A Facile Synthesis of 6*H*-[1,3,5]Triazino[2,1-*b*]quinazolin-6-ones

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Abstract: Triazinoquinazolinone derivatives are synthesized by cyclization of aminobenzamide-substituted triazine compounds in the presence of a proton source such as trifluoroacetic acid or hydrochloric acid. The reaction is mild, general, and gives high yield (>90%) of the cyclized product. This procedure allows, for the first time, access to triazinoquinazolinone compounds bearing different functionalities on the benzene and triazine moieties that are not available by other routes.

Key words: amides, heterocycles, cyclization, carboxylic acids, esters

As part of our effort to prepare new fused *s*-triazino heterocycles, the synthesis of a triazinoquinazolinone **1** was explored with the aim of producing rigid analogues with potentially improved oral bioavailability (Figure 1). Both triazine[1] and quinazoline[2] scaffolds provide the basis for the design of biologically relevant molecules with widespread application as therapeutics, and so a fused heterocycle containing both moieties was of interest. Recently published biological results suggest that a triazinoquinazolinone nucleus could be a promising new scaffold for the development of potential anticancer agents.[3] Two methods for the preparation of 6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one derivatives **2** appear in the literature. The first strategy is a multi-step procedure that requires stepwise construction of the triazinoquinazolinone ring.[4,5] This process requires the use of high temperatures, and proceeds in moderate to low yield, which limits its use. Furthermore, no analytical data or assessment of purity of the final product was reported.

The second approach[6,7] requires the use of a substituted triazine, such as **3**, as a starting material for the formation of the triazinoquinazolinone derivative. This method is not general, and is limited to substrates with substituents on the phenyl and triazine rings that tolerate the harsh reaction conditions. The reaction required high temperature, did not proceed to completion, and required the use of acetic acid as solvent, which was difficult to remove from the final product. Furthermore, a disadvantage of this procedure was the concomitant hydrolysis of the dimethyl amine and decarboxylation of the starting material **3** under the reaction conditions. Herein, we report a mild, simple, efficient, and high-yielding general procedure for the synthesis of 6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-ones and their derivatives as exemplified by the general structure **2**, where R^2 and R^3 represent primary amines, and R = H, CH_3, F, NO_2, NH_2, or OMe. This reaction thus provides access to triazinoquinazolinone derivatives with a range of different functionalities.

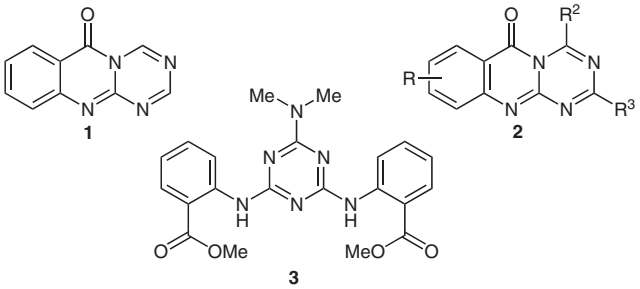

Figure 1

Our study started with the selection of a triazine derivative as a model compound for the cyclization reaction. In order to avoid complications arising from regioselectivity, and to provide a clear ^{1}H NMR fingerprint, the bis(isobutylamino) amide **5** and ester **7** were chosen as key molecules for this study; their preparation is summarized in Scheme 1. Dichloro compounds **4** or **6** were treated with excess isobutylamine in tetrahydrofuran to give the final product in high yield (>75%). A number of cyclization trials were carried out starting with compounds **5** or **7** in order to produce triazinoquinazolinone derivative **26**. For amide **5**, quantitative conversion was achieved at ambient temperature in the presence of a proton source, such as 20% trifluoroacetic acid in dichloromethane, 0.8 M HCl in dioxane–dichloromethane (1:4), or 20% 1 M aqueous HCl in acetonitrile. No reaction was observed when the cyclization was undertaken in the presence of either Lewis acid (aluminum chloride/dichloromethane), or base such as diisopropylethylamine or aqueous sodium hydroxide. For substituted amides, the yield was dependent on the bulk of the alkyl groups. For example, the *N*,*N*-dimethyl amide **11**, cyclized readily to give quantitative conversion into **26**, whereas amide **10** gave only low yield of cyclic triazine **26** (<10%) under acidic conditions (1 M HCl). Use of benzyl amine **14** gave no cyclized material; both ester **7** and acid **8** failed to give any cyclized product **26** using the same procedure. All the above results indicate the importance of the amide group for the formation of cyclic triazine **26** under these mild conditions. Cyclization also proceeded smoothly with a variety of substituents on the benzamide ring, such as methyl **27**, nitro **28**, amino **29**, fluoro **30** or methoxy **31**. We then investigated the role of the substituents on the triazine in the cyclization. Replace-

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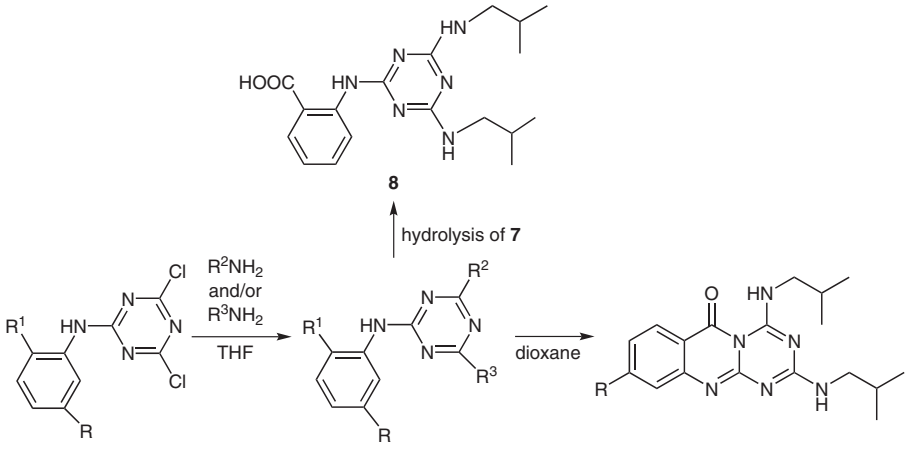


4; $R^1 = CONH_2$; R = H
6; R^1 = COOMe; R = H
9; R^1 = CONH-*s*-Bu; R = H
12; $R^1 = CH_2NHBoc$; R = H
15; $R^1 = CONH_2$; R = Me
17; $R^1 = CONH_2$; $R = NO_2$
20; $R^1 = CONH_2$; R = F

5; $R^1 = CONH_2$; R = H; $R^2 = R^3$ = NH-*i*-Bu
7; R^1 = COOMe; R = H; $R^2 = R^3$ = NH-*i*-Bu
10; R^1 = CONH-*s*-Bu; R = H; $R^2 = R^3$ = NH-*i*-Bu
11; $R^1 = CONMe_2$; R = H; $R^2 = R^3$ = NH-*i*-Bu
13; $R^1 = CH_2NHBoc$; R = H; $R^2 = R^3$ = NH-*i*-Bu
14; $R^1 = CH_2NH_2$; R = H; $R^2 = R^3$ = NH-*i*-Bu
16; $R^1 = CONH_2$; R = Me; $R^2 = R^3$ = NH-*i*-Bu
18; $R^1 = CONH_2$; $R = NO_2$; $R^2 = R^3$ = NH-*i*-Bu
19; $R^1 = CONH_2$; $R = NH_3$; $R^2 = R^3$ = NH-*i*-Bu
21; $R^1 = CONH_2$; R = F; $R^2 = R^3$ = NH-*i*-Bu
22; $R^1 = CONH_2$; R = OMe; $R^2 = R^3$ = NH-*i*-Bu
23; $R^1 = CONH_2$; R = H; $R^2 = R^3$ = OMe
24; $R^1 = CONH_2$; R = H; R^2 = OMe; $R^3 = NEt_2$
25; $R^1 = CONH_2$; R = H; $R^2 = R^3 = NMe_2$

26; R = H
27; R = Me
28; $R = NO_2$
29; $R = NH_2$
30; R = F
31; R = OMe

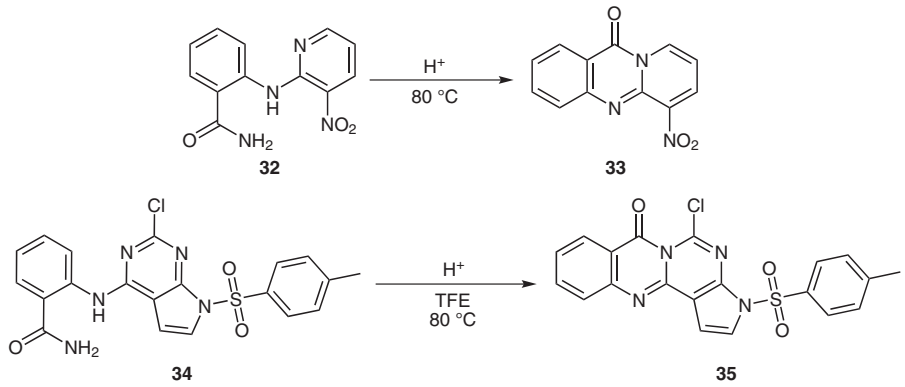
Scheme 1

ment of the primary amine groups (R^2 and/or R^3) of **5** with dichloro **4**, dimethoxy **23**, dimethylamino **25**, or methoxy and diethylamino **24** resulted in compounds that did not cyclize under these conditions. Based on these results, the NH group of the alkylamine appears to be essential for the cyclization.

Limited reports of similar cyclizations of 2-(heterocycle-amino)-substituted benzamides have appeared in the literature. For example, 2-(pyridin-2-ylamino)benzamide[8] **32** and the substituted 2-(pyrrolo[2,3-*d*]pyrimidin-4-yl)aminobenzamide[9] **34** were cyclized to the corresponding quinazolinone derivatives **33** and **35** in the presence of an acid at 80 °C (Scheme 2). However, ester cyclizations of similar compounds required harsh conditions, namely very high temperature (>160 °C), and gave low yields.[10]

Cyclization of **5** to **26** is characterized by a loss of 17 mass units (NH_3) in the mass spectrum, and can be readily followed by ^{1}H NMR analysis due to the non-equivalency of the two isobutylamino groups in **26**, as compared to **5**. Analysis of the ^{13}C NMR spectra reveals a large shift in the carbonyl signal from δ = 171.82 ppm in **5** to δ = 162.35 ppm in **26**. The HMBC spectrum of **26** was not helpful because of the lack of proton substitution in the heterocyclic portion of the ring system. A ^{1}H NMR experiment was therefore performed to follow the cyclization of **5** with CF_3CO_2D in CD_2Cl_2; under these conditions, an immediate change in the spectrum was observed upon addition of CF_3CO_2D, presumably due to a protonation event, followed by conversion of the new species into **26** over the course of several hours (complete conversion within 6.5 h). A similar experiment conducted with the methyl benzoate compound **7** also showed an immediate change in peak shifts upon addition of CF_3CO_2D, but no subsequent reaction was observed.

Additional support for the structure of **26** was provided by observing the reaction with nucleophiles. For example, reaction of **26** with dimethylamine yielded the *N*,*N*-dimeth-



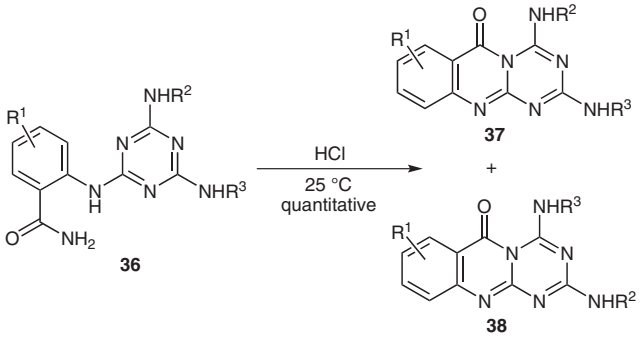
Scheme 2

ylbenzamide **11**; incubation of **26** in MeOH at 21 °C, gave 59% conversion into the corresponding methyl benzoate **7** after 13 days.

The general synthetic procedure for 6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one derivatives is outlined in Scheme 3. The cyclization proceeded quantitatively at room temperature overnight in HCl/dioxane, and was general for a variety of substituents on the phenyl and triazine rings. As expected, when R^2 and R^3 differed, two isomers **37** and **38** were formed in a 1:1 ratio.

The potential utility of this approach was illustrated by the facile synthesis of triazinoquinazolinones **41** and **42** (Scheme 4). These two compounds are rigid analogues of compound **39**. The latter has been found to possess antimicrobial activity against Gram-positive bacteria.[11] Thus, treatment of triazine **40** with HCl in dioxane at room temperature for three hours induced both cyclization and concomitant removal of the Boc protecting group, to give the two isomers, **41** and **42** (1:1), in high yield (81%).

In summary, we report for the first time a mild, general and efficient route for the preparation of triazinoquinazolinones **2** bearing different substituents on the benzene and triazine moieties. This procedure is practical and amenable to scale-up. The potential utility of this route is exemplified by the preparation of cyclic compounds **41** and **42**, which are not easily available by other methods.



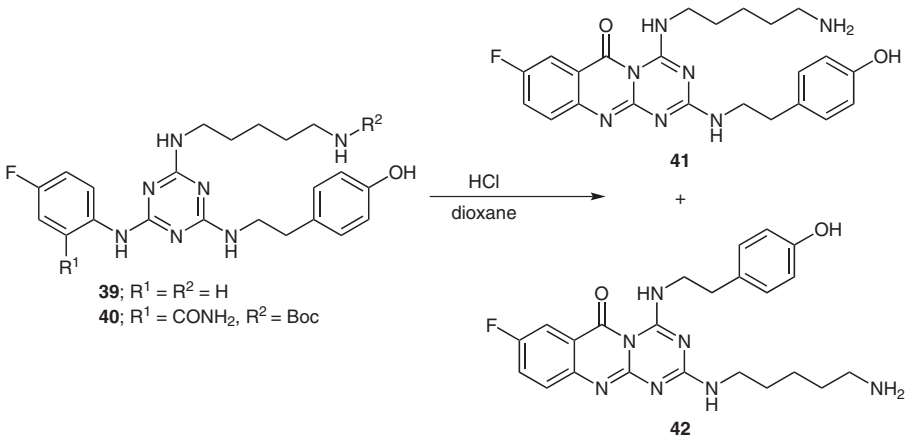
Scheme 3

Melting points were obtained with an Electrothermal MEL-TEMP® melting point apparatus. NMR spectra were recorded at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR, and 377 MHz for ^{19}F NMR. All HPLC and mass spectra were recorded with an HP 1100 LC-MS Agilent instrument, using a diode array detector, monitoring at 230 and 254 nm, and an analytical C18 column (75 × 4.6 mm, 5 μm); MeCN–H_2O (15–99%) containing 0.05% TFA; flow rate: 2 mL/min (temperature 30 °C).

Preparation of Monosubstituted Dichloro[1,3,5]triazines 4, 6, 9, 12, 15, 17 and 20; General Procedures

Procedure A

A mixture of substituted aniline (1 equiv) and cyanuric chloride (1



Scheme 4

equiv) in 1,4-dioxane (5–10 mL per mmol) was treated with DIPEA (3 equiv), and the mixture was stirred at ambient temperature overnight. Solvent was evaporated in vacuo and the residue washed with H_2O (20 mL per mmol), then dried to give the dichloro[1,3,5]triazine compound.

Procedure B

Cyanuric chloride (1 equiv) in acetone (1 vol) was cooled to 0 °C and treated with ice (0.2 vol). A suspension of substituted aniline (1 equiv) in either acetone or MeCN (2 vol) was added, followed by a further portion of ice (0.4 vol). The reaction was stirred at 0 °C for 10 min, and the pH was adjusted from 1 to 7 with 5% $NaHCO_3$. The reaction was stirred at 0 °C for a further 5 h and then partitioned between EtOAc and H_2O. The organic phase was washed with 1 M HCl and with saturated aq NaCl, dried (Na_2SO_4), filtered and evaporated in vacuo to give the dichloro[1,3,5]triazine compound.

2-(4,6-Dichloro-[1,3,5]triazin-2-ylamino)benzamide (4)

2-Aminobenzamide (5.0 g, 36.7 mmol) was reacted according to general procedure B to give the title compound.

Yield: 8.5 g (81%); off-white solid; HPLC: t_R = 3.3 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.18 (s, 1 H), 8.29 (s, 1 H), 8.14 (d, J = 7.8 Hz, 1 H), 7.83 (s, 1 H), 7.80 (dd, J = 8.0, 1.4 Hz, 1 H), 7.59 (ddd, J = 7.9, 7.9, 1.4 Hz, 1 H).

MS (ESI): m/z (%) = 283.9/285.9/288.0 (100) [Cl_2-pattern, MH^+].

Methyl 2-(4,6-Dichloro[1,3,5]triazin-2-ylamino)benzoate (6)

Methyl 2-aminobenzoate (2.1 mL, 16.3 mmol) was reacted according to general procedure B to give the title compound.

Yield: 4.75 g (98%); off-white solid; HPLC: t_R = 2.6 min.

^{1}H NMR (500 MHz, acetone-d_6): δ = 11.36 (s, 1 H), 8.51 (d, J = 8.5 Hz, 1 H), 8.08 (dd, J = 8.0, 1.5 Hz, 1 H), 7.69–7.72 (m, 1 H), 7.26–7.30 (m, 1 H), 3.93 (s, 3 H).

MS (ESI): m/z (%) = 298.0/300.0/301.9 (100) [Cl_2-pattern, MH^+].

***N*-(But-2-yl)-2-(4,6-dichloro[1,3,5]triazin-2-ylamino)benzamide (9)**

2-Amino-*N*-(but-2-yl)benzamide (282 mg, 1.5 mmol) was reacted according to general procedure A to give the title compound.

Yield: 364 mg (73%); pale-yellow crystals; HPLC: t_R = 4.5 min.

^{1}H NMR (400 MHz, acetone-d_6 + CD_3OD): δ = 8.27 (dd, J = 8.4, 1.2 Hz, 1 H), 8.18 (d, J = 6.5 Hz, 1 H), 7.70 (dd, J = 7.8, 1.4 Hz, 1 H), 7.49–7.54 (m, 1 H), 7.23 (ddd, J = 7.6, 7.6, 1.0 Hz, 1 H), 3.93–4.02 (m, 1 H), 1.48–1.60 (m, 2 H), 1.16 (d, J = 6.7 Hz, 3 H), 0.90 (t, J = 7.4 Hz, 3 H).

MS (ESI): m/z (%) = 340.0/342.0/344.1 (100) [Cl_2-pattern, MH^+].

2-[(*tert*-Butoxycarbonylaminomethyl)phenyl]amino-4,6-dichloro[1,3,5]triazine (12)

2-(*tert*-Butoxycarbonylaminomethyl)aniline (898 mg, 4.04 mmol) was reacted according to general method A to give the title compound.

Yield: 426 mg (28%); pale-yellow solid; HPLC: t_R = 4.4 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.03 (s, 1 H), 7.78 (d, J = 8.0 Hz, 2 H), 7.37 (ddd, J = 8.2, 7.4, 1.9 Hz, 2 H), 7.26 (dd, J = 7.6, 1.9 Hz, 1 H), 7.22 (ddd, J = 7.6, 7.4, 1.0 Hz, 2 H), 5.22 (t, J = 6.5 Hz, 1 H), 4.24 (d, J = 6.5 Hz, 2 H), 1.43 (s, 9 H).

MS (ESI): m/z (%) = 370.2/372.2/374.2 [Cl_2-pattern, MH^+].

2-(4,6-Dichloro[1,3,5]triazin-2-ylamino)-4-methylbenzamide (15)

2-Amino-4-methylbenzamide (251 mg, 1.67 mmol) was reacted according to general method A to give the title compound.

Yield: 484 mg (97%); off-white solid; HPLC: t_R = 3.6 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.37 (s, 1 H), 8.23 (s, 1 H), 8.02 (s, 1 H), 7.75 (s, 1 H), 7.72 (d, J = 8.0 Hz, 1 H), 7.07 (dd, J = 8.0, 1.0 Hz, 1 H), 2.35 (s, 3 H).

MS (ESI): m/z (%) = 298.0/300.0/301.9 (100) [Cl_2-pattern, MH^+].

2-(4,6-Dichloro[1,3,5]triazin-2-ylamino)-4-nitrobenzamide (17)

2-Amino-4-nitrobenzamide (131 mg, 0.72 mmol) was reacted according to general method B to give the title compound.

Yield: 208 mg (80%); pale-yellow solid; HPLC: t_R = 3.6 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.10 (s, 1 H), 8.98 (d, J = 2.3 Hz, 1 H), 8.53 (s, 1 H), 8.11 (s, 1 H), 8.09 (dd, J = 8.6, 2.3 Hz, 1 H), 8.01 (d, J = 8.6 Hz, 1 H).

MS (ESI): m/z = 351.0/353.0/354.9 (Cl_2-pattern, MNa^+).

2-(4,6-Dichloro[1,3,5]triazin-2-ylamino)-4-fluorobenzamide (20)

2-Amino-4-fluorobenzamide (200 mg, 1.30 mmol) was reacted according to general method B, to give the title compound.

Yield: 356 mg (91%); off-white solid; HPLC: t_R = 3.7 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.68 (s, 1 H), 8.41 (s, 1 H), 8.32 (s, 1 H), 8.14 (dd, $J_{H–H}$ = 2.6, $J_{H–F}$ = 11.6 Hz, 1 H), 7.95 (dd, $J_{H–H}$ = 8.9, $J_{H–F}$ = 6.4 Hz, 1 H), 7.13 (ddd, $J_{H–H}$ = 8.4, 2.6, $J_{H–F}$ = 8.4 Hz, 1 H).

^{19}F NMR (377 MHz, DMSO-d_6): δ = –106.24 to –106.17 (m, 1 F).

MS (ESI): m/z (%) = 302.0/304.0/306.0 (100) [Cl_2-pattern, MH^+].

Preparation of Bis(isobutylamino)-Substituted Triazines 5, 7, 10, 13, 16, 18, 21 and Bis (dimethylamino)-Substituted Triazine 25; General Procedure C

A suspension of dichloro[1,3,5]triazine (1 equiv) in 1,4-dioxane (5–10 mL per mmol) was treated with isobutylamine (10 equiv) and the reaction was heated at 80 °C in a sealed tube overnight. The suspension was treated with MeOH to give a clear solution, and evaporated onto silica gel. Purification by flash chromatography gave the bis(isobutylamino) substituted triazine compound.

2-[4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino]benzamide (5)

A mixture of **4** (1.00 g, 3.5 mmol) and isobutylamine (2.9 mL, 28.2 mmol) in THF (10 mL) and MeOH (2 mL) was heated at 130 °C for 10 min in a microwave apparatus. Solvent was evaporated in vacuo, and the crude material was purified by flash chromatography (SiO_2; EtOAc–hexanes, 10% then THF–hexanes, 20→50%) to give a white solid (1.3 g). This material was dissolved in a minimum of EtOAc and added dropwise to hexanes (180 mL). The solid was collected by filtration, washed with hexanes (2 × 25 mL) and dried in vacuo to give the title compound.

Yield: 0.8 g (64%); white solid; HPLC: t_R = 2.5 min.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.62–8.78 (m, 1 H), 7.66 (d, J = 7.4 Hz, 1 H), 7.39–7.43 (m, 1 H), 6.99 (dd, J = 7.6, 7.4 Hz, 1 H), 3.08–3.20 (m, 4 H), 1.85–1.97 (m, 2 H), 0.94 (d, J = 6.5 Hz, 12 H).

MS (ESI): m/z (%) = 358.3 (100) [MH^+].

Methyl 2-[4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino]benzoate (7)

A solution of **6** (53 mg, 0.18 mmol) and isobutylamine (0.09 mL, 0.91 mmol) in THF (5 mL) was heated at 50 °C for 18 h. Solvent was evaporated in vacuo, and the crude material was purified by flash chromatography (SiO_2; EtOAc–hexanes, 0→100%) to give the title compound.

Yield: 57 mg (86%); white solid; HPLC: t_R = 3.4 min.

^{1}H NMR (400 MHz, acetone-d_6): δ = 10.39–10.57 (m, 1 H), 9.05–9.13 (m, 1 H), 7.98–8.03 (m, 1 H), 7.44–7.57 (m, 1 H), 6.96–7.02 (m, 1 H), 6.39–6.45 (m, 1 H), 6.17–6.24 (m, 1 H), 3.92 (s, 3 H), 3.23–3.27 (m, 4 H), 1.85–2.03 (m, 2 H), 0.95 (d, *J* = 6.8 Hz, 12 H).

MS (ESI): *m*/*z* (%) = 387.2 (100) [MH$^+$].

2-[4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino]-*N*,*N*-dimethylbenzamide (11)

A suspension of **26** (24 mg, 0.07 mmol) in MeCN (1.5 mL) was treated with dimethylamine hydrochloride (114 mg, 1.4 mmol) and aq NaOH (1 M, 1.4 mL), and the heterogeneous reaction mixture was stirred vigorously at ambient temperature for 5 d. The reaction was quenched by addition of MeOH (1 mL), and was stirred in MeOH (10 mL) for 4 d. Purification by flash chromatography (SiO_2; EtOAc–hexanes, 10→100%) gave the title compound **11**.

Yield: 1.6 mg (6%); colorless glass; HPLC: t_R = 3.4 min.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.12–8.32 (m, 1 H), 7.39 (dd, *J* = 7.8, 7.6 Hz, 1 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 7.12 (dd, *J* = 7.6, 7.4 Hz, 1 H), 3.31 (s, 3 H), 3.03–3.20 (m, 4 H), 2.95 (s, 3 H), 1.83–1.93 (m, 2 H), 0.93 (d, *J* = 6.8 Hz, 12 H).

MS (ESI): *m*/*z* (%) = 386.2 (100) [MH$^+$].

2-[4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino]-*N*-[but-2-yl]benzamide (10)

Compound **9** (170 mg, 0.50 mmol) was reacted according to general procedure C to give the title compound **10**.

Yield: 172 mg (83%); white solid; HPLC: t_R = 3.1 min.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.30–8.62 (m, 1 H), 7.55 (d, *J* = 7.0 Hz, 1 H), 7.38–7.42 (m, 1 H), 7.23 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1 H), 3.97–4.04 (m, 1 H), 3.08–3.19 (m, 4 H), 1.82–1.93 (m, 2 H), 1.51–1.61 (m, 2 H), 1.18–1.23 (m, 3 H), 0.88–0.98 (m, 15 H).

MS (ESI): *m*/*z* (%) = 414.2 (100) [MH$^+$].

2-{[2-(*tert*-Butoxycarbonylaminomethyl)phenyl]amino}-4,6-bis(isobutylamino)[1,3,5]triazine (13)

Compound **12** (200 mg, 0.54 mmol) was reacted according to general procedure C to give the title compound.

Yield: 223 mg (92%); pale-yellow solid; HPLC: t_R = 3.2 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.85 (m, 2 H), 7.20–7.31 (m, 2 H), 7.01–7.12 (m, 1 H), 5.00–5.32 (m, 3 H), 4.20–4.32 (m, 2 H), 3.08–3.35 (m, 4 H), 1.74–1.83 (m, 2 H), 1.43 (s, 9 H), 0.89 (d, *J* = 6.3 Hz, 12 H).

MS (ESI): *m*/*z* (%) = 444.3 (100) [MH$^+$].

2-[4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino]-4-methylbenzamide (16)

Compound **15** (149 mg, 0.50 mmol) was reacted according to general procedure C to give the title compound.

Yield: 142 mg (77%); white solid; HPLC: t_R = 2.7 min.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.43–8.68 (m, 1 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 6.82 (d, *J* = 7.8 Hz, 1 H), 3.10–3.23 (m, 4 H), 2.38 (s, 3 H), 1.82–1.97 (m, 2 H), 0.92–1.00 (s, 12 H).

MS (ESI): *m*/*z* (%) = 372.1 (100) [MH$^+$].

2-{4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino}-4-nitrobenzamide (18)

Compound **17** (100 mg, 0.31 mmol) was reacted according to the general procedure C to give the title compound.

Yield: 62 mg (51%); pale-yellow solid; HPLC: t_R = 3.0 min.

^{1}H NMR (400 MHz, CD_3OD): δ = 9.85–9.97 (m, 1 H), 7.87 (d, *J* = 8.6 Hz, 1 H), 7.79 (dd, *J* = 8.7, 2.1 Hz, 1 H), 3.10–3.35 (m, 4 H), 1.83–1.95 (m, 2 H), 0.95–1.02 (m, 12 H).

MS (ESI): *m*/*z* (%) = 403.1 (100) [MH$^+$].

4-Amino-2-{4,6-bis(isobutylamino)-[1,3,5]triazin-2-ylamino}benzamide (19)

A mixture of **17** (44 mg, 0.11 mmol) and ammonium formate (33 mg, 0.52 mmol) in EtOH (3 mL) was treated with 10% Pd/C (11 mg), and the reaction was stirred at ambient temperature for 18 h. The reaction mixture was filtered through Celite, and evaporated in vacuo to give the title compound.

Yield: 41 mg (100%); white solid; HPLC: t_R = 3.20 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.32 (s, 1 H), 8.07–8.23 (m, 1 H), 7.64 (br s, 1 H), 7.43 (d, *J* = 8.6 Hz, 1 H), 6.96 (br s, 1 H), 6.82–6.88 (m, 1 H), 6.65–6.72 (m, 1 H), 6.07–6.11 (m, 1 H), 5.41 (s, 2 H), 3.00–3.18 (m, 4 H), 1.76–1.85 (m, 2 H), 0.85 (d, *J* = 6.0 Hz, 12 H).

MS (ESI): *m*/*z* (%) = 373.4 (100) [MH$^+$].

2-{4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino}-4-fluorobenzamide (21)

Compound **20** (100 mg, 0.33 mmol) was reacted according to general procedure C to give the title compound.

Yield: 48 mg (39%); white solid; HPLC: t_R = 2.9 min.

^{1}H NMR (400 MHz, CD_3OD): δ = 9.70–9.81 (m, 1 H), 7.73 (dd, $J_{H–H}$ = 8.2, $J_{H–F}$ = 6.7 Hz, 1 H), 6.65–6.72 (m, 1 H), 3.08–3.22 (m, 4 H), 1.84–1.97 (m, 2 H), 0.95–1.02 (m, 12 H).

^{19}F NMR (377 MHz, CD_3OD): δ = –108.52 to –108.26 (m, 1 F).

MS (ESI): *m*/*z* = 376.1 [MH$^+$].

2-{4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino}-4-methoxybenzamide (22)

Reaction of 2-amino-4-methoxybenzamide (339 mg, 2.04 mmol) according to general method A gave a mixture of mono- and di-addition products. This crude mixture was reacted according to general method C to give the title compound.

Yield: 51 mg (6.5%); white solid; HPLC: t_R = 3.7 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.30 (s, 1 H), 8.50–8.54 (m, 1 H), 7.98 (s, 1 H), 7.69 (d, *J* = 8.8 Hz, 1 H), 7.35 (s, 1 H), 7.06–7.15 (m, 1 H), 6.77–6.97 (m, 1 H), 6.45–6.52 (m, 1 H), 3.79 (s, 3 H), 3.00–3.20 (m, 4 H), 1.75–1.87 (m, 2 H), 0.85 (d, *J* = 6.6 Hz, 12 H).

MS (ESI): *m*/*z* (%) = 388.4 (100) [MH$^+$].

2-{4,6-Dimethoxy[1,3,5]triazin-2-ylamino}benzamide (23)

A mixture of compound **4** (203 mg, 0.71 mmol) and Et_3N (0.30 mL, 2.2 mmol) in MeOH (2.5 mL) was heated at 120 °C for 30 min in a microwave apparatus. The complex mixture of products was purified by flash chromatography (SiO_2; EtOAc–hexanes, 10–100%) to give the title compound.

Yield: 11 mg (5.5%); white solid; HPLC: t_R = 2.6 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.60 (s, 1 H), 8.56 (d, *J* = 8.4 Hz, 1 H), 8.29 (s, 1 H), 7.78 (d, *J* = 7.6 Hz, 1 H), 7.74 (s, 1 H), 7.51 (dd, *J* = 8.0, 7.6 Hz, 1 H), 7.09 (dd, *J* = 7.6, 7.2 Hz, 1 H), 3.89 (s, 6 H).

MS (ESI): *m*/*z* (%) = 276.1 (100) [MH$^+$].

2-{4-Diethylamino-6-methoxy-[1,3,5]triazin-2-ylamino}benzamide (24)

The title compound was isolated as a side product during the formation of compound **23**.

Yield: 8.2 mg; colorless glass; HPLC: t_R = 3.3 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.66 (dd, *J* = 8.5, 0.9 Hz, 1 H), 7.70 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.45 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1 H), 7.04 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1 H), 3.91 (s, 3 H), 3.59–3.64 (m, 4 H), 1.19–1.23 (m, 6 H).

MS (ESI): *m*/*z* (%) = 317.3 (100) [MH$^+$].

2-{4,6-Bis(dimethylamino)-[1,3,5]triazin-2-ylamino}benzamide (25)

Compound **4** (284 mg, 1.00 mmol) was reacted according to general procedure C, but replacing isobutylamine with a mixture of dimethylamine hydrochloride (872 mg, 10.7 mmol) and DIPEA (1.8 mL, 10 mmol) to give the title compound.

Yield: 269 mg (89%); lustrous white solid; HPLC: t_R = 2.6 min.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.27 (dd, *J* = 8.4, 1.0 Hz, 1 H), 7.77 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.56 (ddd, *J* = 8.4, 7.4, 1.6 Hz, 1 H), 7.25 (ddd, *J* = 7.8, 7.4, 1.0 Hz, 1 H), 3.23 (s, 12 H).

MS (ESI): *m*/*z* (%) = 301.8 (100) [MH$^+$].

Cyclization; General Procedure

Method A

A solution of the compound in CH_2Cl_2 (4 vol) was treated with TFA (1 vol), and the reaction was stirred at ambient temperature overnight. Solvent and acid were evaporated in vacuo to give the cyclized material.

Method B

A solution (suspension) of the compound in either CH_2Cl_2 or 1,4-dioxane (4 vol) was treated with 4 M HCl (1 vol) in 1,4-dioxane, and the reaction was stirred at ambient temperature overnight. Solvents and acid were evaporated in vacuo to give the cyclized material.

Method C

The compound was treated with 2 M or 4 M HCl in 1,4-dioxane, and the reaction was stirred at ambient temperature overnight. Solvent and acid were evaporated in vacuo to give the cyclized material.

2,4-Bis(isobutylamino)-6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one (26)

Compound **5** was cyclized on different scales under different acidic conditions using methods A–C, to give the title compound.

White solid; HPLC: t_R = 2.6 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.28 (t, *J* = 5.5 Hz, 1 H), 10.10 (t, *J* = 5.5 Hz, 1 H), 9.03–9.12 (m, 1 H), 8.08 (dd, *J* = 8.6, 8.4 Hz, 1 H), 7.86 (dd, *J* = 8.4, 8.4 Hz, 1 H), 7.51–7.60 (m, 1 H), 7.38–7.45 (m, 1 H), 3.33–3.40 (m, 2 H), 3.14–3.20 (m, 2 H), 1.95–2.07 (m, 1 H), 1.83–1.93 (m, 1 H), 0.93 (d, *J* = 6.7 Hz, 6 H), 0.89 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.35, 159.44, 152.97, 150.79, 138.75, 138.19, 128.81, 125.66, 117.41, 115.63, 49.50, 49.00, 28.71, 27.80, 20.76 (2C), 20.59 (2C).

MS (ESI): *m*/*z* (%) = 341.2 (100) [MH$^+$].

HRMS: *m*/*z* [MH$^+$] calcd for $C_{18}H_{25}N_6O^+$: 341.20844; found: 341.20877.

2,4-Bis(isobutylamino)-9-methyl-6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one (27)

Compound **16** (20 mg, 0.054 mmol) was cyclized according to general cyclization method C (2 M HCl) to give the title compound.

White solid; HPLC: t_R = 2.7 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.24 (s, 1 H), 13.06 (s, 1 H), 10.31 and 10.14 (2 × t, *J* = 5.8 and 5.6 Hz, 1 H), 8.98–9.04 (m, 1 H), 7.95–8.00 (m, 1 H), 7.27 (d, *J* = 7.8 Hz, 1 H), 3.63–3.70 (m, 1 H), 3.40–3.48 (m, 1 H), 3.16–3.23 (m, 2 H), 2.43 (s, 3 H), 1.96–2.05 (m, 1 H), 1.83–1.93 (m, 1 H), 0.89–0.95 (m, 6 H).

MS (ESI): *m*/*z* (%) = 355.1 (100) [MH$^+$].

2,4-Bis(isobutylamino)-9-nitro-6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one (28)

Compound **18** (5.3 mg) was cyclized according to general cyclization method B (CH_2Cl_2) to give the title compound.

Pale-yellow solid; HPLC: t_R = 2.9 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.18 and 9.97 (2 × t, *J* = 5.8 and 5.6 Hz, 1 H), 9.34 and 9.25 (2 × t, *J* = 6.3 and 6.5 Hz, 1 H), 8.30–8.44 (m, 2 H), 6.65–6.83 (m, 2 H), 3.36–3.43 (m, 2 H), 3.17–3.22 (m, 2 H), 1.98–2.06 (m, 1 H), 1.83–1.93 (m, 1 H), 0.93 (d, *J* = 6.6 Hz, 6 H), 0.89 (d, *J* = 6.8 Hz, 6 H).

MS (ESI): *m*/*z* (%) = 386.1 (100) [MH$^+$].

9-Amino-2,4-bis(isobutylamino)-6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one (29)

Cyclization of compound **19** was inefficient under the general methods due to precipitation of the aryl-ammonium salt upon HCl addition. As an alternative, a suspension of compound **19** (5.0 mg) in MeCN (0.5 mL) was treated with 2.4 M aq HCl (0.7 mL), and the clear solution was stirred at ambient temperature for 5 h. Evaporation of solvents give the pure title compound.

Pale-beige solid; HPLC: t_R = 3.7 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.55 and 10.41 (2 × t, *J* = 5.8 and 5.8 Hz, 1 H), 8.85 and 8.78 (2 × t, *J* = 6.0 and 6.1 Hz, 1 H), 7.68–8.72 (m, 1 H), 6.56–6.61 (m, 1 H), 6.40 (d, *J* = 1.6 Hz, 1 H), 6.3–7.8 (very broad, 3 H), 3.30–3.36 (m, 2 H), 3.13–3.18 (m, 2 H), 1.93–2.03 (m, 1 H), 1.81–1.90 (m, 1 H), 0.92 (d, *J* = 6.5 Hz, 6 H), 0.89 (d, *J* = 6.68 Hz, 6 H).

MS (ESI): *m*/*z* (%) = 356.4 (100) [MH$^+$].

HRMS: *m*/*z* [M + Na$^+$] calcd for $C_{18}H_{25}N_7NaO^+$: 378.20128; found: 378.20153.

2,4-Bis(isobutylamino)-9-fluoro-6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one (30)

Compound **21** (5.1 mg) was cyclized according to general cyclization method B (CH_2Cl_2) to give the title compound.

White solid; HPLC: t_R = 2.6 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.26 and 10.07 (2 × t, *J* = 6.0 and 5.6 Hz, 1 H), 9.20 and 9.15 (2 × t, *J* = 6.2 and 6.0 Hz, 1 H), 8.14–8.20 (m, 1 H), 7.24–7.44 (m, 2 H), 3.35–3.40 (m, 2 H), 3.15–3.20 (m, 2 H), 1.97–2.06 (m, 1 H), 1.83–1.92 (m, 1 H), 0.88–0.94 (m, 12 H).

^{19}F NMR (377 MHz, CD_3OD): δ = –98.68 to –98.46 (m, 1 F).

MS (ESI): *m*/*z* (%) = 359.2 (100) [MH$^+$].

2,4-Bis(isobutylamino)-9-methoxy-6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one (31)

Compound **22** (5.1 mg) was cyclized according to general cyclization method B (CH_2Cl_2) to give the title compound.

Off-white solid; HPLC: t_R = 3.8 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.03 (s, 1 H), 10.36 and 10.19 (2 × t, *J* = 5.5 and 5.6 Hz, 1 H), 9.03 (t, *J* = 5.8 Hz, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 7.64–7.70 (m, 1 H), 6.91–7.03 (m, 1 H), 3.89 (s, 3 H), 3.30–3.40 (m, 2 H), 3.14–3.19 (m, 2 H), 1.97–2.06 (m, 1 H), 1.83–1.91 (m, 1 H), 0.93 (d, *J* = 6.6 Hz, 6 H), 0.89 (d, *J* = 6.6 Hz, 6 H).

MS (ESI): *m*/*z* (%) = 371.2 (100) [MH$^+$].

HRMS: *m*/*z* [MH$^+$] calcd for $C_{19}H_{27}N_6O_2^+$: 371.21900; found: 371.21968.

Cyclization of 2-[4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino]-*N*-[but-2-yl]benzamide (10) to Compound 26

Compound **10** (20 mg, 0.048 mmol) was reacted by general cyclization method B (1,4-dioxane). LCMS analysis showed an 11:89 mixture of compound **26** and starting material. The mixture was further reacted by general cyclization method C (2 M HCl) to give a 75:25 mixture (LCMS analysis) of compound **26** and starting material.

Cyclization of 2-[4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino]-*N*,*N*-dimethylbenzamide (11) to Compound 26

Compound **11** (1.5 mg, 0.0039 mmol) was reacted by general cyclization method C. LCMS and ^{1}H NMR analyses showed complete conversion into compound **26**.

2-[2-Aminomethylphenylamino]-4,6-bis(isobutylamino)-[1,3,5]triazine (14)

Compound **13** (10 mg, 0.023 mmol) was deprotected according to general cyclization method A (CH_2Cl_2), followed by conversion into the free base, to give the title compound.

Yield: 6.2 mg (80%); white solid; HPLC: t_R = 1.7 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–8.32 (m, 1 H), 7.23–7.27 (m, 1 H), 7.12–7.19 (m, 1 H), 6.94–6.98 (m, 1 H), 4.95–5.20 (m, 2 H), 3.99 (s, 2 H), 3.17–3.26 (m, 4 H), 1.80–1.93 (m, 2 H), 0.93–0.99 (m, 12 H).

MS (ESI): *m*/*z* (%) = 344.3 (100) [MH$^+$].

2-[4,6-Bis(isobutylamino)-[1,3,5]triazin-2-ylamino]benzoic Acid (8)

A solution of **7** (25 mg, 0.067 mmol) in MeCN (5 mL) and MeOH (3 drops) was treated with a solution of LiOH (8.3 mg, 0.35 mmol) in H_2O (0.25 mL), and the reaction was stirred at ambient temperature for 5 d. The mixture was filtered and the filtrate was treated with 0.5 M aq HCl (10 mL). The white precipitate was extracted with EtOAc (2 × 10 mL) and the combined extracts were washed with H_2O (10 mL) and sat. aq NaCl (12 mL), then dried (Na_2SO_4), filtered and evaporated in vacuo to give the title compound.

Yield: 24 mg (quant.); white solid; HPLC: t_R = 3.6 min.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.38–8.45 (m, 1 H), 7.93 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.33 (dd, *J* = 7.6, 7.6 Hz, 1 H), 6.96–7.01 (m, 1 H), 3.13–3.20 (m, 4 H), 1.82–1.91 (m, 2 H), 0.89 (d, *J* = 6.6 Hz, 12 H).

MS (ESI): *m*/*z* (%) = 359.2 (100) [MH$^+$].

2-{4-(5-*tert*-Butoxycarbonyl-aminopentylamino)-6-(4-hydroxyphenethylamino)-[1,3,5]triazin-2-ylamino}-5-fluorobenzamide (40)

A suspension of 2-(4,6-dichloro[1,3,5]triazin-2-ylamino)-5-fluorobenzamide (100 mg, 0.33 mmol) and tyramine (46 mg, 0.34 mmol) in MeOH (5 mL) and THF (5 mL), was treated with DIPEA (0.06 mL, 0.34 mmol) and the reaction was stirred at ambient temperature for 140 min. Solvents were evaporated in vacuo, and the residue was washed with H_2O (20 mL), and dried in vacuo to give 2-{4-chloro-6-(4-hydroxyphenethylamino)-[1,3,5]triazin-2-ylamino}-5-fluorobenzamide as an off-white solid (124 mg, 93%). A sample was taken for LCMS analysis {LRMS (ESI): *m*/*z* (%) = 403.3/405.2 (100) [Cl isotope pattern, MH$^+$]; HPLC: t_R = 3.27 min}, and the remaining material was used immediately in the next reaction.

A mixture of 2-{4-chloro-6-(4-hydroxyphenethylamino)-[1,3,5]triazin-2-ylamino}-5-fluorobenzamide (124 mg, 0.31 mmol) and 5-(*tert*-butoxycarbonylamino)pentylamine (72 mg, 0.36 mmol) in MeOH (1 mL) and THF (1 mL), was treated with DIPEA (0.08 mL, 0.46 mmol) and the reaction was heated at 140 °C for 20 min in a microwave apparatus. Solvents were evaporated in vacuo, and the crude material was purified by flash chromatography (SiO_2; EtOAc–hexanes, 50→100%) to give the title compound.

Yield: 95 mg (54%); white solid; HPLC: t_R = 2.6 min.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.60–8.70 (m, 1 H), 7.40–7.47 (m, 1 H), 7.15–7.23 (m, 1 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 6.71 (d, *J* = 8.4 Hz, 2 H), 3.46–3.54 (m, 2 H), 3.30–3.41 (m, 2 H), 3.03 (t, *J* = 7.0 Hz, 2 H), 2.73–2.79 (m, 2 H), 1.56–1.64 (m, 2 H), 1.50 (tt, *J* = 7.2, 7.2 Hz, 2 H), 1.41 (s, 9 H), 1.33–1.43 (m, 2 H).

MS (ESI): *m*/*z* (%) = 569.3 (100) [MH$^+$].

4-(5-Aminopentylamino)-8-fluoro-2-(4-hydroxyphenethylamino)-6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one (41) and 2-(5-Aminopentylamino)-8-fluoro-4-(4-hydroxyphenethylamino)-6*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one (42)

Compound **40** (90 mg, 0.14 mmol) was deprotected and cyclized according to general cyclization method B (1,4-dioxane; two cycles) to give a 1:1 mixture of the title compounds as a white solid. The isomers could be separated by reverse-phase HPLC.

More polar isomer: HPLC: t_R = 3.3 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.24 and 10.07 (2 × t, *J* = 5.3 and 5.5 Hz, 1 H), 9.27–9.32 (m, 1 H), 8.93–8.98 (m, 1 H), 7.73–7.84 (m, 5 H), 7.47–7.50 (m, 1 H), 7.04–7.10 (m, 2 H), 6.69–7.10 (m, 2 H), 3.62–3.73 (m, 2 H), 3.35–3.42 (m, 2 H), 2.73–2.85 (m, 4 H), 1.51–1.62 (m, 4 H), 1.31–1.38 (m, 2 H).

^{19}F NMR (377 MHz, DMSO-d_6): δ = –116.7 to –116.0 (m, 1 F).

MS (ESI): *m*/*z* = 452.2 [MH$^+$].

Less polar isomer: HPLC: t_R = 3.7 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.24 and 10.07 (2 × t, *J* = 5.6 and 5.5 Hz, 1 H), 8.87–8.96 and 9.28–9.35 (2 × m, 1 H), 7.74–7.83 (m, 5 H), 7.45–7.52 (m, 1 H), 7.02–7.05 (m, 2 H), 6.67–7.00 (m, 2 H), 3.42–3.58 (m, 4 H), 2.74–2.81 (m, 4 H), 1.52–1.69 (m, 4 H), 1.35–1.41 (m, 2 H).

^{19}F NMR (377 MHz, DMSO-d_6): δ = –116.8 to –115.9 (m, 1 F).

MS (ESI): *m*/*z* = 452.2 [MH$^+$].

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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