Supporting information

Isoxazolone based inhibitors of p38 MAP kinases

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Contents

Synthetic procedures, routine spectroscopic data and IR-data.

Purity data: Elemental Analysis.

Experimental section

General. All commercially available reagents and solvents are used without further purification. Melting points were determined with a Büchi melting point B-545 apparatus, IR data were determined with a Perkin-Elmer Spectrum One (ATR Technik), and ^{1}H NMR (200MHz) and ^{13}C NMR (200MHz) were determined with a Bruker Advance 200 using TMS as internal standard. The chemical shifts are reported in ppm. LC-MS data were generated by using a Thermo Finnigan Survey MS Pump and a Thermo Finnigan TSQ Quantum triple quadrupol MS. Bischoff Prontosil 120-5-C18-ace-EPS 5.0micron 50x3mm column was used.

4-Fluorobenzaldehyde oxime (4)

24.8 g (200mmol) of 4-fluorobenzaldehyde were placed in a three-necked round-bottomed flask furnished with a dropping funnel, thermometer and condenser, and, under stirring, H_2O /ice/ethanol: 60ml/90g/60ml were added. 19g (270mmol) of hydroxylamine chloride were added, the suspension cooled on an ice bath and 150 mL of 50% aqueous sodium hydroxide were added dropwise keeping the temperature below 10°C. The reaction mixture was allowed

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to come to RT and stirred for another hour at RT. The solution was then neutralized with concentrated hydrochloric acid and the formed white precipitate was extracted with diethyl ether. The organic phase was concentrated under vacuum affording **4** as yellow foam.

C_7H_6FNO (MW 139.04)

Melting point: 82 °C

Yield: 27.5g, η%: 99%

IR: 3257, 3018, 1605, 1509, 1228, 957

^{1}H-NMR ($CDCl_3$): δ (ppm) 7.05-7.15 (m, 2H, 4F-Ph), 7.54-7.61 (m, 2H, 4F-Ph), 8.13 (s, 1H), 11.2 (s,1H, exchangeable)

4-Fluorobenzyl chloride oxime (5)

To a solution of 12.21 g (87.8 mmol) of 4-Fluoro-benzaldehyde oxime in 18 mL of DMF 11.68 g (87.8 mmol) of NCS were added. The limpid pale yellow reaction mixture was allowed to stir for 2h at RT. The reaction mixture was then poured into ice and extracted with diethyl ether. The organic phases were collected, washed with water, brine, and again with water and dried over Na_2SO_4. Removal of the solvent afforded yellow oil, which solidified upon storage at 4 °C.

C_7H_5ClFNO (MW 173.57)

Yield: 13g, η%: 87%

IR: 3371, 3200, 2852, 1598, 1505, 1234, 831

^{1}H-NMR ($CDCl_3$): δ (ppm) 7.06-7.16 (m, 2H, 4F-Ph), 7.81-7.96 (m, 2H, 4F-Ph).

3-(4-Fluoro-phenyl)-4-pyridin-4-yl-2*H*-isoxazol-5-one (6)

To a vigorously stirred solution of 1 g (6 mmol) of ethyl 4-pyridyl acetate in 4 mL of THF, 9.08 ml (18 mmol) of a 2M solution of NaHMDS in THF was added dropwise over 45 min. The reaction mixture was allowed to stir for 45 min at RT. A solution of 1.03 g (6 mmol) of 4-Fluorobenzyl chloride oxime in 8 mL of THF was added dropwise and the resulting suspension was stirred for 6h at RT. The base was then hydrolyzed by adding 400 µl of water. The reaction mixture was filtered over a Buechner funnel and concentrated under vacuum. The residue was chromatographically separated on SiO_2, side products and residual starting materials were eluted first by ethyl acetate, then the wanted product fraction was

eluted with MeOH. The alcoholic solution was concentrated under reduced pressure. A first crop of **6** (O^- form) was obtained by crystallization from MeOH. The organic solution was then concentrated in vacuum and water was added. The precipitate was filtered off to yield a second crop of **6**. Two parts collected together, dissolved in 5ml of water, cooled at 0 °C and combined with concentrated HCl. Tthe formed precipitate crystallized from MeOH.

$C_{14}H_9FN_2O_2$ (MW 256.23)

Yield: 940 mg, η% 61

Melting point: 240°C

IR: 3259, 3054, 2670, 1676, 1616, 1520, 1471, 1439, 1363, 1225, 1200, 965, 850, 822

MS: 257.1 (M+1)

MS2: 257.1 (M+1), 239.1, 229.1, 213.2, 210.3

^{1}H-NMR (DMSO-d_6): δ (ppm) 7.29-7.51 (m, 6H), 8.03-8.07 (m, 2H).

^{1}H-NMR ($CDCl_3$): δ (ppm) 5.30 (s, 1H), 7.14-7.26 (m, 2H, 4FPh), 7.65-7.72 (m, 2H, 4FPh), 8.04-8.07(m, 2H, Py), 8.90-8.94 (m, 2H, Py).

^{13}C-NMR (DMSO-d_6): δ (ppm) 90.0 (C^4 isox), 120.2, 121.0, 134.2 (J=2.9, C^4 4FPh), 135.7 (J=8.5, C^3/C^5 4FPh), 143.7, 155.2 (C^3 isox), 166.2 (C^5 isox), 167.7 (J=229.0 Hz, C^1 4FPh), 178.8

^{13}C-NMR (90% D_2O- 10% DMSO): δ (ppm) 84.6 (C^4 isox), 116.1 (J=21.5, C^2/C^6 4FPh), 120.4, (J= 21.5, C^2/C^6 4FPh), 127.6 (J=2.9, C^4 4FPh), 130.2 (J=8.5, C^3/C^5 4FPh), 142.9, 147.9 (C^3 isox), 163.0 (C^5 isox), 163.0 (J=229.0 Hz, C^1 4FPh), 176.0

^{13}C-NMR (89.98% D_2O- 10% DMSO- 0.02% NaOH): δ (ppm) 87.1 (C^4 isox), 117.4 (J=21.1 Hz, C^2/C^6 4FPh) , 122.6, 128.7 (J=2.9 Hz, C^4 4FPh), 131.9 (J=7.2 Hz, C^3/C^5 4FPh), 144.4, 149.6 (C^3 isox), 164.9 (J=245.3Hz, C^1 4FPh), 165.3 (C^5 isox), 177.9

Anal. ($C_{14}H_9FN_2O_2$) C, H, N, O.

Synthesis of 5-alkoxyisoxazoles. General procedure I.

To a suspension of **6** in DMF (2ml/1mmol compound **6**) Et_3N (3 eq) was added and the reaction mixture refluxed for 2h. The limpid solution was then combined with halogen halide (1.8 eq) and the mixture stirred under reflux for additional 2h and subsequently at RT overnight. The reaction mixture was poured into water, the two phases partitioned and the water phase was extracted twice with DCM. The collected organic phases were washed with H_2O/brine /H_2O, dried over Na_2SO_4 and concentrated under vacuum. The final compound was then purified by column chromatography on SiO_2.

4-[3-(4-Fluoro-phenyl)-5-methoxy-isoxazol-4-yl]-pyridine (7a)

7a was synthesized according to the general procedure I reacting 111 µl (1.8 mmol) of methyl iodide and 256 mg (1 mmol) of **6.** The product was purified by column chromatography on SiO_2 (eluent THF).

$C_{15}H_{11}FN_2O_2$ (MW 270.26)

Yield: 160mg, η% 22

Melting point: 229°C

MS: 271 (m+1), 254, 243, 227, 212, 134, 94

FTIR: 3049, 2965, 1676, 1619, 1517, 1475, 1443, 1415, 1366, 1219, 1202, 956, 883, 844

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.84 (s, 3H, -CH_3), 7.29-7.51 (m, 6H), 8.03-8.06 (d, 2H)

^{13}C-NMR (DMSO-d_6): δ (ppm) 45.0, 85.4 (C^4 isox), 115.7, 116.3 (J=22.0 Hz, C^4 4FPh), 128.9 (J=2.9 Hz, C^2 4FPh), 129.3 (J=8.5 Hz, C^3/C^5 4FPh), 142.1, 149.1, 161.4 (C^3 isox), 163.0 (J=229.0 Hz, C^1 4FPh), 174.0 (C^5 isox).

Anal. ($C_{15}H_{11}FN_2O_2$) C, H, N, O.

4-[5-Ethoxy-3-(4-fluoro-phenyl)-isoxazol-4-yl]-pyridine (7b)

7b was synthesized according to the general procedure I reacting 111µl (1.8 mmol) of ethyl chloride and 256 mg (1 mmol) of **6**. The product was purified by column chromatography on SiO_2 (eluent THF).

$C_{16}H_{13}FN_2O_2$ (MW 284.29)

Yield: 270mg, η%: 95%

Melting point: 240°C

IR: 3045, 1677, 1618, 1571, 1529, 1432, 1188, 836

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.34 (t, 3H, CH_3), 4.10 (q, 2H, CH_2), 7.10-7.18 (m, 6H), 8.15 (d, J= 1.5Hz, 2H)

^{13}C-NMR (DMSO-d_6): δ (ppm) 16.2, 53.1, 85. 6 (C^4 isox), 115.8, 116.4 (J=21.7 Hz, C^2/C^6 4FPh), 129.3 (J=2.7 Hz, C^4 4FPh), 131.1 (J= 8.5 Hz, C^3/C^5 4FPh) 141.0, 149.2, 161.4 (C^3 isox), 162.2 (J= 249.0 Hz, C^1 4FPh), 174.0 (C^5 isox).

Anal. ($C_{16}H_{13}FN_2O_2$) C, H, N, O.

4-[3-(4-Fluoro-phenyl)-5-oxiranylmethyl-isoxazol-4-yl]-pyridine (7c)

7c was synthesized according to the general procedure I reacting 165 mg (1.8 mmol) of 2-Chloromethyl-oxirane with 256 mg (1 mmol) of **6**. The product was purified by column chromatography on SiO_2 (eluent acetone: dichloromethane=2:1).

$C_{17}H_{13}FN_2O_3$ (MW 284.29)

Yield: 50mg, η%: 10%

Melting point: 270°C

IR: 3204, 1668, 1607, 1519, 1199, 841

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.54-3.60 (m, 1H), 3.90-3.94 (m, 1H), 4.23-4.32 (m, 1H), 5.78 (d, J=2.4 Hz, 2H), 7.30-7.52 (m, 4H), 8.03 (d, J=1.8 Hz, 2H).

^{13}C-NMR (DMSO-d_6): δ (ppm) 47.1, 60.8, 69.7, 85.8 (C^4 isox), 115.4, 116.3 (J= 21.7, C^2/C^6 4FPh), 129.3 (J= 2.7 Hz, C^4 4FPh), 131.0 (J=8.5 Hz, C^3/C^5 4FPh), 141.9, 149.5, 161.4 (C^3 isox), 163.0 (J=249.0 Hz, C^1 4FPh), 173.9 (C^5 isox).

Anal. ($C_{17}H_{13}FN_2O_3$) C, H, N, O.

4-[5-Cyclopropylmethoxy-3-(4-fluoro-phenyl)-isoxazol-4-yl]-pyridine (7d)

7d was synthesized according to the general procedure I reacting 368 mg (4.06 mmol) of chloromethyl-cyclopropane with 580 mg (2.26 mmol) of **6**. The product was purified by column chromatography on SiO_2 (eluent acetone: dichloromethane=2:1).

$C_{18}H_{15}FN_2O_2$ (MW 313.32)

Yield: 250mg, η%: 35%

Melting point: 176°C

IR: 3034, 1677, 1612, 1526, 1185, 956, 839

^{1}H-NMR (DMSO-d_6): δ (ppm) 0.38-0.58 (m, 4H), 1.18-1.26 (m, 1H), 3.95 (d, J=2.5 Hz, 1H), 8.17 (d, J=1.5 Hz, 2H)

^{13}C- NMR (DMSO-d_6): δ (ppm) 3.9, 12.1, 61.8, 85.7 (C^4 isox), 115.7, 116.3 (J=21.7, C^2/C^6 4FPh), 129.3 (J=2.7 Hz, C^4 4FPh), 130.5 (J=8.5 Hz, C^3/C^5 4FPh), 141.0, 149.3, 161.5 (C^3 isox), 163.0 (J=249.0 Hz, C^1 4FPh), 174.0 (C^5 isox).

Anal. ($C_{18}H_{15}FN_2O_2$) C, H, N, O.

4-[3-(4-Fluoro-phenyl)-5-methoxymethoxy-isoxazol-4-yl]-pyridine (7e)

7e was synthesized according to the general procedure I reacting 391 mg (4.86 mmol) of chloro-methoxy-methane with 711 mg (2.70 mmol) of **6**. The product was purified by column chromatography on SiO_2 (eluent acetone: dichloromethane=2:1).

$C_{16}H_{13}FN_2O_3$ (MW 300.28)

Yield: 300mg, η%: 35%

Melting point: 201°C

IR: 3043, 1681, 1617, 1520, 1089, 835

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.32 (s, 3H), 5.33(s, 2H), 6.85-7.59 (m, 6H), 8.3 (d, J=1.5 Hz, 2H).

^{13}C-NMR (DMSO-d_6): δ (ppm) 56.8, 86.8, 87.1 (C^4 isox), 115.2, 116.4 (J=21.7 Hz, C^2/C^6 4FPh), 129.3 (J=2.7 Hz, C^4 4FPh), 131.1 (J=8.5 Hz, C^3/C^5 4FPh), 140.4, 150.3, 160.6, 163.0 (J=249.0 Hz, C^1 4FPh), 173.8 (C^5 isox).

Anal. ($C_{16}H_{13}FN_2O_3$) C, H, N, O.

4-[3-(4-Fluoro-phenyl)-5-methoxy-ethoxy-isoxazol-4-yl]-pyridine (7f)

7f was synthesized according to the general procedure I reacting 335 mg (3.54 mmol) of 1-chloro-2-methoxy-ethane with 506 mg (1.97 mmol) of **6** in $CHCl_3$. The product was purified by column chromatography on SiO_2 (eluent acetone: dichloromethane=2:1).

$C_{17}H_{15}FN_2O_3$ (MW 314.31)

Yield: 200mg, η%: 30%

Melting point: 160°C

IR: 3036, 1677, 1614, 1515, 1107, 835

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.20 (s, 3H), 3.63(t, 2H), 4.25(t, 2H), 7.3-7.52(m, 6H), 8.07 (d, J=1.5 Hz, 2H)

^{13}C-NMR (DMSO-d_6): δ (ppm) 57.3, 58.5, 70.6, 85.8 (C^4 isox), 115.4, 116.3 (J=21.7 Hz, C^2/C^6 4FPh), 129.3, 131.1 (J=8.5 Hz, C^3/C^5 4FPh), 149.4, 161.5, 163.0 (J=249.0 Hz, C^1 4FPh), 174.0 (C^5 isox).

Anal. ($C_{17}H_{15}FN_2O_3$) C, H, N, O.

3-[3-(4-Fluoro-phenyl)-4-pyridin-4-yl-isoxazol-5-yloxy]-propan-1-ol (7g)

7g was synthesized according to the general procedure I reacting 335 mg (3.54 mmol) of 3-chloro-propan-1-ol with 506 mg (1.97 mmol) of **6** in $CHCl_3$. The product was purified by crystallization from dichloromethane.

$C_{17}H_{15}FN_2O_2$ (Mw) 298.11

Yield: 200mg, η%: 30%

Melting point: 205°C

IR: 3332, 3054, 1668, 1597, 1518, 845

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.86 (q, 2H), 4.14 (t, 2H), 4.67(t, 2H), 7.3-7.52 (m, 6H), 8.07 (d, 2H)

^{13}C-NMR (DMSO-d_6): δ (ppm) 33.3, 55.3, 57.3, 85.6 (C^4 isox), 115.7, 116.3 (J=21.7 Hz, C^2/C^6 4FPh), 129.3, 131.1 (J=8.5 Hz, C^3/C^5 4FPh), 141.4, 149.2, 161.4, 163.0 (J=249.0 Hz, C^1 4FPh), 174.0 (C^5 isox).

Anal. ($C_{17}H_{15}FN_2O_2$) C, H, N, O.

3-[3-(4-Fluoro-phenyl)-4-pyridin-4-yl-isoxazol-5-yloxy]-ethanol (7h)

7h was synthesized according the general procedure I reacting 282mg (3.50mmol) of 2-chloro-ethanol with 500mg (1.95 mmol) of **6** in $CHCl_3$. The product was purified by crystallization from dichloromethane.

$C_{16}H_{13}FN_2O_3$ (MW 300.28)

Yield: 150mg, η%: 25%

Melting point: 182°C

IR: 3228, 1659, 1596, 1516, 1475, 1363, 1222, 1196, 1054, 836

LC: 11.90min

MS: 301 (M+1)

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.69 (t, 2H), 4.12 (t, 2H), 5.09 (t, 1H, exchangeable), 7.3-7.48 (m, 6H), 8.06 (d, J=1.5Hz, 2H)

^{13}C-NMR (DMSO-d_6): δ (ppm) 60.3, 85.6 (C^4 isox), 115.5, 116.3 (J=21.7 Hz, C^2/C^6 4FPh), 129.3 (J=8.5 Hz, C^3/C^5 4FPh), 131.0, 141.7, 149.4, 161.5, 163.0 (J=249.0 Hz, C^1 4FPh), 174.0 (C^5 isox). CH_2 signal shifted under solvent signal

^{13}C-NMR (MeOD): δ (ppm) 58.7, 59.0, 84.4 (C^4 isox), 114.1, 115.3 (J=21.7 Hz, C^2/C^6 4FPh), 126.5, 128.9 (J=8.5 Hz, C^3/C^5 4FPh), 139.5, 148.8, 160.5, 163.0 (J= 249.0 Hz, C^1 4FPh), 174.0 (C^5 isox).

Anal. ($C_{16}H_{13}FN_2O_3$) C, H, N, O.

4-[3-(4-Fluoro-phenyl)-5-isopropoxy-isoxazol-4-yl]-pyridine (7i)

7i was synthesized according to the general procedure I reacting 279 mg (3.54 mmol) of 2-chloro-propane with 506 mg (1.97 mmol) of **6** in DMF. The product was purified by column chromatography on SiO_2 (eluent acetone: dichloromethane=1:1). The reaction had been performed also in $CHCl_3$ obtaining the same compound.

$C_{17}H_{15}FN_2O_2$ (MW 298.31)

Yield: 150mg, η%: 25%

Melting point: 208°C

IR: 3063, 1670, 1612, 1518, 1435, 1366, 1093, 834

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.39 (d, 6H), 4.46 (m, 1H), 7.3-7.48 (m, 6H), 8.06 (d, J=1.9 Hz, 2H)

^{13}C- NMR (DMSO-d_6): δ (ppm) 22.5, 85.6 (C^4 isox), 115.8 (J= 21.7 Hz, C^2/C^6 4FPh), 116.3, 129.3, 131.1, 139.4, 149.5, 161.5, 163.0 (J= 249.0 Hz, C^1 4FPh), 174.0 (C^5 isox).

Anal. ($C_{17}H_{15}FN_2O_2$) C, H, N, O.

2-(4-Fluoro-phenyl)-3-oxo-3-pyridin-4-yl-propionacid ethylester (8)

To a suspension of 3.3 g (26.8 mmol) of isonicotinic acid in 15 mL of DMF, 7.3g (45mmol) of CDI were added. The reaction mixture was stirred at RT for 1h. The limpid orange solution was then cooled down to 0 °C and 5g (27.4 mmol) of (4-fuoro-phenyl)-acetic acid ethyl ester and 1.7 g (70.8 mmol) of NaH were added. The brilliant yellow foam was stirred at 0°C for 15 min, and then the temperature was raised to RT and kept under vigorous stirring for 4h. The reaction mixture was poured into water/ice, the pH adjusted to value 6 and the mixture extracted with ethylacetate. The combined organic layers were collected, dried over Na_2SO_4 and concentrated under vacuum affording a brownish oil that was chromatographically purified on SiO_2 (eluent: DCM/acetone: 1/1) to yield a yellow oil.

$C_{16}H_{13}FNO_3$ (MW 286.28)

Yield: 5.1g, η%: 66%

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.17-1.29 (m, 3H, Keto+ 3H Enol, CH_3), 4.17-4.31 (m, 2H Keto+ 2H Enol, CH_2), 5.50 (s, 1H Keto, Methin-H), 6.97-7.12 (m, 2H Keto 4-F-Ph and 2H Enol 4-F-Ph), 7.25-7.27 (m, 2H Enol, 4-Pyr), 8.47-8.50 (m, 2H Enol, 4-Pyr), 8.78-8.80 (m, 2H Keto, 4-Pyr), 13.5 (s, 1H, exchangeable, Enol-OH).

4-(4-Fluoro-phenyl)-3-pyridin-4-yl-isoxazol-5-ol (9)

A suspension of 5.2 g (18.1 mmol) of **8** and 1.41 g (20.27mmol) of hydroxylamine hydrochloride in 1.5 mL of H_2O was warmed to 80 °C. 8 ml of MeOH were added and the resulting limpid yellow solution allowed to reflux for 4h. The reaction mixture was then cooled back to RT and stored at 4°C overnight. A first crop of **9** crushed down from the methanolic aqueous solution that was isolated by filtration. The solution was concentrated

under vacuum and the brilliant yellow residue chromatographically purified on SiO_2 (eluents: 1. EtOAc, 2. MeOH) giving a second crop of **9** that crystallized from MeOH.

$C_{14}H_9FN_2O_2$ (MW 256.23)

Yield: 3.4g, η%: 74%

Melting point: 225°C

MS: 257.0 (M+1)

MS2 (257): 257.0, 239.1, 229.1, 227.1, 213.2

FTIR: 3095, 3056, 2457, 2110, 1630, 1598, 1583, 1539, 1515, 1457, 1438, 1304, 1208, 1158, 1098, 1003, 964, 827.

^{1}H-NMR (DMSO-d_6): δ (ppm) 7.08-7.30 (m, 4H, 4F-Ph), 7.53 (dd, J=0.5/1.4 Hz; 2H), Py), 8.72 (dd, J=0.5/1.4 Hz;2H, Py).

^{13}C-NMR (DMSO-d6): 92.5 (C^4 isoxazolone), 115.6 (J= 21.3 Hz, C^2/C^6 4FPh). 123.5, 127.0 (J= 3.1 Hz, C^4 4FPh). 130.3 (J= 7.9 Hz, C^3/C^5 4FPh), 139.2, 149.1, 158.4 (C^3 isoxazolone), 161.0 (J= 240.0 Hz, C^1 4FPh), 171.7 (C^5 isoxazolone).

^{13}C-NMR (90% D_2O): 89.01 (C^4 isoxazolone), 116.8 (J=21.3 Hz, C^2/C^6 4FPh), 124.5, 129.7 (J= 3.1 Hz, C^4 4FPh). 131.8 (J=7.9 Hz, C^3/C^5 4FPh), 141.6, 150.6, 161.3 (C^3 isoxazolone), 162.9 (J= 240.0 Hz, C^1 4FPh), 178.3 (C^5 isoxazolone).

^{13}C-NMR (90% D_2O - 10% NaOH): 115.0 (C^4 isoxazolone), 115.6 (J=21.3 Hz, C^2/C^6 4FPh). 123.3, 128.5 (J=3.1 Hz, C^4 4FPh). 129.3 (J=7.9 Hz, C^3/C^5 4FPh), 139.2, 147.9, 158.2 (C^3 isoxazolone), 161.1 (J= 240.0 Hz, C^1 4FPh), 172.3 (C^5 isoxazolone).

Anal. ($C_{14}H_9FN_2O_2$) C, H, N, O.

N-alkylation of 9. General procedure II.

To a suspension of **9** (1 eq) in DMF (2ml/1mmol of compound **9**) Et_3N (1.8eq) was added and the reaction mixture refluxed for 2h. The cooled reaction mixture (RT) was then combined with alkyl halide (1.5 eq) (if not specified elsewise, the chloride was used) and stirred for 3h at RT. The reaction was then worked up following method a, b or c depending on the nature of the residue.

Method a. The reaction mixture was combined with ethyl acetate and the resulting precipitate was separated by filtration and crystallized from an appropriate solvent.

Method b. The solvent was removed under vacuum. The residue was then purified by chromatography on SiO_2.

Method c. The solvent was removed under vacuum. The residue was then purified by crystallization from an appropriate solvent.

2-ethyl-4-(4-fluoro-phenyl)-3-(pyridin-4-yl)isoxazol-5(2*H*)-one (10a)

10a was synthesized according to the general procedure II reacting 120mg (1.8mmol) of ethyl chloride a with 256mg (1mmol) of **9**. Purification following method b (eluent MeOH) afforded the title compound.

$C_{16}H_{13}FN_2O_2$ (MW 284.1)

Yield: 50mg, η%: 10%

Melting point: 175°C

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.53 (s, 3H, -CH_3), 4.56 (q, 2H, -CH_2-), 6.93-7.18 (m, 2H, 4F-Ph), 7.21-7.25 (m, 2H, 4F-Ph) 7.99 (dd, J=0.5/1.4Hz; 2H), Py), 8.99 (dd, J=0.5/1.4Hz; 2H), Py).

^{13}C-NMR (DMSO-d6): δ (ppm) 14.3, 65.5, 82.8 (C^4 isoxazolone), 114.9 (J=21.3 Hz, C^2/C^6 4FPh), 125.6, 128.4 (J=3.1 Hz, C^4 4FPh), 131.3 (J=7.9 Hz, C^3/C^5 4FPh), 144.7, 149.9 (C^3 isoxazolone), 153.1 (J=240.0 Hz, C^1 4FPh), 176..0 (C^5 isoxazolone).

Anal. ($C_{16}H_{13}FN_2O_2$) C, H, N, O.

4-(4-Fluoro-phenyl)-2-isopropyl-3-pyridin-4-yl-2*H*-isoxazol-5-one (10b)

10b was synthesized according to the general procedure II reacting 1.27g (16.2mmol) of 2-chloro-propane with 2.32 g (9.0 mmol) of **9**. Purification following method a (crystallized from methanol) afforded the title compound.

$C_{17}H_{15}FN_2O_2$ (MW 298.11)

Yield: 1.34 g , η%: 50%

Melting point: 166.6°C

FTIR: 3359, 3009.8, 2674, 1614, 1515, 1214, 1156, 838

^{1}H-NMR (DMSO-d_6): δ(ppm) 1.58 (d, J=2.1Hz, 6H), 5.00 (m, 1H), 6.85-6.94 (m, 2H, 4FPh), 7.18-7.25 (m, 2H, 4FPh), 87.3 (d, J=1.7 Hz, 2H), 8.55 (d, J=1.7 Hz, 2H).

^{13}C-NMR (DMSO-d_6): δ(ppm) 22.5, 63.9, 82.8 (C^4 isoxazolone), 114.9 (J= 18.9 Hz, C^2/C^6 4FPh), 128.5 (J=8.3 Hz, C^3/C^5 4FPh), 131.3 (J=2.8 Hz, C^4 4FPh), 143.2, 150.0 (C^3 isoxazolone), 156.8, 158.9 (J=251.0 Hz, C^1 4FPh), 76.0 (C^5 isoxazolone).

Anal. ($C_{17}H_{15}FN_2O_2$) C, H, N, O.

2-Cyclopropylmethyl-4-(4-fluoro-phenyl)-3-pyridin-4-yl-2*H*-isoxazol-5-one (10c)

10c was synthesized according to the general procedure II reacting 407 mg (4.5 mmol) of chloromethyl-cyclopropane with 620 mg (2.5 mmol) of **9**. Purification following method a (crystallized from methanol) afforded the title compound as crystals.

$C_{17}H_{14}FN_2O_2$ (MW 297.1)

Yield: 371 mg , η%: 50%

Melting point: 155°C

FTIR: 3359, 3009.8, 2674, 1614, 1515, 1214, 1156, 838

^{1}H-NMR (DMSO-d_6): δ(ppm) 0.56-0.66 (m, 4H), 1.23-1.43 (m, 1H), 4.45 (d, 2H), 6.94-7.03 (m, 2H), 7.18-7.25 (m, 2H), 8.00 (d, 2H), 9.02 (d, 2H).

^{13}C-NMR ($CDCl_3$): δ(ppm) 4.4, 8.9, 46.0, 82.7 (C^4 isoxazolone), 114.9 (J=18.9 Hz, C^2/C^6 4FPh), 125.6, 128.4 (J=8.3 Hz, C^3/C^5 4FPh), 131.4 (J=2.8 Hz, C^4 4FPh), 144.7, 150.1 (C^3 isoxazolone), 156.4, 159.1 (J=251.0 Hz, C^1 4FPh), 175.9(C^5 isoxazolone).

Anal. ($C_{17}H_{14}FN_2O_2$) C, H, N, O.

4-(4-Fluoro-phenyl)-2-oxiranylmethyl-3-pyridin-4-yl-2*H*-isoxazol-5-one (10d)

10d was synthesized according to the general procedure II reacting 1.66 mg (18 mmol) of 2-chloromethyl-oxirane with 2.56 g (10 mmol) of **9**. Purification following method a (no further crystallization was required) afforded the title compound.

$C_{17}H_{13}FN_2O_3$ (MW 312.09)

Yield: 2.34 g , η%: 75%

Melting point: 187°C

FTIR: 3027, 2839, 2740, 1619, 1515, 1322, 1223, 968, 832

^{1}H-NMR (DMSO-d_6): δ(ppm) 3.63-3.73 (m, 1H), 4.14-4.17 (m, 1H), 4.75-4.83 (m, 1H), 5.98 (d, 2H), 6.92-6.98 (m, 2H, 4FPh), 7.17-7.25 (m, 2H, 4FPh), 8.03 (d, J=1.5 Hz, 2H, Py), 8.87 (d, J=1.6 Hz, 2H, Py).

^{13}C-NMR (DMSO-d_6): δ(ppm) 47.0, 63.6, 82.6 (C^4 isoxazolone), 114.9 (J=20.1 Hz, C^2/C^6 4FPh), 125.3 (J=7.9 Hz, C^3/C^5 4FPh), 128.3 (J=2.8 Hz, C^4 4FPh), 131.4, 145.8, 150.3 (C^3 isoxazolone), 156.4, 159.1 (J=249.0 Hz, C^1 4FPh), 176.0 (C^5 isoxazolone).

Anal. ($C_{17}H_{13}FN_2O_3$) C, H, N, O.

4-(4-Fluoro-phenyl)-2-methoxymethyl-3-pyridin-4-yl-2*H*-isoxazol-5-one (10e)

10e was synthesized according to the general procedure II reacting 1.56 mg (19.6 mmol) of chloro-methoxy-methane with 2.8 g (10.9mmol) of **9**. Purification following method b (eluent: DCM:acetone=20:1) afforded the title compound.

$C_{16}H_{13}FN_2O_3$ (MW 300.09)

Yield: 1.47 g , η%: 45%

Melting point: 198°C

FTIR: 3454, 2934, 1730, 1584, 1511, 1232, 1081, 841, 823

^{1}H-NMR (DMSO-d_6): δ(ppm) 3.38 (s, 3H, -CH_3), 4.90 (s, 2H, CH_2), 7.11-7.31 (m, 4H), 7.45 (d, J: 1.6Hz, 2H, Py), 8.75 (d, J: 1.6Hz, 2H, Py).

^{1}H-NMR (MeOD): δ(ppm) 3.41 (s, 3H, -CH_3), 4.91 (s, 2H, CH_2), 7.01-7.28 (m, 2H), 7.29-7.35 (m, 2H), 7.50 (d, J=1.6 Hz, 2H, Py), 8.76 (d, J=1.6Hz, 2H, Py).

^{13}C-NMR ($CDCl_3$): δ(ppm) 58.0, 80.8, 105.4 (C^4 isoxazolone), 115.9 (J=19.5 Hz, C^2/C^6 4FPh), 123.2, 124.8 (J=2.8 Hz, C^4 4FPh), 130.7 (J=7.3 Hz, C^3/C^5 4FPh), 134.3, 150.8, 158.7 (C^3 isoxazolone), 161.9 (J=251.0 Hz, C^1 4FPh), 168.6 (C^5 isoxazolone).

Anal. ($C_{16}H_{13}FN_2O_3$) C, H, N, O.

4-(4-Fluoro-phenyl)-2-(2-methoxy-ethyl)-3-pyridin-4-yl-2*H*-isoxazol-5-one (10f)

10f was synthesized according to the general procedure II reacting 663 mg (7.0 mmol) of 1-Chloro-2-methoxy-ethane with 1 g (3.9 mmol) of **9**. Purification following method b (eluent: DCM:acetone=20:1) afforded the title compound.

$C_{17}H_{15}FN_2O_3$ (MW 314.11)

Yield: 100 mg , η%: 10%

Melting point: 138.4°C

FTIR: 3445, 3051, 2897, 1735, 1620, 1510, 1410, 1223, 1118, 1012, 819, 835.

EI: 314.1 [M], 269, 211, 121

^{1}H-NMR (DMSO-d_6): δ(ppm) 3.26 (s, 3H, -CH_3), 3.63 (t, 2H,-CH_2-), 4.48 (t, 2H, -CH_2-), 7.16-7.24 (m, 2H), 8.01(d, J=1.6 Hz, 2H, Py), 8.97(d, J=1.6 Hz, 2H, Py)

^{13}C-NMR ($CDCl_3$): δ(ppm) 29.7, 40.2, 69.8, 105.1 (C^4 isoxazolone), 114.9 (J=18.9 Hz, C^2/C^6 4FPh), 125.5, 128.2 (J=8.3 Hz, C^3/C^5 4FPh), 131.4 (J=2.8 Hz, C^4 4FPh), 145.3, 150.3 (C^3 isoxazolone), 158.5 (J=251.0 Hz, C^1 4FPh), 175.9 (C^5 isoxazolone).

4-(4-Fluoro-phenyl)-2-(2-methylsulfanyl-ethyl)-3-pyridin-4-yl-2*H*-isoxazol-5-one (10g)

10g was synthesized according to the general procedure II reacting 774 mg (7.0 mmol) of 1-Chloro-2-methylsulfanyl-ethane with 1 g (3.9 mmol) of **9**. The solvent was removed under vacuum and the residue taken up with ice/water. NaOH 20% was added and pH adjusted to value 9. Filtration afforded the title compound as a solid.

$C_{17}H_{15}FN_2O_2S$ (MW 330.08)

Yield: 1.17 g , η%: 30%

Melting point: 188.2°C

FTIR: 2997, 2912, 1628, 1515, 1484, 1325, 1215, 961, 837, 757.

^{1}H-NMR (DMSO-d_6): δ(ppm) 2.10 (s, 3H), 3.09 (t, 2H), 4.75 (t, 2H), 6.93-7.02 (m, 2H), 7.16-7.24 (m, 2H), 8.01(d, J=1.6 Hz,2H), 8.97(d, J=1.6 Hz, 2H).

^{13}C-NMR ($CDCl_3$): δ(ppm) 14.7, 34.1, 58.8, 82.7 (C^4 isoxazolone), 114.9 (J=18.9 Hz, C^2/C^6 4FPh), 125.5, 128.2 (J=8.3 Hz, C^3/C^5 4FPh), 131.4 (J=2.8 Hz, C^4 4FPh), 145.3, 150.3 (C^3 isoxazolone), 158.5 (J= 251.0 Hz, C^1 4FPh), 175.9 (C^5 isoxazolone).

Anal. ($C_{17}H_{15}FN_2O_2S$) C, H, N, O.

4-(4-Fluoro-phenyl)-2-(2-hydroxy-ethyl)-3-pyridin-4-yl-2*H*-isoxazol-5-one (10h)

10h was synthesized according to the general procedure II reacting 1.12 g (14.4 mmol) of 2-chloro-ethanol with 2 g (7.8 mmol) of **9**. Purification following method c (crystallization from acetone) afforded the title compound.

$C_{16}H_{13}FN_2O_3$ (MW 300.09)

Yield: 600 mg , η%: 30%

FTIR: 3375, 2979, 2603, 2497, 1606, 1474, 1397, 1171, 1035, 807

^{1}H-NMR (DMSO-d_6): δ(ppm) 1.22 (t, 3H), 3.05 (q, 2H), 5.70 (s, exchangeable), 6.85-6.94 (m, 2H), 7.18-7.25 (m, 2H), 87.3 (d, 2H), 8.55 (d, 2H).

^{13}C-NMR ($CDCl_3$): δ(ppm) 62.0, 82.9 (C^4 isoxazolone), 114.6 (J=18.9 Hz, C^2/C^6 4FPh), 123.0, 127.7 (J=8.3 Hz, C^3/C^5 4FPh), 131.9 (J=2.8 Hz, C^4 4FPh), 141.9, 150.0 (C^3 isoxazolone), 158.8, 159.4 (J= 251.0 Hz, C^1 4FPh), 175.8 (C^5 isoxazolone).

Anal. ($C_{16}H_{13}FN_2O_3$) C, H, N, O.

4-(4-Fluoro-phenyl)-2-(3-hydroxy-propyl)-3-pyridin-4-yl-2*H*-isoxazol-5-one (10i)

10i was synthesized according to the general procedure II reacting 1.32 g (14.4 mmol) of 3-chloro-propan-1-ol with 2 g (7.8 mmol) of **9**. Purification following method c (crystallization from acetone) afforded the title compound.

$C_{17}H_{15}FN_2O_3$ (MW 314.11)

Yield: 734 mg , η%: 30%

MS: 315 [M+1]

^{1}H-NMR (DMSO-d_6): δ(ppm) 1.22 (t, 2H), 3.55 (q, 2H), 4.14 (t, 2H), 5.70 (s, exchangeable), 6.85-6.94 (m, 2H), 7.18-7.25 (m, 2H), 87.3 (d, J=1.3 Hz, 2H), 8.55 (d, J=1.3 Hz,2H).

^{13}C-NMR ($CDCl_3$): δ(ppm) 35.6, 45.8, 57.7, 82.3 (C^4 isoxazolone), 114.6 (J=18.9 Hz, C^2/C^6 4FPh), 123.0, 127.4 (J=8.3 Hz, C^3/C^5 4FPh), 130.6 (J=2.8 Hz, C^4 4FPh), 142.1, 150.0 (C^3 isoxazolone), 161.0, 161.2 (J=251.0 Hz, C^1 4FPh), 175.8 (C^5 isoxazolone).

Anal. ($C_{17}H_{15}FN_2O_3$) C, H, N, O.

4-(4-fluoro-phenyl)-2-((2-methoxyethoxy)methyl)-3-(pyridin-4-yl)isoxazol-5(2*H*)-one (10l)

10l was synthesized according to the general procedure II reacting 896 mg (7.2 mmol) of 1-chloromethoxy-2-methoxy-ethane with 1 g (3.9 mmol) of **9**. Purification following method b (eluent: ethylacetate) afforded the title compound as oil.

$C_{18}H_{17}FN_2O_4$ (MW 344.12)

Yield: 500 mg , η%: 36%

^{1}H-NMR (DMSO-d_6): δ(ppm) 3.21 (s, 3H), 3.37 (m, 2H), 3.68 (m, 2H), 4.88 (s, 2H), 6.84-6.92 (m, 2H), 7.17-7.26 (m, 5H).

^{13}C-NMR (DMSO-d_6): δ(ppm) 58.7, 70.9, 71.6, 80.0 (C^4 isoxazolone), 107.3, 115.5 (J= 20.1 Hz, C^2/C^6 4FPh), 122.9, 123.8 (J=7.9 Hz, C^3/C^5 4FPh), 129.9 (J=2.8 Hz, C^4 4FPh), 134.9, 150.8 (C^3 isoxazolone), 158.0, 162.1 (J=249.0 Hz, C^1 4FPh), 168.7 (C^5 isoxazolone).

Anal. ($C_{18}H_{17}FN_2O_4$) C, H, N, O.

4-(4-Fluoro-phenyl)-2-(2-piperidin-1-yl-ethyl)-3-pyridin-4-yl-2*H*-isoxazol-5-one (10m)

10m was synthesized according to the general procedure II reacting 1.32 g (7.2 mmol) of 1-(2-chloroethyl)piperidine HCl with 1 g (3.9 mmol) of **9**. The solvent was removed under vacuum and the residue taken up with ice/water. NaOH 20% was added and pH adjusted to value 9, the aqueous solution was then extracted with EtOAc. The combined organic phases were concentrated under reduced pressure. Purification of the residue by preparative TLC (eluent MeOH) afforded the title compound.

$C_{21}H_{22}FN_3O_2$ (MW 367.17)

Yield: 20 mg , η%: 2%

Melting point: 140.8 °C

FTIR: 3506, 2938, 2805, 1633, 1513, 1481, 1221, 963, 830, 750, 674

^{1}H-NMR (DMSO-d_6): δ(ppm) 1.22 (m,6H), 2.68 (t, J=6,7 Hz, 4H), 2.75 (t, J=8.1 Hz,2H), 4.62 (t, J=7.9 Hz, 2H), 6.91 (m,2H, 4FPh), 7.15-7.22 (m,2H, 4FPh), 7.97 (d, J=1.5 Hz, 2H, Py), 8.88 (d, J=1.5 Hz, 2H, Py).

^{13}C-NMR (DMSO-d_6): δ(ppm) 24.1, 25.9, 54.0, 57.7, 58.0, 82.6 (C^4 isoxazolone), 114.8 (J= 18.9 Hz, C^2/C^6 4FPh), 125.1, 128.1 (J=8.3 Hz, C^3/C^5 4FPh), 131.4 (J=2.8 Hz, C^4 4FPh), 145.4, 149.9 (C^3 isoxazolone), 156.5, 162.5 (J=251.0 Hz, C^1 4FPh), 175.9 (C^5 isoxazolone).

Anal. ($C_{21}H_{22}FN_3O_2$) C, H, N, O.

2-(2-(4-(4-fluoro-phenyl)-5-oxo-3-(pyridin-4-yl)isoxazol-2(5*H*)-yl)ethyl)isoindoline-1,3-dione (10n)

10n was synthesized according to the general procedure II reacting 1.50 g (7.2 mmol) of N-(2-bromoethyl)phtalimide with 1 g (3.9 mmol) of **9**. Purification following method b (eluent

DCM: acetone=20:1) afforded the title compound, which was then further purified by crystallization from methanol.

$C_{24}H_{16}FN_3O_4$ (Mw 429.11)

Yield: 350 mg , η%: 21%

Melting point: 165 °C

FTIR: 3427, 3055, 2098, 1771 (imide ring), 1709 (imide ring), 1621, 1600, 1511, 1392, 1038, 836, 722

^{1}H-NMR (DMSO-d_6): δ(ppm) 4.02 (t, 2H, J=1.3 Hz), 4.71 (t, 2H, J=1.3 Hz), 7.07-7.15 (m, 4H, 4FPh), 7.50 (d, 2H, J=0.37 Hz, J=1.21 Hz, Py), 7.80-7.88 (m, 4H, 4FPh), 8.74 (dd, 2H, J=0.37/ 1.21 Hz, Py).

^{13}C-NMR (DMSO-d_6): δ(ppm) 37.4, 69.6, 93.8 (C^4 isoxazolone), 115.9 (J=21.5 Hz, C^2/C^6 4FPh), 123.5, 123.8, 124.0 (J=2.1 Hz, C^4 4FPh), 131.3 (J=8.3 Hz, C^3/C^5 4FPh), 131.8, 134.9, 139.7, 148.1 (C^3 isoxazolone), 161.8, 162.1 (J=251.0 Hz, C^1 4FPh), 168.0, 168.9 (C^5 isoxazolone).

Anal. ($C_{24}H_{16}FN_3O_4$) C, H, N, O.

4-(4-Fluoro-phenyl)-2-(1-phenyl-ethyl)-3-pyridin-4-yl-2*H*-isoxazol-5-one (10o)

10o was synthesized according to the general procedure II reacting 1.00 g (7.2 mmol) of (1-chloro-ethyl)-benzene with 1 g (3.9 mmol) of **9**. Purification following method a (crystallized from methanol) afforded the title compound.

$C_{22}H_{17}FN_2O_2$ (MW 360.13)

Yield: 912 mg , η%: 60%

Melting point: 160.5 °C

FTIR: 2929, 1751, 1735, 1633, 1453, 1225, 979, 839, 751, 700

^{1}H-NMR (DMSO-d_6): δ(ppm) 2.01 (d, 3H); 5.09 (q, 1H), 7.08-7.66 (m, 9H), 8.24 (d, J=1.5 Hz, 2H, Py), 9.52 (d, J=1.5 Hz, 2H, Py).

^{13}C-NMR (DMSO-d_6): δ(ppm) 21.1, 70.3 (C^4 isoxazolone), 107.4, 116.1 (J=18.9 Hz, C^2/C^6 4FPh), 123.9, 128.1, 128.8 (J=8.3 Hz, C^3/C^5 4FPh), 129.6, 131.0 (J=2.8 Hz, C^4 4FPh), 137.3, 143.1, 145.3, 151.3 (C^3 isoxazolone), 156.8 (J=251.0 Hz, C^1 4FPh), 162.1, 168.4 (C^5 isoxazolone).

Anal. ($C_{22}H_{17}FN_2O_2$) C, H, N, O.

4-(4-fluoro-phenyl)-3-(pyridin-4-yl)-2-tosylisoxazol-5(2*H*)-one (10p)

10p was synthesized according to the general procedure II reacting 1.36 g (7.2 mmol) of 4-Methyl-benzenesulfonyl chloride with 1 g (3.9 mmol) of **9**. Purification following method c (crystallization from acetone) afforded the title compound.

$C_{21}H_{15}FN_2O_4S$ (MW 410.07)

Yield: 50 mg, η%: 3%

mp (°C): 198°C

FTIR: 3053, 1770, 1638, 1590, 1509, 1384, 1228, 1173, 1158, 954, 848, 812, 690

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.51 (s, 3H, -CH_3), 6.96-7.26 (m, 4H), 7.37-7.43 (m, 4H), 7.64 (dd, J=0.5/1.4 Hz; 2H), Py), 8.78 (dd, J=0.5/1.4 Hz; 2H), Py).

^{13}C-NMR (DMSO-d_6): δ (ppm) 21.8, 114.9 (C^4 isoxazolone), 116.1 (J=19.0 Hz, C^2/C^6 4FPh), 121.4 (J=3.5 Hz, C^4 4FPh), 121.9, 125.8, 126.9, 127.6, 130.3 (J=8.4 Hz, C^3/C^5 4FPh), 140.5, 147.6, 149.9, 155.6 (C^3 isoxazolone), 163.0 (J=251.0 Hz, C^1 4FPh), 167.0 (C^5 isoxazolone).

Anal. ($C_{21}H_{15}FN_2O_4S$) C, H, N, O.

2-acetyl-4-(4-fluoro-phenyl)-3-(pyridin-4-yl)isoxazol-5(2*H*)-one (10q)

To a solution of 1 g (3. 9mmol) of **9** in 20 mL of acetic anhydride 48 mg (0.4 mmol) of DMAP and 0.2 g (3.9 mmol) of Na_2CO_3.were added. The reaction was completed after 12 h of reflux. The residual acetic anhydride then was distilled off, the residue taken up with EtOAc and washed with H_2O. The organic layer was collected and concentrated under vacuum affording **10q**.

$C_{16}H_{11}FN_2O_3$ (MW 298.08)

Yield: 300 mg , η%: 50%

Melting point: 118 °C

ESI-TOF: Measured: 258.0741, 257.0710, Calculated: 258.0752, 257.0721

FTIR: 3071, 3040, 1748, 1720, 1584, 1513, 1300, 963, 837, 819

^{1}H-NMR (DMSO-d_6): δ(ppm) 2.49 (s, 3H), 6.92-7.00 (m, 2H, 4FPh), 7.19-7.32 (m, 4H, 4FPh+Py), 8.72 (d, 2H, J=1.3 Hz, Py).

^{13}C-NMR (DMSO-d_6): δ(ppm) 22.7, 108.6 (C^4 isoxazolone), 115.8 (J=21.5 Hz, C^2/C^6 4FPh), 122.2 (J=2.1 Hz, C^4 4FPh), 123.0, 130.3 (J=8.3 Hz, C^3/C^5 4FPh), 135.9, 150.0, 162.4 (J=251.0 Hz, C^1 4FPh), 164.6 (C^3 isoxazolone) , 165.1, 174.2 (C^5 isoxazolone).

Anal. ($C_{16}H_{11}FN_2O_3$) C, H, N, O.

General Procedure III

To a solution of **9** (1eq) in DMF (1ml/ 1mmol of **9**) sodium hydride (1eq) and the appropriate isocyanate (1.5eq) were added. The reaction mixture was stirred for 12h at RT, and then combined with water. Filtration of the formed precipitate afforded the title compound. A further purification step was not necessary.

N-ethyl-4-(4-fluoro-phenyl)-5-oxo-3-(pyridin-4-yl)isoxazole-2(5*H*)-carboxamide (10r)

10r was synthesized according to the general procedure III starting from 1 g (3.9 mmol) of **9**, and 0.4 g (5.8 mmol) of ethylisocyanate.

$C_{17}H_{14}FN_3O_3$ (MW 327.1)

Yield: 293mg, η%: 23%

Melting point: 200 °C

FTIR: 3072, 2923, 2854, 1750, 1723, 1579, 1508, 1219, 954, 841, 826.

^{1}H- NMR (DMSO-d_6): δ (ppm) 1.03 (t, 3H), 3.08 (m, 2H), 7.08-7.25 (m, 4H, 4FPh), 7.45 (d, 2H, J=1.6 Hz, Py), 8.45 (t, 1H, exch.), 8.65 (d, 2H, J=1.6 Hz, Py).

^{13}C-NMR (DMSO-d_6): δ (ppm) 14.9, 22.5, 105.5 (C^4 isoxazolone), 115.9 (J=21.3 Hz, C^2/C^6 4FPh), 123.0 (J=3.1 Hz, C^4 4FPh), 124.2, 131.0 (J=7.9 Hz, C^3/C^5 4FPh), 136.9, 148.2, 149.9, 154.4 (C^3 isoxazolone), 161.9 (J=240.0 Hz, C^1 4FPh), 166.2 (C^5 isoxazolone).

Anal. ($C_{17}H_{14}FN_3O_3$) C, H, N, O.

2-acetyl-4-(4-fluoro-phenyl)-3-(pyridin-4-yl)isoxazol-5(2*H*)-one (10s)

10s was synthesized according to the general procedure III starting from 1 g (3.9 mmol) of **9**, and 0.85 g (5.8 mmol) of 4-fluoro-phenylisocyanate.

$C_{21}H_{13}F_2N_3O_3$ (MW 393.09)

Yield: 767mg, η%: 50%

Melting point: 118 °C

FTIR: 3293, 2457, 2111, 1628, 1601, 1563, 1507, 1208, 828

^{1}H- NMR (DMSO-d_6): δ (ppm) 7.10-7.51 (m, 10H), 8.70 (d, J=0.4 Hz, 2H), 9.74 (s, NH).

^{13}C-NMR (DMSO-d_6): δ (ppm) 115.3 (J=10.1 Hz, C^2/C^6 4FPh´´), 115.7 (J=9.0 Hz, C^2/C^6 4FPh´), 117.0 (C^4 isoxazolone), 123.1, 126.6(J=7.9 Hz, C^4 4FPh´´), 128.5 (J=´8.9 Hz, C^4 4FPh´), 130.2 (J=3.9 Hz, C^3/C^5 4FPh´´), 136.0 (J=2.9 Hz, C^3/C^5 4FPh), 139.1, 158.6 (C^3 isoxazolone), 159.5 (J=241.3 Hz, C^1 4FPh), 161.0 (J=242.7 Hz, C^1 4FPh), 171.8 (C^5 isoxazolone), 180.7.

Anal. ($C_{21}H_{13}F_2N_3O_3$) C, H, N, O.

N,4-bis(4-fluoro-phenyl)-5-oxo-3-(pyridin-4-yl)isoxazole-2(5*H*)-carbothioamide (10t)

10t was synthesized according to the general procedure III starting from 1 g (3.9 mmol) of **9**, and 0.90 g (5.8 mmol) of 4-fluoro-phenylisothiocyanate.

$C_{21}H_{13}F_2N_3O_2S$ (MW 409.07)

Yield: 334mg, η%: 21%

Melting point: 195 °C

FTIR: 3217, 3095, 3056, 3020, 2103, 1741 (vw), 1630, 1599, 1584, 1538, 1500, 1227,827.

^{1}H-NMR (DMSO-d_6): δ (ppm) 7.10-7.29 (m, 10H), 8.70 (dd, J=0.4/1.7 Hz, 2H, Py), 9.74 (exchangeable, NH).

^{13}C-NMR (DMSO-d_6): δ (ppm) 115.2 (J=10.1 Hz, C^2/C^6 4FPh´´), 115.7 (J= 9.0 Hz, C^2/C^6 4FPh´), 117.2 (C^4 isoxazolone), 123.1, 126.6 (J=7.9 Hz, C^4 4FPh´´), 128.5 (J=8.9 Hz, C^4 4FPh´), 130.2 (J=3.9 Hz, C^3/C^5 4FPh´´), 136.0 (J=2.9 Hz, C^3/C^5 4FPh), 139.1, 149.3, 158.5 (C^3 isoxazolone), 159.5 (J=241.3 Hz, C^1 4FPh), 161.0 (J=242.7 Hz, C^1 4FPh), 171.8 (C^5 isoxazolone), 180.7.

Anal. ($C_{21}H_{13}F_2N_3O_2S$) C, H, N, O.

Ethyl3-(4-(4-fluoro-phenyl)-5-oxo-3-(pyridin-4-yl)-2,5-dihydroisoxazole-2-carboxamido)propanoate (10u)

10u was synthesized according to the general procedure III starting from 1 g (3.9 mmol) of **9**, and 0.82 g (5.8 mmol) of ethyl-3-isocyanato propionate. The compound was then purified by column chromatography on SiO_2 (eluent: acetone/methanol=10/1).

$C_{20}H_{18}FN_3O_5$ (MW 399.12)

Yield: 100mg, η%: 18%

Melting point: 220 °C

MS: 400 [M+1]

^{1}H- NMR (DMSO-d_6): δ (ppm) 1.13 (t, J= 8.6 Hz, 3H), 2.4 (t, J=2.4 Hz, 2H), 3.2 (q, 2H), 4.02 (q, J=7.9 Hz, 2H), 6.84-6.93 (m, 2H, 4FPh), 7.12-7.21 (m, 2H, 4FPh), 7.3 (d, J=1.5 Hz, Py), 8.5 (d, J=1.5 Hz, Py).

Anal. ($C_{20}H_{18}FN_3O_5$) C, H, N, O.