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Rapid analogue synthesis of C-5 substituted 1,2,3-triazolo-[1,5-*a*]quinazolines

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Abstract—A rapid analogue synthetic strategy has been developed to allow easy variation of the C-5 position of 1,2,3-triazolo[1,5-*a*]-quinazolines. A range of directly linked and carbon tethered aromatic heterocyclic groups have been introduced utilising palladium catalysed cross-coupling reactions on an imino tosylate.

As part of an ongoing medicinal chemistry programme directed towards the identification of subtype selective ligands for the benzodiazepine binding site of GABA-A receptors, we were interested in preparing a series of novel 1,2,3-triazolo[1,5-*a*]quinazolines bearing a variety of substituents at the C-5 position,[1] in particular, directly linked aromatic heterocycles (**A**) and heterocyclic groups linked by a short carbon chain (**B**) (Fig. 1).

Although the first synthesis of 1,2,3-triazolo[1,5-*a*]quinazolines was reported 36 years ago,[2] this class of compounds has subsequently received little attention. Although there are references in the literature describing compounds substituted at the C-5 position with O-linked functionality,[3] there are few references describing triazoloquinazolines substituted at C-5 with nitrogen[4–6] or carbon linked groups.[7,8] Indeed, the only examples described for C-5 carbon linked triazoloquinazolines are those bearing simple alkyl and aryl groups which are introduced prior to the formation of the core triazoloquinazoline from *ortho*-azidophenylketones. This method is not suitable for rapid analogue synthesis and thus could not be employed to rapidly establish structure activity relationships for this class of compound. Herein, we describe our strategy and solution for the synthesis of C-5 carbon linked triazoloquinazolines enabling structural changes to be made simply and efficiently.

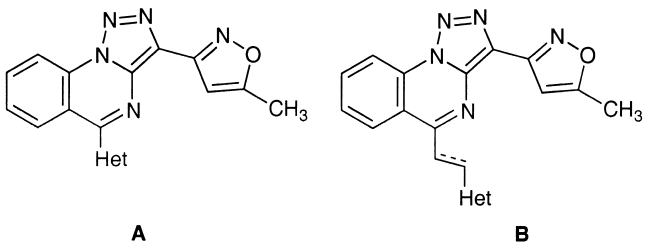
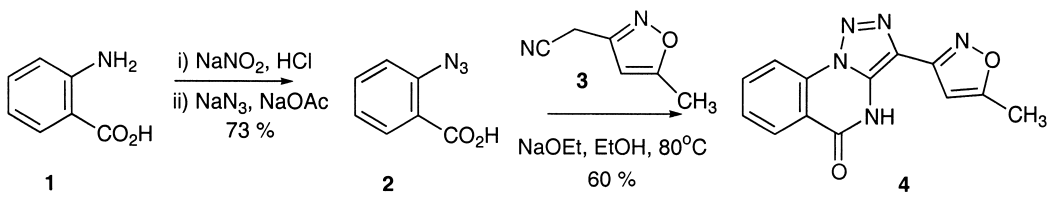


Figure 1.

The triazoloquinazolinone framework was prepared by the method of Tennant.[2] Anthranilic acid (**1**) was readily converted into 2-azidobenzoic acid (**2**) by diazotisation and displacement with sodium azide (Scheme 1). Treatment of an equimolar mixture of the aryl azide with the isoxazole acetonitrile **3** in the presence of sodium ethoxide at 80°C leads to the desired core skeleton **4**. The reaction proceeds by deprotonation of the acetonitrile followed by addition



Scheme 1.

Keywords: triazoloquinazolines; nitrogen heterocycles; coupling reactions; imidic acids and derivatives.
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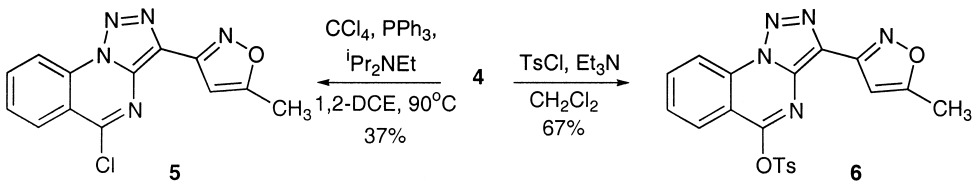


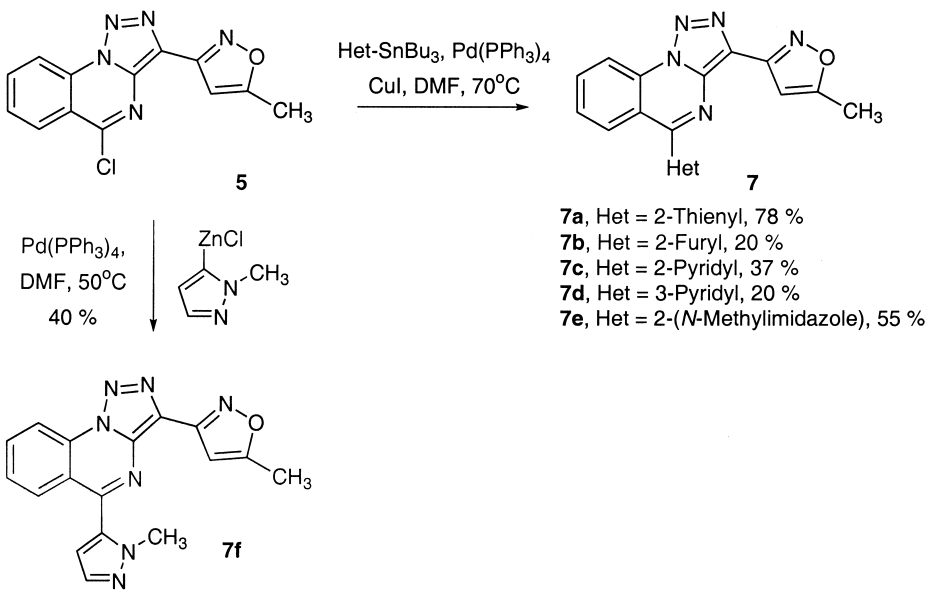
Scheme 2.

onto the azido group. Subsequent 5-*exo*-cyclisation onto the nitrile group furnishes the triazole group after proton migration. Ring closure to the triazoloquinazolinone then occurs readily.

With the core ring system to hand it was then necessary to elaborate the C-5 position into a suitable leaving group to enable rapid functionalisation at this position (Scheme 2). Although attempts to prepare the imino chloride **5** using $SOCl_2$ gave the desired material on small scale, the reaction proved not to be reproducible. Likewise, other chlorinating agents such as $POCl_3$ also gave unsatisfactory results. However, treatment of the lactam with CCl_4 and PPh_3 in the presence of $^iPr_2NEt$ gave the imino chloride in a modest, but reproducible, 30–40% yield. In an attempt to prepare other suitable leaving groups at the C-5 position it was discovered that the imino tosylate **6** could be readily prepared in excellent yield by treatment of the lactam with tosyl chloride in the presence of Et_3N.

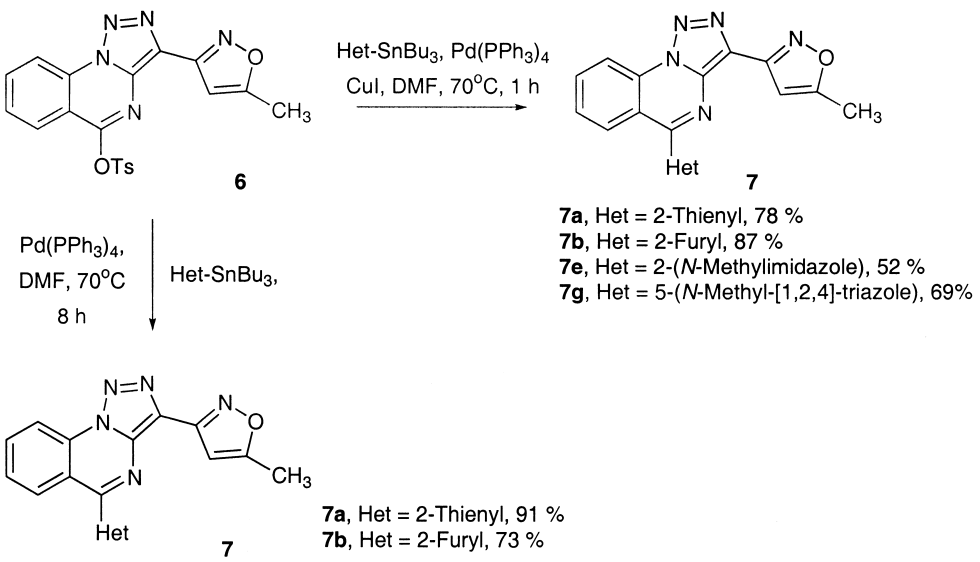
With the imino chloride **5** to hand cross-coupling reactions were readily carried out with a range of heteroaromatic stannanes using Stille conditions,[9] resulting in the coupled products **7** in modest to high yields (Scheme 3). Delighted with this result, a Negishi cross-coupling was attempted using 5-(1-*N*-methylpyrazole)zinc chloride, prepared by lithiation of *N*-methylpyrazole at −78°C followed by transmetallation with $ZnCl_2$.[10] The cross-coupling reaction occurred readily under palladium catalysis to give triazoloquinazoline **7f** in 40% yield.

Due to the ready availability of the imino tosylate **6** a speculative cross-coupling reaction was attempted (Scheme 4). Despite literature precedent, tosylates are not used routinely in palladium catalysed couplings.[11] Although the Ni-catalysed Suzuki coupling of aryl tosylates has been reported,[11a] there is only one example of the successful cross-coupling of an imino tosylate reported in the patent literature,[12] despite the widespread use of imino triflates in synthesis.[13] When the imino tosylate **6** was treated with 2 equiv. of 2-tributylstannyl-*N*-methylimidazole the coupled product **7e** was obtained in 52% yield, the same as the corresponding reaction on the imino chloride. Other reactions using heteroarylstannanes yielded similar results. A control reaction was carried out in the absence of CuI to ascertain whether the palladium was undergoing oxidative addition into the imino tosylate or whether initial reaction between the CuI and the imino tosylate yielded an imino iodide which in turn reacted. When the tosylate was reacted with 2-tributylstannylthiophene in the presence of $Pd(PPh_3)_4$ we were delighted to find that cross-coupling occurred, albeit in longer reaction time, affording 91% isolated yield of **7a** in 8 h compared to 78% yield in 1 h with CuI. Similar findings were obtained with 2-tributylstannylfuran, 87% yield of **7b** in 1 h in the presence of CuI, compared to 73% in 8 h in the absence of CuI. This clearly demonstrates the potential of imino tosylates for cross-coupling reaction. At this stage, the rate enhancement due to CuI could be attributed to either in situ formation of an imino iodide, thereby allowing faster oxidative insertion into the C–I bond, or to the formation of a more active



7a, Het = 2-Thienyl, 78 %
7b, Het = 2-Furyl, 20 %
7c, Het = 2-Pyridyl, 37 %
7d, Het = 3-Pyridyl, 20 %
7e, Het = 2-(*N*-Methylimidazole), 55 %

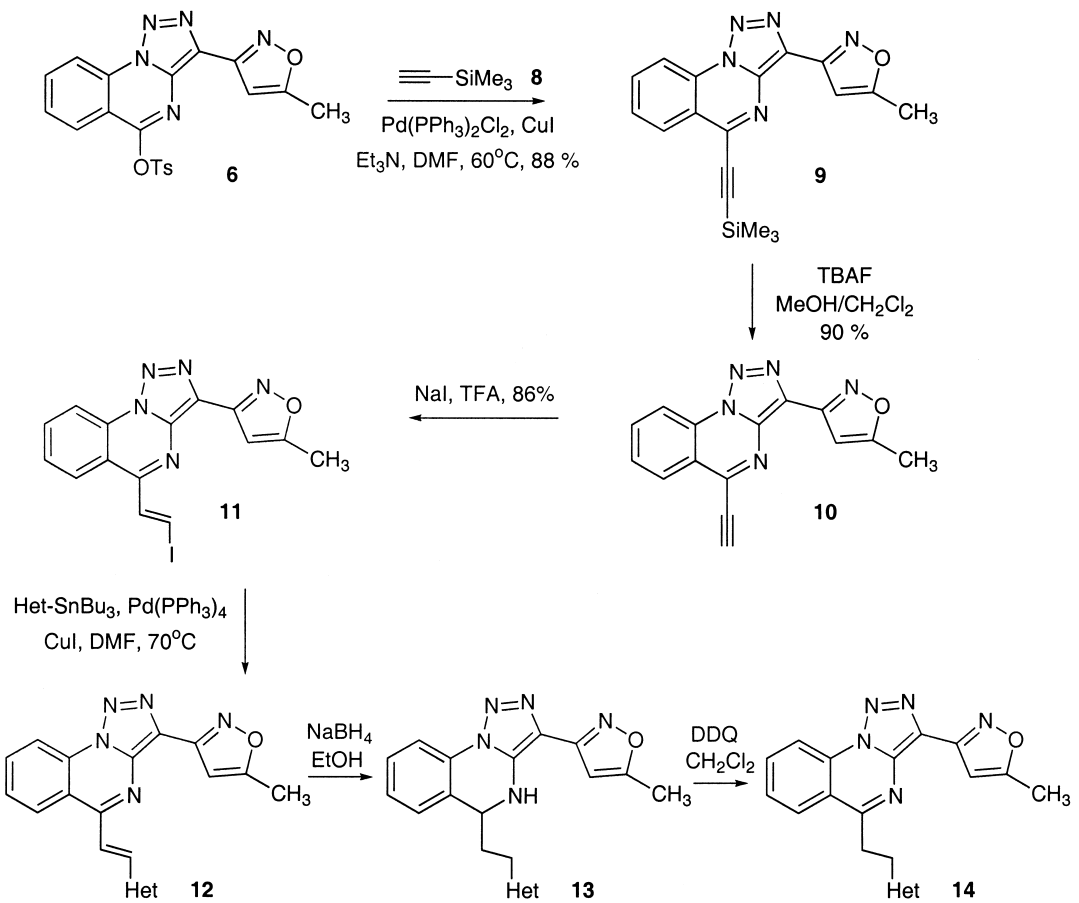
Scheme 3.



Scheme 4.

palladium species by the removal of a PPh_3 from the $Pd(PPh_3)_4$ as has been described by Liebeskind.[14]

As well as triazoloquinazolines linked directly to heteroaromatic groups there was also interest in preparing a series of compounds linked by an ethynyl, ethenyl or ethanyl spacer. In the interest of efficiency, it was decided to try to prepare the ethynyl-linked derivative and then perform stepwise reductions to yield the other products. All attempts at coupling 2-ethynylpyridine with **6** under a variety of Sonogashira–Hagihara coupling conditions failed.[15] However, **6** coupled readily to trimethylsilylacetylene **8** in the presence of $Pd(PPh_3)_2Cl_2$ and CuI to give **9** in 88% yield (Scheme 5). The reaction necessitated the use of Et_3N, as $^iPr_2NH$ and other secondary amines resulted in rapid cleavage of the imino tosylate to the lactam **4**. Deprotection of **9** with TBAF in $MeOH/CH_2Cl_2$ gave the unsubstituted alkyne **10** in good yield. However, subsequent



Scheme 5.

Table 1. Isolated yields for cross-coupling/reduction/oxidation reactions

No.	Het	Yield **12** (%)	Yield **13** (%)	Yield **14** (%)
a	2-Furyl	80	56	88
b	2-Pyridyl	95	67	82
c	3-Pyridyl	28	53	N/A
d	2-(*N*-Methylimidazole)	94	59	27
e	5-(*N*-Methyl-[1,2,4]-triazole)	66	63	67

Sonogashira–Hagihara cross-coupling reactions on **10** with iodobenzene failed to give any of the desired 5-phenylethylene-[1,2,3]-triazolo[1,5-*a*]quinazoline.

In order to circumvent the problems of the failed Sonogashira reactions attempts were made to convert the acetylene into a vinyl iodide. Having observed the high reactivity of **6** it was proposed that the acetylene may behave in a similar manner to a propionate and undergo conjugate addition with NaI in a manner similar to that described by Taniguchi.[16] Addition of NaI to a solution of **10** in TFA gave the desired *E*-vinyl iodide **11** exclusively, in high yield. Unfortunately, when the conditions reported to prepare the *Z*-vinyl iodide were tried (NaI, AcOH) only the *E*-isomer **11** could be detected.

The vinyl iodide **11** proved to be a useful synthetic intermediate and further Stille cross-coupling reactions were carried out in excellent yield to give the ethenyl products **12** (Table 1). Reduction of these compounds into their saturated counterparts **14** proved troublesome, and most methods gave a complex mixture of products. A satisfactory resolution proved to be reduction of both the double bond and the triazoloquinazoline core in tandem to yield the 4,5-dihydro-[1,2,3]-triazolo[1,5-*a*]quinazolines **13** in high yield, further demonstrating that the C=N double bond of the triazoloquinazoline can function as an isolated imine rather than as part of an aromatic heterocyclic system. In turn, this compound could be oxidised efficiently to the desired triazoloquinazolines **14** by addition of DDQ.

In summary, we have devised a short and flexible strategy for the synthesis of a variety of C-5 substituted 1,2,3-triazolo[1,5-*a*]quinazolines from the key imino tosylate **6**. Selective variation of the heterocycle and linking group is possible using this approach. This is the first demonstration that imino tosylates may have wide application in palladium catalysed cross-coupling reactions.

1. Experimental

1.1. General

^{1}H NMR spectra were recorded at 360 or 400 MHz. Flash column chromatography was carried out on silica gel (E. Merck Art 7734). Reagents and dry solvents were purchased from Sigma Aldrich or Frontier Scientific Europe Ltd. and used without purification. Glassware was dried prior to use and reactions were performed under a nitrogen atmosphere unless otherwise specified. Organic solvents were evaporated on a rotary evaporator at reduced pressure. (5-Methylisoxazol-3-yl)acetonitrile (**3**),[17] 2-tributylstannyl-*N*-methylimidazole,[18] and 5-tributylstannyl-*N*-methyl-[1,2,4]-triazole[19] were prepared according to published methods.

1.1.1. 2-Azidobenzoic acid (2). A solution of sodium nitrite (4.75 g, 69 mmol) in H_2O (63 mL) was added to a solution of anthranilic acid (10 g, 73 mmol) in H_2O (125 mL) and conc. HCl (125 mL) at 5°C under N_2 and then stirred for 10 min. The mixture was then filtered through a chilled frit into a flask cooled in a −78°C bath. This solution was then added dropwise over 25 min to a stirred solution of sodium azide (4.2 g, 65 mmol) and sodium acetate trihydrate (105 g, 0.77 mol) in H_2O (125 mL) at −5°C under N_2. The resulting mixture was stirred at 0°C for 5 min and then warmed to room temperature and stirred for a further 90 min. The resulting precipitate was filtered and washed with H_2O (200 mL) and hexanes (200 mL) and dried under reduced pressure to yield the desired azide (8.68 g, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (1H, d, J=7.4 Hz), 7.61 (1H, t, J=8.1 Hz), 7.30–7.22 (2H, m). ^{13}C NMR (d^6-DMSO, 90 MHz) δ 168.7 (s), 141.0 (s), 135.3 (d), 133.4 (d), 127.2 (d), 126.3 (s), 123.1 (d).

1.1.2. 3-(5-Methylisoxazol-3-yl)-4*H*-[1,2,3]-triazolo[1,5-*a*]-quinazolin-5-one (4). Sodium (1.77 g, 77 mmol) was added portionwise to EtOH (200 mL) at room temperature under N_2. Upon complete disappearance of the sodium, the nitrile **3** (4.14 g, 33.9 mmol) was added and the solution stirred for 15 min. A solution of the azide **2** (5.02 g, 30.8 mmol) in EtOH (20 mL) was added and the reaction stirred at room temperature for 1 h and then warmed to 80°C and heated at reflux for 5 h. After cooling to room temperature, the EtOH was removed under reduced pressure and H_2O (250 mL) added. This mixture was acidified with 1 M citric acid solution (100 mL) and filtered. The solid was then washed with H_2O (200 mL) and toluene (2×100 mL), and dried under reduced pressure to yield the desired lactam (4.96 g, 60%). ^{1}H NMR (d^6-DMSO, 400 MHz) δ 12.15 (1H, s), 8.36 (1H, d, J=7.9 Hz), 8.24 (1H, d, J=7.9 Hz), 8.02 (1H, t, J=7.9 Hz), 7.71 (1H, t, J=7.9 Hz), 6.82 (1H, s), 2.50 (3H, s). ^{13}C NMR (d^6-DMSO, 90 MHz) δ 172.2 (s), 161.2 (s), 156.6 (s), 137.8 (d), 136.7 (s), 135.2 (s), 130.7 (d), 130.5 (d), 122.0 (s), 119.7 (s), 117.5 (d), 102.6 (d), 14.1 (q). MS (ES$^+$) $C_{13}H_9N_5O_2$ requires 267, found: 268 (M+H$^+$, 100%).

1.1.3. 5-Chloro-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (5). A mixture of the triazoloquinazolinone **4** (500 mg, 1.75 mmol), PPh_3 (981 mg, 3.7 mmol), ^{i}Pr$_2$NEt (648 μL, 3.7 mmol) in CCl_4 (15 mL) and 1,2-DCE (15 mL) was heated at 90°C for 10 min and then cooled to room temperature. The resulting mixture was filtered through a pad of silica and the pad washed with DCM. The filtrate was concentrated under reduced pressure and dry loaded onto silica. Column chromatography on silica using 5% MeOH/DCM yielded the desired chloride (200 mg, 37%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (1H, d, J=8.1 Hz), 8.40 (1H, d, J=8.1 Hz), 8.11 (1H, t, J=8.1 Hz), 7.85 (1H, t, J=8.1 Hz), 6.81 (1H, s), 2.56 (3H, s). ^{13}C NMR (d^6-DMSO, 90 MHz) δ 169.9 (s), 154.8 (s), 154.5 (s), 136.5 (s), 136.2 (d), 133.8 (s), 129.6 (s), 128.9 (d), 128.6 (d), 117.5 (s), 116.1 (d), 100.7 (d), 11.3 (q). MS (ES$^+$) $C_{13}H_8N_5OCl$

requires 285, found: 286, 288 (3:1) (M+H$^+$, 100%). HRMS (ES$^+$) *m/z* 286.0495, $C_{13}H_9N_5O^{35}Cl$ requires 286.0496.

1.1.4. Toluene-4-sulfonic acid 3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazolin-5-yl ester (6). Tosyl chloride (1.32 g, 6.89 mmol) was added portionwise over 5 min to a stirred solution of the triazoloquinazolinone **4** (0.92 g, 3.44 mmol) and Et_3N (0.95 mL, 6.89 mmol) in DCM (30 mL) at room temperature under N_2. The resulting mixture was then stirred overnight, during which period a precipitate formed, this was subsequently filtered off and washed with DCM (20 mL). After drying under reduced pressure the desired tosylate was obtained (1.29 g, 89%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.68 (1H, d, *J*=8.3 Hz), 8.43 (2H, d, *J*=8.2 Hz), 8.31 (1H, d, *J*=8.1 Hz), 8.06 (1H, t, *J*=8.2 Hz), 7.77 (1H, t, *J*=8.2 Hz), 7.44 (2H, d, *J*=8.2 Hz), 6.79 (1H, s), 2.59 (3H, s), 2.49 (3H, s). ^{13}C NMR (d^6-DMSO, 90 MHz) δ 172.2 (s), 161.1 (s), 157.8 (s), 149.0 (s), 147.9 (s), 139.8 (s), 137.6 (d), 136.7 (s), 132.3 (s), 132.0 (s), 130.8 (d), 130.4 (d), 130.3 (d), 127.8 (d), 117.6 (d), 102.5 (d), 13.1 (q), 14.3 (q). MS (ES$^+$) $C_{20}H_{15}N_5O_4S$ requires 421, found: 422 (M+H$^+$, 100%). [Found: C, 55.8; H, 3.7; N, 16.2. $C_{20}H_{15}N_5O_4S{\cdot}0.5H_2O$ requires C, 55.8; H, 3.7; N, 16.3].

1.2. Method 1: cross-coupling with the chloroimidate 5

1.2.1. 3-(5-Methylisoxazol-3-yl)-5-(thiophen-2-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7a). A solution of the chloroimidate **5** (87 mg, 0.31 mmol) and 2-(tributylstannyl)thiophene (387 μL, 1.2 mmol) in DMF (5 mL) was degassed with a stream of N_2 for 10 min. $Pd(PPh_3)_4$ (40 mg, 10 mol%) and CuI (6 mg, 10 mol%) were added and the reaction heated at 70°C overnight. The resulting mixture was cooled to room temperature and concentrated under reduced pressure and then azeotroped with xylene (2×10 mL), prior to absorbing onto silica with DCM and MeOH. The resulting residue was purified by column chromatography on silica eluting with 0.5% MeOH in DCM to yield the desired triazoloquinazoline (79 mg, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85 (1H, d, *J*=7.9 Hz), 8.60 (1H, d, *J*=8.1 Hz), 8.07 (1H, t, *J*=7.8 Hz), 7.85–7.75 (2H, m), 7.70 (1H, d, *J*=4.9 Hz), 7.30–7.25 (1H, m), 6.88 (1H, s), 2.56 (3H, s). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.6 (s), 156.8 (s), 154.9 (s), 139.9 (s), 134.9 (d), 133.8 (s), 131.9 (s), 131.4 (d), 130.9 (d), 129.1 (s), 128.8 (d), 128.3 (d), 128.2 (d), 117.2 (s), 116.4 (d), 100.8 (d), 12.4 (q). MS (ES$^+$) $C_{17}H_{11}N_5OS$ requires 333, found: 334 (M+H$^+$, 100%). HRMS (ES$^+$) *m/z* 334.0773, $C_{17}H_{12}N_5OS$ requires 334.0763.

1.2.2. 5-(Furan-2-yl)-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7b). The reaction was carried out as described for **7a** using the chloroimidate **5** (87 mg, 0.31 mmol) and 2-tributylstannylfuran (384 μL, 1.2 mmol) at 70°C for 30 min to yield the desired triazoloquinazoline (20 mg, 20%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.07 (1H, d, *J*=8.2 Hz), 8.83 (1H, d, *J*=8.1 Hz), 8.04 (1H, t, *J*=8.1 Hz), 7.84–7.74 (2H, m), 7.64 (1H, d, *J*=3.1 Hz), 6.86 (1H, s), 6.72 (1H, d, *J*=3.1 Hz), 2.56 (3H, s). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.4 (s), 155.0 (s), 152.3 (s), 150.1 (s), 145.9 (d), 137.0 (s), 134.6 (d), 133.9 (s), 129.6 (s), 128.9 (d), 128.2 (d), 117.0 (d), 116.4 (s), 115.9 (d), 112.6 (d), 100.7 (d), 12.3 (q). MS (ES$^+$) $C_{17}H_{11}N_5O_2$ requires 317, found: 318 (M+H$^+$, 100%). [Found: C, 63.9; H, 3.5; N, 21.7. $C_{17}H_{11}N_5O_2$ requires C, 64.3; H, 3.5; N, 22.1]. HRMS (ES$^+$) *m/z* 318.0991, $C_{17}H_{12}N_5O_2$ requires 318.0991.

1.2.3. 3-(5-Methylisoxazol-3-yl)-5-(pyridin-2-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7c). The reaction was carried out as described for **7a** using the chloroimidate **5** (87 mg, 0.31 mmol) and 2-tributylstannylpyridine (449 mg, 1.2 mmol) overnight at 70°C to yield the desired triazoloquinazoline (37 mg, 37%) after recrystallisation from DCM/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (1H, d, *J*=7.8 Hz), 8.85–8.80 (2H, m), 8.34 (1H, d, *J*=8.0 Hz), 8.10–7.96 (2H, m), 7.77 (1H, t, *J*=8.2 Hz), 7.55–7.48 (1H, m), 6.86 (1H, s), 2.56 (3H, s). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.5 (s), 159.6 (s), 155.9 (s), 155.1 (s), 148.5 (d), 137.5 (d), 134.7 (d), 134.1 (s), 130.7 (d), 130.3 (s), 128.0 (d), 127.9 (s), 125.8 (d), 124.7 (d), 117.5 (s), 115.7 (d), 100.8 (d), 12.3 (q). MS (ES$^+$) $C_{18}H_{12}N_6O$ requires 328 found: 329 (M+H$^+$, 100%). [Found: C, 65.7; H, 3.7; N, 25.3. $C_{18}H_{12}N_6O$ requires C, 65.8; H, 3.7; N, 25.6]. HRMS (ES$^+$) *m/z* 329.1146, $C_{18}H_{13}N_6O$ requires 329.1151.

1.2.4. 3-(5-Methylisoxazol-3-yl)-5-(pyridin-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7d). The reaction was carried out as described for **7a** using the chloroimidate **5** (79 mg, 0.28 mmol) and 3-tributylstannylpyridine (408 mg, 1.1 mmol) overnight at 70°C to yield the desired triazoloquinazoline (18 mg, 20%) after recrystallisation from DCM/EtOAc. ^{1}H NMR (d^6-DMSO, 360 MHz) δ 9.02 (1H, s), 8.88 (1H, d, *J*=3.6 Hz), 8.80 (1H, d, *J*=8.1 Hz), 8.33–8.21 (2H, m), 8.11 (1H, d, *J*=8.0 Hz), 7.89 (1H, t, *J*=8.0 Hz), 7.71 (1H, dd, *J*=7.8, 4.9 Hz), 6.95 (1H, s), 2.53 (3H, s). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.8 (s), 166.2 (s), 164.9 (s), 154.2 (s), 151.2 (d), 150.3 (d), 148.3 (s), 145.1 (s), 137.4 (d), 135.2 (d), 128.9 (d), 128.3 (d), 123.6 (d), 118.7 (s), 118.3 (s), 116.3 (d), 100.8 (d), 12.3 (q). MS (ES$^+$) $C_{18}H_{12}N_6O$ requires 328, found: 329 (M+H$^+$, 100%). HRMS (ES$^+$) *m/z* 329.1138, $C_{18}H_{13}N_6O$ requires 329.1151.

1.2.5. 5-(1-Methyl-1*H*-imidazol-2-yl)-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7e). The reaction was carried out as described for **7a** using the chloroimidate **5** (79 mg, 0.28 mmol) and 2-tributylstannyl-*N*-methylimidazole (205 mg, 0.56 mmol) at 70°C for 1 h to yield the desired triazoloquinazoline (51 mg, 55%) after recrystallisation from DCM/hexanes. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.58 (1H, d, *J*=8.2 Hz), 8.78 (1H, d, *J*=8.0 Hz), 8.03 (1H, t, *J*=7.8 Hz), 7.80 (1H, t, *J*=7.9 Hz), 7.34 (1H, s), 7.21 (1H, s), 6.81 (1H, s), 4.28 (3H, s), 2.56 (3H, s). ^{13}C NMR ($CDCl_3$+10% CD_3OD, 90 MHz) δ 169.8 (s), 155.0 (s), 151.4 (s), 136.6 (s), 135.0 (d), 133.8 (s), 131.0 (d), 130.1 (s), 129.0 (d), 128.4 (d), 125.7 (s), 125.0 (s), 117.6 (d), 115.3 (d), 100.4 (d), 36.5 (q), 12.0 (q). MS (ES$^+$) $C_{17}H_{13}N_7O$ requires 331, found: 332 (M+H$^+$, 100%). [Found: C, 59.9; H, 3.8; N, 28.4. $C_{17}H_{13}N_7O{\cdot}0.5H_20$ requires C, 60.0; H, 4.1; N, 28.1]. HRMS (ES$^+$) *m/z* 332.1241, $C_{17}H_{14}N_7O$ requires 332.1260.

1.2.6. 3-(5-Methylisoxazol-3-yl)-5-(2-methyl-2*H*-pyrazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7f). A solution of BuLi (1.54 mmol) in hexane (1.6 M, 0.96 mL) was added to a stirred solution of ^{i}Pr$_2$NH (215 μL, 1.54 mmol)

in THF (2 mL) at 0°C under N_2. The resulting solution was stirred for 20 min and then cooled to −78°C and *N*-methyl pyrazole (116 μL, 1.4 mmol) was added. The mixture was stirred for 1 h at −78°C and then a solution of $ZnCl_2$ (210 mg, 1.54 mmol) in THF (2 mL) was added and then the reaction was allowed to warm to room temperature. DMF (5 mL) was added, followed by a slurry of the chloroimidate (150 mg, 0.53 mmol) in DMF (3 mL) and then $Pd(PPh_3)_4$ (40 mg, 6 mol%). The reaction was then heated at 50°C for 45 min, cooled to room temperature and concentrated under reduced pressure and azeotroped with xylene (20 mL). The crude residue was dissolved in DCM (70 mL) and washed with 1N HCl (30 mL), dried ($MgSO_4$) and absorbed onto silica under reduced pressure. The residue was purified by column chromatography on silica eluting with 5–10% EtOAc in DCM to yield the desired triazoloquinazoline (69 mg, 40%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.77 (1H, d, J=8.2 Hz), 8.29 (1H, d, J=8.2 Hz), 8.02 (1H, t, J=8.2 Hz), 7.71 (1H, t, J=8.2 Hz), 7.60 (1H, d, J=1.8 Hz), 6.74 (1H, s), 6.71 (1H, d, J=1.8 Hz), 4.17 (3H, s), 2.48 (3H, s). ^{13}C NMR ($CDCl_3$+10% CD_3OD, 100 MHz) δ 170.0 (s), 154.6 (s), 153.4 (s), 138.1 (d), 136.8 (s), 136.6 (s), 135.6 (d), 133.8 (s), 130.3 (s), 128.8 (d), 128.6 (d), 118.0 (s), 116.0 (d), 110.9 (d), 100.6 (d), 38.6 (q), 12.1 (q). MS (ES^+) $C_{17}H_{13}N_7O$ requires 331, found: 332 ($M+H^+$, 100%). HRMS (ES^+) m/z 332.1268, $C_{17}H_{14}N_7O$ requires 332.1260.

1.3. Method 2: by coupling with the imino tosylate 6

1.3.1. 5-(1-Methyl-1*H*-imidazol-2-yl)-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7e). A suspension of the tosylate **6** (100 mg, 0.24 mmol) and 2-tributylstannyl-*N*-methylimidazole (176 mg, 0.48 mmol) in DMF (5 mL) was degassed with a stream of N_2 for 10 min. The mixture was then warmed to 70°C. At 40°C, the solids dissolved and $Pd(PPh_3)_4$ (40 mg, 10 mol%) and CuI (6 mg, 10 mol%) were added. The reaction was heated at 70°C for 1 h. The resulting mixture worked up as previously to yield the desired triazoloquinazoline **7e** (41 mg, 52%) after recrystallisation from DCM/hexanes.

1.3.2. 3-(5-Methylisoxazol-3-yl)-5-(2-methyl-2*H*-[1,2,4]-triazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7g). The reaction was carried out as described directly above for **7e** using the tosylate **6** (100 mg, 0.24 mmol) and 5-tributylstannyl-*N*-methyl-[1,2,4]-triazole (176 mg, 0.48 mmol) to yield the desired triazoloquinazoline (55 mg, 69%) after recrystallisation from DCM/hexanes. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.40 (1H, d, J=8.3 Hz), 8.84 (1H, d, J=8.1 Hz), 8.13 (1H,s), 8.09 (1H, t, J=8.2 Hz), 7.84 (1H, t, J=8.1 Hz), 6.82 (1H, s), 4.49 (3H, s), 2.57 (3H, s). ^{13}C NMR ($CDCl_3$+10% CD_3OD, 90 MHz) δ 170.1 (s), 154.8 (s), 150.0 (d), 149.6 (s), 149.0 (s), 136.0 (s), 135.7 (d), 133.7 (s), 130.8 (s), 130.0 (d), 128.7 (d), 117.2 (s), 115.5 (d), 100.4 (d), 39.0 (q), 11.9 (q). MS (ES^+) $C_{16}H_{12}N_8O$ requires 332, found: 333 ($M+H^+$, 100%). [Found: C, 57.3; H, 3.6; N, 33.0. $C_{16}H_{12}N_8O{\cdot}0.25H_2O$ requires C, 57.0; H, 3.7; N, 33.3]. HRMS (ES^+) m/z 333.1206, $C_{16}H_{13}N_8O$ requires 333.1212.

1.3.3. 3-(5-Methylisoxazol-3-yl)-5-(thiophen-2-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7a). The reaction was carried out as described for **7e** using the tosylate **6** (100 mg, 0.24 mmol) and 2-tributylstannylthiophene (178 mg, 0.48 mmol) to yield the desired triazoloquinazoline (62 mg, 78%).

1.3.4. 5-(Furan-2-yl)-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7b). The reaction was carried out as described for **7e** using the tosylate **6** (100 mg, 0.24 mmol) and 2-tributylstannylfuran (170 mg, 0.48 mmol) to yield the desired triazoloquinazoline (66 mg, 87%).

1.4. Method 3: by coupling with the imino tosylate 6 in the absence of CuI

1.4.1. 3-(5-Methylisoxazol-3-yl)-5-(thiophen-2-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7a). A suspension of the tosylate **6** (100 mg, 0.24 mmol) and 2-tributylstannylthiophene (178 mg, 0.48 mmol) in DMF (5 mL) was degassed with a stream of N_2 for 10 min. The mixture was then warmed to 70°C. At 40°C the solids dissolved and $Pd(PPh_3)_4$ (40 mg, 10 mol%) was added. The reaction was heated at 70°C for 8 h. The resulting mixture worked up as previously to yield the desired triazoloquinazoline (72 mg, 91%).

1.4.2. 5-(Furan-2-yl)-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (7b). The reaction was carried out as described directly above for **7a** using the tosylate **6** (100 mg, 0.24 mmol) and 2-tributylstannylfuran (170 mg, 0.48 mmol) to yield the desired triazoloquinazoline (55 mg, 73%).

1.5. Alternative linkers at the C-5 position

1.5.1. 3-(5-Methylisoxazol-3-yl)-5-(trimethylsilanylethynyl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (9). A solution of the tosylate **6** (5.0 g, 11.9 mmol), trimethylsilylacetylene (5.0 mL, 35.7 mmol), $Pd(PPh_3)_2Cl_2$ (416 mg, 5 mol%) and CuI (339 mg, 15 mol%) in DMF (300 mL) at 60°C was degassed with a stream of N_2 for 15 min and then Et_3N (4.1 mL, 29.8 mmol) was added and the reaction heated at 60°C for 30 min. The resulting mixture was concentrated under reduced pressure while azeotroping with xylene (200 mL). The residue was taken up in DCM (300 mL) and washed with H_2O (2×150 mL), dried ($MgSO_4$), and concentrated under reduced pressure while dry loading onto silica. The residue was purified by column chromatography on silica eluting with 2% MeOH in DCM to yield the desired triazoloquinazoline (3.62 g, 88%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.73 (1H, d, J=8.2 Hz), 8.45 (1H, d, J=8.1 Hz), 8.05 (1H, t, J=8.1 Hz), 7.81 (1H, t, J=8.1 Hz), 6.85 (1H, s), 2.56 (3H, s), 0.40 (9H, s). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.6 (s), 154.8 (s), 146.5 (s), 137.5 (s), 135.2 (d), 133.1 (s), 130.4 (s), 128.9 (d), 128.4 (d), 119.2 (s), 115.6 (d), 106.5 (s), 100.9 (d), 99.3 (s), 12.3 (q), −0.6 (q). MS (ES^+) $C_{18}H_{17}N_5OSi$ requires 347, found: 348 ($M+H^+$, 100%). HRMS (ES^+) m/z 348.1280, $C_{18}H_{18}N_5OSi$ requires 348.1281.

1.5.2. 5-Ethynyl-3-(5-methylisoxazol-3-yl)-[1,2,3]triazolo[1,5-*a*]quinazoline (10). A solution of TBAF (2.4 mmol) in THF (1.0 M, 2.4 mL) was added to a stirred solution of the TMS–acetylene **9** (554 mg, 1.6 mmol) in DCM (10 mL) and MeOH (5 mL) and the mixture was

stirred at room temperature for 10 min. H_2O (20 mL) was added and the organics were extracted with DCM (2×50 mL). The organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure while dry loading onto silica. The residue was purified by column chromatography on silica eluting with 2% MeOH in DCM to yield the desired triazoloquinazoline (393 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (1H, d, J=8.2 Hz), 8.48 (1H, d, J=8.2 Hz), 8.07 (1H, t, J=8.2 Hz), 7.82 (1H, t, J=8.1 Hz), 6.85 (1H, s), 3.78 (1H, s), 2.56 (3H, s). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.6 (s), 154.5 (s), 145.9 (s), 135.4 (d), 134.5 (s), 132.8 (s), 128.9 (s), 128.5 (d), 128.4 (d), 127.8 (s), 118.8 (s), 115.6 (d), 100.7 (d), 78.8 (d), 12.2 (q). MS (ES^+) $C_{15}H_9N_5O$ requires 275, found: 276 ($M+H^+$, 100%). HRMS (ES^+) m/z 276.0888, $C_{15}H_{10}N_5O$ requires 276.0885.

1.5.3. (*E*)5-(2-Iodovinyl)-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (11). NaI (90 mg, 0.6 mmol) was added in one portion to a stirred solution of the acetylene **10** (150 mg, 0.55 mmol) in TFA (1 mL) and the resulting mixture was stirred at room temperature for 30 min and then H_2O (25 mL) was added. The organics were extracted with DCM (75 mL), dried ($MgSO_4$), and concentrated under reduced pressure while dry loading onto silica. The residue was purified by column chromatography on silica eluting with 5% EtOAc in DCM to yield the desired triazoloquinazoline (190 mg, 86%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.80 (1H, d, J=8.1 Hz), 8.35 (1H, d, J=14.2 Hz), 8.27 (1H, J=8.1 Hz), 8.22 (1H, d, J=14.2 Hz), 8.06 (1H, t, J=8.1 Hz), 7.80 (1H, t, J=8.1 Hz), 6.82 (1H, s), 2.56 (3H, s). ^{13}C NMR (d^6-DMSO, 90 MHz) δ 172.3 (s), 159.0 (s), 156.3 (s), 140.1 (d), 139.8 (s), 138.7 (s), 138.0 (d), 135.1 (s), 130.6 (d), 129.7 (d), 118.9 (s), 117.7 (d), 103.4 (d), 99.8 (d), 14.3 (q). MS (ES^+) $C_{15}H_{10}IN_5O$ requires 403, found: 404 ($M+H^+$, 100%). HRMS (ES^+) m/z 404.0018, $C_{15}H_{11}N_5O^{127}I$ requires 404.0008.

1.5.4. (*E*)5-(2-Furan-2-ylvinyl)-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (12a). A solution of the vinyl iodide **11** (190 mg, 0.47 mmol) and 2-(tributylstannyl)furan (297 μL, 0.94 mmol) in DMF (10 mL) was degassed with a stream of N_2 for 10 min. $Pd(PPh_3)_4$ (40 mg, 10 mol%) and CuI (6 mg, 10 mol%) was added and the reaction heated at 70°C for 1 h. The resulting mixture was cooled to room temperature and concentrated under reduced pressure and then azeotroped with xylene (2×15 mL), prior to absorbing onto silica with DCM. The resulting residue was purified by column chromatography on silica eluting with 8% EtOAc in hexanes to yield the desired triazoloquinazoline (129 mg, 80%) which was recrystallised from DCM/hexanes. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.78 (1H, d, J=8.2 Hz), 8.42 (1H, d, J=8.2 Hz), 8.12 (1H, d, J=15.1 Hz), 8.04 (1H, t, J=8.2 Hz), 7.85–7.73 (2H, m), 7.56 (1H, s), 6.86 (1H, s), 6.80–6.75 (1H, m), 6.58–6.53 (1H, m), 2.57 (3H, s). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.4 (s), 157.0 (s), 155.4 (s), 152.3 (s), 144.5 (d), 138.1 (s), 134.4 (d), 133.4 (s), 129.1 (s), 127.9 (d), 127.3 (d), 126.0 (d), 117.9 (s), 117.3 (d), 116.1 (d), 115.2 (d), 112.7 (d), 100.8 (d), 12.3 (q). MS (ES^+) $C_{19}H_{13}N_5O_2$ requires 343, found: 344 ($M+H^+$, 100%). HRMS (ES^+) m/z 344.1154, $C_{19}H_{14}N_5O_2$ requires 344.1147.

1.5.5. (*E*)3-(5-Methylisoxazol-3-yl)-5-[2-(pyridin-2-yl)-vinyl]-[1,2,3]-triazolo[1,5-*a*]quinazoline (12b). The reaction was carried out as described for **12a** using the vinyl iodide **11** (185 mg, 0.46 mmol) and 2-tributylstannylpyridine (337 mg, 0.92 mmol) to yield the desired triazoloquinazoline (154 mg, 95%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.85–8.80 (1H, m), 8.75–8.68 (1H, m), 8.60–8.50 (2H, m), 8.27 (1H, d, J=14.9 Hz), 8.05 (1H, t, J=8.2 Hz), 7.85–7.72 (2H, m), 7.58 (1H, d, J=7.7 Hz), 7.37–7.30 (1H, m), 6.89 (1H, s), 2.59 (3H, s). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.4 (s), 157.1 (s), 154.9 (s), 153.5 (s), 150.0 (d), 139.1 (d), 138.3 (s), 138.0 (d), 134.7 (d), 133.1 (s), 129.1 (s), 128.0 (d), 126.6 (d), 125.4 (d), 124.0 (d), 123.7 (d), 118.4 (s), 116.1 (d), 100.9 (d), 12.3 (q). MS (ES^+) $C_{20}H_{14}N_6O$ requires 354, found: 355 ($M+H^+$, 100%). HRMS (ES^+) m/z 355.1292, $C_{20}H_{15}N_6O$ requires 355.1307.

1.5.6. (*E*)3-(5-Methylisoxazol-3-yl)-5-[2-(pyridin-3-yl)-vinyl]-[1,2,3]-triazolo[1,5-*a*]quinazoline (12c). The reaction was carried out as described for **12a** using the vinyl iodide **11** (185 mg, 0.46 mmol) and 3-tributylstannylpyridine (337 mg, 0.92 mmol) to yield the desired triazoloquinazoline (46 mg, 28%) after recrystallisation from DCM/hexanes. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 9.00 (1H, s), 8.83–8.78 (1H, m), 8.65 (1H, d, J=4.8 Hz), 8.43 (1H, d, J=7.8 Hz), 8.29 (1H, d, J=15.5 Hz), 8.10–8.03 (2H, m), 7.92 (1H, d, J=15.5 Hz), 7.82 (1H, t, J=8.2 Hz), 7.40 (1H, dd J=7.7, 4.7 Hz), 6.87 (1H, s), 2.56 (3H, s). MS (ES^+) $C_{20}H_{14}N_6O$ requires 354, found: 355 ($M+H^+$, 100%). [Found: C, 63.8; H, 3.9; N, 22.7. $C_{20}H_{14}N_6O\cdot1.1H_2O$ requires C, 64.2; H, 4.3; N, 22.5]. HRMS (ES^+) m/z 355.1297, $C_{20}H_{15}N_6O$ requires 355.1307.

1.5.7. (*E*)5-[2-(1-Methyl-1*H*-imidazol-2-yl)-vinyl]-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (12d). The reaction was carried out as described for **12a** using the vinyl iodide **11** (200 mg, 0.5 mmol) and 2-tributylstannyl(*N*-methylimidazole) (368 mg, 0.99 mmol) to yield the desired triazoloquinazoline (167 mg, 94%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.78 (1H, d, J=8.2 Hz), 8.53 (1H, d, J=8.2 Hz), 8.36 (1H, d, J=14.8 Hz), 8.19 (1H, d, J=14.8 Hz), 8.05 (1H, t, J=8.2 Hz), 7.80 (1H, t, J=8.2 Hz), 7.25 (1H, s), 7.05 (1H, s), 6.83 (1H, s), 3.92 (3H, s), 2.57 (3H, s). MS (ES^+) $C_{19}H_{15}N_7O$ requires 357, found: 358 ($M+H^+$, 100%). HRMS (ES^+) m/z 358.1403, $C_{19}H_{16}N_7O$ requires 358.1416.

1.5.8. (*E*)3-(5-Methylisoxazol-3-yl)-5-[2-(2-methyl-2*H*-[1,2,4]-triazol-3-yl)-vinyl]-[1,2,3]-triazolo[1,5-*a*]quinazoline (12e). The reaction was carried out as described for **12a** using the vinyl iodide **11** (200 mg, 0.50 mmol) and 5-tributylstannyl(1-*N*-methyl-[1,2,4]-triazole) (369 mg, 0.99 mmol) to yield the desired triazoloquinazoline (118 mg, 66%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.84 (1H, d, J=8.2 Hz), 8.49 (1H, d, J=8.2 Hz), 8.48 (1H, d, J=14.8 Hz), 8.17 (1H, d, J=14.8 Hz), 8.08 (1H, t, J=8.2 Hz), 7.99 (1H, s), 7.83 (1H, t, J=8.2 Hz), 6.84 (1H, s), 4.13 (3H, s), 2.58 (3H, s). MS (ES^+) $C_{18}H_{14}N_8O$ requires 358, found: 359 ($M+H^+$, 100%). HRMS (ES^+) m/z 359.1383, $C_{18}H_{15}N_8O$ requires 359.1369.

1.5.9. 5-[2-(Furan-2-yl)ethyl]-3-(5-methylisoxazol-3-yl)-4,5-dihydro-[1,2,3]-triazolo[1,5-*a*]quinazoline (13a). $NaBH_4$ (40 mg, 1.0 mmol) was added to a stirred suspension of the alkene (70 mg, 0.20 mmol) in EtOH (6 mL) and the

mixture was heated at reflux for 90 min. The resulting mixture was cooled to room temperature, quenched with 2N HCl (5 mL) and concentrated under reduced pressure to remove the EtOH. The aqueous solution was neutralised with 2N NaOH (5 mL), extracted with DCM (3×30 mL), dried ($MgSO_4$), and concentrated under reduced pressure while dry loading onto silica. The residue was purified by column chromatography on silica eluting with 1.5% MeOH in DCM to yield the desired dihydrotriazoloquinazoline (40 mg, 56%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.61 (1H, s), 7.32–7.20 (2H, m), 7.07 (1H, t, J=7.6 Hz), 6.95 (1H, d, J=8.0 Hz), 6.59 (1H, s), 6.21 (1H, dd, J=3.1, 1.9 Hz), 6.03–5.95 (2H, m), 2.80–2.52 (4H, m), 2.50 (3H, s), 2.40–2.28 (1H, m). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.3 (s), 156.7 (s), 154.0 (s), 141.1 (d), 135.3 (s), 134.9 (s), 129.2 (d), 127.5 (d), 122.9 (d), 118.3 (s), 117.8 (s), 115.4 (d), 110.1 (d), 105.5 (d), 99.2 (d), 57.3 (d), 36.6 (t), 23.0 (t), 12.2 (q). MS (ES^+) $C_{19}H_{17}N_5O_2$ requires 347, found: 348 ($M+H^+$, 100%).

1.5.10. 3-(5-Methylisoxazol-3-yl)-5-[2-(pyridin-2-yl)-ethyl]-4,5-dihydro-[1,2,3]-triazolo[1,5-*a*]quinazoline (13b). The reaction was carried out as described for **13a** using the alkene **12b** (125 mg, 0.35 mmol) to yield the desired dihydrotriazoloquinazoline (85 mg, 67%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.48–8.40 (1H, m), 7.68–7.03 (7H, m), 6.95 (1H, d, J=8.0 Hz), 6.55 (1H, s), 6.00 (1H, dd, J=5.6, 3.3 Hz), 2.84–2.65 (3H, m), 2.55–2.40 (1H, m), 2.48 (3H, s). MS (ES^+) $C_{20}H_{18}N_6O$ requires 358, found: 359 ($M+H^+$, 100). HRMS (ES^+) m/z 3579.1622, $C_{20}H_{19}N_6O$ requires 359.1622.

1.5.11. 3-(5-Methylisoxazol-3-yl)-5-{2-(pyridin-3-yl)-ethyl]-4,5-dihydro-[1,2,3]-triazolo[1,5-*a*]quinazoline (13c). The reaction was carried out as described for **13a** using the alkene **12c** (61 mg, 0.17 mmol) to yield the desired dihydrotriazoloquinazoline (33 mg, 53%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.48–8.30 (2H, m), 7.73–6.95 (7H, m), 6.59 (1H, s), 6.02 (1H, t, J=4.5 Hz), 2.78–2.22 (4H, m), 2.50 (3H, s). MS (ES^+) $C_{20}H_{18}N_6O$ requires 358, found: 359 ($M+H^+$, 100).

1.5.12. 5-[2-(1-Methyl-1*H*-imidazol-2-yl)-ethyl]-3-(5-methylisoxazol-3-yl)-4,5-dihydro-[1,2,3]-triazolo[1,5-*a*]-quinazoline (13d). The reaction was carried out as described for **13a** using the alkene **12d** (128 mg, 0.36 mmol) to yield the desired dihydrotriazoloquinazoline (77 mg, 59%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.71 (1H, s), 7.35 (1H, d, J=7.7 Hz), 7.26 (1H, t, J=7.7 Hz), 7.07 (1H, t, J=7.7 Hz), 6.95 (1H, d, J=7.7 Hz), 6.89 (1H, s), 6.75 (1H, s), 6.58 (1H, s), 5.99 (1H, dd, J=6.6, 3.5 Hz), 3.49 (3H, s), 2.88–2.70 (1H, m), 2.67 (2H, t, J=8.0 Hz), 2.49 (3H, s), 2.53–2.35 (1H, m). MS (ES^+) $C_{19}H_{19}N_7O$ requires 361, found: 362 ($M+H^+$, 100).

1.5.13. 3-(5-Methylisoxazol-3-yl)-5-[2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-ethyl]-4,5-dihydro-[1,2,3]-triazolo-[1,5-*a*]quinazoline (13e). The reaction was carried out as described for **13a** using the alkene **12e** (95 mg, 0.27 mmol) to yield the desired dihydrotriazoloquinazoline (57 mg, 63%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.76 (1H, s), 7.69 (1H, s), 7.33 (1H, d, J=7.7 Hz), 7.28 (1H, t, J=7.7 Hz), 7.08 (1H, t, J=7.7 Hz), 6.97 (1H, d, J=7.7 Hz), 6.58 (1H, s), 6.00–5.92 (1H, m), 3.76 (3H, s), 2.88–2.70 (3H, m), 2.50 (3H, s), 2.50–2.40 (1H, m). MS (ES^+) $C_{18}H_{18}N_8O$ requires 362, found: 363 ($M+H^+$, 100).

1.5.14. 5-[2-(Furan-2-yl)ethyl]-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (14a). DDQ (39 mg, 0.17 mmol) was added in one portion to a stirred solution of the dihydrotriazoloquinazoline **13a** (40 mg, 0.12 mmol) in DCM (4 mL) and then stirred at room temperature for 1 h. The resulting mixture was then concentrated under reduced pressure while dry loading onto silica and purified by column chromatography on silica eluting with 2% MeOH/DCM to yield the desired triazoloquinazoline (35 mg, 88%) which was recrystallised from DCM/hexanes. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.78 (1H, d, J=8.1 Hz), 8.18 (1H, d, J=8.1 Hz), 8.01 (1H, t, J=8.1 Hz), 7.74 (1H, t, J=8.1 Hz), 7.35–7.32 (1H, m), 6.84 (1H, s), 6.31–6.25 (1H, m), 6.15–6.08 (1H, m), 3.69 (2H, t, J=8.2 Hz), 3.38 (2H, t, J=8.2 Hz), 2.56 (3H, s). ^{13}C NMR ($CDCl_3$+10% CD_3OD, 90 MHz) δ 169.8 (s), 165.8 (s), 154.5 (s), 153.4 (s), 140.9 (d), 134.6 (d), 132.6 (s), 128.8 (s), 128.0 (d), 126.3 (d), 118.0 (s), 117.1 (s), 115.7 (d), 110.0 (d), 105.5 (d), 100.4 (d), 33.1 (t), 25.4 (t), 11.8 (q). MS (ES^+) $C_{19}H_{15}N_5O_2$ requires 345, found: 346 ($M+H^+$, 100%). HRMS (ES^+) m/z 346.1304, $C_{19}H_{16}N_5O_2$ requires 346.1304.

1.5.15. 3-(5-Methylisoxazol-3-yl)-5-[2-(pyridin-2-yl)-ethyl]-[1,2,3]-triazolo[1,5-*a*]quinazoline (14b). The reaction was carried out as described for **14a** using the dihydrotriazoloquinazoline **13b** (85 mg, 0.24 mmol) to yield the desired triazoloquinazoline (70 mg, 82%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.76 (1H, d, J=8.2 Hz), 8.55 (1H, d, J=4.8 Hz), 8.31 (1H, d, J=8.2 Hz), 7.99 (1H, t, J=8.2 Hz), 7.74 (1H, t, J=7.7 Hz), 7.65–7.55 (1H, m), 7.38 (1H, d, J=7.7 Hz), 7.20–7.10 (1H, m), 6.81 (1H, s), 3.86 (2H, t, J=7.5 Hz), 3.53 (2H, t, J=7.5 Hz), 2.57 (3H, s). ^{13}C NMR ($CDCl_3$+10% CD_3OD, 100 MHz) δ 169.7 (s), 165.2 (s), 160.1 (s), 154.9 (s), 148.7 (d), 143.2 (s), 137.1 (d), 134.8 (d), 132.9 (s), 128.7 (s), 128.3 (d), 126.9 (d), 124.1 (d), 121.7 (d), 118.3 (s), 115.9 (d), 100.7 (d), 34.8 (t), 34.4 (t), 12.1 (q). MS (ES^+) $C_{20}H_{16}N_6O$ requires 356, found: 357 ($M+H^+$, 100%). HRMS (ES^+) m/z 357.1474, $C_{20}H_{17}N_6O$ requires 357.1464.

1.5.16. 5-[2-(1-Methyl-1*H*-imidazol-2-yl)-ethyl]-3-(5-methylisoxazol-3-yl)-[1,2,3]-triazolo[1,5-*a*]quinazoline (14d). The reaction was carried out as described for **14a** using the dihydrotriazoloquinazoline **13d** (77 mg, 0.21 mmol) and DDQ (120 mg, 0.52 mmol) to yield the desired triazoloquinazoline (21 mg, 27%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.68 (1H, d, J=8.2 Hz), 8.45 (1H, d, J=8.2 Hz), 8.01 (1H, t, J=8.2 Hz), 7.82 (1H, t, J=8.2 Hz), 7.18 (1H, s), 7.01 (1H, s), 6.77 (1H, s), 4.41 (2H, br s), 4.16 (3H, s), 3.70 (2H, br s), 2.56 (3H, s). MS (ES^+) $C_{19}H_{17}N_7O$ requires 359, found: 360 ($M+H^+$, 100%). HRMS (ES^+) m/z 360.1579, $C_{19}H_{18}N_7O$ requires 360.1573.

1.5.17. 3-(5-Methylisoxazol-3-yl)-5-[2-(2-methyl-2*H*-[1,2,4]-triazol-3-yl)-ethyl]-[1,2,3]-triazolo[1,5-*a*]quinazoline (14e). The reaction was carried out as described for **14a** using the dihydrotriazoloquinazoline **13e** (57 mg, 0.16 mmol) and DDQ (88 mg, 0.39 mmol) to yield the desired triazoloquinazoline (38 mg, 67%). ^{1}H NMR

($CDCl_3$, 360 MHz) δ 8.71 (1H, d, J=8.3 Hz), 8.27 (1H, d, J=8.3 Hz), 8.00 (1H, t, J=8.3 Hz), 7.76 (1H, t, J=8.3 Hz), 7.73 (1H, s), 6.67 (1H, s), 4.04 (3H), 3.96 (2H, t, J=6.7 Hz), 3.54 (2H, t, J=6.7 Hz), 2.53 (3H, s). ^{13}C NMR ($CDCl_3$+ 10% CD_3OD, 100 MHz) δ 169.7 (s), 163.6 (s), 154.9 (s), 149.3 (d), 149.2 (s), 136.8 (s), 135.0 (d), 132.6 (s), 128.9 (s), 128.4 (d), 126.5 (d), 118.2 (s), 115.7 (d), 100.5 (d), 35.1 (q), 31.3 (t), 21.2 (t), 11.8 (q). MS (ES^+) $C_{18}H_{16}N_8O$ requires 360, found: 361 ($M+H^+$, 100%). HRMS (ES^+) *m/z* 361.1529, $C_{18}H_{17}N_8O$ requires 361.1525.

References

1. Bryant, H. J.; Chambers, M. S.; Jones, P.; MacLeod, A. M.; Maxey, R. J. (Merck, Sharp and Dohme Ltd., UK). WO 0144250, 2001.
2. Tennant, G. *J. Chem. Soc. (C)* **1966**, 2290–2295.
3. Biagi, G.; Giorgi, I.; Livi, O.; Scartoni, V.; Velo, S.; Lucacchini, A.; Senatore, G.; De Santis, B.; Martinelli, A. *Il Farmaco* **1996**, *51*, 131–136.
4. Bertelli, L.; Biagi, G.; Giorgi, I.; Livi, O.; Manera, C.; Scartoni, V.; Lucacchini, A.; Giannaccini, G.; Barili, P. L. *Eur. J. Med. Chem.* **2000**, *35*, 333–341.
5. Sutherland, D. R.; Tennant, G. *J. Chem. Soc., Chem. Commun.* **1969**, 423–424.
6. Sutherland, D. R.; Tennant, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 534–540.
7. Hooper, D. L.; Manning, H. W.; LaFrance, R. J.; Vaughan, K. *Can. J. Chem.* **1986**, *64*, 250–254.
8. Porter, T. C.; Smalley, R. K.; Tequiche, M.; Purwono, B. *Synthesis* **1997**, 773–777.
9. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998.
10. Yagi, K.; Ogura, T.; Numata, A.; Ishii, S.; Arai, K. *Heterocycles* **1997**, *45*, 1463–1466.
11. For use in Ni-catalysed Suzuki couplings see: (a) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049–3051. (b) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060–1065. For use in Pd-catalysed Stille couplings see: (c) Badone, D.; Cecchi, R.; Guzzi, U. *J. Org. Chem.* **1992**, *57*, 6321–6323. For use in Ni-catalysed coupling with Grignard reagents see: (d) Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894–4899.
12. Chikashi, N.; Minoru, M.; Shigeki, S. (Mitsubishi Chem. Corp.). JP 9124687, 1997.
13. For representative examples see: (a) Patel, M.; Rodgers, J. D.; McHugh, R. J.; Johnson, B. L.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Ko, S. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3217–3220. (b) Gordon, D. W. *Synlett* **1998**, 1065–1066. (c) Guiller, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Queguiner, G.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 292–296.
14. Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359–5364.
15. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470. (b) For a review see: Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Int.* **1995**, *27*, 127–160.
16. Taniguchi, M.; Kobayashi, S.; Nakagawa, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4763–4766.
17. Gainer, J.; Howarth, G. A.; Hoyle, W.; Roberts, S. M.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 994–997.
18. Kosugi, M.; Koshiba, M.; Atoh, A.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 677–679.
19. Blurton, P.; Burkamp, F.; Cheng, S. K. -F.; Fletcher, S. R.; MacLeod, A. M.; Van Niel, M. B. (Merck, Sharp and Dohme Ltd., UK). WO 0043362, 2000.