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Synthesis and biological activity of some heterocyclic compounds containing quinoxaline and coumarin moieties

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2,3-Dichloroquinoxaline (**2**) condensed with 7,8-dihydroxy-4-methylcoumarin to give the 1,4-dioxane derivative **4**. 2.3-Dichloroquinoxaline (**2**) reacted with 4-hydroxycoumarin, 7-hydroxy-4-methylcoumarin and acyl hydrazide **13** to give either the 2,3-(dicoumarin-4-yloxy)quinoxaline (**6**) or the 2,3-di-(4-methylcoumarin-7-yloxy)quinoxaline (**7**) or the 2-chloro-3-(coumarin-4-yloxy)quinoxaline (**8**) or the 2-chloro-3-(4-methylcoumarin-7-yloxy) quinoxaline (**9**) or the ditriazoloquinoxaline **14** or the oxadiazinoquinoxaline **16**, depending on the relative ratios of the reactants and the reaction conditions.

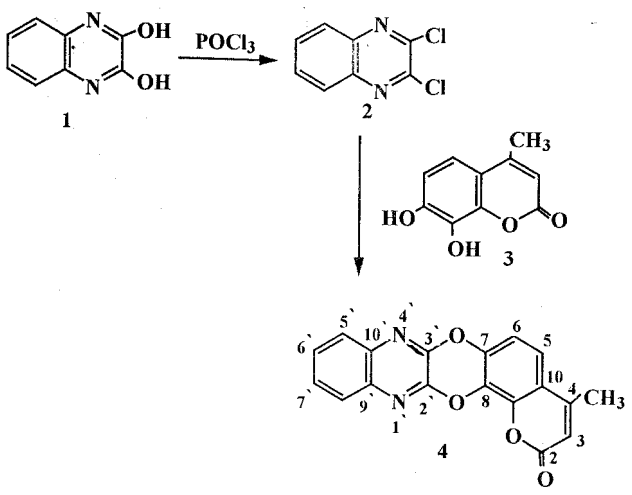
Keywords: 2,3-dichloroquinoxaline, reaction with coumarin derivatives.

Among a wide variety of nitrogen heterocycles that have been explored for developing pharmaceutically important molecules, quinoxalines have played an important role in medicinal chemistry,[1–5] anticancer treatment,[6] as herbicids,[7] as well as for the detection and estimation of metals,[8,9] and as heat stable oil additives.[10] In view of these and in continuation of our work[11–14] in this area, the synthesis of some new heterocyclic compounds containing quinoxaline and coumarin moieties are reported here.

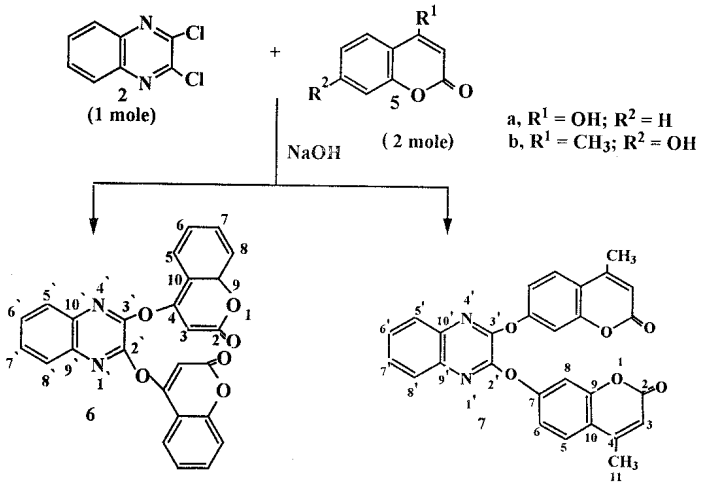
RESULTS AND DISCUSSION

The 2,3-dichloroquinoxaline (**2**) was prepared by the reaction of *o*-phenylenediamine with oxalic acid to give 2,3-dihydroxyquinoxaline (**1**), followed by the treatment of **1** with phosphorus oxychloride. The condensation of 2,3-dichloroquinoxaline (**2**) with 7,8-dihydroxy-4-methylcoumarin (**3**) under alkaline conditions[15] gave the corresponding 1,4-dioxane derivative **4**, (Scheme 1).

One molar equivalent of 2,3-dichloroquinoxaline (**2**) was allowed to react with two molar equivalent[5] of a 7,4-disubstituted coumarin **5**, such as 4-hydroxycoumarin or 7-hydroxy-4-methylcoumarin, in alkaline medium affording the corresponding 2,3-(dicoumarin-4-yloxy)quinoxaline (**6**) and 2,3-di-(4-methylcoumarin-7-yloxy)quinoxaline (**7**) (Scheme 2), respectively.



Scheme 1.

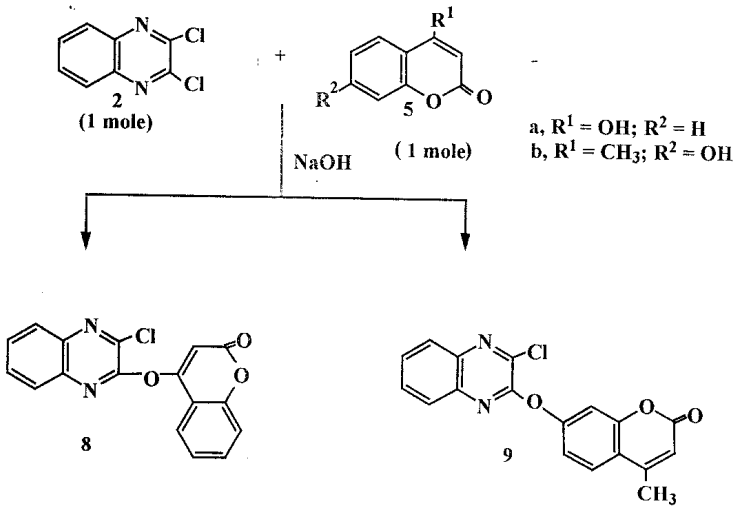


Scheme 2.

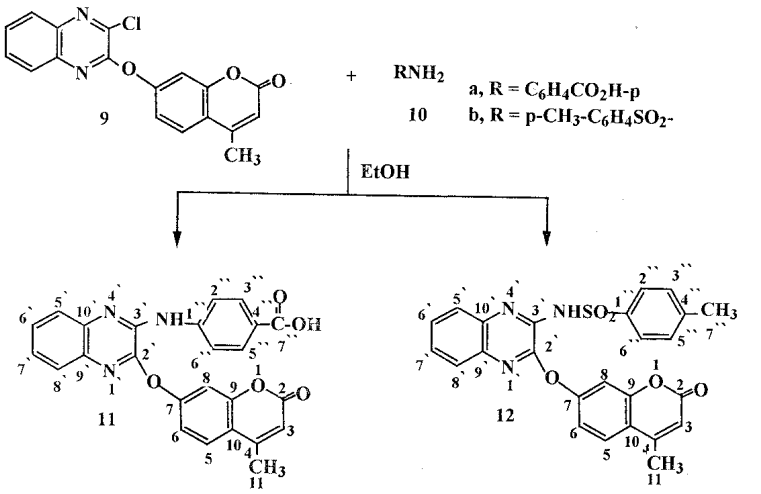
In addition, one molar equivalent of 2,3-dichloroquinoxaline (**2**) reacted with one molar equivalent of a 7,4-disubstitued coumarin **5**, such as 4-hydroxycoumarin or 7-hydroxy-4-methylcoumarin, in alkaline medium led to the formation of 2-chloro-3-(coumarin-4-yloxy)quinoxaline (**8**) and 2-chloro-3-(4-methylcoumarin-7-yloxy)quinoxaline (**9**) (Scheme 3), respectively.

An ethanolic solution of **9** when allowed to react with an amine derivative **10**, such as 4-aminobenzoic acid or 4-tolylsulphonamide, afforded the corresponding 3-(4-carboxyphenylamino)-2-(4-methylcoumarin-7-yloxy)quinoxaline (**11**) and 3-(4-tolylsulphonamido)-2-(4-methylcoumarin-7-yloxy)quinoxaline (**12**) (Scheme 4), respectively.

The ditraizoloquinoxaline derivative **14** was obtained by the reaction of one molar equivalent 2,3-dichloroquinoxaline (**2**) with two molar equivalent of 4-



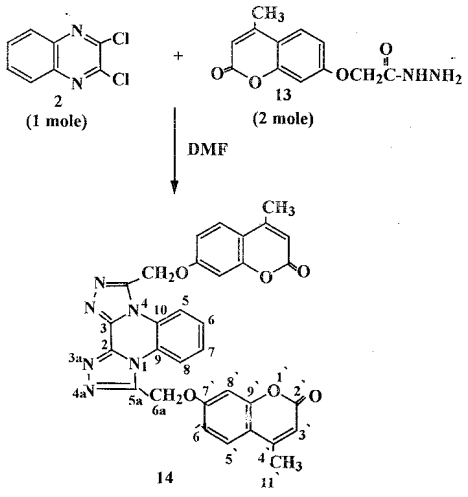
Scheme 3.



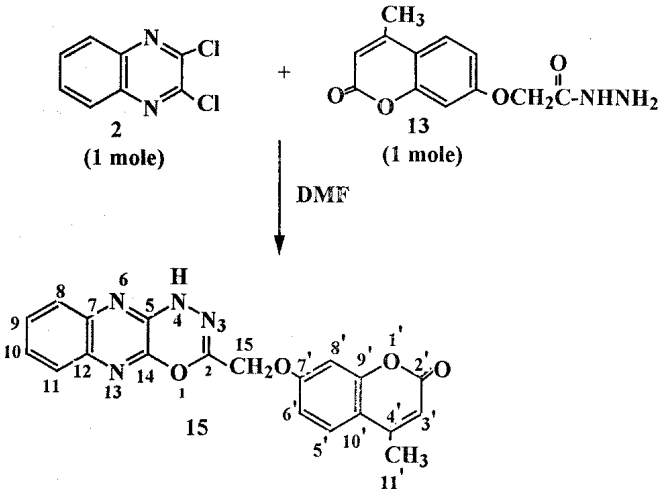
Scheme 4.

methylcoumarin-7-yloxyacetyl hydrazide (**13**) in dimethyl formamide under reflux (Scheme 5).

In the present investigation it was expected that the reaction of one molar equivalent of 2,3-dichloroquinoxaline (**2**) with one molar equivalent of compound **13** in dimethyl formamide under reflux would produce 2-chloro-3-triazolo [4,3-*a*]quinoxaline *via* cyclocondensation. However, the new product proved to be the oxadiazino [2,3-*b*]quinoxaline derivative (**15**) (Scheme 6).



Scheme 5.



Scheme 6.

Biological activity

Applying the nutrient agar plate diffusion method (Philipp *et al.,* 1994) all of the newly synthesized compounds were screened *in vitro* for antibacterial activity against *Eschericia coli, Salmonella* and *Staphylococci* which were isolated from humans. A few crystals of the tested compounds were placed on the cultivated plates. The plates were incubated at 37 °C/48 h. The activity was determined by measuring the diameter of the inhibition zone. The screening results given in Table I indicated that all the compounds exhibited antibacterial activities against one or other type of bacteria. Compounds **6** and **7** gave the very good results with all three types of bacteria.

TABLE I. Antibacterial activity of some synthesized comopounds

Compod.	Gram–ve		Gram+ve
	Esch. Coli	Salmonella	Staphylococci
4	+	+	+
6	++++	+++	++++
7	+++	++++	++++
8	+	+	+++
9	+	+	+++
10	+	+	+
11	+	–	–
14	–	+	++++
16	–	–	+

– No antibacterial activity, + Mild activity, ++ Moderate activity, +++ Marked activity, ++++ Strong marked activity

EXPERIMENTAL

Melting points were determined on a Boetius hot apparatus. Microanalyses were carried out on an elemental analyzer, Hereaus CHN-OS-Rapid. IR spectra were recoreded on a Perkin-Elmer FTIR 1725 spectrometer. Mass spectra were taken on a VG 12-250 instrument (70 eV EI ionaztion, Source temperature 200 °C). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian unity 400 spectrometer at 200 MHz, with TMS as the internal standard.

*1,4-Dioxane derivative (**4**)*

A solution of **3** (0.01 mol) and sodium hydroxide (0.02 mol) in water (5 mL) was added to a solution of **2** (0.01 mol) in methanol (70 mL). The reaction mixture was heated on a water bath for 2–3 h, then cooled and acidified with hydrochlroic acid (1 mol/L). The deposited solid was filtered off and purified by crystallization from benzene to give **4** as pale yellow crystals, yield 73%, m.p. 83 °C. ν_{max} (KBr): 1712 (C=O), 1630 (C=N), 1209, 1015 cm^{-1}. δ_H ($CDCl_3$): 2.41 (*s*, 3H, CH_3), 7.31 – 7.96 (*m*, 7H, Ar-H and pyranone ring) ppm. δ_C ($CDCl_3$): 160.32 (C-2), 112.38 (C-3), 137.24 (C-4), 126.36 (C-5), 129.63 (C-6), 143.52 (C-7), 150.31 (C-8), 152.27 (C-9), 118.46 (C-10), 32.18 (C-11), 149.01 (C-2', 3'), 130.01 (C-5', 8'), 130.21 (C-6', 7'), 143.61 ((C-9', 10') ppm. *m/z* (%); 319 (M^+ + 1, 31), 318 (M^+, 52), 190 (100), 160 (65), 161 (69), 159 (5), 158 (4), 148 (2), 147 (11), 145 (3), 144 (7), 119 (20), 118 (3), 104 (36), 103 (15), 92 (4), 91 (2), 90 (9), 77 (15), 65 (11). Anal. $C_{18}H_{10}N_2O_4$. Calcd.: C, 67.92; H, 3.15; N, 8.81. Found: C, 67.69; H, 3.01; N, 8.58.

*2,3-(Dicoumarin-4-yloxy)quinoxaline (**6**)*
*2,3-Di(4-methylcoumarin-7-yloxy)quinoxaline (**7**)*

A solution of **5a** or **5b** (0.02 mol) and sodium hydroxide (0.02 mol) in water (5 mL) was added to a solution of **2** (0.01 mol) in methanol (70 mL). The reaction mixture was heated on a water bath for 2-3 h, then cooled and acidified with hydrochloric acid (1 mol/L). The solid obtained was filtered off and purified by crystallization from ethanol to give **6** or **7**. ν_{max} (KBr): 2905, 1710–1720, 1630–1620, 1260, 1095 cm^{-1}.

Compound **6** as colourless crystals, yield 72%, m.p. 168 °C. δ_H (DMSO-d_6): 7.21–7.98 (*m*, 14H, Ar-H and pyranone ring) ppm. δ_C (DMSO-d_6): 160.32 (C-2), 112.35 (C-3), 150.36 (C-4), 128.42 (C-5), 122.72 (C-6), 131.63 (C-7), 116.32 (C-8), 153.89 (C-9), 118.62 (C-10), 149.35 (C-2', 3'),

130.00 (C-5', 8'), 130.22 (C-6', 7'), 143.68 (C-9', 10') ppm. *m/z* (%): 451 (M^+ + 1, 11), 450 (M^+, 21), 189 (8), 161 (100), 119 (75), 92 (85), 91 (43), 76 (35), 65 (12). Anal. $C_{26}H_{14}N_2O_6$. Calcd.: C, 69.33; H, 3.11; N, 6.22. Found: C, 69.06; H, 3.02; N, 6.03.

Compound **7** as colourless crytals, yield 74%, m.p.: 153 °C. δ_H (DMSO-d_6): 2.41 (*s*, 6H, 2x CH_3), 7.20–7.97 (*m*, 12H, Ar-H and pyranone ring) ppm. δ_C (DMSO-d_6): 160.83 (C-2), 111.92 (C-3), 140.32 (C-4), 129.72 (C-5), 114.03 (C-6), 159.63 (C-7), 105.32 (C-8), 154.80 (C-9), 111.63 (C-10), 32.12 (C-11), 149.30 (C-2', 3'), 130.02 (C-5', 8'), 130.20 (C-6', 7'), 143.52 (C-9', 10') ppm. *m/z* (%): 479 (M^+ + 1, 16), 478 (M^+, 26), 176 (100), 175 (51), 161 (10), 146 (36), 128 (10), 118 (56), 104 (13), 91 (59), 65 (50). Anal. $C_{28}H_{18}N_2O_6$. Calcd. C, 70.29; H, 3.76; N, 5.86. Found: C, 70.01; H, 3.52; N, 5.31.

*2-Chloro-3-(coumarin-4-yloxy)quinoxaline (***8***)*
*2-Chloro-3-(4-methylcoumarin-7-yloxy)quinoxaline (***9***)*

A solution of **5a** or **5b** (0.01 mol) and sodium hydroxide (0.01 mol) in water (54 mL) was added to a solution of **2** (0.01 mol) in methanol (70 mL). The reaction mixture was heated on a water bath for 2–3 h, then cooled and acidified with hydrochloric acid (1 mol/L). The deposited solid was filtered off and purified by crystallization from ethanol to give **8** or **9**. ν_{max} (KBr): 2905, 1711–1718, 1623–1618, 1210, 1100 cm^{-1}.

Compound **8** as colourless crystals, yield 63%, m.p. 138 °C. δ_H ($CDCl_3$): 7.27–7.98 (m, 9H, Ar-H and pyranone ring) ppm. *m/z* (%): 326 (M^+ + 2, 17), 324 (M^+, 31), 163 (15), 162 (100), 161 (3), 129 (17), 120 (85), 92 (40), 63 (14), Anal. $C_{17}H_9ClN_2O_3$. Calcd.: C, 62.96; H, 2.77; N, 8.64; Cl, 10.80. Found: C, 62.71; H, 2.48; N, 8.40; Cl, 10.52.

Compound **9** as colourless crystals, yield 68%, m.p. 105 °C. δ_H ($CDCl_3$): 2.44 (*s*, 3H, CH_3), 7.25–7.98 (*m*, 8H, Ar-H and pyranone ring) ppm. *m/z* (%): 340 (M^+ + 2, 6), 339 (M^+ + 1, 18), 338 (M^+, 48), 176 (100), 175 (50), 164 (18), 163 (29), 147 (33), 144 (9), 130 (14), 128 (45), 118 (62), 104 (41), 91 (60), 77 (48), 65 (53). Anal. $C_{18}H_{11}ClN_2O_3$. Calcd.: C, 63.91; H, 3.25; N, 8.28; Cl, 10.36. Found: C, 63.60; H, 3.05; N, 7.98; Cl, 10.01

*2-(Substituted amine)-3-(4-methylcoumarin-7-yloxy)quinoxalines (***11** *and* **12***)*

A solution of **9** (0.01 mol) and an amine derivative **10a** or **10b** (0.01 mol) (such as 4-aminobenzoic acid or 4-tolylsulphonamide) in ethanol (70 mL) was heated under reflux for 6 h. The solid obtained after cooling was filtered off and recrystallized from ethanol to give **11** and **12**.

Compound **11** as pale yellow crystals, yield 67%, m.p. 265 °C. ν_{max} (KBr): 3220 (NH), 3325 – 2890 (broad OH), 1705–1718 (C=O), 1625 (C=N), 1280, 1030 cm^{-1}. δ_H (DMSO-d_6): 2.38 (*s*, 3H, CH_3), 7.20–7.98 (*m*, 12 H, Ar-H and pyranone ring), 9.5 (*s*, 1H, OH), 10.5 (*s*, 1H, NH) ppm. δ_c (DMSO - d_6): 160.62 (C-2), 112.01 (C-3), 139.65 (C-4), 129.68 (C-5), 114.10 (C-6), 159.51 (C-7), 106.32 (C-8), 154.73 (C-9), 111.53 (C-10), 32.16 (C-11), 149.35 (C-2'), 145.09 (C-3'), 130.01 (C-5',8'), 130.21 (C',7'), 143.62 (C-9', 10'), 143.82 (C-1''), 114.21 (C-2'', 6''), 129.95 (C-3'', 5''), 129.43 (C-4''), 172.25 (C-7'') ppm. *m/z* (%): 439 (M^+, 17), 438 (M^+ – 1, 12), 395 (12), 394 (10), 265 (7), 264 (34), 221 (5), 220 (18), 174 (5), 145 (7), 144 (4), 104 (7), 102 (6), 90 (17), 77 (5). Anal. $C_{25}H_{17}N_3O_5$. Calcd.: C, 68.34; H, 3.87; N, 9.57. Found: C, 68.02; H, 3.62; N, 9.28.

Compound **11** as pale yellow crystals, yield 65%, m.p. 120 °C. ν_{max} (KBr): 3240 (NH), 1712 (C=O), 1625 (C=N), 1205, 1030 cm^{-1}. δ_H (DMSO-d_6): 2.30 (*s*, 3H, CH_3), 2.43 (*s*, 3H, CH_3), 7.15 – 7.96 (*m*, 12H, Ar-H and pyranone ring), 10.3 (*s*, 1H, NH) ppm. δ_C (DMSO-d_6): 160.65 (C-2), 112.1 (C-3), 139.72 (C-4), 129.67 (C-5), 114.16 (C-6), 159.53 (C-7), 106.30 (C-8), 154.70 (C-9), 111.52 (C-10), 32.13 (C-11), 149.36 (C-2'), 145.10 (C 3'), 130.00 (C-5', 8'), 130.21 (C-6', 7'), 143.61 (C-9', 10'), 142.60 (C-1''), 125.71 (C-2'', 6''), 129.40 (C-3'', 5''), 139.58 (C-4''), 21.0 (C-7'') ppm. *m/z* (%): 473 (M^+, 25), 298 (35), 234 (45), 175 (100), 145 (23), 90 (16), 77 (31). Anal. $C_{25}H_{19}N_3O_5S$. Calcd.: C, 63.42; H, 4.02; N, 8.88; S, 6.76. Found: C, 63.17; H, 3.86; N, 8.58; S, 6.49.

*Ditriazoloquinoxaline (**14**)*

A mixture of **2** (0.01 mol) and acyl hydrazide **13** (0.02 mol) in dimethyl formamide (50 mL) was refluxed for 16 h. The reaction mixture was cooled and then poured onto water. The solid that separated was crystallized from acetic acid to give **14** as yellow crystals, yield 73%, m.p. 280–281 °C. ν_{max} (KBr): 1716, 1630, 1305, 1215, 1095 cm^{-1}. δ_H (DMSO-d_6): 2.41 (*s*, 6H, 2x CH_3), 4.53 (*s*, 4H, 2x $-CH_2O-$), 7.21–7.98 (*m*, 12H, Ar-H and pyranone ring) ppm. δ_C (DMSO-d_6): 155.34 (C-2,3), 130.08 (C-5, 8), 130.23 (C-6,7), 143.43 (C-9, 10), 154.86 (C-5a), 57.82 (C-6a), 160.63 (C-2'), 112.15 (C-3'), 139.70 (C-4'), 129.58 (C-5'), 114.15 (C-6'), 159.56 (C-7'), 106.27 (C-8'), 154.71 (C-9'), 111.50 (C-10'), 32.15 (C-11'), ppm. *m/z* (%): 562 (M^+, 17), 388 (13), 387 (19), 175 (100), 147 (97), 146 (79), 130 (14), 118 (11), 102 (27), 91 (24), 77 (15), 65 (12). Anal: $C_{30}H_{22}N_6O_6$. Calcd.: C. 64.06; H, 3.91; N, 14.95. Found: C, 63.89; H, 3.62; N, 14.70.

*Oxadiazino [2,3-b]quinoxaline (**16**)*

A mixture of **2** (0.01 mol) and acyl hydrazide **13** (0.01 mol) in dimethyl formamide (30 mL) was heated under reflux for 12 h. The reaction mixture was cooled and then poured onto water yielding the crude product which was filtered and purified by recrystallization from acetic acid to give **16** as pale yellow crystals, yield 74%, m.p. 264 – 265 °C. ν_{max} (KBr): 3240 (NH), 1714, 1625, 1201, 1095 cm^{-1}. δ_H (DMSO-d_6): 2.42 (*s*, 3H, CH_3), 4.51 (*s*, 2H, $-CH_2O-$), 7.21—7.97 (*m*, 8H, Ar-H and pyranone ring), 10.4 (*s*, 1H, NH) ppm. δ_C (DMSO-d_6): 158.52 (C-2), 155.31 (C-5), 143.41(C-7, 12), 130.02 (C-8, 11), 130.22 (C-9, 10), 158.76 (C-14), 57.63 (C-15), 160.54 (C-2'), 112.20 (C-3'), 139.72 (C-4'), 129.56 (C-5'), 114.12 (C-6'), 159.53 (C-7'), 106.24 (C-8'), 154.59 (C-9'), 111.32 (C-10'), 32.13 (C-11'), ppm. *m/z* (%): 375 ($M^+ + 1$, 2), 374 (M^+, 5), 233 (12), 226 (17), 199 (11), 176 (100), 175 (7), 147 (81), 131 (10), 128 (3), 120 (15), 102 (10), 91 (21), 77 (9), 65 (8). Anal. $C_{20}H_{14}N_4O_4$. Calcd.: C, 64.17; H, 3.74; N, 14.97. Found: C, 64.01; H, 3.49; N, 14.61.

И З В О Д

СИНТЕЗА И БИОЛОШКА АКТИВНОСТ НЕКИХ ХЕТЕРОЦИКЛИЧНИХ ЈЕДИЊЕЊА КОЈА САДРЖЕ ХИНОКСАЛИНСКО И КУМАРИНСКО ЈЕЗГРО

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Кондензацијом 2,3-дихлорохиноксалина (**2**) и 7,8-дихидрокси-4-метилкумарина добијен је 1,4-диоксански дериват **4**. Реаговањем **2** са 4-хидроксикумаримом, 7-хидрокси-4-метилкумаримом и хидразидом **13**, добијен је или 2,3-(дикумарин-4-илокси)-хиноксалин (**6**), 2,3-ди-(4-метилкумарин-7-илокси)хиноксалин (**7**), 2-хлоро-3-(кумарин-4-илокси)хиноксалин (**8**), 2-хлоро-3-(4-метилкумарин-7-илокси)хиноксалин (**9**), односно дитриазолохиноксалин **14** или оксадиазинохиноксалин **16**, у зависности од међусобних релативних односа реактаната и услова реакције.

(Примљено 28. јуна 1999)

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