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Efficient synthesis of novel bis(dihydropyrano[2,3-*c*]pyrazoles), bis(4*H*-chromenes) and bis(dihydropyrano[3,2-*c*]chromenes) with amide functionality

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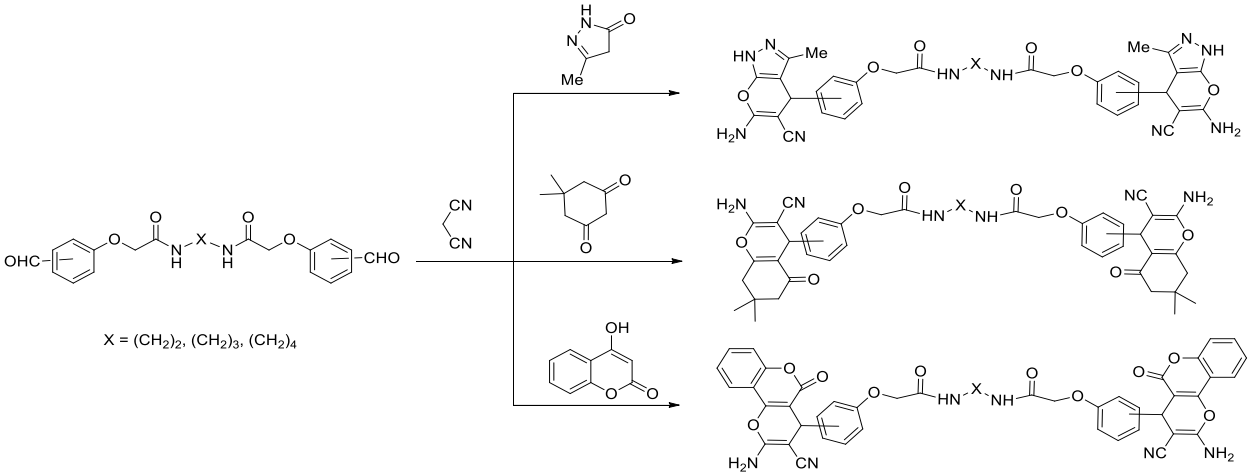
Abstract

A synthesis of novel bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles), bis(4*H*-chromene-3-carbonitriles) and bis(dihydropyrano[3,2-*c*]chromenes), which are linked to aliphatic spacers *via* amide linkages was achieved *via* multicomponent reactions (MCR) of the appropriate bis-aldehyde with two equivalents of both of malononitrile and 3-methylpyrazol-5-one, dimedone or 4-hydroxycoumarin in a basic solution.



Keywords: Bis(pyrano[2,3-*c*]pyrazole), bis(chromene), bis(pyrano[3,2-*c*]chromene), amide linkages

Introduction

The amide group is one of the most popular and reliable functionalities in organic chemistry. Amides are a core structural unit in the skeleton of proteins and frequently occur in a wide variety of molecules, such as natural products and biologically active compounds including pharmaceuticals (e.g., the marketed drugs Atorvastatin **1**, Lisinopril **2** and Valsartan **3** (Figure 1).

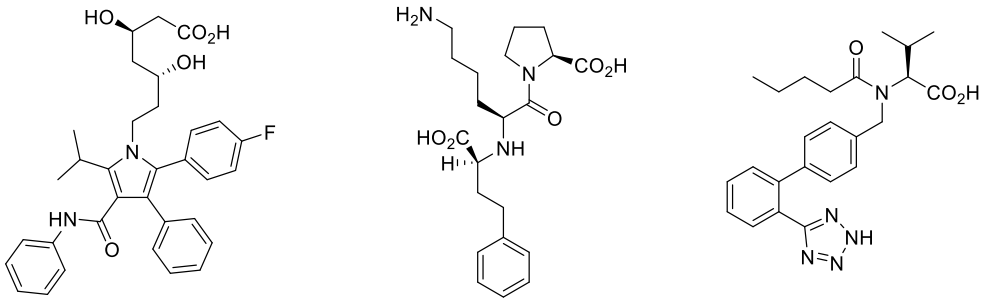


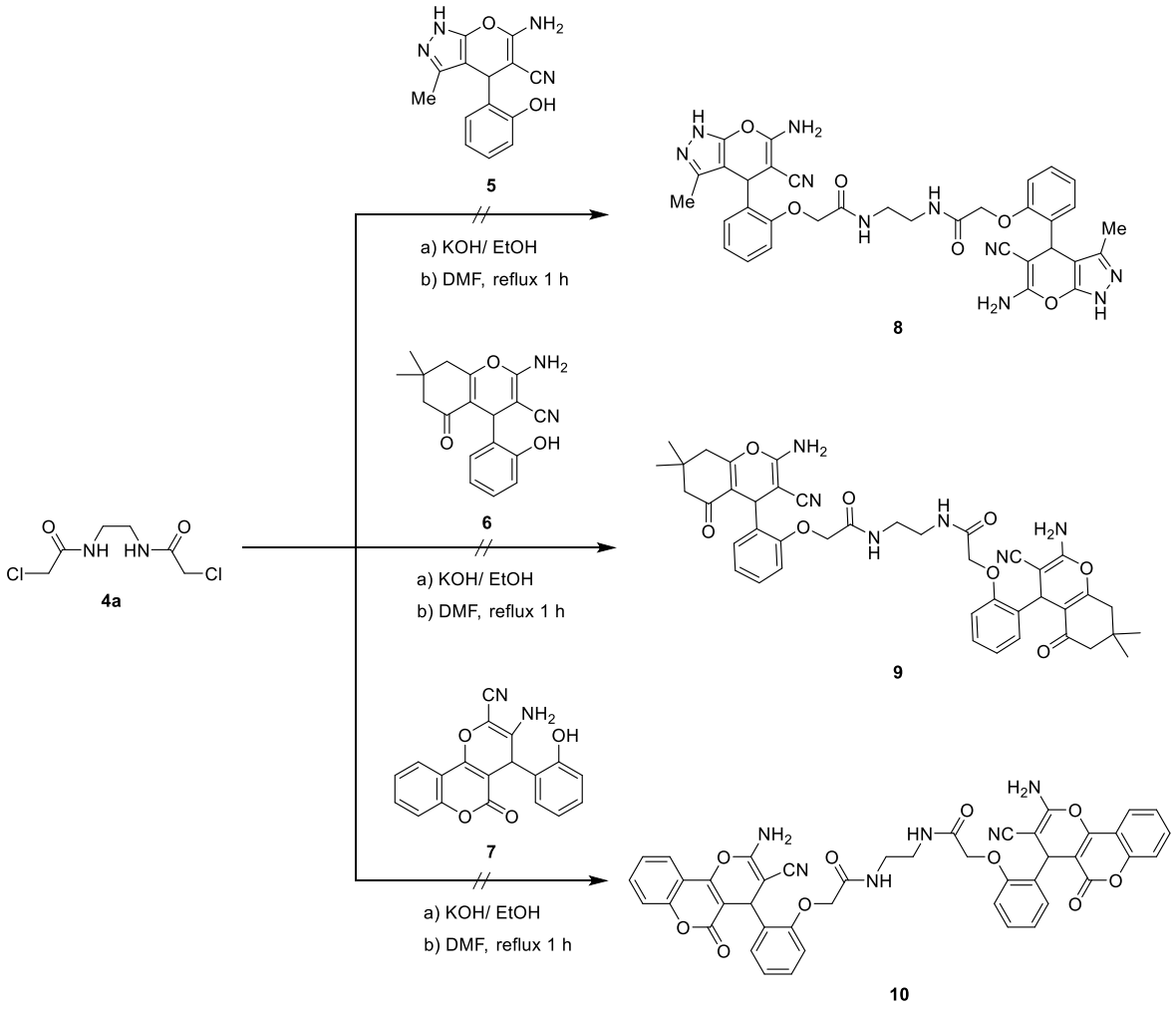
Figure 1. Chemical structures of some amidic marketed drugs.

The favorable properties of amide groups, such as high polarity, stability and conformational diversity stimulated authors to search for improved methods for the synthesis of novel amide-based molecules.[1–7] The Michael addition reaction represents a powerful synthetic approach in the area of synthetic heterocyclic chemistry. Its applications in pharmaceutical research and drug discovery have been the subject of many publications in the last decades.[8–11] On the other hand, MCRs are efficient synthetic tools for one-pot syntheses of complex organic molecules. MCRs have the advantages of being eco-friendly and intrinsically atom-economical reaction.[12–14] This has inspired many advances in the design and implementation for the construction of diverse heterocyclic scaffolds.[15–18] Pyrans constitute an important class of biologically active natural and synthetic products. Pyrans and their fused analogues especially, pyrano[2,3-*c*]pyrazole, chromene and pyrano[3,2-*c*]chromenes play a fundamental role in bioorganic chemistry due to their diverse biological applications including anticancer, antiviral and anti-inflammatory activities.[19–22] Furthermore, the presence of more than one active moiety in the molecule is believed to alter positively the activity for the intended application. In the last decade, we reported extensively on the Michael addition reaction[23–26] as well as the chemistry of bis-(heterocycles) whose heterocyclic moieties were linked *via* different aliphatic and aromatic spacers.[8,24,26–33] In continuation of the aforementioned effort, we report herein, the synthesis of new bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile), bis(4*H*-chromene-3-carbonitrile) and bis(dihydropyrano[3,2-*c*]chromene) containing molecules which are linked to aliphatic spacers by amide linkages *via* a MCR procedure aiming at increased biocompatibility for the application as bioactive agents.

Results and Discussion

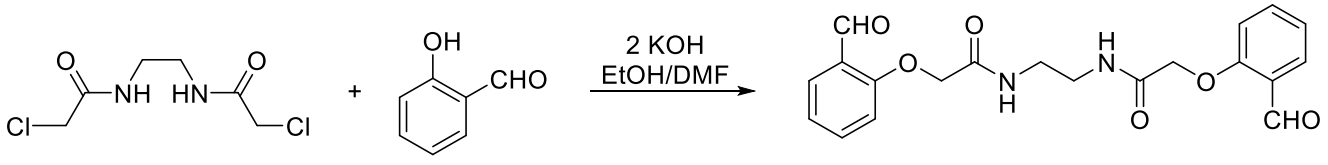
Our first approach to synthesize the bis(fused dihydropyrans) **8-10** included first the synthesis of dihydropyrano[2,3-*c*]pyrazole **5**, tetrahydro-4*H*-chromene **6** and dihydropyrano[3,2-*c*]chromene **7**, each bearing a 2-hydroxylphenyl group at the position 4.[34–37] These compounds can then undergo simple bis-

alkylation reaction with bis(2-chloroacetamide) **4a** in basic medium to give the target molecules **8-10**. The TLC of the reaction mixtures indicates the presence of a mixture of products which could unfortunately not be separated or identified (Scheme 1).



Scheme 1. Attempted bis-alkylation of 4-(2-hydroxyphenyl)-substituted dihydropyrano[2,3-*c*]pyrazole **5**, tetrahydro-4*H*-chromene **6** and dihydropyrano[3,2-*c*]chromene **7** with bis(2-chloroacetamide) **4.**

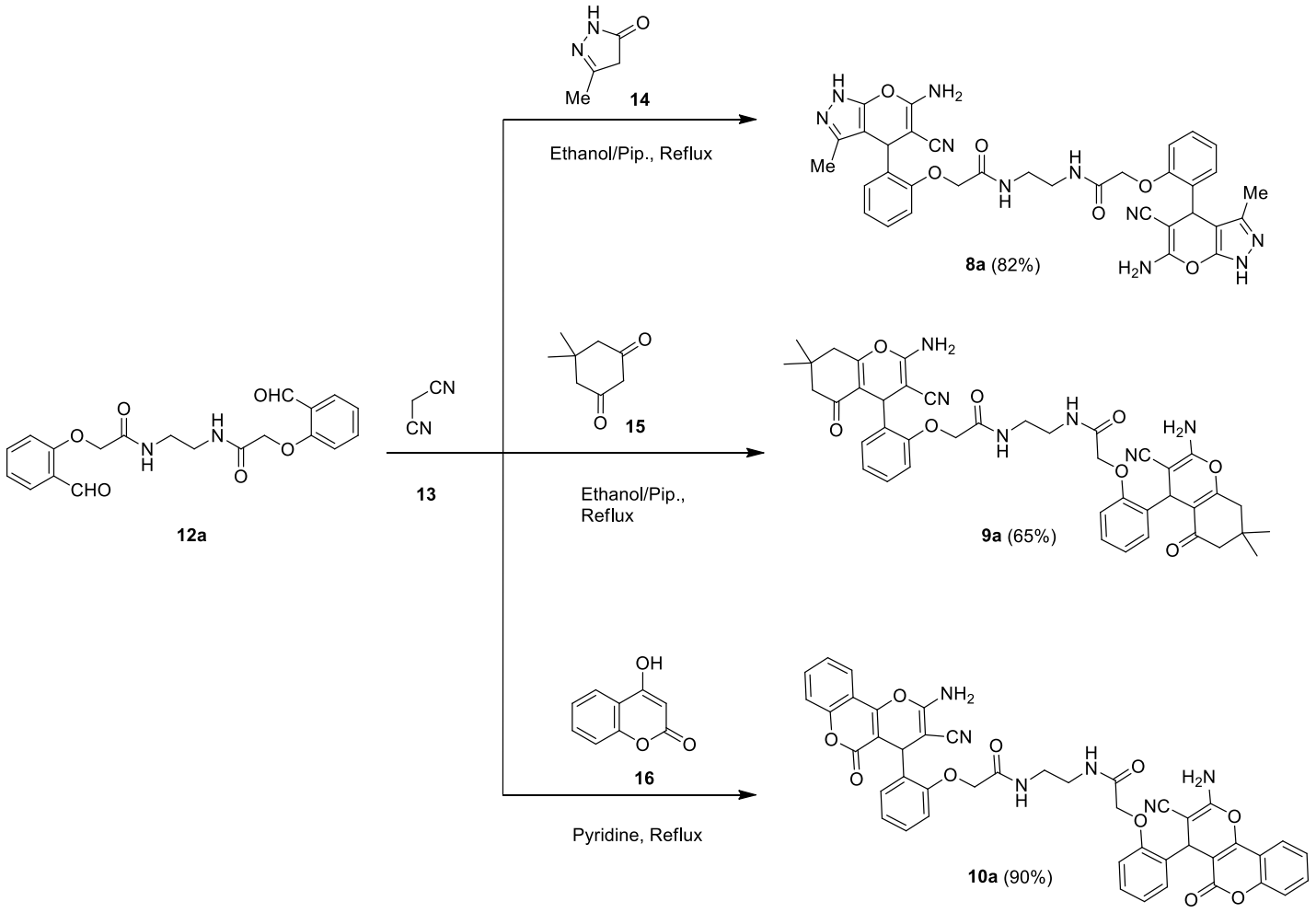
In the second approach, the bis-aldehyde **12a** containing an amide linkage was prepared following the reported methods described by our group[8,38–41] *via* the reaction of the potassium salt of the salicylaldehyde **11** with the corresponding bis(2-chloroacetamide) **4a** in boiling DMF (Scheme 2).



4a **11** **12a** (80%)

Scheme 2. Synthesis of bis-aldehyde **12a.**

A subsequent MCR of **12a** with two equivalents of both of malononitrile **13** and 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one **14** or dimedone **15** in ethanol heated at reflux in the presence of piperidine gave bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) **8a** and bis(4*H*-chromene-3-carbonitrile) **9a** in 82 and 65% yields, respectively. Similarly, the MCR of compound **12a** with malononitrile and 4-hydroxycoumarin **16** in pyridine heated at reflux gave bis(dihydropyrano[3,2-*c*]chromene) **10a** in 90% yield (Scheme 3).



Scheme 3. Synthesis of bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) **8a**, bis(4*H*-chromene-3-carbonitrile) **9a** and bis(dihydropyrano[3,2-*c*]chromene) **10a.**

The structure of compounds **8a-10a** were supported by their elemental analysis and spectral data. Thus, IR spectrum of compound **8a** indicated the presence of primary amino groups at *v* 3348 and 3310 cm^{-1}, and a cyano group at *v* 2191 cm^{-1}. The carbonyl group appeared as a broad band at *v* 1668 cm^{-1}. The ^1H NMR spectrum indicated the presence of the pyran-H4 as singlet signal at δ_H 5.25. Moreover, the pyrazole methyl, and the methylene groups, OCH_2 and NCH_2, were featured as three signals at δ_H 1.79, 4.47 and 3.29, respectively.

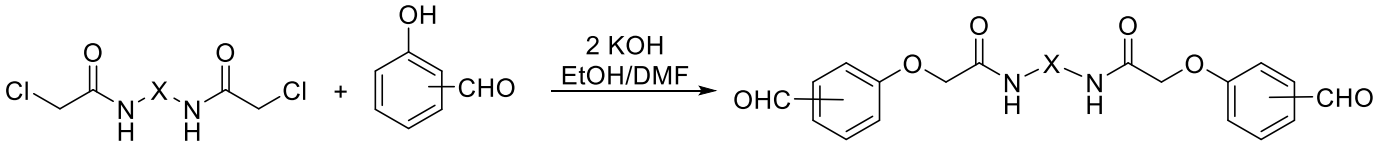
The IR spectra of compound **9a** revealed the presence of primary amino groups by absorptions at *v* 3487 and 3410 cm^{-1} in addition to the cyano and the carbonyl groups at *v* 2175 and 1674 cm^{-1}, respectively. The ^1H NMR spectrum of compound **9a** showed the presence of two singlets integrated by 12 protons at δ_H 0.97 and 1.01 assigned to four CH_3 groups. In addition, it showed a singlet signal at 4.76 ppm assigned to the pyran-H4.

The IR spectrum of compound **10a** showed the presence of primary amino groups by absorptions at *v* 3325 and 3279 cm^{-1}. In addition, it revealed the cyano band at *v* 2184 cm^{-1}. The carbonyl groups showed a broad band at 1671 cm^{-1}. The ^1H NMR spectrum of **10a** showed the presence of the pyran-H4 as a singlet signal at δ_H 5.02. It is worthy to note that compounds **9a** and **10a** featured the methylene ether linkage OCH_2 as a multiplet signal at δ_H 4.44–4.59, although their precursor **12a** exhibits a singlet for these protons at δ_H 4.63. This may be attributed to the generation of stereogenic centers (in the dihydropyran rings) in the products, which are close enough to the diastereotopic CH_2 protons. All other protons were seen at the expected chemical shifts and integral values (see Experimental Section and Supporting Information).

To extend the scope of these MCRs, a series of bis-aldehydes **12a-h** containing amide linkages have been prepared by the reaction of the potassium salt of appropriate hydroxybenzaldehydes **11a-c** with the corresponding bis(2-chloroacetamides) **4a-d** in boiling DMF (Table 1).

A novel series of bis(dihydropyrano[3,2-*c*]chromenes) **10a-g** were successfully prepared in 87-93% yields by MCRs of the appropriate aldehydes **12a-g** with malononitrile **13** and 4-hydroxycoumarin **16** in pyridine heated at reflux (Table 2).

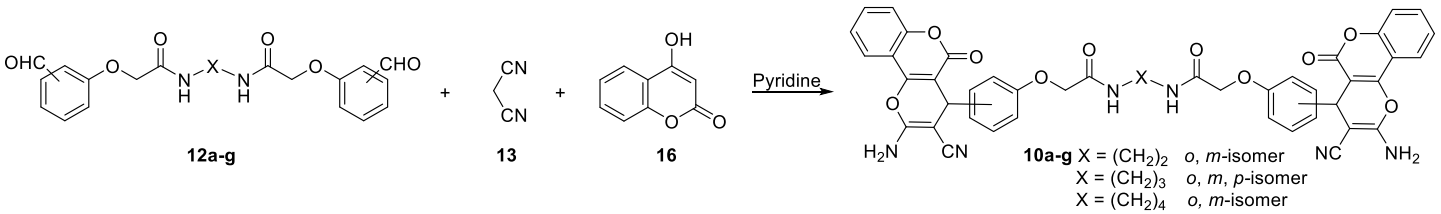
Table 1. Synthesis of bis-aldehydes **12a-h** containing amide linkages



4a, X = $(CH_2)_2$ **11a**, *o*-isomer **12a-h**
b, X = $(CH_2)_3$ **b**, *m*-isomer
c, X = $(CH_2)_4$ **c**, *p*-isomer

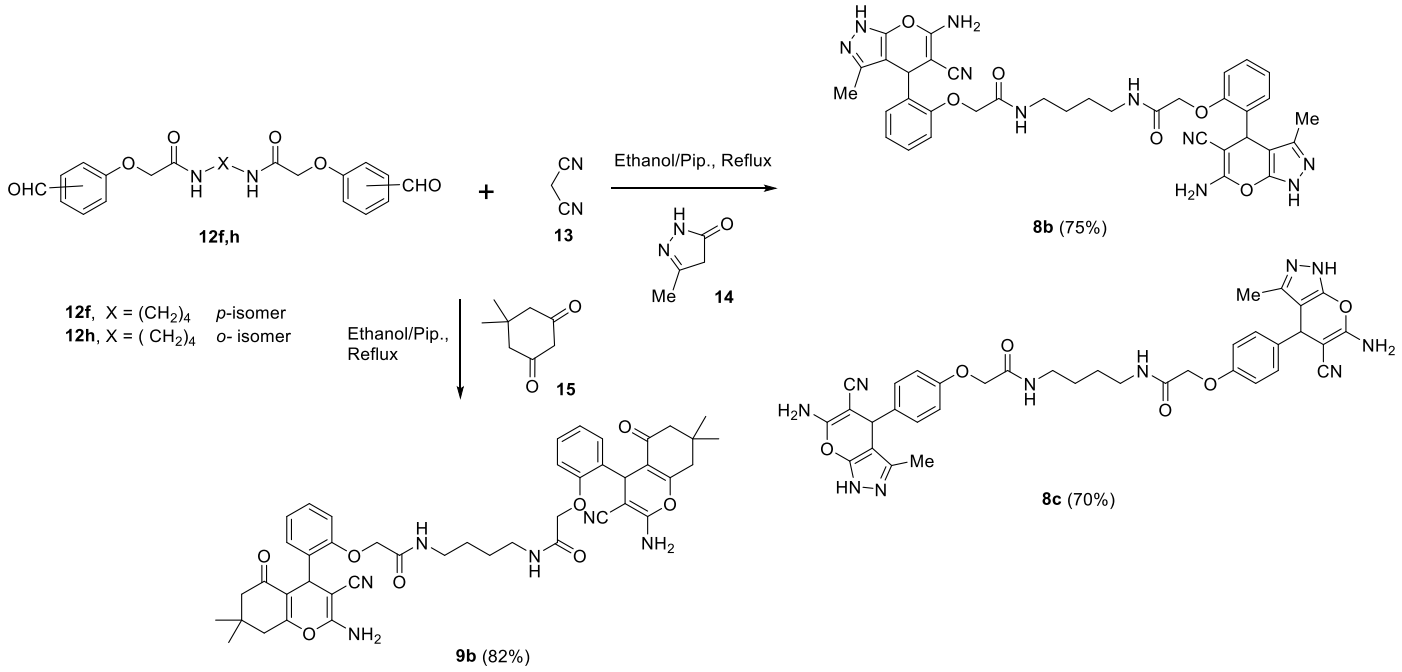
Entry	X	CHO (*o-, m-, p-*)	Yield **12** (%)
1	$(CH_2)_2$	*o*	**12a** (80)
2	$(CH_2)_2$	*m*	**12b** (70)
3	$(CH_2)_3$	*o*	**12c** (75)
4	$(CH_2)_3$	*m*	**12d** (74)
5	$(CH_2)_3$	*p*	**12e** (76)
6	$(CH_2)_4$	*o*	**12f** (83)
7	$(CH_2)_4$	*m*	**12g** (74)
8	$(CH_2)_4$	*p*	**12h** (79)

Table 2. Synthesis of bis(dihydropyrano[3,2-*c*]chromenes) **10a-g**



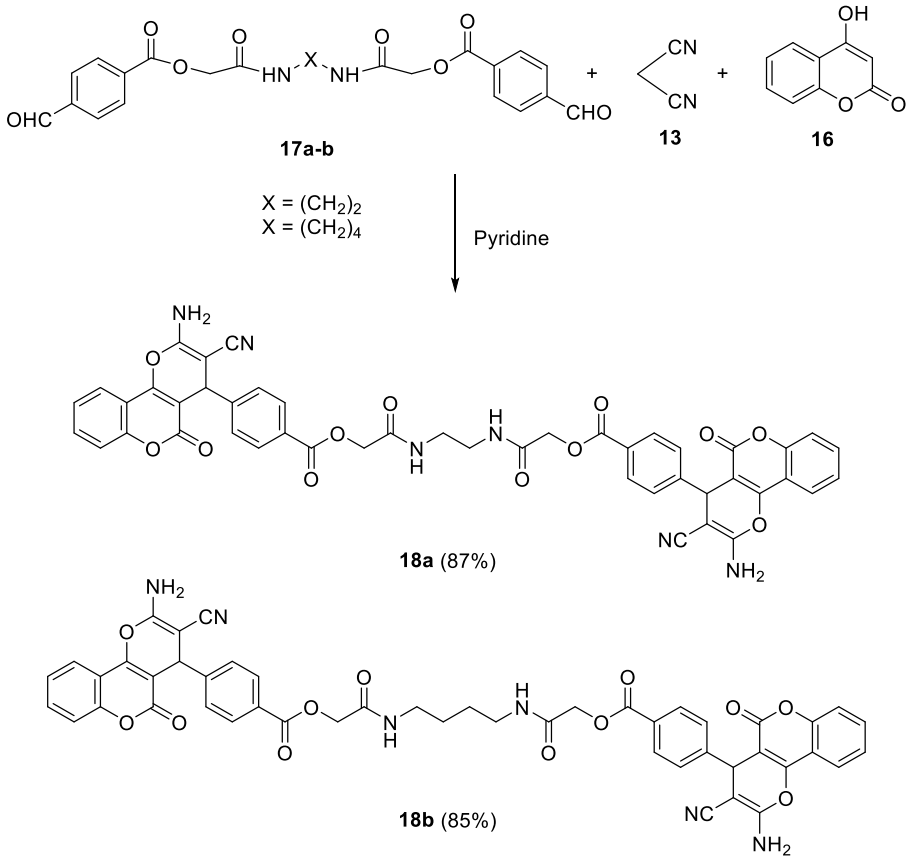
Entry	X	Isomer (*o-*, *m-*, *p-*)	Yields **10** (%)
1	$(CH_2)_2$	*o*	**10a** (90)
2	$(CH_2)_2$	*m*	**10b** (73)
3	$(CH_2)_3$	*o*	**10c** (87)
4	$(CH_2)_3$	*m*	**10d** (89)
5	$(CH_2)_3$	*p*	**10e** (91)
6	$(CH_2)_4$	*o*	**10f** (93)
7	$(CH_2)_4$	*m*	**10g** (87)

Bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles) **8b** and **8c** could be obtained in 75 and 70% yields, respectively, by MCRs of bisaldehydes **12f** and **12h** with two equivalents of both of malononitrile and 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one in ethanol heated at reflux in the presence of piperidine. Also, the bis(4*H*-chromene-3-carbonitrile) **9b** was obtained in 82% yield from the reaction of bisaldehyde **12f** with two equivalents of both of malononitrile **13** and dimedone **15** (Scheme 4).



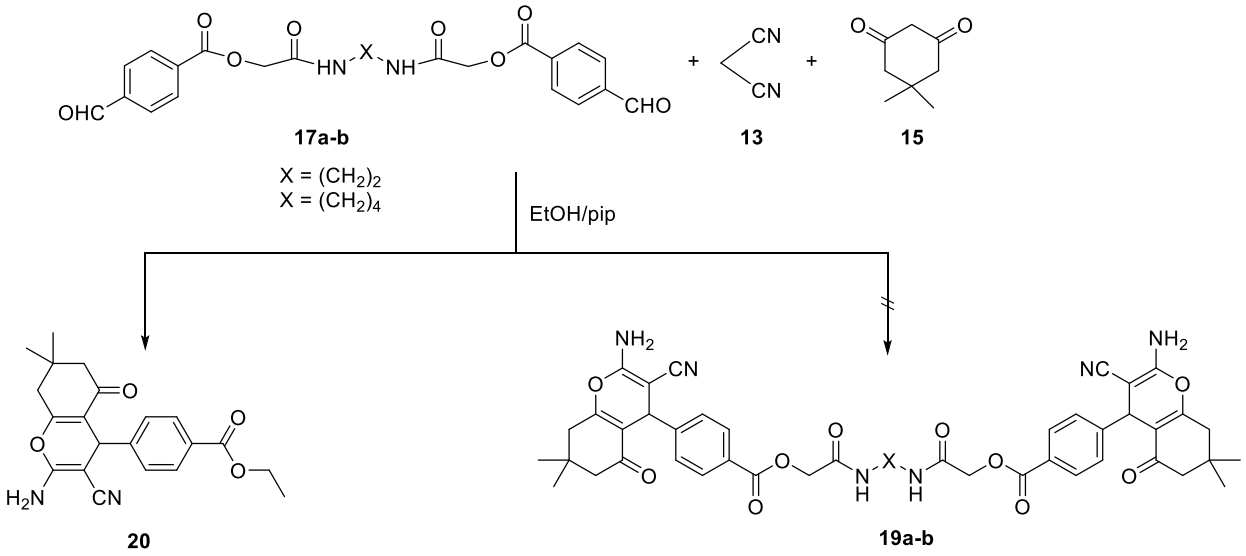
Scheme 4. Bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles) **8b** and **8c** as well as bis(4*H*-chromene-3-carbonitrile) **9b.**

Our study was extended to include the synthesis of bis(dihydropyrano[3,2-*c*]chromenes) **18a,b** which are linked to aliphatic spacers *via* both of amide and ester linkages. Thus, a MCR of **17a,b** with two equivalents of both of malononitrile and of 4-hydroxycoumarin in pyridine heated at reflux afforded **18a** and **18b** in 87 and 85% yields, respectively (Scheme 5).



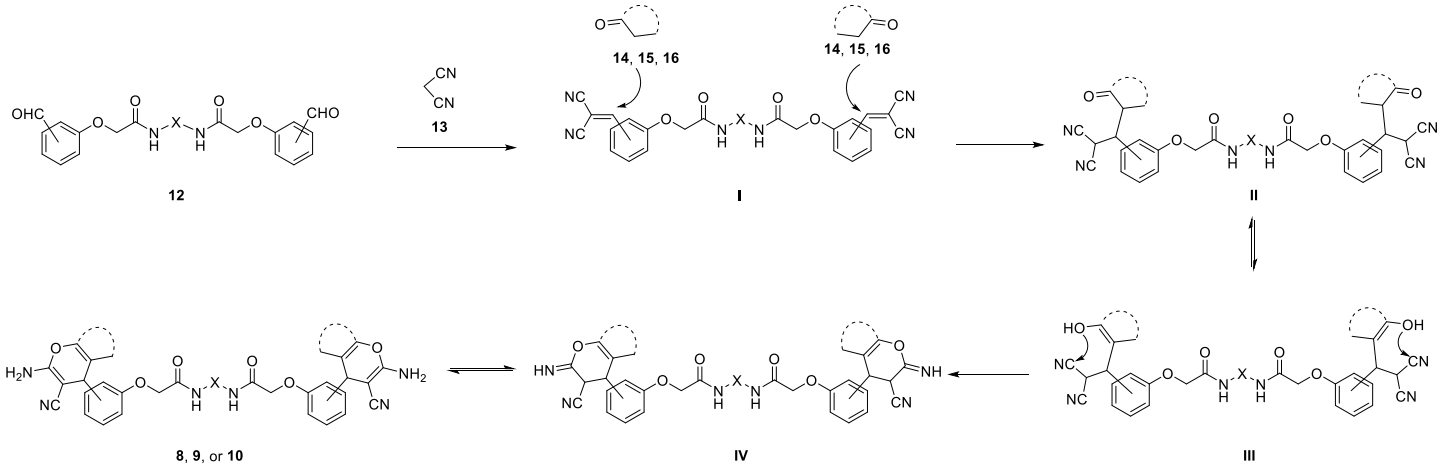
Scheme 5. Synthesis of bis(dihydropyrano[3,2-*c*]chromenes) **18a,b.**

On the other hand, attempts to synthesize bis(4*H*-chromene-3-carbonitriles) **19a,b** by a MCR of each of **17a** and **17b** with two equivalents of both of malononitrile **13** and dimedone **15** in ethanol in the presence of piperidine heated at reflux were unsuccessful. Instead, the reactions gave in both cases ethyl 4-(2-amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-4-yl)benzoate **20** in 85 and 82% yields, respectively (Scheme 6). It is suggested that compound **19a** and **19b** formed initially and then underwent transesterification under the reaction conditions.



Scheme 6. Unexpected formation of ethyl 4-(2-amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-4-yl)benzoate **20** (82-85%).

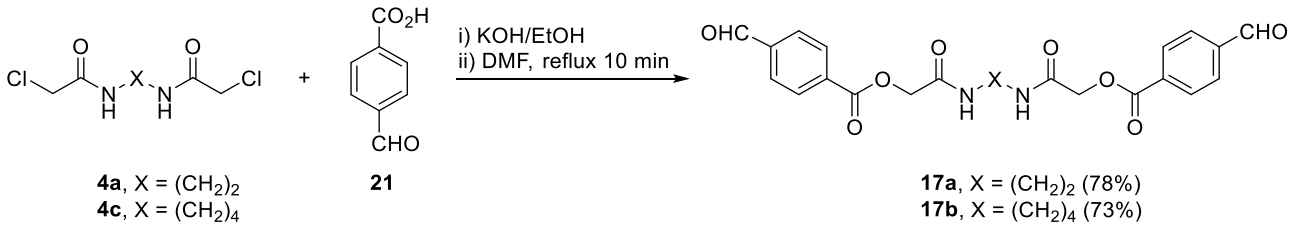
The synthesis of compounds **8**, **9** and **10** proceeded *via* initial condensation of the bis(aldehydes) **12** with two moles of malononitrile **13** to yield bis(arylidenemalononitrile) derivatives **I** which then react with two moles of active methylene compounds **14**, **15**, or **16** to yield the intermediate Michael adduct **II**. The intermediate **II** underwent tautomerization to **III** and subsequent cyclization to give the cyclic intermediates **IV**. Tautomerization of the latter intermediate **IV** led to the formation of compounds **8**, **9**, and **10**, respectively. (Scheme 7).



Scheme 7. A proposed mechanism for the synthesis of compounds **8**, **9** and **10.**

The structure of compound **20** was confirmed by spectral as well as elemental analyses. The IR spectrum of **20** showed absorption bands at *v* 3325, 3387 and 2191 cm^{-1} due to NH_2 and cyano groups, respectively. Also, its mass spectrum revealed the expected molecular ion peaks at *m/z* 366. Moreover, the ^1H NMR spectra of **20** showed a singlet signal at δ_H 4.33 attributed to pyran-H4 in addition to triplet and quartet signals at δ_H 1.28-1.32 and δ_H 4.27-4.31 characteristic for the ethoxy group. All other protons appeared at the expected chemical shifts and integral values.

The bis-aldehydes **17a** and **17b** containing amide-ester linkages were prepared by the reaction of the potassium salt of appropriate 4-formylbenzoic acid **21** with the corresponding bis(2-chloroacetamides) **4a** and **4c** in boiling DMF (Scheme 8).



Scheme 8. Synthesis of bisaldehydes **17 a, b.**

HMBC characterization

The chemical structures of compounds **8a**, **9b** and **10f** as representative examples were supported by their HMBC spectra. The HMBC spectra revealed correlation peaks in accordance with their proposed structures and thus the possibility of the other regioisomers [**8a (II)**, **9b (II)** and **10f (II)**] (Figure 2) were excluded.

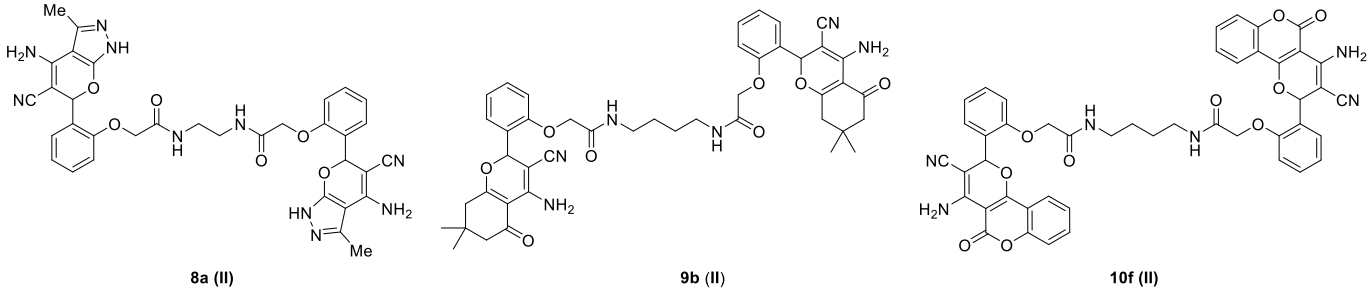
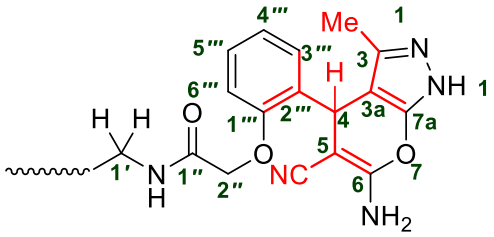


Figure 2. Structures of the possible regioisomers **8a (II)**, **9b (II)** and **10f (II).**

The full HMBC spectrum of compound **8a** (Figure 3) showed that H4 correlates with each of C3 (δ_C 135.8 [**F**]), CN (δ_C 121.6 [**C**]), C6 (δ_C 161.7 [**H**]), C7a (δ_C 155.6 [**G**]), and C3''' (δ_C 129.4 [**D**]) in addition to three ^3J-coupling with each of C5 (δ_C 57.5 [**A**]), C3a (δ_C 98.2 [**B**]) and C2''' (δ_C 132.9 [**E**]).



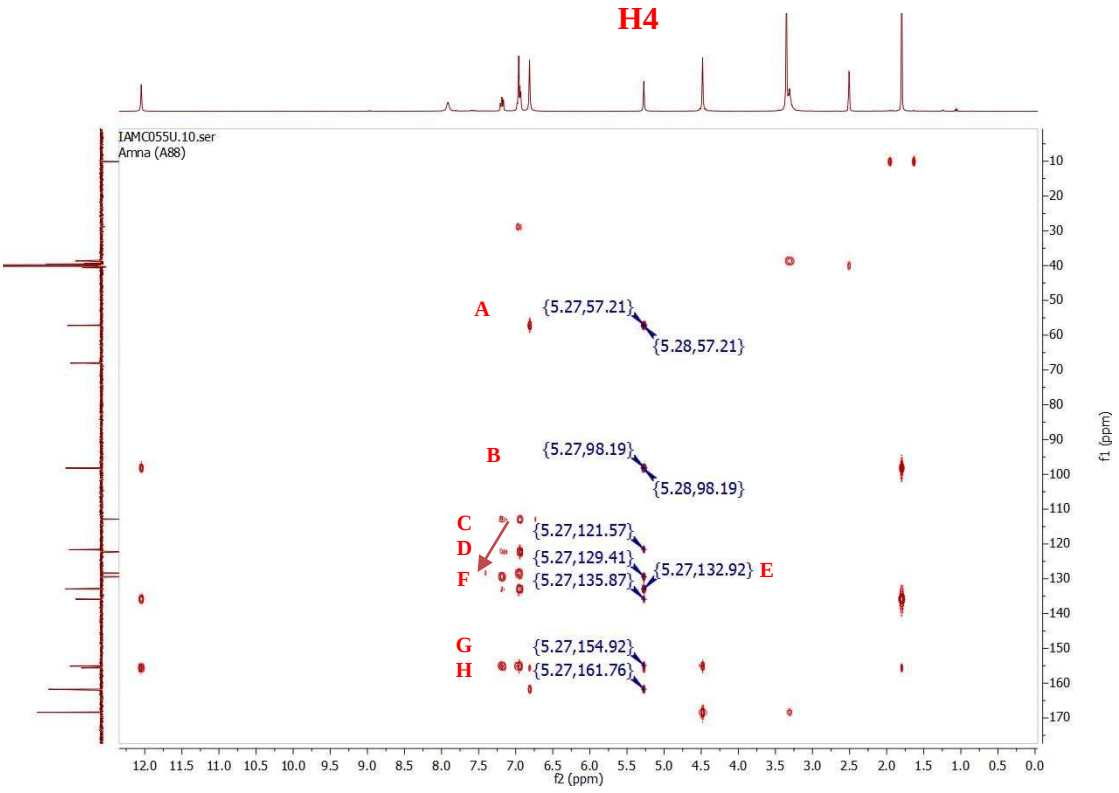
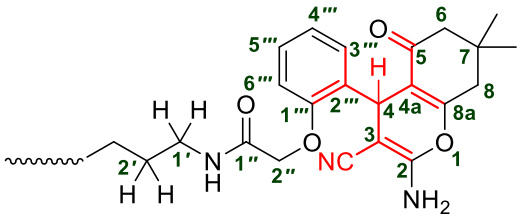


Figure 3. HMBC spectrum of compound **8a.**

The full HMBC spectrum of compound **9b** (Figure 4) revealed characteristic long-range ^{4}J-correlations between H4 (δ_H 4.77) and each of ketonic CO (C5, δ_C 196.9 [**I**]), CN (δ_C 120.6 [**I**]), C2 (δ_C 159.2 [**G**]), C8a (δ_C 163.8 [**H**]), C1''' (δ_C 154.5 [**F**]) and C3''' (δ_C 128.9 [**C**]) in addition to three ^{3}J-coupling with each of C3 (δ_C 58.3 [**A**]), C4a (δ_C 113.2 [**B**]) and C2''' (δ_C 133.6 [**E**]).



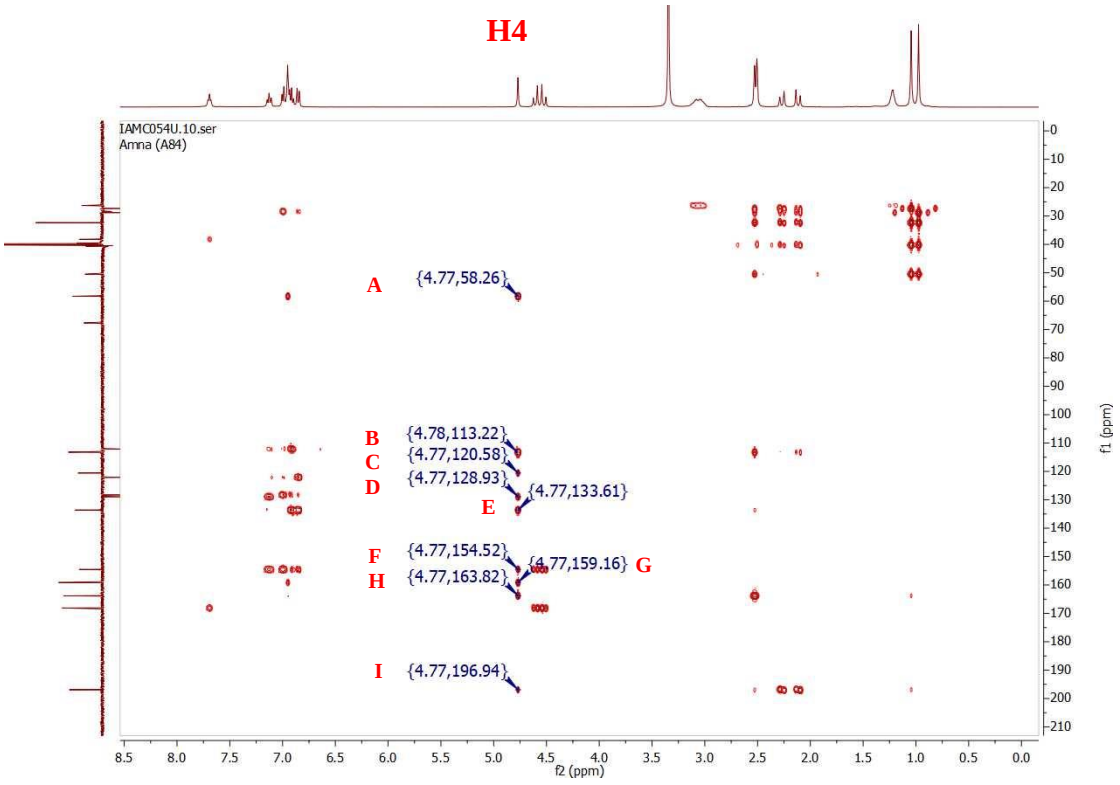
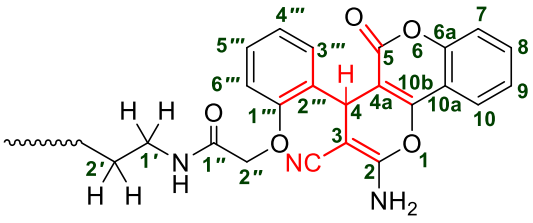


Figure 4. HMBC spectrum of compound **9b.**

Finally, the HMBC spectrum of compound **10f** (Figure 5) showed distinct long-range coupling (^4J-coupling) between H4 (δ_H 4.96) and each of CO ester (C5 δ_C 160.4 [**I**]), CN (δ_C 120.2 [**C**]), C2 (δ_C 155.1 [**G**]), C10b (δ_C 158.8 [**H**]), C1''' (δ_C 154.5 [**F**]) and C3''' (δ_C 129.7 [**D**]) besides three ^3J-coupling between H4 (δ_H 4.95) and each of C3 (δ_C 57.7 [**A**]), C4a (δ_C 104.2 [**B**]) and C2''' (δ_C 132.0 [**E**]).



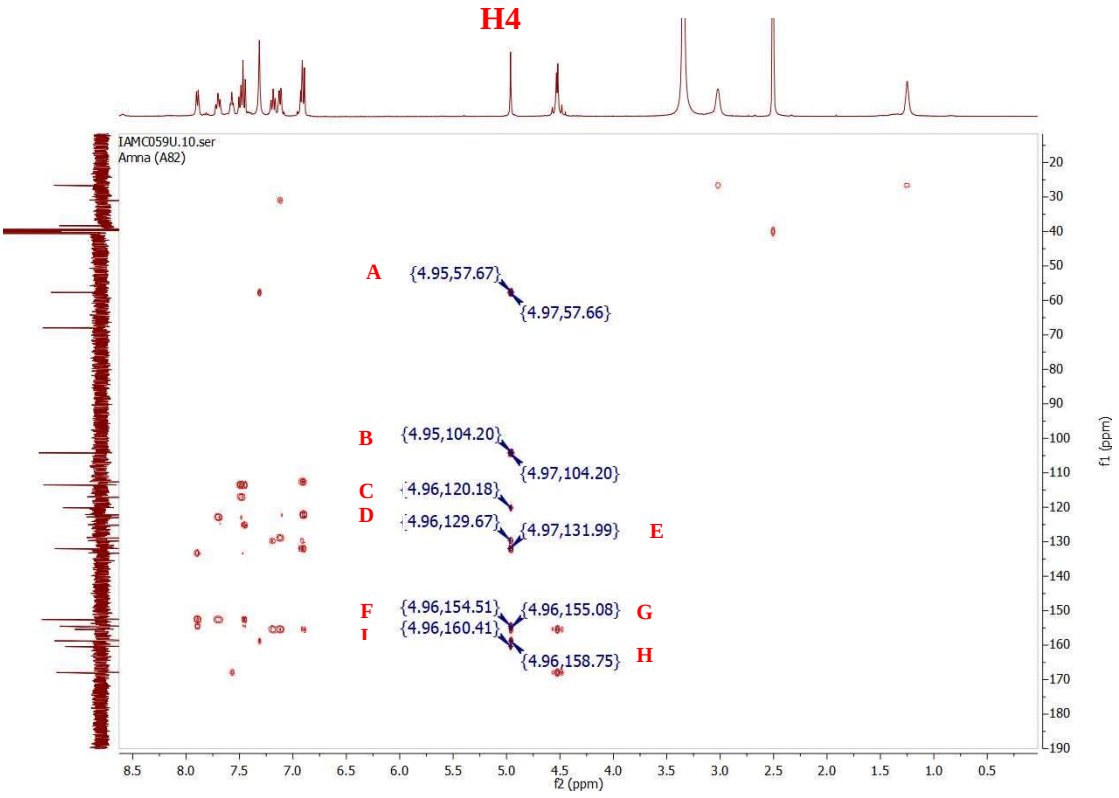


Figure 5. HMBC spectrum of **10f.**

Conclusions

We developed an efficient approach for the synthesis of new bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile), bis(4*H*-chromene-3-carbonitrile) and bis(dihydropyrano[3,2-*c*]chromene) compounds which are linked to aliphatic spacers *via* amide linkages. Structural assignments for these products were supported by the spectral data and elemental analyses. The mild reaction conditions, good yields and easily accessible starting material are the advantages of this reaction which can then be considered a useful methodology to new bis-heterocycles.

Experimental Section

General. Melting points were measured with a Stuart melting point apparatus and are 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 solvent on Varian Gemini NMR spectrometer at 300 and 75 MHz, respectively, using TMS as an internal standard. Chemical shifts were reported as δ values (ppm) while couplings constants (*J*) are measured in hertz (Hz). 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 synthesis of compounds 10a–g, 18a and 18b

A mixture of the appropriate bis-aldehydes (**12a-g**, **17a** or **17b**) (1 mmol), malononitrile **13** (2 mmol), and 4-hydroxy-2*H*-chromen-2-one **16** (2 mmol) in pyridine (10 mL) was heated at reflux for 2 h. The crude solid was collected by filtration and recrystallized from the appropriate solvent.

***N,N'*-(Ethane-1,2-diyl)bis{2-[2-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano[3,2-*c*]chromen-4-yl)phenoxy]-acetamide} (10a).** Pale yellow powder (723 mg, 90%), Mp 245-248 °C (dioxane/EtOH), IR (KBr): *v* 3325, 3279 (NH_2), 2184 (CN), 1671 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 3.27 (br, 4H, CH_2N), 4.44-4.59 (m, 4H, OCH_2), 5.02 (s, 2H, Pyran H-4), 6.86-7.85 (m, 22H, Ar-H+ $2NH_2$+2NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 30.5, 38.4, 57.8, 67.9, 104.1, 112.6, 113.3, 116.9, 120.0, 122.2, 122.7, 125.1, 128.8, 129.4, 132.3, 133.2, 152.5, 154.5, 155.2, 158.5, 160.3, 168.4. MS (EI, 70 eV): *m/z* (%) 804 [M^+]. Anal. Calcd for $C_{44}H_{32}N_6O_{10}$: C, 65.67; H, 4.01; N, 10.44 found C, 65.90; H, 4.28; N, 10.74.

***N,N'*-(Ethane-1,2-diyl)bis{2-[3-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano[3,2-*c*]chromen-4-yl)phenoxy]-acetamide} (10b).** Pale yellow powder (589 mg, 73%), Mp 195-198 °C (EtOH/dioxane), IR (KBr): *v* 3325, 3266 (NH_2), 2159 (CN), 1674 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 3.2 (br, 4H, CH_2N), 4.38 (s, 4H, OCH_2), 4.43 (s, 2H, Pyran H-4), 6.82-7.91 (m, 20H, Ar-H+ $2NH_2$), 8.15 (br, 2H, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 38.6, 39.5, 58.3, 67.4, 104.2, 113.1, 113.4, 115.2, 117.0, 119.6, 121.3, 122.9, 125.2, 130.0, 133.5, 145.4, 152.6, 153.9, 158.3, 158.4, 160.0, 168.3. MS (EI, 70 eV): *m/z* (%) 804 [M+]. Anal. Calcd for $C_{44}H_{32}N_6O_{10}$: C, 65.67; H, 4.01; N, 10.44 found C, 65.88; H, 4.24; N, 10.23.

***N,N'*-(Propane-1,3-diyl)bis{2-[2-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano[3,2-*c*]chromen-4-yl)phenoxy]-acetamide} (10c).** Pale yellow powder (711 mg, 87%), Mp 252-255 °C (dioxane/EtOH), IR (KBr): *v* 3363, 3325 (NH_2), 2198 (CN), 1674 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.40-1.53 (m, 2H, CH_2), 2.97-3.01 (m, 4H, CH_2N), 4.45-4.56 (m, 4H, OCH_2), 4.98 (s, 2H, Pyran H-4), 6.91-7.89 (m, 22H, Ar-H+$2NH_2$+2NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 28.9, 30.6, 35.9, 57.3, 67.7, 103.6, 112.3, 112.9, 116.4, 119.4, 121.6, 122.3, 124.4, 128.3, 129.0, 131.5, 132.6, 152.0, 153.9, 154.9, 158.2, 159.7, 167.4. MS (EI, 70 eV): *m/z* (%) 818 [M^+]. Anal. Calcd for $C_{45}H_{34}N_6O_{10}$: C, 66.01; H, 4.19; N, 10.26 found C, 66.27; H, 4.47; N, 10.45.

***N,N'*-(Propane-1,3-diyl)bis{2-[3-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano[3,2-*c*]chromen-4-yl)phenoxy]-acetamide} (10d).** Pale yellow powder (728 mg, 89%), Mp 190-193 °C (EtOH), IR (KBr): 3325, 3179 (NH_2), 2191 (CN), 1674 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.49-1.54 (m, 2H, CH_2), 2.99-3.01 (m, 4H, CH_2N), 4.39 (s, 4H, OCH_2), 4.43 (s, 2H, Pyran H-4), 6.84-8.07 (m, 20H, Ar-H+$2NH_2$), 8.10 (br, 2H, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 29.1, 35.7, 36.9, 57.9, 67.0, 103.8, 112.8, 112.9, 114.7, 116.5, 119.1, 120.8, 122.5, 124.7, 129.6, 132.9, 144.9, 152.1, 153.5, 157.8, 157.9, 159.5, 167.5. MS (EI, 70 eV): *m/z* (%) 818 [M^+]. Anal. Calcd for $C_{45}H_{34}N_6O_{10}$: C, 66.01; H, 4.19; N, 10.26 found C, 65.75; H, 4.41; N, 10.53.

***N,N'*-(Propane-1,3-diyl)bis{2-[4-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano[3,2-*c*]chromen-4-yl)phenoxy]-acetamide} (10e).** Pale yellow powder (744 mg, 91%), Mp 180-182 °C (MeOH), IR (KBr): 3432, 3367 (NH_2), 2199 (CN), 1674 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.47-1.52 (m, 2H, CH_2), 2.98-3.12 (m, 4H, CH_2N), 4.40 (s, 4H, OCH_2), 4.42 (s, 2H, Pyran H-4), 6.90 (d, 4H, Ar-H, *J* 8.7 Hz), 7.20 (d, 4H, Ar-H, *J* 8.7 Hz), 7.33 (s, 4H, $2NH_2$), 7.43-7.91 (m, 8H, Ar-H), 8.01 (br, 2H, NHCO). (^{13}C NMR data could not be collected owing to solubility issues in hot DMSO-d6).MS (EI, 70 eV): *m/z* (%) 818 [M^+]. Anal. Calcd for $C_{45}H_{34}N_6O_{10}$: C, 66.01; H, 4.19; N, 10.26 found C, 66.29; H, 4.43; N, 10.05.

***N,N'*-(Butane-1,4-diyl)bis{2-[2-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano[3,2-*c*]chromen-4-yl)phenoxy]-acetamide} (10f).** Pale yellow powder (774 mg, 93%), Mp 266-269 °C (dioxane/EtOH), IR (KBr): *v* 3371, 3317 (NH_2), 2191 (CN), 1667 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.25 (br, 4H, CH_2), 3.03 (br, 4H, CH_2N), 4.46-4.53 (m, 4H, OCH_2), 4.95 (s, 2H, Pyran H-4), 6.88-7.90 (m, 22H, Ar-H+$2NH_2$+2NHCO). ^{13}C NMR (75 MHz,

DMSO-d_6): δ_C 26.6, 30.9, 38.3, 57.6, 67.9, 104.2, 112.6, 113.5, 117.0, 120.1, 122.2, 122.9, 125.2, 128.9, 129.7, 131.9, 133.3, 152.6, 154.5, 155.4, 158.7, 160.4, 167.9. MS (EI, 70 eV): *m/z* (%) 832 [M^+]. Anal. Calcd for $C_{46}H_{36}N_6O_{10}$: C, 66.34; H, 4.36; N, 10.09 found C, 66.57; H, 4.17; N, 9.89.

***N,N'*-(Butane-1,4-diyl)bis{2-[3-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano[3,2-*c*]chromen-4-yl)phenoxy]-acetamide) (10g).** Pale yellow powder (724 mg, 87%), Mp 185-188 °C (EtOH), IR (KBr): *v* 3163, 3071 (NH_2), 2191 (CN), 1674 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.40 (br, 4H, CH_2), 3.10 (br, 4H, CH_2N), 4.43 (s, 4H, OCH_2), 4.44 (s, 2H, Pyran H-4), 6.82-7.92 (m, 20H, Ar-H+2NH_2), 8.04 (br, 2H, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 26.4, 36.8, 37.9, 57.8, 66.9, 103.7, 112.6, 112.8, 114.5, 116.4, 119.0, 120.6, 122.4, 124.5, 129.4, 132.8, 144.8, 152.0, 153.4, 157.7, 157.8, 159.4, 167.2. MS (EI, 70 eV): *m/z* (%) 832 [M^+]. Anal. Calcd for $C_{46}H_{36}N_6O_{10}$: C, 66.34; H, 4.36; N, 10.09 found C, 66.55; H, 4.11; N, 9.90.

[Ethane-1,2-diylbis(azanediyl)]bis(2-oxoethane-2,1-diyl)bis[4-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano-[3,2-*c*]chromen-4-yl)benzoate] (18a). Pale yellow powder (748 mg, 87%), Mp 266-269 °C (EtOH), IR (KBr): *v* 3441, 3359 (NH_2), 2199 (CN), 1671 (CO), 1641 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.20 (br, 4H, CH_2N), 4.44 (s, 4H, OCH_2), 4.70 (s, 2H, Pyran H-4), 7.24-8.0 (m, 20H, Ar-H+2NH2), 8.12 (br, 2H, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 36.9, 38.5, 57.3, 62.8, 103.1, 112.7, 116.4, 118.8, 120.4, 122.5, 124.6, 127.9, 129.7, 132.9, 148.7, 152.1, 153.6, 157.9, 159.4, 164.9, 166.8. MS (EI, 70 eV): *m/z* (%) 860 [M^+]. Anal. Calcd for $C_{46}H_{32}N_6O_{12}$: C, 64.19; H, 3.75; N, 9.76 found C, 64.45; H, 3.54; N, 9.99.

[Butane-1,4-diylbis(azanediyl)]bis(2-oxoethane-2,1-diyl)bis[4-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano-[3,2-*c*]chromen-4-yl)benzoate] (18b). Pale yellow powder (755 mg, 85%), Mp 205-208 °C (EtOH), IR (KBr): *v* 3449, 3332 (NH_2), 2191 (CN), 1628 (CO), 1674 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.43 (br, 4H, CH_2), 3.15 (br, 4H, CH_2N), 4.60 (s, 4H, OCH_2), 4.70 (s, 2H, Pyran H-4), 7.33-8.01 (m, 22H, Ar-H+2NH_2+2NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 26.4, 36.9, 38.1, 57.3, 62.9, 103.2, 112.8, 116.5, 118.8, 122.5, 124.6, 127.9, 128.1, 129.7, 130.9, 148.7, 152.2, 153.7, 157.9, 159.4, 164.9, 166.3. MS (EI, 70 eV): *m/z* (%) 888 [M^+]. Anal. Calcd for $C_{48}H_{36}N_6O_{12}$: C, 64.86; H, 4.08; N, 9.46 found C, 64.58; H, 3.87; N, 9.76.

General method for the synthesis of compounds 8a, 8b and 8c. To a mixture of bisaldehyde **12a, 12f** or **12h** (1 mmol), malononitrile **13** (0.15 g, 2.2 mmol) and pyrazolone **14** (0.31 g, 2.2 mmol) in absolute ethanol (15 mL) was added piperidine (0.2 mL) and the mixture was heated at reflux for 3 h. The crude solid was isolated by filtration and recrystallized from the appropriate solvent.

***N,N'*-(Ethane-1,2-diyl)bis{2-[2-(6-amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-4-yl)phenoxy]acetamide} (8a).** Pale yellow powder (554.3 mg, 82%), Mp >300 °C (EtOH), IR (KBr): *v* 3348, 3310 (NH_2), 2191 (CN), 1668 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.79 (s, 6H, 2CH_3), 3.29 (br, 4H, CH_2N), 4.47 (s, 4H, OCH_2), 5.25 (s, 2H, Pyran H-4), 6.77 (s, 4H, 2NH_2), 6.92-7.20 (m, 8H, Ar-H), 7.87 (br, 2H, NHCO), 12.02 (s, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 10.2, 19.8, 38.7, 67.2, 68.0, 98.2, 112.9, 121.6, 122.2, 128.4, 129.4, 132.9, 135.8, 155.1, 155.6, 161.7, 168.3. MS (EI, 70 eV): *m/z* (%) 676 [M^+]. Anal. Calcd for $C_{34}H_{32}N_{10}O_6$: C, 60.35; H, 4.77; N, 20.70 found C, 60.10, H, 4.56; N, 20.99.

***N,N'*-(Butane-1,4-diyl)bis{2-[2-(6-amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-4-yl)phenoxy]-acetamide} (8b).** Pale yellow powder (528 mg, 75%), Mp 205-208 °C (EtOH), IR (KBr): *v* 3387, 3317 (NH_2), 2191 (CN), 1651 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.43 (br, 4H, CH_2), 1.79 (s, 6H, 2CH_3), 3.16 (br,4H, CH_2N) 4.48 (s, 4H, OCH_2), 5.19 (s, 2H, Pyran H-4), 6.80 (s, 4H, 2NH_2), 6.92-7.20 (m, 8H, Ar-H), 7.64 (br, 2H, NHCO), 12.03 (s, 2H, NH). (^{13}C NMR data could not be collected owing to solubility issues in hot DMSO-d_6).

MS (EI, 70 eV): *m/z* (%) 704[M^+]. Anal. Calcd for $C_{36}H_{36}N_{10}O_6$: C, 61.35; H, 5.15; N, 19.88 found C, 61.65; H, 5.37; N, 20.17.

***N,N'*-(Butane-1,4-diyl)bis{2-[4-(6-amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-4-yl)phenoxy]-acetamide} (8c).** Pale yellow powder (493 mg, 70%), Mp >300 °C (EtOH), IR (KBr): *v* 3290, 3208 (NH_2), 2183

(CN), 1673 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.46 (br, 4H, CH_2), 1.79 (s, 6H, $2CH_3$), 3.18 (br, 4H, CH_2N), 4.67 (s, 4H, OCH_2), 5.73 (s, 2H, Pyran H-4), 6.93 (s, 4H, NH_2), 7.36 (d, 4H, Ar-H, *J* 8.4), 8.0 (d, 4H, Ar-H, *J* 8.4), 8.16 (br, 2H, NHCO), 12.18 (s, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 10.2, 25.7, 27.0, 38.5, 65.9, 63.3, 97.4, 121.0, 128.3, 128.5, 130.3, 139.5, 150.5, 161.4, 165.6, 168.9. MS (EI, 70 eV): *m/z* (%) 704 [M^+]. Anal. Calcd for $C_{36}H_{36}N_{10}O_6$: C, 61.35; H, 5.15; N, 19.88 found C, 61.10; H, 5.36; N, 19.64.

General methods for synthesis of compounds 9a, 9b and 20

To a mixture of bisaldehydes **12a, 12f** or **17a-b** (1 mmol), malononitrile **13** (2.2 mmol), and dimedone **15** (2.2 mmol) in absolute ethanol (15 mL), piperidine (0.2 mL) was added, and the reaction mixture was heated at reflux for3 h. The crude solid was isolated by filtration and recrystallized from the appropriate solvent.

***N,N'*-(Ethane-1,2-diyl)bis{2-[2-(2-amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-4-yl)phenoxy]acetamide} (9a).** Pale yellow powder (494 mg, 65%), Mp 200-203 °C (EtOH), IR (KBr): *v* 3487, 3410 (NH_2), 2175 (CN), 1674 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 0.97 (s, 6H, $2CH_3$), 1.01 (s, 6H, $2CH_3$), 2.12 (d, 2H, H8, *J* 16.2), 2.25 (d, 2H, H8, *J* 16.2), 2.50 (s, 4H, H6), 3.21 (br, 4H, CH_2N), 4.46-4.59 (m, 4H, OCH_2), 4.76 (s, 2H, Pyran H-4), 6.87-7.15 (m, 12H, Ar-H+$2NH_2$), 7.85 (br, 2H, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 27.2, 29.1, 32.2, 38.5, 39.4, 50.4, 58.4, 67.7, 112.3, 113.2, 120.5, 120.6, 122.1, 128.3, 128.7, 133.7, 154.6, 159.0, 168.5, 196.9. MS (EI, 70 eV): *m/z* (%) 760 [M^+]. Anal. Calcd for $C_{42}H_{44}N_6O_8$: C, 66.30; H, 5.83; N, 11.05 found C, 66.53; H, 6.10; N, 11.29.

***N,N'*-(Butane-1,4-diyl)bis{2-[2-(2-amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-4-yl)phenoxy]acetamide} (9b).** Pale yellow powder (646 mg, 82%), Mp 212-215 °C (EtOH), IR (KBr): *v* 3363, 3330 (NH_2), 2191 (CN), 1651 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 0.97 (s, 6H, $2CH_3$), 1.01 (s, 6H, $2CH_3$), 1.22 (br, 4H, CH_2), 2.14 (d, 2H, H8, *J* 16.2), 2.29 (d, 2H, H8, *J* 16.2), 2.50 (s, 4H, H6), 3.06 (br, 4H, CH_2N), 4.50-4.62 (m, 4H, OCH_2), 4.76 (s, 2H, Pyran H-4), 6.83-7.15 (m, 12H, Ar-H+$2NH_2$), 7.85 (br, 2H, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 26.8, 27.9, 28.3, 31.8, 38.7, 38.9, 50.0, 57.8, 67.2, 111.6, 112.7, 120.0, 121.5, 127.7, 128.4, 133.1, 154.1, 158.6, 163.3, 167.6, 196.4. MS (EI, 70 eV): *m/z* (%) 788 [M^+]. Anal. Calcd for $C_{44}H_{48}N_6O_8$: C, 66.99; H, 6.13; N, 10.65 found C, 66.71; H, 6.37; N, 10.43.

2-Amino-4-(4-ethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (20). Pale yellow powder (311 mg, 85%), Mp 252-255 °C (EtOH), IR (KBr): *v* 3367, 3325 (NH_2), 2191 (CN), 1712 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 0.95 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.28-1.32 (t, 3H, CH_3), 2.12 (d, 2H, H8, *J* 16.2), 2.29 (d, 2H, H8, *J* 16.2), 2.50 (s, 4H, H6), 4.27-4.31 (q, 2H, OCH_2), 4.33 (s, 1H, Pyran H-4), 7.06 (s, 2H, NH_2), 7.31 (d, 2H, Ar-H, *J* 8.4), 7.89 (d, 2H, Ar-H, *J* 8.4). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 14.6, 27.2, 38.8, 32.3, 36.2, 50.4, 57.9, 61.0, 112.6, 119.9, 128.1, 128.7, 129.8, 150.5, 158.9, 163.3, 165.9, 196.1. MS (EI, 70 eV): *m/z* (%) 366 [M^+]. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65 found C, 69.07; H, 6.23; N, 7.89.

General procedure for the synthesis of compounds 12a-h, 17a and **17b.** A solution of the potassium salt of salicylaldehyde, *m*-hydroxybenzaldehyde or *p*-formylbenzoic acid (10 mmol) (prepared by dissolving aldehydes **11a-c** or *p*-formylbenzoic acid **21** (10 mmol) in absolute EtOH (5 mL) containing KOH (0.56 g, 10 mmol) and evaporating the ethanol under reduced pressure) and the appropriate dichloro compounds **4a-d** (5 mmol) in DMF (10 mL) was heated at reflux for 5 min. The potassium chloride was separated by filtration, the solvent was then removed in vacuo and the remaining residue was washed with water and purified by recrystallization from the appropriate solvent to give the corresponding compounds **12a-h, 17a** and **17b**.

***N,N'*-(Ethane-1,2-diyl)bis[2-(2-formylphenoxy)acetamide] (12a).** Pale yellow plates (307 mg, 80%), Mp 182-184 °C (EtOH) (lit. Mp 188-190 °C).[42] ^1H NMR ($CDCl_3$) δ_H 3.64 (d, 4H, CH_2NH), 4.58 (s, 4H, *J* 5.80, CH_2OAr), 6.90–7.73 (m, 10H, ArH's, NH), 8.05 (br, 2H, NH), 10.11 (s, 2H, CHO).

***N,N'*-(Ethane-1,2-diyl)bis[2-(3-formylphenoxy)acetamide] (12b).** Colorless plates (289 mg, 70%), ,Mp 188-190 °C (H_2O), IR (KBr): *v* 3363 (NH), 1693 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 3.26 (br, 4 H, CH_2N), 4.55 (s, 4

H, OCH_2), 7.29-7.54 (m, 8 H, Ar-H), 8.24 (br, 2 H, NH), 9.97 (s, 2 H, CHO). (^{13}C NMR data could not be collected owing to solubility issues in hot DMSO-d_6). MS (EI, 70 eV): *m/z* 384 [M^+]. Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29 found C, 62.70; H, 55; N, 7.48.

***N,N*′-(Propane-1,3-diyl)bis[2-(2-formylphenoxy)acetamide] (12c).** Colorless powder (298.5 mg, 75%), Mp 164-166 °C (EtOH) (lit Mp 164-165 °C).[42] ^{1}H NMR ($CDCl_3$) δ_H 1.83 (t, 2H, *J* 6.0, CH_2CH_2NH), 3.42 (q, 4H, *J* 6.0, CH_2NH), 4.57 (s, 4H, OCH_2), 6.90–8.00 (m, 10H, ArH's, NH), 10.28 (s, 2H, CHO).

***N,N*′-(Propane-1,3-diyl)bis[2-(3-formylphenoxy)acetamide] (12d).** Colorless powder (294.5 mg, 74%), Mp 122-124 °C (EtOH), IR (KBr): *v* 3348 (NH), 1697 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.57-1.61 (m, 2H, CH_2), 3.10-3.17 (m, 2H, CH_2N), 4.57 (s, 4 H, OCH_2), 7.29-7.55 (m, 8H, Ar-H), 8.16 (br, 2H, NH), 9.97 (s, 2H, CHO). (^{13}C NMR data could not be collected owing to solubility issues in hot DMSO-d_6). MS (EI, 70 eV): *m/z* (%) 398 [M^+]. Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03 found C, 63.09; H, 5.26; N, 7.24.

***N,N*′-(Propane-1,3-diyl)bis[2-(4-formylphenoxy)acetamide] (12e).** Colorless powder (278.6 mg, 70%), Mp 90-92 °C (H_2O), IR (KBr): *v* 3340 (NH), 1687 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.58-1.64 (m, 2H, CH_2), 3.12-3.16 (m, 2H, CH_2N), 4.61 (s, 4H, OCH_2), 7.15 (d, 4H, Ar-H, *J* 8.7), 7.90 (d, 4H, Ar-H, *J* 8.7), 8.21 (br, 2H, NH), 9.90 (s, 2H, CHO). (^{13}C NMR data could not be collected owing to solubility issues in hot DMSO-d_6). MS (EI, 70 eV): *m/z* (%) 398 [M^+]. Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03 found C, 63.52; H, 5.39; N, 7.30.

***N,N*′-(Butane-1,4-diyl)bis[2-(2-formylphenoxy)acetamide] (12f).** Colorless powder (342 mg, 83%), Mp 180-182 °C (EtOH) (lit Mp 178 °C).[42] ^{1}H NMR ($CDCl_3$) δ_H 1.73 (br, 4H, CH_2CH_2NH), 3.40 (q, 4H, *J* 5.8, CH_2NH), 4.58 (s, 4H, OCH_2), 6.90–7.79 (m, 10H, ArH's, NH), 10.16 (s, 2H, CHO).

***N,N*′-(Butane-1,4-diyl)bis[2-(3-formylphenoxy)acetamide] (12g).** Colorless powder (305 mg, 74%), Mp 210-212 °C (EtOH), IR (KBr): *v* 3309 (NH), 1693 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): 1.41 (br, 4H, CH_2), 3.13 (br, 4H, CH_2N), 4.56 (s, 4H, OCH_2), 7.31-7.55 (m, 8H, Ar-H), 8.12 (br, 2H, NH), 9.97 (s, 2H, CHO). (^{13}C NMR data could not be collected owing to solubility issues in hot DMSO-d_6).

MS (EI, 70 eV): *m/z* (%) 412 [M^+]. Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79 found C, 64.34; H, 6.09; N, 6.93.

***N,N*′-(Butane-1,4-diyl)bis[2-(4-formylphenoxy)acetamide] (12h).** Colorless powder (325.5 mg, 79%), Mp 208-210 °C (EtOH), IR (KBr): *v* 3282 (NH), 1689 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.42 (br, 4H, CH_2), 3.11 (br, 4H, CH_2N), 4.60 (s, 4H, OCH_2), 7.12-7.15 (d, *J* 8.1, 4H, Ar-H), 7.85-7.88 (d, *J* 8.1, 4H, Ar-H), 8.24 (br, 2H, NH), 9.87 (s, 2H, CHO). (^{13}C NMR data could not be collected owing to solubility issues in hot DMSO-d_6). MS (EI, 70 eV): *m/z* (%) 412 [M^+]. Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79 found C, 64.37; H, 6.12; N, 6.90.

[Ethane-1,2-diylbis(azanediyl)]bis(2-oxoethane-2,1-diyl)bis(4-formylbenzoate) (17a). Colorless powder (343 mg, 78%), Mp 232-234 °C (EtOH/AcOH), IR (KBr): *v* 3325 (NH), 1662 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.23 (br, 4H, CH_2N), 4.75 (s, 4H, OCH_2), 8.01-8.04 (d, *J* 8.7, 4H, Ar-H), 8.20-8.23 (m, 6H, Ar-H +NH), 10.11 (s, 2H, CHO). (^{13}C NMR data could not be collected owing to solubility issues in hot DMSO-d_6). MS (EI, 70 eV): *m/z* (%) 440.12 [M^+]. Anal. Calcd for $C_{22}H_{20}N_2O_8$: C, 60.00; H, 4.58; N, 6.36 found C, 59.85; H, 4.79; N, 6.52.

[Butane-1,4-diylbis(azanediyl)]bis(2-oxoethane-2,1-diyl)bis(4-formylbenzoate) (17b). Colorless powder (342 mg, 73%), Mp 238-240 °C (EtOH/AcOH), IR (KBr): *v* 3302 (NH), 1658 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.44 (br, 4H, CH_2), 3.13 (br, 4H, CH_2N), 4.74 (s, 4H, OCH_2), 8.05-8.07 (d, *J* 8.1, 4H, Ar-H), 8.13 (br, 2H, NH), 8.20-8.23 (d, *J* 8.1, 4H, Ar-H), 10.12 (s, 2H, CHO). (^{13}C NMR data could not be collected owing to solubility issues in hot DMSO-d_6). MS (EI, 70 eV): *m/z* (%) 468 [M^+]. Anal. Calcd for $C_{24}H_{24}N_2O_8$: C, 61.53; H, 5.16; N, 5.98 found C, 61.87; H, 5.49; N, 5.76.

Supplementary Material

Supplementary material related to this article, including Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) figures for compounds **8a, 8b**; **8c**; **9a, 9b, 10a, 10b, 10c, 10d, 10e, 10f, 10g, 18a, 20** and HMBC spectra for compounds **8a, 9b** and **10f** are available in the online version of the text.

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