Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(21):17-21
(http://www.derpharmachemica.com/archive.html)

The Synthesis of Potential Anti-Inflammatory Substances among 4-Amino-5-(Pyridin-4-yl)-1,2,4-Triazole(4*н*)-3-yl-Thioacetamides and their Chemical Modification

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ABSTRACT

Synthesis of new 4-amino-5-(pyridin-4-yl)-1,2,4-triazole(4H)-3-ylthio-acetamides and their pyrrolyl derivatives is described in an article. The initial compound – 4-amino-3-thio-5-(pyridin-4-yl)-1,2,4-triazole(4H) were synthesized by esterification of the initial 4-pyridinecarboxylic acid, and further interaction of resulting methyl ester with hydrazide and potassium 4-pyridine dithiocarbazate wjth the following cyclisation with hydrazine hydrate. The acetamides were obtained by alkylation of the 4-amino-3-thio-5-(pyridin-4-yl)-1,2,4-triazole(4H) with N-arylsubstituted α-chloracetamides in the presence of KOH. Using Paal-Knorr condensation, the amino group at position 4 was modified into the pyrrole fragment by the action of of 2,5-dimethoxytetrahydrofuran in acetic acid. The preliminary prediction of the possible pharmacological activity by computer prognosis (PASS software) was carried out. Due to the prognosis and analysis of logical data, the substances synthesized will be examined as possible anti-inflammatory agents.

Keywords: 4-amino-3-thio-1,2,4-triazole, Pyridine, Synthesis, Anti-inflammatory activity

INTRODUCTION

In recent decades, the number of publications concerning the methods of synthesis, chemical reactions, physical, chemical and biological properties of 1,2,4-triazole derivatives steadily increases. Primarily it is predetermined by the wide range of pharmacological activities of this class of compounds.

Thus, the compounds with antitumor [1], antibacterial [2], antifungal [3], anticonvulsant [4], antioxidant [5], antiulcer [6,7], anti-cancer [8] and other types of pharmacological activity are found among them. Having analyzed the published data, we noticed that a number of publications regarding the study of anti-inflammatory action of 1,2,4-triazole derivatives also enlarges [9-11].

After analizing the structure of modern COX inhibitors—oxicams and studying the publications of the structure-activity relationships [12], we noted that the presence of hydroxyl group, acetamide residue and Sulfur atom influents on the anti-inflammatory activity of this class of compounds. Besides, the presence of pyridine moiety in a modern drug Tenoxicam affects its inhibitory effect on COX-2.

Considering all these data, we chose 4-amino-3-thio-1,2,4-triazole with the pyridine substituent at position 5 as the basic structure. The presence of mercapto group allows obtaining a series of acetamide derivatives while the amino group is going to be modified into pyrrole cycle for further structure-activity study. The introduction of pyrrole ring into position 4 is conditioned by the published data concerning its role in the manifestation of the anti-inflammatory activity [13].

The research aimed at synthesizing series of 4-amino-3-thio-5-(pyridine-4-yl)-4H-1,2,4-triazoloacetamides and their 4 pyrrolyl derivatives as possible anti-inflammatory agents.

To establish the prospects of synthesis and an optimization of the further pharmacological screening, we performed a prediction of a biological activity that was planned for the synthesis of the compounds using a computer PASS program [14]. Acetamides

of 4-amino-3-thio-5-(pyridin-4-yl)-1,2,4-triazole(4H) and their 4-pyrrolyl derivatives were selected for a synthesis. A marked psychotropic activities such as antiepileptic, anxiolytic, antidepressant, antineurotic, and convulsant activities (Ra ≥ 0.50) was predicted for these compounds.

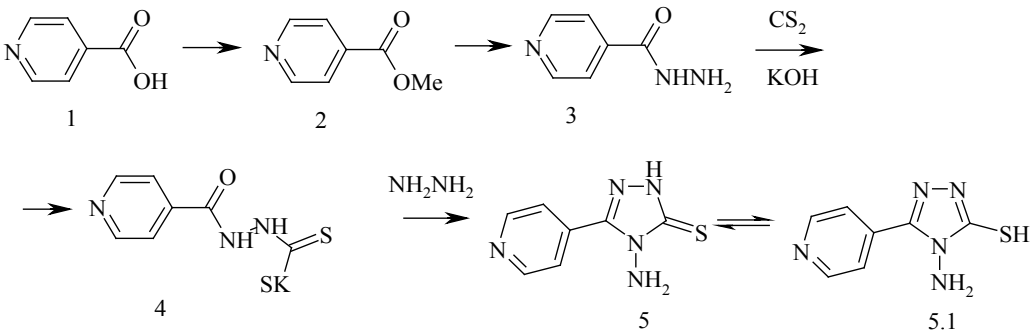
Synthesis of an intermediate product of reaction - 4-amino-3-thio-5- (pyridine-4-yl)-4H-1,2,4-triazole 5 was carried out by the classical procedure of the formation of triazole cycle using the hydrazides of carboxylic acids [15]. The methyl ester 2 obtained in reaction of esterification of the initial 4-pyridinecarboxylic 1 was subjected to hydrazinolysis. The resulting carbohydrazide 3 with the interaction of carbon disulfide in an alkaline medium formed potassium dithiocarbazinate 4. Condensation of dithiocarbazinate 4 with the hydrazine led to the formation of the intermediate target -4-amino-3-thio-5-(pyridine-4-yl)-4H-1,2,4-triazole 5 (Scheme 1).

The synthesized product of the reaction can possibly exist in two tautomeric forms such as thione 5 and tiol 5.1. In the 1H NMR spectrum, a singlet at 13.62 ppm was recorded which corresponds to the protons of NH group. In addition, in the IR spectrum of compound 5 an absorption band at 3241.1 cm^{-1}, corresponding to stretching vibrations of NH-group is present as well as stretching vibration band C=S at 1282.1 -1sm. The stated above data confirms the formation of thione form 5.

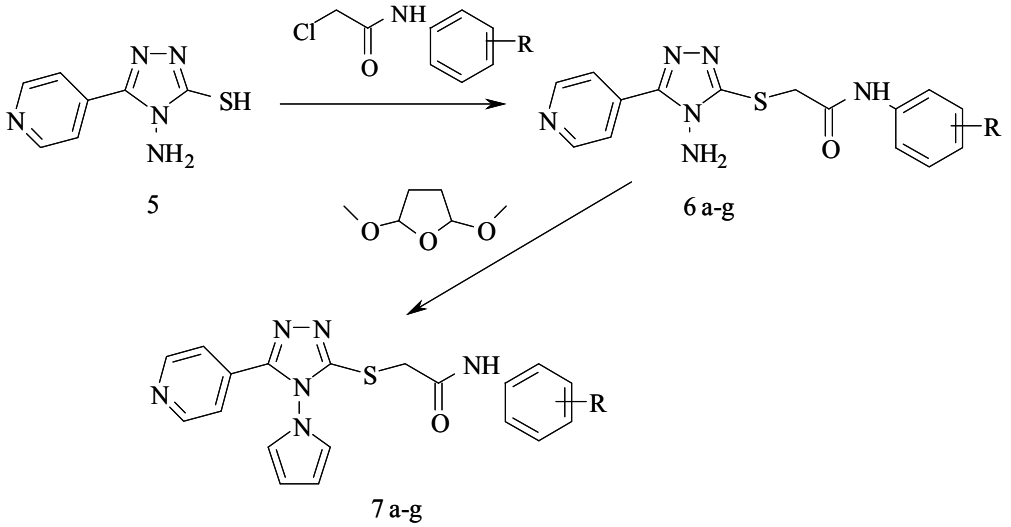
The following modification of the resulting 4-amino-5-(pyridine-4-yl) -2,4-dihydro-3H-1,2,4-triazole-3-thione 5, we carried out by its alkylation with N-aryl substituted α-chloroacetamides (Scheme 2). The reaction mixture of an initial triazole 5 was refluxed for an hour with an appropriate acetamide in ethanol in the presence of KOH (Scheme 2).

Aiming at introducing an additional pharmacophore fragment, as well as establishing the influence of amino group at position 4 of triazole cycle on the pharmacological activity, we modified 4-amino-5-(pyridine-4-yl)-4H-1,2,4-triazolo-3-ylthio-acetamides **6** by converting the amino groups into pyrrole residue. For conducting this reaction, we used the condensation of Paal-Knorr: the interaction of 1,4-dicarbonyl compounds with the primary amines on heating in the presence of acetic acid [13]. As the primary amine, 4-amino derivatives of 1,2,4-triazole **6** as well as the dicarbonyl component – 2,5 dimetoxytetrahydrofuran were used in the research.

Acetamides 6 a-g and their 4-pirrolyl derivatives 7 a-g we obtained with the satisfactory yields (Table 1). According to chromatomass-spectrometry data, the synthesized products are individual substances. After the crystallization from etanol, the synthesized compounds turn into white or light yellow crystalline substances with the well-defined melting points.



Scheme 1: Formation of the intermediate target



6, 7d - NMePh

Scheme 2: Reaction mixture

Table 1: Data of obtained acetamides of 4-amino-3-thio-5-(pyridin-4-yl)-1,2,4-triazole(4H) 6a-g and 4-pyrrolyl derivatives 7a-g

Compounds	R	Yield, %	M.p., °C	N,% Calc. Found	S,% Calc. Found	Molecular formula	[MH$^+$]
5	-	91	249-3	-	-	$C_7H_7N_6S$	–
6a	4-OMe	88	218-20	23,58 23,61	9,00 8,94	$C_{16}H_{16}N_6O_2S$	–
6b	3,5-diCl	85	206-8	21,26 21,30	8,11 8,09	$C_{15}H_{12}Cl_2N_6OS$	396
6c	4-Bu	78	200-2	21,97 21,99	8,38 8,33	$C_{19}H_{22}N_6OS$	–
6d	H	84	184-6	24,69 24,72	9,42 9,37	$C_{16}H_{16}N_6OS$	–
6e	4-NO_2	80	248-50	26,40 26,46	8,63 8,59	$C_{15}H_{13}N_7O_3S$	–
6f	3-COMe	83	123-5	22,81 22,87	8,70 8,67	$C_{17}H_{16}N_6O_2S$	372
6g	3,4-diOMe	76	116-8	21,75 21,80	8,30 8,28	$C_{17}H_{18}N_6O_3S$	–
7a	4-OMe	88	170-2	20,68 20,70	7,89 7,85	$C_{20}H_{18}N_6O_2S$	407
7b	3,5-diCl	85	188-90	18,87 18,90	7,20 7,18	$C_{19}H_{14}Cl_2N_6OS$	–
7c	4-Bu	78	179-81	19,43 19,50	7,41 7,38	$C_{23}H_{24}N_6OS$	–
7d	H	84	211-3	21,52 21,59	8,21 8,19	$C_{20}H_{18}N_6OS$	–
7e	4-NO_2	80	156-8	23,27 23,30	7,61 7,59	$C_{19}H_{15}N_7O_3S$	422
7f	3-COMe	83	145-8	20,08 20,12	7,66 7,60	$C_{21}H_{18}N_6O_2S$	-
7g	3,4-diOMe	76	135-7	19,25 19,30	7,35 7,32	$C_{21}H_{20}N_6O_3S$	–

The structure of the substances 6,7a-g synthesized has been proven by the data of elemental analysis, IR- and NMR spectra.

Common to the synthesized compounds 6,7a-g are the proton signals of the pyridine residue in position 5 of triazole cycle, which appears as two doublets around 7.99-8.00 and 8.72-8.75 ppm; a singlet signal at of SCH_2 group at 3.83-4.23 ppm; a singlet of NH-group of an acetamide residue in a weak field (10.24-11.27 ppm) and the signals of aromatic protons of the phenyl radical which correspond to the placement of substituents due to multiplicity and intensity.

The presence of singlet protons of the amino group in position 4 of the triazole cycle around 6.29-6.36 ppm is typical for the compounds 6 a-g. The modification of this amino group of pyrrolyl derivatives 7 a-g is accompanied by a change of ^{1}H NMR spectra: Instead of the amino group signal there appears a triplet signal of CH protons of the pyrrole cycle at the position 3,4 (6.33-7.61 ppm) and a doublet signal of 2,5-methine protons at 7,19-7,92 ppm. In the spectra of compounds 7c, the signals of protons of pyrrole cycle and aromatic protons overlap and appear as a multiplet.

MATERIALS AND METHODS

All of the solvents and reagents were obtained from the commercial sources. The melting points (°C) were determined by the open capillary tube. ^{1}H NMR spectra were recorded on a Bruker WM spectrometer (300 MHz); solvents – $CDCl_3$ or DMSO-d_6; chemical shifts were in ppm, TMS was used as an internal standard. The purity of the compounds synthesized has been monitored by TLC. LC/MS was recorded with PE SCIEX API 150EX chromatograph equipped with a mass-spectrometer.

Experimental part

Methyl pyridine-4-carboxylate: To 4-pyridinecarboxylic acid (0.1 mol) in methanol (100 mL), add conc. sulfuric acid (5.7 mL) in a round bottom flask. Reflux the mixture for 4-6 h. Distil off an excess of methanol and after cooling transfer the content to a separating funnel containing 100 mL of distilled water. Extract the ester 2 synthesized several times with chloroform (30 mL). Wash the combined organic layers with 20% solution of sodium bicarbonate. After washing with distilled water, dry the organic layer over anhydrous $MgSO_4$. Then distil off chloroform under reduced pressure obtaining ester 2. Yield – 91%, m.p. – 200-202°C (ethanol).

Pyridin-4-carbohydrazide: To hydrazine hydrate (99%) (5.7 mL, 0.15 mol), add the solution of ester 2 (0.1 mol) in ethanol in a flat bottom flask dropwise with gentle stirring. After complete addition, transfer the mixture into a round bottomed flask

and reflux for 4-6 h. Distill off ethanol under the reduced pressure. Filter the precipitate of carbohydrazide, and crystallize it from ethanol.

Potassium 2-(pyridil-4-yl) dithiocarbazinate: Treat the absolute ethanol and (0.1 mol) of 3 with (0.15 mol) of carbon disulfide. Dilute the reaction mixture with 75 mL of absolute ethanol and stir at a room temperature for 12-16 h. Distill off the solvent under reduced pressure. The salt prepared as described above is obtained in nearly quantitative yield and is employed without further purification.

4-Amino-5-(pyridin-4-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione: Reflux the suspension of (0.1 mol) of 4 in absolute ethanol, (0.2 mol) of 99% hydrazine hydrate and 6 mL of water for 2-3 h. The color of the reaction mixture is changed to green with the evolution of hydrogen sulfide gas resulting in a homogenous solution. Add cold distilled water (100 mL) and acidify the solution with conc. HCl. Filter the precipitated solid, wash with 2 × 30 mL portions of cold water and crystallize. Yield – 81%, m.p. – 249-3, Mol. formula $C_7H_7N_6S$.

IR (KBr, cm 1): 3457.4 (NH_2), 3241.1 (NH), 1620.6, (C=N), 1282.1 (C=S).

^{1}H NMR spectrum: 6.32 (2H, s, NH_2); 8.01 (2H, d., Ar); 8.71 (2H, d., Ar); 13.62 (1H, br.s., NH).

4-Amino-5-(pyridin-4-yl)-1,2,4-triazole(4H)-3-ylthioacetamides (6a-g) (general procedure): To the solution of 0.002 mol of 4-amino-5-(pyridin-4-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione 5 in 20 ml of ethanol add 20 ml of 0.002 M aqueous solution of KOH. To the obtained solution, add the solution of (0.002 mol) the corresponding chloroacetamide 6 while stirring. Reflux the reaction mixture for about 1 hour, cool, and place it into 200 ml of water. Collect and dry the precipitate, crystallize it from ethanol.

N-phenyl-2-(5-(pyridin-4-yl)-4-(1H-1-pyrrolyl)-4H-1,2,4-triazole-3-ylthio)acetamides (7a-g) (general procedure) (Table 1). To the solution of 0.005 mol of corresponding 4-amino-5-(pyridin-4-yl)-1,2,4-triazole(4H)-3-ylthio acetamide 6a-g in 40 ml of acetic acid add 0,005 mol of 2,5-dimethoxytetrahydrofuran. Reflux the mixture for approximately 1 hour, cool, and place into 200 ml of water. Collect the precipitate and dry, crystallize it from ethanol.

1H NMR spectra (compounds 5): 2-[4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl]thio-N-(4-methoxyphenyl)-acetamide (6a): 3.70 (3H, s., OCH_3); 4.17 (2H, s., SCH_2); 6,33 (2H, s., NH_2), 6.90 (2H, d. J=9.2, 2,6-Ar); 7.51 (2H, d. J=9.2, 3,5-Ar); 7.99 (2H, d. J=6, py); 7.80 (2H, d. J=6, Ar); 8.73 (2H, J=6, d., py); 10.26 (1H, s., NH).

2-[4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl]thio-N-(3,5-dichlorophenyl)acetamide (6b): 4.21 (2H, s., SCH_2); 6,32 (2H, s., NH_2), 7.33 (1H, s. 4-Ar); 7.65 (2H, s., 2,6-Ar); 7.99 (2H, d. J=6, py); 8.75 (2H, J=6, d., py); 11.27 (1H, s., NH).

2-[4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl]tio-N-(4-butylphenyl)acetamide (6c): 0.87 (2H, t., CH_3); 1.25-1.31 (2H, m., CH_2); 1.51-1.3 (2H, q., CH_2); 2.50 (2H, t., CH_2); 4.14 (2H, s., SCH_2); 6,33 (2H, s., NH_2), 7.12 (2H, d. J=9.2, 2,6-Ar); 7.51 (2H, d. J=9.2, 3,5-Ar); 8.00 (2H, d. J=6, py); 7.80 (2H, d. J=6, Ar); 8.72 (2H, J=6, d., py); 10.35 (1H, s., NH).

2-[4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl]tio-N-phenyl-N-(propan-2-yl)acetamide (6d): 0.99 (3H, s., CH_3); 1.02 (3H, s., CH_3); 3.82 (2H, s., SCH_2); 4.69-4.89 (1H, m., CH), 6,29 (2H, s., NH_2), 7.35 (2H, d. J=12, 2,6-Ar); 7.60-7,42 (3H, m., 3,4,5-Ar); 7.96 (2H, d. J=6, py); 8.72 (2H, J=6, d., py).

2-[4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl]tio-N-(4-nitrophenyl)acetamide (6e): 4.27 (2H, s., SCH_2); 6.36 (2H, s., NH_2), 7.85 (2H, d. J=8, 2,6-Ar); 7.99 (2H, d. J=6, CH py); 8.24 (2H, d. J=8, 3,5-Ar); 8.73 (2H, J=6, d., CH py); 11.00 (1H, s., NH).

2-[5-(pyridin-4-yl)-4-(1H-pyrrol-1-yl)-4H-1,2,4-triazol-3-yl]tio-N-(3-acetylphenyl)-acetamide (6f): 3.79 (3H, s., $COCH_3$); 4.12 (2H, s., SCH_2); 6,33 (2H, s., NH_2), 6.90 (1H, s., 2-Ar); 7.51-7.61 (3H, m.,4,5,6-Ar); 7.99 (2H, d. J=6, py); 7.80 (2H, d. J=6, Ar); 8.73 (2H, J=6, d., py); 10.26 (1H, s., NH).

2-[4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl]thio-N-(3,4-dimethoxyphenyl)acetamide (6g): 3.71 (6H, s., $2OCH_3$); 4.16 (2H, s., SCH_2); 6,35 (2H, s., NH_2), 6.90 (2H, d. J=9.2, 2,6-Ar); 7.51 (2H, d. J=9.2, 3,5-Ar); 7.99 (2H, d. J=6, py); 8.00 (2H, d. J=6, Ar); 8.74 (2H, J=6, d., py); 10.27 (1H, s., NH).

2-[5-(pyridin-4-yl)-4-(1H-pyrrol-1-yl)-4H-1,2,4-triazol-3-yl]thio-N-(4-methoxyphenyl)acetamide (7a): 3.73 (3H, s., OCH_3); 4.21 (2H, s., SCH_2); 6,38 (2H, t. J=4, 3,4-CH, pyrrole), 6.89 (2H, d. J=8, 2,6-Ar); 7.14 (2H, d. J=8, 3,5-Ar); 7.30 (2H, d. J=4, 2,5-CH, pyrrole); 8.62 (2H, d., J=6, CH py), 10.24 (1H, s., NH).

2-[5-(pyridin-4-yl)-4-(1H-pyrrol-1-yl)-4H-1,2,4-triazol-3-yl]thio-N-(3,5-dichlorophenyl)acetamide (7b): 4.21 (2H, s., SCH_2); 6,38 (2H, t. J=4, 3,4-CH, pyrrole), 7.34 (1H, s. 4-Ar); 7.30 (2H, d. J=4, 2,5-CH, pyrrole); 7.65 (2H, s., 2,6-Ar); 7.99 (2H, d. J=6, py); 8.75 (2H, J=6, d., py), 11.27 (1H, s., NH)..

2-[5-(pyridin-4-yl)-4-(1H-pyrrol-1-yl)-4H-1,2,4-triazol-3-yl]thio-N-(4-butylphenyl)acetamide (7c): 0.87 (2H, t., CH_3); 1.25-1.31 (2H, m., CH_2); 1.51-1.3 (2H, q., CH_2); 2.50 (2H, t., CH_2); 4.23 (2H, s., SCH_2); 6.39 (2H, d. J=4, 2,6-Ar); 7.14-6.69 (4H, m. J=4, CH pyrrole), 7.30 (2H, d. J=4, 3,5-Ar); 7.46 (2H, d. J=8, CH py); 8.62 (2H, J=8, d., CH py); 10.31(1H, s., NH).

[5-(pyridin-4-yl)-4-(1H-pyrrol-1-yl)-4H-1,2,4-triazol-3-yl]tio-N-phenyl-N-(propan-2-yl)acetamide (7d): 0.99 (3H, s., CH_3); 1.02 (3H, s., CH_3); 3.82 (2H, s., SCH_2); 4.69-4.90 (1H, m., CH), 6,38 (2H, d. J=4, 2,5-CH, pyrrole), 7.08 (2H, d. J=12, 2,6-Ar); 7.20 (2H, t. J=4, 3,4- CH, pyrrole); 7.35 (2H, d. J=8, py); 7.60-7,42 (3H, m., 3,4,5-Ar); 8.60 (2H, d. J=8, py).

2-[5-(pyridin-4-yl)-4-(1H-pyrrol-1-yl)-4H-1,2,4-triazol-3-yl]thio-N-(4-nitrophenyl)acetamide (7e): 4.27 (2H, s., SCH_2); 7.19-7.39 (4H, m., Ar); 7.61 (2H, d., CH pyrrole); 7.92-8.30 (4H, m., CH pyrrole); 8.62 (2H, J=6, d., CH py); 11.00 (1H, s., NH).

2-[5-(pyridin-4-yl)-4-(1H-pyrrol-1-yl)-4H-1,2,4-triazol-3-yl]tio-N-(3-acetylphenyl)-acetamide (7f): 3.79 (3H, s., $COCH_3$); 4.12 (2H, s., SCH_2); 6,38 (2H, t. J=4, 3,4-CH, pyrrole), 6.90 (1H, s., 2-Ar); 7.30 (2H, d. J=4, 2,5-CH, pyrrole); 7.51-7.61 (3H, m.,4,5,6-Ar); 7.99 (2H, d. J=6, py); 7.80 (2H, d. J=6, Ar); 8.73 (2H, J=6, d., py); 10.26 (1H, s., NH).

2-[5-(pyridin-4-yl)-4-(1H-pyrrol-1-yl)-4H-1,2,4-triazol-3-yl]thio-N-(3,4-dimethoxyphenyl)acetamide (7g): 3.71 (6H, s., $2OCH_3$); 4.16 (2H, s., SCH_2); 6.90 (2H, d. J=9.2, 2,6-Ar); 7.30 (2H, d. J=4, 2,5-CH, pyrrole); 7.48 (2H, n. J=4, 3,4-CH pyrrole); 7.51 (2H, d. J=9.2, 3,5-Ar); 7.99 (2H, d. J=6, py); 8.00 (2H, d. J=6, Ar); 8.74 (2H, J=6, d., py); 10.27 (1H, s., NH).

CONCLUSION

Using PASS program a synthesis of possible anti-inflammatory agents was planned. The series of 4-amino-3-thio-5-(pyridine-4-yl) -4H-1,2,4-triazoloacetamides were synthesized and using Paal-Knorr condensation, the amino group at position 4 was modified into the pyrrole fragment. The structure of the obtained compounds was confirmed by ^{1}H NMR and chromatomass-spectrometry.

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