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Synthesis and preliminary pharmacological screening of novel imidazo[2,1-f]theophylline derivatives

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Abstract

The three different kinds of imidazo[2,1-f]theophylline derivatives were synthesized and tested for their CNS activity. A series of alkoxy-alkylamides and amino-alkylamides with basic function, derived from 8-benzyl-6,7-dihydroimidazo[2,1-f]theophylline-7-carboxylic acid showed stimulating influence on CNS as they increased the locomotor activity (compound **8** and **10**) or enhanced amphetamine and apomorphine effects in mice (compounds **3**, **4** and **9**). Compounds **1**, **5**, **8**–**10** and **12** had anticonvulsant activity in the pentetrazole test; **12** with anellated imidazol-7-on ring (lactam structure) showed sedative properties and antiserotonin effects.

Keywords: Imidazo[2,1-f]theophyllines; CNS activity of fused [2,1-f]theophyllines

1. Introduction

In our previous studies on tricyclic theophylline derivatives we have synthesized and tested on CNS series of compounds with anellated at 7,8-position of theophylline, five, six or seven member heterocyclic ring of lactam or non-lactam structure modified by a basic substituent at N8, N9 and N10 position (Fig. 1).

The investigated compounds generally represented sedative profile of pharmacological activity on CNS [1–4]. Several structure–activity relationships concerning a kind of a basic substituent and length of the spacer between dialkyl-amino rest and tricyclic system, in the aspect of serotonine 5-HT_1, adenosine A_1 receptors and behavioral properties in animals, for several representatives of this class of the structure were described [5]. N8-Arylpiperazino-alkyl derivatives of 6,7-dihydro-[8H]-imidazo[2,1-f]theophylline and N8-benzyl-6,8-dihydroimidazol-7-on[2,1-f]theophylline possessed sedative and analgesic activity [5] similar to the described earlier for pyrimido[2,1-f]theophylline [1,2,4] and diazepino[2,1-f]theophylline [3] analogs. Lactam and non-lactam derivatives of ω-alkyl-1-arylpiperazines containing terminal pyrimidopurine or 1,3-diazepinopurine with phenyl in arylpiperazine rest, in several behavioral models demonstrated postsynaptic antagonism towards 5-HT_{1A} receptors whereas their pyrimidopiperazine analogs were classified as 5-HT_{1A} partial agonists [6]. 3′-Chloro or 2′-methoxyphenyl piperazinopropyl derivatives of this tricyclic systems acted as partial agonists or full agonists of pre- and post-synaptic 5-HT_{1A} receptors [7]. Removal of the 1,3-diazepine ring in tricyclic phenylpiperazinoalkyl derivatives of diazepino[2,1-f]theophyllines resulted in a 12-fold decrease in 5-HT_{1A} affinity of 7,8-disubstituted analogs with alkyl in seven position and phenylpiperazinopropyl-amine rest in the position 8. The increasing of lipophilicity of the seven-substituent also did not improve binding properties [8]. It showed that the third ring fused to theophylline plays an important role in binding affinity and 5-HT_{1A}–5-HT_{2A} selectivity of these compounds [8].

The aim of the present work was to synthesize some imidazo[2,1-f]theophylline derivatives with carboxylic function in fused third ring (Fig. 2) modified by ester (type I), alkoxypropylamides, di-alkyl (-methyl, -ethyl) aminoalkylamides, morpholinopropylamides or N4-methylpiperazinopropylamide (type II). Additionally

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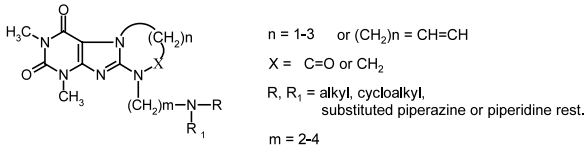


Fig. 1. The structure of pharmacologically investigated imidazo-, pyrimido- and diazepino[2,1-f]theophylline derivatives.

6-methyl-8-benzyl-6,8-dihydroimidazol-7-on[2,1-f]theophylline was obtained (type III) and tested in the same manner as a reference structure, analogically to previously investigated N8, N9 or N10-benzyl derivatives of imidazol-7-on-, pyrimidin-8-on- and diazepin-9-on-[2,1-f]theophylline [3,4,8].

The chemical structure of I and II represents tricyclic theophylline derivatives with *N*-benzylproline fused in the position 7,8- of the mother compound. The chemical modification of 8-benzyl-6,7-dihydro-[8H]-imidazo-[2,1-f]theophylline-7-carboxylic acid (8-benzyl-prolino-theophylline) **2** via ester **1**, alkoxy-propylamides (**3**, **4**) and dialkylamino-alkylamides (**5**–**8**) also morpholine and *N*-methylpiperazine analogs (**9**, **10**) allow to expect an interesting biological activity, first of all some stimulating effects on CNS in behavioral tests. We were particularly interested whether the presence of amino acid derivative in tricyclic structure (**1**–**10**) can influence the profile of activity in comparison with parent dialkylamino-alkyl derivatives of imidazo-, pyrimido- and diazepino[2,1-f]theophyllines.

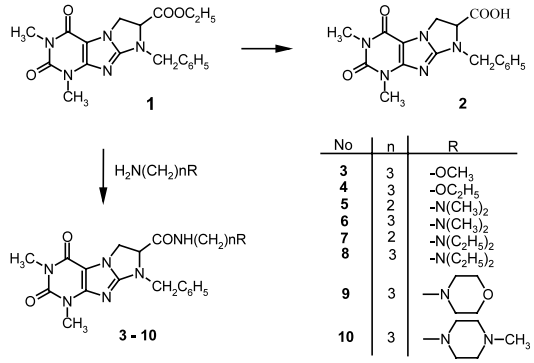
2. Investigations, results and discussion

2.1. Chemistry

Several steps' synthesis of the ethyl ester of 8-benzyl-6,7-dihydro-[8H]-imidazo[2,1-f]theophylline-7-carboxylic acid **1** and the corresponding acid **2** (type **I**) were described previously [9].

Some alkoxy-propylamides (**3**, **4**), dialkylamino-alkylamides (**5**–**8**) and their morpholine **9** or methylpiperazine **10** analogs were synthesized according to Scheme 1.

Alkoxy-propylamides (**3**, **4**) as well as basic amides (**5**–**10**) were obtained in the reaction of **1** with double amount of appropriate ethyl- or propyl-amine derivatives in anhydrous ethanol. The structure of compound



Scheme 1.

1 and **2** was elucidated previously on the basis of NMR experiments performed for its carboxylic derivatives [9]. The signals of AMX and AX spin-systems with diastereotopic CH_2 protons of CH_2–CH fragments of the third ring and benzyl substituent in high-field region of the spectrum ($\delta = 4.19$–4.89) are present [9]. In the spectrum of analyzed compounds **3**–**10** those characteristic signals appeared in the region $\delta = 3.95$–4.52 which unambiguously confirms their N9-benzylimidazo-structure. The signals of alkyl or alkylen protons of *N*,*N*-dialkyl-amino-alkyl part of the amide structures are present in low-field region of the spectrum of compounds **5**–**10**. The place of the triplet signal of NH depends on the length of the alkylen between amide and tertiary amine rest and on the kind of basic center of the substituent. For two carbon chain (compounds **5**, **7**) one proton triplet signal appeared at $\delta = 6.92$, for propylene analogs **6**, **8**–**10** NH signal is placed at $\delta = 7.96$–8.51 for dialkyl-amino and morpholino derivatives **6**, **8** and **9** at $\delta = 8.20$–8.51; but at $\delta = 7.96$ for N4-methylpiperazine analog **10**. The singlet signals of methyl protons in 3 and 1 position at $\delta = 3.36$ and 3.55 in $CDCl_3$ or $\delta = 3.15$ and 3.35 in DMSO confirm dimethylxanthine structure. In UV spectra of the synthesized compounds two maxima of absorbance were observed in the region characteristic for 8N-benzylamino- and 8-(*N*-benzyl-*N*-alkylamino)-theophyllines [10,11].

Compound **12** was obtained according to the Scheme 2.

In the reaction of 8-benzylaminotheophylline sodium salt with α-bromopropanoic acid in anhydrous DMF the 8-benzylaminotheophylline-7-α-propanoic acid **11** was obtained. Intramolecular cyclocondensation of **11** to 6-methyl-8-benzyl-6,8-dihydroimidazol-7-

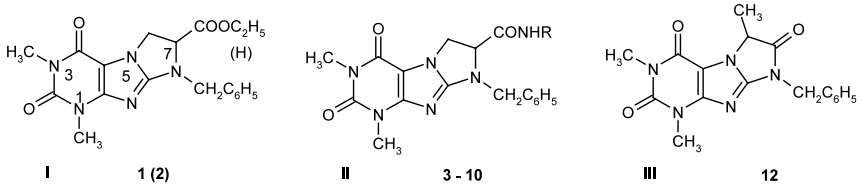
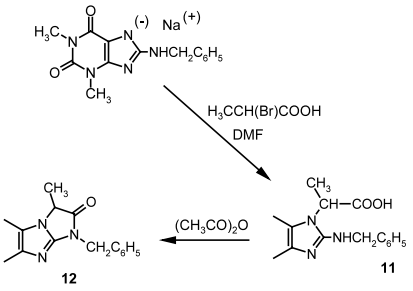


Fig. 2. Imidazo[2,1-f]theophyllines subjected for CNS activity screening.

on[2,1-f]theophylline **12** was carried out by refluxing in acetic anhydride.

2.2. Pharmacology

The compounds **1**–**10** and **12** were examined pharmacologically for their influence on CNS. The acute toxicity of all compounds as the LD_{50} [12] is presented in Table 1. Compound **12** had the lowest toxicity but



Scheme 2.

Table 1
Acute toxicity of the compounds in mice

Comp.	LD_{50} 95% confidence limits
1	1100 mg/kg (917–1320)
2	1150 mg/kg (983–1346)
3	1650 mg/kg (1571–1733)
4	1800 mg/kg (1636–1980)
5	230 mg/kg (169–313)
6	280 mg/kg (200–392)
7	125 mg/kg (92–170)
8	160 mg/kg (119–214)
9	580 mg/kg (509–661)
10	540 mg/kg (462–632)
12	> 2000 mg/kg

Table 2
The influence of all substances on the spontaneous locomotor activity of mice

Comp.	Number of movement (mean ± SE)
Vehicle	240 ± 25.7
1	189 ± 80.1
2	218 ± 32.1
3	170 ± 44.9
4	144 ± 28.8*
Vehicle	187 ± 24.4
5	249 ± 27.1
6	225 ± 43.4
7	252 ± 29.8
8	301 ± 57.0*
9	269 ± 57.6
10	298 ± 27.1**
12	179 ± 19.0

Explanations: *, $P < 0.05$; **, $P < 0.01$.

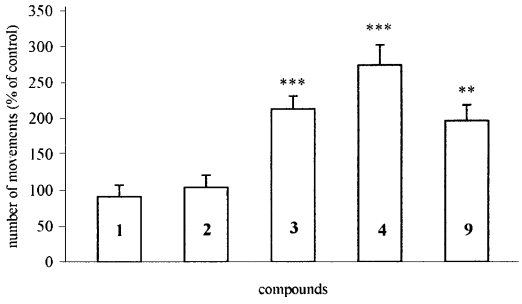


Fig. 3. The influence of compounds **1**–**4** and **9** on amphetamine-induced hyperactivity of mice. Explanations: amphetamine 5 mg/kg was injected s.c. Number of movements in the control (100%) groups was 479–661. **, $P < 0.01$; ***, $P < 0.001$ (Student's t-test).

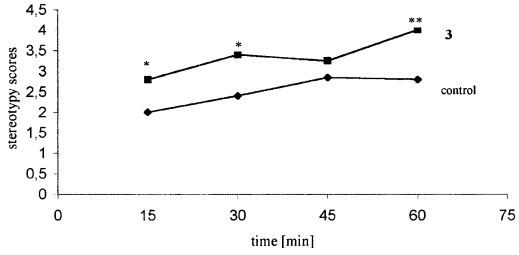


Fig. 4. The influence of compound **3** on apomorphine-induced stereotypy in rats. Explanations: apomorphine 3 mg/kg was injected s.c. *, $\alpha < 0.1$; **, $\alpha < 0.01$ (Mann–Whitney U-test).

particularly marked increase of acute toxicity was observed after administration of substances **5**–**8** (amides containing dimethyl- or diethyl-amine group). Morpholine or methylpiperazine derivatives (**9**, **10**) showed moderate toxicity.

The pharmacological profile of action of some investigated 8-benzyl-imidazo[2,1-f]theophylline derivatives seems to be rather stimulating on CNS, for example: in the spontaneous locomotor activity test compounds **8** and **10** significantly induced the increase of mobility (Table 2).

Similarly substances **3**, **4**, and **9** were able to potentiate amphetamine-induced hyperactivity (Fig. 3) and compound **3** enhanced also apomorphine stereotypy (Fig. 4).

The results demonstrate that compounds **3**, **4** and **9** are able to intensify dopaminergic neurotransmission, in this regard they show similarity to their parent drug—theophylline.

Substances **2**, **5**, **8**–**10** and **12** had weak protective action in pentetrazole convulsions (Table 3), but not in maximal electroshock test.

Compounds **5**–**7** and **12** induced very small and short-lasting (up to 60 min) prolongation of the reaction time of mice on the nociceptive stimulus in the hot plate test. Moreover, substance **12** has shown some antiserotonin properties, as it diminished 5-HTP-induced head twitch reactions in mice.

Analyzing the results of preliminary investigations of the new class of tricyclic theophylline derivatives in which amino acid (proline) is fused to purine structure and the carboxylic function is modified also by different amide rest, from the point of view of structure–activity relationship, it may be concluded that:

- In contrast to described earlier tricyclic lactam or non-lactam aminoalkyl derivatives the investigated amides, especially containing basic center in the substituent, exhibited stimulating activity on CNS, in this aspect they showed similar profile of pharmacological activity to parent drugs—methylxanthines.
- The alkoxy-propylamides and morpholine-propylamide possessing the ether in the molecule showed significant stimulating effects on dopaminergic neurotransmission in the CNS.

Some of the presented data summarized in this article remain open to further investigation.

3. Experimental

3.1. Chemistry

Melting points are reported uncorrected. TLC was performed on Merck plates (Kieselgel 60 F_{254}) solvent A (benzene:acetone:methanol 1:1:1), solvent B (chloroform:methanol 8:2). UV spectra were obtained on the UV–Vis spectrophotometer Perkin–Elmer Lambda 12. ^{1}H NMR spectra were recorded on Varian 200 BB (200 MHz) instrument with TMS as internal standard (chemical shifts in δ ppm). Elemental analyses were within $\pm$0.4% of the theoretical value and they are not reported.

Table 3
The influence of all compounds on pentetrazole (85 mg/kg s.c.) induced convulsions in mice

Comp.; 0.1 LD_{50}	Number of mice with tonic convulsions	Lethality
Vehicle	8/16	4/16
1	7/8	5/8
2	1/8*	1/8
3	6/8	4/8
4	8/8	5/8
5	1/8*	0/8
6	2/8	0/8
7	2/8	0/8
8	0/8**	0/8
9	1/8*	1/8
10	0/8**	0/8
12	0/8**	0/8

* $\alpha < 0.05$.
** $\alpha < 0.01$ (χ^2-test).

3.2. Chemical procedures and analytical data

3.2.1. Ethyl ester of 8-benzyl-6,7-dihydro-[8H]-imidazo[2,1-f]theophylline-7-carboxylic acid **1** and 8-benzylcarboxylic acid **2**

Published by Pawłowski and co-workers [9].

3.2.2. General procedure for the synthesis of amides **3**–**10**

A mixture of **1** (3.8 g, 0.01 mol) and 0.02 mol of appropriate amine:methoxypropylamine (for **3**), ethoxypropylamine (for **4**), *N*,*N*-dimethylaminoethylamine (for **5**), *N*,*N*-dimethylaminopropylamine (for **6**), *N*,*N*-diethylaminoethylamine (for **7**), *N*,*N*-diethylaminopropylamine (for **8**), morpholinopropylamine (for **9**), N1-methyl-piperazino-N4-propylamine (for **10**), in 20 ml anh. C_2H_5OH was refluxed for 6 h. After refrigeration the crude products were filtered off, washed with water and recrystallized.

3.2.3. 8-Benzyl-6,7-dihydro-[8H]-imidazo[2,1-f]theophylline-7-carboxylic acid (3-methoxy-propyl)-amide **3**

Yield: 3.7 g (87%); m.p. 223–225 °C (ethanol); *Anal*. ($C_{21}H_{26}N_6O_4$) C, H, N; TLC $R_f = 0.91$ (A); UV: (methanol) λ_{max1} (log ε) = 216 nm (4.43); λ_{max2} (log ε) = 298 nm (4.12); ^{1}H NMR (DMSO): $\delta = 1.50$–1.60 (q, 2H, $J = 6.6$ Hz, CH_2–CH_2–CH_2); 3.02–3.09 (m, 2H, $J = 6.3$ Hz, NH–CH_2–CH_2); 3.15 (s, 3H, N3–CH_3); 3.18 (s, 3H, OCH_3); 3.20–3.30 (t, 2H, $J = 6.0$ Hz, CH_2–CH_2–O); 3.35 (s, 3H, N1–CH_3); 3.95–4.05 (dd, 1H, $J = 5.7$ Hz, $J = 9.3$ Hz, C6H_2); 4.25–4.32 (d, 1H, $J = 15.7$ Hz, N8–CH_2); 4.35–4.43 (dd, 1H, C6H_2); 4.45–4.50 (dd, 1H, C7H); 4.65–4.72 (d, 1H, $J = 15.4$ Hz, N8–CH_2); 7.26–7.39 (m, 5H, arom.); 8.23–8.27 (t, 1H, $J = 5.5$ Hz, CONH–CH_2).

3.2.4. 8-Benzyl-6,7-dihydro-[8H]-imidazo[2,1-f]theophylline-7-carboxylic acid (3-ethoxy-propyl)-amide **4**

Yield: 3.2 g (72%); m.p. 199–201 °C (ethanol); *Anal*. ($C_{22}H_{28}N_6O_4$) C, H, N; TLC $R_f = 0.92$ (A); UV: (methanol) λ_{max1} (log ε) = 216 nm (4.45); λ_{max2} (log ε) = 298 nm (4.16); ^{1}H NMR (DMSO): $\delta = 1.04$–1.09 (t, 3H, $J = 6.9$ Hz, CH_2–CH_3); 1.52–1.60 (q, 2H, $J = 6.6$ Hz, CH_2–CH_2–CH_2); 3.02–3.09 (m, 2H, $J = 6.3$ Hz, NH–CH_2–CH_2); 3.16 (s, 3H, N3–CH_3); 3.25–3.30 (q, 2H, OCH_2–CH_3); 3.31 (s, 3H, N1–CH_3); 3.31–3.35 (t, 2H, $J = 6.3$ Hz, CH_2–CH_2–O); 3.96–4.02 (dd, 1H, $J = 5.5$ Hz, $J = 9.3$ Hz, C6H_2); 4.26–4.31 (d, 1H, $J =$ 15.4 Hz, N8–CH_2); 4.36–4.43 (dd, 1H, C6H_2); 4.46–4.50 (dd, 1H, C7H); 4.66–4.72 (d, 1H, $J = 15.4$ Hz, N8–CH_2); 7.26–7.39 (m, 5H, arom.); 8.22–8.27 (t, 1H, $J = 5.5$ Hz, CONH–CH_2).

3.2.5. 8-Benzyl-6,7-dihydro-[8H]-imidazo[2,1-f]theophylline-7-carboxylic acid (2-N,N-dimethylamine-ethyl)-amide ***5***

Yield: 3.0 g (71%); m.p. 179–181 °C (methanol); *Anal*. ($C_{21}H_{27}N_7O_3$) C, H, N; TLC $R_f = 0.17$ (A), $R_f = 0.35$ (B); UV: (methanol) λ_{max1} (log ε) = 216 nm (4.48); λ_{max2} (log ε) = 298 nm (4.20); ^{1}H NMR ($CDCl_3$): δ = 2.22 (s, 6H, N(CH_3)$_2$); 2.34–2.40 (t, 2H, $J = 6.0$ Hz, CH_2–CH_2–N); 3.26–3.32 (m, 2H, $J = 5.4$ Hz, NH–CH_2–CH_2); 3.36 (s, 3H, N3–CH_3); 3.56 (s, 3H, N1–CH_3); 4.13–4.20 (dd, 1H, $J = 5.3$ Hz, $J = 7.7$ Hz, C6H_2); 4.30–4.39 (d, 1H, $J = 14.9$ Hz, N8–CH_2); 4.30–4.35 (dd, 1H, C6H_2); 4.44–4.50 (dd, 1H, C7H); 4.80–4.86 (d, 1H, $J = 14.8$ Hz, N8–CH_2); 6.90–6.98 (t, 1H, CONH–CH_2); 7.27–7.37 (m, 5H, arom.).

3.2.6. 8-Benzyl-6,7-dihydro-[8H]-imidazo[2,1-f]theophylline-7-carboxylic acid (3-N,N-dimethylamine-propyl)-amide ***6***

Yield: 2.2 g (51%); m.p. 184–186 °C (methanol); *Anal*. ($C_{22}H_{29}N_7O_3$) C, H, N; TLC $R_f = 0.14$ (A); UV: (methanol) λ_{max1} (log ε) = 216 nm (4.55); λ_{max2} (log ε) = 298 nm (4.20); ^{1}H NMR ($CDCl_3$): δ = 1.55–1.67 (q, 2H, $J = 6.0$, CH_2–CH_2–CH_2); 2.15 (s, 6H, N(CH_3)$_2$); 2.34–2.40 (t, 2H, $J = 5.3$ Hz, CH_2–CH_2–N); 3.26–3.34 (m, 2H, NH–CH_2–CH_2); 3.36 (s, 3H, N3–CH_3); 3.56 (s, 3H, N1–CH_3); 4.17–4.21 (dd, 1H, $J = 6.1$ Hz, C6H_2); 4.24–4.31 (d, 1H, $J = 14.8$ Hz, N8–CH_2); 4.34–4.39 (dd, 1H, C6H_2); 4.44–4.49 (dd, 1H, C7H); 4.85–4.93 (d, 1H, $J = 14.9$ Hz, N8–CH_2); 7.23–7.38 (m, 5H, arom.); 8.47–8.51 (m, 1H, CONH–CH_2).

3.2.7. 8-Benzyl-6,7-dihydro-[8H]-imidazo[2,1-f]theophylline-7-carboxylic acid (2-N,N-diethylamine-ethyl)-amide 7

Yield: 2.0 g (44%); m.p. 172–174 °C (methanol); *Anal*. ($C_{23}H_{31}N_7O_3$) C, H, N; TLC $R_f = 0.26$ (A), $R_f = 0.38$ (B); UV: (methanol) λ_{max1} (log ε) = 216 nm (4.52); λ_{max2} (log ε) = 298 nm (4.21); ^{1}H NMR ($CDCl_3$): δ = 0.94–1.00 (t, 6H, $J = 7.1$ Hz, (CH_2–CH_3)$_2$); 2.45–2.56 (m, 6H, CH_2–CH_2N(CH_2–CH_3)$_2$); 3.23–3.33 (m, 2H, $J = 6.4$ Hz, NH–CH_2–CH_2); 3.36 (s, 3H, N3–CH_3); 3.57 (s, 3H, N1–CH_3); 4.15–4.20 (dd, 1H, $J = 7.0$ Hz, C6H_2); 4.25–4.33 (d, 1H, $J = 14.8$ Hz, N8–CH_2); 4.30–4.35 (dd, 1H, C6H_2); 4.44–4.50 (dd, 1H, C7H); 4.80–4.86 (d, 1H, $J = 14.8$ Hz, N8–CH_2); 6.90–6.98 (t, 1H, CONH–CH_2); 7.27–7.37 (m, 5H, arom.).

3.2.8. 8-Benzyl-6,7-dihydro-[8H]-imidazo[2,1-f]theophylline-7-carboxylic acid (2-N,N-diethylamine-propyl)-amide ***8***

Yield: 1.6 g (35%); m.p. 168–169 °C (methanol); *Anal*. ($C_{24}H_{33}N_7O_3$) C, H, N; TLC $R_f = 0.15$ (A); UV: (methanol) λ_{max1} (log ε) = 216 nm (4.41); λ_{max2} (log ε) = 298 nm (4.10); ^{1}H NMR ($CDCl_3$): δ = 0.88–0.96 (t, 6H, $J = 7.1$ Hz, (CH_2–CH_3)$_2$); 1.57–1.80 (q, 2H, CH_2–CH_2–CH_2); 2.41–2.52 (q, 4H, $J = 7.2$ Hz, N(CH_2–CH_3)$_2$); 2.41–2.52 (t, 2H, CH_2–CH_2N); 3.30–3.39 (m, 2H, NH–CH_2–CH_2); 3.36 (s, 3H, N3–CH_3); 3.57 (s, 3H, N1–CH_3); 4.13–4.17 (dd, 1H, $J = 8.2$ Hz, C6H_2); 4.21–4.30 (d, 1H, $J = 14.8$ Hz, N8–CH_2); 4.31–4.35 (dd, 1H, C6H_2); 4.44–4.50 (dd, 1H, C7H); 4.86–4.94 (d, 1H, $J = 14.8$ Hz, N8–CH_2); 7.22–7.36 (m, 5H, arom.); 8.20–8.35 (t, 1H, CONH–CH_2).

3.2.9. 8-Benzyl-6,7-dihydro-[8H]-imidazo[2,1-f]theophylline-7-carboxylic acid (morpholine-propyl)-amide ***9***

Yield: 3.1 g (65%); m.p. 180–181 °C (ethanol); *Anal*. ($C_{24}H_{31}N_6O_4$) C, H, N; TLC $R_f = 0.59$ (A); UV: (methanol) λ_{max1} (log ε) = 216 nm (4.55); λ_{max2} (log ε) = 298 nm (4.25); ^{1}H NMR (DMSO): δ = 1.45–1.50 (q, 2H, $J = 6.9$ Hz, CH_2–CH_2–CH_2); 2.16–2.21 (t, 2H, $J = 7.1$ Hz, CH_2–CH_2N); 2.23–2.28 (m, 4H, N(CH_2–CH_2)$_2$); 3.01–3.08 (m, 2H, NH–CH_2–CH_2); 3.15 (s, 3H, N3–CH_3); 3.35 (s, 3H, N1–CH_3); 3.50–3.53 (t, 4H, (CH_2–CH_2)$_2$O); 3.97–4.02 (dd, 1H, $J = 8.2$ Hz, C6H_2); 4.26–4.32 (d, 1H, $J = 15.6$ Hz, N8–CH_2); 4.37–4.44 (dd, 1H, C6H_2); 4.47–4.52 (dd, 1H, C7H); 4.66–4.72 (d, 1H, $J = 15.4$ Hz, N8–CH_2); 7.25–7.36 (m, 5H, arom.); 8.24–8.28 (t, 1H, $J = 5.5$ Hz, CONH–CH_2).

3.2.10. 8-Benzyl-6,7-dihydro-[8H]-imidazo[2,1-f]theophylline-7-carboxylic acid [(1-methyl-4-piperazinyl)-propyl]-amide ***10***

Yield: 2.6 g (53%); m.p. 205–207 °C (anh. ethanol); *Anal*. ($C_{25}H_{34}N_8O_3$) C, H, N; TLC $R_f = 0.83$ (A); UV: (methanol) λ_{max1} (log ε) = 216 nm (4.54); λ_{max2} (log ε) = 298 nm (4.23); ^{1}H NMR ($CDCl_3$): δ = 1.58–1.68 (q, 2H, $J = 5.9$ Hz, CH_2–CH_2–CH_2); 2.21 (s, 3H, N–CH_3); 2.30–2.60 (m, 10H, CH_2–CH_2–N(CH_2–CH_2)$_2$N); 3.13–3.25 (m, 2H, NH–CH_2–CH_2); 3.36 (s, 3H, N3–CH_3); 3.55 (s, 3H, N1–CH_3); 4.05–4.14 (dd, 1H, $J = 8.9$ Hz, C6H_2); 4.30–4.38 (d, 1H, $J = 14.7$ Hz, N8–CH_2); 4.35–4.40 (dd, 1H, C6H_2); 4.39–4.44 (dd, 1H, C7H); 4.77–4.85 (d, 1H, $J = 14.7$ Hz, N8–CH_2); 7.25–7.39 (m, 5H, arom.); 7.93–7.99 (t, 1H, CONH–CH_2).

3.2.11. 8-Benzylamino-theophyllinyl-7-α-propanoic acid ***11***

A mixture of 8-benzylaminotheophylline sodium salt (25.0 g, 0.08 mol), 2.0 g triethylbenzylammonium chloride (TEBA) and α-bromopropanoic acid (24.5 g, 0.16 mol) in 80 ml of anh. DMF was refluxed for 18 h. The reaction mixture was filtered off while hot to separate inorganic salts and the filtrate was evaporated under reduced pressure. To the oily product 100 ml of C_2H_5OH was added. After cooling the crude product was filtered off, washed with cold water and C_2H_5OH.

Yield: 17.1 g (60%); m.p. 195–197 °C (ethanol); *Anal*. ($C_{17}H_{19}N_5O_4$) C, H, N; UV: (chloroform) λ_{max} (log ε) = 297 nm (4.05); ^{1}H NMR (DMSO): δ = 1.65–

1.67 (d, 3H, CH–CH_3); 3.19 (s, 3H, N1–CH_3); 3.37 (s, 3H, N3–CH_3); 4.58–4.60 (d, 2H, CH_2–C_6H_5); 5.20–5.30 (m, 1H, CH–CH_3); 7.27–7.30 (m, 3H, 3′4′5′-phenyl); 7.35–7.40 (m, 2H, 2′6′-phenyl); 7.64–7.66 (t, 1H, NH–CH_2); 12.7–12.9 (brs, 1H, COOH).

3.2.12. 6-Methyl-8-benzyl-6,8-dihydroimidazol-7-on[2,1-f]theophylline **12**

The mixture of **11** (1.8 g, 0.005 mol) and 10 ml of $(CH_3CO)_2O$ was refluxed for 8 h. After cooling the $(CH_3CO)_2O$ was evaporated under reduced pressure. To the oily product 10 ml of C_2H_5OH was added. After refrigeration the precipitate was filtered off, recrystallized from C_2H_5OH.

Yield: 1.3 g (74%); m.p. 211–212 °C (ethanol); *Anal*. ($C_{17}H_{17}N_5O_3$); UV: (chloroform) λ_{max} (log ε) = 300 nm (4.05); ^{1}H NMR ($CDCl_3$): $\delta = 1.76$–1.80 (d, 3H, CH–CH_3); 3.36 (s, 3H, N3–CH_3); 3.56 (s, 3H, N1–CH_3); 4.68–4.79 (q, $J = 7$ Hz, 1H, CH–CH_3); 4.90 (s, 2H, CH_2–C_6H_5); 7.26–7.37 (m, 3H, 3′4′5′-phenyl); 7.43–7.48 (m, 2H, 2′6′-phenyl); MS *m*/*z* (%): 339(54) $[M]^+$, 311(0.32), 282(0.39), 248(6), 91(100), 82(3), 65(5), 56(0.5), 42(2).

3.3. Pharmacology

The experiments were conducted using male Swiss mice (20–25 g) and Wistar rats (180–220 g), kept at ambient temperature on a natural day–night cycle, with free access to food and water before the experiments. Each experimental group consisted of five to eight animals. All investigated compounds were injected i.p. 1 h before the test as suspension in 0.5% tylose solution. The toxicity of the compounds was assessed with the method of Litchfield and Wilcoxon [12]; the LD_{50} was calculated on the basis of mortality within 48 h.

The doses corresponding to 0.1 LD_{50} of all compounds were administered in all tests.

Spontaneous locomotor activity and amphetamine-induced hyperactivity in mice were observed in photoresistor actometers for 30 min. Analgesic effects were assessed using the hot plate (56 °C) test in mice, and body temperature was measured with termistor thermometer in a rectum of mice. Anticonvulsant action was evaluated in maximal electroshock (ear electrodes, 50 mA, 0.2 s) and in pentetrazole (85 mg/kg s.c.)-induced seizures in mice. Motor coordination was measured in mice in the rota-rod test [13]. Stereotyped behavior was observed in rats after the injection of apomorphine (3 mg/kg s.c.) according to a four point scale [14]. The influence of the compounds on serotonin neurotransmission was evaluated in the 'head twitch' responses after 5-hydroxytryptophane (5-HTP) injection according to Corne et al. [15].

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