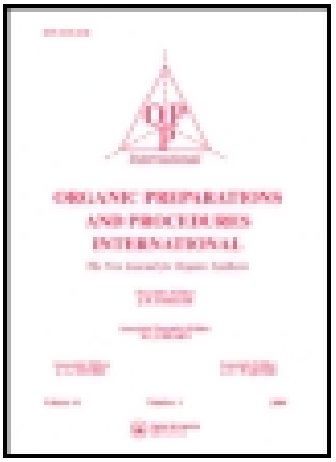

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SYNTHESIS OF 2(3H)-BENZOXAZOLINONE DERIVATIVES AS POTENTIAL MELATONIN RECEPTOR LIGANDS

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SYNTHESIS OF 2(3*H*)-BENZOXAZOLINONE DERIVATIVES AS POTENTIAL MELATONIN RECEPTOR LIGANDS

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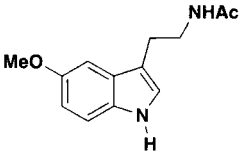
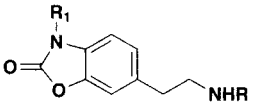
In the course of our search for melatonin (*N*-acetyl-5-methoxytryptamine) receptor ligands, we recently reported[1-5] a number of compounds including naphthalene, benzofuran, benzothiophene and tetralin derivatives. Most of them exhibited high affinity for melatonin receptors and structure-affinity relationships were specified for all these bioisosteric series. As a part of this research program, the well studied 2(3*H*)-benzoxazolinone heterocycle[6-10] has also been investigated as a potential carrier for the β-acetamidoethyl side-chain and this report describes the synthesis of this type of compound (**9a-e**) which showed a moderate affinity for the melatonin receptors.



Melatonin
(N-acetyl-5-methoxytryptamine)

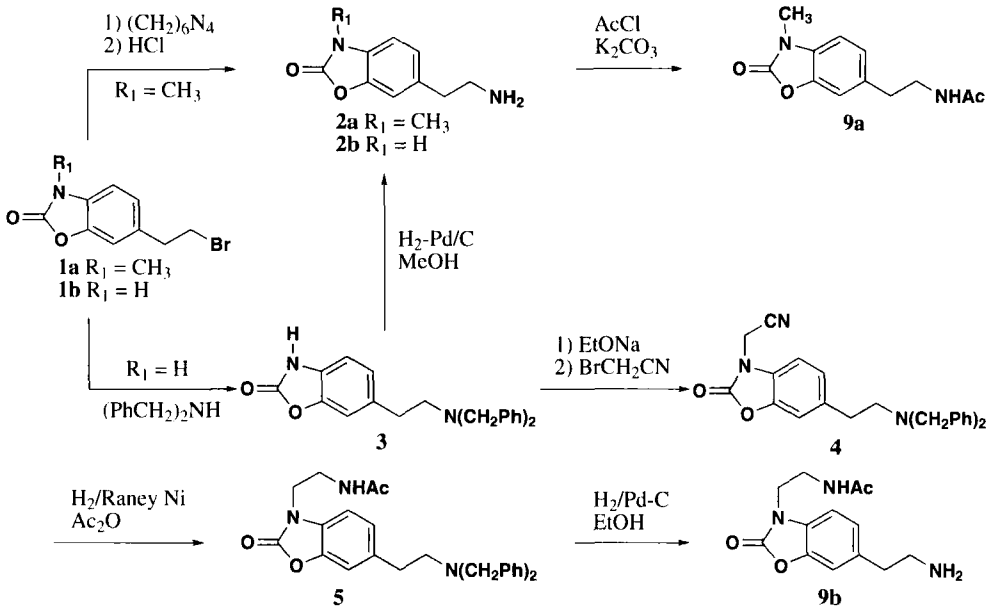


Benzoxazolinone Derivatives

The required primary amines **2a** and **2b** were prepared as shown in Scheme 1. While compound **2a** was obtained *via* the Delepine condensation[11] of the bromomethyl derivative (**1a**)[9,10] with hexamethylenetetramine in good yield (65%), application of this procedure to access compound **2b** was unsuccessful. Indeed, heating of the *N*-unsubstituted derivative **1b**[9,10] in the presence of hexamethylenetetramine led to polymerization and we therefore used the condensation of **1b** with dibenzylamine gave the tertiary amine **3**, which was then debenzylated using hydrogen and palladium on charcoal in MeOH to the primary amine **2b** in 54% overall yield.

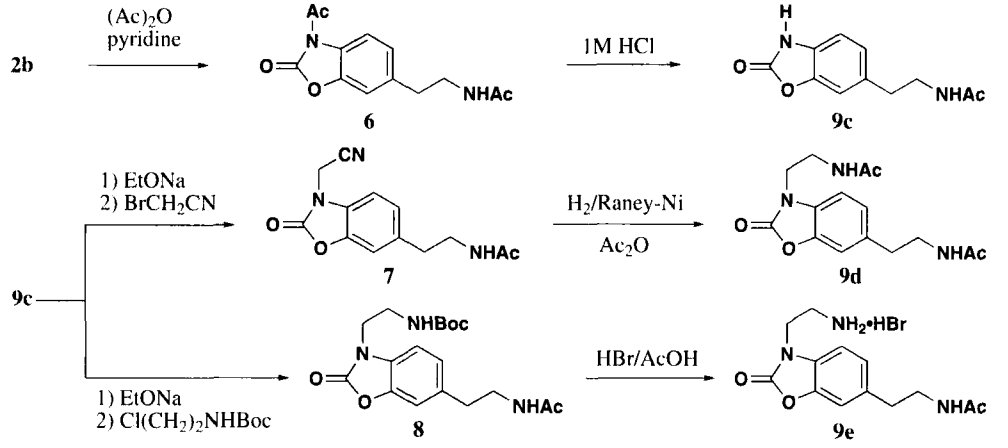
Treatment of **2a** with acetyl chloride in the presence of potassium carbonate in a biphasic medium according to a variant of the Schotten-Baumann procedure[12,13] gave **9a**; similar acetylation of **2b** under the same experimental conditions failed, apparently due to its insolubility. *N*-Alkylation of **3** with bromoacetonitrile and EtONa in DMF afforded **4** in good yield (83%). Selective reduction of the

cyano group of **4** was accomplished with hydrogen (60 atm, 60°) in the presence of Raney nickel in acetic anhydride, followed by debenzylation of **5** using hydrogen and palladium on charcoal in EtOH to provide **9b** (*Scheme 1*).



Scheme 1

Acetylation of **2b** with excess of acetic anhydride in pyridine generated the doubly acetylated product **6**. Gentle hydrolysis of **6** with 1M HCl selectively removed the 3-acetyl group to provide **9c**. Compounds **7** and **8** were obtained by *N*-alkylation of **9c** with the appropriate haloalkyl derivatives and EtONa in DMF. Catalytic hydrogenation of **7** in acetic anhydride in the presence of Raney nickel led to compound **9d**. Removal of the *tert*-butyloxycarbonyl protecting-group of **8** was carried using the acetic acid/hydrobromic acid reagent to give **9e**.



Scheme 2

EXPERIMENTAL SECTION

Mps (uncorrected) were determined in open capillary tubes using a Büchi 530 melting point apparatus. ^{1}H NMR spectra were recorded using a Brücker AC 300 spectrometer in DMSO-d_6 or $CDCl_3$ at ambient temperature using TMS as internal reference (δ). All compounds were found homogenous in TLC (Merck silicagel 60F254). Elemental analyses were performed by the "Service Central de Microanalyses", CNRS, Vernaison (France). Compounds **1a** and **1b** were synthesized according to the previously described procedures.[9,10]

3-Methyl-6-(2-aminoethyl)-2(3*H*)-benzoxazolinone Hydrochloride (2a).- Hexamethylene tetramine (5.6 g, 0.04 mol) in $CHCl_3$ (50 mL) was added portionwise to a solution of **1a** (7.70 g, 0.013 mol) in $CHCl_3$ (30 mL). The reaction mixture was heated under reflux for 150 h. After cooling, the precipitate was collected by filtration, and dissolved in EtOH (150 mL). Aqueous HCl (30 mL) was added, and the reaction mixture was refluxed for 2h. The solvent was evaporated *in vacuo*, and the residue was recrystallized from MeOH to give 5.94 g (65%) of **2a**, mp 243 – 245°; ^{1}H NMR : δ 3.05-3.10 (m, 4H, $\underline{CH_2}NH_3$, and $ArCH_2$), 3.30 (s, 3H, NCH_3), 7.15-7.25 (m, 3H, H_4, H_5, H_7), 9.10 (broad s, 3H).

Anal. Calcd for $C_{10}H_{12}N_2O_2$•HCl: C, 52.51; H, 5.73; N, 12.25. Found: C, 52.63; H, 5.67; N, 12.22

6-(2-Dibenzylaminoethyl)-2(3*H*)-benzoxazolinone (3).- To a solution of **1b** (4.85 g, 0.025 mol) in acetonitrile (50 mL), was added under stirring dibenzylamine (4.90 g, 0.025 mol). The reaction mixture was heated under reflux for 72 h. After cooling the hydrobromide salt of the title compound was filtered, dissolved in 2M aqueous solution of NaOH, and precipitated by bubbling CO_2. The solid was collected and air-dried to yield 6.98 g (78%) of **3**, mp 181-183°; ^{1}H NMR: δ 2.70-2.83 (m, 4H, CH_2CH_2), 3.61 (s, 4H, NCH_2 of dibenzylamine), 6.81-8.87 (m, 3H, H_4, H_5, H_7), 7.00 (broad s, 1H, NH), 7.23 (s, 10H, aromatic H).

Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.81. Found: C, 76.86; H, 6.29; N, 7.59

6-(2-Aminoethyl)-2(3*H*)-benzoxazolinone Hydrochloride (2b).- A solution of compound **3** (5.40 g, 0.015 mol) in MeOH (400 mL), was hydrogenated over 10% of Pd/C (0.25 g) at 60°/1 atm. for 36h. The reaction mixture was filtered and evaporated *in vacuo*. The residue was dissolved in dry ether and treated with gaseous HCl to give, after filtration and recrystallization from EtOH, 2.25 g (70%) of **2b**, mp >265°C; ^{1}H NMR: δ 3.03-3.15 (m, 4H, $\underline{CH_2}NH_3$, and $ArCH_2$), 7.00-7.20 (m, 3H, H_4, H_5, H_7), 9.00 (broad s, 4H, NH, and NH_3).

Anal. Calcd for $C_9H_{10}N_2O_2$•HCl: C, 50.36; H, 5.16; N, 13.05. Found: C, 50.44; H, 5.00; N, 12.85

3-Cyanomethyl-6-(2-dibenzylaminoethyl)-2(3*H*)-benzoxazolinone (4).- To a freshly prepared solution of EtONa (0.38 g, 0.0056 mol) in absolute EtOH (30 mL), was added compound **3** (1.8 g, 0.005 mol). The reaction mixture was stirred at room temperature for 30 min, and then evaporated. The residue was dissolved in DMF (40 mL) and then bromoacetonitrile (0.43 mL, 0.0062 mol) was added dropwise. After stirring at 80° for 10h, the solution was poured into ice H_2O and the precipitate was collected by filtration and recrystallized from EtOH to give 1.64 g (83%) of **4**, mp 150-152°; ^{1}H NMR: δ 2.70-2.86 (m, 4H, CH_2N, and $ArCH_2$), 3.64 (s, 4H, CH_2 of dibenzylamine), 4.75 (s, 2H,

CH_2CN), 6.96-7.60 (m, 13H, H_4, H_5, H_7, and aromatic H).

Anal. Calcd for $C_{25}H_{23}N_3O_2$: C, 75.55; H, 5.83; N, 10.57. Found: C, 75.48; H, 5.62; N, 10.42

3-(2-Acetamidoethyl)-6-(2-dibenzylaminoethyl)-2(3*H*)-benzoxazolinone (5).- A solution of **4** (1.58 g, 0.004 mol) in acetic anhydride was hydrogenated over Raney nickel under pressure (60 bars) at 60° for 6 h. After filtration and evaporation, the residue was taken with H_2O, and treated with an aqueous solution of potassium carbonate. The precipitate was filtered, dried, and recrystallized from MeOH to give 1.27 g (71 %) of **5**. mp 157-158°; ^{1}H NMR: δ 1.66 (s, 3H, $COCH_3$), 2.68 (m, 2H, $ArCH_2$), 3.25-3.45 (m, 4H, CH_2N, and $\underline{CH_2}NH$), 3.58 (s, 4H, CH_2 of dibenzylamine), 3.83 (m, 2H, NCH_2), 6.94-7.50 (m, 13H, H_4, H_5, H_7, and aromatic H), 8.00 (broad s, 1H, NH).

Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 73.11; H, 6.59; N, 9.47. Found: C, 73.28; H, 6.62; N, 9.53

3-Acetyl-6-(2-acetamidoethyl)-2(3*H*)-benzoxazolinone (6).- A solution of compound **2b** (1.78 g, 0.010 mol) in acetic anhydride (2.85 mL, 0.030 mol) and dry pyridine (20 mL) was stirred at room temperature for 12 h. The solution was poured into cold H_2O and the aqueous mixture was adjusted to pH 5.0 with aqueous 6M HCl. The resulting precipitate was collected by filtration, washed with H_2O and recrystallized from toluene to give 1.80 g (69%) of **6**, mp 170-175°; ^{1}H NMR: δ 1.95 (s, 3H, $COCH_3$), 2.72 (s, 3H, $NCOCH_3$), 2.90 (t, 2H, J = 6.57 Hz, $ArCH_2$), 3.50 (m, 2H, $\underline{CH_2}NH$), 5.55 (broad s, 1H, NH), 7.00-7.10 (m, 2H, H_4, H_5), 7.95 (s, 1H, H_7).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.46; H, 5.32; N, 10.53

3-Cyanomethyl-6-(2-acetamidoethyl)-2(3*H*)-benzoxazolinone (7).- Starting from, **9c** (1.05 g, 0.005 mol), EtONa (0.38 g, 0.0056 mol) and bromoacetonitrile (0.43 mL, 0.0062 mol) the reaction was carried out as described for compound **4**. Recrystallization from toluene gave 0.58 g (40%) of **7**, mp 144-146°; ^{1}H NMR: δ 1.75 (s, 3H, $COCH_3$), 2.80 (t, 2H, J = 6.63 Hz, $ArCH_2$), 3.25 (m, 2H, CH_2N), 5.15 (s, 2H, CH_2CN), 7.12 (d, 1H, J = 8.65 Hz, H_4), 7.30 (d, 1H, J = 8.65 Hz, H_5), 7.38 (s, 1H, H_7), 7.90 (broad s, 1H, NH).

Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.20. Found: C, 60.43; H, 5.02; N, 16.42

3-(2-*tert*-Butyloxycarbonylaminoethyl)-6-(2-acetamidoethyl)-2(3*H*)-benzoxazolinone (8).- Starting from **9c** (1.26 g, 0.006 mol), EtONa (0.45 g, 0.0067 mol) and *tert*-butyl bromoacetate (1.06 mL, 0.0072 mol) the reaction was carried out as described for compound **4**. Recrystallization from toluene gave 1.52 g (70 %) of **8**, mp 151-153°; ^{1}H NMR: δ 1.40 (s, 9H, $C(CH_3)_3$), 1.80 (s, 3H, $COCH_3$), 2.80 (t, 2H, J = 6.68 Hz, $ArCH_2$), 3.42-3.64 (m, 4H, 2 CH_2N), 3.95 (t, 2H, J = 5.57 Hz, NCH_2), 4.85 (broad s, 1H, NHBoc), 5.60 (broad s, 1H, $NHCOCH_3$), 6.96-7.15 (m, 3H, H_4, H_5, H_7).

Anal. Calcd for $C_{18}H_{25}N_3O_5$: C, 59.49; H, 6.93; N, 11.56. Found: C, 59.28; H, 6.71; N, 11.40

3-Methyl-6-(2-acetamidoethyl)-2(3*H*)-benzoxazolinone (9a).- Potassium carbonate (2.66 g, 0.020 mol) was added to a solution of **2a** (2.28 g, 0.010 mol) in 60 mL of H_2O and 100 mL of $CHCl_3$. The mixture was cooled to 0° and acetyl chloride (0.84 mL, 0.012 mol) was added dropwise at this temperature. The mixture was then stirred at room temperature for 1 h. The organic layer was separated, washed with H_2O, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was recrystallized from toluene, affording 1.92 g (82%) of **9a**, mp 149 - 150°; ^{1}H NMR: δ 1.96 (s, 3H, $COCH_3$),

2.85 (t, 2H, J = 6.93 Hz, $ArCH_2$), 3.36 (s, 3H, NCH_3), 3.50 (m, 2H, $\underline{CH_2}NH$), 5.66 (broad s, 1H, NH), 6.90 (d, J = 8.16 Hz, H_4), 7.00-7.13 (m, 2H, H_5, H_7).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.39; H, 6.01; N, 11.77

3-(2-Acetamidoethyl)-6-(2-aminoethyl)-2(3*H*)-benzoxazolinone Hydrochloride (9b).- A solution of compound **5** (1 g, 0.00225 mol) in EtOH (100 mL), was hydrogenated over 10% of Pd/C (0.1 g) at 60°/1 atm. for 4h. The reaction mixture was filtered, and evaporated *in vacuo* . The residue was dissolved in dry ether and treated with gaseous HCl to give, after filtration and crystallization from EtOH, 0.50 g (73 %) of **9b**, mp 260-262°; ^{1}H NMR: δ 1.68 (s, 3H, $COCH_3$), 2.92-3.00 (m, 4H, $\underline{CH_2}NH_3$ and $ArCH_2$), 3.35 (m, 2H, $\underline{CH_2}NH$), 3.85 (t, 2H, J = 5.63 Hz, NCH_2), 7.13 (d, 1H, J = 8.57 Hz, H_4), 7.18 (d, 1H, = 8.57 Hz, H_5), 7.29 (s, 1H, H_7), 8.10 (broad s, 4H, NH, and NH_3).

Anal. Calcd. for $C_{13}H_{17}N_3O_3$•HCl; 0.5 H_2O: C, 50.57; H, 5.87; N, 13.61.

Found: C, 50.98; H, 6.05; N, 13.62

6-(2-Acetamidoethyl)-2(3*H*)-benzoxazolinone (9c).- To a solution of compound **6** (2.62 g, 0.010 mol) in EtOH (40 mL), was added aqueous 1M HCl (100 mL). The reaction mixture was heated at 50° for 2h. After cooling, the precipitate was filtered, dried, and recrystallized from MeOH-H_2O (4:1) to give 2.09 g (95%) of **9c**, mp 204-206°; ^{1}H NMR: δ 1.75 (s, 3H, $COCH_3$), 2.70 (t, 2H, J = 7.14 Hz, $ArCH_2$), 3.25 (m, 2H, CH_2N), 5.58 (broad s, 1H, NH), 7.00-7.05 (m, 2H, H_4, H_5), 7.15 (s, 1H, H_7), 7.85 (broad s, 1H, NH).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.12; H, 5.42; N, 12.62

3-(2-Acetamidoethyl)-6-(2-acetamidoethyl)-2(3*H*)-benzoxazolinone (9d).- Starting from **7** (2 g, 0.005 mol) the reaction was carried out as described for compound **5**. Recrystallization from toluene gave 1.29 g (85%) of **9d**, mp > 260°; ^{1}H NMR: δ 1.67 (s, 3H, $COCH_3$), 1.77 (s, 3H, $COCH_3$), 2.72 (t, 2H, J = 7.40 Hz, $ArCH_2$), 3.25 (m, 2H, CH_2N), 3.35 (m, 2H, CH_2N), 3.82 (t, 2H, J = 5.55 Hz, NCH_2), 7.05 (d, 1H, J = 8.66 Hz, H_4), 7.15 (d, 1H, J = 8.66 Hz, H_5), 7.22 (s, 1H, H_7), 7.90 (broad s, 1H, NH), 8.00 (broad s, 1H, NH).

Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.00; H, 6.27; N, 13.76. Found: C, 58.92; H, 6.32; N, 13.65

3-(2-Aminoethyl)-6-(2-acetamidoethyl)-2(3*H*)-benzoxazolinone Hydrobromide (9e).- To a solution of compound **8** (0.72 g, 0.002 mol) in acetic acid (20 mL) was added a solution of 33% of hydrobromic acid in acetic acid (3.45 mL, 0.020 mol). The reaction mixture was stirred for 2h at room temperature, and the hydrobromide salt of the desired compound was filtered, washed with diethylether, and recrystallized from EtOH to give 0.46 g (82 %) of **9e**. mp 192-193° ; ^{1}H NMR: δ 1.80 (s, 3H, $COCH_3$), 2.75 (t, 2H, $ArCH_2$, J = 6.65 Hz), 3.15-3.30 (m, 4H, 2 CH_2N), 4.10 (t, 2H, NCH_2, J = 5.54 Hz), 7.10 (d, 1H, H_4), 7.22-7.30 (m, 2H, H_5, H_7), 7.90 (broad s, 4H, NH_3 and NH).

Anal. Calcd for $C_{13}H_{17}N_3O_3$•HBr: C, 45.36; H, 5.27; N, 12.21. Found: C, 45.48; H, 5.42; N, 12.42.

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