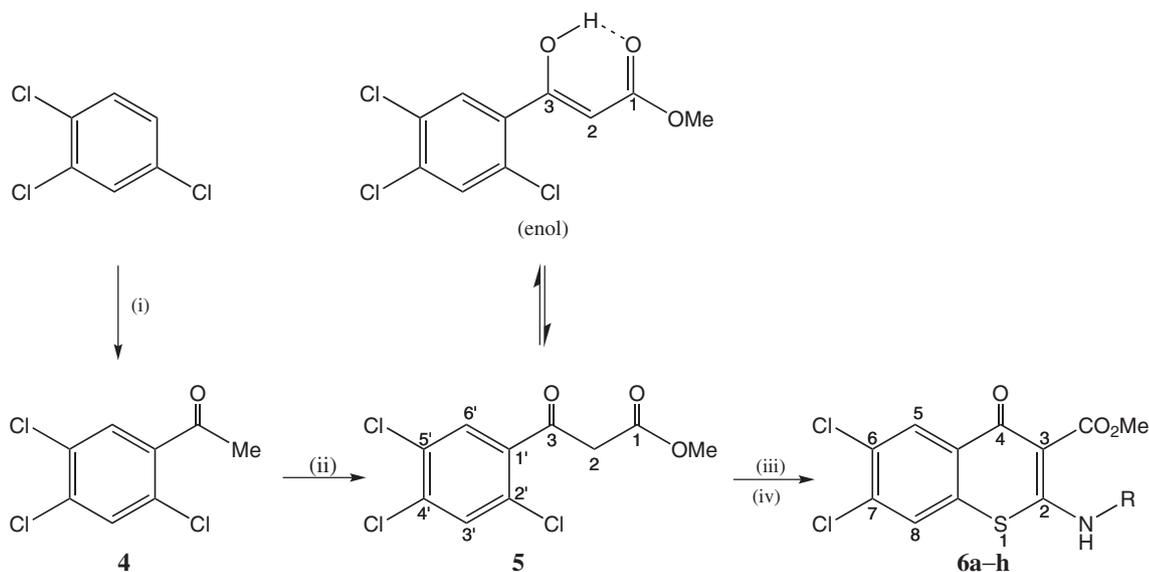
The synthesis of methyl 2-(substituted amino)-6,7-dichloro-4-oxo-4*H*-1benzothiopyran-3-carboxylates **6a–h** is achieved by utilizing 2,4,5-trichloroacetophenone (**4**) as starting material and constructing the thiopyranone nucleus thereupon through two-step conversions as illustrated in Scheme 1. Compound **4**, in turn, is prepared by Friedel–Craft's acylation of 1,2,4-trichlorobenzene using acetyl chloride and anhydrous aluminum trichloride as Lewis acid catalyst. Previously, great difficulty was experienced in a multistep synthesis of 2,4,5-trichloroacetophenone **4** starting from 1,2,4-trichlorobenzene [29]. Compound **4** was also prepared from 2-amino-4,5-dichloroacetophenone [30, 31].

By analogy to the reported procedure for a related system [32], direct interaction of the enolate anion of **4** with dimethyl carbonate delivered compound **5**; this reaction is type of a classical 'crossed-Claisen' condensation, commonly employed for the synthesis of  $\beta$ -keto esters. The targeted 4-oxo-1-benzothiopyrans **6a–h** were finally obtained by interaction of the appropriate isothiocyanate with deprotonated **5** in anhydrous DMF and consequent

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**Fig. 1:** Examples of bioactive 1-benzothiopyran-4-ones (**2**, **3**).

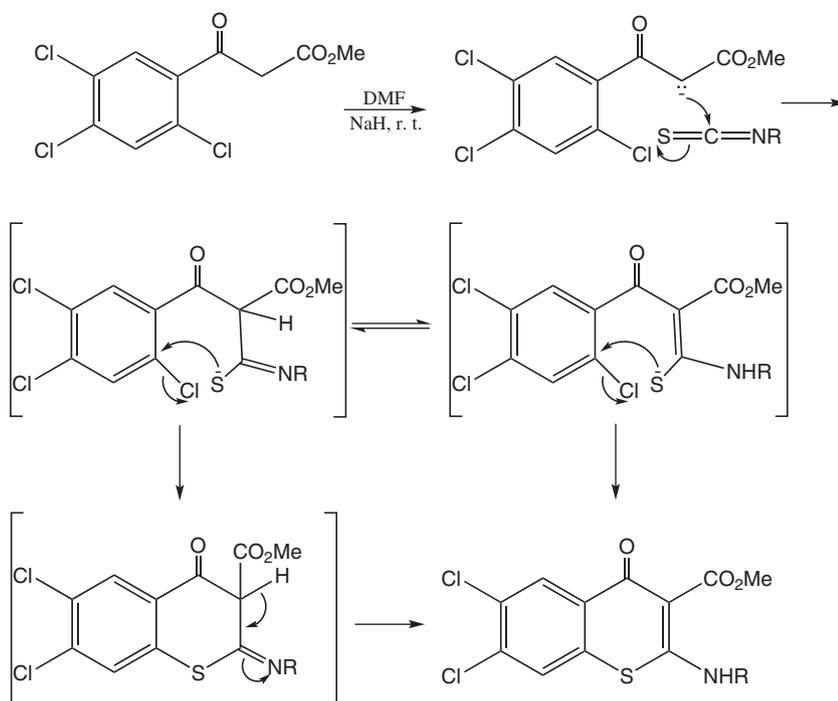


Entry	a	b	c	d	e
R					
Entry	f	g	h		
R					

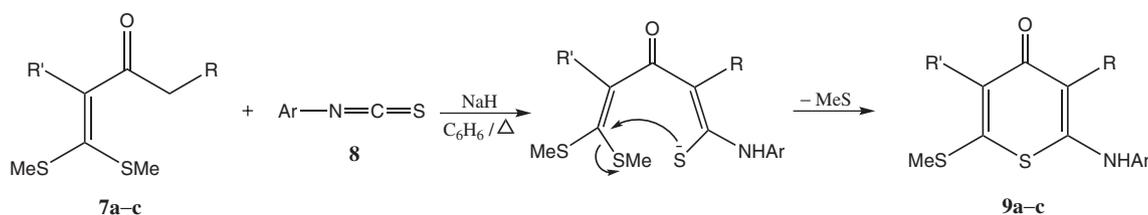
**Scheme 1:** Synthetic route for compounds **6a–h**.

intracyclization of the resulting intermediate adduct at the refluxing temperature (Scheme 2). Herein, treatment of **5** with sodium hydride in dry DMF led to the formation of the enolate anion. The latter ‘carbanion’ adds to the central *sp* carbon of the isothiocyanate reactant. Cyclization of the

intermediate adduct occurred *via* nucleophilic addition of the anionic sulfur at the benzenoid C-2, followed by subsequent displacement of the chloride anion through nucleophilic addition–elimination ( $\text{S}_{\text{N}}\text{AE}$ ) mechanism (Scheme 2). Moderate to low yields of highly pure **6a–h**



**Scheme 2:** A plausible mechanism for the formation of compounds **6a-h**.



compounds **7 / 9**: **a** ( $R = R' = H$ ); **b** ( $R = H, R' = Me$ ); **c** ( $R = R' = Me$ )

compounds **8**:  $Ar = C_6H_5$ ; 4-MeC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>

**Scheme 3:** A reported synthesis [33] of some 4*H*-thiopyran-4-ones utilizing aryl isothiocyanates.

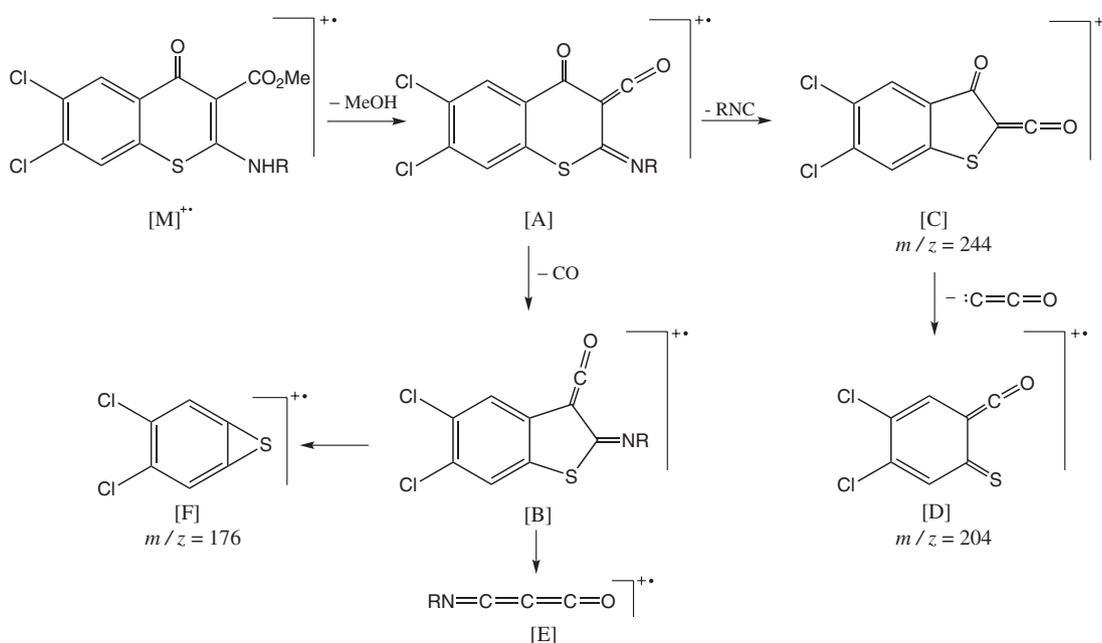
were obtained in DMF, whereas the reaction did neither proceed in THF nor in 1,4-dioxane, and no attempt was made to optimize the yield. In this context, it should be noted that a closely related approach to the construction of the monocyclic 4*H*-thiopyran-4-one ring system, exemplified by its derivatives **9a-c**, has once been reported utilizing the reaction of aryl isothiocyanates **8** with ketene dithioacetals **7a-c** as illustrated in Scheme 3 [33].

The newly synthesized compounds **6a-h** were characterized by elemental analysis, IR, MS, <sup>1</sup>H and <sup>13</sup>C NMR spectral data. These data, detailed in the experimental section, are consistent with the suggested structures. Thus, the mass spectra display the correct molecular peaks for which the measured high resolution (HRMS) data are in good agreement with the evaluated values. Dept. and

2D (correlation spectroscopy, heteronuclear multiple-quantum coherence, heteronuclear multiple-bond correlation) experiments showed correlations that helped in the <sup>1</sup>H and <sup>13</sup>C signal assignments to the different carbons and their attached and/or neighboring hydrogen atoms.

## 2.2 Mass spectra

The major fragment ions are shown in Scheme 4. The principle fragmentation pathway is initiated by loss of MeOH from [M]<sup>+</sup> to give fragment ion [A], [M-32] as base peak in most cases. The latter ion [A] suffered loss of CO to produce ion [B], [M-60], or loss of R-NC to deliver ion [C] ( $m/z=244$ ) which in turn eliminates [ $:C=C=O$ ]



**Scheme 4:** Principle fragmentation pathways of compounds **6a–h** under electron impact (EI).

to form ion  $[D]$  ( $m/z=204$ ). Further fragmentation of ion  $[B]$  generated either ion  $[E]$ ,  $[\text{RN}=\text{C}=\text{C}=\text{O}]$ , or ion  $[F]$  ( $m/z=176$ ). Except for compound **6e**, which incorporates three chlorine atoms, the molecular ion region showed the corresponding isotopic cluster ( $[M]^+$ ,  $[M+2]^+$ ,  $[M+4]^+$ ) with the relative intensity ratios of 9:6:1 which confirms the presence of two chlorine atoms for the rest compounds.

### 3 Conclusion

The present work demonstrates successful application of aryl and alkyl isothiocyanates as sulfur atom source in one-pot synthesis of 2-(aryl/alkylamino)-1-benzothio-*pyran*-4-one derivatives **6a–h** utilizing deprotonated 3-oxo-3-(2,4,5-trichlorophenyl)propanoates **5**. This new route utilizes readily available isothiocyanates together with accessible suitably substituted  $\beta$ -(*o*-haloaryl)- $\beta$ -keto esters and is of promising wide scope and versatility toward synthesis of diverse thiochromone derivatives.

### 4 Experimental section

The aryl and alkyl isothiocyanates used in this study, were purchased from Sigma Aldrich (St. Louis, MO, USA). 1,2,4-Trichlorobenzene, anhydrous aluminum trichloride,

dimethyl carbonate, and sodium hydride (60% dispersion in mineral oil) were purchased from Acros (Geel, Belgium). Dimethyl formamide (DMF) was dried over anhydrous calcium chloride for 24 h, distilled under reduced pressure (53°C/20 mmHg), and stored over molecular sieves (4 Å grade) before use. Melting points (uncorrected) were measured on a Gallenkamp electrothermal melting temperature apparatus (London, UK).  $^1\text{H}$ ,  $^{13}\text{C}$ , and 2D NMR spectra were recorded on a Bruker-DPX 300 MHz spectrometer (Karlsruhe, Germany), using  $\text{CDCl}_3$  as solvent and TMS as internal reference. Mass spectra (EI) and high resolution data (HRMS) were obtained using a Finnigan MAT TSQ-70 spectrometer (IL, USA) at 70 eV; ion source temperature = 200°C. IR spectra were determined as KBr disks on a Nicolet Impact – 400 FT-IR spectrophotometer (Waltham, MA, USA). Elemental analysis was performed at the Microanalytical Lab. of Al-Najah National University, West Bank, Palestine.

#### 4.1 2,4,5-Trichloroacetophenone (4)

To a stirred mixture of 1,2,4-trichlorobenzene (18.2 g, 100 mmol) and anhydrous aluminum trichloride (33.4 g, 250 mmol), acetyl chloride (11.8 g, 150 mmol) was dropwise added at room temperature. The reaction mixture was gradually heated to 120–125°C (oil bath) and maintained at this temperature for 3 h. The resulting viscous mixture was cautiously poured onto ice-water (125 mL),

and the aqueous mixture was extracted with dichloromethane (3×70 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), evaporated, and the residue was distilled under reduced pressure to give a colorless liquid which solidified upon standing at room temperature. Yield: 15.6 g (82%); m. p. 43–45°C, b. p. 135°C/6 mmHg (lit. [29]: m. p. 47°C; lit. [30]: m. p. 44–46°C; lit. [31]: 45.5–46°C, b. p. 114–116°C/2 mmHg).

## 4.2 Methyl 3-oxo-3-(2',4',5'-trichlorophenyl) propanoate (5)

Compound 5 was prepared from 2,4,5-trichloroacetophenone (4) by a similar procedure as reported in [32] for the synthesis of related β-keto ester from its 3-acetyl-2,5-dichlorothiophene: sodium hydride (2.8 g, 60% dispersion in oil; 70 mmol) was portionwise added to a cold solution (5–10°C) of 4 (6.2 g, 34 mmol) in anhydrous dimethyl carbonate (100 mL). The mixture was heated at 84–86°C for 2 h and poured onto ice-cold water (250 mL) containing acetic acid (5 mL). The resulting mixture was extracted with diethyl ether (3×70 mL); the combined organic extracts were dried (MgSO<sub>4</sub>), and the solvent was evaporated. The residual product was recrystallized from pet. ether (40–60°C) giving the title compound 5 as colorless crystals. Yield: 8.1 g (84%); m. p. 71–72°C. – IR (KBr):  $\nu_{\max}$  = 1660, 1626 cm<sup>-1</sup>. – HRMS (EI):  $m/z$  = 279.94581 (calcd. 279.94608 for C<sub>10</sub>H<sub>7</sub>Cl<sub>3</sub>O<sub>3</sub>, [M]<sup>+</sup>). – <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.75 (s, 1.5 H, enol OCH<sub>3</sub>), 3.78 (s, 1.5 H, keto OCH<sub>3</sub>), 4.04 (s, 1H, keto 2-H<sub>2</sub>), 5.63 (s, 0.5 H, enol 2-H), 7.55 (br s, 1H, keto-enol 3'-H), 7.71 (s, 0.5 H, enol 6'-H), 7.75 (s, 0.5 H, keto 6'-H), 12.20 (s, 0.5 H, enol OH). – <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 48.6 (keto CH<sub>2</sub>-2), 51.8 (enol OCH<sub>3</sub>), 52.6 (keto OCH<sub>3</sub>), 93.7 (enol CH-2), 131.3, 131.6 (CH-3', keto-enol), 132.1, 132.3 (CH-6', keto-enol), 130.4, 130.8, 131.5, 132.2, 132.8, 134.8, 136.6, 136.9 (keto-enol pairs of the quaternary carbons: C-1', C-2', C-4', C-5'), 167.0 (enol C-1), 167.7 (keto C-1), 172.7 (enol HO–C-3), 192.1 (keto O=C-3). – C<sub>10</sub>H<sub>7</sub>O<sub>3</sub>Cl<sub>3</sub> (281.52): calcd. C 42.66, H 2.51, Cl 37.78; found C 42.43, H 2.48, Cl 37.52.

## 4.3 General procedure for the preparation of 1-benzothiopyran-4-ones 6a–h

Sodium hydride (2.8 g, 60% dispersion oil; 70 mmol) was portionwise added to a stirred solution of 5 (6.2 g, 34 mmol) in anhydrous DMF (50 mL) during 30 min. A solution of appropriate isothiosynate (10 mmol) in dry DMF (3 mL) was then added to the reaction mixture.

The resulting mixture was gradually heated and maintained at 145–150°C for 16–20 h. The reaction mixture was then neutralized with aqueous acetic acid (5 mL), and extracted with chloroform (3×25 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated to give a viscous product. This crude product was purified by preparative TLC chromatography on precoated silica gel plates employing chloroform-petroleum ether (5:1 v/v) as the developing solvent. The title compound was further purified by recrystallization from chloroform–methanol.

### 4.3.1 Methyl 6,7-dichloro-4-oxo-2-(*N*-phenylamino)-4*H*-1benzothiopyran-3-carboxylate (6a)

Yield: 32%; m. p. 121–122°C. – <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.97 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 7.35 (s, 1H, 8-H), 7.36 (m, 2H, 2'-H/6'-H), 7.42 (m, 1H, 4'-H), 7.50 (m, 2H, 3'-H/5'-H), 8.49 (s, 1H, 5-H), 11.75 (s, 1H, N-H, exchangeable with D<sub>2</sub>O) ppm. – <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 52.4 (CO<sub>2</sub>CH<sub>3</sub>), 100.4 (C-3), 125.2 (C-2'/C-6'), 127.0 (C-8), 127.1 (C-4'), 129.0 (C-6), 129.5 (C-3'/C-5'), 130.0 (C-5), 130.9 (C-7), 132.4 (C-4a), 136.2 (C-8a), 137.3 (C-1'), 166.0 (C-2), 170.2 (CO<sub>2</sub>Me), 175.9 (C-4) ppm. – IR (KBr):  $\nu_{\max}$  = 3421, 3055, 3013, 2953, 1636, 1626 cm<sup>-1</sup>. – HRMS (EI):  $m/z$  = 378.98416 (calcd. 378.98367 for C<sub>17</sub>H<sub>11</sub>Cl<sub>2</sub>NO<sub>3</sub>S, [M]<sup>+</sup>). – EIMS:  $m/z$  (%) = 379 (7) [M]<sup>+</sup>, 347 (100), 319 (9), 244 (4), 204 (17), 143 (19), 176 (13), 77 (72) [R]<sup>+</sup>. – C<sub>17</sub>H<sub>11</sub>Cl<sub>2</sub>NO<sub>3</sub>S (380.25): calcd. C 53.70, H 2.92, N 3.68; found C 53.56, H 2.88, N 3.75.

### 4.3.2 Methyl 6,7-dichloro-2-[*N*-(4-methylphenyl)amino]-4-oxo-4*H*-1-benzothiopyran-3-carboxylate (6b)

Yield: 35%; m. p. 146–147°C. – <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.43 (s, 3H, 4'-CH<sub>3</sub>), 3.96 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 7.22 (d,  $J$  = 8.3 Hz, 2H, 2'-H/6'-H), 7.30 (d,  $J$  = 8.3 Hz, 2H, 3'-H/5'-H), 7.32 (s, 1H, 8-H), 8.48 (s, 1H, 5-H), 11.65 (s, 1H, N-H, exchangeable with D<sub>2</sub>O) ppm. – <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 21.3 (4'-CH<sub>3</sub>), 52.4 (OCH<sub>3</sub>), 100.1 (C-3), 126.4 (C-8), 127.0 (C-2'/C-6'), 129.1 (C-6), 129.4 (C-7), 130.5 (C-3'/C-5'), 130.9 (C-5), 132.3 (C-4a), 133.5 (C-4'), 136.0 (C-8a), 139.2 (C-1'), 166.4 (C-2), 170.2 (CO<sub>2</sub>Me), 175.9 (C-4) ppm. – IR (KBr):  $\nu_{\max}$  = 3422, 3064, 2996, 2951, 1643, 1630 cm<sup>-1</sup>. – HRMS (EI):  $m/z$  = 392.99856 (calcd. 392.99932 for C<sub>18</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>3</sub>S, [M]<sup>+</sup>). – EIMS:  $m/z$  (%) = 393 (14) [M]<sup>+</sup>, 361 (100), 333 (17), 244 (7), 204 (13), 157 (61), 176 (4), 91 (48) [R]<sup>+</sup>. – C<sub>18</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>3</sub>S (394.28): calcd. C 54.83, H 3.32, N 3.55; found C 54.64, H 3.25, N 3.51.

#### 4.3.3 Methyl 6,7-dichloro-2-[*N*-(4-methoxyphenyl)amino]-4-oxo-4*H*-1-benzothiopyran-3-carboxylate (6c)

Yield: 21%; m. p. 201–202°C. – <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 3.88 (s, 3H, 4'-OCH<sub>3</sub>), 3.97 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 7.00 (d, *J* = 8.8 Hz, 2H, 3'-H/5'-H), 7.25 (d, *J* = 8.8 Hz, 2H, 2'-H/6'-H), 7.33 (s, 1H, 8-H), 8.49 (s, 1H, 5-H), 11.56 (s, 1H, N-H, exchangeable with D<sub>2</sub>O) ppm. – <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 52.3 (CO<sub>2</sub>CH<sub>3</sub>), 55.6 (4'-OCH<sub>3</sub>), 100.0 (C-3), 115.1 (C-3'/C-5'), 126.5 (C-8), 128.8 (C-2'/C-6'), 129.0 (C-6), 129.2 (C-1'), 130.6 (C-7), 130.9 (C-5), 132.3 (C-4a), 136.0 (C-8a), 160.0 (C-4'), 167.1 (C-2), 170.3 (CO<sub>2</sub>Me), 175.9 (C-4) ppm. – IR (KBr): ν<sub>max</sub> = 3420, 3014, 2994, 2843, 1668, 1619 cm<sup>-1</sup>. – HRMS (EI): *m/z* = 408.99414 (calcd. 408.99432 for C<sub>18</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>4</sub>S, [M]<sup>+</sup>). – EIMS: *m/z* (%) = 409 (20) [M]<sup>+</sup>, 377 (100), 349 (11), 244 (5), 204 (7), 173 (78), 176 (10), 107 (2) [R]<sup>+</sup>. – C<sub>18</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>4</sub>S (410.28): calcd. C 52.70, H 3.19, N 3.41; found C 52.58, H 3.12, N 3.32.

#### 4.3.4 Methyl 6,7-dichloro-2-[*N*-(4-fluorophenyl)amino]-4-oxo-4*H*-1-benzothiopyran-3-carboxylate (6d)

Yield: 22%; m. p. 173–174°C. – <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 3.96 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 7.18 (dd, *J*<sub>H-H</sub> = 8.7 Hz, <sup>2</sup>*J*<sub>H-F</sub> = 7.4 Hz, 2H, 3'-H/5'-H), 7.33 (dd, *J*<sub>H-H</sub> = 8.7 Hz, <sup>3</sup>*J*<sub>H-F</sub> = 2.8 Hz, 2H, 2'-H/6'-H), 7.35 (s, 1H, 8-H), 8.47 (s, 1H, 5-H), 11.64 (s, 1H, N-H, exchangeable with D<sub>2</sub>O) ppm. – <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 52.4 (OCH<sub>3</sub>), 100.5 (C-3), 117.1 (d, <sup>2</sup>*J*<sub>C-F</sub> = 22.2 Hz, C-3'/C-5'), 126.5 (C-8), 128.8 (C-6), 129.5 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.8 Hz, C-2'/C-6'), 130.5 (C-7), 130.9 (C-5), 132.2 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.2 Hz, C-1'), 132.6 (C-4a), 136.2 (C-8a), 162.6 (d, <sup>1</sup>*J*<sub>C-F</sub> = 250 Hz, C-4'), 166.3 (C-2), 170.2 (CO<sub>2</sub>Me), 175.8 (C-4) ppm. – IR (KBr): ν<sub>max</sub> = 3413, 3065, 2995, 2952, 1646, 1627 cm<sup>-1</sup>. – HRMS (EI): *m/z* = 396.97402 (calcd. 396.97425 for C<sub>17</sub>H<sub>10</sub>Cl<sub>2</sub>FNO<sub>3</sub>S, [M]<sup>+</sup>). – EIMS: *m/z* (%) = 397 (31) [M]<sup>+</sup>, 365 (100), 337 (19), 244 (7), 204 (47), 161 (95), 176 (14), 95 (3) [R]<sup>+</sup>. – C<sub>17</sub>H<sub>10</sub>Cl<sub>2</sub>FNO<sub>3</sub>S (398.24): calcd. C 51.27, H 2.53, N 3.52; found C 51.03, H 2.44, N 3.41.

#### 4.3.5 Methyl 2-[*N*-(4-chlorophenyl)amino]-6,7-dichloro-4-oxo-4*H*-1-benzothiopyran-3-carboxylate (6e)

Yield: 30%; m. p. 177–178°C. – <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 3.96 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 7.31 (d, *J* = 8.6 Hz, 2H, 2'-H/6'-H), 7.47 (d, *J* = 8.6 Hz, 2H, 3'-H/5'-H), 7.34 (s, 1H, 8-H), 8.46 (s, 1H, 5-H), 11.68 (s, 1H, N-H, exchangeable with D<sub>2</sub>O) ppm. – <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 52.4 (OCH<sub>3</sub>), 100.7 (C-3), 126.5 (C-8), 128.5 (C-2'/C-6'), 128.8 (C-6), 130.2 (C-3'/C-5'), 130.5 (C-7), 130.9 (C-5), 132.6 (C-4a), 134.7 (C-4'), 134.8 (C-1'), 136.3 (C-8a), 165.6 (C-2), 170.1 (CO<sub>2</sub>Me), 175.7 (C-4) ppm. – IR (KBr): ν<sub>max</sub> = 3421, 3054, 2991, 2960, 1644,

1634 cm<sup>-1</sup>. – HRMS (EI): *m/z* = 412.94413 (calcd. 412.94470 for C<sub>17</sub>H<sub>10</sub>Cl<sub>3</sub>NO<sub>3</sub>S, [M]<sup>+</sup>). – EIMS: *m/z* (%) = 415 (21) [M]<sup>+</sup>, 381 (100), 253 (11), 244 (7), 204 (45), 177 (64), 176 (10), 111 (12) [R]<sup>+</sup>. – C<sub>17</sub>H<sub>10</sub>Cl<sub>3</sub>NO<sub>3</sub>S (414.69): calcd. C 49.24, H 2.43, N 3.38; found C 49.06, H 2.39, N 3.35.

#### 4.3.6 Methyl 6,7-dichloro-2-[*N*-(1'-naphthyl)amino]-4-oxo-4*H*-1-benzothiopyran-3-carboxylate (6f)

Yield: 22%; m. p. 330°C (decomp.). – <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 4.03 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 7.21 (s, 1H, 8-H), 7.60 (m, 4H, 2'-H + 4'-H + 6'-H + 8'-H), 7.97 (m, 3H, 3'-H + 5'-H + 7'-H), 8.50 (s, 1H, 5-H), 12.04 (s, 1H, N-H, exchangeable with D<sub>2</sub>O) ppm. – <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 52.5 (CO<sub>2</sub>CH<sub>3</sub>), 100.3 (C-3), 122.0 (C-2'), 125.4 (C-4'), 126.0 (C-3'), 126.4 (C-8), 127.2 (C-6'), 127.8 (C-7'), 128.7 (C-8'), 129.2 (C-6), 129.9 (C-5'), 130.6 (C-7), 130.9 (C-5), 132.2 (C-8'a), 132.3 (C-4a), 134.6 (C-1'), 134.7 (C-4'a), 136.0 (C-8a), 167.6 (C-2), 170.4 (CO<sub>2</sub>Me), 176.0 (C-4) ppm. – IR (KBr): ν<sub>max</sub> = 3404, 3081, 2926, 2860, 1653, 1634 cm<sup>-1</sup>. – HRMS (EI): *m/z* = 428.99894 (calcd. 428.99932 for C<sub>21</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>3</sub>S, [M]<sup>+</sup>). – EIMS: *m/z* (%) = 429 (25) [M]<sup>+</sup>, 397 (100), 369 (11), 244 (3), 204 (6), 193 (82), 176 (3), 127 (15) [R]<sup>+</sup>. – C<sub>21</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>3</sub>S (430.31): calcd. C 58.62, H 3.05, N 3.26; found C 58.38, H 2.98, N 3.17.

#### 4.3.7 Methyl 2-[*N*-(cyclohexyl)amino]-6,7-dichloro-4-oxo-4*H*-1-benzothiopyran-3-carboxylate (6g)

Yield: 23%; m. p. 110–112°C. – <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.43–2.07 (m, 10H, 2'-H<sub>2</sub> + 3'-H<sub>2</sub> + 4'-H<sub>2</sub> + 5'-H<sub>2</sub> + 6'-H<sub>2</sub>), 3.64 (m, 1H, 1'-H), 3.91 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 7.46 (s, 1H, 8-H), 8.49 (s, 1H, 5-H), 10.67 (d, *J* = 8 Hz, 1H, N-H, exchangeable with D<sub>2</sub>O) ppm. – <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 24.2 (C'-3/C-5'), 25.2 (C-4'), 32.5 (C-2'/C-6'), 52.1 (CO<sub>2</sub>CH<sub>3</sub>), 53.9 (C-1'), 98.3 (C-3), 126.2 (C-8), 128.3 (C-6), 130.9 (C-5), 131.1 (C-7), 132.4 (C-4a), 135.9 (C-8a), 164.3 (C-2), 170.5 (CO<sub>2</sub>Me), 175.5 (C-4) ppm. – IR (KBr): ν<sub>max</sub> = 3413, 3089, 2928, 2862, 1636, 1619 cm<sup>-1</sup>. – HRMS (EI): *m/z* = 385.03014 (calcd. 385.03062 for C<sub>17</sub>H<sub>17</sub>Cl<sub>2</sub>NO<sub>3</sub>S, [M]<sup>+</sup>). – EIMS: *m/z* (%) = 385 (20) [M]<sup>+</sup>, 354 (4), 325 (21), 244 (41), 204 (25), 148 (100), 176 (5), 83 (38) [R]<sup>+</sup>. – C<sub>17</sub>H<sub>17</sub>Cl<sub>2</sub>NO<sub>3</sub>S (386.30): calcd. C 52.86, H 4.44, N 3.63; found C 52.58, H 4.35, N 3.56.

#### 4.3.8 Methyl 2-[*N*-(1'-adamantyl)amino]-6,7-dichloro-4-oxo-4*H*-1-benzothiopyran-3-carboxylate (6h)

Yield: 24%; m. p. 219–220°C. – <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.62 (br s, 3H, 3'-H + 5'-H + 7'-H), 1.75 (br s, 6H,

4'-H<sub>2</sub>+6'-H<sub>2</sub>+10'-H<sub>2</sub>), 2.20 (br s, 6H, 2'-H<sub>2</sub>+8'-H<sub>2</sub>+9'-H<sub>2</sub>), 3.89 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 7.50 (s, 1H, 8-H), 8.48 (s, 1H, 5-H), 10.65 (s, 1H, N-H, exchangeable with D<sub>2</sub>O) ppm. – <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 29.5 (C-''+C-5'+C-7'), 35.9 (C-4'+C-6'+C-10'), 41.6 (C-2'+C-8'+C-9'), 52.1 (CO<sub>2</sub>CH<sub>3</sub>), 56.3 (C-1'), 99.2 (C-3), 125.9 (C-8), 128.9 (C-6), 130.8 (C-5), 131.1 (C-7), 132.2 (C-4a), 135.8 (C-8a), 163.5 (C-2), 170.5 (CO<sub>2</sub>Me), 175.5 (C-4) ppm. – IR (KBr): ν<sub>max</sub> = 3416, 3098, 2911, 2840, 1651, 1617 cm<sup>-1</sup>. – HRMS (EI): m/z = 437.06161 (calcd. 437.06192 for C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>3</sub>S, [M]<sup>+</sup>). – EIMS: m/z (%) = 437 (30) [M]<sup>+</sup>, 405 (3), 377 (1), 244 (1), 204 (3), 201 (1), 176 (1), 135 (100) [R]<sup>+</sup>. – C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>3</sub>S (438.38): calcd. C 57.54, H 4.83, N 3.20; found C 57.36, H 4.72, N 3.15.

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