SYNTHESIS EVALUATION AND QUANTUM MECHANICAL CHARACTERIZATION OF CYCLOHEXYLAMINE CONTAINING DERIVATIVES OF METHYLXANTHINE

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Abstract: The synthesis of methylxanthine derivatives could provide a sound approach to developing new analogues with similar or novel pharmacological profiles. The synthesis of six new compounds: two derivatives of 8-substituted-1,3,7-trimethylxanthine and four derivatives of 1-propyl-3,7-dimethylxanthine containing a cyclohexyl fragment, are presented. The structures were confirmed by elemental analyses using Furrier Transform Infrared Spectroscopy (FTIR) and Nuclear Magnetic Resonance (NMR) spectral data. The chemical reactivity of the new molecules was assessed, based on computed values for their electrophilicity index, molecular hardness, and chemical potential. The structures were identified as hard molecules, relatively inert to electrophilic attack, whereas Compound10d was outlined as the most prominent for accepting electrons.

Introduction

Xanthine derivatives are of great interest in terms of their various pharmacological activities, which allow for their application in therapy, mainly as psycho- and respiratory-analeptics, bronchodilators, and diuretics (Persson, 1985). Some asymmetrically substituted xanthines are useful for treating central nervous system (CNS) diseases such as Alzheimer's type dementia (Boehringer Ingelheim KG, 1995). The investigation of the structure-activity relationships for methylxanthines is one approach establishing the role of substituents in the emergence of different types of biological activity (Persson, 1985). Another approach in developing new analogueswith similar or novel pharmacologicalprofiles is the synthesis of methylxanthinederivatives.

In a number of cases, the mechanism of action of methylxanthines and their derivatives is complex, and not fully established. The most probable hypothesis connected with this is that it occurs through either concurrent inhibition of the adenosine receptors or inhibition of the enzyme phosphodiesterase (Daly, Butts-Lamb & Padgett, 1983; Daly,Padgett,& Shamim, 1986; Ride, Farghaly,& Ashour, 1977; Kakiuchi, Yamazaki, Teshima, Uenishi & Miyamoto, 1975; Faulds,Chrisp, & Buckley, 1991).

In the search for new compounds with improved bronchodilating properties and lowered toxicity, a quantitative structure-activity relationships (QSAR) study investigated a series of xanthine derivatives containing a cyclohexylamine fragment in the side chain, by applying the Optimized Approach Based on Structure Indices Set (OASIS; Mekenyan &Bonchev, 1986). For this, two new compounds were outlined, and these yielded the beginning of a series of new methylxanthine derivatives, possessing a cyclohexylamine fragment in the side chain at N1 and C8 positions (Mekenyan, Stoyanova, Kamenska, Davkov, & Peikov, 1993).

The aim of this study is to introduce a cyclohexylamine residue at N1 and C8 positions of the methylxanthines, and to evaluate the influence of these changes on certain physicochemical properties of the obtained structures. In order to achieve this, various derivatives of 1-substituted and 8-substituted methylxanthines were prepared and the syntheses thereof were investigated.

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Experiment

Chemistry

The necessary reagents were purchased from Fluktuierende Kaskade (FLUKA) and used without further purification. The corresponding melting points were measured in degrees Celsius (°C) and then corrected (Büchi 535). The Furrier Transform Infrared Spectroscopy FTIR spectra in the region 400–4000 cm^{-1} were recorded on a FT-IR Nicolet iS10 spectrophotometer in Nujol and the ^{1}H Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded at ambient temperature on a Bruker Avance DRX 250 (250 MHz) spectrometer in dimethylsulfoxide (DMSO$_d$). Chemical shifts were expressed as δ values in parts per million (ppm) against tetramethylsilane (TMS) as an internal reference; the coupling constants were expressed in Hertz (Hz). Analytical thin-layer chromatography (TLC) was used, performed on a DCAlufolien Kieselgel 60 F$_{254}$ (Merck; 0.20 mm sheets) using a mobile phase with volumetric parts of 25% ammonium hydroxide: acetone: chloroform: ethanol (1:3:3:4), detected at the ultraviolet (UV) wavelength, 254 nm. The yields were based on an analytically pure product and no effort was made to optimize the yields.

For synthesis of the necessary intermediates, the following is the list of the intermediates with the applied literary methods:

- Synthesis of 8-bromo-1,3,7-trimethylxanthine (Compound 2)

  Gagausov, Peikov, Davkov, & Sharankov (1987) proposed a method for synthesis of 8-bromo-methylxanthines, which was applied to obtain Compound 2 with specifications of a yield of 79% and melting point (mp; ethanol) 206–208 °C.

- Synthesis of 8-(2-hydroxyethylamino)-1,3,7-trimethylxanthine (Compound 4) and 8-(2-chloroethylamino)-1,3,7-trimethylxanthine (Compound 5)

  The Peikov,Zlatkov, Gagauzov, & Kalinkova (1990) method was applied to obtain Compounds4 and 5.

- Synthesis of 1-(3-chlorodopropyl)-3,7-dimethylxanthine (Compound 8) and 1-(3-iodopropyl)-3,7-dimethylxanthine (Compound 9)

  The needed halogen derivative was synthesized from the corresponding sodium salt of the initial theobromine, according to the methodology presented in Peikov,Sidzhakova,& Gagausov (1988).

For the synthesis of the new derivatives, the following lists the derivatives with the applied methods:

- Synthesis of 8-(N-methyl-N-cyclohexyl)-amino-1,3,7-trimethylxanthine (Compound 3)

  In a Kjeldahl flask, 0.01 mol of 8-bromo-1,3,7-trimethylxanthine and 0.01 mol of N-methylcyclohexylamine were mixed. This mixture was heated for 150 min at 100 °C. After cooling to room temperature, a glassy mass was obtained and this was further processed with acetone while heating. After cooling, crystals from the corresponding hydrobromide salt were obtained, which were further recrystallized from ethanol/acetone. The specifications included a yield of 2.6g (69%); IR (cm^{-1}): 1704 (ν C = 0),1668 (ν C = 0), 1602, 1545, and 1525 (ν C = C, ν C = N);^{1}H-NMR (DMSO$_{d6}$): 3.64 (s; 3H; CH$_3$ -7th position); 3.34 (s; 3H; CH$_3$ –Nth position); 3.17 (s; 3H; CH$_3$ -3rd position); and 1.11–1.76 (m; 11H; cyclohexyl);^{13}C NMR (DMSO$_{d6}$):δ 25.6 (C-5′), 26.7 (C-3′ and C-4′), 27.9, 29.6, 31.2 (C-2′ and C-6′), 33.0, 35.0, 57.6 (C-1′), 107.5 (C-5), 146.4 (C-4), 151.25 (C-2), 155.2 (C-6), and 156.5 (C-8);C$_{15}$H$_{23}$N$_5$O$_2$ (305.38); % calculated: C 59.00, H 7.59, and N 22.93; and % found: C 58.85, H 7.60, and N 22.85.

- Synthesis of 8-[2-(N-methyl-N-cyclohexyl)-aminoethyl]-1,3,7-trimethylxanthine (Compound 6)

  In a Kjeldahl flask, 0.01 mol of 8-(2-chloroethylamino)-1,3,7-trimethylxanthine and 0.01 mol of N-methylcyclohexylamine were mixed. This mixture was heated for 150 min at 100 °C. After cooling to room temperature, a glassy mass was obtained and this was further processed with acetone under heating. After cooling of the latter, crystals from the corresponding hydrobromide salt were obtained and these were further recrystallized with ethanol/acetone.

The specifications included a yield of 2.4g (71%); IR (cm^{-1}): 1707 (ν C = 0),1682 (ν C = 0), 1605, 1555, and 1525 (ν C = C, ν C = N);^{1}H-NMR (DMSO$_{d6}$): 3.64 (s, 3H, CH$_3$ -7th position); 3.34 (s; 3H; CH$_3$ -1^{sth} position); 3.17 (s; 3H; CH$_3$ -3rd position); and 1.11–1.76 (m; 11H; cyclohexyl);^{13}C NMR (DMSO$_{d6}$):δ 26.0 (C-5′), 25.0 (C-3′ and C-4′), 28.0, 31.9, 31.3 (C-2′ and C-6′), 37.4, 42.9, 54.8, 63.6 (C-1′), 108.3 (C-5), 147.2 (C-4), 151.2 (C-2), 154.8 (C-6), and 152.1 (C-8); C$_{17}$H$_{28}$N$_6$O$_2$ (348.48); % calculated: C 58.60, H 8.10, and N 24.12; and % found: C 58.45, H 8.02, and N 24.02.

- General procedure for the preparation of derivatives, 10a, 10b, 10c, and 10d, containing cyclohexylamine residue

An amount of 1-(3-iodopropyl)-3,7-dimethylxanthine (0.01 mol) and 0.01mol of the corresponding amine were mixed in a suitable round-bottom flask. The reaction mixture was heated at 100°C while stirring for 30 to 60 minutes, depending on the used amine. After cooling to room temperature, a glassy mass was obtained that was processed with acetone under heating. After cooling, crystals from the corresponding hydrogeniodine salt were obtained and these were further recrystallized with ethanol/acetone. The obtained structures were further elucidated with FTIR and ^{1}H-NMR analysis, and their purity was confirmed for their corresponding melting points and TLC-characteristics.

- Synthesis of 1-[3-(cyclohexylamino)-propyl)-3,7-dimethylxanthine (Compound 10a)

The specifications included a yield of 3.7g (60%); IR (cm^{-1}): 1703 (ν C = 0),1656 (ν C = 0), 1603, 1547, and1545 (ν C = C, ν C = N);^{1}H-NMR (DMSO$_{d6}$): 12.47 (s; 1H; NH); 7.61 (s; 1H; 8th position: xanth); 3.83 (d; 2H; N1-CH$_2$;J = 2.67 Hz); 3.74 (s; 3H; CH$_3$ -7th position); 3.32 (s; 3H; CH$_3$ -3rd position); 2.68 (d; 2H; N-CH$_2$;J = 2.67 Hz); 2.47 (q; 1H; 1^{sth} position: cyclohexyl-N); 1.87 (m; 2H; CH$_2$<u>CH$_2$</u>CH$_2$); 1.48 (m; 4H; 2nd and 6th position: cyclohexyl); 1.47 (m; 4H; 3rd and 5th position: cyclohexyl); and 1.35 (d; 2H; 4th position: cyclohexyl); ^{13}C NMR (DMSO$_{d6}$):δ 25.6 (C-5′), 26.1 (C-3′ and C-4′), 28.3, 28.6, 31.7 (C-2′ and C-6′), 31.5, 42.5, 45.1, 59.5 (C-1′), 107.8 (C-5), 142.5 (C-4), 143.8 (C-8), 155.3 (C-2), and 156.7 (C-6); C$_{16}$H$_{25}$N$_5$O$_2$ (319.41); % calculated: C 60.17, H 7.89, and N 21.93;and% found: C 59.95, H 7.77, and N 21.86.

- Synthesis of 1-[3-(N-methylcyclohexylamino)-propyl)-3,7-dimethylxanthine (Compound 10b)

The specifications included a yield of 2.5g (54%); IR (Nujol): 1707 (ν C = 0),1663 (ν C = 0), 1603, 1573, and 1520 (ν C = C, ν C = N);^{1}H-NMR (DMSO$_{d6}$): 7.61 (s; 1H; 8th position: xanth); 3.83 (d; 2H; N1-CH$_2$;J = 2.67 Hz); 3.74 (s; 3H; CH$_3$ -7th position); 3.32 (s; 3H; CH$_3$ -3rd position); 2.72 (d; 2H; N-CH$_2$;J = 2.67 Hz); 2.46 (q; 1H; 1^{sth} position: cyclohexyl-N); 2.24 (s; 3H; N-CH$_3$); 1.93 (m; 2H; CH$_2$<u>CH$_2$</u>CH$_2$); 1.58 (m; 4H; 2nd and 6th position: cyclohexyl); 1.48 (m; 4H; 3rd and 5th position: cyclohexyl); and 1.36 (d; 2H; 4th position: cyclohexyl); ^{13}C NMR (DMSO$_{d6}$):δ 25.9 (C-5′), 24.9 (C-3′ and C-4′), 26.3, 30.2, 31.4 (C-2′ and C-6′), 31.5, 42.5, 43.0, 52.8, 65.8 (C-1′), 107.9 (C-5), 142.5 (C-4), 147.3 (C-8), 155.2 (C-2),and156.5 (C-6); C$_{17}$H$_{27}$N$_5$O$_2$ (333.43); % calculated: C 61.24, H 8.16, and N 21.00; and % found: C 60.96, H 8.00, and N 20.87.

- Synthesis of 1-[3-(N-ethylcyclohexylamino)-propyl)-3,7-dimethylxanthine (Compound 10c)
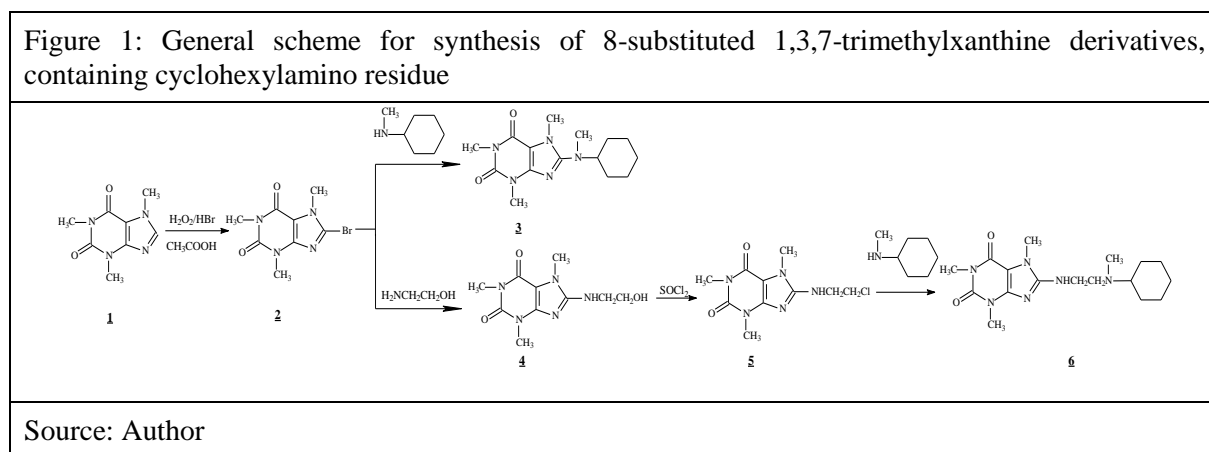
The specifications included a yield of2.3g (49%); IR (cm^{-1}): 1703 (ν C = 0),1654 (ν C = 0), 1600, 1542, and 1507 (ν C = C, ν C = N);^{1}H-NMR (DMSO$_{d6}$): 7.61 (s; 1H; 8th position: xanth); 3.83 (d; 2H; N1-CH$_2$;J = 2.67 Hz); 3.74 (s; 3H; CH$_3$ -7th position); 3.32 (s; 3H; CH$_3$ -3rd position); 2.77 (d; 2H; N-CH$_2$;J = 2.67 Hz); 2.72 (m; 2H; N-<u>CH$_2$</u>CH$_3$); 2.47 (q; 1H; 1^{sth} position: cyclohexyl-N); 1.93 (m; 2H; CH$_2$<u>CH$_2$</u>CH$_2$); 1.64 (m; 4H; 2nd and 6th position: cyclohexyl); 1.49 (m; 4H; 3rd and 5th position: cyclohexyl); and 1.35 (d; 2H; 4th position: cyclohexyl); ^{13}C NMR (DMSO$_{d6}$):δ 11.5, 26.0 (C-5′), 25.5 (C-3′ and C-4′), 28.3, 30.1 (C-2′ and C-6′), 30.7, 31.5, 42.9, 46.3, 52.9, 67.4 (C-1′), 107.9 (C-5), 142.5 (C-4), 143.7 (C-8), 155.3 (C-2), and 156.7 (C-6); C$_{18}$H$_{29}$N$_5$O$_2$ (347.46); % calculated: C 62.22, H 8.41, and N 20.16; and % found: C 62.05, H 8.33, and N 20.08.

- Synthesis of 1-[3-(N,N-dicyclohexylamino)-propyl)-3,7-dimethylxanthine (Compound 10d)

The specifications included a yield of 2.2g (42%); IR (cm^{-1}): 1699 ($\nu C = 0$), 1652 ($\nu C = 0$), 1600, 1571, and 1550 ($\nu C = C$, $\nu C = N$); ^{1}H-NMR (DMSO$_{d6}$): 7.60 (s; 1H; 8th position: xanth); 3.84 (d; 2H; N1-CH$_2$; J = 2.67 Hz); 3.73 (s; 3H; CH$_3$ -7th position); 3.32 (s; 3H; CH$_3$ -3rd position); 2.90 (d; 2H; N-CH$_2$; J = 2.67 Hz); 2.48 (q; 2x1H; 1^{sth} position-cyclohexyl-N); 1.94 (m; 2H; CH$_2$CH$_2$CH$_2$); 1.65 (m; 2x4H; 2nd and 6th position: cyclohexyl); 1.48 (m; 2x4H; 3rd and 5th position: cyclohexyl); 1.35 (d; 2x2H; 5th position: cyclohexyl); and 0.99 (m; 3H; N-CH$_2$CH$_3$); ^{13}C NMR (DMSO$_{d6}$): δ 26.0 (C-5′ and C-5″), 25.1 (C-3′, C-3″, C-4′, and C-4″), 28.3, 31.2, 32.4 (C-2′, C-2″, C-6′, and C-6″), 43.1, 49.5, 65.1 (C-1′ and C-1″), 107.8 (C-5), 142.5 (C-4), 143.8 (C-8), 155.2 (C-2), and 156.7 (C-6); C$_{22}$H$_{35}$N$_5$O$_2$ (401.55); % calculated: C 68.81, H 8.79, and N 17.44; and % found: C 68.85, H 8.68, and N 17.05.

Results and Discussions

The targeted 8-substituted derivatives of 1,3,7-trimethylxanthine, containing a cyclohexylamino residue (Compounds 3 and 6) were obtained from 8-bromocaffeine using the literary method in Gagausov and associates (1987), and according to the scheme given below (Figure 1):

Figure 1: General scheme for synthesis of 8-substituted 1,3,7-trimethylxanthine derivatives, containing cyclohexylamino residue

Source: Author

The amination of 8-bromocaffeine ((2), Figure 1) with the corresponding amino alcohol was carried out at temperature of 130°C, in the absence of solvent, with the reaction time established as 15–25 min. The running of the process was followed by TLC control until exhaustion of the reagents. This method ensured high yields of the obtained 8-(hydroxyethyl)-aminocaffeine ((4), Figure 1). The isolated caffeine derivative was processed with thionyl chloride to obtain the corresponding halogen derivative ((5), Figure 1), which further interacted with the chosen cyclohexylamine to produce the target derivative ((6), Figure 1). The reaction ended with close to quantitative yields.

The next synthetic scheme (Figure 2) represents the synthesis of the cyclohexylamino containing derivatives of 1-propyl-3,7-dimethylxanthine, 10a, 10b, 10c and 10d, as follows:

Figure 2: General scheme for synthesis of derivatives of 1-propyl-3,7-dimethylxanthine, containing a cyclohexylamino residue

Source: Author
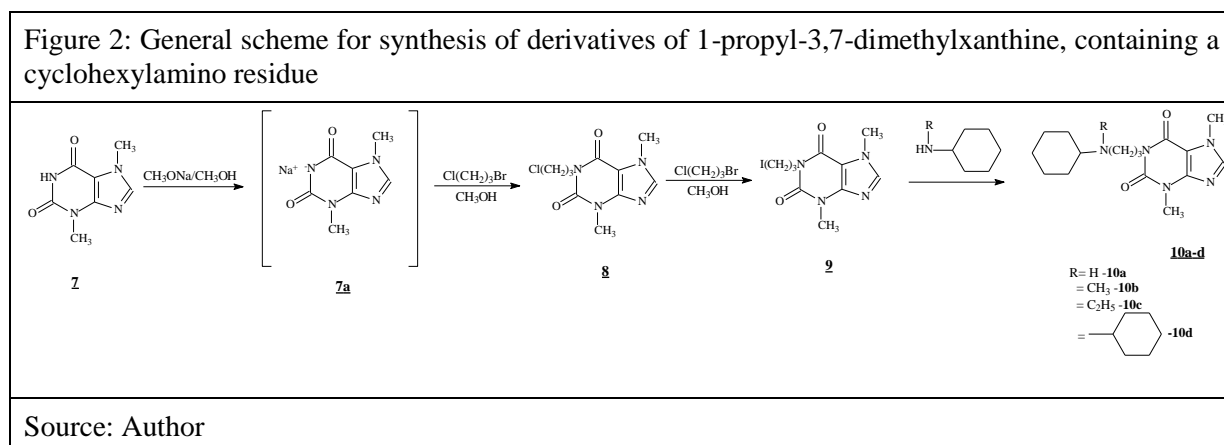
The chemical structures and certain physicochemical properties of the studied N1 or C8 substituted derivatives are presented in Table 1.

Table 1: Chemical structures and certain physicochemical properties of the obtained N1 or C8 substituted derivatives

Compound ID	R	Molecular weight (g/mol)	Melting point (ºC)	Yield (%)
3	CH$_3$	305.38	132–133	69
6	CH$_3$	348.48	161–162	71
10a	H	319.41	214–217	60
10b	CH$_3$	333.43	190–193	54
10c	C$_2$H$_5$	347.46	188–189	49
10d	cyclohexyl	401.55	180–183	42

Source: Author

As the melting point of theobromine is 357 ºC, it became apparent that this temperature declined when the substituent was at position N1, whereas the presence of the alkyl group in the N-atom of the side chain led to a larger decrease in the melting points of the corresponding compounds,10b and10c. The length of this alkyl residue had no significant influence on the value of the decrease.

Considering the melting point of caffeine is 238 ºC, similar observations to those stated above can be made for caffeine. Since there was an apparent decline in the temperatures for derivatives, Compounds 3 and 6 in the presence of a longer alkyl side chain at C8, led to a lower decrease in the melting point. These effects may be explained by the dependence of the corresponding polarity of the "R" substituent (Avadanei et.al., 2011).

The obtained compounds were characterized by microanalyses using FTIR and NMR spectrometry, and the results were consistent with those for the examined structures 3, 6, 10a-d.

The IR spectra of the obtained 1-propyl-3,7-dimethylxantheine and 8-substituted 1,3,7-trimethylxanthine derivatives, which contained a cyclohexyl residue in the region 4000cm^{-1} to 400cm^{-1}, exhibited several characteristic bands. The absorption bands 3555–3267cm^{-1} are ascribable to symmetrical and anti-symmetrical stretching vibrations of NH groups, presented in the spectra of the studied derivatives containing a cyclohexylamino residue. Complex and broad bands, in the region 3100–2810cm^{-1}, were observed in the spectra of the studied compounds. These bands were assigned to the out-of-plane and in-plane asymmetric and symmetric CH$_2$ and CH$_3$ stretching vibrations, respectively. These assignments appeared due to the incorporated cyclohexyl substituents and are supported in literary data (Silverstein, 1981). The two strong bands at 1652 – 1703cm^{-1} were ascribed to stretching vibrations of two carbonyl groups in the xanthine ring. The band of bending vibration of NH – group (amide II) was in the 1603–1549cm^{-1} region where stretching vibrations of C^4=C^5 and C^8=N^9 bands from the xanthine ring appear, though appearing stronger than these latter bands. The absorption bands at about 1377cm^{-1} were ascribed to skeletal vibrations of xanthine ring. Our investigations showed that the stretching vibrations of C=N and C–N bonds had the greatest contribution to these vibrations. Three bands of absorption were observed in this region of the spectra of the studied compounds, and may be due to the solid–state effects (Czuchajowski & Eckstein, 1967).

The ^{1}H and ^{13}C-NMR data determined the proposed structures of the investigated compounds.

In an attempt to establish dependencies between the molecular geometry, i.e., the calculated electro-optical parameters and the compound's structure, the synthesized compounds were subjected to theoretical analysis. The full optimization of the molecular geometry of the studied structures was performed with the program VEGAZZ ver. 3.0.1.22 (http://nova.colombo58.unimi.it/) using PM7 semi empirical method (Stewart, 2013).

The obtained computed values for certain molecular parameters are shown on Table 2.

Table 2: Computed molecular parameters for the new compounds

Properties \ Compound	3	6	10a	10b	10c	10d
Total energy (E) (kcal/mol)	-90203	-102472	-93808	-97386	-100979	-114708
Dipole moment (p) (D)	4.196	4.401	4.009	3.568	2.976	3.141
HOMO (eV)	-8.775	-8.707	-8.950	-8.658	-8.810	-8.586
LUMO (eV)	-0.253	-0.260	-0.341	-0.377	-0.362	-0.323
Surface area ($Å^2$)	521.27	601.18	581.07	554.93	584.45	661.47
Volume ($Å^3$)	891.37	1032.38	974.96	975.90	1026.09	1171.28
Hidration energy (HE) (kcal/mol)	0.54	-1.31	-2.02	-0.57	-0.25	-0.08
Log P	1.40	1.02	0.19	0.56	0.90	2.14
Refractivity (R) ($Å^3$)	83.96	96.69	88.61	93.91	98.65	114.92
Polarizability (α) ($Å^3$)	32.29	37.32	34.13	35.97	37.80	44.37
Mass (amu)	305.38	348.45	319.41	333.43	347.46	401.55

Source: Author

A graphical representation of the deviation in the highest occupied molecular orbital (HOMO) values (eV), computed by HyperChem 8.0.6, is given in Figure 3. The presence of a secondary N-atom in the structure of Compound 10a yielded the lowest HOMO value, and this indicated it was the most stable compound. However, the highest HOMO energy values were observed with substitution in the N-atom with alkyl-and cycloalkyl substituents, whereas the highest HOMO value was observed with Compound10d, containing dicyclohexylamine residue.

Figure 3: Computed value of highest occupied molecular orbital HOMO (eV) for the studied compounds
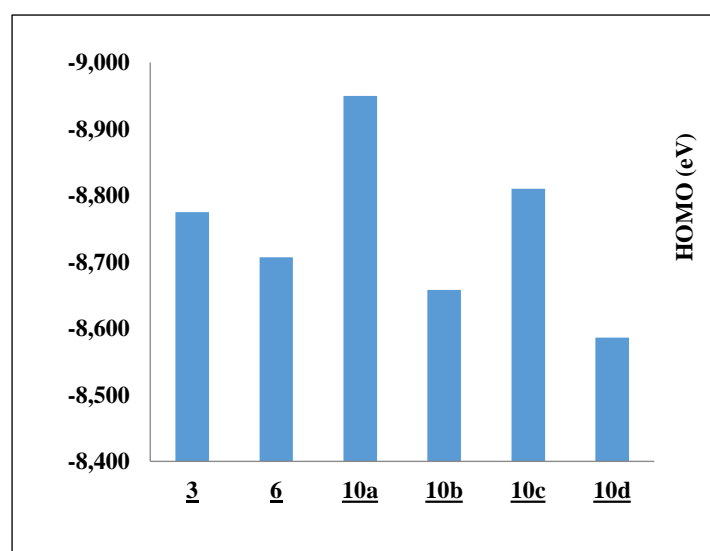

3: 8-(N-methyl-N-cyclohexyl)-amino-1,3,7-trimethylxanthine
6: 8-[2-(N-methyl-N-cyclohexyl)-aminoethyl]-1,3,7-trimethylxanthine
10a: 1-[3-(cyclohexylamino)-propyl)-3,7-dimethylxanthine
10b: 1-[3-(N-methylcyclohexylamino)-propyl)-3,7-dimethylxanthine
10c: 1-[3-(N-ethylcyclohexylamino)-propyl)-3,7-dimethylxanthine
10d: 1-[3-(N,N-dicyclohexylamino)-propyl)-3,7-dimethylxanthine

Source: Author

Certain dependencies of the calculated and presented parameters from the chemical structure and electronic characteristics of the compounds were identified (Table 2). A linear dependency of the computed total energy from the polarizability was established, as presented on Figure 4. It was observed, that the basicity of the N-atom in the side chain of the substituent, at Position 8 in the 1,3,7-thrimethylxantine core, had a strong influence on this dependency, while its strong increase or decrease led to deflections from the linearity.

Figure 4: Computed value of total energy (kcal/mol) vs molecular polarizability for the studied compounds

$y = -0,0213x - 0,2281$
$R^2 = 0,8664$
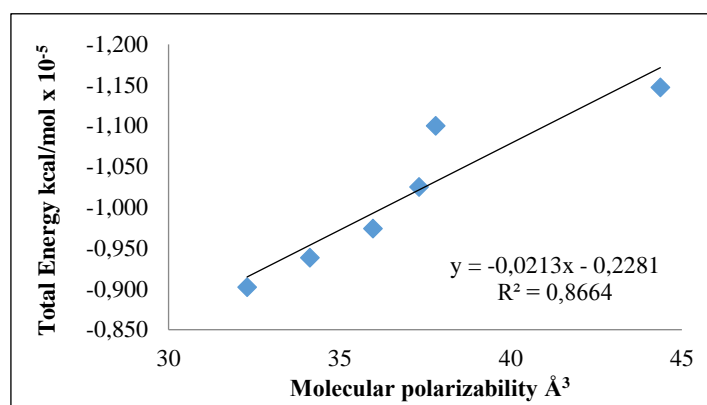
Source: Author

The proposed model was sound, considering the value of the R^2 was close to 1.

Some molecular parameters for the newly synthesized derivatives, like electrophilicity index, chemical potential and molecular hardness, were computed using data in Table 2 to assess their chemical reactivity. The obtained values are presented in Table 3.

Table 3: Chemical potential, hardness, and electrophilicity index of the compounds estimated using data from Table 2

Compound	HOMO	LUMO	$\Delta_{HOMO-LUMO}$	μ	η	s	ω
3	-8.775	-0.253	8.522	-4.51	8.52	0.50	1.20
6	-8.707	-0.260	8.447	-4.48	8.45	0.50	1.19
10a	-8.950	-0.341	8.609	-4.65	8.61	0.50	1.25
10b	-8.658	-0.377	8.281	-4.52	8.28	0.50	1.23
10c	-8.810	-0.362	8.448	-4.59	8.45	0.50	1.24
10d	-8.586	-0.323	8.263	-4.45	8.26	0.50	1.20

HOMO: highest occupied molecular orbital
LUMO: lowest unoccupied molecular orbital

Source: Authors

The electrophilicity index (ω) is a useful descriptor, which represents the tendency of a molecule to accept electrons and is defined by the following equation:

$$\omega = \frac{\mu^2}{2\eta} \qquad (1)$$

where ω is the electrophilicity index; μ is the chemical potential and η is the hardness.

High values of μ and ω establish the molecule as a strong electrophile, while low values of μ and ω identify it as a strong nucleophile (Srivastava et.al., 2012).

The calculated ω values for the elucidated compounds were comparable, indicating all molecules had equal capacity to absorb electrons.

Another informational descriptor for the chemical reactivity of a molecule is the chemical potential (μ). In the present work, μ was calculated, using the formula:

$$\mu = \frac{HOMO+LUMO}{2} \qquad (2)$$

where μ is the chemical potential, HOMO stands for the highest occupied molecular orbital and LUMO stands for the lowest unoccupied molecular orbital.

The obtained values followed the tendency expressed for the electrophilicity index and confirmed the comparability in the potency of the newly synthesized 1-propyl-3,7-dimethylxanthines or 8-substituted 1,3,7-trimethylxanthines containing a cyclohexyl residue to accept electrons.

The hardness (η) is a direct measure of the electrophilic stability of the molecule and is defined by the equation (3):

$$\eta = \frac{LUMO-HOMO}{2} \qquad (3)$$

This parameter indicates the resistance of the molecule to charge transfer. In general, a molecule with a high value of η, will show an inert characteristic of electrophilic attack (Ayres & Parr, 2000). The descriptor that is opposite in meaning, the softness (*s*), is described by the equation (4):

$$s = \frac{1}{2\eta} \qquad (4)$$

which measures the tendency of a charge transfer. Therefore, a molecule with a low value of *s* is expected to be stable under electrophilic attack. Thus, the computed η and *s* values for the discussed structures determine the ability of a compound to attract electrons (Srivastava et.al., 2015). The obtained results for the ability of the discussed structures to attract electrons are in order 10a > 3 > 6 = 10c > 10b > 10d, showing Compound 10d as most prominent.

The HOMO/LUMO gap is a measurement of the redox potential and has been used to determine the bioactivity of the intramolecular charge transfer (Arivazharan & Senthil Kumar, 2012). According to this approach, the lower negative HOMO energies and the negative values of the LUMO energies correspond to compounds with reductive properties. A large value of the gap refers to large excitation energies and is characteristic of "hard" molecules. This study's results for the hardness (η) indicated the studied compounds can be accepted as hard molecules.

Conclusion

Six new derivatives of 1-propyl-3,7-dimethylxanthine and 8-substituted 1,3,7-trimethylxanthine containing a cyclohexylamino residue, were synthesized.The obtained molecules were characterized by microanalyses, using FTIR and NMR spectrometry, and the results were consistent with the assigned structures. The chemical reactivity of the obtained compounds was assessed, using molecular parameters, such as the electrophilicity index, chemical potential, and molecular hardness. The results indicate that all molecules had equal capacity to absorb electrons, while Compound 10d (1-[3-(N, N-dicyclohexylamino)-propyl)-3,7-dimethylxanthine) was the most prominent in accepting electrons. All structures may be considered as hard molecules, relatively inert to electrophilic attack.

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