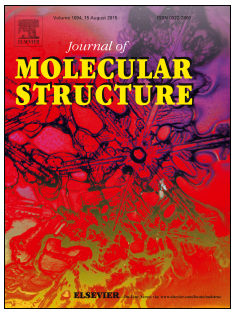


Synthesis, computational and biological activity of heteroatomic compounds based on phenylthiourea and acetophenone

Vagif Farzaliyev, Aleksey Shuriberko, Afsun Sujayev, Sabiya Osmanova, Sevinj Gojayeva, Konul Gahramanova

PII: S0022-2860(20)31169-8

DOI: https://doi.org/10.1016/j.molstruc.2020.128844

Reference: MOLSTR 128844

To appear in: *Journal of Molecular Structure*

Received Date: 19 January 2020

Revised Date: 30 April 2020

Accepted Date: 5 July 2020

Please cite this article as: V. Farzaliyev, A. Shuriberko, A. Sujayev, S. Osmanova, S. Gojayeva, K. Gahramanova, Synthesis, computational and biological activity of heteroatomic compounds based on phenylthiourea and acetophenone, *Journal of Molecular Structure* (2020), doi: https://doi.org/10.1016/j.molstruc.2020.128844.

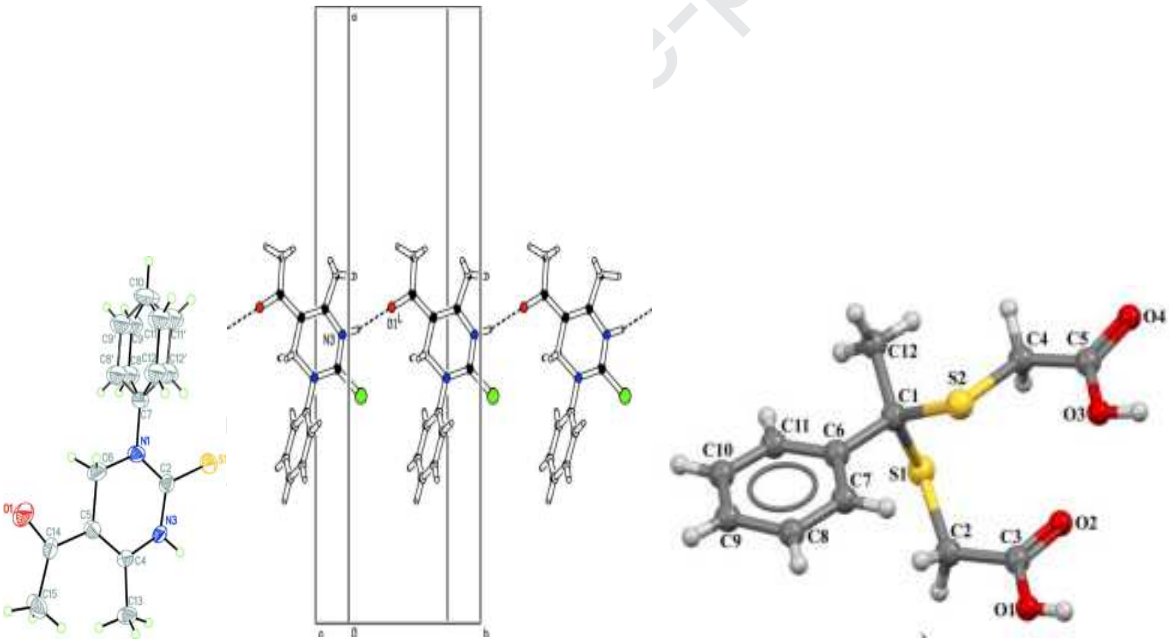
Synthesis, Computational and Biological Activity of Heteroatomic Compounds based on Phenylthiourea and Acetophenone

Vagif Farzaliyev[a], Aleksey Shuriberko[b], Afsun Sujayev[a*], Sabiya Osmanova[a,c], Sevinj Gojayeva[a], Konul Gahramanova[a]

[a]Laboratory of Theoretical Bases of Synthesis and Action Mechanism of Additives, Institute of Chemistry of Additives, Azerbaijan National Academy of Sciences, 1029, Baku, Azerbaijan

[b] Laboratory of Bioregulator, Institute of Biochemistry of Biologically Active Compounds of the NAS of Belarus, 230030, Grodno, Belarus

[c]Department of Natural Sciences, Western Caspian University,1001, Baku, Azerbaijan



Synthesis, Computational and Biological Activity of Heteroatomic Compounds based on Phenylthiourea and Acetophenone

Vagif Farzaliyev[a], Aleksey Shuriberko[b], Afsun Sujayev[a*], Sabiya Osmanova[a,c], Sevinj Gojayeva[a], Konul Gahramanova[a]

[a]Laboratory of Theoretical Bases of Synthesis and Action Mechanism of Additives, Institute of Chemistry of Additives, Azerbaijan National Academy of Sciences, 1029, Baku, Azerbaijan

[b] Laboratory of Bioregulator, Institute of Biochemistry of Biologically Active Compounds of the NAS of Belarus, 230030, Grodno, Belarus

[c]Department of Natural Sciences, Western Caspian University,1001, Baku, Azerbaijan

Address for Correspondences:

*Dr. Afsun Sujayev

[a]Laboratory of Theoretical Bases of Synthesis and

Action Mechanism of Additives

Institute of Chemistry of Additives 1029-Baku, Azerbaijan

Phone : +994503978801

Fax : +994125149210

E-mails : sucayevafsun@gmail.com

ABSTRACT

The presented article is devoted to a promising direction of organic chemistry - the synthesis of new sulfur- and nitrogen-containing thiourea and acetophenone derivatives that have physiological properties. So at first time on the base of phenylthiourea, acetylacetone and 37% water solution of formaldehyde (formaline) in the presence of trifluoracetic acid has been elaborated new effective synthesic method of 1-(6-Methyl-3-phenyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone. Also, according to the reaction of thiylation of acetophenone and some of its p-substituted derivatives Synthesis of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid were obtained by us. A direct amidation reaction of Synthesis of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid with primary amines was conducted. The structure of the new compounds was interpreted by NMR spectra and X-ray structure analysis.

As a result of studies, it was found that the greatest biological activity that can be useful in creating drugs is compound 1-(6-Methyl-3-phenyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone. This compound is characterized by antioxidant effect significant effect on the functioning of biological membranes, and in low concentrations (below 7.5 mg/l) it stabilizes the membranes with an erythrocyte. The effect of an increase in the membrane potential of mitochondria was discovered, probably associated with the ability to bind to carrier proteins. In addition, when virtually predicting the spectrum of biological activity, a number of properties are shown that have promise when creating new drugs.

Key words: phenylthiourea, acetophenone, heterocyclic, computer prediction, biological membranes, antioxidant effect.

Running Head: Biological effects of heteroatomic compounds based on phenylthiourea and acetophenone.

1. INTRODUCTION

In recent years, the study of the synthesis and properties of substances containing thiourea fragments has been gained special attention in the chemistry of heterocyclic compounds. Apparently, this is due to the fact that at present, these compounds have found and continue to find broader areas of application in various branches of medicine, technology, industry and agriculture. As it is seen from the literature, this field contains a large number of research works conducted in various directions [1-4]. However, when analyzing the most recent literature, it becomes clear that the formulation of heterocyclic compound of thiourea by three-component condensation reactions mainly covers the synthesis of dihydropyrimidinethiones [5-8].

The dihydropyrimidinethiones display many pharmacological properties [9], as part of our interest in this kind of materials, we report here the synthesis and crystal structure determination of the title compound. Our synthesis is based in the Bijinelli reaction, which consists on a three-component condensation of an aldehyde, a methyl-ene active compound and an thiourea derivative in acidic media. This procedure is the most simple and useful for the preparation of 3,4-dihydropyrimidene-2(1H) thiones [10-13].

Despite the differences in the methodology used for the synthesis of dihydropyrimidine 2(1H)-ones by the Bijinelli reaction, these methods are not excluded in particularly substituted aromatic and aliphatic aldehydes due to certain difficulties such as long reaction time and low efficiency. However, despite these difficulties and also 125 years having passed after the first application of single-phase three-component condensation method, interest in scientific research in this area has not been reduced, on the contrary, it has increased and the above mentioned area has been expanded much using all three components. Merely, the number of patent and scientific articles published in recent years related to “Bijinelli condensation” is quite large.

At the same time, compounds containing amide groups in the molecule exhibit high biological activity and are used in medicine, chemical technology, and other fields [14-18]. In this regard, the development of effective methods for the synthesis of compounds with an amide group is one of the important directions of modern organic synthesis. It should be noted that the literature describes the amidation reactions of the simplest organic monoacids [19-21] and some diacids [22-24]. However, there is completely no information on the amidation of bis-acids containing heteroatoms in the molecule, in particular sulfur atoms.

2. MATERIALS AND METHODS

2.1. Measurements

The chemical structure of the synthesized compounds **(M, M-1, M-2)** was confirmed using ^{1}H, ^{13}C NMR spectra. At the same time, the structure of **M** and **M-1** compounds was confirmed by the X-ray structure analysis. NMR experiments have been performed on a Bruker FT NMR spectrometer AVANCE 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) with BVT 3200 variable-temperature unit in 5mm sample tubes using Bruker Standard software (Topspin 3.1). The ^{1}H and ^{13}C chemical shifts were referenced to internal tetramethylsilane (TMS). NMR grade DMSO-d_6 (99.7%, containing 0.3% H_2O) was used for the synthesized compounds.

2.2. Crystallography

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F2 , conventional R-factors R are based on F, with F set to zero for negative F2. The threshold expression of F2 > σ(F2) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Data collection: The reaction time and the purity of the substances were controlled by the NTX method (Sorbfil) (ethyl acetate/hexane = 1:2). The structure of the compounds was confirmed by the X-ray analysis: “Bruker APEX II CCD” (*T* = 100 K, λMoKα radiation, graphite monochromatic, φ- and ω-scanning, 2θmax = 56°). SAINT-Plus [25] was exploited for cell refinement and data collection. SHELXTL [26] software was utilized to solve and refine the structures structure.

2.3.Experimental

2.3.1. 1-(6-methyl-3-phenyl-2-sulfanilden-1,2,3,4-tetrahidropirimidin-5) etanon (M-1)

Phenylthiourea, 15.2 g (0.1 mol), 37% water solution of formaldehyde (formaline), 3 g (0.1 mol) and 13 g (0.1 mol) of acetylacetone were dissolved in 10 ml of ethanol and then 0.5 ml of trifluoroacetic acid was added. The mixture was vigorously stirred during 4–5 h at room temperature and then cooled and kept one day at 0°C. The white crystals of 1-(6-Methyl-3-phenyl-2-

sulfanylidene-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone **(M-1)** were filtered and washed with dichloromethane. Suitable single crystals for X-ray analysis were obtained by slow evaporation from ethanol. H atoms were placed in calculated position and refined using a riding model, with C—H distances in the range 0.95-0.99 Å and N—H distance of 0.88 Å, with Uiso(H) = 1.2Ueq(N,Cmethylene and Caromatic) and 1.5 Ueq (Cmethyl). **M-1** possesses orthorhombic orientation (*Pna2$_1$*). Unit cell data, and bond lengths are given in Supporting Information (SI).

1-(6-methyl-3-phenyl-2-sulfanilden-1,2,3,4-tetrahidropirimidin-5) etanon (**M-1**): yield 19.2 g (70%), m.p. =180°C, Rf = 0.35. Eluent - ethanol:hexane (5:2).^{1}H NMR (300 MHz, DMSO-d_6, δ) 1.35 (s, 3H, CH3), 6.8–7.1 (m, H, Ar), 7.4 (m, H, Ar), 9.35 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$, δ) 24, 29, 37, 51, 86, 117, 122, 129, 132, 141, 151, 179 (C=S), 205 (C=O*).*

2.3.2. Synthesis of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid (**M**).

To the acetophenone (12 g, 0.1 mol) in C_6H_6, mercaptoacetic acid (23 g, 0.25 mol) was added dropwise at room temperature. The mixture was stirred at 80°C for 9 h. The synthesized 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid **(M)** is a white crystalline substance, which is separated by recrystallization from water. **M** dissolve well in alcohol, acetone, and poorly in hexane and benzene. Single crystal of **M** was developed with the same procedure mentioned above for **M-1**. Space group of **M** is observed to be P-1 with triclinic orientation. Bond lengths and dehedral angles were given in SI.

2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid (**M**): yield 23.2 g (81.1%), m.p. 136–137°C; ^{1}HNMR (300 MHz, DMSO-d6, *δ*): 1.92 (t, 3H, CH3); 3.38 (q, 2H, CH2); 7.12 (m, 5H, CH-Ar); 12.34 (m, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d6): 25.4; 38.3; 56.6; 127.2; 128.7; 139.2; 173.5.

2.3.3. Synthesis of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))bis(N-phenylacetamide) (M-2)

M-2 was syntheszied from **M** according to the following procedure: Mixture of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid **(M)** (10.0 g, 0.035 mol) and 2-aminopyridine (6.6 g, 0.07 mol) was stirred in benzene solution at 80°C for 10 h. The reaction was carried out in the presence of a catalytic amount of boric acid. Re-crystallization from EtOH gave white crystal substance: When bis-acid (**M**) and amine were mixed, an exothermic effect was observed, which can be explained by salt formation. The synthesized bis-amide was a

crystalline substance with a melting point of 92 °C, readily soluble in polar and insoluble in non-polar solvents.

2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))bis(N-phenylacetamide) (**M-2**): yield, 14.5 g (95.0%), m.p. 92°C, ^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.92 (s., 3H, CH_3); 2.02 (s., 3H, CH_3); 3.33 (d., 2H, CH_2); 7.45; 8.12; 8.25; 8.96 (m., 4H, CH-Ar); 7.12; 7.26 (t., 2H, CH-Ar); 10.01 (m., 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 24.6; 35.6; 55.8; 117.8; 123.8; 128.7; 129.0; 141.6; 143.6; 168.2.

2.4. Biochemical Studies

2.4.1. Effects on biological membranes

The study used compounds M-1, M-2 and an extract of phenolic compounds of ginger root (Zingiber officinale). Solutions of compounds M-1 and M-2 were prepared by dissolving in DMSO; the range of studied concentrations was 240–1.88 mg/L in the final volume of the incubation solution.

Ginger phenolic compounds were extracted from ginger root crushed and dried at 45 °C. A Soxhlet apparatus was used, 96% ethanol and 0.01% HCl as a solvent, extraction temperature of about 50 °C (reduced pressure) for 2 hours. The resulting extract was filtered, partially evaporated on a rotary evaporator at a temperature of 45 °C. The resulting solution was cooled to -20, the precipitated crystalline mass was separated and dried in a vacuum oven. The resulting product is a concentrate of phenolic compounds, with a predominance mainly of shogaols and gingerols. In studies, the extract was also dissolved in DMSO; the range of studied concentrations for hemolysis was 30-0.47 mg/L in the final volume of incubation.

Red blood cells were obtained from heparinized blood of outbred white rats. The first erythrocyte sedimentation from the blood was carried out at 600g for 10 minutes, then it was washed twice with 10-fold saline solution (0.9% NaCl) using the same centrifugation modes. The final mass of red blood cells (1 ml) for experiments was resuspended in 7.5 ml of 0.9% NaCl.

The incubation medium contained 0.5 ml of a suspension of red blood cells, 1 ml of 0.9% NaCl and 10 μl of the test substance in DMSO. As a positive hemolysis sample, 1 ml of dH_2O was added instead of 1 ml of NaCl. A control sample without hemolysis of 0.5 ml of a suspension of red blood cells, 1 ml of 0.9% NaCl and 10 μl of DMSO. The degree of hemolysis was calculated in% according to the formula:

$$X\% = \frac{E_1 + E_2 2 * 100}{2 * E_3}$$

Where E_1 is the optical density of the control (NaCl) sample.

E_2 - optical density of the test sample.

E_3 - optical density of hemolysis (H_2O) sample.

2.4.2. Antioxidant activities

For the preparation of brain homogenate, the freshly isolated brain of outbred white rats was homogenized with PBS at a tissue/buffer ratio of 1:9 per glass/Teflon homogenizer, 1300 rpm, 5-9 strokes. The resulting homogenate was clarified by centrifugation at 1500 g for 10 minutes. The supernatant was used in the experiment.

The incubation medium contained 200 μl of brain homogenate, 800 ml of PBS and 10 μl of sample. We studied M-1 and M-2 at a concentration of 1.88-120 mg/L, ginger extract 1.88-240 mg/L and Trolox at a concentration of 3.3 mg/L as a reference substance. Solutions were prepared in DMSO medium; the control contained 10 μl of DMSO. The mixture was incubated for 1 hour at 37 °C with constant stirring. At this time, another such mixture was prepared, but which was not incubated and was used as a zero point. After that, the MDA content was determined by the method with thiobarbituric acid.

2.4.3. The influence of M-1 and M-2 on the membrane potential of mitochondria of brown adipose tissue and rat liver.

Tissue for isolation of mitochondria (interscapular brown adipose (BF) and liver) was removed from white outbred rats in a cold room. All procedures were carried out at + 4 °C. Mitochondria were isolated by differential centrifugation; for this, the tissues were homogenized in a Potter-Elveyem type homogenizer, tissue/extraction medium ratio 1:9, homogenization mode: 1300 rpm, 15 strokes for BWT and 5 strokes for the liver. The isolation medium of the composition was used: 0.25 M sucrose, 1 mM EGTA, 20 mM HEPES, pH 7.4. The resulting homogenate was centrifuged at 600 g for 10 min, + 4 °C. The supernatant was collected and reprecipitated at 12000g, 20 min. The mitochondrial sediment was repeatedly washed with a 10-fold volume of isolation medium.

The membrane potential was recorded by the change in fluorescence of the penetrating safranin O cation at an excitation wavelength of 495 nm and an emission of 586 nm. The membrane potential recording medium (1 ml) consisted of: 0.125 M sucrose, 0.02 M HEPES, 0.05 M KCl, 1 mM EGTA, 20 mM KH_2PO_4, 5 mM $MgCl_2$, 6 μM safranin O, pH 7.4, 300 μg mitochondrial

protein, incubation temperature 28 °C. To prevent the action of fatty acids adsorbed on mitochondria, 0.01% fat-free bovine serum albumin was added to the incubation medium. As a substrate for oxidation (SUB), a mixture of pyruvate, malate, and succinate is 5.1.5 μM, respectively. To block the action of UCP1 protein and other antiporters, 3 mM guanosine diphosphate (GDP) was added, phosphorylation was started by adding 100 μmol ADP. The membrane potential was discharged (point 0) by administering 1 μM FCCP.

Samples of substances were prepared as previously indicated, as a control, 10 μl of DMSO was added, which at this concentration did not lead to visible changes.

3. RESULTS AND DISCUSSION

3.1. Chemistry

The dihydropyrimidinethiones display many pharmacological properties, as part of our interest in this kind of materials, we report here the synthesis and crystal structure determination of the title compound [27]. Our synthesis is based in the Bijinelli reaction, which consists on a three-component condensation of an aldehyde, a methylene active compound and an thiourea derivative in acidic media. In other words, 1-(6-methyl-3-phenyl-2-sulfanilden-1,2,3,4-tetrahidropirimidin-5) etanon was formed as a result of the interaction of phenylcyanocarbamide, 37% water formaldehyde and acetylacetone [28]. (**M-1**) compound synthesized (Scheme 1):

Scheme 1

The mechanism of this reaction can be predicted by Kappe's theory. Thus, initially, a proton is formed by the combination of a proton. This cation reacts with the enol form of β-diketoefir and forms thioureid. In the latter phase, cycling occurs with the separation of the water molecule.

The effect of aldehydes on the release of the reaction product in the synthesis processes was investigated. It has been shown that the reaction product yield is higher when the aromatic aldehydes are absorbed than the aliphatic aldehydes. This is explained by the fact that in the aromatic aldehydes the carbonyl group has a high activity due to the electron-acceptor properties of phenyl radicals, which increases its reactivity.

The synthesized amides were prepared in two steps. By the thiolation reaction of acetophenone with mercaptoacetic acid, bis-acid, namely 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid (**M**), was obtained in the first step (Scheme 2):

Scheme 2

The reaction was carried out by heating a mixture of components in a benzene solution in the presence of catalytic amounts of benzenesulfonic acid. Acetophenones were found to react with mercaptoacetic acid to produce 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid (**M**). The synthesized 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid (**M**) is a white crystalline substance, which is separated by recrystallization from water. **M** dissolve well in alcohol, acetone, and poorly in hexane and benzene.

In the second step, the reactions of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid (**M**) with 2-aminopyridine [29-33] were carried out and we obtained a new bis-amide - 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))bis(N-phenylacetamide) **(M-2)** (Scheme 3).

Scheme 3

3.2. X-ray structural determination

Crystals for X-ray spectroscopic analysis or X-ray crystallographic analysis are obtained by double crystallization of M-1 and M-2 compoundes. The structure and crystalline form of (M-1) compound have been shown in the figure 1, but the selected difference for bond length and valence angle has been described in SI. (M-1) Crystalline compound holds crystallographical independent molecules in the central bicyclic fragment. (M-1) molecule holds complex three-organic compound system consisting of tetrahydropyrimidine and benzol ring. In bicyclic fragment the cycles of tetrahydropyrimidine take a shape of symmetric platform. In this case benzol cycle in practice directs to the cycle of hexahydropyrimidine prependicularly. The relevant conformation of three cyclic fragment were determined in the previously learned relative compounds.

As can be seen from SI (M-1) molecule is placed at phenylthiourea fragment in compressed form– N(1)-C(2) və N(3)-C(2) bond length becomes short, in C(2)=S(1) bond according to it becomes long in comparison with statistical C-N single and C=S double bonds.

Single crystal X-ray diffraction of compound M-1 was carried out on a Bruker APEX II CCD diffractometer (T = 296 K, λMoKα-radiation, graphite monochromator, φ- and ω-scanning, θmax = 28.4°, θmin = 1.7°). The crystals of (**M1**) (Figure 1). compound ($C_{13}H_{14}N_2OS$, Mr = 246.32) are colourless crystal, with cube structured, sizes 0.30 × 0.30 × 0.30 mm, one striped: a = 24.3527 (10) Å, b = 7.2374 (3) Å, c = 7.0063 (3) Å, θ = 2.9–28.3°, Z = 4, Mo Kα radiation μ = 0.25 mm-1, T = 100 K, 0.30 x0.30x0.30 mm, 13745 measured reflections 3089 independent reflections 2877 reflections with I >2σr(I) Rint = 0.016 19 restraints H-atom parameters con-strained Δρ_max=0.40 e Å^(-3) Δρ_min=-0.35 e Å^(-3). In the compound, the C8, C9, C11 and

C12 atoms of the phenyl ring are disordered over two sets of sites in a 0.60 (3):0.40 (3) ratio. The heterocycle ring is essentially planar (r.m.s.= 0.017 Å) and form a dihedral angle of 82.0 (2)° with the phenyl ring. The crystal packing is stabilized by intermolecular N3—H3N···O1 hydrogen bonds (Table 1), which link the molecules into chains running parallel to the b axis, with graph-set notation C(6). Intermolecular hydrogen bonds are formed with NH groups acting as donors and O atoms as acceptors, N-H…O.

(M-1) compound is diastereoisomer asymmetrical centre of carbon atom. The crystal of the studied compound shows racemate in chiral atoms.

Figure 1

The crystals of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid (**M**) compound ($C_{12}H_{14}O_4S_2$, Mr=286.35) are white crystal, with triclinic structured, sizes 0.260 x 0.240 x 0.210 mm^3, one striped: a = 6.5374(16) Å, b = 7.1581(17) Å, c = 14.551(4) Å, β = 77.273(4)°, V = 654.1(3) $Å^3$, space group P-1, Z= 2, ds = 1.454 Mg/m^3, μ = 0.410 mm^{-1}. 5712 reflection intensity has been measured (2396 nonarbitrary reflections [R(int) = 0.0278]) and semiempirical correction against absorption by the help of SADABS program has been made for them. The crystal packing is stabilized by intermolecular O(1)-H(1)...O(4)#1 and O(3)-H(3)...O(2)#1 hydrogen bonds (Figure 2, Table 2).

3.3. BIOCHEMICAL RESULTS

3.3.1. Study of the effect of M-1 and M-2 on the amount of hemolysis of red blood cells

The hemolysis value shows how much the substance interacts with the biological membrane, in this case, the erythrocyte membrane. High hemolytic activity indicates the ability of a substance to form pores in the membrane or to completely destroy it, leading to the release of intramembrane contents. This test is also important when testing drugs for parenteral administration, since many medicinal substances have this activity and lead to the so-called drug hemolytic anemia.

The experimental results are presented in Figure 3.

Figure 3

As can be seen from the graph, the compound M-2 has an extremely low hemolytic activity, the maximum effects are at a concentration of 120 ml/l (table 3) where 6.80% of erythrocyte hemolysis is observed. The **M-1** substance is characterized by greater activity on the hemolysis

index, so at a concentration of 120 mg/l, 80.03% hemolysis was detected. These values are not significant, since such a high concentration in the blood (120 mg/l) is difficult to achieve and the actual concentration of drugs in the blood is much lower. In addition, concentrations of substances **M-1** and **M-2** below 15-7.5 mg/l even exhibit some membrane-stabilizing effects, where the level of hemolysis was lower than in the control samples.

At the same time, the relatively harmless natural components of ginger root had significant hemolytic activity, so at a concentration of 28-30 mg/l, complete hemolysis of red blood cells was observed in the incubation medium.

Table 3

3.2.2 Study of antioxidant properties.

The study of antioxidant properties was carried out on an in virto model using clarified brain homogenate. During homogenate incubation, a working complex of enzymes and autooxidation of biological substrates leads to the appearance of free radicals, including reactive oxygen species. The occurring free radical processes initiate the oxidation of the unsaturated fatty acids contained in the homogenate and increase the level of malondialdehyde (MDA). This model is more acceptable from the point of view of antioxidants of biological significance since it is as close as possible to processes occurring in the body, unlike, for example, studies based on the reduction of $Fe^{3+} \rightarrow Fe^{2+}$, $Cu^{2+} \rightarrow Cu^{+}$, DPPH, ABTS etc.

Data on testing the test substances for antioxidant activity are presented in Figure 4.

Figure 4

Trolox at a concentration of 3.3 mg / L was chosen as a known molecule with a powerful antioxidant effect for comparison. The **M-2** substance in this test behaved as a prooxidant in the entire concentration range. The maximum prooxidant effect was achieved at a concentration of **M-2** in solution of 60 mg/L and amounted to 31.38% increase in the level of MDA production from the control, where pure DMSO was used (Table 4). The substance **M-1** has some antioxidant effect, although it is relatively small in relation to the same concentrations of the phenolic extract of ginger and Trolox. In small doses (below 3 mg/L), slight induction of MDA formation was observed, and the maximum antioxidant effect was at a concentration of **M-1** of 60 mg/L, which reduced the production of malondialdehyde by 19.09%. Ginger phenolic compounds have quite good antioxidant properties and, at concentrations above 30 mg/L, they almost completely suppress oxidative reactions in this test.

Table 4

Thus, M-2 is a prooxidant, M-1 is an antioxidant 21.2 times weaker than Trolox, ginger phenolic compounds are 1.84 times weaker than Trolox.

3.3.2. The effect of M-1 and M-2 on the mitochondrial membrane potential of brown adipose tissue and rat liver.

The study of the effect of substances on the mitochondrial membrane potential (MP) allows one to judge the effect of the test substance on the mitochondrial membrane and on the activity of the electron transport chain, which includes enzymes for substrate oxidation, electron transfer, and ATP synthesis. An effect on specific transmembrane proteins (carriers, ion channels) can also be detected. In addition, the studied substances themselves may turn out to be sources of ion channel formation and induce the transition of both metal ions and protons, which will affect the proton transmembrane gradient (membrane potential).

Characteristic of the control line. The first minute the incubation medium containing the substrate and BSA is prescribed, after the introduction of mitochondria (Mito), the probe is absorbed by the mitochondria and the MT accumulates. At this stage, the effect of separation by fatty acids was removed, but the active ion channels and mainly UCP1 in BZhT lead to MP dissipation. The following is the introduction of GDF, which blocks UCP1 and other channels, at this stage the MP has maximum value and stability. The increase in MP after HDF indirectly characterizes the activity of UCP1. If MP after the introduction of mitochondria in the presence of BSA almost immediately reached its maximum value and subsequent HDF leads to a slight increase, this indicates a low activity of UCP1. The presence of ADP causes a slight decrease in MP spent on ATP synthesis. FCCP causes a complete reset of the polarization of the membrane and is used as a zero point in the calculations.

It was found that compound **M-1** has a more significant effect than **M-2**, manifested in an increase in membrane potential in the state of substrate stimulation on mitochondria of BZhT (30.34% higher than the control sample at a concentration of 30 mg/l) (Figure 5). At the same time, significant effects on the mitochondria of the liver were not revealed over the entire range of tested concentrations (1.88-120 mg/l) (Figure 6). An increase in membrane potential at the stage of substrate stimulation is associated with blocking of ion channels. Taking into account the fact that **M-1** does not influence a similar stage in liver mitochondria, it should be assumed that M-1 binds and blocks UCP1, since this channel is most significant for BJT mitochondria and is absent in liver mitochondria. A slight increase in MP was also observed after the administration of HDF. Thus, compound **M-1** confirms its stable action on the membrane. In addition, it can probably bind to some proteins on the surface of the membrane, which requires further

study. An **M-1** concentration of 60 mg/L has the same effect as 30, but 120 mg/L leads to MP inhibition and side effects when measuring the fluorescence of a voltage-sensitive probe.

Figure 5

In the range of tested concentrations (1.88–240 mg/L), the **M-1** compound did not cause significant changes in the membrane potential of the liver mitochondria, insignificant line vibrations are associated with optical effects and their effect on fluorescence at high concentrations of the substance (Figure 6).

Figure 6

In similar studies of the **M-2** substance, no significant effects were found on both mitochondria of BWT and the liver (Figure 7 and Figure 8).

Figure 7 and Figure 8

3.3.3. Computer prediction of the spectrum of biological activity

Computer prediction was performed by the PASS program (Prediction of Activity Spectra for Substances). Initial computer screening allows the selection of promising compounds based on their structure and analogy of biological activity with known substances.

The data on the prediction of the biological activity of compound M-1 are presented in table 4. Of the 537 predicted activities, 44 were selected with a forecast probability of over 40%.

Table 5

As can be seen from the table, some types of biological activity (membrane permeability inhibitor - 66.6%, calcium channel blocker -33.6%) are confirmed by the studies above, where **M-1** stabilized red blood cells at low concentrations, leading to an increase in the membrane potential of mitochondria. In addition, the spectrum contains predictive activities that are important in medicine, for example, with a high degree of probability **M-1** will have an analgesic effect, antiviral and an agent for coronary artery disease.

The following table 4 presents the data on the prediction of the biological activity of compound **M-2**. 744 types of activity were detected, the bulk of which is the inhibition of various enzymes, 58 of these activities, a positive prognosis of which above 40% are presented in table 6.

Table 6

According to prediction, **M-2** is an inhibitor of many enzymes, including those important for metabolism (flavoprotein dehydrogenases). However, some effects may still be useful in biology and medicine (esterase inhibitor, TRPA1 agonist, virus attachment inhibitor).

4. CONCLUSİONS

As a result of studies, it was found that the greatest biological activity that can be useful in creating drugs is compound **M-1**. This compound is characterized by antioxidant effect significant effect on the functioning of biological membranes, and in low concentrations (below 7.5 mg/l) it stabilizes the membranes with an erythrocyte. The effect of an increase in the membrane potential of mitochondria was discovered, probably associated with the ability to bind to carrier proteins. In addition, when virtually predicting the spectrum of biological activity, a number of properties are shown that have promise when creating new drugs.

Compound **M-2** is characterized by prooxidant activity, inertness with respect to biological membranes. Although the predicted biological effect based on the structure of the compound is also of interest for further study. The data obtained indicate the promise of this area of research, the need to verify other biological properties of the studied compounds. By varying other substituents in the structure of the compounds, it is possible to obtain preparations with a given biological activity.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgments

This work was carried out as part of international collaborative research of the Institute of Chemistry of Additives of ANAS and the Institute of Biochemistry of Biologically Active Compounds of the NAS of Belarus.

References

[1] Dalinger, D., Stadler, A. & Kappe, C. O. Solid- and solution-phase synthesis of bioactive dihydropyrimidines , Pure Appl. Chem, 2004, 76, 1017–1024.

[2] S. A. Kotharkar, R. R. Nagawade, and D. B. Shinde, “Chlorosulfonic acid catalyzed highly efficient solvent-free synthesis of 3, 4-Dihydropyrimidin-2(1H)-one and thiones,” Ukrainica Bioorganica Acta, 2006, vol. 2, pp. 17–21.

[3] N. Y. Fu, Y. F. Yuan, Z. Cao, S. W. Wang, J. T. Wang, and C. Peppe, "Indium(III) bromide-catalyzed preparation of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction," Tetrahedron, 2002, vol. 58, no. 24, pp. 4801–4807.

[4] H. Xu and Y. G. Wang, "A rapid and efficient Biginelli reaction catalyzed by zinc triflate," Chinese Journal of Chemistry, 2003, vol. 21, no. 3, pp. 327–331.

[5] A. S. Paraskar, G. K. Dewkar, and A. Sudalai, "$Cu(OTf)_2$: a reusable catalyst for high-yield synthesis of 3,4-dihydropyrimidin-2(1H)-ones," Tetrahedron Letters, 2003, vol. 44, no. 16, pp. 3305–3308.

[6] R. Varala, M. M. Alam, and S. R. Adapa, "Bismuth triflate catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2 (1H)-ones: an improved protocol for the Biginelli reaction," Synlett, 2003, no. 1, pp. 67–70.

[7] T. Jin, S. Zhang, and T. Li, "p-toluenesulfonic acid-catalyzed efficient synthesis of dihydropyrimidines: improved high yielding protocol for the Biginelli reaction," Synthetic Communications, 2002, vol. 32, no. 12, pp. 1847–1851.

[8] P. Salehi, M. Dabiri, M. A. Zolfigol, and M. A. Bodaghi Fard, "Silica sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones", Tetrahedron Letters, 2003, vol. 44, no. 14, pp. 2889–2891.

[9] S. Tu, F. Fang, S. Zhu, T. Li, X. Zhang, and Q. Zhuang, "A new Biginelli reaction procedure using potassium hydrogen sulfate as the promoter for an efficient synthesis of 3,4-dihydropyrimidin-2(1H)-one," Synlett, 2004, vol. 3, pp. 537–539.

[10] C. Jiang and Q. D. You, "An efficient and solvent-free one-pot synthesis of dihydropyrimidinones under microwave irradiation," Chinese Chemical Letters, 2007, vol. 18, no. 6, pp. 647–650.

[11] Y. Yu, D. Liu, C. Liu, and G. Luo, "One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using chloroacetic acid as catalyst," Bioorganic and Medicinal Chemistry Letters, 2007, vol. 17, no. 12, pp. 3508–3510.

[12] S. A. Kotharkar, R. R. Nagawade, and D. B. Shinde, "Chlorosulfonic acid catalyzed highly efficient solvent-free synthesis of 3, 4-Dihydropyrimidin-2(1H)-one and thiones," Ukrainica Bioorganica Acta, 2006, vol. 2, pp. 17–21.

[13] A. Hasaninejad, A. Zare, F. Jafari, and A. R. Moosavi-Zare, "P_2O_5/SiO_2 as an efficient, green and heterogeneous catalytic system for the solvent-free synthesis of 3,4-dihydropyrimidin-2-(1H)-ones (and -thiones)," E-Journal of Chemistry, 2009, vol. 6, no. 2, pp. 459–465.

[14] Amino Group Chemistry. From Synthesis to the Life Sciences, Ricci A., Ed.:Wiley VCH: Weinheim, 2007.

[15] Bag B., Bharadwaj P. Perturbation of the PET process in fluorophore-spacer-receptor systems through structural modification: Transition metal induced fluorescence enhancement and selectivity // Journal of Physical Chemistry B, 2005, v. 109, №10, pp. 4377-4390.

[16] Corey E.J., Czako B., Kurti L. Molecules and Medicine, Wiley: Hoboken, 2017;

[17] Gangopadhyay. P.; Radhakrishnan T.P. Influence of alkyl chain length on the crystal structures and optical SHG of N-n-alkyl-2,4-dinitroanilines: Role of dipolar and dispersion energies // Chemistry of Materials, 2000, v.12, № 11, pp. 3362-3368.

[18] Patai series, The Chemistry of Functional Groups, The Chemistry of Anilines, Rappoport Z., Ed.:Wiley:Chichester, 2007, pt.2, chapm 13, 1163 p.

[19] Mokhov V.M., Popov Yu.V., Budko I.I. Direct amidation of carboxylic acids with primary and secondary amines in the presence of colloidal copper particles // Bulletin of the Volgograd State Technical University, 2014, v. 12, No. 7 (134), pp. 52-56.

[20] Gernigon N., Al-Zoubi R., Hall D. Direct Amidation of Carboxylic Acids Catalyzed by ortho-Iodo Arylboronic Acids: Catalyst Optimization, Scope, and Preliminary Mechanistic Study Supporting a Peculiar Halogen Acceleration Effect // Journal of Organic Chemistry, 2012, v. 77, № 19, pp. 8386−8400.

[21] Jursic B., Zdravkovski Z. A Simple preparation of amides from acids and amines by heating of their mixture // Synthetic Communications, 1993, v. 23, № 19, pp. 2761–2770.

[22] Dolzhenko AV, Kolotova NV, Kozminykh VO. and others. Amides of hydrocarbons and dicarbonic acids. Abstract 10. Synthesis and pharmacological activity of amino acids and hydrazides amino acid // Chemical-Pharmaceutical Journal, 2002, Vol. 36, No. 2, pp.6-8.

[23] Kolotova NV, Dolzhenko AV, Kozminykh OV and others. Amide and hydrazine 1,4-dicarboxylic acids. Abstract 8. Synthesis and hypoglycemic activity of amino acids and hydrazidic amino acids // Chemical-Pharmaceutical Journal, 1999, v. 33, No. 12, pp.9-11.

[24] Kolotova NV, Kozminykh VO, Dolzhenko AV and others. Amides of hydrocarbons and dicarbonic acids. Reference 9. Pharmacological activity of the products of 2-aminopyridenes and 2-aminopyridine with anhydride dicarbonic acid // Chemical-pharmaceutical journal, 2001, vol. 35, No. 3, p. 26-30.

[25] Bruker (2001). *SAINT-Plus.* Bruker AXS, Madison, Wisconsin, USA.

[26] Bruker (2005). *APEX2.* Bruker AXS, Madison, Wisconsin, USA.

[27] Zorkun I.S. Synthesis of 4-aryl-3,4-dihidropirimidin-2(1H)thione derivatives as potential calcium channel blockers Text] / Zorkun I.S., Sara S., £elebi S., Erol K. // Bioorg. Med. Chem. 2006. - Vol. 16. - P. 4479-4482.

[28] E. N. Garibov, S. S. Gojayeva, M. A. Allahverdiyev, A. V. G. Gurbanov and I. Brito. 1-(6-Methyl-3-phenyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone, Acta Cryst. (2012). E68, o276.

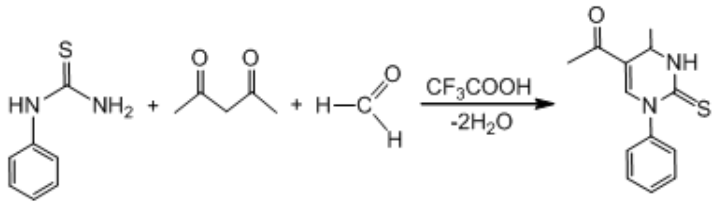
[29] Osmanova S.F., Sardarova S.A. Thiylation of acetophenones with thioglycolic acid and some transformations of reaction products / Conference Cluster for Organic Chemistry OrgChem-2016, St. Petersburg (Repino settlement), June 27-July 01, 2016, p.172.

[30] Osmanova S.F., Sardarova S.A. Amidation reaction of 1,1-bis- (hydroxycarbonylmethyl thio)-1-phenylethane with aromatic amines / Materials of the XXX International Scientific and Technical Conference “Chemical Reagents, Reagents and Processes of Small-tonnage Chemistry” dedicated to the memory of academician of the Republic of Bashkortostan D. L. Rakhmankulov, “Reagent 2016 ”, p. 43.

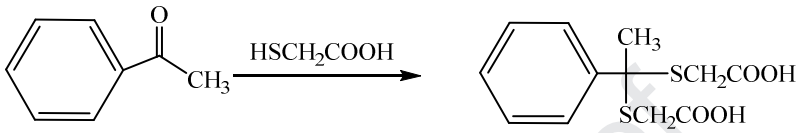
[31] Osmanova S.F. Synthesis and study of new amides - derivatives of acetophenone // Sumgait State University - 55, Scientific news, Natural and technical sciences, 2017, v.17, No. 4, p. 52-55.

[32] Taslimi P., Osmanova S., Gulcin İ. et al. Discovery of potent carbonic anhydrase, acetyl cholineesterase,and butyrylcholinesterase enzymes inhibitors: The new amides and thiazolidine-4-ones synthesized on an acetophenone base// Journal of Biochemical and Molecular Toxicology, 2017, Sep;31(9). doi: 10.1002/jbt.21931.

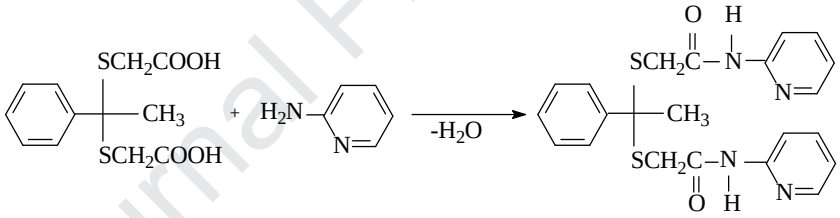
[33] Sardarova SA, Osmanova SF, Mamedov FA, Gamidova Sh. Synthesis and Reaction of Slurry Ethers 1,1-bis-(hydroxycarbonylmethyltio)-1-arylethanates // Chemical problems, 2015, №3, p. 319–322.



Scheme 1. Synthesis of 1-(6-methyl-3-phenyl-2-sulfanilden-1,2,3,4-tetrahidropirimidin-5) etanon (M-1)



Scheme 2. Synthesis of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))diacetic acid (M)



Scheme 3. Synthesis of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))bis(N-phenylacetamide) (M-2)

Table1. Hydrogen-bond geometry (Å, ^{0}) of 1-(6-Methyl-3-phenyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone (M-1)

D - H…*A*	*D*—H	H... *A*	*D*...*A*	*D*—*H*...*A*
N3—H3N... O1[1]	0.88	2.05	2.920 (2)	168

Table 2. Hydrogen bonds for c [Å and °] of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfane-diyl))diacetic acid (M)

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(4)#1	0.85(2)	1.83(9)	2.643(8)	160(25)
O(3)-H(3)...O(2)#1	0.85(2)	1.79(3)	2.635(8)	174(14)

Symmetry transformations used to generate equivalent atoms:
#1 -x,-y+1,-z

Table 3. Data on the degree of hemolysis of red blood cells with substances M-1, M-2 and phenolic extract of ginger.

Concentration (mg/ml)	**The degree of hemolysis (%)**		
	M-1	**M-2**	**Ginger extract**
240	108,03	5,54	-
120	80,03	6,80	-
60	58,82	2,83	-
30	23,66	-0,62	112,76
15	0,66	-0,29	70,87
7,5	0,00	0,54	17,89
3,75	-1,50	1,21	9,17

1,88	-3,56	1,00	4,96
0,94	-	-	3,64
0,47	-	-	3,34

Table 4. Data on testing the antioxidant activity of substances M-1, M-2, ginger extract and Trolox. Negative values indicate the induction of MDA production (prooxidant effect).

Concentration mg/l	The suppression of the operating time MDA (%)		
	M-1	**M-2**	**Ginger extract**
1,875	-5,48	-28,93	31,54
3,75	4,03	-9,37	46,53
7,5	8,16	-3,07	70,47
15	13,86	-10,46	91,18
30	15,42	-16,72	95,14
60	19,09	-31,38	96,89
120	15,69	-30,90	97,94
240			99,90

Table 5. Probable predicted activity of the substance M-1 (reliability of the forecast above 40%)

Probability	Mistake	Predicted Activity
0,728	0,005	Analgesic, non-opioid
0,708	0,009	Analgesic
0,707	0,009	Antianginal
0,682	0,017	Apoptosis agonist
0,659	0,032	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
0,636	0,013	Centromere associated protein inhibitor
0,666	0,054	Membrane permeability inhibitor
0,655	0,062	Antieczematic
0,584	0,029	Chloride peroxidase inhibitor
0,572	0,019	tRNA-pseudouridine synthase I inhibitor

0,558	0,006	Antimitotic
0,589	0,053	Phosphatase inhibitor
0,548	0,055	Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor
0,547	0,057	Acute neurologic disorders treatment
0,501	0,018	Leukopoiesis inhibitor
0,478	0,009	Antiviral (Adenovirus)
0,491	0,028	Antiviral (Rhinovirus)
0,478	0,026	2-Hydroxymuconate-semialdehyde hydrolase inhibitor
0,518	0,068	Oxidoreductase inhibitor
0,473	0,025	Anesthetic general
0,454	0,012	Flavin-containing monooxygenase substrate
0,468	0,027	Chemosensitizer
0,521	0,083	Glutamyl endopeptidase II inhibitor
0,507	0,073	Calcium channel (voltage-sensitive) activator
0,464	0,053	Nitrate reductase (cytochrome) inhibitor
0,464	0,056	Arginine 2-monooxygenase inhibitor
0,458	0,051	Antihypoxic
0,46	0,055	Fragilysin inhibitor
0,445	0,043	Dermatologic
0,458	0,065	Insulysin inhibitor
0,411	0,026	Laccase inhibitor
0,504	0,119	Fibrinolytic
0,47	0,085	Gastrin inhibitor
0,427	0,047	CYP2F1 substrate
0,42	0,043	Lysostaphin inhibitor
0,435	0,062	Histamine release stimulant
0,387	0,029	Loop diuretic
0,387	0,042	Retinoic acid metabolism inhibitor
0,4	0,065	3-Hydroxybenzoate 6-monooxygenase inhibitor
0,339	0,007	Calcium channel (voltage-sensitive) blocker
0,404	0,076	Radiosensitizer

0,336	0,008	Calcium channel blocker
0,408	0,088	1,4-Lactonase inhibitor
0,427	0,11	General pump inhibitor

Table 6. Probable predicted activity of the substance M-2 (reliability of the forecast above 40%)

Probability	Mistake	Predicted Activity
0,694	0,013	Electron-transferring-flavoprotein dehydrogenase inhibitor
0,611	0,028	Fragilysin inhibitor
0,596	0,043	Pro-opiomelanocortin converting enzyme inhibitor
0,572	0,019	Chenodeoxycholoyltaurine hydrolase inhibitor
0,547	0,01	Polyneuridine-aldehyde esterase inhibitor
0,559	0,028	Biotinidase inhibitor
0,556	0,028	Endopeptidase So inhibitor
0,541	0,025	Histidine N-acetyltransferase inhibitor
0,542	0,03	Formaldehyde transketolase inhibitor
0,538	0,039	Oxygen scavenger
0,536	0,045	Glutathione thiolesterase inhibitor
0,542	0,069	Pseudolysin inhibitor
0,514	0,05	Dehydro-L-gulonate decarboxylase inhibitor
0,481	0,02	Transcription factor STAT3 inhibitor
0,483	0,026	Antiulcerative
0,549	0,094	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0,481	0,031	Naphthalene 1,2-dioxygenase inhibitor
0,481	0,031	Ferredoxin-NAD+ reductase inhibitor
0,486	0,039	Sulfur reductase inhibitor
0,526	0,08	Kidney function stimulant
0,471	0,027	Transcription factor STAT inhibitor
0,451	0,01	Botulin neurotoxin A light chain inhibitor

0,51	0,075	Nicotinic alpha4beta4 receptor agonist
0,447	0,018	Glucuronate isomerase inhibitor
0,49	0,061	Thioredoxin inhibitor
0,462	0,051	Fibrolase inhibitor
0,445	0,04	Gamma-guanidinobutyraldehyde dehydrogenase inhibitor
0,424	0,04	tRNA-pseudouridine synthase I inhibitor
0,435	0,051	Peptidyl-dipeptidase Dcp inhibitor
0,507	0,132	Mucomembranous protector
0,448	0,075	Carboxypeptidase Taq inhibitor
0,448	0,076	Limulus clotting factor B inhibitor
0,394	0,023	Thiopurine S-methyltransferase inhibitor
0,396	0,024	PfA-M-1 aminopeptidase inhibitor
0,428	0,057	Manganese peroxidase inhibitor
0,458	0,093	Phthalate 4,5-dioxygenase inhibitor
0,424	0,065	Nitrate reductase (cytochrome) inhibitor
0,393	0,035	Carbon-monoxide dehydrogenase inhibitor
0,37	0,018	HIV attachment inhibitor
0,442	0,099	Complement factor D inhibitor
0,363	0,022	Allyl-alcohol dehydrogenase inhibitor
0,457	0,118	Glycosylphosphatidylinositol phospholipase D inhibitor
0,344	0,01	Allantoin racemase inhibitor
0,385	0,052	Glutamine-phenylpyruvate transaminase inhibitor
0,433	0,104	Nicotinic alpha2beta2 receptor antagonist
0,378	0,05	Cyanoalanine nitrilase inhibitor
0,387	0,062	NAD(P)+-arginine ADP-ribosyltransferase inhibitor
0,406	0,083	Lysine 2,3-aminomutase inhibitor
0,382	0,06	CYP2F1 substrate
0,363	0,041	Focal adhesion kinase 2 inhibitor
0,41	0,09	Fructose 5-dehydrogenase inhibitor

0,4	0,08	Pterin deaminase inhibitor
0,411	0,093	Lysase inhibitor
0,407	0,09	2-Hydroxyquinoline 8-monooxygenase inhibitor
0,391	0,075	5 Hydroxytryptamine release inhibitor
0,41	0,095	Chloride peroxidase inhibitor
0,362	0,047	MAP3K5 inhibitor
0,405	0,092	Antiseborrheic

FIGURE LEGENDS

Figure 1. X-ray structure of 1-(6-methyl-3-phenyl-2-sulfanilden-1,2,3,4-tetrahidropirimidin-5) etanon (M-1).

Figure 2. X-ray structure of synthesis of 2,2'-((1-phenylethane-1,1-diyl)bis(sulfanediyl))-diacetic acid (M).

Figure 3. The degree of hemolysis of red blood cells with substances M-1, M-2 and phenolic extract of ginger.

Figure 4. Antioxidant activity of substances M-1, M-2, ginger extract and Trolox. Negative values indicate the induction of MDA production (prooxidant effect).

Figure 5. The effect of the substance M-1 in various concentrations on the membrane potential of mitochondria of brown adipose tissue of rats.

Figure 6. Effect of M-1 substance in various concentrations on the membrane potential of rat liver mitochondria.

Figure 7. Effect of substance M-2 in various concentrations on the membrane potential of mitochondria of brown adipose tissue of rats.

Figure 8. Effect of M-2 substance in various concentrations on the membrane potential of rat liver mitochondria.

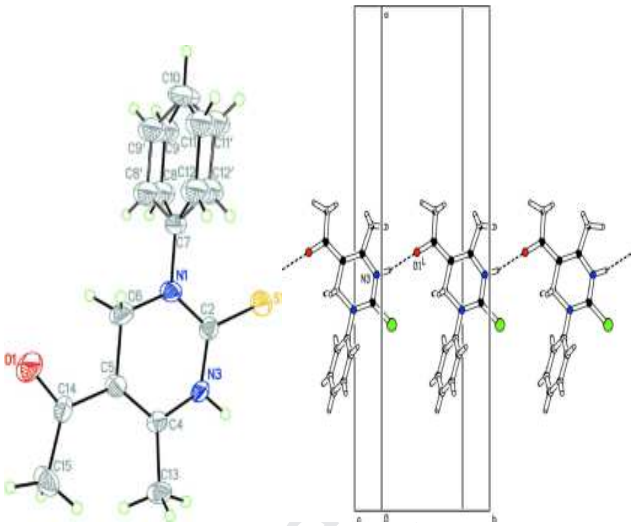


Figure 1.

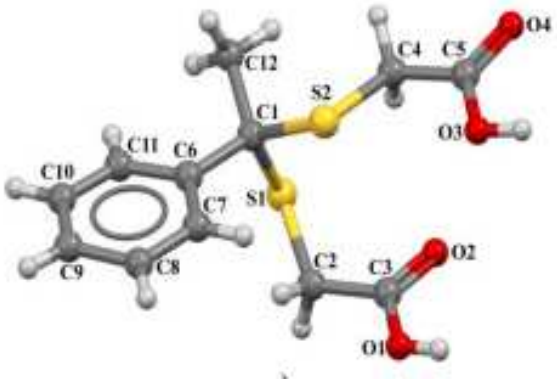


Figure 2.

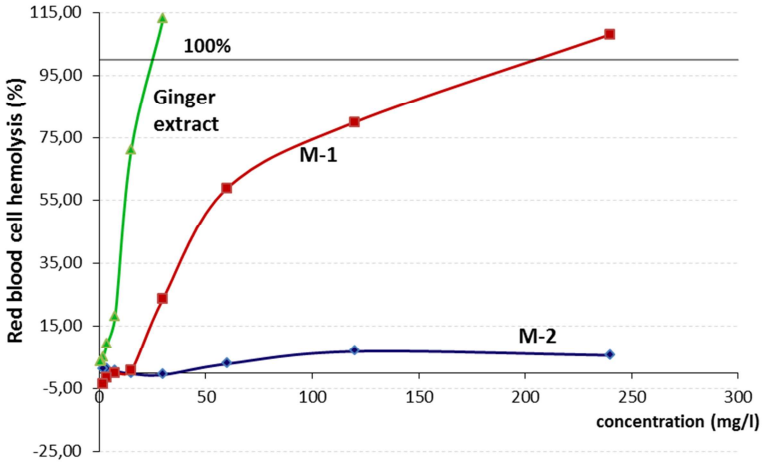


Figure 3.

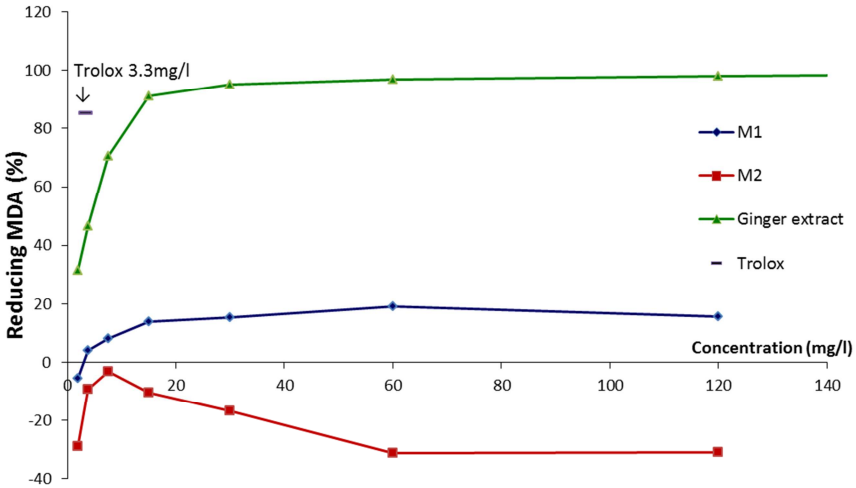


Figure 4.

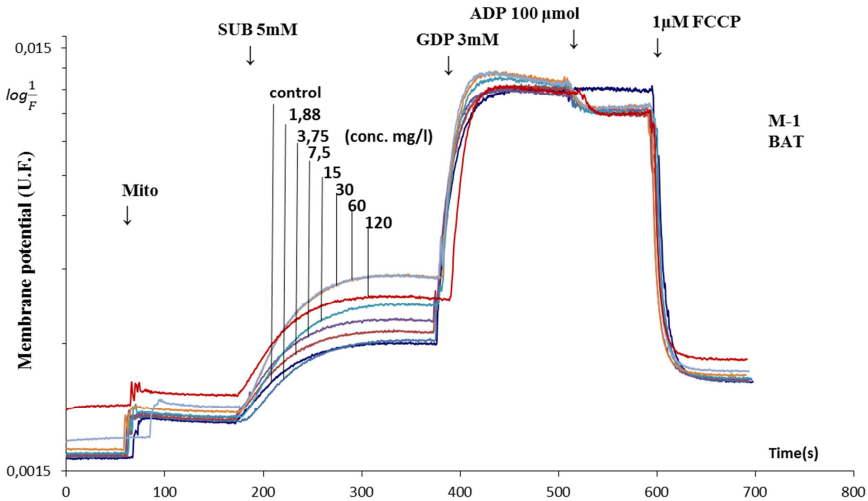


Figure 5.

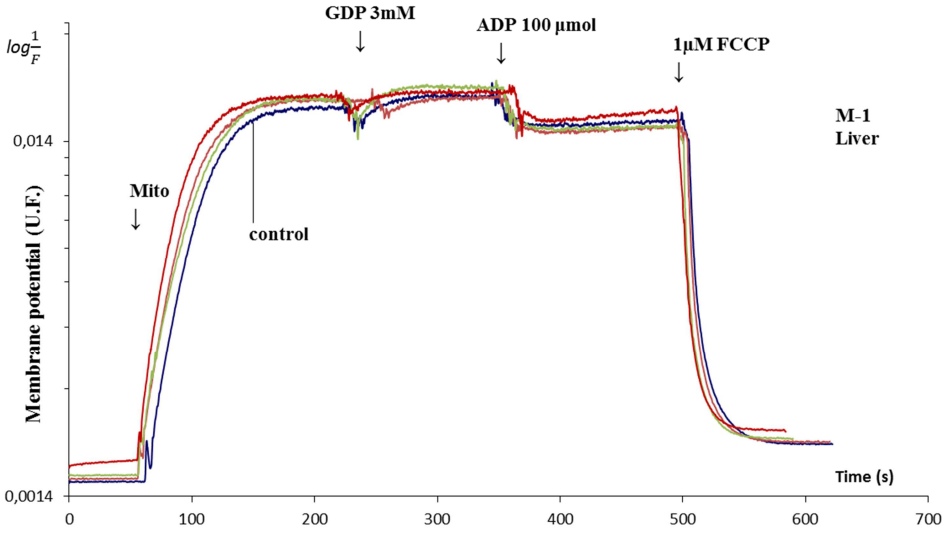


Figure 6.

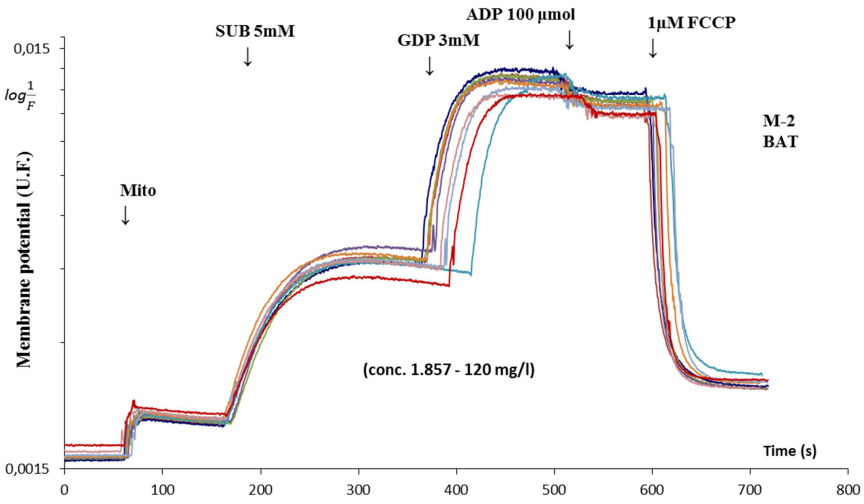


Figure 7.

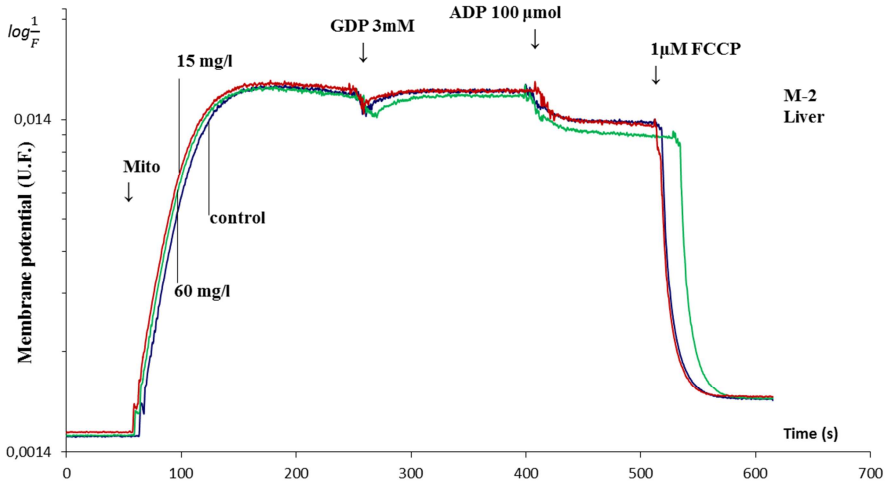


Figure 8.

Highlight

- A serie of heteroatomic compounds (M, M-1 and M-2) was synthesised.
- These precursors have been characterized by ^{1}H and ^{13}C NMR and X-ray spectroscopies.
- Studies of the effect of M-1 and M-2 on the amount of hemolysis of red blood cells.
- Studies of antioxidant properties.
- The effect of M-1 and M-2 on the mitochondrial membrane potential of brown adipose tissue and rat liver.
- Computer prediction of the spectrum of biological activity

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.