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Synthesis and evaluation of pharmacological properties of some new xanthone derivatives with piperazine moiety

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ABSTRACT

A series of new xanthone derivatives with piperazine moiety [**1**–**7**] was synthesized and evaluated for their pharmacological properties. They were subject to binding assays for α_1 and β_1 adrenergic as well as 5-HT_{1A}, 5-HT_6 and 5-HT_{7b} serotoninergic receptors. Five of the tested compounds were also evaluated for their anticonvulsant properties. The compound **3a** 3-methoxy-5-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}-9*H*-xanthen-9-one hydrochloride exhibited significantly higher affinity for serotoninergic 5-HT_{1A} receptors (K_i = 24 nM) than other substances. In terms of anticonvulsant activity, 6-methoxy-2-{[4-(benzyl)piperazin-1-yl]methyl}-9*H*-xanthen-9-one (**5**) proved best properties. Its ED_{50} determined in maximal electroshock (MES) seizure assay was 105 mg/kg b.w. (rats, p.o.). Combining of xanthone with piperazine moiety resulted in obtaining of compounds with increased bioavailability after oral administration.

The xanthone skeleton consists of the γ-pyron moiety condensed with two benzene rings. Its derivatives constitute an important class of compounds which are found in higher plants, fungi and lichens. Especially the *Guttiferae* family is known for being rich in these substances, which occur mostly in forms of polyphenolic derivatives.[1] Xanthone derivatives are also an interesting group of compounds in the field of medicinal chemistry. They proved to possess several beneficial heterogeneous pharmacological properties, for example, analeptic,[2] antiallergic,[3] antilipidemic,[4] diuretic,[5] antitumor,[6] antimycobacterial,[7] and antimicrobial.[8,9] In recent years we have reported their anticonvulsant activity, especially in the in vivo maximal electroshock (MES) seizure model.[10] The most promising compounds were (*R,S*)-, (*R*)- and (*S*)-6-chloro-2-(1-hydroxypropan-2-ylamino)methyl-9*H*-xanthen-9-one (Fig. 1) with MES ED_{50} (median effective dose) values of 56.2, 77.44, and 72.97 mg/kg b.w. (mice, i.p.), respectively.[11,12] Our former research also proved their cardiovascular activity in terms of anti-arrhythmic, hypotensive, α_1- and β_1-adrenoreceptor blocking properties.[9,13]

In the present Letter we report on synthesis and biological activity of seven new xanthone derivatives. Pharmacological studies include in vitro binding to α_1, β_1, and 5-HT_{1A}, 5-HT_6 and 5-HT_{7b} receptors as well as in vivo anticonvulsant assays (for five compounds). All tested substances possessed both xanthone skeleton and an *N*-substituted piperazine moiety joined by a methylene linker. Combining of those moieties was an attempt of rational design of new potentially active substances. Especially incorporation of *N*-(2-methoxyphenyl)piperazine seemed to be promising due to the fact that this moiety is considered an important element for binding to adrenergic as well as serotoninergic receptors.[14] Typical examples of drugs containing this group are urapidil and naftopidil (Fig. 1).[15,16] Moreover, α_1 and β_1 receptors constitute important targets for antihypertensive and antiarrhytmic drugs.[17–19] On the other hand, 5-HT_{1A} ligands with agonist or partial agonist activity seem to possess antianxiety, antidepressant, antiaggressive, and probably neuroprotective properties.[20] As an example, naluzotan (Fig. 1) as an *N*-arylpiperazine derivative and a 5-HT_{1A} ligand, has been developed for various CNS disorders including epilepsy.[21,22] 5-HT_6 and 5-HT_7 receptors play role in depression,

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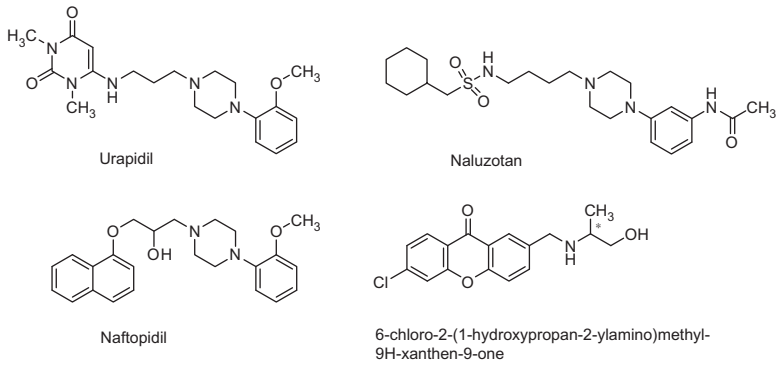


Figure 1. Structures of urapidil, naftopidil, naluzotan, and 6-chloro-2-(1-hydroxypropan-2-ylamino)methyl-9*H*-xanthen-9-one.

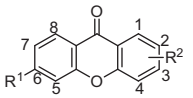
memory deficits, anxiety, as well as other disorders characterized by change of cholinergic neurotransmission.[23]

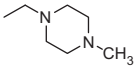
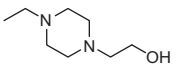
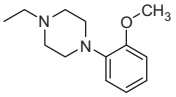
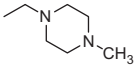
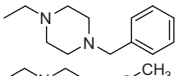
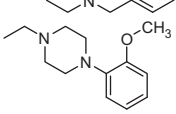
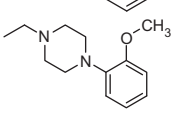
Considering anticonvulsant assays, we were interested how piperazine moiety with a methylene linker could affect the activity of formerly synthesized derivatives of xanthone, and––as a consequence––our aim was to compare the achieved results. Since many pathomechanisms contribute to presence of seizures, it was interesting whether there was a correlation between affinities to the above mentioned receptors and anticonvulsant activity.

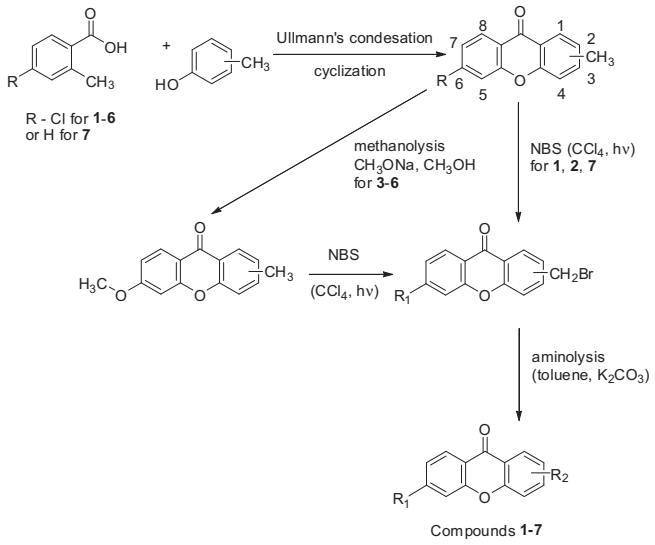
The first step of the research was calculation of several physicochemical parameters by means of Molinspiration online toolkit.[24] Such calculations are important at early stage of drug discovery process in terms of predicting essential parameters and facilitating rational drug design. The parameters include miLog*P*, topological polar surface area TPSA, molecular volume, as well as violations from the Lipinski rule of five. The results are presented in Table 1. The first calculated parameter, miLog*P*, exhibits optimum value for CNS active compounds of about **2** and **3** and was found in the range 3.239–4.98.[25] The most beneficial value of TPSA should be <120 Å^2 for orally administered drugs and <60–70 Å^2 for compounds designed to penetrate blood–brain barrier,[26,27] and all proposed structures are consistent with this rule (calculated values are in the range 36.687–56.915 Å^2). None of the compounds exhibited any violations from the Lipinski rule of five,[28] making them potentially promising drug-like agents.

General way of preparation of compounds **1**–**7** is shown in Scheme 1 and their structures are presented in Table 1. The multistage synthesis was performed according to previously published procedures.[12] The first step was the Ullmann's condensation of substituted chlorbenzoic acid and appropriate cresol followed by cyclization resulting in corresponding 9*H*-xanthen-9-one with methyl residue.[29,30] Next step constituted methanolysis in case of synthesis of **3**–**6**. It was performed with a portion of 9*H*-xanthen-9-one methyl derivative. Then all intermediate compounds were subject to free-radical bromination with little excess of *N*-bromosuccinimide (NBS). The last reaction constituted aminolysis of the appropriate bromo-substituted derivative by means of appropriate piperazine derivatives.[9,31] Some portions of amines were converted into hydrochlorides. All compounds were purified by means of recrystallization from appropriate solvents mixtures. The structures were further confirmed using ^{1}H NMR and ^{13}C NMR spectra.

Table 1
Chemical structures of the tested compounds **1**–**7**



Compd	R^1	Position of R^2	R^2	nHCl	miLog*P*	TPSA [Å]	Volume
1	Cl	4		**1a** 2HCl	3.871	36.687	301.41
2	Cl	4		**2a** 2HCl	3.239	56.915	326.471
3	H_3C–O	4		**3a** HCl	4.956	55.155	393.814
4	H_3C–O	2		**4a** 2HCl	3.274	45.921	313.42
5	H_3C–O	2		**5a** 2HCl	4.673	45.921	385.07
6	H_3C–O	2		**6a** HCl	4.98	55.155	393.814
7	H	2		**7a** HCl	4.947	45.921	368.268



Scheme 1. Chemical procedure of preparation of compounds **1**–**7**.

Table 2
Results of binding to serotoninergic and adrenergic receptors of reference and tested compounds **1**–**7**

Compd	K_i [nM]				
	5-HT_{1A}[a]	5-HT_6[a]	5-HT_{7b}[a]	α_1[b]	β_1[b]
1a	13340	19460	10490	650	n.a.
2a	4503	14420	17420	3930	n.a.
3a	24	9363	195	170	n.a.
4a	15840	19100	16950	490	n.a.
5a	1671	8836	13500	310	n.a.
6a	429	13600	1145	380	>30,000
7a	117	5939	426	3660	>10,000
Buspiron	12	––	––	––	––
Clozapine	143	4	18	––	––
Phentolamine	––	––	––	18	––
Propranolol	––	––	––	––	7

n.a.––Compound did not bind to receptor at 50 μM, inhibition constants (K_i) were calculated according to the equation of Cheng and Prusoff[31]. Radioligand binding assays to rats brain tissues using [^{3}H]8-OH-DPAT for 5-HT_{1A}, [^{3}H]-LSD for 5-HT_6, [^{3}H]-5-CT for 5-HT_7, [^{3}H]prazosin for α_1 and [^{3}H]CGP-12177 for β_1.
[a] $n = 3$.
[b] $n = 2$.

In vitro pharmacological profile of the new compounds was evaluated by radioligand binding assays. The inhibition constants (K_i) were calculated from the Cheng–Prusoff equation.[32] Membrane preparation and general assay procedures for cloned receptors were adjusted to 96-microwell format on the basis of protocols described previously.[33–35] The obtained results are presented in Table 2. Compound **3a** showed the highest affinity for serotoninergic 5-HT_{1A} receptors expressed in HEK293 (K_i = 24 nM) as well as for α1 receptors (K_i = 195 nM). Compounds **2a**, **4a**, **5a**, **6a** and **7a** displaced [^{3}H]8-OH-DPAT from HEK293 serotonin binding sites in moderate concentration range (K_i = 117–15840 nM). None of tested compounds inhibited [^{3}H]CGP12177 binding to cortical β_1-adrenoreceptors.

Preclinical research and discovery of potential antiepileptic drugs rely heavily on the use of animal models of seizures. The explanation of this fact is that there is no single pathomechanism related with development of epilepsy. As a consequence, most of existing antiepileptic drugs have been discovered with use of either of the anticonvulsant in vivo tests: maximal electroshock (MES) or subcutaneous metrazole (ScMet). These two methods serve as 'gold standards' in screening for potential anticonvulsants, giving premises for activity in human *grand mal* or *petit mal* epilepsy, respectively. The procedures are routinely carried on at National Institutes of Neurological Disorders and Stroke, NINDS, National Institutes of Health NIH (Rockville, MD, USA) within Anticonvulsant Screening Project ASP and the procedures have been published.[36,37]

Many antiepileptic drugs exhibit significant toxicity. Therefore, the ASP program includes a screening model for neurotoxicity–rotarod. The ability of an animal to stay on a slowly rotating rod (6 rpm) without falling is measured (3 times within 1 min). If it falls after 0.5 or 4 h of a dose of 30 mg/kg b.w. (mice, i.p.), the minimal motor impairment observed for the compound excludes it from further testing (class 4 ASP, Table 3).[36,37]

Five of the synthesized compounds were tested for their anticonvulsant activity within the ASP program and the results are presented in Tables 3–5. Preliminary screening included intraperitoneal (i.p.) administration to mice at 0.5 or 4 h before the test. The doses 30, 100, and 300 mg/kg b.w. were used. Prevention of seizures is considered protection.

Compounds **2a**, **4** and **5** exhibited protection in MES. **2a** and **4** were especially active, but their neurotoxicity was noticeable. Thus, **5** proved better properties because it showed no neurotoxicity at two test time points. It was active in MES while tested at 4 h after administration at the doses of 100 and 300 mg/kg. **2a**, **4** and **5** were also tested at the dose of 30 mg/kg in rats after oral administration for activity in MES and neurotoxicity. The results are presented in Table 4. This kind of test enables to evaluate to some extent the bioavailability in p.o. route which is most popular way of administration of drugs. **2a** and **5** proved to be more active than **4**. Compound **5** showed activity at 4 time points and it was used in quantitative assay. Time to peak effect (TPE) was shown to be 4 h after administration. Its median effective dose (dose of the compound which gives protection against seizures in 50% of tested animals, ED_{50}) was determined at the value of 105 mg/kg while median toxic dose (dose of the compound which produces neurotoxicity in 50% of tested animals, TD_{50}) was greater than 300 mg/kg which resulted in protection index ($PI = TD_{50}/ED_{50}$) more than 2.86.

In conclusion, in the present paper we report on preliminary pharmacological properties of seven new xanthone derivatives. They all possessed additional pharmacophore forming fragment that is, arylpiperazine moiety. In spite of former encouraging data of pharmacological activity of compounds from that group[9,13] the title compounds did not show satisfactory binding affinities to α_1 and β_1 adrenoreceptors or to 5-HT_{1A} receptors. Even though introducing of *N*-(2-methoxyphenyl)piperazine moiety resulted in some improvement of binding properties to α_1 receptor which was seen in case of compound **3a**, of which K_i value was the lowest among the tested series.

It is consistent with known facts that if a compound exhibits some affinity towards α_1 receptor, it is likely to bind to 5-HT_{1A} receptors as well. A good example in our study is **3a**––K_i for α_1 and 5-HT_{1A} are 170 nM and 24 nM, respectively.

Another observation is that substitution with piperazine moiety in position four of the xanthone structure is more beneficial than in position two (compound **3a** was clearly more active than **6a** and **7a**). Compound **3a** exhibited the best affinity to 5-HT_{1A} receptors which suggest that it could be scheduled to further pharmacological testing for its antianxiety and/or antidepressant activity.

The most promising results concern anticonvulsant activity of five compounds. The activity showed in maximal electroshock was encouraging. However, **3a** which was the most active ligand in the binding studies did not exhibit optimum in vivo activity. In fact, it did not prevent seizures and it was neurotoxic at 300 mg/kg b.w. (mice, i.p.). Other compounds: **2a**, **4** and **5** were ad-

Table 3
Results of anticonvulsant activity evaluation (mice, ip) of compounds **2a**–**6**

Compd	Dose mg/kg	MES[a]		ScMet[a]		TOX[b]		ASP class[c]
		0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	
2a	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	3/3	0/3	0/1 (1d)	0/1 (1d)	5/8	0/4	
	300	––	––	––	––	4/4 (4)*	––	
3a	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	3/4	0/2	
4	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	4/7	0/3	0/1	0/1	1/8	0/4	
	300	4/5	1/1	0/1	0/1	4/4	1/2(1)*	
5	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	0/3	1/3	0/1	0/1	0/8	0/4	
	300	0/1	1/1	0/1	0/1	0/4	0/2	
6	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	3/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	

[a] Number of animals protected/number of animals tested in the MES and ScMet tests.
[b] Number of animals displaying motor impairment/number of animals used in the rotarod test.
[c] ASP classification: (1)––anticonvulsant activity at doses 100 mg/kg or less; (2)––anticonvulsant activity at doses greater than 100 mg/kg; (3)––compound inactive at 300 mg/kg; (4)––compound either active or inactive but toxic at doses of 30 mg/kg. '––'The compound was not tested in the particular case.
* Number of animals which died during test are stated in brackets.

Table 4
Results of anticonvulsant activity evaluation for compounds **2a**, **4** and **5** (rats, p.o.)

Compd	Test	Dose [mg/kg]	Time [h]				
			0.25	0.5	1.0	2.0	4.0
2a	MES[a]	30	0/4	2/4	2/4	0/4	4/4
	TOX[b]	30	0/4	0/4	0/4	0/4	0/4
4	MES[a]	30	0/4	0/4	0/4	0/4	1/4
	TOX[b]	30	0/4	0/4	0/4	0/4	0/4
5	MES[a]	30	0/4	2/4	2/4	3/4	3/4
	TOX[b]	30	0/4	0/4	0/4	0/4	0/4

[a] Number of animals protected/number of animals tested in the MES test.
[b] Number of animals displaying motor impairment/number of animals used in neurotoxicity test.

vanced to evaluation in rats after oral (p.o.) administration. All of them proved some activity without neurotoxicity during the whole study (Table 4). Although the ED_{50} value of 105 mg/kg b.w. for **5** (Table 5) seem high, the important thing is the oral route of administration to rats which justifies this dose. Orally administered drugs are most preferable for patients, therefore, compounds which are characterized by good absorption are the most appreciated. Formerly reported compounds were evaluated in quantitative assays after i.p. administration in mice, for example, (*R*,*S*)-, (*R*)- and (*S*)-6-chloro-2-(1-hydroxypropan-2-ylamino)methyl-9*H*-xanthen-9-one with anti-MES ED_{50} values of 56.2, 77.44, and 72.97 mg/kg b.w., respectively.[11,12] Therefore, still bearing in mind change in species from mice to rats, due to this improvement of route of administration, compound **5** should be considered superior.

Another conclusion is that–unlike in the binding results–anticonvulsant properties are not so correlated with position of xanthone substitution, because the best anticonvulsant properties are observed for **2a**: 6-chloro-4-[4*N*-(2-hydroxyethyl)piperazinyl]methyl-9*H*-xanthen-9-one and **5**: 6-methoxy-2-[4*N*-(2-methoxyphenyl)piperazinyl]methyl-9*H*-xanthen-9-one, which are xanthones substituted in positions 4, 6 and 2, 6, respectively.

Currently reported compounds differ in the structure from our previous studies. A substituted piperazine moiety was used instead of aminoalkanol residue. As a result, the change in the structure caused increase of bioavailability after oral administration which means that further modification could result in discovering more potent anticonvulsants.

Acknowledgments

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Table 5
Results of anticonvulsant quantification of compound **5** (rats, p.o.)

Compd	ED_{50} MES[a] [mg/kg] (confidence interval)	ED_{50} ScMet[a] [mg/kg]	TD_{50}[b] [mg/kg]
5	105[d] (34.01–319.03) PI > 2.86	>250[d]	>300[c]

[a] Dose of the compound which gives protection against seizures in 50% of tested animals; 95% confidence interval is shown in brackets.
[b] Dose of the compound which produces neurotoxicity in 50% of tested animals; PI = TD_{50}/ED_{50}.
[c] Results observed after 0.0 h of administration of the compound.
[d] Results observed after 4.0 h of administration of the compound.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.05.062. These data include MOL files and InChiKeys of the most important compounds described in this article.

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