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Synthesis of a series of carbon-14 labeled tetrahydropyrido[4,3-d]pyrimidin-4(3H)-ones

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A series of tetrahydropyrido[4,3-d]pyrimidin-4(3H)-ones labeled with carbon-14 in the 2-position of pyrimidinone moiety were prepared as part of a 3-step sequence from benz[*amidino*-^{14}C]amidine hydrochloride as a key synthetic intermediate.

Keywords: piperidine derivatives; piperidine-pyrimidone fused skeleton; carbon-14

Introduction

The fused skeleton piperidine-pyrimidones have been a rich source of biologically active molecular entities and are related to a wide family of compounds with well-known pharmacological properties.[1–5] Among the different substitution patterns that are known, tetrahydropyrido[4,3-d]pyrimidines are important because of their potential biological and pharmaceutical activities. The tetrahydropyridopyrimidine core is a key pharmacophore in several reported preclinical drug candidates, including selective P2X7 receptor antagonists, inhibitors of platelet aggregation, gastric anti-lesion agents, and phosphor diesterase 10 inhibitors. These compounds also show anti-inflammatory, diuretic, and coronary dilator effects.[6–10] A series of novel tetrahydropyrido [4,3-d]pyrimidin-4(3H)-ones as possible effective MBL(metallo-β-lactamase) enzymes inhibitors were introduced by Peter Vella and coworkers.[11]

To further elucidate the mechanism of action and investigate the pharmacokinetics and drug metabolism of these compounds, the preparation of suitable metabolically stable carbon-14 labels were required.[12] In this paper, we present a convenient synthetic pathway for the synthesis of a series of tetrahydropyrido[4,3-d] pyrimidines **2a-d** labeled with carbon-14 via benz[*amidino*-^{14}C] amidine hydrochloride **1** as a key synthetic intermediate which have been synthesized as part of a 4-step sequence from potassium [^{14}C]cyanide. Figure 1

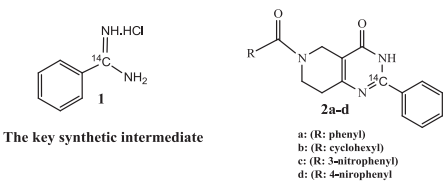

Figure 1. The key synthetic intermediate 1 for ^{14}C-labelling of tetrahydropyrido [4,3-d]pyrimidines 2a-d.

Results and discussion

In this approach, according to the synthetic pathway shown in Scheme 1, after conversion of potassium [^{14}C]cyanide **3** to zinc [$^{14}C_2$]cyanide **5** in the presence of an aqueous solution of zinc chloride, benzo[*cyano*-^{14}C]nitrile **7** was derived from reaction of iodobenzene **6** with zinc [$^{14}C_2$]cyanide **5** in the presence of tetrakis(triphenylphosphine)palladium(0) in dry DMF, with good yield.[13–15] The latter product **7** could then be converted to methyl benz[*imido*-^{14}C]imidate **8** by treatment with sodium methoxide in anhydrous methanol under N_2-atmosphere during 24 h.[16] In the next step, benz[*amidino*-^{14}C]amidine hydrochloride **1** was achieved by reaction of **8** with ammonium chloride in methanol solution.[17] Methyl 1-benzyl-4-oxopiperidine-3-carboxylate part of the molecule (**2a-d**) has been synthesized as part of a 2-step sequence from methyl acrylate **10** and benzyl amine **9**.[18] Then 6-benzyl-2-phenyl-[2-^{14}C]-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4(3H)-one **13** was produced via the coupling of methyl 1-benzyl-4-oxopiperidine-3-carboxylate **12** with benz[*amidino*-^{14}C] amidine hydrochloride **1** in the presence of a solution of sodium ethoxide in dry ethanol in 62% yield. The latter product **13** could then be converted to 2-phenyl-[2-^{14}C] -5,6,7,8-tetrahydropyrido [4,3-d]pyrimidin-4(3H)-one **14** in quantitative yield by treatment with hydrogen gas in anhydrous ethanol in the presence of Pd/C 5% under reflux condition during 48 h.[19] In the final step, the coupling of **14** with acyl chloride **15a-d** was carried out in the presence of

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triethylamine and DMAP in THF, and 6-acyl-2-phenyl-[2-^{14}C] -5,6,7, 8-tetrahydropyrido[4,3-d]pyrimidin-4(3H)-one **2a-d** were achieved in good yield.[20]

Experimental

Barium [^{14}C] carbonate (235.9 MBq/mmol) was converted to potassium [^{14} C]cyanide according to the standard procedure.[21] Infrared (IR) spectra were recorded on a Nicolet IR 550 spectrometer (USA) and all ^{1}H-NMR spectra were recorded on Bruker AVANCE 500, 400, or 300 MHz spectrometers (Germany). HPLC: equipment consisted of: a Waters 1525 Binary HPLC pump (USA), a Waters 2487 Dual λ Absorbance Detector, a Waters Breeze Data processing system, Column: μ Bondapak$_{18}$ (150 × 4.6 mm), and 5 μm diameters and uv detection at λ = 254 nm. The isocratic elution was used for chromatographic separation in room temperature. The eluent was CH_3CN: H_2O: triethylamine (600 : 400 : 0.75) with flow rate: 1 mL/min. Radioactivity was determined using a Beckman LS6500 (USA) liquid scintillation spectrometer. Mass spectra were obtained on a Finnigan TSQ-70 instrument (USA).

Zinc[$^{14}C_2$]-cyanide 5

To a solution of zinc chloride **4** (710 mg) in water (2 mL) was added dropwise an aqueous solution of potassium [^{14}C]cyanide **3** (450 mg, 1630 MBq, 235.45 MBq/mmol) in water (4 mL) at room temperature. Precipitation of the white zinc [$^{14}C_2$]cyanide **5** started immediately. The reaction mixture was stirred at room temperature for 5 min and then centrifuged. The supernatant was removed and the remaining solid was washed with water (4 × 3 mL) and diethyl ether (2 × 3 mL). The obtained white crystals were dried overnight by using high vacuum, affording the desired product **5** (391 mg, 1561 MBq, 468.7 MBq/mmol) in 95.7% yield.

Benzo[*cyano*-^{14}C]nitrile 7

Iodobenzene **6** (1.3 g) , zinc [$^{14}C_2$]-cyanide **5** (360 mg, 1437.2 MBq, 468.7 MBq/mmol), and tetrakis(triphenylphosphine) palladium(0) (352 mg) were weighed in a dry flask charged with argon. Freshly deoxygenated DMF (20 mL) was added and yellow slurry was heated to 80°C under argon until HPLC showed no starting material remaining (1-2 h). The mixture was cooled to room temperature, diluted with ethyl acetate (200 mL), and washed twice with ammonium hydroxide (2N, 40 mL). The ethyl acetate solution was then washed with brine (20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*, and the residue was purified by silica gel chromatography by using ethyl acetate: Hexane (15%) as eluant to give the title compound **7** (567 mg, 1269 MBq, 230.53 MBq/mmol) in 88.3% yield. IR(KBr): 3092, 2240,1600, 1490, and 1450 cm^{-1}.

Benz[*amidino*-^{14}C]amidine hydrochloride 1

A catalytic amount of sodium metal (15 mg, 0.65 mmol) was dissolved in 10 mL dry methanol and benzo[*cyano*-^{14}C]nitrile **7** (550 mg, 1230.9 MBq, 230.53 MBq/mmol) was added, and the reaction was allowed to stir under N_2-atmosphere for 24 hours at 35-40°C. Ammonium chloride (300 mg) was added, and stirring was continued for an additional 24 hours at 35-40°C. The reaction mixture was concentrated under reduced pressure and the crude residue was washed with Et_2O (3 × 15 mL), dissolved in ethanol (15 mL), and filtered. The organic solvent was removed under reduced pressure to give the product **1** (457 mg, 672 MBq, 230.13 MBq/mmol) as white solid in 54.6% yield.

^{1}H NMR (400 MHz, DMSO): δ 8.40 (4H, sb, N**H**.HCl, NH_2), 7.87 (2H, d, *J* = 7.6 Hz, ArH), 7.72 (1H, t, *J* = 7.3 Hz, ArH), 7.59 (2H, t, *J* = 7.7 Hz, ArH), MS (70 eV): *m/z* = 123 [M+H] $^{+}$.

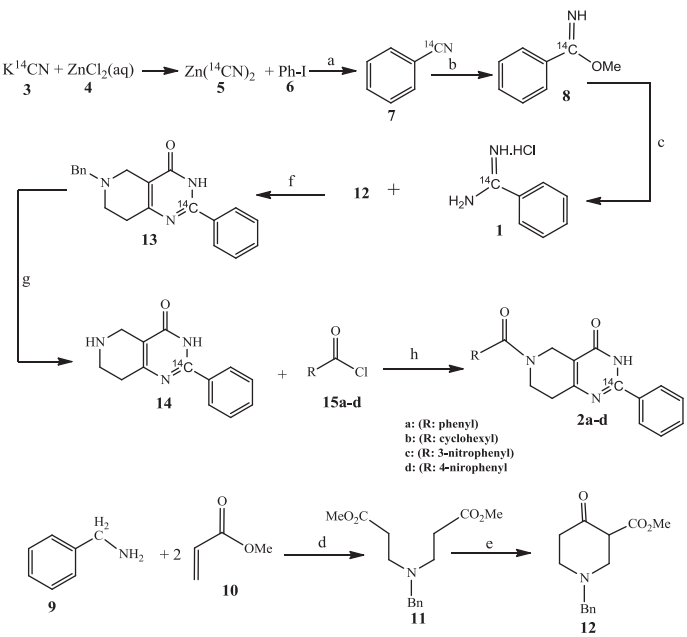
3-[(2-Methoxycarbonylethyl) benzyl amino]propionic acid methyl ester 11

To a stirred solution of methyl acrylate **10** (3.2 mL, 35.5 mmol) in methanol (8 mL) was slowly added a solution of benzylamine **9** (1 mL, 9.2 mmol) in methanol (8 ml) and was heated under reflux overnight. The residue were concentrated under reduced pressure to give the product **11** (2.54 g) as yellow oil in 99% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.17 (5H, m, ArH), 3.61 (6H, s, OCH_3), 3.55 (2H, s, N**CH$_2$**Ph), 2.76 (4H, *t*, *J*=7.2 Hz, NCH_2), 2.43 (4H, *t*, *J*=7.2 Hz, $COCH_2$). ^{13}C NMR (300 MHz, $CDCl_3$): δ 172.87 (CO), 138.99 (Ar), 128.67 (Ar), 128.18 (Ar), 127 (Ar), 58.30 (N**CH$_2$**Ph), 51.47 (OCH_3), 49.17(NCH_2), 32.58 (CO**CH$_2$**).

Methyl 1-benzyl-4-oxopiperidine-3-carboxylate 12

The amine **11** (2.4 g, 8.6 mmol) was added dropwise under stirring to a suspension of fresh sodium methoxide* (698 mg, 12.90 mmol) in dry



Scheme 1. a) Pd(PPh$_3$)$_4$, DMF; b) NaOMe, MeOH; c) NH_4Cl, MeOH; d) MeOH, Heat; e) NaOMe, Toluene; f) NaOEt, EtOH; g) Pd/C 5%, EtOH, H_2(g); h) DMAP, Et_3N, THF.

toluene (520 mL). The mixture was stirred for 48 hours under reflux condition then cooled to 0°C and poured into water. The mixture was stirred until the ketone sodium salt dissolved completely, the organic phase was separated and the aqueous phase was neutralized with acetic acid and extracted with toluene (85 mL). The combined toluene phases were dried over Na_2SO_4 and evaporated under reduced pressure to give the pure product **12** (960 mg, 3.9 mmol) as yellow solid in 45% yield. * Sodium methoxide: Sodium (300 mg, 13 mmol) dissolved in dry methanol (50 mL), after complete dissolving under nitrogen, the organic solvent evaporated under reduced pressure to give the fresh sodium methoxide (704 mg, 13 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71-7.60 (dd, 2H, $J_1 = 2.5$ Hz, $J_2 = 7.5$ Hz, ArH), 7.48-7.38 (*m*, 3H, ArH), 4.34-4.16 (*m*, 2H, Ph**CH$_2$**N), 4.01-3.88 (db, 1H), 3.75 (s, 3H, OCH_3), 3.58-3.44 (*m*, 2H), 3.35-3.17 (*m*, 1H), 3.07-2.91 (*m*, 1H), 2.49 (dt, 1H, $J_1 = 18.6$ Hz , $J_2 = 4.6$ Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.42 (CH_2**CO**CH), 167.97 (CH**CO**OCH_3), 131.33 (Ar), 130.37 (Ar), 129.44 (Ar), 127.86 (Ar), 91.54 (N**CH$_2$**Ph), 59.19 (CH**CH$_2$**N), 52.13 (CO**CH**CO), 46.92 (CH_2**CH$_2$**N), 46.53 (OCH_3), 25.36 (**CH$_2$**CO).

6-Benzyl-2-phenyl-[2-^{14}C]-5,6,7,8-tetrahydro-pyrido[4,3-d] pyrimidin-4(3H)-one 13

To a solution of methyl 1-benzyl-4-oxopiperidine-3-carboxylate **12** (645 mg, 2.61 mmol) and benz[*amidino*-^{14}C]amidine hydrochloride **1** (400 mg, 588 MBq, 230.13 MBq/mmol) in dry ethanol (2.1 mL) was added a solution of sodium (188 mg) in dry ethanol (2.1 mL). The mixture was heated under reflux for 24 h then evaporated to dryness under reduced pressure. The residue was suspended in water overnight until appearing solid crystal was filtered off and washed with water. The residue was recrystallized from ethanol to give the product **13** (505 mg, 363 MBq, 227.90 MBq/mmol) as white solid in 62% yield. ($R_t = 3.18$ min from HPLC analysis according to the aforementioned condition), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (2H, d, , $J = 8.2$ Hz, ArH), 7.55-7.26 (8H, *m*, ArH), 3.73 (2H, s, Ph**CH$_2$**N(CH_2)CH_2), 3.51 (2H, s, BnN**CH$_2$**C), 2.89-2.82 (2H, m, N**CH$_2$**CH_2C), 2.82-2.73 (2H, *m*, NCH_2**CH$_2$**C). MS (70 eV): *m/z* = 319 (M^+).

2-Phenyl-[2-^{14}C] -5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4 (3H)-one 14

The compound **13** (475 mg, 341 MBq, 227.90 MBq/mmol) was dissolved in 50 mL ethanol. The catalyst Pd/C 5% (100 mg) was added and the resulting suspension was hydrogenated under reflux for 48 h. After removal of the catalyst by filtering, the organic solvent was evaporated under reduced pressure. The product **14** was obtained as a white solid (329 mg, 322 MBq, 222.17 MBq/mmol) in 94 % yield. ($R_t = 3.46$ min from HPLC analysis according to aforementioned condition), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06-7.99 (2H, *m*, ArH), 7.45-7.43 (3H, *m*, ArH), 3.87 (2H, s, NH**CH$_2$**C), 3.16 (2H, *t*, $J = 5.8$ Hz, NH**CH$_2$**CH_2C), 2.74 (2H, *t*, $J = 5.8$ Hz, $NHCH_2$**CH$_2$**C), MS (70 eV): *m/z* = 230 $[M+H]^+$.

6-Benzoyl-2-phenyl-[2-^{14}C]-5,6,7,8-tetrahydropyrido[4,3-d] pyrimidin-4(3H)-one 2a

A mixture of **14** (100 mg, 97.94 MBq, 222.17 MBq/mmol), benzoyl chloride **15a** (125 mg, 0.88 mmol), triethylamine (185 µl) and DMAP (5 mg) in THF (50 mL) was stirred vigorously at room temperature for 12 h, then the organic solvent evaporated under reduced pressure and the reaction mixture was quenched by addition of potassium hydroxide (50 mL, 1 M) and extracted with ethyl acetate, the solvent and triethylamine evaporated under reduced pressure to give the product **2a** (115 mg, 76.49 MBq, 220.16 MBq/mmol) as white solid in 78.1%yield. ($R_t = 2.75$ min from HPLC analysis according to the aforementioned condition), ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.06 (2H, d, $J = 6.9$ Hz, ArH), 7.58-7.40 (8H, *m*, ArH), 4.74 (1H, sb, CON**CH$_2$**C), 4.48 (1H, sb, CON**CH$_2$**C), 4.06 (1H, sb, CON**CH$_2$**CH_2C), 3.70 (1H, sb, CON**CH$_2$**CH_2C) 2.91 (2H, sb, $CONCH_2$**CH$_2$**C). ^{1}H NMR (400 MHz, $CDCl_3$, 313 K): δ 8.06 (2H, d, $J = 7.5$ Hz, ArH), 7.57-7.38 (8H, *m*, ArH), 4.57 (2H, sb, CON**CH$_2$**C), 3.92 (2H, sb, CON**CH$_2$**CH_2C), 2.89 (2H, s, $CONCH_2$**CH$_2$**C). MS (70 eV): *m/z* = 333 (M^+).

6-(Cyclohexanecarbonyl)-2-phenyl-[2-^{14}C]-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4(3H)-one 2b

The **2b** was prepared according to the described procedure in the earlier texts for **2a**, by stirring **14** (80 mg, 78.35 MBq, 222.17 MBq/mmol), cyclohexanecarbonyl chloride **15b** (100 mg, 0.68 mmol), triethylamine (148 µl) and DMAP (4 mg) in THF (40 mL) at room temperature during 12 h. The title compound **2b** (85 mg, 55.39 MBq, 219.61 MBq/mmol) was obtained in 71% yield. ($R_t = 2.69$ min from HPLC analysis according to aforementioned condition), ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ 8.00-8.13 (2H, *m*, ArH), 7.47-7.60 (3H, *m*, ArH), 4.60 (1H, s, CON**CH$_2$**C), 4.50 (1H, s, CON**CH$_2$**C), 3.88 (1H, *t*, $J = 5.2$ Hz, CON**CH$_2$**CH_2C), 3.77 (1H, sb, CON**CH$_2$**CH_2C), 2.75-2.90 (2H, *m*, $CONCH_2$**CH$_2$**C), 2.5-2.68 (1H, *m*, NH), 1.62-1.88 (5H, *m*, cyclohexane), 1.10-1.40 (5H, *m*, cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$, 313 K): δ 8.37 (2H, b, ArH), 7.48-7.60 (3H, *m*, ArH), 4.53 (2H, sb, CON**CH$_2$**C), 3.86 (2H, sb, CON**CH$_2$**CH_2C), 2.82 (2H, sb, $CONCH_2$**CH$_2$**C), 2.60 (1H, sb, NH), 1.55-1.90 (6H, *m*, cyclohexane), 1.15-1.40 (4H, *m*, cyclohexane). MS (70 eV): *m/z* = 339 (M^+).

6-(3-Nitrobenzoyl) -[2-^{14}C] -2-phenyl-5,6,7,8-tetrahydropyrido [4,3-d]pyrimidin-4(3H)-one 2c

The **2c** was prepared according to the described procedure mentioned earlier in the texts for **2a**, by stirring **14** (80 mg, 78.35 MBq, 222.17 MBq/mmol), 3-nitrobenzoyl chloride **15c** (135 mg, 0.73 mmol), triethylamine (148 µl) and DMAP (4 mg) in THF (40 mL) at room temperature during 12 h. The title compound **2c** (93 mg, 54.39 MBq, 219.90 MBq/mmol) was obtained in 69.4 % yield. ($R_t = 2.81$ min from HPLC analysis according to the aforementioned condition), ^{1}H NMR (400 MHz, DMSO, 298 K): δ 8.38-8.23 (*m*, 2H, ArH), 8.06 (sb, 2H, ArH), 7.96 (1H, d, $J = 7.6$ Hz, ArH), 7.78 (1H, t, $J = 7.9$ Hz, ArH), 7.60-7.46 (3H, *m*, ArH), 4.51 (1H, s, CON**CH$_2$**C), 4.25 (1H, s, CON**CH$_2$**C), 3.94 (1H, s, CON**CH$_2$**CH_2C), 3.60 (1H, s, CON**CH$_2$**CH_2C), 2.78 (2H, s, $CONCH_2$**CH$_2$**C). ^{1}H NMR (400 MHz, DMSO, 353 K): δ 8.34-8.23 (2H, *m*, ArH), 8.13-8.03 (*m*, 2H, ArH), 7.93 (dt, 1H, $J_1 = 4.0$ Hz, $J_2 = 1.3$ Hz, ArH), 7.78 (1H, *t*, $J = 8.4$ Hz, ArH), 7.60-7.44 (*m*, 3H, ArH), 4.41 (s, 2H, CON**CH$_2$**C), 3.78 (s, 2H, CON**CH$_2$**CH_2C), 2.80 (2H, *t*, $J = 8.4$ Hz, $CONCH_2$**CH$_2$**C). MS (70 eV): *m/z* = 378 (M+).

6-(4-Nitrobenzoyl)-2-phenyl-[2-^{14}C]-5,6,7,8-tetrahydropyrido [4,3-d]pyrimidin-4(3H)-one 2d

The **2d** was prepared according to the described procedure mentioned earlier in the texts for **2a**, by stirring **14** (60 mg, 58.76 MBq, 222.17 MBq/mmol), 4-nitrobenzoyl chloride **15d** (99 mg, 0.53 mmol), triethylamine (111 µl) and DMAP (3 mg) in THF (30 ml) at room temperature during 12 h. The title compound **2d** (67 mg, 39.01 MBq, 218.92 MBq/mmol) was obtained in 66.4% yield. ($R_t = 2.85$ min from HPLC analysis according to aforementioned condition), ^{1}H NMR (400 MHz, DMSO, 298 K): δ8.35-8.15 (4H, *m*, ArH), 7.72 (2H, *t*, $J = 9$ Hz, ArH), 7.30 (3H, sb, ArH), 4.38 (1H, s, CON**CH$_2$**C), 4.07 (1H, s, CON**CH$_2$**C), 3.88 (1H, *t*, $J = 5.9$ Hz, CON**CH$_2$**CH_2C), 3.46 (1H, *t*, $J = 5.4$ Hz, CON**CH$_2$**CH_2C), 2.68-2.54 (2H, *m*, $CONCH_2$**CH$_2$**C). ^{1}H NMR (400 MHz, DMSO, 353 K): δ 8.35-8.05 (4H, *m*, ArH), 7.69 (2H, d, $J = 8.7$ Hz, ArH), 7.36-7.22 (3H, *m*, ArH), 4.24 (2H, sb, CON**CH$_2$**C), 3.72 (2H, sb, CON**CH$_2$**CH_2C), 2.61 (2H, t, $J = 10.9$ Hz, $CONCH_2$**CH$_2$**C). MS (70 eV): *m/z* = 378 (M^+).

Conclusion

In this paper, we have presented a convenient synthetic pathway for labeling of a series of 6-acyl-2-phenyl-5,6,7,8-tetrahydropyrido [4,3-d]pyrimidin-4(3H)-ones with carbon-14 in the 2-position of pyrimidinone moiety by using benz[*amidino*-^{14}C]amidine hydrochloride as a key synthetic intermediate.

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Conflict of Interest

The authors did not report any conflict of interest.

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