Bis(enaminones): Key Intermediates for Novel α,ω-Bis(pyrazolylphenoxy), Bis(pyranylphenoxy), and Bis(benzo[*b*]furanylphenoxy) Alkanes

Ashraf A. Abbas* [1]

Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt
*E-mail: ashrafaa50@yahoo.com

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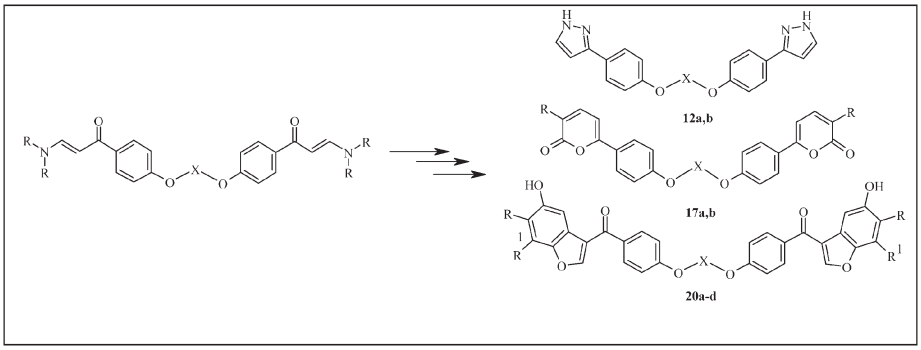

New bis(enaminone) derivatives, **5a,b** and **9a,b**, were prepared in good yields. Their synthetic utilities as key intermediates for the synthesis of novel bis(pyrazole) **12a,b**, bis(pyrane) **17a,b**, and bis(benzo[*b*]-furan) **20a–d** derivatives were also investigated.

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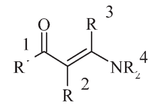
INTRODUCTION

There has been continuous interest in the synthesis of new heterocyclic systems containing pyrazole, pyrane, and benzofuran moieties because of their wide applications in different areas. Various series of pyrazole and their annelated derivatives are reported to have diverse biological activities as antifungal [2], antitumor [3], anti-inflammatory [4], and antinociceptive activities [4,5]. In addition, some pyrazole derivatives have been reported to be useful as inhibitor for cyclooxygenase-2, lipoxygenase [6], elastase [7], and factor Xa (fXa) [8]. Moreover, some of bis(pyrazole) palladium complexes are used as phenylacetylene polymerization catalyst [9]. On the other hand, pyrane and its related fused heterocycles are of interest as potential bioactive molecules. They are known to be used as anticancer [10], antibacterial [11], and anti-inflammatory agents [12] and to inhibit the amidolytic activity of human thrombin [13]. In addition, benzofuran derivatives constitute a structural unit of a number of natural products and biologically active compounds [14–17]. Furthermore, bis(compounds) have received great attention as being model compounds for main chain polymers [18–22]. It is also reported that many biologically active natural and synthetic products have molecular symmetry [23].

Keeping the above facts in mind and in continuation of our interest in the synthesis of bis(hetrocycles) [24–27], we describe herein a simple and efficient route for the synthesis of novel bis(enaminones) and studied their synthetic utilities as key intermediates for the synthesis of novel bis(pyrazolylphenoxy), bis(pyranylphenoxy), and bis(benzo[*b*]furanylphenoxy)alkanes.

RESULTS AND DISCUSSION

Recently, enaminones **1** were prepared by different synthetic approaches and their use as key intermediates for the synthesis of a wide variety of heterocycles have been investigated [28].



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In continuation of these studies, we report here on the synthesis of the novel α,ω-bis(enaminones) and investigated its synthetic utility as building blocks for new symmetrical bis(heterocycles). Two strategies were studied for the synthesis of the target enaminones **5**. In the

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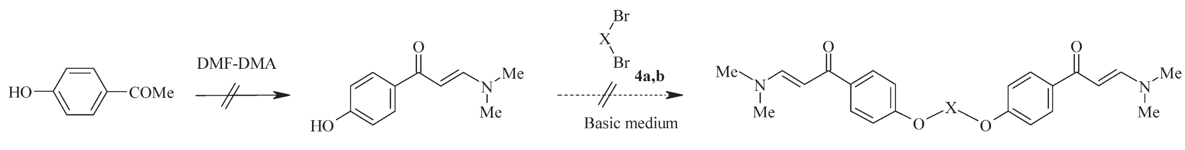
Scheme 1



first one, we planed to prepare compound **5** starting from 4-hydroxyacetophenone (**2**) by reaction with dimethylformamide-dimethylacetal (DMF-DMA) to give the corresponding enaminone **3** followed by bis-alkylation with the appropriate dibromoalkanes **4a,b** as shown in Scheme 1.

Unfortunately, reaction of **2** with DMF-DMA afforded oily residue that cannot be handled and could not be characterized.

In the second strategy, we investigated the synthesis of **5** using α,ω-bis(4-acetylphenoxy)alkanes **7a,b** as starting materials. Compounds **7a,b** could be obtained by the reaction of the potassium salt **6** (obtained upon treatment of 4-hydroxyacetophenone (**2**) with ethanolic potassium hydroxide) with the appropriate dibromoalkanes **4a,b** in boiling DMF. Solventless heating of compounds **7a,b** with DMF-DMA furnished the corresponding bis(enaminone) derivatives **5a,b** in moderate yields. The ^{1}H NMR spectra of the isolated products revealed, in each case, one singlet near δ 3.0 due to the *N,N*-dimethylamino protons and two doublets near δ 5.7 and 7.8 characteristic for the olefinic–C*H*=C*H*—N protons with the same coupling constant value $J = 12$ Hz (typical for trans-configuration) [29], in addition to the other signals characteristic for the alkane and the aromatic moieties. The mass spectra of **5a,b** showed their correct molecular ion peaks at *m*/*z* 422 and 436, respectively.

Treatment of the bis(enaminone) derivatives **5a,b** with piperidine in refluxing ethanol afforded the new bis(enaminones) **9a,b** in 65 and 64% yields, respectively. Furthermore, treatment of the bis(enaminone) **5a,b** with morpholine under similar reaction conditions gave the bis(enaminones) **9c,d** in 60% yields, respectively. The formation of the bis(enaminones) **9a–d** from **5a,b** is suggested to proceed through the formation of the intermediate **8a–d** followed by elimination of two molecules of dimethylamine as outlined in Scheme 2.

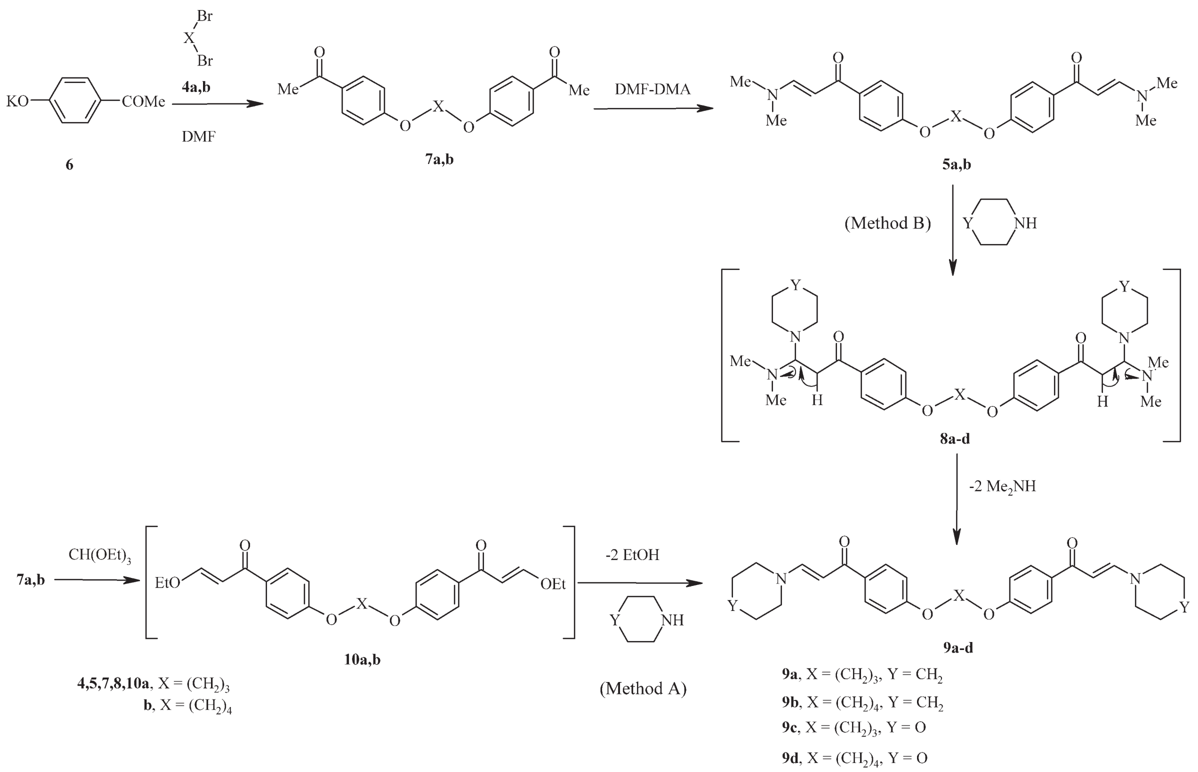
In view of the low yield of the above synthetic methodology, compounds **9a–d** could be obtained by alternative procedures through heating a mixture of the α,ω-bis(acetyl) derivatives **7a,b**, and triethylorthoformate with piperidine or morpholine to afford the corresponding bis(enaminone) derivatives **9a–d** in 71–82% yields. It is proposed that triethylorthoformate reacts with the bis(acetyl) **7a,b** to give the nonisolable bis(vinyl) ethers **10a,b**. Reaction of **10a,b** with piperidine or morpholine *via* Michael-type addition followed by ethanol elimination to give compounds **9a–d**. Elemental analyses and spectral data (IR, MS, ^{1}H NMR, and ^{13}C NMR) of the reaction products confirmed the assigned structures **9a–d**. The ^{1}H NMR spectrum of **9a**, for example, showed two multiplets at δ 1.57 and 3.38 integrated for 12 and 8 protons, respectively, for the piperidyl-CH_2's, a quintet at δ 2.19 and a triplet at δ 4.19 ($J = 5.7$ Hz) due to the propane-2-CH_2 and 1,3-CH_2O-, respectively, in addition to two doublet at δ 5.96 and 7.60 corresponding to the olefinic–C*H*=C*H*—N protons ($J = 12.3$ Hz, typical for trans-configuration) and two doublets at δ 6.96 and 7.87 due to the 1,4-disubstituted phenyl protons ($J = 7.2$ Hz). Its mass spectrum also showed the correct molecular ion peak at *m*/*z* 502.

Having now available the new bis(enaminones) **5a,b** and **9a,b** prompted us to study their synthetic utilities as key intermediates for novel bis(5- and 6-membered) heterocycles. Thus, heating the 1,3-bis(enaminone) **5a**, as a representative example, with hydrazine hydrate in glacial acetic acid resulted in the formation of the 1,3-bis(1*H*-3-pyrazolylphenoxy)propane (**12a**) in 66% yield as depicted in Scheme 3. The structure of compound **12a** was substantiated from its elemental and spectral analyses. Its IR spectrum showed the absence of an absorption band characteristic for C=O as well as the presence of pyrazole-NH absorption at 3199 cm^{-1}. The ^{1}H NMR spectrum of **12a** showed three singlet signals at δ 3.47, 6.56, and 7.62 due to the pyrazole 1-NH, 4-CH, and 5-CH protons, respectively. Similarly, treatment of bis(enaminone) **5b** with hydrazine in acetic acid gave the corresponding 1,4−bis(1*H*-3-pyrazolylphenoxy) butane **12b** in 70% yield (Scheme 3).

It is noteworthy to mention that the bis(pyrazolylphenoxy)alkanes **12a,b** could also be prepared from the appropriate bis(enaminones) **9a,b** in 48 and 55% yields, respectively, using the above synthetic methodology (Scheme 3).

The formation of the bis(pyrazoles) **12a,b** from **5a,b** or **9a,b** is supposed to proceed through the formation of the nonisolable intermediates **11a,b** followed by the elimination of two molecules of the appropriate secondary amines as depicted in Scheme 3.

Scheme 2

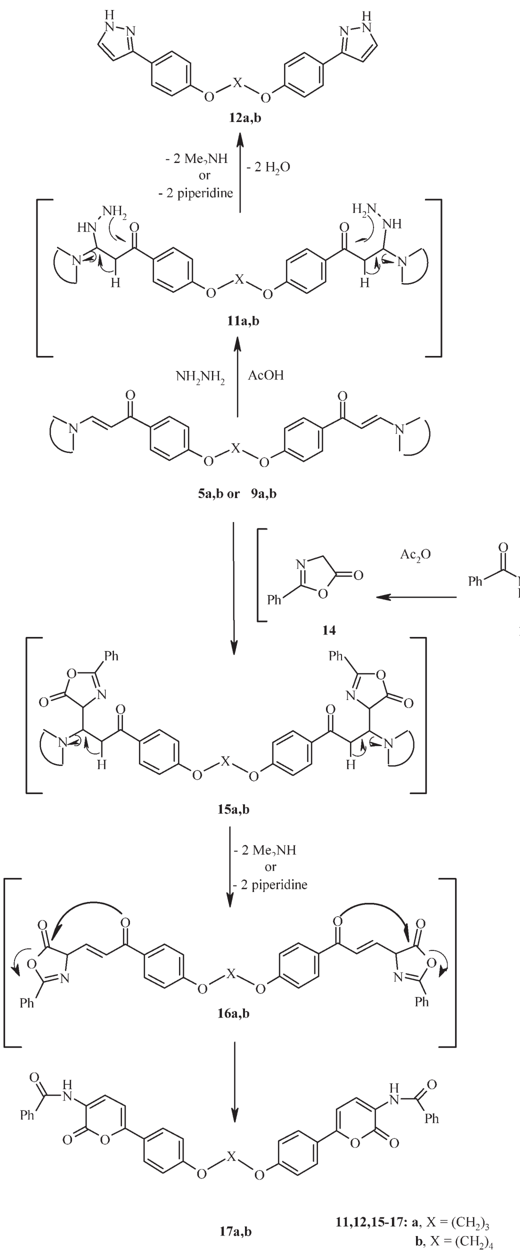


Our study is now extended to include the synthesis of new bis(pyran) derivatives **17a**,**b**. Thus, the bis(enaminone) **5a** was allowed to react with *N*-benzoylglycine **13** in refluxing acetic anhydride to give a single product as examined by TLC. Elemental analyses and mass spectrum of the isolated product were completely in agreement with the molecular formula $C_{39}H_{30}N_2O_8$. The structure of the product is assumed to be **17a** according to the rationale outlined in Scheme 3, which is also similar to analogous reported results [30,31]. Firstly, the nonisolable oxazolone **14** was supposed to be formed from *N*-benzoylglycine **13** upon reaction with acetic anhydride. The latter compound reacts with the enaminone **5a** to form the intermediates **15a**, which eliminate two molecules of dimethylamine or piperidine to give **16a**. The latter then undergoes intramolecular cyclization accompanied with ring opening to give compound **17a** in 74% yield. The ^{1}H NMR of compound **17a** was free of any aliphatic protons except that of the 1,3-dioxypropane moiety and exhibited two characteristic doublets at δ 7.03 and 8.16 each integrated for 2H with J = 7.2 Hz (for 5-H and 4-H protons of the pyranone moiety). In addition, two doublets at δ 7.8 and 7.94 each one integrated for four protons with J = 7.8 Hz (for the two 1,4-disubstituted phenyl moieties) besides the aromatic multiplet for two phenyl groups. Furthermore, the appearance of NH absorption at 3405 cm^{-1} in the IR spectrum as well as its appearance as a broad singlet at δ 9.50 in the ^{1}H NMR spectrum strongly supported this assignment. Similarly, reaction of compound **5b** or **9a,b** with *N*-benzoylglycine **13** under the same reaction conditions gave the corresponding bis(pyranylphenoxy) alkane derivatives **17b** in 77% or **17a,b** in 45 and 52% yields, respectively, as depicted in Scheme 3.

Next, we have also described the synthesis of the new bis(benzofuran) derivatives **20a–d** in 61–79% by the reaction of the appropriate bis(enaminone) derivatives **5a,b** or **9a,b** with the corresponding quinones **18a,b**. Thus, reaction of **5a,b** or **9a,b** with 4-benzoquinone (**18a**) in refluxing acetic acid afforded the corresponding 1,3-bis(benzofuran) derivatives **20a,b** in 43–79% yields. Similarly, reaction of **5a,b** or **9a,b** with 1,4-naphthoquinone (**18b**) under the same reaction conditions gave the target bis(naphthofuran) **20c,d** in 31–74% yields as outlined in Scheme 4. It is assumed that quinines **18a,b** are initially added to the enaminones **5a,b** or **9a,b** to give the nonisolable intermediate **19a–d**. Subsequent intermolecular cyclization *via* dimethylamine or piperidine elimination gave the target compounds **20a–d**. The structures of compounds **20a–d** were inferred from different spectroscopic and analytical data.

It is noteworthy to mention here that the bis(heterocycles) **12a,b**, **17a,b**, and **20a–d** were also prepared from the corresponding enaminones **9c,d** but in very

Scheme 3



low yields compared with those obtained from **5a,b** and **9a,b**.

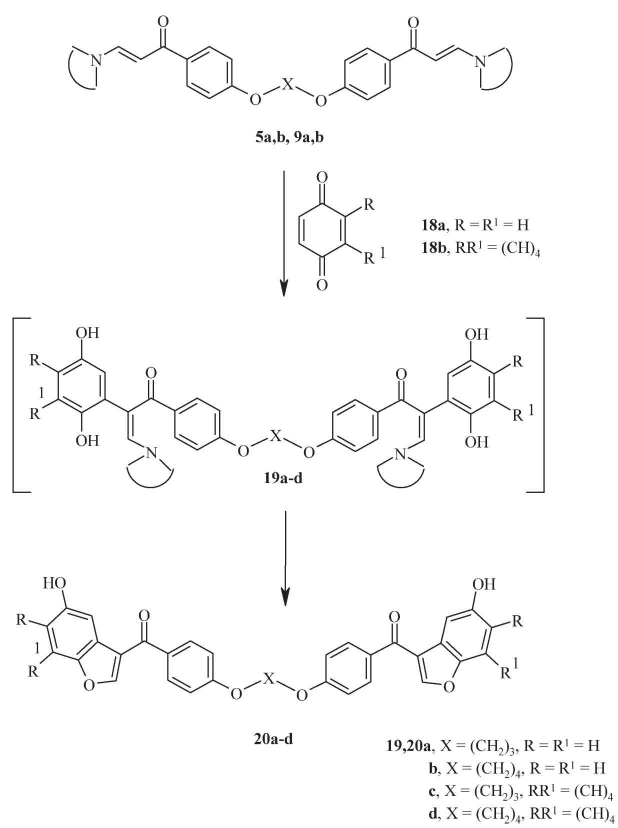
In conclusion, the present investigation describes an efficient method for access toward bis(enaminones) as well as novel bis(heterocycles) containing two biologically active moieties. We believe that these new series of symmetrical bis(hetrocycles) may exhibit potentially diverse useful applications in the field of medicinal chemistry. Also, development of the above synthetic methodology should lead to synthesis of a large number of symmetrical bis(hetrocycles) with a wide variety of substituents as well as different bridges. Moreover, our synthetic methodology offers the advantage of their easy use on a large scale in a simple procedure from inexpensive starting materials.

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ or DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical center of Cairo University. 1,3-Dibromopropane, 1,4-dibromobutane, 1,4-benzoquinone (**18a**), and 1,4-naphthoquinone (**18b**) were used as purchased from Aldrich.

Synthesis of α,ω-bis(4-acetylphenoxy)alkanes 7a,b. 4-Hydroxyacetophenone (**2**) (20 mmol) was dissolved in hot ethanolic KOH solution [prepared by dissolving 1.12 g (20 mmol) of KOH in 20 mL of absolute ethanol], and the solvent was then removed *in vacuo*. The remaining material was dissolved in DMF (15 mL) and the appropriate dibromides **4a,b** (10 mmol) was added. The reaction mixture was refluxed for 5 min during which KCl was separated. The solvent was then removed *in vacuo* and the remaining material was poured over crushed ice. The solid obtained was recrystallized from ethanol to give colorless crystals of compound **7a**, mp 125–127°C (ref. [32] mp 126°C) and compound **7b** mp 146–148°C (ref. [33] mp 149°C).

Scheme 4



Synthesis of bis(enaminones) 5a,b. A mixture of bis(acetyl) derivatives 7**a,b** (10 mmol) and dimethylformamide-dimethylacetal (DMF-DMA) (5.4 g, 45 mmol) was refluxed for 10 h. The reaction mixture was left to cool to room temperature and the resulting yellow solid products were collected by filtration, washed with ethanol, dried, and finally recrystallized from ethanol to afford the corresponding bis(enaminone) derivatives **5a,b**, as pale yellow crystals respectively.

1,3-Bis{4-[(*E*)-3-(*N*,*N*-dimethylamino)prop-2-enoyl]phenoxy}propane (5a). Yield 2.62 g (62%); mp 170–172°C; IR (KBr) ν_{max}/cm^{-1} 1642 (C=O), 1599 (C=C); ^{1}H NMR ($CDCl_3$) δ 2.29 (quintet, *J* = 6 Hz, 2H, $OCH_2CH_2CH_2O$), 3.01 (brs, 12H, 4 NCH_3), 4.21 (t, *J* = 6 Hz, 4H, $OCH_2CH_2CH_2O$), 5.69 (d, *J* = 12 Hz, 2H, 2 N—CH=*CH*—CO), 6.91 (d, *J* = 9 Hz, 4H, ArH), 7.77 (d, *J* = 12 Hz, 2H, 2 N—*CH*=CH—CO), 7.88 (d, *J* = 9 Hz, 4H, ArH); MS: *m*/*z* (%) 422 (M^+, 5), 403 (15.4), 307 (6.8), 213 (5.4), 160 (12.1), 121 (25.8), 107 (19.3), 98 (100), 70 (75.5). Anal. for $C_{25}H_{30}N_2O_4$ Calcd: C, 71.07; H, 7.16; N, 6.63. Found: C, 70.84; H, 7.22; N, 6.48%.

1,4-Bis{4-[(*E*)-3-(*N*,*N*-dimethylamino)prop-2-enoyl]phenoxy}butane (5b). Yield 2.49 g (57%); mp 200–202°C; IR (KBr) ν_{max}/cm^{-1} 1640 (C=O), 1600 (C=C); ^{1}H NMR ($CDCl_3$) δ 2.0 (brs, 4H, $OCH_2CH_2CH_2CH_2O$), 3.02 (brs, 12H, 4 NCH_3), 4.1 (brs, 4H, $OCH_2CH_2CH_2CH_2O$), 5.71 (d, *J* = 12 Hz, 2H, 2 N—CH=*CH*—CO), 6.90 (d, *J* = 9 Hz, 4H, ArH), 7.78 (d, *J* = 12 Hz, 2H, 2 N—*CH*=CH—CO), 7.89 (d, *J* = 9 Hz, 4H, ArH); MS: *m*/*z* (%) 436 (M^+,7.6), 418 (18.7), 363 (7.0), 245 (14.7), 227 (12.6), 161 (15.1), 120 (36.8), 97 (100), 70 (90.2). Anal. for $C_{26}H_{32}N_2O_4$ Calcd: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.80; H, 7.22; N, 6.18%.

Synthesis of bis(piperidyl) and bis(morpholinyl) enaminones 9a–d ***Method A: General procedure.*** A mixture of the bis(acetyl) derivatives **7a,b** (5 mmol), triethylorthoformate (4.5 g, 15 mmol), and the appropriate cyclic amine (piperidine or morpholine) (20 mmol) was heated at refluxing temperature for 6 h. The reaction mixture was then allowed to cool and the resulting precipitate was collected by filtration, washed with ethanol, and dried. Recrystallization from EtOH/DMF afforded the corresponding bis(cyclic) amine derivatives 9**a–d** in 70–82% yield.

Method B: General procedure. A mixture of the bis(enaminone) derivative **5a,b** (5 mmol) and the appropriate cyclic amine (piperidine or morpholine) (20 mmol) in ethanol (30 mL) was refluxed for 8 h. After cooling, the precipitated product was collected by filtration, washed with ethanol, and dried. Recrystallization from the EtOH/DMF afforded compounds identical in all respects with 9**a–d** obtained above but in slightly lower yields 60–65%.

1,3-Bis{4-[(*E*)-3-(*N*-piperidyl)prop-2-enoyl]phenoxy}propane (9a). Yield: method A/method B (80/65%); yellow powder; mp 160–162°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1638 (C=O), 1600 (C=C); ^{1}H NMR (DMSO-d_6) δ 1.57 (brs, 12H, 6 piperidyl-CH_2), 2.20 (quintet, *J* = 5.7 Hz, 2H, $OCH_2CH_2CH_2O$), 3.38 (brs, 8H, 4 piperidyl-NCH_2), 4.19 (t, *J* = 5.7 Hz, 4H, $OCH_2CH_2CH_2O$), 5.96 (d, *J* = 12.3 Hz, 2H, 2 N—CH=*CH*—CO), 6.96 (d, *J* = 7.2 Hz, 4H, ArH), 7.60 (d, *J* = 12.3 Hz, 2H, 2 N—*CH*=CH—CO) 7.87 (d, *J* = 7.2 Hz, 4H, ArH); MS: *m*/*z* (%) 502 (M^+, 2), 485 (5.7), 420 (10.2), 347 (6.4), 160 (6.8), 137 (8.7), 120 (24.5), 109 (100), 83 (29.3), 54 (39.3). Anal. for $C_{31}H_{38}N_2O_4$ Calcd: C, 74.07; H, 7.62; N, 5.57. Found: C, 74.15; H, 7.41; N, 5.69%.

1,4-Bis{4-[(*E*)-3-(*N*-piperidyl)prop-2-enoyl]phenoxy}butane (9b). Yield: method A/method B (71/64%); yellow powder; mp 250–252°C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 1674 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.58 (brs, 12H, 6 piperidyl-CH_2), 1.89 (brs, 4H, $OCH_2CH_2CH_2CH_2O$), 3.39 (brs, 8H, 4 piperidyl-NCH_2), 4.10 (brs, 4H, $OCH_2CH_2CH_2CH_2O$), 5.97 (d, *J* = 12 Hz, 2H, 2 N—CH=*CH*—CO), 6.95 (d, *J* = 9 Hz, 4H, ArH), 7.60 (d, *J* = 12 Hz, 2H, 2 N—*CH*=CH—CO) 7.87 (d, *J* = 9 Hz, 4H, ArH); MS: *m*/*z* (%) 517 (M+1, 15.4), 498 (40.1), 434 (36.8), 110 (100), 95 (24.4). Anal. for $C_{32}H_{40}N_2O_4$ Calcd: C, 74.39; H, 7.80; N, 5.42. Found: C, 74.52; H, 7.98; N, 5.50%.

1,3-Bis{4-[(*E*)-3-(*N*-morpholinyl)prop-2-enoyl]phenoxy}-propane (9c). Yield: method A/method B (82/60%); yellow crystals; mp 205–207°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1664 (C=O); ^{1}H NMR ($CDCl_3$) δ 2.30 (quintet, *J* = 6 Hz, 2H, $OCH_2CH_2CH_2O$), 3.38 (t, *J* = 5.1 Hz, 8H, 4 NCH_2CH_2O), 3.76 (t, *J* = 5.1 Hz, 8H, 4 OCH_2CH_2N), 4.22 (t, *J* = 6 Hz, 4H, $OCH_2CH_2CH_2O$), 5.87 (d, *J* = 12.6 Hz, 2H, 2 N—CH=*CH*—CO), 6.93 (d, *J* = 7.2 Hz, 4H, ArH), 7.70 (d, *J* = 12.6 Hz, 2H, 2 N—*CH*=CH—CO) 7.88 (d, *J* = 7.2 Hz, 4H, ArH); MS: *m*/*z* (%) 506 (M^+, 43.3), 423 (100), 310 (38.5), 256 (26.9), 218 (34.6), 186 (34.6), 149 (25.0), 133 (49.0), 121 (53.8), 91 (23.1), 81 (60.6), 68 (36.5). Anal. for $C_{29}H_{34}N_2O_6$ Calcd: C, 68.76; H, 6.76; N, 5.53. Found: C, 69.01; H, 6.58; N, 5.32%.

1,4-Bis{4-[(*E*)-3-(*N*-morpholinyl)prop-2-enoyl]phenoxy}-butane (9c). Yield: method A/method B (74/60%); yellow crystals; mp 211–213°C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 1671 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.86 (brs, 4H, $OCH_2CH_2CH_2CH_2O$), 3.46 (m, 8H, 4 NCH_2CH_2O), 3.62 (brs, 8H, 4 OCH_2CH_2N), 4.06 (brs, 4H, $OCH_2CH_2CH_2CH_2O$), 6.04 (d, *J* = 12.6 Hz, 2H, 2 N—CH=*CH*—CO), 6.95 (d, *J* = 8.4 Hz, 4H, ArH), 7.63 (d, *J* = 12.6 Hz, 2H, 2 N—*CH*=CH—CO) 7.89 (d, *J* = 8.4 Hz, 4H, ArH); ^{13}C NMR (DMSO-d_6) δ 25.2, 46.0, 65.6, 67.2, 113.7, 129.1, 130.3, 132.4, 152.1, 160.9, 185.3; MS: *m*/*z* (%) 520 (M^+, 17.3), 437 (31.3), 407 (92.7), 272 (22.9), 191 (64.1), 149 (65.1), 112 (72.4), 82 (95.8), 55 (100). Anal. for $C_{30}H_{36}N_2O_6$ Calcd: C, 69.21; H, 6.97; N, 5.38. Found: C, 69.58; H, 7.11; N, 5.45%.

Synthesis of the bis(pyrazole) Derivatives 12a,b. ***Method A: General procedure.*** A mixture of the bis(enaminone) derivatives **5a,b** (2 mmol) and hydrazine hydrate (1 mL, 99%) in glacial acetic acid (20 mL) was left to stir at room temperature overnight. The precipitated product was collected by filtration, washed with ethanol, and dried. Recrystallization from ethanol furnished the corresponding pyrazole derivatives **12a** and **12b** in 66 and 70% yields, respectively.

Method B: General procedure. The reactions were carried out under the same conditions in method A by replacing the enaminones **5a,b** with piperidyl ones **9a,b**. The yields of this method were lower than that of method A (**12a**: 48% and **12b**: 55%).

1,3-Bis[4-(1*H*-pyrazol-3-yl)phenoxy]propane (12a). Colorless powder, mp 182–184°C; IR (KBr) ν_{max}/cm^{-1} 3199 (NH), 1602 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.25 (m, 2H, $OCH_2CH_2CH_2O$), 3.47 (brs, 2H, 2 NH, D_2O-exchangeable), 4.18 (m, 4H, $OCH_2CH_2CH_2O$), 6.56 (s, 2H, 2 pyrazole-4-CH), 7.62 (s, 2H, 2 pyrazole-5-CH), 7.69 (d, *J* = 8.1 Hz, 4H, ArH), 7.84 (d, *J* = 8.1 Hz, 4H, ArH); MS *m*/*z* (%) 360 (M^+, 57.8), 201 (100), 159 (68.8), 131 (72.5), 116 (48.6), 89 (41.3). Anal. for

$C_{21}H_{20}N_4O_2$ Calcd: C, 69.98; H, 5.59; N, 15.54. Found: C, 69.62; H, 5.74; N, 15.30%.

1,4-Bis[4-(1*H*-pyrazol-3-yl)phenoxy]butane (12b). Colorless powder, mp 227–229°C; IR (KBr) ν_{max}/cm^{-1} 3186 (NH), 1612 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.91 (s, 4H, $OCH_2CH_2CH_2CH_2O$), 3.3 (brs, 2H, 2 NH, D_2O-exchangeable), 4.07 (s, 4H, $OCH_2CH_2CH_2CH_2O$), 6.59 (d, J = 2.1 Hz, 2H, 2 pyrazole-4-CH), 6.98 (d, J = 8.4 Hz, 4H, ArH), 7.64 (d, J = 1.8 Hz, 2H, 2 pyrazole-5-CH), 7.70 (d, J = 8.4 Hz, 4H, ArH); MS: *m*/*z* (%) 374 (M^+, 17.7), 215 (100), 173 (55.5), 160 (31.2), 131 (27.1), 77 (22.2), 55 (28.3). Anal. for $C_{22}H_{22}N_4O_2$ Calcd: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.94; H, 5.78; N, 14.86%.

Synthesis of the bis(pyran-2-one) derivatives 17a,b ***Method A: General procedure.*** A solution of the bis(enaminones) **5a,b** (1 mmol) and *N*-benzoylglycine (**13**) (0.36 g, 2 mmol) in acetic anhydride (20 mL) was heated under reflux for 1 h then left to cool to room temperature. The solid product that formed upon cooling was collected by filtration and recrystallized from DMF/water to give the bis(pyran-2-one) derivatives **17a,b**, in 74 and 77% yields, respectively.

Method B: General procedure. The reactions were carried out under the same experimental conditions mentioned in method A earlier using the piperidyl derivatives **9a,b** instead of the enaminones **5a,b** to afford the bis(pyran-2-one) derivatives **17a,b** in 45 and 52% yields, respectively.

1,3-Bis[4-(3-benzoylamino-2-oxo-2*H*-pyran-6-yl)phenoxy]-propane (17a). Orange-colored powder, mp 250–252°C; IR (KBr) ν_{max}/cm^{-1} 3405 (NH), 1705, 1671 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.24 (m, 2H, $OCH_2CH_2CH_2O$), 4.25 (m, 4H, $OCH_2CH_2CH_2O$), 7.03 (d, J = 7.2 Hz, 2H, 2 pyranone-5-CH), 7.1–7.96 (m, 18H, ArH), 8.16 (d, J = 7.2 Hz, 2H, 2 pyranone-4-CH), 9.50 (brs, 2H, 2 NH, D_2O-exchangeable); MS: *m*/*z* (%) 654 (M^+, 48.5), 105 (100), 77 (23.1), 50 (16.4). Anal. for $C_{39}H_{30}N_2O_8$ Calcd: C, 71.55; H, 4.62; N, 4.28. Found: C, 71.86; H, 4.43; N, 4.21%.

1,4-Bis[4-(3-benzoylamino-2-oxo-2H-pyran-6-yl)phenoxy]-butane (17b). Orange-colored powder, mp > 300°C; IR (KBr) ν_{max}/cm^{-1} 3403 (NH), 1698, 1637 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.91 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 4.14 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 7.03–7.13 (m, 20H, ArH, 2 pyranone-5-CH), 8.16 (d, J = 7.5 Hz, 2H, 2 pyranone-4-CH), 9.56 (brs, 2H, 2 NH, D_2O-exchangeable); Anal. for $C_{40}H_{32}N_2O_8$ Calcd: C, 71.85; H, 4.82; N, 4.19. Found: C, 72.11; H, 4.65; N, 4.38%.

Synthesis of the bis(benzofurans) 20a,b and bis(naphthofurans) 20c,d ***Method A: General procedure.*** To a stirred solution of the bis(enaminones) **5a,b** (2 mmol) in acetic acid (20 mL), *p*-benzoquinone (**18a**) or 1,4-naphthoquinone (**18b**) (4 mmol) was added and the reaction mixture was stirred overnight at room temperature. The solid product formed was collected by filtration, washed with water and ethanol, dried, and finally recrystallized from EtOH/DMF to give the corresponding bis(benzofurans) **20a,b** and bis(naphthofurans) **20c,d**, respectively.

Method B: General procedure. This method is similar to method A except that the enaminone derivatives **9a,b** were used instead of **5a,b** to afford the corresponding bis(benzofurans) **20a,b** and bis(naphthofuran) derivatives **20c,d** but in lower yields compared to that obtained in method A.

1,3-Bis[4-(5-hydroxybenzo[*b*]furan-3-ylcarbonyl)phenoxy]propane (20a). Yield: method A/method B (66/43%); pale yellow powder, mp 190–192°C; IR (KBr) ν_{max}/cm^{-1} 3258 (OH), 1658 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.25 (m, 2H, $OCH_2CH_2CH_2O$), 4.28 (m, 4H, $OCH_2CH_2CH_2O$), 6.83–6.88 (m, 2H, ArH), 7.05–7.15 (m, 5H, ArH), 7.45–7.52 (m, 2H, ArH), 7.87–7.94 (m, 5H, ArH), 8.54 (s, 2H, 2 furan-2-CH), 9.44 (brs, 2H, 2 OH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6): δ 28.4, 64.6, 106.5, 111.9, 114.3, 114.5, 119.9, 125.9, 130.4, 131.02, 148.9, 153.4, 154.6, 162.03, 187.9; MS: *m*/*z* (%) 548 (M^+, 50), 161 (100), 121 (26.8), 105 (36.2), 93 (26.1), 76 (25.4), 51 (24.6). Anal. for $C_{33}H_{24}O_8$ Calcd: C, 72.26; H, 4.41. Found: C, 72.63; H, 4.27%.

1,4-Bis[4-(5-hydroxybenzo[*b*]furan-3-ylcarbonyl)phenoxy]butane (20b). Yield: method A/method B (79/47%); pale yellow powder, mp 283–285°C; IR (KBr) ν_{max}/cm^{-1} 3277 (OH), 1662 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.94 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 4.15 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 6.84–7.09 (m, 6H, ArH), 7.45–7.52 (m, 4H, ArH), 7.85–7.92 (m, 4H, ArH), 8.53 (s, 2H, 2 furan-2-CH), 9.38 (brs, 2H, 2 OH, D_2O-exchangeable); MS: *m*/*z* (%) 562 (M^+, 35.2), 428 (60.2), 309 (25), 254 (25.8), 161 (100), 121 (64.8), 76 (32), 55 (65.6). Anal. for $C_{34}H_{26}O_8$ Calcd: C, 72.59; H, 4.66. Found: C, 72.44; H, 4.84%.

1,3-Bis[4-(5-hydroxynaphtho[1,2-*b*]furan-3-ylcarbonyl)-phenoxy]propane (20c). Yield: method A/method B (61/31%); pale yellow powder, mp 258–260°C; IR (KBr) ν_{max}/cm^{-1} 3224 (OH), 1672 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.24 (m, 2H, $OCH_2CH_2CH_2O$), 4.26 (m, 4H, $OCH_2CH_2CH_2O$), 7.04–7.16 (m, 6H, ArH), 7.55–7.95 (m, 10H, ArH), 8.18–8.28 (m, 2H, ArH), 8.62 (s, 2H, 2 furan-2-CH), 10.17 (s, 2H, 2 OH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6): δ 28.4, 64.6, 114.3, 114.5, 119.3, 120.8, 121.1, 121.5, 123.3, 123.5, 124.9, 127.4, 130.5, 131.2, 144.5, 150.8, 151.7, 162.3, 188.2. Anal. for $C_{41}H_{28}O_8$ Calcd: C, 75.92; H, 4.35. Found: C, 76.22; H, 4.29%.

1,4-Bis[4-(5-hydroxynaphtho[1,2-*b*]furan-3-ylcarbonyl)-phenoxy]butane (20d). Yield: method A/method B (74/40%); pale yellow powder, mp > 300°C; IR (KBr) ν_{max}/cm^{-1} 3213 (OH), 1706 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.93 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 4.12 (m, 4H, $OCH_2CH_2CH_2CH_2O$—), 7.09–7.13 (m, 6H, ArH), 7.54–7.96 (m, 10H, ArH), 8.18–8.28 (m, 2H, ArH), 8.64 (s, 2H, 2 furan-2-CH), 10.25 (brs, 2H, 2 OH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6): δ 25.3, 67.6, 114.0, 114.3, 119.3, 120.7, 121, 121.4, 123.3, 123.5, 124.9, 127.3, 129.1, 131.1, 144.5, 150.7, 151.5, 162.3, 188.2. Anal. for $C_{42}H_{30}O_8$ Calcd: C, 76.12; H, 4.56. Found: C, 76.00; H, 4.44%.

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