CHAPTER-4

Synthesis of 2-(1-naphtho[2,1-b]furan-2-ylcarbonyl)-3,5-disubstituted-2,3-
dihydro-1H-pyrazoles.
Introduction

Nitrogen, oxygen and sulphur containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activities. The pyrazole ring is a prominent structural moiety found in numerous pharmaceutically active compounds. Due to the easy preparation and rich biological activity, pyrazole framework plays an important role in biologically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemistry. The pyrazole based derivatives have shown several biological activities, many of them are currently being tested and/or clinically evaluated for new drug discovery. Encouraged by these reports, scientists all over the world took up major research programme in their laboratories, which was directed not only towards synthesis of condensed pyrazoles, biheterocyclic pyrazoles and linked pyrazoles, but also towards evaluation of newly synthesized compounds for various biological and pharmacological activities.

The detailed discussion regarding these investigations is not within the limits of this thesis. However, a few important compounds enclosing pyrazole moiety are described in the following paragraphs.

Synthetic pyrazoline derivatives I-IV possess antinociceptive effect in mice and also exhibit antifungal activity.
Verma and Nagal synthesized N1-4-(fluorobenzoyl)-5-5'-dimethylcyclohexane-4-(sulpha/substituted phenylazo)1,2-diazoles and found that the few synthesized derivatives exhibited significant insecticidal activity against American cockroaches *Periplaneta Americana*. 3,5-Diphenyl-1H pyrazole derivatives have been synthesized and on evaluation for antipyretic, in vitro platelet antiaggregating activities, analgesic, antiarrhythmic, hypotensive and local anesthetic activities in rats and mice, it was observed that few of the compounds showed remarkable activities.

Daidone *et al.*, synthesized pyrazole-4-carbohydrazide V, and used it as key intermediate to accomplish the synthesis of various pharmaceutically important heterocyclic compounds.

Some of the pyrazole derivatives also serve as intermediates in the dye industry. Recently, investigation on photochemical isomerization of pyrazole has been carried out using *ab initio* methods.
The condensed heterocyclic compounds, encompassing pyrazole moiety have been explored for their antimicrobial and other pharmacological activities. In this regard Akbas and Berber condensed pyrazole ring with pyridazine nucleus and evaluated antibacterial and antifungal activities of these novel heterocyclic compounds by MIC method.

When pyrazoles nucleus was fused with appropriate steroid, it was observed that the novel steroidal pyrazoles act as substrates for bile acid transporters. Wang et al., synthesized new 1H-pyrazolo[3,4-b]quinoxaline derivatives VI and found that these compounds exhibit photoluminescence and electro luminescence properties.

There are several reports regarding fusion of pyrazole ring with triazoles, oxazepines, pyridazines, norborane, pyrimidines, isoquinolines, pyran and quinolines.

Several biheterocyclic compounds containing pyrazole nucleus have been reported. Tanitame et al., novel series of DNA gyrase inhibitors in which pyrazole ring is directly connected to piperidine nucleus VII. Evaluation of antibacterial activity by MIC method indicated that some of the compounds exhibited activity against gram positive and gram-negative bacteria.
Pyrazole based biheterocycles containing pyrimidine VIII have been synthesized for possible antiviral, anticancer and antimicrobial activity\textsuperscript{20}.

The pyrazole nucleus on connecting with oxadiazole and thiadiazole rings, the resulting compounds IX and X, have been found to exhibit potential antimigratory activity, inhibit neovascularization, decreases VEGF production and increase apoptosis of tumor cell\textsuperscript{21}.
Antimalarial activity of 4-(5-trifluoromethyl)-1H-pyrazole-1-yl-chloroquinine analogues XI have been investigated by Cunico et al.\textsuperscript{22}.

\begin{center}
\includegraphics[width=0.4\textwidth]{image1.png}
\end{center}

There are reports in connection with synthesis of biheterocycles XII in which bioactive furan nucleus is involved\textsuperscript{23}.

\begin{center}
\includegraphics[width=0.4\textwidth]{image2.png}
\end{center}

Babu et al., synthesized pyrazolines bearing benzofuran and evaluated them for antitubercular, antimicrobial and anti-inflammatory activities\textsuperscript{24}.

There are few reports relating with linking of pyrazole nucleus with other heterocycles via one or two atoms. Such a system XIII has been synthesized and found to exhibit considerable antibacterial activity\textsuperscript{25}.

\begin{center}
\includegraphics[width=0.4\textwidth]{image3.png}
\end{center}
Very interesting report of screening the bridged heterocycles XIV for antagonism studies, receptors binding studies and brain imaging has appeared in literature\textsuperscript{26-27}.

Receiving impetus from these reports, it was contemplated to link bioactive naphtho[2,1-\textit{b}]furan with pyrazole via carbonyl group and evaluate them for various biological and pharmacological activities.
Present work

The various biological activities associated with compounds formed by the combination of pyrazole with various heterocyclic systems prompted us to the synthesis and investigate biological activities of pyrazole derivatives involving naphthofuran.

It was contemplated to explore newer methods for linking two heterocycles viz. naphtho[2,1-b]furan and pyrazole via nitrogen or carbon. Such, linked heterocycles have gathered enormous interest because of their wide spectrum of application. It was envisaged to use ethyl naphtho[2,1-b]furan-2-carboxylate 2 as starting material, which enables to link pyrazole moiety via carbon bridge.

The synthetic route for such synthesis involved the following steps:

3. Synthesis of chalcones, from substituted acetophenones and substituted aromatic aldehydes 6a-o.
1. **Synthesis of ethyl naphtho[2,1-b]furan-2-carboxylate. 2**

The required starting material ethyl naphtho[2,1-b]furan-2-carboxylate was obtained by the reaction of 2-hydroxy-1-naphthaldehyde 1 with ethyl chloroacetate in presence of anhydrous potassium carbonate and in dry DMF at reflux temperature. Both condensation as well as cyclisation occurred in single step and produced ethyl naphtho[2,1-b]furan-2-carboxylate 2 in good yield.

![Chemical structure of 1, 2 and 3](image)

The structure of 2 was confirmed by comparing IR, $^1$H NMR and elemental analysis with known sample$^{28}$.

2. **Synthesis of naphtho[2,1-b]furan-2-carbohydrazide. 3**

The synthesis of naphtho[2,1-b]furan-2-carbohydrazide 3 from ethyl naphtho[2,1-b]furan-2-carboxylate 2 was a straightforward reaction, which was accomplished by reacting ethyl naphtho[2,1-b]furan-2-carboxylate 2 with hydrazine hydrate in presence of acid catalyst in ethanolic medium.
\( ^1\text{H NMR Spectrum of 2} \)

**Current Data Parameters**
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- **EXPNO**: 5
- **PROCNO**: 1

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- **PULPROG**: zg
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- **FIDRES**: 0.442286 Hz
- **AQ**: 1.1305460 sec
- **RG**: 2048
- **DW**: 69.000 usec
- **DE**: 86.25 usec
- **TE**: 300.0 K
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- **D1**: 1.00000000 sec
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**F2 - Processing parameters**
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- **WDW**: EM
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- **PC**: 0.60
The structure of 3 was well confirmed by elemental analysis and spectral studies. The IR spectrum of 3 exhibited broad absorption band at 3304-2969 cm\(^{-1}\) due to NH\(_2\) and a sharp absorption band at 1657 due to C=O group. \(^1\)H NMR spectrum of naphtho[2,1-b]furan-2-carbohydrazide 3 was consistent with the assigned structure. 

\[
\delta \ 4.6, \text{s(b), 1H, NH, (D}_2\text{O exchangeable), } \delta \ 7.6-8.4, \text{ m, 7H, ArH and } \delta \ 10.0, \text{ s, 2H, NH}_2. \]

3. **Synthesis of 1,3-disubstituted-prop-2-en-1-ones. 6a-o**

The synthesis of title compounds required another reactant i.e., chalcones 6a-o. These chalcones were synthesized by Claisen condensation employing substituted acetophenones 4a-c and different aromatic aldehydes 5a-e. The selection of substituted acetophenones and substituted aromatic aldehydes was based on presence of electron withdrawing and electron releasing groups which would assist in later studies, on structure activity relationship.

The structure of 6a was well established by elemental analysis and spectral studies\(^{29}\).
\[^{1}H\) NMR Spectrum of 3

Current Data Parameters
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PROCNO 1

F2 - Acquisition Parameters
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PULPROG zgpr
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SOLVENT DMSC
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DS 0
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FIDRES 0.442284 Hz
AQ 1.1305460 sec
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TE 300.0 K
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DI2 0.00002000 sec
HL2 55 dB
P18 1500000.00 usec
DI3 0.00000400 sec
PL 11.50 usec
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NUCLEUS 1H

F2 - Processing parameters
SI 32768
SF 400.1362837 MHz
WDM EM
SSB 0
LB 0.00 Hz
GB 0
PC 0.60
4. **Synthesis of 2-(1-naphtho[2,1-b]furan-2-yl-carbonyl)-3,5-disubstituted-2,3-dihydro-1H-pyrazoles. 7a-o**

The reaction of naphtho[2,1-b]furan-2-carboxyhydrazide 3 with chalcones 6a-o to obtain the title compounds 7a-o was attempted by employing various reagents and reaction conditions. However the desired condensation was successful only when the reaction was carried out by using acetic acid as catalyst and dioxane as a solvent at reflux temperature. The target compounds 1-(naphtho[2,1-b]furan-2-ylcarbonyl-3,5-disubstituted-1H-pyrazoles 7a-o were obtained in good yield. (Scheme-2)

**Scheme-2**

![Scheme-2 diagram](image_url)

<table>
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<th></th>
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<th>R₂</th>
<th></th>
<th>R₁</th>
<th>R₂</th>
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<td>H</td>
<td>4-OCH₃</td>
<td>7f</td>
<td>4-Cl</td>
<td>H</td>
<td>7k</td>
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<td>H</td>
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<tr>
<td>7b</td>
<td>H</td>
<td>4-NO₂</td>
<td>7g</td>
<td>4-Cl</td>
<td>4-OCH₃</td>
<td>7l</td>
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<td>4-OCH₃</td>
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<tr>
<td>7c</td>
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<td>4-OH</td>
<td>7i</td>
<td>4-Cl</td>
<td>4-OH</td>
<td>7n</td>
<td>4-OH</td>
<td>4-NO₂</td>
</tr>
<tr>
<td>7e</td>
<td>H</td>
<td>H</td>
<td>7j</td>
<td>4-Cl</td>
<td>4-Cl</td>
<td>7o</td>
<td>4-OH</td>
<td>4-OH</td>
</tr>
</tbody>
</table>
To confirm the assigned structure to 7a-o, the IR, $^1$H NMR, $^{13}$C NMR and mass spectra of representative compounds in the series i.e., 7a-e were recorded. The IR spectrum of 7a exhibited the absorption band at 1663 cm$^{-1}$ due carbonyl group (C=O). The $^1$H NMR spectrum recorded in DMSO exhibited the following peaks, which substantiated the structure assigned to 7a $\delta$ 3.8 (s, 3H, -OCH$_3$), $\delta$ 6.0 (s, 1H, NH) and $\delta$ 7.0-8.5 (m, 17H, ArH and CH=C). The $^{13}$C NMR spectrum exhibited a peak at $\delta$ 189.12 due to carbonyl carbon atom. Peaks at $\delta$ 108.97, 112.26, 113.67, 114.44, 119.67, 122.59, 123.54, 125.36, 127.26, 127.79, 128.37, 128.71, 128.88, 130.21, 130.76, 131.50, 132.85, 137.90, 141.04, 142.70, 143.99, 152.09, 161.42 and 166.97 are attributed to twenty seven carbon atoms. A peak at $\delta$ 55.39 has been attributed to methoxy carbon atom.

Finally mass spectrum of 7a also confirmed the structure. It exhibited a molecular ion peak at m/z 446 corresponding to its molecular weight. Other peaks appearing at m/z 368, 346, 326, 313, 237, 143 and 100 were in accordance with the fragmentation pattern as shown in the Scheme-3.

The mechanism of the reaction is depicted in scheme-4.

Thus, based on this spectroscopic data and earlier observations the structures of compounds 7b-e were confirmed and reported in Table-4.1.
IR Spectrum of 7a

[Chemical structure image]
"^H NMR Spectrum of 7a

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PROCNO 1

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Time 20.23
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PULPROG 2g
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SOLVENT DMSO
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DS 0
FIDRES 8196.734 Hz
AQ 0.9994740 sec
DG 1024
DE 61.000 usec
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NUCLEUS 1H

F2 - Processing parameters
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SF 400.1362837 MHz
WDW Emt
SSB 0
LB 0.00 Hz
GB 0
PC 0.10
$\text{H}_2\text{CO}$

$^{13}\text{C} \text{NMR Spectrum of 7a}$

**Current Data Parameters**
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- **PROCNO**: 1

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- **Time**: 18.05
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- **DW**: 18.00 usec
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- **CPDPRG**: waltz16
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- **HL1**: 17 dB
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**F2 - Processing parameters**
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- **FC**: 0.10
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Sample ID: HSR/345/02  
Data File Name: D:\DATA\ESI\2006\BMS1\DI\BMS1.152.lcd  
Method File Name: D:\METHOD\GEN_ESI_DI.Icm  
Data Acquired: 2/15/2006 3:20:55 PM

**LC CONDITIONS:**

MOBILE PHASE: A: B (50:50)  
A: WATER : ACN : HCOOH (90:10:0.02)  
B: WATER : ACN : HCOOH (10:90:0.02)  
FLOW RATE: 0.2 mL/min

**MS CHROMATOGRAM**

Segment 1 (x10,000,000)

- TIC at 1.00
- TIC at 2.00

**MS Spectrum Graph**

- Ret. Time: Single 0.543 (Scan#: 33)
- BG Mode: None
- Mass Peaks: 790 Base Peak: 478.15 (2112546) Polarity: Pos Segment 1 - Event 1

** MASS Spectrum of 7a**
Scheme-3

Mass fragmentation pattern of 7a.
Scheme-4

3

6a

\[ \text{H}_3\text{CO} \]

\[ \text{H}_3\text{CO} \]

7a
Table 4.1: IR and NMR Spectral data of
2-(1-naphtho[2,1-b]furan-2-yl-carbonyl)-3,5-disubstituted-2,3-dihydro-1H-
pyrazoles. 7a-e

![Compound Structure](image)

<table>
<thead>
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<th>Comp.</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>IR (KBr) cm&lt;sup&gt;-1&lt;/sup&gt; (C=O)</th>
<th>&lt;sup&gt;1&lt;/sup&gt;H NMR in ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>H</td>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1663</td>
<td>δ 3.8 (s, 3H, OCH&lt;sub&gt;3&lt;/sub&gt;), δ 6.0 (s, 1H, NH), δ 7.0-8.5 (m, 17H, CHCPh +16ArH)</td>
</tr>
<tr>
<td>7b</td>
<td>H</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1678</td>
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</tr>
<tr>
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<td>H</td>
<td>4-Cl</td>
<td>1683</td>
<td>δ 5.8 (s, 1H, NH), δ 7.4-8.6 (m, 17H, CHCPh +16ArH)</td>
</tr>
<tr>
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<td>H</td>
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<td>1675</td>
<td>δ 4.7 (b, 1H, OH), δ 6.1 (s, 1H, NH), δ 7.3-8.6, (m, 17H, CHCPh +16ArH)</td>
</tr>
<tr>
<td>7e</td>
<td>H</td>
<td>H</td>
<td>1694</td>
<td>δ 6.1 (s, 1H, NH), δ 7.3-8.5 (m, 18H, CHCPh +17ArH)</td>
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Experimental

Synthesis of ethyl naphtho[2,1-b]furan-2-carboxylate. 2

To a solution of 2-hydroxy-1-naphthaldehyde 1 (5.16 g, 0.03 mol) in dry N,N-dimethylformamide (25 mL), ethyl chloroacetate (3.66 g, 0.03 mol) and anhydrous potassium carbonate (12.4 g, 0.9 mol) were added and the reaction mixture was refluxed on water bath for 24 hrs. The reaction mixture was then poured into ice cold water, to obtain the product as solid which was collected by filtration, dried and recrystallised from ethanol 2.

Synthesis of naphtho[2,1-b]furan-2-carbohydrazide. 3

Ethyl naphtho[2,1-b]furo-2-carboxylate 2 (2.40 g, 0.01 mol), catalytic amount of conc. hydrochloric acid and hydrazine hydrate (1 g, 0.02 mol) were refluxed in absolute ethanol (25 mL) for 2 hrs on water bath. Then the reaction mixture was cooled to room temperature, the solid thus obtained was filtered and dried. The product obtained was recrystallised from ethanol 3.

Synthesis of 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one. 6a

Freshly distilled acetophenone (2.6 g, 0.0215 mol) was added to a cooled mixture of sodium hydroxide (1.1 g, 0.0275 mol), water (10 mL) and rectified spirit (6 mL). To this mixture pure 4-methoxybenzaldehyde (2.9 g, 0.0215 mol) was added drop wise maintaining the temperature at 15-30\(^\circ\) C. After the addition was over the reaction mixture was stirred vigorously until the reaction mixture becomes thick. It was cooled in ice chest for overnight. The solid obtained was filtered and washed with cold water and rectified spirit. The crude chalcone was dried and recrystallised from rectified spirit 6a.

The compounds 6b-o were synthesized by the same method described above using different substituted acetophenones and aromatic aldehydes.
Synthesis of 2-(1-naphtho[2,1-b]furan-2-ylcarbonyl)-3-(4-methoxyphenyl)-5-phenyl-2,3-dihydro-1H-pyrazole. 7a

To a solution of 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one 6a (1.38 g, 0.005 mol) in dioxane (25 mL), acetic acid (0.5 mL) was added and the mixture was kept for stirring for 30 minutes. To this mixture naphtho[2,1-b]furan-2-carbohydrazide 3 (1.01g, 0.005 mol) was added and refluxed for 24 hrs. After the reaction was complete the reaction mixture was poured to ice cold water, solid separated was filtered and dried. The crude product was recrystallised from ethanol.

The compounds 7b-o were synthesized by the same method described above.

Physical data of newly synthesized compounds reported in Table-4.2.
Table-4.2: Physical data of newly synthesised compounds.

<table>
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<tr>
<th>Comp.</th>
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<th>M.p. 0°C</th>
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<td>100</td>
<td>85</td>
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</tr>
<tr>
<td>3</td>
<td>----</td>
<td>----</td>
<td>225</td>
<td>90</td>
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<td>68.8 (69.0) 4.3 (4.4) 12.2 (12.3)</td>
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<tr>
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<td>H</td>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>241</td>
<td>65</td>
<td>C&lt;sub&gt;29&lt;/sub&gt;H&lt;sub&gt;20&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>78.2 (78.3) 4.4 (4.5) 6.2 (6.3)</td>
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<tr>
<td>7b</td>
<td>H</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>&gt;250</td>
<td>62</td>
<td>C&lt;sub&gt;28&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>73.1 (73.2) 3.6 (3.7) 9.0 (9.1)</td>
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<tr>
<td>7c</td>
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<td>4-Cl</td>
<td>&gt;250</td>
<td>70</td>
<td>C&lt;sub&gt;28&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;Cl</td>
<td>74.8 (74.9) 3.7 (3.8) 6.1 (6.2)</td>
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<tr>
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<td>4-OH</td>
<td>248</td>
<td>63</td>
<td>C&lt;sub&gt;28&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>78.0 (78.1) 4.1 (4.2) 6.4 (6.5)</td>
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<tr>
<td>7e</td>
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<td>&gt;250</td>
<td>71</td>
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<td>74.8 (74.9) 3.7 (3.8) 6.1 (6.2)</td>
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<td>72.6 (72.7) 3.8 (4.0) 5.7 (5.8)</td>
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<td>&gt;250</td>
<td>65</td>
<td>C&lt;sub&gt;28&lt;/sub&gt;H&lt;sub&gt;16&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;Cl</td>
<td>67.9 (68.0) 3.1 (3.2) 8.4 (8.5)</td>
</tr>
<tr>
<td>7i</td>
<td>4-Cl</td>
<td>4-OH</td>
<td>&gt;250</td>
<td>68</td>
<td>C&lt;sub&gt;28&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;Cl</td>
<td>72.2 (72.3) 3.5 (3.6) 5.9 (6.0)</td>
</tr>
<tr>
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<td>4-Cl</td>
<td>4-Cl</td>
<td>&gt;250</td>
<td>70</td>
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<td>69.4 (69.5) 3.2 (3.3) 5.7 (5.8)</td>
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<tr>
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<td>4-OH</td>
<td>H</td>
<td>&gt;250</td>
<td>66</td>
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<td>78.0 (78.1) 4.1 (4.2) 6.4 (6.5)</td>
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<tr>
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<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>71</td>
<td>C&lt;sub&gt;29&lt;/sub&gt;H&lt;sub&gt;20&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>75.5 (75.6) 4.3 (4.3) 5.9 (6.0)</td>
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<td>4-Cl</td>
<td>&gt;250</td>
<td>68</td>
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<td>72.2 (72.3)</td>
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Reference:


