Synthesis and anticonvulsant activity of arylpiperazinyl-alkyl and -sulfonylalkyl derivatives of β-tetralinohydantoin

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• INTRODUCTION

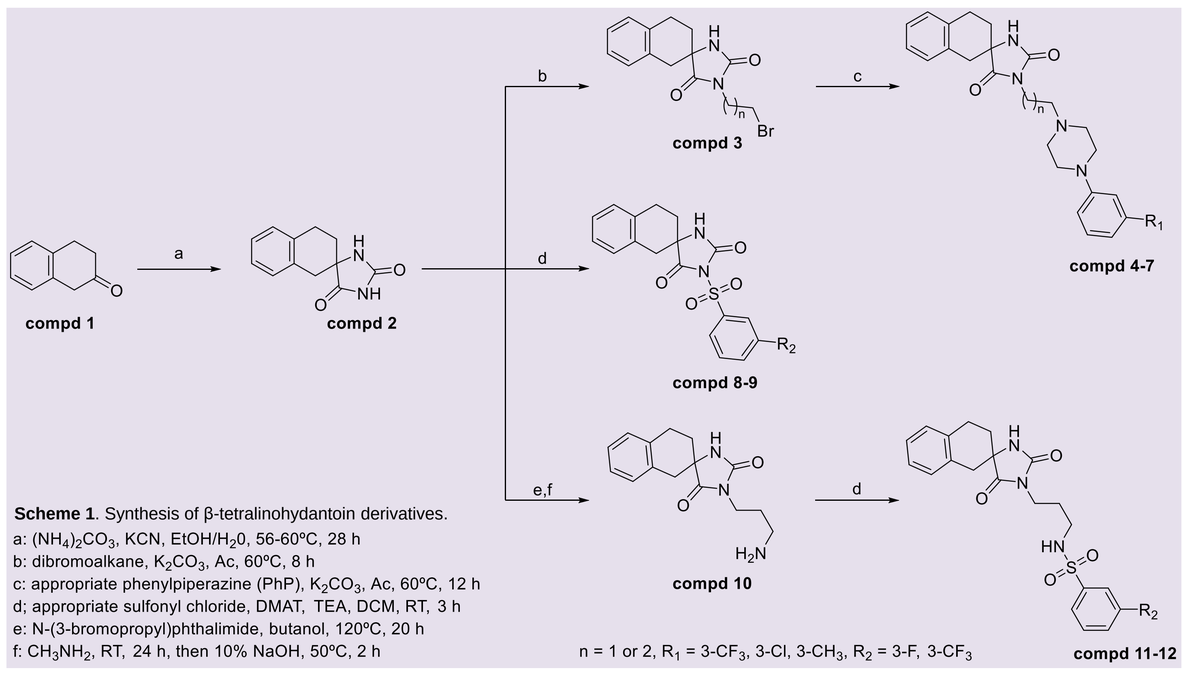
Epilepsy is a chronic, multifactorial, neurological disorder affecting people of all ages, race and social class. More than 60 million people live with epilepsy worldwide, and among them, the risk of early death is three times higher than that in the general population [1]. Although epilepsy is properly controlled in 70% of patients, about 30% remain resistant to currently used pharmacotherapy. Despite introduced to the market new antiepileptic drugs during the past two decades, a treatment of epilepsy, in particular drug-resistant one, remains a great clinical challenge.

• PURPOSE OF RESEARCH

In present studies, we have combined in one molecule, the hydantoin ring present in well-known antiepileptic drug – phenytoin and arylpiperazine moieties chosen based on the most active anticonvulsant derivatives described previously [2,3]. The combination of two pharmacophore systems may lead to increased anticonvulsant activity of these molecules. The newly designed compounds differ in the length and a type of the linker between hydantoin ring and arylpiperazine fragment and in substituent at aryl ring.

• CHEMICAL SYNTHESIS

The starting β-tetralinohydantoin (compd **2**), was prepared from 3,4-dihydronaphthalen-2(1H)-one (compd **1**) in Bucherer-Bergs reaction with modifications described by Goodson *et al*. (Scheme 1). In the next steps, the synthesis was carried out in parallel. Arylpiperazinylalkyl derivatives were obtained in alkylation and condensation reactions (compd **4**-**7**), whereas sulfonamide derivatives (**8**, **9**, **11**, **12**) were synthesized from appropriate arylsulfonyl chloride and β-tetralinohydantoin or β-tetralino-hydantoinalkyl amine derivatives.



Scheme 1. Synthesis of β-tetralinohydantoin derivatives.
a: $(NH_4)_2CO_3$, KCN, EtOH/H_20, 56-60ºC, 28 h
b: dibromoalkane, K_2CO_3, Ac, 60ºC, 8 h
c: appropriate phenylpiperazine (PhP), K_2CO_3, Ac, 60ºC, 12 h
d; appropriate sulfonyl chloride, DMAT, TEA, DCM, RT, 3 h
e: N-(3-bromopropyl)phthalimide, butanol, 120ºC, 20 h
f: CH_3NH_2, RT, 24 h, then 10% NaOH, 50ºC, 2 h
n = 1 or 2, R_1 = 3-CF_3, 3-Cl, 3-CH_3, R_2 = 3-F, 3-CF_3

• PHARMACOLOGY

The anticonvulsant evaluation of arylpiperazinylalkyl derivatives was performed within the Antiepileptic Drug Development (ADD) Program in the Epilepsy Branch, National Institutes of Health, National Institute of Neurological Disorders and Stroke, Rockville, MD, USA [4], whereas sulfonamide derivatives were examined in the Department of Pharmacodynamics JU MC. The initial studies involved three tests: maximal electroshock (MES), subcutaneous pentylenetetrazole (*sc*PTZ), and rotorod test for acute neurological toxicity (NT) (Table 1).

Table 1. Anticonvulsant screening results

Compd	n	$R_{1or\ 2}$	MES*		scPTZ*		NT*	
			0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
4	1	3-Cl	-	100	-	-	100	100
5	1	3-CF_3	-	100	100	-	-	100
6	1	3-CH_3	-	100	-	-	30	100
7	2	3-CF_3	300	100	-	-	100	100
8	-	3-F	-	nt	nt	nt	-	nt
9	-	3-CF_3	-	nt	nt	nt	100	nt
11	-	3-F	-	nt	nt	nt	100	nt
12	-	3-CF_3	-	nt	nt	nt	100	nt
Phenytoin	-	-	30	30	-	-	100	100

nt – not tested, *The compounds were injected *i.p.* into mice at doses of 30, 100 or 300 mg/kg

- All arylpiperazinylalkyl derivatives of β-tetralinohydantoin (**4**-**7**) exhibited anticonvulsant activity in screening studies (Table 1), but non of sulfonamide derivatives (**8**, **9**, **11**, **12**) were active.
- Among them, compound **7**, showed the most potent anticonvulsant effect, and protected 100% of tested animals (not indicated in Table 1).
- In the next step, the most potent compound **7** was selected for quantitative evaluation in rats (*p.o.*) and mice (*i.p.*). After per os administration in rats, compound **7** displayed two times higher ED_{50} value than reference drug phenytoin, with excellent protective index (PI=41), but it was ten times less active than phenytoin after intraperitoneal administration into mice (Table 2).
- In the electrophysiology studies, compound **7** substantially enhanced the GABA-madiated chloride currents as well as inhibited potently the voltage-dependent sodium currents, especially at -60 mV holding potential (Table 3).

Table 2. Quantitative anticonvulsant data for compound **7** and phenytoin

Compd	Rote of administration	Time to peak [h]	MES ED_{50}, [mg/kg]	scPTZ ED_{50} [mg/kg]	NT TD_{50} [mg/kg]	PI (NT/MES)
7	rats, *p.o.*	4	12.07	> 250	> 500	> 41.4
	mice, *i.p.*	2	63.05	>370	305.74	4.8
Phenytoin	rats, *p.o.*	4	23.20	-	> 500	> 21.6
	mice, *i.p.*	2	6.50	-	42.8	6.6

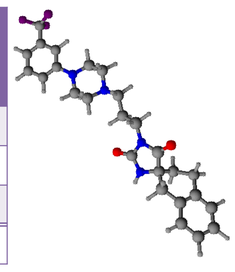


Table 3. Electrophysiology studies

Test	Add Compd Conc. [μM]	Cells	% Control + SEM*	Holding Potential [mV]
GABA	100	10	194 ± 12	**-70**
Sodium	100	5	92 ± 2	**-90**
Sodium	**100**	**7**	**68 ± 2**	**-60**

*** Significantly different from control**

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