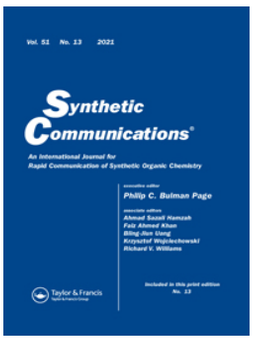

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Bis(sulfanediyl)*bis*(6-aminopyrimidin-4-ones): Versatile precursors for novel *bis*(sulfanediyl)*bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-diones) linked to aliphatic spacer via multi-component reactions

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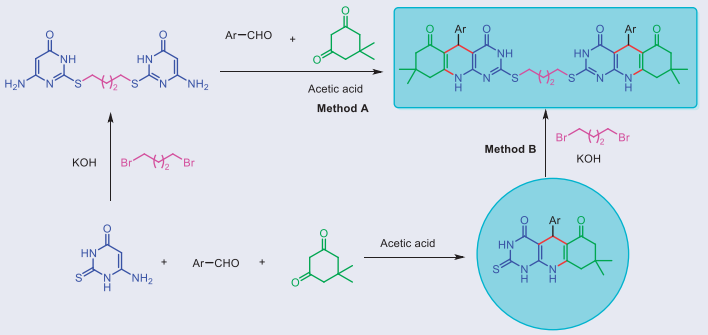
ABSTRACT

A synthesis of novel *bis*(sulfanediyl)*bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-diones), linked to aryl, heteroaryl, and spirocyclic-oxindole moieties at position-5, as novel hybrid molecules was reported. 2,2′-(Butane-1,4-diyl*bis*(sulfanediyl))*bis*(6-aminopyrimidin-4(1*H*)-one) was utilized as a precursor to our target compounds *via* a multicomponent reaction with two equivalents of both of the appropriate aldehyde and dimedone. The target compounds were alternatively obtained by *bis*-(alkylation) of the appropriate 5-aryl-2-thioxohexahydropyrimido[4,5-*b*]quinoline-4,6-dione with 1,4-dibromobutane in moderate basic medium.

GRAPHICAL ABSTRACT



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Introduction

Pyrimidine derivatives represent an important class of nitrogen-containing heterocycles that exhibit remarkable biological activities[1] including antifungal,[2,3] antibacterial,[4–10] antioxidant,[11] anti-inflammatories,[12] antiviral,[13] antihypertensive,[14,15] antidiabetic,[16] and anticancer activities.[17,18] Besides, the syntheses pyrimido[4,5-*b*]quinoline derivatives

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have received much attention over the past years because of their wide range of applications including their utility as radioprotective[19] and as anticancer agents.[19,20]

Moreover, the hybridization approach that involves the combination of two distinctive pharmacophoric moieties to form a molecule with improved efficacy as well as to overcome the drug resistance, has recently been reviewed.[21–25] The hybrid molecules design provides unique advantages such as low cost, high efficacy, and reduction of the risk of drug-drug interaction. Hybrid drugs are distributed within the body, metabolized, and excreted at one rate. Therefore there is no competition for plasma protein binding that can lead to drug interactions.[26] "According to Muregi and Ishih,[26] hybrid drugs can be classified as conjugates in which the pharmacophores are separated by a distinct linker group; cleavage conjugates in which the pharmacophores are separated by a metabolized linker; fused hybrid molecules with reduced linker between pharmacophores, resulting in the closeness of the pharmacophores and merged hybrid in which the framework is merged".[25]

Furthermore, growing interest has been paid to the synthesis of *bis*-heterocycles, in which two bioactive heterocycles are linked by an adaptable linker, due to their bioactivity that includes anticancer,[27–33] antifungal and antibacterial properties.[34–37] They also have various applications as chelating agents,[38] metal ligands,[38] and electrically conducting materials.[39]

Moreover, the wide range of application of multicomponent reactions (MCRs) have gained much attention in organic synthesis as their wide range of applications in medicinal chemistry, drug discovery programs, heterocyclic and combinational chemistry, natural product synthesis, agrochemistry, and polymer chemistry have increased significantly. Multicomponent reactions are classified as synthetic protocols which combine three or more substrates to deliver structurally complex organic molecules in a highly regio- and stereoselective manner.[40–48]

In conjunction to our research interest on the Michael addition reactions[29,49–54] Hantzsch reaction,[53,55–60] the synthesis of bis(heterocycles) synthesis[42,61–68] as well as the utility of enamines as precursors in organic synthesis,[69–76] we report herein the results of our investigations concerning the multicomponent reactions of *bis*(sulfanediyl))*bis*(6-aminopyrimidin-4-one) derivatives with the appropriate aldehyde and dimedone aiming at the synthesis of novel *bis*(sulfanediyl)bis(8,8-dimethyl-5-phenyl-5,8,9,10-tetrahydropyrimido[4,5-*b*] quinoline-4,6-diones).

Results and discussion

Very recently, we have described the synthesis of some *bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-diones) **1** in which the two heterocyclic systems are linked to alkyl core *via* phenoxymethyl linkage[77]. The present study aims to synthesize *bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-dione) **2** which are linked by *bis*(sulfanediyl) linker **2** (Figure 1). It is expected that the combination of the two scaffolds (tetrahydropyrimido[4,5-*b*]quinoline-4,6-dione) *via bis*(sulfanediyl) linker can lead to the discovery of new active drugs due to the reported pharmacological activities of sulfur-containing compounds.[78,79]

Firstly, the *bis*(sulfanediyl)*bis*(6-aminopyrimidin-4-one) **5**, which has been chosen as a precursor to our target compounds, is prepared through the direct *bis*-*S*-alkylation

reaction of 6-aminothiouracil **3** with the 1,4-dibromobutane **4** in the presence of anhydrous KOH (Scheme 1). The tautomeric isomer **6** and other possible *bis*-*N*-alkylated **7** or *S*-*N*-alkylated **8** products are excluded based on NMR spectroscopy and theoretical calculations of similar compounds.[67]

Also, the ^{13}C NMR spectrum revealed the methylene carbon at δ 29.5 which proves that the methylene carbons are attached to sulfur. Besides, it indicated the absence of C=S signal[80] which strongly supports the alkylation of sulfur.

Having established the structure of the starting compound **5**, its reactivity in the Michael addition reaction toward the activated double bond has then been investigated. Thus, the reaction of one equivalent of **5** with two equivalents of both of *p*-chlorobenzaldehyde **9a** and dimedone **10** afforded the Michael addition product that can be formulated as *bis*(sulfanediyl)*bis* (tetrahydropyrimido[4,5-*b*]quinoline-4,6-dione) **2**, or *bis*(sulfanediyl))*bis*(tetrahydropyrimido[4,5-*c*]isoquinoline-1,7-dione) **11** (Scheme 2).

A reasonable reaction pathway for the formation of **2** and **11** is represented in Scheme 3. Firstly, the acetic acid as an acidic catalyst increases the nucleophilicity and

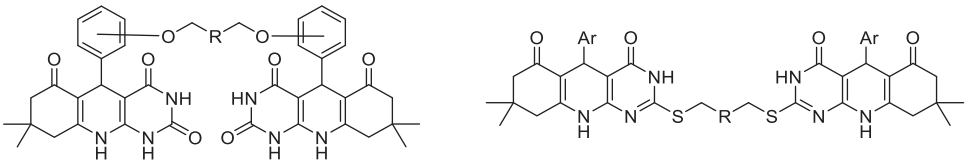
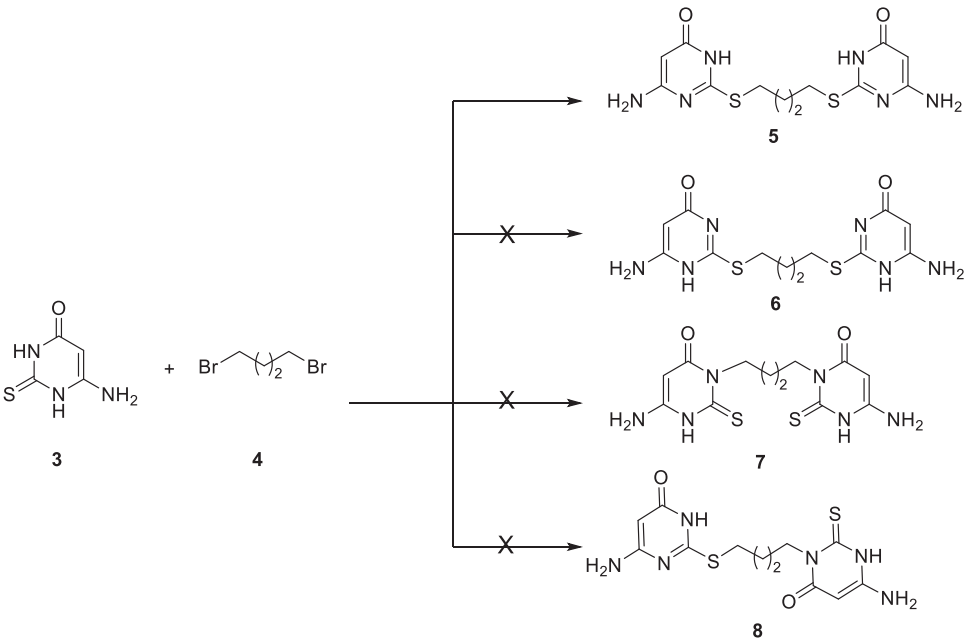
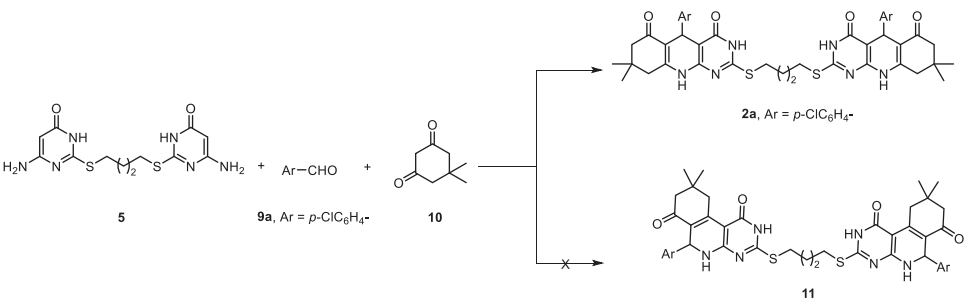


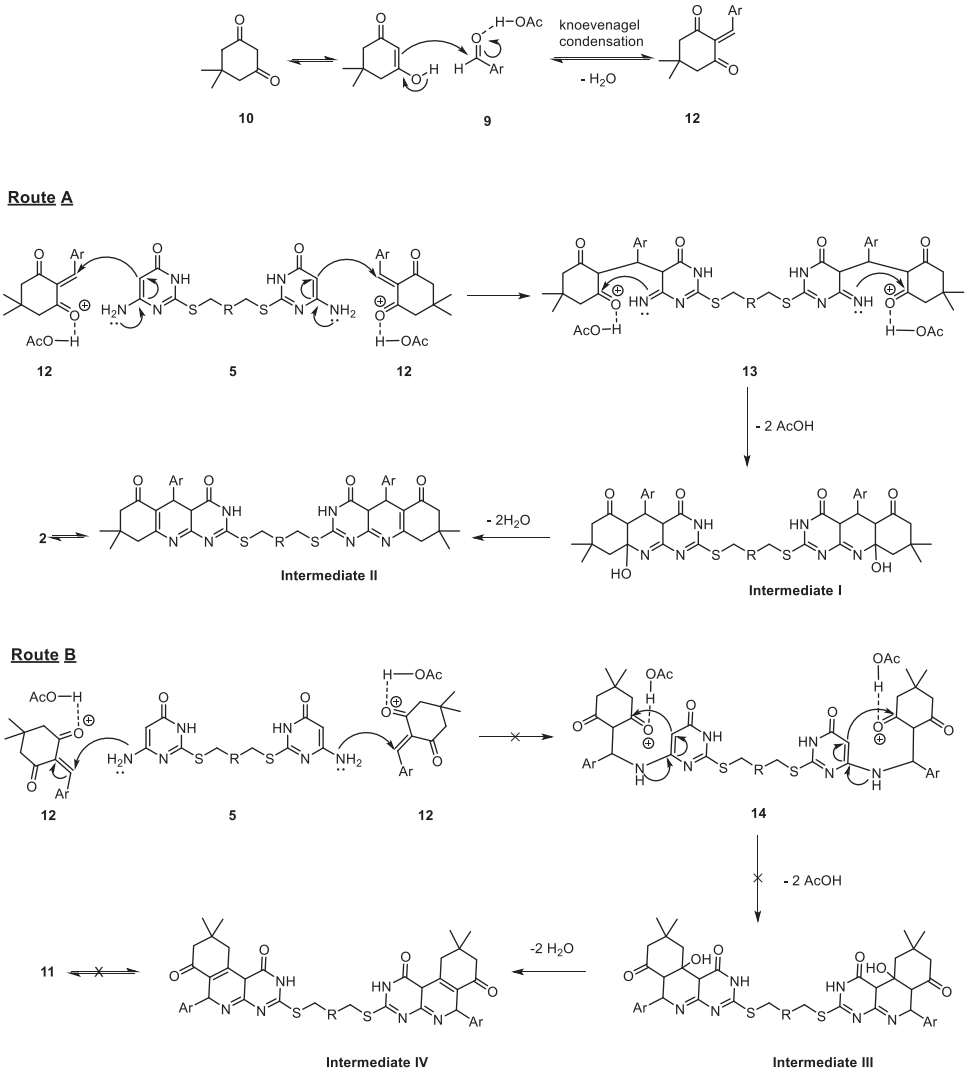
Figure 1. Structures of some *bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-diones) **1** and **2**.



Scheme 1. Possible *bis*-alkylated products from the reaction of 6-aminothiouracil **3** with the 1,4-dibromobutane **4**.



Scheme 2. Possible expected **2a** and **11** from the reaction of one equivalent of **5** with two equivalents of both aldehydes **9a** and dimedone **10**.



Scheme 3. Reasonable reaction routes (A and B) for the formation of compounds **2** and **11**.

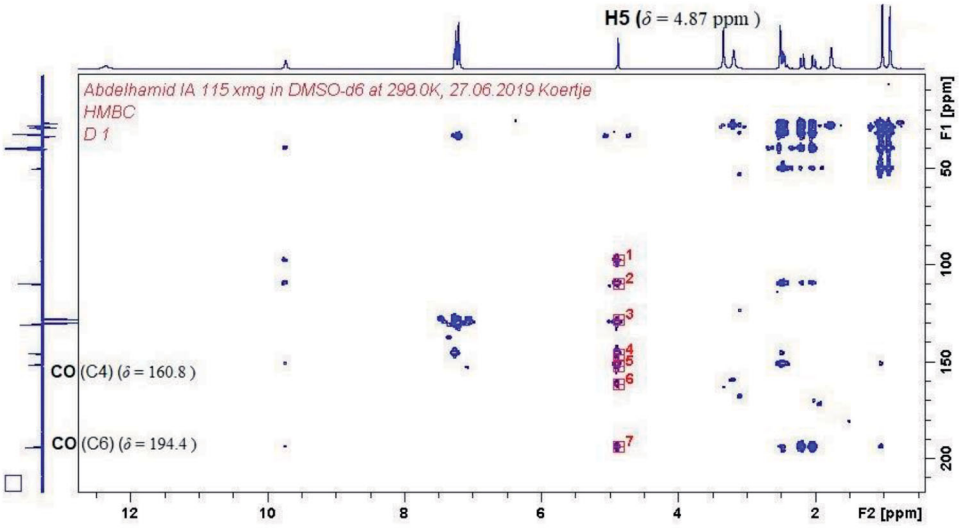
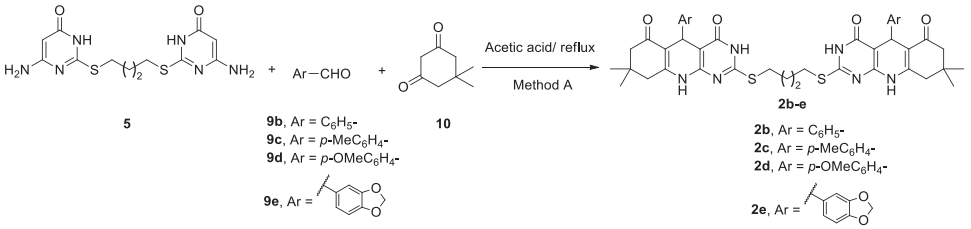


Figure 2. 2 D-HMBC spectrum of **2a**.

reactivity of carbonyl group of aldehydes **9** toward the activated methylene group of dimedone **10** through Knoevenagel condensation reaction to form the corresponding 2-arlylidene intermediate **12**. The Michael addition of pyrimidine-H5 and NH_2 of *bis*(sulfanediyl)*bis*(6-aminopyrimidin-4-one) **5** toward arylidene-dimedone **12** follows one of the following two routes (Routes A and B). Compound **2** is formed through route A that involves the initial nucleophilic addition of pyrimidine-H5 of compound **5** to the activated β-carbon of the of arylidene-dimedone **12**. Cyclization involving the nucleophilic addition of the amino group of compounds **5** to the activated carbonyl of compound **12** affords the Michael adduct **13**. Subsequent removal of the acid catalyst and two molecules of water leads to the formation of the final isolable product **2** through intermediated **I** and **II**. Route B encompasses the initial addition of the amino group of compounds **5** to the β-carbon of the arylidene-dimedone **12** followed by nucleophilic addition of pyrimidine-H5 of compound **5** to the activated carbonyl of compound **12** to afford the Michael adduct **14**. Removal of acid catalyst and water affords **11** through intermediated **III** and **IV** (Scheme 3).

Although the ^{1}H-NMR and ^{13}C-NMR spectra cannot simply discriminate between the two isomers **2** and **11**, the HMBC spectrum of the isolated product (Ar = *p*–ClC_6H_4–) provide an evidence for the formation of **2a** as the sole product. Thus, the ^3J-coupling cross-correlations between *H*5 signal at δ 4.87 ppm and the two carbonyl groups δ 160.8 (cross peak-6) and 194.4 (cross peak-7) ppm in compound **2** is considered the strongest proof of our proposed structure (Figure 2). Otherwise, isomer **11** would have shown ^3J-CH cross-correlations between H-5 and one carbonyl only.

Moreover, the ^{1}H NMR displayed of **2a** revealed also the aromatic protons as two doublets at δ 7.19 and δ 7.25 . Besides, its mass spectrum showed a molecular ion peak at *m/z* 829 [M^+]. The IR spectrum revealed broad absorption bands at ν_{max} 3170 and 3240 cm^{-1} for the two NH groups. Also, it featured a characteristic stretching band at ν_{max} 1646 cm^{-1} for the carbonyl group.



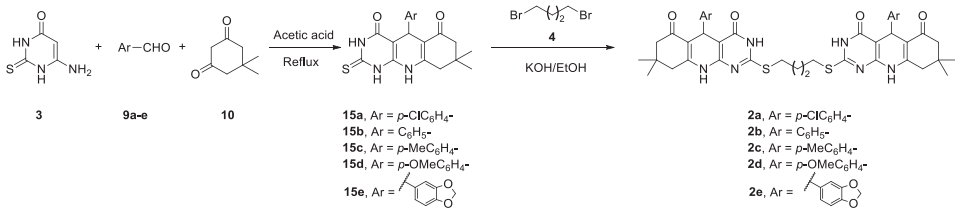
Scheme 4. Synthesis of *bis*(sulfanediyl)*bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-diones) **2 b-e** *via* multi-component reactions.

Motivated by this result, and in a trial to extend the scope and the generality of this reaction, we investigated the synthesis of *bis*(sulfanediyl)*bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-dione) **2 b–e**, through the direct reaction of compound **5** with two equivalents of both dimedone **10** and the appropriate aldehydes **9 b–e** (Scheme 4).

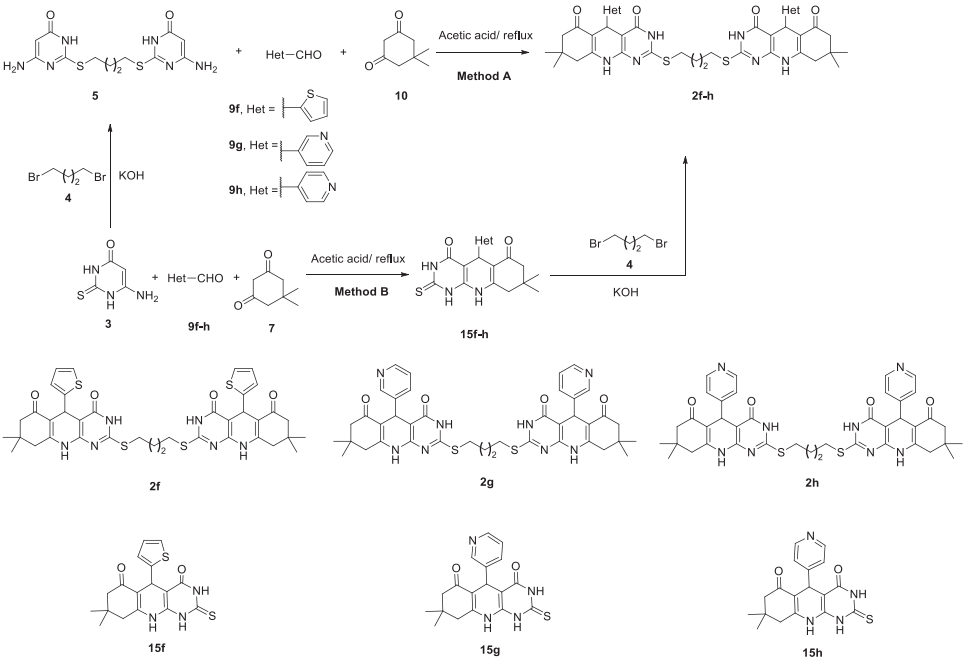
It is worth mentioning that, the same products **2a-e** were obtained *via* the *bis*(alkylation) of the initially formed 5-aryl-2-thioxohexahydropyrimido[4,5-*b*]quinoline-4,6-diones **15** with the 1,4-dibromobutane **4** in basic medium. Compounds **15** were obtained in good yields by a three-component reaction of 6-aminothiouracil **3**, aldehydes **9**, and dimedone **10** in acetic acid at reflux. *Bis*-alkylation of compound **15** with the 1,4-dibromobutane leads to the formation of the target products **2** in good to excellent yields (Scheme 5, method B).

Encouraged by this success and in a trial to achieve the concept of molecular hybridization, we extended the scope of this reaction to prepare *bis*(sulfanediyl)*bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-diones) **2f–h**, which are linked to thiophen-2-yl, pyridin-3-yl, or pyridin-4-yl at position-5 by using a variety of the respective heterocyclic aldehydes (thiophene-2-carbaldehyde, nicotinaldehyde, and isonicotinaldehyde). Thus, the reaction of one equivalent of compound **5** with two equivalents of both heterocyclic aldehydes **9f–h** and dimedone **10** affords the Michael addition products **2f–h** in good yields (Scheme 6, method A). Similarly, as in the case of compounds **2a–e**, compounds **2f–h** were alternatively prepared *via* the *bis*(alkylation) of the initially formed monopodal 5-hetroaryl-2-thioxohexahydropyrimido[4,5-*b*]quinoline-4,6-dione **15f–h** with the 1,4-dibromobutane **5** in basic medium (Scheme 6, method B).

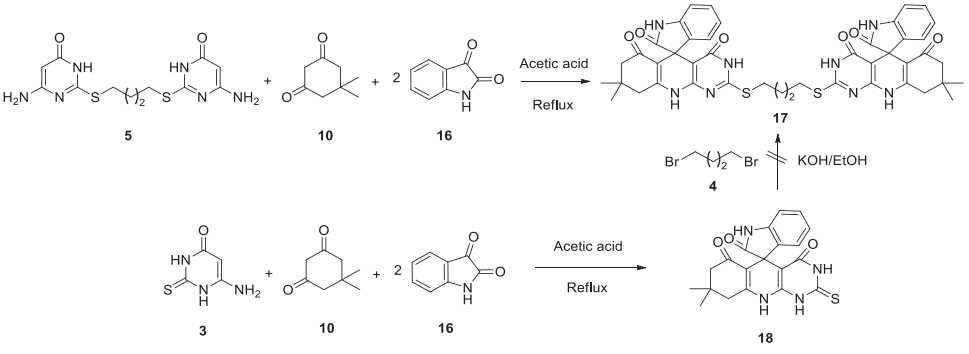
Interestingly, to extend the scope of this reaction we replaced aldehydes with isatin aiming at the synthesis of *bis*(sulfanediyl)*bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-dione) linked to spirocyclic-oxindole. It is reported that spirocyclic-oxindole containing compounds represent an important class of compounds that exhibit a wide range of bioactivities.[81–85] Thus, *bis*(sulfanediyl))*bis*(spiro[indoline-3,5′-pyrimido[4,5-*b*]quinoline]-2,4′,6′-trione) **17** was prepared in excellent yields *via* the direct reaction of one mole of **5**, with two equivalents of both dimedone **10** and isatin **16.** It is worthy to mention that attempts to synthesize **17** *via bis*(alkylation) of the initially formed 1′*H*-spiro[indoline-3,5′-pyrimido[4,5-*b*]quinoline]-2,4′,6′(7'*H*,10'*H*)-trione **18** with 1,4-dibromobutane **5** in basic medium were unsuccessful. Compound **18** was obtained in good yield by a three-component reaction of 6-aminothiouracil **3**, isatin **16**, and dimedone **10** in acetic acid at reflux.[86] (Scheme 7). The structure of **17** was confirmed by elemental analyses as well as spectral tools.



Scheme 5. Synthesis of *bis*(sulfanediyl)*bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-diones) **2 b-e** *via* *bis*-alkylation.



Scheme 6. Synthesis of *bis*(sulfanediyl)*bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-diones) **2f-h** and **16f-h** liked to heteroaryl moieties *via* two routes.



Scheme 7. Synthesis of *bis*(sulfanediyl))*bis*(spiro[indoline-3,5′-pyrimido[4,5-*b*]quinoline]-2,4′,6′-trione) **17**.

Conclusions

We synthesized *bis*(sulfanediyl)*bis*(tetrahydropyrimido[4,5-*b*]quinoline-4,6-diones) linked to aliphatic spacer and connected to aryl, heteroaryl and spirocyclic-oxindole moieties at position-5 as novel hybrid molecules. Two strategies have been performed to achieve our goal. The first one included the multicomponent reaction of *bis*(sulfanediyl)*bis*(6-aminopyrimidin-4-one) with two equivalents of both of the appropriate aldehyde and dimedone. In the second strategy, 5-aryl-2-thioxohexahydropyrimido[4,5-*b*]quinoline-4,6-diones were utilized as precursors which could then underwent *bis*(alkylation) with 1,4-dibromobutane in moderate basic medium to give the target products. Although both strategies led to the formation of the target products through two step reactions, the first strategy was found to give better overall yields compared with the second one. The successful synthesis of the target products *via* two synthetic approaches should open access to novel *bis*(heterocycles) of expected promising applications.

Experimental

Melting points were measured with a Stuart melting point apparatus and were uncorrected. The IR spectra were recorded using a FTIR Bruker-vector 22 spectrophotometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 as a solvent with Varian Mercury VXR-300 NMR spectrometer operating at 300 MHz and 75 MHz and Bruker AVS NMR spectrometer at 400 MHz and 100 MHz, respectively, using TMS as an internal standard.

Chemical shifts were reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS-QP-1000 EX mass spectrometer in EI (70 eV) model. The elemental analyses were performed at the Micro analytical center, Cairo University.

*General method for the synthesis of 2,2′-(butane-1,4-diyl*bis*(sulfanediyl))*bis*(6-aminopyrimidin-4(1*H*)-one) (5)*

To a solution of 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**3**) (2 mmol) and KOH (2 mmol) in absolute EtOH (20 ml), 1,4-dibromobutane (**4**) (1 mmol) was added. The reaction mixture was heated at reflux for 2 hrs and was then allowed to cool to rt. Thereupon it was poured over crushed ice and the formed precipitate was filtered off, dried, and purified by recrystallization from (EtOH/DMF [1:3]) mixture.

*2,2′-(Butane-1,4-diyl*bis*(sulfanediyl))*bis*(6-aminopyrimidin-4(3*H*)-one) (5)*

Colorless powder (83%), (AcOH). Mp 250–253 °C; IR (KBr) υ 3428 (NH), 3323, 3207 (NH_2), 1621 (C = O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.71 (br, 4H, $2CH_2$), 3.09 (br, 4H, 2S-CH_2), 4.89 (*s*, 2H, pyrimidine-5-H), 6.42 (br, 4H, $2NH_2$), 11.52 (br, 2H, 2NH) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 28.5, 29.2, 81.8, 162.6, 163.9, 164.7 ppm. MS (EI, 70 eV): *m/z* (%) 340] M^{+}[. Anal. Calcd for $C_{12}H_{16}N_6O_2S_2$: C, 42.34; H, 4.74; N, 24.69. Found: C, 42.07; H, 4.61; N, 24.43.

General methods for the synthesis of bis(sulfanediyl)bis(tetrahydropyrimido[4,5-b]quinoline-4,6-dione) 2(a-h)

Method A

A solution of dimedone (**10**) (2 mmol), the appropriate aldehyde **9a–h** (2 mmol) and *bis*(sulfanediyl)bis(6-aminopyrimidin-4-one) (**5**) (1 mmol) in glacial acetic acid (10 ml) was heated at reflux for 6 hrs. The obtained solid products were collected and crystallized from (EtOH/DMF [1:3]) mixture to give **2(a–h)**.

Method B

To a solution of pyrimido[4,5-*b*]quinoline-4,6-dione **15a–h** (2 mmol) and KOH (2 mmol) in EtOH (20 ml), 1,4-dibromobutane (**4**) (1 mmol) was added. The reaction mixture was heated at reflux for 2 hrs and was then allowed to cool to rt.

Thereupon it was poured over crushed ice and the formed precipitate was filtered off, dried, and purified by recrystallization from (EtOH/DMF [1:3]) mixture.

*2,2′-(Butane-1,4-diyl*bis*(sulfanediyl))*bis*(5-(4-chlorophenyl)-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-4,6(3H,7H)-dione) (2a).* Creamy powder (method A: 77%, method B: 63%). Mp <300 °C; IR (KBr) υ 3240 (NH), 3170 (NH), 1704 (C = O), 1646 (C = O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.90 (*s*, 6H, $2CH_3$), 1.01 (*s*, 6H, $2CH_3$), 1.76 (br, 4H, $2CH_2$), 1.99–2.21 (*m*, 4H, $2CH_2$), 2.45–2.47 (*m*, 4H, $2CH_2$), 3.19 (br, 4H, 2S-CH_2), 4.87 (s, 2H, 2CH), 7.19 (d, 4H, *J* 8.3 Hz), 7.25 (d, 4H, *J* 8.2 Hz), 9.72 (br.s, 2H, 2NH), 12.35 (br.s, 2H, 2NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.2, 28.3, 29.4, 29.5, 32.6, 33.9, 50.6, 98.1, 109.7, 128.2, 129.8, 130.8, 145.9, 151.6, 158.1, 161.5, 163.8, 194.4 ppm. MS (EI, 70 eV): *m/z* (%) 829] M^+[. Anal. Calcd for $C_{42}H_{42}Cl_2N_6O_4S_2$: C, 60.79; H, 5.10; N, 10.13. Found: C, 60.67; H, **5.03; N, 10.02.**

General methods for the synthesis of 5-aryl and (hetroaryl)-2-thioxohexahydropyrimido[4,5-b]quinoline-4,6-dione (15a-h)

A solution of dimedone (**10**) (1 mmol), 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**3**) (1 mmol) and the appropriate aldehyde **9a–h** (1 mmol) in glacial acetic acid (5 ml) was heated at reflux for 6 hrs. The obtained solid products were collected and crystallized from (EtOH/DMF [1:3]) mixture.

5-(4-Chlorophenyl)-8,8-dimethyl-2-thioxo-2,3,5,8,9,10-hexahydropyrimido[4,5-b]quinoline-4,6(1H,7H)-dione (15a)

Creamy powder (67%). Mp <300 °C; IR (KBr) υ 3356 (NH), 3224 (NH), 1689 (C = O), 1643 (C = O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.89 (*s*, 3H, CH_3), 1.02 (*s*, 3H, CH_3), 2.01–2.23 (*m*, 2H, CH_2), 2.40–2.47 (*m*, 2H, CH_2), 4.74 (*s*, H, CH), 7.20–7.27 (*m*, 4H, Ar-H), 8.52 (br, H, NH), 11.71 (br, H, NH), 12.21 (br, H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.9, 29.3, 32.6, 33.3, 50.5, 94.1, 111.2, 128.2, 129.9, 131.1, 144.0, 145.1, 149.3, 160.5, 173.9, 194.8 ppm. MS (EI, 70 eV): *m/z* (%) 387] M^+[. Anal. Calcd for $C_{19}H_{18}ClN_3O_2S$: C, 58.83; H, 4.68; N, 10.83. Found: C, 58.62; H, 4.*44; N, 10.59.*

General method for the synthesis of bis*-spirocyclic compound 17*

A solution of dimedone **(10)** (2 mmol), isatin **(16)** (2 mmol) and bis(sulfanediyl)bis(6-aminopyrimidin-4-one) **(5)** (1 mmol) in glacial acetic acid (3 ml) was heated at reflux for 6 hr. The solid formed was collected and crystalized from DMF.

*2′,2′′′-(Butane-1,4-diyl*bis*(sulfanediyl))*bis*(8′,8′-dimethyl-8′,9′-dihydro-1′*H*-spiro[indoline-3,5′-pyrimido[4,5-*b*]quinoline]-2,4′,6′(7′*H*,10′*H*)-trione) (17)*

Colorless crystals (method A: 91%), Mp <300 °C; IR (KBr) υ 3441 (NH), 3348 (NH), 3309 (NH), 1635 (C = O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (*s*, 6H, $2CH_3$), 1.01 (*s*, 6H, $2CH_3$), 1.78 (br, 4H, $2CH_2$), 1.87–2.11 (*m*, 4H, 2 CH_2), 2.44–2.49 (*m*, 4H, $2CH_2$), 3.19 (br, 4H, 2S-CH_2), 6.61–7.03 (*m*, 8H, Ar-H), 9.76 (br, 2H, 2NH), 10.03 (br, 2H, 2NH), 12.42 (br, 2H, 2NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.5, 27.9, 28.4, 29.0, 31.9, 48.5, 50.8, 107.8, 109.1, 120.5, 122.7, 127.1, 136.1, 143.1, 151.4, 159.7, 179.6, 192.9 ppm. MS (EI, 70 eV): *m/z* (%) 842]M^+ [. Anal. Calcd for $C_{44}H_{42}N_8O_6S_2$: C, 62.69; H, 5.02; N, 13.29. Found: C, 62.54; H, 4.88; N, 13.06.

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