Synthesis and Characterization of Some New Theophylline Derivatives

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This paper presents the synthesis of some new theophylline derivatives with potential bronchodilatatory properties. The compounds were synthesized starting from theophylline and 8-R-theophyllines (R=Br, NO_2, pyrrolidinyl, piperidinyl, morpholinyl, imidazolyl) that were reacted with 4-(2,3-epoxy-propyloxy)-acetanilide. The new compounds, which have not been mentioned in the literature concerning this domain, have been characterized by their physical constants (melting point, solubility) and the chemical structure was confirmed by elemental and spectral (FT-IR, ^{1}H-NMR, ^{13}C-NMR) analysis. The DL_{50} values of new synthesized theophylline derivatives have been also established.

Keywords: theophylline, acethaminophen, ^{1}H-NMR, ^{13}C-NMR

Asthma and pulmonary chronic obstructive diseases are severe diseases with growing incidence that represents an important cause of death in the whole world. The physiopathogenic components of these diseases are bronchospasm, viscous and obstructive bronchial hypersecretion, inflammation and edema of bronchial mucous [1-2]. The first line therapy for the last 20 years were beta 2-adrenergic agonists in combination with glucocorticoids. By inhibition of bronchonstriction the beta 2-adrenergic agonists represents a symptomatic treatment while glucocoticoids by their anti-inflammatory action interfere with the evolution of the disease [3]. This therapeutic strategy is often associated with serious side effects like tachycardia, palpitations, headache etc.

In order to improve the therapeutics used actually in the management of asthma we designed new compounds that include two structurally different moieties – theophylline and acethaminophen. Theophylline is a methylxanthine compound, known as an efficient bronchodilatator drug, having also anti-inflammatory and immunomodulatory effects [4-9] while acethaminophen (4-hydroxy-acetanilide) has antipyretic, analgesic and also anti-inflammatory effects [10, 11]. These compounds could be a safe alternative than beta-2 adrenergic agonists and glucocorticoids .

Experimental part

All melting points were determined on a Melt-Temp R apparatus equipped with a digital thermometer and are uncorrected. The combustion analysis was performed on an Elemental Exeter Analytical CE 440 Apparatus. The IR spectra were measured as potassium bromide pellets on a Digilab Scimitar Series FT-IR Spectrophotometer; the wave numbers are given in cm^{-1}. The NMR spectra were recorded using BRUKER AVANCE DRX apparatus at 400 MHz for ^{1}H and 100 MHz for ^{13}C using solutions in DMSO-d6 as solvent. Chemical shifts were recorded as δ values in parts per millions (ppm) and were indirectly referenced to tetramethylsilane as internal standard. The toxicity degree and the lethal dose, DL50, were established using white male mice. All chemical reagents were obtained from the Aldrich Chemical Company.

The synthesis of 4-(2,3-epoxy-propyloxy)-acetanilide

To a solution of sodium hydroxide (1.5 g, 0.0375 mol) in water there were added acetaminophen (4.5 g, 0.0298 mol), and then 3.5 mL (0.0447 mol) epichlorhydrine were dropwised. The reaction mixture was stirred at room temperature for 16 h. It was obtained a white precipitated that was separated by vacuum filtration and then washed with more water.

The synthesis of 7-[2-hydroxy-3-(4-acetyl-amino-phenoxy)-propyl]-theophylline derivatives. General procedure.

2.07 g (0.01 mol) 4-(2,3-epoxy-propyloxy)-acetanilide were solved into ethanol under heating and then an ethanol solution of theophylline and 8-R-theophylline respectively was added. The reaction mixture was heated under reflux for 10 h and then the solvent was removed by distillation under reduced pressure to from initial volume. The rough products were separated by filtration under vacuum, dried and recrystallized from ethanol.

Toxicity study

The acute toxicity was estimated by intraperitoneally administration of the compounds **11-17** as a suspension (20 mg/mL) in sodium carboxymethylcellulose 0.5% to groups of six male mice, each weighing 20-22 g, according to the classical laboratory methodology [12]. The animals were monitored and the death rate ascertained after 24 h, 48 h and 7 days. The DL_{50} was established using the Spearman-Karber method [13].

Results and discussions

Chemistry

The designed compounds are 8-R-theophyline derivatives having in the 7th position an acetaminophen moiety linked *via* hydroxyalkyl chain. The synthesis of the theophylline derivatives was performed in several steps (scheme 1). In the first step, the acetaminophen (**1**) was turned into its phenoxy form (**2**) in alkaline medium, which further reacts with epichlorhydrine to form 4-(2,3-epoxy-propyloxy)-acetanilide (**3**).

In the last step this intermediary reacts in mild conditions at the boiling temperature of the ethanol with 8-substituted

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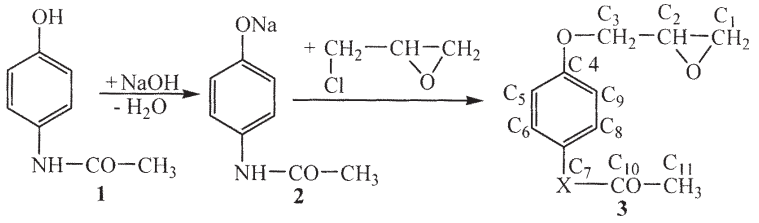
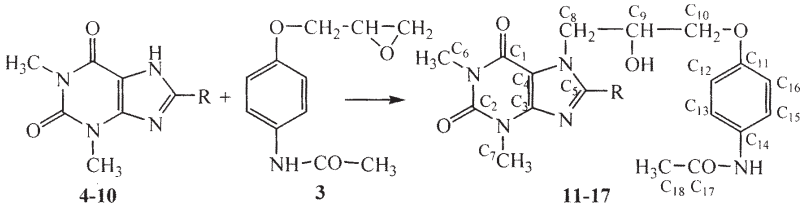


Scheme 1. Synthesis of 4-(2, 3-epoxy-propyloxy)-acetanilide



Scheme 2. Synthesis of 7-[2-hydroxy-3-(4-acetyl-amino-phenoxy)-propyl]-theophylline derivatives

theophylline (8-R-theophylline; R = hydrogen, bromo, nitro, pyrrolidinyl, piperidinyl, morpholinyl, imidazolyl radicals) (**4-10**) [14] when new 7-[2-hydroxy-3-(4-acetyl-amino-phenoxy)-propyl]-theophylline derivatives (**11-17**) have been obtained.

The structure of the synthesized compounds was established through spectroscopic (IR, ^{1}H-NMR, ^{13}C-NMR) as well as through elemental analyses data. In the IR spectra were identified two characteristic absorption bands for OH bond - at 3250-3400 cm^{-1} (OH linked) and 1190-1210 cm^{-1} (OH free) respectively that confirm the structure of the compounds. The ^{1}H-NMR spectra of the new theophylline derivatives are divided into two spectra corresponding to the xanthine system and to 4-acetyl-amino-phenoxy radical that are linked *via* hydroxyl-alkyl chain. In the ^{1}H-NMR spectra the protons corresponding to the hydroxyl-alkyl chain appear as four signals at 2.00-2.08 ppm (OH), 3.58-3.72 ppm (CH), 3.86-3.94 ppm (CH_2) and 4.08-4.20 ppm (-OCH_2) respectively. In the ^{13}C-NMR spectra the carbons of the hydroxyl-alkyl chain that links the classical entities – theophylline and acetaminophen were identified at 38.2-46.7 ppm, 70.4-71.7 ppm and 76.8-77.8 ppm respectively.

4-(2, 3-epoxi-propyloxy)-acetanilide (3)

Recrystallization from ethanol gave pure white solid (98.92% yield), mp 116-117°C. IR (cm^{-1}, KBr) ν: 1610 cm^{-1} (-NH-CO); 1480 cm^{-1}, 780 cm^{-1}, 700 cm^{-1} (-C_6H_4-); 1380 cm^{-1} (-CO-CH_3); 1350 cm^{-1} (-O-CH_2-); 2900 cm^{-1} (-CH_3, -CH_2-); ^{1}H-NMR (DMSO-d_6) δ: 2.02 (s, 3H, CH_3), 2.50 (d, 2H, CH_2), 3.04 (m, 1H, CH), 4.07 (d, 2H, CH_2), 6.75 (d, 2H, C_6H_4), 7.53 (d, 2H, C_6H_4), 8.00 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 17.6 (C-11), 43.0 (C-1), 50.1 (C-2), 75.5 (C-3), 114.4 (C-5, C-9), 121.0 (C-6, C-8), 132.4 (C-7), 154.4 (C-4), 168.2 (C-10). Anal. Calcd. for $C_{11}H_{13}NO_3$ (%): C, 63.70; H, 5.30; N, 6.75; Found: C, 63.98; H, 5.51; N, 7.02.

7-[2-hydroxy-3-(4-acethyl-amino-phenoxy)-propyl]-1,3-dimethyl-xanthine (11)

Recrystallization from ethanol gave pure white solid (90.08 % yield), mp 202-204°C. IR (cm^{-1}, KBr) ν: 3300 cm^{-1} (linked OH); 1200 cm^{-1} (free OH); 2900 cm^{-1} (>N-CH_3); 2650 cm^{-1} (>C=O): 1660 cm^{-1} (>C=C<$_{N}$); 1580 cm^{-1} (>C=C<$_{CO}$); 1510 cm^{-1}(>C=N); 1610 cm^{-1} (-NH-CO); 1480 cm^{-1}, 780 cm^{-1}, 700 cm^{-1} (-C_6H_4-); 1380 cm^{-1} (-CO-CH_3); 2900 cm^{-1} (CH_3, -CH_2-); 1350 cm^{-1} (-O-CH_2); ^{1}H-NMR (DMSO-d_6) δ: 2.02 (d, 1H, OH), 2.06 (s, 3H, CH_3), 2.70 (s, 6H, 2CH_3), 3.70 (m, 1H, CH), 3.88 (d, 2H, CH_2), 4.09 (d, 2H, OCH_2), 6.80 (d, 2H, C_6H_4), 7.59 (d, 2H, C_6H_4), 7.98 (s, 1H, NH), 8.12 (s, 1H, CH); ^{13}C-NMR (DMSO-d_6) δ: 17.8 (C-18), 28.3 (C-6), 36.8 (C-7), 46.7 (C-8), 71.4 (C-9), 77.4 (C-10), 115.2 (C-12, C-16), 123.2 (C-13, C-15), 134.1 (C-14), 136.08 (C-3), 140.2 (C-4), 149.4 (C-5), 155.8 (C-11), 156.7 (C-2), 166.2 (C-1), 168.2 (C-17); Anal. Calcd. for $C_{18}H_{21}N_5O_5$ (%): C, 55.80; H, 5.46; N, 18.08; Found: C, 56.08; H, 5.58; N, 18.29.

7-[2-hydroxy-3-(4-acethyl-amino-phenoxy)-propyl]-8-bromo-1,3-dimethy-xanthine (12).

Recrystallization from ethanol gave a white solid (92.21% yield), mp 230-231°C. IR (cm^{-1}, KBr) ν: 3400 cm^{-1}(linked OH); 1210 cm^{-1} (free OH); 2900 cm^{-1} (>N-CH_3); 2650 cm^{-1} (>C=O); 1690 cm^{-1} (>C=C<$_{N}$); 1590 cm^{-1} (>C=C<$_{CO}$); 1520 cm^{-1} (>C=N); 1610 cm^{-1} (-NH-CO); 1480 cm^{-1}, 780 cm^{-1}, 700 cm^{-1} (-C_6H_4-); 1380 cm^{-1} (-CO-CH_3); 2920 cm^{-1} (-CH_3, -CH_2-); 1320 cm^{-1} (-O-CH_2); 690 cm^{-1} (-C-Br); ^{1}H-NMR (DMSO-d_6) δ: 2.0 (d, 1H, OH), 2.04 (s, 3H, CH_3), 2.72 (s, 6H, 2CH_3), 3.70 (m, 1H, CH), 3.94 (d, 2H, CH_2), 4.15 (d, 2H, OCH_2), 6.84 (d, 2H, C_6H_4), 7.49 (d, 2H, C_6H_4), 7.85 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 17.7 (C-18), 28.2 (C-6), 36.9 (C-7), 39.4 (C-8), 71.7 (C-9), 76.8 (C-10),115.6 (C-12, C-16), 123.8 (C-13, C-15), 134.5 (C-14), 136.2 (C-3), 140.7 (C-4), 49.2 (C-5), 157.8 (C-11), 156.4 (C-2), 166.8 (C-1), 168.5 (C-17); Anal. Calcd. for $C_{18}H_{20}N_5O_5Br$ (%): C, 46.36; H, 4.32; N, 15.02; Found: C, 46.54; H, 4.49; N, 15.26.

7-[2-hydroxy-3-(4-acethyl-amino-phenoxy)-propyl]-8-nitro-1,3-dimethyl-xanthine (13)

Recrystallization from ethanol gave a white solid (81.01% yield), mp 213 - 215°C.IR (cm^{-1}, KBr) ν: 3300 cm^{-1}(linked OH); 1210 cm^{-1} (free OH); 2790 cm^{-1} (>N-CH_3); 2650 cm^{-1} (>C=O); 1650 cm^{-1} (>C=C<$_{N}$); 1570 cm^{-1} (>C=C<$_{CO}$); 1500 cm^{-1} (>C=N); 1620 cm^{-1} (-NH-CO); 1480 cm^{-1}, 780 cm^{-1}, 700 cm^{-1} (-C_6H_4-); 1380 cm^{-1} (-CO-CH_3); 2900 cm^{-1} (-CH_3, -CH_2-); 1310 cm^{-1} (-O-CH_2); 1560 cm^{-1} (-C-NO_2); ^{1}H-NMR (DMSO-d_6) δ: 2.06 (d, 1H, OH), 2.10 (s, 3H, CH_3), 2.62 (s, 6H, 2CH_3), 3.58 (m, 1H, CH), 3.86 (d, 2H, CH_2), 4.20 (d, 2H, OCH_2), 6.54 (d, 2H, C_6H_4), 7.41 (d, 2H, C_6H_4), 8.04 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 17.8 (C-18), 28.3 (C-6), 36.4 (C-7), 38.2 (C-8), 70.5 (C-9), 77.8 (C-10), 114.4 (C-12, C-16), 121.4 (C-13, C-15), 132.6 (C-14), 141.6 (C-4), 147.3 (C-3), 154.4 (C-11), 156.1 (C-2), 164.3 (C-5), 166.2 (C-1), 168.8 (C-17) Anal. Calcd. for $C_{18}H_{20}N_6O_7$ (%): C, 49.99; H, 4.66; N, 19.43; Found: C, 50.25; H, 4.81; N, 19.64.

7-[2-hydroxy-3-(4-acetyl-amino-phenoxy)-propyl]-8-(pyrrolidin-1-yl)-1,3-dimethyl xanthine (14)

Recrystallization from ethanol gave a white solid (72.36 % yield), mp 268-270°C. IR (cm^{-1}, KBr) ν: 3400 cm^{-1} (linked OH); 1190 cm^{-1} (free OH); 2790 cm^{-1} (>N-CH_3); 2640 cm^{-1} (>C=O); 1660 cm^{-1} (>C=C<$_{N-}$); 1550 cm^{-1} (>C=C<$_{CO}$); 1500 cm^{-1} (>C=N); 1590 cm^{-1} (-NH-CO); 1460 cm^{-1}, 800 cm^{-1}, 700 cm^{-1} (-C_6H_4-); 1390 cm^{-1} (-CO-CH_3); 2900 cm^{-1} (-CH_3, -CH_2-); 1310 cm^{-1} (-O-CH_2); 3090 cm^{-1} (>N-);); ^{1}H-NMR (DMSO-d_6) δ: 1.59 (m, 4H, 2CH_2), 2.04 (d, 1H, OH), 2.08 (s, 3H, CH_3), 2.70 (s, 6H, 2CH_3), 2.80 (t, 4H, 2CH_2), 3.67 (m, 1H, CH), 3.88 (d, 2H, CH_2), 4.15 (d, 2H, OCH_2), 6.78 (d, 2H, C_6H_4), 7.53 (d, 2H, C_6H_4), 8.10 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 17.6 (C-18), 23.1 (2$C_{pyrolidinyl\ radical}$), 28.5 (C-6), 37.4 (C-7), 38.9 (C-8), 53.9 (2$C_{pyrrolidinyl\ radical}$), 71.4 (C-9), 77.6 (C-10), 115.4 (C-12, C-16), 121.3 (C-13, C-15), 132.4 (C-14), 136.1 (C-3), 140.4 (C-4), 149.1 (C-5), 154.8 (C-11), 156.7 (C-2), 166.5 (C-1), 168.2 (C-17); Anal. Calcd. for $C_{22}H_{28}N_6O_5$ (%): C, 57.88; H, 6.82; N, 18.41; Found: C, 58.04; H, 7.10; N, 18.64.

7-[2-hydroxy-3-(4-acethyl-amino-phenoxy)-propyl]-8-(piperidin-1-yl)-1,3-dimethyl xanthine (15)

Recrystallization from ethanol gave a white solid (72.34% yield), mp 227-229°C. IR (cm^{-1}, KBr) n: 3390 cm^{-1} (linked OH); 1200 cm^{-1} (free OH); 2900 cm^{-1} (>N-CH_3); 2650 cm^{-1} (>C=O); 1680 cm^{-1} (>C=C<$_{N-}$); 1580 cm^{-1} (>C=C<$_{CO}$); 1500 cm^{-1} (>C=N); 1610 cm^{-1} (-NH-CO); 1460 cm^{-1}, 780 cm^{-1}, 700 cm^{-1} (-C_6H_4-); 1380 cm^{-1} (-CO-CH_3); 3100 cm^{-1} (-CH_3, -CH_2-); 1310 cm^{-1} (-O-CH_2); 3300 cm^{-1} (>N-); ^{1}H-NMR (DMSO-d_6) δ: 1.50 (m, 6H, 3CH_2), 2.02 (d, 1H, OH), 2.10 (s, 3H, CH_3), 2.74 (s, 6H, 2CH_3), 2.76 (t, 4H, 2CH_2), 3.72 (m, 1H, CH), 3.92 (d, 2H, CH_2), 4.09 (d, 2H, OCH_2), 6.75 (d, 2H, C_6H_4), 7.58 (d, 2H, C_6H_4), 8.0 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 17.9 (C-18), 25.2 (3$C_{piperidinyl\ radical}$), 28.4 (C-6), 36.8 (C-7), 38.2 (C-8), 54.7 (2$C_{piperidinyl\ radical}$), 77.4 (C-10), 114.8 (C-12, C-16), 121.8 (C-13, C-15), 132.8 (C-14), 136.4 (C-3), 140.2 (C-4), 149.5 (C-5), 154.4 (C-11), 156.2 (C-2), 166.4 (C-1), 168.5 (C-17); Anal. Calcd. for $C_{23}H_{30}N_6O_5$ (%): C, 58.71; H, 6.26; N, 17.86; Found: C, 58.92; H, 6.48; N, 18.04.

7-[2-hydroxy-3-(4-acetyl-amino-phenoxy)-propyl]-8-(morfolin-4-yl)-1,3-dimethyl-xanthine (16)

Recrystallization from ethanol gave a white solid (68.56% yield), mp 330 - 331°C. IR (cm^{-1}, KBr) ν: 3400 cm^{-1} (linked OH); 1200 cm^{-1} (free OH); 2900 cm^{-1} (>N-CH_3); 2640 cm^{-1} (>C=O); 1660 cm^{-1} (>C=C<$_{N-}$); 1580 cm^{-1} (>C=C<$_{CO}$); 1510 cm^{-1} (>C=N); 1620 cm^{-1} (-NH-CO); 1480 cm^{-1}, 780 cm^{-1}, 710 cm^{-1} (-C_6H_4-); 1370 cm^{-1} (-CO-CH_3); 2900 cm^{-1} (-CH_3, -CH_2-); 1350 cm^{-1} (-O-CH_2); 3120 cm^{-1} (>N-); ^{1}H-NMR (DMSO-d_6) δ: 2.02 (d, 1H, OH), 2.10 (s, 3H, CH_3), 2.68 (s, 6H, 2CH_3), 2.90 (t, 4H, 2CH_2), 3.67 (t, 4H, 2CH_2), 3.70 (m, 1H, CH), 3.88 (d, 2H, CH_2), 4.15 (d, 2H, OCH_2), 6.78 (d, 2H, C_6H_4), 7.53 (d, 2H, C_6H_4), 8.05 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 17.6 (C-18), 28.3 (C-6), 36.7 (C-7), 38.5 (C-8), 58.9 (2$C_{morfolinyl\ radical}$), 71.4 (C-9, 2$C_{morfolinyl\ radical}$), 77.6 (C-10), 114.4 (C-12, C-16), 121.0 (C-13, C-15), 132.4 (C-14), 136.8 (C-3), 141.0 (C-4), 149.8 (C-5), 154.7 (C-11), 156.8 (C-2), 166.8 (C-1), 168.2 (C-17); Anal. Calcd. for $C_{22}H_{28}N_6O_6$ (%): C, 55.92; H, 5.92; N, 17.78; Found: C, 56.14; H, 6.21; N, 18.03.

7-[2-hydroxy-3-(4-acetyl-amino-phenoxy)-propyl]-8-(imidazol-1-yl)-1,3-dimethyl-xanthine (17)

Recrystallization from methanol: DMFA (1:1) mixture gave a white solid (61.73% yield), mp 266-267°C. IR (cm^{-1}, KBr) ν: 3250 cm^{-1} (linked OH); 1200 cm^{-1} (free OH); 2900 cm^{-1} (>N-CH_3); 2650 cm^{-1} (>C=O); 1640 cm^{-1} (>C=C<$_{N-}$); 1540 cm^{-1} (>C=C<$_{CO}$); 1490 cm^{-1} (C=N); 1610 cm^{-1} (-NH-CO); 1480 cm^{-1}, 780 cm^{-1}, 700 cm^{-1} (-C_6H_4-); 1380 cm^{-1} (-CO-CH_3); 2900 cm^{-1} (-CH_3, -CH_2-); 1350 cm^{-1} (-O-CH_2); 3080 cm^{-1} (>N-); ^{1}H-NMR (DMSO-d_6) δ: 2.08 (d, 1H, OH), 2.04 (s, 3H, CH_3), 2.72 (s, 6H, 2CH_3), 3.69 (m, 1H, CH), 3.92 (d, 2H, CH_2), 4.08 (d, 2H, OCH_2), 6.81 (d, 2H, C_6H_4), 6.90 (d, 2H, CH), 7.57 (d, 2H, C_6H_4), 8.06 (s, 1H, NH), 8.15 (s, 1H, CH), ^{13}C-NMR (DMSO-d_6) δ: 17.5 (C-18), 28.5 (C-6), 36.4 (C-7), 38.6 (C-8), 70.8 (C-9), 77.2 (C-10), 114.9 (C-12, C-16), 118.8 ($C_{imidazolyl}$), 121.5 (C-13, C-15), 129.7 ($C_{imidazolyl}$), (132.14 (C-14), 136.5 (C-3), 137.7 ($C_{imidazolyl}$), 139.4 (C-4), 149.6 (C-5), 154.8 (C-11), 156.7 (C-2), 166.1 (C-1), 168.72 (C-17); Anal. Calcd. for $C_{21}H_{23}N_7O_5$ (%): C, 55.60; H, 5.11; N, 21.61; Found: C, 55.84; H, 5.32; N, 21.86.

Toxicological study

Table 1
DL50 VALUES OF THE TESTED COMPOUNDS

Comp.	DL_{50} (mg/kg body weight)			
	24 hours	48 hours	7 days	Average
11	328	328	280	312
12	423	423	380	409
13	524	524	480	509
14	601	601	570	591
15	489	489	450	476
16	439	439	390	423
17	412	412	398	407

The synthesized compounds were investigated for their toxicity (table 1) and the values of the DL50 were comparative with theophylline (DL_{50} = 200 mg/kg).

The results obtained show that substitution of theophylline in the 7th position with acetaminophen moiety *via* hydroxyalkyl chain and in the 8th position with cyclic and noncyclic radicals had a favorable influence on toxicity degree; all compounds being less toxic than theophylline. The most favorable influence had nitro, pirolidinyl and piperidinyl radicals the corresponding 8-substitited theophylline derivatives being 2.5 times, 2.4 times and 3 times less toxic than theophylline. The previous toxicological evaluation and the proper physico-chemical analysis are important [15].

Conclusions

New theophyline derivatives having in the 7th position an acetaminophen moiety linked *via* hydroxyalkyl chain and in the 8th position cyclic and noncyclic radicals have been synthesized. The obtained compounds have been characterized by some physical properties and their structure was confirmed by elemental and spectral (FT-IR, ^{1}H-NMR, ^{13}C-NMR) analysis. The toxicological profile was established and the DL50 values were ascertained. All tested compounds have low toxicity, being less toxic than theophyline.

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