SOME NUCLEOPHILIC CYCLIZATION REACTIONS WITH 3-[4-(BENZO[1,3]DIOXOLYLMETHYLENE)PYRAZOLYL]QUINOLONE

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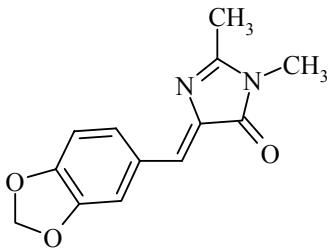
Abstract

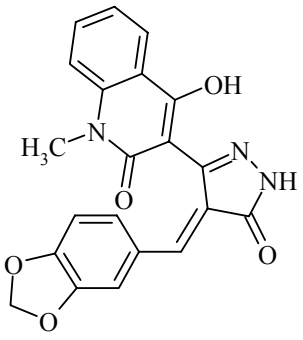
Cyclization of 3-[4-(Benzo[1,3]dioxolylmethylene)-5-oxo-3-pyrazolyl]-4-hydroxy-1-methyl-quinolin-2(1*H*)-one with certain bifunctional nucleophilic reagents is described. The cyclization reactions led to the formation of many biologically interesting fused heterocyclic systems derived from pyrazolinone and bearing quinolinone moiety e.g. pyrazolopyrazole, isoxazolopyrazole, pyrazolopyrimidine, pyrazolothiazine, pyrazolopyridine, dipyrazolo-pyridine, dipyrazolopyran and many pyrazolopyran derivatives. The structures of all the new products were checked with analytical and spectral methods.

Introduction

Pyrazole derivatives have attracted particular interests during the last twenty-five years due to use of such ring system as the core structure in many drug substances, covering wide range of pharmacological applications.[1-6] Recently an important natural mediator of inflammation Leucettamine B was isolated and since then attempts to synthesis this compound and its analogues were continued.[7] We found that Leucettamine B is of near structure to a pyrazolinone derivative that described in ours previous work.[8]



Leucettamine B



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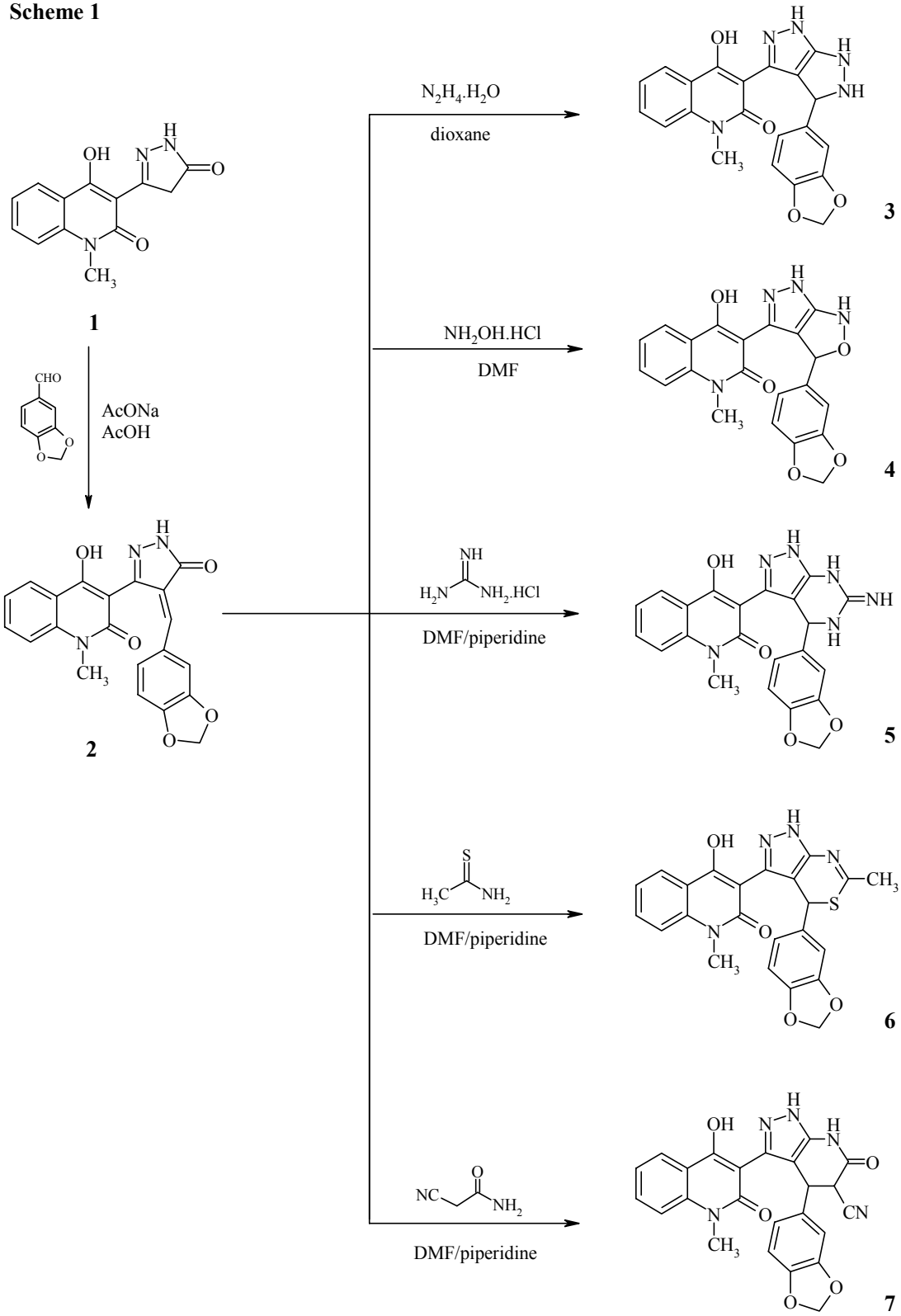
This encouraged us to use the titled pyrazolylquinolinone to obtain other new heteropolycyclic derivatives including both quinolinone and pyrazole moieties in one

molecular frame. These novel heterocyclic systems are expected to sustain interesting biological activities. Herein we go for derivation of an arylidenepyrazolinone utilizing the well-known *Michael* addition reaction with certain N, O, S and C-nucleophiles.[9]

Results and discussion

Recently we have described the synthesis of 3-[4-(Benzo[1,3]dioxolylmethylene)-5-oxo-3-pyrazolyl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (**2**) from *Knoevenagel* condensation of the active methylene pyrazolinone **1** with piperonaldehyde in the presence of freshly fused sodium acetate in glacial acetic acid.[8] Addition-condensation cyclization of the compound **2** with hydrazine hydrate and/or hydroxylamine hydrochloride, involving exo-cyclic enone grouping, led to the formation of the fused five-membered rings pyrazolopyrazole **3** and pyrazoloisoxazole **4**, respectively. On the other hand six-membered heterocyclo-pyrazoles were achieved via similar addition-condensation cyclization reactions with different 1,3-bidentate nucleophiles. Thus, treatment of compound **2** with guanidine hydrochloride gave the pyrazolopyrimidine **5**, which its ^{1}H NMR spectrum (DMSO) revealed the presence of five broad signals at δ: 8.85, 9.70, 11.90, 12.46 and 14.20 ppm, disappear on deutration, indicating that this compound assumes iminotetrahydropyrimidine form. Also IR spectrum of this compound showed the same structural phenomenon, as there is no indication for specific absorption vibrations of amino group, instead broad absorption band centered at ν: 3246 cm^{-1} is observed due to different N–H groups. Reaction of the compound **2** with thioacetamide, in the presence of piperidine as catalyst, afforded pyrazolothiazine **6**. The ^{1}H NMR spectrum of the product **6** represents two methyl singlets at δ: 2.21 and 3.68 ppm, due to 6-methylpyrazolothiazine and N-methylquinolinone, respectively. These results along with IR spectrum and elemental data emphasis that an addition of S-thioacetamide to the methylene of enone moiety took place and followed by condensation of the amino group with the oxo-pyrazoline. The reactivity of compound **2** towards *Michael* reaction with some C-nucleophiles was investigated when its reaction with certain active methylene compounds was carried out in the presences of suitable basic catalyst. It is well known that *Michael* addition reactions of activated alkenes with

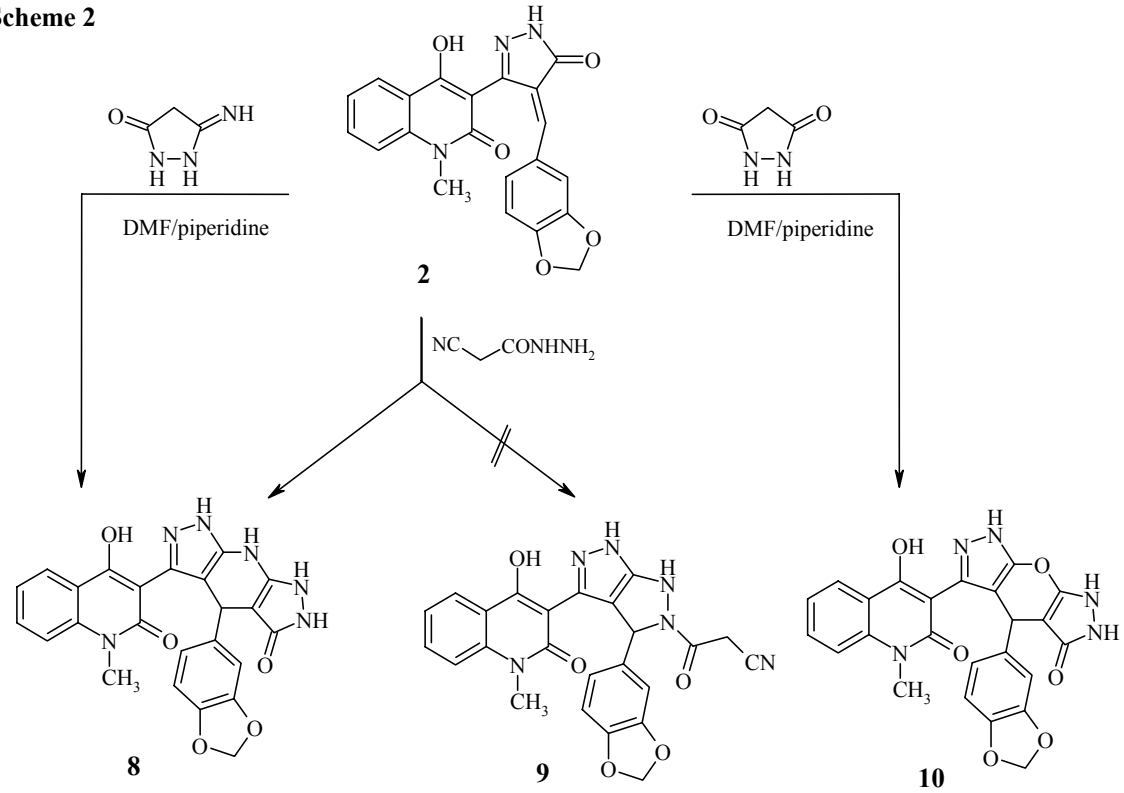
Scheme 1



C-nucleophiles lead to the formation of (C–C) extra bond at the position of addition; hence to affect a consequent cyclization it is worthwhile to use the proper reagent of

general formula (X–CH_2–Y). These selected reagents must contain appropriate X and Y groups which are capable for a further intramolecular reaction with the tautomeric (NH–C=O ↔ N=C–OH) of the pyrazoline moiety. The reaction of compound **2** with cyanacetamide was considered and the product was characterized as pyrazolopyridone **7** (Scheme 1). The presence of the specific absorption peak of (C≡N) group, at ν: 2220 cm^{-1} in its IR spectrum besides broad band at ν: 3227 cm^{-1} due to (N–H) and two carbonyl absorption vibrations at 1665 and 1645 cm^{-1} due to both pyridone and quinolinone moieties, respectively, suggested that an addition reaction occurred at first followed by intramolecular condensation of the enolized pyrazolinone (C=O) with the acetamide (NH_2) group.

Scheme 2



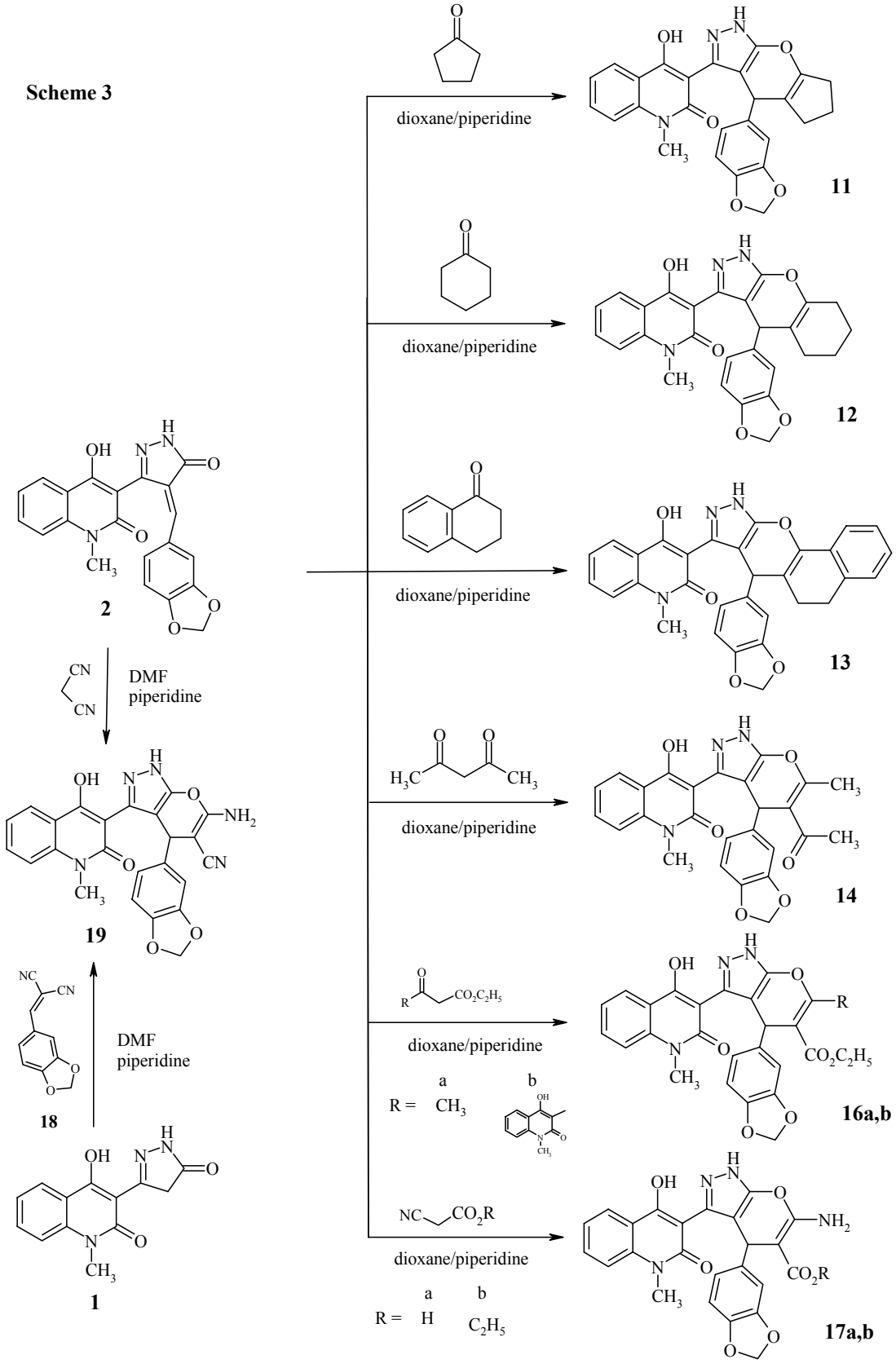
Surprisingly, it was found that reaction of compound **2** with cyanoaceto-hydrazide does not lead to the expected pyrazolinopyrazole **9** but instead the dipyrazolopyridine **8** had been obtained. The structure of compound **8** was established on basis of its spectral and analytical data, in which there is no evidence for (N≡C–CH_2–CO) grouping in both

^{1}H NMR and IR spectra. This leads to a hypothetical suggestion that firstly cyanoacetohydrazide might be cyclized, giving 3-imino-5-oxopyrazolidine, which consequentially reacts with compound **2**. This proposition was verified when the commercially available 3-imino-5-oxopyrazolidine was reacted with compound **2** at the same conditions to give the same product **8** This is in conformity to findings cited for similar reactions in the literature.[10] Similarly, reaction of compound **2** with pyrazolidene-3,5-dione gave the dipyrazolopyranone **10**. Structure of the latter product was elucidated upon basis of its spectral and analytical results. Thus, ^{1}H NMR spectrum revealed a set of four deuterium exchangeable protons confirming the presence of three different pyrazole/pyrazoline (N–H) groups in addition to the (O–H) group. This is coincident with the outputs of reading IR chart for compound **10**, which showed two absorption vibrational bands due to stretching of (C=O) at ν: 1668 and 1630 cm^{-1} of both pyrazolinone and quinolinone carbonyls (Scheme 2).

Reaction of some cycloalkanones namely; cyclopentanone, cyclohexanone and tetralone with compound **2**, in dioxane in the presence of piperidine as catalyst, furnished the polycyclic systems: cyclopentano[5,6]pyranopyrazole **11**, chromeno-pyrazole **12** and pyrazolobenzo[h]chromene **13**, respectively (Scheme 3). The ^{1}H NMR spectra of the pyranopyrazoles **11** and **12** revealed multiplets in the range of δ: 1.4-2.25 ppm due to $(CH_2)_n$ cyclic chain protons.

Also, the multi-functional pyranopyrazoles **14**, **16**, **17** and **19** were prepared via similar cyclization process used here above replacing these cyclic ketones with certain acyclic active methylene compounds, which always leads to 5,6-disubstiuted pyranopyrazoles. Thus, the reaction of compound **2** with acetylacetone yielded 5-acetyl-6-methylpyranopyrazole **14**, while addition-condensation reaction of compound **2** with β-ketoesters; ethyl acetoacetate and/or ethyl 3-(4-hydroxy-1-methyl-2-ox-1,2-dihydroquinolin-3-yl)-3-oxopropanoate (**15**) gave the ethyl 6-methyl-3-quinolinyl-pyranopyrazole-5-carboxylates **16a** and ethyl 3,6-di(quinolinyl)-pyranopyrazole-5-carboxylates **16b**, respectively (Scheme 3). IR spectra of these esters evidently revealed the characteristic carbonyl absorption vibrational bands due to carboxylate groups. Also, ^{1}H NMR spectra of the esters **16a,b** obviously showed the presence of an ethyl group set of protons for each of them. These results arose the conclusion that without any doubt

Scheme 3


dioxane/piperidine
11
12
13
14
16a,b
17a,b
2
19
18
1
DMF
piperidine
R = a: CH3, b:
R = a: H, b: C2H5

carboxylate group is not involved in the intramolecular condensation reaction but the keto-group does.

Treatment of compound **2** with cyanoacetic acid and/or ethyl cyanoacetate, under the same conditions, resulted in the amino-carboxylic acid **17a** and amino-ester **17b**, respectively (Scheme 3). Apparently, the latter cyclization process proceeds through two addition steps; the first one is intermolecular addition of the active methylene to the enone (C=C) moiety in compound **2**, the second step is intramolecular addition of enolic (OH) to a nitrile group. This asserted the non-existence of condensation reaction between either carboxylic or ester groups. Otherwise we have to expect presence of characteristic band due to (C≡N) group in IR spectra of such products. This probability was perfectly excluded, as the spectra of both derivatives **17a** and **17b** do not show this ν(C≡N) and instead characteristic ν(NH_2) appear at 3420 and 3310 cm^{-1}, in addition to ν(C=O) at 1705 cm^{-1} of the acid **17a** and ν(C=O) at 1730 cm^{-1} of the ester **17b**. Malononitrile was reacted with compound **2** to give the 6-amino-pyranopyrazole-5-carbonitrile **19**. Here again two addition steps take place to afford such cyclization product. Alternatively, piperonalidene-malononitrile **18** was reacted with pyrazolinone **1** under the same conditions cited here before and the product of this reaction was identified identical in every respect to the latterly obtained compound **19**. This confirms what we have discussed herein about the two-step addition cyclization reaction and highlights that C–C bond formation via *Michael* addition is previously to cyclization involving intramolecular addition of (OH) to a nitrile group.

Conclusions

Reaction of arylidenepyrazolinone with certain nucleophilic reagents under *Michael* reaction conditions leads to formation of different multi-functional polycyclic derivatives of pyrazole. In general the cyclic active methylene compounds give linear polycyclic compounds while acyclic active methylene nitriles give substituted pyranopyrazoles. Addition-cyclization takes place in preference faster than its competitive condensation reaction whenever it is possible.

Experimental

Melting points are uncorrected and were determined in open capillary tubes on a digital Gallen-Kamp MFB-595. IR spectra were taken on a Perkin-Elmer FT-IR 1650 spectrophotometer (ν, cm^{-1}), using samples in KBr disks. ^1H NMR spectra were recorded on a Bruker AC200 (200 MHz) spectrometer (δ, ppm), using DMSO-d_6 as solvent and TMS as internal standard.

3-[4-(Benzo[1,3]dioxol-5-yl)-1,4,5,6-tetrahydropyrazolo[3,4-*c*]pyrazol-3-yl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (3). A mixture of compound **2** (3.89 g, 0.01 mol) and hydrazine hydrate (0.5 mL, 0.01 mol), in dioxane (50 mL), was heated under reflux for 4h. The solid deposits so formed during the course of the reaction were filtered off, washed with ethanol (10 mL) and crystallized from DMF to give yellow crystals of the product **3** (2.66 g, 66%), m.p. 270-2 °C. *Anal*. Calculated for $C_{21}H_{17}N_5O_4$ (403.40): C, 62.53; H, 4.25; N, 17.36. Found: C, 62.70; H, 4.00; N, 17.10. IR, ν: 3240, 3220-3180 (N–H, O–H), 1628 (C=O), 1600 (C=N), 1581, 1504, 1450, 1396, 1230, and 1119. ^1H NMR, δ: 3.66 (s, 3H, N–CH_3), 5.53 (s, 1H, C4–$H_{pyrazoline}$), 5.95 (s, 2H, O–CH_2–O), 6.63 (br s, 1H, N–H), 7.25-8.12 (m, 7H, H_{arom}), 10.30 (br s, 1H, N–H), 10.43 (br s, 1H, N–$H_{pyrazole}$) and 14.02 (br s, 1H, O–H).

3-[3-(Benzo[1,3]dioxol-5-yl)-3,6-dihydropyrazolo[3,4-*c*]isoxazol-4-yl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (4). A mixture of equimolar amounts (0.01 mol) of compound **2** (3.89 g) and hydroxylamine hydrochloride (0.7 g), in DMF (30 mL), was treated with triethylamine (0.1 mL) and heated under reflux for 3h. The yellow crystals so separated on cooling were collected by filtration and recrystallized from DMF affording the product **4** (2.38 g, 59%), m.p. 267-8 °C. *Anal*. Calculated for $C_{21}H_{16}N_4O_5$ (404.39): C, 62.37; H, 3.99; N, 13.85. Found: C, 62.20; H, 3.80; N, 13.80. IR, ν: 3240-3120 (N–H, O–H), 1650 (C=O), 1610 (C=N), 1590, 1505, 1442, 1157 and 1103. ^1H NMR, δ: 3.64 (s, 3H, N–CH_3), 5.96 (s, 2H, O–CH_2–O), 6.43 (s, 1H, C3–$H_{isoxazoline}$), 7.15-8.10 (m, 7H, H_{arom}), 9.55 (br s, 1H, N–H), 11.25 (br s, 1H, N–$H_{pyrazole}$) and 14.12 (br s, 1H, O–H).

3-[4-(Benzo[1,3]dioxol-5-yl)-6-imino-4,5,6,7-tetrahydropyrazolo[3,4-*d*]-pyrimidin-3-yl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (5). A mixture of compound **2** (3.89 g, 0.01 mol), guanidine hydrochloride (0.97 g, 0.01 mol) and piperidine (0.1 mL), in DMF (30 mL), was heated under reflux for 3h. The mixture was left to cool at room temperature, poured onto cold water and then acidified with few drops of dilute hydrochloric acid. The solid precipitate so obtained was filtered off, washed with ethanol (20 mL) and crystallized from DMF-water (3:1) to give pale brown crystals of the product **5** (2.49 g, 58%), m.p. >300 °C. *Anal*. Calculated for $C_{22}H_{18}N_6O_4$ (430.43): C, 61.39; H, 4.22; N, 19.52. Found: C, 61.60; H, 4.10; N, 19.40. IR, ν: 3246-3164 (N–H, O–H), 1648 (C=O), 1622 (C=N), 1584, 1509, 1459 and 1120. ^{1}H NMR, δ: 3.68 (s, 3H, N–CH_3), 6.09 (s, 2H, O–CH_2–O), 6.15 (s, 1H, C4–$H_{pyrimidine}$), 7.05-8.11 (m, 7H, H_{arom}), 8.85 (br s, 1H, N–H_{imino}), 9.70 (br s, 1H, N–$H_{pyrimidine}$), 10.90 (br s, 1H, N–$H_{pyrimidine}$), 11.38 (br s, 1H, N–$H_{pyrazole}$) and 14.25 (br s, 1H, O–H).

3-[4-(Benzo[1,3]dioxol-5-yl)-6-methyl-1,2-dihydropyrazolo[3,4-*d*][1,3]thiazin-3-yl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (6). To a mixture of compound **2** (3.89 g, 0.01 mol), thioacetamide (0.75 g, 0.01 mol), in DMF (30 mL), piperidine (0.1 mL) was added and the mixture was heated under reflux for 4h. Afterwards the reaction mixture was left to cool acidified with few drops of dilute acetic acid to give a yellowish-brown precipitate. The solid precipitate was collected by filtration and crystallized from DMF-water (4:1) to give the product **6** (3.26 g, 73%), m.p. >300 °C. *Anal*. Calculated for $C_{23}H_{18}N_4O_4S$ (446.49): C, 61.87; H, 4.06; S, 7.18. Found: C, 61.80; H, 3.80; S, 6.90. IR, ν: 3247-3173 (N–H, O–H), 1647 (C=O), 1620 (C=N), 1585, 1508, 1455, 1241 and 1110. ^{1}H NMR, δ: 2.21 (s, 3H, CH_3), 3.64 (s, 3H, N–CH_3), 5.15 (s, 1H, $H_{thiazine}$), 5.90 (s, 2H, O–CH_2–O), 7.15-8.12 (m, 7H, H_{arom}), 10.97 (br s, 1H, N–$H_{pyrazole}$) and 14.35 (br s, 1H, O–H).

4-(Benzo[1,3]dioxol-5-yl)-3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-*b*]pyridine-5-carbonitrile (7). To a solution of compound **2** (3.89 g, 0.01 mol), in DMF (50 mL), cyanoacetamide (0.85 g, 0.01 mol)

and piperidine (0.1 mL) were added and the mixture was heated under reflux for 4h. Then the reaction mixture was cooled acidified with dilute acetic acid till precipitation. The solid precipitate was filtered off and crystallized from DMF to give the nitrile **7** (3.05 g, 67%), m.p. >300 °C. *Anal*. Calculated for $C_{24}H_{17}N_5O_5$ (455.43): C, 63.30; H, 3.76; N, 15.38. Found: C, 63.10; H, 3.60; N, 15.20. IR, ν: 3227-3192 (N–H, O–H), 2220 (C≡N), 1665 ($C=O_{pyridone}$), 1645 ($C=O_{quinolone}$), 1620 (C=N), 1583, 1505, 1449 and 1120. ^{1}H NMR, δ: 3.58 (s, 3H, N–CH_3), 4.14 (d, 1H, C3–$H_{pyridone}$), 4.88 (d, 1H, C4–$H_{pyridone}$), 5.95 (s, 2H, O–CH_2–O), 7.16-8.05 (m, 7H, H_{arom}), 10.46 (br s, 1H, N–$H_{pyrazole}$), 10.92 (br s, 1H, N–$H_{pyridone}$) and 13.97 (br s, 1H, O–H).

4-(Benzo[1,3]dioxol-5-yl)-5-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1,4,7,8-tetrahydro-2*H*-dipyrazolo[3,4-*b*; 4`,3`-*e*]pyridin-3-one (8). Procedure A. Using the same method for preparation of compound **7**, compound **2** (3.89 g, 0.01 mol) was reacted with cyanoacetohydrazide (1 g, 0.01 mol) and piperidine (0.1 mL), in boiling DMF (50 mL) and worked up as above. The product was crystallized from DMF to result in dipyrazolopyridone **8** (3.48 g, 74%), m.p. >300 °C. *Anal*. Calculated for $C_{24}H_{18}N_6O_5$ (470.45): C, 61.28; H, 3.86; N, 17.86. Found: C, 61.10; H, 3.80; N, 17.60. IR, ν: 3241-3196 (N–H, O–H), 1670 ($C=O_{pyrazolinone}$), 1635 ($C=O_{quinolone}$), 1612 (C=N), 1600, 1585, 1508, 1435 and 1120. ^{1}H NMR, δ: 3.65 (s, 3H, N–CH_3), 3.86 (s, 1H, C4–$H_{pyridine}$), 6.10 (s, 2H, O–CH_2–O), 7.20-8.12 (m, 7H, H_{arom}), 8.85 (br s, 1H, N–$H_{pyridine}$), 9.28 (br d, 1H, N–$H_{pyrazolone}$), 10.80 (br s, 1H, N–$H_{pyrazole}$), 11.60 (br d, 1H, N–$H_{pyrazolone}$) and 14.14 (br s, 1H, O–H).

Procedure B. A mixture of equimolar amounts (0.005 mol) of each of compound **2** (1.95 g) and 3-imino-5-oxopyrazolidene (0.5 g), in DMF (25 mL), was treated with two drops of piperidine and heated under reflux for 5h. The brown crystals so separated on hot were collected by filtration and recrystallized from DMF affording compound **8** (2.16 g, 92%), identified by m.p., mixed m.p. and spectra.

4-(Benzo[1,3]dioxol-5-yl)-5-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1,4,7,8-tetrahydro-2*H*-dipyrazolo[3,4-*b*; 4`,3`-*e*]pyran-3-one (10). A mixture of equimolar amounts (0.005 mol) of each of compound **2** (1.95 g) and pyrazolidene-3,5-

dione (0.51 g), in DMF (25 mL), was treated with two drops of piperidine and heated under reflux for 5h. The deep brown precipitate so formed on hot was filtered off and recrystallized from DMF affording dipyrazolopyran **10** (1.96 g, 83%), m.p. >300 °C. *Anal*. Calculated for $C_{24}H_{17}N_5O_6$ (471.43): C, 61.15; H, 3.63; N, 14.86. Found: C, 60.90; H, 3.50; N, 14.60. IR, ν: 3236-3190 (N–H, O–H), 1668 ($C=O_{pyrazolinone}$), 1630 ($C=O_{quinolone}$), 1608 (C=N), 1600, 1583, 1505, 1445 and 1120. ^{1}H NMR, δ: 3.58 (s, 3H, $N–CH_3$), 3.95 (s, 1H, $C4–H_{pyran}$), 6.12 (s, 2H, $O–CH_2–O$), 7.22-8.08 (m, 7H, H_{arom}), 9.56 (br d, 1H, $N–H_{pyrazolone}$), 10.95 (br s, 1H, $N–H_{pyrazole}$), 11.70 (br d, 1H, $N–H_{pyrazolone}$) and 14.14 (br s, 1H, O–H).

Reaction of Active Methylene Compounds With Pyrazolinone 2. ***General Procedure.***

To a mixture of compound **2** (3.89 g, 0.01 mol) and the proper active methylene compound (0.01 mol), in dioxane (50 mL), piperidine (0.1 mL) was added and the reaction mixture was heated under reflux on a boiling-water bath for 2-4h. Afterwards, the reaction mixture was left to cool and acidified using dilute acetic acid till complete precipitation. The precipitate so obtained was filtered off, washed thoroughly with cold ethanol (10 mL) and crystallized to give pyranopyrazoles **11-14**, **16a**,**b** and **17a**,**b**.

4-(Benzo[1,3]dioxol-5-yl)-3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4,5,6,7-tetrahydro-cyclopentano[5,6]pyrano[2,3-*c*]pyrazole (11). This compound was prepared from compound **2** and cyclopentanone (0.9 mL), yield (2.87 g, 63%), m.p. 298-9 °C (dioxane). *Anal*. Calculated for $C_{26}H_{21}N_3O_5$ (455.47): C, 68.56; H, 4.65; N, 9.23. Found: C, 68.40; H, 4.40; N, 9.00. IR, ν: 3240-3110 (N–H, O–H), 1640 (C=O), 1620 (C=N), 1580, 1505, 1442 and 1118. ^{1}H NMR, δ: 1.90-2.25 (m, 6H, $(CH_2)_3$), 3.65 (s, 3H, $N–CH_3$), 3.88 (s, 1H, $C4–H_{pyran}$), 5.95 (s, 2H, $O–CH_2–O$), 7.20-8.11 (m, 7H, H_{arom}), 11.80 (br s, 1H, N–H) and 14.05 (br s, 1H, O–H).

4-(Benzo[1,3]dioxol-5-yl)-3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1,4,5,6,7,8-hexahydrochromeno[2,3-*c*]pyrazole (12). This compound was obtained from compound **2** and cyclohexanone (1 mL), yield (3.38 g, 72%), m.p. 300-2 °C

(dioxane). *Anal*. Calculated for $C_{27}H_{23}N_3O_5$ (469.50): C, 69.07; H, 4.94; N, 8.95. Found: C, 68.80; H, 4.80; N, 8.90. IR, ν: 3280-3120 (N–H, O–H), 1635 (C=O), 1610 (C=N), 1581, 1535, 1495, 1444 and 1110. ^{1}H NMR, δ: 1.40-2.24 (m, 8H, $(CH_2)_4$), 3.62 (s, 3H, N–CH_3), 3.82 (s, 1H, C4–H_{pyran}), 5.92 (s, 2H, O–CH_2–O), 7.15-8.05 (m, 7H, H_{arom}), 11.90 (br s, 1H, N–H) and 13.95 (br s, 1H, O–H).

7-(Benzo[1,3]dioxol-5-yl)-8-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5,6,7-trihydropyrazolo[3,4-*c*]benzo[*h*]chromene (13). This compound was obtained from compound **2** and α-tetralone (1.36 mL), yield (3.2 g, 62%), m.p. 220-2 °C (dioxane). *Anal*. Calculated for $C_{31}H_{23}N_3O_5$ (517.55): C, 71.94; H, 4.48; N, 8.12. Found: C, 72.00; H, 4.30; N, 7.90. IR, ν: 3225-3180 (N–H, O–H), 1632 (C=O), 1608 (C=N), 1589, 1546, 1504, 1449 and 1118. ^{1}H NMR, δ: 2.65-2.80 (m, 4H, $(CH_2)_2$), 3.65 (s, 3H, N–CH_3), 3.97 (s, 1H, C4–H_{pyran}), 5.95 (s, 2H, O–CH_2–O), 7.05-8.11 (m, 11H, H_{arom}), 11.85 (br s, 1H, N–H) and 14.30 (br s, 1H, O–H).

3-[5-Acetyl-4-(benzo[1,3]dioxol-5-yl)-6-methyl-1,4-dihydropyrano[2,3-*c*]-pyrazol-3-yl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (14). This compound was prepared from compound **2** and acetylacetone (1 mL), yield (2.7 g, 57%), m.p. 235-7 °C (dioxane). *Anal*. Calculated for $C_{26}H_{21}N_3O_6$ (471.47): C, 66.24; H, 4.49; N, 8.91. Found: C, 66.10; H, 4.50; N, 8.80. IR, ν: 3217-3168 (N–H, O–H), 1705 ($C=O_{acetyl}$), 1632 ($C=O_{quinolone}$), 1600 (C=N), 1589, 1540, 1445 and 1110. ^{1}H NMR, δ: 2.15 (s, 3H, CH_3), 2.25 (s, 3H, $COCH_3$), 3.65 (s, 3H, N–CH_3), 4.10 (s, 1H, C4–H_{pyran}), 5.96 (s, 2H, O–CH_2–O), 7.15-8.10 (m, 7H, H_{arom}), 11.45 (br s, 1H, N–H) and 13.29 (br s, 1H, O–H).

Ethyl 4-(benzo[1,3]dioxol-5-yl)-3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydro-quinolin-3-yl)-6-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate (16a). This ester was formed from compound **2** and ethyl acetoacetate (1.3 mL), yield (3.15 g, 63%), m.p. 234 °C (ethanol). *Anal*. Calculated for $C_{27}H_{23}N_3O_7$ (501.50): C, 64.67; H, 4.62; N, 8.38. Found: C, 64.50; H, 4.60; N, 8.30. IR, ν: 3240-3120 (N–H, O–H), 1722 ($C=O_{ester}$), 1646 ($C=O_{quinolone}$), 1605 (C=N), 1598, 1550, 1495, 1440, 1125 and 1110. ^{1}H NMR, δ: 1.23 (t, 3H, OCH_2–*CH_3*), 2.35 (s, 3H, α-CH_3), 3.60 (s, 3H, N–CH_3), 4.03 (q,

2H, O*CH*$_2$–CH$_3$), 4.40 (s, 1H, C4–H$_{pyran}$), 5.98 (s, 2H, O–CH$_2$–O), 7.10-8.05 (m, 7H, H$_{arom}$), 11.90 (br s, 1H, N–H) and 14.25 (br s, 1H, O–H).

Ethyl 4-(benzo[1,3]dioxol-5-yl)-3,6-di(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate (16b). This ester was obtained from compound **2** and ethyl 3-quinolinyl-3-oxopropanoate **15**[11] (2.89 g), yield (3.96 g, 60%), m.p. 244-5 °C (acetone). *Anal*. Calculated for $C_{36}H_{28}N_4O_9$ (660.65): C, 65.45; H, 4.27; N, 8.48. Found: C, 65.30; H, 4.10; N, 8.40. IR, ν: 3240-2720 (br, N–H, O–H), 1725 (C=O$_{ester}$), 1645-1635 (C=O$_{quinolone}$), 1610 (C=N), 1586, 1545, 1485, 1443, 1212 and 1120.

6-Amino-4-(benzo[1,3]dioxol-5-yl)-3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylic acid (17a). This acid was obtained from compound **2** and cyanoacetic acid (0.85 g), yield (3.9 g, 82%), m.p. 263-5 °C (dioxane). *Anal*. Calculated for $C_{24}H_{18}N_4O_7$ (474.43): C, 60.76; H, 3.83; N, 11.81. Found: C, 60.70; H, 3.70; N, 11.80. IR, ν: 3435, 3340 (NH_2), 3210-2600 (H-bonded O–H), 1705 (C=O$_{carboxylic}$), 1647 (C=O$_{quinolone}$), 1618 (C=N), 1593, 1545, 1492, 1445 and 1120. ^{1}H NMR, δ: 3.64 (s, 3H, N–CH$_3$), 4.80 (s, 1H, C4–H$_{pyran}$), 5.95 (s, 2H, O–CH$_2$–O), 7.12-8.08 (m, 7H, H$_{arom}$), 8.95 (br s, 2H, NH$_2$), 11.30 (br s, 1H, N–H), 13.95 (br s, 1H, O–H$_{quinolinol}$) and 14.58 (br s, 1H, O–H$_{carboxylic}$).

Ethyl 6-amino-4-(benzo[1,3]dioxol-5-yl)-3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydro-quinolin-3-yl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate (17b). This ester was obtained from compound **2** and ethyl cyanoacetate (1 mL), yield (3.97 g, 79%), m.p. 175-7 °C (dioxane). *Anal*. Calculated for $C_{26}H_{22}N_4O_7$ (502.49): C, 62.15; H, 4.41; N, 11.15. Found: C, 62.00; H, 4.40; N, 11.10. IR, ν: 3420, 3310 (NH$_2$), 3182 (N–H), 1730 (C=O$_{ester}$), 1635 (C=O$_{quinolone}$), 1612 (C=N), 1590, 1550, 1495, 1445 and 1110.

6-Amino-4-(benzo[1,3]dioxol-5-yl)-3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (19). A mixture of equimolar amounts (0.01 mol) of compound **2** (3.89 g) and malononitrile (0.65 g), in DMF (30 mL), was treated with 3 drops of piperidine and heated under reflux for 3h. On

cooling of the reaction mixture, yellow crystals were separated, which were filtered off and recrystallized from dioxane to yield the nitrile **19** (3.8 g, 83%), m.p. 266 °C. *Anal*. Calculated for $C_{24}H_{17}N_5O_5$ (455.43): C, 63.30; H, 3.76; N, 15.38. Found: C, 63.20; H, 3.60; N, 15.40. IR, ν: 3440, 3355 (NH_2), 3250-3190 (N–H, O–H), 2206 (C≡N), 1635 ($C=O_{quinolone}$), 1620 (C=N), 1600, 1585, 1550, 1492 and 1120. ^{1}H NMR, δ: 3.62 (s, 3H, $N–CH_3$), 4.40 (s, 1H, $C4–H_{pyran}$), 5.95 (s, 2H, $O–CH_2–O$), 6.82 (br s, 2H, NH_2), 7.20-8.05 (m, 7H, H_{arom}), 11.32 (br s, 1H, N–H) and 13.90 (br s, 1H, O–H).

The same product **19**, m.p., mixed m.p. and spectra, was obtained using the same procedure above from compound **1** (2.57 g) and piperonalidenemalononitrile **18** (1.98 g), yield (3.28g, 72%).

References and Notes

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Povzetek

Opisana je reakcija ciklizacije 3-[4-(benzo[1,3]dioksolilmetilen)-5-okso-3-pirazolil]-4-hidroksi-1-metil-kinolin-2(*1H*)-ona z nekaterimi bifunkcionalnimi nukleofilnimi reagenti. Pri reakcijah ciklizacije se tvorijo številni biološko zanimivi kondenzirani heterociklični sistemi, ki nastajajo iz pirazolinonov in vsebujejo kinolinonski strukturni del, kot so pirazolopirazol, izooksazolopirazol, pirazolopirimidin, pirazolotiazin, pirazolopiridin, dipirazolopiridin, dipirazolopiran in številni derivati pirazolopirana. Strukture vseh novih spojin so preverjene z analitskimi in spektroskopskimi metodami.