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Synthesis of isotope-labeled HSP90 inhibitor: [$^{13}CD_3$] and [^{14}C]-TAK-459

Mihaela Plesescu,* Eric L. Elliott, Yuexian Li, and Shimoga R. Prakash

[$^{13}CD_3$]-TAK-459 (1A), an HSP90 inhibitor, was synthesized from [$^{13}CD_3$]-sodium methoxide in three steps in an overall yield of 29%. The key intermediate [$^{13}CD_3$]-2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was synthesized in two steps from 2,6-dibromopyridine and stable isotope-labeled sodium methoxide. [^{14}C]-TAK-459 (1B) was synthesized from [^{14}C(U)]-guanidine hydrochloride in five steps in an overall radiochemical yield of 5.4%. The key intermediate, [^{14}C]-(*R*)-2-amino-7-(2-bromo-4-fluorophenyl)-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one, was prepared by microwave-assisted condensation.

Keywords: [$^{13}CD_3$]-TAK-459; [^{14}C]-TAK-459; microwave chemistry; HSP90 inhibitor

Introduction

Heat shock or stress dramatically increases cellular production of highly conserved chaperone proteins, commonly known as heat shock proteins (HSPs).[1] Many HSPs are molecular chaperons organized into families according to their size or function (e.g. HSP100, HSP90, HSP70, HSP60, HSP40, and small HSPs).[2] The HSP90 family represents one of the most cellular abundant proteins (1–2% of unstressed cells; 4–6% of stressed cells). HSP90 exerts its chaperone function via a cycle that involves many oncogenic signaling proteins,[3] and therefore, a rationale exists for the development of HSP90 inhibitors for the treatment of many cancers.[4] TAK-459, (*R*,*Z*)-2-amino-7-(4-fluoro-2-(6-methoxypyridin-2-yl)phenyl)-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one *O*-(*S*)-3,4-dihydroxybutyl oxide (**1**, Figure 1), is a potent and selective HSP90 inhibitor that has demonstrated antitumor activities in preclinical studies.[5]

The stable isotope-labeled TAK-459 was required for bioanalytical studies. In general, a labeled version that is at least 3 amu higher than the unlabeled version is required as an Mass Spectrometry (MS) internal standard. As described in the succeeding texts, [$^{13}CD_3$]-TAK-459 (**1A**) was rapidly synthesized in three steps from the labeled sodium methoxide.

The radiolabeled version was prepared to support metabolite profiling and whole body autoradiography in experimental animals. [^{14}C]-TAK-459 (**1B**) was prepared in five steps from commercially available [^{14}C(U)]-guanidine hydrochloride (**9B**). The key step in this synthesis was the microwave-assisted guanidine condensation.

Results and discussion

At first glance, the easiest synthetic approach to the labeled TAK-459 appears to be demethylation of the pyridine moiety, followed by realkylation with stable isotope-labeled methyl iodide (Scheme 1, pathway A). However, this method would likely require additional steps for the protection and deprotection of the terminal diol **2**. It is also possible that other moieties within the molecule could be alkylated, leading to undesired by-products.

Attention was therefore focused on adapting the previously developed nonlabeled synthetic methodology for construction of TAK-459 (pathway B).[6] This procedure was centered on the Suzuki cross-coupling between a labeled pyridine boronate derivative (**4A**) and the late-stage intermediate of TAK-459 (**3**) available from early development work in the Process Chemistry Research and Development department. The synthesis of compound **3** is not presented in this manuscript.

Our first attempt to label the 2-methoxy-6-methylpyridine boronate adapted a procedure described by Gray *et al.*, in which 2-hydroxy-6-methylpyridine, silver carbonate, and iodomethane were stirred in chloroform protected from light for 40 h.[7] Unfortunately, this method did not work when using an analog substrate, 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-ol (Scheme 2, right side). We suspected the purity and stability of the pyridine boronate **5** to be the culprit for the reaction failure.

An alternative preparation of the desired labeled boronate involved the two-step synthesis illustrated in Scheme 2, left side. According to the literature procedure described by Nguyen *et al.*, 2,6-dibromopyridine can be selectively converted to 2-bromo-6-methoxypyridine.[8] Replacing methanol with $^{13}CD_3OD$ resulted in the production of **7A** in 90% yield. Classical Suzuki conditions using bis(pinacolato)diboron in the presence of potassium acetate and $PdCl_2$dppf in Dimethyl sulfoxide (DMSO) did not yield the desired boronate ester **4A**.[9] In a different approach, compound **7A** was first converted to the lithiated species by the treatment with *n*-butyl lithium at −78 °C, followed by graduate additions of

Department of Drug Metabolism and Pharmacokinetics, Isotope Chemistry Group, Millennium Pharmaceuticals Inc, 40 Landsdowne Street, Cambridge, MA 02139, USA

**Correspondence to: Mihaela Plesescu, Department of Drug Metabolism and Pharmacokinetics, Isotope Chemistry Group, Millennium Pharmaceuticals Inc, 40 Landsdowne Street, Cambridge, MA 02139, USA.*
E-mail: Miki.Plesescu@takeda.com

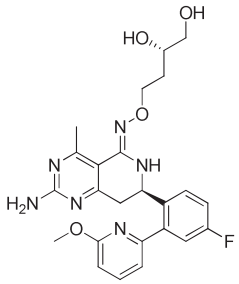

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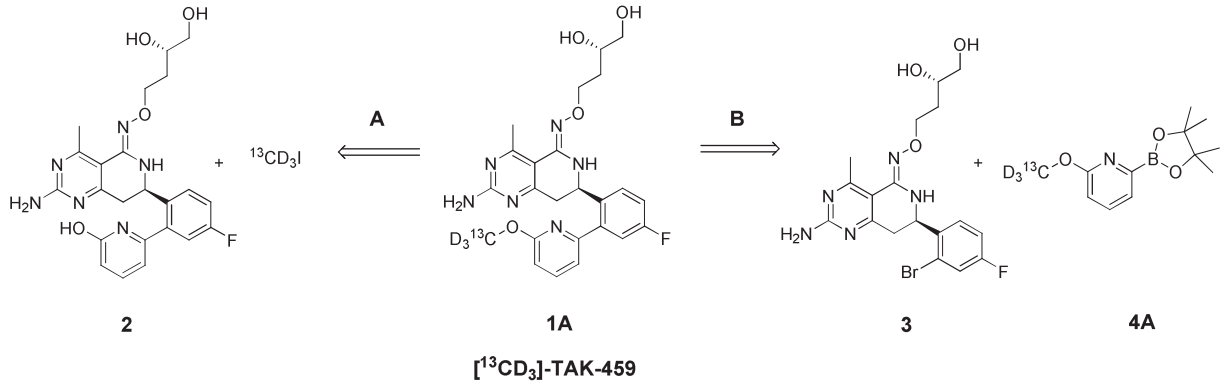
Figure 1. Structure of TAK-459.

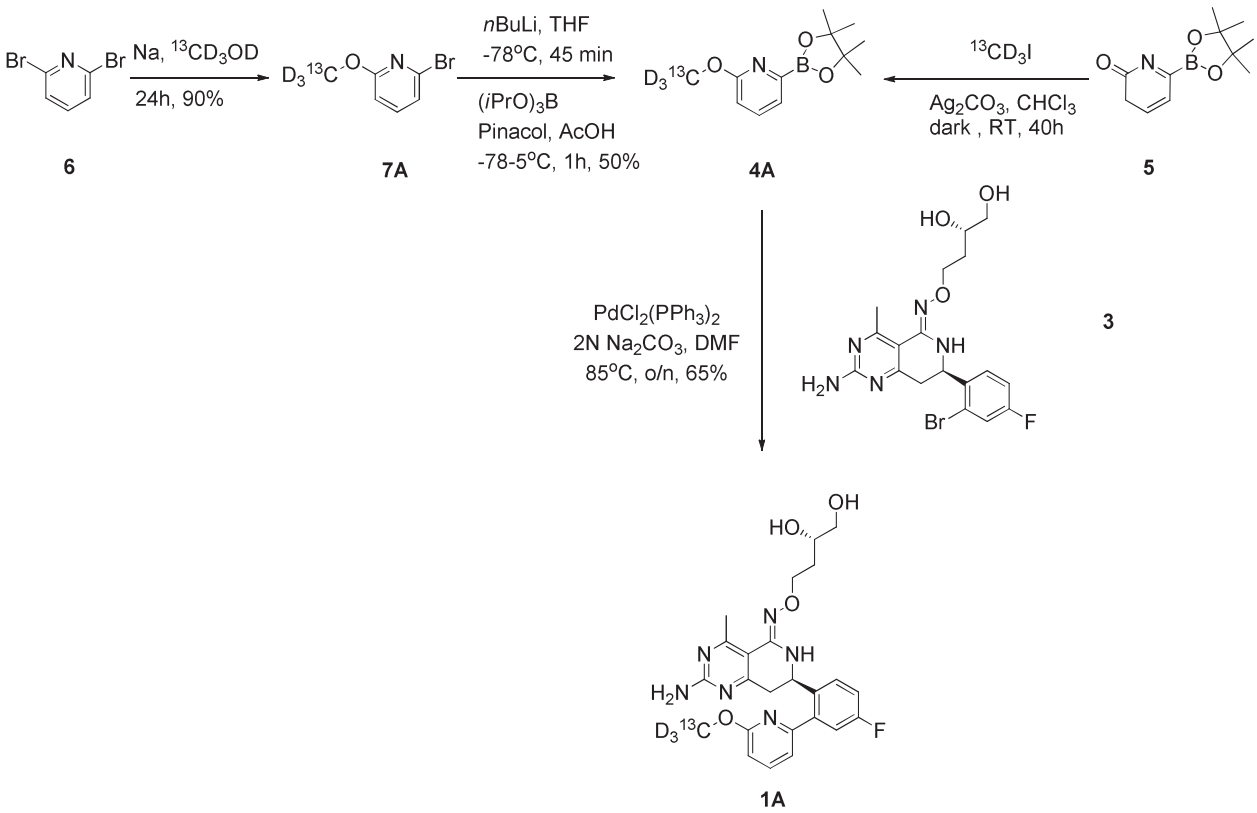
triisopropylborate and pinacol, and final quench with acetic acid.[10] Because of its poor stability, the crude boronic ester **4A** was immediately subjected to Suzuki coupling conditions[5] to give the desired internal standard of TAK-459 (**1A**) in 32.5% two-step yield.

For the preparation of [^{14}C]-TAK-459, we chose a metabolically stable position as determined by the early *in vitro* studies. According to the published patent application,[11] the enamine **8** can be condensed with guanidine to afford 2-amino-7,8-dihydro-6*H*-pyrido [4,3-*d*]pyrimidin-5-one compound **10B**. The use of microwaves resulted in accelerated completion of this reaction. Under the superheated and elevated conditions possible with microwaves, the condensation that took 24 h of refluxing in a conventional jacketed reactor was instead completed in 60 min. In addition, the reaction was carried out with less impurities and radioactive waste.

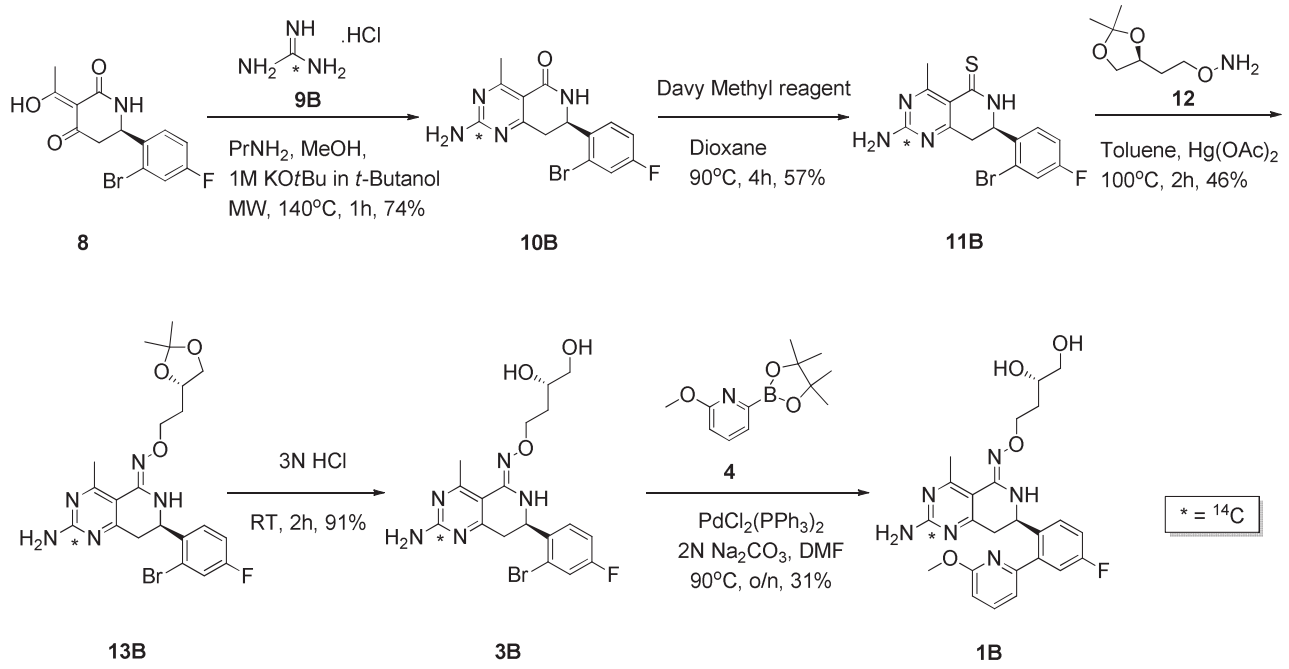
Conversion of lactam **10B** to the more reactive thiolactam **11B** was effected with Davy's reagent.[5] No other sulfonation reagent gave the same yield and clean product as reported internally by



Scheme 1. Retrosynthetic analysis of stable isotope-labeled TAK-459.



Scheme 2. Synthesis of [^{13}CD$_3$]-TAK-459.



Scheme 3. Synthesis of [^{14}C]-TAK-459.

the Process Chemistry researchers. It was followed by the treatment with the substituted alkoxyamine **12**. Lastly, diol deprotection under acidic conditions followed by Suzuki coupling with the suitable boronic ester gave the desired final compound (**1B**) (Scheme 3).

Conclusion

In summary, a practical method for the preparation of stable isotope-labeled 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was established. This key intermediate was added to the TAK-459 precursor in the final synthetic step providing [$^{13}CD_3$]-TAK-459 in a short sequence with 29% overall yield.

In order to address the lengthy and high temperature requirements for the enamine cyclization with radiolabeled guanidine, we found that microwave chemistry was a fast and clean alternative. The radiolabeled version of TAK-459 was prepared in five steps from commercially available [^{14}C(U)]-guanidine hydrochloride with 5.4% radiochemical yield.

Experimental

General

All commercial reagents and solvents were used as supplied unless otherwise noted. [^{14}C(U)]-Guanidine hydrochloride was purchased from American Radiolabeled Chemicals, Inc. (St. Louis, MO, USA) Column chromatography was carried out using a Teledyne Isco Combiflash Companion (Teledyne Isco, Inc Lincoln, NE, USA) purification system or a Biotage Flash System (Biotage, NC, USA) with their respective prepacked silica gel columns. The microwave chemistry was carried out on a Biotage Initiator microwave synthesizer using their 2–5 mL reaction vials. ^{1}H-NMR spectra were recorded on Varian 300 MHz or Bruker 500 MHz spectrometers. Radioactivity was quantified by liquid scintillation counting using Beckman LS6500 counter (Beckman Coulter, Inc., CA, USA). Purities were determined by HPLC (Agilent 1100) using Phenomenex Luna C18(2) 4.6 × 150 mm, 5 µm column, using the solvent combination of A (water, 0.1% formic acid) and B (acetonitrile, 0.1% formic acid) at 1 mL/min under gradient conditions: time 0–1 min 5%B; time 14–17 min 90%B; time 17.1–20 min 5%B. Radioactive detection employed a LabLogic β-ram model 4 flow detector using Ultima-Flo M scintillant (Perkin-Elmer Life Sciences, Waltham, MA, USA) at 3 mL/min. MS determinations were performed on Agilent (Agilent Technologies, Inc., Santa Clara, CA, USA) and Thermo LCQ mass spectrometers (Thermo Fisher Scientific Inc., Waltham, MA, USA).

[$^{13}CD_3$]-2-Bromo-6-methoxypyridine (7A)

A solution of [$^{13}CD_3$]-sodium methoxide in methanol {freshly prepared from sodium (0.7 g, 30 mmol) in anhydrous [$^{13}CD_3$]-methanol (7 mL)} was added to a suspension of 2,6-dibromopyridine (**6**, 4 g, 0.5 eq) in anhydrous [$^{13}CD_3$]-methanol (8 mL), and the resulting mixture was refluxed for 24 h. The reaction mixture was allowed to cool to room temperature and was then quenched by adding cold 5% aq. $NaHCO_3$ in D_2O. The product was extracted into ether, washed with brine (NaCl in D_2O), and dried over K_2CO_3. The filtrate was concentrated by rotary evaporation and then dried a few hours under high vacuum. The crude product was used as it is in the next step (3 g, 90%).

^{1}H-NMR (DMSO): δ 7.63–7.69 (1H, dd), 7.21–7.25 (1H, d), 6.85–6.89 (1H, d).

MS (ESI+): *m/z* 192 (M + 1, 100%), 193 (M + 2, 20%), 194 (M + 3, 77%), 195 (M + 4, 12%).

[$^{13}CD_3$]-2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyridine (4A)

A slurry of 2.5 M butyllithium in hexanes (4.5 mL, 11 mmol, 1.2 eq) in tetrahydrofuran (8 mL) was cooled at −78 °C under an atmosphere of nitrogen. To this mixture was added slowly a solution of [$^{13}CD_3$]-2-bromo-6-methoxypyridine (**7A**, 1.73 g, 9 mmol) in 1.5-mL tetrahydrofuran. The resulting dark yellow solution was allowed to react at this temperature for 45 min. A solution of triisopropyl borate (2.5 mL, 11 mmol, 1.2 eq) in 1.5-mL THF was added dropwise. The mixture was allowed to warm to room temperature and stirred for an additional hour. It became cloudy and yellow in color.

A solution of 2,3-dimethyl-2,3-butanediol (1.4 g, 12 mmol, 1.3 eq) in 2.5-mL THF was added, and the mixture turned milky white. After 5 min, acetic acid (0.6 mL, 10 mmol, 1 eq) was added, and the solution precipitated as a gel. It was filtered through a pad of celite, extracted by 5% aq. NaOH solution (15 mL). Some water was added, and the layers separated. The resulting aqueous layer was collected and acidified to pH 6–7 by adding dropwise a solution of 10% HCl, while keeping the

internal temperature below 5 °C. At the same temperature, the aqueous layer was extracted with methylene chloride (3 × 20 mL) and the organic extracts were kept over ice bath. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to an oil. The crude product was used immediately in the next step (1 g, 50%).

^{1}H-NMR (DMSO): δ 7.63–7.69 (1H, dd), 7.21–7.25 (1H, d), 6.85–6.89 (1H, d), 1.30–1.35 (6H, s), 1.05–1.10 (6H, s).

MS (ESI+): *m/z* 240 (M + 1).

[$^{13}CD_3$]-(R,Z)-2-amino-7-(4-fluoro-2-(6-methoxypyridin-2-yl)phenyl)-4-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-5(6H)-one O-(S)-3,4-dihydroxybutyl oxime (1A)

To a solution of (*R*,*Z*)-2-amino-7-(2-bromo-4-fluorophenyl)-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one *O*-(*S*)-3,4-dihydroxybutyl oxime (**3**, 100 mg, 0.2 mmol) in DMF (3 mL) was added [$^{13}CD_3$]-2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**4A**) in 2 M sodium carbonate solution (2 mL, 4 mmol). The mixture was placed under vacuum and purged with nitrogen alternatively for three times. After 20 min was added bis(triphenylphosphine) palladium(II) chloride (20 mg, 0.03 mmol), and the reaction was heated in 85 °C oil bath overnight. The reaction was diluted with ethyl acetate and water, and the layers were separated. The organic extract was dried over sodium sulfate and concentrated to a crude residue. It was purified by column chromatography, using a slow gradient 0–5% methanol in dichloromethane, to give yellow oil that solidified overnight. Upon adding 2 mL methylene chloride, a tan solid precipitated. The suspension was cooled in an ice bath for 30 min then filtered and washed with additional ice-cold methylene chloride (1.5 mL). It was dried under high vacuum to yield the desired compound **1A** (70 mg, 65%).

^{1}H-NMR (CD_3OD): δ 7.71–7.75 (1H, dd), 7.55–7.67 (1H, dd), 7.24–7.15 (2H, m), 7.05–7.13 (1H, d), 6.73–6.82 (1H, d), 6.21–6.28 (1H, s), 4.92–5.02 (1H, m), 4.07–4.23 (2H, m), 3.67–3.79 (1H, m), 3.43–3.51 (2H, m), 3.05–3.16 (1H, m), 2.91–3.03 (1H, m), 2.58–2.66 (3H, s), 1.90–2.04 (1H, m), 1.59–1.74 (1H, m).

MS (ESI+): *m/z* 487 (M + 1, 100%), 488 (M + 2, 35%), 489 (M + 3, 2%).

[^{14}C]-(R)-2-amino-7-(2-bromo-4-fluorophenyl)-4-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-5(6H)-one (10B)

The reaction was carried out in two separate batches. Into a microwave glass vial (2–5 mL), [^{14}C(U)]-guanidine hydrochloride (**9B**, 195 mg, 2 mmol, 50 mCi/mmol) was dissolved in 2-mL methanol. To this solution was added 1 M of potassium *t*-butoxide in *t*-butyl alcohol, and the reaction mixture turned cloudy and tan in color. After stirring for 15 min, (*R*,*E*)-6-(2-bromo-4-fluorophenyl)-3-(1-hydroxyethylidene)piperidine-2,4-dione (**8**, 450 mg, 1.4 mmol) and 1-propanamine (0.6 mL, 7 mmol) were added, and the mixture turned bright yellow. It was then submitted to microwave irradiation for 1 h at 140 °C. A pressure of 7–8 barr was reported by the microwave synthesizer. After the reaction was completed, all solvent was removed, and upon adding water (7 mL), a yellow solid precipitated out. It was filtered, washed well with water, and dried under high vacuum to obtain the desired compound (359 mg, 74%, 96% radiochemical purity).

MS (ESI+): *m/z* 353 (M + 0, 100%), 354 (M + 1, 20%), 355 (M + 3, 90%), 356 (M + 4, 15%).

[^{14}C]-(R)-2-amino-7-(2-bromo-4-fluorophenyl)-4-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-5(6H)-thione (11B)

A sealed vial containing [^{14}C]-(*R*)-2-amino-7-(2-bromo-4-fluorophenyl)-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one (**10B**, 359 mg) and Davy methyl reagent (340 mg, 1.2 mmol) in 1,4-dioxane (3 mL) was heated at 90 °C for 4 h. Upon completion, the reaction was cooled to room temperature, diluted with ethyl acetate (5 mL), and washed with brine (3 × 3 mL). Combined aqueous washes were back extracted into ethyl acetate (3 mL). Both organic extracts were dried over Na_2SO_4, filtered, and concentrated to brown foam that was used directly in the next step (214 mg, 57%, 97.4% radiochemical purity).

MS (ESI+): *m/z* 369 (M + 0, 100%), 370 (M + 1, 20%), 371 (M + 2, 94%), 373 (M + 3, 13%), 374 (M + 4, 5%).

[^{14}C]-(R,Z)-2-amino-7-(2-bromo-4-fluorophenyl)-4-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-5(6H)-one O-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl oxime (13B)

To a solution of [^{14}C]-(*R*)-2-amino-7-(2-bromo-4-fluorophenyl)-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidine-5(6*H*)-thione (**11B**, 214 mg, 0.6 mmol) in 3 mL toluene was added (*S*)-*O*-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl) hydroxylamine (**12**, 650 mg, 4 mmol) and mercury (II) acetate (647 mg, 2 mmol). The mixture was heated to 100 °C till completion by Liquid Chromatography - Mass Spectrometry (LC-MS) (2 h). It was cooled, filtered through celite, and rinsed with ethyl acetate. The filtrate was concentrated and purified by column chromatography using 40% ethyl acetate in hexane to obtain brown foamy solid (227 mg, 46%, 98.5% radiochemical purity).

MS (ESI+): *m/z* 496 (M + 0, 100), 497 (M + 1, 20%), 498 (M + 2, 86%), 499 (M + 3, 17%), 500 (M + 4, 4%).

[^{14}C]-(R,Z)-2-amino-7-(2-bromo-4-fluorophenyl)-4-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-5(6H)-one O-(S)-3,4-dihydroxybutyl oxime (3B)

To a round bottom flask containing [^{14}C]-(*R*,*Z*)-2-amino-7-(2-bromo-4-fluorophenyl)-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one *O*-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl oxime (**13B**, 227 mg, 0.46 mmol) was added 3.0 M HCl solution, and the mixture was stirred at room temperature. After 2 h, a brown cloudy solution was observed, and the completion of the reaction was determined by LC-MS. To this mixture was added 5 mL of 5% aq. $NaHCO_3$ solution and 3 mL 1 N NaOH to make it basic (pH > 10). A tan foamy suspension was formed, and after stirring at room temperature for 30 min, it was filtered and washed with 5 mL water. The tan solid was dried under high vacuum overnight to give the title compound **3B** (189 mg, 91%, 98.5% radiochemical purity).

MS (ESI+): *m/z* 456 (M + 0), 457 (M + 1, 20%), 458 (M + 2, 97%), 459 (M + 3, 17%), 460 (M + 4, 4%).

[^{14}C]-(R,Z)-2-amino-7-(4-fluoro-2-(6-methoxypyridin-2-yl)phenyl)-4-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-5(6H)-one O-(S)-3,4-dihydroxybutyl oxime (1B)

To a solution of [^{14}C]-(*R*,*Z*)-2-amino-7-(2-bromo-4-fluorophenyl)-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one *O*-(*S*)-3,4-dihydroxybutyl oxime (**3B**, 189 mg 0.41 mmol) in DMF (3 mL) was added 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**4**, 498 mg, 2.12 mmol), $PdCl_2(PPh_3)_2$ (29 mg, 0.041 mmol) and 2 ml of 2 N solution of Na_2CO_3 in water. The resulting mixture was heated at 90 °C overnight. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and filtered through celite. The filtrate was treated with water (5 mL), and the layers separated. Aqueous extract was further washed with ethyl acetate and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to brown oil. It was subjected to purification by column chromatography using a gradient of methanol in methylene chloride up to 10%. Fractions of interest were combined and concentrated to yellow oil that solidified under high vacuum (13.7 mCi). Upon adding 3 mL methylene chloride, a precipitate was formed, and it was heated to reflux (more solvent was added to dissolve all solids). The solution was cooled slowly to room temperature and finally in ice bath for 2 h to afford a solid that was filtered and dried under high vacuum (93 mg, 9.7 mCi, 96% radiochemical purity). In order to improve the purity, the solid was subjected to another silica column normal-phase purification using 0–3% ethyl acetate in methanol, followed by the same crystallization procedure to afford 62.5 mg title compound (31%, 99.3% radiochemical purity).

^{1}H-NMR (CD_3OD): δ 7.73–7.78 (1H, dd), 7.60–7.64 (1H, dd), 7.14–7.21 (2H, m), 7.09–7.12 (1H, d), 6.76–6.80 (1H, d), 6.20–6.23 (1H, s), 4.95–5.00 (1H, m), 4.10–4.20 (2H, m), 3.88–3.93 (3H, s), 3.70–3.78 (1H, m), 3.43–3.51 (2H, m), 3.08–3.10 (1H, m), 2.94–3.01 (1H, m), 2.60–2.65 (3H, s), 1.92–2.02 (1H, m), 1.64–1.73 (1H, m).

MS (ESI+): *m/z* 485 (M + 1, 100), 486 (M + 2, 26%), 487 (M + 3, 4%).

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Conflict of Interest

The authors did not report any conflict of interest.

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