CHAPTER-6

THE COMPOUNDS ENCOMPASSING FURAN NUCLEUS ARE WIDELY DISTRIBUTED IN NATURE, PARTICULARLY AMONGST THE PLANT KINGDOM. MANY OF THESE COMPOUNDS ARE WELL KNOWN FOR THEIR USEFUL PHYSIOLOGICAL AND PHARMACOLOGICAL PROPERTIES. THIS GENERATED CONSIDERABLE INTEREST IN THE INVESTIGATION OF COMPOUNDS CONTAINING FURAN MOIETY FOR PHARMACOLOGICAL ACTIVITIES. AS A RESULT OF SUCH INVESTIGATIONS 5-NITROFURAN AND OTHER FURAN DERIVATIVES WERE BROUGHT TO LIGHT AND WERE FOUND TO POSSESS INTERESTING BIOLOGICAL ACTIVITIES. SINCE THEN, MANY RESEARCH GROUPS ARE INVOLVED IN THE SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS CONTAINING FURAN NUCLEUS AND EVALUATING THEM FOR VARIOUS BIOLOGICAL ACTIVITIES. A NUMBER OF SYNTHETIC BENZOFRAN DERIVATIVES HAVE BEEN FOUND TO POSSESS WIDE RANGE OF BIOLOGICAL ACTIVITIES SUCH AS ANTIMICROBIAL, ANALGESIC, ANTI-INFLAMMATORY, ANALEPTIC AND ANTIVIRAL. THIS RESEARCH HAS RESULTED IN THE ACCUMULATION OF VOLUMINOUS WORK ON BENZOFRANS AND SEVERAL MONOGRAPHS" DEVOTED TO THE STUDY OF BENZOFRANS HAVE APPEARED IN LITERATURE FROM TIME TO TIME.

FURAN NUCLEUS IS OFTEN FOUND FUSED WITH OXYGEN HETEROCYCLES RATHER THAN NITROGEN HETEROCYCLES IN NATURE. ALTHOUGH THE LATTER TYPE OF COMPOUNDS ARE VERY LESS IN NUMBER, THEY HAVE OCCUPIED A PROMINENT PLACE IN MEDICINAL CHEMISTRY. MORPHINE 1, GALANTHAMINE 2, HEROIN 3, CODEINE 4 AND RELATED ALKALOIDS ARE THE EXAMPLES OF SUCH COMPOUNDS IN WHICH FURAN NUCLEUS IS CONDENSED WITH NITROGEN HETEROCYCLE.
These compounds are well known for their analgesic activity and further research work has indicated that furan ring is an essential part of the structures of these molecules for medicinal properties.

During last few years, interest in this area was hence focused on synthesis and investigation of biological activities of various benzofurans fused with nitrogen heterocycles such as pyrimidine, pyridine, diazepine, triazepine, oxazine, pyridazine, thiazole, pyrazole, benzoxazole, quinoline, indole, benzimidazole, benzothiazole, quinoxaline etc.

In contrast with furan and benzofuran derivatives, naphthofuran and its derivatives are very rarely found in nature. Only few of them are reported to occur in some plants in the form of naphthofuroquinones. Mansonone D was found to be present in the extracts of leaves of *Mansonia altissima* belonging to Stuculiacae family. This
compound was identified as 3,4,8-trimethyl-2,3-dihydronaphtho[2,1-b]furan-5,6-dione. Price et al. isolated a new compound named as Dunnione 6 from the leaves of Streptocarpus dunnii and later assigned the structure 2,3,3-trimethylnaphtho[1,2-b]furan-4,5-dione on the basis of spectral studies.

Heartwood of Tabebuia pentaphylla was found to contain many derivatives of 2-acetylnaphtho[2,3-b]furan-4,9-diones.

Encouraged by these reports some researchers attempted the synthesis of some naphthofuran derivatives in the laboratory. First report in this connection appeared in the literature way back in 1897 by Stoermer. He reported the synthesis of parent heterocycle, naphtho[2,1-b]furan from 1-naphthoxyacetaldheyde. Same author could synthesize 2-acetylnaphtho[2,1-b]furan 8 by reacting 2-hydroxy-1-naphthaldehyde with chloroacetone in presence of dry acetone and metallic sodium.
Since then Emmott et al., Loader et al., Chatterjee et al., Weillthevorrot et al., Gilotdelhalle et al., Arrault et al., and few other researchers have synthesized some derivatives of naphtho[2,1-b]furan. Some of the compounds were found to possess mutagenic and carcinogenic activities.

Receiving impetus from these reports, synthesis of naphthofuran derivatives especially coupled or fused or bridged with nitrogen heterocycle was initiated in our laboratory. Several research papers describing the synthesis, characterization and biological activities of naphthofuran compounds have been published from our laboratory. These derivatives are found to possess various biological and pharmacological activities such as antibacterial, antifungal, analgesic, anti-inflammatory, anthelmintic and diuretic activities.

In the present investigation, our interest is to search a new non-steroidal drug possessing wide spectrum of pharmacological activities including antifertility activity. Thus, the importance of the less explored naphthofuran and biologically active nitrogen heterocycles encouraged us to take up the work of annulating suitable nitrogen heterocycle on easily accessible naphtho[2,1-b]furan derivatives. The obvious choice of the nitrogen heterocycle was pyrimidine, which is devoted with the important biodynamic properties. Pyrimidines have been explored to a maximum extent by various chemists and
biochemists and this has resulted in the accumulation of voluminous work in this field of research and numerous research papers have appeared in literature. Detailed discussion of the work carried out on pyrimidines is not within the scope of this thesis. However to point out the importance of pyrimidine derivatives, only few recent reports in this regard have been discussed in the following pages.

Pyrimidine nucleus occurs in biologically important products such as nucleic acids, vitamins, coenzymes and pharmacologically useful natural products of plant origin. The major interest in fused pyrimidines is mainly due to purine based components of nucleic acids. The two purine bases adenine 9 and guanine 10, which are imidazo pyrimidine derivatives, are most important components of DNA, RNA and ultimately the genetic materials.

Several synthetic analogues of the natural nucleosides, adenosine and guanosine are prepared by modifying the base component for different purposes such as exploration of antiviral and anticancer agents. Such modified base involved in the fusion of pyrimidine with various nitrogen heterocycles like pyrrole, pyrazole, triazole, thiazole etc. Hence fusion of pyrimidine ring on different heterocyclic systems resulted in novel compounds possessing one or the other biological or pharmacological activities41-51.

Some derivatives of thiazolo[3,2-c]pyrimidines 11 have been synthesized and tested for antimicrobial activity and anthelmintic activity on a number of strains52.
Itoh et al., reported the synthesis of pyrrolo[3,2-d]pyrimidines 12 and studied the effect of these compounds on dihydrofolate reductase.

![11](image1) ![12](image2)

In search for novel agrochemicals with high activity and low toxicity, a series of diheterocyclic compounds containing 1,2,4-triazolo[1,5-a]pyrimidine rings were designed and synthesized by a four step synthetic route. When preliminary bioassay against herbicidal activity was carried out, it was observed that some of the compounds displayed activity at the low concentration of 100 ppm.

Moukha et al., have synthesized some pyrazolo[3,4-d]pyrimidine 13 derivatives and evaluated for their inhibitory effects against the replication of HIV-1 (IIIB), HIV-2 (ROD), various DNA viruses, tumor cell lines and tuberculosis.

![13](image3)

Pyrimido[2,1-b]benzothiazole and benzothiazolo[2,3-b]quinazoline derivatives have been synthesized and tested for their antitumor and antiviral activities. Some of the compounds showed potential activity against Herpes simplex type-1 (HSV-1).

Pyrrolo[3,4-e][1,2,3]-triazolo[1,5-a]pyrimidine and Pyrrolo[3,4-d][1,2,3]-triazolo[1,5-a]pyrimidine, new tricyclic systems of biological interest have been reported by Lauria et al.
New polycyclic pyrimidine derivatives have been synthesized and investigated for their biological activities. 5-Pyrrolidino-2-methyl-thiobenzopyrano[4,3-d]pyrimidine was found to fulfill the chemical requirements to exhibit antiplatelet activity with gastro protective effect. Biagi et al., have synthesized some 6-substituted pyrazolo[3,4-d]pyrimidine derivatives and tested as inhibitors of the xanthine oxidase enzyme.

Tricyclic conformationally restricted tetrahydropyrido annulated furo[3,2-d]pyrimidines have been synthesized and are reported as non classical antifoliate inhibitors of dihydrofolate reductase.

This fact revealed the wide scope for systematic investigation in this area of heterocyclic chemistry. This led Agasimundin et al., to initiate an exhaustive research programme devoted to the synthesis and biological evaluation of benzofuro[3,2-d]pyrimidines. The results of such investigations are published in a series of research papers. However there are no reports of fusion of pyrimidine ring with naphthofuran moiety in literature.

Present work

The initial work was devoted to the general synthetic approaches for this ring system and later it was directed towards the synthesis of various substituted naphtho[2,1-b]furo[3,2-d]pyrimidines. Invitro screening of these compounds has shown that many of these compounds possess wide spectrum of biological activities.

As a logical extension of earlier work, it was thought worthwhile to take up the study of synthesis of naphtho[2,1-b]furo[3,2-d]pyrimidines and evaluation for various pharmacological activity in addition to antifertility activity.
In the present work, logically there appears to be three different synthetic strategies for the construction of pyrimidine nucleus with naphtho[2,1-b]furan.

a) The desired nitrogen heterocyclic ring system may be fused on a preformed naphthofurans.

b) Naphthofuran ring system may be fused on a preformed nitrogen heterocycle with suitable functionalities.

c) The two preformed naphthofuran and nitrogen heterocycles may be fused together.

In the present investigation, the synthetic strategy “a” involving the construction of desired nitrogen heterocycle onto a preformed naphthofuran is followed for the synthesis of condensed naphthofurans with nitrogen heterocycle, because of easy availability of appropriately substituted naphthofuran derivatives through convenient synthetic methods.

One of the methods for the construction of pyrimidine nucleus requires o-amino carboxamide system. For building pyrimidine moiety on naphtho[2,1-b]furan nucleus, such a functionality in 2- and 3- positions was necessary. This necessiated the synthesis of 2-hydroxy-1-naphthonitrile, which was subsequently converted into 2-substituted-4-chloronaphtho[2,1-b]furo[3,2-d]pyrimidines by a sequence of reactions as shown in the Scheme-1.
The various steps involved in the synthetic strategy are as follows,

1) Synthesis of 2-hydroxy-1-naphthonitrile


4) Nucleophilic substitution reactions of 2-substituted-4-chloronaphtho[2,1-b]furo[3,2-d]pyrimidines to get the title compounds.
1. Synthesis of 2-hydroxy-1-naphthonitrile

2-Hydroxy-1-naphthonitrile 14 was synthesized by traditional method of dehydration of the corresponding oxime by a well-established procedure in our laboratory. The required 2-hydroxy-1-naphthaldehyde was prepared from 2-naphthol by Reimer-Tiemann reaction and then converted into its oxime by adopting literature procedure. The treatment of oxime with acetic anhydride formed initially naphthisoxazole, which without isolation was converted into the desired 2-hydroxy-1-naphthonitrile by treatment with sodium ethoxide followed by acidification (Scheme-2).

Scheme-2

The structure of 2-hydroxy-1-naphthonitrile thus synthesized was ascertained by superimposable IR and 1H NMR with that of authentic sample and by mixed melting point.

2-Hydroxy-1-naphthonitrile 14 was condensed with chloroacetamide in presence of anhydrous potassium carbonate and dry acetone, to obtain the desired condensed product 1-cyano-2-naphthoxyacetamide 15.


The IR spectrum (Figure-6.1) of 15 exhibited absorption bands at 3451 cm\(^{-1}\), 2220 cm\(^{-1}\) and 1683 cm\(^{-1}\) due to \(-\text{NH}_2\), \(-\text{C}≡\text{N}\) and \(\text{C}=\text{O}\) stretching frequencies. The structure assigned was further supported by its \(^1\text{H}\) NMR spectrum (Figure-6.2). It exhibited a singlet at \(δ 4.6\) integrating for two protons of \(\text{CH}_2\) and a broad singlet at \(δ 5.8\) (\(\text{D}_2\text{O}\) exchangeable) also integrating for two protons of \(\text{NH}_2\) group. In addition, it also showed a multiplet at \(δ 7.0 - δ 8.4\) integrating for six aromatic protons.

The proposed structure was confirmed by recording its mass spectrum (Figure-6.3). It exhibited a molecular ion peak at \(\text{m/z} 226\) corresponding to its molecular weight. The other peaks found in the mass spectrum correspond with the fragmentation pattern as depicted in Scheme-3.
SCAN GRAPH. Flagging=M/z.

Scan 2-0:24. Entries=217. 100% Int.=18686.
The IR spectrum (Figure-6.4) of 16 was conspicuous by the absence of peak at 2220 cm$^{-1}$ due to $\text{-C=N}$. As expected the absorption band due to $\text{-C=O}$ group appeared at 1689 cm$^{-1}$. The absorption at this frequency may be attributed to the involvement of carbonyl group in intramolecular hydrogen bonding with $\text{-NH}_2$ group on adjacent carbon atom. In the $^1\text{H}$ NMR spectrum (Figure-6.5) of compound 16, the peak due to $\text{-CH}_2$ group at $\delta$ 4.6, which was observed in its precursor, was conspicuously absent. This supported the involvement of $\text{-CH}_2$ group in Thorpe-Ziegler cyclization. The $^1\text{H}$ NMR spectrum exhibited a singlet at $\delta$ 3.9 and another broad singlet at $\delta$ 6.0 (D$_2$O exchangeable), which were attributed to $\text{-NH}_2$ and $\text{-CONH}_2$ protons. Six aromatic protons appeared as a multiplet at $\delta$ 7.0 - $\delta$ 8.2. To obtain further evidence for the structure assigned to compound 3, its mass spectrum was recorded (Figure-6.6). It exhibited a
sample 2

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PROCNO 1

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SOLVENT cdc13
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FIDRES 0.186023 Hz
AQ 2.6870260 sec
RG 256
DW 82.000 usec
DE 102.50 usec
TE 300.0 K
HL1 1 dA
D1 1.0000000 sec
P1 6.82 usec
SF01 400.1364282 MHz
NUCLEUS 1H

F2 - Processing parameters
SI 32768
SF 400.1343949 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

FIGURE-6.5
molecular ion peak at m/z 226 coinciding with its molecular weight. Even though the molecular weights of compounds 15 and 16 are same, the mass spectra were different as regards the fragmentation pattern. The fragmentation of compound 16 followed the pattern as depicted in Scheme-4.

Scheme-4

[Scheme showing the fragmentation pattern of compound 16 with molecular ion peak at m/z 226 and other fragments at m/z 209, 182, 181, 154, 126, and 155]

3-Aminonaphtho[2,1-b]furan-2-carboxamide 16 was converted into corresponding acyl derivatives by treatment with acetyl chloride and benzoyl chloride in presence of alkali. These acylated compounds underwent smooth ring closure on reaction with aqueous sodium hydroxide and resulted in the formation of 2-substituted-4-oxo-naphtho[2,1-b]furo[3,2-d]pyrimidines.

The structure of 2-methyl-4-oxo-naphtho[2,1-b]furo[3,2-d]pyrimidine 18a was established by recording various spectra. The IR spectrum (Figure-6.7) exhibited carbonyl stretching frequency at 1687 cm$^{-1}$. The $^1$H NMR spectrum (Figure-6.8) exhibited a singlet at $\delta$ 2.5 due to three protons of methyl group. A multiplet was
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F2 - Processing parameters
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SSB  0
LB  0.30 Hz
GB  0
PC  1.00

FIGURE-6.8
observed at δ 7.2 - δ 8.2 integrating for six protons was assignable to aromatic protons. The NH proton appeared as a singlet (D₂O exchangeable) at δ 9.3. The mass spectrum (Figure-6.9) showed a molecular ion peak at m/z 250 corresponding to its molecular weight. The fragment ions appearing at m/z 209, 181, 153 and 127 were in accordance with the fragmentation pattern as depicted in Scheme-6.
SCAN GRAPH. Flagging=M/z.

Scan 3-0.38. Entries=119. 100% Int.=5173.

FIGURE-6.9
It is well-established fact that the change in substitutions at position 2 and 4 will have marked effect on biological properties of compounds. Hence it was thought of interest to synthesize various substituted naphtho[2,1-b]furo[3,2-d]pyrimidines and investigate their biological activities with special reference to the effect of substituents.

With this view, 2-alkyl/aryl-4-oxo-naphtho[2,1-b]furo[3,2-d]pyrimidines were converted into 4-chloro derivatives by refluxing with POCl₃. The formation of 4-chloro compounds was confirmed by their IR spectra, which showed absence of absorption bands due to both -C=O and -NH stretching frequencies. The structure of 2-methyl-4-chloronaphtho[2,1-b]furo[3,2-d]pyrimidine was further confirmed by recording ¹H NMR spectrum which exhibited a singlet at δ 2.5 due to three protons of methyl group. A multiplet observed at δ 7.2 - δ 8.2 integrating for six protons was assignable to aromatic protons.


2-Alkyl/aryl-4-chloronaphtho[2,1-b]furo[3,2-d]pyrimidines 19a-b were subjected for substitution reactions with different nucleophilic reagents in order to obtain various 4-substituted compounds. The main purpose of carrying out these reactions was to investigate the effect of different kinds of substituents on biological activities. Thus the compounds 19a-b was heated with various alcohols, phenols and amines to obtain 2-substituted-4-alkoxynaphtho[2,1-b]furo[3,2-d]pyrimidines 20a-d, 2-substituted-4-aryloxy naphtho[2,1-b]furo[3,2-d]pyrimidines 21a-h and 2-substituted-4-alkyl/arylamino naphtho[2,1-b]furo[3,2-d]pyrimidines 22a-t respectively. Various amines selected in the
Sample 15

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PROCNO 1

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DE 102.50 usec
TE 300.0 K
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DI 1.0000000 sec
P1 6.82 usec
SFO1 400.1364282 MHz
NUCLEUS 1H

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The present study contained either electron donating groups or electron withdrawing groups in different positions of the aromatic system.

The displacement of chlorine atom by alkoxide ions was effected by heating the compound 19a-b with sodium alkoxide in respective alcohols. There was separation of sodium chloride in the reaction. The IR spectral data of some selected compounds is shown in Table-6.1.

On the other hand 2-substituted-4-aryloxynaphtho[2,1-b]furo[3,2-d]pyrimidines were synthesized by heating corresponding phenol with ammonium carbonate and subsequently worked up by basification to get the compounds 21a-h in considerably good yield. The IR spectral data of some selected compounds is shown in Table-6.1.
Table-6.1 IR spectral data of 2-substituted-4-alkoxy/aryloxy-naphtho[2,1-b]furo[3,2-d]pyrimidines

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Table-6.1 IR spectral data of 2-substituted-4-alkoxy/aryloxy-naphtho[2,1-b]furo[3,2-d]pyrimidines

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<th>Compound</th>
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A series of 2-substituted-4-alkyl/arylaminonaphtho[2,1-b]furo[3,2-d]pyrimidines were prepared by the reaction of 19a-b with various primary and secondary aliphatic and aromatic amines. The amines such as ethylamine, which is commercially available in aqueous solution, was condensed with 19a-b in aqueous solution of the amine itself. The condensation with aniline, 4-methoxyaniline, 4-bromoaniline, m-toluidine, p-toluidine, 4-aminobenzoic acid, 3-nitroaniline, 4-nitroaniline and 4-hydroxyaniline was carried out in an ethanolic solution.

The structures of all these products were routinely checked by recording IR spectra of representative compounds in the series. The IR spectral data of some selected compounds is shown in Table-6.2

![Chemical Structures](image)

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Table-6.2 IR spectral data of 2-substituted-4-alkylamino/arylamino[naphtho[2',1-b]furo[3,2-d]pyrimidines

![Structural diagram](image)

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<td>1578</td>
<td>3360</td>
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</tr>
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Experimental

1-Cyano-2-naphthoxyacetamide 15

To a solution of 2-hydroxy-1-naphthonitrile 14 (16 g, 0.07 mol) in dry acetone (175 ml), 2-chloroacetamide (7 g, 0.074 mol) and anhydrous potassium carbonate (30 g) were added and refluxed for 8 hr. The reaction mixture was filtered and the filtrate on evaporation of the solvent gave 15 as light yellow colored solid. Some amount of 15 was recovered from the potassium salts by suspending in large excess of water and collecting the insoluble material. The combined yield was 96%. It was recrystallized from ethanol.

Yield, 96% ; m.p. 107°C ; Found : C, 69.00; H, 4.40; N, 12.26 ; C_{13}H_{10}N_{2}O_{2} required : C, 69.02; H, 4.42; N, 12.38%.

3-Aminonaphtho[2,1-b]furan-2-carboxamide 16

The compound 15 (12 g, 0.05 mol), in a solution of potassium hydroxide (8 g, 0.05 mol) in ethanol (160 ml) was refluxed for 2 hr on a water bath. The reaction mixture was diluted with water and cooled in ice and neutralized. The brown colored solid thus separated was collected, dried and recrystallized from aqueous ethanol.

Yield, 86% ; m.p. 96°C ; Found : C, 68.97; H, 4.38; N, 12.28 ; C_{13}H_{10}N_{2}O_{2} required : C, 69.02; H, 4.42; N, 12.38%.

3-Acetylaminonaphtho[2,1-b]furan-2-carboxamide 17a

A mixture of 16 (5 g, 0.01 mol) and acetyl chloride (25 ml) was warmed on water-bath for 15-20 min and then decomposed in ice water to get a crystalline solid of 17a. It was recrystallized from aqueous ethanol.

Yield, 74% ; m.p. 148°C ; Found : C, 67.00; H, 4.41; N, 10.37 ; C_{15}H_{12}N_{2}O_{3} required : C, 67.16; H, 4.47; N, 10.44%.
3-Benzoylaminonaphtho[2,1-b]furan-2-carboxamide 17b

The compound 16 (5 g, 0.01 mol) was warmed on water-bath for 20 min with benzoyl chloride (4 ml) in presence of aqueous sodium hydroxide (2N, 2 ml). The product 17b thus separated as solid was collected and recrystallized from aqueous ethanol.

Yield, 70% ; m.p. 152°C ; Found : C, 72.64; H, 4.14; N, 8.40 ; C18H14N2O3 required : C, 72.72; H, 4.24; N, 8.48%.

2-Methyl-4-oxo-naphtho[2,1-b]furo[3,2-d]pyrimidine 18a

**Method A** - Forgoing acetyl compound 17a (5 g, 0.02 mol) was suspended in aqueous sodium hydroxide (1N, 500 ml) and warmed on water-bath for 20 min. The resulting solution when acidified with dilute hydrochloric acid gave 18a as solid, which was recrystallized from aqueous ethanol.

Yield, 64% ; m.p. 160°C ; Found : C, 71.88; H, 4.00; N, 11.03 ; C15H10N2O2 required : C, 72.00; H, 4.00; N, 11.20%.

**Method B** - To a mixture of hydrogen peroxide (3 %, 20 ml) and aqueous potassium hydroxide (10 %, 15 ml), the acetyl compound 17a (1.5 g, 0.006 mol) was added and the mixture was heated at 70-75°C for about 30 min. The resulting solution when acidified with glacial acetic acid furnished 18a as light brown colored crystals, which was identical with the sample obtained in method (a).

2-Phenyl-4-oxo-naphtho[2,1-b]furo[3,2-d]pyrimidine 18b

The benzoyl derivative 17b (5 g, 0.015 mol) was suspended in aqueous sodium hydroxide (1N, 500 ml) and warmed on water-bath for 2 hr. The resulting solution when
acidified with dilute hydrochloric acid gave 18b as solid, which was recrystallized from aqueous ethanol

Yield, 61% ; m.p. 144°C ; Found : C, 76.84; H, 3.72; N, 8.78 ; C_{20}H_{12}N_{2}O_{2} required : C, 76.92; H, 3.84; N, 8.97%.

2-Substituted-4-chloronaphtho[2,1-b]furo[3,2-d]pyrimidines 19a-b

Compound 18a (5 g, 0.02 mol) in freshly distilled phosphorus oxychloride (50 ml) was heated under reflux until a clear solution was obtained. The resulting solution was cooled and poured into crushed ice with stirring. The chloro compound 19a thus separated was collected and recrystallized from ethanol. Compound 19b was prepared from 18b in the similar way. The physical and analytical data of the compounds synthesized is presented in Table-6.3.

2-Substituted-4-methoxynaphtho[2,1-b]furo[3,2-d]pyrimidine 20a, 20c

To a solution of 19a (0.6 g, 0.0022 mol) in absolute methanol (10 ml), a solution of sodium methoxide prepared from sodium metal (0.3 g) and absolute methanol (10 ml) was added. Immediately sodium chloride separated. The reaction mixture was warmed on water-bath for 30 min, cooled and diluted with water. 20a was collected and recrystallized from methanol. Similarly 20c was also prepared. The physical and analytical data of the compounds synthesized is presented in Table-6.3.
2-Substituted-4-ethoxynaphtho[2,1-b]furo[3,2-d]pyrimidine 20b, 20d

To a solution of 19a (0.6 g, 0.0022 mol) in absolute ethanol (10 ml), a solution of sodium ethoxide prepared from sodium metal (0.3 g) and absolute ethanol (10 ml) was added. Immediately sodium chloride was separated. The reaction mixture was warmed on water-bath for 30 min, cooled and diluted with water. 20b was collected and recrystallized from methanol. Similarly 20d was also prepared. The physical and analytical data of the compounds synthesized is presented in Table-6.3.

Table-6.3

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Molecular formula</th>
<th>Yield %</th>
<th>m.p. °C</th>
<th>Found (Calculated) %</th>
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<td></td>
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<td>C</td>
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<td>19a</td>
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<td>(66.94)</td>
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<tr>
<td>19b</td>
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<td>122</td>
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<tr>
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<td>139</td>
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<tr>
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<td>134</td>
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<td>(77.52)</td>
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2-Substituted-4-aryloxynaphtho[2,1-b]furo[3,2-d]pyrimidines 21a-h

A mixture of 19a (0.6 g, 0.0022 mol), freshly distilled phenol (6 g) and powdered ammonium carbonate (2 g) was initially heated gently followed by heating on water-bath for 40-50 min. Upon dilution with appropriate amount of aqueous sodium hydroxide solution (10%), the solid 21a-d that separated was filtered, washed with water and recrystallized from suitable solvent. Compounds 21e-h were also prepared in the same way. The physical and analytical data of the compounds synthesized is presented in Table-6.4.

Table-6.4

<table>
<thead>
<tr>
<th>Comp</th>
<th>R</th>
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<th>Molecular formula</th>
<th>Yield %</th>
<th>m.p. °C</th>
<th>Found (Calculated) %</th>
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<td></td>
<td></td>
<td>C</td>
</tr>
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<td>150</td>
<td>77.30 (77.26) 4.29 (4.19) 8.58 (8.51)</td>
</tr>
<tr>
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<td>C₂₂H₁₆N₂O₂</td>
<td>70</td>
<td>136</td>
<td>77.64 (77.62) 4.70 (4.55) 8.23 (7.98)</td>
</tr>
<tr>
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<td>CH₃</td>
<td>OC₆H₄-3-CH₃</td>
<td>C₂₂H₁₆N₂O₂</td>
<td>64</td>
<td>153</td>
<td>77.64 (77.58) 4.70 (4.66) 8.23 (7.96)</td>
</tr>
<tr>
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<td>OC₆H₄-4-CH₃</td>
<td>C₂₂H₁₆N₂O₂</td>
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<td>160</td>
<td>77.64 (77.60) 4.70 (4.74) 8.23 (8.02)</td>
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<td>210</td>
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<td>218</td>
<td>80.59 (80.49) 4.47 (4.38) 6.96 (6.90)</td>
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2-Substituted-4-alkyl/arylaminonaphtho[2,1-b]furo[3,2-d]pyrindines 22a-t

A mixture of 19a (0.6 g, 0.0022 mol) and appropriate amine (0.005 mol) in absolute ethanol (12 ml) was heated on a water-bath for 4-6 hr. After diluting with water, it was allowed to stand overnight. The solid product 22a-j was collected and recrystallized from suitable solvent. Compounds 22k-t were also prepared in the same way. The physical and analytical data of the compounds synthesized is presented in Table-6.5.

Table-6.5

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<th>Molecular formula</th>
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<td>C</td>
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<td>42</td>
<td>129</td>
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<tr>
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<td>NHC₆H₅</td>
<td>C₂₁H₁₃N₃O</td>
<td>58</td>
<td>136</td>
<td>77.54 (77.62)</td>
</tr>
<tr>
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<td>142</td>
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<td>153</td>
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</tr>
<tr>
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<td>142</td>
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</tr>
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<td>77.87 (77.81)</td>
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<td>200</td>
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<td>168</td>
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</tr>
<tr>
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<td>86</td>
<td>186</td>
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<td>C₂₇H₁₉N₃O</td>
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</tr>
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<td>C₆H₅</td>
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<td>C₂₇H₁₇N₃O₃</td>
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<td>238</td>
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Some of the selected compounds have been evaluated for antibacterial, anthelmintic, anti-inflammatory and antifertility activities and the description of the pharmacological activities is discussed in Chapter-8.
References


