Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/d1ob01315g

Nucleophile–nucleofuge duality of azide and arylthiolate groups in the synthesis of quinazoline and tetrazoloquinazoline derivatives†

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Received 6th July 2021,
Accepted 14th August 2021

DOI: 10.1039/d1ob01315g

rsc.li/obc

5-Arylthio-tetrazolo[1,5-*c*]quinazolines (tautomers of 2-arylthio-4-azido-quinazolines) undergo facile nucleophilic aromatic substitution reactions with amines, alcohols and alkylthiols. This, combined with the recently reported arylsulfanyl group dance, provides straightforward access to 4-azido-2-*N*-, *O*-, *S*-substituted quinazolines and/or their tetrazolo tautomers from commercially available 2,4-dichloroquinazoline. The azidoazomethine-tetrazole tautomeric equilibrium and the electron-withdrawing character of the fused tetrazolo system plays a central role in the developed transformations. 5-Amino-substituted tetrazolo[1,5-*c*]quinazolines undergo media-controlled tautomeric equilibrium, which permits them to demonstrate the reactivity traditionally associated with the azido substituent. Furthermore, a method for 5-*O*-substitited tetrazolo[1,5-*a*]quinazolines from 2,4-diazidoquinazoline was developed during the structural elucidation of the substitution products. The developed methodology will facilitate medicinal chemistry investigations into quinazoline derivatives and the discovered fluorescent properties of some of the products (*e.g.*, 4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-2-(4-methylpiperazin-1-yl)quinazoline: $\lambda_{em.}$ = 461 nm, Φ_{DCM} = 0.89) could serve as a starting point for their further applications in analytical and materials science.

Introduction

The quinazoline moiety represents a privileged class of scaffolds with a broad spectrum of biological activities. Several marketed anticancer drugs such as gefitinib, lapatinib, erlotinib and Afatinib are built around this heterocyclic core.[1–3] These substances possess the ability to bind to the tyrosine kinase active site and inhibit its messenger activity, thus blocking the signaling process within cancer cells.[4,5] Variation of the substituents also paved the way for potential apoptosis inducers and inhibitors,[6] as well as alpha-adrenergic blocking agents[7] in the case of the quinazoline based drug prazosin. Quinazoline compounds also possess antibacterial,[8,9] antimalarial[10] and anticonvulsant[11] activities.

The ability of the 2/4-azidoquinazolines to reach an azidoazomethine-tetrazole (azide-tetrazole) tautomeric equilibrium, and cyclize to the corresponding tetrazolo[1,5-*a*/*c*]quinazolines has been known for several decades.[12] However, the impact and synthetic application of such tautomerism in quinazolines has not been thoroughly studied owing to the dominant presence of the tetrazole tautomeric form. On the other hand, the addition of another condensed heterocycle to the quinazoline core has increased interest towards possible pharmacological applications. Despite the fact that only a few substances with sufficient evaluation of their biological properties are reported in the literature, potential antiallergy,[13] antiulcer,[13] antimicrobial,[14,15] antitumor,[14–16] bronchodilator,[17] anticonvulsant[18] and antidepressant[18] activities have been found among the 5-substituted tetrazolo[1,5-*a*]quinazolines and substituted tetrazolo[1,5-*c*]quinazolines.

Strategies for the introduction of an azide group/fused tetrazole ring at the C4 position of quinazoline (see Scheme 1) include: (**1**) S_NAr reactions with sodium azide, substituting halogens (LG = Cl),[19,20] heterocycles (LG = isoxazolone)[21] or oxygen-centered leaving groups (LG = *O*-benzotriazole, O–$P^+(NMe_2)_3$);[22] (**2**) diazotization of 4-hydrazinoquinazoline derivatives with sodium nitrite and the subsequent azide-tetrazole tautomerization;[11,23,24] (**3**) the pyrimidine ring-closing reaction of 2-tetrazolylaniline and potassium ethylxanthogenate[14] or *tert*-butyl isocyanide with the addition of a cobalt[25] or palladium[26] catalyst; and (**4** the microwave assisted domino cyclization-S_NAr procedure using anthranilic acid, formamide and $TMSN_3$.[27] In the past few decades, a significant amount of attention has also been focused on the synthesis and bioactiv-

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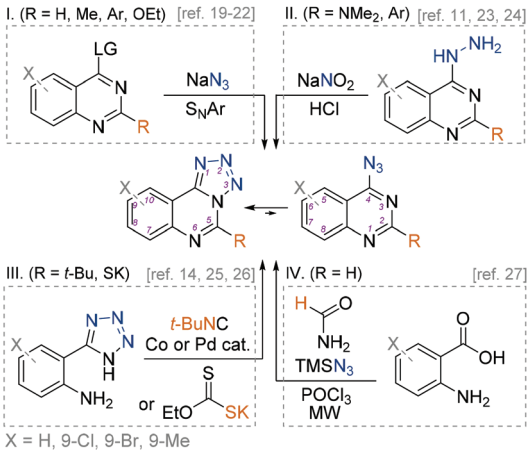
†Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ob01315g



Scheme 1 Different approaches to the synthesis of the tetrazolo[1,5-*c*] quinazolines.

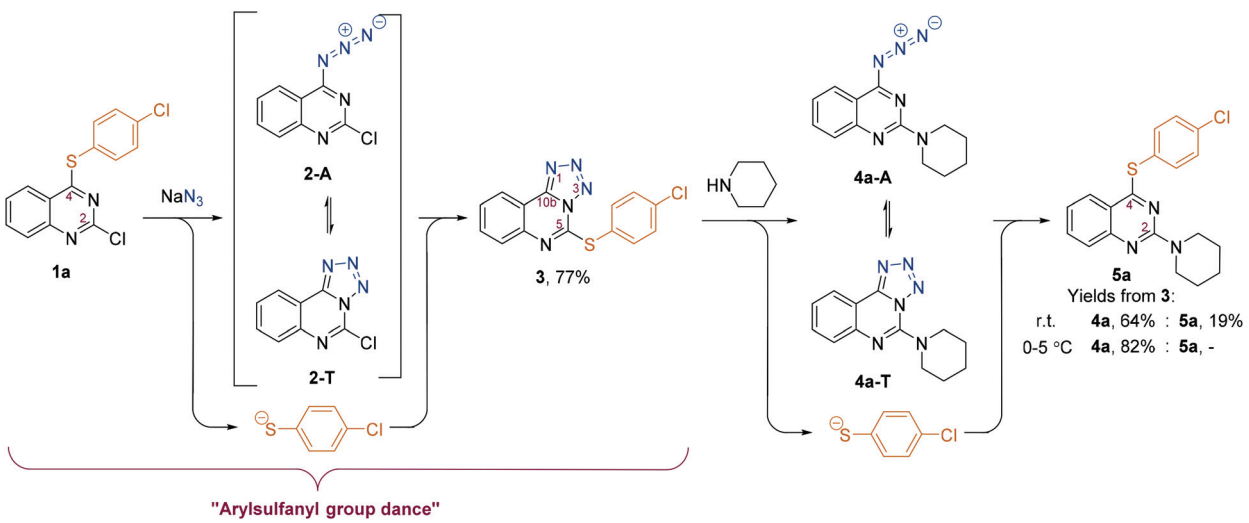
ity of the quinazoline derivatives, which contain azolyl substituents (imidazolyl, 1,2,4-triazolyl, 2-pyrazolyl groups) at the C4 position or azoles fused to the quinazoline core.[28–31] To acquire such structures, the prior construction of a substituted quinazoline core and pyrimidine-ring closing reactions are necessary.

Our group has developed several synthetic methodologies that make use of azidoquinazoline,[32,33] azidopurine,[34–37] and azido-7-deazapurine[38,39] derivatives as versatile starting materials. We have extended various S_NAr approaches that use an azido group as a leaving group. Moreover, we have recently developed a sulfanyl group dance around a quinazoline core and a sulfonyl group dance around a purine cycle, which demonstrates the synthetic application of the innate ability of the azido substituent to reach the azidoazomethine-tetrazole tautomeric equilibrium.[33,40]

In this paper, we report an array of synthetic applications for modifying the quinazoline core that utilize the arylthiolate leaving group and the intrinsic properties of the azide group to act as a regioselectivity switch, providing access to a "less active" C2 position of quinazoline and facilitating S_NAr reactions. The research led to the development of a novel synthetic method for the preparation of the 5-substituted tetrazolo[1,5-*c*] quinazolines and their further synthetic applications, as the hidden azide group can be accessed *via* the azide-tetrazole equilibrium and introduced into copper(I) catalyzed azide–alkyne cycloaddition (CuAAC), Staudinger and other azide reactions.

Results and discussion

The recently reported arylsulfanyl group dance[33] demonstrated the ability of the arylsulfanyl group to act as both a nucleophile and a leaving group (Scheme 2). When combined with the azidoazomethine-tetrazole tautomeric equilibrium, this led to the successful sequence of events **1** → **2** → **3**. This raised further questions about whether the arylsulfanyl group at the C2 position of quinazoline (C5 of tetrazolo[1,5-*c*]quinazoline) can be further exchanged with other nucleophiles and how resistant the products will be in the presence of the aryl thiolate anion. Indeed, the S_NAr process **3** → **4** provides access to the 4-azido-2-heteroatom-substituted quinazolines and/or their tetrazole tautomers. It should be emphasized that the virtually straightforward monosubstitution of 2,4-dichloroquinazoline with an azide at C4 (compound **2**), which would provide access for another substitution at C2, is not synthetically practical owing to the azide-tetrazole equilibrium.[32,33] The latter provides the tetrazolo-form **2-T** as an intermediate, which is extremely susceptible towards the next nucleophile attack and 2,4-diazidoquinazoline is formed in the presence of azide ions.



Scheme 2 Arylthioquinazoline rearrangement reaction sequence.

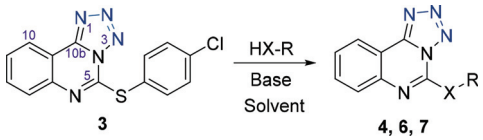
Therefore, the synthetic sequence 2,4-dichloroquinazoline →**1** → **3** → **4** has the potential to provide an easy functionalization at the C5 position of the tetrazolo[1,5-*c*]quinazoline core.

Hence, we tested the susceptibility of compound **3** towards piperidine as a model nucleophile. Indeed, the substitution of the aryl thiolate moiety at C2 was observed (product **4a**), and at room temperature this was accompanied by the nucleophilic attack of the expelled thiolate at C4 (product **5a**). This rearrangement is similar to the arylsulfanyl group dance previously reported by our group,[33] although it moves in the opposite direction, going from the C2 position to C4. Starting from the initial dance substrate **1**, the sulfanyl group goes full circle around the quinazoline core.

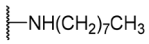
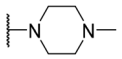
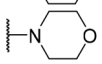
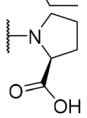
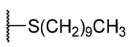
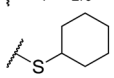
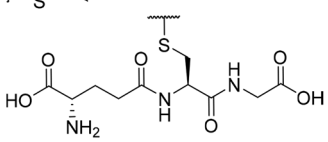
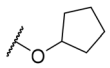
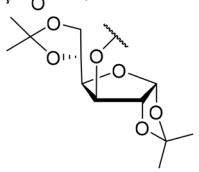
Synthesis of the 5-*N*-/*S*-/*O*-substituted tetrazolo[1,5-*c*]quinazolines

After the initial trials with piperidine, we investigated the scope of the S_NAr reactions with other nucleophiles (Table 1). Out of all previously synthesized 5-(arylthio)-tetrazolo-[1,5-*c*] quinazoline derivatives,[33] the 4-chlorophenyl-sulfanyl group bearing derivative **3** was chosen as a starting material for all further modifications owing to its excellent leaving group properties and synthetic availability.

Table 1 Synthesis of the 5-substituted tetrazolo[1,5-*c*]quinazolines **4**, **6** and **7**



3 **4, 6, 7**

Entry	–XR	Solvent	Base	Temp., °C	Time, h	Yield, %
1		DMF	—	0–5	1	**4a**, 82
2		DMF	—	0–5	1.5	**4b**, 78
3		DMF	—	0–5	1.5	**4c**, 91
4		DMF	—	0–5	1	**4d**, 62
5		DMF	—	r.t.	3	**4e**, 45
6		DMF	—	r.t.	5 days	**4f**, 42
7		THF/H_2O	NEt_3	r.t.	6 h	**4g**, 73
8		THF	K_2CO_3	r.t.	1.5	**6a**, 82
9		DMF	K_2CO_3	r.t.	1.5	**6b**, 76
10		DMF	K_2CO_3	0–5	1	**6c**, 96
11		DMSO	NEt_3	r.t.	5	**6d**, 52
12		THF	K_2CO_3	50	3	**7a**, 80
13		THF	K_2CO_3	50	1.5	**7b**, 55
14		abs. DMF	NaH	0–5	1.5	**7b**, 71
15		abs. DMF	NaH	0–5	3	**7c**, 55

The nucleophilic aromatic substitution reaction between the 5-(arylthio)tetrazolo[1,5-*c*]quinazoline derivative **3** and various primary and secondary amines leads to a class of 5-(alkylamino)tetrazolo[1,5-*c*]quinazolines **4** (entries 1–7, Table 1). In most cases the substitution proceeded readily, even at a reduced temperature, while reactions with diethylamine and morpholine required considerably longer reaction times to reach full conversion. The use of solvents such as dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) and MeCN afforded the desired products, however, the reactions in dimethylformamide (DMF) proceeded at a slightly higher rate. The cooling of the reaction mixture to 0–5 °C was imperative during the synthesis of compounds **4a** and **d** (entries 1 and 4, Table 1), otherwise formation of the rearrangement product **5** was observed in isolated yields up to 19% (Scheme 2). Finally, the reaction with L-proline and NEt_3 in the THF/H_2O system afforded the amino acid conjugate **4g** in a 73% yield (entry 7, Table 1).

5-(Alkylthio)tetrazolo[1,5-*c*]quinazoline derivatives **6a–c** can be obtained by further S_NAr reaction with the corresponding thiols (entries 8–11, Table 1). Although 5-(alkylthio)tetrazolo[1,5-*c*]quinazolines **6** are only rarely mentioned in the literature, they have already been found to possess a variety of biological activities, including antibacterial, antifungal and anticancer properties.[14] However, previous synthetic approaches to similar compounds required harsh pyrimidine ring-closing reactions, while we propose a simple pathway with an overall higher yield (entries 8–10, Table 1).[14,15] Substitution to the alkylsulfanyl group proceeded rather quickly, reaching full conversion in 1.5 h at room temperature. Potassium carbonate was found to be a suitable base for the reactions, affording a clean conversion with a simple purification protocol. The change in solvents had little impact on the conversion rate, therefore, the choice was based on the preferred product purification method. The synthesis of the decylthio derivative **6a** was carried out in THF (entry 8, Table 1), while reactions with cyclohexane and 2-propanethiol afforded the best yield by product precipitation from the DMF/brine mixture (entries 9–11, Table 1).

Scarce information can be found in the literature about 5-(alkoxy)tetrazoloquinazolines **7**, and only the methoxy and ethoxy quinazoline derivatives are known.[20] Previously such compounds required complex reaction sequences with subsequent opening and closing of the pyrimidine ring.[20] We have already introduced a simple approach for the synthesis of the ethoxy bearing derivative[33] and now we have developed a synthetic pathway leading to the alkoxy substituted tetrazolo[1,5-*c*]quinazolines **7** with high yields (entries 12–15, Table 1). Two methods were investigated, the first one required potassium carbonate as the base and alcohol as a co-solvent with THF (entries 12 and 13, Table 1). The addition of THF was necessary owing to the poor solubility of starting material **3** in alcohols. The use of potassium carbonate only afforded the desired products in the presence of excess amounts (>10 eq.) of low molecular weight alcohols, such as ethanol and isopropanol. The second method, already applied in purine chemistry,[41] proved superior for bulkier alcohols, requiring sodium hydride as a strong base in anhydrous DMF (entries 14 and 15, Table 1). However, the hydride had to be fully consumed during alkoxide formation before the addition of starting material **3**, otherwise degradation of the azide/tetrazole moiety was observed.

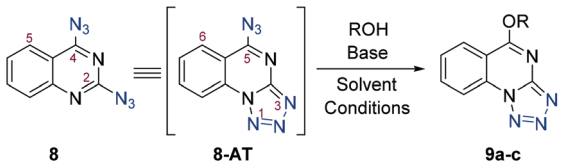
With the developed methods in hand, we modified the quinazoline core with more complex biomolecular substituents, such as peptides and sugar moieties. The sulfanyl group containing tripeptide glutathione underwent a regioselective S_NAr reaction leading to the quinazoline–peptide conjugate **6d** (entry 11, Table 1). The triethylamine/DMSO system was proved to be suitable for glutathione and afforded homogeneous media, while trials with potassium carbonate had a considerably slower conversion rate.[36] The introduction of the sugar moiety to the quinazoline core was also studied. The reaction with diacetone glucose yielded the quinazoline–carbohydrate conjugate **7c** with an acceptable yield (entry 15, Table 1).

Proof of regioselectivity *via* synthesis of the isomer

The obtained 5-(alkylamino) and 5-(alkylthio)tetrazolo[1,5-*c*]quinazoline derivatives **4** and **6** exhibit spectroscopic differences in their tetrazolo[1,5-*a*] regioisomers, the structures of which were proved using X-ray data.[32,33] Both regioisomers can be easily distinguished using NMR, the main difference is the chemical shift of the proton at the C5 position of quinazoline (the C10 position of tetrazolo[1,5-*c*]quinazoline) that owing to the electron withdrawing effect of tetrazole is shifted downfield (see ESI†).

The distinct structures of the *O*-substituted tetrazoloquinazolines **7** and **9** have been investigated previously, using the ethoxy group bearing derivative.[33] The class of inverted *O*-substituted tetrazolo[1,5-*a*]quinazolines **9** is already known to possess antidepressant and anticonvulsant activities.[18] However, the previously reported synthetic pathway with the subsequent addition of alcohol and sodium azide requires a long reaction time.[18] We propose an alternative approach (Table 2), employing the azidoazomethine-tetrazole equilibrium of 2,4-diazido-quinazoline **8** in the form of **8-AT** that

Table 2 Synthesis of the 5-(alkyl/aryloxy)tetrazolo[1,5-*a*]quinazolines **9**

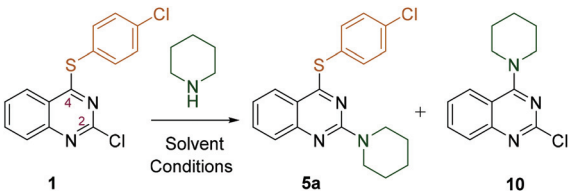


8 **8-AT** **9a-c**

Entry	R	9	Yield, %
1[a]	Ph	**9a**	85
2[b]	Bn	**9b**	49
3[c]	*n*-Hex	**9c**	75

[a] Conditions: K_2CO_3, *i*-PrOH, 60 °C, 4 h. [b] Conditions: NaH, abs. DMF, room temperature (r.t.), 2.5 h. [c] Conditions: NaH, abs. DMF, 0–5 °C, 6 h.

Table 3 Solvent optimization for the synthesis of 4-arylthio-2-piperidinylquinazoline **5a**



1 5a 10

Entry	Solvent	Temp.	Yield of **5a**, %	Yield of **10**, %
1	DMF	r.t.	17	63
2	THF	r.t.	64	23
3	*i*-PrOH	50 °C	71	17

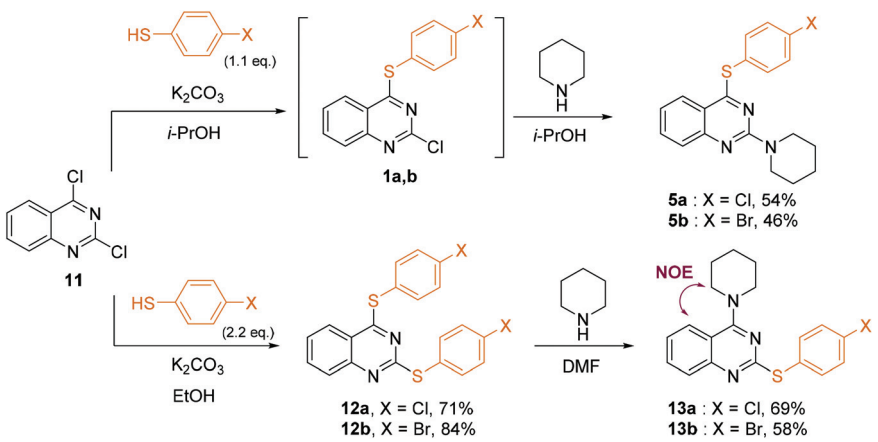
facilitates S_NAr reactions at the C4 position of quinazoline (C5 of tetrazolo[1,5-*a*]quinazoline), previously reported by our group.[33] The starting material **8** was obtained in the S_NAr reaction between the commercially available 2,4-dichloroquinazoline (**11**) and sodium azide in DMF with a 97% yield.[33] Further reactions with alcohols were performed in a similar fashion to methods developed for compounds **7**, although providing products **9** in a higher overall yield, which can be advantageous for medicinal chemistry applications. This is yet another example of how the regioselectivity switch executed by the azide-tetrazole tautomeric equilibrium can be combined with the leaving group potential of the azido group.

4-Arylthio-2-piperidinylquinazolines **5** are rarely mentioned in the literature. To prove the exact structure of the rearrangement product **5a** (Scheme 2), we investigated several synthetic methods. The main disadvantage of the previously reported rearrangement reaction (Scheme 2) is the oxidation of the cleaved arylthiolate to the inert disulfide in the presence of oxygen and basic media. The addition of the disulfide reducing agents, such as H_3PO_2, led to the reduction of the tetrazole moiety. The nucleophilic aromatic substitution of the corresponding 4-arylthio-2-chloroquinazoline **1** with piperidine was proved to be more efficient (Table 3). However, the stability of the arylsulfanyl group at the C4 position was heavily affected by the choice of solvent, the reaction in DMF lead to dominant substitution at the C4 position (entry 1, Table 3). On the other hand, the use of THF and *i*-PrOH as solvents favored the substitution at the C2 position and product **5a** was afforded in a good yield (entries 2 and 3, Table 3). In the case of *i*-PrOH, heating was necessary to achieve the conversion owing to the low solubility of the starting material **1**. With the developed method in hand, 4-arylthio-2-piperidinylquinazolines **5a–b** were synthesized from commercially available 2,4-dichloroquinazoline (**11**) in a two-step one-pot procedure with good yields (Scheme 3). To prove the position of the substituents, inverted regioisomers **13a–b** were also synthesized from the 2,4-disulfanyl quinazolines **12**, carrying out a regioselective substitution at the C4 positions. Two pairs of regioisomers have distinguishable UV spectra and the difference is also detectable using NMR data, while the exact position of the substituents can be proved using nuclear Overhauser effect spectroscopy (NOESY) spectra.[36]

NMR study of the azidoazomethine-tetrazole equilibrium

The previously mentioned compounds **3**, **6** and **7** exist in both the solid form and in solution in the tautomeric tetrazolo[1,5-*c*]quinazoline form. However, several 5-(alkylamino)tetrazolo[1,5-*c*]quinazoline derivatives **4** in the solutions revealed the presence of an open azido-tautomer that had the ability to facilitate different transformations, such as the previously mentioned rearrangement reaction (Scheme 2).

To gain insights into this matter, we investigated the azide-tetrazole equilibrium of compounds **4** using NMR (Fig. 1). It was found that the amino substituent has a substantial impact on the azide-tetrazole ratio, the monosubstituted amino-quinazoline **4b** showed only the tetrazole form, but for the heteroatom containing cyclic structures the equilibrium had shifted towards the azide form. Moreover, the acyclic diethylamino derivative **4f** had a considerably higher azide ratio than the slightly strained pyrrolidinyl substituted product **4c**.



Scheme 3 Synthesis of the arylthio-piperidinylquinazoline regioisomers **5** and **13**.

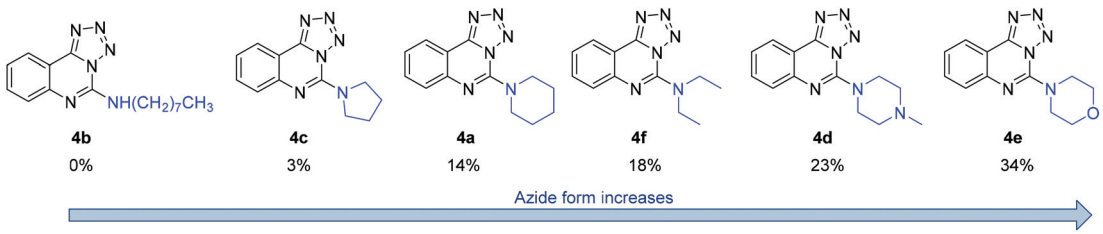


Fig. 1 Amount of the azide tautomer (%) in the $CDCl_3$ solutions of tetrazoloquinazolines **4a–f** (500 MHz, 22 °C).

In comparison with the general rules of azidoazomethine-tetrazole tautomeric equilibrium this particular case is inconsistent with the known correlations between the substituent electronic effects and the nucleophilicity parameters of the corresponding amines.[42–45] In line with the *S*-, *O*- and *N*-substituted tetrazoloquinazolines, the compounds of type **4** should have the least amount of azide owing to the strong electron donating properties of the amino group, facilitating the formation of the electron withdrawing tetrazole ring.

However, a similar exception was also observed in the 4-azidopyrimidines, in which the bulkier amino substituents shifted the equilibrium towards the azide.[44] To study this further, other equilibrium affecting factors, such as temperature and solvents were also investigated (Fig. 2). The effect of the solvent polarity and temperature on the tautomeric equilibrium of the substituted tetrazolo[1,5-*c*]quinazolines has rarely been presented in the literature owing to the dominant presence of the tetrazole form.[47]

However, these experiments have been thoroughly studied for azidopyrimidines and pyridines,[48,49] establishing general patterns to help predict the ratio of the forms. The temperature was proved to exhibit a linear effect, and the solvent permissibility had a logarithmic correlation with the tautomeric equilibrium.[42,43] Despite having the reverse substituent effect, compounds **4** are in line with the other accepted rules: a higher temperature provides more of the azide and polar solvents facilitate the formation of a tetrazole.

The *N*-methylpiperazinyl derivative **4d** exhibited a wide range of tautomeric ratios, from 7 to 59% for the azide form, depending on the media. The results of both the solvent polarity and the temperature effects can be used to form a continuous surface plot that can be used to predict the ratio of tautomeric forms at any given point (Fig. 2). The highest azide ratio of compound **4d** was observed in acetic acid at elevated temperatures (up to 59% at 70 °C, see ESI†), which implied the possible effect of the pH on the tautomeric equilibrium.

Further investigation revealed that the possible partial protonation of amine nitrogen leads to the formation of a strong electron withdrawing effect that significantly shifts the equilibrium towards the azide. This effect was the most pronounced in the case of compound **4c**, that has completely different tautomeric form ratios (A : T) in chloroform (3 : 97) and acetic acid (79 : 21) (Fig. 3).

This steep change in the equilibrium can be used for reactions that require the presence of an azide, such as cycloaddition reactions.

Exploring the reactivity and novel compound classes

Despite having a hidden azido substituent, previously known tetrazolo[1,5-*c*]quinazoline derivatives,[33] as well as compounds **3**, **6** and **7**, were completely inactive towards azide–alkyne cycloaddition reactions and heating the reaction mixture above 100 °C led to the slow degradation of the tetrazole/azide moiety. Similar trials with 5,6,7,8-tetrahydroquinazoline were

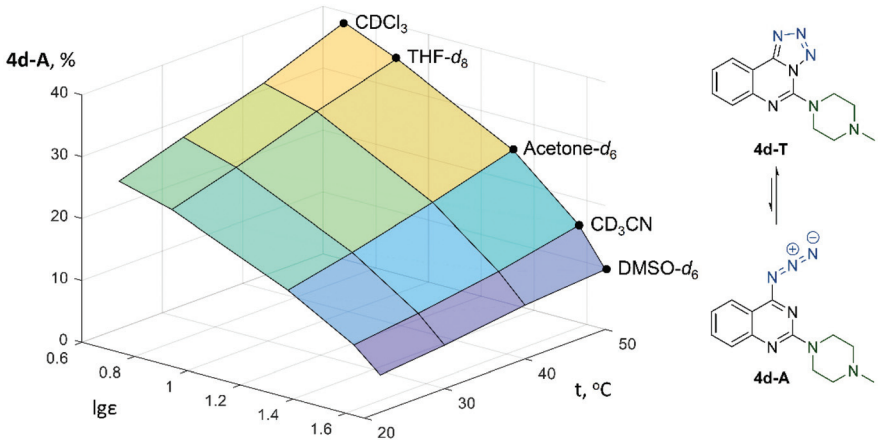


Fig. 2 Azide form content (A, %) of compound **4d** depending on the temperature and solvent dielectric constant ε.[46]

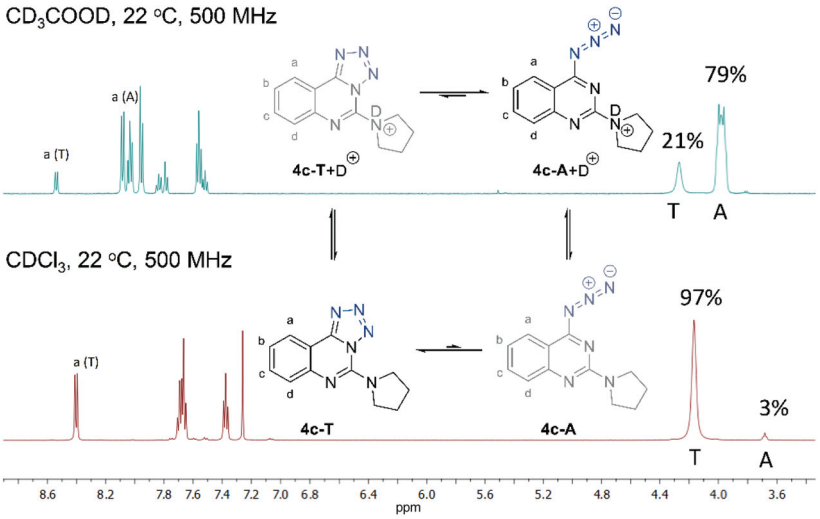


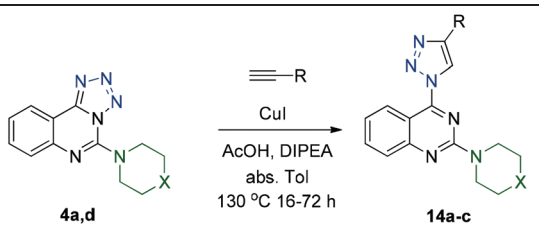
Fig. 3 Protonation effect on the azide-tetrazole equilibrium of compound **4c**.

only successful for transformation into the electron-withdrawing *N*-oxide.[50] However, the observed azide-tetrazole equilibrium and the presence of the azide tautomer in compounds **4** can be applied for the synthesis of novel 4-triazolylquinazolines **14** *via* CuAAC (Table 4).

At elevated temperatures and in non-polar media the degradation process was sufficiently diminished for compounds **4a** and **4d** to undergo transformation, introducing the previously unknown class of quinazolines **14a–c**, containing the 1,4-disubstituted triazole moiety at the C4 position. Despite the observed pH effect on the tautomeric equilibrium, switching the solvent to acetic acid led to a considerably higher rate of azide reduction, affording products **14** in lower yields or leading to complete degradation of the tetrazole moiety.

The corresponding RuAAC reaction was also investigated, however, instead of the expected 1,5-triazole derivatives, only the formation of the 1,4-substituted product **14a** was observed, while the degradation rate was considerably higher than in CuAAC. The highest isolated yield of **14a** of 24% was achieved by $CpRuCl(PPh_3)_2$ and $RuCl(PPh_3)_3OAc$ (see ESI†).

Table 4 Synthesis of 2-amino-4-triazolylquinazolines **14** *via* CuAAC



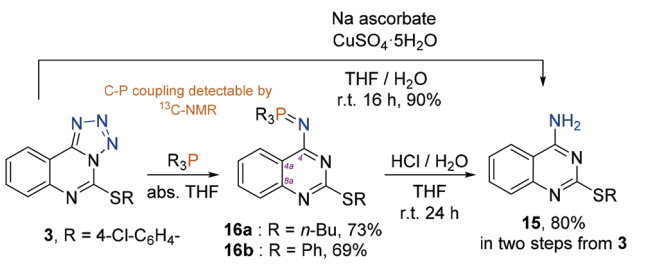
Entry	–R	–X–	14	Yield, %
1	–Ph	$-CH_2-$	**14a**	40
2	–Ph	>N–Me	**14b**	48
3	$-(CH_2)_3CN$	$-CH_2-$	**14c**	52

The fused tetrazole ring can be easily transformed into the corresponding 4-aminoquinazolines by classical azide reduction (Scheme 4). The use of the copper(II) sulfate pentahydrate/sodium ascorbate system afforded product **15** in an excellent 90% yield using an easy purification process.[51,52] Despite the absence of a detectable open azido tautomer, compound **3** also underwent the Staudinger reaction, however, the intermediate imino-phosphorane **16** was proved to possess a high hydrolytic stability. The method also required the additional removal of phosphine oxide by recrystallization to afford product **15** in an 80% yield.

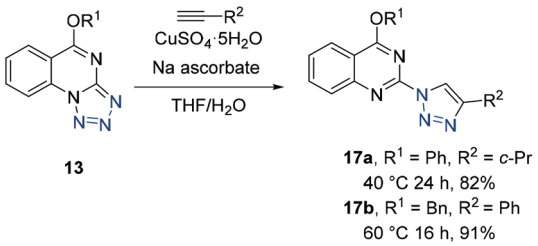
The stability of the observed iminophosphorane intermediates **16** raised the opportunity to isolate them. The reaction of tetrazolo[1,5-*c*]quinazoline **3** with phosphines in anhydrous THF led to a quick conversion to the desired products **16a–b** with yields of up to 73% (Scheme 4).

The obtained quinazoline iminophosphorane derivatives **16** showed characteristic carbon-phosphorus coupling through the C4, C4a and C8a positions of the quinazoline core, as observed in their ^{13}C NMR spectra (see ESI†).

The aforementioned compounds are also stable enough to withstand mild aqueous conditions, including extraction and analytical chromatographic conditions (reverse phase). Despite



Scheme 4 Reduction of fused tetrazole ring to 4-aminoquinazoline derivative **15**.



Scheme 5 Synthesis of the 4-(alkyl/aryloxy)-2-triazolylquinazolines **17**.

the reactive nature of the conventional iminophosphoranes, these particular compounds were proved to exhibit poor nucleophilic properties and, to our surprise, they did not react with electrophiles, including aldehydes, ketones, carbon disulphide or isocyanates. To the best of our knowledge, this is the first example of a series of tetrazolo[1,5-*c*]quinazolines in which the azide-tetrazole equilibrium can be successfully used to explore the azide reactivity: CuAAC, RuAAC and Staudinger reaction.

As previously reported by our group, 5-thiosubstituted tetrazolo[1,5-*a*]quinazolines have a higher tautomeric ratio in the azide form, which can be applied in cycloaddition reactions.[33]

In addition, the obtained 5-(alkyl/aryloxy)tetrazolo[1,5-*a*] quinazolines **13** easily undergo CuAAC reactions, leading to novel 4-(alkyl/aryl-oxy)-2-triazolylquinazolines **17** with excellent yields (Scheme 5).

Some of the synthesized quinazoline derivatives demonstrated promising photophysical properties, applicable in both fluorescent sensing technologies and materials science (Fig. 4). The triazolyl quinazolines **14** possess distinct fluorescent properties with a blue emission and quantum yields of up to 0.89 in DCM solution (see ESI†). These emission properties are presumably inherent owing to the prominent "push–pull" system found in the molecule. The pair of regioisomers **5b** and **13b** have distinguishable UV emission spectra with a quantum yield of up to 0.57 in DCM for compound **5b** and no emission for compounds **13b** (see ESI†). Quinazoline iminophosphoranes **16** were also found to possess a mediocre fluorescence with a violet emission and a quantum yield up to 0.29 in DCM.

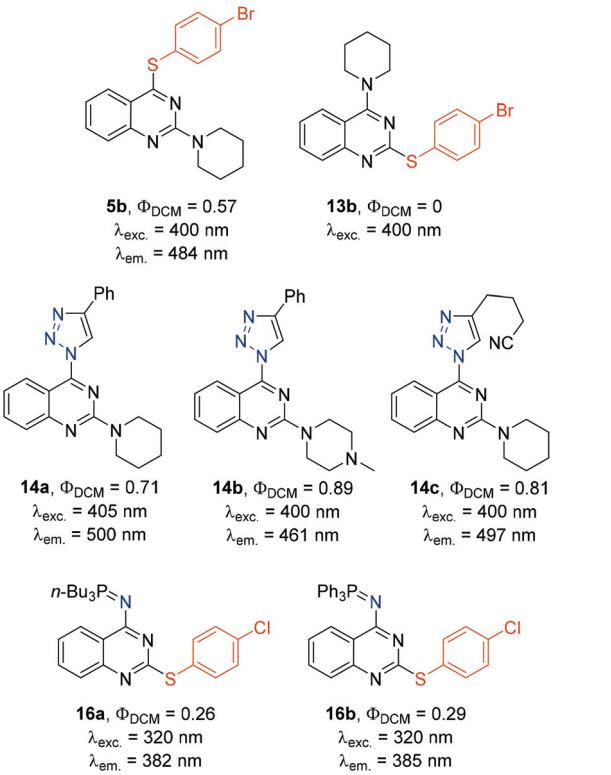


Fig. 4 Photophysical properties of the synthesized quinazoline derivatives.

Experimental

Materials and methods

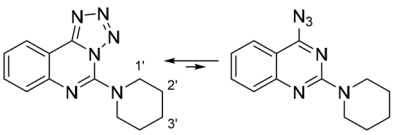
The solvents used in the reactions were dried using standard drying agents and freshly distilled prior to use. Commercially available reagents were used as received. All reactions were followed using thin layer chromatography (TLC) on E. Merck Kieselgel 60 F254, with detection by UV light, HPLC, and NMR analyses. Column chromatography was performed on silica gel (60 Å, 40–63 μm, ROCC). Melting points were recorded with a Fisher Digital Melting Point Analyzer Model 355 apparatus. The infrared spectroscopy (IR) spectra were recorded in hexachlorobutadiene (4000–2000 cm^{-1}) and paraffin oil (2000–450 cm^{-1}) with a FTIR Perkin–Elmer Spectrum 100 spectrometer. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded using a Bruker 300 MHz or Bruker 500 MHz spectrometer in $CDCl_3$, DMSO-d_6 or acetic acid-d_4. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. Residual solvent (^{1}H) or solvent ($^{13}C\{^{1}H\}$) peaks were used as an internal reference ($CDCl_3$ δ = 7.26 ppm, DMSO-d_6 δ = 2.50 ppm, acetic acid-d_4 δ = 2.45 ppm for ^{1}H NMR: $CDCl_3$ δ = 77.2 ppm, DMSO-d_6 δ = 39.5 ppm, acetic acid-d_4 δ = 179.0 ppm for $^{13}C\{^{1}H\}$ NMR). High performance liquid chromatography (HPLC) analyses were performed using an Agilent Technologies 1200 Series system equipped with an X Bridge C18 column, 4.6 × 150 mm, particle size 3.5 μm, with a flow rate of 1 mL min^{-1}, using 0.1% TFA/H_2O and MeCN for the mobile phase. The wavelength of detection was 260 nm. High resolution mass spectrometry (HRMS) analyses were performed on an Agilent 1290 Infinity series UPLC system equipped with column Extend C_{18} RRHD 2.1 × 50 mm, 1.8 μm, connected to an Agilent 6230 TOF LC/MS mass spectrometer. UV–vis absorption spectra were recorded with a PerkinElmer Lambda 35 UV/vis spectrometer in DCM using a 5 mm cell quartz cell. Emission spectra and Φ_{PL} were measured using QuantaMaster 40 steady state spectrofluorometer (Photon Technology International, Inc.) equipped with 6 inch integrating sphere by LabSphere, using the software package provided by the manufacturer.

General procedures and characterization of products

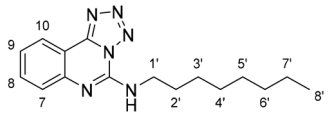
Compounds **1**,[33] **3**[33] and **12**[12] were prepared according to existing literature procedures. The spectroscopic data for compounds **9a** and **9c** matched that previously reported in the literature.[18]

Synthesis of the 5-(alkylamino)tetrazolo[1,5-*c*]quinazoline derivatives 4

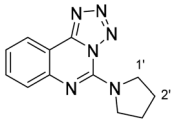
Tautomeric mixture of 5-(piperidin-1-yl)tetrazolo[1,5-*c*]quinazoline (4a-T) and 4-azido-2-(piperidin-1-yl)quinazoline (4a-A). Piperidine (0.27 mL, ρ = 0.86 g mL^{-1}, 2.71 mmol, 3.0 eq.) was added to a stirred solution of **3** (265 mg, 0.90 mmol, 1.0 eq.) in DMF (3 mL). The mixture was stirred at 0–5 °C for 1 h, controlled using HPLC. Once the reaction was complete, brine solution (30 mL) was added, and the mixture was left in the freezer for 16 h. The water suspension was filtered and the solid was purified using silica gel column chromatography (Hex/EtOAc; 5 → 11%). Yield: 188 mg (82%); orange solid; R_f (Tol/MeCN; 10 : 1) 0.60; m.p. 101–104 °C. Only the tetrazolo form was characterized from a 96 : 4 mixture of **4a-T**/**4a-A**: ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 8.36 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 7.82 (dd, 1H, ^3J = 8.3, 7.3 Hz, H–C(8)), 7.72 (d, 1H, ^3J = 8.3 Hz, H–C(7)), 7.53 (dd, 1H, ^3J = 7.9, 7.3 Hz, H–C(9)), 4.03–3.98 (m, 4H, 2 × H$_2$–C(1′)), 1.77–1.71 (m, 6H, 2 × H$_2$–C(2′), H$_2$–C(3′)). ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d$_6$): δ 151.2, 144.3, 142.4, 133.5, 125.6, 125.0, 123.9, 111.5, 48.7, 25.2, 23.9. IR ν (cm^{-1}): 3057, 3033, 2935, 2865, 2849, 1624, 1607, 1562, 1529, 1481, 1467, 1451, 1415, 1371. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{13}H_{15}N_6$ 255.1353; found 255.1340 (5.10 ppm).



5-(Octylamino)tetrazolo[1,5-*c*]quinazoline (4b). Octylamine (0.47 mL, ρ = 0.78 g mL^{-1}, 2.85 mmol, 3.0 eq.) was added to a stirred solution of **3** (298 mg, 0.95 mmol, 1.0 eq.) in DMF (5 mL). The mixture was stirred at 0–5 °C for 1.5 h, controlled using HPLC. Once the reaction was complete, brine solution (30 mL) was added, and the mixture was neutralized with acetic acid to pH ≈7. The water suspension was extracted with a mixture of hexane and ethylacetate (40 and 20 mL, respectively). The organic phase was washed with brine (5 × 10 mL) and water (3 × 5 mL), and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. Yield: 222 mg (78%); colorless solid; R_f (Tol/MeCN; 10 : 1) 0.55; m.p. 150–152 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.46 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 7.81–7.73 (m, 2H, H–C(7), H–C(8)), 7.47 (ddd, 1H, ^3J = 7.9, 6.4 Hz, ^4J = 2.0 Hz, H–C(9)), 6.21 (t, 1H, ^3J = 5.8 Hz, (–NH–)), 3.76 (td, 2H, ^3J = 7.4, 5.8 Hz, H$_2$–C(1′)), 1.80 (quintet, 2H, ^3J = 7.4 Hz, H$_2$–C(2′)), 1.48 (quintet, 2H, ^3J = 7.4 Hz, H$_2$–C(3′)), 1.39 (quintet, 2H, ^3J = 7.4 Hz, H$_2$–C(4′)), 1.34–1.26 (m, 6H, 3 × (–CH$_2$–)), 0.88 (t, 3H, ^3J = 6.7 Hz, H$_3$–C(8′)). ^{13}C{^{1}H} NMR (125.7 MHz, CDCl$_3$): δ 145.0, 145.4, 140.6, 133.7, 126.1, 124.82, 124.79, 111.3, 41.7, 31.9, 29.4 (2C, assigned with HSQC spectrum), 29.3, 27.0, 22.8, 14.2. IR ν (cm^{-1}): 3255, 3054, 2922, 2853, 1647, 1564, 1541, 1481, 1466, 1456, 1438, 1389, 1378. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{23}N_6$ 299.1979; found 299.1962 (5.68 ppm).

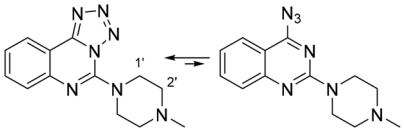


5-(Pyrrolidin-1-yl)tetrazolo[1,5-*c*]quinazoline (4c). Pyrrolidine (0.18 mL, ρ = 0.87 g mL^{-1}, 2.20 mmol, 3.0 eq.) was added to a stirred solution of **3** (230 mg, 0.73 mmol, 1.0 eq.) in DMF (3 mL). The mixture was stirred at 0–5 °C for 1.5 h, controlled using HPLC. Once the reaction was complete, a brine solution (30 mL) was added, and the mixture was left in the freezer overnight. The water suspension was filtered and the solid was washed with hexane (2 × 10 mL). Yield: 160 mg (91%); colorless solid; R_f (Tol/MeCN; 10 : 1) 0.58; m.p. 154–156 °C. ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 8.30 (d, 1H, ^3J = 7.8 Hz, H–C(10)), 7.77 (dd, 1H, ^3J = 8.3, 7.5 Hz, H–C(8)), 7.63 (d, 1H, ^3J = 8.3 Hz, H–C(7)), 7.43 (dd, 1H, ^3J = 7.8, 7.5 Hz, H–C(9)), 4.12–3.95 (m, 4H, 2 × H$_2$–C(1′)), 2.05–1.99 (m, 4H, 2 × H$_2$–C(2′)). ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d$_6$): δ 150.9, 145.4, 141.1, 133.6, 125.0, 124.0, 123.8, 110.5, 50.0, 25.0. IR ν (cm^{-1}): 3147, 3055, 3028, 2976, 2957, 1616, 1561, 1528, 1478, 1451, 1408, 1366, 1340. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{12}H_{13}N_6$ 241.1196; found 241.1170 (10.8 ppm).

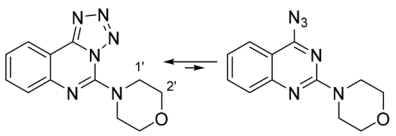


Tautomeric mixture of 5-(4-methylpiperazin-1-yl)tetrazolo[1,5-*c*]quinazoline (4d-T) and 4-azido-2-(4-methylpiperazin-1-yl)quinazoline (4d-A). *N*-Methylpiperazine (0.23 mL, ρ = 0.90 g mL^{-1}, 2.10 mmol, 3.0 eq.) was added to a stirred solution of **3** (220 mg, 0.70 mmol, 1.0 eq.) in DMF (3 mL). The mixture was stirred at 0–5 °C for 1 h, controlled using HPLC. Once the reaction was complete, a brine solution (30 mL) was added, and the mixture was left in the freezer overnight. The water suspension was filtered and the solid was washed with hexane (2 × 10 mL). Yield: 117 mg (62%); yellow solid; R_f (Tol/EtOAc; 1 : 4) 0.67; m.p. 119–121 °C. Only the tetrazolo form was characterized from a 95 : 5 mixture of **4d-T**/**4d-A**: ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 8.40 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 7.85 (dd, 1H, ^3J = 7.9, 7.4 Hz, H–C(8)), 7.76 (d, 1H, ^3J = 7.9 Hz, H–C(7)), 7.57 (dd, 1H, ^3J = 7.9, 7.4 Hz, H–C(9)), 4.06–3.99 (m, 4H, 2 × H$_2$–C(1′)), 2.59–2.55 (m, 4H, 2 × H$_2$–C(2′)), 2.27 (s, 3H, (–CH$_3$)). ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d$_6$): δ 151.1, 144.1, 142.5, 133.6, 125.8, 125.3, 124.0, 111.8, 54.0, 47.5, 45.6. IR ν (cm^{-1}): 2973, 2942, 2830, 2792, 2759, 1625, 1606, 1562, 1531, 1480, 1452, 1409, 1382, 1365. HRMS

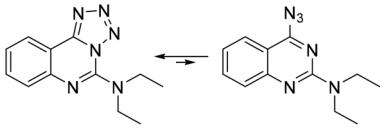
(ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{16}N_7$ 270.1462; found 270.1443 (7.03 ppm).



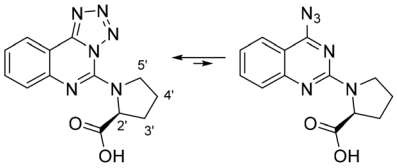
Tautomeric mixture of 5-(morpholin-4-yl)tetrazolo[1,5-*c*]quinazoline (4e-T) and 4-azido-2-(morpholin-4-yl)quinazoline (4e-A). Morpholine (0.14 mL, ρ = 1.01 g mL^{-1}, 1.59 mmol, 3.0 eq.) was added to a stirred solution of **3** (165 mg, 0.53 mmol, 1.0 eq.) in DMF (3 mL). The mixture was stirred at r.t. for 3 h, controlled using HPLC. Once the reaction was complete, brine solution (30 mL) was added, and the mixture was left in the freezer overnight. The water suspension was filtered and the solid was washed with hexane (2 × 10 mL), then purified using silica gel column chromatography (DCM). Yield: 61 mg (45%); orange solid; R_f (Tol/EtOAc; 1 : 4) 0.70; m.p. 185–190 °C. Only the tetrazolo form was characterized from a 92 : 8 mixture of **4e-T**/**4e-A**: ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 8.41 (dd, 1H, ^3J = 7.9 Hz, ^4J = 0.9 Hz, H–C(10)), 7.86 (ddd, 1H, ^3J = 8.2, 7.4 Hz, ^4J = 0.9 Hz, H–C(8)), 7.77 (d, 1H, ^3J = 8.2 Hz, H–C(7)), 7.58 (ddd, 1H, ^3J = 7.9, 7.4 Hz, ^4J = 0.8 Hz, H–C(9)), 4.03 (dd, 4H, ^3J = 4.9, 4.6 Hz, 2 × H$_2$–C(1′)), 3.85 (dd, 4H, ^3J = 4.9, 4.6 Hz, 2 × H$_2$–C(2′)). ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d$_6$): δ 151.1, 144.0, 142.5, 133.7, 125.8, 125.5, 124.0, 111.8, 65.7, 48.0. IR ν (cm^{-1}): 3054, 2974, 2916, 2866, 1625, 1608, 1562, 1526, 1478, 1466, 1455, 1446, 1392. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{13}N_6O$ 257.1145; found 257.1145 (<0.01 ppm).



Tautomeric mixture of 5-(diethylamino)tetrazolo[1,5-*c*]quinazoline (4f-T) and 4-azido-2-(diethylamino)quinazoline (4f-A). Diethylamine (0.18 mL, ρ = 0.71 g mL^{-1}, 1.71 mmol, 3.0 eq.) was added to a stirred solution of **3** (107 mg, 0.341 mmol, 1.0 eq.) in DMF (3 mL). The mixture was stirred at r.t. for 5 d, controlled by HPLC. Once the reaction was complete, the brine solution (30 mL) was added, and the mixture was extracted with a solution of Hex and EtOAc (6 : 1) (3 × 10 mL). The organic phase was combined, washed with water (5 × 5 mL), dried over anhydrous Na_2SO_4, evaporated and purified using silica gel column chromatography (Tol/MeCN; 0 → 15%). Yield: 35 mg (42%); off-white solid; R_f (Tol/MeCN; 10 : 1) 0.62; m.p. 83–85 °C. Only the tetrazolo form was characterized from a 94 : 6 mixture of **4f-T**/**4f-A**: ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 8.33 (d, 1H, ^3J = 7.8 Hz, H–C(10)), 7.79 (dd, 1H, ^3J = 8.3, 7.3 Hz, H–C(8)), 7.66 (d, 1H, ^3J = 8.2 Hz, H–C(7)), 7.47 (dd, 1H, ^3J = 7.8, 7.3 Hz, H–C(9)), 3.95 (q, 4H, ^3J = 6.9 Hz, 2 × (–CH$_2$–)), 1.34 (t, 6H, ^3J = 6.9 Hz, 2 × (–CH$_3$)). ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d$_6$): δ 151.3, 144.8, 141.7, 133.6, 125.2, 124.2, 123.9, 110.9, 44.6, 13.4. IR ν (cm^{-1}): 2975, 2933, 2923, 2874, 2855, 1624, 1614, 1561, 1534, 1484, 1465, 1533. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{15}N_6$ 243.1353; found 243.1376 (9.46 ppm).



Tautomeric mixture of tetrazolo[1,5-*c*]quinazolin-5-yl-L-proline (4g-T) and (4-azidoquinazolin-2-yl)-L-proline (4g-A). Triethylamine (0.23 mL, ρ = 0.73 g mL^{-1}, 1.68 mmol, 2.5 eq.) was added to a stirred suspension of **3** (210 mg, 0.67 mmol, 1.0 eq.) and L-proline (92 mg, 0.80 mmol, 1.2 eq.) in a mixture of THF (10 mL) and water (5 mL). The mixture was stirred at r.t. for 6 h, controlled using HPLC. Once the reaction was complete, acetic acid was added until the solution was pH 5. The resulting mixture was evaporated and purified using silica gel column chromatography (DCM/MeOH; 0 → 10%). Yield: 139 mg (73%); yellow solid; R_f (DCM/MeOH; 9 : 1) 0.42; decomposes at 142 °C. Only the tetrazolo form was characterized from a 97 : 3 mixture of **4g-T**/**4g-A**: ^{1}H NMR (500 MHz, DMSO-d$_6$, 50 °C): δ 8.34 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 7.80 (dd, 1H, ^3J = 8.2, 7.5 Hz, H–C(8)), 7.66 (d, 1H, ^3J = 8.2 Hz, H–C(7)), 7.49 (dd, 1H, ^3J = 7.9, 7.5 Hz, H–C(9)), 5.26 (br.s., 1H, H–C(2′)), 4.14 (br.s., 2H, H$_2$–C(5′)), 2.49–2.39 (m, 1H, H$_a$–C(3′)), 2.22–2.15 (m, 1H, H$_b$–C(3′)), 2.11–2.01 (m, 2H, H$_2$–C(4′)). ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d$_6$, 50 °C): δ 173.0, 150.6, 144.8, 140.6, 133.6, 125.1, 124.2, 123.8, 110.4, 61.9, 50.4, 29.9, 23.1. IR ν (cm^{-1}): 3150, 3039, 3021, 2971, 2954, 1715, 1578, 1528, 1478, 1451, 1412, 1367, 1353. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{13}N_6O_2$ 283.0943; found 283.0952 (3.18 ppm).

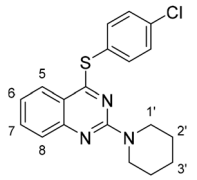


Synthesis of 4-(arylthio)-2-(piperidinyl)quinazoline derivatives 5

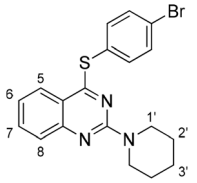
4-[(4-Chlorophenyl)thio]-2-(piperidin-1-yl)quinazoline (5a). *Method A*: To a solution of 2-chloro-4-[(4-chlorophenyl)thio] quinazoline (**1a**) (182 mg, 0.59 mmol, 1.0 eq.) in *i*-PrOH (10 mL) piperidine (0.17 mL, ρ = 0.86 g mL^{-1}, 1.77 mmol, 3.0 eq.) was added and the mixture was stirred at 50 °C for 5 h, controlled using HPLC. After completion of the reaction the mixture was purified using silica gel column chromatography (Tol). Yield: 128 mg (71%); slightly green solid; R_f (Tol/MeCN; 10 : 1) 0.74; m.p. 148–151 °C.

Method B: The suspension of 2,4-dichloroquinazoline (**9**) (200 mg, 1.00 mmol, 1.0 eq.), K_2CO_3 (166 mg, 1.20 mmol, 1.2 eq.) and 4-chlorothiophenol (158 mg, 1.10 mmol, 1.1 eq.) in *i*-PrOH (10 mL) was stirred at 0–5 °C for 1 h, controlled using

HPLC. Then piperidine (0.30 mL, ρ = 0.88 g mL^{-1}, 3.00 mmol, 3.0 eq.) was added and the mixture was stirred at 50 °C for 5 h, controlled using HPLC. After the completion of the reaction the mixture was purified using silica gel column chromatography (Tol). Yield: 192 mg (54%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.89 (d, 1H, ^3J = 8.1 Hz, H–C(5)), 7.70 (dd, 1H, ^3J = 8.3, 7.1 Hz, H-(7)), 7.65 (d, 2H, ^3J = 8.5 Hz, 2 × H–C(Ar)), 7.58 (d, 2H, ^3J = 8.5 Hz, 2 × H–C(Ar)), 7.45 (d, 1H, ^3J = 8.3 Hz, H–C(8)), 7.25 (dd, 1H, ^3J = 8.1, 7.1 Hz, H-(6)), 3.51 (br.s., 4H, 2 × H_2–C (1′)), 1.60–1.53 (m, 2H, H_2–C(3′)), 1.44–1.31 (m, 4H, 2 × H_2–C (2′)). ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6): δ 169.9, 156.6, 151.0, 137.7, 134.7, 134.4, 129.2, 126.3, 125.7, 123.5, 122.3, 116.8, 44.3, 25.2, 24.3. IR ν (cm^{-1}): 2998, 2927, 2851, 1610, 1563, 1541, 1507, 1476, 1451, 1425, 1389, 1347. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{19}H_{19}ClN_3S$ 356.0983; found 356.0981 (0.56 ppm).

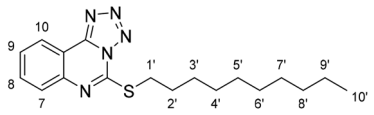


4-[(4-Bromophenyl)thio]-2-(piperidin-1-yl)quinazoline (5b). The suspension of 2,4-dichloroquinazoline (**11**) (100 mg, 0.50 mmol, 1.0 eq.), K_2CO_3 (76 mg, 0.55 mmol, 1.1 eq.) and 4-bromothiophenol (104 mg, 0.55 mmol, 1.1 eq.) in *i*-PrOH (10 mL) was stirred at 0–5 °C for 1 h, controlled using HPLC. Then piperidine (0.15 mL, ρ = 0.86 g mL^{-1}, 1.50 mmol, 3.0 eq.) was added and the mixture was stirred at 50 °C for 5 h, controlled using HPLC. After the completion of the reaction the mixture was purified using silica gel column chromatography (Tol). Yield: 91 mg (46%); slightly green solid; R_f (Tol/MeCN; 10 : 1) 0.78; m.p. 142–145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, 1H, ^3J = 8.1 Hz, H–C(5)), 7.60 (dd, 1H, ^3J = 7.9, 7.4 Hz, H–C(7)), 7.57 (d, 2H, ^3J = 8.4 Hz, 2 × H–C(Ar)), 7.49 (d, 1H, ^3J = 7.9 Hz, H–C(8)), 7.47 (d, 2H, ^3J = 8.4 Hz, 2 × H–C(Ar)), 7.15 (dd, 1H, ^3J = 8.1, 7.4 Hz, H–C(6)), 3.61–3.53 (m, 4H, 2 × H_2–C(1′)), 1.63–1.59 (m, 2H, H_2–C(3′)), 1.50–1.45 (m, 4H, 2 × H_2–C(2′)). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ 170.5, 157.4, 151.8, 137.8, 133.9, 132.1, 127.8, 126.1, 123.9 (2C, assigned using heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond correlation (HMBC) spectra), 121.8, 117.8, 45.0, 25.9, 25.0. IR ν (cm^{-1}): 2924, 2850, 1610, 1564, 1542, 1507, 1479, 1425, 1388, 1347. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{19}H_{19}BrN_3S$ 400.0478; found 400.0456 (5.50 ppm).



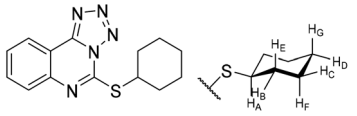
Synthesis of 5-(alkylthio)tetrazolo[1,5-*c*]quinazoline derivatives 6

5-(Decylthio)tetrazolo[1,5-*c*]quinazoline (6a). Decanethiol (0.07 mL, ρ = 0.84 g mL^{-1}, 0.32 mmol, 1.2 eq.) and K_2CO_3 (48 mg, 0.35 mmol, 1.3 eq.) were added to a stirred solution of 5-[(4-chlorophenyl)thio]tetrazolo[1,5-*c*]quinazoline (**3**) (85 mg, 0.27 mmol, 1.0 eq.) in THF (3 mL). The suspension was stirred at r.t. for 1.5 h, controlled using HPLC. Then the mixture was evaporated, suspended in toluene (10 mL) and washed with water (3 × 2 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and purified using silica gel column chromatography (Tol). Yield: 76 mg (82%); off-white solid; R_f (Tol/MeCN; 10 : 1) 0.69; m.p. 94–96 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.57 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 7.97 (d, 1H, ^3J = 8.3 Hz, H–C(7)), 7.87 (dd, 1H, ^3J = 8.3, 7.6 Hz, H–C(8)), 7.69 (dd, 1H, ^3J = 7.9, 7.6 Hz, H–C(9)), 3.48 (t, 2H, ^3J = 7.4 Hz, H_2–C(1′)), 1.90 (quintet, 2H, ^3J = 7.4 Hz, H_2–C(2′)), 1.54 (quintet, 2H, ^3J = 7.4 Hz, H_2–C (3′)), 1.42–1.35 (m, 2H, H_2–C(4′)), 1.33–1.24 (m, 10H, 5 × (–CH_2–)), 0.87 (t, 3H, ^3J = 6.9 Hz, H_2–C(10′)). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ: 148.7, 147.3, 143.8, 133.7, 128.3, 127.5, 124.8, 113.5, 32.0, 31.0, 29.7, 29.6, 29.4, 29.2, 28.9, 28.8, 22.8, 14.2. IR ν (cm^{-1}): 2955, 2926, 2849, 1618, 1586, 1560, 1489, 1478, 1473, 1451, 1422, 1381. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{18}H_{26}N_5S$ 344.1910; found 344.1909 (2.91 ppm).

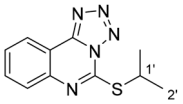


5-(Cyclohexylthio)tetrazolo[1,5-*c*]quinazoline(6b). Cyclohexanethiol (0.06 mL, ρ = 0.95 g mL^{-1}, 0.49 mmol, 1.2 eq.) and K_2CO_3 (73 mg, 0.53 mmol, 1.3 eq.) were added to a stirred solution of **3** (139 mg, 0.44 mmol, 1.0 eq.) in THF (3 mL). The suspension was stirred at r.t. for 1.5 h, controlled using HPLC. Then, the NaClO/H_2O solution (10 mL) and EtOH (3 mL) were added, and the mixture was stirred for 5 min. The organic solvents were evaporated, and the leftover water suspension was extracted using DCM (3 × 15 mL). The organic phase was washed with water (3 × 5 mL), dried over anhydrous Na_2SO_4, filtered, the solvent was evaporated and purified using silica gel column chromatography (Tol/MeCN; 10 : 1). Yield: 95 mg (76%); off-white solid; R_f (Tol/MeCN; 10 : 1) 0.66; m.p. 139–141 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 7.98 (d, 1H, ^3J = 8.3 Hz, H–C(7)), 7.87 (dd, 1H, ^3J = 8.3, 7.6 Hz, H–C(8)), 7.69 (dd, 1H, J = 7.9, 7.6 Hz, H–C(9)), 4.27 (tt, 1H, ^3J = 10.1, 3.8 Hz, H_A), 2.31–2.22 (m, 2H, 2 × H_B), 1.90–1.83 (m, 2H, 2 × H_C), 1.78–1.67 (m, 3H, H_D, 2 × H_E), 1.63–1.54 (m, 2H, 2 × H_F), 1.48–1.38 (m, 1H, H_G). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ 148.8, 147.1, 143.8, 133.6, 128.2, 127.6, 124.8, 113.6, 44.9, 32.8, 25.9, 25.7. IR ν (cm^{-1}): 2937, 2909, 2872, 2862, 2844, 1618, 1584, 1560, 1487, 1474, 1447, 1378. HRMS (ESI) *m*/*z*:

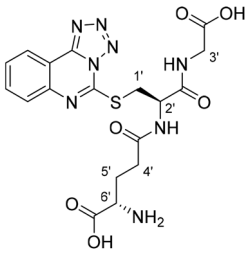
$[M + H]^+$ calcd for $C_{14}H_{16}N_5S$ 286.1121; found 286.1109 (4.19 ppm).



5-(Isopropylthio)tetrazolo[1,5-*c*]quinazoline (6c). Propane-2-thiol (0.05 mL, ρ = 0.81 g mL^{-1}, 0.53 mmol, 1.1 eq.) was added to a stirred suspension of 5-(arylthio)tetrazolo[1,5-*c*]quinazoline **3** (150 mg, 0.48 mmol, 1.0 eq.) and K_2CO_3 (79 mg, 0.58 mmol, 1.2 eq.) in DMF (3 mL). The suspension was stirred at 0–5 °C for 1 h, controlled using HPLC. Once the reaction was complete, NaClO/H_2O solution (10 mL) and EtOH (3 mL) were added, and the mixture was stirred for 10 min. Then the organic solvents were evaporated, and the leftover water suspension was extracted using DCM (3 × 15 mL). The organic phase was washed with water (3 × 5 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated. Yield: 112 mg (96%); off-white solid R_f (Tol/MeCN; 10 : 1) 0.61; m.p. 141–143 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 8.00 (d, 1H, ^3J = 8.2 Hz, H–C(7)), 7.89 (dd, 1H, ^3J = 8.2, 7.4 Hz, H–C(8)), 7.71 (dd, 1H, ^3J = 7.9, 7.4 Hz, H–C(9)), 4.38 (heptet, 1H, ^3J = 6.9 Hz, H–C(1′)), 1.62 (d, 6H, ^3J = 6.9 Hz, 2 × (H_3–C(2′))). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ 148.8, 147.1, 143.9, 133.7, 128.3, 127.6, 124.9, 113.6, 37.4, 22.9. IR ν (cm^{-1}): 3049, 2974, 2923, 2863, 1620, 1584, 1562, 1488, 1452, 1382, 1366. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{12}N_5S$ 246.0808; found 246.0807 (0.41 ppm).

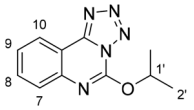


Glutathione–tetrazolo[1,5-*c*]quinazoline conjugate 6d. To a stirred solution of **3** (153 mg, 0.49 mmol, 1.0 eq.) and glutathione (165 mg, 0.54 mmol, 1.1 eq.) in DMSO (10 mL) trimethylamine (0.17 mL, ρ = 0.73 g mL^{-1}, 1.23 mmol, 2.5 eq.) was added and the mixture was stirred at r.t. for 5 h, controlled using HPLC. Then methyl tertiary-butyl ether (MTBE) (40 mL) was added, and the suspension was filtered and washed with MTBE (3 × 3 mL). The solids were suspended in a mixture of MeCN (25 mL) and water (10 mL), and 0.5 M hydrochloric acid was added until the pH reached 6–7. Afterwards the suspension was recrystallized, filtered and washed with water (4 × 5 mL). Yield: 121 mg (52%); off-white solid; R_f (MeOH) 0.60; decomposes at 205 °C. ^{1}H NMR (500 MHz, CD_3COOD): δ 9.08 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 8.57 (d, 1H, ^3J = 8.3 Hz, H–C(7)), 8.41 (dd, 1H, ^3J = 8.3, 7.3 Hz, H–C(8)), 8.23 (dd, 1H, ^3J = 7.9, 7.3 Hz, H–C(9)), 5.69 (dd, 1H, ^3J = 8.1, 5.2 Hz, H–C(2′)), 4.66 (dd, 1H, ^2J = 14.3 Hz, ^3J = 5.2 Hz, H_a–C(1′)), 4.54–4.46 (m, 3H, H_2–C(3′), H–C(6′)), 4.21 (dd, 1H, ^2J = 14.3 Hz, ^3J = 8.1 Hz, H_b–C(1′)), 3.05 (t, 2H, ^3J = 6.7 Hz, H_2–C(4′)), 2.70 (m, 1H, H_a–C(5′)), 2.60 (m, 1H, H_b–C(5′)). ^{13}C{^{1}H} NMR (125.7 MHz, CD_3COOD): δ 176.4, 175.1, 174.8, 173.1, 150.6, 148.2, 145.4, 135.8, 130.4, 129.4, 126.5, 115.2, 55.6, 54.2, 42.6, 33.5, 33.2, 27.4. IR ν (cm^{-1}): 3348, 3317, 3293, 3291, 1740, 1640, 1619, 1591, 1575, 1542, 1494, 1476, 1451. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{21}N_8O_6S$ 477.1299; found 477.1275 (5.03 ppm).



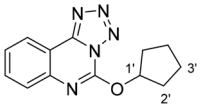
Synthesis of 5-(alkyloxy)tetrazolo[1,5-*a*/*c*]quinazoline derivatives 7 and 9

5-(Isopropoxy)tetrazolo[1,5-*c*]quinazoline (7a). 5-[(4-Chlorophenyl)thio]tetrazolo[1,5-*c*]quinazoline (**3**) (336 mg, 1.07 mmol, 1.0 eq.) and K_2CO_3 (177 mg, 1.28 mmol, 1.2 eq.) were suspended in *i*-PrOH (15 mL) and THF (5 mL). The mixture was stirred at 50 °C for 3 h, controlled using HPLC. After the completion of the reaction the mixture was evaporated and purified using silica gel column chromatography (Tol/MeCN; 6 → 9%). Yield: 190 mg (80%); colorless solid; R_f (Tol/MeCN; 10 : 1) 0.54; m.p. 210–213 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 7.86 (d, 1H, ^3J = 8.2 Hz, H–C(7)), 7.82 (dd, 1H, ^3J = 8.2, 7.3 Hz, H–C(8)), 7.62 (dd, 1H, ^3J = 7.9, 7.3 Hz, H–C(9)), 5.78 (septet, 1H, ^3J = 6.3 Hz, H–C(1′)), 1.62 (d, 6H, ^3J = 6.3 Hz, 2 × H_3–C(2′)). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ 151.4, 143.7, 143.4, 133.8, 127.0, 126.9, 125.0, 113.1, 75.4, 21.8. IR ν (cm^{-1}): 2973, 2926, 1630, 1562, 1524, 1483, 1454, 1418, 1405, 1399, 1367. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{12}N_5O$ 230.1036; found 230.1012 (10.43 ppm).

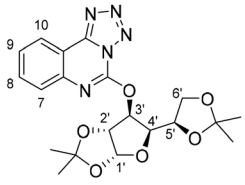


5-(Cyclopentyloxy)tetrazolo[1,5-*c*]quinazoline (7b). Sodium hydride (60% dispersion in mineral oil corresponding to 11 mg, 0.44 mmol, 1.5 eq. of pure sodium hydride) was added to a solution of cyclopentanol (0.05 mL, ρ = 0.94 g mL^{-1}, 0.58 mmol, 2.0 eq.) in absolute DMF (4 mL). The mixture was stirred in an ice bath for 45 min. Then a suspension of **3** (90 mg, 0.29 mmol, 1.0 eq.) in absolute DMF (1 mL) was added, and the mixture was stirred in an ice bath for 1.5 h, controlled using HPLC. After completion of the reaction brine (25 mL) was added, and the mixture was placed in the freezer for 2 h. Then the suspension was filtered and washed with H_2O (5 × 5 mL) and hexane (5 × 5 mL). Yield: 52 mg (71%); colorless solid; R_f (Tol/MeCN; 10 : 1) 0.57; m.p. 210–214 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 7.88 (d, 1H, ^3J = 8.1 Hz, H–C(7)), 7.84 (dd, 1H, ^3J = 8.1, 7.4 Hz, H–C(8)),

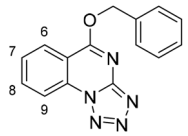
7.63 (dd, 1H, ^3J = 7.9, 7.4 Hz, H–C(9)), 5.96–5.84 (m, 1H, H–C(1′)), 2.21–2.12 (m, 4H, 2 × H_2–C(2′)), 2.00–1.91 (m, 2H, 2 × H_a–C(3′)), 1.80–1.71 (m, 2H, 2 × H_b–C(3′)). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ 151.4, 143.8, 143.7, 133.8, 126.98, 126.96, 125.0, 113.1, 84.4, 32.9, 24.0. IR ν (cm^{-1}): 3063, 2968, 2873, 1630, 1561, 1524, 1482, 1454, 1419, 1407, 1399. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{14}N_5O$ 256.1193; found 256.1189 (1.56 ppm).



Diacetone glucose–quinazoline conjugate 7c. Sodium hydride (60% dispersion in mineral oil corresponding to 19 mg, 0.80 mmol, and 1.2 eq. of pure sodium hydride) was added to a solution of diacetone glucose (226 mg, 0.869 mmol, 1.3 eq.) in absolute DMF (5 mL). The mixture was stirred in an ice bath for 45 min. Then a suspension of **3** (210 mg, 0.67 mmol, 1.0 eq.) in absolute DMF (2 mL) was added, and the mixture was stirred in an ice bath for 3 h, controlled using HPLC. After completion of the reaction brine (25 mL) was added, and the mixture was placed in the freezer for 2 h. Then the suspension was filtered, washed with H_2O (5 × 5 mL) and hexane (5 × 5 mL). The solids were purified using silica gel column chromatography (Tol/MeCN; 0 → 15%). Yield: 149 mg (52%); colorless solid; R_f (Tol/MeCN; 10 : 1) 0.38; m.p. 175–177 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 8.52 (d, 1H, ^3J = 7.9 Hz, H–C(10)), 8.01–7.96 (m, 2H, H–C(7), H–C(8)), 7.80–7.75 (m, 1H, H–C(9)), 6.06 (d, 1H, ^3J = 3.8 Hz, H–C(1′)), 5.76 (d, 1H, ^3J = 2.2 Hz, H–C(3′)), 5.00 (d, 1H, ^3J = 3.8 Hz, H–C(2′)), 4.52–4.46 (m, 2H, H–C(4′), H–C(5′)), 4.24–4.19 (m, 1H, H_a–C(6′)), 4.10–4.05 (m, 1H, H_b–C(6′)), 1.52, 1.35, 1.28, 1.21 (4s, 12H, 4 × ($-CH_3$)). $^{13}C\{^1H\}$ NMR (125.7 MHz, DMSO-d_6): δ 151.2, 142.8, 142.7, 134.0, 127.5, 126.7, 124.4, 113.3, 111.5, 108.2, 104.7, 81.8, 81.2, 78.6, 72.4, 65.4, 26.5, 26.4, 26.1, 25.1. IR ν (cm^{-1}): 2990, 2937, 2894, 1634, 1565, 1525, 1484, 1457, 1412, 1373, 1348. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{24}N_5O_6$ 430.1721; found 430.1732 (2.56 ppm).



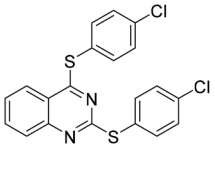
5-(Benzyloxy)tetrazolo[1,5-*a*]quinazoline (9b). Sodium hydride (60% dispersion in mineral oil corresponding to 68 mg, 2.83 mmol, and 1.2 eq. of pure sodium hydride) was added to a solution of benzyl alcohol (0.29 mL, ρ = 1.04 g mL^{-1}, 2.83 mmol, 1.2 eq.) and 2,4-diazidoquinazoline (**8**) (500 mg, 2.36 mmol, 1.0 eq.) in absolute DMF (7 mL). The mixture was stirred at r.t. for 2.5 h, controlled using HPLC. After completion of the reaction toluene (60 mL) was added, and the mixture was washed with 5% LiCl/H_2O solution (5 × 8 mL). The aqueous phases were combined and back-extracted with toluene (3 × 5 mL). Then the organic phases were combined, dried over anhydrous Na_2SO_4, filtered, evaporated and recrystallized from EtOH (50 mL). Yield: 277 mg (49%); off-white solid; R_f (Tol/MeCN 10 : 1) 0.31; m.p. 171–173 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.52 (d, 1H, ^3J = 8.3 Hz, H–C(9)), 8.35 (d, 1H, ^3J = 8.1 Hz, H–C(6)), 8.04 (dd, 1H, ^3J = 8.3, 7.5 Hz, HC(8)), 7.74 (dd, 1H, ^3J = 8.1, 7.5 Hz, H–C(7)), 7.58 (d, 2H, ^3J = 7.2 Hz, 2 × H–C(Ph)), 7.44 (t, 2H, ^3J = 7.2 Hz, 2 × H–C(Ph)), 7.40 (t, 1H, ^3J = 7.2 Hz, H–C(Ph)), 5.78 (s, 2H, ($-CH_2-$)). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ 164.4, 153.2, 135.7, 134.9, 134.0, 129.1, 128.99, 128.95, 128.5, 126.7, 116.3, 113.0, 70.8. IR ν (cm^{-1}): 1618, 1603, 1548, 1478, 1455, 1421, 1394, 1343, 1305. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{12}N_5O$ 278.1036; found 278.1060 (8.63 ppm).



Synthesis of the 2,4-bis-(arylthio)quinazoline derivatives 12

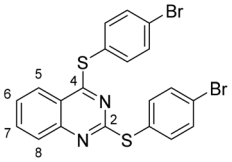
This method was used to synthesize compounds **12a** and **12b**.

2,4-Bis-[(4-chlorophenyl)thio]quinazoline (12a). Anhydrous K_2CO_3 (1.52 g, 11.0 mmol, 2.2 equiv.) was added to a stirred solution of arylthiol (11.0 mmol, 2.2 equiv.) and 2,4-dichloroquinazoline (**11**) (1.0 g, 5.0 mmol, 1.0 equiv.) in EtOH (50 mL) under argon. The reaction mixture was stirred at 40 °C for 18 h, controlled using HPLC. Then the mixture was cooled to room temperature and filtered. The precipitate was washed with water (2 × 8 mL) and EtOH (3 × 6 ml) and dried in a vacuum. Yield 1.5 g (71%); colorless solid, R_f (Tol) 0.37, m.p. 135–137 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (dd, 1H, ^3J = 8.3 Hz, ^4J = 1.3 Hz, H–C(5)), 7.72–7.66 (m, 2H, H–C(7), H–C(8)), 7.39 (ddd, 1H, ^3J = 8.3, 6.5 Hz, ^4J = 1.7 Hz, H–C(6)), 7.23 (d, 2H, ^3J = 8.5 Hz, 2 × H–C(Ar)), 7.20 (d, 2H, ^3J = 8.7 Hz, 2 × H–C(Ar)), 7.17 (d, 2H, ^3J = 8.7 Hz, 2 × H–C(Ar)), 7.12 (d, 2H, ^3J = 8.5 Hz, 2 × H–C(Ar)). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ 171.3, 166.3, 149.3, 136.9, 136.3, 136.2, 135.2, 134.6, 129.4, 129.1, 128.3, 127.8, 126.6, 125.0, 123.9, 120.9. IR ν (cm^{-1}): 3089, 3047, 3010, 1697, 1613, 1571, 1556, 1519, 1474, 1434. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{13}Cl_2N_2S_2$ 414.9892; found 414.9896 (0.96 ppm).



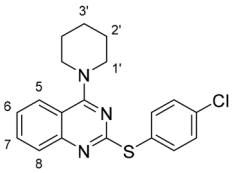
2,4-Bis-[(4-bromophenyl)thio]quinazoline (12b). Yield (from 0.5 g (2.5 mmol) of **11**) 1.0 g (84%); colorless solid; R_f (Tol) 0.38; m.p. 156–158 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.07 (dd, 1H, ^3J = 8.3 Hz, ^4J = 1.3 Hz, H–C(5)), 7.81 (ddd, 1H, ^3J = 7.9, 6.7 Hz, ^4J = 1.3 Hz, H–C(7)), 7.77 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.4 Hz, H–C(8)), 7.51 (ddd, 1H, ^3J = 8.3, 6.7 Hz, ^4J = 1.4 Hz, H–C(6)), 7.45 (d, 2H,

^3J = 8.4 Hz, 2 × H–C(Ar)), 7.40 (d, 2H, ^3J = 8.4 Hz, 2 × H–C(Ar)), 7.27 (d, 2H, ^3J = 8.4 Hz, 2 × H–C(Ar)), 7.24 (d, 2H, ^3J = 8.4 Hz, 2 × H–C(Ar)). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ 171.3, 166.2, 149.3, 137.1, 136.6, 134.7, 132.5, 132.1, 129.1, 127.8, 126.7, 125.8, 124.5, 124.0, 123.5, 121.0. IR ν (cm^{-1}): 3091, 306, 3046, 2943, 2911, 1614, 1554, 1518, 1471, 1434. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{13}Br_2N_2S_2$ 504.8861; found 504.8857 (0.79 ppm).

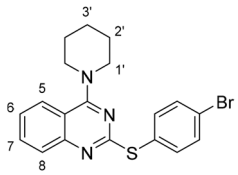


Synthesis of 2-(arylthio)-4-(piperidinyl)quinazoline derivatives 13

2-[(4-Chlorophenyl)thio]-4-(piperidin-1-yl)quinazoline (13a). To a solution of **12a** (280 mg, 0.68 mmol, 1.0 eq.) in DMF (5 mL) piperidine (0.20 mL, ρ = 0.86 g mL^{-1}, 2.04 mmol, 3.0 eq.) was added and the mixture was stirred at r.t. for 5 h, controlled using HPLC. After completion of the reaction brine (25 mL) was added, and the mixture was placed in the freezer for 2 h. Then the suspension was filtered and washed with H_2O (5 × 5 mL) and hexane (5 × 5 mL). The solids were recrystallized from EtOH (20 mL). Yield: 166 mg (69%); off-white solid; R_f (Tol/MeCN 10 : 1) 0.73; m.p. 88–91 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, 1H, ^3J = 8.3 Hz, H–C(5)), 7.65 (d, 1H, ^3J = 8.4 Hz, H–C(8)), 7.63–7.59 (m, 3H, H–C(7), 2 × H–C(Ar)), 7.37 (d, 2H, ^3J = 8.5 Hz, 2 × H–C(Ar)), 7.28 (dd, 1H, ^3J = 8.3, 7.0 Hz, H–C(6)), 3.60–3.56 (m, 4H, 2 × H_2–C(1′)), 1.72–1.67 (m, 2H, H_2–C(3′)), 1.66–1.61 (m, 4H, 2 × H_2–C(2′)). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ 165.9, 163.7, 152.9, 136.7, 134.7, 132.6, 129.8, 128.7, 127.4, 125.3, 123.9, 114.4, 50.6, 25.9, 24.7. IR ν (cm^{-1}): 2936, 2861, 1608, 1557, 1500, 1476, 1429, 1389, 1357, 1343, 1290. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{19}ClN_3S$ 356.0983; found 356.0982 (0.28 ppm).

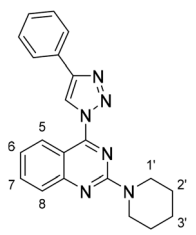


2-[(4-Bromophenyl)thio]-4-(piperidin-1-yl)quinazoline (13b). To a solution of **12b** (150 mg, 0.30 mmol, 1.0 eq.) in DMF (10 mL) piperidine (0.09 mL, ρ = 0.86 g mL^{-1}, 0.90 mmol, 3.0 eq.) was added and the mixture was stirred at r.t. for 5 h, controlled using HPLC. After completion of the reaction brine (25 mL) was added, and the mixture was placed in the freezer for 2 h. Then the suspension was filtered and washed with H_2O (5 × 5 mL). The solids were purified using silica gel column chromatography (Tol/MeCN 3%). Yield: 70 mg (58%); off-white solid; R_f (Tol/MeCN; 10 : 1) 0.63; m.p. 114–116 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, 1H, ^3J = 8.3 Hz, H–C(5)), 7.65 (d, 1H, ^3J = 8.3 Hz, H–C(8)), 7.61 (dd, 1H, ^3J = 8.3, 6.9 Hz, H–C(7)), 7.55 (d, 2H, ^3J = 8.6 Hz, 2 × H–C(Ar)), 7.51 (d, 2H, ^3J = 8.6 Hz, 2 × H–C(Ar)), 7.28 (dd, 1H, ^3J = 8.3, 6.9 Hz, H–C(6)), 3.61–3.56 (m, 4H, 2 × H_2–C(1′)), 1.72–1.67 (m, 2H, H_2–C(3′)), 1.65–1.61 (m, 4H, 2 × H_2–C(2′)). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ 165.9, 163.8, 153.0, 137.0, 132.7, 131.8, 130.5, 127.6, 125.4, 123.9, 123.0, 114.5, 50.7, 26.0, 24.8. IR ν (cm^{-1}): 2942, 1931, 2917, 2850, 1609, 1564, 1524, 1498, 1471, 1463, 1438, 1364, 1352. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{19}BrN_3S$ 400.0478; found 400.0473 (1.25 ppm).



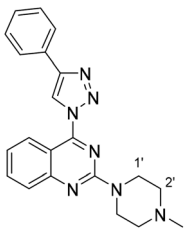
Synthesis of 2-amino-4-(1*H*-1,2,3-triazol-1-yl)quinazoline derivatives 14

4-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-2-(piperidin-1-yl)quinazoline (14a). To a solution of **4a** (130 mg, 0.51 mmol, 1.0 eq.) in absolute toluene (10 mL) acetic acid (0.03 mL, 0.56 mmol, 1.1 eq.), DIPEA (0.10 mL, ρ = 0.74 g mL^{-1}, 0.56 mmol, 1.1 eq.), phenylacetylene (0.11 mL, ρ = 0.93 g mL^{-1}, 1.02 mmol, 2.0 eq.) and CuI (5 mg, 0.026 mmol, 5 mol-%) were subsequently added and the mixture was stirred in a high-pressure flask at 130 °C for 16 h, controlled using HPLC. After completion of the reaction the mixture was evaporated, suspended in DCM (30 mL) and washed with saturated ethylenediaminetetraacetic acid (EDTA) solution (3 × 10 mL). The aqueous layers were combined and back-extracted with DCM (3 × 5 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, evaporated and purified using silica gel column chromatography (Tol/EtOAc 9 → 11%). Yield: 73 mg (40%); bright yellow solid; R_f (Tol/MeCN 10 : 1) 0.77; m.p. 175–178 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.89 (d, 1H, ^3J = 8.3 Hz, H–C(5)), 8.78 (s, 1H, H–C(triazole)), 8.00 (d, 2H, ^3J = 7.5 Hz, 2 × H–C(Ph)), 7.71 (dd, 1H, ^3J = 8.3, 7.6 Hz, H–C(8)), 7.64 (d, 1H, ^3J = 8.3 Hz, H–C(7)), 7.50 (t, 2H, ^3J = 7.5 Hz, 2 × H–C(Ph)), 7.41 (t, 1H, ^3J = 7.5 Hz, H–C(Ph)), 7.28 (dd, 1H, ^3J = 8.3, 7.6 Hz, H–C(6)), 3.95 (dd, 4H, ^3J = 5.5, 4.8 Hz, 2 × H_2–C(1′)), 1.77–1.67 (m, 6H, 2 × H_2–C(2′), H_2–C(3′)). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ 157.8, 156.6, 154.3, 147.1, 134.8, 130.0, 129.1, 128.8, 127.4, 126.3, 126.2, 123.5, 119.6, 111.3, 45.3, 26.0, 25.0. IR ν (cm^{-1}): 3148, 3103, 3061, 2931, 2851, 1619, 1589, 1548, 1514, 1483, 1452, 1422, 1351. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{21}N_6$ 357.1822; found 357.1796 (7.28 ppm).

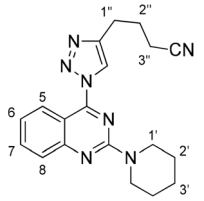


4-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-2-(4-methylpiperazin-1-yl) quinazoline (14b). 4d (35 mg, 0.13 mmol, 1.0 eq.), absolute toluene (4 mL), acetic acid (0.01 mL, 0.14 mmol, 1.1 eq.), DIPEA (0.02 mL, ρ = 0.74 g mL^{-1}, 0.14 mmol, 1.1 eq.), phenylacetylene (0.03 mL, ρ = 0.93 g mL^{-1}, 0.26 mmol, 2.0 eq.), and CuI (1 mg, 0.01 mmol, 5 mol-%) were combined and reacted for 16 h. Purified using silica gel column chromatography (DCM : MeOH 0 → 5%). Yield: 23 mg (48%); bright yellow solid; R_f (EtOAc) 0.15; m.p. 180–182 °C.

Method B: To a solution of **4d** (75 mg, 0.30 mmol, 1.0 eq.) in absolute toluene (2 mL), phenylacetylene (0.07 mL, ρ = 0.93 g mL^{-1}, 0.60 mmol, 2.0 eq.) and $CpRuCl(PPh_3)_2$ (11 mg, 0.015 mmol, 5 mol%) were added and the mixture was stirred in a high-pressure flask at 140 °C for 48 h, controlled using HPLC. After completion of the reaction the mixture was evaporated and purified using silica gel column chromatography (DCM/EtOAc 0 → 5%). Yield: 26 mg (24%) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.93 (d, 1H, ^3J = 8.3 Hz, H–C(5)), 8.79 (s, 1H, H–C(triazole)), 8.00 (d, 2H, ^3J = 7.6 Hz, 2 × H–C(Ph)), 7.74 (dd, 1H, ^3J = 8.3, 7.4 Hz, H–C(8)), 7.67 (d, 1H, ^3J = 8.3 Hz, H–C(7)), 7.50 (t, 2H, ^3J = 7.6 Hz, 2 × H–C(Ph)), 7.41 (t, 1H, ^3J = 7.6 Hz, H–C(Ph)), 7.32 (dd, 1H, ^3J = 8.3, 7.4 Hz, H–C(6)), 4.02 (dd, 4H, ^3J = 4.8, 4.5 Hz, 2 × (H_2–C(1′))), 2.56 (dd, 4H, ^3J = 4.8, 4.5 Hz, 2 × (H_2–C(2′))), 2.39 (s, 3H, (–CH_3)). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ 157.7, 156.4, 154.4, 147.1, 135.0, 129.9, 129.1, 128.9, 127.4, 126.31, 126.26, 124.0, 119.6, 111.6, 55.1, 46.4, 44.3. IR ν (cm^{-1}): 3149, 3058, 3002, 2956, 2932, 2795, 1619, 1594, 1547, 1520, 1484, 1456, 1429. HRMS (ESI) *m*/*z*: [M − H]$^-$ calcd for $C_{21}H_{20}N_7$ 370.1786; found 370.1784 (0.54 ppm).



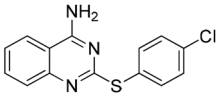
4-[4-(3-Cyanoprop-1-yl)-1*H*-1,2,3-triazol-1-yl]-2-(piperidin-1-yl)quinazoline (14c). 4a (66 mg, 0.26 mmol, 1.0 eq.), absolute toluene (4 mL), acetic acid (0.02 mL, 0.31 mmol, 1.1 eq.), DIPEA (0.05 mL, ρ = 0.74 g mL^{-1}, 0.29 mmol, 1.1 eq.), 5-hexynenitrile (0.08 mL, ρ = 0.89 g mL^{-1}, 0.78 mmol, 2.0 eq.), and CuI (2 mg, 0.013 mmol, 5 mol-%) were combined and reacted time for 72 h. Purified using silica gel column chromatography (Tol/MeCN 1 → 6%). Yield: 47 mg (52%); bright yellow solid; R_f (Tol/MeCN 10 : 1) 0.40; m.p. 182–184 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.82 (d, 1H, ^3J = 8.6 Hz, H–C(5)), 8.41 (s, 1H, H–C(triazole)), 7.69 (dd, 1H, ^3J = 8.6, 8.5 Hz, H–C(7)), 7.63 (d, 1H, ^3J = 8.5 Hz, H–C(8)), 7.28–7.24 (m, 1H, H–C(6)), 3.95–3.90 (m, 4H, 2 × H_2–C(1′)), 3.04 (t, 2H, ^3J = 7.2 Hz, H_2–C(1″)), 2.52 (t, 2H, ^3J = 7.2 Hz, H_2–C(3″)), 2.22 (quintet, 2H, ^3J = 7.2 Hz, H_2–C(2″)), 1.75–1.66 (m, 6H, 2 × H_2–C(2′), H_2–C(3′)). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ 157.7, 156.6, 154.2, 145.1, 134.8, 127.3, 126.2, 123.5, 121.7, 119.4, 111.2, 45.3, 26.0, 25.0 (2C, assigned with HSQC spectrum), 24.3, 16.8. IR ν (cm^{-1}): 3164, 3118, 3073, 3009, 2939, 2916, 2854, 2249, 1621, 1587, 1547, 1516, 1486, 1466, 1429. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{19}H_{22}N_7$ 348.1931; found 348.1934 (0.86 ppm).



Synthesis of 4-amino-2-[(4-chlorophenyl)thio]quinazoline (15)

Method A: To a solution of **3** (90 mg, 0.29 mmol, 1.0 eq.) in absolute THF (2 mL) tributylphosphine (0.11 mL, ρ = 0.82 g mL^{-1}, 0.43 mmol, 1.5 eq.) was added and the yellow mixture was stirred at r.t. under argon for 10 min, until the color disappeared. Then 1 M HCl/H_2O solution (2 mL) was added and the mixture was stirred at r.t. for 24 h, controlled using HPLC. After completion of the reaction the mixture was evaporated, suspended in EtOAc (20 mL) and washed with a saturated $NaHCO_3$/H_2O solution (5 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and recrystallized from $CHCl_3$ (20 mL). Yield: 66 mg (80%); off-white solid; R_f (Tol/MeCN; 10 : 1) 0.31; decomposes at 255 °C.

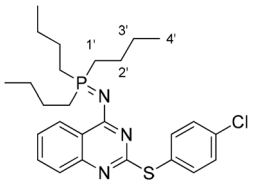
Method B: To a solution of **3** (110 mg, 0.35 mmol, 1.0 eq.) in THF (5 mL) solutions of $CuSO_4$·5H_2O (9 mg, 0.04 mmol, 10 mol–%) in H_2O (1 mL) and sodium ascorbate (76 mg, 0.39 mmol, 1.1 eq.) in H_2O (1 mL) were subsequently added and the mixture was stirred at r.t. for 16 h, controlled using HPLC. After completion of the reaction the mixture was evaporated, suspended in EtOAc (20 mL) and washed with saturated EDTA/H_2O solution (2 × 5 mL) and water (2 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. Yield: 91 mg (90%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.13 (d, 1H, ^3J = 8.4 Hz, H–C(5)), 7.92 (br.s., 2H, (–NH_2)), 7.67 (dd, 1H, ^3J = 8.1, 7.5 Hz, H–C(7)), 7.64 (d, 2H, ^3J = 8.5 Hz, 2 × H–C(Ar)), 7.50 (d, 2H, ^3J = 8.5 Hz, 2 × H–C(Ar)), 7.40–7.35 (m, 2H, H–C(6), H–C(8)). $^{13}C\{^1H\}$ NMR (125.7 MHz, DMSO-d_6): δ 165.9, 161.5, 150.1, 136.2, 133.4, 133.3, 129.7, 128.9, 126.2, 124.7, 123.8, 112.8. IR ν (cm^{-1}): 3398, 3312, 3120, 1648, 1615, 1568, 1538, 1505, 1476, 1460, 1444. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{14}H_{11}ClN_3S$ 288.0357; found 288.0343 (4.86 ppm).



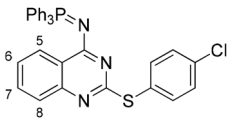
Synthesis of quinazoline iminophosphorane derivatives 16

2-[(4-Chlorophenyl)thio]-4-[(tributylphosphoronylidene) amino]-quinazoline (16a). To a solution of **3** (120 mg, 0.382 mmol, 1.0 eq.) in absolute THF (3 mL) tributylphosphine

(0.19 mL, ρ = 0.82 g mL^{-1}, 0.76 mmol, 2.0 eq.) was added and the yellow mixture was stirred at r.t. under argon for 10 min, until the colour disappears. After completion of the reaction the mixture was evaporated, suspended in hexane (20 mL) and left in the freezer for 1 h. The white suspension was filtered and washed with hexane (2 × 3 mL). Yield: 136 mg (73%); colorless solid; R_f (Tol/MeCN; 10 : 1) 0.38; m.p. 132–134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, 1H, ^3J = 7.9 Hz, H–C(5)), 7.61 (d, 2H, ^3J = 8.3 Hz, 2 × H–C(Ar)), 7.58–7.53 (m, 2H, H–C(7), H–C(8)), 7.35 (d, 2H, ^3J = 8.3 Hz, 2 × H–C(Ar)), 7.23 (ddd, 1H, ^3J = 7.9, 6.5 Hz, ^4J = 1.7 Hz, H–C(6)), 1.75–1.67 (m, 6H, 3 × H_2–C(1′)), 1.41–1.33 (m, 12H, 3 × H_2–C(2′), 3 × H_2–C(3′)), 0.92 (t, 9H, ^3J = 6.8 Hz, 3 × H_3–C(4′)). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ 168.5 (D, $^2J_{C–P}$ = 8 Hz), 167.1, 151.1 (D, $^4J_{C–P}$ = 3 Hz), 137.9, 134.8, 132.5, 130.8, 129.1, 126.4, 125.7, 124.0, 120.5 (D, $^3J_{C–P}$ = 21 Hz), 24.3 (D, $^2J_{C–P}$ = 16 Hz), 23.9 (D, $^3J_{C–P}$ = 4 Hz), 23.5 (D, $^1J_{C–P}$ = 61 Hz), 13.8. ^{31}P NMR (202 MHz, $CDCl_3$): δ 37.02. IR ν (cm^{-1}): 2956, 2930, 2899, 2867, 1609, 1566, 1499, 1478, 1456, 1428, 1350, 1337. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{26}H_{36}ClN_3PS$ 488.2051; found 488.2061 (2.23 ppm).

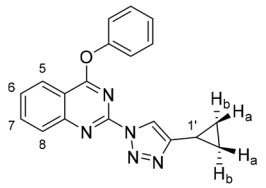


2-[(4-Chlorophenyl)thio]-4-[(triphenylphosphoronylidene)-amino]quinazoline (16b). To a solution of **3** (150 mg, 0.48 mmol, 1.0 eq.) in absolute THF (4 mL) triphenylphosphine (250 mg, 0.96 mmol, 2.0 eq.) was added and the mixture was stirred at r.t. under argon for 1 h, controlled using HPLC. After completion of the reaction the mixture was evaporated, suspended in MeCN (20 mL) and left in the freezer for 1 h. The white suspension was filtered and washed with MeCN (5 × 3 mL) and hexane (2 × 5 mL). Yield: 182 mg (69%); colorless solid; R_f (Tol/MeCN; 10 : 1) 0.50; m.p. 247–249 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (d, 1H, ^3J = 8.1 Hz, H–C(5)), 7.65–7.55 (m, 11H, H–C(7), H–C(8), 9 × H–C(Ph)), 7.43 (td, 6H, ^3J = 7.7 Hz, ^4J = 3.0 Hz, 6 × H–C(Ph)), 7.36 (dd, 1H, ^3J = 8.1, 7.4 Hz, H–C(6)), 7.18 (d, 2H, ^3J = 8.4 Hz, 2 × H–C(Ar)), 6.89 (d, 2H, ^3J = 8.4 Hz, 2 × H–C(Ar)). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ 167.3 (D, $^2J_{C–P}$ = 7 Hz), 166.4, 151.1 (D, $^4J_{C–P}$ = 3 Hz), 136.0, 133.7, 133.2 (D, $^3J_{C–P}$ = 10 Hz), 132.7, 132.3 (D, $^4J_{C–P}$ = 3 Hz), 130.2, 128.7 (D, $^2J_{C–P}$ = 13 Hz), 128.4 (D, $^1J_{C–P}$ = 101 Hz), 128.0, 126.8, 126.0, 124.3, 121.4 (D, $^3J_{C–P}$ = 22 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 16.5. IR ν (cm^{-1}): 3060, 1608, 1566, 1498, 1474, 1449, 1434, 1354, 1330, 1261. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{32}H_{24}ClN_3PS$ 548.1112; found 548.1100 (2.19 ppm).



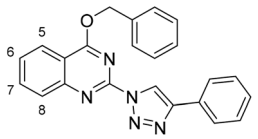
Synthesis of 4-(alkyl/aryloxy)-2-(1*H*-1,2,3-triazol-1-yl) quinazoline derivatives 17

2-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)-4-(phenyloxy)quinazoline (17a). To a solution of **9a** (75 mg, 0.29 mmol, 1.0 eq.) and cyclopropylacetylene (0.05 mL, ρ = 0.78 g mL^{-1}, 0.58 mmol, 2.0 eq.) in THF (10 mL) solutions of $CuSO_4$·5H_2O (4 mg, 0.014 mmol, 5 mol-%) in H_2O (1 mL) and sodium ascorbate (6 mg, 0.029 mmol, 10 mol-%) in H_2O (1 mL) were subsequently added and the mixture was stirred at 40 °C for 24 h, controlled using HPLC. After completion of the reaction the mixture was evaporated, suspended in DCM (20 mL) and washed with saturated EDTA solution (4 × 10 mL). The aqueous phases were combined and back-extracted with DCM (3 × 5 mL). Organic phases were combined, dried over anhydrous Na_2SO_4, filtered, evaporated and purified using silica gel column chromatography (Tol/MeCN 14%) and recrystallization from hexane (30 mL). Yield: 77 mg (82%); off-white solid; R_f (Tol/MeCN 10 : 1) 0.19; m.p. 162–164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, 1H, ^3J = 8.1 Hz, H–C(5)), 8.15 (d, 1H, ^3J = 8.3 Hz, H–C(8)), 7.97 (dd, 1H, ^3J = 8.3, 7.4 Hz, H–C(7)), 7.89 (s, 1H, H–C(triazole)), 7.68 (dd, 1H, ^3J = 8.1, 7.4 Hz, H–C(6)), 7.52 (t, 2H, ^3J = 7.5 Hz, 2 × H–C(Ph)), 7.37 (t, 1H, ^3J = 7.5 Hz, H–C(Ph)), 7.34 (d, 2H, ^3J = 7.5 Hz, 2 × H–C(Ph)), 1.98 (tt, 1H, ^3J = 8.9, 4.4 Hz, H–C(1′)), 0.99–0.93 (m, 2H, 2 × H_a), 0.90–0.85 (m, 2H, 2 × H_b). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ 168.6, 152.5, 152.2, 150.4, 149.7, 135.5, 129.9, 128.4, 127.8, 126.4, 124.1, 121.8, 119.0, 115.5, 7.9, 6.8. IR ν (cm^{-1}): 3053, 2914, 1619, 1597, 1571, 1509, 1493, 1472, 1456, 1429, 1391, 1376. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{16}N_5O$ 330.1349; found 330.1360 (3.33 ppm).



4-(Benzyloxy)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)quinazoline (17b). To a solution of **9b** (55 mg, 0.20 mmol, 1.0 eq.) and phenylacetylene (0.04 mL, ρ = 0.93 g mL^{-1}, 0.40 mmol, 2.0 eq.) in THF (10 mL) solutions of $CuSO_4$·5H_2O (3 mg, 0.01 mmol, 5 mol-%) in H_2O (1 mL) and sodium ascorbate (4 mg, 0.02 mmol, 10 mol-%) in H_2O (1 mL) were subsequently added and the mixture was stirred at 60 °C for 16 h, controlled using HPLC. After the completion of the reaction DCM (30 mL) and saturated NaHS/H_2O solution (10 mL) were added and the mixture was stirred for 3 min, filtered through Celite and then the layers were separated. The organic phase was washed with water (3 × 5 mL). The aqueous phases were combined and back-extracted with DCM (3 × 5 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, evaporated and recrystallized from hexane (30 mL). Yield: 69 mg (91%); off-white solid; R_f (Tol/MeCn 10 : 1) 0.47; m.p. 135–138 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (s, 1H, H–C(triazole)), 8.26 (d,

1H, ^3J = 8.1 Hz, H–C(5)), 8.06 (d, 1H, ^3J = 8.3 Hz, H–C(8)), 8.00 (d, 2H, ^3J = 7.5 Hz, 2 × H–C(Ph)), 7.91 (dd, 1H, ^3J = 8.3, 7.4 Hz, H–C(7)), 7.63 (d, 2H, ^3J = 7.4 Hz, 2 × H–C(Bn)), 7.60 (dd, 1H, ^3J = 8.1, 7.4 Hz, H–C(6)), 7.49 (t, 2H, ^3J = 7.5 Hz, 2 × H–C(Ph)), 7.45 (t, 2H, ^3J = 7.4 Hz, 2 × H–C(Bn)), 7.42–7.37 (m, 2H, H–C(Ph), H–C(Bn)), 5.82 (s, 2H, (–CH_2–)). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ 168.8, 151.7, 150.1, 148.0, 135.5, 135.1, 130.3, 129.0, 128.90, 128.85, 128.8, 128.7, 128.0, 127.5, 126.2, 124.2, 118.7, 115.9, 70.1. IR ν (cm^{-1}): 3104, 3057, 3004, 2968, 1618, 1601, 1571, 1548, 1499, 1478, 1468, 1455, 1436, 1421. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{18}N_5O$ 380.1506; found 380.1500 (1.57 ppm).



Conclusions

In conclusion, we have demonstrated the dual nucleophile/nucleofuge nature of the azide and arylthiolate groups and developed synthetic approaches towards a variety of 5-substituted tetrazolo[1,5-*c*]quinazolines (4-azido-2-*N*-, *O*-, *S*-substituted quinazolines). This results from the intrinsic property of the azido substituent that allows it to reach azidoazomethine-tetrazole tautomeric equilibrium and is due to the electron-withdrawing characteristics of the fused tetrazolo system, which facilitates S_NAr substitution reactions. In this context the azide substituent can be regarded as an activating group or reactivity switch, which through the tautomerism facilitates quinazoline S_NAr reactions at the less accessible C2 position. Many of the amino-substituted compounds demonstrated a media-controlled azide-tetrazole tautomeric equilibrium that allowed the use of a hidden azido group in the tetrazolo[1,5-*c*]quinazoline core and was able to facilitate CuAAC and Staudinger iminophosporane synthesis. Structural elucidation and the synthesis of opposite regioisomers also led to the development of the synthetic method for 5-(alkyl/aryloxy) tetrazolo[1,5-*a*]quinazolines from 2,4-diazidoquinazoline. The developed synthetic procedures for 5-substituted tetrazolo[1,5-*a*/*c*]quinazolines will be a valuable addition to the medicinal chemistry tool-box, but the photophysical properties of the described compound classes revealed in this research can serve as a starting point for further applications in materials science.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank the Latvian Council of Science grant LZP-2020/1-0348 for financial support, Dr chem. Kristīne Lazdoviča for IR analysis and Mr Dāgs Dāvis Līpiņš for assistance in acquiring the experimental data.

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