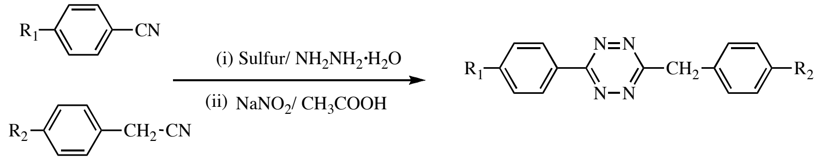
Synthesis, Structures of some Unsymmetrical 3,6-Disubstituted-1,2,4,5-Tetrazines

Wei-Xiao Hu* and Feng Xu

College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310032, People's Republic of China
*E-mail: huyang@mail.hz.zj.cn

Received September 13, 2007



	a	b	c	d	e	f	g	h	i
R_1	H	H	H	CF_3	CF_3	CF_3	Cl	Cl	Cl
R_2	H	OCH_3	Cl	H	OCH_3	Cl	H	OCH_3	Cl

A series of new unsymmetrical 3-phenyl-6-benzyl-1,2,4,5-tetrazine derivatives **10a-i** were synthesized and characterized by IR, NMR, MS, and element analysis. The structures of **4a**, **10c, 10d** and **10h** were analyzed by X-ray crystallography, which had intermolecular C-H···N, C-H···Cl, C-H···Π and Π···Π interactions.

J. Heterocyclic Chem., **45**, 1745 (2008).

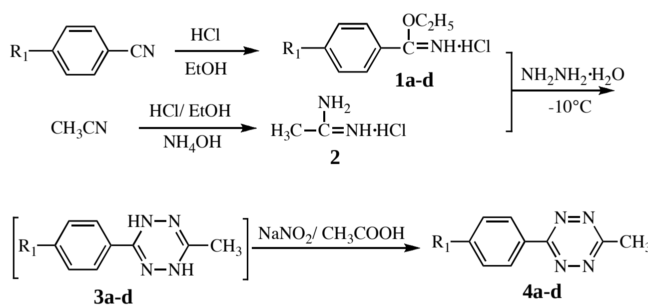
INTRODUCTION

Compounds containing the 1,2,4,5-tetrazine skeleton can be used as dyes [1], herbicides [2], and antibacterial [3]. In addition, recently, some 1,2,4,5-tetrazine derivatives have been found with good antitumor activity by our research team [4-8]. Although some synthesis and crystallographic studies of 1,2,4,5-tetrazine have been published [9], only a few of them referred to unsymmetrical 3,6-disubstituted-1,2,4,5-tetrazines [10], which is due to the difficulty and troublesome work in separation and purification of unsymmetrical 3,6-disubstituted-1,2,4,5-tetrazines.

According to Lang's method **[**10a,b**]**, the traditional way to synthesize unsymmetrical 3,6-disubstituted-1,2,4,5-tetrazines is as follows: ethyl (*p*-substituted) iminobenzoate hydrochloride **1a-d** and acetamidine hydrochloride **2** were reacted with hydrazine hydrate to form dihydro-1,2,4,5-tetrazines **3a-d**, a series of somewhat unstable compounds, which were then easily oxidized by sodium nitrite and acetic acid to obtain corresponding unsymmetrical 3-(substitutedphenyl)-6-methyl-1,2,4,5-tetrazines **4a-d** (Scheme I). However, when using this method to prepare 3-phenyl-6-benzyl-1,2,4,5-tetrazine, the yield was very low(<5%), the main product we obtained was 4-amino-3-benzyl-5-phenyl-1,2,4-trizole **6**, which may have been formed by the isomerization of 3-phenyl-6-benzyl-1,4-dihydro-1,2,4,5-tetrazine **5** under acid conditions [11] (Scheme II) .

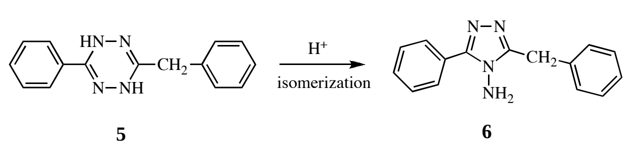
In this contribution we want to report about a facile preparation of a series of new unsymmetrical 3-phenyl-6-benzyl-1,2,4,5-tetrazine derivatives.

Scheme I



	a	b	c	d
R_1	H	CH_3	Cl	OCH_3

Scheme II



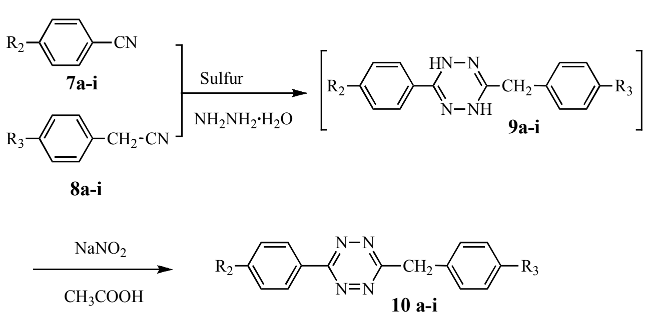
RESULTS AND DISCUSSION

Synthesis. The synthetic procedures of our new unsymmetrical 3-phenyl-6-benzyl-1,2,4,5-tetrazine derivatives **10a-i** are shown in scheme III. The *p*-substituted benzonitrile **7a-i** and *p*-substituted benzylcyanide **8a-i** were reacted with 85% hydrazine hydrate in the presence of sulfur powder, to initially form 3-(*p*-substituted-phenyl)-6-*p*-(substitutedbenzyl)-1,4-dihydro-1,2,4,5-tetrazine **9a-i**, which were then easily oxidized by sodium nitrite and acetic acid to obtain 3-phenyl-6-benzyl-1,2,4,5-

tetrazine derivatives **10a-i**. In addition to **10a-i**, this reaction also caused other two series of products: symmetrical 3,6-disubstituted phenyl-1,2,4,5-tetrazines and 3,6-disubstituted benzyl-1,2,4,5-tetrazine, which were formed by **7a-i** and **8a-i**, respectively. When the reaction performed in the absence of sulfur powder, product **10a** was not detected even when the reaction time was prolonged from 3 hours to 10 hours. When the molar ratio of **7a**-**8a**-sulfur was 1:1:1, the yield of **10a** was 33.8 %. By increasing the amount of sulfur power and changing the molar ratio of **7a**-**8a**-sulfur to 1:1:2, the yield of **10a** decreased to 28.2 %. These results showed that adding a suitable amount of sulfur powder had a significant effect on the yield of **10a**.

From these results the reaction conditions we choose were **7a-i** (25 mmol), **8a-i** (25 mmol), sulfur powder (25 mmol), and 85% hydrazine hydrate (10 mL). Using this reaction system, a series of new unsymmetrical 3-phenyl-6-benzyl-1,2,4,5-tetrazine derivatives **10a-i** were synthesized. The results are summarized in Table 1. From the Table, it can be seen that, for **10a-i,** when R_2 are the same, the yields increase with the enhancement of electron withdrawing ability of R_3 group (Cl>H>OCH_3). On the contrary, when R_3 are the same, the yields decrease with the enhancement of electron withdrawing ability of R_2 group (H> Cl>CF_3).

Scheme III



	a	b	c	d	e	f	g	h	i
R_2	H	H	H	CF_3	CF_3	CF_3	Cl	Cl	Cl
R_3	H	OCH_3	Cl	H	OCH_3	Cl	H	OCH_3	Cl

Table 1

The synthetic results of **10a-i**

Entry	R_2	R_3	Isolated yield$^{\alpha}$
10a	H	H	33.8
10b	H	OCH_3	21.8
10c	H	Cl	39.2
10d	CF_3	H	23.9
10e	CF_3	OCH_3	18.6
10f	CF_3	Cl	25.6
10g	Cl	H	26.2
10h	Cl	OCH_3	19.1
10i	Cl	Cl	30.2

$^{\alpha}$all yields are based on **7a-i**(or **8a-i**).

Crystal structures. The selected bond lengths and angles for compounds **4a**, **10c-d** and **10h** are given in Table 3. Parameters for data collection and refinement of **4a, 10c-d** and **10h** are summarized in Table 4. It should be noted that, although the synthesis of **4a** have been reported [13], the crystal structure has not previously been presented. The ORTEP view of **4a** with atom numbering scheme is shown in Figure 1. It is obvious that the tetrazine ring N1-C6 (centroid Cg1), the phenyl ring C8-C13 (centroid Cg2) and the C7 atom are almost coplanar, the crystal packing (Figure 2) exhibits weak Π–Π stacking interaction, proved by the short distance Cg1···Cg2^{i} of 3.758(3)Å. [symmetry codes: (i)1-x,1-y,1-z]. The C···C distance is within the range associated with Π–Π interactions [3.3-3.8 Å] [12].

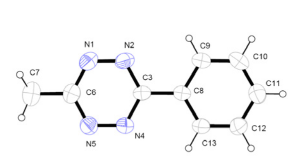


Figure 1. ORTEP view of compound **4a** with atom numbering scheme. Ellipsoids are drawn at the 50% probability level (arbitrary spheres for H atoms).

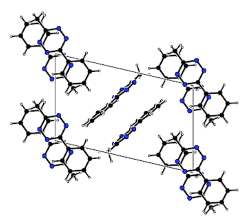
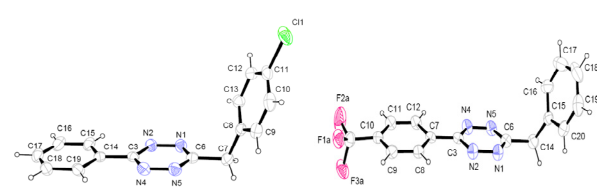


Figure 2. The packing diagram of compound **4a** view along the a axis.

The atom-labelling schemes of compound **10c** and **10d** are shown in Figure 3. It is clear to see that **10c** and **10d** have similar crystal structure. The central tetrazine rings N1-C6 of **10c** and **10d** are almost coplanar with the phenyl rings C14-C19 and C7-C12, with the dihedral angles of 2.46(3)° and 5.90(2)°, respectively, but twisted with respect to the benzyl-phenyl rings C8-C13 and C15-C20, with the dihedral angles of 69.40(3)°and 76.70(2)°,



10c **10d**

Figure 3. ORTEP view of compounds **10c** and **10d** with atom numbering schemes. Ellipsoids are drawn at the 30% probability level (arbitrary spheres for H atoms) .For **10d**, only the major component of the disordered CF_3 group is shown.

respectively. The central bond lengths C3-C14 in molecule **10c** and C3-C7 in molecule **10d** are 1.469(4) Å and 1.462(4) Å, respectively, which are similar to that of C3-C8 in **4a** [1.461(3)Å]. The packing diagram of **10c** is shown in Figure 4, which indicates the weak C—H---N hydrogen bonding occurs between neighboring molecules (Table 5).

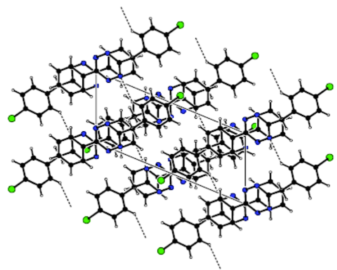


Figure 4. The packing diagram of compound **10c** view along the b axis (the dotted line representing C-H---Cl hydrogen bonding).

The ORTEP view of **10h** with atom numbering scheme is shown in Figure 5. Compound **10h** crystallizes with two crystallographically independent molecules in the asymmetric unit that differ in the orientation of the methoxy group. In both molecules the chlorophenyl ring is almost coplanar with the central tetrazine ring, but the methoxyphenyl ring is twisted. C7-C12 and C14-C19 benzene rings make dihedral angles of 2.32(3)° and 76.74(2)°, respectively, with the central tetrazine ring N1-C6. The C27-C37 and C34-C39 benzene make dihedral angles of 2.32(3)° and 80.47(2)°, respectively, with the central tetrazine ring N21-C26.

In the crystal structure (Figure 6), a C-H---Cl hydrogen bonding is observed between the two independent molecules, pair of C-H--∏ interactions involving the C34-C39 ring (centroid Cg1) link the molecules into a dimer(Table 6).

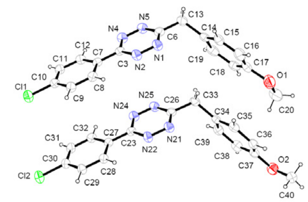


Figure 5. ORTEP view of compound **10h** with atom numbering scheme. Ellipsoids are drawn at the 30% probability level (arbitrary spheres for H atoms).

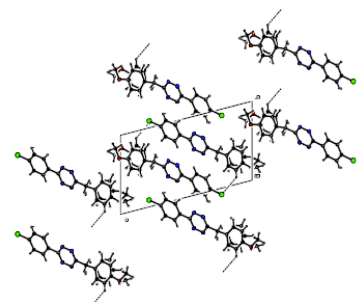


Figure 6. The packing diagram of compound **10h** view along the a axis (the dotted line representing C-H---Cl hydrogen bonding).

In conclusion, we have adopted two different methods to prepare some unsymmetrical disubstituted-1,2,4,5-tetrazines **4a-d** and **10a-i**. The structures of **4a, 10c, 10d** and **10h** were analyzed by X-ray crystallography, and these X-ray data may be helpful to find out the potential drug-enzyme interactions between these compounds and some tumor receptors, which we are studying on.

EXPERIMENTAL

Solvents and reagents were commercially available and used without further purification. Melting points were measured on an XRC-1 apparatus and are uncorrected. Infrared spectra were

Table 3

Selected bond lengths(Å) and bond angles(°) for **4a, 10c, 10d** and **10h.**

			4a				
N1-N2	1.319(3)	N1-C6	1.327(3)	N2-C3	1.335(2)	C3-N4	1.334(2)
N4-N5	1.320(2)	N5-C6	1.323(3)	C6-C7	1.475(3)	C3-C8	1.461(3)
N2-N1-C6	118.50(2)	N1-N2-C3	118.17(2)	N4-C3-N2	123.10(2)	N5-N4-C3	118.29(2)
N5-C6-N1	123.6(2)	N4-N5-C6	118.41(2)	N1-C6-C7	118.30(2)	N2-C3-C8	118.85(2)
			10c				
Cl1-C11	1.730(3)	N1-N2	1.325(3)	N1-C6	1.328(3)	N2-C3	1.329(3)
N4-N5	1.314(3)	N5-C6	1.332(4)	C3-N4	1.337(3)	C7-C8	1.505(4)
C6-C7	1.501(4)	C3-C14	1.469(4)	N2-N1-C6	117.5(2)	N1-N2-C3	118.4(2)
N2-C3-N4	123.5(3)	N2-C3-C14	118.3(2)	N5-N4-C3	118.2(2)	N4-N5-C6	117.9(2)
N1-C6-N5	124.4(3)	N1-C6-C7	118.4(3)	C6-C7-C8	112.1(2)	C10-C11-Cl1	120.2(3)
			10d				
N1-N2	1.325(4)	N1-C6	1.333(4)	N2-C3	1.342(3)	C3-N4	1.340(3)
C3-C7	1.462(4)	N4-N5	1.324(4)	N5-C6	1.335(4)	C6-C14	1.482(4)
C14-C15	1.503(4)	N2-N1-C6	118.8(3)	N1-N2-C3	118.0(2)	N4-C3-N2	123.0(3)
N2-C3-C7	118.3(2)	N5-N4-C3	118.7(2)	N4-N5-C6	118.1(2)	N1-C6-N5	123.4(3)
N1-C6-C14	118.1(3)	C6-C14-C15	112.5(2)				

Table 3 (continued)

			10h				
Cl1-C10	1.701(4)	O1-C20	1.384(6)	O1-C17	1.552(6)	N1-C6	1.259(5)
N1-N2	1.303(5)	N2-C3	1.394(5)	C3-N4	1.250(4)	N4-N5	1.302(5)
N5-C6	1.379(5)	C6-C13	1.454(6)	C13-C14	1.617(6)	C3-C7	1.446(5)
C20-O1-C17	118.8(5)	C6-N1-N2	112.2(4)	N1-N2-C3	122.7(3)	N4-C3-N2	125.0(4)
C3-N4-N5	111.9(4)	N4-N5-C6	123.6(3)	N1-C6-N5	124.6(4)	N5-C6-C13	123.3(4)
C8-C7-C3	115.8(4)	N2-C3-C7	122.6(3)	C9-C10-Cl1	124.5(3)		

Table 4

X-ray structure data collection and refinement parameters for **4a, 10c, 10d** and **10h**.

	4a	**10c**	**10d**	**10h**
Formula	$C_9H_8N_4$	$C_{15}H_{11}ClN_4$	$C_{16}H_{11}F_3N_4$	$C_{16}H_{13}ClN_4O$
Recrystallization solvent	Acetone	THF/EtOH=1:4(V/V)	THF	THF/EtOH=1:4(V/V)
M/(g mol-1)	172.19	282.73	316.29	312.75
Crystal system	Triclinic	Monoclinic	Monoclinic	Triclinic
Space group	P-1	P21/C	P21/C	P-1
Unit cell				
a/(Å)	7.311(3)	6.246(2)	4.701(2)	9.471(3)
b/(Å)	8.746(4)	16.671(6)	30.810(4)	10.170(3)
c/(Å)	14.164(6)	14.173(4)	10.899(5)	16.911(7)
α/(°)	76.400(5)	90	90	101.429(6)
β/(°)	82.966(6)	112.611(2)	109.490(3)	97.597(6)
γ/(°)	85.491(6)	90	90	107.012(4)
V/ (Å)	872.5(7)	1361.9(8)	1486.8(3)	1495.0(9)
Z	4	4	4	4
Index ranges	-8≤h≤7	-7≤h≤8	-6≤h≤3	-11≤h≤11
	-6≤k≤10	-18≤k≤21	-40≤k≤39	-12≤k≤11
	-16≤l≤16	-18≤l≤16	-12≤l≤14	-16≤l≤20
Linear absorption coefficient/(mm-1)	0.086	0.275	0.114	0.262
No. Measured reflections	3626	6707	9146	8415
No. independent reflections	3008	2976	3418	5475
No. Refined parameters	238	182	236	399
F(000)	360	584	648	648
Goodness-of-fit(F^2)	0.97	0.96	1.00	0.95
R1(F)/ωR2(F2)(I>2σ(I))	0.051/0.164	0.077/0.233	0.073/0.261	0.076/0.286
Largest different peak and hole (e $Å^{-3}$)	0.150/-0.184	0.249/-0.400	0.410/-0.304	0.625/-0.312

Table 5

Hydrogen-bond geometry (Å, °) of **10c**.

D-H···A	D-H	H···A	D···A	D-H···A
C13-H13···N5^i	0.93	2.55	3.295(4)	137

Symmetric code: (i) x-1,y,z.

Table 6

Hydrogen-bond geometry (Å, °) of **10h**.

D-H···A	D-H	H···A	D···A	D-H···A
C16-H16…C12^i	0.93	2.82	3.555(6)	137
C20-H20A…Cg1^i	0.96	2.64	3.482(8)	147

Symmetric code: (i) -x,-y+1,-z+1. Cg1 is the centroid of the C14-C19 ring

recorded from KBr discs on a Nicolex FI-IR-170 instrument. ^{1}H NMR spectra were run on a Bruker AC400(400 MHz). Mass spectra were obtained on a HP5989A spectrometer at an ionising voltage of 70 eV by electron impact. Elemental analyses were performed on a ThermoFinnigan Flash EA 1112 instrument. X-ray single diffraction was carried with Enraf-Nonius CAD-4 diffractometer by the Analysis center of Fu-Dan university. Data were collected and refined by CAD-4 EXPR- ESS. Program(s) used to solve and refine the structure were SHELXS97. Molecular graphics were solved by ORTEX. The software used to prepare material for publication was SHELXL 97.

General Procedure for the Synthesis of **4a-e** were according to the Lang's method [10].

3-Phenyl-6-methyl-1,2,4,5-tetrazine (4a). Red prism, yield: 22.0%. mp: 74~76 °C (74.5-76 °C [13]). IR (KBr, cm^{-1}): 3050 (Ar-H), 2926 (CH_2), 1402, 1361 (C=N), 1088. MS (m/z, %): 172 (M^+, 12), 103 (100), 76 (16).

3-(4-Methylphenyl)-6-methyl-1,2,4,5-tetrazine (4b). Red prism, yield: 26.5%. mp: 116~118 °C (115~118 °C [10b]). IR (KBr, cm^{-1}): 3056 (Ar-H), 2928 (CH_2), 1404, 1381 (C=N), 1087. MS (m/z, %): 186 (M^+, 25), 117 (100), 90 (32), 63(7).

3-(4-Chlorophenyl)-6-methyl-1,2,4,5-tetrazine (4c). Red prism, yield: 32.5%. mp: 142~144 °C (143~145 °C [10a]). IR (KBr, cm^{-1}): 3049 (Ar-H), 2980 (CH_2), 1405, 1364 (C=N), 1093. MS (m/z, %): 206 (M^+, 15), 136 (100), 102 (25), 75(10).

3-(4-Methoxyphenyl)-6-methyl-1,2,4,5-tetrazine (4d). Red prism, yield: 20.2%. mp: 103~105 °C (103~106 °C [10a]). IR

(KBr, cm^{-1}): 3056 (Ar-H), 2985 (CH_2), 1401, 1360 (C=N), 1088. MS (m/z, %): 202 (M^+, 35), 133 (100), 103 (24), 89(28), 63(7).

General Procedure for the Synthesis of 10a-i. Under a N_2 atmosphere, 85% hydrazine hydrate (10 mL, 170 mmol) was added dropwise to an anhydrous ethanol solution (15 mL) of *p*-substituted benzyl cyanide (25 mmol) **8a-i** and *p*-substituted benzonitrile (25 mmol) **7a-i** at 298 K with existing sulfur powder (0.8 g, 25 mmol). After refluxing for 3 h, the mixture was cooled to room temperature and the resulting yellow solid product was collected by filtration. The solid product was then dissolved in diethyl ether (15 mL); to this solution was added 10 mL aqueous solution of sodium nitrite (1.0 g, 14 mmol) and was then added dropwise of 8 mL aqueous solution of acetic acid (0.9 g, 14 mmol). After standing for 4 h, the purple precipitate was collected and washed with cold anhydrous ethanol (5 mL), which was then chromatographed on a silica gel column using cyclohexane–dichloromethane (V/V, 4:1) as the eluent. The first eluting material, a pink crystal, was 3,6-di(p-substituted phenyl)-s-tetrazine. The second one, a red crystal, was 3-(*p*-substituted phenyl)-6-(*p*-substituted benzyl)-s-tetrazine **10a-i**; the third one, a red crystal, was 3,6-di(*p*-substituted benzyl)-s-tetrazine.

Crystal Structure Determination. Single-crystal X-ray stucuture determination were made on crystal of molecule **4a**, **10c-d** and **10h**. Data collection for the block-shaped single crystals of **4a**, **10c-d** and **10h** was performed on a Bruker CCD system with graphite monochromated Mo Kα radiation (λ= 0.71073 Å) at 293 K. The model type of the diffractometer was CCD area detector. The sizes of the crysrals used for data collection were 0.25×0.20×0.15 mm^3 for **4a**, 0.25×0.20×0.20 mm^3 for **10c**, 0.30×0.25×0.20 mm^3 for **10d**, and 0.25×0.20 ×0.15 mm^3 for **10h**. The structure was solved by direct methods and refined on F^2 using SHELXTL software. Anisotropic thermal parameters were applied for all the non-hydrogen atoms. All hydrogen atoms were positioned geometrically and refined as riding, with C-H distances of 0.97(2) Å and with U_{iso}(H)=1.2Ueq(C). Crystallographic parameters and agreement factors are contained in Table 4. CCDC-634552, 621205, 642406 and 642405 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-1223/336-033; Email: depoist@ccdc.cam.ac.uk] .

3-Phenyl-6-benzyl-1,2,4,5-tetreazine(10a). Red prism, yield: 2.1 g. mp: 112~113 °C (110~111 °C [14]). IR (KBr, cm^{-1}): 3064 (Ar-H), 2926 (CH_2), 1385 (C=N), 1089. ^{1}H NMR ($CDCl_3$, ppm) δ 8.57 (d, 2 H, J= 9.2 Hz), 7.58-7.66 (m, 3 H, Ar-H), 7.48 (d, 2 H, J = 8.0 Hz), 7.29-7.38 (m, 3 H, Ar-H), 4.62 (s, 2 H), 3.78 (s, 3 H). MS (m/z, %): 248 (M^+, 10), 117 (90), 103 (98), 90 (36), 76 (42).

3-Phenyl-6-(4-methoxybenzyl)-1,2,4,5-tetreazine (10b). Red prism, yield: 1.5 g. mp: 120~123 °C. IR (KBr, cm^{-1}): 3066 (Ar-H), 2937 (CH_2), 2837 (CH_3), 1381(C=N), 1247, 1089. ^{1}H NMR ($CDCl_3$, ppm) δ8.57 (d,2 H, J = 6.8 Hz), 7.55-7.61 (m, 3 H, Ar-H), 7.37 (d, 2 H, J = 8.4 Hz), 6.87 (d, 2 H, J = 8.4Hz), 4.62 (s, 2 H), 3.78 (s, 3 H). MS (m/z, %): 278 (M^+, 17), 238 (92), 147 (80), 135 (67), 121 (25), 103 (100), 91 (7), 77 (57). *Anal.* Calcd. for $C_{16}H_{14}N_4O$ (278.31): C, 69.05; H, 5.07; N, 20.13. Found: C, 68.78; H, 5.13; N, 20.06.

3-Phenyl-6-(4-chlorobenzyl)-1,2,4,5-tetreazine (10c). Red prism, yield: 2.8 g. mp: 143~145°C. IR (KBr, cm^{-1}): 3054 (Ar-H), 2937 (CH_2), 1384 (C=N), 1088, 740 (Ar-Cl). ^{1}H NMR ($CDCl_3$, ppm) δ8.58 (d, 2 H, J = 6.8 Hz), 7.57-7.63 (m, 3 H, Ar-H), 7.40 (d, 2 H, J = 8.0 Hz), 6.87 (d, 2 H, J = 8.0 Hz), 4.65 (s, 2 H). MS (m/z, %): 282 (M^+, 4), 151 (33), 116 (82), 103(100), 89 (14), 75 (21). *Anal.* Calcd. for $C_{15}H_{11}N_4Cl$ (282.07): C, 63.72; H, 3.92; N,19.82. Found: C, 63.68; H, 3.84; N, 19.80.

3-[4-(Trifluoromethyl)phenyl]-6-benzyl-1,2,4,5-tetreazine (10d). Red needles, yield: 1.9 g. mp: 135~136°C. IR (KBr, cm^{-1}): 3071 (Ar-H), 2950 (CH_2), 1328 (C=N), 1123 (CF_3), 1091. ^{1}H NMR (DMSO-d_6, ppm) δ 8.66 (d, 2 H, J = 8.4 Hz), 8.04 (d, 2 H,J = 8.4 Hz), 7.28-7.44 (m, 5 H,Ar-H), 4.71 (s, 2 H). MS (m/z, %): 316(M^+, 5), 297 (4), 117 (62), 152 (22), 117 (100), 102 (8), 90 (35), 75 (8).*Anal.* Calcd. for $C_{16}H_{11}N_4F_3$ (316.28): C, 60.76; H, 3.51; N, 17.71. Found: C, 60.79; H, 3.37; N, 17.69.

3-[4-(Trifluoromethyl)phenyl]-6-(4-methoxybenzyl)-1,2,4,5-tetreazine (10e). Red needles, yield: 1.6 g. mp: 137~138°C. IR (KBr, cm^{-1}): 3071 (Ar-H), 2958 (CH_2), 2837 (CH_3), 1328 (C=N), 1112 (CF_3), 1090. ^{1}H NMR ($CDCl_3$, ppm) δ8.70 (d, 2 H, J = 8.8 Hz), 7.84 (d, 2 H, J = 8.8 Hz), 7.38 (d, 2 H, J = 8.8 Hz), 6.88 (d, 2 H, J = 8.8 Hz), 4.65 (s, 2 H), 3.78(s, 3 H). MS (m/z, %): 346 (M^+, 5), 317 (10), 171 (60), 145 (45), 97 (60), 72 (80). $C_{17}H_{13}N_4F_3O$ (346.31): C, 58.96; H, 3.78; N, 16.18. Found: C, 58.78; H, 3.53; N, 15.94.

3-[4-(Trifluoromethyl)phenyl]-6-(4-chlorobenzyl)-1,2,4,5-tetreazine (10f). Red needles, yield: 2.2 g. mp: 140~142 °C. IR (KBr, cm^{-1}): 3071 (Ar-H), 2950 (CH_2), 1326 (C=N), 1113 (CF_3), 1090, 709 (Ar-Cl). ^{1}H NMR (DMSO-d^6) δ8.66 (d, 2 H, J = 8.8 Hz), 8.05 (d, 2 H, J = 8.8 Hz), 7.47 (d, 2 H, J = 8.8 Hz), 7.42 (d, 2 H, J = 8.8 Hz), 4.73 (s, 2 H). MS (m/z, %): 350 (M^+, 5), 171 (70), 151 (37), 116 (100), 102 (8), 89 (20), 75 (15). $C_{16}H_{10}N_4F_3Cl$ (350.73): C, 54.79; H, 2.87; N, 15.97.Found: C, 54.87; H, 2.77; N, 15.86.

3-(4-Chlorophenyl)-6-benzyl-1,2,4,5-tetreazine (10g). Red flat crystal, yield: 1.8 g. mp: 157~158°C. IR (KBr, cm^{-1}): 3087 (Ar-H), 2924 (CH_2), 1384 (C=N), 1091, 737 (Ar-Cl). ^{1}H NMR ($CDCl_3$, ppm) δ8.54 (d, 2 H, J = 8.8 Hz), 7.57 (d, 2 H, J = 8.8 Hz), 7.47 (d, 2 H, J = 8.0 Hz), 7.27-7.37 (m, 3 H, Ar-H), 4.70 (s, 2 H). MS (m/z, %): 282 (M^+, 12), 137 (100), 117 (98), 102 56), 90 (45), 75 (23). *Anal.* Calcd. for $C_{15}H_{11}N_4Cl$ (282.73): C, 63.72; H, 3.92; N, 19.82. Found: C, 63.65; H, 3.84; N, 19.81.

3-(4-Chlorophenyl)-6-(4-methoxybenzyl)-1,2,4,5-tetreazine (10h). Red flat crystal, yield: 1.5 g. mp: 153~155°C. IR (KBr, cm^{-1}): 3089 (Ar-H), 2930 (CH_2), 2850 (CH_3), 1388 (C=N), 1093, 715 (Ar-Cl). ^{1}H NMR ($CDCl_3$, ppm) δ8.53 (d, 2 H, J = 8.8 Hz), 7.57 (d, 2 H, J = 8.8 Hz), 7.38 (d, 2 H, J = 8.4 Hz), 6.88 (d, 2 H, J = 8.4 Hz), 4.64 (s, 2 H), 3.80 (s, 3 H). MS (m/z, %): 312 (M^+, 17), 147 (98), 137 (100), 116 (8), 102 (35), 91 (5), 77 (23). *Anal.* Calcd. for $C_{16}H_{13}N_4ClO$ (312.75): C, 61.44; H,4.19; N, 17.91. Found: C, 61.14; H, 4.13; N, 17.55.

3-(4-Chlorophenyl)-6-(4-chlorobenzyl)-1,2,4,5-tetreazine (10i). Red flat crystal, yield: 2.4 g.mp: 181~183°C. IR (KBr, cm^{-1}): 3089 (Ar-H), 2937 (CH_2), 1389 (C=N), 1094, 725 (Ar-Cl). ^{1}H NMR ($CDCl_3$, ppm): δ8.52 (d, 2 H, J = 8.8 Hz), 7.56 (d, 2 H, J = 8.8 Hz), 7.39 (d, 2 H, J = 8.4 Hz), 7.31 (d, 2 H, J = 8.4 Hz), 4.65(s, 2 H). MS (m/z, %): 316 (M^+, 10), 151 (17), 137 (100), 116 (65), 102 (33), 89 (15),75 (15). *Anal.* Calcd. for $C_{15}H_{10}N_4Cl_2$ (317.17): C, 56.50; H, 3.18; N,17.66. Found: C, 56.53; H, 3.22; N, 17.47.

Acknowledgement. We are indebted to the National Natural Science Foundation of China (grant No. 20272053) for financial support.

REFERENCE

[1] Karl, S.; Ernst, A. German Patent 923,028, 1955; *Chem. Abstr.* **1959**, *53*,1747.

[2] Albert, W. L. Unite State Patent 3,392,167, 1968; *Chem. Abstr.* **1968**, *69*, 96789n.

[3] Arthur, K. G.; Howard, B. Britain Patent 1,245,443, 1971; *Chem. Abstr.* **1972**, *77*844t.

[4] Rao, G. -W.; Hu, W. -X. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3174.

[5] Hu, W. -X.; Shi, H. -B.; Yuan, Q.; Sun, Y. -Q. *J. Chem. Res., Synop.* **2005**, *2*, 91.

[6] Hu, W. -X.; Rao, G. -W.; Sun, Y. -Q. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1177.

[7] Hu, W. -X.; Sun, Y. -Q.; Yuan, Q. *Chem. J. Chin. Univ*. **2002**, *23*, 1887.

[8] Cai, Z. -B.; Zhou, M.; Hu, W. -X.; Yang, Z. -Y. *Acta Pharmacol. Sin.* **2000**, *35*, 793.

[9] See for examples: [a] Hunter, D.; Neilson, D. G.; Weakley, T. J. R. *J. Chem. Soc., Perkin Trans. 1* **1982**,1165. [b] Infantes, L.; Mahon, M. F.; Male, L.; Raithby, P. R.; Teat, S. J.; Sauer, J.; Jagerovic, N.; Elguero, J.; Motherwell, S. *Helv. Chim. Acta* **2003**, *86*, 1205**.** [c] Gao, H. -X; Wang, R. -H.; Twamley, B.; Hiskeyb, M. A.; Shreeve, J. M. *Chem. Commun.* **2006**, 4007. [d] Gomb- osuren, N.; Novak, Z.; Kotschy,A.; Mincsovics, E.; Dibo, G. *J. Biochem. Biophys. Methods* **2007**, *69*, 239.

[10] See for examples: [a] Lang Jr., S. A.; Johnson, B. D.; Cohen, E. *J. Heterocycl. Chem.* **1975**, *12*, 1143 [b] Lang Jr., S. A.; Johnson, B. D.; Cohen, E.; Sloboda, A. E., Greenblatt, E. *J. Med. Chem.* **1976**, *19(12)*, 1404.[c] Nunez-Polo, P.; Prieto; Neunhoeffer, H. *Heterocycl. Commun.* **1998**, *4(4)*, 301.

[11] Frabzen, H.; Kraft, F. *J. Prakt. Chem.* **1911**, *84*, 122.

[12] See for examples: [a] Prout, K. C.; Orley, T. M.; Tickle, I. J.; Wright, J. D. *J. Chem. Soc., Perkin Trans. II* **1973**, 523. [b] Kubo, K.; Mori, A.; Ujiie, S.; Tschierske, C. *J. Oleo Sci.* **2005**, *54*, 179. [c] Takahashi, H.; Takechi, H.; Kubo, K.; Matsumoto, T. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2005**, *E61*, o3041. [d] Kubo, K.; Matsumoto, T.; Katahira, K.; Mori, A. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2005**, *E61*, o2750.

[13] Counotte- potman, A.; Van der Plas, H.C.; Van Veldhuizen, B. *J. Org. Chem*. **1981**, *46*, 2138

[14] Bowie, R. A.; Gardner, M. D.; Neilson, D. G.; Watson, K. M.; Mahmood, S. *J. Chem. Soc., Perkin Trans. I* **1972**, 2395.