Structure–Activity Relationship Study of Selective Excitatory Amino Acid Transporter Subtype 1 (EAAT1) Inhibitor 2-Amino-4-(4-methoxyphenyl)-7-(naphthalen-1-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (UCPH-101) and Absolute Configurational Assignment Using Infrared and Vibrational Circular Dichroism Spectroscopy in Combination with ab Initio Hartree–Fock Calculations

The excitatory amino acid transporters (EAATs) play essential roles in regulating the synaptic concentration of the neurotransmitter glutamate in the mammalian central nervous system. To date, five subtypes have been identified, named EAAT1–5 in humans, and GLAST, GLT-1, EAAC1, EAAT4, and EAAT5 in rodents, respectively. In this paper, we present the design, synthesis, and pharmacological evaluation of seven 7-N-substituted analogues of UCPH-101/102. Analogue 9 inhibited EAAT1 in the micromolar range (IC50 value 20 μM), whereas analogues 8 and 10 were inactive (IC50 values >100 μM). The diastereomeric pairs 11a/11b and 12a/12b were separated by HPLC and the absolute configuration assigned by VCD technique in combination with ab initio Hartree–Fock calculations. Analogues 11a (RS-isomer) and 12b (RR-isomer) inhibited EAAT1 (IC50 values 5.5 and 3.8 μM, respectively), whereas analogues 11b (SS-isomer) and 12a (SR-isomer) failed to inhibit EAAT1 uptake (IC50 values >300 μM).

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