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Research Article

Syntheses of [^{14}C] and [$^{2}H_4$]PD0205520, an inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor

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Summary

5-(4-Methyl-piperazin-1-yl)-pent-2-ynoic acid [4-(3-chloro-4-fluoro-phenylamino)-pyrido[3,4-d]pyrimidin-6-yl]-amide, PD0205520, was under investigation as a potential inhibitor of the tyrosine kinase (TK) activity of the epidermal growth factor receptor (EGFR) for cancer treatment. Both radio- and stable-isotope-labeled compounds were required for drug absorption, distribution, metabolism and excretion (ADME) and quantitative mass spectrometry bio-analytical studies. PD0205520 ^{I4}C-labeled in the pyrimidine ring system was prepared in seven steps in an overall radiochemical yield of 26% from [^{14}C]thiourea. PD0205520 ^{2}H-Iabeled in the piperazine ring was synthesized in four steps in a 32% overall yield. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: carbon-14; deuterium; [^{14}C]thiourea; [^{2}H]piperazine; [^{14}C]formamidine acetate; EGFR TK inhibitor; anticancer

Introduction

The epidermal growth factor receptor (EGFR) is a marker for poor prognosis in a significant proportion of human tumours.[1] Selective inhibitors of tyrosine phosphorylation by EGFR have become an important class of potential anticancer drugs.[2a,b] 5-(4-Methyl-piperazin-1-yl)-pent-2-ynoic acid [4-(3-chloro-4-fluoro-phenylamino)-pyrido[3,4-d]pyrimidin-6-yl]-amide, PD0205520, was under investigation as a potential EGFR tyrosine kinase (TK) inhibitor for chronic therapy in adjuvant treatment of cancers and in chemo-prevention in individuals with a high risk for developing cancer. Both radio- and stable-isotope-labeled compounds were required for drug absorption, distribution,

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metabolism and excretion (ADME) and use as an internal standard for quantitative mass spectrometry (MS) bio-analytical studies. In this paper we wish to report the efficient syntheses of [^{14}C]PD0205520 and [^{2}H]PD0205520.

Results and discussion

From the retrosynthetic analysis, the target could be prepared from pyramidine ring system **1** and a side chain, *N*-methyl piperazine derivative **3** (Figure 1). The former pyramidine ring system **1** might be made from the condensation of 5-amino-2-fluoropyridine-4-carboxylic acid **4** and formamidine acetate **5**, both of which may be the radiolabeled starting material. The latter *N*-methyl piperazine derivative **3** could be easily labeled with deuterium. Based on the above analysis, the efficient synthetic approaches to radiolabeled 5-amino-2-fluoropyridine-4-carboxylic acid **4** or formamidine acetate **5**, and [^{2}H]*N*-methyl piperazine derivative **3** were developed.

Synthesis of [^{14}C]PD0205520

At the beginning of our development work, we attempted to label the carboxylic group at the 4-position of pyridine by a carboxylation reaction (Scheme 1). With a large excess CO_2 gas, compound **10** was prepared in 64% yield. However, when CO_2 gas was generated from $BaCO_3$ (1.2 equiv.) the carboxylation reaction gave a poor yield (24%) with various bases (*n*-BuLi/TMEDA, *s*-BuLi/TMEDA, LDA) and solvents (THF, diethyl ether, MTBE).

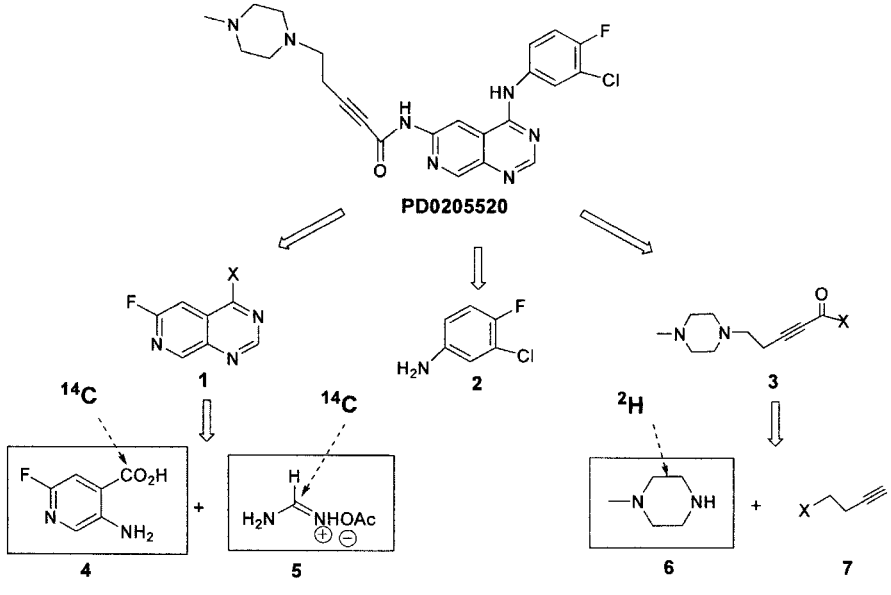

Figure 1. Retrosynthesis of [^{14}C]/[^{2}H]PD0205520

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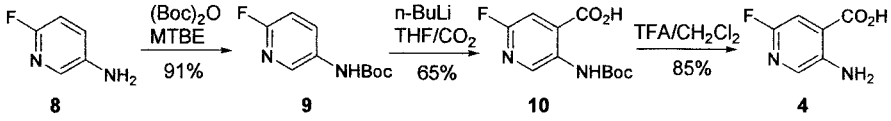
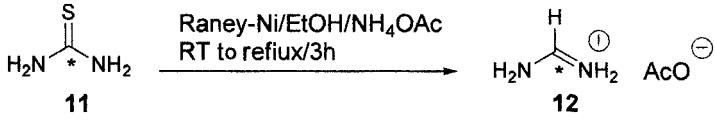


Scheme 1. Synthesis of 5-amino-2-fluoropyridine-4-carboxylic acid 4

Therefore, compound **4** was synthesized as a cold intermediate in three steps from the commertially available material, 5-amino-2-fluoropyridine **8** (Scheme 1).

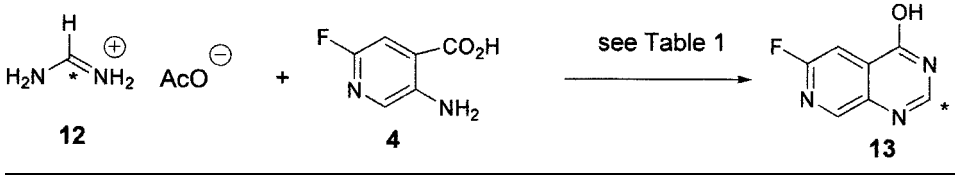
A detailed literature search revealed that the unlabeled formamidine HCl salt can be prepared by the reduction of thiourea with Raney-Ni in the presence of NH_4Cl.[3] By changing NH_4Cl to NH_4OAc we were able to prepare the desired [^{14}C]formamidine acetate (FAA) **12** in nearly quantitative yield (Scheme 2).

The ring closure of 5-amino-2-fluoropyridine-4-carboxylic acid **4** with 2.2 equiv. formamidine acetate in *n*-butanol was quite straightforward giving the desired product in 65% yield,[4] while reducing the mole ratio of formamidine acetate from 2.2 equiv. to 1.5 equiv. resulted in a much lower yield. Several solvents were screened in hopes of improving the yields (Table 1). By addition of triethylamine (TEA, 1.1 equv.) to the reaction mixture in methoxylethanol,



Scheme 2. Synthesis of [^{14}C] formamidine acetate 12

Table 1. Solvent selection for ring closure reaction



Entry	Solvents	4/FAA (mole ratio)	Reaction time (h)	Yield (%)
1	*n*-Butanol	1:2.2	15	65
2	*n*-Butanol	1:1.5	15	37
3	DBE	1:1.5	15	32
4	Methoxyethanol	1:1.5	15	47
5	Methoxyethanol/TEA	1:1.2	5	66

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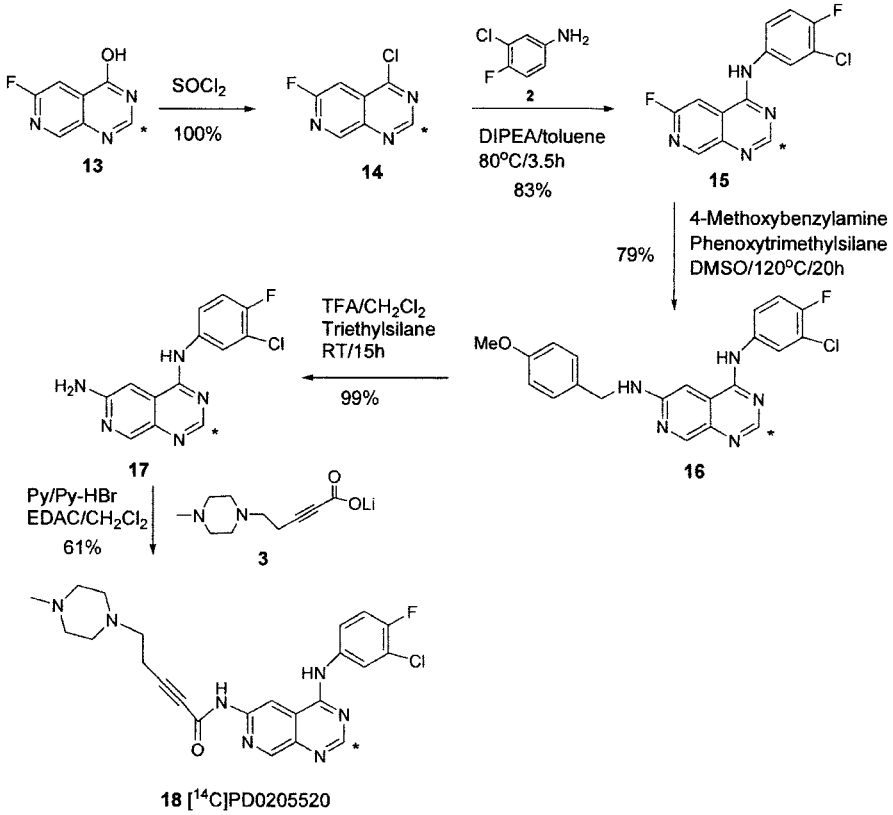
the reaction time was reduced from 15 to 5 h and the yield increased from 47 to 66% with less excess [^{14}C]formamidine acetate (FAA). The addition of triethylamine changes the pH of the reaction mixture, and might increase the reactivity of formamidine **12**.

[^{14}C]PD0205520 was then prepared in five steps in an overall radiochemical yield of 39% (Scheme 3). Conversion of fluoropyrido[3,4-d] [2-^{14}C]pyrimidin-4(3H)-one **13** to its chloride **14** was performed in a typical manner by reaction with thionyl chloride. The crude chloride **14** was used directly in the aniline **2** substitution to obtain compound **15** in 83% yield. To convert the 6-fluoro to a 6-amino group in the pyridine ring, a known two-step reaction approach[5] was modified. By addition of phenoxytrimethylsilane to the reaction mixture we were able to isolate the pure product **16** by simple solvent trituration. Also the application of triethylsilane for the de-protection reaction allowed us to reduce the amount of TFA and lower the reaction temperature from 120 to 25°C, and obtain almost quantitative yield of **17**. In the final coupling reaction, due to the instability of the free acid of **3** the excess lithium salt **3** was used to form the amide **18**, [^{14}C]PD0205520.



Scheme 3. Synthesis of [^{14}C]PD0205520

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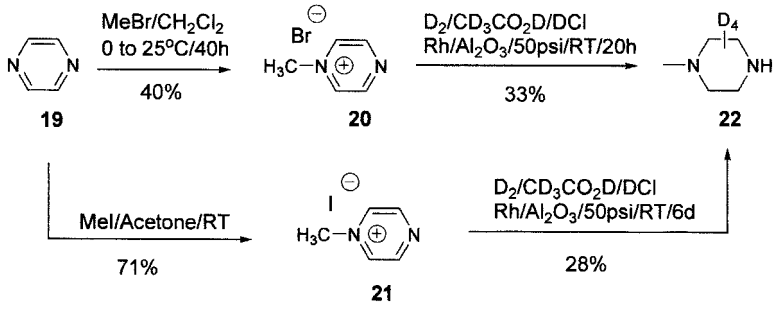
Synthesis of [$^{2}H_4$]PD0205520

The stable-isotope-labeled compound could be synthesized using [$^{13}C_2$, ^{15}N]thiourea by following the procedures for the seven-step synthesis of [^{14}C]PD0205520. However, a short and less expensive synthesis could be developed by preparing a deuterium-labeled side chain.

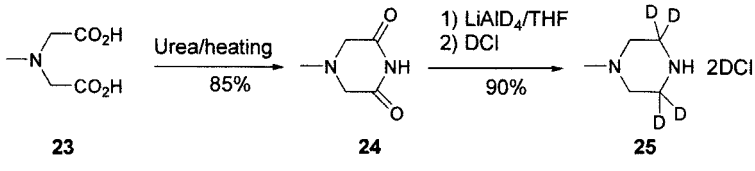
The hydrogenation of *N*-methyl pyrazine halide salts with deuterium gas in the presence of catalyst, Rh/Al_2O_3, was first investigated by modifying a known procedure[6] (Scheme 4). However, changing solvents from ethanol to acetic acid and pressure from 30 to 50 psi did not improve the yields (38%). It was also difficult to purify the material due to low boiling point and high water solubility of *N*-methyl[$^{2}H_4$]piperazine **22**.

The $LiAlD_4$ reduction reaction of l-methyl-3,5-piperazinedione **24** was straightforward,[7] and the pure compound **25** can be isolated as a DCl salt simply by the addition of 12 M DCl to the solution of the crude compound in THF (Scheme 5).

N-Alkylation of *N*-methyl piperazine **25** with tosylate **26** was studied using a different solvent and a limited amount of the labeled compound **25** (Table 2). For the preparation of unlabeled version of compound **27**, *N*-methylpiperazine was used not only as a reactant but also as a solvent. However, using heptane as a solvent and 1.2:1 mole ratio of **25** and **26**, we were able to obtain the desired labeled compound **27** in 70% yield (Table 2).



Scheme 4. Synthesis of *N*-methyl[$^{2}H_4$]piperazine 22



Scheme 5. Synthesis of *N*-methyl[$^{2}H_4$]piperazine 25

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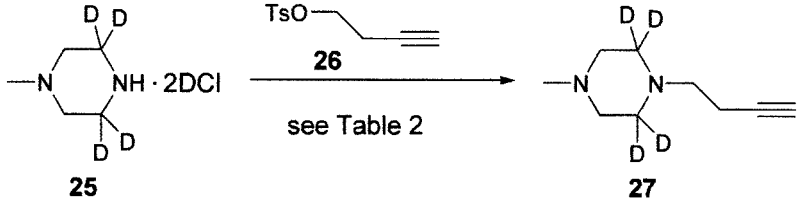
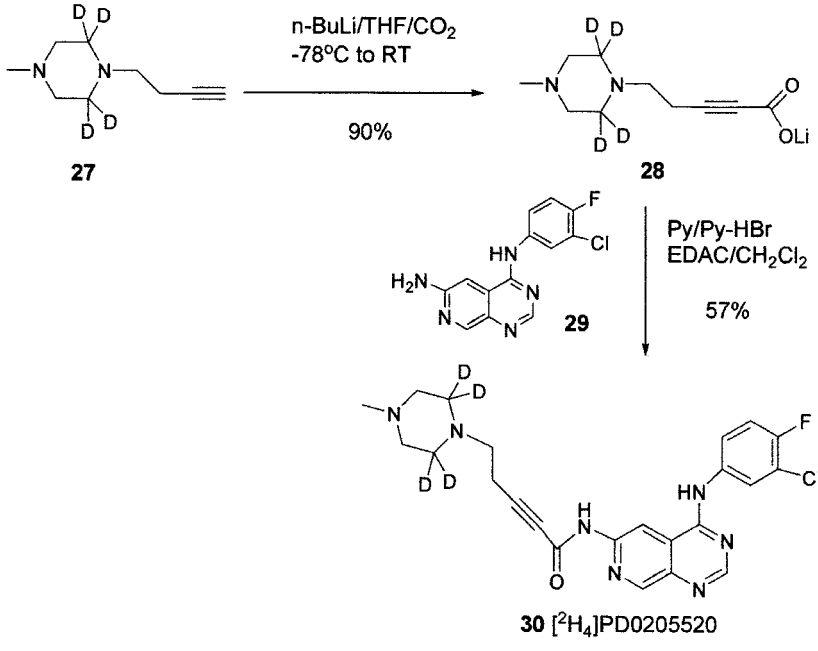
Table 2. Alkylation of *N*-Methyl [$^2H_4$]piperazine 27



Entry	Condition (equiv. **25**/equiv. **26**)	Yield (%)
1	100°C/3 h(10/l)	71
2	K_2CO_3/THF/reflux/15 h (1.2/1)	35
3	K_2CO_3/MeCN/reflux/15 h (1.2/1)	45
4	K_2CO_3/Heptane/reflux/15 h (1.2/1)	70

The carboxylation of the alkyne **27** produced the acid lithium salt **28** which was isolated instead of the free acid since the latter was not stable and hard to purify. For the unlabeled synthesis, the final amination reaction was carried out using a large excess of unlabeled **28** to give 55% yield of PD0205520. By reversing the mole ratio of **28** (1 equiv.) and **29** (4 equiv.) we were able to produce the final labeled product **30**, [$^2H_4$]PD0205520, in 61% yield (Scheme 6).



Scheme 6. Synthesis of [$^2H_4$]PD0205520

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In summary, both [^{14}C] and [$^{2}H_4$]PD0205520 were prepared in good overall yields from [^{14}C]thiourea and $LiAD_4$, respectively. The preparation of the key labeled materials, [^{14}C]formamidine acetate **12** and *N*-methyl[$^{2}H_4$]piperazine **25**, by simple reduction reactions allowed us to make the target compounds more efficiently.

Experimental

All reactions were carried out under an atmosphere of nitrogen unless otherwise stated. ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 or 400 MHz. Chemical purity of all labeled compounds was determined by HPLC and GC-MS or LC-MS. Purifications were done by flash column chromatography on Biotage Flash 40 system. $LiAlD_4$ (98 at% D) was purchased from Cambridge Isotope Lab. [^{14}C]Thiourea (600 mCi, 57 mCi/mmol) was purchased from PerkinElmer Life Sciences. All prepared stable-isotope-labeled compounds contained less than 0.1% of unlabeled material based on LC-MS analysis.

tert-Butyl N-(6-fluoro-3-pyridyl)carbamate (**9**)

To a solution of 5-amino-2-fluoro-pyridine (5.60 g, 51.4 mmol) in MTBE (12 ml), was added di-*tert*-butyl dicarbonate (44.8 g, 205.5 mmol) at room temperature. The mixture was heated to 40–45°C. The resulting mixture was stirred for 10 h. Activated carbon (2.0 g) was added to the reaction mixture, and then the mixture was filtered. The filtrate was added to hexane (50 ml), to form the precipitate. The product was filtered and washed with additional hexane. Drying at 50°C under vacuum gave the titled compound **9** as gray-colored crystals (9.92 g, 91%): m.p. 114–116°C (lit.[4]113.5–115°C).

2-Fluoro-5-(tert-butoxycarbonylamino)yridine-4-carboxylic acid (**10**)

To a mixture of the compound **9** (5.0 g, 23.5 mmol), TMEDA (8.75 ml) and MTBE (70 ml) was added a solution of *n*-BuLi (2.5 M in hexane, 22.30 ml) at −70°C. After completion of the addition, the mixture was heated to −10 to −15°C, and held at this temperature for 3 h. Dry CO_2 gas was sparged at −70°C for 2 h. The mixture was heated to 5°C, and then water (60 ml) was added. The aqueous phase was collected and the organic phase was extracted with 1 M NaOH. To the combined aqueous solution was added MTBE (20 ml). 6 M HCl was then added slowly to this mixture to adjust the pH to 2.5–3.0. The product as precipitate was filtered and was washed with MTBE and hexane (1:1). Drying under vacuum at 50°C gave the title compound **10** (3.84 g, 64%): m.p. 252–254°C (lit.[4] m.p. 252–254.5°C).

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5-Amino-2-fluoropyridine-4-carboxylic acid (**4**)

To a solution of the compound **10** (6.0 g, 23.4 mmol) in CH_2Cl_2 (20 ml) was added trifluoroacetic acid (10.8 ml) at 0°C. The resulting solution was stirred at room temperature for 3 h. The mixture was concentrated under vacuum to an oily residue. MTBE (16 ml) was added to the residue to form a slurry, which was then filtered and washed with MTBE. Drying under vacuum at 50°C gave the title product **4** as an off-white solid (3.12 g, 85%): m.p. 259°C (lit.[4] m.p. 259°C decomp).

[^{14}C]formamidine acetate (**12**)

[^{14}C]Thiourea (600 mCi, 57 mCi/mmol) and NH_4OAc (1.2 g, 15.7 mmol) were suspended in dry EtOH (15 ml), and then heated at 85°C for 15 min to form a homogenous solution. To this solution was added Raney-Ni (5 g, wet in EtOH) rapidly in small portions. The resulting mixture was stirred at 90–95°C for 3 h. A little charcoal was added to the mixture, and then the solid was filtered off, washed with hot EtOH (20 ml). The filtrate was evaporated to dryness. The residue was extracted with dry EtOH (10 ml). Any solid was removed by filtration. The filtrate was evaporated with toluene (10 ml) to dryness. Drying the residue under vacuum for 15 h at room temperature gave the product **12** as a greenish solid (1.21 g, 100%). TLC RCP > 98%, $R_f = 0.11$, silica gel, EtOAc/MeOH/NH_4OH (40/4/1).

6-Fluoropyrido[3,4-d] [2-^{14}C]pyrimidin-4(3H)-one (**13**)

The compound **4** (1.72 g, 8.80 mmol) and [^{14}C] formamidine acetate **12** (1.10 g, 10.52 mmol) were dissolved in 2-methoxylethanol (10 ml) and triethylamine (1.5 ml). The resulting solution was stirred at 140°C for 1.5 h, and then evaporated to remove a half of the solvent. After cooling to 25°C, the precipitate was filtered off, and washed with 2-methoxylethanol (2 × 2 ml), and then suspended in saturated $NaHCO_3$ solution (10 ml). The suspension was stirred for 30 min at 25°C, and then cooled at 0°C. The slurry was filtered and the cake was washed with water. Drying under vacuum at 50°C for 15 h gave the title product **13** as a rusty red solid (0.957 g, 66%). TLC RCP > 98%, $R_f = 0.33$, silica gel, EtOAc/hexane (2:1), m.p. 285°C (lit.[4] 287°C decomp).

4-(3-Chloro-4-fluoro-phenylamino)-6-fluoro-pyrido [3,4-d] [2-^{14}C]pyrimidine (**15**)

A suspension of the compound **13** (0.491 g, 2.98 mmol) in $SOCl_2$ (4 ml) and DMF (0.1 ml) was heated at 65–75°C for 20 h. The reaction mixture was evaporated to remove the excess $SOCl_2$ and HCl. The residue was dissolved in toluene (5 ml), and the solution was evaporated again to dryness (0.54 g). To a solution of the above crude product in dry toluene (7 ml), was added 3-chloro-4-fluoroaniline (0.472 g, 3.2 mmol), and then diisopropylethylamine (0.52 ml).

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The resulting mixture was stirred at 80–85°C for 7 h. The solvent was evaporated, and then co-evaporated again with MeCN (3 ml) to dryness under vacuum. The residue was stirred in MeCN (4 ml) and water (4 ml) at 50°C for 20 min. After cooling to room temperature, the precipitates were collected and washed with MeCN/H_2O (1:1, 1 ml). Drying under vacuum at room temperature for 10 h gave the product **15** as a yellowish solid (0.725 g, 83%): TLC RCP > 98%, $R_f = 0.46$, silica gel, EtOAc/hexane (2/1); m.p. 267–269°C (lit.[5] m.p. 267–269°C).

4-[3-Chloro-4-fluoro-phenylamino]-6-(4-methoxylbenzylamino)-pyrido [3,4-d] [^{14}C]pyrimidine (**16**)

A mixture of the compound **15** (0.725 g, 2.47 mmol), *p*-methoxyl-benzylamine (0.563 g, 4.10 mmol) and phenoxytrimethylsilane (0.342 g) in DMSO (3.6 ml) was stirred at 120°C for 20 h. The solid in the reaction mixture was filtered off and washed with DMSO (1 ml) and MeOH (3 ml). The filtrate was evaporated under vacuum to dryness. The residue was dissolved in EtOAc (1 ml), and cooled to room temperature. The precipitates were collected and washed with EtOAc/Hexane (2:1, 2 ml). Drying the solid under vacuum at room temperature for 10 h gave the product **16** as a yellowish solid (0.80 g, 79%): TLC RCP > 98%, $R_f = 0.33$, silica gel, EtOAc: m.p. 196–197°C (lit.[5] 196–197°C).

4-[3-Chloro-4-fluoro-phenylamino]-6-amino-pyrido [3,4-d] [^{14}C]pyrimidine (**17**)

To a suspension of the compound **16** (0.80 g, 1.95 mmol) and triethylsilane (0.64 ml) in CH_2Cl_2 (12 ml), was added trifluoroacetic acid (3.1 ml) slowly at 0°C. The resulting solution was stirred at room temperature for 15 h, and then evaporated under vacuum to dryness. The residue was triturated with hexane (8 ml) at 55°C for 30 min. The solid was stirred in NH_3/MeOH (2.0 M, 8 ml) at 50°C for 30 min and then cooled to room temperature. The solid was filtered off. Drying under vacuum at 60°C for 20 h gave the product **17** as a yellow solid (0.56 g, 99%). TLC RCP > 98%, $R_f = 0.36$, silica gel, EtOAc/MeOH (1:1); m.p. 263–265°C (lit.[5] 263–266°C).

5-(4-Methyl-piperazin-1-yl)-pent-2-ynoic acid [4-(3-chloro-4-fluorophenylamino)-pyrido [3,4-d] [^{14}C]pyrimidin-6-yl]-amide ([^{14}C]PD0205520) (**18**)

A suspension of the compound **17** (0.425 g, 1.46 mmol), pyridine-HBr (1.62 g, 10.1 mmol), pyridine (6.5 ml) and 4-methylpiperazin-1-yl)-pent-2-ynoic acid lithium salt **3** (1.742 g, 8.6 mmol) in CH_2Cl_2 (6.5 ml) was stirred at 25°C for 10 min. To this suspension was added EDAC (1.68 g, 8.76 mmol) at 0°C. The resulting mixture was stirred at 5°C for 6.5 h. After water (10 ml) was added to the reaction mixture, the mixture was evaporated to remove CH_2Cl_2. The

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precipitate was filtered off, and washed with water (3 ml). The crude product was subjected to flash chromatography (eluent: MeOH/EtOAc/NH_3 3:1:0.1) to obtain the product (0.415 g, 61%). TLC RCP > 99%, $R_f = 0.34$, silica gel, MeOH/EtOAc/NH_4OH: 4/1/0.1; m.p. 210–212°C; ^{1}H-NMR (DMSO-d_6) δ 9.00 (s, 1H), 8.750 (s, 1H), 8.630 (s, 1H), 8.12 (d, 1H), 7.780 (m, 1H), 7.450 (t, 1H), 2.550 (s, 4H), 2.42 (b, 4H), 2.280 (b, 4H),2.11 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ 157.57, 155.62, 155.15, 153.20, 151.64, 148.02, 142.48, 136.60, 125.09, 123.90 (d), 121.49, 119.47 (d), 117.23 (d), 105.16, 89.1277.14, 56.12, 55.20, 52. 69, 46.23, 17.17; MS (ESI): 468 [M + H]. Radiochemical purity: 98.63%; Chemical purity: 99.25%; Specific activity: 61.72 μCi/mg; Total activity: 25.6 mCi. HPLC Column: HyPurity Advance 5 μ, 250 × 4.6 mm; Mobile phase: A = [0.025 M $NH_4H_2PO_4$ & 0.05 M TFA] pH 3.0 w/H_3PO_4, B = CH_3CN. Initial 25% B, gradient to 70% B over 14 min, hold A:B 30:70 to 30 min; Flow rate: 1.0 ml/min; UV detection: 240 nm.

N-methyl[$^2H_4$]piperazine dihydrochloride (**25**)

To a stirred suspension of $LiAlD_4$ (3.8 g) in dry THF (25 ml), was added dropwise a solution of l-methylpiperazine-3,5-dione **24** (3.8 g, 29.6 mmol, prepared by following Houghton's procedure[8]) in dry THF (60 ml) at room temperature. The resulting mixture was stirred at 85°C for 2.5 h, and then at room temperature for 12 h. To the reaction mixture was added ether (40 ml), D_2O (3.8 ml), 15% NaOD (3.8 ml) and D_2O (5 ml) at 0°C. The mixture was stirred at 0°C for 1 h. The precipitate was filtered off, and extracted with ether (150 ml) for 2 h using soxhlet. The combined ether layers were dried with $MgSO_4$, and then concentrated to dryness. The residue was dissolved in dry THF. To this THF solution was added concentrated DCl to make the solution strongly acidic. The acidic solution was evaporated under vacuum to dryness. The residue was lyophilized overnight. Further drying at 80°C under vacuum gave the product **25** as a white solid (4.72 g, 90%): m.p. 240–242°C (lit.[7] 241.5–243°C).

3-(N-methyl[$^2H_4$]peperazine)-prop-1-yne (**27**)

A mixture of *N*-methyl-[$^2H_4$]piperazine DCl salt **25** (3.67 g, 20.27 mmol) and K_2CO_3 (9.80 g, 70.96 mmol) was finely ground, and then heated in heptane (50 ml) at 100°C for 15 h. To the above suspension was added 3-hydroxy-prop-1-yne tosylate **26** (4.84 g, 21.5 mmol) at 50°C. The resulting mixture was heated at 110°C for 15 h. The solid was filtered off and washed with heptane (25 ml × 3). The combined heptane solution was evaporated under vacuum to give a yellowish residue, which was subjected to flash chromatography (eleunt: EtOAc/hexane, 7/3). The product **27** was obtained as a colorless liquid (2.20 g, 70%). ^{1}H-NMR ($CDCl_3$) δ 2.599 (t, 2H), 2.479 (bm, 4H), 2.364 (t, 2H), 2.307

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(s, 3H), 1.963 (t, 1H); ^{13}C-NMR ($CDCl_3$) δ 82.81, 69.32, 56.95, 54.91, 52.20 (m), 46.06, 16.95 (d); MS (ESI): 157 [M + H].

5-(4-Methyl[$^{2}H_4$]piperazin-1-yl)-pent-2-ynoic acid Li salt (**28**)

To a solution of the compound **27** (1.62 g, 10.38 mmol) in THF (32 ml), was added a solution of *n*-BuLi (2.5 M in hexane, 4.15 ml) at −78°C. The resulting solution was stirred at −78°C for 2 h. Dry CO_2 gas was sparged at −70°C for 2 h. The mixture was stirred at room temperature for 24 h, and then concentrated to dryness. The residue was then stirred with THF (2.5 ml) and MTBE (25 ml) at room temperature for 5 h. The white precipitate was collected by filtration under N_2 gas. Drying under vacuum at 60°C for 17 h gave the product **28** (1.89 g, 90%). ^{1}H-NMR (D_2O) δ 2.433 (t, 2H), 2.40–2.30 (b, 4H), 2.306 (t, 2H), 2.035 (s, 3H), 1.963 (t, 1H); ^{13}C-NMR (D_2O) δ 161.46, 82.13, 77.59, 55.21, 53.07, 50.73 (m), 44.44, 15.51; MS (ESI): 201 [M + H].

5-(4-Methyl[$^{2}H_4$]piperazin-1-yl)-pent-2-ynoic acid [4-(3-chloro-4-fluoro-phenylamino)-pyrido [3,4-d]pyrimidin-6-yl]-amide ([$^{2}H_4$]PD0205520) (**30**)

A suspension of 4-[3-Chloro-4-fluorophenylamino]-6-aminopyrido [3,4-d] pyrimidine **29** (4.50 g, 15.53 mmol), pyridine-HBr (1.0 g, 6.25 mmol), pyridine (5 ml) and 4-(*N*-methyl[$^{2}H_4$]piperazin-1-yl)-pent-2-ynoic acid lithium salt **28** (0.80 g, 3.88 mmol) in CH_2Cl_2 (5 ml) was stirred at 25°C for 20 min. To the suspension was added EDAC (1.40 g, 7.33 mmol) at 0°C. The resulting mixture was stirred at 5°C for 15 h. After water (6 ml) was added to the reaction mixture, the mixture was evaporated to dryness under vacuum. The residue was triturated with water (8 ml), and then the precipitate was collected, and subjected to flash chromatography (eluent: MeOH/EtOAc/NH_4OH, 3:1:0.1) to obtain the title product **30** (1.11 g, 61%). ^{1}H-NMR (DMSO-d_6) δ 11.43 (s, 1H), 10.32 (s, 1H), 8.99 (s, 1H), 8.76 (s, 1H), 8.61 (s, 1H), 8.09 (s, 1H), 7.77 (s, 1H), 7.44 (t, J = 9.10 Hz, 1H), 2.55 (s, 4H), 2.36–2.16 (m, 4H), 2.12 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ 157.55, 154.38 (d, J = 243.2 Hz), 155.09, 151.69, 151.55, 148.02, 142.41, 136.71, 125.05, 123.89 (d, J = 6.90 Hz), 121.57, 119.54 (d, J = 18.41 Hz), 117.24 (d, J = 21.48 Hz), 105.25, 89.18, 77.12, 56.07, 55.14, 52.07 (m), 46.45, 17.17; MS (ESI): 472 [M + H].

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