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Chemistry

SYNTHESIS OF NEW 3-MORPHOLYL-SUBSTITUTED 4-ARYL-2-ARYLIMINO-2,3-DIHYDROTHIAZOLE DERIVATIVES AND THEIR ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY

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Abstract. New 4-aryl-3-(morpholin-4-yl)-2-arylimino-2,3-dihydrothiazole derivatives **1.1-1.16** were obtained using the Hantzsch reaction by condensation of N-(morpholin-4-yl)-N'-arylthioureas with the corresponding α-bromoacetophenones in alcohols. Synthesized hydrobromides **1.1-1.8** were formed as crystalline precipitates during the boiling of the reaction mixture. Bases **1.9-1.16** were obtained by neutralizing the corresponding hydrobromides with NH_4OH solution. It has been proposed a possible mechanism of the reaction that is based on the study of the structure of the synthesized compounds. The structures of the synthesized compounds were confirmed by ^1H NMR spectroscopy with its special techniques (NOESY and ROESY experiments). It has been shown the formation of the isomer 4-(4'-chlorophenyl)-3-(morpholin-4-yl)-2-(4'-chlorophenylamino)-2.3-dihydrothiazole on the basis of compound 1.14. Pharmacological screening of synthesized derivatives of 4-aryl-2-arylimino-2,3-dihydrothiazole compounds revealed the analgesic effect in the model of visceral pain caused by the introduction of acetic acid to white mice. The anti-inflammatory effect of the synthesized compounds was evaluated *in vivo* by reducing limb edema in rats with carrageenan-induced inflammation. Thus, the synthesized compounds have analgesic and anti-inflammatory activity.

Keywords: 2,3-dihydrothiazole derivatives, Hantzsch reaction, N-(morpholin-4-yl)-N'-arylthioureas, anti-inflammatory activity, analgesic activity.

1. Introduction

The search for new compounds with anti-inflammatory and analgesic effects is an urgent problem due to the prevalence of inflammatory processes of different genesis. Analgesics and anti-inflammatory drugs presented in the pharmaceutical market are not effective and safe enough. Their side effects and the complexity of their pharmacological correction during the application with drugs of other pharmacotherapeutic groups determine the feasibility of searching for new compounds with anti-inflammatory and analgesic effects.[1-4]

The thiazole heterocycle is an important pharmacophore. The use of various substituents in the thiazole fragment gives new biologically active compounds.[5-6] Thiazole derivatives exhibit a wide range of biological properties and are important reagents. Some of them such as Troglitazone, Rosiglitazone, Pioglitazone, Teneligliptin are widely used in the treatment of type 2 diabetes T2D.[7]

The known thiazole compounds have demonstrated antitumor activity on the studied cell lines.[8] Pharmacological screening for antimicrobial activity of 1,3-thiazoline derivatives with N-methylpiperazine moiety indicates their potent antimicrobial activity against sulfate-reducing bacteria *Desulfovibrio sp. M.4.1*.[9]

The antioxidant activity of novel N3 and C6 substituted 5,7-dimethyl-3H-thiazolo[4,5-b]pyridine-2-one derivatives has been evaluated *in vitro* by the method of scavenging effect on 2,2-diphenyl-1-picrylhydrazyl radicals.[10] The synthesis and prognosis of antihypertensive activity *in silico* of new Mannich bases containing

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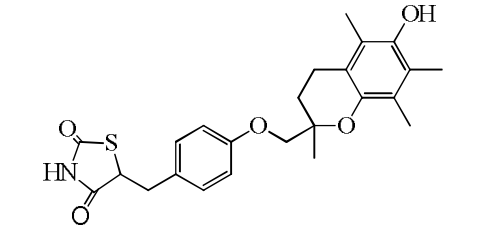
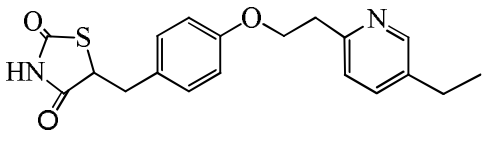
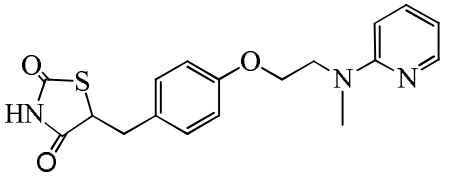
a nitrogen-containing fragment are known.[11] Based on pharmacological studies among 2-arylimino-4-methyl-2,3-dihydro-1,3-thiazoles, compounds for in-depth pharmacological studies have been proposed as potential cardioprotective agents.[12] A series of 2-aryl-thiazole hydrazone derivatives have a stronger anti-inflammatory effect than meloxicam.[13,14] Thiazolotriazoles containing 2,4-dichloro-5-fluorophenyl moiety show anti-inflammatory, analgesic and antimicrobial activities.[15]



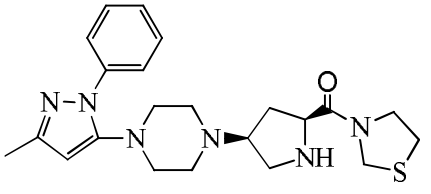
Troglitazone



Pioglitazone



Rosiglitazone



Teneligliptin

Thiazole derivatives have been used in the study of the kinetics of thermo-induced radical polymerization.[16] A method of voltammetric determination of Pd (II) using 5-hydroxyimino-4-imino-1,3-thiazolidine-2-one in the pH range from 1.0 to 10.0, after thermal activation, has also been proposed.[17]

The aim of this work is the synthesis of new 3-morpholyl-substituted 4-aryl-2-arylimino-2,3-dihydrothiazole derivatives, the study of their physicochemical properties, the anti-inflammatory and analgesic effects.

2. Experimental part

2.1. Chemical part

The objects of the study were 3-morpholyl-substituted 4-aryl-2-arylimino-2,3-dihydrothiazole derivatives. 4-Aryl-3-(morpholin-4-yl)-2-arylimino-2,3-dihydrothiazole derivatives were obtained under the conditions of the Hantzsch reaction (scheme 1).[12]

The method for the synthesis of 4-phenyl-3-(morpholin-4-yl)-2-phenylimino-2,3-dihydrothiazole hydrobromide ***1.1***. Boil 2.37 g (0.01 mol) of *N*-(morpholin-4-yl)-*N'*-phenylthiourea and 1.2 g (0.01 mol) of α-bromoacetophenone in 40 mL of ethanol for 1 hour. Filter the resulting precipitation, wash with water, and dry. Crystallize from propanol-2. Yield – 3.35 g (80 %).

Compounds **1.1-1.3** were obtained similarly.

The method for the synthesis of 4-(4-chlorophenyl-3-(morpholin-4-yl)-2-phenylimino-2,3-dihydrothiazole hydrobromide ***1.4***. Boil 2.37 g (0.01 mol) of *N*-(morpholin-4-yl)-*N'*-phenylthiourea and 2.33 g (0.01 mol) of α-bromo-4-chloroacetophenone in 40 mL of ethanol for 1 hour. Filter the resulting precipitation, wash with water, and dry. Crystallize from propanol-2. Yield – 3.76 g (83 %).

Compounds **1.5-1.8** were obtained similarly.

The method for the synthesis of 4-(3,4-dimethoxyphenyl)-3-(morpholin-4-yl)-2-phenylimino-2,3-dihydrothiazole ***1.9***. Boil 2.37 g (0.01 mol) of *N*-(morpholin-4-yl)-*N'*-phenylthiourea and 2.59 g (0.01 mol) of α-bromo-3',4'-dimethoxyacetophenone in 40 mL of ethanol for 3 hours. Evaporate the reaction mixture to a volume of 15–20 mL and neutralize by adding 20 mL of 10 % ammonia solution. Filter the resulting precipitation, wash with water, and dry. Crystallize from propanol-2. Yield – 2.73 g (70 %).

Compounds **1.10-1.12** were obtained similarly.

The method for the synthesis of 4-(4'-chlorophenyl)-3-(morpholin-4-yl)-2-(2',3'-dimethylphenyl) imino-2,3-dihydrothiazole ***1.13***. Boil 2.65 g (0.01 mol) of *N*-(morpholin-4-yl)-*N'*-(2,3-dimethylphenyl)thiourea and 2.33 g (0.01 mol) of α-bromo-4'-chloroacetophenone in 40 mL of ethanol for 3 hours. Evaporate the reaction mixture to a volume of 15–20 mL and neutralize by adding 20 mL of 10 % ammonia solution. Filter the resulting precipitation, wash with water, and dry. Crystallize from heptane. Yield – 3.16 g (79 %).

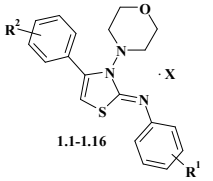
Compounds **1.14-1.16** were obtained similarly.

The structure and individuality of the 3-morpholyl-substituted 4-aryl-2-arylimino-2,3-dihydrothiazole derivatives synthesized were confirmed by ^{1}H NMR-spectroscopy, elemental analysis data (Tables 1 and 2).

2.1. Biological part

An experimental study of the anti-inflammatory activity of the compounds was conducted on male (albino) rats weighing (160 ± 5.7) g, which were kept on a standard balanced diet in a vivarium with a free access to food and water at a temperature of (293-295) K and relative humidity 40–60 %.[18,19] The research was conducted in compliance with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986).

Table 1. Physicochemical properties of 3-morpholyl-substituted 4-aryl-2-arylimino-2,3-dihydrothiazole derivatives **1.1-1.16**



Compound	Gross formula	Yield, %	Melting point, °C	Elemental analysis	
				Calculated, %	Found, %
1.1	$C_{19}H_{19}N_3OS \cdot HBr$	80	241–243	C 54.55; H 4.82; N 10.04; S 7.66	C 54.63; H 4.93; N 10.28; S 7.78
1.2	$C_{19}H_{18}BrN_3OS \cdot HBr$	80	258–260	C 45.89; H 3.85; N 8.45; S 6.45	C 46.02; H 3.93; N 8.56; S 6.48
1.3	$C_{19}H_{18}N_4O_3S \cdot HBr$	72	238–240	C 49.25; H 4.13; N 12.09; S 6.92	C 49.37; H 4.22; N 12.32; S 7.05
1.4	$C_{19}H_{18}ClN_3OS \cdot HBr$	83	196–198	C 50.40; H 4.23; N 9.28; S 7.08	C 50.58; H 4.18; N 9.41; S 7.16
1.5	$C_{21}H_{22}ClN_3O_2S \cdot HBr$	81	197–198	C 50.77; H 4.67; N 8.46; S 6.45	C 50.93; H 4.81; N 8.38; S 6.57
1.6	$C_{20}H_{20}ClN_3O_2S \cdot HBr$	78	196–198	C 49.75; H 4.38; N 8.70; S 6.64	C 49.88; H 4.45; N 8.67; S 6.76
1.7	$C_{20}H_{20}ClN_3OS \cdot HBr$	75	197–199	C 51.46; H 4.53; N 9.00; S 6.87	C 51.62; H 4.47; N 9.17; S 6.98
1.8	$C_{20}H_{20}ClN_3OS \cdot HBr$	76	198–200	C 51.46; H 4.53; N 9.00; S 6.87	C 51.62; H 4.67; N 9.12; S 6.81
1.9	$C_{21}H_{23}N_3O_3S$	70	185–187	C 63.46; H 5.83; N 10.57; S 8.07	C 63.61; H 5.95; N 10.72; S 8.02
1.10	$C_{20}H_{21}N_3O_2S$	74	147–149	C 65.37; H 5.76; N 11.43; S 8.73	C 65.39; H 5.87; N 11.58; S 8.78
1.11	$C_{20}H_{21}N_3OS$	76	153–155	C 68.35; H 6.02; N 11.96; S 9.12	C 68.47; H 6.13; N 12.05; S 9.35
1.12	$C_{20}H_{21}N_3O_2S$	76	140–142	C 68.35; H 6.02; N 11.96; S 9.12	C 68.39; H 5.94; N 12.09; S 9.22
1.13	$C_{21}H_{22}ClN_3OS$	79	112–114	C 63.07; H 5.54; N 10.51; S 8.02	C 63.21; H 5.57; N 10.43; S 8.13
1.14	$C_{19}H_{17}Cl_2N_3OS$	87	150–152	C 56.16; H 4.22; N 10.34; S 7.89	C 56.33; H 4.27; N 10.49; S 7.78
1.15	$C_{20}H_{20}ClN_3OS$	75	139–140	C 62.25; H 5.22; N 10.89; S 8.31	C 62.34; H 5.38; N 11.02; S 8.46
1.16	$C_{20}H_{20}ClN_3O_2S$	74	188–190	C 59.77; H 5.02; N 10.45; S 7.98	C 59.92; H 4.89; N 10.62; S 8.14

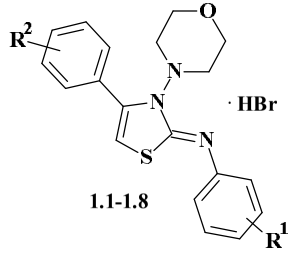
The anti-inflammatory effect of the compounds was studied on the model of carrageenan-induced edema.[4] By random sampling, the animals were divided into groups of seven rats each. The first (control) group included animals, in which the inflammatory process was induced by injecting a solution of carrageenan (an aqueous 1.0 % solution) into the subplantar area of the hind paw subcutaneously in the volume of 0.1 mL. The second group was rats with induction of the inflammatory process one hour after the introduction of the test compounds. The third group included animals with the induction of the inflammatory process of 30 min after administration of the reference drug – diclofenac sodium, one of the most powerful anti-inflammatory medicines in the group of nonsteroidal anti-inflammatory drugs. The fourth group was animals that were given carrageenan 30 min after ibuprofen administration. A separate group consisted of intact animals. Diclofenac was used in an average effective dose by the anti-inflammatory activity – 8.0 mg/kg of the animal body weight. The compounds were administered in the dose of approximately 1/7 of the average lethal dose of the compound – 50 mg/kg of the rat body weight. An effective dose of ibuprofen to reduce the inflammatory response is 50 mg/kg. Therefore, ibuprofen was chosen as another reference drug (by the dose load). The route of administration of the compounds synthesized, ibuprofen and diclofenac are intraperitoneal with the preliminary emulsification of the compounds studied in the form of a suspension in one drop of Tween-80™ and preparation of solutions of the appropriate concentrations using water for injection.

The volume of the affected (hind) paw was measured using an electronic volumeter immediately before administration of the test compounds (initial values) and 4 hours after the inflammation induction. The antiexudative activity (AEA) was determined by the indicator of the paw edema reduction in rats, calculated by the following equation and expressed as a percentage:

$$AEA,\% = \frac{\Delta V_{control} - \Delta V_{experiment}}{\Delta V_{control}} \cdot 100\,\%$$

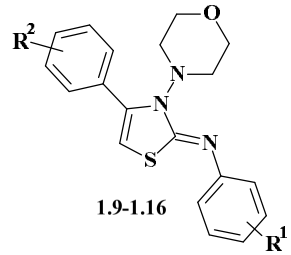
where $\Delta V_{control}$ and $\Delta V_{experiment}$ are the average values of the difference in the volume of the hind paw for animals of the control and experimental groups, respectively.

Table 2. Chemical shifts of protons (δ, ppm) in ^{1}H NMR spectra of 3-morpholyl-substituted 4-aryl-2-arylimino-2,3-dihydrothiazole derivatives **1.1-1.16**



1.1-1.8

1.1 $R^1 = R^2 = H$
1.2 $R^1 = H$, $R^2 = 4$-Br
1.3 $R^1 = H$, $R^2 = 3$-NO_2
1.4 $R^1 = H$, $R^2 = 4$-Cl
1.5 $R^1 = 4$-OC_2H_5, $R^2 = 4$-Cl
1.6 $R^1 = 2$-OCH_3, $R^2 = 4$-Cl
1.7 $R^1 = 2$-CH_3, $R^2 = 4$-Cl
1.8 $R^1 = 4$-CH_3, $R^2 = 4$-Cl



1.9-1.16

1.9 $R^1 = H$, $R^2 = 3,4$-di-OCH_3
1.10 $R^1 = H$, $R^2 = 4$-OCH_3
1.11 $R^1 = H$, $R^2 = 4$-CH_3
1.12 $R^1 = H$, $R^2 = 3$-CH_3
1.13 $R^1 = 2,3$-di-CH_3, $R^2 = 4$-Cl
1.14 $R^1 = 4$-Cl, $R^2 = 4$-Cl
1.15 $R^1 = 3$-CH_3, $R^2 = 4$-Cl
1.16 $R^1 = 4$-OCH_3, $R^2 = 4$-Cl

Compound	^{1}H NMR (400 MHz), δ (ppm), J (Hz)					
	-H_2C-N-CH_2-	-H_2C-O-CH_2-	5-H, thiazole	ArH	NH^+	Other groups
1.1	2.87-2.94m (4H)	3.53-3.59m (4H)	7.14-7.51m (11H, 5H-thiazole + Ar-H)		11.20 (1H)	—
1.2	2.79-2.86m (4H)	3.74-3.79m (4H)	6.93s (1H)	7.13-7.64m (9H)	11.60s (1H)	—
1.3	2.88-2.95m (4H)	3.59-3.64m (4H)	7.41-8.17m (10H, 5H-thiazole + Ar-H)		10.90s (1H)	—
1.4	2.83br.s (4H)	3.67br.s (4H)	7.49s (1H)	7.16-7.31m (4H), 7.56m (5H)	10.80s (1H)	—
1.5	2.88br.s (4H)	3.67br.s (4H)	7.04-7.19m (4H, Ar-H), 7,35-7,55m (5H, 5H-thiazole + ArH)		10.70s (1H)	1.33t (3H, OCH_2CH_3), 4.07kv (2H, OCH_2CH_3)
1.6	2.89br.s (4H)	3.65br.s (4H)	7.03-7.23m (5H, Ar-H), 7.38-7.55m (4H, 5H-thiazole + ArH)		10.76s (1H)	3.65s (3H, OCH_3)
1.7	2.86br.s (4H)	3.62br.s (4H)	6.92-7.18m (4H, Ar-H), 7.27-7.52m (4H, 5H-thiazole + ArH)		10.82s (1H)	2.28s (3H, CH_3)
1.8	2.91br.s (4H)	3.72br.s (4H)	7.04-7.45m (9H, 5H-thiazole + ArH)		10.70s (1H)	2.34s (3H, CH_3)
1.9	2.57-2.63m (4H)	3.50-3.56m (4H)	6.35s (1H)	6.52-7.34m (8H)	—	3.68s (6H, 2*OCH_3)
1.10	2.53-2.59m (4H)	3.59-3.65m (4H)	6.28s (1H)	6.78d (2H, J = 7.6 Hz), 7.05d (2H, J = 7.7 Hz), 7.16-7.35m (5H)	—	3.68s (3H, OCH_3)
1.11	2.61-2.67m (4H)	3.65-3.72m (4H)	6.04s (1H)	6.92-6.96m (4H), 7.11-7.29m (5H)	—	2.27s (3H, CH_3)
1.12	2.58-2.64m (4H)	3.63-3.69m (4H)	6.46s (1H)	6.60-7.38m (9H)	—	3.57s (3H, OCH_3)
1.13	2.60br.s (4H)	3.66br.s (4H)	6.35s (1H)	6.86-7.11m (5H), 7.20d (2H. J = 7.5 Hz)	—	2.03s, 2.25s (6H, 2*CH_3)
1.14	2.59br.s (4H)	3.64br.s (4H)	6.49s (1H)	7.12d (2H, J = 7.6 Hz), 7.19d (2H, J = 7.5 Hz), 7.30d (2H, J = 7.4 Hz), 7.38d (2H, J = 7.5 Hz)	—	—
1.15	2.63br.s (4H)	3.68br.s (4H)	6.43s (1H)	6.95-7.20m (4H), 7.13d (2H, J = 7.4 Hz), 7.26d (2H, J = 7.5 Hz)	—	2.23s (3H, CH_3)
1.16	2.60br.s (4H)	3.67br.s (4H)	6.34s (1H)	6.85d (2H. J = 7.7 Hz), 7.06d (2H, J = 7.6 Hz), 7.12d (2H, J = 7.5 Hz), 7.24d (2H, J = 7.6 Hz)	—	3.75s (3H, OCH_3)

The analgesic activity (AA) of the compounds synthesized was studied on the model of visceral pain in white mice induced by intraperitoneal administration of 0.75 % acetic acid solution, which could cause activation of the kallikrein-kinin system, prostaglandins, biogenic amines, which were endogenous mediators of inflammation and contributed to the development of abdominal muscle writhings.[4]

Immediately before administration to animals 0.75 % solution of glacial acetic acid (c.p.; 99.8 %) was prepared. Acetic acid was administered intraperitoneally in the volume of 0.1 mL per 10 g of the mouse weight.

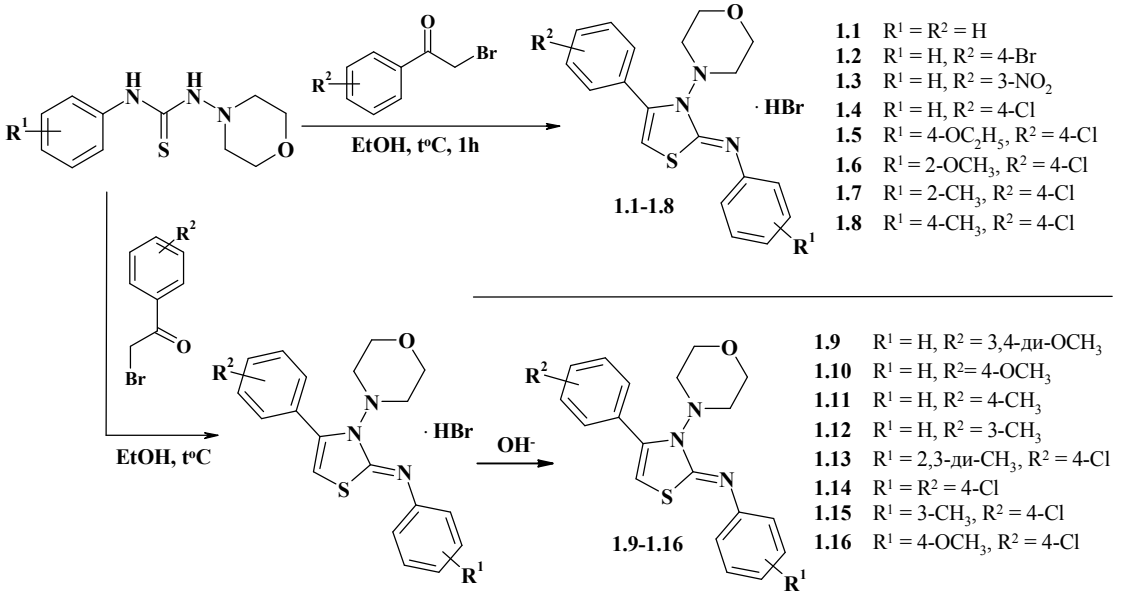
The animals were kept on a standard diet with free access to water under the appropriate laboratory conditions. The day before the start of the experiment, the animals were weighed and randomized into groups of 7 mice each (4 females and 3 males). The first group included animals without a test sample, but they were injected intraperitoneally with acetic acid (control). In the following two groups, there were mice injected with the test compounds and ketorolac in 1 % starch suspension intragastrically through a special metal probe in the doses of 50 mg/kg and 3 mg/kg of the animal body weight (the therapeutic dose calculated with reference to animals), respectively, 60 minutes before the induction of a pain response. Ketorolac was chosen as the reference drug with the proven significant analgesic effect. The selected dose of ketorolac was the average effective dose by the analgesic effect. After the introduction of acetic acid, the animals were placed on a paper mat located on a laboratory table and covered with a special glass cap with a hole for free air access. There were no more than 2 mice under one cap. One researcher observed no more than two animals at the same time.

The animals were monitored for 30 minutes after the introduction of the pathogenic agent, and the number of writhings was recorded from 5 to 15 minutes inclusively. An indicator of the analgesic effect was a decrease in the number of writhings in animals injected with the test compound or the reference drug. The analgesic activity was expressed as a percentage and calculated as the ratio of the difference in the number of writhings in animals of the control and experimental groups to the number of writhings in mice of the control group.

3. Results and Discussion

4-Aryl-3-(morpholin-4-yl)-2-arylimino-2,3-dihydrothiazole derivatives **1.1-1.16** were obtained using the Hantzsch reaction by condensation of N-(morpholin-4-yl)-N'-arylthioureas with the corresponding α-bromoacetophenones in ethanol (Scheme1). Hydrobromides **1.1-1.8** synthesized were formed as crystalline precipitates when the reaction mixture was boiled for 3 hours. Bases **1.9-1.16** were obtained by neutralizing the corresponding hydrobromides with 10 % NH_4OH solution according to Scheme 1.

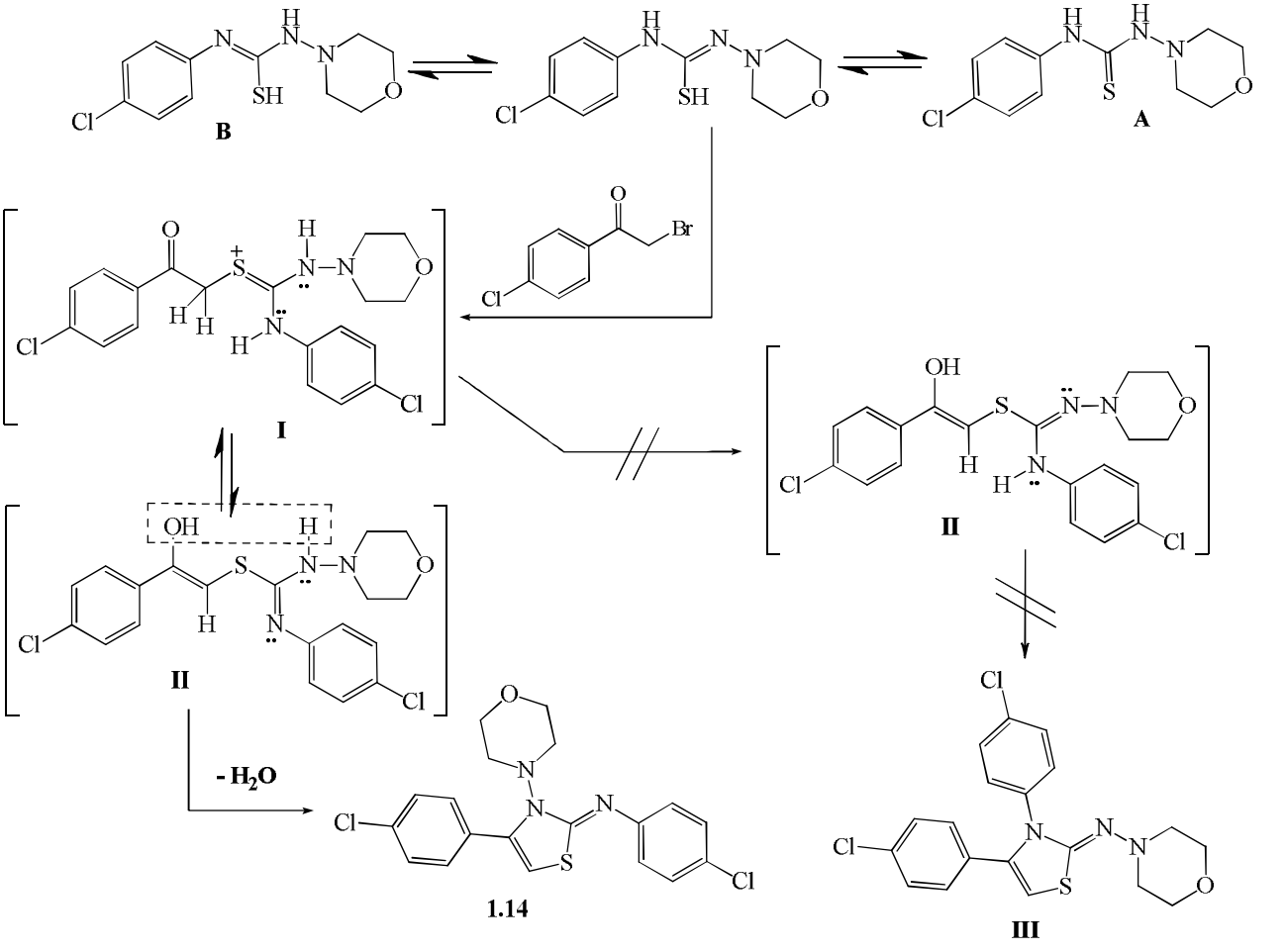
Compounds **1.1-1.16** synthesized are white and light-yellow crystalline substances, soluble in methanol, ethanol, propanol-2, DMF and DMSO, sparingly soluble in heptane, insoluble in chloroform. Hydrobromides **1.1-1.8** obtained are soluble in water.



Scheme 1

For compounds **1.1-1.16** synthesized, proton signals of the thiazole cycle are interpreted in the region of 6.04–7.04 ppm as singlets. The morpholine fragment is characterized by signals in the region of δ = 2.59-2.92 ppm as multiplets or wide singlets of the $–CH_2-N-CH_2–$ group, and signals in the region of δ = 3.54–3.78 ppm as multiplets or wide singlets for the $–CH_2-O-CH_2–$ fragment. The fixation of aromatic proton shift signals in the region of δ = 6.60–8.17 ppm as doublets or multiplets is characteristic. For compounds **1.1**, **1.3**, **1.5**, and **1.8**, the shift signals of aromatic protons and the thiazole cycle are superimposed and displayed as multiplets in the region of δ = 7.14–8.17 ppm. Compounds **1.5-1.8** with ethoxyl or methyl substituents in position 4 of the phenyl ring are characterized by the overlap of aromatic and thiazole proton signals in the region of δ = 7.04–7.55 ppm as a multiplet or doublet-doublet. For salts (compounds **1.1-1.8**) in a weak field in the region of δ = 10.70–11.90 ppm signals of protons of the NH^+ group are characteristic as singlets.

Taking into account the fact that substituted thiourea are tautomeric compounds the reaction products can be two isomers A and B (Scheme 2). To determine the true structure of the substances obtained, data from such modern physicochemical methods of analysis as chromatography-mass spectrometry, ^1H, ^{13}C-NMR-spectroscopy and correlation 2D NMR-spectroscopy (NOEZY, ROEZY) were used. Individually each of these methods did not allow identifying the reaction product. Thus, chromatography-mass spectroscopy for compounds **1.6, 1.7** confirmed the course of the reaction in one direction (determination of molecular weights and one high chromatographic peak). ^1H, ^{13}C-NMR-spectroscopy data provided information about the presence of only one set of signals (Hydrogen and Carbon atoms, respectively). 2D NMR-spectroscopy (Nuclear Overhauser effect) and ROEZY (Rotating Overhauser effect) examined the spatial structure of the reaction product. In the complex, the data of these physicochemical methods were used for the example of identification of compound **1.14** – a product of the interaction of N-morpholin-4-yl-N'-(4-chlorophenyl)thiourea and α-bromo-4-chloroacetophenone (Scheme 2).



Scheme 2

On the ^{13}C NMR spectrum of compound **1.14** (Fig. 1), 13 signals are interpreted: a signal at 101.6 ppm corresponding to the C-4 carbon of the thiazole cycle; two signals of the morpholine fragment carbons in the aliphatic region; four double-intensity signals indicate the presence of carbons in the *ortho*- and *meta*-positions of aromatic cycles; six signals are in weak fields. The ^{1}H NMR spectrum (Fig. 2) the test substance **1.14** has two extended singlets of the morpholine fragment in the region of δ = 2.59 and 3.64 ppm, a singlet of the methine proton of the thiazoline cycle at δ = 6.49 ppm, as well as four two-proton doublets characteristic of two *para*-substituted aromatic nuclei in the region of δ = 7.12 ppm and 7.30 ppm for one and δ = 7.19 ppm and 7.38 ppm for the other (assignment of aromatic core signals is made on the basis of data of the NOESY experiment) (Fig. 3). The presence of cross-peaks between the signal δ = 2.59 ppm of morpholine protons and *ortho*-protons of both aromatic nuclei (signals at δ = 7.12 ppm and 7.19 ppm) (based on data of the NOESY experiment) (Fig. 4) indicates the location of the morpholine fragment between these two nuclei. Thus, the structure studied is 4-(4'-chlorophenyl)-3-(morpholin-4-yl)-2-(4'-chlorophenylamino)-2,3-dihydrothiazole **1.14**.

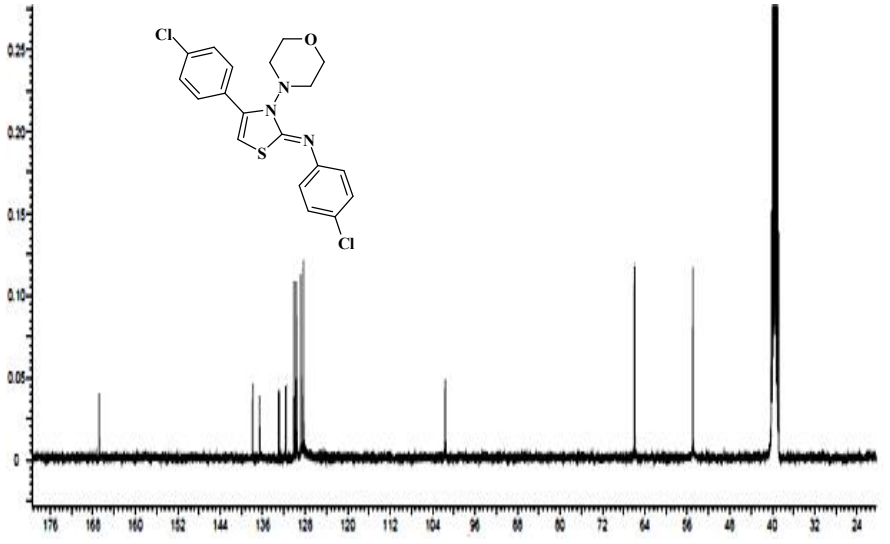


Fig. 1. ^{13}C NMR spectrum of product of the interaction of N-morpholin-4-yl-N'-(4-chlorophenyl)thiourea and α-bromo-4-chloroacetophenone (compound **1.14**)

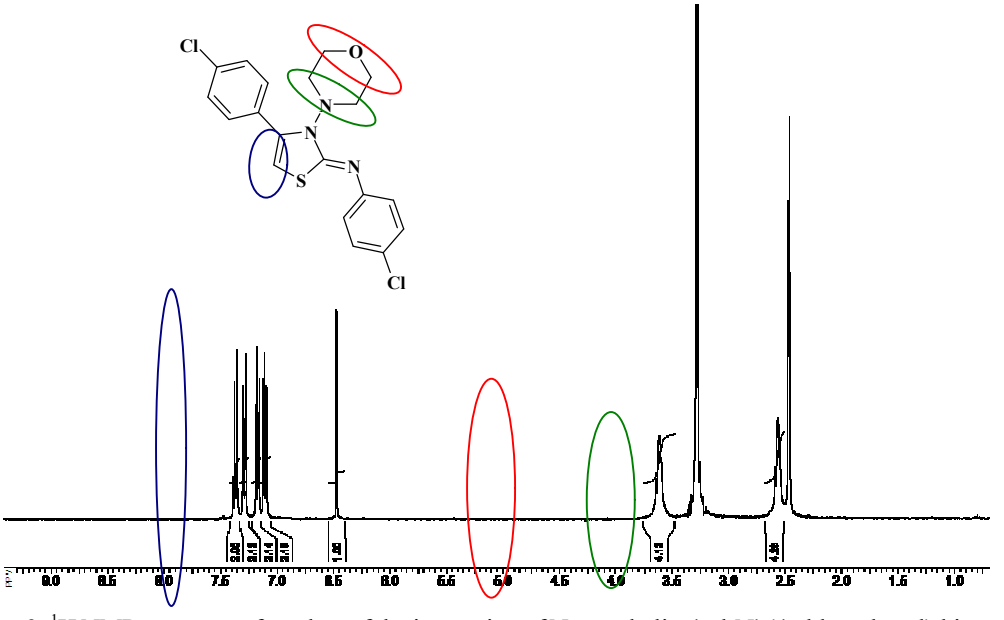


Fig. 2. ^{1}H NMR spectrum of product of the interaction of N-morpholin-4-yl-N'-(4-chlorophenyl)thiourea and α-bromo-4-chloroacetophenone (compound **1.14**)

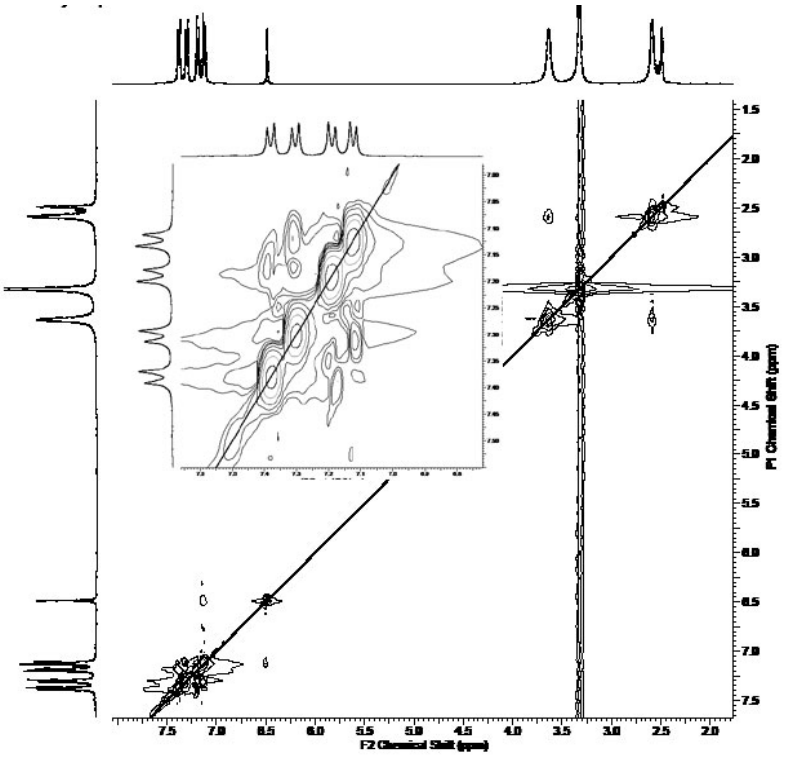


Fig. 3. NOESY- spectrum of product of the interaction of N-morpholin-4-yl-N'-(4-chlorophenyl)thiourea and α-bromo-4-chloroacetophenone (compound **1.14**)

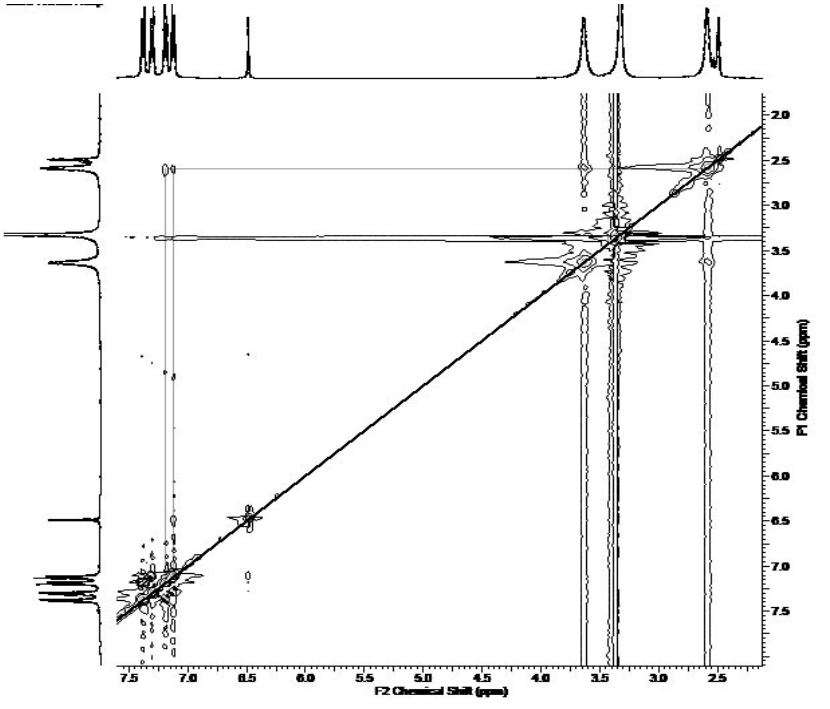


Fig. 4. ROESY-spectrum of product of the interaction of N-morpholin-4-yl-N'-(4-chlorophenyl)thiourea and α-bromo-4-chloroacetophenone (compound **1.14**)

3.1. Anti-inflammatory activity

An increase in the foot volume by 130.6 % in white rats with the induction of the inflammatory process was observed 4 hours after the subplantar introduction of carrageenan (Table 3). All test samples had antiexudative activity. Reference drug diclofenac had the most pronounced anti-inflammatory activity at the level of 42.5 %, as expected. At the same time, a fairly significant anti-inflammatory effect, which, in fact, was identical to the action of ibuprofen, was inherent to 4-(4-methoxyphenyl)-3-(morpholin-4-yl)-2-phenylimino-2,3-dihydrothiazole (compound **1.10**), as evidenced by its AEA – 35.2 %.

The obtained results allow to state the presence of anti-edematous activity in the studied compounds, and the most promising for development as a compound with anti-inflammatory action is compound **1.10**.

3.2. Analgesic activity

The studies of the analgesic effect in the dose of 50.0 mg/kg of the compounds synthesized **1.2, 1.6, 1.8, 1.19, 1.10, 1.15** on the model of visceral pain showed the analgesic activity – 18.7–42 %, as evidenced by a decrease in the number of writhings compared to the group of untreated animals (Table 4).

Table 3. The antiexudative activity of compounds on the model of carrageenan-induced inflammation in white rats (the data is presented as M±m, n=7 in each group)

Groups	The initial value of the foot volume, CU	The foot volume, CU, 4 hours after the inflammation induction	AEA, %
Intact animals	0.99±0.12	0.99±0.12	–
Carrageenan, 1 % (control)	0.98±0.13	2.26±0.21	–
Diclofenac	1.0±0.12	1.3±0.16*	42.5
Ibuprofen	0.99±0.13	1.45±0.14*	35.8
1.1	1.0±0.11	1.82±0.14*	19.1
1.2	1.0±0.10	1.54±0.14*	31.6
1.3	0.99±0.13	1.88±0.14*	17.1
1.4	0.99±0.13	1.89±0.12*	16.5
1.5	0.98±0.15	1.79±0.12*	21.2
1.6	1.0±0.12	1.62±0.14*	28.1
1.7	0.99±0.11	1.84±0.14*	18.3
1.8	0.99±0.10	1.51±0.12*	32.8
1.9	0.99±0.13	1.64±0.14*	27.3
1.10	0.98±0.14	1.46±0.12*	35.2
1.11	0.99±0.19	1.89±0.12*	16.5
1.12	0.98±0.11	1.82±0.14*	19.4
1.13	1.0±0.12	1.86±0.14*	17.6
1.14	0.99±0.13	1.76±0.14*	21.4
1.15	0.99±0.12	1.60±0.12*	27.6
1.16	1.0±0.12	1.74±0.14*	22.8

* $p \leq 0.05$ relative to the control.

Table 4. The analgesic activity of compounds on the model of "acetic writhings" in white mice (the data is presented as M±m, n=7 in each group)

Groups of animals	Number of writhings within 20 min	Analgesic activity
Model pathology (control)	14.7±2.2	–
Ketorolac	4.5±0.3*	68.9
1.2	6.9±0.7*	42.0
1.6	12.2±0.7*	18.7
1.8	11.8±0.7*	19.7
1.9	10.8±0.6*	24.3
1.10	9.6±0.5*	32.1
1.15	9.9±0.7*	29.6

* $p \leq 0.05$ relative to the control group.

All test compounds showed analgesic activity compared to the reference drug ketorolac (68.9 %). A fairly significant analgesic effect was inherent to 4-(4-bromophenyl)-3-(morpholin-4-yl)-2-phenylimino-2,3-dihydrothiazole hydrobromide **1.2** (42 %), 4-(4-methoxyphenyl)-3-(morpholin-4-yl)-2-phenylimino-2,3-dihydrothiazole **1.10** (32.1 %) and 4-(4-chlorophenyl)-3-(morpholin-4-yl)-2-(2-methylphenyl)imino-2,3-dihydrothiazole **1.15** (29.6 %). Compounds with an analgesic activity of 30 % or more can be considered as potential analgesics. Particular attention should be paid to the fact that compound **1.10** exhibits not only a fairly high analgesic but also anti-inflammatory effect.

Thus, the studies conducted indicate the presence of the anti-inflammatory and analgesic activity of the compounds synthesized on the models of carrageenan-induced edema and visceral pain, respectively, in the experiments *in vivo*.

4. Conclusions

A promising series of new biologically active compounds 3-morpholyl -substituted 4-aryl-2-arylimino-2.3-dihydrothiazole derivatives were synthesized by the condensation reaction of N-(morpholin-4-yl)-N'-arylthiourea with the corresponding α-bromoacetophenones in ethanol during boiling of the reaction mixture in the form of hydrobromides **1.1-1.8.** The bases of 4-aryl-3-(morpholin-4-yl)-2-arylimino-2.3-dihydrothiazole derivatives **1.9-1.16** were obtained by neutralization of the synthesized hydrobromides with 10 % ammonium hydroxide solution. It was found the formation of only one of the two possible isomeric structures (**1.14** and **III**) – isomer **1.14** 4-(4'-chlorophenyl)-3-(morpholin-4-yl)-2-4'-chlorophenylamino)-2.3-dihydrothiazole in the Hantzsch reaction. According to the results of pharmacological screening, the synthesized compounds have analgesic and anti-inflammatory effects. Compounds **1.2, 1.6, 1.8, 1.19, 1.10**, and **1.15** have an analgesic effect, as evidenced by the value of analgesic activity of 18.7–42 %. The anti-exudative activity of compounds **1.1-1.16** is 16.5-35.2 %. Compounds 4-(4-bromophenyl)-3-(morpholin-4-yl)-2-phenylimino-2,3-dihydrothiazole **1.2** and 4-(4-methoxyphenyl)-3-(morpholin-4-yl)-2-phenylimino-2,3-dihydrothiazole **1.10** showed the highest degree of analgesia and compound **1.10** also demonstrated the significant anti-inflammatory activity.

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СИНТЕЗ НОВИХ 3-МОРФОЛІЛЗАМІЩЕНИХ ПОХІДНИХ 4-АРИЛ-2-АРИЛІМІНО-2,3-ДИГІДРОТІАЗОЛУ ТА ЇХНЯ ПРОТИЗАПАЛЬНА ТА АНАЛЬГЕТИЧНА АКТИВНІСТЬ

Анотація. *Нові похідні 4-арил-3-(морфолін-4-іл)-2-аріліміно-2,3-дигідротіазолу* ***1.1-1.16*** *були синтезовані за реакцією Ганча через конденсацію N-(морфолін-4-іл)-N'-арилтіосечовини з відповідними α-бромацетофенонами в спиртах. Синтезовані гідробромідиі* ***1.1-1.8*** *утворились у формі кристалічних осадів при кип'ятінні реакційної суміші. Основи* ***1.9-1.16*** *отримали нейтралізацією відповідних гідробромідів розчином NH_4OH. Запропоновано можливий механізм реакції на основі вивчення будови синтезованих сполук. Структури синтезованих сполук були підтверджені ^1H ЯМР-спектроскопією, а також методами NOESY та ROESY. Показано утворення ізомеру 4-(4'-хлорфеніл)-3-(морфолін-4-іл)-2-(4'-хлорфеніламіно)-2.3-дигідротіазолу на основі сполуки* ***1.14****. Фармакологічний скринінг синтезованих похідних 4-арил-2-аріліміно-2,3-дигідротіазолу виявив їхню анальгетичну дію на моделі вісцерального болю, спричиненого введенням оцтової кислоти білим мишам. Протизапальну дію синтезованих сполук оцінювали in vivo на моделі карагенінового набряку кінцівки щурів. Таким чином, синтезовані сполуки проявляють анальгетичну та протизапальну дію.*

Ключові слова: *похідні 2,3-дигідротіазолу; реакція Ганча; морфолін; протизапальна активність; анальгетична активність.*