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One pot access to 2-iodo-2-deoxy nucleosides directly from glycals and unprotected nucleobases and their biological evaluation on the Japanese Encephalitis Virus[†]

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An expedient one-pot stereo- and regioselective synthesis of 2-iodo-nucleosides from protected glycals and nucleobases using easily available iodine and hexamethyldisilane as halogenating, and silylating agents respectively has been developed. Most of the products synthesized characterized as diastereomerically pure β -1,2-trans-diequatorial nucleosides hitherto not reported. The *in vitro* studies unveil the cogent antiviral activity of these newly synthesized nucleoside derivatives against the Japanese Encephalitis Virus (flavivirus) in the Vero cell line.

Nucleoside analogs (NAs) represent potent antiviral medications utilized in the treatment of various viral infections.¹ The ongoing emergence of new viral strains necessitates the development of innovative antiviral agents. Diversifying the structural characteristics of these agents is crucial for combating drug resistance and improving the effectiveness of combination therapies. Herein, we report the design and synthesis of nucleoside analogues with pyranose sugar as a novel template for antiviral with activity against Japanese Encephalitis Virus.

Japanese Encephalitis Virus (JEV) is a concerning pathogen, particularly prevalent in parts of Asia, where it's transmitted through mosquito bites.² A WHO study from 2019 states that there were around 68 000 cases of JE reported annually, with a 20–30% mortality rate. Globally, JEV was predicted to have caused around 100 308 clinical cases and 20 000–30 000 casualties in 2015, according to research that used age-stratified case data and mathematical modelling.²

Unfortunately, there's no specific medicine to combat JEV infection, and the existing treatments primarily focus on alleviating symptoms and supportive care.³ To address the lack of

proper medicines and the need for New Chemical Entities (NCEs), scientists and pharmaceutical companies are continually researching and developing novel antiviral therapies. These efforts aim to discover compounds that can effectively target the virus and inhibit its replication, thereby reducing the severity and duration of the infection. One class of compounds that has shown promise in antiviral therapy is nucleoside analogs. Nucleosides are the building blocks of nucleic acids like DNA and RNA. Nucleoside analogs are synthetic compounds designed to mimic natural nucleosides, but with modifications that make them effective against viruses.^{4–6}

The known nucleoside analogs as antivirals against flavivirus have already been mentioned in previous studies.^{4–6} Another known nucleoside inhibitor is ribavirin (1-[(2*R*,3*R*,4*S*,5*R*)-3,4-

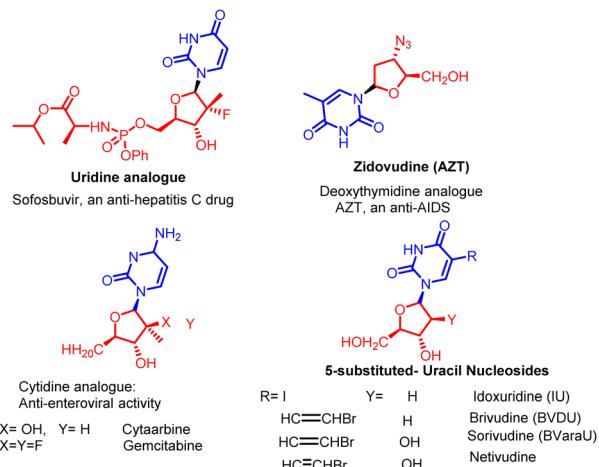


Fig. 1 Nucleoside analogues as potent antiviral agents.

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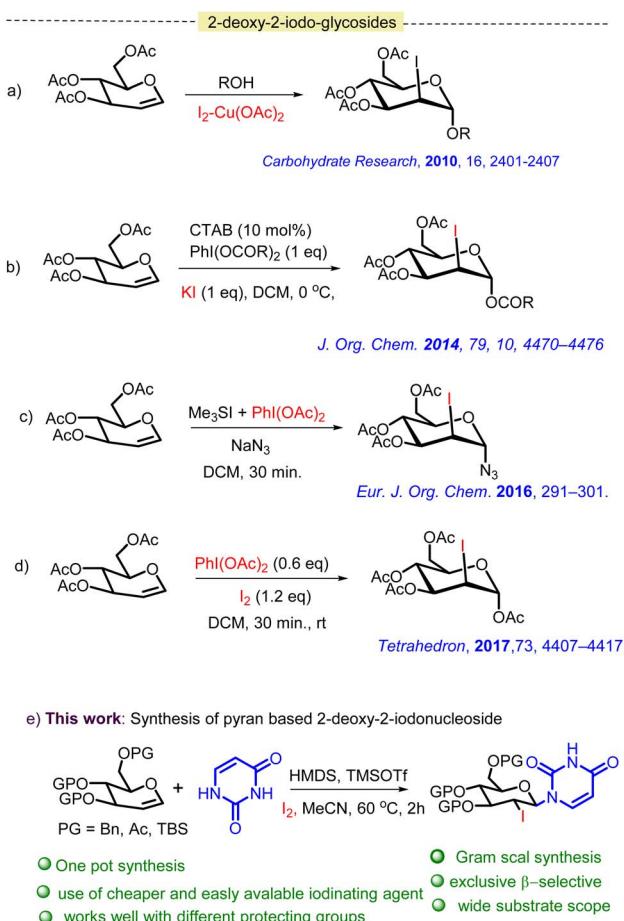
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Scheme 1 Prior art and this work.

Table 1 Optimization of the reaction conditions^a

Entry	Iodinating reagents (equiv)	Solvent	Temp. (°C)	Time (h)	Yield ^b (%)	β/α^c
1	NIS (2.0)	MeCN	80	2	54	1:1
2	NIS (2.0)	MeCN	60	3	58	1:0.5
3	NIS (2.0)	MeCN	40	5	15	1:0.5
4	NIS (2.0)	DCM	60	3	20	1:0.5
5	NIS (2.0)	DCE	60	2	52	1:0.5
6	I ₂ (2.0)	MeCN	60	2	85	1:0
7	I ₂ (1.5)	MeCN	60	2	67	1:0
8	I ₂ (1.0)	MeCN	60	2	56	1:0
9	I ₂ (2.5)	MeCN	60	2	80	1:0
10	ICl (2.0)	MeCN	60	2	62	1:0.1
11	IBX (2.0)	MeCN	60	2	59	1:0.1
12	I ₂ (2.5)	MeCN	80	2	60	1:0
13	ICl (2.0)	MeCN	80	2	42	1:0.5
14	IBX (2.0)	MeCN	80	2	40	1:0.5

^a Reaction conditions: in all cases, the reaction was carried out by heating uracil (3.0 equiv) in HMDS (4.5 equiv) and TMSOTf (0.3 equiv) in a solvent at 80 °C for 1.5 h followed by the addition of benzyl protected glucal (1.0 equiv) and iodinating reagent at the temperature mentioned in the table.

^b Isolated overall yields. ^c Diastereomeric ratio.

dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1H-1,2,4-triazole-3-carboxamide) effectively inhibits the replication in west nile virus and yellow fever virus.^{7,8} Some of the nucleoside drugs used as potent antiviral agents⁷⁻⁹ are illustrated in Fig. 1. But these nucleosides have drawbacks of their instability against both acidic and enzymatic hydrolysis, drug resistance and they also cause severe side effects to the host.¹⁰

Traditional methods primarily involve altering the nucleobase, as seen with antivirals like ribavirin, molnupiravir and clevudine.⁸ Alternatively, other approaches focus on simplifying, substituting, or modifying the ribose core. However, these nucleoside analogues (NAs) are not widely used due to the lack of anomeric stabilization, which frequently results in unnatural conformations and reduced biological activity.¹¹ The most studied among them is the ring size of sugar moiety has been modified to study the impact on biological activity and conformation. Replacement of furanoid sugar with a six-membered pyran ring of carbohydrate moiety were found more resistant to glycoside hydrolysis and was proved beneficial for their potential antiviral and antibiotic properties and as building blocks in nucleic acid synthesis.¹²

As per the synthesis of 2-deoxy-2-iodo-glycosides is concerned, a variety of efficient and practical methods have been developed for the synthesis of 2-deoxy-2-iodo glycosides and glycoconjugates from glycals. Using I₂-Cu(OAc)₂, tri-O-acetyl-D-glucal reacts with various alcohols to give 2-deoxy-2-iodo-O-glycosides in high yields with good anomeric selectivity (Scheme 1a).¹³ Islam *et al.* employed PhI(OAc)₂ with CTAB and KI to generate C2-deoxy-2-iodo glycoconjugates in good to excellent yields, which could be further transformed into amino acid glycoconjugates *via* dehalogenation (Scheme 1b).¹⁴ Reddy *et al.* utilized an *in situ*



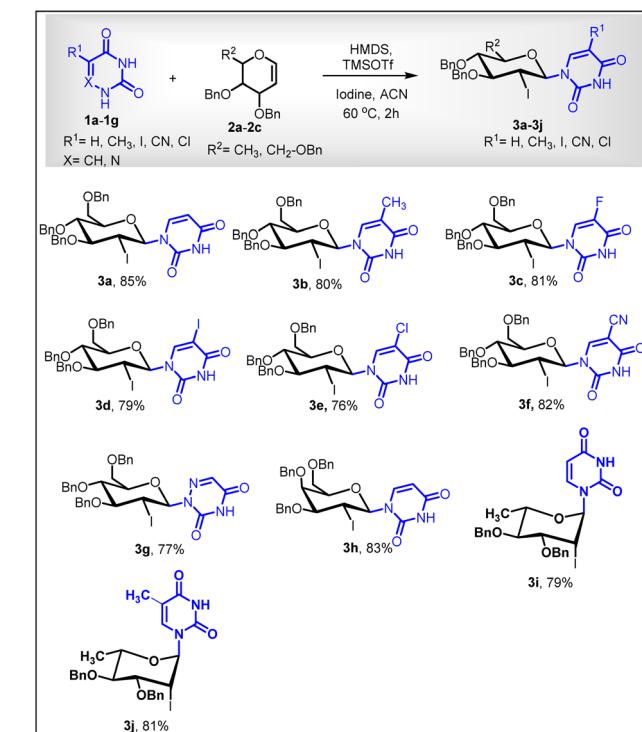
generated sulfonium-iodine(I) reagent from Me_3Si and $\text{PhI}(\text{OAc})_2$ for vicinal functionalization of glycals (Scheme 1c).¹⁵ Additionally, Saidhareddy *et al.* reported IBX- I_2 and $\text{PhI}(\text{OAc})_2\text{-I}_2$ mediated methods to afford 2-deoxy-2-iodoglycosyl acetates and *O*-iodobenzoates with high stereoselectivity (Scheme 1d).¹⁶ Herein, we present the stereo and regioselective synthesis of 2 deoxy-2-iodohexopyranose nucleosides directly from glycals and unprotected nucleobases (Scheme 1e).

We have started the optimization study by taking unprotected uracil and benzyl-protected glucal. Tri-*O*-benzyl-D-glucal (1.0 equiv) and NIS (2.0 equiv) were added to a preheated solution of uracil with HMDS (4.5 equiv) and TMSOTf (0.3 equiv) in MeCN at 80 °C and the resulting mixture was further

Table 2 Comparison of reaction outcomes between iodinating agents^a

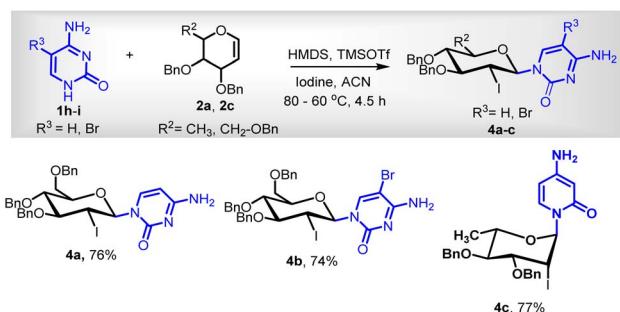
Entry	Iodinating reagents (equiv)	Yield ^b (%)	β/α^c
01	NIS (2.0)	54	1 : 1
02	I_2 (2.0)	85	1 : 0
03	ICl (2.0)	62	1 : 0.1
04	IBX (2.0)	40	1 : 0.5

^a Reaction conditions: all the reactions were carried out under optimised condition.

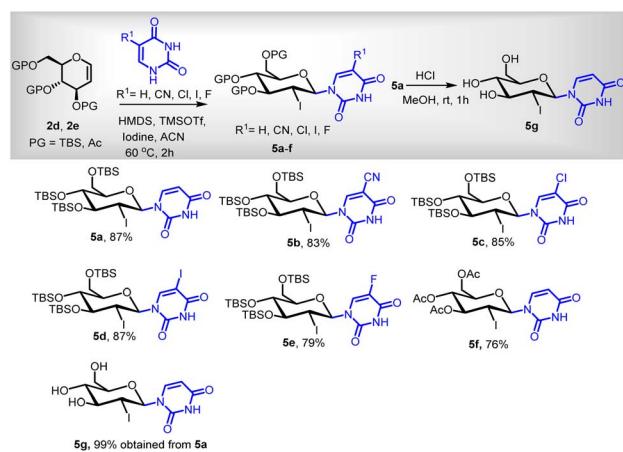


Scheme 2 Substrate scope of reaction using benzyl sugar enol ethers as donors and different uracils.

heated at the same temperature for 2 h only to get **3a** as a diastereomeric mixture in the ratio 1 : 1 (Table 1, entry 1).^{17,18} Temperature played a critical role in the selectivity and yield of the reaction. Decreasing the temperature to 60 °C results in an increase in yield with better β -selectivity (Table 1, entries 2). Further decreasing the temperature to 40 °C results in the reduction of yield (Table 1, entry 3). We screened different solvents like DCM, DCE and MeCN and concluded that MeCN is the solvent of choice (Table 1, entries 4–5). On switching the iodinating reagent from NIS to molecular iodine we were delighted to obtain our desired product in excellent yield with exclusive β -selectivity (Table 1, entry 6). On reducing the proportion of iodine, a reduction in the yield was observed (Table 1, entries 7, 8) however by using 2.5 equivalent of iodine has no effect on the yield (Table 1, entry 9). Other iodinating reagents like ICl and IBX were not proven beneficial (Table 1, entries 10, 11). In order to check the effect of temperature on reaction with iodinating agents I_2 , ICl and IBX, reaction was carried out 80 °C and the results were summarised in entry 12–14. Consolidating the outcome of our optimization study, heating the solution of uracil (3 equiv), HMDS (4.5 equiv), and TMSOTf (0.3 equiv) in MeCN at 80 °C for 1.5 h followed by the addition of 1.0 equiv protected glycal and I_2 (2.0 equiv) after cooling the reaction mixture down to 60 °C and allowing the



Scheme 3 The substrate scope of reaction using benzyl protected sugar enol ethers as donors and cytosine.



Scheme 4 The substrate scope of reaction using TBS and acetate-protected glycals as donors and different uracils.

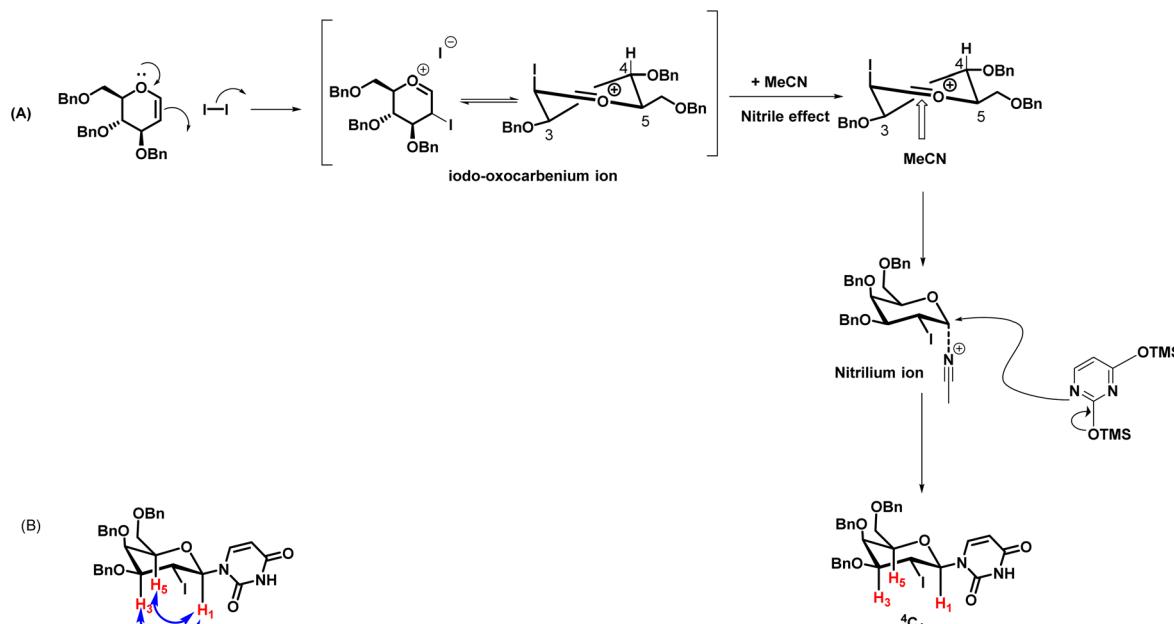


reaction mixture to stir for 2 h at the same temperature gives the desired 2-deoxy-2-iodo nucleoside in good to excellent yield. All the protected nucleosides having *J* value in between 8–10 Hz which confirms their existence in ${}^4\text{C}_1$ conformation. All Compounds are >95% pure by HPLC analysis. Furthermore, NMR Spectrums also depicts the purity of compounds.

The comparision of reaction outcomes (yield, α/β ratio) between I_2 , NIS, ICl and IBX under identical conditions, demonstrating I_2 's superior selectivity has been shown in Table 2.

The substrate scope of the reaction was checked by reacting 3,4,6-tri-*O*-benzyl-*D*-glucal **2a** with various 5-substituted uracil

derivatives (Scheme 2, **3b–f**). In all cases, the reaction proceeded smoothly affording the desired nucleosides in good to excellent yields. Uracils carrying EDG provided the desired products in better yields as compared to those having EWG (Scheme 2, **3b–f**). 6-Azauracil also reacted well under optimized reaction conditions to afford the corresponding product (Scheme 2, **3g**). Utility of different sugars was tested for substrate scope, benzyl protected galactal on reaction with uracil also produced the desired product in excellent yield (Scheme 2, **3h**). Further 3, 4-di-*O*-benzyl-*L*-rhamnal reacted well and yielded the desired products in excellent yields (Scheme 2, **3i, 3j**).



Scheme 5 (A) Plausible mechanism (B) NOESY correlation of compound **5g**.

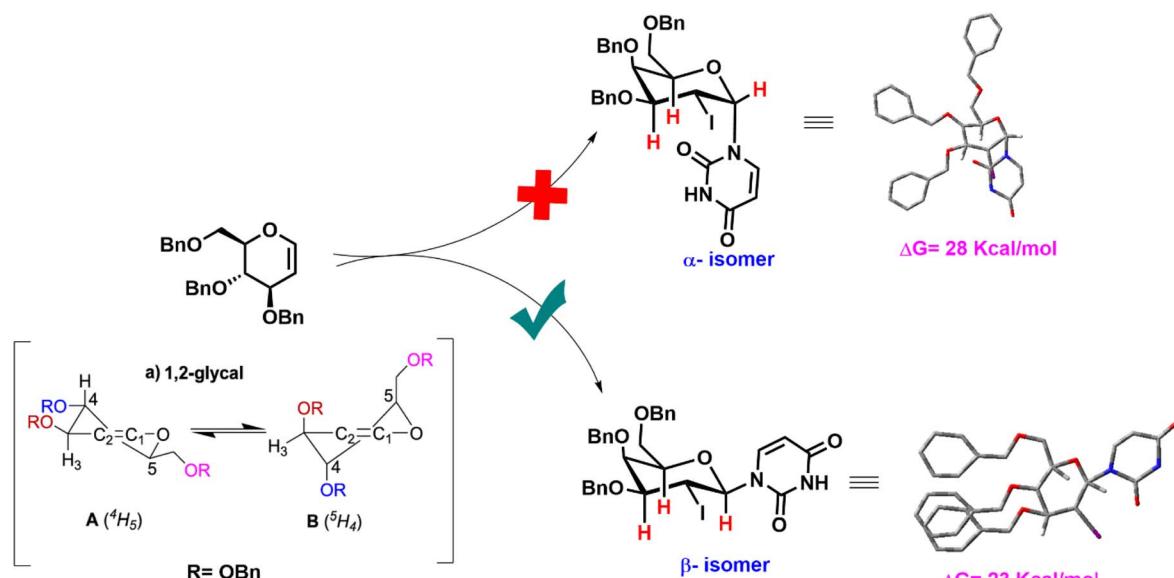


Fig. 2 Relative stability of both the isomers (Optimization of isomers performed at B3LYP D3/6-31 + G(d) level of theory).



Table 3 Results ($IC_{50} \pm SD \mu M$) of 20 compounds summarized and analyzed for *in vitro* anti-JEV activity

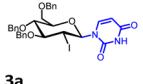
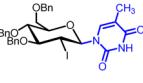
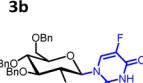
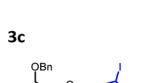
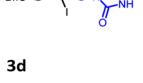
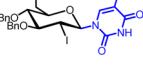
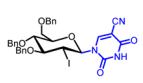
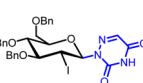
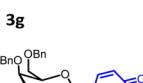
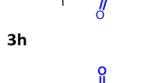
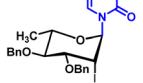
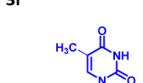
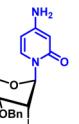
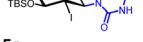
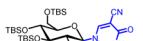
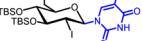
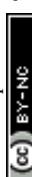
Structure id	Formula	CC ₅₀	IC ₅₀
	C ₃₁ H ₃₁ IN ₂ O ₆	>50 μM	1.51 ± 0.27 μM
	C ₃₂ H ₃₃ IN ₂ O ₆	>50 μM	Inactive
	C ₃₁ H ₃₀ FIN ₂ O ₆	>50 μM	4.98 ± 0.15 μM
	C ₃₁ H ₃₀ I ₂ N ₂ O ₆	>50 μM	1.67 ± 0.45 μM
	C ₃₁ H ₃₀ ClIN ₂ O ₆	>50 μM	6.41 ± 0.34 μM
	C ₃₂ H ₃₀ IN ₃ O ₆	>50 μM	4.20 ± 1.97 μM
	C ₃₀ H ₃₀ IN ₃ O ₆	>50 μM	38.92 ± 0.69 μM
	C ₃₁ H ₃₁ IN ₂ O ₆	<10 μM	—
	C ₂₄ H ₂₅ IN ₂ O ₅	>50 μM	8.57 ± 0.46 μM
	C ₂₅ H ₂₇ IN ₂ O ₅	>50 μM	3.68 ± 0.46 μM
	C ₃₁ H ₃₂ IN ₃ O ₅	42.8 μM	3.7 ± 0.35 μM
	C ₃₁ H ₃₁ BrIN ₃ O ₅	>50 μM	Inactive

Table 3 (Contd.)

Structure id	Formula	CC ₅₀	IC ₅₀
	C ₂₄ H ₂₆ IN ₃ O ₄	>50 μM	Inactive
	C ₂₈ H ₅₅ IN ₂ O ₆ Si ₃	<10 μM	—
	C ₂₉ H ₅₄ IN ₃ O ₆ Si ₃	76.3 μM	1.10 ± 0.18 μM
	C ₂₈ H ₅₄ ClIN ₂ O ₆ Si ₃	12.5 μM	—
	C ₂₈ H ₅₄ I ₂ N ₂ O ₆ Si ₃	9.25 μM	—
	C ₂₈ H ₅₄ FIN ₂ O ₆ Si ₃	>25 μM	3.21 ± 0.87 μM
	C ₁₆ H ₁₉ IN ₂ O ₉	>50 μM	2.59 ± 0.28 μM
	C ₁₀ H ₁₃ IN ₂ O ₆	25 μM	6.4 ± 0.32 μM

We further checked the substrate scope by reacting pyrimidine base cytosine with benzylated glycal to give the desired product with complete stereoselectivity (Scheme 3, **4a**). EWG group containing cytosine such as 5-bromocytosine also produced the product in good yield (Scheme 3, **4b**). L-sugar such as benzylated rhamnal reacted well and result in the formation of the product in good yield (Scheme 3, **4c**). Also, the gram scale synthesis of **3a** is achieved in excellent yield.

The functional group tolerance of the method was checked by treating 3,4,6-tri-*tert*-butyldimethylsilyl glucal sugars with various substituted uracil under the optimized reaction conditions to get the 2-deoxy-2-iodo- β -nucleoside selectively with excellent yield (Scheme 4, **5a–e**). But the ester-bearing sugars such as 3,4,6-tri-*O*-acetyl-D-glucal result in the formation of the product with an anomeric mixture of β : α (1 : 0.3) (Scheme 4, **5f**) which was determined by integration of the anomeric protons in the ¹H NMR spectrum. Deprotection of compound **5a** yielded



the desired product where glycosidic linkage survived under acidic conditions (Scheme 4, 5f).

The Plausible mechanism has been illustrated in Scheme 5. The reaction begins with the formation of iodo-oxocarbenium ion intermediate which is stable in half chair conformation. Then, the acetonitrile interacts with the iodo-oxocarbenium ion intermediate preferentially from the α -face, leading to the generation of a transient nitrilium ion. This intermediate, stabilized *via* the nitrile effect, competes with the nucleophilic acceptor and may reduce the overall reaction rate by transiently occupying the electrophilic site. Nonetheless, it effectively directs the nucleophilic attack of the nucleobase from the β -face, thereby favoring the stereoselective formation of the β -nucleoside. Stereochemistry of the product 5g was confirmed by 2D-NMR spectroscopy (COSY, NOESY, and HSQC). In the NOESY spectrum of 5g, H-1 showed strong correlations with H-3 and H-5 which proved that the linkage at the anomeric center is β (Scheme 5B).

The relative Gibbs free energies of both isomers were also calculated, further supporting the greater stability of the β -nucleoside (Fig. 2).

Further the compounds have been screened for activity against Japanese Encephalitis Virus. In *in vitro* screening, out of 20 test compounds, four compounds 3e, 3i, 3g, and 5g were found mildly effective in the viral detection assay against JEV. The IC_{50} of these five compounds were detected as $6.4 \pm 0.34 \mu\text{M}$, $8.57 \pm 0.46 \mu\text{M}$, $38.92 \pm 0.69 \mu\text{M}$ and $6.4 \pm 0.32 \mu\text{M}$ respectively, which indicates that there is need of further optimizations for these three compounds except 3g compound to make more active compounds. Five compounds were found moderately effective against JEV replication with the average

IC_{50} $4.98 \pm 0.15 \mu\text{M}$, $4.20 \pm 1.97 \mu\text{M}$, $3.68 \pm 0.46 \mu\text{M}$, $3.21 \pm 0.87 \mu\text{M}$ and $3.7 \pm 0.35 \mu\text{M}$ respectively (Table 2). Compounds 3a, 3d, 5f and 5b are found significant active inhibitors against JEV with a productive IC_{50} $1.51 \pm 0.27 \mu\text{M}$, $1.67 \pm 0.45 \mu\text{M}$, $2.59 \pm 0.28 \mu\text{M}$ and $1.10 \pm 0.18 \mu\text{M}$ respectively. Results predict that these four compounds might be worked out as hit compounds in the way to develop therapeutic antiviral drugs against JEV, as there are existence of no approved drugs. The rest of the compounds 3h, 5a, 5c, and 5d were found cytotoxic, so these were not tested for inhibitory effect. Compounds 4b, 3b and 4c were found inactive against the JEV in the viral detection assay [The IC_{50} was calculated through online software ("Quest Graph™ IC_{50} Calculator." AATBIO quest, Inc., 11 Apr. 2023, <https://www.aatbio.com/tools/ic50> calculator (Table 3).]

The data was also analyzed through Graphpad Prism 5, graphs were plotted through Graphpad Prism (Fig. 3). These synthesised pyrimidine nucleosides are nucleoside analogs which mimic naturally occurring nucleosides and function by terminating the growing viral DNA/RNA chain.^{17,18} Here, these 20 nucleoside analogs were analyzed for invitro antiviral activity against the Japanese Encephalitis Virus. In this *in vitro* anti-JEV assay, firstly the compounds were analyzed for cytotoxicity through MTT Assay, the data was compared with healthy cells and then test compound concentrations for screening anti-JEV activity were selected based on the cytotoxicity (CC_{50}) of compounds. The test compound concentrations were selected in the range of $20 \mu\text{M}$ to $0.625 \mu\text{M}$ ($20 \mu\text{M}$, $10 \mu\text{M}$, $5 \mu\text{M}$, $2.5 \mu\text{M}$, $1.25 \mu\text{M}$, and $0.625 \mu\text{M}$) where the CC_{50} of compounds are $>50 \mu\text{M}$ or the compounds are non-toxic as shown in Table 3. The inhibitory concentration (IC_{50}) of compounds was evaluated and these compounds were categorized in our result into three

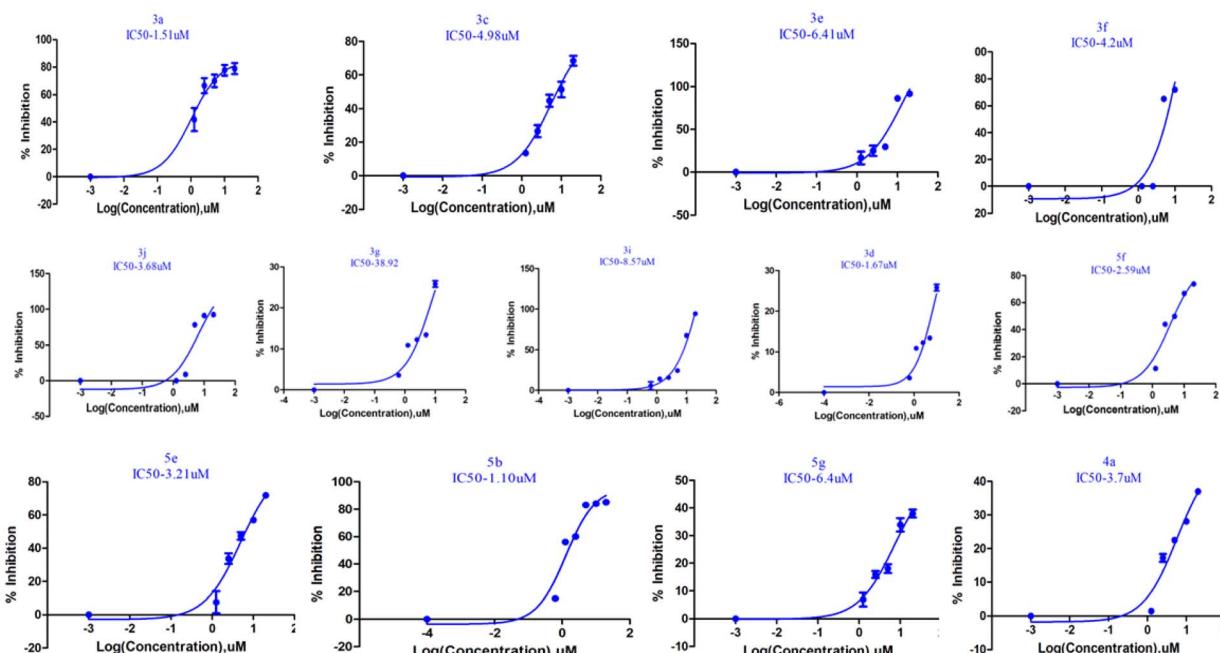


Fig. 3 Graphical representation of *in vitro* cell release assay dose-response curves of test compounds 3a, 3c, 3e, 3f, 3j, 3g, 3i, 3d, 5f, 5e, 5b, 5g and 4a, which showed antiviral activity against Japanese Encephalitis Virus in Vero cells. Error bars represent the SEM of the IC_{50} obtained from the three independent experiments.



types: mild effective, moderately effective, and significant effective compounds against JEV.

Conclusion

In summary, we have developed a highly efficient one-pot synthesis by 2-iodo nucleosides. The scope of the *N*-glycosylation approach is very broad, as exemplified by the synthesis of 20 pyrimidine nucleosides. Notably, all of the 20 pyrimidine nucleosides were synthesized in more than 70% yields and were further tested against the Japanese Encephalitis virus. These compounds have potential for anti-JEV activity.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

“There are no conflicts to declare”.

Acknowledgements

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