Regioselective Synthesis of Pyrimido[5,4-c][2,1]benzothiazines by Reactions of β-Chloroaldehydes with N-C-N Binucleophiles

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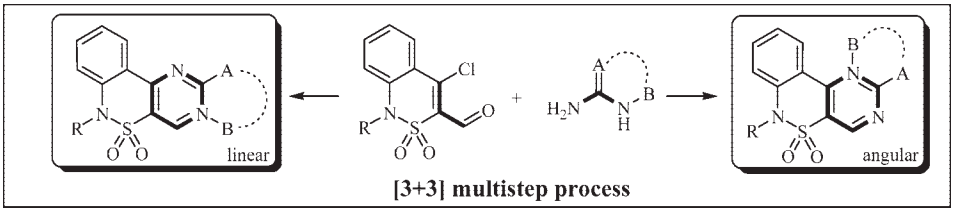

The method of pyrimidine ring fusion at the [*c*] side of benzothiazines based on the reaction of their chloroaldehyde derivatives with amidines is described. Formation of the structural isomers of reaction products was investigated, and regioselectivity of heterocyclization reactions was shown. A number of novel pyrimidobenzothiazines were synthesized.

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INTRODUCTION

Among benzothiazine derivatives, there are a number of compounds known to show biological activity [1]. In particular, heterocyclic ring fusion on a side [*c*] of benzothiazine leads to the condensed systems some representatives of which are known as drugs. Thus, 5-methyl-3-(2-pyridyl)-2H,5H-1,3-oxazino[5,6c][1,2]benzo thiazin-2, 4-(3H)-dione-6,6-dioxide **1** [2] is a well-known anti-inflammatory agent (trade name ''Droxicam''), and (4-methoxy-3,5-dimethyl-phenyl)-(9-methyl-9H-10-thia-2,4,9-triaza-phenantren-3-yl)-amine **2** is a protein tyrosine kinase inhibitor [3] (Fig. 1). However, condensed benzothiazines currently used in medicine have a number of adverse effects [4].

RESULTS AND DISCUSSION

In our previous paper [5], we have reported the synthesis of some novel benzo[*e*][2,1]thiazine derivatives—chloroaldehydes **3a–e** (Fig. 2), and their chemistry was shown to be quite diverse. Compounds **3** contain labile chlorine atom at C-4 and carbonyl group at C-3 position of the ring. We assumed that the studies of chloroaldehyde fragment reactivity could provide a way to obtain new condensed benzothiazines devoid of side effects or less toxic.

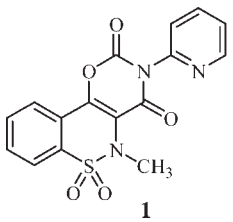
In this article, we describe the method of pyrimidine ring fusion at the [*c*] side of benzothiazines. The route developed by our group involves the interaction of chloroaldehydes **3a–e** with bis-nucleophilic agents **4a–i** containing N-C-N fragment (Table 1). When amidines **4a–c** are used as nucleophiles, the formation of pyrimidobenzothiazines as only products is expected. In case of asymmetric bis-nucleophiles **4d–i**, structural isomers of the reaction product can be formed. Depending on which electrophilic center is attacked by nucleophile at the first stage of heterocyclization process, linear- or angular-type fused compound is obtained.

Pyrazoles **4d–f** and benzoimidazole **4h** both contain two N-nucleophilic centers, thus in reactions with chloroaldehydes **3** two different isomeric pyrazolobenzothiazine products are possible (Scheme 1). Triazole **4g** and quinazalone **4i** contain three N-nucleophilic centers each, which causes four possible isomeric products in reaction with **3** (Scheme 2). One of current research goals was to establish exactly which isomer is formed in every case.

The interaction of chloroaldehydes **3a,b** with amidines **4a–c** (Scheme 3) led to pyrimidobenzothiazines **5a–f**. Reactions proceeded under mild conditions, and no first-stage intermediates were observed in the reaction mixtures.

The next step of this work was to investigate the reactions of compounds **3** with aminopyrazoles **4d–f**. The heating of **3** with **4d–f** resulted in crystalline products **6** (Scheme 4). We have expected the formation of angular products, and ^{1}H NMR spectra of compounds **6a–l** did not contradict angular structures, as H-1 phenylene proton doublet was observed to undergo low-field shift. However, X-ray analysis proved the structure of compounds **6a–l** to be linear (Fig. 3). It seems that the signal of phenylene proton in compound **6** can shift to 8.5 ppm due to the effect of nitrogen atom of pyrimidine ring.

We have not found in the literature any example of the reaction of β-halogenvinylcarbonyl compounds with



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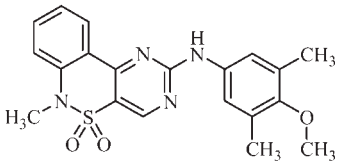

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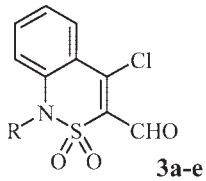
Figure 1. Examples of biologically active condensed benzothiazines.



3a-e

Label	R
3a	-CH_3
3b	-C_2H_5
3c	-*n*-C_3H_7
3d	-*n*-C_4H_9
3e	-CH_2Ph

Figure 2. 4-Chloro-benzo[c][1,2]thiazine-3-carbaldehydes **3a–e**.

amidine nucleophiles proceeding *via* nucleophilic substitution of halogen atom at the first stage of the reaction followed by nucleophilic addition to carbonyl group resulting in the products of linear type. All reactions of analogous nature described until now proceed by Schiff base formation at first stage, then displacement of chlorine. What we observe is opposite to that route. Aldehyde group in compounds **3** is more sterically available than C-4 carbon atom; therefore, its reactions have to proceed under kinetic control, whereas the substitution of chlorine is rather thermodynamically controlled process. We assume the nucleophilic substitution of chlorine atom to be the ''push–pull'' process, with addition of exocyclic amino function of **4d–f** to C-4 carbon followed by halogen cleavage with C3–C4 double bond restoration.

The interaction of **3b,c** with 2-aminobenzoimidazole **4h** proceeds in a similar way (Scheme 5). Upon mild heating (30–35°C) of the reaction solution in DMF, the mixture of the Schiff base **8a,b** and the heterocyclization product **9a,b** is formed in the equimolar ratio (^{1}H NMR data). Subsequent temperature increase (50–70°C) acts in favor of the cyclic derivative **9a,b** (1:2 ratio). Heating the mixture to 100°C results in the formation of **9a,b** only. The interaction between the protons with chemical shifts 7.51 and 8.45 ppm (Scheme 5) observed during 1D-NOESY experiment proved angular structure of products **9**. Analysis of 3D molecular models led to the conclusion that compounds **9** most probably adopt helical-type structure.

When 3-aminotriazole **4g** was used as a nucleophile, the reaction with **3a–c** proceeded in more common manner: the initial condensation of exocyclic amino function with carbonyl group is followed by the displacement of chlorine atom (Scheme 6). Depending on which nitrogen atom (N-2 or N-4) attacks the C-4 position at the second stage of the heterocyclization, formation of structural isomers of the reaction products **7** can occur. 1D-NOESY experiment revealed strong interaction between the protons with chemical shifts 8.82 and 9.58 ppm (Scheme 6) that proved N-4 (but not N-2) nitrogen atom of 3-aminotriazole to participate in the ring formation.

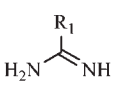
The reactions of chloroaldehydes **3** with 2-aminoquinazolin-4-one **4i** give angular compounds **10a–c** (Scheme 7).

To determine the structure of the product isolated from the reaction mixture, ^{1}H and ^{13}C NMR spectroscopy was used. The investigation of 3D models of the product showed that in the structure **10** the doublet of H-1 proton should be shifted to low field due to the neighboring carbonyl oxygen effect.

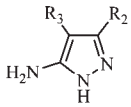
In experimental NMR spectrum, we observe a pronounced shift of the doublet that due to homonuclear (COSY) and heteronuclear (^{1}H-^{13}C HMBC, HMQC) correlation experiments originated from the H-5 proton of starting benzothiazine **3**. Thus, the reaction proceeds regioselectively; the ''amide'' nitrogen of the starting quinazoline **4i** participates in cyclization.

Table 1

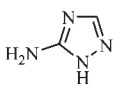
Structures of bis-nucleophilic reagents.



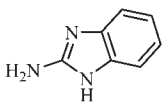
Label	R_1
4a	-*i*-C_3H_7
4b	-Ph
4c	-Thienyl



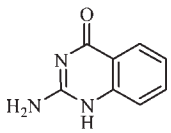
Label	R_2, R_3
4d	-CH_3, -H
4e	-CH_3, -*m*-Cl-Ph
4f	-H, CO_2Et



4g

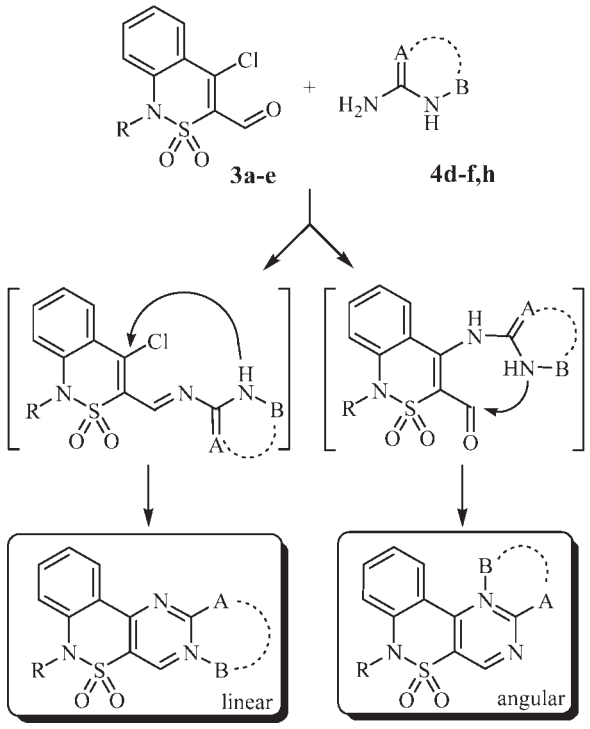


4h



4i

Scheme 1



Structures of all aforementioned compounds were established on the basis of their ^{1}H NMR, ^{13}C NMR, Mass spectrometry data, and elemental microanalyses.

In summary, we disclose the synthesis of novel benzo [*e*][2,1]thiazine derivatives, in particular substituted pyrimidobenzothiazines and pyrazolo-, imidazo-, triazolopyrimidobenzothiazines. These compounds were obtained in high yields (∼70–80%) *via* convenient protocols involving heterocyclization reactions of chloroaldehydes **3a–e** with N-C-N bisnucleophiles **4a–i**.

EXPERIMENTAL

The NMR spectra were measured on a Varian 400 spectrometer at 25°C using DMSO-d_6. All chemical shifts are reported in ppm relative to TMS.

Starting materials used were obtained from Makrochim and used without further purification. Dry solvents were prepared according to the standard methods.

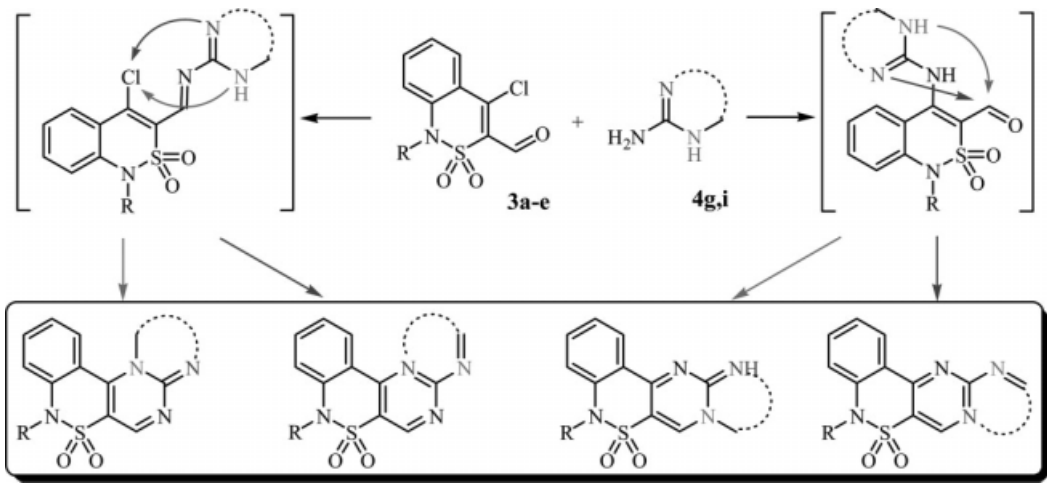
6-Alkyl-6H-pyrimido[5,4-c][2,1]benzothiazine-5,5-dioxides (5a–f); general procedure. The mixture of β-chloroaldehyde **3** (1 mmol) with the corresponding amidine **4a–c** (1.2 mmol) was dissolved in 2 mL of dry DMF. Triethylamine (2 mL) was added and the reaction mixture was heated for 6 h at 80°C. The mixture was cooled to room temperature, quenched with water (20 mL), solid product was filtered off, and then washed with ethanol. The pure product was obtained by crystallization from DMF (64–86%).

Product 5a (77%, R Me, R$_1$ i-Pr). m.p.: 103–104°C; ^{1}H NMR (400 MHz, DMSO): δ = 1.42 (d, *J* = 7.8 Hz, 6H), 3.48 (quin. *J* = 7.7 Hz, 1H), 3.58 (s, 3H), 7.48(t, *J* = 7.8, 1H), 7.63(d, *J* = 7.8 Hz, 1H), 7.75(t, *J* = 7.8 Hz, 1H), 8.68(d, *J* = 7.75 Hz, 1H), 9.11 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 14.55 (×2), 43.78, 49.13, 122.63, 125.36, 128.65, 129.47, 135.34, 141.17, 143.19, 153.17, 156.22, 164.62; MS (CI): 290(M+H)$^+$; Anal. calcd. C, 58.11; H, 5.23; N, 14.52; found C, 58.14; H, 5.25; N, 14.54.

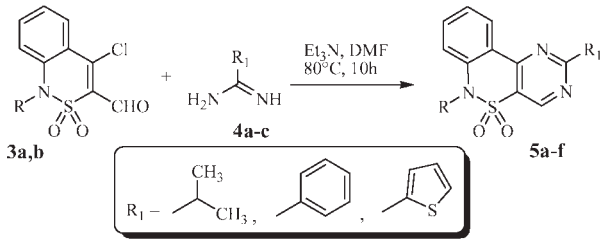
Product 5b (79%, R Me, R$_1$ Ph). m.p.: 202–203°C; ^{1}H NMR (400 MHz, DMSO): δ = 3.59 (s, 3H) 7.45–7.63 (m, 5H), 7.82 (t, *J* = 7.8 Hz, 1H), 8.57(d, *J* = 8 Hz, 2H), 8.83 (d, *J* = 7.8 Hz, 1H) 9.30 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 38.22, 120.51, 123.34, 126.72, 126.97, 127.62, 129.38, 129.68, 133.29, 135.07, 136.54, 140.07, 141.04, 142.57, 152.88, 156.23, 166.91; MS (CI): 324(M+H)$^+$; Anal. calcd. C, 63.14; H, 4.05; N, 12.99; found C, 63.17; H, 4.07; N, 13.02.

Product 5c (64%, R Me, R$_1$ Thienyl). m.p.: 194–195°C; ^{1}H NMR (400 MHz, DMSO): δ = 3.59 (s, 3H) 7.26 (t, *J* = 8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.74–7.81 (m, 2H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.69 (d, *J* = 7.8 Hz, 1H), 9.15 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 37.74, 120.44, 123.75, 125.37, 126.74, 128.68, 129.15, 129.94, 133.45, 135.89, 136.35, 141.94, 152.56, 156.84, 164.89; MS

Scheme 2

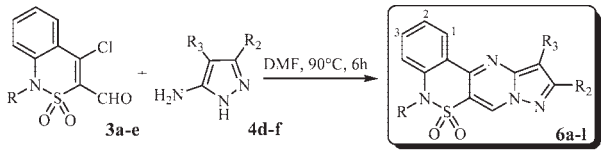


Scheme 3



Synthesis of pyrimido-annelated benzothiazines **5**

Scheme 4



Condensation with aminopyrazoles **4d-f**

(CI): 330(M+H)$^+$; Anal. calcd. C, 54.69; H, 3.37; N, 12.76; found C, 54.72; H, 3.40 N, 12.77.

Product 5d (82%, R Et, R_1 i-Pr). m.p.: 114–115°C; ^{1}H NMR (400 MHz, DMSO): δ = 1.22 (t, *J* = 8 Hz, 3H), 1.42 (d, *J* = 7.8 Hz, 6H), 3.48 (quin. *J* = 7.8 Hz, 1H), 4.08 (q, *J* = 8 Hz, 2H), 7.46(t, *J* = 7.8, 1H), 7.60(d, *J* = 7.8 Hz, 1H), 7.78(t, *J* = 7.8 Hz, 1H), 8.63(d, *J* = 7.8 Hz, 1H), 9.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 14.64 (×2), 44.25, 49.02, 121.60, 123.37, 125.76, 127.65, 129.78, 132.15, 135.33, 141.09, 142.18, 152.77, 156.20, 162.82; MS (CI): 304(M+H)$^+$; Anal. calcd. C, 59.38; H, 5.65; N, 13.85; found C, 59.40; H, 5.66; N, 13.85.

Product 5e (86%, R Et, R_1 Ph). m.p.: 214–215°C; ^{1}H NMR (400 MHz, DMSO): δ = 1.23 (t, *J* = 7.6 Hz, 3H), 4.08 (q, *J* = 7.6 Hz, 2H), 7.49–7.67 (m, 5H), 7.80 (t, *J* = 7.8 Hz, 1H), 8.61(d, *J* = 8 Hz, 2H), 8.80 (d, *J* = 7.8 Hz, 1H) 9.32 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 14.71, 44.22, 121.52, 123.64, 125.76, 126.59, 127.82, 129.35, 129.62, 132.89, 135.27, 136.59, 141.02, 152.60, 156.12, 165.93; MS (CI): 338(M+H)$^+$; Anal. calcd. C, 64.08; H, 4.48; N, 12.45; found C, 64.09; H, 4.47; N, 12.47.

Product 5f (71%, R Et, R_1 Thienyl). m.p.: 205–206°C; ^{1}H NMR (400 MHz, DMSO): δ = 1.21 (t, *J* = 8 Hz, 3H), 4.07 (q, *J* = 8 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.75–7.82 (m, 2H), 8.17 (d, *J* = 8 Hz, 1H), 8.67 (d, *J* = 7.8 Hz, 1H), 9.18 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 14.73, 22.05, 43.96, 121.43, 123.50, 125.68, 126.37, 135.16, 140.88, 152. 07, 155.60, 178.09; MS (CI): 344(M+H)$^+$; Anal. calcd. C, 55.96; H, 3.82; N, 12.24; found C, 55.96; H, 3.83; N, 12.27.

5-Alkyl-5*H*-pyrazolo[1′,5′:1,2]pyrimido[5,4-*c*][2,1]benzo thiazin-6,6-dioxides (6a–l); general procedure. The mixture of β-chloroaldehyde **3** (1 mmol) with the corresponding aminopyrazole **4d–f** (1.2 mmol) was dissolved in 2 mL of dry DMF. The reaction mixture was heated for 10 h at 90°C. The mixture was cooled to room temperature; solid product was filtered off and washed with ethanol. The pure product was obtained by crystallization from DMF (59–86%).

Product 6a (68%, R Me, R_2 Me, R_3 H). m.p.: 178–179°C; ^{1}H NMR (400 MHz, DMSO): δ = 3.35 (s, 3H), 3.37 (s, 3H), 6.81 (s, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 8.47 (d, *J* = 8 Hz, 1H), 9.86 (s, 1H); MS (CI): 301(M+H)$^+$; Anal. calcd. C, 55.99; H, 4.03; N, 18.65; found C, 56.02; H, 4.03; N, 18.68.

Product 6b (70%, R Et, R_2 Me, R_3 H). m.p.: >250°C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ = 1.03 (t, *J* = 6.8 Hz, 3H), 3.35 (s, 3H), 3.91 (q, *J* = 6.8 Hz, 2H), 6.80 (s, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 9.83 (s, 1H); MS (CI): 315 (M+H)$^+$; Anal. calcd. C, 57.31; H, 4.49; N, 17.82; found C, 57.32; H, 4.51; N, 17.81.

Product 6c (86%, R Pr, R_2 Me, R_3 H). m.p.: >250°C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ = 0.80 (t, *J* = 6.8 Hz,3H), 1.54 (m, 2H), 2.50 (s, 3H), 3.83 (t, *J* = 6.8 Hz,2H), 6.67 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 9.61 (s, 1H); MS (CI): 329(M+H)$^+$; Anal. calcd. C, 58.52; H, 4.91; N, 17.06; found C, 58.53; H, 4.93; N, 17.07.

Product 6d (75%, R Bu, R_2 Me, R_3 H). m.p.: >250°C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ = 0.83 (t, *J* = 6.8 Hz,3H), 1.22 (m, 2H), 1.50 (m, 2H), 2.54 (s, 3H), 3.86 (t, *J* = 6.8 Hz, 2H), 6.67 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 9.61 (s, 1H); MS (CI): 343(M+H)$^+$; Anal. calcd. C, 59.63; H, 5.30; N, 16.36; found C, 59.64; H, 5.33; N, 16.36.

Product 6e (78%, R Bn, R_2 Me, R_3 H). m.p.: >250°C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ = 2.55 (s, 3H), 5.08 (s, 2H), 6.65 (s, 1H), 7.12–7.15 (m, 5H), 7.41–7.45 (m, 2H), 7.59 (t, *J* = 7.8 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 9.63 (s, 1H); MS (CI): 377(M+H)$^+$; Anal. calcd. C, 63.81; H, 4.28; N, 14.88; found C, 63.83; H, 4.29; N, 14.90.

Product 6f (63%, R Me, R_2 Me, R_3 m-Cl-Ph). m.p.: 219–220°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.68 (s, 3H), 3.41 (s, 3H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.44–7.52 (m, 3H), 7.68–7.74 (m, 2H), 7.83 (s, 1H), 8.48 (d, *J* = 8 Hz, 1H), 9.75 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 13.99, 15.16, 19.84, 30.18, 49.53, 108.72, 119.39, 123.53, 125.62, 126.74, 127.44, 127.72, 128.62, 131.18, 133.18, 140.62, 145.83, 147.95, 156.77; MS (CI): 411(M+H)$^+$; Anal. calcd. C, 58.46; H, 3.68; N, 13.64; found C, 58.48; H, 3.70; N, 13.65.

Product 6g (59%, R Et, R_2 Me, R_3 m-Cl-Ph). m.p.: 232–233°C; ^{1}H NMR (400 MHz, DMSO): δ = 1.28 (t, *J* = 6.7 Hz, 3H), 2.62 (s, 3H), 3.93 (q, *J* = 6.7 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.42–7.53 (m, 3H), 7.68–7.75 (m, 2H), 7.82 (s, 1H),

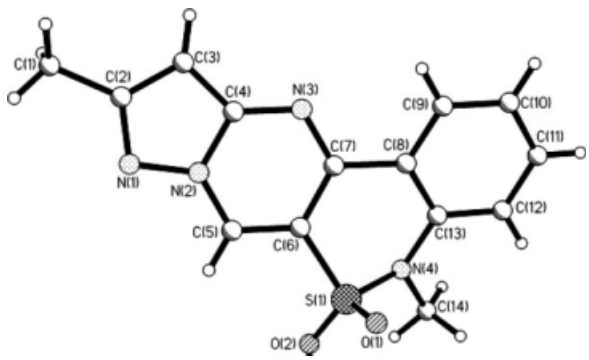
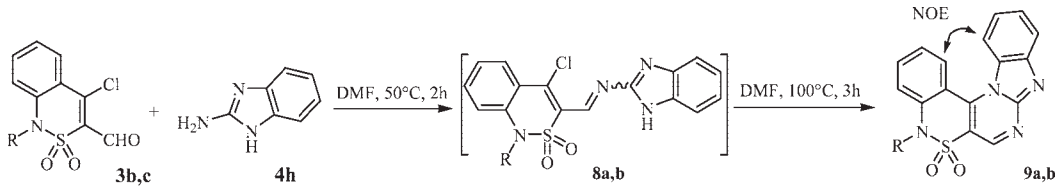


Figure 3. X-ray structure of compound **6a**.

Scheme 5



Two stage reaction with 2-aminobenzoimidazole **4h**

8.51 (d, J = 7.8 Hz, 1H), 9.73 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 15.04, 30.24, 53.22, 118.86, 123.72, 126.07, 126.88, 127.36, 128.49, 129.67, 132.96, 133.86, 136.63, 140.36, 147.37, 149.14, 159.63; MS (CI): 425(M+H)$^+$; Anal. calcd. C, 59.36; H, 4.03; N, 13.19; found C, 59.36; H, 4.05; N, 13.23.

Product 6h (67%, R Pr, R_2 Me, R_3 m-Cl-Ph). m.p.: >250°C; ^{1}H NMR (400 MHz, DMSO): δ = 0.86 (t, J = 6.8 Hz, 3H), 1.65 (m, J = 6.8 Hz, 2H), 2.72 (s, 3H), 4.03 (t, J = 6.8 Hz, 2H), 7.35 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.77 (s, 1H), 7.86 (t, J = 7.8 Hz, 1H), 8.92 (s, 1H), 9.74 (d, J = 8 Hz, 1H); MS (CI): 439.5(M+H)$^+$; Anal. calcd. C, 60.20; H, 4.36; N, 12.76; found C, 60.23; H, 4.39; N, 12.77.

Product 6i (61%, R Bu, R_2 Me, R_3 m-Cl-Ph). m.p.: >250°C; ^{1}H NMR (400 MHz, DMSO): δ = 0.84 (t, J = 6.8 Hz, 3H), 1.23 (m, 2H), 1.50 (m, 2H), 2.68 (t, J = 7.8 Hz, 2H), 3.89 (s, 3H), 7.35–7.85 (m, 7H), 8.48 (d, J = 7.8 Hz, 1H), 9.71 (s, 1H); MS (CI): 453.5(M+H)$^+$; Anal. calcd. C, 60.99; H, 4.67; N, 12.37; found C, 61.04; H, 4.69; N, 12.36.

Product 6j (60%, R Bn, R_2 Me, R_3 m-Cl-Ph). m.p.: >250°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.69 (s, 3H), 5.09 (s, 2H), 7.16 (s, 5H), 7.34 (d, J = 7.8 Hz, 1H), 7.41–7.46 (m, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.59 (t, J = 8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.82 (s, 1H), 8.42 (d, J = 8 Hz, 1H), 9.72 (s, 1H); MS (CI): 487.5(M+H)$^+$; *Anal.*calcd. C, 64.13; H, 3.93; N, 11.51; found C, 64.15; H, 3.97; N, 11.54.

Product 6k (79%, R Me, R_2 H, R_3 CO_2Et). m.p.: >250°C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ = 1.23 (t, J = 6.8 Hz, 3H), 3.46 (s, 3H), 3.89 (q, J = 6.7 Hz, 2H), 7.37 (t, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 7.8 Hz, 1H), 7.86 (s, 1H), 8.49 (d, J = 7.8 Hz, 1H), 9.75 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 15.03, 34.80, 61.02, 117.69, 122.04, 124.47, 126.27, 133.34, 134.08, 141.87, 147.31, 149.32, 159.68; MS (CI): 359(M+H)$^+$; Anal. calcd. C, 53.62; H, 3.94; N, 15.63; found C, 53.64; H, 3.94; N, 15.62.

Product 6l (82%, R Et, R_2 H, R_3 CO_2Et). m.p.: >250°C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ = 1.27 (t, J = 6.8 Hz, 3H), 1.46 (t, J = 6.8 Hz, 3H), 3.67 (q, J = 6.8 Hz,2H), 3.89 (q, J = 6.8 Hz, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.89 (s, 1H), 8.43 (d, J = 7.8 Hz, 1H), 9.78 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 14.28, 15.02, 34.78, 60.44, 108.55, 118.29, 122.04, 124.36, 127.15, 128.55, 131.16, 133.69, 134.27, 141.98, 145.86, 147.87, 156.98; MS (CI): 373(M+H)$^+$; Anal. calcd. C, 54.83; H, 4.33; N, 15.04; found C, 54.85; H, 4.36; N, 15.05.

7-Alkyl-7*H*-[1,2,4]triazolo[3′,4′:2,3]pyrimido[5,4-*c*][2,1] benzothiazine-6,6-dioxides (7a–c); general procedure. The mixture of the β-chloroaldehyde **3** (1 mmol) with the aminotriazole **4g** (0.1 g, 1.2 mmol) was dissolved in 2 mL of dry DMF. The reaction mixture was heated for 2.5 h at 80°C. The mixture was cooled to room temperature; solid product was filtered off and washed with ethanol. The pure product was obtained by crystallization from DMF (52–57%).

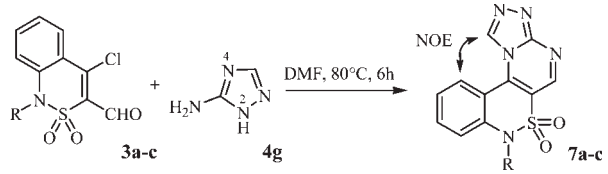
Product 7a (54%, R Me). ^{1}H NMR (400 MHz, DMSO): δ = 3.51 (s, 3H), 7.62 (t, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.90 (t, J = 7.8 Hz, 1H), 8.60 (d, J = 7.8 Hz, 1H), 9.06 (s, 1H), 10.04 (s, 1H); MS (CI): 288(M+H)$^+$; Anal. calcd. C, 50.17; H, 3.16; N, 24.38; found C, 50.19; H, 3.16; N, 24.39.

Product 7b (52%, R Et). ^{1}H NMR (400 MHz, DMSO): δ = 1.28 (t, J = 6.8 Hz, 3H), 4.09 (q, J = 6.8 Hz, 2H), 7.61 (t, J = 7.8 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.88 (t, J = 8 Hz, 1H), 8.60 (d, J = 8 Hz, 1H), 9.04 (s, 1H), 10.02 (s, 1H); MS (CI): 302(M+H)$^+$; Anal. calcd. C, 51.82; H, 3.68; N, 23.24; found C, 51.82; H, 3.67; N, 23.27.

Product 7c (57%, R Pr). ^{1}H NMR (400 MHz, DMSO): δ = 0.86 (t, J = 6.8 Hz, 3H), 1.67 (m, 2H), 4.04 (t, J = 6.8 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.89 (t, J = 7.8 Hz, 1H), 8.89 (d, J = 7.8 Hz, 1H), 9.07 (s, 1H), 10.04 (s, 1H); MS (CI): 317(M+H)$^+$; Anal. calcd. C, 53.32; H, 4.16; N, 22.21; found C, 53.33; H, 4.13; N, 22.22.

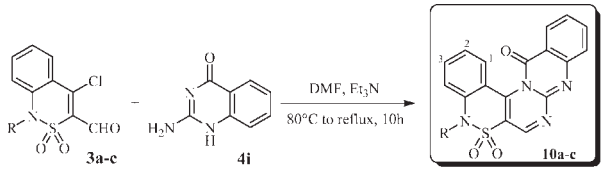
5-Alkyl-5*H*-benzimidazo[2′,1′:2,3]pyrimido[5,4-*c*][2,1] benzothiazin-6,6-dioxides (9a,b); general procedure. The mixture of the chloroaldehyde **3** (1 mmol) with the aminobenzoimidazole **4h** (0.16 g, 1.2 mmol) was dissolved in 3 mL of dry DMF. The reaction mixture was heated for 2 h at 50°C, 2 h at 70°C, and 1 h at 100°C. The mixture was cooled to room

Scheme 6



Condensation with aminotriazole **4g**, 1D-NOESY correlation is shown

Scheme 7



Reaction with 2-aminoquinazoline-4-one **4i**

temperature; solid product was filtered off and washed with ethanol. The pure product was obtained by crystallization from DMF (61–63%).

Product 9a (61%, R Et). m.p.: >250°C (decomp.); ^{1}H NMR (400 MHz, TFA): δ = 1.49 (t, *J* = 6.8 Hz, 3H), 4.29 (q, *J* = 6.8 Hz, 2H), 7.70–7.75 (m, 2H), 7.89 (d, *J* = 7.8 Hz, 1H), 8.02 (t, *J* = 7.8 Hz, 1H), 8.12 (m, 2H), 8.24 (d, *J* = 8 Hz, 1H), 8.53 (d, *J* = 8 Hz, 1H), 9.57 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 14.63, 49.34, 115.62, 117.19, 120.01, 121.16, 122.76, 123.67, 125.28, 128.48, 128.79, 135.64, 139.95, 143.84, 145.89, 148.43, 151.79; MS (CI): 351(M+H)$^+$; Anal. calcd. C, 61.70; H, 4.03; N, 15.99; found C, 61.72; H, 4.04; N, 15.99.

Product 9b (63%, R Pr). m.p.: >250°C (decomp.); ^{1}H NMR (400 MHz, TFA): δ = 0.98 (t, *J* = 6.8 Hz, 3H), 1.90 (m, 2H), 4.16 (q, *J* = 6.8 Hz, 2H), 7.71–7.77 (m, 2H), 7.86 (d, *J* = 7.8 Hz, 1H), 8.10 (t, *J* = 7.8 Hz, 1H), 8.15 (m, 2H), 8.27 (d, *J* = 8 Hz, 1H), 8.50 (d, *J* = 7.8 Hz, 1H), 9.58 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 11.62, 21.93, 49.74, 116.63, 118.18, 120.21, 121.15, 122.34, 123.92, 125.20, 128.50, 128.76, 135.61, 139.89, 143.87, 145.88, 148.20, 151.78; MS (CI): 365(M+H)$^+$; Anal. calcd. C, 62.62; H, 4.43; N, 15.37; found C, 62.65; H, 4.45; N, 15.39.

5-Alkyl-14-oxo-5,14-dihydroquinazolino[2′,3′:2,3]pyrimido[5,4-*c*][2,1]benzothiazin-6,6-dioxides (10a–c); general procedure. The mixture of 2-amino-quinazolin-4-one **4i** (0.21 g, 1.3 mmol) and a catalytic amount of triethylamine in 2 mL of dry DMF was heated to 100°C. To the resulting solution chloroaldehyde **3** (1 mmol) was added in portions at 80°C. The reaction mixture was heated for 10 h at reflux and then cooled to room temperature. Solid product was filtered off and washed with ethanol. The pure product was obtained by crystallization from DMF (56–59%).

Product 10a (58%, R Me). m.p.: 206–207°C; ^{1}H NMR (400 MHz, TFA): δ = 3.98 (s, 3H), 7.12 (m, 2H), 7.78 (m, 2H), 7.89 (t, *J* = 8 Hz, 1H), 8.08 (t, *J* = 8 Hz, 1H), 8.46 (d, *J* = 8 Hz, 1H), 8.65 (t, *J* = 7.8 Hz, 1H), 9.35 (s, 1H)

^{13}C NMR (100 MHz, TFA): δ = 50.01, 108.65, 118.86, 119.47, 123.58, 125.89, 126.87, 127.35, 129.08, 130.43, 131.24, 133.41, 135.64, 140.46, 145.79, 147.97, 156.92, 159.61; MS (CI): 365(M+H)$^+$; Anal. calcd. C, 59.33; H, 3.32; N, 15.38; found C, 59.35; H, 3.36; N, 15.41.

Product 10b (59%, R Et). m.p.: 234°C; ^{1}H NMR (400 MHz, TFA): δ = 1.37 (t, *J* = 6.8 Hz, 3H), 4.24 (q, *J* = 6.8 Hz, 2H), 7.63 (m, 2H), 7.78 (m, 2H), 7.87 (t, *J* = 7.8 Hz, 1H), 8.11 (t, *J* = 7.8 Hz, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.67 (t, *J* = 7.8 Hz, 1H), 9.38 (s, 1H). ^{13}C NMR (100 MHz, TFA): δ = 15.09, 54.02, 118.67, 124.01, 126.12, 126.87, 127.43, 128.66, 129.54, 133.04, 135.61, 137.76, 140.72, 142.85, 144.50, 146.08, 147.76, 149.34, 159.76; MS (CI): 379(M+H)$^+$; Anal. calcd. C, 60.31; H, 3.73; N, 14.81; found C, 60.34; H, 3.75; N, 14.81.

Product 10c (56%, R Pr). m.p.: >250°C (decomp); ^{1}H NMR (400 MHz, TFA): δ = 0.91 (t, *J* = 6.8 Hz, 3H), 1.77 (m, 2H), 4.14 (q, *J* = 6.8 Hz, 2H), 7.13 (m, 2H), 7.77 (m, 2H), 7.85 (t, *J* = 7.8 Hz, 1H), 8.10 (t, *J* = 7.8 Hz, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.66 (t, *J* = 7.8 Hz, 1H), 9.37 (s, 1H). ^{13}C NMR (100 MHz, TFA): δ = 15.04, 38.44, 53.22, 118.86, 123.69, 126.06, 126.85, 127.37, 128.49, 132.94, 135.63, 137.76, 140.37, 142.58, 144.51, 146.03, 147.36, 149.14, 150.05, 159.62; MS (CI): 393(M+H)$^+$; Anal. calcd. C, 61.21; H, 4.11; N, 14.28; found C, 61.22; H, 4.14; N, 14.31.

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