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Synthesis and transformations of novel formyl-substituted quinolines

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Abstract

In the present contribution we study the reaction of 4-hydroxy- and 4-chloro-2-methylquinolines with Vilsmeier-Haack reagent. The reaction of 2-(4-chloroquinolin-2-yl)-3-hydroxyacrylaldehydes thus obtained with nucleophiles leads to potentially bioactive quinolines that contain pyrazole and piperidine groups.

Keywords: malonic dialdehyde; quinoline; Vilsmeier-Haack reagent; 2-(4-Chloroquinolin-2-yl)-3-hydroxyacrylaldehyde.

Introduction

Derivatives of quinoline are an important class of heterocyclic compounds because these ring systems occur in various natural products particularly in alkaloids (Michael, 2003; Milcent, 2003), which exhibit a wide variety of biological activities (Zhuang et al., 2003; Embrey et al., 2005; Atanasova et al., 2007) including anti-bacterial (Chen et al., 2001), immunosuppressive (Papageorgiou et al., 2001), analgesic (Shinkai et al., 2000), vasorelaxing (Ferline et al., 2002), anti-plasmodial (Kaschula et al., 2002), anti-cancer (Joseph et al., 2002; Kociubinska et al., 2002), PDE_4 inhibitory (Billah et al., 2002) and anti-malarial (Madrid et al., 2005), and are used ubiquitously in medical practice. All these findings prompted us to take up this project for synthesizing novel derivatives of quinoline by introducing known biologically active moieties into their structures hoping to get valuable compounds.

The general interest towards the heterocyclic compounds containing an aldehyde group has increased recently because they are convenient starting materials for the synthesis of pharmacologically active compounds.

Among various formylation reactions, we chose Vilsmeier-Haack reaction because of its ease of inserting the CHO groups in aromatic/heteroaromatic systems. Also, the Vilsmeier-Haack reagent reacts rapidly with various alkens, carbonyl compounds, compounds which containing active methyl and methylene groups and O- and N-containing nucleophiles (Marston, 1992; Su et al., 2010).

Results and discussion

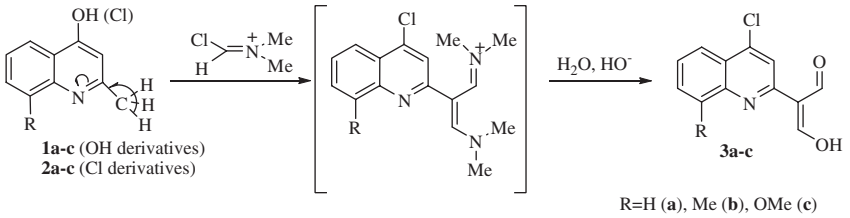
In this work, we studied the reaction between 4-hydroxy and 4-chloro-2-methylquinolines (**1a–c** and **2a–c**, respectively) and Vilsmeier-Haack reagent – a chloroiminium salt, obtained *via* the reaction of di-substituted formamides with chlorinating agent ($POCl_3$, $COCl_2$, SO_2Cl_2).

The imine salt was prepared by mixing DMF (*N,N*-dimethylformamide) with $POCl_3$ at 10–20°C. The imine salt is an electrophilic reagent that undergoes a reaction with electron rich quinolines **1a–c** and **2a–c**. Most probably in both cases the reaction of 2-methyl group with Vilsmeier-Haack reagent leads to the formation of quinolyl substituted malonic dialdehyde, which exists mainly in the enol form, i.e., as β-oxyacrolein (Eagleson, 1994).

In the case of 4-hydroxyquinolines **1a–c** the reaction proceeds at 75–80°C, whereas a higher temperature of 120°C is required for the less nucleophilic 4-chloroquinolines **2a–c**. Related investigations have been carried out by Kumar and co-workers (Kumar et al., 2003), who have observed formylation of both the activated methyl group and the unsubstituted position 3 of the quinoline leading to a mixture of products. In our experiments only formylation of the methyl group took place. The products **3a–c** (Scheme 1) were obtained in high yields and their structure was confirmed by ^1H and ^{13}C NMR data (Tables 1 and 2).

The analysis of the ^1H and ^{13}C NMR spectra taken in $CDCl_3/CCl_4$ (1:1) shows that compounds **3a–c** contains two aldehyde groups that give rise to two distinct signals. In contrast, in the solution of DMSO-d_6/CCl_4 with the ratio of 1:3 the signals merge into one absorption. It is clear that the nature of the solvent cannot be ignored when interpreting these observations. In addition, in the first case a doublet with J~1.4 Hz originating from a proton NH group is observed, whereas in the second case the signal is a slightly broadened singlet. These data indicate that compounds **3a–c** exist in different tautomeric forms (Scheme 2).

Heterocycles of quinoline, pyrazole and pyrimidine are the bases of many natural and synthetic alkaloids. They are part of various drugs and possess different strongly manifested biological activities. Attempting to synthesize such quinoline derivatives with a pyrazole or pyrimidine substituent, we investigated the reaction of quinolines **3a–c** with



Scheme 1 Synthesis of **3a–c**.

phenylhydrazine and guanidine. The first reaction, carried out at room temperature in acetic acid, leads to 4-chloro-2-(1-phenyl-1*H*-pyrazol-4-yl)quinolines **4a–c** in high yields (Scheme 3).

Interestingly, the formation of **4a–c** was not accompanied by the nucleophilic substitution of chlorine atom in **3a–c**. The structure of **4a–c** is fully consistent with the NMR data (Tables 3 and 4).

An interesting result was observed during an attempted synthesis of quinolines **A** containing pyrimidine substituent (Scheme 3). Thus, guanidine hydrochloride was dissolved in DMF and the solution heated in the presence of piperidine to release a free base of guanidine (Strakova et al., 2007). The free base was then treated with **3a–c**. This treatment yielded products **5a–c** resulting from nucleophilic displacement of the chlorine atom in **3a–c** by piperidine. (Scheme 3; Tables 5 and 6). The presence of a strong electron acceptor group at position two of the quinoline is most likely to activate the chlorine substituent at position four toward nucleophilic displacement. The reaction of **5a–c** with phenylhydrazine at room temperature in acetic acid yielded 2-(1-phenyl-1-*H*-pyrazol-4-yl)-4-piperidinoquinolines **6a–c** (Scheme 3). In contrast, compounds **6a–c** could not be obtained by treatment of **4a–c** with piperidine under a variety of conditions. This result is consistent with less activation of the chlorine atom by a pyrazole moiety in **4a–c** toward nucleophilic displacement than the activation of the chlorine atom in substrates **3a–c**.

Table 1 ^{1}H NMR spectra (δ) of **3a–c**[a].

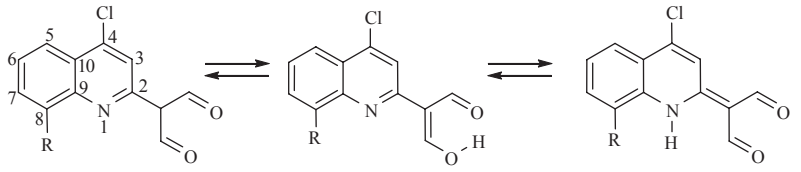
	H-3	H-5	H-6	H-7	R	NH/OH
3a[b]	9.12 s	8.02 dd ^{3}J 8.4 ^{4}J 1.1	7.91 ddd ^{3}J 8.4, 7.1 ^{4}J 1.3	7.68 ddd ^{3}J 8.4, 7.1 ^{4}J 1.1	8.18 dd ^{3}J 8.3 ^{4}J 1.3	16.33 br
3b[c]	9.22 d ^{4}J 1.3	8.08 dd ^{3}J 8.3 ^{4}J 1.3	7.53 dd ^{3}J 8.3, 7.3	7.68 ddq ^{3}J 8.3 ^{4}J 1.3, 1.0	2.79 d ^{4}J 1.0	16.65 br
3c[b]	9.14 s	7.71 dd ^{3}J 8.4 ^{4}J 1.1	7.60 dd ^{3}J 8.4 ^{3}J 8.0	7.46 dd ^{3}J 8.0 ^{4}J 1.1	4.21 s	16.35 br
3c[c]	9.28 d ^{4}J 1.4	7.76 dd ^{3}J 8.4 ^{4}J 1.0	7.53 dd ^{3}J 8.4 ^{3}J 8.0	7.23 dd ^{3}J 8.0 ^{4}J 1.0	4.19 s	16.41 br

[a]The {^{1}H-^{1}H} double resonance, NOESY and HMQC 2D spectra were used for the assignment of hydrogen atoms.
[b]Spectra taken in DMSO-d_6/CCl_4 (1:3).
[c]Spectra taken in $CDCl_3$/CCl_4 (1:1).

Table 2 ^{13}C NMR spectra (δ) of **3a–c**[a].

	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	2-C	CHO
3a[b]	151.5	117.9	135.8	119.6	126.5	133.1	124.2	146.4	122.2	105.2	189.2 br
3b[c]	152.1	119.1	135.8	123.3	126.6	134.0	128.0	148.4	123.7	106.6	189.2 192.3
3c[c]	151.3	119.9	128.0	116.5	126.8	111.4	149.0	147.7	124.2	106.4	189.4 192.2

[a]The {^{1}H-^{1}H} double resonance, NOESY and HMQC 2D spectra were used for the assignment of carbon atoms.
[b]Spectra taken in DMSO-d_6/CCl_4 (1:3); δ_{Me}=17.5 ppm.
[c]Spectra taken in $CDCl_3$/CCl_4 (1:1); δ_{OMe}=55.9 ppm.



Scheme 2 Tautomeric forms of **3a–c**.

Conclusions

The utility of the Vilsmeier-Haack reaction for synthesizing novel potential biologically active quinolines containing pyrazole and piperidine substituents has been demonstrated. The suggested reaction path could also be used for constructing other heterocyclic compounds.

Experimental section

General

All solvents were dried by standard methods and reactions carried out under an inert atmosphere. Each m.p. was determined on an SMP-10 melting point apparatus. IR spectra were measured by Nicolet FTIR NEXUS spectrophotometers in Nujol. ALUGRAM Xtra SIL G/UV-254 plates were used for TLC, iodine vapors were used for visualization. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300Vx spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C) with TMS as an internal standard. Substrates **1a–c** (Reynolds et al., 1955) and **2a–c** (Avetisyan et al., 2007) were prepared by known methods.

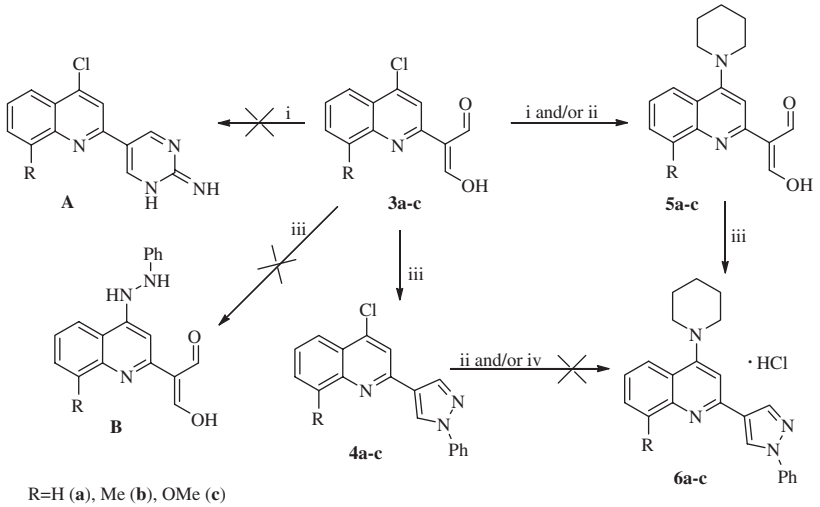
General procedure for 3a–c

Method A To 17 ml (0.22 mol) of DMF at a temperature of 10–20°C, 11.4 ml (0.125 mol) of phosphorus oxychloride was added dropwise. With vigorous stirring, 0.025 mol of **1a–c** in 50 ml of DMF was added dropwise. The mixture was stirred for 1 h in a boiling water bath, then cooled and poured onto 400 g of crushed ice, put aside overnight and treated with aqueous NaOH to pH 6–6.5. The resultant precipitate was filtered, dried and crystallized from acetic acid/water (1:7) mixture.

Method B To 9.7 ml (0.125 mol) of DMF at a temperature of 10–20°C, 9.1 ml (0.1 mol) of phosphorus oxychloride was added dropwise. With vigorous stirring, 0.025 mol of **2a–c** in 30 ml of DMF was added dropwise and the mixture was stirred at 120–125°C for 1 h. Further processing was carried out as described in Method A.

2-(4-Chloroquinolin-2-yl)-3-hydroxyacrylaldehyde (3a) This compound was obtained as a yellow solid; yield 4.55 g (78%) (Method A) and 4.8 g (82%) (Method B); m.p. 195–197°C; IR: (3260, 3210, 2723, 1723, 1650, 1612, 1592, 1590 cm^{-1}; ^{1}H and ^{13}C NMR data are given (Tables 1 and 2). Analysis: calculated for $C_{12}H_8ClNO_2$: C, 61.69; H, 3.45; Cl, 15.17; N, 5.99. Found: C, 61.56; H, 3.56; Cl, 15.05; N, 6.14.

2-(4-Chloro-8-methylquinolin-2-yl)-3-hydroxyacrylaldehyde (3b) This compound was obtained as a yellow solid; yield 5.2 g (84%) (Method A) and 5.51 g (89%) (Method B); m.p. 223–225°C; IR: (3255, 3207, 2730, 1731, 1650, 1615, 1593, 1591 cm^{-1}; ^{1}H and ^{13}C NMR data are given (Tables 1 and 2). Analysis: calculated for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; Cl, 14.31; N, 5.66. Found C, 62.91; H, 4.21; Cl, 14.10; N, 5.73.



R=H (**a**), Me (**b**), OMe (**c**)

i, guanidine hydrochloride, piperidine, EtOH and/or DMF; ii, piperidine, EtOH;
iii, 1. $PhNHNH_2$, AcOH, 2. HCl; iv, piperidine, EtOH, HCl.

Scheme 3 Some transformations of **3a–c**.

Table 3 ^{1}H NMR spectra (δ) of **4a–c** in DMSO/CCl_4 (1:3)[a].

	H-3	H-5	H-6	H-7	R	H-3 Pyr.	H-5 Pyr.
4a[b]	8.11 s	8.14 dd ^{3}J 8.4 ^{4}J 1.4	7.58 ddd ^{3}J 8.4, 6.9 ^{4}J 1.1	7.75 ddd ^{3}J 8.4, 6.9 ^{4}J 1.4	8.02 dd ^{3}J 8.4 ^{4}J 1.1	8.36 s	9.17 s
4b[b]	8.07 s	7.99 dd ^{3}J 8.3 ^{4}J 1.2	7.44 dd ^{3}J 8.3, 7.0	7.58 dd ^{3}J 7.0 ^{4}J 1.2	2.85 s	8.35 s	9.12 s
4c[b]	8.09 s	7.69 dd ^{3}J 8.4 ^{4}J 1.1	7.47 dd ^{3}J 8.4, 7.8	7.15 dd ^{3}J 7.8 ^{4}J 1.1	4.08 s	8.35 s	9.12 s

[a]NOESY and HMQC 2D spectra were used for the assignment of hydrogen atoms.
[b]Phenyl protons: δ 7.30 (m, H_{para}), 7.49 (m, H_{meta}), 7.92 (m, H_{orto}).

2-(4-Chloro-8-methoxyquinolin-2-yl)-3-hydroxyacrylaldehyde (3c) This compound was obtained as a yellow solid; yield 5.33 g (81%) (Method A) and 5.73 g (87%) (Method B); m.p. 265–267°C; IR: (3258, 3213, 2725, 1727, 1652, 1617, 1591, 1587 cm^{-1}; ^{1}H and ^{13}C NMR data are given (Tables 1 and 2). Analysis: calculated for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; Cl, 13.45; N, 5.31. Found C, 59.34; H, 3.70;Cl, 13.31; N 5.48.

General procedure for 4a–c

A mixture of 0.01 mol of **3a–c** and 0.012 mol of phenylhydrazine in 10 ml of acetic acid was stirred at room temperature for 24 h. The resultant precipitate was filtered and crystallized from ethanol.

4-Chloro-2-(1-phenyl-1*H*-pyrazol-4-yl)quinoline (4a) This compound was obtained as a milk-white solid, yield 2.78 g (87%), m.p. 138–140°C; IR: (3027, 1701, 1691, 1678, 1637, 1613, 1594, 1568, 1558 cm^{-1}; ^{1}H and ^{13}C NMR data are given (Tables 3 and 4). Analysis: calculated for $C_{18}H_{12}ClN_3$: C, 70.71; H, 3.96; Cl, 11.60; N, 13.74. Found C, 70.48; H, 3.63; Cl, 11.87;N 13.55.

4-Chloro-8-methyl-2-(1-phenyl-1*H*-pyrazol-4-yl)quinoline (4b) This compound was obtained as a milk-white solid; yield 2.84 g (89%); m.p. 162–164°C, IR: (3031, 1709, 1700, 1650, 1605, 1593, 1578, 1569 cm^{-1}; ^{1}H and ^{13}C NMR data are given (Tables 3 and 4). Analayisis: calculated for $C_{19}H_{14}ClN_3$ C, 71.36, H, 4.41, Cl, 11.09, N 13.14. Found C, 71.22, H, 4.53, Cl, 11.24, N, 13.27.

Table 4 ^{13}C NMR spectra (δ) of **4a–c** in DMSO/CCl_4 (1:3)[a–c].

	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
4a	151.1	118.7	139.3	123.2	126.0	129.8	128.8	148.5	124.0
4b	150.8	118.3	136.6	121.1	125.7	129.9	149.7	147.3	124.4
4c	149.4	119.0	139.3	114.8	126.2	109.1	155.0	140.5	125.3

[a]NOESY and HMQC 2D spectra were used for the assignment of carbon atoms.
[b]Phenyl carbon atoms: 118.2 (C_{orto}), 125.8 (C_{para}), 128.7 (C_{meta}), 141.4 (C_{ipso}).
[c]Pyrazol carbon atoms: 124.3 (C-4), 126.5 (C-5), 139.4 (C-3).

Table 5 ^{1}H NMR spectra (δ) of **5a–c** in DMSO/CCl_4 (1:3)[a].

	H-3	H-5	H-6	H-7	R	CHO	NH
5a[b]	8.39 br	7.87 dd ^{3}J 8.3 ^{4}J 1.2	7.70 ddd ^{3}J 8.3, 6.8 ^{4}J 1.2	7.45 ddd ^{3}J 8.3, 6.8 ^{4}J 1.2	7.77 dd ^{3}J 8.3 ^{4}J 1.2	9.24 s 9.24 s	15.52 br
5b[b]	8.40 d ^{4}J 1.0	7.74 dd ^{3}J 8.3 ^{4}J 1.3	7.35 dd ^{3}J 8.3, 7.3	7.57 ddq ^{3}J 7.3 ^{4}J 1.3, 1.0	2.69 d ^{4}J 1.3	9.27 s 9.27 s	15.70 br
5c[b]	8.42 br	7.41 dd ^{3}J 8.4 ^{4}J 1.2	7.36 dd ^{3}J 8.4, 7.5	7.22 dd ^{3}J 7.5 ^{4}J 1.5	4.15 s	9.25 s 9.25 s	15.46 br

[a]NOESY and HMQC 2D spectra were used for assignment hydrogen and carbon atoms.
[b]Piperidine protons: δ 1.79 (2H, m, γ-CH_2), 1.85-1.95 (4H, m, β-CH_2), 3.42 (4H, m, α-CH_2).

Table 6 ^{13}C NMR spectra (δ) of **5a–c** in DMSO/CCl_4 (1:3)[a].

	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	2-C	CHO
5a[b]	152.0	102.7	160.2	124.3	124.0	131.1	119.5	136.7	118.9	105.2	189.2 189.2
5b[b]	151.5	102.6	160.7	122.1	123.5	131.6	126.9	135.9	119.0	105.6	189.2 189.2
5c[b]	150.8	103.1	128.2	115.5	123.8	109.7	160.0	148.5	119.6	105.4	189.1 189.1

[a]NOESY and HMQC 2D spectra were used for the assignment of carbon atoms.
[b]Other carbon atoms: δ 23.6 (γ-CH_2 of the piperidine, δ 25.2 (β-CH_2 of the piperidine), δ 52.5 (α-CH_2 of the piperidine), δ 16.8 (CH_3), δ 56.0 (OCH_3).

4-Chloro-8-methoxy-2-(1-phenyl-1*H*-pyrazol-4-yl)quinoline (4c) This compound was obtained as a milk-white solid; yield 3.15 g (94%); m.p. 227–228°C; IR: (3030, 1710, 1699, 1675, 1640, 1610, 1590, 1570, 1560 cm^{-1}; ^1H and ^{13}C NMR data are given (Tables 3 and 4). Analysis: calculated for $C_{19}H_{14}ClN_3O$: C, 67.96;H, 4.20; Cl, 10.56; N, 12.51. Found C, 67.77; H, 4.45; Cl, 10.23; N 4.48.

General procedure for 5a–c

A mixture of 0.01 mol of **3a–c** and 1.02 g (1.2 ml, 0.012 mol) of piperidine in 30 ml of ethanol was heated in a boiling water bath for 2–3 h. Then the alcohol was removed and the residue was treated with water. This mixture was stirred and the resultant solid was filtered and washed with ether.

3-Hydroxy-2-(4-piperidinoquinolin-2-yl)acrylaldehyde (5a) This compound was obtained as a pale yellow solid; yield 2.43 g (86%); m.p. 200–202°C, IR: (3118, 3023, 2754, 2720, 1733, 1645, 1602, 1590, 1583 cm^{-1}; ^1H and ^{13}C NMR data are given (Tables 5 and 6). Analysis: calculated for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found C, 72.47; H, 6.28; N, 10.07.

3-Hydroxy-2-(8-methyl-4-piperidinoquinolin-2-yl)acrylaldehyde (5b) This compound was obtained as a pale yellow solid; yield 2.49 g (84%); m.p. 168–170°C, IR: (3122, 3028, 2751, 2722, 1730, 1648, 1610, 1595, 1578 cm^{-1}; ^1H and ^{13}C NMR data are given (Tables 5 and 6). Analysis: calculated for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found C, 73.11; H, 6.68; N, 9.61.

3-Hydroxy-2-(8-methoxy-4-piperidinoquinolin-2-yl)acrylaldehyde (5c) This compound was obtained as a pale yellow solid; yield 3.0 g (96%); m.p. 213-215°C; IR: (3111, 3030, 2747, 2716, 1723, 1642, 1612, 1592, 1581 cm^{-1}; ^1H and ^{13}C NMR data are given (Tables 5 and 6). Analysis: calculated for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found C, 69.34; H, 6.33; N, 8.83.

General procedure for 6a–c

A mixture of 0.01 mol of **5a–c** and 0.012 mol of phenylhydrazine in 10 ml of acetic acid was stirred at room temperature for 24 h. The mixture was poured onto crushed ice and acidified with hydrochloric acid to pH 1. The precipitate was filtered and crystallized from ethanol.

2-(1-Phenyl-1*H*-pyrazol-4-yl)-4-piperidinoquinoline hydrochloride (6a) This compound was obtained as a light brown solid; yield 3.6 g (92%); m.p. 148–150°C; IR: (3365, 3078, 3040, 1710, 1615, 1593, 1548 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/CCl_4, 1:3): δ_H 1.80–1.96 (m, 6H, β,γ-CH_2), 3.75 (m, 4H, α-CH_2), 7.34 (tt, 1H, ^3J 7.4, ^4J 1.1, H-4 Ph), 7.48 (s, 1H, H-3), 7.53 (m, 2H, H-3,5 Ph), 7.53 (m, 1H, C_6H_4), 7.82 (ddd, 1H, ^3J 8.6, 7.1, ^4J 1.1, C_6H_4), 7.93 (m, 2H, H-2,6 Ph), 7.93 (m, 1H, C_6H_4), 8.87 (s, 1H, H-3 Pyr.), 8.92 (d, 1H, ^3J 8.5, C_6H_4), 10.46 (s, 1H, H-5 Pyr.), 15.57 (br., 1H, HCl). Analysis: calculated for $C_{23}H_{23}ClN_4$: C, 70.67; H, 5.93; Cl, 9.07; N, 14.33. Found C, 70.89; H, 6.14; Cl, 9.21; N, 14.62.

8-Methyl-2-(1-phenyl-1*H*-pyrazol-4-yl)-4-piperidinoquinoline hydrochloride (6b) This compound was obtained as a light brown solid; yield 3.84 g (95%); m.p. 195–196°C, IR: (3361, 3071, 3048, 1712, 1610, 1591, 1553 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/CCl_4, 1:3): δ_H 1.77–1.95 (m, 6H, β,γ-CH_2), 2.99 (s, 3H, CH_3), 3.69 (m, 4H, α-CH_2), 7.29 (tt, 1H, ^3J 7.4, ^4J 1.1, H-4 Ph), 7.38 (dd, 1H, ^3J 8.4, 7.0, C_6H_3), 7.47 (m, 2H, H-3,5 Ph), 7.55 (s, 1H, H-3), 7.58 (d, 1H, ^3J 7.0, C_6H_3), 7.74 (d, 1H, ^3J 8.4, C_6H_3), 7.99 (m, 2H, H-2,6 Ph), 8.62 (s, 1H, H-3 Pyr.), 10.15 (br., 1H, H-5 Pyr.), 12.50 (br., 1H, HCl). Analysis: calculated for $C_{24}H_{25}ClN_4$: C, 71.19; H, 6.22; Cl, 8.76; N, 13.84. Found C, 70.96; H, 6.51; Cl, 8.98; N, 14.12.

8-Methoxy-2-(1-phenyl-1*H*-pyrazol-4-yl)-4-piperidinoquinoline hydrochloride (6c) This compound was obtained as a light brown solid; yield 4.04 g (96%); m.p. 220–221°C, IR: (3359, 3064, 3046, 1702, 1615, 1588, 1550 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/CCl_4, 1/3): δ_H 1.80–1.96 (m, 6H, β,γ-CH_2), 3.81 (m, 4H, α-CH_2), 4.15 (s, 3H, OCH_3), 7.31 (tt, 1H, ^3J 7.4, ^4J 1.1, H-4 Ph), 7.34 (m, 1H, C_6H_3), 7.46–7.53 (m, 2H, H-3,5 Ph), 7.46–7.53 (m, 2H, C_6H_3), 7.68 (s, 1H, H-3), 8.06 (m, 2H, H-2,6 Ph), 8.67 (s, 1H, H-3 Pyr.), 10.41 (s, 1H, H-5 Pyr.), 12.50 (br., 1H, HCl). Analysis: calculated for $C_{24}H_{25}N_4Cl$: C, 68.48; H, 5.99; Cl, 8.42; N, 13.31. Found C, 68.61; H, 5.81; Cl, 8.64; N, 13.15.

Acknowledgements

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