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Design, synthesis, and biological evaluation of the *N*-diarylalkenyl-piperidinecarboxylic acid derivatives as GABA uptake inhibitors (I)

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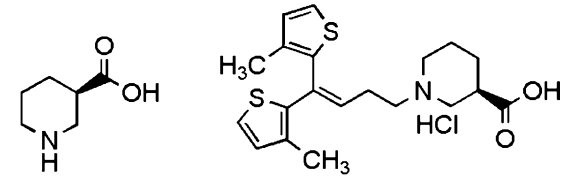
Abstract—Twenty novel *N*-diarylalkenyl-piperidinecarboxylic acid derivatives were synthesized and evaluated as γ-aminobutyric acid uptake inhibitors. The biological assay showed that (*R*)-1-[4,4-bis(3-phenoxymethyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic hydrochloride (**4e**) possessed almost as strong GAT1 inhibitory activity as tiagabine. The synthesis and structure–activity relationships are discussed.

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). Dysfunction of GABA-ergic synapses has been invoked for diseases such as Parkinson's disease, Huntington's chorea, epilepsy, and some forms of schizophrenia.[1–4] Several kinds of methods were introduced to palliate GABA deficiency in human, including GABA receptor agonists,[5] inhibitors of the GABA uptake,[6] or inhibitors of GABA enzymatic breakdown.[7] Because the rapid termination of neurotransmitter action is an essential property of synaptic transmission, GABA transporters (GAT) are key functional components of GABA transmission in the CNS to regulate the magnitude and duration of GABA action. Four GABA transporters (GAT1–GAT4) have been cloned.[8–11] The study of pharmacologic criteria and immunohistochemical localization suggested that GAT1 is the predominant neuronal transporter in the rodent brain.[12,13]

Many cyclic amino acids and their derivatives have been found to inhibit GAT1, such as nipecotic acid (**1**) and tiagabine[14] (**2**) (Fig. 1). Tiagabine has been selected as an anticonvulsant and launched in the treatment of epilepsy.[15]

The three-dimensional quantitative structure relationship studies (3D-QSAR)—comparative molecular field analysis (CoMFA) on *N*-diarylalkenyl-piperidinecarboxylic acid analogues about GAT1 inhibitory activity have previously been reported by us.[16] It suggests that, either one or two of the aryl rings substituted with bulky group in the *ortho* position may improve the GAT1 inhibitory activity, and the negative groups



Nipecotic acid (**1**) Tiagabine (**2**)

Figure 1. Structures of representative known GABA uptake inhibitors.

Keywords: GABA uptake inhibitors; GAT1; Antiepileptic; *N*-Diarylalkenyl-piperidinecarboxylic acid derivatives.
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(e.g., carboxylic acid) in the position 3 of the piperidine ring would also be beneficial for the interaction of inhibitors with GAT1.

To observe the difference of predicted result and that of practical work, this paper reports the design, synthesis, and GAT1 inhibitory activities of a series of novel *N*-diarylalkenyl-piperidinecarboxylic acid derivatives **3a**–**g**, **4b**–**g**, and **5a**–**g** (Fig. 2). The feature of these compounds is a bulky group in *ortho* position on aryl rings and a carboxylic acid group in different position on the piperidine ring.

The symmetrical *N*-diarylalkenyl-piperidinecarboxylic acid derivatives were prepared as shown in Figure 2. 2-Bromo-3-methyl-thiophene was brominated to afford 2-bromo-3-bromomethyl-thiophene **6**, which reacted with alcohol or phenol to obtain compounds **7b**–**g**. Then, bromo-3-methyl-thiophene and **7b**–**g** were treated with *n*-butyllithium, and then reacted with ethyl 4-bromobutyrate ester at low temperature to afford **8a**–**g**, subsequently dehydrated to furnish **9a**–**g**. The ethyl piperidinecarboxylate was reacted with **9a**–**g** to afford **10a**–**g**, **11b**–**g**, and **12a**–**g**, which were saponified under basic conditions to provide target compounds in the form of hydrochloride salts.

The newly synthesized *N*-diarylalkenyl-piperidinecarboxylic acid derivatives were tested on the GAT1 transport assay[17] compared to nipecotic acid (**1**) and tiagabine (**2**). The inhibition data of these compounds are summarized in Table 1.

In conclusion, the IC_{50} values show that most of the compounds inhibit GAT1 transport activities. These

Table 1. Biological activity of *N*-diarylalkenyl-piperidinecarboxylic acid derivatives

Compounds	IC_{50} (μM)
3a	1.36
5a	>100
3b	12.30
4b	2.80
5b	>100
3c	>100
4c	7.10
5c	>100
3d	0.94
4d	0.68
5d	1.24
3e	0.65
4e	0.34
5e	1.50
3f	27.60
4f	0.84
5f	4.34
3g	>100
4g	66.30
5g	>100
1	81.50
2	0.28

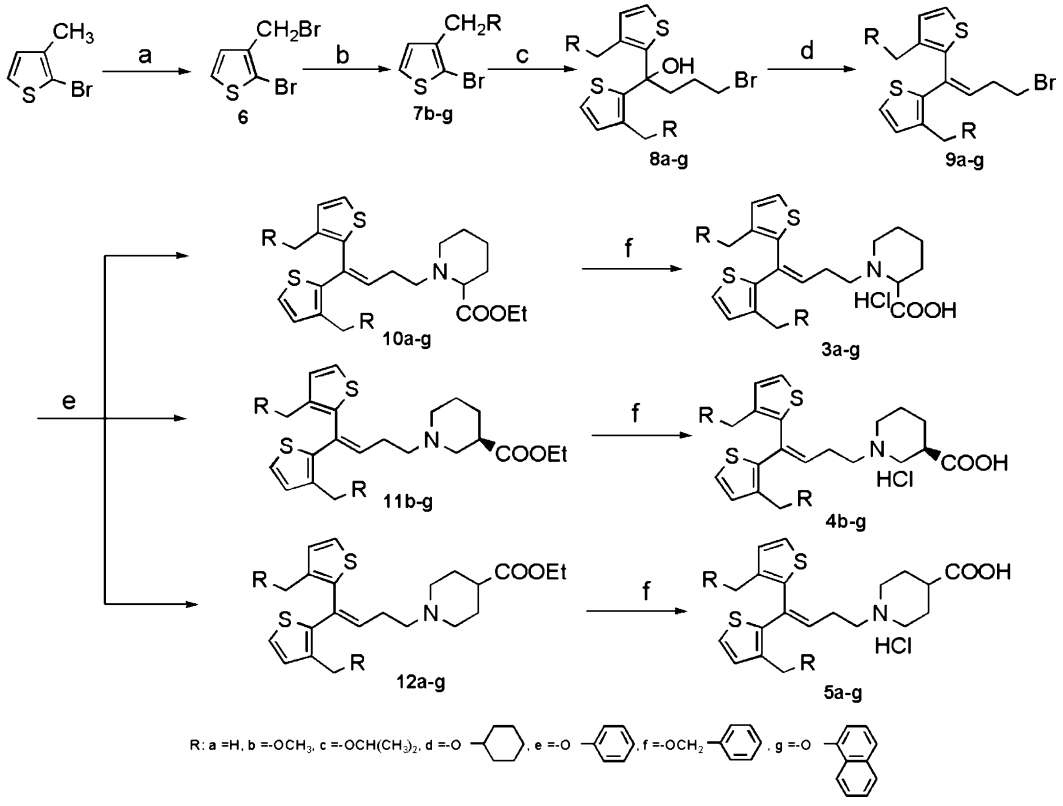

Figure 2. Reagents and conditions: (a) NBS, CCl_4, benzoyl peroxide, 76 °, 72%; (b) corresponding alcohol (phenol), Na or K_2CO_3, 75%; (c) *n*-BuLi, ethyl 4-bromobutyrate, Et_2O, −70°, 60%; (d) H_2SO_4, 2-propanol, 73%; (e) ethyl piperidinecarboxylate, K_2CO_3, KI, acetone, 61%; (f) i—NaOH, EtOH, ii—HCl, 59%.

results, in agreement with our previous 3D-QSAR study,[16] suggest that introduction of suitable bulky moieties such as phenoxymethyl and benzyloxymethyl in *ortho* position on an aryl ring may increase GAT1 inhibitory activity of the parent compound, for example, the most potent compound (*R*)-1-[4,4-bis(3-phenoxymethyl-2-thienyl)-3-butenyl]-3-piperidine- carboxylic acid hydrochloride **4e** ($IC_{50} = 0.34\ \mu M$) showed potent GAT1 inhibitory activity close to the marketed antiepileptic drug tiagabine (**2**, $IC_{50} = 0.28\ \mu M$). This fact means that the proper steric effect in *ortho* position on thiophene ring may play a critical role for potential GAT1 inhibitory activity. The influence of the different position of carboxylic acid group on the piperidine ring for the activity of GAT1 inhibition is also observed, for example, the *N*-diarylalkenyl-3-piperidinecarboxylic acid derivatives displayed greater potency than corresponding 2 or 4 piperidinecarboxylic acid derivatives.

Acknowledgment

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17. D8 cells, grown in RMPI1640 medium (Gibco-BRL Life Technologies) containing 10% FBS (Gibco-BRL Life Technologies) to near confluence in 48-well tissue culture plates (Costar) (approximately 60,000 cells per well in 48-well plates), were rinsed once with phosphate-buffered saline (PBS) and pre-incubated in 100 μL Hanks' balanced salt solution (HBSS) for 10 min at room temperature. [^{3}H]GABA (Amersham Pharmacia Biotech) was added to final concentrations of 151 nM. The cells were incubated for 20 min at room temperature. The reaction was terminated by aspiration of the HBSS and the cells were washed three times rapidly (10 s/wash) with cold PBS. The cells were then solubilized in 2 N NaOH and an aliquot was measured by liquid scintillation counting (Beckman LS 5000 TA) to quantify the uptake of [^{3}H]GABA. Inhibition studies were performed by adding inhibitor at the beginning of the transport assay and IC_{50} values were determined by linear regression analysis.