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ORIGINAL ARTICLE

Synthesis of 8-Quinolinol Mannich Reaction Products

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ABSTRACT

Objective: To synthesize biologically significant molecules applying Mannich reaction conditions.

Method: Equimolar quantities of corresponding aldehydes and amines were mixed with 8-quinolinol (8-HQ) in absolute ethanol at room temperature and pressure without using any catalyst. The reaction progress was monitored through TLC.

Results: The condensation of privileged 8-quinolinol (8-HQ, **1**) with various substituted aldehydes and amines has resulted in the synthesis of ten products (**2**-**11**) under Mannich reaction conditions. These include four Mannich bases (**2-5**), three *bis*-products (**6-8**) and three imines (**9-11**). Nine of these derivatives are new and only one of them is known (**11**). The chemical characterizations of these molecules have been made through extensive study of ^{1}H, ^{13}C NMR and 2D NMR techniques. The long range interaction of H-4 and H-5 with C-10 in HMBC plot, revised the assignment of C-9 and C-10 in 8-quinolinol moiety of newly synthesized derivatives.

Conclusion: Several new derivatives of 8-quinolinol have been prepared under Mannich reaction condition without any catalyst. Exact characterization of these new molecules will serve as a reference spectral data for future study. As Mannich products generally possess significant biological properties, future pharmacological study may turn them as an important target for drug synthesis.

Keywords: 8-Quinolinol, Retro-Mannich reaction, bis-product, Mannich base, imine.

INTRODUCTION

The ensemble of chemical functionality in Mannich bases plays a significant role as drug or drug predecessor [1,2]. Mannich bases have been reported as neuroprotective [3], anticancer, antimicrobial and antiparasitic agents [4]. Mannich base and its derivatives are frequently used in the production of natural products and macromolecules [2]. 8-Quinolinol (8-HQ, 1) is a well-known privileged heterocyclic scaffold. Many of 8-HQ derivatives have been recognized for its potency against neurodegenerative disorders as it is able to cross blood brain barrier and can selectively remove the Cu (II) and Zn (II) from amyloid beta-peptide and has capability to inhibit acetyl cholinesterase and monoamine oxidase [5]. 8-HQ polymeric micelles have promising activity against visceral leishmaniasis [6]. The 8-quinolinoyl jasmonate is found to inhibit different types of carcinomas [7] while gluconjugates have been reported to possess antiproliferative activity [8]. The invitro study of compounds having 8-HQ moiety with amino benzothiazole revealed IC 50 <1 M for the inhibition of DENV-2 protease in dengue virus type-2 [9]. Recently, diaza-18-crown-6-hydroxyquinoline synthesized via Mannich reaction, is

reported for sensitive Mg^{2+} analysis as a fluorescent probe for quantitative use within the cell [10] while the copper bis-products of 8-HQ found to possess anticancer activity [11]. Hence, the scope of 8-HQ (1) plus chemical functionality of Mannich reaction rationalize the use of 8-HQ Mannich products in future drug designing and drug discovery.

Keeping all this in view, different 8-HQ derivatives have been prepared applying Mannich reaction conditions. Current approach has resulted in the synthesis of Mannich bases (2-5), bis-products (6-8) and imines (9-10) which according to Science Finder research engine [12] have not been reported earlier.

METHODOLOGY

UV (in MeOH) and IR (in KBr disc) spectra were recorded on Thermo evolution 300 vision pro version 4.10 and FTIR-8900 (Shimadzu, Japan) spectrophotometers respectively. EI-MS was recorded on JMS 600H (Tokyo, Japan); HREI-MS on Thermo Finnigan MAT 95 XP (Germany); ESI-MS on Qstar XL/MS/MS system (USA). The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6 and acetone-d_6 at 24-27°C with Bruker Aspect AM-300, AM-400 and AM-500 spectrometers (Switzerland) working at 300, 400 and 500 MHz for ^1H NMR and 75, 100 and 125 MHz for ^{13}C NMR, respectively. Exact assignment of ^{13}C NMR spectral assignments was made partially through DEPT, HMQC and HMBC spectra and partially through literature values [13,14] and (ACD/Labs) software [15]. The precoated cards (0.2mm thickness) E. Merck Kiesel gel 60 GF_{254} were used for thin layer chromatography. Chromatograms were visualized by UV at 254 and 365 nm. All the chemichydroals and solvents used were of analytical grade.

General Synthetic Procedures for Mannich Products

In each case, the measured quantity of corresponding aldehydes and amines (except for *bis*-products 6-8, where amine used was dimethyl amine for 6 & 8 and aniline for 7) were mixed with 8-HQ in equimolar proportion (0.005 M) in absolute ethanol at room temperature and pressure. The reaction mixture afforded products after 10 (9, 102mg), 13 (4, 638mg), 14 (10, 175mg; 11, 174mg), 30 (2, 136mg; 3, 500mg; 6, 64mg) and more than 60 (5, 866mg; 7, 386mg; 8, 889mg) days. The reaction progress was monitored through TLC and envisioned in UV light (366 nm and 254 nm). The crude products formed were separated from respective mother liquors, filtered and washed with methanol.

7-[α-(2″Methoxy, 5″-nitroanilino)-2′-thienyl]-8-hydroxyquinoline (2)

UV λ_{max} MeOH nm: 248, 304. IR (KBr) ν_{max} cm^{-1}: 3387 (OH), 1517 (C=C), 1337 (C-N), 1260 (C-O). HREIMS m/z: 407.0921 (M^+, calculated for $C_{21}H_{17}N_3O_4S$, 407.18701). EIMS m/z (%): 407 (2), 238 (100), 168 (79), 122 (29). ^1H NMR: Table **1**, ^{13}C NMR: Table **2**.

7-[α-(2″-Methoxy, 5″-nitro-anilino)-3′-hydroxybenzyl]-8-hydroxyquinoline (3)

UV λ_{max} MeOH nm: 207, 247. IR (KBr) ν_{max} cm^{-1}: 3634 (OH), 3544 (NH), 3086 (CH) 1580-1502 (C=C), 1380 (C-N), 1268 (C-O). EIMS m/z (%): 417 (1), 260 (10), 242 (15), 168 (100), 142 (19), 144 (9).^1H NMR: Table **1**, ^{13}C NMR: Table **2**.

7-[α-(2″, 5″-Dichloroanilino)-2′, 3′-dimethoxybenzyl]-8-hydroxyquinoline (4)

UV λ_{max} MeOH nm: 248, 307. IR (KBr) ν_{max} cm^{-1}: 3620 (OH), 3363 (NH), 3004 (CH), 1589- 1508 (C=C), 1342 (C-N), 1188 (C-O), 729 (C-Cl). HREIMS m/z: 454.0848 (M^+, calculated for, $C_{24}H_{20}Cl_2N_2O_3$, 454.0853), 294.1106 ($C_{18}H_{16}NO_3$), 161.0453 ($C_6H_4Cl_2N$), 145.0542 (C_9H_7NO). EIMS m/z (%): 454 (8), 294 (36), 161 (100), 145 (5).^1H NMR: Table **1**, ^{13}C NMR: Table **2**.

7-[α-(2″,5″-Dichloroanilino)-3′,4′-dimethoxybenzyl]-8-hydroxyquinoline (5)

UV λ_{max} MeOH nm: 248, 307. IR (KBr) ν_{max} cm^{-1}: 3620 (OH), 3360 (NH), 3005 (CH), 1570- 1510 (C=C), 1340 (C-N), 1180 (C-O). HREIMS m/z: 454.0847 (M^+, calculated for, $C_{24}H_{20}Cl_2N_2O_3$, 454.0853). EIMS m/z (%): 454 (4), 294 (36), 161 (100), 145 (5).^1H NMR: Table **1**, ^{13}C NMR: Table **2**.

7,7′-Benzyl-bis-8-hydroxyquinoline (6)

UV λ_{max} MeOH nm: 222, 250, 322. IR (KBr) ν_{max} cm^{-1}: 3361 (OH), 3058 (NH), 3024 (CH), 1541-1508 (C=C), 1120 (C-O). HREIMS m/z: 378.1355 (M^+, calculated for, $C_{25}H_{18}N_2O_2$, 378.1360). EIMS m/z (%): 378 (71), 301 (16), 145 (33). ^1H NMR: Table **1**, ^{13}C NMR: Table **2**.

7,7′-4-Isopropylbenzyl-bis-8-hydroxyquinoline (7)

UV λ_{max} MeOH nm: 222, 248. IR (KBr) ν_{max} cm^{-1}: 3359 (OH), 3038 (NH), 3021 (CH), 2958 (aliphatic CH),

1600-1595 (C=C), 1120 (C-O). HREIMS m/z: 420.1800 (M^+, calculated for, $C_{28}H_{24}N_2O_2$, 420.1839). EIMS m/z (%): 420 (32), 377 (2), 276 (33), 145 (14). ^{1}H NMR: Table **1**.

7,7′-Methylene-(3″-indolyl)-bis-8-hydroxyquinoline (**8**)

UV λ_{max} MeOH nm: 222, 248. IR (KBr) v_{max} cm^{-1}: 3392 (OH), 3012 (NH), 3010 (CH), 1649-1541 (C=C), 1342 (C-N). HREIMS m/z: 417.1477 (M^+, calculated for, $C_{27}H_{19}N_3O_2$, 417.1478). EIMS m/z (%): 417 (100), 400 (4), 273 (20), 145 (16). ^{1}H NMR: Table **1**, ^{13}C NMR: Table **2**.

2-methoxy-5-nitro-N-(benzylidine)-2′-hydroxy aniline (**9**)

UV λ_{max} MeOH nm: 229, 283. IR (KBr) v_{max} cm^{-1}: 3301 (OH), 3076 (CH), 1616 (C=N), 1580-1533 (C=C). HREIMS m/z: 272.0812 (M^+, calculated for, $C_{14}H_{12}N_2O_4$, 272.0798). EIMS m/z (%): 272 (50), 241 (7), 179 (4), 165 (52), 120 (54), 77 (70). ^{1}H NMR: Table **1**, ^{13}C NMR: Table **2**.

2-Methoxy-5-nitro-N-(benzylidine)-2′, 5′-dihydroxy aniline (**10)**

UV λ_{max} MeOH nm: 244, 288, 373. IR (KBr) v_{max} cm^{-1}: 3749 (OH), 3055 (CH), 1615 (C=N), 1577-1510 (C=C), 1269 (C-O). EIMS m/z (%): 288 (100), 241 (22), 227 (18), 198 (11), 170 (13), 154 (96), 136 (40), 135 (41), 92 (19). ^{1}H NMR: Table **1**, ^{13}C NMR: Table **2**.

2,5-Dihydroxy-N-(benzylidine) aniline (**11**)

UV λ_{max} MeOH nm: 247, 374. IR (KBr) v_{max} cm^{-1}: 3361 (OH), 3058 (CH), 1577 (C=N). HREIMS m/z: 213.0784 (M^+, calculated for, $C_{13}H_{11}NO_2$, 213.0790). EIMS m/z (%): 213 (40), 104 (11), 93 (11). ^{1}H NMR: Table **1**.

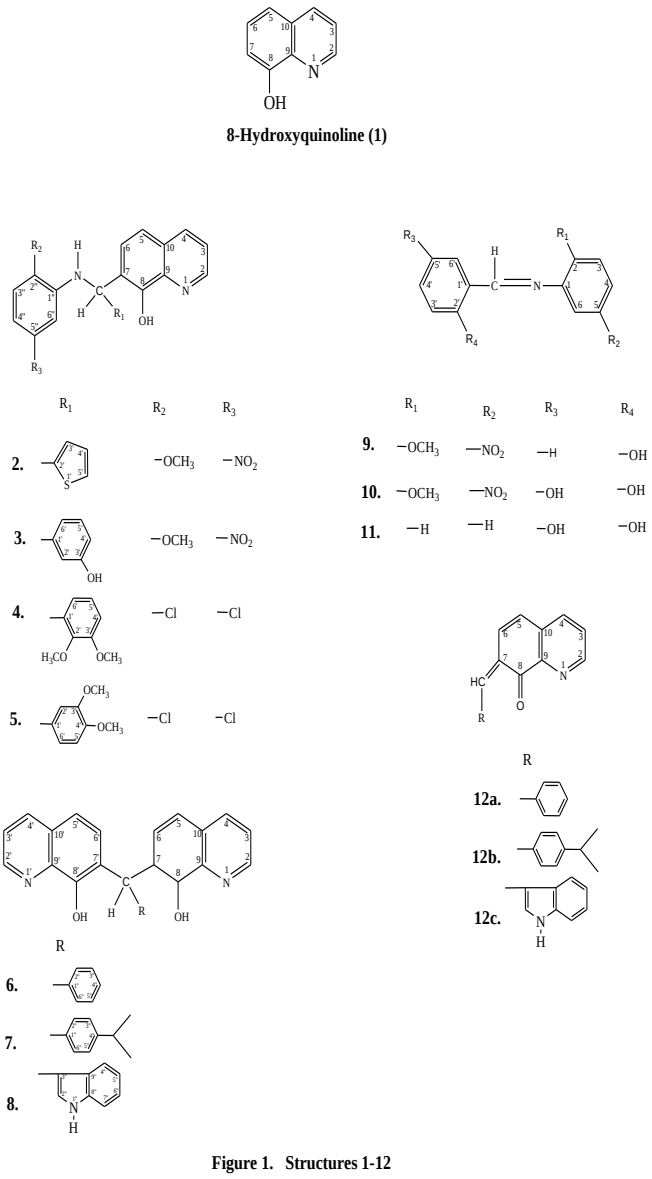

Figure 1. Structures 1-12.

RESULT AND DISCUSSION

Mannich bases (**2**-**5**) were produced by attack of 8-quinolinol (**1**) on imine (formed as a result of reaction between aniline and aromatic aldehyde) in usual manner. However, some of the reaction combinations failed to generate Mannich bases, instead they gave 8-quinolinol *derivatives* can be related to the reaction between quinone methide (12a/12b/12c) and 1 formed from corresponding unstable Mannich bases via deamination and retro Mannich reaction respectively [14,16].

NMR spectral data, particularly 2DNMR of these products revealed diagnostic and unambiguous assignments to the molecular structure. HMBC analysis of molecules altered the chemical shift values of C-9 and C-10 in 8-quinolinol moiety of Mannich bases (2-5) and bis derivatives (6 and 8). Current HMBC spectral study clearly indicated long range heteronuclear interaction of H-4 with C-10 at

138.09-138.27 in molecules 2-6 and 8 (Tables **1** and **2** are shown at the end of the article as an Annexure).

However, interaction between H-5 and C-10 was observed only in Mannich bases 4 and 5. Earlier, high frequency chemical shift was designated to C-10 and low frequency for C-9 in similar compounds [13,14].

It is noteworthy to mention that C 118.0 for C-3′ in Mannich base (2) was not observed in 1D ^{13}CNMR spectra (BB and DEPT). Its assignment is based on heteronuclear relationship between 7.39 (H-3′) and 118.0 (C-3′) in HSQC spectrum and long distant contact among 6.95 (H-4′) and 118.0 (C-3′) in HMBC plot. H-4′ in (2) resonated as a multiplet at 6.95 and resolved into doublet of doublet ($J_{4',3'}$4.3, $J_{4',5'}$ 4.1 Hz) when shaked with D_2O. H-5′ appeared as a broad singlet at 6.93 and converted into doublet ($J_{5',4'}$ 3.1 Hz) when treated with D_2O. 4″-Isopropyl substituent in *bis*-8-quinolinol (7) obviously illustrates the electron donating inductive effect and showed high field resonance at 7.08 (H-2″, 6″) and 7.02 (C-3″, 5″) in ^{1}HNMR spectrum as compared to corresponding protons at 8.19 (H-2″, 6″) and 7.24 (C-3″, 5″) in compound (6).

Among imines, 9 and 10 showed comparable chemical shifts for 2-methoxy-5-nitrophenyl imine moiety. As was not unexpected, H-4′ appeared at high resonance (6.88) in 10 than corresponding proton in 9 due to presence of heteronuclear atom at adjacent carbon. ^{1}HNMR data of 11 presented in Table **1** showed clear multiplicity pattern as compared to the literature values [17].

Table 1. ^{1}H NMR chemical shifts and their multiplicities of compounds 2-11 in $CDCl_3$.

Assignment	2[a]	3[a]	4	5	6	7	8[b]	9[a]	10[a]	11
2	8.87d (3.0)	8.85dd (4.5, 1.5)	8.73dd (4.2,1.5)	8.76dd (4.2, 1.5)	8.73dd (4.2, 1.5)	8.72m	8.77dd (4.5, 1.5)	-	-	7.34 d (8.0)
3	7.55m	7.54 m	7.38 dd (8.4, 4.2)	7.45 dd (8.4, 4.2)	7.37 dd (8.4, 4.2)	7.34 m	7.47 dd (8.5, 4.5)	7.34 d (9.0)	7.32 d (9.0)	7.48 dd (8.0,7.6)
4	8.30 d (7.2)	8.28 dd (8.5, 1.5)	8.08 dd (8.4, 1.5)	8.11 dd (8.4, 1.5)	8.09 dd (8.4, 1.5)	8.09 m	8.27 dd (8.5, 1.5)	8.21 dd (9.0,2.5)	8.19 dd (9.0,3.0)	7.42 dd (8.0,7.6)
5	7.43 m	7.54 m	7.27 d (8.7)	7.31 d (8.4)	7.30 d (8.7)	7.35m	7.35 d (8.0)	-	-	7.48 dd (8.0,7.6)
6	7.55 m	7.59 d (8.5)	7.54 d (8.7)	7.47 d (8.7)	7.59 d (8.4)	7.59 m	7.53 d (8.0)	8.29 d (2.5)	8.25 d (3.0)	7.34 d (8.0)
2′	-	6.83 s	-	6.57 d (2.4)	8.73dd (4.2, 1.5)	8.72m	8.77dd (4.5, 1.5)	-	-	-
3′	7.39br.s	-	-	-	7.37 dd (8.4, 4.2)	7.34 m	7.47 dd (8.5, 4.5)	6.96 d (8.5)	6.79 d (8.5)	7.07 dd (8.5, 1.0)
4′	6.95m	6.63 dd (8.0, 2.0)	6.84 dd (7.2, 2.4)	-	8.09 dd (8.4, 1.5)	8.09 m	8.27 dd (8.5, 1.5)	7.45dt (8.5,1.5)	6.88dd (9.0, 3.0)	7.16 dd (8.5, 1.5)
5′	6.93br.s	7.12 t (8.0)	7.01 m	6.59 m	7.30 d (8.7)	7.35m	7.35 d (8.0)	6.98ddd (8.5,7.5, 0.5)	-	-
6′	-	6.87 d(7.5)	7.01 m	6.92 dd (8.1, 7.4)	7.59 d (8.4)	7.59 m	7.53 d (8.0)	7.68dd (7.5,1.5)	7.68 d (3.0)	7.26 br.s
2″	-	-	-	-	8.19dd (8.7,2.4)	7.08 m	7.31 br.s	-	-	-
3″	7.03 d (8.4)	7.02 d (8.5)	7.13 d (8.4)	7.13 d (8.4)	7.24 dd (9.0,8.7)	7.02m	-	-	-	-
4″	7.68 d (8.4)	7.38 d (8.5)	6.54 dd (8.4, 2.4)	6.79 dd (8.4, 2.4)	7.05 dd (9.0,8.7)	-	7.51 d(6.5)	-	-	-
5″	-	-	-	-	7.24 dd (9.0,8.7)	7.02m	7.21 m	-	-	-
6″	7.37 d (2.4)	7.22d (3.0)	6.60 d (2.1)	6.99 d (1.8)	8.19dd (8.7,2.4)	7.08 m	7.25m	-	-	-
7″	-	-	-	-	-	-	7.41 d (6.0)	-	-	-
CH	6.45d* (7.8)	6.12 d* (6.4)	6.43 d* (6.6)	6.09 d* (5.4)	6.72 s	6.89 s	7.01 s	9.08 s	8.96 s	8.76 s
NH	6.12d**(7.8)	5.84 d** (6.4)	5.40 d** (6.6)	5.19 d** (5.4)	-	-	10.09 br.s**	-	-	-
2″-OCH_3	3.95s	3.95 s	3.78 s	3.83[#] s	-	-	-	-	-	-
3″- OCH_3	-	-	3.84 s	3.82[#] s	-	-	-	-	-	
8-OH	10.33**s	9.35**s	NO	NO	NO	NO	10.03s**	-	-	-
2′-OH	-	-	-	-	-	-	-	13.18s**	12.34 s**	10.45s**
5′-OH	-	-	-	-	-	-	-	-	9.13 s**	8.01s**

Coupling constants are given in parentheses.
*[a]Solvent $(CD_3)_2SO$, [b]Solvent$(CD_3)_2CO$,*Changed to singlet when shaked with D_2O; ** Disappeared when shaked with D_2O; [#] Exchangeable; NO: Not observed; **7**CH $(CH_3)_2$, □□2.86m;CH $(CH_3)_2$, □ 1.19 d (6.9); **9** 2-OCH_3 □ 3.99s; **10** 2-OCH_3 □ 3.94s.*

Table 2. ^{13}CNMR chemical shifts of compounds 2-10 in $CDCl_3$.

Assignments	2[a]	3[a]	4	5	6	8[b]	9[a]	10[a]
1	-	-	-	-	-	-	137.23	137.74
2	148.45	148.36	148.14	148.22	147.92	148.42	157.94	157.96
3	122.06	121.86	121.77	121.94	121.41	122.68	112.19	112.13
4	136.15	136.03	136.07	136.05	135.88	136.93	123.64	123.51
5	113.73	113.21	117.78	118.19	117.25	118.04	140.94	140.95
6	126.32	126.42	126.93	126.89	128.48	122.99	114.53	114.53
7	123.36	123.77	122.95	122.88	124.75	123.49	-	-
8	152.12	151.89	**152.92**	154.52	151.10	149.62	-	-
9	128.06	127.69	127.80	127.74	129.11	127.05	-	-
10	138.20	138.09	138.23	138.21	138.18	139.78	-	-
1′	-	137.22	134.73	133.90	-	-	119.22	119.22
2′	117.74	113.82	147.00	117.41	147.92	148.42	160.56	153.43
3′	*118.00	157.45	149.**40**	148.48	121.41	122.68	116.70	117.32
4′	126.92	114.16	112.16	149.06	135.88	136.93	133.78	121.79
5′	125.31	129.54	120.02	112.40	117.25	118.04	119.10	149.57
6′	-	117.62	124.02	119.13	128.48	122.99	132.76	117.32
7′	-	-	-	-	124.75	123.49	-	-
8′	-	-	-	-	151.10	149.62	-	-
9′	-	-	-	-	129.11	127.05	-	-
10′	-	-	-	-	138.18	139.78	-	-
1″	141.37	141.37	144.00	143.99	142.81	-	-	-
2″	136.85	149.98	117.45	116.93	128.31	129.67	-	-
3″	109.27	109.01	129.65	129.58	129.54	117.56	-	-
4″	126.92	117.70	117.13	111.23	126.56	122.21	-	-
5″	145.92	143.14	133.59	129.57	129.54	119.99	-	-
6″	103.90	103.48	112.10	110.59	128.31	122.52	-	-
7″	-	-	-	-	-	112.94	-	-
8″	-	-	-	-	-	138.27	-	-
9″	-	-	-	-	-	137.89	-	-
CH	51.30	55.05	51.94	55.93	45.02	37.21	165.18	164.88

Not observed in ^{13}CNMR; [a]Solvent $(CD_3)_2SO$, [b]Solvent $(CD_3)_2CO$, **2, 2″-OCH_3 δ 56.49; **3,** 2″-OCH_3 δ 56.39; **4,** 2′-OCH_3 δ 60.73, 3′-OCH_3 δ 55.79; **5,** 3′-OCH_3 δ 55.93, 4′-OCH_3 δ 55.88; **9,** 2-OCH_3 δ 56.85; **10,** 2-OCH_3 δ 56.83.*

CONCLUSION

Several new compounds comprising amine and 8-Quinolinol (8-HQ) have been generated under Mannich reaction condition without any catalyst. Revised spectral values and new spectral data may serve as a reference for similar compounds. Further study on pharmacology of these small molecules may refurbish them as a key for modern drug discovery.

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