Synthesis of 2,2′-Diaminobischromones Using a Modified Procedure for the Rearrangement of 5-(2-Hydroxyphenyl)isoxazole to 2-Aminochromone

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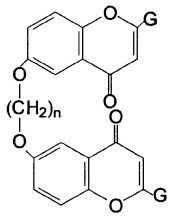
Abstract: A modified procedure for the rearrangement of 5-(2-hydroxyphenyl)isoxazoles **6a–e** to 2-aminochromones **8a–e** was developed and this procedure was utilised in the synthesis of hitherto unreported bischromones **3a–c**. The isoxazoles **6a–e** were prepared regioselectively from aminovinylketones **5**.

Key words: heterocycles, chromones, regioselectivity, rearrangements, isoxazoles

Bischromones **1** and **2** having ester or carboxylic acid functionalities at their 2 and 2′-positions (Figure 1) are capable of exhibiting various biological activities. They are inhibitors of certain types of antigen–antibody reactions, they are antiallergic and antiasthmatic and can cure hay fever, urticaria and viral infections. They can be compounded with bronchodilators when used in inhalation preparations.[1] Although a considerable amount of work has been done for the synthesis of bischromones having ester or acid functionalities at the 2- and 2′-positions,[2] little attention has been given to the synthesis of bischromones containing other functionalities.

The 2-aminochromone class of compounds are important for their antiplatelet activity.[3] Our present interest in the field of 2-aminochromone system[4] gave us an impetus to synthesise 2,2′-diaminobischromones **3** (Figure 1).



1: G = CO_2R
2: G = CO_2H
3: G = NH_2

Figure 1

The different synthetic routes to 2-aminochromone include: (i) condensation of methyl salicylate with alkyl nitrile in the presence of $NaNH_2$ in liquid ammonia, where 2-aminochromone was assigned as its tautomer 4-hydroxyiminocoumarin on the basis of elemental analysis only;[5] (ii) Curtius rearrangement of chromone 2-acid azide to 2-aminochromone via chromone 2-isocyanate;[6] (iii) thermal cyclisation of 2-hydroxybenzoylacetonitrile (**7**);[7] and (iv) tandem rearrangement and cyclisation of 5-(2-hydroxyphenyl)isoxazole (**6**) or its 3-carboxy derivative either by heating above their mps[8] or by heating in quinoline at 200 °C.[9] Considering the effect of base and heat in the conversion of 5-(2-hydroxyphenyl)isoxazole (**6**) to **8**, we intended to carry out this transformation under milder conditions by heating the isoxazole **6** in the presence of a suitable base and solvent.

With regards to the synthesis of isoxazole **6**, different groups have studied the reaction of hydroxylamine with chromone under different conditions.[10] In most of the cases, a mixture of isomeric isoxazoles along with other products were found to form. Most of these processes could not be considered as a preparative process to isoxazole **6** because of poor yield and separation problems. Synthesis of isoxazole from chalcones **5** (Ar in place of NMe_2) leads to 3-(2-hydroxyphenyl)isoxazole, a regiomer of **6**.[11] Dialkylaminovinyl ketones are found to be very good substrates for the regioselective synthesis of isoxazole.[12] Here dialkylaminovinyl ketone **5**, obtained from **4**, was utilized for the synthesis of the desired isoxazole **6** (Scheme 1). 1-(2-Hydroxyphenyl)-3-*N*,*N*-dimethylaminopropenone (**5**),[13] obtained from *o*-hydroxyacetophenone (**4**) and dimethylformamide dimethyl acetal (DMFDA), was heated with $NH_2OH{\cdot}HCl$ in ethanol under reflux for 30 min. The desired isoxazole **6** was obtained in moderate yield (60–70%). Conversion of 5-(2-hydroxyphenyl)isoxazole (**6**) to 2-aminochromone (**8**) consists of two steps: (i) base catalysed rearrangement of **6** to 2-hydroxybenzoylacetonitrile (**7**); and (ii) thermal cyclisation of **7** to **8** (Scheme 1). In order to accomplish these two steps under mild conditions, we attempted with various bases and solvents to optimize the reaction conditions (Table 1). Comparing different bases such as NH_3, pyridine, Et_3N, DABCO and solvents such as EtOH, dioxane or DMF, it was observed that heating **6** in DMF under reflux in the presence of Et_3N for ca. 8 h is the most effective and convenient method for the preparation of **8** (entries 13–17). This reaction can also be carried out at relatively lower temperature by heating under reflux in EtOH in the presence of Et_3N, but it takes around 20–25 h for completion (entries 3, 10–12). Although DABCO in place of Et_3N can effect this transformation in lower yield (entry 7), pyridine fails to effect this transformation (entries 4–6).

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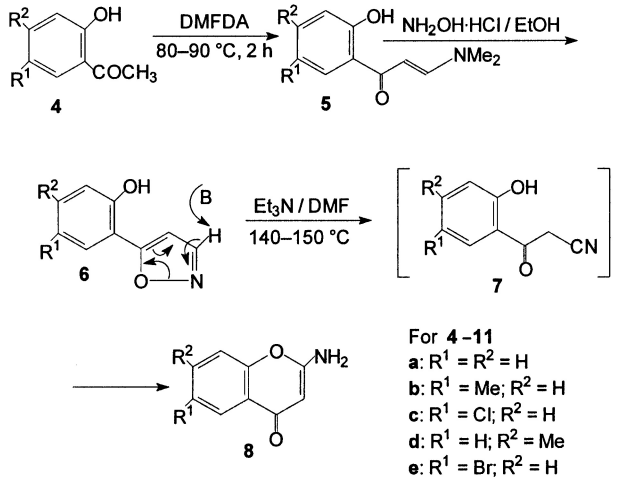
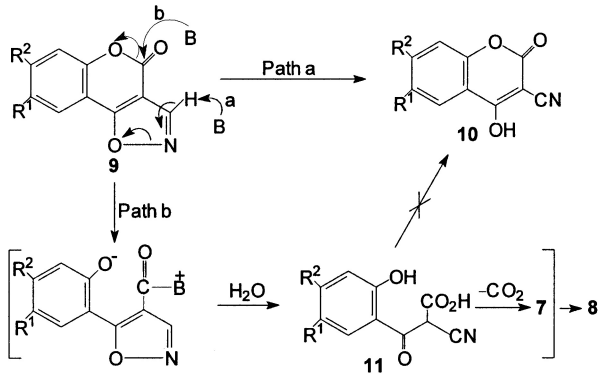


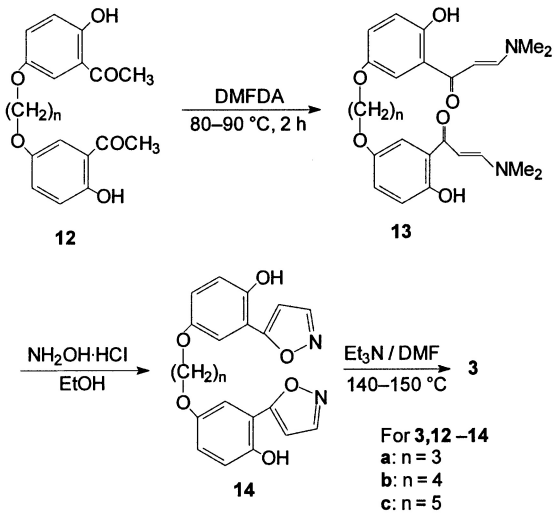
Scheme 1

Recently, we have synthesised 4*H*-1-benzopyrano[3,4-*d*]isoxazol-4-one (**9**) from 3-(*N*-alkylaminomethylene)chroman-2,4-dione.[14] In an endeavour to synthesise 4-hydroxy-2-oxo-2*H*-1-benzopyran-3-carbonitrile (**10**) from **9** (Scheme 2, Path a) by a base-catalysed isoxazole ring-opening process, **9** was heated with Et_3N in DMF under reflux for 8 h. Surprisingly, the product obtained was 2-aminochromone **8** in good yield (70–75%) instead of our expected product **10**. A plausible mechanism is depicted in Scheme 2. Of the two rings between coumarin or isoxazole, the one which opens first could not be predicted firmly; however, the facile decarboxylation of **11** may be considered more favourable entropically over pyran ring closure (Scheme 2).



Scheme 2

The convenient one-pot transformation of isoxazole **6** to 2-aminochromone **8** was then utilised in the synthesis of bischromone **3** having amine functionalities at its 2,2′-positions. Compound **12** containing two molecules of 2,5-dihydroxyacetophenone moieties tethered by an alkyl chain through ethereal linkage was the substrate of our choice. Linkage through the 5-position of 2,5-dihydroxyacetophenone leads to 6,6′-bischromone, which shows greater pharmaceutical potency than other linkages.[2] Bis(2-hydroxyacetophenone) **12** was obtained by heating a mixture of 2,5-dihydroxyacetophenone, α,ω-dibromoalkane, anhydrous K_2CO_3 and a catalytic amount of NaI in acetone under reflux for 72 h with stirring.[1] The enamino ketone **13**, obtained by treating **12** with DMFDA at 80–90 °C, was heated with $NH_2OH·HCl$ in EtOH for 2 h to get isoxazole **14**, which on heating under reflux with Et_3N in DMF for 8 h produced bischromone **3** in good to excellent yields (Scheme 3).



Scheme 3

One noticeable thing in the ^1H NMR spectra of **13**, **14** and **3** is that the methylene protons in compounds **13b**, **14b** and **3b** (having a 4-carbon chain) appear as singlets although those in compounds **12a–c**, **13a**,**c**, **14a**,**c**, and **3a**,**c** they appear with their usual multiplicities.

The recorded mps are uncorrected. IR spectra were recorded in KBr on a Beckman IR 20a and NMR spectra in DMSO-d_6 on a 300 MHz spectrometer. Light petroleum refers to the fraction with bp 60–80 °C unless stated otherwise. All chemicals used are of commercial grade and are used as such.

5-(2-Hydroxyphenyl)isoxazoles (6a–e); General Procedure

To an EtOH solution (15 mL) of enamino ketone **5** (1 mmol), $NH_2OH·HCl$ (105 mg, 1.5 mmol) was added. The reaction mixture was heated under reflux. Within 5 min, the yellow colour of the enamino ketone **5** disappeared. The reaction mixture was heated for 30 min. Solvent was removed under reduced pressure. Ice-cold H_2O (10 mL) was added to the residue, the precipitated white solid was filtered off, washed with H_2O, dried in air and recrystallised (EtOAc–light petroleum) to afford white fine crystalline solids **6**.

Compound 6a

Yield: 110 mg (68%); mp 182–184 °C (Lit.[10a] 181 °C).

IR: 3250, 1625, 1575, 1135 cm^{-1}.

^1H NMR: δ = 6.95 (d, *J* = 1.5 Hz, 1 H, 4-H), 7.15–7.30 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.70 (dd, *J* = 8.2, 2.0 Hz, 1 H, 6′-H), 8.45 (d, *J* = 1.5 Hz, 1 H, 3-H), 10.38 (s, exchangeable, 1 H, OH).

Table 1 2-Aminochromones **8** from Isoxazoles **6** by Heating in Various Solvents in the Presence of Various Bases

Entry	Isoxazole	R^1	R^2	Solvent	Base	Time (h)	Product	Yield (%)	Mp (°C)
1	**6a**	H	H	EtOH	NH_3	10	No reaction		
2	**6a**	H	H	EtOH	NH_3 + Et_3N	10	**8a**	25	270[a]
3	**6a**	H	H	EtOH	Et_3N	25	**8a**	45	274[a]
4	**6c**	Cl	H	EtOH	Pyridine	22	No reaction		
5	**6a**	H	H	Pyridine	–	10	No reaction		
6	**6c**	Cl	H	Dioxane	Pyridine	22	No reaction		
7	**6a**	H	H	EtOH	DABCO	20	**8a**	20	272[a]
8	**6a**	H	H	Dioxane	DABCO	30	Could not be isolated		
9	**6a**	H	H	Dioxane	Et_3N	20	**8a**	30	274[a]
10	**6b**	Me	H	EtOH	Et_3N	25	**8b**	55	320[b]
11	**6c**	Cl	H	EtOH	Et_3N	22	**8c**	57	>325
12	**6d**	H	Me	EtOH	Et_3N	25	**8d**	67	300–302[c]
13	**6a**	H	H	DMF	Et_3N	7	**8a**	72	272–274[a]
14	**6b**	Me	H	DMF	Et_3N	8	**8b**	75	320–322[b]
15	**6c**	Cl	H	DMF	Et_3N	8	**8c**	77	>325
16	**6d**	H	Me	DMF	Et_3N	8	**8d**	81	302–304[c]
17	**6e**	Br	H	DMF	Et_3N	8	**8e**	78	>325

[a] Lit.[5] mp 275 °C.
[b] Lit.[9] mp 323–325 °C.
[c] Lit.[9] mp 304–306 °C.

Compound 6b
Yield: 110 mg (65%); mp 172–174 °C (Lit.[9] double mp 171–172 °C and 324–26 °C).

IR: 3125, 1625, 1590, 1120 cm^{-1}.

^1H NMR: δ = 2.38 (s, 3 H, CH_3), 6.94 (d, *J* = 1.4 Hz, 1 H, 4-H), 7.13–7.30 (m, 2 H, 3′-H and 4′-H), 7.71 (d, *J* = 2.0 Hz, 1 H, 6′-H), 8.66 (d, *J* = 1.4 Hz, 1 H, 3-H), 10.40 (s, exchangeable, 1 H, OH).

Compound 6c
Yield: 135 mg (70%); mp 196–198 °C.

IR: 3240, 1637, 1550, 1148 cm^{-1}.

^1H NMR: δ = 6.92 (d, *J* = 1.6 Hz, 1 H, 4-H), 7.30–7.55 (m, 2 H, 3′-H, 4′-H), 7.91 (d, *J* = 1.9 Hz, 1 H, 6′-H), 8.65 (d, *J* = 1.6 Hz, 1 H, 3-H), 10.42 (s, exchangeable, 1 H, OH).

Anal. Calcd for $C_9H_6NClO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.30; H, 3.12; N, 7.20.

Compound 6d
Yield: 105 mg (60%); mp 187–189 °C (Lit.[9] double mp 189–190 °C and 303–306 °C).

IR: 3210, 1630, 1585, 1125 cm^{-1}.

^1H NMR: δ = 2.32 (s, 3 H, CH_3), 6.90 (d, *J* = 1.5 Hz, 1 H, 4-H), 7.00–7.20 (m, 2 H, 3′-H and 5′-H), 7.72 (d, *J* = 8.1 Hz, 1 H, 6′-H), 8.55 (d, *J* = 1.5 Hz, 1 H, 3-H), 10.45 (s, exchangeable, 1 H, OH).

Compound 6e
Yield: 175 mg (72%); mp 208–210 °C.

IR: 3151, 1606, 1473, 1407, 1299 cm^{-1}.

^1H NMR: δ = 6.92 (d, *J* = 1.8 Hz, 1 H, 4-H), 7.01 (d, *J* = 8.7 Hz, 1 H, 3′-H), 7.47 (dd, *J* = 8.7, 2.5 Hz, 1 H, 4′-H), 7.86 (d, *J* = 2.5 Hz, 1 H, 6′-H), 8.64 (d, *J* = 1.8 Hz, 1 H, 3-H), 10.96 (s, exchangeable, 1 H, OH).

Anal. Calcd for $C_9H_6NBrO_2$: C, 45.02; H, 2.51; N, 5.83. Found: C, 44.70; H, 2.77; N, 5.83.

2-Amino-4*H*-1-benzopyran-4-ones (8a–e); General Procedure
Et_3N (200 mg, 2 mmol) was added to a solution of isoxazole **6a–e** (1 mmol) in DMF (10 mL). The reaction mixture was heated in an oil bath maintaining the bath temperature at 140–150 °C for 8 h. DMF was removed under reduced pressure and ice-cold H_2O was added to the residue. The separated solid was filtered off and recrystallised from MeOH to get faintly yellow crystalline compounds **8**.

Compound 8a
Yield: 115 mg (72%); mp 272–274 °C (Lit.[5] 275 °C).

IR: 3303, 3098, 1644, 1609, 1546, 1276, 755 cm^{-1}.

^1H NMR: δ = 5.19 (s, 1 H, 3-H), 7.32–7.38 (m, 2 H, 6-H, 8-H), 7.53 (s, exchangeable, 2 H, NH_2), 7.57–7.63 (m, 1 H, 7-H), 7.90 (dd, *J* = 7.7, 1.4 Hz, 1 H, 5-H).

Compound 8b
Yield: 130 mg (75%); mp 320–322 °C (Lit.[9] 323–325 °C).

IR: 3283, 3059, 1655, 1613, 1557, 1276, 809 cm^{-1}.

^1H NMR: δ = 2.37 (s, 3 H, CH_3), 5.15 (s, 1 H, 3-H), 7.25 (d, *J* = 8.2 Hz, 1 H, 8-H), 7.41 (dd, *J* = 8.2, 1.0 Hz, 1 H, 7-H), 7.45 (s, exchangeable, 2 H, NH_2), 7.69 (d, *J* = 1.0 Hz, 1 H, 5-H).

Compound 8c
Yield: 150 mg (77%); mp >325 °C.

IR: 3280, 3060, 1660, 1615, 1550, 1265, 810 cm^{-1}.

^1H NMR: δ = 5.20 (s, 1 H, 3-H), 7.42 (d, *J* = 8.8 Hz, 1 H, 8-H), 7.64 (dd, *J* = 8.8, 2.5 Hz, 1 H, 7-H), 7.68 (s, exchangeable, 2 H, NH_2), 7.82 (d, *J* = 2.5 Hz, 1 H, 5-H).

Anal. Calcd for $C_9H_6NClO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.28; H, 3.12; N, 7.21.

Compound 8d
Yield: 140 mg (81%); mp 302–304 °C (Lit.[9] 304–306 °C).

IR: 3273, 3055, 1658, 1610, 1545, 1260, 812 cm^{-1}.

^1H NMR: δ = 2.46 (s, 3 H, CH_3), 5.16 (s, 1 H, 3-H), 7.12 (dd, *J* = 8.2, 1.0 Hz, 1 H, 6-H), 7.15 (d, *J* = 1.0 Hz, 1 H, 8-H), 7.46 (s, exchangeable, 2 H, NH_2), 7.75 (d, *J* = 8.2 Hz, 1 H, 5-H).

Compound 8e
Yield: 190 mg (78%); mp >325 °C.

IR: 3265, 3128, 1653, 1543, 1284, 817 cm^{-1}.

^1H NMR: δ = 5.19 (s, 1 H, 3-H), 7.37 (d, *J* = 8.7 Hz, 1 H, 8-H), 7.70 (s, exchangeable, 2 H, NH_2), 7.75 (dd, *J* = 8.7, 2.4 Hz, 1 H, 7-H), 7.95 (d, *J* = 2.4 Hz, 1 H, 5-H).

Anal. Calcd for $C_9H_6NBrO_2$: C, 45.02; H, 2.51; N, 5.83. Found: C, 45.01; H, 2.76; N, 5.77.

Treatment of 4*H*-1-Benzopyrano[3,4-d]isoxazol-4-ones (9a–b) with Et_3N in DMF
To a solution of 1-benzopyranoisoxazole **9a**–**b** (0.5 mmol) in DMF (5 mL), Et_3N (100 mg, 1 mmol) was added and the resultant solution was heated under reflux for 8 h. Solvent from the reaction mixture was removed under reduced pressure. Cold H_2O (10 mL) was added to the residue. The precipitated solid was filtered off, washed with H_2O, dried in air and recrystallised (MeOH) to afford faint yellow crystalline compounds **8a**–**b**, identical in all respects to those produced from **6a**,**b**, respectively.

1,1′-{(α,ω-Alkanediol)bis[oxy(4-hydroxyphen)-3-yl]}bis(3-*N*,*N*-dimethylaminopropenones) (13a–c); General Procedure
A suspension of bis(2-hydroxyacetophenone) **12** (1 mmol) in DMFDA (2 mL) was stirred at 80–90 °C. A clear solution was observed after 15 min. Within 30 min, a yellow precipitate began to appear. After stirring for 2 h in these conditions, the reaction mixture was filtered, washed with light petroleum and dried. The solid was recrystallised from $CHCl_3$ to afford bright yellow solids **13**.

Compound 13a
Yield: 410 mg (90%); mp 202–204 °C.

IR: 3280, 2950, 2870, 1640, 1535, 1285 cm^{-1}.

^1H NMR: δ = 2.23 (quin, *J* = 6.0 Hz, 2 H, CH_2), 2.93 (s, 6 H, 2 NMe), 3.18 (s, 6 H, 2 NMe), 4.15 (t, *J* = 6.0 Hz, 4 H, 2 OCH_2), 5.67 (d, *J* = 11.3 Hz, 2 H, 2 C*H*=CHNMe$_2$), 6.87 (d, *J* = 8.9 Hz, 2 H, 2 3-H), 7.02 (dd, *J* = 8.9, 2.8 Hz, 2 H, 2 4-H), 7.21 (d, *J* = 2.8 Hz, 2 H, 2 6-H), 7.87 (d, *J* = 11.3 Hz, 2 H, 2 CH=C*H*NMe$_2$), 11.85 (s, exchangeable, 2 H, 2 OH).

Anal. Calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 66.01; H, 6.61; N, 6.10.

Compound 13b
Yield: 400 mg (85%); mp 212–214 °C.

IR: 3300, 2940, 2870, 1636, 1533, 1285 cm^{-1}.

^1H NMR: δ = 1.97 (s, 4 H, 2 CH_2), 2.93 (s, 6 H, 2 NMe), 3.19 (s, 6 H, 2 NMe), 4.03 (s, 4 H, 2 OCH_2), 5.67 (d, *J* = 11.1 Hz, 2 H, 2 C*H*=CHNMe$_2$), 6.87 (d, *J* = 8.9 Hz, 2 H, 2 3-H), 7.00 (dd, *J* = 8.9, 2.6 Hz, 2 H, 2 4-H), 7.19 (d, *J* = 2.6 Hz, 2 H, 2 6-H), 7.86 (d, *J* = 11.3 Hz, 2 H, 2 CH=C*H*NMe$_2$), 11.82 (s, exchangeable, 2 H, 2 OH).

Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.58; H, 6.90; N, 5.90.

Compound 13c
Yield: 450 mg (93%); mp 168 °C.

IR: 3250, 2938, 2872, 1638, 1534, 1280 cm^{-1}.

^1H NMR: δ = 1.64–1.72 (m, 2 H, CH_2), 1.81–1.90 (m, 4 H, 2 CH_2), 2.94 (s, 6 H, 2 NMe), 3.18 (s, 6 H, 2 NMe), 3.97 (t, *J* = 6.2 Hz, 4 H, 2 OCH_2), 5.69 (d, *J* = 11.6 Hz, 2 H, 2 C*H*=CHNMe$_2$), 6.86 (d, *J* = 8.9 Hz, 2 H, 2 3-H), 6.99 (dd, *J* = 8.9, 2.9 Hz, 2 H, 2 4-H), 7.19 (d, *J* = 2.9 Hz, 2 H, 2 6-H), 7.87 (d, *J* = 11.6 Hz, 2 H, 2 CH=C*H*NMe$_2$), 11.80 (s, exchangeable, 2 H, 2 OH).

Anal. Calcd for $C_{27}H_{34}N_2O_6$: C, 67.20; H, 7.10; N, 5.80. Found: C, 67.25; H, 7.14; N, 5.90.

5,5′-{(α,ω-Alkanediol)bis[oxy(4-hydroxyphen)-3-yl]}bisisoxazoles (14a–c); General Procedure
To a suspension of aminovinyl ketone **13** (1 mmol) in EtOH (20 mL), $NH_2OH{\cdot}HCl$ (210 mg, 3 mmol) was added and the reaction mixture was heated under reflux. Within 5 min, a clear solution was obtained and after 30 min a white solid began to separate. Heating was continued for 2 h under these conditions. The separated solid was filtered off, washed with H_2O, dried in air and recrystallised (EtOAc–MeOH, 1:1) to afford white solids **14**.

Compound 14a
Yield: 250 mg (63%); mp 210–212 °C.

IR: 3135, 2965, 2890, 1575, 1516, 1480, 1210 cm^{-1}.

^1H NMR: δ = 2.13–2.17 (m, 2 H, CH_2), 4.13 (t, *J* = 6.0 Hz, 4 H, 2 OCH_2), 6.88 (d, *J* = 1.7 Hz, 2 H, 2 4-H), 6.97–7.00 [m, 4 H, 2 (3′-H + 4′ H)], 7.32 (d, *J* = 1.0 Hz, 2 H, 2 6′-H), 8.59 (d, *J* = 1.7 Hz, 2 H, 2 3-H), 10.17 (s, exchangeable, 2 H, 2 OH).

Anal. Calcd for $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.60; N, 7.10. Found: C, 63.90; H, 4.55; N, 7.00.

Compound 14b
Yield: 285 mg (70%); mp 232–234 °C.

IR: 3136, 2959, 2886, 1574, 1516, 1477, 1209 cm^{-1}.

^1H NMR: δ = 2.50 (s, 4 H, 2 CH_2), 4.03 (s, 4 H, 2 OCH_2), 6.88 (d, *J* = 1.5 Hz, 2 H, 2 4-H), 6.94–6.96 [m, 4 H, 2 (3′-H + 4′ H)], 7.30 (d, *J* = 1.0 Hz, 2 H, 2 6′-H), 8.60 (d, *J* = 1.5 Hz, 2 H, 2 3-H), 10.13 (s, exchangeable, 2 H, 2 OH).

Anal. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.66; H, 4.90; N, 6.80.

Compound 14c
Yield: 275 mg (65%); mp 210–212 °C.

IR: 3130, 2955, 2880, 1570, 1520, 1480, 1210 cm^{-1}.

^1H NMR: δ = 1.58–1.63 (m, 2 H, CH_2), 1.74–1.80 (m, 4 H, 2 CH_2), 3.98 (t, *J* = 6.2 Hz, 4 H, 2 OCH_2), 6.88 (d, *J* = 1.8 Hz, 2 H, 2 4-H),

6.93–6.95 [m, 4 H, 2 (3′-H + 4′ H)], 7.28 (d, *J* = 1.2 Hz, 2 H, 2 6′-H), 8.59 (d, *J* = 1.8 Hz, 2 H, 2 3-H), 10.13 (s, exchangeable, 2 H, 2 OH).

Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.42; H, 5.30; N, 6.60.

6,6′-[(α,ω-Alkanediol)bis(oxy)]bis(2-amino-4*H*-1-benzopyran-4-ones) (3a–c); General Procedure

Excess of Et_3N (1 mL, ca. 7 mmol) was added to a solution of bis-isoxazole **14** (1 mmol) in DMF (10 mL). The reaction mixture was heated under reflux in an oil bath at 140–150 °C for 8 h. The separated solid was filtered off and recrystallised (EtOAc–MeOH, 1:1) to afford faint yellow solids **3**.

Compound 3a

Yield: 340 mg (86%); mp 322–324 °C.

IR: 3300, 3075, 2935, 1650, 1610, 1560, 1455, 1280 cm^{-1}.

^1H NMR: δ = 2.21–2.23 (m, 2 H, CH_2), 4.20 (t, *J* = 5.6 Hz, 4 H, 2 OCH_2), 5.17 (s, 2 H, 2 3-H), 7.20 (dd, *J* = 8.7, 2.2 Hz, 2 H, 2 7-H), 7.31 (d, *J* = 8.7 Hz, 2 H, 2 8-H), 7.37 (d, *J* = 2.2 Hz, 2 H, 2 5-H), 7.46 (s, exchangeable, 4 H, 2 NH_2).

MS (positive ion electrospray): *m*/*z* = 417 ($M + Na^+$).

Anal. Calcd for $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.60; N, 7.10. Found: C, 63.99; H, 4.65; N, 7.15.

Acetate of 3a

Mp 298–300 °C.

^1H NMR: δ = 2.14 (s, 6 H, 2 CH_3), 2.22–2.24 (m, 2 H, CH_2), 4.25 (t, *J* = 5.0 Hz, 4 H, 2 OCH_2), 6.76 (s, 2 H, 2 3-H), 7.36–7.48 [m, 6 H, 2 (5-H + 7-H + 8-H)], 11.22 (br s, exchangeable, 2 H, 2 NHCO).

Compound 3b

Yield: 390 mg (96%); mp >325 °C.

IR: 3298, 3084, 2937, 1649, 1610, 1558, 1456, 1278 cm^{-1}.

^1H NMR: δ = 1.91 (s, 4 H, 2 CH_2), 4.09 (s, 4 H, 2 OCH_2), 5.16 (s, 2 H, 2 3-H), 7.17 (dd, *J* = 8.9, 2.7 Hz, 2 H, 2 7-H), 7.31 (d, *J* = 8.9 Hz, 2 H, 2 8-H), 7.35 (d, *J* = 2.7 Hz, 2 H, 2 5-H), 7.44 (s, exchangeable, 4 H, 2 NH_2).

MS (positive ion electrospray): *m*/*z* = 431 $(M + Na)^+$.

Anal. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.65; H, 4.90; N, 6.90.

Compound 3c

Yield: 340 mg (80%); mp >325 °C.

IR: 3300, 3070, 2933, 1651, 1612, 1556, 1456, 1278 cm^{-1}.

^1H NMR: δ = 1.58–1.62 (m, 2 H, CH_2), 1.77–1.83 (m, 4 H, 2 CH_2), 4.02 (t, *J* = 6.2 Hz, 4 H, 2 OCH_2), 5.17 (s, 2 H, 2 3-H), 7.13 (dd, *J* = 8.9, 2.9 Hz, 2 H, 2 7-H), 7.28 (d, *J* = 8.9 Hz, 2 H, 2 8-H), 7.33 (d, *J* = 2.9 Hz, 2 H, 2 5-H), 7.44 (s, exchangeable, 4 H, 2 NH_2).

MS (positive ion electrospray): *m*/*z* = 445 ($M + Na^+$).

Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.20; H, 5.10; N, 6.55.

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