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# SYNTHESIS OF NOVEL BICYCLIC AND TRICYCLIC THIAZOLE AND IMIDAZOLE CONTAINING 2-AMINOPROPIONIC ACIDS

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**Abstract:**
Synthesis of four novel bicyclic and tricyclic amino acids (2-amino-3-benzo[4,5]imidazo[2,1-*b*]thiazol-3-ylpropionic acid, 2-amino-3-benzo[*d*]imidazo[2,1-*b*]thiazol-2-ylpropionic acid, 2-amino-3-thiazolo[3,2-*b*][1,2,4]triazol-6-ylpropionic acid, 2-amino-3-(2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)propionic acid) were carried out.
**Keywords:** 2-amino-3-benzo[4,5]imidazo[2,1-*b*]thiazol-3-ylpropionic acid, 2-amino-3-benzo[*d*]imidazo[2,1-*b*]thiazol-2-ylpropionic acid, 2-amino-3-thiazolo[3,2-*b*][1,2,4]triazol-6-ylpropionic acid, 2-amino-3-(2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)propionic acid

## Introduction

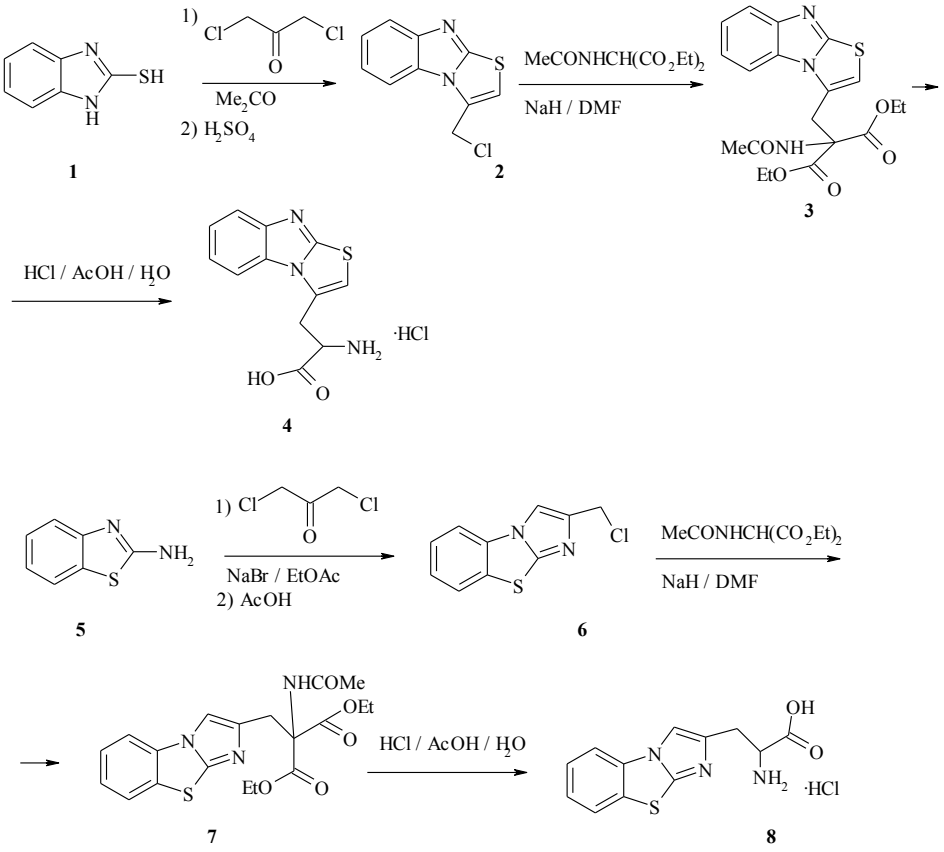
Amino acid derivatives are of interest because of wide range of biological activity. Beside this amino acid derivatives are widely used as substrates in the organic synthesis [1]. Among natural heterocyclic 2-aminopropionic acids histidine (thus, imidazole containing amino acid) was widely applied in organic synthesis because of biological importance [2-12]. Some works were dedicated to investigation of synthesis and reactions of thiazole containing 2-aminpropionic acid [13, 14]. There is data connecting to synthesis and transformation of different derivatives of 2-amino-(triazolo[4,3-*a*]pyridin-3-yl)propionic acid in the chemical literature [15]. Our interest to bicyclic or tricyclic imidazole and thiazole containing amino acids (for example, imidazothiazole derivatives) are connected with a wide range of biological activity of above heterocyclic system [16, 17]. Beside this synthesis of amino acid derivatives containing benzo[4,5]imidazo[2,1-*b*]thiazole, benzo[*d*]imidazo[2,1-*b*]thiazole, thiazolo[3,2-*b*][1,2,4]triazole, alkylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazole ring systems were not investigated till now and therefore is the main aim of present work.

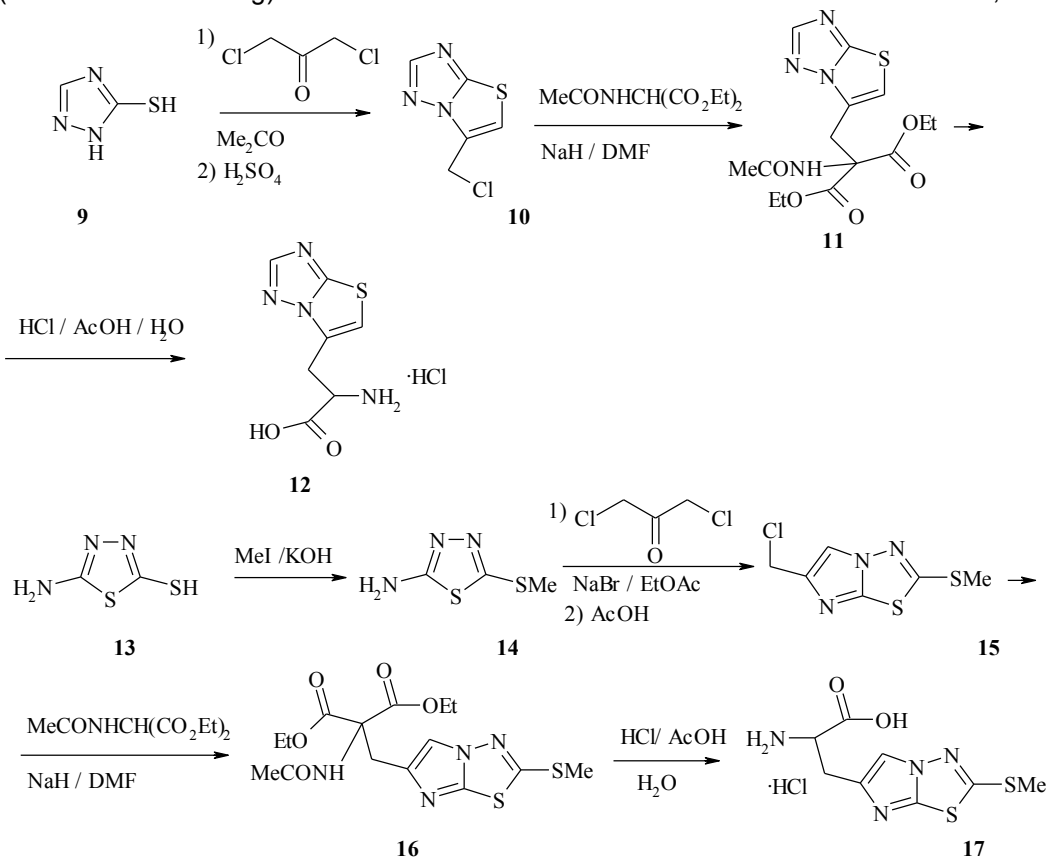
## Results and Discussion

We carried out synthesis of four novel amino acids - 2-amino-3-benzo[4,5]imidazo[2,1-*b*]thiazol-3-ylpropionic acid (**4**), 2-amino-3-benzo[*d*]imidazo[2,1-*b*]thiazol-2-ylpropionic acid (**8**), 2-amino-3-thiazolo[3,2-*b*][1,2,4]triazol-6-ylpropionic acid (**12**) and 2-amino-3-(2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)propionic acid (**17**).

2-Amino-3-benzo[4,5]imidazo[2,1-*b*]thiazol-3-ylpropionic acid hydrochloride (**4**) was prepared in three steps from 2-mercaptoimidazole (**1**). Thus, treatment of compound **1** with 1,3-dichloroacetone in acetone, followed by cyclization with sulfuric acid, leads to 3-chloromethylbenzo[4,5]imidazo[2,1-*b*]thiazole (**2**) [18]. Subsequent interaction of product **2** with sodium salt of diethyl acetamidomalonate afforded malonic acid derivative **3** in 43% yield. Hydrolysis-decarboxylation of malonic ester **3** in a mixture of HCl and AcOH leads to 2-amino-

3-benzo[4,5]imidazo[2,1-*b*]thiazol-3-ylpropionic acid hydrochloride (**4**) in almost quantitative yield.






Treatment of 2-aminobenzothiazole (**5**) with 1,3-dichloroacetone in the presence of NaBr in EtOAc, followed by cyclization in refluxing acetic acid, afforded 2-chloromethyl[*d*]imidazo[2,1-*b*]thiazole (**6**). Interaction of alkyl chloride **6** with sodium salt of diethyl acetamidomalonate in DMF, followed by acidic hydrolysis (HCl / AcOH) of an intermediate **7**, leads to 2-amino-3-benzo[*d*]imidazo[2,1-*b*]thiazol-2-ylpropionic acid hydrochloride (**8**).

2-Amino-3-thiazolo[3,2-*b*][1,2,4]triazol-6-ylpropionic acid hydrochloride (**12**) was obtained similarly to compound **4**.

We also carried out four-step synthesis of 2-amino-3-(2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)propionic acid (**17**). Thus, selective S-methylation of 2-amino-5-mercaptothiadiazole (**13**) was realized in the presence of KOH in water. 2-Amino-5-methylsulfanylthiadiazole (**14**) was isolated as single product in 60% yield. Further cyclization of amine **14** in the presence of NaBr and acetic acid afforded 6-chloromethyl-2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazole (**15**) in 19% yield. Treatment of alkyl chloride **15** with diethyl acetamidomalonate / NaH / DMF, followed by acidic hydrolysis (HCl / AcOH) of an intermediate **16**, leads to 2-amino-3-(2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)propionic acid hydrochloride (**17**).

## Experimental section

$^{1}$H and $^{13}$C NMR spectra were recorded on a Mercury 200 (Varian) instrument at 200 and 50.3 MHz in $CDCl_3$ or DMSO-$D_6$ using hexamethyldisiloxane (HMDSO) as internal standard. 2-

Mercaptobenzimidazole (**1**), 2-aminobenzothiazole (**5**), 2-mercaptotriazole (**9**), 2-amino-5-mercaptothiadiazole (**13**), 1,3-dichloroacetone, NaH (all AlfaAesar) and diethyl acetamidomalonate (Acros) were used without additional purification. 3-Chloromethylbenzo[4,5]imidazo[2,1-*b*]thiazole (**2**) and 6-chloromethylthiazolo[3,2-*b*][1,2,4]triazole (**10**) were obtained in the system $ClCH_2COCH_2Cl$ / $Me_2CO$ / $H_2SO_4$ according procedure [18].

**2-Amino-3-benzo[4,5]imidazo[2,1-*b*]thiazol-3-ylpropionic acid hydrochloride (4).** To suspension of NaH (60% in oil) (0.20 g, 4.5 mmol) in dry DMF (15 ml) was added dropwise a solution of diethyl acetamidomalonate (0.98 g, 4.5 mmol) in DMF (10 ml). Reaction mixture was stirred for 2 h at room temperature and 3-chloromethylbenzo[4,5]imidazo[2,1-*b*]thiazole (**2**) (1.0 g, 4.5 mmol) was added. Reaction mixture was heated at 100°C for 12 h. Then ethyl acetate (100 ml) was added and reaction mixture was washed with brine (4x50 ml). Product was purified by column chromatography (eluent ethyl acetate). Yield of diethyl ester of 2-acetylamino-2-benzo[4,5]imidazo[2,1-*b*]thiazol-2-ylmethylmalonic acid (**3**) 0.77 g (43 %) with m.p. 144-145°C. $^1$H NMR ($CDCl_3$) δ ppm: 1.19 (t, 6H, J = 6 Hz, Me); 1.92 (s, 3H, COMe); 4.09-4.30 (m, 6H, $CH_2$); 6.35 (s, 1H, 2-H); 6.87 (s, 1H, NH); 7.24-7.35 and 7.73-7.89 (both m, 4H, Ph).

Mixture of diethyl ester of 2-acetylamino-2-benzo[4,5]imidazo[2,1-*b*]thiazol-2-ylmethylmalonic acid (**3**) (0.7 g, 1.7 mmol), 36% aq. HCl (6 ml), acetic acid (6 ml) and water (6 ml) was heated at 80°C for 20 h. Reaction mixture was evaporated and dried under reduced pressure. Product was crystallized using 20 ml of dry acetonitrile. Yield of 2-amino-3-benzo[4,5]imidazo[2,1-*b*]thiazol-3-ilpropionic acid hydrochloride **(4)** 0.47 g (96 %) with m.p. >230°C. $^1$H NMR (DMSO-$D_6$) δ ppm: 3.72 and 4.29 (both m, 3H, $CHCH_2$); 7.21 (1H, s, H-2); 7.38-7.49, 7.77-7.81 and 8.02-8.05 (all m, 4H, Ph); 8.62 (bs, 3H, $NH_3$). $^{13}$C NMR (DMSO-$D_6$) δ ppm: 27.93, 49.83, 112.57, 114.19, 116.03, 122.88, 125.30, 127.82, 128.98, 140.00, 155.47, 169.24. LC-MS: 261 ($M^+$).

**2-Amino-3-benzo[*d*]imidazo[2,1-*b*]thiazol-2-ylpropionic acid hydrochloride (8).** Mixture of 2-aminobenzothiazole (**5**) (1.0 g, 6.7 mmol), solid NaBr (1.38 g, 13.4 mmol) and 1,3-dichloroacetone (0.92 g, 7.3 mmol) in ethyl acetate (30 ml) was stirred at room temperature for 5 days. The formed precipitates were dissolved in acetic acid and heated at 100°C for 1 h. An excess of acetic acid (15 ml) was evaporated at reduced pressure and the residue was neutralized with aqueous $NaHCO_3$ to pH 9. 2-Chloromethyl[*d*]imidazo[2,1-*b*]thiazole (**6**) was extracted with ethyl acetate (2x 40 ml). Yield of compound **6** 1.25 g (84%) with m.p. >230°C. $^1$H NMR ($CDCl_3$) δ ppm: 4.62 (s, 2H, $CH_2$); 7.36-7.72 (m, 4H, Ph); 7.74 (s, 1H, imidazole proton).

To suspension of NaH (60% in oil) (0.20 g, 4.5 mmol) in dry DMF (15 ml) was added dropwise solution of diethyl acetamidomalonate (0.98 g, 4.5 mmol) in DMF (10 ml). Reaction mixture was stirred for 2 h at room temperature and 2-chloromethylbenzyl[*d*]imidazo[2,1-*b*]thiazole (**6**) (1.0 g, 4.5 mmol) was added. Reaction mixture was heated at 100°C for 12 h. Then ethyl acetate (100 ml) was added and reaction mixture was washed with brine (4x50 ml). Product was purified by column chromatography (eluent ethyl acetate). Yield of diethyl ester of 2-acetylamino-2-benzo[*d*]imidazo[2,1-*b*]thiazol-2-ylmethylmalonic acid (**7**) 0.74 g (41 %) with m.p. 132-133°C. $^1$H NMR ($CDCl_3$) δ ppm: 1.28 (t, 6H, J = 7 Hz, Me); 2.01 (s, 3H, COMe); 3.72 (s, 2H, $CH_2$); 4.29 (q, 4H, J = 7 Hz, $CH_2$); 6.35 (s, 1H, NH); 6.87 (s, 1H, 2-H); 7.24-7.35 and 7.73-7.89 (both m, 4H, Ph); 7.43 (s, 1H, imidazole proton).

Mixture of diethyl ester of 2-acetylamino-2-benzo[*d*]imidazo[2,1-*b*]thiazol-2-ylmethylmalonic acid (**7**) (0.7 g, 1.7 mmol), 36% aq. HCl (6 ml), acetic acid (6 ml) and water (6 ml) was heated at 80°C for 20 h. Reaction mixture was evaporated and dried under reduced

pressure. Product was crystallized using 20 ml of dry acetonitrile. Yield of 2-amino-3-benzo[*d*]imidazo[2,1-*b*]thiazol-2-ylpropionic acid hydrochloride (**8**) 0.33 g (66 %) with m.p. >230°C. $^1$H NMR (DMSO-$D_6$) δ ppm: 3.67 and 4.68 (both m, 3H, $CHCH_2$); 7.83-8.04 and 8.47-8.51 (both m, 4H, Ph); 8.64 (s, 1H, imidazole proton); 8.81 (bs, 3H, $NH_3$). $^{13}$C NMR (DMSO-$D_6$) δ ppm: 27.81, 51.57, 112.88, 112.86, 114.03, 125.20, 125.95, 127.10, 129.05, 131.35, 146.22, 169.67. LC-MS: 261 ($M^+$+1).

**2-Amino-3-thiazolo[3,2-*b*][1,2,4]triazol-6-ylpropionic acid hydrochloride (12).** To suspension of NaH (60% in oil) (0.074 g, 3.1 mmol) in dry DMF (10 ml) was added dropwise a solution of diethyl acetamidomalonate (0.67 g, 3.1 mmol) in DMF (5 ml). Reaction mixture was stirred for 2 h at room temperature and 6-chloromethylthiazolo[3,2-*b*][1,2,4]triazole (**10**) (0.54 g, 3.1 mmol) was added. Reaction mixture was heated at 100°C for 12 h. Then ethyl acetate (70 ml) was added and reaction mixture was washed with brine (4x40 ml). Product was purified by column chromatography (eluent ethyl acetate: hexane 1:1). Yield of diethyl ester of 2-acetylamino-2-thiazolo[3,2-*b*][1,2,4]triazol-6-ylmethylmalonic acid (**11**) 0.26 g (26 %) with m.p. 85°C. $^1$H NMR ($CDCl_3$) δ ppm: 1.27 (t, 6H, J = 7 Hz, Me); 2.00 (s, 3H, COMe); 4.04 (s, 2H, $CH_2$); 4.27 (q, 4H, J = 7 Hz, $CH_2$); 6.70 (s, 1H, thiazole proton); 8.05 (s, 1H, triazole proton).

Mixture of diethyl ester of 2-acetylamino-2-thiazolo[3,2-*b*][1,2,4]triazol-6-ylmethylmalonic acid (**11**) (0.26 g, 0.74 mmol), 36% aq. HCl (3 ml), acetic acid (2 ml) and water (3 ml) was heated at 80°C for 23 h. Reaction mixture was evaporated and dried under reduced pressure. Product was crystallized using 10 ml of dry acetonitrile. Yield of 2-amino-3-thiazolo[3,2-*b*][1,2,4]triazol-6-ylpropionic acid hydrochloride (**12**) 0.058 g (31 %) with m.p. >230°C. $^1$H NMR (DMSO-$D_6$) δ ppm: 3.56 and 4.42 (both m, 3H, $CHCH_2$); 7.39 (s, 1H, thiazole proton); 8.35 (s, 1H, triazole proton); 8.46 (bs, 3H, $NH_3$). LC-MS: 213 ($M^+$+1).

**2-Amino-3-(2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)propionic acid hydrochloride (17).** To suspension of 2-amino-5-mercaptothiadiazole (**13**) (1.0 g, 7.5 mmol) in 30 ml of water was added KOH (0.42 g, 7.5 mmol). Reaction mixture was stirred at 50°C for 20 minutes and methyl iodide (0.56 ml, 9 mmol) was added. Reaction mixture was refluxed for 1 h, cooled to room temperature, 2-amino-5-methylsulfanylthiadiazole (**14**) was filtered off and after drying obtained 0.66 g (60%) with m.p. 180°C. $^1$H NMR ($CDCl_3$) δ ppm: 2.58 (s, 3H, Me); 7.22 (bs, 2H, $NH_2$).

Mixture of 2-amino-5-methylsulfanylthiadiazole (**14**) (0.48 g, 3.3 mmol), solid NaBr (0.68 g, 6.6 mmol) and 1,3-dichloroacetone (0.46 g, 3.6 mmol) in ethyl acetate (20 ml) was stirred at room temperature for 3 days. The formed precipitates were dissolved in acetic acid (10 ml) and heated at 110°C for 1.5 h. An excess of acetic acid was evaporated at reduced pressure and the residue was neutralized with aqueous $NaHCO_3$ to pH 9. Product **15** was extracted with ethyl acetate (2x 30 ml). Yield of 6-chloromethyl-2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazole (**15**) 0.123 g (19 %) as yellow oil. $^1$H NMR ($CDCl_3$) δ ppm: 2.72 (s, 3H, Me); 5.11 (s, 2H, $CH_2$); 7.69 (s, 1H, imidazole proton).

To suspension of NaH (60% in oil) (0.026 g, 1.1 mmol) in dry DMF (5 ml) was added dropwise solution of diethyl acetamidomalonate (0.12 g, 0.55 mmol) in DMF (5 ml). Reaction mixture was stirred for 2 h at room temperature and 6-chloromethyl-2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazole (**15**) (0.12 g, 0.55 mmol) was added. Reaction mixture was heated at 100°C for 12 h. Then ethyl acetate (30 ml) was added and reaction mixture was washed with brine (4x20 ml). Product was purified by column chromatography (eluent ethyl acetate: hexane 1:1). Yield of diethyl ester 2-acetylamino-2-(2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-ylmethylmalonic acid (**16**) 0.0373 g (24 %) with m.p. 49-50°C. $^1$H NMR

($CDCl_3$) δ ppm: 1.29 (t, 6H, J = 7 Hz, Me); 2.07 (s, 3H, COMe); 2.72 (s, 3H, Me); 4.21-4.29 (m, 4H, $CH_2$); 5.11 (s, 2H, $CH_2$); 7.69 (s, 1H, imidazole proton).

Mixture of diethyl ester of 2-acetylamino-2-(2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-ylmethylmalonic acid (**16**) (0.0373 g, 0.1 mmol), 36% aq. HCl (0.5 ml), acetic acid (0.5 ml) and water (0.5 ml) was heated at 80°C for 23 h. Reaction mixture was evaporated and dried under reduced pressure. Product was crystallized using 3 ml of dry acetonitrile. Yield of 2-amino-3-(2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)propionic acid hydrochloride (**17**) 0.0214 g (74 %) with m.p. >230°C. $^1$H NMR (DMSO-$D_6$) δ ppm: 2.76 (s, 3H, Me), 3.68 and 4.44 (both m, 3H, $CHCH_2$); 7.97 (s, 1H, imidazole proton); 8.15 (bs, 3H, $NH_3$). LC-MS: 259 ($M^+$).

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