Synthesis, spectral and microbial studies of some novel quinoline derivatives *via* Vilsmeier–Haack reagent

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Abstract

Novel symmetric double quinoline derivatives were synthesized using the Vilsmeier–Haack reagent and symmetric double acetamides of 1,1'-bis(*R*,4-aminophenyl)cyclohexane/methane. The structure of the intermediates (SDA-1 to SDA-3) and final products (SDQ-1 to SDQ-3) were supported by UV, FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopic measurements. Compounds SDA-1 to SDA-3 and SDQ-1 to SDQ-3 possess moderate to good antibacterial and antifungal activities.

Keywords: Vilsmeier-Haack reagent, quinoline derivatives, spectral analysis, biological activity

Introduction

Quinolines and their derivatives are important constituents of several pharmacologically active synthetic compounds,[1-3] including biological activities such as DNA binding capability,[4] antitumor,[5,6] and DNA-intercalating carrier.[7] The development of general methods for the synthesis and biological evaluation of new agents retaining the 'core' quinoline moiety is the subject of considerable synthetic effort. Certain small heterocyclic molecules act as highly functional scaffolds and are known as pharmacophores of a number of biologically active and medicinally useful molecules.[8]

The Vilsmeier–Haack reagent is an efficient, economical and mild reagent for the formylation of reactive aromatic and heteroaromatic substrates.[9-10] The use of Vilsmeier–Haack reactions has led to novel and convenient routes for the synthesis of various heterocyclic compounds and its importance in various synthetic methodologies[11-15] including microwave chemistry[16-20] is remarkable and inspiring.

The classical Vilsmeier–Haack reaction involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt to yield the corresponding iminium species. The present work deals with the synthesis of novel quinoline derivatives *via* the Vilsmeier–Haack reagent with the prospect of incorporating diverse bioactive heterocyclic nuclei, intact, for

evaluating antibacterial and antifungal significance and also as a reagent for effecting functional group interconversion.[21-25]

Results and Discussion

The Vilsmeier–Haack reagent facilitated formylation of SDQ-1 to SDQ-3 using phosphorus oxychloride and dimethylformamide, at 85 °C for 9-13 h giving yields of 69% or better of novel quinoline derivatives. [26,27] Comparative analytical data of SDA-1 to SDA-3 and SDQ-1 to SDQ-3 are reported in Table 1. The products were purified through column using chloroform: methanol (90:10 v/v). The final purity of the compounds was checked by TLC using an appropriate solvent system.

Spectral analysis

UV spectra of SDA-1 to SDA-3 and SDQ-1 to SDQ-3 were scanned at room temperature using 1, 4-dioxane as a solvent. Wavelength of maximum absorption (λ_{max}) of all the compounds are reported in Table 2 from which it is observed that a considerable change is observed in case of SDA-2 and SDQ-2 probably due to methyl substitution in the aromatic ring.

IR spectra of SDA-1 to SDA-3 and SDQ-1 to SDQ-3 were scanned over the frequency range of 4000-400 cm^{-1}. The characteristic absorption frequencies are reported in Table 3.

The absorption bands due to C=O stretching, N-H stretching and bending vibration and C-N stretching of amide group of SDA-1 to SDA-3 are observed in the frequency range of 1667-1653, 3306-3295, 1537-1510 and 1319-1306 cm^{-1}, respectively, while absorption bands due to C=O stretching of the CHO group, C=N and C-N stretching of quinoline ring and C-Cl stretching of SDQ-1 to SDQ-3 are observed in the frequency range of 1696-1694, 1580-1576, 1341-1335 and 753-716 cm^{-1}, respectively. Thus, disappearance of absorption bands due to amide group and appearance of new bands due to quinoline ring confirmed cyclization reaction of SDA-1 to SDA-3.

^{1}H NMR chemical shifts (ppm), coupling constants (*J*) and types of protons of SDA-1 to SDA-3 and SDQ-1 to SDQ-3 are reported in Table 4 along with predicted chemical shift values. $^{1}HNMR$ spectra of SDA-III and SDQ-III were not measured. The peak due to residual $CHCl_3$ is observed at about 7.26 ppm either as a separate peak or overlapped with aromatic proton signals. ^{13}C NMR chemical shifts (ppm) and types of carbon atoms of SDA-1 to SDA-3 and SDQ-1 to SDQ-3 are reported in Table 5. The molecular ion peaks were low in abundance. Important fragments ions of SDA-1 to SDA-3 are recorded in Table 6.

Table 1. Analytical data of SDA-1 to SDA-3 and SDQ-1 to SDQ-3

Code	R	M.F.	M.W.	M.p °C	Color	TLC data		Time, h	Yield, %
						Solvent system	R_f value		
SDA-1	H	$C_{22}H_{26}N_2O_2$	350	116	Off white	CF : MeOH (90:10 v/v)	0.74	2.5	78.5
SDA-2	CH_3	$C_{24}H_{30}N_2O_2$	378	240	Off white	CF : MeOH (90:10 v/v)	0.68	2.0	81.4
SDA-3	H	$C_{17}H_{18}N_2O_2$	282	131	Off white	Hex.:EA (70:30 v/v)	0.70	3.0	84.8
SDQ-1	H	$C_{26}H_{20}N_2O_2Cl_2$	463	170	Yellow	CF : MeOH (90:10 v/v)	0.65	10.5	71.4
SDQ-2	CH_3	$C_{28}H_{24}N_2O_2Cl_2$	491	213	Yellow	CF : MeOH (90:10 v/v)	0.58	12.5	68.8
SDQ-3	H	$C_{23}H_{16}N_2O_2Cl_2$	422	154	Orange	Hex.:EA (70:30 v/v)	0.63	9.5	74.2

CF: Chloroform, MeOH: Methanol, EA: Ethyl acetate, Hex. : Hexane

Table 2. UV spectral data (1,4-dioxane) of SDA-1 to SDA-3 and SDQ-1 to SDQ-3

Code	SDA-1	SDA-2	SDA-3	SDQ-1	SDQ-2	SDQ-3
λ_{max}, nm	253.4 221.0	246.2 220.6	255.2 221.2	253.2 299.4	263.8 254.3 221.2	256.0 302.5

Table 3. Characteristic IR absorption frequencies of SDA-1 to SDA-3 and SDQ-1 to SDQ-3

Code	IR absorption Frequencies, cm^{-1}				Code	IR absorption Frequencies, cm^{-1}			
	N-H str.	C=O str.	N-H ipd	C-N str.		C=O (CHO) str.	C=N str.	C-N str.	C-Cl str.
SDA-1	3304	1663	1533 1510	1318	SDQ-1	1695	1575	1334	752
SDA-2	3294	1666	1518	1305	SDQ-2	1695	1579	1340	715
SDA-3	3306	1653	1537 1514	1317	SDQ-3	1693	1577	1334	735

Table 4. ^{1}H NMR chemical shift (ppm) and coupling constant data of SDA-1 to SDA-3 and SDQ-1 to SDQ-3

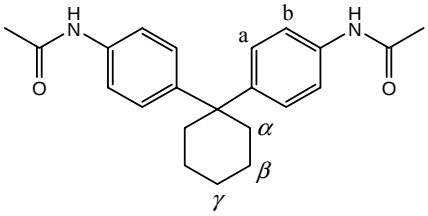
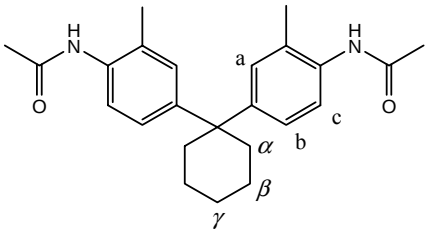
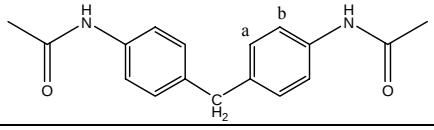
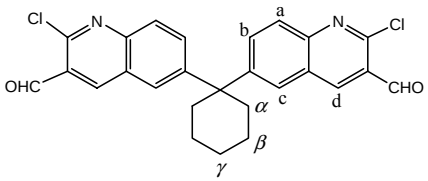
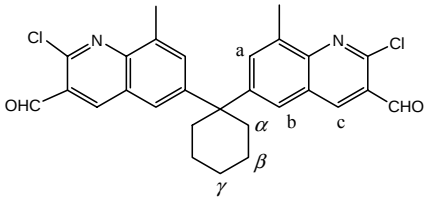
Code	Structure	Chemical shifts, δppm {predicted values}
SDA-1 (d_6-DMSO)		1.47-1.52 [d, 6H, β + γ –CH_2–], 2.02 [s, 6H, -CH_3], 2.21 [s, 4H, α , -CH_2-], 7.14-7.16 [d, 4H, Ar-H(a), *J_{ab}=8.7*], 7.44-7.46 [d, 4H, Ar-H(b), *J_{ba}=8.7*], 9.41 [s, 2H, -NH] {1.44 [6H, β + γ –CH_2–], 2.02 [6H, -CH_3 + 4H, α , -CH_2-], 7.11 [4H, Ar-H(a)], 7.56 [4H, Ar-H(b)], 8.0 [2H, -NH]}
SDA-2 ($CDCl_3$)		1.47-1.53 [d, 6H, β + γ –CH_2–], 2.10-2.22 [m, 16H, α ,-CH_2- + Ar-CH_3 + -CH_3], 7.04 [s, 2H, -NH] 7.09-7.11 [m, 4H, Ar-H(a+b) *J_{ab}=1.6, J_{ba}=7.6*], 7.54-7.56 [d, 2H, Ar-H(c) *J_{cb}=8.4*] {1.44[6H, β + γ –CH_2–], 2.02 [6H, -CH_3 + 4H, α , -CH_2-], 2.35 [6H, Ar-CH_3], 6.91 [2H, Ar-H(a)], 6.92 [2H, Ar-H(b), 7.44 [2H, Ar-H(c)], 8.0 [2H, -NH]}
SDA-3		{2.02 [6H, -CH_3], 3.81 [2H, -CH_2-], 7.04 [4H, Ar-H(a)], 7.52 [4H, Ar-H(b)] 8.0 [2H, -NH]}
SDQ-1 (d_6-DMSO)		1.66-1.67 [d, 6H, β + γ ,–CH_2–], 2.52 [s, 4H, α -CH_2-], 7.78-7.79 [d-d, 2H, Ar-H(b) J_{ba}=8.9, *J_{bc}=2*], 7.88-7.91 [d, 2H, Ar-H(a) *J_{ab}=8.8*)], 8.09-8.09 [d, 2H, Ar-H(c) *J_{cb}=1.6*], 8.79 [s, 2H, Ar-H(d)], 10.49 [s, 2H, Ar-CHO] {1.44 [6H, β + γ ,–CH_2–], 2.02 [4H, α -CH_2-], 7.47 [4H, Ar-H(b)=Ar-H(c)], 7.99 [2H, Ar-H(a)] 8.68 [2H, Ar-H(d)], 9.61 [2H, Ar-CHO]}
SDQ-2 ($CDCl_3$)		1.57-1.66 [d, 6H, β + γ, –CH_2–], 2.17-2.71 [m, 10H, α -CH_2- + -CH_3], 7.16 [s, 2H, Ar-H(a)], 7.58 [s, 2H, Ar-H(b)], 8.70 [s, 2H, Ar-H(c)], 10.54 [s, 2H, Ar-CHO] {1.44 [6H, β + γ ,–CH_2–], 2.02 [4H, α -CH_2-], 2.35 [6H, Ar-CH_3], 7.25 [2H, Ar-H(a)], 7.31 [2H, Ar-H(b)], 8.65 [2H, Ar-H(c)], 9.61 [2H, Ar-CHO]}

Table 4. Continued

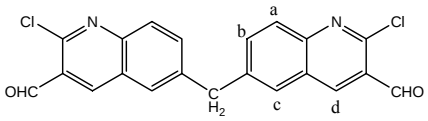
SDQ-3		{3.81 [2H, -CH_2-], 7.47 [4H, Ar-H(b)=Ar-H(c)], 7.99 [2H, Ar-H(a)], 8.68 [2H, Ar-H(d)], 9.61 [2H, Ar-CHO]}

Table 5. ^{13}C NMR chemical shifts of SDA-1 to SDA-3 and SDQ-1 to SDQ-3

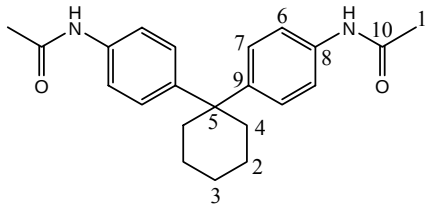
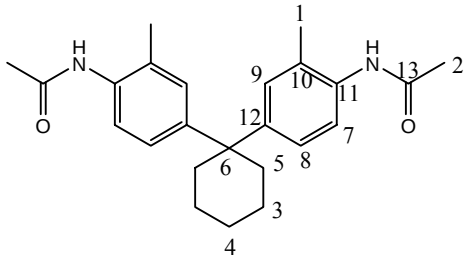
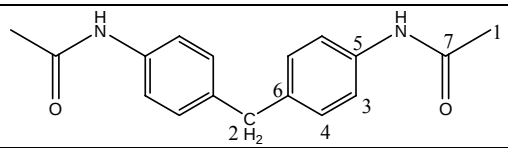
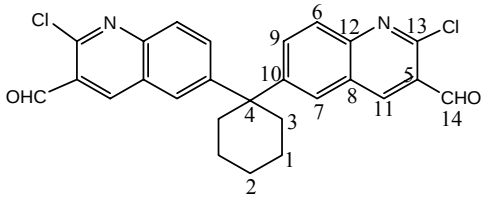
Code	Structure	Chemical shift, ppm
SDA-1 (d_6-DMSO & $CDCl_3$)		22.4 (C_1), 23.7 (C_2), 25.8 (C_3), 36.4 (C_4), 40.7 (C_5), 119.0 (C_6), 126.7 (C_7), 136.1 (C_8), 143.1 (C_9), 168.2 (C_{10}) {22.9 (C_1), 22.8 (C_2), 28.6 (C_3), 39.7 (C_4), 39.7 (C_5), 122.1 (C_6), 128.5 (C_7), 136.0 (C_8), 141.7 (C_9), 168.9 (C_{10})}
SDA-2 ($CDCl_3$)		18.2 (C_1), 22.8 (C_2), 23.8 (C_3), 26.3 (C_4), 36.9 (C_5), 45.3 (C_6), 123.9 (C_7), 125.1 (C_8), 129.1 (C_9), 130.1 (C_{10}), 132.9 (C_{11}), 145.7 (C_{12}), 169.0 (C_{13}) {15.5 (C_1), 22.9 (C_2), 22.8 (C_3), 28.6 (C_4), 39.7 (C_5), 40.3 (C_6), 122.0 (C_7), 125.5 (C_8), 130.3 (C_9), 134.8 (C_{10}), 134.9 (C_{11}), 141.6 (C_{12}), 168.9 (C_{13})}
SDA-3		{17.6 (C_1), 41.3 (C_2), 120.9 (C_3), 128.6 (C_4), 138.3 (C_5), 138.6 (C_6), 168.2 (C_7)}
SDQ-1 ($CDCl_3$)		22.7 (C_1), 26.0 (C_2), 36.8 (C_3), 46.8 (C_4), 126.5 (C_5), 126.5 (C_6), 127.0 (C_7), 128.8 (C_8), 133.8 (C_9), 140.3 (C_{10}), 147.5 (C_{11}), 148.2 (C_{12}), 150.1 (C_{13}), 189.1 (C_{14}) {22.8 (C_1), 28.6 (C_2), 39.7 (C_3), 40.5 (C_4), 126.3 (C_5), 126.8 (C_6), 128.2 (C_7), 128.9 (C_8), 135.4 (C_9), 136.7 (C_{10}), 142.9 (C_{11}), 144.2 (C_{12}), 147.6 (C_{13}), 191.0 (C_{14})}

Table 5. Continued

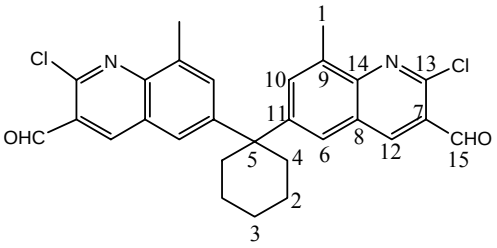
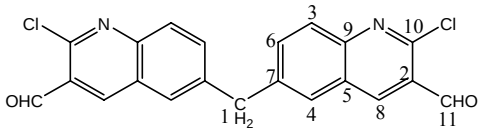
SDQ-2 (d_6-DMSO & $CDCl_3$)		17.5 (C_1), 22.2 (C_2), 25.5 (C_3), 36.1 (C_4), 45.9 (C_5), 124.5 (C_6), 125.6 (C_7), 126.0 (C_8), 133.3 (C_{9+10}), 136.3 (C_{11}), 140.2 (C_{12}), 146.9 (C_{13}), 147.9 (C_{14}), 188.8 (C_{15}) { 20.2 (C_1), 22.8 (C_2), 28.6 (C_3), 39.7 (C_4), 41.1 (C_5), 126.4 (C_6), 125.6 (C_7), 128.7 (C_8), 134.9 (C_9), 135.8 (C_{10}), 137.3 (C_{11}), 143.2 (C_{12}), 147.1 (C_{13}), 152.1 (C_{14}), 191.0 (C_{15})}
SDQ-3		{42.1 (C_1), 127.0 (C_2), 127.9 (C_3), 128.4 (C_4), 129.3 (C_5), 135.2 (C_6), 136.7 (C_7), 142.8 (C_8), 145.4 (C_9), 151.0 (C_{10}), 190 (C_{11})}

Table 6. Important mass fragments of SDA-1 to SDA-3

Code	m/e
SDA-1	351, 350, 349, 308, 307, 281, 265, 223, 195, 172, 148, 130, 106, 93, 77, 43
SDA-2	379, 378, 363, 336, 335, 309, 293, 223, 186, 144, 130, 120, 106, 91, 77, 43
SDA-3	283, 282, 240, 239, 198, 197, 182, 181, 180, 106, 93, 77, 43

Antimicrobial activity

The zones of inhibition (mm) at various dilutions for standard drugs and samples after correction due to solvent are reported in Table 7 from which it is observed that as compared to standard drugs, the compounds possess moderate to good antibacterial activity and antifungal activity. It is interesting to note that methyl substitution and a methylene bridge caused reduction in the biological activity especially antifungal activity. SDQ-1 to SDQ-3 are some what more biologically active than SDA-1 to SDA-3.

Table 7. Biological activity of standard drugs and SDA-1 to SDA-3 and SDQ-1 to SDQ-3

Code	Bacteria								Fungi			
	E. coli				S. aureus				A.niger			
	0.1%	0.2%	0.3%	0.4%	0.1%	0.2%	0.3%	0.4%	0.1%	0.2%	0.3%	0.4%
SDA-1	3	5	6	11	4	7	12	18	5	9	13	22
SDA-2	2	2	5	10	2	6	10	15	2	5	9	15
SDA-3	2	2	4	9	3	5	7	13	2	4	8	9
SDQ-1	4	6	7	14	5	9	14	21	7	10	14	23
SDQ-2	3	4	7	12	4	7	11	19	5	7	10	13
SDQ-3	2	3	6	10	3	6	9	17	4	6	10	12
C1	4	7	9	15	6	10	15	22				
C2	2	5	7	13	3	8	12	20				
C3									8	12	19	25
C4									7	10	18	24

C1: Ciprofloxacine
C2: Cephalexin
C3: Gentamicine
C4: Griseofulvin

Conclusions

Symmetric diamines were cyclized via Vilsmeier–Haack reagent to give corresponding derivatives. The structures of the starting and end materials were supported by spectroscopic techniques. They possess moderate to good antibacterial and antifungal activities. Methyl side substituents or a methylene bridge caused lowering in the said activities.

Experimental Section

General Procedures. Solvents and chemicals used in the present investigation were of LR grade and used either as such or purified by fractional distillation. Symmetric diamines (I) were synthesized and recrystallized according to our recent work.[28] Melting points were determined in open capillary tubes and were uncorrected. Purity of the compounds was checked by TLC and column by using chloroform: methanol (90:10 v/v) system. IR spectra (KBr pellets) were scanned on a Shimadzu FTIR- 8400 spectrophotometer. The NMR spectra were scanned on a Brucker FTNMR (Avance II 400 MHz) spectrophotometer by using d_6-DMSO (SDA-1 and SDQ-1) or $CDCl_3$ (SDA-2 and SDQ-2) as a solvent and TMS as an internal standard. ^{13}CNMR

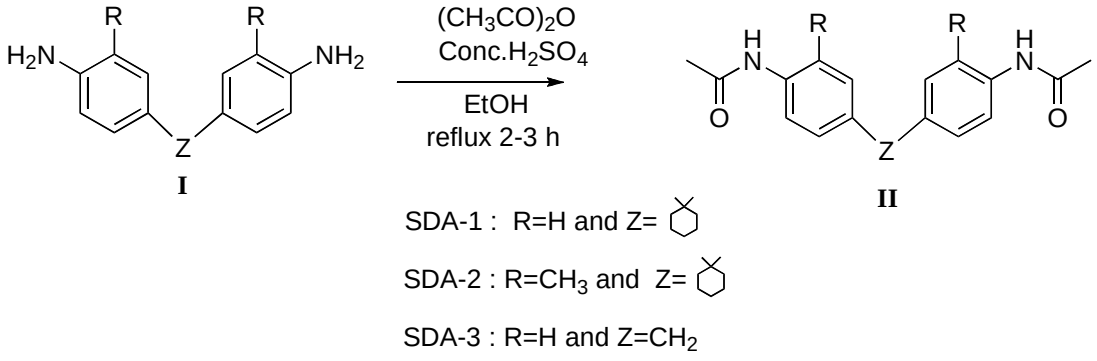
spectra were scanned in the mixture of d_6-DMSO+ $CDCl_3$ (SDA-1 and SDQ-2) or $CDCl_3$ (SDA-2 and SDQ-1). Mass spectra were measured on a Shimadzu GC-MS-QP 2010 by using E.I. (0.7 kV) detector. The ion source temperature was at 220 ^oC and interface temperature was 240 ^oC.

Antimicrobial activity

Antibacterial and antifungal activities of the compounds were assessed by *in vitro* growth inhibitory activity against *Escherichia coli, Staphylococcus aureus and Aspergillus niger* by using the disc diffusion method.[29,30] The bacteria were cultured in nutrient agar medium and used as inoculum for this study. Bacterial cells were swabbed on to nutrient agar medium [prepared from NaCl (5.0 g), peptone (5.0 g), beef extract powder (3.0 g), yeast extract powder (3.0 g), Agar (20.0 g) in 100 ml distilled water; pH = 7.5 ± 0.2)] in petri plates. The fungi was cultured in potato dextrose agar medium (prepared from potato 150 g; dextrose 5 g and agar 2 g in 200 ml distilled water) was poured in sterilized petriplates and allowed to solidify. The plates were inoculated with a spore suspension of *A. niger* (10^6 spores/ml of medium). The compounds to be tested were dissolved in DMF to final concentrations (weight/volume) of 0.1%, 0.2% 0.3% and 0.4% and soaked in filter paper (Whatman No 4) discs of 6 mm diameter and 1 mm thickness. The discs were placed on the already bacterial and fungal seeded plates and incubated at 35 ± 2 °C for 24 h and 28 ± 2 °C for 4 days, respectively. Ciprofloxacine and Cephalexin were used as standard antibacterial drugs, while Gentamicine and Griseofulvin were used as standard antifungal drugs. The inhibition zones were measured after subtracting inhibition due to solvent used.

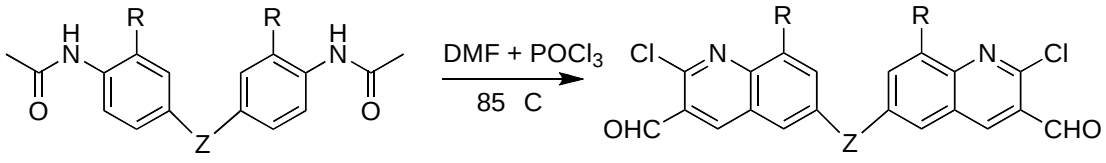
Synthesis of symmetric double acetamides (SDA-1 to SDQ-3)

Acetic anhydride (0.02 mol) was added dropwise to a 250 ml round bottomed flask containing 0.01 mol diamine (I) in 20 ml ethanol and 0.1 ml concentrated sulfuric acid and the mixture refluxed for 2-3 h. The progress of the reaction was monitored by TLC. The solvent was distilled off and product was isolated from water, filtered, washed well with distilled water and dried at 50 °C. SDA-1 to SDA-3 were recrystallized at least three times from an appropriate solvent system. Analytical data for SDA-1 to SDA-3 are reported in Table 1.



Synthesis of quinoline derivatives *via* Vilsmeier–Haack reagent

In order to synthesize quinoline derivatives (III), Vilsmeier–Haack reagent (0.05 mol) was prepared by reacting 32.5 ml phosphorus oxychloride and 9.2 ml dimethylformamide at 0-5 °C.[27] Thus, 0.05 mol Vilsmeier–Haack reagent and 0.025 mol corresponding SDA-1 to SDA-3 were reacted with stirring at 85 °C for 9-13 h. The progress of the reaction was monitored by TLC. The product was isolated from chilled water, filtered, washed well with water and dried at 50 °C. SDQ-1 to SDQ-3 were recrystallized at least three times from ethyl acetate. Analytical data for SDQ-1 to SDQ-3 are reported in Table 2.



II **III**

SDQ-1 : R=H, Z=

SDQ-2 : R=CH_3, Z=

SDQ-3 : R=H, Z=CH_2

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