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[C005]

NEW QUINOLINE DERIVATIVES POSSESSING HERBICIDAL ACTIVITY

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Abstract: The series of quinoline derivatives were prepared. The synthetic procedures of compounds are presented. All the prepared derivatives were analyzed using the reversed phase high performance liquid chromatography (RP-HPLC) method for the lipophilicity measurement. In the present study the correlation between RP-HPLC retention parameter Log *K* (the logarithm of capacity factor *K*) and various calculated Log *P* data is shown. The prepared compounds were tested for their photosynthesis-inhibiting activity (the inhibition of photosynthetic electron transport in spinach chloroplasts (*Spinacia oleracea* L.) and the reduction of chlorophyll content in *Chlorella vulgaris* Beij.). Structure-activity relationships between the chemical structure and the biological activities of the evaluated compounds are discussed.

Keywords: Quinoline derivatives; Styrylquinoline analogues; Photosynthesis inhibition; Lipophilicity; Structure-activity relationships; *Chlorella vulgaris*; Spinach chloroplasts.

1. INTRODUCTION

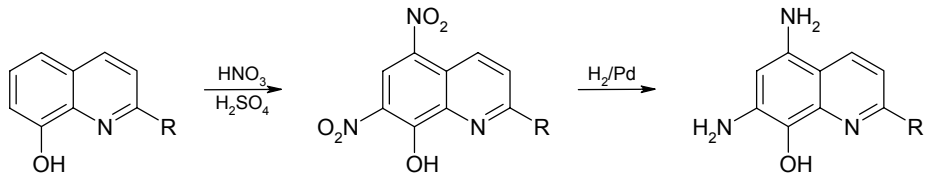
The compounds possessing the quinoline pharmacophore in the molecule have been clinically used as antifungal, antibacterial and antiprotozoic drugs as well as antineoplastics [1]. Styrylquinolines showed strong activity as HIV integrase inhibitors [2-4] as well. Also recently published results described that some new 8-hydroxyquinoline derivatives possessed interesting antifungal and herbicidal activities [5-7]. New efficient synthesis methods of 8-hydroxyquinoline and styrylquinoline derivatives were developed [8-10] and the compounds prepared by means of these new pathways were evaluated as potential herbicides. Structure-activity relationships (SAR) are discussed in this work.

2. RESULTS AND DISCUSSION

2.1 Chemistry

Compounds **1-4** were obtained from 8-hydroxyquinoline or 8-hydroxyquinaldine as shown in Scheme 1.

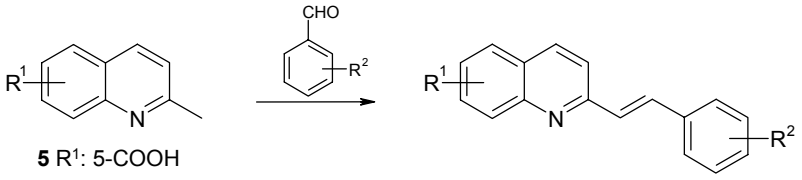
Scheme 1: Synthesis of quinoline derivatives **1-4**.



1 R: -H
2 R: -CH_3
3 R: -H
4 R: -CH_3

Microwave assisted organic synthesis was used to obtain the group of styrylquinoline-like compounds, see Scheme 2. The appropriate quinaldine (1.0 equiv.) was mixed with aldehyde (4.0 equiv.) and irradiated in microwave oven for 6 min at different power level [9].

Scheme 2: Preparation of styrylquinoline derivatives **5-13**.

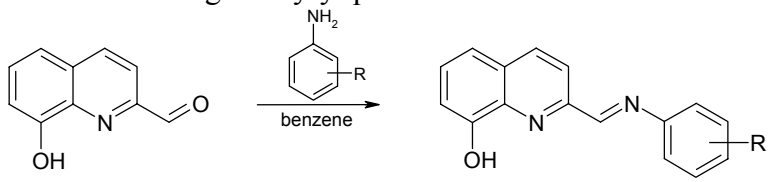


5 R^1: 5-COOH

6 R^1: 5-COOH, R^2: 4-Cl
7 R^1: 6-COOH, R^2: 2-Cl
8 R^1: 7-COOH, R^2: 3-Cl
9 R^1: 8-COOH, R^2: 2-OMe
10 R^1: 5,8-COOH, R^2: 3-Br
11 R^1: 8-OH, R^2: 3-Cl
12 R^1: 8-OH, R^2: 4-Cl
13 R^1: 8-OH, R^2: 4-Br

Azaanalogues of styrylquinolines were obtained from quinoline-2-carbaldehyde and the appropriate amine. This reaction should be performed in dry benzene to generate the required product, see Scheme 3.

Scheme 3: Synthesis of azaanalogues styrylquinoline derivatives **14-16**.



14 R: 2-OH
15 R: 3-OH
16 R: 4-OH

2.2 Lipophilicity

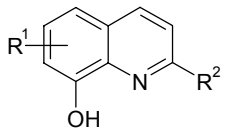
Hydrophobicities (Log *P*/CLog *P* data) of the studied compounds were calculated using two commercially available programs and measured by means of RP-HPLC determination of capacity factors *K* with a subsequent calculation of Log *K*. The results are shown in Tables 1-3. It can be assumed, the results show that the experimentally determined Log *K* values relatively correlate with calculated Log *P*/CLog *P* data within individual series of compounds. Capacity factor *K*/calculated Log *K* values specify lipophilicity within individual series of compounds.

2.3 Herbicidal activities

Sixteen prepared compounds were handed over for biological assays. Some compounds could not be tested for both herbicidal activities due to low solubility in the testing medium or their interaction with the applied artificial electron acceptor 2,6-dichlorophenol-indophenol (DCPIP), which caused discolouration of this reagent.

The studied compounds can be divided into three groups according to their structure, see Tables 1-3. The activities of these compounds are shown in Tables 1-3.

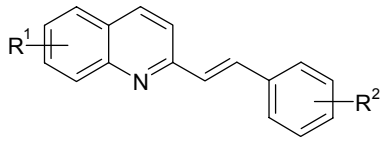
Table 1: Comparison of calculated lipophilicities (Log *P*/CLog *P*) and determined Log *K* of compounds **1**-**4**. *In vitro* photosynthesis inhibition (IC_{50}) of the selected compounds in comparison with standard (DCMU). IC_{50} values are related to PET inhibition in spinach chloroplasts and reduction of chlorophyll content in *C. vulgaris*.

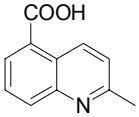


Comp.	R^1	R^2	Log *P*/CLog*P* ChemOffice	Log *P* ACD/Log *P*	Log *K*	IC_{50} [µmol/l]	
						spinach chloroplasts	*Chlorella vulgaris*
1	5,7-NO_2	-H	1.80 / 1.91868	2.18 ± 0.34	0.7154	82	*a*
2	5,7-NO_2	-CH_3	2.50 / 2.41769	2.64 ± 0.35	0.7292	26	95
3	5,7-NH_2	-H	0.12 / 1.3435	-0.84 ± 0.34	0.0522	185	114
4	5,7-NH_2	-CH_3	0.83 / 1.8425	-0.38 ± 0.35	0.2707	142	*a*
DCMU	-	-	2.76 / 2.691	2.78 ± 0.38	-	1.9	7.3

[a] not tested due to low solubility in the testing medium or interaction with DCPIP – discolouration.

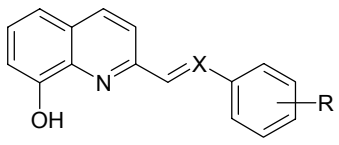
Table 2: Comparison of calculated lipophilicities (Log *P*/CLog *P*) and determined Log *K* of compounds **5-10**. *In vitro* photosynthesis inhibition (IC_{50}) of the selected compounds in comparison with standard (DCMU). IC_{50} values are related to PET inhibition in spinach chloroplasts and reduction of chlorophyll content in *C. vulgaris*.



Comp.	R^1	R^2	Log *P*/CLog*P* ChemOffice	Log *P* ACD/Log *P*	Log *K*	IC_{50} [µmol/l]	
						spinach chloroplasts	*Chlorella vulgaris*
5			2.38 / 2.57925	2.22 ± 0.72	0.3629	146	*a*
6	6-COOH	4-Cl	4.85 / 5.48525	4.97 ± 0.73	1.3976	487	96
7	7-COOH	2-Cl	4.85 / 5.48525	5.02 ± 0.32	1.4787	215	115
8	8-COOH	3-Cl	4.85 / 5.48525	4.97 ± 0.73	1.2858	*A*	*a*
9	5,8-COOH	2-OCH_3	4.16 / 4.69125	3.62 ± 0.35	1.1922	*A*	*a*
10	5-COOH	3-Br	4.67 / 5.65006	4.49 ± 0.80	1.2171	*A*	*a*
DCMU	-	-	2.76 / 2.691	2.78 ± 0.38	-	1.9	7.3

[a] not tested due to low solubility in the testing medium or interaction with DCPIP – discolouration.

Table 3: Comparison of calculated lipophilicities (Log *P*/CLog *P*) and determined Log *K* of compounds **11-16**. *In vitro* photosynthesis inhibition (IC_{50}) of the selected compounds in comparison with standard (DCMU). IC_{50} values are related to PET inhibition in spinach chloroplasts and reduction of chlorophyll content in *C. vulgaris*.



Comp.	R	X	Log *P*/CLog*P* ChemOffice	Log *P* ACD/Log *P*	Log *K*	IC_{50} [µmol/l]	
						spinach chloroplasts	*Chlorella vulgaris*
11	3-Cl	CH	4.90 / 5.4825	5.08 ± 0.32	1.5395	146	33
12	4-Cl	CH	4.90 / 5.4825	5.08 ± 0.32	1.5558	448	*a*
13	4-Br	CH	5.17 / 5.6325	5.26 ± 0.38	1.5802	135	*a*
14	2-OH	N	3.63 / 2.43151	1.09 ± 0.79	0.4308	*a*	11
15	3-OH	N	3.63 / 2.43151	1.51 ± 0.79	0.8860	*a*	168
16	4-OH	N	3.63 / 2.43151	1.32 ± 0.79	1.0911	*a*	17
DCMU	-	-	2.76 / 2.691	2.78 ± 0.38	-	1.9	7.3

[a] not tested due to low solubility in the testing medium or interaction with DCPIP – discolouration.

2.3.1 PET inhibition in spinach chloroplasts

Ten studied compounds inhibited photosynthetic electron transport in spinach chloroplasts, see Tables 1-3. The IC_{50} values ranged from 26 to 487 μmol/l. The inhibitory activity of the studied compounds was relatively low, the most efficient inhibitor was compound **2** (IC_{50}: 26 μmol/l).

Group 1 (Table 1) showed the highest biological activity compound **2**. In general, the inhibitory activity of 5,7-dinitrosubstituted compounds (**1, 2**) was higher than that of comparable 5,7-diaminosubstituted derivatives (**3, 4**) and a lipophilicity increase of the compounds contributed to enhanced of biological activity.

Groups 2 and 3 (Tables 2, 3) showed no or moderate effect on PET inhibition in spinach chloroplasts. Comparison of the PET-inhibiting activities of compounds **6** and **7** as well as **12** and **13** also indicated that a lipophilicity increase is connected with an increase of the biological activity.

The addition of diphenylcarbazide (an artificial electron donor acting in the intermediate Z^+/D^+ on the donor side of photo system II) to spinach chloroplasts inhibited by **2** caused complete restoration of the photosynthetic electron transport [11]. This indicates that the primary donor of PS II (P680) was not damaged by this compound. Previous EPR experiments showed that the site of action of related compounds in the photosynthetic apparatus of spinach chloroplasts was intermediate D^+, i.e. tyrosine radical situated in the 161st position of the protein D_2 located on the donor side of photo system II [5,7,12]. We assume the same site of action also for the studied compounds with nitro groups (**1** and **2**).

2.3.2 Reduction of chlorophyll content in Chlorella vulgaris

Eight studied compounds inhibited chlorophyll production in *C. vulgaris*, see Tables 1-3. The IC_{50} values ranged from 11 to 168 μmol/l. The inhibitory activity of the majority of the studied compounds was relatively low, the most efficient inhibitor was compound **14** (IC_{50}: 11 μmol/l).

Groups 1 and 2 (Tables 1, 2) Four tested compounds (**2, 3, 6** and **7**) showed only moderate effect on chlorophyll content in *C. vulgaris.*

Group 3 (Table 3) showed the highest biological activity, especially compounds **14** and **16**. Substitution of the $C_{(8)}$ position of quinoline and the $C_{(2)}$ or $C_{(4)}$ position of benzene by the phenolic groups (compounds **14**, **16**) was more advantageous from the viewpoint of biological activity than substitution at $C_{(3)}$ position (compound **15**). Substitution of phenyl ring by halogens caused a decrease of the activity. The presence of the nitrogen atom in the olefinic linker influenced the activity positively. Higher activity of compound **14** in comparison to that of compound **16** could be explained by the interaction of the phenolic moiety in $C_{(2)}$ of benzene (compound **14**) with the nitrogen atom in the olefinic linker. Any dependence between lipophilicity and inhibition of chlorophyll production in *C. vulgaris* was found.

3. CONCLUSIONS

Some new interesting routes for design and synthesis of quinoline derivatives possessing herbicidal activity are discussed in this paper. The sixteen compounds were prepared and tested for their photosynthesis-inhibiting activity (the inhibition of photosynthetic electron transport in spinach chloroplasts (*Spinacia oleracea* L.) and the reduction of chlorophyll content in *Chlorella vulgaris* Beij.). Their lipophilicity (Log *K*) was also determined by means of RP-HPLC. 2-Methyl-5,7-dinitroquinolin-8-ol (**2**) was the most efficient PET inhibitor in spinach chloroplasts; IC_{50}: 26 μmol/l. The most intensive reduction of chlorophyll

content in the green algae *C. vulgaris* showed 2-[(2-hydroxyphenolimino)methyl]quinolin-8-ol (**14**); IC_{50}: 11 μmol/l.

4. EXPERIMENTAL

4.1 Lipophilicity HPLC determination (capacity factor K/calculated Log *K*)

The HPLC separation module Waters Alliance 2695 XE and Waters Photodiode Array Detector 2996 (Waters Corp., Milford, MA, U.S.A.) were used. The chromatographic column Symmetry® C_{18} 5 μm, 4.6×250 mm, Part No. WAT054275, (Waters Corp., Milford, MA, U.S.A.) was used. The HPLC separation process was monitored by Millennium32® Chromatography Manager Software, Waters 2004 (Waters Corp., Milford, MA, U.S.A.). The mixture of MeOH p.a. (55.0%) and H_2O-HPLC – Mili-Q Grade (45.0%) was used as a mobile phase. The total flow of the column was 0.9 ml/min, injection 30 μl, column temperature 25 °C and sample temperature 10 °C. The detection wavelength 240 nm was chosen. The KI methanolic solution was used for the dead time (T_D) determination.
The capacity factors *K* were calculated using the Millennium32® Chromatography Manager Software. The Log *K* values of the individual compounds are shown in Tables 1-3.

4.2 Lipophilicity calculations

Log *P*, *i. e.* the logarithm of the partition coefficient for *n*-octanol/water, was calculated using the programs CS ChemOffice Ultra ver. 7.0 (CambridgeSoft, Cambridge, MA, U.S.A.) and ACD/Log *P* ver. 1.0 (Advanced Chemistry Development Inc., Toronto, Canada). CLog *P* values (the logarithm of *n*-octanol/water partition coefficient based on established chemical interactions) were generated by means of CS ChemOffice Ultra ver. 7.0 (CambridgeSoft, Cambridge, MA, U.S.A.) software. The results are shown in Tables 1-3.

4.3 Herbicidal activities

4.3.1 Study of photosynthetic electron transport inhibition in spinach chloroplasts

Chloroplasts were prepared by the procedure of Walker [13] from spinach (*Spinacia oleracea* L.). The inhibition of photosynthetic electron transport (PET) in spinach chloroplasts was determined spectrophotometrically (Kontron Uvikon 800, Kontron, Muenchen, Germany) using an artificial electron acceptor 2,6-dichlorophenol-indophenol (DCIPP) according to Kralova et al. [14] and the rate of photosynthetic electron transport was monitored as a photoreduction of DCPIP. The measurements were carried out in phosphate buffer (0.02 mol/l, pH 7.2) containing sucrose (0.4 mol/l), $MgCl_2$ (0.005 mol/l) and NaCl (0.015 mol/l). The chlorophyll content was 30 mg/l in these experiments and the samples were irradiated (~100 W/m^2) from 10 cm distance with a halogen lamp (250 W) using a 4 cm water filter to prevent warming of the samples (suspension temperature 22 °C). The studied compounds were dissolved in DMSO due to their limited water solubility. The applied DMSO concentration (up to 4%) did not affect the photochemical activity in spinach chloroplasts (PET). The inhibitory efficiency (concentration) of the studied compounds has been expressed by IC_{50} values, i.e. by molar concentration of the compounds causing 50% decrease in the oxygen evolution relative to the untreated control. Comparable IC_{50} value for a selective herbicide 3-(3,4-dichlorophenyl)-1,1-dimethylurea, DCMU (DIURON) was about 1.9 μmol/l. The results are summarized in Tables 1-3.

4.3.2 Study of chlorophyll content reduction in Chlorella vulgaris Beij.

The green algae *C. vulgaris* Beij. was cultivated statically at room temperature according to Kralova et al. [15] (photoperiod 16 h light/8 h dark; photosynthetic active radiation 80

μmol/m^2.s; pH 7.2). The effect of the compounds on algal chlorophyll (Chl) content was determined after 7-day cultivation in the presence of the tested compounds. The Chl content in the algal suspension was determined spectrophotometrically (Kontron Uvikon 800, Kontron, Muenchen, Germany) after extraction into methanol according to Wellburn [16]. The Chl content in the suspensions at the beginning of the cultivation was 0.05 mg/l. Because of the low solubility of the studied compounds in water, these were dissolved in DMSO. DMSO concentration in the algal suspensions did not exceed 0.25% and the control samples contained the same DMSO amount as the suspensions treated with the tested compounds. The antialgal activity of compounds was expressed as IC_{50}. Comparable IC_{50} value for a selective herbicide DCMU was about 7.3 μmol/l. The results are summarized in Tables 1-3.

4.4 Chemistry

All studied compounds had been synthesised as a part of research focused on searching new bioefectors. Comprehensive discussion about laboratory aspects of structure properties will be published elsewhere. Below spectra and elemental analysis of some new compounds involved into this work is listed. NMR data are given relative to internal standard (TMS). When diffused, easily exchangeable protons are not listed.

6. ^{1}H NMR (DMSO-d_6, 500MHz) δ: 7.46 (d, *J*=8.24 Hz, 2H); 7.51(d, *J*=16.3Hz, 1H); 7.75 (d, *J*=8.3Hz, 2H); 7.9 (d, *J*=16.2Hz, 1H); 7.94 (d, *J*=8.6Hz, 1H); 8.2 (d, *J*=8.7Hz, 1H); 8.18 (d, *J*=8.6Hz, 1H); 8.55 (d, *J*=8.5Hz, 1H); 8.6 (s, 1H).

A.E. found: C=68.02%, H=4.52% calcd.: *1/2H_2O C=67.83%, H=4.11%

7. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 6.91 (t, *J*=7.5 Hz, 1H); 7.04 (d, *J*=8.1Hz, 1H); 7.29 (t, *J*=7.8 Hz, 1H); 7.62 (d, *J*=7.8Hz, 1H); 7.94 (d *J*=16.3Hz, 1H); 8.1 (s, 1H); 8.32-8.35 (m, 2H); 8.5 (d, *J*=9.1Hz, 1H); 8.55 (d, *J*=8.4Hz, 1H); 9.61 (d, *J*=9.3Hz, 1H); 10.8 bs; 13.7 bs

A.E. found: C=70.0%, H=5.10% calcd.: *H_2O C=69.89%, H=4.89%

8. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 6.90(t, *J*=8.1Hz, 1H); 6.94 (d, *J*=7.8Hz, 1H); 7.12 (d, *J*=8.8Hz, 1H); 7.17 (t, *J*=7.9Hz, 1H); 7.3-7.42 (m, 2H); 7.52 (*J*=16.1Hz, 1H); 7.68(d, *J*=7.7Hz, 1H); 7.8 (d, *J*=8.6Hz, 1H), 8.12(d, *J*=16.1Hz, 1H); 8.24 (d, *J*=7.7Hz, 1H).

A.E. found: C=65.48%, H=4.62% calcd.: *H_2O C=65.96%, H=4.31%

9. ^{1}H NMR (DMSO-d_6, 300MHz) δ 3.93(s, 3H), 7.04(t, *J*=7.5Hz, 1H), 7.12(d, *J*=8.3Hz, 1H), 7.4(t, *J*=6.9Hz, 1H), 7.54(d, *J*=16.5Hz, 1H), 7.83(d, *J*=7.7Hz, 1H), 8.04(d, *J*=16.5Hz, 1H), 8.12(d, *J*=9.2Hz, 1H), 8.27(d, *J*=7.7Hz, 1H), 8.56(d, *J*=7.7Hz, 1H), 9.37(d, *J*=9.1Hz, 1H).

A.E. found: C=68.81%, H=4.29% calcd.: C=68.76%, H=4.33%

10. ^{1}H NMR (DMSO-d_6, 300MHz) δ 7.4-7.5 (m, 2H); 7.6 (d, *J*=16.5Hz, 1H); 7.75 (d, *J*=7.5Hz, 1H); 7.82-7.9 (m, 3H); 7.98 (d, *J*=9Hz, 1H); 8.2-8.28 (m, 2H); 9.3 (d, *J*=9Hz, 1H); 13.2 bs.

A.E. found: C=66.11%, H=4.31% calcd.: *H_2O C=65.96%, H=4.31%

11. ^{1}H NMR (DMSO-d_6, 300MHz) δ 6.9 (t, *J*=7.4 Hz, 1H); 6.96 (d, *J*=7.4Hz, 1H); 7.1 (d, *J*=7 Hz, 1H); 7.2 (t, *J*=7.1 Hz, 1H); 7.33-7.41 (m, 2H); 7.54 (d, *J*=16.5Hz, 1H); 7.63 (d, *J*=7.9Hz, 1H); 7.8 (d, *J*=8.7Hz, 1H); 8.13 (d, *J*=16.4Hz, 1H); 8.26 (d, *J*=8.5Hz, 1H); 8.33 bs.

A.E. calcd.: C=72.47%, H=4.29% found: C=72.51%, H=4.10%

12. ^{1}H NMR (DMSO-d_6, 300MHz) δ 7.08 (d, 1H, *J*=7.3Hz), 7.71 (d, 2H, *J*=8.4Hz), 7.75 (d, 1H, *J*=8.5), 7.33-7.4 (m, 2H), 7.46-7.49 (m, 3H), 8.1 (d, 1H, *J*=16.1Hz), 8.27 (d, 1H, *J*=8.5).

A.E. found: C=72.11%, H=4.50% calcd.: C=72.47%, H=4.29%

13. ^{1}H NMR (DMSO-d_6, 300MHz) δ 7.08 (d, 1H, *J*=7.2Hz), 7.49 (d, 2H, *J*=8.4Hz), 7.75 (d, 1H, *J*=8.5), 7.34-7.39 (m, 2H), 7.5-7.6 (m, 4H), 8.1 (d, 1H, *J*=16.2Hz), 8.27 (d, 1H, *J*=8.53).

A.E. found: C=62.61%, H=3.80% calcd.: C=62.60%, H=3.71%

15. ^{1}H NMR (DMSO-d6, 500MHz) δ: 6.72 (s, 1H); 7.12(t, 1H); 7.2-7.25(m, 2H); 7.4-7.48(m, 2H); 7.5 (d, *J*=7.6Hz, 1H); 8.23(d, *J*=8.5Hz, 1H); 8.41(d, *J*=8.5Hz, 1H); 8.71 (t, 1H); 9.66 (s, 1H); 10.05 (bs, 1H).
AE found C, 69.98%; H, 4.60%; calcd for $C_{16}H_{12}N_2O_2$*1/2H_2O C, 70.32%; H, 4.79%

16. ^{1}H NMR (DMSO-d6, 500MHz) δ: 6.83 (dd, *J*=7.5 Hz, 2H); 7.11 (dd, *J*= 7.5Hz, 2H); 7.31 (d, *J*=8.3 Hz, 1H); 7.4 (d, *J*=7.9 Hz, 1H), 7.45 (t, 1H); 8.19 (d, *J*= 7.9Hz, 1H); 8.34(d, *J*=7.8Hz, 1H); 8.74 (s, 1H); 9.67(s, 1H), 9.88(bs, 1H).
AE Found: C, 72.53%; H, 4.68%; calcd for $C_{16}H_{12}N_2O_2$: C, 72.72%; H, 4.58%.

5. ACKNOWLEDGEMENTS

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