

## Synthesis of new bis-heterocyclic hybrids linked by *iso*-propanol unit via Hantzsch, Michael, and Biginelli reactions

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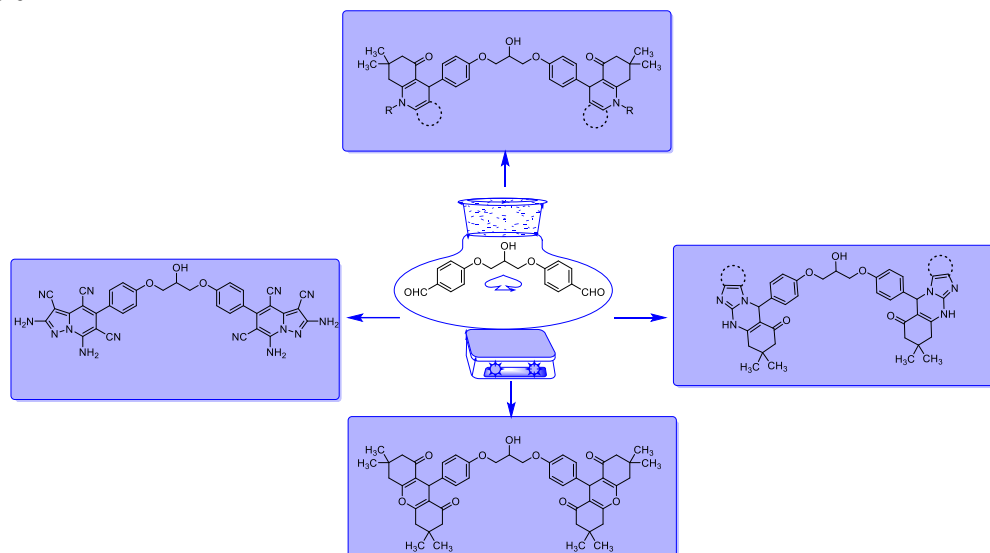
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### Abstract

Combining compounds with complementary bioactivities to create hybrid molecules is a new idea in drug research. In this work, we created novel hybrid molecules including bis-heterocycles connected by an isopropanol unit. This is accomplished by the condensation of 4,4'-((2-hydroxypropane-1,3-diyl)bis(oxy))dibenzaldehyde with the appropriate reagents using Hantzsch, Michael, and Biginelli reactions. The structures of the newly synthesized compounds are determined by elemental analysis, <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, and MS spectra.



**Keywords:** Bis(aldehyde) tethered *iso*-propanol unit, Hantzsch reaction, Michael addition reaction, hybrid molecules

## Introduction

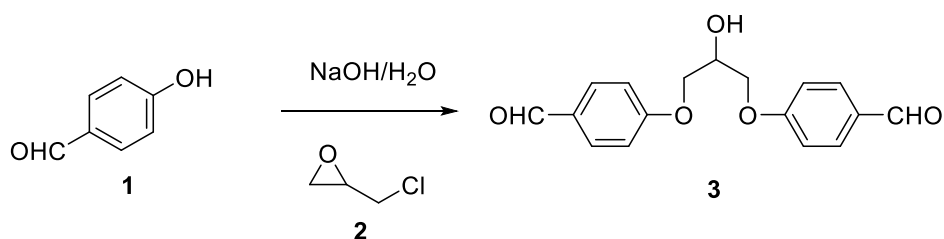
The role of hydroxyl groups in medicinal chemistry is important. Even though in physiological conditions hydroxyls lack a complete nominal charge, their polarized oxygen-hydrogen bond makes it possible for them to form hydrogen bonds with the right partners, such as solvent molecules or functional groups. Data from publicly available databases and literature sources were used to assess the prevalence of hydroxyl groups in marketed drugs. Information on the structural compositions of drugs containing hydroxyls can be obtained from the ChEMBL database,<sup>1,2</sup> from which a data set of 2053 unique marketed drugs was extracted.

Molecular hybridization is a concept in drug design and development based on the combination of pharmacophoric moieties of different bioactive substances to produce a new hybrid compound with improved affinity and efficacy when compared to the parent drugs. In recent years this field has been increasingly grown significantly and several hybrid molecules incorporating powerful biologically relevant heterocycles of widespread use in the pharmaceutical and agrochemical industry have been recognized in fields related to drug discovery.<sup>3,4</sup> Heterocyclic compounds have emerged as promising candidates for the development of new antiviral, antioxidant, anticancer, and antibacterial agents.<sup>5-8</sup> Among different heterocycles pyridine and its precursor, dihydropyridine, are among the most common structural units in the pharmaceutical industry. The features of pyridines, such as their weak basicity, water solubility, chemical stability, capacity to form hydrogen bonds, and tiny molecular size, make them significant in the field of medicine. Fused heterocyclic compounds containing pyridine moiety represent a variety of biological activities in different areas. Pyridine scaffold is an essential core in the chemical structure of a variety of approved drugs in the pharmaceutical market.<sup>9-11</sup>

Moreover, substituted, and fused pyrimidines are widely used heterocyclic moieties in drug discovery and development processes. Its derivatives exhibit numerous biological activities including antiviral, antimicrobial, antileishmanial, anti-inflammatory, neuroprotective, and cardiovascular.<sup>12-14</sup> Herein, we report the synthesis of novel isopropanol-based bis-fused dihydropyridine as well as bis-fused pyrimidines as new hybrid molecules. Our recent interest in the synthesis of heterocycles and bis-heterocycles by Hantzsch, Michael, and Biginelli reactions is continued in this study.<sup>15-41</sup>

## Results and Discussion

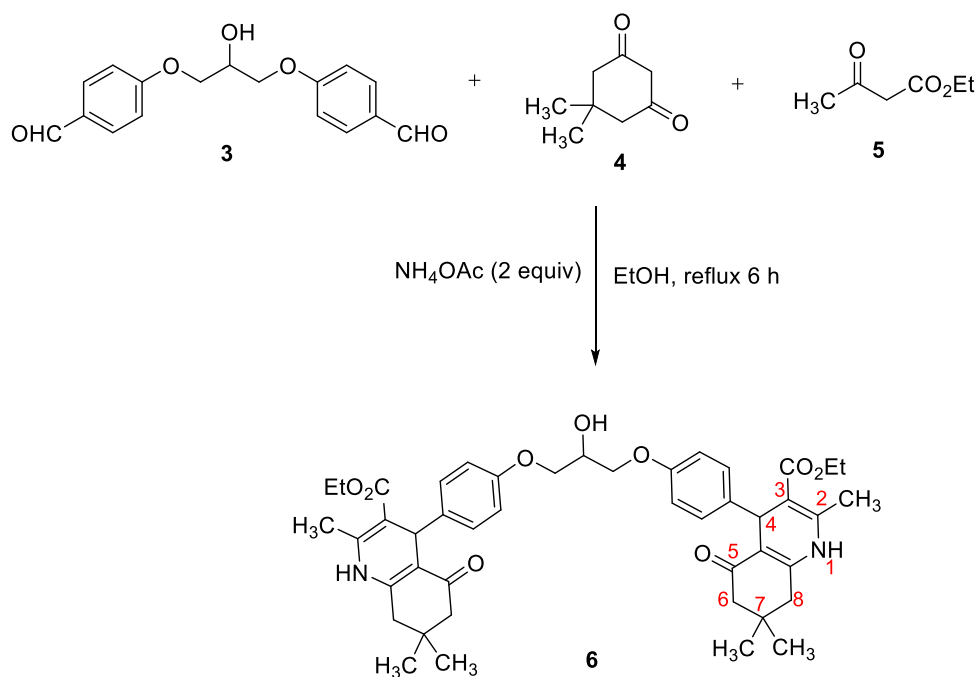
Bis-aldehyde **3** connected by a 2-propanol unit was selected as a precursor for our target products. Dibenzaldehyde **3**, also known as 4,4'-((2-hydroxypropane-1,3-diyl)bis(oxy))dibenzaldehyde, was created by reacting *p*-hydroxybenzaldehyde (**1**) with epichlorohydrin (**2**) in aqueous NaOH (Scheme 1).<sup>42</sup>



**Scheme 1.** Synthesis of 4,4'-((2-hydroxypropane-1,3-diyl)bis(oxy))dibenzaldehyde **3**.

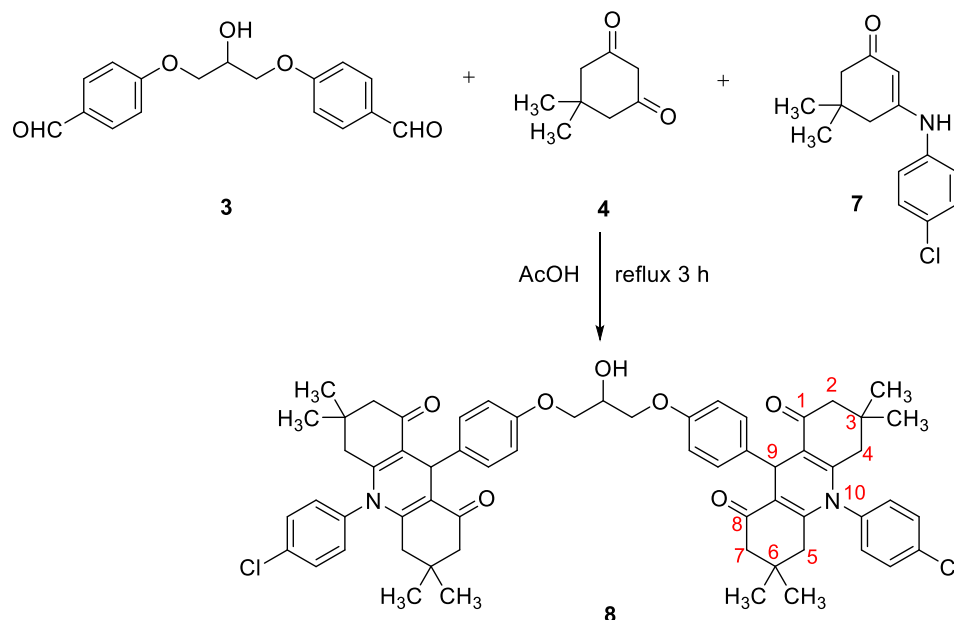
We first studied the synthesis of polyhydroquinoline **6** *via* Hantzsch's four-component condensation reactions of bis-aldehyde **3**, dimedone, ethyl acetoacetate, and ammonium acetate (Scheme 2). The target product was obtained in 80% yield after heating in ethanol at reflux for 6 h.

The structure of the target compound **6** was established based on spectral data. Thus, its IR spectra indicated the presence of the NH group at  $3208\text{ cm}^{-1}$ . In addition, it revealed the carbonyl group at  $1691$  and  $1607\text{ cm}^{-1}$ . The  $^1\text{H}$  NMR spectrum of **6** indicated the presence of two singlets integrated by 24 protons at  $\delta$  0.84 and  $\delta$  1.00 ppm assigned to four  $\text{CH}_3$  groups. Moreover, the singlet signal at 4.78 ppm corresponds to H9. The NH group appeared as a broad singlet signal at 9.02 ppm. All other signals appeared at their expected positions. Moreover, the  $^{13}\text{C}$  NMR spectrum of **6** agreed with the proposed structure, it showed the C9 at 50.43 ppm and the carbonyl group at 194.77 ppm.



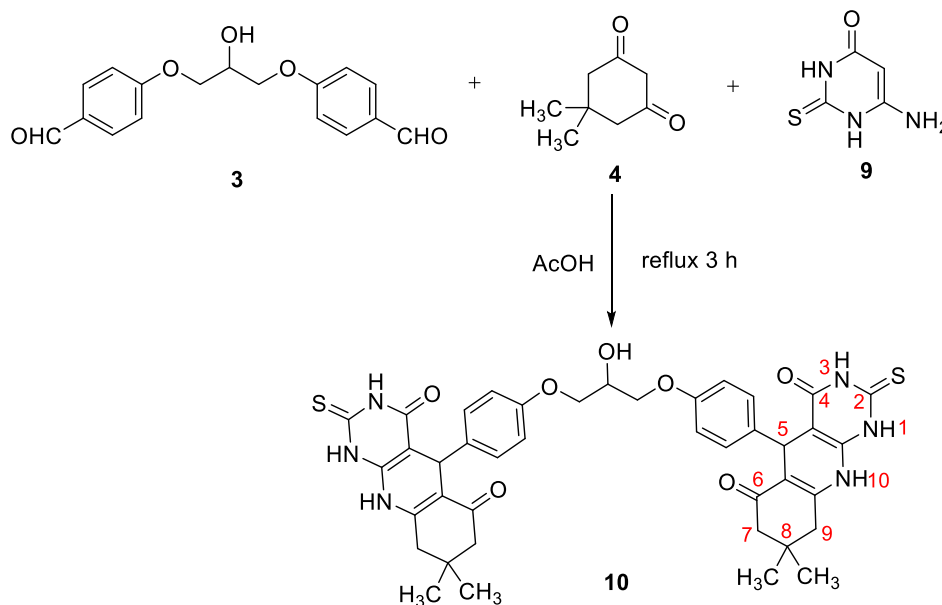
**Scheme 2.** Synthesis of hexahydroquinoline **6**.

The multi-component reaction of 4,4'-((2-hydroxypropane-1,3-diyl)bis(oxy))dibenzaldehyde (**3**) with 5,5-dimethyl-1,3-cyclohexanedione (**4**) and 5-((4-chlorophenyl)amino)-3,3-dimethylcyclohexan-1-one (**7**) afforded the target bis(hexahydroacridinedione) **8** in 82% yield. The reaction was performed by heating in refluxing acetic acid (Scheme 3). The structure of compound **8** was established based on spectral data. Thus, its IR spectrum revealed the presence of OH and carbonyl groups at  $3459$  and  $1639\text{ cm}^{-1}$ , respectively. The  $^1\text{H}$  NMR spectrum of **8** indicated the presence of two singlets integrated by 24 protons at  $\delta$  0.72 and  $\delta$  0.89 assigned to eight  $\text{CH}_3$  groups. Moreover, the singlet signal at  $\delta$  4.98 corresponds to acridine-H9. All other signals appeared at their expected positions. Moreover, the  $^{13}\text{C}$  NMR spectrum of **8** showed the C9 at  $\delta$  31.96 and the carbonyl group at  $\delta$  195.11. All other carbon signals appeared at their expected positions.



**Scheme 3.** Synthesis of bis(hexahydroacridinedione-1,8(2*H*,5*H*)-dione) **8**.

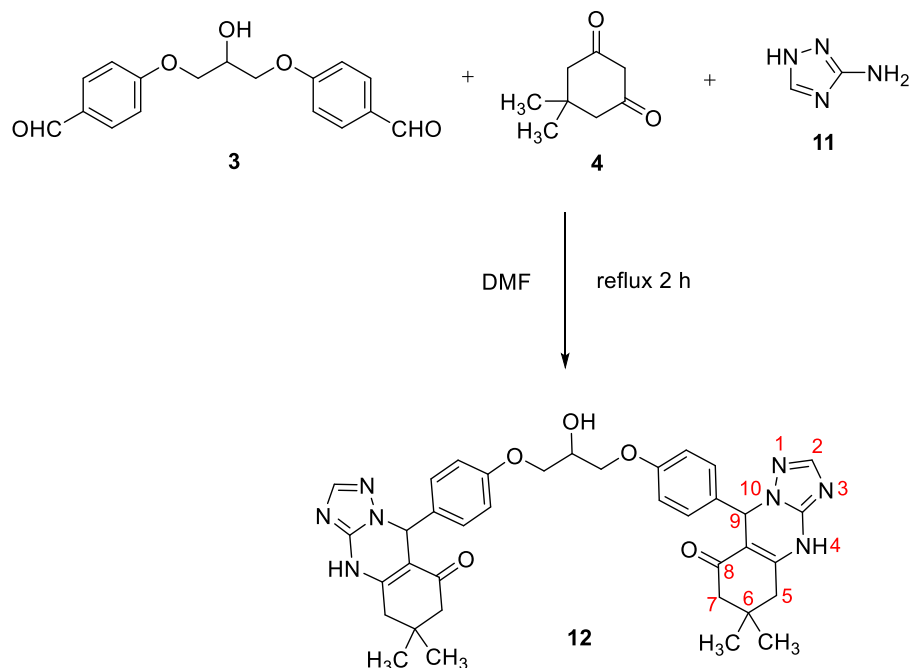
A three-component reaction of dibenzaldehyde **3** with two-mole equivalents of both dimedone **4** and 6-amino-pyrimidine-2,4-dione **9** in acetic acid at reflux produced the corresponding bis(8,8-dimethyl-2-thioxo-2,3,5,8,9,10-hexahydropyrimido[4,5-*b*]quinoline-4,6(1*H*,7*H*) dione) **10** in 70 % yield (Scheme 4).



**Scheme 4.** Synthesis of bis(hexahydropyrimido[4,5-*b*]quinoline-4,6(1*H*,7*H*) dione) **10**.

The constitution of compound **10** was confirmed by the existence of NH groups at 3320 and 3225  $\text{cm}^{-1}$  by its IR spectra. Furthermore, the carbonyl groups emerged approximately at 1665 and 1557  $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR spectra of **10** indicated the presence of a singlet signal at 4.70 ppm, which corresponded to H5. At 8.45, 11.67, and 12.13 ppm, the NH group showed as wide signals. All other signals appeared in their proper places.

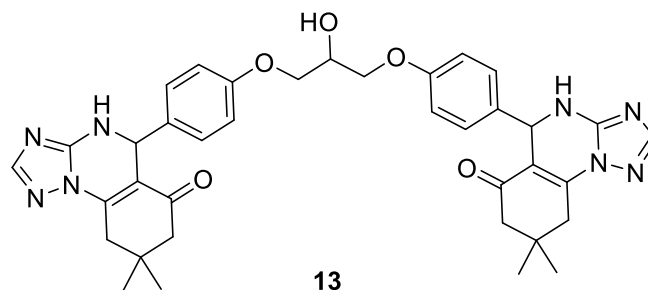
The Biginelli-like reaction of aldehydes **3** with the one-mole equivalent of both dimedone (**4**) and 3-amino-4*H*-1,2,4-triazole (**11**) in DMF at reflux afforded the target bis(hexahydro-[1,2,4]triazolo[5,1-*b*]quinazoline) **12** in 78% yield (Scheme 5).



**Scheme 5.** Synthesis of bis(hexahydro-[1,2,4]triazolo[5,1-*b*]quinazoline) **12**.

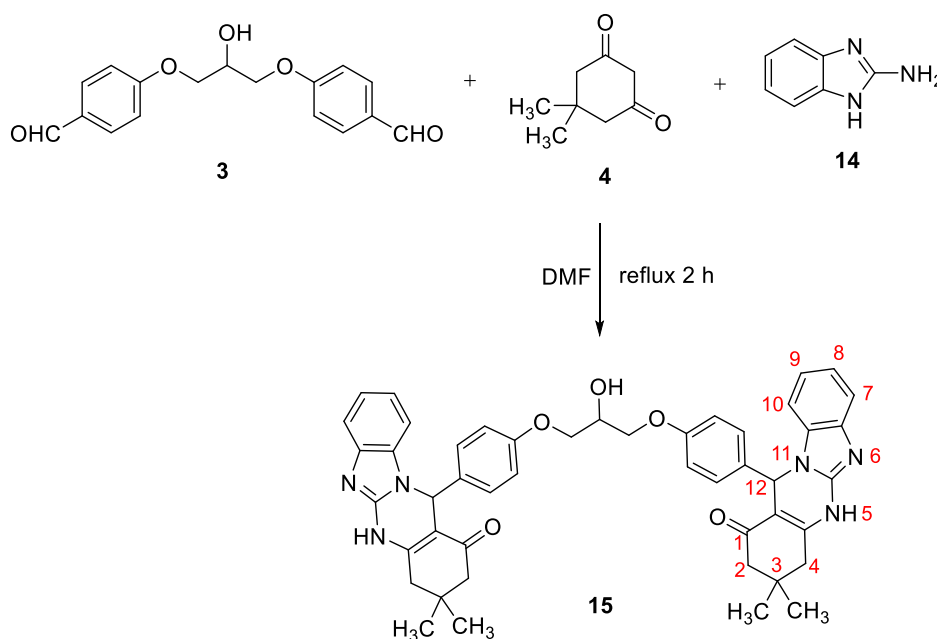
The constitution of product **12** was proved based on spectral data. Thus, the mass spectrum of **12** showed a molecular ion peak at  $m/z$  676. Its IR spectrum displayed a broad band at  $\nu$  3200  $\text{cm}^{-1}$  for N-H stretches, besides one characteristic band at  $\nu$  1645  $\text{cm}^{-1}$  for the ketonic carbonyl stretching vibrations. Moreover, the  $^1\text{H}$  NMR spectrum of **12** showed two singlet signals at 0.97 and 1.04 ppm for two methyl protons; multiplet at 3.90 – 4.07 ppm for diastereotopic H5 and H7; four singlet signals at 3.96, 6.15, 7.66 and 11.04 ppm for  $\text{OCH}_2$ , H9, H2, and NH protons, respectively; as well as signals for aromatic protons at 6.84 – 7.08 ppm. The  $^{13}\text{C}$  NMR spectrum fits well with the confirmed structure and showed signals of aliphatic carbons at 26.94, 28.64, 32.29, 35.93, 57.46, and 69.31 ppm corresponding to two methyl, C6, C9, C5, C7, and  $\text{OCH}_2$ , respectively. It also displayed one characteristic signal at  $\delta$  193.22 for ketonic carbon. The peaks of olefinic and aromatic carbons appeared at their appropriate positions.

It is worth mentioning that the exclusion of the possible isomeric bis(8,8-dimethyl-5,7,8,9-tetrahydro-[1,2,4]triazolo[1,5-*a*]quinazolin-6(4*H*)-one) **13** (Figure 1) was done using DFT calculations, 2D-HMBC spectroscopy<sup>34</sup>, and x-ray crystal structure elucidation of related compounds<sup>43</sup>.



**Figure 1.** Structure of the possible isomeric bis(tetrahydro-[1,2,4]triazolo[1,5-*a*]quinazolin-6(4*H*)-one) **13**.

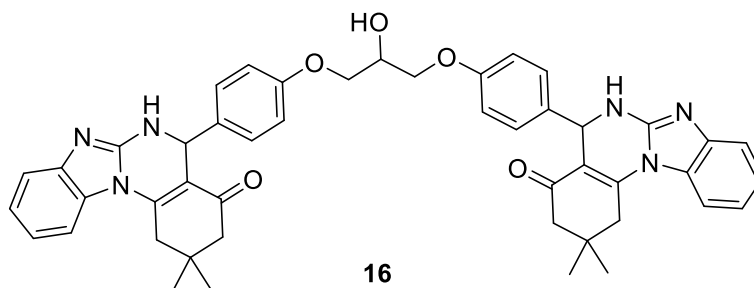
Accordingly, under the same reaction conditions, the cyclo-condensation reaction of 4,4'-((2-hydroxypropane-1,3-diyl)bis(oxy))dibenzaldehyde (**3**) with two equivalents of both dimedone (**4**) and 2-amino-1*H*-benzo[*d*]imidazole (**14**) progressed easily and yielded the fused tetracyclic bis(dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine) **15** (Scheme 6).



**Scheme 6.** Synthesis of bis(dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine) **15**.

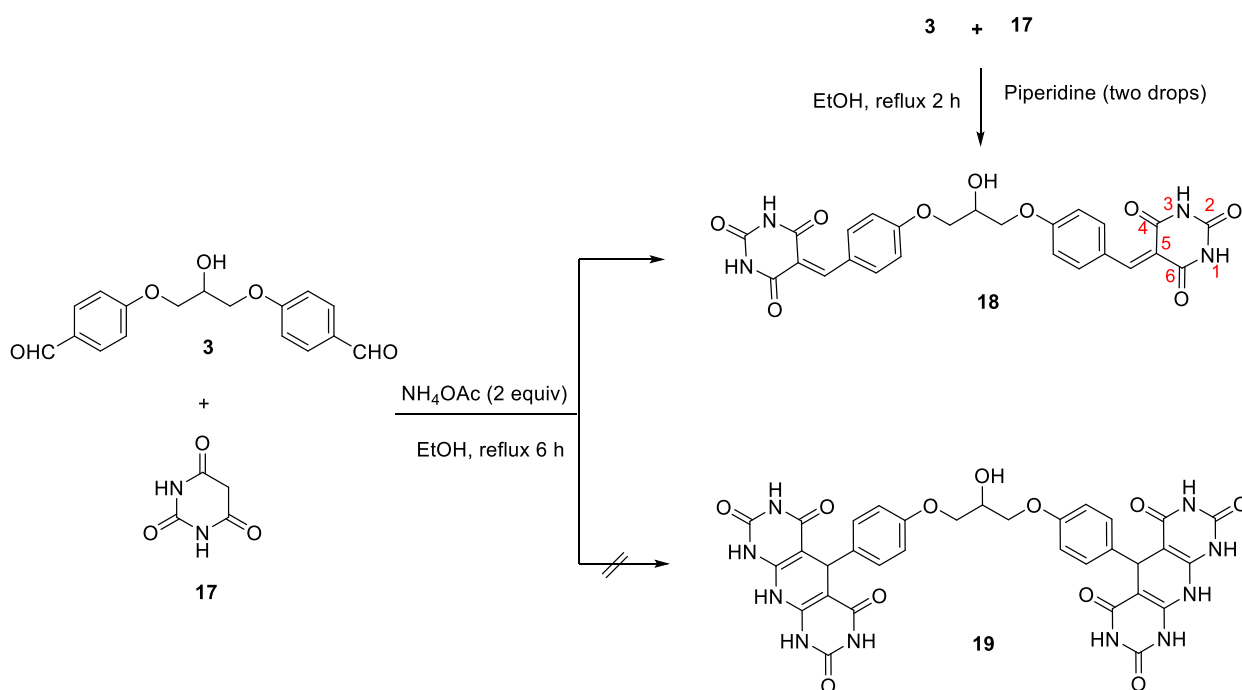
Moreover, the constitution of compound **15** was confirmed spectroscopically. For instance, the mass spectrum of **15** showed a molecular ion peak at  $m/z$  774. The IR spectrum indicated characteristic vibrational bands at  $\nu$  3234, 3053, and 1645  $\text{cm}^{-1}$  for two NH and ketonic carbonyl stretches. The  $^1\text{H}$  NMR revealed signals of aliphatic protons as two singlet signals at 1645 and 1.03 ppm for two methyl protons; a multiplet at  $\delta$  2.02 – 2.62 for diastereotropic protons H2 and H4; and two singlets at  $\delta$  3.84 and 6.32 for  $\text{OCH}_2$  and H12. It also showed singlets at  $\delta$  11.02 for NH protons. Signals of aromatic protons appeared at their expected position (6.76 – 7.33 ppm).

Based on X-ray crystallography and theoretical calculations of related compounds, the possible formation of the other regioisomer bis(2,2-dimethyl-2,3,5,6-tetrahydrobenzo[4,5]imidazo[1,2-*a*]quinazolin-4(1*H*)-one) **16** has been excluded (Figure 2).<sup>44–47</sup>



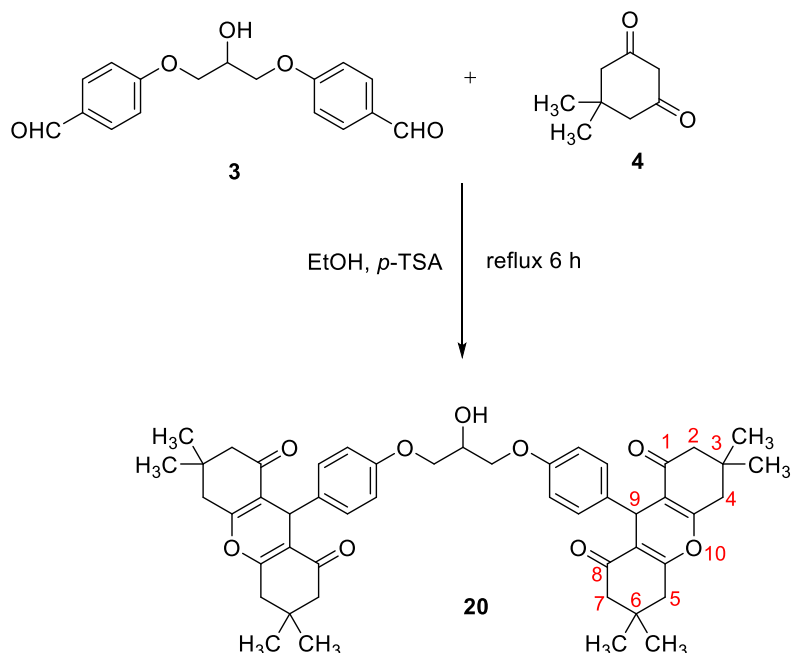
**Figure 2.** Structure of the possible isomeric bis(2,2-dimethyl-2,3,5,6-tetrahydrobenzo[4,5]imidazo[1,2-*a*]quinazolin-4(1*H*)-one) **16**.

Furthermore, the reaction of bis-aldehyde **3** with two equivalents of barbituric acid **17** as an active methylene reagent in the presence of ammonium acetate in acetic acid at reflux afforded the Knoevenagel condensation product, bis[(methanelylidene)bis(pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione)] **18**. Even in minute amounts, the predicted bis(decahydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine) **19** was not generated (Scheme 13). The structure of the latter compound was verified by comparing its physical data with samples prepared by condensation of one mole of aldehyde **3** with one mole of barbituric acid **17** in refluxing ethanol containing a few drops of piperidine (Scheme 7).



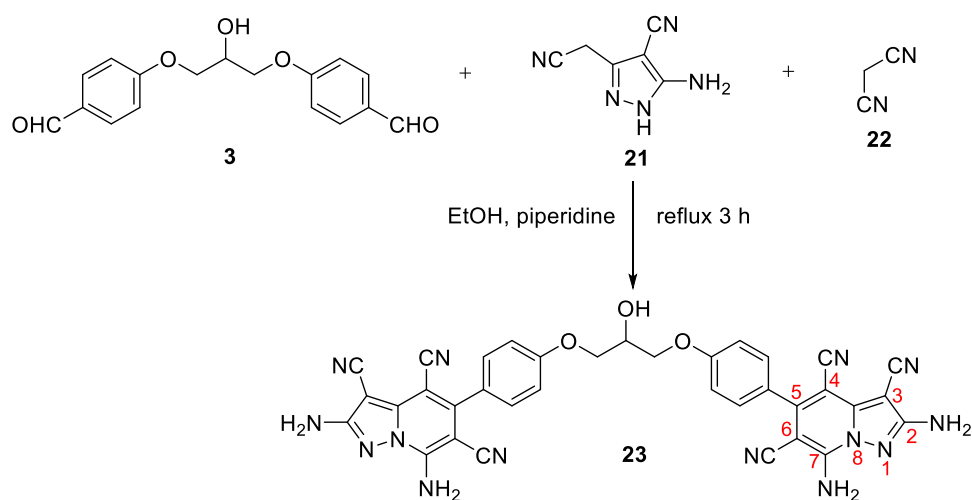
**Scheme 7.** Attempted synthesis of bis(decahydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine) **19**.

The synthesis of bis(hexahydro-1*H*-xanthene-1,8(2*H*)-dione) **20** was achieved by the reaction of one equivalent of bis-aldehyde **3** with four equivalents of 5,5-dimethyl-1,3-cyclohexanedione (**4**) in the presence of 15 mol% of *p*-TSA in refluxing ethanol (Scheme 8).



**Scheme 8.** Synthesis of bis(hexahydro-1*H*-xanthene-1,8(2*H*)-dione) **20**.

The structure of target compound **20** was established based on spectral data. Thus, its IR spectra revealed the carbonyl group at  $1664\text{ cm}^{-1}$ . In the  $^1\text{H}$  NMR spectrum, the hydrogen atom of the pyran ring was observed at 4.46 ppm. Moreover, the  $^{13}\text{C}$  NMR spectrum of **20** was found to agree with the proposed structure, it showed the pyran C-4 at 39.93 ppm and the carbonyl group at 196.51 ppm. Further structural verification was obtained from its mass spectroscopy, which showed the correct molecular ion peak at  $m/z$  788. Furthermore, the reaction of the bis(aldehyde) **3** with malononitrile **22**, and 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **21** in ethanol at reflux in the presence of a catalytic amount of piperidine afforded bis(pyrazolo[1,5-*a*]pyridine) **23** as a sole product (Scheme 9).



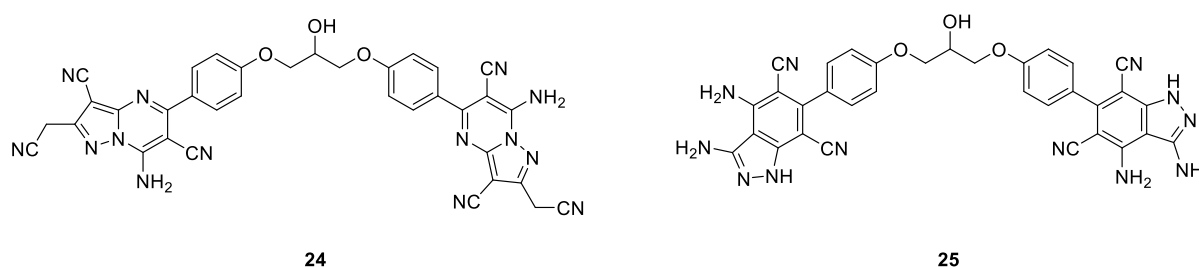
**Scheme 9.** Synthesis of bis(pyrazolo[1,5-*a*]pyridine) **23**.

The structure of compound **23** was confirmed based on spectral data. The IR spectrum of **23** showed the presence of  $\text{NH}_2$  group ( $\nu = 3365, 3301\text{ cm}^{-1}$ ), and a CN group ( $\nu = 2219\text{ cm}^{-1}$ ). The  $^1\text{H}$  NMR spectrum of

compound **23** showed a multiplet signal integrated by five protons at  $\delta$  4.18 - 4.26 ppm assigned to the two CH<sub>2</sub> linking groups and CH. It indicated the four NH<sub>2</sub> groups as two broad signals at 6.69 and 8.58 ppm. The aromatic protons appear as multiplets in the area of 7.18 - 7.51 ppm.

The reaction could also yield two other possible products; bis(pyrazolopyrimidine) **24**, and bis(benzopyrazole) **25** depending on which tautomeric form of the aminopyrazole reacts with the bis(arylidene malononitrile), formed *in situ* from the reaction of bis-aldehyde **3** with malononitrile **22** (Figure 3).

Compound **24** was excluded based on <sup>1</sup>H NMR spectrum that featured the disappearance of -CH<sub>2</sub>CN group in 3-5 ppm. In addition, compound **25** was excluded based on the mass spectrum that does not indicate the removal of HCN.



**Figure 3.** Structures of the possible isomeric bis(pyrazolopyrimidine) **24**, and bis(benzopyrazole) **25**.

## Conclusions

Despite the progress in the development of new bioactive heterocycles, there is still room for new findings of new potent and safer compounds. In this regard, we successfully synthesized different bis-heterocycle scaffolds linked via isopropanol unit as a new class of hybrid molecules with promising improved activity. The ease of preparation of the target compounds functionalized with pyridine and pyrimidine systems produces privileged structures for drug design.

## Experimental Section

**General.** Melting points were determined in open glass capillaries with a Gallenkamp apparatus. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The infrared spectra were recorded as potassium bromide disks on a PyeUnicam SP 3-300 and Shimadzu FTIR 8101 infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer operating at (300 MHz and 75 MHz) or Bruker AVS NMR spectrometer at (400 MHz and 101 MHz), respectively, using TMS as an internal standard. Chemical shifts were reported as  $\delta$  values in ppm. Mass spectra (EI) were obtained at 70 eV with a Shimadzu GCMQP 1000 EX spectrometer.

**4,4'-((2-Hydroxypropane-1,3-diyl)bis(oxy))dibenzaldehyde (**3**).** To a solution of KOH (2 mmol) in 5 mL of water, (2 mmol) of *p*-hydroxybenzaldehyde **2** or **3** was added. The mixture was warmed to 70 °C and kept under vigorous stirring for 40 minutes. Then epichlorohydrin (1 mmol) was added over 1 h. The reaction

mixture was stirred at 70°C for an additional 4 h. After cooling, the precipitate was filtered off, washed with water, and dried. The crude product was purified by recrystallization from ethanol/water (1:1, v/v) to give compound **3** as pale yellow solid (66%); mp 144–146°C (142-144);<sup>47</sup> IR bands (cm<sup>-1</sup>):  $\nu$  = 3493 (-OH), 2840, 2760 (CHO), 1680 (C=O). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ /ppm: 9.89 (s, 2H, COH), 7.85–7.83 (d, 4H, Ar), 7.13–7.11 (d, 4H, Ar), 5.44 (d, 1H, -OH), 4.23 (s, 1H, CH), 4.19 (m, 4H, CH<sub>2</sub>).

**Diethyl 4,4'-(((2-hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))bis(2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate) (6)**. A mixture of bis(aldehyde) **3** (1 mmol), dimedone **4** (2 mmol), and ethyl acetoacetate **5** (2 mmol) was heated at reflux for 5 h in absolute ethanol (10 mL) in the presence of ammonium acetate (5 mmol). The formed crude product was collected by filtration, and crystallized from ethanol to give compound **6** as pale yellow solid (612 mg, 80%); mp 110-112 °C; IR (KBr,  $\nu$  cm<sup>-1</sup>): 3287 (OH), 3208 (NH), 1691 (CO), 1607 (ester-CO). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  0.84 (s, 6H, -CH<sub>3</sub>), 1.00 (s, 6H, -CH<sub>3</sub>), 1.12 (t, *J* 7.1 Hz, 6H, -CH<sub>3</sub>), 1.76-2.46 (m, 14H, -CH<sub>2</sub> and -CH<sub>3</sub>), 3.96 -3.97 (m, 9H, -OCH<sub>2</sub>, -CH), 4.19 (br. s, 1H, -OH) 4.78 (s, 2H, pyridine-H 4), 6.74 (d, *J* = 8.5 Hz, 4H, Ar-H), 7.03 (d, *J* 8.5 Hz, 4H, Ar-H), 9.02 (s, 2H, -NH). <sup>13</sup>C NMR (75 MHz, DMSO)  $\delta$  14.4, 18.4, 21.6, 26.6, 29.4, 32.3, 35.2, 50.4, 59.3, 67.7, 69.3, 104.2, 110.4, 113.9, 128.7, 140.4, 144.9, 149.7, 156.8, 167.20, 194.8. MS (EI, 70 eV): *m/z* 766 [M]<sup>+</sup>. Anal. For C<sub>45</sub>H<sub>54</sub>N<sub>2</sub>O<sub>9</sub> Calcd: C, 70.47; H, 7.10; N, 3.65. Found: C, 70.58; H, 7.23; N, 3.53%.

**9,9'-(((2-Hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))bis(10-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione) (8)**. A mixture of bis(aldehyde) **3**, dimedone **4** (2 mmol), and 5-((4-chlorophenyl)amino)-3,3-dimethylcyclohexan-1-one **7** (2 mmol) was heated at reflux for 3 h in acetic acid (10 mL). The formed crude product was collected by filtration and purified by crystallization from DMF/EtOH to give compound **8** as pale yellow solid (826 mg, 82%); mp 196-200 °C; IR (KBr,  $\nu$  cm<sup>-1</sup>): 3459 (OH), 1639 (CO). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  0.72 (s, 12H, -CH<sub>3</sub>), 0.89 (s, 12H, -CH<sub>3</sub>), 1.77-2.22 (m, 16H, -CH<sub>2</sub>), 3.90 - 4.11 (m, 5H, -CH<sub>2</sub> and -CH), 4.98 (s, 2H, acridine-H 9), 5.28 (d, *J* 5.2 Hz, 1H, -OH), 6.81 (d, *J* 8.6 Hz, 4H, Ar-H), 7.19 (d, *J* 8.7 Hz, 4H, Ar-H), 7.44 (d, *J* 7.6 Hz, 4H, Ar-H), 7.67 (d, *J* 8.8 Hz, 4H, Ar-H). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  26.1, 29.3, 32.0, 40.9, 49.6, 67.5, 69.2, 113.3, 113.9, 128.5, 133.9, 137.4, 138.6, 149.9, 156.2, 156.6, 195.1. MS (EI, 70 eV): *m/z* 1008 [M]<sup>+</sup>. Anal. For C<sub>61</sub>H<sub>64</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>7</sub> Calcd: C, 72.68; H, 6.40; N, 2.78. Found: C, 72.79; H, 6.52; N, 2.89%.

**5-(4-(3-(4-(8,8-Dimethyl-4,6-dioxo-2-thioxo-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-*b*]quinolin-5-yl)phenoxy)-2-hydroxypropoxy)phenyl)-8,8-dimethyl-4-thioxo-4,5,7,8,9,10-hexahydropyrimido[4,5-*b*]quinoline-2,6(1H,3H)-dione (10)**. A mixture of bis(aldehyde) **3**, dimedone **4** (2 mmol) (2 mmol), and 6-amino-2-thioxo-2,3-dihydropyrimidin-4-one **9** (2 mmol) was heated at reflux for 3 hrs in acetic acid (10 mL). The formed crude product was collected by filtration, and purified by crystallization from DMF/EtOH to give compound **10** as pale yellow Solid (AcOH) (555.8 mg, 70%); mp 256-260 °C; IR (KBr,  $\nu$  cm<sup>-1</sup>): 3422 (OH), 3320 and 3225 (NH), 1665 (CO), 1557 (amide-CO). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  0.89 (s, 6H, -CH<sub>3</sub>), 1.01 (s, 6H, -CH<sub>3</sub>), 1.94 - 2.45 (m, 8H, -CH<sub>2</sub>), 3.92 - 4.17 (m, 5H, -CH<sub>2</sub> and -CH), 4.70 (s, 2H, pyridine-H 4), 5.29 (br. s, 1H, -OH), 6.77 (d, *J* 8.7 Hz, 4H, Ar-H), 7.08 (d, *J* 8.8 Hz, 4H, Ar-H), 8.45 (s, 2H, -NH), 11.67 (s, 2H, -NH), 12.13 (s, 2H, -NH). <sup>13</sup>C NMR (75 MHz, DMSO)  $\delta$  26.5, 29.0, 32.2, 50.2, 56.2, 67.6, 69.3, 94.5, 111.4, 113.9, 128.7, 138.3, 143.4, 148.5, 157.0, 160.2, 173.4, 194.5. MS (EI, 70 eV): *m/z* 794 [M]<sup>+</sup>. Anal. For C<sub>41</sub>H<sub>42</sub>N<sub>6</sub>O<sub>7</sub>S<sub>2</sub> Calcd: C, 61.95; H, 5.33; N, 10.57. Found: C, 61.82; H, 5.44; N, 10.43%.

**9,9'-(((2-Hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))bis(6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4H)-one) (12)**. A mixture of bis(aldehyde) **3** (1 mmol), dimedone **4** (2 mmol), and 3-amino-4*H*-1,2,4-triazole **11** (2 mmol) was heated at reflux in DMF (5 mL) for 6 h. After cooling, the crude product was collected by filtration, and purified by recrystallization from DMF/EtOH to give compound **12** as pale yellow Solid (527.3 mg, 78%); mp 252-256 °C; IR (KBr,  $\nu$  cm<sup>-1</sup>): 3423 (OH), 3200 (NH), 1645 (CO). <sup>1</sup>H NMR

(300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  0.97 (s, 6H, -CH<sub>3</sub>), 1.04 (s, 6H, -CH<sub>3</sub>), 2.05-2.52 (m, 8H, -CH<sub>2</sub>), 3.90 – 4.07 (m, 5H, -CH<sub>2</sub> and -CH), 5.31 (d, *J* 5.1 Hz, 1H, -OH), 6.15 (s, 2H, pyrimidine-H 4), 6.84 (d, *J* 8.6 Hz, 4H, Ar-H), 7.08 (d, *J* 8.6 Hz, 4H, Ar-H), 7.66 (s, 2H, triazole-H 3), 11.04 (s, 2H, -NH). <sup>13</sup>C NMR (75 MHz, DMSO)  $\delta$  26.9, 28.6, 32.3, 35.9, 49.9, 57.5, 67.5, 69.3, 105.9, 114.3, 128.3, 134.1, 146.9, 150.1, 150.4, 158.1, 193.2. MS (EI, 70 eV): *m/z* 676 [M]<sup>+</sup>. Anal. For C<sub>37</sub>H<sub>40</sub>N<sub>8</sub>O<sub>5</sub> Calcd: C, 65.67; H, 5.96; N, 16.56. Found: C, 65.76; H, 5.84; N, 16.62%.

**12,12'-(((2-Hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))bis(3,3-dimethyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1(2*H*)-one) (15).** A mixture of bis(aldehyde) **3** (1 mmol), dimedone **4** (2 mmol), and 2-amino-1*H*-benzo[*b*]imidazole **14** (266 mg, 2 mmol) was heated at reflux in DMF (5 mL) for 6 h. After cooling, the so-formed crude product was collected by filtration, and purified by recrystallization from DMF/EtOH to give compound **15** as off-white solid (688.9 mg, 89%), mp > 300 °C; IR (KBr,  $\nu$  cm<sup>-1</sup>): 3424 (OH), 3234, 3053 (NH), 1645 (CO). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  0.91 (s, 6H, -CH<sub>3</sub>), 1.03 (s, 6H, -CH<sub>3</sub>), 2.02-2.62 (m, 8H, -CH<sub>2</sub>), 3.79 – 4.00 (m, 5H, CH<sub>2</sub> and CH), 5.22 – 5.25 (m, 1H, -OH), 6.32 (s, 2H, pyrimidine-H4), 6.76 (d, *J* 8.5 Hz, 4H, Ar-H), 6.92 (t, *J* 7.6 Hz, 2H, Ar-H), 7.02 (t, *J* 8.1 Hz, 2H, Ar-H), 7.20 (t, *J* 7.9 Hz, 6H, Ar-H), 7.33 (d, *J* 7.9 Hz, 2H, Ar-H), 11.02 (s, 2H, NH). MS (EI, 70 eV): *m/z* 774 [M]<sup>+</sup>. Anal. For C<sub>47</sub>H<sub>46</sub>N<sub>6</sub>O<sub>5</sub> Calcd: C, 72.85; H, 5.98; N, 10.85. Found: C, 72.77; H, 5.90; N, 10.73%.

**5,5'-((((2-Hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))bis(methaneylidene))bis(pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) (18).** Method A. A mixture of bis(aldehyde) **3**, pyrimidine-2,4,6-trione **17** (2 mmol), and ammonium acetate (5 mmol) was heated at reflux for 3 hrs in acetic acid (10 mL). The formed crude product was collected by filtration, and purified by crystallization from DMF/EtOH to give compound **18**. Method B. A mixture of bis(aldehyde) **3**, pyrimidine-2,4,6-trione **17** (2 mmol), and ammonium acetate (5 mmol) was heated at reflux for 3 hrs in ethanol (10 mL) containing 3 drops of piperidine. The formed crude product was collected by filtration and further purified by crystallization from DMF/EtOH to give compound **18** as pale yellow (Method A: 457.6 mg, 88%); Method B: 468 mg, 90%); mp > 300°C; IR (KBr,  $\nu$  cm<sup>-1</sup>): 3456 (OH), 3206 (NH), 1670 (CO). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  4.14 – 4.28 (m, 5H, CH<sub>2</sub> and CH), 5.45 (br. s, 1H, -OH), 7.09 (d, *J* 8.6 Hz, 4H, Ar-H), 8.24 (s, 2H, -CH=), 8.35 (d, *J* 8.6 Hz, 4H, Ar-H), 11.14 (s, 2H, -NH), 11.27 (s, 2H, -NH). MS (EI, 70 eV): *m/z* 520 [M]<sup>+</sup>. Anal. For C<sub>25</sub>H<sub>20</sub>N<sub>4</sub>O<sub>9</sub> Calcd: C, 57.69; H, 3.87; N, 10.77. Found: C, 57.61; H, 3.94; N, 10.69%.

**9,9'-((((2-Hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))bis(3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione) (20).** A mixture of bis(aldehyde) **3** (1 mmol) and dimedone **4** (4 mmol) in ethanol (10 mL) containing a catalytic amount of *p*-TSA was heated at reflux for 6 h. The reaction mixture was then allowed to cool to room temperature. The collected product was filtered, dried, and recrystallized from ethanol to give **20** as colorless crystals (614.6 mg, 78%); mp 222-225 °C; IR (KBr,  $\nu$  cm<sup>-1</sup>): 3437 (OH), 1664 (CO). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  0.90 (s, 12H, -CH<sub>3</sub>), 1.03 (s, 12H, -CH<sub>3</sub>), 2.04 - 2.59 (m, 16H, -CH<sub>2</sub>), 3.88 - 4.06 (m, 5H, CH<sub>2</sub> and CH), 4.46 (s, 2H, pyran-H4), 5.27 (d, *J* 6.0 Hz, 1H, -OH), 6.78 (d, *J* 6.2 Hz, 4H, Ar-H), 7.06 (d, *J* 6.2 Hz, 4H, Ar-H). <sup>13</sup>C NMR (75 MHz, DMSO)  $\delta$  26.61, 28.93, 30.54, 32.04, 39.93, 50.25, 67.68, 69.24, 114.00, 114.80, 129.26, 136.78, 157.03, 163.00, 196.52. MS (EI, 70 eV): *m/z* 788 [M]<sup>+</sup>. Anal. For C<sub>49</sub>H<sub>56</sub>O<sub>9</sub> Calcd: C, 74.60; H, 7.15 Found: C, 74.68; H, 7.09%.

**5,5'-((((2-Hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))bis(2,7-diaminopyrazolo[1,5-*a*]pyridine-3,4,6-tricarbonitrile) (23).** A mixture of bis(aldehyde) **3** (1 mmol), 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **21** (2 mmol), and malononitrile **22** (2 mmol) in ethanol (10 mL) containing 2 drops of piperidine was heated at reflux for 6 h. The isolated precipitate was filtered, dried, and recrystallized from EtOH/DMF to give compound **23** as pale (624.3 mg, 91%); mp 175-177 °C; IR (KBr,  $\nu$  cm<sup>-1</sup>): 3418 (OH), 3365, 3301 (NH<sub>2</sub>), 2219 (CN). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  4.18 - 4.26 (m, 5H, CH<sub>2</sub> and CH), 5.54 (d, *J* 5.9 Hz, 1H, -OH), 6.69 (s, 4H, -NH<sub>2</sub>), 7.18 (d, *J* 6.9 Hz, 4H, Ar-H), 7.51 (d, *J* 6.8 Hz, 4H, Ar-H), 8.58 (s, 4H, NH<sub>2</sub>). <sup>13</sup>C NMR (75 MHz, DMSO)  $\delta$

67.4, 69.4, 70.9, 78.7, 83.6, 112.7, 114.6, 115.3, 126.3, 130.6, 142.1, 147.5, 151.3, 159.9, 160.7. MS (EI, 70 eV):  $m/z$  686 [M]<sup>+</sup>. Anal. For C<sub>35</sub>H<sub>22</sub>N<sub>14</sub>O<sub>3</sub> Calcd: C, 61.22; H, 3.23; N, 28.56. Found: C, 61.17; H, 3.28; N, 28.47%.

## Supplementary Material

Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of new compounds are given in the supplementary material associated with this manuscript.

## References

1. Bento, A. P.; Gaulton, A.; Hersey, A.; Bellis, L. J.; Chambers, J.; Davies, M.; Krüger, F. A.; Light, Y.; Mak, L.; McGlinchey, S.; et al. *Nucleic Acids Res.* **2014**, *42* (D1), D1083.  
<https://doi.org/10.1093/nar/gkt1031>
2. Cramer, J.; Sager, C. P.; Ernst, B. *J. Med. Chem.* **2019**, *62* (20), 8915. DOI: 10.1021/ACS.JMEDCHEM.9B00179/ASSET/IMAGES/MEDIUM/JM-2019-001799\_0001.GIF.  
<https://doi.org/10.1021/acs.jmedchem.9b00179>
3. Alkhzem, A. H.; Woodman, T. J.; Blagbrough, I. S. *RSC Adv.* **2022**, *12* (30), 19470.  
<https://doi.org/10.1039/D2RA03281C>
4. Sampath Kumar, H. M.; Herrmann, L.; Tsogoeva, S. B. *Bioorg. Med. Chem. Lett.* **2020**, *30* (23), 127514.  
<https://doi.org/10.1016/j.bmcl.2020.127514>
5. Sadek, K. U.; Mekheimer, R. A.; Abd-Elmonem, M.; Abo-Elhoud, F. A.; Hayallah, A. M.; Mostafa, S. M.; Abdellattif, M. H.; Abourehab, M. A. S.; Farghaly, T. A.; Elkamhawy, A. *J. Mol. Struct.* **2023**, *1286*, 135616.  
<https://doi.org/10.1016/j.molstruc.2023.135616>
6. Hassan, R.; Mohi-ud-din, R.; Dar, M. O.; Shah, A. J.; Mir, P. A.; Shaikh, M.; Pottoo, F. H. *Anticancer. Agents Med. Chem.* **2021**, *22* (3), 551.  
<https://doi.org/10.2174/1871520621666210901112954>
7. Aatif, M.; Raza, M. A.; Javed, K.; Nashre-ul-Islam, S. M.; Farhan, M.; Alam, M. W. *Antibiotics* **2022**, *11* (12), 1750.  
<https://doi.org/10.3390/antibiotics11121750>
8. Ruan, B.-F.; Guo, Q.-L.; Li, Q.-S.; Li, L.-Z.; Deora, G. S.; Zhou, B.-G. *Curr. Top. Med. Chem.* **2022**, *22* (7), 578.  
<https://doi.org/10.2174/1568026622666220202123651>
9. Ling, Y.; Hao, Z. Y.; Liang, D.; Zhang, C. L.; Liu, Y. F.; Wang, Y. *Drug Des. Devel. Ther.* **2021**, *15*, 4289.  
<https://doi.org/10.2147/DDDT.S329547>
10. De, S.; SK, A. K.; Shah, S. K.; Kazi, S.; Sarkar, N.; Banerjee, S.; Dey, S. *RSC Adv.* **2022**, *12* (24), 15385.  
<https://doi.org/10.1039/D2RA01571D>
11. Elsayed, M. A.; Elsayed, A. M.; Sroor, F. M. *Med. Chem. Res.* **2024**, *33* (3), 476.  
<https://doi.org/10.1007/s00044-024-03188-1>
12. Abbas, N.; Swamy, P. M. G.; Dhiwar, P.; Patel, S.; Giles, D. *Pharm. Chem. J.* **2021**, *54* (12), 1215.  
<https://doi.org/10.1007/s11094-021-02346-8>
13. Abbas, N.; Matada, G. S. P.; Dhiwar, P. S.; Patel, S.; Devasahayam, G. *Anticancer. Agents Med. Chem.* **2020**, *21* (7), 861.  
<https://doi.org/10.2174/1871520620666200721104431>

14. Ahmed, K.; Choudhary, M. I.; Saleem, R. S. Z. *Eur. J. Med. Chem.* **2023**, *259*, 115701.  
<https://doi.org/10.1016/j.ejmech.2023.115701>
15. Ibrahim, N. S.; Mohamed, M. F.; Elwahy, A. H. M.; Abdelhamid, I. A. *Let. Drug Des. Discov.* **2018**, *15* (10), 1036.  
<https://doi.org/10.2174/1570180815666180105162323>
16. Ghozlan, S. A. S.; Abdelmoniem, A. M.; Butenschön, H.; Abdelhamid, I. A. *Tetrahedron* **2015**, *71* (9), 1413.  
<https://doi.org/10.1016/j.tet.2015.01.026>
17. Sayed, O. M.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. *J. Heterocycl. Chem.* **2016**, *53*, 1113.  
<https://doi.org/10.1002/jhet.2373>
18. Ibrahim, Y. A.; Abbas, A. A.; Elwahy, A. H. M. *J. Heterocycl. Chem.* **2004**, *41* (2), 135.  
<https://doi.org/10.1002/jhet.5570410202>
19. A. Ibrahim, Y.; H.M. Elwahy, A.; A. Abbas, A. *Tetrahedron* **1994**, *50* (39), 11489.  
[https://doi.org/10.1016/S0040-4020\(01\)89286-3](https://doi.org/10.1016/S0040-4020(01)89286-3)
20. Elwahy, A. H. M.; Abbas, A. A. *Synth. Commun.* **2000**, *30* (16), 2903.  
<https://doi.org/10.1080/00397910008087441>
21. Mekky, A. E. M.; Elwahy, A. H. M. *J. Heterocycl. Chem.* **2014**, *51* (S1), E34.  
<https://doi.org/10.1002/jhet.2012>
22. Elwahy, A.; Shaaban, M. *Curr. Org. Synth.* **2014**, *11* (6), 835 . DOI: 10.2174/157017941106141023114039.  
<https://doi.org/10.2174/157017941106141023114039>
23. Elwahy, A. H. M.; Abbas, A. A. *J. Heterocycl. Chem.* **2008**, *45* (1), 1.  
<https://doi.org/10.1002/jhet.5570450101>
24. Darweesh, A. F.; Abd El-Fatah, N. A.; Abdel-Latif, S. A.; Abdelhamid, I. A.; Elwahy, A. H. M.; Salem, M. E. *Arkivoc* **2021**,(8), 23.  
<https://doi.org/10.24820/ark.5550190.p011.415>
25. Radwan, I. T.; Elwahy, A. H. M.; Darweesh, A. F.; Sharaky, M.; Bagato, N.; Khater, H. F.; Salem, M. E. *J. Mol. Struct.* **2022**, *1265*, 133454 .  
<https://doi.org/10.1016/j.molstruc.2022.133454>
26. Diab, H. M.; Salem, M. E.; Abdelhamid, I. A.; Elwahy, A. H. M. *RSC Adv.* **2020**, *10* (72), 44066.  
<https://doi.org/10.1039/D0RA09025E>
27. Fathi, E. M.; Sroor, F. M.; Mahrous, K. F.; Mohamed, M. F.; Mahmoud, K.; Emara, M.; Elwahy, A. H. M.; Abdelhamid, I. A. *ChemistrySelect* **2021**, *6* (24), 6202.  
<https://doi.org/10.1002/slct.202100884>
28. Salem, M. E.; Ahmed, A. A.; Shaaban, M. R.; Shibl, M. F.; Farag, A. M. *Spectrochim. Acta - Part A Mol. Biomol. Spectrosc.* **2015**, *148*, 175.  
<https://doi.org/10.1016/j.saa.2015.03.102>
29. El-Gabry, Y. A.; Salem, M. E.; Ibrahim, N. S.; Elwahy, A. H. M.; Abdelhamid, I. A.; Diab, H. M. *J. Mol. Struct.* **2024**, *1296* (P2), 136857.  
<https://doi.org/10.1016/j.molstruc.2023.136857>
30. Diab, H. M.; Elsayed, B.; Darweesh, A. F.; Abdelhamid, I. A.; Elwahy, A. H. M. *Polycycl. Aromat. Compd.* **2023**, *43* (5), 4084.  
<https://doi.org/10.1080/10406638.2022.2083192>
31. Diab, H. M.; Abdelmoniem, A. M.; Shaaban, M. R.; Abdelhamid, I. A.; Elwahy, A. H. M. *RSC Advances*. 2019, pp 16606–16682.  
<https://doi.org/10.1039/C9RA02749A>

32. Ghozlan, S. A. S.; Ramadan, M. A.; Abdelmoniem, A. M.; Elwahy, A. H. M.; Abdelhamid, I. A. *Turk. J. Chem.* **2017**, *41* (3), 410.  
<https://doi.org/10.3906/kim-1609-42>
33. Abdelmoniem, A. M.; Abdelhamid, I. A. *Curr. Org. Chem.* **2016**, *20* (14), 1512.  
<https://doi.org/10.2174/1385272820666160216224951>
34. El-Fatah, N. A. A.; Darweesh, A. F.; Mohamed, A. A.; Abdelhamid, I. A.; Elwahy, A. H. M. *Monatsh. Chem.* **2017**, *148* (12), 2107.  
<https://doi.org/10.1007/s00706-017-2040-7>
35. Sroor, F. M.; Abdelmoniem, A. M.; Abdelhamid, I. A. *ChemistrySelect* **2019**, *4* (34), 10113.  
<https://doi.org/10.1002/slct.201901415>
36. Mohamed, M. F.; Ibrahim, N. S.; Elwahy, A. H. M.; Abdelhamid, I. A. *Anticancer. Agents Med. Chem.* **2018**, *18* (15), 2156.  
<https://doi.org/10.2174/1871520618666181019095007>
37. WalyEldeen, A. A.; Sabet, S.; El-Shorbagy, H. M.; Abdelhamid, I. A.; Ibrahim, S. A. *Chem. Biol. Interact.* **2023**, *369*, 110297.  
<https://doi.org/10.1016/j.cbi.2022.110297>
38. Ghozlan, S. A. S.; Abdelhamida, I. A.; Ibrahim, H. M.; Elnagdia, M. H. *Arkivoc* **2006**, *2006* (15), 53.  
<https://doi.org/10.3998/ark.5550190.0007.f07>
39. Al-Awadi, N. A.; Abdelkhalik, M. M.; Abdelhamid, I. A.; Elnagdi, M. H. *Synlett* **2007**, No. 19, 2979.  
<https://doi.org/10.1055/s-2007-992355>
40. Ghozlan, S. A. S.; Mohamed, M. H.; Abdelmoniem, A. M.; Abdelhamid, I. A. *Arkivoc* **2009**, No. 10, 302.  
<https://doi.org/10.3998/ark.5550190.0010.a27>
41. Al-mousawi, S. M.; Sherief, M.; Abdelhamid, I. A.; Elnagdi, M. H. *Curr. Org. Chem.* **2011**, *15* (19), 3503.  
<https://doi.org/10.2174/138527211797374760>
42. Li, J.; Yang, S.; Wang, L.; Wang, X.; Liu, L. *Macromolecules* **2013**, *46* (17), 6832.  
<https://doi.org/10.1021/ma400948j>
43. Krishnamurthy, G.; Jagannath, K. V. *J. Chem. Sci.* **2013**, *125* (4), 807.  
<https://doi.org/10.1007/s12039-013-0398-6>
44. Chen, L. H.; Chung, T. W.; Narhe, B. D.; Sun, C. M. *ACS Comb. Sci.* **2016**, *18* (3), 162.  
<https://doi.org/10.1021/acscombsci.5b00186>
45. Insuasty, B.; Salcedo, A.; Quiroga, J.; Abonia, R.; Nogueras, M.; Cobo, J.; Salido, S. *Heterocycl. Commun.* **2004**, *10* (6), 399.  
<https://doi.org/10.1515/HC.2004.10.6.399>
46. Hemmati, B.; Javanshir, S.; Dolatkah, Z. *RSC Adv.* **2016**, *6* (56), 50431.  
<https://doi.org/10.1039/C6RA08504K>
47. Stewart, J. J. P. *J. Mol. Model.* **2007**, *13* (12), 1173.  
<https://doi.org/10.1007/s00894-007-0233-4>

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