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SYNTHESIS AND CHARACTERIZATION OF POLYSUBSTITUTED 5-QUINOLINECARBALDEHYDE DERIVATIVES

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Abstract – A new quinolinecarbaldehyde, 7-(carboxymethoxy)-6-hydroxy-3-sulfo-quinoline-5-carbaldehyde (**1**), was synthesized from eugenol, a natural phenol, by four successive reaction steps. The condensation of **1** with various amino compounds afforded 12 Schiff-bases (**2** – **13**) and 3 hydrazones (**14** – **16**). The structures of the aldehyde, its Schiff-bases and the hydrazone derivatives were determined by analyzing their IR, 1D NMR, 2D NMR and MS spectra. ^{1}H NMR and NOESY data show that the imine -CH=N- group in the reported Schiff-bases and hydrazones exists in *E*-configuration.

The quinoline scaffold is an important class of heterocyclic compounds that possesses diverse chemotherapeutic activities. Several quinoline compounds isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use.[1-5] Many quinolinecarbaldehyde derivatives exhibit high antituberculosis,[6] antibacterial,[7,8] and anticancer[9,10] activities. The quinolinecarbaldehyde derivatives, in particular Schiff-base, are also reported as corrosion inhibitors,[11,12] as organic ligands for synthesis of various interesting complexes,[13-15] and as intermediates for synthesis of new heterocycles.[16] Many hydrazones containing quinoline ring exhibit significant antitubercular properties[17,18] and high antimalarial activity.[19,20]

Recently, we have reported on an efficient and simple method for the synthesis of 7-(carboxymethoxy)-6-hydroxy-3-sulfoquinoline starting with eugenol,[21] the main constituent of *Ocimum sanctum L*. oil (a cheap natural source for commercial extraction of eugenol[22]). This quinoline derivative could act as a key compound in order to prepare useful poly-functionalized quinolines. In this study, we present the synthesis and the structure of a new polysubstituted quinolinecarbaldehyde, 7-(carboxymethoxy)-6-hydroxy- 3-sulfoquinoline-5-carbaldehyde, its Schiff-bases and hydrazones.

The precursor for the preparation of the title aldehyde is 7-(carboxymethoxy)-6-hydroxy-3-sulfoquinoline (**Q**, Figure 1) which has been synthesized from eugenol (l-hydroxy-2-methoxy-4-allylbenzene) by three successive reaction steps: Condensing eugenol with chloroacetic acid to form eugenoxyacetic acid (2-methoxy-4-(2-propenyl)phenoxyacetic acid); Treating eugenoxyacetic acid with excess of nitric acid in acetic acid to give 4-(*aci*-nitro)-2-(carboxymethoxy)-5-(3-nitro-2-(nitrooxy)propyl)cyclohexa-2,5-dienone; Reducing the latter with $Na_2S_2O_4$ to afford **Q**.[21] Compound **Q** is converted to 7-(carboxymethoxy)-6-hydroxy-3-sulfoquinoline-5-carbaldehyde (**1**) by means of Reimer-Tiemann reaction with chloroform in alkaline solution (see Frigure 1 and Experimental).

When **1** was reacted with various primary aromatic or aliphatic amines we received Schiff-bases **2** – **13** with yields above 50% but with *p*-nitroaniline or 2-aminopyridine we received a complicated mixture of **1**, the unconsumed amine and only a little of expected Schiff-base. The condensation of **1** and some phenylhydrazines leads to hydrazones **14** - **16** (see Figure 1, the numeration in the formulas is given specially for NMR analysis only).

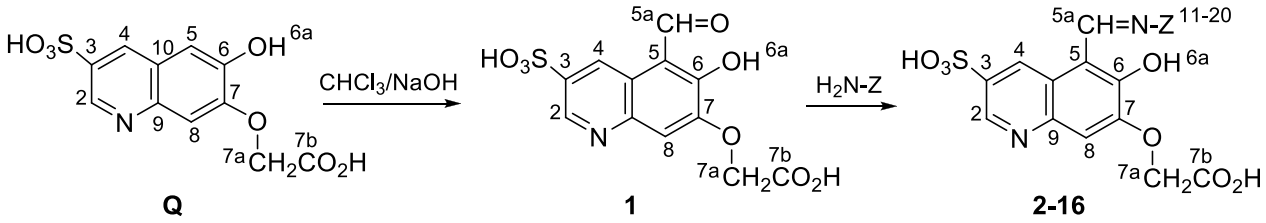


Figure 1. Synthesis of quinolinecarbaldehyde **1**, its Schiff-bases and hydrazones

Z: C_6H_5 (**2**); 2-MeC_6H_4 (**3**); 4-MeC_6H_4 (**4**); 2-$MeOC_6H_4$ (**5**); 3-$MeOC_6H_4$ (**6**); 4-$MeOC_6H_4$ (**7**); 4-ClC_6H_4 (**8**); 4-IC_6H_4 (**9**); 3-HOC_6H_4 (**10**); 1-naphthyl (**11**); $C_6H_5CH_2$ (**12**); cyclohexyl (**13**); C_6H_5NH (**14**); 2,4-$(O_2N)_2C_6H_3NH$ (**15**); 2-(3-Me-furoxan-4-yl)-4,5-$(MeO)_2C_6H_2NH$ (**16**).

Compound **1** is a new polysubstituted quinolinecarbaldehyde, the key compound in our present work. In order to ascertain the structure of **1** its IR, ^{1}H NMR, ^{13}C NMR and MS spectra were recorded. In the IR spectrum of **1** strong absorption band at 1736 cm^{-1} belongs to the CO_2H group, other strong band at 1662 cm^{-1} and medium band at 2765 cm^{-1} shows the presence of CH=O group. The ^{1}H NMR and ^{13}C NMR signals of **1** were assigned using their chemical shift and their cross peaks in HMBC spectrum as follows.

In the ^{1}H NMR spectrum of **1** (the vertical line in Figure 2), according to chemical shift, the singlets at 10.74 ppm (1H), the singlet at 5.10 ppm (2H), the singlet at 7.64 ppm (1H) belong to H5a, H7a and H8, respectively.

In the ^{13}C NMR spectrum of **1** (the horizontal line in Figure 2), it can also be easily to recognize the signals of C5a, C7a and C7b at 191.15 ppm, 65.89 ppm and 168.90 ppm, respectively.

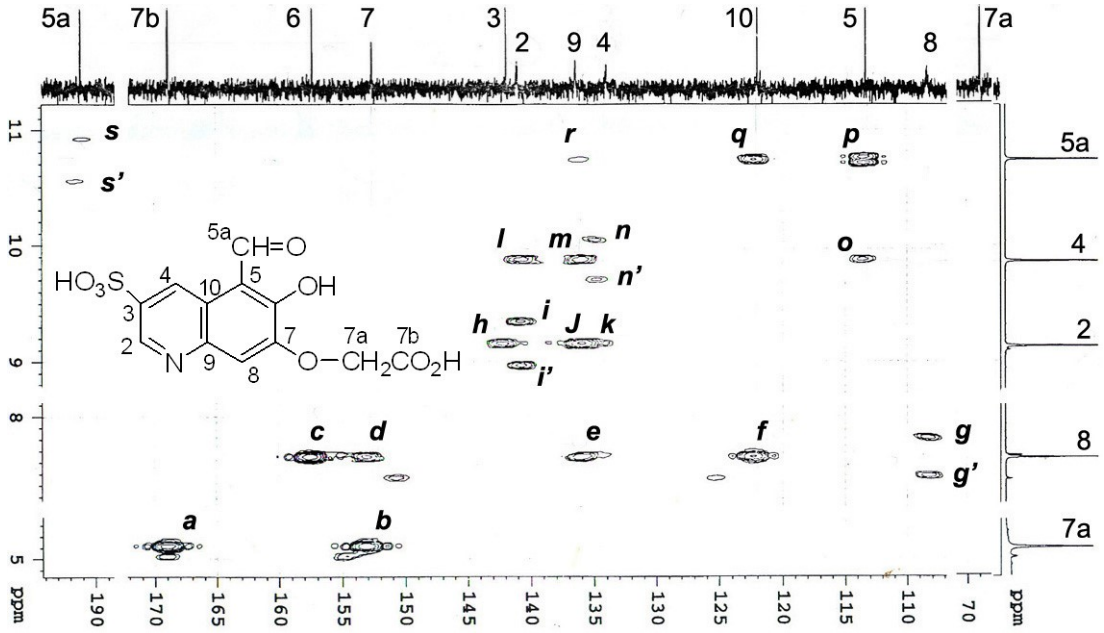


Figure 2. HMBC spectrum of aldehyde **1**

Subsequently, the cross peaks *a* and *b* of H7a show signals of C7b and C7, respectively; the cross peaks *c, d, e* and *f* of H8 show signals of C6, C7, C9 and C10, respectively; the cross peaks *p, q* and *r* of H5a show signals of C5, C10 and C9, respectively. The proton signal at 9.86 ppm gives rise to the cross peak *o* with C5, the proton signal at 9.13 ppm does not have cross peak with C5, thus the former was assigned to H4 and the latter to H2. The cross peaks *h, j* and *k* of H2 show signals of C3, C9 and C4, respectively. The cross peaks *l, m* and *o* of H4 show signals of C2, C9 and C5, respectively.

The negative mode mass spectrum of **1** showed pseudomolecular ions $(M-H)^-$ as follows (au/%): 326/100, 327/18 (^{13}C), 328/7 (^{34}S). These correspond to molecular mass of **1** (327 au) which contains one S atom.

Using the same manner as shown above for compound **1**, the assignment of ^1H NMR and ^{13}C NMR signals of examined compounds was based on their chemical shift, spin-spin splitting patterns, and 2D NMR spectra for several compounds. For example, 7 naphthyl proton signals of **11** located at 7.6 - 8.3 ppm are assigned based on NOESY spectrum as shown in Figure 4. The ^1H signals of the reported compounds are listed in Tables 1 and 2.

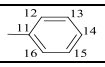
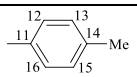
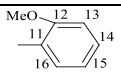
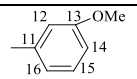
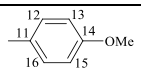
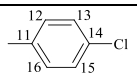
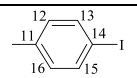
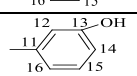
For **Q** the chemical shift of H2 is larger than that of H4. The electron-withdrawing formyl group in the C5 position of **1** inverted chemical shift order of H2 and H4 and this order is maintained for **2-16** (Table 1). The resonance signals of H5a, H4, H2, H8 and H7a of **2-16** are shifted to stronger field than those of **1** due to the formation of CH=N group. Also, the strong decrease of the chemical shifts of the carbonyl moiety protons of **12** and **13** is associated with the electron-donating effect of the benzyl and cyclohexyl groups.

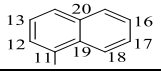
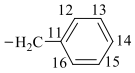
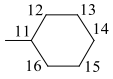
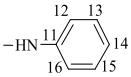
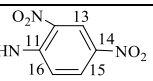
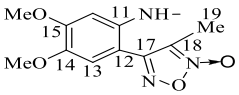
Table 1. The ^{1}H NMR signals of the carbonyl moiety of **1-16** (Figure 1), δ (ppm), *J* (Hz)

Compd.	**Z**	H5a	H4	H2	H8	H7a	H6a
Q	-	H5: 7.69 s	8.98 d; ^4J 1	9.04 d; ^4J 1	7.58 s	5.00 s	-
1	-	10.74	9.86 d; ^4J 1.5	9.13 d; ^4J 1.5	7.64 s	5.10 s	-
2	C_6H_5	9.77 s	9.43 s	8.91 s	7.27 s	4.95 s	15.72 brd. s (*)
3	2-MeC_6H_4	9.59 s	8.82 d; ^4J 1.5	8.71 d; ^4J 1.5	7.17 s	4.85 s	16.01 brd. s
4	4-MeC_6H_4	9.72 s	9.34 s	8.87 s	7.22 s	4.94 s	15.82 brd. s
5	2-$MeOC_6H_4$	9.78 s	9.42 s	8.87 s	7.24 s	4.94 s	15.67 brd. s
6	3-$MeOC_6H_4$	9.59 s	9.03 s	8.78 s	7.19 s	4.89 s	15.75 brd. s
7	4-$MeOC_6H_4$	9.48 s	8.78 s	8.71 s	7.17 s	4.85 s	16.12 brd. s
8	4-ClC_6H_4	9.73s	9.39 s	8.90 s	7.27 s	4.95 s	15.65 brd. s
9	4-IC_6H_4	9.69s	9.28 s	8.87 s	7.25 s	4.93 s	15.60 brd. s
10	3-HOC_6H_4	9.60 s	9.20 s	8.84 s	7.23 s	4.92 s	15.62 brd. s
11	1-naphthyl	9.77 s	8.89 s	8.74 s	7.24 s	4.90 s	16.75 brd. s
12	$C_6H_4CH_2$	9.40 s	8.57 s	8.67 s	7.11 s	4.30 s	13.25 brd. s
13	cyclohexyl	9.27 s	8.64 d; ^4J 1.5	8.53 d; ^4J 1.5	7.14 s	4.23 s	13.52 brd. s
14	C_6H_4NH	9.92 s	9.15 s	8.79 s	7.42 s	5.05 s	11.73 brd. s
15	2,4-$(O_2N)_2C_6H_3NH$	9.93 s	9.55 s	9.05 s	7.47 s	5.05 s	11.30 brd. s
16	2-Fu-4,5-$(MeO)_2C_6H_2NH$	9.37 s	8.93 s	8.87 s	7.31 s	4.97 s	11.10 brd. s

(*): Broadened singlet

Table 2. The ^{1}H NMR signals of the amino moiety of **2-16** (Figure 1), δ (ppm), *J* (Hz)

	Z	H12	H13	H14	H15	H16	Others
2		7.85 d; ^3J 8	7.55 t; ^3J 8	7.38 t; ^3J 8	7.55 t; ^3J 8	7.85 d; ^3J 8	-
3		-	7.37 d; ^3J 8	7.24 t; ^3J 8	7.37 t; ^3J 8	8.09 d; ^3J 8	Me: 2.47 s
4		7.74 d; ^3J 8	7.35 d; ^3J 8	-	7.35 d; ^3J 8	7.74 d; ^3J 8	Me: 2.36 s
5		-	7.23 d; ^3J 8.5	7.35 t; ^3J 8.5	7.15 t; ^3J 8.5	8.30 d; ^3J 8.5	MeO: 4.00 s
6		7.18 s	-	6.92 d; ^3J 8	7.41 t; ^3J 8	7.30 d; ^3J 8	MeO: 3.85 s
7		7.71 d; ^3J 9	7.07 d; ^3J 9	-	7.07 d; ^3J 9	7.71 d; ^3J 9	MeO: 3.82 s
8		7.88 d; ^3J 7	7.59 d; ^3J 7	-	7.59 d; ^3J 7	7.88 d; ^3J 7	-
9		7.87 d; ^3J 8	7.65 d; ^3J 8	-	7.65 d; ^3J 8	7.87 d; ^3J 8	-
10		7.20 s	-	6.76 d; ^3J 8	7.32 t; ^3J 8	7.19 d; ^3J 8	HO: 9.20 brd. s (*)

11		8.21 d; ^3J 8	7.66 t; ^3J 8	8.05 d; ^3J 8	7.92 d; ^3J 8	7.64 t; ^3J 8	H17: 7.74 t; ^3J 8 H18: 8.27 d; ^3J 8
12		7.41-7.43 m	7.41-7.43 m	7.41-7.43 m	7.41-7.43 m	7.41-7.43 m	CH_2: 4.98. s
13		e: 1.97 m a: 1.41 m	e: 1.72 m a: 1.41 m	e: 1.57 m a: 1.25 m	e: 1.72 m a: 1.41 m	e: 1.97 m a: 1.41 m	H11: 3.88 brd. s
14		7.11 d; ^3J 8	7.28 t; ^3J 8	6.84 t; ^3J 8	7.28 t; ^3J 8	7.11 d; ^3J 8	HN: 10.80. s
15		-	8.89 d; ^4J 2	-	8.29 dd; ^3J 9.5; ^4J 2	8.09 d ; ^3J 9.5	HN: 11.97. s
16		-	6.98 s	H14a (MeO): 3.75 s	H15a (MeO): 3.95 s	7.16 s	HN: 10.07. s, H19 (Me): 2.09. s

In the ^{1}H NMR of many derivatives of **Q** (for instance the compounds reported in [21]) the proton signal of the phenol OH group (H6a) does not always appear (since the phenolic hydroxyl proton is exchangeable) but for compounds **2-16** the signal of H6a usually appears at 11.1 – 16.8 ppm. This can be ascribed to the formation of strong intramolecular hydrogen bond of H6a and the imine N atom (see Figures 3 and 4iii).

The spectroscopic data given in Table 2 with the absence of the H_2N proton signals are in good agreement with the structure of amino moiety of **2-15**.

In addition, in IR spectra of **2-15** the strong absorption band at 1662 cm^{-1} of the CH=O group in **1** was replaced by a band at 1622 – 1641 cm^{-1} indicating the successful transformation of the aldehyde to the imine CH=N group. In ESI MS spectra of examined compounds (**2**, **5**, **16**) the base peaks (intensity 100%) are pseudomolecular ion peaks at *m/z* values corresponding to their molecular formula (see Experimental). In the HMBC spectra of **3**, **5** and **11** there are strong cross peaks between H5a of the carbonyl moiety and C11 of the amino moiety; in the HMBC spectra of **12** there is strong cross peak between H5a of the carbonyl moiety and C11a of the benzylamino moiety. These cross peaks confirm the formation of CH=N bond from the aldehyde **1** and the used primary amines.

An anomaly in ^{13}C NMR spectra of the examined compounds can be seen from Table 3.

Table 3. The chemical shift of C5, C6, C7 and C7b in examined compounds, δ (ppm)

Compound	C5	C5a	C6 (C-OH)	C7 (C-OR)	C7b (C=O)
1	113.36	191.15	157.31	152.64	168.90
2 -15	103.26 – 109.90	151.62 – 154.21	168.89 – 172.67	150.77 – 156.78	165.50 – 170.51

The chemical shift of C6 (C-OH) in **2-15** strongly increases, while the chemical shift of C5 decreases significantly, and the chemical shift of C5a decreases dramatically in comparison with those in **1**. In other word, the chemical shift of C6 (C-OH) in **2-15** is too much larger than that of a normal phenol C-OH (for instance C6 in **1** and C7 in the others). Indeed, it falls into the C=O region (for instance C7b).

It is possible that strong intramolecular hydrogen bond of H6a and imine N atom makes structure **B** more important than **A**, hence C6 becomes more like a carbonyl carbon and C5 and C5a become ethylenic carbons as shown in Figure 3.

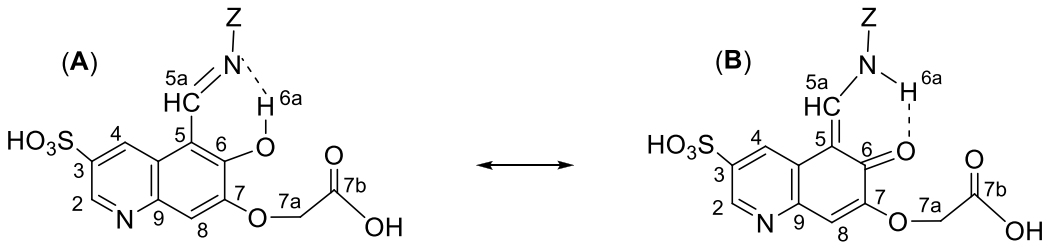


Figure 3. Two possible structures of **2** – **16**

Concerning the *Z*- or *E*-configuration of Schiff bases, there is generally an ambiguity on account of the many different experimental and theoretical studies.[23-25] It has also been reported that imines having *E*- or *Z*-configuration in the solid state, afford in solution at ambient temperature equilibrium mixtures, even in non polar solvents such as cyclohexane.[26] In order to determine the configuration of the reported compounds, the NOESY spectra of representative Schiff-bases **5**, **6**, **7**, **8** and **11** were analyzed, for instance the spectrum of **11** is presented in Figure 4.

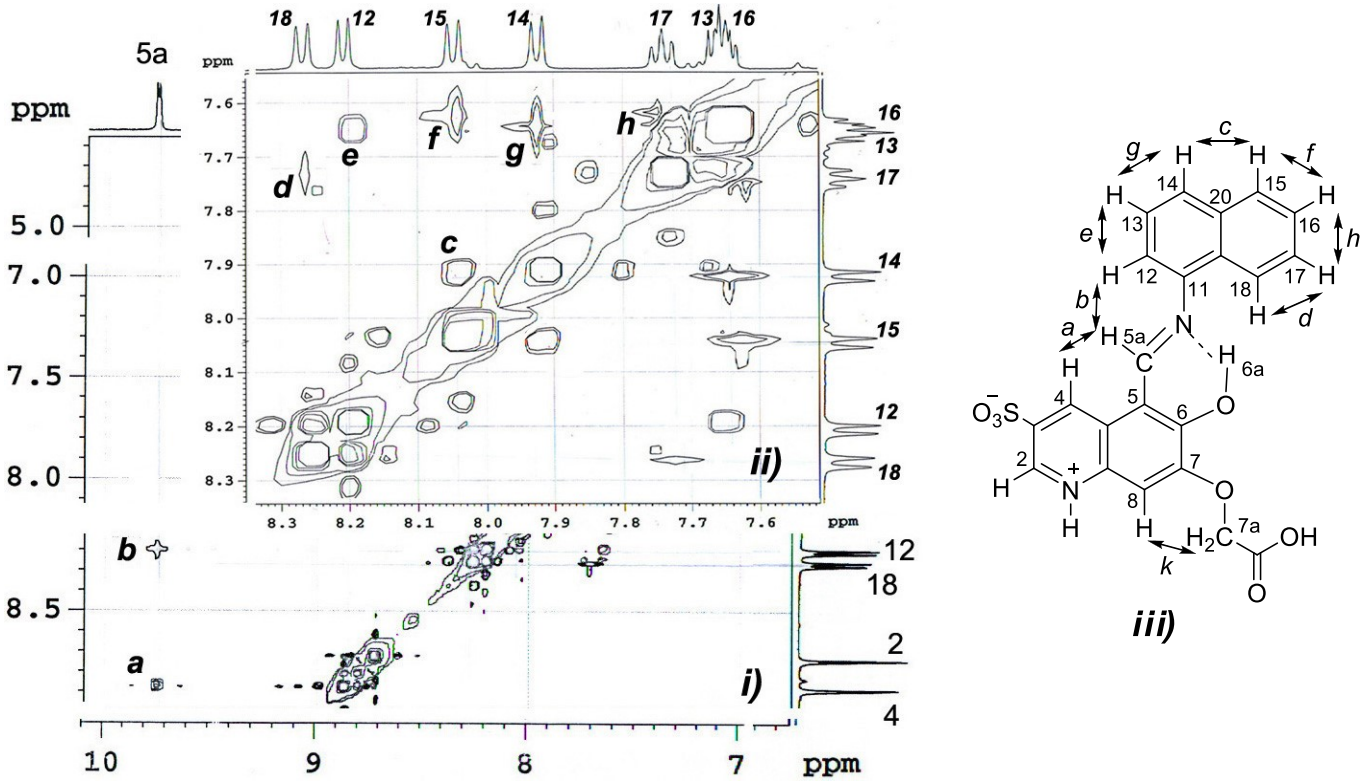


Figure 4. Partial NOESY spectrum of **11**: *i*) 10 - 7 ppm region; *ii*) 8.3 - 7.6 ppm region; *iii*) NOESY-interaction (↔) and structure of **11**: Each double-headed arrow shown the spatial closeness between two protons, each letter accompanied with the double-headed arrow associates with one cross peak in the NOESY spectrum.

In Figure 4, the cross peaks *a* of H5a affirms that H4 is more downfield than H2 as assigned in Figure 2. The cross peaks *b* of H5a shows that the doublet at 8.21 ppm belongs to H12. The cross peaks *e* of H12 in turn shows that the triplet at 7.66 ppm belongs to H13. The cross peaks *g* of H13 shows that the doublet at 7.92 ppm belongs to H14. The cross peaks *c* of H14 shows the doublet of H15. The cross peaks *f* of H15 shows that the triplet at 7.64 ppm associated with H16. The cross peaks *h* of H16 allows to assign the triplet at 7.74 ppm to H17. The cross peaks *d* of H17 shows that the doublet at 8.27 ppm associated with H18. It is note that H7a (at 4.90 ppm) and H8 (at 7.24 ppm) give rise to cross peak *k* (in Figure 4i) which is hided by Figure 4ii.

The appearance of two cross peak *a, b* and the absence of a cross peak of H5a with H18 (in Figure 4i) shown that H5a is in the proximity of both H4, H12 and remote from H18 as presenting in Figure 4iii. The formation of intramolecular hydrogen bond places H6a of **2-11** in the shielding region of the aromatic ring of the amino moiety (Figure 4iii) leading to the stronger shift to low field of H6a for **2-11** (15.60 - 16.75 ppm) in comparison with H6a for **12** - **16** (11.10 - 13.52 ppm, Table 1). All these ^{1}H NMR and NOESY data allow us to suggest that the imine -CH=N- group in **2-16** exists in *E*-configuration.

In conclusion, a new polysubstituted quinolinecarbaldehyde, 7-(carboxymethoxy)-6-hydroxy-3-sulfo-quinoline-5-carbaldehyde, its 12 Schiff-bases and 3 hydrazones were synthesized and characterized. The ^{1}H NMR and NOESY data show that the imine -CH=N- group in reported Schiff-bases and hydrazones exists in *E*-configuration.

EXPERIMENTAL

General

IR spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr discs at 400–4000 cm^{-1}. ESI mass spectra were recorded using Agilent LC-MSD-Trap-SL series 1100 spectrometer. NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer, in DMSO d_6 with TMS as the internal standard, at 298–300 K. C, H, and N were analyzed on a LECO CHNS model 932 elemental analyser.

Preparation

7-(Carboxymethoxy)-6-hydroxy-3-sulfoquinoline-5-carbaldehyde (**1**). To a solution of 7-(carboxy-methoxy)-6-hydroxy-3-sulfoquinoline (2.99 g, 10 mmol, **Q**, previously prepared in reference[21]) in 5M NaOH solution (40 mL) at 70 ^{o}C was slowly added $CHCl_3$ (5 mL). The reaction mixture was stirred for 3 h at room temperature and allowed to stand for additional 4 h. The precipitate was filtered out and dissolved in water (40 mL). The solution was acidified with 2M HCl solution to pH 5. The resulting yellow solid was collected by filtration and recrystallized from water to give 1.21 g of **1** in 37% yield, yellow needles, decomposed at 165 ^{o}C. IR (cm^{-1}): 3457, 3490 (OH); 3065, 2958, 2865, 2765 (C-H); 1736,

1632 (C=O); 1600, 1501 (ring). ^{1}H NMR see Tables 1. ^{13}C NMR, δ, ppm (assigned according to the HMBC spectrum): 141.08 (C2); 141.93 (C3); 134.01 (C4); 113.36 (C5); 157.31 (C6); 152.64 (C7); 108.42 (C8); 136.48 (C9); 122.01 (C10); 191.15 (C5a); 65.89 (C7a); 168.90 (C7b). ESI -MS, *m/z* (au)/relative intensity (%): 326/100 (M-H^{+}), 327/18 (^{13}C), 328/7 (^{34}S). *Anal.* Calcd for $C_{12}H_9NO_8S$ (M 327.27): C, 44.04; H, 2.77; N, 4.28. Found: C, 44.26; H, 3.02; N, 4.05.

The general procedure for the preparation of Schiff-bases 2-13 and hydrazones 14-16:

A solution of **1** (327 mg, 1 mmol) in DMSO (3 mL) was added to a solution of amine or arylhydrazine (1 mmol) in EtOH (10 mL). The mixture was refluxed for 2-4 h. The solution was allowed to cool to room temperature. The resulting precipitate was filtered out and recrystallized from a suitable solvent.

2-(6-Hydroxy-3-sulfo-5-((phenylimino)methyl)quinolin-7-yloxy)acetic acid (**2**). Yellow needle crystals (from EtOH/H_2O/dioxane 1/2/1 by volume), yield 63%, decomposed at about 190 ºC. IR (cm^{-1}): 3443 (OH); 3065, 2943 (C-H); 1718 (C=O); 1630, 1600, 1514 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm: 144.21 (C2); 141.32 (C3); 123.98 (C4); 105.73 (C5); 171.54 (C6); 155.48 (C7); 112.67 (C8); 139.43 (C9); 123.98 (C10); 153.27 (C5a); 65.08 (C7a); 169.15 (C7b); 139.56 (C11); 122.78 (C12); 130.59 (C13); 127.83 (C14); 130.59 (C15); 122.78 (C16). ESI -MS, *m/z* (au)/relative intensity (%): 401/100 [M-H^{+}]; 402/19 (^{13}C), 403/7 (^{34}S). *Anal.* Calcd for $C_{18}H_{14}N_2O_7S$ (M 402.38): C, 53.73; H, 3.51; N, 6.96. Found: C, 54.02; H, 3.33; N, 7.20.

2-(6-Hydroxy-3-sulfo-5-((*o*-tolylimino)methyl)quinolin-7-yloxy)acetic acid (**3**). Yellow crystals (from EtOH/dioxane 3/2 by volume), yield 60%, decomposed at about 190 ºC. IR (cm^{-1}): 3460 (OH); 3053, 2925, 2885 (C-H); 1732 (C=O); 1630, 1600, 1546 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm (assigned according to the HMBC spectrum): 143.80 (C2); 140.50 (C3); 123.76 (C4); 106.46 (C5); 171.38 (C6); 152.55 (C7); 113.90 (C8); 142.31 (C9); 123.65 (C10); 152.14 (C5a); 64.87 (C7a); 169.61 (C7b); 138.48 (C11); 128.66 (C12); 130.91 (C13); 127.33 (C14); 126.45 (C15); 117.61 (C16). *Anal.* Calcd for $C_{19}H_{16}N_2O_7S$ (M 416.40): C, 54.80; H, 3.87; N, 6.73. Found: C, 54.50; H, 4.13; N, 7.01.

2-(6-Hydroxy-3-sulfo-5-((*p*-tolylimino)methyl)quinolin-7-yloxy)acetic acid (**4**). Yellow crystals (from DMF/H_2O/dioxane 1/3/5 by volume), yield 71%, decomposed at about 198 ºC. IR (cm^{-1}): 3454 (OH); 3060, 2938, 2890 (C-H); 1717 (C=O); 1633, 1540 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm: 144.53 (C2); 141.50 (C3); 124.01 (C4); 104.98 (C5); 171.90 (C6); 156.50 (C7); 107.50 (C8); 137.12 (C9); 123.50 (C10); 154.04 (C5a); 65.29 (C7a); 169.03 (C7b); 136.01, 130.23, 119.90, 135.0 (C11-C16); 20.67 (C14a). *Anal.* Calcd for $C_{19}H_{16}N_2O_7S$: C, 54.80; H, 3.87; N, 6.73. Found: C, 54.55; H, 4.11; N, 6.97.

2-(6-Hydroxy-3-sulfo-5-((*o*-methoxyphenylimino)methyl)quinolin-7-yloxy)acetic acid (**5**). Yellow crystals (from DMF/EtOH/dioxane 1/3/2 by volume), yield 60%, decomposed at about 195 ºC. IR (cm^{-1}): 3391 (OH); 3058, 2945, 2860 (C-H); 1726 (C=O); 1638, 1605, 1511 (C=N, C=C). ^{1}H NMR see Table 1.

^{13}C NMR, δ, ppm (assigned according to the HMBC spectrum): 135.60 (C2); 135.61 (C3); 130.50 (C4); 105.10 (C5); 172.52 (C6); 156.78 (C7); 104.60 (C8); 141.51 (C9); 126.96 (C10); 151.62 (C5a); 65.25 (C7a); 168.85 (C7b); 126.89 (C11); 149.68 (C12); 112.12 (C13); 128.19 (C14); 121.12 (C15); 118.33 (C16); 56.30 (C12a). ESI, -MS *m/z* (au)/relative intensity (%): 431/100 [M-H$^+$], 432/23 (^{13}C), 433/9 (^{34}S). *Anal.* Calcd for $C_{19}H_{16}N_2O_8S$ (M 432.40): C, 52.78; H, 3.73; N, 6.48. Found: C, 53.04; H, 3.48; N, 6.21.

2-(6-Hydroxy-3-sulfo-5-((*m*-methoxyphenylimino)methyl)quinolin-7-yloxy)acetic acid (**6**). Yellow crystals (from DMF/EtOH/dioxane 1/3/2 by volume), yield 56%, decomposed at about 195 °C. IR (cm^{-1}): 3475 (OH); 3060, 2941, 2868 (C-H); 1743 (C=O); 1632, 1594, 1542 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm: 141.75 (C2); 141.96 (C3); 130.97 (C4); 104.25 (C5); 168.89 (C6); 155.90 (C7); 103.05 (C8); 143.86 (C9); 127.11(C10); 154.21 (C5a); 65.39 (C7a); 166.93 (C7b); 136.50, 113.98, 160.41, 110.69, 128.65, 124.76 (C11-C16); 55.46 (C13a). *Anal.* Calcd for $C_{19}H_{16}N_2O_8S$: C, 52.78; H, 3.73; N, 6.48. Found: C, 53.08; H, 3.45; N, 6.19.

2-(6-Hydroxy-3-sulfo-5-((*p*-methoxyphenylimino)methyl)quinolin-7-yloxy)acetic acid (**7**). Yellow crystals (from DMF/EtOH/dioxane 1/3/2 by volume), yield 62%, decomposed at about 205 °C. IR (cm^{-1}): 3458 (OH); 3063, 2920, 2840 (C-H); 1733 (C=O); 1637, 1600, 1540 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm: 141.17 (C2); 139.40 (C3); 127.16 (C4); 106.65 (C5); 169.05 (C6); 156.88 (C7); 109.55 (C8); 142.50 (C9); 128.80 (C10); 153.20 (C5a); 65.42 (C7a); 165.50 (C7b); 123.56 C11); 122.15 (C12); 115.38 (C13); 161.09 (C14); 115.38 (C15); 122.15 (C16); 55.73 (C14a). *Anal.* Calcd for $C_{19}H_{16}N_2O_8S$: C, 52.78; H, 3.73; N, 6.48. Found: C, 52.49; H, 3.95; N, 6.73.

2-(6-Hydroxy-3-sulfo-5-((*p*-chlorophenylimino)methyl)quinolin-7-yloxy)acetic acid (**8**). Light yellow crystals (from DMF/EtOH/dioxane 1/3/3 by volume), yield 53%, decomposed at about 200 °C. IR (cm^{-1}): 3420 (OH); 3050, 2954, 2845 (C-H); 1717 (C=O); 1622, 1538 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm: 137.54 (C2); 136.02 (C3); 131.43 (C4); 104.94 (C5); 171.89 (C6); 156.41 (C7); 105.21 (C8); 141.57 (C9); 126.70 (C10); 154.21 (C5a); 65.34 (C7a); 168.80 (C7b); 135.67 (C11); 121.94 (C12); 129.53 (C13); 130.96 (C14); 129.53 (C15); 121.94 (C16). *Anal.* Calcd for $C_{18}H_{13}ClN_2O_7S$: C, 49.49; H, 3.00; N, 6.41. Found: C, 49.12; H, 2.85; N, 6.65.

2-(6-Hydroxy-3-sulfo-5-((*p*-iodophenylimino)methyl)quinolin-7-yloxy)acetic acid (**9**). Dark green crystals (from DMF/EtOH/dioxane 2/3/3 by volume), yield 61%, decomposed at above 185 °C. IR (cm^{-1}): 3431 (OH); 3048, 2935, 2870 (C-H); 1724 (C=O); 1634, 1540 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm: 138.62 (C2); 136.88 (C3); 132.56 (C4); 103.31 (C5); 169.84 (C6); 156.14 (C7); 104.23 (C8); 139.68 (C9); 128.96 (C10); 155.35 (C5a); 65.31 (C7a); 169.12 (C7b); 137.52, 122.14, 131.45, 112.36, 131.45, 122.14 (C11-C16). *Anal.* Calcd for $C_{18}H_{13}IN_2O_7S$: C, 40.92; H, 2.48; N, 5.30. Found: C, 41.21; H, 2.25; N, 5.52.

2-(6-Hydroxy-3-sulfo-5-((*m*-hydroxyphenylimino)methyl)quinolin-7-yloxy)acetic acid (**10**). Yellow crystals (from DMF/EtOH/dioxane 1/3/2 by volume), yield 66%, decomposed at about 200 ºC. IR (cm^{-1}): 3426 (OH); 3078, 2951, 2845 (C-H); 1702 (C=O); 1638, 1610, 1535 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm: 140.68 (C2); 139.25 (C3); 130.45 (C4); 103.26 (C5); 169.14 (C6); 155.64 (C7); 102.57 (C8); 141.27 (C9); 129.36 (C10); 153.98 (C5a); 65.87 (C7a); 166.38 (C7b); 137.85, 115.21, 158.32, 109.38., 127.35, 124.14 (C11-C16). *Anal.* Calcd for $C_{18}H_{14}N_2O_8S$: C, 51.67; H, 3.37; N, 6.70. Found: C, 51.96; H, 3.61; N, 6.44.

2-(6-Hydroxy-3-sulfo-5-((α-naphthylimino)methyl)quinolin-7-yloxy)acetic acid (**11**). Rouge crystals (from DMF/EtOH/H_2O 1/1/2 by volume), yield 73%, decomposed at about 200 ºC. IR (cm^{-1}): 3450 (OH); 3064, 2922, 2862 (C-H); 1693 (C=O); 1628, 1547 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm (assigned according to the HSQC and HMBC spectra): 144.19 (C2); 140.56 (C3); 124.21 (C4); 107.40 (C5); 169.69 (C6); 152.24 (C7); 114.01 (C8); 142.41 (C9); 123.38 (C10); 154.53 (C5a); 64.92 (C7a); 169.50 (C7b); 136.91 C11); 115.62 (C12); 126.27 (C13); 126.83 (C14); 128.66 (C15); 126.89 (C16); 127.49 (C17); 120.87 (C18); 125.53 (C19); 133.71 (C20). *Anal.* Calcd for $C_{22}H_{16}N_2O_7S$: C, 58.40; H, 3.56; N, 6.19. Found: C, 58.76; H, 3.31; N, 5.92.

2-(6-Hydroxy-3-sulfo-5-((benzylimino)methyl)quinolin-7-yloxy)acetic acid (**12**). Yellow crystals (from DMF/EtOH 1/4 by volume), yield 68%, decomposed at about 195 ºC. IR (cm^{-1}): 3456 (OH); 3049, 2897, 2870 (C-H); 1690 (C=O); 1638, 1582, 1524 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm (assigned according to the HMBC spectrum): 142.91 (C2); 140.17 (C3); 122.57 (C4); 103.81 (C5); 172.67 (C6); 153.55 (C7); 113.25 (C8); 142.15 (C9); 123.78 (C10); 160.16 (C5a); 67.72 (C7a); 170.50 (C7b); 137.05 (C11); 128.43 (C12); 128.63 (C13); 127.60 (C14); 128.63 (C15); 128.43 (C16). *Anal.* Calcd for $C_{19}H_{16}N_2O_7S$: C, 54.80; H, 3.87; N, 6.73. Found: C, 55.28; H, 3.65; N, 6.51.

2-(6-Hydroxy-3-sulfo-5-((cyclohexylimino)methyl)quinolin-7-yloxy)acetic acid (**13**). Light yellow crystals (from EtOH/H_2O 1/1 by volume), yield 65%, decomposed at about 190 ºC. IR (cm^{-1}): 3459 (OH); 3045, 2940, 2852 (C-H); 1698 (C=O); 1641, 1600, 1539 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm: 141.32 (C2); 139.58 (C3); 122.12 (C4); 104.26 (C5); 171.25 (C6); 153.71 (C7); 108.54 (C8); 140.62 (C9); 122.96 (C10); 159.14 (C5a); 67.13 (C7a); 169.72 (C7b); 67.15 (C11); 25.04 (C12); 24.17 (C13); 24.93 (C14); 24.17 (C15); 25.04 (C16). *Anal.* Calcd for $C_{18}H_{20}N_2O_7S$: C, 52.93; H, 4.94; N, 6.86. Found: C, 53.20; H, 4.71; N, 6.58.

2-(5-((2-Phenylhydrazono)methyl)-6-hydroxy-3-sulfoquinolin-7-yloxy)acetic acid (**14**). Red crystals (from dioxane/H_2O 3/1 by volume), yield 82%, decomposed at about 175 ºC. IR (cm^{-1}): 3468 (OH); 3263 (NH); 3050, 2932 (C-H); 1745 (C=O); 1636, 1601, 1546 (C=N, C=C). ^{1}H NMR see Table 1. ^{13}C NMR, δ, ppm: 142.14 (C2); 140.35 (C3); 121.01 (C4); 107.14 (C5); 169.58 (C6); 150.34 (C7); 110.68 (C8);

139.65 (C9); 122.89 (C10); 151.42 (C5a); 65.16 (C7a); 169.02 (C7b); 143.13, 115.58, 128.47, 123.18, 128.47, 115.58 (C11-C16). *Anal.* Calcd for $C_{18}H_{15}N_3O_7S$: C, 51.80; H, 3.62; N, 10.07. Found: C, 52.07; H, 3.41; N, 9.84.

2-(5-((2-(2,4-Dinitrophenyl)hydrazono)methyl)-6-hydroxy-3-sulfoquinolin-7-yloxy)acetic acid (**15**). Yellow crystals (from dioxane/H_2O 3/1 by volume), yield 80%, decomposed at about 160 ºC. IR (cm^{-1}): 3437 (OH); 3273 (NH); 3031, 2932 (C-H); 1736 (C=O); 1641, 1613, 1582, 1510 (C=N, C=C). ^1H NMR see Table 1. ^{13}C NMR, δ, ppm: 144.01 (C2); 140.81 (C3); 121.56 (C4); 109.90 (C5); 170.00 (C6); 150.77 (C7); 112.27 (C8); 140.80 (C9); 123.01 (C10); 152.30 (C5a); 65.76 (C7a); 169.05 (C7b); 145.82, 130.02, 123.01, 137.38, 129.72, 116.95 (C11-C16). *Anal.* Calcd for $C_{18}H_{13}N_5O_{11}S$: C, 42.61; H, 2.58; N, 13.80. Found: C, 42.86; H, 2.34; N, 13.58.

2-(5-((2-(2-(3-Methylfuroxan-4-yl)-4,5-dimethoxyphenyl)hydrazono)methyl)-6-hydroxy-3-sulfoquinolin-7-yloxy)acetic acid (**16**). This compound was synthesized from **1** (164 mg, 0.5 mmol) and 2-(3-methylfuroxan-4-yl)-4,5-dimethoxyphenylhydrazine (113 mg, 0.5 mmol, prepared according to our method[27]). Red crystals (from DMF/H_2O 2/1 by volume), yield 65%, decomposed at about 164 ºC. IR (cm^{-1}): 3401 (OH); 3166 (NH); 3052, 2925, 2860 (C-H); 1695 (C=O); 1623, 1588, 1535 (C=N, C=C). ^1H NMR see Table 1. ESI MS, *m/z* (au)/relative intensity (%), positive mode: 576/100 [$M+H^+$]; 577/24 (^{13}C), 578/10 (^{34}S); negative mode: 574/100 [$M-H^+$]; 575/29 (^{13}C), 576/12 (^{34}S). *Anal.* Calcd for $C_{23}H_{21}N_5O_{11}S$: C, 48.00; H, 3.68; N, 12.17. Found: C, 48.27; H, 3.45; N, 12.44.

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