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

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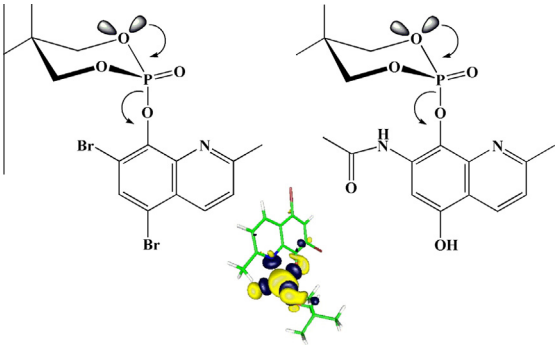
## HIGHLIGHTS

- 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = −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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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) $\delta$ = 51.19; $^{19}F$ NMR ($CDCl_3$; 470.5 MHz) $\delta$ = −127.44; MS: (ESI) $[M+H]^+$ = 358 (56%).

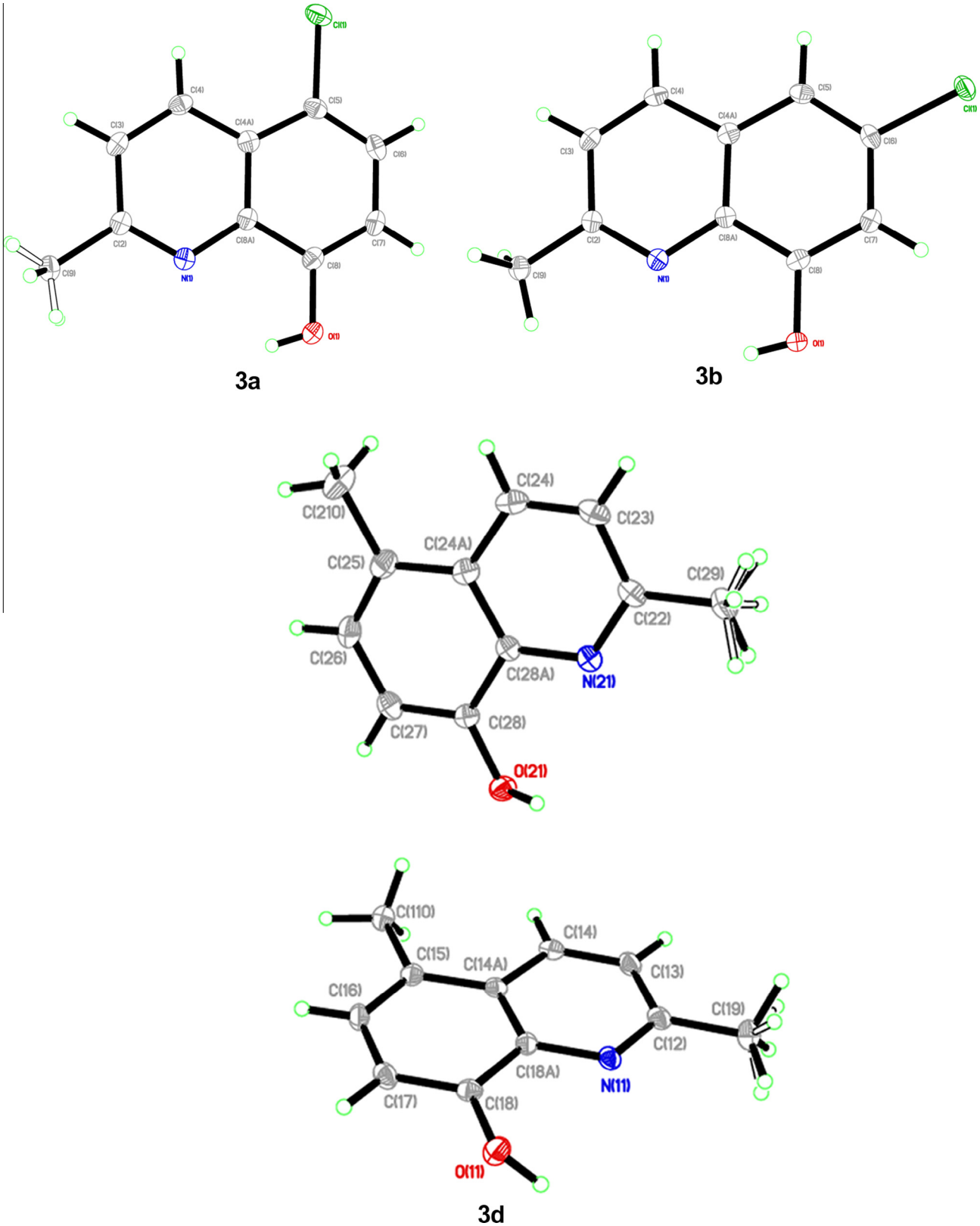



**Fig. 1.** ORTEP drawing of **3a**, **3b**, **3d**, **5c** and **6b** molecules with 50% probability displacement ellipsoids.

*8-[(5,5-Dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)oxy]-5-fluoro-2-methylquinoline (**5b** and **5b'**)* (brown); 76%; $mp_{dec.}$ = 190.1 °C; $^1H$ NMR ($CDCl_3$; 400.2 MHz) $\delta$ = 0.92 (s, 3H, $CH_3$), 1.32 (s, 3H, $CH_3$), 2.71 (s, 3H, $CH_3$), 3.94 (m, 2H, $CH_{2e}$), 4.82 (bd, $J$ = 10.4 Hz, 2H, $CH_{2a}$), 7.08 (pseudo-t, $J$ = 8.6 Hz, 1H, aromatic), 7.37 (d, $J$ = 8.6 Hz, 1H, aromatic), 7.71 (ddd, $J$ = 8.5, 5.0, 1.7 Hz, 1H, aromatic), 8.28 (d,

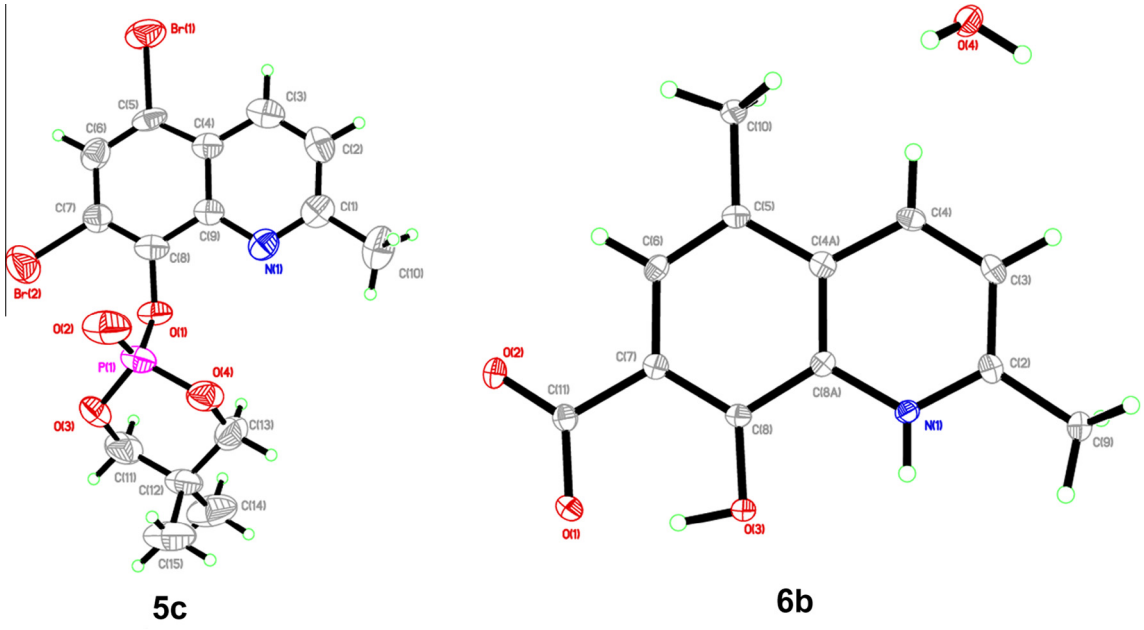



**Fig. 1** (*continued*)

$J$ = 8.6 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR (DMSO-$d_6$; 100.6 MHz) $\delta$ = 19.28, 21.03, 24.97, 31.79 (d, $J$ = 5.8 Hz), 78.27 (d, $J$ = 6.9 Hz), 109.24 (d, $J$ = 17.8 Hz), 117.51 (d, $J$ = 18.0 Hz), 119.28 (d, $J$ = 9.4 Hz), 123.58, 129.45, 139.33 (d, $J$ = 114.3 Hz), 141.18 (d, $J$ = 4.0 Hz), 155.29, 160.47; $^{31}P\{^1H\}$ NMR ($CDCl_3$; 162.0 MHz) $\delta_{e,a}$ = −12.93 and −13.10; $^{19}F\{^1H\}$ NMR ($CDCl_3$; 470.5 MHz) $\delta_{e,a}$ = −125.55 and −125.56; $^{19}F$ NMR ($CDCl_3$; 470.5 MHz) $\delta_{e,a}$ = −125.55 (ddd, $J$ = 7.1, 4.7, 1.9 Hz); MS: (ESI) $[M+H]^+$ = 326 (100%).

*8-[(5,5-Dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)oxy]-5,7-dibromo-2-methylquinoline* (***5c***) (white); 89%; $mp_{dec.}$ = 186.7 °C; $^1H$ NMR ($CDCl_3$; 400.2 MHz) $\delta$ = 0.96 (s, 3H, $CH_3$), 1.37 (s, 3H, $CH_3$), 2.73 (s, 3H, $CH_3$), 4.08 (dd, $J$ = 23.2, 11.1 Hz, 2H, $CH_{2e}$), 4.73 (d, $J$ = 10.7 Hz, 2H, $CH_{2a}$), 7.36 (d, $J$ = 8.7 Hz, 1H, aromatic), 7.88 (s, 1H, aromatic), 8.24 (d, $J$ = 8.7 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR (DMSO-$d_6$; 100.6 MHz) $\delta$ = 20.37, 22.20, 25.15, 32.21 (d, $J$ = 5.7 Hz), 78.59 (d, $J$ = 7.2 Hz), 115.56 (d, $J$ = 5.9 Hz), 117.96 (d, $J$ = 2.6 Hz), 123.92, 126.10, 132.24 (d, $J$ = 1.8 Hz), 135.50, 141.76 (d, $J$ = 2.5 Hz), 144.79 (d, $J$ = 8.5 Hz), 160.75; $^{31}P\{^1H\}$ NMR ($CDCl_3$; 162.0 MHz) $\delta$ = −14.29; $^{31}P$ NMR ($CDCl_3$; 162.0 MHz) $\delta$ = −14.29 (t, $J$ = 23.1 Hz); MS: (ESI) $[M+H]^+$ = 467 (100%), $[M+Na]^+$ = 488 (18%); CCDC 940334.

(***5c′***) $^1H$ NMR ($CDCl_3$; 400.2 MHz) $\delta$ = 0.89 (s, 3H, $CH_3$), 1.31 (s, 3H, $CH_3$), 2.74 (s, 3H, $CH_3$), 3.98 (ddd, $J$ = 24.4, 9.8, 1.4 Hz, 2H, $CH_{2e}$), 4.47 (d, $J$ = 10.7 Hz, 2H, $CH_{2a}$), 7.37 (d, $J$ = 8.7 Hz, 1H, aromatic), 7.88 (s, 1H, aromatic), 8.25 (d, $J$ = 8.6 Hz, 1H, aromatic); $^{31}P\{^1H\}$ NMR ($CDCl_3$; 162.0 MHz) $\delta$ = −21.12.

Quinoline-7-carboxylic(carbodithioic) acids **6** were synthesized according to our procedure described in the literature [20].

*5-Chloro-8-hydroxy-2-methylquinoline-7-carboxylic acid* (***6a***) (yellow); 9%; mp = 206 °C; $^1H$ NMR (KOD/$D_2O$/DMSO-$d_6$; 400.2 MHz) $\delta$ = 2.52 (s, 3H, $CH_3$), 7.30 (d, $J$ = 8.6 Hz, 1H, aromatic), 7.49 (s, 1H, aromatic), 8.13 (d, $J$ = 8.5 Hz, 1H, aromatic); $^1H$ NMR ($D_2SO_4$/$D_2O$/DMSO-$d_6$; 400.2 MHz) $\delta$ = 2.85 (s, 3H, $CH_3$), 7.50 (s, 1H, aromatic), 7.90 (d, $J$ = 8.9 Hz, 1H, aromatic), 8.73 (d, $J$ = 8.9 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR (KOD/$D_2O$/DMSO-$d_6$; 125.78 MHz) $\delta$ = 25.13, 110.86, 122.74, 124.64, 127.54, 129.33, 134.24, 145.58, 157.17, 164.05, 177.32; MS: (ESI) $M^-$ = 237 (40%).

*8-Hydroxy-2,5-dimethylquinoline-7-carboxylic acid* (***6b***) (yellow); 68%; mp = 222.2 °C; $^1H$ NMR (KOD/$D_2O$; 400.2 MHz) $\delta$ = 1.92 (s, 3H, $CH_3$), 2.36 (s, 3H, $CH_3$), 6.82 (d, $J$ = 8.6 Hz, 1H, aromatic), 6.97 (s, 1H, aromatic), 7.37 (d, $J$ = 8.6 Hz, 1H, aromatic); $^1H$ NMR ($D_2SO_4$/$D_2O$/DMSO-$d_6$; 400.2 MHz; 70 °C) $\delta$ = 2.37 (s, 3H, $CH_3$), 2.81 (s, 3H, $CH_3$), 7.53 (s, 1H, aromatic), 7.81 (d, $J$ = 8.8 Hz, 1H, aromatic), 8.75 (d, $J$ = 8.7 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR (KOD/$D_2O$; 125.78 MHz) $\delta$ = 16.80, 23.23, 113.57, 122.81, 123.04, 124.80, 127.79, 132.76, 137.34, 154.83, 157.11, 175.69; CCDC 939809.

*5-Chloro-8-hydroxy-2-methylquinoline-7-carbodithioic acid* (***6c***) (brick red); 23%; $mp_{dec.}$ = 164.3 °C; $^1H$ NMR ($K_2CO_3$/$D_2O$; 400.2 MHz) $\delta$ = 2.61 (s, 3H, $CH_3$), 6.66 (d, $J$ = 8.4 Hz, 1H, aromatic), 7.30 (d, $J$ = 8.4 Hz, 1H, aromatic), 7.36 (d, $J$ = 8.7 Hz, 1H, aromatic), 8.30 (d, $J$ = 8.7 Hz, 1H, aromatic); $^{13}C\{^1H\}$ NMR (KOD/$D_2O$/DMSO-$d_6$; 125.78 MHz) $\delta$ = 23.68, 112.28, 113.73, 122.74, 125.57, 127.47, 133.45, 142.94, 156.49, 167.94, 242.34.

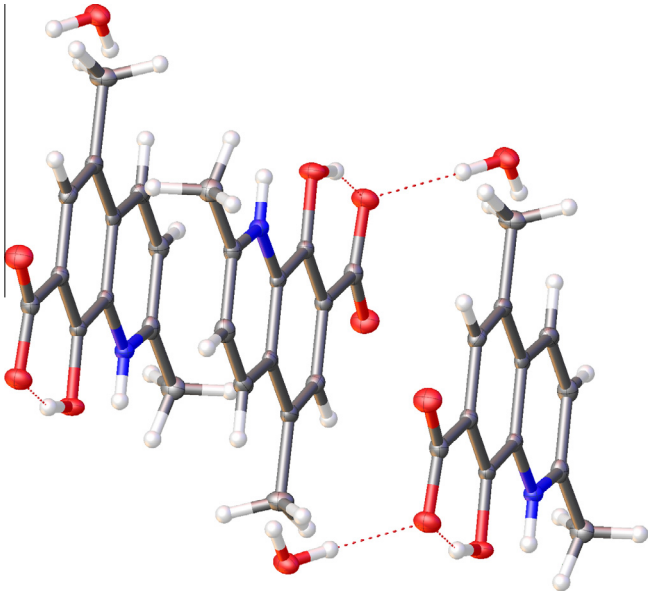


**Fig. 2.** π-Stacking interaction in the molecular structure of **6b**.

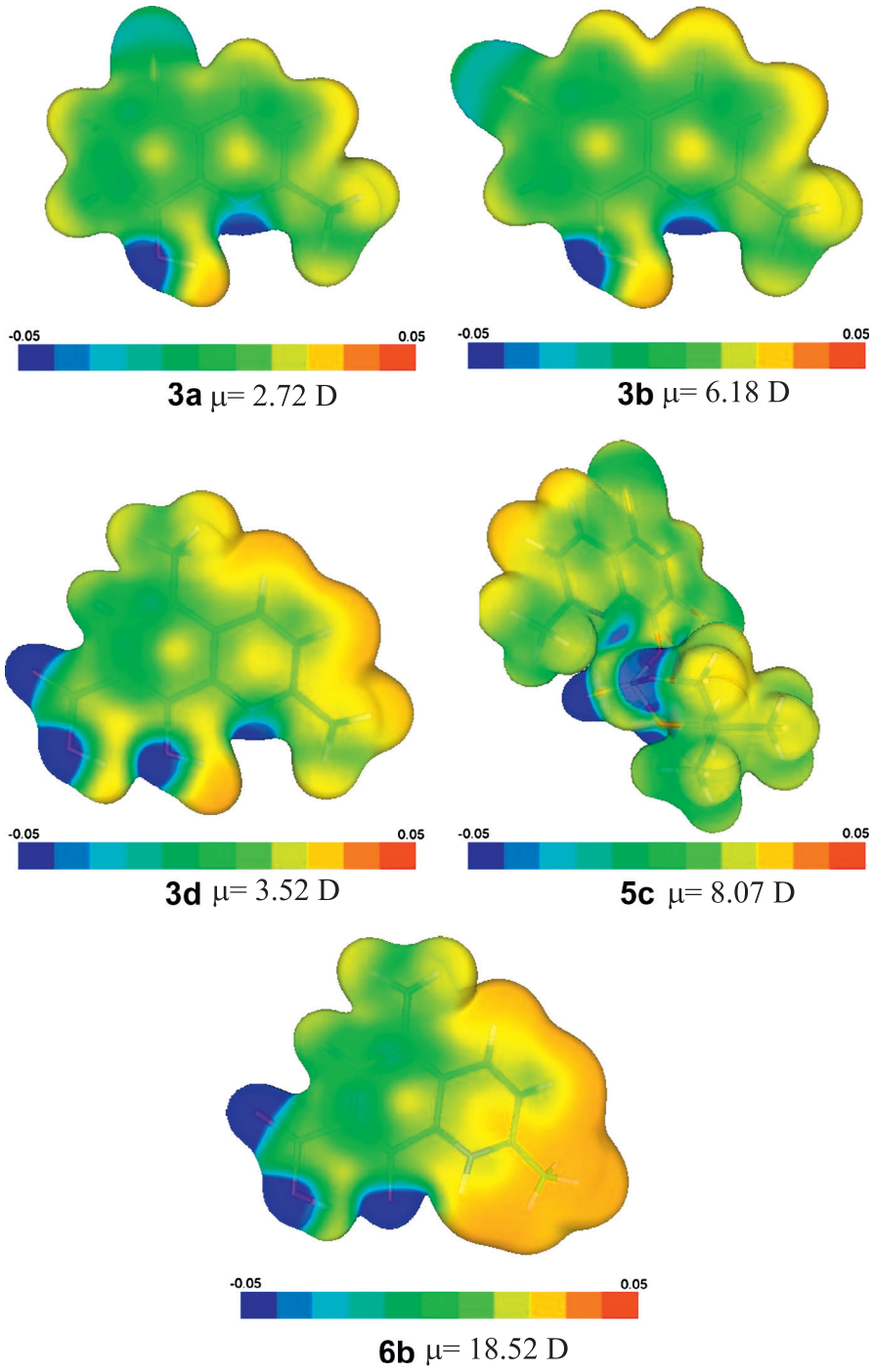



**Fig. 3.** The electrostatic potential (ESP) surfaces on molecules **3a**, **3b**, **3d**, **5c** and **6b**.

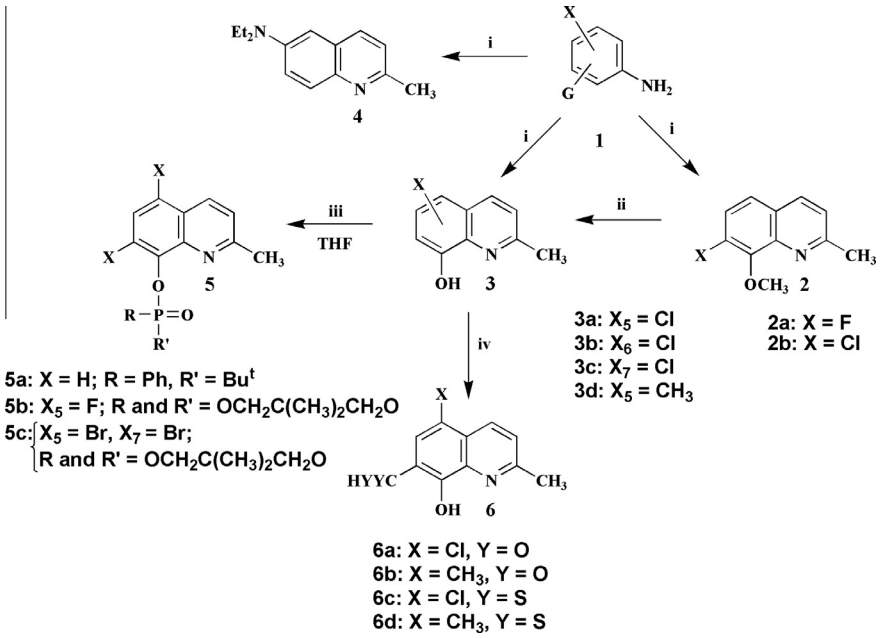
*8-Hydroxy-2,5-dimethylquinoline-7-carbodithioic acid (**6d**)* (brick red); 64%; $mp_{dec.}$ = 206.7 °C; $^1H$ NMR ($K_2CO_3/D_2O$; 400.2 MHz) $\delta$ = 2.49 (s, 3H, $CH_3$), 2.67 (s, 3H, $CH_3$), 6.77 (d, $J$ = 7.7 Hz, 1H, aromatic), 7.17 (d, $J$ = 7.8 Hz, 1H, aromatic), 7.39 (d, $J$ = 8.6 Hz, 1H, aromatic), 8.26 (d, $J$ = 8.6 Hz, 1H, aromatic); MS: (ESI) $[M-H]^-$ = 216 (30%).

*Crystallization*

The crystals suitable for X-ray analysis were obtained from hot hexane solution for **3a**, **3b**, **3c**, hot $CHCl_3$ solution for **5c** and from hot DMSO solution ca.100 °C for **6b**.

*DFT calculations*

The calculations were carried out by using Gaussian 09 program [21]. The DFT/B3LYP method was used for the geometry optimization and electronic structure determination [22]. The geometry optimization was made for gas phase molecule and a frequency calculation was carried out, verifying that the optimized molecular structure obtained corresponds to energy minimum, thus only positive frequencies were expected. The absence of the imaginary frequencies, as well as of negative eigenvalues of the second derivative matrix has been obtained in geometry optimization of all compounds. The calculations were performed using the polarization




**Scheme 1.** Synthesis of **2**, **3**, **4**, **5** and **6**. *Reagents and conditions*: (i) $CH_3CHCHCHO$, HCl, reflux; (ii) HBr aq., reflux; (iii) $Bu^tOK$, RR'P(O)Cl, reflux, (iv) $Bu^tOK$, $CO_2$ or $CS_2$.

functions for all atoms: 6-31G** – carbon, nitrogen, oxygen, chlorine and hydrogen and 6-311G** for phosphorus. Natural bond orbital analyses were also made for all compounds using the NBO 5.0 package included in Gaussian 09 [23].

*Crystal structure determination and refinement*

The crystals of the quinoline derivatives were mounted in turn on an Xcalibur, Oxford Diffraction automatic diffractometer equipped with a CCD detector for data collection. X-ray intensity data were collected with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$) Å at temperature of 100(1) K (**3a**, **3b**, **3c**, **6d**) and 295.0(2) K (**5c**), with $\omega$ scan mode. Ewald sphere reflections were collected up to $2\theta = 50.10$. Details of crystal data and refinement are gathered in Table S1 (Supplementary data) and selected bond lengths and angles for compounds in Table S2 (Supplementary data). During the data reduction, the decay of the correction coefficient was taken into account. Lorentz, polarization and empirical absorption correction using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm were applied [24]. The structures were solved by direct method. All the non-hydrogen atoms were refined anisotropically using full-matrix, least-squares technique on $F^2$. All the hydrogen atoms were found from the difference of the Fourier synthesis after four cycles of anisotropic refinement, and refined as "riding" on the adjacent atom with individual isotropic temperature factor equal to 1.2 times the value of equivalent temperature factor of the parent atom, with geometry idealization after each cycle. The Olex2 and SHELXS97, SHELXL97 programs were used for all the calculations [25,26]. Atomic scattering factors were those incorporated in the computer programs.

*X-ray and DFT studies*

The studied quinoline derivatives **3a**, **3b**, **3d** and **5c** crystallize in monoclinic $P2_1/c$ and $C2/c$ while **6b** in triclinic $P-1$ space groups and theirs molecular structures are displayed as *ORTEP* representations in Fig. 1. As one can see from the Fig. 1 that the compound **3a** has two independent molecules in the asymmetric unit. These two molecules are twisted, which prevents the existence of higher crystallographic symmetry.

The structures of the compounds are stabilized by hydrogen bonds described in Table S3 (Supplementary data), which form different type of dimers from simply $D_1^1(2)$, intramolecular $S_1^1(6)$ to cyclic intermolecular $R_2^2(10), R_4^4, R_4^4(18)$. Moreover structures of these compounds are stabilized by π-stacking interactions (see Table S4, Supplementary data); interactions between quinoline rings create ordered stocks as one can see in Fig. 2.

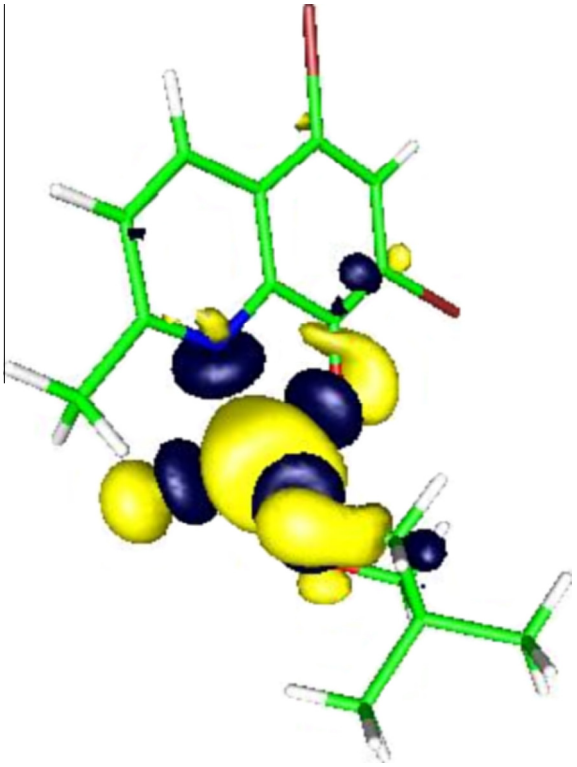
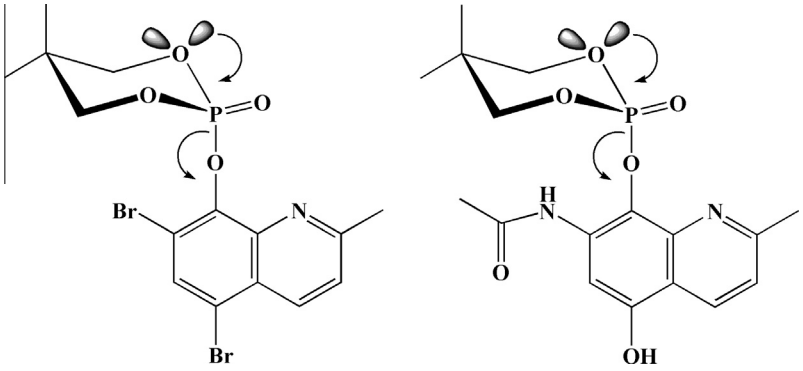


**Fig. 4.** The stabilizing hyperconjugation interaction of non-bonding *p* oxygen orbitals *via* phosphorus with 5,7-dibromo-2-methylquinolin-8-ol antybonding π*-accepting orbitals.




**Scheme 2.** The hyperconjugation in **5c** (left) and *N*-{8-[(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)oxy]-5-hydroxy-2-methylquinolin-7-yl}acetamide (right) [31].

*DFT*

The geometry of the compounds **3a**, **3b**, **3d**, **5c** and **6b** were optimized in singlet states using the DFT method with the B3LYP functional. The atomic charge calculations can give a feature for the relocation of the electron density of the compounds, but the local concentration and local depletion of electron charge density allow us to determine whether the nucleophile or electrophile can be attracted.

Fig. 3 presents the plots of the electrostatic potential for the compounds. The isoelectronic contour is plotted at 0.05 a.u. (3.1 kcal/mol). The color code of the map is in the range of 0.05 a.u. (deepest red) to −0.05 a.u. (deepest blue), where blue indicates the strongest attraction and red indicates the strongest repulsion. Regions of negative V(r) are usually associated with the lone pair of electronegative atoms. The negative potentials are localized on the oxygen (−0.7) and nitrogen (−0.5) atoms. Chloro and bromo substituents have charges close to zero (similarly to our previous results), but there are some visible differences depend on position in quinoline ring [27]. Therefore, chloro substituent in position 5 is more charged (−0.063) than in position 6 (−0.054), similarly bromo in position 5 has slightly higher charges density than in position 7.

## Results and discussion

In our previous studies the synthesis and characterization of some hydroxyquinolines and their derivatives have been reported [20,27,28]. X-ray crystal structure analysis showed the presence of hydrogen-bond donating and accepting sites between the pyridine and hydroxyl functional groups. The solution and solid state NMR studies demonstrated that there is a tautomeric equilibrium in the neutral, cationic and anionic species of hydroxyquinoline carboxylic acids obtained by protonation or deprotonation, which was evaluated by $^{13}C$ and $^{15}N$ chemical shifts [28]. To the best of our knowledge about literature data, there are few examples of the X-ray crystal structures of hydroxyquinoline carboxylic acids or halogenohydroxyquinolines including our attempts [20,27]. Therefore, further experiments were carried out in order to obtain a deeper understanding of the chemical properties of selected hydroxyquinolines and their analogues or derivatives contained methoxy, fluoro, chloro, carboxylic, carbodithioic and phosphinate or dioxaphosphinane groups (Scheme 1).

In this paper we present the syntheses of two 7-halogeno-8-methoxy-2-methylquinolines **2a** and **2b**, four 2-methylquinolin-8-ols **3a**, **3b**, **3c** and **3d**, and **4** together with their X-ray structures (Fig. 1). Our protocol was based on Skraup–Doebner–Miller quinoline synthesis with Matsugi modification [20,29]. One of the serious drawbacks of the Skraup–Doebner–Miller transformation is the difficulties of isolating complex reaction mixtures, mostly due to the formation of the target product accompanied by regioisomers. Results from our previous studies and literature data showed that the reaction of various anilines with crotonaldehyde usually favored the quinoline products with the phosphorus, fluoro or carboxylic group in 5 position [20,27,28,30]. By applying our protocol, the previous and present results showed that the syntheses are fast, general and simple in use, afforded the product in up to 24% for **2**, 43% or 98% for **3** and 46% yield for **4** after 4.5 h (Scheme 1), respectively. Comparing with other methods like Friedländer reaction, our starting reagents are commercially available and cheap.

Our following work was also presented regarding the synthesis of some hydroxyquinoline carboxylic acids **6a** and **6b**, and hydroxyquinoline carbodithioic acids **6c** and **6d**, which possess hydroxyl and carboxylic (carbodithioic) function in vicinal position, by direct carboxylation of certain phenols by $CO_2$ ($CS_2$), respectively [20]. In order to obtain more understanding about the synthetic abilities of hydroxyquinoline carboxylic acids (carbodithioic acids), a study of hydroxyquinolines (Figs. 1 and 3) have been undertaken, including both the experimental (from single crystal X-ray diffraction) and computational analysis of the distribution of electron densities and electrostatic potentials. Considering our previous results and the present work, the relation between electron density inside the quinolines and the yield of products was investigated [20,27]. Higher yields were observed for **6b** 68% and **6d** 64% (Scheme 1), where starting reagent **3d** possessed higher electron density. Low yields were obtained for the syntheses of **6a** 9% and **6c** 23%, where applying starting material **3b** was electron poorer. The syntheses of 6-chloro-8-hydroxy-2-methylquinoline-7-carboxylic acid and 6-chloro-8-hydroxy-2-methylquinoline-7-carbodithioic acid from **3b** were unsuccessful, possibly due to the negative potential value, −0.314 on the C6 carbon atom in **3b** (Fig. 2).

The presented phosphorus esters of halogeno-2-methylquinolines **5a**, **5b** and **5c** could have potential influence not only on their chemical reactivity but on biological activity as well.

The X-ray structure of **5c** was compared with that obtained for *N*-{8-[(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)oxy]-5-hydroxy-2-methylquinolin-7-yl}acetamide [31].

Both compounds and **5b** attracted our attention due to observed chair conformers. The conformation studies on saturated 1,3,2-dioxaphosphinane rings were first started by Bentrude and Hargis [32]. The assignments of conformation were based on NMR, X-ray and literature analysis [33]. According to the Karplus equation and taking into consideration of the coupling constant, the order of chemical shifts for $CH_2$ protons, $\delta$ $H_a > \delta$ $H_e$ was determined.

The presence of the anomeric effect for **5b**, **5c** or *N*-{8-[(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)oxy]-5-hydroxy-2-methylquinolin-7-yl}acetamide, compounds with

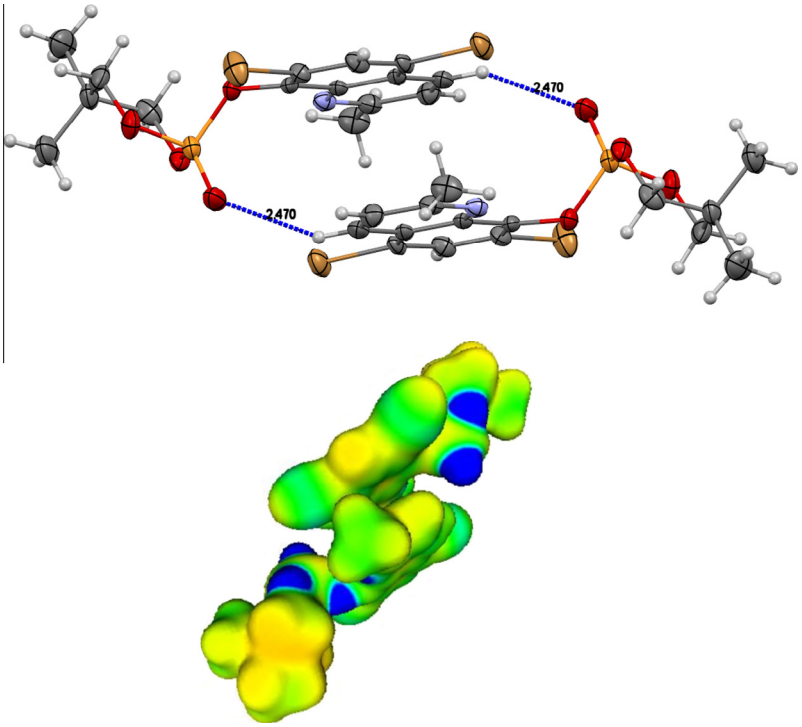



**Fig. 5.** Short contact interaction and electrostatic potential surface in the molecular structure of **5c** dimer.

1,3,2-dioxaphosphinane rings was evidenced by the results that the preferential axial position of substituents was the one adjacent to oxygen [31]. In literature there were several proposed explanations for the validity of the anomeric effect. One of the explanation could be a stabilizing hyperconjugation contribution between the unshared electron pair on the oxygen atom in a 1,3,2-dioxaphosphinane ring and the $\sigma^*$ orbital for the P—O bond in the axial position (Fig. 4).

The anomeric effect is presented in Scheme 2 where the nonbonding p oxygen orbitals interact with phosphorus and the charge is transferred through oxygen atom to quinoline part, which possesses empty $\pi$-accepting orbitals. Nevertheless in the molecular structure of **5c** $\pi$-stacking interactions are associated with intermolecular short contact interaction between P═O and quinoline ring, presented in Fig. 5, which has impact on the geometry of the molecule. In the formed dimer, the anomeric effect may be enhanced by electrostatic interactions between quinolone rings. Moreover reciprocal interaction of quinoline rings in the dimer exerts influence on the charge relocation.

The geometrical data collected in Table S2 (Supplementary data) for ester **5c** show that the compound crystallized as anomer with oxygen atom in the equatorial position. This is in accordance with the observation of an increased tendency that adopt an axial position with the electron-withdrawing character of an anomeric substituent, **5c** here the P(1)—O(1) bond. More electronegative groups tend to preferentially take the axial position in the chair conformations of six-membered rings, and the trend increases if the anomeric substituent has electron-withdrawing character, due to lowering the energy of the exocyclic $s^*$(P—X) orbital.

*NMR studies*

The $^1$H NMR solution spectra of hydroxyquinolines and their derivatives or analogues showed distinctive H-1 signals from aromatic protons and $CH_3$ group (Table S5, Supplementary data). The analysis of the trend in $^1$H chemical shifts revealed that the deprotonation of molecules (solvents: KOD/$D_2O$/DMSO-$d_6$) significantly increased the shielding effect (upfield effect, smaller $\delta$) resulting in the decreased chemical shifts of selected H-1 signals in comparison with in neutral solvent, such as DMSO-*d*6. The protonation of molecules using solvents: $D_2SO_4$/$D_2O$/DMSO-$d_6$ showed opposite effect, the chemical shifts were moved to downfield (larger $\delta$), this trend is elegantly showed particularly for protons from pyridine ring of **6a** and **6b**. This is a consequence of simple protonation or deprotonation of pyridine rings in quinoline constitution. This corresponds well with the electrostatic potential surfaces (ESP) (Fig. 3). The largest difference in C-13 NMR spectroscopy is visible by comparing carboxylic group for molecules **6a**, **6b** and dithiocarboxylic group for **6c**, similarly to previous results [20]. The chemical shifts were moved significantly to downfield (larger $\delta$) for **6c**. The deshielding effect (downfield shift) is quite visible for dithiocarboxylic group for **6c**, which can be explained in the frame of electron density. Sulfur is less electronegative than oxygen and makes the carbon atom less positive than that of oxygen. Thus, the carbon atom is more deshielded from the applied magnetic field, $B_o$. $^{13}$C NMR spectra for compound **6d** were not obtained due to their poor solubility. In the case of **2b** both aromatic protons coincidentally have practically the same chemical shift, and very low coupling constants.

## Conclusions

The presented research has been focused on the synthesis of crystalline hydroxyquinolines and their analogues or derivatives containing methoxy, fluoro, chloro, carboxylic, carbodithioic and phosphinate or dioxaphosphinane groups. The compounds were further characterized by analytical methods and rationalized on the basis of DFT calculation method with B3LYP functional. After comparing to the literature methods, our simpler protocols provides high yield of products. The experimental (from single crystal X-ray diffraction) and computational analysis of the distribution of

electron densities and electrostatic potentials revealed the relationship between the structure factor and the synthesis yields. The proton transfer reactions between the pyridine and carboxylic acid functional groups or generally simple protonation or deprotonation of pyridine rings in quinoline constitution could be used as a pH indicator. The largest effect should be visible in the $^{15}N$ NMR spectra which allow distinguishing between species with protonated and deprotonated pyridine rings. Another example of compound with anomeric effect was reported.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2013.08.031.

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