NOVEL METHOD FOR THE SYNTHESIS OF SYMMETRICAL AND ASYMMETRICAL AZINES INVOLVING NAPHTHO [2,1-b] FURAN AND THEIR ANTIMICROBIAL ACTIVITY

M.N. Kumaraswamy and V.P. Vaidya*
Department of Chemistry, Kuvempu University, Jnana Sahyadri,
Shankaraghatta-577 451

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The reaction of 2-hydroxy-1-naphthaldehyde with chloroacetone/phenacyl bromide in presence of weak base gave 2-acylnaphtho [2,1-b] furans 1a-b. The reaction of 1a-b with hydrazine hydrate produced corresponding hydrazones 2a-b, which on treatment with various aromatic aldehydes under different reaction conditions yielded symmetrical azines 3a-d and asymmetrical azines 4a-d & 5a-d. All the synthesized compounds have been characterized by elemental analysis and spectral studies and evaluated for antimicrobial activity by MIC method.

Naphtho [2,1-b] furans are associated with wide spectrum of biological and pharmacological activities. Encouraged by these findings, synthesis of various derivatives of naphtho [2,1-b] furan was taken up as a major research program in our laboratory and we report in this paper some interesting results obtained during the synthesis of symmetrical and asymmetrical azines involving pharmacologically important naphtho [2,1-b] furan.

The synthesis of key starting materials 2-acylnaphtho [2,1-b] furans 1a-b from 2-hydroxy-1-naphthaldehyde with chloroacetone/phenacetyl bromide in the presence of weak base, K$_2$CO$_3$, in acetone has been well established in our laboratory. The 2-acylnaphtho [2,1-b] furan hydrazones 2a-b were prepared by the reaction of 1a-b with hydrazine hydrate in the presence of catalytic amount of hydrochloric acid in refluxing ethanol. The reaction was monitored by TLC and the structures were confirmed by spectral data. The IR spectrum of 2a exhibited the absorption band at 1630 cm$^{-1}$ due to C=N and 3450 due to NH. In $^1$H NMR spectrum (CDCl$_3$) singlets at 5 2.3, 5.6 and multiplet at 7.2-8.2 were due to CH$_3$, NH and aromatic protons respectively. The acid catalyzed reaction of 2-acylnaphtho [2,1-b] furan hydrazone 2a with benzaldehyde, 4-nitrobenzaldehyde, 4-chloro benzaldehyde and 4-methoxy benzaldehyde, in 1:1 mol ratio, at reflux temperature in ethanol produced a mixture of two compounds which were identified as symmetrical azines 3a-d and regenerated 2-acylnaphtho [2,1-b] furan 1a (Scheme-1). The IR spectrum of 3b exhibited the absorption band at 1623 due to C=N. In $^1$H NMR spectrum (CDCl$_3$) singlet at 8.8 for two CH protons and multiplet at 7.2-8.2 for aromatic protons were seen. The $^1$H NMR data of 3a,c-d were consistent with their structures.

Interestingly, the condensation of 2a with these aldehydes, in 1:1 mol ratio, in the absence of hydrochloric acid at reflux temperature in ethanol gave a single product. The products thus formed, in each case, were identified as asymmetrical azines 4a-d of 2-acylnaphtho [2,1-b] furan hydrazone and respective aldehydes. The IR spectrum of 4b exhibited the absorption band at 1608 due to C=N. In $^1$H NMR spectrum (CDCl$_3$) singlet at 2.8 for CH$_3$, singlet at 8.8 for two CH protons and multiplet at 7.2-8.2 for aromatic protons were observed. The $^1$H NMR data of 4a,c-d were consistent with their structures.

On the other hand, the condensation of 2a with these aldehydes, in 1:1 mol ratio, in the absence of hydrochloric acid at reflux temperature in ethanol gave a single product. The products thus formed, in each case, were identified as asymmetrical azines 5a-d of 2-acylnaphtho [2,1-b] furan hydrazone 2a respectively were also isolated and characterized on the basis of spectral data.

When the same reaction was carried out using 2a and respective aldehydes in 1:2 mol ratio, in absence of acid, the product was found to be a mixture of two compounds which were identified as asymmetrical azines 3a-d and regenerated 2-acylnaphtho [2,1-b] furan 1a (Scheme-1). The IR spectrum of 3b exhibited the absorption band at 1623 due to C=N. In $^1$H NMR spectrum (CDCl$_3$) singlet at 8.8 for two CH protons and multiplet at 7.2-8.2 for aromatic protons were seen. The $^1$H NMR data of 3a,c-d were consistent with their structures.

Interestingly, the condensation of 2-benzoylnaphtho [2,1-b] furan hydrazone 2b with salicylaldehyde, 4-nitrobenzaldehyde, 4-chlorobenzaldehyde and 4-methoxy benzaldehyde, under different reaction conditions, resulted in the formation of single compound which were identified as asymmetrical azines 5a-d.
respectively. The IR spectrum of 5a exhibited the absorption band at 1615 due to C=N. In 1H NMR spectrum (CDCl₃) singlet at 11.0 (1H, OH), singlet at 8.6 (1H, CH) and multiplet at 6.2-8.4 (16H, ArH) were seen. The 1H NMR data of 5b-d were consistent with their structures.

**Antimicrobial activity**

Compounds 3a-d, 4a-d and 5a-d have been tested for their antibacterial activity against *Pseudomonas aerogenosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Pencillus notatum* by Agar Dilution Minimum Inhibitory Concentration (MIC) method. Chloramphenicol and Fluconazole were used as standards respectively.

All the compounds exhibited better activity than the standard drug. The compounds 3a-d, 4a-d, 5a-d have shown good results compared to standard.

**Experimental**

Melting points were recorded in open capillaries and are uncorrected. The IR spectra were recorded on a Shimadzu FT-IR spectrophotometer. The 1H NMR spectra were recorded on Varian EM-390 spectrometer.
Table-1

Physical data of various compounds synthesized

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>R'</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
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<tr>
<td>1a</td>
<td>CH₃</td>
<td>−</td>
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<td>80</td>
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<tr>
<td>1b</td>
<td>C₆H₅</td>
<td>−</td>
<td>130</td>
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<tr>
<td>2b</td>
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<td>245</td>
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</tr>
<tr>
<td>3a</td>
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<td>169</td>
<td>49</td>
</tr>
<tr>
<td>3b</td>
<td>−</td>
<td>4-NO₂-C₆H₄</td>
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<td>40</td>
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<tr>
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<td>43</td>
</tr>
<tr>
<td>3d</td>
<td>−</td>
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<td>47</td>
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<tr>
<td>4a</td>
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<td>C₆H₅</td>
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<tr>
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<td>5d</td>
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<td>4-OCH₃-C₆H₄</td>
<td>311</td>
<td>65</td>
</tr>
</tbody>
</table>

All compounds gave correct elemental data.

All the reactions were monitored by Thin Layer Chromatographic method. TLC was run on silica gel using ethyl acetate petroleum ether (5:95) as eluent. The newly synthesized products are separated and purified by column chromatography using silica gel (60-120 mesh).

Synthesis of 2-acylnaphtho [2,1-b] furanhydrazones 2a-b

A mixture of 2-acylnaphtho [2,1-b] furan 1a (5.25g, 0.025 mol), hydrazine hydrate (1.2 ml, 0.025 mol) and 3-4 drops of conc. hydrochloric acid in ethanol (30 ml) was refluxed on a water bath for 4 hr. The reaction mixture was poured into ice water and neutralized with aq sodium hydroxide (5%). Solid (2a) thus separated was collected by filtration, dried and recrystallized from ethanol.

Similarly 2-benzoylnaphtho [2,1-b] furanhydrazone 2b was synthesized from 1b.

Synthesis of symmetrical azines 3a-d

**Method A**

A mixture of 2-acylnaphtho [2,1-b] furanhydrazone (1.12g, 0.005 mol) 2a, benzaldehyde (0.53g, 0.005 mol) in ethanol (60 ml) and 3-4 drops of conc hydrochloric acid was refluxed on a water bath for 3 hr. The reaction mixture was poured into ice water and neutralized with aq sodium hydroxide (5%). Solid thus separated was collected by filtration and dried. The crude product was a mixture of three compounds as observed by TLC having Rₜ values 0.8, 0.5 and 0.2. These compounds were separated by column chromatography using silica gel 60-120 mesh size. The regenerated 2-acylnaphtho [2,1-b] furan 1a and unreacted 2-acylnaphtho [2,1-b] furanhydrazone 2a were eluted using composition of ethyl acetate and pet ether (5:95 v/v) and symmetrical azine 3a was eluted using ethyl acetate. Similar procedure was adopted to obtain the compounds 3b-d from 2a.

**Method B**

To a solution of 2-acylnaphtho [2,1-b] furanhydrazone 2a (1.12g, 0.005 mol), benzaldehyde (1.06g, 0.01 mol) in ethanol (60 ml), 3-4 drops of conc. hydrochloric acid were added and refluxed on a water bath for 3 hr. The reaction mixture was poured into ice water and neutralized with aq sodium hydroxide solution (5%). Solid thus separated was collected and dried. The crude product was found to be a mixture of two compounds by TLC with Rₜ value 0.8 and 0.2. These compounds were separated by column chromatography using silica gel 60-120 mesh size. The regenerated 2-acylnaphtho [2,1-b] furan 1a was eluted using composition of ethyl acetate and petroleum ether (5:95 v/v).
v/v) and symmetrical azine 3a was eluted using ethyl acetate. Similar procedure was repeated to get the compounds 3b-d from 2a.

**Synthesis of asymmetrical azines 4a-d**

A mixture of 2-acetylnaphtho [2,1-fa] furanhydrazone 2a (1.12g, 0.005 mol) and benzaldehyde (0.53g, 0.005 mol) in ethanol (60 ml) was kept for reflux on a water bath for 3 hr. The reaction mixture was poured into ice water solid separated out was collected and dried. The product was identified as condensed asymmetrical azine 4a. Similar procedure was repeated to get the compounds 4b-d from 2a.

**Synthesis of asymmetrical azines 5a-d**

A mixture of 2-benzoylnaphtho [2,1-b] furanhydrazone 2b (1.43g, 0.005 mol) and salicylaldehyde (0.61g, 0.005 mol) in ethanol (60 ml) was kept for reflux on a water bath for 3 hr. The reaction mixture was poured into ice water, separated solid was collected and dried. The product was identified as condensed asymmetrical azine 5a. Similar procedure was repeated to get the compounds 5b-d from 2b.

**Acknowledgment**

The authors are thankful to the Head, Sophisticated Instruments Facility, IISc, Bangalore for spectral data. One of the authors M.N. Kumaraswamy is thankful to CSIR and UGC, New Delhi for awarding JRF.

**References**


Dear Sir,

Please find enclosed your manuscript entitled “Synthesis and Pharmacological evaluation of 2-mercapto-4-substituted-naphtho [2,1-b] furo[3,2-d]pyrimidines-res-” for making major revision as a Research Paper according to the suggestions made by Referee/Editor (copy enclosed)

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Asst. Editor
PAPERS PRESENTED AT CONFERENCES

   **M.N. Kumaraswamy** and V.P. Vaidya.
   Presented at 22nd Indian Council of Chemists held at IIT Roorkee from 17th-19th October-2003.

   **M.N. Kumaraswamy**, G. Malateshappa and V.P. Vaidya.

   **M.N. Kumaraswamy**, H. Shivakumar and V.P. Vaidya.
   Presented at National conference held at Kuvempu University, Shankaraghatta from 6th-8th January 2006.

   Presented at International Symposium on Advances in Organic Chemistry held at Mahatma Gandhi University, Kottayam, Kerala from 9th-12th January 2006.

   **M.N. Kumaraswamy**, V.P. Vaidya, D. Ramesh and H. Rajashekhara.
   Presented at 2nd International Symposium on Drug Discovery and Process Research, held at KLE’S college of Pharmacy, Belgaum from 10th-12th February-2006.

M.N. Kumaraswamy and V.P. Vaidya
Department of Chemistry, Kuvempu University, Shankaraghatta, Shimoga, Karnataka, 577 451

Recently the derivatives of naphtho-[2,1-b] furan have gained importance owing to their diverse pharmacological activities. In continuation of our earlier work on naphtho-[2,1-b] furans, we report in this paper, the synthesis of symmetrical azines involving naphtho-[2,1-b] furan, which otherwise are not easily obtainable, in addition to unsymmetrical azines. To achieve the synthesis of desired azines, 2-acetyl/benzoinaphtho-[2,1-b] furanhydrazone \( \text{la-b} \), obtained by using 2-hydroxy-1-naphthaldehyde and chloroacetone/phenacylbromide, were reacted with appropriate aldehydes under different reaction conditions and in different molar ratios in ethanol.

Thus the reaction of compound of \( \text{la} \) with various aldehydes in ethanol and in the presence of catalytic amount of hydrochloric acid, in the molar ratio of 1:1 furnished symmetrical azines, whereas similar reaction in absence of catalyst yielded unsymmetrical azines involving naphtho-[2,1-b] furan. Interestingly this reaction, when carried out in the molar ratio of 1:2, resulted in the formation of two compounds, which were separated by column chromatography and identified as symmetrical azine and starting material 2-acetyl/benzoynaphtho-[2,1-b] furan. The structures of the newly synthesized azines have been confirmed by IR and NMR spectral studies.
OP-17 : ANTIMICROBIAL ACTIVITY OF NEWLY SYNTHESISED SYMMETRICAL AND ASYMMETRICAL AZINES INVOLVING NAPHTHO [2, 1-b] FURAN.

M.N. Kumaraswamy¹, G. Malateshappa², and V. P. Vaidya¹
¹Department of Chemistry, Kuvempu University, Shankaraghatta-577451. Dist: Shimoga, Karnataka.
²Department of Chemistry, Sahyadri Science College, Shimoga-577203 Karnataka.

The azines play an important role in the construction of five membered heterocyclic compounds parallel to Diels-Alder reaction in construction of six membered rings. Azines containing heterocyclic substituents are extensively used as ligands for the formation of novel organometallic compounds and the asymmetrical azines containing donor and acceptor aryl groups are very good for organic non-linear optical materials. Such compounds are also known to exhibit antimicrobial activity to certain extent. The compounds containing naphtho [2, 1-b] furan have gained importance, owing to their diverse pharmacological activities. In continuation of our earlier work on naphtho [2, 1-b] furans, we report in this paper, the antimicrobial activity of various symmetrical and asymmetric azine derivatives involving naphtho [2, 1-b] furan. Compounds 3a-d, 4a-d and 5a-d have been tested for their antibacterial activity against Pseudomonas aeruginosa and Staphylococcus aureus and antifungal activity against Aspergillus niger and Pencillium notatum by Minimum Inhibitory Concentration method. Fluconazole and chloramphenical were used as internal standards. All compounds shown very good activity against both fungii and bacteria. They are very active in minimum concentration in terms of µg/ml.
Synthesis and investigation of antipyretic activity of 2-azetidinone derivatives involving naphtho[2,1-b]furan

M.N. Kumaraswamy¹, H. Shivakumar² and V.P. Vaidya¹*

¹Department of P.G. Studies in Chemistry, Jnana Sahyadri, Kuvempu University, Shankaraghatta, Shimoga.

²Department of Pharmacology, SCS College of Pharmacy, Harapanahalli, Davanagere.
KARNATAKA. Pin: 583 131

The 2-azetidinone moiety is present in many antibiotics like penicillin. It is also found in β-lactamase inhibitors, cephems, monobactams, penems, carbapenems and triems antibiotics. β-lactams possess anti viral, anti-inflammatory, anti fungal and antibacterial activity. β-lactams acts as cholesterol absorption inhibitors. These observations prompted us to take up the present work of synthesis of 2-azetidinone derivatives involving pharmacologically potent naphtho[2,1-b]furan moiety.

The reaction of ethyl naphtho[2,1-b]furo-2-carboxylate 2 with hydrazine hydrate in presence of catalytic amount conc. HCl in ethanol at reflux temperature afforded naphtho[2,1-b]furan-2-carbohydrazide 3 in good yield. The reaction of 3 with substituted aromatic aldehydes in presence acid in dioxane yielded corresponding N¹-(substituted)methylene]naphtho[2,1-b]furan-2-carbohydrazide 4a-f (Schiff bases). These Schiff bases on reaction with chloroacetyl chloride in presence of triethylamine in dioxane at reflux temperature produced N-(3-chloro-2-oxo-4-(substituted)azetidin-1-yl)naphtho[2,1-b]furan-2-carboxamide 5a-f. The structures of newly synthesized compounds have been established by elemental analysis and spectral studies. In addition, they have been screened for antipyretic activity by yeast induced pyrexia method by using Swiss rats weighing 150-200 gm. The activity was evaluated by using paracetamol as standard. All the compounds exhibit considerable antipyretic activity.

M. N. Kumaraswamy, D.A. Prathima Mathias, C. Chandrashekhar and V. P. Vaidya*

'Department of Studies in Chemistry, Jnana Sahyadri, Kuvempu University, Shankarghatta, Shimoga, Karnataka.
E-mail: vaidyavijaya@hotmail.com

Nitrogen, oxygen and sulphur containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activities. Pyrimidine based heterocyclic compounds are of interest as potential bioactive molecules and exhibit analgesic, antihypertensive, antipyretic, antiviral and anti-inflammatory activities. The compounds in which pyrimidine ring is fused with furan nucleus exhibit various biological activities with increased potency. These observations prompted us to take up present study.

2-Hydroxy-1-naphthonitrile 1 on treatment with different β-haloketones in presence of potassium carbonate affords corresponding 2-acyl-3-aminonaphtho [2,1-b]furans (2a-d). These compounds 2a-d on reaction with ammonium thiocyanate and benzoyl chloride produce N-acyl-N′-(2-acylnaphtho[2,1-b]furanyl)thiourea (3a-d), which on further refluxing with sodium hydroxide yield 2-mercapto-1-acylnaphtho[3,1-b]furo[3,2-d]pyrimidines (4a-d). These on stirring with chloroacetic acid in presence of sodium carbonate give S-(4-acylnaphtho[2,1-b]furo[3,2-d]pyrimidine)-mercaptoacetic acid (5a-d). The structures of newly synthesized compounds have been established by elemental analysis and spectral studies. In addition, they have been screened for antimicrobial, diuretic and anti-inflammatory activities. All compounds found to be active against bacteria and fungi. And exhibit significant diuretic and anti-inflammatory activity.
SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF SUBSTITUTED 1,5-BENZODIAZEPINE AND 1,3,4-THIAZIDIAZEPINE DERIVATIVES INVOLVING NAPHTHO[2,1-B]FURAN

M.N.Kumaraswamy, V.P.Vaidya, D.Ramesh and H.Rajashekhara.


1,5-Benzodiazepine and 1,2,4-triazolo[3,4-b][1,3,4]thiadiazepine derivatives possess antibacterial, antifungal, anti-inflammatory, analgesic, antipyretic, anticonvulsant, anticancer, cytotoxic, CNS depressant, antimalarial and activities. 1,5-Benzodiazepine derivatives also act as potential antipsycotic drug and they have been found to possess HIV reverse transcriptase inhibition. These observations prompted us to take up the present work of coupling 1,5-benzodiazepine and 1,2,4-triazolo[3,4-b][1,3,4]thiadiazepine with pharmacologically potent naphtho[2,1-b]furan moiety.

The reaction of 2-acetylnaphtho[2,1-b]furan 2 with substituted aromatic aldehydes in presence of base at reflux temperature in ethanol produced 1-naphtho[2,1-b]furan-2-yl-3-(substituted)-prop-2-en -1-ones (chalcones) 3a-f in good yield. These chalcones 3a-f on treatment with o-phenylenediamine in presence alkali in ethanol furnished 4-naphtho[2,1-b]furan-2-yl-3-(substituted)-2,3-dihydro-1H-1,5-benzodiazepine 4a-f. Similar reaction of compounds 3a-f with 5-aryl-4-amino-1,2,4-triazolo in the presence of piperidine in ethanol yielded 6-naphtho[2,1-b]furan-2-yl-8-phenyl-7,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine 5a-f.

The structures of newly synthesized compounds have been established by elemental analysis and spectral studies. In addition, they have been screened for analgesic activity by acetic acid induced writhing method by using swiss mice. The activity was evaluated by using acetyl salicylic acid as standard. All the compounds exhibit considerable analgesic activity.