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ORIGINAL ARTICLE

Synthesis and evaluation of new 3-substituted-4-chloro-thioxanthone derivatives as potent anti-breast cancer agents

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Abstract A series of 3-substituted-4-chloro-thioxanthones and their corresponding *S,S*-dioxidethioxanthone derivatives were designed and synthesized. The effects of our synthesized compounds on cell viability toward the MCF-7 and MDA-MB-468 breast cancer cell lines were evaluated. The most active compound was **4f,** which was active against the MCF-7 and MDA-MB-468 cell lines with respective IC_{50} values of 7.2 and 3.9 μM. Interestingly, compound **4f** did not impair cell viability of the cardiac myoblast H9C2 cell line (IC_{50} > 25 μM), indicating that this compound might not exhibit cytotoxic effects on the normal cardiac cells. Further, compounds **4b**, **4f**, **4j**, **4s**, **5b**, **5f**, **5j,** and **5s** were characterized by the NCI screening system. Results revealed that compounds **4f** and **4s** had effective anticancer activities against various cancer cell lines. Finally, our results indicated that the 3-substituted-4-chloro-thioxanthone derivatives have the potential to be further developed as promising small molecules for anticancer applications.

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1. Introduction

Thioxanthones belong to an important class of synthetic compounds, which have been studied and described since 1891 (Graebe and Schultess, 1891; Paiva et al., 2013). They are structurally similar to xanthone, acridone, and anthraquinone tricyclic scaffolds (Pouli and Marakos, 2009; Belmont and Dorange, 2008; Huang et al., 2007), and were found to exhibit

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interesting chemical properties including photoinitiated polymerization (Davidson et al., 1983; Fouassier and Rabek, 1993; Yilmaz et al., 2010; Mishra and Yusuf, 2008). Thioxanthones also reveal unique pharmacologic characteristics depending on the structure and scaffold substituents (Paiva et al., 2013; Pouli and Marakos, 2009). Over the years, thioxanthone derivatives have been extensively synthesized and studied owing to their diverse biological activities such as antischistosomal effects (Archer et al., 1988), antibiotic activity (Bessa et al., 2015; Verbanac et al., 2012), monoamine oxidase inhibitory activity (Harfenist et al., 1996), activation of P-glycoprotein (Silva et al., 2015), and especially their antitumor activities (Woo et al., 2008; Kostakis et al., 2001; Palmeira et al., 2012). Interestingly, hycanthone as one of the thioxanthone derivatives (Fig. 1), was found to exhibit antischistosomal, antitumor, and anti-metastatic activities against breast cancer, so it was selected to proceed to clinical trials as an anticancer drug candidate in the 1980s, but was withdrawn due to its toxicity and mutagenicity (Paiva et al., 2013; Cioli et al., 1995). After chemical modification, SR271425, a third-generation thioxanthone compound derived from hycanthone, was developed and entered clinical trials based on robust *in vivo* antitumor activity, but it did not proceed due to its cardiotoxicity (Goncalves et al., 2008; Campone et al., 2007; Lockhart et al., 2009). Because of the potential demonstrated by this scaffold, thioxanthone is still a promising lead structure as an anticancer agent that warrants further lead optimization. Therefore, the development of new thioxanthone analogs with potential anticancer properties and determination of their structure–activity relationships remain attractive goals in cancer research.

In this report, we synthesized 38 new thioxanthone analogs (**4a–4s, 5a–5s**) bearing various substituents. The thioxanthone core (**4a**) was prepared by the Ullmann condensation reaction and Friedel–Crafts intramolecular ring closure reaction based on the literature (Jílek et al., 1981; Lory et al., 2006). According to the literature, we noted that introduction of a suitable functional group at the 3-position of the thioxanthone scaffold could enhance the pharmacophore motifs required for biological activities, especially anticancer activity (Woo et al., 2008; Chae et al., 2015). In order to understand the structure–activity relationships of the substituents at the 3-position of thioxanthones, we prepared a series of thioxanthone derivatives (**4b–4s**) with various substituted phenylthio groups at the 3-position of the core structure. Based on previous studies, *S*,*S*-dioxidethioxanthone analogs derived from thioxanthone were shown to possess potential biological activities (Harfenist et al., 1997; Christodoulou et al., 2011). In order to verify the significance of the biologic activities of the *S*,*S*-dioxide group on the thioxanthone scaffold, we prepared corresponding *S*,*S*-dioxidethioxanthone analogs (**5a–5s**) of the thioxanthones (**4a–4s**).

Based on published reports revealing that thioxanthone derivatives exhibit potent anticancer activities toward several cancer types such as breast cancer (Verbanac et al., 2012; Woo et al., 2008; Palmeira et al., 2012; Varvaresou et al., 1996), we evaluated the effects of our synthetic thioxanthone derivatives (**4a–4s** and **5a–5s**) on cell viability of the MCF-7 and MDA-MB-468 breast cancer cell lines using an MTT assay. Further, we tested the toxicities of our thioxanthone derivatives against the H9C2 cardiomyoblastic cell line as a normal cell control to detect any cytotoxicity of our compounds toward normal cells. Moreover, compounds **4b** (NSC753740), **5b** (NSC763938), **4f** (NSC753748), **5f** (NSC763940), **4j** (NSC753741), **5j** (NSC763942), **4s** (NSC753744) and **5s** (NSC763947) were selected by the NCI to test under a one-dose screening program. Results showed that compound **4f** was the most-active derivative against the MCF-7 and MDA-MB-468 breast cancer cell lines without remarkable cytotoxicity toward the normal H9C2 cells.

2. Chemistry

2.1. Materials and instruments

The synthesis procedures and physical data of compounds **4a–4s** and **5a–5s** are described in this investigation. We investigated the role of the systematic heterocyclic pharmacophore and introduced a series of substituted phenylthio groups linked to the thioxanthone core structure (Scheme 1). All chemicals and solvents used were commercially available, and were purchased from Aldrich or Merck without further purification. All reactions were monitored by analytical TLC (silica gel 60 F_{254}) using various solvent systems. Melting points were determined in open capillary tubes with a Büchi 545 melting point determination apparatus. Both ^{1}H-nuclear magnetic resonance

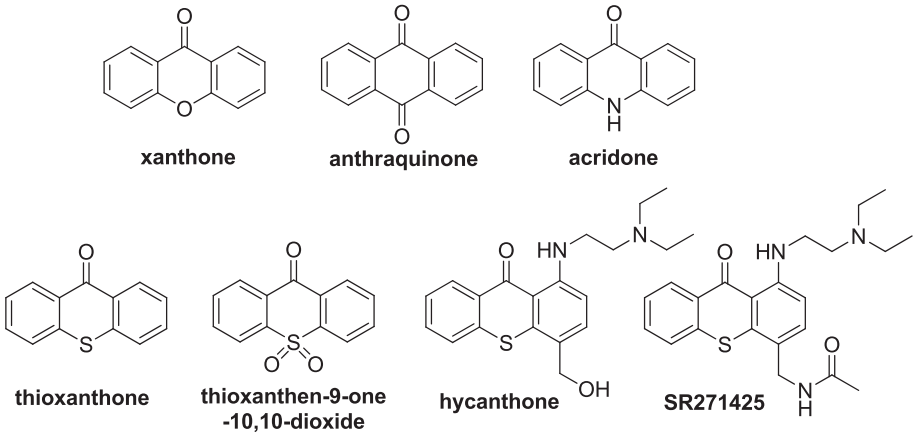
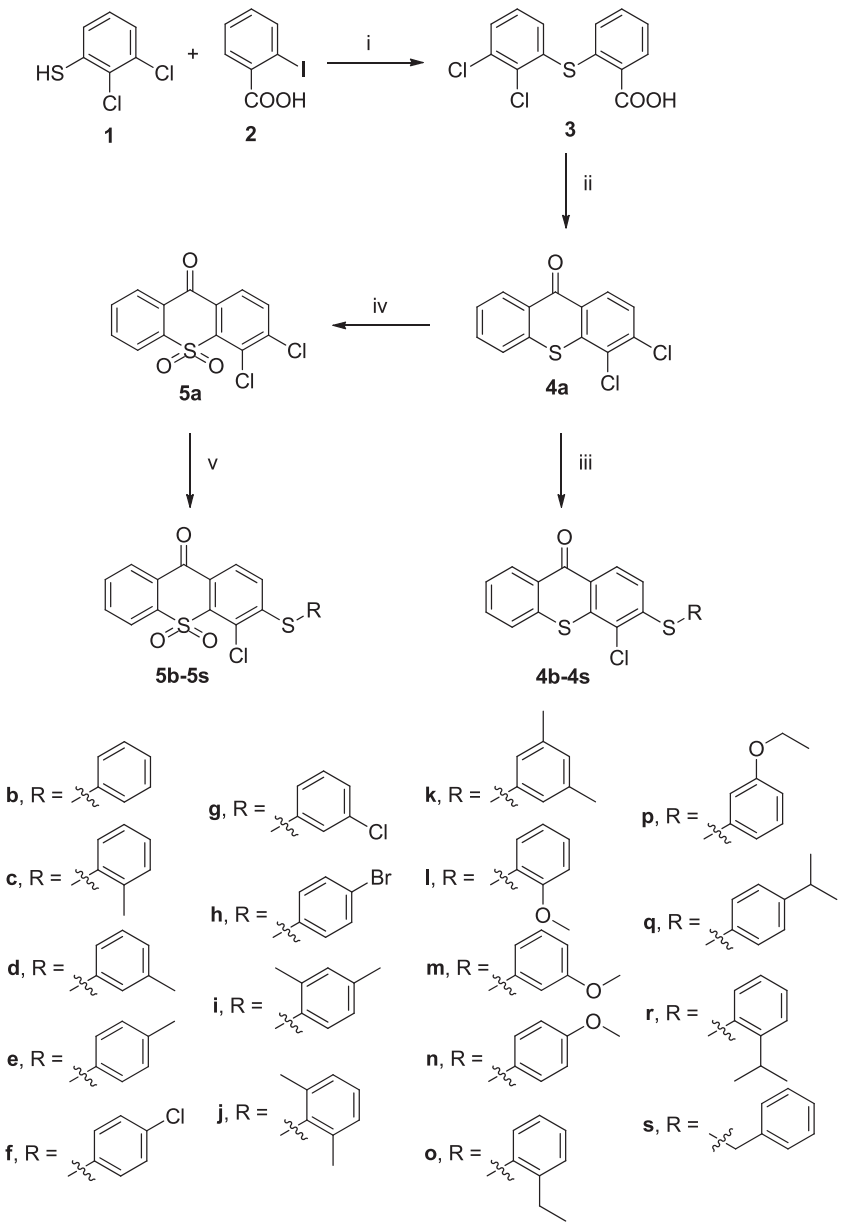


Figure 1 Structures related to thioxanthone and thioxanthone derivatives.



Scheme 1 [a]Overall synthetic routes of the 3-substituted-4-chloro-thioxanthone analogs. [a]Reagents and conditions: (i) 1 M $KOH_{(aq)}$, Cu, DMF, 120 °C, 8 h. (ii) 75% $H_2SO_{4(aq)}$, 110 °C, 6 h, miniclave. (iii) RSH, $NaOCH_3$, MeOH, THF, reflux, 2 h. (iv) H_2O_2, HOAc, reflux, 2 h. (v) RSH, $NaOCH_3$, MeOH, THF, reflux, 2 h.

(NMR) and ^{13}C NMR spectra of compounds were recorded at 25 °C with an Agilent 400 MR DD2 (400 MHz) spectrometer. Chemical shift (δ) values in delta parts per million (ppm) were determined using $CDCl_3$ as a solvent. Multiplicities were expressed as a singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sex), septet (sep), doublet of doublets (dd), triplet of doublets (td), doublet of triplets (dt), or multiplet (m). Coupling constants (J) were expressed in Hz. High-resolution mass spectra were determined by Finnigan MAT-95XL high-resolution electron impact ionization. A single crystal of compound **4c** was selected for X-ray diffractometry, and data were acquired by a crystallographic assay using a Bruker Kappa CCD diffractometer, employing graphite-monochromated Mo Ka radiation at 200 K and the qe2q scan mode. The space group for compound **4c** was analyzed on the basis of intensity statistics and systematic absences. The structure of compound **4c** was resolved by direct methods using SIR92 or SIR97 and refined with SHELXL-97. The purity of these thioxanthone derivatives was determined on a C18 reverse-phase column (XBridge BEH Shield RP18 Column, 130 Å, 5 μm, 4.6 mm × 250 mm, Waters) by HPLC (model l-2000, HITACHI) with UV detection (model l-2400, HITACHI). Thioxanthone derivative (1 mg) was dissolved in methanol (20 mL) and analyzed by HPLC. The mobile phase was MeOH/water. A preliminary evaluation of the UV absorbance and λ_{max} for each compound was determined by spectrophotometric analysis. The purity of these thioxanthone derivatives was greater than 95%.

2.2. Synthesis of target compounds **3, 4a–4s** and **5a–5s**

2.2.1. Synthetic procedure i: preparation of 2-((2,3-dichlorophenyl)thio)benzoic acid (**3**)

At room temperature, an aqueous solution of 1 M KOH (10 mL) was added dropwise with stirring to a solution of 2,3-dichlorothiophenol (**1**) (0.9 g, 5 mmol) in DMF (10 mL). After 10 min, the mixture was treated with 2-iodobenzoic acid (**2**) (1.24 g, 5 mmol) in DMF (10 mL) using copper powder (0.315 g) as a catalyst with stirring at 120 °C for 8 h. The mixture was filtered while hot, and the filtrate was acidified with 1 M $HCl_{(aq)}$ (10 mL) to precipitate the crude product. The crude product was collected, washed with water, and dried in vacuo to get the desired 2-((2,3-dichlorophenyl)thio)benzoic acid (**3**) (Jílek et al., 1981).

2.2.2. Synthetic procedure ii: preparation of compound **4a**

2-((2,3-Dichlorophenyl)thio)benzoic acid (**3**) (0.3 g, 1 mmol) was added to a 75% H_2SO_4 solution (10 mL) at 0 °C in a mini-clave, then mixture was heated to 110 °C for 6 h. After cooling, the reaction mixture was poured into ice water (200 mL), and the precipitate was obtained after 20 min. The precipitate was dissolved in dichloromethane, extracted with dichloromethane/water system, and dried over $MgSO_4$. The solvent was removed in vacuo obtaining **4a** as an off-white powder.

2.2.3. General procedure iii: preparation of compounds **4b–4s**

To a mixture of sodium methoxide (0.108 g, 2 mmol) in methanol (10 mL), the substituted-benzenethiol derivative (2 mmol) was added with stirring for 15 min. Compound **4a** in tetrahydrofuran (10 mL) was added to the reaction mixture, which was then refluxed for 2 h. The mixture was filtered while hot, and the filtrate was collected and concentrated in vacuo. Then, it was extracted with dichloromethane, and the organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product obtained was recrystallized from ethanol.

2.2.4. Synthetic procedure iv: preparation of compound **5a**

A solution of compound **4a** (0.313 g, 1 mmol) in acetic acid (20 mL) was treated with 30% hydrogen peroxide (10 mL), warmed slowly for 1 h at 45 °C, and then refluxed for 2 h. A slight exothermic reaction was noted during the early heating. After cooling, the reaction was diluted with 200 mL of ice water. The resulting solid was removed by filtration, washed with water, and dried, yielding the pale-yellow solid compound.

2.2.5. General procedure v: preparation of compounds **5b–5s**

To a mixture of sodium methoxide (0.108 g, 2 mmol) in methanol (10 mL), the substituted-benzenethiol derivative (1 mmol) was added with stirring for 15 min. Compound **5a** in tetrahydrofuran (20 mL) was added to the reaction mixture, and refluxed for 2 h. The mixture was filtered while hot, and the filtrate was collected and concentrated in vacuo. Then, it was extracted with dichloromethane, the organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product obtained was recrystallized from ethanol.

2.3. Physical data

2.3.1. 3,4-Dichloro-9H-thioxanthen-9-one (**4a**)

The pure compound was obtained as an off-white powder (yield 60%). Mp 194–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.52–7.56 (m, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.65–7.71 (m, 2H), 8.52 (d, J = 8.4 Hz, 1H), 8.58 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 126.51, 127.16, 127.36, 127.96, 128.10, 129.13, 129.23, 129.81, 132.89, 136.62, 137.80, 138.58, 179.28. HRMS-EI m/z calcd for $[M]^+$: 279.9516, found: 279.9514.

2.3.2. 4-Chloro-3-(phenylthio)-9H-thioxanthen-9-one (**4b**)

The pure compound was obtained as a pale-yellow powder (yield 34%). Mp 180–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.79 (d, J = 8.8 Hz, 1H), 7.49–7.53 (m, 4H), 7.59–7.62 (m, 2H), 7.65–7.66 (m, 2H), 8.33 (d, J = 8.4 Hz, 1H), 8.54–8.56 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 123.73, 124.83, 126.51, 126.85, 127.67, 128.14, 128.28, 129.44, 129.69, 130.10, 130.17, 132.58, 135.67, 136.57, 137.37, 145.33, 179.38. HRMS-EI m/z calcd for $[M]^+$: 353.9940, found: 353.9943.

2.3.3. 4-Chloro-3-(o-tolylthio)-9H-thioxanthen-9-one (**4c**)

The pure compound was obtained as pale-yellow crystals (yield 41%). Mp 208–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.39 (s, 3H), 6.60 (d, J = 8.8 Hz, 1H), 7.32 (td, J = 7.2 Hz, J = 2.4 Hz, 1H), 7.41–7.52 (m, 3H), 7.59–7.66 (m, 3H), 8.30 (d, J = 8.8 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 20.68, 122.88, 124.70, 126.50, 126.82, 127.48, 127.61, 128.17, 128.27, 128.32, 129.67, 130.83, 131.45, 132.55, 136.54, 137.11, 137.39, 143.35, 144.72, 179.38. HRMS-EI m/z calcd for $[M]^+$: 368.0096, found: 368.0092.

2.3.4. 4-Chloro-3-(m-tolylthio)-9H-thioxanthen-9-one (**4d**)

The pure compound was obtained as a pale-yellow powder (yield 38%). Mp 169–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.41 (s, 3H), 6.79 (d, J = 8.8 Hz, 1H), 7.31–7.33 (m, 1H), 7.36–7.42 (m, 3H), 7.47–7.51 (m, 1H), 7.63–7.64 (m, 2H), 8.31 (d, J = 8.8 Hz, 1H), 8.54 (dt, J = 7.6 Hz, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.94, 123.68, 124.61, 126.47, 126.79, 127.50, 128.05, 128.23, 128.97, 129.63, 129.94, 130.94, 132.51, 132.69, 136.17, 136.53, 137.25, 140.19, 145.57, 179.32. HRMS-EI m/z calcd for $[M]^+$: 368.0096, found: 368.0095.

2.3.5. 4-Chloro-3-(p-tolylthio)-9H-thioxanthen-9-one (**4e**)

The pure compound was obtained as a pale-yellow powder (yield 51%). Mp 203–204 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.45 (s, 3H), 6.75 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.48–7.52 (m, 3H), 7.64–7.66 (m, 2H), 8.31 (d, J = 8.4 Hz, 1H), 8.55 (dt, J = 7.6 Hz, J = 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.41, 123.39, 124.38, 125.52, 126.50, 126.80, 127.42, 128.05, 128.27, 129.65, 131.00, 132.53, 135.84, 136.55, 137.26, 140.64, 145.97, 179.38. HRMS-EI m/z calcd for $[M]^+$: 368.0096, found: 368.0100.

*2.3.6. 4-Chloro-3-(4-chlorophenylthio)-9H-thioxanthen-9-one (**4f**)*

The pure compound was obtained as a pale-yellow powder (yield 47%). Mp:223–224 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.80 (d, J = 8.8 Hz, 1H), 7.46–7.55 (m, 5H), 7.64–7.67 (m, 2H), 8.35 (d, J = 8.8 Hz, 1H), 8.55 (d, J = 8.0 Hz 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 123.71, 125.13, 126.51, 126.92, 127.88, 128.03, 128.21, 128.26, 129.70, 130.43, 132.65, 136.48, 136.57, 136.76, 137.51, 144.44, 179.32. HRMS-EI m/z calcd for $[M]^+$: 387.9550, found: 387.9511.

*2.3.7. 4-Chloro-3-(3-chlorophenylthio)-9H-thioxanthen-9-one (**4g**)*

The pure compound was obtained as a pale-yellow powder (yield 55%). Mp:181–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.86 (d, J = 8.8 Hz, 1H), 7.41–7.54 (m, 4H), 7.59 (t, J = 1.6 Hz, 1H), 7.64–7.67 (m, 2H), 8.37 (d, J = 8.8 Hz, 1H), 8.56 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 124.20, 125.57, 126.52, 126.94, 128.10, 128.21, 128.34, 129.72, 130.17, 131.11, 131.72, 132.67, 133.25, 134.81, 135.66, 136.50, 137.57, 143.84, 179.33. HRMS-EI m/z calcd for $[M]^+$: 387.9550, found: 387.9551.

*2.3.8. 3-(4-Bromophenylthio)-4-chloro-9H-thioxanthen-9-one (**4h**)*

The pure compound was obtained as a pale-yellow powder (yield 48%). Mp 222–223 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.83 (d, J = 8.8 Hz, 1H), 7.45 (dt, J = 6.8 Hz, J = 1.9 Hz, 2H), 7.49–7.53 (m, 1H), 7.61–7.67 (m, 4H), 8.35 (d, J = 8.8 Hz, 1H), 8.54–8.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 123.88, 124.75, 125.31, 126.52, 126.93, 127.98, 128.25, 128.29, 128.82, 129.72, 132.66, 133.39, 136.50, 136.87, 137.54, 144.22, 179.32. HRMS-EI m/z calcd for $[M]^+$: 431.9045, found: 431.9037.

*2.3.9. 4-Chloro-3-(2,4-dimethylphenylthio)-9H-thioxanthen-9-one (**4i**)*

The pure compound was obtained as a pale-yellow powder (yield 28%). Mp 172–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.34 (s, 3H), 2.41 (s, 3H), 6.60 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.47–7.51 (m, 2H), 7.64–7.65 (m, 2H), 8.29 (d, J = 8.8 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 20.56, 21.31, 122.74, 124.48, 124.69, 126.49, 126.79, 127.36, 128.10, 128.31, 128.43, 129.65, 132.32, 132.50, 136.56, 137.12, 137.33, 141.24, 143.17, 145.24, 179.38. HRMS-EI m/z calcd for $[M]^+$: 382.0253, found: 382.0258.

*2.3.10. 4-Chloro-3-(2,6-dimethylphenylthio)-9H-thioxanthen-9-one (**4j**)*

The pure compound was obtained as a pale-yellow powder (yield 30%). Mp 215–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.42 (s, 6H), 6.49 (d, J = 8.4 Hz, 1H), 7.25–7.27 (m, 2H), 7.33–7.36 (m, 1H), 7.48–7.52 (m, 1H), 7.65–7.66 (m, 2H), 8.28 (d, J = 8.4 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.63, 121.95, 124.85, 126.50, 126.80, 127.36, 127.81, 128.27, 128.32, 128.99, 129.67, 130.49, 132.52, 136.54, 137.44, 144.29, 144.31, 179.38. HRMS-EI m/z calcd for $[M]^+$: 382.0253, found: 382.0259.

*2.3.11. 4-Chloro-3-(3,5-dimethylphenylthio)-9H-thioxanthen-9-one (**4k**)*

The pure compound was obtained as pale-yellow crystals (yield 46%). Mp 183–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.37 (s, 6H), 6.81 (d, J = 8.8 Hz, 1H), 7.13 (s, 1H), 7.22 (s, 2H) 7.48–7.52 (m, 1H), 7.64–7.65 (m, 2H), 8.32 (d, J = 8.8 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.18, 123.79, 124.57, 126.50, 126.80, 127.48, 128.05, 128.30, 128.65, 129.66, 131.92, 132.52, 133.23, 136.60, 137.23, 139.95, 145.85, 179.39. HRMS-EI m/z calcd for $[M]^+$: 382.0253, found: 382.0249.

*2.3.12. 4-Chloro-3-(2-methoxylphenylthio)-9H-thioxanthen-9-one (**4l**)*

The pure compound was obtained as a pale-yellow powder (yield 58%). Mp 181–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.82 (s, 3H), 6.71 (d, J = 8.8 Hz, 1H), 7.05–7.09 (m, 2H), 7.48–7.55 (m, 2H), 7.58 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.64–7.65 (m, 2H), 8.31 (d, J = 8.8 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 55.98, 111.82, 116.72, 121.77, 123.31, 124.75, 126.49, 126.75, 127.47, 127.84, 128.31, 129.64, 132.42, 132.48, 136.63, 137.20, 137.58, 144.52, 160.18, 179.44. HRMS-EI m/z calcd for $[M]^+$: 384.0045, found: 384.0038.

*2.3.13. 4-Chloro-3-(3-methoxylphenylthio)-9H-thioxanthen-9-one (**4m**)*

The pure compound was obtained as a pale-yellow powder (yield 44%). Mp 208–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.84 (s, 3H), 6.85 (d, J = 8.5 Hz, 1H), 7.03–7.06 (m, 1H), 7.13 (t, J = 2.0 Hz, 1H), 7.17–7.20 (m, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.49–7.53 (m, 1H), 7.65–7.66 (m, 2H), 8.34 (d, J = 8.8 Hz, 1H), 8.55 (dt, J = 8.4 Hz, J = 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 55.47, 116.21, 120.36, 123.78, 124.75, 126.50, 126.84, 127.63, 127.72, 128.14, 128.23, 129.66, 130.28, 130.94, 132.57, 136.53, 137.31, 145.20, 160.58, 179.35. HRMS-EI m/z calcd for $[M]^+$: 384.0045, found: 384.0045.

*2.3.14. 4-Chloro-3-(4-methoxylphenylthio)-9H-thioxanthen-9-one (**4n**)*

The pure compound was obtained as a pale-yellow powder (yield 65%). Mp 163–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.89 (s, 3H), 6.72 (d, J = 8.8 Hz, 1H), 7.03 (dt, J = 9.6 Hz, J = 2.6 Hz, 2H), 7.48–7.55 (m, 3H), 7.64–7.65 (m, 2H), 8.31 (d, J = 8.8 Hz, 1H), 8.54 (dt, J = 8.0 Hz, J = 1.0 Hz, 1H). ^{13}C- R (100 MHz, $CDCl_3$): δ ppm 55.48, 115.79, 119.32, 123.10, 124.06, 126.50, 126.79, 127.36, 128.04, 128.31, 129.66, 132.51, 136.55, 137.23, 137.72, 146.49, 161.34, 179.37. HRMS-EI m/z calcd for $[M]^+$: 384.0045, found: 384.0046.

*2.3.15. 4-Chloro-3-(2-ethylphenylthio)-9H-thioxanthen-9-one (**4o**)*

The pure compound was obtained as a pale-yellow powder (yield 61%). Mp 165–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.20 (t, J = 7.6 Hz, 3H), 2.78 (q, J = 7.6 Hz, 2H), 6.61 (d, J = 8.8 Hz, 1H), 7.32 (td, J = 7.4 Hz, J = 1.5 Hz, 1H), 7.44–7.52 (m, 3H), 7.57 (dd, J = 7.8 Hz, J = 1.0 Hz,

1H), 7.65–7.66 (m, 2H), 8.30 (d, J = 8.8 Hz, 1H), 8.55 (d, J = 8.0, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.27, 27.31, 123.17, 124.59, 126.50, 126.82, 127.44, 127.61, 127.80, 128.12, 128.31, 129.67, 129.94, 131.02, 132.54, 136.56, 137.32, 137.43, 145.49, 149.11, 179.39. HRMS-EI m/z calcd for $[M]^+$: 382.0253, found: 382.0252.

*2.3.16. 4-Chloro-3-(3-ethoxylphenylthio)-9H-thioxanthen-9-one (**4p**)*

The pure compound was obtained as a pale-yellow powder (yield 63%). Mp 149–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.43 (t, J = 7.0 Hz, 3H), 4.05 (q, J = 7.1 Hz, 2H), 6.85 (d, J = 8.8 Hz, 1H), 7.02–7.05 (m, 1H), 7.11 (t, J = 2.0 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.49–7.53 (m, 1H), 7.65–7.67 (m, 2H), 8.34 (d, J = 8.8 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.70, 63.77, 116.74, 120.89, 123.87, 124.81, 126.51, 126.84, 127.53, 127.67, 128.14, 128.29, 129.69, 130.27, 130.92, 132.56, 136.57, 137.32, 145.29, 160.01, 179.37. HRMS-EI m/z calcd for $[M]^+$: 398.0202, found: 398.0204.

*2.3.17. 4-Chloro-3-(4-isopropylphenylthio)-9H-thioxanthen-9-one (**4q**)*

The pure compound was obtained as a pale-yellow powder (yield 71%). Mp 160–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.31 (d, J = 7.2 Hz, 6H), 3.00 (sep, J = 6.9 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.47–7.53 (m, 3H), 7.64–7.65 (m, 2H), 8.32 (d, J = 8.8 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 23.81, 34.01, 123.48, 124.40, 125.83, 126.49, 126.79, 127.45, 128.06, 128.29, 128.38, 129.65, 132.51, 135.87, 136.57, 137.25, 145.94, 151.40, 179.36. HRMS-EI m/z calcd for $[M]^+$: 396.0409, found: 396.0409.

*2.3.18. 4-Chloro-3-(2-isopropylphenylthio)-9H-thioxanthen-9-one (**4r**)*

The pure compound was obtained as pale-yellow crystals (yield 59%). Mp 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.20 (d, J = 6.8 Hz, 6H), 3.47 (sep, J = 6.9 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 7.28–7.32 (m, 1H), 7.47–7.55 (m, 3H), 7.57 (d, J = 7.6 Hz, 1H), 7.63–7.64 (m, 2H), 8.29 (d, J = 8.8 Hz, 1H), 8.53 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 23.82, 31.06, 123.18, 124.42, 126.46, 126.77, 127.15, 127.22, 127.36, 127.43, 128.05, 128.26, 129.63, 131.22, 132.49, 136.50, 137.27, 137.41, 145.77, 153.55, 179.32. HRMS-EI m/z calcd for $[M]^+$: 396.0409, found: 396.0404.

*2.3.19. 3-(Benzylthio)-4-chloro-9H-thioxanthen-9-one (**4s**)*

The pure compound was obtained as a pale-yellow powder (yield 41%). Mp 196–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 4.31 (s, 2H), 7.30–7.38 (m, 4H), 7.43–7.45 (m, 2H), 7.49–7.53 (m, 1H), 7.63–7.66 (m, 2H), 8.48 (d, J = 8.4 Hz, 1H), 8.57 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 36.67, 122.79, 125.69, 126.49, 126.83, 127.48, 127.89, 128.25, 128.29, 128.87, 128.90, 129.69, 132.60, 134.90, 136.61, 137.30, 143.84, 179.45. HRMS-EI m/z calcd for $[M]^+$: 368.0096, found: 368.0097.

*2.3.20. 3,4-Dichloro-9H-thioxanthen-9-one-10,10-dioxide (**5a**)*

The pure compound was obtained as a pale-yellow powder (yield 33%). Mp 233–235 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.82 (td, J = 7.6 Hz, J = 0.9 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.94 (td, J = 7.7 Hz, J = 1.2 Hz, 1H), 8.19 (dd, J = 7.8 Hz, J = 0.6 Hz, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.36 (dd, J = 7.8 Hz, J = 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 123.87, 128.46, 128.68, 128.76, 130.08, 130.24, 133.29, 133.93, 135.52, 139.52, 142.07, 142.21, 176.42. HRMS-EI m/z calcd for $[M]^+$: 311.9415, found: 311.9408.

*2.3.21. 4-Chloro-3-(benzenethio)-9H-thioxanthen-9-one 10,10-dioxide (**5b**)*

The pure compound was obtained as a pale-yellow powder (yield 31%). Mp 241–242 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.94 (d, J = 8.4 Hz, 1H), 7.51–7.61 (m, 5H), 7.78 (td, J = 7.6 Hz, J = 1.1 Hz, 1H), 7.91 (td, J = 7.7 Hz, J = 1.2 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.19 (dd, J = 8.0 Hz, J = 0.4 Hz, 1H), 8.32 (dd, J = 7.8 Hz, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 123.73, 126.22, 127.74, 127.94, 128.43, 128.53, 128.75, 128.97, 130.54, 130.70, 133.08, 135.17, 136.00, 137.96, 142.22, 151.39, 176.58. HRMS-EI m/z calcd for $[M]^+$: 385.9838, found: 385.9837.

*2.3.22. 3-(2-Methylbenzenethio)-4-chloro-9H-thioxanthen-9-one 10,10-dioxide (**5c**)*

The pure compound was obtained as a pale-yellow powder (yield 57%). Mp 254–255 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.37 (s, 3H), 6.77 (d, J = 8.4 Hz, 1H), 7.32–7.37 (m, 1H), 7.43–7.50 (m, 2H), 7.59 (d, J = 7.6 Hz, 1H), 7.78 (td, J = 7.7 Hz, J = 0.9 Hz, 1H), 7.91 (td, J = 7.7 Hz, J = 1.3 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.19 (dd, J = 8.0 Hz, J = 0.4 Hz, 1H), 8.32 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 20.57, 123.72, 126.37, 127.45, 127.81, 127.83, 127.95, 128.23, 128.52, 128.77, 131.33, 131.70, 133.07, 135.14, 137.23, 138.03, 142.20, 143.50, 150.49, 176.59. HRMS-EI m/z calcd for $[M]^+$: 399.9995, found: 399.9987.

*2.3.23. 3-(3-Methylbenzenethio)-4-chloro-9H-thioxanthen-9-one 10,10-dioxide (**5d**)*

The pure compound was obtained as a pale-yellow powder (yield 57%). Mp 247–249 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.42 (s, 3H), 6.96 (d, J = 8.8 Hz, 1H), 7.35–7.44 (m, 4H), 7.78 (t, J = 7.6 Hz, 1H), 7.91 (t, J = 7.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 7.6 Hz 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.31, 123.73, 126.14, 127.71, 127.85, 128.06, 128.52, 128.77, 129.05, 130.32, 131.53, 132.96, 133.07, 135.15, 136.43, 137.90, 140.66, 142.23, 151.65, 176.61. HRMS-EI m/z calcd for $[M]^+$: 399.9995, found: 399.9989.

*2.3.24. 4-Chloro-3-(4-methylbenzenethio)9H-thioxanthen-9-one 10,10-dioxide (**5e**)*

The pure compound was obtained as a pale-yellow powder (yield 72%). Mp 246–247 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.46 (s, 3H), 6.93 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.78 (t, J = 7.6 Hz, 1H), 7.91 (t, J = 7.6 Hz, 1H), 8.07 (d,

J = 8.8 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.43, 123.71, 124.67, 126.02, 127.66, 127.77, 128.50, 128.75, 128.82, 131.33, 133.05, 135.13, 135.96, 137.86, 141.25, 142.21, 151.91, 176.60. HRMS-EI m/z calcd for $[M]^+$: 399.9995, found: 399.9990.

*2.3.25. 4-Chloro-3-(4-chlorobenzenethio)-9H-thioxanthen-9-one 10,10-dioxide (**5f**)*

The pure compound was obtained as a pale-yellow powder (yield 57%). Mp 249–251 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.96 (d, J = 8.4 Hz, 1H), 7.50–7.55 (m, 4H), 7.79 (t, J = 7.6 Hz, 1H), 7.92 (t, J = 7.2 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 123.75, 126.45, 126.95, 127.86, 128.21, 128.58, 128.71, 128.94, 129.30, 130.84, 133.14, 135.24, 137.20, 137.36, 142.18, 150.55, 176.54. HRMS-EI m/z calcd for $[M]^+$: 419.9448, found: 419.9447.

*2.3.26. 3-(3-Chlorophenylthio)-4-chloro-9H-thioxanthen-9-one 10,10-dioxide (**5g**)*

The pure compound was obtained as a pale-yellow powder (yield 57%). Mp 262–263 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.00 (d, J = 8.8 Hz, 1H), 7.47–7.55 (m, 3H), 7.60–7.61 (m, 1H), 7.79 (td, J = 8.2 Hz, 1.2 Hz, 1H), 7.92 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 8.33 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.33 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 123.76, 126.66, 127.94, 128.40, 128.59, 128.74, 129.25, 130.53, 130.91, 131.51, 133.13, 133.86, 135.23, 135.44, 136.06, 138.19, 142.23, 150.09, 176.54. HRMS-EI m/z calcd for $[M]^+$: 419.9448, found: 419.9450.

*2.3.27. 3-(4-Bromobenzenethio)-4-chloro-9H-thioxanthen-9-one 10,10-dioxide (**5h**)*

The pure compound was obtained as a pale-yellow powder (yield 80%). Mp 256–258 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.97 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.79 (t, J = 7.6 Hz, 1H), 7.92 (t, J = 7.4 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 123.75, 125.59, 126.53, 127.67, 127.87, 128.28, 128.58, 128.74, 129.02, 133.12, 133.80, 135.22, 137.34, 138.16, 142.22, 150.36, 176.53. HRMS-EI m/z calcd for $[M]^+$: 463.8943, found: 463.8941.

*2.3.28. 4-Chloro-3-(2,4-dimethylbenzenethio) 9H-thioxanthen-9-one 10,10-dioxide (**5i**)*

The pure compound was obtained as a pale-yellow powder (yield 70%). Mp 235–236 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.33 (s, 3H), 2.42 (s, 3H), 6.77 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.56–7.95 (m, 3H), 8.06 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 20.44, 21.33, 123.72, 123.86, 123.89, 127.74, 128.18, 128.50, 128.68, 128.76, 128.81, 132.55, 133.04, 135.10, 135.52, 137.12, 141.80, 142.25, 143.23, 150.99, 176.63. HRMS-EI m/z calcd for $[M]^+$: 414.0151, found: 414.0155.

*2.3.29. 4-Chloro-3-(2,6-dimethylbenzenethio)-9H-thioxanthen-9-one 10,10-dioxide (**5j**)*

The pure compound was obtained as a pale-yellow powder (yield 81%). Mp 285–286 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.39 (s, 6H), 6.77 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 7.6 Hz, 2H), 7.34–7.36 (m, 1H), 7.78 (td, J = 7.6 Hz, J = 0.9 Hz, 1H), 7.91 (td, J = 7.7 Hz, J = 1.2 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 8.19 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H), 8.32 (dd, J = 7.2 Hz, J = 1.0 Hz 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.49, 123.72, 127.42, 127.72, 127.93, 128.51, 128.69, 128.77, 128.81, 129.23, 130.90, 133.07, 135.11, 135.52, 142.21, 144.26, 149.84, 176.61. HRMS-EI m/z calcd for $[M]^+$: 414.0151, found: 414.0154.

*2.3.30. 4-Chloro-3-(3,5-dimethylbenzenethio)9H-thioxanthen-9-one 10,10-dioxide (**5k**)*

The pure compound was obtained as a pale-yellow powder (yield 69%). Mp 275–276 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.38 (s, 6H), 6.98 (d, J = 8.4 Hz, 1H), 7.17 (s, 1H), 7.20 (s, 2H), 7.78 (t, J = 7.4 Hz, 1H), 7.91 (td, J = 7.6 Hz, J = 0.8 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.18, 123.72, 126.09, 127.67, 127.75, 127.79, 128.50, 128.80, 129.13, 132.45, 133.03, 133.41, 135.11, 137.88, 140.38, 142.27, 151.87, 177.63. HRMS-EI m/z calcd for $[M]^+$: 414.0151, found: 414.0151.

*2.3.31. 4-Chloro-3-(2-methoxyphenylthio)-9H-thioxanthen-9-one 10,10-dioxide (**5l**)*

The pure compound was obtained as a pale-yellow powder (yield 44%). Mp 274–276 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.82 (s, 3H), 6.87 (d, J = 8.8 Hz, 1H), 7.06–7.11 (m, 2H), 7.54–7.59 (m, 2H), 7.78 (t, J = 7.4 Hz, 1H), 7.91 (t, J = 7.4 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 55.98, 111.95, 115.74, 121.98, 123.72, 126.32, 127.42, 127.75, 128.48, 128.67, 128.85, 133.00, 135.08, 137.76, 137.84, 142.28, 150.30, 160.18, 176.72. HRMS-EI m/z calcd for $[M]^+$: 415.9944, found: 415.9947.

*2.3.32. 4-Chloro-3-(3-methoxyphenylthio)-9H-thioxanthen-9-one 10,10-dioxide (**5m**)*

The pure compound was obtained as a pale-yellow powder (yield 58%). Mp 231–233 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.84 (s, 3H), 7.00 (d, J = 8.4 Hz, 1H), 7.08–7.12 (m, 2H), 7.18 (d, J = 7.6 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.91 (t, J = 7.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 55.53, 116.81, 120.62, 123.73, 126.23, 127.76, 127.97, 128.00, 128.54, 128.79, 129.14, 129.38, 131.32, 133.07, 135.15, 137.98, 142.25, 151.30, 160.89, 176.60. HRMS-EI m/z calcd for $[M]^+$: 415.9944, found: 415.9939.

*2.3.33. 4-Chloro-3-(4-methoxyphenylthio)-9H-thioxanthen-9-one 10,10-dioxide (**5n**)*

The pure compound was obtained as a pale-yellow powder (yield 58%). Mp 263–265 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.89 (s, 3H), 6.92 (d, J = 8.4 Hz, 1H), 7.03–7.07 (m,

2H), 7.48–7.52 (m, 2H), 7.78 (td, J = 7.2 Hz, J = 0.8 Hz, 1H), 7.91 (td, J = 7.7 Hz, J = 1.0 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.32 (dd, J = 7.6 Hz, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 55.52, 116.12, 118.47, 123.72, 125.88, 127.66, 127.76, 128.51, 128.66, 128.81, 133.04, 135.11, 137.74, 137.89, 142.27, 152.36, 161.66, 176.64. HRMS-EI m/z calcd for $[M]^+$: 415.9944, found: 415.9946.

2.3.34. 3-(2-Ethylbenzenethio)-4-chloro-9H-thioxanthen-9-one 10,10-dioxide (**5o**)

The pure compound was obtained as a pale-yellow powder (yield 71%). Mp 215–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.19 (t, J = 7.6 Hz, 3H), 2.75 (q, J = 7.5 Hz, 2H), 6.78 (d, J = 8.8 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H), 7.46–7.56 (m, 3H), 7.78 (t, J = 7.6 Hz, 1H), 7.91 (t, J = 7.6 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 7.6 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.36, 27.30, 123.73, 126.24, 126.92, 127.76, 127.79, 127.96, 128.52, 128.81, 130.23, 131.54, 133.06, 135.12, 137.50, 137.97, 142.24, 149.32, 151.28, 176.61. HRMS-EI m/z calcd for $[M]^+$: 414.0151, found: 414.0158.

2.3.35. 3-(3-Ethoxyphenylthio)-4-chloro-9H-thioxanthen-9-one 10,10-dioxide (**5p**)

The pure compound was obtained as a pale-yellow powder (yield 81%). Mp 226–228 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.43 (t, J = 7.0 Hz, 3H), 4.06 (q, J = 7.1 Hz, 2H), 7.01 (d, J = 8.8 Hz, 1H), 7.06–7.10 (m, 2H), 7.16 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.78 (t, J = 7.0 Hz, 1H), 7.91 (t, J = 7.4 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.68, 63.85, 117.30, 121.13, 123.73, 126.20, 127.75, 127.79, 127.97, 128.53, 128.79, 129.14, 129.27, 131.30, 133.06, 135.15, 137.96, 142.25, 151.39, 160.27, 176.61. HRMS-EI m/z calcd for $[M]^+$: 430.0100, found: 430.0100.

2.3.36. 4-Chloro-3-(4-isopropylbenzenethio)9H-thioxanthen-9-one 10,10-dioxide (**5q**)

The pure compound was obtained as a pale-yellow powder (yield 66%). Mp 264–266 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.32 (d, J = 6.8 Hz, 6H), 3.00 (sep, J = 7.0 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.78 (td, J = 7.4 Hz, J = 1.2 Hz, 1H), 7.91 (td, J = 7.8 Hz, J = 1.1 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H), 8.32 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 23.78, 34.05, 123.73, 125.00, 126.05, 127.70, 127.82, 128.51, 128.74, 128.81, 128.92, 133.04, 135.12, 136.03, 137.92, 142.28, 151.91, 152.01, 176.63. HRMS-EI m/z calcd for $[M]^+$: 428.0308, found: 428.0314.

2.3.37. 4-Chloro-3-(2-isopropylphenylthio)-9H-thioxanthen-9-one 10,10-dioxide (**5r**)

The pure compound was obtained as a pale-yellow powder (yield 66%). Mp 226–228 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.20 (d, J = 6.8 Hz, 6H), 3.39 (sep, J = 6.9 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 7.33 (td, J = 7.3 Hz, J = 1.6 Hz, 1H), 7.51–7.58 (m, 3H), 7.78 (td, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.91 (td, J = 7.4 Hz, J = 1.1 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.19 (dd J = 8.0 Hz, J = 0.8 Hz, 1H), 8.32 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 23.86, 31.14, 123.73, 126.15, 126.37, 127.46, 127.70, 127.76, 127.80, 128.53, 128.57, 128.82, 131.74, 133.07, 135.13, 137.44, 137.96, 142.23, 151.62, 153.79, 176.61. HRMS-EI m/z calcd for $[M]^+$: 428.0308, found: 428.0306.

2.3.38. 3-(Benzylthio)-4-chloro-9H-thioxanthen-9-one 10,10-dioxide (**5s**)

The pure compound was obtained as a pale-yellow powder (yield 32%). Mp 214–215 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 4.30 (s, 2H), 7.32–7.45 (m, 5H), 7.52 (d, J = 8.4 Hz, 1H), 7.79 (td, J = 7.4 Hz, J = 1.2 Hz, 1H), 7.91 (td, J = 7.7 Hz, J = 0.9 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.34 (dd, J = 7.6 Hz, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 36.69, 123.74, 127.31, 127.58, 127.90, 128.08, 128.13, 128.53, 128.74, 128.83, 129.02, 133.08, 133.99, 135.17, 137.94, 142.18, 149.51, 176.62. HRMS-EI m/z calcd for $[M]^+$: 399.9995, found: 399.9994.

2.4. Cell culture and MTT assay

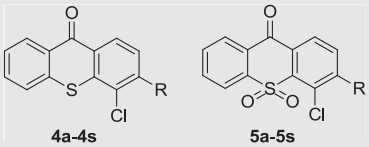
The human breast carcinoma cell lines, MCF-7 and MDA-MB-468 (both obtained from the American Type Culture Collection, USA) as well as the rat cardiac myoblast cell line H9C2 (obtained from the Food Industry Research and Development Institute, Taiwan) were cultured in Dulbecco's modified Eagle's medium (DMEM) (Gibco BRL, USA) supplemented with 10% heat-inactivated fetal bovine serum (FBS) in a humidified, 5% (v/v) CO_2 atmosphere at 37 °C.

A 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide (MTT) (Sigma, USA) assay was performed to determine the cell viability and IC_{50} values (the concentration of drug required to inhibit cell growth by 50% of the mean) of our synthetic compounds against the MCF-7, MDA-MB-468, and H9C2 cell lines (Mosmann, 1983; Denizot and Lang, 1986). MCF-7 (3000 cells/well), MDA-MB-468 (5000 cells/well), and H9C2 (10^4 cells/well) cells were seeded in 96-well microplates with DMEM supplemented with 10% FBS and treated with various concentrations of compounds for 72 h. After treatment, plates were washed with phosphate-buffered saline (PBS) three times, 100 μL of the MTT solution (0.5 mg/mL final concentration in the medium) was added to each well, and cells were incubated at 37 °C for 1 h. MTT is converted to blue formazan crystals by mitochondrial succinate dehydrogenase. The plates were then washed with PBS and solubilized in 100 μL of dimethyl sulfoxide (DMSO) per well. The absorbances at 540 nm were determined using an enzyme-linked immunosorbent assay (ELISA) microplate reader. Effects of our synthetic compounds on cell viability were demonstrated as the relative activity (relative to the DMSO control group).

2.5. NCI in vitro 60-cell drug screening experiments

Eight of our synthesized compounds were selected by the NCI, and their anticancer activities at a dose of 10 μM were determined by a sulforhodamine B (SRB) colorimetric assay according to previous protocols (Kandeel et al., 2015; Sikic, 1991; Monks et al., 1997; Chen et al.). Cells

Table 1 Inhibition activities of our synthetic compounds on the cell viability of MCF-7 and MDA-MB-468 cell lines.



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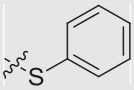
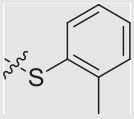
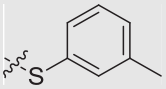
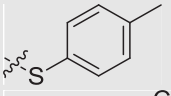
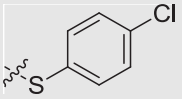
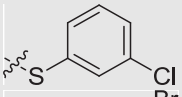
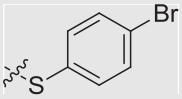
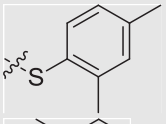
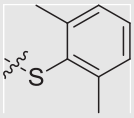
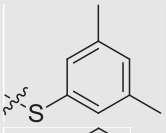
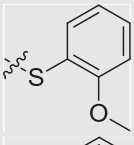
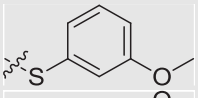
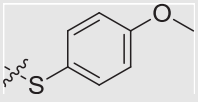
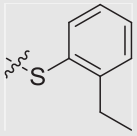
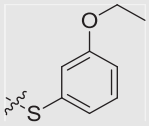
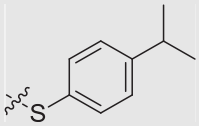
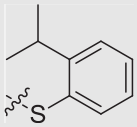
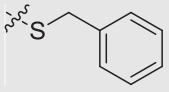
Compd. No.	Cell type/MCF-7			Cell type/MDA-MB-468	
	R	Cell viability % ± SD (at 12.5 μM)[a]	IC_{50} (μM)[b]	Cell viability % ± SD (at 12.5 μM)	IC_{50} (μM)
4a		91.2 ± 5.0	> 25	50.2 ± 8.2	15.2
5a		101.9 ± 6.6	> 25	71.6 ± 1.6	> 25
4b		88.3 ± 11.3	> 25	74.4 ± 9.7	> 25
5b		91.8 ± 6.4	> 25	68.6 ± 0.9	> 25
4c		84.5 ± 3.5	–[c]	69.4 ± 7.9	–
5c		95.6 ± 12.7	–	104.0 ± 9.4	–
4d		78.1 ± 8.0	–	90.9 ± 9.8	–
5d		81.5 ± 5.2	–	70.4 ± 5.0	–
4e		89.8 ± 8.0	> 25	84.1 ± 3.3	> 25
5e		81.9 ± 4.6	> 25	47.9 ± 4.9	12.1
4f		41.8 ± 6.2	7.9	23.9 ± 1.7	3.9
5f		76.2 ± 5.8	> 25	54.7 ± 2.7	18.6
4g		88.8 ± 2.3	–	68.8 ± 5.9	–
5g		87.0 ± 4.9	–	57.4 ± 5.8	–
4h		51.6 ± 4.4	10.7	21.4 ± 7.3	7.9
5h		74.8 ± 1.4	> 25	42.7 ± 2.2	4.0
4i		72.1 ± 8.7	> 25	72.3 ± 5.4	> 25
5i		86.5 ± 6.8	> 25	42.0 ± 1.3	7.8
4j		80.1 ± 9.2	–	66.4 ± 1.4	–
5j		97.8 ± 5.5	–	86.7 ± 7.3	–
4k		91.1 ± 7.0	–	93.8 ± 5.5	–
5k		96.0 ± 8.0	–	93.2 ± 8.6	–
4l		65.6 ± 10.2	–	69.7 ± 9.4	–
5l		88.1 ± 7.1	–	75.2 ± 5.3	–
4m		99.5 ± 7.5	–	91.1 ± 8.4	–
5m		77.6 ± 9.0	–	72.9 ± 3.0	–
4n		64.0 ± 8.2	> 25	73.4 ± 7.2	> 25
5n		76.3 ± 3.1	> 25	48.5 ± 3.6	11.8

(*continued on next page*)

Table 1 (*continued*)

Compd. No.	Cell type/MCF-7			Cell type/MDA-MB-468	
	R	Cell viability % ± SD (at 12.5 μM)[a]	IC_{50} (μM)[b]	Cell viability % ± SD (at 12.5 μM)	IC_{50} (μM)
4o		78.1 ± 3.3	–	70.2 ± 6.0	
5o		75.1 ± 10.3	–	51.4 ± 3.8	–
4p		92.2 ± 8.1	–	78.5 ± 6.2	–
5p		88.4 ± 8.1	–	86.6 ± 6.7	–
4q		90.3 ± 4.2	> 25	95.6 ± 5.7	> 25
5q		82.5 ± 8.0	> 25	50.0 ± 5.7	12.5
4r		93.3 ± 2.3	–	69.0 ± 5.1	–
5r		76.3 ± 5.0	–	46.4 ± 1.0	–
4s		63.5 ± 8.9	> 25	36.6 ± 11.3	7.2
5s		109.7 ± 5.2	> 25	66.6 ± 1.3	> 25
Doxorubicin[d]		9.0 ± 0.8	0.13	4.01 ± 0.1	0.04

[a] SD: standard derivation, and all experiments were independently performed at least three times.
[b] IC_{50} is the concentration of drug (μM) required to inhibit cell growth by 50% of the mean ($N = 3$).
[c] –: not determined.
[d] Doxorubicin as a reference drug.

Table 2 Cytotoxic effects of our synthetic compounds toward the cardiac myoblast cell line H9C2.

Cell type/H9C2			
Compd. No.	IC_{50}[a]	Compd. No.	IC_{50}
4a	> 25	**5h**	> 25
5a	> 25	**4i**	> 25
4f	> 25	**5i**	> 25
5f	> 25	**4s**	7.5
4h	> 25	**5s**	> 25
Doxorubicin[b]	0.16		

[a] IC_{50} is the concentration of drug (μM) required to inhibit cell growth by 50% of the mean ($N = 5$).
[b] Doxorubicin as a reference drug.

(5000–10,000 cell/100 μL/well) were seeded into 96-well microtiter plates for 24 h at 37 °C, with 5% CO_2, 95% air, and 100% relative humidity. Two plates of each cell line were fixed with trichloroacetic acid (TCA) as a control of the cell population for each cell line at the time of drug exposure (T_0). After additional incubation with the vehicle (DMSO) or the test compounds for 48 h, cells were fixed with cold 50% (w/v) TCA (final concentration, 10% TCA) and then incubated for 60 min at 4 °C. Plates were then washed with tap water, and cells were treated with 100 μL of the SRB solution at 0.4% (w/v) in 1% acetic for 10 min at room temperature. After staining, the plates were washed with 1% acetic acid to remove any unbound dye, and SRB-bound cells were solubilized with 0.01 M Trizma base. The absorbance was measured using a spectrophotometer at a wavelength of 515 nm. Using the absorbance measurements, including time zero (T_0), control growth (C), and test growth in the presence of a drug (T_X), the percentage growth was calculated for each compound as $100 - [(T_X - T_0)/(C - T_0)] \times 100$ for concentrations for which $T_X \geqslant T_0$.

3. Results and discussion

The synthetic methods of 3-substituted-4-chloro-thioxanthones are depicted in Scheme 1. The intermediate 2-((2,3-dichlorophenyl)thio)benzoic acid (**3**) was obtained from the reaction of 2,3-dichlorobenzenethiol (**1**) with 2-iodobenzoic acid (**2**) *via* the Ullmann condensation reaction (Jílek et al., 1981). It is a common reaction to provide phenylthiobenzoic acid products through copper-catalysis in basic conditions (Brindle and Doyle, 1983; Paiva et al., 2013). The formation of the thioxanthone ring was established by Friedel–Crafts intramolecular ring closure of phenylthiobenzoic acid in concentrated acid conditions (Lory et al., 2006). Herein, it was carried out in a miniclave and produced 3,4-dichloro-9*H*-thioxanthen-9-one (**4a**) from 2-((2,3-dichlorophenyl)thio)benzoic acid (**3**) in sulfuric acid. Subsequently, oxidation of compound **4a** with excess 30% hydrogen peroxide in acetic acid provided the desired *S*,*S*-dioxidethioxanthone derivative, **5a**. This oxidative protocol was previously reported for similar thioxanthone derivatives (Harfenist et al., 1997). In addition, the chloro group was shown to be the reactive halide under

Table 3 *In-vitro* anticancer activities of selected compounds against the NCI's 60 human cancer cell lines at a dose of 10 μM.

Compd. No.	**4b**	**5b**	**4f**	**5f**	**4j**	**5j**	**4s**	**5s**
Leukemia								
CCRF-CEM	96.58[a]	102.82	68.42	99.24	88.07	87.93	59.07	106.21
HL-60(TB)	103.53	82.90	105.61	94.23	109.07	87.56	115.59	93.37
K-562	101.65	82.93	96.64	90.81	97.86	82.58	86.95	91.94
MOLT-4	99.77	87.52	94.77	93.35	104.33	82.83	98.34	91.78
RPMI-8226	102.11	101.12	88.56	101.79	101.60	98.55	89.98	105.73
SR	91.41	85.05	51.19	82.91	95.93	94.42	36.57	75.48
Non-Small Cell Lung Cancer								
A549/ATCC	N.T[b]	99.02	N.T.	99.70	N.T.	95.68	N.T.	89.11
EKVX	94.90	102.97	73.14	N.T.	103.89	107.10	93.46	91.59
HOP-62	N.T.	103.53	N.T.	103.42	N.T.	105.94	94.64	96.14
HOP-92	76.04	N.T.	49.52	N.T.	88.79	N.T.	74.60	N.T.
NCI-H226	85.36	93.29	81.05	94.97	109.77	94.92	90.97	97.05
NCI-H23	84.67	98.36	83.03	97.89	93.96	98.33	97.59	95.49
NCI-H322M	96.11	98.13	56.53	95.78	113.78	113.47	70.18	82.25
NCI-H460	108.87	93.95	40.25	106.17	110.85	106.80	29.14	91.01
NCI-H522	84.11	83.21	80.48	78.75	100.28	77.04	95.48	71.46
Colon Cancer								
COLO 205	103.82	108.11	87.02	104.36	110.46	105.93	63.36	102.21
HCC-2998	106.34	91.97	98.92	107.20	103.54	107.26	101.78	112.10
HCT-116	98.18	109.18	54.33	111.75	105.21	109.55	41.74	103.56
HCT-15	92.60	99.39	85.15	93.70	99.05	95.76	82.20	99.25
HT29	102.56	100.42	86.36	95.26	103.86	100.49	60.70	84.13
KM12	99.82	104.68	73.79	105.30	113.08	106.11	104.90	94.44
SW-620	96.96	108.52	75.00	107.86	105.40	111.40	69.53	107.82
CNS Cancer								
SF-268	93.39	102.54	81.14	109.30	98.33	111.63	100.29	100.86
SF-295	100.33	90.22	57.86	N.T.	98.15	110.51	63.22	92.38
SF-539	104.85	99.54	86.15	102.71	106.48	103.32	102.89	101.87
SNB-19	98.01	101.18	74.97	109.81	N.T.	108.78	83.57	102.12
SNB-75	82.75	90.38	76.16	69.89	90.00	91.69	75.12	93.26
U251	94.85	98.85	47.77	95.36	95.70	93.30	38.89	96.08
Melanoma								
LOX IMVI	96.25	90.45	63.24	96.98	105.37	96.12	62.94	99.88
MALME-3M	92.44	92.54	76.90	93.20	100.81	100.01	93.38	88.53
M14	104.30	114.69	89.62	121.73	105.63	120.38	102.67	112.72
MDA-MB-435	103.22	104.68	85.11	N.T.	107.09	111.18	91.01	113.12
SK-MEL-2	104.71	91.45	105.36	106.10	108.94	101.47	116.81	97.20
SK-MEL-28	113.07	103.82	114.93	105.05	110.00	110.53	119.10	96.40
SK-MEL-5	95.50	86.36	88.35	95.87	104.77	95.48	99.73	89.67
UACC-257	102.79	110.31	99.23	92.72	92.09	101.98	109.84	125.12
UACC-62	79.70	102.84	82.23	109.94	N.T.	110.25	90.92	107.30
Ovarian Cancer								
IGROV1	91.62	97.32	53.39	98.53	98.49	90.85	56.63	92.40
OVCAR-3	108.01	115.25	90.37	114.82	113.05	109.68	76.97	105.54
OVCAR-4	99.56	104.89	31.58	106.65	107.51	99.38	15.10	67.71
OVCAR-5	104.51	117.99	107.36	113.92	96.86	98.32	94.34	114.57
OVCAR-8	94.68	108.40	64.49	105.95	96.86	99.92	82.11	108.67
NCI/ADR-RES	96.88	98.90	81.27	104.52	105.14	103.89	90.62	101.50
SK-OV-3	96.13	N.T.	73.85	N.T.	111.32	N.T.	94.39	N.T.
Renal Cancer								
786-0	111.45	112.17	84.66	109.42	108.98	108.37	78.53	104.97
ACHN	94.03	105.62	39.55	102.25	103.68	102.06	26.15	101.35
CAKI-1	84.00	90.76	48.21	N.T.	89.35	90.92	54.75	84.92
RXF 393	110.95	91.68	97.81	100.63	N.T.	97.45	106.84	90.20
SN12C	87.55	108.02	70.19	105.54	N.T.	106.63	79.25	104.91
TK-10	97.85	106.38	88.86	94.36	99.22	125.54	95.49	112.29
UO-31	73.68	86.73	69.61	89.01	87.03	81.81	66.76	84.49

(*continued on next page*)

Table 3 (*continued*)

Compd. No.	**4b**	**5b**	**4f**	**5f**	**4j**	**5j**	**4s**	**5s**
Prostate Cancer								
PC-3	90.81	97.31	77.10	100.05	98.56	103.79	83.92	92.23
DU-145	108.05	102.97	108.68	106.84	109.56	113.24	107.70	98.04
Breast Cancer								
MCF7	82.14	79.36	83.90	63.74	94.01	90.83	89.62	80.93
MDA-MB-231/ATCC	93.94	119.41	77.55	118.77	108.12	114.68	71.98	109.91
HS 578T	119.59	129.54	102.79	108.91	107.64	106.46	91.28	93.13
BT-549	107.30	113.52	87.92	115.29	105.28	127.71	84.98	101.74
T-47D	87.90	89.24	85.63	93.01	97.56	93.42	82.55	88.91
MDA-MB-468	82.54	86.23	87.73	80.41	113.20	90.91	73.81	82.09
Mean	96.75	99.62	78.44	100.11	102.52	101.62	81.22	96.83
Delta	23.07	20.26	46.86	36.37	15.49	24.58	66.12	29.12
Range	45.91	50.18	83.35	57.99	26.75	50.67	104.00	57.41

[a] Data obtained from NCI *in vitro* 60-cell drug screen program at 10 μM concentration. The values reported are the growth percentages determined relative to the no-drug control at time zero. The values of growth percentages are between 0 and 100. A value of 0 represents no net growth over the course of the experiment and a value of 100 represents no growth inhibition.
[b] N.T.: Not tested.

vigorous conditions in direct nucleophilic aromatic substitution reactions (Sharghi and Tamaddon, 2001). Hence, the synthetic strategy of compounds **4b–4s**, and **5b–5s** was accomplished via the reaction of an appropriate benzenethiol with compound **4a** or **5a** in methanol/tetrahydrofuran then treatment with sodium methoxide to obtain the desired compounds, which were purified by recrystallization. Herein, the position of the nucleophilic substituent on thioxanthone and the structure of compound **4c** were confirmed by X-ray (Fig. S1). All synthetic methods are summarized in the general procedure section (i–v).

The effects of the synthesized thioxanthone derivatives **4a–5s** on cell viability of the MCF-7 and MDA-MB-468 breast cancer cell lines were experimentally assessed by performing a MTT assay. Results are illustrated in Table 1 and are expressed as percentages of cell viability. From the obtained results, we observed that some thioxanthone derivatives exhibited interesting anticancer activities on the tested cell lines. We found that the most potent compounds against MCF-7 cells were **4f** and **4h** with respective cell viability values of 41.8 ± 6.2% and 51.6 ± 4.4%, respectively at the concentration of 12.5 μM. In addition, the most potent compounds against MDA-MB-468 cells were **4a** (50.2 ± 8.2%), **4f** (23.9 ± 1.7%), **4h** (21.4 ± 7.3%), **4s** (36.6 ± 11.3%), **5e** (47.9 ± 4.9%), **5h** (42.7 ± 2.2%), **5i** (42.0 ± 1.3%), **5n** (48.5 ± 3.6%), **5q** (50.0 ± 5.7%), and **5r** (46.4 ± 1.0%) which showed low percentages of cell viability at a concentration of 12.5 μM. Of the compounds analyzed, we observed that introduction of substituted phenylthio groups at the 3-position of the thioxanthone scaffold could modulate the inhibition of cell viability of MCF-7 and MDA-MB-468 compared to the thioxanthone derivatives **4a** and **5a** which possess two chloro groups.

Further, the micromolar IC_{50} values of some potent compounds are presented in Table 1. Some thioxanthone derivatives showed IC_{50} values in the low micromolar range. Among these, compounds **4f** (IC_{50} = 7.9 μM) and **4h** (IC_{50} = 10.7 μM) showed potent inhibitory effects on cell viability of MCF-7 cells. In addition, compounds **4f** (IC_{50} = 3.9 μM), **4h** (IC_{50} = 7.9 μM), **4s** (IC_{50} = 7.2 μM), **5e** (IC_{50} = 12.1 μM), **5h** (IC_{50} = 4.0 μM), **5i** (IC_{50} = 7.8 μM), **5n** (IC_{50} = 11.8 μM), and **5q** (IC_{50} = 12.5 μM) showed potent inhibitory effects on cell viability of MDA-MB-468 cells. We found that the thioxanthone derivatives **4f**, **4h**, and **5h** possessing para-substituted phenylthio groups were more potent in inhibiting the cell viability of the tested cell lines compared to **4b** and **5b**. Based on these results, we concluded that the para-substituted phenylthio groups might be important for the inhibition activities of this class of compounds on the cell viability. Moreover, the cytotoxic effects of our compounds toward the normal cardiac myoblast H9C2 cells were also determined (Table 2). Interestingly, the tested compounds showed IC_{50} values of >25 μM toward H9C2 cells except for compound **4s** (IC_{50} = 7.5), suggesting that they had slight or no cytotoxicity toward normal cell H9C2 cells at concentrations higher than that needed to inhibit breast cancer. We found that the most-active compound was **4f** which was active against MCF-7 and MDA-MB-468 cells with IC_{50} values of 7.9 and 3.9 μM, respectively. Furthermore, it did not impair cell viability of the cardiac myoblast H9C2 cells (IC_{50} > 25 μM).

In addition, the effects of compounds **4b**, **5b**, **4f**, **5f**, **4j**, **5j**, **4s**, and **5s** on cell viability were evaluated against the NCI'60 human cancer cell lines at a single dose (10 μM) *in vitro* using the SRB protein-binding dye (Kandeel et al., 2015; Sikic, 1991; Monks et al., 1997; Chen et al.). Results, expressed as a growth percentage, mean growth, range of growth, and growth relative to the most-sensitive cell lines are summarized in Table 3 and Figs. S2–S9. Results showed that compound **4f** was still the most active among the tested compounds with a minimum mean growth percentage of 78.44. Maximum inhibition was observed for non-small cell lung cancer (HOP-92 and NCI-H460), CNS cancer (U251), ovarian cancer (OVCAR-4), and renal cancer (ACHN and CAKI-1) with growth percentages less than 50% as shown in Table 3. The next potent compound was **4s** which showed a mean growth percentage of 81.22, and it could impair the proliferation of cardiac myoblast H9C2 cells (IC_{50} = 7.5 μM) in our test.

4. Conclusion

Because of the anticancer potential demonstrated by the thioxanthone scaffold, an approach for synthesizing 3-substituted-4-chloro-thioxanthones and their corresponding *S*,*S*-dioxidethioxanthone derivatives was developed, and the inhibition activities of the synthesized compounds on cell viability were evaluated. Based on our biological data, it was envisioned that introducing different phenylthio groups at the 3-position of the thioxanthone scaffold caused loss of cell viability of the breast cancer cell lines MCF-7 and MDA-MB-468 cells. Among the synthesized compounds, **4f** (with a 4-chlorophenylthio group) was the most-active compound exhibiting potent inhibitory activity on the cell viability of MCF-7 and MDA-MB-468 cells. Interestingly, compound **4f** did not impair the cell viability of cardiac myoblast H9C2 cells at concentrations higher than that needed to inhibit breast cancer. Moreover, compound **4f** also appeared to be the best anticancer member of our compounds with the minimum mean growth percentage for the NCI drug screening program experiments. Through a series of promising *in vitro* experiments, we found that 3-substituted-4-chloro-thioxanthone derivatives, especially compound **4f**, exhibited preferential growth inhibition effects toward several cancer cell lines. Based on our results and structure–activity relationship studies, compound **4f** could be a potent anti-breast cancer candidate and promising lead compound that warrants further structure optimization.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2015.10.010.

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