Synthesis of Novel Quinoline Analogues of Nimesulide: An Unusual Observation

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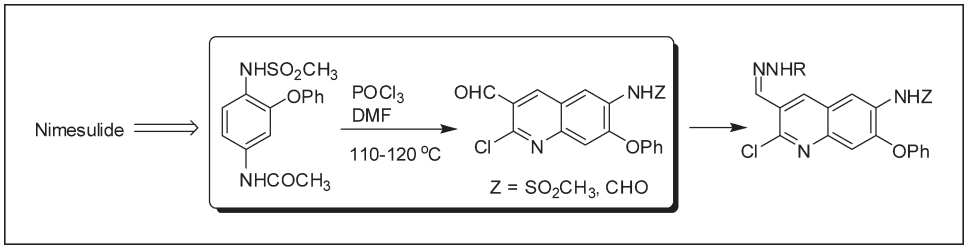

Reduction of nimesulide followed by treating the *N*-acyl derivative of resulting arylamine with Vilsmeier-Haack reagent provided novel 2-chloro-3-formylquinoline derivatives. The construction of quinoline ring using Vilsmeier-Haack reagent afforded an unexpected compound, *N*-(2-chloro-3-formyl-7-phenoxy quinolin-6-yl)formamide, in addition to the expected product. The structure of this unexpected quinoline derivative was established via single-crystal X-ray analysis and its formation could be explained by an unprecedented N-S bond cleavage under Vilsmeier-Haack reaction conditions. The 2-chloro-3-formylquinoline derivatives obtained were converted to a number of corresponding Schiff bases with potential pharmacological importance.

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INTRODUCTION

Nimesulide, a preferential COX-2 inhibitor, is a non-carboxylic acid nonsteroidal anti-inflammatory drug (NSAID) that has been in clinical use for treatment of pain for more than 20 years [1]. Several derivatives of nimesulide have shown antiviral, anticancer [2] and COX-2 inhibiting [3] properties. 2-Chloroquinoline derivatives, on the other hand, have shown a range of biological activities [4,5]. Thus combining nimesulide with 2-chloroquinoline in a single molecule would provide new chemical entities of potential pharmacological interest (Fig. 1). In continuation to our interest in the synthesis and biological activity of nimesulide derivatives [6], we decided to prepare a series of novel molecules **A** for *in vitro* pharmacological studies. Herein, we report for the first time the synthesis of a series of hybrid molecules structurally related to both nimesulide and 2-chloroquinoline.

Although different methods have been reported [7] for the construction of a quinoline ring, the approach of employing an aromatic primary amine i.e., C—C—N unit as the nucleophilic nitrogen donating component and an electrophilic three carbon unit, usually carbonyl compounds, is of particular interest. For example, most of the classical routes to quinoline e.g., Skraup, Doebner-von Miller, Combes and Conrad-Limpach syntheses are based on this strategy. We anticipated that this strategy would be beneficial in our study because the required aniline component could be readily prepared. However, to construct the quinoline ring possessing the desired functional groups we opted for the Vilsmeier-Haack cyclization of acetanilides leading to the 2-chloro-3-formylquinoline derivatives [8,9]. Our interest in 2-chloro-3-formylquinoline moiety stem from the fact that it can be utilized for further [*b*]-annelation to afford a wide variety of rings and for various functional group inter conversions. Our synthesis of novel quinoline analogues structurally related to nimesulide is shown in Scheme 1.

RESULTS AND DISCUSSION

The nimesulide was converted to the corresponding aromatic amine via reduction of its nitro group following a known procedure [6]. The primary amine was then converted to the corresponding *N*-acetyl derivative **1,**

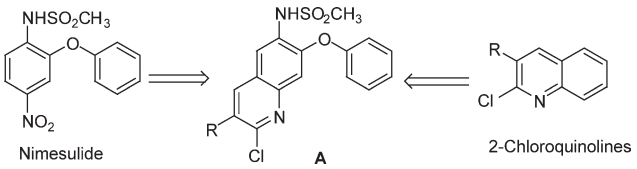


Figure 1. Design of novel molecules based on nimesulide and 2-chloroquinolines.

which upon treatment with the Vilsmeier-Haack reagent ($POCl_3$ /DMF) afforded the desired product **2** along with another product **3** (Scheme 1). In a typical procedure, compound **1** (1.0 equiv) in DMF (3.3 equiv) was treated with $POCl_3$ (6.6 equiv) under nitrogen at 110–120°C for 4 h. After usual workup and purification by column chromatography two quinoline derivatives i.e., compounds **2** and **3** were isolated in 85% overall yield (approximate ratio 1:1). Based on the analysis of their spectral data (NMR, IR and MS) generated (for ^{1}H NMR, see Fig. 2), the compound **2** was identified as *N*-(2-chloro-3-formyl-7-phenoxyquinolin-6-yl)methanesulfonamide and the compound **3** as *N*-(2-chloro-3-formyl-7-phenoxy quinolin-6-yl)formamide. Since the formation of compound **3** was unusual we decided to conduct further studies on this reaction. To prepare compound **3** as the sole product we carried out the reaction of **1** with $POCl_3$/DMF at room temperature and at a higher temperature i.e., 140–145°C in addition to that at 110–120°C as described earlier. The reaction did not proceed at room temperature (or at other temperature below 100°C), whereas both products i.e., **2** and **3,** were isolated in 1:1 ratio with 50% overall yield when the reaction was conducted at 140–145°C. Moreover, a tar like material was isolated while conducting the reaction 140–145°C thereby reducing the overall yield of compounds **2** and **3**. Thus the optimum temperature was found to be 110–120°C. In a separate study, the progress of this reaction with time was closely monitored by maintaining the reaction temperature at 110–120°C. Initially, compound **2** was formed as indicated by TLC, but subsequent formation of **3** was observed as the reaction progressed further. Notably, the reaction did not proceed further after completing 4 h when a mixture of **2** and **3** was formed in 1:1 ratio. This experiment though remained inconclusive suggested that compound **3** was perhaps formed via **2** instead of directly from **1**.

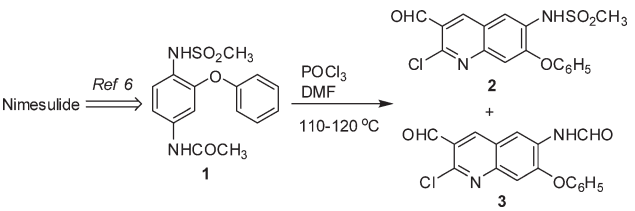
The compound **3** was characterized by spectral data and its structure was confirmed unambiguously via single-crystal X-ray analysis [10]. Intensity data of **3** were collected at Daresbury Laboratory (station 9.8) using a Bruker SMART CCD area detector using silicon monochromated synchrotron radiation ($\lambda = 0.6945$ Å) at 150(2) K using φ and ω scan method. The crystal was twinned via a 180° rotation about the [100] direction and the correct unit cell was found by the program CELL_NOW [11] using 1023 reflections in the θ angular range of 2.77–25.73°. Data were corrected for Lp and absorption effects. The structure was solved by direct methods and refined by full-matrix least-squares technique on F^2 using SHELXS-97 and SHELXL-97 [12]. Hydrogen atoms were located from difference Fourier maps and refined without any restraint.

An ORTEP diagram [13] of molecule **3** with atom numbering scheme is shown in Figure 3. The bond distances and angles are consistent with the reported values for other chloroquinoline derivatives [14–18]. The 2-chloroquinoline ring is essentially planar with a maximum deviation of 0.024(1) Å of C9 atom from the least-squares plane through the remaining nonhydrogen atoms. The dihedral angle between the planes of quinoline [C1-C9, N1] and phenyl [C10-C15] rings is 77.7(1)°.

In the quinoline fragment of **3**, the C—C bond lengths (C5-C6, C2-C3, and C1-C9) and C—N bond distances (C8-N1 and C7-N1) (Table 1) are shorter and the remaining bond distances are longer than the mean value of aromatic C-C bond length of 1.387 Å [19]. Such features are reported also for other quinoline containing structures [20–25]. The formamide group is planer and the planarity of the formamide group is provided by the delocalization of lone pair of O2 and N2 atoms, which results in a shortening of C16-O2 [1.213(2) Å] and N2-C16 [1.357(2) Å] bond lengths than the average values reported in the literature. The extended conformation of the formamide group is established by the torsion angles C1-C2-N2-C16 [170.8(2)°] and C2-N2-C16-O2 [0.2(3)°].

Molecular packing of compound **3** is stabilized by N—H...O and C—H...O hydrogen bonding. In compound **3**, a pair of intermolecular C—H...O hydrogen bonds between centrosymmetrically related molecules involving the quinoline C5 atom in the molecule at (x, y, z) and formamide atom O2 in the molecule at (1-x, 1-y, 2-z) generates an R_2^2 (16) dimeric ring centred at ($^1/_2$, $^1/_2$, 1) [Fig. 4(a)]. Propagation of these R_2^2 (16) rings along the [010] direction forms a C(9) chain [Fig. 4(b)]

Scheme 1. Preparation of novel 2-chloro-3-formylquinoline derivatives from nimesulide.



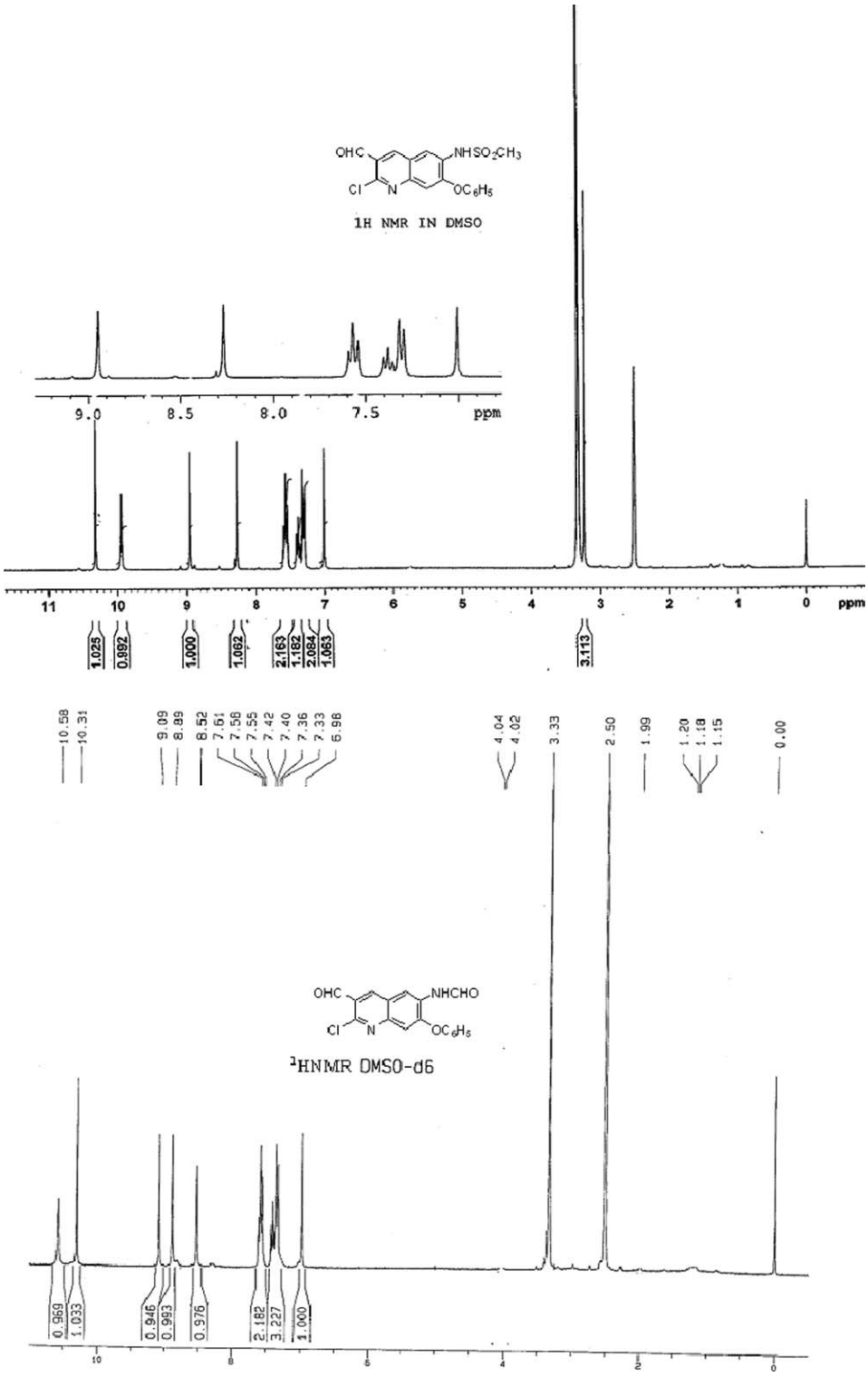


Figure 2. ^{1}H NMR (300 MHz) of compound **2** and **3** in DMSO-d_6.

via another type of intermolecular N—H. . .O hydrogen bond between formamide N2 atom and aldehyde O3 atom (Table 2).

The generation of *N*-(2-chloro-3-formyl-7-phenoxyquinolin-6-yl) methanesulfonamide (**2**) can be explained mechanistically by the well documented synthesis of

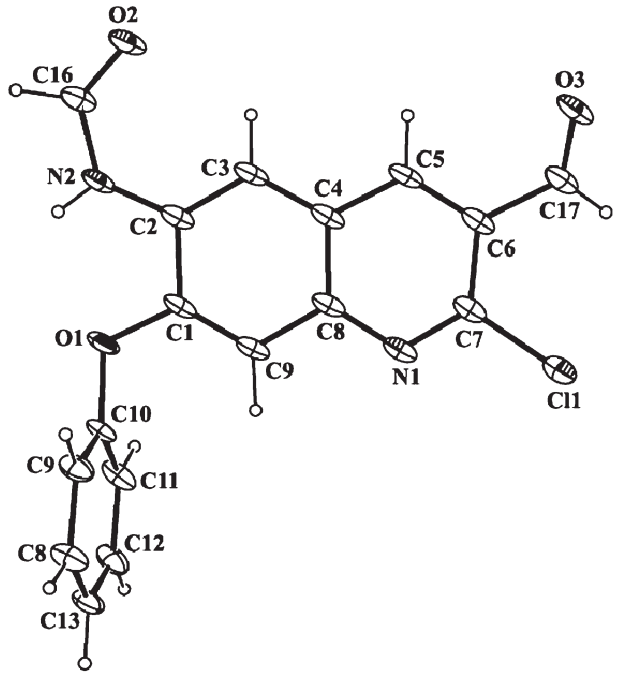


Figure 3. An ORTEP view of molecule **3** with atom-labeling scheme. Displacement ellipsoids are drawn at 40% probability level and the H-atoms are shown as small spheres of arbitrary radii.

Table 1

Selected geometric parameters (Å, °) for **3**.

C1-C9	1.354(3)
C2-C3	1.379(2)
C5-C6	1.370(3)
C8-N1	1.362(2)
C7-N1	1.296(2)
C7-Cl1	1.743(2)
O2-C16	1.213(2)
N2-C16	1.357(2)
N1-C7-Cl1	115.6(1)
C1-C2-N2-C16	170.8(2)
C2-N2-C16-O2	0.2(3)

quinolines via Vilsmeier-Haack cyclization of acetanilides. However, the reason for the formation of *N*-(2-chloro-3-formyl-7-phenoxy quinolin-6-yl)formamide (**3**) as a side product in the same reaction is not clearly understood. Perhaps the presence of excess of Vilsmeier-Haack reagent generated *in situ* was responsible for this side product formation. Thus the interaction of —$NHSO_2Me$ group of **2** through its nitrogen lone pair with $[Me_2N{=}CH{-}Cl]^+$ generated *in situ* from DMF and $POCl_3$ followed by the cleavage of N—S bond provides the intermediate possessing $Me_2N{=}CH{-}NH{-}$ group. This moiety on subsequent hydrolysis could be converted into a —NHCHO group. There is, however, no direct evidence to support this pathway. To the best of our knowledge, this is the first example of an N—S bond cleavage under Vilsmeier-Haack reaction condition.

Generation of Schiff bases from 2-chloro-3-formyl-quinoline has been a topic for studying not only nonlinear optical phenomenon arising due to the extended conjugation within the molecules [16] but also for analgesic properties [4]. In our effort to generate a library of molecules of potential pharmacological interest we decided to prepare Schiff bases from **2** and **3**. Accordingly, **3** was initially reacted with a variety of hydrazines (Scheme 2) and the results are summarized in Table 3.

A number of Schiff bases **5a-f** has been prepared from **3** in good yields by using a variety of hydrazines **4a-f** (Table 4) including hydrazinecarboxamide and hydrazinecarbothioamide. The presence of both electron donating (Entries 1, 4 and 5, Table 3) and withdrawing groups (Entries 2 and 6, Table 3) on the phenyl ring of hydrazine moiety was well tolerated. The formamide group on the quinoline ring at C-6 was also well

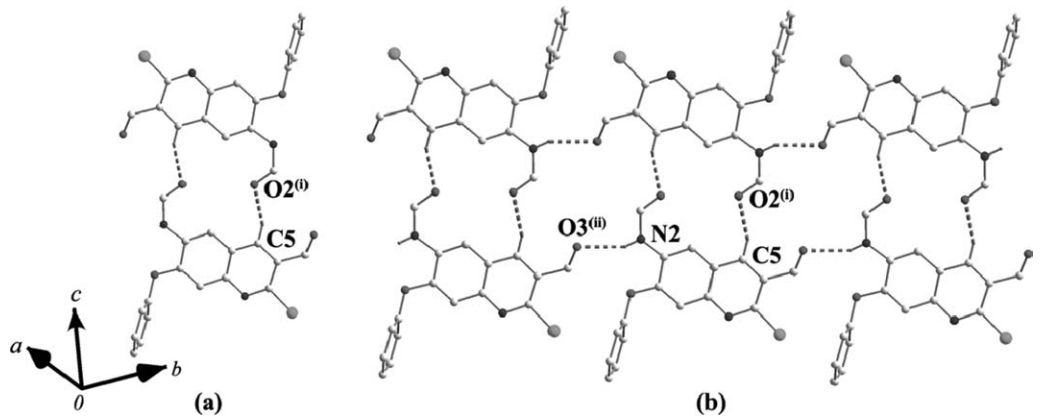


Figure 4. (a) Formation of R_2^2 (16) dimeric ring in $C_{17}O_3N_2H_{11}Cl$. (**3**) [Symmetry code: (i) 1-*x*, 1-*y*, 2-*z*]. (b) Propagation of R_2^2 (16) rings in $C_{17}O_3N_2H_{11}Cl$ (**3**) along the [010] direction. H-atoms not involved in the hydrogen bonding have been omitted for clarity. [Symmetry codes: (i) 1-*x*, 1-*y*, 2-*z*; and (ii) 1+*x*, -1+*y*, *z*]

Table 2
Intermolecular contacts (Å, °) for **3**.

D—H...A	D—H	H...A	D...A	D—H...A	Symmetry code
C5—H5...O2[i]	0.97	2.33	3.183(2)	147	**1-x,1-y,2-z**
N2—H2N...O3[ii]	0.82	2.29	3.053(2)	155	**1+x,-1+y,z**
N2—H2N...O1	0.82	2.25	2.614(2)	107	**x, y, z**
C3—H3...O2	0.95	2.30	2.899(2)	120	x, y, z

tolerated. Schiff base was also generated from compound **2** (Scheme 2) using hydrazines (**4b**, **4g**, and **4h**) as shown in Table 4.

CONCLUSIONS

In conclusion, reduction of nimesulide followed by treating the *N*-acyl derivative of resulting arylamine with Vilsmeier-Haack reagent provided novel 2-chloro-3-formylquinoline derivatives. The methanesulfonamide group was found to be sensitive to the Vilsmeier-Haack reagent as the construction of quinoline ring using this reagent afforded an unusual product i.e., *N*-(2-chloro-3-formyl-7-phenoxy quinolin-6-yl)formamide in addition to the expected product, *N*-(2-chloro-3-formyl-7-phenoxyquinolin-6-yl)methanesulfonamide. The structure of this unexpected quinoline derivative was established unambiguously via single-crystal X-ray analysis. Its formation can be explained by an N-S bond cleavage under Vilsmeier-Haack reaction conditions. The synthetic utility of 2-chloro-3-formylquinoline derivatives has been demonstrated by converting them into the corresponding Schiff bases with potential pharmacological importance.

EXPERIMENTAL

Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. ^{1}H NMR spectra were determined in a solvent as specified on a 300 MHz spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. A ^{13}C NMR spectrum was recorded in DMSO-d_6 at 75 MHz. Infrared spectra were recorded on a FT- IR spectrometer. Melting points were determined by using melting point apparatus and are uncorrected. MS spectra were obtained on a JMS-D 300 spectrometer.

Preparation of 2-Chloro-3-formylquinoline derivatives (2 and 3). A mixture of compound **1** (1.0 g, 3.0 mmol), DMF (0.7 mL, 10 mmol) and $POCl_3$ (2.0 mL, 20 mmol) was stirred at 0–5°C. After 0.5 h the temperature of the reaction mixture was increased to 120°C and maintained for 4 h. The mixture was then cooled to room temperature, poured into crushed ice (50 mL) and extracted with $CHCl_3$ (3 × 25 mL). The organic layers were collected, combined, washed with water, dried over anhydrous Na_2SO_4 and concentrated. The brown solid obtained was purified by column chromatography to give the desired product.

***N*-(2-Chloro-3-formyl-7-phenoxyquinolin-6-yl)methanesulfonamide (2).** Light yellow powder; yield 55%; R_f 0.7 ($CHCl_3$: EtOAc 9:1); mp 172–174°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.3 (1H, s, CHO), 10.0 (1H, D_2O exchange, s, NH), 8.9 (1H, s, ArH), 8.3 (1H, s, ArH), 7.8–7.3 (5H, m, ArH), 7.0 (1H, s, ArH), 3.2 (3H, s, SO_2CH_3); ^{13}CNMR (75 MHz, DMSO-d_6) δ 189, 156, 154, 149, 147, 141, 131, 130, 126, 125, 124, 123, 121, 111, 40; MS (m/z, CI method) 377.1 (M^+, 100), 379 (M+2, 33); IR (KBr, cm^{-1}) 3418 (NH), 3255, 2924, 1689, 1622, 1579, 1498.

Elemental Analysis found: C, 54.34; H, 3.40; N, 7.15 $C_{17}H_{13}Cl\,N_2O_4S$ Requires: C, 54.19; H, 3.48; N, 7.43.

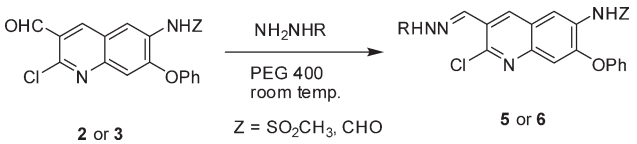
***N*-(2-Chloro-3-formyl-7-phenoxy quinolin-6-yl)formamide (3).** Off white solid; yield 45%; R_f 0.8 ($CHCl_3$: EtOAc 9:1); mp 206–208°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.5 (1H, D_2O exchange, s, NH), 10.2 (1H, s, CHO), 9.1 (1H, s, NHCHO), 8.9 (1H, s, ArH), 8.5 (1H, s, ArH), 7.7–7.4 (5H, m, ArH), 7.0 (1H, s, ArH); ^{13}CNMR (75 MHz, DMSO-d_6) δ 189.7, 161.5, 154, 140.9, 131, 129.7, 126.4, 125.7, 122.8, 121.1, 119.3, 110.6; MS (m/z, CI method) 327.1 (M^+, 100), 329 (M+2, 33); IR (KBr, cm^{-1}) 3330 (NH), 1699, 1682, 1620, 1580, 1526.

Elemental Analysis found: C, 62.38; H, 3.30; N, 8.89 $C_{17}H_{11}ClN_2O_3$ Requires: C, 62.49; H, 3.39; N, 8.57.

Preparation of Schiff bases (5 and 6). A solution of compound **2** (3.8 g, 10.0 mmol) or **3** (3.3 g, 10.0 mmol) and an appropriate hydrazine **4a–h** (11.0 mmol) as indicated in Tables 3 and 4 in PEG 400 (10 mL) was stirred at room temperature according to the time indicated in Tables 3 and 4. After completion of the reaction, as indicated by TLC, the mixture was diluted by using ice cold water (25 mL) with vigorous stirring. The solid separated was filtered, washed with ice cold water and recrystallized from ethanol to afford the expected product (**5a–f** or **6a–c**).

[(2-Chloro-6-formamido-7-phenoxyquinolin-3-yl)methylene]-*N*-(4-methoxyphenyl)hydrazinecarbothioamide (5a). Light green crystalline solid; R_f 0.58 ($CHCl_3$: EtOAc 9:1); mp 118–120°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.50 (1H, D_2O exchangeable, NH), 9.05 (1H, s, NHCHO), 8.95 (1H, s, ArH), 8.50 (1H, s, ArH), 7.60 (2H, t, J = 7.7 Hz, ArH), 7.40

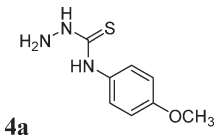
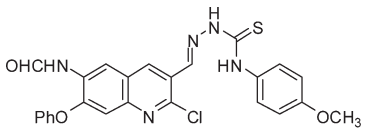
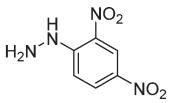
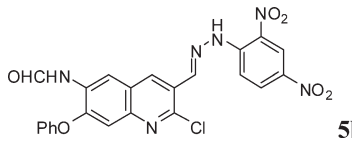
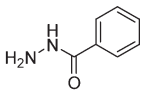
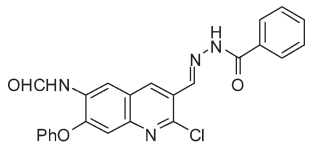
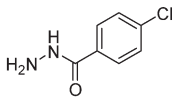
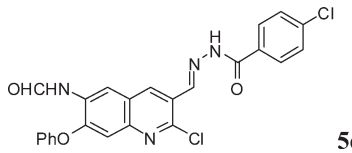
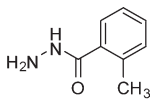
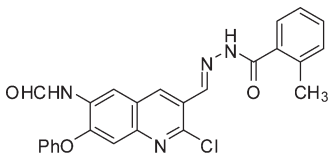
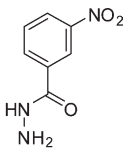
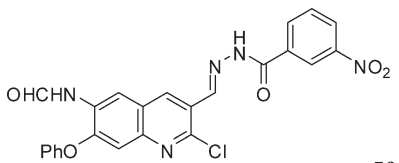
Scheme 2. Preparation of Schiff bases from **2** to **3**.



2 or **3** **5** or **6**

Table 3

Preparation of Schiff bases from compound **3**.[a]

Entry	Hydrazines (**4**)	Time (h)		
1.	 **4a**	3.0	 **5a**	70
2.	 **4b**	4.0	 **5b**	83
3.	 **4c**	4.0	 **5c**	74
4.	 **4d**	3.0	 **5d**	76
5.	 **4e**	6.0	 **5e**	81
6.	 **4f**	6.0	 **5f**	60

[a] All the reactions were carried out using compound **3** (10.0 mmol) and **4** (11.0 mmol) in PEG 400 at room temperature.

(8H, m, ArH + NH), 7.15 (2H, d, J = 8.7 Hz, ArH), 6.90 (1H, s, —CH=) 3.80 (3H, s, OCH_3); IR (KBr, cm^{-1}) 3236 (NH), 1691 (C=O); MS (m/z, CI method) 506 (M+, 100%).

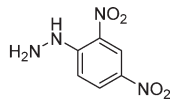
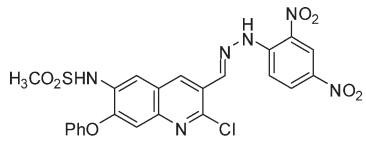
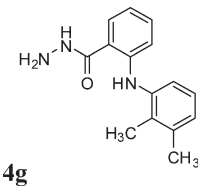
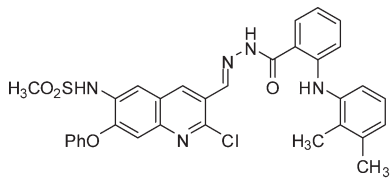
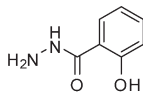
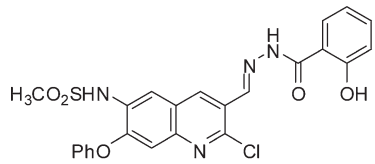
Elemental Analysis found: C, 59.64; H, 3.90; N, 13.65 $C_{25}H_{20}N_5SO_3Cl$ Requires: C, 59.34; H, 3.98; N, 13.84.

***N*-(2-Chloro-3-[(2-(2,4-dinitrophenyl)hydrazono)methyl]-7-phenoxyquinolin-6-yl)formamide (5b).** Orange crystalline solid; R_f 0.62 ($CHCl_3$: EtOAc 9:1); mp 268–270°C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.5 (1H, s, D_2O exchangeable, NH), 10.50 (1H, s, D_2O exchangeable, NH), 9.10 (3H, m, NHCHO + ArH), 8.90 (1H, s, ArH), 8.60 (1H, s, ArH), 8.4 (1H, s, ArH), 8.3 (1H, s, ArH), 7.60 (2H, m, ArH), 7.30 (3H, m, ArH), 7.0 (1H, s, —CH=); IR (KBr, cm^{-1}) 3267 (NH), 1691(C=O); MS (m/z, CI method) 507 (M+,100%).

Elemental Analysis found: C, 54.74; H, 2.90; N, 16.35 $C_{23}H_{15}N_6O_6Cl$ Requires: C, 54.50; H, 2.98; N, 16.58.

Table 4

Preparation of Schiff bases from compound **2**.[a]

Entry	Hydrazines (**4**)	Time (h)	Products (**6**)	Yields (%)
1.	 **4b**	4.0	 **6a**	68
2.	 **4g**	3.0	 **6b**	70
3.	 **4h**	4.0	 **6c**	74

[a] All the reactions were carried out using compound **2** (10.0 mmol) and **4** (11.0 mmol) in PEG 400 at room temperature.

***N*-(3-[(2-Benzoylhydrazono)methyl]-2-chloro-7-phenoxyquinolin-6-yl)formamide (5c).** Cream colored crystalline solid; R_f 0.53 ($CHCl_3$: EtOAc 9:1); mp 218–216°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.20 (1H, s, D_2O exchangeable, NH), 10.50 (1H, s, D_2O exchangeable, NH), 9.10 (1H, s, NHCHO), 8.80 (2H, d, J = 8.8 Hz, ArH), 8.50 (1H, s, ArH), 8.0 (2H, m, ArH), 7.55 (5H, m, ArH), 7.20 (3H, m, ArH) 7.0 (1H, s, ═CH═); IR (KBr, cm^{-1}) 3360 (NH), 1708 (C═O), 1661 (NHCHO), 1621, 1588, 1577; MS (m/z, CI method) 445 (M+, 100%).

Elemental Analysis found: C, 64.54; H, 3.90; N, 12.63 $C_{24}H_{17}N_4O_3Cl$ Requires: C, 64.80; H, 3.85; N, 12.59.

***N*-(2-Chloro-3-[(2-(4-chlorobenzoyl)hydrazono)methyl]-7-phenoxyquinolin-6-yl)formamide (5d).** White crystalline solid; R_f 0.58 ($CHCl_3$: EtOAc 9:1); mp 298–300°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.20 (1H, s, D_2O exchangeable, NH), 10.50 (1H, s, D_2O exchangeable, NH), 9.10 (1H, s, -NHCHO), 8.90 (2H, m, ArH), 8.50 (1H, s, ArH), 8.0 (2H, d, J = 8.7 Hz, ArH), 7.70 (2H, d, J = 7.7 Hz, ArH), 7.60 (2H, t, J = 7.7 Hz, ArH), 7.30 (3H, m, ArH), 7.0 (1H, s, ═CH═); IR (KBr, cm^{-1}) 3396, 1704, 1659, 1592, 1524.9, 1491.8; MS (m/z, CI method) 479 (M+, 100%).

Elemental Analysis found: C, 60.41; H, 3.35; N, 11.56 $C_{24}H_{16}N_4O_3Cl_2$ Requires: C, 60.14; H, 3.36; N, 11.69.

***N*-(2-Chloro-3-[(2-(2-methylbenzoyl)hydrazono)methyl]-7-phenoxyquinolin-6-yl)formamide (5e).** Cream colored crystalline solid; R_f 0.65 ($CHCl_3$: EtOAc 9:1); mp 242–244°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.0 (1H, s, D_2O exchangeable, NH), 10.50 (1H, s, D_2O exchangeable, NH), 8.61 (4H, m, ArH + ═NHCHO), 7.43 (9H, m, ArH), 6.98 (1H, s, ═CH═), 2.41 (3H, s, CH_3); IR (KBr, cm^{-1}) 3294, 1705, 1584; MS (m/z, CI method) 459 (M+100%).

Elemental Analysis found: C, 68.94; H, 4.05; N, 12.50 $C_{25}H_{19}N_4O_3Cl$ Requires: C, 68.63; H, 4.17; N, 12.21.

***N*-(2-Chloro-3-[(2-(3-nitrobenzoyl)hydrazono)methyl]-7-phenoxyquinolin-6-yl)formamide (5f).** Pale yellow crystalline solid; R_f 0.62 ($CHCl_3$: EtOAc 9:1); mp 258–260°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.50 (1H, s, D_2O exchangeable, NH), 10.40 (1H, bs, D_2O exchangeable, NH), 8.86 (2H, m, ArH), 8.45 (5H, m, ArH), 7.32 (5H, m, ArH), 7.16 (2H, m, ArH); IR (KBr, cm^{-1}) 3318, 1695, 1527; MS (m/z, CI method) 490 (M+, 100%).

Elemental Analysis found: C, 58.94; H, 3.10; N, 14.35 $C_{24}H_{16}N_5O_5Cl$ Requires: C, 58.84; H, 3.29; N, 14.30.

***N*-(2-Chloro-3-[(2-(2,4-dinitrophenyl)hydrazono)methyl]-7-phenoxyquinolin-6-yl)methanesulfonamide (6a).** Light orange crystalline solid; R_f 0.50 ($CHCl_3$: EtOAc 9:1); mp 244–246°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.1 (1H, s, D_2O exchangeable, NH), 10.5 (1H, s, D_2O exchangeable, NH), 8.95 (2H, m, ArH), 8.0 (1H, d, J = 8.8 Hz, ArH), 7.90 (1H, d, J = 8.8 Hz, ArH), 7.6 (2H, m, ArH), 7.30 (3H, m, ArH), 7.0 (3H, m, ArH + ═CH═), 3.80 (3H, s, SO_2CH_3); IR (KBr, cm^{-1}) 3382, 2923, 1616, 1643, 1589; MS (m/z, CI method) 557 (M+, 100%).

Elemental Analysis found: C, 49.66; H, 3.01; N, 15.01 $C_{23}H_{17}ClN_6O_7S$ Requires: C, 49.60; H, 3.08; N, 15.09.

***N*-(2-Chloro-3-[(2-(2-(2,3-dimethylphenylamino)benzoyl)hydrazono)methyl]-7-phenoxyquinolin-6-yl)methanesulfonamide (6b).** Light yellow solid; R_f 0.65 ($CHCl_3$: EtOAc 9:1); mp 202–204°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.3 (1H, s, D_2O exchangeable, NH), 10.5 (1H, s, D_2O exchangeable, NH), 9.4 (1H, s, D_2O exchangeable, NH), 9.0 (1H, s, ArH), 8.90 (2H, m, ArH), 8.50 (1H, s, ArH), 7.8 (1H, d, J = 8.8 Hz, ArH), 7.15 (11H, m, ArH + ═CH═), 3.7 (3H, s, SO_2CH_3), 2.4 (3H, s, CH_3) 2.2 (3H, s, CH_3); IR (KBr, cm^{-1}) 2869, 1687, 1620, 1555; MS (m/z, CI method) 614 (M+, 100%).

Elemental Analysis found: C, 62.50; H, 4.65; N, 11.48 $C_{32}H_{28}ClN_5O_4S$ Requires: C, 62.58; H, 4.60; N, 11.40.

***N*-(2-Chloro-3-[(2-(2-hydroxybenzoyl)hydrazono)methyl]-7-phenoxyquinolin-6-yl)methanesulfonamide (6c).** Cream colored solid; R_f 0.62 ($CHCl_3$: EtOAc 9:1); mp 218–220°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.5 (1H, s, D_2O exchangeable, NH), 9.9 (1H, s, D_2O exchangeable, NH), 9.1 (2H, m, ArH), 8.90 (1H, s, ArH), 8.50 (1H, s, ArH), 8.2 (s, 1H, ArH), 7.87 (1H, d, J = 8.8 Hz, ArH), 7.5 (2H, m, ArH), 7.30 (3H, m, ArH), 7.15 (2H, d, J = 8.8 Hz, ArH), 6.9 (1H, s, ═CH═), 3.8 (3H, s, SO_2CH_3); IR (KBr, cm^{-1}) 3377, 2923, 1678, 1605; MS (m/z, CI method) 511 (M+, 100%).

Elemental Analysis found: C, 56.49; H, 3.74; N, 10.90 $C_{24}H_{19}ClN_4O_5S$ Requires: C, 56.42; H, 3.75; N, 10.97.

X-ray crystallographic study of N-(2-chloro-3-formyl-7-phenoxy quinolin-6-yl)formamide (3). Molecular formula $C_{17}O_3N_2H_{11}Cl$, M = 326.7, triclinic, space group P-1, a = 5.3015(9), b = 9.0196(19), c = 15.454(4) Å, α = 99.011(4), β = 92.710(4), γ = 93.355(2)°, V = 727.4(4) Å^3, Z = 2, F(000) = 336, T = 150 (2)K, λ = 0.6945 Å, D_c = 1.492 Mg m^{-3}, μ = 0.280 mm^{-1}, Final R_1 = 0.0540, WR_2 = 0.1219, S = 1.100 for 2968 reflections; for 2578 observed reflections [I> 2σ (I)] R_1 = 0.0486, WR_2 = 0.1165, $\Delta\rho_{max}/\Delta\rho_{min}$ = 0.447/−0.456 eÅ^{-3}

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