Synthesis A. Jeminejs et al. Paper

Application of Azide-Tetrazole Tautomerism and Arylsulfanyl Group Dance in the Synthesis of Thiosubstituted Tetrazolo-quinazolines

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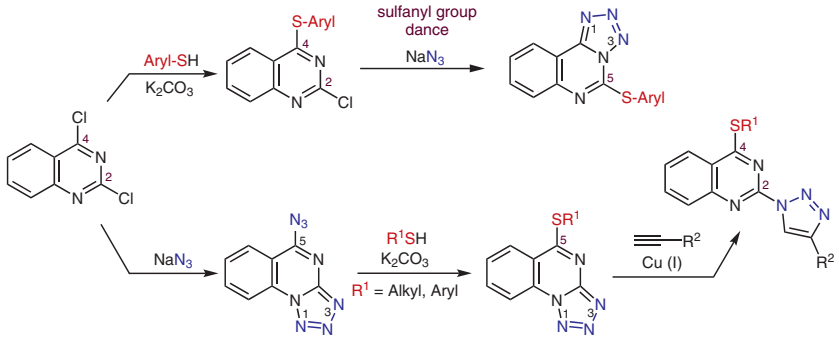

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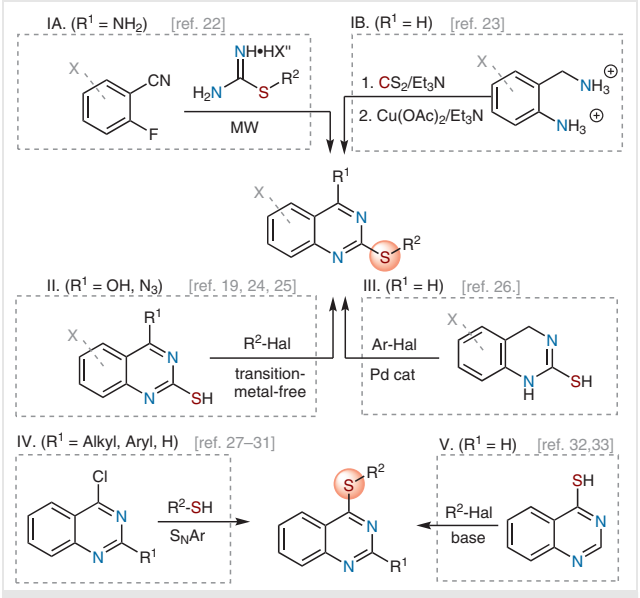
Abstract Nucleophilic aromatic substitution reaction between 4-arylthio-2-chloroquinazolines and NaN_3 takes place with an unusual sulfanyl group dance and leads to the formation of 5-(arylthio)tetrazolo[1,5-*c*]quinazolines, which do not form the azide tautomer and do not undergo CuAAC reactions with alkynes. On the other hand, 5-azidotetrazolo[1,5-*a*]quinazoline (formally described as 2,4-diazidoquinazoline) undergoes regioselective nucleophilic aromatic substitution with thiols at C5 and forms 5-(alkyl/arylthio)tetrazolo[1,5-*a*]quinazolines, the structure of which has been proved by X-ray crystallography. The latter exist in tautomeric equilibrium with their 2-azidoquinazoline form, which provides possibility for copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition reaction, leading to the 4-alkyl/arylthio-2-(1*H*-1,2,3-triazol-1-yl)quinazolines.

Key words quinazolines, nucleophilic aromatic substitution, azide-tetrazole equilibrium, thiols, azides, triazoles

Heterocyclic core of quinazoline belongs to the privileged molecular scaffolds in terms of medicinal chemistry.[1] For example, marketed anticancer drugs such as erlotinib, gefitinib, lapatinib, and afatinib contain quinazoline core. These substances block the signaling process within the cancer cells by inhibiting the messenger activity of the tyrosine kinase and the quinazoline fragment is recognized as the kinase hinge binder.[2] Other quinazoline based molecules are known as apoptosis inducers and apoptosis inhibitors depending on the exocyclic decoration.[3,4] Additionally, among the approved sympatholytic drugs there is also quinazoline derivative prazosin, which is an α_1-blocker.[5] On the other hand, biological activities like antibacterial,[6] antimalarial,[7] anticonvulsant[8] and antiviral[9] are described for quinazoline compounds.

The importance of thioquinazoline derivatives has increased lately. Potential antibacterial,[10,11] antimicrobial,[12] antiviral,[13] antitumor,[14–17] bronchodilatory[18] activity, and monoamine oxidase inhibitor activity,[19] which is important for the treatment of Parkinson's disease were found among 2-substituted 4(3*H*)-quinazoline-4-thiones, substituted 2-thioquinazolin-4-one analogues, and unsubstituted or 2-substituted 4-thioquinazolines. Compounds from the 4-thioquinazoline series are also known as agriculture antimicrobials.[20,21]



Scheme 1 Different approaches for the synthesis of C4/C2 substituted thioquinazolines

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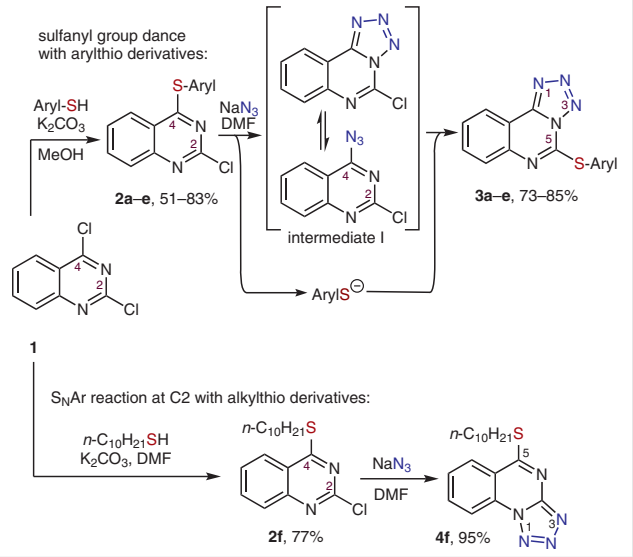
Various approaches are used for the synthesis of thioquinazoline derivatives. Strategies for introduction of alkyl/arylthio group at C2 position of quinazoline include: 1) cyclization reactions of *o*-fluorobenzonitriles with S-substituted isothiouronium salts under microwave irradiation[22] or cyclization of 2-aminobenzylamines and carbon disulfide;[23] 2) transition-metal-free alkylation/arylation of 2-thioquinazoline or its potassium salt with alkyl/aryl halides under neutral or basic conditions;[19,24,25] and 3) transition-metal-catalyzed cross-coupling reactions of 2-thioquinazolines and alkyl/aryl/heteroaryl halides[26] (Scheme 1).

Strategies for introduction of alkyl/arylthio group at C4 position of quinazoline include: 1) S_NAr reactions between 4-chloroquinazoline derivatives and alkyl/aryl/heteroaryl thiols;[27–31] and 2) alkylation of thio group at C4 position with alkyl halides[32,33] (Scheme 1).

In the past decades, great attention was focused also on the synthesis and bioactivity of quinazoline derivatives, which contain azolyl substituents (imidazolyl, 1,2,4-triazolyl, 2-pyrazolyl groups) at C2 or C4 position or azoles fused to quinazoline core.[34–36] To the best of our knowledge, there is no synthetic studies available on the preparative methodologies towards 2-azido-4-alkyl/arylthioquinazolines and 4-azido-2-alkyl/arylthioquinazolines and their applications in the synthesis of the corresponding 1,2,3-triazole derivatives.

Our group has developed several synthetic methodologies that make use of azidoquinazoline,[37] azidopurine,[38] and azido-7-deazapurine[39] derivatives as versatile starting materials. We have extended various S_NAr approaches involving azido group as a leaving group. Moreover, we have recently developed a sulfonyl group dance around purine cycle, which is a synthetic application of the intrinsic property of the azido substituent to undergo azidoazomethine-tetrazole tautomeric equilibrium.[40] In this paper, we report unusual sulfanyl group dance around the quinazoline core that leads to novel synthetic developments for the preparation of 2/4-azido-4/2-alkyl/arylthioquinazolines and their further synthetic applications, which are based on both leaving group capability of azido group and azidoazomethine-tetrazole tautomeric equilibrium.

First, several 4-alkyl/arylthio-2-chloroquinazoline derivatives **2** were obtained in 51–83% yields from commercially available 2,4-dichloroquinazoline (**1**), using C4-selective S_NAr reaction with thiols. The azide group was then introduced to the quinazoline core. In the case of alkylthiols (e.g., *n*-$C_{10}H_{21}SH$, Scheme 2), the compound **2f** underwent a further S_NAr reaction at C2 leading to product **4f** in excellent yield. On the other hand, the azide reaction with 4-arylthio-2-chloroquinazolines **2a–e** resulted in an unusual sulfanyl group dance around the quinazoline core and products **3a–e** were obtained in 73–85% yield (Scheme 2, Table 1). Arylthio substituents are better leaving groups than their aliphatic congeners, therefore, the S_NAr substitution with the azide ion occurs at C4. This leads to the azide-tetrazole tautomerism and the formed fused tetrazole intermediate I (Scheme 2) can activate the system for further S_NAr attack, albeit at C2. Moreover, the nucleofugal $ArylS^-$ group from the first S_NAr process now becomes a nucleophile for the second S_NAr reaction. Investigation of reaction mechanism was encumbered by the fact that transformation **2** + NaN_3 → **3** is very fast and NMR studies in DMSO-d_6 did not reveal the presence of any intermediate (see SI). To the best of our knowledge, this is one of the very few sulfanyl group dances in quinazolines, apart from some historic examples reported in 1940s.[41]



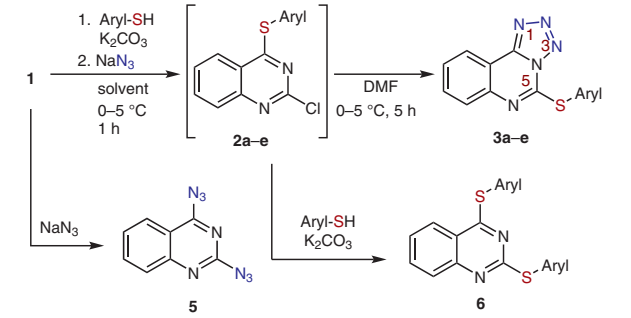
Scheme 2 Synthesis of 5-(arylthio)tetrazolo[1,5-*c*]quinazolines **3** and 5-(decylthio)tetrazolo[1,5-*a*]quinazoline **4f**

Table 1 Yields for Transformations **1** → **2** and **2** → **3** (Scheme 2)

Entry	Aryl	Product **2**	Yield (%)	Product **3**	Yield (%)
1	C_6H_5	**2a**	55	**3a**	73
2	4-BrC_6H_4	**2b**	62	**3b**	85
3	4-FC_6H_4	**2c**	83	**3c**	81
4	4-ClC_6H_4	**2d**	51	**3d**	77
5	4-$CH_3C_6H_4$	**2e**	70	**3e**	84

Additionally, the one-pot synthetic procedure was briefly studied for compounds **3** (Scheme 3, Table 2). Upon completion, the crude reaction mixture was suspended in brine and filtered, then easily recrystallized. To ensure the formation of product **3**, kinetic rates of competing thiol and azide substitution reactions must be taken into account. We have found that the molar ratio between starting material **1**, NaN_3, and thiol should be kept close to 1:1:1. Any notable excess of NaN_3 (>1.1 equiv) lead to formation of significant amounts of 2,4-diazidoquinazoline **5**, and any excess of thiol (>1.1 equiv) lead to formation of 2,4-bisthio derivative **6**.

The initial combination of reagents in DMF (Table 2, entry 1) leads to predominant formation of undesired diazide **5**, although the subsequent addition gives target product **3d** in 58% yield (entry 2).



Scheme 3 One-pot synthesis of 5-(arylthio)tetrazolo[1,5-*c*]quinazolines **3**

If the reaction medium is switched to ethanol (Table 2, entry 3), the formation of diazide **5** is suppressed. However, due to low solubility of intermediate **2** in ethanol the next reaction proceeded slowly and full conversion of **2** to **3** could not be reached. On the other hand, telescopic switch of the solvents (entries 4–9) yielded the best result with minimal interference among competing reactions. In the case of 4-bromothiophenol (entry 5) azide must be added only upon the full conversion of starting material **1** to exclude formation of by-products. In all other cases, NaN_3 was added in the beginning. The sulfanyl group dance is not observed for 4-alkylthioquinazolines (entries 10 and 11).

Products **3a–e** exist in their tetrazole form. Equilibrium towards azide form was not practically observed in this series, with only exception being 4-fluorophenylthio derivative **3c**, for which trace amounts of open chain tautomer were observed at elevated temperatures in toluene (Figure 1). It appeared that the tetrazole tautomers are particularly stable for compounds **3a–e** and they were totally inactive in CuAAC reactions with various alkynes.

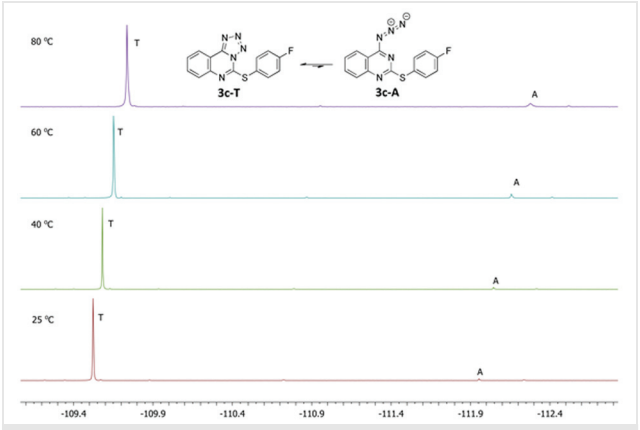


Figure 1 Azide-tetrazole equilibrium of compound **3c** in Tol-d_8 (^{19}F NMR 470.5 MHz) depending on temperature. Tetrazole:azide (%) = 98:2 at 25 °C; 97:3 at 40 °C; 94:6 at 60 °C; 92:8 at 80 °C.

To investigate and prove the regioselectivity of the acquired products, we have also explored a possibility to obtain isomer compounds of type **4** by a reverse order of S_NAr reactions. One of the key starting materials – 2,4-diazidoquinazoline (**5**) – was obtained in S_NAr reaction between commercially available 2,4-dichloroquinazoline (**1**) and sodium azide in 97% yield (Scheme 4). It should be pointed out that the name 'diazide' is used as a simplification and the compound in solutions exists in tetrazole tautomeric forms **5AT** and **5TT**, respectively.[37,42]

Table 2 One-Pot Transformation **1** → **3** (Scheme 3)

Entry	Aryl	Compound **3**	Solvent	NMR yield of product **3**[a] (%)	Compound composition of crude product **2**:**3**:**5**:**6**	Yield of crystallized product **3** (%)
1[b]	4-ClC_6H_4	**3d**	DMF	33	0: **37**:42:21	–
2[c]			DMF	73	1:**78**:0:21	58
3[b]			EtOH	51	40:**57**:0:3	–
4[b]			EtOH → DMF	86	1:**93**:2:4	80
5[b]	4-BrC_6H_4	**3b**	EtOH → DMF	22	1:**29**:49:21	–
6[c]			EtOH → DMF	69	3:**75**:12:10	56
7[b]	4-$CH_3C_6H_4$	**3e**	EtOH → DMF	74	1:**80**:5:14	69
8[b]	4-FC_6H_4	**3c**	EtOH → DMF	71	4:**81**:2:13	62
9[b]	C_6H_5	**3a**	EtOH → DMF	70	1:**95**:0:4	52
10[c]	$CH_3(CH_2)_9$	–	DMF	0	–	–
11[b]			DMF	0	–	–

[a] Determined on crude reaction mixture with 1,2,3-trimethoxybenzene as an internal standard.
[b] NaN_3 (1.1 equiv) was added at the beginning together with the thiol (1.1 equiv).
[c] NaN_3 (1.1 equiv) was added upon full conversion of starting material **1**.

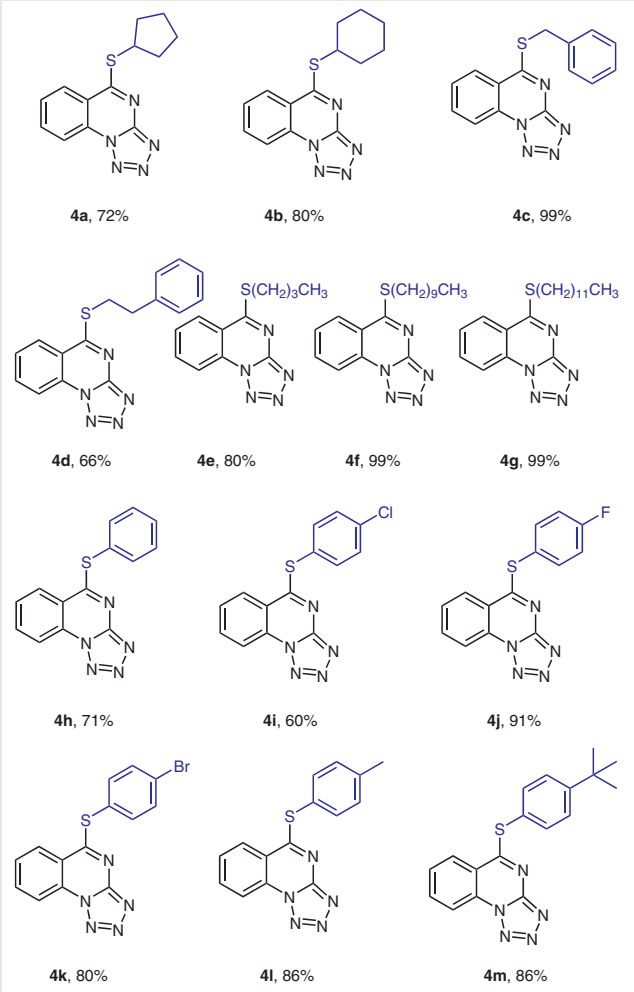
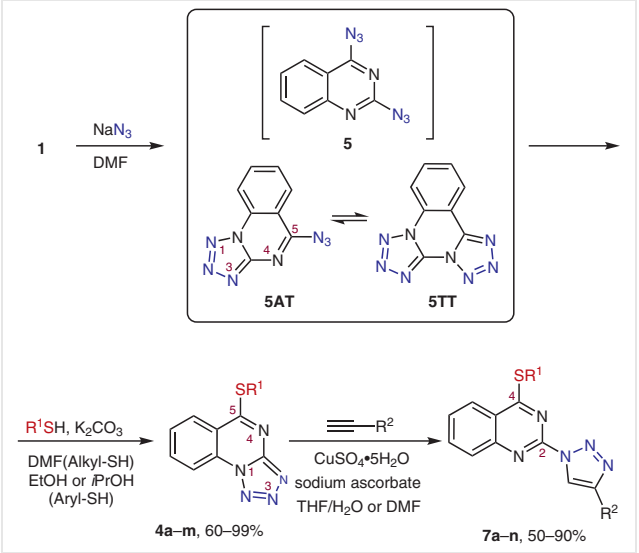


Figure 2 Substrate **4** scope for the synthesis of 4-alkyl/arylthio-2-(1*H*-1,2,3-triazol-1-yl)quinazolines **7** according to Scheme 4

Tautomer **5AT** explains the leaving group ability of the azido group at C5 position of tetrazoloquinozaline (= C4 position of quinazoline) in the S_NAr reactions with thiols: 1) it liberates position C5; 2) the formed tetrazole as electron-withdrawing substituent activates the substrate for the nucleophile attack. The substitution proceeds easily with alkyl or aryl thiols in EtOH, *i*PrOH, or DMF, providing derivatives **4** in 60–99% yields (Scheme 4, Figure 2).

Structure of 5-(decylthio)tetrazolo[1,5-*a*]quinazoline (**4f**) was unambiguously established by X-ray analysis (Figure 3), which showed that the product adopted tetrazolo[1,5-*a*]quinazoline form in the solid state. In this context, thioquinazoline derivatives exhibit a similar azide-tetrazole tautomerism to their amino substituted congeners, as shown by us earlier on the example of 5-(piperidin-1-yl)tetrazolo[1,5-*a*]quinazoline.[37]



Scheme 4 Synthesis of 4-alkyl/arylthio-2-(1*H*-1,2,3-triazol-1-yl)-quinazolines **7a–n**. *Reagents and conditions*: a) **5** → **4** rt–50 °C, DMF, EtOH or *i*PrOH, 1.5–48 h; b) **4** → **7** rt–70 °C, 3–24 h.

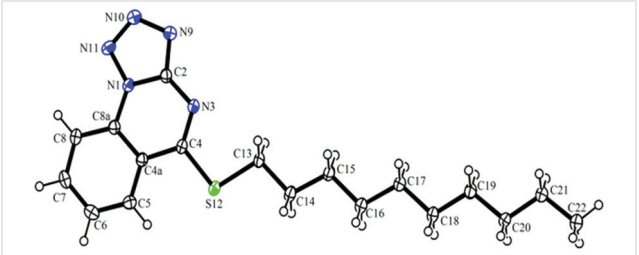


Figure 3 Single crystal X-ray analysis of 5-(decylthio)tetrazolo[1,5-*a*]-quinazoline (**4f**)[43]

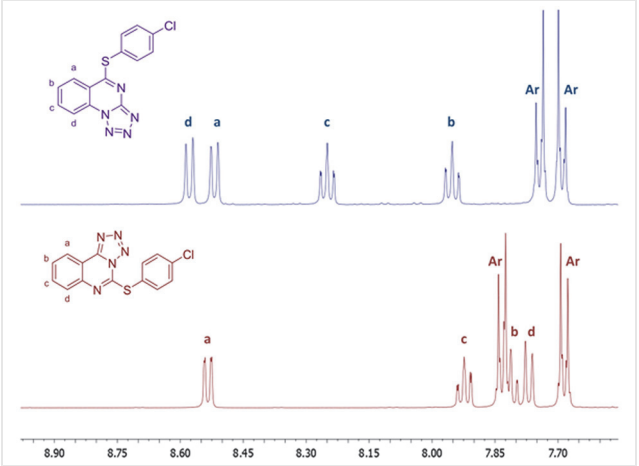


Figure 4 ^{1}H NMR (500 MHz, DMSO-d_6) spectral comparison of compounds **4i** and **3d**. Δδ = 0.81 ppm between CH (d) signals: CH [**4i** (d)] = 8.58 ppm; CH [**3i** (d)] = 7.77 ppm.

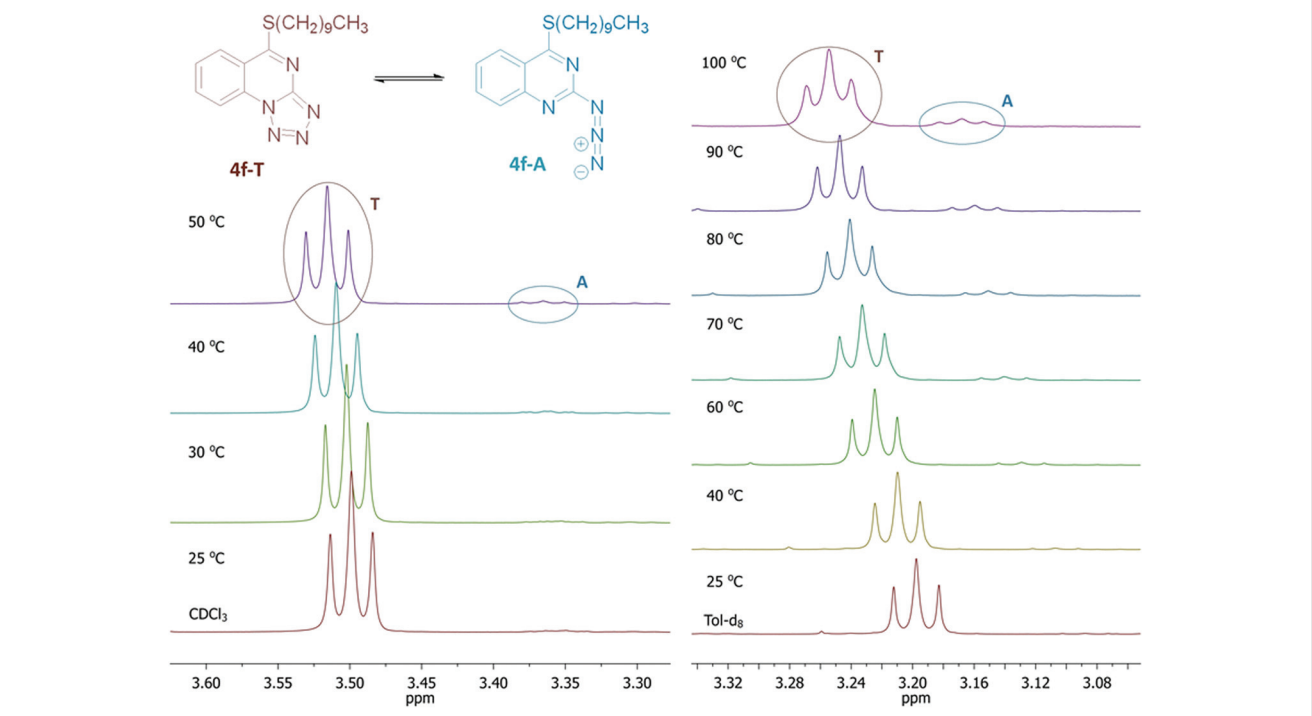


Figure 5 Azide-tetrazole equilibrium of compound **4f** in $CDCl_3$ and toluene-d_8 at different temperatures studied by ^1H NMR (500 MHz) spectroscopy

The inversed regioselectivity of products **3a–e** was proven chemically by comparison of NMR spectra from two independent experiments. Thus, the NMR data of isomeric compounds **4i** and **3d** showed distinct differences. It is interesting to note that the difference between CH(d) protons of compounds **4i** and **3d** is 0.81 ppm (Figure 4).

In the solution, products **4a–m** exhibited azide-tetrazole equilibrium, which was studied in different solvents at different temperatures by ^1H NMR spectroscopy. Spectral analysis was performed for compounds **4f**, **4j**, and **4l**. For 5-(decylthio)tetrazolo[1,5-*a*]quinazoline (**4f**) azide-tetrazole equilibrium was studied in $CDCl_3$ at 25–50 °C and in toluene-d_8 at 25–100 °C (Table 3, Figure 5). At room temperature the azide form was weakly present in both solvents: 1.3% and 2.2% in $CDCl_3$ and toluene-d_8, respectively. Heating of the solutions somewhat increased the amount of azide form: 3% ($CDCl_3$ at 50 °C) and 11% (toluene-d_8 at 100 °C). The azide-tetrazole equilibrium of arylthio derivatives **4j** and **4l** in $CDCl_3$, DMSO-d_6, and toluene-d_8 exhibited a similar pattern (see SI). It goes in line with the general rule that nonpolar solvents and higher temperatures shift the equilibrium towards azide form.[44] Substituent effect also shows an influence and for (4-fluorophenyl)thioquinazoline **4j** the amount of azide tautomer is higher than for the congeners with electron-donating substituents (e.g., **4l** and **4m**).

To our delight the presence of azido tautomer in the solutions of compounds **4a–m** was sufficient to perform the copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition reactions[45] with different aliphatic and aromatic alkynes. Products **7a–n** containing 1,4-disustituted triazole[45] moiety were obtained in good to excellent yields (Table 4). In this context quinazolines **4a–m** exhibit a similar

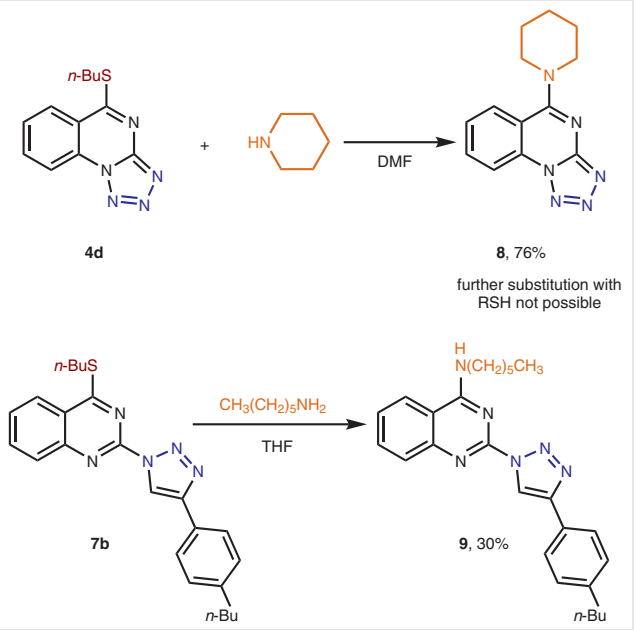
Table 3 Azide-Tetrazole Equilibrium of Compound **4f** Depending on Temperature in Toluene-d_8 and $CDCl_3$[a]

Equilibrium in toluene-d_8		
Temp (°C)	Azide (%)	Tetrazole (%)
25	1.3	98.7
40	2.1	97.9
60	3.8	96.2
70	5.5	94.5
80	7.2	92.8
90	8.6	91.4
100	10.5	89.5
Equilibrium in $CDCl_3$		
25	2.2	97.8
30	2.3	97.7
40	2.7	97.3
50	3.1	96.9

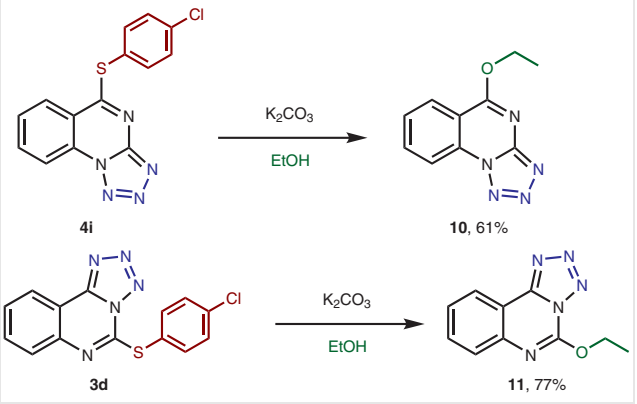
[a] Amount of both forms was determined using 1,2,3-trimethoxybenzene as an internal standard.

Table 4 Synthesis of 4-Alkyl/arylthio-2-(1*H*-1,2,3-triazol-1-yl)quinazolines **7** from 5-(Alkyl/arylthio)tetrazolo[1,5-*a*]quinazolines **4** (Scheme 4)

Entry	Starting material **4**	R^2	Product **7**	Yield (%)
1	**4c**	C_6H_5	**7a**	70
2	**4e**	4-$CH_3(CH_2)_3C_6H_4$	**7b**	90
3	**4f**	4-$CH_3(CH_2)_5$	**7c**	65
4		$CH_3(CH_2)_3$	**7d**	74
5		*c*-Pr	**7e**	71
6		4-$CH_3OC_6H_4$	**7f**	70
7	**4g**	C_6H_5	**7g**	79
8		4-$CH_3C_6H_4$	**7h**	87
9	**4h**	C_6H_5	**7i**	80
10	**4i**	C_6H_5	**7j**	50
11	**4j**	C_6H_5	**7k**	73
12		4-$F_3CC_6H_4$	**7l**	74
13	**4k**	C_6H_5	**7m**	82
14	**4m**	C_6H_5	**7n**	90



Scheme 5 S_NAr reactions between 4-alkylthioquinazoline derivatives **4d** and **7b** with N-nucleophiles. *Reagents and conditions*: a) **4d** → **8** 90 °C, 3 h; b) **7b** → **9** 35 °C, 72 h.



Scheme 6 S_NAr reactions between 5-(arylthio)tetrazoloquinazoline isomers **4i** and **3d** with O-nucleophile. *Reagents and conditions*: a) **4i** → **10** 40 °C, 5 h; b) **3d** → **11** 40 °C, 5 h.

reactivity to other fused 2-azidopyrimidines reported by us earlier.[38,39]

With several novel quinazoline derivatives in hand, we have also briefly explored their chemical reactivity. It was found that the alkylthio group at C5 position in **4d** can be substituted with secondary amines (e.g., piperidine) giving product **8**[37] in 76% yield (Scheme 5). Due to the fact that amine is not a good leaving group in the present constellation, this reaction is irreversible and further substitution of product **8** with thiols is not possible. Also compound **7b** underwent C4-selective S_NAr reaction with *n*-hexylamine and alkylthio substituent acted as the leaving group. 1,2,3-Triazolyl substituent, which on some occasions also have been reported as a leaving group, remained intact in this particular transformation.

On the other hand, arylthio substituents can be used as good leaving groups in reactions with nucleophiles at both C2 and C4 positions. For example, 5-(4-chlorophenylthio)tetrazoloquinazoline regioisomers **4i** and **3d** each undergoes selective substitution of sulfanyl group with EtOH in the presence of K_2CO_3, leading to products **10**[46] and **11** in good yields (Scheme 6). Acquired regioisomers exhibit the same pattern of quinazoline core NMR signals as previously described (Figure 4, see SI).

In conclusion, we have developed synthetic approaches towards 5-(arylthio)tetrazolo[1,5-*c*]quinazolines **3a–e** by an unusual sulfanyl group dance around the quinazoline core. The latter methodology demonstrates a synthetic application of azide-tetrazole tautomerism in the quinazoline activation towards a C2-selective S_NAr reaction. Due to the fact that C2 position of quinazolines is traditionally less reactive, here described C2-selective modification is particularly interesting. We have also explored isomeric 4-alkyl/arylthio-substituted tetrazoloquinazolines. The developed methodology for the synthesis of 5-(alkyl/arylthio)tetrazolo-[1,5-*a*]quinazolines **4a–m** makes use of azido substituent as a leaving group in the S_NAr reactions. Additionally, we have disclosed the azide-tetrazole tautomerism of obtained new compound classes. In those cases when the azido form is present, we have shown a further application of these scaffolds in CuAAC reactions yielding 2-(1*H*-1,2,3-triazol-1-yl)-4-(alkyl/arylthio)quinazolines **7a–n**. Quinazoline derivatives belong to the privileged structures in terms of medicinal chemistry, therefore the developed synthetic methods will serve as an important addition to the synthetic toolbox of medicinal chemists.

Commercial reagents (Acros, Alfa Aesar, Sigma Aldrich) were used as received. Reactions and purity of the synthesized compounds were monitored by TLC using silica gel 60 F254 aluminum plates precoated with a 0.25 mm layer of silica gel (Merck). Visualization was accomplished by UV light. Column chromatography was performed using silica gel 60 (0.040–0.063 mm) (Merck). Yields refer to chromatographically and spectroscopically homogeneous materials (with purity ≥95%).

NMR spectra were recorded on Bruker Avance 300 and Bruker Avance 500 spectrometers. ^{1}H NMR spectra were recorded at 500 and 300 MHz, respectively, with internal references from residual nondeuterated solvents (δ = 7.26 for $CDCl_3$, δ = 2.50 for DMSO-d_6, and δ = 2.09 for Tol-d_8). ^{13}C NMR spectra were recorded at 125.7 and 75.5 MHz with internal references from solvent carbon signals (δ = 77.1 for $CDCl_3$ and δ = 39.5 for DMSO-d_6). ^{19}F NMR spectra were recorded at 470.5 MHz with no internal reference. Coupling constants are reported in Hz and chemical shifts of signals are given in ppm and standard abbreviations were used for multiplicity assignments. IR spectra were recorded on a PerkinElmer Spectrum BX spectrophotometer and are reported in cm^{-1}.

For HPLC analyses Agilent Technologies 1200 Series system was used (X Bridge C18 column, 4.6 × 150 mm, particle size 3.5 µm). Eluent A: 0.1% aq TFA/CH_3CN (95:5, v/v), eluent B: CH_3CN. Gradient: 30–95% B 5 min, 95% B 5 min, 95–30% B 2 min. Flow rate: 1 mL/min. Wavelength of detection was set to 260 nm.

HRMS analysis was performed on an Agilent 1290 Infinity series UPLC system, connected to Agilent 6230 TOF LC/MS mass spectrometer; column Extend C18 RRHD 2.1 × 50 mm, 1.8 µm. Eluents: formic acid in CH_3CN (0.1%) and aq 0.1% formic acid.

4-Arylthio-2-chloroquinazolines 2a–e; General Procedure

2,4-Dichloroquinazoline (**1**; 0.5 g, 2.5 mmol, 1.0 equiv) and anhyd K_2CO_3 (0.39 g, 2.8 mmol, 1.1 equiv) were added to cooled (5–10 °C) MeOH (10–15 mL) and the mixture was stirred under argon for 10 min. The suspension was cooled to 0 °C and the corresponding thiol (2.8 mmol, 1.1 equiv) was added in small portions over 10–15 min. The mixture was stirred at 0–5 °C for 5 h, controlled by HPLC. For completion, the reaction the mixture was allowed to stand at 8–10 °C overnight. The suspension was filtered, the precipitate was washed with H_2O (2 × 10 mL) and EtOH (3 × 8 mL), and recrystallized from EtOH or purified by column chromatography.

2-Chloro-4-(phenylthio)quinazoline (2a)

Yield: 0.76 g (55% from 1.0 g, 5.0 mmol of **1**); colorless solid; R_f = 0.45 (Tol); mp 140–142 °C.

IR (KBr): 3075, 3060, 3037, 2995, 2924, 2849, 1612, 1558, 1525, 1480, 1471, 1443 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.20 (d, ^3J = 8.2 Hz, 1 H, HC5), 7.92–7.86 (m, 2 H, HC8, HC7), 7.65–7.61 (m, 3 H, C_6H_5, HC6), 7.52–7.49 (m, 3 H, C_6H_5).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 174.5, 156.4, 150.2, 135.7, 135.0, 130.2, 129.6, 128.2, 127.8, 126.3, 124.0, 121.7.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{14}H_{10}ClN_2S$: 273.0248; found: 273.0241.

4-[(4-Bromophenyl)thio]-2-chloroquinazoline (2b)

Yield: 0.55 g (62%); colorless solid; R_f = 0.31 (Tol); mp 166–168 °C.

IR (KBr): 3066, 3042, 1611, 1558, 1530, 1478, 1473, 1443 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, ^3J = 8.4 Hz, 1 H, HC5), 7.93–7.83 (m, 2 H, HC8, HC7), 7.67–7.56 (m, 3 H, 2 H_{arom}, HC6), 7.48 (d, ^3J = 8.5 Hz, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 156.3, 150.1, 137.1, 135.1, 132.8, 128.2, 127.9, 125.3, 124.9, 123.9, 121.5.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{14}H_9BrClN_2S$: 350.9353; found: 350.9346.

2-Chloro-4-[(4-fluorophenyl)thio]quinazoline (2c)

Product was washed with hot EtOH (2 × 6 mL); yield: 0.60 g (83%); colorless solid; R_f = 0.27 (Tol); mp 139–141 °C.

IR (KBr): 3095, 3063, 1630, 1610, 1589, 1559, 1527, 1479, 1443 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, ^3J = 8.2 Hz, 1 H, HC5), 7.91–7.84 (m, 2 H, HC8, HC7), 7.63–7.55 (m, 3 H, 2 H_{arom}, HC6), 7.18 (t, ^3J = 8.7 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 174.3, 164.0 (d, $^1J_{C,F}$ = 251 Hz), 156.3, 150.1, 137.9 (d, $^3J_{C,F}$ = 9 Hz), 135.0, 128.2, 127.9, 123.9, 121.5, 121.4 (d, $^4J_{C,F}$ = 3 Hz), 116.9 (d, $^2J_{C,F}$ = 22 Hz).

^{19}F NMR (470.5 MHz, $CDCl_3$): δ = –109.9.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{14}H_9FClN_2S$: 291.0154; found: 291.0138.

2-Chloro-4-[(4-chlorophenyl)thio]quinazoline (2d)

Yield: 0.39 g (51%); colorless solid; R_f = 0.28 (Tol); mp 154–156 °C.

IR (KBr): 3095, 3060, 1614, 1558, 1529, 1483, 1475, 1444 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, ^3J = 8.3 Hz, 1 H, HC5), 7.92–7.87 (m, 2 H, HC8, HC7), 7.63 (ddd, ^3J = 8.3, 7.0 Hz, ^4J = 2.4 Hz, 1 H, HC6), 7.56 (d, ^3J = 8.5 Hz, 2 H_{arom}), 7.47 (d, ^3J = 8.5 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 173.8, 156.3, 150.2, 136.9, 136.6, 135.1, 129.8, 128.3, 127.9, 124.7, 123.9, 121.6.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{14}H_9Cl_2N_2S$: 306.9858; found: 306.9864.

2-Chloro-4-(*p*-tolylthio)quinazoline (2e)

Product was washed with hot EtOH (2 × 6 mL); yield: 1.0 g (70% from 1.0 g, 5.0 mmol of **1**); slightly yellow solid; R_f = 0.19 (Tol); mp 138–140 °C.

IR (KBr): 2873, 1619, 1587, 1563, 1533, 1497, 1486, 1472, 1449 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19 (d, ^3J = 8.2 Hz, 1 H, HC5), 7.92–7.84 (m, 2 H, HC8, HC7), 7.61 (ddd, ^3J = 8.2, 6.4 Hz, ^4J = 1.8 Hz, 1 H, HC6), 7.51 (d, ^3J = 8.0 Hz, 2 H_{arom}), 7.30 (d, ^3J = 8.0 Hz, 2 H_{arom}), 2.44 (s, 3 H, CH_3).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 174.9, 156.5, 150.1, 140.4, 135.6, 134.9, 130.4, 128.2, 127.7, 124.1, 122.7, 121.7, 21.6.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{15}H_{12}ClN_2S$: 287.0404; found: 287.0400.

2-Chloro-4-(decylthio)quinazoline (2f)

K_2CO_3 (0.76 g, 5.5 mmol) was added to a solution of 1-decanethiol (0.96 g, 5.5 mmol) in DMF (15 mL) and the mixture was stirred for 15–20 min at rt under argon. A solution of 2,4-dichloroquinazoline (**1**; 1.0 g, 5.0 mmol) in DMF (10 mL) was added and the reaction mixture was stirred at 40–50 °C for 5 h, controlled by HPLC. After completion of the reaction, H_2O (40–50 mL) was added, the suspension was cooled, and filtered. The precipitate was washed with H_2O (2 × 8 mL), EtOH (3 × 8 mL), recrystallized from EtOH (120 mL), and dried in vacuo; yield: 1.30 g (77%); colorless solid; R_f = 0.41 (Tol); mp 51–53 °C.

IR (KBr) 3054, 3029, 2964, 2917, 2848, 1614, 1560, 1524, 1482, 1467, 1442 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz, 1 H, HC5), 7.86 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1 H, HC8), 7.82 (ddd, ^3J = 8.2, 6.9 Hz, ^4J = 1.4 Hz, 1 H, HC7), 7.54 (ddd, ^3J = 8.3, 6.9 Hz, ^4J = 1.5 Hz, 1 H, HC6), 3.37 (t, ^3J = 7.3 Hz, 2 H, H_2C1', 1.79 (quint, ^3J = 7.3 Hz, 2 H, H_2C2'), 1.48 (quint, ^3J = 7.3 Hz, 2 H, H_2C3'), 1.35 (quint, ^3J = 7.3 Hz, 2 H, H_2C4'), 1.32–1.21 [m, 10 H, $(CH_2)_5$], 0.87 (t, ^3J = 6.9 Hz, 3 H, H_3C10').

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 175.2, 156.1, 149.5, 134.5, 128.0, 127.3, 124.0, 122.3, 31.9, 30.1, 29.55, 29.49, 29.3, 29.1, 28.9, 28.6, 22.7, 14.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}ClN_2S$: 337.1500; found: 337.1503.

5-(Arylthio)tetrazolo[1,5-*c*]quinazolines 3a–e; General Procedure

Method A: NaN_3 (195 mg, 3.0 mmol, 1.5 equiv) was added to a stirred solution of the corresponding 4-arylthio-2-chloroquinazoline **2** (2.0 mmol, 1.0 equiv) in DMF (15 mL) at 0–5 °C under argon. The mixture was stirred at 0–5 °C for 5 h, controlled by HPLC. Cold brine (30 mL) was added and after 1–5 h at 8–10 °C, the suspension was filtered, washed with H_2O (2 × 5 mL), EtOH (3 × 5 mL) and dried in vacuo.

Method B: 2,4-Dichloroquinazoline (**1**; 50 mg, 0.25 mmol, 1.0 equiv) was added to a suspension of anhyd K_2CO_3 (38 mg, 0.28 mmol, 1.1 equiv) and the corresponding thiol (0.28 mmol, 1.1 equiv) in cold (0 °C) EtOH (4 mL). The mixture was stirred at 0–5 °C for 5 min, then NaN_3 (18 mg, 0.28 mmol, 1.1 equiv) was added and the suspension was stirred at 0–5 °C for another hour. After full conversion to **2a–e**, the mixture was evaporated at rt under reduced pressure and cold (0 °C) abs DMF (4 mL) was added. The solution was stirred at 0–5 °C for 5 h, controlled with HPLC. Cold brine (30 mL) was added and after 1–5 h at 8–10 °C the suspension was filtered, washed with H_2O (2 × 5 mL), cold EtOH (3 × 5 mL), and recrystallized from EtOH.

5-(Phenylthio)tetrazolo[1,5-*c*]quinazoline (3a)

Method A, yield: 95 mg (73% from 0.13 g, 0.48 mmol of **2a**); Method B, yield: 36 mg (52%); colorless solid; R_f = 0.30 (Tol); mp 179–181 °C.

IR (KBr): 1619, 1587, 1560, 1532, 1488, 1472, 1451, 1440, 1379 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.58 (dd, ^3J = 8.1 Hz, ^4J = 1.3 Hz, 1 H, HC10), 7.80 (ddd, ^3J = 8.4, 7.0 Hz, ^4J = 1.3 Hz, 1 H, HC8), 7.78–7.73 (m, 3 H, 2 H C_6H_5, HC7), 7.69 (ddd, ^3J = 8.1, 7.0 Hz, ^4J = 1.1 Hz, 1 H, HC9), 7.61–7.52 (m, 3 H, C_6H_5).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 149.0, 146.7, 143.7, 136.1, 133.6, 130.7, 129.8, 128.6, 128.1, 125.1, 124.7, 113.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}N_5S$: 280.0651; found: 280.0656.

5-[(4-Bromophenyl)thio]tetrazolo[1,5-*c*]quinazoline (3b)

Method A, yield: 90 mg (85% from 0.10 g, 0.3 mmol of **2b**); Method B, yield: 50 mg (56%); yellow solid; R_f = 0.19 (Tol); mp 186–188 °C.

IR (KBr): 2954, 2924, 2870, 2852, 1618, 1590, 1494, 1464, 1377 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, ^3J = 7.8 Hz, 1 H, HC10), 7.83 (dd, ^3J = 7.8, 6.9 Hz, 1 H, HC8), 7.79 (d, ^3J = 7.8 Hz, 1 H, HC7), 7.74–7.66 (m, 3 H, 2 H_{arom}, HC9), 7.62 (d, ^3J = 8.4 Hz, 2H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 149.0, 146.0, 143.7, 137.6, 133.7, 133.0, 128.8, 128.1, 125.7, 124.8, 124.1, 113.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9BrN_5S$: 357.9757; found: 357.9748.

5-[(4-Fluorophenyl)thio]tetrazolo[1,5-*c*]quinazoline (3c)

Product was washed with hot EtOH (2 × 4 mL); Method A, yield: 0.35 g (81% from 0.29 g, 1.0 mmol of **2c**); Method B, yield: 0.46 g (62%); colorless solid; R_f = 0.16 (Tol); mp 174–176 °C.

IR (KBr): 3099, 3074, 2954, 2924, 2853, 1618, 1591, 1489, 1463, 1378 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.52 (dd, ^3J = 8.1 Hz, ^4J = 1.1 Hz, 1 H, HC10), 7.92 (ddd, ^3J = 8.3, 7.1 Hz, ^4J = 1.1 Hz, 1 H, HC8), 7.86 (dd, ^3J = 8.2 Hz, $^4J_{H,F}$ = 5.3 Hz, 2 H_{arom}), 7.80 (dd, ^3J = 8.1, 7.1 Hz, 1 H, HC9), 7.73 (d, ^3J = 8.3 Hz, 1 H, HC7), 7.47 (dd, $^3J_{H,F}$ = 8.9 Hz, ^3J = 8.2 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 164.4 (d, $^1J_{C,F}$ = 252 Hz), 149.0, 146.6, 143.7, 138.4 (d, $^3J_{C,F}$ = 9 Hz), 133.7, 128.8, 128.0, 124.8, 120.3 (d, $^4J_{C,F}$ = 4 Hz), 117.1 (d, $^2J_{C,F}$ = 22 Hz), 113.9.

^{19}F NMR (470.5 MHz, DMSO-d_6): δ = –109.82.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9FN_5S$: 298.0557; found: 298.0560.

5-[(4-Chlorophenyl)thio]tetrazolo[1,5-*c*]quinazoline (3d)

Product was washed with hot EtOH (2 × 4 mL); Method A, yield: 0.24 g (77% from 0.30 g, 1.0 mmol of **2d**); Method B, yield: 119 mg (80% from 100 mg, 0.5 mmol of **1**); colorless solid; R_f = 0.11 (Tol); mp 185–187 °C.

IR (KBr): 2952, 2925, 2855, 1742, 1617, 1591, 1463, 1377 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.53 (dd, ^3J = 8.1 Hz, ^4J = 1.2 Hz, 1 H, HC10), 7.92 (ddd, ^3J = 8.3, 7.1 Hz, ^4J = 1.2 Hz, 1 H, HC8), 7.83 (d, ^3J = 8.4 Hz, 2 H_{arom}), 7.81 (dd, ^3J = 8.1, 7.1 Hz, 1 H, HC9), 7.77 (d, ^3J = 8.3 Hz, 1 H, HC7), 7.69 (d, ^3J = 8.4 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 149.3, 146.1, 143.6, 137.7, 136.1, 134.2, 130.3, 129.3, 127.9, 124.7, 124.7, 114.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9ClN_5S$: 314.0262; found: 314.0260.

5-(*p*-Tolylthio)tetrazolo[1,5-*c*]quinazoline (3e)

Method A, yield: 0.49 g (84%); Method B, yield: 102 mg (69% from 100 mg, 0.5 mmol of **1**); colorless solid; R_f = 0.13 (Tol); mp 176–178 °C.

IR (KBr): 2873, 1619, 1587, 1563, 1533, 1497, 1486, 1472, 1449 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.51 (d, ^3J = 8.0 Hz, 1 H, HC10), 7.75–7.69 (m, 2 H, HC8, HC7), 7.61 (dd, ^3J = 8.0, 7.1 Hz, 1 H, HC9), 7.55 (d, ^3J = 7.9 Hz, 2 H_{arom}), 7.28 (d, ^3J = 8.0 Hz, 2 H_{arom}), 2.41 (s, 3 H, CH_3).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 149.0, 147.1, 143.8, 141.2, 136.0, 133.6, 130.6, 128.5, 128.1, 124.7, 121.4, 113.8, 21.7.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_5S$: 294.0808; found: 294.0817.

5-(Alkyl/arylthio)tetrazolo[1,5-*a*]quinazolines 4a–m; General Procedure

Method A: The corresponding thiol (2.2 mmol, 1.1 equiv) was dissolved in EtOH or *i*PrOH (20 mL) under argon at rt. Then 2,4-diazidoquinazoline (**5**; 0.42 g, 2.0 mmol, 1.0 equiv) was added. Finally, anhyd K_2CO_3 (0.30 g, 2.2 mmol, 1.1 equiv) was added and the reaction mixture was stirred under argon at rt or 36–50 °C for 8–48 h, controlled by HPLC. After completion of the reaction, the obtained suspension was cooled and filtered, the precipitate was washed with H_2O (2 × 6 mL), EtOH or *i*PrOH (3 × 5 mL), recrystallized from EtOH (40–50 mL), and dried in vacuo.

Method B: Anhyd K_2CO_3 (0.75 g, 5.4 mmol, 2.3 equiv) was added to a solution of the corresponding thiol (1.7 equiv) in DMF (10 mL). The solution was stirred under argon at rt for 15 min. Then a solution of 2,4-diazidoquinazoline (**5**; 0.5 g, 2.36 mmol, 1.0 equiv) in DMF (5 mL) was added. The reaction mixture was stirred at rt for 1.5–3 h, controlled by HPLC. After completion of the reaction, brine (10 mL) was added, the suspension was filtered (after 1–2 h), the precipitate was washed with H_2O (2 × 6 mL) and EtOH (3 × 5 mL), and recrystallized from EtOH (40–50 mL), and dried in vacuo.

5-(Cyclopentylthio)tetrazolo[1,5-*a*]quinazoline (4a)

Method A: reaction time 48 h at 40 °C in EtOH; yield: 0.39 g (72%); colorless solid; R_f = 0.74 (Tol/EtOAc 1:1); mp 153–155 °C.

IR (KBr): 3056, 2963, 2866, 2361, 2344, 1609, 1589, 1537, 1412, 1333 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, ^3J = 8.2 Hz, 1 H, HC9), 8.25 (d, ^3J = 8.2 Hz, 1 H, HC6), 8.02 (dd, ^3J = 8.2, 7.5 Hz, 1 H, HC8), 7.73 (dd, ^3J = 8.2, 7.5 Hz, 1 H, HC7), 4.45 (quint, ^3J = 7.6 Hz, 1 H, HCS), 2.47–2.31 (m, 2 H, 2 H_a), 1.84–1.67 (m, 6 H, 2 H_b, 2 × CH_2).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 173.0, 152.7, 135.4, 131.4, 128.4, 126.3, 118.5, 116.7, 44.2, 33.2, 25.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}N_5S$: 272.0964; found: 272.0961.

5-(Cyclohexylthio)tetrazolo[1,5-*a*]quinazoline (4b)

Method A: reaction time 48 h at 40 °C in EtOH; yield: 0.40 g (80%); colorless solid; R_f = 0.74 (Tol/EtOAc 1:1); mp 184–185 °C.

IR (KBr): 3057, 2931, 2851, 1613, 1589, 1535, 1447, 1411, 1332 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.52 (dd, ^3J = 8.4 Hz, ^4J = 1.1 Hz, 1 H, HC9), 8.28 (dd, ^3J = 8.3 Hz, ^4J = 1.2 Hz, 1 H, HC), 8.01 (ddd, ^3J = 8.4, 7.4 Hz, ^4J = 1.2 Hz, 1 H, HC8), 7.72 (ddd, ^3J = 8.3, 7.4 Hz, ^4J = 1.1 Hz, 1 H, HC7), 4.42–4.31 (m, 1 H, H_A), 2.26–2.13 (m, 2 H_B), 1.86–1.76 (m, 2 H, 2 H_C), 1.72–1.53 (m, 5 H, H_D, 2 H_E, 2 H_F), 1.42–1.31 (m, 1 H, H_G) (see SI for H_A, etc. assignments).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 172.1, 152.6, 135.4, 131.5, 128.4, 126.3, 118.6, 116.7, 44.2, 32.7, 26.0, 25.7.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}N_5S$: 286.1121; found: 286.1118.

5-(Benzylthio)tetrazolo[1,5-*a*]quinazoline (4c)

Method A: reaction time 8 h at rt in EtOH; yield: 0.58 g (99%); colorless solid; R_f = 0.71 (Tol/EtOAc 1:1); mp 146–148 °C.

IR (KBr): 3090, 3037, 1614, 1590, 1531, 1494, 1449, 1409 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.52 (d, ^3J = 8.3 Hz, 1 H, HC9), 8.33 (d, ^3J = 8.2 Hz, 1 H, HC6), 8.17 (dd, ^3J = 8.3, 7.8 Hz, 1 H, HC8), 7.84 (dd, ^3J = 8.2, 7.8 Hz, 1 H, HC7), 7.55 (d, ^3J = 7.2 Hz, 2 H, C_6H_5), 7.36 (t, ^3J = 7.2 Hz, 2 H, C_6H_5), 7.29 (t, ^3J = 7.2 Hz, 1 H, C_6H_5), 4.74 (s, 2 H, CH_2).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 170.7, 152.1, 136.1, 136.1, 131.1, 129.3, 128.8, 128.6, 127.6, 125.8, 117.8, 116.2, 33.8.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_5S$: 294.0808; found: 294.0809.

5-[(2-Phenyl)ethylthio]tetrazolo[1,5-*a*]quinazoline (4d)

Method A: reaction time 12 h at 40 °C in EtOH; yield: 0.20 g (66% from 0.21 g, 1.0 mmol of **5**); colorless solid; R_f = 0.75 (Tol/EtOAc 1:1); mp 153–156 °C.

IR (KBr): 3024, 2934, 1591, 1560, 1534, 1499, 1431, 1412, 1333 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, ^3J = 8.3 Hz, 1 H, HC9), 8.20 (d, ^3J = 8.2 Hz, 1 H, HC6), 7.97 (dd, ^3J = 8.3, 7.4 Hz, 1 H, HC8), 7.68 (dd, ^3J = 8.2, 7.4 Hz, 1 H, HC7), 7.31–7.22 (m, 4 H, C_6H_5), 7.21–7.15 (m, 1 H, C_6H_5), 3.69 (t, ^3J = 7.5 Hz, 2 H, CH_2), 3.10 (t, ^3J = 7.5 Hz, 2 H, CH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.9, 152.6, 139.5, 135.6, 131.4, 128.8, 128.7, 128.5, 126.9, 126.3, 118.5, 116.7, 34.9, 32.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}N_5S$: 308.0964; found: 308.0969.

5-(Butylthio)tetrazolo[1,5-*a*]quinazoline (4e)

Method B: reaction time 1.5 h; yield: 0.29 g (80% from 0.30 g, 1.42 mmol of diazide **5**); yellow solid; R_f = 0.12 (hexane/EtOAc 15:1); mp 99–101 °C.

IR (KBr): 2940, 2925, 1590, 1535, 1410 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.51 (dd, ^3J = 8.3 Hz, ^4J = 1.1 Hz, 1 H, HC9), 8.35 (dd, ^3J = 8.2 Hz, ^4J = 1.2 Hz, 1 H, HC6), 8.18 (ddd, ^3J = 8.3, 7.4 Hz, ^4J = 1.2 Hz, 1 H, HC8), 7.86 (ddd, ^3J = 8.3, 7.4 Hz, ^4J = 1.1 Hz, 1 H, HC7), 3.45 (t, ^3J = 7.3 Hz, 2 H, H_2C1'), 1.78 (quint, ^3J = 7.2 Hz, 2 H, H_2C2'), 1.50 (sext, ^3J = 7.3 Hz, 2 H, H_2C3'), 0.96 (t, ^3J = 7.3 Hz, 3 H, H_3C4').

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 171.3, 152.2, 136.0, 131.0, 128.7, 125.8, 118.0, 116.2, 30.1, 29.5, 21.5, 13.5.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}N_5S$: 260.0964; found: 260.0953.

5-(Decylthio)tetrazolo[1,5-*a*]quinazoline (4f)

Method A: Reaction time 2 days at rt; yield: 0.60 g [88% from 0.42 g, 2.0 mmol of 2,4-diazidoquinazoline (**5**) in EtOH (20 mL)].

Method B: Reaction time 3 h; yield: 0.87 g (99%).

Method C: NaN_3 (1.2 g, 18.5 mmol, 4.2 equiv) was added to a solution of 4-decylthio-2-chloroquinazoline (**2f**; 1.49 g, 4.4 mmol, 1.0 equiv) in DMF (6 mL) at rt. The reaction mixture was stirred for 10 min, then TFA (10–20 µL) was added and the mixture was stirred for 5 h at 30 °C, controlled by HPLC. After completion of the reaction, 2–3 volumes of H_2O were added, the obtained suspension was cooled and filtered, the precipitate washed with H_2O (2 × 10 mL) and EtOH (3 × 5 mL), recrystallized from EtOH (100 mL), and dried in vacuo; yield: 0.40 g (95%); colorless solid; R_f = 0.74 (Tol/EtOAc 1:1); mp 98–100 °C.

IR (KBr): 3080, 2920, 2850, 1590, 1535, 1460, 1405 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.51 (d, ^3J = 8.3 Hz, 1 H, HC9), 8.34 (d, ^3J = 8.2 Hz, 1 H, HC6), 8.18 (dd, ^3J = 8.3,7.8 Hz, 1 H, HC8), 7.86 (dd, ^3J = 8.2, 7.8 Hz, 1 H, HC7), 3.43 (t, ^3J = 7.2 Hz, 2 H, H_2C1'), 1.79 (quint, ^3J = 7.2 Hz, 2 H, H_2C2'), 1.47 (quint, ^3J = 7.2 Hz, 2 H, H_2C3'), 1.38–1.18 (m, 12 H, 6 × CH_2), 0.83 (t, 3 H, ^3J = 6.5 Hz, H_3C10').

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 171.4, 152.2, 136.0, 131.0, 128.7, 125.8, 118.1, 116.2, 39.5, 31.2, 29.8, 28.9, 28.9, 28.6, 28.5, 28.3, 27.9, 13.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}N_5S$: 344.1910; found: 344.1909.

5-(Dodecylthio)tetrazolo[1,5-*a*]quinazoline (4g)

Method B: reaction time 1.5 h; yield: 2.11 g (99% from 1.0 g, 1.42 mmol of diazide **5**); colorless solid; R_f = 0.88 (Tol/EtOAc 1:1); mp 101–103 °C.

IR (KBr): 2925, 2845, 1615, 1590, 1530, 1465 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (dd, ^3J = 8.4 Hz, ^4J = 1.1 Hz, 1 H, HC9), 8.30 (dd, ^3J = 8.3 Hz, ^4J = 1.2 Hz, 1 H, HC6), 8.03 (ddd, ^3J = 8.4, 7.4 Hz, ^4J = 1.2 Hz, 1 H, HC8), 7.74 (dd, ^3J = 8.3, 7.4 Hz, ^4J = 1.1 Hz, 1 H, HC7), 3.49 (t, ^3J = 7.4 Hz, 2 H, H_2C1′), 1.84 (quint, ^3J = 7.4 Hz, 2 H, H_2C2′), 1.51 (quint, ^3J = 7.4 Hz, 2 H, H_2C3′), 1.35 (quint, ^3J = 7.4 Hz, 2 H, H_2C4′), 1.31–1.22 [m, 14 H, $(CH_2)_7$], 0.87 (t, ^3J = 7.0 Hz, 3 H, H_3C12′).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 172.4, 152.7, 135.5, 131.4, 128.5, 126.3, 118.6, 116.7, 32.0, 31.0, 29.8, 29.75, 29.70, 29.6, 29.5, 29.3, 29.1, 28.6, 22.8, 14.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{30}N_5S$: 372.2216; found: 372.2222.

5-(Phenylthio)tetrazolo[1,5-*a*]quinazoline (4h)

Method A: reaction time 16 h at 40 °C in EtOH (10 mL); yield: 0.20 g (71% from 0.21 g, 1.0 mmol of diazide **5**); colorless solid; R_f = 0.78 (Tol/EtOAc 1:1); mp 204–210 °C.

IR (KBr): 3049, 2376, 2346, 1615, 1590, 1533, 1477, 1407 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.55 (d, ^3J = 8.4 Hz, 1 H, HC9), 8.51 (d, ^3J = 8.4 Hz, 1 H, HC6), 8.23 (dd, ^3J = 8.4, 7.7 Hz, 1 H, HC8), 7.93 (dd, ^3J = 8.4, 7.7 Hz, 1 H, HC7), 7.77–7.67 (m, 2 H, C_6H_5), 7.65–7.56 (m, 3 H, C_6H_5).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 170.9, 152.1, 136.4, 135.9, 131.3, 130.5, 129.9, 129.0, 125.9, 125.6, 117.6, 116.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}N_5S$: 280.0651; found: 280.0627.

5-[(4-Chlorophenyl)thio]tetrazolo[1,5-*a*]quinazoline (4i)

Method A: reaction time 6 h at 50 °C in *i*PrOH; yield: 0.38 g (60%); colorless solid; R_f = 0.81 (Tol/EtOAc 1:1); mp 199–202 °C.

IR (KBr): 3084, 2370, 2346, 1612, 1591, 1535, 1476, 1406 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.58 (dd, ^3J = 8.3 Hz, ^4J = 1.1 Hz, 1 H, HC9), 8.52 (dd, ^3J = 8.2 Hz, ^4J = 1.2 Hz, 1 H, HC6), 8.25 (ddd, ^3J = 8.3, 7.6 Hz, ^4J = 1.2 Hz, 1 H, HC8), 7.95 (ddd, ^3J = 8.2, 7.6 Hz, ^4J = 1.1 Hz, 1 H, HC7), 7.74 (d, ^3J = 8.6 Hz, 2 H_{arom}), 7.69 (d, ^3J = 8.6 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 171.3, 152.5, 137.4, 137.3, 136.0, 131.8, 130.2, 128.8, 126.1, 123.6, 117.9, 116.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9ClN_5S$: 314.0262; found: 314.0244.

5-[(4-Fluorophenyl)thio]tetrazolo[1,5-*a*]quinazoline (4j)

Method A: reaction time 5 h at 40 °C in EtOH; yield: 0.54 g (91%); slightly yellow solid; R_f = 0.81 (Tol/EtOAc 1:1); mp 204–206 °C.

IR (KBr): 3095, 3074, 1616, 1589, 1535, 1489, 1408 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (dd, ^3J = 8.4 Hz, ^4J = 1.1 Hz, 1 H, HC9), 8.42 (dd, ^3J = 8.3 Hz, ^4J = 1.2 Hz, 1 H, HC6), 8.10 (ddd, ^3J = 8.4, 7.4 Hz, ^4J = 1.2 Hz, 1 H, HC8), 7.83 (ddd, ^3J = 8.3, 7.4 Hz, ^4J = 1.1 Hz, 1 H, HC7), 7.62 (dddd, ^3J = 8.9 Hz, $^4J_{H,F}$ = 5.2 Hz, ^4J = 3.0 Hz, ^5J = 2.2 Hz, 2 H_{arom}), 7.22 (dddd, ^3J = 8.9 Hz, $^3J_{H,F}$ = 8.7 Hz, ^4J = 3.0 Hz, ^5J = 2.2 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 171.7, 164.4 (d, $^1J_{C,F}$ = 252 Hz), 152.5, 138.3 (d, $^3J_{C,F}$ = 9 Hz), 136.0, 131.7, 128.7, 126.1, 120.4 (d, $^4J_{C,F}$ = 4 Hz), 117.9, 117.3 (d, $^2J_{C,F}$ = 22 Hz), 116.9.

^{19}F NMR (470.5 MHz, $CDCl_3$): δ = –109.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9FN_5S$: 298.0557; found: 298.0554.

5-[(4-Bromophenyl)thio]tetrazolo[1,5-*a*]quinazoline (4k)

Method A: reaction time 48 h at 40 °C in EtOH (30 mL); yield: 0.80 g (80% from 0.63 g, 3.0 mmol of diazide **5**); colorless solid; R_f = 0.74 (Tol/EtOAc 1:1); mp 249–253 °C.

IR (KBr): 3068, 3037, 2360, 2343, 1610, 1590, 1530, 1472, 1412 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.58 (d, ^3J = 8.2 Hz, 1 H, HC9), 8.51 (d, ^3J = 8.2 Hz, 1 H, HC6), 8.25 (dd, ^3J = 8.2, 7.8 Hz, 1 H, HC8), 7.95 (dd, ^3J = 8.2, 7.8 Hz, 1 H, HC7), 7.82 (d, ^3J = 8.4 Hz, 2 H_{arom}), 7.66 (d, ^3J = 8.4 Hz, 2 H_{arom}).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 170.4, 152.1, 137.8, 136.5, 132.8, 131.4, 129.0, 125.9, 125.2, 124.5, 117.6, 116.4.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9BrN_5S$: 359.9736; found: 359.9695.

5-(*p*-Tolylthio)tetrazolo[1,5-*a*]quinazoline (4l)

Method A: reaction time 5 h at rt in *i*PrOH; yield: 0.50 g (86%); colorless solid; R_f = 0.86 (Tol/EtOAc 1:1); mp 226–228 °C.

IR (KBr): 3079, 3040, 2913, 1614, 1588, 1531, 1495, 1407 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (dd, ^3J = 8.3 Hz, ^4J = 1.1 Hz, 1 H, HC9), 8.44 (dd, ^3J = 8.2 Hz, ^4J = 1.2 Hz, 1 H, HC6), 8.08 (ddd, ^3J = 8.3, 7.3 Hz, ^4J = 1.2 Hz, 1 H, HC8), 7.81 (ddd, ^3J = 8.2, 7.3 Hz, ^4J = 1.1 Hz, 1 H, HC7), 7.52 (d, ^3J = 8.1 Hz, 2 H_{arom}), 7.32 (d, ^3J = 8.1 Hz, 2 H_{arom}), 2.45 (s, 3 H, CH_3).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 172.3, 152.6, 141.2, 136.0, 135.7, 131.7, 130.8, 128.6, 126.2, 121.6, 118.0, 116.8, 21.6.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_5S$: 294.0808; found: 294.0803.

5-[(4-*tert*-Butylphenyl)thio]tetrazolo[1,5-*a*]quinazoline (4m)

Method A: reaction time 9 h at 40 °C in EtOH; yield: 0.57 g (86%); colorless solid; R_f = 0.88 (Tol/EtOAc 1:1); mp 183–185 °C.

IR (KBr): 2959, 2867, 1611, 1589, 1530, 1459, 1434, 1409 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (dd, ^3J = 8.4 Hz, ^4J = 1.1 Hz, 1 H, HC9), 8.45 (dd, ^3J = 8.3 Hz, ^4J = 1.2 Hz, 1 H, HC6), 8.08 (ddd, ^3J = 8.4, 7.4 Hz, ^4J = 1.2 Hz, 1 H, HC8), 7.81 (ddd, ^3J = 8.3, 7.4 Hz, ^4J = 1.1 Hz, 1 H, HC7), 7.57 (d, ^3J = 8.6 Hz, 2 H_{arom}), 7.53 (d, ^3J = 8.6 Hz, 2 H_{arom}), 1.39 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 172.2, 154.0, 152.6, 135.75, 135.67, 131.6, 128.6, 127.1, 126.2, 121.7, 118.0, 116.8, 35.1, 31.4.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}N_5S$: 336.1277; found: 336.1273.

4-(Alkyl/arylthio)-2-(1*H*-1,2,3-triazol-1-yl)quinazolines 7a–n; General Procedure

Sodium ascorbate (0.08 mmol, 0.1 equiv), $CuSO_4·5H_2O$ (0.04 mmol, 0.05 equiv), and substituted acetylene (1.6 mmol, 2.0 equiv) were subsequently added to a stirred solution of **4** (0.80 mmol, 1.0 equiv) in a mixture of THF (6 mL) and H_2O (1 mL). The reaction mixture was stirred at 60 °C for 4–24 h, controlled by HPLC. The mixture was evaporated, dissolved in DCM or $CHCl_3$ (20 mL), washed with aq NaHS (2 × 5 mL) and H_2O (2 × 5 mL), dried (anhyd Na_2SO_4), and evaporated. The remaining solid was suspended in CH_3CN or EtOH (10 mL), filtered, washed several times with appropriate solvent, and purified by recrystallization or column chromatography.

4-(Benzylthio)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)quinazoline (7a)

Reaction time: 6 h at 56 °C; yield: 0.14 g (70%); yellow solid; R_f = 0.91 (Tol/EtOAc 1:1); mp 214–216 °C.

IR (KBr): 3161, 3061, 3028, 1611, 1569, 1547, 1496, 1462, 1416 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.82 [s, 1 H, HC(triazole)], 8.12 (d, ^3J = 8.2 Hz, 1 H, HC5), 8.07 (d, ^3J = 8.4 Hz, 1 H, HC8), 7.99 (d, ^3J = 7.8 Hz, 2 H, C_6H_5), 7.91 (dd, ^3J = 8.4, 7.1 Hz, 1 H, HC7), 7.62–7.57 (m, 3 H, HC6, 2 H, $CH_2C_6H_5$), 7.48 (t, ^3J = 7.8 Hz, 2 H, C_6H_5), 7.40 (t, ^3J = 7.8 Hz, 1 H, C_6H_5), 7.36 (t, ^3J = 7.5 Hz, 2 H, $CH_2C_6H_5$), 7.29 (t, ^3J = 7.5 Hz, 1 H, $CH_2C_6H_5$), 4.77 (s, 2 H, $CH_2C_6H_5$).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 174.8, 149.5, 148.9, 148.0, 136.4, 135.2, 130.3, 129.4, 129.05, 129.00, 128.9, 128.7, 127.9, 127.7, 126.2, 124.3, 122.9, 118.7, 34.7.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{18}N_5S$: 396.1277; found: 396.1275.

2-[4-(4-Butylphenyl)-1*H*-1,2,3-triazol-1-yl]-4-(butylthio)quinazoline (7b)

Reaction time 24 h at rt; yield: 0.15 g (90% from 0.09 g, 0.35 mmol of **4e**); yellow solid; R_f = 0.14 (hexane/EtOAc 15:1); mp 89–91 °C.

IR (KBr): 2955, 2930, 1550, 1465, 1370 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 9.34 [s, 1 H, HC(triazole)], 8.21 (d, ^3J = 8.2 Hz, 1 H, HC5), 8.11–8.02 (m, 2 H, HC8, HC7), 7.96 (d, ^3J = 8.0 Hz, 2 H_{arom}), 7.76 (ddd, ^3J = 8.2, 6.0 Hz, ^4J = 2.1 Hz, 1 H, HC6), 7.33 (d, ^3J = 8.0 Hz, 2 H_{arom}), 3.57 (t, ^3J = 7.3 Hz, 2 H H_2C1'), 2.63 (t, ^3J = 7.6 Hz, 2 H, H_2C1''), 1.82 (quint, ^3J = 7.3 Hz, 2 H, H_2C2'), 1.60 (quint, ^3J = 7.6 Hz, 2 H, H_2C2''), 1.53 (sext, ^3J = 7.3 Hz, 2 H, H_2C3'), 1.33 (sext, ^3J = 7.6 Hz, 2 H, H_2C3''), 0.96 (t, ^3J = 7.3 Hz, 3 H, H_3C4'), 0.96 (t, ^3J = 7.6 Hz, 3 H, H_3C4'').

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.9, 149.0, 148.0, 146.9, 142.8, 135.7, 128.9, 128.33, 128.30, 127.3, 125.6, 124.1, 122.4, 119.5, 34.6, 33.0, 30.4, 29.3, 21.8, 21.5, 13.8, 13.5.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{28}N_5S$: 418.2060; found: 418.2058.

4-(Decylthio)-2-(4-hexyl-1*H*-1,2,3-triazol-1-yl)quinazoline (7c)

Reaction time: 24 h at rt; yield: 0.14 g (65% from 0.16 g, 0.47 mmol of **4f**); colorless solid; R_f = 0.14 (hexane/EtOAc 15:1); mp 78–79 °C.

IR (KBr): 2925, 2855, 1575, 1550, 1465, 1355 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.37 [s, 1 H, HC(triazole)], 8.12 (dd, ^3J = 8.2 Hz, ^4J = 1.3 Hz, 1 H, HC5), 8.07 (dd, ^3J = 8.3 Hz, ^4J = 1.1 Hz, 1 H, HC8), 7.89 (ddd, ^3J = 8.3, 7.0 Hz, ^4J = 1.3 Hz, 1 H, HC7), 7.58 (ddd, ^3J = 8.2, 7.0 Hz, ^4J = 1.1 Hz, 1 H, HC6), 3.47 (t, ^3J = 7.3 Hz, 2 H, H_2C1'), 2.85 (t, ^3J = 7.6 Hz, 2 H, H_2C1''), 1.87 (quint, ^3J = 7.3 Hz, 2 H, H_2C2'), 1.76 (quint, ^3J = 7.6 Hz, 2 H, H_2C2''), 1.53 (quint, ^3J = 7.3 Hz, 2 H, H_2C3'), 1.44–1.23 [m, 18 H, $(CH_2)_9$], 0.89 (t, ^3J = 6.2 Hz, 3 H, CH_3), 0.87 (t, ^3J = 6.2 Hz, 3 H, CH_3).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 175.6, 149.6, 148.9 (2 C), 135.0, 129.1, 127.5, 124.3, 123.1, 119.9, 32.0, 31.7, 30.5, 29.69 (2 C), 29.48, 29.45, 29.4, 29.2, 29.1, 28.9, 25.9, 22.8, 22.7, 14.24, 14.22

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{40}N_5S$: 454.2999; found: 454.2998.

4-(Decylthio)-2-(4-butyl-1*H*-1,2,3-triazol-1-yl)quinazoline (7d)

Reaction time: 24 h at rt; yield: 0.18 g (74% from 0.20 g, 0.58 mmol of **4f**); brown solid; R_f = 0.14 (hexane/EtOAc 15:1); mp 71–73 °C.

IR (KBr): 2920, 2855, 1575, 1550, 1465, 1470 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.38 [s, 1 H, HC(triazole)], 8.12 (d, ^3J = 8.3 Hz, 1 H, HC5), 8.07 (d, ^3J = 8.2 Hz, 1 H, HC8), 7.89 (dd, ^3J = 8.2, 7.6 Hz, 1 H, HC7), 7.58 (dd, ^3J = 8.3, 7.6 Hz, 1 H, HC6), 3.47 (t, ^3J = 7.3 Hz, 2 H, H_2C1'), 2.86 (t, ^3J = 7.6 Hz, 2 H, H_2C1''), 1.87 (quint,^3J = 7.3 Hz, 2 H, H_2C2'), 1.76 (quint, ^3J = 7.6 Hz, 2 H, H_2C2''), 1.53 (quint, ^3J = 7.3 Hz, 2 H, H_2C3'), 1.44 (sext, ^3J = 7.6 Hz, 2 H, H_2C3''), 1.40–1.34 (m, 2 H, H_2C4'), 1.32–1.22 [m, 10 H, $(CH_2)_5$], 0.97 (t, ^3J = 7.6 Hz, 3 H, H_3C4''), 0.87 (t, ^3J = 6.8 Hz, 3 H, H_3C10').

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 175.6, 149.6, 148.84, 148.82, 135.0, 129.1, 127.5, 124.3, 123.2, 119.9, 32.0, 31.6, 30.5, 29.7 (2 C), 29.44, 29.40, 29.2, 28.9, 25.5, 22.8, 22.5, 14.2, 14.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{36}N_5S$: 426.2686; found: 426.2673.

4-(Decylthio)-2-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)quinazoline (7e)

Reaction time: 7 h at 60 °C; yield: 0.14 g (71% from 0.16 g, 0.47 mmol of **4f**); yellow solid; R_f = 0.14 (hexane/EtOAc 15:1); mp 76–78 °C.

IR (KBr): 2930, 2850, 1570, 1550, 1465 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.67 [s, 1 H, HC(triazole)], 8.18 (d, ^3J = 8.2 Hz, 1 H, HC5), 8.09–7.97 (m, 2 H, HC8, HC7), 7.74 (dd, ^3J = 8.2, 6.7 Hz, 1 H, HC6), 3.49 (t, ^3J = 7.2 Hz, 2 H, H_2C1'), 2.15–2.05 [m, 1 H, HC(cyclopropyl)], 1.79 (quint, ^3J = 7.2 Hz, 2 H, H_2C2'), 1.46 (quint, ^3J = 7.2 Hz, 2 H, H_2C3'), 1.38–1.15 [m, 12 H, $(CH_2)_6$], 1.04–0.96 (m, 2 H_a), 0.92–0.85 (m, 2 H_b), 0.82 (t, ^3J = 6.6 Hz, 3 H, H_3C10').

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.5, 149.5, 148.8, 147.9, 135.3, 128.0, 127.8, 123.8, 122.1, 119.1, 31.0, 29.3, 28.65, 28.60, 28.4, 28.3, 28.2, 28.0, 21.8, 13.6, 7.4, 6.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{32}N_5S$: 410.2373; found: 410.2376.

4-(Decylthio)-2-[4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]quinazoline (7f)

Reaction time: 15 h at 60 °C; yield: 0.21 g (70% from 0.22 g, 0.64 mmol of **4f**); yellow solid; R_f = 0.14 (hexane/EtOAc 15:1); mp 83–85 °C.

IR (KBr): 2920, 2850, 1565, 1550, 1465 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 9.24 [s, 1 H, HC(triazole)], 8.15 (d, ^3J = 8.2 Hz, 1 H, HC5), 8.08–7.99 (m, 2 H, HC8, HC7), 7.97 (d, ^3J = 8.8 Hz, 2 H_{arom}), 7.72 (ddd, ^3J = 8.2, 6.0 Hz, ^4J = 2.1 Hz, 1 H, HC6), 7.04 (d, ^3J = 8.8 Hz, 2 H_{arom}), 3.81 (s, 3 H, OCH_3), 3.51 (t, ^3J = 7.2 Hz, 2 H, H_2C1'), 1.78 (quint, ^3J = 7.2 Hz, 2 H, H_2C2'), 1.45 (quint, ^3J = 7.2 Hz, 2 H, H_2C3'), 1.29 (quint, ^3J = 7.2 Hz, 2 H, H_2C4'), 1.22–1.09 [m, 10 H, $(CH_2)_5$], 0.78 (t, ^3J = 6.7 Hz, 3 H, H_3C10').

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.7, 159.4, 148.9, 147.9, 146.6, 135.4, 128.2, 128.0, 126.9, 123.9, 122.33, 122.27, 118.6, 114.2, 55.1, 31.1, 29.4, 28.8, 28.7, 28.5, 28.4, 28.3, 28.1, 21.8, 13.7.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{34}N_5OS$: 476.2479; found: 476.2491.

4-(Dodecylthio)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)quinazoline (7g)

Reaction time: 24 h at 70 °C; yield: 0.23 g (79% from 0.20 g, 0.54 mmol of **4g**); brown solid; R_f = 0.14 (hexane/EtOAc 15:1); mp 74–76 °C.

IR (KBr): 2920, 2850, 1570, 1545, 1465, 1370 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.30 [s, 1 H, HC(triazole)], 8.16 (d, ^3J = 8.2 Hz, 1 H, HC8), 8.08–7.99 (m, 4 H, HC5, HC6, C_6H_5), 7.73 (ddd, ^3J = 8.2, 6.0 Hz, ^4J = 2.3 Hz, 1 H, HC7), 7.49 (t, ^3J = 7.5 Hz, 2 H, C_6H_5), 7.39 (t, ^3J = 7.5 Hz, 1 H, C_6H_5), 3.53 (t, ^3J = 7.2 Hz, 2 H, H_2C1'), 1.81 (quint, ^3J = 7.2 Hz, 2 H, H_2C2'), 1.47 (quint, ^3J = 7.2 Hz, 2 H, H_2C3'), 1.31 (quint, ^3J = 7.2 Hz, 2 H, H_2C4'), 1.25–1.12 [m, 14 H, $(CH_2)_7$], 0.80 (t, ^3J = 6.7 Hz, 3 H, H_3C12').

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.8, 148.8, 147.8, 146.6, 135.4, 129.7, 128.7, 128.2, 128.1, 128.0, 125.5, 123.8, 122.3, 119.5, 31.0, 29.4, 28.70, 28.65, 28.64, 28.61, 28.4, 28.24, 28.19, 28.0, 21.7, 13.6

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{36}N_5S$: 474.2686; found: 474.2694.

4-(Dodecylthio)-2-[4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]quinazoline (7h)

Reaction time: 24 h at 70 °C; yield: 0.23 g (87% from 0.20 g, 0.54 mmol of **4g**); brown solid; R_f = 0.14 (hexane/EtOAc 15:1); mp 83–84 °C.

IR (KBr): 2920, 2850, 1565, 1545, 1465, 1370 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.27 ([s, 1 H, HC(triazole)], 8.21 (d, ^3J = 8.3 Hz, 1 H, HC5), 8.11–8.02 (m, 2 H, HC8, HC7), 7.93 (d, ^3J = 8.0 Hz, 2 H_{arom}), 7.76 (ddd, ^3J = 8.3, 6.0 Hz, ^4J = 1.9 Hz, 1 H, HC6), 7.31 (d, ^3J = 8.0 Hz, 2 H_{arom}), 3.56 (t, ^3J = 7.2 Hz, 2 H, H_2C1'), 2.37 (s, 3 H, CH_3), 1.84 (quint, ^3J = 7.2 Hz, 2 H, H_2C2'), 1.50 (quint, ^3J = 7.2 Hz, 2 H, H_2C3'), 1.41–1.30 (m, 2 H, H_2C4'), 1.30–1.11 [m, 14 H, $(CH_2)_7$], 0.83 (t, ^3J = 6.7 Hz, 3 H, H_3C12').

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 175.8, 149.5, 148.8, 148.0, 138.6, 135.0, 129.7, 129.1, 127.6, 127.5, 126.1, 124.3, 123.2, 118.2, 32.0, 30.5, 29.82, 29.77, 29.7 (2 C), 29.5, 29.4, 29.3, 28.9, 22.8, 21.5, 14.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{38}N_5S$: 488.2842; found: 488.2854.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-4-(phenylthio)quinazoline (7i)

Reaction time: 5 h at 60 °C; yield: 0.15 g (80%); colorless solid; R_f = 0.73 (Tol/EtOAc 1:1); mp 196–198 °C.

IR (KBr): 3150, 3053, 1605, 1568, 1551, 1499, 1465, 1416, 1372, 1347 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (dd, ^3J = 8.2 Hz, ^4J = 1.3 Hz, 1 H, HC5), 8.18 (dd, ^3J = 8.4 Hz, ^4J = 1.1 Hz, 1 H, HC8), 8.08 [s, 1 H, HC(triazole)], 7.96 (ddd, ^3J = 8.4, 7.1 Hz, ^4J = 1.3 Hz, 1 H, HC7), 7.79 (d, ^3J = 7.5 Hz, 2 H, C_6H_5), 7.72 (d, ^3J = 8.0 Hz, 2 H, SC_6H_5), 7.67 (ddd, ^3J = 8.2, 7.1 Hz, ^4J = 1.1 Hz, 1 H, HC6), 7.65–7.58 (m, 3 H, SC_6H_5), 7.44 (t, ^3J = 7.5 Hz, 2 H, C_6H_5), 7.35 (t, ^3J = 7.5 Hz, 1 H, C_6H_5).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 175.3, 149.4, 149.2, 147.6, 136.4, 135.4, 130.3, 130.2, 129.7, 129.3, 129.0, 128.5, 127.9, 126.8, 126.0, 124.1, 122.4, 118.8.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{16}N_5S$: 382.1121; found: 382.1102.

4-[(4-Chlorophenyl)thio]-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-quinazoline (7j)

Reaction time: 6 h at 60 °C; yield: 0.10 g (50%); brown solid; R_f = 0.75 (Tol/EtOAc 1:1); mp 185–187 °C.

IR (KBr): 3153, 3052, 2924, 1609, 1568, 1549, 1499, 1463, 1415, 1371 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.64 [s, 1 H, HC(triazole)], 8.33 (d, ^3J = 8.3 Hz, 1 H, HC5), 8.18–8.08 (m, 2 H, HC8, HC7), 7.89 (d, ^3J = 7.3 Hz, 2 H, C_6H_5), 7.87–7.78 (m, 3 H, HC6, 2 H_{arom}), 7.73 (d, ^3J = 8.4 Hz, 2 H_{arom}), 7.51 (t, ^3J = 7.3 Hz, 2 H, C_6H_5), 7.41 (t, ^3J = 7.3 Hz, 1 H, C_6H_5).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 174.8, 149.5, 149.1, 147.7, 137.8, 137.0, 135.6, 130.0 (2 C) (the signal was assigned from HMBC spectrum), 129.4, 129.1, 128.7, 128.1, 125.9, 125.3, 124.0, 122.3, 118.7.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{15}ClN_5S$: 416.0731; found: 416.0721.

4-[(4-Fluorophenyl)thio]-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)quinazoline (7k)

Reaction time: 3 h at 60 °C; yield: 0.14 g (73%); yellow solid; R_f = 0.74 (Tol/EtOAc 1:1); mp 194–196 °C.

IR (KBr): 3161, 3061, 1611, 1569, 1547, 1496, 1462, 1416, 1367 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.20 (d, ^3J = 8.2 Hz, 1 H, HC5), 8.15 (d, ^3J = 8.4 Hz, 1 H, HC8), 8.13 [s, 1 H, HC(triazole)], 7.95 (dd, ^3J = 8.4, 7.1 Hz, 1 H, HC7), 7.80 (d, ^3J = 7.6 Hz, 2 H_{arom}), 7.73–7.68 (m, 2 H, C_6H_5), 7.67 (dd, ^3J = 8.2, 7.1 Hz, 1 H, HC6), 7.44 (dd, ^3J = 7.6 Hz, $^3J_{H,F}$ = 7.5 Hz, 2 H_{arom}), 7.37–7.28 (m, 3 H, C_6H_5).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 175.0, 164.2 (d, $^1J_{C,F}$ = 252 Hz), 149.4, 149.2, 147.7, 138.5 (d, $^3J_{C,F}$ = 9 Hz), 135.5, 130.0, 129.3, 129.0, 128.6, 128.0, 125.9, 124.0, 122.3, 122.0 (d, $^4J_{C,F}$ = 3 Hz), 118.6, 117.0 (d, $^2J_{C,F}$ = 22 Hz).

^{19}F NMR (470.5 MHz, $CDCl_3$): δ = –109.6.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{15}FN_5S$: 400.1027; found: 400.1027.

2-{4-[4-(Trifluoromethyl)phenyl]-1*H*-1,2,3-triazol-1-yl}-4-[(4-fluorophenyl)thio]quinazoline (7l)

Reaction time: 4 h at 55 °C; yield: 0.17 g (74%); colorless solid; R_f = 0.85 (Tol/EtOAc 1:1); mp 237–243 °C.

IR (KBr): 3154, 3057, 1624, 1588, 1568, 1550, 1491, 1462, 1423, 1412 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, ^3J = 8.3 Hz, 1 H, HC5), 8.19 [s, 1 H, HC(triazole)], 8.16 (d, ^3J = 8.4 Hz, 1 H, HC8), 7.97 (dd, ^3J = 8.4, 7.7 Hz, 1 H, HC7), 7.90 (d, ^3J = 8.1 Hz, 2 H_{arom}), 7.74–7.67 (m, 5 H, HC6, 2 H_{arom}, 2 H, SAr), 7.33 (dd, ^3J = 8.6 Hz, $^3J_{H,F}$ = 8.4 Hz, 2 H, SAr).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 175.2, 164.3 (d, $^1J_{C,F}$ = 252 Hz), 149.3, 149.0, 146.3, 138.6 (d, $^3J_{C,F}$ = 9 Hz), 135.6, 133.4, 130.4 (q, $^2J_{C,F}$ = 33 Hz), 129.3, 128.2, 126.00 (q, $^3J_{C,F}$ = 4 Hz), 125.96, 124.2 (q, $^1J_{C,F}$ = 272 Hz), 124.0, 122.3, 122.0 (d, $^4J_{C,F}$ = 4 Hz), 119.4, 117.0 (d, $^2J_{C,F}$ = 22 Hz).

^{19}F NMR (470.5 MHz, $CDCl_3$): δ = –62.6, –109.5.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{14}F_4N_5S$: 468.0901; found: 468.0904.

4-[(4-Bromophenyl)thio]-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-quinazoline (7m)

Reaction time: 12 h at 60 °C; yield: 0.19 g (82%); colorless solid; R_f = 0.75 (Tol/EtOAc 1:1); mp 244–246 °C.

IR (KBr): 3155, 3058, 3047, 1612, 1568, 1550, 1499, 1461, 1414 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19 (dd, ^3J = 8.1 Hz, ^4J = 1.3 Hz, 1 H, HC5), 8.17 (d, ^3J = 8.4 Hz, 1 H, HC8), 8.08 [s, 1 H, HC(triazole)], 7.96 (ddd, ^3J = 8.4, 7.1 Hz, ^4J = 1.3 Hz, 1 H, HC7) 7.84 (d, ^3J = 7.5 Hz, 2 H, C_6H_5), 7.76 (d, ^3J = 8.4 Hz, 2 H_{arom}), 7.68 (dd, ^3J = 8.1, 7.1 Hz, 1 H, HC6), 7.58 (d, ^3J = 8.4 Hz, 2 H_{arom}), 7.45 (t, ^3J = 7.5 Hz, 2 H, C_6H_5), 7.35 (t, ^3J = 7.5 Hz, 1 H, C_6H_5).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 174.6, 149.5, 149.0, 147.7, 138.0, 135.6, 132.9, 129.9, 129.4, 129.1, 128.6, 128.1, 126.0, 125.9, 125.2, 124.0, 122.3, 118.7.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{15}BrN_5S$: 460.0226; found: 460.0213.

4-[(4-*tert*-Butylphenyl)thio]-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-quinazoline (7n)

Reaction time: 6 h at 60 °C; yield: 0.20 g (90%); colorless solid; R_f = 0.74 (Tol/EtOAc 1:1); mp 234–236 °C.

IR (KBr): 3143, 2961, 2901, 2866, 1612, 1568, 1551, 1498, 1465, 1416 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, ^3J = 8.2 Hz, 1 H, HC5), 8.19 (d, ^3J = 8.4 Hz, 1 H, HC8), 8.12 [s, 1 H, HC(triazole)], 7.95 (dd, ^3J = 8.4, 7.3 Hz, 1 H, HC7), 7.78 (d, ^3J = 7.2 Hz, 2 H, C_6H_5), 7.67 (dd, ^3J = 8.2, 7.3 Hz, 1 H, HC6), 7.65–7.60 (m, 4 H_{arom}), 7.39 (t, ^3J = 7.2 Hz, 2 H, C_6H_5), 7.34 (t, ^3J = 7.2 Hz, 1 H, C_6H_5), 1.45 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 175.6, 154.0, 149.4, 149.1, 147.5, 136.1, 135.3, 130.1, 129.3, 128.8, 128.5, 127.9, 126.7, 125.9, 124.1, 123.1, 122.3, 119.0, 35.1, 31.4.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{24}N_5S$: 438.1747; found: 438.1748.

2-[4-(4-Butylphenyl)-1*H*-1,2,3-triazol-1-yl]-4-(hexylamino)-quinazoline (9)

Hexylamine (0.18 mL, ρ = 0.77 g/mL, 1.38 mmol, 1.0 equiv) was added to a solution of 2-[4-(4-butylphenyl)-1*H*-1,2,3-triazol-1-yl]-4-(butylthio)quinazoline (**7b**; 115 mg, 0.28 mmol, 1.0 equiv) in THF (3 mL) and H_2O (3 mL) and the mixture was stirred for 3 days at 35 °C, controlled by HPLC. After completion of the reaction, the mixture was evaporated and suspended in H_2O (3 mL). The suspension was filtered and the solid product was dried in vacuo. The product was dissolved in DCM (15 mL) and washed with brine (2 × 10 mL) and H_2O (2 × 10 mL). The organic phase was dried (anhyd Na_2SO_4), evaporated, and suspended in CH_3CN (5 mL). The suspension was filtered and dried in vacuo; yield: 35 mg (30%); slightly green solid; R_f = 0.67 (Tol/EtOAc 10:1); mp 194–196 °C.

IR (KBr): 3270, 2925, 1595, 1560, 1380 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6 + D_2O): δ = 9.10 [s, 1 H, HC(triazole)], 8.30 (d, ^3J = 8.2, 1 H, HC5), 7.88 (d, ^3J = 8.1 Hz, 2 H_{arom}), 7.85–7.76 (m, 2 H, HC7, HC8), 7.55 (dd, ^3J = 8.2, 6.7 Hz, 1 H, HC6), 7.30 (d, ^3J = 8.1 Hz, 2 H_{arom}), 3.69 (t, ^3J = 7.1 Hz, 2 H, H_2C1′), 2.62 (t, ^3J = 7.5 Hz, 2 H, H_2C1″), 1.71 (quint, ^3J = 7.1 Hz, 2 H, H_2C2′), 1.58 (quint, ^3J = 7.4 Hz, 2 H, H_2C2″), 1.45–1.22 [m, 8 H, $(CH_2)_4$], 0.90 (t, ^3J = 7.3 Hz, 3 H, H_3C4″), 0.83 (t, ^3J = 7.0 Hz, 3 H, H_3C6′).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 161.1, 150.9, 149.3, 142.2, 133.2, 128.4, 127.5, 127.1, 125.6, 125.5, 125.3, 122.9, 118.8, 114.1, 40.7, 34.3, 32.6, 30.7, 28.1, 25.8, 21.7, 21.3, 13.4, 13.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_8H_6N_6$: 429.2761; found: 429.2757.

5-(Ethoxy)tetrazolo[1,5-*c*]quinazoline (11)

Quinazoline **3d** (30 mg, 0.10 mmol, 1.0 equiv) was added to a suspension of K_2CO_3 (15 mg, 0.11 mmol, 1.1 equiv) in EtOH (5 mL) and stirred for 5 h at 40 °C, controlled by HPLC. After completion of the reaction, the mixture was evaporated, suspended in DCM (30 mL), and washed with H_2O (3 × 5 mL). Aqueous phases were back-extracted with DCM (2 × 5 mL). The organic phase was dried (anhyd Na_2SO_4), filtered, and evaporated. The product was then suspended in DCM (3 drops) and hexane (30 mL). The precipitate formed was filtered, washed with hexane (5 mL), and dried in vacuo; yield: 17 mg (77%); slightly green solid; R_f = 0.63 (Tol/CH_3CN 3:1); mp 174–177 °C.

IR (KBr): 3059, 2992, 2908, 1634, 1619, 1561, 1525, 1482 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, ^3J = 8.0 Hz, 1 H, HC10), 7.89 (d, ^3J = 8.1 Hz, 1 H, HC7), 7.85 (dd, ^3J = 8.1, 7.6 Hz, 1 H, HC8), 7.65 (dd, ^3J = 8.0, 7.6 Hz, 1 H, HC9), 4.91 (q, ^3J = 7.1 Hz, 2 H, CH_2), 1.66 (t, ^3J = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 151.4, 143.9, 143.7, 133.9, 127.2, 127.0, 125.1, 113.3, 66.9, 14.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}N_5O$: 216.0880; found: 216.0891.

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Supporting Information

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