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X-ray Crystallography structure analysis of MAP Kinase inhibitor molecule

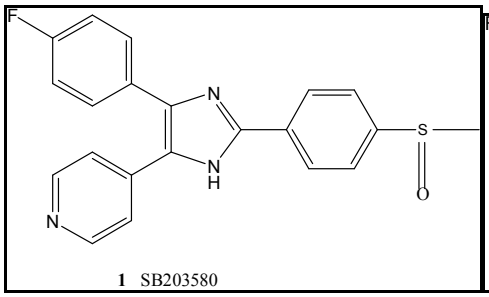
Periyasamy Murugan*

Department of Chemistry, Vel Tech University, Avadi, Chennai-600 062, India

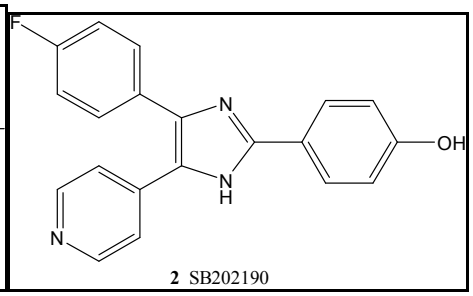
Abstract: This paper reports that synthesis and x-ray crystallography analysis of quinoxalines (**5**) from the reaction with unsymmetrical diketone (**4**). The aforementioned compound having 4-pyridyl,4-fluorophenyl in 2,3 positions respectively. Structure of compound **5** has been unambiguously elucidated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

Introduction

A number of excellent prototypical, low –molecular–weight P^{38} 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 vivo[1,2,3].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 respectively[4].Recently ,several reports and reviews covering new P^{38}MAP kinase inhibitors have been reported[5-12].



1 SB203580



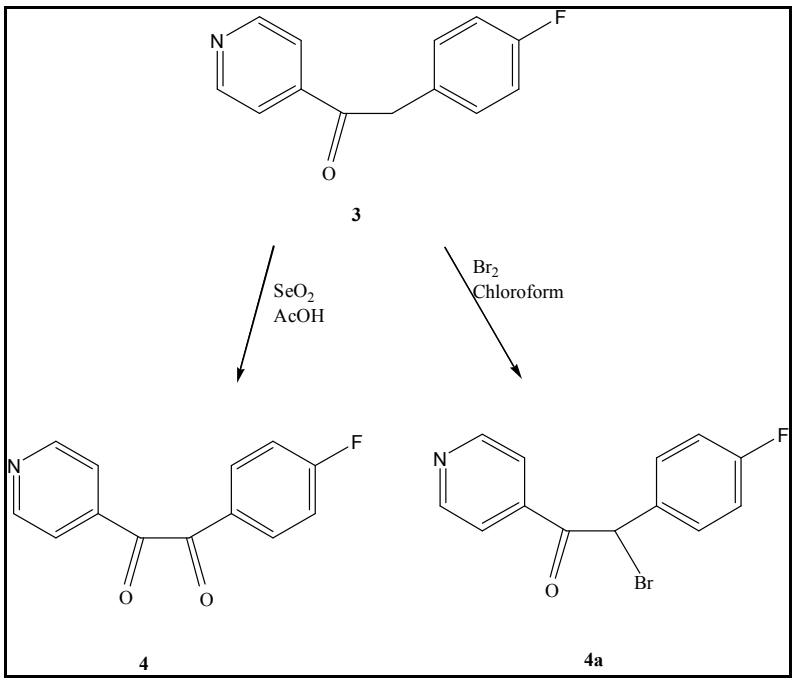
2 SB202190

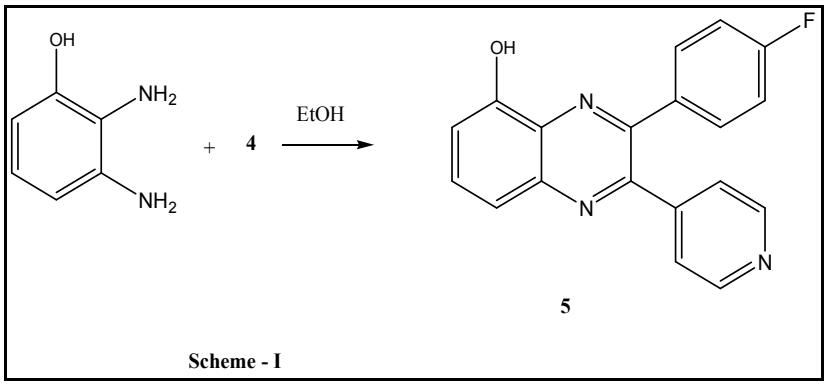
Numerous of reports and reviews are reveal the importance of quinoxaline ring systems, most of them exhibits the number of biological activities[13] and molecules shows a variety of medicinal applications[14].

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 I**), The compound **5** was well characterized by IR, ^{1}H & ^{13}C –NMR, Mass and Elemental analysis.

The compound **3** was synthesized by literature method[15], which is converted in to stable unsymmetrical diketone [1-(4-fluorophenyl)-2-(4-pyridyl) glyoxal] **4** by treatment with SeO_2 in refluxing acetic acid[16]. Further treatment of **3** ,with bromine in chloroform furnished a yellow solid[17] **4a.**

Treatment of **4** with 2,3-diaminophenol in refluxing ethanol furnished the substituted quinoxalines[18] derivatives **5**, Surprisingly to give exclusively only one regioisomer **5** , which is unambiguously characterized by x-ray crystallographic structure (**Fig I & Table 1-2**), x-ray data complied that both the phenolic – OH and 4-fluorophenyl groups are same plane on the quinoxaline ring.





Scheme - I

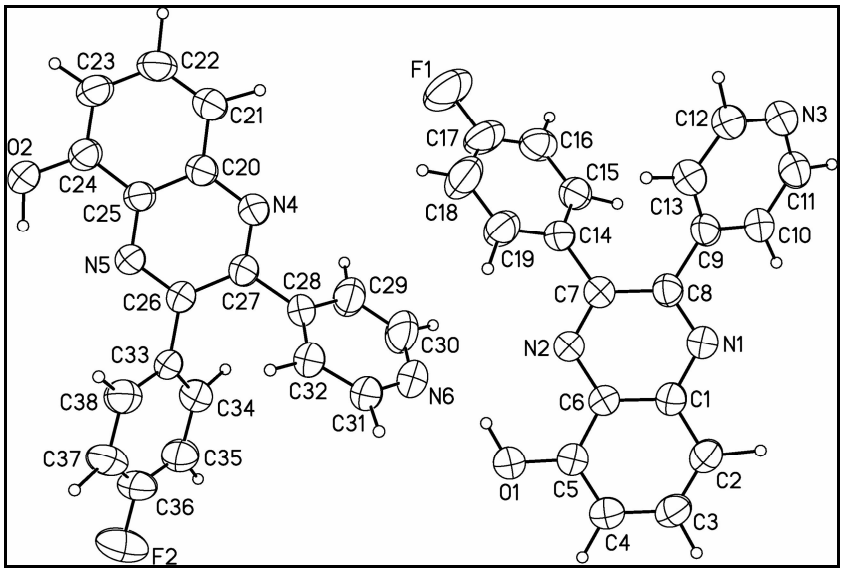


Fig-I. Molecular Structure of Compound 7, Showing 50% displacement Ellipsoids.

Table -I Crystallographic data for the compound 5

Empirical formula	**$C_{19}H_{12}FN_3O$**
Formula weight	317.32
Crystal system	Triclinic
Space group	P-1
a, Å	7.9697(4)
b, Å	14.2929(8)
c, Å	14.4200(8)
α,°	108.222(1)
β,°	90.372(1)
γ,°	97.911(1)
Volume, $Å^3$	1543.22(14)
Z	4
D_{calc} , g cm^{-3}	1.366
μ , mm^{-1}	0.096
T, °C	295(2)
λ , Å	0.71073
Number of unique data [1 > 2σ(1)]	7603
Number of variables	433
R_1^a	0.0479
w R_2^b	0.1031
Goodness – of –fit	0.834

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

6- membered rings and centers of rings			
Ring	Members		Ring Centre-of-Gravity
Cg(1)	C(1),C(2),C(3),C(4),C(5),C(6)		0.693479, 0.641319, 0.474952
Cg(2)	N(3),C(11),C(10),C(9),C(13),C(12)		-0.000711, 0.586989, 0.235164
Cg(3)	C(14),C(15),C(16),C(17),C(18),C(19)		0.258049, 0.294388, 0.141724
Cg(4)	C(20),C(21),C(22),C(23),C(24),C(25)		0.628299, 0.273170, 0.936251
Cg(5)	N(6),C(30),C(29),C(28),C(32),C(31)		0.302521, -0.170088, 0.708443
Cg(6)	C(33),C(34),C(35),C(36),C(37),C(38)		-0.031735, 0.062677, 0.667969
Short Ring-Interactions with Cg-Cg distances			
Plane numbers	Distance (Ang.)		Dihedral Angle between rings (Deg)
Cg(2) > Cg(1) [-1+X,Y,Z]	4.1773		35.90
Cg(3) > Cg(4) [X,Y,-1+Z]	4.1684		37.07
X-H...Cg(Pi-Ring) Interactions			
X--H(I)	Cg(J)	H..Cg Distance (Ang.)	X-H..Cg Angle (Deg)
C(10)-H(10A)	Cg(4)[1-X,1-Y,1-Z]	3.0385	109.22
C(11)-H(11A)	Cg(6)[-X,1-Y,1-Z]	3.1259	114.15
C(19)-H(19A)	Cg(5)[1-X,-Y,1-Z]	3.3987	112.50

Experimental

All melting points are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8300 model and BOMEM (Hartmann&Braun). ^{1}H and ^{13}C-NMR spectra were recorded on JEOL GMX 400 MHz ,JEOLFX 90Q 90MHz, Varian 400 MHz ,Varian Unity Inova 500 MHz spectrometer with $CDCl_3$ and DMSO-d_6 as the solvent with tetramethylsilane as the internal standard.Mass spectra were taken using Hewlett-Packard 5985(70ev), Shimadzu QP 1000A. 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 procedure[18].

Yield : 0.380g(55%) :MP : 240-242°C: IR(KBr) : ν= 3420(b), 1602, 1549, 1508 cm^{-1}
^{1}H-NMR(500MHz, DMSO $-D_6$) : δ 10.41(bs, 1H, OH,D_2O 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).
^{13}C-NMR(100MHz,$DMSOD_6$):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.
HRMS calcd for 317.3217 $C_{19}H_{12}FON_3$: 317.0955.
Anal calcd for $C_{19}H_{12}FON_3$: C, 71.91 ; H, 3.81 ; N,13.24 .found C,71.71 ;H,3.97 ; N,13.54.

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 I & Tabel 1-2**, and the x-ray data complied that both the phenolic – OH and 4-fluorophenyl groups are same plane on the quinoxaline ring.

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