DEVELOPMENT OF AN OPTIMIZED SYNTHETIC APPROACH FOR SYNTHESIS OF CAFFEINE-8-THIOGLYCOLIC ACID AND ITS ESTER DERIVATIVES

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Summary: Modified and optimized methods for synthesis of 8-bromocaffeine, caffeine-8-thioglycolic acid and its ester derivatives were developed. The modification of 8-bromocaffeine synthesis included a change in the brominating agent, which resulted in cost reduction. Some investigations were performed on the influence of the catalyst type and concentration, using a model reaction of esterification of caffeine-8-thioglycolic acid with methanol. It was established that the application of the ion-exchane resign Wofatit P as catalyst resulted into significant increase of the ester yields and facilitation of its isolation. Thus the optimal parameters of the caffeine-8-thioglycolic acid esterification were: 35 fold excess of methanol, temperature of 65°C and catalyst Wofatit P at 4 wt. % of total acid weight. Thus four other caffeine-8-thioglycolates were synthesized with high yields (78-98%) and purity and their structures were confirmed.

Key words: caffeine-8-thioglicolyc acid, 8-bromocaffeine, caffeine-8-thioglicolates.

РАЗРАБОТВАНЕ НА ОПТИМИЗИРАН ПОДХОД ЗА СИНТЕЗ НА КОФЕИН-8-ТИОГЛИКОЛОВА КИСЕЛИНА И НЕЙНИ ЕСТЕРНИ ПРОИЗВОДНИ

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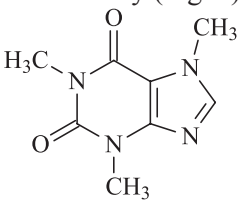
Резюме: Разработени са модифицирани и оптимизирани методи за получаване на 8-бромокофеин, кофеин-8-тиогликолова киселина и нейни естерни производни. Модификацията на метода за получаване на 8-бромокофеин включва промяна на бромиращия реагинт, което води до снижаване на разходите. Проведени са изследвания върху влиянието на вида и количеството на катализатора при използване на моделно взаимодействие на кофеин-8-тиогликолова киселина и метанол. Установено е, че използването на йонообменната смола Wofatit P като катализатор води до значително увеличаване на добива на естера и улеснава изолирането му. Оптималните параметри при естерификацията на кофеин-8-тиогликолова киселина са: 35 кратен излишък на метанол, температура 65°C и катализатор Wofatit P в количество 4% от общата маса на киселината. По този начин са синтезирани четири други кофеин-8-тиогликолати с високи добиви (78-98%) и чистота. Структурите на съединенията са потвърдени.

Ключови думи: кофеин-8-тиогликолова киселина, 8-бромокофеин, кофеин-8-тиогликолати.

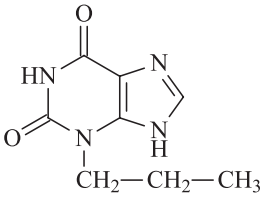
Introduction

Natural products are an attractive source of varied structures that exhibit potent biological activities, and desirable pharmacological profiles. Xanthines have been an important class of biologically active structures. Their activities have ranged from antagonists of adenosine receptors (such as caffeine), to phosphodiesterase (PDE) inhibitors (enprofylline) to anticancer agents (Fig. 1). Xanthine-based structures for new drug leads have been explored in various therapeutic areas [1-3] including the treatment of CNS disorders such as Alzheimer's type dementia [4]. For example, recently a new xanthine derivative, propentophylline, was introduced as a drug with neuroprotective properties for treatment of brain dementia [5], boosting the search for new xanthine derivatives with neuro-

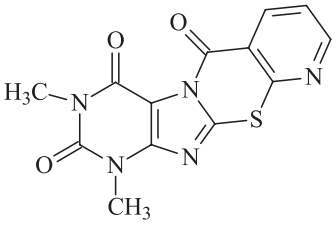
protective activity. However, 8-thiosubstituted xanthines and the structures derived from them have not been well studied. There are 8-thio substituted derivatives of methylxanthines that possess radioprotector [6], antibacterial [7], antidiabetic (as DPP-IV inhibitors) [8], and typical of methylxanthines bronchodilator activity [7]. Some 8-mercaptoxanthines have been used as intermediates for new purine-based heterocyclic ring systems, such as purinobenzothiazines and pyridothiazonopurines [9] which have shown antitumor activity (Fig. 1).



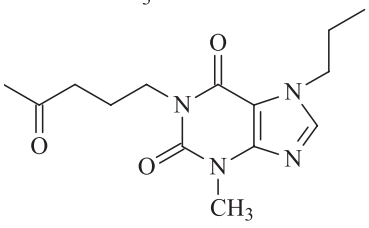
Caffeine



Enprofylline



Anticancer Agent



Propentofylline

Fig. 1 *Biologically active xanthine analogues.*

Our interest is pointed to caffeine-8-thioglycolic acid and its ester derivatives. Literature survey has shown that the most favored and efficient method to synthesize 8-thio substituted xanthines is from their corresponding 8-bromo-, 8-chloro-, and 8-oxo-xanthines [10-12]. Organic esters are a very important class of chemicals with applications as very useful perfumery agents, flavours, pharmaceuticals, pharmaceutical intermediates, solvents and plasticisers. Esterification of carboxylic acids with alcohols in presence of acid catalysts has been the subject of investigation by many research workers. First major drawback of the reaction is that it is equilibrium limited and the second is that typical homogenous catalysts like H_2SO_4, HCl and H_3PO_4 are used but due to their miscibility with the reaction medium, separation becomes a problem [13]. Therefore heterogeneous catalyst become an attractive alternative catalyst which is nonpolluting, non corrosive and has long activity life. The ion-exchange resin is a promising material for the replacement of the homogeneous acid catalysts. The solid type of material has good physical and chemical properties, and shows no corrosion as well as pollution, and show both high selectivity and thermal stability [13-15].

Based on the literature conditions we have designed an optimised synthetic sequence for the synthesis of caffeine-8-thioglycilates.

Materials and methods

Apparatuses and devices

The used chromatographic system for TLC control and purity elucidation is based on an alimunium sheets Silica gel F254 (Merck, Darmstadt, Germany), using $CHCl_3$/CH_3CH_2OH/Acetone as a mobile phase with detection at UV 254 nm. Yields were calculated for purified products. The IR spectra 400–4000cm^{-1} were recorded on a Nicolet iS10 FT-IR Spectrometer in KBr. The ^{1}H-NMR spectra were registered at 250 MHz on spectrometer Bruker-Spectrospin WM250MHz (Faenlanden, Switzerland) as δ (ppm) relative to TMS as internal standard and the coupling constants (J) are expressed in Hertz (Hz). All OH and NH protons were D_2O exchangeable. All names were generated by using ACD/Name Version 2.51 [16].

The starting materials were of commercially available research - grade chemicals. (Merck, Darmstadt, Germany). Commercial strong acidic ion-exchange resin Wofatit P (Germany) was used as solid acidic catalysts. Physical properties of ion-exchange resin catalyst are summarized in Table 1.

Synthesis of 8-bromocaffeine

The bromination of caffeine was carried out in a laboratory-scale reactor in the form of a four-neck round bottom flask (total volume 1000 ml) placed in

Table 1 *Characteristics of ion-exchange resin Wofatit P*

Bulk weight (t/m^3)		Coefficient of swelling	Limits of grains size (mm)	Average particle diameter(mm)	Wear away for year (%)	Exchange capacity (g-eq/m^3)
in air-dry state	in swollen state					
0.62	0.50*	1.19	0.3 – 2.0	1.26	3-4	1400

** - excluding the weight of absorbed water*

a heating mantle with a mechanical stirrer and temperature controller. The centre neck was fitted with mechanical stirrer whose speed was maintained at 700 rpm. A thermometer for temperature control and a Liebig condenser for reflux were inserted into two of the side necks. The other side neck allowed sampling of the reaction mixture. To 300 ml of water 0.35 mol (42 g) potassium bromide and 0.1 mol (18.4 g) caffeine were added. Then at temperature below 60°C and with stirring 26 ml of sulfuric acid were added dropwise, after which the temperature was rised to 80°C. After complete homogenization of the reaction mixture 25 ml 30% hydrogen peroxide were added dropwise. Reaction mixture was left under the same conditions for 4 hours, then cooled to room temperature and decolourized with sodium sulphite. The colorless solution was poured into 400 ml ice water and kept for 12 hours at 4°C. The separated precipitate of 8-bromocaffeine was filtered under reduced pressure and recrystallised from ethanol. Yield – 23.2 g (85%), m.p. – 205°C. The structure of the compound was confirmed by IR spectral analysis and comparison with the standard substance.

Synthesis of caffeine 8-thioglicolic acid

The reaction was carried out in reactor of 500 mL capacity which was equipped with mechanical stirrer (speed was maintained at 700 rpm) and a reflux condenser was placed on top of the reactor in order to prevent the escape of volatile compounds. Ethanol (100 ml) and 66 ml of 0.1 mol sodium hydroxide solution were mixed and thioglicolic acid (0.05 mol, 3.5 ml) was added to the mixture. Then 8-bromocaffeine (0.05 mol, 13.65 g) was added and the reaction mixture was heated under reflux for 1 hour. The reaction was controlled by TLC and stopped after exhaustion of the starting compounds. After cooling 200 ml water were added for separation of the unreacted 8-bromocaffeine. The obtained precipitate was filtered and the clear filtrate was acidified with hydrochloric acid until pH = 2. After 6 hours the precipitated caffeine 8-thioglicolic acid was filtered and purified by recrystallization from acetic acid/water mixture in 1:10 ratio. Yield – 13.6 g (96%), m.p. – 229–231°C. The structure of the compound was confirmed by IR spectral analysis and its purity was elucidated by TLC.

General procedure for the synthesis of the caffeine-8-thioglicolates

Esterification of caffeine-8-thioglycolic acid (0.01 mol, was performed in a three-necked reactor of 150 mL capacity equipped with mechanical stirrer and a reflux condenser to avoid alcohol vaporization. The three-necked reactor was immersed in a constant temperature water bath equipped with a temperature controller. In order to eliminate external mass transfer effects, the stirring speed was adjusted to 1000 rpm. Esterifcation reaction were carried out in the temperature range of 60–80°C. Resin catalyst (35 wt% of total acid weight) and 1,4-dioxan of known amount were charged into reactor and also, in predetermined amount of corresponding alcohol (0.35 mol) were added into the reactor. After reaching desired temperature, caffeine-8-thioglycolic acid dissolved in small amount of 1,4-dioxan was placed in the reactor. This was considered as the starting time of the reaction. The reaction was monitored by TLC and the sampling were done manually at reaction times of 3, 5, 10 min and every 20 min after that. After the end of the reaction time the ion-exchange resin was filtrated and 50 ml water was added to the filtrate. The mixture was kept 2 hours at 4°C until formation of a volumetric precipitate, which was filtrated and purified by re-crystallization from ethanol, if necessary.

The IUPAC names of the newly synthesized compounds together with the interpretation of their IR spectra are presented below; the chemical structures are presented on Scheme 7, the relevant melting points and the individual yields are presented in Table 3.

Methyl 2-((1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio)acetate (**4a**): IR (KBr): ν 2939, 1704, 1664, 1558 and 1539, 1360, 1289 and 1232; ^{1}H NMR (250 MHz, DMSO-d_6) δ, ppm: 3.43 (s, 3H, N1-CH_3), 3.47 (s, 3H, N3-CH_3), 3.68 (s, 3H, COO-CH_3), 3.75 (s, 2H, S-CH_2), 3.81 (s, 3H, N7-CH_3).

2-Phenoxyethyl 2-((1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio)acetate (**4b**): IR (KBr): ν 3100, 2939, 1733, 1699, 1661, 1558 and 1539, 1232, 744; ^{1}H NMR (250 MHz, DMSO-d_6) δ, ppm: 3.43 (s, 3H, N1-CH_3), 3.47 (s, 3H, N3-CH_3), 3.74 (s, 2H, S-CH_2), 3.81 (s, 3H, N7-CH_3), 4.40 (q, 2H, C_6H_5O-CH_2, *J=7*), 4.44 (q, 2H, COO-CH_2, *J=7*), 6.80 (d, 1H, C_6H_5-H4, *J=7.45*), 6.88 (d, 1H, C_6H_5-H3, *J=8.15*), 6.88 (d, 1H, C_6H_5-H5, *J=8.15*), 6.91 (d, 1H, C_6H_5-H2, *J=0.17*), 6.91 (d, 1H, C_6H_5-H6, *J=0.17*).

2-Methoxyethyl 2-((1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio)acetate (**4c**): IR (KBr): ν 2935, 1703, 1699, 1557, 1289, 1041, 744; ^{1}H NMR (250 MHz, DMSO-d_6) δ, ppm: 3.20 (s, 3H, O-CH_3), 3.43 (s, 3H, N1-CH_3), 3.45 (d, 2H, CH2-O-CH_3, *J=7*), 3.47 (s, 3H, N3-CH_3), 3.74 (s, 2H, S-CH_2), 3.81 (s, 3H, N7-CH_3), 4.32 (d, 2H, COO-CH_2, *J=7*).

2-Ethoxyethyl 2-((1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio)acetate (**4d**): IR (KBr): ν 2939, 1699, 1562, 1537, 1487, 1269, 744; ^{1}H NMR (250 MHz, DMSO-d_6) δ, ppm: 1.05 (d, 3H, O- CH_2CH_3, *J=6.69*), 3.43 (s, 3H, N1-CH_3), 3.45 (m, 2H, -O CH_2CH_3), 3.47 (s, 3H, N3-CH_3), 3.61 (d, 2H, CH_2-O, *J=7*), 3.74 (s, 2H, S-CH_2), 3.81 (s, 3H, N7-CH_3), 4.28 (d, 2H, COO-CH_2, *J=7*).

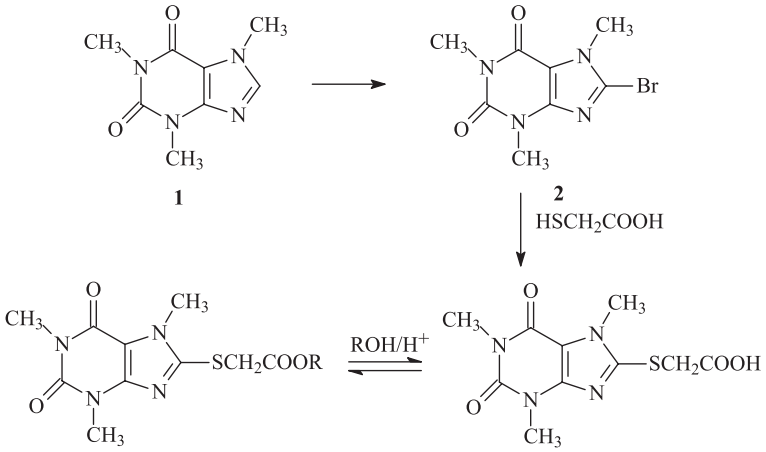
2-Isopropoxyethyl 2-((1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio)acetate (**4e**): IR (KBr): ν 2939, 1701, 1689, 1590, 1232, 1175; ^{1}H NMR (250 MHz, DMSO-d_6) δ, ppm: 1.30 (d, 6H, 2xCH_3, *J=6.3*), 3.43 (s, 3H, N1-CH_3), 3.47 (s, 3H, N3-CH_3), 3.74 (s, 2H, S-CH_2), 3.81 (s, 3H, N7-CH_3), 4.93 (m, 1H, O-CH).

Results and Discussion

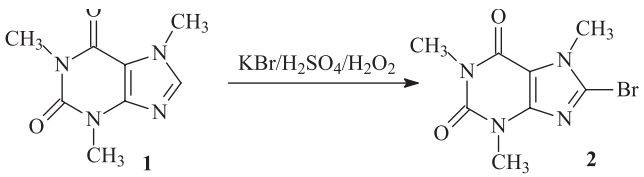
The synthesis of caffeine-8-thioglycolates consists of brominating of caffeine to obtain the 8-bromocaffeine (**2**), its further interaction with thioglycolic acid and subsequent esterification of obtained caffeine-8-thioglycolic acid according to **Scheme 1**:

The synthesis of 8-bromocaffeine (**2**) was carried out via oxidative bromination of caffeine (**1**) in aqueous media. This synthetic approach is a variant of a literary method [17] based on application of HBr and H_2O_2 in glacial acetic acid. In our modification the required bromine was obtained *in situ* after oxidation of hydrogen bromide with hydrogen peroxide. The nessessary HBr was derived from interaction of potassium bromide and sulphuric acid. At these conditions the reaction is more cost-effective but the time of 5 hours and the corresponding yield of recrystallised 8-bromocaffeine (85%) are kept unchanged (**Scheme 2**):

The second stage of our synthetic sequence is obtaining of caffeine-8-thioglycolic acid (**3**). The known method for synthesis of **3** [18] includes interaction of



Scheme 1. *General scheme of synthesis of caffeine-8-thioglycolic acid.*



Scheme 2. *Modified method for synthesis of 8-bromo caffeine.*

2 with thioglycolic acid in DMF at 140°C. The duration of the reaction is published to be 6 hours with 40% yield. The authors do not provide an explanation of the relatively small yield of **3**, but probably this is due to side reactions. We consider that the most probable side reaction is hydrolysis of **2** to 1,3,7-trimethyluric acid. This reaction is most probable having in mind the high temperature of the reaction and ability of DMF to absorb water very well and forms alkaline media (pH ≈ 9) – all of this forms conditions suitable for this reaction [19]

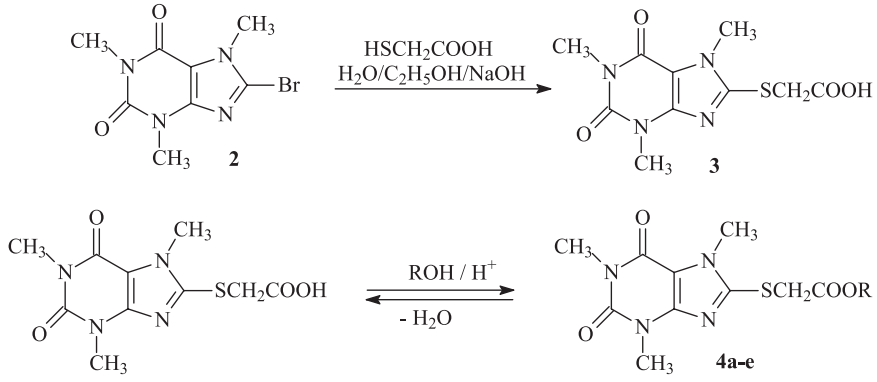
In an attempt to optimize the yield and the reaction time we changed the reaction conditions, whereat the reaction was led in water/ethanol media, in the presence of sodium hydroxide, according to **Scheme 3**:

At these conditions side reaction is not observed, the reaction time was shortened up to 1 hour and the yield was increased up to 96 %.

The synthesis of the targeted esters was conducted according to **Scheme 4**.

The classical esterification method is optimized by variation of the conditions of synthesis of the methyl ester of caffeine-8-thioglycolic acid (**4a**). The reaction was carried out in 35 fold excess of methanol to shift the equilibrium towards the products and was monitored by TLC. The type and amount of catalyst were varied and the results are shown **Table 2**.

As a result the yield of the obtained ester derivative is in the range of 62-98%, and the reaction time varies from 90 to 300 min. Best results were obtained, using concentrated sulfuric acid as catalyst (with molar ratio of caffeine-8-thioglicolyc acid : catalyst equal to 1:10) with 90% yield for 60 min. and in the presence of Wofatit P (1g) with yield 98% for 90 min. Despite a strong catalytic effect, the use of sulfuric acid as homogeneous catalyst, suffers from



Scheme 3. *Modified method for synthesis of caffeine-8-thioglycolic acid.*

4a, R = CH_3

4b, R = $-CH_2-CH_2-O-C_6H_5$

4c, R = $CH_3OCH_2CH_2$

4d, R = $CH_3CH_2OCH_2CH_2$

4e, R = $-CH(CH_3)_2$

Scheme 4. *General scheme for synthesis of esters of caffeine-8-thioglycolic acid.*

Table 2. *Variation of the conditions for synthesis of methyl ester of caffeine-8-thioglycolic acid (4a).*

caffeine-8-thioglycolic acid, mol	H_2SO_4 mol	H_3PO_4 mol	PTSA mol	Wofatit P	Time min	Yield %
0.01	0.01				300	62
0.01	0.02				300	68
0.01	0.05				300	83
0.01	0.1				60	90
0.01		0.05			300	80
0.01		0.1			60	85
0.01			0.05		300	81
0.01			0.1		240	83
0.01				0.5 g	120	75
0.01				1.0 g	90	98

Table 3. *Reaction conditions and the corresponding reaction time and yield and melting points for the synthesis of each of the targeted products.*

compound	temperature, °C	reaction time min.	Yield %	melting point, °C
4b	80°	90	98	119-120
4c	80°	120	85	105-106
4d	80°	120	80	109-111
4e	80°	100	78	168-170

drawbacks, such as difficulty in isolating of the final product.

The use of ion-exchange resin Wofatit P as solid catalysts have many advantages over homogeneous acid catalysts. It can be separated from liquid reaction mixture by filtration or decantation, reaction was carried out at low temperature, the yield is highest compared to yields obtained in the presence of homogeneous acid catalysts which fulfill some of conditions of "green chemistry". Wofatit P is a condensation product of phenol, formaldehyde and sodium sulfite, sulfonated with concentrated sulfuric acid and contains sulfo groups in benzene rings and in the side chains. Wofatit P compared to some other ion exchange resins is more active and more resistant to mechanical factors, does not crumble and is not subject to abrasion powder. Its loss of activity is slow and may be consequently applied for 10-20 times [20].

Using the optimized method four other esters derivatives were synthesized.

The reaction conditions and the corresponding reaction time and yield for each of the targeted products are given in **Table 3**.

It is clearly seen in Table 3 that target products **4b-e** are obtained with high yield and purity. The structure of newly synthesized compounds was proven by elemental analysis, IR and ^{1}H-NMR spectroscopy.

Conclusion

The synthesis of caffeine-8-thioglycolates consists of bromination of caffeine to obtain the corresponding 8-bromocaffeine and its further interaction with thioglycolic acid. The corresponding ester derivatives are further obtained by esterification with the desired alcohol. For the synthesis of the initial 8-bromocaffeine a change in the brominating agent was applied, which resulted in reduction in the cost, but maintaining the time and the corresponding yield unchanged. The effects of catalyst type and catalyst concentration on the model reaction of esterification of caffeine-8-thioglycolic acid with methanol were investigated and was found that they significantly influenced the acid conversion. When homogenous acid catalyst was used, the increase of catalyst concentration leads to increasing of yield of the ester but there are problems in isolating the final product. The use of ion exchange resin as solid acid catalyst leads to significant increase in the yield of the ester and facilitates its isolation. The optimal parameters for esterification of caffeine-8-thioglycolic acid with methanol were: 35 fold excess of methanol, temperature of 65 °C and catalyst Wofatit P at 4 wt.% of total acid weight. Using the optimized method four other caffeine-8-thioglycolates were synthesized with high yields (78-98%) and purity and their structures were confirmed. Solid acid catalysis is very effective from the point of view of activity and reusability compared with homogeneous catalysts. We found that after recycling, the resin catalyst showed high catalytic activities and could be used repeatedly.

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References:

1. Pastorin G., C. Bolcato, B. Cacciari, S. Kachler, K.-N. Klotz, C. Montopoli, S. Moro, G., Synthesis, biological studies and molecular modeling investigation of 1,3-dimethyl-2,4-dioxo-6-methyl-8-(substituted) 1,2,3,4-tetrahydro [1,2,4]-triazolo [3,4-f]-purines as potential adenosine receptor antagonists. *Il Farmaco*, **60**, 2005, 299–306
2. Kramer G. L., J. E. Garst, S. S. Mitchel, J. N. Wells. Selective inhibition of cyclic nucleotide phosphodiesterases by analogs of 1-methyl-3-isobutylxanthine, *Biochemistry*, **16**, 1977, 3316–3321
3. Laursen L. C. Anti asthmatic effects and pharmacokinetics of enprofylline--a new xanthine derivate. *Danish Medical Bulleti*, 34, 1987, **6**, 289–97.

4. Muhl-Kufner U., H. Ensinger, J. Mierau, F.J. Kuhn, E. Lehr and E. Muller, Unsymmetrisch substituierte Xanthine, DE 43 25 254 /03. 1995 (Boehringer Ingelheim KG)
5. Rother M., B. Kittner, K. Rudolphi, M. Rössner and K. H. Labs, HWA 285 (propentofylline)-a new compound for the treatment of both vascular dementia and dementia of the Alzheimer type, *Ann. N. Y. Acad. Sci. 777*, 1996, 404-409
6. Berdichevskii E. G., F. J. Rachinskii, E. K. Novoselova. *Zh. Obshch. Khim*, **28**, 1958, 3, 689–692
7. Hayallah A. M., W. A. Elgaher, O. I. Salem, A. A. M. Abdel Alim. Design and synthesis of some new theophylline derivatives with bronchodilator and antibacterial activities, *Arch. Pharm. Res.*, **34**, 2011, 1, 3-21
8. Jaehne G., E. Defossa, G. Billen, C. Buning, G. Tschang, U. Werner. Xanthine derivative and DPP IV inhibitor, WO 2006/015691 A1, 2006
9. Settimo A. D., A. M. Marini, G. Primofiore, F.D. Settimo, D. Bertini, Synthesis of purinobenzothiazine and pyridothiazinopurine derivatives. Two new heterocyclic ring systems. *J. Heterocycl. Chem.*, **35**, 1998, 57–60
10. Garmash S. N., N. V. Koval, B. A. Priimenko, N. A. Klyuev, E. A. Skulskaya, Synthesis, physicochemical properties, and mass spectrometric study of some 8-methyl-6H-thiazolo[3,2-f]xanthines, *Chem. Heterocycl. Compd. (Engl. Transl.)* **23**, 1987, 1228–1233;
11. DE 133300, 1988
12. Toor A. P., M. Sharma, G. Kumar, R. K. Wanchoo. Kinetic Study of Esterification of Acetic Acid with nbutanol and isobutanol Catalyzed by Ion Exchange Resin. *Bulletin of Chemical Reaction Engineering & Catalysis*, 6 (1), 2011, 23 – 30.
13. Gangadwala J., S. Mankar, S. Mahajani, A. Kienle, E. Stein, Esterification of acetic acid butanol in the presence of ion-exchange resins as catalysts, *Ind. Eng. Chem. Res.*, **42**, 2003, 10, 2146-2155.
14. Ali S. H., S. Q. Merchant. Kinetics of the esterification of acetic acid with 2-propanol: Impact of different acidic cation exchange resins on reaction mechanism, *Int. J. Chem. Kinet.*, **38**, 2006, 593- 612.
15. Chem Draw Ultra, Version 9.0, CambridgeSoft.
16. Gagausov J., Pl. Peikov, D. Davkov, K. Sharankov. Synthesis of 8-bromo-methylxanthines. *Pharmacia*, **37** (1987), 6, 8-10
17. Piimenko B. A., N. I. Romanenko, I. V. Fedulova, L. P. Orestenko, A. Yu. Chervinskyi, S. N. Garmash, Synthesis and biological properties of (3-methyl-7-alylxanthinyl-8) thioglycolic acids derivatives, Chimico-pharmacevticheskih journal, **11**, 1986, 1322-1324.
18. Zlatkov Al., Pl. Peikov. Investigation on obtaining of by-product in interaction of 8-bromo-1,3,7-trimethylxanthine and diethanolamine. *Pharmacia*, **43**, 1995, 3, 5-7.
19. http://www.ngpedia.ru/id594551p2.html

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