

Inhibition of impurities formation in the synthesis of *N*-alkyltheobromines stimulated by microwave irradiation. Cationic and anionic response of membrane electrodes

A. Skwierawska · A. Pazik

Received: 8 July 2011 / Accepted: 17 November 2011 / Published online: 11 December 2011
© The Author(s) 2011. This article is published with open access at Springerlink.com

Abstract *N*-Alkyltheobromine (**1–9**) derivatives were obtained by reacting theobromine with appropriate alkyl halide under microwave irradiation at 100–150 W and by conventional synthesis. Formation of by-products of oxygen atom alkylation and 1-*N*-alkyltheobromine ring opening were considered. The presented compounds **1–5** have been studied as ion carriers in ion-selective membrane electrodes. Selectivity of these membranes was studied towards various anions in addition to transition and heavy metal cations.

Keywords Theobromine · Alkylation · Impurities · Microwave irradiation · Membrane electrodes · Selectivity

Introduction

Methylxanthines are pharmacologically and biologically active compounds, which are commonly used as mild stimulants, bronchodilators and adenosine receptor antagonist [1]. One of the *N*-alkyltheobromines derivatives, which is clinically useful for the treatment of peripheral vascular disease, cerebrovascular disease and a number of other illnesses involving a defective regional microcirculation is pentoxifylline [2]. This active hemorheological agent inhibits the synthesis of tumor necrosis factor- α [3] and this effect has been attributed to inhibition of cyclic AMP phosphodiesterase [4]. The most general method of synthesis 1-substituted theobromine is based on cyclization

reaction of imidazole or 6-aminouracil derivatives [5]. Alternative approaches to the previous method is two-step cyclocondensation of 4-amino-5-alkoxycarbonyl-imidazoles with isocyanates or treatment theobromine with an excess of alkyl halide, sometimes under pressure, at temperature of 80–100 °C [6–11]. Preliminary studies have shown that similar derivatives could be obtained by using microwave irradiation [12, 13]. According to present knowledge this method is high yield and less time consuming. It is often used for multi-step synthesis, drug production and whenever easy purification is highly recommended. The aim of this work was preparation of *N*-alkyltheobromines and presentation of their properties in ion-selective membrane electrodes (Fig. 1). There are only few papers dealing with this subject. The behavior of these compounds as ionophores in ion-selective membrane electrodes has received no attention yet in the literature.

Results and discussion

Synthesis

Theobromine molecule has two potential sites for *N*-alkylation showing different acidities of the N–H bond. Under alkaline conditions alkylation of theobromine proceeds in N₁ position, because the nucleophilicity of N₉ is much lower than the former. The electrophilic attack on the N₉ position proceeds under special condition. Theobromine, like other purines exist in two tautomeric forms (Fig. 2).

Ketone form dominates under the equilibrium. At the presence of sodium or sodium/potassium hydroxide the equilibrium is shifted and *O*-alkylation is possible. Under basic conditions, another reaction is opening of uracil ring (Scheme 1).

A. Skwierawska · A. Pazik (✉)
Department of Chemical Technology,
Gdansk University of Technology, G. Narutowicza Street 11/12,
80-233 Gdansk, Poland
e-mail: mikaga20@wp.pl

Fig. 1 Chemical structures of the *N*-alkyltheobromines (1–9)

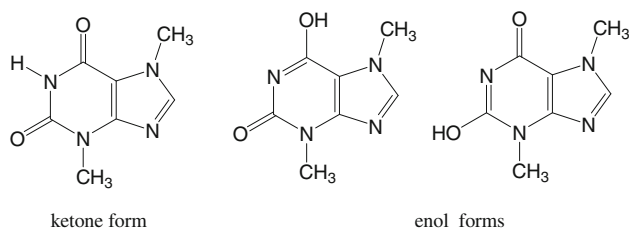
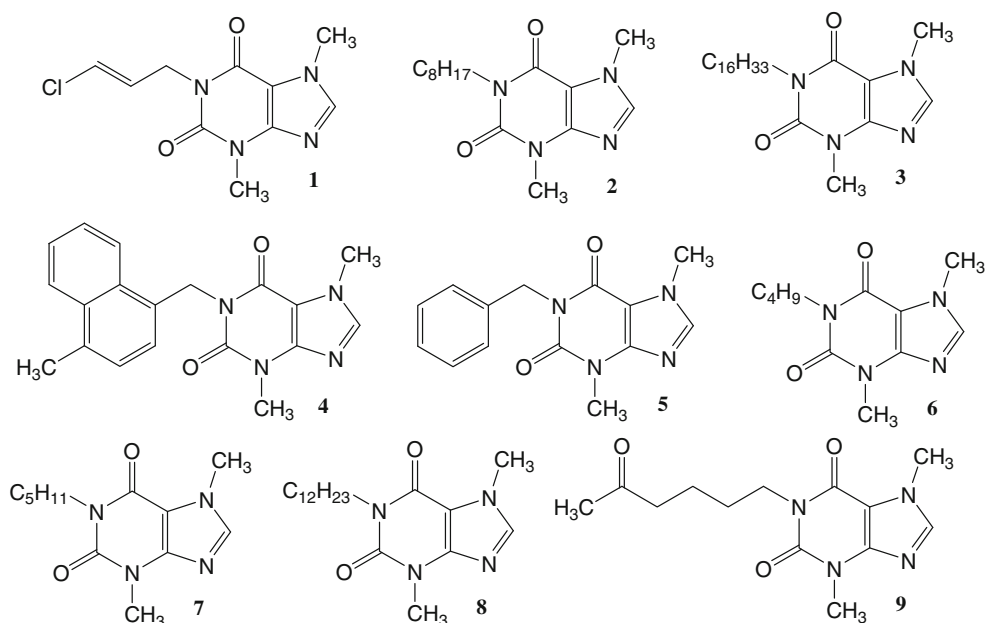
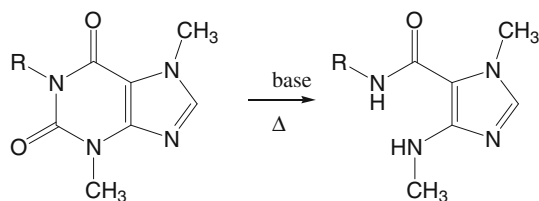


Fig. 2 Tautomeric forms of theobromine



Scheme 1 Opening of uracil ring of theobromine

In the light of the above properties we decided to test influence of factors such as, solvent, temperature, time, microwave irradiation and presence of phase transfer catalyst on selectivity of 1-*N* substitution. Reaction rate and side product formation was monitored by thin layer chromatography (TLC).

Synthesis of pentoxifylline in reaction of theobromine with 6-chlorohexanone was chosen as a research model. In all reaction 2.5 mmol of theobromine and 2.5 mmol of 6-chlorohexanone were used. Solvents volume was 5 mL, quantity of base and phase transfer catalyst was 5 and 0.25 mmol, respectively. The crude product was obtained by solvent evaporation under reduced pressure, extraction with petroleum ether (unreacted electrophilic reagent

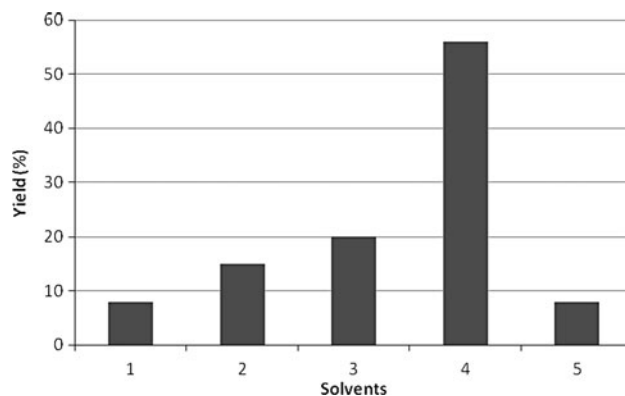


Fig. 3 Solvent influence on yield of theobromine reaction product with 6-chlorohexanone. 1 Methanol (8%), 2 ethanol (15%), 3 propan-2-ol (20%), 4 DMF (56%), 5 DMSO (8%)

removal) and methylene chloride, filtration of inorganic salts, theobromine and insoluble impurities, and solvent evaporation from the filtrate.

First five common industrial solvents possessing different properties were examined (Fig. 3). The mixture of theobromine and 6-chlorohexanone and appropriate solvent was stirred for 8 h under reflux in case of alcohols and at 100 °C if DMF and DMSO were used.

The best yield was achieved using DMF as solvent. Reactions in methanol, ethanol and propan-2-ol gave very low yield. We assumed that the reason was relatively low boiling point of alcohols and highly insufficient solubility of theobromine. The reaction in DMSO required longer time and gave a lot of by-products. Furthermore, solvent free conditions were applied. Reaction was carried out in an excess of alkyl halide at 100 °C for 5 and 12 h. After 5 h of reaction only small progress was observed. After 12 h

the product was highly contaminated. It implies that prolonged reaction/heating time determinates formation of by-products. Due to promising results, in next experiments only DMF was used as solvent.

Limited solubility of theobromine suggested usage of phase transfer catalyst. Five different catalysts were tested (NMe₄Br, NEt₄Br, NBut₄Br, NBzEt₄Br, and NBut₄I). The mixture of theobromine, 6-chlorohexanone and phase transfer catalyst in DMF was stirred at 100 °C for 8 h. The highest yield of crude product was obtained when tetrabutylammonium iodide was applied (see Fig. 4).

Usually, alkylation of nitrogen atom requires presence of appropriate base, which allows formation of ionic intermediates, which is involved in catalytic phase transfer reaction in solid–liquid system. In experiments anhydrous potassium carbonate, sodium carbonate, lithium carbonate and potassium bicarbonate were tested. The highest yield was obtained in case of potassium bicarbonate (Fig. 5). Use

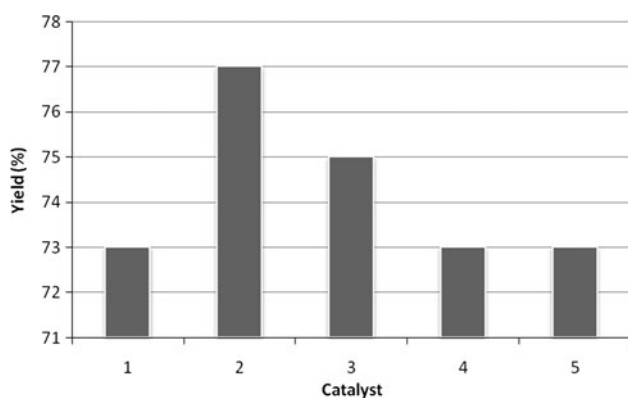


Fig. 4 Phase transfer catalyst influence on yield of theobromine reaction product with 6-chlorohexanone. 1 NEt₄Br (73%), 2 But₄I (77%), 3 NBzEt₄Br (75%), 4 NEt₄Br (73%), 5 NMe₄Br (73%)

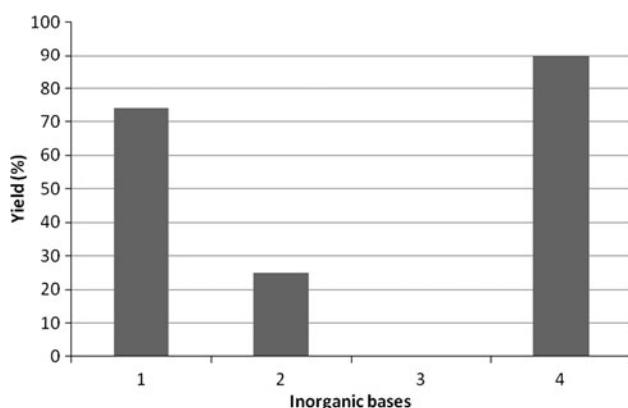


Fig. 5 Base influence on yield of theobromine reaction product with 6-chlorohexanone. 1 K₂CO₃ (73%), 2 Na₂CO₃ (77%), 3 Li₂CO₃ (0%), 4 KHCO₃ (90%)

of stronger bases such as potassium hydroxide increases formation of by-products.

To investigate influence of temperature, the reaction was carried out in a 60–140 °C range of temperature (Fig. 6). The yield of desired product was insufficient at temperature of 60–90 °C. At 120–140 °C the reaction rate was satisfactory, but the product was strongly contaminated. Considering reaction chart (Fig. 6) the optimal temperature 100–110 °C was assumed to be favorable.

We noticed that formation of impurities is time dependent. The optimal time was 8 h. Increasing the time of reaction caused sufficient increase of by-products concentration, especially detectable under UV ($\lambda = 365$ nm). Moreover, the reaction mixture is darkening with time and isolation of the desired product becomes more complicated (Fig. 7).

We found that xanthine's ring degradation is fast in presence of strong base (KOH). Under mild conditions (K₂CO₃) higher temperature and longer time of reaction is required. Figure 8 exemplifies the ¹H NMR of pentoxifylline and its degradation product.

Alkylation of oxygen atom was observed when strong base (KOH) was used. Therefore only isomer with alkylated oxygen atom in two position was isolated by column chromatography. In case of potassium carbonate the

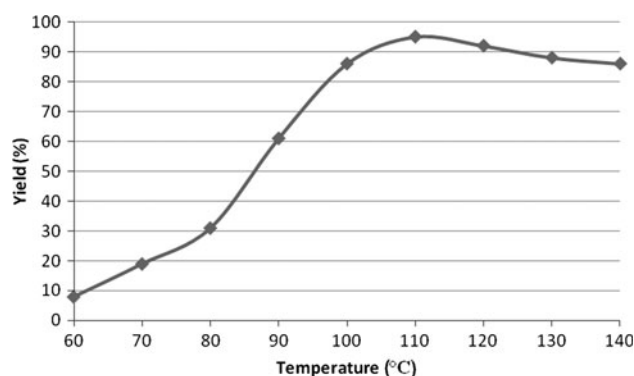


Fig. 6 Influence of temperature on the yield of pentoxifylline

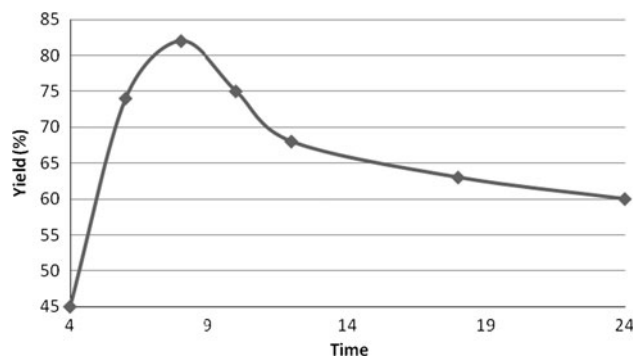


Fig. 7 Time influence on the yield of pentoxifylline

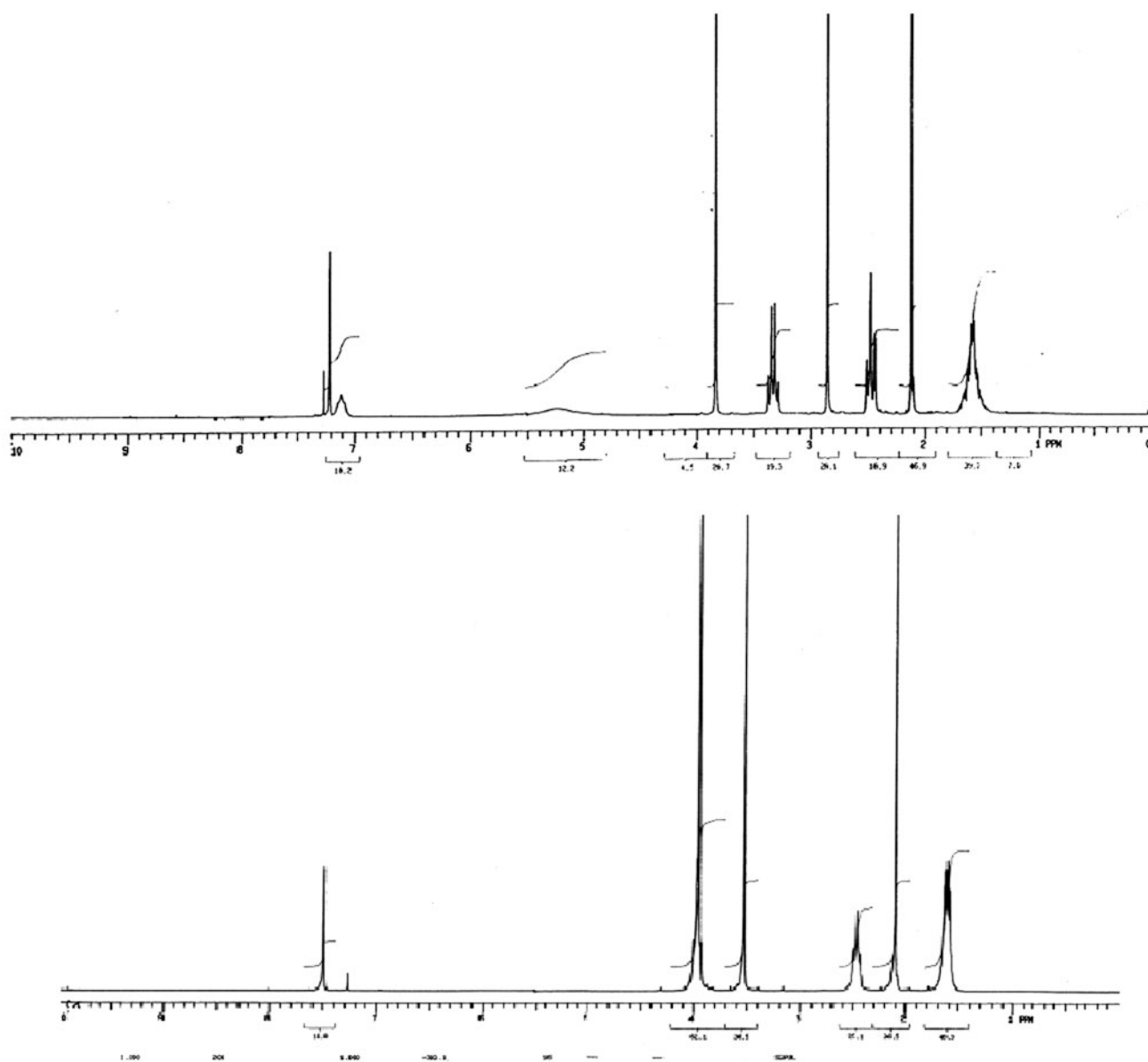


Fig. 8 ¹H NMR (200 MHz, CDCl₃) of pentoxifylline and its degradation product

mixture of two isomers was obtained, but the yield was very poor. Figure 9 shows alkylation products of enol form of theobromine with 6-chlorohexanone. The main compound was 3,7-dihydro-2-(5-oxohexyloxy)-3,7-dimethyl-6H-purine-6-one. The isomer ratio is roughly 2:1.

A mixture of: theobromine, appropriate alkylating reagent, K₂CO₃, [CH₃(CH₂)₃]₄Ni in dry DMF was stirred for 8 h at temperature 100 °C in next experiments. Then solvent was evaporated under reduced pressure. The residue was extracted with petroleum ether to remove remaining hydrocarbon halide, then with methylene chloride to separate the product from inorganic salts, theobromine and insoluble impurities. The crude product and its

discussed impurities obtained after solvent evaporation were separated by column chromatography (Table 1).

Syntheses on microwave irradiation are very popular, recently. Microwave-assisted organic synthesis has several advantages over conventional reactions in that the microwave allows for an increase in reaction rate, rapid reaction optimization, and rapid analogue synthesis. It also uses both less energy and solvent, and it enables difficult compound synthesis. Therefore, in next experiments microwave reactor was used. The applied device reactor has maximum delivered power of 1,000 W. It has built in magnetic stirrer, and power and temperature control units. The mixture described above was irradiated for 20, 30 or

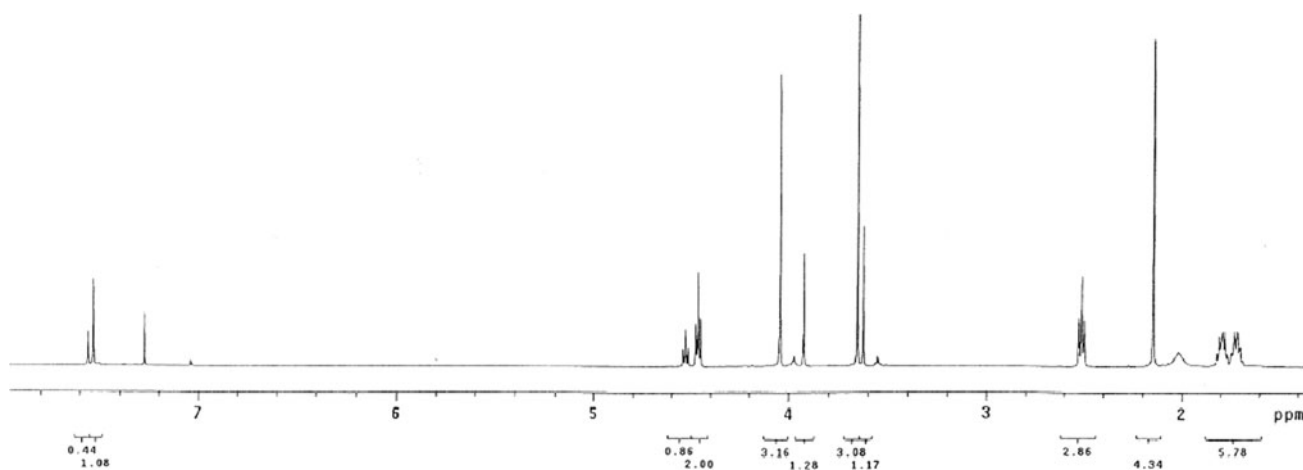


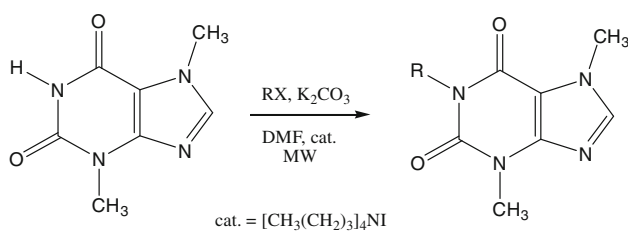
Fig. 9 ^1H NMR (500 MHz, CDCl_3) of pentoxifylline and its alkylated oxygen products

Table 1 The yields of separated products by column chromatography

Compound	Yield (%) of R-N product	Yield (%) of R-O product	Yield (%) of opening product
1	90	2	5
2	70	2	10
3	90	2	6
4	90	3	5
5	89	3	5
6	87	3	8
7	80	3	9
8	89	2	8
9	87	3	8

Table 2 Characteristic parameters of reaction for compounds 1–9 under microwave irradiation

Compound	Temperature ($^{\circ}\text{C}$)	Power of MS (W)	Time (h)	Yield (%)
1	80–90	150	0.5	98
2	90–100	100	0.5	83
3	90–100	150	0.33	92
4	90–100	100	1	98
5	90–100	150	0.33	99
6	90–100	100	1	87
7	100–110	150	0.5	83
8	90–100	100	0.5	92.5
9	90–100	100	0.5	97



Scheme 2 Alkylation reaction of theobromine with hydrocarbon halides

60 min at 10–15% of microwave power (Scheme 2). The yield of the products ranged from 83 to 99%. Moreover, all obtained compounds were extremely pure. Discussed impurities have not been noticed. Results of our experiments are presented in Table 2.

Membrane electrode

In general, all membranes for ion response contained 1 wt% ionophore (1–5), 30–33 wt% polyvinyl chloride

(PVC), 66–67 wt% 2-nitrophenyl octyl ether (*o*-NPOE) and 0.1 wt% of potassium tetrakis(4-chlorophenyl) borate (KTpCIPB). The membrane components, total 100 mg, were dissolved in 1 mL of freshly distilled THF. The solution (1 \div 0.5 μL) was applied onto graphite screen-printed electrodes and the electrodes were left to dry over 24 h. Next after evaporation of the solvent overnight the electrodes were conditioned in deionized water for 10 h. A double-junction Ag/AgCl, KCl 1 M reference electrode (Monokrystaly RAE 112) was used with 1 M NH_4NO_3 solution in the bridge cell. The measurements were carried out at 20 $^{\circ}\text{C}$, using the following cell: Ag/AgCl/internal electrolyte/ion-selective membrane/sample/1 M NH_4NO_3 /1 M KCl/AgCl/Ag and 16-channel LAWSON LAB potentiometer.

Potentiometric selectivity coefficients were determined by the separate solution method (SSM), according to a procedure established by Bakker [14]. Selectivity coefficients were calculated according to equation below, by using the EMF values for the highest measured ion activities that belongs to the linear response range for a given

ion. In order to achieve unbiased values of selectivity coefficients the calibration of the electrodes was performed for various cations, starting preferably from the most discriminating. Activity coefficients for ions were calculated in agreement with Debye–Huckel approximation.

$$\log K_{I,J}^{pot} = \frac{z_I F (E_J - E_I)}{2.303 RT} + \log \left(\frac{a_I}{a_J^{z_I/z_J}} \right)$$

As yet no data have been reported on behavior of compounds **1–5** in ion-selective membrane electrodes. We expected that *N*-alkyltheobromines should be selective to some transition and heavy metal cations. The solutions of nitrate of Zn(II), Cu(II), Ni(II), Co(II), Cd(II), Pb(II), Ag(II) and Hg(I) cations were examined. In a preliminary experiments the ion-selective membrane electrodes doped with **1–5** were selective for the copper(II) cation. The electrode slopes for Cu(II) have been found close to the Nernstian value: 28.7 mV/dec (compound **1**), 29.3 mV/dec (compound **2**), 27.9 mV/dec (compound **3**), 28.3 mV/dec (compound **4**) and 27.3 mV/dec for compound **5**. The selectivity coefficients are presented in Table 3 and Fig. 10. Column 6 represents the selectivity for electrodes with PVC/*o*-NPOE based membranes without ionophore

Table 3 Potentiometric selectivity coefficients given as $\log K_{Cu,J}$ of membrane electrodes with ionophores (**1–5**) and for comparison blank electrode

Ion	1	2	3	4	5	Blank
Zn ²⁺	1.749	3.063	1.73	1.193	-0.659	1.946
Ni ²⁺	0.376	2.676	1.388	0.798	1.292	0.461
Co ²⁺	-0.362	2.554	2.62	-0.281	2.693	1.898
Cd ²⁺	0.098	0.085	2.50	-0.427	2.937	-1.99
Pb ²⁺	-0.48	0.035	0.172	-0.247	0.930	-0.29
Ag ⁺	4.916	3.953	3.90	4.881	3.372	4.34
Hg ⁺	4.598	3.113	3.92	4.829	3.2	4.279
H ⁺	1.255	0.838	0.76	1.31	1.303	1.017

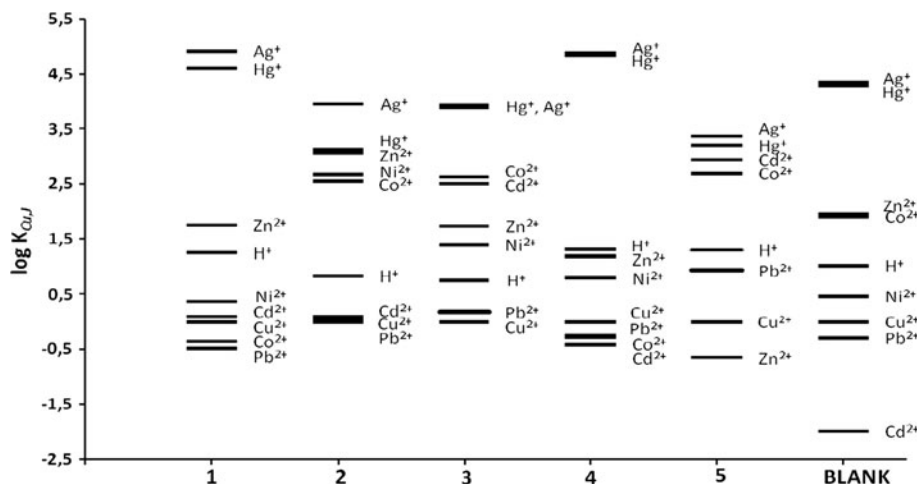
(blank electrode) and containing the cation exchanger. The results show that the Pb(II), Co(II) and Zn(II) belongs to ions most discriminated by the studied *N*-alkyltheobromines. Membrane doped with compound **5** shows better affinity towards Pb(II), Cd(II) and Zn(II) than electrode with compound **4**. That might be caused by the further aromatic ring which contributes the highest values of selectivity coefficients for Ag(I) and Hg(I): $\log K_{Cu,J} = 4.881$ and $\log K_{Cu,J} = 4.829$, respectively. Moreover, it can be seen from Fig. 10 that the incorporation of longer carbon chain (18 carbon) induce selectivities slight different from the selectivity based on compound **2** with eight carbon chain. Membranes doped with the compound **2** show higher affinity towards Zn(II) ($\log K_{Cu,J} = 3.063$) and Ni(II) ($\log K_{Cu,J} = 2.676$), whereas membranes with compound **3** are more selective towards Cd(II) ($\log K_{Cu,J} = 2.50$).

In the preliminary experiments we investigate the potentiometric response towards various anions, such as: bromide, iodide, fluoride and acetate. Before measurements electrodes were conditioned in Cu(NO₃)₂ 0.01 M solution for 10 h. The selectivity pattern of an electrode based on the *N*-alkyltheobromines is presented in Fig. 11. Electrodes based on **1**, **3**, **4** responded with nearly theoretical slopes (-52 to -60 mV/dec) for iodide ion.

Conclusions

In conclusion, alkylation of theobromine with appropriate alkyl halide under microwave irradiation have been performed. The microwave-assisted process comparing to conventional heating, gives the higher yields in much shorter time without by-products such as oxygen atom alkylation and 1-*N*-alkyltheobromine ring opening. This method confirms that microwave irradiation allow products synthesis with potential medical application in easy way

Fig. 10 Selectivity coefficient, determined as $\log K_{Cu,J}$ by the SSM



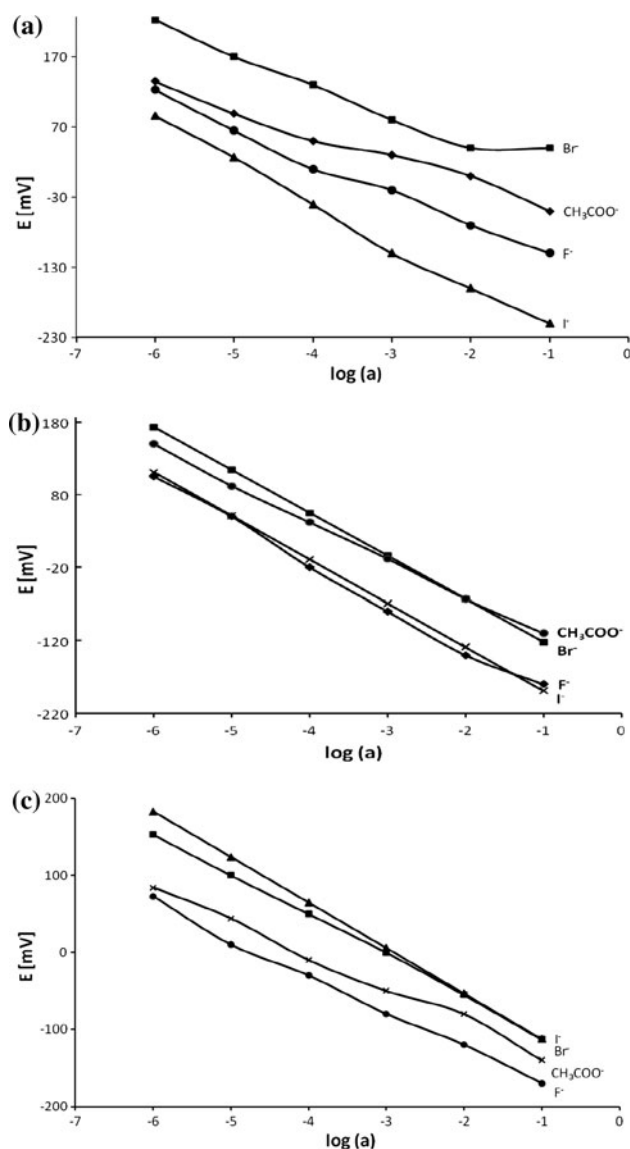


Fig. 11 Selectivity pattern of an electrode based on the compounds: **a 1, b 3, c 4**. The electrode was exposed to sodium: bromide, iodide, fluoride and acetate

with good yields. The properties of *N*-alkyltheobromine derivatives have been characterized potentiometrically in polymeric ion-selective membranes.

Experimental section

All materials and solvents used for syntheses were of analytical reagent grade. TLC were performed on aluminium plates covered with Silica gel 60 F_{254} (Merck). ^1H NMR spectra, all in CDCl_3 , were taken on Varian instruments at 200 and 500 MHz. IR and mass spectra were recorded on AMD-604 and Genesis II (Mattson) apparatus, respectively. Mass spectra were determined with AMD 604

instrument. Elemental analyses were obtained on EAGER 200 apparatus. The melting points were uncorrected. The microwave-assisted reactions were performed in microwave reactor, Plazmatronika (RM 800). The microwave has a power supply— $230 \text{ V} \pm 10\%/50 \text{ Hz}$ with a maximum delivered power of 1,000 W. High molecular weight PVC, KTpCIPB, NPOE and tetrahydrofuran were purchased from Fluka. The screen-printed graphite electrodes used were obtained from Institute of Electronic Materials Technology, Warsaw (plates of 18–15 mm with six electrodes, openings area ca. 1 mm^2). All aqueous solution were prepared from salts of p.a. purity using deionized water. All measurements were performed at room temperatures.

Syntheses

Conventional synthesis—general procedure

A mixture of theobromine (0.45 g, 2.5 mmol), alkyl halide (2.5 mmol), potassium carbonate (0.69 g, 5 mmol), tetrabutylammonium iodide (10 mmol%) and dimethylformamide (5 mL) was stirred for 8 h in 100°C . Then the DMF excess was removed on a rotary evaporator. The residue was extracted with petroleum ether (20 mL) to remove remained electrophilic reagent and next the product was extracted with CH_2Cl_2 (20 mL). The undissolved material was filtered off. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel.

Microwave-assisted synthesis—general procedure

A mixture of theobromine (0.45 g, 2.5 mmol), alkyl halide (2.5 mmol), potassium carbonate (0.69 g, 5 mmol), tetrabutylammonium iodide (10 mmol%) and dimethylformamide (5 mL) was carried out in a Microwave reactor. The reaction mixtures were irradiated under temperatures and microwave power reported in Table 2. The reaction progress was monitored by TLC. After reaction the solvent was removed on a rotary evaporator. The solid residue was extracted with petroleum ether (20 mL) to remove remained electrophilic reagent and then the product was extracted with CH_2Cl_2 (20 mL). The solvent was removed under reduced pressure and the crude product was purified by recrystallization using a suitable solvent.

3,7-Dihydro-3,7-dimethyl-1-(3-chloropropene)-1H-purine-2,6-dione (1) White solid, mp $135\text{--}137^\circ\text{C}$, solvent for crystallization: ethyl acetate/petroleum ether (1/1). ^1H NMR (200 MHz, CDCl_3): $\delta = 7.56$ (s, 1H, CH), 6.4 (d, $J = 14.3 \text{ Hz}$, 1H, =CH–Cl), 6.11–5.98 (m, 1H, –CH=), 4.0 (d, $J = 7.12 \text{ Hz}$, 2H, $\text{CH}_2\text{--N}$), 3.98 (s, 3H, CH_3), 3.57

(s, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₀H₁₁ClN₄O₂: $m/z = 254.05705$, found: 254.05689. IR (film): 2959, 2926, 2855, 1705, 1661, 1605, 1550, 1461, 1358, 1324, 1286, 1234, 1121, 763, 750, 616 cm⁻¹. Anal. calcd. for C₁₀H₁₁ClN₄O₂: C 47.27, H 4.36, N 22.05, Cl 13.95; found: C 47.29, H 4.41, N 22.13, Cl 13.89.

1-Methyl-4-(methylamino)-1H-imidazole-5-N-(3-chloropropene)-carboxamide Yellow oil. ¹H NMR (200 MHz, CDCl₃): $\delta = 7.45$ (s, 1H, CH), 6.90 (N–H, 2H), 6.7 (d, $J = 14.1$ Hz, 1H, =CH–Cl), 6.65–6.50 (m, 1H, –CH=), 4.04 (d, $J = 7.10$ Hz, 2H, CH₂–N), 3.84 (s, 3H, CH₃), 3.43 (s, 3H, CH₃) ppm. HRMS (EI) calcd. for C₉H₁₃ClN₄O: $m/z = 228.67872$, found: 228.67925. IR (film): 3129, 3010, 2959, 2926, 2855, 1705, 1661, 1605, 1461, 1358, 1324, 1286, 1234, 1121, 1025, 973, 763, 750, 616, 550 cm⁻¹. Anal. calcd. for C₉H₁₃ClN₄O: C 47.27, H 5.73, N 24.50, Cl 15.50; found: C 47.35, H 5.68, N 24.49, Cl 15.63.

3,7-Dihydro-2-chloropropenoxy-3,7-dimethyl-6H-purine-6-one Colorless oil. ¹H NMR (200 MHz, CDCl₃): $\delta = 7.56$ (s, 1H, CH), 6.27–6.22 (m, 1H, =CH–Cl), 6.15–6.10 (m, 1H, –CH=), 5.04 (d, $J = 6.8$ Hz, CH₂O), 4.02 (s, 3H, CH₃), 3.79 (s, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₀H₁₁ClN₄O₂: $m/z = 254.05705$, found: 254.05739. IR (film): 3010, 2959, 2926, 2875, 2855, 1705, 1605, 1461, 1358, 1324, 1286, 1234, 1270, 1121, 1075, 763, 750, 616 cm⁻¹. Anal. calcd. for C₁₀H₁₁ClN₄O₂: C 47.27, H 4.36, N 22.05, Cl 13.95; found: C 47.32, H 4.46, N 22.19, Cl 13.98.

3,7-Dihydro-3,7-dimethyl-1-(octyl)-1H-purine-2,6-dione (2) White solid, mp 89–93 °C, solvent for crystallization: ethanol. ¹H NMR (500 MHz, CDCl₃): $\delta = 7.52$ (s, 1H, CH), 4.03–3.99 (m, 5H, N–CH₂, CH₃), 3.59 (s, 3H, CH₃), 1.71–1.63 (m, 2H, CH₂), 1.34–1.28 (m, 10H, 5CH₂), 0.89 (t, $J = 6.83$ Hz, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₅H₂₄N₄O₂: $m/z = 292.18993$, found: 292.18917. IR (film): 2952, 1705, 1660, 1603, 1550, 1454, 1359, 1323, 1286, 1234, 1123, 763, 616 cm⁻¹. Anal. calcd. for C₁₅H₂₄N₄O₂: C 61.66, H 8.28, N 19.17; found: C 61.54, H 8.61, N 19.03.

1-Methyl-4-(methylamino)-1H-imidazole-5-N-(octyl)-carboxamide Brown oil. ¹H NMR (500 MHz, CDCl₃): $\delta = 7.49$ (s, 1H, CH), 7.10 (s, 1H, N–H), 5.42–5.20 (N–H, 1H), 3.93–3.87 (m, 5H, N–CH₂, CH₃), 3.46 (s, 3H, CH₃), 1.69–1.64 (m, 2H, CH₂), 1.32–1.26 (m, 10H, 5CH₂), 0.86 (t, $J = 6.81$ Hz, 3H) ppm. HRMS (EI) calcd. for C₁₄H₂₆N₄O: $m/z = 266.38367$, found: 266.38285. IR (film): 3120, 3002, 2952, 2869, 1705, 1660, 1603, 1454, 1359, 1323, 1286, 1234, 1123, 1020, 973, 763, 616,

540 cm⁻¹. Anal. calcd. for C₁₄H₂₆N₄O: C 63.12, H 9.84, N 21.03; found: C 63.58, H 9.49, N 21.15.

3,7-Dihydro-2-octyloxy-3,7-dimethyl-6H-purine-6-one Colorless oil. ¹H NMR (500 MHz, CDCl₃): $\delta = 7.50$ (s, 1H, CH), 4.02 (s, 3H, CH₃), 3.86–3.81 (m, 2H, CH₂O), 3.79 (s, 3H, CH₃), 1.75–1.66 (m, 2H, CH₂), 1.36–1.27 (m, 10H, 5CH₂), 0.88 (t, $J = 6.26$ Hz, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₅H₂₄N₄O₂: $m/z = 292.18993$, found: 292.18897. IR (film): 3009, 2952, 2869, 1705, 1603, 1454, 1359, 1323, 1286, 1260, 1234, 1170, 1123, 763, 616 cm⁻¹. Anal. calcd. for C₁₅H₂₄N₄O₂: C 61.66, H 8.28, N 19.17; found: C 61.78, H 8.32, N 19.37.

3,7-Dihydro-3,7-dimethyl-1-(hexadecyl)-1H-purine-2,6-dione (3) White solid, mp 80–82 °C, solvent for crystallization: methanol. ¹H NMR (500 MHz, CDCl₃): $\delta = 7.54$ (s, 1H, CH), 4.03–3.99 (m, 5H, N–CH₂, CH₃), 3.6 (s, 3H, CH₃), 1.68–1.65 (m, 2H, CH₂), 1.27–1.36 (m, 26H, 13CH₂), 0.9 (t, $J = 6.83$ Hz, 3H, CH₃) ppm. HRMS (EI) calcd. for C₂₃H₄₀N₄O₂: $m/z = 404.31513$, found: 404.31479. IR (film): 2955, 2918, 2850, 1713, 1660, 1555, 1469, 1214, 1122, 770, 617 cm⁻¹. Anal. calcd. for C₂₃H₄₀N₄O₂: C 68.32, H 9.96, N 13.86; found: C 68.28, H 9.91, N 13.79.

1-Methyl-4-(methylamino)-1H-imidazole-5-N-(hexadecyl)-carboxamide Brown oil. ¹H NMR (500 MHz, CDCl₃): $\delta = 7.25$ (s, 1H, CH), 7.11 (s, 1H, N–H), 5.42–5.20 (N–H, 1H), 3.93–3.80 (m, 5H, N–CH₂, CH₃), 3.5 (s, 3H, CH₃), 1.65–1.63 (m, 2H, CH₂), 1.30–1.22 (m, 26H, 13CH₂), 0.87 (t, $J = 6.82$ Hz, 3H) ppm. HRMS (EI) calcd. for C₂₂H₄₂N₄O: $m/z = 378.59695$, found: 378.59524. IR (film): 3135, 3000, 2955, 2918, 2870, 2850, 1713, 1660, 1469, 1214, 1122, 1027, 980, 770, 617, 530 cm⁻¹. Anal. calcd. for C₂₂H₄₂N₄O: C 69.79, H 11.18, N 14.79; found: C 69.62, H 11.27, N 14.63.

3,7-Dihydro-2-hexadecyloxy-3,7-dimethyl-6H-purine-6-one Colorless oil. ¹H NMR (500 MHz, CDCl₃): $\delta = 7.50$ (s, 1H, CH), 4.02 (s, 3H, CH₃), 3.86–3.81 (m, 2H, CH₂O), 3.78 (s, 3H, CH₃), 1.76–1.67 (m, 2H, CH₂), 1.32–1.25 (m, 26H, 13CH₂), 0.89 (t, $J = 7.25$ Hz, 3H, CH₃) ppm. HRMS (EI) calcd. for C₂₃H₄₀N₄O₂: $m/z = 404.31513$, found: 404.31438. IR (film): 3000, 2955, 2918, 2870, 2850, 1713, 1469, 1214, 1122, 1060, 770, 617 cm⁻¹. Anal. calcd. for C₂₃H₄₀N₄O₂: C 68.32, H 9.96, N 13.86; found: C 68.54, H 9.87, N 13.94.

3,7-Dihydro-3,7-dimethyl-1-(4-methyl-1-methylnaphthalene)-1H-purine-2,6-dione (4) White solid, mp 206–208 °C, solvent for crystallization: ethyl acetate/petroleum ether (1/1). ¹H NMR (200 MHz, CDCl₃): $\delta = 8.31$ –8.26 (m, 1H, H_{Ar}), 8.05–8.0 (m, 1H, H_{Ar}), 7.62–7.5 (m, 3H, CH, 2-H_{Ar}),

7.24–7.14 (m, 2H, H_{Ar}), 5.69 (s, 2H, N–CH₂), 3.99 (s, 3H, CH₃), 3.60 (s, 3H, CH₃), 2.65 (s, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₉H₁₈N₄O₂: m/z = 334.14298, found: 334.14372. IR (film): 2957, 2931, 2859, 1705, 1659, 1605, 1549, 1484, 1454, 1358, 1326, 1286, 1234, 1122, 764, 750, 615 cm⁻¹. Anal. calcd. for C₁₉H₁₈N₄O₂: C 68.29, H 5.43, N 16.77; found: C 68.35, H 5.39, N 16.68.

1-Methyl-4-(methylamino)-1H-imidazole-5-N-(4-methyl-1-methylnaphthalene)-carboxamide Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 8.29–8.22 (m, 1H, H_{Ar}), 8.0–7.9 (m, 1H, H_{Ar}), 7.58–7.49 (m, 3H, CH, 2-H_{Ar}), 7.2 (s, 1H, N–H), 7.19–7.1 (m, 2H, H_{Ar}), 6.9 (N–H, 1H), 5.63 (s, 2H, N–CH₂), 3.81 (s, 3H, CH₃), 3.58 (s, 3H, CH₃), 2.54 (s, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₈H₂₀N₄O: m/z = 308.37915, found: 308.37821. IR (film): 3133, 3006, 2957, 2931, 2859, 1705, 1659, 1605, 1484, 1454, 1358, 1326, 1286, 1234, 1122, 1023, 973, 761, 756, 610 cm⁻¹. Anal. calcd. for C₁₈H₂₀N₄O: C 70.11, H 6.54, N 18.17; found: C 70.38, H 6.48, N 18.09.

3,7-Dihydro-2-(4-methyl-1-methylnaphthalene)-3,7-dimethyl-6H-purin-6-one Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 8.24–8.21 (m, 1H, H_{Ar}), 7.93–7.91 (m, 1H, H_{Ar}), 7.77–7.74 (m, 1H, H_{Ar}), 7.55 (s, 1H, CH), 7.47–7.45 (m, 1H, H_{Ar}), 7.22–7.09 (m, 2H, H_{Ar}), 5.53 (s, 2H, CH₂O), 4.03 (s, 3H, CH₃), 3.76 (s, 3H, CH₃), 2.73 (s, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₉H₁₈N₄O₂: m/z = 334.14298, found: 334.14156. IR (film): 3006, 2957, 2931, 2875, 2859, 1705, 1605, 1484, 1454, 1358, 1326, 1286, 1234, 1122, 1060, 750, 615 cm⁻¹. Anal. calcd. for C₁₉H₁₈N₄O₂: C 68.29, H 5.43, N 16.77; found: C 68.41, H 5.38, N 16.59.

3,7-Dihydro-3,7-dimethyl-1-(benzyl)-1H-purine-2,6-dione (5) White solid, mp 140–143 °C, solvent for crystallization: ethyl acetate/petroleum ether (1/1). ¹H NMR (500 MHz, CDCl₃): δ = 7.52–7.50 (m, 3H, CH, 2-H_{Ar}), 7.39–7.27 (m, 3H, H_{Ar}), 5.22 (s, 2H, CH₂Ph), 4.00 (s, 3H, CH₃), 3.59 (s, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₄H₁₄N₄O₂: m/z = 270.11168, found: 270.11047. IR (film): 2960, 2932, 2872, 1706, 1658, 1606, 1550, 1485, 1454, 1358, 1327, 1287, 1237, 1116, 943, 764, 616 cm⁻¹. Anal. calcd. for C₁₄H₁₄N₄O₂: C 62.25, H 5.22, N 20.74; found: C 62.31, H 5.19, N 20.82.

1-Methyl-4-(methylamino)-1H-imidazole-5-N-(benzyl)-carboxamide Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.50–7.48 (m, 3H, CH, 2-H_{Ar}), 7.35–7.26 (m, 3H, H_{Ar}), 7.1 (s, 1H, N–H), 5.6 (N–H, 1H), 5.19 (s, 2H, CH₂Ph), 3.88 (s, 3H, CH₃), 3.57 (s, 3H, CH₃) ppm. HRMS

(EI) calcd. for C₁₃H₁₆N₄O: m/z = 244.29349, found: 244.29285. IR (film): 3129, 2960, 2932, 2872, 1706, 1658, 1606, 1485, 1454, 1358, 1327, 1287, 1237, 1020, 1116, 973, 943, 764, 616, 550 cm⁻¹. Anal. calcd. for C₁₃H₁₆N₄O: C 63.91, H 6.60, N 22.93; found: C 63.84, H 6.72, N 22.79.

3,7-Dihydro-2-benzyloxy-3,7-dimethyl-6H-purine-6-one Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.56 (s, 1H, CH), 7.50–7.27 (m, 5H, H_{Ar}), 4.88 (s, 2H, PhCH₂O), 4.02 (s, 3H, CH₃), 3.69 (s, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₄H₁₄N₄O₂: m/z = 270.11168, found: 270.11198. IR (film): 3100, 2960, 2932, 2872, 2870, 1706, 1606, 1485, 1454, 1358, 1327, 1287, 1237, 1200, 1116, 1070, 943, 764, 616 cm⁻¹. Anal. calcd. for C₁₄H₁₄N₄O₂: C 62.25, H 5.22, N 20.74; found: C 62.47, H 5.47, N 20.97.

3,7-Dihydro-3,7-dimethyl-1-(butyl)-1H-purine-2,6-dione (6) White solid, mp 109–112 °C, solvent for crystallization: ethyl acetate. ¹H NMR (500 MHz, CDCl₃): δ = 7.52 (s, 1H, CH), 4.02 (t, J = 7.81 Hz, 2H, CH₂), 4.0 (s, 3H, CH₃), 3.59 (s, 3H, CH₃), 1.65 (q, J = 7.81 Hz, 2H, CH₂), 1.45–1.39 (m, 2H, CH₂), 0.97 (t, J = 7.32 Hz, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₁H₁₆N₄O₂: m/z = 236.12733, found: 236.12626. IR (film): 2959, 1705, 1660, 1602, 1549, 1485, 1454, 1320, 1285, 1235, 1125, 752, 616 cm⁻¹. Anal. calcd. for C₁₁H₁₆N₄O₂: C 55.95, H 6.83, N 23.72; found: C 55.89, H 6.85, N 23.67.

1-Methyl-4-(methylamino)-1H-imidazole-5-N-(butyl)-carboxamide Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.18 (s, 1H, CH), 5.75–5.6 (m, 2H, N–H), 3.83 (s, 3H, CH₃), 3.46 (s, 3H, CH₃), 3.18–3.13 (m, 2H, N–CH₂), 1.56–1.31 (m, 4H, CH₂CH₂), 0.82 (t, J = 7.1 Hz, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₀H₁₈N₄O: m/z = 210.27703, found: 210.27618. IR (film): 3130, 3000, 2959, 1705, 1660, 1602, 1485, 1454, 1320, 1285, 1235, 1125, 1025, 973, 752, 616, 550 cm⁻¹. Anal. calcd. for C₁₀H₁₈N₄O: C 57.12, H 8.62, N 26.64; found: C 57.63, H 8.58, N 26.78.

3,7-Dihydro-2-butyloxy-3,7-dimethyl-6H-purine-6-one Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.52 (s, 1H, CH), 3.91 (t, J = 7.76 Hz, 2H, CH₂O), 4.0 (s, 3H, CH₃), 3.79 (s, 3H, CH₃), 2.65–2.51 (m, 2H, CH₂), 1.78–1.72 (m, 2H, CH₂), 0.84 (t, J = 6.57 Hz, 3H, CH₃) ppm. HRMS (EI) calcd. for C₁₁H₁₆N₄O₂: m/z = 236.12733, found: 236.12814. IR (film): 3002, 2959, 2870, 1704, 1601, 1483, 1454, 1320, 1284, 1235, 1123, 1060, 752 cm⁻¹. Anal. calcd. for C₁₁H₁₆N₄O₂: C 55.95, H 6.83, N 23.72; found: C 55.82, H 6.95, N 23.58.

3,7-Dihydro-3,7-dimethyl-1-(pentyl)-1H-purine-2,6-dione (7) Yellow solid, mp 98–100 °C, solvent for crystallization: diethyl ether. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.53$ (s, 1H, CH), 4.02–3.99 (m, 5H, CH_2CH_3), 3.59 (s, 3H, CH_3), 1.38–1.35 (m, 6H, 3CH_2), 0.92 (t, $J = 6.84$ Hz, 3H, CH_3) ppm. HRMS (EI) calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}_2$: $m/z = 250.14298$, found: 250.14410. IR (film): 2958, 1704, 1660, 1605, 1549, 1485, 1454, 1354, 1283, 1234, 1122, 703, 617 cm^{-1} . Anal. calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}_2$: C 57.62, H 7.25, N 22.39; found: C 57.59, H 7.19, N 22.36.

1-Methyl-4-(methylamino)-1H-imidazole-5-N-(pentyl)-carboxamide Colorless oil. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.48$ (s, 1H, CH), 5.37–5.2 (m, 2H, N–H), 3.94–3.89 (m, 5H, CH_2CH_3), 3.55 (s, 3H, CH_3), 1.35–1.32 (m, 6H, 3CH_2), 0.9 (t, $J = 6.83$ Hz, 3H, CH_3) ppm. HRMS (EI) calcd. for $\text{C}_{11}\text{H}_{20}\text{N}_4\text{O}$: $m/z = 224.30369$, found: 224.30284. IR (film): 3131, 3008, 2958, 1704, 1660, 1605, 1549, 1485, 1454, 1354, 1283, 1234, 1122, 1024, 971, 703, 617, 550 cm^{-1} . Anal. calcd. for $\text{C}_{11}\text{H}_{20}\text{N}_4\text{O}$: C 58.97, H 8.98, N 24.98; found: C 58.88, H 8.69, N 24.75.

3,7-Dihydro-2-pentyloxy-3,7-dimethyl-6H-purine-6-one Colorless oil. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.50$ (s, 1H, CH), 4.02 (s, 3H, CH_3), 3.89–3.86 (m, 2H, CH_2O), 3.79 (s, 3H, CH_3), 1.81–1.75 (m, 2H, CH_2), 1.49–1.37 (m, 4H, 2CH_2), 0.93 (t, $J = 6.96$ Hz, 3H, CH_3) ppm. HRMS (EI) calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}_2$: $m/z = 250.14298$, found: 250.14308. IR (film): 3018, 2958, 2876, 1704, 1605, 1485, 1454, 1354, 1283, 1234, 1122, 1065, 703, 617 cm^{-1} . Anal. calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}_2$: C 57.62, H 7.25, N 22.39; found: C 57.78, H 7.43, N 22.28.

3,7-Dihydro-3,7-dimethyl-1-(dodecyl)-1H-purine-2,6-dione (8) White solid, mp 69–71 °C, solvent for crystallization: petroleum ether/methanol (1/1). ^1H NMR (500 MHz, CDCl_3): $\delta = 7.53$ (s, 1H, CH), 4.03–3.99 (m, 5H, CH_2CH_3), 3.6 (s, 3H, CH_3), 1.68–1.63 (m, 2H, CH_2), 1.38–1.27 (m, 18H, 9CH_2), 0.9 (t, $J = 6.83$ Hz, 3H, CH_3) ppm. HRMS (EI) calcd. for $\text{C}_{19}\text{H}_{32}\text{N}_4\text{O}_2$: $m/z = 348.25253$, found: 348.25124. IR (film): 2958, 1705, 1660, 1603, 1549, 1485, 1454, 1370, 1305, 1234, 1124, 750, 617 cm^{-1} . Anal. calcd. for $\text{C}_{19}\text{H}_{32}\text{N}_4\text{O}_2$: C 65.52, H 9.26, N 16.09; found: C 65.61, H 9.29, N 16.13.

1-Methyl-4-(methylamino)-1H-imidazole-5-N-(dodecyl)-carboxamide Colorless oil. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.48$ (s, 1H, CH), 5.39–5.26 (m, 2H, N–H), 4.0–3.89 (m, 5H, CH_2CH_3), 3.55 (s, 3H, CH_3), 1.61–1.67 (m, 2H, CH_2), 1.25–1.39 (m, 18H, 9CH_2), 0.89 (t, $J = 6.81$ Hz, 3H, CH_3) ppm. HRMS (EI) calcd. for $\text{C}_{18}\text{H}_{34}\text{N}_4\text{O}$: $m/z = 322.49031$, found: 322.49149. IR (film): 3129, 3005, 2958, 1705, 1660, 1603, 1549, 1485, 1454, 1370, 1305, 1234, 1124, 1020, 970, 750, 617, 550 cm^{-1} . Anal. calcd. for $\text{C}_{18}\text{H}_{34}\text{N}_4\text{O}$: C 67.04, H 10.63, N 17.37; found: C 67.11, H 10.56, N 17.28.

3,7-Dihydro-2-dodecyloxy-3,7-dimethyl-6H-purine-6-one Colorless oil. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.50$ (s, 1H, CH), 4.02 (s, 3H, CH_3), 3.86–3.81 (m, 2H, CH_2O), 3.79 (s, 3H, CH_3), 1.76–1.67 (m, 2H, CH_2), 1.37–1.25 (m, 18H, 9CH_2), 0.88 (t, $J = 6.25$ Hz, 3H, CH_3) ppm. HRMS (EI) calcd. for $\text{C}_{19}\text{H}_{32}\text{N}_4\text{O}_2$: $m/z = 348.25253$, found: 348.25311. IR (film): 3015, 2958, 2874, 1705, 1603, 1485, 1454, 1370, 1305, 1234, 1124, 1070, 750, 617 cm^{-1} . Anal. calcd. for $\text{C}_{19}\text{H}_{32}\text{N}_4\text{O}_2$: C 65.52, H 9.26, N 16.09; found: C 65.41, H 9.35, N 16.20.

3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione (9) White solid, mp 102–105 °C, solvent for crystallization: ethyl acetate/petroleum ether (1/1). ^1H NMR (200 MHz, CDCl_3): $\delta = 7.51$ (s, 1H, CH), 4.0–3.93 (m, 5H, CH_2CH_3), 3.56 (s, 3H, CH_3), 2.49 (t, $J = 6.96$ Hz, 2H, CH_2), 2.13 (s, 3H, CH_3), 1.65–1.63 (m, 4H, 2CH_2) ppm. HRMS (EI) calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_3$: $m/z = 278.13789$, found: 278.13680. IR (film): 2955, 2920, 2849, 1703, 1659, 1603, 1549, 1462, 1358, 1324, 1284, 1228, 1124, 941, 763, 617 cm^{-1} . Anal. calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_3$: C 56.14, H 6.52, N 20.14; found: C 56.19, H 6.48, N 20.09.

1-Methyl-4-(methylamino)-1H-imidazole-5-N-(5-oxohexyl)-carboxamide Colorless oil. ^1H NMR (200 MHz, CDCl_3): $\delta = 7.21$ (s, 1H, CH), 7.13 (s, 1H, N–H), 5.25–5.31 (N–H, 1H), 3.83 (s, 3H, CH_3), 3.30 (q, $J = 6.4$ Hz, 2H, CH_2), 2.85 (s, 3H, CH_3), 2.48 (t, $J = 6.8$ Hz, 2H, CH_2), 2.12 (s, 3H, CH_3), 1.51–1.66 (m, 4H, 2CH_2) ppm. HRMS (EI) calcd. for $\text{C}_{12}\text{H}_{20}\text{N}_4\text{O}_2$: $m/z = 252.3139$, found: 252.31285. IR (film): 3130, 3000, 2955, 2920, 2849, 1703, 1659, 1603, 1549, 1462, 1358, 1324, 1284, 1228, 1124, 1010, 970, 941, 763, 617, 550 cm^{-1} . Anal. calcd. for $\text{C}_{12}\text{H}_{20}\text{N}_4\text{O}_2$: C 57.12, H 7.99, N 22.21; found: C 57.23, H 7.86, N 22.32.

3,7-Dihydro-2-(5-oxohexyloxy)-3,7-dimethyl-6H-purine-6-one Colorless oil. ^1H NMR (200 MHz, CDCl_3): $\delta = 7.56$ (s, 1H, CH), 4.25 (m, 2H, CH_2O), 4.08 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 2.49–2.43 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 1.68–1.62 (m, 4H, 2CH_2) ppm. HRMS (EI) calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_3$: $m/z = 278.13789$, found: 278.13826. IR (film): 3008, 2955, 2920, 2870, 2849, 1703, 1659, 1603, 1462, 1358, 1324, 1284, 1228, 1170, 1124, 941, 763, 617 cm^{-1} . Anal. calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_3$: C 56.14, H 6.52, N 20.14; found: C 56.27, H 6.45, N 20.29.

3,7-Dihydro-2-(5-oxohexyloxy)-3,7-dimethyl-6H-purine-6-one Colorless oil. ^1H NMR (200 MHz, CDCl_3): $\delta = 7.56$ (s, 1H, CH), 4.25 (m, 2H, CH_2O), 4.08 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 2.49–2.43 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 1.68–1.62 (m, 4H, 2CH_2) ppm. HRMS (EI) calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_3$: $m/z = 278.13789$, found: 278.13826. IR (film): 3008, 2955, 2920, 2870, 2849, 1703, 1659, 1603, 1462, 1358, 1324, 1284, 1228, 1170, 1124, 941, 763, 617 cm^{-1} . Anal. calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_3$: C 56.14, H 6.52, N 20.14; found: C 56.27, H 6.45, N 20.29.

Acknowledgments Financial support of this work from Gdansk University of Technology, grant no. BW 014694/038, BW 014694/039 is kindly acknowledged.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

References

1. Müller, C.E., Shi, D., Manning, M., Daly, J.W.: Synthesis of paraxanthine analogs (1,7-disubstituted xanthines) and other xanthines unsubstituted at the 3-position: structure–activity relationships at adenosine receptors. *J. Med. Chem.* **36**, 3341–3349 (1993)
2. Ward, A., Clissold, S.P.: Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. *Drugs* **34**, 50–97 (1987)
3. Strieter, R.M., Remick, D.G., Ward, P.A., Spengler, R.N., Lynch III, J.P., Larrick, J., Kunkel, S.L.: Cellular and molecular regulation of tumor necrosis factor- α production by pentoxifylline. *Biochem. Biophys. Res. Commun.* **155**, 1230–1236 (1988)
4. Cottam, H.B., Shih, H., Tehrani, L.R., Wasson, B., Carson, D.A.: Substituted xanthines, pterinediones, and related compounds as potential antiinflammatory agents. Synthesis and biological evaluation of inhibitors of tumor necrosis factor α . *J. Med. Chem.* **39**, 2–9 (1996)
5. Speer, J.H., Raymond, A.L.: Some alkyl homologs of theophylline. *J. Am. Chem. Soc.* **75**, 114–115 (1953)
6. Pascal, J.C., Beranger, S., Pinhas, H., Poizot, A., Désiles, J.P.: New antihistaminic theophylline or theobromine derivatives. *J. Med. Chem.* **28**, 647–652 (1985)
7. Daly, J.W., Padgett, W.L., Shamim, M.T.: Analogs of caffeine and theophylline: effect of structural alterations on affinity at adenosine receptors. *J. Med. Chem.* **29**, 1305–1308 (1986)
8. He, R., Ching, S.M., Lam, Y.L.: Traceless solid-phase synthesis of substituted xanthines. *J. Comb. Chem.* **8**, 923–928 (2006)
9. Madyastha, K.M., Sridhar, G.R.: Highly efficient C-8 oxidation of substituted xanthines with substitution at the 1-, 3-, and 7-positions using biocatalyst. *J. Chem. Soc. Perkin Trans.* **1**, 677–680 (1999)
10. Daly, J.W., Padgett, W.L., Shamim, M.T.: Adenosine receptors: target for future drugs. *J. Med. Chem.* **25**, 197–207 (1982)
11. Bram, G., Decodts, G.: *N*-alkylation of pyrimidine and purine derivatives (9 uracils, xanthines, adenine) using solid/liquid phase-transfer catalysis without solvent. *Synthesis* **5**, 543–545 (1985)
12. Khalafi-Nezhad, A., Zare, A., Parhami, A., Hasaninejad, A., Moosavi Zare, A.R.: Quaternary ammonium salts as highly efficient and green alkylating agents for *N*-alkylation of azaheterocycles under microwave irradiation. *J. Iran. Chem. Soc.* **5**(Suppl.), 40–46 (2008)
13. Ding, J., Wu, H., Zhao, X.: *N*-hydrocarbylation of theobromine under microwave. *Hecheng Huaxue* **9**(4), 368–369 (2001)
14. Bakker, E.: *Anal. Chem.* **69**, 1061 (1997)