Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal





Cite this: DOI: 10.1039/d0ob01172j

# A light- and heat-driven glycal diazidation approach to nitrogenous carbohydrate derivatives with antiviral activity†

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Received 6th June 2020,
Accepted 13th July 2020

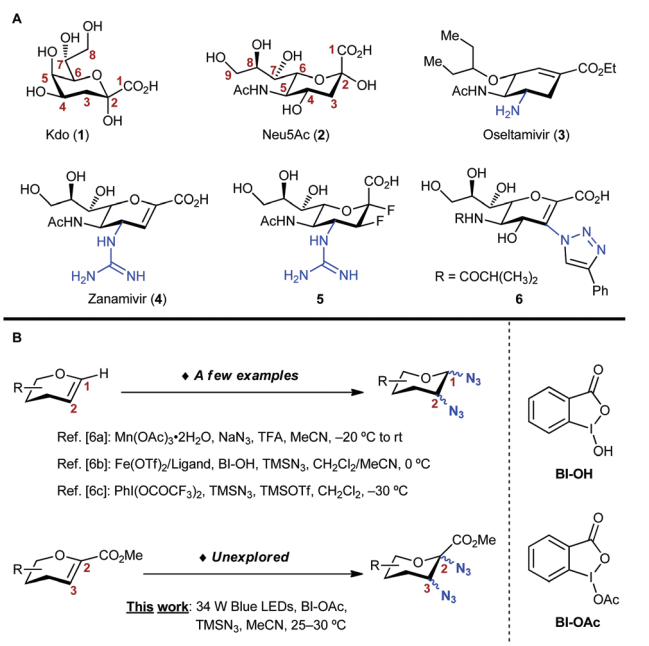
DOI: 10.1039/d0ob01172j

rsc.li/obc

The aminated mimetics of 2-keto-3-deoxy-sugar acids such as the anti-influenza clinical drugs oseltamivir (Tamiflu) and zanamivir (Relenza) are important bioactive molecules. Development of synthetic methodologies for accessing such compound collections is highly desirable. Herein, we describe a simple, catalyst-free glycal diazidation protocol enabled by visible light-driven conditions. This new method requires neither acid promoters nor transition-metal catalysts and takes place at ambient temperature within 1–2 hours. Notably, the desired transformations could be promoted by thermal conditions as well, albeit with lower efficacy compared to the light-induced conditions. Different sugar acid-derived glycal templates have been converted into a range of 2,3-diazido carbohydrate analogs by harnessing this mild and scalable approach, leading to the discovery of new antiviral agents.

## Introduction

2-Keto-3-deoxy-sugar acids belong to an intriguing class of molecules that play vital roles in biological processes.[1] Two representative members are 2-keto-3-deoxy-D-manno-octulosonic acid (Kdo, **1**, Scheme 1A)[2] and *N*-acetylneuraminic acid (**2**, Neu5Ac, also known as sialic acid).[3] The former is an essential component of lipopolysaccharide (LPS) in Gram-negative bacteria, while the latter nine-carbon saccharide constitutes the most widespread member of the sialic acid family, mainly found at the terminal position of glycolipids and glycoproteins on mammalian cells. Such structural motifs have served as important templates for identifying bioactive compounds. In particular, their aminated mimetics are recognized as known or potential pharmaceutics.[4] For instance, two effective anti-influenza clinical drugs, oseltamivir (Tamiflu, **3**)[4a,b] and zanamivir (Relenza, **4**),[4c] were inspired by associated acidic carbohydrates. In addition, compound **5** bearing C2,C3-diflouro substituents and a C4 guanidinium group exhibited broad-spectrum influenza antiviral activity,[4d] while compound **6** with




**Scheme 1** (A) Structures of Kdo (**1**), Neu5Ac (**2**), and their aminated mimetics **3**–**6**. (B) Glycal diazidation approaches to diazido sugars.

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†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra, and X-ray crystallographic data. CCDC 1975133, 1975134, 1975130, 1975131, 1975132, 1975126, 1975127, 1975128 and 1975129. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob01172j

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a unique C3 triazole moiety was evaluated as a human parainfluenza virus 3 (hPIV-3) inhibitor.[4g]

Functionalization of the double bonds in glycals has proved to be a versatile way for the preparation of various carbohydrate derivatives.[5] Among these transformations, diazidation of glycals allows the generation of 1,2-diazido sugars and enables facile access to diverse aminated saccharides (Scheme 1B).[6] In 1998, Snider and Lin disclosed that stoichiometric $Mn(OAc)_3{\cdot}2H_2O$ was effective to mediate glycal diazidation in the presence of TFA *via* a radical pathway.[6a] Later, Xu *et al*. converted a glycal substrate into its diazido derivatives by means of a new iron-catalysed radical diazidation process.[6b] More recently, Vankar and co-workers demonstrated the feasibility of $PhI(OCOCF_3)/TMSN_3/TMSOTf$ reagent combination in diazidation of glycals through a plausible ionic pathway.[6c] To the best of our knowledge, direct diazidation of the C2–C3 alkenes in glycals derived from 2-keto-3-deoxy-sugar acids remains unexplored. We envisioned that such a process would yield new carbohydrate analogs with nitrogen-containing functionalities at the C2 and C3 positions on this significant class of molecular templates, which might be of potential biological value. Nevertheless, diazidation of this type of glycal substrates could be unpredictable and challenging due to the presence of an electron-withdrawing carboxylic group at the anomeric center as well as the intrinsic multi-functionality characters of carbohydrates.

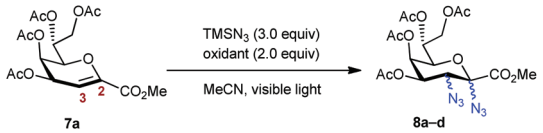
Traditionally, the olefin diazidation reaction relied heavily on the use of stoichiometric amounts of transition metals (*e.g.*, $Fe^{II}/Fe^{III}$, $Mn^{III}$).[6a,7] Recently, metal-catalysed diazidation of various types of olefins has been developed to deliver vicinal diazide compounds.[6b,8] In order to avoid the use of expensive metal salts, numerous transition metal-free protocols have been documented.[9] However, the majority suffer from the use of superstoichiometric quantities of explosive $NaN_3$, addition of acid promoters, harsh reaction conditions, or limited olefin substrate scopes. In their search for mild and green approaches for olefin diazidation, very recently, the groups of Lin and Vincent independently demonstrated that electrochemical technology was capable of promoting the diazidation of certain alkenes.[9g,h] Notably, visible light represents a sustainable energy source to facilitate various chemical reactions;[10] however, its application in olefin diazidation has yet to be investigated. As our interest in the design and utilization of photo-induced transformations,[11] here we disclose a visible light-accelerated and metal- and photocatalyst-free strategy for the diazidation of sugar acid-based glycals, leading to a group of nitrogenous carbohydrate derivatives with antiviral activity.

## Results and discussion

### Reaction development

With the purpose of realizing a photo-induced diazidation of the C2–C3 double bonds in sugar acid glycals, a Kdo-derived compound **7a**[12] was selected as the starting model substrate. We first examined the diazidation of **7a** using $TMSN_3$ as the $N_3$ source in the presence of an oxidant (Table 1, entries 1–8) under the irradiation of 8 W blue LED strips at ambient temperature (25–30 °C). Initial experiments revealed that while no reaction was detected employing benzoquinone (BQ, entry 1) or $K_2S_2O_8$ (entry 2), generation of the desired product **8** (46% isolated yield, 53% conversion, entry 3) was observed with the use of PhIO over 15 h. Among the various hypervalent iodine oxidants surveyed (entries 4–8), acetoxybenziodoxole (BI-OAc, entry 6) proved to be a superior one that afforded **8** in 69% yield with complete conversion of the starting glycal **7a** within 10 h. HPLC and NMR analyses of the isolated product indicated that the reaction produced all four diastereomers **8a–d** with a ratio of 43 : 30 : 23 : 4. Subsequently, different light sources (entries 9–12) were evaluated. Irradiation of the reaction by 26 W CFL (entry 9) or 15 W green LEDs (entry 10) gave inferior results compared to that of entry 6. By contrast, subjecting **7a** to 30 W white LEDs (entry 11) or 34 W blue LEDs irradiation (entry 12) allowed improved reaction efficacy; in particular, the diazidation process occurred in a dramatically shortened reaction time (1.5 h) and delivered **8** with 83% yield using 34 W blue LEDs. Conducting the reaction in the dark led to 17% conversion of **7a** and 13% yield of **8** in 1.5 h (entry 13). The conversion was increased to 33% with a prolonged time (15 h, entry 14). These resutls implied slow and limited transformation of **7a** in darkness at ambient temperature. In addition, the formation of **8** was completely suppressed when

**Table 1** Optimization of the reaction conditions[a]




| Entry | Oxidant | Light source | $T^b$ (°C) | $t$ (h) | Conv.[c] (%) | Yield[d] (%) |
|---|---|---|---|---|---|---|
| 1 | BQ | 8 W blue LEDs | 25–30 | 15 | 0 | 0 |
| 2 | $K_2S_2O_8$ | 8 W blue LEDs | 25–30 | 15 | 0 | 0 |
| 3 | PhIO | 8 W blue LEDs | 25–30 | 15 | 53 | 46 |
| 4 | $PhI(OAc)_2$ | 8 W blue LEDs | 25–30 | 15 | 87 | 66 |
| 5 | BI-OH | 8 W blue LEDs | 25–30 | 15 | 87 | 60 |
| 6 | BI-OAc | 8 W blue LEDs | 25–30 | 10 | 100 | 69 |
| 7 | IBX | 8 W blue LEDs | 25–30 | 15 | 33 | 25 |
| 8 | $NaIO_4$ | 8 W blue LEDs | 25–30 | 12 | 100 | 33 |
| 9 | BI-OAc | 26 W CFL | 25–30 | 15 | 87 | 14 |
| 10 | BI-OAc | 15 W green LEDs | 25–30 | 15 | 63 | 50 |
| 11 | BI-OAc | 30 W white LEDs | 25–30 | 6 | 100 | 77 |
| 12 | BI-OAc | 34 W blue LEDs | 25–30 | 1.5 | 100 | 83 |
| 13 | BI-OAc | Dark | 25 | 1.5 | 17 | 13 |
| 14 | BI-OAc | Dark | 25 | 15 | 33 | 11 |
| 15 | None | 34 W blue LEDs | 25–30 | 10 | 0 | 0 |
| 16 | BI-OAc | Dark | 30 | 15 | 67 | 44 |
| 17 | BI-OAc | Dark | 40 | 15 | 83 | 65 |
| 18 | BI-OAc | Dark | 50 | 15 | 83 | 55 |
| 19 | BI-OAc | Dark | 60 | 15 | 87 | 47 |

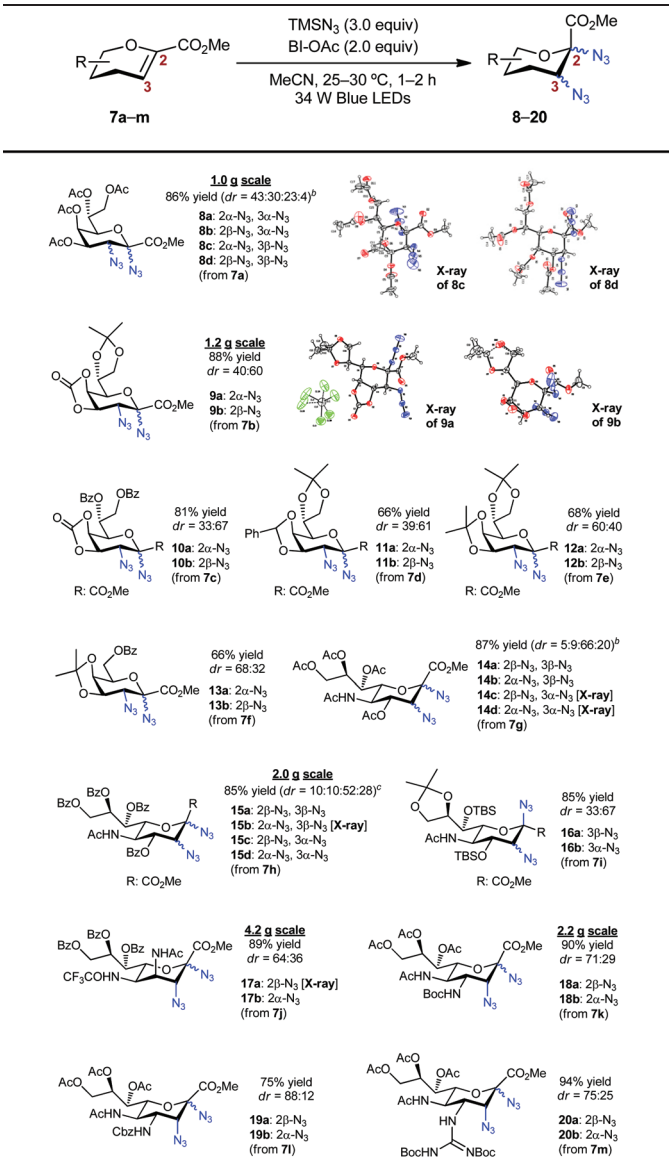
[a] Reactions were conducted on 0.075 mmol scale. [b] Ambient temperature or temperatures of the oil bath. [c] Conversions were calculated based on the recovered starting glycal **7a** after column chromatography. [d] Yields were determined according to the isolated material *via* column chromatography.

the reaction was performed in the absence of BI-OAc (entry 15). On the other hand, subjection of **7a** to BI-OAc and $TMSN_3$ under thermal conditions in darkness (entries 16–19) ensured the formation of diazido products as well. However, these reactions suffered from incomplete conversion of the starting glycal substrate even after 15 h. The optimal isolate yield (65%) was obtained when conducting the reaction at 40 °C (entry 17), which was less effective compared to the light-promoted conditions (entry 12).

After identifying the optimal reaction conditions (34 W blue LEDs, BI-OAc, $TMSN_3$, MeCN, 25–30 °C), we next explored the scope of the glycal substrates of this photocatalyst-free diazidation method (Table 2).[13] First, several Kdo-derived glycals were prepared and tested in the diazidation reaction. Subjecting 1.0 g of 4,5,7,8-tetra-*O*-Ac-protected Kdo glycal **7a** to the reaction conditions resulted in the generation of **8a–d** (dr = 43 : 30 : 23 : 4) with a slightly improved yield (86%) compared to the small-scale reaction (Table 1, entry 12). While the configurations of the newly generated C2 and C3 stereocenters in products **8c** and **8d** were determined by X-ray crystallographic analysis, the stereochemistries of the other two diastereomers **8a** and **8b** were verified through comparison of their deprotected compounds with those derived from the following related diazidation products.[14] It was found that excellent control of the C3 diastereoselectivity was achieved with the Kdo glycal substrates **7b–f** bearing cyclic 4,5-*O*-protecting groups (*i.e.*, products **9–13**), presumably due to increased steric repulsion exerted by the 4,5-cyclic structural units. For instance, the carbonate-containing glycals **7b** and **7c** were converted to the corresponding 2,3-diazido products as a pair of separable diastereomers: **9a**/**b** (88% yield, dr 40 : 60) and **10a**/**b** (81% yield, dr 33 : 67), respectively. Substrates possessing acetonides or benzylidene acetals likewise proved suitable for the diazidation process (*i.e.*, products **11a**/**b** and **12a**/**b**). Of note, the C8-nor Kdo glycal **7f**, that is, with only one carbon attached at C6, displayed analogous reactivity and afforded the diazidation products **13a**/**b** (66% yield, dr 68 : 32) smoothly under the reaction conditions. All the products **8a**/**b–13a**/**b** possessed a uniform α-oriented $N_3$ group at the C3 position. Their structures were fully confirmed based on the X-ray crystallographic data of **9a** and **9b**, as well as by interconversions between each intermediate.[14]

On the other hand, various glycals **7g–m** derived from Neu5Ac could also be employed in the diazidation reaction (Table 2). Specifically, the 4,7,8,9-tetra-*O*-Ac/Bz-protected substrates **7g** and **7h** underwent diazidation to give the corresponding products **14a–d** (87% yield, dr 5 : 9 : 66 : 20) and **15a–d** (85% yield, dr 10 : 10 : 52 : 28) in good yields and moderate diastereoselectivity, respectively. Two diastereomers **16a** and **16b** were synthesized using 4,7-di-*O*-TBS-7,8-*O*-acetonide Neu5Ac glycal **7i** as the reaction substrate. In addition, diazidation of Neu5Ac glycals **7j–m** with C4 nitrogenous functionalities such as amide, carbamate, and guanidine moieties proceeded smoothly, delivering the corresponding products **17a**/**b–20a**/**b** with four contiguous nitrogen-containing groups at positions C2 to C5. The orientation of the C4 nitrogenous

**Table 2** Substrate scope of the glycal diazidation[a]

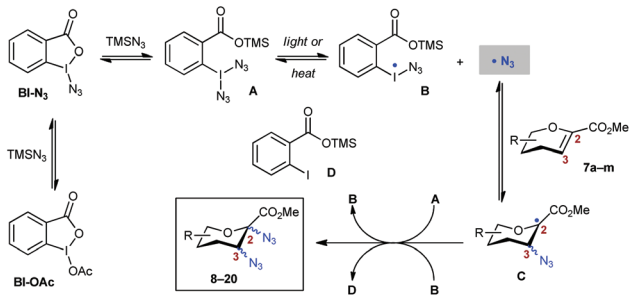



[a] Yields and dr values were calculated based on isolated material unless otherwise stated. [b] Dr values were determined through HPLC analysis. [c] Dr values were obtained by combination of column chromatography and HPLC analysis.

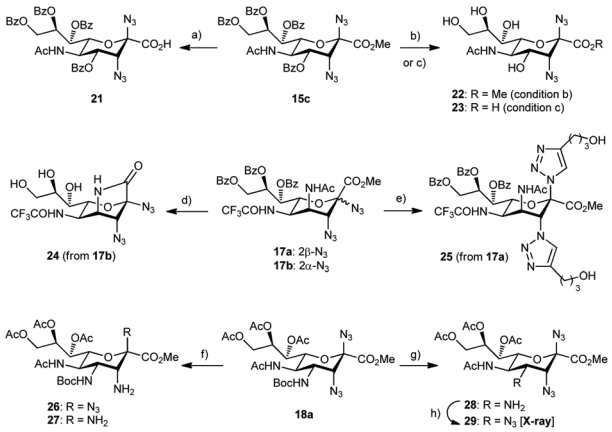
functional groups exerted no influence on the stereochemical outcomes of the diazaidation reaction. Notably, the newly generated C3 stereocenter was formed exclusively with an α-oriented $N_3$ substituent in products **17a**/**b–20a**/**b**. All the diastereomers were separable, the structures of which were determined *via* NMR data interpretation, X-ray crystallographic analysis, and chemical intercommunication of related compounds.[14]

## Mechanistic considerations

After investigating the substrate scope, we carried out additional experiments to gain insights into the mechanism of



Scheme 2 Proposed mechanism for the light- and heat-driven glycal diazidation.



Scheme 3 Diversification of the 2,3-diazido sugar acid derivatives. Reagents and conditions: (a) LiI (10.0 equiv.), pyridine, 90 °C, 86%; (b) NaOMe (3.0 equiv.), MeOH, rt, 63%; (c) NaOH (1 M in $H_2O$, 2.0 equiv.), MeOH, rt, 81%; (d) NaOMe (5 M in MeOH, 3.0 equiv.), MeOH, 30 °C, 61%; (e) 4-pentynyl alcohol (2.2 equiv.), $CuSO_4{\cdot}5H_2O$ (0.4 equiv.), sodium ascorbate (4.0 equiv.), THF/$H_2O$ (1 : 1), rt, 83%; (f) 10% Pd/C, $H_2$, MeOH, rt, **26** (62%), **27** (12%); (g) TFA/$CH_2Cl_2$ (1 : 5 v/v), 0 °C to rt, 84%; (h) $TfN_3$ (10.0 equiv.), DMAP (3.0 equiv.), $CH_2Cl_2$, 0 °C to rt, 47% (68% brsm).

this light- and heat-induced reaction. It was found that when TEMPO was added to the reaction system, generation of the diazidation product was completely suppressed. Instead, an azido-TEMPO addition product was generated,[14] suggesting that an azido radical is likely involved in the diazidation reaction. Meanwhile, analysis of the reaction components by UV/Vis absorption spectroscopy and NMR titration experiments largely excluded the formation of an electron donor–acceptor (EDA) complex.[15] Although detailed mechanistic studies are beyond the scope of this report, we proposed a plausible reaction pathway (Scheme 2) based on the aforementioned results as well as literature examples.[6b,16] Initially, BI-OAc can be reversibly converted into BI-$N_3$ and then into diazide species **A** in the presence of $TMSN_3$. Subsequent light- or heat-promoted disassociation of **A** leads to an iodo radical **B** and an azido radical. The latter then adds onto the double bond of the glycal substrate (*i.e.*, **7a–m**) to furnish a carbon radical (intermediate **C**) in a reversible fashion. At this stage, both **A** and **B** can serve as the precursors of another azido radical, which coupled with **C** to yield the diazidation product (*i.e.*, **8–20**). Meanwhile, TMS *o*-iodobenzoate (intermediate **D**)[17] was generated from **B**.

## Synthetic transformations

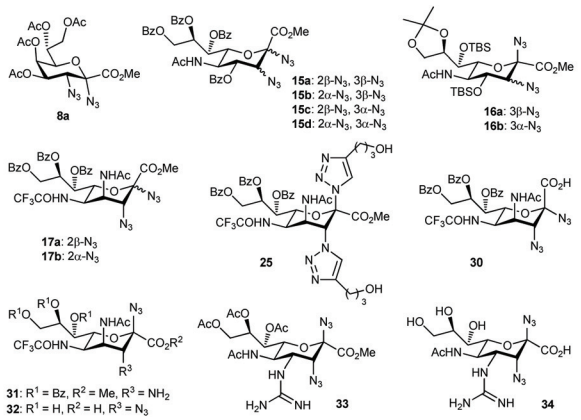
Having this visible light-induced glycal diazidation protocol established, we further explored the transformations of related 2,3-diazido products into diverse derivatives.[14] Representative examples are illustrated in Scheme 3. Selective saponification of the carboxylic ester in **15c** proceeded with LiI/pyridine to afford the corresponding acid **21** (86% yield). On the other hand, treatment of **15c** with NaOMe/MeOH removed the four benzoyl groups to give **22**, and global saponification employing a stronger base (NaOH) converted **15c** into **23**. Of note, the [3.2.1] bicyclic lactam **24** was obtained in 61% yield upon subjecting **17b** to NaOMe/MeOH *via* one-pot saponification and lactamization. Additionally, transformations of the azido groups in the diazidation products would lead to compounds with versatile functionalities. For example, a double [3 + 2] azide–alkyne click reaction of **17a** with 4-pentynyl alcohol allowed formation of the bistriazole product **25** with 83% yield. Moreover, subjecting **18a** to the azide reduction conditions (Pd/C, $H_2$, MeOH) furnished amine **26** and diamine **27** in one pot. Removal of the Boc group in **18a** occurred in the presence of TFA to yield amine **28**; the latter underwent diazo-transfer employing trifluoromethanesulfonyl azide ($TfN_3$) and DMAP to provide **29**.[18] Remarkably, compound **29** possessed three adjacent azido groups and its structure was determined by X-ray crystallography, which in turn verified the C2 and C3 configurations in **18a**.

## Antiviral activity

Next, we evaluated the antiviral activity of the synthetic 2,3-diazido carbohydrates and their derivatives (see Table S7 in the ESI†).[14] The $IC_{50}$, $CC_{50}$, and SI (selectivity index, *i.e.*, $CC_{50}$/$IC_{50}$ ratio) values for the anti-ZIKV (Zika virus) and anti-HRV (human rhinovirus) activity of selected compounds are listed in Table 3. Whereas most analogs obtained from Kdo glycals were inactive or moderately active (*e.g.*, **8a**), several groups of the Neu5Ac-derived compounds (*e.g.*, **15–17**) displayed promising antiviral effects. In particular, **16a** and **17a** showed good inhibitory activity with $IC_{50}$ values of 1.41 μM (against ZIKV) and 0.93 μM (against HRV), respectively. The anti-ZIKV activity of compound **16b** was significant with low cytotoxicity ($CC_{50}$ > 200 μM) and an excellent SI value of over 105.26. Interestingly, various derivatives containing triazoles, free carboxylic acids, primary amines, and alcohols (*e.g.*, **25**, **30–32**) exhibited inferior activity compared to their parent molecules. For instance, there was a sharp contrast between **17a** ($IC_{50}$: 5.50 μM, 0.93 μM) and its saponification product **32** ($IC_{50}$: >200 μM, 113.99 μM) bearing polar carboxylic and hydroxyl groups. Moreover, the corresponding saccharide derivatives bearing a 4-guanidino substituent (*e.g.*, **33** and **34**) were ineffective in our assay. Unlike the currently known antiviral

Table 3 Antiviral activity of selected compounds

| | anti-ZIKV | | | anti-HRV | | |
|---|---|---|---|---|---|---|
| Compd. | $IC_{50}$ [a] (μM) | $CC_{50}$ [b] (μM) | SI[c] | $IC_{50}$ [a] (μM) | $CC_{50}$ [b] (μM) | SI[c] |
| **8a** | >200 | — | — | 95.24 | >200 | >2.10 |
| **15a** | 31.05 | >200 | >6.44 | >200 | — | — |
| **15b** | 8.67 | >200 | >23.07 | >200 | — | — |
| **15c** | 9.24 | >200 | >21.65 | >200 | — | — |
| **15d** | 9.20 | >200 | >21.74 | >200 | — | — |
| **16a** | 1.41 | 7.68 | 5.45 | 4.58 | 9.25 | 2.02 |
| **16b** | 1.90 | >200 | >105.26 | 18.89 | 49.11 | 2.60 |
| **17a** | 5.50 | 21.89 | 3.98 | 0.93 | 6.68 | 7.18 |
| **17b** | 7.30 | 20.29 | 2.78 | 2.05 | 5.74 | 2.80 |
| **25** | 15.02 | 193.31 | 12.87 | >200 | — | — |
| **30** | 22.73 | 29.32 | 1.29 | 1.87 | 64.70 | 34.60 |
| **31** | 25.05 | 67.89 | 2.71 | 5.39 | 41.02 | 7.61 |
| **32** | >200 | — | — | 113.99 | >200 | >1.75 |
| **33** | 105.56 | >200 | >1.89 | >200 | — | — |
| **34** | >200 | — | — | 70.49 | >200 | >2.84 |
| **NITD008**[d] | 0.87 | >20 | >22.99 | | | |
| **Rupintrivir**[d] | | | | 0.08 | >10 | >125 |




[a] $IC_{50}$: The concentration of test compounds that reduced the activity by 50% of the untreated (control) cell cultures. Each value was calculated from duplicate assays. [b] $CC_{50}$: The concentration of test compounds that reduced cell viability to 50% of the untreated (control) cell cultures. Each value was calculated from duplicate assays. [c] SI: Selectivity index, the ratio of $CC_{50}$ to $IC_{50}$ ($CC_{50}/IC_{50}$). [d] NITD008[19] and rupintrivir[20] were used as positive controls, respectively.

agents with similar structural templates (*e.g.*, **3–6**,[4] Scheme 1) that require polar functionalities, the unique molecules disclosed herein possibly function *via* a different antiviral mechanism according to the above-mentioned results.

## Conclusions

In conclusion, we have developed a visible light-accelerated photocatalyst-free diazidation reaction of sugar acid-derived glycals that provides efficient access to the corresponding 2,3-diazido products as well as associated derivatives.[21] Compared to existing methods, the present approach is operationally simple and scalable and proceeds under mild conditions without additional acid promoters or metal catalysts. Preliminary biological studies indicate that the nitrogenous carbohydrate compounds prepared in this work may represent a new class of antiviral agents. Further explorations concerning the mechanism and applications of this photo-induced reaction are underway.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support was provided by National Natural Science Foundation of China (21732005 and 21921002) and the Drug Innovation Major Project (2018ZX09711003-015 and 2018ZX09711001). We would like to thank Dr Daibing Luo at the Analytical & Testing Center of Sichuan University for X-ray crystallographic structure determination.

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