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Synthesis of a ^{11}C-Labelled Nitrated 1,4-Dihydroquinoxaline-2,3-dione, the NMDA Glycine Receptor Antagonist ACEA 1021 (Licostinel)

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Abstract

ACEA 1021 (6,7-dichloro-5-nitro-1,4-dihydroquinoxaline-2,3-dione, Licostinel) is a potent antagonist for the glycine site of the NMDA receptor. With the purpose of evaluating the drug's biodistribution *in vivo* as well as its potential as a PET tracer for the glycine binding sites, ACEA 1021 was labelled in the heterocyclic ring with carbon-11 in a five-step synthesis. The radiolabelling precursor, derived from [^{11}C]cyanide, was diethyl [1-^{11}C]oxalate. Yields of its cyclization with the deactivated nitrated diamine, 4,5-dichloro-3-nitro-1,2-phenylenediamine, were too low to be reliable for the planned *in vivo* studies. Instead, diethyl [1-^{11}C]oxalate was reacted with 4,5-dichloro-1,2- phenylenediamine to give [2-^{11}C]6,7-dichloro-1,4-dihydroquinoxaline-2,3-dione (DCQX). Interference from the excess diamine during the subsequent nitration reaction was reduced by two methods. After formation of [2-^{11}C]DCQX, unlabelled diethyl oxalate was added and allowed to cyclize before adding the nitrating agent, giving a carrier-added product suitable for use in pharmacokinetic studies. For the non-carrier-added tracer studies, the diamine was condensed with acetic acid before adding fuming HNO_3/concentrated H_2SO_4. Both procedures gave high conversions of [2-^{11}C]DCQX to [^{11}C]ACEA 1021, which was subsequently isolated by semi-preparative liquid chromatography. The total synthesis time was 70-80 min. The conversions according to radio-analytical LC were 25-30% and isolated yields for the five-step synthesis were ≈ 5-10% (decay-corrected, based on [^{11}C]CN^- at end of trapping). The specific activity of the no-carrier-added product was 15-20 GBq/μmol at end-of-synthesis.

Key words: NMDA, glycine site, ACEA 1021, 1,4-dihydroquinoxaline-2,3-dione, carbon-11, PET

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Introduction

The *N*-methyl-D-aspartic acid (NMDA) receptors are involved in pathophysiological processes such as ischemia, epilepsy, stroke and trauma-related damage. These diseases cause neuronal degeneration and may even lead to death. NMDA receptors are regulated at the phencyclidine binding site, the L-glutamate recognition site, the glycine "coagonist" sites and the polyamine sites

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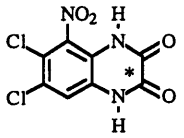
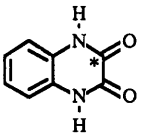
(for a review see (1)). Glycine up-regulates the receptor function. Sustained ability to open the ion channel is probably dependent on the extracellular glycine levels. Glycine agonists have been thought to have potential as cognitive enhancers while glycine antagonists have been found to be anticonvulsants, neuroprotectants, analgesics and anxiolytics in studies in animal models (for a review see (2)). Many potent and selective antagonists have been reported. However, most of these have poor systemic bioavailability and they often do not cross the blood-brain barrier.

Substituted 1,4-dihydroquinoxaline-2,3-diones (QXs), first reported to be antagonists at the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) sites (3), have also shown antagonist activity at the glycine-NMDA site (4). In structure-activity studies, tri-substituted QXs were found to be particularly potent and selective glycine antagonists, especially when they possessed a nitro group at the 5-position and either bromine or chlorine at the 6- and 7-positions (5,6). ACEA 1021 (6,7-dichloro-5-nitro-1,4-dihydroquinoxaline-2,3-dione, Licostinel) is one of the most potent (K_i=5 nM) antagonists, with a selectivity for glycine site/non-NMDA receptor ≈ 250 (6). It has been reported to be a neuroprotectant in rat focal ischemia, an anticonvulsant in protection against seizures induced by electroshock, and acts as an analgesic in animal models of chronic pain (5,7,8,9). ACEA 1021 has been proposed to modulate the mechanism of propagation of spreading depression (10), has attenuated myoclonus in cardiac-arrested rats (11) and has recently undergone clinical trials as a neuroprotectant for stroke.

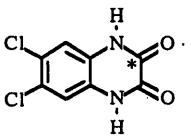
In order to correlate the pharmacological effects of ACEA 1021 to its *in vivo* biodistribution and to evaluate its potential as a tracer for studies of the NMDA glycine site using positron emission tomography (PET), we have labelled the drug in the heterocyclic ring with carbon-11 in the 2- or 3-position in the heterocyclic ring (1). The method (presented preliminarily in (12)) is an extension of our previous studies using the radiolabelling precursor diethyl [1-^{11}C]oxalate (Scheme I) to condense with the corresponding diamines to give the labelled 1,4-dihydroquinoxaline-2,3-dione (QX), 2, (13) and 6,7-dichloro-1,4-dihydroquinoxaline-2,3-dione (DCQX), 3, (14). However, the nitrodiamine precursor, which is considerably deactivated due to the nitro group compared to those used to synthesize 2 and 3, proved to be critical for the labelling strategies utilized.



[^{11}C]ACEA 1021, 1
(6,7-dichloro-5-nitro-1,4-dihydroquinoxaline-2,3-dione)



[2-^{11}C]QX, 2
(1,4-dihydroquinoxaline-2,3-dione)



[2-^{11}C]DCQX, 3
(6,7-dichloro-1,4-dihydro-quinoxaline-2,3-dione)

Results and Discussion

Similar to QX and DCQX, ACEA 1021 has no substituents that can be labelled with ^{11}C (or ^{18}F). Therefore, labelling the heterocyclic ring carbons via cyclization of the appropriate diamine with a ^{11}C-labelled 2-carbon precursor was also deemed to be the most feasible route here. Two possible routes were considered (a) the diamine should already have the NO_2 group in place prior to the

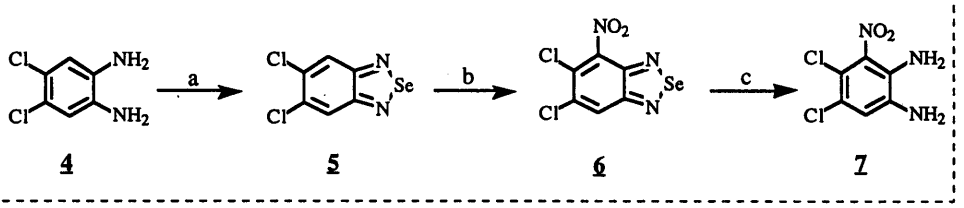
cyclization labelling reaction or (b) the nitro group should be added post-cyclization. The production of the diethyl [1-^{11}C]oxalate precursor from [^{11}C]CN$^-$ (Scheme I) involves two synthesis steps and two transfers (13). Due to the losses from decay ($t_{1/2}$ = 20 min), incomplete conversions and handling procedures, only ≈30% of the starting ^{11}C is available for the cyclization reaction at t ≈ 20 min. The number of *additional* transformations and losses tolerated is obviously limited.

Scheme I

Reagents: (a) Q^+OH^-, H_2O, CH_2Cl_2; (b) HCl (g) / EtOH (4-5 M)

Therefore, to keep the number of radiolabelling steps to a minimum, the first route attempted for ^{11}C-labelling ACEA 1021 utilized the nitrated diamine starting material, 4,5-dichloro-3-nitro-1,2-phenylenediamine, **7**. It was prepared by a three-step synthesis (Scheme II) from 4,5-dichloro-1,2-phenylenediamine, **4**. The diamine function of **4** was protected from degradation during the nitration reaction by converting it to the benzoselenadiazole **5**. Compound **5** is formed in a facile reaction between **4** and selenium (IV) oxide in 1N HCl (15). The subsequent nitration with nitric and sulfuric acids required 2 days and warming to 30 °C to give a yield of 81%. Treatment of **6** with hydroiodic acid in concentrated HCl cleaves the benzoselenadiazole to the desired product **7** (16). Unreacted **6** was removed by column chromatography was required to give purified (99%) diamine **7**. The yield of this deprotection step was modest (54%) and could almost certainly be improved with further development of the reaction conditions. The overall yield was 41 % .

Scheme II

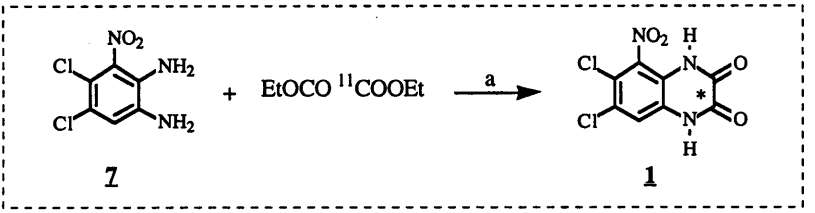


Reagents: (a) SeO_2, 1 N HCl; (b) fuming HNO_3, conc. H_2SO_4; (c) conc. HCl, HI

Cyclization of **7** with diethyl [1-^{11}C]oxalate (Scheme III) was attempted in acidic media (from 50% to concentrated HCl or H_2SO_4) or in DMSO at reaction temperatures up to 175 °C. At most, only ≈ 10% conversions to the desired product were detected (by radio-analytical LC) after reaction times up to 20 min. In most cases, one major new radioactive peak was observed which eluted with the same retention time as [1-^{11}C]oxalic acid, the hydrolysis product of diethyl [1-^{11}C]oxalate. The maximum total yields of **1** (2-3%, prior to clean-up and based on [^{11}C]CN$^-$) were thus too low and

too irreproducible after LC purification, even for use in small animal PET investigations. Albeit lower than we had hoped, these yields are consistent with our expectation that the electron-withdrawing *ortho*-NO_2 group would have a deactivating effect on the condensation of diamine with diethyl [1-^{11}C]oxalate.

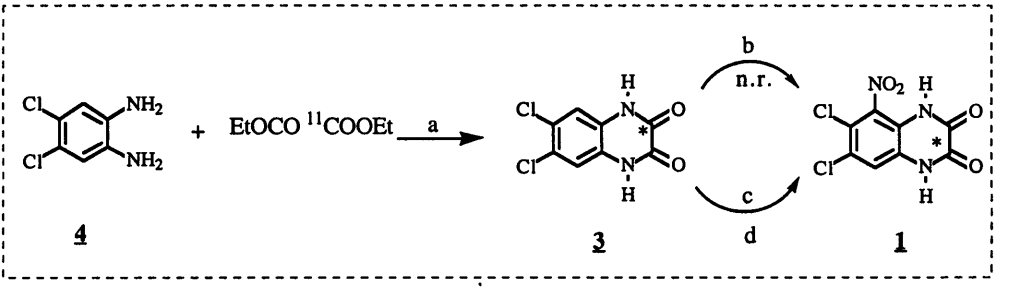
Scheme III



Reagents: (a) conc. H_2SO_4

Under conventional synthetic conditions, the aromatic nitration of 6,7-substituted-quinoxaline-2,3-diones can readily be performed using KNO_3 or fuming HNO_3 in concentrated H_2SO_4 (17). Nitration of DCQX (6) in either the 5*th* or 8*th* position produces ACEA 1021, since the molecule is symmetrical. Therefore, this two-step route to **1** (Scheme IV, path b) was undertaken. Compound **3** was synthesized by reacting diethyl [1-^{11}C]oxalate with **4** in H_2SO_4 (conversions ≈ 50%, 175 °C, 10 min) (14). The subsequent nitration was attempted by varying the reaction temperature, time and amounts of nitrating agent (KNO_3 or fuming HNO_3 in concentrated H_2SO_4). Compound **1** was not detected by radio-analytical LC in any of the attempts. Gas evolution was observed during the addition, which indicated that the nitrating reagent was reacting with something in the mixture and obviously to the extent that it interfered with the desired aromatic nitration of **3**. Aromatic amines are oxidized by mixed nitric and sulfuric acids, even under relatively mild conditions. The large excess of **4** used to drive the cyclization reaction presumably consumed the nitrating agent.

Scheme IV



Reagents: (a) 50 % H_2SO_4; (b) fuming HNO_3, conc. H_2SO_4;
(c) diethyl oxalate, then HNO_3 /H_2SO_4; (d) glacial acetic acid, then HNO_3 /H_2SO_4

Two routes for rapidly circumventing this problem were found. The first approach (Scheme IV, path c) gives a low specific activity product which is potentially useful for *in vivo* studies of doses typically used in therapeutic applications. After generating **3**, carrier diethyl oxalate (molar excess to the amine) was added and the mixture was heated at 175 °C for an additional 5 min. The reaction mixture was cooled and HNO_3 / H_2SO_4 (1:5 v/v) was added. After stirring for 2 min at 0-5 °C, complete conversion of **3** to **1** was achieved, according to radio-analytical LC.

For production of no-carrier added **1**, the second approach (Scheme IV, path d) makes use of the facts that *(a)* primary aromatic amines are usually protected as amides prior to performing aromatic nitration and that *(b)* carboxylic acids react readily with phenylenediamines to give benzimidazole derivatives. Therefore, after forming **3**, glacial acetic acid was added instead of carrier diethyl oxalate to reduce or remove the interference from the aromatic amines. The reaction mixture was again heated at 175 °C for an additional 5 min. The nitration was performed as above for the carrier-added approach and an essentially complete conversion of **3** to **1** was again obtained.

The acidic media was rapidly removed by a solid phase extraction procedure using a SepPak C18 cartridge. The desired product **1** was eluted from the cartridge in CH_3CN for injection on the semi-preparative LC column. Eluting after 11-13 min, **1** was collected, the mobile phase evaporated and the residue redissolved in tromethamine (Tris) before Millipore filtration.

In summary: The synthesis of **1** from [^{11}C]CN^- consisted of the following steps/procedures: trapping of [^{11}C]CN^-, phase transfer reaction with methyl chloroformate to give methyl [^{11}C]cyanoformate, phase separation, ethanolysis, solvent evaporation, condensation with **4** to give **3**, addition and reaction with the appropriate amine scavenger (diethyl oxalate or glacial acetic acid), nitration to give **1**, SepPak pre-cleaning, isolation by semi-preparative LC and formulation. The total synthesis time was 70-80 min starting from trapped [^{11}C]CN^-. The radiochemical yield was 5-10 % (decay-corrected) based on trapped [^{11}C]CN^-. The specific activity of the no-carrier-added product at the end-of-synthesis varied between 15-20 GBq/μmol (n=4). Therefore, starting with as little as ≈10 GBq of [^{11}C]CN^-, sufficient amounts of ^{11}C-labelled ACEA 1021 for preliminary animal screening studies with PET can be synthesized by this procedure. Such studies are currently being pursued and will be the subject of a separate report.

Experimental

The following chemicals were commercially available and were used without further purification: methyl chloroformate, **4**, and diethyl oxalate from Aldrich; tetrabutylammonium hydroxide (0.8 M in methanol) from Fluka and tromethamine and acetic-, nitric- and sulfuric acids from Merck. Reference DCQX was purchased from Research Biochemicals Incorporated, Natick, MA, USA and reference ACEA 1021 was provided by Novartis Pharmaceutical, NJ, USA. All the solvents used were of analytical grade and were used without further purification. SepPaks C-18 (Waters) were pretreated with ethanol (10 mL) and water (10 mL) before use.

Chemical ionization mass spectroscopy was performed on a Finnigan 4600 mass spectrometer utilizing isobutane as the reagent gas. Spectroscopic characterization was also performed using 300 MHz ^{1}H-NMR and 75 MHz ^{13}C-NMR spectroscopy on Bruker NMR instruments. TLC chromatograms were performed on silica gel F-254 plates (5 x 10 cm, 250 μm thickness, E. Merck). Visualization was achieved either by UV (λ=254 nm) or exposure to subliming iodine. Liquid chromatography (LC) of 7 was performed on a Waters HPLC system consisting of a Waters 600E pump module, a WISP 717A auto-sampler, a 484 variable wavelength UV detector, and a Waters 996 photo-diode array (PDA) detector. A RC-8 column (Zorbax, 4.6 x 250 mm) was used with a mobile phase of CH_3CN:buffer = 60:40. The buffer was heptane sulfonic acid (15mM) adjusted to pH= 3 with H_2SO_4. UV detection was at 280 nm with PDA at 200-400 nm. Elemental analysis was performed by Robertson Microlit Laboratories, Inc. (Madison, NJ).

Radio-analytical LC was performed using a Shimadzu LC 6A pump, a Valco injector (C6W with a 250 μL loop), a Shimadzu SPD 5A UV-detector (λ=210 or 270 nm) in series with a Beckman 170 β-flow radiodetector. The detectors were connected to a Shimadzu C-R2AX data processor for integration of the peak areas. Semi-preparative LC was performed using a Shimadzu LC 6A pump, a Valco VICI injector with a 1 mL loop, a LDC Spectromonitor II in series with a GM tube for UV- and radioactivity detection respectively. Both detectors were connected to a BBC goertz Metrawatt SE120 two-channel recorder. The columns used were μBondapak C-18 (Waters, 10 μm, 300 x 3.9 mm and 300 x 7.8 mm for radioanalysis and purification, respectively). The mobile phases were CH_3CN:H_3PO_4 (0.01 M) 20:80, 1.5 mL/min, for the analysis of diethyl [1-^{11}C]oxalate; CH_3CN:H_3PO_4 (0.01 M) 25:75, 3.5 mL/min for the analysis of 1 and CH_3CN:H_3PO_4 (0.01 M) 27:73, 6 mL/min for the semi-preparative isolation.

Synthesis of 4,5-dichloro-3-nitro-1,2 phenylenediamine, 7 (Scheme II)

5,6-Dichlorobenzoselenadiazole, 5 : Into a 500 mL, 3-neck round bottom flask equipped with a mechanical stirrer, a dropping funnel and a condenser, was added 4 (7.081 g, 40 mmol) followed by 1 N HCl (80 mL). The mixture was stirred and heated to 80 °C. Selenium (IV) dioxide (4.438 g, 40 mmol) was dissolved in water (32 mL) and added to the reaction mixture via the dropping funnel over 30 min. The reaction mixture was cooled to room temperature and stirred for 2.5 h. TLC, using methylene chloride as a mobile phase, showed the reaction to be complete. The precipitate was isolated by filtration, washed with water and cold ethanol, and dried *in vacuo* at 32 °C overnight. The yield was 9.552 g (37.9 mmol, 94.7%). MH^+ = 253 (isobutane DCI). ^{1}H-NMR δ (DMSO) = 8.32 (s).

5,6-Dichloro-4-nitrobenzoselenadiazole, 6 : Compound 5 (9.552 g, 37.9 mmol) was dissolved in concentrated sulfuric acid and cooled in an ice bath to 0 °C. Next, a solution of concentrated sulfuric acid and fuming nitric acid (12 mL, 2:1 v/v) which had been cooled to 0 °C, was added from a dropping funnel. The reaction mixture was stirred for 20 h, during which time, it was allowed to come to room temperature. TLC using methylene chloride as the mobile phase, indicated the reaction was not complete. The reaction mixture was heated to 30 °C and stirred for an

additional 24 h. It was then poured onto ice, stirred for 20 min. The product was isolated by filtration. The filter cake was washed with cold water until the filtrate was neutral to pH paper. The product was dried *in vacuo* overnight to give 9.13 g (30.7 mmol, 81.0%). MH^+= 298 (isobutane DCI). ^{1}H-NMR δ (DMSO) = 8.60 (s).

4,5-Dichloro-3-nitro-1,2-phenylenediamine, 7 : Compound **6** (9.130 g, 30.7 mmol) and concentrated HCl (77 mL) were added to a 500 mL round bottom flask equipped with a dropping funnel. The starting material was stirred at room temperature for 15 min, then 47% hydroiodic acid (27 mL) was added dropwise over 30 min at room temperature, with stirring. Stirring was continued for two days. Sodium hydrogen sulfite (77 mL of 10% aqueous solution) was added and the mixture was stirred for 30 min at room temperature. Sodium hydroxide was added until the pH was > 9. The reaction mixture was extracted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with four portions of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, and evaporated. TLC (ethyl acetate) of the resulting residue showed the presence of the non-nitrated side product. The residue was purified by column chromatography (ethyl acetate on silica gel) to give 3.65 g (53.8%) of product. The purity by PDA at maximum absorbance was 98.97% ± 0.15%, at 280 nm it was 99.13% ± 0.01%. No single impurity >0.05% appeared in either case. MH^+= 222 (isobutane DCI). ^{1}H-NMR δ (DMSO) = 6.81 (1H, s); 5.62 (2H, s); 5.60 (2H, s). ^{13}C-NMR δ (DMSO) = 137.48, 135.84, 129.07, 118.74, 113.59, 108.12. Elemental analysis calc. for $C_6H_5Cl_2N_3O_2$ C, 32.44; H, 2.27; N, 18.92; Cl, 31.96. Found C, 32.44; H, 2.31; N, 18.73; Cl, 32.37.

Production of diethyl [1-^{11}C]oxalate (Scheme I)

The production of diethyl [1-^{11}C]oxalate has been described previously (13,14). Briefly, [^{11}C]HCN was trapped in a solution of tetrabutylammonium hydroxide (50 µL, 40 µmol) in H_2O (0.5 mL). After completion of trapping, methyl chloroformate (50 µL, 0.65 mmol) dissolved in CH_2Cl_2 (0.5 mL) was added and the solution was vigorously stirred for 5 min at room temperature. The organic phase was removed and added to HCl (4-5 M in ethanol). The mixture was heated for 10 min at 80 °C under stirring or treated with microwaves (70 W, 30 sec) in a single-mode cavity (18). The solvents were subsequently evaporated.

[^{11}C]-6,7-Dichloro-5-nitro-1,4-dihydroquinoxaline-2,3-dione, 1, (Scheme III)

Compound **7** (7-10 mg, 32-45 µmol) was dissolved in H_2SO_4 (0.5 mL, 18 M) and added to the diethyl [1-^{11}C]oxalate residue. The mixture was heated at 175 °C for 10 min. According to radioanalytical LC, ≈10% of the total radioactivity was **1**. The reaction mixture was cooled, H_2O (2 mL) was added and the mixture was applied to a pretreated SepPak C-18. The column was washed with H_2O (5 mL) and the labelled product was eluted with CH_3CN (1-1.3 mL). The solvent was reduced under a stream of N_2 and injected onto the preparative LC system. Although the desired product **1** eluted after ≈ 11-13 min, collection of the product was difficult since the amounts of product were very small due to physical losses on the column combined with the low labelling

yields. Coelution with reference ACEA 1021 on the radio-analytical LC confirmed the identity of the collected product.

[^{11}C]-6,7-Dichloro-5-nitro-1,4-dihydroquinoxaline-2,3-dione, 1 (Scheme IV)

Compound 4 (7-10 mg, 40-57 μmol) was dissolved in H_2SO_4 (0.5 mL, 9 M) and added to the diethyl [1-^{11}C]oxalate residue. The mixture was heated at 175 °C for 10 min to give 3. Carrier diethyl oxalate (10 μL, 74 μmol) (path c) or glacial acetic acid (15 μL, 262 μmol) (path d) was added and the mixture was heated for an additional 5 min at 175 °C. The reaction mixture was cooled in an ice bath and a mixture (1.2 mL, 1:5 v/v) of fuming HNO_3 and concentrated H_2SO_4 was added dropwise. After stirring the reaction mixture for 2 min at 0-5 °C, LC analysis showed essentially complete conversion of 3 to the desired product, 1. H_2O (2 mL) was added and the mixture was applied to a pretreated SepPak C18. The column was washed with H_2O (5 mL) and the labelled product was eluted with CH_3CN (1-1.3 mL). The solution was rapidly concentrated by heating at 100 °C under a stream of N_2 and injected into the preparative LC system. [^{11}C]ACEA 1021 eluted between 11-13 min. After evaporation of the mobile phase, 1 was redissolved in Tris (0.05 M) and filtered through a Millipore filter (0.22 μm) into a 10 mL sterile injection vial. Co-chromatographic elution of an aliquot with reference ACEA 1021 confirmed the identity of the labelled product, which was >99% radiochemically pure.

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