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Uncatalyzed addition of indoles and *N*-methylpyrrole to 3-formylchromones: synthesis and some reactions of (chromon-3-yl)bis(indol-3-yl)methanes and *E*-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-ones

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ABSTRACT

(Chromon-3-yl)bis(indol-3-yl)methanes and *E*-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-ones have been obtained in good yields from 3-formylchromones on reaction with indoles and *N*-methylpyrrole under solvent-free conditions. Reactions of (chromon-3-yl)bis(indol-3-yl)methanes with guanidine carbonate and hydrazine hydrate proceed with the participation of the chromone ring system and lead to the formation of the corresponding pyrimidines and pyrazoles bearing the bis(indol-3-yl)-methyl moiety.

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1. Introduction

3-Formylchromones **1** are an important and well-studied class of 3-substituted chromones, which can serve as the starting materials for the syntheses of a broad range of heterocyclic systems due to the presence of three electrophilic centers in their molecules (the C-2 and C-4 atoms of the chromone system and the carbonyl carbon of 3-formyl group).[1] The reactivity of 3-formylchromones **1** is of considerable current interest. Most pertinent to the present research are the reactions involving the additions of *C*-mononucleophiles to **1** (with the exception of active methylene compounds). To the best of our knowledge, there are only two related examples reported in the literature. Harnisch has investigated the addition of tertiary aromatic amines to the formyl group of 3-formylchromone **1** and obtained 3-benzhydrylchromones **2**, which were subsequently oxidized with $Pb(OAc)_4$ in AcOH to the cationic (chromon-3-yl)diarylmethine dyes **3**.[2] Very recently,[3] there has been a communication of the reaction of **1** with a range of tertiary aromatic amines, anisole, and 1,3-dimethoxybenzene to give 3-benzhydrylchromones **2**, which by the oxidation with *p*-chloranil afford novel acetals, 3-(diarylmethylene)-2-methoxychroman-4-ones **4**. Oxidation of pyrazoles with benzhydryl moiety **5**, derived from **2** and hydrazines, gave 4,4-diaryl-2,4-dihydrochromeno[4,3-*c*]pyrazoles **6** (Fig. 1).[3]

However, published data on the reactions of 3-formylchromones **1** with azoles, such as indoles and pyrroles, are scarce. It is known that they react with pyrrole at the aldehyde group to form *meso*-tetrakis(chromon-3-yl)porphyrins.[4] At the same time, indoles and pyrroles react readily with aldehydes and ketones to form bis(indolyl)methane[5] and dipyrromethane[6] derivatives, which are important bioactive metabolites of terrestrial and marine origin.[7] Chromones are more widely distributed in nature, especially in the plant kingdom, and exhibit low toxicity along with a wide spectrum of useful properties. They have been shown to be tyrosine and protein kinase C inhibitors, as well as antifungal, antiviral, antitubulin, and antihypertensive agents. Chromone derivatives are also active at benzodiazepine receptors and on lipoxygenases and cyclooxygenases.[8] We envisaged that the combination of a chromone system with indole or pyrrole rings would allow the development of a new class of biologically active molecules and useful synthetic building blocks in organic and medicinal chemistry.

In this context, our attention was drawn to the fact that, although 1,2-addition of nucleophilic indoles and pyrroles to

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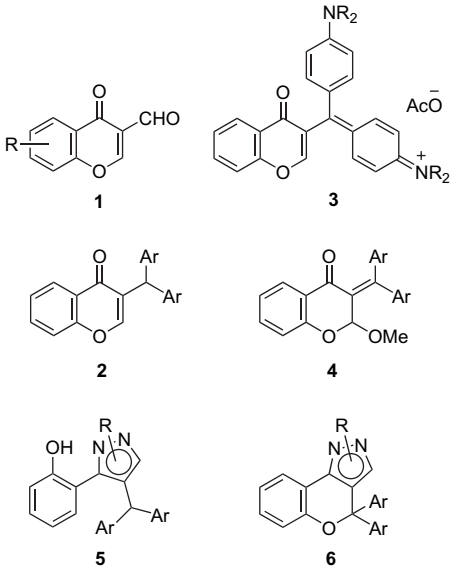
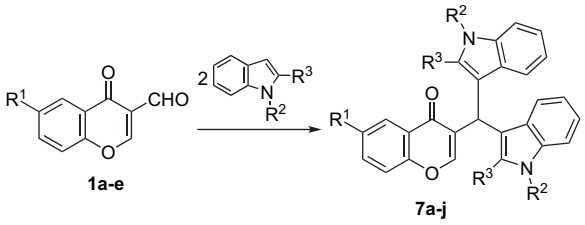


Figure 1.



Chromone	R^1	R^2	R^3	Product	Yield (%)
1a	H	H	H	**7a**	54
1a	H	Me	H	**7b**	65
1a	H	H	Me	**7c**	37
1b	Me	H	H	**7d**	68
1b	Me	Me	H	**7e**	78
1b	Me	H	Me	**7f**	51
1c	MeO	H	H	**7g**	79
1c	MeO	H	Me	**7h**	61
1d	Cl	H	H	**7i**	55
1e	NO_2	H	H	**7j**	58

Scheme 1.

carbonyl compounds and tertiary aromatic amines to 3-formylchromones **1** has been well studied,[2–6] the use of **1** as an acceptor in the reaction with azoles as nucleophiles has never been reported. Based on the literature data,[1] one could assume that the reactions of π-electron-rich azoles and 3-formylchromones **1** would proceed either at the CHO group (1,2-addition) or at the C-2 atom (1,4-addition). The latter reaction is usually accompanied by pyrone ring opening followed by recyclization due to the phenolic hydroxyl and aldehyde groups. We have shown quite recently[9] that the reaction of 3-(polyfluoroacyl)chromones with indoles and *N*-methylpyrrole proceeds solely through 1,4-addition, and after recyclization involving the OH and R^FCO groups, affords a mixture of *Z*- and *E*-isomers of 3-(azolylmethylene)-2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones substantially favoring the *Z*-isomer. At the same time, (chromon-3-yl)bis(indol-3-yl)methanes and *E*-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-ones have been obtained in good yields from 3-formylchromones **1** on reaction with indoles and *N*-methylpyrrole under solvent-free conditions.[10] Herein, we report full details of this study. In addition to our preliminary communication,[10] some novel (chromon-3-yl)bis(indol-3-yl)methanes as well as pyrimidines and pyrazoles bearing bis(indol-3-yl)methyl moiety have been prepared.

2. Results and discussion

We found that, unlike 3-(polyfluoroacyl)chromones,[9] 3-formylchromones **1a**–**c** react with excess indole, 1-methyl- or 2-methylindole (3 equiv) to give (chromon-3-yl)bis(indol-3-yl)methanes **7a**–**h**. The reaction occurs at 85–90 °C in 5 h and requires no solvent or catalyst. As in the case of aromatic aldehydes, this reaction does not stop after mono-addition but affords bis-adducts **7a**–**h** in 37–79% yields (Scheme 1). The same compounds were formed but in lower yields when 1 equiv of indole was used (e.g., **7e** was obtained in 52% yield). Since the 3-position of indole is the preferred site for electrophilic reactions, substitution occurred exclusively at this position, and *N*-substituted products were not detected in the reaction mixture. Note that under classical conditions (reflux in solvent in the presence of acid or base), 3-formylchromones reacted with indoles to give complicated mixtures of products.

The reaction turned out to be very sensitive to the nature of the substituent at C-6 of **1**. Reaction of 6-chloro-3-formylchromone **1d** and 3-formyl-6-nitrochromone **1e** with indole under solvent-free conditions gave polymeric products, which were insoluble in standard solvents. However, the use of butanol as solvent in the presence of catalytic $HClO_4$ at ~20 °C made it possible to produce bis-adduct **7i** in 55% yield from **1d** and indole. Under similar conditions, the reaction of indole with **1e** resulted in resinification of the reaction mixture, and bis-adduct **7j** was synthesized on heating of the reactants in water at 85–90 °C for 5 h as a mixture with *E*-2-hydroxy-6-nitro-3-(indol-3-ylmethylene)chroman-4-one **8a** in variable amounts (for **1d** these conditions were inappropriate, and only a polymeric product was isolated instead of **7i**). The solvent-free reaction between **1e** and *N*-methylindole afforded a mixture of bis-adduct **7k** and *E*-2-hydroxy-6-nitro-3-(1-methylindol-3-ylmethylene)chroman-4-one **8b** in a ratio of 33:67. It is noteworthy that the formation of **7** can be explained by both 1,2- and 1,4-addition reactions, whereas structure **8** indicates unambiguous attack at C-2 followed by recyclization involving the phenolic OH and CHO group (Fig. 2).

A similar reaction of 6,8-dibromo-3-formylchromone **1f** with indole proceeded exclusively via 1,4-addition followed by recyclization to form a mixture of *E*-**8c** (91%) and *Z*-**8c** (9%) (Scheme 2). An attempt to obtain the corresponding mono- or bis-adduct by treatment of 2-amino-3-formylchromone[11] with indole under solvent-free conditions failed and only starting material was recovered. Reaction of 3-cyanochromone with indole in refluxing pyridine gave a high melting solid (mp ~315 °C) in low yield, which was insoluble in solvents such as DMSO, DMF, AcOH, and acetone, which was not investigated in detail.

In the case of chromones **1a**–**d**, we suppose that indoles initially attack the CHO group at the 3-position, as occurs in the case of

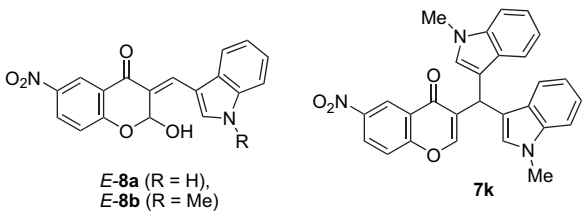
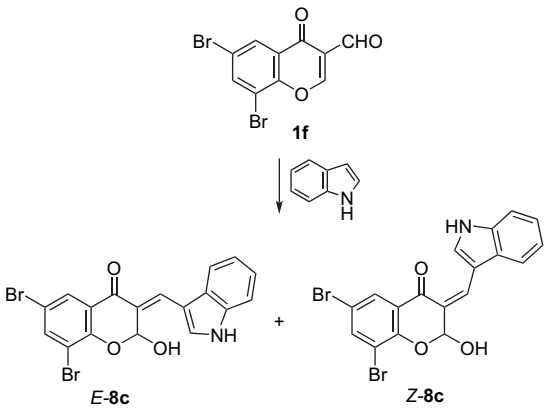


Figure 2.

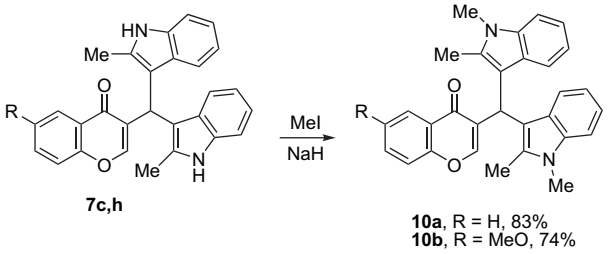


Scheme 2.

aromatic aldehydes.[5] A plausible pathway includes nucleophilic 1,2-addition of indoles to give compounds **9**, which through highly delocalized cation **A** afford bis-adducts **7**. However, the presence of electron-withdrawing substituents on the benzene ring of the chromones favors the alternative nucleophilic 1,4-addition and inhibits the formation of bis-adducts **7**. This pathway includes the Michael addition of indoles to the C-2 atom with concomitant opening of the pyrone ring and subsequent intramolecular cyclization of intermediate **B** at the CHO group to chromanone **8**. We also cannot exclude the formation of **7** from **8** through cation **A**. The change in the reaction pathway in the case of **1e**,**f** is probably due to the fact that the attack on the C-2 atom is accompanied by the cleavage of the C–O bond, and the strong electron-withdrawing groups favor stabilization of the leaving phenolate anion, thus facilitating the pyrone ring opening (Scheme 3).

The ^{1}H NMR spectra of compounds **7a**–**j** in DMSO-d_6 are characterized by the doubled number of the indole protons suggesting their equivalence and two singlets or doublets with J=0.6–1.0 Hz as a result of allylic coupling due to the CH and H-2 protons at δ 5.92–6.06 and 7.66–8.01 ppm, respectively. The geometrical isomers **8c** were identified by comparison of the ^{1}H NMR chemical shifts of the olefinic and indole H-2′ hydrogens in both isomers. The diagnostic signal for the olefinic proton in the *Z*-isomer, which appeared at 7.75 ppm, was shifted downfield in the *E*-isomer (8.23 ppm) due to the deshielding effect of the carbonyl group as indicated in the case of the reaction of 3-(polyfluoroacyl)chromones with indoles.[9] In addition, another characteristic feature of the ^{1}H NMR spectrum in DMSO-d_6 was the appearance of two doublets at δ 9.20 and 7.95 ppm ($J_{H,NH}\approx$3.0 Hz) for the indole H-2′ proton of the *Z*- and *E*-isomers, respectively. The assignment of the indole signals is based on the literature data.[12]

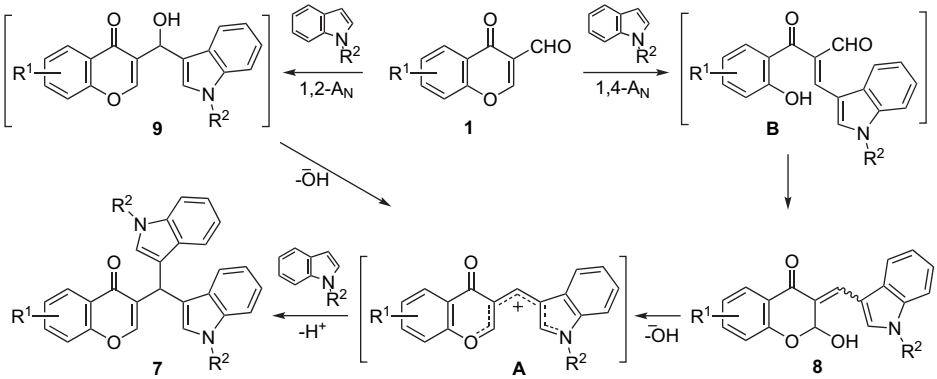
(Chromon-3-yl)bis(indol-3-yl)methanes **7** represent a new class of tris(heteroaryl)methanes, in which two different heterocycles with remarkably important biological and pharmaceutical activities are linked at the same carbon atom. In addition, in view of the easy functionalization of the chromone ring at the 2- and 4-positions by nucleophilic reagents, compounds **7** could serve as promising building blocks for novel three-dimensional molecules of structural and physicochemical interest. In connection with this, it was of interest to evaluate the reactivity of compounds **7** toward some electrophilic and nucleophilic reagents. We have found that bis-adducts **7c** and **7h** react with an excess of sodium hydride and MeI in refluxing THF to afford 3-[bis(1,2-dimethylindol-3-yl)methyl]chromones **10a**,**b** in high yields. Thus, methylation of **7c**,**h** was achieved without destruction of the chromone ring system (Scheme 4).



Scheme 4.

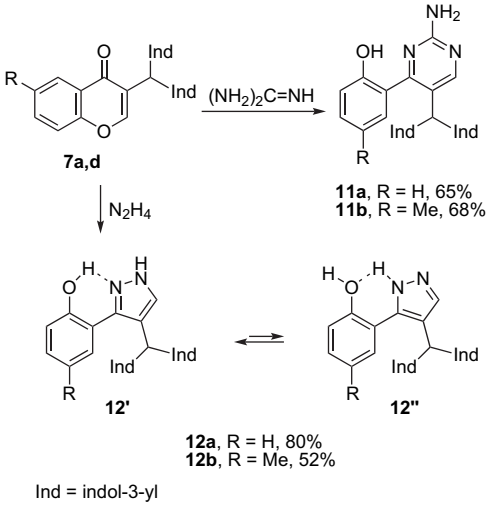
It is known that reactions of chromones, and especially 2-unsubstituted chromones, with amines proceed at the C-2 atom with pyrone ring opening to β-aminovinylketones,[13] however, compound **7a** did not react with benzylamine in DMF at 85 °C for 5 h and only starting material was recovered. To demonstrate the ability of bis-adducts **7** to undergo heterocyclization reactions, compounds **7a**,**d** were allowed to react with guanidine carbonate and hydrazine hydrate. Our results showed that **7a**,**d** smoothly react with guanidine carbonate in refluxing DMF for 7 h to produce the expected 2-amino-4-(2-hydroxyaryl)-5-[bis(indol-3-yl)methyl]pyrimidines **11a**,**b** in good yields (Scheme 5). In the NMR spectra of these products in DMSO-d_6, a singlet at δ 8.03–8.05 ppm for the pyrimidine proton H-4 appeared in place of the disappearance of a signal at δ 7.88–7.91 ppm assigned to a proton at 2-position of chromones **7a**,**d**. It was also observed that all protons of the benzene ring shifted to higher field and, hence, opening of the pyrone ring took place under the action of guanidine carbonate. The amino group and the methine proton appeared as two singlets at δ 6.51–6.54 (2H) and 5.65–5.66 (1H) ppm; the signals at δ 10.3 (1H) and 10.8 (2H) ppm are due to the resonances of OH and NH protons, respectively.

The reactions of chromones **7a**,**d** with an excess of hydrazine hydrate in refluxing isopropanol for 8 h led to the formation of the previously unknown pyrazoles **12a**,**b** with bis(indol-3-yl)methyl moiety in 80 and 52% yields, respectively (Scheme 5). Thus, the



Scheme 3.

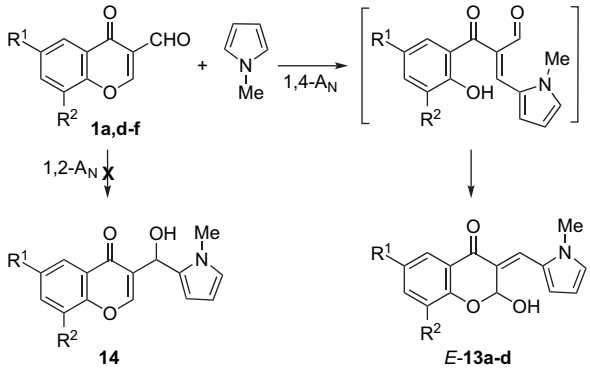
ready accessibility and high reactivity of **7** toward dinucleophiles have made them useful substrates for constructing highly functionalized biologically and medicinally important products.



Scheme 5.

It is important that the ^{1}H NMR spectra of **12a**,**b** in a DMSO-d_6 solution (the solubility of these compounds in $CDCl_3$ is very small) showed two sets of signals due to the possibility of annular prototropy of the pyrazole ring. It is well known that annular tautomerism in NH azoles is a very fast process in the NMR time scale.[14] However, in each of our cases, four signals exhibiting broadening at higher frequency values were observed, indicating that pyrazoles **12a**,**b** exist in DMSO-d_6 as a 7:3 mixture of tautomers **12′** and **12″**, respectively, due to the presence of intramolecular hydrogen bonds in each tautomer (OH···N and NH···O). The structural assignments were based on the signals due to the NH and OH protons at ca. δ_{NH}=11.0–11.2, δ_{OH}=13.0 ppm (tautomer **12′**) and δ_{NH}=12.5, δ_{OH}=9.7–9.9 ppm (tautomer **12″**), which are very similar to those of 4-arylmethyl-3(5)-(2-hydroxyphenyl)pyrazoles prepared by treatment of 3-benzylchromones with hydrazine hydrate in hot pyridine.[15] Tautomers **12′** are the more abundant (70%) since their intramolecular O–H···N=C hydrogen bond is stronger than the intramolecular N–H···O–C hydrogen bond in tautomers **12″**. It should be noted that the ^{1}NMR spectra of 4-arylmethyl-3(5)-(2-hydroxyphenyl)pyrazoles[15] and 4-benzhydryl-3(5)-(2-hydroxyphenyl)pyrazoles[3] in $CDCl_3$ were well resolved with only the OH (δ 10.7–11.0 ppm) and NH (δ 10.0–10.3 ppm) signals. Thus, in this solvent the proton exchange is too fast and only average signals were observed. Previously, 2-amino-4-(2-hydroxyaryl)-5-(dialkylaminomethyl)pyrimidines and 4-(dialkylaminomethyl)-3(5)-(2-hydroxyphenyl)pyrazoles were obtained by the reaction of 3-(dialkylaminomethyl)chromones with guanidine carbonate in the presence of EtONa and hydrazine hydrate, respectively.[16]

Next, taking into account the above results and that the pyrrole ring is an important structural fragment of many natural and biologically active substances,[17] it was of interest to evaluate the reactivity of 3-formylchromones **1** with *N*-methylpyrrole. We anticipated that *N*-methylpyrrole might undergo similar bis-addition to give the corresponding bis-adducts. However, significantly different reactivity was observed in this case. Unlike indoles, *N*-methylpyrrole reacted with **1a**,**d**–**f** under solvent-free conditions exclusively via 1,4-addition followed by recyclization to form *E*-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-ones **13a**–**d** in good yields. The reactions were complete within 45 min and no bis-adducts of type **7** were observed even in the crude products. 3-Formyl-6-methylchromone **1b** did not react with *N*-methylpyrrole under the same conditions. Obviously, the electron-withdrawing substituents facilitate the initial nucleophilic addition at the C-2 atom and the electron-donating methyl group complicates this process as it was observed in the case of indoles. Attempts to use pyrrole in the reaction with chromones **1a**,**c**,**f** failed to produce the desired product under solvent-free conditions, affording only an intractable brown gum even at room temperature. The formation of compounds **13**, in which the more nucleophilic C-2 atom of the pyrrole ring is involved, follows the reaction pathway described in Scheme 6.



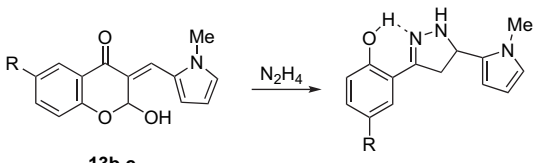
Chromone	R^1	R^2	Product	Yield (%)
1a	H	H	**13a**	58
1d	Cl	H	**13b**	68
1e	NO_2	H	**13c**	77
1f	Br	Br	**13d**	83

Scheme 6.

The choice between structures **13** and **14** was made in favor of the former on the basis of spectroscopic data. The ^{1}H NMR spectra of compounds **13a**–**d** in DMSO-d_6 consisted of a characteristic singlet due to the *exo*-methylene proton in the region of δ 7.72–7.83 ppm and two doublets due to the CH and OH protons at δ 6.39–6.54 and 7.79–8.22 ppm (J=6.0–6.6 Hz), respectively. The main features of the ^{13}C NMR spectrum of product **13a** were resonances at 93.5 (C-2) and 179.6 ppm (C=O), and no signal was observed at 153–155 ppm, where the C-2 atom of chromones usually appears. Comparison of these data with the ^{1}H and ^{13}C NMR spectra of carbinols of type **14**, which have recently been synthesized under Baylis–Hillman conditions by the reaction of chromone or 6-methylchromone with aromatic and heteroaromatic aldehydes,[18] unambiguously proved the structures of **13**.

We anticipated that chromanones **13**, prepared from 3-formylchromones **1** and *N*-methylpyrrole, under the action of dinucleophiles, such as hydrazine and hydroxylamine, might undergo nucleophilic addition reactions giving novel pyrazole and isoxazole derivatives. However, the deformylation of **13** under mild reaction conditions limited our attempts to synthesize these compounds. In fact, treatment of **13b**,**c** with hydrazine hydrate in refluxing ethanol gave only pyrazolines **15a**,**b** in 28 and 21% yield, respectively. Their formation is readily explained by the deformylation of **13b**,**c** into the corresponding pyrrolylchalcones followed by heterocyclization to **15a**,**b** (Scheme 7). In the ^{1}H NMR spectra of these compounds, the three protons attached to the C-4 and C-5 carbon atoms of the pyrazoline unit gave an ABX spin system (δ_{CH_2} = 3.24—3.60, δ_{CH}=5.00 ppm; J_{AB}=16.4–16.8, J_{AX}=10.7–10.9, J_{BX}=7.9–9.5 Hz).

Treatment of chromanone **13b** with hydroxylamine hydrochloride (2 equiv) in refluxing ethanol in the presence of a catalytic amount of HCl produced only a high melting solid (mp ~300 °C) in low yield. Measurement of the ^{1}H and ^{13}C NMR spectra of this compound was unsuccessful due to low solubility in solvents such as DMSO, DMF, AcOH, and acetone.



13b,c

15a, R = Cl, 28%
15b, R = NO_2, 21%

Scheme 7.

3. Conclusions

In conclusion, we have shown that the reaction of 3-formylchromones with indoles is a simple and practical method for the preparation of a new class of biologically interesting (chromon-3-yl)bis(indol-3-yl)methanes. The reaction with *N*-methylpyrrole proceeds via 1,4-addition followed by recyclization to *E*-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-ones. The resulting products are of considerable interest as reactive precursors for the synthesis of other useful organic materials.

4. Experimental

4.1. General

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-d_6 with TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer Spectrum BX-II instrument as KBr discs. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. All solvents used were dried and distilled per standard procedures. The starting 3-formylchromones **1a–f** were prepared according to described procedure.[19]

4.2. General procedure for the synthesis of 3-[bis(indol-3-yl)methyl]chromones (7a–h)

A solution of 3-formylchromone **1** (2.5 mmol) in an excess of indole, 1-methyl- or 2-methylindole (7.5 mmol) was heated at 85–90 °C for 5 h. Completion of the reaction was determined by the appearance of the solid reaction mixture. The precipitate, obtained from the hot solution, was twice recrystallized from *n*-butanol/*p*-xylene (4:1), washed with ethanol, and dried at 90 °C for 1 day to give compounds **7** as colorless crystals.

*4.2.1. 3-[Bis(indol-3-yl)methyl]chromone (**7a**)*

Yield 54%, mp 233–234 °C; IR (KBr) 3389, 1633, 1614, 1572, 1465 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.05 (d, 1H, CH, ^4J=0.8 Hz), 6.91 (ddd, 2H, 2H-5′, ^3J=8.0, 7.1 Hz, ^4J=1.0 Hz), 6.98 (d, 2H, 2H-2′, J=1.8 Hz), 7.06 (ddd, 2H, 2H-6′, ^3J=8.0, 7.1 Hz, ^4J=1.0 Hz), 7.36 (dd, 4H, 2H-4′, 2H-7′, ^3J=8.0 Hz, ^4J=1.0 Hz), 7.49 (ddd, 1H, H-6, ^3J=8.0, 7.2 Hz, ^4J=1.0 Hz), 7.60 (dd, 1H, H-8, ^3J=8.5 Hz, ^4J=1.0 Hz), 7.78 (ddd, 1H, H-7, ^3J=8.5, 7.2 Hz, ^4J=1.7 Hz), 7.91 (d, 1H, H-2, ^4J=0.8 Hz), 8.10 (dd, 1H, H-5, ^3J=8.0 Hz, ^4J=1.7 Hz), 10.86 (d, 2H, 2NH, J=1.8 Hz). Anal. Calcd for $C_{26}H_{18}N_2O_2$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.66; H, 4.47; N, 6.99.

*4.2.2. 3-[Bis(1-methylindol-3-yl)methyl]chromone (**7b**)*

Yield 65%, mp 265–266 °C; IR (KBr) 1631, 1608, 1572, 1465 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.70 (s, 6H, 2Me), 6.04 (d, 1H, CH, ^4J=0.6 Hz), 6.95 (ddd, 2H, 2H-5′, ^3J=7.8, 7.0 Hz, ^4J=0.9 Hz), 6.98 (s, 2H, 2H-2′), 7.13 (ddd, 2H, 2H-6′, ^3J=8.2, 7.0 Hz, ^4J=1.0 Hz), 7.38 (t, 4H, 2H-4′, 2H-7′, ^3J=8.2 Hz), 7.49 (ddd, 1H, H-6, ^3J=8.0, 7.2 Hz, ^4J=1.0 Hz), 7.60 (dd, 1H, H-8, ^3J=8.5 Hz, ^4J=1.0 Hz), 7.79 (ddd, 1H, H-7, ^3J=8.5, 7.2 Hz, ^4J=1.7 Hz), 7.92 (d, 1H, H-2, ^4J=0.6 Hz), 8.09 (dd, 1H, H-5, ^3J=8.0 Hz, ^4J=1.7 Hz). Anal. Calcd for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.05; H, 5.24; N, 6.62.

*4.2.3. 3-[Bis(2-methylindol-3-yl)methyl]chromone (**7c**)*

Yield 37%, mp 310–312 °C; IR (KBr) 3403, 3230, 1631, 1606, 1570, 1492, 1465 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (s, 6H, 2Me), 5.95 (br s, 1H, CH), 6.74 (ddd, 2H, 2H-5′, ^3J=8.0, 7.1 Hz, ^4J=0.8 Hz), 6.92 (ddd, 2H, 2H-6′, ^3J=8.0, 7.1 Hz, ^4J=0.9 Hz), 7.09 (d, 2H, 2H-7′, ^3J=8.0 Hz), 7.24 (d, 2H, 2H-4′, ^3J=8.0 Hz), 7.47 (ddd, 1H, H-6, ^3J=8.0, 7.2 Hz, ^4J=0.9 Hz), 7.61 (d, 1H, H-8, ^3J=8.4 Hz), 7.70 (d, 1H, H-2, ^4J=1.0 Hz), 7.78 (ddd, 1H, H-7, ^3J=8.4, 7.2 Hz, ^4J=1.7 Hz), 8.05 (dd, 1H, H-5, ^3J=8.0 Hz, ^4J=1.7 Hz), 10.80 (s, 2H, 2NH). Anal. Calcd for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69. Found: C, 79.98; H, 5.17; N, 6.51.

*4.2.4. 3-[Bis(indol-3-yl)methyl]-6-methylchromone (**7d**)*

Yield 68%, mp 252–254 °C; IR (KBr) 3350, 1631, 1607, 1572, 1483 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 3H, Me), 6.04 (s, 1H, CH), 6.90 (ddd, 2H, 2H-5′, ^3J=7.9, 7.1 Hz, ^4J=1.0 Hz), 6.96 (d, 2H, 2H-2′, J=1.8 Hz), 7.03–7.08 (m, 2H, 2H-6′), 7.32–7.37 (m, 4H, 2H-4′, 2H-7′), 7.50 (d, 1H, H-8, ^3J=8.6 Hz), 7.60 (dd, 1H, H-7, ^3J=8.6, ^4J=2.2 Hz), 7.88 (s, 1H, H-2), 7.89 (br s, 1H, H-5), 10.85 (br d, 2H, 2NH, J=1.8 Hz). Anal. Calcd for $C_{27}H_{20}N_2O_2 \cdot 0.5p$-$Me_2C_6H_4$: C, 81.38; H, 5.51; N, 6.12. Found: C, 81.35; H, 5.55; N, 5.96.

*4.2.5. 3-[Bis(1-methylindol-3-yl)methyl]-6-methylchromone (**7e**)*

Yield 78%, mp 262–263 °C; IR (KBr) 1640, 1619, 1577, 1546, 1486, 1473 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 3H, Me), 3.69 (s, 6H, 2MeN), 6.04 (br s, 1H, CH), 6.95 (ddd, 2H, 2H-5′, ^3J=7.8, 7.1 Hz, ^4J=0.9 Hz), 6.96 (s, 2H, 2H-2′), 7.13 (ddd, 2H, 2H-6′, ^3J=8.1, 7.1 Hz, ^4J=1.0 Hz), 7.36 (d, 2H, 2H-4′, ^3J=7.8 Hz), 7.39 (d, 2H, 2H-7′, ^3J=8.1 Hz), 7.50 (d, 1H, H-8, ^3J=8.6 Hz), 7.60 (dd, 1H, H-7, ^3J=8.6 Hz, ^4J=2.2 Hz), 7.88 (d, 1H, H-5, ^4J=2.2 Hz), 7.89 (d, 1H, H-2, ^4J=0.6 Hz). Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.39; H, 5.71; N, 6.58.

*4.2.6. 3-[Bis(2-methylindol-3-yl)methyl]-6-methylchromone (**7f**)*

Yield 51%, mp 263–264 °C; IR (KBr) 3401, 3270, 1633, 1616, 1574, 1484 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13 (s, 6H, 2Me), 2.41 (s, 3H, Me), 5.92 (br s, 1H, CH), 6.73 (ddd, 2H, 2H-5′, ^3J=8.0, 7.1 Hz, ^4J=0.8 Hz), 6.91 (ddd, 2H, 2H-6′, ^3J=8.0, 7.1 Hz, ^4J=0.9 Hz), 7.07 (d, 2H, 2H-7′, ^3J=8.0 Hz), 7.23 (d, 2H, 2H-4′, ^3J=8.0 Hz), 7.52 (d, 1H, H-8, ^3J=8.6 Hz), 7.60 (dd, 1H, H-7, ^3J=8.6 Hz, ^4J=2.2 Hz), 7.66 (d, 1H, H-2, ^4J=1.0 Hz), 7.81 (d, 1H, H-5, ^4J=2.2 Hz), 10.78 (s, 2H, 2NH). Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.15; H, 5.41; N, 6.43.

*4.2.7. 3-[Bis(indol-3-yl)methyl]-6-methoxychromone (**7g**)*

Yield 79%, mp 187–188 °C; IR (KBr) 3426, 3326, 1628, 1617, 1606, 1573, 1515, 1485 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.85 (s, 3H, MeO), 6.06 (d, 1H, CH, J=0.7 Hz), 6.90 (ddd, 2H, 2H-5′, ^3J=7.9, 7.1 Hz, ^4J=0.8 Hz), 6.97 (d, 2H, 2H-2′, J=2.0 Hz), 7.03–7.08 (m, 2H, 2H-6′), 7.33–7.37 (m, 4H, 2H-4′, 2H-7′), 7.38 (dd, 1H, H-7, ^3J=9.1 Hz, ^4J=3.1 Hz), 7.46 (d, 1H, H-5, ^4J=3.1 Hz), 7.56 (d, 1H, H-8, ^3J=9.1 Hz), 7.90 (s, 1H, H-2), 10.85 (d, 2H, 2NH, J=2.0 Hz). Anal. Calcd for $C_{27}H_{20}N_2O_3 \cdot 0.5p$-$Me_2C_6H_4$: C, 78.63; H, 5.32; N, 5.92. Found: C, 78.62; H, 5.28; N, 5.71.

*4.2.8. 3-[Bis(2-methylindol-3-yl)methyl]-6-methoxychromone (**7h**)*

Yield 61%, mp 289–290 °C; IR (KBr) 3388, 3290, 1628, 1612, 1576, 1484 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13 (s, 6H, 2Me), 3.83 (s, 3H, MeO), 5.93 (s, 1H, CH), 6.73 (t, 2H, 2H-5′, ^3J=7.5 Hz), 6.91 (t, 2H, 2H-6′, ^3J=7.5 Hz), 7.06 (d, 2H, 2H-7′, ^3J=8.0 Hz), 7.23 (d, 2H, 2H-4′, ^3J=8.0 Hz), 7.37–7.41 (m, 2H, H-7, H-5), 7.59 (d, 1H, H-8, ^3J=9.0 Hz), 7.68 (d, 1H, H-2, ^4J=0.9 Hz), 10.77 (s, 2H, 2NH). Anal. Calcd for $C_{29}H_{24}N_2O_3$: C, 77.66; H, 5.39; N, 6.25. Found: C, 77.27; H, 5.38; N, 6.17.

*4.2.9. 3-[Bis(indol-3-yl)methyl]-6-chlorochromone (**7i**)*

Indole (760 mg, 6.50 mmol) and two drops of 50% $HClO_4$ were added to a hot solution of 6-chloro-3-formylchromone **1d** (450 mg, 2.16 mmol) in *n*-butanol (5 mL). The resulting dark-red reaction mixture was kept for 24 h at ~20 °C, then the precipitated crystals were filtered, washed with ethanol, and recrystallized from *n*-butanol to give compound **7i** as colorless crystals. Yield 500 mg (55%), mp 235–236 °C; IR (KBr) 3407, 1638, 1605, 1568, 1467, 1455 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.03 (s, 1H, CH), 6.91 (t, 2H, 2H-5′, ^3J=7.5 Hz), 6.99 (d, 2H, 2H-2′, J=2.0 Hz), 7.06 (t, 2H, 2H-6′, ^3J=7.5 Hz), 7.35 (d, 2H, 2H-7′, ^3J=8.0 Hz), 7.36 (d, 2H, 2H-4′, ^3J=8.0 Hz), 7.67 (d, 1H, H-8, ^3J=9.0 Hz), 7.82 (dd, 1H, H-7, ^3J=9.0 Hz, ^4J=2.6 Hz), 7.94 (s, 1H, H-2), 8.02 (d, 1H, H-5, ^4J=2.6 Hz), 10.87 (br d, 2H, 2NH, J=2.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.1, 111.5, 115.5, 118.4, 118.7, 120.9, 121.0, 124.0, 124.2, 124.4, 126.3, 126.8, 129.7, 133.8, 136.7, 154.4, 155.1, 174.7. Anal. Calcd for $C_{26}H_{17}ClN_2O_2$: C, 73.50; H, 4.03; N, 6.59. Found: C, 73.15; H, 3.72; N, 6.32.

*4.2.10. 3-[Bis(indol-3-yl)methyl]-6-nitrochromone (**7j**)*

A mixture of 3-formyl-6-nitrochromone **1e** (350 mg, 1.60 mmol) and indole (560 mg, 4.79 mmol) in water (5 mL) was heated at 85–90 °C for 5 h. The resultant product was filtered, washed with water, dried, and recrystallized from *n*-butanol/toluene (1:1) to give compound **7j** as pale yellow crystals. Yield 400 mg (58%), mp 204–205 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 6.04 (s, 1H, CH), 6.91 (t, 2H, 2H-5′, ^3J=7.5 Hz), 7.02 (d, 2H, 2H-2′, J=1.8 Hz), 7.06 (t, 2H, 2H-6′, ^3J=7.5 Hz), 7.37 (d, 2H, 2H-7′, ^3J=8.0 Hz), 7.38 (d, 2H, 2H-4′, ^3J=8.0 Hz), 7.86 (d, 1H, H-8, ^3J=9.2 Hz), 8.01 (s, 1H, H-2), 8.54 (dd, 1H, H-7, ^3J=9.2 Hz, ^4J=2.8 Hz), 8.79 (d, 1H, H-5, ^4J=2.8 Hz), 10.89 (br d, 2H, 2NH, J=1.8 Hz); according to the ^1H NMR spectrum, compound **7j** contained 5% of **8a**. Anal. Calcd for $C_{26}H_{17}N_3O_4$: C, 71.72; H, 3.94; N, 9.65. Found: C, 71.42; H, 3.93; N, 9.28.

*4.2.11. E-2-Hydroxy-6-nitro-3-(indol-3-ylmethylene)chroman-4-one (**8a**)*

This compound was obtained analogously to **7j**. Yield 10%, mp 244–246 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 6.65 (br d, 1H, CH, J=6.2 Hz), 7.24 (td, 1H, H-5′, ^3J=7.7 Hz, ^4J=1.0 Hz), 7.28 (td, 1H, H-6′, ^3J=7.7 Hz, ^4J=1.0 Hz), 7.31 (d, 1H, H-8, ^3J=9.0 Hz), 7.54 (d, 1H, H-7′, ^3J=7.7 Hz), 7.89 (d, 1H, H-4′, ^3J=7.7 Hz), 7.96 (d, 1H, H-2′, J=2.8 Hz), 8.23 (br d, 1H, OH, J=6.2 Hz), 8.28 (s, 1H, =CH), 8.41 (dd, 1H, H-7, ^3J=9.0 Hz, ^4J=2.9 Hz), 8.65 (d, 1H, H-5, ^4J=2.9 Hz), 12.34 (br s, 1H, NH); according to the ^1H NMR spectrum, compound **8a** contained 14% of **7j**. Anal. Calcd for $C_{18}H_{12}N_2O_5$: C, 64.29; H, 3.60; N, 8.33. Found: C, 64.32; H, 4.06; N, 8.05.

*4.2.12. 3-[Bis(1-methylindol-3-yl)methyl]-6-nitrochromone (**7k**) and E-2-hydroxy-6-nitro-3-(1-methylindol-3-ylmethylene)-chroman-4-one (**8b**)*

This mixture was obtained analogously to **7a**–**h**. ^1H NMR (400 MHz, DMSO-d_6) (**7k**, 33%) δ 3.70 (s, 6H, 2Me), 6.03 (d, 1H, CH, ^4J=0.7 Hz), 6.96 (ddd, 2H, 2H-5′, ^3J=7.8, 7.0 Hz, ^4J=0.9 Hz), 7.02 (s, 2H, 2H-2′), 7.14 (ddd, 2H, 2H-6′, ^3J=8.1, 7.0 Hz, ^4J=1.0 Hz), 7.37–7.42 (m, 4H, 2H-4′, 2H-7′), 7.88 (d, 1H, H-8, ^3J=9.2 Hz), 8.04 (d, 1H, H-2, ^4J=0.7 Hz), 8.55 (dd, 1H, H-7, ^3J=9.2 Hz, ^4J=2.9 Hz), 8.78 (d, 1H, H-5, ^4J=2.9 Hz); (**8b**, 67%) δ 3.95 (s, 3H, Me), 6.65 (d, 1H, CH, J=7.0 Hz), 7.26–7.37 (m, 2H, H-5′, H-6′), 7.32 (d, 1H, H-8, ^3J=9.1 Hz), 7.62 (d, 1H, H-7′, ^3J=8.1 Hz), 7.91 (d, 1H, H-4′, ^3J=7.7 Hz), 7.97 (s, 1H, H-2′), 8.19 (d, 1H, OH, J=7.0 Hz), 8.25 (s, 1H, =CH), 8.41 (dd, 1H, H-7, ^3J=9.1 Hz, ^4J=2.9 Hz), 8.64 (d, 1H, H-5, ^4J=2.9 Hz).

*4.2.13. 6,8-Dibromo-2-hydroxy-3-(indol-3-ylmethylene)-chroman-4-one (**8c**)*

This compound was obtained analogously to **7a**–**h** in 30% yield as orange crystals, mp 255–256 °C (*n*-butanol/toluene, 1:1); IR (KBr) 3468, 3385, 1634, 1619, 1585, 1559, 1544, 1516, 1489 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (*E*-**8c**, 91%) δ 6.66 (d, 1H, CH, J=6.7 Hz), 7.20–7.30 (m, 2H, H-5′, H-6′), 7.53 (d, 1H, H-7′, ^3J=7.8 Hz), 7.88 (d, 1H, H-4′, ^3J=7.6 Hz), 7.95 (d, 1H, H-2′, J=2.4 Hz), 7.95 (d, 1H, H-7, ^4J=2.4 Hz), 8.12 (d, 1H, H-5, ^4J=2.4 Hz), 8.20 (d, 1H, OH, J=6.7 Hz), 8.23 (s, 1H, =CH), 12.34 (s, 1H, NH); (*Z*-**8c**, 9%) δ 6.52 (br s, 1H, CH), 7.75 (s, 1H, =CH), 9.20 (d, 1H, H-2′, J=3.1 Hz), 10.89 (br s, 1H, OH), 12.11 (br s, 1H, NH). Anal. Calcd for $C_{18}H_{11}Br_2NO_3$: C, 48.14; H, 2.47; N, 3.12. Found: C, 48.45; H, 2.48; N, 3.01.

*4.2.14. 3-[Bis(1,2-dimethylindol-3-yl)methyl]chromone (**10a**)*

Powdered sodium hydride (110 mg, 4.58 mmol) was added to a solution of **7c** (360 mg, 0.86 mmol) in THF (10 mL) and the mixture was refluxed for 2 h. Then to a stirred suspension MeI (2.5 g, 17.7 mmol) was added in one portion, the resulting mixture was heated at reflux for 1 h, and allowed to stand for 1 day at room temperature. The inorganic salts were filtered off and washed with THF (5 mL). Evaporation of the filtrate at heating gave a solid, which was recrystallized from a *n*-BuOH/*p*-xylene mixture to give colorless crystals. Yield 320 mg (83%), mp 209–210 °C; IR (KBr) 1645, 1614, 1608, 1572, 1558, 1463 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 6H, 2Me), 3.64 (s, 6H, 2NMe), 5.97 (d, 1H, CH, J=1.0 Hz), 6.76 (ddd, 2H, 2H-5′, ^3J=7.9, 7.1 Hz, ^4J=0.9 Hz), 6.98 (ddd, 2H, 2H-6′, ^3J=8.0, 7.1 Hz, ^4J=1.0 Hz), 7.12 (d, 2H, 2H-7′, ^3J=8.0 Hz), 7.36 (d, 2H, 2H-4′, ^3J=7.9 Hz), 7.47 (ddd, 1H, H-6, ^3J=8.0, 7.1 Hz, ^4J=1.0 Hz), 7.62 (d, 1H, H-8, ^3J=8.4 Hz), 7.70 (d, 1H, H-2, ^4J=1.0 Hz), 7.80 (ddd, 1H, H-7, ^3J=8.4, 7.1 Hz, ^4J=1.7 Hz), 8.00 (dd, 1H, H-5, ^3J=8.0 Hz, ^4J=1.7 Hz); ^{13}C NMR (100 MHz, DMF-d_7) δ 10.5, 29.6, 31.9, 109.6, 110.7, 119.0, 119.1, 120.5, 124.1, 125.9, 126.0, 127.5, 128.3, 129.4, 134.5, 134.8, 137.3, 155.3, 156.9, 176.7. Anal. Calcd for $C_{30}H_{26}N_2O_2$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.38; H, 5.72; N, 6.14.

*4.2.15. 3-[Bis(1,2-dimethylindol-3-yl)methyl]-6-methoxychromone (**10b**)*

This compound was prepared from **7h** analogously to **10a**. Yield 74%, mp 211–212 °C; IR (KBr) 1641, 1615, 1584, 1559, 1482, 1468 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 6H, 2Me), 3.64 (s, 6H, 2NMe), 3.81 (s, 3H, MeO), 5.98 (d, 1H, CH, J=1.0 Hz), 6.76 (ddd, 2H, 2H-5′, ^3J=8.0, 7.1 Hz, ^4J=1.0 Hz), 6.98 (ddd, 2H, 2H-6′, ^3J=8.0, 7.1 Hz, ^4J=1.0 Hz), 7.10 (d, 2H, 2H-7′, ^3J=8.0 Hz), 7.36 (d, 2H, 2H-4′, ^3J=8.0 Hz), 7.37 (d, 1H, H-5, ^4J=3.1 Hz), 7.39 (dd, 1H, H-7, ^3J=9.0 Hz, ^4J=3.1 Hz), 7.59 (d, 1H, H-8, ^3J=9.0 Hz), 7.68 (d, 1H, H-2, ^4J=1.0 Hz). Anal. Calcd for $C_{31}H_{28}N_2O_3\cdot H_2O$: C, 75.28; H, 6.11; N, 5.66. Found: C, 75.29; H, 6.20; N, 5.34.

*4.2.16. 2-Amino-4-(2-hydroxyphenyl)-5-[bis(indol-3-yl)methyl]pyrimidine (**11a**)*

A mixture of **7a** (250 mg, 0.64 mmol) and guanidine carbonate (230 mg, 1.28 mmol) in DMF (5 mL) was refluxed for 7 h. After cooling, water (40 mL) was added and the solid obtained was filtered, washed with water, and purified by boiling in toluene and filtration. Yield 200 mg (65%), mp 277–278 °C; IR (KBr) 3436, 3398, 3317, 3135, 1654, 1589, 1572, 1543, 1510, 1484, 1453 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 5.65 (s, 1H, CH), 6.51 (s, 2H, NH_2), 6.61 (t, 1H, H-4, ^3J=7.5 Hz), 6.66 (br s, 2H, 2H-2′), 6.81 (t, 2H, 2H-5′, ^3J=7.5 Hz), 6.89 (d, 1H, H-6, ^3J=8.0 Hz), 6.95 (d, 1H, H-3, ^3J=8.0 Hz), 7.02 (t, 2H, 2H-6′, ^3J=7.5 Hz), 7.13 (d, 2H, 2H-4′, ^3J=8.0 Hz), 7.17 (t, 1H, H-5, ^3J=8.0 Hz), 7.32 (d, 2H, 2H-7′, ^3J=8.0 Hz), 8.03 (s, 1H, H-6 pyrim.), 10.33 (s, 1H, OH), 10.78 (s, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.3, 111.4, 115.9, 117.4, 118.2, 118.3, 119.0, 120.8, 120.9, 123.8, 123.9, 124.5, 126.2, 129.8, 136.6, 154.9, 158.9, 161.4, 164.1. Anal. Calcd for $C_{27}H_{21}N_5O\cdot 0.5H_2O$: C, 73.62; H, 5.03; N, 15.90. Found: C, 73.41; H, 4.89; N, 15.81.

*4.2.17. 2-Amino-4-(2-hydroxy-5-methylphenyl)-5-[bis(indol-3-yl)methyl]pyrimidine (**11b**)*

This compound was prepared from **7d** analogously to **11a**. Yield 68%, mp 261–262 °C; IR (KBr) 3418, 3329, 3182, 1658, 1608, 1591,

1572, 1541, 1502, 1456 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H, Me), 5.66 (s, 1H, CH), 6.54 (s, 2H, NH_2), 6.65 (d, 1H, H-6, ^4J=2.0 Hz), 6.70 (d, 2H, 2H-2′, J=2.0 Hz), 6.83 (t, 2H, 2H-5′, ^3J=7.5 Hz), 6.84 (d, 1H, H-3, ^3J=8.2 Hz), 6.98 (dd, 1H, H-4, ^3J=8.2 Hz, ^4J=2.0 Hz), 7.03 (t, 2H, 2H-6′, ^3J=7.5 Hz), 7.11 (d, 2H, 2H-4′, ^3J=7.9 Hz), 7.33 (d, 2H, 2H-7′, ^3J=8.1 Hz), 8.05 (s, 1H, H-6 pyrim.), 10.29 (s, 1H, OH), 10.81 (d, 2H, 2NH, J=2.0 Hz). Anal. Calcd for $C_{28}H_{23}N_5O$: C, 75.49; H, 5.20; N, 15.72. Found: C, 75.18; H, 5.02; N, 15.35.

4.2.18. 2-{4-[Bis(indol-3-yl)methyl]-1H-pyrazol-3-yl}phenol (**12a**)

A solution of **7a** (350 mg, 0.90 mmol) and 60% hydrazine hydrate (300 mg, 3.59 mmol) in isopropanol (20 mL) was refluxed for 8 h. After partial evaporation of the solvent the product was isolated by filtration, washed with isopropanol, and dried to give a colorless powder. Yield 290 mg (80%), mp 260–261 °C; IR (KBr) 3437, 3409, 3291, 1650, 1619, 1587, 1547, 1507, 1454 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (**12′a**, OH···N, 70%) δ 5.97 (br s, 1H, CH), 6.60–7.35 (m, 15H, arom.), 10.76 (br s, 2H, 2NH ind.), 11.21 (br s, 1H, NH), 13.00 (br s, 1H, OH); (**12″a**, NH···O, 30%) δ 5.73 (br s, 1H, CH), 6.60–7.35 (m, 15H, arom.), 9.88 (br s, 1H, OH), 10.76 (br s, 2H, 2NH ind.), 12.52 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.9, 30.2, 111.5, 115.8, 117.7, 118.2, 118.8, 119.0, 120.8, 122.4, 123.2, 123.5, 126.3, 126.8, 128.6, 129.6, 136.6, 146.2, 153.3 (all signals are broadened). Anal. Calcd for $C_{26}H_{20}N_4O$: C, 77.21; H, 4.98; N, 13.85. Found: C, 76.98; H, 5.03; N, 13.69.

4.2.19. 2-{4-[Bis(indol-3-yl)methyl]-1H-pyrazol-3-yl}-4-methylphenol (**12b**)

This compound was prepared from **7d** analogously to **12a**. Yield 52%, mp 227–228 °C; IR (KBr) 3405, 3370, 1639, 1617, 1592, 1552, 1500, 1476, 1455 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (**12′b**, OH···N, 70%) δ 1.78 (br s, 3H, Me), 5.99 (br s, 1H, CH), 6.75–7.37 (m, 14H, arom.), 10.79 (br s, 2H, 2NH ind.), 11.04 (br s, 1H, NH), 12.97 (br s, 1H, OH); (**12″b**, NH···O, 30%) δ 2.01 (br s, 3H, Me), 5.75 (br s, 1H, CH), 6.75–7.37 (m, 14H, arom.), 9.65 (br s, 1H, OH), 10.73 (br s, 2H, 2NH ind.), 12.48 (br s, 1H, NH). Anal. Calcd for $C_{27}H_{22}N_4O$: C, 77.49; H, 5.30; N, 13.39. Found: C, 77.41; H, 5.35; N, 13.56.

4.3. General procedure for the synthesis of *E*-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-ones (13a–d)

A solution of 3-formylchromone **1** (1.0 mmol) in an excess of *N*-methylpyrrole (3.0 mmol) was heated at 85–90 °C for 45 min. Completion of the reaction was determined by the appearance of the solid reaction mixture. The precipitate, obtained from the hot solution, was cooled and treated with hexane (5 mL). The residue was filtered, washed with hexane, recrystallized from *n*-butanol/dioxane (3:1), and washed with ethanol to give compounds **13** as yellow crystals.

4.3.1. E-2-Hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-one (**13a**)

Yield 58%, mp 190–191 °C; IR (KBr) 3376, 3277, 1645, 1608, 1585, 1557, 1485 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.77 (s, 3H, Me), 6.29 (dd, 1H, H-4′, J=4.0, 2.5 Hz), 6.39 (d, 1H, H-2, J=6.3 Hz), 6.75 (dd, 1H, H-5′, J=4.0, 1.2 Hz), 7.04 (d, 1H, H-8, ^3J=8.0 Hz), 7.12 (ddd, 1H, H-6, ^3J=7.8, 7.3 Hz, ^4J=0.9 Hz), 7.24 (t, 1H, H-3′, J=1.8 Hz), 7.58 (ddd, 1H, H-7, ^3J=8.0, 7.3 Hz, ^4J=1.7 Hz), 7.72 (s, 1H, =CH), 7.79 (d, 1H, OH, J=6.3 Hz), 7.86 (dd, 1H, H-5, ^3J=7.8 Hz, ^4J=1.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.0 (qd, Me, J=139.7, 2.4 Hz), 93.5 (ddd, C-2, J=169.7, 10.6, 3.4 Hz), 110.1 (ddd, C-4′, J=172.9, 7.8, 3.4 Hz), 116.8 (dm, C-3′, J=172.2 Hz), 118.5 (dd, C-8, J=162.8, 7.5 Hz), 121.6 (ddd, C-3, J=7.8, 4.5, 1.3 Hz), 121.7 (dd, C-5, J=163.3, 7.9 Hz), 125.9 (t, C-4a, J=4.9 Hz), 126.5 (d, =CH, J=153.7 Hz), 126.5 (ddd, C-6, J=161.8, 8.4, 1.3 Hz), 127.1 (qd, C-2′, J=6.7, 1.8 Hz), 129.7 (dquintd, C-5′, J=186.4, 8.0, 3.6 Hz), 135.5 (ddd, C-7, J=160.6, 9.2, 2.0 Hz), 157.2 (m, C-8a), 179.6 (dtd, C-4, J=6.2, 4.1, 1.7 Hz). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.38; H, 5.14; N, 5.41.

4.3.2. E-6-Chloro-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-one (**13b**)

Yield 68%, mp 193–194 °C; IR (KBr) 3253, 1637, 1605, 1579, 1557, 1539, 1492 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.78 (s, 3H, Me), 6.31 (dd, 1H, H-4′, J=3.5, 2.6 Hz), 6.41 (d, 1H, H-2, J=6.3 Hz), 6.78 (br d, 1H, H-5′, J=3.4 Hz), 7.11 (d, 1H, H-8, ^3J=8.8 Hz), 7.28 (br t, 1H, H-3′, J=1.5 Hz), 7.62 (dd, 1H, H-7, ^3J=8.8 Hz, ^4J=2.7 Hz), 7.76 (s, 1H, =CH), 7.79 (d, 1H, H-5, ^4J=2.7 Hz), 7.92 (d, 1H, OH, J=6.3 Hz). Anal. Calcd for $C_{15}H_{12}ClNO_3$: C, 62.19; H, 4.17; N, 4.83. Found: C, 62.13; H, 4.35; N, 4.55.

4.3.3. E-2-Hydroxy-6-nitro-3-(1-methylpyrrol-2-ylmethylene)chroman-4-one (**13c**)

Yield 77%, mp 229–230 °C; IR (KBr) 3325, 1652, 1615, 1594, 1569, 1522, 1511, 1491 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.80 (s, 3H, Me), 6.34 (dd, 1H, H-4′, J=4.0, 2.5 Hz), 6.54 (d, 1H, H-2, J=6.0 Hz), 6.82 (dd, 1H, H-5′, J=4.0, 1.0 Hz), 7.30 (d, 1H, H-8, ^3J=9.1 Hz), 7.33 (t, 1H, H-3′, J=1.7 Hz), 7.83 (s, 1H, =CH), 8.22 (d, 1H, OH, J=6.0 Hz), 8.40 (dd, 1H, H-7, ^3J=9.1 Hz, ^4J=2.9 Hz), 8.61 (d, 1H, H-5, ^4J=2.9 Hz). Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 60.06; H, 3.95; N, 9.34.

4.3.4. E-6,8-Dibromo-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-one (**13d**)

Yield 83%, mp 205–206 °C; IR (KBr) 3300, 1629, 1584, 1562, 1537, 1488 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 3H, Me), 6.33 (dd, 1H, H-4′, J=4.0, 2.5 Hz), 6.53 (d, 1H, H-2, J=6.6 Hz), 6.81 (dd, 1H, H-5′, J=4.0, 1.0 Hz), 7.31 (t, 1H, H-3′, J=1.7 Hz), 7.78 (s, 1H, =CH), 7.91 (d, 1H, H-7, ^4J=2.4 Hz), 8.12 (d, 1H, H-5, ^4J=2.4 Hz), 8.20 (d, 1H, OH, J=6.6 Hz). Anal. Calcd for $C_{15}H_{11}Br_2NO_3$: C, 43.62; H, 2.68; N, 3.39. Found: C, 43.71; H, 2.87; N, 3.25.

4.3.5. 4-Chloro-2-[5-(1-methylpyrrol-2-yl)-4,5-dihydropyrazol-3-yl]phenol (**15a**)

A solution of **13b** (300 mg, 1.04 mmol) and 60% hydrazine hydrate (160 mg, 3.11 mmol) in ethanol (5 mL) was refluxed for 2.5 h and the solvent was evaporated to half of its initial volume. After cooling, the precipitate formed was filtered, washed with aqueous ethanol, and dried to give colorless needles. Yield 80 mg (28%), mp 128–129 °C; IR (KBr) 3292, 1614, 1593, 1564, 1488 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.24 (dd, 1H, C*H*H, J=16.4, 7.9 Hz), 3.44 (dd, 1H, CH*H*, J=16.4, 10.7 Hz), 3.67 (s, 3H, Me), 5.00 (dd, 1H, CH, J=10.7, 7.9 Hz), 6.05–6.08 (m, 2H, H-4′, H-5′), 6.63 (t, 1H, H-3′, J=2.2 Hz), 6.94 (d, 1H, H-6, ^3J=8.7 Hz), 7.15 (d, 1H, H-3, ^4J=2.6 Hz), 7.20 (dd, 1H, H-5, ^3J=8.7 Hz, ^4J=2.6 Hz), 10.3–11.5 (br s, 2H, NH, OH). Anal. Calcd for $C_{14}H_{14}ClN_3O$: C, 60.98; H, 5.12; N, 15.24. Found: C, 60.63; H, 5.10; N, 15.16.

4.3.6. 2-[5-(1-Methylpyrrol-2-yl)-4,5-dihydropyrazol-3-yl]-4-nitrophenol (**15b**)

This compound was prepared from **13c** analogously to **15a**. Yield 21%, mp 171–172 °C; IR (KBr) 3288, 1630, 1593, 1565, 1525, 1486 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.32 (dd, 1H, C*H*H, J=16.8, 9.5 Hz), 3.60 (dd, 1H, CH*H*, J=16.8, 10.9 Hz), 3.62 (s, 3H, Me), 5.00 (ddd, 1H, CH, J=10.9, 9.5, 2.6 Hz), 5.90 (dd, 1H, H-4′, J=3.5, 2.7 Hz), 6.01 (dd, 1H, H-5′, J=3.5, 1.7 Hz), 6.72 (t, 1H, H-3′, J=2.2 Hz), 7.12 (d, 1H, H-6, ^3J=9.0 Hz), 7.98 (d, 1H, NH, J=2.6 Hz), 8.14 (dd, 1H, H-5, ^3J=9.0 Hz, ^4J=2.8 Hz), 8.23 (d, 1H, H-3, ^4J=2.8 Hz), 12.22 (br s, 1H, OH). Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.40; H, 4.71; N, 19.60.

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