Synthesis and *In Vitro* Evaluation of 2-Aminoquinazolin-4(3*H*)-one-Based Inhibitors for tRNA-Guanine Transglycosylase (TGT)

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tRNA-Guanine transglycosylase (TGT) plays a key role in the post-transcriptional modification of tRNA. It has been linked with the pathogenicity of *shigellae*, the causative agents of bacillary dysentery (shigellosis). Here, we report structure–activity relationships (SARs) for a new series of 2-aminoquinazolin-4(3*H*)-one-based inhibitors of TGT, resulting from structure-based design (*Fig. 2*). Versatile synthetic protocols allow selective functionalization of the 2-aminoquinazolin-4(3*H*)-one core (*Schemes 1–6*) with H-bond-donor groups in position 6 (for H-bonding to the C=O group of Leu231) and lipophilic residues in position 8 for reaching into a shallow, newly discovered lipophilic pocket lined by Val282, Val45, and Leu68. The binding mode of several of these ligands in the active site of TGT was established by crystal structure analyses (*Figs. 4* and *6*). A dramatic S effect was observed, with the replacement of the S-atom in the (phenylsulfanyl)methyl residue in position 8 of inhibitor **1c** (K_i = 100 nM) by the O-atom (in **1h**, K_i = 5.6 μM) or CH_2 (in **1i**, K_i = 3.6 μM), resulting in a massive loss of activity (*Fig. 3*). Crystal structure analysis showed that the lipophilic Me group points into a highly polar region of the active site encompassed by the side chains of Asp280 and Asp102 and collides directly (d(C···O) = 3.1 Å) with one of the O-atoms of the carboxylate of Asp102. Similarly, lipophilic linkers departing from position 8 and orienting residues in the shallow hydrophobic pocket presumably encounter analogous unfavorable contacts, accounting for the modest contribution to the binding free enthalpy upon introduction of these residues. These findings provide a valuable starting point for future structure-based lead optimization cycles leading to TGT inhibitors with increased *in vitro* potency.

1. Introduction. – The bacterial infection shigellosis (bacillary dysentery) kills 1.1 million people and affects more than 150 millions each year [1]. Increased bacterial resistance toward a panel of antimicrobial drugs has become a main threat in healthcare, and this phenomenon is observed with the *Shigella* organisms as well [2]; moreover, the longstanding non-availability of vaccines demands the development of novel therapeutic treatment [3].

tRNA-Guanine transglycosylase (TGT, EC 2.4.2.29) has been recognized as one of the key enzymes in the regulation of bacterial virulence in *S. flexneri* [4]. In eukaryotes and prokaryotes, TGT is involved in the biosynthesis of the highly modified nucleobase queuine (Q) found in the anticodon loop of specific tRNAs (*Fig. 1*) [5][6]. Bacterial TGT catalyzes the exchange of guanine by the modified nucleobase $preQ_1$, whereas eukaryotes use queuine as substrate. In archaebacteriae, the related $preQ_0$ serves as modified nucleobase, which is transformed in additional biosynthetic steps to archeosine G* in tRNA [7][8].

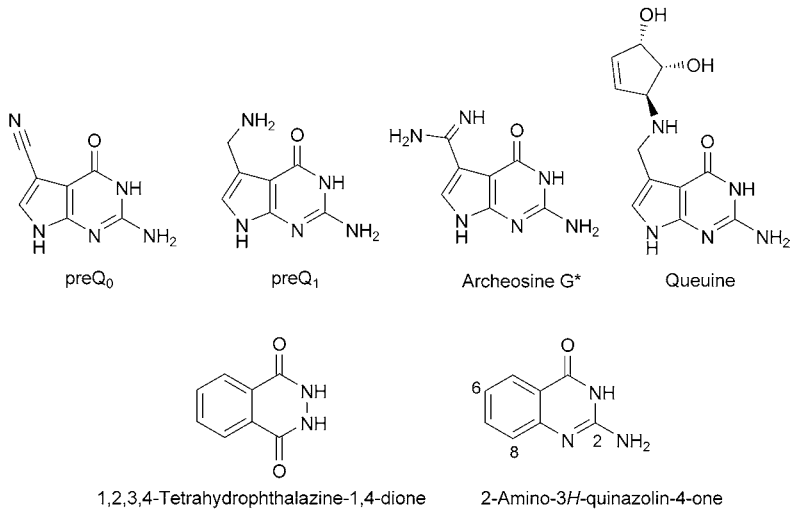


Fig. 1. Top: *Modified nucleobases entered into the anticodon loop of tRNAs with the assistance of TGT.* Bottom: *Synthetic inhibitors of TGT.*

Recently, *Xie et al.* clarified the catalytic mechanism of TGT-mediated transglycosylation by trapping the covalent intermediate formed by displacement of guanine from bound tRNA [9]. Crystal-structure analysis of the covalent TGT–tRNA adduct surprisingly revealed that Asp280[1]) is the catalytically active nucleophile displacing guanine, whereas Asp102, previously thought to be the active nucleophile [10], serves as general acid/base.

The first crystal structure of TGT (originating from the prokaryotic organism *Zymomonas mobilis*) was reported in 1996 by *Romier et al.*, together with the structure of the complex with its natural substrate $preQ_1$ [11]. In addition, initial crystallographic studies of TGT complexed with pyridazinediones (1,2,3,4-tetrahydrophthalazine-1,4-dione derivatives) established TGT as a suitable target for the *de novo* design of drugs against shigellosis [12]. Here, we describe the synthesis and *in vitro* evaluation of a new series of TGT inhibitors with a 2-aminoquinazolin-4(3*H*)-one scaffold, resulting from structure-based design, a strategy pursued in our laboratory in a variety of other medicinal-chemistry projects [13–15] (for a preliminary communication of parts of this work, see [16]; for a detailed crystallographic analysis of the complexes of 2-aminoquinazolin-4(3*H*)-one-based inhibitors bound to TGT, see [17]).

2. Results and Discussion. – 2.1. *Design of the Lead Structure.* Chemical-structure intuition and careful analysis of the enzyme active site with the molecular-modeling program MOLOC [18] led to the proposal of 2,6-diaminoquinazolin-4(3*H*)-one as a promising lead structure for TGT inhibition. For the modeling, the crystal structure of TGT from prokaryotic *Z. mobilis* was used; all the targeted amino acid residues located in the binding pocket are highly conserved in TGT from *Z. mobilis* and *S. flexneri*, the

[1]) For clarity, *Z. mobilis* numbering will be used throughout this paper.

only difference being the replacement of Tyr106 with Phe [19]. However, this change does not alter the kinetic parameter of TGT [20]. The designed inhibitors, similar to the natural substrates, feature the characteristic guanine-like H-bonding edge and should specifically bind through several H-bonds to Gly230, Gln203, and Asp156 (*Fig. 2*). The NH_2 group at C(6) was introduced to specifically interact with the C=O group of Leu231, thereby mimicking the NH_2CH_2 group in $preQ_1$. Furthermore, the aromatic heterocycle is intercalated between the flexible phenolic side chain of Tyr106 and the side chain of Met260 (for a review on sulfur–aromatic interactions, see [21]). During our analysis of the active-site environment, we discovered a shallow lipophilic pocket defined by Val45, Leu68, and Val282 at the bottom of the site, quite remote from the nucleobase binding pocket. Modeling suggested that apolar substituents could be conveniently directed into this lipophilic site if attached by a linker to C(8) of the quinazolinone scaffold.

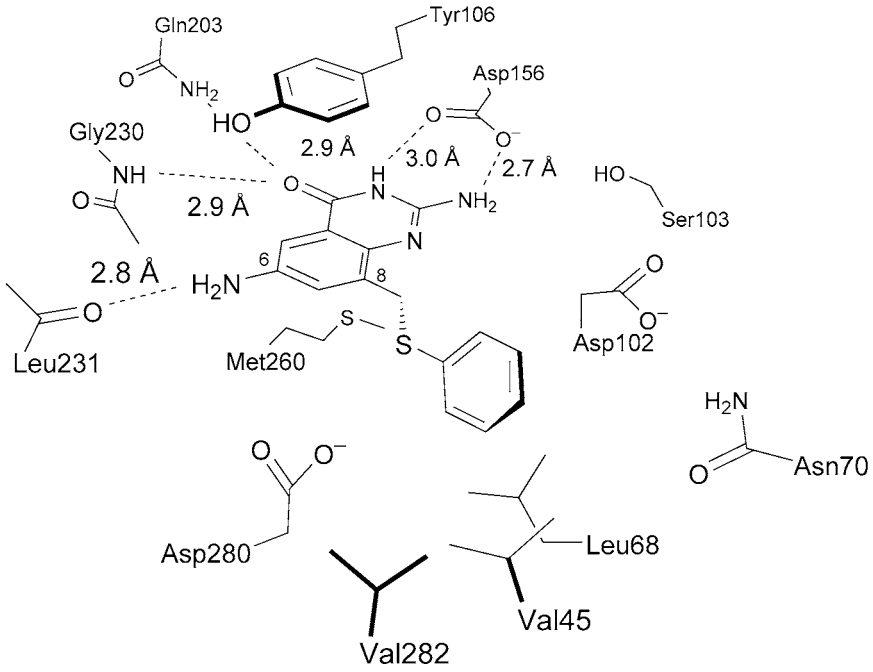


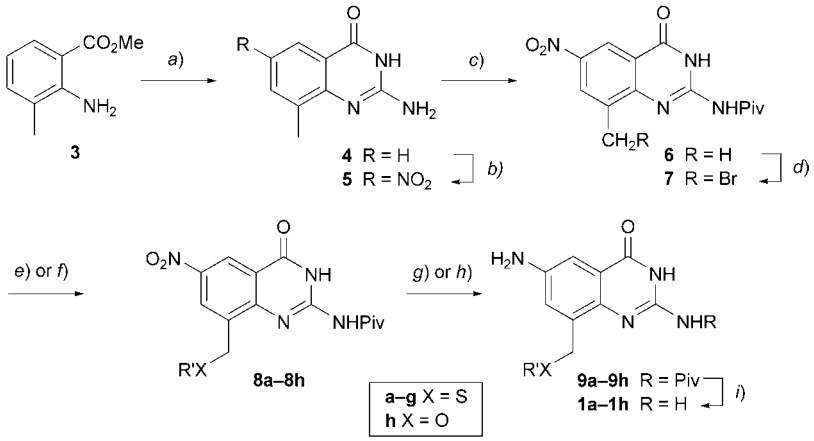
Fig. 2. *A quinazolinone-based inhibitor modeled into the active site of TGT at the design stage.* The H-bonds are represented as dotted lines.

2.2. *Targeting the Remote Lipophilic Pocket.* A small set of quinazolinone inhibitors (**1a**–**1i** and control compound **2**) were selected, bearing apolar substituents at C(8) (aliphatic, alicyclic, aromatic, heterocyclic) for binding within the small lipophilic pocket defined by Leu68, Val45, and Val282. In addition, a tertiary amine substituent was also chosen in view of potentially favorable ion-pairing (in the protonated form) with the (presumably) deprotonated carboxylate side chain of Asp280.

First-generation inhibitors were synthesized starting from commercially available 3-methyl-2-nitrobenzoic acid that was esterified (HCl, MeOH) and subsequently

hydrogenated (H_2, Pd/C, MeOH) to give amino ester **3** (76%). Quinazolinone **4** was formed by treatment of **3** with chloroformamidinium chloride (88%; *Scheme 1*) [22], and the following nitration provided exclusively the desired C(6)-NO_2 isomer **5** in good yield (72%). The solubility of **5** in common organic solvents was dramatically increased by introduction of the pivaloyl group at C(2)-NH_2, which allowed the subsequent benzylic bromination of **6** in CCl_4. The $BrCH_2$ derivative **7** was subjected to substitution with various commercially available thiols affording **8a**–**8f** (for R′ in *Scheme 1*, see *Fig. 3*) [23], while reaction with PhOH resulted in aryl ether **8h**. [1,1′-Biphenyl]-3-thiol for the synthesis of **8g** was prepared from 3-bromo-1,1′-biphenyl and sodium ethanethiolate [24]. In the substitution with 2-sulfanyl-1*H*-imidazole to give **8e**, *N*-alkylation of the 1*H*-imidazole moiety was prevented by using Cs_2CO_3 in THF. Reduction of the NO_2 group in **8a**–**8h** to give amines **9a**–**9h** was carried out with $SnCl_2$ or Zn in AcOH/H_2O, the latter condition being far more convenient for the isolation of the product. Finally, removal of the pivaloyl group provided inhibitors **1a**–**1h** (see *Fig. 3*). Due to the increased H_2O solubility of inhibitor **1d**, its purification was carried out by ion-exchange chromatography.

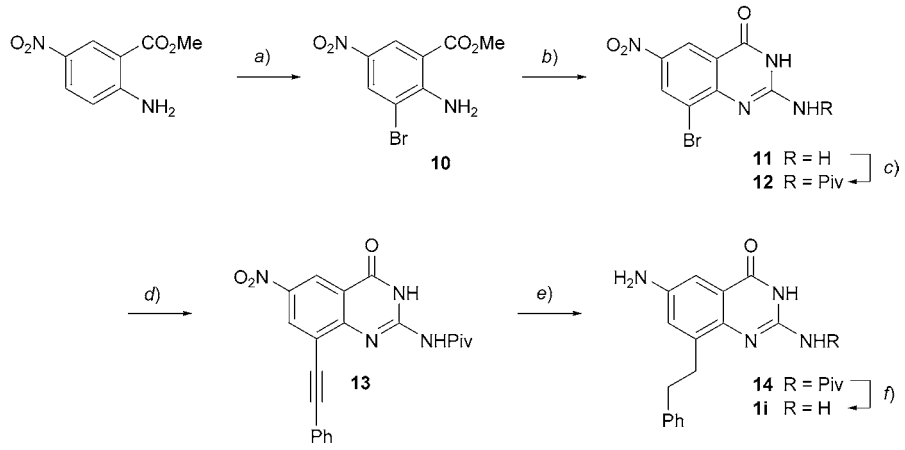
Scheme 1. *Synthesis of Inhibitors* **1a**–**1h**



a) Chloroformamidinium chloride, dimethyl sulfone, 150°, 2 h; 88%. *b*) HNO_3, H_2SO_4, r.t., 12 h; 72%. *c*) PivCl, Py, DMA, 110°, 12 h; 82%. *d*) NBS, Bz_2O_2, CCl_4, Δ, 12 h; 59%. *e*) R′SH, BuLi, or Cs_2CO_3, THF, r.t., 3–4 h; 58–79%. *f*) PhOH, NaH, THF, 0 → r.t., 4 h; 52%. *g*) $SnCl_2$, EtOH, 70°, 6 h; 25–51% (X = S). *h*) Zn, AcOH, H_2O, r.t., 3 h; 50–74% (X = S, O). *i*) HCl, EtOH, 70°, 3 h; 40–94%. Bz = benzoyl; DMA = *N*,*N*-dimethylacetamide; NBS = *N*-bromosuccinimide; Piv = pivaloyl; Py = pyridine. See *Fig. 3* for R′ in R′SH, **8a**–**8h**, **9a**–**9h**, and **1a**–**1h**.

The 2-phenylethyl derivative **1i** was prepared starting from 2-amino-5-nitrobenzoic acid that was esterified ($SOCl_2$, MeOH; 77%) and brominated (Br_2, AcOH; 92%) to give methyl 2-amino-3-bromo-5-nitrobenzoate **10** (*Scheme 2*). Ring closure with guanidinium chloride provided **11** and *N*-protection gave **12**. *Sonogashira* cross-coupling [25] with phenylacetylene led to **13** that was transformed by hydrogenation (→ **14**) and deprotection into the desired ligand **1i**.

Scheme 2. *Synthesis of Inhibitor* **1i**



a) Br_2, AcOH, r.t., 4 h; 92%. *b*) Guanidinium chloride, EtONa, EtOH, Δ, 60 h; 63%. *c*) PivCl, Py, DMA, 110°, 8 h; 71%. *d*) PhC≡CH, $[Pd(OAc)_2]$, P(*o*-tol)$_3$, CuI, Et_3N, Δ, 15 h; 23%. *e*) H_2, Pd/C (10%), EtOH, 70°, 4 h; 46%. *f*) HCl, EtOH, 70°, 4 h; 93%. tol = toluyl.

2.3. *Biological Activity and Crystallographic Studies.* The *in vitro* activity of compounds **1a**–**1i** and **2** toward TGT (*Z. mobilis*) was determined in an assay based on radiolabeled substrates (*Fig. 3*; for a description of the assay, see [12]). The high activity of the most potent inhibitor, phenyl thioether **1c** ($K_i = 100$ nM), validated our strategy to occupy the apolar binding pocket defined by Val45, Leu68, and Val282, with lipophilic residues. However, the other inhibitors showed decreased activity (0.6–7.7 μM) with respect to the parent heterocyclic scaffold **2** ($K_i = 350$ nM). The modest binding affinity of **1d** (3.5 μM) and **1e** (1.4 μM) indicated that no significant H-bonding interaction to Asp280 was achieved.

Unexpectedly at first, the replacement of the S-atom in the thioether inhibitor **1c** ($K_i = 100$ nM) by the O-atom (in **1h**; $K_i = 5.6$ μM) or by a CH_2 group (in **1i**; $K_i = 3.6$ μM)

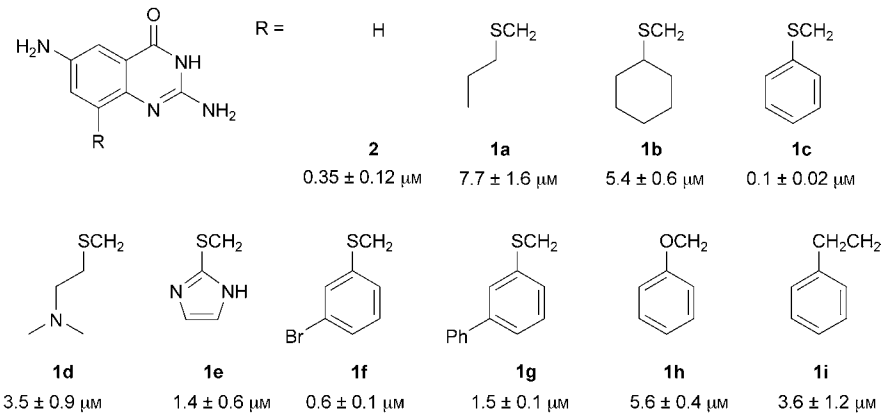


Fig. 3. *Biological activity* (K_i values) *of the first series of TGT inhibitors*

resulted in a substantial loss of activity. This observation can be rationalized by a combination of hydrophobicity, conformational, and stereoelectronic effects, as discussed in detail in [16]. The phenyl thioether residue is quite hydrophobic and can reach deeper into the hydrophobic pocket, while maintaining an energetically favorable conformation. Also noticeable is the large difference in binding affinity between cyclohexyl (**1b**; $K_i = 5.4$ μM) and phenyl (**1c**; $K_i = 100$ nM) thioethers, which suggests that the shallow lipophilic pocket is better filled with a flat aromatic rather than a bulkier alicyclic residue. The limited size of this pocket is further evidenced by the decreased binding affinity of the 3-bromophenyl thioether **1f** ($K_i = 0.6$ μM) and 1,1′-biphenyl derivative **1g** ($K_i = 1.5$ μM). The latter results were actually rather surprising since, according to the molecular modeling, Br and Ph substituents in *meta*-position of the phenyl thioether residue were expected to undergo favorable *Van der Waals* interactions in the surrounding of the hydrophobic pocket.

Several crystal structures of the inhibitors soaked into TGT crystals were solved, confirming, in general, the binding mode proposed for the diaminoquinazolinone scaffold. The pyrimidone ring forms H-bonds with Asp156, Gln203, and Gly230, the amino group at C(6) interacts with the C=O group of Leu231, and the bicyclic scaffold is sandwiched between the side chains of Tyr106 and Met260 (*Fig. 4*) [16][17]. In agreement with the modeling predictions, substituents at C(8) of the quinazolinone scaffold are correctly oriented for reaching into the lipophilic pocket formed by Val45, Leu68, and Val282. This is illustrated in *Fig. 4*,*a*, for the thiopropyl side chain of inhibitor **1a** (soaked at pH 8.5 into TGT crystals). Its imidazole-substituted counterpart **1e** was soaked for solubility reasons at two different pH values, 8.5 and 5.5. This change in pH induced a profound conformational reorganization of the carboxylate side chain of Asp102. Whereas, in the structure at pH 8.5, this residue is pointing away from the heterocyclic ligand that interacts with a bound H_2O molecule (as also seen in *Fig. 4*,*a*), the carboxylate side chain turns around at lower pH, displaces the previously present H_2O, and undergoes H-bonding with N(1) and C(2)–NH_2 of the quinazolinone scaffold (*Fig. 4*,*b*). Moreover, two distinct conformations of the imidazole substituent were deduced from the location of the S-atom above and below the quinazolinone core. Rotational flexibility accounts for the non-observable electron density of the imidazole moiety; this is consistent with the lack of a dominant H-bond to Asp280. Finally, the weak activity of **1d** ($K_i = 3.5$ μM) is readily rationalized based on the crystal-structure analysis: the (presumably protonated) 2-(dimethylamino)ethyl group of **1d** does not reach into the hydrophobic pocket but is rather oriented toward bulk H_2O (for a more detailed discussion of the crystallographic analysis, see [17]).

2.4. *Variation of the H-Bond Donor at C(6)*. Aromatic NH_2 groups at C(6) of the quinazolinone scaffold, as in **1a**–**1i**, are only modest H-bond donors, and, therefore, we decided to introduce different H-bond donors to interact with the C=O group of Leu231. In a series of inhibitors featuring the phenyl thioether substituent at C(8), we first prepared ligand **15** lacking any H-bond donor at C(6), to confirm the importance of the H-bond to Leu231, as previously demonstrated by *Graedler et al.* for pyrazinediones [12]. The synthesis of **15** followed the one shown in *Scheme 1*, with pivaloyl derivatives **16** and **17** as isolated intermediates (*Scheme 3*).

Changing the aromatic amino to the more acidic phenolic OH group (pK_a of aniline: 27 *vs.* phenol: 10) was expected to increase the strength of the H-bonding

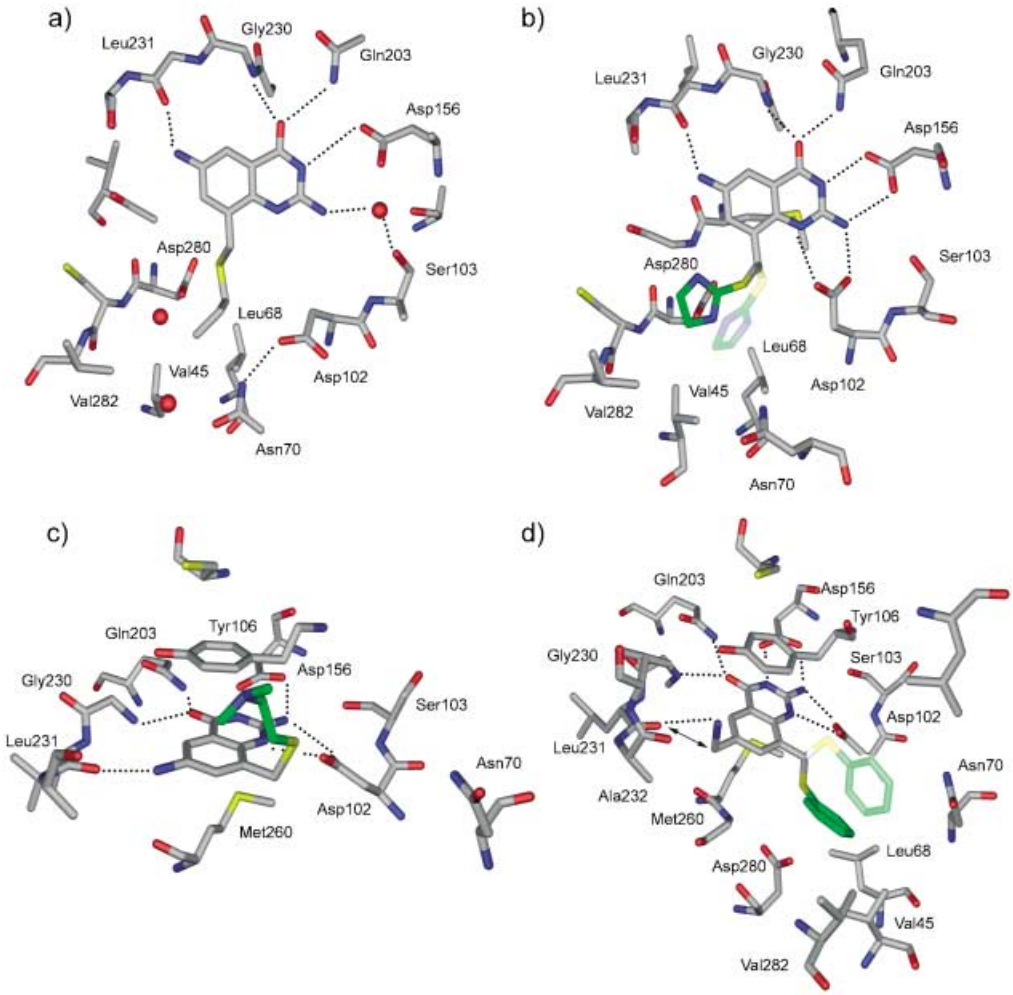
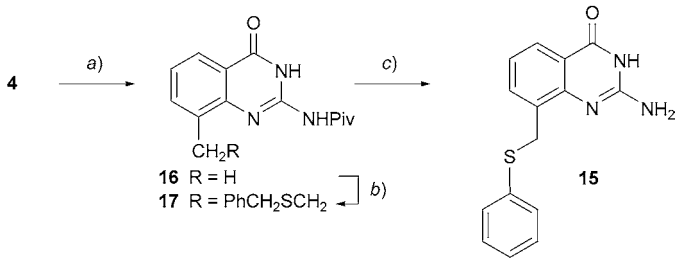


Fig. 4. *Four different crystal structures of TGT–inhibitor complexes* [16][17]. The green color denotes parts of the residues departing from position 8 of the quinazolinone scaffold without detectable electron density, and the transparent portion represents the alternative conformation taken by these substituents. *a*) **1a**, red spheres are isolated bound H_2O molecules; PDB code: 1K4 H (soaking at pH 8.5; 1.8-Å resolution). *b*) **1e**, PDB code: 1Q63 (soaking at pH 5.5; 1.85-Å solution). *c*) **1d**, PDB-code: 1Q65 (soaking at pH 5.5, 2.1-Å resolution). *d*) **34**, PDB code: 1Q66 (soaking at pH 5.5, 1.75-Å resolution). The arrow marks a repulsive (C)=O ··· CH_2 contact (3.0 Å). At pH 5.5 (*Fig. 4*,*b–d*), Asp102 undergoes a conformational rearrangement and points toward the inhibitor, thereby displacing a bound H_2O molecule present at pH 8.5 (*Fig. 4*,*a*). Color coding: N: blue, O: red, S: yellow, C: grey.

interaction with the C=O group of Leu231. For this purpose, regioselective bromination of methyl anthranilate **3** in AcOH afforded **18** in 93% yield (*Scheme 4*). Cyclization to **19** and introduction of the pivaloyl group provided quinazolinone **20**. After radical bromination to **21**, the phenyl and thiophenoxy substituents were introduced as described in *Scheme 1*. Deprotection of **22a** and **22b** furnished the

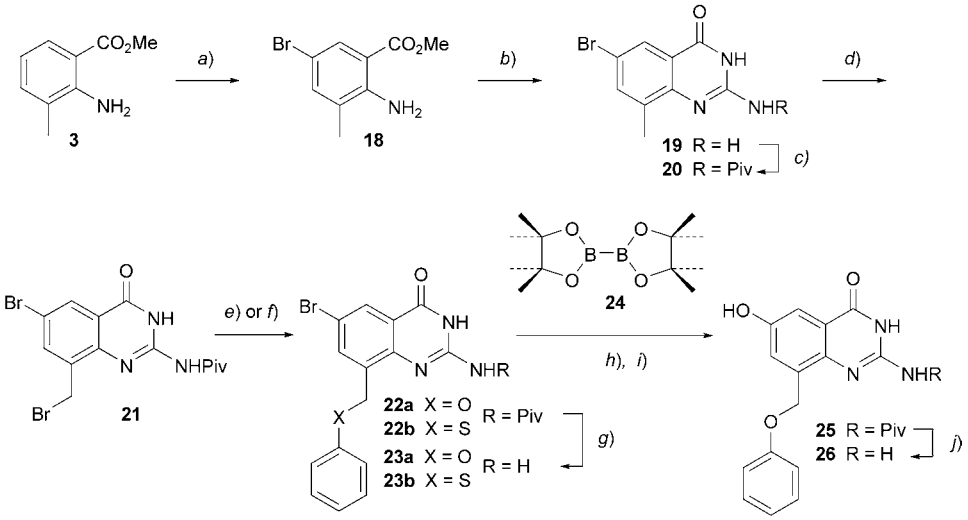
Scheme 3. *Synthesis of Inhibitor* **15**



a) PivCl, Py, DMA, 110°, 3 h; 44%. *b*) NBS, AIBN, CCl_4, Δ, 18 h; then PhSH, BuLi, THF, r.t., 4 h; 57%. *c*) HCl, EtOH, 70°, 4 h; 70%. AIBN = Azobis[isobutyronitrile].

potential ligands **23a** and **23b**, respectively, bearing a Br substituent at C(6). Borylation of **22a** with 4,4,4′,4′,5,5,5′,5′-octamethyl[2,2′-bi[1,3,2]dioxaborolanyl] (**24**) in the presence of [$PdCl_2$(dppf)] and subsequent oxidation of the crude boronic ester with H_2O_2 led to **25** (80% over two steps) [26], and acidic deprotection yielded inhibitor **26**.

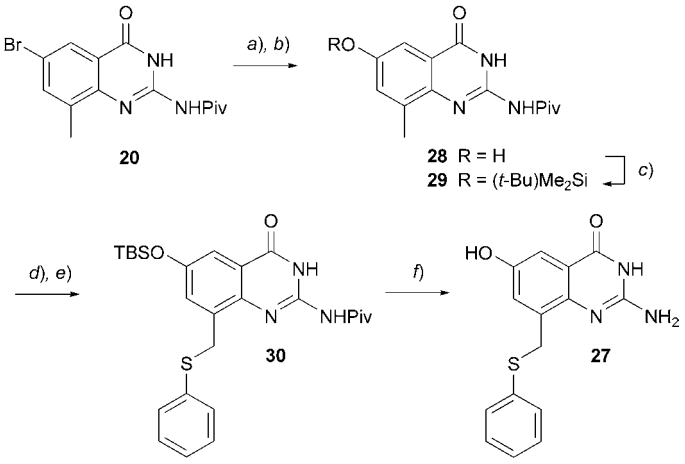
Scheme 4. *Synthesis of Inhibitors* **23a**, **23b**, *and* **26**



a) Br_2, AcOH, 30 min, 10°; 93%. *b*) Chloroformamidinium chloride, dimethyl sulfone, 140°, 1 h; 90%. *c)* PivCl, NEt_3, DMA, 100°, 3 h; 76%. *d*) NBS, AIBN, CCl_4, 80°, 18 h; 76%. *e*) PhOH, NaH, THF, 0° → r.t., 3 h; 80% (**22a**). *f*) PhSH, BuLi, THF, 0 → r.t., 3 h; 87% (**22b**). *g*) HCl, EtOH, 75°, 2–3 h; 67% (**23a**); 60% (**23b**). *h*) [$PdCl_2$(dppf)], AcOK, Me_2SO, 80°, 18 h. *i*) H_2O_2, AcOH, r.t., 6 h; 80% over 2 steps. *j*) HCl, EtOH, 75°, 4 h; 40%. dppf = 1,1′-Bis(diphenylphosphino)ferrocene.

As the phenylsulfanyl derivative **23b** would not survive the oxidative cleavage of the boronic ester, another route was pursued to produce phenol **27**. Starting from bromoquinazolinone **20**, the OH group was introduced in good yield by borylation followed by oxidation (*Scheme 5*). Protection of **28** with (*t*-Bu)Me_2SiCl provided **29**

Scheme 5. *Synthesis of Inhibitor* **27**



a) **24**, [$PdCl_2$(dppf)], AcOK, Me_2SO, 80°, 18 h. *b*) H_2O_2, AcOH, r.t., 5 h; 84% over 2 steps. *c*) Me_2(*t*-Bu)SiCl, 1*H*-imidazole, DMF, 0° → r.t., 18 h; 88%. *d*) NBS, AIBN, CCl_4, 80°, 18 h. *e*) PhSH, BuLi, THF, 0° → r.t., 3 h; 77% over 2 steps. *f*) HCl, EtOH, 75°, 4 h; 80%.

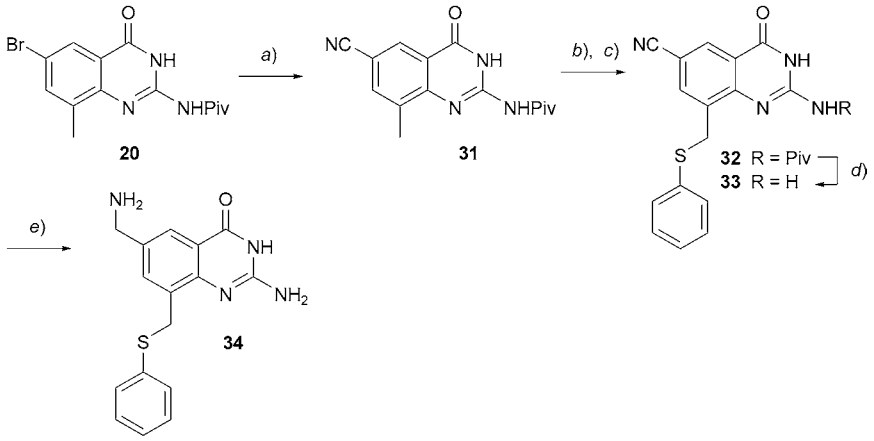
(88%). Bromination and subsequent thioether formation furnished **30**, which, upon acidic cleavage of both protecting groups, yielded inhibitor **27** (80%).

We also introduced an NH_2CH_2 substituent at C(6) of the quinazolinone core, in analogy to the natural substrate $preQ_1$ (*Fig. 1*). We expected that, under the biological testing conditions (pH 7.3), the primary NH_2 group would be protonated and experience favorable ionic H-bonding interactions with the neighboring C=O groups of Leu231 and Ala232. Starting from **20**, Br → CN exchange was performed in good yield with CuCN in refluxing DMF (*Scheme 6*) [27]. Bromination of carbonitrile **31** and substitution with phenylsulfanyl group provided **32**, which was deprotected to yield the potential inhibitor **33**. Finally, chemoselective reduction of the CN group with Li[Et_3BH] in THF furnished the target compound **34**.

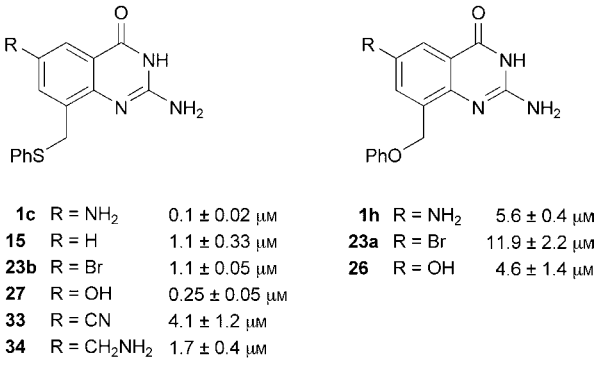
2.5. *Biological Activity of the Second Inhibitor Series.* The comparison between **1c** ($K_i = 0.1$ μM) and **15** ($K_i = 1.1$ μM) shows that the introduction of the NH_2 group at C(6) enhances the binding affinity by a factor of 10 ($\Delta(\Delta G) \approx 1.4$ kcal mol^{-1}), most probably due to H-bonding to the C=O group of Leu231 (*Fig. 5*). On the other hand, the introduction of an HO substituent as a potentially better H-bond donor does not have a beneficial effect on the biological activity (**27**; $K_i = 0.25$ μM). Ligands with Br or CN substituents, lacking H-bond donor capacity, expectedly are modest binders. The large difference in binding affinity between phenyl ether **1h** and phenyl thioether **1c** (factor of 56) was well reproduced in the series of inhibitors bearing either Br or OH groups at C(6) (**23a**: $K_i = 11.9$ μM *vs.* **23b**: $K_i = 1.1$ μM, and **26**: $K_i = 4.6$ μM *vs.* **27**: $K_i = 0.25$ nM).

Unexpectedly at first, the NH_2CH_2-substituted inhibitor **34** displayed a substantially reduced activity ($K_i = 1.7$ μM) with respect to the anilino derivative **1c**. Later, the crystal structure of **34** complexed with TGT revealed that the (presumably) protonated

Scheme 6. *Synthesis of Inhibitor* **34**



a) CuCN, DMF, Δ, 20 h; 56%. *b*) NBS, AIBN, CCl_4, 80°, 18 h. *c*) PhSH, BuLi, THF, 0° → r.t., 3 h; 40% over 2 steps. *d*) HCl, EtOH, 75°, 4 h; 94%. *e*) Li[Et_3BH], THF, −78° → r.t., 4 h; 50%.



1c	R = NH_2	0.1 ± 0.02 μM	**1h**	R = NH_2	5.6 ± 0.4 μM
15	R = H	1.1 ± 0.33 μM	**23a**	R = Br	11.9 ± 2.2 μM
23b	R = Br	1.1 ± 0.05 μM	**26**	R = OH	4.6 ± 1.4 μM
27	R = OH	0.25 ± 0.05 μM			
33	R = CN	4.1 ± 1.2 μM			
34	R = CH_2NH_2	1.7 ± 0.4 μM			

Fig. 5. *Biological activities* (K_i values) *of the second series of TGT inhibitors*

aminomethyl group is too distant from the C=O group of Leu231 ($d(N\cdots O) = 3.3$ Å) to be engaged in an effective ionic H-bond (*Fig. 4,d*) [17]. Furthermore, the CH_2 group of the NH_2CH_2 residue forms a repulsive contact with this C=O group ($d(C\cdots O) =$ 3.0 Å).

2.6. *Two Simple Inhibitors with an 2-Aminoquinazolin-4(3*H*)-one Core: Crystallography Studies.* In the course of this work, two scarcely substituted 2-aminoquinazolinones were tested for their TGT binding. Both lack a H-bond-donor group at C(6), the synthetic intermediate **4** shows a Me group at C(8), whereas **35** is unsubstituted at this position (*Fig. 6*) [12].

The crystal structures of both compounds bound to TGT were solved and revealed marked differences of the active site environments in the two complexes. Me Derivative **4** and unsubstituted **35** displayed the normal complexation mode with the

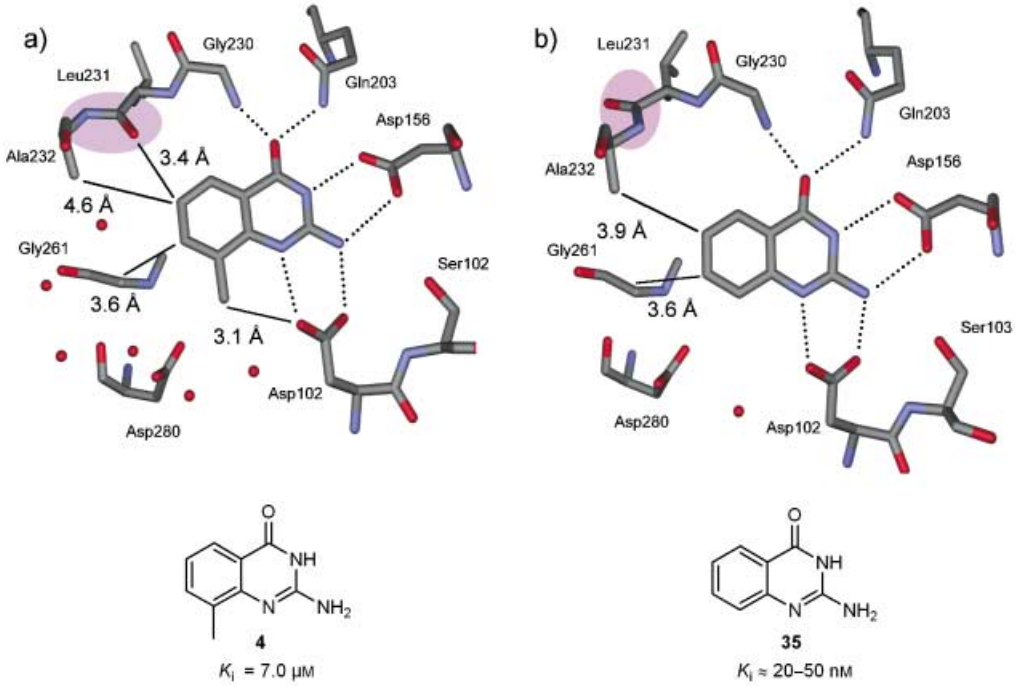


Fig. 6. *Unexpected conformational change of the peptidic backbone at Leu231/Ala232 upon a minimal change in the inhibitor structure. a*) Crystal structure of **4** complexed with TGT (1.81-Å resolution, PDB code 1S38). *b*) Crystal structure of **35** complexed with TGT (1.95-Å resolution, PDB code 1S39). Crystals were soaked with inhibitor at pH 5.5. Dotted lines: H-bonds; straight lines: other significant intermolecular contacts, red spheres: H_2O molecules.

Asp102 in the 'turn-on' conformation (carboxylate group rotated toward inhibitor), expected for soaking conditions at pH 5.5 [17]. For **4**, the C=O O-atom of Leu231 is pointing toward the inhibitor (*Fig. 6*,*a*). In contrast, the complex with **35** revealed a *ca.* 180° rotation of this C=O group toward the outside of the active site, with the adjacent N–H residue now turned inwards (*Fig. 6*,*b*). This flip of the peptide-bond region at Leu231–Ala232, previously described for pyridazinediones and $preQ_0$, allows TGT to switch between presenting donor (N–H) and acceptor (C=O) functionality, thereby modulating the recognition properties of the substrate binding site [20][28].

We assume that this backbone flip is ligand-induced depending on the properties of the H-bond functionality presented by the ligand in this region. Both **4** and **35** lack such functionality. Interestingly, they provoke different conformations of the Leu231–Ala232 peptide bond, which suggests that both protein conformers are rather close in energy. Tiny differences in the binding modes of **4** and **35** stabilize this flip in either orientation. The applied assay conditions reveal **4** to be of 7.0μM affinity in agreement with the lack of a H-bond donor at C(6).

Futhermore, the major contributor to the weaker binding of **4** clearly is the Me group at C(8). This lipophilic substituent orients into a highly polar environment formed by several H_2O molecules as well as the two catalytic residues Asp280 and

Asp102. In fact, the crystal structure shows a strongly repulsive contact between the Me group of **4** and one of the O-atoms of the carboxylate side chain of Asp102 (d(C···O) = 3.1 Å)(*Fig. 6*,*a*; the 'turn-on' conformation of Asp102 seen in the two co-crystal structures is most likely occurring at the biological testing conditions (pH 7.3) as well). A lipophilic group protruding into the solvation sphere of a carboxylate group clearly is highly detrimental to binding affinity.

To our surprise, the binding assay suggested significantly stronger binding of **35** in the submicromolar range (20–50 nM). Although quite speculative, this unexpectedly low value is possibly pretended by the superimposed tRNA binding. In this discussion, it has to be considered that binding affinities are determined in presence of $tRNA^{Tyr}$ [12]. In the assay, the quinazolinone ligands inhibit the TGT-catalyzed exchange of guanine (G)34 in the anticodon loop with [8-^{3}H]G, leading to radiolabeled $tRNA^{Tyr}$ [12]. The recently solved crystal structure of the complex of 9-deazaguanine with TGT covalently bound to tRNA [9] indicates that a small ligand of a size similar to 9-deazaguanine, such as **35**, could still be accommodated at the binding site in presence of covalently bound tRNA. This would imply rather different binding conditions for **35** compared to the other inhibitors exhibiting a side chain at C(8). Supposedly, *via* their occupation of the remote lipophilic pocket formed by Val45, Leu68, and Val282, they pretend or at least strongly interfere (*e.g.*, for **4** *via* its Me group) with the binding of tRNA. This substrate is also accommodated in this pocket by its ribose ring and the adjacent phosphate group as demonstrated in the crystal structure of the ternary TGT complex with 9-deazaguanine. We further assume that the currently used CH_2X linkers, departing from C(8), pay a large penalty while passing through the highly hydrophilic environment encompassed by Asp280 and Asp102 (at 6.1 Å distance from each other) to direct lipophilic residues (such as a Ph ring) into that pocket. Possibly, the observed S-effect is also determined by the fact that a well-polarizable S-atom in the pivotal position between the two carboxylate side chains of Asp102 and Asp280 is more favorable than an O-atom. To better cope with the given local requirements for interactions, in a next lead optimization cycle, we, therefore, intend to introduce more-polar, possibly positively charged linkers to eliminate the unfavorable interactions seen with the current generation of inhibitors.

3. Conclusions. – This study establishes 2-aminoquinazolin-4(3*H*)-ones as promising inhibitors for tRNA-guanine transglycosylase, an enzymatic target against shigellosis. Structure-based design (*Fig. 2*) and versatile synthetic protocols (*Schemes 1–5*) afforded a series of potent inhibitors, with activities up to K_i = 100 nM (**1c**; *Figs. 3* and *5*). The binding mode of several of these ligands in the active site of TGT was established by crystal-structure analyses (*Figs. 4* and *6*). The following results were obtained, providing valuable guidelines for future lead optimization cycles: *i*) The pyrimidone ring of the heterocyclic core undergoes H-bonding with Asp156, Gln203, and Gly230, and the bicyclic scaffold is nicely sandwiched between the side chains of Tyr106 and Met260. *ii*) A shallow lipophilic pocket formed by Val45, Leu68, and Val282 was identified, and its occupancy by a phenylsulfanyl moiety was shown to enhance binding affinity. However, to reach into this remote pocket, $PhXCH_2$ linkers (X = S, O, CH_2) departing from C(8) of the quinazolinone scaffold need to pass across a very hydrophilic region of the active site encompassed by the catalytic residues

Asp280 and Asp102. During this passage, unfavorable contacts of the linker, protruding in the solvation sphere of the carboxylate of Asp102, are difficult to avoid. We intend using more-polar and even positively charged linkers in future generations of inhibitors to avoid these unfavorable contacts. *iii*) A dramatic S-effect was observed, with the replacement of the S-atom in phenylsulfanyl inhibitor **1c** ($K_i = 100$ nM) by the O-atom (in **1h**; $K_i = 5.6$ μM) or CH_2 (in **1i**; $K_i = 3.6$ μM), resulting in a substantial loss of activity. The phenylsulfanyl residue is quite hydrophobic and can reach deeper into the hydrophobic pocket, while maintaining an energetically favorable conformation. *iv*) The free enthalpy increment of the H-bond between an NH_2 group at C(6) and the C=O group of neighboring Leu231 was quantified as $\Delta(\Delta G) \leq 1.4$ kcal · mol^{-1}. *v*) Flexibility in two regions of the active site was observed in the crystal structures, namely the rotation of the Asp102 toward the inhibitor upon changing the pH from 8.5 to 5.5 during the soaking of TGT crystals with the inhibitor, and a flip of the peptidic backbone at Ala232/Leu231.

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Experimental Part

General. Solvents and reagents were reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. The following compounds were prepared according to literature procedures: chloroformamidinium chloride [29], **2** [30], and **35** [31]. THF was freshly distilled from sodium benzophenone ketyl. Evaporation *in vacuo* was conducted at H_2O aspirator pressure. All products were dried under high vacuum (h.v., 10^{-2} Torr) before anal. characterization. Column chromatography (CC): SiO_2 *60* (40–63 mm) from *Fluka*, 0–0.3 bar pressure. TLC: SiO_2 *60* F_{245}, *Merck*, visualization by UV light at 254/356 nm. M.p.: *Büchi B540* melting-point apparatus; uncorrected. IR spectra [cm^{-1}]: *Perkin-Elmer 1600-FT* spectrometer. NMR spectra (^{1}H, ^{13}C): *Varian Gemini-200*, *Varian Gemini-300*, or *Bruker AMX-500*; spectra were recorded at r.t. with solvent peak as reference. MS (*m/z* (%)): EI-MS: *VG-TRIBRID* spectrometer at 70 eV; ESI-MS: *Perkin-Elmer Sciex API III* spectrometer; HR-MALDI-MS: *IonSpec Ultima* (2,5-dihydroxybenzoic acid (DHB) matrix or 2-[(2*E*)-3-[4-(*tert*-butyl)phenyl]-2-methylprop-2-enylidene]malonitrile, (DTCB)). Elemental analyses were performed by the *Mikrolabor* at the *Laboratorium für Organische Chemie*, *ETH-Zürich*. The nomenclature was generated with the computer program *ACD-Name* (*ACD/Labs*) [32].

Crystallization and Soaking. TGT was crystallized and soaked with inhibitors at pH 8.5 or 5.5 as described in [17][28]. The new structures of TGT · **4** and TGT · **35** have been deposited in the *Protein Data Bank* (*PDB*) with codes 1S38 and 1S39, resp. The crystal data of these structures are summarized in the *Table*.

Determination of Apparent Inhibition Constants. The apparent K_i values were measured as described by *Graedler et al.* [12]. The error given amounts to the standard deviation of two independent measurements with different substrate concentrations. Due to the elaborate determination of the K_i values, the actual error is assumed to be $\approx \pm 20-30\%$.

Cyclization with Chloroformamidinium Chloride: General Procedure A (*GP A*). A mixture of the anthranilate (1 equiv.), chloroformamidinium chloride (1.5 equiv.), and dimethyl sulfone (50 equiv.) was heated to 150° for 2–3 h. After addition of conc. aq. NH_4OH soln. (2 ml), the mixture was diluted with H_2O and filtered. The residue was washed with H_2O, MeOH, acetone, and $CHCl_3$. The crude product was precipitated from hot DMF and H_2O and dried under h.v. at 80°.

Thioether Formation: General Procedure B (*GP B*). To a soln. of BuLi (1.6M in hexane; 2.5 equiv.) in abs. THF, the thiol (3.0 equiv.) was added dropwise at 0°. The soln. was allowed to warm to r.t. for 15 min, after which a soln. of the benzyl bromide (1.0 equiv.) in abs. THF was added. After stirring at r.t. for 3 h, the mixture was concentrated *in vacuo*. The residue was taken up in sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2 (3×). The combined org. phases were washed with sat. aq. NaCl soln. (1×), dried ($MgSO_4$), and evaporated *in vacuo*.

Table. *Crystal-Structure Data for the Complexes of TGT with Inhibitors* **4** *and* **35**

Crystal data	TGT · **4**	TGT · **35**
pH	5.5	5.5
Space group	*C2*	*C2*
Cell constants		
a [Å]	90.60	89.71
b [Å]	65.48	64.72
c [Å]	70.43	70.66
β [deg.]	96.53	95.76
Resolution [Å]	20–1.81	20–1.95
Total No. of refl.	85,968	70,409
No. of unique refl.	35,820	29,337
Completeness of all data [%] (outer shell)	95.7 (94.7)	99.7 (93.8)
R_{symm} for all data [%] (outer shell)[a])	8.8 (46.0)	7.2 (51.5)
R_{free} [%][b])	22.2	24.2
R Factor [%][b])	19.7	20.9
r.m.s. dev., angle [deg.]	1.4	1.2
r.m.s. dev., bond [Å]	0.006	0.006

[a]) $R_{symm} = \Sigma | I - \langle I \rangle | / \Sigma I$, where I is the observed intensity and $\langle I \rangle$ is the average intensity for multiple measurements. [b]) R_{free} [33] was calculated from a random selection of reflections constituting 10% of the data; the *R*-factor was calculated with the remaining intensities.

Reduction with $SnCl_2$: General Procedure C (*GP C*). To a soln. of the NO_2 derivative (1.0 equiv.) in EtOH, $SnCl_2 \cdot 2\ H_2O$ (4.0 eq) was added, and the mixture was heated to 70° for 6 h. After removal of the solvent *in vacuo*, the residue was taken up in sat. aq. $NaHCO_3$ soln./CH_2Cl_2. The suspension was filtered, and the filtrate was extracted with CH_2Cl_2 (3×). The combined org. phases were washed with sat. aq. NaCl soln. (1×), dried ($MgSO_4$), and evaporated *in vacuo*.

Reduction with Zn: General Procedure D (*GP D*). To a suspension of the NO_2 derivative (1.0 equiv.) in AcOH and H_2O, Zn powder (10.0 equiv.) was added portionwise at r.t. The mixture was stirred for 1–3 h at r.t., filtered, and the solvent was evaporated *in vacuo*. A 2M aq. NH_3 soln. was added to the residue, and the aq. phase was extracted with CH_2Cl_2 (3×). The combined org. phases were washed with sat. aq. NaCl soln. (1×), dried ($MgSO_4$), and evaporated *in vacuo*.

Removal of the Pivaloyl Protecting Group: General Procedure E (*GP E*). The pivaloyl-protected derivative was taken up at r.t. in ethanolic HCl soln. (EtOH/conc. aq. HCl 10:1), and the mixture was heated to 70° for 3–4 h. The mixture was adjusted to pH 8 with 1N NaOH and sat. aq. Na_2CO_3 soln. The precipitate formed was filtered, washed with H_2O, acetone, and $CHCl_3$, and dried several hours under h.v. at 70°.

*2-Amino-8-methylquinazolin-4(3*H*)-one* (**4**). *GP A* with **3** (2 g, 12.1 mmol) and chloroformamidinium chloride (2 g, 17.4 mmol). Precipitation from Me_2SO/H_2O yielded **4** (1.86 g, 88%). White woolly solid. M.p. 300°. IR (KBr): 3379*s*, 3134*s*, 2922*m*, 1650*s*, 1605*s*, 1561*s*, 1519*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 11.39 (br. *s*, 1 H); 7.74 (*d*, *J* = 7.4, 1 H); 7.46 (*d*, *J* = 7.4, 1 H); 7.04 (*t*, *J* = 7.4, 1 H); 6.76 (br. *s*, 2 H); 2.34 (*s*, 3 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 160.5; 149.9; 143.8; 133.4; 127.9; 122.3; 120.4; 114.8; 15.6. HR-MALDI-MS (DHB): 176.0818 (MH^+, $C_9H_{10}N_3O^+$; calc. 176.0824). Anal. calc. for $C_9H_9N_3O$ (175.19): C 61.70, H 5.18, N 23.99, O 9.13; found: C 61.54, H 5.09, N 23.83, O 9.37.

*2-Amino-8-methyl-6-nitroquinazolin-4(3*H*)-one* (**5**). Conc. H_2SO_4 (15 ml) was poured into 65% HNO_3 (15 ml) at 0°, and **4** (1.0 g, 5.7 mmol) was added portionwise in a way to keep $T \leq 10°$. The ice bath was removed, and the mixture was allowed to stir overnight at r.t. The mixture was poured on to ice and treated with conc. aq. NH_4OH soln. The precipitate formed was collected by filtration, washed with H_2O, and dried under h.v.: 0.9 g (72%) of **5**. Yellow solid. M.p. >325°. IR (KBr): 3410*m*, 3141*m*, 1689*m*, 1657*m*, 1595*s*, 1493*s*, 1336*s*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 11.39 (br. *s*, 1 H); 8.52 (*d*, *J* = 2.3, 1 H); 8.23 (*d*, *J* = 2.3, 1 H); 7.04 (br. *s*, 2 H); 2.43 (*s*, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 161.8; 155.6; 153.9; 140.1; 134.0; 127.7; 120.4; 115.9; 17.5. HR-MALDI-MS (DTCB): 219.0526 ($[M-H]^-$, $C_9H_7N_4O_3^-$; calc. 219.0518).

N-*(3,4-Dihydro-8-methyl-6-nitro-4-oxoquinazolin-2-yl)-2,2-dimethylpropanamide* (**6**). To a suspension of **5** (500 mg, 2.27 mmol) in DMA (12 ml), pyridine (0.36 ml, 4.54 mmol) and 2,2-dimethylpropanoyl chloride (0.36 ml, 2.95 mmol) were sequentially added at r.t., and the mixture was heated to 110° overnight. After cooling to r.t., the mixture was poured into H_2O (200 ml), and the precipitate formed was collected by filtration. CC (SiO_2; CH_2Cl_2/MeOH 99:1) provided **6** (570 mg, 82%). Yellow solid. M.p. 207–208° ($CHCl_3$/hexane). IR ($CHCl_3$): 3426*w*, 3196*w*, 3035*w*, 1685*s*, 1626*s*, 1587*s*, 1441*w*, 1340*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 12.12 (br. *s*, 1 H); 8.92 (*d*, *J* = 3.0, 1 H); 8.33 (*dd*, *J* = 3.0, 0.9, 1 H); 8.20 (br. *s*, 1 H); 2.55 (*s*, 3 H); 1.39 (*s*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 180.5; 160.1; 151.9; 147.8; 143.8; 136.7; 128.6; 121.0; 120.0; 40.5; 27.9; 17.7. HR-MALDI-MS (DHB): 305.1245 (MH^+, $C_{14}H_{17}N_4O_4^+$; calc. 305.1250). Anal. calc. for $C_{14}H_{16}N_4O_4$ (304.30): C 55.26, H 5.30, N 18.41; found: C 55.21, H 5.47, N 18.51.

N-*[8-(Bromomethyl)-3,4-dihydro-6-nitro-4-oxoquinazolin-2-yl]-2,2-dimethylpropanamide* (**7**). To a suspension of **6** (9.30 g, 30.6 mmol) and NBS (5.44 g, 30.6 mmol) in CCl_4 (700 ml), a cat. amount of Bz_2O_2 was added, and the mixture was heated to reflux overnight. After removal of the solvent *in vacuo*, the residue was washed with hot H_2O. CC (SiO_2; hexane/AcOEt 7:3) provided **7** (5.9 g, 50%). White solid. M.p. 201–202°. IR (neat): 3214*w*, 3086*w*, 2986*w*, 1660*s*, 1620*s*, 1581*s*, 1496*s*, 1341*s*, 1247*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 12.22 (br. *s*, 1 H); 9.04 (*d*, *J* = 2.7, 1 H); 8.58 (*d*, *J* = 2.7, 1 H); 8.29 (br. *s*, 1 H); 4.84 (*s*, 2 H); 1.40 (*s*, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 180.8; 159.6; 151.2; 148.8; 143.8; 135.3; 129.6; 123.6; 120.8; 40.6; 27.1; 27.0. HR-MALDI-MS (DHB): 383.0352 (MH^+, $C_{14}H_{16}N_4O_4^+$; calc. 383.0355).

N-*{3,4-Dihydro-6-nitro-4-oxo-8-[(propylsulfanyl)methyl]-2,2-dimethylquinazolin-2-yl}-2,2-dimethylpropanamide* (**8a**). *GP B* with BuLi (1.6M in hexane; 4.06 ml, 6.5 mmol) in abs. THF (10 ml), PrSH (0.71 ml, 7.8 mmol), **7** (1.0 g, 2.6 mmol) in abs. THF (10 ml). CC (SiO_2; $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 99:1) provided **8a** (750 mg, 76%). Yellow solid. M.p. 153–155°. IR (KBr): 3211*w*, 3000*w*, 2923*m*, 1665*s*, 1627*s*, 1604*s*, 1583*s*, 1521*m*, 1468*m*, 1436*m*, 1339*s*, 1247*s*, 1137*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 12.19 (br. *s*, 1 H); 8.99 (*d*, *J* = 2.6, 1 H); 8.47 (*d*, *J* = 2.6, 1 H); 8.29 (*s*, 1 H); 4.04 (*s*, 2 H); 2.50 (*t*, *J* = 7.3, 2 H); 1.57–1.72 (*m*, 2 H); 1.40 (*s*, 9 H); 1.01 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 178.4; 157.6; 149.1; 146.0; 141.6; 134.8; 126.0; 119.8; 118.4; 38.1; 31.7; 28.5; 24.6; 20.2; 11.0. HR-MALDI-MS (DHB): 379.1434 (MH^+, $C_{17}H_{23}N_4O_4S^+$; calc. 379.1440).

N-*{8-[(Cyclohexylsulfanyl)methyl]-3,4-dihydro-6-nitro-4-oxoquinazolin-2-yl}-2,2-dimethylpropanamide* (**8b**). *GP B* with BuLi (1.6M in hexane; 4.06 ml, 6.5 mmol) in abs. THF (10 ml), cyclohexanethiol (0.96 ml, 7.8 mmol), **7** (1.0 g, 2.6 mmol) in abs. THF (10 ml). CC (SiO_2; $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 99:1) provided **8b** (800 mg, 74%). Yellow solid. M.p. 97–102°. IR (KBr): 3177*w*, 2922*m*, 2844*w*, 1674*s*, 1602*s*, 1516*w*, 1388*s*, 1250*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 12.16 (br. *s*, 1 H); 8.90 (*d*, *J* = 2.6, 1 H); 8.50 (*d*, *J* = 2.6, 1 H); 8.42 (*s*, 1 H); 4.00 (*s*, 2 H); 2.52–2.68 (*m*, 1 H); 1.87–2.03 (*m*, 2 H); 1.66–1.70 (*m*, 2 H); 1.52–1.65 (*m*, 1 H); 1.36 (*s*, 9 H); 1.13–1.37 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 181.0; 160.3; 151.6; 148.5; 144.2; 137.9; 128.6; 122.2; 120.8; 43.9; 40.6; 33.5; 29.2; 27.0; 26.0; 25.8. HR-MALDI-MS (DHB): 419.1748 (MH^+, $C_{20}H_{27}N_4O_4S^+$; calc. 419.1753).

N-*{3,4-Dihydro-6-nitro-4-oxo-8-[(phenylsulfanyl)methyl]quinazolin-2-yl}-2,2-dimethylpropanamide* (**8c**). *GP B* with BuLi (1.6M in hexane; 4.06 ml, 6.5 mmol) in abs. THF (10 ml), PhSH (0.8 ml, 7.8 mmol), **7** (1.0 g, 2.6 mmol) in abs. THF (10 ml). CC (SiO_2; CH_2Cl_2 then CH_2Cl_2/MeOH 99:1) provided **8c** (850 mg, 79%). Yellow solid. M.p. 148–150°. IR (KBr): 3272*m*, 3077*w*, 2966*w*, 1664*s*, 1624*s*, 1583*s*, 1522*s*, 1433*s*, 1339*s*, 1245*s*, 1139*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 12.17 (br. *s*, 1 H); 8.96 (*d*, *J* = 2.8, 1 H); 8.20 (*d*, *J* = 2.8, 1 H); 8.19 (*s*, 1 H); 7.23–7.33 (*m*, 5 H); 4.40 (*s*, 2 H); 1.33 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 180.7; 159.9; 151.3; 148.3; 143.6; 135.8; 135.1; 131.1; 129.1; 128.5; 127.3; 122.3; 120.5; 40.5; 34.2; 27.0. HR-MALDI-MS (DHB): 413.1277 (MH^+, $C_{20}H_{21}N_4O_4S^+$; calc. 413.1284).

N-*[8-({[(2-Dimethylamino)ethyl]sulfanyl}methyl)-3,4-dihydro-6-nitro-4-oxo-quinazolin-2-yl]-2,2-dimethylpropanamide* (**8d**). *GP B* with BuLi (1.6M in hexane; 8.12 ml, 13.0 mmol) in abs. THF (10 ml), 2-(dimethylamino)ethanethiol hydrochloride (1.21 g, 8.58 mmol), **7** (1.0 g, 2.6 mmol) in abs. THF (10 ml). CC (SiO_2; CH_2Cl_2/MeOH/NEt_3 98:1:1) provided **8d** (740 mg, 74%). Yellow solid. M.p. 161–163°. IR (KBr): 3211*w*, 2995*w*, 2923*m*, 1662*s*, 1625*s*, 1600*s*, 1521*m*, 1468*m*, 1435*m*, 1353*s*, 1240*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.65 (br. *s*, 2 H); 8.90 (*d*, *J* = 2.6, 1 H); 8.43 (*d*, *J* = 2.6, 1 H); 4.00 (*s*, 2 H); 2.46–2.66 (*m*, 4 H); 2.22 (*s*, 6 H); 1.36 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 181.2; 160.4; 151.7; 148.9; 144.0; 137.3; 128.6; 122.4; 120.8; 59.0; 45.4; 40.6; 31.2; 30.3; 27.0. HR-MALDI-MS (DHB): 408.1712 (MH^+, $C_{18}H_{26}N_5O_4S^+$; calc. 408.1705).

N-*{3,4-Dihydro-8-[(1H-imidazol-2-ylsulfanyl)methyl]-6-nitro-4-oxoquinazolin-2-yl}-2,2-dimethylpropan* (***8e***). *To a soln. of 2-sulfanyl-1H-*imidazole (104 mg, 1.04 mmol) in abs. THF (10 ml), Cs_2CO_3 (338 mg, 1.04 mmol) was added at r.t. To the resulting suspension, **7** (200 mg, 0.52 mmol) in abs. THF (10 ml) was added, and the mixture was stirred at r.t. for 4 h. After removal of the solvent *in vacuo*, the residue was taken up in CH_2Cl_2/sat. aq. Na_2CO_3 soln. and extracted with CH_2Cl_2 (3×). The combined org. phases were washed with sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated *in vacuo*. CC (SiO_2; CH_2Cl_2/MeOH 98.5:1.5) provided **8e**

(132 mg, 63%). Yellow solid. M.p. 224–226°. IR (KBr): 2980*m*, 2888*w*, 1663*s*, 1628*s*, 1584*s*, 1529*s*, 1438*m*, 1343*s*, 1249*s*, 1137*s*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 12.44 (br. *s*, 1 H); 11.78 (br. *s*, 2 H); 8.59 (*d*, *J* = 2.7, 1 H); 8.15 (*d*, *J* = 2.7, 1 H); 7.02 (*s*, 2 H); 4.56 (*s*, 2 H); 1.26 (*s*, 9 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 180.5; 158.1; 150.0; 148.2; 140.8; 136.0; 134.5; 126.1; 122.8; 119.3; 118.0; 30.9; 24.4; C of *t*-Bu hidden by $(CD_3)_2SO$ peaks. HR-MALDI-MS (DHB): 403.1198 (*M*H$^+$, $C_{17}H_{19}N_6O_4S^+$; calc. 403.1188).

N-*(8-{[(3-Bromophenyl)sulfanyl]methyl}-3,4-dihydro-6-nitro-4-oxoquinazolin-2-yl)-2,2-dimethylpropanamide* (**8f**). *GP B* with BuLi (1.6M in hexane; 2.45 ml, 3.9 mmol) in abs. THF (10 ml), 3-bromothiophenol (0.5 ml, 4.3 mmol), **7** (0.5 g, 1.3 mmol) in abs. THF (10 ml). CC (SiO_2; AcOEt/hexane 2:8) provided **8f** (373 mg, 58%). Yellow oil. IR ($CHCl_3$): 3428*w*, 3028*w*, 2969*w*, 1687*s*, 1624*s*, 1607*s*, 1586*s*, 1342*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 12.22 (*s*, 1 H); 8.90 (*d*, *J* = 2.5, 1 H); 8.49 (br. *s*, 1 H); 8.30 (*d*, *J* = 2.5, 1 H); 7.39 (*dd*, *J* = 1.5, 1.5, 1 H); 7.25 (*ddd*, *J* = 7.8, 1.5, 1.5, 1 H); 7.12 (*ddd*, *J* = 7.8, 1.5, 1.5, 1 H); 7.05 (*t*, *J* = 7.8, 1 H); 4.36 (*s*, 2 H); 1.37 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 180.7; 159.7; 151.3; 148.5; 143.6; 137.7; 135.2; 132.0; 130.2; 129.6; 128.6; 128.2; 122.7; 122.4; 120.4; 40.7; 31.1; 27.1. HR-MALDI-MS (DHB): 491.0392 (*M*H$^+$, $C_{20}H_{20}BrN_4O_4S^+$; calc. 491.0389).

N-*(8-{[([1,1′-Biphenyl]-3-yl)sulfanyl]methyl}-3,4-dihydro-6-nitro-4-oxoquinazolin-2-yl)-2,2-dimethylpropanamide* (**8g**). *GP B* with BuLi (1.6M in hexane; 2.0 ml, 3.7 mmol) in abs. THF (10 ml), [1,1′-biphenyl]-3-thiol (0.70 g, 3.7 mmol), **7** (0.64 g, 1.7 mmol) in abs. THF (7 ml). CC (SiO_2; CH_2Cl_2/AcOEt 1 to 10%) provided **8g** (0.59 g, 72%). Yellow solid. M.p. 84–85°. IR ($CHCl_3$): 3430*w*, 3153*w*, 2953*w*, 2252*m*, 1685*s*, 1624*s*, 1606*s*, 1585*s*, 1530*m*, 1503*m*, 1474*m*, 1441*m*, 1375*w*, 1341*s*, 1251*m*, 1209*s*, 1127*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 12.15 (br. *s*, 1 H); 8.92 (*d*, *J* = 2.8, 1 H); 8.27 (*d*, *J* = 2.8, 1 H); 8.18 (br. *s*, 1 H); 7.24–7.49 (*m*, 9 H); 4.42 (*s*, 2 H); 1.32 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 180.5; 159.7; 151.1; 148.3; 143.5; 142.0; 140.0; 135.6 (2×); 129.2; 128.9; 128.8; 128.7; 128.5; 127.6; 126.9; 125.7; 122.2; 120.4; 40.5; 33.7; 27.0. HR-MALDI-MS (DHB): 489.1595 (*M*H$^+$, $C_{26}H_{25}N_4O_4S^+$; calc. 489.1591).

N-*[3,4-Dihydro-6-nitro-4-oxo-8-(phenoxymethyl)quinazolin-2-yl]-2,2-dimethylpropanamide* (**8h**). To a soln. of PhOH (610 mg, 6.5 mmol) in abs. THF (15 ml), NaH (60% in oil, 260 mg, 6.5 mmol) was added at 0°, and the mixture was stirred for 15 min. Subsequently, **7** (1.0 g, 2.6 mmol) in abs. THF (7 ml) was added, and the mixture was stirred for 4 h at r.t. After removal of the solvent *in vacuo*, the residue was taken up in H_2O/CH_2Cl_2 and extracted with CH_2Cl_2 (3×). The combined org. phases were washed with sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated *in vacuo*. CC (SiO_2; CH_2Cl_2, then CH_2Cl_2/AcOEt 95:5) provided **8h** (500 mg, 52%). White solid. M.p. 205–206° (CH_2Cl_2/hexane). IR ($CHCl_3$): 3425*w*, 3200*w*, 3015*w*, 1689*s*, 1625*s*, 1591*s*, 1533*m*, 1497*m*, 1411*w*, 1341*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 12.18 (br. *s*, 1 H); 9.03 (*d*, *J* = 2.7, 1 H); 8.72 (*d*, *J* = 2.7, 1 H); 8.16 (br. *s*, 1 H); 7.30–7.36 (*m*, 2 H); 6.83–7.18 (*m*, 3 H); 5.38 (*s*, 2 H); 1.39 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.4; 157.4; 155.9; 148.0; 146.1; 142.0; 132.8; 127.3; 124.6; 120.1; 119.2; 117.9; 112.5; 62.5; 38.1; 24.5. HR-MALDI-MS (DHB): 397.1503 (*M*H$^+$, $C_{20}H_{21}N_4O_5^+$; calc. 397.1512). Anal. calc. for $C_{20}H_{20}N_4O_5$ (396.40): C 60.60, H 5.09, N 14.13; found: C 60.68, H 5.22, N 14.17.

N-*{6-Amino-3,4-dihydro-4-oxo-8-[(propylsulfanyl)methyl]quinazolin-2-yl}-2,2-dimethylpropanamide* (**9a**). *GP C* with **8a** (140 mg, 0.37 mmol), $SnCl_2 \cdot 2\,H_2O$ (333 mg, 1.48 mmol) in EtOH (25 ml). CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 98:1:1) provided **9a** (65 mg, 50%). Yellow solid. M.p. 201–203°. IR ($CHCl_3$): 3436*w*, 3231*w*, 2954*m*, 2913*m*, 2851*w*, 1667*s*, 1631*s*, 1451*m*, 1364*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 11.88 (br. *s*, 1 H); 8.09 (br. *s*, 1 H); 7.38 (*d*, *J* = 2.6, 1 H); 7.10 (*d*, *J* = 2.6, 1 H); 3.97 (*s*, 2 H); 3.92 (br. *s*, 2 H); 2.49 (*t*, *J* = 7.2, 2 H); 1.56–1.74 (*m*, 2 H); 1.35 (*s*, 9 H); 0.99 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 180.2; 161.3; 144.1; 143.3; 139.4; 136.2; 124.0; 122.0; 109.1; 40.2; 34.1; 30.9; 27.2; 22.8; 13.6. HR-MALDI-MS (DHB): 349.1690 (*M*H$^+$, $C_{17}H_{25}N_4O_2S^+$; calc. 349.1698).

N-*{6-Amino-8-[(cyclohexylsulfanyl)methyl]-3,4-dihydro-4-oxoquinazolin-2-yl}-2,2-dimethylpropanamide* (**9b**). *GP C* with **8b** (0.65 g, 1.55 mmol), $SnCl_2 \cdot 2\,H_2O$ (1.40 g, 6.2 mmol) in EtOH (25 ml). CC (SiO_2; CH_2Cl_2/MeOH 99:1) provided **9b** (150 mg, 27%). Yellow solid. M.p. 179° (CH_2Cl_2/hexane). IR ($CHCl_3$): 3436*w*, 3231*w*, 2944*m*, 2851*w*, 1669*s*, 1634*s*, 1450*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 11.85 (br. *s*, 1 H); 8.07 (br. *s*, 1 H); 7.35 (*d*, *J* = 2.7, 1 H); 7.11 (*d*, *J* = 2.7, 1 H); 3.98 (*s*, 2 H); 3.89 (*s*, 2 H); 2.59–2.71 (*m*, 1 H); 1.93–2.06 (*m*, 2 H); 1.50–1.82 (*m*, 2 H); 1.55–1.65 (*m*, 1 H); 1.33 (*s*, 9 H); 1.19–1.42 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 177.5; 158.7; 141.6; 140.6; 137.8; 134.1; 121.4; 119.4; 106.5; 41.1; 37.7; 31.0; 26.7; 24.7; 23.6; 23.4. HR-MALDI-MS (DHB): 389.2007 (*M*H$^+$, $C_{20}H_{29}N_4O_2S^+$; calc. 389.2011).

N-*{6-Amino-3,4-dihydro-4-oxo-8-[(phenylsulfanyl)methyl]quinazolin-2-yl}-2,2-dimethylpropanamide* (**9c**). *GP C* with **8c** (0.70 mg, 1.7 mmol), $SnCl_2 \cdot 2\,H_2O$ (1.53 g, 6.8 mmol) in EtOH (25 ml). CC (SiO_2; CH_2Cl_2/MeOH 99:1) provided **9c** (330 mg, 51%). Yellow solid. M.p. 234–235° (CH_2Cl_2/hexane). IR ($CHCl_3$): 3260*w*, 3010*s*, 2976*m*, 1667*s*, 1633*s*, 1552*m*, 1478*m*, 1420*m*, 1230*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 11.92 (*s*, 1 H); 7.98 (*s*, 1 H); 7.35 (*d*, *J* = 2.8, 1 H); 7.16–7.35 (*m*, 5 H); 6.95 (*d*, *J* = 2.8, 1 H); 4.37 (*s*, 2 H); 3.79 (*s*, 2 H); 1.33 (*s*, 9 H).

^{13}C-NMR (50 MHz, $CDCl_3$): 177.6; 158.6; 141.4; 140.8; 136.8; 134.4; 132.1; 127.5; 126.5; 124.0; 121.4; 119.4; 106.7; 37.7; 31.2; 24.7. HR-MALDI-MS (DHB): 383.1538 (MH^+, $C_{20}H_{23}N_4O_2S^+$; calc. 383.1542).

N-*[6-Amino-8-([[2-(dimethylamino)ethyl]sulfanyl]methyl)-3,4-dihydro-4-oxoquinazolin-2-yl]-2,2-dimethylpropanamide* (**9d**). *GP D* with **8d** (600 mg, 1.45 mmol), Zn powder (958 mg, 14.7 mmol) in AcOH (35 ml) and H_2O (5 ml). CC (SiO_2; CH_2Cl_2/MeOH/NH_3 79:20:1) provided **9d** (372 mg, 67%). Yellow solid. M.p. 168–170°. IR (KBr): 3682*w*, 3436*w*, 3220*w*, 1669*s*, 1633*s*, 1472*m*, 1456*m*, 1364*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 11.65 (br. *s*, 1 H); 8.19 (br. *s*, 1 H); 7.35 (*d*, *J* = 2.7, 1 H); 7.08 (*d*, *J* = 2.7, 1 H); 3.97 (*s*, 2 H); 3.88 (*s*, 2 H); 2.48–2.66 (*m*, 4 H); 2.23 (*s*, 6 H); 1.33 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 179.7; 160.7; 143.7; 142.8; 138.9; 135.8; 123.6; 121.7; 108.8; 59.0; 45.4; 40.2; 31.0; 29.8; 27.1. HR-MALDI-MS (DHB): 378.1971 (MH^+, $C_{18}H_{28}N_5O_2S^+$; calc. 378.1964).

N-*{6-Amino-3,4-dihydro-8-[[(1*H*-imidazol-2-yl)sulfanyl]methyl}-4-oxoquinazolin-2-yl}-2,2-dimethylpropanamide* (**9e**). *GP C* with **8e** (0.52 g, 1.23 mmol), $SnCl_2 \cdot 2\,H_2O$ (1.02 g, 5.17 mmol) in EtOH (25 ml). CC (SiO_2; CH_2Cl_2/MeOH 95:5) provided **9e** (120 mg, 25%). Yellow solid. M.p. 207–210° (CH_2Cl_2/hexane). IR (KBr): 3433*w*, 3178*w*, 2968*m*, 1678*s*, 1625*s*, 1600*s*, 1578*s*, 1527*m*, 1491*m*, 1339*s*, 1244*m*, 1142*s*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 12.15 (br. *s*, 1 H); 12.01 (br. *s*, 1 H); 10.58 (br. *s*, 1 H); 7.11 (*s*, 1 H); 7.06 (*d*, *J* = 2.6, 1 H); 6.94 (*d*, *J* = 2.6, 1 H); 6.93 (*s*, 1 H); 5.41 (*s*, 2 H); 4.50 (*s*, 2 H); 1.23 (*s*, 9 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 180.9; 160.2; 145.9; 142.8; 139.0; 137.0; 134.1; 129.1; 122.7; 121.0; 118.2; 106.4; 39.7; 32.6; 26.4. HR-MALDI-MS (DHB): 373.1434 (MH^+, $C_{17}H_{21}N_6O_2S^+$; calc. 373.1447).

N-*{6-Amino-8-[[(3-bromophenyl)sulfanyl]methyl}-3,4-dihydro-4-oxoquinazolin-2-yl)-2,2-dimethylpropanamide* (**9f**). *GP D* with **8f** (0.25 g, 0.65 mmol), Zn powder (0.42 g, 6.5 mmol) in AcOH (20 ml) and H_2O (10 ml). CC (SiO_2; CH_2Cl_2/MeOH 99:1) provided **9f** (160 mg, 53%). Yellow solid. M.p. 196–196°. IR ($CHCl_3$): 3684*w*, 3240*w*, 3023*w*, 1669*s*, 1633*s*, 1573*w*, 1499*w*, 1476*m*, 1458*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 11.87 (br. *s*, 1 H); 7.96 (br. *s*, 1 H); 7.54 (*dd*, *J* = 1.5, 1.5, 1 H); 7.37 (*d*, *J* = 2.7, 1 H); 7.30 (*ddd*, *J* = 7.8, 1.5, 1.5, 1 H); 7.19 (*ddd*, *J* = 7.8, 1.5, 1.5, 1 H); 7.11 (*t*, *J* = 7.8, 1 H); 7.04 (*d*, *J* = 2.7, 1 H); 4.40 (*s*, 2 H); 3.84 (br. *s*, 2 H); 1.36 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 179.6; 160.6; 143.7; 143.0; 139.0; 138.9; 133.7; 131.4; 129.9; 128.9; 127.5; 123.7; 122.5; 121.7; 109.3; 40.2; 33.0; 27.2. HR-MALDI-MS (DHB): 461.0640 (MH^+, $C_{20}H_{22}BrN_4O_2S^+$; calc. 461.0647).

N-*{6-Amino-8-[[([1,1′-biphenyl]-3-yl)sulfanyl]methyl}-3,4-dihydro-4-oxoquinazolin-2-yl}-2,2-dimethylpropanamide* (**9g**). *GP D* with **8g** (500 mg, 1.0 mmol), Zn powder (650 mg, 10.0 mmol) in AcOH (10 ml) and H_2O (30 ml). CC (SiO_2; CH_2Cl_2/MeOH 99:1) provided **9g** (220 mg, 50%). Yellow solid. M.p. >105° (dec.). IR (KBr): 3201*m*, 2360*s*, 1700*m*, 1684*m*, 1653*s*, 1635*s*, 1560*m*, 1473*s*, 1457*s*, 1399*m*, 1363*w*, 1256*w*, 1153*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 11.91 (br. *s*, 1 H); 8.39 (br. *s*, 1 H); 7.17–7.44 (*m*, 10 H); 7.01 (*d*, *J* = 2.7, 1 H); 4.34 (*s*, 2 H); 4.01 (br. *s*, 2 H); 1.22 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 179.9; 160.8; 143.9; 143.2; 141.6; 140.3; 139.0; 137.3; 134.1; 129.1; 128.7; 127.5; 127.4; 127.2; 126.9; 124.7; 124.0; 121.6; 109.2; 40.2; 33.1; 27.1. HR-MALDI-MS (DHB): 459.1849 (MH^+, $C_{26}H_{27}N_4O_2S^+$; calc. 459.1852). Anal. calc. for $C_{26}H_{26}N_4O_2S \cdot 2$ MeOH (522.66): C 64.34, H 6.56, N 10.72; found: C 64.35, H 6.25, N 10.64.

N-*[6-Amino-3,4-dihydro-4-oxo-8-(phenoxymethyl)quinazolin-2-yl]-2,2-dimethylpropanamide* (**9h**). *GP D* with **8h** (500 mg, 1.26 mmol), Zn powder (817 mg, 12.60 mmol) in AcOH (75 ml) and H_2O (15 ml). CC (SiO_2; CH_2Cl_2/AcOEt 8:2) provided **9h** (340 mg, 74%). Yellow foam. IR ($CHCl_3$): 3245*w*, 3231*w*, 2927*m*, 2851*w*, 1672*s*, 1633*s*, 1595*m*, 1454*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 11.88 (br. *s*, 1 H); 7.98 (br. *s*, 1 H); 6.95–7.41 (*m*, 7 H); 5.35 (*s*, 2 H); 3.90 (br. *s*, 2 H); 1.35 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 177.6; 158.5; 156.5; 141.8; 140.8; 136.0; 131.6; 127.2; 119.7; 119.2; 118.7; 112.6; 106.7; 63.1; 37.4; 24.7. HR-MALDI-MS (DHB): 367.1764 (MH^+, $C_{20}H_{23}N_4O_3^+$; calc. 367.1770).

*2,6-Diamino-8-[(propylsulfanyl)methyl]quinazolin-4(3*H*)-one* (**1a**). *GP E* with **9a** (206 mg, 0.59 mmol), ethanolic HCl soln. (11 ml): **1a** (132 mg, 84%). Yellow solid. M.p. 300° (dec.). IR (KBr): 3418*m*, 3328*s*, 3199*m*, 3056*w*, 2922*w*, 1680*s*, 1632*s*, 1480*s*, 1437*m*, 1346*s*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.66 (*s*, 1 H); 6.96 (*d*, *J* = 2.7, 1 H); 6.92 (*d*, *J* = 2.7, 1 H); 5.86 (*s*, 2 H); 4.98 (*s*, 2 H); 3.84 (*s*, 2 H); 2.39 (*t*, *J* = 7.2, 2 H); 1.47–1.59 (*m*, 2 H); 0.88 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 162.1; 148.1; 142.9; 140.4; 133.2; 122.9; 117.9; 106.5; 33.0; 29.9; 22.2; 13.3. HR-MALDI-MS (DHB): 265.1117 (MH^+, $C_{12}H_{17}N_4OS^+$; calc. 265.1112).

*2,6-Diamino-8-[(cyclohexylsulfanyl)methyl]quinazolin-4(3*H*)-one* (**1b**). *GP E* with **9b** (105 mg, 0.27 mmol), ethanolic HCl soln. (11 ml): **1b** (54 mg, 66%). Yellow solid. M.p. 283° (dec.). IR (KBr): 3411*w*, 3328*m*, 3189*w*, 2925*m*, 2844*w*, 1680*m*, 1633*s*, 1600*s*, 1480*m*, 1443*m*, 1343*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.68 (br. *s*, 1 H); 6.96 (*d*, *J* = 2.7, 1 H); 6.95 (*d*, *J* = 2.7, 1 H); 5.88 (br. *s*, 2 H); 5.02 (br. *s*, 2 H); 3.90 (*s*, 2 H); 2.55–2.68 (*m*, 1 H); 1.85–2.00 (*m*, 2 H); 1.59–1.77 (*m*, 2 H); 1.48–1.58 (*m*, 1 H); 1.32–1.40 (*m*, 5 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): 162.1; 148.0; 143.0; 140.4; 133.6; 122.9; 117.9; 106.5; 42.6; 33.2; 28.4; 25.4; 25.4. HR-MALDI-MS (DHB): 305.1433 (MH^+, $C_{15}H_{21}N_4OS^+$; calc. 305.1436).

*2,6-Diamino-8-[(phenylsulfanyl)methyl]quinazolin-4(3*H*)-one* (**1c**). *GP E* with **9c** (210 mg, 0.55 mmol), ethanolic HCl soln. (11 ml): **1c** (82 mg, 50%). Yellow solid. M.p. 303° (dec.). IR (KBr): 3329*m*, 3156*m*, 2955*w*, 1672*m*, 1635*s*, 1561*m*, 1480*s*, 1441*m*, 1358*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 11.00 (br. *s*, 1 H); 7.13–7.33 (*m*, 5 H); 6.99 (*s*, 2 H); 6.10 (*s*, 2 H); 4.99 (*s*, 2 H); 4.40 (*s*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 163.0; 149.3; 143.0; 140.7; 137.7; 131.1; 129.1; 127.4; 125.4; 123.0; 118.3; 107.3; 31.5. HR-MALDI-MS (DHB): 299.0964 (*M*H$^+$, $C_{15}H_{15}N_4OS^+$; calc. 299.0967).

*2,6-Diamino-8-({[2-(dimethylamino)ethyl]sulfanyl}methyl)quinazolin-4(3*H*)-one* (**1d**). Compound **9d** (206 mg, 0.59 mmol) was dissolved in ethanolic HCl soln. (11 ml) and heated to 70° for 3 h. The pH of the mixture was adjusted to 8 with 1N NaOH and sat. aq. Na_2CO_2 soln., and the solvent was removed *in vacuo*. The residue was dissolved in 1N HCl and loaded onto a column of *Dowex® 50 Wx4*, (NH_4^+, 1 cm × 25 cm). Washing with H_2O (500 ml) and MeOH (200 ml), and elution with H_2O with an added gradient of conc. aq. NH_4OH (1–5%; 100-ml fractions), followed by removal of the solvent *in vacuo*, provided **1d** (75 mg, 40%). Beige solid. M.p. >250° (dec.). IR (KBr): 3410*m*, 3323*s*, 3198*m*, 2922*w*, 1678*m*, 1630*s*, 1610*s*, 1480*m*, 1344*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.70 (br. *s*, 1 H); 6.98 (*d*, *J* = 2.4, 1 H); 6.95 (*s*, *J* = 2.4, 1 H); 5.90 (*s*, 2 H); 5.03 (*s*, 2 H); 3.88 (*s*, 2 H); 2.34–2.53 (*m*, 4 H); 2.08 (*s*, 6 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 162.1; 148.1; 142.9; 140.4; 133.2; 122.9; 118.0; 106.7; 59.0; 44.9; 30.1; 28.8. HR-MALDI-MS (DHB): 294.1395 (*M*H$^+$, $C_{13}H_{20}N_5OS^+$; calc. 294.1389).

*2,6-Diamino-8-{[(1*H*-imidazol-2-yl)sulfanyl]methyl}quinazolin-4(3*H*)-one* (**1e**). *GP E* with **9e** (80 mg, 0.21 mmol), ethanolic HCl soln. (5.5 ml): **1e** (39 mg, 63%). Yellow-beige solid. M.p. 266° (dec.). IR (KBr): 3300*w*, 3136*s*, 1689*m*, 1651*s*, 1611*s*, 1572*m*, 1483*s*, 1439*m*, 1361*m*, 1328*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 10.74 (br. *s*, 1 H); 7.01 (*s*, 2 H); 6.97 (*d*, *J* = 3.0, 1 H); 6.81 (*d*, *J* = 3.0, 1 H); 5.99 (*s*, 2 H); 4.96 (*s*, 2 H); 4.37 (*s*, 2 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): 162.1; 148.5; 142.9; 140.3; 139.6; 131.9; 128.5; 122.9; 118.1; 107.1; 32.9. HR-MALDI-MS (DHB): 289.0866 (*M*H$^+$, $C_{12}H_{12}N_6OS^+$; calc. 289.0872).

*2,6-Diamino-8-{[(3-bromophenyl)sulfanyl]methyl}quinazolin-4(3*H*)-one* (**1f**). *GP E* with **9f** (120 mg, 0.26 mmol), ethanolic HCl soln. (1M; 11 ml). Precipitation from Me_2SO/H_2O provided **1f** (54 mg, 55%). White solid. M.p. >250° (dec.). IR (KBr): 3415*m*, 3330*m*, 3201*m*, 2926*w*, 1680*m*, 1632*s*, 1599*s*, 1480*m*, 1343*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.72 (br. *s*, 1 H); 7.50 (*s*, 1 H); 7.19–7.32 (*m*, 3 H); 7.00 (*s*, 2 H); 5.97 (*s*, 2 H); 5.04 (*s*, 2 H); 4.42 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 162.7; 149.1; 143.8 (2×); 141.1; 131.5; 131.4; 129.4; 128.5; 126.5; 123.6; 122.8; 118.8; 108.0; 31.6. HR-MALDI-MS (DHB): 377.0073 (*M*H$^+$, $C_{15}H_{14}BrN_4OS^+$; calc. 377.0072).

*2,6-Diamino-8-{[([1,1′-biphenyl]-3-yl)sulfanyl]methyl}quinazolin-4(3*H*)-one* (**1g**). *GP E* with **9g** (200 mg, 2.0 mmol), ethanolic HCl soln. (15 ml EtOH, 2 ml conc. HCl): **1g** (150 mg, 94%). Yellow solid. M.p. >240° (dec.). IR (KBr) 3317*s*, 3167*s*, 1700*m*, 1675*s*, 1653*s*, 1635*s*, 1560*s*, 1507*m*, 1476*m*, 1448*m*, 1399*m*, 1363*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 7.28–7.58 (*m*, 9 H); 7.11 (*s*, 1 H); 7.06 (*s*, 1 H); 6.32 (br. *s*, 2 H); 4.50 (*s*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 161.6; 148.9; 142.5; 140.7; 140.7; 139.4; 137.6; 130.4; 129.3; 128.8; 127.5; 126.6; 126.3; 125.0; 123.6; 123.1; 117.8; 108.0; 30.9. HR-MALDI-MS (DHB): 375.1277 (*M*H$^+$, $C_{21}H_{19}N_4OS^+$; calc. 375.1274).

*2,6-Diamino-8-(phenoxymethyl)quinazolin-4(3*H*)-one* (**1h**). *GP E* with **9h** (120 mg, 0.33 mmol), ethanolic HCl soln. (11 ml): **1h** (67 mg, 72%). Yellow solid. M.p. >300° (dec.). IR (KBr): 3444*m*, 3333*m*, 3168*m*, 1648*s*, 1594*m*, 1487*m*, 1439*m*, 1223*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.76 (br. *s*, 1 H); 7.28 (*dd*, *J* = 8.4, 6.9, 2 H); 7.05 (*m*, 2 H); 6.96 (*d*, *J* = 8.4, 2 H); 6.91 (*t*, *J* = 6.9, 1 H); 6.00 (br. *s*, 2 H); 5.25 (*s*, 2 H); 5.01 (br. *s*, 2 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 160.4; 157.0; 146.9; 141.6; 138.3; 129.4; 127.9; 119.9; 118.8; 116.3; 112.9; 105.5; 63.4. HR-MALDI-MS (DHB): 283.1190 (*M*H$^+$, $C_{15}H_{15}N_4O_2^+$; calc. 283.1195).

Methyl 2-Amino-3-bromo-5-nitrobenzoate (**10**). Br_2 (0.26 ml, 5.1 mmol) was added slowly at r.t. to a soln. of methyl 2-amino-5-nitrobenzoate (1.0 g, 5.1 mmol) [34] in AcOH (120 ml). After stirring at r.t. for 4 h, H_2O was added, and the suspension was filtered. The residue was washed with H_2O and dried under h.v. to yield **10** (1.29 g, 92%). Golden-yellow platelets. M.p. 200–202° (CH_2Cl_2/hexane). IR ($CHCl_3$): 3483*m*, 3348*m*, 3020*w*, 2955*w*, 1701*s*, 1610*s*, 1550*m*, 1514*m*, 1333*s*, 1276*s*, 1226*s*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 8.62 (*d*, *J* = 2.6, 1 H); 8.48 (*d*, *J* = 2.6, 1 H); 7.84 (br. *s*, 2 H); 3.92 (*s*, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 166.3; 152.3; 135.5; 131.9; 127.2; 109.0; 52.7; signal of C(1) not visible or masked. ESI-MS: 275.1 (100, M^+). Anal. calc. for $C_8H_7BrN_2O_4$ (275.06): C 34.93, H 2.57, N 10.18, O 23.27, Br 29.05; found: C 35.13, H 2.70, N 10.07, O 23.14, Br 29.21.

*2-Amino-8-bromo-6-nitroquinazolin-4(3*H*)-one* (**11**). To a soln of guanidinium chloride (17.36 g, 181.8 mmol) in EtOH (200 ml), EtONa (12.37 g, 181.8 mmol) and **10** (10.00 g, 36.4 mmol) were added, and the yellow suspension was heated to reflux for 60 h. After evaporation *in vacuo*, H_2O was added, and the mixture was acidified (pH 5) with AcOH. The solid formed was isolated by filtration and recrystallized from DMF/H_2O to give **11** (6.68 g, 63%). Yellow solid. M.p. >300° (DMF/H_2O). IR (KBr): 3401*s*, 3143*s*, 1700*s*, 1656*s*, 1589*s*, 1337*s*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 11.57 (*s*, 1 H); 8.55 (*d*, *J* = 2.8, 1 H); 8.53 (*d*, *J* = 2.8, 1 H); 7.26 (br. *s*,

2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 161.1; 154.7; 154.4; 140.1; 131.2; 122.0; 118.6; 117.0. EI-MS: 284.0 (M^+). Anal. calc. for $C_8H_5BrN_4O_3$ (283.97): C 33.71, H 1.77, N 19.65; found: C 33.98, H 1.99, N 19.54.

N-*(8-Bromo-3,4-dihydro-6-nitro-4-oxoquinazolin-2-yl)-2,2-dimethylpropanamide* (**12**). To a suspension of **11** (2.0 g, 7.0 mmol) in DMA (50 ml), pyridine (1.13 ml, 14.0 mmol) and pivaloyl chloride (1.73 ml, 14.0 mmol) were added, and the mixture was stirred for 1 h at r.t., then for 8 h at 110°. The mixture was poured into H_2O (400 ml), and the formed precipitate was isolated by filtration, and washed with H_2O and a small amount of EtOH. CC (SiO_2; CH_2Cl_2/MeOH 99:1) gave **12** (1.83 g, 71%). Colorless solid. M.p. 237–238°. IR ($CHCl_3$): 3180*w*, 3036*w*, 1691*s*, 1623*s*, 1604*s*, 1529*m*, 1433*m*, 1342*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 12.37 (br. *s*, 1 H); 9.05 (*d*, $J = 2.6$, 1 H); 8.79 (*d*, $J = 2.6$, 1 H); 8.62 (br. *s*, 1 H); 1.40 (*s*, 9 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): 181.6; 159.6; 151.4; 150.1; 144.1; 132.5; 122.9; 121.5; 121.0; 40.8; 26.9. HR-MALDI-MS (DHB): 369.0185 (MH$^+$, $C_{13}H_{14}BrN_4O_4^+$; calc. 369.0198). Anal. calc. for $C_{13}H_{13}BrN_4O_4$ (369.17): C 42.30, H 3.55, N 15.18; found: C 42.10, H 3.50, N 15.21.

N-*[3,4-Dihydro-6-nitro-4-oxo-8-(phenylethinyl)quinazolin-2-yl]-2,2-dimethylpropanamide* (**13**). To a mixture of **12** (250 mg, 0.68 mmol), $[Pd(OAc)_2]$ (19 mg, 0.08 mmol), P(*o*-tol)$_3$ (43 mg, 0.14 mmol), CuI (16 mg, 0.08 mmol), and Et_3N (0.95 ml) in MeCN (10 ml), phenylacetylene (83 µl, 0.76 mmol) was added. The mixture turned black and was heated to reflux for 15 h. After evaporation *in vacuo*, CC (SiO_2; hexane/AcOEt 9:1, then SiO_2; CH_2Cl_2) afforded **13** (60 mg, 23%). Yellow solid. M.p. 203–205°. IR ($CHCl_3$): 3155*w*, 2253*s*, 1724*m*, 1625*m*, 1593*s*, 1476*m*, 1337*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 12.63 (br. *s*, 1 H); 8.90 (*d*, $J = 2.0$, 1 H); 8.79 (*d*, $J = 2.0$, 1 H); 7.47–7.59 (*m*, 5 H); 6.89 (*s*, 1 H); 0.81 (*s*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 194.2; 158.3; 147.6; 145.7; 144.5; 139.3; 131.4; 129.6; 129.2; 128.2; 128.1; 122.3; 118.4; 113.7; 111.3; 42.4; 26.4. HR-MALDI-MS (DHB): 413.1224 ($[M + Na]^+$, $C_{21}H_{18}N_4O_4Na^+$; calc. 413.1226).

N-*[6-Amino-3,4-dihydro-4-oxo-8-(2-phenylethyl)quinazolin-2-yl]-2,2-dimethylpropanamide* (**14**). To a soln. of **13** (670 mg, 1.716 mmol) in AcOEt/MeOH (90 ml, 1:2), Pd/C (10%, 600 mg) was added, and hydrogenation was performed for 3 h under H_2 (760 Torr) at r.t. Filtration over *Celite* and washing the plug with MeOH provided a soln. that was evaporated *in vacuo*. CC (SiO_2; CH_2Cl_2/MeOH 99:1) and recrystallization ($CHCl_3$/hexane) gave **14** (320 mg, 51%). Yellowish solid. M.p. 170–172°. IR (KBr): 3367*m*, 3220*m*, 2970*w*, 1634*s*, 1475*m*, 1349*w*, 1254*w*, 1164*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 11.85 (br. *s*, 1 H); 8.03 (br. *s*, 1 H); 7.34 (*d*, $J = 2.6$, 1 H); 7.16–7.33 (*m*, 5 H); 6.87 (*d*, $J = 2.6$, 1 H); 3.87 (br. *s*, 2 H); 3.15, 2.94 (*AA′BB′*, $J = 10.6, 8.6, 4$ H); 1.35 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 180.1; 161.5; 144.1; 142.9; 142.3; 139.6; 139.4; 128.7; 128.5; 126.2; 123.8; 121.8; 108.0; 40.2; 36.7; 32.6; 27.2. HR-MALDI-MS (DHB): 365.1979 (MH$^+$, $C_{21}H_{25}N_4O_2^+$; calc. 365.1978).

*2,6-Diamino-8-(2-phenylethyl)quinazolin-4(3*H*)-one* (**1i**). *GP E* with **14** (280 mg, 0.77 mmol), ethanolic HCl soln. (1M; 22 ml): **1i** (170 mg, 79%). Yellow solid. M.p. 302° (Me_2SO/H_2O; dec.). IR (KBr): 3414*m*, 3327*s*, 3198*m*, 3068*w*, 2922*w*, 1679*m*, 1633*s*, 1600*s*, 1480*m*, 1445*m*, 1344*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.6 (br. *s*, 1 H); 7.14–7.32 (*m*, 5 H); 6.94 (*d*, $J = 2.0$, 1 H); 6.82 (*d*, $J = 2.0$, 1 H); 5.90 (*s*, 2 H); 4.97 (br. *s*, 2 H); 2.80–3.02 (*m*, 4 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 162.8; 148.4; 143.2; 142.4; 140.8; 136.3; 128.5; 128.4; 125.8; 122.8; 118.1; 105.8; 35.8; 32.8. ESI-MS: 281.3 (100, M^+). HR-MALDI-MS (DHB): 281.1399 (MH$^+$, $C_{16}H_{17}N_4O^+$; calc. 281.1402).

N-*(3,4-Dihydro-8-methyl-4-oxoquinazolin-2-yl)-2,2-dimethylpropanamide* (**16**). To a suspension of **4** (663 mg, 3.79 mmol) in DMA (15 ml), Et_3N (1.19 ml, 8.53 mmol) was added at r.t., and the resulting soln. was heated to 110°. Pivaloyl chloride (1.16 ml, 9.47 mmol) was added, and the mixture heated for 3 h at 110°. After cooling to r.t., H_2O (500 ml) was added, and the precipitate formed was isolated by filtration. The residue was washed with H_2O, taken up in sat. aq. $NaHCO_3/CH_2Cl_2$, and extracted with CH_2Cl_2 (3×). The combined org. layers were dried ($MgSO_4$) and evaporated *in vacuo*. Recrystallization (hexane/CH_2Cl_2) provided **16** (430 mg, 44%). Colorless solid. M.p. 183–184°. IR (neat): 3189*w*, 2973*w*, 1659*s*, 1627*s*, 1576*m*, 1296*m*, 1457*s*, 1231*s*, 1148*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 11.93 (br. *s*, 1 H); 8.28 (br. *s*, 1 H); 8.06 (*d*, $J = 7.8$, 1 H); 7.64 (*t*, $J = 7.8$, 1 H); 7.52 (*d*, $J = 7.8$, 1 H); 2.47 (*s*, 3 H); 1.35 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 179.9; 161.2; 146.9; 145.1; 135.2; 134.1; 124.7; 124.5; 120.2; 40.3; 27.2; 17.7. HR-MALDI-MS (DHB): 260.1390 (MH$^+$, $C_{14}H_{18}N_3O_2^+$; calc. 260.1399).

N-*{3,4-Dihydro-4-oxo-8-[(phenylsulfanyl)methyl]quinazolin-2-yl}-2,2-dimethylpropanamide* (**17**). To a suspension of **16** (400 mg, 1.54 mmol) and NBS (288 mg, 1.62 mmol) in CCl_4 (20 ml), a cat. amount of AIBN was added, and the mixture was heated to reflux for 18 h. After removal of the solvent *in vacuo*, the residue was washed with hot H_2O (300 ml) and taken up in CH_2Cl_2. Drying ($MgSO_4$) and evaporation *in vacuo* left a crude product that was used without further purification in the next step. *GP B* with BuLi (1.6M in hexane; 2.77 ml) in abs. THF (10 ml), PhSH (0.45 ml, 4.43 mmol), crude benzyl bromide (500 mg) in abs. THF (10 ml). CC (SiO_2; AcOEt/hexane 2:8) provided **17** (320 mg, 57%). White solid. M.p. 156°. IR (neat): 3157*w*, 2974*w*, 1649*s*, 1633*s*, 1603*s*, 1576*m*, 1497*m*, 1453*s*, 1236*s*, 1156*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 11.94 (br. *s*, 1 H); 8.13 (*dd*, $J = 7.8, 1.5$,

1 H); 8.08 (br. *s*, 1 H); 7.52 (*d*, *J* = 7.8, 1.5, 1 H); 7.19–7.34 (*m*, 6 H); 4.43 (*s*, 2 H); 1.36 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 180.3; 161.3; 146.9; 145.9; 136.7; 135.3; 133.5; 130.3; 129.0; 126.7; 126.4; 125.0; 121.0; 40.5; 34.2; 27.3. HR-MALDI-MS (DHB): 368.1424 (*M*H$^+$, $C_{20}H_{22}N_3O_2S^+$; calc. 368.1433).

*2-Amino-8-[(phenylsulfanyl)methyl]quinazolin-4(3*H*)-one* (**15**). *GP E* with **17** (270 mg, 0.73 mmol), ethanolic HCl soln. (11 ml): **15** (146 mg, 70%). White solid. M.p. >250° (DMF/H_2O, dec.). IR (neat) 3052*w*, 2900*w*, 1717*s*, 1698*m*, 1652*s*, 1621*s*, 1568*m*, 1520*s*, 1483*m*, 1438*s*, 1334*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 11.97 (br. *s*, 1 H); 7.83 (*d*, *J* = 7.2, 1 H); 7.51 (*d*, *J* = 7.2, 1 H); 7.12–7.36 (*m*, 7 H); 7.01 (*t*, *J* = 7.2, 1 H); 4.46 (*s*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 160.6; 151.4; 135.5; 135.1; 129.0 (2×); 128.7; 127.9; 126.0; 125.5; 122.3; 116.6; 32.3. HR-MALDI-MS (DHB): 284.0853 (*M*H$^+$, $C_{15}H_{14}N_3OS^+$; calc. 284.0858). Anal. calc. for $C_{15}H_{13}N_3OS \cdot H_2O$ (301.37): C 59.78, H 5.02, N 13.94; found: C 59.76, H 4.90, N 13.85.

Methyl 2-Amino-5-bromo-3-methylbenzoate (**18**). To a soln. of **3** (10 g, 60 mmol) in AcOH (200 ml), Br_2 (3.1 ml, 60 mmol) in AcOH (100 ml) was slowly added at 10°. After stirring for 30 min at r.t., the solvent was evaporated *in vacuo*. The residue was taken up in sat. aq. Na_2CO_3 soln. and extracted with CH_2Cl_2 (3×). The combined org. phases were dried (Na_2SO_4) and evaporated *in vacuo*. Recrystallization from hexane yielded **18** (13.7 g, 93%). Yellow solid. M.p. 57–58°. IR ($CHCl_3$): 3511*s*, 3380*s*, 2953*m*, 1694*s*, 1609*s*, 1297*s*, 1233*m*, 1203*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.88 (*d*, *J* = 2.4, 1 H); 7.28 (*d*, *J* = 2.4, 1 H); 5.83 (br. *s*, 2 H); 3.86 (*s*, 3 H); 2.14 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.3; 148.3; 137.4; 131.5; 125.5; 111.7; 107.1; 51.9; 17.2. ESI-MS: 245.0 (100, *M*$^+$). Anal. calc. for $C_9H_{10}BrNO_2$ (244.08): C 44.29, H 4.13, N 5.74; found: C 44.23, H 4.21, N 5.70.

*2-Amino-6-bromo-8-methylquinazolin-4(3*H*)-one* (**19**). *GP A* with **18** (23.0 g, 94 mmol), chloroformamidinium chloride (14.1 g, 122 mmol), and dimethyl sulfone (80 g). Precipitation from Me_2SO/H_2O yielded **19** (21.5 g, 90%). Yellowish solid. M.p. >300°. IR (KBr): 3311*w*, 3155*w*, 2922*m*, 2777*m*, 1682*s*, 1644*s*, 1611*m*, 1544*m*, 1494*m*, 1455*s*, 1338*m*, 1200*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 11.06 (br. *s*, 1 H); 7.76 (*d*, *J* = 2.4, 1); 7.56 (*d*, *J* = 2.4, 1 H); 6.44 (br. *s*, 2 H); 2.31 (*s*, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 161.5; 151.5; 148.5; 136.4; 134.5; 125.3; 118.2; 112.5; 17.1. HR-MALDI-MS (DHB): 253.9922 (*M*H$^+$, $C_9H_9BrN_3O^+$; calc. 253.9929).

N-*(6-Bromo-3,4-dihydro-8-methyl-4-oxoquinazolin-2-yl)-2,2-dimethylpropanamide* (**20**). To a suspension of **19** (9 g, 35.4 mmol) in DMA (250 ml), Et_3N (11.1 ml, 79.7 mmol) was added at r.t., and the resulting soln. was heated to 100°. Pivaloyl chloride (10.9 ml, 88.6 mmol) was added, and the mixture was heated to 100° for 3 h. After cooling to r.t., H_2O (500 ml) was added, and the precipitate formed was isolated by filtration, washed with H_2O, and recrystallized from EtOH to yield **20** (9.1 g, 76%). Yellow solid. M.p. 199°. IR ($CHCl_3$): 3431*m*, 3226*w*, 2971*m*, 1677*s*, 1629*s*, 1489*m*, 1435*m*, 1254*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 11.98 (br. *s*, 1 H); 8.19 (*d*, *J* = 2.3, 1 H); 8.13 (br. *s*, 1 H); 7.64 (*dd*, *J* = 2.3, 0.8, 1 H); 2.47 (*s*, 3 H); 1.36 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 178.1; 157.9; 143.8; 143.3; 135.7; 134.4; 124.7; 119.3; 115.8; 37.9; 24.6; 14.9. HR-MALDI-MS (DHB): 338.0501 (*M*H$^+$, $C_{14}H_{17}BrN_3O_2^+$; calc. 338.0704).

N-*[6-Bromo-3,4-dihydro-8-(bromomethyl)-4-oxoquinazolin-2-yl]-2,2-dimethylpropanamide* (**21**). To a suspension of **20** (4 g, 11.8 mmol) and NBS (2.1 g, 11.8 mmol) in CCl_4 (130 ml), a cat. amount of AIBN was added at 0°, and the mixture was heated to reflux for 18 h. After removal of the solvent *in vacuo,* the residue was washed with hot H_2O to yield crude **21** (3.79 g, 76%) that was used without further purification in the next step. For anal. purposes, a small amount was purified by CC (SiO_2; CH_2Cl_2). Yellow foam. M.p. 187–188° (THF). IR ($CHCl_3$): 3429*w*, 3222*w*, 2971*w*, 1679*s*, 1627*s*, 1489*m*, 1436*m*, 1328*w*, 1285*m*, 1252*m*, 1221*w*, 1138*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 12.08 (br. *s*, 1 H); 8.30 (br. *s*, 1 H); 8.28 (*d*, *J* = 2.6, 1 H); 7.84 (*d*, *J* = 2.6, 1 H); 4.75 (*s*, 2 H); 1.36 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 180.7; 159.9; 146.6; 145.8; 139.0; 135.8; 130.3; 122.6; 118.3; 40.5; 34.0; 27.1. HR-MALDI-MS (DHB): 415.9587 (*M*H$^+$, $C_{14}H_{16}Br_2N_3O_2^+$; calc. 415.9589). Anal. calc. for $C_{14}H_{15}Br_2N_3O_2$ (417.09): C 40.31, H 3.62, N 10.07; found: C 40.38, H 3.77, N 9.98.

N-*[6-Bromo-3,4-dihydro-4-oxo-8-(phenoxymethyl)quinazolin-2-yl]-2,2-dimethylpropanamide* (**22a**). To a soln. of PhOH (1.13 g, 12.0 mmol) in abs. THF (20 ml), NaH (60% in oil, 0.29 g, 12.0 mmol) was added at 0°, and the mixture was stirred for 20 min. Compound **21** (1.40 g, 3.36 mmol) in abs. THF (20 ml) was added at 0°, and the mixture was stirred at r.t. for 24 h. After removal of the solvent *in vacuo*, the residue was taken up in sat. aq. Na_2CO_3/CH_2Cl_2 and extracted with CH_2Cl_2 (3×). The combined org. phases were dried ($MgSO_4$) and evaporated *in vacuo*. CC (SiO_2; CH_2Cl_2, then CH_2Cl_2/AcOEt 4:1) provided **22a** (1.15 g, 80%). White solid. M.p. 185° ($CHCl_3$/hexane). IR ($CHCl_3$): 3245*w*, 3220*w*, 3015*w*, 1679*s*, 1629*s*, 1595*m*, 1496*m*, 1247*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 12.06 (br. *s*, 1 H); 8.33 (*d*, *J* = 2.4, 1 H); 8.16 (br. *s*, 1 H); 8.02 (*d*, *J* = 2.4, 1 H); 6.98–7.40 (*m*, 5 H); 5.35 (*s*, 2 H); 1.38 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 178.0; 157.4; 156.3; 143.8; 142.5; 133.8; 132.2; 127.2; 126.4; 119.4; 118.9; 116.3; 112.6; 62.6; 37.9; 24.6. HR-MALDI-MS (DHB): 430.0765 (*M*H$^+$, $C_{20}H_{21}BrN_3O_3^+$; calc. 430.0766). Anal. calc. for $C_{20}H_{20}BrN_3O_3$ (430.30): C 55.83, H 4.68, N 9.77; found: C 55.67, H 5.06, N 9.67.

N-*{6-Bromo-3,4-dihydro-4-oxo-8-[(phenylsulfanyl)methyl]quinazolin-2-yl}-2,2-dimethylpropanamide* (**22b**). *GP B* with BuLi (1.6M in hexane; 6.27 ml, 10.0 mmol) in abs. THF (15 ml), PhSH (1.23 ml, 12.0 mmol), **21** (1.67 g, 4.0 mmol) in abs. THF (10 ml). CC (SiO_2; AcOEt/hexane 3:7) provided **22b** (1.56 g, 87%). Yellow solid. M.p. 128–129°. IR ($CHCl_3$): 3430*w*, 3222*w*, 3018*s*, 2400*w*, 1677*s*, 1628*s*, 1482*m*, 1438*s*, 1214*s*, 1139*w*, 1046*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 12.01 (br. *s*, 1 H); 8.03 (br. *s*, 1 H); 8.24 (*d*, *J* = 2.4, 1 H); 7.54 (*d*, *J* = 2.4, 1 H); 7.20–7.34 (*m*, 5 H); 4.35 (*s*, 2 H); 1.36 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 178.1; 157.6; 143.7; 143.3; 135.4; 133.5; 130.4; 128.2; 126.6; 126.1; 124.5; 119.7; 115.6; 37.9; 31.2; 24.6. HR-MALDI-MS (DHB): 446.0537 (MH^+, $C_{20}H_{21}BrN_3O_2S^+$; calc. 446.0517). Anal. calc. for $C_{20}H_{20}BrN_3O_2S$ (446.36): C 53.82, H 4.52, N 9.41; found: C 53.80, H 4.80, N 9.49.

*2-Amino-6-bromo-8-(phenoxymethyl)quinazolin-4(3*H*)-one* (**23a**). *GP E* with **22a** (130 mg, 0.38 mmol), ethanolic HCl soln. (11 ml). Recrystallization from MeOH and drying at 80° provided **23a** (70 mg, 67%). White solid. M.p. >250° (dec.). IR (KBr): 3334*m*, 3155*m*, 1617*s*, 1594*s*, 1551*m*, 1495*s*, 1455*s*, 1239*s*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 11.18 (br. *s*, 1 H); 7.89 (*d*, *J* = 2.6, 1 H); 7.73 (*d*, *J* = 2.6, 1 H); 7.28 (*d*, *J* = 7.5, 2 H); 6.98 (*d*, *J* = 7.5, 2 H); 6.92 (*t*, *J* = 7.5, 1 H); 6.58 (br. *s*, 2 H); 5.27 (*s*, 2 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 161.8; 158.1; 152.6; 148.3; 134.5; 133.0; 129.5; 127.2; 120.7; 118.6; 114.5; 112.2; 64.4. HR-MALDI-MS (DHB): 346.0182 (MH^+, $C_{15}H_{13}BrN_3O_2^+$; calc. 346.0191).

*2-Amino-6-bromo-8-[(phenylsulfanyl)methyl]quinazolin-4(3*H*)-one* (**23b**). *GP E* with **22b** (150 mg, 0.33 mmol), ethanolic HCl soln. (10 ml). Recrystallization from MeOH and drying at 80° provided **23b** (70 mg, 60%). Yellowish solid. M.p. 270–272° (MeOH). IR ($CHCl_3$): 3361*w*, 3139*w*, 2918*s*, 2849*m*, 1687*m*, 1649*s*, 1616*m*, 1537*m*, 1513*w*, 1462*m*, 1405*w*, 1338*m*, 1262*w*, 1087*w*, 1020*w*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 11.20 (br. *s*, 1 H); 7.86 (*d*, *J* = 2.7, 1 H); 7.60 (*d*, *J* = 2.7, 1 H); 7.20–7.40 (*m*, 5 H); 6.61 (br. *s*, 2 H); 4.44 (*s*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 160.9; 151.6; 148.6; 136.2; 133.9; 130.9; 129.0; 128.3; 126.8; 125.8; 118.7; 112.1; 31.3. HR-MALDI-MS (DHB): 361.9960 (MH^+, $C_{15}H_{13}BrN_3OS^+$; calc. 361.9963). Anal. calc. for $C_{15}H_{12}BrN_3OS \cdot H_2O$ (380.26): C 47.38, H 3.71, N 11.05; found: C 47.15, H 3.71, N 10.92.

N-*[3,4-Dihydro-6-hydroxy-4-oxo-8-(phenoxymethyl)quinazolin-2-yl]-2,2-dimethylpropanamide* (**25**). To degassed abs. Me_2SO (8 ml), **22a** (400 mg, 0.93 mmol), [$PdCl_2$(dppf)] (68 mg, 0.09 mmol), AcOK (273 mg, 2.70 mmol), and **24** (354 mg, 1.40 mmol) were added, and the mixture was heated to 80° for 18 h. After cooling to r.t., H_2O was added, and the aq. phase was extracted with CH_2Cl_2 (3×). The combined org. layers were washed with H_2O (2×), dried (Na_2SO_4), filtered over *Celite*, and evaporated *in vacuo*. To a soln. of the crude boronic ester in THF (4 ml), AcOH (0.11 ml, 1.80 mmol) and 15% aq. H_2O_2 soln. (0.4 ml, 1.80 mmol) were added with stirring at *ca.* 10°. After 1 and 2 h, respectively, the same amounts of reagents were added again. The mixture was stirred at r.t. for 6 h, then H_2O was added. The aq. phase was extracted with CH_2Cl_2 (3×). The combined org. layers were dried ($MgSO_4$) and evaporated *in vacuo*. CC (SiO_2; AcOEt/hexane 1:1) and recrystallization from MeOH provided **25** (273 mg, 80%). White solid. M.p. 217–218°. IR ($CHCl_3$): 3425*w*, 3233*w*, 2971*w*, 1669*s*, 1634*s*, 1598*m*, 1498*m*, 1450*m*, 1367*w*, 1262*w*, 1223*s*, 1208*s*, 1143*w*, 1017*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 12.22 (br. *s*, 1 H); 10.73 (br. *s*, 1 H); 9.97 (br. *s*, 1 H); 7.36 (*s*, 2 H); 7.32 (*d*, *J* = 8.2, 2 H); 7.03 (*d*, *J* = 8.2, 2 H); 6.97 (*t*, *J* = 7.0, 1 H); 5.46 (*s*, 2 H); 1.28 (*s*, 9 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 181.1; 160.0; 158.1; 154.4; 144.5; 139.1; 134.3; 129.5; 122.6; 120.8; 120.6; 114.6; 108.7; 64.5; 39.8; 26.3. HR-MALDI-MS (DHB): 368.1605 (MH^+, $C_{20}H_{22}N_3O_4^+$; calc. 368.1610). Anal. calc. for $C_{20}H_{21}N_3O_4 \cdot MeOH$ (399.44): C 63.14, H 6.31, N 10.52; found: C 63.06, H 6.24, N 10.46.

*2-Amino-6-hydroxy-8-(phenoxymethyl)quinazolin-4-(3*H*)-one* (**26**). *GP E* with **25** (100 mg, 0.27 mol), ethanolic HCl soln. (11 ml). Precipitation from DMF provided **26** (30 mg, 40%). Beige solid. M.p. 278° (dec.). IR (KBr): 3478*s*, 3344*s*, 3144*s*, 2344*w*, 1688*w*, 1644*s*, 1600*s*, 1566*s*, 1494*m*, 1455*m*, 1433*m*, 1366*m*, 1289*w*, 1233*m*, 1189*w*, 1133*m*, 1039*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.86 (br. *s*, 1 H); 9.37 (br. *s*, 1 H); 6.84–7.30 (*m*, 7 H); 6.11 (br. *s*, 2 H); 5.26 (*s*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 161.7; 151.6; 149.4; 146.8; 141.9; 131.9; 129.5; 122.0; 120.3; 117.7; 114.5; 108.5; 64.8. HR-MALDI-MS (DHB): 284.1030 (MH^+, $C_{15}H_{14}N_3O_3^+$; calc. 284.1035).

N-*(3,4-Dihydro-6-hydroxy-8-methyl-4-oxoquinazolin-2-yl)-2,2-dimethylpropanamide* (**28**). To **20** (2 g, 5.92 mmol), [$PdCl_2$(dppf)] (433 mg, 0.59 mmol), AcOK (1.74 g, 17.7 mmol), and **24** (2.25 g, 8.87 mmol), degassed abs. Me_2SO (40 ml) was added, and the mixture was heated to 80° for 18 h. After cooling to r.t., H_2O was added, and the aq. phase was extracted with CH_2Cl_2 (3×). The combined org. layers were washed with H_2O (2×), dried (Na_2SO_4), filtered over *Celite*, and evaporated *in vacuo*. To a soln. of the crude boronic ester in THF (20 ml), AcOH (0.7 ml, 12 mmol) and 15% aq. H_2O_2 soln. (2.4 ml, 12 mmol) were added under stirring at *ca.* 10°. After 1 and 2 h, respectively, the same amounts of AcOH and H_2O_2 were added. After stirring r.t. for 5 h, H_2O was added and the aq. phase extracted with CH_2Cl_2 (3×). The combined org. layers were dried ($MgSO_4$) and evaporated *in vacuo*. CC (SiO_2; AcOEt/hexane 1:1) and recrystallization from MeOH provided **28** (1.37 g, 84%). White solid. M.p. 206–207° ($CHCl_3$/hexane). IR ($CHCl_3$): 3425*w*, 3232*w*, 2974*w*, 1667*s*, 1633*s*, 1476*m*,

1453*m*, 1364*w*, 1272*w*, 1220*s*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 12.12 (br. *s*, 1 H); 10.62 (br. *s*, 1 H); 9.78 (br. *s*, 1 H); 7.23 (*d*, *J* = 3.0, 1 H); 7.13 (*d*, *J* = 3.0, 1 H); 2.47 (*s*, 3 H); 1.28 (*s*, 9 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 179.4; 158.9; 152.6; 142.1; 138.8; 134.4; 122.9; 119.1; 105.2; 38.59; 24.7; 15.6. HR-MALDI-MS (DHB): 276.1343 (*M*H$^+$, $C_{14}H_{18}N_3O_3^+$; calc. 276.1348). Anal. calc. for $C_{14}H_{17}N_3O_3$ (275.30): C 61.08, H 6.22, N 15.26; found: C 60.84, H 6.50, N 15.09.

N-*{6-[[(*tert-*Butyl)dimethylsilyl]oxy}-3,4-dihydro-8-methyl-4-oxoquinazolin-2-yl)-2,2-dimethylpropanamide* (**29**). 1*H*-Imidazole (0.74 g, 10.9 mmol), **28** (1 g, 3.63 mmol), and (*t*-Bu)Me_2SiCl (0.67 g, 4.36 mmol) were dissolved at 0° in DMF (20 ml). After stirring at r.t. for 16 h, (*t*-Bu)Me_2SiCl (0.42 g, 2.73 mmol) was added again, and the mixture was stirred for 2 h at r.t. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 ×). The combined org. layers were washed with sat. aq. NH_4Cl and sat. aq. NaCl solns., dried ($MgSO_4$), and evaporated *in vacuo*. CC (SiO_2; AcOEt/hexane 3:7) provided **29** (1.38 g, 88%). White solid. M.p. 145–146° ($CHCl_3$/hexane). IR ($CHCl_3$): 3433*w*, 3237*w*, 2960*m*, 2855*w*, 1671*s*, 1633*s*, 1459*m*, 1351*m*, 1260*s*, 1209*w*, 1131*m*, 1018*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 11.87 (br. *s*, 1 H); 8.09 (br. *s*, 1 H); 7.47 (*d*, *J* = 2.8, 1 H); 7.08 (*d*, *J* = 2.8, 1 H); 2.45 (*s*, 3 H); 1.36 (*s*, 9 H); 0.99 (*s*, 9 H); 0.23 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 177.7; 170.8; 158.9; 150.5; 141.4; 133.7; 126.8; 118.9; 110.7; 37.8; 24.6; 23.2; 15.7; 15.0; −7.0. HR-MALDI-MS (DHB): 390.2207 (*M*H$^+$, $C_{20}H_{32}N_3O_3Si^+$; calc. 390.2213).

N-*{6-[[(*tert-*Butyl)dimethylsilyl]oxy}-3,4-dihydro-4-oxo-8-[(phenylsulfanyl)methyl]quinazolin-2-yl}-2,2-dimethylpropanamide* (**30**). To a suspension of **29** (1.38 g, 3.54 mmol) and NBS (0.63 g, 3.54 mmol) in CCl_4 (25 ml), a cat. amount of AIBN was added at 0°, and the mixture was heated to reflux overnight. A second portion of NBS was added (0.12 g, 0.71 mmol), and, after 2 h at reflux temp., the solvent was evaporated *in vacuo*. The residue was washed with hot H_2O (300 ml) and taken up in CH_2Cl_2. The soln. was dried ($MgSO_4$) and evaporated *in vacuo*, and the crude $BrCH_2$ derivative (1.7 g) was used without further purification in the next step. *GP B* with BuLi (1.6M in hexane; 5.54 ml, 8.86 mmol) in abs. THF (15 ml), PhOH (1.09 ml, 10.6 mmol), benzyl bromide (1.66 g) in abs. THF (10 ml). CC (SiO_2; AcOEt/hexane 2:8) provided **30** (1.36 g, 77%). White foam. M.p. 160–162° (hexane). IR ($CHCl_3$): 3432*w*, 3234*w*, 2960*m*, 2844*w*, 1672*s*, 1633*s*, 1447*s*, 1350*m*, 1257*m*, 1143*w*, 1119*m*, 1009*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 11.89 (br. *s*, 1 H); 8.03 (br. *s*, 1 H); 7.52 (*d*, *J* = 3.0, 1 H); 7.19–7.53 (*m*, 5 H); 7.08 (*d*, *J* = 3.0, 1 H); 4.39 (*s*, 2 H); 1.36 (*s*, 9 H); 0.95 (*s*, 9 H); 0.15 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 180.2; 161.0; 153.0; 144.3; 141.4, 136.6; 135.2; 130.4; 129.1; 128.8; 127.9; 121.9; 115.0; 40.3; 33.8; 27.2; 25.7; 18.2; −4.5. HR-MALDI-MS (DHB): 498.2241 (*M*H$^+$, $C_{26}H_{36}N_3O_3SSi^+$; calc. 498.2247). Anal. calc. for $C_{26}H_{35}N_3O_3SSi$ (497.73): C 62.74, H 7.09, N 8.44; found: C 62.91, H 7.11, N 8.41.

*2-Amino-6-hydroxy-8-[(phenylsulfanyl)methyl]quinazolin-4(3*H*)-one* (**27**). *GP E* with **30** (100 mg, 0.2 mmol), ethanolic HCl soln. (11 ml): **27** (40 mg, 80%). Yellow solid. M.p. 250° (dec.). IR (KBr): 3350*s*, 3144*s*, 1646*s*, 1616*s*, 1567*s*, 1505*m*, 1479*m*, 1428*m*, 1361*m*, 1267*w*, 1233*w*, 1194*w*, 1133*m*, 1061*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 10.84 (br. *s*, 1 H); 9.32 (br. *s*, 1 H); 7.13–7.31 (*m*, 5 H); 7.11 (*d*, *J* = 3.0, 1 H); 7.05 (*d*, *J* = 3.0, 1 H); 6.09 (br. *s*, 2 H); 4.39 (*s*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 162.2; 151.6; 149.6; 142.7; 137.2; 132.5; 129.1; 127.9; 125.6; 123.7; 118.1; 108.7; 31.5. HR-MALDI-MS (DHB): 300.0801 (*M*H$^+$, $C_{15}H_{14}N_3O_2S^+$; calc. 300.0807).

N-*(6-Cyano-3,4-dihydro-8-methyl-4-oxoquinazolin-2-yl)-2,2-dimethylpropanamide* (**31**). A suspension of **20** (6.0 g, 17 mmol) and CuCN (6.36 g, 71 mmol) in degassed abs. DMF (60 ml) was heated to reflux for 20 h. After removal of the solvent *in vacuo*, the residue was taken up in CH_2Cl_2, and the mixture was filtered. The filtrate was washed with H_2O (2 ×) and sat. aq. LiCl soln. (1 ×). The aq. phases were extracted with CH_2Cl_2, and the combined org. phases were dried ($MgSO_4$) and evaporated *in vacuo*. CC (SiO_2; CH_2Cl_2/AcOEt 95:5) provided **31** (2.71 g, 56%). White solid. M.p. 255–256°. IR ($CHCl_3$): 3428*w*, 3217*w*, 2973*w*, 2233*m*, 1686*s*, 1628*s*, 1605*s*, 1478*m*, 1441*m*, 1283*m*, 1247*m*, 1220*s*, 1129*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 12.06 (br. *s*, 1 H); 8.35 (*d*, *J* = 1.8, 1 H); 8.13 (br. *s*, 1 H); 7.68 (*d*, *J* = 1.8, 1 H); 2.48 (*s*, 3 H); 1.36 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 180.2; 159.7; 150.3; 147.2; 136.4; 136.2; 129.7; 120.4; 118.3; 107.8; 40.5; 27.1; 17.6. HR-MALDI-MS (DHB): 285.1348 (*M*H$^+$, $C_{15}H_{17}N_4O_2^+$; calc. 285.1346). Anal. calc. for $C_{15}H_{16}N_4O_2$ (285.31): C 63.37, H 5.67, N 19.71; found: C 63.39, H 5.78, N 19.78.

N-*{6-Cyano-3,4-dihydro-4-oxo-8-[(phenylsulfanyl)methyl]quinazolin-2-yl}-2,2-dimethylpropanamide* (**32**). To a suspension of **31** (2.50 g, 8.79 mmol) and NBS (1.72 g, 9.67 mmol) in CCl_4 (100 ml), a cat. amount of AIBN was added, and the mixture was heated to reflux for 6 h. After a second addition of NBS (0.33 g, 1.86 mmol), the mixture was heated to reflux for additional 12 h. After removal of the solvent *in vacuo*, the residue was washed with hot H_2O (300 ml) and taken up in CH_2Cl_2. The soln. was dried ($MgSO_4$) and evaporated *in vacuo*, and the crude benzyl bromide was used without further purification in the next step. *GP B* with BuLi (1.6M in hexane; 6.44 ml, 10.30 mmol) in abs. THF (20 ml), PhSH (1.05 ml, 10.3 mmol), crude benzyl bromide (2.5 g, 6.87 mmol) in abs. THF (20 ml). CC (SiO_2; AcOEt/hexane 3:7) provided **32** (690 mg, 40%).

Yellowish solid. M.p. 125–126°. IR ($CHCl_3$): 3427*w*, 3202*w*, 2980*w*, 2230*m*, 1683*s*, 1628*s*, 1602*s*, 1478*m*, 1444*m*, 1371*w*, 1251*m*, 1218*m*, 1134*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 12.08 (br. *s*, 1 H); 8.37 (*d*, *J* = 1.8, 1 H); 8.08 (br. *s*, 1 H); 7.52 (*d*, *J* = 1.8, 1 H); 7.24–7.26 (*m*, 5 H); 4.32 (*s*, 2 H); 1.34 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 180.4; 159.4; 149.7; 147.8; 136.1; 135.4; 135.0; 130.9; 130.6; 128.9; 127.0; 120.8; 117.9; 107.6; 40.5; 33.8; 27.0. HR-MALDI-MS (DHB): 393.1384 (*M*H$^+$, $C_{21}H_{21}N_4O_2S^+$; calc. 393.1380).

2-Amino-3,4-dihydro-4-oxo-8-[(phenylsulfanyl)methyl]quinazoline-6-carbonitrile (**33**). *GP E* with **32** (800 mg, 2.0 mmol), ethanolic HCl soln. (66 ml): **33** (591 mg, 94%). White solid. M.p. >260° (DMF/H_2O, dec.). IR (KBr): 3166*s*, 2227*m*, 1889*w*, 1723*s*, 1659*s*, 1613*s*, 1560*s*, 1476*s*, 1437*s*, 1346*s*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 8.13 (*d*, *J* = 2.4, 1 H); 7.69 (*d*, *J* = 2.4, 1 H); 7.19–7.34 (*m*, 5 H); 4.41 (*s*, 2 H); 4.16 (br. *s*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 159.9; 153.0; 136.2; 135.1; 131.0; 130.4; 129.5; 128.9; 126.4; 126.4; 118.3; 117.3; 103.2; 32.1. HR-MALDI-MS (DHB): 309.0811 (*M*H$^+$, $C_{16}H_{13}N_4OS^+$; calc. 309.0810).

*2-Amino-6-(aminomethyl)-8-[(phenylsulfanyl)methyl]quinazolin-4(3*H*)-one* (**34**). To a suspension of **33** (100 mg, 0.32 mmol) in abs. THF (11 ml), 1M $LiEt_3BH$ soln. (1.3 ml, 1.30 mmol) in THF (11 ml) was added dropwise at −78°, and the mixture was allowed to warm to r.t. After stirring for 4 h at r.t., 1N HCl (10 ml) was added, and the mixture was stirred for 20 min. THF was removed *in vacuo*, and the aq. phase was washed with AcOEt (3×). The pH of the aq. phase was adjusted to 8 with 1N NaOH, and the precipitate formed was isolated by filtration. The solid was washed with H_2O, $CHCl_3$, and cold MeOH. Recrystallization from MeOH provided **34** (50 mg, 50%). Light-orange solid. M.p. 179–182°. IR (KBr): 3133*s*, 2360*m*, 1700*m*, 1653*s*, 1609*s*, 1506*m*, 1479*s*, 1437*m*, 1349*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 7.77 (*s*, 1 H); 7.50 (*s*, 1 H); 7.14–7.35 (*m*, 5 H); 6.39 (*s*, 2 H); 4.43 (*s*, 2 H); 3.65 (*s*, 2 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): 162.3; 151.1; 137.2; 136.3; 133.9; 130.3; 128.9; 128.9; 127.9; 125.5; 123.1; 116.9; 44.9; 32.0. HR-MALDI-MS (DHB): 313.1121 (*M*H$^+$, $C_{16}H_{17}N_4OS^+$; calc. 313.1118).

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