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SPECTRAL AND QUANTUM-MECHANICAL CHARACTERIZATION OF 7-[2-HYDROXY-3(-4-ACETYL-AMINO)-PHENOXY-PROPYL]-1,3 DIMETHYL XANTHINE DERIVATIVES

M. AVADANEI[*a], MIHAELA DULCESCU[b], LENUTA PROFIRE[c], VIRGIL BARBOIU[a]
DANA-ORTANSA DOROHOI[a,b]
[a]*"Petru Poni" Institute of Macromolecular Chemistry, 41A Grigore Ghica Voda Alley, Iasi, RO-700487, Iasi, Romania*
[b]*"Alexandru Ioan Cuza" University, Faculty of Physics, 11 Carol I Blv, Iasi, RO-700506, Romania*
[c]*"Gr.T. Popa" Medicine and Pharmacy University, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, 16 University Street, RO 700115, Iasi, Romania*

In the search of improving the pharmacological properties of theophylline in the field of the bronchodilatory action, five new theophylline derivatives have been synthesized, starting from 8-substituted theophylline and a paracetamol derivative. The variety of radicals used as substituents, such as hydrogen, bromo, nitro, pyrrolidinyl, piperidinyl and morpholinyl has lead to different behavior of the obtained compounds as concerning the tracheal smooth muscle relaxation. The chemical structure was investigated by means of FTIR and ^{1}H-NMR spectroscopy. The optimized geometry and the electro-optical characteristics have been determined using quantum chemical calculations in AM1 approximation. The infrared spectral characteristics were compared to those obtained through computational approaches. The energetic characteristics of the compounds under study are relevant for both their chemical reactivity and biological action.

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Keywords: Xanthine derivatives; Optimized molecular geometry; Electro - optical parameters; NMR spectra; Infrared spectra

1. Introduction

Xanthine (3,7-dihydro-purine-2,6-dione) is a purine base found in most human body tissues and fluids. The poly-substituted xanthines, collectively known as xanthenes, are a group of alkaloids commonly used for their effects as mild stimulants and as bronchodilators, notably in treating the symptoms of asthma. Active compounds of the xanthines type at the level of the central nervous [1-3], of the cardio – vascular [4-7] and the broncho – pulmonary systems [8-10] are known. Recently, actions of xanthines were evidenced at the level of the endocrine glands, the reproduction apparatus or at the gastro – intestinal tract [11-13]. The pharmacological activity of xanthine derivatives depends on both the substitution site and the chemical structure of the substituent. Thus, substitution at the 8-position of the purine ring has shown to dramatically increase the binding affinity to the human adenosine receptors subtypes [14-17]. The 1,3-substituted xanthines are used as stimulants, phosphodiesterase inhibitors [18-19], as anti-

[*]Corresponding author: mavadanei@icmpp.ro

asthmatic drugs [20] or adenosine receptors antagonists [21]. One of the most prominent members of this class is theophylline (1,3-dimethylxanthine) whose bronchodilator action has been used in treating the acute and chronic asthma [20], [22] and the vascular diseases [21], and it behaves as a very efficient immunomodulatory [23] and anti-inflammatory drug [24]. However, there are adverse effects associated with theophylline's use, such as tachycardia, agitation and occasionally seizures [25], as well as the central nervous system stimulation and gastric acid hyper secretion [26].

The improvement of theophylline properties continues to be a subject of intense research, originating in the need of enlarging the clinical applications and the library of its derivatives and, in addition, of counterbalancing its side effects. In our study, the 8-substituted theophyllines have been used as precursors in the preparation of new and selective bronchodilators, with enhanced effects than the parent drug. This task was accomplished by reaction with a paracetamol derivative, which is epoxy-propyl-acetaminophen. In such way, the special properties of theophylline are combined with the antipyretic, analgesic and anti-inflammatory effects of the acetaminophen [27-30]. The structural modifications of these new 7-[2-hydroxy-3-(4-acetyl-amino)-phenoxy]-propyl]-theophylline derivatives were obtained by varying the substitution on the 8-position of the purine ring. The alteration of the chemical structure was investigated by FTIR and ^{1}H-NMR spectroscopy. The spectral properties were used in conjunction with quantum chemical calculations of the geometry and electro-optical properties in order to obtain a complete characterization of these newly obtained compounds.

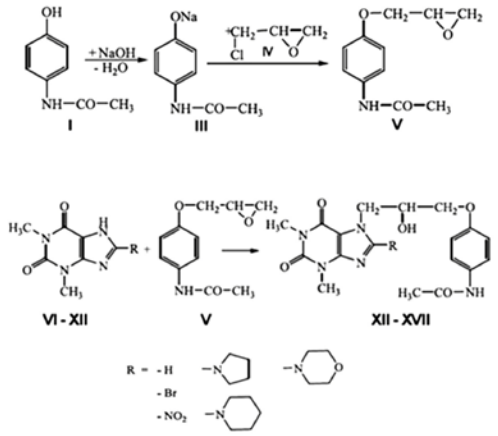
2. Experimental

2.1. Chemistry

Theophylline, epichlorhydrin, sodium hydroxide and acetaminophen were purchased from the Aldrich Chemical Company and used without further purification. Melting points were recorded with a Pyrus Diamond DSC model power-compensated differential calorimeter (Perkin Elmer). Infrared spectra were measured on a Bruker Vertex 70 FTIR spectrometer, using the KBr disk technique. A minimum of 32 scans were signal-averaged at a spectral resolution of 2 cm^{-1}. The ^{1}H-NMR spectra were acquired in DMSO-d_5 on a Bruker Advance DRX 400 spectrometer, operating at 400 MHz.

2.2. Synthesis

The designed compounds are the 8-substituted theophylline bearing in the 7-position an acetaminophen moiety linked *via* hydroxyalkyl chain. According to our previously described method [31–33], the synthesis of 8-substituted 7-[2-hydroxy-3-(4-acetyl-amino)-phenoxy-propyl)-l,3-dimethyl-xanthine derivative was performed in three stages (Scheme 1). In the first stage, the p-hydroxy-acetanilide (paracetamol, (I)) was turned into phenoxy form (III) in alkaline medium. The second stage is the reaction of phenoxy form (III) with epichlorhydrin (IV). The reaction mixture was stirred at room temperature for 16 hours. It was obtained a white precipitate that was separated by vacuum filtration and then it was washed with water. Recrystallization from ethanol gave 7-(2,3-epoxy-propyl-oxy-acetanilide) (V) (paracetamol derivative) as a white solid compound, m.p. 116-117°C. In the third stage, the 7-(2,3-epoxy-propyl-oxy-acetanilide (V) reacts in mild conditions at the ethyl alcohol boiling temperature with the 8-substituted theophyllines (where the radicals are hydrogen, bromo, nitro, pyrrolidinyl, piperidinyl and morpholinyl) (VI-XII). The reaction mixture was heated under reflux for 10 h and then the solvent was removed by distillation under reduced pressure to ¼ from initial volume. The rough products were separated by filtration under vacuum, dried and recrystallized from ethanol, yielding the theophylline derivatives XII-XVII.



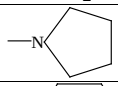
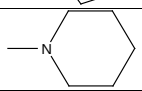
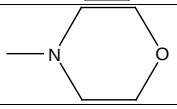
Scheme 1. The synthetic route to the 8-substituted theophyllines

3. Results and discussions

3.1. Thermal analysis

The chemical structures and the physico-chemical properties of the studied theophylline derivatives are presented in Table 1. As the melting temperature of theophylline is 274°C [31], this point dropped by substitution in the 7-position down to 204°C. The substitution of various R radicals on the 8-position influenced the melting point of the studied compounds, depending on the R-substitute polarity.

Table 1. Structure, molecular weight and melting point of the studied theophylline derivatives

Compound code	R	Molecular weight (g/mol)	Melting point (°C)
-H	XII	387.41	204
-Br	XIII	466.31	219
$-NO_2$	XIV	432.41	208
	XV	456.46	267
	XVI	470.53	231
	XVII	472.51	220

The atoms of the compound XII are indexed as in Fig.1.

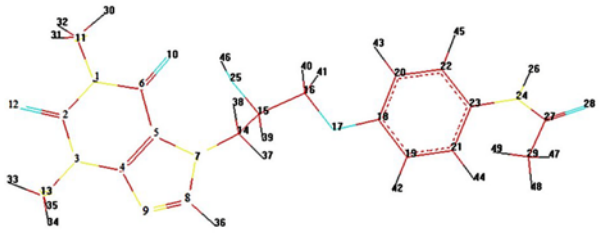


Fig. 1. The spatial configuration of compound XII (C – red, N- yellow, H – black, O – blue)

3.2. FTIR analysis

FTIR and ^{1}H-NMR spectroscopy have been used for characterizing the imidazole ring substitution, that is to say the spectra of the 8-substituted-7-hydroxy-3-(4-acetyl-amino)-phenoxy-propyl]-l,3-dimethyl-xanthine derivatives (XIII – XVII) were compared with those of the unsubstituted molecule (XII). In spectral investigation, the structural features of the analyzed species could be divided into xanthine core modes, the modes arising from 2-hydroxy-3(-4-acetyl-amino)-phenoxy-propyl radical substituted at the 7-position and those belonging to the groups substituted on the 8-position, respectively.

The recorded FTIR spectra of the compounds XIII – XVII are presented in Fig. 2 in comparison with the parent compound, XII. The FTIR spectrum of XII has been analyzed on the analogy of that of caffeine, having the 1,3,7 – substituted purine ring in common with it.

The high frequency region, 3700 – 2700 cm^{-1}, is associated with stretching vibrations of the type ν(OH) (around 3400 cm^{-1}), ν(NH) (3320 cm^{-1}), ν(=C-H) (3160 – 3020 cm^{-1}), ν(CH_2) and ν(CH_3) (3000 – 2800 cm^{-1}) from the 2-hydroxy-3(-4-acetyl-amino)-phenoxy-propyl radical. The ν(=C-H) (imidazole) at 3122 cm^{-1} and ν(CH_3), observed at 2949 cm^{-1}, are related to the purine ring. In the mid-frequency region, the dominant features are carbonyl absorptions, whose assignments in the caffeine spectrum are well established [34-35].

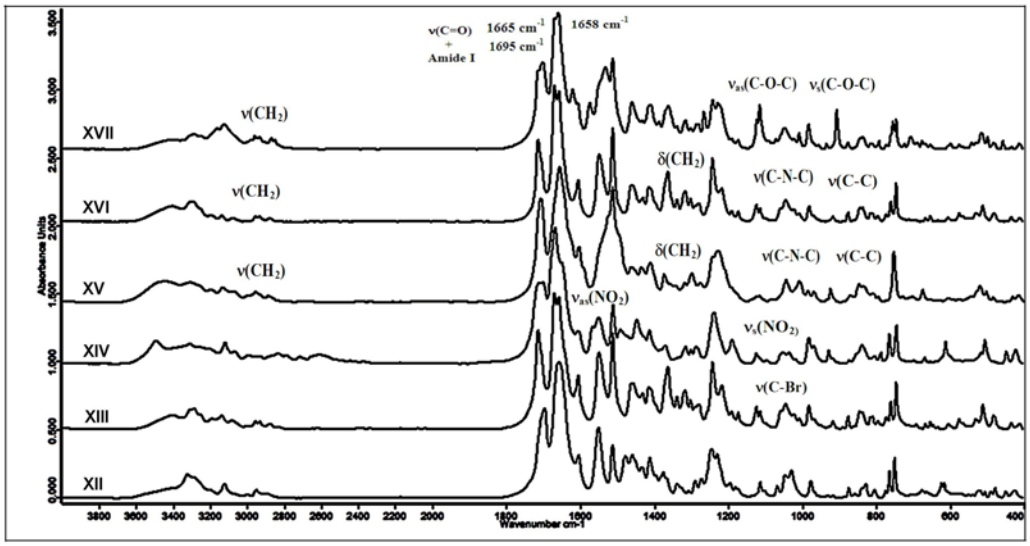


Fig. 2. FTIR spectra of the studied 8-substituted theophyllines; Comparison between the spectra of the parent compound, XII, and its derivatives, XIII – XVII

The asymmetric stretching vibration of the isolated C_2=O_{12} group occurs at 1695 cm^{-1}, while the absorption band at 1658 cm^{-1} is due to the stretching vibration of conjugated carbonyl C_6=O_{10} Fig. 2 (XII). It is to be noted that the latter absorption is split in two, due to the presence of the amide I band in the 2-hydroxy-3(-4-acetyl-amino)-phenoxy-propyl radical at 1665 cm^{-1}. In the 1615 – 1400 cm^{-1} domain, medium to strong bands (due to the imidazole, pyrimidine and phenyl ring stretching (ν(C=C) and ν(C=N)), respectively) are observed at 1549, 1511, 1477 and 1411 cm^{-1}. Additionally, the ν(C=C) from the phenoxy moiety is seen at 1603 cm^{-1} and the amide II band is overlapped by the purine ring stretching at 1549 cm^{-1}.

The methyl asymmetric bending vibration is responsible for the bands at 1477, 1458, 1432 and 1411 cm^{-1}, with contributions from methylene scissoring and also imidazole and phenyl ring stretching. Within 1400 – 900 cm^{-1}, medium bands are observed due to CH_3 symmetric bending (1368 cm^{-1}) and rocking (1288, 1228, 1194, 1066 cm^{-1}), with contributions from the C-N stretching and bending modes in pyrimidine – imidazole fused rings and phenyl, as well as the CH_2 twisting and asymmetric and symmetric stretching ν(=C-O-C=$_{ring}$) (1244 and 1112 cm^{-1}) in aromatic ether group, respectively. The bands bellow 900 cm^{-1} represent the in-plane and out-of-

plane deformations occurring in pyrimidine, imidazole and phenyl rings, some of them involving simultaneous vibrations of these rings, in addition to C=O deformation and CH_2 rocking. The band at 837 cm^{-1} may arise from the in-plane deformation in pyrimidine ring, while the absorption at 749 cm^{-1} could be attributed to the in-plane deformation in pyrimidine and imidazole rings. The splitted band with maxima at 622 and 615 cm^{-1} describes the imidazole ring out-of-plane bending; therefore it could be sensitive to substitution.

From the comparison of the FTIR spectra before and after substitution in the 8-position, several remarks could be drawn. The addition of a group in the place of the H atom does affect the imidazole ring vibrations and bring about new absorptions. Spectral changes are noticed by the disappearance of the various bands assigned to the un-substituted compound, XII, the most significant being that of the splitted band centered at 620 cm^{-1}, for all the FTIR spectra of the XIII – XVII compounds. In the spectra of XIII (Fig. 2 (XIII)), an additional band assigned to =C-Br stretching vibration appears at 1058 cm^{-1}. The nitro group in XIV (Fig. 2 (XIV)) showed up as two absorption bands at 1566 and 1315 cm^{-1}, which could be attributed to the asymmetric and symmetric =C–NO_2 stretching vibrations [36].

By introducing a pyrrolidine ring in the place of H_{36}, the compound XV is obtained and its spectra presents the CH_2 stretching at 2886 cm^{-1}, and weaker bands attributed to C-N-C stretching at 1316 cm^{-1}, C-C stretching at 1007 cm^{-1} and ring vibration at 923 cm^{-1}, respectively (Fig. 2 (XV)) [37].

The FTIR spectrum of the pyrrolidine – substituted species (Fig. 2 (XVI)) is similar to that of piperidine – substituted compound, XVI, due to the resemblance of their structures. The CH_2 stretching vibrations can be observed at 2940 (asymmetric) and 2853 cm^{-1} (symmetric), while the scissoring CH_2 vibration overlaps that attributed to methyl asymmetric bending and contributes to its enhancement. The bands at 1353 and 1298 cm^{-1} may originate from wagging and twisting CH_2 modes, respectively. The C-N-C stretching is located at 1315 cm^{-1} and the C-C stretching appears at 933 cm^{-1}.

In the FTIR spectrum of XVII (Fig. 2 (XVII)), the ring stretching vibration (mainly asymmetric ν(C-O-C)) in morpholinyl is observed at 1112 cm^{-1} [38] and the intense peak at 906 cm^{-1} is attributed to the symmetric ν(C-O-C).

In addition to the observed changes in the FTIR spectra, which validate the substitution on C_8, one may notice the asymmetry of the ν(C_2=O_{12}) band at 1695 cm^{-1}, with a shoulder near 1703 cm^{-1}. Studies on caffeine and caffeine hydrates have shown that the purine ring have a planar conformation [39] and could be involved in intermolecular hydrogen bonds of the type C_8H_{36} ••• O_{12} [40] or in stacking associations by interplanar interactions [41]. These interactions are affecting directly the intensity and the position of the isolated carbonyl bond, therefore the frequency of the ν(C_2=O_{12}) is decreasing by 20 cm^{-1} by intermolecular bonding [33-35] and is shifting to higher frequencies as a result of self – association [41].

The ν(C_2=O_{12}) is evident at 1693 cm^{-1} in non-associated caffeine and is found in our study at 1695 cm^{-1} for the parent compound XII. The FTIR spectra of the studied species XII – XVII show the shoulder near 1703 cm^{-1}. In the case of pyrrolidine – substituted xanthine XV, the ν(C_2=O_{12}) is shifted to 1705 cm^{-1}. The substituted species XIII – XVII resulted from replacing the H_{36} (see Fig. 1) and the ν(C_2=O_{12}) undergoes an upshift, so the intermolecular bonding is ruled out. The presence of the second band in the ν(C_2=O_{12}) absorption seems to suggest the self-association of the molecules XIII – XVII, but further studies are needed.

3.3. ^{1}H-NMR analysis

Figure 3 shows the ^{1}H-NMR spectra of the un-substituted compound XII and its 8-substituted derivatives, XII – XVII. The spectrum of XII (Fig. 3 (XII)) exhibits a multiplet in the region 3.9 – 4.5 ppm due to the protons in the epichlorhydrin fragment from the 2-hydroxy-3(-4-acetyl-amino)-phenoxy-propyl moiety. The acetanilide fragment presents the proton resonances from the methyl group at 2.02 ppm (singlet) and that from the amide at 9.806 ppm (singlet), besides the two doublets observed at 6.9 and 7.48 ppm, which are assigned to the aromatic ring protons. The two singlets at chemical shifts of 3.40 and 3.169 ppm belong to the protons of the 1-

and 3- methyl groups in purine ring, respectively. The singlet peak at 7.99 ppm due to the imidazole H_{36} proton in XII is absent in its derivatives XIII – XVII, thus indicating the substitution.

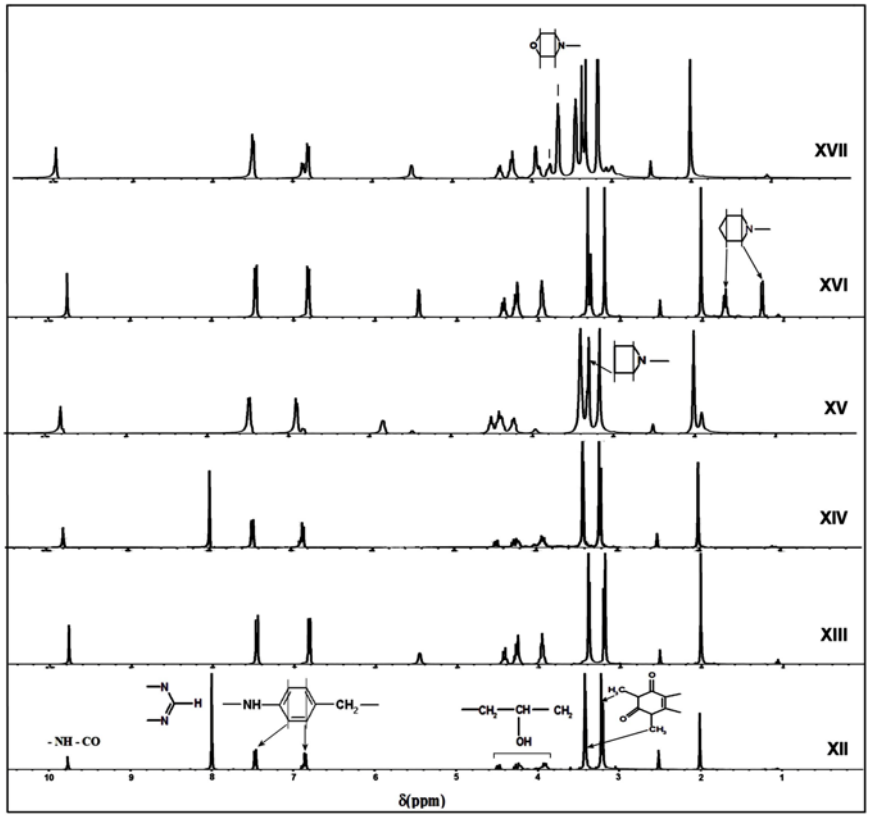


Fig. 3. ^{1}H-NMR spectra of the studied compounds

In the ^{1}H-NMR spectra of the 8-derivative xanthines, all the peaks originating from 2-hydroxy-3(-4-acetyl-amino)-phenoxy-propyl moiety and pyrimidine ring are present at almost the same positions. In the spectrum of XV (Fig. 3 (XV)), the methylene protons in the 3- and 4-position of pyrrolidinyl gave a singlet at 3.3 ppm, while those bonded with the nitrogen atom resonate at 1.91 ppm. The resonances in piperidinyl moiety (Fig. 3 (XVI)) appear as a multiplet with chemical shifts of 1.45 ppm, (for two protons in the $–CH_2$ group) and of 1.61 ppm for four protons in two adjacent CH_2 groups. In the ^{1}H-NMR spectrum of morpholine - substituted compound, XVII (Fig. 3 (XVII)) one may notice the quasi-triplets at 3.45 and 3.67 ppm, assigned to the protons in two methylene groups linked to the nitrogen atom, and to the oxygen atom, respectively.

3.4. Molecular geometry and determination of the electro-optical parameters

The molecular geometry of the six compounds studied in this paper was optimized with HyperChem8.0.6 [42] by AM1 procedure, the most accurate semi-empirical calculation method, This procedure solves the Schrödinger equation, with certain approximations, in order to describe the electron properties of atoms and molecules. To simplify and shorten these calculations, semi-empirical methods make many simplifications, including: calculating only for valence electrons; neglecting the integrals for certain interactions; using standard, non-optimized, electron orbital basis functions; and using parameters derived from experiments. Experimental parameters eliminate the need to calculate certain quantities and to correct the errors resulting from approximations [28].

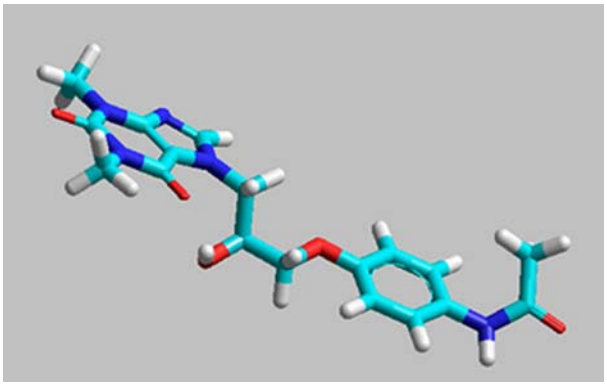


Fig. 4. The AM1 optimized geometry of the parent compound, 7-[2-hydroxy-3-(4-acetyl-amino)-phenoxy-propyl)-l,3-dimethyl-xanthine (XII) (C – light blue, N – blue, O – red, H – white).

Table 2. Computed parameters of the studied molecules.

Properties \ Name	XII	XIII	XIV	XV	XVI	XVII
Total energy (E) (kcal/mol)	-120579	-128408	-139725	-139384	-142983	-146771
Dipole moment (p) (D)	1.50	3.29	4.20	2.66	5.54	4.15
HOMO (eV)	-9.068	-8.970	-8.580	-8.932	-8.745	-8.530
LUMO (eV)	-0.487	-0.837	-1.618	-0.420	-0.269	-0.469
Surface area ($Å^2$)	570.06	613.56	618.17	616.18	660.98	669.80
Volume ($Å^3$)	1071.35	1124.96	1124.45	1246.83	1313.07	1292.38
Hidration energy (HE) (kcal/mol)	-10.80	-11.3	-15.47	-9.05	-7.49	-11.21
Log P	-0.97	0.6	-0.53	0.46	0.63	-0.44
Refractivity (R) ($Å^3$)	99.60	106.99	105.64	118.83	124.69	121.62
Polarizability (α) ($Å^3$)	38.58	41.21	40.43	46.5	48.34	47.14
Mass (amu)	387.40	466.29	432.39	456.5	470.53	472.5

The results of the optimization of the compound XIII geometry is depicted in Fig. 4, from which one can see that the heterocycle of theophylline is parallel on the figure plane, while the plane of the aromatic ring of the paracetamol is tilted related to the first plane.

Table 2 shows some electro-optical parameters of XII – XVII. One can notice the influence of the 8-substituted radical on the electric dipole moment of the molecules. It follows that particularly the presence of the oxygen atom produces large variations in the dipole moment value, being known that this parameter is very sensitive to the electronic charge distribution, derived from alterations of the chemical structure. From Table 2 it results that XII is the most stable compound, because it has the smallest electric dipole moment and the lowest HOMO value.

Contrarily, the highest value of HOMO corresponds to the compounds XIV and XVII having Oxygen atoms in 8-substituted radical (see Table 1 and Fig.5).

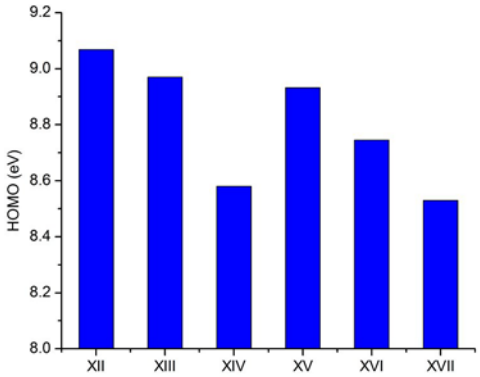


Fig. 5 Absolute value of HOMO (eV) for the studied compounds computed by HyperChem6.0.8

XII possess the *smallest* values of refractivity and polarizability, as it results from Table 2. The biggest values of refractivity and of polarizability correspond to the compound XVI. The compound XIV has the highest absolute value of the hydration energy and that is explaining its good solubility.

Some molecular parameters can also be computed using Table 2 (see Table 3). The computed hydration energy (Table2) of the studied compounds fits linearly vs. electrophilicity index (ω) (see Table3) defined by:

$$\omega = \frac{\mu^2}{2h} \tag{1}$$

where the chemical potential (μ) was calculated with the formula:

$$\mu = \frac{HOMO + LUMO}{2} \tag{2}$$

and the molecular hardness (h) is expressed by:

$$h = LUMO - HOMO \tag{3}$$

The smallest values for the hardness (Table 3) were obtained for compounds XIV and XVII with Oxygen atoms in the 8-substituted structure.

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

	XII	XIII	XIV	XV	XVI	XVII
Chemical potential (μ) (eV)	-4.78	-4.90	-5.10	-4.68	-4.51	-4.50
Hardness (h) (eV)	8.58	8.3	6.96	8.51	8.48	8.06
Electrophilicity (ω) (eV)	1.33	1.48	1.87	1.28	1.20	1.26

From Tables 2 and 3 it results a linear dependence between the absolute value of the total energy E*10^{-5} (kcal/mol) and the polarizability α (Å ^{3}) computed by AMI from Hyperchem8.0.6 (SEE Fig.6). The points corresponding to the compounds having oxygen atom in molecule are deviated from the linearity in Fig. 6. The great electronegativity of oxygen decreases the molecular polarizability of the studied compounds.

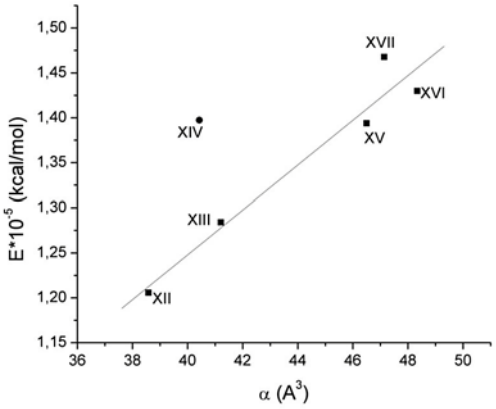


Fig.6 Absolute value of total computed energy vs. molecular polarizability

The chemical potential is related to the free energy corresponding to one molecule when it is into condensed state. In the graphs from Fig.7 of the computed molecular dipole moment vs. the chemical potential, the points are placed near two lines with different slopes.

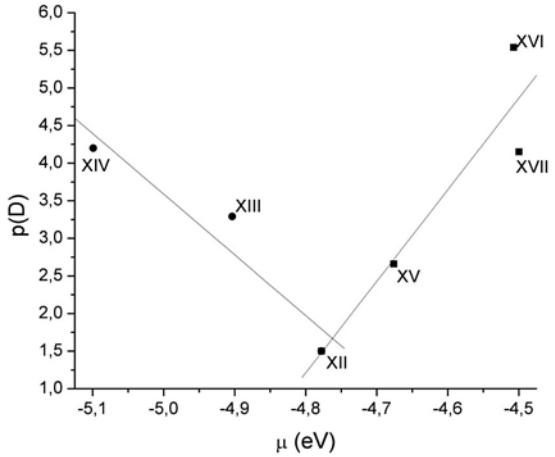


Fig. 7. Computed molecular dipole moments vs. chemical potential

From Fig.7 it results an increase of the molecular dipole moment with the chemical potential for the compounds with atomic substituents in 8-position. Contrarily, if in the 8-position are polyatomic substituents, the molecular dipole moment decreases with the increase of chemical potential.

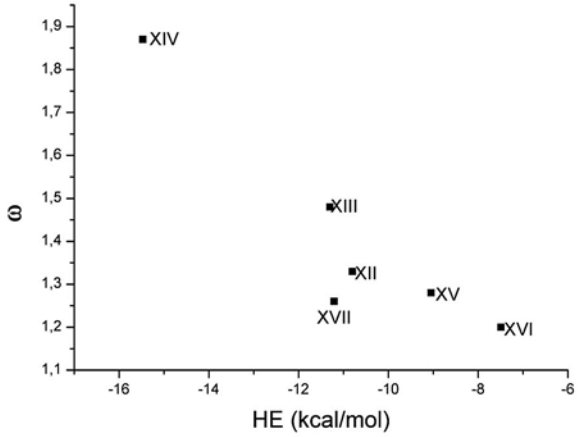


Fig. 8 Electrophilicity index vs. hydration energy.

A linear dependence between the electrophilicity index and the hydration energy is also illustrated in Fig. 8. The highest deviation from linear dependence corresponds to the compound XVII.

The electronic charge near the atom O_{12} is smaller than the charge near O_{10} because in the molecular structure the groups C_2=O_{12} is neighboring two atoms (N_1, N_2), while C_6=O_{10} is neighboring of one N and one C atoms. The higher electronegativity of the N atom compared to that of the C atom explains this difference in the atomic charges. The atomic groups C_6=O_{10} and C_{27}=O_{28} are located near the similar covalent bonds (Fig. 1) and consequently are characterized by appropriate lengths of the chemical bonds (Table 4). The presence of the atomic groups C=O could lead to an increase in the solubility in water.

Table 4. Bond lengths of the covalent bonds C=O.

	XII	XIII	XIV	XV	XVI	XVII
$C_2 = O_{12}$	1.250	1.2495	1.2482	1.2507	1.2508	1.2502
$C_6 = O_{10}$	1.2483	1.2465	1.2443	1.245	1.2482	1.2464
$C_{27} = O_{28}$	1.2473	1.2475	1.2443	1.2472	1.2436	1.2441

The electronic charges on N_7, covalently bonded with three carbon atoms, is smaller than the charge on N_9, which have a double bond that hinders the negative charge delocalization. The electronic charge on carbon C_8 neighbor to the substituted radicals changes its sign when passing from –H, -Br, -NO_2 substitutes to cyclic substitutes.

Table 5. Experimental and calculated frequencies of the IR bands for the un-substituted compound XII.

Chemical bonds	Wavenumber IR (cm^{-1})	Calculated wavenumber (cm^{-1})
O-H	3400	3434
N-H	3320	3448
C-H	3160-3020	3192-2969
-CH_3	2949	2969.8
>C=C<$_N$	1603	1626
>C=N	1510	1576
-NH-CO-	1610	1645
-C-CH_3	1368	1377.6
-CH_2	2900	2969.8
-CO-CH_3	1350	1365
-NO_2	1566	1569

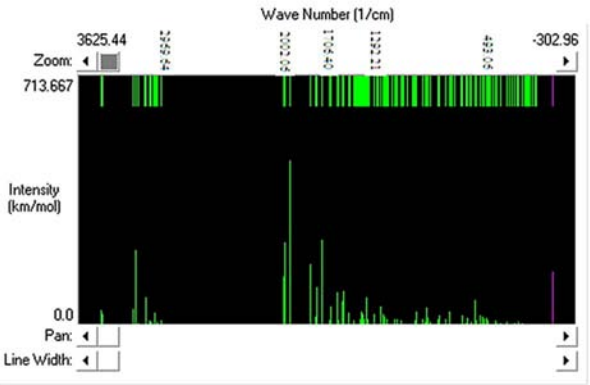


Fig. 9. The simulated FTIR spectrum of the parent drug, XII.

The theoretical infrared spectrum (Fig. 9) was generated on the basis of the calculated vibration frequencies and afterwards it was compared with the experimental FTIR spectrum. The results presented in Table 5 show the shifts between the calculated and the experimental frequencies. The differences can appear due to the fact that the computed spectrum corresponds to an isolated molecule, while the experimental IR spectrum is recorded in KBr pills. Generally, the values are overestimated and the larges deviations can be noticed for the stretching vibrations of the C=N and -NH-CO- bonds.

4. Conclusions

HyperChem 8.0.6 was used to establish the most stable conformation and the QSAR parameters of the studied molecules. A good correspondence between the computed and the experimental frequencies in IR spectra was obtained. Important deviations from the IR experimental spectrum were obtained for the intensity of the bands in computed one.

The chemical shifts (ppm) from ^{1}H-NMR spectra are in accordance with the computed charges on the hydrogen atoms.

The computed molecular hardness, the electrophilicity index and the hydrophilicity are physical parameters very important for the biological activity of the studied compounds. This study could be used in medical applications of dimethyl xanthine derivatives in which the hydrophilicity and biological activity are of great importance.

References

[1] S. Ceccareli, M. Altobelli, A. D'Alessandro, A. Paesano, Res. Commun. Mol. Pathol. Pharmacol. **87**, 101 (1995).
[2] H.W. Herzer, Y. Zhang, E.K. Jackson, Life. Sci. **54**, 277 (1994).
[3] B.S. Jaiswal, G.C. Majunder, Int. J. Androl. **19**, 97 (1996).
[4] P. Donoso, S.C. O'Neill, K.W. Dilly, N. Negretti, D.A. Eisner, Brit. J. Pharmacol. **111**, 455 (1994).
[5] J. Duarte, F.P. Vizcaino, A. Zarzuelo, J. Jimenez, J. Tamargo, Gen. Pharmac. **24**, 1359 (1993).
[6] F. Sanae, S. Ohmae, D. Kobayashi, K. Takaga, K. Miyamoto, J. Pharmacol. Exp. Therapeut. **277**, 54 (1996).
[7] T. Tanaka, Y. Tache, P.H. Guth, Eur. J. Pharmacol. **243**, 221 (1993).
[8] M. Aubier, P.J. Barnes, Eur. Respir. J. **8**, 347 (1995).
[9] C. Moritani, S. Ishioka, Y. Haruta, M. Kambe, M. Yamakido, Chest. **113**, 452 (1998).
[10] M. Williams, Drug Dev. Res. **28**, 438 (1993).
[11] V. Devreux, P.O. Plasman, P. Lebrun, A. Herchuelz, Arzneim. Forsch. **40**, 268 (1990).
[12] A.H. Fayed, Contraception **53**, 181 (1996).
[13] K. Mano, Nippon. Rinsho. **54**, 3093 (1996).
[14] J. C. Burbiel, J. Hockemeyer. C. E Müller, Beilstein J. Org. Chem. **2**, 20 *(*2006).
[15] R. Bansal, G. Kumar, D. Gandhi, L. C. Young, A. L. Harvey, Eur. J. Med. Chem. **44**, 2122 (2009).
[16] B. Berk, H. Akgün, K. Erol, B. Sırmagül, Z.-G. Gao, K. A. Jacobson, Il Farmaco **60**, 974 (2005).
[17] J. E. Rodríguez-Borges, X. García-Mera, M. C. Balo, J. Brea, O. Caamaño, F. Fernández, C. López, M. I. Loza, M. I. Nieto, Bioorg. Med. Chem. **18**, 2001 (2010).
[18] Wang, Y.; Chackalamannil, S.; Hu, Z.; Boyle, C. D.; Lankin, C. M.; Xia, Y.; Xu, R.; Asberom, T.; Pissarnitski, D.; Stamford, A. W.; Greenlee, W. J.; Skell, J.; Kurowski, S.; Vemulapalli, S.; Palamanda, J.; Chintala, M.; Wu, P.; Myers, J.; Wang, P. Bioorg. Med. Chem. Lett. **12**, 3149 (2002).
[19] N. J. Arnold, R. Arnold, D. Beer, G. Bhalay, S. P. Collingwood, S. Craig, N. Devereux, M. Dodds, A. R. Dunstan, R. A. Fairhurst, D. Farr, J. D. Fullerton, A. Glen, S. Gomez, S. Haberthuer, J. D.I. Hatto, C. Howes, D. Jones, Th. H. Keller, B. Leuenberger, Bioorganic & Med. Chem. Lett. **17**, 2376 (2007).

[20] M. Kraft, J. Pak, L. Borish, R. J. Martin, J. Allergy Clin. Immun. **98**, 251 (1996).
[21] K. Yasui, A. Komiyama, Int. J. Hematol. **73**, 87 (2001).
[22] Y. Tohda, M. Muraki, T. Iwanaga, H. Kubo, M. Fukuoka, S. Nakajima, Int. J. Immunopharm. **20**, 173 (1998).
[23] J. Chorostowska-Wynimko, J. Kus, E. Skopińska-Rózewska, J. Physiol. Pharmacol. **58 Suppl 5** (2007).
[24] M. Kanehara, A. Yokoyama, Y. Tomoda, N. Shiota, H. Iwamoto, N. shikawa, Y. Taooka, Y. Haruta, N. Hattori, N. Kohno, Pulm. Pharmacol. Ther. **21**, 874 (2008).
[25] P. J. Barnes, Am.J.Respir. Crit.Care Med. **167**, 813 (2003).
[26] J.A. Auchampach, L.M. Kreckler, T.C. Wan, J.E. Maas, D. van der Hoeven, E. Gizewski, J. Narayanan, G.E. Maas, J. Pharmacol. Exp. Ther. **329**, 2 (2009).
[27] L. Sratthaphut, N. Ruangwises, Yakugaku Zasshi, J. Pharm. Soc. Japan **120**, 1723 (2007).
[28] A.S. El-Shahawy, S.M. Ahmed, N.Kh. Sayed, Spectrochim. Acta Part A **66**, 143 (2007).
[29] F. Huq, J. Pharm. Toxic. **2**, 142 (2007).
[30] (a) S. Majumdar, K.B. Sloan, Int J Pharm. **332**, 64 (2007); (b) S. Majumdar, K.B. Sloan, Int J Pharm. **337**, 48 (2007).
[31] Gh. Danila, L. Profire, G, .G. Bumbu, C. Vasile, Thermochim. Acta **343**, 69 (2000).
[32] L. Profire, G, .G. Bumbu, M. Costuleanu, Gh. Danila, C. Vasile, Thermochim. Acta **381**, 19 (2002).
[33] L. Profire, V. Sunel, D. Lupascu, M. C. Baican, N. Bibire, C. Vasile, Farmacia **58**, 170 (2010).
[34] M. Falk, M. Gil, N. Iza, Can. J. Chem. **68**, 1293 (1990).
[35] De Taeye, Th. Zeegers-Huyskens, J. Pharm. Sci. **74**, 660 (1985).
[36] G. Socrates, Infrared and Raman Characteristic Group Frequencies. Tables and Charts. 3rd Edition, John Wiley and Sons, 2004.
[37] P. J. Krueger, J. Jan, Can. J. Chem., **48**, 3236 (1970).
[38] A. Jezierska, J. J. Panek, G. Z. Żukowska, A. Sporzyński, J. Phys. Org. Chem. **23**, 451 (2010).
[39] I. Pavel, A. Szeghalmi, D. Moigno, S. Cinta ,W. Kiefer**,** Biopolym. (Biospectroscopy), **72**, 25 (2003).
[40] G. M. Edwards, E. Lawson, M. de Matas, L. Shields, P. York, J Chem Soc Perkin Trans **II 10** 1985 (1997).
[41] A.A. Maevsky, B.I.Sukhorukov, Nucleic Acids Research, **8**, 3029 (1980).
[42] *** HyperChem8.0.6, Molecular visualization and Simulation Program Package, Hypercube, Inc., Gainesville