Synthesis and Antitubercular Activity of Some Novel \([1\{(1\text{-phenylethylidene})\ \text{amino}\naphtho\,[2,1-B]\text{-furan-2-yl}]4\text{-substituted pyrimidin-2-amine Derivatives}

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INTRODUCTION

Pyrimidine is the most important member of all the diazine as this ring system occurs widely in living organisms. Pyrimidine is a versatile lead molecules for a broad range of biological effects, including antifungal,\textsuperscript{1} anti-inflammatory,\textsuperscript{2} cardiovascular,\textsuperscript{3} analgesic,\textsuperscript{4} antiviral,\textsuperscript{5} antimalarial,\textsuperscript{6} antioxidant,\textsuperscript{7} antimicrobial,\textsuperscript{8} anthelmintic,\textsuperscript{9} anti-HIV,\textsuperscript{10} antitumor,\textsuperscript{10} activities has been ascribed to these partly reduced pyrimidine derivatives. Additionally, dihydropyrimidines have been found active to transport medication across biological membranes. Several marine alkaloids containing the DHPMs is founding nature and in potent HIV gp-120-CD4 inhibitors. In recent years microwave assisted organic synthesis has gained the popularity among the organic chemists due to their reduced reaction time, ecofriendliness, enhanced selectivity and better workup procedures.\textsuperscript{11} Our research group has been interested in the synthesis of some novel \([1\{(1\text{-phenylethylidene})\ \text{amino}\naphtho\,[2,1-B]\text{-furan-2-yl}]4\text{-Substituted pyrimidin-2-amine derivatives using microwave irradiation and their antitubercularactivity.}

MATERIALS AND METHODS

All reagents and solvents used were of laboratory (LR) grade and were obtained from SD fine chemicals (Mumbai, India), Merck (Mumbai, India) and Sigma-Aldrich (Mumbai, India) and were used without further purification. Precoated silica gel \(F_{254}\) plates, obtained from Merck (Mumbai, India), were used for analytical and preparative TLC. Melting points were determined in an open capillary tube on Chemline CL726 melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu FT-IR 157 spectrophotometer using KBr pellets. \(^1\text{H}\)NMR (δ, ppm) spectra were recorded onBruker advance III 500 MHz NMR spectrophotometer in CDCl\(_3\) or DMSO-\(d_6\). In the \(^1\text{H}\) NMR spectra was used TMS as internal reference. Mass spectra were obtained on a Shimadzu GC-MS QP 2010 mass spectrometer. Elemental analyses were performed on a Elementar Vario EL III analyzer.

General procedure of 1-{1-aminonaphtho[2,1-b]furan-2-yl}ethanone (1)

To a solution of 2-hydroxy-1-naphthonitrite (0.02 mol) in dry acetone (100ml), chloroacetone (0.02 mol) and anhydrous potassium carbonate were added and the reaction mixture was refluxed on water bath for 8 hr. The potassium salt was filtered off and washed thoroughly with acetone. Removal of solvent from the filtrate and recrystallized from ethanol. The yield of the product was 89% and M.P 187-190°C.

General procedure of 1-{1-[1-(Phenyl ethylidene)amino]naphtho[2,1-b]furan-2-yl}ethanone (2)

A mixture of compound (1) (0.01 mol), appropriate acetonophenone (0.01 mol) and DMF (5drops) was subjected to microwave irradiation at 200 watts intermittently at 10 sec intervals for specified time. On completion of reaction (monitored by TLC), the reaction mixture was cooled and digested with water. The solid obtained was filtered and recrystallized from ethanol. The yield of the product was 78% and M.P 203-207°C.

General procedure of substituted chalcone (3)

Equimolar quantities (0.01 mol) of Aromatic aldehyde and compound (2) (0.01 mol) were taken in 100ml conical flask and dissolved in 20ml of ethanol to this (0.03 mol) of...
NaOH in minimum quantity of water was added. The mixture was stirred on a magnetic stirrer and the reaction was monitored with TLC. Reaction mixture was diluted with water and acidified with concentrated hydrochloric acid. The precipitated chalcone was filtered and recrystallized from absolute ethanol. The yield of the product was 69% and M.P 195-200°C.

**General procedure of 4-1- [(1-phenylethylidene) amino] naphtha [2,1-b]furan-2-yl] 4-(4- substituted pyrimidin-2-amine derivatives (4a-4j))

**Conventional method**

A compound (3) (0.01 mol) and guanidine hydrochloride (0.01 mol) were dissolved in absolute alcohol (20 ml). Few drops of concentrated HCl were added and the reaction mixture was refluxed and the reaction was monitored by TLC. After completion of reaction, it was poured into 250 ml of ice cold water and kept for some time. The crude solid was filtered and subjected to column chromatography. Elution with solvent ethyl acetate/petroleum ether (60-80°) gave pure compound and recrystallized from appropriate solvent.

**Microwave Assisted Method**

The condensation of the compound (3) (0.001 mol) with guanidine hydrochloride (0.001 mol) in alkaline medium viz, in potassium hydroxide (0.003 mol) in the presence of ethanol (10 mL), the entire reaction mixture was microwave irradiated at 180 watts for about 2-16 minutes, then kept aside for 2-3hrs, resulted the formation of corresponding pyrimidine derivatives. Reaction completion was identified by TLC precoated plates and recrystallized from appropriate solvent.


**M.P 182-185°C: I.R: 3254.02 cm⁻¹(N-H str), 2989.76 cm⁻¹(Ar C-H str), 2837.38 cm⁻¹(AI C-H str),1294.28 cm⁻¹(C-C str), 1681.98 cm⁻¹(C=N str),1625.05 cm⁻¹(C=C str),1421.58 cm⁻¹(C-N str), 1058.96 cm⁻¹(C-O-C str). ¹HNMR(CDCλ): 6.49(s,2H,NH₂) D₂O exchangeable, 1.84(s,3HCH₃),7.57-8.52(m,17H,Ar-H). MS: m/z 471(M+1); Anal. Calcld. for C₂₀H₂₆N₄O₂ C, 76.58; H, 4.71; N, 11.91. Found: C, 76.59; H, 4.74; N, 11.95.


**M.P 160-162°C: I.R: 3490.87 cm⁻¹(O-H str),3194.23 cm⁻¹(N-H str), 2972.40 cm⁻¹(Ar C-H str), 2860.53 cm⁻¹(AI C-H str), 1621.49 cm⁻¹(C-C str), 1568.84 cm⁻¹(C=N str), 1597.11 cm⁻¹(C-C str), 1446.66 cm⁻¹(C-N str), 1070.53 cm⁻¹(C-O-C str). ¹HNMR(CDCλ): 6.79(s,2H,NH₂) D₂O exchangeable, 1.92(s,3HCH₃), 6.86-8.88(m,16H,Ar-H). MS: m/z 490(M+1); Anal. Calcld. for C₂₀H₂₆N₄O₂ C, 73.69; H, 4.33; N, 11.46. Found: C, 73.71; H, 4.35; N, 11.49.


**M.P 150-155°C: I.R: 3548.89 cm⁻¹(O-H str),3192.30 cm⁻¹(N-H str), 2976.26 cm⁻¹(Ar C-H str), 2862.46 cm⁻¹(AI C-H str), 1621.49 cm⁻¹(C-C str), 1568.84 cm⁻¹(C=N str), 1593.25 cm⁻¹(C=C str), 1473.66 cm⁻¹(C-N str), 1134.18 cm⁻¹(C-O-C str). ¹HNMR(CDCλ): 6.70(s,2H,NH₂) D₂O exchangeable, 1.85(s,3HCH₃),9.87(s,1H,OH),6.72-8.88(m,18H,Ar-H). MS: m/z 520.4(M⁺); Anal. Calcld. for C₂₆H₂₆N₄O₂ C, 78.44; H, 4.65; N, 10.76. Found: C, 78.49; H, 4.68; N, 10.79.


**M.P 172-175°C: I.R: 3259.81 cm⁻¹(N-H str), 2956.97 cm⁻¹(Ar C-H str), 2839.31 cm⁻¹(AI C-H str),1292.35 cm⁻¹(C-C str),1683.91 cm⁻¹(C=N str),1626.05 cm⁻¹(C=C str),1427.37 cm⁻¹(C-N str),1058.95 cm⁻¹(C-O-C str). ¹HNMR(CDCλ): 6.70(s,2H,NH₂) D₂O exchangeable, 1.92(s,3HCH₃),3.48(s,3H,OH),6.70-8.88(m,16H,Ar-H). MS: m/z 484(M⁺); Anal. Calcld. for C₂₀H₂₆N₄O₂ C, 76.84; H, 4.99; N, 11.56. Found: C, 76.87; H, 5.12; N, 11.59.


**M.P 166-168°C: I.R: 3196.15 cm⁻¹(N-H str), 2974.33 cm⁻¹(Ar C-H str), 2806.52 cm⁻¹(AI C-H str),1269.20 cm⁻¹(C-C str),1656.91 cm⁻¹(C=N str),1597.11 cm⁻¹(C=C str),1413.87 cm⁻¹(C-N str), 1072.46 cm⁻¹(C-O-C str). ¹HNMR(CDCλ): 6.70(s,2H,NH₂) D₂O exchangeable, 1.80(s,3HCH₃),2.45(s,3HCH₃),6.72-8.87(m,16H,Ar-H). MS: m/z 497(M⁺); Anal. Calcld. for C₂₂H₂₄N₅O₂ C, 77.24; H, 5.47; N, 14.07. Found: C, 77.27; H, 5.49; N, 14.10.
RESULTS AND DISCUSSION

A mixture of chalcone and guanidine in ethanol in presence alkaline medium i.e. potassium hydroxide under microwave irradiation resulted in the formation of final product. This present route, besides being advantageous in simple reaction conditions and easy work-up procedures, less time consuming and eco-friendly, has resulted in better yields over the conventional methods. All the three synthetic methods are compared in terms of yield and reaction time. All the synthesized compounds (4a-4j) were screened for their antitubercular activity against Mycobacterium tuberculosis H37Rv by the broth dilution method according to recommended procedure by the National Committee for Clinical Laboratory Standards for the determination of minimum inhibitory concentration (MIC). The results of antitubercular activity are shown in Table 2. The investigation of antitubercular screening revealed that some of the tested compounds 4b, 4c and 4h showed moderate to good antitubercular activity.

Table 1: Comparison Between Various Synthetic Methods of [1[(phenylthiolylidene) amino] naphtho[2,1-b]furan-2-yl]4-(4-methyl phenyl)pyrimidin-2-amine derivatives (4a-4j)

<table>
<thead>
<tr>
<th>Compds.</th>
<th>Conventional method</th>
<th>Microwave assisted method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reaction time (hr)</td>
<td>% Yield*</td>
</tr>
<tr>
<td>4a</td>
<td>6.0</td>
<td>67</td>
</tr>
<tr>
<td>4b</td>
<td>6.0</td>
<td>52</td>
</tr>
<tr>
<td>4c</td>
<td>6.0</td>
<td>57</td>
</tr>
<tr>
<td>4d</td>
<td>6.0</td>
<td>53</td>
</tr>
<tr>
<td>4e</td>
<td>6.0</td>
<td>50.6</td>
</tr>
<tr>
<td>4f</td>
<td>6.0</td>
<td>47.3</td>
</tr>
<tr>
<td>4g</td>
<td>6.0</td>
<td>56</td>
</tr>
<tr>
<td>4h</td>
<td>6.0</td>
<td>55</td>
</tr>
<tr>
<td>4i</td>
<td>6.0</td>
<td>53</td>
</tr>
<tr>
<td>4j</td>
<td>6.0</td>
<td>45</td>
</tr>
</tbody>
</table>

* Yield refers to pure isolated products
Table 2 Antitubercular activity of 4[1{(1phenylethylidene)amino}naphtha[2,1-b]furan-2-yl]4-Substituted pyrimidin-2-amine derivatives. (4a-4j)

<table>
<thead>
<tr>
<th>Compds.</th>
<th>MIC (μg/ml) Acid fast M. tuberculosis</th>
</tr>
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<tbody>
<tr>
<td>4a</td>
<td>&gt;100</td>
</tr>
<tr>
<td>4b</td>
<td>50</td>
</tr>
<tr>
<td>4c</td>
<td>100</td>
</tr>
<tr>
<td>4d</td>
<td>&gt;100</td>
</tr>
<tr>
<td>4e</td>
<td>&gt;100</td>
</tr>
<tr>
<td>4f</td>
<td>&gt;100</td>
</tr>
<tr>
<td>4g</td>
<td>100</td>
</tr>
<tr>
<td>4h</td>
<td>&gt;100</td>
</tr>
<tr>
<td>4i</td>
<td>&gt;100</td>
</tr>
<tr>
<td>4j</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

CONCLUSION

A simple, quick and efficient method for the synthesis of 4[1{(1phenylethylidene)amino}naphtha[2,1-b]furan-2-yl]4-Substituted pyrimidin-2-amine derivatives by condensation of Chalcone and guanidine in presence of con. HCl has been developed. Ease of separation of pure product, selectively and in high yields. A novel, microwave assisted eco-friendly convenient route, for the synthesis 4[1{(1phenylethylidene)amino}naphtha[2,1-b]furan-2-yl]4-Substituted pyrimidin-2-amine derivatives has been developed which gave excellent yields in short reaction times.

REFERENCES


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