CHAPTER II
EXPERIMENTAL

2.1 General

Elemental analysis were performed by Ms. Amporn Ungpakornkaew on a Perkin-Elmer CHN Elemental Analyzer model PE 2400 series II at the Research Equipment Centre, Chulalongkorn University. Routine ^1H NMR spectra were recorded in deuterated solvents ($CDCl_3$, DMSO, D_2O) on a Bruker ACX200 NMR spectrometer at 200 MHz, unless otherwise noted. Chemical shifts are reported in part per million (ppm, δ) and coupling constants are reported in Hz down field relative to tetramethylsilane. Spectral patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; dt, doublet of triplet; td, triplet of doublet; br, broad. MALDI-TOF mass spectra of all cycloguanil derivatives were analysed by Ms. Nathiga Panchan on Bruker BIFLEX^{Tm} using doubly recrystallized 2-cyano-4-hydroxy cinnamic acid (CCA) as matrix. The spectrometer was calibrated with human angiotensin II (M+H, 1047). 0.1% Trifluoroacetic acid in acetonitrile:water (70:30) was used as diluting agent for MALDI-TOF samples.

Thin layer chromatography (TLC) was performed on Merck D.C. silica gel 60 F_{254} 0.2 mm pre-coated aluminium plates cat no. 1.05554. Column chromatography was performed on silica gel 70-230 mesh or 230-400 Mesh (for flash column chromatography).

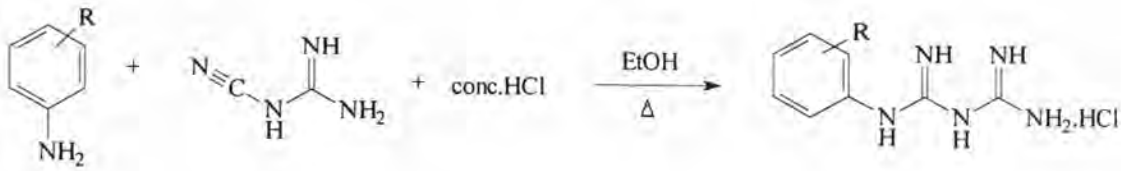
All chemicals and solvents were obtained from commercial suppliers (Aldrich, BDH, Fluka and Merck). Anhydrous DMF was obtained from Fluka and used without further purification.

Removal of solvents was carried out on a Buchi rotary evaporator attached to a water aspirator. Analytical samples were dried under vacuum at room temperature for several hours.

Anti DHFR (wild type and mutant $A_{16}VS_{108}T$ type) activities of all samples were analysed by Dr. Sumalee Kamchonwongpaisom and Ms. Duenpen Japroong at the National Science and Technology Development Agency (NSTDA).

2.2 Synthesis of 1-aryl-4,6-diamino-1,2-dihydro-1,3,5-triazines

2.2.1 Synthesis of arylbiguanide hydrochloride



General Procedure

To a suspension of the arylamine (25 mmol) in an appropriate volume of absolute ethanol (10 mL) containing conc. HCl (2.39 mL, 27.5 mmol) and dicyanodiamide (2.31 g, 27.5 mmol) was heated to reflux until the reaction gave positive biguanide test (6-10 hours). On cooling in the refrigerator, a white crystalline solid precipitated which was collected by filtration and washed with ethanol, acetone, then Et_2O and air dried.

Phenylbiguanide hydrochloride **(I-1)**

4.81 g, 90% yield (25 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless prisms. ^{1}H NMR (D_2O) δ_H 7.11 and 7.24 (5H, 2xm, aromatic C-H).

4-Methylphenylbiguanide hydrochloride **(I-2)**

10.17 g, 89% yield (50 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless prisms. ^{1}H NMR (D_2O) δ_H 2.12 (3H, s, C$\underline{H}_3$), 6.97 and 7.07 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H).

4-Ethylphenylbiguanide hydrochloride **(I-3)**

13.15 g, 53% yield (100 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless prisms. ^{1}H NMR (D_2O) δ_H 0.98 (3H, t, J = 7.0 Hz, C$\underline{H}_3$), 2.44 (2H, q, J = 7.0 Hz, C$\underline{H}_2$), 7.00 and 7.11 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H).

4-Bromophenylbiguanide hydrochloride **(I-4)**

5.98 g, 82% yield (25 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless leaflets. ^{1}H NMR (D_2O) δ_H 7.00 and 7.37 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H).

4-Chlorophenylbiguanide hydrochloride **(I-5)**

19.73 g, 79% yield (100 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 7.00 and 7.37 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H).

3-Chlorophenylbiguanide hydrochloride **(I-6)**

8.38 g, 68% yield (50 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless prisms. ^{1}H NMR (D_2O) δ_H 7.00 and 7.10 (2x1H, d, J = 8.0 Hz, aromatic C-H), 7.18 (2H, m, aromatic C-H).

2,4-Dichlorophenylbiguanide hydrochloride **(I-7)**

9.36 g, 66% yield (50 mmol scale), purified by recrystallization from methanol-water and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 7.19 and 7.42 (3H, 2xm, aromatic C-H).

3,4-Dichlorophenylbiguanide hydrochloride **(I-8)**

23.45 g, 83% yield (100 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless leaflets. ^{1}H NMR (D_2O) δ_H 6.97 (1H, dd, J = 8.5, 2.6 Hz, aromatic C-H) and 7.31 (2H, m, aromatic C-H).

4-Chloro-3-nitrophenylbiguanide hydrochloride **(I-9)**

8.14 g, 56% yield (50 mmol scale), purified by recrystallization from methanol and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 7.30 and 7.42 (2x1H, 2xd, J = 7.8 Hz, aromatic C-H) 7.77 (1H, s, aromatic C-H).

3-Bromophenylbiguanide hydrochloride **(I-10)**

5.43 g, 61% yield (30 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (D_2O) δ_H 7.03 and 7.24 (1x1H, d, J = 7.6

Hz, aromatic C-H) 7.12 (1H, t, J = 7.5 Hz, aromatic C-H) and 7.31 (1H, t, J = 1.8 Hz, aromatic C-H).

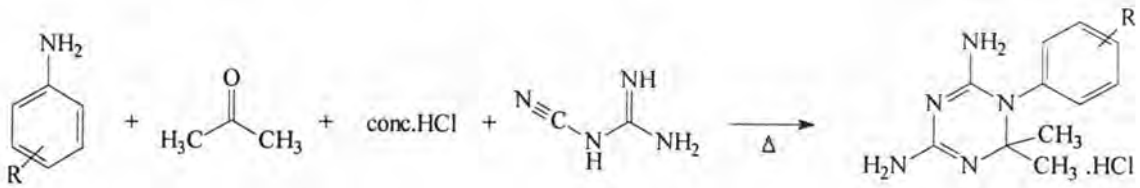
3,5-Dichlorophenylbiguanide hydrochloride **(I-11)**

10.11 g, 71% yield (50 mmol scale), purified by recrystallization from methanol and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 7.07 (2H, m, aromatic C-H) and 7.12 (1H, dd, J = 1.6, 1.7 Hz, aromatic C-H).

3,4-Methylenedioxyphenylbiguanide hydrochloride **(I-12)**

5.58 g, 72% yield (30 mmol scale), purified by recrystallization from methanol and obtained as colorless prisms. ^{1}H NMR (D_2O) δ_H 5.81 (2H, s, CH_2), 6.57 (1H, dd, J = 8.2, 2.1 Hz, aromatic C-H) 6.65 (1H, d, J = 1.9 Hz, aromatic C-H) and 6.71 (1H, d, J = 8.2 Hz, aromatic C-H).

2.2.2 Synthesis of 1-Aryl-2,2-dimethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine by three-component method (for acetone as the carbonyl component)



General Procedure

A suspension of arylamine (10 mmol) in acetone (20 mL) containing conc. HCl (0.87 mL, 10 mmol) (or *p*-toluenesulfonic acid) and dicyanodiamide (0.84 g, 10 mmol) was heated to reflux until the reaction gave negative biguanide test (10-36 hours). On cooling in the refrigerator, a white crystalline solid precipitated which was collected by filtration and washed with ethanol, acetone then Et_2O and air dried.

1-(3'-Carboxyphenyl)-2,2-dimethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine *p*-toluene sulfonate **(II-1)**

3.45 g, 79% yield (10 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 1.29 (6H, s, CH_3-2 (x2)), 2.20 (3H, s, *p*-TsOH CH_3), 7.17 and 7.49 (2x2H, AB doublet, J = 8.0 Hz,

aromatic C-H) 7.82 (1H, s, aromatic C-H) and 7.98 (1H, dd, J = 6.0, 4.0 Hz, aromatic C-H); *m/z* (MALDI-TOF) 262 ($M.H^+$).

1-(4′-Carboxyphenyl)-2,2-dimethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine *p*-toluene sulfonate **(II-2)**

3.71 g, 86% yield (10 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^1H NMR (D_2O) δ_H 1.29 (6H, s, 2xCH_3-2), 2.19 (3H, s, *p*-TsOH CH_3), 7.17 and 7.49 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H), 7.36 and 7.99 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H); *m/z* (MALDI-TOF) 262 ($M.H^+$).

1-(3′-Chlorophenyl)-2,2-dimethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-3)**

2.28 g, 79% yield (10 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. Anal. Calcd. for $C_{11}H_{15}Cl_2N_5$ + 0.4 H_2O: C, 44.7; H, 5.4; N, 23.7%. Found: C, 44.9; H, 5.5; N, 23.4%. ^1H NMR (D_2O) δ_H 1.25 (6H, s, 2xCH_3-2), 7.10-7.40 (4H, m, aromatic C-H); *m/z* (MALDI-TOF) 252, 254 ($M.H^+$).

1-(4′-Chloro-3′-nitrophenyl)-2,2-dimethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-4)**

2.48 g, 75% yield (10 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^1H NMR (D_2O) δ_H 1.33 (6H, s, 2xCH_3-2), 7.58 (1H, m, aromatic C-H), 7.72 (1H, d, J = 8.0 Hz, aromatic C-H) and 8.02 (1H, s, aromatic C-H); *m/z* (MALDI-TOF) 297, 299 ($M.H^+$).

1-(3′,5′-Dichlorophenyl)-2,2-dimethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-5)**

TLC and biguanide test indicated that no reaction had occurred.

2.2.3 Synthesis of 1-Aryl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride by two-component (for aldehydes as the carbonyl component)

General procedure

To a suspension of the arylbiguanide hydrochloride (5 mmol) in absolute ethanol (3,4 mL) containing conc. HCl (0.42 mL) was added the aldehyde (10 mmol). The reaction mixture was heated to reflux until a negative biguanide test was obtained (30 min to several hours). On cooling in the refrigerator, a white crystalline solid precipitated which was collected by filtration and washed with ethanol, acetone then Et_2O and air dried.

1-Phenyl-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-6)**

0.61 g, 51% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. Anal. Calcd. for $C_{10}H_{14}ClN_5 + H_2O$: C, 46.6; H, 6.2; N, 27.2%. Found: C, 47.0; H, 6.2; N, 27.7%. ^{1}H NMR (D_2O) δ_H 1.16 (3H, d, J = 6.4 Hz, C<u>H</u>$_3$-2), 4.96 (1H, q, J = 6.0 Hz, <u>H</u>-2), 7.20 and 7.36 (5H, 2xm, aromatic C-H) (Figure 1); *m/z* (MALDI-TOF) 204 ($M.H^+$).

1-Phenyl-2-ethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-7)**

0.47 g, 37% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.72 (3H, t, J = 6.4 Hz, C<u>H</u>$_3$CH$_2$-2), 1.54 (2H, m, CH$_3$C<u>H</u>$_2$-2), 4.84 (1H, dd, J = 6.4, 4.0 Hz, <u>H</u>-2), 7.22 and 7.36 (5H, 2xm, aromatic C-H) (Figure 2); *m/z* (MALDI-TOF) 218 ($M.H^+$).

1-Phenyl-2-propyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-8)**

0.50 g, 38% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.66 (3H, t, J = 7.0 Hz,

$C\underline{H}_3CH_2CH_2$-2), 1.18 (2H, m, $CH_3C\underline{H}_2CH_2$-2), 1.52 (2H, m, $CH_3CH_2C\underline{H}_2$-2), 4.86 (1H, dd, J = 6.4, 4.0 Hz, $\underline{H}$-2), 7.22 and 7.36 (5H, 2xm, aromatic C-H); *m/z* (MALDI-TOF) 232 ($M.H^+$).

1-Phenyl-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-9)**
0.43 g, 32% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. ^1H NMR (D_2O) δ_H 0.64 and 0.78 (2x3H, 2xd, J = 6.8 Hz, $CH(C\underline{H}_3)_2$-2), 1.90 (1H, m, $C\underline{H}(CH_3)_2$-2), 4.76 (1H, d, J = 3.2 Hz, $\underline{H}$-2), 7.26 and 7.38 (5H, 2xm, aromatic C-H) (Figure 3); *m/z* (MALDI-TOF) 232 ($M.H^+$).

1-Phenyl-2-butyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-10)**
0.25 g, 18% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^1H NMR (D_2O) δ_H 0.62 (3H, t, J = 6.8 Hz, $C\underline{H}_3(CH_2)_3$-2), 1.10 (4H, m, $CH_3(C\underline{H}_2)_2CH_2$-2), 1.54 (2H, m, $CH_3(CH_2)_2C\underline{H}_2$-2), 4.88 (1H, dd, J = 6.4, 4.0 Hz, $\underline{H}$-2), 7.22 and 7.36 (5H, 2xm, aromatic C-H) (Figure 4); *m/z* (MALDI-TOF) 246 ($M.H^+$).

1-Phenyl-2-cyclohexyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-11)**
0.93 g, 60% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless prisms. ^1H NMR (D_2O) δ_H 0.94 (4H, m, 2xcyclohexyl $C\underline{H}_2$), 1.21 (1H, m, cyclohexyl $C\underline{H}$), 1.57 (6H, m, 3xcyclohexyl $C\underline{H}_2$), 4.74 (1H, d, J = 2.4 Hz, $\underline{H}$-2), 7.26 and 7.40 (5H, 2xm, aromatic C-H) (Figure 5); *m/z* (MALDI-TOF) 272 ($M.H^+$).

1-Phenyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-12)**
1.17 g, 78% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as white microcrystalline solids. Anal. Calcd. for $C_{15}H_{16}ClN_5$ + 1.5 HCl: C, 50.5; H, 4.9; N, 19.6%. Found: C, 50.7; H, 4.6; N, 19.2%. ^1H NMR (D_2O) δ_H 5.98 (1H, s, $\underline{H}$-2), 7.02 (2H, dd, J = 6.4, 4.0 Hz, aromatic C-H) and 7.22 (8H, m, aromatic C-H); *m/z* (MALDI-TOF) 266 ($M.H^+$).

1-(4'-Methylphenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochlorid **(II-13)**

0.68 g, 27% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. Anal. Calcd. For $C_{11}H_{16}ClN_5$ + HCl + 0.5 H_2O: C, 44.1; H, 6.0; N, 23.4%. Found: C, 43.8; H, 6.2; N, 22.8%. ^{1}H NMR (D_2O) δ_H 1.18 (3H, d, J = 6.5 Hz, C<u>H</u>$_3$-2), 2.15 (3H, s, C<u>H</u>$_3$-4′), 5.05 (1H, q, J = 6.5 Hz, <u>H</u>-2), 7.08 and 7.20 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 6); *m/z* (MALDI-TOF) 218 ($M.H^+$).

<u>1-(4′-Methylphenyl)-2-ethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-14)**

2.07 g, 77% yield (10 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as white crystalline solids. ^{1}H NMR (D_2O) δ_H 0.72 (3H, t, J = 6.0 Hz, C<u>H</u>$_3$CH$_2$-2), 1.65 (2H, m, CH$_3$C<u>H</u>$_2$-2), 2.18 (3H, s, C<u>H</u>$_3$-4′), 4.94 (1H, dd, J = 6.0, 5.0 Hz, <u>H</u>-2), 7.15 and 7.25 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 7); *m/z* (MALDI-TOF) 232 ($M.H^+$).

<u>1-(4′-Methylphenyl)-2-propyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochlorid</u> **(II-15)**

1.18 g, 83% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless prisms. Anal. Calcd. for $C_{13}H_{20}ClN_5$ + HCl: C, 49.1; H, 6.6; N, 22.0%. Found: C, 49.5; H, 6.8, N, 21.9%. ^{1}H NMR (D_2O) δ_H 0.64 (3H, t, J = 7.0 Hz, C<u>H</u>$_3$CH$_2$CH$_2$-2), 1.15 (2H, m, CH$_3$C<u>H</u>$_2$CH$_2$-2), 1.60 (2H, m, CH$_3$CH$_2$C<u>H</u>$_2$-2), 2.18 (3H, s, C<u>H</u>$_3$-4′), 4.94 (1H, dd, J = 6.0, 4.0 Hz, <u>H</u>-2), 7.12 and 7.22 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 8); *m/z* (MALDI-TOF) 246 ($M.H^+$).

<u>1-(4′-Methylphenyl)-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-16)**

1.19 g, 85% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. Anal. Calcd. for $C_{13}H_{20}ClN_5$ + HCl + CH_3OH: C, 48.0; H, 7.2; N, 20.0%. Found: C, 47.5; H, 6.8; N, 20.2%. ^{1}H NMR (D_2O) δ_H 0.65 and 0.75 (2x3H, 2xd, J = 7.0 Hz, CH(C<u>H</u>$_3$)$_2$-2), 1.88 (1H, m, C<u>H</u>(CH$_3$)$_2$-2), 2.18 (3H, s, C<u>H</u>$_3$-4′), 4.82 (1H, d, J = 3.0 Hz, <u>H</u>-2), 7.12 and 7.22 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 9); *m/z* (MALDI-TOF) 246 ($M.H^+$).

1-(4′-Methylphenyl)-2-butyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-17)**

0.87 g, 59% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.62 (3H, t, J = 6.5 Hz, $CH_3(CH_2)_3$-2), 1.08 (4H, m, $CH_3(CH_2)_2CH_2$-2), 1.58 (2H, m, $CH_3(CH_2)_2CH_2$-2), 2.20 (3H, s, CH_3-4′), 4.88 (1H, dd, J = 6.0, 4.0 Hz, H-2), 7.12 and 7.22 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 10); *m/z* (MALDI-TOF) 260 ($M.H^+$).

1-(4′-Methylphenyl)-2-cyclohexyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-18)**

0.94 g, 59% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.94 (4H, m, 2xcyclohexyl CH_2), 1.21 (1H, m, cyclohexyl CH), 1.58 (6H, m, 3xcyclohexyl CH_2), 2.20 (3H, s, CH_3-4′), 4.68 (1H, d, J = 2.2 Hz, H-2), 7.12 and 7.22 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 11); *m/z* (MALDI-TOF) 286 ($M.H^+$).

1-(4′-Methylphenyl)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-19)**

1.38 g, 88% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 2.05 (3H, s, CH_3-4′), 5.87 (1H, s, H-2), 6.82 and 6.98 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H), 7.16 (5H, m, aromatic C-H) (Figure 12); *m/z* (MALDI-TOF) 280 ($M.H^+$).

1-(4′-Ethylphenyl)-2-ethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-21)**

1.02 g, 72% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.76 (3H, t, J = 6.0 Hz, CH_3CH_2-2), 1.05 (3H, t, J = 6.0 Hz, CH_3CH_2-4′), 1.60 (2H, m, CH_3CH_2-2), 2.54 (2H, q, J = 7.0 Hz, CH_3CH_2-4′), 4.88 (1H, dd, J = 6.0, 4.0 Hz, H-2), 7.18 and 7.28 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 14); *m/z* (MALDI-TOF) 246 ($M.H^+$).

1-(4′-Ethylphenyl)-2-propyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-22)**

0.93 g, 63% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.70 (3H, t, J = 6.0 Hz, $CH_3CH_2CH_2$-2), 1.04 (3H, t, J = 6.0 Hz, CH_3CH_2-4′), 1.24 (2H, m, $CH_3CH_2CH_2$-2), 1.56 (2H, m, $CH_3CH_2CH_2$-2), 2.56 (2H, q, J = 7.0 Hz, CH_3CH_2-4′), 4.86 (1H, dd, J = 6.0, 4.0 Hz, H-2), 7.18 and 7.28 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 15); *m/z* (MALDI-TOF) 260 ($M.H^+$).

1-(4′-Ethylphenyl)-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-23)**

0.92 g, 62% yield (5 mmol scale), purified by recrystallization from ethanol and obtained as colorless leaflets. ^{1}H NMR (D_2O) δ_H 0.70 and 0.84 (2x3H, 2xd, J = 6.0 Hz, $CH(CH_3)_2$-2), 1.05 (3H, t, J = 6.0 Hz, CH_3CH_2-4′), 1.98 (1H, m, $CH(CH_3)_2$-2), 2.54 (2H, q, J = 6.4 Hz, CH_3CH_2-4′), 4.86 (1H, d, J = 3.0 Hz, H-2), 7.22 and 7.32 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 16); *m/z* (MALDI-TOF) 260 ($M.H^+$).

1-(4′-Ethylphenyl)-2-butyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-24)**

0.83 g, 54% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.66 (3H, t, J = 6.5 Hz, $CH_3(CH_2)_3$-2), 1.06 (3H, t, J = 7.0 Hz, CH_3CH_2-4′), 1.12 (4H, m, $CH_3(CH_2)_2CH_2$-2), 1.62 (2H, m, $CH_3(CH_2)_2CH_2$-2), 2.54 (2H, q, J = 6.4 Hz, CH_3CH_2-4′), 4.96 (1H, dd, J = 6.0, 4.0 Hz, H-2), 7.18 and 7.28 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 17); *m/z* (MALDI-TOF) 274 ($M.H^+$).

1-(4′-Ethylphenyl)-2-cyclohexyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-25)**

0.40 g, 24% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless leaflets. ^{1}H NMR (D_2O) δ_H 0.96 (4H, m, 2xcyclohexyl CH_2), 1.04 (3H, t, J = 7.0 Hz, CH_3CH_2-4′), 1.22 (1H, m, cyclohexyl CH), 1.58 (6H, m, 3xcyclohexyl CH_2), 2.54 (2H, q, J = 6.4 Hz, CH_3CH_2-4′), 4.68 (1H, d, J = 2.4 Hz, H-2), 7.18 and 7.28 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 18); *m/z* (MALDI-TOF) 300 ($M.H^+$).

1-(4′-Ethylphenyl)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride

(II-26)

1.28 g, 78% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. Anal. Calcd. for $C_{17}H_{20}ClN_5$: C, 61.9; H, 6.1; N, 21.2%. Found: C, 61.8; H, 6.2, N, 21.2%. ^{1}H NMR (D_2O) δ_H 0.91 (3H, t, J = 6.5 Hz, CH_3CH_2-4′), 2.36 (2H, q, J = 7.3 Hz, CH_3CH_2-4′), 5.95 (1H, s, H-2), 6.87 and 7.03 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H), 7.17 (5H, m, aromatic C-H) (Figure 19); *m/z* (MALDI-TOF) 294 ($M.H^+$).

1-(4′-Chlorophenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride

(II-27)

2.01 g, 49% yield (15 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless prisms. Anal. Calcd. for $C_{10}H_{13}Cl_2N_5$: C, 43.8; H, 4.8; N, 25.6%. Found: C, 43.8; H, 4.9; N, 25.4%. ^{1}H NMR (D_2O) δ_H 1.20 (3H, d, J = 6.0 Hz, CH_3-2), 5.06 (1H, q, J = 6.0 Hz, H-2), 7.22 and 7.40 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H); *m/z* (MALDI-TOF) 238, 240 ($M.H^+$).

1-(4′-Chlorophenyl)-2-ethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride

(II-28)

3.97 g, 92% yield (15 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless prisms. Anal. Calcd. for $C_{11}H_{15}Cl_2N_5$: C, 45.8; H, 5.2; N, 24.3%. Found: C, 45.9; H, 5.2; N, 24.2%. ^{1}H NMR (D_2O) δ_H 0.94 (3H, t, J = 6.5 Hz, CH_3CH_2-2), 1.52 (2H, m, CH_3CH_2-2), 4.84 (1H, dd, J = 6.5, 4.0 Hz, H-2), 7.22 and 7.38 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H); *m/z* (MALDI-TOF) 252, 254 ($M.H^+$).

1-(4′-Chlorophenyl)-2-propyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride

(II-29)

1.30 g, 86% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless rosettes. Anal. Calcd. for $C_{12}H_{17}Cl_2N_5 + H_2O$: C, 45.0; H, 6.0; N, 21.9%. Found: C, 45.6; H, 5.7; N, 21.5%. ^{1}H NMR (D_2O) δ_H 0.65 (3H, t, J = 6.5 Hz, $CH_3CH_2CH_2$-2), 1.15 (2H, m, $CH_3CH_2CH_2$-2), 1.55 (2H, m, $CH_3CH_2CH_2$-2),

4.94 (1H, dd, J = 6.0, 4.0 Hz, H-2), 7.25 and 7.42 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H); *m/z* (MALDI-TOF) 266, 268 ($M.H^+$).

1-(4′-Chlorophenyl)-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-30)**

1.48 g, 98% yield (5 mmol scale), purified by recrystallization from ethanol and obtained as colorless needles. Anal. Calcd. for $C_{12}H_{17}Cl_2N_5$: C, 47.7; H, 5.7; N, 23.2%. Found: C, 47.6; H, 5.6; N, 23.1%. ^{1}H NMR (D_2O) δ_H 0.69 and 0.80 (2x3H, 2xd, J = 6.8 Hz, $CH(CH_3)_2$-2), 1.94 (1H, m, $CH(CH_3)_2$-2), 4.80 (1H, d, J = 2.8 Hz, H-2), 7.38 and 7.44 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H); *m/z* (MALDI-TOF) 266, 268 ($M.H^+$).

1-(4′-Chlorophenyl)-2-butyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-31)**

1.40 g, 89% yield (5 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless needles. Anal. Calcd. For $C_{13}H_{19}Cl_2N_5 + 3.5\ H_2O$: C, 41.1; H, 7.3; N, 18.5%. Found: C, 41.2; H, 6.9; N, 18.5%. ^{1}H NMR (D_2O) δ_H 0.60 (3H, t, J = 6.5 Hz, $CH_3(CH_2)_3$-2), 1.08 (4H, m, $CH_3(CH_2)_2CH_2$-2), 1.55 (2H, m, $CH_3(CH_2)_2CH_2$-2), 4.69 (1H, dd, J = 6.5, 4.0 Hz, H-2), 7.25 and 7.40 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 20); *m/z* (MALDI-TOF) 280, 282 ($M.H^+$).

1-(4′-Chlorophenyl)-2-cyclohexyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-32)**

1.63 g, 95% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.96 (4H, m, 2xcyclohexyl CH_2), 1.24 (1H, m, cyclohexyl CH), 1.57 (6H, m, 3xcyclohexyl CH_2), 4.70 (1H, d, J = 2.2 Hz, H-2), 7.24 and 7.42 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 21); *m/z* (MALDI-TOF) 306, 308 ($M.H^+$).

1-(4′-Chlorophenyl)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-33)**

1.42 g, 85% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. Anal. Calcd. for $C_{15}H_{15}Cl_2N_5$: C, 53.6; H, 4.5;

N, 20.8%. Found: C, 53.4; H, 4.4; N, 20.9%. ^{1}H NMR (D_2O) δ_H 5.95 (1H, s, H-2), 6.98 (2H, part of AB doublet, J = 8.0 Hz, aromatic C-H), 7.20 (7H, m, aromatic C-H); *m/z* (MALDI-TOF) 300, 302 ($M.H^+$).

1-(4′-Bromophenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-34)**

1.71 g, 53% yield (10 mmol scale), purified by recrystallization from ethanol and obtained as colorless prisms. Anal. Calcd. for $C_{10}H_{13}BrClN_5$: C, 37.7; H, 4.1; N, 22.0%. Found: C, 37.4; H, 4.1; N, 21.7%. ^{1}H NMR (D_2O) δ_H 1.16 (3H, d, J = 6.0 Hz, CH_3-2), 5.00 (1H, q, J = 6.0 Hz, H-2), 7.14 and 7.55 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 22); *m/z* (MALDI-TOF) 282, 284 ($M.H^+$).

1-(4′-Bromophenyl)-2-ethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-35)**

3.09 g, 93% yield (10 mmol scale), purified by recrystallization from ethanol and obtained as colorless needles. Anal. Calcd. for $C_{11}H_{15}BrClN_5$: C, 39.7; H, 4.6; N, 21.0%. Found: C, 39.9; H, 4.6; N, 21.1%. ^{1}H NMR (D_2O) δ_H 0.74 (3H, t, J = 6.5 Hz, CH_3CH_2-2), 1.50 (2H, m, CH_3CH_2-2), 4.92 (1H, dd, J = 6.5, 4.0 Hz, H-2), 7.20 and 7.50 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 23); *m/z* (MALDI-TOF) 296, 298 ($M.H^+$).

1-(4′-Bromophenyl)-2-propyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-36)**

1.28 g, 74% yield (5 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless needles. Anal. Calcd. for $C_{12}H_{17}BrClN_5 + H_2O$: C, 39.5; H, 5.2; N, 19.2%. Found: C, 39.8; H, 5.1; N, 19.1%. ^{1}H NMR (D_2O) δ_H 0.68 (3H, t, J = 6.0 Hz, $CH_3CH_2H_2$-2), 1.18 (2H, m, $CH_3CH_2CH_2$-2), 1.60 (2H, m, $CH_3CH_2CH_2$-2), 4.92 (1H, dd, J = 6.0, 4.0 Hz, H-2), 7.20 and 7.50 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 24); *m/z* (MALDI-TOF) 310, 312 ($M.H^+$).

1-(4′-Bromophenyl)-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-37)**

1.22 g, 71% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless rosettes. Anal. Calcd. for $C_{12}H_{17}BrClN_5$: C, 41.6; H, 4.9; N, 20.2%. Found: C, 41.4; H, 4.8; N, 20.2%. ^{1}H NMR (D_2O) δ_H 0.66 and 0.76 (2x3H, 2xd, J = 7.0 Hz, $CH(C\underline{H}_3)_2$-2), 1.88 (1H, m, $C\underline{H}(CH_3)_2$-2), 4.78 (1H, d, J = 3.0 Hz, H-2), 7.18 and 7.56 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 25); *m/z* (MALDI-TOF) 310, 312 ($M.H^+$).

1-(4′-Bromophenyl)-2-butyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-38)**

1.57 g, 87% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.62 (3H, t, J = 6.5 Hz, $C\underline{H}_3(CH_2)_3$ -2), 1.08 (4H, m, $CH_3(C\underline{H}_2)_2CH_2$-2), 1.55 (2H, m, $CH_3(CH_2)_2C\underline{H}_2$-2), 4.69 (1H, dd, J = 6.0, 4.0 Hz, H-2), 7.16 and 7.56 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 26); *m/z* (MALDI-TOF) 324, 326 ($M.H^+$).

1-(4′-Bromophenyl)-2-cyclohexyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-39)**

1.73 g, 90% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.95 (4H, m, 2xcyclohexyl $C\underline{H}_2$), 1.24 (1H, m, cyclohexyl C<u>H</u>), 1.58 (6H, m, 3xcyclohexyl $C\underline{H}_2$), 4.70 (1H, d, J = 2.2 Hz, H-2), 7.20 and 7.58 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 27); *m/z* (MALDI-TOF) 350, 352 ($M.H^+$).

1-(4′-Bromophenyl)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-40)**

1.77 g, 93% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. Anal. Calcd. for $C_{15}H_{15}BrClN_5$: C, 47.3; H, 4.0; N, 18.4%. Found: C, 47.4; H, 4.0; N, 18.4%. ^{1}H NMR (D_2O) δ_H 5.88 (1H, s, H-2), 6.88 and 7.34 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H), 7.20 (5H, m, aromatic C-H) (Figure 28); m/z (MALDI-TOF) 344, 346 ($M.H^+$).

1-(3′-Chlorophenyl)-2-ethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-42)**

1.38 g, 96% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.76 (3H, t, J = 7.0 Hz, CH_3CH_2-2), 1.68 (2H, m, CH_3CH_2-2), 4.98 (1H, dd, J = 6.5, 4.0 Hz, H-2), 7.20 and 7.40 (4H, 2xm, aromatic C-H); *m/z* (MALDI-TOF) 252, 254 ($M.H^+$).

1-(3′-Chlorophenyl)-2-propyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-43)**

1.18 g, 78% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.68 (3H, t, J = 6.8 Hz, $CH_3CH_2H_2$-2), 1.18 (2H, m, $CH_3CH_2CH_2$-2), 1.60 (2H, m, $CH_3CH_2CH_2$-2), 4.96 (1H, dd, J = 6.5, 4.0 Hz, H-2), 7.22 and 7.38 (4H, 2xm, aromatic C-H); *m/z* (MALDI-TOF) 266, 268 ($M.H^+$).

1-(3′-Chlorophenyl)-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-44)**

1.19 g, 79% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.66 and 0.76 (2x3H, 2xd, J = 7.0 Hz, $CH(CH_3)_2$-2), 1.90 (1H, m, $CH(CH_3)_2$-2), 4.76 (1H, d, J = 2.4 Hz, H-2), 7.22 and 7.36 (4H, 2xm, aromatic C-H) (Figure 29); *m/z* (MALDI-TOF) 266, 268 ($M.H^+$).

1-(3′-Chlorophenyl)-2-butyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-45)**

1.04 g, 66% yield (5 mmol scale), purified by recrystallization from ethanol-diethyl ether and obtained as colorless prisms. ^{1}H NMR (D_2O) δ_H 0.62 (3H, t, J = 6.8 Hz, $CH_3(CH_2)_3$-2), 1.08 (4H, m, $CH_3(CH_2)_2CH_2$-2), 1.60 (2H, m, $CH_3(CH_2)_2CH_2$-2), 4.94 (1H, dd, J = 6.8, 4.0 Hz, H-2), 7.20 and 7.36 (4H, 2xm, aromatic C-H) (Figure 30); *m/z* (MALDI-TOF) 280, 282 ($M.H^+$).

1-(3′-Chlorophenyl)-2-cyclohexyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-48)**

0.82 g, 48% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless prisms. ^{1}H NMR (D_2O) δ_H 0.96 (4H, m, 2xcyclohexyl

$C\underline{H}_2$), 1.24 (1H, m, cyclohexyl C<u>H</u>), 1.61 (6H, m, 3xcyclohexyl $C\underline{H}_2$), 4.74 (1H, d, J = 2.2 Hz, <u>H</u>-2), 7.25 and 7.39 (4H, 2xm, aromatic C-H) (Figure 33); *m/z* (MALDI-TOF) 306, 308 ($M.H^+$).

<u>1-(3′-Chlorophenyl)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-49)**

1.48 g, 99% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless prisms. Anal. Calcd. for $C_{15}H_{15}Cl_2N_5 + H_2O$: C, 46.4; H, 4.2; N, 18.0%. Found: C, 46.9; H, 4.4; N, 18.0%. ^1H NMR (D_2O) δ_H 5.95 (1H, s, <u>H</u>-2), 6.90 and 7.18 (4H, 2xm, aromatic C-H), 7.20 (5H, m, aromatic C-H); *m/z* (MALDI-TOF) 300, 302 ($M.H^+$).

<u>1-(2′,4′-Dichlorophenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-50)**

0.63 g, 41% yield (5 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless prisms. ^1H NMR (D_2O) δ_H 1.08 and 1.18 (2x3H, 2xd, J = 7.0 Hz, $C\underline{H}_3$-2 minor and major), 4.94 and 5.05 (2x1H, 2xq, J = 6.0 Hz, <u>H</u>-2 major and minor), 7.32 and 7.56 (3H, 2xm, aromatic C-H) (Figure 34); *m/z* (MALDI-TOF) 272, 274, 276 ($M.H^+$).

<u>1-(2′,4′-Dichlorophenyl)-2-ethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-51)**

1.49 g, 93% yield (5 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless prisms. ^1H NMR (D_2O) δ_H 0.69 and 0.72 (2x3H, 2xt, J = 7.0 Hz, $C\underline{H}_3CH_2$-2 minor and major), 1.53 and 1.62 (2x2H, 2xm, $CH_3C\underline{H}_2$-2 minor and major), 4.72 and 4.88 (2x1H, 2xdd, J = 6.0, 4.0 Hz, <u>H</u>-2 major and minor), 7.32 and 7.56 (3H, 2xm, aromatic C-H) (Figure 35); *m/z* (MALDI-TOF) 286, 288, 290 ($M.H^+$).

<u>1-(2′,4′-Dichlorophenyl)-2-propyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-52)**

1.26 g, 75% yield (5 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless needles. ^1H NMR (D_2O) δ_H 0.64 and 0.68 (2x3H, 2xt, J = 7.0 Hz, $C\underline{H}_3CH_2CH_2$-2 minor and major), 1.18 (2H, m, $CH_3C\underline{H}_2CH_2$-2), 1.52 (2H, m,

$CH_3CH_2C\underline{H}_2$-2), 4.74 and 4.91 (2x1H, 2xdd, J = 6.0, 4.0 Hz, H-2 major and minor), 7.32 and 7.36 (3H, 2xm, aromatic C-H) (Figure 36); *m/z* (MALDI-TOF) 300, 302, 304 ($M.H^+$).

1-(2′,4′-Dichlorophenyl)-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-53)**

1.51 g, 92% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless prisms. ^1H NMR (D_2O) δ_H 0.68 and 0.78 (2x3H, 2xd, J = 7.0 Hz, $CH(C\underline{H}_3)_2$-2), 1.92 (1H, m, $C\underline{H}(CH_3)_2$-2), 4.79 (1H, d, J = 2.4 Hz, H-2), 7.32 and 7.58 (3H, 2xm, aromatic C-H) (Figure 37); *m/z* (MALDI-TOF) 300, 302, 304 ($M.H^+$).

1-(2′,4′-Dichlorophenyl)-2-butyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-54)**

0.88 g, 50% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless needles. ^1H NMR (D_2O) δ_H 0.58 and 0.64 (2x3H, 2xt, J = 7.0 Hz, $C\underline{H}_3(CH_2)_3$-2 minor and major), 1.12 (4H, m, $CH_3(C\underline{H}_2)_2CH_2$-2), 1.58 (2H, m, $CH_3(CH_2)_2C\underline{H}_2$-2), 4.78 and 4.94 (2x1H, 2xdd, J = 6.5, 4.0 Hz, H-2 major and minor), 7.34 and 7.58 (3H, 2xm, aromatic C-H) (Figure 38); *m/z* (MALDI-TOF) 314, 316, 318 ($M.H^+$).

1-(2′,4′-Dichlorophenyl)-2-cyclohexyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-55)**

1.69 g, 90% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless needles. ^1H NMR (D_2O) δ_H 0.99 (4H, m, 2xcyclohexyl $C\underline{H}_2$), 1.26 (1H, m, cyclohexyl C<u>H</u>), 1.60 (6H, m, 3xcyclohexyl $C\underline{H}_2$), 4.66(1H, d, J = 2.2 Hz, H-2), 7.35 and 7.60 (3H, 2xm, aromatic C-H) (Figure 39); *m/z* (MALDI-TOF) 340, 342, 344 ($M.H^+$).

1-(2′,4′-Dichlorophenyl)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-56)**

1.38 g, 75% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless needles. ^1H NMR (D_2O) δ_H 5.95 and 6.02 (2x1H, 2xs, H-2

major and minor), 7.15-7.25 (8H, m, aromatic C-H); *m/z* (MALDI-TOF) 334, 336, 338 ($M.H^+$).

1-(3′,4′-Dichlorophenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-57)**

7.08 g, 76% yield (30 mmol scale), purified by recrystallization from methanol-water and obtained as colorless needles. Anal. Calcd. for $C_{10}H_{12}Cl_3N_5$ + HCl + H_2O: C, 33.1; H, 4.2; N, 19.3%. Found: C, 33.4; H, 4.3; N, 19.0%. ^{1}H NMR (D_2O) δ_H 1.18 (3H, d, J = 6.5 Hz, $C\underline{H}_3$-2), 5.04 (1H, q, J = 6.5 Hz, $\underline{H}$-2), 7.15 (1H, dd, J = 8.5, 2.6 Hz, aromatic C-H) and 7.50 (2H, m, aromatic C-H); *m/z* (MALDI-TOF) 272, 274, 276 ($M.H^+$).

1-(3′,4′-Dichlorophenyl)-2-ethyl-4.6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-58)**

1.28 g, 91% yield (4.4 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. Anal. Calcd. for $C_{11}H_{14}Cl_3N_5$: C, 40.8; H, 4.4; N, 21.7%. Found: C, 40.8; H, 4.4; N, 21.7%. ^{1}H NMR (D_2O) δ_H 0.72 (3H, t, J = 7.0 Hz, $C\underline{H}_3CH_2$-2), 1.56 (2H, m, $CH_3C\underline{H}_2$-2), 4.84 (1H, dd, J = 6.0, 4.0 Hz, $\underline{H}$-2), 7.18 (1H, dd, J = 8.5, 2.5 Hz, aromatic C-H) and 7.52 (2H, m, aromatic C-H); *m/z* (MALDI-TOF) 286, 288, 290 ($M.H^+$).

1-(3′,4′-Dichlorophenyl)-2-propyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-59)**

1.21 g, 82% yield (4.4 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.70 (3H, t, J = 7.0 Hz, $C\underline{H}_3CH_2CH_2$-2), 1.20 (2H, m, $CH_3C\underline{H}_2CH_2$-2), 1.58 (2H, m, $CH_3CH_2C\underline{H}_2$-2), 4.91 (1H, dd, J = 8.4, 2.4 Hz, aromatic C-H) and 7.56 (2H, m, aromatic C-H); *m/z* (MALDI-TOF) 300, 302, 304 ($M.H^+$).

1-(3′,4′-Dichlorophenyl)-2-isopropyl-4.6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-60)**

1.17 g, 79% yield (4.4 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (D_2O) δ_H 0.70 and 0.80

(2x3H, 2xd, J = 7.0 Hz, $CH(C\underline{H}_3)_2$-2), 1.92 (1H, m, $C\underline{H}(CH_3)_2$-2), 4.79 (1H, d, J = 2.2 Hz, $\underline{H}$-2), 7.25 (1H, dd, J = 8.5, 2.4 Hz, aromatic C-H) and 7.58 (2H, m, aromatic C-H); m/z (MALDI-TOF) 300, 302, 304 ($M.H^+$).

1-(3′,4′-Dichlorophenyl)-2-butyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-61)**

1.50 g, 97% yield (4.4 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^1H NMR (D_2O) δ_H 0.66 (3H, t, J = 6.8 Hz, $C\underline{H}_3(CH_2)_3$-2), 1.12 (4H, m, $CH_3(C\underline{H}_2)_2CH_2$-2), 1.60 (2H, m, $CH_3(CH_2)_2C\underline{H}_2$-2), 4.94 (1H, dd, J = 6.0, 4.0 Hz, $\underline{H}$-2), 7.22 (1H, dd, J = 8.5, 2.5 Hz, aromatic C-H) and 7.56 (2H, m, aromatic C-H) (Figure 40); *m/z* (MALDI-TOF) 314, 316, 318 ($M.H^+$).

1-(3′,4′-Dichlorophenyl)-2-pentyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-62)**

1.52 g, 84% yield (5 mmol scale), purified by recrystallization from ethanol and obtained as colorless needles. ^1H NMR (D_2O) δ_H 0.63 (3H, t, J = 6.5 Hz, $C\underline{H}_3(CH_2)_4$-2), 1.12 (6H, m, $CH_3(C\underline{H}_2)_3CH_2$-2), 1.57 (2H, m, $CH_3(CH_2)_3C\underline{H}_2$-2), 4.91 (1H, dd, J = 6.0, 4.0 Hz, $\underline{H}$-2), 7.21 (1H, dd, J = 8.6, 2.4 Hz, aromatic C-H) and 7.54 (2H, m, aromatic C-H) (Figure 41); *m/z* (MALDI-TOF) 328, 330, 332 ($M.H^+$).

1-(3′,4′-Dichlorophenyl)-2-heptyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-63)**

0.71 g, 36% yield (5 mmol scale), purified by recrystallization from ethanol and obtained as colorless needles. ^1H NMR (D_2O) δ_H 0.63 (3H, t, J = 6.6 Hz, $C\underline{H}_3(CH_2)_6$-2), 1.01 (10H, m, $CH_3(C\underline{H}_2)_5CH_2$-2), 1.53 (2H, m, $CH_3(CH_2)_5C\underline{H}_2$-2), 4.88 (1H, dd, J = 6.0, 4.0 Hz, $\underline{H}$-2), 7.22 (1H, dd, J = 8.5, 2.5 Hz, aromatic C-H) and 7.53 (2H, m, aromatic C-H) (Figure 42); *m/z* (MALDI-TOF) 356, 358, 360 ($M.H^+$).

1-(3′,4′-Dichlorophenyl)-2-cyclohexyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-64)**

1.52 g, 81% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as white crystalline solids. ^1H NMR (D_2O) δ_H 1.01 (4H, m,

2xcyclohexyl C<u>H</u>$_2$), 1.26 (1H, m, cyclohexyl C<u>H</u>), 1.60 (6H, m, 3xcyclohexyl C<u>H</u>$_2$), 4.72(1H, d, J = 2.2 Hz, <u>H</u>-2), 7.22 (1H, dd, J = 6.0, 4.0 Hz, aromatic C-H) and 7.56 (2H, m, aromatic C-H) (Figure 43); *m/z* (MALDI-TOF) 304, 342, 344 ($M.H^+$).

<u>1-(3′,4′-Dichlorophenyl)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-65)**

1.85 g, 100% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless needles. Anal. Calcd. for $C_{15}H_{14}Cl_3N_5$: C, 48.6; H, 3.8; N, 18.9%. Found: C, 48.7; H, 4.0; N, 18.7%. ^{1}H NMR (D_2O) δ_H 5.89 (1H, s, <u>H</u>-2), 6.90 (1H, dd, J = 8.0, 2.5 Hz, aromatic C-H), 7.15 (5H, m, aromatic C-H), 7.30 (2H, m, aromatic C-H); *m/z* (MALDI-TOF) 334, 336, 338 ($M.H^+$).

<u>1-(4′-Ethylphenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-20)**

TLC and biguanide test indicated that no reaction had occurred.

<u>1-(3′-Chlorophenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-41)**

No reaction had occurred (according to TLC and biguanide test).

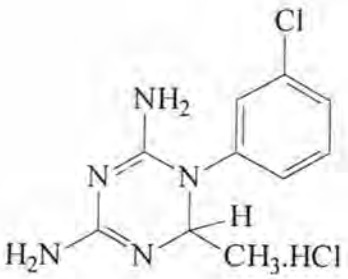
<u>1-(3′-Chlorophenyl)-2-pentyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-46)**

TLC and biguanide test indicated that no reaction had occurred.

<u>1-(3′-Chlorophenyl)-2-heptyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride</u> **(II-47)**

No reaction had occurred (according to TLC and biguanide test).

Attempted synthesis of 1-(3′-chlorophenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-41)**



Method A

To a suspension of 3-chlorophenylbiguanide hydrochloride **(I-6)** (1 mmol) in an appropriate volume of absolute methanol (5 mL) was added acetaldehyde (5 mmol), triethyl orthoacetate (0.75 mL) and conc. HCl (0.023 mL) respectively. The reaction mixture was stirred at room temperature for 72 hours. TLC and biguanide test indicated that no reaction had occurred.

Method B

To a suspension of 3-chlorophenylbiguanide hydrochloride **(I-6)** (1 mmol) in acetaldehyde dimethylacetal (0.91 mL) was added conc. HCl (0.023 mL). The reaction mixture was stirred at room temperature for 24 hours. TLC and biguanide test indicated no reaction had occurred. Absolute methanol (1 mL) was then added in the reaction. After stirring overnight, TLC and biguanide test indicated on reaction had occurred. The reaction was heated to reflux for 3 hours. No reaction had occurred (according to TLC and biguanide test).

Method C

To a suspension of 3-chlorophenylbiguanide hydrochloride **(I-6)** (1 mmol) in an appropriate volume of absolute methanol (2 mL) was added acetaldehyde dimethylacetal (1 mL) and conc. HCl (0.023 mL). The reaction mixture was heated to reflux for 6 hours but no reaction had occurred (according to TLC and biguanide test).

Method D

To a suspension of 3-chlorophenylbiguanide hydrochloride **(I-6)** (1 mmol) in an appropriate volume of absolute methanol (5 mL) was added acetaldehyde dimethylacetal (5 mmol), triethyl orthoacetate (0.5 mL) and conc. HCl (0.023 mL)

respectively. The reaction mixture was heated to reflux for 26 hours. TLC and biguanide test indicated that no reaction had occurred.

Method E

To a suspension of the 3-chlorophenylbiguanide hydrochloride **(I-6)** (5 mmol) in an appropriate volume of absolute isopropanol (5 mL) containing conc. HCl (0.069 mL) was added acetaldehyde (15 mmol). The reaction mixture was stirred at room temperature until a negative biguanide test was obtained (24 hours). On cooling in the refrigerator, a white crystalline solid precipitated which was collected by filtration and washed with isopropanol, acetone then Et_2O and air dried (1.04 g, 76% yield). The product was purified by recrystallization from ethanol-diethyl ether and obtained as colorless rosettes. Anal. Calcd. For $C_{10}H_{13}Cl_2N_5$: C, 43.8; H, 4.8; N, 25.6%. Found: C, 43.9; H, 4.7; N, 25.4%. ^{1}H NMR (D_2O) δ_H 1.24 (3H, d, J = 6.0 Hz, C<u>H</u>$_3$-2), 5.08 (1H, q, J = 6.0 Hz, <u>H</u>-2), 7.18 and 7.36 (4H, 2xm, aromatic C-H); *m/z* (MALDI-TOF) 238, 240 ($M.H^+$).

Synthesis of 1-(4'-methylphenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-13)**

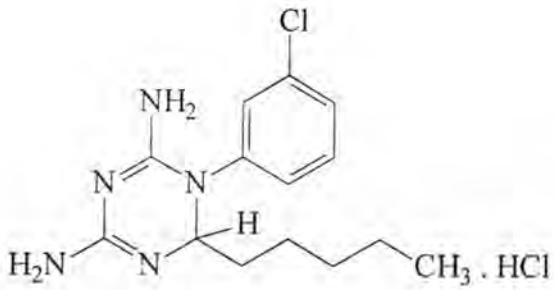
0.64 g, 51% yield (5 mmol scale) of 1-(4'-methylphenyl)-2-methyl-4,6-diamio-1,2-dihydro-1,3,5-triazine hydrochloride **(II-13)** was obtained as described above. It was purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. Anal. Calcd. For $C_{11}H_{16}ClN_5$ + HCl + 0.5 H_2O: C, 44.1; H, 6.0; N, 23.4%. Found: C, 43.8; H, 6.20; N, 22.8%. ^{1}H NMR (D_2O) δ_H 1.18 (3H, d, J = 6.5 Hz, C<u>H</u>$_3$-2), 2.15 (3H, s, C<u>H</u>$_3$-4'), 5.05 (1H, q, J = 6.5 Hz, <u>H</u>-2), 7.08 and 7.20 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H) (Figure 6); *m/z* (MALDI-TOF) 218 ($M.H^+$).

Synthesis of 1-(4'-ethylphenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-20)**

0.58 g, 43% yield (5 mmol scale) of 1-(4'-ethylphenyl)-2-methyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-20)** was obtained as described above. It was purified by recrystallization from ethanol-diethyl ether and obtained as colorless needles. Anal. Calcd. for $C_{12}H_{18}ClN_5$: C, 53.8; H, 6.7; N, 26.1%. Found: C, 53.8; H, 6.6, N, 26.1%. ^{1}H NMR (D_2O) δ_H 1.01 (3H, t, J = 7.0 Hz, C<u>H</u>$_3$CH$_2$-4'), 1.16 (3H, d, J

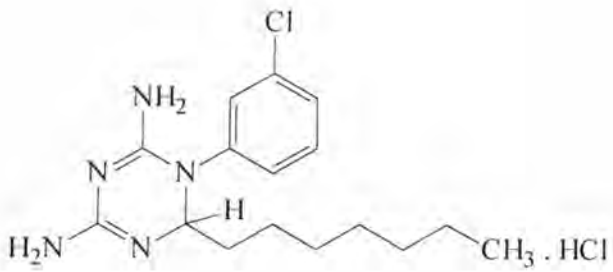
= 5.9 Hz, C<u>H</u>$_3$-2), 2.05 (2H, q, J = 7.4 Hz, $CH_3C\underline{H}_2$-4'), 4.93 (1H, q, J = 6.4 Hz, <u>H</u>-2), 7.13 and 7.24 (2x2H, AB doublet, J = 8.2 Hz, aromatic C-H) (Figure 13); *m/z* (MALDI-TOF) 232 ($M.H^+$).

Synthesis of 1-(3'-chlorophenyl)-2-pentyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-46)**



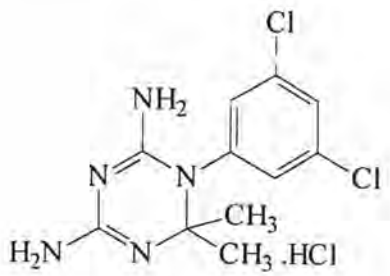
A suspension of the 3-chlorophenylbiguanide hydrochloride **(I-6)** (5 mmol) in an appropriate volume of absolute isopropanol (3.4 mL) containing conc. HCl (0.42 mL) was added 1-hexanal (10 mmol). The reaction mixture was heated to reflux until a negative biguanide test was obtained (3 hours). On cooling in the refrigerator, the precipitated solid was filtered, washed with isopropanol, acetone the Et_2O and air dried (0.92 g, 56% yield). The product was purified by recrystallization from methanol-diethyl ether and obtained as white crystalline solids. ^1H NMR (D_2O) δ_H 0.62 (3H, t, J = 6.3 Hz, C<u>H</u>$_3$(CH$_2$)$_4$-2), 1.10 (6H, m, CH$_3$(C<u>H</u>$_2$)$_3$CH$_2$-2), 1.58 (2H, m, CH$_3$(CH$_2$)$_3$C<u>H</u>$_2$-2), 4.95 (1H, dd, J = 6.9, 3.6 Hz, H-2), 7.22 and 7.37 (4H, 2xm, aromatic C-H) (Figure 31); *m/z* (MALDI-TOF) 294, 296 ($M.H^+$).

Synthesis of 1-(3'-chlorophenyl)-2-heptyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-47)**



0.69 g, 39% yield (5 mmol scale) of 1-(3′-chlorophenyl)-2-heptyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-47)** was obtained as described above. It was purified by recrystallization from methanol-diethyl ether and obtained as white crystalline solids. ^{1}H NMR (D_2O) δ_H 0.61 (3H, t, J = 6.6 Hz, $C\underline{H}_3(CH_2)_6$-2), 1.00 (10H, m, $CH_3(C\underline{H}_2)_5CH_2$-2), 1.59 (2H, m, $CH_3(CH_2)_5C\underline{H}_2$-2), 4.94 (1H, dd, J = 6.7, 3.7 Hz, H-2), 7.20 and 7.36 (4H, 2xm, aromatic C-H) (Figure 32); *m/z* (MALDI-TOF) 322, 324 ($M.H^+$).

Attempted synthesis of 1-(3′,5′-dichlorophenyl)-2,2-dimethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-5)**



Method A

To a suspension of 3,5-dichloroaniline (10 mmol) in an appropriate volume of absolute ethanol (3 mL) containing dicyanodiamide (10 mmol), acetone (12 mL) and conc. HCl (0.90 mL) was stirred at room temperature for 6 hours. TLC analysis indicated that no reaction had occurred.

Method B

A suspension of 3,5-dichlorophenylbiguanide hydrochloride **(I-11)** (5 mmol) in an appropriate volume of absolute methanol (2.85 mL) containing acetone (7.14 mL) and conc. HCl (0.21 mL) was stirred at room temperature for 2 days. TLC and biguanide test indicated that no reaction had occurred.

Method C

To a suspension of 3,5-dichlorophenylbiguanide hydrochloride **(I-11)** (5 mmol) in an appropriate volume of absolute methanol (5 mL) was added acetone (0.37 mL, 5 mmol), triethyl orthoacetate (0.75 mL) and conc. HCl (0.023 mL)

respectively. The reaction mixture was stirred at room temperature for 2 days. TLC and biguanide test indicated that no reaction had occurred.

Attempted synthesis of 1-(3',4'-methylenedioxyphenyl)-2,2-dimethyl-4,6-diamino-1,2-dihyro-1,3,5-triazine hydrochloride **(II-66)**

Similar procedures as described above were employed in the synthesis of 1-(3',4'-methylenedioxyphenyl)-2,2-dimethyl-4,6-diamino-1,2-dihyro-1,3,5-triazine hydrochloride **(II-66)**, 3,5-dichlorophenylbiguanide hydrochloride **(I-11)** being replaced by 3,4-methylenedioxyphenylbiguanide hydrochloride **(II-12)**. TLC and biguanide test indicated that no reaction had occurred.

Attempted synthesis of 1-(4'-chloro-3'-nitrophenyl)-2,2-dimethyl-4,6-diamino-1,2-dihyro-1,3,5-triazine hydrochloride **(II-4)**

Similar procedures as described above were employed in the synthesis of 1-(4'-chloro-3'-nitrophenyl)-2,2-dimethyl-4,6-diamino-1,2-dihyro-1,3,5-triazine hydrochloride **(II-4)**, 3,5-dichlorophenylbiguanide hydrochloride **(I1-1)** being replaced by 4-chloro-3-nitrophenylbiguanide hydrochloride **(I-9)**. TLC and biguanide test indicated the no reaction had occurred.

Attempted synthesis of 1-(4'-Chloro-3'-nitrophenyl)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-67)**

To a suspension of 4-chloro-3-nitrophenylbiguanide hydrochloride **(I-9)** (1 mmol) in 5 mL of absolute methanol was added benzaldehyde (5 mmol), triethyl orthoacetate (0.75 mL) and conc. HCl (0.023 mL) respectively. The reaction mixture was stirred at room temperature for 3 hours. TLC and biguanide test indicated that no reaction had occurred.

2.3 Synthesis of 1-alkyl-4,6-diamino-1,2-dihydro-1,3,5-triazines

Synthesis of benzylamine hydrochloride **(I-13a)**

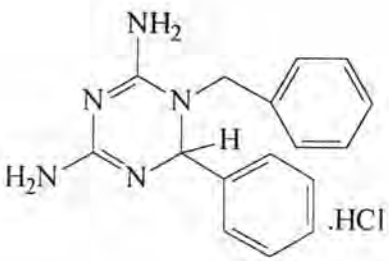
Benzylamine (10.9 mL, 100 mmol) was slowly added to conc. HCl (8.72 mL, 100 mmol) and stirred at room temperature to give a white solid. The solid was

collected by filtration, washed with acetone, ether and air dried (8.08 g, 56% yield). ^{1}H NMR (D_2O) δ_H 3.98 (2H, s, C$\underline{H_2}$), 7.27 (5H, s, aromatic C-H).

Synthesis of benzylbiguanide hydrochloride **(I1-3)**

Benzylamine hydrochloride **(I1-3a)** (100 mmol) and dicyanodiamide (100 mmol) were intimately mixed in a round-bottomed flask and heated at 153-165 °C (temperature of the mixture) for 2 hours. Trituration with acetone gave a product as a white solid. The solid was collected by filtration, washed with acetone, ether and air dried (1.98 g, 87% yield). ^{1}H NMR (D_2O) δ_H 4.25 (2H, s, C$\underline{H_2}$), 7.20 (5H, s, aromatic C-H).

Attempted synthesis of 1-benzyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-68)**



Method A

To a suspension of the benzylbiguanide hydrochloride **(I-13)** (5 mmol) in an appropriate volume of absolute ethanol (3.4 mL) containing conc. HCl (0.42 mL) was added the benzaldehyde (10 mmol). The reaction mixture was heated to reflux for 2 hours. No reaction had occurred according to TLC and biguanide test.

Method B

A suspension of the benzylbiguanide hydrochloride **(I-13)** (1 mmol) in absolute methanol (5 mL) was added benzaldehyde (5 mmol), triethyl orthoacetate (0.75 mmol) and conc. HCl (0.023 mL) respectively. The reaction mixture was stirred at room temperature for 3 days. TLC and biguanide test indicated that no reaction had occurred.

Method C

To a suspension of the benzylbiguanide hydrochloride **(I-13)** (1 mmol) in an appropriate volume of absolute ethanol (3.4 mL) containing conc. HCl (0.23 mL) was added benzaldehyde (10 mmol). The reaction mixture was heated to reflux for 5 hours. No reaction had occurred according to TLC and biguanide test.

Attempted synthesis of 1-benzyl-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-69)**

Similar procedures as described above were employed in the synthesis of 1-benzyl-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-69)**, benzaldehyde being replaced by isobutyraldehyde. TLC and biguanide test indicated that no reaction had occurred.

Attempted synthesis of 1-benzyl-2-butyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-70)**

Similar procedures as described above were employed in the synthesis of 1-benzyl-2-butyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-70)**, benzaldehyde being replaced by valeraldehyde. No reaction had occurred according to TLC and biguanide test.

Attempted synthesis of 1-benzyl-2-ethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-71)**

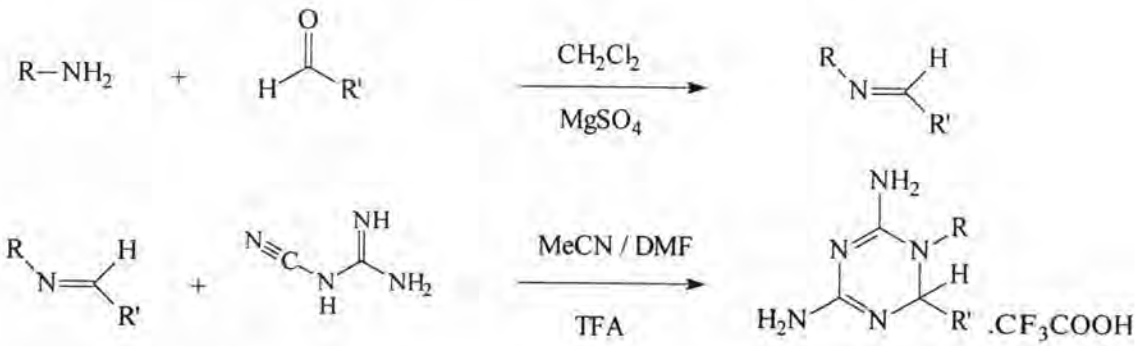
To a suspension of the benzylbiguanide hydrochloride **(I-13)** (1 mmol) in an appropriate volume of absolute isopropanol (5 mL) was added conc. HCl (0.023 mL) and propionaldehyde (0.36 mL, 5 mmol). The reaction mixture was stirred at room temperature for 3 days. TLC and biguanide test indicated that no reaction had occurred.

Attempted synthesis of 1-benzyl-2,2-dimethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-72)**

A suspension of the benzylbiguanide hydrochloride **(I-13)** (1 mmol) in absolute methanol (5 mL) was added acetone (0.37 mL, 5 mmol), triethyl orthoacetate (0.75 mL) and conc. HCl (0.023 mL) respectively. The reaction mixture was stirred at

room temperature for 3 days. No reaction had occurred according to TLC and biguanide test.

2.3.1 Synthesis of 1-alkyl-4,6-diamino-1,2-dihydro-1,3,5-triazine by the reaction of Schiff Bases with dicyanodiamide.



General Procedure

A suspension of the amine (5 mmol) and aromatic aldehyde (5 mmol) in dichloromethane (3 mL) containing $MgSO_4$ was stirred at room temperature until complete disappearance of starting material (1-4 days) was observed. $MgSO_4$ was then removed by filtration. The filtrate was evaporated under reduced pressure to give an imine. Acetronitrile (3 mL) and trifluoroacetic acid (5 mmol, 0.38 mL) were added to the imine and the reaction was stirred at room temperature for 10 min. Dicyanodiamide (5 mmol) and DMF (1.8 mL) were then added to the reaction and the stirring was continued at room temperature for 1-5 days. Ether was added to precipitate the product as trifluoroacetate salt, which was collected by filtration, washed with ether and air dried.

1-Benzyl-2-(2'-methoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-73)**

1.62 g, 76% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless prisms. ^{1}H NMR (DMSO) δ_H 3.79 (3H, s, OC<u>H</u>$_3$-2'), 4.15 and 4.94 (2x1H, 2xd, J = 16.7 Hz, benzyl C<u>H</u>$_2$), 5.81 (1H, s, <u>H</u>-2), 7.08 and 7.25 (4H, 2xm, aromatic C-H), 7.38 (5H, m, aromatic C-H), 7.76 and 8.53 (3H, br m, N<u>H</u>) (Figure 44); *m/z* (MALDI-TOF) 310 ($M.H^+$).

1-Benzyl-2-(3′-methoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-74)**

1.35 g, 74% yield (4.9 mmol scale), purified by recrystallization from methanol-water and obtained as colorless prisms. ^{1}H NMR (DMSO) δ_H 3.74 (3H, s, OC<u>H</u>$_3$-3′), 4.27 and 5.00 (2x1H, 2xd, J = 16.7 Hz, benzyl C<u>H</u>$_2$), 5.71 (1H, s, <u>H</u>-2), 6.86 (2H, m, aromatic C-H) 6.97 and 7.28 (2H, 2xm, aromatic C-H), 7.40 (5H, m, aromatic C-H), 7.78 and 9.14 (3H, br m, N<u>H</u>) (Figure 45); *m/z* (MALDI-TOF) 310 (M.H$^+$).

1-Benzyl-2-(4′-methoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-75)**

1.36 g, 64% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless prisms. ^{1}H NMR (DMSO) δ_H 3.75 (3H, s, OC<u>H</u>$_3$-4′), 4.19 and 4.96 (2x1H, 2xd, J = 16.7 Hz, benzyl C<u>H</u>$_2$), 5.65 (1H, s, <u>H</u>-2), 6.99 and 7.26 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H), 7.25-7.46 (5H, m, aromatic C-H), 7.76 and 9.14 (3H, br m, N<u>H</u>) (Figure 46); *m/z* (MALDI-TOF) 310 (M.H$^+$).

1-Benzyl-2-(2′,4′-dimethoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-76)**

1.10 g, 50% yield (4.9 mmol scale), purified by recrystallization from methanol-water and obtained as brown rosettes. ^{1}H NMR (DMSO) δ_H 3.76 (2x3H, s, OC<u>H</u>$_3$-2′ and 4′), 4.11 and 4.93 (2x1H, 2xd, J = 16.6 Hz, benzyl C<u>H</u>$_2$), 5.72 (1H, s, <u>H</u>-2), 6.50-6.63 (2H, m, aromatic C-H) and 7.00 (1H, d, J = 8.3 Hz, aromatic C-H), 7.22-7.44 (5H, m, aromatic C-H), 7.72 and 8.66 (3H, br m, N<u>H</u>) (Figure 47); *m/z* (MALDI-TOF) 340 (M.H$^+$).

1-Benzyl-2-(2′,5′-dimethoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-77)**

1.67 g, 74% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 3.70 and 3.74 (2x3H, 2xs, OC<u>H</u>$_3$-2′ and 5′), 4.18 and 4.93 (2x1H, 2xd, J = 16.7 Hz, benzyl C<u>H</u>$_2$), 5.78 (1H, s, <u>H</u>-2), 6.61 and 6.99 (2x1H, 2xd, J = 2.7 Hz, aromatic C-H) 7.02 (1H, s, aromatic C-H), 7.23-7.43 (5H, m, aromatic C-H), 7.76 and 8.50 (2H, br m, N<u>H</u>) (Figure 48); *m/z* (MALDI-TOF) 340 (M.H$^+$).

1-Benzyl-2-(3′,4′-dimethoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-78)**

1.27 g, 57% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless prisms. ^{1}H NMR (DMSO) δ_H 3.71 and 3.75 (2x3H, 2xs, OC<u>H</u>$_3$-3′ and 4′), 4.25 and 4.96 (2x1H, 2xd, J = 16.8 Hz, benzyl C<u>H</u>$_2$), 5.66 (1H, s, <u>H</u>-2), 6.82 and 7.00 (2x1H, 2xd, J = 8.3 Hz, aromatic C-H) and 6.95 (1H, s, aromatic C-H), 7.25-7.46 (5H, m, aromatic C-H), 7.76 and 9.18 (2H, br m, N<u>H</u>) (Figure 49); *m/z* (MALDI-TOF) 340 (M.H$^+$).

1-Benzyl-2-(3′,5′-dimethoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-79)**

1.66 g, 74% yield (4.9 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless prisms. ^{1}H NMR (DMSO) δ_H 3.73 (2x3H, s, OC<u>H</u>$_3$-3′ and 5′), 4.27 and 4.98 (2x1H, 2xd, J = 16.7 Hz, benzyl C<u>H</u>$_2$), 5.64 (1H, s, <u>H</u>-2), 6.44 (2H, s, aromatic C-H) and 6.55 (1H, s, aromatic C-H), 7.25-7.45 (5H, m, aromatic C-H), 7.76 (2H, br m, N<u>H</u>) (Figure 50); *m/z* (MALDI-TOF) 340 (M.H$^+$).

1-Benzyl-2-(3′,4′,5′-trimethoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-80)**

1.57 g, 65% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless prisms. ^{1}H NMR (DMSO) δ_H 3.65 (3H, s, OC<u>H</u>$_3$-4′) and 3.73 (2x3H, s, OC<u>H</u>$_3$-3′ and 5′), 4.32 and 4.93 (2x1H, 2xd, J = 16.8 Hz, benzyl C<u>H</u>$_2$), 5.67 (1H, s, <u>H</u>-2), 6.59 (2H, s, aromatic C-H), 7.23-7.42 (5H, m, aromatic C-H), 7.77 and 8.92 (2H, br m, N<u>H</u>) (Figure 51); *m/z* (MALDI-TOF) 370 (M.H$^+$).

1-Benzyl-2-(3′-fluorophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-81)**

1.32 g, 71% yield (4.5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless rosettes. ^{1}H NMR (DMSO) δ_H 4.34 and 5.00 (2x1H, 2xd, J = 16.8 Hz, benzyl C<u>H</u>$_2$), 5.79 (1H, s, <u>H</u>-2), 7.09-7.17 (1H, m, aromatic C-H), 7.29-7.37 (5H, m, aromatic C-H), 7.39-7.53 (3H, m, aromatic C-H), 7.81 and 9.03 (3H, br m, N<u>H</u>) (Figure 52); *m/z* (MALDI-TOF) 298 (M.H$^+$).

1-Benzyl-2-(4′-fluorophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-82)**

1.07 g, 52% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (DMSO) δ_H 4.72 and 4.95 (2x1H, 2xd, J = 16.8 Hz, benzyl C$\underline{H}_2$), 5.72 (1H, s, $\underline{H}$-2), 7.26 and 7.38 (2x2H, AB doublet, J = 7.3 Hz, aromatic C-H), 7.34 (5H, m, aromatic C-H), 7.79 and 8.72 (2H, br m, N$\underline{H}$) (Figure 53); *m/z* (MALDI-TOF) 298 (M.H$^+$).

1-Benzyl-2-(2′-chlorophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-83)**

1.13 g, 58% yield (4.5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 4.17 and 4.95 (2x1H, 2xd, J = 16.6 Hz, benzyl C$\underline{H}_2$), 5.92 (1H, s, $\underline{H}$-2), 7.22-7.38 (5H, m, aromatic C-H), 7.42-7.54 (4H, m, aromatic C-H), 7.95 and 9.10 (3H, br m, N$\underline{H}$) (Figure 54); *m/z* (MALDI-TOF) 314, 316 (M.H$^+$).

1-Benzyl-2-(3′-chlorophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-84)**

1.61 g, 54% yield (7 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 4.35 and 5.02 (2x1H, 2xd, J = 16.8 Hz, benzyl C$\underline{H}_2$), 5.82 (1H, s, $\underline{H}$-2), 7.24-7.36 (5H, m, aromatic C-H), 7.43-7.55 (4H, m, aromatic C-H), 7.84 and 9.26 (3H, br m, N$\underline{H}$) (Figure 55); *m/z* (MALDI-TOF) 314, 316 (M.H$^+$).

1-Benzyl-2-(4′-chlorophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-85)**

1.45 g, 68% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 4.28 and 4.99 (2x1H, 2xd, J = 16.7 Hz, benzyl C$\underline{H}_2$), 5.77 (1H, s, $\underline{H}$-2), 7.24-7.44 (5H, m, aromatic C-H), 7.31 and 7.51 (2x2H, AB doublet, J = 8.7 Hz, aromatic C-H), 7.81 and 9.21 (3H, br m, N$\underline{H}$) (Figure 56); *m/z* (MALDI-TOF) 314, 316 (M.H$^+$).

1-Benzyl-2-(2',4'-dichlorophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-86)**

1.31 g, 57% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 4.22 and 4.92 (2x1H, 2xd, J = 16.6 Hz, benzyl C$\underline{H}_2$), 5.91 (1H, s, $\underline{H}$-2), 7.20-7.41 (5H, m, aromatic C-H), 7.54 (2H, dd, J = 8.3, 2.1 Hz, aromatic C-H), 7.68 (1H, s, aromatic C-H), 7.97 and 9.17 (3H, br m, N$\underline{H}$) (Figure 57); *m/z* (MALDI-TOF) 348, 350, 352 ($M.H^+$).

1-Benzyl-2-(2',6'-dichlorophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-87)**

1.51 g, 66% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 4.13 and 4.67 (2x1H, 2xd, J = 17.5 Hz, benzyl C$\underline{H}_2$), 6.50 (1H, s, $\underline{H}$-2), 7.12-7.34 (5H, m, aromatic C-H), 7.39-7.49 (3H, m, aromatic C-H), 7.77 and 8.92 (3H, br m, N$\underline{H}$) (Figure 58); *m/z* (MALDI-TOF) 348, 350, 352 ($M.H^+$).

1-Benzyl-2-(3',4'-dichlorophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-88)**

1.50 g, 66% yield (4.9 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as white crystalline solids. ^{1}H NMR (DMSO) δ_H 4.37 and 4.97 (2x1H, 2xd, J = 16.7 Hz, benzyl C$\underline{H}_2$), 5.80 (1H, s, $\underline{H}$-2), 7.24-7.44 (5H, m, aromatic C-H), 7.52 (1H, s, aromatic C-H) 7.72 and 7.76 (2x1H, 2xs, aromatic C-H), 7.85 and 8.86 (2H, br m, N$\underline{H}$) (Figure 59); *m/z* (MALDI-TOF) 348, 350, 352 ($M.H^+$).

1-Benzyl-2-(2'-bromophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-89)**

1.09 g, 45% yield (5.2 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 4.12 and 4.95 (2x1H, 2xd, J = 16.6 Hz, benzyl C$\underline{H}_2$), 5.86 (1H, s, $\underline{H}$-2), 7.21-7.42 (7H, m, aromatic C-H) 7.48 and 7.67 (2x1H, 2xd, J = 7,8 Hz, aromatic C-H), 7.97 and 9.05 (3H, br m, N$\underline{H}$) (Figure 60); *m/z* (MALDI-TOF) 358, 360$M.H^+$).

1-Benzyl-2-(4′-bromophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine tifluoroacetate **(II-90)**

1.49 g, 64% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless needles. ^{1}H NMR (DMSO) δ_H 4.28 and 4.98 (2x1H, 2xd, J = 16.7 Hz, benzyl C$\underline{H}_2$), 5.75 (1H, s, $\underline{H}$-2), 7.24-7.49 (5H, m, aromatic C-H), 7.38 and 7.66 (2x2H, AB doublet, J = 7.9 Hz, aromatic C-H), 7.81 and 9.10 (2H, br m, N$\underline{H}$) (Figure 61); *m/z* (MALDI-TOF) 358, 360 ($M.H^+$).

1-Benzyl-2-(3′-nitrophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-91)**

1.75 g, 80% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as pale yellow prisms. ^{1}H NMR (DMSO) δ_H 4.43 and 5.00 (2x1H, 2xd, J = 16.5 Hz, benzyl C$\underline{H}_2$), 5.97 (1H, s, $\underline{H}$-2), 7.24-7.42 (5H, m, aromatic C-H), 7.74 (2H, m, aromatic C-H) 8.13 (1H, s, aromatic C-H) and 8.25 (1H, dd, J = 5.82, 3.45 Hz, aromatic C-H), 7.49 and 8.13 (2H, br m, N$\underline{H}$) (Figure 62); *m/z* (MALDI-TOF) 325 ($M.H^+$).

1-Benzyl-2-(4′-nitrophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-92)**

1.55 g, 71% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as white microcrystalline solids. ^{1}H NMR (DMSO) δ_H 4.38 and 5.01 (2x1H, 2xd, J = 16.4 Hz, benzyl C$\underline{H}_2$), 5.93 (1H, s, $\underline{H}$-2), 7.25-7.43 (5H, m, aromatic C-H), 7.56 and 8.31 (2x2H, AB doublet, J = 8.7 Hz, aromatic C-H), 7.89 and 8.98 (2H, br m, N$\underline{H}$) (Figure 63); *m/z* (MALDI-TOF) 325 ($M.H^+$).

1-Benzyl-2-(4′-cyanophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-93)**

1.69 g, 82% yield (5 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless crystals. ^{1}H NMR (DMSO) δ_H 4.36 and 5.00 (2x1H, 2xd, J = 16.6 Hz, benzyl C$\underline{H}_2$), 5.87 (1H, s, $\underline{H}$-2), 7.25-7.43 (5H, m, aromatic C-H), 7.48 and 7.94 (2x2H, AB doublet, J = 8.2 Hz, aromatic C-H), 7.86 and 9.04 (2H, br m, N$\underline{H}$) (Figure 64); *m/z* (MALDI-TOF) 305 ($M.H^+$).

1-Benzyl-2-(2′-chloro-5′-nitrophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-94)**

1.63 g, 71% yield (4.9 mmol scale), purified by recrystallization from methanol-water and obtained as yellow rosettes. ^{1}H NMR (DMSO) δ_H 4.42 and 4.88 (2x1H, 2xd, J = 16.5 Hz, benzyl C$\underline{H}_2$), 6.09 (1H, s, $\underline{H}$-2), 7.20-7.30 (5H, m, aromatic C-H), 7.79 (1H, d, J = 8.7 Hz, aromatic C-H) 7.96 (1H, d, J = 2.6 Hz, aromatic C-H) and 8.23 (1H, dd, J = 8.7, 2.6 Hz, aromatic C-H), 8.08 and 9.22 (3H, br m, N$\underline{H}$) (Figure 65); *m/z* (MALDI-TOF) 359, 361 (M.H$^+$).

1-Benzyl-2-(4′-chloro-3′-nitrophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-95)**

1.66 g, 73% yield (4.8 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as yellow prisms. ^{1}H NMR (DMSO) δ_H 4.42 and 4.97 (2x1H, 2xd, J = 16.7 Hz, benzyl C$\underline{H}_2$), 5.91 (1H, s, $\underline{H}$-2), 7.23-7.43 (5H, m, aromatic C-H), 7.58 (1H, dd, J = 8.4, 2.1 Hz, aromatic C-H) 7.88 (1H, d, J = 8.4 Hz, aromatic C-H) and 7.98 (1H, d, J = 2.0 Hz, aromatic C-H), 7.91 and 8.92 (2H, br m, N$\underline{H}$) (Figure 66); *m/z* (MALDI-TOF) 359, 361 (M.H$^+$).

1-Benzyl-2-(2′-chloro-6′-fluorophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-96)**

2.22 g, 100% yield (5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 4.20 and 4.76 (2x1H, 2xd, J = 17.1 Hz, benzyl C$\underline{H}_2$), 6.20 (1H, s, $\underline{H}$-2), 7.15-7.32 (5H, m, aromatic C-H), 7.34-7.45 (3H, m, aromatic C-H), 7.80 and 9.10 (3H, br m, N$\underline{H}$) (Figure 67); *m/z* (MALDI-TOF) 332, 334 (M.H$^+$).

1-Benzyl-2-(4′-*tert*-butylphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-97)**

1.53 g, 68% yield (5 mmol scale), purified by recrystallization from methanol and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 1.27 (9H, s, C(C$\underline{H}_3$)$_3$-4′), 4.24 and 4.90 (2x1H, 2xd, J = 16.7 Hz, benzyl C$\underline{H}_2$), 5.67 (1H, s, $\underline{H}$-2), 7.24 and 7.46 (2x2H, AB doublet, J = 8.0 Hz, aromatic C-H), 7.35 (5H, m, aromatic C-H), 7.74 and 8.94 (2H, br m, N$\underline{H}$) (Figure 68); *m/z* (MALDI-TOF) 336 (M.H$^+$).

1-Benzyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-98)**

1.06 g, 60% yield (4.5 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless prisms. ^{1}H NMR (DMSO) δ_H 4.26 and 4.98 (2x1H, 2xd, J = 16.7 Hz, benzyl C$\underline{H}_2$), 5.72 (1H, s, $\underline{H}$-2), 7.24-7.35 (5H, m, aromatic C-H), 7.39-7.48 (5H, m, aromatic C-H), 7.79 and 8.74 (2H, br m, N$\underline{H}$); *m/z* (MALDI-TOF) 280 (M.H$^+$).

1-Phenylethyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-99)**

1.19 g, 61% yield (4.8 mmol scale), purified by recrystallization from methanol-water and obtained as pale yellow leaflets. ^{1}H NMR (DMSO) δ_H 2.77 and 2.89 (2x1H, 2xtd, J_d = 14.8 Hz, J_t = 5.9 Hz, $CH_2C\underline{H}_2Ph$), 3.18 and 3.84 (2x1H, 2xtd, J_d = 14.8 Hz, J_t = 5.9 Hz, $C\underline{H}_2CH_2Ph$), 5.77 (1H, s, $\underline{H}$-2), 7.19-7.34 (5H, m, aromatic C-H), 7.38-7.47 (5H, m, aromatic C-H), 7.71 and 9.26 (3H, br m, N$\underline{H}$) (Figure 70); *m/z* (MALDI-TOF) 294 (M.H$^+$).

1-Phenylpropyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-100)**

0.74 g, 46% yield (3.9 mmol scale), purified by recrystallization from ethanol and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 1.71 and 1.84 (2x1H, 2xm, $CH_2C\underline{H}_2CH_2Ph$), 2.53 (2H, t, J = 7.0 Hz, $CH_2CH_2C\underline{H}_2Ph$), 3.06 and 3.56 (2x1H, 2xtd, J_d = 14.8 Hz, J_t = 5.9 Hz, $C\underline{H}_2CH_2CH_2Ph$), 5.78 (1H, s, $\underline{H}$-2), 7.10-7.15 and 7.39-7.46 (5H, m, aromatic C-H), 7.18-7.36 (5H, m, aromatic C-H), 7.67 and 8.99 (3H, br m, N$\underline{H}$) (Figure 71); *m/z* (MALDI-TOF) 308 (M.H$^+$).

1-Methoxypropyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-101)**

0.87 g, 51% yield (4.6 mmol scale), purified by recrystallization from ethanol and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 1.73 (2H, m, $CH_2C\underline{H}_2CH_2OCH_3$), 3.08 and 3.59 (2x1H, 2xtd, J_d = 14.9 Hz, J_t = 7.2 Hz, $C\underline{H}_2CH_2CH_2OCH_3$), 3.19 (3H, s, $OC\underline{H}_3$), 3.33 (2H, t, J = 7.2 Hz, $CH_2CH_2C\underline{H}_2OCH_3$), 5.74 (1H, s, $\underline{H}$-2), 7.27-7.36 (5H, m, aromatic C-H), 7.62 and 8.98 (3H, br m, N$\underline{H}$) (Figure 72); *m/z* (MALDI-TOF) 262 (M.H$^+$).

1-Propyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-102)**
0.95 g, 57% yield (4.9 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless crystals. ^{1}H NMR (DMSO) δ_H 0.82 (3H, t, J = 7.3 Hz, $CH_2CH_2C\underline{H}_3$), 1.51 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.96 and 3.50 (2x1H, 2xtd, J_d = 14.7 Hz, J_t = 7.2$_t$ Hz, $C\underline{H}_2CH_2CH_3$), 5.75 (1H, s, $\underline{H}$-2), 7.23-7.33 (2H, m, aromatic C-H) 7.42-7.50 (3H, m, aromatic C-H), 7.23, 8.26 and 8.66 (3H, br m, N$\underline{H}$) (Figure 73); *m/z* (MALDI-TOF) 232 ($M.H^+$).

1-Isopropyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-103)**
0.14 g, 9% yield (4.6 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless prisms. ^{1}H NMR (DMSO) δ_H 0.90 and 1.27 (2x3H, 2xd, J = 6.5 Hz, $CH(C\underline{H}_3)_2$) , 4.30 (1H, m, $C\underline{H}(CH_3)_2$), 5.92 (1H, s, $\underline{H}$-2), 7.29-7.42 (5H, m, aromatic C-H), 7.71 and 8.72 (3H, br m, N$\underline{H}$) (Figure 74); *m/z* (MALDI-TOF) 232 ($M.H^+$).

1-Isobutyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-104)**
0.91 g, 53% yield (4.8 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as white rosettes. ^{1}H NMR (DMSO) δ_H 0.87 and 0.92 (2x3H, 2xd, J = 6.5 Hz, $CH(C\underline{H}_3)_2$), 2.00 (1H, m, $C\underline{H}(CH_3)_2$), 2.75 and 3.55 (2x1H, 2xdd, J = 14.6, 8.4 Hz, $C\underline{H}_2$), 5.70 (1H, s, $\underline{H}$-2), 7.25-7.30 (3H, m, aromatic C-H) 7.39-7.47 (2H, m, aromatic C-H), 7.62 and 8.84 (2H, br m, N$\underline{H}$) (Figure 75); *m/z* (MALDI-TOF) 246 ($M.H^+$).

1-Heptyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-105)**
1.30 g, 82% yield (4 mmol scale), purified by recrystallization from methanol-diethyl ether and obtained as colorless crystals. ^{1}H NMR (DMSO) δ_H 0.83 (3H, t, J = 6.7 Hz, $(CH_2)_6C\underline{H}_3$) 1.14-1.58 (10H, m, $(C\underline{H}_2)_6CH_3$) 2.97 and 3.50 (2x1H, 2xtd, J_d = 14.8 Hz, J_t = 7.2 Hz, $C\underline{H}_2(CH_2)_5CH_3$), 5.74 (1H, s, $\underline{H}$-2), 7.28-7.32 (2H, m, aromatic C-H) 7.39-7.44 (3H, m, aromatic C-H), 7.18, 7.62 and 8.82 (3H, br m, N$\underline{H}$) (Figure 76); *m/z* (MALDI-TOF) 288 ($M.H^+$).

1-Decyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-106)**

0.65 g, 30% yield (5 mmol scale), purified by recrystallization from ethanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 0.82 (3H, t, J = 6.7 Hz, $CH_2(CH_2)_8C\underline{H}_3$) 1.18-2.00 (16H, m, $CH_2(C\underline{H}_2)_8CH_3$) 2.96 and 3.49 (2x1H, 2xtd, J = 14.8_d, 7.2_t Hz, $C\underline{H}_2(CH_2)_8CH_3$), 5.73 (1H, s, H-2), 7.26-7.31 (2H, m, aromatic C-H) 7.40-7.44 (3H, m, aromatic C-H), 7.72 and 8.73 (2H, br m, N$\underline{H}$) (Figure 77); *m/z* (MALDI-TOF) 330 ($M.H^+$).

1-Tetradecyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-107)**

0.58 g, 26% yield (4.5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 0.83 (3H, t, J = 6.4 Hz, $CH_2(CH_2)_{12}C\underline{H}_3$) 1.22-1.51 (24H, m, $CH_2(C\underline{H}_2)_{12}CH_3$) 2.97 and 3.50 (2x1H, 2xtd, J_d = 14.8 Hz, J_t = 7.2 Hz, $C\underline{H}_2(CH_2)_{12}CH_3$), 5.77 (1H, s, H-2), 7.29-7.32 (2H, m, aromatic C-H) 7.38-7.48 (3H, m, aromatic C-H), 7.61 and 9.12 (3H, br m, N$\underline{H}$) (Figure 78); *m/z* (MALDI-TOF) 386 ($M.H^+$).

1-Octadecyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-108)**

1.60 g, 59% yield (4.9 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 0.83 (3H, t, J = 6.7 Hz, $CH_2(CH_2)_{16}C\underline{H}_3$) 1.22-1.56 (32H, m, $CH_2(C\underline{H}_2)_{16}CH_3$) 2.97 and 3.45 (2x1H, 2xtd, J_d = 14.8 Hz, J_t = 7.2 Hz, $C\underline{H}_2(CH_2)_{16}CH_3$), 5.75 (1H, s, H-2), 7.27-7.32 (2H, m, aromatic C-H), 7.36-7.49 (3H, m, aromatic C-H), 7.23, 7.60 and 8.92 (4H, br m, N$\underline{H}$) (Figure 79); *m/z* (MALDI-TOF) 442 ($M.H^+$).

1-Cyclohexyl-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-109)**

0.52 g, 30% yield (4.3 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 0.98-1.80 (10H, m, 5xcyclohexyl $C\underline{H}_2$) 3.96 (1H, m, cyclohexyl C$\underline{H}$), 5.99 (1H, s, H-2), 7.29-7.43 (5H, m, aromatic C-H), 7.74 and 9.27 (3H, br m, N$\underline{H}$) (Figure 80); *m/z* (MALDI-TOF) 272 ($M.H^+$).

1-Benzyl-2-(3′-phenoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-110)**

1.13 g, 53% yield (4.4 mmol scale), purified by recrystallization from ethanol and obtained as white crystalline solids. ^{1}H NMR (DMSO) δ_H 4.31 and 4.96 (2x1H, 2xd, J = 16.7 Hz, benzyl C$\underline{H}_2$), 5.71 (1H, s, $\underline{H}$-2), 6.97-7.08 (5H, m, aromatic C-H), 7.17-7.31 (5H, m, aromatic C-H), 7.34-7.45 (4H, m, aromatic C-H), 7.74 and 8.84 (2H, br m, N$\underline{H}$) (Figure 69); *m/z* (MALDI-TOF) 372 ($M.H^+$).

1-Phenylpropyl-2-(3′-phenoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-111)**

0.62 g, 61% yield (2 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 1.77 (2H, m, $CH_2C\underline{H}_2CH_2Ph$), 2.53 (2H, t, J = 6.7 Hz, $CH_2CH_2C\underline{H}_2Ph$), 3.09 and 3.59 (2x1H, 2xtd, J_d = 14.8 Hz, J_t = 7.2 Hz, $C\underline{H}_2CH_2CH_2Ph$), 5.77 (1H, s, $\underline{H}$-2), 6.97-7.02 (5H, m, aromatic C-H), 7.11-7.29 (5H, m, aromatic C-H), 7.34-7.44 (4H, m, aromatic C-H), 7.68 (2H, br m, N$\underline{H}$) (Figure 81); *m/z* (MALDI-TOF) 400 ($M.H^+$).

1-Decyl-2-(3′-phenoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-112)**

0.49 g, 46% yield (2 mmol scale), purified by recrystallization from methanol-water and obtained as colorless leaflets. ^{1}H NMR (DMSO) δ_H 0.84 (3H, t, J = 6.9 Hz, $CH_2(CH_2)_8C\underline{H}_3$), 1.10-1.60 (16H, m, $CH_2(C\underline{H}_2)_8CH_3$), 3.02 and 3.52 (2x1H, 2xtd, J_d = 14.8 Hz, J_t = 7.2 Hz, $C\underline{H}_2(CH_2)_8CH_3$), 5.77 (1H, s, $\underline{H}$-2), 6.99-7.20 (5H, m, aromatic C-H), 7.36-7.45 (4H, m, aromatic C-H), 7.28, 7.62 and 8.98 (3H, br m, N$\underline{H}$) (Figure 82); *m/z* (MALDI-TOF) 422 ($M.H^+$).

1-(3′-Morpholin-4′-ylpropyl)-2-phenyl-4,6-diamino-i,2-dihydro-1,3,5-triazine trifluoroacetate **(II-113)**

1.23 g, 63% yield (4.5 mmol scale), purified by recrystallization from methanol-water and obtained as colorless rosettes. ^{1}H NMR (DMSO) δ_H 1.59 (2H, m, $CH_2C\underline{H}_2CH_2N$), 2.27 (8H, m, N-($C\underline{H}_2C\underline{H}_2$)$_2$-O), 3.14 and 3.50 (2x1H, 2xtd, J_d = 14.8 Hz, J_t = 7.2 Hz, $C\underline{H}_2CH_2CH_2N$), 3.54 (2H, t, J = 4.7 Hz, $CH_2CH_2C\underline{H}_2N$), 5.79 (1H, s, $\underline{H}$-2), 7.31-7.35

(2H, m, aromatic C-H) 7.43-7.48 (3H, m, aromatic C-H), 7.76 and 8.73 (3H, br m, NH) (Figure 83); m/z (MALDI-TOF) 317 ($M.H^+$).

1-Benzyl-2-(3′-hydroxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-114)**

TLC indicated that reaction had occurred but the product could not purified by recrystallization.

1-Benzyl-2-(4′-hydroxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-115)**

TLC indicated that reaction had occurred but the product could not purified by recrystallization.

1-Benzyl-2-(2′-hydroxy-3′-methoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-116)**

TLC indicated that reaction had occurred but the product could not purified by recrystallization.

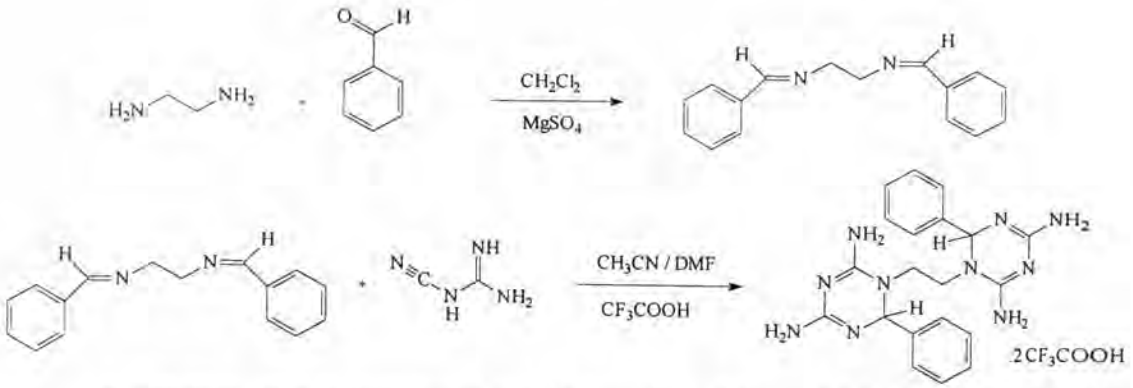
1-Benzyl-2-(4′-hydroxy-3′-methoxyphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-117)**

TLC indicated that reaction had occurred but the product could not purified by recrystallization.

1-Benzyloxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-118)**

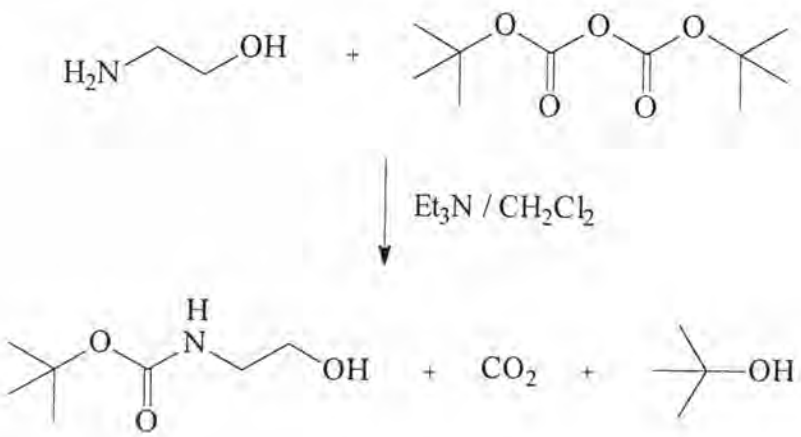
TLC indicated that reaction had occurred but the product could not purified by recrystailization.

Synthesis of bis-(2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazin-1-yl)ethane bistrifluoroacetate **(II-119)**



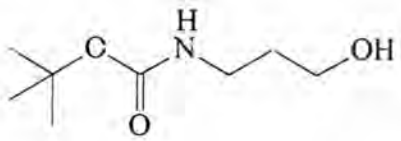
A solution of 1,2-diaminoethane (5 mmol) and benzaldehyde (10 mmol) in dichloromethane (3 mL) containing $MgSO_4$ (100 mg) was stirred at room temperature until complete disappearance of starting material was observed (1-3 days). $MgSO_4$ was then removed by filtration. The filtrate was evaporated under reduced pressure to give the imine. Acetronitrile (3 mL) and trifluoroacetic acid (10 mmol) were added to the imine (4.6 mmol) and the reaction was stirred at room temperature for 10 min. Dicyanodiamide (10 mmol) and DMF (2.2 mL) were then added to the reaction and stirred at room temperature for 4 days. Ether was added to precipitate the trifluoroacetate salt, which was collected by filtration, washed with ether and air dried. The product (0.58 g, 20% yield) was purified by recrystallization from methanol-diethyl ether and obtained as colorless microcrystalline solids. ^{1}H NMR (DMSO) δ_H 3.19 and 3.90 (2x2H, 2xd, J = 9.4 Hz, C$\underline{H}_2$ (x2)), 5.87 (2H, s, $\underline{H}$-2 (x2)), 7.24-7.28 (4H, m, aromatic C-H), 7.40-7.45 (6H, m, aromatic C-H), 7.78 and 9.27 (3H, br m, N$\underline{H}$) (Figure 84); *m/z* (MALDI-TOF) 406 ($M.H^+$).

Synthesis of N-(tert-butoxycarbonyl)-2-aminoethanol **(II-120a)**



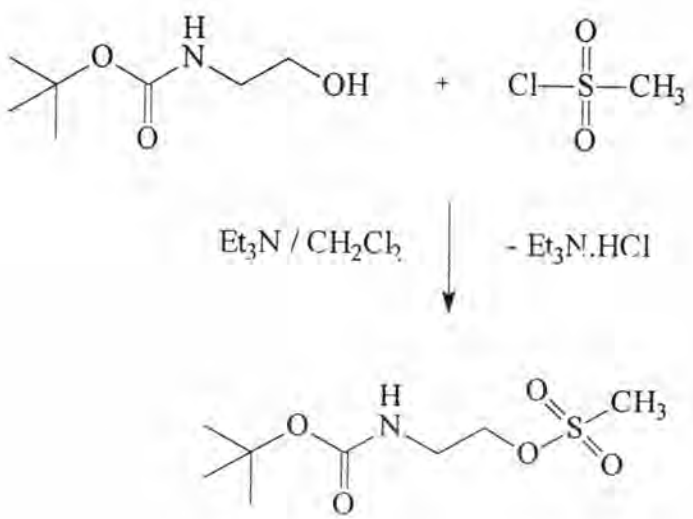
To a suspension of di-*tert*-butyl dicarbonate (20 mmol) and ethanolamine (20 mmol) in dichloromethane (13.4 mL) was added a solution of triethylamine (2.93 mL, 21 mmol) in dichloromethane (5 mL) with stirring at room temperature. The reaction was completed within a few hours and was worked up by washing with 1 N HCl (50 mL) and H_2O. The organic phase was then dried with $MgSO_4$, filtered, concentrated under reduce pressure to give the crude product as a colorless oil (2.15 g, 68% yield). ^{1}H NMR ($CDCl_3$) δ_H 1.43 (9H, s, Boc C<u>H</u>$_3$ (x3)), 3.26 (2H, br m, N-C<u>H</u>$_2$), 3.68 (2H, t, J = 4.5 Hz, C<u>H</u>$_2$-OH), 4.91 (1H, br m, N<u>H</u>).

Synthesis of N-(tert-butoxycarbonyl)-3-aminopropanol **(II-121a)**



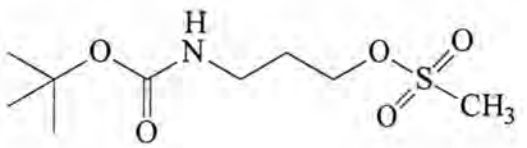
N-(*tert*-butylcarbonyl)-3-aminopropanol was similarly prepared as a colorless oil (3.07g, 87% yield, 20 mmol scale). ^{1}H NMR ($CDCl_3$) δ_H 1.39 (9H, s, Boc C<u>H</u>$_3$ (x3)), 1.61 (2H, m, CH_2C<u>H</u>$_2$$CH_2$), 3.22 (2H, dt, J_t = 12.4 Hz, J_d = 6.3 Hz, N-C<u>H</u>$_2$), 3.60 (2H, t, J = 5.4 Hz, C<u>H</u>$_2$-OH), 5.25 (1H, br m, N<u>H</u>).

Synthesis of N-(tert-butyloxycarbonyl)-2-(methylsulfonyloxy)ethylamine **(II-120b)**



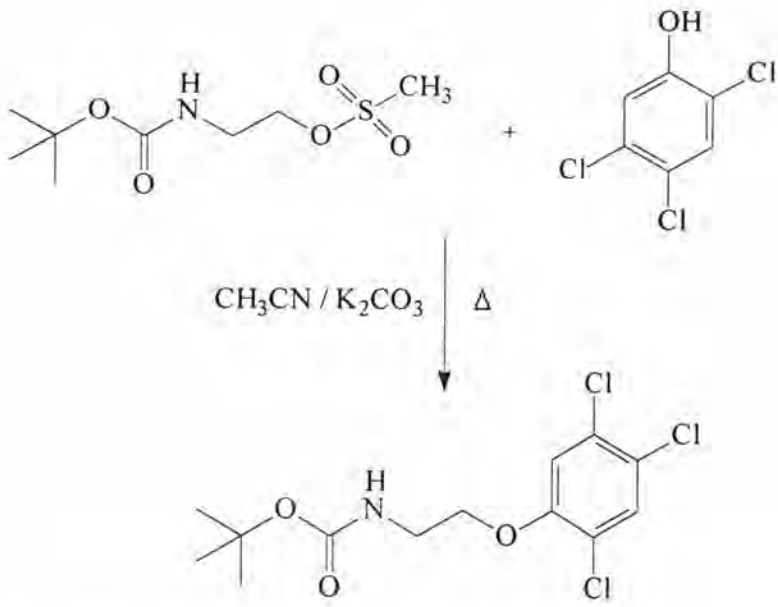
N-(*tert*-butoxylcarboxyl)-2-amionethanol **(II-120a)** (0.70 g, 4.4 mmol) was dissolved in dichloromethane (3 mL) in a round bottom flask. Methanesulfonyl chloride (0.34 mL, 4.4 mmol) was added to the solution with stirring. Triethylamine (0.64 mmol) was then added dropwise at room temperature. Stirring was continued for 1 hour. The reaction was worked up by washing with 1 N HCl (15 mL), H_2O, 1 N Na_2CO_3 (15 mL) and H_2O. The organic phase was then dried with $MgSO_4$, filtered, concentrated under reduce pressure to give the crude product as a colorless oil (0.99 g, 95% yield). ^{1}H NMR ($CDCl_3$) δ_H 1.43 (9H, s, Boc C<u>H</u>$_3$ (x3)), 3.01 (3H, s, S-C<u>H</u>$_3$), 3.45 (2H, q, J = 4.8 Hz, N-C<u>H</u>$_2$), 4.26 (2H, t, J = 4.7 Hz, C<u>H</u>$_2$-O), 4.87 (1H, br m, N<u>H</u>).

Synthesis of N-(tert-butyloxycarbonyl)-3-(methylsulfonyloxy)propylamine **(II-121b)**



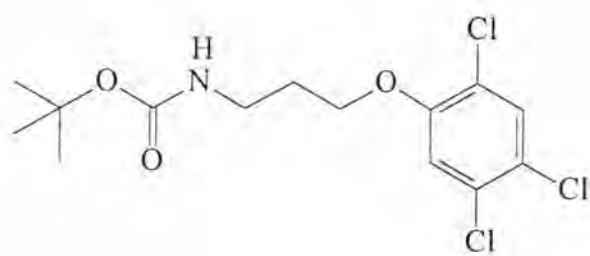
N-(*tert*-butyloxycarbonyl)-3-(methylsulfonyloxy)propylamine **(II-121b)** was similarly prepared as a colorless oil (3.11 g, 93% yield, 13.2 mmol scale). ^{1}H NMR ($CDCl_3$) δ_H 1.39 (9H, s, Boc C<u>H</u>$_3$ (x3)), 1.89 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.99 (3H, s, S-C<u>H</u>$_3$), 3.21 (2H, q, J = 6.1 Hz, N-C<u>H</u>$_2$), 4.25 (2H, t, J = 6.1 Hz, C<u>H</u>$_2$-O), 5.26 (1H, br m, N<u>H</u>).

Synthesis of [2-(2',4',5'-trichlorophenyl)ethyl]carbamic acid tert-butyl ester **(II-120c)**



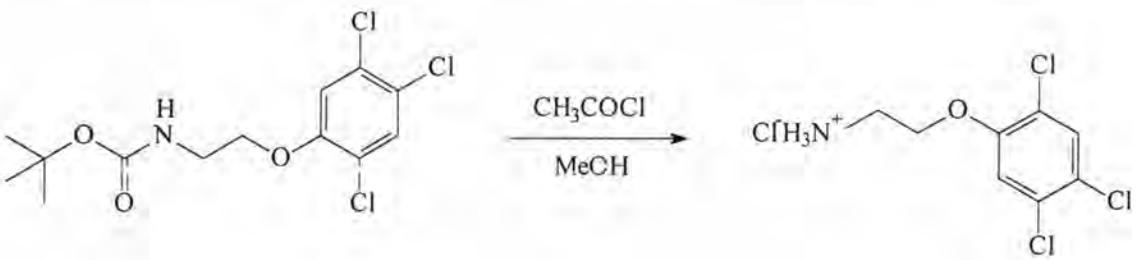
A suspension of *N*-(*tert*-butyloxycarbonyl)-2-(methylsulfonyloxy)ethylamine **(II-120b)** (0.99 g, 4.1 mmol), anhydrous potassium carbonate (1.43 g, 10.25 mmol) and 2,4,5-trichlorophenol (0.90 g, 4.51 mmol) in acetonitrile (70 mL) was heated to reflux until reaction was complete (9-12 hours). The solution was diluted with dichloromethane and washed with water several times. The organic phase was then dried with $MgSO_4$, filtered and concentrated under reduce pressure to give the crude product as a red oil. The crude product was purified by flash column chromatography using 20% ethyl acetate-hexane as eluent to give one major product as a white solid (0.82 g, 58% yield). ^{1}H NMR ($CDCl_3$) δ_H 1.43 (9H, s, Boc C$\underline{H}_3$ (x3)), 3.56 (2H, q, J = 10.7, 5.3 Hz, N-C$\underline{H}_2$), 4.03 (2H, t, J = 5.0 Hz, C$\underline{H}_2$-O), 4.97 (1H, br m, N$\underline{H}$), 6.98 and 7.44 (2x1H, 2xs, aromatic C-H) (Figure 85).

Synthesis of [3-(2',4',5'-trichlorophenoxy)propyl]carbamic acid tert-butyl ester **(II-121c)**



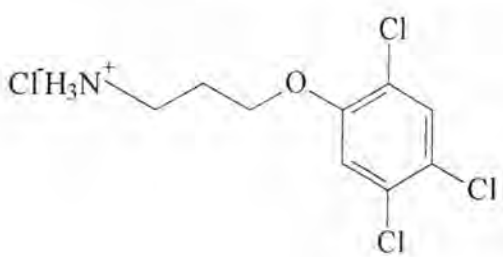
[3-(2′,4′,5′-Trichlorophenoxy)propyl]carbamic acid *tert*-butyl ester **(II-121c)** was similarly prepared and purified by flash column chromatography using 5% ethyl acetate-hexane as a eluent to give one major product as a white solid (1.87 g, 43% yield, 12.3 mmol scale). ^{1}H NMR ($CDCl_3$) δ_H 1.42 (9H, s, Boc C<u>H</u>$_3$ (x3)), 2.10 (2H, m, $CH_2C\underline{H}_2CH_2$), 3.34 (2H, q, J = 12.2, 6.0 Hz, N-C<u>H</u>$_2$), 4.05 (2H, t, J = 5.7 Hz, C<u>H</u>$_2$-O), 5.02 (1H, br m, N<u>H</u>), 6.97 and 7.43 (2x1H, 2xs, aromatic C-H) (Figure 86).

Synthesis of 2-(2′,4′,5′-trichlorophenoxy)ethylamine hydrochloride **(II-120d)**



[2-(2′,4′,5′-Trichlorophenyl)ethyl]carbamic acid *tert*-butyl ester **(II-120c)** (0.82 g, 2.4 mmol) was dissolved in methanol (2 mL) in a round bottom flask. Acetyl chloride (0.34 mL, 4.8 mmol) was added in the solution with stirring. The stirring was continued for 12 hours. The solution was evaporated under reduced pressure and the residue was purified by washing with acetone to give a white crystalline solid (0.40 g, 61% yield). ^{1}H NMR ($CDCl_3$) δ_H 3.22 (2H, t, J = 4.6 Hz, N-C<u>H</u>$_2$), 4.31 (2H, t, J = 5.1 Hz, C<u>H</u>$_2$-O), 7.54 and 7.84 (2x1H, 2xs, aromatic C-H).

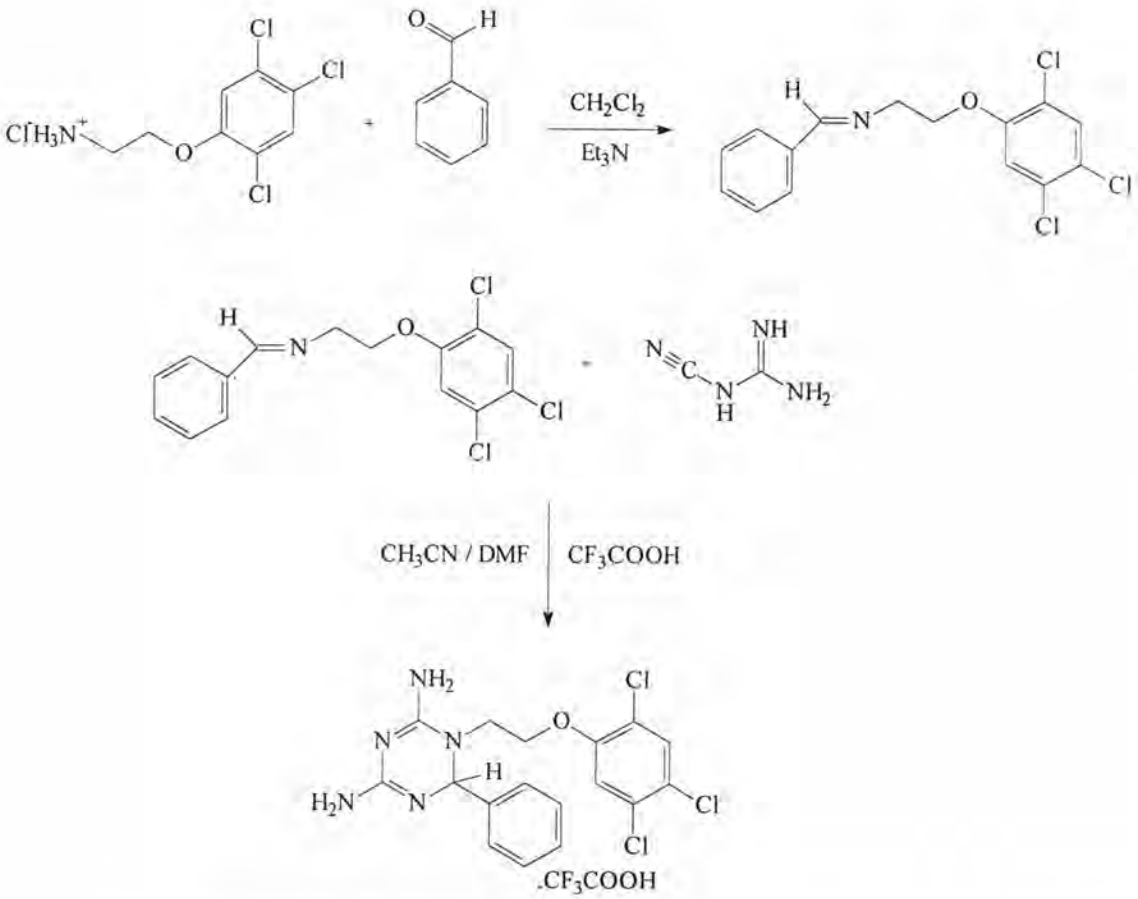
Synthesis of 3-(2′,4′,5′-trichlorophenoxy)propylamine hydrochloride **(II-121d)**



3-(2′,4′,5′-Trichlorophenoxy)propylamine hydrochloride **(II-121d)** was similarly prepared as a white crystalline solid (1.36 g, 89% yield, 5.25 mmol scale).

^{1}H NMR ($CDCl_3$) δ_H 2.04 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.94 (2H, t, J = 7.6 Hz, N-$C\underline{H}_2$). 4.19 (2H, t, J = 6.0 Hz, $C\underline{H}_2$-O), 7.45 and 7.81 (2x1H, 2xs, aromatic C-H) (Figure 87).

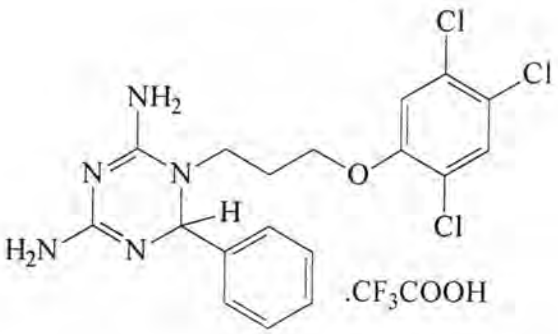
Synthesis of 1-[2'-(2'',4'',5''-trichlorophenoxy)ethyl]-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-120)**



To a suspension of 2-(2',4',5'-trichlorophenoxy)ethylamine hydrochloride **(II-120d)** (0.27 g, 1 mmol) and benzaldehyde (0.10 mL, 1 mmol) in dichloromethane (2 mL) was added triethylamine (0.14 mL, 1 mmol) with stirring at room temperature until complete disappearance of starting material was observed (1 day). The reaction was worked up by washing with H_2O and the organic phase was dried with $MgSO_4$, filtered and evaporated under reduced pressure to give the imine as a white crystalline solid (0.31 g, 94% yield). Acetonitrile (3 mL) and trifluoroacetic acid (0.07 mL, 0.9 mmol) were added to the imine (0.29 g, 0.9 mmol). The reaction was stirred at room temperature for 10 min. Dicyanodiamide (0.075 g, 0.9 mmol) and DMF (0.5 mL) were then added and the reaction stirred at room temperature for 1 day. Ether was

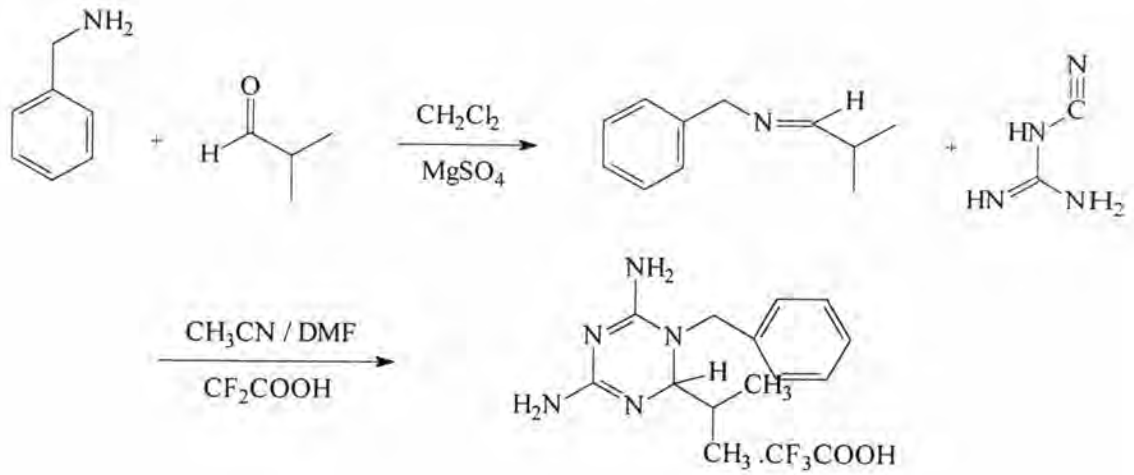
added to pricipitate the trifluoroacetate salt, which was collected by filtration, washed with ether and air dried. The product (0.47 g, 100% yield) was purified by recrystallization from ethanol and obtained as colorless prisms. ^{1}H NMR (DMSO) δ_H 3.56 and 4.07 (2x1H, 2xdt, J_d = 14.2 Hz, J_t = 7.1 Hz, N-C<u>H</u>$_2$), 4.26 (2H, t, J = 5.4 Hz, C<u>H</u>$_2$-O), 5.90 (1H, s, <u>H</u>-2), 7.31-7.43 (5H, m, aromatic C-H), 7.40 and 7.83 (2x1H, 2xs, aromatic C-H), 7.74 and 8.86 (3H, br m, N<u>H</u>) (Figure 88); *m/z* (MALDI-TOF) 412, 414, 416 ($M.H^+$).

Synthesis of 1-[3'-(2'',4'',5''-trichlorophenoxy)propyl]-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-121)**



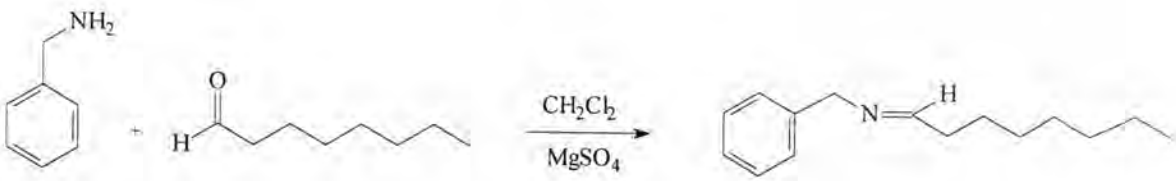
0.65 g, 27% yield (4.4 mmol scale) of 1-[3'-(2'',4'',5''-trichlorophenoxy) propyl]-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-121)** was similarly prepared and purified by recrystallization from methanol-water and obtained as colorless needles. ^{1}H NMR (DMSO) δ_H 1.87 and 2.04 (2x1H, 2xm, $CH_2C\underline{H}_2CH_2$), 3.20 and 3.62 (2x1H, 2xdt, J = 14.2$_d$, 7.1$_t$ Hz, N-C<u>H</u>$_2$), 4.11 (2H, t, J = 5.3 Hz, C<u>H</u>$_2$-O), 5.74 (1H, s, <u>H</u>-2), 7.28-7.46 (5H, m, aromatic C-H), 7.38 and 7.80 (2x1H, 2xs, aromatic C-H), 7.67 and 8.90 (3H, br m, N<u>H</u>) (Figure 89); *m/z* (MALDI-TOF) 426, 428, 430 ($M.H^+$).

Attempted synthesis of 1-benzyl-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-122)**



Similar procedures as described in general procedure of 2.3.1 were employed in the synthesis of 1-benzyl-2-isopropyl-4,6-diamino-1,2-dihydro-1,3,5-triazine trifluoroacetate **(II-122)**, aromatic aldehyde being replaced by isobutyraldehyde. ^{1}H NMR indicated that no reaction had occurred.

Attempted synthesis of heptylidenebenzylamine **(II-123a)**

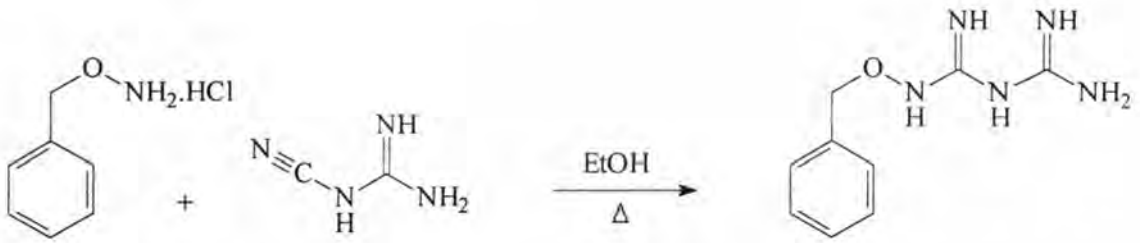


A suspension of the benzylamine (5 mmol, 0.55 mL) and caprylic aldehyde (5 mmol, 0.78 mL) in dichloromethane (3 mL) containing $MgSO_4$ (100 mg) was stirred at room temperature until complete disappearance of starting material (1-4 days) was observed. $MgSO_4$ was then removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product as a colorless oil. ^{1}H NMR indicated that no desired product had formed.

2.4 Synthesis of 1-alkyloxy-4,6-diamino-1,2-dihydro-1,3,5-triazines

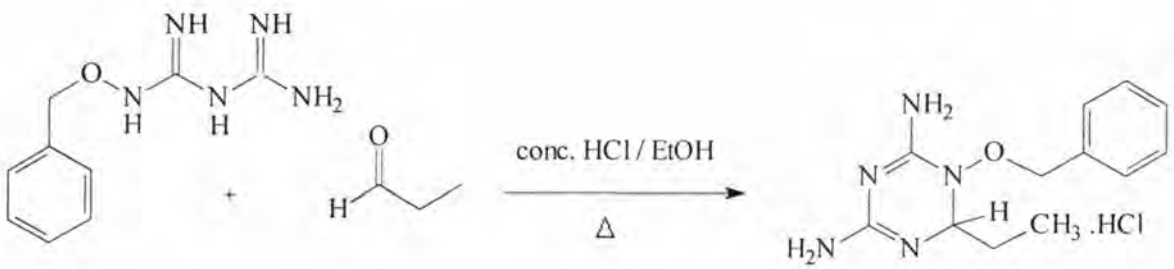
2.4.1 Synthesis of 1-alkyloxy-4,6-diamino-1,2-dihydro-1,3,5-triazines by two-component condensation

Synthesis of 1-benzyloxybiguanide **(I-14)**



To a suspension of O-benzylhydroxylamine (25 mmol) and dicyanodiamide (25 mmol) in an appropriate volume of absolute ethanol was heated to reflux until the reaction has completed (9-12 hours). The mixture was evaporated to dryness and the residue was adjusted to pH 10 with aqueous potassium carbonate. The solution was extracted 3 times with ethyl acetate. The combined organic phase was dried over $MgSO_4$, filtered and evaporated to give white solids (4.73 g, 91% yield) which was pure enough for practical purposes. ^1H NMR (DMSO) δ_H 4.88 (2H, s, PhC<u>H</u>$_2$-), 7.26-7.35 (5H, m, aromatic C-H).

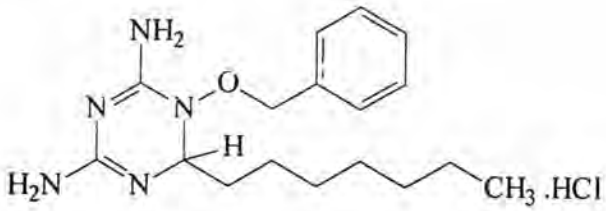
Synthesis of 1-benzyloxy-2-ethyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-124)**



To a suspension of 1-benzyloxybiguanide **(I-14)** (1 mmol) in absolute ethanol (5 mL) containing conc. HCl (3.5 mmol) was added propionaldehyde (6.5 mmol). The reaction mixture was heated to reflux for 6 hours. The solution was then evaporated to

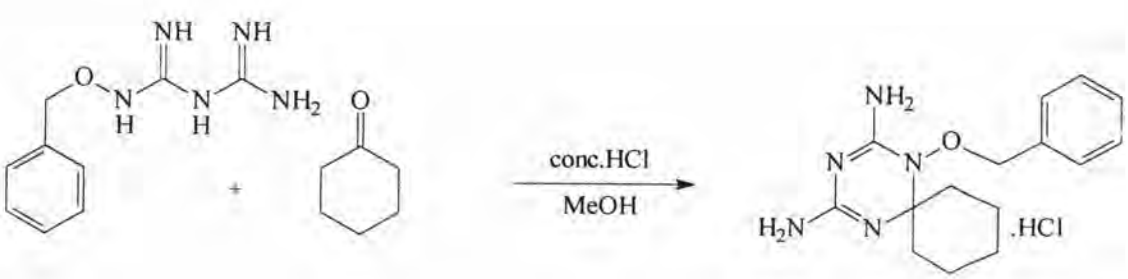
give the crude product as an colorless oil. Trituration with ether-acetone (1:1) gave the product as a white solid. The solid was collected by filtration and washed with acetone, ether and air dried (0.11 g, 39 % yield). The product was recrystallized from methanol-diethyl ether and obtained as white crystalline solids. ^{1}H NMR (DMSO) δ_H 0.83 (3H, t, J = 7.4 Hz, C<u>H</u>$_3$CH$_2$-2), 1.65 (2H, m, CH$_3$C<u>H</u>$_2$-2), 4.75 (1H, m, <u>H</u>-2), 4.93 (2H, s, PhC<u>H</u>$_2$O-), 7.34-7.42 and 7.49-7.54 (5H, 2xm, aromatic C-H), 8.00, 8.37 and 8.90 (3H, br m, N<u>H</u>) (Figure 90); *m/z* (MALDI-TOF) 248 (M.H$^+$).

Synthesis of 1-benzyloxy-2-heptyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-125)**



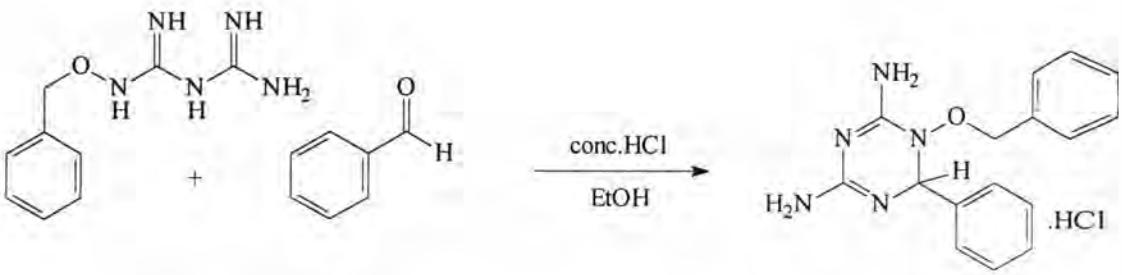
0.09 g, 26% **(II-125)** yield of 1-benzyloxy-2-heptyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide was similarly prepared and purified by recrystallization from methanol-diethyl ether and obtained as white crystalline solids. ^{1}H NMR (DMSO) δ_H 0.83 (3H, t, J = 6.4 Hz, C<u>H</u>$_3$(CH$_2$)$_6$-2), 1.21 and 1.60 (12H, m, CH$_3$(C<u>H</u>$_2$)$_6$-2), 4.73 (1H, m, <u>H</u>-2), 4.92 (2H, s, PhC<u>H</u>$_2$O-), 7.37-7.40 and 7.48-7.51 (5H, 2xm, aromatic C-H), 8.01, 8.37 and 8.76 (3H, br m, N<u>H</u>) (Figure 91); *m/z* (MALDI-TOF) 318 (M.H$^+$).

Synthesis of 1-benzyloxy-2,2-cyclohexylidene-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-126)**



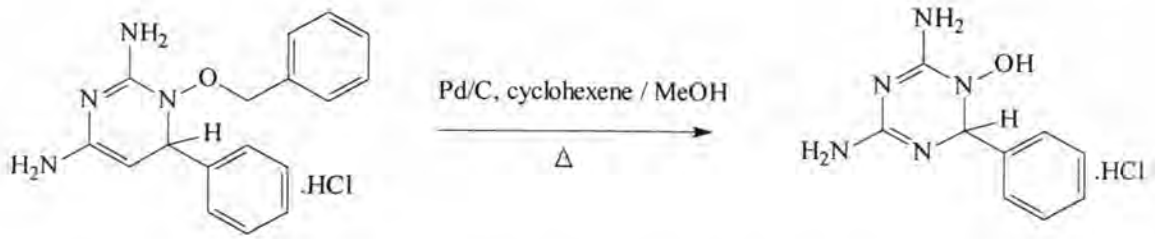
A suspension of 1-benzyloxybiguanide **(I-14)** (2.25 mmol) in absolute methanol (4 mL) containing conc. HCl (0.39 mL, 5 mmol) was added cyclohexanone (0.40 mL, 3.8 mmol). The reaction mixture was stirred at room temperature for 45 hour. After 5 days, the colorless needles precipitated was collected by filtration and washed with methanol, ether and air dried. The product was recrystallized from methanol and obtained as colorless needles (0.39 g, 53% yield). ^{1}H NMR (DMSO) δ_H 1.54-1.73 (10H, m, cyclohexylidene C<u>H</u>$_2$), 4.93 (2H, s, PhC<u>H</u>$_2$O-), 7.37-7.42 and 7.50-7.754 (5H, m, aromatic C-H), 8.00, 8.59 and 9.29 (3H, br m, N<u>H</u>); *m/z* (MALDI-TOF) 288 ($M.H^+$).

Synthesis of 1-benzyloxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-127)**



To a suspension of the 1-benzyloxybiguanide **(I-14)** (2.1 g) in absolute ethanol (10 mL) containing conc.HCl (1.9 mL) was added benzaldehyde (2.0 g). The reaction mixture was stirred at room temperature for 72 hours. The crystalline precipitate formed was collected by filtration, washed with ethanol and ether (1.97 g, 59% yield). The product was purified by recrystallization from ethanol and obtained as colorless needles. (lit[19] m.p. 249-250 °C). ^{1}H NMR (DMSO) δ_H 4.72 and 4.92 (2x1H, 2xd, J = 10.4 Hz, PhC<u>H</u>$_2$O-), 5.90 (1H, s, <u>H</u>-2), 7.33-7.46 (10H, m, aromatic C-H), 8.06, 8.55 and 9.42 (3H, br m, N<u>H</u>); *m/z* (MALDI-TOF) 296 ($M.H^+$).

Synthesis of 1-hydroxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-128)**



To a suspension of 1-benzyloxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-127)** (5 mmol) in absolute methanol (40 mL) was added cyclohexene (20 mmol) and Pd/C (80 mg) as catalyst. The reaction was heated to reflux until the reaction was completed (8-13 hours). Then Pd/C was removed by filtration through celite and washed with methanol. The solution was evaporated to dryness to give white solids (1.16 g, 96% yield) which was pure enough for practical purposes. ^{1}H NMR (DMSO) δ_H 5.72 (1H, s, H-2), 7.40-7.47 (5H, m, aromatic C-H), 7.94, 8.28 and 8.79 (3H, br m, NH), 10.45 (1H, br m, OH); m/z (MALDI-TOF) 206 ($M.H^+$).

2.4.2 Synthesis of 1-Alkyloxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine by alkylation method

General Procedure

To a suspension of 1-benzyloxy-2-phenyl-4,6,-diamino-1,2-dihydro-1,3,5-triazine hydrochloride **(II-127)** (0.8 mmol) in an appropriate volume of absolute methanol (7 mL) was added KOH (0.96 mmol). The reaction mixture was stirred at room temperature for 3-12 hours and the methanol was removed by evaporation to give a white solid. DMF (2 mL) and alkyl bromide (1.6 mmol) were then added and the mixture stirred at room temperature for 10-24 hours. Ether was added to precipitate the hydrobromide salt, which was collected by filtration, washed with ether and air dried. The product was futher purified by recrystallization from methanol-water.

1-Phenethyloxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-129)**

Purified by recrystallization from methanol-water and obtained as colorless prisms (0.14 g, 36% yield, 1 mmol scale). ^{1}H NMR (DMSO) δ_H 2.80 (2H, m, PhC$\underline{H}_2$CH$_2$O-), 3.79 and 4.08 (2x1H, 2xtd, J_d = 8.0 Hz, J_t = 7.4 Hz, PhCH$_2$C$\underline{H}_2$O-), 5.87 (1H, s, $\underline{H}$-2), 7.07-7.11 (3H, m, aromatic C-H) and 7.38-7.43 (2H, m, aromatic C-H), 7.20-7.34 (5H, m, aromatic C-H), 8.07, 8.58 and 9.08 (3H, br m, N$\underline{H}$) (Figure 92); *m/z* (MALDI-TOF) 310 (M.H$^+$).

1-(3′-Phenylpropoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-130)**

Purified by recrystallization from methanol-water and obtained as colorless crystalline solids (0.18 g, 56% yield). ^{1}H NMR (DMSO) δ_H 1.78 (2H, t, J = 7.1 Hz, PhC$\underline{H}_2$CH$_2$CH$_2$O-), 2.41 (2H, m, PhCH$_2$C$\underline{H}_2$CH$_2$O-), 3.60 and 3.91 (2x1H, 2xtd, J_d = 8.7 Hz, J_t = 7.5 Hz, PhCH$_2$CH$_2$C$\underline{H}_2$O-), 5.95 (1H, s, $\underline{H}$-2), 7.07-7.29 (5H, m, aromatic C-H), 7.45 (5H, m, aromatic C-H), 8.07, 8.57 and 9.07 (3H, br m, N$\underline{H}$) (Figure 93); *m/z* (MALDI-TOF) 324 (M.H$^+$).

1-(2′-Bromobenzyloxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-131)**

Purified by recrystallization from methanol-water and obtained as colorless prisms (0.09 g, 25% yield). ^{1}H NMR (DMSO) δ_H 4.93 and 5.05 (2x1H, 2xd, J = 10.6 Hz, 2-BrPhC$\underline{H}_2$O-), 5.67 (1H, s, $\underline{H}$-2), 7.30-7.46 (7H, m, aromatic C-H) 7.56 and 7.66 (2x1H, 2xd, J = 8.2 Hz, aromatic C-H), 8.07, 8.64 and 9.00 (3H, br m, N$\underline{H}$) (Figure 94); *m/z* (MALDI-TOF) 374, 376 (M.H$^+$).

1-(3′-Bromobenzyloxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-132)**

Purified by recrystallization from methanol-water and obtained as colorless needles (0.25 g, 69% yield). ^{1}H NMR (DMSO) δ_H 4.67 and 4.93 (2x1H, 2xd, J = 10.3 Hz, 3-BrPhC$\underline{H}_2$O-), 5.93 (1H, s, $\underline{H}$-2), 7.20-7.55 (9H, m, aromatic C-H), 8.16, 8.61 and 9.03 (3H, br m, N$\underline{H}$) (Figure 95); *m/z* (MALDI-TOF) 374, 376 (M.H$^+$).

1-(4′-Bromobenzyloxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-133)**

Purified by recrystallization from methanol-water and obtained as colorless needles (0.23 g, 64% yield). ^{1}H NMR (DMSO) δ_H 4.69 and 4.89 (2x1H, 2xd, J = 10.6 Hz, 4-BrPhC$\underline{H}_2$O-), 5.85 (1H, s, $\underline{H}$-2), 7.28 and 7.55 (2x2H, AB doublet, J = 8.4 Hz, aromatic C-H), 7.35-7.48 (5H, m, aromatic C-H), 8.09, 8.56 and 9.04 (3H, br m, N$\underline{H}$) (Figure 96); *m/z* (MALDI-TOF) 374, 376 (M.H$^+$).

1-(4′-methylbenzyloxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-134)**

Purified by recrystallization from methanol-water and obtained as colorless needles (0.19 g, 61% yield). ^{1}H NMR (DMSO) δ_H 2.28 (3H, s, 4-C$\underline{H}_3$C$_6$H$_4$-), 4.69 and 4.85 (2x1H, 2xd, J = 10.3 Hz, C$\underline{H}_2$O-), 5.83 (1H, s, $\underline{H}$-2), 7.15 and 7.23 (2x2H, AB doublet, J = 7.9 Hz, aromatic C-H), 7.36-7.47 (5H, m, aromatic C-H), 8.03, 8.53 and 9.08 (3H, br m, N$\underline{H}$) (Figure 97); *m/z* (MALDI-TOF) 314 (M.H$^+$).

1-(Naphthalen-2′-ylmethoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-135)**

Purified by recrystallization from methanol-water and obtained as colorless microcrystalline solids (0.19 g, 56% yield). ^{1}H NMR (DMSO) δ_H 4.90 and 5.08 (2x1H, 2xd, J = 10.5 Hz, C$\underline{H}_2$O-), 5.85 (1H, s, $\underline{H}$-2), 7.40-7.58 (7H, m, aromatic CH), 7.83-7.94 (5H, m, aromatic C-H), 8.16, 8.58 and 9.14 (3H, br m, N$\underline{H}$) (Figure 98); *m/z* (MALDI-TOF) 346 (M.H$^+$).

1-(1′-Methoxycarbonylmethoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-136)**

Purified by recrystallization from methanol-water and obtained as colorless prisms (0.19 g, 68% yield). ^{1}H NMR (DMSO) δ_H 3.68 (3H, s, C$\underline{H}_3$OCOCH$_2$O-), 4.57 (2H, s, CH$_3$OCOC$\underline{H}_2$O-), 6.16 (1H, s, $\underline{H}$-2), 7.37-7.49 (5H, m, aromatic C-H), 8.25, 8.75 and 9.12 (3H, br m, N$\underline{H}$) (Figure 99); *m/z* (MALDI-TOF) 278 (M.H$^+$).

1-Allyloxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-137)**

Purified by recrystallization from methanol-water and obtained as colorless needles (0.15 g, 58% yield). ^{1}H NMR (DMSO) δ_H 4.20 and 4.25 (2x1H, 2xtd, J_d = 15.2 Hz, J_t = 7.0 Hz, CH_2=CHC$\underline{H}_2$O-), 5.22 (1H, d, J = 7.1 Hz) and 5.29 (1H, s, C$\underline{H}_2$=CHCH_2O-), 5.92 (1H, m, CH_2=C$\underline{H}$CH_2O-), 5.95 (1H, s, $\underline{H}$-2), 7.37-7.48 (5H, m, aromatic C-H), 8.13, 8.55 and 9.13 (3H, br m, N$\underline{H}$) (Figure 100); *m/z* (MALDI-TOF) 246 ($M.H^+$).

1-Propoxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-138)**
Purified by recrystallization from methanol-water and obtained as colorless needles (0.13 g, 50% yield). ^{1}H NMR (DMSO) δ_H 0.68 (3H, t, J = 7.4 Hz, C$\underline{H}_3$CH_2CH_2O-), 1.48 (2H, m, CH_3C$\underline{H}_2$CH_2O-), 3.53 and 3.84 (2x1H, 2xtd, J_d = 8.7 Hz, J_t = 6.6 Hz, $CH_3CH_2C\underline{H}_2O$-), 5.95 (1H, s, $\underline{H}$-2), 7.38-7.47 (5H, m, aromatic C-H), 8.03, 8.54 and 9.12 (3H, br m, N$\underline{H}$) (Figure 101); *m/z* (MALDI-TOF) 248 ($M.H^+$).

1-Pentyloxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-139)**
Purified by recrystallization from methanol-water and obtained as colorless prisms (0.13 g, 45% yield). ^{1}H NMR (DMSO) δ_H 0.65 (3H, t, J = 6.8 Hz, C$\underline{H}_3$CH_2CH_2CH_2CH_2O-), 1.08-1.14 (4H, m, CH_3C$\underline{H}_2$C$\underline{H}_2$CH_2CH_2O-), 1.41-1.48 (2H, m, $CH_3CH_2CH_2C\underline{H}_2CH_2O$-), 3.51 and 3.86 (2x1H, 2xtd, J_d = 8.5 Hz, J_t = 6.6 Hz, $CH_3CH_2CH_2CH_2C\underline{H}_2O$), 5.93 (1H, s, $\underline{H}$-2), 7.44 (5H, m, aromatic C-H), 8.02, 8.54 and 9.10 (3H, br m, N$\underline{H}$) (Figure 102); *m/z* (MALDI-TOF) 276 ($M.H^+$).

1-Decyloxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-140)**
Purified by recrystallization from methanol-water and obtained as colorless needles (0.16 g, 47% yield). ^{1}H NMR (DMSO) δ_H 0.83 (3H, t, J = 6.6 Hz, C$\underline{H}_3$(CH_2)$_9$O-), 1.03-1.47 (16H, m, CH_3($C\underline{H}_2$)$_8$CH_2O-), 3.52 and 3.86 (2x1H, 2xtd, J_d = 8.4 Hz, J_t = 7.0 Hz, $CH_3(CH_2)_8C\underline{H}_2O$), 5.93 (1H, s, $\underline{H}$-2), 7.38-7.47 (5H, m, aromatic C-H), 8.02, 8.53 and 9.10 (3H, br m, N$\underline{H}$) (Figure 103); *m/z* (MALDI-TOF) 346 ($M.H^+$).

1-Isobutoxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-141)**
Purified by recrystallization from methanol-water and obtained as colorless microcrystalline solids (0.09 g, 33% yield). ^{1}H NMR (DMSO) δ_H 0.64 and 0.71 (2x3H, 2xd, J = 6.7 Hz, ($C\underline{H}_3$)$_2$CHCH_2O-), 1.82 (1H, m, (CH_3)$_2$C$\underline{H}$CH_2O-), 3.33 and

3.70 (2x1H, 2xdd, J = 7.6, 7.2 Hz, $(CH_3)_2CHC\underline{H}_2O$-), 5.94 (1H, s, $\underline{H}$-2), 7.39-7.47 (5H, m, aromatic C-H), 7.95, 8.56 and 9.17 (3H, br m, N$\underline{H}$) (Figure 104); *m/z* (MALDI-TOF) 262 ($M.H^+$).

1-(3′-Methylbutoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-142)**

Purified by recrystallization from methanol-water and obtained as colorless rosettes (0.16 g, 55% yield). ^{1}H NMR (DMSO) δ_H 0.67 and 0.74 (2x3H, 2xd, J = 5.8 Hz, $(C\underline{H}_3)_2CHCH_2CH_2O$-), 1.34 (3H, m, $(CH_3)_2C\underline{H}C\underline{H}_2CH_2O$-), 3.55 and 3.88 (2x1H, 2xtd, J_d = 8.5 Hz, J_t = 5.2 Hz, $(CH_3)_2CHCH_2C\underline{H}_2O$-), 5.96 (1H, s, $\underline{H}$-2), 7.39-7.47 (5H, m, aromatic C-H), 8.03, 8.55 and 9.19 (3H, br m, N$\underline{H}$) (Figure 105); *m/z* (MALDI-TOF) 276 ($M.H^+$).

1-Cyclohexylmethoxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-143)**

Purified by recrystallization from methanol-water and obtained as colorless crystals (0.11 g, 37% yield). ^{1}H NMR (DMSO) δ_H 0.67 (1H, m, C$\underline{H}$), 1.05 and 1.49 (10H, 2xm, cyclohexyl C$\underline{H}_2$), 3.36 and 3.74 (2x1H, 2xdd, J = 7.5, 7.5 Hz, O-C$\underline{H}_2$), 5.93 (1H, s, $\underline{H}$-2), 7.39-7.48 (5H, m, aromatic C-H), 7.93, 8.55 and 9.12 (3H, br m, N$\underline{H}$) (Figure 106); *m/z* (MALDI-TOF) 302 ($M.H^+$).

1-(3′-Bromopropoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-144)**

Purified by recrystallization from methanol-water and obtained as colorless rosettes (0.12 g, 38% yield). ^{1}H NMR (DMSO) δ_H 2.05 (2H, t, J = 6.6 Hz, $BrC\underline{H}_2CH_2CH_2O$-), 3.34 and 3.46 (2x1H, 2xm, $BrCH_2C\underline{H}_2CH_2O$-), 3.70 and 3.98 (2x1H, 2xtd, J_d = 7.7 Hz, J_t = 6.5 Hz, $BrCH_2CH_2C\underline{H}_2O$-), 3.95 (1H, s, $\underline{H}$-2), 7.46 (5H, m, aromatic C-H), 8.10, 8.59 and 9.04 (3H, br m, N$\underline{H}$) (Figure 107); *m/z* (MALDI-TOF) 326, 328 ($M.H^+$).

1-(2′-Phenoxyethoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-145)**

Purified by recrystallization from methanol-water and obtained as colorless rosettes (0.18 g, 75% yield). ^{1}H NMR (DMSO) δ_H 4.14 (4H, m, PhC$\underline{H}_2$C$\underline{H}_2$O-), 5.99 (1H, s, $\underline{H}$-2), 6.91 and 7.27 (5H, 2xm, aromatic C-H), 7.42 (5H, m, aromatic C-H), 8.02, 8.63 and 9.12 (3H, br m, N$\underline{H}$) (Figure 108); *m/z* (MALDI-TOF) 326 ($M.H^+$).

1-(3′-Phenoxypropoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-146)**

Purified by recrystallization from methanol-water and obtained as colorless leaflets (0.18 g, 72% yield). ^{1}H NMR (DMSO) δ_H 1.95 (2H, m, PhOCH$_2$C$\underline{H}_2$CH$_2$O-), 3.71 and 4.07 (2x1H, 2xtd, J_d = 7.2 Hz, J_t = 6.1 Hz, PhOCH$_2$CH$_2$C$\underline{H}_2$O-), 3.79 (2H, t, J = 5.7 Hz, PhOC$\underline{H}_2$CH$_2$CH$_2$O-), 5.96 (1H, s, $\underline{H}$-2), 6.89 and 7.28 (5H, 2xm, aromatic C-H), 8.11, 8.59 and 9.09 (3H, br m, N$\underline{H}$) (Figure 109); *m/z* (MALDI-TOF) 340 ($M.H^+$).

1-[3′-(4″-Chlorophenoxy)propoxy]-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-147)**

Purified by recrystallization from methanol-water and obtained as colorless leaflets (0.30 g, 83% yield). ^{1}H NMR (DMSO) δ_H 1.91 (2H, m, 4-ClC$_6$H$_4$OCH$_2$C$\underline{H}_2$CH$_2$O-), 3.69 and 4.04 (2x1H, 2xtd, J_d = 8.6 Hz, J_t = 5.9 Hz, 4-ClC$_6$H$_4$OCH$_2$CH$_2$C$\underline{H}_2$O-), 3.80 (2H, t, J = 6.3 Hz, 4-ClC$_6$H$_4$OC$\underline{H}_2$CH$_2$CH$_2$O-), 5.95 (1H, s, $\underline{H}$-2), 6.86 and 7.32 (2x2H, AB doublet, J = 8.8 Hz, aromatic C-H), 7.38 (5H, m, aromatic C-H), 8.11, 8.59 and 9.13 (3H, br m, N$\underline{H}$) (Figure 110); *m/z* (MALDI-TOF) 374, 376 ($M.H^+$).

1-[3′-(4″-Methoxycarbonylphenoxy)propoxy]-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-148)**

Purified by recrystallization from methanol-water and obtained as colorless needles (0.20 g, 53% yield). ^{1}H NMR (DMSO) δ_H 1.94 (2H, m, 4-CH$_3$OCOC$_6$H$_4$OCH$_2$C$\underline{H}_2$CH$_2$O-), 3.72 and 4.07 (2x1H, 2xtd, J_d = 8.9 Hz, J_t = 5.9 Hz, 4-CH$_3$OCOC$_6$H$_4$OCH$_2$CH$_2$C$\underline{H}_2$O-), 3.80 (3H, s, 4-CH$_3$OCOC$_6$H$_4$OCH$_2$CH$_2$CH$_2$O-), 3.87 (2H, t, J = 6.1 Hz, 4-CO$_2$CH$_3$PhOC$\underline{H}_2$CH$_2$CH$_2$O-), 5.95 (1H, s, $\underline{H}$-2), 6.90 and 7.91 (2x2H, AB doublet, J = 8.8 Hz, aromatic C-H), 7.38 (5H, m, aromatic C-H), 8.13, 8.60 and 9.08 (3H, br m, N$\underline{H}$) (Figure 111); *m/z* (MALDI-TOF) 398 ($M.H^+$).

1-[3′-(4″-Acetamidophenoxy)propoxy]-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-149)**

Purified by recrystallization from methanol-water and obtained as colorless crystals (0.31 g, 82% yield). ^{1}H NMR (DMSO) δ_H 1.90 (2H, m, 4-$CH_3CONHC_6H_4OCH_2C\underline{H}_2CH_2O$-), 1.99 (3H, s, 4-$C\underline{H}_3CONHC_6H_4OCH_2CH_2CH_2O$-), 3.71 and 4.04 (2x1H, 2xtd, J_d = 8.4 Hz, J_t = 6.5 Hz, 4-$CH_3CONHC_6H_4OCH_2CH_2C\underline{H}_2O$-), 3.76 (2H, t, J = 5.3 Hz, 4-$CH_3CONHC_6H_4OC\underline{H}_2CH_2CH_2O$-), 5.95 (1H, s, H-2), 6.77 and 7.46 (2x2H, AB doublet, J = 8.9 Hz, aromatic C-H), 7.38 (5H, m, aromatic C-H), 8.10, 8.59 and 9.10 (3H, br m, N$\underline{H}$) (Figure 112); *m/z* (MALDI-TOF) 397 ($M.H^+$).

1-[3′-(Biphenyl-4″-yloxy)propoxy]-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-150)**

Purified by recrystallization from methanol-water and obtained as colorless microcrystalline solids (0.23 g, 58% yield). ^{1}H NMR (DMSO) δ_H 1.98 (2H, m, 4-$PhPhOCH_2C\underline{H}_2CH_2O$-), 3.79 and 4.10 (2x1H, 2xtd, J_d = 8.7 Hz, J_t = 6.4 Hz, 4-$PhPhOCH_2CH_2C\underline{H}_2O$-), 3.86 (2H, t, J = 6.3 Hz, 4- $PhPhOC\underline{H}_2CH_2CH_2O$-),), 5.99 (1H, s, H-2), 6.94 and 7.59 (2x2H, AB doublet, J = 8.7 Hz, aromatic C-H), 7.26-7.46 (10H, m, aromatic C-H), 8.14, 8.62 and 9.18 (3H, br m, N$\underline{H}$) (Figure 113); *m/z* (MALDI-TOF) 416 ($M.H^+$).

1-(3′-Phenylthiopropoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-151)**

Purified by recrystallization from methanol-water and obtained as colorless leaflets (0.27 g, 77% yield). ^{1}H NMR (DMSO) δ_H 1.77 (2H, t, J = 6.4 Hz, $C_6H_5SC\underline{H}_2CH_2CH_2O$-), 2.73 (2H, m, $C_6H_5SCH_2C\underline{H}_2CH_2O$-), 3.67 and 4.01 (2x1H, 2xtd, J_d = 8.8 Hz, J_t = 6.1 Hz, $C_6H_5SCH_2CH_2C\underline{H}_2O$-), 5.95 (1H, s, H-2), 7.14-7.32 (5H, m, aromatic C-H), 7.39-7.47 (5H, m, aromatic C-H), 8.10, 8.57 and 9.11 (3H, br m, N$\underline{H}$) (Figure 114); *m/z* (MALDI-TOF) 356 ($M.H^+$).

1-(1′-Phenylcarbonylmethoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-152)**

TLC indicated that no reaction had occurred.

1-(2'-Hydroxy-2'-phenylethoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine **(II-153)**

Starting from styrene oxide instead of alkyl bromide. TLC indicated that reaction had occurred but the product could not purified by recrystallization.

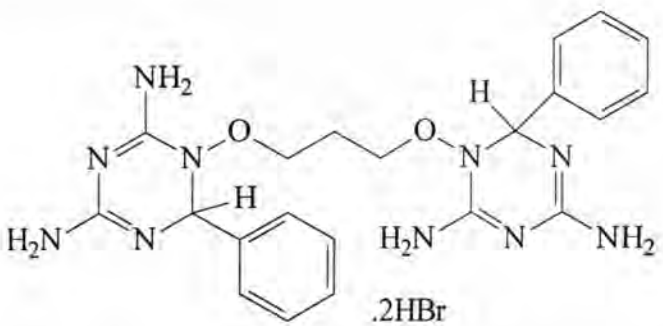
1-(3'-Cyanopropyloxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-154)**

^{1}H NMR indicated that no reaction had occurred.

1-(2'-Hydroxyethoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-155)**

TLC indicated that no reaction had occurred.

Attempted synthesis of bis-(2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazin-1-yloxy) propane dihydrobromide **(II-156)**



Similar procedures as described above were employed in the synthesis of bis-(2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazin-1-oxy)propane dihydrobromide **(II-156)**, 1.6 mmol of alkyl bromide being replaced by 0.4 mmol of 1,3-dibromopropane.^{1}H NMR indicated that the product was 1-(3'-bromopropoxy)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine hydrobromide **(II-144)** (0.11 g, 34% yield).

Enzyme assays and inhibition by cycloguanil analogues

The activities of wild-type and A16VS108T mutant pfDHFRs were determined spectrophotometrically according to the method previously described.[39] The reaction (200 μL) contained 1x DHFR buffer (50 mM TES, pH 7.0, 75 mM β-mercaptoethanol, 1 mg/mL Bovine Serum Albumin), 100 μM each of the substrate H_2folate and cofactor NADPH, and appropriate amount (0.001-0.005 units) of the affinity-purified enzymes. The inhibition of the enzymes with cycloguanil analogues and combinatorial libraries was investigated in a 96 well plate with 200 μL reaction of the above mixture, in the presence of antifolate. The kinetic reaction was followed by a microplate reader (Labsystems, Finland). The K_i values of the inhibitors for the enzymes were then determined by fitting to the equation $IC_{50} = K_i (1+([S]/K_m))$,[40] where IC_{50} is the concentration of inhibitor which inhibits 50% of the enzyme activity under the standard assay condition and K_m is the Michaelis constant for the substrate H_2folate.