X-ray Crystallography structure analysis of MAP Kinase inhibitor molecule

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Abstract: This paper reports that synthesis and x-ray crystallography analysis of quinoxalines (5) from the reaction with unsymmetrical diketone (4). The aforementioned compound having 4-pyridyl,4-fluorophenyl in 2,3 positions respectively. Structure of compound 5 has been unambiguously elucidated by x-ray crystallographic analysis.

Key Words: X-ray crystallography, imidazole, quinoxaline.

Introduction

A number of excellent prototypical, low–molecular–weight P38 MAP kinase inhibitor 2,4,5-triarylimidazoles(1 SB203580, 2 SB202190) is known to reduce levels of TNF-α and IL-1β both in vitro and in vivo1,2,3. Most of the potent 2,4,5-triarylimidazole inhibitors bearing 4-florophenyl, 4-pyridyl and 4-polar groups substituted phenyl are in 4,5,2-positions respectively4. Recently, several reports and reviews covering new P38 MAP kinase inhibitors have been reported5-12.

Numerous of reports and reviews are reveal the importance of quinoxaline ring systems, most of them exhibits the number of biological activities13 and molecules shows a variety of medicinal applications14.

Based on the biological importance of the heterocyclic compounds, we wish to synthesis of quinoxaline (5) bearing 4-fluorophenyl and 4-pyridyl groups in 2,3-positions respectively (scheme 1), The compound 5 was well characterized by IR,1H & 13C –NMR, Mass and Elemental analysis.

The compound 3 was synthesized by literature method15, which is converted in to stable unsymmetrical diketone [1-(4-fluorophenyl)-2-(4-pyridyl) glyoxal] 4 by treatment with SeO₂ in refluxing acetic acid16. Further treatment of 3, with bromine in chloroform furnished a yellow solid17 4a.

Treatment of 4 with 2,3-diaminophenol in refluxing ethanol furnished the substituted quinoxalines18 derivatives 5, Surprisingly to give exclusively only one regioisomer 5, which is unambiguously characterized by x-ray crystallographic structure (Fig 1 & Table 1-2), x-ray data complied that both the phenolic – OH and 4-fluorophenyl groups are same plane on the quinoxaline ring.
Scheme 1

Fig-1. Molecular Structure of Compound 7, Showing 50% displacement Ellipsoids.
The compound 5 is crystallized in the triclinic space group P-1, with two asymmetric units in a unit cell. In one asymmetric unit, there are two non-central symmetric molecules together to grow in central symmetric space group. Crystallographic data are listed in (Table – I). The structure, as shown in (Fig-I), has been solved by Direct method and refined by least squares method with SHELX program [ref. G. M. Sheldrick, 1997] to a final R factor of 0.0479 based on 3533 observations, whose I>2σ(I). The crystal packing is based on intermolecular short Ring-interactions and Pi-Ring interactions, as listed in (Table-2). The former contributes to stability in (1,0,0) and (0,0,1), and the later stabilizes the structure in (1,1,1) direction.

### Table-2  Short Ring-interactions and Pi-Ring interactions

<table>
<thead>
<tr>
<th>6-membered rings and centers of rings</th>
<th>Ring Centre-of-Gravity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cg(1) C(1),C(2),C(3),C(4),C(5),C(6)</td>
<td>0.693479, 0.641319, 0.474952</td>
</tr>
<tr>
<td>Cg(2) N(3),C(11),C(10),C(9),C(13),C(12)</td>
<td>-0.000711, 0.586989, 0.235164</td>
</tr>
<tr>
<td>Cg(3) C(14),C(15),C(16),C(17),C(18),C(19)</td>
<td>0.258049, 0.294388, 0.141724</td>
</tr>
<tr>
<td>Cg(4) C(20),C(21),C(22),C(23),C(24),C(25)</td>
<td>0.628299, 0.273170, 0.936251</td>
</tr>
<tr>
<td>Cg(5) N(6),C(30),C(29),C(28),C(32),C(31)</td>
<td>0.302521, -0.170088, 0.708443</td>
</tr>
</tbody>
</table>

### Short Ring-interactions with Cg-Cg distances

<table>
<thead>
<tr>
<th>Plane numbers</th>
<th>Distance (Ang.)</th>
<th>Dihedral Angle between rings (Deg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cg(2) &gt; Cg(1) [-1+X,Y,Z]</td>
<td>4.1773</td>
<td>35.90</td>
</tr>
<tr>
<td>Cg(3) &gt; Cg(4) [X,Y,-1+Z]</td>
<td>4.1684</td>
<td>37.07</td>
</tr>
</tbody>
</table>

### X-H..Cg(Pi-Ring) Interactions

<table>
<thead>
<tr>
<th>X--H(I)</th>
<th>Cg(J)</th>
<th>H..Cg Distance (Ang.)</th>
<th>X-H..Cg Angle (Deg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(11)-H(11A)</td>
<td>Cg(6) [-X,1-Y,1-Z]</td>
<td>3.1259</td>
<td>114.15</td>
</tr>
<tr>
<td>C(19)-H(19A)</td>
<td>Cg(5)[ 1-X,-Y,1-Z]</td>
<td>3.3987</td>
<td>112.50</td>
</tr>
</tbody>
</table>
Experimental

All melting points are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8300 model and BOMEM (Hartmann&Braun). 1H and 13C-NMR spectra were recorded on JEOL GMX 400 MHz, JEOLFX 90Q 90MHz, Varian 400 MHz, Varian Unity Inova 500 MHz spectrometer with CDCl3 and DMSO-d6 as the solvent with tetramethylsilane as the internal standard. Mass spectra were taken using Hewlett-Packard 5985 (70ev), Shimadzu QP1000A. HRMS (High Resolution Mass Spectra) data were recorded on Thermo Finnigan (Model : MAT 95XL).

3-(4-fluorophenyl)--5- hydroxy-2-(4-pyridyl)- quinoxaline (5)

Synthesis of compound 5 following the general procedure18.

Yield : 0.380g(55%) :MP : 240-242°C: IR(KBr) : ν= 3420(b), 1602, 1549, 1508 cm⁻¹
1H-NMR(500MHz, DMSO –D6): δ10.41(bs, 1H, OH, D2O exchange), 8.58-8.57(m, 2H), 7.75-7.70(m, 1H), 7.60-7.57(m, 2H), 7.53-7.51(m, 2H), 7.45-7.44(m, 1H), 7.24-7.21(m, 3H).
13C-NMR(100MHz, DMSOD6): δ163.52, 161.56, 153.65, 150.68, 149.44, 146.36, 141.66, 134.68, 134.46, 132.39, 132.02, 131.71, 124.35, 118.69, 115.19, 115.09.

Conclusion

Based on the biological importance of heterocyclic compounds, we wish to synthesis of quinoxaline bearing 4-fluorophenyl and 4-pyridyl groups in 2,3-positions respectively. The crystallography structure of compound 5 shown in Fig 1 & Fig 1-2, and the x-ray data complaid that both the phenolic – OH and 4-fluorophenyl groups are same plane on the quinoxaline ring.

Acknowledgement

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References


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