Syntheses of Some Aminopiperidinecarboxylic Acids Related to Nipecotic Acid

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This paper describes the syntheses of (3RS,5SR)-5-hydroxypiperidine-3-carboxylic acid (8), (3RS, 5SR)-5-aminopiperidine-3-carboxylic acid (9), (RS)-3-hydroxypiperidine-3-carboxylic acid (13), (RS)-\(\alpha\)-amino-3-pyridineacetic acid (18), and \(\alpha\)-amino-3-piperidineacetic acid (19), compound 19 probably being a mixture of diastereomeric racemates. The compounds 8 and 9 were prepared from 5-aminonicotinic acid by catalytic hydrogenation. The relative stereochemistry of 9 was established by 270 MHz \(^1\)H NMR spectroscopy. The \(\alpha\)-hydroxy acid 13 was prepared via cyanhydrin reaction of the 3-piperidone derivative 11. The \(\alpha\)-amino acids 18 and 19 were prepared from 3-pyridineacetic acid by nitrosation and subsequent catalytic hydrogenation.

\((R)(-)-\text{Nipecotic acid}\),\textsuperscript{1,3} \((S)(+)-2,4\text{-diaminobutyric acid (DABA)}),\textsuperscript{4,5} (1RS,3SR)-3-aminocyclohexanecarboxylic acid (ACHC),\textsuperscript{6} and probably also (3RS,4SR)-4-hydroxypiperide 8 (Scheme 1), are substrate competitive inhibitors of the neuronal GABA uptake system. Of these inhibitors DABA and in particular ACHC have selective effects on the neuronal GABA uptake system, whereas nipecotic acid and \(\text{cis}-4\text{-hydroxypiperide acid}\), which are the most potent inhibitors, also interact with the transport process for GABA in glial cells.\textsuperscript{7}

As an attempt to develop compounds with high and specific affinity for the neuronal GABA uptake system a series of amino acids, analogous with the above-mentioned inhibitors, has been synthesized. These compounds, i.e. 8, 9, 13, 18, and 19, however, have very little or no effect when tested as inhibitors of the neuronal uptake of \(^{[3}\text{H}]\text{-GABA using the procedure described in a previous paper}\),\textsuperscript{9} emphasizing the substrate specificity of the neuronal GABA transport system.\textsuperscript{10}

Hydrogenation of 5-aminonicotinic acid (2) using \(\text{PtO}_2\) as a catalyst gave a complex mixture of products. After treatment of the reaction mixture with methyl chloroformate the compounds 5 and 6 and an inseparable mixture of 3 and 4 could be isolated (Scheme 2), the desired protected diamino acid 6 being the major product. Subsequent acetylation of the mixture of 3 and 4 gave 4 and 7, which were separated by column chromatography.

Stepwise hydrogenation of the pyridine ring of 2 could probably cause the formation of an intermediate ene-diamine (Scheme 2), which spontaneously would be hydrolyzed in the acidic aqueous medium to the corresponding 5-oxo derivative. Hydrogenation of this compound followed by treatment with methyl chloroformate would give the 5-hydroxycarboxylic acid derivative 5. In support of this proposal, low pressure hydrogenation of methyl 3-oxo-1-piperidine-1-carboxylate\textsuperscript{11} (10) using \(\text{PtO}_2\) as a catalyst gave the corresponding 3-hydroxypiperidine 3 (Scheme 2), indicating the high reactivity of this \(\alpha\)-amino ketone derivative.

\textbf{Scheme 1.}

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The 3,5-carbolactone 4 could be transformed into the 5-hydroxypiperidine-3-carboxylic acid derivative 5 using mild acidic conditions, and this conversion unequivocally indicates a 3,5-cis configuration of 5. The mechanisms underlying the formation of 4 are unknown. A possible mechanism could be an intramolecular nucleophilic addition/elimination reaction of the proposed ene-diamine intermediate. Alternatively, the lactone 4 could be formed via a hydroxylated intermediate during the treatment with methyl chloroformate.

The mechanism for the formation of 3 is unknown, but hydrogenation of pyridine-3-carboxylic acids using PtO₂ as a catalyst is frequently accompanied by decarboxylation.₁²,₁³

Hydrogenation of 2 using rhodium-Al₂O₃ as a catalyst by analogy with a method described for the hydrogenation of nicotinic acid ¹⁴ gave 9 as the only product. Acid treatment of the protected diamino acid 6 also gave 9 as the only product.

The α-hydroxy acid 13 was prepared via cyanhydrin reaction of 11 using acetylating conditions (Scheme 3). Methanolation of 12 and subsequent acid hydrolysis of the intermediate α-hydroxy ester gave 13.

Treatment of 14 with butyl nitrite in sodium amide-liquid ammonia (Scheme 4) gave a mixture of the corresponding α-hydroxyimino ethyl ester, butyl ester and amide (15), judging from the ¹H NMR spectra. Treatment of this mixture of compounds with saturated ammonia gave the amide 15 as the major product. The hydroxyimino group in 15 could be selectivity hydrogenated to give the pyridine derivative 16 (Scheme 4). Extended hydro-

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Scheme 3.
Scheme 4.

genation with an increased amount of catalyst gave the piperidine derivative 17 as the only product. Acid treatment of 16 and 17 gave the α-amino acid dihydrobromides 18 and 19.

The structures of the new compounds 3–9, 12, 13 and 15–19 were established by elemental analysis, IR and 1H NMR spectroscopy. The relative configuration of 6, and consequently that of 9 according to a previous paper,18 was established by analysis of the 270 MHz 1H NMR spectrum of 6.

In simple piperidine derivatives the equatorial protons on C(2) and C(6) are found downfield from their axial counterparts.15 In the 270 MHz 1H NMR spectrum of 6 the signals for H2a and H2b are observed at δ 4.13 and 2.55, respectively. The vicinal coupling constants between the C(3) and C(2) protons, determined by decoupling experiments, are typical for axial-axial and axial-equatorial configurations of these protons. This is consistent with a predominantly equatorial orientation of the C(3) carboxylic acid group. An analysis producing the coupling constant between the C(3) and C(4) protons supports this assignment. The coupling patterns of the C(4), C(5), and C(6) protons unequivocally indicate an axial orientation of the C(5) proton, and therefore a 3,5-cis configuration of 6.

The observed chemical shift values and coupling constants parallel data previously found in other piperidines.16–18 The interpretation of the vicinal coupling constants in terms of ring conformation follows the general treatment of 6-membered rings.19

EXPERIMENTAL

Melting points, determined in capillary tubes, are corrected. Elemental analyses were performed by Mr. P. Hansen, Chemical Laboratory II, University of Copenhagen. TLC and column chromatography (CC) were accomplished by using silica gel F254 plates (Merck) and silica gel (Woelm 0.063–0.100 mm), respectively. Columns were developed by stepwise gradient elution. The pKₐ values were determined as earlier described.20 A Perkin-Elmer grating infrared spectrophotometer model 247 and a JEOL JNM-C-60HL (60 MHz) 1H NMR instrument were used. The 270 MHz 1H NMR spectra were obtained on a Bruker HX 270 S instrument. Fourier transform method was used to obtain the spectrum with a spectral width of 1500 Hz. Quadrature detection and homodecoupling were used. A frequency of 19,506,582 Hz was used for nitrogen decoupling. 1H NMR spectra were recorded using TMS as an internal standard, except for the compounds dissolved in D₂O, where DSS was used. The computations in connection with the analyses of the 270 MHz 1H NMR spectra were performed on a Varian 620/1 computer using the SIMEQ program21 and on a Nicolet 1180 computer using the ITRCAL program.22

5-Aminonicotinic acid (2). The compound 2 was prepared from 123 (15.0 g; 74.3 mmol) as described elsewhere.23 The yield of recrystallized (water) 2 was 6.5 g (63 %), m.p. 293.0–295.0°C (293–294°C).22 Anal. C₆H₆N₂O₂: C, H, N. IR (KBr): 3350 (s), 3200 (s), 2800–2100 (w, several bands), 1660 (s), 1595 (s), 1470 (m), 1400 (s), 1330 (s) cm⁻¹. 1H NMR (60 MHz, D₂O + DMSO-d₆): δ 8.67 (1 H, m), 8.40 (2 H, m).

Reduction of 5-aminonicotinic acid (2) using PtO₂ as a catalyst. A solution of 2 (3.0 g; 24.6 mmol) in 4 M aqueous hydrochloric acid (12.3 ml; 49.2
mmol) and water (100 ml) was hydrogenated (ca. 300 kPa) for 24 h in a PARR low pressure hydrogenation apparatus using PtO₂ (0.5 g) as a catalyst. To an ice-cooled solution of the filtered and evaporated reaction mixture in water (30 ml) an iced solution of potassium carbonate (13 g; 94 mmol) in water (15 ml) was added with stirring followed by addition of methyl chloroformate (7.0 g; 74.4 mmol). Stirring was continued at 0° C for 1 h and then at 24° C for 1 h.

The basic reaction mixture was continuously extracted with ether—dichloromethane (3:1) for 3 h. The organic phase was dried (Na₂SO₄) and evaporated in vacuo, and to a solution of the crude evaporated product in pyridine (27 ml) was added excess of acetic anhydride (3 ml). The mixture was heated at 80° C for 24 h. CC [silica gel: 50 g; eluents: toluene containing ethyl acetate (80—90%) and formic acid (2%)] of the evaporated reaction mixture gave the following products:

a. (RS)-Methyl-3-acetoxypropidin-1-carboxylic acid (7) (1.0 g; 20%). Anal. C₃H₅NO₂C: H, N. IR (film): 3500 (w), 2950 (s), 2850 (m), 1730 (s), 1700 (s), 1440 (s), 1400 (s), 1360 (s) cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 4.8 (1 H, m), 3.70 (3 H, s), 3.5 (4 H, m), 2.03 (3 H, s), 1.7 (4 H, m).

b. (3RS,5SR)-1-Methoxybenzylpropidin-3-carboxylic acid (4) (0.45 g; 10%). IR (film): 3500 (w), 3000—2800 (w, several bands), 1780 (s), 1700 (s), 1450 (s), 1400 (m), 1360 (m), 1200 (s) cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 4.9 (1 H, m), 4.5—4.0 (2 H, m), 3.72 (3 H, s), 3.4 (1 H, m), 3.2 (1 H, m), 2.8 (2 H, m), 2.0 (1 H, m).

To the basic aqueous extraction phase, from which the mixture of 3 and 4 was extracted, was added at 0° C aqueous hydrochloric acid (2 M) to pH = 2. The solution was continuously extracted with ether—dichloromethane (3:1) for 24 h. The organic phase was dried (Na₂SO₄) and evaporated in vacuo. CC [silica gel: 100 g; eluents: toluene containing ethyl acetate (80—90%) and formic acid (2%)] gave the following products:

c. (3RS,5SR)-Methyl-3-hydroxy-3-carboxypropidin-1-carboxylic acid (5) (0.47 g; 10%), recrystallized from ethyl acetate—cyclohexane, m.p. 127.5—129.0° C. Anal. C₆H₁₃NO₂C: H, N. IR (KBr): 3400 (s), 3100—2600 (m, several bands), 1720 (s), 1660 (s), 1480 (s), 1440 (s), 1410 (m) cm⁻¹. ¹H NMR (60 MHz, CDCl₃ + DMSO-d₄): δ 7.4 (2 H, m), 4.1 (2 H, m), 3.65 (3 H, s), 3.6—3.4 (2 H, m), 3.0—2.6 (2 H, m), 2.0 (2 H, m).

d. (3RS,5SR)-Methyl 5-methoxybenzylamino-3-carboxypropidin-1-carboxylic acid (6) (1.91 g; 30%), recrystallized from ethyl acetate—cyclohexane, m.p. 196.0—197.0° C. Anal. C₁₅H₁₆N₂O₄C: H, N. IR (KBr): 3600—2800 (m—s, several bands), 1720 (s), 1690 (s), 1660 (s), 1560 (m), 1530 (m), 1500 (m), 1450 (m), 1260 (s) cm⁻¹. ¹H NMR (270 MHz, CDCl₃): δ 2.77, δ 2.42, δ 2.45, δ 1.52, δ 2.25, δ 3.45, δ 2.55, δ 1.53, δ 1.31, δ 0.47, δ COOH: 3.66, δ COOH: 3.62, δ COOH: 9.0, Jₐ₂₉: 13.24 Hz, J₂₉: 11.03 Hz, J₂₉: 4.23 Hz, Jₐ₉: 11.4 Hz, Jₐ₉: 4.22 Hz, Jₐ₉: 12.68 Hz, J₂₉: 12.13 Hz, Jₐ₉: 5.2 Hz, Jₐ₉: 10.52 Hz, Jₐ₉: 4.41 Hz, Jₐ₉: 12.68 Hz.

Conversion of (3RS,5SR)-1-methoxycarbonylpropidin-3,5-carboxylic acid (4) into (3RS,5SR)-methy-5-hydroxy-3-carboxypropidin-1-carboxylate (5).

A mixture of 4 (100 mg; 0.54 mmol) and aqueous hydrochloric acid (5 ml; 5 M) was stirred at 24° C for 5 days. The solution was continuously extracted with ether—dichloromethane (3:1) for 24 h. The organic phase was dried (Na₂SO₄) and evaporated in vacuo. Recrystallization (ethyl acetate-cyclohexane) gave 5 (65 mg; 59%), the IR spectrum of which was identical with that of 5 prepared as described above.

(3RS,5SR)-5-Hydroxy-3-carboxypropidin-1-carboxylate (6).

A solution of 5 (70 mg; 0.34 mmol) in aqueous hydrobromic acid (5 ml; 48%) was refluxed for 45 min. Evaporation in vacuo and recrystallization (water—ethanol) gave 6 (40 mg; 52%), m.p. ca. 170° C (decomp.). Anal. C₁₅H₁₄N₂O₄Br: 1 H₂O: C, H, N, Br. IR (KBr): 3350 (s), 3000—2400 (m, several bands), 1700 (s), 1550 (m), 1460 (w), 1400 (w), 1350 (w), 1260 (s) cm⁻¹. ¹H NMR (60 MHz, D₂O): δ 4.1 (1 H, m), 3.6—3.0 (5 H, m), 2.1 (2 H, m).

(3RS,5SR)-5-Aminopropidin-3-carboxylic acid dichloroiodide (9).

Method a. A solution of 6 (300 mg; 1.2 mmol) in aqueous hydrochloric acid (10 ml; 6 M) was refluxed for 5 h. Evaporation in vacuo and recrystallization (water—acetic acid) gave 9 (170 mg; 50%), m.p. 245° C (decomp.). Anal. C₁₅H₁₄N₂O₂Cl₂: C, H, N, Cl. IR (KBr): 3450 (w), 3200—2400 (w—s, several bands), 1720 (s), 1600 (w), 1520 (w), 1380 (m), 1220 (s) cm⁻¹. ¹H NMR (60 MHz, D₂O): δ 3.8 (3 H, m), 3.1 (3 H, m), 2.0 (2 H, m). pKₐ values (H₂O, 24° C): 2.55 ± 0.05, 6.76 ± 0.01, 9.99 ± 0.01.

Method b. A solution of 2 (0.7 g; 5.1 mmol) in water (90 ml) and aqueous ammonia (2 ml; 25%) was hydrogenated (ca. 300 kPa) for 72 h in a PARR low pressure hydrogenation apparatus by using a 5% rhodium-Al₂O₃ (280 mg) catalyst. To the evaporated reaction product was added aqueous hydrochloric acid (5 ml; 4 M). Evaporation in vacuo and recrystallization (water—acetic acid) gave 9 (0.55 g; 55%), the IR spectrum of which was identical with that of 9 prepared from 6 as described above.

(3RS)-Methyl-3-hydroxypropidin-1-carboxylate (3). A solution of 10⁻¹¹ (0.2 g; 1.3 mmol) in ethanol (100 ml) was hydrogenated (ca. 300 kPa) for 48 h in a PARR low pressure hydrogenation apparatus by using PtO₂ (60 mg) as a catalyst. CC [silica gel: 20 g; eluents: toluene containing ethyl acetate (80—90%) and formic acid (2%) of the filtered and evaporated reaction mixture gave 3 (0.13 g; 60%). Anal. C₁₅H₁₄N₂O₂C: H, N. IR (film): 3400 (s, broad band), 2950 (s), 2850 (m), 1690 (s), 1480 (s), 1440 (s), 1410 (s),...
1260 (s), 1240 (s) cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 4.0 – 3.5 (2 H, m), 3.76 (3 H, s), 3.4 – 3.0 (3 H, m), 3.05 (1 H, s), 1.9 – 1.5 (4 H, m).

(RS)-Methyl 3-cyano-3-acetoxypiperidine-1-carboxylate (12). A solution of 11 (3.6 g; 229 mmol) and potassium cyanide (3.0 g; 46 mmol) in glacial acetic acid (15 ml) was left at 25 °C for 30 min. Acetic anhydride (4.0 ml; 42 mmol) was added and the solution was heated at 60 °C for 72 h. The evaporated reaction mixture was treated with water (100 ml), and the solution was extracted with ethyl acetate (3 × 75 ml). The combined organic phases were dried (Na₂SO₄) and evaporated in vacuo. CC [silica gel: 200 g; eluents: toluene containing ethyl acetate (50 – 75 %)] gave 12 (2.3 g; 45 %). An analytical sample was purified by bulb to bulb distillation at 100 Pa (oven temperature 200 °C). Anal. C₁₀H₁₄N₂O₄: C, H, N. IR (film): 3500 (w), 2950 (s), 2850 (m), 1760 (s), 1700 (s), 1450 (s), 1410 (s), 1370 (m), cm⁻¹. ¹H NMR (60 MHz, CDCl₃): δ 3.95 (2 H, s), 3.80 (3 H, s), 3.5 (2 H, m), 2.2 (2 H, m), 2.13 (3 H, s), 1.8 (2 H, m).

(RS)-3-Hydroxy-3-carboxypiperidinium bromide hydrate (13). A solution of 12 (2.0 g; 88 mmol) in methanolic hydrogen chloride (40 ml; 10 %) was left at 24 °C for 24 h. The solution was concentrated to 15 ml in vacuo. Water (30 ml) was added, and the solution was left at 24 °C for 15 min. The evaporated reaction product was extracted with dichloromethane (2 × 25 ml). The combined organic phases were dried (Na₂SO₄) and evaporated in vacuo. A solution of the crude reaction product in aqueous hydrobromic acid (30 ml; 48 %) was refluxed for 45 min. Evaporation in vacuo and recrystallization (water – acetic acid) gave 12 (1.3 g; 65 %), m.p. ca. 102 °C (decomp.). Anal. C₁₀H₁₄N₂O₄Br, 1 H₂O: C, H, N, Br. IR (KBr): 3400 (s), 3200 – 2600 (m – s, several bands), 1730 (s), 1630 (w), 1580 (s), 1170 (s) cm⁻¹. ¹H NMR (60 MHz, D₂O): δ 3.4 (4 H, m), 2.0 (4 H, m). pKₐ values (H₂O, 24 °C): 2.86 ± 0.08, 10.29 ± 0.01.

α-Hydroxyiminio-3-pyridineacetamide (15). Sodium (ca. 2 g) was added in small pieces at -70 °C to anhydrous liquid ammonia (150 ml) containing Fe(NO₃)₃, 9 H₂O (30 mg). When the blue colour had vanished, and the mixture had assumed a grey colour (about 15 min), 14 (3.0 g; 14.9 mmol) was added with stirring at -33 °C during 10 min. The mixture was left at -33 °C for 20 min, and then a solution of butyl nitrite (5.0 g; 44.3 mmol) in ether (10 ml) was added during 15 min. The mixture was left at -33 °C for 45 min, whereupon a solution of ammonium sulfate (10 g; 75 mmol) in water (40 ml) was added. After stirring for 1 h, the reaction mixture was saturated with ammonia at 0 °C, and then left with stirring for 24 h. A solution of the evaporated reaction product in water (100 ml) was washed with ether (2 × 50 ml), and then continuously extracted with ethyl acetate for 24 h. The ethyl acetate phase was evaporated in vacuo. Recrystallization (water) gave 15 (1.4 g; 55 %), m.p. 198.0 – 200.0 °C. Anal. C₁₁H₁₀N₂O₄: C, H, N. IR (KBr): 3450 (m), 3300 – 2500 (m, several bands), 1700 (s), 1640 (w), 1580 (m), 1400 (m), 1050 (s) cm⁻¹. ¹H NMR (60 MHz, DMSO-d₆): δ 12.2 (1 H, s), 8.6 (1 H, m), 7.8 (1 H, m), 7.5 (2 H, m).

(4S)-α-Amino-3-pyridineacetamide dihydrochloride (16). A solution of 15 (0.5 g; 3.1 mmol) in methanol (150 ml) was hydrogenated at ca. 300 kPa in a PARR low pressure hydrogenation apparatus for 3 h using a Pd-C catalyst (125 mg; 5 %). To the evaporated reaction product was added aqueous hydrochloric acid (5 ml; 4 M). Evaporation in vacuo and recrystallization (methanol – ether) gave 16 (360 mg; 57 %), m.p. 235 °C (decomp.). Anal. C₁₁H₁₀N₂O₄Cl₂: C, H, N, Cl. IR (KBr): 3400 – 2500 (m, several bands), 1720 (s), 1640 (m), 1620 (w), 1560 (m), 1500 (m), 1480 (m) cm⁻¹. ¹H NMR (60 MHz, D₂O): δ 9.0 (3 H, m), 8.3 (1 H, m), 5.53 (1 H, s).

α-Amino-3-piperidineacetamide dihydrochloride (17). A solution of 15 (0.5 g; 3.1 mmol) in methanol (150 ml) was hydrogenated at ca. 300 kPa in a PARR low pressure hydrogenation apparatus for 24 h using a Pd-C catalyst (1.2 g; 5 %). To the evaporated reaction mixture was added aqueous hydrochloric acid (5 ml; 5 M). Evaporation in vacuo and recrystallization (methanol – ether) gave 17 (0.4 g; 58 %), m.p. 250 °C (decomp.). Anal. C₁₁H₁₀N₂O₄Cl₂: C, H, N, Cl. IR (KBr): 3350 (m), 3200 – 2400 (m – s, several bands), 1710 (s), 1700 (s), 1650 (m), 1500 (s), 1420 (m) cm⁻¹. ¹H NMR (60 MHz, D₂O): δ 3.97 (1 H, d), 3.5 (2 H, m), 3.0 (3 H, m), 1.9 (4 H, m).

(4S)-α-Amino-3-pyridineacetic acid dihydrobromide (18). A solution of 16 (0.3 g; 1.3 mmol) in aqueous hydrobromic acid (10 ml; 48 %) was refluxed for 1 h. Evaporation in vacuo and recrystallization (water – acetic acid) gave 19 (0.2 g; 48 %), m.p. 190 °C (decomp.). Anal. C₁₁H₁₀N₂O₂Br₂: C, H, Br. IR (KBr): 3450 (w), 3100 – 2500 (m, several bands), 1750 (s), 1610 (m), 1560 (s), 1470 (s), 1400 (m) cm⁻¹. ¹H NMR (60 MHz, D₂O): δ 8.8 (3 H, m), 8.3 (1 H, m), 5.51 (1 H, s).

α-Amino-3-piperidineacetic acid dihydrobromide (19). A solution of 17 (0.3 g; 1.3 mmol) in aqueous hydrobromic acid (10 ml; 48 %) was refluxed for 1 h. Evaporation in vacuo and recrystallization (water – acetic acid) gave 19 (0.2 g; 50 %), m.p. 240 °C (decomp.). Anal. C₁₁H₁₀N₂O₂Br₂: C, H, Br. IR (KBr): 3450 (w), 3100 – 2500 (m, several bands), 1740 (s), 1580 (m), 1490 (s), 1220 (s), 1210 (s) cm⁻¹. ¹H NMR (60 MHz, D₂O): δ 4.03 (1 H, d), 3.4 (2 H, m), 2.9 (3 H, m), 1.9 (4 H, m). pKₐ values (H₂O, 24 °C): 2.20 ± 0.10, 8.30 ± 0.07, 10.46 ± 0.03.

Inhibition of neuronal GABA uptake: The procedures used for the isolation of the crude synaptosomal fraction from rat brains, and for the measurement of the inhibition of the uptake of [³H]-GABA.
are described elsewhere in detail.\textsuperscript{8,24} None of the compounds concerned, \textit{i.e.} 8, 9, 13, 18 and 19, inhibited GABA uptake by more than 50\% at concentrations of 2 \times 10^{-4} \text{ M}.

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