From 3-chloromethyl-1,2,4-triazine 4-oxides to various substituted pyridines and 1,2,4-triazines*

V. N. Kozhevnikov,[a,b] D. N. Kozhevnikov,[a,b] O. V. Shabunina,[a] N. N. Kataeva,[a] S. A. Yushchuk,[a] V. L. Rusinov,[a,b] and O. N. Chupakhin[a,b]*

[a]*Ural State Technical University (UPI), 19 ul. Mira, 620002 Ekaterinburg, Russian Federation. Fax: +7 (343) 374 0458. E-mail: dnk@htf.ustu.ru*

[b]*I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 22 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation. Fax: +7 (343) 374 1189. E-mail: chupakhin@ios.uran.ru*

An efficient strategy for the synthesis of new pyridine and 1,2,4-triazine derivatives starting from available 6-aryl-3-chloromethyl-1,2,4-triazine 4-oxides was proposed. The deoxygenative nucleophilic hydrogen substitution in the triazine-oxide ring, nucleophilic substitution of the chlorine atom in the side chain, and transformations of the 1,2,4-triazine ring into the pyridine ring *via* the inverse-electron-demand Diels—Alder reactions, being used in different orders, are a rather flexible tool for the functionalization of the titled heterocycles. The cyanide anion, indoles, thiophenols, amines, and triphenylphosphine were used as nucleophiles. The direct introduction of indole residues into the 1,2,4-triazine ring followed by the substitution of the chlorine atom by a residue of the primary or secondary aliphatic amine was found to be the most convenient method for the library synthesis.

Key words: pyridine, indole, 1,2,4-triazine, nucleophilic substitution, inverse-electron-demand Diels—Alder reaction, Wittig reaction.

Pyridine derivatives are undoubtedly among the most abundant heterocyclic compounds with useful properties.[1] It is mentioned[2] that "The wide ranging biological activity associated with many pyridine derivatives, both naturally occurring and synthetic, ensures that the synthesis of this important ring systems remains a topic of current interest." Moreover, the pyridine derivatives are interesting as ligands for the preparation of transition metal complexes with valuable photophysical[3,4] or magnetic properties[5,6] and find use as chemosensors[7] or catalysts.[8]

In this work, we propose a strategy for the synthesis of new pyridine derivatives, including the preparation of 1,2,4-triazines, their functionalization mainly due to nucleophilic hydrogen substitution (S_N^H), and the transformation into the pyridine derivatives *via* the inverse-electron-demand Diels—Alder reaction. This sequence of reactions makes it possible to obtain new compounds under the conditions of library liquid-phase synthesis. It should be noted that the 1,2,4-triazines used can be of independent interest. For instance, the 1,2,4-triazine derivatives are used as analytical reagents[9,10] or selective extracting agents for actinides during spent nuclear fuel processing.[11,12]

The proposed strategy for the synthesis of functionalized pyridines and 1,2,4-triazines includes the four main stages (Scheme 1). The first stage is the preparation of the starting 6-aryl-3-chloromethyl-1,2,4-triazine 4-oxides **1** from different aryl methyl ketones using an earlier described approach.[13]

The nucleophilic attack in 1,2,4-triazine 4-oxides **1** can be directed on either the chloromethyl group or the carbon atom in position 5 of the heterocycle. Thus, it can be expected that the substitution of a chlorine atom is the next stage for further modification (see Scheme 1, routes *a*: variation of the Nu′ residues). The third stage, *viz.*, the introduction of C-nucleophile residues into the heterocycle by hydrogen atom substitution (see Scheme 1, routes *b*: variation of the Nu residues), is the reaction typical of 1,2,4-triazine 4-oxides.[14—16] The last stage includes the transformation of functionalized 1,2,4-triazines to the corresponding pyridines (where the substituents introduced in the previous steps were retained) due to the inverse-electron-demand Diels—Alder reaction (see Scheme 1, routes *c*).[17—19] As a whole, a possibility of consecutive employment of these reactions in different combinations using different nucleophiles and dienophiles can be assumed.

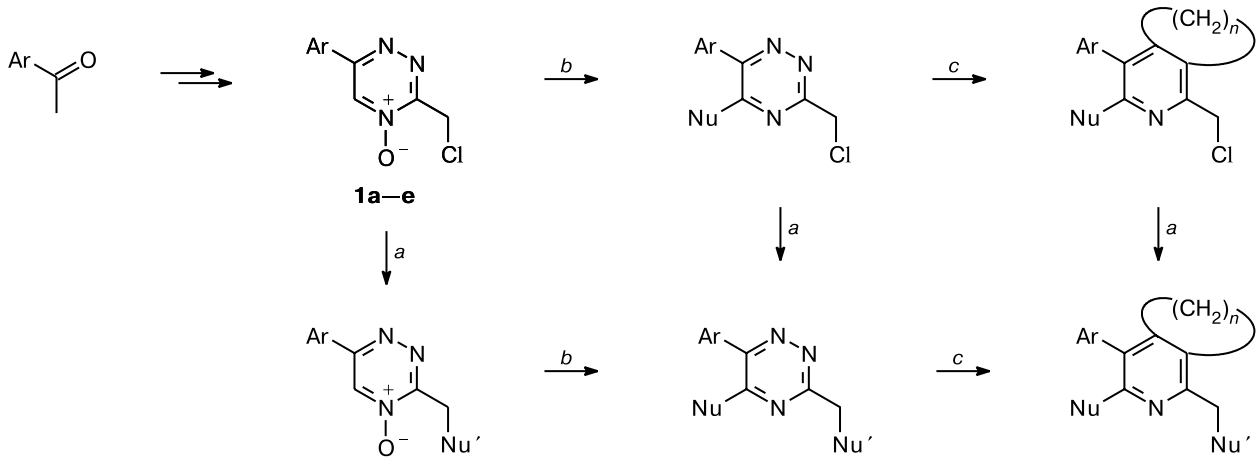
Route b—c—a (Scheme 1). One of the most interesting substituents, which can be introduced into the 1,2,4-tri-

* Dedicated to Academician N. S. Zefirov on the occasion of his 70th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 2122—2131, September, 2005.

1066-5285/05/5409-2187

Scheme 1



Ar = Ph (**1a**), *p*-Tol (**1b**), 4-ClC_6H_4 (**1c**), 4-$MeOC_6H_4$ (**1d**), naphth-2-yl (**1e**)

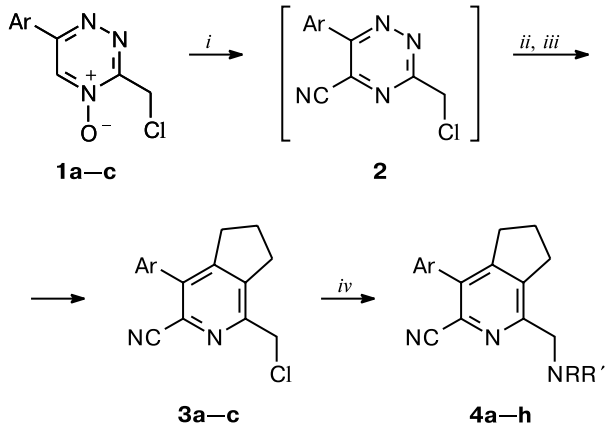
azine cycle according to the proposed approach (reaction *b*, Scheme 1), is a cyano group. Its transformations produce heterocycles bearing different functional substituents (from the carboxyl or carboxamide group to the pyridine[20] or oxazoline[21] fragments). In addition, due to pronounced donor-acceptor properties of the cyano group, its presence in the 1,2,4-triazine cycle considerably facilitates the inverse-electron-demand Diels—Alder reactions.[22]

An attempt to directly cyanate triazine oxides **1** under the earlier proposed conditions (acetone cyanohydrin in the presence of triethylamine[23]) resulted, unfortunately, in the resinification of the reaction mixture. However, 6-aryl-3-chloromethyl-5-cyano-1,2,4-triazines **2** are actually formed: according to the TLC data, triazine oxides **1** are completely converted into cyanotriazines **2** within 7—10 min, after which the product is rapidly resinified. We decided to exclude the isolation of cyanotriazines **2** from the reaction mixture but to perform immediately the subsequent reaction: cycloaddition. In fact, the gas (N_2) begins to evolve upon the addition of 1-morpholinocyclopentene 5—10 min after the onset of cyanation, indicating the Diels—Alder reaction followed by retrodecomposition.

The final transformation of the 1,2,4-triazine ring into the pyridine cycle is achieved by the elimination of a morpholine molecule due to the heating of the intermediate cycloadduct in acetic acid without its additional purification. As a result, a series of 5-aryl-2-chloromethyl-6-cyano-3,4-cyclopentenopyridines **3** in 45—50% yields are formed (Scheme 2).

The resulting chloromethylpyridines **3** are convenient building blocks for the synthesis of other pyridine derivatives by the nucleophilic substitution of halogen, for instance, by amine residues. In the framework of this work,

Scheme 2



Ar = Ph (**1a**, **3a**, **4a—c**), *p*-Tol (**1b**, **3b**, **4d—g**), naphthyl-2 (**1c**, **3c**, **4h**)

NRR′ = pyrrolidino (**4a**), 2-methylpiperidino (**4b**), 3-methylpiperidino group (**4c**), 4-(2-hydroxyethyl)-piperazin-1-yl (**4d**), (1-hydroxy-2-methyl-2-yl)-amino (**4e**), dimethylamino group (**4f**), 4-methyl-piperazin-1-yl (**4g**), morpholino group (**4h**)

Reagents and conditions: *i*. Acetone cyanohydrin, NEt_3, CH_2Cl_2, 40 °C, 10 min; *ii*. 1-Morpholinocyclopentene, 20 °C, 1 h; *iii*. AcOH, 117 °C, 10 min; *iv*. HNRR′, 80 °C, 2 h.

we synthesized a library of 36 aminomethylpyridines **4** by the action of excess aliphatic amines on chloromethylpyridines **3a—c**. The reaction is very convenient from the preparative point of view, because aminomethylpyridines **4** are readily isolated from the reaction mixture (dilution with water and filtration-off of residues) and need no additional purification. Here we present the characteris-

tics of eight synthesized compounds **4a—h** of the whole series (see Scheme 2 and Experimental).

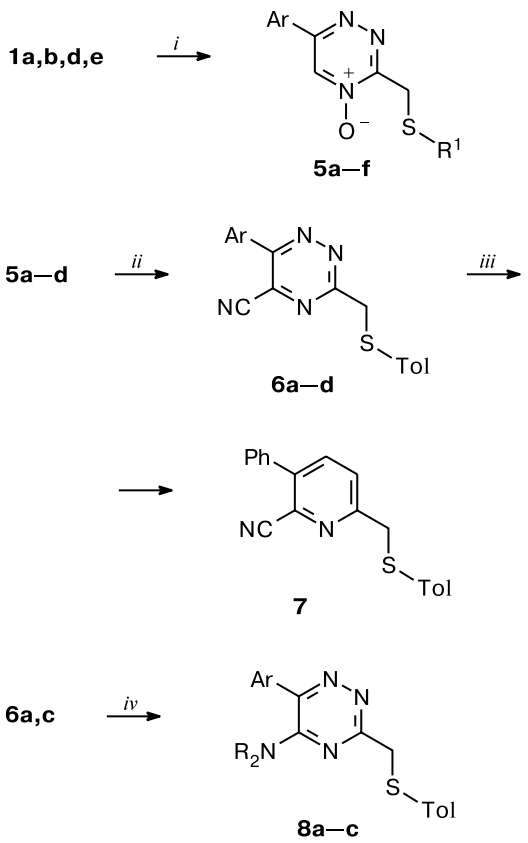
As a whole, the proposed approach is convenient for the synthesis of new pyridine derivatives with a possibility to vary in a rather wide range the Ar substituents (starting from substituted acetophenones), the annelated cycloalkyl fragment (using different enamines in the inverse-electron-demand Diels—Alder reactions), and the NRR′ group.

Route a—b—c (Scheme 1). Resinification in the cyanation reaction can be avoided if the chlorine atom can be replaced by a less labile group. The arylthiol group was chosen as such a group in this work. For instance, the reactions of 3-chloromethyl-1,2,4-triazine 4-oxides **1** with different thiophenols under basic conditions afford 6-aryl-3-arylthiomethyl-1,2,4-triazine 4-oxides **5**. Under the action of acetone cyanohydrin in the presence of triethylamine, the latter are transformed into the corresponding 5-cyano derivatives **6**, which are convenient building blocks for new heterocyclic compounds (Scheme 3). They rather easily undergo the Diels—Alder reactions to form functionalized pyridines. For instance, the reflux of 5-cyano-1,2,4-triazines **6** with excess 2,5-norbornadiene in toluene affords 3-aryl-6-arylthiomethyl-2-cyanopyridines **7** (see Scheme 3), which can hardly be prepared *via* any other route. In addition, the cyano group in 5-cyano-1,2,4-triazines **6** acts as a good leaving group in nucleophilic substitution reactions. The action of excess aliphatic amines on compounds **6** produces the corresponding 5-amino-6-aryl-2-arylthiomethyl-1,2,4-triazines **8** in high yields (see Scheme 3).

Routes b—a and a—b (Scheme 1). The presence of the *N*-oxide group in the 1,2,4-triazine cycle enables one to introduce residues of other nucleophiles, which differ from the nitrile group, into the heterocycle *via* the S_NH reactions.[14] We have chosen indoles as nucleophiles that are of independent interest for synthetic chemists. The proposed approach using these nucleophiles can be considered as a method for preparing functional derivatives of this pharmacophoric fragment. For example, the reactions of 1,2,4-triazine 4-oxides **1** with indole and 1-methylindole in the presence of benzoyl chloride afford the corresponding 6-aryl-3-chloromethyl-5-(indol-3-yl)-1,2,4-triazines **9** in 50—65% yields. The subsequent substitution of the chlorine atom by thiophenol residues occurs under the above-described conditions to form 6-aryl-3-arylthiomethyl-5-(indol-3-yl)-1,2,4-triazines **10** (Scheme 4).

An attempt to change the reaction sequence does not produce the expected product **10**. The reaction of triazine oxide **5a** with indole in the presence of an equimolar amount of benzoyl chloride affords benzoyl-[4-hydroxy-5-(indol-3-yl)-4,5-dihydro-1,2,4-triazin-3-ylmethyl](*p*-tolyl)sulfonium chloride **11** (see Scheme 4). The reaction ceases at the step of nucleophile addition to position 5 of

Scheme 3



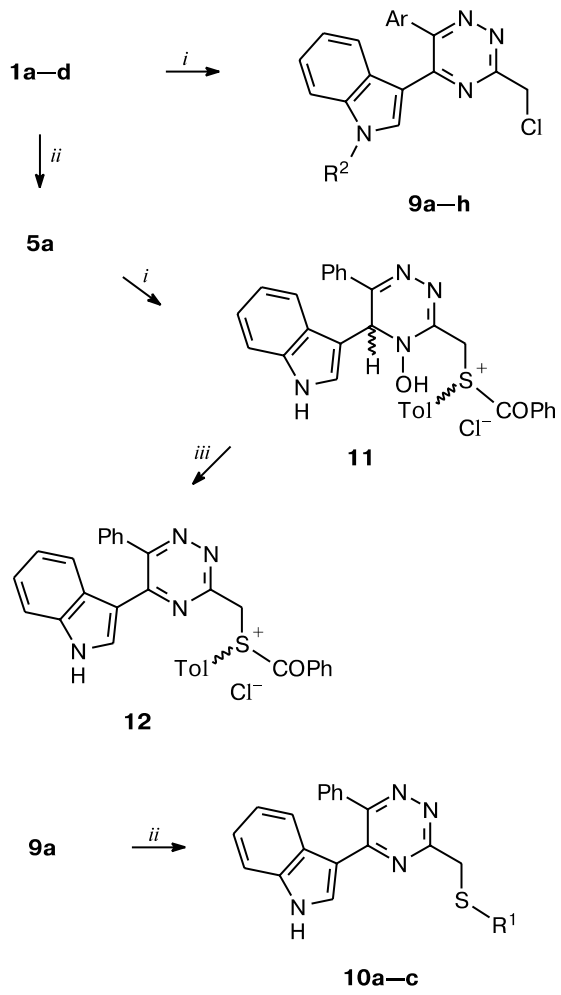
5, 6: Ar = Ph (**a**), *p*-Tol (**b**), 4-ClC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**);
5: R^1 = *p*-Tol (**a—d**), **5e:** Ar = Ph, R^1 = 3-$MeOC_6H_4$,
5f: Ar = Ph, R^1 = 4-ClC_6H_4
8: Ar = Ph (**a**), 4-ClC_6H_4 (**b**, **c**), R_2N is pyrrolidino (**a**, **b**), morpholino group (**c**)

Reagents and conditions: *i*. R^1SH, ethanol, NEt_3, 50 °C, 1 h; *ii*. acetone cyanohydrin, NEt_3, CH_2Cl_2, 20 °C, 30 min; *iii*. 2,5-norbornadiene, toluene, 110 °C, 4 h; *iv*. HNR′R″, 80 °C, 1 h.

the triazine ring with the formation of a σ^H-adduct, because the acylating agent that is necessary for aromatization (benzoyl chloride) is consumed to the acylation of the sulfur atom. The reaction with a twofold excess of benzoyl chloride or the interaction of adduct **11** with 1 equivalent of benzoyl chloride affords an aromatic product of hydrogen substitution: benzoyl(indolyltriazinylmethyl)(tolyl)sulfonium chloride **12** (see Scheme 4).

The addition of indole with simultaneous *S*-acylation produces adduct **11** with two asymmetric centers: the carbon atom in position 5 of the triazine ring and the sulfur atom. The double set of signals in the ^1H NMR spectra of compound **11** with the almost equal integral intensities indicates that a mixture of diastereomers **11** in a ratio of ~1 : 1 is formed. For instance, the signal of the proton in position 5 of the triazine ring is presented by two singlets

Scheme 4



Ar = Ph (**9a**, **e**), *p*-Tol (**9b**, **f**), 4-ClC_6H_4 (**9c**, **g**), 4-$MeOC_6H_4$ (**9d**, **h**); R^2 = H (**9a—d**), Me (**9e—h**); R^1 = *p*-Tol (**10a**), 3-$MeOC_6H_4$ (**10b**), 4-ClC_6H_4 (**10c**)

Reagents and conditions: *i*. Indole or 1-methylindole, PhCOCl (1 equiv.), THF, 20 °C, 15 h; *ii*. R^1SH, ethanol, NEt_3, 50 °C, 1 h; *iii*. PhCOCl (1 equiv.), THF, 20 °C, 15 h.

at δ 6.41 and 6.47. It should be mentioned that the nonequivalent protons of the *S*-methylene fragment are presented by the single-proton singlets (J_{gem} = 0 Hz) in both adduct **11** and aromatic hydrogen-substitution product **12**.

1,2,4-Triazine 4-oxide **1a** acts as an alkylating agent in the reactions of triphenylphosphine to form (4-oxido-6-phenyl-1,2,4-triazin-3-yl)methyltriphenylphosphonium chloride (**13**), which is easily isolated from the reaction mixture. The resulting phosphonium salt **13** undergoes the Wittig reaction with benzaldehydes in the presence of triethylamine under mild conditions to form the corresponding 3-styryl-1,2,4-triazine 4-oxides **14a—e** (Scheme 5). As follows from the values of the spin-spin coupling constants between the protons of the CH=CH fragment (J = 16.1—16.7 Hz) in the ^{1}H NMR spectra of compounds **14**, only the *E*-isomers are formed. The reaction of indolyltriazine **9a** with triphenylphosphine followed by the treatment with anisaldehyde affords the Wittig reaction product **16** (see Scheme 5) (intermediate phosphonium salt **15** was not isolated from the reaction mixture).

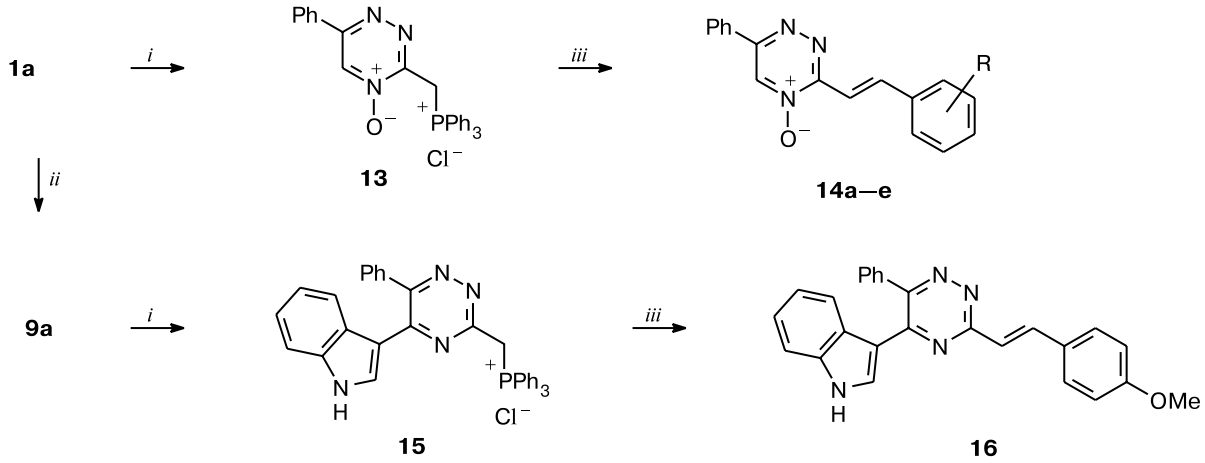
It is found that the chlorine atom in 5-indolyl-1,2,4-triazines **9** is rather easily substituted by residues of primary and secondary aliphatic amines. For example, the reactions of triazines **9a,d** with chiral amines, *viz.*, (−)-cytisine and *L*-alaninol, in a DMF solution in the presence of triethylamine afford the corresponding 3-aminomethyl-6-aryl-5-(indol-3-yl)-1,2,4-triazine **17a—c** in 60—71% yields (Scheme 6).

Many of the reactions described here are convenient from the preparative point of view and occur in good yields. We distinguished three reactions, namely, the formation of 3-chloromethyl-1,2,4-triazine 4-oxides **1**, the introduction of indole residues into the triazine ring, and the substitution of the chlorine atom by the amino group, which can be used under the conditions of library liquid-phase synthesis. In this case, the products can be varied by an independent change in three components: isonitrosoacetophenone hydrazones **18** (replacement of Ar), indoles, and amines. All reactions proceed rather smoothly, which makes it possible to exclude the stages of purification of intermediate compounds **1** and **9** and simplifies the isolation of final aminomethyltriazines **17**. The solvents were chosen in such a way that evaporation steps were excluded, and only filtration of precipitates remained (intermediates **1** and **9** are crystallized from the reaction mixture, whereas the latter are crystallized as hydrochlorides). To form a precipitate of aminomethyltriazines **17**, it is enough to dilute the reaction mixture with water.

Thus, of four hydrazones **18** and two indoles, eight chloromethyltriazines **9a—h** were synthesized. They were introduced into the reaction with twelve aliphatic amines. As a result, a library of ninety-six 3-aminomethyl-1,2,4-triazines **17** was obtained. Products **17** were obtained without purification as individual compounds (according to the data of ^{1}H NMR spectroscopy) in 45—90% yields in the last step (for all compounds **17** of the library). In this article, we present a representative set of five thus obtained compounds **17a—e** (see Scheme 6).

The structures of new compounds were determined from the data of elemental analysis, mass spectrometry, and NMR spectroscopy. The following signals were used as characteristic chemical shifts in the ^{1}H NMR spectra of the synthesized products. For all compounds, these are the signals of the protons of the methylene group bonded to the heteroatom: δ 4.8—5.0 for CH_2Cl (compounds **3** and **9**), δ 3.5—4.1 for CH_2N (compounds **4** and **17**), δ 4.2—4.6 for CH_2S (compounds **5—8**, **10**), δ 6.5—7.2 for

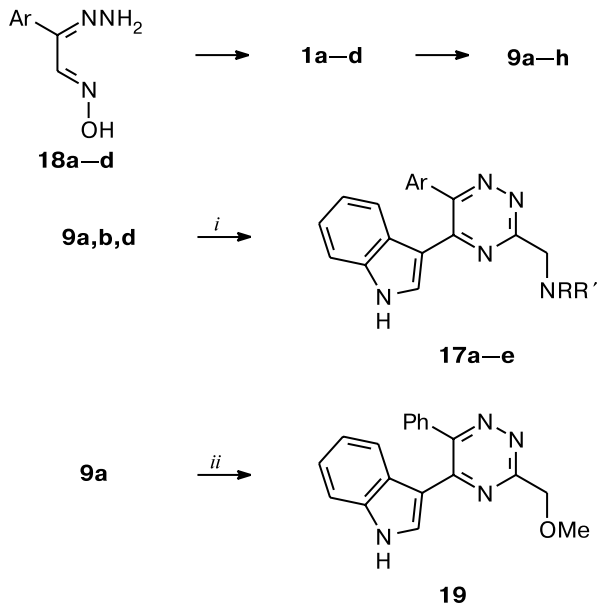
Scheme 5



R = 4-NO_2 (**14a**), 3-NO_2 (**14b**), 4-Br (**14c**), 4-MeO (**14d**), 4-NMe_2 (**14e**)

Reagents and conditions: *i*. Ph_3P, MeCN, NEt_3, 80 °C, 1 h; *ii*. Indole, PhCOCl, THF, 20 °C, 15 h; *iii*. 4-$MeOC_6H_4CHO$, NEt_3, EtOH, 20 °C, 15 h.

Scheme 6



Ar = Ph (**17a,c,d 18a**), *p*-Tol (**17e, 18b**), 4-ClC_6H_4 (**18c**), 4-$MeOC_6H_4$ (**17b**, **18d**);
NRR′ is cytisino (**17a,b**), (1-hydroxypropyl-2)amino (**17c**), isopropylamino group (**17d**), 4-(2-hydroxyethyl)-piperazin-1-yl (**17e**); R^2 = H (**17a—e**)

Reagents and conditions: *i*. HNRR′; *ii*. MeONa, BuOH, 118 °C.

CH_2S^+Bz (compounds **11** and **12**), and δ 5.85 for CH_2P (compound **13**). In the spectra of products **4b**, **11**, **12**, and **17a—c**, the signals of the protons of the methylene group undergo diastereotopic splitting due to their neighboring with the asymmetric center (benzoylated sulfur atom; asymmetric carbon atoms of the residues of cytisine, alaninol, and 2-methylpiperidine). For 5-indolyl-1,2,4-triazines **9**, **10**, **12**, **16**, **17**, and **19**, the characteristic signal of the proton in position 4 of the indol fragment exhibits a considerable downfield shift (δ 8.4—8.5) compared to the signals of other indole protons (δ 6.8—7.5) due to the anisotropic influence of the aromatic substituent in position 6 of the triazine ring.[15]

Naturally, the spectra of the products contain signals of protons of the introduced substituents in their usual region. For 1,2,4-triazine 4-oxides **5**, **13**, and **14**, the signal of the proton in position 5 of the triazine ring at δ 9.2—9.3 is characteristic. The transformation of the 1,2,4-triazine ring into the pyridine cycle is accompanied by the appearance in the ^1H NMR spectra of high-field signals of the $—CH_2—CH_2—CH_2—$ fragments (pyridines **3** and **4**) or two low-field doublets of the protons of the central pyridine cycle (compounds **7**).

However, it should be noted that the proposed synthetic strategy has several restrictions. For instance, the chlorine atom in compounds **9** is not substituted in the reaction with ammonia, whereas substitution by an alcohol residue occurs under drastic conditions: only a prolonged reflux of chloromethyltriazine **9a** in butanol with sodium methoxide provides 3-hydroxymethyl-1,2,4-triazine **19** (see Scheme 6). Attempts to carry out at first the substitution reactions of the chlorine atom in 1,2,4-triazine 4-oxides **1** by the amine residue and then the substitution of a hydrogen atom by any C-nucleophile were unsuccessful, because the 1,2,4-triazine ring decomposed in the first step under the action of amines. Indolyltriazines **9**, **10**, and **16** were not either transformed into the corre-

sponding indolylpyridines because, most likely, the introduction of the electron-releasing indole fragment decreases sharply the reactivity of 1,2,4-triazines in the inverse-electron-demand Diels—Alder reactions.

It should be mentioned in conclusion that the accessibility of 3-chloromethyl-1,2,4-triazine 4-oxides, their easy chemical modification using the nucleophilic substitution of hydrogen and halogen in different combinations and with different nucleophiles, and the use of other transformations (Wittig reactions, inverse-electron-demand Diels—Alder reactions) allow one to obtain various pyridine and 1,2,4-triazine derivatives. These circumstances are important for the library liquid-phase synthesis.

Experimental

NMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz) using a DMSO-d_6—CCl_4 (1 : 1) mixture as the solvent and Me_4Si as the internal standard. Mass spectra were obtained on a Varian MAT-311A instrument (electron ionization). The starting hydroxyiminoacetophenone hydrazones **18** [24] and 3-chloromethyl-1,2,4-triazine 4-oxides **1** [13] were synthesized according to known procedures.

Synthesis of 2-chloromethyl-6-cyano-3,4-cyclopentenopyridines 3 (general procedure). The corresponding 3-chloromethyl-1,2,4-triazine 4-oxide **1** (20 mmol) was dissolved in CH_2Cl_2 (20 mL), acetone cyanohydrin (2.0 mL, 22.2 mmol) and triethylamine (3.1 mL, 22.2 mmol) were added, and the resulting mixture was refluxed for 10 min. Morpholinocyclopentene (3.5 mL, 22.2 mmol) was poured to the mixture, the resulting mixture was refluxed for 10 min, and toluene (10 mL) was added. The reaction mixture was concentrated under reduced pressure to a volume of 10 mL. A precipitate that formed was filtered off, dried in air, and dissolved with boiling in acetic acid (13 mL). The obtained solution was cooled and diluted with water. A precipitate that formed was filtered off and recrystallized from ethanol.

2-Chloromethyl-6-cyano-5-phenyl-3,4-cyclopentenopyridine (3a). The yield was 2.41 g (44%), m.p. 109—110 °C. Found (%): C, 71.60; H, 4.92; N, 10.28. $C_{16}H_{13}ClN_2$. Calculated (%): C, 71.51; H, 4.88; N, 10.42. ^{1}H NMR, δ: 2.13 (m, 2 H, J = 7.5 Hz); 2.90, 3.17 (both t, 2 H each, J = 7.5 Hz); 4.78 (s, 2 H, CH_2Cl); 7.46 (m, 2 H); 7.53 (m, 3 H).

2-Chloromethyl-6-cyano-5-(*p*-tolyl)-3,4-cyclopentenopyridine (3b). The yield was 2.94 g (52%), m.p. 123—124 °C. Found (%): C, 72.20; H, 5.27; N, 10.05. $C_{17}H_{15}ClN_2$. Calculated (%): C, 72.21; H, 5.35; N, 9.91. ^{1}H NMR, δ: 2.14 (m, 2 H, J = 7.5 Hz); 2.43 (s, 3 H); 2.90, 3.16 (both t, 2 H each, J = 7.5 Hz); 4.75 (s, 2 H, CH_2Cl); 7.32 (s, 4 H, Tol).

2-Chloromethyl-6-cyano-5-(2-naphthyl)-3,4-cyclopentenopyridine (3c). The yield was 2.94 g (52%), m.p. 145—146 °C. Found (%): C, 75.29; H, 4.76; N, 8.62. $C_{20}H_{15}ClN_2$. Calculated (%): C, 75.35; H, 4.74; N, 8.79. ^{1}H NMR, δ: 2.17 (m, 2 H, J = 7.5 Hz); 2.95, 3.20 (both t, 2 H each, J = 7.5 Hz); 4.79 (s, 2 H, CH_2Cl); 7.57, 7.97 (both m, 3 H each); 8.03 (d, 1 H, J = 8.5 Hz).

Library synthesis of 3-aminomethylpyridines (4) (general procedure). The synthesis was carried out in 18 (3×6) glass 15-mL vessels (Aldrich) equipped with screw-tops with a Teflon layer and immersed into a water bath. Each of the three vessels was loaded with the corresponding amine (0.5 mL), DMF (1 mL), and one of chloromethylpyridines **3a—c** (100 mg). The mixture was heated for 2 h in a water bath at 70 °C and diluted with water (8—13 mL). A precipitate that formed in some time was filtered off and washed with water.

6-Cyano-5-phenyl-2-pyrrolidinomethyl-3,4-cyclopentenopyridine (4a). The yield was 88 mg (78%), m.p. 66—68 °C (EtOH). Found (%): C, 79.17; H, 6.98; N, 13.85. $C_{20}H_{21}N_3$. Calculated (%): C, 79.17; H, 6.98; N, 13.85. ^{1}H NMR, δ: 1.87 (m, 4 H); 2.12 (m, 2 H, J = 7.6 Hz); 2.86 (m, 6 H); 3.11 (t, 2 H, J = 7.6 Hz); 3.71 (s, 2 H, CH_2N); 7.45 (m, 2 H); 7.55 (m, 3 H).

6-Cyano-2-(2-methylpiperidino)methyl-5-phenyl-3,4-cyclopentenopyridine (4b). The yield was 78 mg (64%), m.p. 136—138 °C. Found (%): C, 79.61; H, 7.74; N, 12.90. $C_{25}H_{25}N_3$. Calculated (%): C, 79.72; H, 7.60; N, 12.68. ^{1}H NMR, δ: 1.12 (d, 3 H); 1.25 (m, 2 H); 1.28, 1.45 (both m, 1 H each); 1.60 (m, 2 H); 2.07 (m, 3 H); 2.37 (m, 1 H); 2.61 (m, 2 H); 2.78 (dd, 1 H, J = 14.2 Hz, J = 7.6 Hz); 2.86 (dd, 1 H, J = 17.0 Hz, J = 7.6 Hz); 3.11 (dt, 1 H, J = 17.0 Hz, J = 7.6 Hz); 3.18 (dt, 1 H, J = 14.2 Hz, J = 7.2 Hz); 3.29, 4.09 (both d, 1 H each, CH_2N, J = 13.1 Hz); 7.52 (m, 5 H).

6-Cyano-2-(3-methylpiperidino)methyl-5-phenyl-3,4-cyclopentenopyridine (4c). The yield was 87 mg (71%), m.p. 97—99 °C. Found (%): C, 79.81; H, 7.78; N, 12.84. $C_{25}H_{25}N_3$. Calculated (%): C, 79.72; H, 7.60; N, 12.68. ^{1}H NMR, δ: 0.82 (d, 3 H, J = 6.8 Hz); 0.85, 1.43 (both m, 1 H each); 1.60 (m, 3 H); 1.69 (t, 2 H, J = 7.6 Hz); 2.02 (m, 2 H, J = 7.6 Hz); 2.72 (m, 2 H); 3.15 (t, 2 H, J = 7.6 Hz); 3.58 (s, 2 H, CH_2N); 7.52 (m, 5 H).

6-Cyano-2-[4-(2-hydroxyethyl)piperazino]methyl-5-(*p*-tolyl)-3,4-cyclopentenopyridine (4d). The yield was 85 mg (64%), m.p. 149—150 °C. Found (%): C, 75.08; H, 6.60; N, 13.29. $C_{20}H_{21}N_3O$. Calculated (%): C, 75.21; H, 6.63; N, 13.16. ^{1}H NMR, δ: 2.07 (m, 2 H, J = 7.6 Hz); 2.37 (t, 2 H, J = 6.1 Hz); 2.43 (s, 3 H); 2.45 (m, 8 H); 2.84, 3.13 (both t, 2 H each, J = 7.6 Hz); 3.47 (m, 2 H, J = 6.1 Hz, J = 2.4 Hz); 3.59 (s, 2 H, CH_2N); 3.99 (br.t, 1 H, OH, J = 2.4 Hz); 7.30 (s, 4 H, Tol).

6-Cyano-2-(1-hydroxy-2-methylprop-2-yl)aminomethyl-5-(*p*-tolyl)-3,4-cyclopentenopyridine (4e). The yield was 69 mg (58%). ^{1}H NMR, δ: 1.04 (s, 6 H); 2.07 (m, 2 H, J = 7.6 Hz); 2.42 (s, 3 H); 2.85, 3.09 (both t, 2 H each, J = 7.6 Hz); 3.24 (d, 2 H, J = 2.0 Hz); 3.76 (s, 2 H, CH_2N); 4.39 (br.s, 1 H, OH, J = 2.0 Hz); 7.30 (s, 4 H, Tol).

6-Cyano-2-dimethylaminomethyl-5-(*p*-tolyl)-3,4-cyclopentenopyridine (4f). The yield was 81 mg (79%). ^{1}H NMR, δ: 2.08 (m, 2 H, J = 7.6 Hz); 2.30 (s, 6 H); 2.42 (s, 3 H); 2.85, 3.12 (both t, 2 H each, J = 7.6 Hz); 3.52 (s, 2 H, CH_2N); 7.30 (s, 4 H, Tol).

6-Cyano-2-(4-methylpiperazino)methyl-5-(*p*-tolyl)-3,4-cyclopentenopyridine (4g). The yield was 104 mg (85%). ^{1}H NMR, δ: 2.07 (m, 2 H, J = 7.6 Hz); 2.17 (s, 3 H); 2.31 (m, 4 H); 2.42 (s, 3 H); 2.50 (m, 4 H); 2.84, 3.12 (both t, 2 H each, J = 7.6 Hz); 3.59 (s, 2 H, CH_2N); 7.31 (s, 4 H, Tol).

6-Cyano-2-morpholinomethyl-5-(2-naphthyl)-3,4-cyclopentenopyridine (4h). The yield was 102 mg (88%). ^{1}H NMR, δ: 2.13 (m, 2 H, J = 7.6 Hz); 2.48 (m, 4 H); 2.91, 3.18 (both t, 2 H each, J = 7.6 Hz); 3.60 (m, 4 H); 3.73 (s, 2 H, CH_2N); 7.60, 7.95 (both m, 3 H each); 8.02 (d, 1 H).

Synthesis of 3-arylthiomethyl-1,2,4-triazine 4-oxides 5 (general procedure). The corresponding 1,2,4-triazine 4-oxide **1**

(2 mmol) was dissolved in ethanol (10 mL) in the presence of triethylamine (0.7 mL, 3 mmol) at 50 °C with stirring, the corresponding thiophenol (2.1 mmol) was added, and the mixture was stirred at the same temperature for 30 min. Crystals precipitated after cooling were filtered off and recrystallized from ethanol.

6-Phenyl-3-(*p*-tolyl)thiomethyl-1,2,4-triazine 4-oxide (5a). The yield was 460 mg (75%), m.p. 140—145 °C. Found (%): 66.05; H, 4.96; N, 13.63. $C_{17}H_{15}N_3OS$. Calculated (%): C, 66.00; H, 4.89; N, 13.58. ^{1}H NMR, δ: 2.30 (s, 3 H, Me); 4.43 (s, 2 H, CH_2S); 7.09, 7.32 (both m, 2 H); 7.52 (m, 3 H); 8.13 (m, 2 H); 9.23 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 309 [M^+] (3).

6-(*p*-Tolyl)-3-(*p*-tolyl)thiomethyl-1,2,4-triazine 4-oxide (5b). The yield was 586 mg (90%), m.p. 158—160 °C. Found (%): 66.41; H, 5.88; N, 12.90. $C_{18}H_{19}N_3OS$. Calculated (%): C, 66.43; H, 5.88; N, 12.91. ^{1}H NMR, δ: 2.31, 2.43 (both s, 3 H each); 4.44 (s, 2 H, CH_2S); 7.12 (m, 2 H); 7.34 (m, 4 H); 8.03 (m, 2 H); 9.21 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 325 [M^+] (4).

6-(4-Chlorophenyl)-3-(*p*-tolyl)thiomethyl-1,2,4-triazine 4-oxide (5c). The yield was 600 mg (87%), m.p. 178—180 °C. Found (%): 59.41; H, 4.12; N, 12.30. $C_{17}H_{14}ClN_3OS$. Calculated (%): C, 59.39; H, 4.10; N, 12.22. ^{1}H NMR, δ: 2.29 (s, 3 H); 4.43 (s, 2 H, CH_2S); 7.09, 7.32, 7.53, 8.16 (all m, 2 H each); 9.29 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 343 (15) and 345 (6) [M^+].

6-(4-Methoxyphenyl)-3-(*p*-tolyl)thiomethyl-1,2,4-triazine 4-oxide (5d). The yield was 545 mg (81%), m.p. 155—157 °C. Found (%): C, 63.71; H, 5.08; N, 12.4.7. $C_{18}H_{17}N_3O_2S$. Calculated (%): C, 63.70; H, 5.05; N, 12.38. ^{1}H NMR, δ: 2.29, 3.85 (both s, 3 H each); 4.43 (s, 2 H, CH_2S); 7.08 (m, 4 H); 7.32, 8.11 (both m, 2 H each); 9.19 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 339 [M^+] (20).

3-(3-Methoxyphenyl)thiomethyl-6-phenyl-1,2,4-triazine 4-oxide (5e). The yield was 550 mg (85%), m.p. 135—140 °C. Found (%): C, 62.85; H, 4.86; N, 12.80. $C_{17}H_{15}N_3O_2S$. Calculated (%): C, 62.75; H, 4.65; N, 12.91. ^{1}H NMR, δ: 3.77 (s, 3 H, OMe); 4.52 (s, 2 H, CH_2S); 6.75 (dd, 1 H, J = 8.2 Hz, J = 2.5 Hz); 7.00 (dd, 1 H, J = 8.2 Hz, J = 1.2 Hz); 7.04 (dd, 1 H, J = 2.5 Hz, J = 1.2 Hz); 7.19 (dd, 1 H, J = 8.2 Hz, J = 8.2 Hz); 7.52 (m, 3 H); 8.14 (m, 2 H); 9.26 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 325 [M^+] (9).

3-(4-Chlorophenyl)thiomethyl-6-phenyl-1,2,4-triazine 4-oxide (5f). The yield was 570 mg (87%), m.p. 140—145 °C. Found (%): C, 58.31; H, 3.49; N, 12.72. $C_{16}H_{12}ClN_3OS$. Calculated (%): C, 58.27; H, 3.67; N, 12.74. ^{1}H NMR, δ: 4.52 (s, 2 H, CH_2S); 7.32, 7.47 (both m, 2 H each); 7.55 (m, 3 H); 8.14 (m, 2 H); 9.26 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 331 (2) and 329 (6) [M^+].

Synthesis of 5-cyano-3-(*p*-tolyl)thiomethyl-1,2,4-triazines 6 (general procedure). Acetone cyanohydrine (0.27 mL, 3 mmol) and triethylamine (0.35 mL, 1.5 mmol) were added to a solution of the corresponding 3-arylthiomethyl-1,2,4-triazine 4-oxide **5** (1.5 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was refluxed for 10—15 min (the end of the reaction was monitored by TLC) and concentrated *in vacuo*. The residue was stirred with a small amount of ethyl acetate for 30 min, filtered off, and recrystallized from propan-2-ol.

5-Cyano-6-phenyl-3-(*p*-tolyl)thiomethyl-1,2,4-triazine (6a). The yield was 315 mg (66%), m.p. 74—76 °C. Found (%): C, 67.94; H, 4.43; N, 17.61. $C_{18}H_{14}N_4S$. Calculated (%): C, 67.90; H, 4.43; N, 17.60. ^{1}H NMR, δ: 2.26 (s, 3 H); 4.67 (s, 2 H, CH_2S); 7.14, 7.33 (both m, 2 H each); 7.66 (m, 3 H); 8.00 (m, 2 H).

5-Cyano-6-(*p*-tolyl)-3-(*p*-tolyl)thiomethyl-1,2,4-triazine (6b). The yield was 299 mg (60%), m.p. 86—88 °C. Found (%): C, 64.31; H, 4.01; N, 16.75. $C_{19}H_{16}N_4S$. Calculated (%): C, 64.27; H, 3.90; N, 16.66. ^{1}H NMR, δ: 2.29, 2.46 (both s, 3 H each); 4.56 (s, 2 H, CH_2S); 7.09, 7.29, 7.42, 7.90 (all m, 2 H each).

6-(4-Chlorophenyl)-5-cyano-3-(*p*-tolyl)thiomethyl-1,2,4-triazine (6c). The yield was 320 mg (60%), m.p. 96—98 °C. Found (%): C, 61.31; H, 3.69; N, 15.75. $C_{18}H_{13}ClN_4S$. Calculated (%): C, 61.27; H, 3.71; N, 15.88. ^{1}H NMR, δ: 2.24 (s, 3 H); 4.58 (s, 2 H, CH_2S); 7.10, 7.30, 7.64, 8.01 (all m, 2 H each).

5-Cyano-6-(4-methoxyphenyl)-3-(*p*-tolyl)thiomethyl-1,2,4-triazine (6d). The yield was 380 mg (73%), m.p. 70—72 °C. Found (%): C, 65.51; H, 4.58; N, 16.05. $C_{19}H_{16}N_4OS$. Calculated (%): C, 65.50; H, 4.63; N, 16.08. ^{1}H NMR, δ: 2.29, 3.89 (both s, 3 H each); 4.55 (s, 2 H, CH_2S); 7.16 (m, 4 H); 7.29, 7.99 (both m, H each).

6-Cyano-5-phenyl-2-(*p*-tolyl)pyridine (7a). Cyanotriazine **6a** (1.5 mmol) and 2,5-norbornadiene (0.27 mL, 3 mmol) were refluxed in toluene for 1—10 g. The course of the reaction was monitored by TLC. The solvent was evaporated, and the residue was recrystallized from ethanol. The yield was 280 mg (59%), m.p. 70—75 °C. Found (%): C, 75.87; H, 5.12; N, 8.78. $C_{20}H_{16}N_2S$. Calculated (%): C, 75.92; H, 5.10; N, 8.85. ^{1}H NMR, δ: 2.30 (s, 3 H); 4.29 (s, 2 H, CH_2S); 7.08, 7.24 (both m, 2 H each); 7.53 (m, 5 H); 7.69, 7.93 (both d, 1 H each, J = 8.3 Hz).

Synthesis of 5-amino-3-(*p*-tolyl)thiomethyl-1,2,4-triazines 8 (general procedure). The corresponding 5-cyano-1,2,4-triazine **6** (0.5 mmol) and amine (1 mL) were heated at 80 °C. The mixture was stored for 30 min and diluted with water. The resulting precipitate was filtered off, washed with water, and recrystallized from acetonitrile.

6-Phenyl-5-pyrrolidino-3-(*p*-tolyl)thiomethyl-1,2,4-triazine (8a). The yield was 125 mg (68%), m.p. 125—130 °C. Found (%): C, 69.46; H, 6.11; N, 15.55. $C_{12}H_{22}N_4S$. Calculated (%): C, 69.58; H, 6.12; N, 15.46. ^{1}H NMR, δ: 1.78 (m, 4 H); 2.29 (s, 3 H); 3.07 (m, 4 H); 4.16 (s, 2 H, CH_2S); 7.07, 7.33 (both m, 2 H each); 7.44 (m, 5 H).

6-(4-Chlorophenyl)-5-pyrrolidino-3-(*p*-tolyl)thiomethyl-1,2,4-triazine (8b). The yield was 130 mg (70%), m.p. 115—120 °C. Found (%): C, 63.48; H, 5.30; N, 14.12. $C_{21}H_{21}ClN_4S$. Calculated (%): C, 63.54; H, 5.33; N, 14.11. ^{1}H NMR, δ: 1.80 (m, 4 H); 2.29 (s, 3 H); 3.10 (m, 4 H); 4.16 (s, 2 H, CH_2S); 7.07, 7.33, 7.45, 7.51 (all m, 2 H each).

6-(4-Chlorophenyl)-5-morpholino-3-(*p*-tolyl)thiomethyl-1,2,4-triazine (8c). The yield was 460 mg (75%), m.p. 120—125 °C. Found (%): C, 61.06; H, 5.11; N, 13.55. $C_{21}H_{21}ClN_4OS$. Calculated (%): C, 61.08; H, 5.13; N, 13.57. ^{1}H NMR, δ: 2.29 (s, 3 H); 3.29, 3.50 (both m, 4 H each); 4.20 (s, 2 H, CH_2S); 7.07, 7.30, 7.49, 7.67 (all m, 2 H each).

Synthesis of chloromethylindolyltriazines 9 (general procedure). Benzoyl chloride (1.25 mL, 10.5 mmol) was added to a suspension of the corresponding 1,2,4-triazine 4-oxide **1** (10 mmol) and indole or 1-methylindole (10 mmol) in THF (50 mL) at 60 °C, and the mixture was stored for 12 h at ~20 °C. The precipitate was filtered off and recrystallized from ethanol.

3-Chloromethyl-5-(indol-3-yl)-6-phenyl-1,2,4-triazine (9a). The yield was 2.4 g (65%), m.p. 203—204 °C. Found (%):

C, 60.58; H, 4.05; N, 15.43. $C_{18}H_{13}ClN_4 \cdot HCl$. Calculated (%): C, 60.69; H, 3.96; N, 15.73. ^{1}H NMR, δ: 5.02 (s, 2 H, CH_2Cl); 6.75 (d, 1 H, $H(2)_{indole}$, J = 3.0 Hz); 7.2 (m, 2 H); 7.42 (m, 1 H); 7.06 (m, 5 H); 8.57 (m, 1 H, $H(4)_{indole}$); 11.82 (br.d, 1 H, NH, J = 3.0 Hz). Mass spectrum, m/z (I_{rel} (%)): 320 (43) and 322 (14) [M^+].

3-Chloromethyl-5-(indol-3-yl)-6-(*p*-tolyl)-1,2,4-triazine (9b). The yield was 2.5 g (68%), m.p. 217—218 °C. Found (%): C, 68.23; H, 4.24; N, 16.84. $C_{19}H_{15}ClN_4$. Calculated (%): C, 68.16; H, 4.52; N, 16.73. ^{1}H NMR, δ: 2.47 (s, 3 H); 4.98 (s, 2 H, CH_2Cl); 6.85 (d, 1 H, $H(2)_{indole}$, J = 3.0 Hz); 7.19 (m, 2 H); 7.38 (m, 3 H); 7.50 (m, 2 H); 8.53 (m, 1 H, $H(4)_{indole}$); 11.68 (br.d, 1 H, NH, J = 3.0 Hz). Mass spectrum, m/z (I_{rel} (%)): 334 (41) and 336 (15) [M^+].

3-Chloromethyl-6-(4-chlorophenyl)-5-(indol-3-yl)-1,2,4-triazine (9c). The yield was 2.2 g (57%), m.p. 140—145 °C. Found (%): C, 55.24; H, 3.20; N, 13.96. $C_{18}H_{12}Cl_2N_4 \cdot HCl$. Calculated (%): C, 55.34; H, 3.36; N, 14.34. ^{1}H NMR, δ: 4.98 (s, 2 H, CH_2Cl); 6.94 (d, 1 H, $H(2)_{indole}$, J = 2.9 Hz); 7.18 (m, 2 H); 7.41 (m, 1 H); 7.59, 7.64 (both m, 2 H each); 8.46 (m, 1 H, $H(4)_{indole}$); 11.72 (br.d, 1 H, NH, J = 2.9 Hz). Mass spectrum, m/z (I_{rel} (%)): 354 (37), 356 (23), and 358 (4) [M^+].

3-Chloromethyl-6-(4-methoxyphenyl)-5-(indol-3-yl)-1,2,4-triazine (9d). The yield was 1.8 g (52%), m.p. 223—224 °C. Found (%): C, 65.39; H, 4.39; N, 16.03. $C_{19}H_{15}ClN_4O$. Calculated (%): C, 65.05; H, 4.31; N, 15.97. ^{1}H NMR, δ: 3.88 (s, 3 H); 4.97 (s, 2 H, CH_2Cl); 6.93 (d, 1 H, $H(2)_{indole}$, J = 3.0 Hz); 7.08, 7.18 (both m, 2 H each); 7.41 (m, 1 H); 7.56 (m, 2 H); 8.50 (m, 1 H, $H(4)_{indole}$); 11.70 (br.d, 1 H, NH, J = 3.0 Hz). Mass spectrum, m/z (I_{rel} (%)): 350 (53) and 352 (19) [M^+].

3-Chloromethyl-5-(1-methylindol-3-yl)-6-phenyl-1,2,4-triazine (9e). The yield was 2.1 g (56%), m.p. 175—176 °C. Found (%): C, 61.74; H, 4.10; N, 14.89. $C_{19}H_{15}ClN_4 \cdot HCl$. Calculated (%): C, 61.63; H, 4.36; N, 15.13. ^{1}H NMR, δ: 3.67 (s, 3 H); 4.99 (s, 2 H, CH_2Cl); 6.80 (s, 1 H, $H(2)_{indole}$); 7.23 (m, 2 H); 7.44 (m, 1 H); 7.65 (m, 5 H); 8.47 (m, 1 H, $H(4)_{indole}$). Mass spectrum, m/z (I_{rel} (%)): 334 (53) and 336 (16) [M^+].

3-Chloromethyl-5-(1-methylindol-3-yl)-6-tolyl-1,2,4-triazine (9f). The yield was 2.0 g (53%), m.p. 130—135 °C. Found (%): C, 62.41; H, 4.57; N, 14.67. $C_{20}H_{17}ClN_4 \cdot HCl$. Calculated (%): C, 62.51; H, 4.72; N, 14.58. ^{1}H NMR, δ: 2.48, 3.69 (both s, 3 H each); 4.97 (s, 2 H, CH_2Cl); 6.90 (s, 1 H, $H(2)_{indole}$); 7.22, 7.33 (both m, 2 H each); 7.43 (m, 1 H); 7.52 (m, 2 H); 8.46 (m, 1 H, $H(4)_{indole}$). Mass spectrum, m/z (I_{rel} (%)): 348 (51) and 350 (18) [M^+].

3-Chloromethyl-6-(4-chlorophenyl)-5-(1-methylindol-3-yl)-1,2,4-triazine (9g). The yield was 2.5 mg (62%), m.p. 142—144 °C. Found (%): C, 56.37; H, 3.65; N, 13.99. $C_{19}H_{14}Cl_2N_4 \cdot HCl$. Calculated (%): C, 56.25; H, 3.73; N, 13.81. ^{1}H NMR, δ: 3.71 (s, 3 H); 5.09 (s, 2 H, CH_2Cl); 7.08 (s, 1 H, $H(2)_{indole}$); 7.27 (m, 2 H); 7.54 (m, 1 H); 7.61, 7.71 (both m, 2 H each); 8.47 (m, 1 H, $H(4)_{indole}$). Mass spectrum, m/z (I_{rel} (%)): 368 (30), 370 (18), and 372 (4) [M^+].

3-Chloromethyl-6-(4-methoxyphenyl)-5-(1-methylindol-3-yl)-1,2,4-triazine (9h). The yield was 2.30 g (57%), m.p. 153—154 °C. Found (%): C, 65.78; H, 4.57; N, 15.46. $C_{20}H_{17}ClN_4O$. Calculated (%): C, 65.84; H, 4.70; N, 15.39. ^{1}H NMR, δ: 3.71, 3.88 (both s, 3 H each); 4.96 (s, 2 H, CH_2Cl); 6.99 (s, 1 H, $H(2)_{indole}$); 7.04, 7.22 (both m, 2 H each); 7.47 (m, 1 H); 7.58 (m, 2 H); 8.43 (m, 1 H, $H(4)_{indole}$). Mass spectrum, m/z (I_{rel} (%)): 364 (76) and 366 (27) [M^+].

Synthesis of 3-arylthiomethyl-5-indolyl-1,2,4-triazines 10 (general procedure). 3-Chloromethyl-5-indolyl-1,2,4-triazine **9a** (714 mg, 2 mmol) was dissolved in ethanol (10 mL) in the presence of triethylamine (0.7 mL, 3 mmol) with stirring and heating, and the corresponding thiophenol (2.1 mmol) was added. The resulting solution was stirred at room temperature for 30 min. A precipitate that formed was filtered off and recrystallized from ethanol.

5-(Indol-3-yl)-6-phenyl-3-(*p*-tolyl)thiomethyl-1,2,4-triazine (10a). The yield was 735 mg (90%), m.p. 180—182 °C. Found (%): C, 73.53; H, 4.89; N, 13.77. $C_{25}H_{20}N_4S$. Calculated (%): C, 73.50; H, 4.93; N, 13.71. ^{1}H NMR, δ: 2.26 (s, 3 H); 4.49 (s, 2 H, CH_2S); 6.74 (s, 1 H, $H(2)_{indole}$); 7.15 (m, 4 H); 7.36 (m, 3 H); 7.55 (m, 5 H); 8.33 (m, 1 H, $H(4)_{indole}$); 11.57 (br.s, 1 H, NH). Mass spectrum, m/z (I_{rel} (%)): 408 [M^+] (35).

5-(Indol-3-yl)-3-(3-methoxyphenyl)thiomethyl-6-phenyl-1,2,4-triazine (10b). The yield was 750 mg, 88%, m.p. 180—185 °C. Found (%): C, 70.82; H, 4.59; N, 13.25. $C_{25}H_{20}N_4OS$. Calculated (%): C, 70.73; H, 4.75; N, 13.20. ^{1}H NMR, δ: 3.71 (s, 3 H); 4.56 (s, 2 H, CH_2S); 6.68 (dd, 1 H, J = 8.1 Hz, J = 2.5 Hz); 6.75 (d, 1 H, $H(2)_{indole}$, J = 3.0 Hz); 7.10 (m, 5 H); 7.36 (m, 1 H); 7.56 (m, 5 H); 8.39 (m, 1 H, $H(4)_{indole}$); 11.58 (br.d, 1 H, NH, J = 3.0 Hz). Mass spectrum, m/z (I_{rel} (%)): 424 [M^+] (30).

3-(4-Chlorophenyl)thiomethyl-5-(indol-3-yl)-6-phenyl-1,2,4-triazine (10c). The yield was 860 mg, 85%, m.p. 175—180 °C. Found (%): C, 67.26; H, 3.88; N, 13.15. $C_{24}H_{17}ClN_4S$. Calculated (%): C, 67.20; H, 3.99; N, 13.06. ^{1}H NMR, δ: 4.56 (s, 2 H, CH_2S); 6.75 (m, 1 H); 7.14 (m, 2 H); 7.35 (m, 3 H); 7.56 (m, 7 H); 8.33 (m, 1 H, $H(4)_{indole}$); 11.59 (br.s, 1 H, NH). Mass spectrum, m/z (I_{rel} (%)): 428 (21) and 430 (8) [M^+].

Benzoyl[4-hydroxy-5-(indol-3-yl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3-ylmethyl](*p*-tolyl)sulfonium chloride (11). Benzoyl chloride (0.098 mL, 0.84 mmol) was added to a suspension of 6-phenyl-3-(*p*-tolyl)thio-1,2,4-triazine 4-oxide (**5a**) (260 mg, 0.84 mmol) and indole (98 mg, 0.84 mmol) in tetrahydrofuran (5 mL) at 60 °C, and the mixture was stored at ~20 °C for 12 h. The precipitate was filtered off and recrystallized from ethanol. The yield was 340 mg (72%), m.p. 193 °C (decomp.). Found (%): C, 67.66; H, 4.86; N, 9.69. $C_{32}H_{27}ClN_4O_2S$. Calculated (%): C, 67.77; H, 4.80; N, 9.88. ^{1}H NMR, δ: 2.14 и 2.29 (both s, 1.5 H each); 6.41 and 6.47 (both s, 0.5 H each, H(5)); 6.75 and 6.77 (both s, 0.5 H each, CH_2S); 7.09 (m, 8 H); 7.18 and 7.22 (both s, 0.5 H each, CH_2S); 7.45 (m, 5 H); 7.80 (m, 4 H); 8.17 (m, 2 H); 11.50 (br.s, 1 H, NH).

Benzoyl[5-(indol-3-yl)-6-phenyl-1,2,4-triazin-3-ylmethyl](*p*-tolyl)sulfonium chloride (12). Adduct **11** (280 mg, 0.5 mmol) and benzoyl chloride (0.066 mL, 0.55 mmol) in tetrahydrofuran (15 mL) were refluxed for 1 h. The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, $CHCl_3$ as eluent). The yield was 180 mg (66%), m.p. > 250 °C (decomp.). Found (%): C, 70.09; H, 4.51; N, 10.02. $C_{32}H_{25}ClN_4OS$. Calculated (%): C, 70.00; H, 4.59; N, 10.20. ^{1}H NMR, δ: 2.29 (s, 3 H); 6.48 (s, 1 H, CH_2S); 7.11 (m, 8 H); 7.20 (s, 1 H, CH_2S); 7.48 (m, 5 H); 7.66 (m, 1 H); 7.85 (m, 3 H); 8.14 (m, 2 H); 11.50 (br.s, 1 H, NH).

(4-Oxido-6-phenyl-1,2,4-triazin-3-ylmethyl)triphenylphosphonium chloride (13). Triphenylphosphine (920 mg, 3.5 mmol) and 3-chloromethyl-1,2,4-triazine 4-oxide **1a** (900 mg, 3.5 mmol) were dissolved in acetonitrile (10 mL), and the mix-

ture was refluxed for 30 min. A precipitate that formed after cooling was filtered off and recrystallized from DMF. The yield was 1.27 g (75%), m.p. 175—180 °C. Found (%): C, 69.49; H, 4.79; N, 8.68. $C_{28}H_{23}ClN_3OP$. Calculated (%): C, 69.49; H, 4.79; N, 8.68. ^{1}H NMR, δ: 5.85 (d, 2 H, CH_2P, J = 14.0 Hz); 7.52 (m, 6 H); 7.84 (m, 15 H); 8.08 (m, 2 H); 9.33 (s, 1 H, H(5)).

Synthesis of 3-styryl-1,2,4-triazine 4-oxides 14 (general procedure). The corresponding benzaldehyde (0.75 mmol) was dissolved in ethanol (5 mL) in the presence of triethylamine (0.18 mL, 0.75 mmol) with stirring for 20 min. Continuing stirring, a solution of (4-oxido-1,2,4-triazin-3-ylmethyl)triphenylphosphonium chloride **13** (390 mg, 0.75 mmol) in ethanol was added dropwise. The solution was stirred at ~20 °C for 30 min. A precipitate that formed was filtered off and recrystallized from DMF.

3-(4-Nitrostyryl)-6-phenyl-1,2,4-triazine 4-oxide (14a). The yield was 110 mg (46%), m.p. > 300 °C. Found (%): C, 63.68; H, 3.78; N, 17.49. $C_{17}H_{12}N_4O_3$. Calculated (%): C, 63.75; H, 3.78; N, 17.49. ^{1}H NMR, δ: 7.58 (m, 3 H); 7.95, 8.38 (both d, 1 H each, J = 16.2 Hz); 8.07 (m, 2 H); 8.22 (m, 4 H); 9.26 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 320 [M^+] (50).

3-(3-Nitrostyryl)-6-phenyl-1,2,4-triazine 4-oxide (14b). The yield was 130 mg (53%), m.p. 238—240 °C. Found (%): C, 63.79; H, 3.82; N, 17.48. $C_{17}H_{12}N_4O_3$. Calculated (%): C, 63.75; H, 3.78; N, 17.49. ^{1}H NMR, δ: 7.57 (m, 3 H); 7.74 (m, 1 H); 7.89, 8.36 (both d, 1 H each, J = 16.7 Hz); 8.20 (m, 4 H); 8.57 (m, 1 H); 9.20 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 320 [M^+] (20).

3-(4-Bromostyryl)-6-phenyl-1,2,4-triazine 4-oxide (14c). The yield was 119 mg (45%), m.p. 235—237 °C. Found (%): C, 57.46; H, 3.41; N, 12.03. $C_{17}H_{12}BrN_3O$. Calculated (%): C, 57.65; H, 3.41; N, 11.86. ^{1}H NMR, δ: 7.60 (m, 3 H); 7.65, 7.78 (both m, 2 H each); 7.80 and 8.26 (both d, 1 H each, J = 16.5 Hz); 8.19 (m, 2 H); 9.24 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 354 (30) and 352 (29) [M^+].

3-(4-Methoxystyryl)-6-phenyl-1,2,4-triazine 4-oxide (14d). The yield was 140 mg (60%), m.p. 207—209 °C. Found (%): C, 70.91; H, 4.96; N, 13.89. $C_{18}H_{15}N_3O_2$. Calculated (%): C, 70.81; H, 4.95; N, 13.76. ^{1}H NMR, δ: 3.82 (s, 3 H, MeO); 7.02 (m, 2 H); 7.55 (m, 3 H); 7.63 and 8.25 (both d, 1 H each, J = 16.1 Hz); 8.17 (m, 2 H); 9.13 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 305 [M^+] (50).

3-(4-*N,N*-Dimethylaminostyryl)-6-phenyl-1,2,4-triazine 4-oxide (14e). The yield was 110 mg (45%), m.p. 210 °C. Found (%): C, 71.71; H, 5.67; N, 17.60. $C_{19}H_{18}N_4O$. Calculated (%): C, 71.68; H, 5.70; N, 17.60. ^{1}H NMR, δ: 3.01 (s, 6 H, 2 Me); 6.77 (m, 2 H); 7.49 and 8.20 (both d, 1 H each, J = 16.0 Hz); 7.57 (m, 3 H); 7.61, 8.18 (both m, 2 H each); 9.15 (s, 1 H, H(5)). Mass spectrum, m/z (I_{rel} (%)): 318 [M^+] (50).

5-(Indol-3-yl)-3-(4-methoxystyryl)-6-phenyl-1,2,4-triazine (16). A solution of triphenylphosphine (920 mg, 3.5 mmol) and 3-chloromethyl-1,2,4-triazine **9a** (1120 mg, 3.5 mmol) in acetonitrile (10 mL) was refluxed for 30 min, and the reaction mixture was evaporated to dryness and dissolved in ethanol (15 mL). The resulting solution was added dropwise with stirring to a solution of benzaldehyde (3.5 mL, 3.5 mmol) in ethanol (20 mL) in the presence of triethylamine (0.5 mL, 3.5 mmol), and the mixture was stirred for 1 h and left to stand for 18 h. A crystalline precipitate that formed was filtered off and recrystallized from acetonitrile. The yield was 1.2 g (85%), m.p. 214—215 °C. Found (%): C, 77.23; H, 4.96; N, 13.88. $C_{26}H_{20}N_4O$. Calculated (%): C, 77.21; H, 4.98; N, 13.85. ^{1}H NMR, δ: 3.84 (s, 3 H, MeO); 6.86 (d, 1 H, $H(2)_{indole}$, J = 3.05 Hz); 6.98, 7.18 (both m, 2 H each); 7.31 and 8.09 (both d, 1 H each, J = 16.3 Hz); 7.40 (m, 1 H); 7.52 (m, 3 H); 7.61, 7.69 (both m, 2 H each); 8.50 (m, 1 H, $H(4)_{indole}$); 11.55 (br.d, 1 H, NH). Mass spectrum, m/z (I_{rel} (%)): 404 [M^+] (70).

Synthesis of 3-aminomethyl-5-(indol-3-yl)triazines 17a—c (general procedure). A solution of the corresponding 5-indolyl-1,2,4-triazine **9** (0.5 mmol) and amine (0.7 mmol) in DMF (5 mL) was stored for 5 h in the presence of triethylamine (1 mmol) at room temperature, diluted with water (50 mL), and extracted with CH_2Cl_2. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography (silica gel, $CHCl_3$ and then EtOH as eluents).

3-Cytisinomethyl-5-(indol-3-yl)-6-phenyl-1,2,4-triazine (17a). The yield was 160 mg (67%), m.p. 148—149 °C. Found (%): C, 71.29; H, 5.88; N, 16.17. $C_{30}H_{28}N_6O_2$. Calculated (%): C, 71.41; H, 5.59; N, 16.65. ^{1}H NMR, δ: 1.79 (m, 2 H); 2.42 (m, 1 H); 2.73 (m, 2 H); 3.10 (m, 3 H); 3.76 (m, 2 H); 3.84 and 4.00 (both d, 1 H each, CH_2N, J = 12.3 Hz); 6.04, 6.24, 6.83 (all m, 1 H each); 7.17 (m, 3 H); 7.37 (m, 1 H); 7.57 (m, 5 H); 8.19 (m, 1 H, $H(4)_{indole}$); 11.59 (br.d, 1 H, NH).

3-Cytisinomethyl-5-(indol-3-yl)-6-(4-methoxyphenyl)-1,2,4-triazine (17b). The yield was 151 mg (60%), m.p. 148—149 °C. Found (%): C, 73.52; H, 5.74; N, 17.68. $C_{29}H_{26}N_6O$. Calculated (%): C, 73.40; H, 5.52; N, 17.71. ^{1}H NMR, δ: 1.71 (m, 2 H); 2.49, 2.57 (both m, 1 H each); 2.71 (m, 1 H); 3.07 (m, 3 H); 3.76 (m, 2 H); 3.84 (s, 3 H, OMe); 3.86 and 3.98 (both d, 1 H each, CH_2N, J = 12.0 Hz); 6.11, 6.22, 6.91 (all m, 1 H each); 7.09, 7.79 (both m, 2 H each); 7.32, 7.42 (both m, 1 H each); 7.53 (m, 2 H); 8.26 (m, 1 H, $H(4)_{indole}$); 11.71 (br.d, 1 H, NH).

5-(Indol-3-yl)-3-(1-hydroxyprop-2-yl)aminomethyl-6-phenyl-1,2,4-triazine (17c). The yield was 78 mg (71%), m.p. 103—104 °C. Found (%): C, 70.19; H, 5.87; N, 19.48. $C_{21}H_{21}N_5O$. Calculated (%): C, 70.18; H, 5.89; N, 19.48. ^{1}H NMR, δ: 1.07 (m, 3 H, Me); 2.86 (m, 1 H); 3.35 (m, 2 H); 4.11 and 4.24 (both d, 1 H each, CH_2N, J = 14.8 Hz); 6.79 (d, 1 H); 7.16 (m, 2 H); 7.38 (m, 1 H); 7.57 (m, 5 H, Ph); 8.46 (m, 1 H, $H(4)_{indole}$); 11.52 (br.d, 1 H, NH).

Synthesis of 3-aminomethyl-5-(indol-3-yl)-triazines (17d,e) (general procedure). The synthesis was carried out in 15-mL vessels (Aldrich) equipped with screw-tops with a Teflon layer and immersed into a water bath. Each of the vessels was loaded with the corresponding amine (0.5 mL), DMF (1 mL), and one of the chloromethyltriazines **9a,b** (100 mg) and heated on a water bath at 70 °C for 2 h. The mixture was diluted with water (8—13 mL), and a precipitate that formed after 1—12 h was filtered off and washed with water.

5-(Indol-3-yl)-3-isopropylaminomethyl-6-phenyl-1,2,4-triazine (17d). The yield was 98 mg (61%), m.p. 165 °C. Found (%): C, 73.44; H, 6.16; N, 20.39. $C_{21}H_{21}N_5$. Calculated (%): C, 73.41; H, 6.16; N, 20.35. ^{1}H NMR, δ: 1.12 (m, 6 H, Me); 2.97 (m, 1 H); 4.13 (s, 2 H, CH_2N); 6.78 (d, 1 H); 7.17 (m, 2 H); 7.38 (m, 1 H); 7.52 (m, 5 H, Ph); 8.43 (m, 1 H, $H(4)_{indole}$); 11.53 (br.s, 1 H, NH).

3-[1-(2-Hydroxyethyl)piperazinomethyl]-5-(indol-3-yl)-6-(*p*-tolyl)-1,2,4-triazine (17e). The yield was 90 mg (70%), m.p. 186 °C. Found (%): C, 69.96; H, 6.59; N, 19.75. $C_{25}H_{28}N_6O$. Calculated (%): C, 70.07; H, 6.59; N, 19.61. ^{1}H NMR, δ: 2.48 (m, 1 H); 2.70 (m, 4 H); 3.48 (m, 2 H); 3.96 (s, 2 H, CH_2N);

4.00 (br.t, 1 H, OH); 6.84 (d, 1 H); 7.36 (m, 7 H); 8.52 (m, 1 H, $H(4)_{indole}$); 11.53 (br.d, 1 H, NH).

5-(Indol-3-yl)-3-methoxymethyl-6-phenyl-1,2,4-triazine (19). 1,2,4-Triazine **9a** (357 mg, 1 mmol) in butanol (5 mL) in the presence of sodium methoxide (2 mmol) was refluxed for 30 min. A precipitate that formed was filtered off and recrystallized from butanol. The yield was 210 mg (60%). Found (%): C, 68.90; H, 5.24; N, 16.51. $C_{20}H_{18}N_4O_2$. Calculated (%): C, 69.35; H, 5.24; N, 16.17. ^{1}H NMR, δ: 3.50, 3.83 (both s, 3 H each, MeO); 4.81 (s, 2 H, CH_2O); 6.90 (d, 1 H); 7.10, 7.12 (both m, 2 H each); 7.44, 7.56 (both m, 1 H each); 7.17 (m, 2 H); 8.53 (s, 1 H, $H(4)_{indole}$); 11.75 (br.d, 1 H, NH).

This work was financially supported in part by the Russian Foundation for Basic Research (Project No. 05-03-32134), the US Civilian Research and Development Foundation (CRDF, Grants EK-005-X1 and Y1-05-03), and the Council on Grants of the President of the Russian Federation (Program for State Support of Leading Scientific Schools of the Russian Federation, Grant NSh 1766.2003.3).

References

1. G. Henry, *Tetrahedron*, 2004, **60**, 6043.
2. K. E. Bashford, M. B. Burton, S. Cameron, A. L. Cooper, R. D. Hogg, P. D. Kane, D. A. MacManus, C. A. Matrunola, C. J. Moody, A. A. B. Robertson, and M. Warne, *Tetrahedron Lett.*, 2003, **44**, 1627.
3. K. Kalyanasundaram, *Photosensitization and Photocatalysis Using Inorganic and Organic Compounds*, Eds K. Kalyanasundaram and M. Grätzel, Kluwer Academic Publishers, Dordrecht, 1993, 247.
4. E. C. Constable, A. M. W. Cargill Thompson, D. A. Tocher, and M. A. M. Daniels, *New J. Chem.*, 1992, **16**, 855.
5. G. Zoppellaro, A. Ivanova, V. Enkelmann, A. Geies, and M. Baumgarten, *Polyhedron*, 2003, **22**, 2099.
6. R. Ziessel, G. Ulrich, R. C. Lawson, and L. Echegoyen, *J. Mater. Chem.*, 1999, **9**, 1435.
7. M. H. Keefe, K. D. Benkstein, and J. T. Hupp, *Coord. Chem. Rev.*, 2000, **205**, 201.
8. G. Chelucci and R. P. Thummel, *Chem. Rev.*, 2002, **102**, 3129.
9. P. L. Croot and K. A. Hunter, *Anal. Chim. Acta*, 2000, **406**, 289.
10. H. Katano, H. Kuboyama, and M. Senda, *J. Electroanal. Chem.*, 2000, **483**, 117.
11. Z. Kolarik, U. Mullich, and F. Gassner, *Solv. Extr. Ion Processes*, 1999, **17**, 23.
12. P. B. Iveson, C. Riviere, M. Nierlich, P. Thuery, M. Ephritikhine, D. Guillaneux, and C. Madic, *J. Chem. Soc., Chem. Commun.*, 2001, 1512.
13. D. N. Kozhevnikov, N. N. Kataeva, V. L. Rusinov, and O. N. Chupakhin, *Izv. Akad. Nauk*, *Ser. Khim.,* 2004, 1243 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 1295 (Engl. Transl.)].
14. D. N. Kozhevnikov, V. L. Rusinov, and O. N. Chupakhin, *Adv. Heterocycl. Chem.*, Ed. A. R. Katritzky, 2002, **82**, 261.
15. V. L. Rusinov, D. N. Kozhevnikov, I. S. Kovalev, O. N. Chupakhin, and G. G. Aleksandrov, *Zh. Org. Khim.*, 2000, **36**, 1081 [*Russ. J. Org. Chem.*, 2000, **36**, 1050 (Engl. Transl.)].
16. D. N. Kozhevnikov, V. L. Rusinov, O. N. Chupakhin, M. Makosza, A. Rykowski, and E. Wolinska, *Eur. J. Org. Chem.*, 2002, 1412.
17. G. R. Pabst, K. Schmid, and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 6691.
18. V. N. Kozhevnikov, D. N. Kozhevnikov, T. V. Nikitina, V. L. Rusinov, O. N. Chupakhin, M. Zabel, and B. Koenig, *J. Org. Chem.*, 2003, **68**, 2882.
19. S. P. Stanforth, B. Tarbit, and M. D. Watson, *Tetrahedron Lett.*, 2002, **43**, 6015.
20. G. Chelucci, M. Faloni, and G. Giacomelli, *Synthesis*, 1990, 1121.
21. S. Gladiali, L. Pinna, G. Delogu, E. Graf, and H. Brunner, *Tetrahedron: Asymmetry*, 1990, 937.
22. D. N. Kozhevnikov, V. N. Kozhevnikov, T. V. Nikitina, V. L. Rusinov, O. N. Chupakhin, I. L. Eremenko, and G. G. Aleksandrov, *Tetrahedron Lett.,* 2002, **43**, 4923.
23. D. N. Kozhevnikov, V. N. Kozhevnikov, I. S. Kovalev, V. L. Rusinov, O. N. Chupakhin, and G. G. Aleksandrov, *Zh. Org. Khim*, 2002, **38**, 780 [*Russ. J. Org. Chem.*, 2002, **38**, 744 (Engl. Transl.)].
24. B. B. Dey, *J. Chem. Soc.*, 1914, **105**, 1039.

Received July 4, 2005;
in revised form September 12, 2005