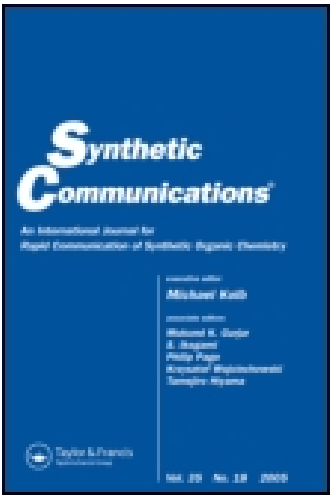

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Synthesis of the Four 3-Aminotricyclo [2.2.1.0(2,6)] Heptane-1,3-Dicarboxylic Acid Isomers

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ABSTRACT

A process to prepare the four stereoisomers of the tricyclic 3-amino-tricyclo[2.2.1.0(2,6)] heptane-1,3-dicarboxylic acid, a potent selective inhibitor of the EAAT2 transporter, is described.

Key Words: EAAT2 transporter inhibitor; Excitatory amino acid transporter; Glutamate.

Glutamate receptors and transporters are important central nervous system drug targets[1,2] since (S)-glutamic acid is the major excitatory

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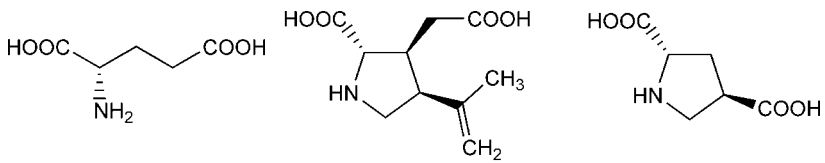
amino acid in the CNS participating in a vast number of physiological and pathophysiological processes.[3] Once released into the synaptic cleft, (S)-glutamic acid triggers a host of pre- and postsynaptic receptors. Those receptors belong to either the G-protein coupled receptor class (metabotropic glutamate receptors) or to the ligand-gated ion channels (ionotropic glutamate receptors). Termination of synaptic transmission occurs when (S)-glutamic acid is transported into neuronal or glial cells by excitatory amino acid transporters (EAATs). Among the five different human EAAT subtypes cloned, the EAAT1-3 subtypes are thought to be primarily responsible for the (S)-glutamic acid uptake process.[2] Since many pathological conditions are believed to be caused by either too low or too high levels of (S)-glutamic acid in the synaptic cleft, the EAATs have been suggested as appropriate drug targets.[1] Only a few compounds have been shown to interact with the EAATs and just a small number of agents inhibit the EAATs in a subtype selective manner,[1] as, for example, kainic acid and (2S, 4R)-2,4-PDC that have been shown[4,5] to inhibit the EAAT2 subtype (Fig. 1).

We would like to report a series of novel bridged tricyclic 3-amino-tricyclo [2.2.1.0(2,6)]heptane-1,3-dicarboxylic acids described by the formula I first disclosed by Stack et al.[6] The four stereoisomers represented by compound I are illustrated in Fig. 2.

The compounds described in this paper are selective inhibitors of human type 2 excitatory amino acid transporter (EAAT2) that are located, for the most part, on glial cells. Their mode of action causes an increase in synaptic glutamate levels by inhibiting glutamate re-uptake and thus may show utility for the treatment of diseases characterized by glutamate hypofunction, such as schizophrenia, schizoaffective disorder, and schizophreniform disorders, with particular effectiveness against the negative symptoms of schizophrenia. Alternatively, agents of this type may be useful in the treatment of conditions responsive to increased glutamate, such as the cognitive deficits due to aging, stroke, Alzheimer's disease, or other neurodegenerative diseases. The compounds described are also useful as selective tools for the investigation of excitatory amino acid transport, especially for the identification of agents,



(S)-Glutamic acid Kainic acid (2S,4R)-2,4-PDC

Figure 1. Natural agonist ligand and known inhibitors of EAAT2.

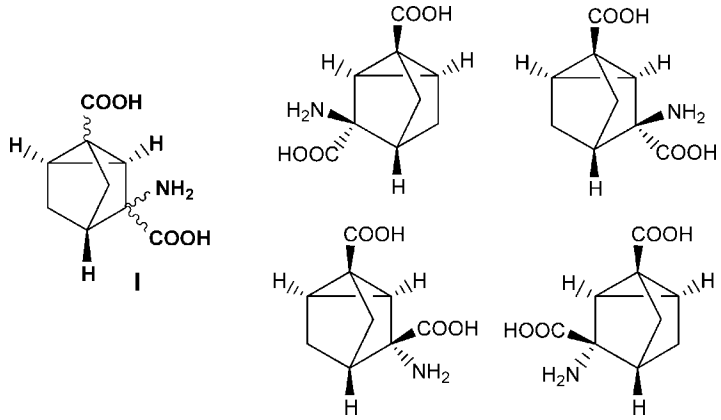


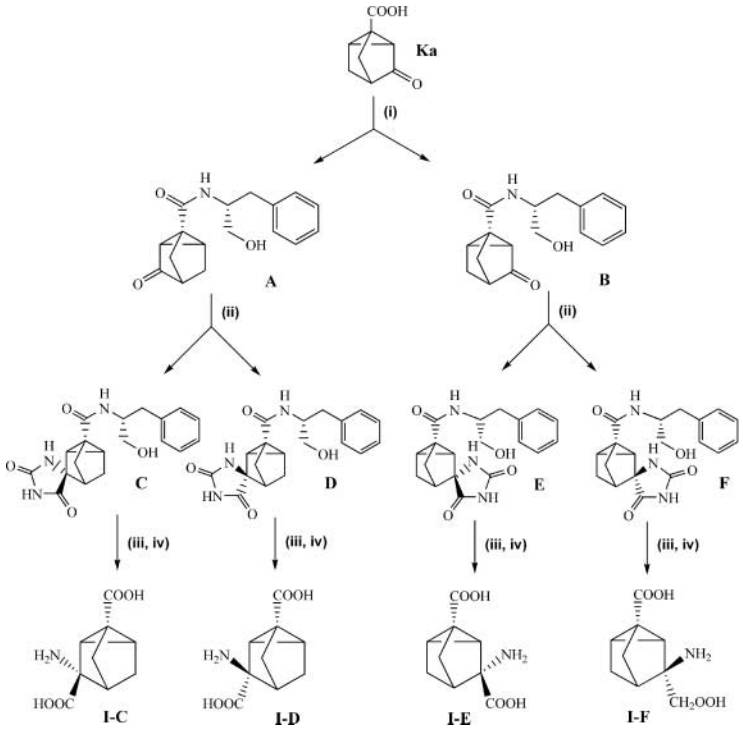
Figure 2. Racemic compound I and the four stereoisomers.

which selectively stimulate glutamate re-uptake. Throughout this paper the designations R* and S* are used to indicate relative stereochemistry, employing the Chemical Abstracts convention, which automatically assigns R* to the lowest numbered asymmetric center.

The stereoisomers of compound I can be prepared as illustrated in Sch. 1. The starting keto-acid (Ka) is prepared according to literature procedure[6] and then derivatized to a chiral amide using (*R*)-2-amino-3-phenyl-1-propanol via a coupling reaction in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate (TBTU). The resulting mixture of diastereomers is separated using reversed-phase chromatography (A and B). The separated diastereomers are individually converted to spiro-fused hydantoins by treatment with ammonium carbonate and potassium cyanide, in methanol/water. The resulting mixtures of diastereomers (C, D and E, F) are again separated using reversed-phase chromatography. The resulting four diastereomers (C, D, E, and F) are individually hydrolyzed using sodium hydroxide followed by elution through an ion exchange column to yield all four aminodicarboxylic acid stereoisomers (I-C, I-D, I-E, and I-F).

EXPERIMENTAL

(1S*,2R*,4S*,6S*)-N-[(1R)-1-benzyl-2-hydroxyethyl]-3-oxotricyclo[2.2.1.0(2,6)]heptane-1-carboxamide (A); and (1R*,2S*,4R*,6R*)-N-[(1R)-1-benzyl-2-hydroxyethyl]-3-oxotricyclo [2.2.1.0(2,6)] heptane-1-carboxamide (B): A mixture of 3-oxotricyclo[2.2.1.0(2,6)]heptane-1-carboxylic acid (0.3 g, 1.946 mmol, prepared according to Alder Hartmann, and Roth,[7] R-(+)2-



Scheme 1. Reagents: (i) TBTU, (R)-2-amino-3-phenyl-1-propanol, HPLC (ii) KCN, ammonium carbonate, methanol, water, HPLC (iii) 2N NaOH (iv) Ion exchange.

amino-3-phenyl-1-propanol (0.324 g, 2.141 mmole), and 4-methylmorpholine (0.86 mL, 7.784 mmol) in dimethylformamide (7 mL) was stirred at ambient temperature. 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetra-methyluronium tetrafluoroborate (TBTU, 0.75 g, 2.335 mmol) was added to the reaction mixture and stirring was continued for 18 hours. The reaction mixture was diluted with ethyl acetate (35 mL), the organic layer separated, washed with 5% aqueous citric acid (2×30 mL), followed by saturated $NaHCO_3$ solution (2×30 mL), and finally washed with brine (50 mL). The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness. Using a reversed-phase HPLC (C-18, 8 μM particle size, 41.4 mm and 4.6 mm ID, 25 cm L) column, 10–70% CH_3CN/Water, both diastereomers were isolated as light yellow oils. The retention times for the diastereomers A (Yield: 544 mg, 29.4%) and B (Yield: 491 mg, 26.5%) were 15.3 min. and 15.8 min., respectively. A: MS (EI, M^+ @ m/z) 285 B: MS (APCI, $[M + H]^+$ @ m/z) 286.

Spiro-hydantoin diastereomers of (1S*,2R*,4S*,6S*)-N-[(1R)-1-benzyl-2-hydroxyethyl]-3-oxo tricyclo[2.2.1.0(2,6)]heptane-1-carboxamide (A): A mixture of (1S*,2R*,4S*,6S*)-N-[(1R)-1-benzyl-2-hydroxyethyl]-3-oxotricyclo[2.2.1.0(2,6)]heptane-1-carboxamide (A, 0.63 g, 2.207 mmol), ammonium carbonate (1.048 g, 10.091 mmol), and potassium cyanide (0.173 g, 2.648 mmol) was stirred in methanol/water (2 : 1, 15 mL) at 50°C for 72 hours. After evaporation of the solvent in vacuo the products were isolated using reversed-phase HPLC (C-18, 8 μm particle size, 41.4 mm and 4.6 mm ID, 25 cm L) column, 10–70% CH_3CN/water. Both diastereomers were isolated in 31% (122 mg) yield (C) and 53% (206 mg) yield (D) as white solids; mp's A, >260°C (Decomposition) and B, 167–9°C. The retention times for the pure diastereomers C and D were 12.6 min. and 13.7 min., respectively. C: MS (+APCI, $[M+H]^+$ @ m/z) 356, D: MS (+APCI, $[M+H]^+$ @ m/z) 356.

Spiro-hydantoin diastereomers of (1R*,2S*,4R*,6R*)-N-[(1R)-1-benzyl-2-hydroxyethyl]-3-oxotricyclo [2.2.1.0(2,6)]heptane-1-carboxamide (B): A mixture of (1R*,2S*,4R*,6R*)-N-[(1R)-1-benzyl-2-hydroxyethyl]-3-oxotricyclo[2.2.1.0(2,6)] heptane-1-carboxamide (B, 0.52 g, 1.822 mmol), ammonium carbonate (0.9 g, 9.366 mmol), and potassium cyanide (0.142 g, 2.186 mmol) was stirred in methanol/water (2 : 1, 15 mL) at 50°C for 72 hours. After evaporation of the solvent in vacuo the products were isolated using reversed-phase HPLC (C-18, 8 μm particle size, 41.4 mm and 4.6 mm ID, 25 cm L) column, 10–70% CH_3CN/water. Both pure diastereomers were isolated in 34% (109 mg) yield (E) and 76% (246 mg) yield (F) as white solids; mp's E, 270–2°C (Decomposition) and F, 80–2°C. The retention times for the diastereomers E and F were 14.7 min. and 15.3 min., respectively. E: MS (+APCI, $[M+H]^+$ @ m/z) 356, F: MS (+APCI, $[M+H]^+$ @ m/z) 356.

General procedure for the preparation of all four stereoisomers of 3-aminotricyclo[2.2.1.0(2,6)]heptane-1,3-dicarboxylic acid: A mixture of the starting spiro-hydantoin-N-[(1R)-1-benzyl-2-hydroxyethyl]-3-oxotricyclo [2.2.1.0 (2,6)]heptane-1-carboxamide (0.5 mmol) and 2N NaOH (3 mL) was refluxed for 20 hours. The reaction mixture was cooled to ambient temperature and washed with dichloromethane (2 × 20 mL). The aqueous layer was separated and the pH adjusted to 11 using 10% aqueous acetic acid and eluted through an ion-exchange column (Bio-Rad AG1-X8 resin, acetate form, 100–200 mesh). The products were eluted with 1 M acetic acid and the combined fractions were collected and concentrated on a lyophilizer to give the desired pure stereoisomers as white solids.

(−)-(1R*,2R*,3R*,4S*,6S*)-3-Aminotricyclo[2.2.1.0(2,6)]heptane-1, 3-dicarboxylic acid (I-D): Yield: 98%; MS (APCI, $[M+H]^+$ @ m/z) 198; mp > 260°C (Decomposition); Optical Rotation (water & NaOH) $[\alpha\text{-D}]^{25} = -32.1^\circ$.

(+)-(1R*,2R*,3R*,4S*,6S*)-3-Aminotricyclo[2.2.1.0(2,6)]heptane-1, 3-dicarboxylic acid (I-F): Yield: 45%; MS (APCI, $[M-H]^+$ @ m/z) 196; mp $> 260^\circ$C (Decomposition); Optical Rotation (water & NaOH) $[\alpha\text{-D}]^{25} = +31.01^\circ$.

(+)-(1R*,2S*,3R*,4R*,6S*)-3-Aminotricyclo[2.2.1.0(2,6)]heptane-1, 3-dicarboxylic acid (I-E): Yield: 51%; MS (APCI, $[M-H]^+$ @ m/z) 196; mp $> 280^\circ$C (Decomposition); Optical Rotation (water & NaOH) $[\alpha\text{-D}]^{25} = +21.01^\circ$.

(−)-(1R*,2S*,3S*,4R*,6R*)-3-Aminotricyclo[2.2.1.0(2,6)]heptane-1, 3-dicarboxylic acid (I-C): Yield: 50%; MS (APCI, $[M-H]^+$ @ m/z) 196; mp $> 260^\circ$C (Decomposition); Optical Rotation (water & NaOH) $[\alpha\text{-D}]^{25} = -18.02^\circ$.

The configuration of all four stereoisomers is relative rather than absolute.

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