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Regioselective and stereoselective route to N2-β-tetrazolyl unnatural nucleosides via S_N2 reaction at the anomeric center of Hoffer's chlorosugar

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ABSTRACT

We are reporting a regioselective and stereoselective route to N2-β-tetrazolyl aromatic donor/acceptor unnatural nucleosides as new class of possible DNA base analogs. The S_N2 substitution reaction at the anomeric center of Hoffer's chlorosugar with various 5-substituted aromatic tetrazoles in THF in presence of K_2CO_3 proceeds with regioselectivity at N2-tetrazoles and stereoselectivity at α-chlorosugar with very good yield. The stereoelectronic and steric effects play a crucial role for the observed outcome which is also supported from a theoretical (DFT) study. The methodology is simple, eco-compatible and the tetrazolyl unnatural nucleosides might find applications in decorating DNA for various biotechnological and DNA based material science applications.

The discovery of ribavirin,[1a] shodomycin,[1b] pyrazomycin[1c] nucleosides has led to a great interest for the synthesis of nucleosides containing five-membered heterocycles as nucleobase. As for example, a number a triazolyl nucleosides have been synthesized and reported with this aim.[2] Moreover, the introduction of non-H-bonding unnatural nucleobase surrogates by Kool et al. has paved the path for the design of several hydrophobic unnatural DNA base analogs.[2,3] Recently, we also have demonstrated that the charge transfer complexation force in a designed triazolyl donor–acceptor nucleobase pair inside a DNA duplex is good enough for duplex stabilization.[2b] Our results of triazolyl nucleosides in DNA and their interesting photophysical properties inspired us for the design of new tetrazolyl nucleosidic bases which might find applications for the investigation of hydrophobic or charge transfer interactions forces if incorporated in DNA. The logic behind our choice of 6π-azapyrrole-type tetrazole unit to be the nucleobase lies on the (a) easy associability with other biological molecules via hydrogen bonding, stacking, and electrostatic interaction, (b) resistivity to metabolic degradation and (c) potent biological activity of tetrazoles.[4] Because of such attractive structural and biological features, tetrazoles have been successfully utilized for the design of various kinds of commercial drug candidates[4] including a few tetrazole-based nucleosides.[5] However, regioselective and stereoselective synthesis of N2-glycosilated tetrazolyl nucleosides has not been explored till the date.[4,5]

Though, the regioselective alkylation of tetrazoles was studied enormously, the knowledge is not generalized as it often depends on the electronic, steric as well as solvent polarity.[6] Thus, there exists only a few report of 2,5-disubstituted tetrazoles.[6] Moreover, the reported methodologies for the synthesis of 1,5- or 2,5-disubstituted tetrazoles suffers from several shortcomings such as harsh reaction conditions, use/presence of hazardous chemicals/catalysts, and formation of mixtures of regioisomers.[6,7] Furthermore, in case of synthesis of tetrazolyl nucleosides, one has to consider two possibilities of stereochemical outcome—first, N1 versus N2-glycosylation; and second, whether the tetrazole attachment on the sugar is in α- or β-configuration. So, there is always a logical chance of having four possible structural isomers of tetrazolyl nucleosides (N1-α-; N1-β-; N2-α- or N2-β-) while dealing with a substitution reaction on Hoffer's α-chlorosugar[8] with various 5-substituted/unsubstituted aromatic tetrazoles (Fig. 1). As for an example, Muller[8a] have reported both the formation of α/β-anomers with N1/N2 glycosylation in case of unsubstituted tetrazoles without any selectivity. Therefore, there is a special need to address regioselective as well as stereoselective glycosylation aspects often encountered in tetrazole-based nucleoside chemistry.

As a part of our continuous efforts in designing new nucleoside base surrogates, herein, we want to address both the problems of regioselective N2-alkylation of 5-substituted tetrazoles and the

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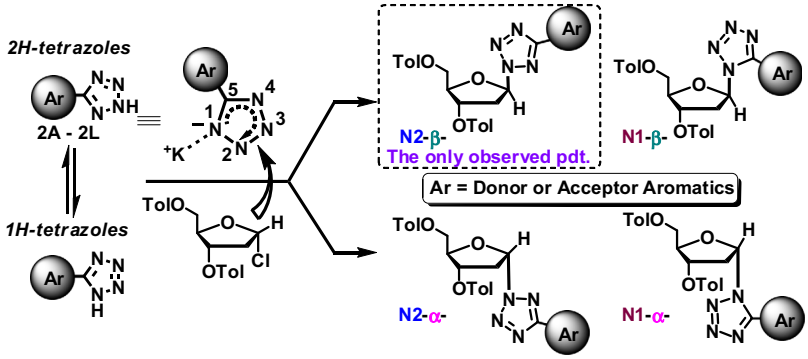
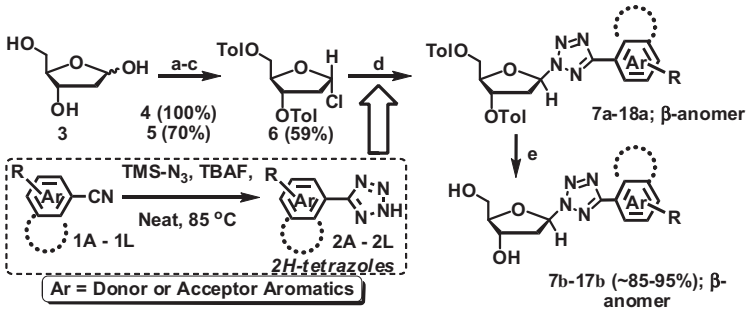


Figure 1. Schematic presentation showing the four possible isomers of tetrazolyl nucleosides (N1-α-; N1-β-; N2-α- or N2-β).



Scheme 1. Regio-selective and stereoselective synthesis of the tetrazolyl unnatural nucleosides. Reagents and conditions: (a) MeOH, 1% HCl, rt; (b) pyridine, *p*-toluoyl chloride, DMAP, 0 °C, 12 h; (c) ether, dry HCl gas, 0 °C; (d) K_2CO_3, THF, rt; (e) NaOMe, MeOH, rt.

Table 1
Summary of yield of toluoyl protected and deprotected β-tetrazolyl donor–acceptor nucleosides

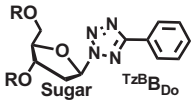
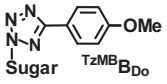
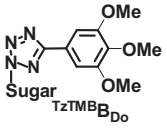
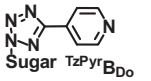
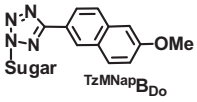
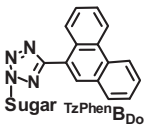
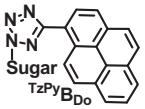
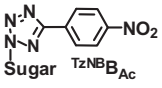
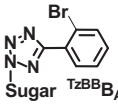
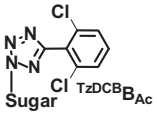
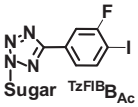
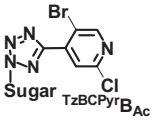
Entry	Nucleosides [R = toluoyl or H]	Yield (%)	
		β-Isomer [R = toluoyl] (compound no.)	β-Isomer [R = H] (compound no.)
1		75 (**7a**)	95 (**7b**)
2		75 (**8a**)	98 (**8b**)
3		83 (**9a**)	86 (**9b**)
4		78 (**10a**)	81 (**10b**)
5		70 (**11a**)	95 (**11b**)
6		84 (**12a**)	92 (**12b**)

Table 1 (*continued*)

Entry	Nucleosides [R = toluoyl or H]	Yield (%)	
		β-Isomer [R = toluoyl] (compound no.)	β-Isomer [R = H] (compound no.)
7		76 (**13a**)	92 (**13b**)
8		70 (**14a**)	96 (**14b**)
9		79 (**15a**)	90 (**15b**)
10		65 (**16a**)	91 (**16b**)
11		74 (**17a**)	85 (**17b**)
12		60 (**18a**)	–

stereoselective formation of β-glycosylated tetrazolyl nucleosides. We envisioned that the steric bulk of the C-5 aromatic units of tetrazoles and the stereoelectronic interactions with sugar might influence the exclusive formation of N2-β-glycosylated nucleosides. Moreover, comparatively less polar aprotic solvent such as THF and larger K^+ ion might also influence both regioselectivity at N2-tetrazole as well as stereoselective glycosylation on Hoffer's chlorosugar. Our experimental results suggested the stereoselective and regioselective formation of N2-β-tetrazolyl donor/acceptor aromatic nucleosides in all the cases with good yield and no other side reaction. We also carried out theoretical calculation (DFT) to support our experimental results and explained on the basis of both steric and electronic factors operative in the S_N2 transition state of Hoffer's α-chlorosugar with 5-substituted tetrazole nucleophiles. We believe that this work would have great potential not only in regioselective alkylation of tetrazoles or stereoselective glycosylation but surely draw attention to synthetic chemists.

For the creation of new class of donor/acceptor tetrazolyl nucleosides we first synthesized 5-substituted aromatic tetrazoles. Most of the reported route to 5-substituted tetrazoles suffers from several disadvantages,[6,7] we, therefore, employed a solvent free eco-compatible strategy following a modified literature protocol.[7c–e] Thus, the aromatic tetrazoles (**2A**–**L**) were prepared via a cycloaddition reaction of aryl nitriles (**1A**–**L**) with TMS-N_3 under solvent free condition at 85 °C using TBAF as an efficacious basic activator (Scheme 1 and SI Sections 2 and 3). All the tetrazoles except **2A**, **2B** and **2H** are new and were characterized by ^1H, ^{13}C and mass spectrometry.[7e]

The synthesis of tetrazolyl aromatic nucleosides started with bis-toluoylated Hoffer's α-chlorosugar, **6**, prepared via our reported procedure,[2b,c] which was made to undergo substitution reaction with aromatic tetrazoles (**2A**–**L**, Scheme 1) and K_2CO_3 as the base at room temperature in THF. The substitution of the chloro- by 5-aryl-tetrazoles afforded N2-tetrazolyl-β-nucleosides exclusively with very good yields (**7a**–**18a**, Scheme 1 and Table 1). Most of the reported base mediated strategies for N2-alkylation of tetrazoles offered a mixture of both N2-/N1-regiomers except only a few examples reported by Ovoskii et al.[6a,b,d] Therefore, in the field of regioselective alkylation, our result of exclusive formation of N2-glycosylated tetrazoles would have great impact which we report for the first time and explain on the basis of both steric as well as electronic effects. The bis-toluoylated nucleosides (**7a**–**18a**) were then deprotected using NaOMe in methanol to afford tetrazolyl donor/acceptor nucleosides, **7b**–**17b**, in very good yield (Scheme 1 and Table 1). The pyridyl (**18a**) tetrazolyl nucleoside was not deprotected. All the toluoyl protected and deprotected nucleosides were characterized by NMR, mass, IR, melting temperature and in two cases by single crystal X-ray analysis (SI Sections 2–4). Therefore, our experimental observations suggested the regioselective and stereoselective formation of N2-tetrazolyl-β-nucleosides as the sole products while no trace of α-anomers or N1-tetrazolyl nucleosides were observed. The β-stereoselectivity was also supported by the only existing report of sodium salt glycosylation observed by Ravankar.[5c] The tetrazolyl nucleosides reported herein were found to be highly stable under strongly basic or acidic solution or thermal condition. Therefore, during DNA synthesis the tetrazole nucleosides would expected not to lead α/β-anomeric scrambling or loss of the bases.

The β-configuration of the nucleosides was next established via NOESY spectra of a representative tetrazolyl nucleoside, $^{TzPy}\mathbf{B}_{Do}$ (**10a**) which shows a cross peak between H1′–H2′α and H1′–H4′. In case of other tetrazolyl nucleosides, the signals of the sugar protons H1′ and H3′ give rise to intense cross-peaks to the signals of H2″ and H2′, respectively, supporting the β-anomeric configurations (SI Section 5).

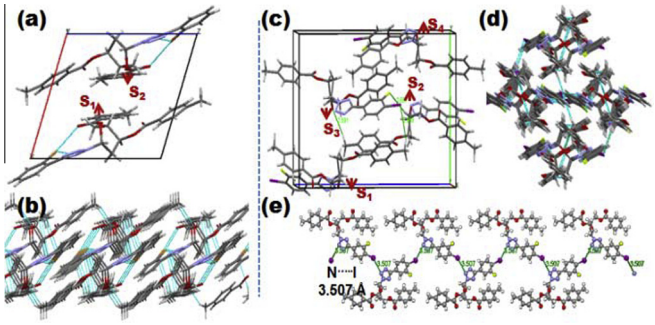
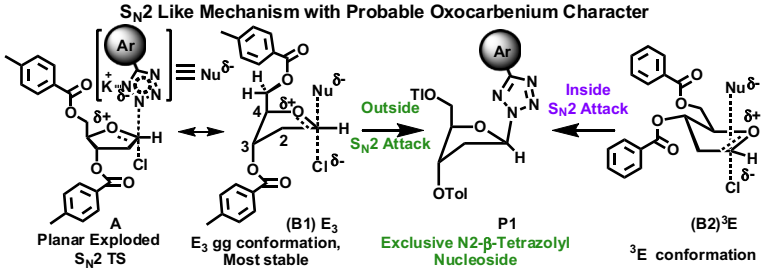


Figure 2. Crystal packing (a) and molecular arrangement (b) of nucleoside **15a** [CCDC 1015970]. Crystal packing (c), molecular arrangement (d) and N…I bonded molecular arrangement of nucleoside **17a** [CCDC 1015969].

The β-anomeric configuration and the N2-alkylation was further confirmed from a X-ray single crystal structure analysis of bis-toluoylated tetrazolyl nucleosides, $^{TzBB}\mathbf{B}_{Ac}$ (**15a**) and $^{TzFlB}\mathbf{B}_{Ac}$ (**17a**) (Fig. 2, SI Section 4). The X-ray diffraction analysis showed that the orientation of the tetrazolyl bromobenzene ring of the nucleoside **15a** with respect to the sugar unit was locked via the self-bonding interaction like $N_{(tetrazole)}\cdots Br_{(bromobenzene)}$ (3.070 Å) and $Br_{(bromobenzene)}\cdots O{=}C_{(5'\text{-toluoyl})}$ (3.189 Å). Overall the nucleoside **15a** adopted a unidirectional layered structure (Fig. 2a and b). On the other hand, the sugars of two consecutive molecules pointed antiparallel and the nucleoside **17a** adopted a layered structure held via π–π stacking and H-bonding like short interactions (Fig. 2c–e) with an inter-layer distance of 3.872 Å.

Next, we studied the sugar and N2-glycosidic conformation. Sugar puckers in nucleosides $^{TzBB}\mathbf{B}_{Ac}$ (**15a**) and $^{TzFlB}\mathbf{B}_{Ac}$ (**17a**) were South (*S*) (2′-*endo*) and the tetrazole bases displayed *anti*-conformations with respect to the glycosyl torsion angle which was evidenced from a strong $^3J_{H1'-H2'}$ (7.2 for **15a** and 7.0 for **17a** Hz) coupling (SI, Section 5). Other modified nucleosides also maintained a natural DNA-like C_2'-*endo* sugar conformation as was revealed from the NOESY cross peak intensity and strong $^3J_{H1'-H2'}$ coupling constants.[9] A theoretical calculation based on B3LYP/6-31G* functional using G09 program package[10a] also supported the sugar conformations as *S*-locked nucleoside. A dihedral scan for the glycosidic angle revealed that the adopted *anti*-glycosyl conformation ($\zeta = -62°$) of the tetrazole base was energetically highly favorable compared to any other conformation (SI, Section 5) which is probably due to the less repulsion between the lone pair of tetrazole-N1 and O4′ compared to the repulsion between tetrazoles-N3, N4 and O4′. This repulsive force restrict the rotation of the glycosyl bond and thus, fix the *S*-sugar conformation of tetrazolyl nucleosides leading to the *syn*-disposition of the aryl substituted tetrazolyl bases. Therefore, the tetrazolyl nucleosides behaved the same way as the natural nucleosides. It is therefore anticipated that the introduction into short oligonucleotide sequence the tetrazolyl nucleoside with locked-*S*(*anti*) geometry could fix the conformational state and would help understanding the impact of conformational restrictions in DNA.[9a,b]

It is a fact that, in addition to the α-/β-diastereomers, tetrazole can in principle give rise to two regiomers N1- or N2-, upon formation of a glycosidic bond, the same was reported by Muller.[8a] However, the electronic consideration based on Sadlej-Sosnowska's theoretical calculation[11a] and solvent polarity,[11b,c] in combination with steric factors might have some bearing on our repeated experimental observation on the regioselective formation of N2-tetrazolyl-β-nucleosides. In aprotic solvents, potassium salt of tetrazolate anion might exist as $N1^-\cdots K^+$ bonded complex which essentially remained electronically either as free anion or as ion pair. In this scenario, the aromaticity of the



Scheme 2. The most probable reaction mechanism to account for both regioselective and stereoselective outcome.

tetrazole was considerably disrupted. Therefore, the electrophilic attack would be directed through the frontal side toward N2—N3 bond of tetrazole (Fig. 1, Scheme 2 and SI Section 2) rather than normally to the plane of the heterocycle as it occurs in the case of highly aromatic tetrazolate anions irrespective of the nature of substituent at C-5. Moreover, the obviously increased steric hindrance among the C-5-aryl units of tetrazole donors and the crowded electrophilic center of chlorosugar would led to a sterically (crowded) destabilized S_N2 transition state in case of N1-glycosylation thereby favoring ultimately the formation of N2-glycosilation product (2,5-disubstituted tetrazoles) exclusively. This fact was corroborated by the reported observed regioselectivity while using sodium hydride[6c] or triethylamine as base.[6b,d] Furthermore, the comparatively less polar solvent tetrahydrofuran might play a role in driving predominant 2*H*-tetrazole stabilization which in turn afforded the regioselective formation of N2-glycosylated nucleoside.[6b,7c] That the THF is a good solvent for regioselective N2-alkylaion of 5-substituted tetrazole was also supported by Aerschot et al.[7c]

On the other hand, the exclusive formation of β-anomer (stereoselectivity of glycosylation) can be explained as follows. Since the starting Hoffer's chlorosugar[8b] has the α-configuration,[8d] the exclusive and stereoselective formation of 2′-deoxy-N2-β-tetrazolyl nucleosides in the present study can be viewed to be due to a direct Walden inversion (S_N2) at the anomeric C1-carbon by the anionic N2-tetrazolates.[12a] This explanation was also supported by previously reported literatures utilizing the sodium salt glycosylation procedure at room temperature.[12] Combining these two effects the below conclusion can be made about the regioselective and stereoselective outcome of the present investigation. The incoming tetrazole nucleophile with $N1^{-}\ldots K^{+}$ bonding might involve in electrostatic interaction with sugar 'O_4'. Then, the tetrazole attacked the electrophilic anomeric C1-carbon of the chlorosugar through nucleophilic N2-solely from the β-face of the sugar via an S_N2 substitution leading to exclusive formation of N2-β-tetrazolyl nucleoside.

Following the enormous literature reports of C-glycosylation, one might argue to see the observed stereoselectivity via the formation of an oxocarbenium ion intermediate that is preferentially attacked by the tetrazolyl-N2-nucleophile from the β-face of the anomeric C1-carbon of sugar. Therefore, considering the 'exploded S_N2'[13a] mechanism, the 'outside S_N2 attack' by the nucleophile in the energetically most stable E_3 *gg* conformation, (B1),[13a,b] the same conclusion can be made (Scheme 2).[13] On the other hand, in a purely oxocarbenium ion intermediate the 'inside' approach of the bulky nucleophile would prohibited due to steric bulk of pseudoaxial-3-toluolyl group leading to exclusive formation of β-anomer via the favorable 'outside' approach of the nucleophile (SI, Scheme S3b).[13e] However, this possibility is ruled out as the formation of oxocarbenium intermediate is generally encountered in a strong Lewis acid mediated glycosylation proceeds via S_N1 pathway.[13a] The strong 'N' nucleophile might play a role for the

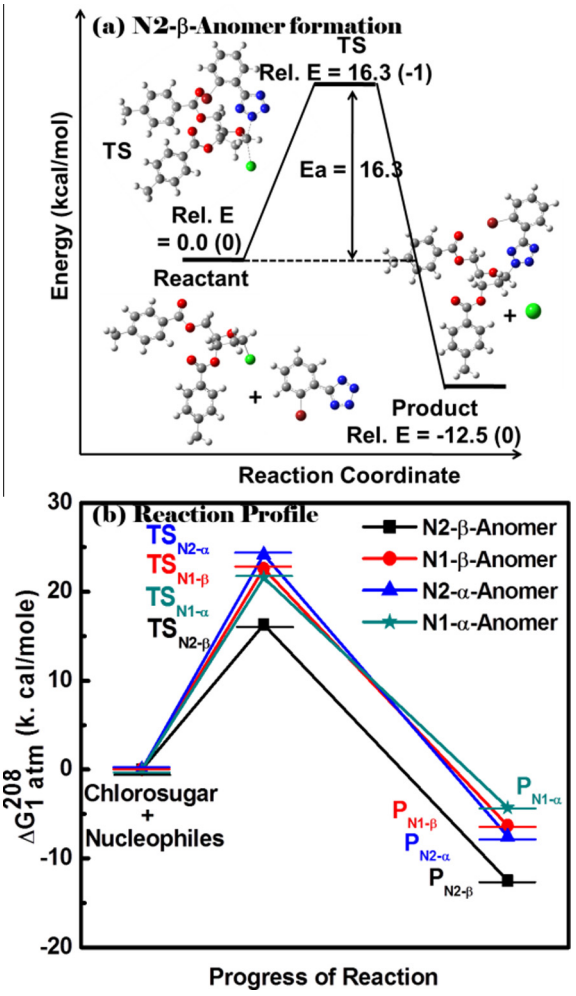


Figure 3. (a) Relative energies with imaginary frequencies for the species involved in the S_N2 reaction for the formation of N2-β-anomer and (b) the reaction profiles for all at B3LYP/6-31G* level.

observed stereoselectivity unlike the highly stereoselectivity reported for 'O/C'-glyocosylation.[13a] Moreover, the role of anchimeric assistance by the neighboring >C=O of toluoyl protecting group at C-3 of sugar and thus to block the α-face could not be ruled out to afford β-anomers as the sole products of glycosylation via the favorable approach of the nucleophile only from the β-face (SI, Scheme S3c).[14] We believe that the reaction is going via a steric and stereoelectronically controlled S_N2 like mechanism.

To better understand the stereoselective and regioselective aspects we carried out theoretical calculation to support the predominant formation of N2-glycosylated β-anomer as the sole

product considering S_N2 like reaction using DFT in a Gaussian 09 program package.[10a] The formation of bromophenyl substituted N2-tetrazolyl-β-nucleoside, $^{TzBB}B_{Ac}$ (**15a**) was taken as a model example. For that purpose, the reactants-chlorosugar, nucleophiles and the products were optimized with B3LYP/6-31G (d) level of theory.[10b] The transition-state structures were calculated using the same level of theory with QST3 program.[10c] The energies and the thermochemistry were compared among the N1-versus N2-glycosilated product formation for both α- and β-anomers of bromophenyl substituted tetrazolyl nucleoside, $^{TzBB}B_{Ac}$ (**15a**).

Theoretical study supported that N2-β product was most stable compared to other possible regio- and stereoisomers (N1-β, N2-α or N1-α). While the activation energy (ΔE_{act}) for the formation of N2-β-anomer was found to be16.3 kcal mol^{-1}, the energies were higher for the formation of other regio-/stereo-isomers (Ea for N1-β,N2-α and N1-α were 22.6, 24.2 and 21.6 kcal mol^{-1}, respectively) (Fig. 3a and b and SI Section 6). Therefore, energetically the formation of N2-β-anomer is favoured by about 6.3–7.9 kcal/mol energy compared to all other possible regio-/stereo-isomers. We also calculated the change in free energy in S_N2-reaction in each case and found that the reaction involving the formation of N2-β-anomer has the highest negative value (−3.17 kcal mol^{-1}) indicating the most feasible product formation with a much higher rate than other possibilities. In fact, our experimental results indicated the formation of N2-β-anomer as the sole product. On the other hand, similar calculation on C-5 unsubstituted tetrazolyl nucleoside reflected the marginal difference in stereoselectivity and little more preference for N2-glycosylation upon substitution reaction supporting the Muller's[8a] experimental observation (SI Section 6). These calculations clearly suggested the role of steric bulk of C-5 aryl substituents in deciding the regioselective and stereoselective formation of N2-β-tetrazolyl nucleosides exclusively.

Finally, we studied their UV–visible and fluorescence photophysical properties. Previously, we and subsequently others have shown that linking of fluorescent/non-fluorescent unit with a triazole moiety led to the installation of fluorescence emission properties to the non-fluorescent molecules and/or modulation of the same to a fluorescent molecule.[15] The synthesized tetrazolyl building blocks also behaved in a similar way with respect to their photophysical properties. We studied the photophysical properties of few of our synthesized β-nucleosides in various organic solvents to test their microenvironment sensitive property.

The UV–visible spectra of the nucleoside $^{TzMB}B_{Do}$ (**8b**) containing a 4-methoxybenzene exhibited very strong absorption maxima at around 255–257 nm in various organic solvents. Excitation at absorption maxima of each solvent showed emission at around 288 nm in lowest polar solvent dioxane which exhibited a bathochromic shift to 340 nm as the solvent polarity increases up to acetonitrile. In methanol and ethanol, the emission spectra showed two bands at 319 and 419 nm and at 316 and 436 nm, respectively (Fig. 4a and b). The nucleoside $^{TzTMB}B_{Do}$ (**9b**) containing a trimethoxybenzene aromatic unit exhibited very strong absorption at 266 nm in lowest polar solvent dioxane which showed a little blue shift to 263 nm as the solvent polarity increases. When excited at the absorption maxima of different solvents, it showed an intramolecular charge transfer (ICT) band appearing at 434 nm in dioxane with a red shift of 38 nm as the solvent polarity increases up to acetonitrile (434 nm in Dioxane→472 in ACN). The trimethoxy benzene acted as donor and the tetrazole ring as an acceptor leading to an ICT band. This kind of installation and modulation of photophysical properties has been observed between the donor and acceptor groups with triazolyl ring acting as the linker.[15] However, the ICT band disappeared in extremely polar solvents like ethanol and methanol most probably due the involvement of the lone pair of methoxy groups in hydrogen bonding with polar protic solvents like ethanol and methanol (Fig. 4c and d).

The nucleoside $^{TzMNap}B_{Do}$ (**11b**) containing a methoxynapthalene aromatic unit exhibited very strong absorption at around 247 and 297 nm. The band at 247 nm showed a blue shift of 2 nm as the solvent polarity increases while the band at

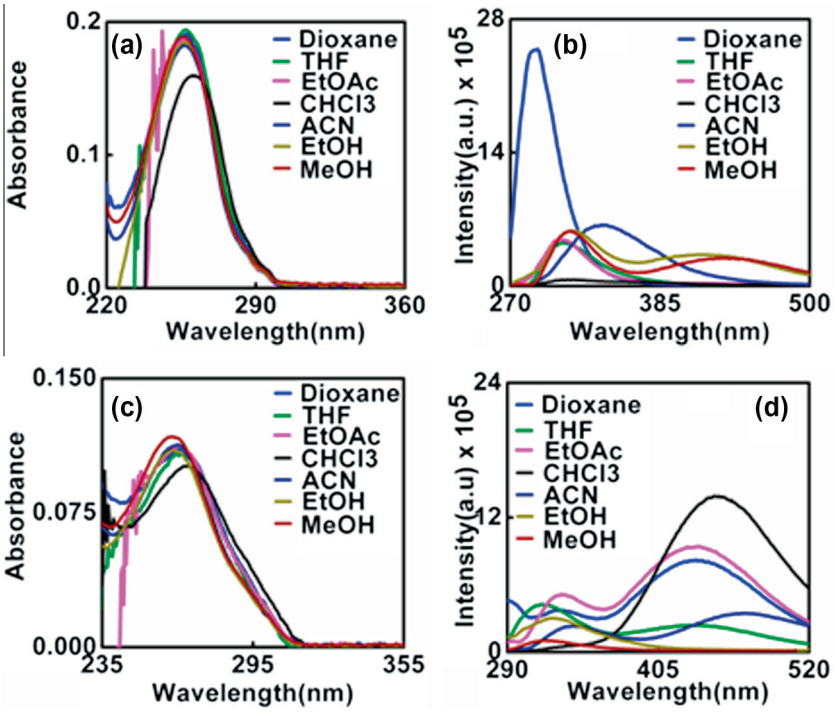


Figure 4. UV–visible and fluorescence spectra of (a and b) nucleoside $^{TzMB}B_{Do}$ (**8b**) and (c and d) nucleoside $^{TzTMB}B_{Do}$ (**9b**) in various organic solvents (Concentration of each nucleoside was 10 μM).

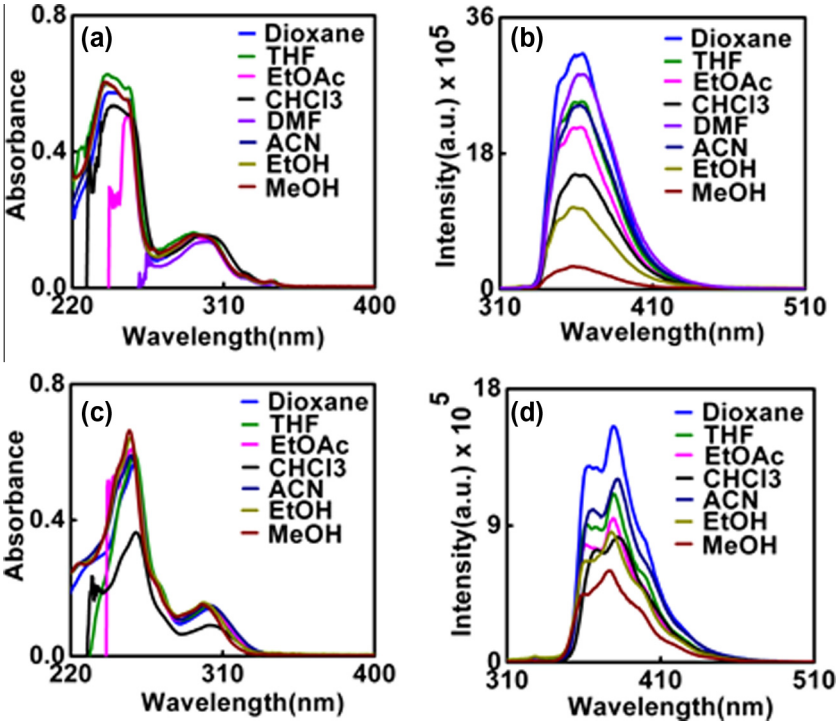


Figure 5. UV–visible and fluorescence spectra of (a and b) nucleoside $^{TzMNap}B_{Do}$ (**11b**, $\lambda_{ex} \sim 290–300$ nm) and (c and d) nucleoside $^{TzPhen}B_{Do}$ (**12b**, $\lambda_{ex} = 300$ nm) in various organic solvents (concentration of each nucleoside was 10 μM).

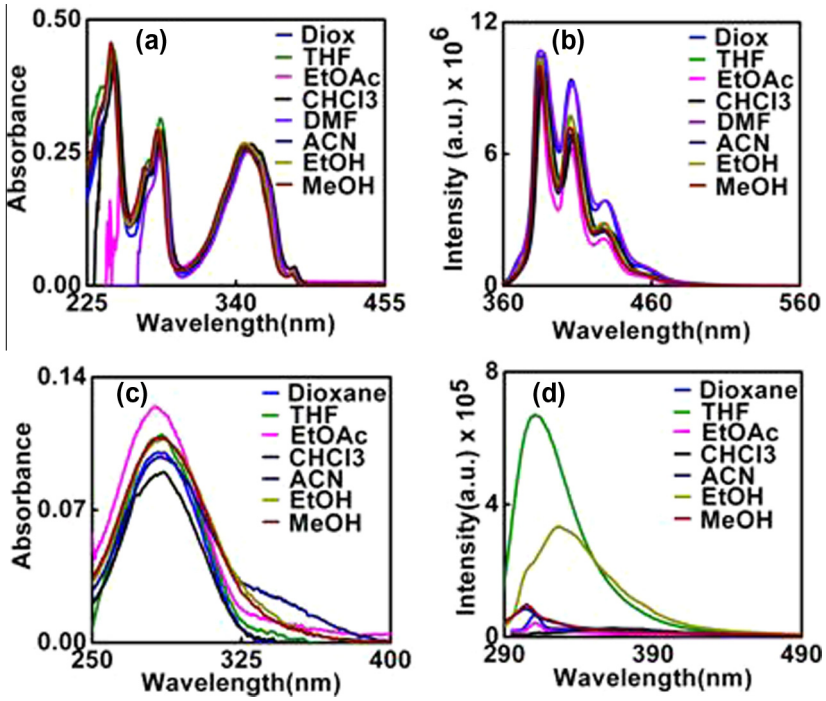


Figure 6. UV–visible and fluorescence spectra of (a and b) nucleoside $^{TzPy}B_{Do}$ (**13b**) $\lambda_{ex} = 350$ nm and (c and d) nucleoside $^{TzNB}B_{Ac}$ (**14b**) in various organic solvents (Concentration of each nucleoside was 10 μM).

297 nm showed a bathochromic shift followed by hypsochromic effect as the solvent polarity increases (Fig. 5a and b). Excitation at absorption maxima (290–300 nm) of each solvent showed structureless emission at around 362 nm with decrease in intensity as the solvent polarity increases. The quantum yield of fluorescence also follows the same trend as for the case of intensity in various solvents.

The $^{TzPhen}B_{Do}$ **(12b)** nucleoside showed very little blue shifted absorbance as the polarity of the solvent increases from dioxane ($\lambda_{max} = 258$ nm) to methanol ($\lambda_{max} = 255$ nm). Upon excitation at

300 nm, the nucleoside $^{TzPhen}\mathbf{B}_{Do}$ showed structured emission band at 363 and 379 nm in dioxane which were very little red shifted to 368 and 382 nm, respectively, as the solvent polarity increases up to chloroform. With further increase in solvent polarity up to methanol, the two structural bands shifted to the blue region and appeared at 360 and 376 nm, respectively (Fig. 5c and d).

Tetrazolylpyrene nucleoside $^{TzPy}\mathbf{B}_{Do}$ (**13b**) showed structureless absorption at 354 nm in dioxane which shifted to 346 nm as the solvent polarity increases from dioxane to methanol. This observation suggested an electronic coupling of pyrenyl π-electron with tetrazole unit. However, it showed a structured emission when excited at 350 nm with appearance of prominent maxima at 385 and 406 nm of almost similar intensities in dioxane which showed a red shift to 387 and 408 nm as the solvent polarity increases up to $CHCl_3$ followed by blue shift to 384 and 405 nm as the solvent polarity further increases (Fig. 6a and b). The quantum yield also follows the same trend as for the case of intensity in various organic solvents. The nucleoside $^{TzNB}\mathbf{B}_{Ac}$ (**14b**) containing a nitro functionality exhibited very strong absorption at around 285 nm in all the solvents tested. Excitation at the absorption maxima of $^{TzNB}\mathbf{B}_{Do}$ (280 nm) showed that it was non-fluorescent except in THF and ethanol in which it exhibited emission at 310 and 326 nm (Fig. 6c and d).

In conclusion, we described a stereoselective and regioselective route for the synthesis of tetrazolyl-N2-β-nucleosides as a new class of nucleoside analogs. To rationalize the outcome we proposed a mechanism involving S_N2 like transition state. The regioselective and stereoselective glycosylation protocol outlined herein is simple and might find potential application in broad synthetic chemistry such as to the preparation of other nucleoside analogs with azoles as bases or regioselective alkylation of azoles. The scope is currently being undertaken to other azole nucleophiles to allow the synthesis of novel nucleoside analogs. The tetrazole nucleosides are quite stable, can be incorporated into short DNA and a donor–acceptor pair tetrazolyl nucleosides are expected to stabilize a duplex DNA via π–π stacking, H-bonding or electrostatic interaction. Such nucleosides, hence, might be useful as probes in DNA or in decorating DNA for DNA based material science applications. Two of the tetrazolyl aromatic nucleosides showed interesting solvatochromic photophysical property. As for example, the trimethoxyphenyl tetrazolyl nucleoside showed an intramolecular charge transfer (ICT) emission with large (38 nm) solvatochromicity. A combination of donor–acceptor pair tetrazolyl nucleosides might form suitable base pair of unnatural DNA and are expected to stabilize a duplex DNA via π–π stacking/charge transfer interaction. Therefore, the tetrazolyl unnatural nucleosides might find application in decorating unnatural DNA usable for various biotechnological and DNA based material science applications.

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Supplementary data

Supplementary data (experimental details, theoretical study and copy of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.02.078.

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