Int J Pharm Bio Sci 2014 Oct; 5(4): (P) 212 - 224

Research Article **Medicinalchemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

SYNTHESIS OF P^{38} MAP KINASE INHIBITOR ANALOGUES COMPOUNDS AND QUINOXALINONE DERIVATIVES

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ABSTRACT

This paper reports the synthesis of nitrogen containing heterocyclic compounds such as quinoxalines (5-7), imidazoles (8, 9,10,11), aminothiazole (12), aminooxazole (13), aminoimidazole (14) and benzothiazine (17) from the reaction with unsymmetrical diketone 4, 3 and 4a respectively. The aforementioned compounds with 4-pyridyl,4-fluorophenyl groups have different positions in their ring skeleton. The quinoxalinone derivatives (19, 20) were synthesized by the reaction of (18) with o-phenylenediamine and 4,5-dimethyl- o-phenylenediamine respectively.

KEYWORDS: **p^{38} MAP kinase inhibitor, inflammatory, triarylimidazole, unsymmetrical diketones, benzothiazine, 1,3,5- trione, o-phenylenediamine, quinoxalinone**.

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INTRODUCTION

The p^{38} mitogen-activated protein (MAP^{α}) kinase, a serine / threonine kinase, is one of the well characterized kinase in the inflammatory process (1). Among the four identified p^{38} isoforms ($p^{38\alpha}$, $p^{38\beta}$, $p^{38\gamma}$, $p^{38\delta}$) , the α-form is the most fully characterized. A number of excellent prototypical, low molecular weight P^{38} MAP kinase inhibitor 2,4,5-triarylimidazoles (1 SB203580, 1a ML3163, 2 SB202190, Fig-I) is known to reduce the levels of TNF-α and IL-1β both in vitro and in vivo (2). Most of the potent 2,4,5-triarylimidazole inhibitors bearing 4-fluorophenyl,4-pyridyl and 4-polar groups substituted phenyl are in 4,5 and 2-positions respectively. Recently, several reports and reviews covering new P^{38}MAP kinase inhibitors have been reported (3-8).

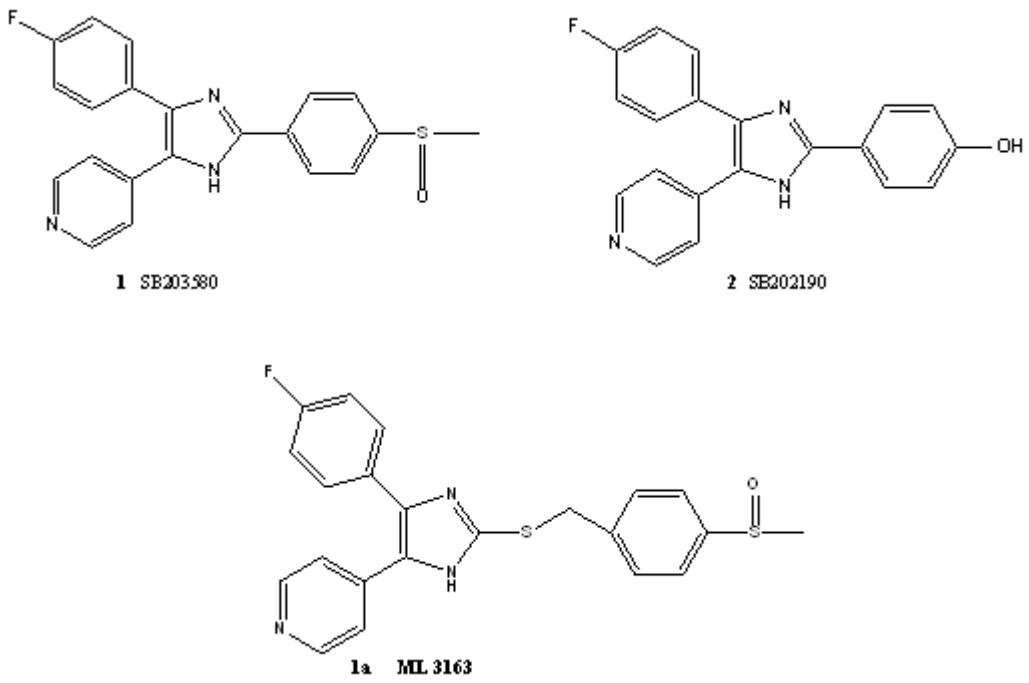


Figure – I

Crystallographic (9-11) data revealed that SB203580 binds in the adenosine triphosphate (ATP) binding site of p^{38} MAP kinase with hydrogen bond between the pyridine-4-yl moiety and the backbone NH of Met109 in the hinge region (Figure II) (10) . The 4-fluorophenyl ring binds to the hydrophobic pocket I, gaining mainly selectivity. Another possible ligand-protein interaction is a hydrogen bond between Lys53 and N-3 of the imidazole core as well as a π – π stacking between Try35 and the phenyl system. The hydrophobic region II remains unoccupied. Based on Schwable (12), SB203580 seems to bind to both p^{38} α DFG –in and DFG- out conformation.

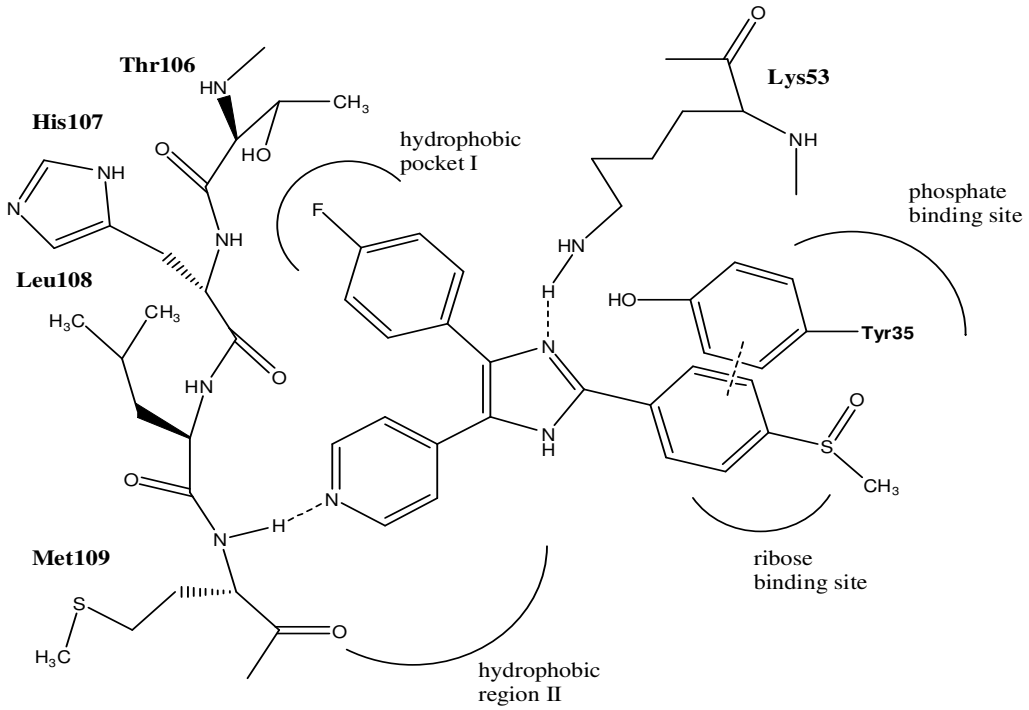
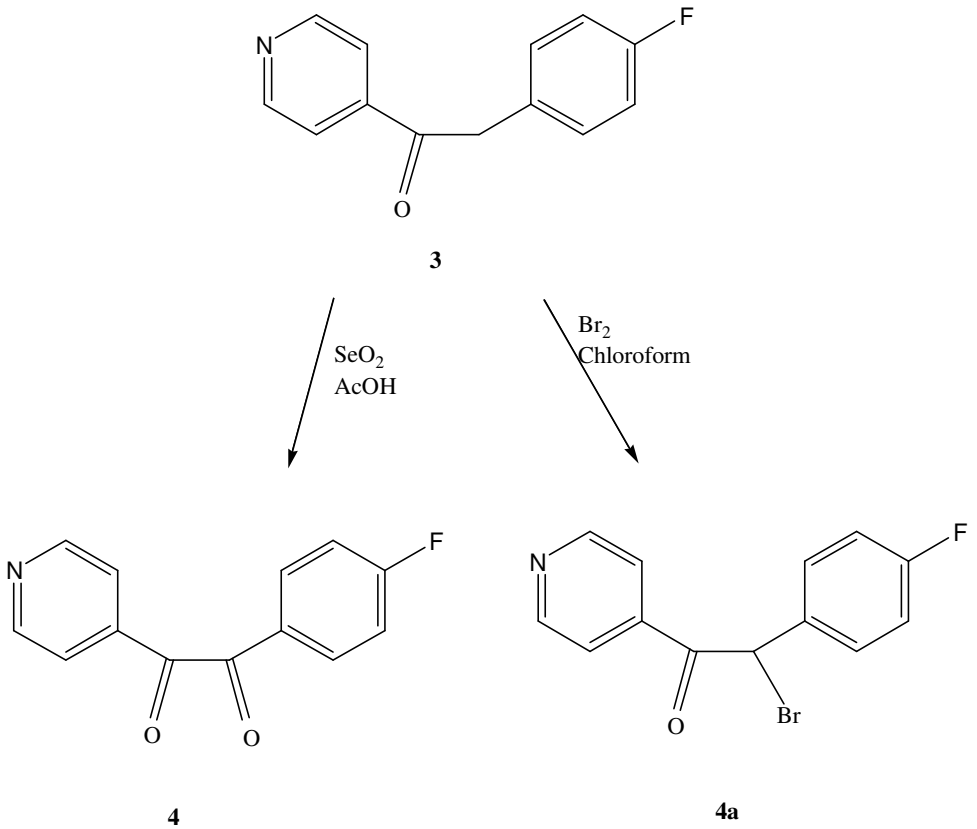


Figure – II .
Schematic drawing for showing some important interactions between the competitive inhibitor SB203580 and the ATP binding site $p^{38}\alpha$.

Numerous reports and reviews reveal the importance of quinoxaline ring systems,most of them exhibit the number of biological activities (13), similarly imidazole containing molecules exhibit a variety of medicinal applications (14).

RESULTS AND DISCUSSION

Based on the biological importance of the above heterocyclic compounds, we wish to report the synthesis of quinoxaline and imidazole rings bearing 4-fluorophenyl and 4-pyridyl groups in 2,3-positions and 4,5-positions respectively (scheme- II) . In addition, we report thiazole, oxazole, imidazole and benzothiazine ring (12-17) containing 4-pyridyl and 4-fluorophenyl groups in 4,5-positions and 3,2- positions respectively (Scheme-III).

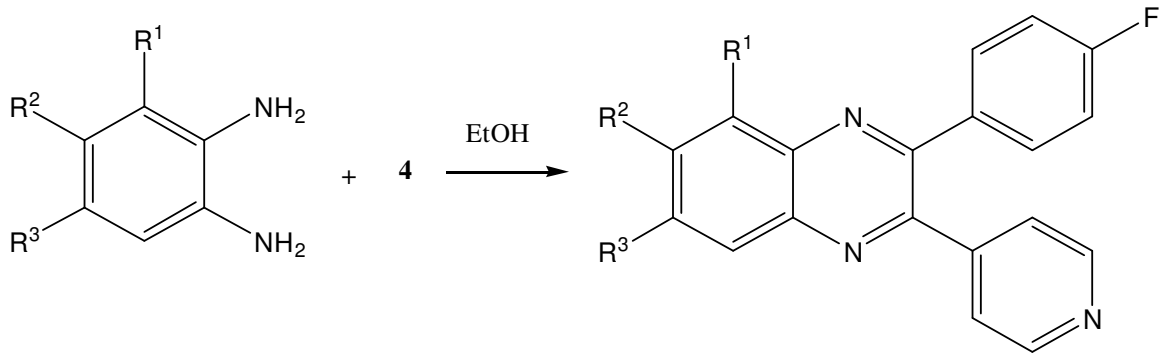


Scheme – I

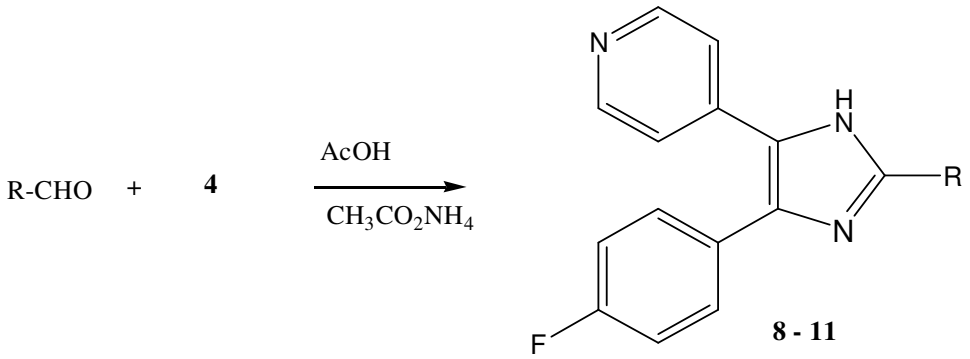
Moreover, the thiazole , oxazole and imidazole ring skeleton compounds 12-16 bear amino group and N - methyl amino group (polar) in 2-position. 4-pyridyl and 4-fluorophenyl groups are in the 4 and 5-positions respectively.

The compound 3, synthesized by literature method (Scheme- I) (15), was again converted into the unsymmetrical diketone, [1-(4-fluorophenyl)-2-(4-pyridyl) glyoxal] 4 by the treatment withSeO_2 in refluxing acetic acid (16). Treatment of 3 with bromine in chloroform furnished a yellow solid (17) 4a. The compounds 3,4 and 4a are the key intermediates for the synthesis of 5-17 in Scheme-II and Scheme -III.

Treatment of 4 with o-phenylenediamine and 4,5-dimethyl o-phenylenediamine in refluxing ethanol furnished the substituted quinoxalines derivatives 5,6 respectively (3c).Similarly, the diketone 4 was condensed with 2,3-diaminophenol to obtain exclusively

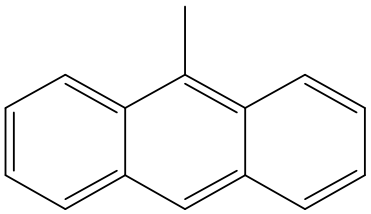


5 = $R^1 = R^2 = R^3 = H$
6 = $R^1 = H$, $R^2 = R^3 = CH_3$
7 = $R^1 = OH$, $R^2 = R^3 = H$

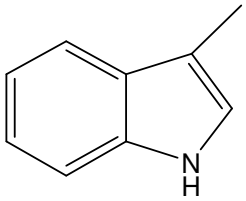


8 - 11

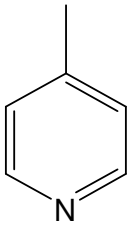
8 = R =



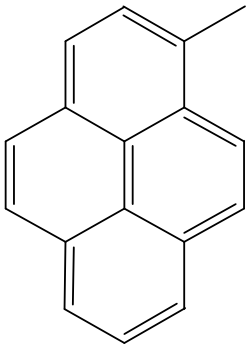
9 = R=



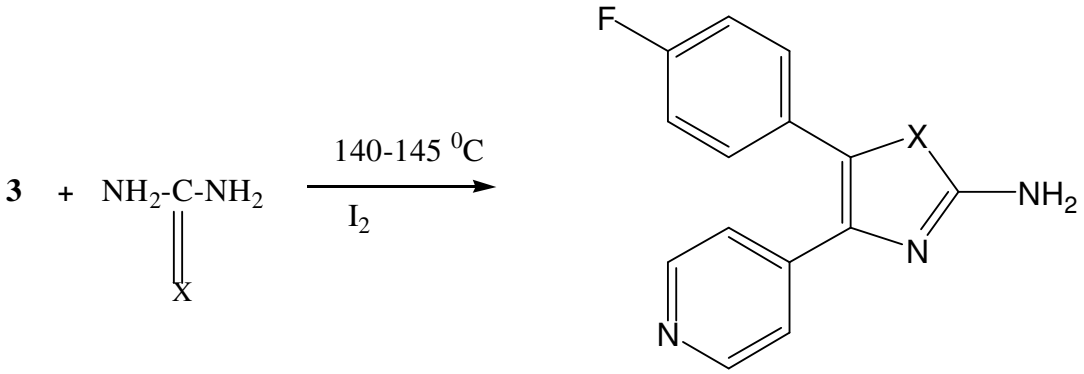
10 = R =



11 = R =



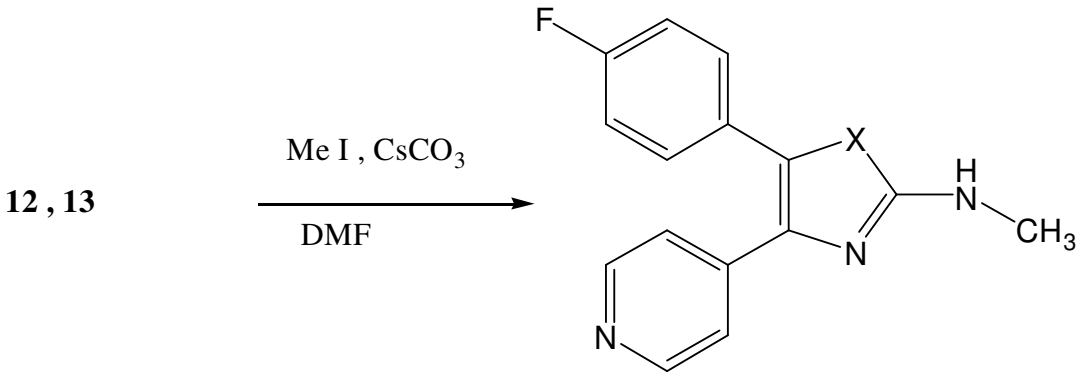
Scheme - II



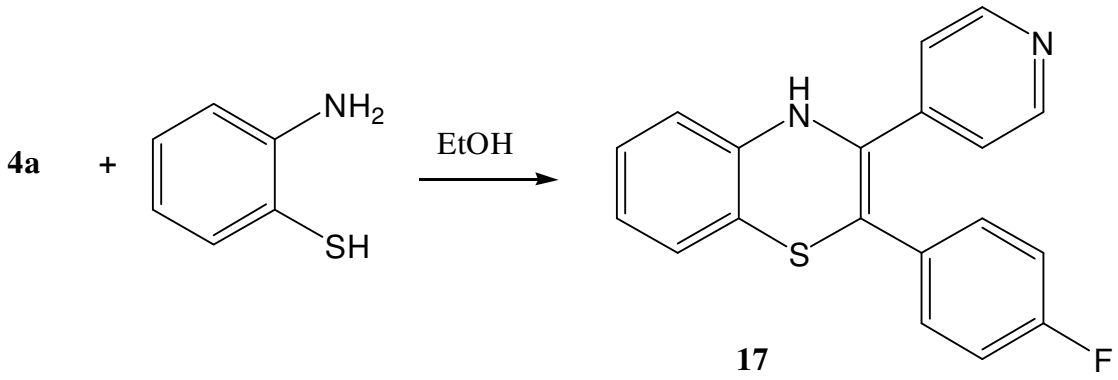
X = S = 12

X= O = 13

X = NH =14



X = S = 15
X = O = 16



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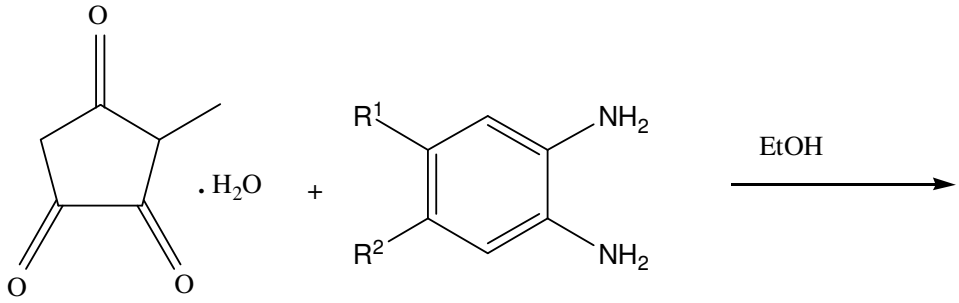
Scheme -III



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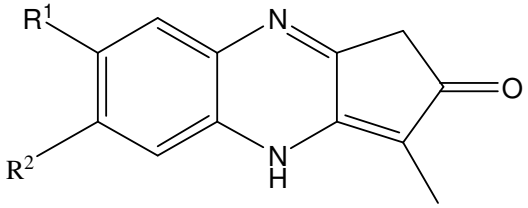
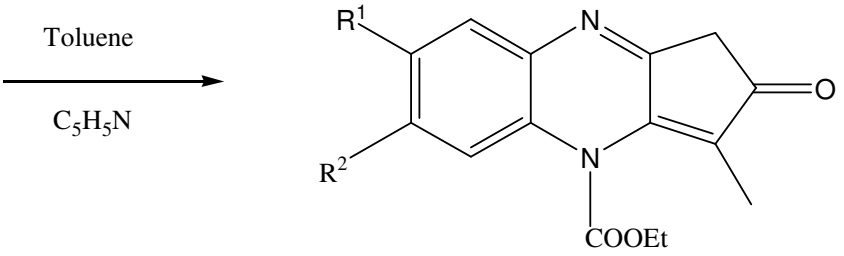


19 = $R^1 = R^2 = H$
20 = $R^1 = R^2 = CH_3$

19 + ClCOOEt



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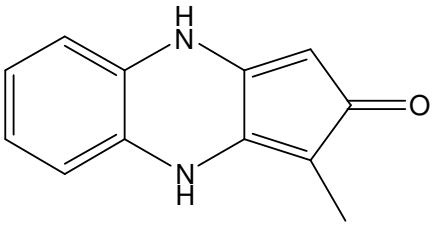

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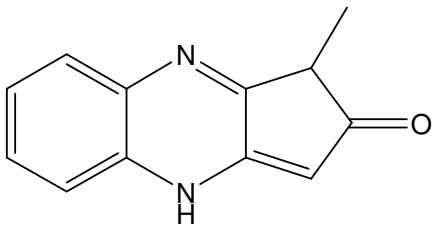

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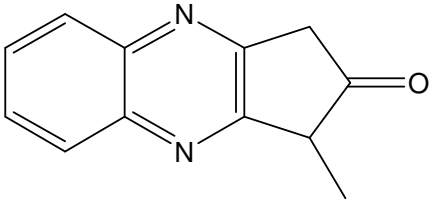

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Scheme- IV

one regioisomer 7, based on x-ray crystallographic analysis. . The diketone 4 when treated with aromatic aldehydes in refluxing acetic acid in the presence of ammonium acetate, yielded the corresponding imidazoles 8 - 11. Compound 3 reacts with thiourea, urea, guinidine in the presence of iodine to furnish the 2- amino subsituted thiazole, oxazole and imidazole (18) derivatives 12, 13,14 respectively in good yield. Further treatment of 12 and 13 treated with methyl iodide in the presence of $CsCO_3$ to afford the compounds 15 and 16. Compound 4a react with 2-amino thiophenol in refluxing ethanol to afford benzothiazine derivative 17. The compounds 5-17 were well characterized by IR, ^{1}H & ^{13}C –NMR, Mass and Elemental analysis. Next we were interested in exploring the reaction of 1,3,5- trione 18 (19). A highly fluorescent compound 19 was obtained from the 18 with o-phenylenediamine, likewise 4,5-dimethyl-o-phenylenediamine gave an analogous compound 20 . Further treatment of 19 with ethyl chloroformate furnished a brown color compound 21 (Scheme – IV) .The other isomeric structures 22, 23, 24 (20) were discarded based on IR, ^{1}H-NMR data. The IR spectrum showed an absorption (for NH) at 3410 cm^{-1}.In ^{1}H-NMR,the methyl protons of 19 appeared as a singlet at δ 1.7, the methylene protons were seen as a singlet at δ 2.9 , which on addition of D_2O, almost disappeared indicating strong enolisation. The ^{1}H –NMR of 21 showed a singlet at a δ 2.15(3H,CH_3) and singlet at δ 3.85 (2H,CH_2) in addition to COOEt protons at δ 1.41(t,3H) and δ 4.40 (q,2H) and aromatic protons at δ 7.60-8.10(2m,4H).

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)-2-(4-pyridyl)-quinoxaline[3c] (5)
General procedure

The 1-(p-fluorophenyl)-2-(4-pyridyl)-glyoxal (4) 0.5g, (2.1mmol) and o-phenylene diamine(0.23g, 2.1mmol) were taken in ethanol (20ml) and refluxed for 5 hours. The reaction mixture was cooled to room temperature, solvent was removed under vacuum and the residue was recrystallized from methanol (three times), to obtain as a brown color solid compound 5.

Yield : 0.42g (64%); MP: 165-167°C(Lit MP: Not reported) ; IR(cm^{-1}) : 1600, 1509, 1458, 1410, 1347; ^{1}HNMR(500MHz, $CDCl_3$) δ: 7.10-7.03 (m,2H), 7.49-7.47 (m,2H), 7.80-7.78 (m,2H), 7.83-7.81 (m,2H), 8.17-8.15 (m,2H), 8.61-8.60 (m,2H); ^{13}CNMR (125MHz, $CDCl_3$) δ : 115.66,115.84,124.17,129.32,131.77,131.83,134.14,134.17,141.10.141.52,146.87,149.88,150.33,151.90,162.41,164.41; MS:(m/z %) = 301(100),300(100),223(10),196(80),150(24),102(10),94(5), 77(12),75(30); HRMS : 301.3218 $C_{19}H_{12}FN_3$ found: 301.3216. Anal. calcd. for $C_{19}H_{12}FN_3$: C, 75.73; H, 4.01; N,13.94. Found: C, 75.51; H, 4.28 ; N, 14.21.

6,7-Dimethyl -3-(4-fluorophenyl)-2-(4-pyridyl)-quinoxaline[3c] (6)
By following the procedure of 5

Yield : 0.38g (53%) ; MP : 150-152°C(Lit MP: Not reported); IR (cm^{-1}) : 1598, 1510, 1485, 1450; ^{1}HNMR(500MHz, DMSO –d_6) δ: 2.48 (s,6H), 7.23-7.19 (m,2H), 7.41-7.40 (d,2H, J=5Hz), 7.50-7.47 (m,2H), 7.92-7.91 (d,2H, J=5Hz), 8.57-8.56(m,2H).^{13}CNMR (125MHz, DMSO-d_6) δ: 20.10,115.18,115.35,124.21,127.73,132.13,134.79,139.35, 141.35,141.83,146.46,149.56,

149.66,150.89,161.51,163.89;MS : (m/z %) = 330(M^{+1}, 50), 329(100), 328(100),103(40),94(10),78(40),77(25); Anal. Calcd. for $C_{21}H_{16}FN_3$: C, 76.57; H, 4.89; N, 12.75. found: C, 76.75; H, 4.62; N,12.82.

3-(4-Fluorophenyl)--5- hydroxy-2-(4-pyridyl)-quinoxaline (7)

*Synthesis of compound **7** following the above general procedure*.

Yield : 0.38g(55%) :MP : 240-242°C: IR(cm^{-1}) : 3420(b), 1602, 1549, 1508; ^{1}H-NMR(500MHz, DMSO –D_6) δ: 7.24-7.21 (m,3H), 7.45-7.44 (m,1H), 7.53-7.51(m,2H), 7.60-7.57 (m,2H), 7.75-7.70 (m,1H), 8.58-8.57 (m,2H), 10.41(bs,1H,OH,D_2O exchange); ^{13}C-NMR(100MHz,$DMSOD_6$) δ : 115.09,115.15,118.69,124.35,131.71,132.02,132.39,134.46,134.86,141.66,146.36,149.44,150.68,15 3.65,161.56,163.52; HRMS : 317.3217 $C_{19}H_{12}FON_3$ found: 317.3245;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.

2-(Anthran-9-yl)-4-(4-fluorophenyl)-5-(4-pyridyl)-imidazole (8)

General procedure for 8-11

The mixture of 0.5g (2.1mmol) 1-(p-fluorophenyl)-2-(4-pyridyl)-glyoxal(4), 0.44g(1.9 mmol) of 9-anthraldehyde, 3g of ammonium acetate(excess) and 10ml of glacial acetic acid is boiled under reflux for 24 hours then stirring vigorously, the reaction mixture was poured into a mixture of ice water containing conc. ammonia solution. The separated solid was filtered and dried, recrystallized from methanol (three times), to obtain yellow compound 8

Yield: 0.35g (38%); MP : 268-270°C; IR(cm^{-1}) :3125,1603, 1540, 1509, 1420, 1345; ^{1}HNMR(400MHz, DMSO – d_6) δ: 7.38-7.31 (m,2H), 7.58-7.51 (m,2H), 7.71-7.68 (m,2H), 7.91-7.88 (m,4H), 8.20-8.19 (m,2H), 8.49-8.48 (m,2H), 8.57-8.56 (m,1H), 8.80-8.79 (m,2H); ^{13}CNMR (100MHz, DMSO-d_6) δ: 115.35,115.56,115.89,120.42,120.87,121.20,125.38,125.83,126.76,128.47,129.61,130.77,130.86,13 9.02,143.93,149.75,150.10,160.20,162.79; HRMS : 415.4687 $C_{28}H_{18}FN_3$ found : 415.4662.

2-(Indol-3-yl)-4-(4-fluorophenyl)-5-(4-pyridyl)-imidazole (9)

Yield : 0.28g(36%) ; MP : 224-226°C;IR(cm^{-1}) : 3110, 1605, 1591, 1548; ^{1}HNMR(500MHz, DMSO – d_6) δ: 7.20-7.14 (m,2H), 7.39-7.34(t,2H, J = 8Hz), 7.46-7.44 (d,1H, J = 8Hz), 7.66-7.62 (m,2H), 7.75-7.74 (d,2H, J = 5HZ), 8.01-8.00(d,1H,J = 5Hz), 8.44-8.43(d,1H,J = 5Hz), 8.55-8.54 (d,2H, J = 5Hz),11.49(bs, NH); ^{13}CNMR (125MHz, $DMSOd_6$)δ:105.61,111.87, 115.61,116.03,116.20,120.09,120.97,121.17,124.88,131.12,131.18,136.33,145.01,145.81,161.32,16 3.28; MS: (m/z %) = 355(M+1, 10), 354(100), 353(20); Anal .calcd. for $C_{22}H_{15}FN_4$; C, 74.56; H, 4.26; N, 15.80 found: C, 74.81; H, 4.51; N, 16.08.

2-5- Di-(4-pyridyl)-4-(4-fluorophenyl)-imidazole (10)

Yield: 0.32g(47%) ; MP : 264-266°C;IR(cm^{-1}) : 3120, 1605, 1591, 1548;
^{1}HNMR(500MHz, DMSO – d_6) δ : 7.34-7.30(m, 2H), 7.48-7.42 (m,4H), 7.79-7.77 (d,2H, J = 5Hz), 8.50-8.48 (d,2H, J = 5Hz), 8.58-8.52(d,2H, J = 5Hz); ^{13}CNMR (125MHz, DMSO-d_6) δ: 116.03,116.20,123.17,127.17,128.88,131.01,131.72,139.18,141.33,145.07,149.81,151.30,159.28,16 3.48; HRMS : 316.5201 $C_{19}H_{13}FN_4$ found 316.5221.

2-(1-Pyrenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-imidazole (11)

Yield: 0.30g(31%) ; MP : 320-322°C;IR (cm^{-1}): 3120,1608, 1598, 1548; ^{1}HNMR(500MHz, DMSO – d_6) δ: 7.32-7.27 (m, 2H), 7.76-7.42(m,4H), 8.17-8.02 (m,4H), 8.28-8.20 (m,4H), 8.59-8.48 (m,1H), 8.70-8.64 (d, 2H, J = 8Hz); ^{13}CNMR (125MHz, DMSO-d_6) δ: 116.13,116.70,124.13,124.40,124.60,124.99,126.07, 126.17,129.88,131.11,131.70,139.18, 141.34,143.07,145.81,153.62,159.23,162.67; HRMS : 439.4916 $C_{30}H_{18}FN_3$ found: 439.4921.

2-Amino-5-(4-fluorophenyl-4-(4-pyridyl)-thiozole (12)

General procedure for 12-14

A mixture of 1-(4-pyridyl)-2-(4-fluorophenyl)ethanone 3, 0.5g (2.3 mmol) and thiourea 0.15g(1.9 mmol) in presence of iodine 0.25g (1.0 mmol) was heated at 140-145°C for 15 hours, then the reaction mixture was cooled to room temperature , ice cold water was added to the reaction mixture, the aqueous layer was extracted with ethyl acetate ,the organic layer was washed with water brine and dried over Na_2SO_4, and then purified by column using silica gel, eluted with dichloromethane : methanol (9:1) to furnish yellow solid 2-amino-5-(4-fluorophenyl-4-(4-pyridyl) - thiazole (12).

Yield: 0.25g (40%) ; MP : 256-258°C; IR(cm^{-1}) : 3290, 3140, 1599, 1540, 1500; ^{1}HNMR(400MHz, DMSO – d_6) δ: 4.2(bs, NH_2, exchanged with D_2O), 7.30-7.26(m,2H), 7.45-7.42 (m,2H), 7.78-7.76 (d,2H, J = 8Hz), 8.71-8.69 (d,2H, J = 8Hz); ^{13}CNMR(100,MHz, DMSO – d_6) δ: 116.01,116.72,124.80,129.18,131.50,131.60,139.35,141.63,149.85,162.89; HRMS : 271.0614 $C_{14}H_{10}FSN_3$ found: 271.0612.

2-Amino-5-(4-fluorophenyl-4-(4-pyridyl)-oxazole (13)

By following the above procedure for 12.

Yield: 0.33g (55%) ; MP : 290-292°C; IR(cm^{-1}) : 3298, 3140, 1590, 1540, 1500; ^{1}HNMR(400MHz, DMSO – d_6) δ: 4.31 (bs, NH_2, exchanged with D_2O),7.31-7.28 (m,2H), 7.44-7.39(m,2H), 7.78-7.75 (d,2H, J = 8Hz), 8.76-8.69(d,2H, J = 8Hz);^{13}CNMR(100,MHz, DMSO – d_6) δ: 116.81, 116.21,124.80,129.48,131.50,131.73,139.25,142.63,150,85,163.49; HRMS : 255.2514 $C_{14}H_{10}FON_3$ found: 255.2512.

2-Amino-5-(4-fluorophenyl-4-(4-pyridyl)-imidazole (14)

Yield: 0.29 (49%) ; MP : 300-302°C; IR(cm^{-1}) : 3270, 3150, 1600, 1540, 1500; ^{1}HNMR(400MHz, DMSO – d_6) δ: 4.2 (bs, NH_2, exchanged with D_2O),7.34-7.28 (m,2H), 7.42-7.38 (m,2H), 7.78-7.75(d,2H, J = 8Hz), 8.76- 8.68(d,2H, J = 8Hz); ^{13}CNMR(100,MHz, DMSO – d_6) δ: 116.21, 116.81,124.80,129.48,131.50,131.70,139.25,142.63,151.83,163.49; HRMS : 254.2673 $C_{14}H_{11}FN_4$ found: 254.2691.

2- N - Methyl amino-5-(4-fluorophenyl-4-(4-pyridyl)-thiazole (15)

A mixture of 2-amino-5-(4-fluorophenyl-4-(4-pyridyl)-thiazole 12, 0.25g (0.98mmol), methyl iodide (excess), $CsCO_3$, 0.8g (2.46mmol) in DMF (5 mL) was heated at 70-75°C for 15 hours; then the reaction mixture was cooled to room temperature , ice cold water was added , the aqueous layer was extracted with ethyl acetate , washed with water , brine and dried over Na_2SO_4, purified by column chromatography using silica gel and eluted with dichloromethane : methanol (9:1) to furnish yellow solid (**15**).Yield: 0.18 (69%) ; MP : 270-272 °C; IR(cm^{-1}) : 3128, 1600, 1540, 1500; ^{1}HNMR(400MHz, DMSO – d_6) δ: 2.75(s, 3H), 7.30-7.26 (m,2H), 7.45-7.41 (m,2H), 7.79-7.77 (d,2H, J = 8Hz), 8.75-8.66 (d,2H, J = 8Hz); ^{13}CNMR(100,MHz, DMSO – d_6) δ:38.55,116.51, 116.92,124.80,130.08,131.90,139.20,139.85, 149.50,153.51,163.55; HRMS : 285.3393 $C_{15}H_{12}FN_3S$ found : 285.3382.

2- N – Methylamino-5-(4-fluorophenyl-4-(4-pyridyl)-oxazole (16)

By following the procedure for 15. Yield: 0.14g(53%) ; MP : 227-230 °C; IR (cm^{-1}) : 3140 ,1600, 1540, 1500; ^{1}HNMR(400MHz, DMSO – d_6) δ : 2.78(s, 3H), 7.30-7.25(m,2H), 7.45-7.41(m,2H), 7.76-7.73 (d,2H,J = 8Hz), 8.75-8.65(d,2H, J = 8Hz); ^{13}CNMR(100,MHz, DMSO – d_6) δ: 38.42,115.62, 116.73,124.21,130.08,131.80,139.20,139.82,151.18,163.55; HRMS : 269.0964 $C_{15}H_{12}FN_3O$ found: 269.0971

2-(4- Fluorophenyl)-3-(4-pyridyl)-4H-1,4-benzothiazine (17)

A mixture of 1-(4-pyridyl)-2-bromo(4-fluorophenyl) ethanone 4a 0.5g (l.7mmol) and 2-amino thiophenol(2.3mmol) in ethanol was refluxed for 15 hours, then the solvent was removed under vaccuo, the residue was poured into ice water, the separated yellow solid filtered, dried, and recrystallized from methanol (3 times) to obtain the compound 17.

Yield: 0.27 g (50%); MP :256-258 °C; IR (cm^{-1}) : 3140, 1596, 1549, 1510; ^{1}HNMR(400MHz, DMSO – d_6) δ: 7.46-7.42 (m,2H), 7.55-7.52 (m,2H), 7.97-7.93(m,4H), 8.12-8.10 (d, 2H, J = 8Hz), 8.77-8.74 (d,2H, J = 8Hz), 8.81(bs,1H,NH); ^{13}CNMR (100MHz, DMSO-d_6) δ: 115.33,121.39,121.88,123.95,126.30,126.87,132.42,132.50,135.23,140.92,150.19,153.91,163.79; MS : (m/z%) = 320(60),288(10), 229(24),212(25),123(100),108(20),95(40); HRMS : 320.2020 $C_{19}H_{13}FSN_2$ found: 320.2038.

3-*Methyl-4H-cyclopenteno (2,3,-b) - quinoxaline-2(1H) one (19)*

(General procedure for 19 and 20)

The 2-methylcyclopentane –1,3,5-trione 18 (1g,7 mmol) and o-phenylenediamine (0.74g, 6 mmol) were taken in ethanol (20 ml) and stirred with a catalytic amount of phosphorous pentoxide for one hour at room temperature. The separated solid was filtered ,dried and crystallized from methanol to obtain 19 as a yellow solid.

Yield (1.0g, 72%); MP:308-310 °C ; UV:λ_{max}394nm (MeOH) ; Flu : λ_{max} 475nm (MeOH); IR(cm^{-1}) : 3410,1640,1560 ; ^{1}H-NMR(90 MHz DMSO-d_6) δ: 1.73(s,3H,-CH_3), 2.97 (s,2H,-CH_2), 7.17-7.60 (m,4H,ArH); MS: (m/z %) =198(90),197(20),183(10), 181(5),169(100),155(10),143(4),129(80),102(8); Anal. Calcd. for $C_{12}H_{10}N_2O$: C,72.71 ; H,5.08 ; N,14.13 . Found C,72.78 ; H ,5.31 ; N,14.35.

3,6,7,Trimethyl –4H-cyclopenteno(2,3-b)- quinoxaline –2 (1H) one (20)

Yield :1.1g(70%) ; MP: 360-362 °C ;UV :λ_{max} 402 nm; (MeOH) ; Flu : λ_{max} 484 nm(MeOH) ; IR (cm^{-1}) : 3410,1648,1560 ; ^{1}H-NMR(90MHz , DMSO-d_6) δ: 1.73(s,3H,-CH_3),2.26 (bs,6H,-Ar-CH_3), 3.01(s,2H,-CH_2), 7.30-7.18 (2m,2H,ArH); Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31 ; H, 6.23 ; N, 12.37.Found C, 74.16 ; H, 6.43 ; N,12.39.

4-Carbethoxy-3-methyl-4H-cyclopenteno (2,3-b)-quinoxalin-2 (1H) one (21)

To a solution of quinoxaline **19** (1g,5mmol) and pyridine (1 ml) in dry toluene (50ml), ethyl chloroformate (0.54g,5mmol) in dry toluene (20ml) was added drop wisely with stirring . After 6 hours , water (50ml) was added and extracted with dichloromethane, the organic layer was dried ($MgSO_4$) and concentrated to give a brown solid 21. Yield:0.9g(66%); MP:128-130 °C ; IR (cm^{-1}) : 1752,1640,1585 [1]; ^{1}H-NMR (300MHzCDCl$_3$) δ: 1.41(t,3H,CH_3), 2.15 (s,3H,CH_3), 3.85(s,2H,CH_2), 4.40 (q,2H,-CH_2), 8.10,7.60 (2m,4H,ArH); ^{13}C-NMR(75 MHz,CDCl$_3$)δ: 12.93,14.72,52.55,60.35,138.02,138.19,138.21,142.37,143.51,151.67,152.14,167.70,204.62; Ms:(m/z %) 270(10),252(15),226(8), 206(21),198(100),197(25),183(5),181(8),169(60); Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C,66.66 ; H,5.22 ; N,10.36. Found : C,66.71 ; H, 5.40 ; N, 10.52.

CONCLUSION

In summary, we report simple, and straightforward synthesis of different substituted quinoxalines 5-7, imidazoles, thiazoles, oxazoles 8-16, benzothiazine 17 as new p^{38} MAP kinase inhibitor. We report simple synthesis of substituted quininoxalin-2-one derivatives 19-21.

ACKOWLEDGEMENT

We thank the National Science Council of the Republic of China for the financial support of this research work, and Prof V.T. Ramakrishnan for generous support for all work.

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