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Discovery of benzothiazine derivatives as novel, orally-active anti-epileptic drug candidates with broad anticonvulsant effect

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ABSTRACT

In order to develop novel anti-epileptic drugs that are effective for both general and partial seizure, we conducted in vivo screening of our chemical library in the mice MES and sc-PTZ models and found the benzothiazine **1** as lead compound. Optimization of this compound led to the discovery of compound **7b**, which showed potent anticonvulsant effect in the MES, scPTZ and rat amygdala kindling models. Since the chemical structure of **7b** is different from that of any existing AED, it is suggested that **7b** may have unique mechanism of action for relieving both partial and generalized epilepsy.

Epilepsy is a complex neurological disorder that affects about 50 million people worldwide.[1] Epileptic seizures can be partial or generalized seizures, and are difficult to control by up to 30% of patients, despite optimal use of available anti-epileptic drugs (AEDs).[2,3] In addition to having limited efficacy, most AEDs have safety concerns, including CNS toxicity, drug–drug interaction, skin rash, teratogenicity, and hepatotoxicity.[4]

Among seizure animal models, the maximal electroshock seizure model (MES) and the subcutaneous pentylenetetrazol model (scPTZ) are well-established, and have been used in anticonvulsants drug discovery.[5] Almost all conventional AEDs (such as, Carbamazepine and Phenytoin) and recently launched AEDs (such as Topiramate and Lamotrigine) have potent anticonvulsant effect in MES model, but only weak efficacy in scPTZ model.[4] Similar findings were clinically confirmed as most AEDs show excellent efficacy for partial seizure, but only limited effect for generalized seizure. Thus, we hypothesized that compounds that can act as potent anticonvulsants in both MES and scPTZ models, would be useful in the treatment of both partial and generalized seizures.[6]

In order to find such compounds, we screened our chemical library using MES and scPTZ models and selected approximately 400 compounds with novel chemical structures compared to existing AEDs, no carboxylic acid group, and a molecular weight less than 300. Among these compounds **1** was identified as a hit com-

Table 1
Anticonvulsant effect of **1** compared to that of existing AEDs

	Dose (mg/kg)	MES	scPTZ
1	400	3/3[a]	2/3[a]
	100	0/3[a]	0/3[a]
Phenytoin	—	8 mg/kg[b]	>300 mg/kg[c]
Zonisamide	—	20 mg/kg[b]	>500 mg/kg[b]
Carbamazepine	—	13 mg/kg[b]	>100 mg/kg[c]

[a] Number of animals; animals with no convulsion/test animals.
[b] ED_{50} values determined in our laboratory.
[c] Ip administration data from Ref. 7, NE: not effective.

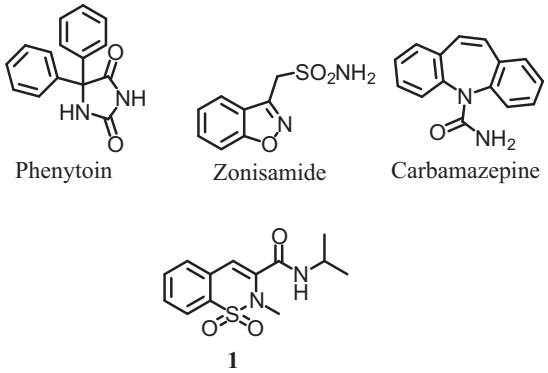

Figure 1. Chemical structures of existing AEDs compared to that of hit compound **1**.

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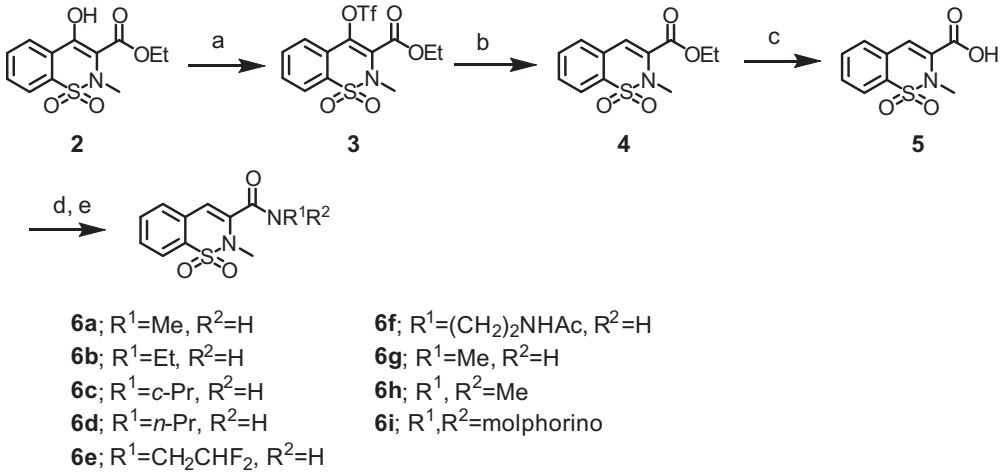
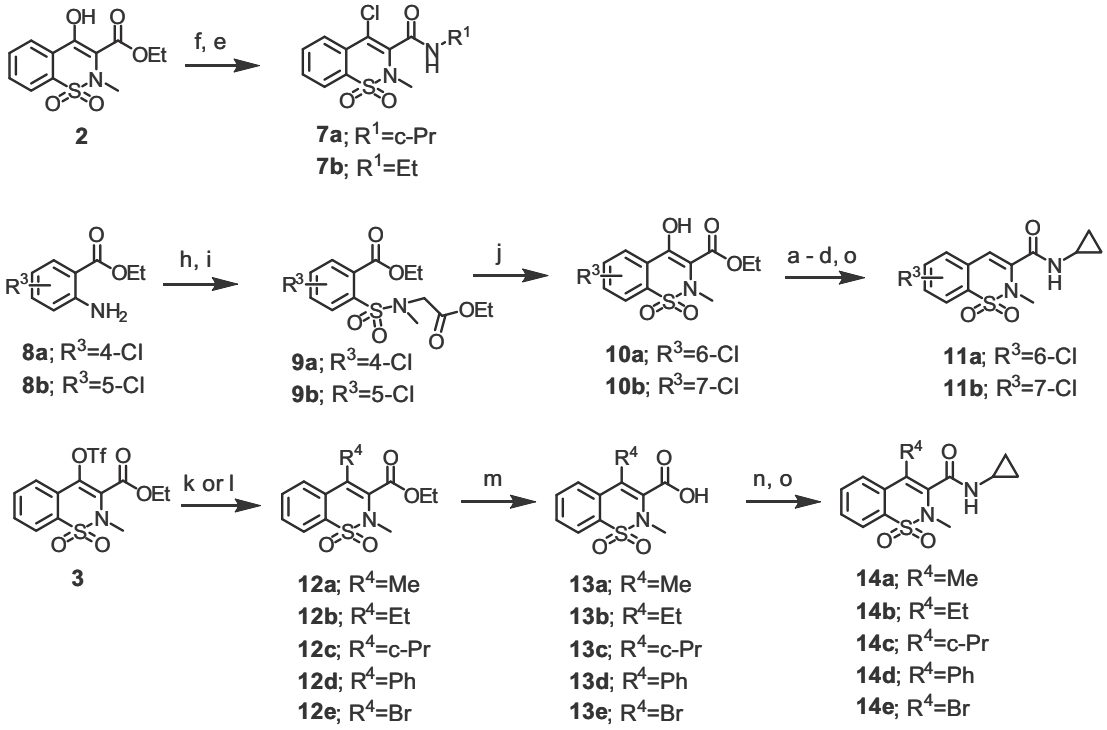


Scheme 1. Synthesis of un-substituted benzothiazine compounds. Reagents and conditions: (a) Tf_2O, Py, CH_2Cl_2; (b) $Pd(OAc)_2$, PPh_3, Et_3SiH, DMF, 70 °C; (c) LiOH, THF, H_2O; (d) $(COCl)_2$, DMF, CH_2Cl_2; (e) R^1R^2NH, THF.

pound with anticonvulsant effect in both MES and scPTZ models (Table 1). Since compound **1** has a novel chemical structure compared to existing AEDs, we speculated that this compound has a unique mechanism of action to treat convulsion. Here, we describe our optimization of compound **1** to obtain potent anticonvulsants (see Fig. 1).

Un-substituted benzothiazine compounds were synthesized as shown in Scheme 1. The commercially available reagent **2** was reacted with trifluoromethanesulfonyl anhydride to give the triflate **3**. Reduction of **3** with triethylsilane in the presence of Pd catalyst afforded the ethyl 2*H*-1,2-benzothiazine-2,2-dioxide-3-carboxylate **4**. Hydrolysis of **4** under LiOH gave carboxylic acid **5**, followed by chlorination with oxalyl chloride and reaction with appropriate amines gave the target carboxamide compounds **6a**–**i**.

Compounds **7a**, **7b**, **11a**, **11b**, and **14a**–**e** were prepared as shown in Scheme 2. Chlorination of the commercially available reagent **2** with PCl_5, followed by amidation with cyclopropylamine or ethylamine afforded compounds **7a** and **7b**. Compounds **11a** and **11b** were synthesized from the commercially available ethyl anthranilate **8a** or **8b** according to a method in the literature. Compounds **8a** and **8b** were converted to sulfonylchlorides by Sandmeyer reaction[8] and then reacted with ethyl *N*-methyl glycinate to give **9a** and **9b**. The intermediate **9a** and **9b** were cyclized to the 4-hydroxy-3-ethyl carbonate **10a** and **10b** using



Scheme 2. Synthesis of substituted benzothiazine compounds. Reagents and conditions: (a) Tf_2O, Py, CH_2Cl_2; (b) $Pd(OAc)_2$, PPh_3, Et_3SiH, DMF, 70 °C; (c) LiOH, THF, H_2O; (d) $(COCl)_2$, DMF, CH_2Cl_2; (e) HNR_1R_2, THF; (f) PCl_5, reflux; (g) *c*-$PrNH_2$, THF; (h) $NaNO_2$, H_2SO_4, THF, then SO_2 gas, $CuCl_2$; (i) DIPEA, THF, Ethyl *N*-methyl glycinate; (j) LDA, THF, −78 °C; (k) R_4-$B(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, 1,4-dioxane, reflux; (l) (1) $Pd(OAc)_2$, PPh_3, Et_3SiH, DMF, 70 °C; (2) NBS, DMF, 70 °C; (m) LiOH, THF, H_2O; (n) $(COCl)_2$, DMF, CH_2Cl_2; (o) *c*-$PrNH_2$, THF.