Chapter - IV

Synthesis of Benzo[6]-1,8-naphthyridines & Pyrimido[4,5-b]quinolines
Introduction

Pyridopyridines (diazanaphthalenes, naphthyridines) are fused heterocyclic systems containing two nitrogen atoms in the adjacent rings. Naphthyridine derivatives attract interest because of the broad spectrum of their biological activities. These compounds are used in diagnostics and treatment of different human diseases (including HIV infection), agriculture, animal husbandry for external- and internal-parasite control, in industry as preservatives and components of lubricating coolants for metal processing, etc. Pyronaridine is an azacrine-type mannich base with the naphthyridine nucleus, which resembles acridine (1). Pyronaridine was first synthesized at the Institute of Parasitic Diseases, Shanghai, in 1970. Clinical trials began in 1971, and by 1980 it was formally released as a new antimalarial drug in China.

Since the discovery, in 1962, of the progenitor 1,8-naphthyridines, nalidixic acid, 1,5-naphthyridine derivatives, like other isomeric pyridopyridines, were found in many natural substances and were used for the construction of a series of efficient medicines. The chemical properties of 1,5-naphthyridines and the possibilities of their use for the preparation of biologically active compounds have been studied extensively. In particular bromination of three isomeric thieno[c][1,5]naphthyridines (2,3,4) and their N-oxides
with tetrabutylammonium perbromide or bromine in the presence of SOCl₂ was investigated⁴.

Naphthyridine derivatives possess anti-tumor⁵, anti-bacterial⁶, tuberculostatic⁷, cardio-tonic⁸, anticonvulsant and insecticidal⁹ properties. They have been reported as potential drugs for the treatment of bladder function disorders¹⁰. 1,6-Naphthyridine derivatives have been tested pharmacologically as potent antagonists at adrenoreceptors¹¹. They are also used as novel potent adenosine 3',5'-cyclic phosphate phosphodiesterase III inhibitors¹². Naphthyridine derivatives constitute an important class of compounds possessing diverse types of biological properties. Hence, the synthetic approach of some pyridine derivatives from tetracyanopropenes are important part of cyano-carbon chemistry and the synthesis of 1,6-napthyridine derivatives have been widely dealt in the literature¹³,¹⁴ as part of a general study on cyclization of dinitriles. The Food and Drug Administration, USA has approved the drug trovafloxain, which contains the naphthyridine moiety, for the treatment of selected pulmonary, surgical, intra-abdominal, gynecologic, pelvic, skin and urinary tract infections. Its spectrum of activity includes aerobic gram-positive and gram-negative organisms as well as anaerobic pathogens¹⁵,¹⁶. The photosensitizing activity of enoxacin, which belongs to the family of naphthyridine analogue, has been studied extensively¹⁷. The pyrrolidine part of the compounds studied has useful medicinal properties. Pyrrolidine derivatives inhibit the production of prostaglandin E₂ and intracellular phospholipase A₂, and are useful for
prevention and treatment of rheumatoid arthritis, asthma, allergic, rhinitis and related
diseases\textsuperscript{18}. Some of the aminopyrrolidine produces are used as pharmaceutical and agro
chemical intermediates\textsuperscript{19}. The pyrrolidine-cyclohexyl compounds act as highly lipophilic
chemically novel potent selective kappa opioid agonists\textsuperscript{20} and were found to be
preferential dopamine auto receptor antagonists\textsuperscript{21}. Some of the arylpyrrolidine derivatives
are used as insecticides, aracicides and herbicides\textsuperscript{22}. The naphthyridine derivatives also
act as dyes\textsuperscript{23}. Since naphthyridine derivatives come under the class of heterocyclic
compounds, it is expected that they possess laser and non-linear optical properties\textsuperscript{24-26}.

Substituted naphthyridines are used for combating exo- and endo-parasites in
agriculture and in cattle breeding, as preservatives and ingredients of cutting fluids, and
also as ligands in analytical chemistry\textsuperscript{27}. Compounds in these classes exhibit fungicidal
activity against phytopathogenic fungi and some of these patent drugs are used for the
treatment of memory loss, aging and Alzheimer’s disease and also as antiallergic
agents\textsuperscript{28}. In particular, naphthyridines and spironaphthyridinones are useful for
suppressing the immune response and in the treatment of autoimmune and other immune
disorders\textsuperscript{29}. Compound (5) had an ED50 of 0.13mg topically in the arachidonic acid
mouse ear test, a measure of its utility in the treatment of hyperproliferative skin
diseases\textsuperscript{30}. A derivative of penicillanic acid (6) was covered by a patent as an
antibiotic\textsuperscript{31}. Derivatives of hydroxy acid (7) were covered by a patent as anthelmintics\textsuperscript{32}.
Indolo[1,7-b,c][2,6]naphthyridine (8) is a strong and selective antagonist of serotonin
receptors of the 5-HT2C/2B subtypes possessing relatively weak affinity for 5-HT2A
subtype receptors\textsuperscript{32-35}. The indolonaphthyridine (8) and (9) were covered by patents as
Benzonaphthyridines & Pyrimido[4,5-6]quinolines

drugs for the treatment of appetite disturbance, obsessive states (phobia and depressions) and other diseases\textsuperscript{35,36}.

![Chemical structures](image)

In a number of studies, the structural 2,7-naphthyridine fragment was found to be a component of alkaloids alangimaridine\textsuperscript{37} (10), isoalamarine\textsuperscript{38} (11), nauclefine\textsuperscript{39,40} (12), eudistones\textsuperscript{41} (13), kuanoniamines\textsuperscript{42} (14), alkaloids (15) exhibiting high antifungal and anticancer activities\textsuperscript{43} an analogue of olivcecin\textsuperscript{44} (16) and benzo derivatives (17) suitable for the treatment of asthma and lowering of blood pressure\textsuperscript{45}. The data on antispasmodic activity of 2,7-naphthyridine derivatives were also reported\textsuperscript{46}. The increasing incidence of resistance to current HIV-1 therapy underscores the need to develop antiretroviral agents with new mechanisms of action. Integrase, one of three viral enzymes essential for HIV-1 replication, presents an important yet unexploited opportunity for drug development. The naphthyridine pharmacophore evolved from the prototypical diketo acid class of integrase inhibitors. The naphthyridine carboxamides (18) provides a platform for the discovery of potent integrase inhibitors\textsuperscript{47}. Also naphthrytidones (19)
Benzonaphthyridines and Pyrimido[4,5-b]quinolines derivative emerged in parallel, enoxacin and tossufloxacin were the first among them, followed by trofloxacin and more recently gemeifloxacin.

Benzonaphthyridines are interesting compounds with respect to their biological activities. Benzo[c][2,7]naphthyridines of the tricyclic hydroxamic acid type are important from a pharmaceutical point of view, because of their potential inhibition of lipooxygenase, whereas the corresponding lactams can be used as educts for the synthesis of drugs of the halofantrine type agents against malaria.
Fused pyrimidine chemistry began in 1776, when Scheele isolated uric acid\(^{25}\) (25). However, more systematic investigations were undertaken around 100 years later, when the works of well-known chemists namely Bischof, Riedel, Niementowski, Gabriel, and Bogert established significant progress in this field\(^{56}\). Particularly, numerous papers on chemistry of pyrimidines (26) and purines (27) have been published since the discovery of the presence of some purine bases in double-stranded nucleic acids. Since the early years of this century, several studies on the synthesis and structure-activity relationships of pyrimidine derivatives have been reported\(^ {56-63}\).

The pyrimidine nucleus is embedded in a large number of alkaloids, drugs, antibiotics, agrochemicals, and antimicrobial agents\(^ {80}\). Many simple fused pyrimidines such as purines (27) and pteridines (28) are biologically active by themselves\(^ {57,58}\), or are essential components of very important naturally occurring substances (i.e.; nucleic acids).
Some pteridine derivatives are also used as anti-leukemic drugs or potassium-conserving diuretics. In addition, several quinazoline alkaloids exhibit hypnotic, bronchodilatory, and antimalarial activities. Some fused thieno[3,2-d]pyrimidines serve as anti-allergy drugs, some act as fungicides. Benzopyrimidines have found application in a wide range of medicinal chemistry because of their diverse biological activities, such as antibacterial, anticonvulsant, antiinflammatory, and antitumor and antifungal activities.
Present Work

The successful development in this laboratory for the synthesis of biologically important new tri and tetracyclic heterocyclic system containing furan, thiophene, pyridine, pyrimidine and pyran rings prompted us to extend this work for the synthesis and investigation of the biological activity of various naphthyridines. Though, the number of naphthyridine derivatives widely occurs in nature and are also produced synthetically, an efficient synthetic route and structural diversity investigation remains active research area. In the present investigation, we focused our interest on the synthesis of benzonaphthyridine and quinolopyrimidine derivatives, which are listed below.

\[
\begin{align*}
R, & - N^2 N^3 R_3 \\
R & = NO_2, Cl, Br \\
R_1 & = NH_2 \\
R_2 & = CN, COCH_3, COOC_2H_5 \\
R_3 & = NH_2, CH_3, OH \\
R_4 & = NH_2, O, S \\
R_5 & = H, S, CH_3
\end{align*}
\]

As mentioned earlier, the convenient approaches for the synthesis of these compounds involves the series of steps and they are as follows.

2. Condensation of 2-aminobenzaldehyde with malononitrile with 2-amino-3-cyanoquinolines.
3. Conversion of 2-amino-3-cyanoquinoline into benzonaphthyridines and quinolopyrimidines.

The synthesis of 2-aminobenzaldehyde and their conversion into 2-amino-3-cyanoquinolines has been already discussed in chapter-2. For the construction of
benzonaphthridines and quinolopyrimidine nucleus of target compounds, we required quinolines with amino group and cyano group at position -2 and -3 respectively. Heterocyclic 2-aminonitriles are well established as versatile starting materials for the synthesis of a wide variety of fused heterocyclic compounds\textsuperscript{86}. Hence, the key intermediate in this synthesis is 2-amino-3-cyanoquinolines (1a-c) [Scheme-1].

![Scheme-1](image)

**General Mechanism**

The applications of malononitrile in organic chemistry for the synthesis of unique heterocyclic systems, which have pharmaceutical applications such as pesticides, fungicides are well known\textsuperscript{87}. Thus the reaction of the 2-amino-3-cyanoquinolines (1a-c) with malononitrile and other analogue like ethyl cyanoacetate, acetyl acetone and diethyl malonate produced new compounds i.e.; (2a-c, 3a-c, 4a-c, 5a-c) respectively.

The reaction of (1a-c) with malononitrile, diethyl malonate, ethyl cyanoacetate and ethyl acetoacetate was carried out, in the mole ratio 1:1. The reaction involved the
condensation of 2-aminobenzaldehydes under basic condition followed by cyclization with amino group led to naphthyridine derivatives [Scheme-2]. These may induce good pharmaceutical properties to the newly synthesized compounds. The structures of all newly synthesized compounds were established on the basis of analytical and spectroscopic studies.

**Scheme-2**

**General Mechanism**
The IR spectrum of \(2a\) [Fig: 4.1] was not so relevant to conclude the structure of \(2a\), due to the fact that the compound \(1a\) were also contains similar substituents, i.e.; -NH₂ and -CN. In the \(^1\text{H-NMR}\) spectrum of \(2a\) [Fig: 4.2] appearance of additional signal at 6.3 \(\delta\) & 7.2 \(\delta\) is due to two -NH₂ groups (D₂O exchangeable) of newly formed pyridine ring system onto quinoline ascertain the structure of \(1a\). However, aromatic protons remained at the same i.e.; 7.5-8.6 \(\delta\) integrated to four protons. Finally, the structure of the \(2a\) was confirmed by studying its mass spectrum.

In the IR spectra of \(3a\) [Fig: 4.3], \(4a\) [Fig: 4.5] and \(5a\) the absorption band for -CN group was found to be absent. This data itself indicates that, the formation of products by the reaction of \(1a\) with diethyl malonate, ethyl cyanoacetate and ethyl acetoacetate respectively. The band corresponds to primary NH₂ group was present in IR spectra. In case of \(5a\) a broad peak at 3475 cm⁻¹ was observed.

The \(^1\text{H-NMR}\) spectrum of \(3a\) [Fig: 4.4] shows the signals as triplet and quartet in the region of 1.37 \(\delta\) and 4.3 \(\delta\) attributed to -O-CH₂-CH₃ group. Appearance of two -NH₂ (D₂O exchangeable) signals at 7.0 \(\delta\) and 7.7 \(\delta\) supports the structure. In case of \(^1\text{H-NMR}\) spectrum of \(4a\) [Fig: 4.6], new signals appeared at 2.5 \(\delta\) and 2.7 \(\delta\) corresponds to -CH₃ and -COCH₃ groups respectively. Aromatic protons remain at 7.6–8.9 \(\delta\). \(^1\text{H-NMR}\) spectrum of \(5a\) displayed a signals corresponds to -OH, -NH₂ (D₂O exchangeable), and -OCH₂CH₃ groups at appropriate place consistent with the assigned structures. Further the structure of all these compounds i.e.; \(3a\), \(4a\) and \(5a\) were also established by their mass spectral studies.

In order to have more and more biologically promising naphthyridine analogues, the 2-amino-3-cyanoquinolines (1a-c) were made to react with CS₂ in DMSO in presence
of piperidine, to produce the pyrimido[4,5-b]quinolin-2,4(1H,3H)-dithiones (6a-c). One more interesting pyrimido[4,5-b]quinolin-4-amines (7a-c) bearing amino group, was obtained by refluxing the 2-amino-3-cyanoquinolines (1a-c) with formamide in absolute ethanol. The more number of derivatives of quinolo pyrimidines was also achieved by the reaction of (1a-c) with acetic anhydride to give the corresponding 2-methylpyrimido[4,5-b]quinolin-4(3H)-ones (8a-c) [Scheme-3]. The spectral and analytical data of (6a-c), (7a-c) and (8a-c) [Fig: 4.7 & 4.8] were in agreement with the assigned structure.
Fig. 4.1; IR Spectrum of 2a

Type: HYPER IR
Abscissa: 1/cm
Min: 401.17
Max: 3998.16
Nd: 1866

Time: 16:36:08
User: vasudha
Ordinate: %T
Data Interval: 1.92868

ND: 20
Detector: standard
Apodization: Happ
Range: 1/cm
Resolution: 4.0
Mirror Speed: 2.8 (low)
Fig: 4.3; IR Spectrum of 3a

- Wavenumbers and %T values are indicated on the chart.
- The molecule structure is shown at the top left.
- The IR spectrum includes various peaks ranging from 1446.5 to 754.1 cm⁻¹.
Fig: 4.5: IR Spectrum of 4a

![IR Spectrum of 4a](image)

- **Type:** HYPER IR
- **Abscissa:** 1/cm
- **Min:** 401.17
- **Ndp:** 1866
- **Gain:** auto
- **Time:** 16:06:12
- **User:** vasudha
- **Ordinate:** %T
- **Max:** 3998.16
- **Data Interval:** 1.92868
- **Aperture:** auto
- **NScans:** 20
- **Detector:** standard
- **Apodization:** Happ
- **Range:** 1/cm
- **Resolution:** 4.0
- **Mirror Speed:** 2.8(low)
Fig: 4.6: $^1$H-NMR Spectrum of 4a
Fig: 4.8; $^1$H-NMR Spectrum of 8a

Current Data Parameters
NAME 6323-Kiran-1h
EXPN0 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20060323
Time 16.00
INSTRUM amx400
PROBHD 5 mm QNP 1H
PULPROG zgpr
TD 16384
SOLVENT DMSO
NS 128
DS 0
SWH 6493.481 Hz
FTDRES 0.396331 Hz
AQ 1.2616180 sec
RG 8192
DE 77.000 usec
TE 96.25 usec
M1 300.0 K
M1 1 dB
M2 0.0000000 sec
M2 55 db
M8 1500000.00 usec
M8 0.0000000 sec
M1 11.50 usec
SF01 400.1376205 MHz
NUCLEUS 1H

F2 - Processing parameters
SI 32768
SF 400.1362928 MHz
WDW E1
SSB 0
LB 0.30 Hz
GB 0
FC 0.30
Experimental

General Procedure for the Preparation of 2,4-Diamino-3-cyano-7-nitrobenzo[b]-1,8-naphthyridine: 2a

A mixture of 2-amino-3-cyano-6-nitroquinoline 1a (2.14 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol) and piperidine (0.5 mL) in freshly distilled DMSO (30 mL) was heated under reflux for 4h. The solid product, which precipitated upon heating, was collected by filtration. Crude product obtained was further purified by column chromatography (hexane: ethyl acetate 80:20 as eluent) to furnish pure product (1.84 g, 66%).

2,4-Diamino-3-cyano-7-nitrobenzo[b]-1,8-naphthyridine: 2a

Yield: 1.84 g, 66 %, mp: 228-230 °C; IR (KBr, v, cm⁻¹): 2221 (CN), 3361-3481 (NH₂); ¹H-NMR (δ, DMSO-d₆): 6.3 & 7.2 (4H, s, 2 NH₂), 7.5-8.6 (4H, m, H_arom); MS: m/z: 280 [M⁺]; Analysis: C₁₃H₁₈N₆O₂ Cal; C 55.72 %; H 2.88 %; N 29.99 %. Found; C 55.23 %; H 2.12 %; N 29.14 %.

2,4-Diamino-3-cyano-7-chlorobenzof[b]-1,8-naphthyridine: 2b.

Yield: 1.72 g, 64 %, mp: 243-245 °C; IR (KBr, v, cm⁻¹): 2225 (CN), 3361-3477 (NH₂); ¹H-NMR (δ, DMSO-d₆): 6.3 & 7.2 (4H, s, 2 NH₂), 7.6-8.5 (4H, m, H_arom); MS: m/z: 270 [M⁺]; Analysis: C₁₃H₁₈ClN₅ Cal; C 57.90 %; H 2.99 %; N 25.97 %. Found; C 57.79 %; H 2.83 %; N 25.83 %.

2,4-Diamino-3-cyano-7-bromobenzof[b]-1,8-naphthyridine: 2c.

Yield: 1.84 g, 59 %, mp: 259-261 °C; IR (KBr, v, cm⁻¹): 2223 (CN), 3362-3475 (NH₂); ¹H-NMR (δ, DMSO-d₆): 6.3 & 7.2 (4H, s, 2 NH₂), 7.6-8.5 (4H, m, H_arom); MS: m/z: 260 [M⁺]; Analysis: C₁₃H₁₈BrN₆ Cal; C 56.97 %; H 2.88 %; N 29.99 %. Found; C 56.23 %; H 2.12 %; N 29.14 %.
General Procedure for the Preparation of Ethyl-2,4-diamino-7-nitrobenzo[6]-1,8-naphthyridin-3-carboxylate: 3a

To the solution of 2-amino-3-cyano-6-nitroquinoline 1a (2.14 g, 0.01 mol), piperidine (0.5 mL) in freshly distilled DMSO (30 mL) was added ethyl cyanoacetate (1.13 g, 0.01 mol). After the solution had been stirred for 10 min, refluxed for 5 h. The reaction mixture was poured into ice-cooled water (150 mL). The precipitated product was filtered, washed with water. The solid obtained was purified by column chromatography over silica-gel (hexane: chloroform 80:20 as eluent) to furnish pure product ethyl 2,4-diamino-7-nitrobenzo[6]-1,8-naphthyridin-3-carboxylate 3a (2.09 g, 64%).

Ethyl-2,4-diamino-7-nitrobenzo[6]-1,8-naphthyridin-3-carboxylate: 3a

Yield: 2.09 g, 64 %, mp: 245-246 °C; IR (KBr, ν, cm⁻¹): 3359-3481 (NH₂); 1703 (CO) ¹H-NMR (δ, DMSO-d6): 1.37 (3H, t, OCH₂CH₃), 4.30 (2H, q, OCH₂CH₃), 7.0 & 7.7 (4H, s, 2 NH₂), 7.6-8.5 (4H, m, Hₐrom); MS: m/z: 327 [M⁺]; Analysis: C₁₅H₁₃N₅O₂ Cal; C 55.05 %; H 4.04 %; N 21.40 %. Found; C 55.74 %; H 4.17 %; N 21.56 %.

Ethyl-2,4-diamino-7-chlorobenzo[6]-1,8-naphthyridin-3-carboxylate: 3b

Yield: 1.99 g, 63 % mp: 261-263 °C; IR (KBr, ν, cm⁻¹): 3353-3474 (NH₂); 1706 (CO); ¹H-NMR (δ, DMSO-d6): 1.37 (3H, t, OCH₂CH₃), 4.30 (2H, q, OCH₂CH₃), 7.0 & 7.7 (4H, s, 2 NH₂), 7.6-8.4 (4H, m, Hₐrom); MS: m/z: 317 [M⁺]; Analysis: C₁₅H₁₃ClN₄O₂ Cal; C 56.88 %; H 4.14 %; N 17.69 %. Found; C 56.72 %; H 4.32 %; N 17.18 %.
Ethyl-2,4-diamino-7-bromobenzo[b]-1,8-naphthyridin-3-carboxylate: 3c

Yield: 2.05 g, 57 %, mp: 270-271 °C; IR (KBr, v, cm⁻¹): 3359-3481 (NH₂); 1701 (CO); ¹H-NMR (δ, DMSO-d₆): 1.37 (3H, t, OCH₂CH₃), 4.30 (2H, q, OCH₂CH₃), 7.0 & 7.7 (4H, s, 2 NH₂), 7.4-8.6 (4H, m, Hₐrom); MS: m/z: 362 [M⁺]; Analysis: C₁₅H₁₃BrN₄O₂ Cal; C 49.88 %; H 3.63 %; N 15.51 %. Found; C 49.72 %; H 3.57 %; N 15.47 %.

General Procedure for the Preparation of 1-(4-Amino-7-nitro-2-methylbenzo[b]-1,8-naphthyridin-3-yl)ethanone: 4a

2-Amino-3-cyano-6-nitroquinoline 1a (2.14 g, 0.01 mol) was added to a stirred solution of acetylacetone (1.00 g, 0.01 mol), piperidine (0.5 mL) in freshly distilled DMSO (30 mL). The reaction mixture was stirred for 3 h. After being quenched in demineralised water (250 mL), the compound separated as solid. The solid obtained was filtered, dried and purified by column chromatography over silica gel (hexane: ethyl acetate 60:40 as eluent) to produce 1-(4-amino-7-nitro-2-methylbenzo[b]-1,8-naphthyridin-3-yl)ethanone 4d (1.83 g, 62 %).

1-(4-Amino-7-nitro-2-methylbenzo[b]-1,8-naphthyridin-3-yl)ethanone: 4a

Yield: 1.83 g, 62 %, mp: 190-192 °C; IR (KBr, v, cm⁻¹): 3327-3431 (NH₂); 1624 (CO); ¹H-NMR (δ, DMSO-d₆): 2.55 (3H, s, CH₃), 2.76 (3H, s, COCH₃); 6.7 (2H, s, NH₂), 7.6-8.8 (4H, m, Hₐrom), MS: m/z: 296 [M⁺]; Analysis: C₁₅H₁₂N₄O₃ Cal; C 60.81 %; H 4.08 %; N 18.91 %. Found; C 60.15 %; H 4.56 %; N 18.75 %.
1-(4-Amino-7-chloro-2-methylbenzo[b]-1,8-naphthyridin-3-yl)ethanone: 4b

Yield: 1.74 g, 61 %, mp: 200-201 °C; IR (KBr, ν, cm⁻¹): 3330-3441 (NH₂); 1625 (CO); ¹H-NMR (δ, DMSO-d₆): 2.55 (3H, s, -CH₃), 2.75 (3H, s, COCH₃); 6.7 (2H, s, NH₂), 7.5-8.6 (4H, m, Hₐrom), MS: m/z: 286 [M⁺]; Analysis: C₁₅H₁₂ClN₃O Cal; C 63.05 %; H 4.23 %; N 14.71 %. Found; C 63.42 %; H 4.32 %; N 12.19 %.

1-(4-Amino-7-bromo-2-methylbenzo[b]-1,8-naphthyridin-3-yl)ethanone: 4c

Yield: 1.94 g, 59 %, mp: 211-213 °C; IR (KBr, ν, cm⁻¹): 3330-3446 (NH₂); 1626 (CO); ¹H-NMR (δ, DMSO-d₆): 2.55 (3H, s, -CH₃), 2.76 (3H, s, COCH₃); 6.7 (2H, s, NH₂), 7.4–8.6 (4H, m, Hₐrom), MS: m/z: 330 [M⁺]; Analysis: C₁₅H₁₂BrN₃O Cal; C 54.56 %; H 3.66 %; N 12.73%. Found; C 54.50 %; H 3.72 %; N 12.19 %.

General Procedure for the Preparation of Ethyl 4-amino-7-nitro-2-hydroxybenzo[b]-1,8-naphthyridin-3-carboxylate: 5a

To a solution 2-amino-3-cyano-6-nitroquinoline 1a (2.14 g, 0.01 mol), piperidine (0.5 mL) in freshly distilled DMSO (30 mL) was added diethyl malonate (1.60 g, 0.01 mol). After the solution had been stirred for 10 min, refluxed for 4 h. The reaction mixture was poured into ice-cooled water (100 mL). The precipitated product was filtered, washed with water, charged into column chromatography over silica-gel (hexane: chloroform 70:30 as eluent) to yield the pure product ethyl 4-amino-7-nitro-2-hydroxybenzo[b]-1,8-naphthyridin-3-carboxylate 5a (2.16 g, 66 %).
Ethyl 4-amino-7-nitro-2-hydroxybenzo[b]-1,8-naphthyridin-3-carboxylate: 5a

Yield: 2.16 g, 66 %, mp: 185-187 °C; IR (KBr, v, cm⁻¹):
3368-3476 (NH₂), 1710 (CO); ¹H-NMR (δ, DMSO-d₆):
1.29 (3H, t, OCH₂CH₃), 4.32 (2H, q, OCH₂CH₃), 6.9 (2H, s, NH₂), 7.7-8.8 (4H, m, Hₐrom), 10.8 (1H, s, OH); MS: m/z: 328 [M⁺]; Analysis: C₁₅H₁₂N₄O₅ Cal; C 54.88 %; H 3.68 %; N 17.07 %. Found; C 54.74 %; H 3.47 %; N 17.53 %.

Ethyl 4-amino-7-chloro-2-hydroxybenzo[b]-1,8-naphthyridin-3-carboxylate: 5b

Yield: 1.96 g, 62 %, mp: 194-196 °C; IR (KBr, v, cm⁻¹):
3363-3477 (NH₂), 1716 (CO); ¹H-NMR (δ, DMSO-d₆):
1.29 (3H, t, OCH₂CH₃), 4.32 (2H, q, OCH₂CH₃), 7.7-8.8 (4H, m, Hₐrom), 6.9 (2H, s, NH₂), 10.9 (1H, OH); MS: m/z: 318 [M⁺]; Analysis: C₁₅H₁₂ClN₃O₃ Cal; C 56.70 %; H 3.81 %; N 13.23 %. Found; C 56.36 %; H 3.42 %; N 13.54 %.

Ethyl 4-amino-7-bromo-2-hydroxybenzo[b]-1,8-naphthyridin-3-carboxylate: 5c

Yield: 2.02 g, 56 %, mp: 176-177 °C; IR (KBr, v, cm⁻¹):
3365-3473 (NH₂), 1702 (CO); ¹H-NMR (δ, DMSO-d₆):
1.28 (3H, t, OCH₂CH₃), 4.33 (2H, q, OCH₂CH₃), 6.9 (2H, s, NH₂), 7.8-8.8 (4H, m, Hₐrom), 10.8 (1H, s, OH); MS: m/z: 363 [M⁺]; Analysis: C₁₅H₁₂BrN₃O₃ Cal; C 49.74 %; H 3.34 %; N 11.06 %. Found; C 49.74 %; H 3.40 %; N 11.01 %.

General Procedure for the Preparation of 7-Nitropyrimido[4,5-b]quinolin-2,4(1H,3H)-dithione: 6a

A mixture of 2-amino-3-cyano-6-nitroquinoline 1a (0.75 g, 0.0035 mol), piperidine (0.5 mL) in DMSO, was added CS₂ (0.3 g 0.004 mol). The reaction mixture was refluxed for 2 h and allowed to stand at room temperature for 6 h. This was poured in
to ice cooled water (200 mL). The precipitated product was filtered, washed with water, charged into column chromatography (chloroform: methanol 95:05 as eluent), to give 7-nitropyrimido[4,5-b]quinoline-2,4(1H,3H)-dithione 6a (0.68 g, 67 %).

7-Nitropyrimido[4,5-b]quinolin-2,4(1H,3H)-dithione: 6a

![Chemical structure of 7-Nitropyrimido[4,5-b]quinolin-2,4(1H,3H)-dithione](image)

Yield: 0.68 g, 67 %, mp: 123-125 °C; IR (KBr, ν, cm⁻¹): 3150-3100 (NH); ¹H-NMR (δ, DMSO-d₆): 7.8-9.1 (6H, m, Harom, 2 NH); MS: m/z: 290 [M⁺]; Analysis: C₁₁H₆N₄O₂S Cal; C 45.51 %; H 2.08 %; N 19.30 %.

Found; C 45.16 %; H 2.42 %; N 19.87 %.

7-Chloropyrimido[4,5-b]quinolin-2,4(1H,3H)-dithione: 6b

![Chemical structure of 7-Chloropyrimido[4,5-b]quinolin-2,4(1H,3H)-dithione](image)

Yield: 0.62 g, 64 %, mp: 113-114 °C; 3155-3110 (NH); ¹H-NMR (δ, DMSO-d₆): 7.4-9.4 (6H, m, Harom, 2 NH); MS: m/z: 280 [M⁺]; Analysis: C₁₁H₆ClN₃S Cal; C 47.22 %; H 2.16 %; N 15.02 %.

Found; C 47.18 %; H 2.40 %; N 15.87 %.

7-Bromopyrimido[4,5-b]quinolin-2,4(1H,3H)-dithione: 6c

![Chemical structure of 7-Bromopyrimido[4,5-b]quinolin-2,4(1H,3H)-dithione](image)

Yield: 0.65 g, 58 %, mp: 107-109 °C; 3160-3145 (NH); ¹H-NMR (δ, DMSO-d₆): 7.8-9.0 (6H, m, Harom, 2NH); MS: m/z: 325 [M⁺]; Analysis: C₁₁H₆BrN₃S Cal; C 40.75 %; H 1.87 %; N 12.96 %.

Found; C 40.12 %; H 1.53 %; N 12.87 %.

**General Procedure for the Preparation of 7-nitropyrimido[4,5-b]quinolin-4-amine: 7a**

A mixture of 2-amino-3-cyano-6-nitroquinoline 1a (0.75 g, 0.0035 mol), and freshly distilled formamide (0.18 g, 0.004 mol) was heated under reflux for 7 h. on cooling the reaction mixture for overnight; the solid obtained was filtered and washed
with water. This was further purified by column chromatography (chloroform: methanol 97:03), to furnish 7-nitropyrimido[4,5-b]quinolin-4-amine 7a (0.57 g, 68%).

7-Nitropyrimido[4,5-b]quinolin-4-amine: 7a

Yield: 0.57 g, 68 %, mp: 141-142 °C; IR (KBr, v, cm⁻¹): 3400-3300 (NH₂); ¹H-NMR (δ, DMSO-d₆): 7.2 (2H, s, 2 NH₂); 7.4-8.4 (4H, m, Hₐrom); 8.6 (1H, s, CH of pyrimidine); MS: m/z: 241 [M⁺]; Analysis: C₁₁H₇N₅O₂ Cal: C 54.77 %; H 2.93 %; N 29.03 %. Found: C 54.12 %; H 2.46 %; N 29.15 %.

7-Chloropyrimido[4,5-b]quinolin-4-amine: 7b

Yield: 0.54 g, 68 %, mp: 155-156 °C; IR (KBr, v, cm⁻¹): 3401-3303 (NH₂); ¹H-NMR (δ, DMSO-d₆): 7.2 (2H, s, 2 NH₂); 7.6-8.4 (4H, m, Hₐrom); 8.6 (1H, s, CH of pyrimidine); MS: m/z: 231 [M⁺]; Analysis: C₁₁H₇ClN₄ Cal: C 57.28 %; H 3.06 %; N 24.29 %. Found: C 57.30 %; H 3.12 %; N 24.50 %.

7-Bromopyrimido[4,5-b]quinolin-4-amine: 7c

Yield: 0.60 g, 63 %, mp: 146-148 °C; IR (KBr, v, cm⁻¹): 3400-3303 (NH₂); ¹H-NMR (δ, DMSO-d₆): 7.2 (2H, s, 2 NH₂); 7.6-8.3 (4H, m, Hₐrom), 8.5 (1H, s, CH of pyrimidine); MS: m/z: 275 [M⁺]; Analysis: C₁₁H₇BrN₄ Cal: C 48.02 %; H 2.56 %; N 20.37 %. Found: C 48.74 %; H 2.97 %; N 20.16 %.

General Procedure for the Preparation of 2-Methyl-7-nitropyrimido [4,5-b]quinolin-4(3H)-one: 8a

Suspended solution of 2-amino-3-cyano-6-nitroquinoline 1a (0.75 g, 0.0035 mol) in acetic anhydride (20 mL) heated under reflux for 2 h. Then the solvent was evaporated to leave the crude product, which was further purified by column chromatography over
silica gel (hexane: ethyl acetate 60:40 as eluent) to furnish the intermediate 2-methyl-7-nitropyrimido[4,5-b]quinolin-4(3H)-one 8a (0.60 g, 68%).

2-Methyl-7-nitropyrimido[4,5-b]quinolin-4(3H)-one: 8a

Yield: 0.60 g, 68 %, mp: 152-154 °C; IR (KBr, v, cm⁻¹): 3127 (NH); 1660 (CO); ¹H-NMR (δ, DMSO-d₆): 2.2 (3H, s, CH₃); 7.6-8.6 (5H, m, Hₐ arom, 1NH); MS: m/z: 256 [M⁺]; Analysis: C₁₂H₈N₄O₃ Cal: C 56.25 %; H 3.15 %; N 21.87 %. Found: C 56.52 %; H 3.74 %; N 21.74 %.

2-Methyl-7-chloropyrimido[4,5-b]quinolin-4(3H)-one: 8b

Yield: 0.55 g, 65 %, mp: 138-139 °C; IR (KBr, v, cm⁻¹): 3130 (NH); 1661 (CO); ¹H-NMR (δ, DMSO-d₆): 2.2 (3H, s, CH₃); 7.6-8.9 (5H, m, Hₐ arom, 1NH); MS: m/z: 246 [M⁺]; Analysis: C₁₂H₉ClN₃O Cal: 58.67 %; H 3.28 %; N 17.10 %. Found: C 58.12 %; H 3.12 %; N 17.74 %.

2-Methyl-7-bromopyrimido[4,5-b]quinolin-4(3H)-one: 8c

Yield: 0.61 g, 61 %, mp: 161-162 °C; IR (KBr, v, cm⁻¹): 3127 (NH); 1660 (CO); ¹H-NMR (δ, DMSO-d₆): 2.2 (3H, s, CH₃); 7.6-8.6 (5H, m, Hₐ arom, 1NH); MS: m/z: 290 [M⁺]; Analysis: C₁₂H₈BrN₃O Cal: 49.68 %; H 2.78 %; N 14.48 %. Found: C 49.98 %; H 2.17 %; N 14.74 %.
References


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