Synthesis and Anticonvulsant Evaluation of 5-Vinyl-pyrrolidin-2-ones: A Potential GABA-AT Inhibitor

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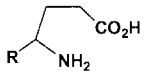
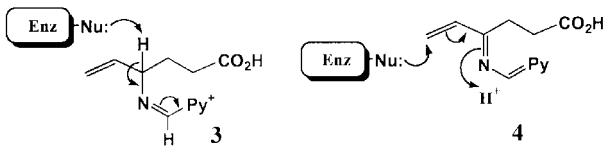
4-Aminobutyric acid (GABA), **1**, is well known for an important neurotransmitter in mammalian central nervous system (CNS).[1] GABA deficiency has been associated with a variety of neurological disorders including Parkinson's disease,[2] epilepsy,[3] Schizophrenia,[3] Huntington's chorea[4] and tardive dyskinesia.[5] Since GABA itself does not effectively penetrate the blood-brain-barrier, there has been a need for pro-drug of GABA or GABA-aminotransferase (GABA-AT) inhibitors that could enhance the concentration of GABA in brain.[6] GABA-AT is a pyridoxal phosphate (PyCHO) dependent enzyme and vigabatrin, **2**, is a typical GABA-AT inhibitor in clinical use for the treatment of epilepsy. The mechanism for the inhibition of aminobutyrate transaminase by vigabatrin, **2**, was proposed previously in which schiff base, **3**, formed from vigabatrin and PyCHO and then a Michael type addition of nucleophiles in the enzyme followed as shown in **4**.[7] On the basis of the mechanism mentioned, we envisioned that *N*-alkenyl lactam will increase lipophilicity to cross the blood-brain-barrier and act as a substrate for the enzyme enhanced nucleophilic addition by opening of ring *via* deprotecting sequence of *N*-alkenyl group.[8]



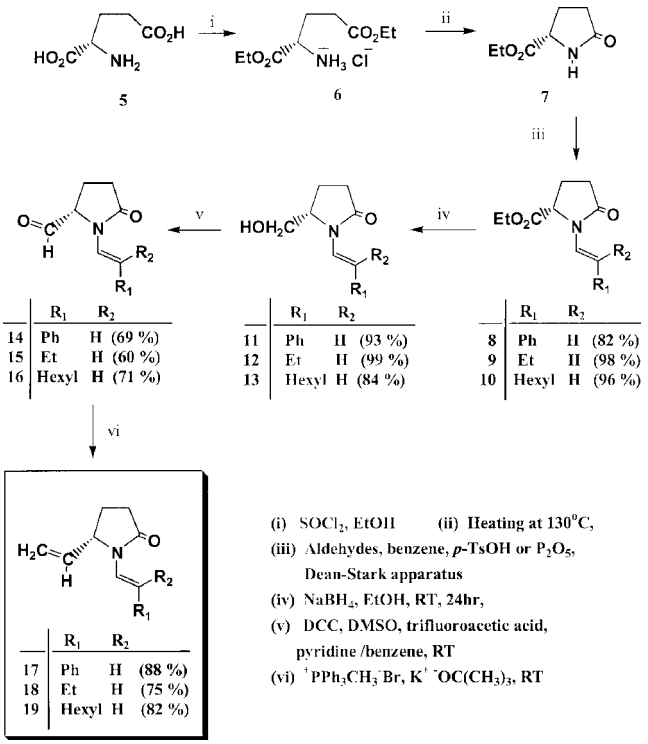
1. R= H
2. R= CH=CH$_2$



3 **4**

In conjunction with development of GABA related pro-drug, a series of work on the synthesis of 5-vinyl-pyrrolidin-2-ones[9] have been carried in our laboratory to investigate if the anticonvulsant activity appears to be influenced by variation of the *N*-alkenyl group. Here we report our results concerning synthesis and anticonvulsant evaluation of 5-vinyl-2-pyrrolidinone analogues, **17**, **18** and **19** prepared from L-glutamic acid.

The route to *N*-alkenyl pyrrolidin-2-one derivatives, **17-19**, is shown in Scheme 1. Lactam, **7**, was obtained in 98%



Scheme 1

yield by reacting L-glutamic acid with thionyl chloride in ethanol.[10] Condensations of **7** with various aldehydes such as butanal, phenylacetaldehyde and octanal in the presence of *p*-TsOH or P_2O_5 using Dean-Stark apparatus in benzene afforded the *N*-alkenyl lactams, **8-10**.[11] Subsequent reduction with sodium borohydride gave **11-13** in 84-99.8% yield. The alkenyl substituents in the lactam ring appeared to be significant to prevent racemization during the next oxidation step. *N*-alkenyl aldehydes **14-16** were remarkably stable to neutral or basic condition but should be stored under argon atmosphere (below 0 °C) to prevent the racemization. Stirring in a solution of DMSO, benzene, pyridine, trifluoroacetic acid and dicyclohexylcarbodiimide (DCC) gave the corresponding aldehydes, **14-16** in 60-71% yields. Wittig reactions of **14-16** with methyltriphenylphosphonium bromide in the presence of potassium *t*-butoxide for 10 hr provided the 75-88% yields of **17-19**.

Table 1. The anticonvulsant evaluation of **17**, **18** and **19**

17	**Dose (mg/kg)**	**75**	**100**	**125**	**150**	**175**	**200**	**225**	**ED_{50} (mg/kg)**
	PTZ[a]	4/4[c]	3/4	3/4	2/4	1/4	–	0/4	153.1
	MES[b]	–	4/4	3/4	2/4	1/4	–	–	150.0
18	**Dose (mg/kg)**	**25**	**50**	**75**	**100**	**150**	**200**	**225**	**ED_{50} (mg/kg)**
	PTZ[a]	4/4[c]	3/4	3/4	3/4	2/4	1/4	0/4	134.4
	MES[b]	4/4[c]	3/4	3/4	2/4	1/4	0/4	–	106.3
19	**Dose (mg/kg)**	**75**	**100**	**125**	**150**	**175**	**200**	**225**	**ED_{50} (mg/kg)**
	PTZ[a]	4/4[c]	4/4	–	4/4	–	4/4	4/4	Not Detected
	MES[b]	4/4[c]	4/4	–	4/4	–	4/4	4/4	Not Detected

[a]The subcutaneous pentylenetetrazole seizure threshold (PTZ) test entailed the administration of 80 mg/kg of pentylenetetrazole in the posterior midline of mice. This amount of pentylenetetrazole was expected to produce seizures in greater than 97% of mice.[b]Maximal electroshock seizures (MES) were elicited with a 60 cycle alternating current of 50 mA intensity delivered for 0.2 second.*via* corneal electrodes. A drop of 0.9% saline was instilled in the eye prior to application of the electrodes so as to prevent the death of the animal. Protection in this test was defined as the abolition of the hind-limb tonic extension component of the seizure.[c]Convulsant animal / treated animal

Biological Anticonvulsant Activities

It was reported that the MES test was correlated to the generalized tonic clonic seizure and the PTZ test to the generalized absence seizure.[12] So these two kinds of seizure test were very meaningful for clinical prediction of the anticonvulsant drug candidates. Therefore, we investigated the anticonvulsant activity (phase 1 evaluation) with male ICR mice for compound **17**, **18** and **19** in both the MES and PTZ test. Seizures were artificially induced by either electroshock and pentylenetetrazole and the animals were observed for 30 minutes.

As seen in Table 1, compound **17** and **18** showed potential effects in both the MES and PTZ test. *N*-butenyl substituent compound **18** gave more stronger activities than phenyl (**17)** or octenyl (**19)** derivatives. In the MES test, ED_{50} value of **18** was 106.3 mg/kg. It was found that *N*-substituents proved to be a major factor for the pharmacological activities. Phenyl analogue **17** showed less active anticonvulsant effect than **18** in both the MES and PTZ test and longer chain substituent such as **19** showed the lowest pharmacological activities.

In conclusion, we have described the synthesis of 5-vinyl-pyrrolidin-2-one derivatives containing the *N*-alkenyl moiety and compared their anticonvulsant activities. *N*-butenyl pyrrolidin-2-one derivatives **18** showed potent inhibitory activities in the MES and PTZ test. As *N*-substituents were longer and bigger, the anticonvulsant activities were decreased. Now we are currently continuing to prepare vinyl-GABA analogs to evaluate their anticonvulsant activities against picrotoxine and bicuculline convulsant in order to develop more active anticonvulsant prodrug candidate.

Experimental Section

Melting points were taken on a Haake Bucher melting point apparatus and are uncorrected. Infrared spectra were recorded with an infrared spectrophotometer model Magna-IR 500 and are reported in wave numbers. Both ^1H and ^{13}C NMR spectra were recorded on a FT-NMR Bruker 300 (300MHz) spectrometer and are reported in ppm using tetramethylsilane as the internal standard. *J* values are given in Hz. Mass spectra were recorded using a Shimazu QP 5000 spectrometer. High resolution mass spectra were obtained by electron impact at 70 eV with a Kratos-MS-50 instrument. Analytical thin-layer chromatography was carried out on Merck 60 F254 silica gel plate and visualization was done with UV light, and/or by spraying with a 5% solution of phosphomolybdic acid followed by charring with a heat gun.

5-Hydroxymethyl-1-styryl-pyrrolidin-2-one, 11. To a solution of 1.12 g (29.61 mmol) of $NaBH_4$ in 100 mL absolute ethanol was added 5.90 g (22.78 mmol) of **9** in 20 mL ethanol *via* syringe at 0 °C. The solution was then stirred 75 hours at room temperature under argon atmosphere and the ethanol was evaporated under reduced pressure. The mixture was extracted with ether/H_2O (3 times) and dried over magnesium sulfate. Evaporation of solvent gave a colorless oil which was purified by silica gel column chromatography (5% methanol + 95% methylene chloride, Rf = 0.21) to give 5.46 g (21.29 mmol, 93.5%) of **11** as a clear oil. $[\alpha]_D^{25}$ = -17.62 ° (c = 1.0, methanol). ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (1H, d, -HC=CPh, *J* = 15.18 Hz), 7.46-7.02 (5H, m, Ph), 6.01 (1H, d, -C=CHPh, *J* = 15.18 Hz), 4.22-4.19 (1H, q), 4.03 (1H, dd, CHH, *J* = 11.43 Hz), 3.75 (1H, dd, CHH, *J* = 11.43 Hz), 2.77-2.19 (4H, m, lactam CH_2) and 1.90-1.78 (1H, s, -OH, br). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.92, 136.63, 129.13, 127.13, 125.99, 122.85, 112.68, 61.95, 58.45, 31.21 and 22.26. Infrared (neat): 3393.1(br), 3052.6, 2937.8, 1696.1, 1684.5, 1680.5(s), 1645.5(s), 1597.6, 1449.3(s), 1406.2(s), 1334.1, 1286.8(s), 1247.9, 1070.7, 1046.7, 1013.2, 950.9(s), 831.1, 754.5(s), 694.9(s) and, 649.1 cm^{-1}. Mass Spectrum: CIMS m/s 218 (M+1).

1-But-1-enyl-5-hydroxylmethyl-pyrrolidin-2-one, 12. Reaction of 5.2 g (24.62 mmol) **9** with 2.33 g (61.55 mmol) of $NaBH_4$ gave after silica gel column chromatography (5% methanol + 95% methylene chloride, Rf = 0.21) 4.16 g (25.58 mmol, 99.8 %) of **12** as a yellow solid. $[\alpha]_D^{25}$ = -2.2° (c = 0.056, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 6.73 (1H, d, *J* = 14.7 Hz), 5.12 (1H, m), 4.01-3.97 (2H, m), 3.61 (1H, m), 3.11 (1H, bs, OH), 2.18-2.04 (4H, lactam CH_2),

2.62-2.38 (2H, m, vinyl CH_2) and 0.99 (3H, t, J = 7.40 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (lactam C=O), 121.9, 115.1, 61.2, 58.4, 30.8, 23.6, 21.7 and 14.5. Infrared (neat): 3400, 1680, 1410, 1280 and 1100 cm^{-1}. Mass Spectrum: EIMS (m/s, relative intensity) P^+ 169 (2), 140 (2, -CH_2OH), 126 (100), 111, 98, 82, 70 and 55.

1-Oct-1-enyl-5-hydroxylmethyl-pyrrolidin-2-one, 13. Reaction of 4g (14.98 mmol) **10** with 0.85 g (22.48 mmol) $NaBH_4$ gave after silica gel column chromatography (5% methanol + 95% methylene chloride, Rf = 0.27) 2.83 g (12.58 mmol, 84%) of **13** as a yellow oil. $[\alpha]_D^{25}$ = -42.72° (c = 1.0, methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (1H, d, -HC=C-hexyl, J = 14.76 Hz), 5.01 (1H, quintet, J = 7.14 Hz), 4.01-3.89 (1H, m, -CHCH$_2$OH), 3.98-3.62 (2H, m), 2.66-2.57 (1H, m), 2.40-2.30 (1H, m), 2.19-2.02 (5H, m), 1.38-1.25 (8H, m, $(CH_2)_4$-) and 0.87 (3H, t, -CH_2CH_3, J = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.11, 122.68, 113.65, 61.92, 58.31, 32.08, 31.14, 30.77, 30.41, 29.21, 23.01, 22.09 and 14.49. Infrared (neat): 3397.9 (br, OH), 2955.2, 2926.4, 2855.0, 2871.5, 1680.1 (s, C=O), 1655.1 (s, NH bend), 1457.9, 1413.4, 1343.7, 1282.7 (s, C-O), 1259.5, 1080.2, 1056.3, 1008.4, 954.0, 812.0, 725.7 and 653.9 cm^{-1}. Mass Spectrum: CIMS m/s 226 (M+1).

5-Oxo-1-styryl-pyrrolidine-2-carbaldehyde, 14. Dissolution of 4.62 g (21.29 mmol) of **11** in 40 mL dry benzene was followed by addition of 52 mL dry DMSO. The clear solution was then treated with 2.32 g (2.37 mL, 29.33 mmol) of anhydrous pyridine (distilled from calcium hydride), 2.93 g (1.98 mL, 25.56 mmol) of trifluoroacetic acid, and 13.2 g (63.98 mmol) of dicyclohexylcarbodiimide in that order. The flask was tightly stoppered and stirred at room temperature for 18 hours under an argon atmosphere. Benzene (100 mL) was added and the crystalline dicyclohexylurea was removed by filtration. The remaining solids were washed with benzene and the combined filtrates and washings were extracted with water (3 times) to remove DMSO. The organic layer was dried with magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (5% methanol + 95% methylene chloride, Rf = 0.22) to give 3.17 g (14.74 mmol, 69.3%) of **14** as a clear oil. $[\alpha]_D^{25}$ = -77.71° (c = 1.0, methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (1H, d, CHO, J = 10.00 Hz), 7.66 (1H, d, HC=CPh, J = 15.06 Hz), 7.34-7.17 (5H, m, Ph), 5.80 (1H, d, HC=CHPh, J = 15.09 Hz), 4.50-4.45 (1H, m, lactam CH), 2.63-2.57 (2H, m), 2.49 -2.38 (1H, m) and 2.26-2.19 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.70, 174.10, 135.89, 129.16, 127.54, 126.21, 123.18, 113.21, 64.22, 30.15 and 20.31. Infrared (neat): 3428.3, 3327.5(s), 3069.8, 3036.8, 2986.2, 2930.1(s), 2917.0, 2848.2(s), 2723.7, 1952.1, 1870.7, 1739.5, 1721.3, 1685.5 (m), 1648.1(s), 1598.3, 1492.2, 1450.6(s), 1431.3, 1375.1, (s), 1292.0(s), 1256.9 (s), 1226.7(s), 1152.6(s), 1088.0, 1069.3, 1021.6, 957.3, 947.5, 840.6, 824.2(s) and 757.4(s) cm^{-1}. Mass Spectrum: CIMS m/s 216 (M+1).

1-But-1-enyl-5-oxo-pyrrolidine-2-carbaldehyde, 15. Reaction of 3 g (17.73 mmol) of **12** with 40 mL dry DMSO, 2.10 g (2.15 mL, 26.60 mmol) of pyridine, 3.05 (2.06 mL, 26.60 mmol) of trifluoroacetic acid and 7.32 g (35.46 mmol) of dicyclohexylcarbodiimide gave after silica gel column chromatography (5% methanol + 95% methylene chloride, Rf = 0.38) 1.77 g (10.59 mmol, 60%) of **15** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.6 (1H, d, J = 1.1 Hz), 6.9 (1H, dd, J = 1.1, 14.8 Hz), 5.1 (1H, dt, J = 6.8, 14.8 Hz), 4.3 (1H, d, J = 2.3, 13.7 Hz), 2.6-2.3 (4H, m), 2.1 (2H, m) and 0.99 (3H, t, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 173.0, 122.4, 115.3, 64.0, 29.9, 23.4, 19.9 and 14.3. Infrared (neat): 3100, 2300, 1730, 1680, 1410, 1070 and 950 cm^{-1}. Mass Spectrum: CIMS m/s 168 (M+1).

1-Oct-1-enyl-5-oxo-pyrrolidine-2-carbaldehyde, 16. Reaction of 0.78 g (3.47 mmol) of **13** with 10 mL dry DMSO, 0.42 g (0.43 mL, 5.31 mmol) of pyridine, 0.60 g (0.41 mL, 5.24 mmol) of trifluoroacetic acid and 2.17 g (10.52 mmol) of dicyclohexylcarbdiimide gave after silica gel column chromatography (5% methanol + 95% methylene chloride, Rf = 0.27) 0.55 g (2.47 mmol, 71%) of **16** as a clear oil. $[\alpha]_D^{25}$ = -67.97° (c = 1.0, methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.54 (1H, d, -CHO, J = 3.36 Hz), 6.89 (1H, d, HC=CH(CH$_2$)$_5$, J = 14.67 Hz), 4.90-4.80 (1H, quintet, HC=CH-(CH$_2$)$_5$), 4.31-4.25 (1H, m, lactam CH), 2.58-2.30 (4H, m, lactam CH_2), 1.99-1.24 (10H, m, -$(CH_2)_5$-) and 0.86 (3H, t, J = 6.93 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.38 (-CHO), 173.20 (lactam C=O), 123.21, 114.31, 64.27, 32.00, 30.44, 30.21, 30.13, 29.07, 22.96, 20.20 and 14.46. Infrared (neat): 3367.8(br), 2955.2, 2927.0(s), 2871.1, 2855.0(s), 1702.6, 1699.1, 1679.4(s), 1661.8(s), 1559.3, 1458.1, 1411.2(s), 1280.2(s), 1235.8, 1113.8, 1064.6(br), 1013.2 and 954.8(s) cm^{-1}. Mass Spectrum: CIMS m/s 224 (M+1).

1-Styryl-5-vinyl-pyrrolidin-2-one, 17. A stirred suspension of methyltriphenylphosphonium bromide (3.90 g, 11.16 mmol; dried in oven, oven temperature 150 °C for 30 minutes) in dry 25 mL THF (freshly distilled over calcium hydride) was treated with 1.33 g (11.90 mmol) of potassium *tert*-butoxide (high vacuumed prior to use) at room temperature. After the mixture was stirred for 30 minutes, 0.80 g (3.72 mmol) of **14** dissolved in dry 5 mL THF was then slowly added *via* syringe at room temperature and the whole reaction mixture was stirred for 15 hours at the same temperature. After this, the reaction mixture was quenched with water and extracted with ether (3 times). The combined extracts were dried with magnesium sulfate, filtered, evaporated and purified by silica gel column chromatography (methylene chloride, Rf = 0.3) to give 0.69 g (3.27 mmol, 88 %) of **17** as a pale yellow oil. $[\alpha]_D^{25}$ = -11.72° (c = 1.0, methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (1H, d, -HC=CHPh, J = 15.01 Hz), 7.31-7.11 (5H, m,-Ph), 5.92 (1H, d, -CH=CHPh, J = 15.01 Hz), 5.84-5.75 (1H, m, -CH=CH$_2$), 5.23-5.16 (2H, m, -CH=CH$_2$), 4.51-4.47 (1H, m, lactam CH), 2.58-1.77 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.06, 136.84, 136.51, 129.05, 127.00, 126.02, 123.01, 115.81, 113.66, 59.67, 29.30 and 26.14. HRMS calculated for $C_{14}H_{15}NO$ 213.115124; Found 213.115364.

1-But-1-enyl-5-vinyl-pyrrolidin-2-one, 18. Reaction of 0.81 g (4.86 mmol) of **15**, 5.2 g (14.6 mmol) of methyltriphenylphosphonium bromide and 1.7 g (15.2 mmol) of

potassium *tert*-butoxide gave after silica gel column chromatography (methylene chloride, Rf = 0.30) 0.61 g (3.65 mmol, 75%) of **18** as a clear oil. $[\alpha]_D^{25}$ = -45.8° (c = 0.035, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (1H, d, J = 14.5 Hz), 5.70 (2H, m), 5.19 (1H, m), 5.10 (1H, m), 4.35 (1H, t, J = 7.4 Hz), 2.6-1.8 (6H, m) and 0.99 (3H, t, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 136.9, 122.0, 116.0, 115.7, 59.4, 29.7,25.8, 23.5 and 14.4. HRMS calculated for $C_{10}H_{15}NO$ 165.11538; Found 165.11622.

1-Oct-1-enyl-5-vinyl-pyrrolidin-2-one, 19. Reaction of 0.55 g (2.47 mmol) of **16**, 2.64 g (7.40 mmole) of methyltriphenylphosphonium bromide and 1.38 g (12.35 mmol) of potassium *tert*-butoxide gave after silica gel column chromatography (methylene chloride, Rf = 0.30) 0.449 g (2.03 mmol, 82%) of **19** as a clear oil. $[\alpha]_D^{25}$ = -20.17° (c = 1.0, methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (1H, d, -HC=CHR, J = 14.6 Hz), 5.81-5.69 (1H, m, -CH=CHR), 5.19-4.96 (3H, m, CH_2=CH-), 4.34 (1H, m, -CH-N), 2.57-2.23 (4H, m, lactam CH_2), 2.05-1.98 (2H, m, -C=CH-CH_2), 1.26 (8H, m), and 0.87 (3H, t, -CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.05, 136.98, 122.78, 116.38, 115.73, 59.75, 32.04, 30.66, 30.34, 30.05, 29.06, 26.10, 22.97 and 14.44 Infrared (neat): 3473.7(br), 2955.9, 2925.8(s), 2871.6, 2854.8 (s), 1707.8(s), 1664.2(s), 1458.7, 1398.3(s), 1338.9, 1287.1 (m), 1234.3, 994.0 and 951.8(s) cm^{-1}. Mass Spectrum: CIMS m/s 222 (M+1). HRMS calculated for $C_{14}H_{23}NO$ 221.17785; Found 221.17736.

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