Synthesis of New Furo[3,4-*b*]quinolin-1(3*H*)-one Scaffolds Derived from γ-Lactone-Fused Quinolin-4(1*H*)-ones

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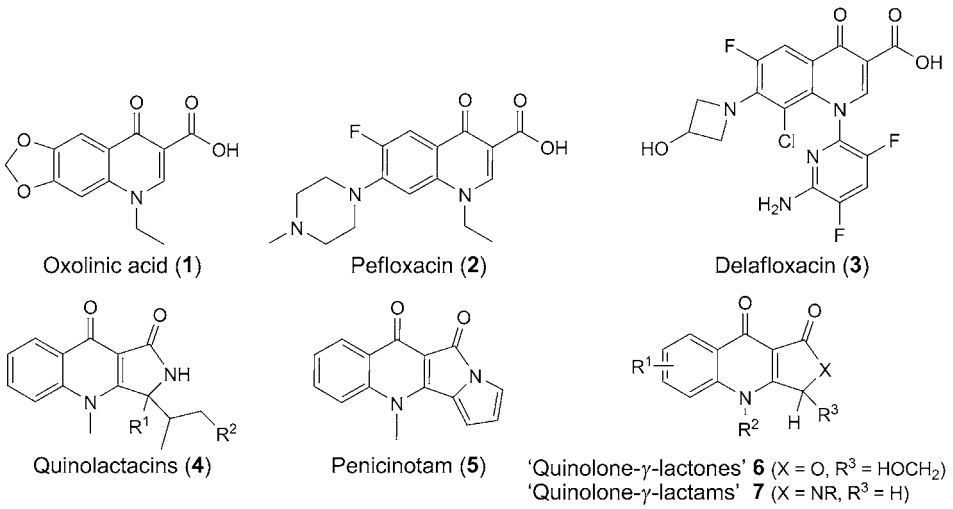
In the context of our aim of discovering new antitumor drugs among synthetic γ-lactone- and γ-lactam-fused 1-methylquinolin-4(1*H*)-ones, we developed a rapid access to 5-methyl-1,3-dioxolo[4,5-*g*]furo[3,4-*b*]quinoline-8,9(5*H*,6*H*)-dione (**9**) exploiting the γ-lactone-fused chloroquinoline **10** previously synthesized in our laboratory (*Scheme 1*). We also elaborated efficient synthetic methods allowing for a rapid access to two nonclassical bioisosteres of **9**, *i.e.*, a deoxy and a carba analogue. The deoxy analogue **11** was prepared in two steps from the γ-lactone-fused quinoline **13** which was also the synthetic precursor of **10** (*Scheme 1*). The carba analogue 6,9-dihydro-5-methyl-9-methylene-1,3-dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (**12**) was easily prepared by HCl elimination from the 9-(chloromethyl)dioxolofuroquinoline **15**, which was obtained *via* a three-component one-pot reaction from *N*-methyl-3,4-(methylenedioxy)aniline (= *N*-methyl-1,3-benzodioxol-5-amine; **16**), commercially available chloroacetaldehyde, and tetronic acid (**17**) (*Scheme 2*).

Introduction. – Quinolin-4(1*H*)-ones are common heterocyclic ketones, and derivatives containing this scaffold have shown a wide range of different biological activities [1]. Among this framework, the 4-oxoquinoline-3-carboxylic acids are the most represented as marketed drugs and constitute one of the largest classes of antimicrobial agents used worldwide [2]. A vast majority of these quinolinone derivatives display a free carboxylate group such as oxolinic acid (**1**) [3], a (methylenedioxy)-substituted derivative classified in the first generation of quinolinone antibiotics, or pefloxacin (**2**) [4], the first fluoroquinolinone derivative on the market belonging to the second generation, and the currently developed delafloxacin (**3**) [5], an *N*-aryl-fluoroquinolinone derivative. On the other hand, a few other compounds of the 4-oxoquinoline-3-carboxylic acid class exhibit a rarely encountered scaffold where the quinolin-4(1*H*)-one moiety is fused with a γ-lactam ring, such as the quinolactacins **4** [6] and penicinotam (**5**) [7]. Both lactams are cytotoxic, and in addition, quinolactacins have also demonstrated inhibition activity of tumor-necrosis-factor (TNF) production in macrophages [6f].

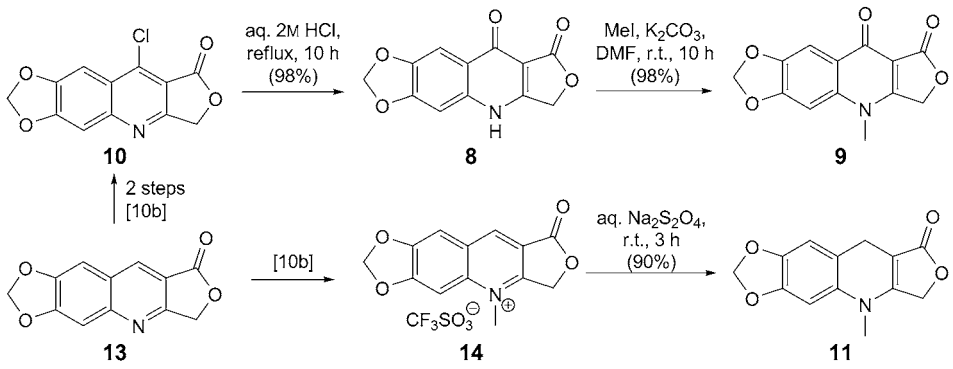
Results and Discussion. – We have previously described the synthesis of diversely substituted γ-lactone- and γ-lactam-fused quinolin-4(1*H*)-ones **6** [8] and **7** [9] respectively. These compounds were developed for a project aiming at the discovery of new antitumor drugs. More recently, we also reported several contributions for the



syntheses of the corresponding lactone-fused dihydroquinoline motif, required in the area of 4-azapodophyllotoxin analogues development [10].

As a complement of our ongoing research on the 4-azapodophyllotoxin pattern and taking into consideration the aforesaid biologically relevant structures **1**–**7**, we first decided to synthesize the (methylenedioxy)-substituted γ-lactone-fused quinolinone derivatives **8** and **9** (*Scheme 1*). Althought the unsubstituted furo[3,4-*b*]quinoline-1,9(3*H*,4*H*)-dione has been previously accessed by the use of a Pd-catalyzed reaction with CO to close the N-heterocycle [11], we decided to exploit the chloroquinoline derivative **10** [10b] synthesized in our laboratory for the rapid preparation of the target quinolinone derivative **9**. Thus, refluxing **10** in an aqueous HCl solution afforded quinolinone derivative **8**, which was then methylated with MeI under basic conditions to provide the *N*-methylquinolinone derivative **9** in very good overall yield (*Scheme 1*).

Scheme 1

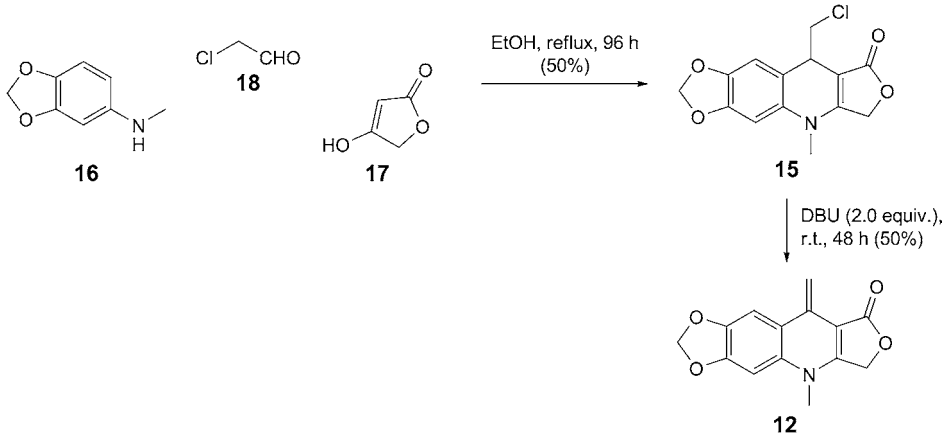


In the context of exploring structural modifications to establish potential structure–activity relationships (SARs), we found that two nonclassical bioisosteres of **9** [12],

deoxy analogue **11** and carba isostere **12**, contain unprecedented heterocyclic structures. Thus, we decided to develop of efficient synthetic methods to access rapidly these two new motifs. The deoxy analogue **11** was prepared in two steps from the γ-lactone-fused quinoline **13** which was also the synthetic precursor of **10** (*Scheme 1*). We have already reported the *N*-methylation of **13** to **14** in the presence of methyl trifluoromethanesulfonate in 90% yield [10b]. Interestingly, methylation was also possible in 88% yield with 'methyl magic', another fluorinated agent, whereas MeI, Me_2SO_4, and methyl toluenesulfonate gave no results. Formation of the new quinoline scaffold **11** was then carried out by reduction of the unstable salt **14** with $Na_2S_2O_4$ (*Scheme 1*).

In regard to carba isostere **12**, we previously reported an original three-component one-pot reaction for the synthesis of 2,3-didehydro-4-azapodophyllotoxin derivatives [10a]. We decided to adapt this synthetic pathway for the preparation of (chloromethyl)-dihydroquinoline derivative **15** as precursor of carba isostere **12** (*Scheme 2*). Intermediate **15** was obtained in 50% yield by refluxing in EtOH a mixture of *N*-methyl-3,4-(methylenedioxy)aniline (= *N*-methyl-1,3-benzodioxol-5-amine; **16**), tetronic acid (= 4-hydroxyfuran-2(5*H*)-one; **17**) and chloroacetaldehyde (**18**). The desired **12** was subsequently prepared from **15** in 50% yield by HCl elimination in the presence of the sterically hindered base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Scheme 2



Conclusion. – The present study describes a rapid access to 5-methyl-1,3-dioxolo[4,5-*g*]furo[3,4-*b*]quinoline-8,9(5*H*,6*H*)-dione (**9**) exploiting the γ-lactone-fused chloroquinoline derivative **10**. To investigate SARs, we also synthesized two nonclassical bioisosteric quinolinone derivatives displaying new structural features, *i.e.*, 6,9-dihydro-5-methyl-1,3-dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (**11**) and 6,9-dihydro-5-methyl-9-methylene-1,3-dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (**12**). Further studies with these structures and their pharmacological activities are underway.

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Experimental Part

General. TLC: *Merck GF 254* silica gel plates. M.p.: *Maquenne* apparatus; uncorrected. IR Spectra: *Nicolet-510* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-AC-400* and *AC-300* spectrometers; in $(D_6)DMSO$; δ in ppm rel. to solvents signal as internal standard, J in Hz; assignments of ^{13}C-NMR signals by HSQC experiments. Elemental analyses: C.N.R.S. Analysis Laboratory, Gif-sur-Yvette.

*1,3-Dioxolo[4,5-*g*]furo[3,4-*b*]quinoline-8,9(5*H*,6*H*)-dione* (**8**). A stirred suspension of chloroquinoline derivative **10** [10b] (56 mg, 0.21 mmol) in 2M aq. HCl (10 ml) was heated under reflux for 10 h. The resulting precipitate was filtered and then recrystallized from DMF: **8** (52 mg, 98%). White solid. M.p. > 260° (DMF). IR (KBr): 3270, 1753, 1654, 1648, 1574, 1561, 1500, 1479, 1264, 1039, 1020. ^1H-NMR ($(D_6)DMSO$): 5.20 (*s*, 2 H); 6.20 (*s*, 2 H); 7.00 (*s*, 1 H); 7.50 (*s*, 1 H); 12.80 (*s*, 1 H). ^{13}C-NMR: poor solubility in DMSO. Anal. calc. for $C_{12}H_7NO_5 \cdot 0.5\ H_2O$ (254.20): C 56.70, H 3.17, N 5.51; found: C 56.64, H 3.11, N 5.25.

*5-Methyl-1,3-dioxolo[4,5-*g*]furo[3,4-*b*]quinoline-8,9(5*H*,6*H*)-dione* (**9**). To a stirred suspension of **8** (54 mg, 0.21 mmol) and K_2CO_3 (29 mg, 0.21 mmol) in anh. DMF (10 ml), MeI (1 ml) was added, and the mixture was stirred at r.t. for 10 h. The MeI in excess was evaporated, and the mixture was diluted with H_2O (30 ml). The resulting precipitate was filtered and recrystallized from DMF: **9** (54 mg, 98%). White solid. M.p. > 260° (DMF). IR (KBr): 1754, 1647, 1577, 1510, 1493, 1430, 1276, 1029. ^1H-NMR ($(D_6)DMSO$): 3.65 (*s*, 3 H); 5.35 (*s*, 2 H); 6.25 (*s*, 2 H); 7.50 (*s*, 1 H); 7.60 (*s*, 1 H). ^{13}C-NMR: poor solubility in DMSO. Anal. calc. for $C_{13}H_9NO_5$ (259.22): C 60.24, H 3.50, N 5.40; found: C 60.07, H 3.47, N, 5.39.

*6,9-Dihydro-5-methyl-1,3-dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one* (**11**). A soln. of freshly prepared quinolinium salt **14** [10b] (0.25 mmol) and $Na_2S_2O_4$ (44 mg, 0.25 mmol) in H_2O (5 ml) was stirred for 3 h at r.t. The resulting precipitate was filtered, washed with EtOH, and recrystallized from EtOH: **11** (57 mg, 90%). Slightly colored solid. M.p. 230° (EtOH). IR (KBr): 1746, 1733, 1661, 1617, 1499, 1251, 1204, 1033, 1012. ^1H-NMR ($(D_6)DMSO$): 3.10 (*s*, 3 H); 3.55 (*s*, 2 H); 4.95 (*s*, 2 H); 6.00 (*s*, 2 H); 6.75 (*s*, 1 H); 6.80 (*s*, 1 H). ^{13}C-NMR ($(D_6)DMSO$): 24.2; 34.5; 66.5; 91.9; 97.3; 102.3; 110.7; 115.1; 134.5; 144.2; 147.8; 162.2; 173.8. Anal. calc. for $C_{13}H_{11}NO_4 \cdot 0.5\ H_2O$ (254.25): C 61.42, H 4.76, N 5.51; found: C 61.23, H 4.63, N 5.50.

*(9*RS*)-9-(Chloromethyl)-6,9-dihydro-5-methyl-1,3-dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one* (**15**). An equimolar mixture (3 mmol) of aniline **16**, tetronic acid (**17**), and chloroacetaldehyde (**18**) in EtOH (10 ml) was heated under reflux for 96 h. The resulting precipitate was filtered, washed with EtOH, and recrystallized from MeOH: **15** (439 mg, 50%). Slightly colored solid. M.p. 198° (MeOH). IR (KBr): 1733, 1625, 1613, 1506, 1487, 1434, 1417, 1254, 1241, 1212, 1040. ^1H-NMR ($(D_6)DMSO$): 3.10 (*s*, 3 H); 3.85 (*d*, $J = 3$, 2 H); 4.35 (*t*, $J = 3$, 1 H); 4.95 (*d*, $J = 15$, 1 H); 5.10 (*d*, $J = 15$, 1 H); 6.00 (*s*, 1 H); 6.05 (*s*, 1 H); 6.85 (*s*, 1 H); 7.00 (*s*, 1 H). ^{13}C-NMR ($(D_6)DMSO$): 34.2; 36.4; 50.5; 65.8; 91.3; 96.4; 101.9; 109.8; 115.8; 134.9; 143.9; 147.7; 162.5; 172.7. Anal. calc. for $C_{14}H_{12}ClNO_4$ (293.71): C 57.25, H 4.12, N 4.77; found: C 57.09, H 4.28, N 5.14.

*6,9-Dihydro-5-methyl-9-methylene-1,3-dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one* (**12**). To a soln. of quinoline **15** (73 mg, 0.25 mmol) in anh. DMF (5 ml) was added DBU (75 µl, 0.5 mmol). The mixture was then stirred for 48 h at r.t., and the resulting precipitate was filtered and recrystallized from DMF: **12** (33 mg, 50%). Slightly colored solid. M.p. > 260° (DMF). IR (KBr): 1727, 1663, 1636, 1490, 1433, 1251, 1180, 1118, 1032, 1006. ^1H-NMR ($(D_6)DMSO$): 3.25 (*s*, 3 H); 5.00 (*s*, 1 H); 5.05 (*s*, 2 H); 5.20 (*s*, 1 H); 6.05 (*s*, 2 H); 7.00 (*s*, 1 H); 7.35 (*s*, 1 H). ^{13}C-NMR ($(D_6)DMSO$): 34.9; 64.9; 91.4; 97.3; 94.4; 102.4; 103.8; 119.2; 131.3; 134.3; 145.6; 149.5; 160.2; 171.2. Anal. calc. for $C_{14}H_{11}NO_4 \cdot 0.25\ H_2O$ (261.75): C 64.24, H 4.43, N 5.35; found: C 63.96, H 4.26, N 5.02.

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