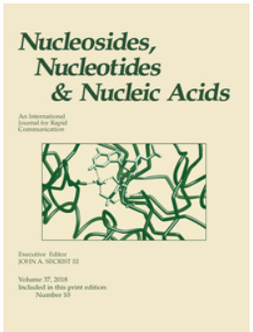

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# 3-Trifluoromethylpyrazolones derived nucleosides: Synthesis and antiviral evaluation

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# 3-Trifluoromethylpyrazolones derived nucleosides: Synthesis and antiviral evaluation

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**ABSTRACT**

Dengue (DENV) viral infection is a global public health problem that infrequently develops life threatening diseases such as dengue hemorrhagic fever (DFS) and dengue shock syndrome (DSS). Middle East respiratory syndrome coronavirus (MERS-CoV) is a highly pathogenic human corona virus with 38% fatality rate of infected patients. A series of 4-arylhydrazono-5-trifluoromethyl-pyrazolones, their ribofuranosyl, and 5′-deoxyribofuranosyl nucleosides were synthesized, geometry optimized using Density functional theory (DFT), and evaluated for their antiviral activity. 2-Nitrophenylhydrazonopyrazolone derivative **5** showed significant activity against MERS-CoV ($EC_{50}$ = 4.6 μM). The nucleoside analog **8** showed moderate activity against DENV-2 ($EC_{50}$ = 10 μM), while the activity was abolished with the corresponding 5′-deoxyribonucleoside analogs. The identified hits in this study set this category of compounds for further future optimizations.

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**KEYWORDS**
Hydrazonopyrazolones; nucleosides; antiviral activity; dengue virus 2; MERS-CoV

## Introduction

Dengue virus (DENV) is a mosquito-borne virus that causes Dengue fever (DF) and infrequently develops life threatening diseases such as dengue hemorrhagic fever (DFS) and dengue shock syndrome (DSS).[1] It is estimated that half of the world's population is at risk of DENV infection with 390 million people infected annually, including 20,000 deaths.[2] There is no approved antiviral drug available for treatment of DENV infections.[3] Middle East respiratory syndrome coronavirus (MERS-CoV) is a highly pathogenic human coronavirus causes severe acute pneumonia and renal failure. MERS-CoV has recently emerged in Saudi Arabia[4] and outbreaks in South Korea.[5] MERS-CoV quickly spread around the globe with a case fatality rate of 38% according to the World Health Organization (WHO).[6] Currently, there are no therapies to treat DENV or MERS-CoV infections.

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lncn.

The development of novel antiviral compounds that combat is urgently needed. We have screened a library of small molecules against several RNA viruses and have identified some 4-arylhydazonopyrazolones derivatives with antiviral activity against DENV-2 and MERS-CoV. The nucleus of these compounds have a 3-trifluoromethylpyrazolone, a five membered heterocycle ring with two nitrogen atoms at the 1 and 2 positions with a keto group at the C-5 position thereby mimic the imidazolyl ring of purine nucleobases. 4-Hydrazonopyrazolones have an interesting structural feature, that the 4-arylhydrazino group most likely forms an internal hydrogen bond with the pyrazolone carbonyl forming a pseudo bicyclic 6,5-ring system,[7] mimicking the shape-structure of 1-substituted purine. $N^1$-3-fluorophenylinosine (**3**) and $N^1$-3-fluorophenylhypoxanthine have been reported to show interesting anti-Hantaan virus activity.[8] Ribavirin (**1**) and Bredinine (**2**) are examples of nucleosides with altered nucleobase structures, where the first has shown a wide range of activity against DNA and RNA viruses.[9] Bredinine, an imidazolyl ribonucleoside antibiotic[10] have reported to have immunosuppressant,[11] anti-rheumatism,[12] and antitumor[13] activities. It is of interest to check whether nucleosides derived from 3-triflumethyloropyrazolone and its 4-hydrazonopyrazolones derivatives, mimics of/or pseudo 1-arylpurines, would show desirable antiviral properties. Herein, we wish to report on the synthesis, the Density function theory (DFT) geometrical optimizations, and the antiviral evaluation of 3-trifluoromethylpyrazolin-5-one and 4-arylhydrazono-3-methylpyrazolin-5-ones derived nucleosides **8–15** (Figure 1).

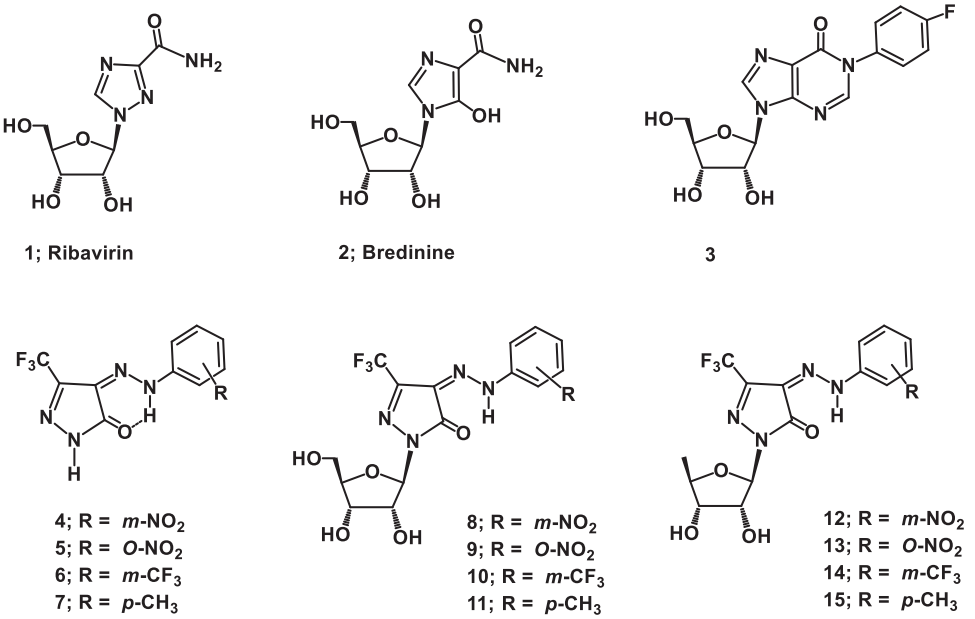



**Figure 1.** Structures of biologically active nucleobase modified nucleosides **1–3** and 3-trifluormethyl-pyrazolones **4–7** and their derived nucleosides **8–15**.

## Results and discussion

3-(Trifluromethyl)-pyrazol-1*H*-5-ol (**16**) was synthesized from ethyl trifluroacetoacetate and hydrazine hydrate in absolute ethanol under reflux temperature.[14] 3-Trifluoromethyl-pyrazolone derivative **16** may exist in three tautomeric forms (I-III) (Figure 2). The distribution ratio of the three tautomers was calculated using Density functional theory (DFT), at B3LYP/631G* level of theory in gas, nonpolar, and polar phases. In gas phase, tautomer (I) showed the lowest global and relative energy and the highest Boltzmann Weight (BW, 0.988), implying its prevalence over the rest of the tautomers. In nonpolar solvent, the equilibrium of the tautomers yet still in favor of the tautomer (I) (BW, 0.907), while the population of tautomer (II) raised to (BW, 0.85). On the other hand, in polar solvent, the equilibrium become in favor of tautomer (II) (BW, 0.878) on the expense of tautomer (I) (BW; 0.11). $^{1}$H-NMR of **16** showed an olefinic singlet peak (5.65 ppm, H-4) and two exchangeable protons at 11.18 and 12.8 ppm. Its $^{13}$C-NMR showed three quaternary signals at 154.59, 140.49, and 121.64 corresponding to C5, C3, and the exocyclic $CF_3$, respectively and the latter group's $^{19}$F-signal appeared at −61.34 ppm. IR spectrum of **16** showed the presence of signals characteristic to OH and NH (3270.25, and 3191.14 $cm^{-1}$) and the presence of two signals characteristic to C=N group (1597 and 1499 $cm^{-1}$). HMBC spectrum of **16** showed a correlation between the hydroxyl proton and the C-5 carbon supporting the structure of the tautomer (I) (Figure 2). Treatment of **16** with diazonium salts generated from *o*-nitro, *m*-nitro, *m*-trifluoromethyl, and *p*-methyl-aniline in the presence of NaOAc in absolute EtOH gave the corresponding 4-hydrozonopyrazolone derivative **4, 5–7,**[15] respectively in good yields (Scheme 2).

Aryl hydrazonopyrazolone derivatives **4, 6, 7** may exist in five tautomeric forms, while the *o*-nitrophenyl derivative **5** may exist in eight tautomeric forms. DFT geometry optipmizations[16] of the tautomeric forms of 4-aryll-hydrazono-pyrazolo-5-ones was performed at B3LYP/631G* level of theory in gas, nonpolar and polar phases (Figure 3). In contrast to 3-(trifluromethyl)-pyrazol-1*H*-5-ol (**16**), DFT energy minimization of the 4-arylhydrazono derivatives **4–7** showed a predominance of the 2-keto-4-hydrazono

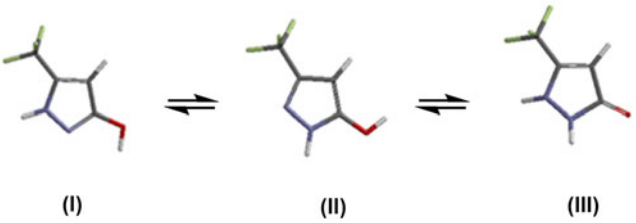



**Figure 2.** Minimized energy of tautomeric forms of compound **16** using DFT at B3LYP/631G* level.

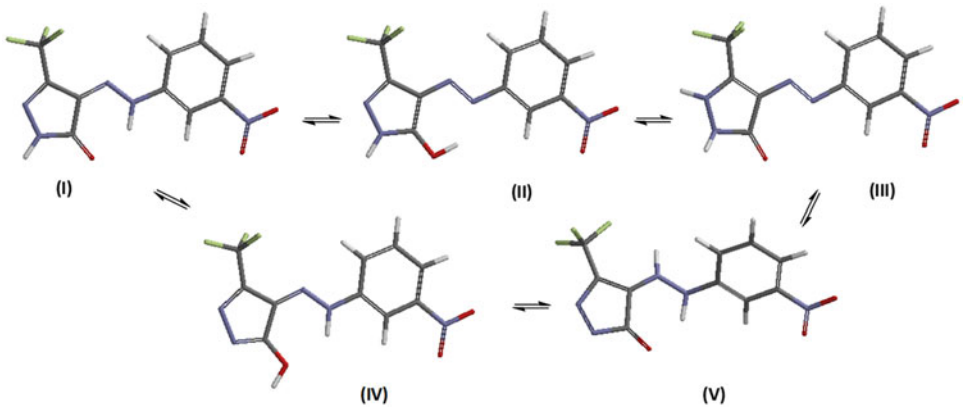
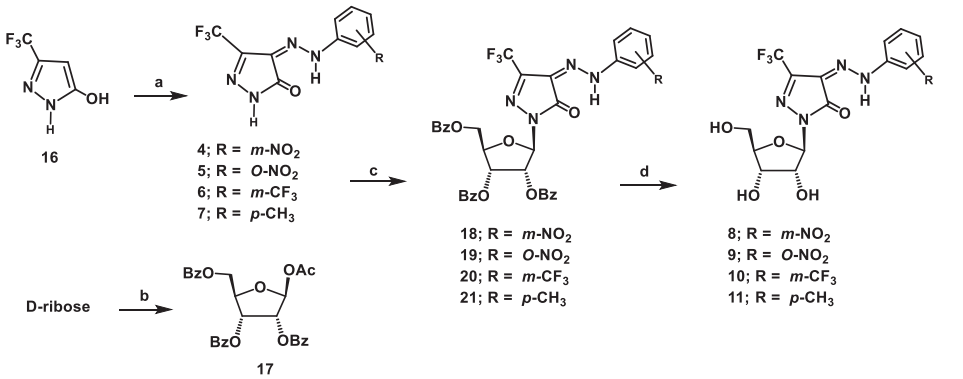
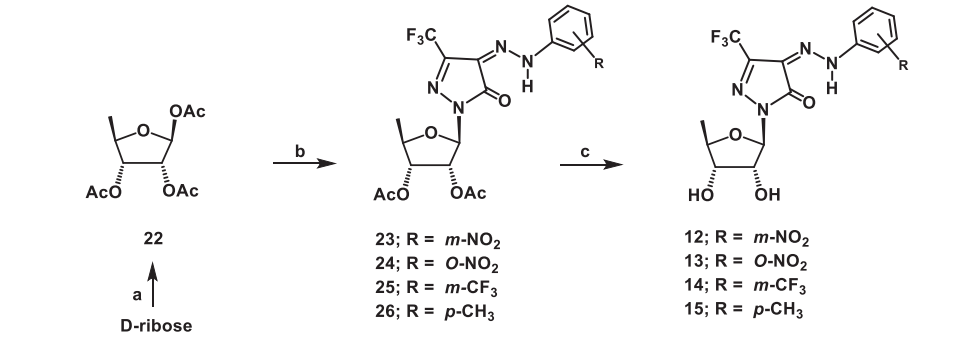



**Figure 3.** Geometry optimization of tautomeric forms of compound **4** using DFT at B3LYP/ 631G* level.




[a]Reagents and conditions. (a)$ArN_2^+Cl^-$, NaOAc, EtOH, 3 h, 0-5°C; b) i) conc. $H_2SO_4$, dry MeOH, 0 °C-r.t., 5 h. ii) BzCl, dry Pyr., 12h , r.t iii) conc. $H_2SO_4$, $Ac_2O$, AcOH, °C-r.t., 5 h. c) BSA, DCM 0 °C, 30 min, rt, then $SnCl_4$ , 3h; b) $NaOCH_3$, dry MeOH, 3 h., rt.

**Scheme 1.** Synthesis of ribonucleosides derived 4-aryl-hydrazono-3-trifluoromethylpyrazolone.




[a]Reagents and conditions. a) Ref 17: i) conc. $H_2SO_4$, MeOH, acetone, , 0 °C-5 °C, r.t., 5 h; ii) MsCl, $Et_3N$, DCM, 2h, r.t.; iii) $NaBH_4$, , LiCl, diglyme, 4 h,80 °C; b) BSA, DCM 0 °C, 30 min, rt, then $SnCl_4$ , 3h; c) $NaOCH_3$, dry MeOH, 3 h., rt.

**Scheme 2.** Synthesis of 5′-deoxyribonucleosides derived 4-aryl-hydrazono-3-trifluoromethylpyrazolone.

tautomer (I) in gas phase, nonpolar solvent and in polar solvent (Figure 3). The tautomer (I) population is energetically favored irrespective to the substituent at the aryl group (H, *m*-$CF_3$, *m*-NO2, *o*-$NO_2$, *p*-$CH_3$), with lowest global and relative energy, and the highest BW. The existence of the hydrazonopyrazolones **4–7** as a single isomers was confirmed by NMR ($^1$H, $^{19}$F, and $^{13}$C) spectra. IR spectra support the structure of the tautomer I, for example, IR (ATR) spectrum of **4** showed three characteristic signals at 1681, 1557 and 1531 $cm^{-1}$ corresponding to exocyclic ν C=O, exocyclic ν C=N, and ring ν C=N groups, respectively. Its $^{13}$C-NMR-APT spectrum showed three quaternary signals of the pyrazolone ring at 158.4 136.5 (q), and 148.58 ppm corresponding to C3, C5, and C4 respectively.

Glycosylation of the silylated 4-(arylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-pyrazolones (**4–7**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**17**)[17] in the presence of $SnCl_4$ in dry $CH_2Cl_2$, under Vorbrüggen glycosylation conditions provided the corresponding $N^2$-β nucleosides (**18–21**), respectively in good yields (Scheme 1). The downfield chemical shift of the anomeric protons (6.24–6.28 ppm), as a result of the anisotropic effect of the 2-oxo moiety of the hydrazopyrazolone ring, confirms the glycosylation at the $N^2$-position in **18–21**. Deprotection of the hydroxyl groups of **19–22** was performed under conventional conditions (NaOMe/MeOH) gave the free nucleosides **8–11,** respectively in good yields. The structures of the free nucleosides **8–11** was assigned by HMBC spectra. DFT geometry optimization of **8**, as an example of the free nucleosides **8–11**, was performed at B3LYP/631G* level of theory in polar solvent and reveals that the nucleoside **8** may exist in three tautomeric forms (Figure 4). The 4-hydrazono-2-keto (tautomer I) scored the lowest global and relative energy with a Boltzmann number of one. All of the three tautomers showed a preference of the 2′-endo conformation of the sugar moiety. $^{13}$C-NMR (APT) spectrum of **8** showed three quaternary carbons of the pyrazolone ring at δ 154.55 (C3), 139.99 (q, C-5), 121.61 (q, $CF_3$) and its UV-vis (MeOH) $\lambda_{max}$ 230, 390 nm supporting the structure of the tautomer (I) and in agreement with DFT results. Whether the compounds **6–9** act as a nucleoside analog or nonnucleoside analogs in their mechanism of interfering with the viral replication machinery, their 5′-deoxy nucleosides **12–15** were synthesized. 1,2,3-Tri-*O*-acetyl-5′-deoxy-β-D-ribofuranose (**22**) was synthesized according to literature procedure.[18] Coupling of **4–7** with **22** under Vorbrüggen glycosylation conditions provided the 5′-deoxyribonucleoside derivative **23–26,** respectively in good yields (Scheme 2). Deprotection of **23–26** was performed with NaOMe in MeOH to give the free nucleosides **12–15** in good yields (Scheme 2). The structures of the nucleosides **23–26** and their free derivatives **12–15** were assigned by $^1$H, $^{13}$C, $^{19}$F-NMR, HMBC, UV-vis, and IR spectroscopy.

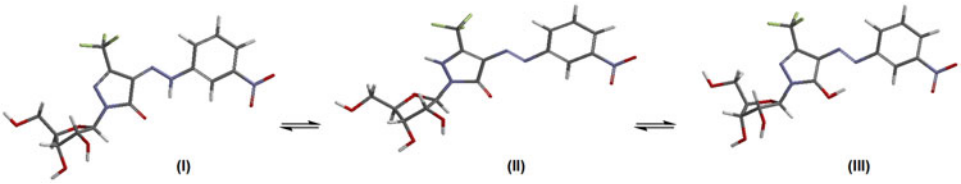



**Figure 4.** Geometry optimization of tautomers(I-III) of compound **6**.

**Table 1.** Antiviral evaluation of compounds 4–11, and 14, 15.

| Compound | MERS-CoV $EC_{50}/(CC_{50})$ μM | Flu A (H1N1) $EC_{50}/(CC_{50})$ μM | RSV $EC_{50}/(CC_{50})$ μM | HCV $EC_{50}/(CC_{50})$ μM | DENV-2 $EC_{50}/(CC_{50})$ μM | HBV $EC_{50}/(CC_{50})$ μM |
|---|---|---|---|---|---|---|
| 4 | 3.2/(6.8) | 0.71/(0.71) | 3.2/(3.2) | 6.34/(10.29) | 2.4/(8.6) | 7.06/(37.34) |
| 5 | 4.6/>(100) | 1.6/(1.6) | 3/(3.3) | >10.83/(>20) | 1.5/(>24) | 8.4/(>38.36) |
| 6 | 3.2/(6.8) | 0.32/(0.86) | 3.2/(3.2) | 7.58/(7.78) | 0.32/(1.5) | 7.06/37.34 |
| 8 | 56/(68) | 33/(98) | >100/(>100) | 20/(>20) | 10/(>100) | >100/(>100) |
| 9 | 32/(>100) | 32/68 | >100/(>100) | 20/(>20) | 24/(>32) | >100/(>100) |
| 10 | 32/(42) | 3.1/(3.6) | 32/100 | 20/(>20) | ND | >100/(>100) |
| 11 | ND | ND | ND | 20/(>20) | >87/(87) | ND |
| 14 | 100/>(100) | ND | ND | ND | 100/>(100) | ND |
| 15 | 100/>(100) | ND | ND | ND | 100/>(100) | ND |
| $M_{12}8_{533}$ | 0.19/(>100) | | | | | |
| Ribavirin | | 7.6/(>320) | 10/(>320) | | | |
| 3TC | | | | | | 0.01/(>2) |
| PSI-7977 | | | | 0.07/(>5) | | |
| 6-azauridine | | | | | 0.32/(>100) | |

$EC_{50}$, compound concentration that reduces viral replication by 50%; $CC_{50}$, compound concentration that reduces cell viability by 50%; ND, not determined.

## Biology

The antiviral activity of compounds **4–7, 8–11**and **14** were assessed against MERS-COV, DENV-2, Influenza Virus A (Flu A, H1N1), Respiratory syncytial virus (RSV), Hepatitis C virus (HCV), Hepatitis B virus (HBV) (Table 1). The 4-arylhydrazonopyrazolone derivatives **4–7** showed significant activity against the tested viruses, however with varying cytotoxicity. Of these compounds, the 4-(*o*-nitrophenylhydrazono)-pyrazolone (**5**) showed significant activity against MERS-CoV ($EC_{50}$ = 4.6 μM, $CC_{50}$ = >100 μM) and against DENV-2 ($EC_{50}$ = 1.5 μM, $CC_{50}$ = >24 μM). While 4-(*m*-trifluoromethylphenylhydrazono)-pyrazolone (**6**) showed cytotoxicity to MERS-CoV, Flu A H1N1, RSV, HCV, and DENV-2 cell lines, it showed moderate activity against HBV ($EC_{50}$ = 7.06 μM, $CC_{50}$ = 37.34 μM) with a narrow selectivity index (SI). A similar pattern of cytotoxicity against all cell lines was observed with the 4-(*m*-nitrophenylhydrazono)pyrazolone (**4**). Interestingly, the SI of ribonucleoside derivative **8** was improved against DENV-2 (SI; 10) compared with compound **4** (SI; 3.5). On the other hand, both the anti-DENV-2 and cytotoxicity was diminished with 4-(*o*-nitrophenylhydrazono)-pyrazolone ribonucleoside derivative **9**. Whether the antiviral activity associated with compound **8** is related to its activation to its ribonucleoside phosphate derivatives, the 5′-deoxyribonucleosides **14–15**

was evaluated for their antiviral evaluation. Both the antiviral activity and the cytotoxicity of these 5′-deoxyribonucleosides were abolished. The hits identified in this study set this category of compounds for further future optimizations, including the synthesis of the 5′-momophosphate prodrugs, as potential antiviral agents.

## Conclusions

We have synthesized a series of 4-(arylhydrazono)-3-trifluoromethyl-1*H*-pyrazol-5(4*H)* -one, bearing electron donating/electron withdrawing substituents on the aryl moiety, their $N^2$-ribofuranosyl nucleosides and 5′-deoxyribonucleosides, and evaluated their antiviral activity against four RNA viruses and against HBV. The 4-arylhydrazonopyrazolone derivatives **4** and **5** showed moderate activity against HBV and the later compound showed significant activity against MERS-CoV. The nucleoside analog **8** showed moderate activity against DENV-2. The identified hits in this study set this category of compounds for further optimizations as potential antiviral agent.

## Acknowledgments

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## Experimental results and protocols

Material, instruments and general considerations. Starting materials and reagents were purchased from Acros-Organics, Alpha Aesar, and Sigma-Aldrich. Reaction progress was monitored by TLC analysis using aluminum-backed plates pre-coated with Merck silica gel 60-F254. Column chromatography was carried out on Agela Technologies Flash silica 40–60 mesh. Melting points recorded on Electrothermal IA 9100 apparatus and were uncorrected. IR spectra (ATR) were recorded on Bruker alpha spectrometer. UV-vis spectra were recorded on Agilent Cary 60. $^{1}$H and $^{13}$C-NMR spectra were recorded on Bruker 400 MHz spectrometer. Elemental analysis were recorded on Vario MICRO Cube elemental

analyzer. Computational details: all the structures of the compounds were built using Wavefunction Spartan 16 V2.0.7 and subjected to energy minimization to remove their strain energies.[19] DFT was adopted in calculating the equilibrium geometry of the compounds using B3LYP functional and 6-31G*/basis set as built-in in Spartan 16 software.[20]

**3-(Trifluromethyl)-pyrazol-1*H*-5-ol (16).** A solution of hydrazine hydrate (3.33 mL, 68.6 mmol) in absolute EtOH (15 mL) was added dropwise to a solution of ethyl 4,4,4-trifluoro-3-oxobutanoate (10 mL, 68.6 mmol) in absolute EtOH (50 mL) at room temperature. The reaction mixture was heated for 18 hours at reflux temperature. The reaction mixture was cooled to room temperature and the solvent was concentrated under reduced pressure. The solid was filtrated to give **16**[14] (9.5 g, 91% yield) as a pale yellow solid. M.P. 128–130 °C; IR (ATR): 3270 ($\nu_{OH}$), 3191 ($\nu_{N\text{-}H}$), 1597 ($\nu_{C=N}$), 1499 $cm^{-1}$; UV-vis (MeOH) $\lambda_{max}$ 230 nm; $^{1}$H-NMR (DMSO-$d_6$) $\delta$ 12.83 (1H, s, OH) 11.18 (1H, s, NH), 5.65 (1H, s, H-4); $^{13}$C-NMR (DMSO-$d_6$) $\delta$ 154.79 (C3), 140.49 (C5), 121.65 ($\underline{C}F_3$), 83.87 (C4) the signals were assigned by APT-$^{13}$C-NMR and 2D-HBMC spectrum; $^{19}$F-NMR (DMSO-$d_6$) $\delta$ −61.34.

## General procedure (A) for the synthesis of compounds 4–7

To a cold solution of 5-trifluoromethyl-2,4-dihydropyrazol-3-one (1) (3.04 g, 20 mmol) in EtOH (40 mL) containing NaOAc (3.28 g, 40 mmol), an aqueous solution of the appropriate aryldiazonium salt (20 mmol/10 mL $H_2O$) was added dropwise with stirring at 0–5 °C. The reaction mixture was stirred at room temperature for 3 hrs and the formed precipitate was collected by filtration, washed several times with cold water, dried, and recrystallized from EtOH to give **4–7**.

**(Z)-4-(2-(3-nitrophenyl)hydrazono)-5-(trifluoromethyl)-2,4-dihydro-3H-pyrazol-3-one (4)**[15a]. Yield (1.27 g, 85%) as a yellow crystals. M.P. 253–255 °C; IR 3155 ($\nu_{N\text{-}H}$), 1681($\nu_{C=O}$); 1531 ($\nu_{C=N}$), 1557 $cm^{-1}$ ($\nu_{C=N}$); UV-vis (MeOH) $\lambda_{max}$ 230, 390 nm; $^{1}$H-NMR (DMSO-*d*6) $\delta$ 12.68 (1H, s, NH) 7.71–8.47 (4H, m, Ar); $^{13}$C-NMR (DMSO-*d*6) $\delta$ 158.40, 148.58, 143.07, 136.5 (q, C5), 119.54 (q, $\underline{C}F_3$), 111.55, 118.29, 122.96, 131.07, 120.31, 124.4. Anal. Clacd for $C_{10}H_6F_3N_5O_3$ (301.19); C, 39.88; H, 2.01; N, 23.25, found C, 39.65; H, 2.21; N, 23.05.

**(Z)-4-(2-(2-nitrophenyl)hydrazono)-5-(trifluoromethyl)-2,4-dihydro-3H-pyrazol-3-one (5).** Yield (1.76 g, 90%) as a yellow solid. M.P. 195–197 °C; IR (ATR) 3166 ($\nu_{N\text{-}H}$);1671 $cm^{-1}$ ($\nu_{C=O}$), 1557 ($\nu_{C=N}$); UV-vis (MeOH) $\lambda_{max}$ 230, 395 nm; $^{1}$H-NMR (DMSO-*d*6) $\delta$ 12.70 (1H, s, NH),7.71–8.45 (4H, m, Ar); $^{19}$F-NMR (DMSO-*d*6) $\delta$ (−63.41); $^{13}$C-NMR (DMSO-*d*6) $\delta$ 158.33 (C-5, s, C=O), 142.80 (C-4), 136.50 (q, C-5), 115.59 (q, $\underline{C}F_3$), 131.15, 148.61 ($\underline{C}H$, s, Ar), 111.54, 120.39, 122.91, 124.52, (4$\underline{C}H$, s, Ar); Anal. Clacd for $C_{10}H_6F_3N_5O_3$ (301.19); C, 39.88; H, 2.01; N, 23.25, found C, 39.58; H, 2.28; N, 23.12.

**(Z)-3-(Trifluoromethyl)-4-(2-(3-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one (6).** Yield (2.85 g, 90%) as orange crystals. M.P. 205–207 °C (Lit.[15b] 206–208 °C); IR (ATR) 3205 ($\nu_{N\text{-}H}$), 1666 ($\nu_{C=O}$); 1556 ($\nu_{C=N}$), 1532($\nu_{C=N}$); UV-vis (MeOH) $\lambda_{max}$ 250, 400 nm; $^{1}$H NMR (DMSO–$d_6$) $\delta$ 12.68 (1H, s, NH), 7.59–7.98 (4H, m, Ar); $^{13}$C NMR (DMSO–$d_6$) $\delta$ 158.58, 148.58, 143.07, 129.5 (q, C-$CF_3$), 121.54(q, $\underline{C}F_3$), 113.58, 113.62, 122.54, 130.14, 120.11, 124.4 (Ar); $^{19}$F-NMR $\delta$ −63.58, −64.41; Anal. Clacd for $C_{11}H_6F_6N_4O$ (324.19); C, 40.75; H, 1.87; N, 17.28; found C, 40.63; H, 1.96; N, 17.04; O.

**(Z)-4-(2-(*p*-Tolyl)hydrazono)-5-(trifluoromethyl)-2,4-dihydro-3H-pyrazol-3-one (7)**[15c]. Yield (2.51 g, 95%) as an orange crystals. M.P. 186–188 °C (Lit15. 187 °C); IR (ATR) 3281 ($\nu_{N\text{-}H}$); 1665 ($\nu_{C=O}$), 1547 ($\nu_{C=N}$); UV-vis (MeOH) $\lambda_{max}$ 255, 430 nm; $^{1}$H-NMR (DMSO-

*d*6) $\delta$ 12.60 (1H, s, NH) 7.26–7.50 (4H, m, Ar), 2.31 (3H, s, $CH_3$); $^{13}$C-NMR (DMSO–*d*6) $\delta$ 159.06, 143.15, 136.16 ($CF_3$, q), 118.41 (q, C5), 136.91, 138.60, 115.73, 121.39, 122.39, 130.13; $^{19}$F-NMR (DMSO–$d_6$) $\delta$ −63.21; $^{19}$F-NMR $\delta$ −63.21; Anal. Clacd for $C_{11}H_9F_3N_4O$ (270.22) C, 48.89; H, 3.36; N, 20.73; found: C, 48.73; H, 3.56; N, 20.59.

**1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (17).** D-(+)ribose (5 g; 33.3 mmol) and methanol (100 mL) were added to a round flask. Thereafter, conc. $H_2SO_4$ (0.5 mL) dissolved in methanol (1 mL) was slowly added dropwise to the reaction mixture. The obtained mixture was stirred at room temperature for 5 hrs. The reaction was quenched with sodium carbonate (10 g), the reaction mixture was filtered and then concentrated under reduced pressure, to obtain 7.79 g of crude 1-*O*-methyl-D-ribofuranose as a yellowish sirup. The crude 1-*O*-methyl-D-ribofuranose (5.46 g) was dissolved in dry pyridine (16 mL) and the solution was cooled to 0 °C and benzoyl chloride (15.56 mL) was added dropwise, the reaction mixture was stirred for 12 hrs. at room temperature. Pyridine was co-evaporated with toluene under reduced pressure, the residue was diluted with ethyl acetate, washed with saturated solution of sodium carbonate, and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give (11 g) of 2,3,5-tri-*O*-benzoyl-1-*O*-methyl-D-ribofuranose as a colorless sirup. To a solution of 7.55 g of the crude 2,3,5-tri-*O*-benzoyl-1-*O*-methyl-D-ribofuranose in acetic acid (13.2 mL) and acetic anhydride (2.25 mL), conc. sulfuric acid (0.85 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 5 hrs at room temperature, and then reaction was quenched with saturated solution of sodium carbonate. The aqueous layer was extracted with ethyl acetate. The organic layer was washed by water, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The product was crystallized from *iso*-propanol to give **17** (6 g, 75%) as a white crystal. M.P. 128–130 °C, IR; 1720 $cm^{-1}$ ($\nu$C=O). $^1$H-NMR ($CDCl_3$) $\delta$ 8.90–8.07 (2H, m, Ar), 8.02–7.99 (2H, m, Ar), 7.90–7.88 (2H, m, Ar),7.61–7.51 (3H, m, Ar), 7.45–7.32 (6H, m, Ar), 6.43 (1H, s, H-1), 5.92–5.89 (1H, m, H-2), 5.79–7.78 (1H, m, H-3), 4.81–7.75 (2H, m, H-4, and H-5), 4.54–4.49 (1H, m, H-5), 2.00 (3H, s, $CH_3$), $^{13}$C-NMR ($CDCl_3$) $\delta$ 169.23 (C=O), 166.14 (C=O), 165.52 (C=O),165.18 (C=O), 133.83 (Ar),133.72 (Ar), 133.42 (Ar), 130.01 (Ar), 129.92 (Ar), 129.74 (Ar), 128.98 (Ar), 128.82 (Ar), 128.70 (Ar), 128.57 (Ar), 128.56 (Ar), 98.56 (C-1), 80.13 (C-2), 75.15 (C-3),71.53 (C-4), 63.88 (C-5), 21.05 ($CH_3$).

**General procedure (B) for the synthesis of compounds 18–21.** Bis-*N,O*-trimethylsilylacetamide (1.63 mL, 6.66 mmol) was added to a mixture of **4–7** (5.6 mmol) and **17** (5.6 mmol) in dry dichloromethane (20 mL) and the mixture was stirred for 30 min. at room temperature under Argon atmosphere. After complete dissolution, the mixture was cooled to 0 °C, and $SnCl_4$ (16.8 mmol) was added dropwise. The reaction mixture was left stirring for 3 hrs, then DMSO (5 mL) was added to the reaction mixture. The formed precipitate was and filtrated off, and the filtrate was washed with $H_2O$. The organic layer was dried (anhydrous $Na_2SO_4$) and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (eluate: Hexane/dichloromethane, 1/1 to 100% dichloromethane) to give **18–21**.

**2-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl](*Z*)-4-(2-(3-nitrophenyl)hydrazono)-5-(trifluoromethyl)-2,4-dihydro-3H-pyrazol-3-one (18).** Compound **18** was prepared by coupling of **4** with **17** according to general procedure (B). Yield (1.9 g, 76%) as a yellow semi-solid; UV-vis (MeOH) $\lambda_{max}$ 230, 390 nm; $^1$H-NMR (DMSO-*d*6) $\delta$ 13.56 (1H, d, HN), 7.36–8.27 (19H, m, Ar), 6.28 (1H, br d, H-1′), 6.15 (1H, br dd, H-2′), 6.02 (1H, br dd, H-3′), 4.81 (1H, m, H-4′), 4.77 (1H, br dd, H-5′$_b$), 4.75 (1H, br dd, H-5′$_a$); $^{19}$F-NMR (DMSO-*d*6) $\delta$ −64.45; $^{13}$C-NMR (DMSO-*d*6) $\delta$ 164.54, 164.66, 165.42, 155.60, 148.51, 143.03, 137.54 (q, C-$CF_3$), 1119.32 (q, $CF_3$), 112.25–133.96, 84.70, 78.68, 72.94, 70.76,

63.22. Anal. Clacd for $C_{36}H_{26}F_3N_5O_{10}$ (745.62): C, 57.99; H, 3.51; N, 9.39; Found C, 57.75; H, 3.66; N, 9.19.

**2-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)](*Z*)-4-(2-(2-nitrophenyl)hydrazono)-3-(trifluoro-methyl)-1H-pyrazol-5(4H)-one (19)**. Compound **18** was prepared by coupling of **5** with **17** according to general procedure (B). Yield (1.75 g, 70%) as a yellow semi-solid; UV-vis (MeOH) $\lambda_{max}$ 230, 395 nm; $^1$H-NMR (DMSO-*d*6) $\delta$ 8.53(1H, s, NH), 7.36–8.12 (19H, m, Ar), 6.25 (1H, br d, H-1′), 6.11–613 (1H, dd, H-2′, *J*=3.6, *J*=5.2 Hz), 5.98 (1H, br dd, H-3′), 5.97 (1H, br t, H-3′), 4.82 (1H, m, H-4′), 4.64–4.68 (1H, dd, H-5′$_a$, *J*=3.2, *J*=12.4 Hz), 4.55–4.60 (1H, dd, H-5′$_b$, *J*=4.0, *J*=12.4 Hz); $^{19}$F-NMR (DMSO-*d*6) $\delta$ −64.57; $^{13}$C-NMR (DMSO-*d*6) $\delta$ 164.54, 164.65, 165.42,155.59, 148.53, 142.96, 137.54 (q, $CF_3$), 133.98, 112.25, 84.70, 78.67, 72.93, 70.75, 63.22; Anal. Clacd for $C_{36}H_{26}F_3N_5O_{10}$ (745.62): C, 57.99; H, 3.51; N, 9.39; Found C, 58.02; H, 3.71; N, 9.19.

**2-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl]*(Z)*-5-(trifluoromethyl)-4-(2-(2-(trifluoro-methyl)-phenyl)hydrazono)-2,4-dihydro-3H-pyrazol-3-one (20).** Compound **20** was synthesized by coupling of **6** with **17** according to the general procedure (A) as described above to give (1.8 g, 72%) as a yellow semi-solid; $^1$H-NMR (DMSO -*d*6) $\delta$ 7.43–8.02 (19H, m, Ar) 6.25 (1H, br d, H-1′), 6.12 (1H, br dd, H-2′), 5.98 (1H, br dd, H-3′) 4.82 (1H, m, H-4′), 4.65–4.68 (1H, br dd, H-5′a), 4.56–4.59 (1H, dd, H-5′b, *J*=3.2, *J*=12.4 Hz); $^{19}$F-NMR (DMSO -*d*6) $\delta$ (−63.62, −61.53, 2 $\underline{C}F_3$); $^{13}$C-NMR (DMSO–*d*6) $\delta$ 164.56, 164. 67, 165.44, 155.76, 137.52, 133.86 (C3), 130.04 ($\underline{C}F_3$), 133.46, 114.35, 84.69, 78.67, 72.96, 70.78, 63.24; Anal. Clacd for $C_{37}H_{26}F_6N_4O8$ (768.63): C, 57.82; H, 3.41; N, 7.29; Found C, 57.96; H, 3.49; N, 7.21.

**2-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl](*Z*)-4-(2-(*p*-tolyl)hydrazono)-3-(trifluoro-methyl)-1H-pyrazol-5(4H)-one (21)**. Compound **21** was synthesized by coupling of **7** with **17** according to the general procedure (B). Yield (1.98 g, 75%) as yellow semi-solid; UV-vis (MeOH) $\lambda_{max}$ 255, 430 nm; $^1$H-NMR (DMSO-*d*6) $\delta$ 7.29–8.02 (19H, m, Ar), 6.24 (1H, br d, H-1′), 6.12 (1H, br dd, H-2′), 5.987 (1H, br dd, H-3′), 4.82 (1H, m, H-4′), 4.66 (1H, br dd, H-5′$_a$), 4.57 (1H, br dd, H-5′$_b$), 2.32 (3H, s, $\underline{C}H_3$), $^{13}$C-NMR (DMSO–*d*6) $\delta$ 165.25, 165.36,166.45, 155.76, 138.96, 139.35 (q, C3), 133.44 (q, $CF_3$), 133.44, 105.48, 84.64, 78.62, 72.94,70.78, 63.23; $^{19}$F-NMR (DMSO-*d*6) $\delta$ −64.30; Anal. Clacd for $C_{37}H_{29}F_3N_4O_8$ (714.65): C, 62.18; H, 4.09; N, 7.84; found C, 62.37; H, 4.23; N, 7.72.

**General procedure (C) for deprotection of the nucleosides 18–21 and 23–26.** NaOMe (1 *M* solution, 2.5 mL) was added dropwise to a solution of the protected nucleoside (1.28 mmol) in dry MeOH (20 mL) at 0 °C, under argon atmosphere. The reaction mixture was stirred at room temperature for 3–4 hrs, then neutralized with AcOH. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (eluate: 1%–10% MeOH/dichloromethane) to give **8–11**.

**2-[(β-D-ribofuranosyl)](Z)-4-(2-(3-nitrophenyl)hydrazono)-5-(trifluoromethyl)-2,4-dihydro-3H-pyrazol-3-one (8).** Compound **8** was synthesized from **18** according to the general procedure C. Yellow semi-solid (0.5 g, 90%): UV-vis (MeOH) $\lambda_{max}$ 230, 390 nm; $^1$H-NMR (DMSO-*d*6) $\delta$ 7.72–8.49 (4H, m, Ar), 5.63 (1H, d, H-1′, *J*=4.4 Hz), 5.36 (1H, s, OH), 5.13 (IH, s, OH), 4.76 (1H, s, OH), 4.36 (1H, br dd, H-2′), 4.07 (1H, br dd, H-3′), 3.83 (1H, m, H-4′), 3.52 (1H, dd, H-5′$_a$ *J*=4.4, *J*=8 Hz), 3.41 (1H, dd, H-5b′, *J*=5.6, J=11.6 Hz); $^{19}$F-NMR (DMSO-*d*6) $\delta$ −63.30; $^{13}$C-NMR (DMSO-*d*6) $\delta$ 171.98, 149 (q, C3), 148.53, 123.41(q, $CF_3$), 112.21, 120.59, 128.54, 130.96, 86.11, 84.76, 71.93,70.45, 62.06; $^{19}$F-NMR (DMSO-*d*6) $\delta$ −63.30; Anal. Clacd for $C_{15}H_{14}F_3N_5O_7$ (433.30): C, 41.58; H, 3.26; N, 16.16; found C, 41.36; H, 3.28; N, 16.08.

**2-[(β-D-ribofuranosyl)](Z)-4-(2-(2-nitrophenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (9)**. Compound **9** was synthesized from **19** according to the general procedure B. Yellow semi-solid (0.5 g, 90%). UV-vis (MeOH) $\lambda_{max}$ 230, 395 nm; $^1$H-NMR (DMSO-*d*6) $\delta$ 7.713–8.48 (4H, m, Ar), 5.63 (1H, d, H-1′, *J*=4.4 Hz), 5.36 (1H, s, OH exchangeable with $D_2O$), 5.13 (1H, s, OH exchangeable with $D_2O$), 4.77 (1H, s, OH exchangeable with $D_2O$), 4.35–4.37 (1H, br dd, H-2′), 4.07 (1H, br dd, H-3′), 3.83 (1H, m, H-4′), 3.52 (1H, dd, H-5′a, *J*=4.8, *J*=8.0 Hz), 3.43 (1H, dd, H-5′$_b$, *J*=5.6, *J*=11.6 Hz); $^{19}$F-NMR (DMSO-*d*6) $\delta$ 63.30; $^{13}$C-NMR (MHz DMSO-*d*6) $\delta$ 172.03, 148.56, 132.87 (q, C3), 130.95 (q, $CF_3$), 112.21, 120.59, 128.54, 130.96, 86.16, 84.76, 72.03,70.50, 62.12, 45.1. Anal. Clacd for $C_{15}H_{14}F_3N_5O_7$ (433.30): C, 41.58; H, 3.26; N, 16.16; found C, 41.36; H, 3.28; N, 16.08.

**2-[(β-D-Ribofuranosyl](Z)-5-(trifluoromethyl)-4-(2-(2-(trifluoromethyl)phenyl)hydrazine-eylidene)-2,4-dihydro-3H-pyrazol-3-one (10)**. Compound **10** was synthesized according to the general procedure (C) as described above to give (0.8 gm 89%) as pale yellow foam: UV-vis (MeOH) $\lambda_{max}$ 250, 400 nm; $^1$H-NMR (DMSO-*d*6) $\delta$ 7.61–8.02 (4H, m, Ar), 5.63 (1H, br d, H-1′), 5.38 (IH, s, OH), 5.15 (1H, s, OH), 4.75 (1H, s, OH), 4.37 (1H, br dd, H-2′), 4.08 (1H, br dd, H-3′), 3.86 (1H, m, H-4′), 3.52 (1H, dd, H-5′a, *J*=4.4, *J*=11.6 Hz), 3.42 (1H, dd, H-5′$_a$, *J*=5.6, *J*=11.6 Hz); $^{19}$F (DMSO-*d*6) $\delta$ −63.52, −61.60; $^{13}$C-NMR (DMSO–$d_6$) $\delta$ 166.97, 156.27 (q, C3), 142.47, 134.04 (q, $CF_3$), 114.16, 118.19, 120.84, 125.13, 128.66, 130.94, 86.11, 84.85,71.99, 70.43, 62.02; Anal. Clacd for $C_{16}H_{14}F_6N_4O_5$ (456.30): C, 42.12; H, 3.09; N, 12.28; found C, 41.91; H, 3.24; N, 12.13.

**2-[β-D-Ribofuranosyl](*Z*)-4-(2-(*p*-tolyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (11)**. Compound **11** was synthesized according to general procedure (C). Yield (0.9 g, 90%) as yellow semi-solid. UV-vis (MeOH) $\lambda_{max}$ 255, 430 nm; $^1$H-NMR (DMSO-*d*6) $\delta$ 7.28–7.55 (4H, m, Ar), 5.61 (1H, d, H-1′, *J*=5.2 Hz), 5.34 (1H, d, 2′ OH, *J*=6 Hz), 5.11 (1H, d, 3′ OH, *J*=4.8 Hz), 4.74 (1H, br t, 5′-OH′), 4.35 (1H, br dd, H-2′) 4.048–4.082 (1H, br dd, H-3′) 3.83 (1H, m, H-4′), 3.37–3.55 (2H, br dd, H-5′$_a$, H-5′$_b$), 2.32 (3H, s, $CH_3$); $^{19}$F-NMR (DMSO-*d*6) $\delta$ −63.21; $^{13}$C-NMR (DMSO–*d*6) $\delta$ 156.72, 136.96, 121.65, 117.74–130.1, 86.04, 84.77, 71.97, 70.44, 62, 20; Anal. Clacd for $C_{16}H_{17}F_3N_4O_5$ (402.33): C, 47.77; H, 4.39; N, 13.93; found C, 47.56; H, 4.26; N, 13.85.

**1,2,3-Tri-*O*-acetyl-5′-deoxy-β-D-ribofuranose (22).** Compound **22** was prepared from D-(+) ribose according reference (**17**) with minor modification. $^1$H-NMR ($CDCl_3$) $\delta$ 6.1 (1H, d, J=1.2 Hz), 5.32 (1H, dd, H-2, J=1.2, J=4.8 Hz), 5.08 (1H, dd, H3, J=4.8, J=11.6 Hz), 4.26 (1H, m, H-4); $^{13}$C-NMR ($CDCl_3$) $\delta$ 170.01, 169.58, 169.43, 98.43, 78.13, 75.10, 74.79, 21.18, 20.63, 19.84, 1.09.

**2-[(5-deoxy-2,3,-Di-*O*-acetyl-β-D-ribofuranosyl](*Z*)-4-(2-(3-nitrophenyl)hydrazono)-5-(trifluoromethyl)-2,4-dihydro-3H-pyrazol-3-one (23)**. Compound **23** was prepared by coupling of **4** with **22** according to general procedure (B). Yield (1.3 g, 78%) as a yellow foam: UV-vis (MeOH) $\lambda_{max}$ 230, 390 nm; $^1$H-NMR ($CDCl_3$) $\delta$ 13.55 (1H, s, NH); 7.62–8.28 (4H, m, Ar), 5.94 (1H, d, H-1′, *J*=4.0 Hz), 5.72 (1H, br dd, H-2′), 5.23 (1H, br dd, H-3′), 4.26 (1H, m, H-4′), 2.12 (6H, s, Ac), 1.42 (3H, d, 5′$CH_3$, *J*=6.4 Hz); $^{19}$F ($CDCl_3$) $\delta$ −64.57; $^{13}$C-NMR ($CDCl_3$) $\delta$ [169.90, 169.73 (2Ac)], 157.90 (C=O), 149.45 (C-3), 141.61 (C-4), 137.54 (q, $CF_3$), 111.71–131.07 (Ar), 85.24, 78.36, 74.93, 73.09, 20.65, 20.74, 18.85; Anal. Clacd for $C_{19}H_{18}F_3N_5O_8$ (501.38): C, 45.52; H, 3.62; N, 13.97; found C, 45.59; H, 3.72; N, 13.81.

**2-[(5-deoxy-2,3,-Di-*O*-acetyl-β-D-ribofuranosyl](Z)-4-[(2-nitrophenyl)hydrazono)]-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (24)**. Compound **24** was prepared by coupling of **5** with **22** according to general procedure (B). Yield (1.2 g, 72%). as a yellow foam. UV-vis (MeOH) $\lambda_{max}$ 230, 295 nm; $^1$H-NMR ($CDCl_3$) $\delta$ 13.61 (1H, s NH) 7.63–8.28 (4H,

m, Ar), 5.94 (1H, br d, H-1′), 5.72 (1H, br dd, H-2′) , 5.24 (1H, br dd, H-3′), 4.27 (1H, m, H-4′), 2.12 (6H, s, 2Ac), 1.42 (3H, d, 5′-$CH_3$, $J$=6.4 Hz);[19]F-NMR ($CDCl_3$) $\delta$ −64.57; [13]C-NMR ($CDCl_3$) $\delta$ 169.89, 169.72 2Ac, 157.91, 149.46, 141.61, 137.54 (q, $CF_3$), 111.71–131.08 (Ar), 85.25, 78.37, 74.93, 73.09, 20.65, 20.74, 18.86; Anal. Clacd for $C_{19}H_{18}F_3N_5O_8$ (501.38): C, 45.52; H, 3.62; N, 13.97; found C, 45.61; H, 3.59; N, 13.86.

**2-[(5-deoxy-2,3,-Di-*O*-acetyl-β-D-ribofuranosyl](Z)-5-(trifluoromethyl)-4-(2-(2-(trifluoro-methyl)phenyl)hydrazono)-2,4-dihydro-3H-pyrazol-3-one (25)**. Compound **25** was prepared by coupling of **6** with **22** according to general procedure (B). Yield (1.45 g, 92%) as a yellow foam; UV-vis (MeOH) $\lambda_{max}$ 230, 400 nm; [1]H-NMR (DMSO-*d6*) $\delta$ 7.63–8.04 (4H, m, Ar), 5.82 (1H, br d, H-1′), 5.63 (1H, br dd, H-2′), 5.14 (1H, br dd, H-3′), 4.20 (1H, m, H-4′), 2.08 (6H, s, 2Ac), 1.30 (3H, d, 5′-$CH_3$, $J$=6 Hz); [19]F-NMR (DMSO-*d6*) $\delta$ −63.62, −61.53, 2$\underline{C}F_3$; [13]C-NMR (DMSO-*d6*) $\delta$169.9, 169.71, 157.99, 149.47, 140.93, 137.54 (q, $CF_3$), 113.66–130.73 (Ar), 85.21, 78.33, 74.96, 73.11, 20.75, 20.65, 18.87; Anal. Clacd for $C_{20}H_{18}F_6N_4O_6$ (524.38): C, 45.81; H, 3.46; N, 10.68; found C, 45.94; H, 3.36; N, 10.53

**2-[(5-deoxy-2,3,-Di-*O*-acetyl-β-D-ribofuranosyl](Z)-4-(*p*-tolylhydrazono)-3-(trifluoro-meth-yl)-1H-pyrazol-5(4H)-one (26)**. Compound **26** was prepared by coupling of **7** with **22** according to general procedure (B). Yield (1.26 g, 73%) a yellow foam; (MeOH) $\lambda_{max}$ 230, 430 nm; [1]H-NMR (DMSO-*d6*) $\delta$ 13.71 (1H, s, NH), 7.28–7.41 (4H, m, Ar), 5.97 (1H, d, H-1′), 5.77 (1H, br dd, H-2′), 5.30 (1H, br dd, H-3′), 4.24–4.30 (1H, m, H-4′), 2.41 (3H, s, $CH_3$), 2.13 (6H, s, 2Ac), 1.44 (3H, d, 5′-$CH_3$, $J$=6 Hz); $^{-19}$F-NMR (DMSO-*d6*) $\delta$ −64.41; [13]C-NMR ($CDCl_3$) $\delta$ 158.28, 154.1, 149.11, 142.83, 139.54 (q, $CF_3$), 116.97–138.13 (6C-Ar), 86.77, 79.64, 75.64, 74.90, 22.83, 21.71, 21.29, 18.89; Anal. Clacd for $C_{20}H_{21}F_3N_4O_6$ (470.41): C, 51.07; H, 4.50; N, 11.91; found C, 51.21; H, 4.35; N, 11.79.

**2-[(5-deoxy-β-D-ribofuranosyl](*Z*)-4-(2-(3-nitrophenyl)hydrazono)-5-(trifluor-omethyl)-2,4-dihydro-3H-pyrazol-3-one (12)**. Compound **12** was prepared by deprotection of compound **23** according to general procedure (C). Yield (0.6 g 73%) as a yellow foam; UV-vis (MeOH) $\lambda_{max}$ 230, 390 nm; [1]H-NMR (DMSO-*d6*) $\delta$ 7.73–8.51 (4H, m, Ar), 5.61 (1H, br d, H-1′), 5.36 (1H, s, OH exchangeable with $D_2O$), 5.11 (1H, s, O$\underline{H}$ exchangeable with $D_2O$), 4.33 (1H, br dd, H-2′), 3.94 (1H, br dd, H-3′), 3.877 (1$\underline{H}$, m, H-4′), 1.20 (3H, d, 5′-C$\underline{H}_3$, $J$=6.4 Hz); [19]F (DMSO-*d6*) $\delta$ −63.42; [13]C-NMR (DMSO–*d6*) $\delta$ 148.56, 130.6$\underline{1}$, 137.05, 120.14 (q, $\underline{C}F_3$), 112.11–131.06 (6C, Ar), 86.47, 74.94, 72.45, 67.47, 19.08; Anal. Clacd for $C_{15}H_{14}F_3N_5O_6$ (417.30): C, 43.17; H, 3.38; N, 16.78; found C, 43.08; H, 3.59; N, 16.61.

**2-[(5-deoxy-β-D-ribofuranosyl](Z)-4-[(2-nitrophenylhydrazono)]-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (13)**. Compound **13** was prepared by deprotection of compound **24** according to general procedure (C). Yield (0.65 gm, 79%) as a yellow semi-solid; UV-vis (MeOH) $\lambda_{max}$ 230, 395 nm; [1]H-NMR (DMSO-*d6*) $\delta$ 7.730–8.514 (4H, m, Ar). 5.61 (1H, br d, H-1′), 5.363 (IH, s, OH), 5.11 (1H, s, OH), 4.94 (1H, br dd, H-2′), 3.33 (1H, br dd, H-3′), 3.94 (1H, m, H-4′), 1.21 (3H, d, 5′-$CH_3$, $J$=6 Hz); [19]F-NMR (DMSO-*d6*) $\delta$ −63.41; [13]C-NMR (′DMSO–*d6*) $\delta$ 149.06, 137 72 (q-C5), 130.43, 125.06, 123.43, 122.94, 121.01 (q, $\underline{C}F_3$), 112.13, 86.46, 76.97, 74.96, 72.47, 19.10; Anal. Clacd for $C_{15}H_{14}F_3N_5O_6$ (417.30): C, 43.17; H, 3.38; N, 16.78; found C, 43.16; H, 3.49; N, 16.63.

**2-[(5-deoxy-β-D-ribofuranosyl](Z)-5-(trifluoromethyl)-4-(2-(2-(trifluoromethyl)-phenyl)-hydrazono)-2,4-dihydro-3H-pyrazol-3-one (14)**. Compound **14** was prepared by deprotection of compound **25** according to general procedure (C). Yield (0.75 g, 90%) a yellow semi-solid; °C; UV-vis (MeOH) $\lambda_{max}$ 250, 400 nm; [1]H-NMR (DMSO-*d6*) $\delta$ 7.64–8.05 (4H, m, Ar), 5.61 (1H, br d, H-1′), 5.40 (1H, s, OH

exchangeable with $D_2O$), 5.142 (1H, s, OH exchangeable with $D_2O$), 4.34 (1H, br dd, H-2′), 3.94 (1H, br dd, H-3′), 3.871 (1H, m, H-4′), 1.21 (3H, d, 5′-$CH_3$, $J$=6 Hz);[19]F-NMR $\delta$ −63.50, 61.51; [13]C-NMR (DMSO–*d*6) $\delta$ 156.01, 130.61, 137.05, 125.08 (q, $CF_3$), 120.72 (q, $CF_3$), 114.05–131.96 (6C, Ar), 86.45, 79.20, 74.88, 72.39, 19.05; Anal. Clacd for $C_{16}H_{14}F_6N_4O_4$ (440.30): C, 43.65; H, 3.21; N, 12.72; found C, 43.69; H, 3.16; N, 12.59.

**2-[(5-deoxy-β-D-ribofuranosyl](Z)-4-(*p*-tolylhydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (15)**. Compound **15** was prepared by deprotection of compound **26** according to general procedure (C). Yield (0.75 g, 90%) as a yellow semi-solid; UV-vis (MeOH) $\lambda_{max}$ 230 nm, 430 nm; [1]H-NMR (DMSO-*d*6) $\delta$ 7.26–7.54 (4H, m, Ar), 5.37 (1H, s, OH), 5.12 (IH, s, OH), 4.34 (1H, br dd, H-2′), 3.93 (1H, br dd, H-3′), 3.87 (1H, m, H-4′), 2.31 (3H, s, $CH_3$), 1.20 (3H, d, 5′-$CH_3$, $J$=6.4 Hz), $^{-19}$F-NMR (DMSO-*d*6) −63.31; [13]C-NMR (DMSO–*d*6) $\delta$ 141.64, 138.61, 137.05, 130.00 (q, C3), 76.93 (q, $CF_3$), 116.77, 117.21, 118.27, 120.96, 122.10, 123.64, 86.44, 74.85, 74.85, 74.85, 74.95, 72.47, 20.60, 19.06; Anal. Clacd for $C_{16}H_{17}F_3N_4O_4$ (386.33): C, 49.74; H, 4.44; N, 14.50; found C, 49.64; H, 4.53; N, 14.29.

## References


[1] Shepard, D. S.; Undurraga, E. A.; Halasa, Y. A.; Stanaway, J. D. The Global Economic Burden of Dengue: A Systematic Analysis. *Lancet. Infect. Dis.* **2016**, *16*, 935–941. DOI: 10.1016/S1473-3099(16)00146-8.

[2] Bhatt, S.; Gething, P. W.; Brady, O. J.; Messina, J. P.; Farlow, A. W.; Moyes, C. L.; Drake, J. M.; Brownstein, J. S.; Hoen, A. G.; Sankoh, O.; et al. The Global Distribution and Burden of Dengue. *Nature* **2013**, *496*, 504–507. DOI: 10.1038/nature12060.

[3] Fibriansah, G.; Lok, S. M. The Development of Therapeutic Antibodies against Dengue Virus. *Antiviral Res.* **2016**, *128*, 7–19. DOI: 10.1016/j.antiviral.2016.01.002.

[4] Assiri, A.; McGeer, A.; Perl, T. M.; Price, C. S.; Al Rabeeah, A. A.; Cummings, D. A.; Alabdullatif, Z. N.; Assad, M.; Almulhim, A.; Makhdoom, H.; et al. Hospital Outbreak of Middle East Respiratory Syndrome Coronavirus. *N Engl. J. Med.* **2013**, *369*, 407–416. DOI: 10.1056/NEJMoa1306742.

[5] Zaki, A. M.; van Boheemen, S.; Bestebroer, T. M.; Osterhaus, A. D.; Fouchier, R. A. Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia. *N. Engl. J. Med.* **2012**, *367*, 1814–1820. DOI: 10.1056/NEJMoa1211721.

[6] WHO. Middle East Respiratory Syndrome Coronavirus (MERS-CoV). http://www.who.int/mediacentre/factsheets/mers-cov/en/

[7] Arnost, M.; Pierce, A.; Ter Haar, E.; Lauffer, D.; Madden, J.; Tanner, K.; Green, J.; Aryl, 4. (3-Aryl-4-(arylhydrazono)-1H-Pyrazol-5-Ones: Highly Ligand Efficient and Potent Inhibitors of GSK3beta. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1661–1664. DOI: 10.1016/j.bmcl.2010.01.072.

[8] Chung, D.-H.; Strouse, J. J.; Sun, Y.; Arterburn, J. B.; Parker, W. B.; Jonsson, C. B. Synthesis and anti- Hantaan Virus Activity of $N^1$-3-Fluorophenyl-Inosine. *Antiviral Res.* **2009**, *83*, 80–85. DOI: 10.1016/j.antiviral.2009.03.007.

[9] (a) Sidwell, R.W., Huffman, J.H., Khare, G.P., Allen, L.B., Withowski, J.T., Robins, R.K. Broad- spectrum antiviral activity of Virazole. 1-$\beta$-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. *Science* **1972**, *177*, 705–706. (b) Sidwell, R.W.; Robins, R.K. Ribavirin: An Antiviral Agent. *Pharmacol. Ther.* **1979**, *6*, 123–146. DOI: 10.1126/science.177.4050.705.

[10] (a) Mizuno, K.; Tsujino, M.; Takeda, M.; Hayashi, M.; Atsumi, K.; Asano, K.; Matsuda, T. Studies on Bredinin. I. Isolation, Characterization and Biological Properties. *J. Antibiot*. **1974**, *27*, 775–782. (b) Yoshioka, H.; Nakatsu, K.; Mizuno, K. Studies on Bredinin. II. Molecular Structure of Bredinin. *Tetrahedron Lett*. **1975**, *46*, 4031–4034.

[11] (a) Amemiya, H.; Itoh, H. *Immunosuppressive Drugs: Developments in Anti-Rejection Therapy*, eds. A.W. Thomson, T.E. Starzl, Edward Arnold Ltd.: London, **1993**; pp. 161–176. (b) Gruber, S.A. Locoregional Immunosuppression of Organ Transplants. *Immunol. Rev*. **1992**, *129*, 5–30. (c) Truka, L.; Dayton, J.; Sinclair, G.; Thompson, C.B.; Mitchell, B.S. Guanine Ribonucleotide Depletion Inhibits T-Cell Activation. Mechanism of Action of the Immunosuppressive Drug Mizoribine. *J. Clin. Invest*. **1991**, *87*(3), 940–948. DOI: 10.1172/JCI115101.

[12] Ichinose, K.; Origuchi, T.; Kawashiri, S.-Y.; Iwamoto, N.; Fujikawa, K.; Aramaki, T.; Kamachi, M.; Arima, K.; Tamai, M.; Nakamura, N.; et al. Efficacy and Safety of Mizoribine by One Single Dose Administration for Patients with Rheumatoid Arthritis. *Intern. Med*. **2010**, *49*, 2211–2218.

[13] Franchetti, P.; Cappellacci, L.; Grifantini, M. IMP Dehydrogenase as a Target of Antitumor and Antiviral Chemotherapy. *Farmaco* **1996**, *51*, 457–469.

[14] Aromi, G.; Bell, A. R.; Helliwell, M.; Raftery, J.; Teat, S. J. A Systematic Exploration of Nickel-Pyrazolinato Chemistry with Alkali Metals: New Cages from Serendipitous Assembly. *Chem. Eur. J*. **2003**, *9*, 3024–3032. DOI: 10.1002/chem.200304939.

[15] (a) Zohdi, H.F.; Rateb, N.M.; Haikal, A. *Molecules* **2001**, *6*, M261. (b) Abdou, I.M.; Saleh, A.M.; Zohdi, H.F. Synthesis and Antitumor Activity of 5-Trifluoromethyl-2,4-Dihydropyrazol-3-One Nucleosides. *Molecules* **2004**, *9*, 109–116. (c) Muralikrishna, S.; Jagadeeswararao, P.; Ravisankarareddy, P. Synthesis of 7-(Morpholinomethyl)-9-(Trifluoromethyl)-4-((4-(Trifluoromethyl)Phenyl)Amino)-1-Thia-4,7,8-Triazaspiro [4.4]Non-8-Ene-3,6-Dione. Heterocyclic Lett. **2017**, *7*(4), 1097–1105. (d) Nasser, S.; Khalil, A. M. A Facile Synthesis, Structure, and Antimicrobial Evaluation of Novel 4-Arylhydrazono-5-Trifluoromethyl-2,4-Dihydropyrazol-3-Ones, Their N- and N,O-Bis-β-D-Glucosides. *Carbohyd. Res*. **2009**, *344*, 1654–1659.

[16] (a) Dalya Al-Saad, M. G. M., and Paolo Quadrelli, Pericyclic Reactions for Anti-HPVAntivirals: Unconventional Nucleoside Analogue Synthesis via Nitrosocarbonyl Chemistry. *Chemistry Select* **2017**, *2*, 10340–10346. (b) Davoodnia, A.; Attar, P.; Morsali, A.; Eshghi, H.; Tavakoli-Hoseini, N.; Khadem, S. Experimental and Theoretical Studies on the Tautomerism in 2-Aminopyridines and 2(1H)-Pyridinones: Synthesis of 2-Amino-4-aryl-3-cyano-6-(3,4-dimethoxyphenyl)pyridines and 4-Aryl-3-cyano-6-(3,4-dimethoxyphenyl)-2(1H)-pyridinones. *Bull. Korean Chem. Soc*. **2011**, *32*(6), 1873–1878. DOI: 10.1002/chin.201143139.

[17] Bozhok Grigorii, T.; Sivets Alexander, S.; Baranovsky Elena, G.; Kalinichenko, V. N. Synthesis of Novel 6-Substituted Thymine Ribonucleosides and Their 3′-Fluorinated Analogues. *Tetrahedron* **2016**, *72*, 6518–6527. DOI: 10.1016/j.tet.2016.08.065.

[18] N.; Mekala, Murthy, V. R. K.; Moturu, Rao, V. L. N.; Dammalapati, Atchuta, R. Parimi, Safe and Alternate Process for the Reductions of Methanesulfonates: Application in the Synthesis of 1,2,3-Triacetyl-5- deoxy-D-Ribofuranoside. *Org. Process Res. Dev*. **2016**, *20*, 609−614. DOI: 10.1021/acs.oprd.5b00286.

[19] *Spartan 16*; Wavefunction, Inc.: Irvine, CA; **2016**.

[20] Lewers, E. G. *Computational Chemistry*. Springer Nature: Peterborough, **2016**; p. 253–8.