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Synthesis, spectroscopy and computational studies of selected hydroxyquinolines and their analogues

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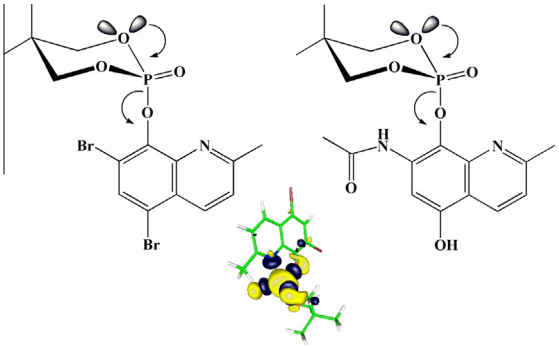
HIGHLIGHTS

- Five of hydroxyquinolines have been characterized by single crystal X-ray diffraction method.
- The NBO analysis of the quinoline ring indicates the charges on chlorine and bromine are nearly zero.
- The X-ray and NMR's indicate the anomeric effect for quinoline esters with dioxaphosphinane group.

GRAPHICAL ABSTRACT



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ABSTRACT

Synthetic, spectroscopy and mechanistic aspects of preparation of selected hydroxyquinolines and their analogues or derivatives contained methoxy, fluoro, chloro, carboxylic, carbodithioic and phosphinate or dioxaphosphinane groups were elaborated. The multinuclear NMR and five single crystal X-ray characteristics of the series of quinolines have been determined. The molecular orbitals of the selected hydroxyquinolines have been calculated by density functional theory. The X-ray and NMR studies of 8-[(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)oxy]-5,7-dibromo-2-methylquinoline and 8-[(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)oxy]-5-fluoro-2-methylquinoline indicate the appearance of anomeric effect.

Introduction

The quinolines are part of the most important compounds among *N*-heterocycles found their broad application in pharmaceutical and agrochemical industries [1]. They are widely seen in a number of natural products and have attracted considerable attention due to their biological activities such as anti-malarial, anti-fungal, anti-bacterial, anti-asthmatic, anti-hypertensive, anti-inflammatory, and trichomonal [2–12]. They are also important synthetic intermediates in preparing a variety of biologically active compounds [6,11–14]. Many of them are ligands in coordination chemistry as a N and/or O atom donors for chelating with metals, such as ruthenium metalloantimalarials and are used for the identification of metals [15–17]. Additionally quinolines have been used in components for molecular electronic devices [18].

We are particularly interested in the functionalization of benzene or phenol ring in quinoline constitution. Compounds with hydroxyquinoline carboxylic acid groups carrying carboxylic and hydroxyl function on benzene ring attracted increasing attentions

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due to their analogy to the precursor of a promising HIV-1 integrase inhibitor, 2-[(*E*)-2-(3,4-dihydroxy-5-methoxyphenyl)ethenyl]-8-hydroxyquinoline-7-carboxylic acid (shortly named FZ-41) which has been demonstrated to block the replication of HIV-1 in cell cultures at nontoxic concentrations [13,19].

The fluoride derivatives of quinolines or related compounds, in which the hydrogen atom is replaced by a fluoride, should be conveniently monitored by ^{19}F NMR techniques and provide so called "NMR probes" to enhance the mechanistic understanding of physiological processes, thus to facilitate and rationalize the design of more biologically active compounds and new drugs. Our studies of biological activity of thioanalogue of hydroxyquinolines are in progress.

In this paper, we reported new quinoline compounds with in-depth spectroscopic characterization. Computational and spectroscopic studies were carried out to compare selected hydroxyquinolines and their methoxy, fluoro, chloro, carboxylic, carbodithioic and phosphinate or dioxaphosphinane derivatives which have not been reported by previous studies.

Experimental

General

NMR spectra were obtained with Bruker Avance 400 and 500 operating at 500.18 or 400.13 MHz (^1H), 125.78 or 100.5 MHz (^{13}C), 202.47 or 162.0 MHz (^{31}P) and 470.5 MHz (^{19}F) at 21 °C. Chemical shifts referenced to ext. TMS (^1H, ^{13}C) or DSS (^1H, ^{13}C), 85% H_3PO_4 (^{31}P) and $CFCl_3$ (^{19}F). Coupling constants are given in Hz. Mass spectra were obtained with a Varian 500 MS with applied ESI technique. Chromatography was carried out on Silica Gel 60 (0.15–0.3 mm) Machery Nagel. Melting points were determined on MPA100 OptiMelt melting point apparatus and uncorrected. 5,7-Dibromo-2-methylquinolin-8-ol (**1a**), *N*,*N*-diethylbenzene-1,4-diamine (**1b**), 2-amino-4-fluorophenol (**1c**), 3-fluoro-2-methoxyaniline (**1d**), 3-chloro-2-methoxyaniline (**1e**), 2-amino-4-chlorophenol (**1f**), 2-amino-5-chlorophenol (**1g**) and 2-amino-4-methylphenol (**1h**) were purchased from Sigma–Aldrich, and were used without further purification. 5-Fluoro-2-methylquinolin-8-ol (**1i**) was synthesized according to procedure described in the literature [20].

The synthesis of quinolines **2**, **3** and **4** followed our procedure described in the literature [20]:

7-Fluoro-8-methoxy-2-methylquinoline (***2a***) (brown oil); 21%; ^1H NMR ($CDCl_3$; 400.2 MHz) δ = 2.78 (s, 3H, CH_3), 4.23 (d, J = 1.8 Hz, 3H, OCH_3), 7.23 (d, J = 8.3 Hz, 1H, aromatic), 7.26 (dd, J = 10.8, 9.1 Hz, 1H, aromatic), 7.43 (dd, J = 9.0, 5.4 Hz, 1H, aromatic), 7.99 (d, J = 8.4 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR ($CDCl_3$; 100.5 MHz) δ = 25.76, 62.33 (d, J = 5.1 Hz, OCH_3), 116.81 (d, J = 23.5 Hz), 121.67 (d, J = 2.6 Hz), 122.50 (d, J = 9.4 Hz), 124.49, 136.37, 141.56 (d, J = 9.7 Hz), 143.13 (d, J = 6.2 Hz), 154.20 (d, J = 247.0 Hz), 159.53; $^{19}F\{^1H\}$ NMR ($CDCl_3$; 470.5 MHz) δ = −129.07; MS: (ESI) $[M+H]^+$ = 192 (100%).

7-Chloro-8-methoxy-2-methylquinoline (***2b***) (brown oil); 24%; ^1H NMR ($CDCl_3$; 400.2 MHz) δ = 2.78 (s, 3H, CH_3), 4.18 (s, 3H, OCH_3), 7.28 (d, J = 8.4 Hz, 1H, aromatic), 7.44 (2d, J = 0.5 Hz, 2H, aromatic), 8.01 (d, J = 8.4 Hz, 1H, aromatic); ^1H NMR ($CDCl_3$; 500.18 MHz) δ = 2.78 (s, 3H, CH_3), 4.18 (s, 3H, OCH_3), 7.28 (d, J = 8.4 Hz, 1H, aromatic), 7.44 (d, J = 0.6 Hz, 2H, aromatic), 8.01 (d, J = 8.4 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR ($CDCl_3$; 100.5 MHz) δ = 25.75, 62.22, 122.41, 123.49, 126.81, 127.25, 127.46, 136.49, 142.94, 151.75, 159.49.

5-Chloro-2-methylquinolin-8-ol (***3a***) (light yellow); 41%; mp = 67.4 °C; ^1H NMR ($CDCl_3$; 500.18 MHz) δ = 2.74 (s, 3H, CH_3), 7.06 (d, J = 8.2 Hz, 1H, aromatic), 7.39 (d, J = 8.6 Hz, 1H, aromatic), 7.42 (d, J = 8.2 Hz, 1H, aromatic), 8.37 (d, J = 8.6 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR ($CDCl_3$; 125.78 MHz) δ = 24.86, 110.03, 120.45, 123.57, 124.68, 126.56, 133.59, 138.25, 151.03, 157.77; MS: (ESI) $[M+H]^+$ = 194 (100%); CCDC 933796.

6-Chloro-2-methylquinolin-8-ol (***3b***) (white); 43% mp = 124.6 °C; ^1H NMR ($CDCl_3$; 400.2 MHz) δ = 2.71 (s, 3H, CH_3), 7.11 (d, J = 2.1 Hz, 1H, aromatic), 7.25 (d, J = 2.1 Hz, 1H, aromatic), 7.31 (d, J = 8.5 Hz, 1H, aromatic), 7.93 (d, J = 8.5 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR ($CDCl_3$; 100.5 MHz) δ = 24.85, 111.54, 116.56, 123.90, 126.99, 132.47, 135.62, 136.28, 152.56, 157.25; MS: (ESI) $[M+H]^+$ = 194 (100%); CCDC 933797.

2,5-Dimethylquinolin-8-ol (***3d***) (light green); 36%; mp = 86.6 °C; ^1H NMR ($CDCl_3$; 400.2 MHz) δ = 2.56 (d, J = 0.9 Hz, 3H, CH_3), 2.73 (s, 3H, CH_3), 7.03 (d, J = 7.7 Hz, 1H, aromatic), 7.18 (dd, J = 7.7, 0.9 Hz, 1H, aromatic), 7.32 (d, J = 8.6 Hz, 1H, aromatic), 8.16 (d, J = 8.6 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR ($CDCl_3$; 100.5 MHz) δ = 17.92, 24.88, 109.33, 122.30, 124.24, 125.84, 126.71, 133.29, 137.99, 150.07, 156.38; MS: (ESI) $[M+H]^+$ = 174 (100%); CCDC 933795.

Diethyl-(2-methyl-[6]quinolyl)-amine (***4***) (yellow); 46%; bp = 153/32 mmHg; ^1H NMR ($CDCl_3$; 500.18 MHz) δ = 1.01 (t, J = 7.1 Hz, 6H, CH_3), 2.51 (s, 3H, CH_3), 3.22 (q, J = 7.1 Hz, 4H, CH_2), 6.57 (d, J = 2.9 Hz, 1H, aromatic), 6.92 (d, J = 8.4 Hz, 1H, aromatic), 7.09 (dd, J = 9.3, 2.9 Hz, 1H, aromatic), 7.63 (d, J = 8.4 Hz, 1H, aromatic), 7.76 (d, J = 9.3 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR ($CDCl_3$; 125.78 MHz) δ = 12.10, 24.21, 43.98, 103.79, 118.38, 121.51, 127.74, 128.59, 133.82, 140.66, 144.93, 153.14.

Synthesis of ester 3c

A solution of **2b** (10.4 g, 0.050 mol) in 48% HBr (50 mL) was heated at 100 °C for 48 h and cooled to room temperature. The water solution was alkalified by aqueous solution of KOH (10%). Reagents were shaken for a few minutes. The mixture was poured into CH_2Cl_2. The organic phase was separated and dried by $MgSO_4$. After the solvent was evaporated, the residue was purified by chromatography:

7-Chloro-2-methylquinolin-8-ol (***3c***) (white); 98% (9.5 g, 0.049 mol); mp = 108.9 °C; ^1H NMR ($CDCl_3$; 400.2 MHz) δ = 2.75 (s, 3H, CH_3), 7.24 (d, J = 8.8 Hz, 1H, aromatic), 7.31 (d, J = 8.4 Hz, 1H, aromatic), 7.41 (d, J = 8.8 Hz, 1H, aromatic), 8.04 (d, J = 8.4 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR ($CDCl_3$; 100.5 MHz) δ = 24.83, 116.18, 118.02, 122.88, 125.25, 128.14, 136.78, 137.65, 147.80, 158.07; MS: (ESI) $[M+H]^+$ = 194 (100%).

Synthesis of esters 5a, 5b, 5b′, 5c and 5c′

$Ph(Bu^t)P(O)Cl$ or 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (5.0 mmol) was added to the suspension of NaH (0.133 g, 5.5 mmol) in THF (25 mL). Subsequently, 5,7-dibromo-2-methylquinolin-8-ol (**1a**), 5-fluoro-2-methylquinolin-8-ol (**1i**) (5.0 mmol) in THF (5 mL), was added. The reaction was carried out for 24 h under reflux. The mixture was allowed to cool to room temperature. The reaction was neutralized with aqueous solution of $KHSO_4$. After extraction with CH_2Cl_2 (3 × 50 mL), the organic phase was dried over $MgSO_4$, followed by filtration and solvent evaporation. The crude product was purified by chromatography and crystallization:

5-Fluoro-2-methylquinolin-8-yl tert-butyl(phenyl)phosphinate (***5a***) (brown); 78%; $mp_{dec.}$ = 176 °C; ^1H NMR (DMSO-d_6; 500.2 MHz) δ = 1.26 (d, J = 16.0 Hz, 9H, *t*-Bu), 2.67 (s, 3H, CH_3), 7.20 (dd, J = 9.1 Hz, 1H, aromatic), 7.47 (dd, J = 7.6, 4.5 Hz, 3H, aromatic), 7.54 (dt, J = 14.3, 8.7 Hz, 2H, aromatic), 7.90 (ddd, J = 9.7, 7.6, 3.2 Hz, 2H, aromatic), 8.33 (d, J = 8.6 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR (DMSO-d_6; 100.6 MHz) δ = 24.47, 25.54, 33.99 (d, J = 99.9 Hz), 117.98 (bs), 122.43 (bs), 127.94 (bs), 129.13 (bs), 132.20 (bs), 133.58 (bs), 139.56 (bs), 143.32 (bs), 158.86 (bs); $^{31}P\{^1H\}$ NMR (DMSO-d_6; 202.5 MHz) δ = 51.19; ^{19}F NMR ($CDCl_3$; 470.5 MHz) δ = −127.44; MS: (ESI) $[M+H]^+$ = 358 (56%).