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SYNTHESIS OF NEW N-ARYL-2-[(4-AMINO-4H-1,2,4-TRIAZOLO-[4,3-b]PYRIDAZIN-3-YL)THIO] ACETAMIDE DERIVATIVES

A.I.Severina, V.A.Yanchenko*, A.R.Hayrulin*,
V.A.Georgiyants, A.M.Demchenko*

National Pharmaceutical University,
53 Pushkinskaya str., Kharkiv, 61002, Ukraine. E-mail: vgeor@ukr.net
Institute of Pharmacology and Toxicology, Kiev, Ukraine

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***N*-aryl-2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]acetamides were prepared by interaction of 4-amino-1,2,4-triazolyl-3-thiol with *N*-aryl-2-chloroacetamides. The condensation of *N*-aryl-2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]acetamides with pentane-2,4-dione resulted in the formation of *N*-aryl-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]acetamide derivatives.**

СИНТЕЗ НОВИХ ПОХІДНИХ N-АРИЛ-2-[(6,8-ДИМЕТИЛ[1,2,4]ТРИАЗОЛО[4,3-b]ПІРИДАЗИН-3-ІЛ)ТІО]АЦЕТАМІДУ

А.И.Северіна, В.О.Янченко, А.Р.Хайрулін, В.А.Георгіянц, А.М.Демченко

***N*-арил-2-[(4-аміно-4H-1,2,4-триазол-3-іл)тіо]ацетаміди були отримані взаємодією 4-аміно-1,2,4-триазоліл-3-тіолу із *N*-арил-2-хлороацетамідами. Конденсацією *N*-арил-2-[(4-аміно-4H-1,2,4-триазол-3-іл)тіо]ацетамідів із пентан-2,4-діоном отримані похідні *N*-арил-2-[(6,8-диметил[1,2,4]триазоло[4,3-b]піридазин-3-іл)тіо]ацетаміду.**

СИНТЕЗ НОВЫХ ПРОИЗВОДНЫХ N-АРИЛ-2-[(6,8-ДИМЕТИЛ[1,2,4]ТРИАЗОЛО[4,3-b]ПИРИДАЗИН-3-ИЛ)ТИО]АЦЕТАМИДА

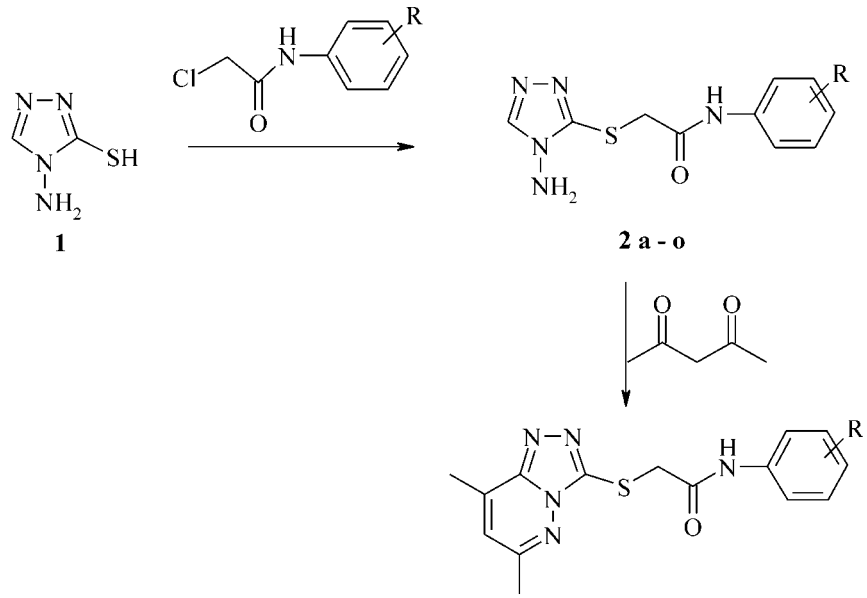
А.И.Северина, В.А.Янченко, А.Р.Хайрулин, В.А.Георгиянц, А.М.Демченко

***N*-арил-2-[(4-амино-4H-1,2,4-триазол-3-ил)тио]ацетамиды были получены взаимодействием 4-амино-1,2,4-триазолил-3-тиола с *N*-арил-2-хлороацетамидами. Конденсацией *N*-арил-2-[(4-амино-4H-1,2,4-триазол-3-ил)тио]ацетамидов с пентан-2,4-дионом получены производные *N*-арил-2-[(6,8-диметил[1,2,4]триазоло[4,3-b]пиридазин-3-ил)тио]ацетамида.**

Heterocyclic system of 1,2,4-triazole and its derivatives have already been of considerable interest for a long time as a source of new biologically active compounds. The simplest 3-amino-1,2,4-triazole is known as herbicide, which is toxic for warm-blooded [1]. Among 1,2,4-triazole derivatives a number of medicines have been introduced into use [2]. 3-mercapto-1,2,4-triazole derivatives deserve for special attention. It is known that for condensed and uncondensed 3-mercapto-1,2,4-triazole derivatives expose wide spectrum of biological activity: antimicrobial [3-5], antituberculosis [6,7], antifungal [8,9], anticancer [10], anti-inflammatory and analgesic [11-13], antioxidant [14], anti-viral [15,16], antihypertensive [17] and so on. It is the variety of pharmacological effects stipulates curiosity of scientists of different countries to the synthesis of 3-mercapto-1,2,4-triazole derivatives and creation of new therapeutic preparations on their basis.

Although chemistry of triazole containing compounds has been already studied well, however the data given about the methods of synthesis and pharmacological properties of the condensed [1,2,4]triazolo[4,3-b]pyridazin-3-thiole derivatives are not enough. There is some information that some [1,2,4]triazolo[4,3-b]pyridazine derivatives expose antiviral, antihypertensive activity, and also they are GABA agonist [18, 19].

The methods development for the synthesis of substituted [1,2,4]triazolo[4,3-b]pyridazin-3-thiole derivatives preparation was the purpose of our researches. The starting material was 4-amino-3-mercapto-1,2,4-triazole **1**, which was obtained by thiocarbohydrazide treatment with excess of formamide by a classic method [20]. Bifunctionality of 4-amino-3-mercapto-1,2,4-triazole **1** stipulates easiness of condensed 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole [21], 1,2,4-triazolo [3,4-b]-1,3,4-thiadiazine [22] and also [1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine [23,24] derivatives formation. However, it is the presence of high-functional mercaptogroup complicates formation of the condensed triazolopyridazine system. Therefore for the achievement of the purpose alkylation of thiogroup of N-aminotriazole has been conducted. There is enough information about the methods of synthesis of un-



1 **2 a - o** **3 a -o**

R= H (a), 4-Et (b), 2,5-diMe (c), 4-But (d), 4-MeO (e), 4-Me (f), 4-F (g), 4-Cl (h), 3-Cl (i), 3,4-diCl (j), 4-Br (k), 2-Cl (l), 3-Ac (m), 4-i-Pr (n), 4-F $_2$CHS (o)

Scheme

condensed derivatives of 4-amino-1,2,4-triazolyl-3-thiole by alkylation [25-27]. In the presented work substituted N-aryl-2-chloroacetamides have been used as the agents of alkylation [28] (Scheme). The study of conducting conditions of this reaction has shown that alkylation of thiogroup of N-aminotriazole **1** are passed well at heating in water-alcohol medium in the presence of the equimolar amounts KOH or K_2CO_3. Products **2 a-o** have been obtained with good yields. Such modification not only blocks thiogroup but also multiplies the amount of pharmacophoric fragments which are perspective for pharmacological screening.

Synthesis of the direct products N-aryl-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]acetamides derivatives **3 a-o** has been carried out by cyclization of an equimolar amounts of derivatives of N-aryl-2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]acet amides **2 a-o** and pentane-2,4-dione by boiling in the acetic acid medium during 3 hours (Scheme). Products **3 a-o** have been obtained with good yields.

Thus, the N-aryl-2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]acetamides derivatives **2** in the reaction with the enone system (?-diketones) behavior as the typical of 1,3-binucleophiles, that results to [1,2,4]triazolo [4,3-b]pyridazine bicyclic forming.

Presence of keto-enole tautomery for β-diketones makes the structure similar to α, β-unsaturated ketones, which are used in the reactions of cycloconden-sation for pyridazine ring forming in the ethyl alcohol medium at addition of catalytic amounts of tertiary amines [29]. However, direct products **3** in similar conditions have been not obtained.

The structures of the synthesized compounds **2 a-o** and **3 a-o** have been confirmed with the elemental analysis, ^{1}H NMR-, IR-spectroscopy, in some cases — mass-spectrometry.

Conclusion

We described a general synthetic rout of the N-aryl-2-[(4-amino-4H-1,2,4-triazolo-3-yl)thio]acetamides derivatives and novel classes of N-aryl-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]acetamides. The present method may be valuable for organic synthesis.

Experimental section

All melting points were determined on a Kofler micro hot stage. IR spectra were recorded on the spectrophotometer "Specord M-82" in tablets KBr. ^{1}H NMR spectra were recorded on spectrometer a Varian Mercury-VX-200 in DMSO-d_6 using TMS as an internal standard (chemical shifts in ppm). Elemental analyses were carried out using Carlo Erba CHNS-O EA 1108 analyzer. LCMS spectra were taken on a Varian GCMS 1200. According to LC/MS data, all compounds have purity near 95%. Starting material **1** was prepared as described in the literature [20]. All other solvents and reagents used in this study were commercially available.

General method of synthesis of N-aryl-2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]acetamides 2 (a-o). In a round-bottom flask, 4-amino-4H-1,2,4-triazole-3-thiol **1** (0,01 mol) was dissolved in 40 mL EtOH containing KOH or K_2CO_3 (0,01 mol) and solution of (0,01 mol) correspondent N-aryl-2-chloroacetamide in 20 mL EtOH was added. The reaction mixture was boiled at reflux for 30 min and cooled. The product **2 (a-o)** precipitated after the addition of water (50-60 mL). The precipitate was crystallized from 2-isopropanole. The yields of the products are 70-86%.

N-phenyl-2-[(4-amino-4H-1,2,4-triazol-3-yl)thio] acetamides 2(a): yield — 81%, m.p. — 172-174°C, ^{1}H

NMR (DMSO-d_6),δ (ppm): 4,11 (s, 2H, SCH_2), 6,15 (s, 2H, NH_2), 7,03-7,59 (m, 5H, Ph), 8,49 (s, 1H, H-5), 10,36 (s, 1H, NH). Found, %: C 48,07; H 4,40; N 28,0. $C_{10}H_{11}N_5OS$. Anal. Calcd. %: C 48,14; H 4,44; N 28,09.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(4-ethylphenyl)acetamide 2(b): yield — 80%, m.p. — 158-160°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 1,10 (t, J 5,2 Hz, 3H, CH_2CH_3), 2,50 (q, J 5,2 Hz, 2H, CH_2CH_3), 4,20 (s, 2H, SCH_2), 6,17 (s, 2H, NH_2), 7,14 (d, J 5,5, 2H, H-2, H-6), 7,44 (d, J 5,5, 2H, H-3, H-5), 8,50 (s, 1H, CH-5), 10,22 (s, 1H, NH). Found, %: C 51,88; H 5,36; N 25,17. $C_{12}H_{15}N_5OS$. Anal. Calcd. %: C 51,96; H 5,45; N 25,25.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(2,5-dimethylphenyl)acetamide 2(c): yield — 79%, m.p. — 157-159°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,13 (s, 3H, CH_3), 2,23 (s, 3H, CH_3), 4,08 (s, 2H, SCH_2), 6,14 (s, 2H, NH_2), 6,94-7,00 (m, 2H, H-3, H-4), 7,30 (d, J 8,1, 1H, H-6), 8,50 (s, 1H, CH-5), 9,64 (s, 1H, NH). Found, %: C 52,15; H 5,39; N 25,25. $C_{12}H_{15}N_5OS$. Anal. Calcd. %: C 52,13; H 5,47; N 25,33.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(4-butylphenyl)acetamide 2(d): yield — 78%, m.p. — 169-171°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 0,90 (t, J 7,2 Hz, 3H, CH_3), 1,22-1,46 (m, 2H, CH_2), 1,52 (p, J 7,5 Hz, 2H, CH_2), 2,52 (t, J 7.2 Hz, 2H, CH_2), 4,09 (s, 2H, SCH_2), 6,14 (s, 2H, NH_2), 7,12 (d, J 8,2 Hz, 2H, H-3, H-5), 7,47 (d, J 8,2 Hz, 2H, H-2, H-6), 8,49 (s, 1H, CH-5), 10,28 (s, 1H, NH). Found, %: C 54,05; H 6,20; N 22,84. $C_{14}H_{19}N_5OS$. Anal. Calcd. %: C 55,06; H 6,25; N 22,93.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(4-methoxyphenyl)acetamide 2(e): yield — 81%, m.p. — 144-146°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 3,38 (s, 3H, OCH_3), 4,11 (s, 2H, SCH_2), 6,14 (s, 2H, NH_2), 7,05 (m, 4H, Ph), 8,51 (s, 1H, CH-5), 9,90 (s, 1H, NH). Found, %: C 47,20; H 4,60; N 24,95. $C_{11}H_{13}N_5O_2S$. Anal. Calcd. %: C 47,30; H 4,69; N 25,07.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(4-methylphenyl)acetamide 2(f): yield — 79%, m.p. — 177-179°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,27 (s, 3H, CH_3), 4,08 (s, 2H, SCH_2), 5,98 (s, 2H, NH_2), 7,10 (d, J 8,6, 2H, H-2, H-6), 7,44 (d, J 8,6, 2H, H-3, H-5), 8,48 (s, 1H, CH-5), 10,10 (s, 1H, NH). Found, %: C 50,10; H 4,89; N 26,46. $C_{11}H_{13}N_5OS$. Anal. Calcd. %: C 50,18; H 4,98; N 26,57.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(4-fluorophenyl)acetamide 2(g): yield — 80%, m.p. — 158-160°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 4,15 (s, 2H, SCH_2), 6,12 (s, 2H, NH_2), 7,49 (d, J 8,5 Hz, 2H, H-2, H-6), 7,70 (d, J 8,5 Hz, 2H, H-3, H-5), 8,46 (s, 1H, CH-5), 10,30 (s, 1H, NH). Found, %: C 44,86; H 3,82; N 26,10. $C_{10}H_{10}N_5OSF$. Anal. Calcd. %: C 44,94; H 3,81; N 26,20.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(4-chlorophenyl)acetamide 2(h): yield — 85%, m.p. — 204-206°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 4,11 (s, 2H, SCH_2), 6,09 (s, 2H, NH_2), 7,29 (d, J 8,6, 2H, H-3, H-5), 7,57 (d, J 8,6 Hz, 2H, H-2, H-6), 8,46 (s, 1H, CH-5), 10,10 (s, 1H, NH). Found, %: C 42,24; H 3,48; N 24,58. $C_{10}H_{10}N_5OSCl$. Anal. Calcd. %: C 42,33; H 3,55; N 24,68.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(3-chlorophenyl)acetamide 2(i): yield — 74%, m.p. — 145-147°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 4,18 (s, 2H, SCH_2), 6,10 (s, 2H, NH_2), 7,12-7,40 (m, 3H, H-4, 5, 6), 7,70 (s, 1H, H-2), 8,40 (s, 1H, CH-5), 10,42 (s, 1H, NH). Found, %: C 42,29; H 3,48; N 24,57. $C_{10}H_{10}N_5OSCl$. Anal. Calcd. %: C 42,33; H 3,55; N 24,68.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(3,4-diclorophenyl)acetamide 2(j): yield — 86%, m.p. — 211-213°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 4,12 (s, 2H, SCH_2), 6,10 (s, 2H, NH_2), 7,42 (d, J 5,8 Hz, 1H, H-6), 7,57 (d, J 5.8 Hz, 1H, H-5), 7,92 (s, 1H, H-2), 8,42 (s, 1H, CH-5), 10,60 (s, 1H, NH). Found, %: C 37,65; H 2,76; N 21,92. $C_{10}H_9N_5OSCl_2$. Anal. Calcd. %: C 37,75; H 2,85; N 22,01.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(4-bromophenyl)acetamide 2(k): yield — 85%, m.p. — 158-160°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 4,12 (s, 2H, SCH_2), 6,14 (s, 2H, NH_2), 7.30-7.70 (m, 4H, Ph), 8,49 (s, 1H, CH-5), 10,28 (s, 1H, NH). Found, %: C 36,50; H 3,00; N 21,26. $C_{10}H_{10}N_5OSBr$. Anal. Calcd. %: C 36,59; H 3,07; N 21,34.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(2-chlorophenyl)acetamide 2(l): yield — 76%, m.p. — 150-152°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 4,09 (s, 2H, SCH_2), 6,12 (s, 2H, NH_2), 7,12 (t, J 7,4 Hz, 1H, H-4), 7,28 (t, J 7,6 Hz, 1H, H-5), 7,40 (d, J 7,2 Hz, 1H, H-3), 7,70 (d, J 8,0 Hz, 1H, H-6), 8,51 (s, 1H, CH-5), 10,00 (s, 1H, NH). Found, %: C 42,25; H 3,44; N 24,59. $C_{10}H_{10}N_5OSCl$. Anal. Calcd. %: C 42,33; H 3,55; N 24,68.

N-(3-acetylphenyl)-2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]acetamide 2(m): yield — 75%, m.p. — 153-155°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,55 (s, 3H, CH_3), 4,16 (s, 2H, SCH_2), 6,14 (s, 2H, NH_2), 7,44 (t, J 7,8 Hz, 1H, H-5), 7,69 (d, J 5,6 Hz, 1H, H-4), 7,76 (d, J 5,6 Hz, 1H, H-6), 8,45 (s, 1H, CH-5), 10,38 (s, 1H, NH). Found, %: C 49,38; H 4,40; N 23,95. $C_{12}H_{13}N_5O_2S$. Anal. Calcd. %: C 49,47; H 4,49; N 24,04.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(4-isopropylphenyl)acetamide 2(n): yield — 72%, m.p. — 169-170°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 1,10 (s, 3H, CH_3), 1,2 (s, 3H, CH_3), 2,70-2,91 (m, 2H, CH), 4,15 (s, 2H, SCH_2), 6,12 (s, 2H, NH_2), 7,10 (d, J 8,6 Hz, 2H, H-2, H-6),7,40 (d, J 8,6 Hz, 2H, H-3, H-5), 8,48 (s, 1H, CH-5), 10,30 (s, 1H, NH). Found, %: C 53,45; H 5,76; N 23,98. $C_{13}H_{17}N_5OS$. Anal. Calcd. %: C 53,58; H 5,88; N 24,03.

2-[(4-amino-4H-1,2,4-triazol-3-yl)thio]-N-(4-mercaptophenyl)acetamide-1,1-difluoroethane 2(o): yield — 70%, m.p. — 181-183°C, ^{1}H NMR (DMSO-d_6), δ (ppm): 4,12 (s, 2H, SCH_2), 6,13 (s, 2H, NH_2), 7.10 (s, 1H, CH), 7,30 (s, 1H, CH), 7,40 (d, J 8,7 Hz, 2H, H-2, H-6), 7,58 (d, J 8.7 Hz, 2H, H-3, H-5), 8,41 (s, 1H, CH-5), 10,40 (s, 1H, NH). Found, %: C 39,79;

H 3,31; N 21,09. $C_{11}H_{11}N_5OS_2F_2$. Anal. Calcd. %: C 39,87; H 3,36; N 21,13.

General method of synthesis of 2-[(6,8-dimethyl [1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]-N-arylacetamides 3(a-o). In a round-bottom flask, correspondent N-aryl-2-[(4-amino-4H-1,2,4-triasol-3-yl)thio]acetamide **2(a-o)** (0,01 mol) was dissolved in 30 mL acetic acid and pentane-2,4-dione (0,01 mol) was added. The reaction mixture was boiling at reflux for 3 hours and cooled. The product **3(a-o)** precipitated after the addition of 50-60 mL water. The precipitate was filtered, washed with water and crystallized from 2-izopropanole.

2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]-N-(4-phenyl)acetamide 3(a): yield — 76%, m.p. — 203-205°C, IR (KBr), υ (cm^{-1}): 3270, 1680, 1610, 1560, 1420, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,47 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 4,24 (s, 2H, SCH_2), 7,06-7,53 (m, 5H, Ph), 7,11 (s, 1H, CH), 10,30 (s, 1H, NH), m/z = 314 [M^+], Found, %: C 57,40; H 4,72; N 22,26. $C_{15}H_{15}N_5OS$. Anal. Calcd. %: C 57,49; H 4,82; N 22,34.

2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]-N-(4-ethylphenyl)acet-amide 3(b): yield — 75%, m.p. — 188-190°C, IR (KBr), υ (cm^{-1}): 3280, 1684, 1600, 1553, 1419, ^{1}H NMR (DMSO-d_6), δ (ppm): 1.14 (t, J 5.2 Hz, 3H, CH_2CH_3), 2,55 (q, J 5,2 Hz, 2H, CH_2CH_3), 3,33 (s, 6H, $2CH_3$), 4,21 (s, 2H, SCH_2), 7,10 (s, 1H, CH), 7,14 (d, J 5,5, 2H, H-2, H-6), 7,44 (d, J 5,5, 2H, H-3,H-5), 10,22 (s, 1H, NH), m/z = 342 [M^+], Found, %: C 59,78; H 5,62; N 20,41. $C_{17}H_{19}N_5OS$. Anal. Calcd. %: C 59,80; H 5,61; N 20,51.

N-(2,5-dimethylphenyl)-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio] acetamide 3(c): yield — 74%, m.p. — 185-187°C, IR (KBr), υ (cm^{-1}): 3196, 1684, 1606, 1555, 1426, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,23 (s, 3H, CH_3), 2,40 (s, 9H, $3CH_3$), 4,10 (s, 2H, SCH_2), 7,11 (s, 1H, CH), 6,94-7,00 (m, 2H, H-3, H-4), 7,30 (d, J 8,1 Hz, 1H, H-6), 10,40 (s, 1H, NH). m/z = 342 [M^+], Found, %: C 59,70; H 5,60; N 20,42. $C_{17}H_{19}N_5OS$. Anal. Calcd. %: C 59,80; H 5,61; N 20,51.

N-(4-butylphenyl)-2-[(6,8-dimethyl[1,2,4]triazolo [4,3-b]pyridazin-3-yl)thio]acet-amide 3(d): yield — 72%, m.p. — 187-189°C, IR (KBr), υ (cm^{-1}): 3224, 1675, 1605, 1560, 1420, ^{1}H NMR (DMSO-d_6), δ (ppm): 0,87 (t, J 7,2 Hz, 3H, CH_3), 1,24-1,29 (m, 2H, CH_2), 1,52 (p, J 7,5 Hz, 2H, CH_2), 2,52 (t, J 7,2 Hz, 2H, CH_2), 4,20 (s, 2H, SCH_2), 7,10 (d, J 8,2 Hz, 2H, H-3, H-5), 7,43 (d, J 8,2 Hz, 2H, H-2, H-6), 7,14 (s, 1H, CH), 10,24 (s, 1H, NH), m/z = 370 [M^+], Found, %: C 62,86; H 6,29; N 19,24. $C_{19}H_{23}N_5OS$. Anal. Calcd. %: C 62,95; H 6,39; N 19,32.

2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]-N-(4-methoxyphenyl)-acetamide 3(e): yield — 78%, m.p. — 192-194°C, IR (KBr), υ (cm^{-1}): 3265, 1682, 1604, 1542, 1425, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,47 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 3,49 (s, 3H, OCH_3), 4,19 (s, 2H, SCH_2), 6,85 (d, J 8,6 Hz, 2H, H-2, H-6), 7,42 (d, J 8,6 Hz, 2H, H-2, H-6), 7,10 (s, 1H, CH), 10,12 (s, 1H, NH), m/z = 344 [M^+], Found, %: C 55,86; H 4,89; N 20,26. $C_{16}H_{17}N_5O_2S$. Anal. Calcd. %: C 55,96; H 4,99; N 20,39.

2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]-N-(4-methylphenyl) acetamide 3(f): yield — 80%, m.p. — 170-172°C, IR (KBr), υ (cm^{-1}): 3245, 1684, 1595, 1550, 1422, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,26 (s, 3H, CH_3) 2,48 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 4,22 (s, 2H, SCH_2), 7,11 (s, 1H, CH), 7,15 (d, J 8,6, 2H, H-2, H-6), 7,43 (d, J 8.6, 2H, H-3, H-5), 10,20 (s, 1H, NH). m/z = 344 [M^+], Found, %: C 58,58; H 5,18; N 21,29. $C_{16}H_{17}N_5OS$. Anal. Calcd. %: C 58,69; H 5,23; N 21,39.

2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]-N-(4-fluorophenyl) acetamide 3(g): yield — 64%, m.p. — 172-174°C, IR (KBr), υ (cm^{-1}): 3230, 1680, 1610, 1555, 1424, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,47 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 4,23 (s, 2H, SCH_2), 7,11 (s, 1H, CH), 7,48 (d, J 8,6, 2H, H-3, H-5), 7,72 (d, J 8.6 Hz, 2H, H-2, H-6), 10,49 (s, 1H, NH), m/z = 332 [M^+], Found, %: C 54,27; H 4,16; N 21,04. $C_{15}H_{14}N_5OSF$. Anal. Calcd. %: C 54,37; H 4,26; N 21,13.

N-(4-chlorophenyl)-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio] acetamide 3(h): yield — 63%, m.p. — 213-215°C, IR (KBr), υ (cm^{-1}): 3245, 1680, 1600, 1552, 1420, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,47 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 4,23 (s, 2H, SCH_2), 7,11 (s, 1H, CH), 7,50 (d, J 8,6, 2H, H-3, H-5), 7,78 (d, J 8,6 Hz, 2H, H-2, H-6), 10,51 (s, 1H, NH). m/z = 348 [M^+], Found, %: C 51,65; H 3,96; N 20,05. $C_{15}H_{14}N_5OSCl$. Anal. Calcd. %: C 51,79; H 4,05; N 20,13.

N-(3-chlorophenyl)-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio] acetamide 3(i): yield — 61%, m.p. — 196-198°C, IR (KBr), υ (cm^{-1}): 3200, 1682, 1615, 1554, 1425, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,47 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 4,20 (s, 2H, SCH_2), 7,11 (s, 1H, CH), 7,13-7,40 (m, 3H, H-4, 5, 6), 7,70 (s, 1H, H-2), 10,50 (s, 1H, NH), m/z = 348 [M^+], Found, %: C 51,69; H 3,98; N 20,05. $C_{15}H_{14}N_5OSCl$. Anal. Calcd. %: C 51,79; H 4,05; N 20,13.

N-(3,4-dichlorophenyl)-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio] acetamide 3(j): yield — 76%, m.p. — 187-189°C, IR (KBr), υ (cm^{-1}): 3270, 1680, 1600, 1556, 1422, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,47 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 4,23 (s, 2H, SCH_2), 7,11 (s, 1H, CH), 7,42 (d, J 5,8 Hz, 1H, H-6), 7,57 (d, J 5,8 Hz, 1H, H-5), 7,92 (s, 1H, H-2), 10,61 (s, 1H, NH), m/z = 382 [M^+], Found, %: C 47,04; H 3,49; N 18,23. $C_{15}H_{13}N_5OSCl_2$. Anal. Calcd. %: C 47,13; H 3,43; N 18,32.

N-(4-bromophenyl)-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio] acetamide 3(k): yield — 75%, m.p. — 176-178°C, IR (KBr), υ (cm^{-1}): 3246, 1682, 1602, 1550, 1422, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,47 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 4,22 (s, 2H, SCH_2), 7,11 (s, 1H, CH), 7,30-7,81 (m, 4H, Ph),

10,45 (s, 1H, NH), m/z = 392 [M^+], Found, %: C 45,82; H 3,49; N 17,74. $C_{15}H_{14}N_5OSBr$. Anal. Calcd. %: C 45,92; H 3,59; N 17,85.

N-(2-chlorophenyl)-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio] acetamide 3(l): yield — 64%, m.p. — 148-150°C, IR (KBr), υ (cm^{-1}): 3198, 1686, 1610, 1560, 1423, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,47 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 4,27 (s, 2H, SCH_2), 7,11 (s, 1H, CH), 7,16 (t, J 7,4 Hz, 1H, H-4), 7,30 (t, J 7,6 Hz, 1H, H-5), 7,45 (d, J 7,2 Hz, 1H, H-3), 7,74 (d, J 8.0 Hz, 1H, H-6), 9,84 (s, 1H, NH). m/z = 349 [M^+], Found, %: C 51,69; H 4,00; N 20,04. $C_{15}H_{14}N_5OSCl$. Anal. Calcd. %: C 51,79; H 4,05; N 20,13.

N-(3-acetylphenyl)-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio] acetamide 3(m): yield — 72%, m.p. — 134-136°C, IR (KBr), υ (cm^{-1}): 3270, 1684, 1600, 1552, 1424, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,45 (s, 3H, CH_3), 2,55 (s, 6H, $2CH_3$), 4,24 (s, 2H, SCH_2), 7,09 (s, 1H, CH), 7,44 (t, J 7,8 Hz, 1H, H-5), 7,69 (d, J 5.6 Hz, 1H, H-4), 7,76 (d, J 5,6 Hz, 1H, H-6), 8,09 (s, 1H, H-2), 10,40 (s, 1H, NH), m/z = 355 [M^+], Found, %: C 57,35; H 4,75; N 19,10. $C_{17}H_{17}N_5O_2S$. Anal. Calcd. %: C 57,45; H 4,82; N 19,17.

2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]-N-(4-isopropylphenyl) acetamide 3(n): yield — 73%, m.p. — 164-166°C, IR (KBr), υ (cm^{-1}): 3194, 1680, 1617, 1553, 1423, ^{1}H NMR (DMSO-d_6), δ (ppm): 1,11 (s, 3H, CH_3), 1,2 (s, 3H, CH_3), 2,55 (s, 6H, $2CH_3$), 2,70-2,91 (m, 1H, CH), 4,19 (s, 2H, SCH_2), 7,10 (d, J 8.6 Hz, 2H, H-2, H-6), 7,19 (s, 1H, CH), 7,43 (d, J 8.6 Hz, 2H, H-3, H-5), 10,41 (s, 1H, NH), m/z = 356 [M^+], Found, %: C 60,78; H 5,85; N 19,60. $C_{18}H_{21}N_5OS$. Anal. Calcd. %: C 60,82; H 5,95; N 19,70.

N-{4-[(difluoromethyl)thio]phenyl}-2-[(6,8-dimethyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)thio]acetamide 3(o): yield — 60%, m.p. — 138-140°C, IR (KBr), υ (cm^{-1}): 3224, 1684, 1605, 1556, 1425, ^{1}H NMR (DMSO-d_6), δ (ppm): 2,45 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 4,20 (s, 2H, SCH_2), 7,09 (s, 1H, CH), 7,39 (s, 1H, CH), 7,48 (d, J 8.7 Hz, 2H, H-2, H-6), 7,61 (d, J 8,7 Hz, 2H, H-3, H-5), 10,50 (s, 1H, NH), m/z = 379 [M^+], Found, %: C 48,49; H 3,76; N 17,62. $C_{16}H_{15}N_5OS_2F_2$. Anal. Calcd. %: C 48,59; H 3,82; N 17,71.

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