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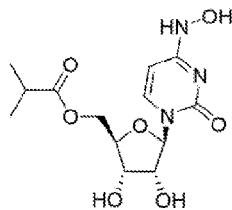
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Formula I

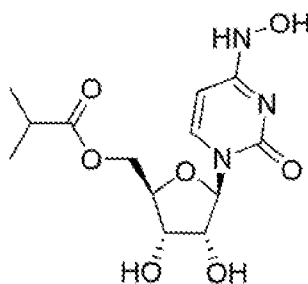
(57) Abstract: Present invention relates to a short and cost-effective synthetic process for synthesis of a broad-spectrum antiviral drug Molnupiravir (EIDD 2801) of formula I. Particularly, the present invention relates to a process for synthesis of a broad-spectrum antiviral drug EIDD 2801 via a short synthetic route from the basic starting material D-ribose. The present invention also decreases the usage of purification processes such as column chromatography after individual steps in comparison to the prior arts which makes the present process a green alternative. Finally, the use of cheap raw materials makes the process cost effective and industrially viable.



A PROCESS FOR PREPARATION OF ANTI VIRAL DRUG MOLNUPIRAVIR (EIDD 2801) FROM D-RIBOSE

FIELD OF THE INVENTION

5 Present invention relates to a short and cost-effective synthetic process for the synthesis of a broad-spectrum antiviral drug Molnupiravir (**EIDD 2801**) of formula **I**. Particularly, the present invention relates to a process for the synthesis of a broad-spectrum antiviral drug **EIDD 2801** from the basic starting material D-ribose.



Formula I

BACKGROUND AND PRIOR ART OF THE INVENTION

The 'Spanish flu' or '1918 influenza pandemic' caused by an H1N1 virus can be considered as the most severe pandemic in recent history. It is estimated that about 500 million people or one-third of the world's population became infected with this virus claiming lives of at least 50 million. Since 1980's after HIV infection was characterized as a severe condition, more than 30 million people have lost their lives. Recently, the world has seen a lot of viral disease outbreaks, the latest ones being Nipah, Ebola and MERS with 60%, 50% and 36% mortality rates respectively. The recent outbreak of corona virus disease (COVID-19) has affected 217 countries causing infection in approximately 72 million individuals claiming more than 1.6 million lives in a short time. The alarming fact is that there are no drugs available which can cure most of the above-mentioned viral infections.

EIDD 2801 (Molnupiravir) is a broad-spectrum antiviral showing promising activities against disease causing RNA viruses such as influenza, SARS, MERS and COVID-19. **EIDD 2801** (Molnupiravir) is an experimental antiviral originally developed by Emory University which was proven to be active against a range of RNA viruses such as chikungunya virus, Venezuelan

equine encephalitis virus (VEEV), respiratory syncytial virus (RSV), hepatitis C virus, norovirus, influenza A and B viruses, and Ebola virus. The researchers at Emory recently have shown that this molecule was active against MERS-CoV by inhibiting the RNA dependent RNA polymerase. This observation has triggered the research on checking whether this molecule would be active against COVID-19. They also claim that this drug could be taken orally which would be an added advantage compared to Remdesivir which is being administered intravenously. (Reference may be made to: (a) Painter *et al.* (WO2019113462A1); (b) Agostini M. L.; *et al. J. Virol.*, 2019, 93, e01348-19; (c) Urakova N.; *et al. J. Virol.*, 2017, 92, e01965-17; (d) Ehteshami M.; *et al. Antimicrob. Agents Chemother.*, 2017, 61, e02395-16; (e) Costantini V. P.; *et al. Antivir. Ther.*, 2012, 17, 981–991; (f) Yoon J.-J.; *et al. Antimicrob. Agents Chemother.*, 2018, 62, 1427; (g) Reynard O.; *et al. Viruses*, 2015, 7, 6233-6240; (h) Stuyver L. J.; *et al. Antimicrob. Agents Chemother.* 2003, 47, 244-254.) This drug is currently in phase 2 clinical trials in USA and UK.

The innovators have made **EIDD 2801** (broad spectrum antiviral) from an advanced intermediate uridine in five steps (WO2019113462A1). The first step of the synthesis involved the protection of the 2' and 3'' hydroxyl of the ribose ring as an acetonide. In the second step, esterification of the 1° alcohol was done with 2-methylpropanoyl 2-methylpropanoate and a base. This was followed by a two-step installation of hydroxylamine moiety on the uracil ring. The final step furnished EIDD 2801 after acetonide-deprotection with formic acid. Recently another route from uridine (five-steps) was reported by reordering the innovators scheme (Steiner A *et al.*; *Eur. J. Org. Chem.*, **2020**, 6736–6739). An enzymatic route towards EIDD 2801 was reported starting from another advanced intermediate cytidine (Vasudevan N.; *et al. Chem. Commun.*, 2020, 56, 13363-13364, doi.org/10.26434/chemrxiv.12818327.v1 and Ahlqvist G A. *et al.*; *ACS Omega* **2021**, 6, 10396–10402.). Very recently, another process was reported starting from D-ribose by utilizing enzymatic reactions (<https://doi.org/10.26434/chemrxiv.13472373.v1>). The four processes mentioned above required the use of advanced intermediates as starting materials, expensive reagents/enzymes and also the intermediates were purified by extensive column chromatography throughout. However, the present invention discloses a novel process towards **EIDD 2801** synthesis.

ABBREVIATIONS USED

HMDS –Hexamethyldisilazane

TMSCl – Trimethylsilyl chloride

TMSOTf – Trimethylsilyl trifluoromethanesulfonate

5 CH₃CN - Acetonitrile

DMAP– 4-(Dimethylamino)pyridine

DCM – Dichloromethane

DCE - 1,2-Dichloroethane

Et₃N – Triethylamine

10 TrCl - Trityl chloride

TLC – Thin layer chromatography

NMR – Nuclear Magnetic Resonance

HRMS – High Resolution Mass Spectroscopy

NH₂OH.HCl - Hydroxylamine hydrochloride

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OBJECTIVES OF THE INVENTION

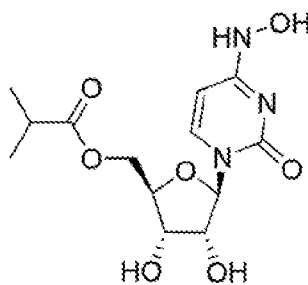
Main objective of the present invention is to provide a short, industrially viable and cost-effective process for the synthesis of broad-spectrum antiviral drug Molnupiravir (**EIDD 2801**).

Another object of the present invention is to provide a process for the synthesis of a broad-spectrum antiviral drug **EIDD 2801** from the basic starting material D-ribose.

Yet another object of the present invention is to provide industrially viable and cost-effective process which utilizes cheap raw materials that are available in plenty in comparison to the prior art.

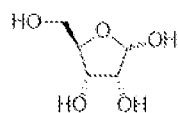
25 **SUMMARY OF THE INVENTION**

Accordingly, the present invention provides a process for the synthesis of anti-viral drug Molnupiravir (**EIDD-2801**) of formula I, comprising the steps of:

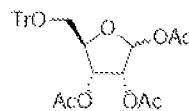


Formula I

- i. protecting primary hydroxyl group of D-ribose of formula 1 by tritylation and acetylation of the remaining secondary hydroxyl groups to obtain a crude compound of formula 2;

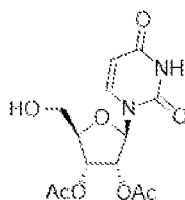


Formula 1



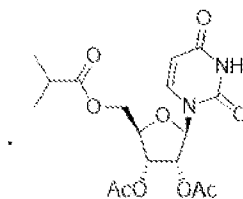
Formula 2

- ii. adding the crude compound of formula 2 as obtained in step (i) with uracil in the presence of **Hexamethyldisilazane** (HMDS), **Trimethylsilyl chloride** (TMSCl) and **trimethylsilyl trifluoromethanesulfonate** (TMSOTf) in acetonitrile to obtain a diacetylated uridine of formula 3;



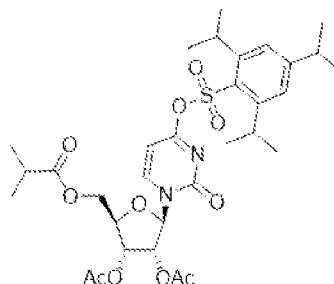
Formula 3

- iii. esterification of the primary hydroxyl-group of formula 3 as obtained in step (ii) with isobutyric anhydride in the presence of pyridine and 4-Dimethylaminopyridine (**DMAP**) in Dichloromethane (**DCM**) to obtain an ester of formula 4;



Formula 4

- iv. treating ester of formula **4** as obtained in step (iii) with 2,4,6-triisopropylbenzenesulfonyl chloride in the presence of Et₃N (triethylamine) and 4-Dimethylaminopyridine (**DMAP**) in Dichloromethane (**DCM**) at room temperature in a range of 20 to 30°C to obtain a tosylate of formula **5**;



Formula **5**

followed by treating the tosylate of formula **5** with excess of NH₂OH.HCl in the presence of Et₃N in DCE (1,2-dichloroethane) at room temperature in a range of 20 to 30°C to obtain anti-viral drug Molnupiravir (**EIDD-2801**) of formula **I**;

optionally treating ester of formula **4** as obtained in step (iii) with NH₂OH.HCl in the presence of imidazole and KHSO₄ in **Hexamethyldisilazane** (HMDS) at temperature in a range of 75 to 85°C for a period in a range of 36 to 48 hours followed by treating with excess of NH₂OH.HCl in the presence of Et₃N (triethyl amine) in DCE (1,2-dichloroethane) at room temperature in a range of 20 to 30°C to obtain anti-viral drug Molnupiravir (**EIDD-2801**) of formula **I**.

In an embodiment of the present invention, step (iv) to (v) are carried out in a one-pot process by avoiding intermediate purification steps.

In another embodiment of the present invention, step (iii) to (v) is carried out directly from compound of formula **3** by avoiding intermediate purification steps.

In an embodiment of the present invention, steps (iii) and (v) are carried out directly from compound of formula **3** by avoiding intermediate purification steps.

BRIEF DESCRIPTION OF THE FIGURES

FIG 1 illustrates the selective protection of D-ribose.

FIG 2 illustrates glycosylation and trityl-deprotection.

FIG 3 illustrates the esterification of the primary hydroxyl group.

FIG 4 illustrates the tosylation of amide carbonyl of uracil.

FIG 5 illustrates the synthesis of **EIDD 2801** by the installation of a hydroxylamine moiety and deprotection of acetyl groups.

5 **FIG 6** illustrates the one-pot synthesis of **EIDD 2801** from the ester by the installation of a hydroxylamine moiety and deprotection of acetyl groups.

FIG 7 illustrates the synthesis of **EIDD 2801** from the glycoside by avoiding intermediate purification processes.

FIG 8 illustrates the synthesis of **EIDD 2801** from D-ribose with only one column chromatography.

10 **FIG 9** illustrates another one-pot synthesis of **EIDD 2801** from the ester by the installation of a hydroxylamine moiety and deprotection of acetyl groups.

FIG 10 illustrates another synthesis of **EIDD 2801** from the glycoside by avoiding intermediate purification processes.

15 DETAILED DESCRIPTION OF THE INVENTION

The present invention discloses a process for the synthesis of broad-spectrum antiviral drug EIDD 2801.

Present invention provides a short process for the synthesis of broad-spectrum antiviral drug EIDD 2801 from a basic starting material, D-ribose.

20 Upon extensive investigations related to the synthetic routes towards the broad spectrum antiviral EIDD 2801, the present invention describes that the molecule could be made in fewer number of chemical transformations starting from cheap and basic starting materials.

The present invention provides an industrially viable and cost-effective process which utilizes cheap raw materials that are available in plenty in comparison to the prior art. The present
25 invention also decreases the usage of purification processes such as column chromatography after individual steps in comparison to the prior art which makes the process a green alternative.

The present invention intends to offer a process which was finalized after extensive optimizations of individual chemical transformations. This has lead to high yielding reactions that has increased the overall yield of the process.

The invention describes the synthesis of **EIDD 2801** starting from D-ribose. The first step involves the selective protection of the primary hydroxyl group of D-ribose by tritylation and acetylation of the remaining secondary hydroxyl groups (FIG. 1).

The present invention intends to disclose a one-pot glycosylation of **2** and trityl-deprotection of the glycoside. The crude product **2** was taken directly to the next step. The second step involves glycosylation of uracil with HMDS, TMSCl and TMSOTf in acetonitrile. In the same pot, the trityl-group deprotection occurred to furnish diacetylated uridine **3** (FIG. 2).

The third step of the process involved the esterification of the primary hydroxyl-group in **3** with isobutyric anhydride in the presence of pyridine and DMAP in DCM which afforded the corresponding ester **4** in 74% yield (FIG. 3).

In the fourth step of the process, the ester **4** is converted to tosylate **5** by treating the former with 2,4,6-triisopropylbenzenesulfonyl chloride in the presence of Et₃N and DMAP in DCM at room temperature from which the product was isolated in 58% yield (FIG. 4). Next, **5** was treated with excess of NH₂OH.HCl in the presence of Et₃N in DCE at room temperature. This transformation afforded **EIDD 2801** in 67% over two transformations, namely nucleophilic substitution and acetyl-deprotection (FIG. 5).

The present invention intends to disclose a one-pot installation of hydroxylamine moiety on **4**. This transformation commenced with the conversion of uridine amide carbonyl of **4** to a leaving group by treating with 2,4,6-triisopropylbenzenesulfonyl chloride in the presence of Et₃N and DMAP in DCM at room temperature. This was followed by the installation of hydroxylamine moiety on the intermediate **5** by a nucleophilic substitution reaction. For this, the intermediate **5** was treated with excess of NH₂OH.HCl in the presence of Et₃N in DCE at rt. This transformation afforded **EIDD 2801** in 40% over three transformations, namely tosylation, nucleophilic substitution and acetyl-deprotection (FIG. 6).

The present invention also describes a synthetic route from glycoside **3** towards **EIDD 2801** by combining some reactions mentioned above in one-pot (FIG 7). After each reaction, the mixtures were worked up or distilled and the crude was taken directly to the next step. From this attempt **EIDD 2801** was obtained in 20% yield.

The present invention also describes a synthetic route from ribose towards **EIDD 2801** by combining some reactions mentioned above in one-pot (FIG 8). In this route only one column

purification was done i.e., for the purification of the glycoside **3**. All the other reaction mixtures were worked up or distilled and the crude was taken directly to the next step.

The present invention also describes a synthetic route from the ester **4** towards **EIDD 2801** (FIG 9). The synthesis was effected by treating **4** with $\text{NH}_2\text{OH}\cdot\text{HCl}$ in the presence of imidazole and KHSO_4 in HMDS at 85°C for 48 hours and upon completion the crude reaction mixture was treated with excess of $\text{NH}_2\text{OH}\cdot\text{HCl}$ in the presence of Et_3N in DCE at room temperature in the range of 20 to 30°C to obtain anti-viral drug Molnupiravir in 73% yield (**EIDD-2801**).

The present invention also describes a synthetic route from glycoside **3** towards **EIDD 2801** by combining some reactions mentioned above in one-pot (FIG 10). After each reaction, the mixtures were worked up or distilled and the crude was taken directly to the next step.

EXAMPLES

Example 1. Synthesis of protected ribose **2**

D-Ribose (**1**) (5.0 g, 33.3 mmol, 1.0 equiv.) was dissolved in 50 mL pyridine. The reaction mixture was cooled to 0°C and to which NEt_3 (10.01 mL, 71.94 mmol, 1.8 equiv.) and TrCl (11.14 g, 39.96 mmol, 1.2 equiv) (for better yield use recrystallized TrCl) were added and was allowed to stir at room temperature [25°C] for 12 hours. After completion of the reaction, pyridine was evaporated under reduced pressure in a rotary evaporator with methanol. The residue was dissolved in EtOAc and washed with brine solution. The organic layer was dried over anhydrous Na_2SO_4 and then the solvent was removed under reduced pressure in a rotary evaporator and dried under vacuum. The crude gummy product obtained was dissolved in 50 mL of pyridine and cooled to 0°C . Then acetic anhydride (12.59 mL, 133.2 mmol, 4.0 equiv.) was slowly added to the reaction and was allowed to stir for 16 h at room temperature ($\sim 30^\circ\text{C}$). After completion of the reaction, the solvent was removed under vacuum and the residue was dissolved in EtOAc . The organic layer was washed with a saturated solution of NaHCO_3 followed by saturated CuSO_4 solution and finally with brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to furnish 12.945 g (75%) of a pale-yellow gummy product **2**.

^1H NMR (CDCl_3 , 500 MHz): δ 7.54-7.52 (m, 7H), 7.36-7.33 (m, 8H), 6.29 (s, 1H), 5.60-5.58 (m, 1H), 5.53 (d, $J = 5$ Hz, 1H), 4.41-4.39 (m, 1H), 3.46-3.43 (m, 1H), 3.26-3.23 (m, 1H), 2.15 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ 169.6, 169.5, 169.4, 143.7,

128.7, 127.8, 127.1, 98.3, 86.8, 80.9, 74.3, 70.8, 63.2, 21.1, 20.5, 20.5 ppm; HRMS (ESI): m/z Calcd for C₃₀H₃₀NaO₈: 541.18384, found: 541.18329.

Example 2. Synthesis of 2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diyl-diacetate 3

5 To a dried two necked RB flask equipped with a magnetic bead, uracil (1.18 g, 10.61 mmol, 1.1 equiv.) was added and the set-up was degassed for 10 min. The reaction set-up was then flushed with argon and to which anhydrous CH₃CN (50 mL) followed by HMDS (5.0 mL, 24.91 mmol, 2.5 equiv.) and TMSCl (0.61 mL, 4.82 mmol, 0.5 equiv.) were added. The reaction mixture was then allowed to continue at 80 °C for 12 h or until the turbid solution becomes clear after which
10 it was allowed to attain ambient temperature (~30 °C). Compound **2** (5.0 g, 9.64 mmol, 1.0 equiv.) was weighed into another two necked RB and was degassed for 10 min. Then, under argon atmosphere, **2** was dissolved in 5.0 mL of anhydrous CH₃CN and this solution was added to the reaction mixture at room temperature (30 °C) followed by TMSOTf (2.61 mL, 14.46 mmol, 1.5 equiv.). The reaction mixture was allowed to stir at 80 °C under argon atmosphere for 1-2 h
15 or until **2** was completely consumed. After the completion of reaction, the solvent was evaporated under vacuum and the residue was dissolved in EtOAc. The organic layer was washed with saturated NaHCO₃ solution and brine and then dried over anhydrous Na₂SO₄. The solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, 100-200 mesh, Hexane-Ethyl acetate 3:7) to yield the product **3** (2.18 g, 69 %). ¹H NMR (CDCl₃, 500MHz): δ 8.33 (brs, 1H), 7.65 (d, J = 8Hz, 1H), 5.99 (d, J = 4.5Hz, 1H), 5.71 (d, J = 8.0 Hz, 1H), 5.40 (d, J = 3.5Hz, 1H), 4.15 (s, 1H), 3.89 (d, J = 12Hz, 1H), 3.80 (d, J = 11.5Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H) ppm; HRMS (ESI): m/z Calcd for C₁₃H₁₆N₂NaO₈: 351.08044, found: 351.08127.

25 **Example 3. Synthesis of 2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((isobutyryloxy)methyl)tetrahydrofuran-3,4-diyl diacetate 4 from glycoside 3**

To a dried two necked RB flask equipped with a magnetic bead, **3** (5.0 g, 15.24 mmol, 1.0 equiv.) was weighed and then degassed for 15 min. The compound **3** was then dissolved in anhydrous DCM and cooled to 0 °C after which pyridine (2.5 mL, 30.47 mmol, 2.0 equiv.),
30 DMAP (465 mg, 7.62 mmol, 0.5 equiv.) and isobutyric anhydride (2.8 mL, 16.73 mmol, 1.1 equiv.) were added and allowed to stir at room temperature (~30 °C) under argon for 12 h. After

the completion of the reaction as monitored by TLC, the mixture was concentrated in vacuo and the crude was immediately purified by column chromatography (silica gel, 100-200 mesh, Hexane- Ethyl acetate, 5:5) to yield product **4** (4.49 g, 74%) as a pale yellow viscous liquid. ¹H NMR (CDCl₃, 500MHz): δ 9.45 (brs, 1H), 7.44 (d, J = 10Hz, 1H), 6.09 (d, J = 5.0 Hz, 1H), 5.80 (d, J = 10.0 Hz, 1H), 5.35-5.34 (m, 2H), 4.41-4.32 (m, 3H), 2.67-2.59 (m, 1H), 2.14 (s, 3H), 2.11 (s, 3H), 1.24-1.22 (m, 3H) ppm; ¹³C NMR (CDCl₃, 125MHz): δ 176.3, 169.7, 162.9, 150.3, 139.2, 103.4, 87.0, 80.1, 72.8, 70.2, 63.1, 34.0, 20.5, 20.4, 19.0, 18.9 ppm; HRMS (ESI): m/z Calcd for C₁₇H₂₂N₂NaO₉: 421.12230, found: 421.12329.

Example 4. Synthesis of tosylate **5** from the isobuytryl ester **4**

The esterified uridine **4** (5.0 g, 12.55 mmol, 1.0 equiv.) and DMAP (153.3 mg, 1.26 mmol, 0.1 equiv.) were taken in a two necked RB, degassed for 10 min, dissolved in 50 mL of dry distilled DCM and cooled to 0 °C under argon atmosphere. To this reaction mixture Et₃N (10.5 mL, 75.3 mmol, 6.0 equiv.) was added and allowed to stir at 0 °C for 30 min followed by the addition of 2,4,6-triisopropyl-benzene sulfonyl chloride (6.46 g, 21.33 mmol, 1.7 equiv.). The reaction mixture was allowed to stir under argon at 0 °C for 1 h and then at room temperature (~30 °C) for additional 12 h. The completion of the reaction was confirmed by checking the TLC, after which the reaction mixture was evaporated under vacuum. The crude was dissolved in DCM and the organic layer was washed with water and then with brine. The organic layer dried over anhydrous Na₂SO₄ was evaporated in vacuo and the crude product was purified by column chromatography on silica gel (100-200 mesh) with mixtures of hexane:ethyl acetate (5:5) as the eluent to obtain the product **5** obtained as pale yellow viscous liquid (4.73 g, 58%). ¹H NMR (CDCl₃, 500MHz): δ 7.90 (d, J = 7.0 Hz, 1H), 7.14 (s, 2H), 6.03 (d, J = 7.0 Hz, 1H), 5.96 (d, J = 4.0 Hz, 1H), 5.27 (d, J = 4.5 Hz, 1H), 5.19 (t, J = 5.5 Hz, 1H), 4.34-4.32 (m, 1H), 4.27-4.24 (m, 1H), 4.20-4.14 (m, 2H), 2.87-2.83 (m, 1H), 2.34-2.51 (m, 1H), 2.03 (s, 3H), 1.99 (s, 3H), 1.24-1.12 (m, 3H) ppm; ¹³C NMR (CDCl₃, 125MHz): δ 176.3, 169.4, 169.3, 167.2, 154.7, 153.4, 151.3, 144.8, 130.4, 124.1, 95.7, 89.1, 79.9, 73.9, 69.2, 62.3, 34.3, 34.0, 29.7, 24.3, 24.5, 23.4, 20.4, 20.4, 19.0, 18.9 ppm; HRMS (ESI): m/z Calcd for C₃₂H₄₄N₂NaO₁₁S: 687.25635, found: 687.26093.

Example 5. Synthesis of EIDD 2801 from tosylate **5**

Compound **5** (5.0 g, 7.68 mmol, 1.0 equiv.) was taken in a two necked RB flask and degassed for 30 min and then dissolved in anhydrous DCE (50.0 mL) under argon atmosphere. To this mixture, Et₃N (4.2 mL, 30.73 mmol, 4.0 equiv.) and NH₂OH.HCl (1.06 g, 15.36 mmol, 2.0 equiv.) were added and allowed to stir at room temperature (~30 °C) for 12 h. After completion of the reaction, **EIDD 2801** was precipitated out from the reaction mixture with methanol as a white solid (1.69 g, 67%). ¹H NMR (CDCl₃, 500 MHz): δ 6.81 (d, J = 8.5 Hz, 1H), 5.72 (d, J = 5.0 Hz, 1H), 5.51 (d, J = 8.5 Hz, 1H), 4.19-4.18 (m, 2H), 4.03-4.02 (m, 1H), 3.99-3.97 (m, 2H), 2.52-2.50 (m, 1H), 1.09 (s, 3H), 1.08 (s, 3H) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ 176.9, 150.2, 144.8, 130.4, 98.2, 89.1, 81.2, 73.0, 70.1, 63.6, 33.8, 18.0, 17.9 ppm; HRMS (ESI): m/z Calcd for C₁₃H₁₉N₃NaO₇: 352.1121, found: 352.1127.

Example 6. Synthesis of EIDD 2801 from 4 without any intermediate purifications

The esterified uridine **4** (5.0 g, 12.55 mmol, 1.0 equiv.) and DMAP (153.3 mg, 1.26 mmol, 0.1 equiv.) were taken in a two necked RB, degassed for 10 minutes, dissolved in 50 mL of dry distilled DCM and cooled to 0 °C under argon atmosphere. To this reaction mixture Et₃N (10.5 mL, 75.3 mmol, 6.0 equiv.) was added and allowed to stir at 0 °C for 30 minutes followed by the addition of 2,4,6-triisopropyl-benzene sulfonyl chloride (6.46 g, 21.33 mmol, 1.7 equiv.). The reaction mixture was allowed to stir under argon at 0 °C for 1 hour and then at room temperature (~30 °C) for additional 12 hours. The completion of the reaction was confirmed by checking the TLC, after which the reaction mixture was evaporated under vacuum and the crude dissolved in DCM was washed with water and then with brine. The organic layer dried over anhydrous Na₂SO₄ was evaporated in vacuo and the crude product **5** was taken in a two necked RB flask, degassed for 30 min then dissolved in 50 mL of dry distilled DCE under argon atmosphere. To this reaction mixture 8.5 mL of Et₃N (60.96 mmol, 4.0 equiv.) and NH₂OH.HCl (2.12 g, 30.48 mmol, 2.0 equiv.) were added and allowed to stir at room temperature (~30 °C) for 12 hours. After completion of the reaction, the solvent was evaporated under vacuum to obtain an oil which was dissolved in EtOH (10 mL). This solution was again evaporated under vacuum and MTBE (20 mL) was added followed by ¹PrOH (2 mL) and the crude was dissolved by heating. While cooling, a solid precipitated out which was filtered and washed to furnish **EIDD 2801** (1.65 g, 40%) as a white solid.

Example 7. Synthesis of EIDD 2801 from glycoside 3 without any intermediate purifications

Compound **3** (5.0 g, 15.24 mmol, 1.0 equiv.) was taken in a two necked RB and degassed for 15 min which was then dissolved in dry distilled DCM and cooled to 0 °C. Then pyridine (2.5 mL, 30.47 mmol, 2.0 equiv.), DMAP (465 mg, 7.62 mmol, 0.5 equiv.) and isobutyric anhydride (2.8 mL, 16.73 mmol, 1.1 equiv.) were added and stirred at room temperature (30 °C) under argon atmosphere for 12 hours. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated, dried and the crude product **4** obtained as a pale yellow viscous liquid was transferred to a two necked RB, degassed for 30 min and DMAP (186.2 mg, 1.52 mmol, 0.1 equiv.) was added which was then dissolved in anhydrous DCE (50 mL) and cooled to 0 °C under argon atmosphere. To this reaction mixture Et₃N (12.7 mL, 91.43 mmol, 6.0 equiv.) was added and allowed to stir at 0 °C. After 30 minutes, 2,4,6-triisopropyl-benzene sulfonyl chloride (7.84 g, 25.91 mmol, 1.7 equiv.) was added and the reaction mixture was allowed to stir under argon atmosphere at 0 °C for 1 hour and then at room temperature (~30 °C) for an additional 12 hours. The completion of the reaction was confirmed by checking the TLC, after which the reaction mixture was washed with water and then with brine. The organic layer was dried over anhydrous Na₂SO₄ was evaporated in vacuo and the crude product **5** was taken in a two necked RB, degassed for 30 minutes and then dissolved in 50 mL of dry distilled DCE under argon atmosphere. To this reaction mixture 8.5 mL of Et₃N (60.96 mmol, 4.0 equiv.) and NH₂OH.HCl (2.12 g, 30.48 mmol, 2.0 equiv.) were added and allowed to stir at room temperature for 12 hours. After completion of the reaction, the solvent was evaporated under vacuum to obtain an oil which was dissolved in EtOH (10 mL). This solution was again evaporated under vacuum and MTBE (20 mL) was added followed by iPrOH (2 mL) and the crude was dissolved by heating. While cooling, a solid precipitated out which was filtered and washed to furnish **EIDD 2801** (1.005 g, 20%) as a white solid.

Example 8. Synthesis of EIDD 2801 from the isobutyryl ester 4

Imidazole (427.2 mg, 6.28 mmol, 0.5 equiv.) taken in a dried reaction tube and degassed for 10 min. To this then HMDS (40 mL) was added and stirred to 85 °C under Ar atmosphere. After 30 minutes to the clear solution, KHSO₄ (4.27 g, 31.38 mmol, 2.5 equiv.) was added and allowed to continue at 85 °C for another 30 min. Then to the reaction mixture, NH₂OH.HCl (1.04 g, 15.06

mmol, 1.2 equiv.) and **4** (5.0 g, 12.5512 mmol, 1 equiv.) were added and allowed to continue at 85 °C for another 48 hours. The completion of the reaction was confirmed by checking the TLC, after which the reaction mixture was extracted with EtOAc and washed with brine solution. The organic layer was dried over anhydrous Na₂SO₄ and the solvent was evaporated under vacuum to
5 obtain the intermediate **5** (crude) as a pale-yellow viscous liquid. The crude compound **5** was taken in a two neck RB and degassed for 30 min and dissolved in 25 mL of dry distilled DCE under argon atmosphere. To this, NEt₃ (2.63 mL, 25.1 mmol, 2.0 equiv.) and NH₂OH.HCl (1.74 g, 25.1 mmol, 2.0 equiv.) were added and allowed to stir at room temperature for 12 h. After the completion of reaction, the solvent was evaporated under vacuum in a rotary evaporator and the
10 residue was purified by column chromatography (silica gel, 100-200 mesh, Hexane-Ethyl acetate 3:7) to yield the product **EIDD 2801** as colourless powder (3.017 g, 73 %).

Example 9. Synthesis of EIDD 2801 from glycoside 3 without any intermediate purifications

15 Compound **3** (1.0 equiv.) was taken in a two necked RB and degassed for 15 min which was then dissolved in dry distilled DCM and cooled to 0 °C. Then pyridine (2.0 equiv.), DMAP (0.5 equiv.) and isobutyric anhydride (1.1 equiv.) were added and stirred at room temperature (30 °C) under argon atmosphere for 12 hours. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated, dried and the crude product **4** obtained as a pale-yellow
20 viscous liquid. Imidazole (0.5 equiv.) was taken in a dried reaction tube, degassed for 10 min, then add HMDS and stirred at 85 °C under Ar atmosphere. After 30 minutes, to this clear reaction mixture, KHSO₄ (2.5 equiv.) was added and then again allowed to continue at 85 °C for another 30 minutes. Then NH₂OH.HCl (1.2 equiv.) and compound **4** (1.0 equiv.) were added and allowed to continue at 85 °C for another 48 hours. The completion of the reaction was confirmed
25 by checking the TLC, after which the reaction mixture was extracted with EtOAc and washed with brine solution and dried over anhydrous NaSO₄. The solvent was evaporated in vacuo and the intermediate product **5** obtained as pale-yellow viscous liquid. The crude intermediate **5** (1.0 equiv.) was taken in a two neck RB and degassed for 30 minutes then dissolved in dry distilled DCE under argon atmosphere. To this NEt₃ (2.0 equiv.) and NH₂OH.HCl (2.0 equiv.) were
30 added and allowed to stir at room temperature for 12 hours. After the completion of reaction, the solvent was evaporated under vacuum in a rotary evaporator and the residue was purified by

column chromatography (silica gel, 100-200 mesh, Hexane-Ethyl acetate 3:7) to yield the product **EIDD 2801** as colourless powder.

ADVANTAGES OF THE INVENTION

- 5 • The process is short, industrially viable and cost effective.
- Synthetic route utilizing cheap raw materials which are available in plenty.
- Synthesis of the crucial glycoside intermediate in one-pot involving two transformations.
- Synthesis of **EIDD 2801** from glycoside intermediate by avoiding intermediate purification.
- 10 • Better yielding process than prior art.
- Decreases the usage of purification processes such as column chromatography after individual steps in comparison to the prior art.

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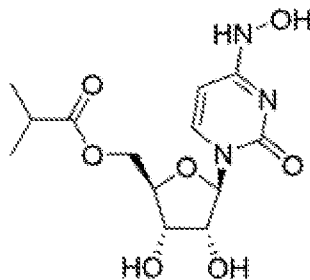
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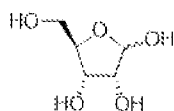
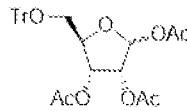
We claim

1. A process for the synthesis of anti-viral drug Molnupiravir (**EIDD-2801**) of formula **I**

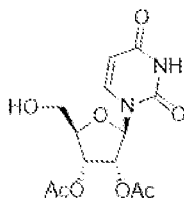
Formula **I**

comprising the steps of:

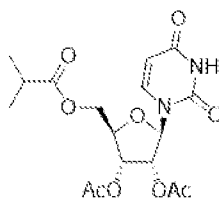
- 5 i. protecting primary hydroxyl group of D-ribose of formula **1** by tritylation and acetylation of the remaining secondary hydroxyl groups to obtain a crude compound of formula **2**;

Formula **1**Formula **2**

- 10 ii. adding the crude compound of formula **2** as obtained in step (i) with uracil in presence of hexamethyldisilazane (HMDS), **trimethylsilyl chloride** (TMSCl) and **trimethylsilyl trifluoromethanesulfonate** (TMSOTf) in acetonitrile to obtain a diacetylated uridine of formula **3**;

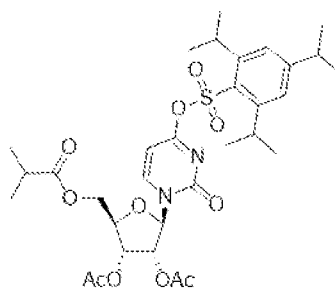
Formula **3**

- 15 iii. esterification of the primary hydroxyl-group of formula **3** as obtained in step (ii) with isobutyric anhydride in presence of pyridine and 4-dimethylaminopyridine (**DMAP**) in dichloromethane (**DCM**) to obtain an ester of formula **4**;



Formula 4

- iv. treating the ester of formula 4 as obtained in step (iii) with 2,4,6-triisopropylbenzenesulfonyl chloride in presence of Et₃N (triethylamine) and 4-dimethylaminopyridine (**DMAP**) in dichloromethane (**DCM**) at room temperature in a range of 20 to 30°C to obtain an intermediate of formula 5;



Formula 5

followed by treating the intermediate of formula 5 with excess of NH₂OH.HCl in presence of Et₃N in DCE (1,2-dichloroethane) at room temperature in a range of 20 to 30°C to obtain an anti-viral drug Molnupiravir (**EIDD-2801**) of formula I; optionally, treating the ester of formula 4 as obtained in step (iii) with NH₂OH.HCl in the presence of imidazole and KHSO₄ in HMDS at temperature in a range of 75 to 85°C for a period in a range of 36 to 48 hours followed by treating with excess of NH₂OH.HCl in the presence of Et₃N (triethyl amine) in DCE (1,2-dichloroethane) at room temperature in the range of 20 to 30°C to obtain an anti-viral drug Molnupiravir (**EIDD-2801**) of formula I.

2. The process as claimed in claim 1, wherein step iv is carried out in a one-pot process by avoiding intermediate purification steps.
3. The process as claimed in claim 1, wherein step iii to iv is carried out directly from compound of formula 3 by avoiding intermediate purification steps.

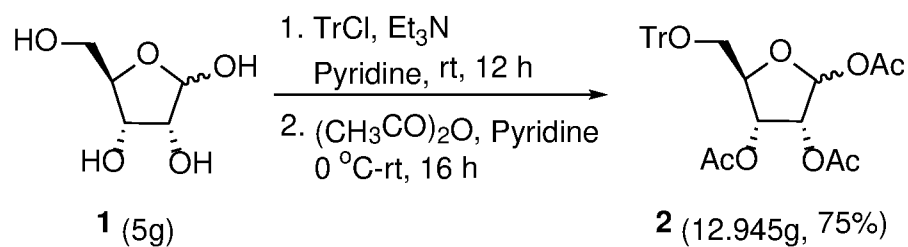


FIG. 1

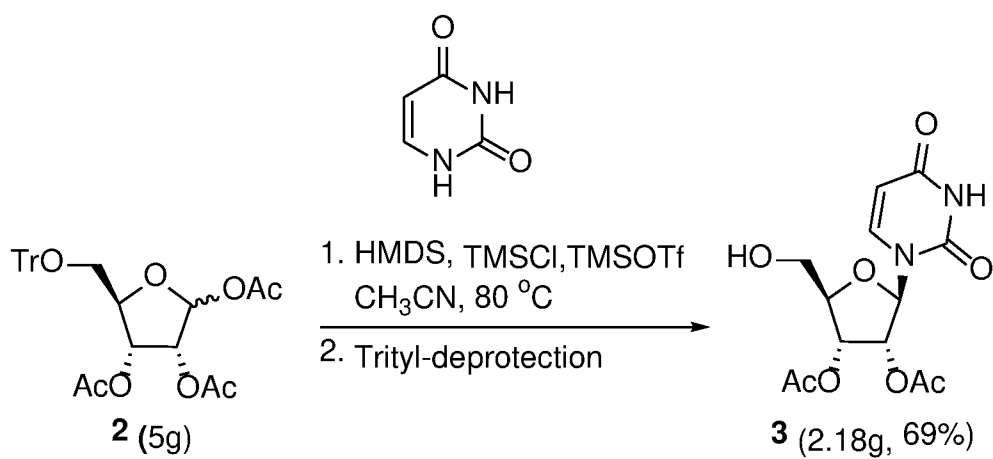


FIG. 2

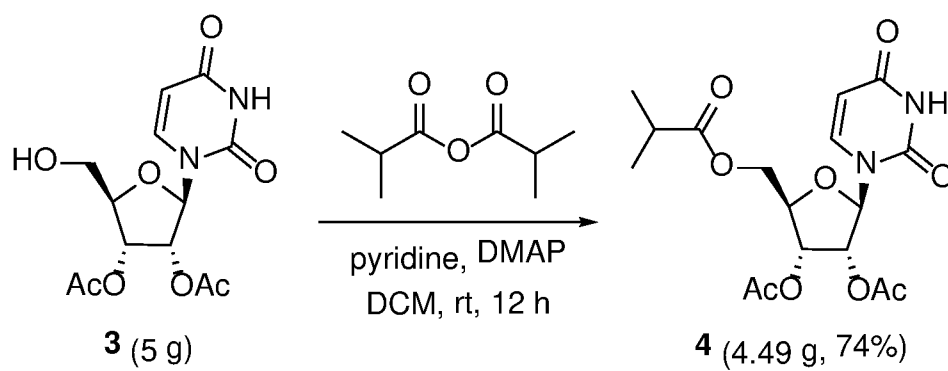


FIG. 3

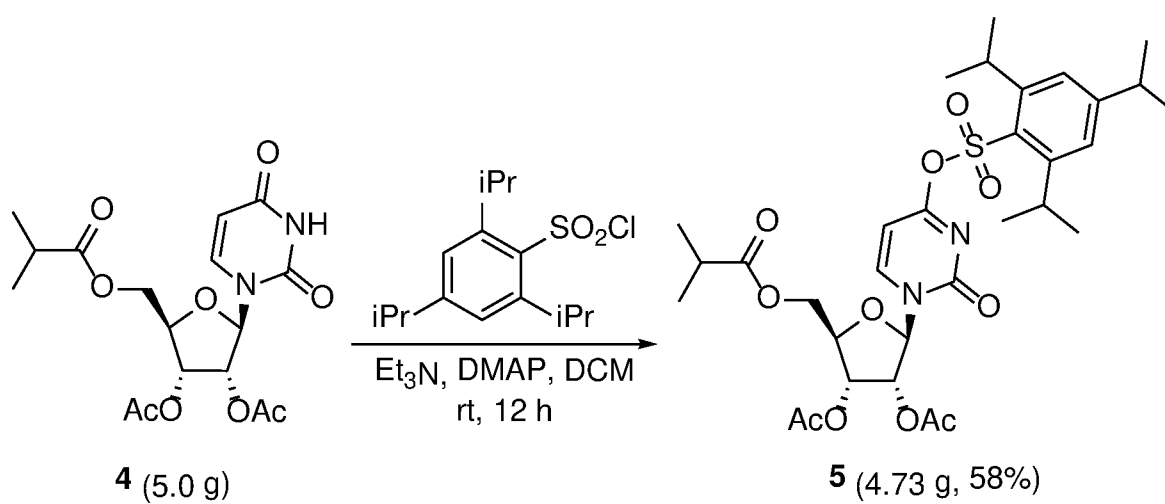


FIG. 4

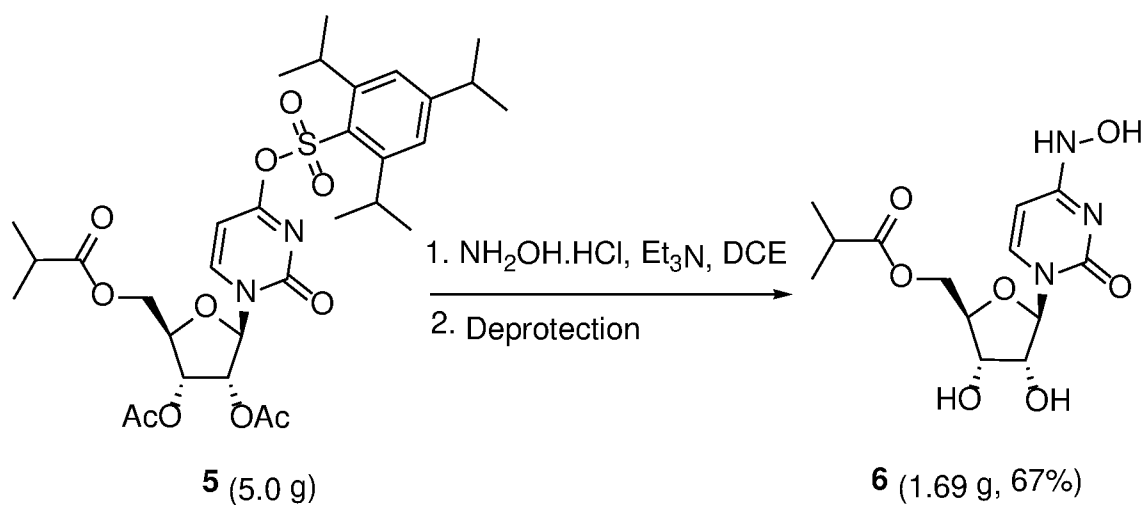


FIG. 5

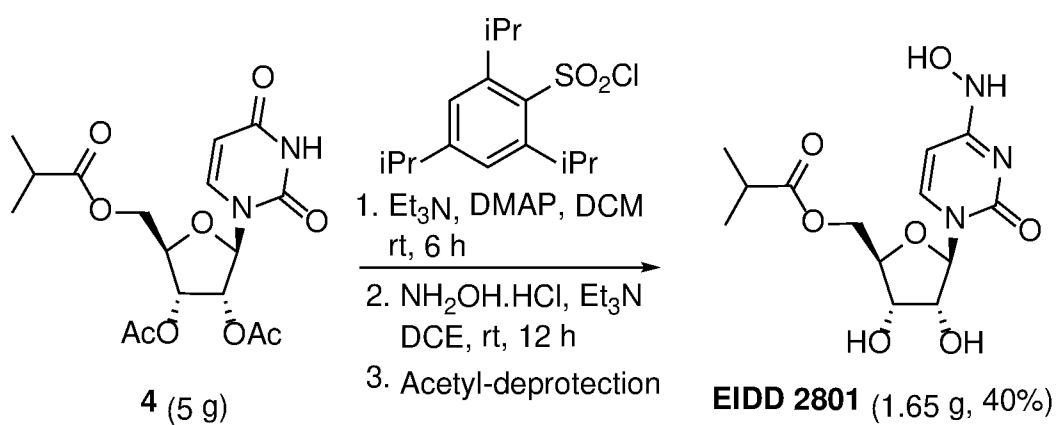


FIG. 6

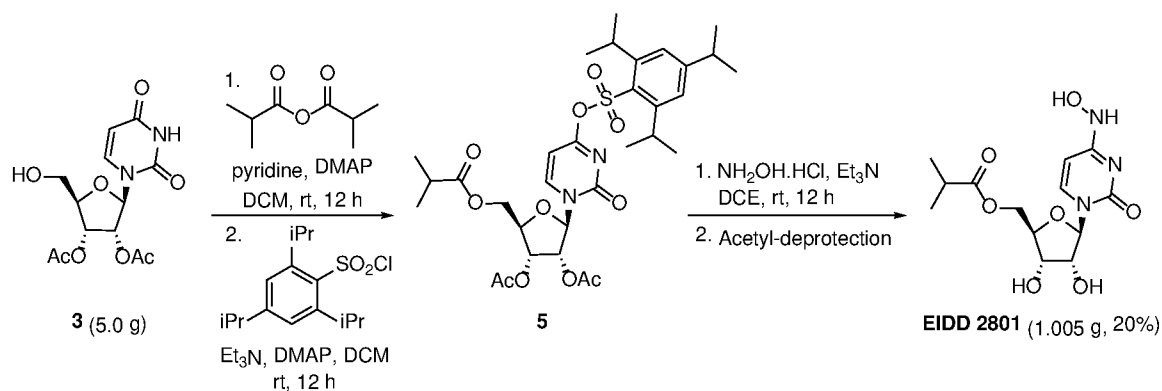


FIG. 7

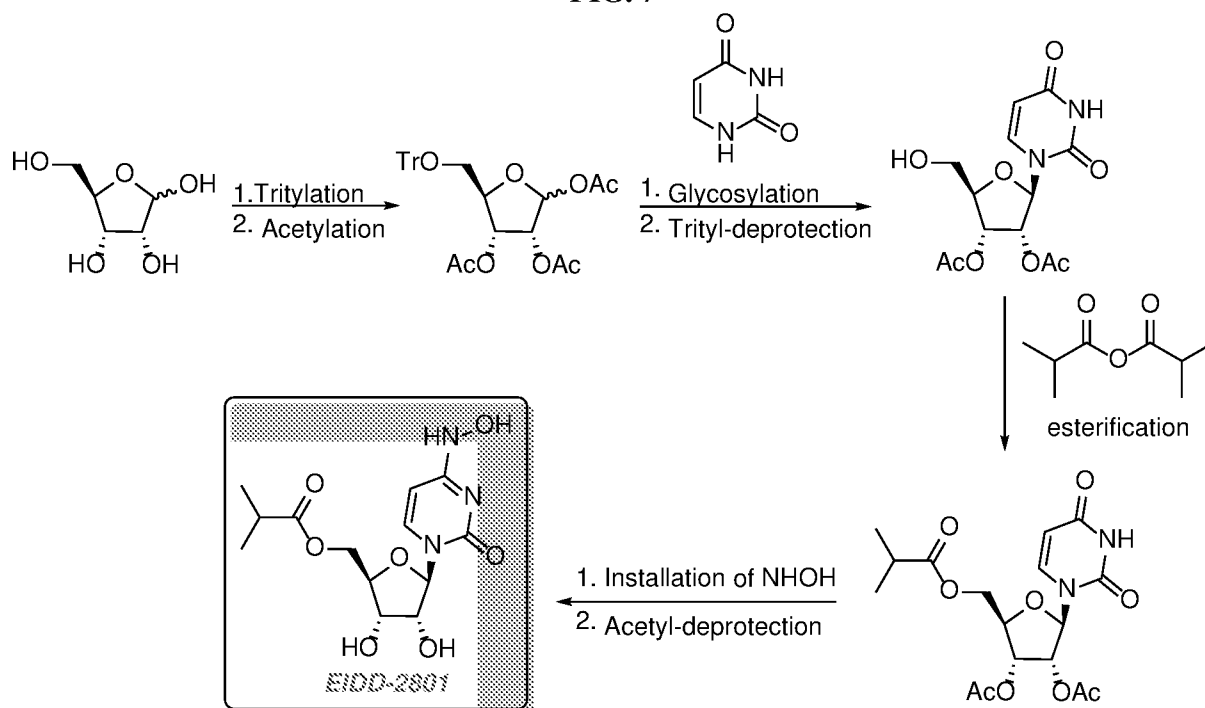


FIG. 8

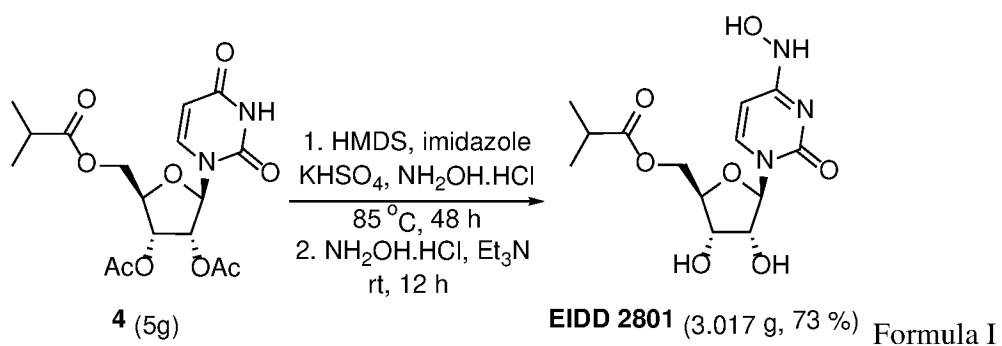


FIG. 9

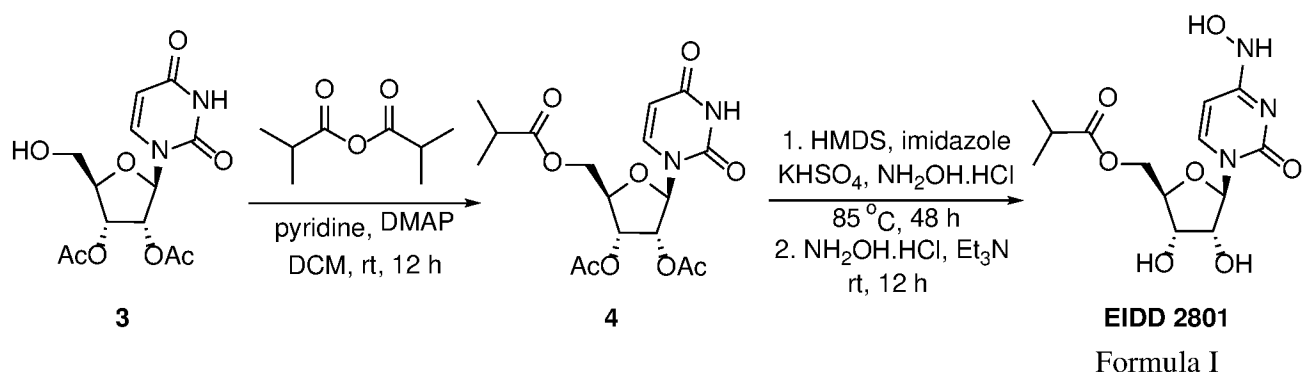


FIG. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2022/050395

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/7004 Version=2022.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Benkovics T, McIntosh J, Silverman S, Kong J, Maligres P, Itoh T, Yang H, Huffman M, Verma D, Pan W, Ho HI. Evolving to an ideal synthesis of molnupiravir, an investigational treatment for COVID-19, 23 December 2020, DOI:10.26434/chemrxiv.13472373. Abstract, schemes 1-7, figure 1	1-3
X	Ahlqvist GP, McGeough CP, Senanayake C, Armstrong JD, Yadaw A, Roy S, Ahmad S, Snead DR, Jamison TF. Progress toward a large-scale synthesis of molnupiravir (MK-4482, EIDD-2801) from cytidine. ACS omega. 2021 Apr 8;6(15):10396-10402. Abstract, figures 1-2	1-3
X	Vasudevan N, Ahlqvist GP, McGeough CP, Paymode DJ, Cardoso FS, Lucas T, Dietz JP, Opatz T, Jamison TF, Gupton FB, Snead DR. A concise route to MK-4482 (EIDD-2801) from cytidine. Chemical Communications. 2020;56(87):13363-13364. Abstract, schemes 1-2, figures 1-3, tables 1-3	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"D" document cited by the applicant in the international application	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"E" earlier application or patent but published on or after the international filing date	"&" document member of the same patent family
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 22-07-2022	Date of mailing of the international search report 22-07-2022
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14, Dwarka, New Delhi-110075 Facsimile No.	Authorized officer Dr. Dasari Ayodhya Telephone No. +91-1125300200