Mannich Bases of Chromones Containing a 2,3-fused Heterocyclic Ring

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Keywords: *aminomethylation, condensed chromones, Mannich bases.*

Aminomethylation of chromones containing a 2,3-fused heterocyclic ring, such as indolizine, pyrroloquinoline and pyrrolothiazole, namely 9-hydroxy-6/8-alkyl-12*H*-chromeno[3,2-*a*]indolizin-12-ones, 10-(alk)oxy-9-R-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-ones and 9-alkyl-8-hydroxy-3-methyl-5-R-11*H*-chromeno[3',2':3,4]pyrrolo[2,1-*b*][1,3]thiazol-11-ones with *bis*dialkylaminomethanes was studied. The α-position of the pyrrole ring and the *ortho*-positions to the hydroxyl group in the benzene ring in the above mentioned systems are active sites and the Mannich reaction can occur at these three positions as shown for 10-hydroxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-one yielding 9,11,13-tri(dialkylaminomethyl) derivative. Using the strategy of introducing substituents into the active centers, as well as replacing the OH group with OAlk, it was possible to obtain mono- and diaminomethylation products. The above systems substituted at positions 6 or 8 of the chromone ring afforded di(dialkylaminomethyl) products, respectively 5,7-di(dimethylaminomethyl)-9-alkyl-8-hydroxy-3-methyl-11*H*-chromeno[3',2':3,4]pyrrolo[2,1-*b*][1,3]thiazol-11-ones, 6,8- or 6,10-di(dimethylaminomethyl)-8/10-alkyl-9-hydroxy-12*H*-chromeno[3,2-*a*]indolizin-12-ones and 11,13-di(dialkylaminomethyl)-9-ethyl-10-hydroxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-ones. Monoaminomethylated products were prepared for 5-acyl-8-hydroxy-3-methyl-11*H*-chromeno[3',2':3,4]pyrrolo[2,1-*b*][1,3]thiazol-11-ones. Aminomethylation of 10-alkoxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-ones occurred only at the pyrrole ring, giving 10-alkoxy-13-dimethylaminomethyl derivatives. Taking into account that derivatives of 7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-one system exhibited hypoglicemic and anabolic activities, the obtained Mannich bases may be of interest as potential biologically active substances.

Introduction

The Mannich reaction rightfully occupies a worthy place as a versatile and convenient approach to bioactive skeletons and a powerful tool for the chemical modification of many biologically active natural substrates and/or well-established drugs [1-3]. The introduction of aminoalkyl Mannich side chain

mainly used to increase the solubility, bioavailability and/or activity of the bioactive molecules. The relative position of Mannich side chain in a molecule plays a crucial role in determining the activity of the molecule. Mannich bases have a great potential in the field of medicinal chemistry as antimicrobial, antimalarial, antitubercular antitumor, antioxidant, analgesic, anti-inflammatory, anticonvulsant agents and anti-AD agents. [1-4].

A huge amount of data on aminomethylation of chromones, which is one of the priority platforms for drug design [5], summarized in review [6], reveals great prospects for introducing new pharmacophore substituents into the chromone cycle and/or designing new oxygen-containing heterocyclic systems. It is known that Mannich bases of chromones are powerful stimulators of the central nervous system [7], antitumor, antibacterial, and antioxidant agents [8–10], ATR kinase inhibitors and anticancer agents [11]. They also exhibit antiplatelet aggregation activity [12, 13] and anticholinesterase inhibitory activity [14].

Data on aminomethylation of condensed chromones are rather scarce. Mannich bases of natural condensed chromones are predominantly represented by aminomethyl derivatives of xanthones and furochromones (**Figure 1**).

2-Dialkylaminomethylxanthones **1** showed capacity to inhibit acetylcholinesterase and antioxidant property, making them potential anti-Alzheimer agents [15-17]. Xanthone Mannich bases **2** have also been promising anticonvulsant agents [16]. (Imidazol-1-yl)methyl derivatives of xanthone **3**, which have shown rather high efficiency as P450-17 inhibitors, represent a new class of non-steroidal aromatase inhibitors and might be new leads for the development of drug candidates for androgen-dependent diseases [18].

Natural furo[3,2-*g*]chromone khellin under Mannich reaction afforded the corresponding 6-dialkylaminomethyl derivatives **4** [19], while norvisnagin provided 9-aminomethyl derivatives **5**, which exhibited DNA binding affinity and antiviral activity [20].

Mannich bases of condensed chromones containing a 2,3-fused heterocyclic ring are represented in the literature only by aminomethyl derivatives of 9-hydroxy-12*H*-chromeno[2,3-*c*]indolizin-12-one and 10-hydroxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-one [21, 22] (**Figure 1**). Aminomethylation can occur at several reaction centers and depending on the substituents present in the condensed systems leads to trisubstituted products **6** and **7**; diaminomethyl derivative **8** in the presence of a substituent in the pyrrole ring and monosubstitution product **9** in the case of the 9-OMe substituent in a condensed system.

The classic Mannich reaction using formaldehyde and amines was applied for access to Mannich bases of xanthones and furochromones [15, 17, 20], while aminomethyl

derivatives of polycyclic systems **6-9** were synthesized by modified Mannich methodology with *bis*dimethylaminomethane [21, 22]. 9-Aminomethyl norvisnagin **5** and 1-(imidazol-1-ylmethyl)-9*H*-9-xanthenone **3** were also obtained by reacting the corresponding chloro- or bromomethyl derivatives with different amines [18, 20].

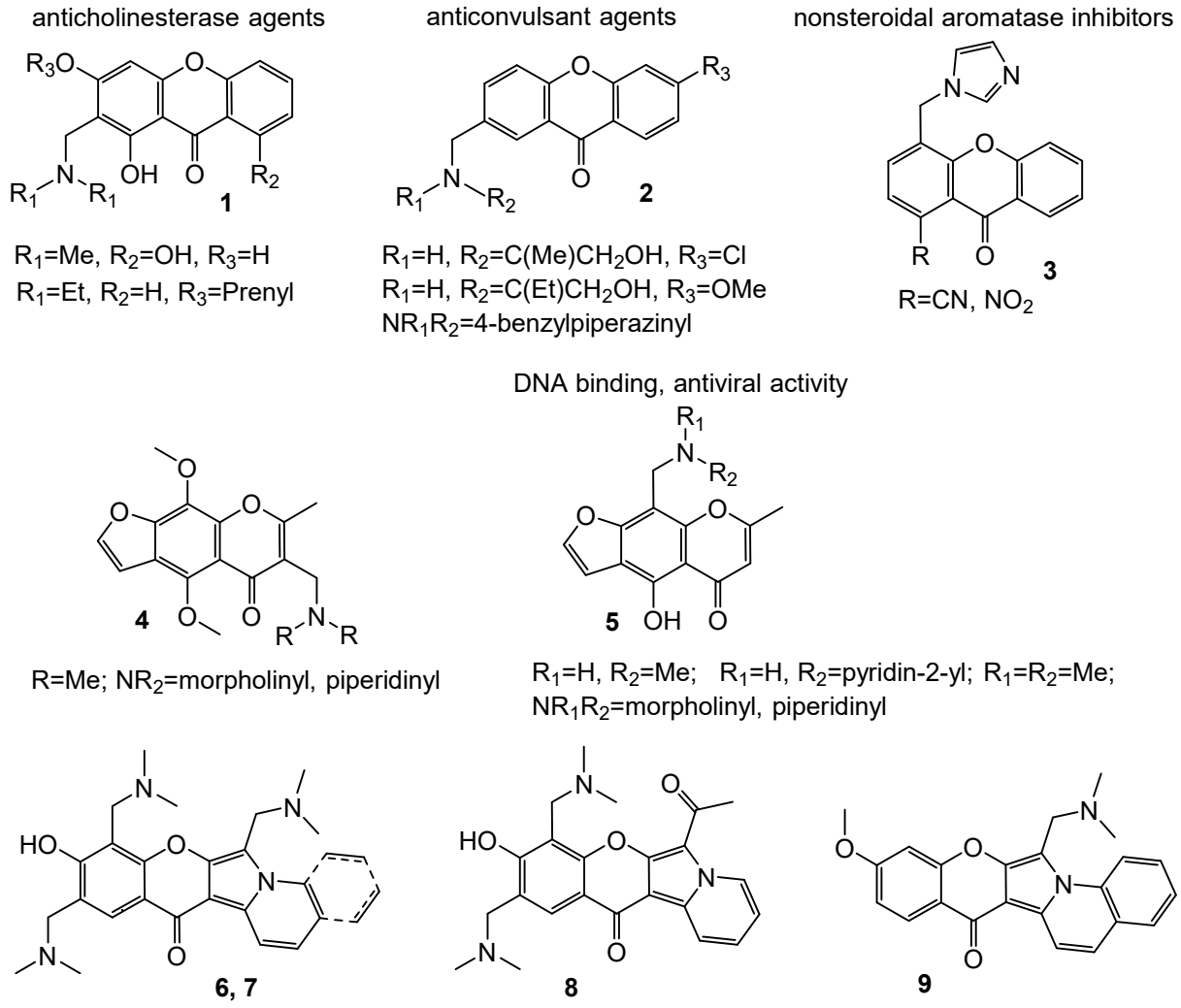


Figure 1. Condensed chromones Mannich bases and their biological activity

The present study is focused on expanding the database of Mannich bases of condensed chromones containing a 2,3-fused heterocyclic ring by varying both 2,3-fused heterocyclic ring and substituents in the condensed system and introduced aminoalkyl substituents.

Experimental part

The reaction progress and identity of obtained compounds were monitored by TLC on Silufol UV-254 plates using $CHCl_3$-MeOH (9:1) system. Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope. NMR spectra were recorded on Varian Mercury 400 spectrometer (at 400.46 for ^1H and 100.7 MHz for ^{13}C) using a DMSO residual solvent signal as an internal standard; chemical shifts (δ) are given in ppm and coupling constants J are given in Hz. Elemental analyses for C, H, and N were performed using Vario micro cube (Elementar Analysen-systeme GmbH).

*9-Alkyl-8-hydroxy-3-methyl-11H-chromeno[3',2':3,4]pyrrolo[2,1-b][1,3]thiazol-11-ones (**10a**, **10b**)* and *5-acyl-9-alkyl-8-hydroxy-3-methyl-11H-chromeno[3',2':3,4]-pyrrolo[2,1-b][1,3]thiazol-11-ones (**10c**, **10d**)* were obtained according to the literature procedures [23]. *9-Hydroxy-10-ethyl-12H-chromeno[3,2-a]indolizin-12-one (**11a**), 9-hydroxy-8-methyl-12H-chromeno[3,2-a]-indolizin-12-one (**11b**)* and *10-hydroxy-7H-chromeno[3',2':3,4]pyrrolo[1,2-a]quinolin-7-one (**12a**)* were synthesized similar to the published protocols [22, 24].

*9-Ethyl-10-hydroxy-7H-chromeno-[3',2':3,4]pyrrolo[1,2-a]quinolin-7-one (**12b**).*
A mixture of α-(quinolin-2-yl)-2,4-dihydroxy-5-ethylacetophenone (0.31 g, 1 mmol), pyridine (0.25 mL, 3 mmol) and chloroacetyl chloride (0.24 ml, 3 mmol) in 5 mL of acetonitrile was refluxed for 2 h. The precipitate, obtained after cooling, was filtered off and dissolved in 3 mL of DMF. 5% Water solution of NaOH (0.2 mL) was added to this solution and refluxed for 10 min, then cooled, neutralized with HCl to pH 7 and the resultant precipitate was filtered off.
Yield 0.22 g (67 %), light yellow solid, mp >300°C (DMF). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 1.18 (3H, t, J=7.6, $\underline{CH_3}CH_2$), 2.61 (2H, q, J=7.6, $CH_3\underline{CH_2}$), 6.88 (1H, s, H-11), 7.57 (1H, t, J=8.4, H-3), 7.70-7.79 (2H, m, H-2, H-5), 7.88 (1H, s, H-8), 8.00 (1H, d, J=8.4, H-4), 8.16 (1H, d, J=9.6, H-6), 8.43 (1H, d, J=8.4, H-1), 8.52 (1H, s, H-13), OH exchanged with D_2O). Found, %: C 76.64; H 4.51; N 4.22. $C_{21}H_{15}NO_3$. Calculated, %: C 76.58; H 4.59; N 4.25.

*10-Alkoxy-7H-chromeno[3',2':3,4]-pyrrolo[1,2-a]quinolin-7-ones **12c**, **12d***, were obtained from the corresponding α-quinolyl-4-alkoxy-2-hydroxyacetophenones (1 mmol) similar to 10-methoxy-7*H*-chromeno-[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-one [22].

*10-Propoxy-7H-chromeno[3',2':3,4]-pyrrolo[1,2-a]quinolin-7-one (**12c**).* Yield 0.14 g (41%), yellow solid, mp 226-227°C (dioxane). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 0.99 (3H, t, J=7.6, $\underline{CH_3}(CH_2)_2$), 1.77 (2H, m, $CH_3\underline{CH_2}CH_2$), 4.08 (2H, t, J=7.6, $CH_3CH_2\underline{CH_2}$), 6.98 (1H, d, J=8.4, H-9), 7.10 (1H, s, H-11), 7.61 (1H, t, J=7.6, H-

3), 7.76-7.79 (2H, m, H-2, H-5), 8.02 (1H, d, J=7.6, H-4), 8.09 (1H, d, J=8.4, H-8), 8.17 (1H, d, J=9.2, H-6), 8.48 (1H, d, J=8.4, H-1), 8.58 (1H, s, H-13), OH exchanged with D_2O). Found, %: C 77.01; H 4.93; N 4.05. $C_{22}H_{17}NO_3$. Calculated, %: C 76.95; H 4.99; N 4.08.

10-(3-Chloropropoxy)-7H-chromeno-[3',2':3,4]pyrrolo[1,2-a]quinolin-7-one ***(12d)***. Yield 0.19 g (50%), yellow solid, mp 239-240°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 2.22 (2H, t, J=6.0, $CH_2\underline{CH_2}CH_2$), 3.82 (2H, t, J=6.0, $ClCH_2$), 4.25 (2H, t, J=6.0, CH_2O), 7.00 (1H, d, J=8.4, H-9), 7.15 (1H, s, H-11), 7.60 (1H, t, J =7.6, H-3), 7.76-7.81 (2H, m, H-2, H-5), 8.02 (1H, d, J=8.8, H-4), 8.11 (1H, d, J=8.4, H-8), 8.18 (1H, d, J=9.2, H-6), 8.48 (1H, d, J=8.4, H-1), 8.59 (1H, s, H-13), OH exchanged with D_2O). Found, %: C 69.85; H 4.35; N 3.78. $C_{22}H_{16}ClNO_3$. Calculated, %: C 69.94; H 4.27; N 3.71.

General procedure for the synthesis of 9-alkyl-8-hydroxy-3-methyl-11H-chromeno-[3',2':3,4]pyrrolo[2,1-b][1,3]thiazol-11-one Mannich bases ***14****, 10-(alk)oxy-7H-chromeno[3',2':3,4]pyrrolo[1,2-a]quinolin-7-one Mannich bases* ***16*** *and 6,8-di(dimethylaminomethyl)-10-ethyl-9-hydroxy-12H-chromeno[3,2-a]indolizin-12-one* ***(15aa)***. The corresponding product **10**, **11a** or **12** (1 mmol) and the corresponding *bis*dialkylaminomethane (**13**) (4 mmol) in 5 mL of dioxane were refluxed for 3 h (5 h for **16ab**) (TLC control). The solution was cooled and the resulted precipitate was filtered off and washed with dioxane. The solvent and the aminal residue for products **14ab**, **15aa** and **16ab** were distilled off in vacuo, triturated with EtOAc and the precipitate was filtered off.

5-Acetyl-7-dimethylaminomethyl-9-ethyl-8-hydroxy-3-methyl-11H-chromeno-[3',2':3,4]pyrrolo[2,1-b][1,3]thiazol-11-one ***(14ca)***. Yield 0.37 g (93%), light yellow solid, mp 267-268°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 1.18 (3H, t, J=7.6, 9-$\underline{CH_3}CH_2$), 2.41 (6H, s, 7-$(CH_3)_2N$), 2.62 (2H, q, J=7.6, 9-$CH_3\underline{CH_2}$), 2.66 (3H, s, 3-CH_3), 2.68 (3H, s, 5-CH_3CO), 4.08 (2H, s, 7-CH_2N), 7.29 (1H, s, H-2), 7.78 (1H, s, H-10), OH exchanged with D_2O). Found, %: C 63.18; H 5.37; N 6.92. $C_{21}H_{22}N_2O_4S$. Calculated, %: C 63.30; H 5.56; N 7.03.

7-Dimethylaminomethyl-8-hydroxy-3-methyl-5-propionyl-9-propyl-11H-chromeno-[3',2':3,4]pyrrolo[2,1-b][1,3]thiazol-11-one ***(14da)***. Yield 0.30 g (70%), light yellow solid, mp 194-195°C (dioxane). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (J, Hz): 0.91 (3H, t, J=7.6, 9-$\underline{CH_3}(CH_2)_2$), 1.23 (3H, t, J=7.6, 5-$\underline{CH_3}CH_2CO$), 1.59-1.62 (2H, m, 9-$CH_3\underline{CH_2}CH_2$), 2.41 (6H, s, 7-$(CH_3)_2N$), 2.57 (2H, t, J=7.6, 9-$CH_3CH_2\underline{CH_2}$), 2.68 (3H, s, 3-CH_3), 3.03 (2H, q, J = 7.6, 5-$CH_3\underline{CH_2}CO$), 4.07 (2H, s, 7-CH_2N), 7.31 (1H, s, H-2), 7.77 (1H, s, H-10), OH exchanged with D_2O). Found, %: C 64.97; H 6.27; N 6.55. $C_{23}H_{26}N_2O_4S$. Calculated, %: C 64.77; H 6.14; N 6.57.

*5,7-Di(dimethylaminomethyl)-9-ethyl-8-hydroxy-3-methyl-11H-chromeno[3',2':3,4]-pyrrolo[2,1-b][1,3]thiazol-11-one (**14aa**).* Yield 0.29 g (70%), light yellow solid, mp 185-186°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 1.22 (3H, t, J=7.6, 9-$\underline{CH_3}CH_2$), 2.22 (6H, s, 5-$(CH_3)_2N$), 2.42 (6H, s, 7-$(CH_3)_2N$), 2.62 (2H, q, J=7.6, 9-$CH_3\underline{CH_2}$), 2.77 (3H, s 3-CH_3), 3.70 (2H, s, 5-CH_2N), 3.99 (2H, s, 7-CH_2N), 7.00 (1H, s, H-2), 7.75 (1H, s, H-10), OH exchanged with D_2O). Found, %: C 64.18; H 6.59; N 10.14. $C_{22}H_{27}N_3O_3S$. Calculated, %: C 63.90; H 6.58; N 10.16.

*5,7-Di(dimethylaminomethyl)-8-hydroxy-3-methyl-9-propyl-11H-chromeno-[3',2':3,4]pyrrolo[2,1-b][1,3]thiazol-11-one (**14ba**).* Yield 0.24 g (56%), light yellow solid, mp 189-190°C (dioxane). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (J, Hz): 0.91 (3H, t, J=7.6, 9-$\underline{CH_3}(CH_2)_2$), 1.56-1.62 (2H, m, 9-$CH_3\underline{CH_2}CH_2$), 2.19 (6H, s, 5-$(CH_3)_2N$), 2.38 (6H, s, 7-$(CH_3)_2N$), 2.58 (2H, t, J = 7.6, 9-$CH_3CH_2\underline{CH_2}$), 2.76 (3H, s 3-CH_3), 3.72 (2H, s, 5-CH_2N), 4.04 (2H, s, 7-CH_2N), 7.10 (1H, s, H-2), 7.75 (1H, s, H-10), OH exchanged with D_2O). Found, %: C 64.46; H 6.98; N 9.82;. $C_{23}H_{29}N_3O_3S$. Calculated, %: C 64.61; H 6.84; N 9.83.

*5,7-Di(diethylaminomethyl)-9-ethyl-8-hydroxy-3-methyl-11H-chromeno[3',2':3,4]-pyrrolo[2,1-b][1,3]thiazol-11-one (**14ab**).* Yield 0.25 g (53%), light yellow solid, mp 138-139°C (EtOAc). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 0.97 (6H, t, J=7.6, 5-$(\underline{CH_3}CH_2)_2N$), 1.09 (6H, t, J=7.6, 7-$(\underline{CH_3}CH_2)_2N$), 1.17 (3H, t, J=7.6, 9-$\underline{CH_3}CH_2$), 2.53 (4H, q, J=7.6, 5-$(CH_3\underline{CH_2})_2N$), 2.59 (2H, q, J=7.6, 9-$CH_3\underline{CH_2}$), 2.68 (4H, q, J=7.6, 7-$(CH_3\underline{CH_2})_2N$), 2.80 (3H, s 3-$CH_3$), 3.91 (2H, s, 5-$CH_2N$), 4.14 (2H, s, 7-$CH_2N$), 7.07 (1H, s, H-2), 7.76 (1H, s, H-10), OH exchanged with D_2O). Found, %: C 66.63; H 7.58; N 8.85. $C_{26}H_{35}N_3O_3S$. Calculated, %: C 66.49; H 7.51; N 8.95.

*6,8-Di(dimethylaminomethyl)-10-ethyl-9-hydroxy-12H-chromeno[3,2-a]indolizin-12-one (**15aa**).* Yield 0.23 g (56%), light yellow solid, mp 250°C (decomp.) (EtOAc). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 1.14 (3H, t, J=7.2, $\underline{CH_3}CH_2$), 2.17 (6H, s, 8-$(CH_3)_2N$), 2.47 (6H, s, 6-$(CH_3)_2N$), 2.57 (2H, q, J=7.2, $CH_3\underline{CH_2}$), 3.52 (2H, s 10-CH_2N), 3.97 (2H, s 6-CH_2N), 7.15 (1H, t, J=8.4, H-2), 7.37 (1H, t, J=8.4, H-3), 7.81 (1H, s, H-11), 8.30 (1H, d, J =8.4, H-1), 8.45 (1H, d, J =6.4, H-4), OH exchanged with D_2O). Found, %: C 70.75; H 7.31; N 10.17. $C_{24}H_{30}N_3O_3$. Calculated, %: %: C 70.56; H 7.40; N 10.29.

*9,11,13-Tri(diethylaminomethyl)-10-hydroxy-7H-chromeno[3',2':3,4]pyrrolo[1,2-a]quinolin-7-one (**16ab**).* Yield 0.32 g (58%), light yellow solid, mp 139-140°C (EtOAc). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 1.10-1.20 (18H, m, 3 $(\underline{CH_3}CH_2)_2N$), 2.62-2.77 (12H, m, 3 $(CH_3\underline{CH_2})_2N$, 4.03 (2H, s, 13-$NCH_2$), 4.16 (4H,

s, 9-NCH_2, 11-CH_2N), 7.51 (1H, t, J=7.6, H-3), 7.61-7.65 (2H, m, H-2, H-5), 7.89 (1H, d, J=6.8 H-4, 7.97 (1H, s, H-8), 8.29 (1H, d, J=8.8, H-6), 9.24 (1H, d, J=6.8, H-1), OH exchanged with D_2O). Found, %: 73.25; H 7.95; N 10.16. $C_{34}H_{44}N_4O_3$. Calculated, %: C 73.35; H 7.97; N 10.06.

*11,13-Di(dimethylaminomethyl)-9-ethyl-10-hydroxy-7H-chromeno[3',2':3,4]pyrrolo[1,2-a]quinolin-7-one (**16ba**).* Yield 0.28 g (63%), light yellow solid, mp 205-206°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 1.18 (3H, t, J=7.6, $\underline{CH_3}CH_2$), 2.36 (6H, s, $N(CH_3)_2$), 2.40 (6H, s, $N(CH_3)_2$), 2.61 (2H, q, J=7.6, $CH_3\underline{CH_2}$), 3.96 (2H, s, 13-NCH_2), 4.09 (2H, s, 11-NCH_2), 7.56 (1H, t, J=8.4, H-3), 7.69-7.75 (2H, m, H-2, H-5), 7.82 (1H, s, H-8), 7.97 (1H, d, J=8.4, H-4), 8.21 (1H, d, J =9.2, H-6), 8.88 (1H, d, J=8.4, H-1), OH exchanged with D_2O). Found, %: 73.12; H 6.59; N 9.47. $C_{27}H_{29}N_3O_3$. Calculated, %: C 73.12; H 6.59; N 9.47.

*11,13-Di(diethylaminomethyl)-9-ethyl-10-hydroxy-7H-chromeno[3',2':3,4]pyrrolo[1,2-a]quinolin-7-one (**16bb**).* Yield 0.30 g (60%), light yellow solid, mp 177-178°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 1.15-1.18 (12H, m, 2 $(\underline{CH_3}CH_2)_2N$), 1.24 (6H, t, J=7.6, 9-$\underline{CH_3}CH_2$), 2.62 (2H, q, J=7.6, 8-$CH_3\underline{CH_2}$), 2.73-2.76 (8H, m, 2 $(CH_3\underline{CH_2})_2N$, 4.13 (2H, s, 13-$NCH_2$), 4.16 (2H, s, 11-$CH_2N$), 7.50 (1H, t, J=7.6, H-3), 7.59-7.62 (2H, m, H-2, H-5), 7.81 (1H, s, H-8), 7.90 (1H, d, J=8.0, H-4), 8.28 (1H, d, J =8.8, H-6), 9.23 (1H, d, J =8.0, H-1), OH exchanged with D_2O). Found, %: 74.38; H 7.45; N 8.46. $C_{31}H_{37}N_3O_3$. Calculated, %: C 74.52; H 7.46; N 8.41.

*13-Dimethylaminomethyl-10-propoxy-7H-chromeno[3',2':3,4]pyrrolo[1,2-a]quinolin-7-one (**16ca**).* Yield 0.24 g (60%), yellow solid, mp 198-199°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 0.99 (3H, t, J=7.6, $\underline{CH_3}(CH_2)_2$, 1.77 (2H, m, $CH_3\underline{CH_2}CH_2$), 2.35 (6H, s, $(CH_3)_2N$), 3.99 (2H, s, CH_2N), 4.08 (2H, t, J=7.6, $CH_3CH_2\underline{CH_2}O$), 6.94 (1H, d, J=8.4, H-9), 7.07 (1H, s, H-11), 7.56 (1H, t, J =7.6, H-3), 7.74-7.76 (2H, m, H-2, H-5), 7.98 (1H, d, J=8.8, H-4), 8.05 (1H, d, J=8.4, H-8), 8.24 (1H, d, J=8.8, H-6), 8.93 (1H, d, J=8.4, H-1), OH exchanged with D_2O). Found, %: C 74.98; H 6.04; N 7.00. $C_{25}H_{24}N_2O_3$. Calculated, %: C 74.98; H 6.04; N 7.00.

*10-(3-Chloropropoxy)-13-dimethyl-aminomethyl-7H-chromeno[3',2':3,4]pyrrolo-[1,2-a]quinolin-7-one (**16da**).* Yield 0.27 g (62%), yellow solid, mp 184-185°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 2.22 (2H, t, J=6.0, $CH_2\underline{CH_2}CH_2$), 2.34 (6H, s, $(CH_3)_2N$), 3.82 (2H, t, J=6.0, CH_2Cl), 3.94 (2H, s, CH_2N), 4.22 (2H, t, J=6.0, CH_2O), 6.91 (1H, d, J=7.6, H-9), 7.06 (1H, s, H-11), 7.54 (1H, t, J=7.6, H-3), 7.70-7.74 (2H, m, H-2, H-5), 7.95 (1H, d, J=7.6, H-4), 8.02 (1H, d, J=8.4, H-8), 8.21 (1H, d, J=7.2, H-6), 8.90 (1H,

d, J=8.4, H-1), OH exchanged with D_2O. ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm (Hz): 31.5 ($CH_2\underline{C}H_2CH_2$), 41.8 ($\underline{C}H_2Cl$), 44.3 ($\underline{C}H_3)_2N$), 52.3 ($\underline{C}H_2N$), 65.1 ($\underline{C}H_2O$), 101.2 (<u>C</u>, C-6b), 101.2 (<u>C</u>H, C-11), 109.6 (<u>C</u>, C-13), 112.2 (<u>C</u>H, C-9), 116.1 (<u>C</u>, C-7a), 116.9 (<u>C</u>H, C-6), 119,2(<u>C</u>H, C-1), 124.5 (<u>C</u>H, C-5), 125.0 (<u>C</u>H, C-3), 125.1 (<u>C</u>, C-4a), 127.0 (<u>C</u>H, C-8), 127.3 (<u>C</u>, C-6a), 128.8 (<u>C</u>H, C-2), 128.9 (<u>C</u>H, C-4), 133.3 (<u>C</u>, C-14a), 147.2 (<u>C</u>, C-12a), 157.7 (<u>C</u>, C-11a), 162.8 (<u>C</u>, C-10), 172.6 (<u>C</u>, C-7).
Found, %: C 69.04; H 5.33; N 6.44. $C_{25}H_{23}ClN_2O_3$. Calculated, %: C 69.04; H 5.33; N 6.44.

*General procedure for the preparation of aminomethyl derivatives **15ba**, **15bb**, **15bc** of 9-hydroxy-8-methyl-12H-chromeno[3,2-a]-indolizin-12-one (**11b**).* A mixture of 9-hydroxy-8-methyl-12*H*-chromeno[3,2-*a*]indolizin-12-one (**11b**) (0.53 g, 2 mmol) and 2 mL of the corresponding aminal **13** in 20 mL of dioxane was refluxed for 5 h (TLC control). The solvent and the aminal residue were distilled off in vacuo, triturated with ether, the precipitate was filtered off and crystallized from methyl ethyl ketone or ethyl acetate.

*6,10-Di(dimethylaminomethyl)-9-hydroxy-8-methyl-12H-chromeno[3,2-a]-indolizin-12-one (**15ba**).* Yield 0.53 g (70%), yellow solid, mp 194-195ºC (MeC(O)Et). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 2.25 (6H, s, 10-$(CH_3)_2N$), 2.30 (3H, s, 8-CH_3), 2.37 (6H, s, 6-$(CH_3)_2N$), 3.79 (2H, s 10-CH_2N), 3.87 (2H, s 6-CH_2N), 7.07 (1H, t, J=7.6, H-3), 7.29 (1H, t, J=7.6, H-2), 7.70 (1H, s, H-11), 8.25 (1H, d, J=7.6, H-1), 8.45 (1H, d, J =6.4, H-4), OH exchanged with D_2O). Found, %: C 69.82; H 6.68; N 11.00. $C_{22}H_{25}N_3O_3$. Calculated, %: C 69.64; H 6.64; N 11.07.

*6,10-Di(diethylaminomethyl)-9-hydroxy-8-methyl-12H-chromeno[3,2-a]indolizin-12-one (**15bb**).* Yield 0.64 g (71%), yellow solid, mp 194-195ºC (MeC(O)Et). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 1.06 (6H, t, J=7.6, 10-$(\underline{CH_3}CH_2)_2N$), 1.12 (6H, t, J=7.6, 6-$(\underline{CH_3}CH_2)_2N$), 2.28 (3H, s, 8-$CH_3$), 2.56 (4H, q, J=7.6, 10-$(CH_3\underline{CH_2})_2N$), 2.66 (4H, q, J=7.6, 6-$(CH_3\underline{CH_2})_2N$), 3.90 (2H, s, 10-$CH_2N$), 4.01 (2H, s, 6-$CH_2N$), 7.05 (1H, t, J=7.6, H-3), 7.26 (1H, t, J=7.6, H-2), 7.69 (1H, s, H-11), 8.23 (1H, d, J=7.6, H-1), 8.41 (1H, d, J=6.4, H-4), OH exchanged with D_2O). Found, %: C 71.83; H 7.65; N 9.70. $C_{26}H_{33}N_3O_3$. Calculated, %: C 71.70; H 7.64; N 9.65.

*6,10-Di(4-methylpiperazin-1-ylmethyl)-9-hydroxy-8-methyl-12H-chromeno[3,2-a]-indolizin-12-one (**15bc**).* Yield 0.69 g (71%), yellow solid, mp 194-195ºC (EtOAc). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 2.15 (3H, s, 10-CH_3N), 2,10-2,30 (16H, 8 CH_2 piperaz) 2.23 (3H, s, 8-CH_3), 2.31 (3H, s, 6-CH_3N), 3.84 (3H, s 10-CH_2N), 3.95 (3H, s 6-CH_2N), 7.07 (1H, t, J=7.6, H-3), 7.30 (1H, t, J=7.6, H-2), 7.70 (1H, s, H-11), 8.25 (1H, d, J=7.6, H-1), 8.45 (1H, d, J=6.4, H-4), OH

exchanged with D_2O). Found, %: C 68.87; H 7.25; N 14.10. $C_{28}H_{35}N_5O_3$. Calculated, %: C 68.69; H 7.21; N 14.30.

Results and discussion

Condensed chromone systems containing 2,3-fused pyrrolothiazole (**10**), indolizine (**11**) and pyrroloquinoline (**12**) cycles were chosen as starting materials (**Figure 2**).

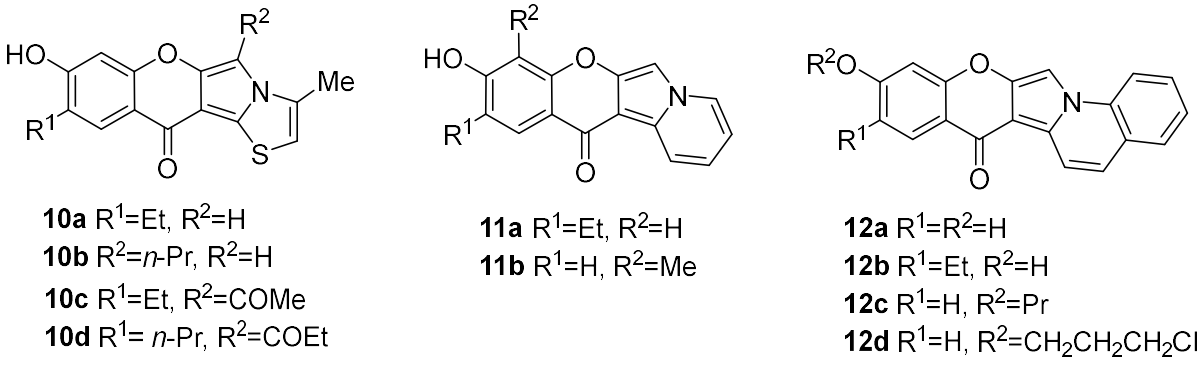
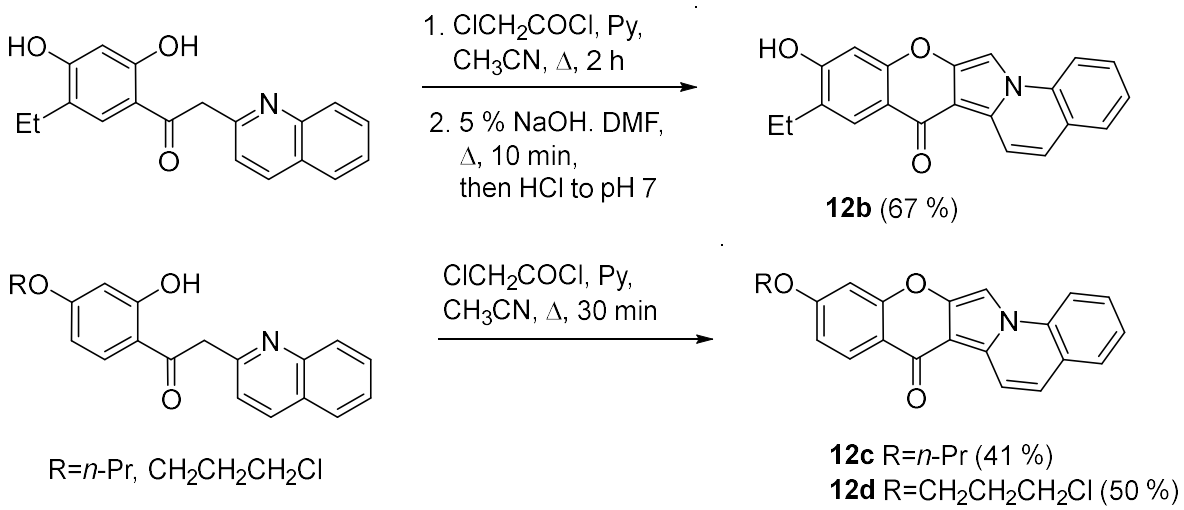


Figure 2. Condensed chromones as starting materials

As we have previously reported, 8-hydroxy-3-methyl-11*H*-chromeno[3',2':3,4]-pyrrolo[2,1-*b*][1,3]thiazol-11-ones (**10a**, **10b**) [23] were obtained by refluxing 2-chloromethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4*H*-4-chromenones, yielded from α-thiazolyl-2,4-dihydroxyacetophenones and chloroacetyl chloride [25, 26], in acetic acid. Their 5-acyl derivatives **10c**, **10d** were obtained similarly under reflux in acetic or propionic anhydrides, followed by acid hydrolysis [23].

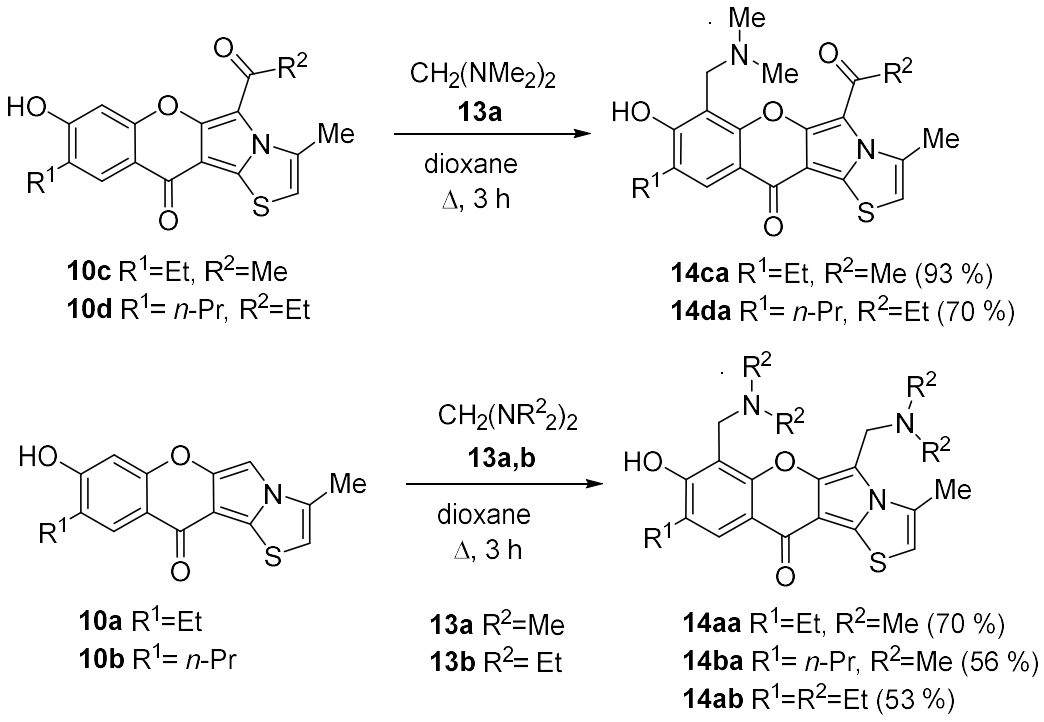
9-Hydroxy-6/8-R-12*H*-chromeno[3,2-*a*]indolizin-12-ones (**11a**, **11b**) [24] and 10-hydroxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-one (**12a**) [22] were previously synthesized *via* the treatment of the corresponding α-pyridyl/quinolyl-2,4-dihydroxyacetophenones with chloroacetyl chloride in acetonitrile in the presence of pyridine, followed by hydrolysis. 9-Ethyl-10-hydroxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-one (**12b**) was obtained similarly according to the **Scheme 1**, while only the first step was used for the synthesis of 10-alkoxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-ones **12c**, **12d**, similar to 10-methoxy derivative [22].



Scheme 1. The synthesis of 10- hydroxy/alkoxy -7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-ones (**12b-d**)

The modified Mannich methodology, using a 4-fold excess of *bis*dialkylaminomethanes **13** as an aminomethylating agent was utilized to synthesize the condensed chromones **10-12** Mannich bases. The reaction was carried out in dioxane at reflux for 3-5 hours.

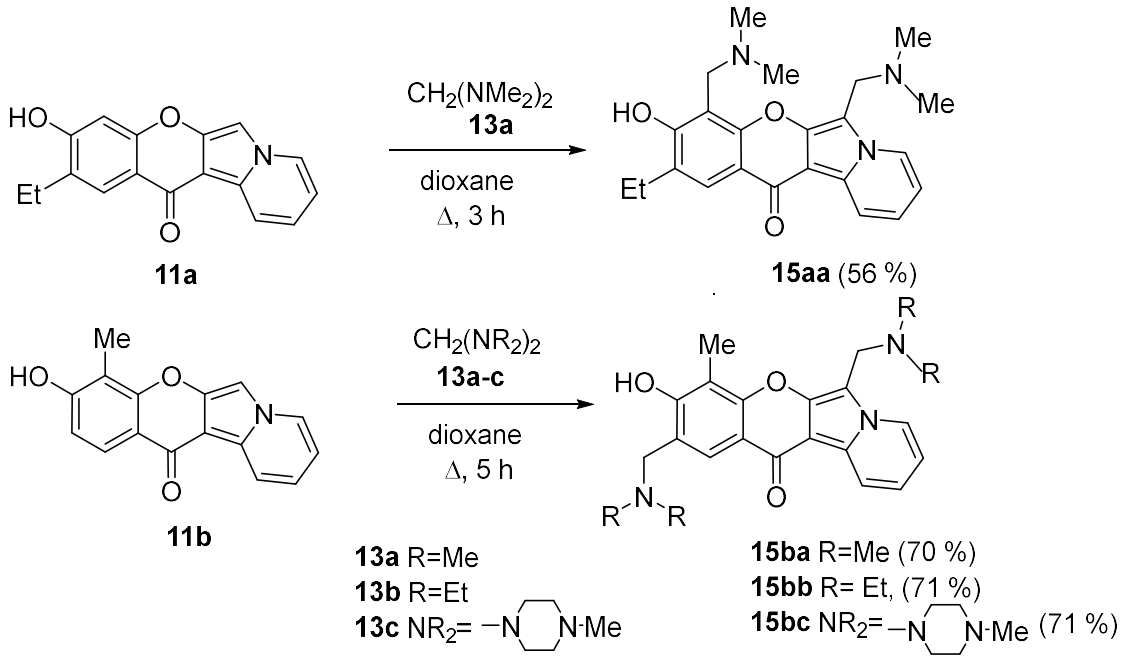
Aminomethylation of 5-acyl-8-hydroxy-3-methyl-11*H*-chromeno[3',2':3,4]pyrrolo[2,1-*b*][1,3]thiazol-11-ones **10c**, **10d** with *bis*dimethylaminomethane (**13a**) proceeded in *ortho* position to hydroxyl group as it is known for aminomethylation of 7-hydroxychromones [4]. It occurred smoothly with formation of 7-aminomethyl derivatives **14ca**, **14da** in 70-93 % yields (**Scheme 2**). The ^{1}H NMR spectra of compounds **14ca**, **14da** in DMSO-d_6 showed the disappearance of the singlet for H-7 at 6.68-6.87 ppm comparing to the initial products **10c**, **10d** and the presence of two new singlets, assigned to the methylene group at 4.07-4.08 ppm and dimethylamino group at 2.41 ppm.



Scheme 2. The synthesis of 9-alkyl-8-hydroxy-3-methyl-11*H*-chromeno[3',2':3,4]pyrrolo[2,1-*b*][1,3]thiazol-11-one Mannich bases **14**

Taking into account that α-position of pyrrole is active to the electrophilic attack, aminomethylation of 5-unsubstituted 8-hydroxy-3-methyl-11*H*-chromeno[3',2':3,4]-pyrrolo[2,1-*b*][1,3]thiazol-11-ones **10a**, **10b** can occur at two electrophilic centers 5 and 7. Indeed, the interaction of products **10a**, **10b** with an excess of *bis*dimethylaminomethane (**13a**) or *bis*diethylaminomethane (**13b**) led to 5,7-di(dialkylaminomethyl) derivatives **14aa, 14ab, 14ba** (**Scheme 2**), which was confirmed by the presence of two singlets for the methylene groups at 3.70-3.91 ppm (5-CH_2N) and 3.99-4.14 ppm (7-CH_2N) and the signals of the two dialkylamino groups.

Aminomethylation of 10-ethyl-9-hydroxy-12*H*-chromeno[3,2-*a*]indolizin-12-one (**11a**) occurs in the same way, giving 6,8-di(dimethylaminomethyl) derivative **15aa** (**Scheme 3**).

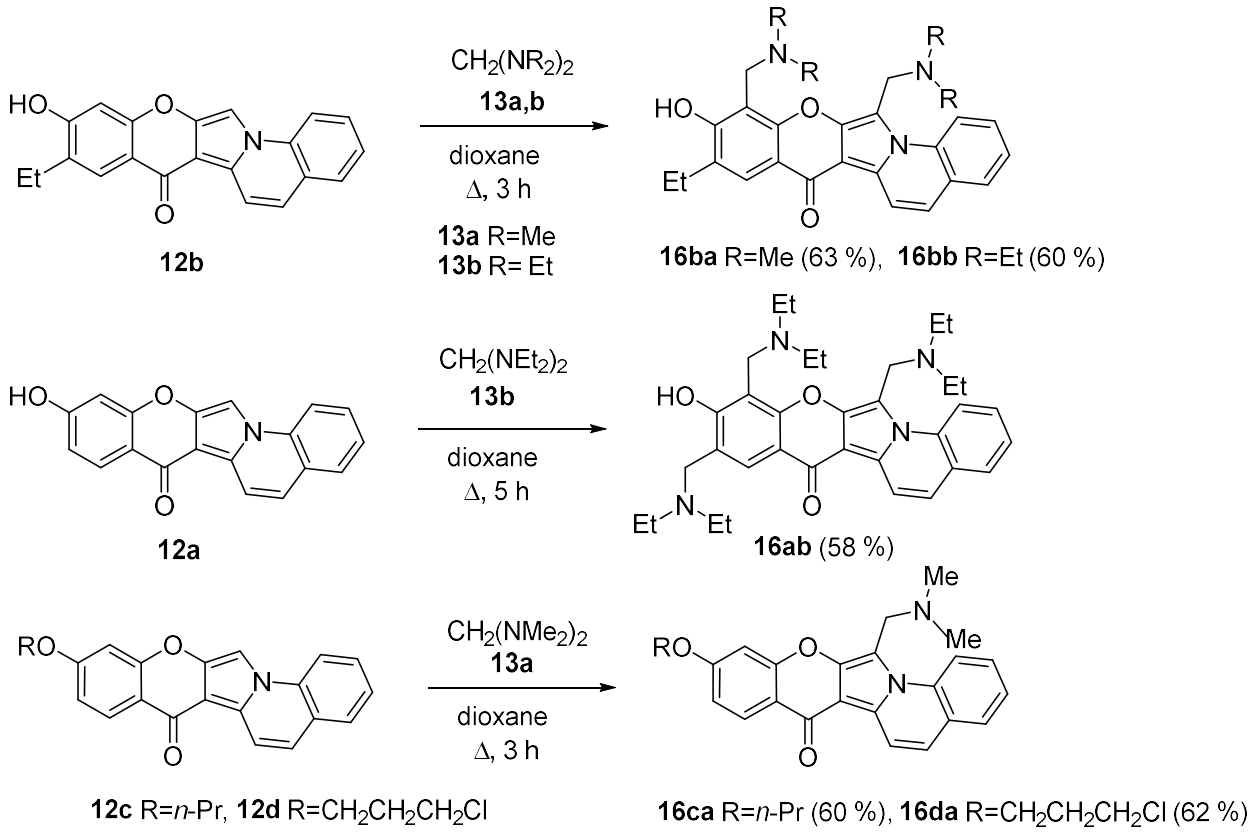


Scheme 3. The synthesis of 6,8- and 6,10-di(dialkylaminomethyl)-9-hydroxy-12*H*-chromeno[3,2-*a*]indolizin-12-ones **15**

In the case of 9-hydroxy-8-methyl-12*H*-chromeno[3,2-*a*]indolizin-12-one **11b** the reaction with *bis*dimethylaminomethane, *bis*diethylaminomethane or *bis*di(4-methyl)piperazinylmethane (**13a-c**) afforded 6,10-di(dialkylaminomethyl) derivatives **15ba**, **15bb**, **15bc** (**Scheme 3**). The ^{1}H NMR spectra of these compounds revealed the presence of only one singlet at 7.69-7.70 ppm assigned to H-11. The appearance of two two-proton singlets for CH_2 groups and a double proton set of N-alkyl substituents support the successful aminomethylation at positions 6 and 10. It should be noted that position 10 of this system, which corresponds to position 6 of the non-condensed 7-hydroxychromone, is less active against electrophilic attack than position 8. Therefore, it took 5 h to reflux the reaction mixture to complete the reaction.

Being that 10-hydroxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-one exhibited hypoglicemic effect [22] and 10-methoxy-9-ethyl-7*H*-chromeno[3',2':3,4]pyrolo-[1,2-*a*]quinolin-7-one had anabolic [27] activity, the derivatives of this system may be promising as potential biologically active substances. That is why it was interesting to expand the range of modified 7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-ones using aminomethylation reaction. It was shown that aminomethylation of 10-hydroxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-one **12a** and **12b** occurred at both the benzene and pyrrole rings, yielding 11,13-di(dialkylaminomethyl)-9-ethyl-10-hydroxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-

7-ones (**16ba, 16bb**) and 9,11,13-tri(diethylaminomethyl)-10-hydroxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-one (**16ab**), respectively. On the other hand aminomethylation of 10-alkoxy-7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-ones (**12c**, **12d**) occurred only at the pyrrole ring, giving 10-alkoxy-13-diaminomethyl products (**16ca**, **16da**).



Scheme 3. The synthesis of 7*H*-chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinolin-7-one Mannich bases **16**

^{1}H NMR data of **16ca**, **16da** revealed only one two-proton singlet at 3.99-3.94 ppm and six-proton singlet at 2.35 ppm assigned to NCH_2 and $N(CH_3)_2$ groups, respectively, in addition to the absence of the corresponding singlet at 8.58-8.59 ppm assigned to the H-13 in the ^{1}H NMR spectrum of the initial compounds **12c**, **12d**. To assign the signals of aromatic protons of chromeno[3',2':3,4]pyrrolo[1,2-*a*]quinoline system, the COSY and 1D-NOE methods were used for compound **16da**. There are NOE effects between proton 8.90 (H-1) and 3.94 (CH_2N), 2.34 ($(CH_3)_2$); between H-5 and H-4. The correlations found are shown in **Figure 3**.

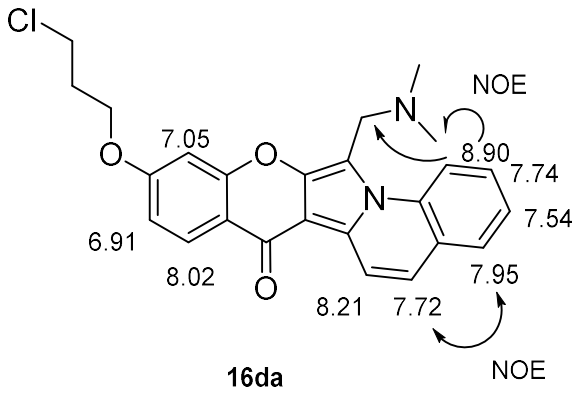


Figure 3. Assignment of ^{1}H chemical shifts by COSY and NOE for **16da**.

DEPT, gHSQC and gHMBC methods were also performed to study the structure of **16da.** The ^{13}C assignment of signals is shown in **Figure 4.**

Obtained Mannich bases were submitted for pharmacological testing

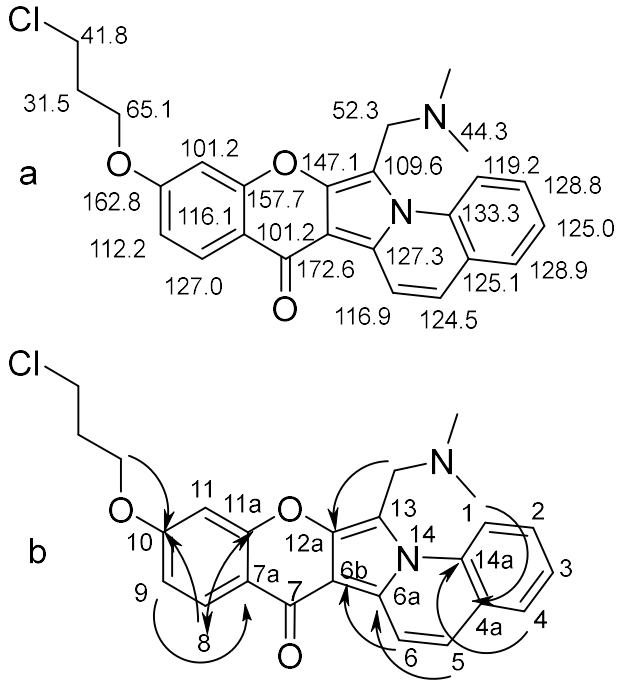


Figure 4. Assignment of ^{13}C chemical shifts - a; gHMBC ^{1}H - ^{13}C correlations - b (arrows) for **16da**

Conclusions

In conclusion, the present study to a certain extent fills the lack of data on the use of condensed chromones containing a 2,3-fused heterocyclic ring as substrates in the Mannich reaction. It was demonstrated that aminomethylation of condensed chromones containing a 2,3-fused indolizine/pyrroloquinoline/pyrrolothiazole heterocyclic ring can be carried out at several reaction centers depending on the structure of the substrate used.

Acknowledgements

The authors are grateful to the European Chemistry School for Ukrainian (ecpsfu.org) for training in the preparation of this publication

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