An efficient access to novel 2*H*-pyrazino[2,1-*b*]quinazoline-1,6-diones *via* intramolecular alkyne hydroamination

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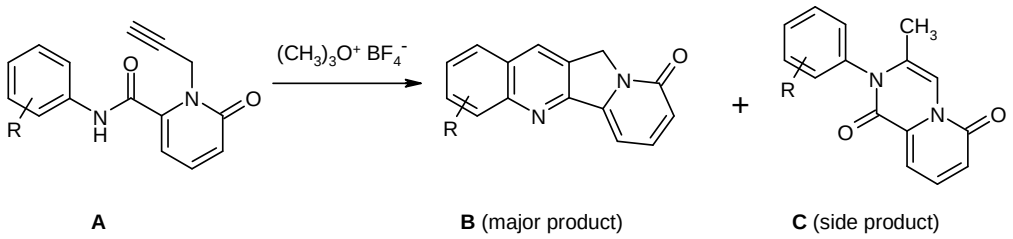
Abstract
Starting from 3-propargylquinazolin-4(3*H*)-ones bearing a primary or secondary carboxamide group at position 2, an intramolecular alkyne hydroamination reaction, catalyzed by mercury(II) acetate, afforded 2*H*-pyrazino[2,1-*b*]quinazoline-1,6-diones in a two-step process that involves a rearrangement of the primary cyclization products. The title compounds represent a novel type of tricyclic heteroaromatic scaffolds.

Keywords: Alkyne hydroamination, rearrangement, quinazolines, pyrazines, pyrazino[2,1-*b*]-quinazolines

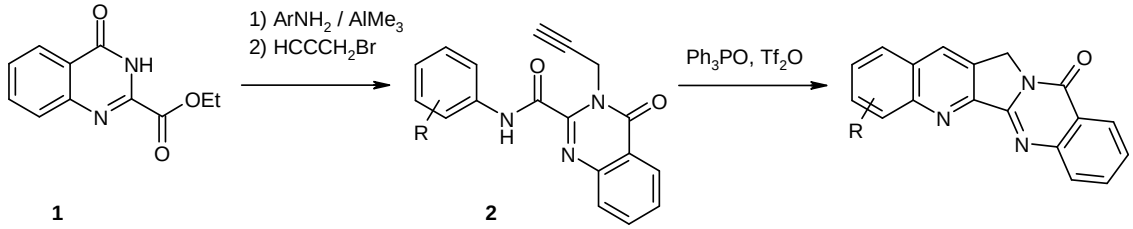
Introduction

N-Propargyl-2(1*H*)-pyridones with an *N*-arylcarboxamide functionality at position 6 (**A**) have been demonstrated to be excellent precursors for the synthesis of Camptothecin analogues *via* an intramolecular [4+2] cycloaddition reaction.[1] In this key step (see Scheme 1), the C/C triple bond of the propargyl residue in compounds of type **A** acts as the dienophile, whereas the azadiene is generated *in situ* from the anilide unit by transformation into an imidoester-type species. For this purpose, employment of Hendrickson's reagent [bis(triphenyl)oxodiphosphonium trifluoro-methanesulfonate] was reported to be the best choice, whereas Meerwein's salt (trimethyl-oxonium fluoroborate) gives lower yields of the cycloaddition product (**B**) and furthermore gives rise to the formation of small amounts (5%) of a 2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione side product (**C**).[1] The latter compound, however, represents an interesting, hitherto unknown example of a *c*-fused pyrazinone.



Scheme 1. A previously reported cyclization reaction of propargyl-containing anilides.[1]

We have recently made extensive use of a similar cycloaddition approach, based on the prototypical example reported by Zhou *et al.*,[2] to prepare a series of A-ring-modified derivatives of the pentacyclic alkaloid, Luotonin A (Scheme 2).[3] As substrates for the hetero-Diels-Alder reaction, various anilides of 4-oxo-3,4-dihydroquinazoline-2-carboxylic acid had been employed which are conveniently accessible in only two steps from ethyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate.



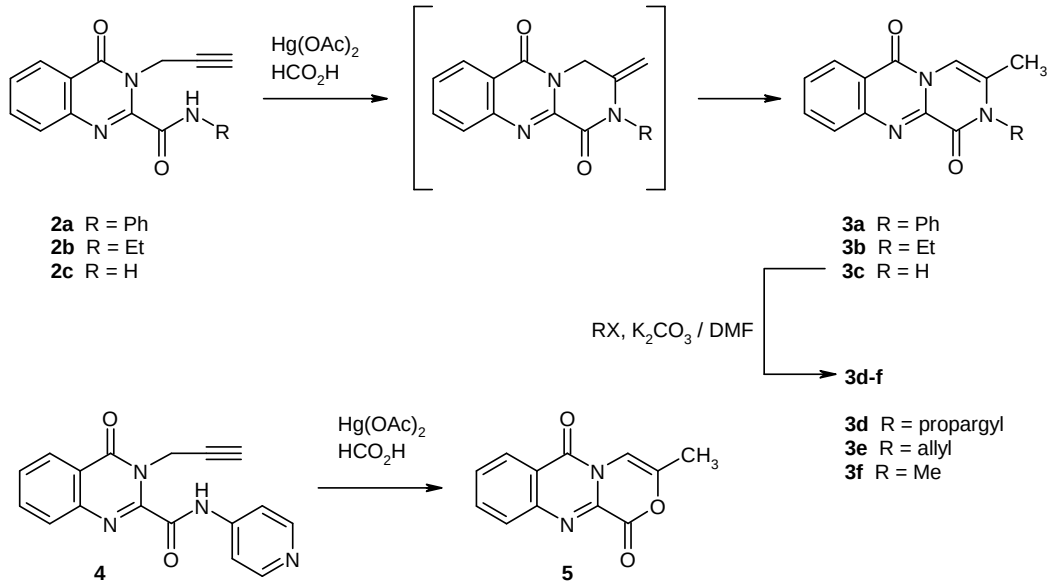
Scheme 2. Synthesis of A-ring modified Luotonin A derivatives.[2,3]

In view of the reported side reaction,[1] leading to the fused pyrazinone (see above), we envisaged our propargyl-substituted quinazolinonecarboxamides as potential precursors for novel tricyclic pyrazinones, although such compounds had never been observed in the cycloaddition reactions of the anilides when Hendrickson's reagent was used as the promotor. Nevertheless, we anticipated that subjecting these amides to reaction conditions that are typically employed for the anti-Markovnikov hydration of alkynes[4] should permit the desired ring closure reaction between the amide nitrogen and the propargyl residue. Here, we wish to report on the application of this concept (known as alkyne hydroamination triggered cyclization[5]) for the convenient synthesis of a small series of novel 3-methyl-2*H*-pyrazino[2,1-*b*]quinazoline-1,6-dione derivatives that represent an interesting new molecular scaffold.

Results and Discussion

Among the numerous conditions that have been used for alkyne hydration,[4] the classical combination of mercury(II) salts with an acidic reaction medium represents a robust, reliable and

inexpensive method. Other reagents that have been successfully used for similar alkyne hydroaminations such as bismuth,[6] silver,[7] gold[7,8] and platinum[6] catalysts can offer specific advanteges in terms of toxicity, efficiency or regioselectivity. Indeed, when the anilide **2a** was refluxed in 90% formic acid in the presence of catalytic amounts of mercury(II) acetate, TLC showed complete consumption of the starting material within 3 hours and the appearnace of a new spot with an intense blue fluorescence. The product isolated in 60% yield after aqueous work-up and chromatographic purification was indeed identified as the expected tricyclic pyrazinone (**3a**). Like in Zhou's side product (see above), the C/C double bond is located inside the pyrazine ring rather than as an exocyclic methylene group that must have been initially formed (examples of such exocyclic methylene cyclization products have been reported previously[9]): in the ^{1}H NMR spectrum, a three-proton signal of the methyl group is observed at 1.92 ppm, whereas the pyrazine proton (4-H) appears at 7.63 ppm. Both resonances show a weak coupling (*J* 1.2 Hz) that is also confirmed by the COSY spectrum. In the ^{13}C NMR spectrum, the corresponding signals of diagnostic relevance are those at 18.5 ppm (CH_3) and 101.4 ppm (4-C). Complete listings and assignments of all ^{1}H and ^{13}C NMR signals, based on HSQC, HMBC, COSY and NOESY experiments, are given in the Experimental. In the mass spectrum, the molecular ion represents the base peak at *m/z* 303. This exocyclic-to-endocyclic rearrangement of the C/C double bond *via* hydrogen shift is obviously driven by a gain in resonance energy for the fully conjugated tricyclic system. It is of interest to note that under basic conditions, such as reported for the intramolecular hydroamination of propargyl-substituted pyrrolecarboxamides,[10] compounds **2** do not cyclize into **3**.



Scheme 3. Synthesis of the tricyclic pyrazinones **3** by intramolecular alkyne hydroamination.

To briefly examine the scope of this route, we also employed an *N*-alkylamide (*N*-ethyl-4-oxo-3-(prop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carboxamide, **2b**) as well as the corresponding

primary amide (**2c**) as substrates in the mercury(II)-catalyzed cyclization reaction. In both cases, the desired tricyclic pyrazinones of type **3** were obtained in satisfactory yields after the usual work-up and purification procedure. It should be noted that in the case of **2c** (which is conveniently available[11]), the reaction conditions had to be modified (room temperature rather than refluxing) to avoid excessive decomposition of the reactant. On the other hand, it is obvious that secondary amides bearing sensitive residues (*e.g.*, a propargyl group) at the amide nitrogen are not compatible with this method. However, such residues can be easily introduced at a later stage, as demonstrated by the facile preparation of the 2-propargyl derivative (**3d**) from the 2-unsubstituted tricycle (**3c**). Further examples for such modifications of **3c** by N-alkylation are given by the synthesis of the allyl compound (**3e**) and the methyl derivative (**3f**).

Interestingly, with the *N*-(pyrid-4-yl)carboxamide **4**,[3] the reaction failed to give a pyridyl-substituted tricycle, but resulted in a complex mixture from which we could isolate another cyclization product (**5**), albeit in very low yield (10%). This compound was identified as 3-methyl[1,4]oxazino[3,4-*b*]quinazoline-1,6-dione. Its ^{1}H NMR spectrum shows a methyl signal at 2.17 ppm and the resonance of the oxazinone proton (4-H) at 7.52 ppm, again with a coupling constant of 1.2 Hz. The corresponding ^{13}C NMR signals are observed at 16.3 ppm (CH_3) and 100.1 ppm (4-C). Like with the tricyclic pyrazinones, the mass spectrum of **5** shows the molecular ion as the base peak (*m/z* 228). This compound obviously results from initial attack of an oxygen atom (probably water) at the C/C triple bond instead of attack by the amide nitrogen. The latter apparently suffers from decreased nucleophilicity because of protonation of the pyridine nitrogen in the strongly acidic medium. Regardless of the actual reaction mechanism (alkyne hydration and then cyclization of the enolic form *versus* addition of the amide oxygen and subsequent partial hydrolysis of the cyclic imidate), ring closure with concomitant loss of 4-aminopyridine in any case affords the tricyclic oxazinone (**5**).

Conclusions

It could be demonstrated that primary as well as secondary amides (either *N*-aryl or *N*-alkyl-amides) of 3-propargyl-4-oxo-3,4-dihydroquinazoline-2-carboxylic acid can be conveniently converted into 3-methyl-2*H*-pyrazino[2,1-*b*]quianzoline-1,6-diones *via* an alkyne hydro-amination triggered cyclization reaction. The products represent an unexplored structural motif that is of some interest from a Medicinal Chemistry perspective as a versatile new scaffold.

Experimental Section

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 Bruker Avance III 400 spectrometer at 400 MHz and 100 MHz, respectively. Mass spectra (EI) were obtained on a

Shimadzu QP5050A DI 50 instrument; high-resolution mass spectra (ESI) were recorded on a Bruker maXis HD spectrometer. 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 60 F_{254}. Ethyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate (**1**),[2,12] 4-oxo-3,4-dihydroquinazoline-2-carboxamide,[12,13] 4-oxo-*N*-phenyl-3-(prop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carboxamide (**2a**),[2] 4-oxo-3-(prop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carboxamide (**2c**),[11] and 4-oxo-3-(prop-2-yn-1-yl)-*N*-(pyrid-4-yl)-3,4-dihydroquinazoline-2-carboxamide (**4**)[3] were prepared according to literature procedures.

***N*-Ethyl-4-oxo-3,4-dihydroquinazoline-2-carboxamide.** In a Teflon-lined autoclave, a mixture of ethyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate (436 mg, 2 mmol) and 10 mL of a 2.0 M ethylamine solution in methanol was heated to 100 °C with magnetic stirring for 20 h. The solution was evaporated to dryness and the solid residue was taken up in water (20 mL) and it was acidified with 2N HCl (pH 1-2). The solid was collected by filtration, washed with water and dried to afford 405 mg (93%) of the product. Recrystallisation from ethanol gave colorless crystals, mp 183–184 °C (sublimation above 130 °C). ^{1}H NMR (DMSO-d_6): δ_H 12.19 (s, 1H, 3-NH), 9.05 (s, 1H, amide NH), 8.17 (dd, *J* 7.9, 1.1 Hz, 1H, 5-H), 7.88 (ddd, *J* 8.5, 7.2, 1.5 Hz, 1H, 7-H), 7.78 (d, *J* 7.7 Hz, 1H, 8-H), 7.64–7.56 (m, 1H, 6-H), 3.39–3.25 (m, 2H, CH_2), 1.14 (t, *J* 7.2 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ_C 160.9 (4-C), 159.2 (amide C=O), 147.1 (8a-C), 145.9 (2-C), 134.7 (7-C), 127.9 (6-C), 127.5 (8-C), 126.2 (5-C), 122.6 (4a-C), 34.1 (CH_2), 14.5 (CH_3). MS (EI): *m/z* 217 (26%, M^+), 189 (46), 146 (58), 145 (60), 119 (100), 91 (27), 90 (85), 63 (30). HRMS calcd for $C_{11}H_{12}N_3O_2$ ($[M+H]^+$): 218.0924; found: 218.0924.

***N*-Ethyl-4-oxo-3-(prop-2-yn-1-yl)-3,4-dihydroquinazoline-2-carboxamide (2b).** In a 50 mL round-bottomed flask, a mixture of *N*-ethyl-4-oxo-3,4-dihydroquinazoline-2-carboxamide (43 mg, 0.2 mmol), K_2CO_3 (20 mg, 0.15 mmol), propargyl bromide (0.2 mL of a 80% solution in toluene, 1.8 mmol) and DMF (20 mL) was stirred for 2 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure and the solid residue was taken up in water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with brine and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (light petroleum/ethyl acetate, 4:1, to ethyl acetate) to give 43 mg (84%) of compound **2b** as colorless crystals mp 123–126 °C (ethyl acetate/light petroleum). ^{1}H NMR ($CDCl_3$) δ_H 8.27 (dd, *J* 8.0, 1.0 Hz, 1H, 5-H), 7.75 (ddd, *J* 8.6, 7.2, 1.5 Hz, 1H, 7-H), 7.70 (br s, 1H, NH), 7.67–7.63 (m, 1H, 8-H), 7.52 (ddd, *J* 8.2, 7.2, 1.2 Hz, 1H, 6-H), 5.48 (d, *J* 2.5 Hz, 2H, propargyl CH_2), 3.50 (qd, *J* 7.3, 6.0 Hz, 2H, ethyl CH_2), 2.24 (t, *J* 2.5 Hz, 1H, acetylenic H), 1.29 (t, *J* 7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ_C 161.2 (4-C), 160.9 (amide C=O), 146.1 (2-C), 145.4 (8a-C), 134.8 (7-C), 128.6 (6-C), 127.7 (8-C), 127.4 (5-C), 121.7 (4a-C), 79.0 (propargyl 2-C), 71.8 (propargyl 3-C), 35.0 (ethyl CH_2), 33.5 (propargyl 1-C), 14.6 (CH_3). MS (EI): *m/z* 255 (27%, M^+), 214 (42), 212 (82), 184 (100), 155 (56), 145 (41), 129 (89), 119 (49), 102 (60), 90 (63), 82 (69), 76 (45). HRMS calcd for $C_{14}H_{14}N_3O_2$ ($[M+H]^+$): 256.1081; found: 256.1080.

3-Methyl-2-phenyl-2*H*-pyrazino[2,1-*b*]quinazoline-1,6-dione (3a). In a 100 mL round-bottomed flask, a mixture of **2a** (303 mg, 1 mmol) and $Hg(OAc)_2$ (32 mg, 0.1 mmol) in 90% formic acid (60 mL) was heated to reflux with magnetic stirring for 3 h. The solution was evaporated to dryness and the brown solid residue was taken up in water (100 mL). The suspension was extracted with CH_2Cl_2 (3 × 100 mL) and the combined extracts were washed with brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (light petroleum/ethyl acetate, 4:1, to ethyl acetate) to give 182 mg (60%) of **3a** as yellow crystals; mp 217–220 °C (ethyl acetate/light petroleum). ^{1}H NMR ($CDCl_3$) δ_H 8.40 (dd, *J* 8.1, 1.2 Hz, 1H, 7-H), 8.06 (d, *J* 8.0 Hz, 1H, 10-H), 7.86 (ddd, *J* 8.4, 7.2, 1.5 Hz, 1H, 9-H), 7.63 (q, unresolved, 1H, 4-H), 7.62–7.58 (m, 1H, 8-H), 7.57–7.48 (m, 3H, phenyl 3'-H, 4'-H, 5'-H), 7.30–7.23 (m, 2H, phenyl 2'-H, 6'-H), 1.92 (d, *J* 1.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ_C 158.2 (6-C), 156.7 (1-C), 146.9 (10a-C), 140.3 (11a-C), 136.8 (phenyl 1'-C), 135.1 (9-C), 130.0 (phenyl 3'-C, 5'-C), 129.7 (10-C), 129.5 (phenyl 4'-C), 128.5 (8-C), 128.2 (phenyl 2'-C, 6'-C), 127.2 (7-C), 125.8 (3-C), 120.0 (6a-C), 101.4 (4-C), 18.5 (CH_3). MS (EI): *m/z* 304 (20%), 303 (100, M^+), 302 (24), 275 (11), 274 (31), 118 (46), 77 (48), 51 (16). HRMS calcd for $C_{18}H_{14}N_3O_2$ ($[M+H]^+$): 304.1081; found: 304.1079.

2-Ethyl-3-methyl-2*H*-pyrazino[2,1-*b*]quinazoline-1,6-dione (3b). In a 100 mL round-bottomed flask, a mixture of **2b** (255 mg, 1 mmol) and $Hg(OAc)_2$ (32 mg, 0.1 mmol) in 90% formic acid (60 mL) was heated to reflux with magnetic stirring for 2 h. The solution was evaporated to dryness and the brown solid residue was taken up in water (100 mL). The suspension was extracted with CH_2Cl_2 (3 × 100 mL) and the combined extracts were washed with brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (light petroleum/ethyl acetate, 4:1, to ethyl acetate) to give 156 mg (61%) of **3b** as yellow crystals, mp 193–200 °C (ethyl acetate/light petroleum). ^{1}H NMR ($CDCl_3$) δ_H 8.38–8.30 (m, 1H, 7-H), 8.06–7.99 (m, 1H, 10-H), 7.82 (ddd, *J* 8.5, 7.1, 1.6 Hz, 1H, 9-H), 7.56 (ddd, *J* 8.2, 7.2, 1.1 Hz, 1H, 8-H), 7.50 (q, unresolved, 1H, 4-H), 4.06 (q, *J* 7.1 Hz, 2H, CH_2), 2.34 (d, *J* 1.2 Hz, 3H, 3-CH_3), 1.34 (t, *J* 7.1 Hz, 3H, ethyl CH_3). ^{13}C NMR ($CDCl_3$) δ_C 158.0 (6-C), 156.3 (1-C), 147.0 (10a-C), 139.8 (11a-C), 135.0 (9-C), 129.5 (10-C), 128.2 (8-C), 127.0 (7-C), 125.0 (3-C), 119.7 (6a-C), 101.6 (4-C), 39.9 (CH_2), 17.2 (3-CH_3), 13.8 (ethyl CH_3). MS (EI): *m/z* 256 (17%), 255 (100, M^+), 227 (31), 199 (42), 198 (33), 130 (21), 102 (29), 76 (16). HRMS calcd for $C_{14}H_{14}N_3O_2$ ($[M+H]^+$): 256.1081; found: 256.1083.

3-Methyl-2*H*-pyrazino[2,1-*b*]quinazoline-1,6-dione (3c). In a 100 mL round-bottomed flask, a mixture of **2c** (454 mg, 2 mmol) and $Hg(OAc)_2$ (50 mg, 0.16 mmol) in 90% formic acid (60 mL) was stirred for 18 h at room temperature. The solution was evaporated to dryness and the brown solid residue was taken up in water (100 mL). The suspension was extracted with CH_2Cl_2 (3 × 150 mL) and the combined extracts were washed with brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (light petroleum/ethyl acetate, 4:1, to ethyl acetate) to give 251 mg (55%) of **3c** as yellow crystals, mp 165–167 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ_H 11.52 (s, 1H, NH), 8.26 (dd, *J* 8.1, 1.0 Hz, 1H, 7-H), 7.94 (ddd, *J* 8.4, 6.9, 1.5 Hz, 1H, 9-H), 7.90–7.85 (m, 1H,

10-H), 7.65 (ddd, *J* 8.2, 6.9, 1.3 Hz, 1H, 8-H), 7.37 (q, unresolved, 1H, 4-H), 2.12 (d, *J* 1.2 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ_C 157.6 (6-C), 156.1 (1-C), 146.2 (10a-C), 140.9 (11a-C), 134.8 (9-C), 128.5 (10-C), 127.9 (8-C), 126.6 (7-C), 124.3 /3-C), 119.4 (6a-C), 99.9 (4-C), 15.9 (CH_3). MS (EI): *m/z* 227 (97%, M^+), 199 (65), 198 (100), 170 (22), 119 (32), 102 (62), 76 (74), 75 (49), 50 (44). HRMS calcd for $C_{12}H_{10}N_3O_2$ ($[M+H]^+$): 228.0768; found: 228.0765.

3-Methyl-2-(prop-2-yn-1-yl)-2*H*-pyrazino[2,1-*b*]quinazoline-1,6-dione (3d). In a 50 mL round-bottomed flask, a mixture of **3c** (45 mg, 0.2 mmol), K_2CO_3 (20 mg, 0.15 mmol) and propargyl bromide (0.2 mL of a 80% solution in toluene, 1.8 mmol) in DMF (20 mL) was stirred for 2 h at room temperature. The solution was evaporated to dryness and the brown solid residue was taken up in water (50 mL). The suspension was extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts were washed with brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (light petroleum/ethyl acetate, 4:1, to ethyl acetate) to give 41 mg (77%) of **3d** as yellow crystals, mp 210–212 ℃ (ethyl acetate/light petroleum). ^{1}H NMR ($CDCl_3$) δ_H 8.39 (dd, *J* 8.1, 1.3 Hz, 1H, 7-H), 8.07 (d, *J* 8.2 Hz, 1H, 10-H), 7.87 (ddd, *J* 8.4, 7.2, 1.5 Hz, 1H, 9-H), 7.61 (ddd, *J* 8.1, 7.2, 1.1 Hz, 1H, 8-H), 7.57 (q, unresolved, 1H, 4-H), 4.85 (d, *J* 2.5 Hz, 2H, CH_2), 2.48 (d, *J* 1.2 Hz, 3H, CH_3), 2.33 (t, *J* 2.5 Hz, 1H, acetylenic H). ^{13}C NMR ($CDCl_3$) δ_C 158.0 (6-C), 156.2 (1-C), 146.9 (10a-C), 139.6 (11a-C), 135.2 (9-C), 129.6 (10-C), 128.6 (8-C), 127.2 (7-C), 124.7 (3-C), 120.0 (6a-C), 102.0 (4-C), 77.3 (propargyl 2-C), 73.3 (propargyl 3-C), 33.6 (propargyl 1-C), 17.0 (CH_3). MS (EI): *m/z* 265 (88%, M^+), 264 (80), 227 (43), 184 (62), 130 (100), 102 (79), 90 (46), 76 (52). HRMS calcd for $C_{15}H_{12}N_3O_2$ ($[M+H]^+$): 266.0924; found: 266.0926.

3-Methyl-2-(prop-2-en-1-yl)-2*H*-pyrazino[2,1-*b*]quinazoline-1,6-dione (3e). In a 50 mL round-bottomed flask, a mixture of **3c** (45 mg, 0.2 mmol), K_2CO_3 (20 mg, 0.15 mmol) and allyl bromide (0.2 mL, 2.3 mmol) in DMF (20 mL) was stirred for 2 h at room temperature. The solution was evaporated to dryness and the brown solid residue was taken up in water (50 mL). The suspension was extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts were washed with brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (light petroleum/ethyl acetate, 4:1, to ethyl acetate) to give 44 mg (82%) of **3e** as yellow crystals, mp 207–209 ℃ (ethyl acetate/light petroleum). ^{1}H NMR ($CDCl_3$) δ_H 8.38 (dd, *J* 8.1, 1.1 Hz, 1H, 7-H), 8.06 (d, *J* 7.9 Hz, 1H, 10-H), 7.85 (ddd, *J* 8.4, 7.1, 1.6 Hz, 1H, 9-H), 7.59 (ddd, *J* 8.2, 7.1, 1.1 Hz, 1H, 8-H), 7.53 (q, unresolved, 1H, 4-H), 5.95 (ddt, *J* 17.2, 10.4, 5.2 Hz, 1H, allyl 2'-H), 5.32–5.14 (m, 2H, allyl 3'-H), 4.68 (dt, *J* 5.2, 1.6 Hz, 2H, allyl 1'-H), 2.34 (d, *J* 1.2 Hz, 3H, 3-CH_3). ^{13}C NMR ($CDCl_3$) δ_C 158.1 (6-C), 156.4 (1-C), 147.0 (10a-C), 139.8 (11a-C), 135.1 (9-C), 131.5 (allyl 2'-C), 129.6 (10-C), 128.4 (8-C), 127.1 (7-C), 125.4 (3-C), 119.8 (6a-C), 117.9 (allyl 3'-C), 101.6 (4-C), 46.6 (allyl 1'-C), 17.1 (3-CH_3). MS (EI): *m/z* 267 (63%, M^+), 252 (40), 198 (27), 170 (23), 130 (100), 102 (74), 90 (38), 76 (38), 75 (29), 54 (37). HRMS calcd for $C_{15}H_{14}N_3O_2$ ($[M+H]^+$): 268.1081; found: 268.1081.

2,3-Dimethyl-2*H*-pyrazino[2,1-*b*]quinazoline-1,6-dione (3f). In a 50 mL round-bottomed flask, a mixture of **3c** (45 mg, 0.2 mmol), K_2CO_3 (20 mg, 0.15 mmol) and iodomethane (0.1 mL, 1.6

mmol) in DMF (20 mL) was stirred for 2 h at room temperature. The solution was evaporated to dryness and the brown solid residue was taken up in water (50 mL). The suspension was extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts were washed with brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (light petroleum/ethyl acetate, 4:1, to ethyl acetate) to give 39 mg (81%) of **3f** as yellow crystals, mp 255–257 °C (ethyl acetate/light petroleum). ^{1}H NMR ($CDCl_3$) δ_H 8.37 (d, *J* 7.8 Hz, 1H, 7-H), 8.06 (d, *J* 8.2 Hz, 1H, 10-H), 7.85 (t, *J* 7.2 Hz, 1H, 9-H), 7.58 (t, *J* 7.6 Hz, 1H, 8-H), 7.55 (s, 1H, 4-H), 3.56 (s, 3H, 2-CH_3), 2.34 (s, 3H, 3-CH_3). ^{13}C NMR ($CDCl_3$) δ_C 158.0 (6-C), 156.9 (1-C), 146.9 (10a-C), 139.6 (11a-C), 135.0 (9-C), 129.5 (10-C), 128.3 (8-C), 127.1 (7-C), 125.6 (3-C), 119.7 (6a-C), 101.4 (4-C), 31.4 (2-CH_3), 17.8 (3-CH_3). MS (EI): *m/z* 241 (92%, M^+), 212 (35), 198 (25), 184 (35), 102 (53), 57 (31), 56 (100), 55 (38). HRMS calcd for $C_{13}H_{12}N_3O_2$ ($[M+H]^+$): 242.0924; found: 242.0926.

3-Methyl[1,4]oxazino[3,4-*b*]quinazoline-1,6-dione (5). In a 100 mL round-bottomed flask, a mixture of **4** (304 mg, 1 mmol) and $Hg(OAc)_2$ (32 mg, 0.1 mmol) in 90% formic acid (60 mL) was heated to reflux with magnetic stirring for 3 h. The solution was evaporated to dryness and the brown solid residue was taken up in water (100 mL), containing K_2CO_3 (2.0 g, 14 mmol). The mixture was extracted with CH_2Cl_2 (5 × 100 mL) and the combined extracts were washed with brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (light petroleum/ethyl acetate, 4:1, to ethyl acetate) to give 22 mg (10%) of **5** as pale yellow cystals, mp 235–240 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ_H 8.29–8.23 (m, 1H, 7-H), 7.98 (ddd, *J* 8.3, 6.9, 1.5 Hz, 1H, 9-H), 7.95–7.91 (m, 1H, 10-H), 7.72 (ddd, *J* 8.3, 6.9, 1.5 Hz, 1H, 8-H), 7.52 (q, unresolved, 1H, 4-H), 2.17 (d, *J* 1.2 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ_C 156.6 (6-C), 154.5 (1-C), 146.0 (10a-C), 139.8 (3-C), 137.1 (11a-C), 135.3 (9-C), 129.1 (8-C), 128.9 (10-C), 126.7 (7-C), 120.4 (6a-C), 100.1 (4-C), 16.3 (CH_3). MS (EI): *m/z* 228 (100%, M^+), 200 (35), 158 (22), 130 (59), 102 (50), 76 (36), 75 (33), 50 (23). HRMS calcd for $C_{12}H_9N_2O_3$ ($[M+H]^+$): 229.0608; found: 229.0608.

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