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2-Amino[1,2,4]triazolo[1,5-*c*]quinazolines and Derived Novel Heterocycles: Syntheses and Structure–Activity Relationships of Potent Adenosine Receptor Antagonists

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2-Amino[1,2,4]triazolo[1,5-*c*]quinazolines were identified as potent adenosine receptor (AR) antagonists. Synthetic strategies were devised to gain access to a broad range of derivatives including novel polyheterocyclic compounds. Potent and selective A_3AR antagonists were discovered, including 3,5-diphenyl[1,2,4]triazolo[4,3-*c*]quinazoline (**17**, K_i human A_3AR 1.16 nM) and 5′-phenyl-1,2-dihydro-3′*H*-spiro[indole-3,2′-[1,2,4]triazolo[1,5-*c*]quinazolin]-2-one (**20**, K_i human A_3AR 6.94 nM). In addition, multitarget antagonists were obtained, such as the dual A_1/A_3 antagonist 2,5-diphenyl[1,2,4]triazolo[1,5-*c*]quinazoline (**13 b**, K_i human A_1AR 51.6 nM, human A_3AR 11.1 nM), and the balanced pan-AR antagonists 5-(2-thienyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (**11 c**, K_i human A_1AR 131 nM, A_{2A}AR 32.7 nM, A_{2B}AR 150 nM, A_3AR 47.5 nM) and 9-bromo-5-phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (**11 q**, K_i human A_1AR 67.7 nM, A_{2A}AR 13.6 nM, A_{2B}AR 75.0 nM, A_3AR 703 nM). In many cases, significantly different affinities for human and rat receptors were observed, which emphasizes the need for caution in extrapolating conclusions between different species.

Introduction

The nucleoside adenosine acts as a neuromodulator via specific receptors in the cell membrane known as adenosine receptors (ARs).[1] They belong to the superfamily of rhodopsin-like G protein-coupled receptors (GPCRs) and comprise four different subtypes, A_1, A_{2A}, A_{2B}, and A_3. Adenosine can be released from cells through equilibrative nucleoside transporters, or it can be formed extracellularly from adenine nucleotides by ectonucleotidases.[1,2] The extracellular concentration of adenosine may increase dramatically, from nanomolar to micromolar concentrations, under hypoxic or inflammatory conditions, or upon cell damage, thereby leading to enhanced activation of ARs under these pathological conditions.[2] In recent years ARs have therefore gained considerable interest as new drug targets.[3]

AR antagonists can be subdivided into three different classes (Figure 1): 1) xanthine derivatives such as the alkaloids theophylline (**1**) and caffeine (**2**), which are moderately potent non-selective AR antagonists, and their more potent derivatives such as the A_{2A}-selective istradefylline (KW6002, **3**), the A_{2B}-selective GS-6201 (CVT-6883, **4**), and the A_3-selective PSB-10 (**5 a**) and PSB-11 (**5 b**); 2) amino-substituted heterocyclic compounds related to adenine, such as the A_{2A} antagonists CGS-15943 (**6 a**) and preladenant (SCH420814, **6 b**); and 3) novel structures identified by screening approaches, such as the A_3 antagonist MRS1523 (**7**).[3] [1,2,4]Triazolo[1,5-*c*]quinazoline derivatives were first discovered to be antagonists for ARs by Francis et al.[4]

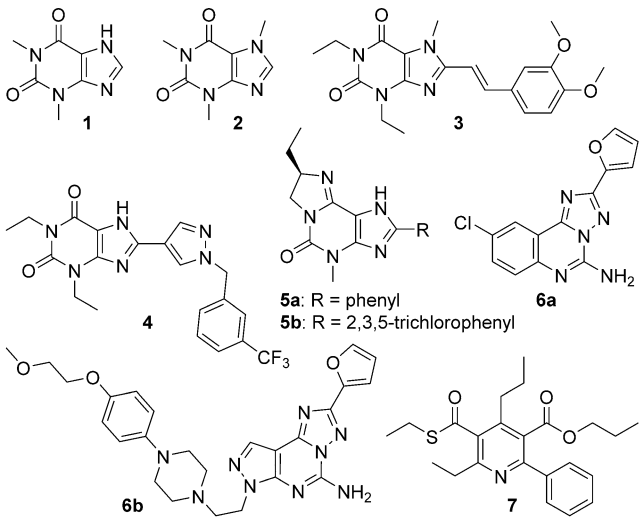

Figure 1. Selection of adenosine receptor antagonists.

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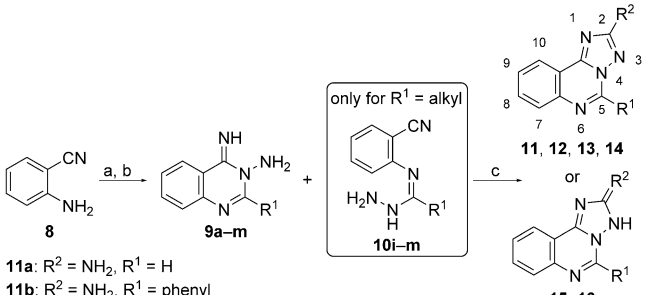
The A_{2A}AR antagonist istradefylline (**3**) has been approved in Japan for the treatment of Parkinson's disease, and several other AR antagonists have been or are under clinical evaluation.[5] For example, A_1-selective AR antagonists have been of interest for the treatment of heart failure with improvement of renal function. However, a recent phase III clinical trial has failed to show significant effects.[6] A_{2A}-selective AR antagonists are evaluated not only as therapeutics for Parkinson's disease, but may also be effective in Alzheimer's disease, restless legs syndrome, depression, addiction and cancer.[7] A_{2A} and A_{2B}AR antagonists have recently been proposed as checkpoint inhibitors for the immunotherapy of cancer, and clinical trials with A_{2A} antagonists have already started.[7f]

GS-6201 (**4**) is the first A_{2B}-selective AR antagonist that was clinically evaluated for asthma therapy. To our knowledge, there are no A_3-selective AR antagonists in clinical development so far. However, preclinical data indicate that they might be useful for the treatment of glaucoma, asthma, stroke, inflammation and cancer,[8] highlighting the need for more such antagonists. The non-selective $A_1/A_{2A}/A_{2B}/A_3$ antagonists theophylline (**1**) and caffeine (**2**) have been applied as drugs for a long time and are still being used for several indications. For example, caffeine is used for central nervous system (CNS) stimulation to restore alertness and to counteract fatigue as well as for the treatment of apnea, especially in premature babies. In combination with different analgesics, including nonsteroidal anti-inflammatory drugs and paracetamol (acetaminophen), caffeine is used for the treatment of pain. Theophylline (**1**) is mainly used for the treatment of bronchial asthma and chronic obstructive pulmonary disease as a second-line treatment, as well as a substitute for caffeine for the prevention of sleep apnea in adults and premature babies. More recently aminophylline (a mixture of theophylline/ethylenediamine = 2:1 with improved solubility) went into clinical trials for faster recovery after sevoflurane anesthesia, as sevoflurane leads to indirect activation of ARs.[9]

Effective drugs for CNS disorders, in particular for psychiatric diseases, frequently do not only address a single target, but may interact with two or even multiple targets.[10] Drugs with a dual or multiple mechanism of action have been proposed as advantageous for the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.[11] Dual A_1A_2 AR antagonists were evaluated in rodent and primate models of Parkinson's disease and found to be highly active.[12,13] Furthermore, a dual A_1/A_{2A} antagonist was found to additionally enhance cognitive function in rodent models via A_1 AR blockade, an effect not observed with the selective A_{2A} antagonist istradefylline that was investigated in the same study.[13] The interest in drugs with dual and multiple mechanisms of action has also been growing in other therapeutic fields; for example, A_{2A}/A_{2B} dual antagonists were shown to be useful in cancer immunotherapy[14] and A_{2B}/A_3 dual antagonists appear to be useful for treating asthma and allergic diseases.[15]

Results and Discussion

In the search for scaffolds suitable for the development of AR antagonists, we identified substituted [1,2,4]triazolo[1,5-*c*]quinazolines (Scheme 1) as a starting point by a screening approach. Initially, R^1 was either H, phenyl or 2-thienyl and R^2 was modified. We observed that an exocyclic amino function as R^2 was favorable to obtain high AR affinities. Thereafter R^2 was kept constant ($R^2 = NH_2$) while R^1 was further investigated using diverse substituents such as aliphatic, aromatic, and heteroaromatic groups as well as substituted amino and thio functions. Moreover, the effect of halogen substituents on the quinazoline ring was also studied.



11a: $R^2 = NH_2$, R^1 = H
11b: $R^2 = NH_2$, R^1 = phenyl
11c: $R^2 = NH_2$, R^1 = 2-thienyl
11d: $R^2 = NH_2$, R^1 = 4-bromophenyl
11e: $R^2 = NH_2$, R^1 = 3-fluorophenyl
11f: $R^2 = NH_2$, R^1 = 4-fluorophenyl
11g: $R^2 = NH_2$, R^1 = 3-thienyl
11h: $R^2 = NH_2$, R^1 = 2-furyl
11i: $R^2 = NH_2$, R^1 = isopropyl
11j: $R^2 = NH_2$, R^1 = benzyl
11k: $R^2 = NH_2$, R^1 = 2-(3,4,5-trimethoxyphenyl)ethyl
11l: $R^2 = NH_2$, R^1 = 2-phenylethyl
11m: $R^2 = NH_2$, R^1 = (*RS*)-1-phenylethyl

12a: $R^2 = R^1$ = H
12b: R^2 = H, R^1 = phenyl
12c: R^2 = H, R^1 = 2-thienyl
13a: R^2 = phenyl, R^1 = H
13b: $R^2 = R^1$ = phenyl
14b: $R^2 = N(CH_3)_2$, R^1 = phenyl

15b: R^2 = O, R^1 = phenyl
15c: R^2 = O, R^1 = 2-thienyl
16b: R^2 = S, R^1 = phenyl
16c: R^2 = S, R^1 = 2-thienyl

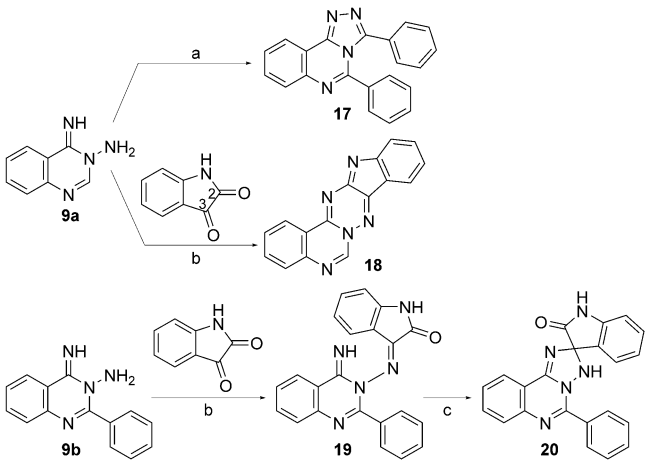
Scheme 1. Method A: a) R^1COCl, pyridine, $CHCl_3$, 0 °C (for **9a**: triethyl orthoformate, microwave irradiation, 20 min, 140 °C); b) hydrazine hydrate, microwave irradiation, 10 min, 120 °C; c) BrCN, K_2CO_3, EtOH, 10 h, 100 °C for **11a**–**m**; triethyl orthoformate, microwave irradiation, 10 min, 160 °C for **12a**–**c**; benzaldehyde, Et_3N, 3 h, 65 °C for **13a**; benzoyl chloride, microwave irradiation, 10 min, 160 °C for **13b**; *N*-(dichloromethylene)-*N*-methylmethanaminium chloride (Viehe's salt), K_2CO_3, CH_2Cl_2, 4 h, RT for **14b**; 1,1′-carbonyldiimidazole, toluene, 2 h, 100 °C for **15b** and **15c**; 1,1′-thiocarbonyldiimidazole, K_2CO_3, CH_2Cl_2/H_2O, 4 h, 0 °C→RT for **16c** and thiophosgene; DMF, 27 h, 60 °C for **16b**.

Synthetic methods

The synthesis of triazolo[1,5-*c*]quinazolines was essentially performed following two methods, A and B, and resulted in various products including unexpected poly-condensed heterocyclic structures, while methods C and D were only used to obtain derivatives bearing substituted amino and thio functions for R^1. In Method A, 4-iminoquinazoline-3-amines **9** were selected as versatile intermediates to prepare various [1,2,4]triazolo[1,5-*c*]quinazolines. The synthesis of **9a**–**l** was achieved by condensation of 2-aminobenzonitrile (**8**) with appropriate acyl halides in chloroform in the presence of pyridine as a base. The resulting 2-cyanobenzamides were subsequently reacted with hydrazine hydrate under microwave conditions.

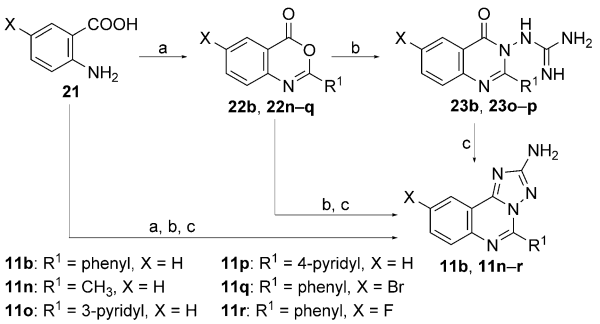
This constituted a new convenient route to produce diversity at position 5 (R^1, see Scheme 1). However, we observed that with aliphatic acyl halides the un-cyclized intermediates **10i–m** were formed in addition to **9i–m**. However, separation of the mixtures obtained was not necessary because both isomers led to the same [1,2,4]triazolo[1,5-*c*]quinazolines in the subsequent condensation step with all different reagents that were used to provide diversity at position 2 (R^2, see Scheme 1).

In some cases, Method A generated unexpected structures. The reaction of **9a** with a large excess of benzoyl chloride under harsh conditions (160 °C and microwave irradiation) yielded 3,5-diphenyl[1,2,4]triazolo[4,3-*c*]quinazoline (**17**), a regioisomer of **13b**. Both structures could be distinguished by their different ^{1}H NMR spectra. The reaction of **9a** with 2,3-indolindione led to a spontaneous cyclization yielding a polycyclic derivative. Supposing that in a first step the exocyclic amino-group of **9a** attacks the 3-carbonyl function of the 2,3-indolindione we suggest structure **18** for the deep-red-colored new compound. In contrast, the reaction of **9b** with 2,3-indolindione under the same conditions stopped at the stage of intermediate **19**, which was isolated and further converted into the spiro-compound **20** by heating in a solution of 10% phosphorus pentoxide in methanesulfonic acid (see Scheme 2).[16]



Scheme 2. Unexpected polycyclic structures obtained using Method A: a) benzoyl chloride, microwave irradiation, 10 min, 160 °C; b) EtOH, 30 min to 1 h, 100 °C; c) 10% P_2O_5/CH_3SO_3H, 170 °C.

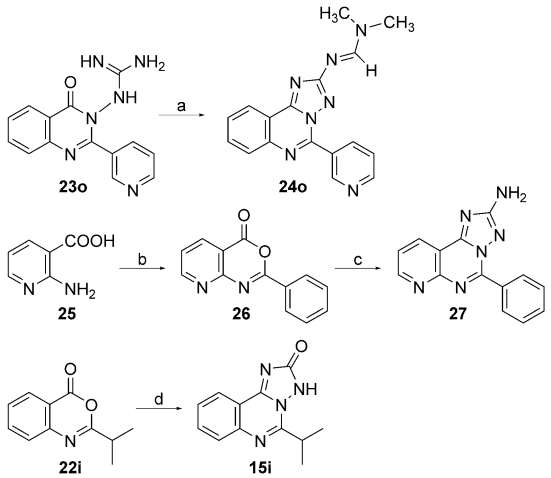
Method B was developed mainly to obtain 2-amino[1,2,4]-triazolo[1,5-*c*]quinazolines **11** with diversity at position 5 (R^1) and the benzene ring of the quinazoline core (see Scheme 3). The required 4*H*-1,3-benzoxazin-4-ones **22** were either purchased or prepared following literature procedures by reaction of 2-aminobenzoic acids **21** with appropriate acyl halides. Compounds **22b** and **22n–q** were reacted with aminoguanidine under microwave irradiation to produce guanidine intermediates **23** that were subsequently, either in situ or after isolation, treated with 10% phosphorus pentoxide in methanesulfonic acid to promote cyclization. Unfortunately, a microwave-assisted one-step procedure described in the literature proved



Scheme 3. Method B: a) R^1COCl/Ac_2O; b) aminoguanidine bicarbonate, pyridine, 24 h, 100 °C; c) 10% P_2O_5/CH_3SO_3H, 170 °C.

to be successful only for 5-methyl derivatives (**11n**, R^1 = Me) in our hands.[17]

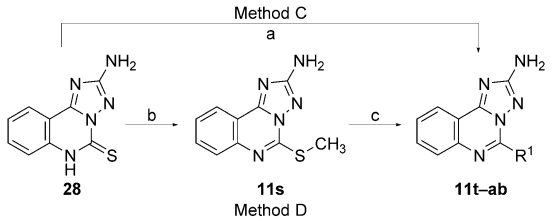
The reaction of **23o** with phosphorous pentoxide in DMF under reflux conditions yielded the corresponding dimethylformamidine derivative **24o** (Scheme 4). Starting from 2-aminonicotinic acid (**25**) and benzoyl chloride pyridooxazinone **26** was



Scheme 4. Synthesis of **24o**, **26**, **27**, and **15i**. a) 10% P_2O_5/DMF, reflux; b) benzoyl chloride, CH_2Cl_2, RT; c) 1. aminoguanidine, pyridine, 24 h at 100 °C, 2. 10% P_2O_5/CH_3SO_3H, 170 °C; d) semicarbazide, pyridine, microwave irradiation, 30 min, 160 °C.

formed, which was subsequently converted into 5-phenylpyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-2-amine (**27**) as the only final product with a nitrogen atom at the 7-position. Two methods were used to obtain [1,2,4]triazolo[1,5-*c*]quinazolin-4(3*H*)-ones **15**. The reaction of **9b** or **9c** with 1,1′-carbonyldiimidazole in toluene at 100 °C led to the final compounds **15b** and **15c**, respectively (see Scheme 1). Treatment of 2-isopropyl-benzo[d][1,3]oxazin-4-one (**22i**) with semicarbazide in pyridine for 30 min at 160 °C under microwave irradiation afforded 5-isopropyl[2,3-*e*][1,2,4]triazolo[1,5-*c*]quinazolin-4(3*H*)-one (**15i**, see Scheme 4).

2-Amino[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-thione (**28**), first described by Leistner and Wagner,[18] was identified as a suita-



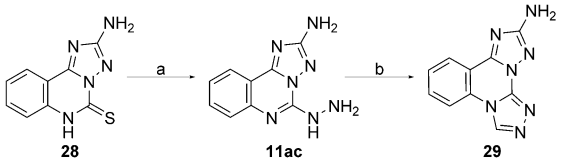
Method C:
11t: R^1 = *N*-pyrrolidinyl
11u: R^1 = *N*-piperidinyl
11v: R^1 = *N*-morpholinyl
11w: R^1 = *N*-butylamino
11x: R^1 = *N*-benzylamino

Method D:
11y: R^1 = *N*-hydroxyethylamino
11z: R^1 = *N*-2-phenylethyl-1-amino
11aa: R^1 = *N*-2-tetrahydrofurfurylamino
11ab: R^1 = *N*-pyridine-3-ylmethylamino

Scheme 5. Method C: corresponding amine, EtOH, 70 °C or corresponding amine, H_2O_2, 100 °C. Method D: a) CH_3I, $NaOH_{(aq)}$, MeOH, 30 min, RT; c) corresponding amine, 90 min, 120–140 °C.

ble precursor for preparing 2-amino[1,2,4]triazolo[1,5-*c*]quinazolines **11** with amino or thio substituents attached to position 5 (R^1) following Methods C and D (Scheme 5). Method C: heating of **28** with the appropriate amine either in the absence or in the presence of H_2O_2 yielded the target compounds **11 t–x**. Methylsulfanyl[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (**11 s**) was prepared by reaction of **28** with methyl iodide. This intermediate was used in Method D: heating of **11 s** with the appropriate amine led to derivatives **11 y–ab**.

Compound **28** was also reacted with hydrazine leading to 5-hydrazino[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (**11 ac**), which was finally cyclized with triethylorthoformate to form the tetracyclic compound **29** (Scheme 6). Similar polyheterocyclic compounds were first described by Pfeiffer et al.[19]



Scheme 6. Preparation of [1,2-4]triazolo[1,5-*c*]quinazolines **11 ac** and the tetracyclic system **29**: a) hydrazine hydrate, EtOH, 1 h, reflux; b) $(EtO)_3CH$, microwave irradiation, 20 min, 160 °C.

Biological evaluation

Radioligand binding at all four recombinant human AR subtypes expressed in Chinese hamster ovary (CHO) cells, and at native rat brain A_1 (cortex) and A_{2A} ARs (striatum) were performed. Selected compounds were additionally tested at rat A_{2B} and A_3 ARs expressed in CHO cells. Cell membrane preparations were used for binding studies using the following radioligands: [^{3}H]2-chloro-*N*^{6}-cyclopentyladenosine ([^{3}H]CCPA) for A_1ARs,[20] [^{3}H]3-(3-hydroxypropyl)-7-methyl-1-propargyl-8-(*m*-methoxystryryl)xanthine ([^{3}H]MSX-2) for A_{2A}ARs,[21] [^{3}H]8-(4-(4-(4-chlorophenyl)piperazine-1-sulfonyl)phenyl)-1-propylxanthine ([^{3}H]PSB-603 for A_{2B}ARs,[22] and [^{3}H]2-phenyl-8-ethyl-4-methyl-(8*R*)-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*i*]purin-5-one ([^{3}H]PSB-11) for human A_3ARs.[23] Because [^{3}H]PSB-11 is not suitable for the labeling of rat A_3ARs the agonist radioligand *N*-ethylcarboxamidoadenosine ([^{3}H]NECA) was used instead.[24] Initially compounds were screened at 10 μM unless otherwise noted. For potent compounds (K_i < 10000 nM at rat ARs or < 1000 nM at human ARs) full concentration–inhibition curves were recorded, and affinity constants (K_i values) were determined by nonlinear regression analysis (see the Experimental Section for further details). For less potent compounds only the percent inhibition at 1 or 10 μM was measured, unless otherwise stated. NaCl shift assays were performed for selected A_{2A} antagonists to confirm their antagonistic properties.

Structure–activity relationships

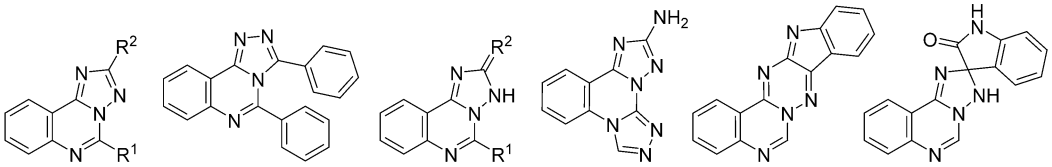
The affinities of the final compounds for the human (h) and rat (r) ARs are listed in Tables 1 and 2. [1,2,4]Triazolo[1,5-*c*]quinazolines **12 a–c** with R^2 = H displayed low affinity for the hAR subtypes regardless of the substitution pattern on R^1. Similar results were obtained with the rat AR subtypes, with the exception of a moderate affinity observed at the rA_1AR subtype with **12 c** having R^1 = 2-thienyl. [1,2,4]Triazolo[1,5-*c*]quinazolines **13 a** and **13 b** bearing phenyl at R^2 displayed moderate to high affinity for the hA_1 and hA_3 AR subtypes and moderate to low affinity for the rat AR subtypes regardless of the substitution pattern on R^1. Interestingly, differences in affinity were observed between **13 b** (R^1 = R^2 = phenyl) and its [1,3,4]triazolo isomer **17**. While the former was dually potent on hA_1 (K_i = 51.6 nM) and hA_3 (K_i = 11.1 nM), the latter was dually potent on hA_{2A} (K_i = 104 nM) and hA_3ARs (K_i = 1.16 nM).

Five [1,2,4]Triazolo[1,5-*c*]quinazolines bearing either O or S (R^2) were tested and revealed at best moderate affinity for some AR subtypes. Compound **15 b** (R^1 = phenyl, R^2 = O) showed weak affinity for rat A_1 and A_{2A}ARs. Compound **16 b** (R^1 = phenyl, R^2 = S) displayed moderate affinity and selectivity for the hA_3AR, while **15 i** (R^1 = isopropyl, R^2 = O) showed moderate affinity and selectivity for the rA_{2A}AR. Compound **16 c** (R^1 = 2-thienyl, R^2 = O) displayed weak affinity for the hA_1AR and moderate affinity for the hA_3AR, while **15 c** (R^1 = 2-thienyl, R^2 = S) had moderate affinity for the human (and rat) A_1 and A_{2A}ARs and the hA_3AR.

The heteropolycyclic derivatives **18** and **20** were found to be only potent at the hA_3AR with high selectivity versus all other AR subtypes. Most notably compound **20** showed a K_i value of 6.94 nM at the hA_3AR subtype.

Compared with the other substitution patterns, the amino group at position 2 seemed to be responsible for the increase in affinity at the A_1, A_{2A}, and A_{2B}AR subtypes. Compound **11 b** with R^1 = phenyl and R^2 = NH_2 displayed moderate to high affinities for the A_1, A_{2A} and A_{2B}AR subtypes (K_i rA_1 = 280 nM, K_i rA_{2A} = 38.0 nM, K_i hA_1 = 223 nM, K_i hA_{2A} = 79.2, K_i hA_{2B} = 178 nM) and was inactive at the A_3AR (K_i hA_3 > 1000 nM), while **14 b** with R^1 = phenyl, and a dimethylamino group at R^2 showed decreased affinity for the A_1, A_{2A} and A_{2B}AR subtypes (K_i rA_1 > 10000 nM, K_i rA_{2A} > 10000 nM, K_i hA_1 = 443 nM, K_i hA_{2A} = 421 nM, K_i hA_{2B} > 1000 nM) but good affinity for A_3AR (K_i hA_3 = 161 nM). An aromatic group at position 5 was found to be re-

Table 1. Binding affinities of triazolo[1,5-*c*]quinazolines and related polyheterocyclic compounds at rat and human adenosine receptor subtypes.



12a–c, **13a–b**, **24o**, **14b** | **17** | **15b–c**, **15i**, **16b–c** | **29** | **18** | **20**

Compd	R^1	R^2	K_i [nM][a] rA_1 vs. [^{3}H]CCPA	rA_{2A} vs. [^{3}H]MSX-2	hA_1 vs. [^{3}H]CCPA	hA_{2A} vs. [^{3}H]MSX-2	hA_{2B} or rA_{2B} vs. [^{3}H]PSB-603	hA_3 vs. [^{3}H]PSB-11 or rA_3 vs. [^{3}H]NECA
2	caffeine		41 000[25]	12 200 ± 1210	44 900[26]	5640 ± 539	33 800	13 300[27]
3	istradefylline		230[28]	4.46[29]	841[28]	91.2[28]	> 10 000[28]	4470[28]
6a	preladenant		68.7 ± 8.68	0.661 ± 0.126	295 ± 10	0.884 ± 0.232	> 1000	> 1000
12a	H	H	> 10 000 (0%)	> 10 000 (4%)	> 1000 (15%)	> 1000 (26%)	> 1000 (20%)	> 1000 (22%)
12b	phenyl	H	**1230** ± 110	> 10 000 (0%)	> 1000 (32%)	> 1000 (6%)	> 1000 (9%)	> 1000 (20%)
12c	2-thienyl	H	**377** ± 35	**7300** ± 1500	> 1000 (32%)	> 1000 (26%)	> 1000 (11%)	> 1000 (32%)
13a	H	phenyl	**630** ± 177	**2660** ± 290	**187** ± 20	> 1000 (31%)	> 1000 (27%)	**50.7** ± 7.2
13b	phenyl	phenyl	**1940** ± 153	> 10 000 (16%)	**51.6** ± 5.6	> 1000 (28%)	> 1000 (5%)	**11.1** ± 1.7
17	(see above)		> 10 000 (27%)	> 10 000 (10%)	> 1000 (5%)	**104** ± 5	> 1000 (12%)	**1.16** ± 0.39
15b	phenyl	O	**1350** ± 36	**1650** ± 257	> 1000 (37%)	> 1000 (44%)	> 1000 (23%)[b]	> 1000 (34%)
16b	phenyl	S	> 10 000 (9%)	> 10 000 (2%)	> 1000 (36%)	> 1000 (36%)	> 1000 (13%)	**107** ± 9
15c	2-thienyl	O	**130** ± 30	**437** ± 64	**388** ± 38	**442** ± 39	> 1000 (36%)	**477** ± 134
16c	2-thienyl	S	> 10 000 (13%)	> 10 000 (12%)	**950** ± 231	> 1000 (28%)	> 1000 (10%)	**357** ± 28
15i	isopropyl	O	> 10 000 (22%)	> 10 000 (8%)	> 1000 (27%)	> 1000 (47%)	> 1000 (0%)	> 1000 (15%)
24o	3-pyridyl	N=CHN(CH_3)$_2$	> 10 000 (37%)	**8100** ± 1550	**655** ± 8	**248** ± 77	> 1000 (36%)	> 1000 (34%)
14b	phenyl	N(CH_3)$_2$	> 10 000 (33%)	> 10 000 (32%)	**443** ± 57	**421** ± 143	> 1000 (17%)	**161** ± 24
29	(see above)		> 10 000 (12%)	> 10 000 (47%)	> 1000 (15%)	> 1000 (3%)	> 1000 (8%)	> 1000 (11%)
18	(see above)		> 10 000 (39%)	> 10 000 (18%)	> 1000 (39%)	> 1000 (44%)	> 1000 (6%)	(r) > 1000 (0%) **118** ± 9
20	(see above)		> 10 000 (19%)	> 10 000 (31%)	> 1000 (25%)	> 1000 (24%)	> 1000 (0%)	(r) > 1000 (11%) **6.94** ± 1.13

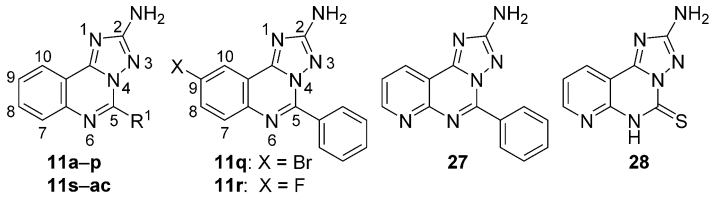
[a] Values are the mean ± SEM of $n = 3$ assays, each carried out in duplicate or triplicate; h = human, r = rat. [b] Percent inhibition at 0.3 μM.

quired for high affinity at the A_1 and A_{2A} as well as the A_{2B}AR subtypes. A notable exception were nitrogen-containing aromatics, such as in **11o** and **11p** (R^1 = 3- and 4-pyridyl, respectively), which were not tolerated leading to dramatically decreased affinity at all subtypes. The most potent compound was **11c** with R^1 = 2-thienyl (K_i rA_1 = 22.0 nM, K_i rA_{2A} = 21.5 nM, K_i hA_1 = 67.7 nM, K_i hA_{2A} = 13.6 nM, K_i hA_{2B} = 75.0 nM and K_i hA_3 = 703 nM). Highly potent derivatives were also obtained when R^1 was either phenyl, 3-thienyl or 2-furyl. Compound **11h** (R^1 = 2-furyl) was found to be a balanced pan-AR antagonist, which also showed high affinity for the hA_3AR (K_i hA_1 = 328 nM, K_i hA_{2A} = 28.2 nM, K_i hA_{2B} = 130 nM and K_i hA_3 = 101 nM). At rat ARs however, it only had high affinity for the A_1 and A_{2A}AR subtypes (K_i rA_1 = 87.0 nM, K_i rA_{2A} = 69.0 nM), but not for the rA_3AR. Halogen-containing aromatic residues at R^1 in **11d**, **11e** and **11f** decreased the affinity on the A_{2B}AR subtype relative to the parent **11b** leading to A_1/A_{2A} dual antagonists. The bromo-substituted derivative **11d** was well tolerated by the A_3AR.

The effects of modifications on the quinazoline ring were studied by comparing the AR affinities of **11b** to those of the fluoro- or bromo-substituted derivatives **11q** and **11r** as well as to **27** containing a nitrogen atom in the quinazoline ring. The fluoro substituent only moderately influenced the affinities at the ARs. In rat, the bromo substituent increased the affinity for the rA_1 and decreased it for rA_{2A}AR. In human, on the other hand, it slightly affected the affinities for hA_1, hA_{2A} and hA_{2B}, and significantly increased the affinity for the hA_3AR (K_i = 47.5 nM), leading to another balanced pan-AR antagonist. The nitrogen atom in **27** was also responsible for a moderate increase in the affinity for the A_3AR, but showed only minor influence on the affinities for the other receptor subtype.

Finally, [1,2,4]triazolo[1,5-*c*]quinazoline-2-amines bearing substituents connected by amino or thio groups at position 5 (R^1) (**28** and **11s–ac**) displayed lower affinities at the hA_{2B}AR than derivatives with aromatic residues (**11b** and **11e–p**). Nonetheless, two exceptions were observed: **11o** bearing a 3-pyridyl ring had no affinity for the hA_{2B}AR subtype, whereas **11z** bearing an *N*-2-phenethylamino residue had moderate affinity for this subtype. Similarly, R^1 = H or methyl decreased the affinity at all AR subtypes. The longer alkyl chain R^1 = isopropyl was only tolerated by the rA_1 and hA_{2A}ARs resulting in the selective potent antagonist **11i**. Benzyl and phenylethyl residues for R^1 were well tolerated by the hA_3AR and also to some extent by

Table 2. Binding affinities of 2-amino[1,2,3]triazolo[1,5-*c*]quinazolines **11** and related compounds for rat and human adenosine receptor subtypes.



11a–p
11s–ac

11q: X = Br
11r: X = F

27

28

Compd	R^1	K_i [nM][a]					
		rA_1 vs. [^{3}H]CCPA	rA_{2A} vs. [^{3}H]MSX-2	hA_1 vs. [^{3}H]CCPA	hA_{2A} vs. [^{3}H]MSX-2	hA_{2B} or rA_{2B} vs. [^{3}H]PSB-603	hA_3 vs. [^{3}H]PSB-11 or rA_3 vs. [^{3}H]NECA
11a	H	**4690** ± 379	**2170** ± 135	> 1000 (29%)	> 1000 (59%)	> 1000 (10%)	> 1000 (32%)
11n	methyl	> 10000 (31%)	**4450** ± 529	> 1000 (3%)	> 1000 (18%)	> 1000 (11%)	> 1000 (13%)
11i	isopropyl	**168** ± 15	**1920** ± 147	> 1000 (38%)	**89.5** ± 26.9	> 1000 (25%)	> 1000 (7%)
11j	benzyl	> 10000 (53%)	**1870** ± 67.0	> 1000 (38%)	> 1000 (42%)	> 1000 (14%)	**183** ± 35
11m	(*R*,*S*)-1-methylbenzyl	**1240** ± 215	**870** ± 212	**332** ± 113	**358** ± 89	> 1000 (11%)	**162** ± 26
11l	2-phenethyl	**4100** ± 1180	**5060** ± 1510	> 1000 (37%)	**964** ± 83	> 1000 (32%)	**178** ± 25
11k	2-(3,4,5-trimethoxyphenyl)ethyl	> 10000 (18%)	> 10000 (28%)	> 1000 (25%)	**640** ± 107	> 1000 (3%)	> 1000 (21%)
11b	phenyl	**280** ± 15	**38.0** ± 5.2	**223** ± 28	**79.2** ± 19.9	**178** ± 57	> 1000 (30%)
11e	3-fluorophenyl	**324** ± 109	**117** ± 27	**271** ± 78	**95.3** ± 24.3	> 1000 (42%)	> 1000 (19%)
11f	4-fluorophenyl	**3090** ± 714	**1710** ± 291	**408** ± 106	**134** ± 42	> 1000 (28%)	> 1000 (44%)
11d	4-bromophenyl	**90.3** ± 2.2	**985** ± 105	**130** ± 14	**231** ± 33	> 1000 (15%)	**60.4** ± 4.4
11c	2-thienyl	**22.0** ± 15.0	**21.5** ± 1.2	**67.7** ± 16.6	**13.6** ± 2.0	**75.0** ± 28.2	**703** ± 110
11g	3-thienyl	**87.0** ± 12.0	**55.5** ± 11.4	**353** ± 47	**51.2** ± 5.1	**198** ± 13	> 1000 (36%)
11h	2-furyl	**87.0** ± 6.0	**69.0** ± 15.0	**328** ± 33	**28.2** ± 5.7	(r) > 1000 (37%)	(r) > 1000 (1%)
						130 ± 7	**101** ± 25
11o	3-pyridyl	**1120** ± 130	**1360** ± 500	> 1000 (35%)	> 1000 (19%)	> 1000 (0%)	**41.7** ± 7.8
11p	4-pyridyl	**1090** ± 67	**420** ± 65	> 1000 (0%)	**464** ± 570	> 1000 (15%)	> 1000 (21%)
11q	(see above)	**87.0** ± 28.0	**150** ± 12	**131** ± 48	**32.7** ± 2.5	(r) **111** ± 38	(r) > 1000 (0%)
						150 ± 11	**47.5** ± 16.8
11r	(see above)	**220** ± 38	**54.8** ± 10.0	**342** ± 167	**145** ± 21	**345** ± 62	> 1000 (33%)
27	(see above)	**73.0** ± 10.0	**97.6** ± 16.5	**184** ± 24	**346** ± 139	**283** ± 42	**468** ± 54
28	S	> 10000 (17%)	> 10000 (43%)	> 1000 (32%)	> 1000 (20%)	> 1000 (2%)	> 1000 (0%)
11s	S-methyl	**962** ± 207	**303** ± 78	**785** ± 181	**247** ± 47	> 1000 (41%)	> 1000 (46%)
11t	*N*-pyrrolidinyl	**864** ± 197	**274** ± 44	**708** ± 197	**338** ± 38	> 1000 (21%)	> 1000 (18%)
11u	*N*-piperidinyl	**2650** ± 164	**845** ± 44	> 1000 (32%)	**535** ± 21	> 1000 (20%)	> 1000 (33%)
11v	*N*-morpholinyl	> 10000 (34%)	**5450** ± 930	> 1000 (2%)	> 1000 (30%)	> 1000 (12%)	> 1000 (8%)
11w	*N*-butylamino	**555** ± 74	**208** ± 41	**892** ± 351	**300** ± 90	> 1000 (27%)	**438** ± 53
11x	*N*-benzylamino	> 10000 (49%)	**2540** ± 661	**244** ± 38	**149** ± 17	> 1000 (29%)	**239** ± 29
11y	*N*-hydroxyethylamino	**1730** ± 420	**2080** ± 40	> 1000 (24%)	> 1000 (34%)	> 1000 (9%)	> 1000 (25%)
11z	*N*-2-phenethylamino	> 10000 (41%)	**7230** ± 147	> 1000 (1%)	**72.0** ± 7.8	**394** ± 28	**241** ± 56
11aa	*N*-2-tetrahydrofurfurylamino	**2280** ± 284	**1340** ± 135	> 1000 (40%)	**502** ± 17	> 1000 (22%)	> 1000 (9%)
11ab	*N*-3-pyridine-3-ylmethylamino	> 10000 (0%)	> 10000 (0%)	> 1000 (17%)	**527** ± 38	> 1000 (33%)	> 1000 (33%)
11ac	NH–NH_2	> 10000 (27%)	> 10000 (48%)	> 1000 (27%)	> 1000 (38%)	> 1000 (14%)	> 1000 (18%)

[a] Values are the mean ± SEM of $n = 3$ assays, each carried out in duplicate or triplicate; h = human, r = rat.

the hA_{2A}AR, while the bulkier derivative **11k** (trimethoxyphenylethyl-substituted) was only moderately tolerated by the hA_{2A}AR.

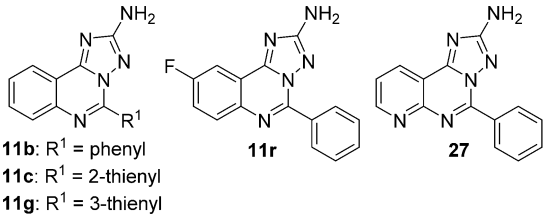
Species differences

Differences in affinities between species were noted for several compounds. The most potent compounds on either rA_1 or rA_{2A}ARs also showed high affinity for either hA_1 or hA_{2A}ARs. However, several compounds displayed significant affinity for the hAR subtypes, but not for the rat subtypes (e.g., **11x**, **11z**, **14b**, and **24o**). Species differences are particularly high for the A_3 receptor, as typically observed for A_3 antagonists.[1,28] This was demonstrated for the potent A_3-selective antagonist **18**. Such differences between species highlight the possible errors in extrapolating results between species and emphasize the importance of determining the affinity constants on the species of interest, for example, on receptors of rodents that are used in preclinical studies.

Functional properties

The antagonistic character of 2-amino[1,2,4]triazolo[1,5-*c*]quinazolines and analogues was confirmed by sodium chloride shift experiments at the A_{2A}ARs using the following procedure. Concentration-dependent inhibition of [^{3}H]MSX-2 binding to rat brain striatal membranes was measured in the presence and absence of 100 mM sodium chloride. The agonist 5′-*N*-ethylcarboxamidoadenosine (NECA), which was used as a reference compound, displays a 16-fold shift. In contrast, for the selected

Table 3. Sodium shift assays of selected triazolo[1,5-*c*]quinazolines.



11b: R^1 = phenyl
11c: R^1 = 2-thienyl
11g: R^1 = 3-thienyl

Compd	IC_{50} [nM][a,c]	IC_{50} [nM][b,c]	Shift
NECA	**109** ± 29	**1740** ± 21	16-fold
11b	**38.0** ± 5.2	**91.5** ± 25.5	2.4-fold
11c	**21.5** ± 1.2	**48.7** ± 9.1	2.2-fold
11g	**55.5** ± 11.4	**94.7** ± 18.7	1.7-fold
11r	**54.8** ± 10.0	**144** ± 23	2.6-fold
27	**97.6** ± 16.5	**119** ± 10	1.2-fold

[a] In the absence of NaCl. [b] In the presence of 100 mM NaCl. [c] Measured at the A_{2A}AR of rat brain striatal membrane preparations; values are the mean ± SEM (n = 3, except for NECA: n = 4), with each assay carried out in duplicate or triplicate.

2-amino[1,2,4]triazolo[1,5-*c*]quinazoline derivatives (**11b**,**c**,**g**,**r**) and the aza-analogue **27**, the presence of sodium chloride did not have a significant influence on the binding affinity (shift < 3-fold, Table 3). These results confirm that the compounds act as antagonists.

Conclusions

In this study we identified 2-aminotriazolo[1,5-*c*]quinazolines as a potent class of AR antagonists. Novel pathways for the synthesis of such derivatives were developed, and we prepared a series of 48 final products. SARs were explored on all four AR subtypes. Besides compounds that bind to several AR subtypes with high potency, A_3-selective derivatives with low nanomolar K_i values were discovered.

Experimental Section

Biology

Radioligands were obtained from the following sources: [^{3}H]CCPA from Amersham (58 Ci mmol^{-1}), [^{3}H]MSX-2 from Amersham (84 Ci mmol^{-1}), [^{3}H]PSB-603 from Amersham (73 Ci mmol^{-1}), [^{3}H]PSB-11 (53 Ci mmol^{-1}) from Quotient Biosciences, and [^{3}H]NECA (15.5 Ci mmol^{-1}) from PerkinElmer. Some of the precursors were synthesized in our laboratory. Membranes from Chinese hamster ovary (CHO) cells stably transfected with either human A_1, human A_{2A}, human A_{2B}, rat A_{2B}, or human A_3 AR were prepared as described previously[22,23,30] and used in radioligand binding assays. Commercially available membrane preparations containing rat A_3AR expressed in human embryonic kidney (HEK) cells were obtained from Biotrend (Cologne, Germany). Frozen rat brains obtained from Pel Freez, Rogers, AR (USA) were dissected as previously described to obtain either cortical membrane preparations[20,21,24,31] for A_1AR assays, or striatal membrane preparations for A_{2A}AR assays.

Radioligand binding assays: Stock solutions of the compounds were prepared in dimethyl sulfoxide (DMSO); the final concentration of DMSO was 2.5%. The radioligand concentrations were: [^{3}H]CCPA, 0.5 nM (rat and human A_1); [^{3}H]MSX-2 1.0 nM (rat and human A_{2A}); [^{3}H]PSB-603, 0.3 nM (rat and human A_{2B}); [^{3}H]PSB-11, 0.5 nM (human A_3); [^{3}H]NECA, 10 nM (rat A_3). Binding assays were performed as described previously.[20,21,23,32,33] About 30–70 μg mL^{-1} of protein were used in the assays. At least three separate experiments were performed, each in duplicate or triplicate. Data were analyzed with GraphPad Prism ver. 4 (San Diego, CA, USA). For calculation of K_i values by nonlinear regression analysis, the Cheng–Prusoff equation and K_D values of 0.5 nM (rat A_1); 0.61 nM (human A_1) for [^{3}H]CCPA, 8 nM for [^{3}H]MSX-2 (human and rat A_{2A}); 0.41 nM for [^{3}H]PSB-603 (human A_{2B}); 0.2 nM (rat A_{2B}); 4.9 nM for [^{3}H]PSB-11 (human A_3); and 48 nM for [^{3}H] NECA (rat A_3) were used. Sodium shift assays were performed as previously described.[34]

Chemistry

Microwave-assisted reactions were carried out in 10 mL sealed glass tubes in a focused mono-mode microwave oven ("Discover", CEM Corporation, Matthews, NC, USA). Mass spectra were recorded on an API 2000 mass spectrometer (electrospray ion source, Applied Biosystems, Darmstadt, Germany) coupled with an Agilent 1100 HPLC system using a Macherey–Nagel Nucleodur C_{18} Gravity 3 μm column (50 × 2.00 mm, particle size: 3 μm) that was used to measure purity of the compounds. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer. Chemical shifts are referenced to residual solvent signals, and coupling constants are reported in Hz. ^{13}C NMR spectra were recorded for selected compounds from each subfamily only, or if necessary for structural assignment. Starting materials **22b**,[35] **22i**,[36] **22o**,[35] **22p**,[37] **22q**,[38] **26**,[39] **28**,[18] and **30**[40] were prepared according to published procedures. Syntheses of products **11b**,[41] **11n**,[41b,c] **12b**,[42] **13a**,[43] **13b**,[42,43b,44] **15b**,[45] and **16b**[45,46] were previously reported. (*R*,*S*)-2-Phenylpropionyl chloride and 3-(3,4,5-trimethoxyphenyl)propionyl chloride were prepared from the corresponding acids. Purification by column chromatography was performed with silica gel 60. All commercially available reagents and solvents were used without further purification. The petroleum ether (PE) used had a boiling point of 40–60 °C.

General procedure 1: in a first step, 2-aminobenzonitrile (**8**, 2.36 g, 20 mmol) and pyridine (2.0 g, 25 mmol) were dissolved in anhydrous $CHCl_3$ (20 mL) and cooled to 0 °C. To this mixture, a solution of the corresponding acyl chloride (24 mmol) in anhydrous $CHCl_3$ (20 mL) was slowly added. After stirring for 5 h at RT, all volatile components were removed under reduced pressure. Water (40 mL) and solid sodium carbonate were added to the residue until pH 9 was reached. After vigorous stirring, the precipitate was collected and washed with cold water (20 mL). The 2-cyanobenzamides thus obtained were dried at 110 °C and used without further purification. In a second step, the 2-cyanobenzamide (5.0 mmol) and hydrazine hydrate (2 g, 40 mmol) were heated under microwave conditions (120 °C, 40 W) for 10 min. After the addition of EtOH (2 mL) the mixture was heated at 70–80 °C and then left at 4 °C for several hours. The precipitate (**9** or a mixture of **9** and **10**, respectively) was collected, washed with EtOH (2 × 2 mL) and dried at 80 °C.

General procedure 2: the starting 4-iminoquinazoline-3-amine **9** and either triethyl orthoformate for R^2 = H or the corresponding benzoyl halide for R^2 = benzyl were stirred at 160 °C under microwave irradiation (60 W) for 10 min. EtOH (5 mL) was added, and the mixture was heated at 80 °C, then left at 4 °C overnight. A precipitate was formed, which was collected, washed with EtOH (2 × 1 mL) and dried at 80 °C.

General procedure 3: the appropriate 4-iminoquinazoline-3-amine **9** (0.5 mmol), potassium carbonate (0.14 g, 1.0 mmol), cyanogen bromide (64 mg, 0.6 mmol) and EtOH (5 mL) were heated at 100 °C in a sealed glass tube for 10 h. Several times during the reaction, the mixture was cooled to 50 °C in order to safely release the formed gas. Thereafter, the mixture was allowed to cool to RT, water (10 mL) was added and the solution was left at 4 °C overnight. The formed precipitate was collected, washed with water (10 mL) and EtOH (2 mL) then dried at 100 °C.

General procedure 4: the appropriate (4*H*)-3,1-benzoxazin-4-one **22** (1.0 mmol), aminoguanidine bicarbonate (0.20 g, 1.5 mmol), and pyridine (2 mL) were stirred at 100 °C for 24 h. After cooling to RT, the suspension was acidified to pH ~1 using HCl (2 N) and subsequently filtered. The filtrate was neutralized with solid sodium carbonate and left at 4 °C overnight. The formed precipitate was collected, washed with water (2×5 mL) and dried at 100 °C.

General procedure 5: starting from the appropriate guanidine derivative **23** (0.5 mmol) 10% phosphorus pentoxide in methanesulfonic acid (1 mL) were added. The suspension was heated at 170 °C until white fumes emerged (~1 min). After cooling to RT, water (2 mL) was added and solid sodium carbonate was used to bring the solution to neutral pH, at which a precipitate formed. It was collected, washed with water (2 mL) and dried at 100 °C.

General procedure 6: the appropriate (4*H*)-3,1-benzoxazin-4-one **22** (1.0 mmol), aminoguanidine bicarbonate (0.20 g, 1.5 mmol), and pyridine (2 mL) were stirred at 100 °C for 24 h. After cooling to RT, the suspension was acidified to pH ~1 using HCl (2 N) and filtered. The filtrate was neutralized with solid sodium carbonate and left at 4 °C overnight. The formed precipitate was collected, washed with water (2×5 mL), dried, and then suspended in a 10% phosphorus pentoxide in methanesulfonic acid (2 mL). The suspension was heated at 170 °C until white fumes emerged (~1 min). After cooling to RT, water (5 mL) was added, and solid sodium carbonate was used to bring the solution to neutral pH, at which a precipitate formed. It was collected, washed with water (5 mL), and dried at 100 °C.

General procedure 7: a mixture of **28** (0.11 g, 0.5 mmol) and the appropriate amine (2 mL) was stirred at 60 °C. A 30% solution of aqueous hydrogen peroxide was added slowly until no remaining compound **28** could be detected by TLC. After cooling to RT, water (10 mL) was added. The formed precipitate was collected, washed with water (10 mL) and dried at 100 °C.

General procedure 8: a mixture of **11 s** (0.12 g, 0.5 mmol) and the appropriate amine (2 mL) was heated at 120 °C for an appropriate time. The resulting solution was allowed to cool to RT, then water (5 mL) was added, and the mixture was kept at 4 °C overnight. The formed precipitate was collected, washed with water (10 mL), and dried at 100 °C.

Synthesis of triazoloquinazolines using Method A

4-Iminoquinazolin-3-amine (9 a): 2-aminobenzonitrile (2.36 g, 20 mmol) and triethyl orthoformate (3.7 g, 25 mmol) were placed in a microwave tube and stirred at 140 °C under microwave irradiation (60 W) for 20 min. After removal of all volatiles at 80 °C under reduced pressure, the remaining residue was stirred at RT for 16 h in EtOH (2 mL) in the presence of hydrazine hydrate (1.5 g, 30 mmol). The resulting precipitate was collected, washed with EtOH (2×4 mL) and dried at 80 °C to yield **9 a** as a yellow solid (1.93 g, 60%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.54 (br s, 1H, NH), 8.20 (dd, J = 1.3 Hz, J = 7.9 Hz, 1H), 7.95 (br s, 1H), 7.58 (dt, J = 1.3 Hz, J = 7.6 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 5.60 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 161 (100) [*M* + H]$^+$, purity: 94.1%.

4-Imino-2-phenylquinazolin-3-amine (9 b): following general procedure 1, starting from benzoyl chloride and 2-aminobenzonitrile, **9 b** was obtained as a yellow solid (0.71 g, 60%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.63 (s, 1H, NH), 8.56 (m, 2H), 8.19 (d, J = 8.2 Hz, 1H), 7.74 (m, 2H), 7.49 (m, 3H), 7.44 (ddd, J = 2.7 Hz, J = 5.4 Hz, J = 8.2 Hz, 1H), 4.89 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 237 (100) [*M* + H]$^+$, purity: 96.3%.

4-Imino-2-(2-thienyl)quinazolin-3-amine (9 c): following general procedure 1, starting from 2-thiophenecarbonyl chloride and 2-aminobenzonitrile, **9 c** was obtained as a yellow solid (0.42 g, 35%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.68 (s, 1H, NH), 8.15 (d, J = 8.2 Hz, 1H), 8.03 (dd, J = 1.3 Hz, J = 3.6 Hz, 1H), 7.71 (t, J = 7.3 Hz, 1H), 7.66 (m, 2H), 7.40 (t, J = 7.1 Hz, 1H), 7.17 (dd, J = 3.6 Hz, J = 5.1 Hz, 1H), 4.87 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 243 (100) [*M* + H]$^+$, purity: 94.7.

2-(4-Bromophenyl)-4-iminoquinazolin-3-amine (9 d): following general procedure 1, starting from 4-bromobenzoyl chloride and 2-aminobenzonitrile **9 d** was obtained as an off-white solid (0.85 g, 54%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.68 (s, 1H, NH), 8.51 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 3.8 Hz, 2H), 7.68 (dt, J = 1.9 Hz, J = 8.5 Hz, 2H), 7.45 (dt, J = 4.1 Hz, J = 8.2 Hz, 1H), 4.90 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 317 (97), 315 (100) [*M* + H]$^+$, purity: 94.6%.

2-(3-Fluorophenyl)-4-iminoquinazolin-3-amine (9 e): following general procedure 1, starting from 3-fuorobenzoyl chloride and 2-aminobenzonitrile, **9 e** was obtained as off-white crystals (0.60 g, 47%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.69 (s, 1H, NH), 8.40 ppm (d, J = 7.6 Hz, 1H), 8.31 (dquart, J = 1.3 Hz, J = 10.7 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.45 (ddd, J = 3.2 Hz, J = 4.7 Hz, J = 8.2 Hz, 1H), 7.76 (m, 2H), 7.53 (dt, J = 6.0 Hz, J = 7.9 Hz, 1H), 7.31 (dt, J = 2.5 Hz, J = 8.0 Hz, 1H), 4.91 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 255 (100) [*M* + H]$^+$, purity: 98.3%.

2-(4-Fluorophenyl)-4-iminoquinazolin-3-amine (9 f): following general procedure 1 starting from 4-fluorobenzoyl chloride and 2-aminobenzonitrile, a mixture was obtained as orange crystals. Analytically pure **9 f** was obtained after column chromatography (SiO$_2$, CHCl$_3$/MeOH 98:2, 0.71 g, 56%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.66 (s, 1H, NH), 8.61 (dd, J = 5.7 Hz, J = 8.8 Hz, 2H), 8.18 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 3.8 Hz, 2H), 7.43 (quint, J = 4.1 Hz, 1H), 7.31 (dt, J = 2.4 Hz, J = 8.8 Hz, 2H), 4.89 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 255 (100) [*M* + H]$^+$, purity: 99.5%.

4-Imino-2-(3-thienyl)quinazolin-3-amine (9 g): following general procedure 1, starting from 3-thiophenecarbonyl chloride and 2-aminobenzonitrile, **9 g** was obtained as a yellow solid (0.50 g, 51%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.59 (s, 1H, NH), 8.45 (dd, J = 1.3 Hz, J = 3.2 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 4.7 Hz, 1H), 7.69 (m, 2H), 7.58 (dd, J = 3.2 Hz, J = 4.7 Hz, 1H), 7.40 (t, J = 6.5 Hz, 1H), 4.89 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 243 (100) [*M* + H]$^+$, purity: 89.7%.

4-Imino-2-(2-furyl)quinazolin-3-amine (9 h): following general procedure 1, starting from 2-furoyl chloride and 2-aminobenzonitrile, **9 h** was obtained as a yellow solid (0.19 g, 33%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.64 (s, 1H, NH), 8.14 (d, J = 8.2 Hz, 1H), 7.84 (s, 1H), 7.70 (m, 2H), 7.40 (m, 1H), 7.35 (dd, J = 0.9 Hz, J = 3.5 Hz, 1H), 6.65 (dd, J = 1.7 Hz, J = 3.3 Hz, 1H), 4.84 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 227 (100) [*M* + H]$^+$, purity: 91.1%.

4-Imino-2-isopropylquinazolin-3-amine (9i) and *N*-(2-cyanophenyl)-isopropylcarboximidic acid hydrazide (10i): according to general procedure 1, starting from isobutyryl chloride and 2-aminobenzonitrile, a clear green solution evolved after the addition of EtOH, from which green oil separated upon the addition of water (10 mL). The supernatant was decanted and the residual oil taken up in diethyl ether. After solvent evaporation PE was added, leading to a yellow solid which was collected washed with PE and dried at 60 °C, to yield a yellow solid mixture (0.39 g, 38%).

4-Imino-2-isopropylquinazolin-3-amine (9i) (70% of the ^{1}H NMR signals): ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.45 (s, 1H, NH), 8.10 (d, J = 8.5 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 4.71 (s, 2H, NH$_2$), 2.96 (hept, J = 6.8 Hz, 1H), 1.35 ppm (d, J = 6.9 Hz, 6H); MS (EI, 70 eV) *m/z* (%): 203 (100) $[M+H]^+$, purity: 68.4%.

***N*-(2-Cyanophenyl)isopropylcarboximido acid hydrazide (10i) (30% of the ^{1}H NMR signals)**: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.31 (s, 1H, NH), 7.60 (d, J = 8.2 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.02 (t, J = 7.1 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 5.79 (s, 2H, NH$_2$), 2.59 (hept, J = 6.9 Hz, 1H), 1.20 ppm (d, J = 6.7 Hz, 6H); MS (EI, 70 eV) *m/z* (%): 203 (100) $[M+H]^+$, purity: 28.0%.

2-Benzyl-4-iminoquinazolin-3-amine (9j) and *N*-(2-cyanophenyl)-2-phenylacetimidic acid hydrazide (10j): according to general procedure 1, starting from phenylacetic acid (2-cyanophenyl)amide (**30**) (5.0 mmol) and hydrazine hydrate (40 mmol), yielded a green solid mixture (0.19 g, 37%).

2-Benzyl-4-iminoquinazolin-3-amine (9j) (67% of the ^{1}H NMR signal): ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.55 (s, 1H, NH), 8.09 (m, 1H), 7.67 (m, 1H), 7.61 (m, 1H), 7.15–7.43 (m), 4.72 (s, 2H, NH$_2$), 4.02 ppm (s, 2H); MS (EI, 70 eV) *m/z* (%): 251 (100) $[M+H]^+$, purity: 66.5%

***N*-(2-Cyanophenyl)-2-phenylacetimidic acid hydrazide (10j) (33% of the ^{1}H NMR signal)**: 1H NMR (500 MHz, [D$_6$]DMSO): δ = 10.66 (s, 1H, NH), 7.61 (m, 1H), 7.15–7.43 (m, 8H), 7.04 (m, 1H), 6.93 (m, 1H), 5.76 (s, 2H, NH$_2$), 3.65 ppm (s, 2H); MS (EI, 70 eV) *m/z* (%): 251 (100) $[M+H]^+$, purity: 31.1%.

2-(3,4,5-Trimethoxyphenethyl)-4-iminoquinazolin-3-amine (9k) and *N*-(2-cyanophenyl)-2-(3,4,5-trimethoxyphenyl)propionic imido acid hydrazide (10k): according to procedure 1, starting from 3-(3,4,5-trimethoxyphenyl)propionyl chloride and 2-aminobenzonitrile, a clear yellow solution evolved after the addition of EtOH. The green solid precipitate formed upon addition of water (20 mL) was filtered off, washed with water (2×4 mL), and dried in a desiccator, to yield a green solid mixture (0.12 g, 33%).

2-(3,4,5-Trimethoxyphenethyl)-4-iminoquinazolin-3-amine (9k) (70% of the ^{1}H NMR signal): ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.51 (s, 1H, NH), 7.67 (t, J = 7.6 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H),7.38 (t, J = 7.1 Hz, 1H), 6.57 (s, 2H), 4.73 (s, 2H, NH$_2$), 3.71 (s, 6H), 3.60 (s, 3H), 3.04 ppm (m, 4H); MS (EI, 70 eV) *m/z* (%): 355 (100) $[M+H]^+$, purity: 67.5%.

***N*-(2-Cyanophenyl)-2-(3,4,5-trimethoxyphenyl)propionic imido acid hydrazide (10k) (30% of the ^{1}H NMR signal)**: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.47 (s, 1H, NH), 7.60 (d, J = 8.2 Hz, 1H), 7.22 (t, J = 7.1 Hz, 1H), 7.03 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.59 (s, 2H), 5.82 (s, 2H, NH$_2$), 3.72 (s, 6H), 3.61 (s, 3H), 2.95 (t, J = 8.0 Hz, 2H), 2.66 ppm (t, J = 7.9 Hz, 2H); MS (EI, 70 eV) *m/z* (%): 355 (100) $[M+H]^+$, purity: 28.6%.

2-Phenethyl-4-iminoquinazolin-3-amine (9l) and *N*-(2-cyanophenyl)-2-phenylacetimidic acid hydrazide (10l): according to general procedure 1, starting from 3-phenylpropanoyl chloride and 2-aminobenzonitrile, a clear yellow solution evolved after the addition of EtOH. Water (20 mL) was mixed with the ethanolic solution and the products were extracted in $CHCl_3$ (2×20 mL). The organic phases were combined and washed with brine (2×10 mL), dried over $MgSO_4$, filtered, and solvents were evaporated under reduced pressure to yield a green oily mixture (0.51 g, 96%).

2-Phenethyl-4-iminoquinazolin-3-amine (9l) (38% of the ^{1}H NMR signals): ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.48 (s, 1H, NH), 8.09 (dd, J = 1.3 Hz, J = 7.9 Hz, 1H), 7.54 (dt, J = 1.6 Hz, J = 7.6 Hz, 1H), 7.13–7.30 (m), 7.37 (d, J = 7.3 Hz, 1H), 4.12 (s, 2H, NH$_2$), 3.00 (m, 2H), 2.94 ppm (m, 2H); MS (EI, 70 eV) *m/z* (%): 265 (100) $[M+H]^+$, purity: 36.2%.

***N*-(2-Cyanophenyl)-3-phenylpropanimidic acid hydrazide (10l) (62% of the ^{1}H NMR signals)**: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.92 (s, 1H, NH), 7.35 (dd, J = 1.6 Hz, J = 7.9 Hz, 1H), 7.13–7.30 (m), 6.78 (d, J = 8.5 Hz, 1H), 6.57 (dt, J = 1.3 Hz, J = 7.6 Hz, 1H), 5.97 (s, 2H, NH$_2$), 2.80 (t, J = 7.7 Hz, 2H), 2.31 ppm (t, J = 7.8 Hz, 2H); MS (EI, 70 eV) *m/z* (%): 265 (100) $[M+H]^+$, purity: 59.7%.

[1,2,4]Triazolo[1,5-*c*]quinazoline (12a): following general procedure 2, starting from **9a** (80 mg, 0.5 mmol) and triethyl orthoformate (1 mL), the product obtained was collected recrystallized from EtOH (2 mL) then dried at 80 °C to yield golden platelets (36 mg, 42%), purity: 99.9%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.24 (s, 1H), 8.55 (ddd, J = 0.8 Hz, J = 1.6 Hz, J = 7.9 Hz, 1H), 8.42 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.86 (ddd, J = 1.3 Hz, J = 6.9 Hz, J = 8.5 Hz, 1H), 7.76 ppm (ddd, J = 1.2 Hz, J = 7.3 Hz, J = 8.2 Hz, 1H); MS (EI, 70 eV) *m/z* (%): 171 (100) $[M+H]^+$, purity: 99.9%.

5-Phenyl[1,2,4]triazolo[1,5-*c*]quinazoline (12b): following general procedure 2, starting from **9b** (0.12 g, 0.5 mmol) and triethyl orthoformate (1 mL) the product was obtained as light-yellow needles (0.10 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.95 (s, 1H), 8.67 (d, J = 7.9 Hz, 1H), 8.03 (dd, J = 0.8 Hz, J = 8.2 Hz, 1H), 7.93 (m, 2H), 7.81 (dt, J = 1.6 Hz, J = 7.7 Hz, 1H), 7.72 (dt, J = 1.3 Hz, J = 7.6 Hz, 1H), 7.65 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.5, 141.5, 136.0, 132.3, 132.2, 132.0, 129.5 (2C), 129.4, 148.5, 128.7, 128.5 (2C), 123.7, 115.7 ppm; MS (EI, 70 eV) *m/z* (%): 147 (100) $[M+H]^+$, purity: 99.9%.

5-(2-Thienyl)[1,2,4]triazolo[1,5-*c*]quinazoline (12c): following general procedure 2, starting from **9c** (0.12 g, 0.5 mmol) and triethyl orthoformate (1 mL), the product was obtained as a colorless solid (0.07 g, 55%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.85 (s, 1H), 8.49 (ddd, J = 0.5 Hz, J = 1.6 Hz, J = 8.5 Hz, 1H), 8.30 (dd, J = 0.9 Hz, J = 3.8 Hz, 1H), 8.03 (dd, J = 0.9 Hz, J = 5.0 Hz, 1H), 7.85 (ddd, J = 1.6 Hz, J = 7.3 Hz, J = 8.2 Hz, 1H), 7.95 (m, 1H), 7.75 (ddd, J = 1.2 Hz, J = 7.3 Hz, J = 7.9 Hz, 1H), 7.36 ppm (dd, J = 3.8 Hz, J = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 147.8, 140.8, 139.6, 137.1, 135.3, 132.8, 132.1, 131.3, 129.0, 128.9, 127.9, 122.9, 115.5 ppm; MS (EI, 70 eV) *m/z* (%): 253 (100) $[M+H]^+$, purity: 98.8%.

2-Phenyl[1,2,4]triazolo[1,5-*c*]quinazoline (13a): 4-imino-quinazolin-3-amine (**9a**) (0.16 g, 1.0 mmol), benzaldehyde (0.2 g, 2.0 mmol), EtOH (5 mL) and a drop of triethylamine were stirred at 65 °C for 3 h. The mixture was cooled to RT and kept at 4 °C overnight. The precipitate formed was collected, washed with EtOH (2×1 mL) and dried at 80 °C to yield a colorless, cotton-like solid (0.11 g, 43%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.23 (s, 1H); 8.61 (dd, J = 1.0 Hz, J = 7.6 Hz, 1H), 8.34 (m, 2H), 8.06 (d, J = 8.5 Hz, 1H), 7.85 (ddd, J = 1.6 Hz, J = 7.3 Hz, J = 8.5 Hz, 1H), 7.75 (dt, J = 1.3 Hz, J = 7.6 Hz, 1H), 7.50 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.1, 151.4, 142.9, 137.7, 132.0, 130.6, 130.0 (2C), 129.0, 128.9, 128.8, 127.6 (2C),

123.8, 118.2 ppm; MS (EI, 70 eV) *m/z* (%): 247 (100) $[M+H]^+$, purity: 99.9%.

2,5-Diphenyl[1,2,4]triazolo[1,5-*c*]quinazoline (13 b): following general procedure 2, starting from **9 b** (0.12 g, 0.5 mmol) and benzoyl chloride (1 mL), the product was obtained as colorless solid (0.08 g, 51%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.64$ (m, 3H), 8.40 (dd, $J=1.3$ Hz, $J=7.9$ Hz, 2H), 8.11 (d, $J=8.2$ Hz, 1H), 7.84 (t, $J=7.7$ Hz, 1H), 7.71 (t, $J=7.4$ Hz, 1H), 7.61 (m, 3H), 7.51 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=163.9$, 152.9, 146.5, 143.0, 132.1, 131.8, 131.6, 130.5 (2C), 130.2, 128.8 (2C), 128.4 (br, 3C), 128.3 (2C), 127.7 (2C), 123.9, 117.3 ppm; MS (EI, 70 eV) *m/z* (%): 323 (100) $[M+H]^+$, purity: 98.9%.

[1,2,4]Triazolo[1,5-*c*]quinazolin-2-amine (11 a): starting from **9 a** and following general procedure 3, a light-orange solid was obtained (53 mg, 39%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=9.21$ (s, 1H), 8.23 (dd, $J=1.3$ Hz, $J=8.2$ Hz, 1H), 7.94 (d, $J=7.9$ Hz, 1H), 7.83 (ddd, $J=1.6$ Hz, $J=7.0$ Hz, $J=8.5$ Hz, 1H), 7.71 (dt, $J=1.3$ Hz, $J=7.6$ Hz, 1H), 6.42 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, $[D_6]$DMSO): $\delta=166.5$, 149.9, 142.7, 137.9, 131.6, 128.3, 128.2, 123.0, 116.4 ppm; MS (EI, 70 eV) *m/z* (%): 186 (100) $[M+H]^+$, purity: 98.0%.

5-Phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 b): starting from **9 b** and following general procedure 3, a colorless solid was isolated (102 mg, 78%). The synthesis of this compound is also described following Method B. ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=8.45$ (m, 2H), 8.27 (ddd, $J=0.6$ Hz, $J=1.6$ Hz, $J=7.9$ Hz, 1H), 7.99 (dt, $J=0.8$ Hz, $J=7.9$ Hz, 1H), 7.85 (ddd, $J=1.6$ Hz, $J=7.3$ Hz, $J=8.5$ Hz, 1H), 7.71 (ddd, $J=1.1$ Hz, $J=6.9$ Hz, $J=9.1$ Hz, 1H), 7.59 (m, 3H), 6.49 ppm (s, 2H, NH); ^{13}C NMR (125 MHz, $[D_6]$DMSO): $\delta=166.0$, 151.6, 145.1, 142.6, 132.2, 131.9, 131.2, 130.1 (2C), 128.3, 128.2 (2C), 127.9, 123.1, 115.7 ppm; MS (EI, 70 eV) *m/z* (%): 262 (100) $[M+H]^+$, purity: 99.3%.

5-(2-Thienyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 c): starting from **9 c** and following general procedure 3, a yellow solid was isolated (93 mg, 70%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=8.79$ (dd, $J=1.2$ Hz, $J=3.9$ Hz, 1H), 8.24 (dd, $J=1.3$ Hz, $J=8.0$ Hz, 1H), 7.99 (dd, $J=1.3$ Hz, $J=5.0$ Hz, 1H), 7.92 (d, $J=8.5$ Hz, 1H), 7.83 (ddd, $J=1.4$ Hz, $J=7.1$ Hz, $J=8.4$ Hz, 1H), 7.66 (ddd, $J=1.1$ Hz, $J=7.2$ Hz, $J=8.2$ Hz, 1H), 7.34 (dd, $J=3.8$ Hz, $J=5.0$ Hz, 1H), 6.59 ppm (s, 2H, NH_2); MS (EI, 70 eV) *m/z* (%): 268 (100) $[M+H]^+$, purity: 98.1%.

5-(4-Bromophenyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 d): starting from **9 d** and following general procedure 3, a yellow solid was isolated (152 mg, 90%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=8.46$ (m, 2H), 8.26 (dd, $J=1.0$ Hz, $J=7.9$ Hz, 1H), 7.98 (d, $J=7.9$ Hz, 1H), 7.85 (ddd, $J=1.6$ Hz, $J=7.3$ Hz, $J=8.5$ Hz, 1H), 7.80 (m, 2H), 7.71 (ddd, $J=1.0$ Hz, $J=7.0$ Hz, $J=7.9$ Hz, 1H), 6.52 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, $[D_6]$DMSO): $\delta=166.0$, 151.6, 144.0, 142.5, 132.1 (2C), 131.9, 131.4, 131.3 (2C), 128.3, 128.1, 125.1, 123.2, 115.7 ppm; MS (EI, 70 eV) *m/z* (%):342 (97), 340 (100) $[M+H]^+$, purity: 98.2%.

5-(3-Fluorophenyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 e): starting from **9 e** and following general procedure 3, a yellow solid was isolated (190 mg, 85%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=8.35$ (m, 2H), 8.28 (dd, $J=1.0$ Hz, $J=7.6$ Hz, 1H), 8.01 (d, $J=7.9$ Hz, 1H), 7.87 (ddd, $J=1.6$ Hz, $J=7.3$ Hz, $J=8.5$ Hz, 1H), 7.73 (ddd, $J=1.0$ Hz, $J=6.9$ Hz, $J=8.2$ Hz, 1H), 7.65 (dt, $J=6.0$ Hz, $J=8.2$ Hz, 1H), 7.48 (ddd, $J=1.0$ Hz, $J=2.5$ Hz, $J=8.5$ Hz, 1H), 6.54 ppm (s, 2H, NH_2); MS (EI, 70 eV) *m/z* (%): 280 (100) $[M+H]^+$, purity: 98.5%.

5-(4-Fluorophenyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 f): starting from **9 f** and following general procedure 3, a tan solid was isolated (190 mg, 85%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=8.57$ (dd, $J=6.0$ Hz, $J=8.8$ Hz, 2H), 8.26 (d, $J=7.9$ Hz, 1H), 7.85 (t, $J=7.4$ Hz, 1H), 7.71 (t, $J=7.6$ Hz, 1H), 7.44 (t, $J=8.8$ Hz, 2H), 6.51 ppm (s, 2H, NH_2); MS (EI, 70 eV) *m/z* (%): 280 (100) $[M+H]^+$, purity: 97.3%.

5-(3-Thienyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 g): starting from **9 g** and following general procedure 3, a yellow solid was isolated (109 mg, 82%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=9.16$ (dd, $J=1.3$ Hz, $J=3.2$ Hz, 1H), 8.25 (dd, $J=1.0$ Hz, $J=7.9$ Hz, 1H), 8.17 (dd, $J=1.3$ Hz, $J=5.0$ Hz, 1H), 7.96 (d, $J=8.2$ Hz, 1H), 7.84 (ddd, $J=1.6$ Hz, $J=7.3$ Hz, $J=8.5$ Hz, 1H), 7.75 (dd, $J=2.8$ Hz, $J=5.0$ Hz, 1H), 7.66 (ddd, $J=1.0$ Hz, $J=7.2$ Hz, $J=8.0$ Hz, 1H), 6.52 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, $[D_6]$DMSO): $\delta=166.0$, 151.5, 142.6, 140.6, 133.5, 132.4, 131.9, 128.8, 128.1, 127.6, 126.5, 123.1, 115.4 ppm; MS (EI, 70 eV) *m/z* (%): 268 (100) $[M+H]^+$, purity: 98.3%.

5-(2-Furyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 h): starting from **9 h** and following general procedure 3, a yellow solid was isolated (106 mg, 84%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=8.25$ ppm (dd, $J=0.9$ Hz, $J=7.9$ Hz, 1H), 8.14 (d, $J=3.3$ Hz, 1H), 8.12 (m, 1H), 7.97 (d, $J=8.2$ Hz, 1H), 7.84 (ddd, $J=1.4$ Hz, $J=6.9$ Hz, $J=7.9$ Hz, 1H), 7.67 (ddd, $J=0.9$ Hz, $J=7.0$ Hz, $J=8.0$ Hz, 1H), 6.86 (dd, $J=1.9$ Hz, $J=3.6$ Hz, 1H), 6.56 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, $[D_6]$DMSO): $\delta=166.1$, 151.2, 147.1, 144.6, 142.5, 136.3, 132.0, 128.1, 127.7, 123.1, 119.7, 115.3, 112.7 ppm; MS (EI, 70 eV) *m/z* (%): 252 (100) $[M+H]^+$, purity: 97.6%.

5-Isopropyl[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 i): starting from the mixture of **9 i** and **10 i** and following general procedure 3, a yellow solid was isolated (81 mg, 71%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=8.20$ (dd, $J=1.0$ Hz, $J=8.2$ Hz, 1H), 7.88 (d, $J=8.2$ Hz, 1H), 7.79 (ddd, $J=1.6$ Hz, $J=7.3$ Hz, $J=8.5$ Hz, 1H), 7.64 (ddd, $J=1.1$ Hz, $J=7.3$ Hz, $J=8.2$ Hz, 1H), 6.41 (s, 2H, NH_2), 3.72 (hept, $J=6.8$ Hz, 1H), 1.39 ppm (d, $J=6.9$ Hz, 6H); ^{13}C NMR (125 MHz, $[D_6]$DMSO): $\delta=165.8$, 153.3, 150.3, 142.5, 131.5, 127.9, 127.3, 123.0, 115.6, 30.6, 19.6 ppm (2C); MS (EI, 70 eV) *m/z* (%): 228 (100) $[M+H]^+$, purity: 98.7%.

5-Benzyl[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 j): starting from the mixture of **9 j** and **10 j** and following general procedure 3, an off-white solid was isolated (218 mg, 93%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=8.20$ ppm (dd, $J=1.3$ Hz, $J=8.2$ Hz, 1H), 7.87 (d, $J=7.9$ Hz, 1H), 7.79 (ddd, $J=1.6$ Hz, $J=7.3$ Hz, $J=8.5$ Hz, 1H), 7.66 (ddd, $J=1.3$ Hz, $J=7.3$ Hz, $J=8.2$ Hz, 1H), 7.39 (m, 2H), 7.30 (tt, $J=1.8$ Hz, $J=7.6$ Hz, 2H), 7.23 (tt, $J=1.8$ Hz, $J=7.3$ Hz, 1H), 6.45 (s, 2H, NH_2), 4.51 ppm (s, 2H); ^{13}C NMR (125 MHz, $[D_6]$DMSO) $\delta=165.9$, 150.4, 147.9, 142.5, 135.9, 131.7, 129.1, 128.6, 127.9, 127.6, 126.9, 123.1, 115.6, 38.4 ppm; MS (EI, 70 eV) *m/z* (%): 276 (100) $[M+H]^+$, purity: 99.3%.

5-(3′,4′,5′-Trimethoxy-2-phenethyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 k): starting from **9 k** and following general procedure 3, a yellow solid (112 mg, 60%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=8.20$ (dd, $J=1.0$ Hz, $J=8.2$ Hz, 1H), 7.90 (d, $J=8.2$ Hz, 1H), 7.80 (ddd, $J=1.6$ Hz, $J=7.3$ Hz, $J=8.5$ Hz, 1H), 7.66 (ddd, $J=1.3$ Hz, $J=7.3$ Hz, $J=8.2$ Hz, 1H), 6.60 (s, 2H), 6.43 (s, 2H, NH_2), 3.71 (s, 6H), 3.60 (s, 3H), 3.46 (t, $J=7.7$ Hz, 2H), 3.18 ppm (t, $J=7.9$ Hz, 2H); MS (EI, 70 eV) *m/z* (%): 380 (100) $[M+H]^+$, purity 98.4%.

5-(2-Phenethyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 l): starting from the mixture of **9 l** and **10 l** and following general procedure 3, a brown residue was isolated and purified by column chromatography (SiO_2, $CHCl_3$/EtOH 98:2) to yield colorless solid (80 mg, 28%). ^{1}H NMR (500 MHz, $[D_6]$DMSO): $\delta=8.20$ (ddd, $J=0.6$ Hz, $J=1.6$ Hz, $J=7.9$ Hz, 1H), 7.89 (d, $J=7.9$ Hz, 1H), 7.80 (ddd,

J=1.6 Hz, J=7.0 Hz, J=8.5 Hz, 1H), 7.65 (ddd, J=1.3 Hz, J=7.3 Hz, J=8.2 Hz, 1H), 7.29 (m, 3H), 7.18 (tt, J=1.7 Hz, J=6.9 Hz, 1H), 6.43 (s, 2H, NH_2), 3.45 (t, J=7.9 Hz, 2H), 3.23 ppm (t, J=7.9 Hz, 2H); MS (EI, 70 eV) *m/z* (%): 290 (100) $[M+H]^+$, purity: 99.9%.

5-((*R*,*S*)-1-Phenethyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11m): (*R*,*S*)-2-phenylpropionyl chloride (1.6 g, 1 mmol) and hydrazine hydrate (2 g, 40 mmol) were stirred at 120 °C under microwave irradiation (40 W) for 10 min. The mixture was allowed to cool to RT, and EtOH (2 mL) was added. Then the solution was heated at 70–80 °C and subsequently left at 4 °C for 16 h. The resulting turbid solution was filtered, and water (10 mL) was added to the filtrate. After extraction with $CHCl_3$ (3×10 mL) the combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield a viscous pale-green oil (528 mg). Starting from this oil and following general procedure 3, a brown residue was obtained. It was purified by column chromatography (SiO_2, $CHCl_3$/EtOH 98:2) to yield an off-white solid (448 mg, 15%). ^{1}H NMR (500 MHz, DMSO): δ=8.20 (dd, J=1.0 Hz, J=7.9 Hz, 1H), 7.96 (d, J=8.2 Hz, 1H), 7.82 (ddd, J=1.6 Hz, J=7.3 Hz, J=8.5 Hz, 1H), 7.67 (ddd, J=1.3 Hz, J=7.3 Hz, J=8.2 Hz, 1H), 7.37 (m, 2H), 7.28 (t, J=7.6 Hz, 2H), 7.19 (tt, J=1.3 Hz, J=7.3 Hz, 1H), 6.38 (s, 2H, NH_2), 4.99 (quart, J=7.2 Hz, 1H), 1.73 ppm (d, J=7.3 Hz, 3H); MS (EI, 70 eV) *m/z* (%): 290 (100) $[M+H]^+$, purity: 98.8%.

2-Dimethylamino-5-phenyl[1,2,4]triazolo[1,5-*c*]quinazoline (14b): a mixture of **9b** (0.12 g, 0.5 mmol), *N*-(dichloromethylene)-*N*,*N*-dimethylammonium chloride (125 mg, 0.75 mmol), anhydrous potassium carbonate (0.17 g, 1.2 mmol), and $CHCl_3$ (10 mL) was stirred at RT for 4 h. After addition of water (15 mL), the mixture was extracted with $CHCl_3$ (2×15 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered, and evaporated under reduced pressure to yield a yellow solid (134 mg, 93%). ^{1}H NMR (500 MHz, [D_6]DMSO): δ=8.41 (ddd, J=0.4 Hz, J=1.5 Hz, J=7.9 Hz, 1H), 7.91 (ddd, J=0.4 Hz, J=1.2 Hz, J=8.2 Hz, 1H), 7.79 (m, 3H), 7.70 (dt, J=1.3 Hz, J=7.9 Hz, 1H), 7.60 (dt, J=1.9 Hz, J=7.6 Hz, 1H), 7.51 (m, 2H), 2.39 ppm (s, 6H); MS (EI, 70 eV) *m/z* (%): 290 (100) $[M+H]^+$, purity: 97.5%.

5-Phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-2(3*H*)-one (15b): a mixture of **9b** (0.12 g, 0.5 mmol), carbonyldiimidazole (0.12 g, 0.75 mmol) and toluene (20 mL) was stirred at 100 °C for 2 h. After cooling to RT the mixture was filtered and the residue was washed with PE (2×5 mL), then dried at 80 °C to yield a yellow solid (168 mg) that was suspended in cold water (30 mL). The solution was adjusted to pH 10–11 by the addition of aqueous ammonia solution. The resulting turbid solution was filtered and the filtrate was subsequently acidified to pH 3 using aqueous HCl solution (1 N). Cooling at 4 °C for 1 h resulted in a white precipitate, which was collected by filtration, washed with water (2×5 mL) and dried in a desiccator to yield a colorless solid (76 mg, 58%). ^{1}H NMR (500 MHz, [D_6]DMSO): δ=7.46 (t, J=7.4 Hz, 2H), 7.53 (t, J=7.4 Hz, 1H), 7.61 (dt, J=1.7 Hz, J=8.2 Hz, 1H), 7.73 (m, 4H), 8.12 (d, J=7.9 Hz, 1H), 12.49 ppm (s, 1H, NH); MS (EI, 70 eV) *m/z* (%): 263 (100) $[M+H]^+$, purity: 98.6%.

5-(2-Thienyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2(3*H*)-one (15c): a mixture of **9c** (0.12 g, 0.5 mmol), carbonyldiimidazole (0.12 g, 0.75 mmol) and toluene (20 mL) was stirred at 100 °C for 2 h. After cooling to RT the mixture was filtered and the residue was washed with PE (2×5 mL) and dried at 80 °C to yield a bright-orange solid (210 mg) that was suspended in cold water (30 mL). Then the solution was adjusted to pH 10–11 by the addition of 27% aqueous ammonia solution. The resulting turbid solution was filtered and subsequently acidified to pH 3 using aqueous HCl solution (1 N). Cooling at 4 °C for 1 h resulted in a white precipitate, which was collected by filtration, washed with water (2×5 mL) and dried by desiccator to yield a colorless solid (38 mg, 28). ^{1}H NMR (500 MHz, [D_6]DMSO): δ=12.61 (s, 1H, NH), 8.29 (dd, J=1.2 Hz, J=3.9 Hz, 1H), 8.06 (m, 1H), 7.85 (dd, J=1.1 Hz, J=5.0 Hz, 1H), 7.69 (m, 2H), 7.55 (ddd, J=2.2 Hz, J=6.3 Hz, J=7.9 Hz, 1H), 7.20 ppm (dd, J=3.9 Hz, J=5.0 Hz, 1H); ^{13}C NMR (125 MHz, [D_6]DMSO): δ=149.8, 142.3, 141.2, 141.1, 134.8, 134.4, 132.1, 131.7, 128.4, 127.7, 127.5, 121.7, 116.2 ppm; MS (EI, 70 eV) *m/z* (%): 269 (100) $[M+H]^+$, purity: 98.4%.

5-Phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-2(3*H*)-thione (16b): thiophosgene (70 mg, 0.5 mmol) was slowly added to a mixture of potassium carbonate (70 mg, 0.5 mmol), water (1 mL) and $CHCl_3$ (20 mL) at 0 °C. A solution of **9b** (0.12 g, 0.5 mmol) in $CHCl_3$ (10 mL) at 0 °C was added drop-wise to the mixture. The resulting solution was stirred at RT for 4 h. Then 27% aqueous ammonia solution (1 mL) was added and the mixture was stirred at RT for 2 h. Volatiles were removed at reduced pressure and water (10 mL) was added to the residual solution. Then the solution adjusted to pH 11–12 by the addition of aqueous sodium hydroxide solution (2 N). The resulting turbid solution was filtered and the filtrate was subsequently acidified to pH 3–4 by the addition of HCl (2 N) solution. Cooling at 4 °C for 1 h resulted in the formation of a yellow precipitate, which was collected by filtration, washed with water (2×5 mL) and dried in a desiccator. The product was recrystallized from EtOH (2 mL) to yield a colorless solid (76 mg, 55%). ^{1}H NMR (500 MHz, [D_6]DMSO): δ=14.44 (s, 1H, NH), 8.26 (d, J=7.9 Hz, 1H), 7.83 (m, 2H), 7.70 (t, J=6.8 Hz, 1H), 7.61 (d, J=7.3 Hz, 2H), 7.49 (t, J=7.4 Hz, 1H), 7.42 ppm (t, J=7.6 Hz, 2H); ^{13}C NMR (125 MHz, [D_6]DMSO): δ=162.9, 147.8, 145.7, 141.1, 132.7, 132.6, 130.0 (2C), 129.8, 129.2, 128.2, 126.8 (2C), 122.4, 116.3 ppm; MS (EI, 70 eV) *m/z* (%): 279 (100) $[M+H]^+$, purity: 99.8%.

5-(2-Thienyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2(3*H*)-thione (16c): a mixture of **9c** (0.12 g, 0.5 mmol), thiocarbonyldiimidazole (0.18 g, 1.0 mmol) and DMF (1 mL) was stirred at 60 °C for 27 h. The mixture was poured into water (5 mL) and the solution was adjusted to pH 13 by the addition of aqueous sodium hydroxide (2 N) solution. The resulting turbid solution was filtered and the filtrate subsequently acidified to pH 3 using an aqueous HCl solution (2 N). Cooling overnight at 4 °C resulted a yellow precipitate, which was collected, washed with water (10 mL) and dried at 80 °C to yield a yellow solid (116 mg, 82%). ^{1}H NMR (500 MHz, [D_6]DMSO): δ=14.51 (s, 1H, NH), 8.24 (d, J=7.8 Hz, 1H), 7.83 (m, 2H), 7.79 (dd, J=1.3 Hz, J=5.0 Hz, 1H), 7.70 (ddd, J=2.1 Hz, J=6.5 Hz, J=8.0 Hz, 1H), 7.60 (dd, J=1.2 Hz, J=3.7 Hz, 1H), 7.14 ppm (dd, J=3.7 Hz, J=5.0 Hz, 1H); MS (EI, 70 eV) *m/z* (%): 285 (100) $[M+H]^+$, purity: 98.1%.

3,5-Diphenyl[1,2,4]triazolo[4,3-*c*]quinazoline (17): following general procedure 2, starting from **9a** (80 mg, 0.5 mmol) and benzoyl chloride (1 mL), the product was obtained as a colorless solid (67 mg, 54%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.89 ppm (d, J=8.1 Hz, 1H), 8.62 (dd, J=1.9 Hz, J=7.9 Hz, 2H), 8.46 (dd, J=2.5 Hz, J=7.9 Hz, 2H), 8.15 (d, J=8.2 Hz, 1H), 7.89 (ddd, J=1.3 Hz, J=7.4 Hz, J=8.2 Hz, 1H), 7.77 (dt, J=1.2 Hz, J=7.7 Hz, 1H), 7.62 (m, 3H), 7.53 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=162.5, 152.0, 146.3, 143.2, 133.0, 131.9, 131.3, 131.1, 130.3, 130.6 (2C), 128.9, 128.8, 128.7, 128.5 (2C), 128.0 (2C), 124.7, 116.2 ppm; MS (EI, 70 eV) *m/z* (%): 323(100) $[M+H]^+$, purity: 98.3%.

5,6a,7a,12,13-Pentaazaindeno[1,2-*b*]phenanthrene or 5,6a,7,8,13-pentaazaindeno[2,1-b]phenanthrene (18): a mixture of **9a** (0.16 g, 1.0 mmol), isatin (0.16 g, 1.1 mmol), and EtOH (5 mL)

was stirred in a glass pressure tube at 100 °C for 30 min. The precipitate formed upon cooling to RT was collected by filtration, washed with EtOH (2×1 mL) and dried at 80 °C to yield dark-red crystals (0.21 g, 79%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.40 (s, 1H), 8.89 (dd, J = 0.8 Hz, J = 8.2 Hz, 1H), 8.27 (d, J = 7.6 Hz, 1H), 8.04 (m, 2H), 7.89 (ddd, J = 1.6 Hz, J = 7.0 Hz, J = 8.2 Hz, 1H), 7.82 (dt, J = 1.3 Hz, J = 7.6 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.44 ppm (dt, J = 1.3 Hz, J = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.6, 150.9, 147.4, 146.0, 145.4, 143.1, 134.7, 134.3, 129.3, 128.0, 125.2, 123.5, 122.8, 121.5, 120.0, 119.9 ppm; MS (EI, 70 eV) *m/z* (%): 272 (100) $[M+H]^+$, purity: 99.0%

3-(4-Imino-2-phenyl-4*H*-quinazolin-3-ylimino)-1,3-dihydroindol-2-one (19): A mixture of **9b** (0.12 g, 0.5 mmol), isatin (0.9 g, 0.6 mmol), and EtOH (5 mL) was stirred in a glass pressure tube at 100 °C for 1 h. The precipitate formed upon cooling to RT was collected by filtration, washed with EtOH (2×1 mL) and dried at 80 °C to yield bright-orange needles (0.19 g, 98%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.36 (br s, 1H, NH), 10.66 (s, 1H, NH), 8.44 (d, J = 6.3 Hz, 2H), 8.08 (d, J = 5.7 Hz, 2H), 7.83 (br s, 1H), 7.65 (m, 5H), 7.33 (t, J = 7.4 Hz, 1H), 7.08 (t, J = 7.3 Hz, 1H), 6.88 ppm (d, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 165.6, 146.0, 143.8, 132.9, 131.9, 129.0, 128.2, 127.4, 125.0, 122.1, 117.8, 110.3 ppm; MS (EI, 70 eV) *m/z* (%): 366 (100) $[M+H]^+$, purity: 99.5%.

5′-Phenyl-1,2-dihydro-3′*H*-spiro[indole-3,2′-[1,2,4]triazolo[1,5-*c*]quinazolin]-2-one (20): 3-(4-imino-2-phenyl-4*H*-quinazolin-3-ylimino)-1,3-dihydroindol-2-one (**19**) (10 mg, 0.03 mmol) and a 10% solution of phosphorous pentoxide in methanesulfonic acid (1 mL) were heated at 170 °C until the black solution turned orange (~ 1 min) and then cooled to RT. The precipitate formed upon addition of water (5 mL) and neutralization with solid sodium carbonate, was collected by filtration, washed with water (2×5 mL), and dried at 80 °C to yield a yellow solid (10 mg, 95%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 13.90 (s, 1H), 11.37 (s, 1H), 8.56 (m, 3H), 7.99 (m, 2H), 7.76 (d, J = 6.9 Hz, 1H), 7.56 (m, 3H), 7.74 (ddd, J = 1.6 Hz, J = 6.3 Hz, J = 8.2 Hz, 1H), 7.40 (dt, J = 1.0 Hz, J = 7.6 Hz, 1H), 7.16 (dt, J = 1.0 Hz, J = 7.6 Hz, 1H), 6.99 ppm (d, J = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 163.5, 159.2, 156.4, 151.9, 142.0, 137.6, 135.5, 134.2, 131.3, 130.8, 128.7 (2C), 128.2 (3C), 127.4, 123.5, 122.7, 120.7, 120.3, 112.9, 111.3 ppm; MS (EI, 70 eV) *m/z* (%): 366 (100) $[M+H]^+$, purity: 97.7%.

Synthesis of triazoloquinazolines using Method B

3-Guanidino-2-phenylquinazolin-4(3*H*)-one (23b): following general procedure 4, starting from **22b** a colorless solid (178 mg, 64%) was obtained. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 12.55 (s, 1H, NH), 12.51 (s, 1H, NH), 8.75 (d, J = 8.5 Hz, 1H), 8.10 (m, 3H), 7.61 (m, 3H), 7.38 (t, J = 7.4 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.39 (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 280 (100) $[M+H]^+$, purity 99.5%.

3-Guanidino-2-(3-pyridyl)quinazolin-4(3*H*)-one (23o): following general procedure 4, starting from **22o** a colorless solid (199 mg, 71%) was obtained. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 12.62 (s, 1H, NH), 12.55 (s, 1H, NH), 9.21 (d, J = 1.9 Hz, 1H), 8.80 (dd, J = 1.6 Hz, J = 5.0 Hz, 1H), 8.72 (d, J = 8.2 Hz, 1H), 8.42 (d, J = 7.9 Hz, 1H), 8.10 (d, J = 7.6 Hz, 1H), 7.64 (dd, J = 4.7 Hz, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 6.40 (s, 2H, NH$_2$); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 163.3, 158.0, 156.7, 152.5, 148.7, 148.4, 136.7, 135.0, 130.4, 129.2, 127.6, 124.2, 123.6, 119.9, 119.1; MS (EI, 70 eV) *m/z* (%): 281 (100) $[M+H]^+$, purity 99.0%.

3-Guanidino-2-(4-pyridyl)quinazolin-4(3*H*)-one (23p): following general procedure 4, starting from **22p** a colorless solid (246 mg, 88%) was obtained. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 12.82 (s, 1H, NH), 12.52 (s, 1H, NH), 8.85 (m, 2H), 8.72 (d, J = 8.2 Hz, 2H), 8.10 (d, J = 7.5 Hz, 1H), 7.97 (dd, J = 1.6 Hz, J = 4.4 Hz, 2H), 7.40 (t, J = 7.7 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 6.46 (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 281 (100) $[M+H]^+$, purity 98.2%.

5-Phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11b): following general procedure 5, starting from **23b** a colorless solid (96 mg, 74%) was obtained, purity: 99.1%. Analytical data and preparation via Method A are described above.

5-Methyl[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11n): following general procedure 6, starting from **22n** the product was isolated and further purified by column chromatography (SiO$_2$, in CHCl$_3$/EtOH 95:5) instead of the addition of water, neutralization and filtration, to yield a colorless solid (67 mg, 34%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.19 (ddd, J = 0.6 Hz, J = 1.6 Hz, J = 7.9 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.79 (ddd, J = 1.6 Hz, J = 7.0 Hz, J = 8.5 Hz, 1H), 7.64 (ddd, J = 1.3 Hz, J = 7.3 Hz, J = 8.2 Hz, 1H), 6.40 (s, 2H, NH$_2$), 2.78 ppm (s, 3H); MS (EI, 70 eV) *m/z* (%): 200 (100) $[M+H]^+$, purity 99.7%.

5-(3-Pyridyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11o): following general procedure 5, starting from **22o** golden platelets (65 mg, 50%) were obtained. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.58 (s, 1H, 2′-H), 8.79 (m, 2H), 8.28 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.87 (t, J = 7.3 Hz, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.64 (dd, J = 5.0 Hz, J = 7.0 Hz, 1H), 6.54 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 263 (100) $[M+H]^+$, purity: 99.9%.

5-(4-Pyridyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11p): following general procedure 5, starting from **22p** a solid was obtained, which was further purified by column chromatography (SiO$_2$, CHCl$_3$/EtOH 80:20) to yield a colorless solid (67 mg, 51%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.84 (d, J = 6.0 Hz, 2H), 8.39 (dd, J = 1.6 Hz, J = 4.4 Hz, 2H), 8.04 (d, J = 8.0 Hz, 1H), 8.29 (dd, J = 1.0 Hz, J = 8.1 Hz, 1H), 7.89 (ddd, J = 1.5 Hz, J = 7.1 Hz, J = 8.2 Hz, 1H), 7.76 (ddd, J = 1.3 Hz, J = 7.3 Hz, J = 8.2 Hz, 1H), 6.57 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 263 (100) $[M+H]^+$, purity 99.8%.

9-Bromo-5-phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11q): following general procedure 6, starting from **22q** a dark solid was obtained that was further purified by column chromatography (SiO$_2$, CHCl$_3$/EtOH 98:2) to obtain an analytically pure colorless solid (884 mg, 66%). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.54 (d, J = 2.2 Hz, 1H), 8.43 (m, 2H), 7.91 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 2.2 Hz, J = 8.8 Hz, 1H), 7.48 (m, 3H), 4.75 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 340 (100) 342 (97) $[M+H]^+$, purity: 99.6%.

9-Fluoro-5-phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11r): benzoyl chloride (2.2 equiv, 168 mg, 1.2 mmol) was added dropwise to a stirred solution of 2-amino-5-fluorobenzoic acid (77 mg, 0.5 mmol) in pyridine (1.5 mL). After 30 min, water (15 mL) was added and the formed precipitate was collected by filtration, washed with water, and subsequently used as a starting material for the subsequent reaction following general procedure 6. The obtained product was further purified by column chromatography (SiO$_2$, CHCl$_3$/EtOH 98:2) to provide a colorless solid (57 mg, 41%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.44 (m, 2H), 8.07 (dd, J = 5.0 Hz, J = 9.1 Hz, 1H), 7.92 (dd, J = 2.8 Hz, J = 8.4 Hz, 1H), 7.73 (dt, J = 2.8 Hz, J = 8.8 Hz, 1H), 7.60 (m, 3H), 6.53 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 280 (100) $[M+H]^+$, purity: 99.9%.

***N*,*N*-Dimethyl-*N*′-(5-(3-pyridyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-yl)formamidine (11o)**: following procedure 5 starting from **23o**, performing the cyclization step with phosphorus pentoxide (120 mg) in DMF (3 mL) at 155 °C instead of methanesulfonic acid, yielded a colorless solid (33 mg, 21%). ^{1}H NMR (500 MHz,

[D$_6$]DMSO): δ = 9.58 (s, 1H, 2′-H), 8.85 (dt, J = 1.9 Hz, J = 8.0 Hz, 1H), 8.80 (dd, J = 1.6 Hz, J = 4.8 Hz, 1H), 8.66 (s, 1H), 8.37 (dd, J = 0.9 Hz, J = 7.9 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.90 (dt, J = 1.4 Hz, J = 7.3 Hz, 1H), 7.77 (dt, J = 0.9 Hz, J = 7.3 Hz, 1H), 7.67 (dd, J = 4.9 Hz, J = 7.9 Hz, 1H), 3.17 (s, 3H), 3.05 ppm (s, 3H); MS (EI, 70 eV) *m/z* (%): 318 (100) $[M+H]^+$, purity: 99.5%.

5-Phenylpyrido[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-2-amine (27): following general procedure 5, starting from **26** (0.22 g, 1.0 mmol) yielded a colorless solid (86 mg, 33%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.06 (dd, J = 1.9 Hz, J = 4.4 Hz, 1H), 8.66 (dd, J = 1.9 Hz, J = 7.9 Hz, 1H), 8.51 (m, 2H), 7.71 (dd, J = 4.4 Hz, J = 7.9 Hz, 1H), 7.62 (m, 3H), 6.60 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) *m/z* (%): 263 (100) $[M+H]^+$, purity: 98.6%.

5-Isopropyl[1,2,4]triazolo[1,5-*c*]quinazolin-2(3*H*)-one (15i): **22i** (0.19 g, 1.0 mmol), semicarbazide hydrochloride (0.13 g, 1.2 mmol) and pyridine (2 mL) were heated in a tube at 160 °C under microwave irradiation (60 W) for 30 min. After allowing the mixture to cool to RT, water (5 mL) was added and the resulting solution was stored at 4 °C overnight. The formed solid was filtered off, washed with water (10 mL) and dried in a desiccator to yield a colorless solid (23 mg, 10%). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 11.17 (s, 1H), 8.28 (ddd, J = 0.5 Hz, J = 1.5 Hz, J = 8.1 Hz, 1H), 7,75 (ddd, J = 1.6 Hz, J = 6.9 Hz, J = 8.2 Hz, 1H), 7.70 (ddd, J = 0.5 Hz, J = 1.1 Hz, J = 8.2 Hz, 1H), 7.44 (ddd, J = 1.3 Hz, J = 6.9 Hz, J = 8.1 Hz, 1H), 3.02 (hept, J = 7.0 Hz, 1H), 1.42 ppm (d, J = 7.2 Hz, 6H); MS (EI, 70 eV) *m/z* (%): 229 (100) $[M+H]^+$, purity 98.5%.

***N*,*N*-Dimethyl-*N*′-(5-(3-pyridyl)[1,2,4]triazolo[1,5-*c*]quinazolin-2-yl)formamidine (24o)** was obtained as a colorless solid (13 mg, 21%) when general procedure 5 was applied to **23o** (56 mg, 0.2 mmol) replacing the usual reagent by phosphorus pentoxide (240 mg) in DMF (3 mL). TLC: R_f = 0.1 (eluent: CHCl$_3$/EtOAc = 1:1). ^{1}H NMR (500 MHz, DMSO): δ = 3.05 (s, 3H, CH$_3$), 3.17 (s, 3H, CH$_3$), 7.67 (dd, J = 4.9 Hz, J = 7.9 Hz, 1H), 7.77 (dt, J = 0.9 Hz, J = 7.3 Hz, 1H), 7.90 (dt, J = 1.4 Hz, J = 7.3 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 8.37 (dd, J = 0.9 Hz, J = 7.9 Hz, 1H), 8.66 (s, 1H, N = CH-N), 8.80 (dd, J = 1.6 Hz, J = 4.8 Hz, 1H), 8.85 (dt, J = 1.9 Hz, J = 8.0 Hz, 1H), 9.58 ppm (s, 1H, 2′-H).

Synthesis of triazoloquinazolines using Methods C and D

5-Methylsulfanyl[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11s): methyl iodide (0.78 g, 5.5 mmol) was added to a mixture of 2-amino[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-thione (**28**, 1.09 g, 5.0 mmol), MeOH (5 mL), and 2% aqueous sodium hydroxide solution (15 mL). After stirring for 30 min at RT, the precipitate was collected, washed with water (20 mL), and dried in a desiccator to yield a colorless solid (1.16 g, 97%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.17 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.80 (t, J = 7.3 Hz, 1H), 7.60 (t, J = 7.3 Hz, 1H), 6.52 (s, 2H, NH$_2$), 2.71 ppm (SCH$_3$); ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 165.9, 149.6, 148.4, 143.1, 131.8, 127.0, 126.7, 123.2, 114.3, 12.9 ppm (SCH$_3$); MS (EI, 70 eV) *m/z* (%): 232 (100) $[M+H]^+$, purity: 99.3%.

5-Pyrrolidino[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11t): compound **28** (95 mg, 0.44 mmol), pyrrolidine (1 g) and EtOH (10 mL) were held at reflux for 18 h. The mixture was cooled to RT and left standing for several days. The formed yellow crystals were collected by filtration and dried (45 mg, 38%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.98 (dd, J = 1.0 Hz, J = 7.9 Hz, 1H), 7.56 (ddd, J = 1.6 Hz, J = 7.3 Hz, J = 8.5 Hz, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.25 (ddd, J = 1.3 Hz, J = 7.4 Hz, J = 7.9 Hz, 1H), 6.13 (s, 2H, NH$_2$), 3.94 (m, 4H), 1.92 ppm (m, 4H); MS (EI, 70 eV) *m/z* (%): 255 (100) $[M+H]^+$, purity: 99.9%.

5-Piperidino[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11u): the product was obtained by two different methods. In the first method, **28** (0.11 g, 0.5 mmol) and piperidine (1 mL) were stirred at 100 °C for 9 h. EtOH (~5 mL) was added until a clear boiling solution evolved. After cooling to RT, the solution was left at 4 °C overnight. The precipitate formed was collected, washed with EtOH (5 mL) and dried at 120 °C to yield **11u** as a colorless solid (72 mg, 53%). In the second method, the reaction was performed according to general procedure 7 but at 80 °C starting from piperidine, affording **11u** as a colorless solid (69 mg, 51%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.05 (dd, J = 1.0 Hz, J = 8.2 Hz, 1H), 7.63 (ddd, J = 1.6 Hz, J = 6.9 Hz, J = 8.5 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.36 (ddd, J = 1.3 Hz, J = 7.3 Hz, J = 8.2 Hz, 1H), 6.28 (s, 2H, NH$_2$), 3.88 (m, 4H), 1.66 ppm (br s, 6H); MS (EI, 70 eV) *m/z* (%): 269 (100) $[M+H]^+$, 99.7%.

5-Morpholino[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11v): according to general procedure 7, starting from morpholine, a colorless solid (91 mg, 67%) was obtained. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.08 (dd, J = 0.9 Hz, J = 7.9 Hz, 1H), 7.66 (ddd, J = 1.6 Hz, J = 6.9 Hz, J = 8.2 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.40 (ddd, J = 1.0 Hz, J = 7.9 Hz, 1H), 6.33 (s, 2H, NH$_2$), 3.91 (m, 4H), 3.78 ppm (m, 4H); MS (EI, 70 eV) *m/z* (%): 271 (100) $[M+H]^+$, purity: 98.1%.

5-Butylamino[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11w): according to general procedure 7, starting from butylamine, a colorless solid was obtained (20 mg, 16%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.98 (dd, J = 1.3 Hz, J = 7.9 Hz, 1H), 7.59 (ddd, J = 1.6 Hz, J = 6.9 Hz, J = 8.5 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.30 (t, J = 5.8 Hz, 1H, NH), 7.27 (ddd, J = 1.3 Hz, J = 7.9 Hz, 1H), 6.17 (s, 2H, NH$_2$), 1.63 (quint, J = 7.3 Hz, 2H), 1.63 (quart, J = 6.7 Hz, 2H), 1.36 (sext, J = 7.4 Hz, 2H), 0.92 ppm (t, J = 7.4 Hz, 3H); MS (EI, 70 eV) *m/z* (%): 257 (100) $[M+H]^+$, purity: 98.7%.

5-Benzylamino[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11x): according to general procedure 7 starting from benzylamine a colorless solid (107 mg, 73%) was obtained which was purified by additional washing with EtOH. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8,00 (m, 2H), 7.58 (ddd, J = 1.6 Hz, J = 7.3 Hz, J = 8.5 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 7.6 Hz, 2H), 7.30 (m, 3H), 7.21 (dt, J = 1.3 Hz, J = 7.3 Hz, 1H), 6.21 (s, 2H, NH$_2$), 4.73 ppm (d, J = 6.3 Hz, 2H); MS (EI, 70 eV) *m/z* (%): 291 (100) $[M+H]^+$, purity: 97.8%.

5-(2-Hydroxyethylamino)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11y): according to general procedure 8, starting from ethanolamine and heating at 120 °C for 90 min a colorless solid (103 mg, 84%) was obtained. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.00 (dd, J = 1.6 Hz, J = 7.9 Hz, 1H), 7.60 (ddd, J = 1.6 Hz, J = 7.3 Hz, J = 8.5 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.30 (ddd, J = 1.0 Hz, J = 7.9 Hz, 1H), 7.14 (t, J = 5.5 Hz, 1H, NH), 6.21 (s, 2H, NH$_2$), 4.84 (t, J = 5.4 Hz, 1H, OH), 3.61 ppm (m, 4H); MS (EI, 70 eV) *m/z* (%): 245 (100) $[M+H]^+$, purity: 99.0%

5-(2-Phenethylamino)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11z): according to general procedure 8 using 2-phenethylamine (2 mL) and heating at 120 °C for 15 h a colorless solid (33 mg, 22%) was obtained after washing the crude product with EtOH. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.00 (dd, J = 1.3 Hz, J = 8.2 Hz, 1H), 7.60 (ddd, J = 1.3 Hz, J = 6.6 Hz, J = 8.2 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.37 (t, J = 5.8 Hz, 1H, NH), 7.29 (m, 5H), 7.20 (m, 1H), 6.19 (s, 2H, NH$_2$), 3.75 (m, 2H), 3.00 ppm (t, J = 3.0 Hz, 2H); MS (EI, 70 eV) *m/z* (%): 305 (100) $[M+H]^+$, purity: 98.0%.

5-Tetrahydrofurfurylamino[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11aa): following general procedure 8, starting from tetrahydrofurfurylamine (2 mL) and heating the mixture at 120 °C for

17 h, a colorless solid (96 mg, 68%) was obtained. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.00 (dd, J = 1.3 Hz, J = 7.9 Hz, 1H), 7.60 (ddd, J = 1.6 Hz, J = 7.3 Hz, J = 8.5 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.30 (ddd, J = 1.0 Hz, J = 7.9 Hz, 1H),7.07 (t, J = 5.8 Hz, 1H, NH), 6.24 (s, 2H, NH$_2$), 4.05 (quint, J = 6.3 Hz, 2H), 3.65 (quart, J = 7.1 Hz, 1H), 3.65 (quart, J = 7.3 Hz, 1H), 3.57 (t, J = 5.8 Hz, 2H), 1.89 (m, 2H), 1.67 ppm (m, 1H); MS (EI, 70 eV) m/z (%): 285 (100) [M+H]$^+$, purity: 98.6%.

5-(3-Picolylamino)[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 ab): following general procedure 8, starting from 3-picolylamine (2 mL) the mixture was heated for 9 h at 140 °C. The resulting solution was allowed to cool to RT, isopropanol (5 mL) was added followed by diethyl ether (30 mL). The supernatant was decanted and the residue was recrystallized from isopropanol (10 mL) to yield an off-white solid (22 mg, 8%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.66 (s, 1H), 8.42 (d, J = 3.2 Hz, 1H), 8.12 (t, J = 6.3 Hz, 1H), 8.00 (d, J = 6.9 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 6.9 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.31 (quart, J = 7.4 Hz, 2H), 6.21 (s, 2H, NH$_2$), 4.73 ppm (d, J = 6.3 Hz, 2H); MS (EI, 70 eV) m/z (%): 292 (100) [M+H]$^+$, purity: 98.5%.

5-Hydrazino[1,2,4]triazolo[1,5-*c*]quinazolin-2-amine (11 ac): compound **28** (0.22 mg, 1.0 mmol), hydrazine hydrate (2.0 g, 40 mmol) and EtOH (10 mL) were refluxed for 1 h. The mixture was allowed to cool to RT, then left at 4 °C overnight. The formed precipitate was collected by filtration, washed with EtOH (10 mL), and dried at 100 °C to yield colorless needles (214 mg, 99%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.44 (s, 1H, NH), 8.02 (dd, J = 1.0 Hz, J = 7.9 Hz, 1H), 7.63 (m, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.32 (dt, J = 1.3 Hz, J = 6.9 Hz, 1H), 6.21 (s, 2H, NH$_2$), 4.56 ppm (s, 2H, NH$_2$); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 165.6, 150.7, 145.1, 144.5, 131.6, 125.3, 123.1, 123.0, 112.7 ppm; MS (EI, 70 eV) m/z (%): 216 (100) [M+H]$^+$, purity: 99.9%.

Bis[1,2,4]triazolo[4,3-*a*:1′,5′-*c*]quinazolin-2-amine (29): compound **11 ac** (53 mg, 0.25 mmol) and triethyl orthoformate (2 mL) were placed in a microwave tube and heated at 160 °C under microwave irradiation of 120 W for 20 min. The solution was allowed to cool to RT. The formed precipitate was collected by filtration, washed with EtOH (5 mL), and dried at 100 °C to yield a beige-colored solid (39 mg, 31%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.36 (d, J = 8.5 Hz, 1H), 8.23 (dd, J = 0.9 Hz, J = 7.9 Hz, 1H), 7.88 (dt, J = 1.6 Hz, J = 7.9 Hz, 1H), 7.68 (t, J = 7.7 Hz, 1H), 6.36 ppm (s, 2H, NH$_2$); MS (EI, 70 eV) m/z (%): 226 (100) [M+H]$^+$, purity: 98.2%.

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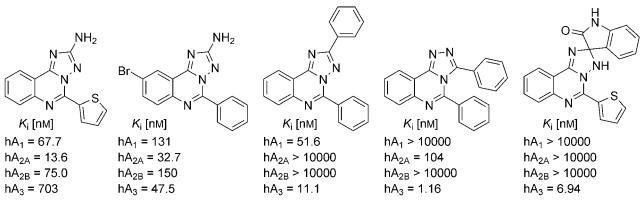
2-Amino[1,2,4]triazolo[1,5-*c*]quinazolines and Derived Novel Heterocycles: Syntheses and Structure–Activity Relationships of Potent Adenosine Receptor Antagonists



The A-team: 2-Amino[1,2,4]triazolo[1,5-*c*]quinazolines and derivatives were identified as novel adenosine receptor (AR) antagonists. Efficient syntheses were developed, allowing broad structural variations, and novel related heterocycles were prepared. Potent and selective A_3AR antagonists as well as antagonists with dual affinity, and those that potently block all AR subtypes, were obtained.