Raltegravir sodium synthesis was achieved from one of the key starting materials with a retro synthetic approach, in which without using its critical starting material chemically known as 5-methyl-1,3,4-oxadiazole-2-carbonyl chloride and which is more unstable during the synthesis of raltegravir potassium. Almost all the existed literatures commonly using this starting material in its synthesis even if it has stability issues and hence to achieve a stable and economically viable synthesis. The current research describes a new route of synthesis by constructing an oxadiazole ring in a retro synthetic manner.

Keywords: Synthesis, 5-methyl-1,3,4-oxadiazole-2-carbonyl chloride, Raltegravir potassium.
during coupling reaction with compound 5 and hence compound 9 is consuming more in equivalents than the actual requirement. Therefore, a new convenient synthesis (Scheme-II) is proposed for making raltegravir potassium. By keeping all the aspects in the view, such as costing, process safety, process stability and commercial process feasibility during industrial scale up.

In the present work, raltegravir potassium synthesis was developed or initiated from commercially and economically available intermediate compound 8. The first and second step of the synthesis very familiar and it is reported in various patents and research articles (Scheme-III), but the main invention will be reflected from third stage of the proposed route of synthesis as shown as in Scheme-II.

The author constructed Fragment-II of raltegravir with ethyl oxalyl chloride with a simple coupling reaction with primary amine which is present in compound 5 to get compound 4. Afterwards, ethyl ester (4) was treated with hydrazine hydrate for resulting compound 3 and then it was condensed with acetic acid and followed by ring cyclization to afford compound 1.

Scheme-I: Synthesis of hydroxy pyrimidinone (8)

Scheme-II: Proposed route of synthesis for raltegravir potassium
Most of the raw materials, solvents and reagents were purchased from commercial manufacturing sources. The techniques which were used for its each stage analysis purpose were such as $^1$H and $^{13}$C NMR (Bruker 400 MHz), mass (Agilent 6110AA ESI and APCI system, FT-IR (Perkin-Elmer spectrum 100 FT-IR spectrometer).

**Synthesis of benzyl 2-(4-(4-fluorobenzylcarbamoyl)-1,6-dihydro-5-hydroxy-1-methyl-6-oxopyrimidin-2-yl)propan-2-ylcarbamate (6):**

In a 250 mL clean and dry round bottom flask, 4-flourobenzylamine was slowly added to a cooled solution of compound 8 (15 g) in 150 mL of absolute ethanol under vigorous stirring. After completion of the addition at 0-5 °C it was slowly heated to reflux temperature and maintained the reaction for 3 h until the starting material complies. The reaction mass was cooled to 50-60 °C, then there added 7 mL of glacial acetic acid followed by 15 mL of water. The resulting solution was cooled to room temperature and maintained for 30 min filtered under nitrogen atmosphere, washed with 10-20 mL of 50 % aqueous ethanol solution and dried to afford 13.2 g of compound 6 with HPLC purity 98.10 %. $^1$H NMR (DMSO-$_d$6): δ 11.04 (s, 1H), 7.93 (s, 1H), 7.33 (m, 5H), 7.10 (t, 4H), 5.23 (s, 2H), 4.97 (s, 2H), 4.46(d, 2H), 3.83(s, 3H), 1.57 (s, 6H); $^{13}$C NMR (DMSO-$_d$6): δ 167.21, 165.11, 162.49, 160.08, 159.85, 154.81, 154.13, 141.53, 137.20, 136.52, 129.17, 128.97, 127.69, 123.30, 114.94, 114.73, 64.97, 56.25, 43.63, 41.07, 32.04, 27.82, 22.55. Mass (m/z): M+: 468.48, M-H: 468.2 (-ve scan), M+H: 469.2 (+ve scan).

**Synthesis of N-(4-fluorobenzyl)-2-(2-aminopropan-2-yl)-1,6-dihydro-5-hydroxy-1-methyl-6-oxopyrimidine-4-carboxamide (5):**

In a 250 mL four necked round bottom flask added 5 g of compound 6 portion-wise to a alcoholic solution of sodium hydroxide (2 g) in $n$-butanol (20 mL) at room temperature under vigorous stirring. The slurry solution was slowly heated to reflux and maintained for 3-4 h until it TLC complies. The resulting brown colored precipitated solution was cooled to 20-25 °C diluted with 50 mL of water to get clear solution. The obtained off-white coloured solid was filtered and dried after reaction mass pH was adjusted to 7.5 with conc. HCl (5 mL) to afford 3 g of compound 5 with HPLC purity 99.4 %.

$^1$H NMR (DMSO-$_d$6): δ 10.55 (s, 1H), 7.27-7.30 (m, 2H), 7.10 (t, 2H), 4.43 (d, 2H), 3.60 (s, 3H), 1.58 (s, 6H); $^{13}$C NMR (DMSO-$_d$6): 167.87, 162.50, 159.95, 152.15, 145.17, 135.77, 129.23, 122.92, 115.10, 56.02, 41.33, 33.01, 27.24. Mass: M+: 334.35, M+H: 435.1 (+ve Scan), M-H: 333.1 (-ve scan).

**Synthesis of ethyl-(2-(4-(4-fluorobenzylcarbamoyl)-1,6-dihydro-5-hydroxy-1-methyl-6-oxopyrimidin-2-yl)propan-2-ylcarbamoyl)formate (4):**

In a clean and dry 3000 mL round bottom flask, it was taken 400 mL of chloroform, 40 g of compound 8 and 38 g of triethylamine at room temperature under gentle stirring, then added 32 g of ethyl oxalyl chloride dropwise over a period of 0.5 h at 0-5 °C. The reaction mass was maintained for 1 h at 0-5 °C and another 1 h at room temperature until the reaction get complies in TLC. After completion of the reaction added 1N HCl (200 mL) to the wine red colour reaction mass to remove excess of triethyl-amine, the obtained organic residue after distillation under reduced pressure was isolated in isopropyl ether (IPE) and got 25 g pure material. $^1$H NMR (DMSO-$_d$6): δ 12.21 (s, 1H), 9.48 (s, 1H), 9.06 (t, 1H), 7.38 (t, 2H), 7.16 (t, 2H), 4.51 (d, 2H), 3.36 (s, 3H), 1.64 (s, 6H); $^{13}$C NMR (DMSO-$_d$6): δ 168.45,
Synthesis of $2\times(2(2-(2\text{-hydrazinyl})-2\text{-oxoacetamido})\text{propan-2-yl})-N-(4\text{-fluorobenzyl})-5\text{-hydroxy-1-methyl-6-oxo-1,6-dihydroprypimidine-4-carboxamide}$ (3): In a clean and dry four necked round bottom flask fitted with mechanical stirrer, 20 g of compound 4 was taken in 250 mL of absolute ethanol under gentle stirring followed by 5 g of 80% hydrazine hydrate at 25-35 °C. The reaction mixture was stirred for 15 min at 25-35 °C and then slowly heated the reaction mass to reflux temperature. After 45 min reaction was completed over TLC and then the reaction mass was cooled to room temperature the obtained off-white color precipitate was filtered and washed with excess ethanol (50 mL) and dried the material under reduced pressure. The resulting yield was 17.5 g with HPLC purity 99.8%. 1H NMR (DMSO-$d_6$): δ 10.68 (t, 1H), 9.09 (bs, 1H), 7.31–7.35 (m, 2H), 7.15 (t, 2H), 4.46 (d, 2H), 4.20–4.25 (q, 2H), 1.68 (s, 6H), 1.25 (t, 3H); 13C NMR (DMSO-$d_6$): δ 167.30, 163.65, 162.22, 159.82, 158.83, 157.97, 152.98, 143.18, 136.34, 129.11, 123.59, 115.02, 62.19, 41.12, 32.41, 27.02. Mass: M$: 420.39, M+H$: 421.2 (-ve scan).

Synthesis of ($E$)-$N$-(2-(2-(4-(4-fluorobenzyl)carbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydroprypimidin-2-yl) propan-2-yl)amino)-2-oxoacetyl)acetohydrazic acid (2): In a 250 mL round flask fitted with dean-stark condenser 10 g of compound 3 and 20 mL of acetic acid was taken in 100 mL of toluene. The reaction mixture was slowly heated to reflux for 4-5 h to collect the condensed water. After completion, the reaction mass was cooled to room temperature and the resulting precipitate was filtered, washed with another 20 mL of fresh toluene. The filter cake was dried and reported the yield as 14 g with HPLC purity 99.0%. 1H NMR (DMSO-$d_6$): δ 12.22 (s, 1H), 10.42 (s, 1H), 9.88 (s, 1H), 9.53 (d, 1H), 9.09 (d, 1H), 7.36-7.40 (m, 2H), 7.16 (t, 2H), 4.51 (d, 2H), 3.42 (s, 3H), 1.87 (t, 2H), 1.70 (s, 6H); 13C NMR (DMSO-$d_6$): δ 168.47, 167.84, 168.29, 167.34, 167.30, 165.98, 165.39, 162.13, 159.73, 158.60, 157.47, 151.91, 137.17, 129.04, 129.04, 128.96, 122.46, 114.91, 114.70, 57.19, 40.87, 32.11, 26.91, 10.64; Mass: M$: 444.42, M+H$: 445.30 (+ve scan). FT-IR: 3428.51, 3176.09, 3030.01, 3010.61, 2959.48, 2636.11, 1631.46, 1544.25, 1516.78, 1575.95, 693.36.

When initiated raltegravir potassium process related impurities synthesis at S.M.S. Pharmaceutical R&D Center, unfortunately got this idea about synthesis raltegravir API with retro approach (Scheme-IV), since the commercial availability of 1H NMR (DMSO-$d_6$): δ 10.68 (t, 1H), 9.09 (bs, 1H), 7.32 (m, 2H), 7.13 (t, 2H), 3.39 (s, 3H), 2.56 (s, 3H), 1.69 (s, 6H); 13C NMR (DMSO-$d_6$): δ 167.34, 165.98, 165.39, 162.13, 159.73, 158.60, 157.47, 151.91, 137.17, 129.04, 129.04, 128.96, 122.46, 114.91, 114.70, 57.19, 40.87, 32.11, 26.91, 10.64; Mass: M$: 444.42, M+H$: 445.30 (+ve scan). FT-IR: 3428.51, 3176.09, 3030.01, 3010.61, 2959.48, 1676.23, 1655.52, 1631.46, 1544.25, 1516.78, 1575.95, 693.36.

RESULTS AND DISCUSSION

When initiated raltegravir potassium process related impurities synthesis at S.M.S. Pharmaceutical R&D Center, unfortunately got this idea about synthesis raltegravir API with retro approach (Scheme-IV), since the commercial availability of

Scheme-IV: Retro synthetic approach for synthesis of raltegravir from compound 5
its critical raw material known as potassium 5-methyl-1,3,4-oxadiazole-2-carboxylate is rare and having some stability issue during the synthesis process. Therefore to circumvent all these issues, a new route of synthesis for raltegravir potassium is developed.

The first step in this work involves N-acylation process between ethyl oxalyl chloride and compound 5 in presence of a base to afford compound 4, which was further treated with hydrazine hydrate in presence of alcohol and then coupled with acetic acid followed by cyclization to afford compound 3, 2 and 1, respectively as shown in Scheme-II.

**Conclusion**

A retro-approach synthesis of raltegravir potassium was explored with possible commercial raw materials in an economic way of synthetic methodology. It will be recommended for commercial manufacturing site to produce raltegravir potassium without using potassium 5-methyl-1,3,4-oxadiazole-2-carboxylate and to avoid the key starting material random stability issues.

**ACKNOWLEDGEMENTS**

The authors are thankful to S.M.S. Pharmaceuticals Ltd. for providing funding to do this.

**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interests regarding the publication of this article.

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