Chapter II

A Simple & Convenient Synthesis of Novel Functionalised Quinolines
Introduction

The quinoline derivatives signify the major class of heterocycles, and a number of preparations have been known since the late 1800's. The quinoline ring system occurs in various natural products, especially in alkaloids. The quinoline skeleton was often used for the design of many synthetic compounds with diverse pharmacological properties. In 1820, quinine was isolated as the active ingredient from the bark of Cinchona trees and successively replaced the crude bark for the treatment of malaria. Despite its relatively low efficacy and tolerability, quinine still plays an important role in the treatment of multiresistant malaria\(^1\). This molecule has also played a historical role in organic chemistry as a target for structural determination and total synthesis\(^2\), and recently both stereoselective\(^3\) and enantioselective\(^4\) total synthesis. Chimanine alkaloids, simple quinolines, isolated from the bark of Galipea longiflora trees of the Rutaceae family\(^5\)\(^-\)\(^7\), are effective against the parasites Leishmania sp., which are the agents of leishmaniasis, a protozoan disease of the tropical areas in South America, particularly in the Amazonian forest.

Cryptolepine is an indoloquinoline alkaloid found in the West African climbing shrub Cryptolepis sanguinolenta. A decoction of the roots of this species is used in traditional medicine for the treatment of malaria as well as for a number of other diseases\(^8\). Dynemicin A and Streptonigrin, naturally occurring members of the class of antitumor antibiotics, whose syntheses are based on the utilization of preformed quinoline derivatives\(^9\)\(^-\)\(^10\). The 8-(diethylaminohexylamino)-6-methoxy-4-methylquinoline is highly effective against the protozoan parasite Trypanosoma cruzi, which is the agent of
Chagas' disease and the 2-(2-methylquinolin-4-ylamino)-N-phenylacetamide is more active than the standard antileishmanial drug sodium antimony gluconate.

The structural core of quinoline has generally been synthesized by various conventional named reactions such as Skraup, Doebner-von Miller, Friedländer, Pfitzinger, Conrad-Limpach, Combes. These classical syntheses are well known and still frequently used for the preparation of pharmaceutical agents, ligands and functional materials bearing a quinoline backbone. However, current methods for quinoline synthesis often do not allow for adequate diversity and substitution on the quinoline ring system.

Recent developments in the chemistry of quinoline derivatives have demonstrated that new metal-catalyzed coupling cyclization or acid catalyzed cycloaddition of appropriate precursors could compete with classical syntheses in the efficacy and rapidity of the quinoline construction. In spite of their generality, versatility and simplicity, these syntheses have considerable drawbacks such as harsh reaction conditions and highly acidic medium, which makes them tedious to isolate the product from the crude mixture.
Present Work

Earlier methods of building the quinoline derivatives involve the reactions of the β-keto nitriles\textsuperscript{19,20,21,22,23} with appropriately substituted 2-aminobenzaldehyde, which gives derivatives of 3-cyanoquinolines\textsuperscript{24} (a). An alternative mode of condensation between 2-aminobenzaldehyde and β-keto ester is noted by Friedlander and Gohring.\textsuperscript{25} Using this method, various derivatives of 3-cyanoquinoline are synthesized\textsuperscript{26,27,28,29,30,31} (b).

Of the different methods available in the literature for the synthesis of the quinoline ring, only few can be applied efficiently for the preparation of 3-cyanoquinoline derivatives\textsuperscript{32}. Hence, to the best of our knowledge there are no reports on the synthesis of 2-hydroxy-3-cyanoquinolines (2a-c) and 2-amino-3-cyanoquinolines (3a-c) by the reaction of 2-aminobenzaldehydes with ethyl cyanoacetate and malononitrile under this condition. This stimulated our area of interest in establishing an efficient, a simple protocol, and a scale up procedure for the synthesis of 3-cyanoquinoline derivatives.

2-Aminobenzaldehydes (1a-c) were thought to be suitable intermediates for the proposed investigation. Hence, we prepared the substituted 2-aminobenzaldehydes (1a-c)
through *Vilsmeier-Haack* reaction. It is well known that the *Vilsmeier-Haack* reaction is the convenient method for the formylation of activated and heteroaromatic compounds. The required starting compounds were prepared by the reaction of 4-substituted aniline. The Vilsmeier salt was prepared from POCl3 / DMF at low temperature. After refluxing and basification during the course of work-up, it afforded substituted 2-aminobenzaldehydes in good yield. [Scheme-1].

The initial reaction of 2-aminobenzaldehydes with ethyl acetoacetate and diethyl malonate did not give the expected products. However, at room temperature, cyano ethylacetate and malononitrile underwent smooth reaction with 2-aminobenzaldehydes in presence of catalytic amount of piperidine in absolute ethanol. This afforded the 2-hydroxy-3-cyanoquinolines (2a-c) and 2-amino-3-cyanoquinolines (3a-c) respectively. These reactions led to the development of versatile method to synthesize the title compounds efficiently with various substituents in good yields. [Scheme-2].
The IR spectrum of 2a [Fig: 2.1] displayed a strong absorption band at 2212 cm\(^{-1}\) due to \(-\text{CN}\) group. This is due to the involvement of condensation of cyano ethylacetate with 2-aminobenzaldehyde. Further, the testified evidence in favor of the above contention was gathered from \(^1\text{H}-\text{NMR}\) spectra [Fig: 2.2 & 2.3], where a broad singlet appeared at 11.00 \(\delta\) (\(\text{D}_2\text{O}\) exchangeable). This signal was attributable to \(-\text{OH}\) group of the quinoline. A multiplet at 7.2–8.3 \(\delta\) was assigned to aromatic protons. The structure of 2a was again evidenced by mass spectral data [Fig: 2.4]. It gave the molecular ion peak at \(m/z 215\).

Interestingly, the presence of the \(-\text{OH}\) group at the 2-position in 2-hydroxy-3-cyanoquinolines (2a-c) was further evidenced by reacting it with DMS to obtain 2-
methoxy-3-cyanoquinolines (4a-c) [Scheme-3]. The $^1$H-NMR spectrum of 4a [Fig: 2.5] showed the absence of –OH proton, instead it gave another new signal at 3.89 δ corresponding to –OCH$_3$ protons. This confirmed the existence of –OH group in compounds (2a-c).

Similarly, the structure of 2-amino-3-cyanoquinolines (3a-c) were also studied using IR, $^1$H-NMR and, Mass spectral data. The IR spectrum of 2-amino-3-cyano-5-nitroquinoline 3a [Fig: 2.6] exhibited a strong absorption band at 2210 cm$^{-1}$ due to –CN and another absorption band at 3207-3421 cm$^{-1}$ corresponds to –NH$_2$ asymmetric stretching. $^1$H-NMR spectrum of 3a [Fig: 2.7] displayed a broad singlet at 7.6 δ integrated to 2 protons of –NH$_2$ group (D$_2$O exchangeable). Aromatic proton appeared in the expected region.

Although various routes were developed for the synthesis of cyanoquinolines under vigorous reaction conditions, to the best of our knowledge, reactions of 2-aminobenzaldehydes (1a-c) with ethyl cyanoacetate and malononitrile were not so far reported.

In summary, the reactions of 2-aminobenzaldehydes (1a-c) with ethyl cyanoacetate and with malononitrile furnish novel 3-cyanoquinolines under simple reaction condition. This provided a very encouraging result, since it demonstrates an inexpensive way for generality of the cyanoquinoline chemistry. With this work, we have
demonstrated that, under simple room temperature condition in presence of piperidine as a catalyst, a major class of functionalized quinoline heterocycle can be developed.
Fig: 2.1 IR Spectrum of 2a

Type: HYPER IR  Time: 16:25:31  NScans: 20
User: vasudha  Detector: standard
Abscissa: 1/cm  Ordinate: %T  Apodization: Happ
Fig. 2.2: $^1$H-NMR Spectrum of 2a

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\text{\begin{align*}
\text{O}_2\text{N} & \quad \text{CN} \\
\text{\text{H}} & \quad \text{OH}
\end{align*}}
\]
Fig. 2.3; $^1$H-NMR Spectrum of 2a

(D$_2$O exchange)
SCANNED GRAPH. Flagging = M/z.
Scan 3-0:43. Entries = 106. 100% Int. = 62140.

Fig: 2.4; Mass Spectrum of 2a
Fig. 2.5: 1H-NMR Spectrum of 4a
Fig. 2.6; IR Spectrum of 3a

Type: HYPER IR
User: vasudha
Detector: standard

Abscissa: 1/cm
Ordinate: %T

Min: 401.17
Max: 3998.16

Ndp: 1866
Data Interval: 1.92868

Gain: auto
Aperture: auto

Time: 15:21:51
NScans: 20

Resolution: 4.0
Mirror Speed: 2.8(low)
Fig: 2.7; $^1$H-NMR Spectrum of 3a

Current Data Parameters
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EXPMO 10
PROCNO 1

F2 - Acquisition Parameters
Date_  20060323
Time  20.22
INSTTRM  amx400
PROBND  5 mm QNP 1H
PULPROG  zg
TD  16384
SOLVENT  DMSO
NS  62
DS  0
SWH  8064.516 Hz
FIDRES  0.492219 Hz
AQ  1.0158581 sec
RG  2048
DM  62.0000 ussec
DE  88.57 ussec
TE  300.0 K
HL1  1 dB
D1  1.00000000 sec
P1  11.50 ussec
FPO1  400.1385724 MHz
NUCLEUS  1H

F2 - Processing parameters
SF  32768
SF  400.1362941 MHz
WDM  EM
SSB  0
LB  0.30 Hz
GB  0
PC  0.30
Functionalised Quinolines

Experimental

General Synthetic Procedure for the Synthesis of Substituted 2-Amino benzaldehydes: 1a-c

Vilsmeier reagent was prepared by mixing ice-cold [< 5°C], dry DMF (0.1 mol, 7.3 g, 7.69 mL) and POCl₃ (0.1 mol, 15.34 g, 9.09 mL). The mixture was then stirred for 15 min at 5°C in the ice-salt mixture bath. To the Vilsmeier reagent was added 4-substituted aniline (0.1 mol) in dry DMF (30 mL) over about 20-30 min at 0-5°C. The reaction mixture was stirred for 30 min at room temperature and heated to 80°C with constant stirring for 2 h. The reaction mixture was poured to ice-cooled water (500 mL) and basified by aqueous NaOH (30%) solution. The product gets precipitate out, collected by filtration. The crude 2-aminobenzaldehydes were recrystallized in absolute alcohol to furnish pure product (1a-c).

General Synthetic Procedure for the Synthesis of 2-Hydroxy-3-cyanoquinolines: 2a-c

To the stirring solution [absolute ethanol (20 mL)] of ethyl cyanoacetate (0.1 mol, 11.32 g) and piperidine (0.5 mL) in was added 2-aminobenzaldehydes (0.1 mol) (1a-c) in absolute ethanol (30 mL). During the addition, the product gets precipitate-out. To ensure the complete cyclization, the reaction mixture was refluxed for 2 h. On cooling, the product gets reappeared as solid, and was collected by filtration, washed with ethanol and dried in an oven. The crude compound was recrystallized from acetone to furnish pure product 2-hydroxy-3-cyanoquinolines (2a-c) with the yield 70-85 %.
2-Hydroxy-6-nitro-3-cyanoquinoline: 2a

Yield: 1.82 g, 85 %; mp: 213-215 °C; IR (KBr, v, cm⁻¹): 1687 (CO), 2212 (CN), 3369-3483 (OH); ¹H-NMR (δ, DMSO-d₆): 7.2-8.3 (4H, m, Hₐrom), 11 (1H, s, OH, D₂O exchangeable); MS: m/z: 215 [M⁺]; Analysis: C₁₀H₅N₃O₃ Cal; C 55.85 %; H 2.34 %; N 19.53 %. Found; C 55.72 %; H 2.83 %; N 19.00 %.

2-Hydroxy 6-chloro-3-cyanoquinoline: 2b

Yield: 1.43 g, 70 %; mp: 195-196 °C; IR (KBr, v, cm⁻¹): 1682 (CO), 2212 (CN), 3367-3479 (OH); ¹H-NMR (δ, DMSO-d₆): 7.3-8.6 (m, 4H, Hₐrom), 11 (s, 1H, OH, D₂O exchangeable); MS: m/z: 204 [M⁺]; Analysis: C₁₀H₅ClN₂O Cal; C 58.70 %; H 2.46 %; N 13.69 %. Found; C 57.42 %; H 2.70 %; N 12.94 %.

2-Hydroxy-6-bromo-3-cyanoquinoline: 2c

Yield: 1.79 g, 72 %; mp: 220-221 °C; IR (KBr, v, cm⁻¹): 1686 (CO), 2218 (CN), 3369-3478 (OH); ¹H-NMR (δ, DMSO-d₆): 7.4-8.6 (4H, m, Hₐrom), 11 (1H, s, -OH, D₂O exchangeable), MS: m/z: 249 [M⁺]; Analysis: C₁₀H₅BrN₂O Cal; C 48.22 %; H 2.02 %; N 11.25 %. Found; C 48.12 %; H 1.78 %; N 11.78 %.

General Synthetic Procedure for the Synthesis of 2-Amino-3-cyanoquinolines: 3a-c

To the ethanolic solution (20 mL of absolute ethanol) of the malanonitrile (0.1 mol, 6.6 g) and piperidine (0.5 mL) was added 2-aminobenzaldehydes (1a-c) (0.1 mol) in absolute ethanol (30 mL) with stirring. During the addition, there itself the product gets
precipitated-out. The reaction mixture was refluxed for 2 h. On cooling the product gets reappeared as solid and was collected by filtration, washed and dried in an oven. The crude compound was recrystallized from hot acetone to give 2-amino-3-cyanoquinolines (3a-c) with the yield 69-82 %.

2-Amino-6-nitro-3-cyanoquinoline: 3a

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\text{Yield: 1.75 g, 82 \%; mp: 260-262 °C; IR (KBr, v, cm}^{-1}]: 2210 (CN), 3207-3421 (NH}_2; \text{ }^{1}H\text{-NMR (δ, DMSO-d}_6): 7.8-9.8 (4H, m, H}_\text{arom}, 7.6 (2H, s, NH}_2; \text{MS: } m/z: 214 [M^+]; \text{Analysis: C}_{10}H_6N_4O_2 Cal; C 56.08 \%; H 2.82 \%; N 26.16 \%. \text{Found: C 56.45 \%; H 2.49 \%; N 26.67 \%.}
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2-Amino-6-chloro-3-cyanoquinoline: 3b

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\text{Yield: 1.44 g, 73 \%; mp: 223-225 °C; IR (KBr, v, cm}^{-1}]: 2213 (CN), 3207-3420 (NH}_2; \text{ }^{1}H\text{-NMR (δ, DMSO-d}_6): 7.8-9.6 (4H, m, H}_\text{arom}, 7.6 (2H, s, NH}_2; \text{MS: } m/z: 203 [M^+]; \text{Analysis: C}_{10}H_6ClN_3 Cal; C 58.98 \%; H 2.97 \%; N 20.64 \%. \text{Found: C 58.79 \%; H 2.83 \%; N 20.83\%.}
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2-Amino-6-bromo-3-cyanoquinoline: 3c

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\text{Yield: 1.71 g, 69 \%; mp: 250-252 °C; IR (KBr, v, cm}^{-1}]: 2217 (CN), 3209-3436 (NH}_2; \text{ }^{1}H\text{-NMR (δ, DMSO-d}_6): 7.8-9.8 (4H, m, H}_\text{arom}, 7.6 (2H, s, NH}_2; \text{MS: } m/z: 248 [M^+]; \text{Analysis: C}_{10}H_6BrN_3 Cal; C 48.41 \%; H 2.44 \%; N 16.94 \%. \text{Found: C 47.96 \%; H 2.83 \%; N 16.14 \%.}
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References


