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SYNTHESIS OF BIS-ARYL PHOSPHATES BASED ON TRIAZINE SCAFFOLD

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Abstract – In view of targeting the Grb2-SH2 signaling protein, the synthesis of potential ligands based on the 1,3,5-triazine scaffold bearing two phenylphosphate groups is described. The triazine functionality was introduced using an orthogonal strategy via the sulfone chemistry.

INTRODUCTION

The 1,3,5-triazine scaffold has occupied an important position in drug discovery programs, especially since Fesik identified it as a privileged structure using screening by NMR.[1] Recent examples illustrate the value of 1,3,5-triazine derivatives for cytotoxic activity,[2] antitumoral activity,[3] inhibition of angiogenesis,[4] antimicrobial activity[5] and anti-HIV activity.[6] The use of this molecular scaffold would be also of interest to design inhibitors of the Grb2 (growth factor receptor bound-protein 2) adaptor protein. Grb2 is involved in RTK signal transduction via the binding of the SH2 domain to phosphotyrosines on the C-terminal end of the activated receptors. Thus, it is implicated in Ras activation but can also play a role in other signaling pathways in mammalian cells (e.g., PI3K signaling pathway). There has been tremendous interest in the development of inhibitors of the SH2 domain of Grb2 as therapeutic agents in treating cancers.[7] Much of the effort in designing active site directed Grb2-SH2 inhibitors has focused on the synthesis of peptidic compounds containing phosphotyrosine (pTyr) or phosphotyrosine mimics.[8] To date, only a limited number of non-peptidic antagonists of Grb-SH2 was reported from the low micromolar range to the high micromolar range, i.e., urea **1**,[9] thiazole **2**,[10] tetrahydropyrimidinone **3**[11] and triazine **4**[12] (Figure 1). The discovery of the latter class of compounds should facilitate the development of more drug-like inhibitors for the treatment of cancers.

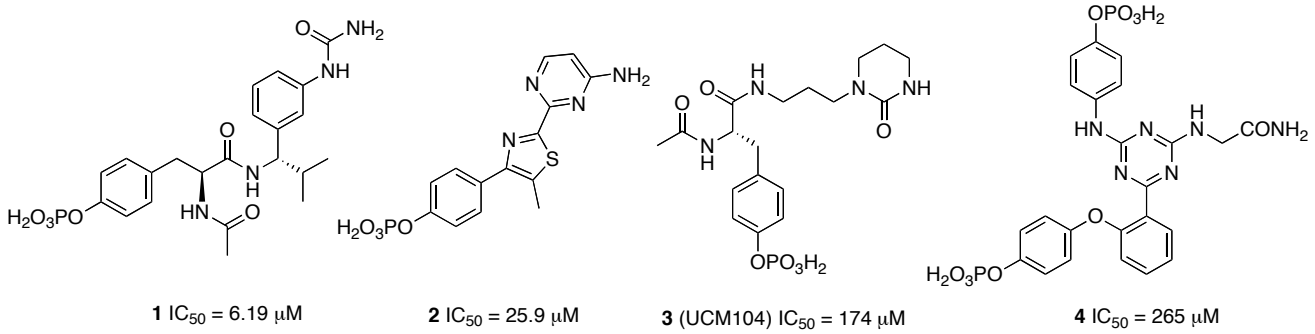


Figure 1. Non-peptidic antagonists **1**-**4**

In the context of our ongoing research on Grb2 targeting,[12-14] we report herein the synthesis of novel triazine scaffold-based bis-aryl phosphates **5**-**7** (Figure 2), the design of which was inspired by the structure of triazine **4**, using a flexible synthetic strategy. We have sought to replace the 4-phenoxyphenyl substructure by the simpler 4-aminomethylphenyl one. For the three compounds, MD simulations showed that this modification enabled to dock, on the one hand, its linked phosphate group into the pTyr-binding pocket encompassing residues Arg 86, Ser 88, Ser 90, Ser 96 and Lys 109; and, on the other hand, the aniline-bound phosphate into the second pTyr pocket, involving residues Arg 142, Asn 143, and Ser 141. In particular, it appeared interesting to introduce a urea functionality on the triazine framework so as to obtain hydrogen-bonding interactions with the main-chain carbonyl of Leu 120 and amide of Lys 109 in the specificity pocket.

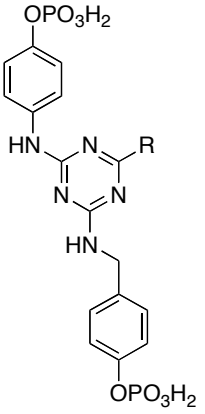
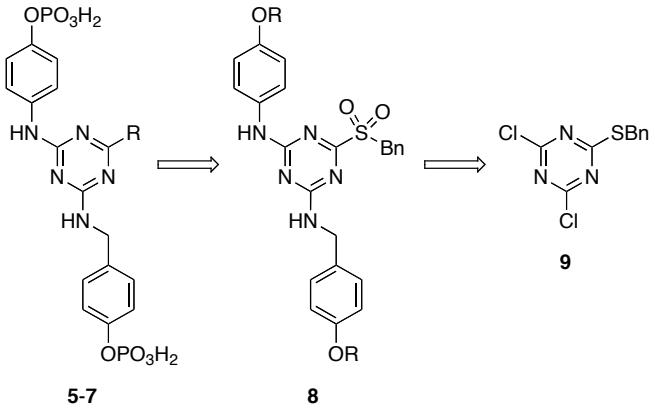


Figure 2. Triazine scaffold-based bis-aryl phosphates **5**-**7**

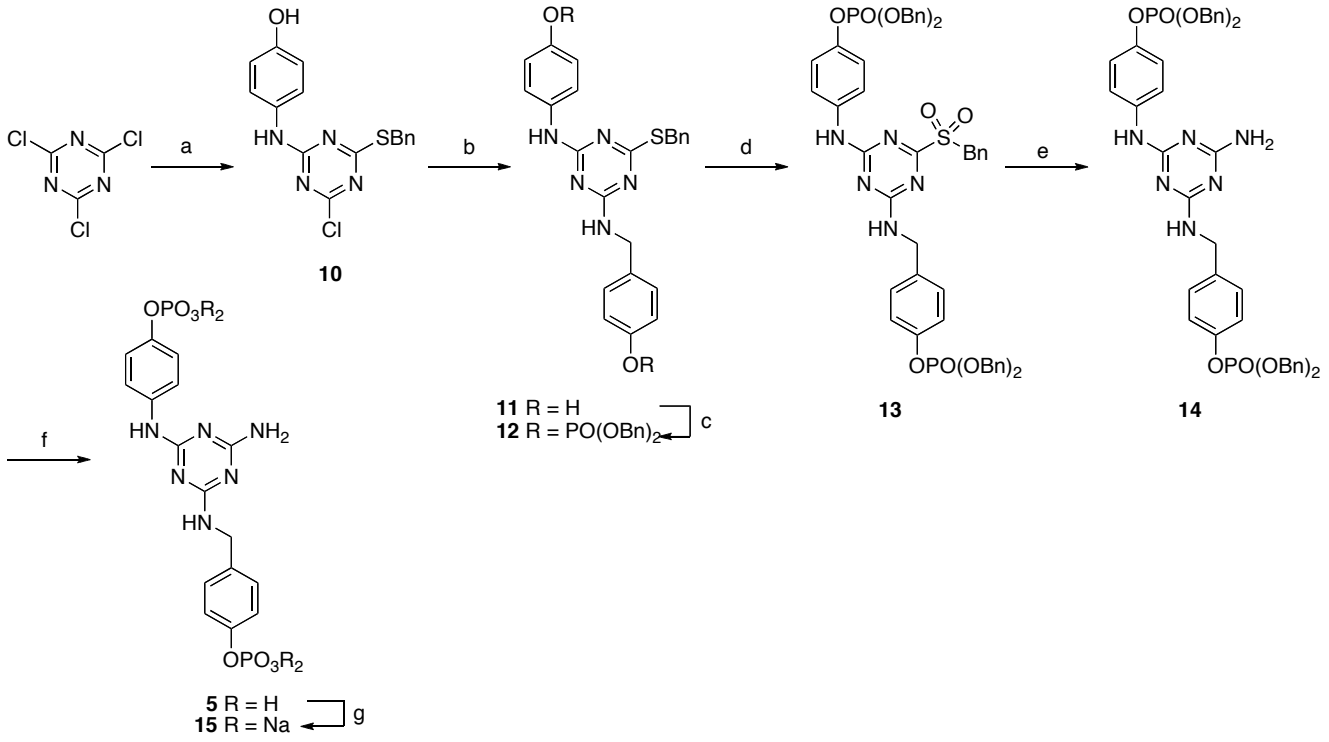
RESULTS AND DISCUSSION

The bis-aryl phosphates **5**-**7** were synthetized using the orthogonal strategy developped by Chang et al.[15] from cyanuric chloride (Scheme 1), wherein the last substitution step takes place via an oxidation-activation of the benzylthioether group of 2-(benzylthio)-4,6-dichloro-1,3,5-triazine **9**.



Scheme 1. Orthogonal strategy via sulfone chemistry

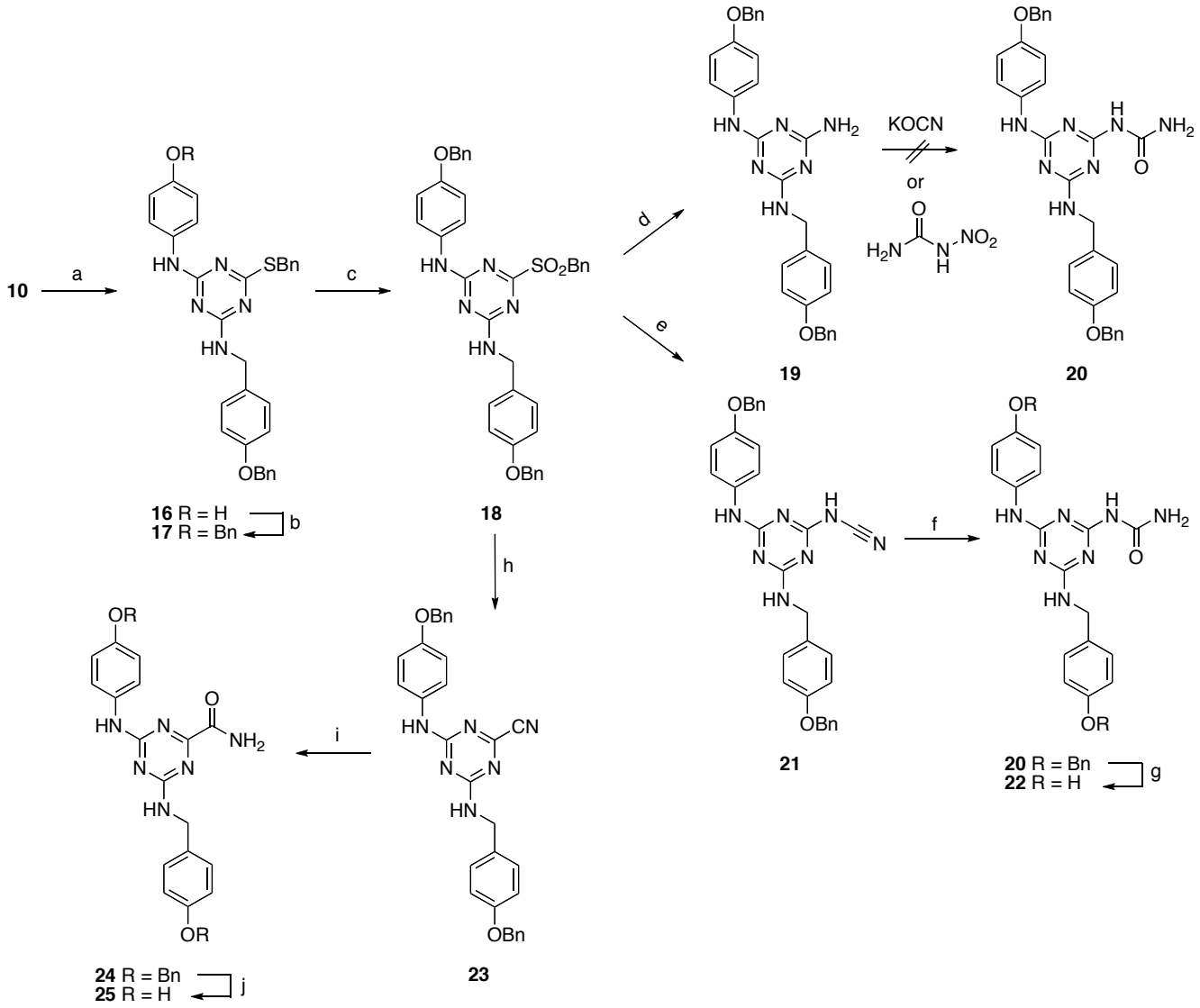
The synthesis of aminotriazine **5** began with a one-pot sequential procedure, involving addition of benzyl mercaptan to cyanuric chloride followed by that of 4-aminophenol to give **10** in 82% yield (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) BnSH (0.94 eq), DIEA (0.95 eq), THF, 0 °C, 1.5 h then 4-$HOC_6H_4NH_2$ (1 eq), DIEA (1 eq), THF, 25 °C, 3 h, 82%; (b) 4-$HOC_6H_4CH_2NH_2$ (1.09 eq), DIEA (1.09 eq), THF, reflux, 36 h, 92%; (c) $HPO(OBn)_2$ (4 eq), DIEA (2 eq), DMAP (1 eq), $MeCN/CCl_4$ (5:1), –15 °C, 1.5 h, 54%; (d) MCPBA (2.5 eq), THF 0 °C, 2 h, 25 °C, 15 min, 79%; (e) NH_3(g), CH_2Cl_2, 25 °C, 15 h, 72%; (f) H_2, 10% Pd/C (50% w/w), MeOH, 25 °C, 15 h, 36%; (g) MeONa (4 eq), MeOH, 0 °C, 2 h, quant.

Subsequent addition of 4-hydroxybenzylamine furnished **11** (75% overall yield). The latter has also been synthesized in a one-pot synthesis from cyanuric chloride but in a lower overall yield (61%). Phosphorylation of **11** with dibenzylchlorophosphate (in situ prepared from dibenzylphosphite) gave

12 in 54% yield.[16] Oxidation of the benzylsulfanyl group with MCPBA led to the desired sulfone **13** in 79% yield. Then, a two-step sequence (i. e., substitution of ammonia and hydrogenation over Pd/C) allowed to obtain amino-triazine **5** of very low solubility which was finally converted into the water-soluble sodium salt **15**. In order to access to urea-triazine **6**, preliminary investigation showed that the formation of the urea group from **14** failed, due to its unreactivity, under classical conditions (KOCN 1-2 eq, AcOH/H_2O or MeOH/1M HCl, rt or 50 °C, 2 h). The clivage of a dibenzylphosphate group was observed when prolonging the reaction time (4 h) with 2.5 eq of KOCN.

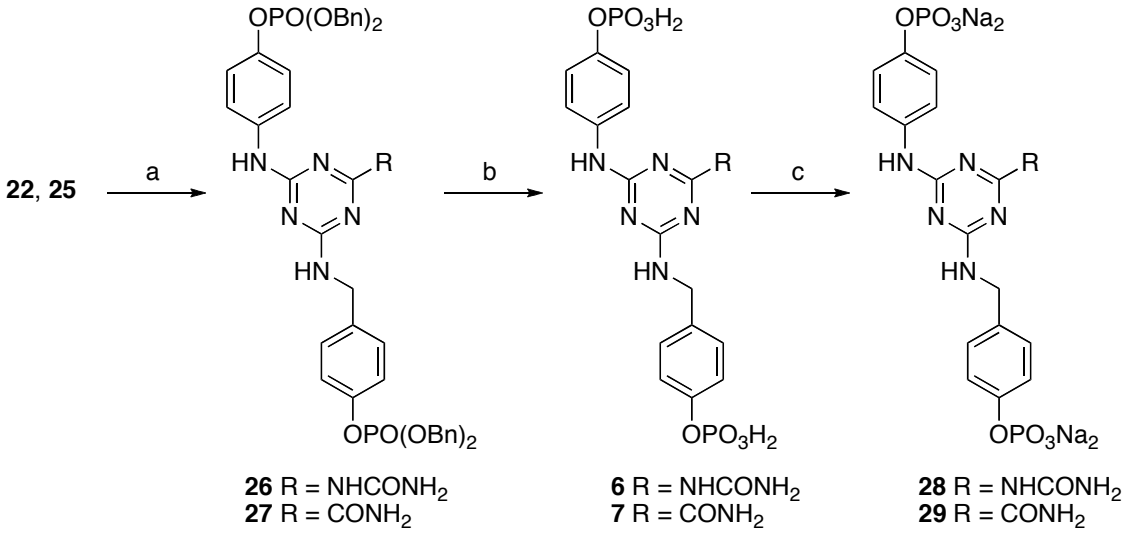


Scheme 3. *Reagents and conditions*: (a) 4-$BnOC_6H_4CH_2NH_2$ (2 eq), DIEA (2 eq), THF/MeOH (5:1), reflux, 15 h, 92%; (b) BnBr (1.5 eq), K_2CO_3 (1.5 eq), DMF, 0 °C, 1 h, 25 °C, 1 h, 75%, (c) MCPBA (3 eq), THF, 0 °C, 2 h, 79%; (d) NH_3(g), CH_2Cl_2, 25 °C, 15 h, 72%; (e) H_2NCN (10 eq), DIEA (2 eq), THF, reflux, 16 h; (f) 4 N HCl/EtOH (1:1), 90 °C, 16 h; (g) H_2, 10% Pd/C, MeOH/AcOH, 25 °C, 16 h, 42% overall yield (three steps); (h) KCN (3 eq), DMF, 80 °C, 3 h, 96% (crude yield); (i) 1N NaOH/ EtOH/ 30% H_2O_2 (6:3:1) 60 °C, 15 h, 64%; (j) H_2, 10% Pd/C (50% w/w), MeOH/AcOH (1:1), 25 °C, 36 h, 63%.

Additionally, benzylation prior to the phosphorylation reaction led us to the synthesis of N^2-(4-(benzyloxy)benzyl)-N^4-(4-(benzyloxy)phenyl)-1,3,5-triazine-2,4,6-triamine **19** (Scheme 3). The latter was accessible via a four-step sequence from **10**, involving the preparation of (4-(benzyloxy)phenyl)methanamine.[17] Triazine **19** was also found unaffected, even under strong conditions (KOCN 2.4 eq, AcOH/H_2O, reflux, 16 h). Moreover, formation of the urea **20** from this protected aminotriazine was also unsuccessful using 1-nitrourea (H_2SO_4 cc 0.05%, EtOH, reflux, 2 h or H_2SO_4 cc 4-8%, EtOH, 80 °C, 16 h). Finally, the sulfone derivative **18** was allowed to react with cyanamide in refluxing tetrahydrofuran, affording the desired compound **21**. Subsequent hydrolysis using sulfuric acid at high temperature led to the corresponding urea **20** which underwent deprotection of the two benzyl groups by hydrogenolysis to give **22** as a precursor of **6**.

The introduction of the carboxamide group was also carried out starting from sulfonyle **18** (Scheme 3). Treatment of **18** with potassium cyanide in dimethylformamide at 80 °C led to nitrile **23**. Note that cyanation from **13** was possible but much less satisfying in terms of yield (KCN 2.5 eq, DMF, 80 °C, 3 h, 43%). Hydrolysis of **23** using the method described by Dragovich *et al.*[18] (sodium hydroxide and hydrogen peroxide at 60 °C) gave the corresponding carboxamide derivative **24**. Hydrogenation over Pd/C then gave compound **25**.

Phosphorylation of both derivatives **22** and **25** gave **26** and **27**, respectively (Scheme 4). Following catalytic hydrogenation, the resulting bis-phosphates (**6** and **7**, resp.) of very low solublity were directly transformed into the sodium salts **28** and **29**, respectively.



Scheme 4. *Reagents and conditions*: (a) $HPO(OBn)_2$ (5 eq), DIEA (8 eq), DMAP (1 eq), MeCN/CCl_4 (5:1), –15 °C, 1.5 h, **26** (61%), **27** (72%); (b) H_2, 10% Pd/C (50% w/w), MeOH, 25 °C, 15 h, **6** (61%), **7** (43%); (c) MeONa (4 eq), MeOH, 0 °C, 2 h, **28** (quant.), **29** (quant.).

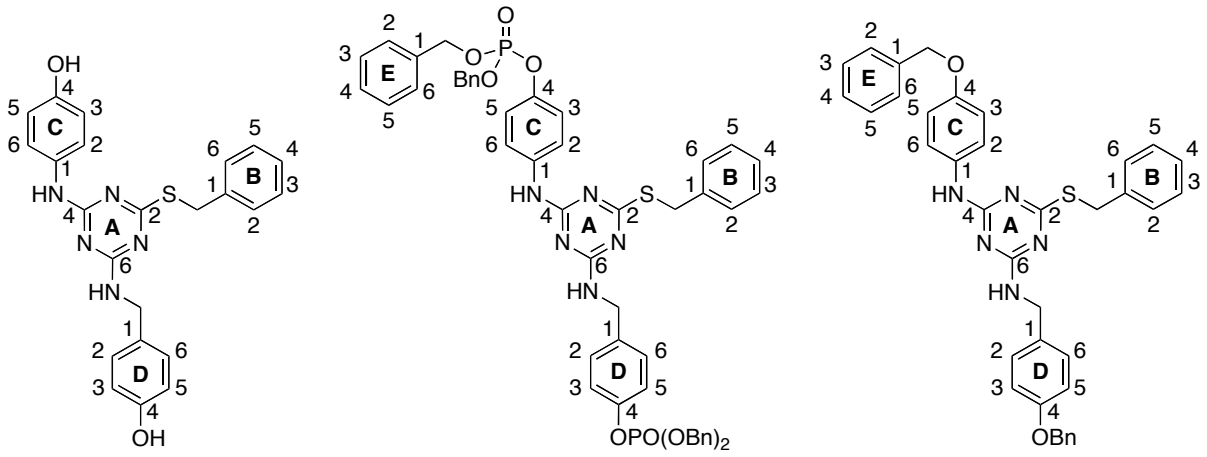
Bis-aryl phosphate sodium salts **15**, **28** and **29** were assayed for binding to Grb2 using an ELISA test.[19] The phosphorylated peptide PSpYVNVPQ (Kd = 9 nM) was used for this competitive binding assay. None of the designed compounds were found to be antagonists of the SH2 domain of Grb2 contrary to earlier predictions from MD simulations of their complexes (unpublished) in the Grb2 SH2 domain structure with implicit solvent. These results reassert the importance of accounting for explicit water molecules in the MD simulations. Water probably plays a critical role in the stability of such Grb2 complexes with peptide and non-peptidic inhibitors as shown recently by Leroux et al.[20]

We have synthesized novel bis-aryl phosphates based on the privileged structure triazine, using an orthogonal strategy from cyanuric chloride, via the sulfone chemistry. In order to strengthen the 1,3,5-trisubstituted triazine scaffold-based ligand design strategy that exploits the use of mimics of phosphates (e.g., keto-acid, IZD),[12] further molecular modeling of such compounds through MD simulations in water should be also considered.

EXPERIMENTAL

All commercial reagents were used without purification and all solvents were reaction grade. When necessary, solvents were previously dried over molecular sieves. Tetrahydrofuran was also dried over molecular sieves 4 Å unless otherwise stated (distilled from sodium/benzophenone under argon). All reactions were performed under an inert atmosphere of argon unless otherwise stated. All reaction mixtures were stirred magnetically and monitored by thin-layer chromatography using Merck silica gel 60 F_{254}, visualized with UV light. Flash chromatography were performed using SDS silica gel 60 (35-70 μm). Melting points (uncorrected) were determined on a Kofler bench. Mass spectra were recorded on a ZQ 2000 MS (ES) or a spectrometer (LC) HRMS ESI/TOF (LCT, Waters).

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AM 300 spectrometer. Chemical shift values are reported in parts per million (ppm) and coupling constants in Hertz (Hz). In order to simplify the reading of the NMR spectra interpretations (COSY, HMQC, HMBC), the following attributions were chosen (Scheme 5): Letter "A" will always refer to the heterocyclic core – whether it is a pyrimidine or a triazine – and letter "B" to the aryl group linked to this heterocycle through an NH bridge. "C" and "D" will refer to the diaryl ether and finally "E" will refer to the benzyl groups, either benzyloxy or dibenzylphosphates. Two AA'BB' systems were observed for the two para-substituted aromatic rings B and D. Compounds **11**, **12** and **17** are described below as examples.



11 **12** **17**

Scheme 5

4-(4-Benzylthio-6-chloro-1,3,5-triazin-2-ylamino)phenol (10)

Benzylthiol (6 mL, 51.0 mmol) and diisopropylethylamine (9 mL, 51.7 mmol) were added to a solution of cyanuric chloride (10 g, 54.2 mmol) in dry THF (200 mL) at 0 °C. After 2 h of stirring at 0 °C, 4-aminophenol (5.9 g, 54.1 mmol) and diisopropylethylamine (9.5 mL, 54.5 mmol) were added. The mixture was then stirred at room temperature for 3 h and the solvent was removed under reduce pressure. Purification by flash chromatography with cyclohexane/EtOAc (4:1) gave **10** as a white solid (14.4 g, 82%). Mp 179 °C; ^{1}H NMR (300 MHz; MeOD): δ 4.28 (2H, s, CH_2), 6.75-6.78 (2H, m, 3_C, 5_C), 7.21-7.23 (3H, m, 3_B, 4_B, 5_B), 7.28-7.31 (2H, m, 2_C, 6_C), 7.35-7.43 (2H, m, 2_B, 6_B); ^{13}C NMR (75 MHz; MeOD): δ 34.8 (CH_2), 115.6 (3_C, 5_C), 123.5 (4_B), 124.1 (3_B, 5_B), 127.5 (1_C), 128.6 (2_C, 6_C), 129.0 (2_B, 6_B), 136.4 (1_B), 154.6 (4_C), 162.7 (4_A), 168.2 (6_A), 183.2 (2_A); MS (ES$^+$) *m/z* 345 $[M+H]^+$, 367 $[M+Na]^+$; MS (ES$^-$) *m/z* 343 $[M-H]^-$; HRMS (ES$^+$) *m/z*: calcd for $C_{16}H_{13}ClN_4OS$ 345.0577 $[M+H]^+$, 367.0396 $[M+Na]^+$; found 345.0583, 367.0404.

4-[4-Benzylthio-6-(4-hydroxybenzylamino)-1,3,5-triazin-2-ylamino]phenol (11)

Compound **10** (234 mg, 0.679 mmol) and 4-(aminomethyl)phenol (91 mg, 0.739 mmol) were dissolved in dry THF. Diisopropylethylamine (140 μL, 0.804 mmol) was added and the mixture was refluxed for 36 h. The solvent was removed under reduce pressure. Purification by flash chromatography with cyclohexane/EtOAc (gradient from 4:1 to 1:1) gave **11** as a white solid (270 mg, 92%). Mp 94-97 °C; ^{1}H NMR (300 MHz; MeOD): δ 4.31 (2H, s, S-CH_2), 4.42 (2H, s, NH-CH_2), 6.72 (4H, br s, 3_C, 5_C, 3_D, 5_D), 7.11-7.14 (2H, m, 2_D, 6_D), 7.20-7.28 (5H, m, 2_B, 3_B, 4_B, 5_B, 6_B), 7.31-7.33 (2H, m, 2_C, 6_C); ^{13}C NMR (75 MHz; MeOD): δ 34.7 (S-CH_2), 44.8 (NH-CH_2), 116.1 (3_C, 5_C, 3_D, 5_D), 124.5 (2_C, 6_C), 129.4, 129.7, 130.0 (2_B, 3_B, 4_B, 5_B, 6_B, 2_D, 6_D), 131.5 (1_C), 132.1 (1_D), 139.5 (1_B), 154.8 (4_C), 157.4 (4_D), 164.2 (4_A), 165.6 (6_A), 180.9 (2_A); MS (ES$^+$) *m/z* 432 $[M+H]^+$, 454 $[M+Na]^+$; MS (ES$^-$) *m/z* 430 $[M-H]^-$.

Dibenzyl 4-[4-benzylthio-6-(4-dibenzylphosphoryloxybenzylamino)-1,3,5-triazin-2-ylamino]-phenyl phosphate (12)

To a solution of **11** (4 g, 9.27 mmol) in dry MeCN (200 mL) cooled at –15 °C was added dry CCl_4 (40 mL) and the mixture was stirred at –15 °C for 5 min. Diisopropylethylamine (12.9 mL, 74.1 mmol) and *N*,*N*-dimethylaminopyridine (1.13 g, 9.27 mmol) were then added and the mixture was stirred at –15 °C for 30 min. Dibenzylphosphite (8.2 mL, 37.1 mmol) was added dropwise and the mixture was stirred at –15 °C for 1 h 30. A 0.5 M solution of potassium dihydrogen phosphate (50 mL) was added, the mixture was warmed up to room temperature and extracted with EtOAc. The combined extracts were then washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. Purification by flash chromatography with CH_2Cl_2/MeOH (99:1) afforded **12** as a colourless oil (4.74 g, 54%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.33 (2H, s, S-CH_2), 4.55 (2H, m, NH-CH_2), 5.10 (m, 4H, 2 × P-O-CH_2), 5.12 (m, 4H, 2 × P-O-CH_2), 7.04-7.11 (4H, m, 3_C, 5_C, 3_D, 5_D), 7.20-7.26 (2H, m, 2_D, 6_D), 7.24-7.31 (25H, m, 4 × 2_E, 4 × 3_E, 4 × 4_E, 4 × 5_E, 4 × 6_E, 2_B, 3_B, 4_B, 5_B, 6_B), 7.40-7.43 (m, 2H, 2_C, 6_C); ^{13}C NMR (75 MHz; $CDCl_3$): δ 34.1 (S-CH_2), 44.1 (NH-CH_2), 69.9 (P-O-CH_2), 120.1, 120.2 (3_C, 5_C, 3_D, 5_D), 121.7 (2_C, 6_C), 127.1, 128.0, 128.4, 128.5, 128.6, 128.7, 128.8 (2_E, 3_E, 4_E, 5_E, 6_E, 2_B, 3_B, 4_B, 5_B, 6_B, 2_D, 6_D), 135.2, 135.3, 135.4 (1_C, 1_D, 1_E), 137.4 (1_B), 146.0 (4_C), 149.7 (4_D), 162.7 (4_A), 164.5 (6_A), 180.3 (2_A).

Dibenzyl 4-[4-benzylsulfonyl-6-(4-dibenzylphosphoryloxybenzylamino)-1,3,5-triazin-2-ylamino]-phenyl phosphate (13)

MCPBA (430 mg, 2.49 mmol) was added portionwise over 20 min to a solution of thioether **12** (1 g, 1.05 mmol) in THF (50 mL) at 0 °C under air. The mixture was stirred at 0 °C for 2 h and at room temperature for 15 min and a saturated aqueous sodium hydrogen carbonate solution was added (50 mL). The product was extracted with EtOAc, the combined extracts were then washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. Purification by flash chromatography with CH_2Cl_2/MeOH (100:1.5) afforded **13** as a beige powder (820 mg, 79%). Mp 47 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.54 (2H, s, NH-CH_2), 4.61 (2H, s, SO_2-CH_2), 5.10 (4H, s, 2 × P-O-CH_2), 5.12 (4H, s, 2 × P-O-CH_2), 7.11 (4H, m, 3_C, 5_C, 3_D, 5_D), 7.17 (2H, m, 2_D, 6_D), 7.31 (25H, br s, 4 × 2_E, 4 × 3_E, 4 × 4_E, 4 × 5_E, 4 × 6_E, 2_B, 3_B, 4_B, 5_B, 6_B), 7.37-7.45 (4H, m, 2_C, 6_C); ^{13}C NMR (75 MHz; $CDCl_3$): δ 44.6 (NH-CH_2), 56.7 (SO_2-CH_2), 70.0 (P-O-CH_2), 70.1 (P-O-CH_2), 120.4, 120.5 (3_C, 5_C, 3_D, 5_D), 122.0 (2_C, 6_C), 126.6 (2_B, 6_B), 128.0 (2_E, 6_E), 128.6, 128.7, 128.8 (3_E, 4_E, 5_E, 2_D, 6_D, 3_B, 4_B, 5_B), 131.4 (1_B), 134.0 (1_D), 134.3 (1_C), 135.4 (1_E), 147.0 (4_C), 150.0 (4_D), 163.7 (4_A), 165.5 (6_A), 172.4 (2_A); MS (ES$^+$) *m/z* 1001 $[M+NH_4]^+$, 1006 $[M+Na]^+$.

4-[4-Amino-6-(4-dibenzylphosphoryloxybenzylamino)-1,3,5-triazin-2-ylamino]phenyl dibenzyl phosphate (14)

Ammonia was bubbled for 1 h into a solution of compound **13** (298 mg, 0.303 mmol) in CH_2Cl_2 (15 mL) at room temperature. The flask was then sealed and the mixture was stirred for 15 h. The solvent was removed under reduce pressure and purification by flash chromatography with CH_2Cl_2/MeOH (100:4) gave **14** as a white solid (184 mg, 72%). Mp 114-117 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.53 (2H, s, NH-CH_2), 5.09 (4H, s, 2 × P-O-CH_2), 5.11 (4H, s, 2 × P-O-CH_2), 7.04-7.10 (4H, m, 3_C, 5_C, 3_D, 5_D), 7.21-7.24 (2H, m, 2_D, 6_D), 7.31 (20H, br s, 4 × 2_E, 4 × 3_E, 4 × 4_E, 4 × 5_E, 4 × 6_E), 7.42-7.45 (2H, m, 2_C, 6_C); ^{13}C NMR (75 MHz; $CDCl_3$): δ 44.1 (NH-CH_2), 70.0 (P-O-CH_2), 70.1 (P-O-CH_2), 120.3, 120.4 (3_C, 5_C, 3_D, 5_D), 121.5 (2_C, 6_C), 128.1 (2_E, 6_E), 128.7 (3_E, 4_E, 5_E), 128.8 (2_D, 6_D), 135.5 (1_E), 135.9, 136.1 (1_D, 1_C), 146.0 (4_C), 149.8 (4_D), 164.7 (4_A), 166.5 (6_A, 2_A); MS (ES$^+$) *m*/*z* 844 $[M+H]^+$, 867 $[M+Na]^+$.

4-[4-Amino-6-(4-phosphoryloxybenzylamino)-1,3,5-triazin-2-ylamino]phenyl phosphate (5)

10% palladium on carbon (60 mg) was added to a solution of compound **14** (121 mg, 0.143 mmol) in MeOH (50 mL). The mixture was stirred under H_2 at room temperature for 15 h. The catalyst was filtered using two filter papers and washed with hot MeOH, affording **5** as a white solid (25 mg, 36%). Mp 216-218 °C with decomposition; MS (ES$^-$) *m*/*z* 241 $[M–2H]^{2–}$.

Tetrasodium 4-[4-amino-6-(4-phosphonatooxybenzyl amino)-[1,3,5]-triazin-2-ylamino]phenyl phosphate (15)

A fresh 0.539 M sodium methoxide solution (276 μL, 149 μmol) was added to a suspension of compound **5** (18 mg, 37.2 μmol) in dry MeOH (2.5 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and the MeOH was removed under reduced pressure to afford **15** as a water-soluble white powder (21 mg, 99%). ^{1}H NMR (300 MHz; D_2O): δ 4.37 (2H, s, NH-CH_2), 7.06 (4H, br s, 3C, 5C, 3D, 5D), 7.16-7.19 (4H, m, 2C, 6C, 2D, 6D); ^{13}C NMR (75 MHz; D_2O): δ 43.3 (NH-CH_2), 120.5, 120.6 (3C, 5C, 3D, 5D), 124.4 (2C, 6C), 127.9 (2D, 6D), 132.0 (1C), 132.7 (1D), 150.8, 152.9 (4C, 4D), 164.6 (4A), 165.6 (6A), 166.8 (2A); ^{31}P NMR (121 MHz; D_2O): δ 0.51; HRMS (ES$^-$) *m*/*z*: calcd for $C_{16}H_{14}N_6Na_4O_8P_2$ 527.0222 $[M–2Na+H]^-$, 505.0403 $[M–3Na+2H]^-$; found 527.0247, 505.0428.

4-[4-(4-Benzyloxybenzylamino)-6-benzylthio-1,3,5-triazin-2-ylamino]phenol (16)

Compound **10** (664 mg, 1.93 mmol) and (4-benzyloxyphenyl)methanamine (821 mg, 3.85 mmol) were dissolved in a THF/MeOH 5:1 mixture (18 mL). Diisopropylethylamine (670 μL, 3.85 mmol) was added and the mixture was refluxed for 15 h. The solvent was removed under reduce pressure and

purification by flash chromatography with cyclohexane/EtOAc (4:1) gave **16** as a white solid (926 mg, 92%). Mp 117 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.32 (2H, s, S-CH_2), 4.51 (2H, s, NH-CH_2), 5.03 (2H, s, O-CH_2), 5.60 (1H, br s, NH-CH_2), 6.71 (2H, s, 3C, 5C), 6.60-6.92 (2H, m, 3D, 5D), 7.17-7.19 (2H, m, 2D, 6D), 7.23-7.40 (12H, m, 2C, 6C, 2B, 3B, 4B, 5B, 6B, 2E, 3E, 4E, 5E, 6E); ^{13}C NMR (75 MHz; $CDCl_3$): δ 34.1 (S-CH_2), 44.3 (NH-CH_2), 70.1 (O-CH_2), 115.0 (3D, 5D), 115.6 (3C, 5C), 123.0 (2C, 6C), 127.1 (4B), 127.5 (2E, 6E), 128.0 (4E), 128.5, 128.6 (3B, 5B, 3E, 5E), 128.8, 128.9 (2D, 6D, 2B, 6B), 130.7 (1D), 131.0 (1C), 136.9 (1E), 136.6 (1B), 152.2 (4C), 158.1 (4D), 162.9 (4A), 164.2 (6A), 179.5 (2A); MS (ES$^+$) *m/z* 522 [M+H]$^+$, 544 [M+Na]$^+$, MS (ES$^-$) *m/z* 520 [M–H]$^-$.

***N*^{2}-(4-Benzyloxybenzyl)-*N*^{4}-(4-benzyloxyphenyl)-6-benzylthio-1,3,5-triazine-2,4-diamine (17)**

Potassium carbonate (1.9 g, 13.7 mmol) was added to a solution of **16** (4.72 g, 9.05 mmol) in dry DMF (200 mL). Benzyl bromide (1.6 mL, 13.5 mmol) was then added dropwise at 0 °C and the mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. Water was added and the mixture was extracted with Et_2O. The combined extracts were washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. Purification by flash chromatography with cyclohexane/EtOAc (5:1) gave **17** as a white powder (4.18 g, 75%). Mp 45-47 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.33 (2H, s, S-CH_2), 4.54 (2H, s, NH-CH_2), 5.04 (4H, s, O-CH_2), 5.61 (1H, br s, NH-CH_2), 6.89-6.94 (4H, m, 3C, 5C, 3D, 5D), 7.02 (1H, br s, NH), 7.23-7.26 (5H, m, 2D, 6D, 3B, 4B, 5B), 7.35-7.41 (14H, m, 2C, 6C, 2B, 6B, 2 × 2E, 2 × 3E, 2 × 4E, 2 × 5E, 2 × 6E); ^{13}C NMR (75 MHz; $CDCl_3$): δ 34.3 (S-CH_2), 44.5 (NH-CH_2), 70.2 (O-CH_2), 115.2 (3C, 5C, 3D, 5D), 122.8 (2C, 6C), 127.2 (4B), 127.6 (2E, 6E), 128.1 (4E), 128.6, 128.7 (2B, 6B, 2D, 6D, 3E, 5E), 129.1 (3B, 5B), 130.9 (1D), 131.8 (1C), 137.1 (1E), 137.5 (1B), 155.3 (4C), 158.3 (4D), 162.9 (4A), 164.6 (6A), 178.7 (2A).

***N*^{2}-(4-Benzyloxybenzyl)-*N*^{4}-(4-benzyloxyphenyl)-6-benzylsulfonyl-1,3,5-triazine-2,4-diamine (18)**

Sulfone **18** was prepared as sulfone **13**, from compound **17** (4.2 g, 6.87 mmol) and MCPBA (3.6 g, 20.9 mmol). Purification via flash chromatography with cyclohexane/EtOAc (5:1) afforded **18** as an off-white solid (3.5 g, 79%). Mp 144-151 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.53 (2H, s, NH-CH_2), 4.62 (2H, s, SO_2-CH_2), 5.06 (4H, s, O-CH_2), 5.86 (1H, br s, NH-CH_2), 6.95 (4H, s, 3_C, 5_C, 3_D, 5_D), 7.19-7.22 (2H, m, 2_D, 6_D), 7.31-7.41 (17H, m, 2_C, 6_C, 2_B, 3_B, 4_B, 5_B, 6_B, 2 × 2_E, 2 × 3_E, 2 × 4_E, 2 × 5_E, 2 × 6_E); ^{13}C NMR (75 MHz; $CDCl_3$): δ 44.9 (NH-CH_2), 56.4 (SO_2-CH_2), 70.1 (O-CH_2), 115.1, 115.2 (3_C, 5_C, 3_D, 5_D), 122.5 (2_C, 6_C), 126.6 (1_B), 127.4 (2_E, 6_E), 128.0 (4_E), 128.6, 128.8 (3_B, 4_B, 5_B, 2_D, 6_D, 3_E, 5_E), 129.1, 129.5 (1_C, 1_D), 131.4 (2_B, 6_B), 136.8 (1_E), 156.0 (4_C), 158.4 (4_D), 163.8 (4_A), 165.6 (6_A), 172.0 (2_A); MS (ES$^+$) *m/z* 666 [M+Na]$^+$.

N^2-(4-Benzyloxybenzyl)-N^4-(4-benzyloxyphenyl)-1,3,5-triazine-2,4,6-triamine (19)

Ammonia was bubbled for 1 h into a solution of sulfone **18** (2 g, 3.11 mmol) in CH_2Cl_2 (100 mL) at room temperature. The flask was then sealed and the mixture was stirred for 15 h. The solvent was removed under reduce pressure and purification by flash chromatography with CH_2Cl_2/MeOH (gradient from 100:2 to 100:5) gave **19** as a white powder (1.12 g, 72%). Mp 77 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.48 (2H, s, NH-CH_2), 5.02 (4H, s, O-CH_2), 5.81 (1H, br s, NH-CH_2), 6.87-6.93 (4H, m, 3_C, 5_C, 3_D, 5_D), 7.19-7.22 (2H, m, 2_D, 6_D), 7,29-7,43 (12H, m, 2_C, 6_C, 2 × 2_E, 2 × 3_E, 2 × 4_E, 2 × 5_E, 2 × 6_E); ^{13}C NMR (75 MHz; $CDCl_3$): δ 44.1 (N-CH_2), 70.0 (O-CH_2), 114.9, 115.0 (3_C, 5_C, 3_D, 5_D), 122.4 (2_C, 6_C), 127.4 (2_E, 6_E), 127.9 (4_E), 128.5 (3_E, 5_E), 128.7 (2_D, 6_D), 131.2 (1_D), 132.0 (1_C), 136.9 (1_E), 154.9 (4_C), 158.0 (4_D), 164.5 (4_A), 166.1 (6_A, 2_A); MS (ES^+) *m/z* 505 $[M+H]^+$, 527 $[M+Na]^+$; MS (ES^-) *m/z* 503 $[M–H]^-$.

***N*-[4-(4-Benzyloxybenzylamino)-6-(4-benzyloxyphenylamino)-1,3,5-triazin-2-yl]cyanamide (21)**

Sulfone **18** (707 mg, 1.10 mmol) was dissolved in THF (100 mL). Cyanamide (461 mg, 11.0 mmol) and diisopropylethylamine (380 μL, 2.18 mmol) were added and the mixture was refluxed overnight. THF was removed under reduce pressure, water was added (50 mL) and the product was extracted with EtOAc. The combined extracts were then washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give an off-white powder (1.05 g). This crude product (**21**) proved to be highly insoluble and was hence used in the next step without purification. MS (ES^+) *m/z* 530 $[M+H]^+$, 552 $[M+Na]^+$, MS (ES^-) *m/z* 528 $[M–H]^-$.

1-[4-(4-Benzyloxybenzylamino)-6-(4-benzyloxyphenylamino)-1,3,5-triazin-2-yl]urea (20)

The crude product **21** (826 mg) was placed into a 4 N HCl/EtOH mixture (1:1, 50 mL). The mixture was heated at 90 °C for 16 h then neutralized with 1 N NaOH. The product was extracted with EtOAc. The combined extracts were then washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a white powder (477 mg). As in the previous reaction, compound **20** was insoluble and therefore used in the next step without purification. MS (ES^+) *m/z* 548 $[M+H]^+$.

1-[4-(4-Hydroxybenzylamino)-6-(4-hydroxyphenylamino)-1,3,5-triazin-2-yl]urea (22)

10% Palladium on carbon (230 mg) was added to a suspension of crude compound **20** (477 mg) in a MeOH/AcOH mixture (1:1, 250 mL). The mixture was stirred under an hydrogen atmosphere at room temperature for 16 h. The catalyst was filtered and the product was purified by flash chromatography with CH_2Cl_2/MeOH (100:8) to give **22** as a white powder (133 mg, 42% yield over 3 steps). Mp

264 °C; ^{1}H NMR (300 MHz; DMSO-d_6): δ 4.32 (2H, s, NH-CH_2), 6.64-6.67 (2H, m, 3_C, 5_C), 6.68-6.71 (2H, m, 3_D, 5_D), 7.09-7.12 (2H, m, 2_D, 6_D), 7.38-7.41 (2H, m, 2_C, 6_C), 9.13 (1H, br s, 4_C-OH), 9.28 (1H, br s, 4_D-OH); ^{13}C NMR (75 MHz; DMSO-d_6): δ 43.1 (NH-CH_2), 114.9 (3_C, 5_C, 3_D, 5_D), 121.7 (2_C, 6_C), 128.5 (2_D, 6_D), 129.8 (1_D), 131.0 (1_C), 152.9 (4_C), 156.0 (CO), 156.2 (4_D), 163.0, 164.9, 165.1 (2_A, 4_A, 6_A); MS (ES$^+$) *m/z* 368 $[M+H]^+$, 390 $[M+Na]^+$.

1-[4-(4-Dibenzylphosphoryloxybenzylamino)-6-(4-dibenzylphosphoryloxyphenylamino)-1,3,5-triazin-2-yl]urea (26)

To a solution of **22** (60 mg, 0.163 mmol) in dry MeCN (10 mL) cooled at –15 °C was added dry CCl_4 (2 mL) and the mixture was stirred at –15 °C for 5 min. Diisopropylethylamine (230 μL, 1.32 mmol) and *N*,*N*-dimethylaminopyridine (20 mg, 0.164 mmol) were then added and the mixture was stirred at –15 °C for 30 min. Dibenzylphosphite (180 μL, 0.815 mmol) was added dropwise and the mixture was stirred at –15 °C for 2 h. A 0.5 M solution of potassium dihydrogen phosphate (5 mL) was added, the mixture was warmed up to room temperature and extracted with EtOAc. The combined extracts were then washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. Purification by flash chromatography with CH_2Cl_2/MeOH (gradient from 100:2 to 100:5) afforded **26** as a colorless oil (89 mg, 61%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.44 (2H, s, NH-CH_2), 5.08 (4H, s, P-O-CH_2), 5.10 (4H, s, P-O-CH_2), 7.03-7.10 (4H, m, 3_C, 5_C, 3_D, 5_D), 7.22-7.26 (2H, m, 2_D, 6_D), 7.30 (20H, br s, 4 × 2_E, 4 × 3_E, 4 × 4_E, 4 × 5_E, 4 × 6_E), 7.56-7.67 (m, 2H, 2_C, 6_C); ^{13}C NMR (75 MHz; $CDCl_3$): δ 44.3 (NH-CH_2), 69.9 (P-O-CH_2), 70.0 (P-O-CH_2), 120.1, 120.5 (3_C, 5_C, 3_D, 5_D), 122.4 (2_C, 6_C), 128.0, 128.3, 128.6 (2_E, 3_E, 4_E, 5_E, 6_E, 2_D, 6_D), 135.4 (1_C, 1_D, 1_E), 147.0 (4_C), 149.9 (4_D), 157.1 (CO), 163.0, 163.3 (2_A, 4_A, 6_A); MS (ES$^+$) *m/z* 888 $[M+H]^+$, 910 $[M+Na]^+$.

1-[4-(4-Phosphoryloxybenzylamino)-6-(4-phosphoryloxyphenylamino)-1,3,5-triazin-2-yl]urea (6)

10% Palladium on carbon (41 mg) was added to a solution of compound **26** (83 mg, 93.4 μmol) in MeOH (30 mL). The mixture was stirred under an hydrogen atmosphere at room temperature overnight. The catalyst was filtered using two filter papers, then washed with both hot MeOH and hot water. Purification by flash chromatography on reverse phase silica gel C_{18} with water/MeCN (95:5) gave **6** as a white solid (30 mg, 61%). Mp 209-211 °C with decomposition; MS (ES$^-$) *m/z* 262 $[M–2H]^{2-}$.

Sodium 1-[4-(4-phosphonatooxybenzylamino)-6-(4-phosphonatooxyphenylamino)-1,3,5-triazin-2-yl]urea (28)

A fresh 0.539 M sodium methoxide solution (205 μL, 111 μmol) was added to a suspension of

compound **6** (14 mg, 27.7 μmol) in dry MeOH (3 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and the MeOH was removed under reduced pressure to afford **28** as a water-soluble white powder (17 mg, 100%). ^{1}H NMR (300 MHz; D_2O): δ 4.37 (2H, s, NH-CH_2), 7.03 (4H, br s, 3_C, 5_C, 3_D, 5_D), 7.15 (2H, br s, 2_D, 6_D), 7.19-7.22 (2H, m, 2_C, 6_C); ^{13}C NMR (75 MHz; D_2O): δ 43.5 (NH-CH_2), 120.6 (3_C, 5_C, 3_D, 5_D), 124.1 (2_C, 6_C), 127.4 (2_D, 6_D), 130.6 (1_C), 132.6 (1_D), 150.4 (4_C), 152.9 (4_D), 157.5, 159.0 (CO, 2_A, 4_A), 164.4 (6_A) ^{31}P NMR (121 MHz; D_2O): δ 0.52; HRMS (ES^-) *m/z*: calcd for $C_{17}H_{15}N_7Na_4O_9P_2$ 592.0100 $[M–Na]^-$; found 592.0108.

4-(4-Benzyloxybenzylamino)-6-(4-benzyloxyphenylamino)-1,3,5-triazine-2-carbonitrile (23)

Potassium cyanide (455 mg, 6.99 mmol) was cautiously added to a solution of compound **18** (1.5 g, 2.33 mmol) in dry DMF (80 mL). The mixture was heated at 80 °C for 3 h and the solvent was removed under high vacuum. Water was added and the mixture was extracted with Et_2O. The combined extracts were washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to afford **23** as a yellow powder (1.15 g, 96%). This product was used in the next step without purification. Mp 147 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.29 (2H, s, NH-CH_2), 5.06 (4H, s, O-CH_2), 6.95 (4H, s, 3_C, 5_C, 3_D, 5_D), 7.22-7.24 (2H, m, 2_D, 6_D), 7.36-742 (12H, m, 2_C, 6_C, $2 \times 2_E$, $2 \times 3_E$, $2 \times 4_E$, $2 \times 5_E$, $2 \times 6_E$); ^{13}C NMR (75 MHz; $CDCl_3$): δ 44.7 (NH-CH_2), 70.2 (O-CH_2), 115.3 (3_C, 5_C, 3_D, 5_D), 123.0, 123.3 (2_C, 6_C, CN), 127.6 (2_E, 6_E), 128.2 (4_E), 128.8 (3_E, 5_E), 129.0 (2_D, 6_D), 129.4 (1_D), 130.3 (1_C), 136.9 (1_E), 156.0 (4_C), 158.5 (4_D), 163.5 (4_A), 165.1 (6_A), 176.4 (2_A) ; MS (ES^+) *m/z* 515 $[M+Na]^+$. HRMS (ES^+) *m/z*: calcd for $C_{31}H_{26}N_6O_2$ 537.2015 $[M+Na]^+$; found 537.2014.

4-(4-Benzyloxybenzylamino)-6-(4-benzyloxyphenylamino)-1,3,5-triazine-2-carboxamide (24)

A solution of compound **23** (150 mg, 0.291 mmol) in a 1 N NaOH/ EtOH/ 30% H_2O_2 mixture (6:3:1, 10 mL) was heated at 60 °C overnight. EtOH was removed under reduce pressure, the mixture was neutralized with 1 N HCl and the product was extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. Purification by flash chromatography with CH_2Cl_2/MeOH (gradient from 100:2 to 100:9) gave **24** as a beige solid (100 mg, 64%). Mp 222 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.43 (2H, m, NH-CH_2), 5.07 (4H, s, O-CH_2), 6.94 (4H, m, 3_C, 5_C, 3_D, 5_D), 7.22-7.43 (12H, m, 2_D, 6_D, $2 \times 2_E$, $2 \times 3_E$, $2 \times 4_E$, $2 \times 5_E$, $2 \times 6_E$), 7.57 (2H, m, 2_C, 6_C); ^{13}C NMR (75 MHz; $CDCl_3$): δ 42.9 (NH-CH_2), 69.2 (O-CH_2), 114.6 (3_C, 5_C, 3_D, 5_D), 121.4 (2_C, 6_C), 127.6 (2_E, 6_E), 127.7 (4_E), 128.4 (3_E, 5_E), 128.8 (2_D, 6_D), 131.6 (1_D), 132.5 (1_C), 137.1 (1_E), 153.9 (4_C), 157.2 (4_D), 163.9, 165.0 (4_A, $CONH_2$), 165.7 (6_A), 166.1 (2_A); MS (ES^+) *m/z* 532 $[M+H]^+$, 555 $[M+Na]^+$. HRMS (ES^+) *m/z*: calcd for $C_{31}H_{28}N_6O_3$ 555.2121 $[M+Na]^+$; found 555.2115.

4-(4-Hydroxybenzylamino)-6-(4-hydroxyphenylamino)-1,3,5-triazine-2-carboxamide (25)

10% Palladium on carbon (77 mg) was added to a solution of compound **24** (770 mg, 1.45 mmol) in a MeOH/AcOH mixture (1:1, 150 mL). The mixture was stirred under H_2 at room temperature for 36 h. The catalyst was filtered and the product was purified by flash chromatography with MeCN/water (100:2.5) to afford **25** as pale yellow oil (322 mg, 63%). ^{1}H NMR (300 MHz; MeOD): δ 4.46 (2H, s, NH-CH_2), 6.71-6.75 (4H, m, 3_C, 5_C, 3_D, 5_D), 7.14-7.19 (2H, m, 2_D, 6_D), 7.37-7.40 (2H, m, 2_C, 6_C); ^{13}C NMR (75 MHz; MeOD): δ 45.1 (NH-CH_2), 116.2, 116.3 (3_C, 5_C, 3_D, 5_D), 123.5 (2_C, 6_C), 129.8 (2_D, 6_D), 131.0, 132.0 (1_D, 1_C), 154.8 (4_C), 157.6 (4_D), 165.7 (4_A, $CONH_2$), 167.5 (6_A), 167.8 (2_A); MS (ES^+) *m/z* 353 $[M+H]^+$, 375 $[M+Na]^+$.

Dibenzyl 4-[4-(4-(dibenzylphosphoryloxy)benzylamino)-6-carbamoyl-1,3,5-triazin-2-ylamino]-phenyl phosphate (27)

To a solution of **25** (322 g, 0.914 mmol) in dry MeCN (50 mL) cooled at –15 °C was added dry CCl_4 (10 mL) and the mixture was stirred at –15 °C for 5 min. Diisopropylethylamine (1.4 mL, 8.04 mmol) and *N*,*N*-dimethylaminopyridine (111 mg, 0.909 mmol) were then added and the mixture was stirred at –15 °C for 30 min. Dibenzylphosphite (1 mL, 4.53 mmol) was added dropwise and the mixture was stirred at –15 °C for 2 h. A 0.5 M solution of potassium dihydrogen phosphate (20 mL) was added, the mixture was warmed up to room temperature and extracted with EtOAc. The combined extracts were then washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. Purification by flash chromatography with CH_2Cl_2/MeOH (gradient from 100:2 to 100:8) afforded **27** as a colorless oil (574 mg, 72%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.57 (2H, m, NH-CH_2), 5.06-5.10 (8H, m, P-O-CH_2), 7.08-7.11 (4H, m, 3_C, 5_C, 3_D, 5_D), 7.21-7.24 (2H, m, 2_D, 6_D), 7.30 (20H, br s, 4 × 2_E, 4 × 3_E, 4 × 4_E, 4 × 5_E, 4 × 6_E), 7.45-7.48 (2H, m, 2_C, 6_C); ^{13}C NMR (75 MHz; $CDCl_3$): δ 44.3 (NH-CH_2), 69.9 (P-O-CH_2), 70.0 (P-O-CH_2), 120.2 (3_C, 5_C, 3_D, 5_D), 121.7 (2_C, 6_C), 128.0 (2_E, 6_E), 128.5 (3_E, 4_E, 5_E), 128.9 (2_D, 6_D), 134.9 (1_C, 1_D), 135.2 (1_E), 146.3 (4_C), 149.8 (4_D), 164.3, 165.1 ($CONH_2$, 4_A), 166.2 (6_A), 169.6 (2_A); MS (ES^+) *m/z* 873 $[M+H]^+$, 895 $[M+Na]^+$.

4-[4-(4-Phosphoryloxybenzylamino)-6-carbamoyl-1,3,5-triazin-2-ylamino]phenyl phosphate (7)

10% Palladium on carbon (75 mg) was added to a solution of compound **27** (153 mg, 0.175 mmol) in MeOH (50 mL). The mixture was stirred under an hydrogen atmosphere at room temperature overnight. The catalyst was filtered on two filter papers and washed with a hot MeOH/AcOH 98:2 mixture. Purification by column chromatography on reverse phase silica gel C_{18} using a water/MeCN 95:5 mixture gave **7** as a yellow solid (39 mg, 43%). Mp 196-199 °C; MS (ES^-) *m/z* 255 $[M–2H]^{2–}$.

Tetrasodium 4-[4-(4-phosphonatooxybenzylamino)-6-carbamoyl[1,3,5]triazin-2-ylamino]phenyl phosphate (29)

A fresh 0.539 M sodium methoxide solution (304 μL, 164 μmol) was added to a suspension of compound **7** (21 mg, 41.0 μmol) in dry MeOH (3 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and the MeOH was removed under reduced pressure to afford **29** as a watersoluble beige powder (24 mg, 98%). ^{1}H NMR (300 MHz; D_2O): δ 4.40 (2H, s, NH-CH_2), 7.03-7.05 (4H, m, 3_C, 5_C, 3_D, 5_D), 7.15-7.17 (2H, m, 2_D, 6_D), 7.27-7.29 (2H, m, 2_C, 6_C); ^{13}C NMR (75 MHz; D_2O): δ 43.4 (NH-CH_2), 120.4, 120.6 (3_C, 5_C, 3_D, 5_D), 123.7 (2_C, 6_C), 128.3 (2_D, 6_D), 131.7 (1_C), 132.0 (1_D), 150.8 (4_C), 152.8 (4_D), 164.3, 164.4 (4_A, $CONH_2$), 165.4 (6_A), 166.8 (2_A); ^{31}P NMR (121 MHz; D_2O): δ 0.43; HRMS (ES^-) *m/z*: calcd for $C_{17}H_{14}N_6Na_4O_9P_2$ 576.9991 $[M–Na]^-$, 533.0352 $[M–3Na+2H]^-$; found 576.9979, 533.0339.

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REFERENCES

1. P. J. Hajduk, M. Bures, J. Praestgaard, and S. W. Fesik, *J. Med. Chem.*, 2000, **43**, 3443.
2. S. Mandal, G. Bérubé, E. Asselin, I. Mohammad, V. J. Richardson, A. Gupta, S. K. Pramanik, A. L. Williams, and S. K. Mandal, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4955.
3. M. Zheng, C. Xu, J. Ma, Y. Sun, F. Du, H. Liu, L. Lin, C. Li, J. Ding, K. Chen, and H. Jiang, *Bioorg. Med. Chem.*, 2007, **15**, 1815.
4. B. L. Hodous, S. D. Geuns-Meyer, P. E. Hughes, B. K. Albrecht, S. Bellon, J. Bready, S. Caenepeel, V. J. Cee, S. C. Chaffee, A. Coxon, M. Emery, J. Fretland, P. Gallant, Y. Gu, D. Hoffman, R. E. Johnson, R. Kendall, J. L. Kim, A. M. Long, M. Morrison, P. R. Olivieri, V. F. Patel, A. Polverino, P. Rose, P. Tempest, L. Wang, D. A. Whittington, and H. Zhao, *J. Med. Chem.*, 2007, **50**, 611.
5. C. Zhou, J. Min, Z. Liu, A. Young, H. Deshazer, T. Gao, Y.-T. Chang, and N. R. Kallenbach, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1308.
6. Y.-Z. Xiong, F.-E. Chen, J. Balzarini, E. De Clercq, and C. Pannecouque, *Eur. J. Med. Chem.*, 2008, **43**, 1230.
7. B. Gay, S. Suarez, C. Weber, J. Rahuel, D. Fabbro, P. Furet, G. Caravatti, and J. Schoepfer, *J. Biol. Chem.*, 1999, **274**, 23311; B. Gay, S. Suarez, G. Caravatti, P. Furet, T. Meyer, and J. Schoepfer, *Int. J. Cancer*, 1999, **83**, 235; G.-Z. Yu, Y. Chen, Y.-Q. Long, D. Dong, X.-L. Mu, and J.-J. Wang,

Oncol. Rep., 2008, **19**, 1191.

8. For reviews, see: H. Fretz, P. Furet, C. García Echeverría, J. Rahuel, and J. Schoepfer, *Curr. Pharm. Des.*, 2000, **6**, 1777; C. B. Vu, *Curr. Med. Chem.*, 2000, **7**, 1081; M. Vidal, V. Gigoux, and C. Garbay, *Crit. Rev. Oncol. Hematol.*, 2001, **40**, 175; W. C. Shakespeare, *Curr. Opin. Chem. Biol.*, 2001, **5**, 409; T. R. Burke, Jr., and K. Lee, *Acc. Chem. Res.*, 2003, **36**, 426; K. Machida and B. J. Mayer, *Biochim. Biophys. Acta,* 2005, **1747**, 1; T. R. Burke, Jr., *Int. J. Pept. Res. Ther.*, 2006, **12**, 33.
9. G. Caravatti, J. Rahuel, B. Gay, and P. Furet, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1973.
10. J. Schoepfer, B. Gay, G. Caravatti, C. García Echeverría, H. Fretz, J. Rahuel, and P. Furet, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2865.
11. López-Rodríguez et al. disclosed a non-peptide inhibitor of Grb2-SH2 **3**, namely UCM104, as a new lead structure, which has also an IC_{50} value in the micromolar range (IC_{50} = 174 μM): see, XX^{th} International Symposium on Medicinal Chemistry, August 31- September 4, 2008, Vienna, Austria. Poster Presentation P527, *Development of non-peptide inhibitors of Her2-Grb2 interaction using molecular modeling and NMR spectroscopy*, M. L. López-Rodriguez, S. Ortega-Gutiérrez, B. Benhamú, Á. L. Orcajo, P. Serrano, A. Viso, I. R. Torrecillas, M. Campillo, L. Pardo, and K. Wüthrich.
12. C. Courme, N. Gresh, M. Vidal, C. Lenoir, C. Garbay, J.-C. Florent, and E. Bertounesque, *Eur. J. Med. Chem.*, 2009, **45**, 244.
13. C. Courme, S. Gillon, N. Gresh, M. Vidal, C. Garbay, J.-C. Florent, and E. Bertounesque, *Tetrahedron Lett.*, 2008, **49**, 4542.
14. W.-Q. Liu, M. Vidal, N. Gresh, B. P. Roques, and C. Garbay, *J. Med. Chem.*, 1999, **42**, 3737.
15. J. T. Bork, J. W. Lee, S. M. Khersonsky, H.-S. Moon, and Y.-T. Chang, *Org. Lett.*, 2003, **5**, 117.
16. L. J. Silverberg, J. L. Dillon, and P. Vemishetti, *Tetrahedron Lett.*, 1996, **37**, 771.
17. M. Soledade, C. Pedras, A. Q. Khan, K. C. Smith, and S. L. Stettner, *Can. J. Chem.*, 1997, **75**, 825.
18. P. S. Dragovich, R. Zhou, and T. J. Prins, *J. Org. Chem.*, 2002, **67**, 741.
19. W.-Q. Liu, M. Vidal, C. Olszowy, E. Million, C. Lenoir, H. Dhôtel, and C. Garbay, *J. Med. Chem.*, 2004, **47**, 1223.
20. V. Leroux, N. Gresh, W.-Q Liu, C. Garbay, and B. Maigret, *J. Mol. Struct., THEOCHEM,* 2007, **806**, 51.