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2-Aryl-3-arylaminoisoxazol-5(2*H*)-ones as sources of indoles and imidazo[1,2-*a*]pyridines

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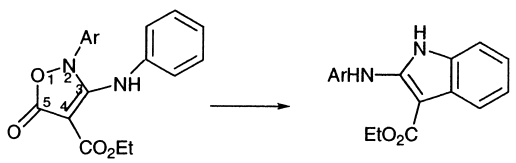
Abstract—2-Aryl-3-arylaminoisoxazol-5(2*H*)-ones undergo solvolysis to form 1,3-dipoles that undergo intramolecular cyclisation to form either imidazopyridines or indoles. The mode of cyclisation is controlled by the electronegativity of the aryl substituents. © 2002 Published by Elsevier Science Ltd.

1. Introduction

We have recently reported[1] that the reaction of 2-aryl-3-arylaminoisoxazolones (**1**) with triethylamine leads to the formation of indoles and carbon dioxide, an outcome that is formally the same as that achieved by photolysis or pyrolysis[2] (Scheme 1). The evidence for the indole structure, rather than that of an isomer, rested on the number of aryl proton signals visible in the ^{1}H NMR spectrum. However, the unusual mechanism proposed suggested to us that further investigation was warranted, particularly by the introduction of both electron-donating and withdrawing substituents into the 3-arylamino ring.

2. Discussion

The required analogues of isoxazolones (**1**) were synthesised by *N*-arylation of the 2*H*-isoxazolones, which in turn were made by a modification of the procedure of Worrall.[3,4] Thus, the reaction of the sodium salt of diethyl malonate in THF with various arylisothiocyanates gave the thiocarbamates (**2**) in good yield, and these were converted to the corresponding isoxazolone (**3**) by reaction with 2 equiv. of hydroxylamine (Scheme 2). As expected, the presence of electron withdrawing groups in the isothiocyanate facilitated both the reaction with the malonate and that with hydroxylamine. The highly acidic isoxazolones (**3**) formed strong complexes with H_2S, as shown by the microanalytical data, and the release of gas on melting. Since the reaction mixture from the formation of (**3**) was acidified, it would appear that the adduct is more likely to be a H-bonded complex than a salt. Similar strong association with water was also noted. *N*-arylation of (**3**) with activated chloroheterocycles then gave the desired starting materials (**4**) (Scheme 2). While the formation of (**4**) appears trivial, the reaction generally proceeded best in the absence of solvent, by heating the required reagents in a sealed tube at 130°C for an hour. The failure to achieve reaction by prior formation of the salt of (**3**), formed readily with potassium carbonate, or the use of dipolar aprotic solvents, supports our hypothesis that the reacting species is the salt (**5**).



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Scheme 1.

The rearrangement of (**4a**), as shown in Scheme 1, proceeded in 68% yield in refluxing ethanol for 1 h in the presence of triethylamine. While the presence of a base was required, other bases were trialled and gave the same product in varying yields: pyrrolidine 38%, diisopropylethylamine 46%, and potassium carbonate 67%. The use of sodium ethoxide or potassium *t*-butoxide, even at room temperature, led to the formation of a plethora of products. In practice, the use of potassium carbonate led to the cleanest products, and was subsequently adopted.

All 2-arylisoxazolones (**4a**-**4g**) reacted with potassium carbonate in ethanol, but those with electron withdrawing

Keywords: isoxazolones; 1,3-dipolar intermediates; indoles; imidazopyridines.

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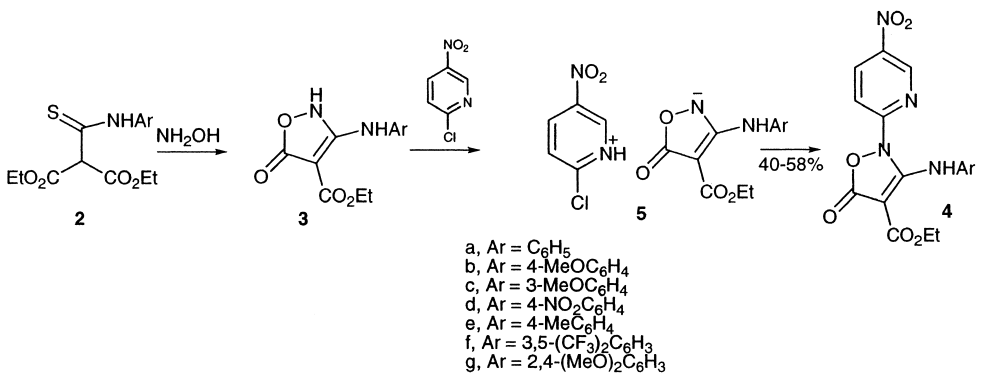


Scheme 2.

groups, **4d** and **4f**, reacted more slowly than the others, and **4d** returned mainly starting material. The major product in each case had similar spectral properties to those of the product from **4a**, which had been assigned the indole structure.[1] Isoxazolone (**4b**) gave significant amounts of a second product, whose spectral properties were more consistant with those expected for the indole. Thus, the major product in each case had its structure reassigned as the imidazo[1,2-*a*]pyridine (Scheme 3), and this assignment has been confirmed by a single crystal X-ray structure of the originally isolated product (**6a**).[5] The imidazopyridine structure (**6b**) could now clearly be deduced from the similarity of the coupling pattern of the protons in the methoxyphenyl ring to that in the starting material (**4b**), and the indole structure (**7b**) had proton couplings similar to those of the nitropyridyl ring in (**4b**).

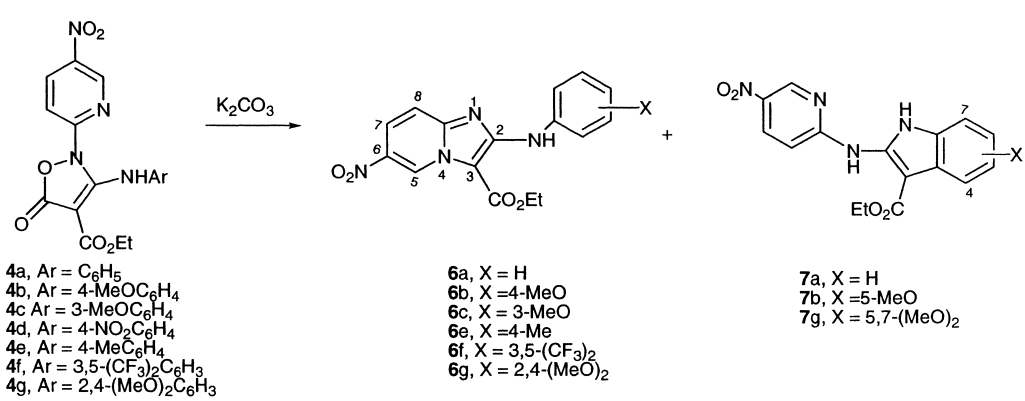
With a number of imidazopyridine structures in hand, the reason for the original misassignment was further investigated. The ^{1}H NMR spectra of all compounds (**6**) showed H-7 to have *meta* coupling with H-5, but in none could the resonance for H-5 be clearly observed. On the addition of TFA, however, the very broad peak for H-5 at 9.9 ppm became quite sharp, and a COSY spectrum now confirmed its *meta* coupling with H-7. The reason for the extreme broadening of this peak is unknown, though quadrupole coupling with *N*-4 is implicated; the X-ray structure of **6a**[5] did not show any unusual interactions.

The proportion of indole (**7**) was highest for the 2,4-dimethoxyphenyl analogue (**4g**) (**7g**/**6g**, 2:3). The change in reaction pathway, from imidazopyridine towards indole, with the presence of *ortho* or *para* methoxyl groups, is reminiscent of that observed in the rearrangement of the nitrene generated by pyrolysis of anthranils.[6]

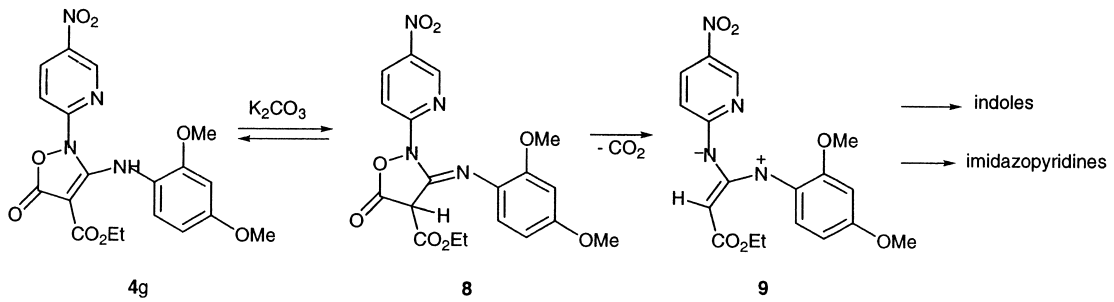
Since the alkoxyphenyl ring does not undergo rearrangement in the present case, we believe the change in product composition in the presence of good electron donating groups is consistent with the pathway shown in Scheme 4 below. This postulates that the weak base favours tautomerisation of **4** to the H-3 tautomer (**8**) or the 5-hydroxy tautomer, the solvolysis of either being the key step, giving a 1,3-dipolar intermediate (**9**), the electron distribution in which will depend vitally on charge delocalisation by substituent groups. The intermediate (**9**) is readily convertible to either the imidazopyridine or the indole. When the anion of isoxazolone (**3a**) was methylated, the product (**10**) could not be induced to undergo similar base catalysed reactions, indicating its solvolytic stability. Nishiwaki and co-workers have proposed that 2-methyl-4-nitroisoxazolone (**11**) is synthetically equivalent to the 1,3-dipole (**12**), although the latter was not postulated as an intermediate.[7]

There is no spectral evidence to suggest that tautomers of **4** have significant populations, and while 5-hydroxy tautomers have previously been proposed to account for the products from photochemical reactions,[2] in those instances homolytic cleavage of the N–O bond had occurred.

In order to investigate the possibility that solvolysis required only a polar solvent, **4g** was refluxed for extended periods of



Scheme 3.

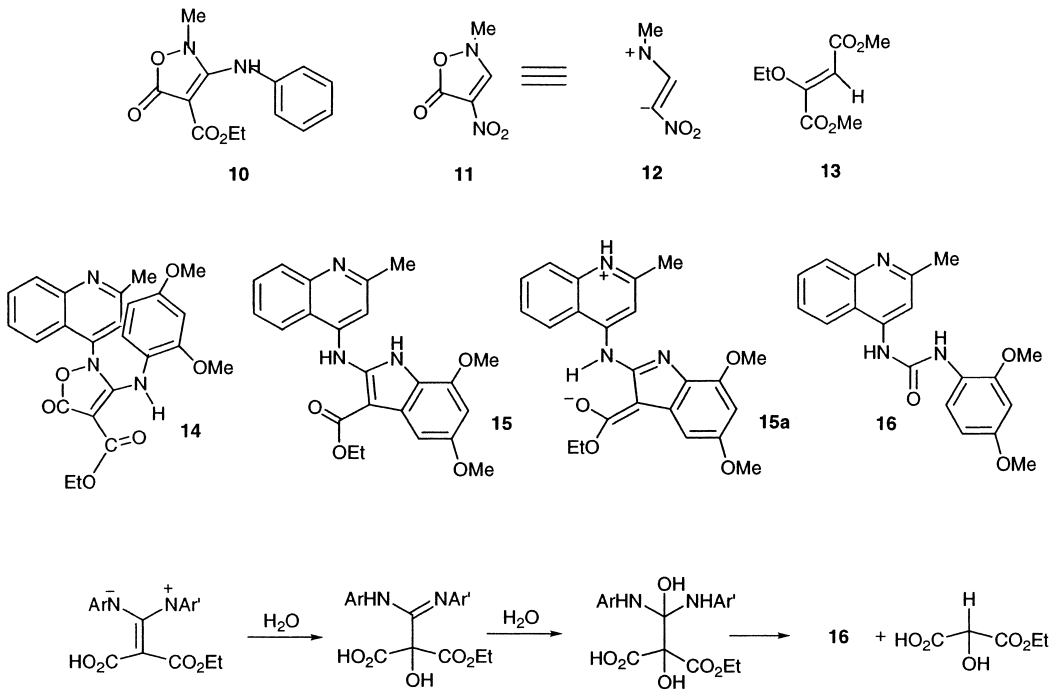


Scheme 4.

time in ethanol and the more polar trifluoroethanol. The reaction in ethanol, without base, occurred slowly over two days, but a number of compounds, including indole (**7g**) and imidazopyridine (**6g**) were formed. While isoxazolone (**11**) was found to undergo cyclisation reactions with dimethyl acetylenedicarboxylate,[7] the latter is not compatible with our required reaction conditions, being converted to the ethoxyfumarate ester (**13**).

Finally, the isoxazolone (**3g**) was reacted with 4-chloro-2-methylquinoline in boiling chlorobenzene to give the *N*-arylated product (**14**). The ^{1}H NMR upfield shifts of H-3 and H-5 in the dimethoxybenzene ring confirms the restricted rotation imposed by the H-bonding. The isoxazolone (**14**) did not react with triethylamine, but did react with potassium carbonate in ethanol to give two products, **15** and **16**, separable by chromatography. The structure of the indole (**15**) followed readily from its NMR spectra, but it could be isolated in two tautomeric forms, which retained different NMR spectra in chloroform, but which had the same UV–Vis spectrum in methanol. The zwitterionic form (**15a**) was obtained after chromatography on alumina, or crystallisation from dilute solution, and the uncharged form (**15**) after crystallisation from concentrated solution. The proportions of **15** and **16** could be altered by the dielectric constant of the solvent. Thus, reaction of **14** with potassium carbonate in a largely aqueous environment led almost exclusively to the indole (**15**), whereas the use of benzyltrimethylammonium hydroxide in THF gave no indole formation at all. The urea structure (**16**) is suggested to arise from an early solvolysis intermediate as shown in Scheme 5.

Preliminary results indicate that the dimethoxyphenyl imidazopyridine (**6g**) and the dimethoxyphenyl indole (**7g**) both exhibit significant cytotoxicity towards mammalian cells. Human peripheral blood derived T-lymphocytes were exposed to the chemicals in culture for 24 h either unstimulated (non-dividing) or following stimulation with the mitogen phytohaemagglutinin. Cytotoxicity was greater towards non-dividing cells (IC_{50}:2 μM, 10 μM) than towards dividing cells (IC_{50}:15 μM, 55 μM) with the indole having the greater cytotoxicity in both cases. These results are interesting and warrant further study of the mechanism



Scheme 5.

of cytotoxicity, in particular to determine whether it is mediated by interaction with DNA.

3. Conclusion

The base catalysed rearrangement of the 3-arylamino-isoxazolones provides indoles and imidazo heterocycles which are clearly suitable synthetic intermediates for a series of new planar polycyclic heterocycles that could be expected to intercalate with DNA.[8,9]

4. Experimental

4.1. General procedures

Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR measurements were recorded on a Gemini Varian 300 spectrometer in deuteriochloroform with tetramethylsilane as internal standard, unless otherwise stated. Infrared spectra were recorded on a Perkin Elmer 1600 FT-infrared spectrophotometer, using fused sodium chloride cells, measured as Nujol mulls or films. Electrospray ionisation (ESI) mass spectra were recorded by Monash University, Melbourne. The protonated molecular ion (MH^+) mass to charge ratio (m/z) is reported. Microanalyses were performed by the University of Otago, New Zealand. X-Ray crystal data were recorded by the University of Canterbury.

4.1.1. Diethyl (4-methoxyphenyl)thiocarbamoylmalonate (2b). To diethyl malonate (0.948 mL, 6.24 mmol) in anhydrous THF (8 mL) was added sodium (0.144 g, 6.24 mmol) and the mixture was refluxed under nitrogen for 2 h. The solution was cooled to room temperature, 4-methoxyphenylisothiocyanate (1.00 mL, 7.24 mmol) was added dropwise, and the resulting yellow solution was stirred at room temperature for 1.5 h before being quenched with ice-cold water. The mixture was extracted with Et_2O (3×30 mL) and the aqueous phase was added dropwise to vigorously stirred, ice-cold 1 M HCl (100 mL), yielding a yellow precipitate. The precipitate was washed with water and recrystallised from ethanol/light petroleum (1:1) to give the thiocarbamate as yellow crystals (1.80 g, 5.55 mmol; 89%) mp 56–58°C (lit.[10] 58.5–59.5°C). IR 3260, 1760, 1717, 1613, 1534, 1511 cm^{-1}; ^{1}H NMR δ 10.71 (bs, 1H), 7.60–7.75 (m, 2H), 6.85–7.00 (m, 2H), 5.08 (s, 1H), 4.29 (q, 4H, J=7.2 Hz), 3.81 (s, 3H), 1.32 (t, 6H, J=7.2 Hz); ^{13}C NMR δ 187.0, 165.8, 158.2, 131.6, 124.8, 114.0, 67.1, 63.0, 55.5, 13.9; Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89; N, 4.30; found: C, 55.63; H, 5.91; N, 4.54.

The thiocarbamates below were made by the same procedure.

4.1.2. Diethyl (3-methoxyphenyl)thiocarbamoylmalonate (2c). Diethyl malonate (0.95 mL, 6.24 mmol) gave **2c** (1.47 g, 4.49 mmol) as a yellow oil (72%). IR 3300, 1734, 1596, 1559, 1490, 1405 cm^{-1}; ^{1}H NMR δ 10.83 (bs, 1H), 7.61–7.65 (m, 1H), 7.18–7.35 (m, 2H), 6.78–6.87 (m, 1H), 5.08 (s, 1H), 4.29 (q, 4H, J=7.1 Hz), 3.81 (s, 3H), 1.32 (t, 6H, J=7.1 Hz); ^{13}C NMR δ 187.1, 165.7, 159.9, 139.6, 129.6, 115.2, 113.0, 108.4, 67.6, 63.0, 55.4, 13.9; Anal. Calcd for $C_{15}H_{19}N_2O_5S$: C, 55.37; H, 5.89; N, 4.30; found: C, 55.55; H, 5.86; N, 4.54.

4.1.3. Diethyl (4-nitrophenyl)thiocarbamoylmalonate (2d). Diethyl malonate (0.95 mL, 6.24 mmol) gave **2d** (1.70 g, 5.00 mmol) as yellow crystals (80%) mp 87–90°C (lit.[11] 89–90°C). IR 3297, 1746, 1720, 1626, 1580, 1520 cm^{-1}; ^{1}H NMR δ 11.20 (bs, 1H), 8.24–8.35 (m, 2H), 8.05–8.17 (m, 2H), 5.09 (s, 1H), 4.31 (q, 4H, J=7.2 Hz), 1.33 (t, 6H, J=7.2 Hz); ^{13}C NMR δ 188.4, 165.6, 145.2, 143.8, 124.6, 122.5, 67.8, 63.4, 13.9; Anal. Calcd for $C_{14}H_{16}N_2O_6S$: C, 49.41; H, 4.74; N, 8.23; found: C, 49.50; H, 4.90; N, 8.30.

4.1.4. Diethyl (4-methylphenyl)thiocarbamoylmalonate (2e). Diethyl malonate (0.95 mL, 6.24 mmol) gave **2e** (1.20 g, 3.87 mmol) as yellow crystals (62%) mp 52–54°C (lit.[10] 55–56°C). IR 3281, 1756, 1721, 1600, 1538, 1511 cm^{-1}; ^{1}H NMR δ 10.75 (bs, 1H), 7.63 (d, 2H, J=8.5 Hz), 7.21 (d, 2H, J=8.5 Hz), 5.09 (s, 1H), 4.30 (q, 4H, J=7.2 Hz), 2.36 (s, 3H), 1.33 (t, 6H, J=7.2 Hz); ^{13}C NMR δ 187.2, 165.8, 137.0, 136.0, 129.4, 123.2, 67.3, 63.0, 21.1, 13.9; Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53; found: C, 58.38; H, 6.27; N, 4.65.

4.1.5. Diethyl (3,5-bistrifluoromethylphenyl)thiocarbamoylmalonate (2f). Diethyl malonate (0.51 mL, 3.35 mmol) gave **2f** (1.12 g, 2.95 mmol) as a yellow solid (88%) mp 62–64°C, after column chromatography. IR 3280, 1767, 1717, 1574 cm^{-1}; ^{1}H NMR δ 11.14 (bs, 1H), 8.36 (s, 2H), 7.77 (s, 1H), 5.10 (s, 1H), 4.32 (q, 4H, J=7.2 Hz), 1.34 (t, 6H, J=7.2 Hz); ^{13}C NMR δ 188.9, 165.6, 139.7, 132.4 (q, J=34 Hz), 123.0, 122.9 (q, J=273 Hz), 120.2, 67.4, 63.4, 13.9; Anal. Calcd for $C_{16}H_{15}F_6NO_4S$: C, 44.55; H, 3.50; N, 3.25; found: C, 44.35; H, 3.79; N, 3.32.

4.1.6. Diethyl (2,4-dimethoxyphenyl)thiocarbamoylmalonate (2g). Diethyl malonate (2.12 mL, 14.0 mmol) gave **2g** (4.36 g, 12.3 mmol) as yellow needles (88%) mp 86–87°C. IR 3304, 1749, 1616, 1549, 1502, 1439, 1412, 1288, 1209, 1160, 1128, 1030 cm^{-1}; ^{1}H NMR δ 11.05 (bs, 1H), 8.86 (d, 1H, J=9.4 Hz), 6.49 (m, 2H), 5.06 (s, 1H), 4.28 (q, 4H, J=7.1 Hz), 3.90 (s, 3H), 3.81 (s, 3H), 1.31 (t, 6H, J=7.1 Hz); ^{13}C NMR δ 184.4, 165.6, 158.6, 151.9, 123.0, 121.9, 103.1, 98.8, 68.2, 62.8, 56.2, 55.5, 13.9; Anal. Calcd for $C_{16}H_{21}NO_6S$: C, 54.07; H, 5.96; N, 3.94; found: C, 53.78; H, 5.73; N, 3.98.

4.1.7. Ethyl 3-(3-methoxyphenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (3c). Hydroxyammonium chloride (0.214 g, 3.08 mmol) was dissolved in ethanol (4 mL)/water (2 mL) and then neutralised with potassium hydrogen carbonate (0.308 g, 3.08 mmol).[3] The filtered solution was added to the thiocarbamate (0.500 g, 1.54 mmol) and the mixture was refluxed for 17 h before being cooled to room temperature. The reaction mixture was quenched with 1 M HCl (5 mL) and extracted with CH_2Cl_2 (3×50 mL) and the extract dried ($MgSO_4$). The solvent was removed in vacuo yielding a yellow solid which was recrystallised from ethanol to give isoxazolone **3c** (320 mg,

1.16 mmol) as yellow needles (75%) mp 64–66°C. IR 3309, 1732, 1674, 1586, 1557, 1495 cm^{-1}; ^1H NMR ($CDCl_3$/TFA) δ 10.20 (bs, 1H), 7.28–7.40 (m, 1H), 6.78–6.92 (m, 3H), 4.35 (q, 2H, J=7.2 Hz), 3.83 (s, 3H), 1.37 (t, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$/TFA) δ 169.7, 165.2, 163.9, 160.7, 135.5, 131.2, 114.5, 113.3, 108.5, 76.6, 61.8, 55.6, 13.9; Anal. Calcd for $(C_{13}H_{14}N_2O_5)_2H_2S$: C, 52.88; H, 5.12; N, 9.49; found: C, 52.84; H, 5.46; N, 9.43.

The compounds below were prepared by the same procedure.

4.1.8. Ethyl 3-(4-methoxyphenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (3b). Thiocarbamate **2b** (500 mg, 1.54 mmol) gave **3b** (229 mg, 0.83 mmol) as yellow needles (54%) mp 163–165°C (accompanied by bubbling). IR 3295, 1733, 1668, 1615, 1557, 1514 cm^{-1}; ^1H NMR ($CDCl_3$/TFA) δ 9.45 (bs, 1H), 7.17–7.28 (m, 2H), 6.89–7.01 (m, 2H), 4.32 (q, 2H, J=7.2 Hz), 3.83 (s, 3H), 1.35 (t, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$/TFA) δ 169.9, 165.2, 164.8, 159.1, 126.8, 125.3, 115.4, 76.3, 61.6, 55.6, 14.0; Anal. Calcd for $(C_{13}H_{14}N_2O_5)_2H_2S$: C, 52.88; H, 5.12; N, 9.49; found: C, 52.19; H, 4.79; N, 9.26.

4.1.9. Ethyl 3-(4-nitrophenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (3d). Thiocarbamate **2d** (500 mg, 1.47 mmol) gave **3d** (347 mg, 1.18 mmol) as yellow crystals (80%) mp 161–163°C. IR 3457, 1721, 1623, 1587, 1509, 1345 cm^{-1}; ^1H NMR ($CDCl_3$/TFA) δ 9.70 (bs, 1H), 8.33 (d, 2H, J=9.0 Hz), 7.50 (d, 2H, J=9.0 Hz), 4.38 (q, 2H, J=7.1 Hz), 1.39 (t, 3H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$/TFA) δ 169.8, 165.2, 163.4, 145.4, 140.7, 126.0, 121.7, 77.9, 62.5, 13.9; Anal. Calcd for $(C_{12}H_{11}N_3O_6)_2H_2S$: C, 46.45; H, 3.90; N, 13.54; found: C, 47.91; H, 4.02; N, 13.77.

4.1.10. Ethyl 3-(4-methylphenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (3e). Thiocarbamate **2e** (500 mg, 1.62 mmol) gave **3e** (308 mg, 1.18 mmol) as yellow crystals (73%) mp 166–168°C (accompanied by bubbling). IR 3302, 1732, 1668, 1606, 1580, 1516 cm^{-1}; ^1H NMR ($CDCl_3$/TFA) δ 9.10 (bs, 1H), 7.24 (d, 2H, J=8.6 Hz), 7.16 (d, 2H, J=8.6 Hz), 4.31 (q, 2H, J=7.2 Hz), 2.36 (s, 3H), 1.34 (t, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$/TFA) δ 169.8, 165.1, 164.4, 138.1, 131.6, 130.7, 122.8, 76.4, 61.5, 20.9, 14.0; Anal. Calcd for $(C_{13}H_{14}N_2O_4)_2H_2S$: C, 55.90; H, 5.41; N, 10.03; found: C, 55.23; H, 5.01; N, 9.86.

4.1.11. Ethyl 3-(3,5-bistrifluoromethylphenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (3f). Thiocarbamate **2f** (350 mg, 0.81 mmol) gave **3f** (288 mg, 0.74 mmol) as white crystals (92%) sub. 160°C, dec. 200°C. IR 3238, 1716, 1674, 1586, 1538 cm^{-1}; ^1H NMR ($CDCl_3$/TFA) δ 9.60 (bs, 1H), 7.82 (bs, 3H), 4.38 (q, 2H, J=7.2 Hz), 1.38 (t, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$/TFA) δ 170.0, 165.2, 163.7, 136.2, 134.0 (q, J=34 Hz), 122.8, 122.5 (q, J=273 Hz), 121.1, 77.5, 62.5, 13.8; Anal. Calcd for $C_{14}H_{10}F_6N_2O_4$: C, 43.76; H, 2.62; N, 7.29; found: C, 43.89; H, 2.62; N, 7.24.

4.1.12. Ethyl 3-(2,4-dimethoxyphenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (3g). Thiocarbamate **2g** (2.00 g, 5.63 mmol) gave **3g** (1.34 g, 4.22 mmol) as white needles (75%) from CH_2Cl_2/petroleum, mp 146–148°C. IR 1751, 1671, 1619, 1588, 1514, 1438, 1324, 1210, 1200, 1107, 1029 cm^{-1}; ^1H NMR δ 9.62 (bs, 1H), 9.20 (bs, 1H), 7.24 (d, 1H, J=7.8 Hz), 6.46–6.53 (m, 2H), 4.32 (q, 2H, J=7.1 Hz), 3.88 (s, 3H), 3.79 (s, 3H),1.35 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 167.2, 165.8, 165.2, 159.3, 152.3, 123.5, 117.6, 104.8, 99.9, 75.9, 60.4, 56.2, 55.6, 14.4; Anal. Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09; found: C, 54.48; H, 4.97; N, 8.89.

4.1.13. Ethyl 3-(4-methoxyphenyl)amino-2-(5-nitropyrid-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (4b). Isoxazolone **3b** (100 mg, 0.359 mmol) and 2-chloro-5-nitropyridine (0.063 g, 0.395 mmol) were heated neat in a sealed vial flushed with nitrogen in a 130°C oven for 1 h. The resulting product was recrystallised from ethanol to give the isoxazolone as yellow crystals (84 mg, 0.208 mmol; 58%) mp 158–161°C. IR 1778, 1673, 1605, 1513, 1344, 1246 cm^{-1}; ^1H NMR δ 10.24 (bs, 1H), 8.91 (d, 1H, J=2.6 Hz), 8.52 (dd, 1H, J=9.0, 2.6 Hz), 7.50 (d, 1H, J=9.0 Hz), 7.08 (d, 2H, J=8.9 Hz), 6.76 (d, 2H, J=8.9 Hz), 4.24 (q, 2H, J=7.1 Hz), 3.75 (s, 3H), 1.28 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 163.9, 163.6, 161.2, 158.1, 153.9, 143.6, 141.7, 134.2, 130.3, 124.0, 115.4, 114.5, 78.6, 61.0, 55.5, 14.3; Anal. Calcd for $C_{18}H_{16}N_4O_7$: C, 54.00; H, 4.03; N, 13.99; found: C, 53.54; H, 3.92; N, 14.01.

The compounds below were prepared by the same method.

4.1.14. Ethyl 3-(3-methoxyphenyl)amino-2-(5-nitropyrid-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (4c). Isoxazolone **3c** (100 mg, 0.359 mmol) gave **4c** (78 mg, 0.194 mmol) as orange crystals (54%) mp 164–168°C. IR 3583, 1780, 1700, 1669, 1602, 1496, 1456, 1338 cm^{-1}; ^1H NMR δ 10.35 (bs, 1H), 8.91 (d, 1H, J=2.6 Hz), 8.55 (dd, 1H, J=9.1, 2.6 Hz), 7.54 (d, 1H, J=9.1 Hz), 7.10–7.18 (m, 1H), 6.64–6.74 (m, 3H), 4.22 (q, 2H, J=7.1 Hz), 3.73 (s, 3H), 1.25 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 163.7, 163.0, 160.4, 160.2, 153.9, 143.5, 141.5, 138.6, 134.3, 130.1, 114.9, 114.1, 111.9, 108.0, 79.0, 61.0, 55.4, 14.2; Anal. Calcd for $C_{18}H_{16}N_4O_7$: C, 54.00; H, 4.03; N, 13.99; found: C, 54.19; H, 3.92; N, 13.74.

4.1.15. Ethyl 3-(4-nitrophenyl)amino-2-(5-nitropyrid-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (4d). Isoxazolone **3d** (100 mg, 0.341 mmol) gave **4d** (65 mg, 0.157 mmol) as cream crystals (46%) mp 225–228°C. IR 3434, 1778, 1691, 1601, 1563, 1530, 1342 cm^{-1}; ^1H NMR ($CDCl_3$/TFA) δ 10.88 (bs, 1H), 9.04 (d, 1H, J=2.3 Hz), 8.70 (dd, 1H, J=9.1, 2.3 Hz), 8.23 (d, 2H, J=8.8 Hz), 7.67 (d, 1H, J=9.1 Hz), 7.36 (d, 2H, J=8.8 Hz), 4.19 (q, 2H, J=7.1 Hz), 1.19 (t, 3H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$/TFA) δ 165.6, 163.5, 158.4, 153.0, 145.4, 143.7, 143.0, 142.0, 135.5, 125.3, 122.1, 114.1, 80.8, 62.5, 13.7; Anal. Calcd for $C_{17}H_{13}N_5O_8$: C, 49.16; H, 3.15; N, 16.86; found: C, 48.60; H, 2.91; N, 16.22.

4.1.16. Ethyl 3-(4-methylphenyl)amino-2-(5-nitropyrid-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (4e). Isoxazolone **3e** (100 mg, 0.381 mmol) gave **4e** (84 mg, 0.221 mmol) as orange needles (58%)[†] mp 59–61°C. IR

[†] Direct crystallisation gave the H_2S complex, mp 150–153°C. Chromatography yielded the uncomplexed material.

3389, 1780, 1669, 1602, 1525, 1456, 1419, 1337 cm^{-1}; ^1H NMR δ 10.31 (bs, 1H), 8.89 (d, 1H, J=2.7 Hz), 8.53 (dd, 1H, J=9.1, 2.7 Hz), 7.52 (d, 1H, J=9.1 Hz), 7.03 (bs, 4H), 4.23 (q, 2H, J=7.1 Hz), 2.27 (s, 3H), 1.26 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 163.8, 163.1, 160.6, 153.9, 143.5, 141.5, 136.4, 135.0, 134.2, 129.9, 122.0, 115.0, 78.7, 60.9, 20.9, 14.2; Anal. Calcd for $C_{18}H_{16}N_4O_6$: C, 56.25; H, 4.20; N, 14.58; found: C, 56.56; H, 4.19; N, 14.23.

4.1.17. Ethyl 3-(3,5-bistrifluoromethylphenyl)amino-2-(5-nitropyrid-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (4f). Isoxazolone **3f** (70 mg, 0.182 mmol) gave **4f** (37 mg, 0.073 mmol) as white crystals (40%) mp 185–190°C (sub. from 166°C). IR 1799, 1696, 1608, 1585, 1561, 1515, 1348, 1288, 1186, 1127 cm^{-1}; ^1H NMR ($CDCl_3$/TFA) δ 11.03 (bs, 1H), 9.08 (d, 1H, J=2.4 Hz), 8.70 (dd, 1H, J=9.0, 2.4 Hz), 7.73 (s, 1H), 7.71 (d, 1H, J=9.0 Hz), 7.64 (s, 2H), 4.13 (q, 2H, J=7.1 Hz), 1.15 (t, 3H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$/TFA) δ 164.1, 162.8, 158.2, 153.2, 143.6, 141.7, 138.9, 135.4, 133.0 (q, J=34 Hz), 122.5 (q, J=273 Hz), 122.2, 119.8, 113.8, 80.3, 61.9, 13.8; Anal. Calcd for $C_{19}H_{12}F_6N_4O_6$: C, 45.07; H, 2.39; N, 11.07; found: C, 45.06; H, 2.13; N, 10.93.

4.1.18. Ethyl 3-(2,4-dimethoxyphenyl)amino-2-(5-nitropyrid-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (4g). Isoxazolone **3g** (250 mg, 0.811 mmol) gave **4g** (138 mg, 0.324 mmol) as yellow needles (40%) mp 182–186°C. IR 1780, 1670, 1607, 1593, 1558, 1517, 1458, 1343, 1288, 1210, 1030 cm^{-1}; ^1H NMR δ 10.20 (bs, 1H), 8.90 (d, 1H, J=2.2 Hz), 8.52 (dd, 1H, J=9.0, 2.2 Hz), 7.50 (d, 1H, J=9.0 Hz), 6.97 (d, 1H, J=8.9 Hz), 6.44 (d, 1H, J=1.9 Hz), 6.26 (dd, 1H, J=8.9, 1.9 Hz), 4.24 (q, 2H, J=7.1 Hz), 3.86 (s, 3H), 3.74 (s, 3H), 1.28 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 163.7, 163.3, 160.5, 159.1, 154.0, 152.8, 143.5, 141.4, 134.1, 123.2, 119.7, 114.8, 104.0, 99.0, 78.6, 60.8, 55.9, 55.5, 14.3; Anal. Calcd for $C_{19}H_{18}N_4O_8$: C, 53.03; H, 4.22; N, 13.02; found: C, 53.21; H, 4.23; N, 13.00.

4.1.19. Ethyl 2-(4-methoxyphenyl)amino-6-nitroimidazo[1,2-*a*]pyridine-3-carboxylate (6b) and ethyl 5-methoxy-2-(5-nitropyridyl-2-amino)indole-3-carboxylate (7b). *N*-aryl isoxazolone **4b** (0.050 g, 0.125 mmol) and potassium carbonate (0.086 g, 0.624 mmol) were refluxed in ethanol (2 mL) for 1 h. After 15 min the solution turned from orange to red. The solution was cooled, quenched with 1 M HCl (5 mL) and extracted with CH_2Cl_2 (3×25 mL). The organic extracts were washed with brine (1×20 mL), dried ($MgSO_4$), and evaporated, yielding a red solid which was purified by flash chromatography on silica gel (CH_2Cl_2) to firstly elute the indole **7b** as an orange solid (0.010 g, 23%) and secondly the imidazopyridine **6b** as a red solid (0.023 g, 52%).

Indole (**7b**): mp 209–213°C. IR 1654, 1637, 1607, 1560, 1507, 1491, 1458, 1342, 1323, 1212 cm^{-1}; ^1H NMR δ 11.41 (bs, 1H), 10.65 (bs, 1H), 9.21 (d, 1H, J=2.7 Hz), 8.37 (dd, 1H, J=9.4, 2.7 Hz), 7.40 (d, 1H, J=2.5 Hz), 7.29 (d, 1H, J=8.8 Hz), 6.87 (d, 1H, J=9.4 Hz), 6.83 (dd, 1H, J=8.8, 2.5 Hz), 4.44 (q, 2H, J=7.1 Hz), 3.88 (s, 3H), 1.49 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 167.8, 156.2, 156.1, 145.2, 144.8, 138.3, 133.4, 126.5, 125.3, 111.7, 111.3, 110.6, 103.6, 89.6, 60.0, 55.8, 14.6; Anal. Calcd for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.72; found: C, 57.17; H, 4.39; N, 15.49.

Imidazopyridine (**6b**): mp 163–166°C. IR 3400, 1684, 1654, 1625, 1580, 1513, 1481, 1343, 1311, 1206, 1084 cm^{-1}; ^1H NMR δ 9.89 (bs, 1H), 8.68 (bs, 1H), 8.12 (dd, 1H, J=9.8, 2.0 Hz), 7.58 (d, 2H, J=8.9 Hz), 7.47 (d, 1H, J=9.8 Hz), 6.92 (d, 2H, J=8.9 Hz), 4.54 (q, 2H, J=7.1 Hz), 3.82 (s, 3H), 1.53 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 160.7, 155.8, 147.1, 136.8, 132.5, 126.8, 122.4, 121.0, 114.4, 113.8, 98.4, 61.0, 55.6, 14.6 (carbonyl unsighted); HRMS calculated for $C_{17}H_{17}N_4O_5$ (MH^+): 357.1199; found: 357.1204.

4.1.20. Ethyl 6-nitro-2-(3-methoxyphenyl)aminoimidazo[1,2-*a*]pyridine-3-carboxylate (6c). The above procedure with **4c** (0.040 g, 0.100 mmol) gave **6c** as orange crystals (0.023 g, 0.064 mmol; 64%) mp 171–174°C. IR 3392, 1679, 1604, 1580, 1548, 1486, 1346, 1315, 1200, 1162, 1102 cm^{-1}; ^1H NMR δ 9.85 (bs, 1H), 8.89 (bs, 1H), 8.14 (dd, 1H, J=9.5, 2.2 Hz), 7.51 (d, 1H, J=9.5 Hz), 7.42–7.47 (m, 1H), 7.13–7.30 (m, 2H), 6.57–6.66 (m, 1H), 4.55 (q, 2H, J=7.1 Hz), 3.85 (s, 3H), 1.54 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 160.4, 146.9, 140.5, 137.0, 129.9, 126.9, 122.4, 114.1, 111.2, 108.0, 104.9, 99.0, 61.1, 55.3, 14.6 (two carbons unsighted); HRMS calculated for $C_{17}H_{17}N_4O_5$ (MH^+): 357.1199; found: 357.1195.

4.1.21. Ethyl 6-nitro-2-(4-methylphenyl)aminoimidazo[1,2-*a*]pyridine-3-carboxylate (6e). The above procedure with **4e** (0.050 g, 0.130 mmol) gave **6e** as red crystals (0.021 g, 0.062 mmol; 48%) mp 183–187°C. IR 3387, 1691, 1664, 1622, 1577, 1480, 1343, 1313, 1207, 1082 cm^{-1}; ^1H NMR δ 9.82 (bs, 1H), 8.78 (bs, 1H), 8.12 (dd, 1H, J=9.7, 2.2 Hz), 7.55 (d, 2H, J=8.2 Hz), 7.48 (d, 1H, J=9.7 Hz), 7.16 (d, 2H, J=8.2 Hz), 4.54 (q, 2H, J=7.1 Hz), 2.33 (s, 3H), 1.53 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 160.8, 147.0, 136.8, 136.7, 132.6, 129.7, 126.8, 122.4, 119.0, 113.9, 98.6, 61.0, 20.8, 14.6 (carbonyl unsighted); Anal. Calcd for $C_{17}H_{16}N_4O_4$: C, 60.00; H, 4.74; N, 16.46; found: C, 59.52; H, 4.73; N, 16.03.

4.1.22. Ethyl 6-nitro-2-(3,5-bistrifluoromethylphenyl)-aminoimidazo[1,2-*a*]pyridine-3-carboxylate (6f). The above procedure with **4f** (0.020 g, 0.100 mmol) gave **6f** as yellow crystals (0.011 g, 0.061 mmol; 61%) sublimes >142°C. IR 3393, 1674, 1625, 1598, 1473, 1380, 1345, 1315, 1276, 1176, 1124, 1087 cm^{-1}; ^1H NMR δ 9.94 (bs, 1H), 9.29 (bs, 1H), 8.28 (bs, 2H), 8.24 (dd, 1H, J=9.6, 2.0 Hz), 7.66 (d, 1H, J=9.6 Hz), 7.54 (bs, 1H), 4.61 (q, 2H, J=7.2 Hz), 1.57 (t, 3H, J=7.2 Hz); ^{13}C NMR δ 146.5, 140.9, 137.6, 132.5 (q, J=33 Hz), 127.0, 123.3 (q, J=273 Hz), 122.7, 118.0, 115.5, 115.0, 99.8, 61.6, 14.6 (two carbons unsighted); HRMS calculated for $C_{18}H_{13}F_6N_4O_4$ (MH^+): 463.0841; found: 463.0842.

4.1.23. Ethyl 6-nitro-2-(2,4-dimethoxyphenyl)aminoimidazo[1,2-*a*]pyridine-3-carboxylate (6g) and ethyl 5,7-dimethoxy-2-(5-nitropyridyl-2-amino)indole-3-carboxylate (7g). The above procedure with **4g** (0.050 g, 0.116 mmol) gave a red solid which was purified by flash chromatography on silica gel (5:1 CH_2Cl_2/petroleum) to firstly elute the indole **7g** as yellow needles (0.013 g, 29%) and secondly the imidazopyridine (**6g**) as red needles (0.021 g, 47%).

Indole (**7g**): mp 250–253°C. IR 3355, 1659, 1615, 1604, 1570, 1507, 1345, 1326, 1307, 1286, 1207 cm^{-1}; ^1H NMR δ 11.38 (bs, 1H), 10.61 (bs, 1H), 9.26 (d, 1H, J=2.6 Hz), 8.37 (dd, 1H, J=9.0, 2.6 Hz), 6.99 (d, 1H, J=1.8 Hz), 6.86 (d, 1H, J=9.0 Hz), 6.36 (d, 1H, J=1.8 Hz), 4.43 (q, 2H, J=7.1 Hz), 3.97 (s, 3H), 3.88 (s, 3H), 1.49 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 167.9, 157.0, 156.2, 146.1, 145.4, 143.7, 138.2, 133.2, 125.6, 116.5, 111.1, 94.8, 94.0, 90.3, 60.0, 55.8, 55.5, 14.6; HRMS calculated for $C_{18}H_{19}N_4O_6$ (MH^+): 387.1305; found: 387.1304.

Imidazopyridine (**6g**): mp 218–221°C. IR 3377, 1679, 1577, 1550, 1482, 1464, 1346, 1318, 1298, 1201, 1098 cm^{-1}; ^1H NMR δ 10.04 (bs, 1H), 9.13 (bs, 1H), 8.47 (d, 1H, J=9.4 Hz), 8.12 (dd, 1H, J=9.7, 2.4 Hz), 7.47 (d, 1H, J=9.7 Hz), 6.54–6.58 (m, 2H), 4.53 (q, 2H, J=7.1 Hz), 3.93 (s, 3H), 3.82 (s, 3H), 1.54 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 160.5, 155.4, 149.0, 147.2, 136.8, 126.6, 122.9, 122.3, 118.5, 113.6, 104.0, 98.8, 98.7, 60.8, 55.8, 55.6, 14.5 (carbonyl unsighted); HRMS calculated for $C_{18}H_{19}N_4O_6$ (MH^+): 387.1305; found: 387.1302.

4.1.24. Ethyl 3-(2,4-dimethoxyphenyl)amino-2-(3-methylquinolin-4-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (14). The isoxazolone **3g** (0.500 g, 1.62 mmol) and 4-chloroquinaldine (0.390 mL, 1.95 mmol) were refluxed in chlorobenzene (15 mL) for 4 h. The solvent was removed in vacuo yielding a brown solid which was recrystallised from ethanol to give **14** as brown crystals (0.426 g, 0.94 mmol; 58%) mp 183–185°C. IR 3277, 2980, 1772, 1670, 1612, 1514, 1497, 1411, 1210, 1041 cm^{-1}; ^1H NMR δ 9.35 (bs, 1H), 8.03 (dd, 1H, J=8.2, 1.4 Hz), 7.91 (dd, 1H, J=8.4, 1.2 Hz), 7.68 (ddd, 1H, J=8.4, 7.0, 1.4 Hz), 7.54 (ddd, 1H, J=8.2, 7.0, 1.2 Hz), 6.84 (s, 1H), 6.77 (d, 1H, J=8.6 Hz), 5.98 (d, 1H, J=2.6 Hz), 5.83 (dd, 1H, J=8.6, 2.6 Hz), 4.44 (q, 2H, J=7.1 Hz), 3.55 (s, 3H), 3.50 (s, 3H), 2.51 (s, 3H), 1.43 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 165.5, 165.3, 164.5, 159.9, 158.4, 153.6, 148.1, 141.7, 130.7, 128.1, 127.2, 125.9, 123.0, 122.4, 118.0, 116.8, 103.9, 98.6, 77.8, 60.7, 55.43, 55.38, 24.5, 14.5; Anal. Calcd for $C_{24}H_{23}N_3O_6$: C, 64.14; H, 5.16; N, 9.35; found: C, 63.86; H, 5.28; N, 9.46.

4.1.25. Ethyl 5,7-dimethoxy-2-(2-methylquinolyl-4-amino)indole-3-carboxylate (15). *N*-aryl isoxazolone **14** (0.100 g, 0.222 mmol) and potassium carbonate (0.154 g, 1.11 mmol) were refluxed in water (2 mL)/ethanol (0.5 mL) for 1 h. The solution was cooled, quenched with 1 M HCl (5 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic extracts were washed with brine (1×30 mL), dried ($MgSO_4$) and filtered. The solvent was removed in vacuo, yielding a yellow-brown solid which was recrystallised from CH_2Cl_2 to give **15** as yellow crystals (0.054 g, 0.67 mmol; 60%) mp 210–215°C (sub. from 168°C). IR (film) 3344, 1643, 1598, 1513, 1441, 1205, 1164, 1122, 1074 cm^{-1}; λ_{max} 290 nm (ε 964 $Lcm^{-1}\,mol^{-1}$), 354 (ε 1540 $Lcm^{-1}\,mol^{-1}$), ε_{400} 236 $Lcm^{-1}\,mol^{-1}$. ^1H NMR δ 11.81 (bs, 1H), 10.97 (s, 1H), 8.24 (d, 1H, J=8.4 Hz), 8.01 (d, 1H, J=8.1 Hz), 7.58 (t, 1H, J=7.5 Hz), 7.44 (t, 1H, J=7.5 Hz), 7.33 (s, 1H), 7.00 (d, 1H, J=2.0 Hz), 6.39 (d, 1H, J=2.0 Hz), 4.39 (q, 2H, J=7.1 Hz), 3.95 (s, 3H), 3.88 (s, 3H), 2.85 (s, 3H), 1.40 (t, 3H, J=7.1 Hz); ^{13}C NMR δ 167.3, 157.1, 155.5, 149.6, 147.0, 139.7, 138.0, 132.9, 127.6, 126.1, 121.3, 120.5, 118.5, 116.6, 104.2, 96.0, 95.3, 94.5, 60.4, 55.8, 55.7, 20.5, 14.4; HRMS calculated for $C_{23}H_{24}N_3O_4$ (MH^+): 406.1766; found: 406.1767.

Chromatography of the original product on alumina gave **15a** as orange plates after crystallisation from dilute ethanol solution. ^1H NMR δ 8.12 (d, 1H, J=8.0 Hz), 8.02 (d, 1H, J=8.0 Hz), 7.67 (t, 1H, J=7.7 Hz), 7.51 (t, 1H, J=7.7 Hz), 7.22 (s, 1H), 7.04 (d, 1H, J=2.0 Hz), 6.37 (d, 1H, J=2.0 Hz), 4.42 (q, 2H, J=7.1 Hz), 3.94 (s, 3H), 3.89 (s, 3H), 2.72 (s, 3H), 1.45 (t, 3H, J=7.1 Hz). Crystallisation from dichloromethane gave **15**, identical with the sample above.

A second product, **16**, was eluted with ethyl acetate as a yellow powder. IR (film) 3290, 1717, 1683, 1605 cm^{-1}; ^1H NMR (conc. dependent) δ 10.8 (bs, 1H), 8.5 (bs, 1H), 8.17 (s, 1H), 8.07 (d, 1H, J=8 Hz), 7.92 (d, 1H, J=8 Hz), 7.82 (d, 1H, J=8 Hz), 7.50 (t, 1H, J=8 Hz), 7.24 (t, 1H, J=8 Hz), 6.42 (dd, 1H, J=10, 2 Hz), 6.38 (d, 1H, J=2 Hz), 3.80 (s, 3H), 3.76 (s, 3H), 2.70 (s, 3H); ^{13}C NMR δ 158.9, 157.3, 153.1, 151.5, 146.1, 144.6, 130.1, 126.8, 125.6, 122.9, 120.9, 120.2, 118.7, 109.6, 104.1, 99.0, 55.5, 24.3; HRMS calculated for $C_{19}H_{20}N_3O_3$ (MH^+): 338.1504; found: 338.1494.

4.2. Cytotoxicity assay

Peripheral blood samples were obtained from a healthy donor with informed consent. Lymphocytes were separated from peripheral blood using Ficoll–Hypaque. Unstimulated lymphocytes were suspended at 1×10^6 cells mL^{-1} modified McCoys 311 medium (medium) containing phytohaemagglutinin at 10 $\mu g\,mL^{-1}$ (PHA) in Sterilin tubes and cultured with various concentrations of either **6g** or **7g** (range 0–100 μM) for 24 h at 37°C in 10% CO_2 in a fully humidified incubator. The chemical was removed by washing twice with medium. Surviving cells were counted by Trypan Blue exclusion and plated into 96 well plates at 100,000 cells/well in medium (200 μL) containing PHA and cultured in the described conditions. Viable cells in two replicate wells were counted on days 4–6 or until viability in the control wells began to diminish significantly. IC_{50} was calculated as the chemical concentration generating 50% inhibition of growth relative to control wells on the same micro-well plate at maximum cell number expansion. To establish cytotoxicity in dividing cells, peripheral T-cells ($1\times10^6\,mL^{-1}$) were incubated in Sterilin tubes in medium containing PHA for three days. Cells were aliquoted into tubes at $1\times10^6\,mL^{-1}$ in a conditioned medium (containing a source of IL-2) for 24 h prior to 24 h exposure to the chemical (range as above). The chemical was then removed and the cells plated at 50,000 cells per well in conditioned medium and counted on days 7–10 as described and the IC_{50} was calculated.

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