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An efficient and selective access to 1-substituted and 3-substituted derivatives of luotonin A

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Dedicated with best wishes to Professor Gottfried Heinisch on the occasion of his 75th birthday

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ABSTRACT

A method for the selective introduction of a substituent into position 1 or position 3 of the antitumour alkaloid, luotonin A, is described. The protocol involves a base-catalysed intramolecular [4+2] cycloaddition reaction of an arylpropargyl unit with a carbonitrile as the key step. These educts are conveniently accessible in two steps from a known precursor. The newly developed route is orthogonal to a previously used cycloaddition approach, which gave access to 2- or 4-substituted luotonin A derivatives.

1. Introduction

As reflected by a recent review article,[1] there is increasing interest in the chemistry of luotonin A, a pentacyclic alkaloid, which had been isolated in 1997 from *Peganum nigellastrum* Bunge (Zygophyllaceae) by Ma and co-workers.[2] This compound was found to be a topoisomerase I poison, acting by a similar mechanism as camptothecin.[3] Its activity is not surprising in view of the structural similarity between these two natural products (Fig. 1): they share the same ABC ring fragment, ring D is slightly different (a pyridone in camptothecin and a pyrimidone in luotonin A), whereas ring E differs markedly (see Fig. 1). Nevertheless, the binding mode of luotonin A to the topoisomerase-I–DNA binary complex might differ to some extent from that of camptothecin.[4]

Luotonin A lacks both the sensitive hydroxylactone structure and the chiral centre of camptothecin, therefore it offers some advantage in terms of chemical stability as well as synthetic accessibility. On the other hand, cytotoxic activity of unmodified luotonin A is considerably lower than that of camptothecin,[3] and this has stimulated a number of investigations directed towards the structural modification of luotonin A in order to identify more potent congeners. In particular, the substitution pattern of ring A has been found to be a promising target for systematic variation,[1] and several A-ring-substituted derivatives of the alkaloid have been found to exhibit higher activity than the lead compound.[5–8] Recently, we reported an improved variant of Yao's[9] total synthesis of luotonin A, which enabled us to obtain not only the parent compound in high yield, but also various 2-substituted, 4-substituted and identically 1,3-disubstituted derivatives (Scheme 1).

As a consequence of the fact that the final step in this sequence is an intramolecular [4+2] cycloaddition reaction between an anilide-derived imidoyl unit (acting as the azadiene) and a propargyl residue (as the dienophile), this route is perfectly suited for such educts where no isomer mixtures can arise from rotation around the aniline C–N bond (i.e., starting from 4-substituted or 2-

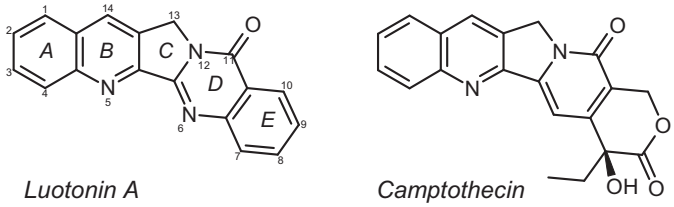

Fig. 1. Structures of luotonin A and camptothecin.

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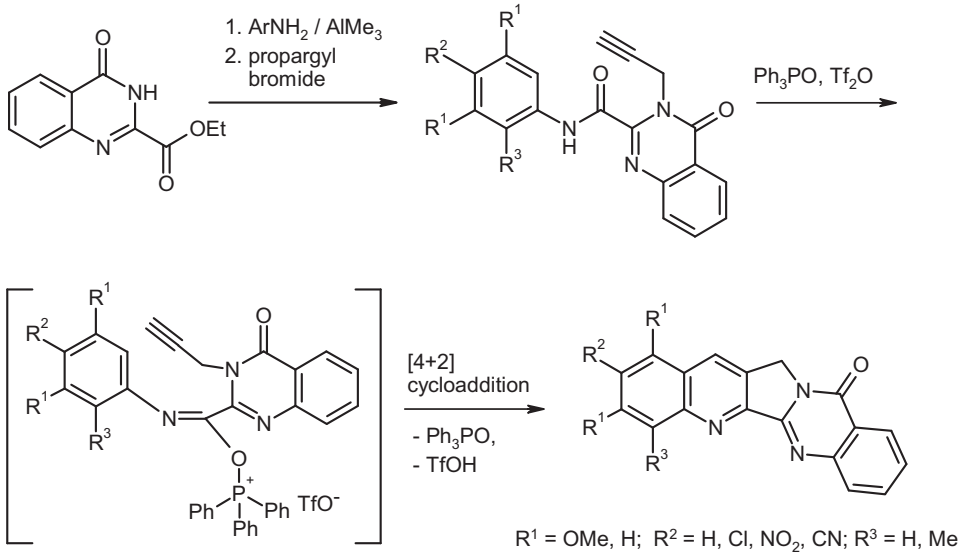


Scheme 1.

substituted or symmetrically 3,5-disubstituted anilines as building blocks). However, this strategy intrinsically fails to provide access to 1-substituted and 3-substituted products in a regioselective manner,[10] and so far there are only very few examples of such 1- or 3-monosubstituted luotonin A derivatives known, which had been prepared from halogen-substituted 2-aminobenzaldehydes as starting materials.[6] In order to close this gap, we now developed a complementary cycloaddition pathway, which enabled us to obtain a series of hitherto unknown 1-substituted and 3-substituted luotonin A derivatives in a concise, flexible and efficient manner.

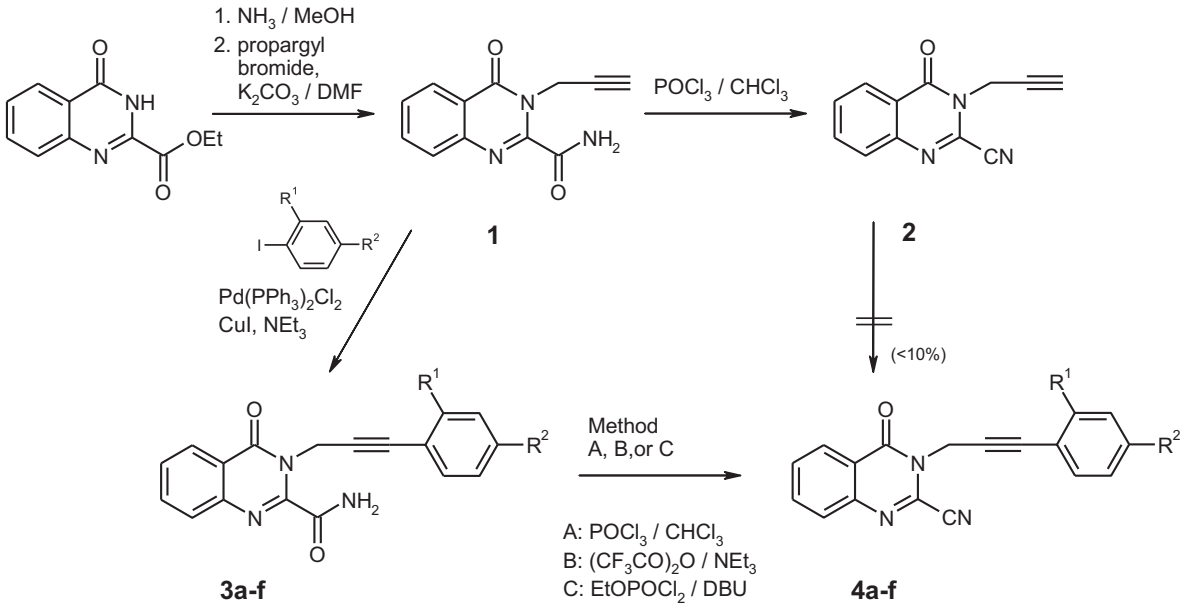
2. Results and discussion

We envisaged that rearranging the topology of diene and dienophile, by attaching the aryl moiety to the propargyl unit and placing the requisite nitrogen atom into the dienophile, should open an access to the desired 1- and 3-substituted luotonin A derivatives. This approach appeared quite promising in view of a previous report by Wang and co-workers who had successfully performed an intramolecular cycloaddition reaction of 1-(3-arylprop-2-yn-1-yl)-1,6-dihydro-6-oxo-2-pyridinecarbonitriles to yield the ABCD ring fragment of camptothecin and some methoxy derivatives thereof. In order to apply this concept to the synthesis of the pentacyclic quinolino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazoline skeleton of luotonin A, an appropriate 4-oxo-3-(3-arylprop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carbonitrile would be required as the key intermediate. Thus, we first developed a convenient and flexible method for the preparation of such synthons.

In order to introduce diversity as late as possible in the envisaged reaction sequence, we first attempted to generate the requisite arylpropargyl-substituted quinazolinonecarbonitriles (**4**) by Sonogashira coupling of appropriate aryl iodides with 4-oxo-3-(prop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carbonitrile (**2**), a b uilding block, which could be conveniently prepared from the known carboxamide (**1**) by dehydration using phosphorus oxychloride in boiling chloroform. However, it turned out that the Pd-catalysed cross-coupling reaction gives very poor results with this alkyne synthon, leading mainly to resinification and producing the desired coupling products in less than 10% yield after chromatographic separation of the complex reaction mixtures. But in contrast, we found that the corresponding carboxamide **1** does not suffer from this drawback and smoothly couples with a variety of aryl iodides under standard Sonogashira conditions, affording the arylpropargyl amides **3a**–**f** in satisfactory yields (Scheme 2). The subsequent dehydration reaction of the primary amides **3** into the nitriles **4** then proved to be more challenging than expected, as some of these compounds are more sensitive towards decomposition than the prototype **1**, which had been easily dehydrated under relatively harsh conditions, as described above. Finally, we could accomplish this transformation by one of three different methods, depending on the respective educt: the desired carbonitriles **4a**–**f** thus were obtained either by refluxing in phosphorus oxychloride/chloroform (method A), treatment with trifluoroacetic anhydride/triethylamine in dry dichloromethane at 0 °C (method B),[12] or reaction with ethyl dichlorophosphate/DBU in dry dichloromethane at room temperature (method C).[13] In all cases, the successful dehydration was indicated by the appearance of a less polar spot on TLC, and the products in their mass spectra expectedly show a molecular ion peak of 18 units less than for the educts **3**, together with the disappearance of the two distinct NH resonances in the ^{1}H NMR spectra and the appearance of a typical nitrile carbon signal at around 110 ppm in the ^{13}C NMR spectra.

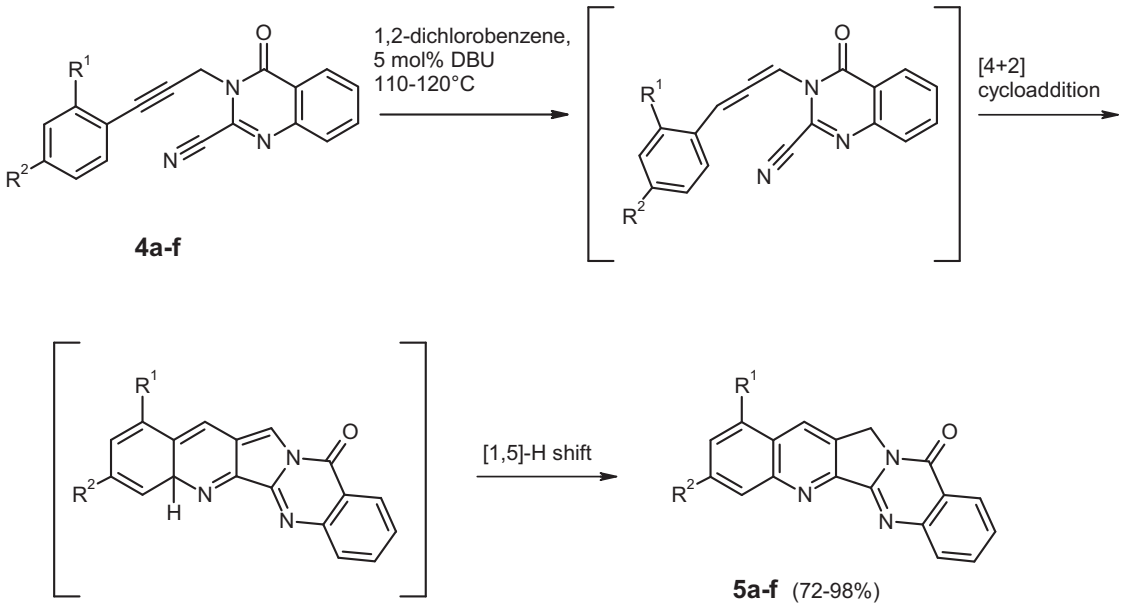
With the key synthons **4** now conveniently available, the stage was set for the final cycloaddition step, which should simultaneously assemble rings B and C of the luotonin A skeleton. By employing Wang's conditions (heating in 1,2-dichlorobenzene at 110–120 °C in the presence of 5 mol % DBU), we found that all of the compounds, almost regardless of electronic and steric properties of the different substituents, cyclised very smoothly into the target luotonin A derivatives **5a**–**f** (Scheme 3). The latter were isolated in excellent yields simply by filtration after dilution of the reaction mixtures with diethyl ether.

The [4+2] cycloaddition reaction presumably takes place after an initial alkyne/allene isomerisation, which is mediated by the base DBU, as proposed previously,[11] but also a stepwise mechanism involving a biradicalic intermediate[14] cannot be ruled out. A 1,5-hydrogen shift in the primary cycloadduct then produces the fully aromatic quinoline scaffold (rings A and B). Reaction times typically are 24 h with the exception of the *ortho*-tolyl substrate **4a** (48 h) and the electron-poor ester **4f** (12 h). Thus, the method is perfectly suitable for the selective introduction of electron-donating as well as electron-withdrawing substituents into position 1 or position 3 of the alkaloid. Moreover, our route is rather



	yields, **3a-f**	yields, **4a-f**	method
a: R^1 = Me, R^2 = H	67%	87%	B
b: R^1 = OMe, R^2 = H	81%	97%	B
c: R^1 = CO_2Et, R^2 = H	48%	87%	B
d: R^1 = H, R^2 = Me	44%	47%	A
e: R^1 =H, R^2 = OMe	45%	96%	C
f: R^1 = H, R^2 = CO_2Et	60%	73%	A

Scheme 2.



Scheme 3.

short, consisting of only three steps from the known amide **1** (the latter, in turn, is conveniently accessible from commercially available anthranilamide by proven protocols[9,15,16]). The structures of the new compounds are in full agreement with their analytical and spectroscopic data. The ^{1}H NMR signal patterns, in particular those of the quinoline protons, can be easily assigned by NOE techniques, making use of the spatial proximity of 14-H and the methylene protons at 13-C as the starting point. The mass spectra of compounds **5**, although they have the same molecular masses as their precursors **4**, show marked differences compared to the latter in terms of significantly less fragmentation, with the molecular ion representing the base peak in all cases.

3. Conclusion

With the described synthetic route, a gap in the systematic variation of the substitution pattern in ring A of the antitumour alkaloid, luotonin A, could be closed, thus enabling further studies of structure–activity relationships within this class of compounds. As demonstrated, the method is compatible both with electron-rich and electron-poor substituents, which can be selectively introduced either into position 1 or position 3 of the pentacyclic skeleton. Together with the previously reported approach,[8,9] there are now two orthogonal cycloaddition pathways available, which allow the selective introduction of various substituents into all available positions at ring A of luotonin A.

4. Experimental

4.1. General

Melting points (uncorrected) were determined on a Kofler hot-stage microscope (Reichert). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity*Plus* 300 spectrometer at 300 MHz and 75 MHz, respectively, and on a Bruker Avance III 400 spectrometer at 400 MHz and 100 MHz, respectively. Mass spectra were obtained on a Shimadzu QP5050A DI 50 instrument, high-resolution mass spectra were recorded on a Finnigan MAT 8230 spectrometer or on a Bruker maXis spectrometer at the Institute of Organic Chemistry, University of Vienna, or on a Shimadzu LCMS-IT-TOF instrument at the Institute of Chemical Technologies and Analytics, Vienna University of Technology. Column chromatography was carried out on Merck Kieselgel 60, 0.063–0.200 mm, thin layer chromatography was done on Merck aluminium sheets pre-coated with Kieselgel 60F_{254}. Microanalyses were performed at the Microanalytical Laboratory, Faculty of Chemistry, University of Vienna. Ethyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate,[9,15] 4-oxo-3,4-dihydroquinazoline-2-carboxamide,[15,17] 4-oxo-3-(prop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carboxamide[16] and ethyl 2-iodobenzoate[18] were prepared according to literature procedures.

4.2. Procedures

*4.2.1. 4-Oxo-3-(prop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carbonitrile (**2**).* To a suspension of 4-oxo-3-(prop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carboxamide (1136 mg, 5.0 mmol) in dry $CHCl_3$ (30 mL) was added $POCl_3$ (10 mL) and the mixture was refluxed for 8 h with exclusion of moisture, then it was stirred at room temperature for another 16 h. The dark-brown solution was chilled and slowly poured into ice-water (200 mL). The two-phase system was vigorously stirred for 30 min, then the phases were separated and the aqueous layer was repeatedly extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried over Na_2SO_4 and passed through a short silica column. Evaporation in vacuo, followed by recrystallisation of the residue from EtOH afforded the nitrile **2** as colourless crystals (649 mg, 62%), mp 141–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37–8.31 (m, 1H, 5-H), 7.91–7.84 (m, 1H, 7-H), 7.83–7.79 (m, 1H, 8-H), 7.71–7.63 (m, 1H, 6-H), 5.07 (d, J=2.4 Hz, 2H, CH_2), 2.44 (t, J=2.4 Hz, 1H, C≡CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 146.1, 135.3, 130.6, 130.3, 128.6, 127.3, 122.6, 111.1, 75.8, 74.2, 35.0; MS (EI, 70 eV) m/z 209 (M^+, 100%), 154 (50), 77 (44), 76 (76), 64 (69), 63 (68), 51 (46), 50 (71). Anal. Calcd for $C_{12}H_7N_3O$: C, 68.89; H, 3.37; N, 20.09. Found: C, 68.77; H, 3.30; N, 19.98.

*4.2.2. 3-(3-Arylprop-2-yn-1-yl)-4-oxo-3,4-dihydroquinazoline-2-carboxamides (**3a**–**f**). General procedure.* A solution of 4-oxo-3-(prop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carboxamide[16] (227 mg, 1.0 mmol) in dry dimethylformamide (1.0 mL) was diluted with dry CH_2Cl_2 (15 mL) and the mixture was flushed with argon. After consecutive addition of the appropriate aryl iodide (1.5 mmol), 2,6-di-*tert*-butyl-4-methylphenol (55 mg, 0.25 mmol), CuI (38 mg, 0.2 mmol), $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol) and triethylamine (243 mg, 2.4 mmol), the mixture was again flushed with argon, then it was stirred in a closed vessel for 3 h at room temperature (TLC monitoring: CH_2Cl_2/EtOH, 9:1). The dark mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a short pad of silica gel, eluting with CH_2Cl_2 (100 mL). The solution was washed with 0.5 N HCl and water, dried (Na_2SO_4) and evaporated. The residue was subjected to column chromatography, eluting first with CH_2Cl_2 (to give some unchanged aryl iodide) and then with CH_2Cl_2/ethyl acetate (4:1), followed by recrystallisation, to afford the pure products.

*4.2.2.1. 3-[3-(2-Methylphenyl)prop-2-yn-1-yl]-4-oxo-3,4-dihydroquinazoline-2-carboxamide (**3a**).* Yield: 213 mg (67%); pale yellow needles, mp 199–203 °C (toluene/ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (br s, 1H, NH), 8.23 (dd, J=7.9, 1.5 Hz, 1H, 5-H), 8.22 (br s, 1H, NH), 7.92 (ddd, J=8.2, 7.2, 1.5 Hz, 1H, 7-H), 7.77 (dd, J=8.2, 1.0 Hz, 1H, 8-H), 7.65 (ddd, J=8.0, 7.2, 1.2 Hz, 1H, 6-H), 7.37 (d, J=7.6 Hz, 1H, phenyl 6′-H), 7.29–7.23 (m, 2H, phenyl 3′-H, 4′-H), 7.19–7.13 (m, 1H, phenyl 5′-H), 5.34 (s, 2H, CH_2), 2.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 160.0, 148.9, 145.9, 140.1, 135.1, 131.8, 129.5, 128.8, 128.3, 127.6, 126.5, 125.7, 121.5, 121.0, 88.4, 81.8, 33.8, 20.1; MS (EI, 70 eV) m/z 317 (M^+, 32%), 273 (14), 144 (13), 129 (28), 128 (100), 127 (30), 102 (16), 77 (14), 63 (9). HRMS (ESI) m/z 318.1240 ($[M+H]^+$ calcd for $C_{19}H_{16}N_3O_2$: 318.1237).

*4.2.2.2. 3-[3-(2-Methoxyphenyl)prop-2-yn-1-yl]-4-oxo-3,4-dihydroquinazoline-2-carboxamide (**3b**).* Yield: 270 mg (81%); pale yellow crystals, mp 179–182 °C (toluene/ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (br s, 1H, NH), 8.22 (br s, 1H, NH), 8.22 (dd, J=8.0, 1.5 Hz, 1H, 5-H), 7.92 (ddd, J=8.2, 7.2, 1.5 Hz, 1H, 7-H), 7.77 (m, 1H, 8-H), 7.65 (ddd, J=8.0, 7.2, 1.2 Hz, 1H, 6-H), 7.36–7.32 (m, 2H, phenyl 4′-H, 6′-H), 7.02 (dd, J=8.9, 1.0 Hz, 1H, phenyl 3′-H), 6.89 (td, J=7.5, 1.0 Hz, 1H, phenyl 5′-H), 5.33 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 160.0, 159.8, 148.9, 145.9, 135.1, 133.5, 130.4, 128.3, 127.6, 126.5, 121.0, 120.3, 111.3, 110.6, 88.0, 79.8, 55.5, 33.7; MS (EI, 70 eV) m/z 333 (M^+, 21%), 289 (8), 275 (8), 145 (31), 144 (100), 116 (23), 115 (88), 102 (25), 91 (21), 76 (23), 63 (22). HRMS (ESI) m/z 334.1192 ($[M+H]^+$ calcd for $C_{19}H_{16}N_3O_3$: 334.1186).

*4.2.2.3. Ethyl 2-[3-(2-carbamoyl-4-oxoquinazolin-3(4H)-yl)prop-1-yn-1-yl]benzoate (**3c**).* Yield: 180 mg (48%); pale yellow needles, mp 183–185 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (br s, 1H, amide-NH), 8.22 (dd, J=8.0, 1.5 Hz, 1H, 5-H), 8.21 (br s, 1H, amide-NH), 7.94–7.90 (m, 1H, 7-H), 7.81 (td, J=7.6, 1.0 Hz, 1H, phenyl 3′-H), 7.77 (dd, J=8.2, 0.6 Hz, 1H, 8-H), 7.67–7.63 (m, 1H, 6-H), 7.57–7.54 (m, 2H, phenyl 5′-H, 6′-H), 7.51–7.46 (m, 1H, phenyl 4′-H), 5.35 (s, 2H, NCH_2), 4.21 (q, J=7.1 Hz, 2H, OCH_2CH_3), 1.18 (t, J=7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.6, 163.2, 160.0, 148.8, 145.9, 135.2, 134.0, 132.2, 131.9, 129.8, 128.8, 128.3, 127.6, 126.5, 121.5, 121.0, 89.2, 81.5, 60.9, 33.9, 13.9. MS (EI, 70 eV) m/z 375 (M^+, 60%), 346 (24), 329 (13), 303 (28), 287 (15), 175 (52), 174 (39), 157 (71), 145 (100), 130 (87), 129 (83), 102 (66), 77 (51), 69 (40). Anal. Calcd for $C_{21}H_{17}N_3O_4 \cdot 0.5H_2O$: C, 65.62; H, 4.72; N, 10.93. Found: 65.59; H, 4.32; N, 10.66. HRMS (ESI) m/z 376.1294 ($[M+H]^+$ calcd for $C_{21}H_{18}N_3O_4$: 376.1292).

*4.2.2.4. 3-[3-(4-Methylphenyl)prop-2-yn-1-yl]-4-oxo-3,4-dihydroquinazoline-2-carboxamide (**3d**).* Yield: 141 mg (44%); pale yellow needles, mp 221–223 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.57 (br s, 1H, amide-H), 8.22 (br s, 1H, amide-H), 8.19 (dd, ^3J=8.0 Hz, ^4J=1.2 Hz, 1H, 5-H), 7.90 (dt, ^3J=7.7 Hz, ^4J=1.5 Hz, 1H, 7-H), 7.75 (d, J=7.8 Hz, 1H, 8-H), 7.63 (dt, ^3J=7.6 Hz, ^4J=1.1 Hz, 1H, 6-H), 7.28 (d, J=8.1 Hz, 2H, phenyl 2′-H, 6′-H), 7.14 (d, J=7.8 Hz, 2H, phenyl 3′-H,

5′-H), 5.25 (s, 2H, CH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.6, 160.3, 149.1, 146.1, 138.9, 135.4, 131.7, 129.4, 128.6, 127.8, 126.7, 121.1, 118.8, 84.0, 83.5, 33.9, 21.2; MS (EI, 70 eV) *m*/*z* 317 (M^+, 73%), 273 (25), 198 (19), 144 (23), 129 (84), 128 (100), 127 (47), 102 (40), 77 (35), 76 (28), 63 (31). Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: 71.58; H, 4.56; N, 12.88.

*4.2.2.5. 3-[3-(4-Methoxyphenyl)prop-2-yn-1-yl]-4-oxo-3,4-dihydroquinazoline-2-carboxamide (**3e**).* Yield: 142 mg (45%); pale yellow needles, mp 215–217 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (br s, 1H, amide-H), 8.22 (br s, 1H, amide-H), 8.20 (d, *J*=8.7 Hz, 1H, 5-H), 7.96–7.86 (m, 1H, 7-H), 7.75 (d, *J*=8.1 Hz, 1H, 8-H), 7.64 (t, *J*=7.5 Hz, 1H, 6-H), 7.35 (d, *J*=8.4 Hz, 2H, phenyl 2′-H, 6′-H), 6.90 (d, *J*=8.4 Hz, 2H, phenyl 3′-H, 5′-H). 5.26 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.3, 159.9, 159.5, 149.0, 145.9, 135.1, 133.1, 128.2, 127.5, 126.5, 120.9, 114.2, 113.5, 83.1, 82.9, 55.2, 33.5; MS (EI, 70 eV) *m*/*z* 333 (M^+, 45%), 275 (20), 145 (100), 144 (69), 135 (27), 130 (24), 102 (58), 76 (44), 75 (29), 63 (32). Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: 68.29; H, 4.37; N, 12.44.

*4.2.2.6. Ethyl 4-[3-(2-carbamoyl-4-oxoquinazolin-3(4H)-yl)prop-1-yn-1-yl]benzoate (**3f**).* Yield: 224 mg (60%); colourless needles, mp 209–211 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (dd, ^3J=4.1 Hz, ^4J=0.9 Hz, 1H, 5-H), 7.96–7.92 (BB′ part of an AA′BB′ system, 2H, phenyl 3′-H, 5′-H), 7.87–7.77 (m, 1H, 7-H), 7.74 (d, *J*=7.5 Hz, 1H, 8-H), 7.66–7.50 (m, 2H, 6-H, amide-H), 7.48–7.43 (AA′ part of an AA′BB′ system, 2H, phenyl 2′-H, 6′-H), 5.80 (br s, 1H, amide-H), 5.78 (s, 2H, CH_2), 4.36 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 1.38 (t, *J*=7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 162.9, 161.2, 145.3, 145.1, 134.8, 131.8, 130.1, 129.3, 128.9, 127.9, 127.4, 127.0, 121.9, 87.3, 82.9, 61.1, 34.0, 14.3; MS (EI, 70 eV) *m*/*z* 375 (M^+, 100%), 159 (27), 130 (28), 129 (33), 114 (42), 113 (33), 102 (38), 77 (30), 76 (27), 63 (40), 44 (25). Anal. Calcd for $C_{21}H_{17}N_3O_4$: C, 67.19; H, 4.56; N, 11.19. Found: C, 67.06; H, 4.38; N, 11.12.

*4.2.3. 3-(3-Arylprop-2-yn-1-yl)-4-oxo-3,4-dihydroquinazoline-2-carbonitriles (**4a**–**f**). General procedure. Method A.* To a solution of the amide **3** (0.3 mmol) in dry $CHCl_3$ (15 mL) was added $POCl_3$ (5 mL) and the mixture was refluxed for 24 h. After cooling, it was slowly poured into ice-water (50 mL) and the mixture was vigorously stirred for 30 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. The dried solution was passed through a short column of silica, eluting with CH_2Cl_2/ethyl acetate (95:5). Evaporation gave a solid residue, which was further purified by recrystallisation from an appropriate solvent.

Method B. To an ice-cooled solution of the amide **3** (0.3 mmol) and triethylamine (2.0 mL) in dry CH_2Cl_2 (2 mL) was slowly added trifluoroacetic anhydride (1.0 mL) with stirring. The cooling bath was removed and stirring was continued for 1 h (TLC monitoring: CH_2Cl_2/EtOH, 9:1). The mixture was poured into ice-water (20 mL) and stirred for 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with 0.5 N HCl, 10% aq $NaHCO_3$ and water. The solution was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography, eluting with CH_2Cl_2/ethyl acetate (95:5). Evaporation gave a solid residue, which was further purified by recrystallisation from an appropriate solvent.

Method C. To a solution of the amide **3** (0.3 mmol) in dry CH_2Cl_2 (5 mL) was added DBU (137 mg, 0.9 mmol) and the mixture was stirred at room temperature for 10 min. Then, ethyl dichlorophosphate (97 mg, 0.6 mmol) was added and stirring was continued for 3 h. Further portions of DBU and ethyl dichlorophosphate (0.3 mmol each) were added and the mixture was stirred for 24 h. It was then slowly poured into ice-water (50 mL) and vigorously stirred for 30 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with 0.5 N HCl, water and brine and dried over Na_2SO_4. The dried solution was passed through a short column of silica, eluting with CH_2Cl_2/ethyl acetate (95:5). Evaporation gave the pure product as a colourless solid.

*4.2.3.1. 3-[3-(2-Methylphenyl)prop-2-yn-1-yl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (**4a**).* Preparation from **3a** by method B; yield: 78 mg (87%); colourless crystals, mp 126–127 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J*=8.1 Hz, 1H, 5-H), 7.90–7.80 (m, 2H, 7-H, 8-H), 7.70–7.64 (m, 1H, 6-H), 7.42 (d, *J*=7.4 Hz, 1H, phenyl 6′-H), 7.25–7.16 (m, 2H, phenyl 3′-H, 4′-H), 7.11 (t, *J*=7.4 Hz, 1H, phenyl 5′-H), 5.34 (s, 2H, CH_2), 2.43 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 146.4, 141.1, 135.4, 132.6, 131.1, 130.4, 129.6, 129.2, 128.8, 127.5, 125.7, 122.9, 121.5, 111.5, 85.1, 85.0, 36.1, 20.8.; MS (EI, 70 eV) *m*/*z* 299 (M^+, 46%), 298 (15), 129 (36), 128 (100), 127 (33), 102 (11), 77 (14), 63 (12). Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.24; H, 4.38; N, 14.04. Found: C, 76.31; H, 4.18; N, 13.81.

*4.2.3.2. 3-[3-(2-Methoxyphenyl)prop-2-yn-1-yl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (**4b**).* Preparation from **3b** by method B; yield: 91 mg (97%); colourless crystals, mp 135–136 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (ddd, *J*=8.0, 1.5, 0.7 Hz, 1H, 5-H), 7.89–7.79 (m, 2H, 7-H, 8-H), 7.66 (ddd, *J*=8.0, 6.7, 1.7 Hz, 1H, 6-H), 7.41 (dd, *J*=7.6, 1.7 Hz, 1H, phenyl 6′-H), 7.33–7.27 (m, 1H, phenyl 4′-H), 6.90–6.83 (m, 2H, phenyl 3′-H, 5′-H), 5.35 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 159.3, 146.4, 135.4, 134.1, 131.3, 130.7, 130.3, 128.8, 127.5, 122.9, 120.5, 111.4, 111.0, 110.8, 85.3, 82.6, 55.9, 36.2; MS (EI, 70 eV) *m*/*z* 315 (M^+, 54%), 272 (66), 196 (23), 145 (31), 144 (78), 116 (24), 115 (100), 91 (27), 76 (27). Anal. Calcd for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33. Found: C, 72.42; H, 4.03; N, 13.27.

*4.2.3.3. Ethyl 2-[3-(2-cyano-4-oxoquinazolin-3(4H)-yl)prop-1-yn-1-yl]benzoate (**4c**).* Preparation from **3c** by method B; yield: 93 mg (87%); colourless needles, mp 129–131 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (ddd, *J*=8.0, 1.5, 0.6 Hz, 1H, 5-H), 7.91 (dd, *J*=7.8, 1.5 Hz, 1H, phenyl 3′-H), 7.89–7.84 (m, 1H, 7-H), 7.82 (ddd, *J*=8.2, 1.5, 0.6 Hz, 1H, 8-H), 7.68–7.64 (m, 1H, 6-H), 7.57 (dd, *J*=7.7, 1.4 Hz, 1H, phenyl 6′-H), 7.44 (dt, *J*=7.6, 1.5 Hz, 1H, phenyl 5′-H), 7.38 (dt, *J*=7.6, 1.5 Hz, 1H, phenyl 4′-H), 5.35 (s, 2H, NCH_2), 4.30 (q, *J*=7.1 Hz, 2H, OCH_2), 1.32 (t, *J*=7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 159.4, 146.4, 135.4, 134.5, 132.9, 131.7, 131.2, 130.5, 130.3, 128.8, 128.8, 127.5, 122.9, 122.1, 111.5, 86.1, 84.8, 61.4, 36.2, 14.4.; MS (EI, 70 eV) *m*/*z* 357 (M^+, 42%), 329 (28), 328 (40), 312 (19), 284 (21), 159 (41), 157 (100), 154 (67), 129 (39), 102 (48), 77 (53). Anal. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.52; H, 3.93; N, 11.62.

*4.2.3.4. 3-[3-(4-Methylphenyl)prop-2-yn-1-yl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (**4d**).* Preparation from **3d** by method A; yield: 43 mg (47%); colourless needles, mp 167–168 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J*=7.8 Hz, 1H, 5-H), 7.92–7.80 (m, 2H, 7-H, 8-H), 7.72–7.63 (m, 1H, 6-H), 7.36 (d, *J*=8.1 Hz, 2H, phenyl 2′-H, 6′-H), 7.11 (d, *J*=7.8 Hz, 2H, phenyl 3′-H, 5′-H), 5.30 (s, 2H, CH_2), 2.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 146.3, 139.3, 135.3, 132.0, 131.0, 130.2, 129.1, 128.6, 127.4, 122.7, 118.5, 111.3, 86.0, 80.5, 35.9, 21.5; MS (EI, 70 eV) *m*/*z* 299 (M^+, 91%), 270 (21), 129 (87), 128 (100), 102 (29), 77 (45), 71 (44), 69 (85), 63 (50), 57 (85), 55 (52). Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.24; H, 4.38; N, 14.04. Found: C, 75.99; H, 4.19; N, 13.83.

*4.2.3.5. 3-[3-(4-Methoxyphenyl)prop-2-yn-1-yl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile (**4e**).* Preparation from **3e** by method C; yield: 91 mg (96%); colourless crystals, mp 183–184 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J*=7.8 Hz, 1H, 5-H), 7.90–7.79 (m, 2H, 7-H, 8-H), 7.71–7.63 (m, 1H, 6-H), 7.43–7.38 (BB′

part of an AA′BB′ system, 2H, phenyl 2′-H, 6′-H), 6.85–6.80 (AA′ part of an AA′BB′ system, 2H, phenyl 3′-H, 5′-H), 5.28 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 159.2, 146.3, 135.3, 133.6, 131.0, 130.2, 128.6, 127.4, 122.8, 114.0, 113.6, 111.3, 85.9, 79.9, 55.3, 36.0; MS (EI, 70 eV) *m*/*z* 315 (M^+, 49%), 272 (63), 145 (100), 144 (46), 115 (25), 102 (59), 101 (30), 90 (22), 76 (60), 75 (48), 63 (50). Anal. Calcd for $C_{19}H_{13}N_3O_2\cdot 0.15H_2O$: C, 71.76; H, 4.22; N, 13.21. Found: C, 71.77; H, 3.93; N, 12.98. HRMS (ESI) *m*/*z* 316.1080 ($[M+H]^+$ calcd for $C_{19}H_{14}N_3O_2$: 316.1081).

*4.2.3.6. Ethyl 4-[3-(2-cyano-4-oxoquinazolin-3(4H)-yl)prop-1-yn-1-yl]benzoate (**4f**).* Preparation from **3f** by method A; yield: 78 mg (73%); colourless crystals, mp 169–171 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (td, *J*=7.8, 0.7 Hz, 1H, 5-H), 7.98 (d, *J*=8.4 Hz, 2H, phenyl 3′-H, 5′-H), 7.92–7.80 (m, 2H, 7-H, 8-H), 7.53–7.65 (m, 1H, 6-H), 7.52 (d, *J*=8.4 Hz, 2H, phenyl 2′-H, 6′-H), 5.33 (s, 2H, CH_2), 4.38 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 1.39 (t, *J*=7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 159.2, 146.3, 135.4, 132.0, 130.8, 130.7, 130.3, 129.4, 128.7, 127.4, 126.0, 122.7, 111.2, 85.0, 83.9, 61.2, 35.8, 14.3; MS (EI, 70 eV) *m*/*z* 357 (M^+, 46%), 284 (40), 187 (38), 159 (42), 114 (47), 113 (44), 76 (50), 69 (73), 63 (100), 57 (67), 55 (65). Anal. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.42; H, 3.97; N, 11.57.

*4.2.4. 1-Substituted and 3-substituted luotonin A derivatives (**5a**–**f**). General procedure.* To a solution of the appropriate nitrile **4** (0.15 mmol) in dry 1,2-dichlorobenzene (4 mL) was added a 0.1 M solution of DBU in 1,2-dichlorobenzene (0.08 mL, 0.008 mmol). After flushing with argon, the vessel was closed and heated to 110–120 °C for 24 h (for compound **5a**: 48 h, for compound **5f**: 12 h). The mixture was cooled and diluted with diethyl ether. It was kept in the refrigerator for 2 h, then the precipitate was collected by filtration and washed with diethyl ether to give the pure product.

*4.2.4.1. 1-Methylquinolino[2′,3′:3,4]pyrrolo[2,1-b]quinazolin-11(13H)-one (1-methylluotonin A) (**5a**).* Yield: 33 mg (72%), colourless crystals, mp 310–312 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, *J*=0.9 Hz, 1H, 14-H), 8.43 (dd, *J*=8.0, 1.2 Hz, 1H, 10-H), 8.32 (d, *J*=8.7 Hz, 1H, 4-H), 8.11 (d, *J*=8.2 Hz, 1H, 7-H), 7.85 (ddd, *J*=8.3, 7.1, 1.6 Hz, 1H, 8-H), 7.72 (dd, *J*=8.6, 7.0 Hz, 1H, 3-H), 7.58 (ddd, *J*=8.2, 7.2, 1.2 Hz, 1H, 9-H), 7.49 (d, *J*=6.9 Hz, 1H, 2-H), 5.35 (d, *J*=1.0 Hz, 2H, CH_2), 2.77 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 152.9, 150.9, 150.0, 149.6, 134.9, 134.7, 130.5, 129.3, 129.3, 129.2, 128.9, 128.5, 128.2, 127.6, 126.6, 121.5, 47.7, 18.6; MS (EI, 70 eV) *m*/*z* 300 (24%), 299 (M^+, 100), 298 (28), 284 (25), 150 (13), 135 (18), 77 (15), 63 (13). Anal. Calcd for $C_{19}H_{13}N_3O\cdot 0.1H_2O$: C, 75.78; H, 4.42; N, 13.95. Found: C, 75.72; H, 4.14; N, 13.72. HRMS (ESI) *m*/*z* 300.1134 ($[M+H]^+$ calcd for $C_{19}H_{14}N_3O$: 300.1131).

*4.2.4.2. 1-Methoxyquinolino[2′,3′:3,4]pyrrolo[2,1-b]quinazolin-11(13H)-one (1-methoxyluotonin A) (**5b**).* Yield: 46 mg (96%), colourless crystals, mp 309–311 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H, 14-H), 8.44 (dd, *J*=7.9, 1.5 Hz, 1H, 10-H), 8.12 (d, *J*=7.7 Hz, 1H, 7-H), 8.05 (d, *J*=8.7 Hz, 1H, 4-H), 7.86 (ddd, *J*=8.2, 7.2, 1.6 Hz, 1H, 8-H), 7.74 (t, *J*=8.2 Hz, 1H, 3-H), 7.65–7.53 (m, 1H, 9-H), 6.99 (d, *J*=7.6 Hz, 1H, 2-H), 5.34 (s, 2H, CH_2), 4.07 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 155.3, 152.9, 151.5, 150.5, 149.6, 134.7, 130.8, 129.0, 128.8, 127.6, 126.9, 126.6, 122.9, 121.8, 121.5, 106.0, 56.2, 47.7; MS (EI, 70 eV) *m*/*z* 316 (21%), 315 (M^+, 100), 300 (52), 272 (30), 243 (13), 158 (21), 136 (23), 122 (21), 69 (26), 63 (23), 57 (45), 55 (36). Anal. Calcd for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33. Found: C, 71.98; H, 3.85; N, 13.11.

*4.2.4.3. Ethyl 11-oxo-11,13-dihydroquinolino[2′,3′:3,4]pyrrolo[2,1-b]quinazoline-1-carboxylate (1-ethoxycarbonylluotonin A) (**5c**).* Yield: 49 mg (92%), colourless crystals, mp 307–308 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H, 14-H), 8.64 (d, *J*=8.6 Hz, 1H, 10-H), 8.44–8.40 (m, 2H, 2-H, 8-H), 8.10 (d, *J*=7.8 Hz, 1H, 7-H), 7.87–7.82 (m, 2H, 4-H, 9-H), 7.57 (dt, *J*=7.5, 1.1 Hz, 1H, 3-H), 7.37 (s, 2H, 5-CH_2), 4.51 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 1.49 (t, *J*=7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 160.7, 152.5, 151.5, 149.6, 149.4, 136.1, 134.7, 132.7, 131.0, 130.4, 129.3, 128.9, 127.8, 127.7, 127.3, 126.6, 121.5, 61.8, 47.8, 14.5; MS (EI, 70 eV) *m*/*z* 358 (25%), 357 (M^+, 100), 329 (23), 328 (26), 312 (7), 284 (16), 156 (7), 142 (14), 128 (8). Anal. Calcd for $C_{21}H_{15}N_3O_3\cdot 0.15H_2O$: C, 70.05; H, 4.28; N, 11.67. Found: C, 70.07; H, 3.99; N, 11.47. HRMS (ESI) *m*/*z* 358.1191 ($[M+H]^+$ calcd for $C_{21}H_{16}N_3O_3$: 358.1186).

*4.2.4.4. 3-Methylquinolino[2′,3′:3,4]pyrrolo[2,1-b]quinazolin-11(13H)-one (3-methylluotonin A) (**5d**).* Yield: 44 mg (98%), colourless crystals, mp 288–290 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, *J*=7.8 Hz, 1H, 10-H), 8.36 (s, 1H, 14-H), 8.22 (s, 1H, 4-H), 8.11 (d, *J*=8.1 Hz, 1H, 7-H), 7.85 (t, *J*=7.5 Hz, 1H, 8-H), 7.79 (d, *J*=8.4 Hz, 1H, 1-H), 7.63–7.54 (m, 1H, 9-H), 7.47 (d, *J*=8.7 Hz, 1H, 2-H), 5.28 (s, 2H, CH_2), 2.62 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 152.8, 151.1, 149.8, 149.4, 141.3, 134.5, 131.2, 131.0, 129.6, 128.8, 127.5, 127.3, 127.0, 126.4, 121.3, 47.3, 22.0; MS (EI, 70 eV) *m*/*z* 299 (M^+, 100%), 298 (33), 284 (18), 270 (9), 150 (22), 135 (15), 77 (13), 63 (9). Anal. Calcd for $C_{19}H_{13}N_3O\cdot 0.15H_2O$: C, 75.56; H, 4.44; N, 13.91. Found: C, 75.62; H, 4.13; N, 13.64. HRMS (ESI) *m*/*z* 300.1134 ($[M+H]^+$ calcd for $C_{19}H_{14}N_3O$: 300.1131).

*4.2.4.5. 3-Methoxyquinolino[2′,3′:3,4]pyrrolo[2,1-b]quinazolin-11(13H)-one (3-methoxyluotonin A) (**5e**).* Yield: 40 mg (84%), colourless crystals, mp 310–312 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, *J*=7.8, 1.5 Hz, 1H, 10-H), 8.36 (s, 1H, 14-H), 8.11 (d, *J*=8.1 Hz, 1H, 7-H), 7.90–7.82 (m, 1H, 8-H), 7.82–7.76 (m, 2H, 4-H, 1H), 7.58 (t, *J*=7.6 Hz, 1H, 9-H), 7.32 (dd, *J*=9.0, 2.6 Hz, 1H, 2-H), 5.30 (s, 2H, CH_2), 4.00 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 160.7, 152.8, 151.4, 151.2, 149.5, 134.5, 131.1, 128.8, 128.7, 127.7, 127.3, 126.5, 124.4, 122.3, 121.3, 108.1, 55.7, 47.3; MS (EI, 70 eV) *m*/*z* 315 (M^+, 100%), 300 (34), 272 (33), 158 (39), 77 (48), 76 (41), 63 (36), 57 (31), 50 (25). Anal. Calcd for $C_{19}H_{13}N_3O_2\cdot 0.2H_2O$: C, 71.55; H, 4.23; N, 13.18. Found: C, 71.66; H, 3.97; N, 12.91. HRMS (ESI) *m*/*z* 316.1082 ($[M+H]^+$ calcd for $C_{19}H_{14}N_3O_2$: 316.1081).

*4.2.4.6. Ethyl 11-oxo-11,13-dihydroquinolino[2′,3′:3,4]pyrrolo[2,1-b]quinazoline-3-carboxylate (3-ethoxycarbonylluotonin A) (**5f**).* Yield: 52 mg (97%), colourless crystals, mp 291–293 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H, 4-H), 8.52 (s, 1H, 14-H), 8.44 (d, *J*=7.8 Hz, 1H, 10-H), 8.29 (d, *J*=8.7 Hz, 1H, 2-H), 8.14 (d, *J*=8.1 Hz, 1H, 7-H), 8.03 (d, *J*=8.7 Hz, 1H, 1-H), 7.94–7.84 (m, 1H, 8-H), 7.66–7.57 (m, 1H, 9-H), 5.39 (s, 2H, CH_2), 4.49 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 1.48 (t, *J*=7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 160.6, 152.4, 152.1, 149.3, 148.9, 134.7, 133.1, 132.5, 131.4, 131.1, 130.9, 128.9, 128.2, 128.0, 127.7, 126.5, 121.4, 61.7, 47.4, 14.3; MS (EI, 70 eV) *m*/*z* 357 (M^+, 100%), 329 (27), 312 (23), 284 (57), 76 (43), 69 (35), 63 (40), 57 (73), 55 (49). Anal. Calcd for $C_{21}H_{15}N_3O_3\cdot 0.3H_2O$: C, 69.53; H, 4.33; N, 11.58. Found: C, 69.56; H, 4.10; N, 11.51. HRMS (ESI) *m*/*z* 358.1187 ($[M+H]^+$ calcd for $C_{21}H_{16}N_3O_3$: 358.1186).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.06.040.

These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Liang, J. L.; Cha, H. C.; Jahng, Y. *Molecules* **2011**, *16*, 4861–4883.
2. Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541–546.
3. Cagir, A.; Jones, S. H.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628–13629.
4. Cagir, A.; Eisenhauer, B. M.; Gao, R.; Thomas, S. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 6287–6299.
5. Dallavalle, S.; Merlini, L.; Beretta, G. L.; Tinelli, S.; Zunino, F. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5757–5761.
6. Rahman, A. F. M. M.; Kim, D. H.; Liang, J. L.; Lee, E.-S.; Na, Y.; Jun, K.-Y.; Kwon, Y.; Jahng, Y. *Bull. Korean Chem. Soc.* **2008**, *29*, 1988–1992.
7. Nacro, K.; Zha, C.; Guzzo, P. R.; Herr, R. J.; Peace, D.; Friedrich, T. D. *Bioorg. Med. Chem.* **2007**, *15*, 4237–4246.
8. Haider, N.; Nuß, S. *Molecules* **2012**, *17*, 11363–11378.
9. Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *J. Org. Chem.* **2007**, *72*, 6270–6272.
10. In order to verify this assumed limitation, we performed a control experiment, employing the *meta*-substituted anilide, *N*-(3-methylphenyl)-4-oxo-3-(prop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carboxamide, as the starting material in the triphenylphosphine oxide/triflic anhydride mediated cyclisation. Indeed, this reaction gave an isomer mixture of 1-methylluotonin A (**5a**) and 3-methylluotonin A (**5d**) in a ratio of approx. 2:3 (see Supplementary data)
11. Dai, W.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2006**, *8*, 4665–4667.
12. Khanna, I. K.; Yu, Y.; Huff, R. M.; Weier, R. M.; Xu, X.; Koszyk, F. J.; Collins, P. W.; Cogburn, J. N.; Isakson, P. C.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Yuan, J.; Yang, D.-C.; Zhang, Y. Y. *J. Med. Chem.* **2000**, *43*, 3168–3185.
13. Kuo, C.-W.; Zhu, J.-L.; Wu, J.-D.; Chu, C.-M.; Yao, C.-F.; Shia, K.-S. *Chem. Commun.* **2007**, 301–303.
14. Bowman, W. R.; Cloonan, M. O.; Fletcher, A. J.; Stein, T. *Org. Biomol. Chem.* **2005**, *3*, 1460–1467.
15. Baker, B. R.; Almaula, P. I. *J. Org. Chem.* **1962**, *27*, 4672–4674.
16. Usifoh, C. O.; Scriba, G. K. E. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 261–266.
17. Joshi, V.; Chaudhari, R. P. *Indian J. Chem. B* **1987**, *26B*, 602–604.
18. Hosangadi, B. D.; Dave, R. H. *Tetrahedron Lett.* **1996**, *37*, 6375–6378.