CHAPTER 3
Synthesis of N-[(substituted-2-chloroquinolin-3-yl)methylidene]-8-nitronaphtho[2,1-b]furan-2-carbohydrazides
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Introduction

Quinoline is a condensed nitrogen heterocycle in which pyridine ring system is fused with benzene nucleus. Thus it is also known as benzo[b]pyridine. It resembles naphthalene in its structure, where in one of the carbon atom at α-position is replaced by nitrogen atom, hence another name for quinoline is 1-azanaphthalene. It was first extracted from coaltar in 1834 by Friedlieb Ferdinand Runge. Quinoline is a colourless liquid with characteristic strong odour. The compounds containing quinoline nucleus form a big family and these compounds form a basis of many useful drugs. These compounds find application as antiseptic, antipyretic, fungicides, flavouring agents etc. They are also used in chemical industries for manufacturing various dyes and rubber.

In fact, quinoline and its derivatives have gained prominent position in the field of medicinal chemistry soon after the isolation of antimalarial drug Quinine 1 from Chinchona bark.

The well-known antihypertensive drugs like Prazosin 2 and Doxazosin 3 encompass quinoline in their molecular structure.
8-Hydroxy quinoline is used as a very common chelating agent and also as a starting material for the synthesis of numerous pesticides. There are numerous reports in literature regarding biological and pharmacological applications of quinoline derivatives. Many of these derivatives are found to be associated with antibacterial, antifungal, antidepressant, anti-inflammatory, anthelmintic, antihypertensive and antihistamine activities. It has been shown that many 4-substituted quinolines exhibit antibacterial activity especially against Gram negative bacteria. Pearce et al., reported that 8-hydroxy-2-methylquinoline derivatives are useful in biological system as sensors. Similarly, Strekonski et al., reported that 2-substituted-4-aminoquinolines act as excellent anti HIV-1 agents.

It is generally observed that when one biodynamic heterocyclic system is condensed or coupled with another heterocyclic system, the resulting compounds exhibit enhanced biological and pharmacological activities. Encouraged by these observations many synthetic organic chemists embarked their research work towards the synthesis of novel heterocycles in which quinoline nucleus is condensed or coupled with another...
bioactive heterocyclic moiety. In this connection valuminous work has been carried out and several research papers have been published. Keeping in view the limitations of this thesis, only important and recent research findings are summarized in the following paragraphs.

Muthumani et al., synthesized some quinoline derivatives enclosing azetidinone ring system in their structure. During the course of their work, they prepared phenyl hydrazone derivative 4 of 2-chloro-3-formyl quinoline.

![Image of derivative 4]

They investigated diuretic, antibacterial, antifungal activity of the synthesized compounds\(^\text{16}\).

Srikanth et al., synthesized some heterocycles in which both quinoline and thiazolidinediones were present and studied them for their hypoglycemic activity by tail vein method\(^\text{17,18}\) using albino rats. They reported that some of the compounds exhibited significant activity especially with ethyl and amino substituents at various positions in the molecule\(^\text{19}\).

Chikhalia\(^\text{20}\) et al., synthesized quinoline derivatives encompassing pyrimidine nucleus. They evaluated these derivatives for antibacterial activity and made an interesting observation that the presence of electron withdrawing groups on the aromatic
ring increased the antimicrobial activity compared with the compounds with electron withdrawing groups.

Considering the importance of quinazoline and imidazole, Parab and Dixit\textsuperscript{21} synthesized biheterocycles 5 enclosing both these ring systems. On evaluation of these compounds for antibacterial activity against both Gram negative and Gram positive bacteria, they observed that introduction of specific functional group or its elimination enhances biological activity of the compounds.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure.png}
\caption{Chemical structures of compounds 5a-d.}
\end{figure}

Nowadays malarial parasites, especially Plasmodium parasite are developing resistance towards most of the clinically used antimalarial drugs. Hence, Singh et al.\textsuperscript{22} synthesized biheterocycle involving quinoline and azetidione ring systems. They carried out \textit{in vitro} antimalarial activity against \textit{P. falciparum}. Calculation of IC\textsubscript{50} value indicated that some of the compounds possessed significant IC\textsubscript{50} value when compared with chloroquine diphosphate, which was used as standard reference drug.

Similarly, Ashok Kumar et al., synthesized quinoline derivatives encompassing acridine nucleus. Some of the derivatives showed considerable antimalarial activity against \textit{P. falsiparum}\textsuperscript{21}. The new heterocyclic compounds 6a-b in which quinoline is coupled with 1,2,3-triazole have been synthesized by Karthik kumar\textsuperscript{24} et al.,
They also synthesized O-glycosides of compound 6a. Antitubercular activity of synthesized compounds was evaluated against *Mycobacterium tuberculosis* H37Rv by luciferase reporter phage assay. They reported that one of the compounds, synthesized by them possessed remarkably higher antitubercular activity.

Alam et al., synthesized novel heterocyclic compounds, in which quinoline is attached to furan-2(3H)-ones 7a-d.

They investigated anti-inflammatory activity of the synthesized compounds using Carrageenan induced rat paw edema method of Winter et al., They used ibuprofen as a standard drug for comparison of anti-inflammatory activity. They observed that some of the compounds exhibited moderate anti-inflammatory activity. The analgesic activity of some of the compounds was evaluated by the acetic acid induced writhing method. Similarly, they studied antioxidant activity and antibacterial activity of the synthesized compounds.
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The foregoing discussion reveals that quinoline ring system has been coupled with various four, five and six membered heterocyclic systems, with the aim to obtain more potent molecules with enhanced biological and pharmacological activities. However, no attempts have been made to incorporate biologically active naphtho[2,1-b]furan moiety with quinoline. Hence, it was thought of to synthesize novel heterocyclic system encompassing two biodynamic nuclei viz., quinoline and naphtho[2,1-b]furan.

Present Work

The discussion summarized in the above paragraphs clearly indicates the importance of quinoline nucleus as one of the partner in biheterocyclic compounds. The pharmacological and biological activity increases due to synergic effect of two different biodynamic heterocyclic moieties. As already pointed out, attempts have not been made to couple quinoline nucleus with benzofuran and naphthofuran moieties. The main objective of the present work is to synthesize novel naphtho[2,1-b]furan derivatives and evaluate them for various pharmacological and biological activities. The importance of nitro groups in various drugs containing furan ring system has been pointed out in chapter 1 of this thesis. Hence, it was planned to synthesize the following type of molecule connecting naphtho[2,1-b]furan and quinoline via $O=\text{C-N-N=}$ bridge. The nitro group was introduced in naphtho[2,1b]furan nucleus to study the impact of electron withdrawing group on biological activity.
The synthetic strategy for the synthesis of the above mentioned compounds was devised by retrosynthetic analysis which is shown in Scheme 3.1.

**SCHEME 3.1**

Thus, the synthetic methodology was devised to obtain molecule A and molecule B separately, followed by condensation of molecules A and B to get the target molecule.

The overall synthetic route is depicted in the Scheme 3.2
Scheme 3.2

- Synthesis of molecule A
Synthesis of Molecule B

\[
\begin{align*}
\text{Ac}_2\text{O} & \quad \text{NH}^+\text{CH}_3 \\
\text{DMF, POCI}_3 & \quad \text{Cl} \\
\end{align*}
\]

- Condensation of Molecules A and B

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{NH}^+\text{NH}_2 \\
\text{4a-g} & \quad \text{O}_2\text{N} & \quad \text{NH}^+\text{NH-N}=\text{NH}_2 \\
\end{align*}
\]

Synthesis of molecule A

The synthesis of molecule A has been carried out in the following three steps.


Step 1: Synthesis of ethyl naphtho[2,1-b]furan-2-carboxylate 1

The synthesis of ethyl naphtho[2,1-b]furan-2-carboxylate 1 was accomplished by using 2-hydroxy-1-naphthaldehyde as a starting material. This aldehyde on treatment
with ethyl chlorocetate in presence of weak base i.e. potassium carbonate underwent both condensation and cyclization simultaneously and produced ethyl naphtho[2,1-b]furan-2-carboxylate 1 in good yield.

\[
\begin{align*}
&\text{CICH}_2\text{COOC}_2\text{H}_5 \quad \text{K}_2\text{CO}_3 \\
&\text{NaOH}
\end{align*}
\]

The IR and \(^1\)H NMR spectra of this compound superimposed with the spectra of an authentic sample \(^3\). The mixed melting point of this compound with a known sample did not show any depression.

Step 2: Nitration of ester 1 to obtain ethyl 8-nitronaphtho[2,1-b]furan-2-carboxylate 2

The nitration of ethyl naphtho[2,1-b]furan-2-carboxylate 1 was carried out by using nitrating mixture of concentrated nitric acid and concentrated sulphuric acid at 0-5°C in acetic acid. The nitration occurred smoothly and produced a single product as detected by thin layer chromatography. This product was earlier identified as ethyl 3-nitronaphtho[2,1-b]furan-2-carboxylate.

\[
\begin{align*}
&\text{Conc. HNO}_3/\text{H}_2\text{SO}_4 \\
&\text{CH}_3\text{COOH}
\end{align*}
\]

The IR spectrum (fig 3.1) exhibited the absorption peak at 1641 and 1586 cm\(^{-1}\) due to carbonyl and nitro groups. The \(^1\)H NMR spectrum (fig 3.2) of this compound
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exhibited a quartet and triplet at $\delta$ 4.1 and $\delta$ 1.4 due to CH$_2$ and CH$_3$ protons and multiplet at $\delta$ 7.3-8.2 due to six aromatic protons.

Fig 3.1: IR Spectrum of Compound 2

Fig 3.2: $^1$H NMR Spectrum of Compound 2
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Earlier it was thought that nitration takes place at C-3 to produce ethyl 3-nitronaphtho[2,1-b]furan-2-carboxylate. The assignment of the structure was based on $^1$H NMR spectral studies. However, when second thought was given to this reaction, electron withdrawing ester group may not assist the entry of nitro group at C-3 and moreover it may cause steric hindrance in the molecule. Therefore to prove the position of nitro group without any ambiguity, attempts were made to obtain single x-ray crystal structure of this product. The attempt were futile as it was not possible to obtain well defined crystal of this nitro compound.

Alternatively, bromination of ethyl naphtho[2,1-b]furan-2-carboxylate was carried out by Shet Prakash et al.\textsuperscript{31} and the product could be obtained in crystalline form. The single x-ray crystal structure of this compound proved the structure of the product as ethyl 8-bromonaphtho[2,1-b]furan-2-carboxylate (Fig 3.3).

Fig 3.3: ORTEP diagram of ethyl 8-bromonaphtho[2,1-b]furan-2-carboxylate
In aralogy with the above observation the nitrated compound 2 was assigned the structure as ethyl 8-nitronaphtho[2,1-b]furan-2-carboxylate, and not ethyl 3-nitronaphtho[2,1-b]furan-2-carboxylate as thought earlier.


![Chemical structure](image)

In support of the structure assigned IR, $^1$H NMR, and mass spectra of compound A were obtained. In IR spectrum of A (Fig 3.4), the carbonyl, NH and NH$_2$ stretching frequency were observed at 1654, 3231 and 3427 cm$^{-1}$ respectively. The $^1$H NMR spectrum of A (Fig 3.5) exhibited a singlet at $\delta$ 4.5 for NH$_2$ protons, a multiplet at $\delta$ 7.5-8.2 for aromatic protons and a singlet at $\delta$ 10.0 for NH proton. The mass spectrum (Fig 3.6) exhibited a peak at m/z 271 corresponds to its molecular weight.
Fig 3.4: IR Spectrum of Compound 3

Fig 3.5: $^1$H NMR Spectrum of Compound 3
Fig 3.6: Mass Spectrum of Compound 3

- Synthesis of molecule B:

6-Substituted-2-chloro-3-formyl-quinolines 4a-g

Various 6-substituted-2-chloro-3-formylquinolines 4a-g were synthesized by well known procedure. For this reaction the following substituted anilines were used as starting materials in order to obtain the compounds 4a-g.

- Aniline
- 4-Fluoroaniline
- 4-Chloroaniline
- 4-Bromoaniline
- 4-Nitroaniline
- 4-Hydroxyaniline
- 4-Methylaniline
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Once again selection of various substituted anilines was based on the presence of electronwithdrawing groups and electron donating groups in order to study the impact of such groups on biological activities which has been described in chapter- 7 of this thesis.

All these substituted anilines were converted into corresponding N-acetyl derivatives by reacting them with acetic anhydride. These N-acetyl derivatives on treatment with Vilsmeier reagent (DMF+POCl₃) underwent ring closure to produce corresponding 8-substituted-2-chloro-3-formylquinolines 4a-g.

\[
\begin{align*}
\text{R} & \quad \text{NH} \rightarrow \text{Ac}_2\text{O} \rightarrow \text{R} \quad \text{NH} \rightarrow \text{O} \\
\text{R} & \quad \text{NH} \rightarrow \text{CH₃} \\
\text{DMF}, \text{POCl}_3 & \quad \rightarrow \text{4a-g (B)} \\
\end{align*}
\]

This useful reaction is placed into the combes category

Condensation of 8-nitronaphtho[2,1-b]furan-2-carbohydrazide 3 (A) and 6-substituted-2-chloro-3-formylquinoline 4a-g (B).

8-Nitronaphtho[2,1-b]furan-2-carbohydrazide 3 (A) was reacted with appropriately substituted 2-chloro-3-formylquinolines 4a-g (B) in the presence of ethanol to produce N'-[substituted2-chloroquinolin-3-yl]methylidene]-8-nitronaphtho[2,1-b]furan-2-carbohydrazide 5a-g.
The structures of compounds 5a-g were well supported by its IR, \(^1\)H NMR and mass spectral data. The IR spectrum of compound \(5b\) (Fig 3.7) exhibited absorption bands at 1653, 1692 and 3234 cm\(^{-1}\) due to C=N, C=O and N-H stretching frequencies respectively.

In the \(^1\)H NMR spectrum of compound \(5b\) (Fig 3.8) a multiplet was observed at \(\delta\) 6.5 - 8.5 integrating for ten aromatic protons. The NH proton appeared as singlet at \(\delta\) 9.7, which was exchangeable with D\(_2\)O. The final proof for the assigned structure was obtained by recording mass spectrum of \(5b\) (Fig 3.9) which exhibited molecular ion peak at \(m/z\) 462 corresponding to its molecular weight. Thus, based on this spectroscopic data and earlier observations the structures of compound \(5a-g\), was confirmed.

The spectral data of other compounds i.e. \(5a-g\) is presented in experimental section of this chapter.
Fig 3.7: IR Spectrum of Compound 5b

Fig 3.8: $^1$H NMR Spectrum of Compound 5b
Fig 3.9: Mass Spectrum of Compound 5b
Experimental

Synthesis of ethyl 8-nitronaphtho[2,1-b]furan-2-carboxylate (2)

A cooled nitrating mixture of concentrated nitric acid and concentrated sulphuric acid (1:2, 15 ml) was added very slowly to a cooled solution of ethyl naphtho[2,1-b]furan-2-carboxylate 1 (2.4 g, 0.01 mol) in glacial acetic acid (4 ml) and the mixture was stirred for about 30 minutes at 0 to 15°C. The stirring was continued for 2 hour and the reaction mixture was poured on to crushed ice. The product that separated as solid was collected, dried and recrystallised from aqueous ethanol (Yield- 2.09 g, 73%) M. P. 122°C.

Synthesis of 8- nitronaphtho[2,1-b]furan-2-carboxyhydrazide (A)

A mixture of ethyl 8-nitronaphtho[2,1-b]furan-2-carboxylate 2 (2.85 g, 0.01 mol) and hydrazine hydrate (2.5 ml, 99%) in ethanol (10 ml) was heated under reflux for 5 hour, cooled to room temperature and the solid thus separated was filtered, washed with ethanol and recrystallised from aqueous DMF to obtain the product as solid (Yield- 2.2g, 81%) M. P. 185°C.


8-Nitronaphtho[2,1-b]furan-2-carboxyhydrazide A (0.285 g, 0.001mol), 2-chloro-6-fluoro-3-formylquinoline 4 (0.01 mol) were taken in ethanol with catalytic amount of acetic acid and heated to refluxed for 6 hour. After completion of the reaction (TLC), the reaction mixture was poured onto crushed ice. The solid mass thus separated out was filtered, washed with water and dried to get the desired compound 5b. Similarly the compounds 5a-g were synthesized from various substituted 2-chloro-3-formylquinolines.
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Spectral data of N-[6-bromo-2-chloroquinolin-3-yl]methylidene-8-nitronaphtho[2,1-b]furan-2-carbohydrazide 5d

IR (cm<sup>-1</sup>): 3233 (N-H), 1696 (C=O), 1601 (C=N); <sup>1</sup>HNMR (300 MHz, DMSO) δ (ppm): 9.9 (1H, S, CONH), 6.7-8.1 (10H, m, ArH); MS m/z = 523.

Spectral data of N-[2-chloro-6-hydroxyquinolin-3-yl)methylidene]-8-nitronaphtho[2,1-b]furan-2-carbohydrazide 5f

IR (cm<sup>-1</sup>): 3314 (N-H), 1699 (C=O), 1589 (C=N); <sup>1</sup>HNMR (300 MHz, DMSO) δ (ppm): 10.6 (1H, S, CONH), 7.3-8.5 (10H, m, ArH); MS m/z = 460.

Spectral data of N-[2-chloro-6-methylquinolin-3-yl]methylidene-8-nitronaphtho[2,1-b]furan-2-carbohydrazide 5g

IR (cm<sup>-1</sup>): 3231 (N-H), 1692 (C=O), 1599 (C=N); <sup>1</sup>HNMR (300 MHz, DMSO) δ (ppm): 10.0 (1H, S, CONH), 7.5-8.5 (6H, m, ArH); MS m/z = 458.
The physical and analytical data of the synthesized compounds is presented in Table 3.1.

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<th>Comp.</th>
<th>R</th>
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References

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