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Synthesis and biological studies of new quinazolines with ether functions in position 2

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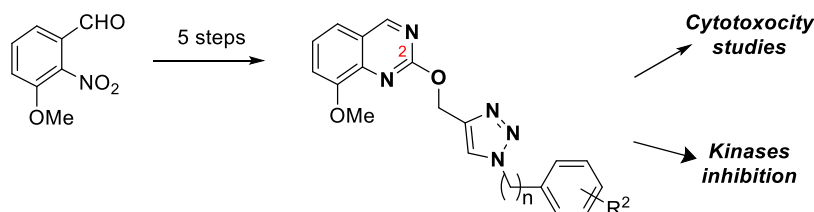
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Abstract

A series of new quinazolines linked to triazoles through an ether chain in position 2 has been designed and synthesized through a flexible route. Cytotoxicity assays on selected cancer cell lines and inhibition studies toward a panel of representative mammalian kinases have been performed on these molecules.



Keywords: Quinazolines, triazoles, cytotoxicity, kinases

Introduction

Many quinazoline alkaloids and derivatives have been isolated already, and the antimalarial (+)- Febrifugine **1** and the cytotoxic Luotonin A **2** are representative examples of this family of natural products (Figure 1).¹ From a structural point of view, almost all of them possess a quinazoline-4(3*H*)-one ring system. On the other hand, the quinazoline nucleus is also a privilege scaffold found in the basic skeleton of various types of drugs and/or bioactive molecules.²⁻⁴ Representative examples are indicated in Figure 1 and it is worth noting that all compounds **3-8**, which are potent kinase inhibitors used as anticancer drugs, have an aniline-type substituent in position 4 of this structure. Some other quinazolines, like Doxazosine **9** and Prazosin **10** (these two derivatives are used against hypertension) have both a primary amine in position 4 and a substituted piperazine in position 2.

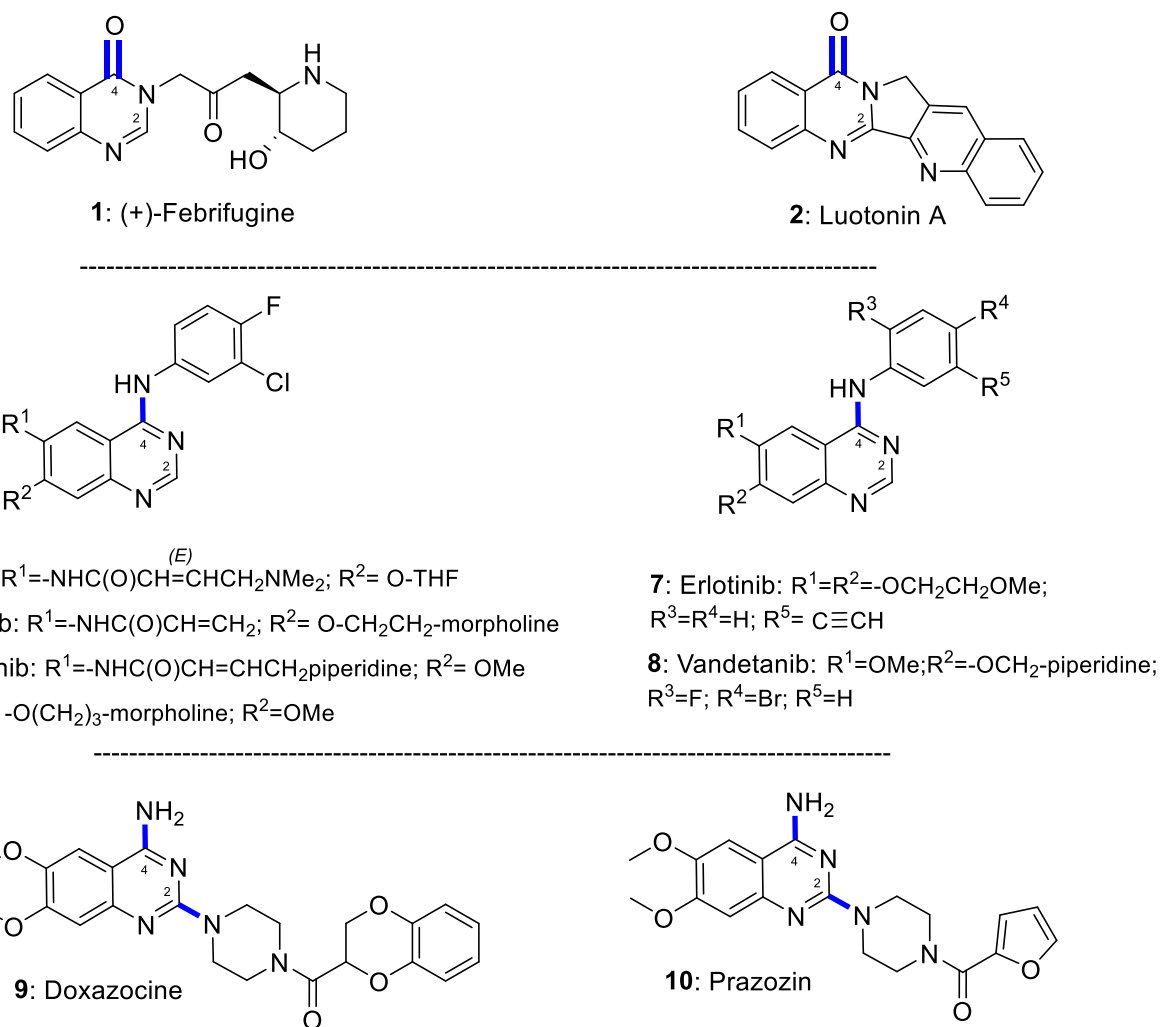


Figure 1. Representative examples of bioactive natural products and drugs with quinazoline cores.

Further, extensive literature search shows that much less is known about type-**A** molecules with **X-R¹** chains in position 2 (**X** being heteroatom like O, S and N and **R¹**= alkyl or substituted alkyl chains, aromatics, heteroaromatics.....) (Figure 2). Therefore, we embarked on a program involving the synthesis and biological evaluation of such derivatives. The goal of this paper is to report the first part of this research, dealing with the

synthesis of a focused library of oxygen-linked molecules **11** with a short linker and triazoles in terminal position. The choice of the triazole nucleus is based upon the fact that this core structure is found also in many biologically active molecules.⁵

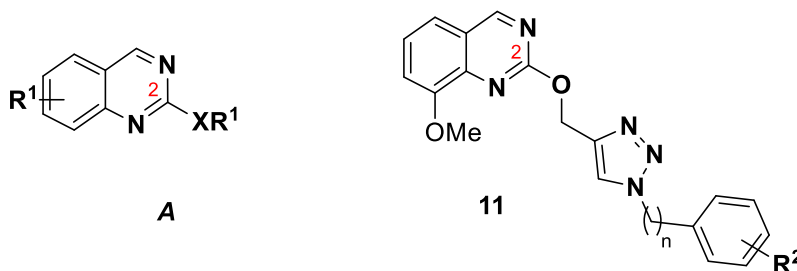
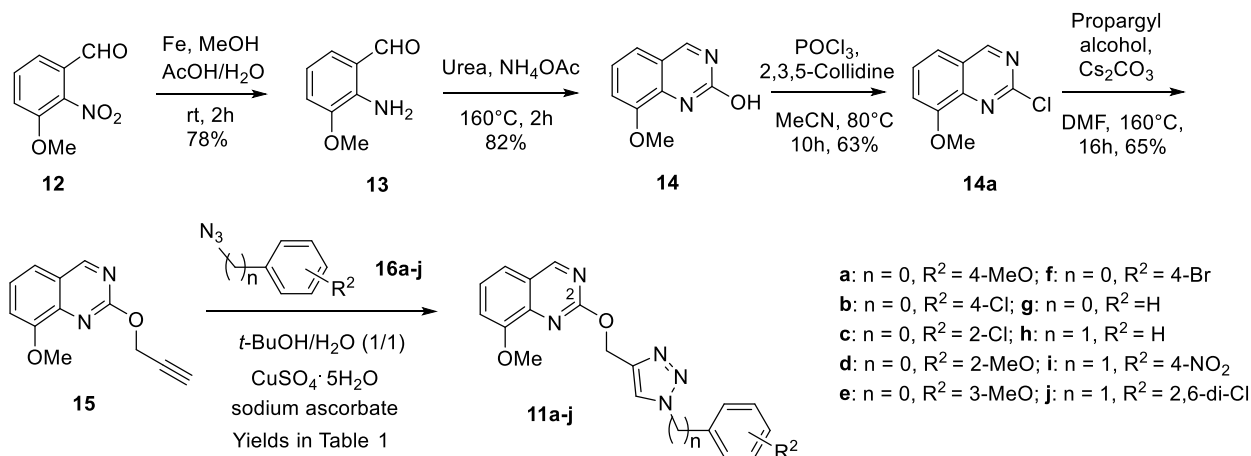


Figure 2. Our target molecules.

Results and Discussion

Chemical synthesis

Various strategies and disconnections have been reported for the synthesis of quinazolines.⁶⁻⁷ In our case we favored the approach through two C-N bond disconnections and starting from an ortho-aminobenzaldehyde derivative **13** (Scheme 1). Reaction with urea gave in good yield quinazoline **14** which was further treated by POCl₃ to give chloroquinazoline **14a**. This intermediate was reacted with propargyl alcohol to isolate in 65% yield propargyl ether **15**. Final click-type reactions,⁸⁻¹¹ with various azido derivatives **16a-j**,¹² afforded the target molecules **11a-j** in good yields (Table 1).



Scheme 1. Synthesis of quinazoline-based triazoles.

Table 1. Synthesis of our target molecules

Entry	n	R ²	Molecule	Yield %
1	0	4-MeO	11a	75
2	0	4-Cl	11b	65
3	0	2-Cl	11c	64
4	0	2-MeO	11d	68
5	0	3-MeO	11e	71
6	0	4-Br	11f	64
7	0	H	11g	74
8	1	H	11h	74
9	1	4-NO ₂	11i	50
10	1	2,6-di-Cl	11j	60

All intermediates and final products have spectral and analytical data in agreement with their structures.

Biological studies

Based on the known biological properties of molecules with quinazoline scaffolds, we performed a few primary biological screenings of the ten molecules **11a-11j**.

First, their cytotoxicity has been checked on seven representative cancer cell lines (HuH7, CaCo-2, MDA-MB231, HCT116, PC3, NCI-H727, MCF7). All compounds were found to be devoid of any significant cytotoxicity at 10 μ M concentration (See Supplementary Material).

Their activity was also screened against a panel of eight representative kinases (*HsCDK5/p25*, *HsCDK9/CyclinT*, *HsPIM1*, *MmCLK1*, *RnDYRK1A*, *HsHASPIN*, *HsGSK3 β* , *HsCK1 ϵ*) and the results are reported in Table 2. Interestingly only one of these kinases (*MmCLK1*) was found to be responding to these derivatives. A few molecules (**11a**, **11c**, **11d**, **11e**, **11f**, **11j**) exhibited a moderate inhibition of this kinase at 10 μ M. On the other hand, these molecules were found to be devoid of any significant activity at 10 μ M concentration on the other kinases.

Table 2. Study of the inhibition of quinazolines **11** against a representative panel of mammalian kinases

Compound	Concentration	HsCDK5/ p25	HsCDK9/ CyclinT	HsPIM1	MmCLK1	RnDYRK1A	HsHASPIN	HsGSK3 β	HsCK1 ϵ
11a	10 μ M	104	87	95	63	104	99	87	108
	1 μ M	109	90	125	102	109	99	89	95
11b	10 μ M	118	89	125	105	98	97	86	121
	1 μ M	135	82	97	101	105	87	74	90
11c	10 μ M	124	86	78	44	88	80	72	101
	1 μ M	110	79	94	102	107	105	87	99
11d	10 μ M	120	104	91	49	103	113	90	96
	1 μ M	106	92	100	98	98	109	86	97
11e	10 μ M	101	103	99	26	98	111	78	87
	1 μ M	109	94	100	84	77	100	93	87
11f	10 μ M	79	110	98	48	117	114	105	105
	1 μ M	111	128	111	100	76	103	89	96
11g	10 μ M	113	101	105	106	110	112	100	97
	1 μ M	98	97	100	87	93	88	94	94
11h	10 μ M	112	112	106	74	100	116	103	116
	1 μ M	114	119	120	99	94	92	78	81
11i	10 μ M	116	128	121	109	144	118	110	113
	1 μ M	104	106	110	108	81	108	63	79
11j	10 μ M	121	121	116	67	100	90	67	95
	1 μ M	113	85	127	129	84	98	55	61

Percentages of residual kinase activity were determined at 1 and 10 μ M concentration for each compound. Kinase activities were assayed in duplicate.

Conclusions

In summary, we designed a short and convergent strategy toward the desired quinazolines linked to triazoles through an ether chain in position 2 of the quinazoline. Some of these derivatives exhibit a moderate, but significant and selective, activity against the *MmCLK1* kinase. Extension of this approach to other quinazoline-derived derivatives is under active study and will be reported in due course.

Experimental Section

Chemical Synthesis

General. All anhydrous reactions were performed in heat gun-dried round-bottomed flasks under a dry argon or nitrogen atmosphere. Air and moisture-sensitive compounds were introduced via syringes or cannula, using

standard inert atmosphere techniques. In addition, the gas stream was passed through glass cylinder filled with P₂O₅ to remove any traces of residual moisture. Reactions were monitored by thin layer chromatography (TLC) using E. Merck silica gel plates and components were visualized by illumination with short wavelength UV light and/or staining (Ninhydrin or basic KMnO₄). THF and Et₂O were dried over sodium-benzophenone and distilled prior to use. Anhydrous CH₂Cl₂ was prepared by refluxing in the presence of CaH₂ and distilled right before use unless otherwise noted. Infrared spectra have been recorded on a Bruker alpha II FTIR spectrometer. ¹H NMR spectra were recorded at 300 and 400 MHz, and ¹³C NMR spectra at 75 and 100 MHz, in CDCl₃ or DMSO-*d*₆ using tetramethylsilane (TMS) as an internal standard on Bruker spectrometers (Avance 300III and Avance 300I and Avance^{III} 400). Assignments were made using standard 2D NMR techniques (COSY, HMQC/HSQC, HMBC). High resolution mass spectra were performed using a time of flight Maxis 4G (Bruker Daltonik GmbH, Bremen, Germany) in Electrospray positive ionization mode. LC-MS analyses were carried out on a Shimadzu [LCMS-2020], SHIMPAK, XR ODS-II column (50 x 2 mm) utilizing the following method. Solvent A = Acetonitrile, B = 0.1% TFA in water; Initial 95% of solvent B, then run gradient, which should reach 90% solvent A within 10 min and hold 90% solvent A for another 10 min. Flow Rate: 0.2 ml/min.

Synthesis of 2-amino-3-methoxybenzaldehyde (13). To a stirred solution of 3-methoxy-2-nitrobenzaldehyde (**12**) (10 g, 54 mmol) in a mixture of methanol (100 mL) and glacial acetic acid (100 mL) and water (50 mL) was added reduced iron powder (16 g, 144 mmol) in lot wise manner. The resulting suspension was stirred at 30-35°C for 2h. The reaction mixture was filtered on Celite bed and washed with methanol (50 mL). The filtrate was concentrated to remove volatiles and it was partitioned between sat. NaHCO₃ (150 mL) and ethyl acetate (200 mL). The basic layer was further extracted with ethyl acetate (100 mL). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄ and concentrated to dryness and purified by chromatography on silica gel eluting with 20% EtOAc in hexane giving a compound **13** (6.5 g, 78% Yield) as a off white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.93 (s, 1H), 8.45 (d, 1H), 7.82 (d, 1H), 6.80 (t, 1H); Mass (*m/z*): 165.2 (M+H).

Synthesis of 8-methoxyquinazolin-2-ol (14). 2-Amino-3-methoxybenzaldehyde (**13**) (5 g, 33.1 mmol), urea (20 g, 336.3 mmol) and cat. NH₄OAc (10 mg) were thoroughly mixed together in a round bottom flask. The solid mixture was heated to 160 °C and the solids quickly melted and stirring was continued for 15 min. A solid started to precipitate from the hot solution, NMP (25 mL) was added to dissolve the solids, the reaction was heated with stirring for an additional 2 h at 155-160 °C. The hot reaction mixture was poured into vigorously stirred ice water (150 mL). The reaction mixture was filtered, washed with water (50 mL) and ethyl acetate (15 mL) giving a brown color solid which was dried to give compound **14** (4.9 g, 82% yield) as a off white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm: 11.3 (br, 1H), 9.23 (s, 1H), 7.43 (t, 1H), 7.34 (d, 2H), 3.90 (s, 3H); Mass (*m/z*): 177.2 (M+H)

Synthesis of 2-chloro-8-methoxyquinazoline (14a). A mixture of compound **14** (4 g, 22 mmol) and 2,3,5-collidine (5 mL, 38.8 mmol) in acetonitrile (80 mL) was stirred at room temperature for 10 min. POCl₃ (22 mL, 222 mmol) was added to reaction mixture at 0 °C and the reaction mixture was heated for 10 h at reflux. The mixture was concentrated to dryness. The obtained residue was partitioned between EtOAc (200 mL) and sat. NaHCO₃ (200 mL). The mixture was stirred cautiously watching gas evolution until the pH reached to 8. The layers were separated and the organic layer was washed with sat. NaHCO₃ (75 ml), brine (50ml), dried (Na₂SO₄), and concentrated to dryness, giving compound **14a** (2.8 g, 63.5% yield) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.25 (s, 1H), 7.61-7.57 (t, *J* 16.0 Hz, 1H), 7.51-7.48 (t, *J* 8.4, 1H), 7.28 (dd, *J* 8.0, 0.8 Hz, 1H), 4.07 (s, 3H); ¹³C NMR (400 MHz, CDCl₃): δ 162.72, 156.93, 154.08, 143.80, 128.59, 124.33, 118.41, 113.08, 56.26. Mass (*m/z*): 195.1 (M+H).

Synthesis of 8-methoxy-2-(prop-2-yn-1-yloxy)quinazoline (15). Propargyl alcohol (518 mg, 9.24 mmol) was added to a stirred suspension of Cs_2CO_3 (3g, 9.24 mmol) and DMF (10 mL), after stirring 15 minutes at 30 °C compound **14a** (600 mg, 3.08 mmol) was added. After stirring at 100 °C for 16h, the reaction mixture was quenched with water (30 mL) and extracted with DCM (2x25 mL). The combined organic extracts were washed with brine (5%, 15 mL), dried over Na_2SO_4 and concentrated to dryness. Purification by chromatography on silica gel (elution with EtOAc in hexane) gave compound **15** (450 mg, 65% yield) as a off white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm: 9.23 (s, 1H), 7.46-7.38 (m, 2H), 7.21 (d, J 7.6, 1.6 Hz, 1H), 5.21 (s, 2H), 4.06 (s, 3H), 2.49 (t, J 2.4 Hz, 1H); ^{13}C NMR (400 MHz, CDCl_3): δ 163.62, 161.11, 153.84, 143.67, 125.43, 122.96, 118.90, 113.06, 78.55, 74.63, 56.33, 55.18. Mass (m/z): 215.1 (M+H).

General procedure for preparation of compounds, 11a-j. To the stirred solution of compound **15** (0.1 mmol, 1.0 eq.) and compound **16a-j** [prepared using general protocol,¹² (0.1 mmol, 1 eq.) in a 1:1 mixture of *t*-butanol and water (0.56 mL) was added copper sulfate pentahydrate (0.01 mmol, 0.1 eq.) and sodium ascorbate (0.03 mmol, 0.3 eq.) at room temperature. The resulting mixture was stirred for overnight. After completion of the reaction, it was diluted with a mixture of ethyl acetate and water (7.5 ml in a 1:1 ratio), the organic layer was separated and washed with 5% ammonium hydroxide solution (0.5 mL) and followed by brine (0.5 mL). The combined organic layers were dried over Na_2SO_4 . The solvents were evaporated under reduced pressure to get the crude product, which was purified by chromatography on silica gel affording target compounds **11a-j** (65-75% yield) as light yellow to brown solids.

8-Methoxy-2-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)quinazoline (11a). Reaction of **15** (25 mg, 0.11 mmol) with **16a** (17.4 mg, 0.11 mmol) gave **11a**: 31.6 mg, 75% yield. mp 179-181 °C; FT-IR (KBr, cm^{-1}): 3137, 2958, 2841, 1584, 1516, 1470, 1419, 1292, 1261, 1175, 1117, 1034, 836, 763. ^1H NMR (300 MHz, CDCl_3): δ 9.23 (s, 1H, *H*-quinazoline), 8.37 (br t, J 0.5 Hz, 1H, *H*-triazole), 7.62 (half part of an A_2X_2 system, 2H meta to OMe), 7.46 (dd, J 8.1, 1.6 Hz, 1H, *H*-C7 of quinazoline), 7.40 (dd, J 8.1, 7.4 Hz, 1H, *H*-C6 of quinazoline), 7.22 (ddd, J 7.4, 1.6, 0.2 Hz, 1H, *H*-C5 of quinazoline), 7.01 (half part of an A_2X_2 system, 2H ortho to OMe), 5.80 (d, J 0.5 Hz, 2H, CH_2), 4.09 (s, 3H, CH_3 , OMe on quinazoline), 3.86 (s, 3H, CH_3 , OMe of 4-methoxyphenyl). ^{13}C NMR (75 MHz, CDCl_3): δ 163.72 (CH, α to N of quinazoline), 161.65 (C, C2 of quinazoline), 159.81 (C, α to OMe), 153.83 (C, C8 of quinazoline), 144.19 (C of triazole), 143.59 (C, C8a of quinazoline), 130.67 (C, δ to OMe), 125.28 (CH, C6 of quinazoline), 122.92 (CH of triazole), 122.89 (C, C4a of quinazoline), 122.15 (2CH, meta to OMe), 118.99 (CH, C7 of quinazoline), 114.78 (2CH, ortho to OMe), 112.87 (CH, C5 of quinazoline), 61.33 (CH_2), 56.23 (CH_3 , OMe on quinazoline), 55.64 (CH_3 , OMe of 4-methoxyphenyl). LC-MS: 363.13 [M]. HRMS-ESI (m/z) [$\text{M}+\text{Na}$]⁺ calcd for $\text{C}_{19}\text{H}_{17}\text{N}_5\text{NaO}_3$: 386.12236, found 386.1222, [$\text{M}+\text{K}$]⁺ calcd for $\text{C}_{19}\text{H}_{17}\text{KN}_5\text{O}_3$: 402.09630, found 402.0957.

2-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-8-methoxyquinazoline (11b). Reaction of **15** (25 mg, 0.11 mmol) with **16b** (17.92 mg, 0.11 mmol) gave **11b**: 28 mg, 65% yield. mp 130 °C (dec); FT-IR (KBr, cm^{-1}): 3339, 3332, 2999, 1581, 1493, 1421, 1382, 1293, 1171, 1108, 1029, 830, 756. ^1H NMR (400 MHz, CDCl_3): δ 9.24 (s, 1H, *H*-quinazoline), 8.47 (s, 1H, *H*-triazole), 7.68 (half part of an A_2X_2 system, 2H meta to Cl), 7.49 (half part of an A_2X_2 system, 2H ortho to Cl), 7.46 (dd, J 8.2, 1.4 Hz, 1H, *H*-C7 of quinazoline), 7.42 (dd, J 8.2, 7.5 Hz, 1H, *H*-C6 of quinazoline), 7.23 (dd, J 7.6, 1.4 Hz, 1H, *H*-C5 of quinazoline), 5.80 (d, J 0.6 Hz, 2H, CH_2), 4.10 (s, 3H, CH_3 , OMe), ^{13}C NMR (100 MHz, CDCl_3): δ 163.77 (CH, α to N of quinazoline), 161.58 (C, C2 of quinazoline), 153.80 (C, C8 of quinazoline), 144.68 (C of triazole), 143.53 (C, C8a of quinazoline), 135.66 (C, δ to Cl), 134.50 (C, α to Cl), 129.94 (2CH, ortho to Cl), 125.36 (CH, C6 of quinazoline), 122.91 (C, C4a of quinazoline), 122.77 (CH of triazole), 121.65 (2CH, meta to Cl), 119.04 (CH, C7 of quinazoline), 112.93 (CH, C5 of quinazoline), 61.17

(CH₂), 56.23 (CH₃, OMe). LC-MS: 367.79 [M]. HRMS–ESI (*m/z*) [M+Na]⁺ calcd for C₁₈H₁₄³⁵ClN₅NaO₂: 390.07282, found 390.0726, [M+K]⁺ calcd for C₁₈H₁₄³⁵ClKN₅O₂: 406.04676, found 406.0460.

2-((1-(2-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-8-methoxyquinazoline (11c). Reaction of **15** (20 mg, 0.093 mmol) with **16c** (14.28 mg, 0.11 mmol) gave **11c**: 22.1 mg, 64% yield. mp 134-136 °C; FT-IR (KBr, cm⁻¹): 3146, 3004, 1580, 1486, 1417, 1382, 1288, 1168, 1119, 1022, 757, 665. ¹H NMR (300 MHz, CDCl₃): δ 9.23 (s, 1H, *H*-quinazoline), 8.48 (br t, *J* 0.5 Hz, 1H, *H*-triazole), 7.66-7.59 (m, 1H, *H*-4 of 2-chlorophenyl), 7.59-7.53 (m, 1H, *H*-5 of 2-chlorophenyl), 7.48-7.40 (m, 3H, *H*-3 and *H*-6 of 2-chlorophenyl and *H*-C7 of quinazoline), 7.40 (dd, *J* 8.1, 7.4 Hz, 1H, *H*-C6 of quinazoline), 7.20 (dd, *J* 7.4, 1.6 Hz, 1H, *H*-C5 of quinazoline), 5.84 (d, *J* 0.5 Hz, 2H, CH₂), 4.06 (s, 3H, CH₃, OMe). ¹³C NMR (75 MHz, CDCl₃): δ 163.74 (CH, α to N of quinazoline), 161.54 (C, C2 of quinazoline), 153.73 (C, C8 of quinazoline), 143.42 (C, C8a of quinazoline), 143.32 (C of triazole), 134.93 (C, α to Cl), 130.75 (CH, C5 of 2-chlorophenyl), 130.62 (CH, C6 of 2-chlorophenyl), 128.29 (C, C1 of 2-chlorophenyl), 127.94 (CH, C3 of 2-chlorophenyl), 127.76 (CH, C4 of 2-chlorophenyl), 126.89 (CH of triazole), 125.29 (CH, C6 of quinazoline), 122.80 (C, C4a of quinazoline), 118.90 (CH, C7 of quinazoline), 112.70 (CH, C5 of quinazoline), 61.03 (CH₂), 56.13 (CH₃, OMe). LC-MS: 367.79 [M]. HRMS–ESI (*m/z*) [M+Na]⁺ calcd for C₁₈H₁₄³⁵ClN₅NaO₂: 390.07282, found 390.0729, [M+K]⁺ calcd for C₁₈H₁₄³⁵ClKN₅O₂: 406.04676, found 406.0462, [M+H]⁺ calcd for C₁₈H₁₅³⁵ClN₅O₂: 368.09088, found 368.0904.

8-Methoxy-2-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)quinazoline (11d). Reaction of **15** (25 mg, 0.11 mmol) with **16d** (17.4 mg, 0.11 mmol) gave **11d**: 29.4 mg, 68% yield. mp 147-149 °C; FT-IR (KBr, cm⁻¹): 3157, 2963, 2838, 1580, 1470, 1417, 1286, 1170, 1119, 1017, 753, 668. ¹H NMR (300 MHz, CDCl₃): δ 9.23 (s, 1H, *H*-quinazoline), 8.44 (br t, *J* 0.6 Hz, 1H, *H*-triazole), 7.77 (ddd, *J* 7.8, 1.7, 0.3 Hz, 1H, *H*6 of 2-methoxyphenyl), 7.45 (dd, *J* 8.2, 1.5 Hz, 1H, *H*-C7 of quinazoline), 7.41 (ddd, *J* 8.2, 7.6, 1.7 Hz, 1H, *H*-C6 of quinazoline), 7.39 (dd, *J* 8.1, 7.4 Hz, 1H, *H*4 of 2-methoxyphenyl), 7.20 (br dd, *J* 7.5, 1.5 Hz, 1H, *H*-C5 of quinazoline), 7.09 (td, *J* 7.7, 1.3 Hz, 1H, *H*5 of 2-methoxyphenyl), 7.07 (br dd, *J* 8.3, 1.1 Hz, 1H, *H*3 of 2-methoxyphenyl), 5.84 (d, *J* 0.6 Hz, 2H, CH₂), 4.07 (s, 3H, CH₃, OMe on quinazoline), 3.84 (s, 3H, CH₃, OMe of 2-methoxyphenyl). ¹³C NMR (75 MHz, CDCl₃): δ 163.63 (CH, α to N of quinazoline), 161.70 (C, C2 of quinazoline), 153.85 (C, C8 of quinazoline), 151.23 (C α to OMe of 2-methoxyphenyl), 143.69 (C, C8a of quinazoline), 143.03 (C of triazole), 130.04 (CH, C4 of 2-methoxyphenyl), 126.47 (CH of triazole), 126.41 (C, C1 of 2-methoxyphenyl), 125.62 (CH, C6 of 2-methoxyphenyl), 125.20 (CH, C6 of quinazoline), 122.85 (C, C4a of quinazoline), 121.22 (CH, C5 of 2-methoxyphenyl), 118.94 (CH, C7 of quinazoline), 112.83 (CH, C5 of quinazoline), 112.27 (CH, C3 of 2-methoxyphenyl), 61.38 (CH₂), 56.23 (CH₃, OMe on quinazoline), 55.94 (CH₃, OMe of 2-methoxyphenyl). LC-MS: 363.13 [M]. HRMS–ESI (*m/z*) [M+Na]⁺ calcd for C₁₉H₁₇N₅NaO₃: 386.12236, found 386.1228, [M+K]⁺ calcd for C₁₉H₁₇KN₅O₃: 402.09630, found 402.0963, [M+H]⁺ calcd for C₁₉H₁₈N₅O₃: 364.14041, found 364.1404.

8-Methoxy-2-((1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)quinazoline (11e). Reaction of **15** (25 mg, 0.11 mmol) with **16e** (17.4 mg, 0.11 mmol) gave **11e**: 30 mg, 71% yield. mp 137-139 °C; FT-IR (KBr, cm⁻¹): 3144, 3002, 1594, 1483, 1420, 1289, 1165, 1015, 1031, 855, 764. ¹H NMR (300 MHz, CDCl₃): δ 9.23 (s, 1H, *H*-quinazoline), 8.48 (br t, *J* 0.6 Hz, 1H, *H*-triazole), 7.46 (dd, *J* 8.2, 1.6 Hz, 1H, *H*-C7 of quinazoline), 7.44-7.36 (m, 2H, *H*-C6 of quinazoline at 7.43 ppm and *H*5 of 3-methoxyphenyl at 7.39 ppm), 7.34 (dd, *J* 2.4, 2.1 Hz, 1H, *H*2 of 3-methoxyphenyl), 7.26 (ddd, *J* 8.0, 2.1, 1.0 Hz, 1H, *H*6 of 3-methoxyphenyl), 7.23 (br dd, *J* 7.5, 1.6 Hz, 1H, *H*-C5 of quinazoline), 6.96 (ddd, *J* 8.3, 2.5, 1.0 Hz, 1H, *H*4 of 3-methoxyphenyl), 5.81 (d, *J* 0.5 Hz, 2H, CH₂), 4.10 (s, 3H, CH₃, OMe on quinazoline), 3.87 (s, 3H, CH₃, OMe of 3-methoxyphenyl). ¹³C NMR (75 MHz, CDCl₃): δ 163.74 (CH, α to N of quinazoline), 161.63 (C, C2 of quinazoline), 160.64 (C, α to OMe of 3-methoxyphenyl), 153.83 (C, C8 of quinazoline), 144.34 (C of triazole), 143.56 (C, C8a of quinazoline), 138.20 (C, C1 of 3-methoxyphenyl), 130.49 (CH, C5 of 3-methoxyphenyl), 125.30 (CH, C6 of quinazoline), 122.96 (CH of triazole), 122.90 (C, C4a of quinazoline), 119.00 (CH, C7 of quinazoline), 114.60 (CH, C4 of 3-methoxyphenyl), 112.88 (CH, C5 of

quinazoline), 112.33 (CH, C6 of 3-methoxyphenyl), 106.31 (CH, C2 of 3-methoxyphenyl), 61.27 (CH₂), 56.24 (CH₃, OMe on quinazoline), 55.64 (CH₃, OMe of 3-methoxyphenyl). LC-MS: 363.13 [M]. HRMS–ESI (*m/z*) [M+Na]⁺ calcd for C₁₉H₁₇N₅NaO₃: 386.12236, found 386.1277, [M+K]⁺ calcd for C₁₉H₁₇KN₅O₃: 402.09630, found 402.0962.

2-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-8-methoxyquinazoline (11f):. Reaction of **15** (25 mg, 0.11 mmol) with **16f** (23.1 mg, 0.11 mmol) gave **11f**: 31 mg, 64% yield. mp 144-146 °C; FT-IR (KBr, cm⁻¹): 3061, 3007, 1581, 1491, 1418, 1291, 1172, 1024, 829, 762. ¹H NMR (400 MHz, CDCl₃): δ 9.24 (s, 1H, *H*-quinazoline), 8.47 (br t, *J* 0.6 Hz, 1H, *H*-triazole), 7.67-7.60 (symmetrical m, 4*H* of 4-bromophenyl), 7.47 (dd, *J* 8.1, 1.4 Hz, 1H, *H*-C7 of quinazoline), 7.42 (dd, *J* 8.1, 7.5 Hz, 1H, *H*-C6 of quinazoline), 7.23 (dd, *J* 7.6, 1.3 Hz, 1H, *H*-C5 of quinazoline), 5.80 (br d, *J* 0.6 Hz, 2H, CH₂), 4.10 (s, 3H, CH₃, OMe). ¹³C NMR (100 MHz, CDCl₃): δ 163.78 (CH, α to N of quinazoline), 161.57 (C, C2 of quinazoline), 153.79 (C, C8 of quinazoline), 144.70 (C of triazole), 143.51 (C, C8a of quinazoline), 136.13 (C, δ to Br), 132.91 (2CH, ortho to Br of 4-bromophenyl), 125.36 (CH, C6 of quinazoline), 122.91 (C, C4a of quinazoline), 122.73 (CH of triazole), 122.34 (C, α to Br), 121.88 (2CH, meta to Br of 4-bromophenyl), 119.07 (CH, C7 of quinazoline), 112.92 (CH, C5 of quinazoline), 61.17 (CH₂), 56.23 (CH₃, OMe). LC-MS: 412.24 [M]. HRMS–ESI (*m/z*) [M+Na]⁺ calcd for C₁₈H₁₄⁷⁹BrN₅NaO₂: 434.02231, found 434.0225, [M+K]⁺ calcd for C₁₈H₁₄⁷⁹BrKN₅O₂: 449.99624, found 449.9959.

8-Methoxy-2-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)quinazoline (11g).

Reaction of **15** (25 mg, 0.11 mmol) with **16g** (13.90 mg, 0.11 mmol) gave **11g**: 29.1 mg, 74% yield. mp 168-170 °C; FT-IR (KBr, cm⁻¹): 3143, 3070, 3003, 1585, 1484, 1418, 1292, 1171, 1117, 1030, 764, 690. ¹H NMR (400 MHz, CDCl₃): δ 9.24 (s, 1H, *H*-quinazoline), 8.48 (s, 1H, *H*-triazole), 7.76-7.71 (m, 2H, *H* ortho of Ph), 7.55-7.49 (m, 2H, *H* meta of Ph), 7.48-7.38 (m, 3H, *H*-C6 of quinazoline, *H*-C7 of quinazoline and *H* para of Ph), 7.23 (dd, *J* 7.6, 1.3 Hz, 1H, *H*-C5 of quinazoline), 5.82 (s, 2H, CH₂), 4.10 (s, 3H, CH₃, OMe). ¹³C NMR (75 MHz, CDCl₃): δ 163.74 (CH, α to N of quinazoline), 161.64 (C, C2 of quinazoline), 153.83 (C, C8 of quinazoline), 144.40 (C of triazole), 143.57 (C, C8a of quinazoline), 137.20 (C ipso of Ph), 129.74 (2CH, meta of Ph), 128.69 (CH, para of Ph), 125.30 (CH, C6 of quinazoline), 122.90 (CH of triazole), 122.85 (C, C4a of quinazoline), 120.52 (2CH, ortho of Ph), 119.01 (CH, C7 of quinazoline), 112.88 (CH, C5 of quinazoline), 61.28 (CH₂), 56.22 (CH₃, OMe). LC-MS: 333.3 [M]. HRMS–ESI (*m/z*) [M+Na]⁺ calcd for C₁₈H₁₅N₅NaO₂: 356.11179, found 356.1121, [M+K]⁺ calcd for C₁₈H₁₅KN₅O₂: 372.08573, found 372.0856.

2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)-8-methoxyquinazoline (11h). Reaction of **15** (20 mg, 0.093 mmol) with **16h** (12.38 mg, 0.093 mmol) gave **11h**: 24.2 mg, 74% yield. mp 109-111 °C; FT-IR (KBr, cm⁻¹): 3006, 1579, 1468, 1414, 1280, 1166, 1117, 1002, 816, 742. ¹H NMR (300 MHz, CDCl₃): δ 9.19 (s, 1H, *H*-quinazoline), 7.84 (s, 1H, *H*-triazole), 7.43 (dd, *J* 8.1, 1.4 Hz, 1H, *H*-C7 of quinazoline), 7.39 (dd, *J* 8.1, 7.5 Hz, 1H, *H*-C6 of quinazoline), 7.37-7.32 (m, 3H, 2*H* meta and 1*H* para of benzyl), 7.29-7.23 (m, 2H, 2*H* ortho of benzyl), 7.18 (dd, *J* 7.5, 1.3 Hz, 1H, *H*-C5 of quinazoline), 5.71 (s, 2H, CH₂ between O and triazole), 5.52 (s, 2H, CH₂ of benzyl), 3.99 (s, 3H, CH₃, OMe). ¹³C NMR (75 MHz, CDCl₃): δ 163.63 (CH, α to N of quinazoline), 161.52 (C, C2 of quinazoline), 153.71 (C, C8 of quinazoline), 144.07 (C of triazole), 143.49 (C, C8a of quinazoline), 134.54 (C ipso of Ph), 129.09 (2CH, meta of benzyl), 128.73 (CH, para of benzyl), 128.15 (2CH, ortho of benzyl), 125.24 (CH, C6 of quinazoline), 124.19 (CH of triazole), 122.77 (C, C4a of quinazoline), 118.89 (CH, C7 of quinazoline), 112.72 (CH, C5 of quinazoline), 61.32 (CH₂ between O and triazole), 56.12 (CH₃, OMe), 54.19 (CH₂ of benzyl). LC-MS: 347.37 [M]. HRMS–ESI (*m/z*) [M+Na]⁺ calcd for C₁₉H₁₇N₅NaO₂: 370.12744, found 370.1277, [M+K]⁺ calcd for C₁₉H₁₇KN₅O₂: 386.10138, found 386.1013.

8-Methoxy-2-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)quinazoline (11i). Reaction of **15** (20 mg, 0.093 mmol) with **16i** (16.56 mg, 0.093 mmol) gave **11i**: 18.4 mg, 50% yield. mp 179-181 °C; FT-IR (KBr, cm⁻¹): 3132, 3008, 1692, 1586, 1519, 1471, 1416, 1342, 1290, 1169, 1117, 1016, 756. ¹H NMR (400 MHz, DMSO-*d*₆): δ

9.43 (s, 1H, *H*-quinazoline), 8.41 (s, 1H, *H*-triazole), 8.21 (half part of an A_2X_2 system, 2*H* ortho to NO_2 of 4-nitrobenzyl), 7.62 (dd, *J* 8.1, 1.3 Hz, 1H, *H*-C7 of quinazoline), 7.53 (half part of an A_2X_2 system with small coupling with CH_2 , 2*H* meta to NO_2 of 4-nitrobenzyl), 7.48 (dd, *J* 8.0, 7.9 Hz, 1H, *H*-C6 of quinazoline), 7.40 (dd, *J* 7.9, 1.2 Hz, 1H, *H*-C5 of quinazoline), 5.81 (s, 2H, CH_2 of 4-nitrobenzyl), 5.55 (s, 2H, CH_2 between O and triazole), 3.96 (s, 3H, CH_3 , *OMe*). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 164.22 (CH, α to N of quinazoline), 160.86 (C, C2 of quinazoline), 153.11 (C, C8 of quinazoline), 147.14 (C, α to NO_2), 143.28 (C para to NO_2 of 4-nitrobenzyl), 142.70 (C of triazole), 142.32 (C, C8a of quinazoline), 128.94 (2CH, meta to NO_2 of 4-nitrobenzyl), 125.73 (CH of triazole), 125.39 (CH, C6 of quinazoline), 123.79 (2CH, ortho to NO_2 of 4-nitrobenzyl), 122.35 (C, C4a of quinazoline), 118.96 (CH, C7 of quinazoline), 113.54 (CH, C5 of quinazoline), 60.09 (CH_2 between O and triazole), 55.84 (CH_3 , *OMe*), 51.84 (CH_2 of 4-nitrobenzyl). LC-MS: 392.37 [M]. HRMS-ESI (*m/z*) [$\text{M}+\text{Na}$] $^+$ calcd for $\text{C}_{19}\text{H}_{16}\text{N}_6\text{NaO}_4$: 415.11252, found 415.1126, [$\text{M}+\text{K}$] $^+$ calcd for $\text{C}_{19}\text{H}_{16}\text{KN}_6\text{O}_4$: 431.08646, found 431.0861.

2-((1-(2,6-Dichlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-8-methoxyquinazoline (11j). Reaction of **15** (25 mg, 0.11 mmol) with **16j** (23.57 mg, 0.11 mmol) gave **11j**: 29.3 mg, 60% yield. mp 186-188 °C; FT-IR (KBr, cm^{-1}): 3002, 1578, 1426, 1268, 1166, 1114, 1016, 758. ^1H NMR (300 MHz, CDCl_3): δ 9.19 (s, 1H, *H*-quinazoline), 7.85 (br s, 1H, *H*-triazole), 7.44 (dd, *J* 8.2, 1.7 Hz, 1H, *H*-C7 of quinazoline), 7.42-7.36 (m, 3H, 2*H* ortho to Cl at 7.38 ppm and *H*-C6 of quinazoline at 7.40 ppm), 7.29 (dd, *J* 9.1, 6.8 Hz, 1H, *H* meta to Cl), 7.19 (dd, *J* 7.3, 1.7 Hz, 1H, *H*-C5 of quinazoline), 5.85 (s, 2H, CH_2 of 2,6-dichlorobenzyl), 5.70 (d, *J* 0.6 Hz, 2H, CH_2 between O and triazole), 4.03 (s, 3H, CH_3 , *OMe*). ^{13}C NMR (75 MHz, CDCl_3): δ 163.61 (CH, α to N of quinazoline), 161.50 (C, C2 of quinazoline), 153.73 (C, C8 of quinazoline), 143.62 (C of triazole), 143.53 (C, C8a of quinazoline), 136.85 (2C, α to Cl), 131.05 (CH, meta to Cl), 130.08 (C, β to Cl), 128.87 (2CH, ortho to Cl), 125.23 (CH, C6 of quinazoline), 123.76 (CH of triazole), 122.78 (C, C4a of quinazoline), 118.89 (CH, C7 of quinazoline), 112.71 (CH, C5 of quinazoline), 61.39 (CH_2 between O and triazole), 56.19 (CH_3 , *OMe*), 49.03 (CH_2 of 2,6-dichlorobenzyl). LC-MS: 416.26 [M]. HRMS-ESI (*m/z*) [$\text{M}+\text{Na}$] $^+$ calcd for $\text{C}_{19}\text{H}_{15}^{35}\text{Cl}_2\text{N}_5\text{NaO}_2$: 438.04950, found 438.0495, [$\text{M}+\text{K}$] $^+$ calcd for $\text{C}_{19}\text{H}_{15}^{35}\text{Cl}_2\text{KN}_5\text{O}_2$: 454.02344, found 454.0229.

Cytotoxicity studies

Cell culture. Skin normal fibroblastic cells are purchased from Lonza (Basel, Switzerland), HuH7, Caco-2, MDA-MB-231, HCT116, PC3, MCF7 and NCI-H727 cancer cell lines were obtained from the ECACC collection (Porton Down, UK). Cells are grown at 37°C, 5% CO_2 in ECACC recommended media: DMEM for HuH7, MDA-MB-231 and fibroblast, EMEM for MCF7 and CaCo-2, McCoy's for HCT116 and RPMI for PC3 and NCI-H727. All culture media are supplemented by 10% of FBS, 1% of penicillin-streptomycin and 2 mM glutamine.

Cytotoxic assay. Chemicals are solubilized in DMSO at a concentration of 10 mM (stock solution) and diluted in culture medium to the desired final concentrations. The dose effect cytotoxic assay of chemical is performed at 25 μM . Cells are plated in 96 wells plates (4000 cells/well). Twenty-four hours after seeding, cells are exposed to chemicals. After 48h of treatment, cells are washed in PBS and fixed in cooled 90% ethanol/5% acetic acid for 20 minutes and the nuclei are stained with Hoechst 33342 (B2261 Sigma). Image acquisition and analysis are performed using a Cellomics ArrayScan VTI/HCS Reader (ThermoScientific). The survival percentages are calculated as the percentage of cell number after compound treatment over cell number after DMSO treatment.

Protein kinase assays

Kinase enzymatic activities were assayed in 384-well plates using the ADP-Glo assay kit (Promega, Madison, WI) according to the recommendations of the manufacturer. This assay is a luminescent ADP detection assay that provides a homogeneous and high-throughput screening method to measure kinase activity by quantifying the amount of ADP produced during a kinase reaction. Briefly, the reactions were carried out in a

final volume of 6 μl for 30 min at 30°C in the following buffer: 10 mM MgCl_2 , 1 mM EGTA, 1 mM DTT, 25 mM Tris-HCl pH 7.5, 50 $\mu\text{g}/\text{ml}$ heparin; with either protein or peptide as substrate in the presence of 10 μM ATP. After stopping the kinase reaction, Kinase Detection Reagent was added for one hour at RT. The transmitted signal was then measured using an Envision microplate luminometer (PerkinElmer, Waltham, MA) and expressed in Relative Light Unit (RLU). *HsCDK5/p25* (human, recombinant, expressed in bacteria) was assayed on 0.8 $\mu\text{g}/\mu\text{l}$ of histone H1 as substrate. *HsCDK9/CyclinT* (human, recombinant, expressed by baculovirus in Sf9 insect cells) was assayed on 0.27 $\mu\text{g}/\mu\text{l}$ of the following peptide: YSPTSPSYSPTSPSYSPTSPSKKKK, as substrate. *HsGSK3 β* (human, recombinant, expressed by baculovirus in Sf9 insect cells) was assayed on 0.010 $\mu\text{g}/\mu\text{l}$ of GS-1 peptide, a GSK-3-selective substrate (YRRAAVPPSPSLSRHSSPHQSpEDEEE). *HsCK1 ϵ* (human, recombinant, expressed by baculovirus in Sf9 insect cells) was assayed on 0.022 $\mu\text{g}/\mu\text{l}$ of the following peptide: RRKHAAIGSpAYSITA (“Sp” stands for phosphorylated serine) as CK1-specific substrate. *RnDYRK1A-kd* (*Rattus norvegicus*, kinase domain aa 1 to 499, expressed in bacteria, DNA vector kindly provided by Dr. W. Becker, Aachen, Germany) was assayed on 0.033 $\mu\text{g}/\mu\text{l}$ of the following peptide: KKISGRLSPIMTEQ as substrate. *MmCLK1* (from *Mus musculus*, recombinant, expressed in bacteria) was assayed on 0.027 $\mu\text{g}/\mu\text{l}$ of the following peptide: GRSRSRSRSR as substrate. *HsPim-1* (human proto-oncogene, recombinant, expressed in bacteria) was assayed on 0.8 $\mu\text{g}/\mu\text{l}$ of histone H1 (Sigma #H5505) as substrate. *HsHaspin-kd* (human, kinase domain, amino acids 470 to 798, recombinant, expressed in bacteria) was assayed on 0.007 $\mu\text{g}/\mu\text{l}$ of Histone H3 (1-21) peptide (ARTKQTARKSTGGKAPRKQLA) as substrate. Peptide substrates were obtained from Proteogenix (Schiltigheim, France).

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Supplementary Material

Electronic Supplementary Information (ESI) available: cytotoxic studies of the quinazolines 11 plus copies of the ^1H and ^{13}C NMR spectra for all new compounds

References

1. Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223-246 and references cited therein.
<https://doi: 10.1039/b509528j>

2. Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. *Eur. J. Med. Chem.* **2015**, *90*, 124-169.
<https://dx.doi.org/10.1016/j.ejmech.2014.10.084>
3. Ajani, O. O.; Audu, O. Y.; Aderohunmu, D. V.; Owalabi, F. E.; Olomieja, A. O. *Am. J. Drug Disc. Dev.* **2017**, *7*, 1-24.
<https://doi: 10.3923/ajdd.2017.1.24>
4. Ji, H.; Dan, H-G.; Rao, G-W. *Heterocycl. Commun.* **2018**, *24*, 1-10.
<https://doi.org/10.1515/hc-2017-0066>
5. For a recent review see: Dheer, D.; Singh, V.; Shankar, R. *Bioorg. Chem.* **2017**, *71*, 30-54.
<https://doi: 10.1016/j.bioorg.2017.01.010>
6. Yamamoto, Y.; Shinkai, I., Eds. *Science of Synthesis*, Thieme Chemistry: Georg Thieme Verlag KG 2004, 2
Hetarenes, Kikelj D. Product class 13: *Quinazolines* pp 573-749.
7. Aitken, R. A. et al.: 2016 *Science of Synthesis: Knowledge Updates 2015/2* DOI: 10.1055/sos-SD-116-01020
Knowledge Updates 2015/216.13.5 Quinazolines (Update 2015).
8. For general reviews on click chemistry see: Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angw. Chem. Int. Ed.* **2001**, *40*,
2004-2021, and references 9, 10 and 11.
[https://doi.org/10.1002/1521-3773\(20010601\)40:11%3C2004::AID-ANIE2004%3E3.0.CO;2-5](https://doi.org/10.1002/1521-3773(20010601)40:11%3C2004::AID-ANIE2004%3E3.0.CO;2-5)
9. Rostovtsev, V. V.; Green, L. G.; Sharpless, K. B. *Ang. Chem. Int. Ed.* **2002**, *41*, 2596-2599.
[https://doi.org/10.1002/1521-3773\(20020715\)41:14%3C2596::AID-ANIE2596%3E3.0.CO;2-4](https://doi.org/10.1002/1521-3773(20020715)41:14%3C2596::AID-ANIE2596%3E3.0.CO;2-4)
10. Tornøe, C. W.; Christensen, C.; Meda, M. *J. Org. Chem.* **2002**, *67*, 3057-3064.
<https://doi: 10.1021/jo011148j>
11. Lutz, J-F. *Ang. Chem. Int. Ed.* **2008**, *47*, 2182-2184.
<https://doi.org/10.1002/anie.200705365>
12. Klein, J. E. M. N.; Holzwarth, M. S.; Hohloch, S.; Sarkar, B.; Plietker, B. *Eur. J. Org. Chem.* **2013**, *28*, 6310 – 6316.
<https://doi.org/10.1002/ejoc.201300902>