Research Article

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Ultrasound-assisted green synthesis and *in silico* study of 6-(4-(butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxypyridazine derivatives

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Abstract: Eco-friendly ultrasound-assisted synthesis of a series of 3-*N*-substituted 6-((4-(butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)pyridazin-3(2*H*)-one derivatives and *in silico* study to predict their biological activities were carried out. Physicochemical and pharmacokinetic properties were obtained. Absorption, distribution, metabolism, excretion and toxicity properties and bioavailability index were calculated. A comparative analysis of structural similarity based on the Tanimoto coefficient was carried out.

Keywords: ultrasound-assisted synthesis, green chemistry, 6-(1,3,5-triazin-2-yl)oxypyridazine, *in silico* study

1 Introduction

Heterocyclic compounds containing a symmetrical 1,3,5-triazine moiety are an interesting class of compounds with a wide spectrum of biological activity. In medical practice, several drugs are used: the respiratory stimulant almitrin (duxil), the antitumor drugs altretamine (hexalen), dioxadet and tretamine, the myorelaxant isocyuronium bromide, the trypanocidal drugs melarsen oxide and melarsomine, the antimalarial drug cycloguanil, and the antiulcer drug irsogladine.

Given the breadth of the spectrum of physiological action, targeted syntheses and studies of the biological activity of new derivatives of 1,3,5-triazine continue. This series includes compounds with antimicrobial [1–4], antituberculosis [5,6], anti-inflammatory [7,8], antiviral [9], antifungal [10], anticancer [11–14], anti-HIV [15,16], antitrypanosomal [17,18], and antimalarial [19–21] activities. Some derivatives of 1,3,5-triazine inhibit monoamine oxidase [22] and are blockers of neuronal sodium channels [23].

Much attention is also paid to the search for new biologically active derivatives of pyridazine. In the last two decades, among them, the compounds with analgesic and anti-inflammatory [24,25], antimicrobial [26–28], antifungal [29], antitumor [30,31], and antinociceptive [32] activities have been found. Some substances have shown inhibitory effects on α1-α2-adrenoceptors [33], c-Met kinase [34], and plant growth [35].

Derivatives of 1,3,5-triazine and pyridazine are also widely used in agriculture. Among the 1,3,5-triazine derivatives, fungicides (anilazine), and herbicides (dipropetryn, trihydroxy triazine, a large number of substituted chlorotriazines, fluoroalkyltriazines, methoxytriazines, methylthiotriazines, triazinones, and also a wide number of triazinylsulfonylurea derivatives) are known [36].

The arsenal of pesticides based on pyridazine includes mainly herbicides (credazune, pyridafol, pyridate, brompyrazon, chloridazon, dimidazon, flufenpyr, metflurazon, norflurazon, oxapyrazon, and pudanon) [36]. Our early studies also identified compounds that have a stimulating effect on plant growth [37–40].

However, the acquisition by harmful organisms of resistance to the substances used necessitates a systematic replenishment of their assortment with new drugs with different mechanisms of action.

In this regard, the purpose of this study was the targeted synthesis of new compounds with a combination of 1,3,5-triazine and pyridazine cycles in the molecule, which can lead to new biologically active derivatives, to which the indicated resistance has not yet been formed.

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2 Materials and methods

2.1 General

An ultrasonic generator I10-840 with an operating frequency of 22 kHz ± 10% and a maximum pulse power of 1,000 W was used to carry out the sonochemical syntheses. In all experiments, the following conditions were applied: irradiation power – 30% (300 W), exposure time – 30 min. The vessel with the reagents subjected to irradiation was placed in a water bath, which was maintained at room temperature (25°C).

The structure and purity of the compounds synthesized were confirmed by ^{1}H and ^{13}C NMR spectra, obtained at 30°C on a Varian Mercury-300 NMR spectrometer (300 and 75 MHz, respectively) in a mixture of CCl_4/DMSO-d_6 solvents (3:1), using a standard pulse sequence; TMS was used as an internal standard. The progress of the reactions and the purity of the obtained compounds were checked by TLC on Silufol UV-254 plates; an acetone/hexane mixture (2:1 or 1:1) was used as the eluent. Elemental analysis was performed on a Eurovector EA3000 CHN analyzer. Melting points were determined on a Stuart SMP10 apparatus and were uncorrected.

2.2 US-assisted syntheses of compounds 2–9

2.2.1 6-((4-(Butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)pyridazin-3(2*H*)-one (2)

The mixture of compound **1** (0.02 mol), and potassium salt of 6-hydroxypyridazin-3(2*H*)-one (0.02 mol) in 20 mL of DMF was subjected to ultrasound irradiation. Yield 83%, m.p., 160–161°C. IR, ν, cm^{-1}: 1,676 (C═O). ^{1}H NMR, *δ*, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.1, C*H*$_3$-Bu); 1.10–1.20 (6H, t, *J* = 7.1, $(CH_3)_2$-Et); 1.33 and 1.50 (4H, m, CH_2CH_2); 3.20 and 3.24 (2H, m, *CH*$_2$NH); 3.40–3.58 (4H, m, $(NCH_2)_2$-Et); 6.82 and 7.20 (2H, d, *J* = 9.0, CH═CH); 6.80 and 7.50 (1H, brs, NH-Bu); 12.45 (1H, brs, NH-pyrid.). ^{13}C NMR, *δ*, ppm: 12.6, 12.9, 13.0, 13.4, 13.5, 19.38, 19.45, 19.5, 30.8, 31.5, 40.1, 40.3, 40.8, 40.9, 130.5,130.8, 148.2, 159.8, 164.8, 166.0, 169.0. Anal. calculated for $C_{15}H_{23}N_7O_2$: C, 54.04; H, 6.95; N, 29.41. Found: C, 54.14; H, 6.90; N, 29.55.

2.2.2 6-((4-(Butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)-2-methylpyridazin-3(2*H*)-one (3)

The mixture of compound **1** (0.02 mol) and potassium salt of 6-hydroxy-2-methylpyridazin-3(2*H*)-one (0.02 mol) in 20 mL of DMF was subjected to ultrasound irradiation. Yield, 75%; m.p., 133–135°C. IR, ν, cm^{-1}: 1,667 (C═O). ^{1}H NMR, *δ*, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.1, C*H*$_3$-Bu); 1.12–1.20 (6H, t, *J* = 7.1, $(CH_3)_2$-Et); 1.32 and 1.50 (4H, m, CH_2CH_2); 3.19 and 3.24 (2H, m, C*H*$_2$NH); 3.43 and 3.55 (4H, m, $(NCH_2)_2$-Et); 3.60 (3H, s, NCH_3); 6.25 and 7.18 (1H, t, *J* = 4.8, NH); 6.90 and 7.23 (2H, d, *J* = 9.0, CH═CH). ^{13}C NMR, *δ*, ppm: 12.76, 12.83, 13.4, 19.4, 30.8, 38.7, 39.7, 40.8, 40.9, 130.0, 146.9, 147.40, 158.5, 164.8, 166.0, 169.0. Anal. calculated for $C_{16}H_{25}N_7O_2$: C, 55.31; H, 7.25; N, 28.22. Found: C, 55.25; H, 7.20; N, 28.11.

2.2.3 6-((4-(Butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)-2-phenylpyridazin-3(2*H*)-one (4)

The mixture of compound **1** (0.02 mol) and potassium salt of 6-hydroxy-2-phenylpyridazin-3(2*H*)-one (0.02 mol) in 20 mL of DMF was subjected to ultrasound irradiation. Yield, 65%; m.p., 162–164°C. IR, ν, cm^{-1}: 1,679 (C═O). ^{1}H NMR, *δ*, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.1, C*H*$_3$-Bu); 1.12–1.20 (6H, t, *J* = 7.1, $(CH_3)_2$-Et); 1.32 and 1.50 (4H, m, C*H*$_2$CH$_2$); 3.20 and 3.25 (2H, m, CH_2NH); 3.44 and 3.57 (4H, m, $(NCH_2)_2$-Et); 6.91 and 7.23 (1H, t, *J* = 4.8, NH); 7.00–7.71 (7H, m, C_6H_5 and CH═CH). ^{13}C NMR, *δ*, ppm: 12.6, 12.9, 13.4, 19.4, 30.8, 39.7, 40.8, 41.0, 124.4, 126.9, 127.8, 130.1, 131.7, 140.7, 148.2, 157.9, 164.8, 166.1, 169.0. Anal. calculated for $C_{21}H_{27}N_7O_2$: C, 61.60; H, 6.65; N, 23.94. Found: C, 61.8; H, 6.69; N, 24.02.

2.2.4 6-((4-(Butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)-2-propylpyridazin-3(2*H*)-one (5)

The mixture of compound **2** (0.02 mol), KOH (0.02 mol), and propylbromide (0.022 mol) in 20 mL of DMF was subjected to ultrasound irradiation. Yield, 71%; m.p., 95–97°C. IR, ν, cm^{-1}: 1,672 (C═O). ^{1}H NMR, *δ*, ppm (*J*, Hz): 0.96–1.23 (12H, m, $(CH_3)_4$); 1.27–1.57 (4H, m, CH_2CH_2); 1.76 (2H, m, CCH_2C-Pr); 3.18 and 3.25 (2H, m, *CH*$_2$NH); 3.43 and 3.55 (4H, m, $(NCH_2)_2$-Et); 3.96 (2H, t, *J* = 7.2, NCH_2-Pr); 6.80 and 7.18 (1H, t, *J* = 4.8, NH); 6.84 and 7.20 (2H, d, *J* = 9.0, CH═CH). ^{13}C NMR, *δ*, ppm: 10.5, 12.6, 12.8, 13.4, 19.36, 19.44, 20.9, 29.0, 30.8, 31.1, 36.7, 40.5, 40.8, 41.0, 51.7, 129.6, 129.9, 130.2, 130.5, 130.7, 147.4, 148.2, 158.3, 159.7, 164.7, 166.1, 169.0. Anal. calculated for $C_{18}H_{29}N_7O_2$: C, 57.58; H, 7.79; N, 26.11. Found: C, 57.66; H, 7.84; N, 26.27.

2.2.5 6-((4-(Butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)-2-ethylpyridazin-3(2*H*)-one (6)

The mixture of compound **2** (0.02 mol), KOH (0.02 mol), and ethyliodide (0.022 mol) in 20 mL of DMF was subjected to

ultrasound irradiation. Yield, 72%; m.p., 120–122°C. IR, ν, cm^{-1}: 1,666 (C═O). ^{1}H NMR, δ, ppm (*J*, Hz): 0.96 (3H, t, *J* = 7.1, C*H*$_3$-Bu); 1.10–1.20 (6H, t, *J* = 7.1, (CH$_3$)$_2$-Et); 1.30 (3H, t, *J* = 7.0, NCH$_2$C*H*$_3$-Et); 1.27–1.57 (4H, m, CH$_2$CH$_2$); 3.20 and 3.27 (2H, m, C*H*$_2$NH); 3.43 and 3.55 (4H, m, (NCH$_2$)$_2$-Et); 4.03 (2H, q, *J* = 7.0, NCH$_2$-Et); 6.92 and 7.20 (1H, t, *J* = 4.8, NH); 6.94 and 7.22 (2H, d, *J* = 9.0, CH═CH). ^{13}C NMR, δ, ppm: 12.6, 12.8, 12.9, 13.3, 19.4, 30.8, 40.8, 41.0, 45.4, 129.7, 130.2, 147.6, 158.0, 164.7, 166.1, 169.0. Anal. calculated for $C_{17}H_{27}N_7O_2$: C, 56.49; H, 7.53; N, 27.13. Found: C, 56.40; H, 7.47; N, 27.01.

2.2.6 2-(3-((4-(Butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)-6-oxopyridazin-1(6*H*)-yl) acetamide (7)

The mixture of compound **2** (0.02 mol), KOH (0.02 mol), and 2-chloroacetamide (0.022 mol) in 20 mL of DMF was subjected to ultrasound irradiation. Yield, 87%; m.p., 188–190°C. IR, ν, cm^{-1}: 1,676 (C═O), 1,680 (C═O). ^{1}H NMR, δ, ppm (*J*, Hz): 0.96 (3H, t, *J* = 7.2, C*H*$_3$-Bu); 1.11 and 1.17 (6H, t, *J* = 7.1, (C*H*$_3$)$_2$-Et); 1.35 and 1.50 (4H, m, CH$_2$CH$_2$); 3.20 and 3.25 (2H, m, CH$_2$NH); 3.43 and 3.55 (4H, m, (NCH$_2$)$_2$-Et); 4.53 (2H, s, NCH$_2$CO); 7.32 (1H, t, *J* = 6.0, NH); 6.91 and 7.26 (2H, d, *J* = 9.8, CH═CH); 6.93 and 7.36 (2H, brs, NH$_2$). ^{13}C NMR, δ, ppm: 12.7, 12.9, 13.4, 19.5, 30.8, 40.76, 40.78, 40.94, 130.2, 130.3, 147.5, 158.5, 164.8, 166.0, 167.4, 168.8. Anal. calculated for $C_{17}H_{26}N_8O_3$: C, 52.30; H, 6.71; N, 28.70. Found: C, 52.22; H, 6.76; N, 28.81.

2.2.7 Methyl 2-(3-((4-(butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)-6-oxopyridazin-1(6*H*)-yl) acetate (8)

The mixture of compound **2** (0.02 mol), KOH (0.02 mol), and methyl 2-chloroacetate (0.022 mol) in 20 mL of DMF was subjected to ultrasound irradiation. Yield, 70%; m.p., 93–95°C. IR, ν, cm^{-1}: 1,683 (C═O), 1,751 (C═O). ^{1}H NMR, δ, ppm (*J*, Hz): 0.93 (3H, t, *J* = 7.1, C*H*$_3$-Bu); 1.12–1.20 (6H, t, *J* = 7.1, (CH$_3$)$_2$-Et); 1.34 and 1.50 (4H, m, CH$_2$CH$_2$); 3.20 and 3.25 (2H, m, CH$_2$NH); 3.42 and 3.53 (4H, m, (NCH$_2$)$_2$-Et); 3.77 (3H, s, OCH$_3$); 4.72 (2H, s, NCH$_2$CO); 6.85 and 7.25 (1H, t, *J* = 5.0, NH); 6.93 and 7.33 (2H, d, *J* = 9.0, CH═CH). ^{13}C NMR, δ, ppm: 12.3, 12.6, 13.1, 19.1, 30.5, 39.8, 40.5, 40.6, 40.7, 51.3, 51.7, 129.9, 130.7, 147.6, 158.0, 164.4, 165.8, 166.5, 168.5. Anal. calculated for $C_{18}H_{27}N_7O_4$: C, 53.32; H, 6.71; N, 24.18. Found: C, 53.38; H, 6.77; N, 24.03.

2.2.8 Ethyl 2-(3-((4-(butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)-6-oxopyridazin-1(6*H*)-yl)acetate (9)

The mixture of compound **2** (0.02 mol), KOH (0.02 mol), and ethyl 2-chloroacetate (0.022 mol) in 20 mL of DMF was subjected to ultrasound irradiation. Yield, 68%; m.p., 68–70°C. IR, ν, cm^{-1}: 1,676 (C═O), 1,761 (C═O). ^{1}H NMR, δ, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.1, C*H*$_3$-Bu); 1.13–1.20 (6H, t, *J* = 7.1, (CH$_3$)$_2$-Et); 1.30 (3H, t, *J* = 7.1, OCH$_2$C*H*$_3$); 1.34 and 1.50 (4H, m, CH$_2$CH$_2$); 3.21 and 3.24 (2H, m, *CH*$_2$NH); 3.42 and 3.54 (4H, m, (NCH$_2$)$_2$-Et); 4.20 (2H, q, *J* = 7.1, OCH$_2$*CH*$_3$); 4.68 (2H, s, NCH$_2$CO); 6.85 and 7.23 (1H, t, *J* = 5.0, NH); 6.93 and 7.33 (2H, d, *J* = 9.0, CH═CH). ^{13}C NMR, δ, ppm: 12.6, 12.8, 13.3, 13.7, 19.4, 30.8, 39.7, 40.8, 40.9, 52.1, 60.5, 130.1, 130.9, 147.8, 158.3, 164.7, 166.0, 166.2, 167.8. Anal. calculated for $C_{19}H_{29}N_7O_4$: C, 54.40; H, 6.97; N, 23.37. Found: C, 54.39; H, 6.82; N, 23.17.

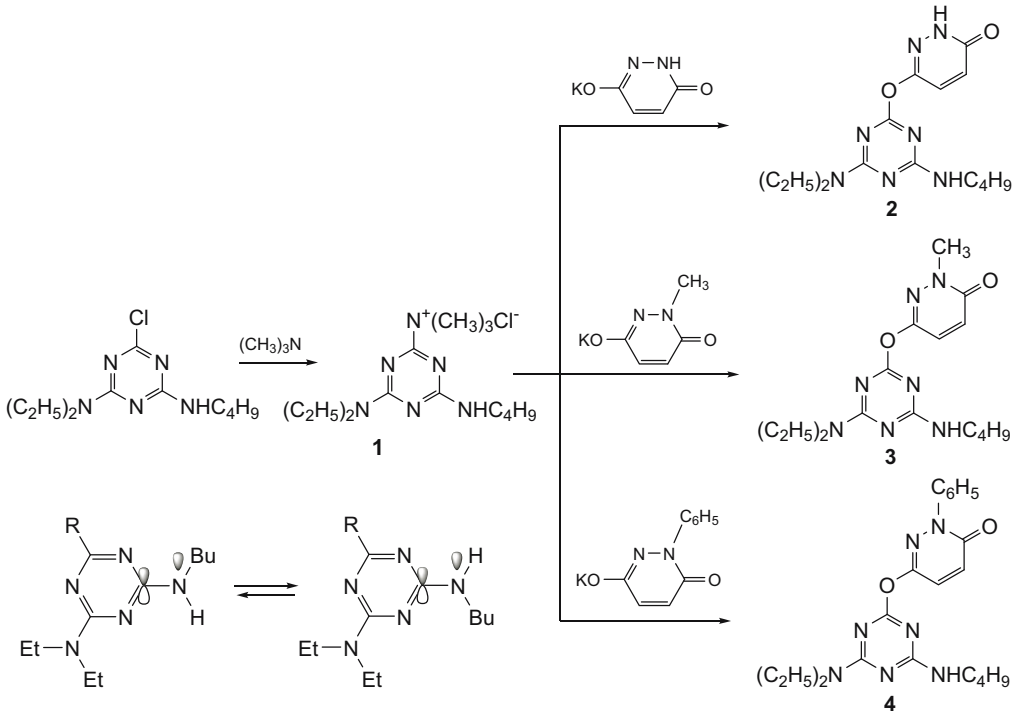
3 Results and discussion

3.1 Chemistry

The initial goal of this work was the target synthesis of triazinyloxypyridazines, which should be obtained by substituting the chlorine atom in the second position of 2-chloro-4-butylamino-6-diethylamino-1,3,5-triazine with an oxypyridazine fragment. However, taking into account that such a reaction proceeds under rather severe conditions, at first the chlorosubstituted derivative was transformed into 4-(butylamino)-6-(diethylamino)-*N*,*N*,*N*-trimethyl-1,3,5-triazine-2-aminium chloride (**1**) and then the subsequent reactions of latter were carried out with potassium salts of the previously obtained 6-hydroxypyridazin-3(2*H*)-one and its 1-methyl- and 1-phenyl substituted derivatives. As a result of these reactions, the corresponding triazinyloxypyridazines (**2–4**) were synthesized (Scheme 1).

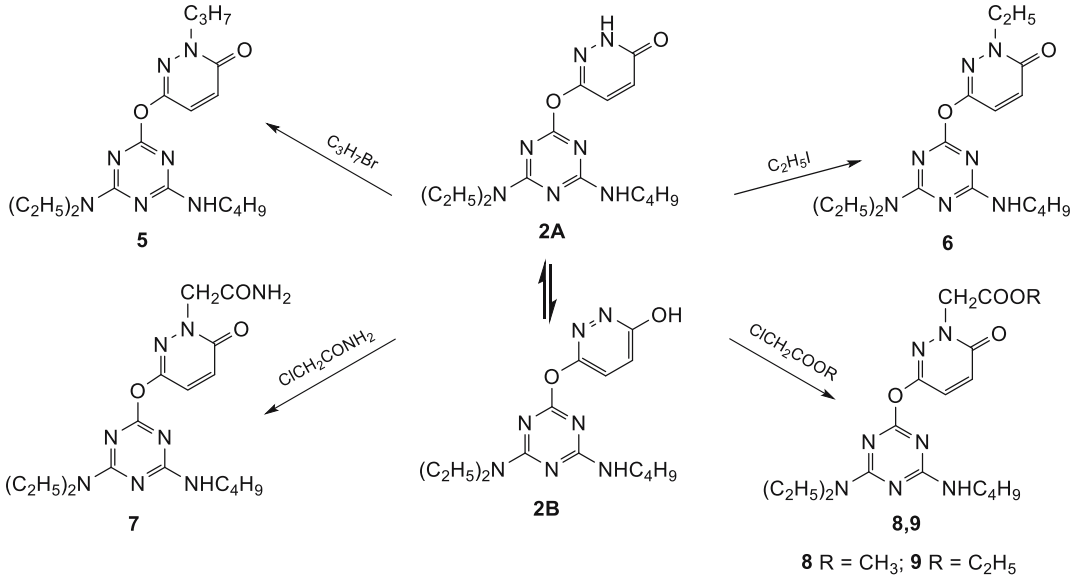
Compounds **3** and **4** can also be obtained from 6-((4-(butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)pyridazin-3(2*H*)-one (**2**). At the same time, the latter can exist in two different tautomeric forms, and, as a result, the substitution reactions can proceed both at the cyclic nitrogen atom (**2A**) or the oxygen atom of the hydroxyl group (**2B**). Compound **2** was alkylated with various alkyl halides (Scheme 2).

In the IR spectra the absorptions at 1,672 cm^{-1} (compound **5**) and 1,666 cm^{-1} (compound **6**), corresponding to the C═O carbonyl groups were obtained, which is consistent with the substitution at the nitrogen atom of the pyridazine ring (**A**). In the IR spectra of compounds **7–9**, for each compound, two absorptions related to the C═O groups are observed, which also indicates N-alkylation (**A**). The structure of compounds **5–9** is also confirmed by the ^{1}H NMR and ^{13}C NMR spectra, in which the chemical shifts of the signals of the alkyl substituents methylene groups are consistent with N-substitution.



Scheme 1: Synthesis of triazinyloxypyridazine derivatives.

It should be noted that the ^{1}H NMR spectra of all synthesized compounds **2–9** contain two sets of signals corresponding to N-alkyl groups (4-butylamino and 6-diethylamino), which is explained by the hindered internal rotation around the N-heterocycle bond. The increase in the order of this bond is associated with the interaction of the p-electron orbital of the carbon atom of the triazine ring with the *n*-orbital of the exocyclic nitrogen atom. This effect was described in detail in our earlier article [41]. For this reason, the number of signals in the ^{13}C NMR spectra of these compounds is greater than the number of carbon atoms in the molecule. The yield and melting points of synthesized compounds are listed in Table 1.



Scheme 2: Synthesis of *N*-substituted derivatives of 6-((4-(butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)pyridazin-3(2*H*)-one (**2**).

Table 1: Characteristics of synthesized compounds **2–9**

No.	Yield (%)	m.p. (°C)	No.	Yield (%)	m.p. (°C)
2	83	160–161	**6**	72	120–122
3	75	133–135	**7**	87	188–190
4	65	162–164	**8**	70	93–95
5	71	95–97	**9**	68	68–70

3.2 *In silico* study

Absorption, distribution, metabolism, excretion and toxicity (ADMET) parameter values were calculated using SwissADME [42] and ADMETlab v.2 [43] platforms. The prediction of possible toxicity was made using the AdmetSAR [44] and PeoTox [45] platforms. Possible biological activities were obtained based on PASS online [46]. Structural

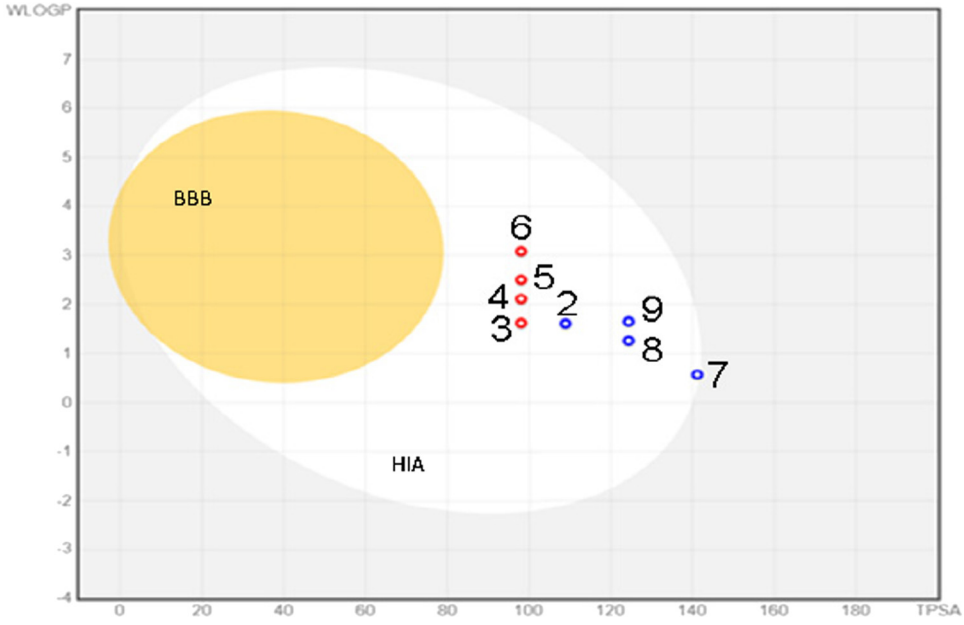


Figure 1: Map of the absorption of compounds through the GIT and BBB. BBB – passage through the BBB, HIA – absorption through the GIT, red dots – active transport, blue dots – passive transport.

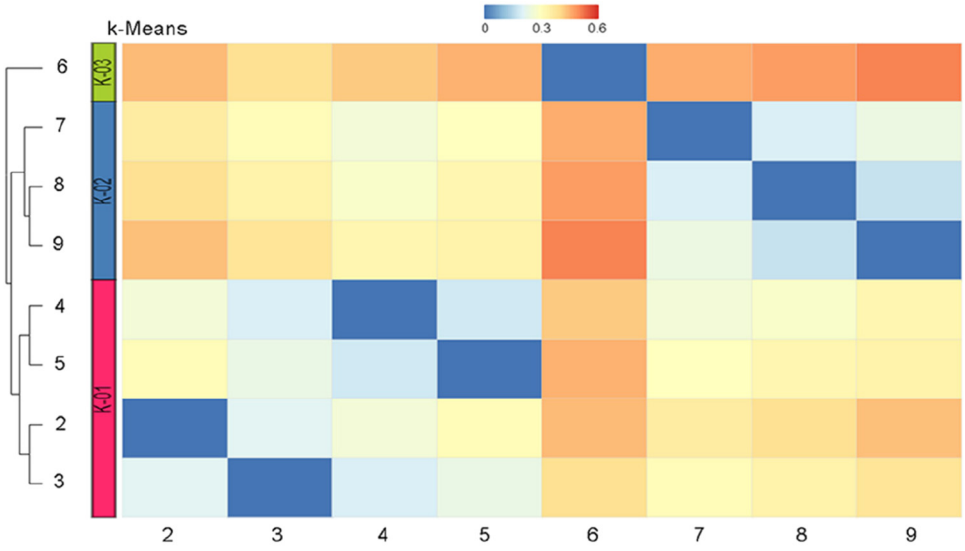


Figure 2: The resulting heat map of the similarity of molecular models based on the Tanimoto coefficient.

similarity parameters based on the Tanimoto coefficient and data clustering were performed using the online platform http://chemmine.ucr.edu/ (Figure 1).

All studied compounds meet the criteria of Lipinski's "Rule of Five" [47]. The calculated values of absorption through the gastrointestinal tract (GIT) and the blood–brain barrier (BBB) indicate that all compounds are well absorbed through the GIT while showing negative values of passage through the BBB. Permeability through the skin is also low at $-6.21\ \mathrm{cm \cdot s^{-1}}$.

It is known that the methodology that reveals the correlation between the structural features of compounds and their activity based on the similarity coefficient is one of the tools of modern drug design. By using QSAR and QSPR methods based on molecular fingerprints, it is possible to compare and group similar compounds in an "all-versus-all" comparison. Data clustering and its visualization simplify data analysis and increase the statistical validity of the experiment [48]. We carried out a comparative analysis and visualization of the structural similarity between the studied compounds. Our result shows that compounds **6** and **9** exhibit the maximum values of the Tanimoto coefficient of 60%.

Clustering based on structural similarity revealed three clusters: compounds **2–5** form cluster 1, **7–9** form cluster 2, and compound **6** forms cluster 3 (Figure 2).

From the point of view of possible biological activity, the compounds included in cluster 2 exhibit an antianginal type of possible activity. Cluster 1 has a similar picture to cluster 2, except for compound **4**, which may exhibit an inhibitory effect on the proteasome ATPase. In the studied series, only compound **6** appears to be a possible enhancer of HMGCS2 expression. It is known that such compounds are therapeutic agents for the treatment of malignant neoplasms of the GIT [49].

Prediction of toxicities based on mutagenicity, carcinogenicity, hepatotoxicity, and ecotoxicity revealed that all the studied compounds can exhibit mutagenicity and high hepatotoxicity. Ecotoxicity values obtained are above average for both pesticides and insecticides. The maximum value of 4.169 is observed for compound **2** with an acceptable standard of ≥11 μg [50]. For other compounds, the value varies from 5.151 to 5.681.

4 Conclusions

In summary, a sonochemical method for the synthesis of a series of novel 3-*N*-substituted 6-((4-(butylamino)-6-(diethylamino)-1,3,5-triazin-2-yl)oxy)pyridazin-3(2*H*)-one derivatives was carried out, which corresponds to the principles of "green chemistry." Comparison of this technique with the traditional methods for the synthesis of the researched, as well as previously obtained compounds with a similar structure [51–54], shows that the reactions with ultrasonic activation of molecules proceed quickly and in high yields. Since industrial ultrasonic reactors exist, the synthesis of these potentially bioactive compounds can be carried out on a large scale, which will have a significant economic effect.

Based on the data of *in silico* analysis, the predicted diversity of the biological activity of the synthesized compounds was established. Our results show that the studied compounds show similar activity within the group. Compound **6** is different and appears to be a possible enhancer of HMGCS2 expression. From the point of view of possible toxicity, the studied compounds may have pesticidal and insecticidal properties.

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Conflict of interest: The authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

[1] Patel D, Patel R, Kumari P, Patel N. Microwave assisted synthesis and *in vitro* antimicrobial assessment of quinolone based *s*-triazines. Heterocycl Commun. 2011;17(1–2):33–41. doi: 10.1515/HC.2011.006.

[2] Cholera AY, Ladva KD. A convenient synthesis of trisubstituted 1,3,5-triazine derivatives and their antimicrobial screening. Der Pharm Chem. 2018;10(4):57–61. www.derpharmachemica.com.

[3] Al-Rasheed HH, Al Alshaikh M, Khaled JM, Alharbi NS, El-Faham A. Ultrasonic irradiation: synthesis, characterization, and preliminary antimicrobial activity of novel series of 4,6-disubstituted-1,3,5-triazine containing hydrazine derivatives. J Chem. 2016;9:Article ID 3464758. doi: 10.1155/2016/3464758.

[4] Vembu S, Pazhamalai S, Gopalakrishnan M. Potential antibacterial activity of triazinedendrimer: Synthesis and controllable drug release properties. Biorg Med Chem. 2015;23(15):4561–6. doi: 10.1016/j.bmc.2015.06.009.

[5] Sunduru N, Gupta L, Chaturvedi V, Dwivedi R, Sinha S, Chauhan PMS. Discovery of new 1,3,5-triazine scaffolds with potent activity against mycobacterium tuberculosis H37Rv. Eur J Med Chem. 2010;45:3335–45. doi: 10.1016/j.ejmech.2010.04.017.

[6] Avupati VR, Yejella RP, Parala VR, Killari KN, Papasani VMR, Cheepurupalli P, et al. Synthesis, characterization and in vitro biological evaluation of some novel 1, 3, 5-triazine-Schiff base conjugates as potential antimycobacterial agents. Biorg Med Chem Lett. 2013;23(21):5968–70. doi: 10.1016/j.bmcl.2013.08.063.

[7] Barakat A, El-Senduny FF, Almarhoon Z, Al-Rasheed HH, Badria FA, Al-Majid AM, et al. Synthesis, X-ray crystal structures, and preliminary antiproliferative activities of new s-triazine-hydroxybenzylidenehydrazone derivatives. J Chem. 2019;10:Article ID 9403908. doi: 10.1155/2019/9403908.

[8] Sun D, Melman G, Letourneau N, Hays AM, Melman A. Synthesis and antiproliferating activity of iron chelators of hydroxyamino-1,3,5-triazine family. Bioorg Med Chem Lett. 2010;20(2):458–60. doi: 10.1016/j.bmcl.2009.11.130.

[9] Krecmerová M, Holý A, Pískala A, Masojídková M, Andrei G, Naesens L, et al. Antiviral activity of triazine analogues of 1-(*S*)-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine (cidofovir) and related compounds. J Med Chem. 2007;50(5):1069–77. doi: 10.1021/jm061281.

[10] Ghaib A, Menager S, Verite P, Lafont O. Synthesis of variously 9,9-dialkylated octahydropyrimido [3,4-a]-s-triazines with potential antifungal activity. Il Farmaco. 2002;57(2):109–16. doi: 10.1016/s0014-827x(01)01181-8.

[11] Kumar R, Gupta L, Pal P, Khan Sh, Singh N, Katiyar SB, et al. Synthesis and cytotoxicity evaluation of (tetrahydro-β-carboline)-1,3,5-triazine hybrids as anticancer agents. Eur J Med Chem. 2010;45(6):2265–76. doi: 10.1016/j.ejmech.2010.02.001.

[12] Makowska A, Saczewski F, Bednarski PJ, Saczewski J, Balewski L. Hybrid molecules composed of 2,4-diamino-1,3,5-triazines and 2-imino-coumarinsand coumarins. Synthesis and cytotoxic properties. Molecules. 2018;23(7):1616–32. doi: 10.3390/molecules23071616.

[13] Patel AB, Chikhalia KH, Kumari P. An efficient synthesis of new thiazolidin-4-one fused s-triazines as potential antimicrobial and anticancer agents. J Saudi Chem Soc. 2014;18(5):646–56. doi: 10.1016/j.jscs.2014.02.002.

[14] Liu B, Sun T, Zhou Z, Du L. A systematic review on antitumor agents with 1,3,5-triazines. Med Chem. 2015;5:131–48. doi: 10.4172/2161-0444.1000255.

[15] Sakakibara N, Balboni G, Congiu C, Onnis V, Demizu Y, Misawa T, et al. Design, synthesis, and anti-HIV-1 activity of 1-substituted 3-(3,5-dimethylbenzyl)triazine derivatives. Antivir Chem Chemother. 2015;24(2):62–71. doi: 10.1177/2040206615612208.

[16] Xiong Y-Z, Chen F-E, Balzarini J, De Clercq E, Pannecouque Ch. Structural modulation of diaryltriazine with potent anti-HIV activity. Eur J Med Chem. 2008;43:1230–6. doi: 10.1016/j.ejmech.2007.08.001.

[17] Klenke B, Stewart M, Barrett MP, Brun R, Gilbert IH, Gorka JB. Synthesis and biological evaluation of *s*-triazine substituted polyamines as potential new anti-trypanosomal drugs. J Med Chem. 2001;44:3440–52. doi: 10.1021/jm010854+.

[18] Baliani A, Bueno GJ, Stewart ML, Yardley V, Brun R. Design and synthesis of a series of melamine-based nitroheterocycles with activity against trypanosomatid parasites. J Med Chem. 2005;48(17):5570–9. doi: 10.1021/jm050177+.

[19] Kumar A, Srivastava K, Kumar SR, Puri SK, Chauhan PMS. Synthesis and bioevaluation of hybrid 4-aminoquinoline triazines as a new class of antimalarial agents. Bioorg Med Chem. 2008;18:6530–3. doi: 10.1016/j.bmcl.2008.10.049.

[20] Sunduru N, Sharma M, Srivastava K, Rajakumar S, Puri S, Saxena JK, et al. Discovery of new 1,3,5-triazine scaffolds with potent activity against mycobacterium tuberculosis H37Rv. Biorg Med Chem. 2009;17(17):6451–62. doi: 10.1016/j.bmc.2009.05.075.

[21] Agarwal A, Srivastava K, Puri S, Chauhan PM. Syntheses of 2,4,6-trisubstituted triazines as antimalarial agents. Biorg Med Chem Lett. 2005;15(3):531–3. doi: 10.1016/j.bmcl.2004.11.052.

[22] Khattab SN, Khalil HH, Bekhit AA, Abd El-Rahman MM, El-Faham A, Albericio F. Synthesis and preliminary biological evaluation of 1,3,5-triazine amino acid derivatives to study their MAO inhibitors. Molecules. 2015;20(9):15976–88. doi: 10.3390/molecules200915976.

[23] Ma X, Poon T-Y, Wong PTH, Chui W-K. Synthesis and in vitro evaluation of 2,4-diamino-1,3,5-triazine derivatives as neuronal voltage-gated sodium channel blockers. Bioorg Med Chem Lett. 2009;19(19):5644–7. doi: 10.1016/j.bmcl.2009.08.052.

[24] Sahin MF, Badiçoglu B, Gökçe M, Küpeli E, Yeşilada E. Synthesis and analgesic and antiinflammatory activity of methyl 6-substituted-3(2H)-pyridazinone-2-ylacetate derivatives. Arch Pharm. 2004;337(8):445–52. doi: 10.1002/ardp.200400896.

[25] Lakshmayya AS, Asif M. Analgesic and anti-inflammatory activities of several 4-substituted-6-(3'-nitrophenyl)pyridazin-(2H)-3-one derivatives. Braz J Pharm Sci. 2013;49(4):903–9. doi: 10.1590/S1984-82502013000400030.

[26] Kandile NG, Mohamed MI, Zaky H, Mohamed H. Novel pyridazine derivatives: Synthesis and antimicrobial activity evaluation. Eur J Med Chem. 2009;44:1989–96. doi: 10.1016/j.ejmech.2008.09.047.

[27] Abd El-Salam NM, Mostafa MS, Ahmed GA, Othman YA. Synthesis and antimicrobial activities of some new heterocyclic compounds based on 6-chloropyridazine-3(2H)-thione. J Chem. 2013;2013:Article ID 890617. doi: 10.1155/2013/890617.

[28] Behalo MS, Gad El-karim IA, Issac YA, Farag MAJ. Synthesis of novel pyridazine derivatives as potential antimicrobial agents. Sulf Chem. 2014;35:661–73. doi: 10.1080/17415993.2014.950661.

[29] Wu J, Song B, Chen H, Bhadury P, Hu D. Synthesis and antifungal activity of 5-chloro-6-phenylpyridazin-3(2H)-one derivatives. Molecules. 2009;14(9):3676–87. doi: 10.3390/molecules14093676.

[30] Kim C, Kim S-B, Park M-S. Synthesis of novel 3-allylseleno-6-alkylthiopyridazines: their anticancer activity against MCF-7 cells. Arch Pharm Res. 2014;37:452–8. doi: 10.1007/s12272-013-0244-x.

[31] Kim C, Kim S-B, Jung J, Park M-S. Design, synthesis, and biological evaluation of selenium-incorporated aminopyridazines as anticancer agents. Bull Korean Chem Soc. 2015;36(6):1669–75. doi: 10.1002/bkcs.10319.

[32] Dogruer DS, Sahin MF, Unlü S, Ito S. Studies on some 3(2H)-pyridazinone derivatives with antinociceptive activity. Arch Pharm (Weinh). 2000;333(4):79–86. doi: 10.1002/(sici)1521-4184(20004)333:4<79::aid-ardp79>3.0.co;2-s.

[33] Corsano S, Strapoghetti G, Barbaro R. Synthesis of new pyridazinone derivatives and their affinity towards α1–α2-adrenoceptors.

Bioorg Med Chem. 1999;7(5):933–41. doi: 10.1016/s0968-0896(99)00046-2.
[34] Kim E-Y, Kang S-T, Jung H, Park CH, Yun C-S, Hwang JY, et al. Discovery of substituted pyrazol-4-yl pyridazinone derivatives as novel c-Met kinase inhibitors. Arch Pharm Res. 2016;39(4):453–64. doi: 10.1007/s12272-015-0703-7.
[35] Zhang M, Hu F-Z, Zhao T, Yang L-Q, Yang H-Z. Synthesis and herbicidal evaluation of 3-N-substituted amino-6-benzyloxypyridazine derivatives. J Heterocycl Chem. 2014;51(5):1404–9. doi: 10.1002/jhet.1831.
[36] http://www.alanwood.net/pesticides/class_pesticides.html.
[37] Yengoyan AP, Shainova RS, Gomktsyan TA, Karapetyan AV. Synthesis of novel 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(2*H*)-one derivatives and their preliminary biological evaluation. J Chem Res. 2018;42(10):535–9. doi: 10.3184/174751918X15389922302823.
[38] Shainova RS, Gomktsyan TA, Karapetyan AV, Yengoyan AP. Synthesis and biological evaluation of 3-O-substituted 1-benzyl-6-oxo-1,6- dihydropyridazine derivatives. J Chem Res. 2019;43(9–10):352–8. doi: 10.1177/1747519819866402.
[39] Shainova RS, Gomktsyan TA, Karapetyan AV, Yengoyan AP. Synthesis and biological properties of novel 3-(pyrazol-1-yl)-6-oxo-pyridazine derivatives. J Chem Res. 2020;26(5–6):271–6. doi: 10.1177/1747519819897523.
[40] Gomktsyan TA, Shainova RS, Karapetyan AV, Yengoyan AP. Synthesis and biological activity of new 3-pyrazolyl-6-hydrazinyl-pyridazine derivatives. Rus J Gen Chem. 2021;91(10):2019–24. doi: 10.1134/S1070363221100145.
[41] Yengoyan AP, Mamyan SS, Gomktsyan TA, Hambardzumyan EN, Vorskanyan AS, Eliazyan KA, et al. Hindered Internal Rotation about a C-N Bond in Some Trisubstituted 1,3,5-Triazines. Chem Heterocycl Comp. 2005;41(8):1059–61.
[42] Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7 Article number42717. doi: 10.1038/srep42717.
[43] Xiong G, Wu Z, Yi J, Fu L, Yang Z, Hsieh C, et al. ADMETlab 2.0: An integrated online platform for accurate and comprehensive predictions of ADMET properties. Nucleic Acids Res. 2021;49(W1):W5–W14. doi: 10.1093/nar/gkab255.
[44] Yang H, Lou C, Sun L, Li J, Cai Y, Wang Z, et al. admetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties. Bioinformatics. 2019;35(6):1067–9. doi: 10.1093/bioinformatics/bty707.
[45] Kamaryan VS, Hunanyan LS, Popugaeva EA. XXVII Symposium on Bioinformatics and Computer-Aided Drug Discovery. 2021. p. 58. (in Russia). http://way2drug.com/dr/download/BCADD/KamaryanVS_BCADD_2021-04-06.pdf.
[46] Filimonov DA, Lagunin AA, Gloriozova TA, Rudik AV, Druzhilovskii DS, Pogodin PV, et al. Prediction of the biological activity spectra of organic compounds using the pass online web resource. Chem Heterocycl Comp. 2014;50(3):444–57. doi: 10.1007/s10593-014-1496-1.
[47] Lipinski ChA. Lead- and drug-like compounds: the rule-of-five revolution. Drug Discovery Today Technol. 2004;1(4):337–41. doi: 10.1016/j.ddtec.2004.11.007.
[48] Vogt M, Bajorath J. ccbmlib – a Python package for modeling Tanimoto similarity value distributions. [version 2; peer review: 2 approved]. F1000 Res. 2020;10:9:Chem Inf Sci-100:1–14. doi: 10.12688/f1000research.22292.2.
[49] Chen SW, Chou CT, Chang CC, Li Y-J, Chen S-T, Lin I-Ch, et al. HMGCS2 enhances invasion and metastasis via direct interaction with PPARα to activate Src signaling in colorectal cancer and oral cancer. Oncotarget. 2017;8(14):22460–76. doi: 10.18632/oncotarget.13006.
[50] Xu X, Zhao P, Wang Z, Zhang X, Wu Z, Li W, et al. In silico prediction of chemical acute contact toxicity on honey bees via machine learning methods. Toxicol Vitro. 2021;72:105089. doi: 10.1016/j.tiv.2021.105089.
[51] Dovlatyan VV, Gomktsyan TA, Oganisyan MG, Khachatryan LA, Yengoyan AP. Synthesis of azinyloxypyridazinyl derivatives of oxy-acids and aryloxyethanols. Hayastani Kimiakan H (Chem J Armen). 2003;56(4):75–9. (Language: Russian).
[52] Dovlatyan VV, Gomktsyan TA, Oganisyan MG. (Azinyloxy)pyridazines. Hayastani Kimiakan H (Chem J Armen). 2003;56(4):68–74. (Language: Russian).
[53] Dovlatyan VV, Gomktsyan TA, Oganisyan MG, Yengoyan AP, Khachatryan LA. O-,N-Derivatives of azinyloxypyridazines. Hayastani Kimiakan H (Chem J Armen). 2003;56(1–2):96–101. (Language: Russian).
[54] Dovlatyan VV, Gomktsyan TA, Karapetyan AV, Yengoyan AP. Synthesis and some reactions of hydroxypyridazinone derivatives. Hayastani Kimiakan H (Chem J Armen). 2006;59(3):95–104. (Language: Russian).