ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2012; 3(3):572-577

ORIGINAL RESEARCH ARTICLE

Synthesis and Pro-Coagulant Properties of New Amide Derivatives of Pyrimidin-8-ON [2,1-F] Theophylline-9-Alkylcarboxylic Acids

Omeran Fhid[*1], Tariq Almog[1], Muacij Pawłowski[2], Anjoue Stepenfski[3]

[1]*Department of Pharmaceutical Chemistry, University of Tripoli, Libya*
[2]*Department of Pharmaceutical Chemistry, Collegium Medicum, Jagiellonian University, Medyczna 9, PL-30-688, Kraków, Poland*
[3]*Department independent Laboratory of Radioligands, Jagiellonian University, 9 Medyczna St. Cracow Poland*

Received 09 Mar 2012; Revised 09 Jun 2012; Accepted 18 Jun 2012

ABSTRACT

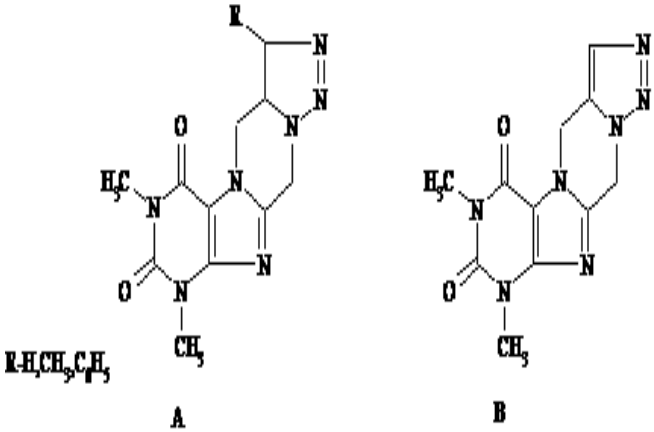
In the alkylation of unsubstituted pyrimidin-8-on [2,1-f]-theophylline I with ethyl-chloroacetate, ethyl-acrylate and ethyl-4-bromobutyrate, the appropriate esters 1-3 were synthesized . Dialkyl amino alkyl amide 4,5 or morpholine-ethyl (-propyl) amide 6-10 were obtained by amidation of esters 1-3. The final amides 4-10 were transformed into its their hydrochlorides 4a-10a. The pharmacological properties of the compounds were tested in their pro-coagulant screening tests. It was found that the most of all of the investigated compounds 4a-10a generally exhibited very mild pro-coagulant properties on activated partial thromboplastin time (APTT) and prolonged thromboplastin time (PTT) by estimate of the clothing time of the blood plasma tested compounds.

Key words: Pyrimidin-8-on [2,1-f]-theophylline-9-alkylcarboxylic acid amides derivatives, pro-coagulant activity of fused [2,1-f] theophylline, tricyclic theophylline derivatives.

INTRODUCTION

Among new drugs, methylxanthines, 7-substituted derivatives were investigated in view of their bronchospasmolytic [1,2,3], anticancer [4], and circulatory blood system effects [5].

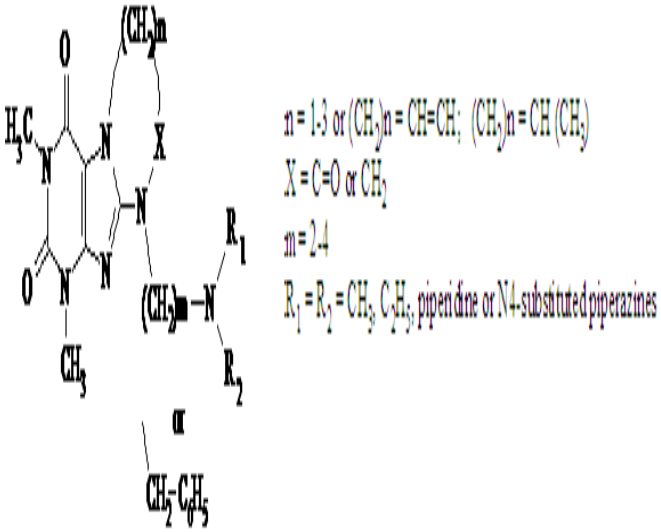
Most of all xanthines are reasonable starting point for the development of a new series inodilators such as 3- Isobutyl-1-methylxanthine (IBMX) is moderately potent, and non selective inhibitor of c AMP and c GMP PDE_S with activity in both positive inotropic and vascular relaxant, the isobutyl group present in IBMX into the pyrimidine ring to form a tricyclic ring system retaining high affinity for the PDE_S [6]. Only few of the synthesized compounds in the group of pyrimidin-8-on[2,1-f]-theophylline derivatives were tested for different profile of their pharmacological activity. Some of the anti-inflammatory agents in the series of 6-hydroxypyrimido-[2,1-f]-theophylline derivatives were described [7]. The compounds from this group were converted by reduction in 2-position to appropriate 2-deoxypyrimido-[2,1-f]- purine – 4,8-(1H, 3H, 9H) dione derivatives [5] and investigated in the treatment of hyperproliferative skin disease [8]. Tetracyclic purine [7,8-g] 6-azapteridines was active against P-388 leukemia [9]. Some tetracyclic theophylline derivatives with complex triazolino [1,5-a] pyrazine A and B fused in 8,9- position were synthesized [10]. They have been showed the activity on the cardio-vascular system; particularly they exhibit anti-angina, anti-arrhythmic activities and also antihypertensive effects [11,12,13].



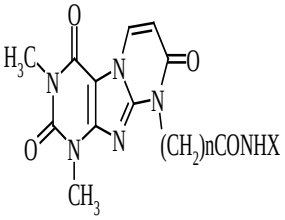
Recently it was found that anellation of five, six or seven membered ring at 7,8-position of theophylline changed the profile of its CNS activity. The Pharmacological evaluation of the series of novel tricyclic theophylline derivatives

***Corresponding Author:** Dr. Omeran Fhid, **Email:** Ofhid@yahoo.com

with imidazo-, pyrimido- or diazepino-[2,1-f]-purine, generally demonstrated their sedative effects on CNS [14-20].



In the present study, we have synthesized and tested for their pro-coagulant properties of the novel, N, N-Dialkylamino-alkylamides and morpholino alkylamides of pyrimidin-8-on [2,1-f] theophylline-9-alkylcarboxylic acids 4-10.



No	N	X
4a	1	$(CH_2)_2$-N $(C_2H_5)_2$
5a	2	$(CH_2)_2$-N$(CH_3)_2$
6a	1	$(CH_2)_2$ - N O
7a	1	$(CH_2)_3$ - N O
8a	2	$(CH_2)_2$ - N O
9a	2	$(CH_2)_3$ - N O
10 a	3	$(CH_2)_2$ - N O

MATERIALS AND METHODS

Experimental

All the melting points were recorded on Fischer-Johns melting point apparatus and were uncorrected. The purity of the products were confirmed by TLC (Kieselgel 60 F_{254}), the respective solvents: benzene + acetone (7:3), and benzene + acetone + methanol (1+1+1) for compounds 4-10 were used. The structure of the new compounds were confirmed by ^{1}H-NMR, MS, UV spectral data and C, H, N analysis (not described).

The synthesis was performed by alkylation of previously described N9-unsubstituted pyrimidin-8-on [2,1-f] theophylline I [16]. In the reaction of I with ethylchloroacetate , ethylacrylate and ethyl-4-bromobutyrate.gave the ethyl ester of pyrimido-[2,1-f]-theophylline-9-alkylcarboxylic acid were obtained 1-3 [18].

N, N dialkyl amino alkyl amide of 1, 3 dimethyl pyrimido [2, 1-f]-purine-2, 4, 8(1H, 3H, 9H)-trione-9-alkyl carboxylic acid 4,5. N-morpholino ethyl (-propyl)-amide of 1,3-dimethyl pyrimido [2,1-f]-purine-2, 4, 8 (1H, 3H, 9H)-trione-9-alkyl carboxylic acid 6-10.

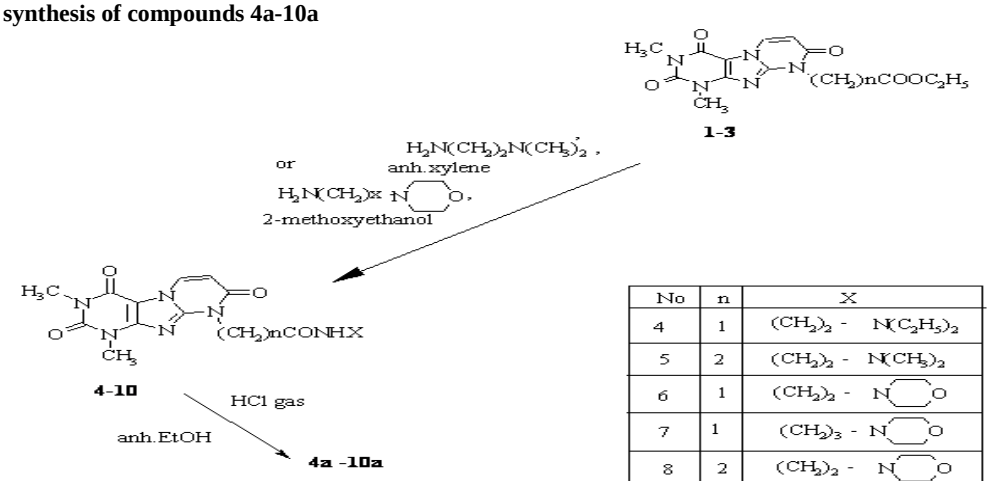
General procedure:

To a solution of compounds ethylester of 1,3-dimethyl pyrimido [2,1-f] -purine- 2,4,8-(1H, 3H, 9H)- trione -9-alkyl carboxylic acid 1-3 (0.005M) Of esters 1, 2 and N, N-dimethylo-amino-ethyl amine 4 (0.88g; 0.01M), and diethylo-amino-ethylamine 5 (1.18g; 0.01M), were carried-out in ($15cm^3$) of anh.xylene, were refluxed 15h for compounds 4,5 after cooling, the precipitate was filtered off, washed with water and then recrystallized from 96% EtOH. In the reaction of (1.66g; 0.005M) of ester 1 (1.73g; 0.005M) of ester 2 and (1.80g; 0.005M) of ester 3, with an appropriate amine of amino ethyl-morpholine (1.22g; 0.01M), amino-propyl-morpholine (1.44g; 0.01M) 6-10, were carried-out in 15 ml of 2-methoxyethanol., and refluxed 10 h for compounds 6-10, after cooling, the precipitate was filtered off, washed with water and then recrystallized from 96% EtOH.

Hydrochlorides of compounds 4-10 (4a –10a)

A suspension of compounds 4-10 (1g) in anh. Ethanol (20ml) was saturated with gaseous HCl, while cooling on an Ice-water bath. The precipitate was gradually dissolved and then hydrochloride was precipitated, the mixture was frozen at –20 C^o for 12h, the precipitate was collected by filtration and recrystallized from anhydrous Ethanol. Scheme of synthesis of compounds 4a-10a are shown in (**Fig 1**).

Fig 1: Scheme of synthesis of compounds 4a-10a



No	n	X
4	1	$(CH_2)_2$ - $N(C_2H_5)_2$
5	2	$(CH_2)_2$ - $N(CH_3)_2$
6	1	$(CH_2)_2$ - N O
7	1	$(CH_2)_3$ - N O
8	2	$(CH_2)_2$ - N O
9	2	$(CH_2)_3$ - N O
10	3	$(CH_2)_2$ - N O

PHARMACOLOGY

Pro-coagulation properties:

The experiment was performed on blood plasma, using reagents (HEMOLAB Thrombicalci-Test and HEMOLAB Silimat). The reagents were manufactured by BioMérieux SA. The data are carried out in duplicate and calculate by the mean of APTT and PTT. Coagulometer produced by BioMérieux (option 4) was used [17]. The dialkylamino-ethyl-amides 4a, 5a and morpholine-ethyl-(-propyl) amides 6a-10a of pyrimidine-8-on [2,1-f]-theophylline-9-alkylcarboxylic acids were investigated on their influence on following parameters: activated partial thromboplastin time (APTT) and prolonged thermoplastin time (PTT) by estimate of the clothing time of the blood plasma, blood plasma with NaCl and blood plasma with tested compounds.

RESULTS AND DISCUSSION

All the synthesized compounds (4a-10a) were purified by successive recrystallization using ethanol. The purity of the synthesized compounds was checked by performing TLC**.** The physicochemical constant data of synthesized compounds were determined and results summarized in (**Table 1**). The structures of the synthesized compounds (4-10) were determined on the basis of their FTIR and 1HNMR data and results were as a following:

N, N-Diethylaminoethylamide of pyrimidin-8-on [2, 1-f] theophylline-9-aceticacid (4):

^{1}H-NMR δ: 1,00-1,06(t, 6H, $N(CH_3)_2$, J=7,2Hz); 2,53-2,62(m,6H,$CH_2N(CH_3)_2$,); 3,27-3,37 (m, 2H, NH, CH_2); 3,40 (s,3H, N3, CH_3); 3,58(s, 3H, N1-CH_3); 4,60(s, 2H, N9CH_2); 6,25-6,28(d,1H, C7-H, J=6,8Hz); 6,70 (brs, 1H, NH); 8,48 -8,50(d,1H, C6-H, J=7,7Hz). UV: λ_1 =255 nm, log ε = 4,73; λ_2 =286 nm, log ε = 4,65.

N,N-Dimethyl aminoethylamide of pyrimidin-8-on[2,1-f]theophylline-9-propanoic acid (5):

^{1}H-NMR δ: 2,29(s, 6H, $N(CH_3)_2$); 2,45-2,51(t,2H,$CH_2N(CH_3)_2$, J=6,0Hz); 2 ,71-2,79 (t, 2H, CH_2CO,J=7,6Hz); 3,30-3,39 (m, 2H, NH, CH_2); 3,43 (s,3H,N3,CH_3); 3,60(s, 3H,N1-CH_3); 4,55-4,62(t, 2H, N9CH_2, J=7,3 Hz); 6,26-6,30(d,1H, C7-H, J=7,8Hz); 6,57(brs,1H,NH); 8,48-8,52 (d,1H, C6-H, J=7,8Hz). UV: λ_1=251 nm, log ε = 4,54; λ_2 =286 nm, log ε = 4,46.

Morpholino-ethyl amide of pyrimidin-8-on [2,1-f]theophylline-9-acetic acid (6):

^{1}H-NMR δ: 2,51-2,58(m, 6H,$CH_2N(CH_2)_2$); 3,46-3,57(t,2H,$NHCH_2$,); 3,42(s, 3H, N3CH_3); 3,68(s, 3H,N1CH_3); 3,71-3,74(t, 4H,$(CH_2)_2CO$); 4,92 (s, 2H, N9CH_2); 6,77 (brs, 1H, NH); 6,31-6,34(d, 1H,C7H, J=7,4 Hz); 8,54-8,57(d,1H, C6 H, J=7,4Hz). UV: λ_1 = 249 nm, log ε = 4,84; λ_2 = 286, log ε = 4,15.

Morpholino-propyl amide of pyrimidin-8-on [2,1-f]theophylline-9-acetic acid (7):

^{1}H-NMR δ: 1,78-1,86 (m, 3H, CH_2 CH_2CH_2); 2,51-2,59(m, 6H, $N(CH_2)_2$); 3,39-3,43(t,2H,$NHCH_2$, J=6,3Hz); 3,44(s, 3H,N3CH_3); 3,62 (s, 3H, N1 CH_3); 3,73-3,79 (t, 4H, $(CH_2)_2CO$); 4,96(s, 2H, N9CH_2); 7,41(brs, 1H, NH); 6,30-6,33(d, 1H,C7 H, J=7,9Hz); 8,58-8,60 (d,1H, C6 H, J=6,6Hz). UV: λ_1=250 nm, log ε = 5,00; λ_2 =289 nm, log ε = 4,75.

Morpholino-ethyl amide of pyrimidin-8-on [2,1-f]theophylline-9-propanoic acid (8): ^{1}H-NMR δ: 2,46-2,52(m, 6H, CH_2 $N(CH_2)_2$); 2,73-2,80 (t, 2H, CH_2CO, J = 7,7Hz); 3,33–3,41(m, 2H, $NHCH_2$); 3,43(s, 3H, N3 CH_3); 3,62 (s, 3H, N1CH_3); 3,69-3,74(t, 4H, $(CH_2)_2CO$); 4,56-4,64(t, 2H, N9CH_2 J=7,5Hz); 6,22(brs, 1H, NH); 6,28-6,31(d, 1H, C7-H, J=8,8Hz); 8,51-8,55(d,1H, C6-H, J=7,7Hz). m/z:

431 (1) M^+, 388(2), 368(1), 344(3), 319(1), 313(1), 248(5), 247(5), 129 (3), 100(100), 98(7), 69(6), 57(9), 40 (24). UV: λ_1 =251 nm, log ε = 4,64; λ_2 =285 nm, log ε = 4,56.

Morpholino-propyl amide of pyrimidin-8-on [2, 1-f] theophylline-9-propanoic acid (9):

^{1}H-NMR δ: 1,67-1,73(m, 2H, $CH_2CH_2CH_2$); 2,46-2,51(m, 6H, $N(CH_2)_2$); 2,73-2,80 (t, 2H, CH_2CO, J=6,3Hz); 3,33-3,36 (m, 2H, NH CH_2); 3,41(s, 3H, N3CH_3); 3,59(s, 3H, N1CH_3); 3,69-3,73(t, 4H, $(CH_2)_2$)O); 4,53-4,57(t, 2H, N9CH_2, J=7,4Hz); 6,25-6,31(d, 1H,C7-H, J=7,7Hz); 7,27(brs, 1H, NH); 8,48-8,52(d,1H,C6-H, J=7,7Hz). MS m/z: 445 (2) M^+, 414(10), 402(15), 359(2), 346(1), 318(2), 302(6), 274(5), 248 (20), 247(40), 218(3), 190(4), 167(3), 162(8), 135(5), 100 (100), 86(7), 70(6), 56(10), 40(8). UV: λ_1 =248 nm, log ε = 4,76; λ_2 =285 nm, log ε = 4,71.

Morpholino-ethyl amide of pyrimidin-8-on [2,1-f]theophylline-9-butanoic acid(10):

^{1}H-NMR δ: 1,65-1,73(m, 2H, N9CH_2 CH_2); 2,45-2,50(m, 6H, CH_2 $N(CH_2)_2$; 2,68-2,73(t, 2H,CH_2 CO, J=7,7Hz); 3,32-3,38(m, 2H, NHCH_2); 3,42 (s,3H, N3 CH_3); 3,60(s, 3H, N1CH_3); 3,66-3,72(m, 4H, $(CH_2)_2$O); 4,55-4,60(t, 2H, N9-CH_2, J=7,4Hz); 6,27-6,29(d,1H,C7-H, J=7,7 Hz); 7,18(brs, 1H, NH); 8,50 –8,53(d,1H, C6-H, J=7,7Hz). UV: λ_1 =253 nm, log ε = 4,97; λ_2 =283 nm, log ε = 4,86.

In accordance with the data obtained from anticoagulant properties as seen in (**Table 2**), all the synthesized tricyclic theophylline containing amide with alkyl carboxylic acid moiety have very mild pro-coagulant properties as compare to blood plasma with NaCl.

Table 1: Physicochemical constant data of synthesized compounds

Comp.	m.p. ^oC	Recryst. Solvent	Yield %	Molecular formula (molecular weight)	TLC (solvent)
4	216-218	96 EtOH	52	$C_{18}H_{25}N_7O_4$ (403.44)	0.45(A), 0.87(B)
4a	246-248	anh EtOH	-	$C_{18}H_{25}N_7O_4$.HCl(439.94)	-
5	222-224	96 EtOH	56	$C_{17}H_{23}N_7O_4$ (389.41)	0.33(A), 0.80(B)
5a	164-166	anh EtOH	-	$C_{17}H_{23}N_7O_4$.HCl (425.51)	-
6	213-215	96 EtOH	48	$C_{18}H_{23}N_7O_5$ (417.41)	0.29 (A) 0.87(B)
6a	273-275	anh. EtOH	-	$C_{18}H_{23}N_7O_5$.HCl (453.88)	-
7	183-185	96 EtOH	46	$C_{19}H_{25}N_7O_5$ (431.45)	0.31(A), 0.80(B)
7a	260-262	anh. EtOH	-	$C_{19}H_{25}N_7O_6$.HCl (467.94)	-
8	253-255	96 EtOH	53	$C_{19}H_{25}N_7O_5$ (431.45)	0,27(A), 0.85(B)
8a	208-210	anh. EtOH	-	$C_{19}H_{25}N_7O_5$.HCl (467.94)	-
9	210-212	96 EtOH	51	$C_{20}H_{27}N_7O_5$ (445.47)	0.31(A), 0.81(B)
9a	182-184	anh. EtOH	-	$C_{20}H_{27}N_7O_5$.HCl (481.97)	-
10	261-263	96 EtOH	45	$C_{20}H_{27}N_7O_5$ (445.47)	0.30(A), 0.83(B)
10a	268-270	anh. EtOH	-	$C_{20}H_{27}N_7O_5$.HCl (481.97)	-

Solvent system: A. Benzene: acetone (7:3), B. benzene: acetone: methanol (1:1:1).

Table 2: Anticoagulant evaluation of synthesized compounds

		APTT			PT		
Comp	Conc (M/dm$^{3)}$	Blood .Plasma (B.P)	B.P & NaCl	B.P & comp	B.P	B.P& NaCl	B.P & comp
4a	10^{-4}	35	36,3	36	14,5	14,8	14,0
		28,8	30,8	28,2	13,6	14,6	14,3
		31,5	33,3	31,7	-	14,1	13,2
		-	-	-	-	-	14,1
5a	10^{-4}	30,9	32,4	30,7	14,2	14,6	14,9
		31,2	32,8	32	15	15,1	15,8
		30,5	31,6	31,1	14,9	16,7	16
		30,3	31,9	31,1	15,7	16,7	16,5
6a	10^{-4}	27,6	30,3	30	15,7	18,2	18,3
		26,8	27,7	27,3	17,2	22,2	20
		27,2	28,3	27,8	18,1	19,3	18,4
		26,3	27,5	28,5	16,2	17,9	17,3
		31,5	32,5	31,8	17,7	19,2	18,9

7a	10^{-3}	25,8	26,7	26,6	16,1	16,7	16,6
		27	28	27,4	16,5	16,8	16,9
		31,8	36	31,7	16,7	16	17,1
		27,6	29	27,9	18,9	20,1	21,7
8a	10^{-3}	31,7	33,3	31,9	13,6	14,2	13,9
		30,8	32,4	32,1	13,3	13,5	13,5
		37,3	38,5	37,3	14,4	15,4	15,2
9a	10^{-3}	27,4	28,4	30,7	17,2	18,3	18,4
		27,6	28	25	17,1	18,2	18,3
		27,8	28,8	28,1	16,5	16,9	16,6
10a	10^{-3}	34,9	35,3	34,6	16,9	17,9	18,9
		31	36,3	35,4	17,4	15,7	18,8
		36,5	38,4	37,2	14,2	15	14,8
		31,1	30,9	31,6	17,8	18,6	18,6
		28,7	29,2	28,7	14,3	16,6	16,3

REFERENCES

1. Corsan S., Scapicchi R., Strappaghetii G. Bronchodilator activity of theophylline derivatives substituted at the 7-position. Arch. Pharm.(Weinheim) 1994; 327: 631-635.
2. Zlatkov A. B., Peikov P. T., Danchev N.D., Ivanov D. I., Tsvetkova B. Synthesis, toxicological, pharmacological assessment, and in vitro bronchodilating activity of some 7-theophyllinylacetyloxyglycols. Arch. Pharm (Weinheim) 1998; 331: 313-318.
3. Sakai R., Konno K., Yamamoto Y., Sanae F., Takagi K., Hasegawa T., Iwasaki N., Kakiuchi M., Kato H., Miyamoto K (1992) Effects of alkyl substitutions of xanthine skeleton on bronchodilation. J. Med. Chem 1992; 35: 4039–4044.
4. Parrick, J., Mehta, L.K. and Hodgkiss, R.J. The synthesis of a potential anti-cancer agent containing the caffeine and 1,2,4-benzotriazine moieties. J. Heterocyclic Chem 1993; 30**:** 323-327.
5. Bovy. P. R., Collins. J. T., Chamberlain.T.S., Gheng.B.K. PCT Int.Appl. WO 92 07, 852, Chem. Abstr 1992; 117: 131218j.
6. Muller. C. E. A_1-Adenosine receptor antagonists. Exp. Opin. Ther. Patents 1997; 7: 419-440.
7. Blythin D J., Kaminski J J., Domalski M S., Spitler J., Solomon D M., Conn D J., et al. Antinflammatory activity of substituted 6-hydroxypyrimido[2,1-f]purine-2, 4, 8 (1H, 3H, 9H)-triones. Atypical nonsteroidal anti-inflammatory agents. J.Med. Chem 1986; 29: 1099-1113.
8. Conn D J., Kaminski J J., Solomon D M., Mc Phail A T. Regiospecific reduction of the 2-carbonyl group of the 6-hydroxypyrimido [2,1-f] purine –2, 4, 8(1H, 3H, 9H)-trione system by selected metal hydrides. A novel reduction of a fused xanthine nucleus. J. Org. Chem 1988; 53: 3265-3271.
9. Taisei U., Tsuneyasu A., Jinsaku S., Masahisa A., Joji N. Syntheses, antitumor activity and vascular relaxing effect of purino [7,8-g]-6-azapterdines and [1,2,4] Triazino-[3,2-f]purines. Chem Pharm Bull 1987; 35: 4031-4038.
10. Xia Yan., Chackalamannil S., Czarniecki M., Tsai H., Vaccaro H., Cleven R., et al. Synthesis and evaluation of Polycyclic Pyrazolo[3,4-d] Pyrimidines as PDE1 and PDE5 c GMP Phosphodiesterase inhibitors., J. Med. Chem 1997; 40: 4372-4377.
11. Dušan.H., Alfonz.R., Františisk.P., Augustin.M., Jaroslav.K. 1,3-dipolar cycloaddition reaction of 7-alkenyl- or 7-alkynyl-8-azidomethyltheophyllines. Collection Czochaslovak. Chem.Commun 1988; 53: 319-328.
12. Drabczynska A., Pawlowski M., Gorczyca M., Malec D., Modzelewski J. Synthesis and preliminary pharmacological assessment of novel 9-alkylamino sunstituted pyrimidino-[2,1-f]-purines. Pol. J. Pharmacol. Pharm 1992; 44: 487-503.
13. Pawlowski M., Drabczynska A., Gorczyca M., Malec D., Modzelewski J. Synthesis and pharmacological screening of novel 10-substituted diazepino-[2,1-f]-purines. Acta Poloniae Pharmaceutica-Drug Research 1994; 51: 385-391.
14. Pawlowski M., Drabczynska A., Gorczyca M., Malec D., Modzelewski J. Chemical and Pharmacological properties of new tetrahydropyrimido-[2,1-f]-purine, Pharmazie, 1995, 50: 453-455.

15. Pawlowski M., Drabczynska A., Gorczyca M., Katlabi J., Malec D., Modzelewski J. Synthesis and CNS activity of tricyclic theophylline derivatives. 8-substituted imidazo [2,1-f]-theophylline., Eur. J.Med.Chem 1999; 34: 1085-1091.
16. Pawłowski M., Katlabi J., Rys B., Szneler E. New tricyclic theophylline derivatives. Reaction of 8-benzylaminotheophylline with ethyl 2,3-dibromopropanoate. Pharmazie 1997; 52: 279-282.
17. Szekers L, Papp G. Handbook of experimental pharmacology (Eds.Schimer J.,Eichler O) Springer-Verlag.Berlin. Heidelberg, New York, 1975.
18. Omeran.F., Maciej. P., Barbara.F., Renata H., Dorota M. Central nervous system activity of new pyrimidine-8-on[2,1-F] theophylline-9-alkylcarboxylic acid derivatives. Polish .J.of pharmacology 2002; 54:245-254.
19. Zagorska, A., Fhid, O., Pawlowski, M., Filipek, B., Zygmunt, M. The Cardiovascular Properties of Some Amide Derivatives of Pyrimidin-8-on[2,1-f]theophylline-9- Alkylcarboxylic Acids. Letters in Drug Design & Discovery 2006; 3 (5): 346-350.
20. Omran. Fhid, Muacij. Pawłowski, Beata Duszynska. Synthesis, characterization and pharmacological evaluation of some tricyclictheophylline Derivatives, Journal of Chemical and Pharmaceutical Research 2012; 4(5):2367-2372.