Chapter – V

Efficient Synthesis of Pyrano and Furanoquinolines Catalyzed by 4-Nitro phthalic acid
Introduction

The products containing pyrano and furanoquinoline moieties are widely distributed in nature and found to associate with a wide range of biological activities. Veprisine (1), 7-dimethylallyloxy-N-methylflindersine (2), 8-hydroxy-N-acetyloxymethylflindersine (3) and the cis-diol of 7-methoxyflindersine (4), oricine (5) are examples of pyranoquinolines which have been isolated in recent years from plant species of the Rutaceae family.\(^1\)-\(^4\) Alkaloids haplophytin-A (6) and flinderine (7) were isolated from a methanol extract of Haplophyllum acutofolium.\(^5\) Zanthosimuline (8) have been isolated from Zanthoxylum simulans.\(^6\) Trans-erioaustralasine have (9) been isolated from the Australian rutaceous plant *Eriostenum australasius* ssp. *banksii* in 1993.\(^7\) Trans-deacetoxyerioaustralasine (10), trans-deacetoxyerioaustralasine hydrate (11), trans-erioaustralasine hydrate (12) and trans-1'-epideacetoxyerioaustralasine hydrate (13) have been isolated from *Halfordia kendack*.\(^8\) These alkaloids possess important biological activities such as anti-allergic,\(^9\) psychotropic,\(^10\) anti-inflammatory,\(^11\) and estrogenic activities.\(^12\)

\[
\begin{align*}
1: & \quad R_1 = \text{OCH}_3, \quad R_2 = \text{CH}_3, \quad R_3 = \text{CH}_3 \\
2: & \quad R_1 = \text{H}, \quad R_2 = \text{CH}_2\text{CH}=\text{C(CH}_3)_2, \quad R_3 = \text{CH}_3 \\
3: & \quad R_1 = \text{H}, \quad R_2 = \text{H}, \quad R_3 = \text{CH}_2\text{OOCCH}_3 \\
4: &
\end{align*}
\]
The alkaloids skimimianine and balfouridine which contain furanoquinoline moieties also show biological activity,\textsuperscript{13} which has led to the synthesis of pyrano and furanoquinolines derivatives over the years. 2-aryl-tetrahydroquinoline derivatives
exhibit interesting biological activity. For example, 2-aryl-2,3-dihydro-4-quinolone (14) exhibits antitumor activity,\textsuperscript{14} and 2-aryl-1,2,3,4-tetrahydroquinoline (15) is a core structure of the compounds possessing 5-lipoxygenase inhibitory properties and potential therapeutic application in asthma.\textsuperscript{15}

Therefore, it is not surprising that many synthetic methods have been developed for these types of compounds. Amongst them, the Lewis acid catalyzed imino Diels-Alder reaction between $N$-benzylideneanlines and nucleophilic olefins such as 3,4-dihydropyran and 2,3-dihydrofuran (Scheme 1) is one of the powerful synthesis tools for the constructing pyrano and furano-2-aryl-tetrahydroquinolines.

This reaction has been extensively studied with use of different Lewis acid such as BF$_3$.\textsubscript{OEt$_2$},\textsuperscript{16} GbCl$_3$,\textsuperscript{17} InCl$_3$,\textsuperscript{18} LiClO$_4$,\textsuperscript{19} ZrCl$_4$,\textsuperscript{20} SbCl$_3$,\textsuperscript{21} VCl$_3$.\textsuperscript{22} Although the imino Diels-Alder reaction promoted by Lewis acid are known, more then stoichiometric
amounts of the *Lewis* acid are required due to co-ordination of the *Lewis* acid to the imine nitrogen and generally, these *Lewis* acid catalysts are moisture sensitive and get easily decomposed or deactivated in the presence of even trace amount of water and are thus difficult to handle. Further disposal of these acids leads to environmental pollution. The imino Diels-Alder reaction has also been successfully carried out using K-10 clay, urea nitrate, lanthanide triflates, KHSO₄, I₂, ionic liquids, ZrOCl₂.8H₂O. In the quest for developing a less toxic, potential green catalyst, we thought of using 4-nitrophthalic acid as a catalyst for this reaction. The 4-nitrophthalic acid is inexpensive, stable solid, water soluble, and easily available as we described in chapter 3.

4-nitrophthalic acid is easier to handle than metal halides such as ZrCl₄, BiCl₃, SbCl₃ and protic acids as TFA, TsOH. In the present work, we have synthesized the substituted pyrano and furanoquinolines via an imino Diels-Alder reaction using 4-npa as a catalyst.
Present Work

Preliminary studies were carried out to study the effect of solvents, catalytic concentration, and temperature on the model reaction of *N*-benzylideneaniline (16a) and 3,4-dihydropyran (17a) in the presence of 4-nitrophthalic acid (4-npa), and the results are summarized in the Table 1. Though reaction proceeds at room temperature, the isolated yields are low and the reaction is sluggish. At reflux temperature, the formation of impurities has been observed. At 50 °C, the reaction proceeds smoothly and gave desired products in good yields. Among the various solvents, acetonitrile was found to be the best solvent for this transformation. Also, we examined the reaction in the acetonitrile/water system. Remarkably, the reaction proceeded smoothly in CH$_3$CN/H$_2$O (3/1, v/v) system and afforded the desired product in good yield. At 10 mol% of catalyst, the reaction was sluggish and at 25 mol %, the optimal results were obtained. Increasing the concentration of the catalyst beyond 25 mol% did not show an appreciable advantage.

Table 1. Screening catalytic activity of 4-npa for the synthesis of quinolines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Amount of Catalyst</th>
<th>Temperature / °C</th>
<th>Time / h</th>
<th>Yield / %$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_3$CN</td>
<td>25 mol % 4-npa</td>
<td>25</td>
<td>8.00</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$CN</td>
<td>10 mol % 4-npa</td>
<td>50</td>
<td>5.00</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>CH$_3$CN</td>
<td>25 mol % 4-npa</td>
<td>50</td>
<td>3.00</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>CH$_3$CN</td>
<td>25 mol % 4-npa</td>
<td>reflux</td>
<td>2.10</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>25 mol % 4-npa</td>
<td>50</td>
<td>5.00</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>MeOH</td>
<td>25 mol % 4-npa</td>
<td>50</td>
<td>4.00</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>25 mol % 4-npa</td>
<td>50</td>
<td>4.00</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>25 mol % 4-npa</td>
<td>50</td>
<td>3.45</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>CH$_2$Cl$_2$</td>
<td>25 mol % 4-npa</td>
<td>reflux</td>
<td>3.30</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>CH$_3$CN</td>
<td>40 mol % 4-npa</td>
<td>50</td>
<td>2.45</td>
<td>88</td>
</tr>
<tr>
<td>11</td>
<td>CH$_3$CN / H$_2$O</td>
<td>25 mol % 4-npa</td>
<td>50</td>
<td>3.00</td>
<td>80</td>
</tr>
</tbody>
</table>

$^a$Isolated yields
Thus, in the presence of 25 mol% of 4-npa, N-benzylidene (16a) was treated with (17a) in acetonitrile at 50 °C. After 3 hrs the pyranoquinolines (18a) and (19a) were obtained in a ratio of 39:61 in over all yields of 90% (Scheme 2). The structures of the compounds were established by IR, $^1$H NMR and Mass spectral analysis. It was observed that the pyran ring was cis-fused in the tetrahydroquinoline moiety and the stereochemistry of the products was established based on the coupling constant of C$_2$-H ($J_{3,2} = 4.4-5.7$) in (18) indicated the cis relationship between C-3 and C-2, whereas in (19) ($J_{3,2} = 10.08-11.12$) the coupling was trans. In all cases, $J_{3,4}$ was found to be 2.6-3.0 Hz indicating a cis ring junction between the quinoline and pyran rings. The results obtained with substituted N-benzylideneanilines (16) and 3,4-dihydropyran (17a)/dihydro ofuran (17b) are summarized in Table 2.

![Scheme 2](image-url)
Table 2. The synthesis of 2-aryl tetrahydroquinolines using 4-npa at 50 °C temperature.

<table>
<thead>
<tr>
<th>Products</th>
<th>R₂</th>
<th>R₃</th>
<th>n</th>
<th>Time / h</th>
<th>Product ratio ¹</th>
<th>Yield / % ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>3.00</td>
<td>39:61</td>
<td>90</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>CH₃</td>
<td>1</td>
<td>3.00</td>
<td>42:58</td>
<td>92</td>
</tr>
<tr>
<td>c</td>
<td>OCH₃</td>
<td>H</td>
<td>1</td>
<td>3.00</td>
<td>35:65</td>
<td>93</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>Cl</td>
<td>1</td>
<td>4.00</td>
<td>30:70</td>
<td>78</td>
</tr>
<tr>
<td>e</td>
<td>Cl</td>
<td>H</td>
<td>1</td>
<td>4.00</td>
<td>45:55</td>
<td>81</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>H</td>
<td>0</td>
<td>4.00</td>
<td>49:51</td>
<td>80</td>
</tr>
<tr>
<td>g</td>
<td>OCH₃</td>
<td>H</td>
<td>0</td>
<td>4.00</td>
<td>56:44</td>
<td>82</td>
</tr>
<tr>
<td>h</td>
<td>H</td>
<td>CH₃</td>
<td>0</td>
<td>5.00</td>
<td>43:53</td>
<td>77</td>
</tr>
<tr>
<td>i</td>
<td>Cl</td>
<td>H</td>
<td>0</td>
<td>4.00</td>
<td>52:48</td>
<td>82</td>
</tr>
</tbody>
</table>

¹Product ratio was based on isolation by column chromatography
²Isolated yields

There are reports in the literature on the three component one pot synthesis of pyrano and furano quinolines using aryl amines, aryl aldehydes and DHP.¹⁷,²¹,²² Hence anticipating the similar results, we tried one pot synthesis by using aniline (20), benzaldehyde and dihydropyran (17a) catalyzed by 4-npa. However, the reaction did not gave expected pyranoquinolines (18a) or (19a), instead it we got pyranoquinolines of type (21a) and (22a) in the ratio of 48:52 (Scheme 3). The results indicates that, in the presence of 4-npa, the masked aldehyde (17a) reacts faster than benzaldehyde with aniline to form the Schiff's base which undergo imino Diels-Alder reaction to yield pyranoquinolines of the type (21a) and (22a). In this 4-npa catalyzed Domino reaction, benzaldehyde remained unreacted. Encouraged by above interesting results, we carried out reaction of various aryl amines with dihydropyran/dihydrofuran (Scheme 4) and results are summarized in Table 3. Similar Domino reaction of aromatic amines with cyclic enol ethers catalyzed by K-10 clay,²³ InCl₃,³⁰ has been reported. These results indicates that 4-npa can be used has an efficient catalyst in the imino Diels-Alder reaction.
of N-benylideneanilines with cyclic enol ethers and also in the Domino reaction of anilines with cyclic enol ethers leading to the formation of pyrano and furanoquinolines.

![Scheme 3](image)

**Scheme 3**

![Scheme 4](image)

**Scheme 4**

**Table 3.** The synthesis of 2-alkoxy tetrahydroquinolines using 4-npa at 50 °C.

<table>
<thead>
<tr>
<th>Products</th>
<th>R₄</th>
<th>n</th>
<th>Time / h</th>
<th>Product ratio a 21:22</th>
<th>Yield / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>1</td>
<td>4.00</td>
<td>48 : 52</td>
<td>82</td>
</tr>
<tr>
<td>b</td>
<td>CH₃</td>
<td>1</td>
<td>3.30</td>
<td>42 : 58</td>
<td>85</td>
</tr>
<tr>
<td>c</td>
<td>OCH₃</td>
<td>1</td>
<td>3.30</td>
<td>45 : 55</td>
<td>86</td>
</tr>
<tr>
<td>d</td>
<td>Cl</td>
<td>1</td>
<td>4.00</td>
<td>51 : 49</td>
<td>75</td>
</tr>
<tr>
<td>e</td>
<td>F</td>
<td>1</td>
<td>4.00</td>
<td>58 : 42</td>
<td>75</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>0</td>
<td>4.00</td>
<td>60 : 40</td>
<td>80</td>
</tr>
<tr>
<td>g</td>
<td>CH₃</td>
<td>0</td>
<td>5.00</td>
<td>74 : 26</td>
<td>75</td>
</tr>
<tr>
<td>h</td>
<td>OCH₃</td>
<td>0</td>
<td>4.00</td>
<td>70 : 30</td>
<td>78</td>
</tr>
<tr>
<td>i</td>
<td>Cl</td>
<td>0</td>
<td>4.00</td>
<td>72 : 38</td>
<td>78</td>
</tr>
<tr>
<td>j</td>
<td>F</td>
<td>0</td>
<td>5.00</td>
<td>80 : 20</td>
<td>76</td>
</tr>
</tbody>
</table>

*Product ratio was based on isolation by column chromatography

*Isolated yields
From these results, we have proposed the following possible mechanism to account for the reaction. An aromatic amine first reacts with cyclic enol ether to form 2-azadiene and the second step proceeds via the imino Diels-Alder reaction between this 2-azadiene and another molecule of cyclic enol ether (Scheme 5).

In conclusion, a very interesting and a facile synthesis of substituted pyrano and furanoquinolines using cheaper, water stable, and water soluble 4-nitrophthalic acid catalyzed imino Diels-Alder reaction of N-benylideneanilines with cyclic enol ethers and the Domino reaction of anilines with cyclic enol ethers have been described.
Experimental

General procedure for the synthesis of tetrahydroquinolines: 18 and 19

0.25 mmol 4-npa was added to a mixture of 1.0 mmol N-benzylidene (16) and 1.2 mmol 3,4-dihydro-2H-pyran (17a) or 2,3-dihydrofuran (17b) in 5 cm³ acetonitrile. The reaction mixture was stirred at 50 °C temperature for the appropriate time. After the completion, the reaction mixtures was quenched with saturated 25 cm³ NaHCO₃ aqueous solution and extracted with 3 X 10 cm³ ethyl acetate. The combined organic layer was dried (Na₂SO₄), concentrated, and purified by column chromatography on SiO₂ with an ethyl acetate and petroleum ether mixture as elutent to afford the corresponding tetrahydroquinolines (18) and (19).

cis-3,4,4a,5,6,10b-hexahydro-5-phenyl-2H-pyrano[3,2-c]quinoHne: 18a

Colorless crystalline solid, M.p.: 130-132 °C; IR (KBr): \( \nu = 3313 \text{ cm}^{-1} \); \(^1\)H NMR (CDCl₃): \( \delta = 7.43-7.25 \text{ (m, 6H), 7.03} \) (tt, \( J = 7.6, 0.6 \text{ Hz, 1H} \)), 6.77 (td, \( J = 7.6, 1.0 \text{ Hz, 1H} \)), 6.58 (dd, \( J = 7.8, 0.9 \text{ Hz, 1H} \)), 5.31 (d, \( J = 5.6 \text{ Hz, 1H} \)), 4.68 (d, \( J = 2.6 \text{ Hz, 1H} \)), 3.58-3.85 (m, 3H), 2.13-2.19 (m, 1H), 1.50-1.25 (m, 4H); \(^1^3\)C NMR (CDCl₃): \( \delta = 145.2, 141.2, 128.4, 128.1, 127.7, 127.6, 126.9, 120.0, 118.4, 114.5, 72.8, 60.7, 59.4, 39.0, 25.5, 18.1 \); MS: \( m/z = 265 \text{ (M+)} \); Anal. Calcd for C₁₈H₁₉NO: C, 81.52; H, 7.16; N, 5.28. Found: C, 81.28; H, 7.23; N, 5.32.

trans-3,4,4a,5,6,10b-hexahydro-5-phenyl-2H-pyrano[3,2-c]quinoHne: 19a

Viscous oil; \(^1\)H NMR (CDCl₃): \( \delta = 7.42-7.36 \text{ (m, 5H), 7.25} \) (dd, \( J = 7.1, 0.5 \text{ Hz, 1H} \)), 7.07 (td, \( J = 7.0, 1.3 \text{ Hz, 1H} \)), 6.70 (td, \( J = 7.0, 1.1 \text{ Hz, 1H} \)), 6.51 (dd, \( J = 7.1, 1.0 \text{ Hz,} \))
1H), 4.72 (d, J = 10.8 Hz, 1H), 4.39 (d, J = 2.7 Hz, 1H), 4.00-4.21 (m, 2H), 3.71 (td, J = 11.6, 2.5 Hz, 1H), 2.07-2.14 (m, 1H), 1.80-1.88 (m, 1H), 1.61-1.72 (m, 1H), 1.42-1.51 (m, 1H), 1.20-1.30 (m, 1H) ppm; 13C NMR (CDCl3): δ = 144.7, 142.3, 130.9, 129.3, 128.6, 127.9, 127.8, 120.7, 117.4, 114.2, 74.5, 68.5, 54.9, 38.9, 24.1, 22.1 ppm; MS: m/z = 265 (M+).

cis-3,4,4a,5,6,10b-hexahydro-5-phenyl-7-methyl-2H-pyrano[3,2-c]quinoline: 18b

Solid, M.p.: 143-144 °C; IR (KBr): ʋ = 3338 cm⁻¹; 1H NMR (CDCl3): δ = 7.48-7.32 (m, 6H), 7.03 (dd, J = 7.5, 0.6 Hz, 1H), 6.75 (t, J = 7.5 Hz, 1H), 5.37 (d, J = 5.5 Hz, 1H), 4.71 (d, J = 2.4 Hz, 1H), 3.34-3.85 (m, 3H), 2.15 (s, 4H), 1.29-1.82 (m, 4H) ppm; 13C NMR (CDCl3): δ = 143.3, 141.5, 129.2, 128.5, 127.6, 126.9, 125.5, 121.6, 119.5, 117.8, 73.0, 60.7, 59.3, 38.8, 25.5, 18.1, 17.5 ppm; MS: m/z = 279 (M+). Anal. Calcd for C19H21NO: C, 81.73; H, 7.52; N, 5.01. Found: C, 81.33; H, 7.63; N, 5.02.

trans-3,4,4a,5,6,10b-hexahydro-5-phenyl-7-methyl-2H-pyrano[3,2-c]quinoline: 19b

Colorless crystalline solid, M.p.: 130-132 °C; IR (KBr): ʋ = 3389 cm⁻¹; 1H NMR (CDCl3): δ = 7.44-7.48 (2H, m), 7.42-7.39 (m, 2H), 7.31-7.33 (m, 1H), 7.12 (dd, J = 7.5, 1.2 Hz, 1H), 7.03 (dd, J = 7.5, 0.6 Hz, 1H), 6.66 (t, J = 7.5 Hz, 1H), 4.77 (d, J = 9.9 Hz, 1H), 4.40 (d, J = 2.7 Hz, 1H), 4.11 (dt, J = 12.3, 2.3 Hz, 1H), 3.90 (b, 1H), 3.73 (td, J = 11.7, 2.5 Hz, 1H), 2.09-2.16 (m, 1H), 2.07 (s, 3H), 1.82-1.89 (m, 1H), 1.60-1.78 (m, 1H), 1.44-1.53 (m, 1H), 1.27-1.37 (m, 1H) ppm; 13C NMR (CDCl3): δ = 142.8, 142.7, 130.3, 128.9, 128.7, 128.0, 127.9, 121.2, 120.2, 117.0, 74.9, 68.7, 55.0, 38.9, 24.2, 22.1,
cis-3,4,4a,5,6,10b-hexahydro-5-phenyl-9-methoxy-2H-pyrano[3,2-c]quinoline: 18c

Colorless crystalline solid, M.p.: 144-146 °C; IR (KBr): $\tilde{\nu}$ = 3401 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ = 7.26-7.44 (m, 5H), 7.02 (d, $J$ = 2.8 Hz, 1H), 6.75 (dd, $J$ = 8.7, 2.8 Hz, 1H), 6.60 (d, $J$ = 8.7 Hz, 1H), 5.30 (d, $J$ = 5.3 Hz, 1H), 4.60 (d, $J$ = 1.9 Hz, 1H), 3.85 (1H, br), 3.75 (s, 3H), 3.53-3.78 (m, 1H), 3.30-3.37 (m, 1H), 2.02-2.08 (m, 1H), 1.24-1.48 (4H, m) ppm; MS: $m/z$ = 295 (M$^+$); Anal. Calcd for C$_{19}$H$_{21}$NO: C, 81.73; H, 7.52; N, 5.01. Found: C, 81.70; H, 7.65; N, 5.13.

trans-3,4,4a,5,6,10b-hexahydro-5-phenyl-9-methoxy-2H-pyrano[3,2-c]quinoline: 19c

Colorless crystalline solid, M.p.: 98-100 °C; $^1$H NMR (CDCl$_3$): $\delta$ = 7.27-7.37 (5H, m), 6.79 (d, $J$ = 2.8 Hz, 1H), 6.65 (dd, $J$ = 8.4, 2.8 Hz, 1H), 6.45 (d, $J$ = 8.4 Hz, 1H), 4.60 (d, $J$ = 10.4 Hz, 1H), 4.31(d, $J$ = 2.8 Hz, 1H), 4.04 (m, 1H), 3.70 (s, 3H), 3.62-3.68 (m, 1H), 2.05-2.22 (m, 1H), 1.72-1.77 (m, 1H), 1.57-1.64 (m, 1H), 1.40-1.47 (m, 2H), 1.22-1.28 (m, 1H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta$ = 152.0, 142.4, 139.0, 128.6, 127.8, 121.4, 116.9, 115.5, 114.9, 74.6, 68.5, 55.9, 55.3, 39.0, 24.2, 22.1 ppm; MS: $m/z$ = 295 (M$^+$); Anal. Calcd for C$_{19}$H$_{21}$NO$_2$: C, 77.30; H, 7.11; N, 4.74. Found: C, 77.48; H, 7.23; N, 4.92.
cis-3,4,4a,5,6,10b-hexahydro-5-phenyl-7-chloro-2H-pyrano[3,2-c]quinoline: 18d

Colorless crystalline solid, M.p.: 154-156 °C; IR (KBr):
\[ \tilde{\nu} = 3306 \text{ cm}^{-1} \]; \(^1\)H NMR (CDCl\(_3\)): \( \delta = 7.29-7.39 \) (6H, m), 7.12 (d, \( J = 7.6 \) Hz, 1H), 6.65 (t, \( J = 7.6 \) Hz, 1H), 5.29 (d, \( J = 5.4 \) Hz, 1H), 4.68 (d, \( J = 2.3 \) Hz, 1H), 4.41 (brs, 1H), 3.52-3.59 (m, 1H), 3.30-3.36 (m, 1H), 2.07-2.14 (m, 1H), 1.41-1.50 (m, 2H), 1.16-1.26 (m, 2H) ppm; MS: \( m/z = 299 \) (M+); Anal. Calcd for C\(_{18}\)H\(_{18}\)ClNO: C, 72.15; H, 6.01; N, 4.67. Found: C, 71.35; H, 6.00; N, 4.85.

trans-3,4,4a,5,6,10b-hexahydro-5-phenyl-7-chloro-2H-pyrano[3,2-c]quinoline: 19d

Colorless crystalline solid, M.p.: 109-101 °C; IR (KBr):
\[ \tilde{\nu} = 3384 \text{ cm}^{-1} \]; \(^1\)H NMR (CDCl\(_3\)): \( \delta = 7.27-7.39 \) (5H, m), 7.11-7.19 (2H, m), 6.64 (t, \( J = 7.7 \) Hz, 1H), 4.66 (d, \( J = 10.7 \) Hz, 1H), 4.58 (brs, 1H), 4.34 (d, \( J = 2.7 \) Hz, 1H), 4.04 (dt, \( J = 10.0, 2.1 \) Hz, 1H), 3.66 (td, \( J = 10.8, 2.6 \) Hz, 1H), 1.97-2.04 (m, 1H), 1.82-1.88 (m, 1H), 1.60-1.66 (m, 1H), 1.45-1.52 (m, 1H), 1.27-1.34 (m, 1H) ppm; \(^1^3\)C NMR (CDCl\(_3\)): \( \delta = 141.9 \) 141.0, 129.7, 129.3, 129.2, 128.8, 128.1, 127.8, 121.9, 118.1, 117.0, 74.4, 68.6, 54.9, 38.8, 24.0, 22.1 ppm; Anal. Calcd for C\(_{18}\)H\(_{18}\)ClNO: C, 72.15; H, 6.01; N, 4.67. Found: C, 72.10; H, 5.99; N, 4.85.

cis-3,4,4a,5,6,10b-hexahydro-5-phenyl-9-chloro-2H-pyrano[3,2-c]quinoline: 18e

Colorless crystalline solid, M.p.: 170-172 °C; IR (KBr):
\[ \tilde{\nu} = 3370 \text{ cm}^{-1} \]; \(^1\)H NMR (CDCl\(_3\)): \( \delta = 7.32-7.39 \) (6H, m), 7.01 (dd, \( J = 8.2, 0.7 \) Hz, 1H), 6.50 (d, \( J = 8.0 \) Hz, 1H), 5.25 (d, \( J = 5.5 \) Hz, 1H), 4.60 (d, \( J = 2.5 \) Hz, 1H), 3.85 (brs, 1H), 3.58-3.64 (m, 1H), 3.47 (brs, 1H).
3.38-3.43 (m, 1H), 2.11-2.17 (m, 1H), 1.45-1.58 (m, 3H), 1.23-1.29 (m, 1H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 143.7, 140.7, 128.5, 128.1, 127.7, 127.3, 126.8, 123.1, 121.7, 115.6, 72.5, 60.8, 59.3, 38.6, 25.3, 18.1$ ppm; MS: $m/z = 300$ (M+1); Anal. Calcd for C$_{18}$H$_{18}$ClNO: C, 72.15; H, 6.01; N, 4.67. Found: C, 72.12; H, 6.02; N, 4.81.

trans-3,4,4a,5,6,10b-hexahydro-5-phenyl-9-chloro-2H-pyrano[3,2-c]quinoline: 19e

Colorless crystalline solid, M.p.: 125-126 °C; IR (KBr):
$\tilde{\nu} = 3298$ cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta = 7.30-7.39$ (5H, m), 7.19 (d, $J = 2.3$ Hz, 1H), 7.01 (dd, $J = 8.0, 1.9$ Hz, 1H), 6.41 (d, $J = 8.1$ Hz, 1H), 4.63 (d, $J = 10.6$ Hz, 1H), 4.30 (1H, d, $J = 2.8$ Hz), 4.00-4.07 (m, 2H), 3.66 (td, $J = 15.0, 3.0$ Hz, 1H), 198-2.05 (m, 1H), 1.71-1.77 (m, 1H), 1.58-1.65 (m, 1H), 1.43-1.47 (m, 1H), 1.24-1.28 (m, 1H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 143.3, 142.0, 130.4, 129.2, 128.7, 128.0, 127.7, 121.9, 121.8, 115.3, 74.0, 68.5, 55.0, 38.7, 24.0, 22.1$ ppm; MS: $m/z = 301$ (M+1); Anal. Calcd for C$_{18}$H$_{18}$ClNO: C, 72.15; H, 6.01; N, 4.67. Found: C, 72.12; H, 6.02; N, 4.81.

cis-2,3,3a,4,5,9b-hexahydro-4-phenyl-furo[3,2-c]quinoline: 18f

Colorless crystalline solid, M.p.: 117-118 °C; IR (KBr):
$\tilde{\nu} = 3348$ cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta = 7.26-7.47$ (6H, m), 7.08 (td, $J = 7.8, 1.5$ Hz, 1H), 6.80 (td, $J = 7.8, 1.1$ Hz, 1H) 6.59 (dd, $J = 7.8, 1.0$ Hz, 1H), 5.26 (d, $J = 8.0$ Hz, 1H), 4.69 (d, $J = 3.0$ Hz, 1H), 3.72-3.82 (m, 3H), 2.73-2.77 (m, 1H), 2.16-2.23 (m, 1H), 1.48-1.54 (m, 1H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 144.9, 142.2, 130.1, 128.6, 128.3, 127.6, 126.5, 122.7, 119.2, 114.9, 75.9, 66.8, 57.5, 45.8, 24.7$ ppm; MS: $m/z = 251$ (M+); Anal. Calcd for C$_{17}$H$_{17}$NO: C, 81.28; H, 6.77; N, 5.58. Found: C, 80.88; H, 6.65; N, 5.29.
trans-2,3,3a,4,5,9b-hexahydro-4-phenyl-furo[3,2-c]quinoline: 19f

Viscous oil; IR (KBr): $\bar{\nu} = 3327 \text{ cm}^{-1}$; $^1$H NMR (CDCl$_3$):

$\delta = 7.24$-$7.46$ (6H, m), 7.12 (td, $J = 7.7, 1.1 \text{ Hz}$, 1H), 6.79 (td, $J = 7.8, 0.9 \text{ Hz}$, 1H), 6.62 (d, $J = 8.0 \text{ Hz}$, 1H), 4.59 (d, $J = 5.1 \text{ Hz}$, 1H), 4.05-4.09 (m, 1H), 3.83-3.89 (m, 3H), 2.43-2.48 (m, 1H), 1.98-2.04 (m, 1H), 1.70-1.76 (m, 1H) ppm; $^1$C NMR (CDCl$_3$): $\delta = 145.3, 141.7, 131.1, 128.8, 128.6, 128.2, 128.0, 120.0, 118.2, 114.6, 76.1, 65.0, 57.6, 43.3, 28.7$ ppm; MS: $m/z = 251$ (M+).

cis-2,3,3a,4,5,9b-hexahydro-4-phenyl-8-methoxy-furo[3,2-c]quinoline: 18g

Colorless crystalline solid, M.p.: 132-133 °C; IR (KBr):

$\bar{\nu} = 3300 \text{ cm}^{-1}$; $^1$H NMR (CDCl$_3$): $\delta = 7.25$-$7.46$ (m, 5H), 6.96 (d, $J = 2.8 \text{ Hz}$, 1H), 6.73 (dd, $J = 8.6, 2.8$ Hz, 1H), 6.52 (d, $J = 8.7 \text{ Hz}$, 1H), 5.23 (d, $J = 8.0 \text{ Hz}$, 1H), 4.64 (d, $J = 2.9 \text{ Hz}$, 1H), 3.77 (s, 3H), 3.52-3.80 (m, 3H), 2.73-2.78 (m, 1H), 2.17-2.24 (m, 1H), 1.49-1.54 (m, 1H) ppm; $^1$C NMR (CDCl$_3$): $\delta = 153.1, 142.4, 139.0, 128.6, 127.6, 126.5, 123.5, 116.2, 115.8, 113.8, 76.3, 66.9, 57.9, 55.7, 45.9, 24.5$ ppm; MS: $m/z = 281$ (M+). Anal. Calcd for C$_{18}$H$_{19}$NO$_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.80; H, 6.77; N, 5.06.

trans-2,3,3a,4,5,9b-hexahydro-4-phenyl-8-methoxy-furo[3,2-c]quinoline: 19g

Colorless crystalline solid, M.p.: 94-96 °C; IR (KBr):

$\bar{\nu} = 3298 \text{ cm}^{-1}$; $^1$H NMR (CDCl$_3$): $\delta = 7.39$-$7.46$ (m, 5H), 6.99 (d, $J = 2.8 \text{ Hz}$, 1H), 6.80 (dd, $J = 8.1, 2.8 \text{ Hz}$, 1H), 6.61 (d, $J = 8.1 \text{ Hz}$, 1H), 4.63 (d, $J = 5.3 \text{ Hz}$, 1H), 4.06 (m, 1H), 3.78 (s, 3H), 3.73-3.87 (2H, m), 2.49 (1H, br), 1.98-2.04 (m, 1H), 1.68-1.73 (m, 1H), 1.18-1.24 (1H, m)
ppm; MS: \( m/z = 281 \) (M+); Anal. Calcd for \( \text{C}_{18}\text{H}_{19}\text{NO}_2 \): C 76.87; H, 6.76; N, 4.98.

\text{Found: C, 77.02; H, 6.85; N, 5.17.}

cis-2,3,3a,4,5,9b-hexahydro-4-phenyl-6-methyl-furo[3,2-c]quinoline: 18h

\[
\text{Colorless crystalline solid, M.p.: 102-103 °C; IR (KBr): } \nu = 3322 \text{ cm}^{-1}; \quad ^1\text{H NMR (CDCl}_3\text{): } \delta = 7.51-7.33 (m, 5H), 7.25 (d, } J = 6.6 \text{ Hz, 1H}), 6.99 (d, } J = 6.6 \text{ Hz, 1H}), 6.77 (t, } J = 7.5 \text{ Hz, 1H}), 5.32 (d, } J = 8.0 \text{ Hz, 1H}), 4.70 (d, } J = 3.0 \text{ Hz, 1H}), 3.66-3.80 (m, 3H), 2.75-2.83 (m, 1H), 2.17-2.24 (m, 1H), 2.14 (s, 3H), 1.43-1.49 (m, 1H) ppm; ^13\text{C NMR (CDCl}_3\text{): } \delta = 143.1, 142.5, 129.4, 128.7, 127.9, 127.7, 126.6, 122.2, 121.8, 118.4, 76.2, 66.7, 57.3, 45.6, 24.6, 17.2 \text{ ppm; MS: } m/z = 265 \text{ (M+).}
\]

trans-2,3,3a,4,5,9b-hexahydro-4-phenyl-6-methyl-furo[3,2-c]quinoline: 19h

\[
\text{Colorless crystalline solid, M.p.: 92-94 °C; IR (KBr): } \nu = 3401 \text{ cm}^{-1}; \quad ^1\text{H NMR (CDCl}_3\text{): } \delta = 7.26-7.46 (6H, m), 6.99 (d, } J = 7.4 \text{ Hz, 1H}), 6.72 (t, } J = 7.5 \text{ Hz, 1H}), 4.55 (d, } J = 4.9 \text{ Hz, 1H}), 4.00-4.08 (m, 2H), 3.75-3.84 (m, 2H), 2.40-2.47 (m, 1H), 2.08 (s, 3H), 1.88-1.95 (m, 1H), 1.62-1.69 (m, 1H) ppm; ^13\text{C NMR (CDCl}_3\text{): } \delta = 143.4, 142.0, 130.0, 129.1, 128.7, 128.4, 128.2, 121.7, 119.4, 117.8, 76.5, 65.1, 57.8, 43.2, 28.9, 17.2 ppm; MS: } m/z = 265 \text{ (M+); Anal. Calcd for } \text{C}_{18}\text{H}_{19}\text{NO}: \text{ C, 81.48; H, 7.16; N, 5.28. Found: C, 81.63; H, 7.28; N, 5.43.}
\]

cis-8-chloro-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline: 18i

\[
\text{Colorless crystalline solid, M.p.: 153-155 °C; IR (KBr): } \nu = 3342 \text{ cm}^{-1}; \quad ^1\text{H NMR (CDCl}_3\text{): } \delta = 7.21-7.42 (6H, m), 6.98 (dd, } J = 8.50, 3.4 \text{ Hz, 1H}), 6.48 (d, } J = 8.5 \text{ Hz, 1H),}
\]
5.16 (d, J = 7.8 Hz, 1H), 4.63 (d, J = 2.9 Hz, 1H), 3.64-3.80 (m, 3H), 2.67-2.75 (m, 1H),
2.11-2.18 (m, 1H), 1.48-1.56 (m, 1H) ppm; \(^{13}\)C NMR (CDCl\(_3\)): \(\delta = 143.4, 141.9, 129.8,
128.8, 128.4, 127.9, 126.6, 124.2, 123.8, 116.2, 75.7, 67.0, 57.4, 45.5, 24.6 \) ppm; MS: \(m/z = 285 \) (M\(^+\)); Anal. Calcd for C\(_{17}\)H\(_{16}\)ClNO: C, 71.48; H, 5.60; N, 4.90. Found: C, 71.34;
H, 5.58; N, 5.13.

\textit{trans-8-chloro-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline: 19i}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{trans-8-chloro-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline.png}
\caption{Structure of trans-8-chloro-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline.}
\end{figure}

Colorless crystalline solid, M.p.: 99-101 °C; IR (KBr):
\(\nu = 3343 \) cm\(^{-1}\); \(^{1}H\) NMR (CDCl\(_3\)): \(\delta = 7.28-7.39 \) (6H, m),
7.05 (dd, \(J = 8.5, 2.4 \) Hz, 1H), 6.51 (d, \(J = 8.5 \) Hz, 1H),
4.50 (d, \(J = 5.1 \) Hz, 1H), 4.25-3.89 (m, 2H), 3.73-3.82 (m, 2H), 2.40-2.46 (m, 1H), 1.96-
2.04 (m, 1H), 1.65-1.71 (m, 1H) ppm; \(^{13}\)C NMR (CDCl\(_3\)): \(\delta = 144.0, 141.3, 130.8, 128.9,
128.8, 128.3, 128.2, 122.9, 121.6, 115.9, 75.7, 65.3, 57.8, 43.3, 28.8 \) ppm; MS: \(m/z = 285 \) (M\(^+\)); Anal. Calcd for C\(_{17}\)H\(_{16}\)ClNO: C, 71.48; H, 5.60; N, 4.90. Found C, 71.39; H, 5.63;
N, 5.07.

\textbf{General Procedure for the Synthesis of Tetrahydroquinolines: 21 and 22}

0.25 mmol 4-npa was added to a mixture of 1.0 mmol aryl amines (20) and 2.5
mmol 3,4-dihydro-2H-pyran (17a) or 2,3-dihydrofuran (17b) in 5 cm\(^3\) acetonitrile. The
reaction mixture was stirred at 50 °C temperature for the appropriate time. After the
completion, the reaction mixtures was quenched with saturated 25 cm\(^3\) NaHCO\(_3\) aqueous
solution and extracted with 3 X 10 cm\(^3\)ethyl acetate. The combined organic layer was
dried (Na\(_2\)SO\(_4\)), concentrated, and purified by column chromatography on SiO\(_2\) with
ethyl acetate and petroleum ether mixture as eluent to afford the corresponding
tetrahydroquinolines (21) and (22).
cis-3,4,4a,5,6,10b-Hexahydro-5-(4-hydroxybutyl)-2H-pyrano[3,2-c]quinoline: 21a

Viscous oil; IR (KBr): $\tilde{\nu} = 3357, 2935, 1608, 1066$ cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta = 7.36$ (d, $J = 7.6$ Hz, 1H), 7.04 (t, $J = 7.2$ Hz, 1H), 6.74 (t, $J = 7.2$ Hz, 1H), 6.50 (d, $J = 6.8$ Hz, 1H), 5.05 (d, 1H, $J = 5.6$ Hz), 3.69 (t, $J = 6.4$ Hz, 2H) 3.35-3.65 (m, 3H), 1.98-2.07 (m, 1H), 1.30-1.80 (m, 10H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 145.06, 128.19, 127.85, 120.49, 118.21, 114.22, 72.72, 62.44, 60.93, 54.31, 35.66, 32.80, 32.15, 25.66, 22.40, 18.07$ ppm; MS: $m/z = 261$ (M+).

trans-3,4,4a,5,6,10b-Hexahydro-5-(4-hydroxybutyl)-2H-pyrano[3,2-c]quinoline: 22a

Viscous oil; $^1$H NMR (CDCl$_3$): $\delta = 7.19$ (d, 1H, $J = 7.2$ Hz), 7.04 (t, $J = 7.2$ Hz, 1H), 6.66 (t, $J = 7.2$ Hz, 1H), 6.52 (d, $J = 6.8$ Hz, 1H), 4.44 (d, $J = 3.2$ Hz, 1H), 3.86-3.95 (m, 1H), 3.51-3.72 (m, 4H) 1.90-1.99 (m, 1H), 1.31-1.80 (m, 10H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 144.92, 130.43, 129.285, 120.39, 117.26, 114.49, 74.10, 67.25, 62.50, 49.82, 36.41, 33.06, 32.95, 24.36, 22.99, 21.41$ ppm; MS: $m/z = 261$ (M+).

cis-3,4,4a,5,6,10b-Hexahydro-5-(4-hydroxybutyl)-9-methyl-pyrano[3,2-c]quinoline: 21b

Viscous oil; IR (KBr): $\tilde{\nu} = 3363, 2934, 1628, 1066$ cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta = 7.20$ (d, $J = 1.6$ Hz, 1H), 6.87 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.49 (d, $J = 8$ Hz, 1H), 5.02 (d, $J = 5.6$ Hz, 1H), 3.68 (t, $J = 6.4$ Hz, 2H), 3.36-3.65 (m, 3H), 2.25 (s, 3H, CH$_3$), 2.01-2.09 (m, 1H), 1.30-1.80 (m, 10H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 143.02, 128.19, 128.85, 127.91, 127.24, 120.29, 114.21, 72.72, 62.44, 61.01 54.53, 33.66, 32.80, 32.15, 25.66, 22.40, 20.93, 18.09$ ppm; MS: $m/z = 275$ (M+).
trans-3,4,4a,5,6,10b-Hexahydro-5-(4-hydroxybutyl)-9-methyl-pyrano[3,2-c]quinoline: 22b

Viscous oil; $^1$H NMR (CDCl$_3$): $\delta$ = 7.03 (d, J = 1.6 Hz, 1H), 6.98 (dd, J = 8.0, 1.6 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 4.40 (d, J = 3.2 Hz, 1H), 3.86-3.98 (m, 1H) 3.58-3.72 (m, 4H), 2.21 (s, 3H, CH$_3$), 1.97-2.05 (m, 1H), 1.30-1.80 (m, 10H) ppm;

$^{13}$C NMR (CDCl$_3$): $\delta$ = 142.62, 130.69, 130.01, 126.47, 120.55, 114.72, 74.26, 67.41, 62.50, 49.83, 36.72, 32.97, 32.93, 24.41, 22.95, 21.44, 20.67 ppm; MS: $m/z$ = 275 (M$^+$).

cis-3,4,4a,5,6,10b-Hexahydro-5-(4-hydroxybutyl)-9-methoxy-2H-pyrano[3,2-c]quinoline: 21c

Viscous oil; IR (KBr): $\nu$ = 3365, 2934, 1620 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ = 6.98 (d, J = 2.8 Hz, 1H), 6.68 (dd, J = 8.4, 2.8 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 5.02 (d, J = 5.6 Hz, 1H), 3.75 (s, 3H, OCH$_3$), 3.68 (t, 2H, J = 6.4 Hz), 3.52-3.64 (m, 1H) 3.20-3.40 (m, 2H), 2.00-2.08 (m, 1H), 1.35-1.85 (m, 10H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta$ = 152.76, 139.39, 121.65, 115.75, 115.08, 112.12, 72.82, 61.13, 56.04, 54.04, 35.77, 32.82, 32.25, 25.56, 22.40, 18.09 ppm; MS: $m/z$ = 291 (M$^+$).

trans-3,4,4a,5,6,10b-Hexahydro-5-(4-hydroxybutyl)-9-methoxy-2H-pyrano[3,2-c]quinoline: 22c

Viscous oil; $^1$H NMR (CDCl$_3$): $\delta$ = 6.80 (d, J = 2.8 Hz, 1H), 6.70 (dd, J = 8.4, 2.8 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 4.43 (d, J = 3.2 Hz, 1H), 3.86-3.95 (m, 1H) 3.73 (s, 3H, OCH$_3$), 3.54-3.72 (m, 2H) 3.20-3.40 (m, 2H), 1.91-2.08 (m, 1H), 1.35-1.85 (m, 10H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta$ = 151.99, 139.06, 121.29, 116.63, 115.91, 102
114.39, 74.02, 67.17, 62.51, 56.04, 50.24, 36.67, 32.99, 32.94, 24.36, 23.03, 21.50 ppm;
MS: m/z = 291 (M+).

cis-3,4,4a,5,6,10b-Hexahydro-5-(4-hydroxybutyl)-9-chloro-2H-pyrano[3,2-c]quinoline: 21d

Viscous oil; IR (KBr): $\tilde{\nu} = 3460, 3355, 1604, 1084$ cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta = 7.35$ (d, $J = 2.3$ Hz, 1H), 7.00 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.44 (d, $J = 8.4$ Hz, 1H), 5.07 (d, $J = 5.6$ Hz, 1H), 3.70 (t, $J = 6.9$ Hz, 2H), 3.55-3.62 (m, 1H), 3.34-3.51 (m, 2H), 1.97-2.08 (m, 1H), 1.31-1.88 (m, 10H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 143.85, 128.22, 127.65, 122.99, 122.02, 115.33, 72.35, 62.72, 61.15, 54.38, 35.35, 32.85, 32.11, 25.55, 22.39, 18.12$ ppm; MS: m/z = 295 (M+).

trans-3,4,4a,5,6,10b-Hexahydro-5-(4-hydroxybutyl)-9-chloro-2H-pyrano[3,2-c]quinoline: 22d

Viscous oil; $^1$H NMR (CDCl$_3$): $\delta = 7.16$ (d, $J = 2.8$ Hz, 1H), 7.01 (dd, $J = 8.9, 2.2$ Hz, 1H), 6.43 (d, $J = 8.6$ Hz, 1H), 4.45 (d, $J = 2.7$ Hz, 1H), 3.61-3.88 (m, 4H), 3.33-3.50 (m, 1H), 1.85-1.93 (m, 1H), 1.28-1.82 (m, 10H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 143.48, 129.80, 129.15, 121.79, 121.70, 115.63, 73.25, 66.89, 62.65, 50.12, 36.15, 32.99, 32.65, 24.36, 23.09, 20.99$ ppm.
cis-3,4,4a,5,6,10b-Hexahydro-5-(4-hydroxybutyl)-9-flouro-2H-pyrano[3,2-c]

quinoline: 21e

![Structure 21e]

Viscous oil; IR (KBr): $\nu = 3368, 2936, 1495, 1060$ cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta = 7.08$ (dd, $J = 8.8, 2.8$ Hz, 1H), 6.75 (dt, $J = 8.8, 2.8$ Hz, 1H), 6.44 (dd, 1H, $J = 8.8, 4.8$ Hz), 5.00 (d, $J = 6.0$ Hz, 1H), 3.68 (t, $J = 6.4$ Hz, 2H), 3.55-3.65 (m, 1H), 3.25-3.43 (m, 2H), 1.99-2.07 (m, 1H), 1.35-1.75 (m, 10H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta =$ 157.86, 155.49, 141.28, 122.15, 115.18, 114.95, 113.99, 113.77, 72.43, 62.84, 61.15, 54.57, 35.45, 32.80, 32.18, 25.52, 22.36, 18.07 ppm; MS: m/z = 279 (M+).

trans-3,4,4a,5,6,10b-Hexahydro-5-(4-hydroxybutyl)-9-flouro-2H-pyrano[3,2-c]

quinoline: 22e

![Structure 22e]

Viscous oil; $^1$H NMR (CDCl$_3$): $\delta = 6.93$ (dd, 1H, $J = 8.8, 2.8$ Hz), 6.78 (dt, $J = 8.8, 2.8$ Hz, 1H), 6.46 (dd, $J = 8.8, 4.8$ Hz, 1H), 4.43 (d, $J = 3.3$ Hz, 1H), 3.84-3.90 (m, 1H), 3.60-3.70 (m, 2H), 3.35-3.53 (m, 2H), 1.87-1.95 (m, 1H), 1.35-1.85 (m, 10H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta =$ 156.91, 154.59, 141.03, 121.33, 116.05, 115.42, 115.18, 73.37, 67.00, 62.85, 50.47, 36.28, 33.09, 32.90, 24.32, 23.16, 21.47 ppm; MS: m/z = 279 (M+).

cis-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-furano[3,2-c]quinoline: 21f

![Structure 21f]

Viscous oil; IR (KBr): $\nu = 3337, 2932, 1608, 1497, 1061$ cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta = 7.29$ (d, $J = 7.6$ Hz, 1H), 7.04 (m, 1H), 6.76 (m, 1H), 6.30 (d, $J = 8.0$ Hz, 1H), 5.10 (d, $J = 8.0$ Hz, 1H), 3.68-3.88 (m, 4H), 3.40-3.48 (m, 1H), 2.58-2.68 (m, 2H),
1.99-2.10 (m, 1H), 1.56-1.90 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta$ = 145.24, 130.25, 128.55, 122.84, 118.92, 114.88, 76.03, 66.81, 62.54, 52.68, 42.69, 30.93, 29.22, 24.22, MS: $m/z = 233$ (M+).

trans-2,3,3a,4,4a,5,9b-hexahydro-4-(3-hydroxypropyl)-furano[3,2-c]quinoline: 22f

Viscous oil; $^1$H NMR (CDCl$_3$): $\delta$ = 7.34 (d, $J$=7.6 Hz, 1H), 7.09 (m, 1H), 6.76(m, 1H.), 6.64 (d, $J$ = 8.0 Hz, 1H), 4.56 (d, $J$ = 5.6 Hz, 1H), 3.75-3.99 (m, 3H), 3.59-3.72 (m, 1H), 2.79-2.87 (m, 1H), 2.64 (brs, 1H) 2.16-2.24 (m, 1H), 1.58-1.90 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta$ =145.16, 131.20, 129.10, 120.48, 118.42, 115.08, 76.10, 65.76, 62.64, 52.16, 41.39, 30.09, 29.37, 28.79 ppm; MS: $m/z = 233$ (M+).

cis-2,3,3a,4,4a,5,9b-hexahydro-4-(3-hydroxypropyl)-8-methyl-furano[3,2-c]quinoline: 21g

Viscous oil; IR (KBr): $\tilde{\nu}$ = 3342, 2923, 1608, 1517, 1060 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta$ = 7.11 (d, $J$ = 2.2Hz, 1H), 6.86 (dd, $J$ = 8.0, 2.8 Hz, 1H), 6.46 (d, $J$ = 8.0 Hz, 1H), 5.08 (d, $J$ = 8.0 Hz, 1H), 3.65-3.85 (m, 4H), 3.35-3.45 (m, 1H), 2.85 (brs, OH), 2.57-2.66 (m, 1H), 2.23 (s, 3H, CH$_3$), 2.01-2.09 (m, 1H), 1.55-1.90 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta$ = 142.94, 130.51 129.32, 128.17, 122.87, 115.00, 76.14, 66.89, 62.54, 53.10, 42.90, 30.97, 29.27, 24.29, 20.80 ppm; MS: $m/z = 247$ (M+).
trans-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-8-methyl-furano[3,2-c]quinoline: 22g

Viscous oil; $^1$H NMR (CDCl$_3$): $\delta$ = 7.17 (d, $J$ = 2.0 Hz, 1H), 6.91 (dd, $J$ = 8.0, 2.2 Hz, 1H), 6.58 (d, $J$ = 8.0 Hz, 1H), 4.55 (d, $J$ = 5.2 Hz, 1H), 3.75-3.95 (m, 3H), 3.61-3.73 (m, 2H), 2.85 (brs, OH), 2.74-2.82 (m, 1H), 2.25 (s, 3H, CH$_3$), 2.16-2.22 (m, 1H), 1.58-1.90 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta$ = 142.77, 131.33 129.81, 127.81, 120.74, 115.24, 76.14, 65.87, 62.64, 52.55, 41.64, 30.17, 29.45, 28.89, 20.73 ppm; MS: $m/z$ = 247 (M$^+$).

cis-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-8-methoxy-furano[3,2-c]quinoline: 21h

Viscous oil; IR (KBr): $\overline{\nu}$ = 3322, 2933, 1508, 1059 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta$ = 6.86 (d, $J$ = 2.8 Hz, 1H), 6.68 (dd, $J$ = 8.4, 2.8 Hz, 1H), 6.52 (d, $J$ = 8.8 Hz, 1H), 5.07 (d, $J$ = 8.0Hz, 1H), 3.77-3.85 (m, 2H), 3 .75 (s, 3H, OCH$_3$), 3.60-3.72 (m, 2H), 3.35-3.46 (m, 1H), 2.84 (brs, OH), 2.58-2.67 (m, 1H), 1.99-2.08 (m, 1H), 1.55-1.90 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta$ = 152.94, 139.51 123.72, 116.17, 115.78, 114.05, 76.24, 66.89, 62.44, 55.90, 53.10, 42.65, 30.97, 29.25, 24.10 ppm; MS: $m/z$ = 263 (M$^+$).

trans-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-8-methoxy-furano[3,2-c]quinoline: 22h

Viscous oil; $^1$H NMR (CDCl$_3$): $\delta$ = 6.92 (d, $J$ = 2.8 Hz, 1H), 6.73 (dd, $J$ = 8.4, 2.8 Hz, 1H), 6.65 (d, 1H, $J$ = 8.8 Hz), 4.56 (d, $J$ = 5.6 Hz, 1H), 3.94-4.01 (m,
cis-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-8-chloro-furano[3,2-c]quinoline:

Viscous oil; IR (KBr): $\tilde{\nu} = 3347$, 2932, 1605, 1490, 1066 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta = 7.24$ (d, $J = 2.4$ Hz, 1H) 6.96 (dd, $J = 8.4$, 2.4 Hz, 1H), 6.44 (d, $J = 8.4$ Hz, 1H) 5.06 (d, $J = 8.0$ Hz, 1H), 3.65-3.87 (m, 4H), 3.39-3.46 (m, 1H), 2.89 (brs, OH), 2.54-2.62 (m, 1H), 1.93-2.03 (m, 1H) 1.56-1.90(m, 5H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 143.66$, 129.62, 128.66, 124.08, 122.42, 116.04, 75.52, 66.91, 62.64, 52.36, 42.29, 30.89, 29.07, 24.01, MS: $m/z = 267$ (M$^+$).

trans-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-8-chloro-furano[3,2-c]quinoline:

Viscous oil; $^1$H NMR (CDCl$_3$): $\delta = 7.30$ (d, $J = 2.4$ Hz, 1H) 7.02 (dd, $J = 8.4$, 2.4 Hz, 1H), 6.55 (d, $J = 8.4$ Hz, 1H), 4.53 (d, $J = 5.6$ Hz, 1H), 3.90-3.98 (m, 1H), 3.70-3.89 (m, 4H), 2.92 (brs, OH), 2.75-2.83 (m, 1H), 2.15-2.25 (m, 1H) 1.60-1.95 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 143.80$, 130.45, 128.88, 122.26, 121.78, 116.22, 75.01, 65.45, 62.49, 52.13, 41.02, 30.03, 29.27, 28.72 ppm.
cis-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-8-fluoro-furano[3,2-c]quinoline:

21j

Viscous oil; IR (KBr): $\tilde{\nu} = 3347, 2932, 1508, 1064$ cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta = 7.00$ (dd, $J = 8.8$, 2.8 Hz, 1H), 6.76(dt, $J = 8.8$, 2.8Hz, 1H), 6.46 (dd, $J = 8.8$, 4.8 Hz, 1H), 5.06 (d, $J = 8.0$ Hz, 1H), 3.68-3.88 (m, 4H), 3.39-3.46 (m, 1H), 2.58-2.65 (m, 1H), 1.96-2.04 (m, 1H) 1.55-1.90 (m, 5H),ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 157.71$, 155.32, 141.33, 124.16, 116.08, 115.82, 115.60, 115.37, 75.82, 66.93, 62.74, 52.86, 42.49, 31.09, 29.17, 24.01ppm; MS: $m/z = 251$ (M+).

trans-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-8-fluoro-furano[3,2-c]quinoline:

22j

Viscous oil; $^1$H NMR (CDCl$_3$): $\delta = 7.06$ (dd, $J = 8.8$, 2.8 Hz, 1H), 6.82 (dt, $J = 8.8$, 2.8Hz, 1H), 6.59 (dd, $J = 8.8$, 4.8 Hz, 1H), 4.52 (d, $J = 8.0$ Hz, 1H), 3.92-3.98 (m, 1H), 3.66-3.85 (m, 4H), 2.73-2.83 (m, 1H), 2.18-2.27 (m, 1H) 1.55-1.90 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 157.26$, 154.91, 141.46, 121.85, 116.85, 116.61, 116.12, 115.88, 75.68, 65.99, 62.81, 52.77, 41.53, 30.19, 29.40, 28.85 ppm.
Chapter V

References:

1. Ayafor, J. F.; Sondengam B. L.; and Ngadjui, B. T. Phytochemistry, 1982, 21, 2733.
27. Xia, M.; and Lu Y-D. Synlett 2005, 2357.
Sample Name: GI818685
Data File: 8102842
Acq. Method: PTC_NONPOLAR.olp
Instrument Code: SC/AD/17-001

Mobile A: 0.1% HCOOH (Aq)
Mobile B: 0.1% HCOOH in ACN
%B: 0.0-0.2min=20% 1.25min=95% 2.0min=20%
Column: BEH C18 (2.1x50)mm; 1.7μm:

Page 1

Sample Report:

3: UV Detector: 254

Mass spectrum of 18a

Peak Number | Time | AreaAbs | Area %Total
---|---|---|---
1 | 0.74 | 7e+004 | 94.00
2 | 1.18 | 5e+003 | 6.00

Peak ID | Time | Peak ID | Time
---|---|---|---
1: (Time: 0.74) | 224.2 | 1:MS ES+ 2: (Time: 1.18) | 114.2
1: (Time: 0.74) | 225.2 | 5.5e+007 | 313.3
2:MS ES- 2: (Time: 1.18) | 264.3 | 372.3 | 370.3
2:MS ES- 2: (Time: 1.18) | 265.3 | 357.3 | 801.4

Peak ID | Time | Peak ID | Time
---|---|---|---
1 | 0.74 | 2 | 1.18
1: (Time: 0.74) | 222.2 | 2: (Time: 1.18) | 371.3
2:MS ES- | 221.1 | 492.7 | 6.8e+00!
2:MS ES- | 222.2 | 8.5e+006 | 801.4

Vial: 1:C, 2
Flow Rate: 0.8 ml/min
Inj Date: 23-May-2008
$^1$H-NMR spectrum of 19a
$^{13}$C-NMR spectrum of 19a
$^1$H-NMR spectrum of 19c
$^{13}$C-NMR spectrum of 19e
$^{13}$C-NMR spectrum of 18g
Method info: A-0.1%HCOOH; B-ACN  Flow = 0.8ML/MIN

Column-Atlantis dC18 (75X4.6mm-5μm ) Positive Mode

Time (min.): 0--1.0 1.0--1.5 1.5--2.5 2.5--3.0 3.0--6.0
% B : 70 70--95 95 95--70 70

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Mass spectrum of 18g
^H-NMR spectrum of 19g
$^1$H-NMR spectrum of 18i
$^1$H-NMR spectrum of 19i
$^{13}$C-NMR spectrum of 191
Method info: A-0.1%HCOOH; B-ACN FLOW 0.8ML/MIN
COLUMN-ATLANTIS C18 75X4.6mm-5µm POSITIVE MOD

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Maximum Chromatogram of C:CHEM32\1\DATA\DEC06\6150142.D, Signal Id A

mass spectrum of 21d

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MSD2 TIC, MS File (C:CHEM32\1\DATA\DEC06\6150142.D) MM-ES+APCI, Pos, Scan, Frag: 50, "TIC SIGNAL-2"

MSD2 SPC, time=1.688-1.825 of C:CHEM32\1\DATA\DEC06\6150142.D MM-ES+APCI, Pos, Scan, Frag: 50, "TIC SIGNAL-2"

Instrument Code: SC/AD/10-004
$^1$H-NMR spectrum of crude (21b+22b)

Current Data Parameters
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EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
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NS  8
DS  0
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FIDRES  0.228425 Hz
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RG  64
DM  56.800 usec
DE  6.00 usec
TE  300.0 K
D1  2.00000000 sec

-------- CHANNEL F1 ----------
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PL1  -5.00 db
SF01  300.1327012 MHz

F2 - Processing parameters
SI  16384
SF  300.1298166 MHz
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SSB  0
LB  0.50 Hz
GB  0
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1D NMR plot parameters
CX  20.00 cm
CY  0.00 cm
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F1  338.1 15 Hz
F2P  -0.276 ppm
F2  -82.80 Hz
PPCH  0.57707 ppm/cm
H2CH  173.19731 Hz/cm
Syngene International Pvt Ltd
A Biocon Company

---------------------------------------------------------------------------------------------------
Data file : C:\CHEM32\1\DATA\DEC06\6145651.D Vial No. : P2-B-03
Injection Date : 12/19/2006 Injection vol : 2 µL
Sample Name : Acq Method : MVY_7030FA.M

Method info : A-0.1%HCOOH; B-ACN FLOW 0.8ML/MIN, COLUMN-GENESIS
C18 50X4.6mm-3µm
TIME (MIN) : 0--1.0 1.0--1.5 1.5--2.5 2.5--3.0 3.0--5
%B 70 70-95 95 95-70 70

\[
\begin{align*}
\text{Mass spectrum of crude (21b+22b)}
\end{align*}
\]

\[
\begin{align*}
\text{MSD2 SPC, time=1.030:1.255 of C:\CHEM32\1\DATA\DEC06\6145651.D MM-ES+APCI, Pos, Scan, Frag: 50, } ^{15} \text{N }
\end{align*}
\]

\[
\begin{align*}
\text{MSD2 SPC, time=1.255:1.542 of C:\CHEM32\1\DATA\DEC06\6145651.D MM-ES+APCI, Pos, Scan, Frag: 50, } ^{15} \text{N }
\end{align*}
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