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SYNTHESIS, STRUCTURAL ANALYSIS AND DRUG-LIKENESS ESTIMATION OF SOME IMIDAZOLE DERIVATIVES

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Summary. The xanthine skeleton, as a basic structure of a lot of physiologically active compounds, provides great opportunities for pharmacologically targeted synthesis of derivatives with various structures. Thus, using alkaline hydrolysis of methylxanthines theophylline (**1**), caffeine (**2**) and ethophylline (**7**), three 1-(un)substituted N-methyl-4-(methylamino)-1H-imidazole-5-carboxamides (**5a,b** and **8**) were synthesized. The hydrolytic process was carried out at mild conditions without heating. Based on IR structural analysis, it was clearly established that under these reaction conditions the xanthine ring was cleaved at position 1,2 to form the corresponding 1-(un)substituted N-methyl-4-(methylamino)-1H-imidazole-5-carboxamides. In order to estimate the drug-likeness of compounds **5a,b** and **8**, a theoretical calculation of some molecular descriptors was made. The obtained values were compared to these of the starting biologically active xanthines **1, 2** and **7**. The results indicate that a good oral bioavailability manifestation may be expected. The possible pharmacological effects and clarification of their potential as prodrugs will be studied in another research.

Key words: alkaline hydrolysis, 1H-imidazole-5-carboxamides, structural analysis, drug-likeness

СИНТЕЗ, СТРУКТУРЕН АНАЛИЗ И ОПРЕДЕЛЯНЕ НА ЛЕКАРСТВЕНО ПОДОБИЕ НА НЯКОИ ИМИДАЗОЛОВИ ПРОИЗВОДНИ

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Резюме. Ксантиновият скелет като основна структура в редица физиологично активни съединения предоставя големи възможности за фармакологично насочен синтез на производни с различна структура. Чрез използване на алкална хидролиза на метилксантините теофилин (**1**), кофеин (**2**) и етофилин (**7**) бяха синтезирани три 1-(не)заместени N-метил-4-(метиламино)-1H-имидазол-5-карбоксамиди (**5a,b** и **8**). Хидролизният процес е проведен при меки условия без нагряване. Въз основа на ИЧ структурен анализ е установено, че при тези реакционни условия ксантиновият пръстен се разкъсва в позиция 1,2 и образува съответните 1-(не)заместени N-метил-4-(метиламино)-1H-имидазол-5-карбоксамиди. С цел определяне на лекарствено подобие на съединенията **5a,b** и **8** са изчислени стойностите на някои молекулни дескриптори. Получените резултати са сравнени с изчислените за изходните биологично активни ксантини и показват, че може да се очаква добра бионаличност след перорално приложение. Възможните фармакологични ефекти на изследваните съединения и изясняването на потенциала им като prodrugs е предмет на бъдещи изследвания.

Ключови думи: алкална хидролиза, 1H-имидазол-5-карбоксамиди, структурен анализ, лекарствено подобие

Introduction

A great number of imidazole derivatives possess various types and varying degrees of biological significance. The physiological role of histidine and histamine and their pharmacological importance, as well as their derivatives and analogs are well known. Certain imidazole structures are reported to manifest antiprotozoal, antifungal, antibacterial, MAO – inhibitory and other type activity [1, 2].

Various methods for synthesis of substituted imidazoles under different reaction conditions and stages are described in the literature. These data defined the purpose of this work – using hydrolysis of methylxanthines to obtain substituted imidazoles in a single synthetic stage. Isolation, characterization and drug-likeness estimation, using some molecular descriptors for the obtained structures were also performed. The possible pharmacological

effects and clarification of their potential as prodrugs will be a purpose of another study.

Experimental part

Chemistry

Melting points were determined on an electrothermal apparatus (Büchi 535, Switzerland) in an open capillary tube and are not corrected. UV spectra were recorded on a Hewlett Packard 8452A Diode Array Spectrophotometer equipped with an HP Vectra 386/25 computer. The IR spectra 400 – 4000 cm^{-1} were recorded on a Nicolet iS10 FT-IR Spectrometer in KBr. The completion of reactions was monitored through TLC, which was performed on DC-Alufolien Kieselgel 60 F254 (Merck) (0.20 mm) sheets with solvents: ethanol–chloroform–acetone (4:3:3 volume parts). The spots were detected at UV 254 nm. Synthetic grade chemicals procured from Merck, Germany, were used for the synthesis of the target compounds, as received. Microanalyses were performed on a Perkin-Elmer 2400-II Element analyzer. All products were shown to be homogeneous by TLC. The given yield is the yield of TLC homogeneous product. No efforts were made to optimize the yields. Ethofylline was obtained in accordance with ref. [3].

Molecular descriptors calculation

Molecular descriptors (logP, total polar surface area (TPSA), number of hydrogen bond acceptors (nON acceptors), number of hydrogen bond donors (nOHNH donors) and number of rotatable bonds (nrotb) were calculated with Molinspiration free online chemoinformatics service tool [4].

Synthesis of N-methyl-4-(methylamino)-1H-imidazole-5-carboxamide (Theophyllidine, ***5a)***[5]. To 50 ml 50% water solution of KOH (17 mmol) 10 g (55 mmol) theophylline (**1**) was added. The reaction mixture was stirred on heating for 5 hours. After cooling the white crystals were separated. After filtration the crude product was dissolved in small amount of water and concentrated HCl was added to pH = 1. The cooled to room temperature reaction mixture was filtered. The obtained grayish crystals were recrystallised from ethanol and dried on air. Yield – 8.91 g (85%); mp 191°C (ethanol) with decomposition and polymorphic transitions at 130°C and 155°C (195°C [5]); Rf = 0.69; IR (cm^{-1}): 3439, 3377, 3288, (νNH), 3102 (νCH – aromatic), 1668 (νCO – amide I), 1610 (δNH – amide II, (δNH – sec. amine) 1553 (νC=C); UV (CH_3OH, nm): λ_{max} = 290. Calculated $C_6H_{10}N_4O.HCl$(190.63) requires: C, 37.80; H, 5.82; N, 29.39; found: C, 37.58; H, 5.55; N, 29.05.

Synthesis of N,1-dimethyl-4-(methylamino)-1H-imidazole-5-carboxamide (Caffeidine, ***5b)*** [6]. A solution of sodium hydroxide (10.3 g, 0.257 mol) in water (130 ml) was added to caffeine 2 (25 g, 0.13 mol). The suspension was stirred for 48 hours at room temperature resulting in colourless solution. Caffeidine nitrate **5b** was obtained as precipitate by the addition of 28 ml of nitric acid (65%) to the cooled reaction mixture. After an additional stirring for an hour, the precipitate was obtained after suction and washed with a small amount of cold water. The product was dried at room temperature on air. Yield – 13.83 g (46%); mp 170-171.5°C (ethanol) (165°C [6]); R_f = 0.56; IR (cm^{-1}): 3413, 3372, (νNH), 3136 (νCH – aromatic), 1654 (νCO – amide I), 1569 (δNH – amide II, (δNH – sec. amine) 1545 (νC=C); UV (CH_3OH, nm): λ_{max} = 290. Calculated $C_7H_{12}N_4O.HNO_3$(231.21) requires: C, 36.36; H, 5.67; N, 30.29; found: C, 35.95; H, 5.25; N, 29.90.

Synthesis of 1-(2-hydroxyethyl)-N-methyl-4-(methylamino)-1H-imidazole-5-carboxamide (Ethofyllidine, ***8)***. A solution of sodium hydroxide (10.3 g, 0.257 mol) in water (130 ml) was added to ethofylline **7** (29.21 g, 0.13 mol). The suspension was stirred for 5 hours at room temperature resulting in colourless solution. Ethofyllidine nitrate **8** was obtained as precipitate by the addition of 28 ml of nitric acid (65%) to the cooled reaction mixture. After an additional stirring for an hour, the precipitate was obtained after suction and washed with a small amount of cold water and recrystallized from ethanol. The product was dried at room temperature on air. Yield – 13.61 g (40%); mp 154-155°C (ethanol); R_f = 0.61; IR (cm^{-1}): 3428, 3384, (νNH), 3305 (νOH), 3129 (νCH – aromatic), 1669 (νCO – amide I), 1662 (δNH – amide II, (δNH – sec. amine) 1559 (νC=C), 1272 (δOH), 1077 (νC–O – alcohol); UV (CH_3OH, nm): λ_{max} = 286. Calculated $C_8H_{14}N_4O_2.HNO_3$(261.74) requires: C, 36.78; H, 5.79; N, 26.81; found: C, 36.52; H, 5.46; N, 26.33.

Results and Discussion

Chemistry

Hydrolysis of 1,3-dimethylxanthine (**1**, Theophylline) and 1,3,7-trimethylxanthine (**2**, Caffeine) in aqueous alkaline solution gave correspponding 1-

(un) methylated N-methyl-4-(methylamino)-1H-imidazole-5-carboxamides (**5a,b**) and 1-(un)methylated 4-(1,3-dimethylureido)-1H-imidazole-5-carboxylic acids (**4a,b**) [5-8]. Probability of cleavage of the pyrimidine ring in 1,2 and 1,6 positions under alkaline hydrolysis conditions exist, as it is outlined on Chart 1.

If the molecule is cleaved in 1,2 position, a substituted imidazole-5-carboxilic acids (**4a,b**) will be formed, but if the cleavage occurs in 1,6-position – the substituted carbamic acids (**3a,b**) will be obtained. In aqueous solution, these two molecules are in equilibrium with xanthine molecules (**1, 2**) [9]. It was established that the probability of cleavage at 1,2 position of the xanthine ring and formation of the corresponding substituted carbamic acids (**3a,b**) under the above conditions are higher. On the other hand, the obtained molecules are also prepared at mild temperature and carboxylation of (**5a,b**). The results of MS, 1H-NMR and IR spectra confirm these findings [10].

For the purpose of our investigation, compounds **5a,b** were obtained at moderate conditions without heating. The same approach (Chart 2) was applied to synthesize 1-(2-hydroxyethyl)-N-methyl-4-(methylamino)-1H-imidazole-5-carboxamide (**8**), named by us Ethofyllidine.

The process was carried out at room temperature for 5 hours. The end of the reaction was determined using TLC. Compound **8** was isolated after addition of nitric acid to the reaction mixture and was recrystallised from ethanol. The isolated product is white needles and must be stored protected from light. The prolonged exposure to light and air lead to change in the crystals color to pale and/or dark pink. The obtained 1-(2-hydroxyethyl)-N-methyl-4-(methylamino)-1H-imidazole-5-carboxamide (**8**) is very soluble in water, sparingly soluble in ethanol and insoluble in chloroform. Its structure is proven by microanalyses, FTIR and UV spectral data. The results were consistent with the assigned structures.

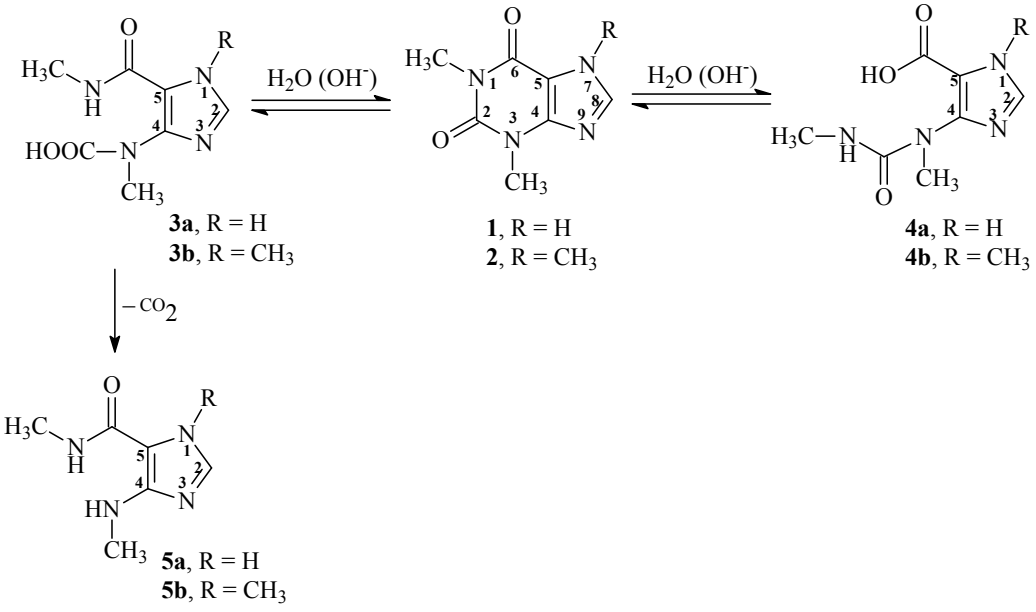


Chart 1

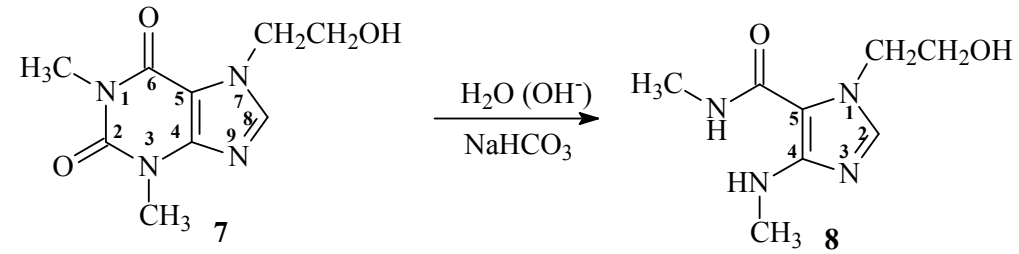


Chart 2

Structural analysis

The FTIR spectra of the synthesized **5a,b** and **8** in the region 4000 cm^{-1} to 400 cm^{-1} (fig. 1-3) exhibit several characteric bands. In order to specify the observed absorption bands, the FTIR spectra of the studied compounds **5a,b** and **8** were compared with these of the starting xanthines **1, 2** and **7**.

CH, NH and OH stretching vibrations

Most organic compounds have CH bonds; a useful rule is that absorption in the 2850–3000 cm^{-1} is due to sp^3–CH stretching whereas absorption above 3000 cm^{-1} is from sp^2 CH stretching. Also the assignments of the CH_2 stretching absorption bands are always ambiguous since they are coupled with the overtone and combination of CH_2 bending vibrations at around 1450 cm^{-1}. Complex broad bands in the range of 2800-3116 cm^{-1} were observed in the spectra of the studied compounds. We assigned these bands to asymmetric and symmetric CH_2 and CH_3 stretching vibrations, respectively. To this region belongs also the stretching vibration of the heteroaromatic C–H bond: C8–H bond in imidazole ring of **1, 2** and **7**, and the same bond (C8–H) in the structure of **5a,b** and **8**.

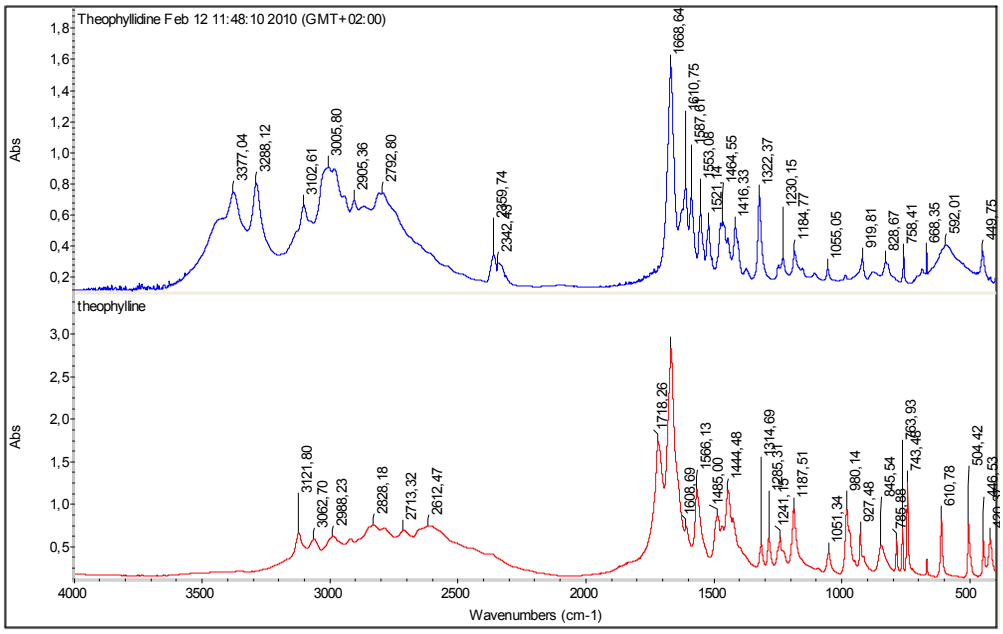


Fig. 1. *FT-IR spectrum of Theophylline (**1**) and Theophyllidine (**5a**)*

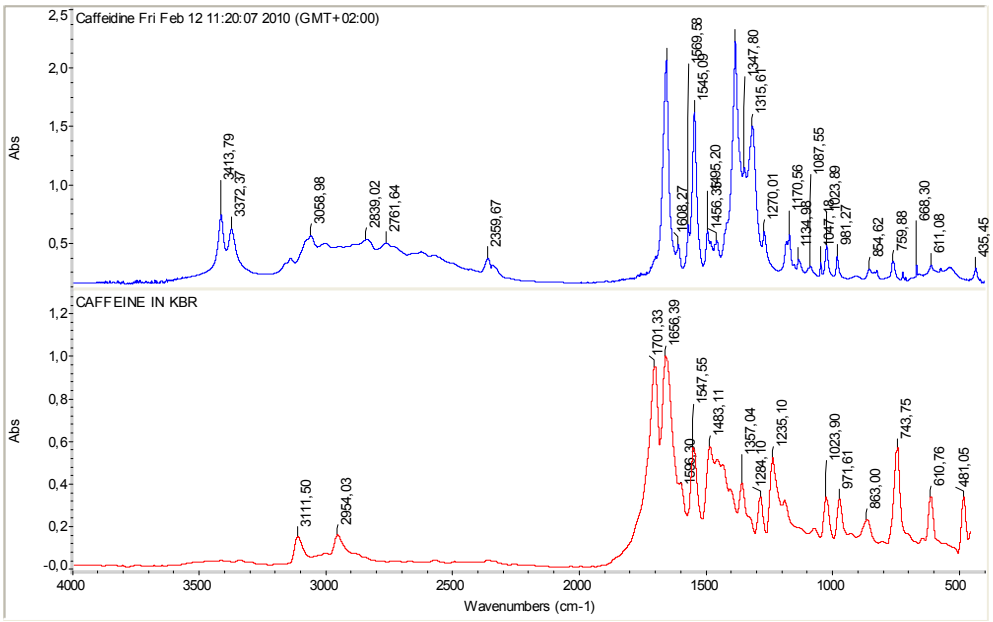


Fig. 2. *FT-IR spectrum of Caffeine (**2**) and Caffeidine (**5b**)*

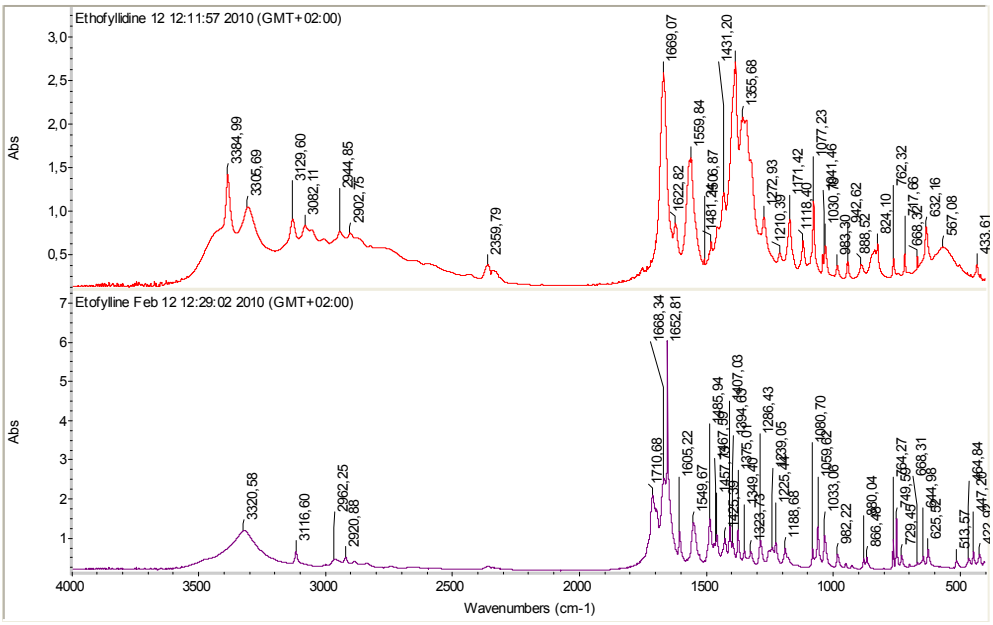


Fig. 3. *FT-IR spectrum of Ethofylline (7) and Ethofyllidine (**8**)*

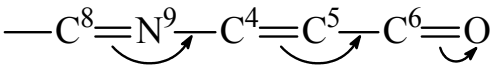
In the spectra of the tested compounds, absorption bands characteristic for NH stretching vibrations were observed. The band appearing at 3121 cm^{-1} in the spectrum of **1** is assigned to the NH stretching vibration from the imidazole ring. The same vibration appears at 3288 cm^{-1} in the spectrum of **5a**. The absorption band ascribable to NH stretching vibration of secondary amine appears at 3377 cm^{-1} (**5a**), 3372 cm^{-1} (**5b**) and 3384 cm-1 (**8**). There are broad multiple absorption bands in the region of 2200-2700 cm^{-1} with maximum at 2359 cm-1. Such spectral behavior is typical for compounds with NH_2^+ groups. The presence of such group in the structures of compounds **5a,b** and **8** is easily explained, since they are isolated as salts. The stretching vibration for secondary amide appears in the spectra of the studied compounds as band at 3439 cm-1 (**5a**), 3413 cm^{-1} (**5b**) and 3428 cm^{-1} (**8**) respectively. These values are characteristic for unassociated NH stretching vibrations of secondary trans-amides [11].

In the spectrum of **8**, there is one additional absorption band at 3305 cm-1 which corresponds to the band at 3320 cm-1 in the spectrum of 7 and was assigned to OH stretching vibration. The values of the wave numbers for this vibration suggest the presence of intermolecular H-bond [11].

C=O and C–O stretching vibrations

The carbonyl group exhibits a strong absorption band due to C=O stretching vibration and is observed in the region 1850-1550 cm^{-1}. The starting compounds **1, 2** and **7** contain two carbonyl groups in meta position and there are two strong bands observed at 1701-1710 cm^{-1} and at 1656-1668 cm^{-1} in the FTIR spectra, accounted to C=O asymmetric and symmetric stretching vibrations in xanthine rind.

Regarding the structures of these compounds (fig. 1), it is obvious that the carbonyl groups in xanthine ring are not equivalent. The conjugation of C-6 carbonyl group is greater due to the presence of the conjugated on the principle of vinylogy system:



Influence of N-3 p-electron lone pair on this system can't be excluded. Due to this conjugation, the rank of multiple bonds decreases, which leads to lowering in their force constants and frequency of vibrations. Such a reduction in the vibration frequency of the carbonyl groups is characteristic for α,β-unsaturated ketones [11]:

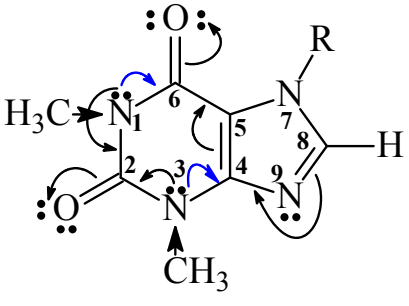


Fig. 4

The vibration frequency of C-6 carbonyl group was influenced by p→π – interaction between N-1 and C-6 carbonyl group (+M effect) which led to additional polarization of C=O bond and decreasing of its vibration frequency. C-2 carbonyl group is mainly subjected to +M effect, realized by p→π – interaction of N-1, N-3 and C-2. Due to this, the reduction of its vibration frequency will be smaller than this for vibration frequency for the C-6 carbonyl group. Thus in our opinion absorption band for C-6 carbonyl group is at 1656-1668 cm^{-1} whereas at 1701-1710 cm^{-1} appears the absorption band of C-2 carbonyl group. It is this absorption band that is missing in the spectra of the studied imidazole derivatives **5a,b** and **8**. There is no change of the wave numbers for the vibration of the second carbonyl group – carboxamide group in **5a,b** and **8**, as the conjugated system containing this group remained essentially unchanged.

In the spectra of **7** and **8**, an absorption band at 1059 cm^{-1} (**7**) and 1077 cm^{-1} (**8**) is observed characteristic for stretching vibration of C–O bond in primary alcohol moiety of the compounds.

C=C stretching vibrations and bending O–H and N–H vibrations

In the spectra of the starting xanthines, as well as of the corresponding derived imidazole compounds, a strong absorption band at 1545-1566 cm^{-1} was observed. This band is assigned to stretching vibration of C=C bond in the xanthine and imidazole rings.

The absorption band characteristic for bending vibration of O–H bond was observed at 1286 cm^{-1} for **7** and 1272 cm^{-1} for **8**. An additional absorption band in the region of 1569-1622 cm^{-1} was observed in the spectra of the studied imidazole derivatives **5a,b** and **8**. This band is ascribable to bending vibrations of N–H bond in secondary amides (amide II) and N–H bond in secondary amines.

Estimation of drug-likeness

The pharmacological properties of the starting xanthines **1, 2** and **7** are wellknown from the literature [2]. However, to our knowledge, there is no information about the pharmacological properties of the imidazole derivatives **5a,b**. Compound **8** is not investigated yet. It is known that **5a** (theophyllidine) was used as indicator for quantitative estimation of theophylline in blood [12] and for obtaining of theophyllidine-base azo dye for the chemicotoxicological analysis of some opioid analgetics [13]. No gene interaction and disease associations have been curated for **5b** (caffeidine) [14]. Its application is known for synthesis of theobromine derivatives [15] and a number of purine-6-ones [16], imidazo-1,4-benzo(ox/di)azepines [17] and 1,2,6-thiadiazine derivatives [18].

Typically, biological activity is a function of the complex influence of many molecular descriptors, but in some cases, highlighting the effect of some individual parameters makes it possible, to estimate the drug-likeness of newly synthesized molecules. Intrinsically, drug-likeness are the descriptors of potency, selectivity, absorption, distribution, metabolism, toxicity and scalability [19]. At present, there are several guidelines for defining drug-like properties [20, 21], such as the 'Lipinski RULE OF FIVE' (RO5) [22], which is used to maximize an oral drug candidate's probability of surviving development. High oral bioavailability is an important factor for the development of bioactive molecules as therapeutic agents. Passive intestinal absorption, reduced molecular flexibility (measured by the number of rotatable bonds), low polar surface area or total hydrogen bond count (sum of donors and acceptors) are found to be important predictors of good oral bioavailability [23-25]. RO5 identifies several key properties that should be considered for compounds with oral delivery in mind. These properties are molecular mass < 500 Da, cLogP < 5, number of hydrogen-bond donors ≤ 5 and number of hydrogen-bond acceptors ≤ 10. A more recent analysis based on the number of rotatable bonds, indicated an upper limit of seven rotatable bonds in orally bioavailable drugs [23] as well as the values of the hydrophobic parameter logP are placed in the range from -0.4 to 5.6 [26].

In order to establish the significance of these parameters on the estimation of the drug-likeness of compounds **5a,b** and **8**, a theoretical calculation of them was made. The obtained values are presented in Table 1, where a calculated percentage of absorption (%ABS), calculated [27] using the expression: %ABS = 109 – 0.345 PSA is contained. The results are compared with the calculated descriptors for **1, 2** and **7**.

Table 1. Calculated absorption (%ABS), total polar surface area (TPSA) and Lipinski parameters of the studied compounds

Compounds	% ABS	TPSA	nON accept.	nOHNH donors	nrotb	MiLogP [25]	Volume	Mw
1	83.92	72.69	6	1	0	– 0.005	150.69	180.17
2	87.67	61.84	6	0	0	0.06	167.63	194.19
7	80.69	82.06	7	1	2	– 0.57	192.69	224.22
5a	84.92	69.81	5	3	2	– 0.66	141.78	154.17
5b	88.66	58.95	5	2	2	– 1.44	158.73	168.20
8	81.68	79.18	6	3	4	– 1.22	183.79	198.23

The tested compounds have several (5 for **5a,b** and 6 for **8**) negative centres for hydrogen bond formation and v. d. Waals interactions with receptor. Although the calculated values of LogP are at the lower limit of the rande, the tested compounds covered Lipinski's RO5. Based on the values of calculated absorption, a good oral bioavailability manifestation may be expected. The possible pharmacological effects and clarification of their potential as prodrugs will be an aim to another research.

Conclusion

Using alkaline hydrolysis of methylxanthines **1, 2** and **7**, three 1-(un)substituted N-methyl-4-(methylamino)-1H-imidazole-5-carboxamides (**5a,b** and **8**) were synthesized. Compound 8 is newly synthesized. The hydrolytic process was carried out at mild conditions without heating.

Based on IR structural analysis, it was clearly established that at these reaction conditions the xanthine ring was cleaved at 1,2 position to form the corresponding 1-(un)substituted N-methyl-4-(methylamino)-1H-imidazole-5-carboxamides. In order to estimate the drug-likeness of compounds **5a,b** and **8**, a theoretical calculation of some molecular descriptors was made. The comparison of the calculated results starting biologically active xanthines **1, 2** and **7** indicate that a good oral bioavailability manifestation may be expected. The possible pharmacological effects and clarification of their potential as prodrugs will be further estimated.

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