A Facile Synthesis of Raltegravir Potassium—An HIV Integrase Inhibitor

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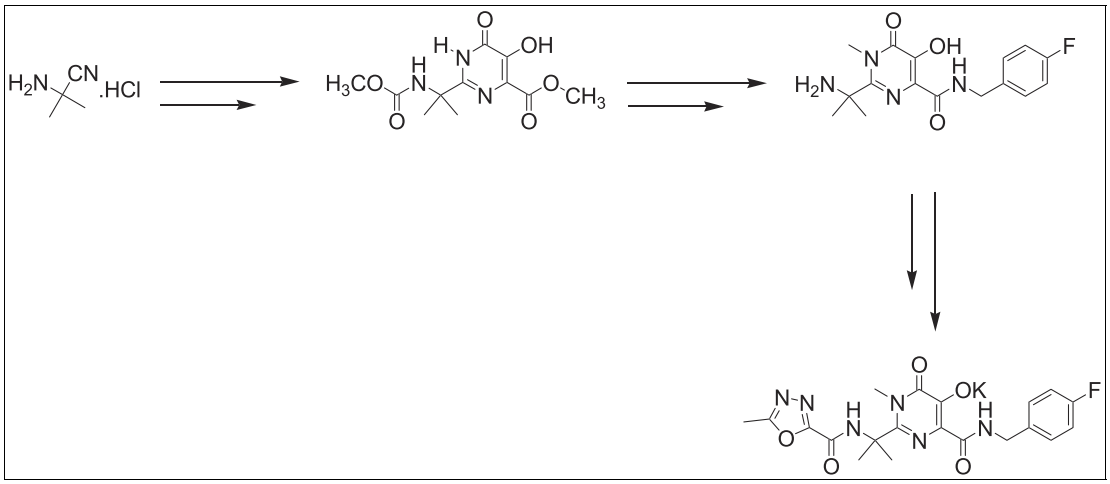

A facile, cost-effective, and commercially viable synthesis of Raltegravir Potassium (**1**) has been developed from 2-(1-amino-1-methyl-ethyl)-*N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-6-oxo-4-pyrimidinecarboxamide (**9**) with high purity and in good yields. In addition, a new approach for the synthesis of key amine intermediate (**9**) of Raltegravir Potassium (**1**) from commercially available 2-amino-2-methylpropanenitrile hydrochloride (**2**) is also described. The key features of the synthesis are fewer synthetic steps, employing the inexpensive reagents and eco-friendly.

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INTRODUCTION

Human immunodeficiency virus type-1 (HIV-1) is the contributory agent of acquired immunodeficiency syndrome. HIV-1 integrase is one of the three virally encoded enzymes essential for replication and therefore a rational target for chemotherapeutic intervention in the treatment of HIV-1 infection. Raltegravir Potassium (**1**) is a commercially available antiretroviral agent, discovered by Merck Research Laboratories. It is the first HIV integrase inhibitor, approved by USFDA for the treatment of HIV-1 infection [1]. Raltegravir Potassium is marketed under the brand name ISENTRESS.

A literature review revealed several synthetic routes of Raltegravir Potassium (**1**). The first generation manufacturing route [2] describes the preparation of **1** starting from Strecker's reaction of commercially accessible acetone cyanohydrin in 10 synthetic steps. Additionally, another variant of process is also described in this literature report [2] by the condensation of methyl-1,6-dihydro-5-(benzoyloxy)-1-methyl-2-(1-methyl-1-{[5-methyl-1,3,4-oxadiazol-2-yl)-carbonyl]amino}ethyl)-6-oxo-4-pyrimidinecarboxylate with 4-fluorobenzylamine to produce **1**. The major disadvantages of the above chemical synthesis include several number low yielding steps, unselective *N*-methylation, Pd/C-catalyzed hydrogenation for benzylchloroformate deprotection (non-eco-friendly), final amidation step, multiple chromatographic purifications, multiple use of halogenated solvents, and using highly toxic and expensive 1,4-dioxane. Furthermore, this chemical process also contains additional protection and deprotection steps for the preparation of **1**. Thus, this chemical synthesis is not preferable for commercial production because of environmental concerns.

Another literature report [3] describes the second-generation manufacturing route for the preparation of **1** by the condensation of pivaloyl-protected amine intermediate (**9**) with oxadiazole carbonyl chloride (**10**). The synthesis of key amine intermediate (**9**) is also started from the benzylchloroformate protection of acetone cyanohydrin [1]. And in the end, the debenzylation is performed by

Pd/C-catalyzed hydrogenation. Additionally, difficulties observed during the Pd/C-catalyzed hydrogenation for debenzylation are also described in this report. Glycolic acid is used as an additive to resolve the solubility issue during the hydrogenation. Furthermore, there is a possibility of desfluoro impurity during the hydrogenation using Pd/C. However, this synthetic route also consists of hydrogenation and pivaloyl protection that are not necessary.

Further, another report [4] discloses the preparation of **1** by the condensation of oxadiazole carbonyl chloride (**10**) with commercially available acetone cyanohydrin [1], in order to avoid protection/deprotection of amino group in acetone cyanohydrin. However, this synthesis consists of operations including acid/base treatments as well as thermal rearrangement at high temperature. Later, another literature report [5] describes the identification and synthesis of potential impurities observed during the manufacturing of **1**. In addition, the formation of some of the impurities due to the degradation of oxadiazole moiety of **1** is also described in this report. Moreover, one of the impurities is synthesized by treating **1** with base. Thus, it clearly indicates the sensitivity and degradation tendency of oxadiazole moiety. Therefore, it is extremely difficult to control the degradation in this route of synthesis. Thus, these synthetic routes are not advantageous for large-scale production.

In consequence, there is a need for substitute synthetic pathways, which, for example, utilize inexpensive reagents and are eco-friendly. In this perspective, we have developed an improved and scalable synthesis for the preparation of Raltegravir Potassium (**1**) with 99.9% chromatographic purity.

RESULTS AND DISCUSSION

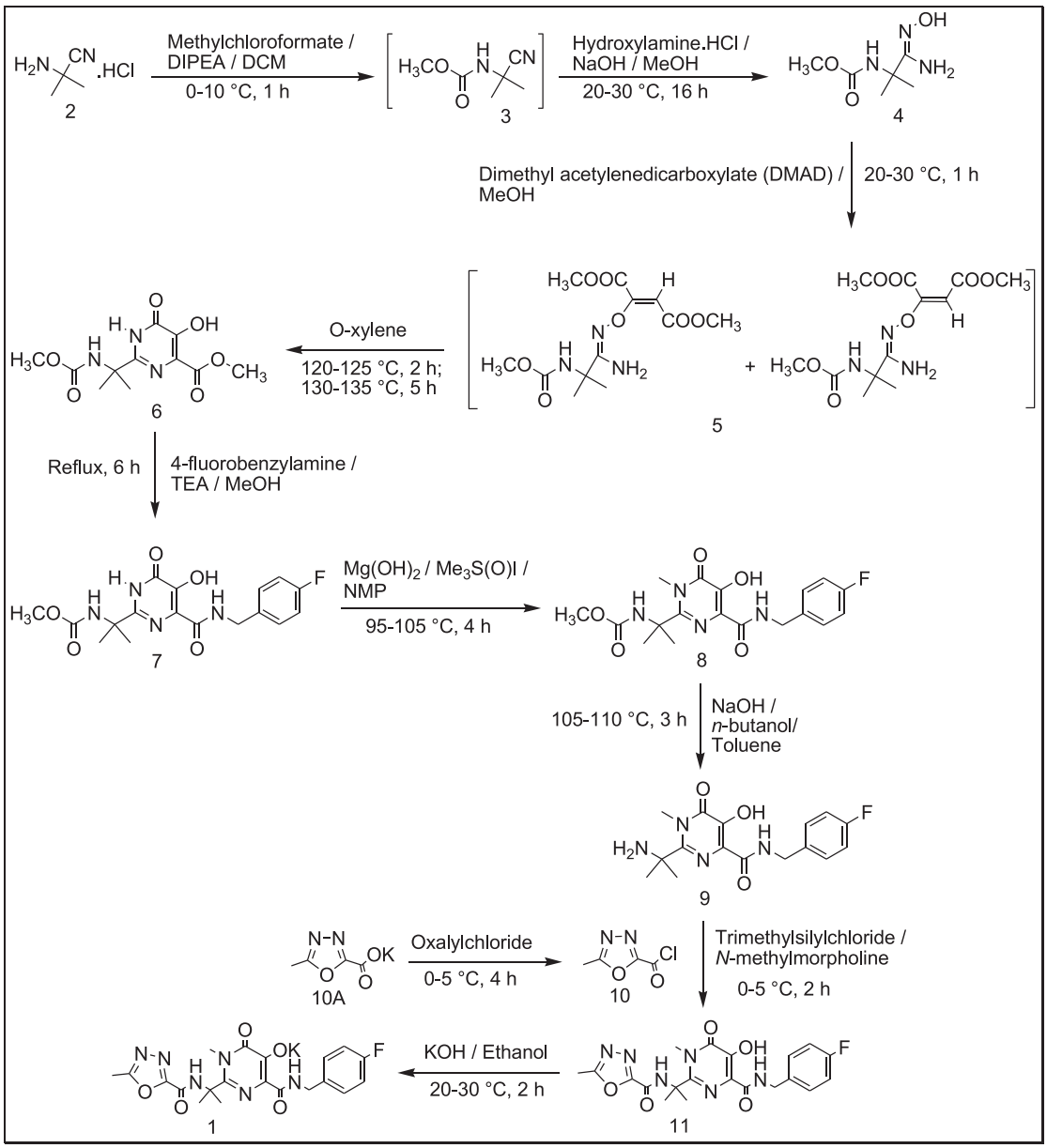
Though, all aforementioned issues for the permanent manufacturing of Raltegravir Potassium (**1**), we recognized and focused on two major challenges, namely, the elimination of inherently hazardous Pd/C-catalyzed hydrogenation as well as the elimination of pivaloyl protection/deprotection that are incompatible.

The present article covered by our patent [6] provides the preparation of Raltegravir Potassium (**1**) (Scheme 1) commenced from commercially available 2-amino-2-methylpropanenitrile hydrochloride (**2**) in seven synthetic steps. Protection of amino group in compound **2** with methylchloroformate (MOC) in the presence of diisopropylethylamine produced (cyano-dimethyl-methyl) carbamic acid methylester (**3**). Addition of hydroxyl amine to **3** generated its corresponding oxime, that is, [1-(*N*-hydroxycarbamimidoyl)-1-methyl-ethyl]carbamic acid methylester (**4**) as a crystalline solid. Michael addition between **4** to dimethyl acetylenedicarboxylate (DMAD) and subsequent thermal rearrangement afforded 2-(1-methyloxycarbonylamino-1-methyl-ethyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methy lester (**6**). Coupling reaction of **6** with 4-fluoroben zylamine in the presence of triethylamine produced *N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-2-[(1-methyl-1-[[(methoxy)carbonyl]amino]ethyl-6-oxo-4-pyrimidine carboxamide (**7**). *N*-methylation of compound **7** with trimethylsulphoxoniumiodide[$Me_3S(O)I$] in the presence of magnesium hydroxide or magnesium oxide resulted *N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[(1-methyl-1-[[(methoxy)carbonyl]amino]ethyl]-6-oxo-4-pyrimidine carboxamide (**8**). The deprotection of MOC group in **8** in the presence of NaOH afforded 2-(1-amino-1-methyl-ethyl)-*N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-6-oxo-4-pyrimidine carboxamide (**9**). The amidation of **9** with oxadiazole carbonyl chloride (**10**) in the presence of *N*-methylmorpholine produced Raltegravir (**11**). Treatment of Raltegravir (**11**) with aqueous KOH in ethanol accomplished Raltegravir Potassium (**1**) as a crystalline colorless solid.

Optimization of compound 4. The first step in our synthesis was initiated from the protection of amino group in **2**. Our aim was to eliminate Pd/C-catalyzed hydrogenation in order to resolve the previous difficulties described in literature for debenzylation. In support of that, several protecting reagents were tested including MOC, ethylchloroformate, di-*tert*-butyl dicarbonate, and fluorenylmethyloxycarbonylchloride that could eliminate the hydrogenation. Among these, we chose commercially inexpensive MOC [7] as a protecting reagent for amino group in **2**. After selecting the suitable protecting reagent, we studied different suitable base reagents including diisopropyl amine, triethylamine, sodium carbonate, and sodium hydroxide. Theoretically, 2 mole equivalents of base reagent and 1 mole equivalent of MOC were required for the amino group protection. However, we achieved best results while 1.1 mole equivalents of MOC and 2.25 mole equivalents of diisopropylethylamine in dichloromethane (DCM) at 0–10°C to obtain the optimum yield and purity.

With compound **3** in hand, the preparation of oxime compound (**4**) from **3** using hydroxyl amine was investigated. As per literature [2,3], the free hydroxyl amine solution was isolated by treating hydroxylamine hydrochloride in methanol in the presence of NaOH. The precipitated salts were removed by filtration, and the filtrate containing free hydroxylamine was used for the oxime preparation. During the initial development, we carried out oxime reaction *in situ* by treating **3** with free hydroxylamine solution in methanol. We tried to execute this process in kilo lab but unfortunately observed the degradation of hydroxylamine solution

Scheme 1. A facile and improved synthesis of Raltegravir Potassium (**1**).



in methanol. To understand the degradation of hydroxylamine solution, we examined the sensitivity/stability of hydroxylamine solution towards temperature, air, and base. Based on the results, we anticipated that the degradation of hydroxylamine solution was due to either oxygen or temperature. Later, we modified the reaction conditions and succeeded substantially by carrying out the reaction *in situ* under nitrogen atmosphere without using free hydroxylamine solution in methanol. And in the workup, the inorganic salts present in the reaction mass were saturated with demineralized water, and the product was collected by filtration to obtain optimum yield and purity.

Optimization of compound 6. After optimizing the robust synthesis of oxime reaction, we then focused on the preparation of DMAD adduct (**5**), which upon thermal rearrangement *in situ* to produce **6**. DMAD adduct (**5**) was prepared by Michael addition of oxime compound (**4**) with 1.1 mole equivalents of DMAD in mild conditions in methanol. After completion of the reaction, DMAD adduct (**5**) was isolated by evaporating methanol under vacuum as an isomeric mixture. Thermal rearrangement [8,9] of the above obtained isomeric

residue at high temperature (120–125°C for 2 h followed by 130–135°C for 5 h) afforded **6**. After studying the key process parameters for the thermal rearrangement, we shifted our attention on isolation of pure product. During the initial lab experiments, we isolated compound **6** from a mixture of MTBE and methanol. But we achieved low yield, poor crystal nature and description of **6**. To resolve the aforementioned issues, we screened several solvents including methanol, acetone, and isopropanol for the isolation of **6**. Agreeably, the best results were achieved while methanol was used for the isolation of **6**.

Optimization of compound 7. The coupling reaction of **6** with 4-fluorobenzylamine resulted desired **7**. During our initial experiments in lab, we carried out the coupling reaction of **6** with 1 mole equivalent of 4-fluorobenzylamine to afford **7**. However, the reaction was not completed. Later, different mole equivalents of 4-fluorobenzylamine were screened for this coupling reaction. Thereafter, the reaction was completed while compound **6** was treated with 2.1 mole equivalents of 4-fluorobenzylamine in methanol under reflux condition. In the view of cost, the reaction was modified by using a mixture of 1.1 mole equivalents of inexpensive triethylamine (as a base) and 1.1 mole equivalents of 4-fluorobenzylamine in order to achieve good conversion for this coupling reaction. Under these optimum conditions, we achieved 98% of conversion and 99% of chromatographic purity.

Optimization of compound 8. Despite several reagents were available for *N*-methylation, trimethylsulfoxoniumiodide [10] was selected to be the suitable reagent because of relative cost, safety profile, and ease of handling. In addition, magnesium hydroxide was selected as a base reagent for *N*-methylation of **7**. With the intention to develop a robust *N*-methylation reaction, different mole ratios of trimethylsulfoxoniumiodide as well as magnesium hydroxide were screened. We attained best results, while 2 mole equivalents of trimethylsulfoxoniumiodide as well as Mg $(OH)_2$ in *N*-methyl-2-pyrrolidinone used for *N*-methylation reaction. Under these specified conditions, highest yield and purity was achieved. Surprisingly, almost same yield and quality were observed while the reaction was performed with magnesium oxide (MgO) instead of Mg $(OH)_2$. The experimental details are stated in Table 1.

Optimization of compound 9. Subsequently, our attention was shifted towards the optimization of MOC group deprotection. Considering the cost, we selected commercially inexpensive NaOH for MOC deprotection reaction. In order to develop the robust synthesis for MOC deprotection reaction, we screened different parameters including solvents, mole ratios of base, and temperature. Gratifyingly, we achieved best results while 3 mole equivalents of NaOH was used at 105–110°C in *n*-butanol. Under these optimum conditions, we achieved 98% of product conversion with 99.8% of chromatographic purity. This deprotection was successfully performed without adding any additive. After the isolation, the amine intermediate **9** was obtained as a monohydrate. To achieve anhydrous amine intermediate **9** for the subsequent amidation reaction, the moisture in amine intermediate **9** was removed by Dean–Stark apparatus. The experimental details are stated in Table 2.

Optimization of Raltegravir (11). Consequently, our aim was to eliminate protection and deprotection of hydroxy group in **9** during the amidation reaction with **10**. In support of that, we carried out the amidation reaction with 2 mole equivalents of expensive oxadiazole carbonyl chloride (**10**) (1 mole equivalent for desired amidation reaction and 1 mole equivalent for the protection of hydroxy group in **9**). As expected, the reaction was completed, but the cost was enhanced. Thus, we intended to reduce the consumption of expensive **10** in this reaction in order to reduce the cost. Later, we introduced commercially inexpensive trimethylsilylchloride [11] as a partial protecting reagent for hydroxy group of amine intermediate **9**. In addition, trimethylsilylchloride was also useful to maintain moisture-free condition in this amidation reaction. Most agreeably, the coupling of trimethylsilyl-protected compound **9** (formed by the treatment of **9** with trimethylsilylchloride) with oxadiazole carbonyl chloride **10**, subsequent treatment with aqueous KOH produced Raltegravir (**11**). This amidation between

Table 1

Reagent, solvent, and time screening studies of **8**.

Entry	$Me_3S(O)I$ (moles)	Mg $(OH)_2$ (moles)	MgO	Solvent	Temp. (°C)	Time (h)	Conversion (%)
1	1.6	1.6	—	NMP	100–110	4	75
2	2.0	2.0	—	NMP	80–85	14	92
3	2.0	2.0	—	NMP	120–125	3	74
4[†]	2.0	2.0	—	NMP	95–105	4	94
5	2.0	—	2.0	NMP	95–105	4	93

NMP, *N*-methyl-2-pyrrolidinone.
[†]Ideal condition.

Table 2

Reagent, solvent, and time screening studies of **9**.

Entry	NaOH (moles)	Solvent	Temp. (°C)	Time (h)	Conversion (%)
1	2.5	Water	95–100	9	NA
2	2.0	Ethanol	75–78	10	64
3	2.5	15% Aq *n*-butanol	100–110	3	68
4	2.5	2% Aq *n*-butanol	105–110	1	90
5[‡]	3.0	*n*-Butanol	105–110	3	98

[‡]Ideal condition.

9 and **10** using trimethylsilylchloride in the presence of *N*-methylmorpholine resulted excellent product conversion. The experimental details of amidation reaction were presented in Table 3. Treatment of Raltegravir (**11**) with aqueous KOH in ethanol generated desired Raltegravir Potassium (**1**).

MATERIALS AND METHODS

All the solvents and raw materials were purchased from the commercial sources and used without purification. The IR spectra were recorded in solid-state KBr dispersion using Perkin Elmer FTIR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-Advance 300 MHz and Varian 500 MHz spectrometers. The chemical shifts were reported in δ ppm relative to tetramethylsilane (TMS) (internal standard). The mass spectra were recorded on API 2000 Perkin Elmer PE-SCIEX mass spectrometer. Melting points were determined and were uncorrected by Polmon melting point apparatus (model no. MP-96). The purity/impurity ratios and the reaction monitoring of compound **3** were determined by GC system with Flame Ionization Detector (Agilent 7890 A GC) with DB-17 column containing 6% cyanopropyl phenyl and 94% dimethyl polysiloxane copolymer capillary column of 60 mL length and 0.53 mm ID, and film thickness was 1 μm. Column flow was 5.0 mL/min, and the run time was 60 min. The purity/impurity ratios and the reaction monitoring of remaining compounds were determined by Eclipse XDB Phenyl 4.6 × 150, 3.5 μm at 25°C with flow rate of 1.0 mL/min. The run time was 40 min, and the detection was at UV, 240 nm.

EXPERIMENTAL

Preparation of [1-(*N*-hydroxycarbamimidoyl)-1-methyl-ethyl]carbamic acid methylester (4). To a suspension of 2-amino-2-methylpropanenitrile hydrochloride (**2**) (250 g, 2.073 mol) in DCM (1750 mL), diisopropylethylamine (602 g, 4.66 mol) was added at 20–30°C under nitrogen atmosphere. The reaction mass was cooled to 0–5°C, and methyl chloroformate (216 g, 2.28 mol) was added for about 60 min. The reaction mass was stirred for 60 min at 0–10°C, and demineralized water (750 mL) was added to the reaction mass. The pH of the reaction mass was adjusted to 2.0 to 2.5 with concentrated HCl at 0–10°C. The reaction mass was warmed to 20–30°C. The organic layer was separated and was washed with demineralized water (500 mL), prior to the distillation under reduced pressure to afford compound **3** as colorless oil.

Separately, in another reactor, hydroxylamine hydrochloride (194.5 g, 2.79 mol) was suspended in methanol (375 mL) at 20–30°C under nitrogen atmosphere. The slurry was cooled to 0–5°C, and NaOH (110 g, 2.73 mol) solution in methanol (625 mL) was added. Compound **3** was diluted in methanol (250 mL) and was added to this reaction mass at 0–10°C. The reaction mass was warmed and stirred at 20–30°C for 16 h. After completion of the reaction, acetic acid (40 g,

Table 3

Reagent optimization studies of amidation reaction.

Entry	9 moles	10 moles	TMSCl (moles)	NMM (moles)	Solvent	Conversion (**11**) (%)
1	1.0	2.10	—	5.0	ACN	74
2	1.0	2.20	—	3.0	DCM	86
3	1.0	1.50	—	3.0	DCM	81
4	1.0	1.25	2.50	3.5	DCM	92
5[§]	1.0	1.20	2.25	3.5	DCM	93

ACN, acetonitrile; DCM, dichloromethane; NMM, *N*-methylmorpholine; TMSCl, trimethylsilylchloride.
[§]Ideal condition.

0.66 mol) was added uniformly. Thereafter, the reaction mass was concentrated under reduced pressure. Demineralized water (500 mL) was added to the concentrated mass, and the slurry was stirred for 1 h at 20–30°C. The product was collected by filtration and dried to afford compound **4** (280 g, 78%) as a colorless solid. Purity by HPLC: 99.8%, mp: 142–146°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.36 (s, 6H), 3.48 (s, 3H), 5.16 (s, 2H), 6.90 (s, 1H), 9.04 (s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ: 155.99, 155.02, 53.24, 50.90, 25.93; HRMS (ESI) calculated for $C_6H_{13}N_3O_3$ $(M + H)^+$ 176.1035, found: 176.1040.

Preparation of 2-(1-methyloxycarbonylamino-1-methyl-ethyl)-5-hydroxy-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methylester (6). To a 15–20°C solution of compound **4** (250 g, 1.427 mol) under nitrogen atmosphere in methanol (1250 mL), DMAD (223 g, 1.56 mol) was added. The reaction mass was stirred for 2 h at 20–30°C. The reaction mass was concentrated under reduced pressure to afford compound **5** as dark brown oil.

O-xylene (625 mL) was added to the above concentrated mass and was warmed to 120–125°C. The reaction mass was stirred for 2 h at 120–125°C and then stirred for 5 h at 130–135°C. The reaction mass was cooled to 40–50°C, and methanol (750 mL) was added. The slurry was warmed and stirred under a gentle reflux for 1 h. The reaction mass was cooled and stirred at 20–25°C for 1 h. The product was collected by filtration and dried to afford compound **6** (262 g, 64%) as a pale brown solid. Purity by HPLC: 99%, mp: 218–219°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.45–1.48 (s, 6H), 3.49 (s, 3H), 3.81–3.84 (d, 2H), 7.29 (s, 1H), 10.24 (s, 1H), 12.53 (s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ: 166.09, 159.35, 155.11, 153.36, 144.71, 127.79, 54.77, 52.15, 51.14, 26.05; HRMS (ESI) calculated for $C_{11}H_{15}N_3O_6$ $(M + H)^+$ 286.1039, found: 286.1046.

Preparation of *N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-2-[(1-methyl-1-[[(methoxy)carbonyl]amino]ethyl-6-oxo-4-pyrimidine carboxamide (7). To a suspension of **6** (200 g, 0.701 mol) in methanol (320 L), triethylamine (78 g, 0.771 mol) followed by 4-fluorobenzylamine (97 g, 0.771 mol) were added slowly portionwise for 30–40 min. The reaction mass was warmed and stirred under a gentle reflux for 6 h. After cooling the reaction mass to 50–55°C, acetic acid (84.13 g, 42.35 mol) and demineralized water (330 mL) were added uniformly. The reaction mass was then cooled and stirred for 2 h at 20–30°C. The product was collected by filtration and dried to afford compound **7** (260 g, 98%) as a pale brown solid. Purity by HPLC: 99.4%, mp: decomposed at 210°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.52 (s, 6H), 3.50 (s, 3H), 4.49–4.52 (d, 2H, J = 6.3 Hz), 7.13–7.21 (m, 2H), 7.36–7.42 (m, 3H), 9.22–9.26 (t, 1H, J = 3.75 Hz), 12.42 (s, 2H); ^{13}C NMR (300 MHz, DMSO-d_6) δ: 168.67, 162.90, 158.33, 155.18, 153.85, 147.45, 134.84 (2C), 129.54 (2C), 125.82, 115.26 (2C), 54.87, 51.51, 26.03; HRMS (ESI) calculated for $C_{17}H_{19}FN_4O_5$ $(M + H)^+$ 379.1418, found: 379.1361.

Preparation of *N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[(1-methyl-1-[[(methoxy)carbonyl] amino]ethyl]-6-oxo-4-pyrimidine carboxamide (8). To a suspension of compound **7** (200 g, 0.528 mol) in *N*-methyl-2-pyrrolidinone (320 mL), trimethylsul phoxoniumiodide (233 g, 1.05 mol) and magnesium hydroxide (62 g, 1.05 mol) were added. The reaction mass was warmed and stirred at 95–105°C for 4 h. The reaction mass was cooled to 20–30°C, and methanol (344 mL) followed by aqueous HCl (5*N*, 172 mL) were added uniformly. The reaction mass was stirred for 15 min, and aqueous sodium metabisulphite solution (2.6*M*, 10 mL) and aqueous HCl (5*N*, 172 mL) were added. The reaction mass was then warmed and stirred at 30–35° for 1 h. The resulting slurry was cooled and stirred at 10–15°C for 1 h. The product was collected by filtration and dried to yield compound **8** (187 g, 90%) as an off-white solid. Purity by HPLC: 99.7%, mp: 206–211°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.61 (s, 6H), 3.34–3.54 (m, 6H), 4.50–4.52 (d, 2H, J = 6.3 Hz), 7.14–7.20 (m, 2H), 7.36–7.41 (m, 2H), 7.94 (s, 1H), 8.99–9.03 (t, 1H, J = 6.45 Hz), 12.17 (s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ: 168.43, 162.87, 159.65, 158.67, 155.03, 152.49, 145.54, 134.86 (2C), 129.50 (2C), 124.27, 115.23 (2C), 56.50, 51.32, 32.55, 27.48; HRMS (ESI) calculated for $C_{18}H_{21}FN_4O_5$ $(M + H)^+$ 393.1574, found: 393.1574.

Preparation of 2-(1-amino-1-methyl-ethyl)-*N*-[(4-fluoro phenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-6-oxo-4-pyrimidine carboxamide (9). To a suspension of compound **8** (200 g, 0.509 mol) in *n*-butanol (600 mL), sodium hydroxide (61 g, 1.52 mol) was added. The reaction mass was warmed and stirred at 105–110°C for 3 h. The reaction mass was cooled to 80–90°C, and *n*-butanol (400 mL) was distilled out from the reaction mass under reduced pressure. Thereafter, the reaction mass was cooled to 0–5°C, and demineralized water (600 mL) was added. The pH of the reaction mass was adjusted to 6.5 to 7.0 with aqueous HCl at 0–5°C. The precipitated product was stirred for 1 h at 0–5°C and was collected by filtration. The wet product was suspended in toluene (2 L), and the moisture was collected by Dean–Stark apparatus. The slurry was cooled and stirred for 2 h at 20–30°C under nitrogen atmosphere. The product was collected by filtration under nitrogen atmosphere and dried to afford compound **9** (150 g, 85%) as an off-white solid. Purity by HPLC: 99.9%, mp: 196–198°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.55 (s, 6H), 3.72 (s, 3H), 4.44–4.46 (d, J = 6.3 Hz), 7.09–7.16 (m, 2H), 7.30–7.34 (m, 2H), 10.00 (s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ: 167.94, 162.73, 161.23,

159.52, 149.81, 135.50 (2C), 129.25 (2C), 123.33, 115.10, 114.82, 55.79, 41.32, 33.20, 28.51 (2C); HRMS (ESI) calculated for $C_{16}H_{19}FN_4O_3$ $(M + H)^+$: 335.1519, found: 335.1523.

Preparation of *N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazole-2-yl)carbonyl]-amino]ethyl]-6-oxo-4-pyrimidine carboxamide (Raltegravir) (11). To a 25–40°C suspension of compound **9** (200 g, 0.598 mol) in DCM (1600 mL), *N*-methylmorpholine (212 g, 2.09 mol) and trimethyl silylchloride (147 g, 1.346) were added portionwise under nitrogen atmosphere. The reaction mass was stirred for 2 h under reflux. The resultant slurry was cooled to 0–5°C.

Meanwhile, in another reactor, to a 0–5°C suspension of 1,3,5-oxadiazole potassium (**10A**) (129 g, 0.778) in DCM (800 mL), *N*,*N*-dimethylformamide (2.2 g, 0.029 mol) followed by oxalyl chloride (91.1 g, 0.714 mol) were added at −5 to 5°C for about 30–40 min under nitrogen atmosphere. The reaction mass was stirred for 4 h at 0–5°C, and the resultant oxadiazole carbonyl chloride (**10**) was added portionwise to the above prepared silylated slurry of compound **9** at 0–5°C. The reaction mass was stirred for 2 h at 0–5°C, and demineralized water (400 mL) was added. The reaction mass was warmed and stirred for 10 min at 20–25°C. The pH of the reaction mass was adjusted to 10.5 with aqueous KOH solution. Further, the reaction mass was stirred for 2 h at 20–25°C, and the pH of the reaction mass was readjusted to 4.4–4.6 with acetic acid. The organic layer was separated and washed with demineralized water (2 × 600 mL). The organic layer was then distilled out completely under reduced pressure. To the obtained residue, ethanol (1200 mL) was added, warmed, and stirred under reflux for 2 h. The resultant slurry was cooled and stirred for 1 h at ambient temperature. The product was collected by filtration and was dried to afford **11** as an off-white solid (266 g, 91%). Purity by HPLC: 99.89%, mp: 216–218°C, lit [1]. 216°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.74 (s, 6H), 2.50–2.56 (m, 3H), 3.33–3.48 (t, J = 38.5 Hz, 3H), 4.52–4.50 (d, 2H, J = 3.2 Hz), 7.15–7.17 (m, 2H), 7.38–7.41 (m, 2H), 9.07 (s, 1H), 9.84 (s, 1H), 12.20 (s, 1H); HRMS (ESI) calculated for $C_{20}H_{21}FN_6O_5$ $(M + H)^+$: 445.1636, found: 445.1631.

Preparation of *N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazole-2-yl)carbonyl]-amino]ethyl]-6-oxo-4-pyrimidine carboxamide potassium salt (Raltegravir Potassium) (1). To a 39–41°C suspension of Raltegravir (**11**) (200 g) in ethanol (2000 mL), 35% w/w aqueous potassium hydroxide solution (81.7 g) was added. The slurry was allowed to cool to ambient temperature and was stirred for 2 h. The product was collected by filtration and dried to afford **1** as a colorless solid (185 g, 85%). Purity by HPLC: 99.91%, mp: 283.62°C, lit [12]. 286°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.69 (s, 6H), 2.56–2.49 (m, 3H), 3.33–3.39 (d, J = 14 Hz, 3H), 4.43–4.44 (d, 2H, J = 3.2 Hz), 7.09–7.13 (m, 2H), 7.31–7.33 (m, 2H), 9.73 (s, 1H), 11.70 (s, 1H).

CONCLUSION

In summary, we described a facile, efficient, and commercially viable synthesis of Raltegravir Potassium. In addition, a new approach for the synthesis of 2-(1-amino-1-methylethyl)-*N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-6-oxo-4-pyrimidinecarboxamide (**9**), a key amine intermediate of Raltegravir Potassium, was also described. This present synthetic approach has the following advantages over the previous reported preparations: (i) avoids non-eco-friendly hydrogenation, (ii) uses inexpensive reagents, for example, MOC and trimethylsilylchloride, (iii) includes a simple workup procedure, (iv) avoids unnecessary synthetic steps, for example, pivaloyl protection, and (v) avoids the usage unnecessary reagents, for example, glycolic acid as an additive for solubility. These modifications make the whole synthesis cost-effective, production-friendly, greener, and practical. These advances have been executed effectively at 12 kg scale in pilot plant.

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ABBREVIATIONS

DCM: dichloromethane
MOC: methylchloroformate
DMAD: dimethyl acetylenedicarboxylate

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SUPPORTING INFORMATION

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