Synthesis of Novel Bis(thiazolylchromen-2-one) Derivatives Linked to Alkyl Spacer *via* Phenoxy Group

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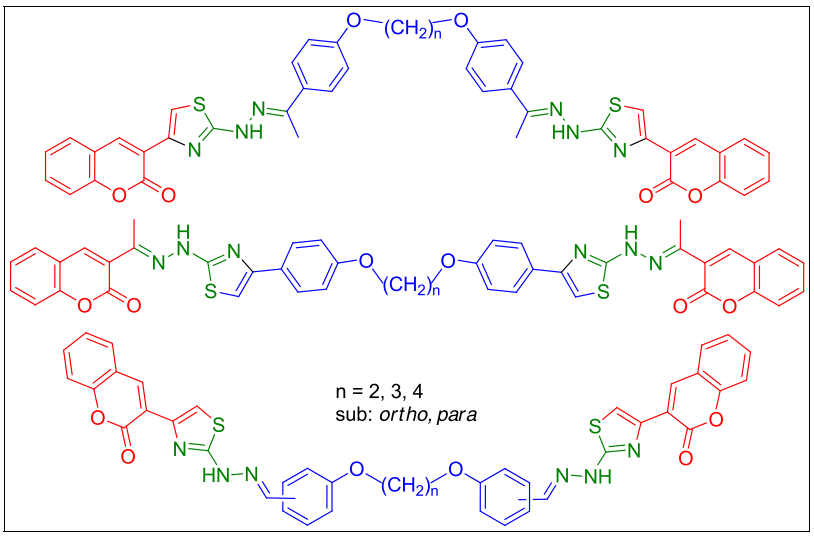


A novel series of bis(thiazolylchromen-2-one) derivatives **8** were prepared in good yields by the reaction of the appropriate bis(α-bromoketones) **7** with 2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene) hydrazinecarbothioamide (**6**) in refluxing EtOH in the presence of few drops of TEA. Some other isomeric derivatives of bis(thiazolylchromen-2-one) **11** and **13** were also successfully obtained by the reaction of bromoacetylcoumarin **9** with the corresponding bis(ethan-1-yl-1-ylidene))bis(hydrazinecarbothioamides) **10** and **12**. The structures of the new compounds were established based on elemental analyses as well as spectral data.

INTRODUCTION

Thiazole derivatives were reported to exhibit a wide variety of biological activities, such as anti-HIV, anti-inflammatory, antimicrobial, antihypertensive, antifungal, anticonvulsant, antiviral, anticancer, antimalarial, and anti-hypolipidemic activities [1–10].

The usefulness of many thiazole derivatives as medicines are well established (Fig. 1) [11–15].

Moreover, coumarins also exhibit various pharmacological properties such as antifungal, antioxidant, anticoagulant, antiviral, antiproliferative, antialzheimer, anticancer, and anti-HIV [16–20]. Coumarin derivatives were reported to have a wide range of biological activity, such as anti-inflammatory [21], anticancer [22,23], anti-coagulant, anti-oxidant, anti-HIV and anti-bacterial [24]. In addition to the therapeutic activities of coumarin derivatives, their less damage to normal cells were also reported [25]. Furthermore, *bis*-heterocyclic compounds exhibit various biological activities, including antibacterial, fungicidal, tuberculostatic, antiamoebic, anthelmintic, and plant growth regulative properties [26–29].

In addition, among libraries of derivatized heterocycles, the most active library compounds were reported to have a bis-heterocyclic [29–32]. Molecular hybridization concept in drug design and development has been recently established. This concept based on the combination of two pharmacophores into a single molecular skeleton aiming at producing a new hybrid compound with dual modes of action and reduced undesired side effects [33–35].

Motivated by these findings and in conjunction with our ongoing research work on bis-heterocycles [36–42], we report herein on the synthesis of novel bis (thiazolylchromen-2-one) derivatives of expected biological application based on the presence of two pharmacophores with dual mode of action.

RESULTS AND DISCUSSION

We are engaged in a project aiming at the synthesis of hybrid compounds in which two pharmacophoric moieties are combining in one molecule to produce new substances with improved affinity and efficacy compared with the parent drugs.

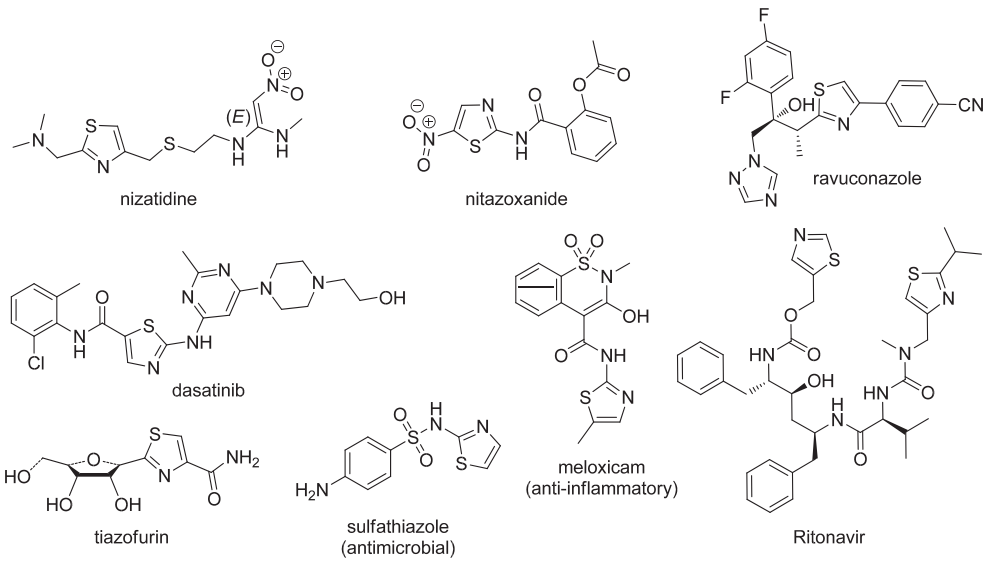


Figure 1. Some drugs incorporating thiazole ring.

In this respect, we recently reported the synthesis of bis (pyrazolylthiazoles) **1** by the reaction of the appropriate bis (hydrazinecarbothioamide) with the corresponding bromoacetylpyrazole in refluxing ethanol in the presence of few drops of TEA (Fig. 2) [37].

In an attempt to improve the biological properties of these compounds, we study here the modification of the structure of **1** by replacement of the pyrazole rings with coumarin units. We aimed also at making a change in the molecular skeleton by separation between the two heterocyclic units. We believe that such modification should be a well-established approach for designing more potent drugs with significant increase in activity.

For this purpose, the starting building units, 3-acetylcoumarin (**2**) [43,44], bis(acetylphenoxy) alkane **3** [45,46], and bis-aldehyde **4** [47,48], were chosen as starting materials and were prepared in good yields as previously reported (Fig. 3).

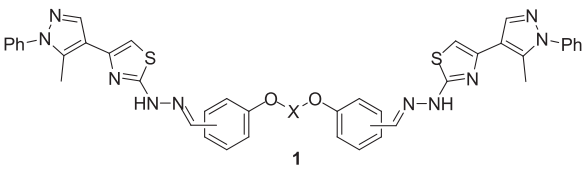


Figure 2. Recently synthesized bis(pyrazolylthiazoles) **1**.

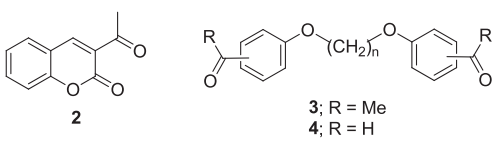


Figure 3. Starting building units, 3-acetylcoumarin (2), bis-(acetylphenoxy) alkane 3, and bis-aldehyde 4.

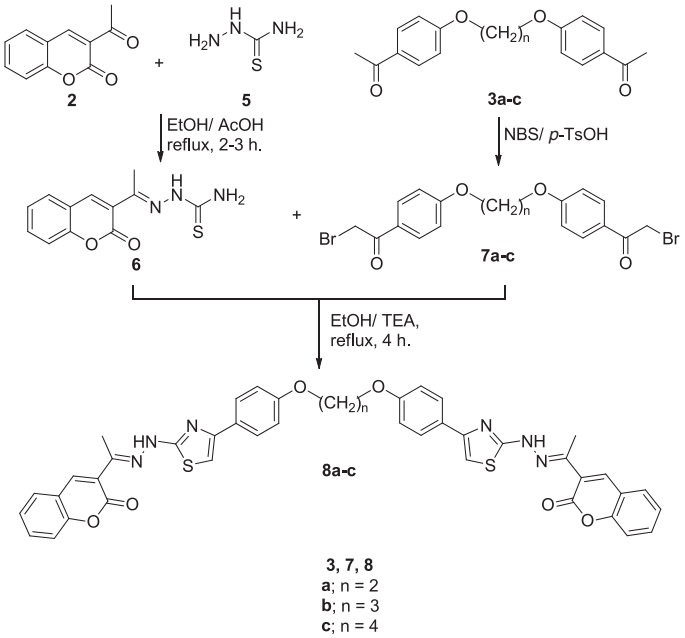
The novel bis(thiazole-4,2-diyl))bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene))-bis(2*H*-chromen-2-ones) **8** in which (ethylidenehydrazinyl) is located between two thiazole and coumarin rings were prepared as outlined in Scheme 1. Thus, the reaction of bis(α-bromoketones) **7a–c** with 2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene) hydrazinecarbothioamide (**6**) in refluxing EtOH in the presence of few drops of TEA afforded the corresponding **8a–c** in 60–65% yields (Scheme 1). Compound **7** was obtained by the reaction of **3** with *N*-bromosuccinimide (NBS) in the presence of *p*-toluenesulfonic acid (*p*-TsOH). Compound **6** was obtained by the reaction of 3-acetylcoumarin (**2**) with thiosemicarbazide (**5**) in refluxing EtOH containing few drops of AcOH.

Our study was extended to include the synthesis of the new bis(ethan-1-yl-1 ylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2*H*-chromen-2-ones) **11a–c**, which are isomeric of **8** as outlined in Scheme 2. Thus, reaction of the bromoacetylcoumarin **9** with the corresponding bis(ethan-1-yl-1-ylidene))bis(hydrazine carbothioamide) derivatives **10a–c** in refluxing EtOH in the presence of few drops of TEA afforded **11a–c** in 70–78% yields.

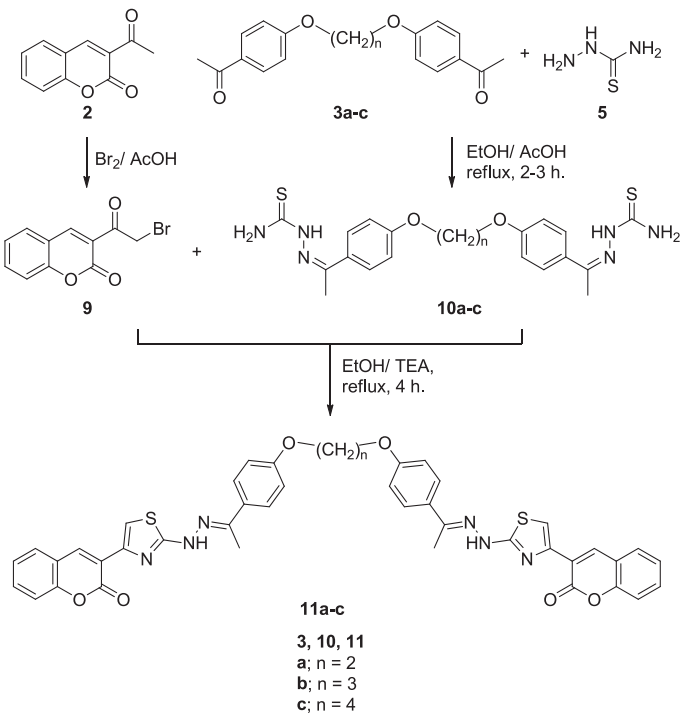
Compound **10** was obtained upon treatment of **3** with thiosemicarabazide **5** in refluxing ethanol containing few drops of acetic acid (Scheme 2). Compound **9** was obtained by bromination of **2** with Br_2 in AcOH.

It is noteworthy to mention that attempts to synthesize each of bis(ethan-1-yl-1-ylidene))bis (hydrazine carbothioamide) **10d–f** and bis(ethan-1-yl-1 ylidene)) bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2*H*-chromen-2-ones) **11d–f**, in which the bis(hydrazine carbothioamide) and bis(thiazole-4,2-diyl))bis(2*H*-

Scheme 1. Synthesis of bis(2*H*-chromen-2-ones) **8**.



Scheme 2. Synthesis of bis(2*H*-chromen-2-ones) **11a-c**.



chromen-2-ones) are located at the *ortho* position with respect to the ether linkage, using a similar approach were unsuccessful (Fig. 4). This may be explained in terms of steric hindrance.

When the same methodology was applied utilizing the bis aldehydes **4a–c** or **4d–f** as intermediates, the bis(thiazole-4,2-diyl))bis(2*H*-chromen-2-ones) **13** were obtained in good yields *via* initial formation of the corresponding bis(hydrazinecarbothioamides) **12a–f** (Scheme 3).

All of the isolated compounds were characterized by elemental analyses, as well as their spectral data, which

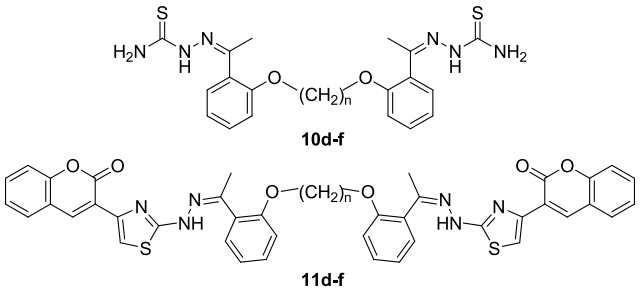
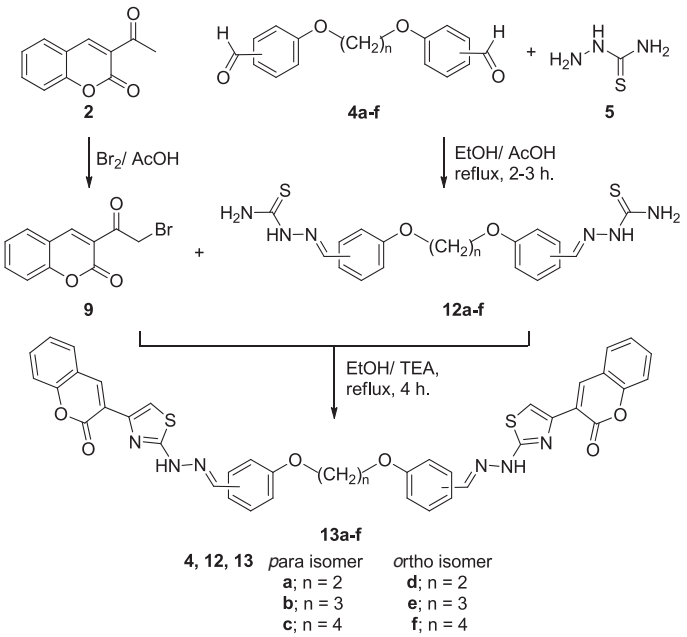


Figure 4. Bis(2*H*-chromen-2-ones) **11d–f**.

Scheme 3. Synthesis of bis(2*H*-chromen-2-ones) **13**.



4, 12, 13 *p*ara isomer: **a**; n = 2, **b**; n = 3, **c**; n = 4 — *o*rtho isomer: **d**; n = 2, **e**; n = 3, **f**; n = 4

agree with the proposed structures. Thus, the IR spectrum of **13b**, as a representative example, showed absorption bands at 3448 cm^{-1} due to (NH) and at 1709 cm^{-1} due to carbonyl stretching frequency. The ^1H NMR spectra of compound **13b** showed a D_2O-exchangeable signal at δ 12.01 due to NH protons, a characteristic singlet signal at δ 8.01 due to one methine proton (–N=CH–), a sharp singlet at δ 8.52 attributed to C-5 proton of the thiazole ring and at δ 7.74 attributed to the C-4 proton of the chromen ring. Moreover, they also featured the methylene ether linkage OCH_2 as a singlet signal at δ 4.18 ppm. All other protons were seen at the expected chemical shifts and integral values. Mass spectrum of compound **13b** showed a weak molecular ion peak at *m*/*z* 766, in agreement with its respective molecular formula.

CONCLUSIONS

We have developed an efficient synthesis of a novel series of bis (thiazolylchromen-2-ones), which are linked to alkyl spacer *via* phenoxymethyl group. The new synthesized compounds are expected to have different biological functions and dual activity for being as hybrid molecules with two distinct pharmacophores. The straightforward synthesis of these compounds in good yields under mild reaction condition from accessible starting material should open a new access for novel bis (functionalized) heterocycles of expected biological and pharmaceutical activities.

EXPERIMENTAL

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus and were not corrected. Infrared spectra were recorded in potassium bromide disks on a PyeUnicam SP3–300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. ^1H and ^{13}C NMR spectra were determined on a Varian Mercury VX 300NMR spectrometer using TMS as an

internal standard and DMSO-*d6* as a solvent. Mass spectra were measured on a GC MS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The starting **6** [49], **7a-c** [50], **9** [51], and **12a–f** [37] were prepared following literature procedures.

General procedure for the synthesis of alkane-diylbis(oxy))bis(phenylene))bis-(thiazole-4,2-diyl))bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene))bis(2H-chromen-2-one) 8a–c. To a solution of 2-(1-(2-oxo-2*H*-chromen-3-yl) ethylidene) hydrazinecarbothioamide (**6**) (2 mmol) and bis(2-bromoethanone) derivatives **7a–c** (1 mmol) in ethanol (25 mL), few drops of TEA were added. The reaction mixture was heated at reflux for 4 h. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from ethanol/DMF to give **8a–c**.

3,3′-((1,1′)-(2,2′-(4,4′-((Ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(thiazole-4,2-diyl))bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene))bis(2H-chromen-2-one) (8a). This compound was obtained as creamy powder, (73% yield), mp >300°C; ir (potassium bromide): NH 3430, CO 1721, C=N 1603 cm^{-1}; ^1H nmr: δ 2.21 (s, 6H, CH_3), 4.61 (s, 4H, CH_2O), 7.02–7.75 (m, 16H, ArH), 7.95 (s, 2H, thiazole-5-H), 8.03 (s, 2H, chromen-4-H), 11.23 ppm (s, 2H, NH); ms: *m/z* (%) 780 (0.21, M^+). *Anal*. Calcd for $C_{42}H_{32}N_6O_6S_2$: C, 64.60; H, 4.13; N, 10.76; S, 8.21. Found: C, 64.49; H, 4.05; N, 10.66; S, 8.17.

3,3′-((1,1′)-(2,2′-(4,4′-((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(thiazole-4,2-diyl))bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene))bis(2H-chromen-2-one) (8b). This compound was obtained as creamy powder, (78% yield), mp >300°C; ir (potassium bromide): NH 3429, CO 1720, C=N 1603 cm^{-1}; ^1H nmr: δ 2.21 (br. s, 2H, CH_2), 2.27 (s, 6H, CH_3), 4.18 (br. s, 4H, CH_2O), 6.99–7.86 (m, 16H, ArH), 7.94 (s, 2H, thiazole-5-H), 8.14 (s, 2H, chromen-4-H), 11.37 ppm (br. s, 2H, NH); ms: *m/z* (%) 794 (0.32, M^+). *Anal*. Calcd for $C_{43}H_{34}N_6O_6S_2$: C, 64.97; H, 4.31; N, 10.57; S, 8.07. Found: C, 64.91; H, 4.28; N, 10.51; S, 7.98.

3,3′-((1,1′)-(2,2′-(4,4′-((Butane-1,4-diylbis(oxy))bis(4,1-phenylene))bis(thiazole-4,2-diyl))bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene))bis(2H-chromen-2-one) (8c). This compound was obtained as creamy powder, (76% yield), mp 285–287°C; ir (potassium bromide): NH 3434, CO 1713, C=N 1603 cm^{-1}; ^1H nmr: δ 1.90 (br. s, 4H, CH_2), 2.28 (s, 6H, CH_3), 4.06 (br. s, 4H, CH_2O), 6.96–7.81 (m, 18H, ArH & thiazole-5-H), 8.15 (s, 2H, chromen-4-H), 11.31 ppm (br. s, 2H, NH); ms: *m/z* (%) 808 (0.38, M^+). *Anal*. Calcd for $C_{44}H_{36}N_6O_6S_2$: C, 65.33; H, 4.49; N, 10.39; S, 7.93. Found: C, 65.25; H, 4.40; N, 10.35; S, 7.87.

General procedure for the synthesis of bis(ethan-1-yl-1-ylidene))bis(hydrazine-carbothioamide) derivatives 10a–c. To a solution of bis acetyl derivatives **3a–c** (1 mmol) and thiosemicarbazide (**5**) (2 mmol) in ethanol (25 mL), few drops of AcOH were added. The reaction mixture was heated at reflux for 2–3 h. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from ethanol/DMF to give **10a–c**.

(2,2′)-2,2′-(((Ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(hydrazinecarbothioamide) (10a). This compound was obtained as white crystal, (81% yield), mp 280–282°C; ir (potassium bromide): NH 3406, NH_2 3235, 3145, CS 1664, C=N 1593 cm^{-1}; ^1H nmr: δ 2.26 (s, 6H, CH_3), 4.36 (s, 4H, CH_2O), 6.97 (d, 4H, *J* = 8.7 Hz), 7.89 (d, 4H, *J* = 9.0 Hz), 8.18 (br. s, 4H, NH_2), 10.06 ppm (br. s, 2H, NH); ms: *m/z* (%) 444 (0.11, M^+). *Anal*. Calcd for $C_{20}H_{24}N_6O_2S_2$: C, 54.03; H, 5.44; N, 18.90; S, 14.43. Found: C, 54.10; H, 5.33; N, 18.81; S, 14.38.

(2,2′)-2,2′-(((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(hydrazinecarbothioamide) (10b). This compound was obtained as white crystal, (83% yield), mp 225–227°C; ir (potassium bromide): NH 3393, NH_2 3199, 3136, CS 1672, C=N 1591 cm^{-1}; ^1H nmr: δ 2.18 (m, 2H, CH_2), 2.25 (s, 6H, CH_3), 4.17 (t, 4H, *J* = 6.3 Hz, CH_2O), 6.94 (d, 4H, *J* = 8.7 Hz), 7.86 (d, 4H, *J* = 9.0 Hz), 8.17 (br. s, 4H, NH_2), 10.08 ppm (br. s, 2H, NH); ^{13}C nmr: δ 13.73, 28.53, 64.32, 114.11, 128.05, 130.12, 147.80, 159.43, 178.71; ms: *m/z* (%) 458 (0.36, M^+). *Anal*. Calcd for $C_{21}H_{26}N_6O_2S_2$: C, 55.00; H, 5.71; N, 18.33; S, 13.98. Found: C, 54.96; H, 5.63; N, 18.25; S, 13.89.

(2,2′)-2,2′-(((Butane-1,4-diylbis(oxy))bis(4,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(hydrazinecarbothioamide) (10c). This compound was obtained as white crystal, (82% yield), mp 250–252°C; ir (potassium bromide): NH 3392, NH_2 3208, 3140, CS 1673, C=N 1592 cm^{-1}; ^1H nmr: δ 1.88 (br. s, 4H, CH_2), 2.26 (s, 6H, CH_3), 4.07 (br. s, 4H, CH_2O), 6.92 (d, 4H, *J* = 9.0 Hz), 7.86 (d, 4H, *J* = 9.0 Hz), 8.17 (br. s, 4H, NH_2), 10.08 ppm (br. s, 2H, NH); ms: *m/z* (%) 472 (0.25, M^+). *Anal*. Calcd for $C_{22}H_{28}N_6O_2S_2$: C, 55.91; H, 5.97; N, 17.78; S, 13.57. Found: C, 55.88; H, 5.90; N, 17.83; S, 13.48.

General procedure for the synthesis of bis(ethan-1-yl-1-ylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2H-chromen-2-ones) 11a–c. To a solution of bis (ethan-1-yl-1-ylidene))bis(hydrazinecarbothioamide) derivatives **10a–c** (1 mmol) and 3-(2-bromoacetyl)-2*H*-chromen-2-one (**9**) (2 mmol) in ethanol (25 mL), few drops of TEA were added. The reaction mixture was heated at reflux for 4 h. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from ethanol/DMF to give **11a–c**.

3,3′-(2,2′-((2,2′)-2,2′-(((Ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2H-chromen-2-one) (11a). This compound was obtained as orange crystals, (70% yield), mp >300°C; ir (potassium bromide): NH 3428, CO 1715, C=N 1569 cm^{-1}; ^1H nmr: δ 2.30 (s, 6H, CH_3), 4.36 (s, 4H, CH_2O), 7.02–7.10 (m, 6H, ArH), 7.35–7.91 (m, 10H,

ArH), 7.94 (s, 2H, chromen-4-H), 8.56 (s, 2H, thiazole-5-H), 11.16 ppm (br. s, 2H, NH); ms: *m/z* (%) 780 (0.11, M^+). *Anal*. Calcd for $C_{42}H_{32}N_6O_6S_2$: C, 64.60; H, 4.13; N, 10.76; S, 8.21. Found: C, 64.49; H, 4.22; N, 10.71; S, 8.16.

3,3′-(2,2′-((2,2′)-2,2′-(((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2H-chromen-2-one) (11b). This compound was obtained as orange crystals, (78% yield), mp 254–256°C; ir (potassium bromide): NH 3428, CO 1718, C=N 1562 cm^{-1}; ^1H nmr: δ 2.20 (t, 2H, *J* = 6.0 Hz, CH_2), 2.29 (s, 6H, CH_3), 4.18 (t, 4H, *J* = 6.0 Hz, CH_2O), 7.00 (d, 4H, *J* = 8.7 Hz), 7.37–7.45 (m, 4H, ArH), 7.59–7.81 (m, 10H, ArH & chromen-4-H), 8.56 (s, 2H, thiazole-5-H), 11.19 ppm (br. s, 2H, NH); ms: *m/z* (%) 794 (0.36, M^+). *Anal*. Calcd for $C_{43}H_{34}N_6O_6S_2$: C, 64.97; H, 4.31; N, 10.57; S, 8.07. Found: C, 64.88; H, 4.24; N, 10.59; S, 8.00.

3,3′-(2,2′-((2,2′)-2,2′-(((Butane-1,4-diylbis(oxy))bis(4,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2H-chromen-2-one) (11c). This compound was obtained as orange crystals, (76% yield), mp 240–242°C; ir (potassium bromide): NH 3395, CO 1719, C=N 1593 cm^{-1}; ^1H nmr: δ 1.87 (br. s, 4H, CH_2), 2.25 (s, 6H, CH_3), 4.06 (br. s, 4H, CH_2O), 6.91 (d, 4H, *J* = 8.7 Hz), 6.95–7.91 (m, 8H, ArH), 7.84 (d, 4H, *J* = 8.7 Hz), 8.12 (s, 2H, chromen-4-H), 8.55 (s, 2H, thiazole-5-H), 10.03 ppm (s, 2H, NH); ^{13}C nmr: δ 13.73, 25.32, 67.23, 110.75, 114.07, 114.30, 115.79, 119.12, 124.63, 127.07, 128.03, 128.60, 129.97, 130.23, 130.36, 137.88, 147.85, 159.58, 169.34, 178.71; ms: *m/z* (%) 808 (0.15, M^+). *Anal*. Calcd for $C_{44}H_{36}N_6O_6S_2$: C, 65.33; H, 4.49; N, 10.39; S, 7.93. Found: C, 65.42; H, 4.54; N, 10.33; S, 7.81.

General procedure for the synthesis of bis(2H-chromen-2-one)thiazol-2-yl)hydrazono)methyl)phenoxy) alkane 13a–f. To a solution of alkylenebis(oxy)bis(2,1-phenylene) bis(methan-1-yl-1-ylidene))bis (hydrazine-carbothioamide) **12a–f** (1 mmol) and 3-(2-bromoacetyl)-2*H*-chromen-2-one (**9**) (2 mmol) in ethanol (25 mL), few drops of TEA were added. The reaction mixture was heated at reflux for 4 h. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from ethanol/DMF to give **13a–f**.

3,3′-(2,2′-((2,2′)-2,2′-(((Ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis (methanylylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2H-chromen-2-one) (13a). This compound was obtained as yellow crystals, (72% yield), mp 280–282°C; ir (potassium bromide): NH 3442, CO 1709, C=N 1572 cm^{-1}; ^1H nmr: δ 4.36 (s, 4H, CH_2O), 7.03–7.94 (m, 16H, ArH), 7.73 (s, 2H, chromen-4-H), 8.01 (s, 2H, CH=N), 8.51 (s, 2H, thiazole-5-H), 12.01 ppm (s, 2H, NH); ms: *m/z* (%) 752 (0.27, M^+). *Anal*. Calcd for $C_{40}H_{28}N_6O_6S_2$: C, 63.82; H, 3.75; N, 11.16; S, 8.52. Found: C, 63.73; H, 3.69; N, 11.11; S, 8.45.

3,3′-(2,2′-((2,2′)-2,2′-(((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(methanylylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2H-chromen-2-one) (13b). This compound was obtained as yellow crystals, (77% yield), mp 272–274°C; ir (potassium bromide): NH 3448, CO 1709, C=N 1576 cm^{-1}; ^1H nmr: δ 2.20 (br. s, 2H, CH_2), 4.18 (br. s, 4H, CH_2O), 7.02 (d, 4H, *J* = 7.8 Hz), 7.35–7.44 (m, 4H, ArH), 7.59 (d, 4H, *J* = 8.1 Hz), 7.74 (s, 2H, chromen-4-H), 7.82–7.84 (m, 4H, ArH), 8.01 (s, 2H, CH=N), 8.52 (s, 2H, thiazole-5-H), 12.01 ppm (s, 2H, NH); ms: *m/z* (%) 766 (0.16, M^+). *Anal*. Calcd for $C_{41}H_{30}N_6O_6S_2$: C, 64.22; H, 3.94; N, 10.96; S, 8.36. Found: C, 64.26; H, 3.87; N, 10.89; S, 8.29.

3,3′-(2,2′-((2,2′)-2,2′-(((Butane-1,4-diylbis(oxy))bis(4,1-phenylene))bis(methanylylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2H-chromen-2-one) (13c). This compound was obtained as yellow crystals, (75% yield), mp 278–280°C; ir (potassium bromide): NH 3444, CO 1707, C=N 1569 cm^{-1}; ^1H nmr: δ 1.90 (br. s, 4H, CH_2), 4.09 (br. s, 4H, CH_2O), 7.00 (d, 4H, *J* = 8.7 Hz), 7.36–7.45 (m, 4H, ArH), 7.59 (d, 4H, *J* = 8.7 Hz), 7.74 (s, 2H, chromen-4-H), 7.83–7.85 (m, 4H, ArH), 8.01 (s, 2H, CH=N), 8.53 (s, 2H, thiazole-5-H), 12.01 ppm (s, 2H, NH); ms: *m/z* (%) 780 (0.13, M^+). *Anal*. Calcd for $C_{42}H_{32}N_6O_6S_2$: C, 64.60; H, 4.13; N, 10.76; S, 8.21. Found: C, 64.45; H, 4.06; N, 10.66; S, 8.17.

3,3′-(2,2′-((2,2′)-2,2′-(((Ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(methanylylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2H-chromen-2-one) (13d). This compound was obtained as yellow crystals, (66% yield), mp 276–278°C; ir (potassium bromide): NH 3414, CO 1695, C=N 1572 cm^{-1}; ^1H nmr: δ 4.46 (s, 4H, CH_2O), 7.07–7.41 (m, 12H, ArH), 7.59–7.85 (m, 6H, ArH & chromen-4-H), 8.43 (br. s, 4H, thiazole-5-H & CH=N), 12.08 ppm (s, 2H, NH); ms: *m/z* (%) 752 (0.13, M^+). *Anal*. Calcd for $C_{40}H_{28}N_6O_6S_2$: C, 63.82; H, 3.75; N, 11.16; S, 8.52. Found: C, 63.70; H, 3.82; N, 11.23; S, 8.43.

3,3′-(2,2′-((2,2′)-2,2′-(((Propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(methanylylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2H-chromen-2-one) (13e). This compound was obtained as orange crystals, (72% yield), mp 216–218°C; ir (potassium bromide): NH 3429, CO 1716, C=N 1567 cm^{-1}; ^1H nmr: δ 2.30 (t, 2H, *J* = 6.0 Hz, CH_2), 4.31 (t, 4H, *J* = 6.0 Hz, CH_2O), 6.99–7.15 (m, 4H, ArH), 7.34–7.61 (m, 8H, ArH), 7.74 (s, 2H, chromen-4-H), 7.77–7.83 (m, 4H, ArH), 8.46 (s, 2H, CH=N), 8.51 (s, 2H, thiazole-5-H), 12.13 ppm (s, 2H, NH); ^{13}C nmr: δ 28.78, 64.75, 110.44, 112.72, 115.81, 119.12, 120.49, 120.89, 122.55, 124.63, 124.99, 128.74, 130.73, 131.59, 137.48, 138.06, 143.91, 152.24, 156.31, 158.68, 167.60; ms: *m/z* (%) 766 (0.05, M^+). *Anal*. Calcd for $C_{41}H_{30}N_6O_6S_2$: C, 64.22; H, 3.94; N, 10.96; S, 8.36. Found: C, 64.14; H, 3.88; N, 10.86; S, 8.30.

3,3′-(2,2′-((2,2′)-2,2′-(((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(methanylylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-4,2-diyl))bis(2H-chromen-2-one) (13f). This compound was obtained as yellow crystals, (75% yield), mp 222–225°C; ir (potassium bromide): NH 3440, CO 1699, C=N 1573 cm^{-1}; ^1H nmr: δ 2.02 (br. s, 4H, CH_2), 4.17 (br. s, 4H, CH_2O), 7.01–7.13 (m, 4H, ArH), 7.33–7.61 (m, 8H, ArH), 7.73 (s, 2H, chromen-4-H), 7.78–7.80 (m, 4H, ArH), 8.48 (s, 2H, CH=N), 8.49 (s, 2H, thiazole-5-H), 12.18 ppm (s, 2H, NH); ms: *m/z* (%) 780 (0.10, M^+). *Anal*. Calcd for $C_{42}H_{32}N_6O_6S_2$: C, 64.60; H, 4.13; N, 10.76; S, 8.21. Found: C, 64.45; H, 4.19; N, 10.68; S, 8.15.

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REFERENCES AND NOTES

[1] Chen, C.; Song, J.; Wang, J.; Xu, C.; Chen, C.; Gu, W.; Sun, H.; Wen, X. Bioorg Med Chem Lett 2017, 27, 845.

[2] Chhabria, M. T.; Patel, S.; Modi, P.; Brahmkshatriya, P. S. Curr Top Med Chem 2016, 16, 2841.

[3] Kesicki, E. A.; Bailey, M. A.; Ovechkina, Y.; Early, J. V.; Alling, T.; Bowman, J.; Zuniga, E. S.; Dalai, S.; Kumar, N.; Masquelin, T.; Hipskind, P. A.; Odingo, J. O.; Parish, T. PLoS One 2016, 11, e0155209.

[4] Aggarwal, R.; Kumar, S.; Kaushik, P.; Kaushik, D.; Gupta, G. K. Eur J Med Chem 2013, 62, 508.

[5] Helal, M. H. M.; Salem, M. A.; El-Gaby, M. S. A.; Aljahdali, M. Eur J Med Chem 2013, 65, 517.

[6] Karuvalam, R. P.; Haridas, K. R.; Nayak, S. K.; Guru Row, T. N.; Rajeesh, P.; Rishikesan, R.; Kumari, N. S. Eur J Med Chem 2012, 49, 172.

[7] Badiger, N. P.; Khan, A.; Kalashetti, M. B.; Khazi, I. M. Med Chem Res 2012, 21, 1544.

[8] Cohen, A.; Verhaeghe, P.; Crozet, M. D.; Hutter, S.; Rathelot, P.; Vanelle, P.; Azas, N. Eur J Med Chem 2012, 55, 315.

[9] Liaras, K.; Geronikaki, A.; Glamočlija, J.; Ćirić, A.; Soković, M. Bioorg Med Chem 2011, 19, 3135.

[10] Omar, K.; Geronikaki, A.; Zoumpoulakis, P.; Camoutsis, C.; Soković, M.; Ćirić, A.; Glamočlija, J. Bioorg Med Chem 2010, 18, 426.

[11] Karthikeyan, M. S. Eur J Med Chem 2009, 44, 827.

[12] Lu, Y.; Li, C.-M.; Wang, Z.; Ross, C. R.; Chen, J.; Dalton, J. T.; Li, W.; Miller, D. D. J Med Chem 2009, 52, 1701.

[13] Fox, L. M.; Saravolatz, L. D. Clin Infect Dis 2005, 40, 1173.

[14] Cuenca-Estrella, M.; Gomez-Lopez, A.; Mellado, E.; Garcia-Effron, G.; Rodriguez-Tudela, J. L. Antimicrob Agents Chemother 2004, 48, 3107.

[15] Barreca, M. L.; Balzarini, J.; Chimirri, A.; De Clercq, E.; De Luca, L.; Ho, H. D.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zappala, M. J Med Chem 2002, 45, 5410.

[16] Mandlik, V.; Patil, S.; Bopanna, R.; Basu, S.; Singh, S. PLoS One 2016, 11, e0164585.

[17] Peng, X.-M.; Zhou, G. L. V. D.; Zhou, C.-H. Curr Pharm Des 2013, 19, 3884.

[18] Donnelly, A. C.; Mays, J. R.; Burlison, J. A.; Nelson, J. T.; Vielhauer, G.; Holzbeierlein, J.; Blagg, B. S. J. J Org Chem 2008, 73, 8901.

[19] Beillerot, A.; Domínguez, J. C. R.; Kirsch, G.; Bagrel, D. Bioorg Med Chem Lett 2008, 18, 1102.

[20] Wu, L.; Wang, X.; Xu, W.; Farzaneh, F.; Xu, R. Curr Med Chem 2009, 16, 4236.

[21] Witaicenis, A.; Seito, L. N.; Da Silveira Chagas, A.; De Almeida, L. D.; Luchini, A. C.; Rodrigues-Orsi, P.; Cestari, S. H.; Di Stasi, L. C. Phytomedicine 2014, 21, 240.

[22] Nasr, T.; Bondock, S.; Youns, M. Eur J Med Chem 2014, 76, 539.

[23] Bronikowska, J.; Szliszka, E.; Jaworska, D.; Czuba, Z. P.; Krol, W. Molecules 2012, 17, 6449.

[24] Canning, C.; Sun, S.; Ji, X.; Gupta, S.; Zhou, K. J Ethnopharmacol 2013, 147, 259.

[25] Murat Bilgin, H.; Atmaca, M.; Deniz Obay, B.; Özekinci, S.; Taşdemir, E.; Ketani, A. Exp Toxicol Pathol 2011, 63, 325.

[26] Hassaneen, H. M.; Shawali, A. S.; Saleh, F. M. J Sulfur Chem 2016, 37, 241.

[27] Shaker, R. M. ARKIVOC 2012, i, 1.

[28] Csuk, R.; Barthel, A.; Raschke, C.; Kluge, R.; Ströhl, D.; Trieschmann, L.; Böhm, G. Arch Pharm (Weinheim) 2009, 342, 699.

[29] Soural, M.; Bouillon, I.; Krchňák, V. J Comb Chem 2008, 10, 923.

[30] Helal, C. J.; Sanner, M. A.; Cooper, C. B.; Gant, T.; Adam, M.; Lucas, J. C.; Kang, Z.; Kupchinsky, S.; Ahlijanian, M. K.; Tate, B.; Menniti, F. S.; Kelly, K.; Peterson, M. Bioorg Med Chem Lett 2004, 14, 5521.

[31] Dolle, R. E. J Comb Chem 2004, 6, 623.

[32] Dolle, R. E. J Comb Chem 2005, 7, 739.

[33] Warszycki, D.; Mordalski, S.; Kristiansen, K.; Kafel, R.; Sylte, I.; Chilmonczyk, Z.; Bojarski, A. J. PLoS One 2013, 8, e84510.

[34] Meunier, B. Acc Chem Res 2008, 41, 69.

[35] Viegas-Junior, C.; Danuello, A.; da Silva Bolzani, V.; Barreiro, E. J.; Fraga, C. A. M. Curr Med Chem 2007, 14, 1829.

[36] Salem, M. E.; Darweesh, A. F.; Farag, A. M.; Elwahy, A. H. M. Tetrahedron 2016, 72, 712.

[37] Salem, M. E.; Darweesh, A. F.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. J Heterocyclic Chem 2017, 54, 226.

[38] Salem, M. E.; Darweesh, A. F.; Farag, A. M.; Elwahy, A. H. M. J Heterocyclic Chem 2017, 54, 586.

[39] El-Fatah, N. A. A.; Darweesh, A. F.; Mohamed, A. A.; Abdelhamid, I. A.; Elwahy, A. H. M. Monatshefte Für Chemie - Chem Mon 2017, 148, 2107.

[40] Salama, S. K.; Darweesh, A. F.; Abdelhamid, I. A.; Elwahy, A. H. M. J Heterocyclic Chem 2017, 54, 305.

[41] Abd El-Fatah, N. A.; Darweesh, A. F.; Mohamed, A. A.; Abdelhamid, I. A.; Elwahy, A. H. M. Tetrahedron 2017, 73, 1436.

[42] Sayed, O. M.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. J Sulfur Chem 2015, 36, 124.

[43] Verma, S.; Kumar, S.; Jain, S. L.; Sain, B. Org Biomol Chem 2011, 9, 6943.

[44] Secci, D.; Carradori, S.; Bolasco, A.; Chimenti, P.; Yáñez, M.; Ortuso, F.; Alcaro, S. Eur J Med Chem 2011, 46, 4846.

[45] Elwahy, A. H. M.; Darweesh, A. F.; Shaaban, M. R. J Heterocyclic Chem 2012, 49, 1120.

[46] Elwahy, A. H. M. J Chem Res 1999, (S) 602.

[47] Ibrahim, Y. A.; Elwahy, A. H. M.; Elkareish, G. M. M. J Chem Res 1994, (S) 414.

[48] Elwahy, A. H. M.; Abbas, A. A.; Ibrahim, Y. A. J Chem Res 1998, (S) 184.

[49] Ranade, D. S.; Bapat, A. M.; Ramteke, S. N.; Joshi, B. N.; Roussel, P.; Tomas, A.; Deschamps, P.; Kulkarni, P. P. Eur J Med Chem 2016, 121, 803.

[50] Shaaban, M. R.; Elwahy, A. H. M. J Heterocyclic Chem 2012, 49, 640.

[51] Ibrar, A.; Zaib, S.; Khan, I.; Jabeen, F.; Iqbal, J.; Saeed, A. RSC Adv 2015, 5, 89919.