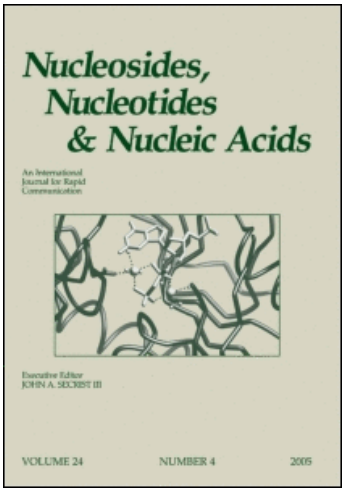

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Efficient Pyrimidine N-1-Alkylation via Activation of Electron Rich Olefins with Oxoammonium Salts: Synthesis of Methoxy TEMPO Substituted Pyrimidine Nucleoside Analogs

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Efficient Pyrimidine N-1-Alkylation via Activation of Electron Rich Olefins with Oxoammonium Salts: Synthesis of Methoxy TEMPO Substituted Pyrimidine Nucleoside Analogs

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ABSTRACT

Our work outlines the use of oxoammonium salts in a formal 1,2 addition process to olefins giving nucleoside analogs as products. Specifically, oxoammonium salts can be added to a solution of olefin and silylated heterocycle to give Methoxy TEMPO substituted nucleoside analogs after hydrolytic workup and chromatographic purification.

Key Words: Synthesis; Oxoammonium salts; 2′-substituted nucleoside analogs.

INTRODUCTION

Over the years a number of synthetic methodologies have evolved to bring about N-glycosylation reactions yielding nucleoside products.[1] Carbon–Nitrogen bond formation is typically effected via the Vorbruggen method which utilizes silylated heterocycles and protected sugar acetates catalyzed by Lewis acids.[2,3] An under-utilized

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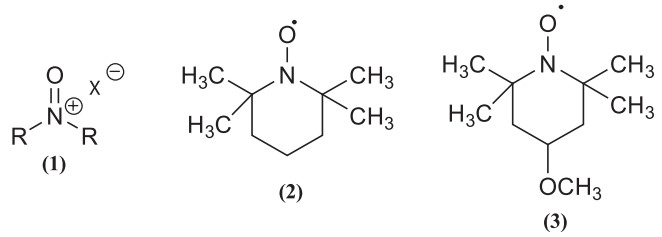
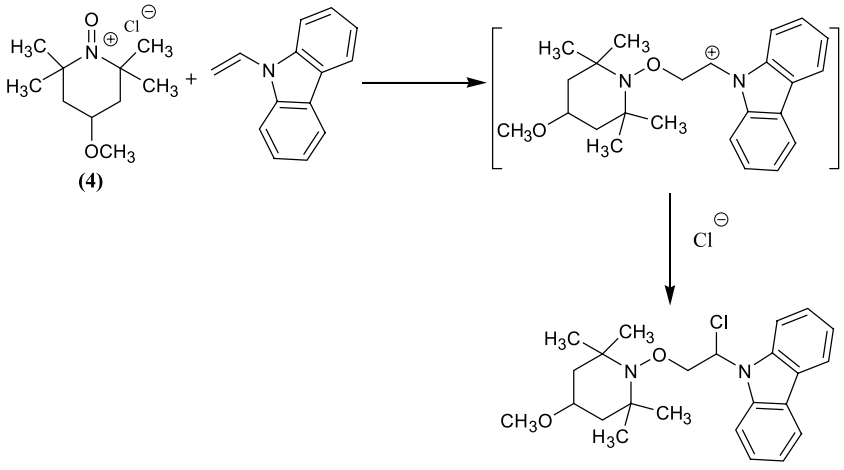


Figure 1. Typical aminoxyl radicals.

strategy involves the addition of an electrophile to a protected fural and subsequent trapping of the intermediate with heterocycle. Lewis acids such as $SnCl_4$ are known to activate furals towards condensations.[4] If the electrophile gives rise to a bridged intermediate then nucleophilic attack must occur in a stereoselective fashion to give *trans* nucleoside products. Treatment of a protected fural with phenylsulfenyl chloride leads to a *trans* β-chloro sulfide which is isolated and then condensed with a heterocycle to give nucleoside products.[5] The same process works equally well with phenylselenenyl chloride to give selenium substituted nucleosides.[6,7] In both processes the intermediate β-chloro sulfide (or selenide) intermediates are isolated and then utilized in the N-glycosylation step. We have shown that adenosine analogs can be isolated by trapping the cyclic intermediate directly in a one pot reaction.[8] Both pyrimidine and purine nucleoside analogs can be formed in a one pot reaction using chlorothiocyanate as the electrophile.[9] The advantages of the electrophilic addition process include high yields, good stereo- and regiochemical control, and the generation of nucleoside analogs substituted at the 2′ position of the sugar.

We wish to communicate the utility of a new procedure utilizing oxoammonium salts as the electrophilic activation reagent. Oxoammonium salts (**1**) have the general



Scheme 1. Addition of oxoammonium salts to electron rich alkenes.

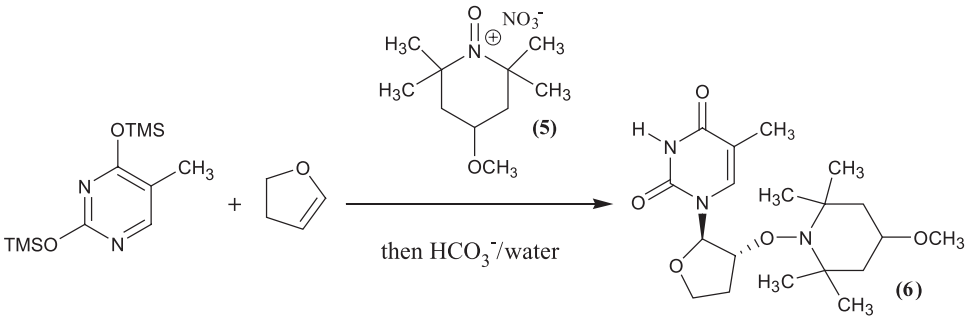
structure shown in Fig. 1. These compounds are generally synthesized by the one electron oxidation of stable aminoxyl radicals such as TEMPO (**2**) and Methoxy TEMPO (**3**).[10]

Oxoammonium salts are very useful in the controlled oxidations of primary alcohols to aldehydes.[11,12] One may also think of (**1**) as an electrophilic form of oxygen. It has been recently shown that these salts react with electron rich olefins to give 1,2 addition products.[13] Specifically, the chloride salt (**4**) is added to a solution of electron rich alkene at low temperatures to give addition products as shown in Scheme 1. A resonance-stabilized carbocation was postulated as an intermediate in this process, which is then trapped by the available chloride nucleophile.

The authors could not rule out however the intermediacy of a cyclic ion intermediate. We felt that it should be possible to trap this electrophilic intermediate with a silylated heterocycle, which would result in the formation of a structurally diverse nucleoside analog. Attempts to do so have been fruitful.

RESULTS AND DISCUSSION

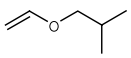
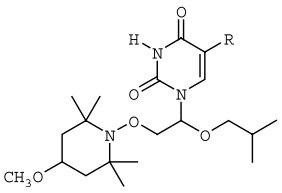
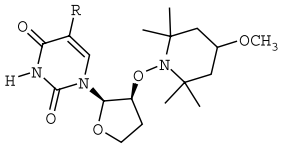
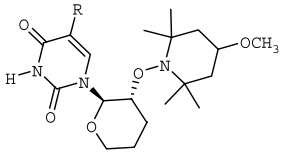
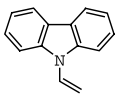
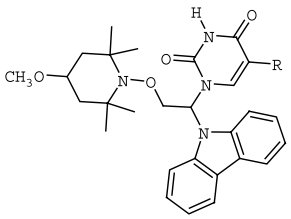
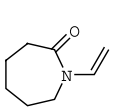
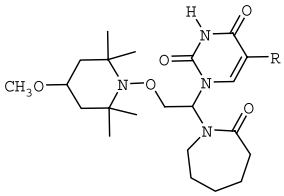
In our hands (**4**) seemed too unstable for general use. The nitrate salt (**5**) shown in Scheme 2 is easily prepared by treatment of (**3**) with concentrated HNO_3 in ether solution giving the yellow salt.[10] The nitrate (**5**) is stable for several months if kept at $-20°C$. As shown in Scheme 2, (**5**) is added slowly to a solution of silylated thymine and 2 equivalents of 2,3-dihydrofuran at room temperature. A new nucleoside analog (**6**) is formed and isolated in 93% yield after hydrolytic workup and flash chromatography. The position of attachment of the heterocycle to the furan at N-1 is indicated by the presence of a free imide proton (N-3) in the ^1H NMR spectrum at δ 10 ppm. Attachment of the heterocycle at C-1 of the furan ring as well as N-1 glycosylation is consistent with the presence of a doublet in the ^1H-NMR spectrum at δ 6.27 ppm. Typically N-3 glycosylated pyrimidines show a characteristic downfield shift at the C-1 proton of up to 1 ppm due to the deshielding effects of two carbonyl groups.[14] The assigned relative stereochemistry of (**6**) is based on room temperature 2D NOESY experiments and coupling constant information compiled in Table 3. All



Scheme 2. Addition of silylated thymine and (5) to 2,3-dihydrofuran.

stereochemical assignments are relative unless indicated otherwise. Several other electron rich olefins proved successful in the process as outlined in Table 1. Typically vinyl ethers and vinyl amines work well in this process giving new thymine and 5-fluorouracil nucleoside analogs. Less electron rich alkenes such as 4-methoxystyrene were unreactive.

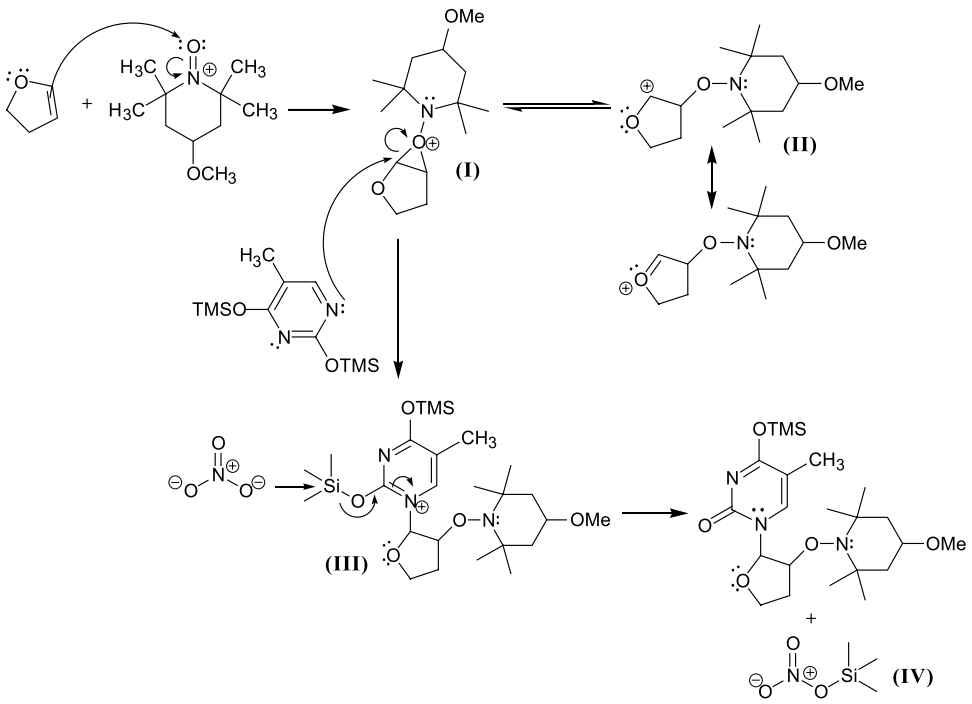
Table 1. Synthesis of methoxy-TEMPO substituted thymine and 5-fluorouracil nucleoside analogs.

Alkene[a]	Major product[b]	Yield [c]
		R = F 62% (12) R = CH_3 43% (7)
		R = F 76% (11) R = CH_3 93% (6)
		R = F 41% (13) R = CH_3 59% (8)
		R = F 32% (14) d R = CH_3 65% (9)
		R = CH_3 78% (10) e

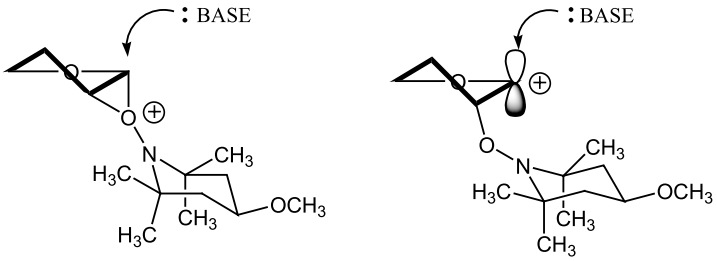
a. All reactions were performed with 2 eq. of alkene and 1.1 eq. of Oxoammonium salt.
b. Major isomer formed, some alkenes gave trace amts. of other stereoisomer. c. All compounds have been characterized by 1H and 13C NMR, IR, UV and Q-TOF electrospray MS.
d. Trace of regioisomer formed. e. 5.5: 1 regioisomer ratio.

In a few cases (6, 8, 11, 13) smaller amounts of stereoisomeric compounds were formed. Given these observations we have proposed the following mechanistic analysis shown in Scheme 3.

Electrophilic addition to the active double bond of dihydrofuran could give either a cyclic oxonium ion (**I**) or a resonance-stabilized carbocation (**II**). These two intermediates could be in equilibrium with each other in which case temperature could be a useful controlling factor. In either case the silylated base could then attack the intermediate giving the charged intermediate (**III**) which is rapidly desilylated via nitrate anion. Trimethylsilyl nitrate (**IV**) has been identified in the process by GC-MS analysis of the reaction before aqueous workup. The silylated intermediate would then give final product upon hydrolytic workup. In most of these reactions minor side products were also isolated resulting from attack of nitrate anion on the cationic intermediate. The reactions we have done to this point appear to be non-stereospecific thus generating both *cis* and *trans* addition products. This result can be rationalized by proposing attack on the carbocation intermediate rather than the cyclic ion as shown in Scheme 4. Nucleophilic attack on the cyclic ion should occur on the least hindered face, giving only *trans* product, whereas attack on the flat carbocation should give both *cis* and *trans* product but would still exhibit some crowding on one face due to the bulky TEMPO substituent. The new methoxy TEMPO substituted compounds are quite stable. The C–O bond in these types of systems can undergo thermolysis to give carbon centered radicals.[15] No degradation was detected when these compounds are



Scheme 3. Proposed mechanism of electrophilic addition to electron rich alkenes.



Scheme 4. The stereochemistry of nucleophile attack on carbocation or cyclic ion intermediate.

subjected to 90°C temperatures in DMF solution containing known radical scavengers such as t-butylmercaptan and oxygen.

Table 2 shows the utility of this process with the formation of N-4-benzoylcytosine analogs (**15–18**). Yields are generally lower in this series possibly due to decreased nucleophilicity of the silylated N-4-benzoyl cytosine.[16]

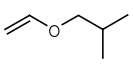
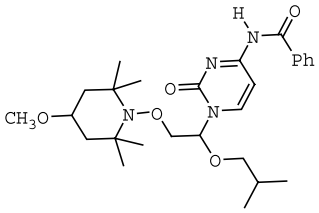
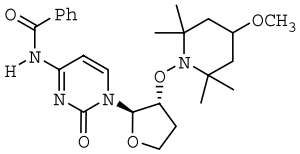
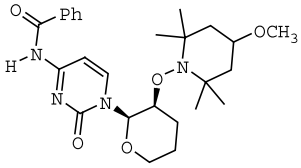
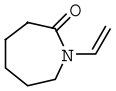
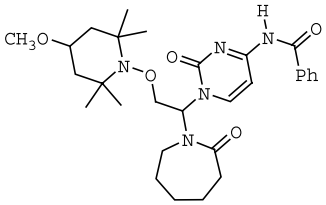
The relative stereochemistries of compounds (**6**), (**8**), (**11**), (**13**), (**16**), (**17**), (**21**) and (**22**) were determined by 2D NOESY experiments the results of which are shown in Table 3. NOESY experiments are challenging to perform on nucleoside analogs because of the conformational flexibility of the sugar ring.[17] These experiments are typically run at lower temperatures to observe NOE contacts. Our NOE contacts were observed at room temperature with a mixing time of 300 milliseconds. We believe our success at observing NOE crosspeaks in these systems is due to the conformational rigidity imparted to the THF, DHP or ribofuranosyl ring by the bulky methoxy TEMPO group.

The *cis* relative stereochemistry of DHP analogs (**8**), (**13**) and (**17**) is in good agreement with several literature results showing large (8 to 9 Hz) anomeric coupling constants for the *trans* isomers of 2′-substituted DHP analogs.[18–20] In our case the small 1.8 Hz coupling would indicate *cis* stereochemistry. Using coupling constants to determine relative stereochemistry in our THF (**6**, **11**, **16**) and ribofuranosyl (**21**, **22**) compounds is however more problematic. Our compounds assigned the *trans* stereochemistry show anomeric coupling constants in the range 6.2 to 7.2 Hz. This result is in contrast to reports on similar systems with *trans* couplings of 1.2 to 1.7 Hz.[21,22] Molecular mechanics modeling of our compounds suggests that larger *trans* couplings are possible when the five membered ring is in the S or C2′-*endo* conformation as opposed to the C3′*endo* conformation.[a] Recently 2′-substituted ribosyl based nucleosides have shown promise in anti-sense oligonucleotide therapy.[23,24] We began our attempts to synthesize 2′-methoxyTEMPO substituted nucleosides with the known trimethylsilyl protected fural (**19**) as shown in Scheme 5.[25]

Addition of (**5**) to a solution of (**19**) and silylated base gave a mixture of mono- and di-silylated nucleoside products, (**20a**) and (**20b**), after hydrolytic workup. Complete deprotection of this mixture was effected with 1 M tetrabutylammonium flouride in THF to give the 2′-methoxy TEMPO substituted analogs (**21**) and (**22**) in

[a]Molecular mechanics modeling was performed using Alchemy III software. Energy minimized structures for (6) and (21) in the S conformation gave a H1′-H2′ dihedral angle of 177 and 177 degrees, respectively, corresponding to coupling constants of 8 to 9 Hz.

Table 2. Synthesis of methoxy-TEMPO substituted n-4-benzoyl cytosine nucleoside analogs.

Alkene[a]	Major product[b]	Yield [c]
		53% (15)
		47% (16)
		38% (17)
		71% (18)[d]

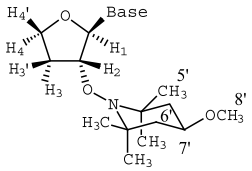
a. Reactions were performed with 2 eq. of alkene and 1.1 eq. of oxoaammonium salt. b. Major isomer formed, some alkenes gave trace amts. of other stereoisomer. c. All compounds have been characterized by 1H and 13 C NMR, IR, UV and Q-TOF electrospray MS. d. Trace of regioisomer formed.

37% and 32% respective yields. These yields may be lower than the other analogs since the alkene is more sterically congested and thus less reactive. Two dimensional COSY and NOESY experiments were used to completely assign structure and stereochemistry in (**21**) and (**22**). Proton NMR couplings can be used to determine the conformational preferences of the sugar ring in modified nucleosides.[26] As shown in Fig. 2 the sugar generally exists in the two twist conformations N and S with the N conformer predominate in RNA and the S in DNA. Proton coupling constants between C1 and C2 of the ribose ring can be used to calculate the equilibrium % S in solution.[27]

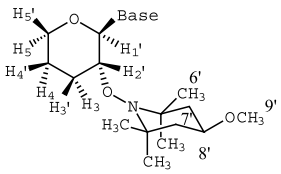
Our compounds, (**21**) and (**22**), exist predominately in the S conformer. We would suggest that the bulky methoxy TEMPO substituent is accommodated better at the pseudo-equatorial position of the S conformer than the pseudo-axial position in the N conformer.

Table 3. Stereochemical assignments based on NOESY experiments and coupling constants.

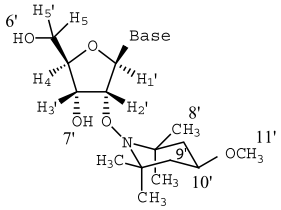
Numbering system for THF, DHP and ribosyl analogs



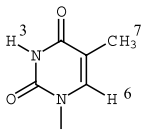
Tetrahydrofuranyl analogs



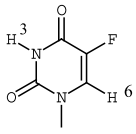
Dihydropyranyl analogs



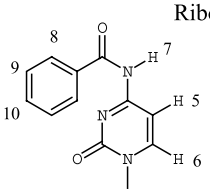
Ribosyl analogs



Thymine



5-Fluorouracil

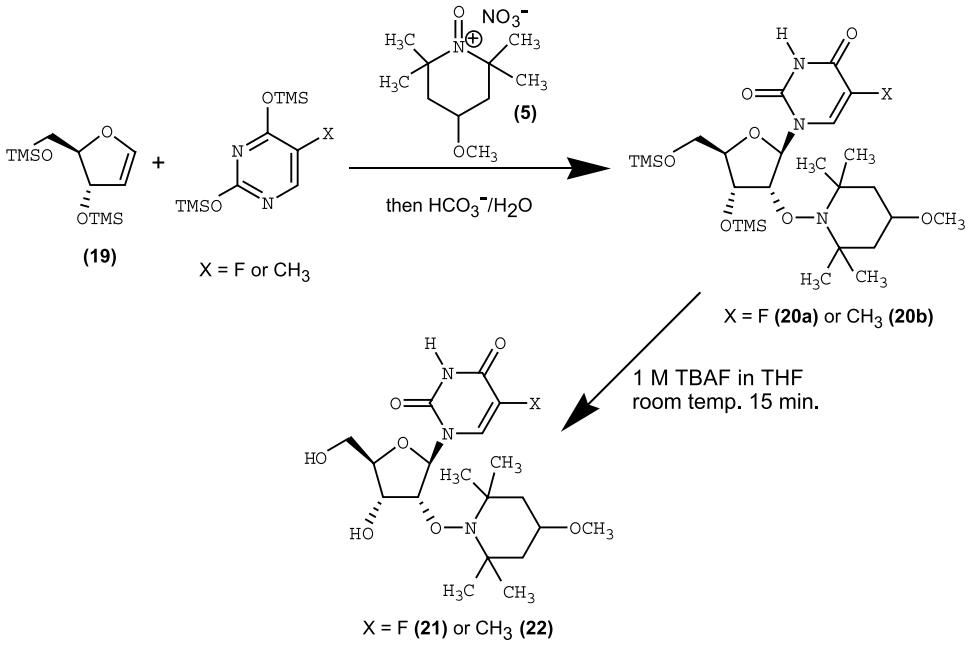


N4-Benzoylcytidine

Stereochemical Assignments Based on NOESY Experiments and Coupling Constants

Compound	Sugar NOE contacts	Base/Sugar NOE Cont.	Base/TEMPO NOE cont.	TEMPO/Sugar NOE cont.	$J_{1,2}$ (Hz)	Assigned Relative Stereochemistry
(6)	H1'- H4'	H6 - H4'	Not detected	Not detected	6.2	**trans**
(11)	H1' - H4' H2' - H4'	H6 – H4'	H6 – H5'	Not detected	3.2	**cis**
(16)	H1' – H4'	H4' – H9 H4' – H10	Not detected	H1' – H5'	6.5	**trans**
(8)	H1' – H5' H2' – H4'	Not detected	H6 – H6' H7 – H6'	Not detected	1.8	**cis**
(13)	H1' – H5'	Not detected	H6 – H6'	Not detected	4.5	**cis**
(17)	H1' – H5'	Not detected	H8 – H6' H9 – H6'	Not detected	1.8	**cis**
(21)	H1' – H4'	H6 – H3' H6 – H5'	Not detected	H1' – H8'	7.0	**trans**
(22)	H1' – H4'	H6 – H3' H6 – H5'	Not detected	H1' – H8'	7.2	**trans**

All experiments performed in $DMSO_{d6}$ at 298 ºK. NOESY experiments obtained on 1K by 256 data sets with zero filling to give 2K by 2K processed data. A mixing time of 300 ms was used in all experiments.



Scheme 5. Synthesis of 2′-methoxy-TEMPO substituted nucleoside analogs.

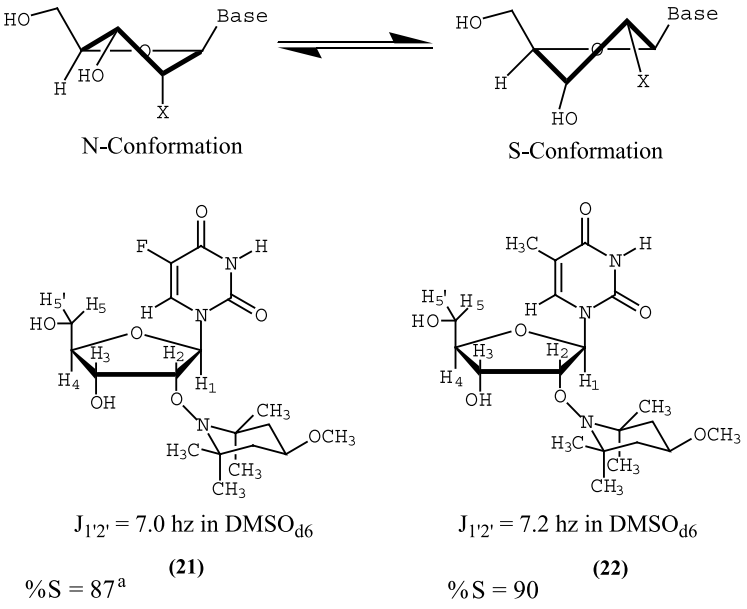


Figure 2. The effect of 2′-methoxy-TEMPO substitution on ribose conformation.

CONCLUSIONS

We have presented a process that utilizes reactive oxoammonium salts to generate a new class of structurally diverse nucleoside analogs. Reduction of the N–O bond in these analogs either by catalytic hydrogenation[28] or zinc dust reduction[29] should allow the formation of acyclic nucleoside analogs with plausible enzyme inhibitory activity. The bulkiness of the methoxy TEMPO group should allow a systematic approach to study how sugar ring conformations can be controlled by 2′-substitution. We plan to incorporate the ribofuranosyl analogs into oligonucleotides and study bow they affect antisense target affinity.

EXPERIMENTAL

General

All chemicals and solvents were of reagent grade purity and used without further purification. Flash chromatographic purifications were performed utilizing Merck 60 silica gel. Whatman glass backed UV indicator impregnated 0.25 μ analytical TLC plates were used exclusively. A Waters Baseline 810 HPLC system was utilized with a 10 μ C-18 Radial Pak cartridge. All separations were carried out at 2 mL/min flow rate under isocratic solvent conditions with 260 nm UV detection. NMR determinations were carried out on a JEOL FX-270 instrument operating at 269.65 MHz for ^{1}H and 67.8 MHz for ^{13}C. All 2 dimensional COSY and NOESY NMR experiments were carried out on a Bruker AVANCE 300 spectrometer. Frequencies are reported in parts per million (ppm) downfield from the internal reference standard tetramethylsilane. Coupling constants (J) are given in hertz. High resolution mass spectrum were determined at the Ohio State University using the Q-TOF Electrospray method.

Representative Synthetic Procedures and Spectroscopic Data

5-Methyl-1-{3-[(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yl)oxy]tetrahydrofuran-2-yl}pyrimidine-2,4-(1H,3H)-dione (6). Thymine (0.5 g, 3.96 mmol) was heated at reflux in 30 mL of 1,1,1,3,3,3-hexamethyldisilizane containing 20 mg of ammonium sulfate for 3 hours. The excess solvent was removed by rotary evaporation. The residue was then dissolved in 12 mL of 1,2-dichloroethane containing 0.6 mL (7.92 mmol) of 2,3-dihydrofuran. To this solution was added via the aide of a solid addition funnel 1.08 g (4.36 mmol) of the oxoammonium salt (**5**) over 15 minutes under an atmosphere of dry N_2. This reaction was stirred at room temperature for 18 hours and poured into 150 mL of saturated bicarbonate solution and stirred for 20 minutes. This solution was extracted 3X with EtOAc and the combined organic extracts dried (Na_2SO_4) and concentrated in vacuo. The residue was subjected to flash chromatography on silica gel with 20% acetone/80% CH_2Cl_2 as eluent. Removal of solvent gave the product as a white foam (1.40 g) in 93% yield. HPLC (55% MeOH/45% H_2O) ret. time = 6.15 min. ^{1}H-NMR($CDCl_3$); δ 10.07 (s, 1H, NH), 7.14 (s, 1H, vinylic H), 6.27 (d, 1H, J = 5.8, CH), 4.72 (dd, 1H, J = 6.2, CH), 4.19 (dt, 1H, CH), 3.80 (dt, 1H, CH), 3.39 (tt, 1H, CH-TEMPO), 3.30 (s, 3H, OCH_3), 2.31 (dd, 2H, CH_2-TEMPO), 1.94 (s, 3H, Thy-CH_3), 1.36 (dd, 2H, CH_2-TEMPO), 1.19 (s, 6H, 2CH_3's-TEMPO), 1.02 (s, 3H, CH_3-TEMPO),

0.94 (s, 3H, CH_3-TEMPO). ^{13}C-NMR($CDCl_3$); δ 164.2, 150.9, 137.8, 109.3, 83.9, 82.8, 71.3, 65.9, 61.1, 59.5, 55.7, 44.9, 34.5, 33.4, 32.2, 21.1, 12.4. IR(KBr); 3557, 3198, 2976, 2939, 1686, 1466, 1376, 1265, 1170, 1094 cm^{-1}. HRMS: $(M + Na)^+$ calcd. for $C_{19}H_{31}N_3O_5Na$; 404.2161. Found; 404.2161.

5-Methyl-1-{3-[(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yl)oxy]tetrahydro-2H-pyran-2-yl}pyrimidine-2,4-(1H,3H)-dione (8). HPLC (65% MeOH/35% H_2O) ret. time = 6.49 min. ^{1}H-NMR($CDCl_3$); δ 10.02 (s, 1H, NH), 7.48 (s, 1H, vinylic H), 5.63 (d, 1H, J = 1.8, CH), 4.17 (dt, 2H, CH_2), 3.72 (dt, 1H, CH), 3.40 (tt, 1H, CH-TEMPO), 3.30 (s, 3H, OCH_3), 2.55 (d, 1H, CH), 1.97 (ddd, 2H, CH_2), 1.93 (s, 3H, Thy-CH_3), 170 (dd, 2H, CH_2), 1.41 (m, 3H, CH + CH_2), 1.27 (s, 3H, CH_3-TEMPO), 1.15 (s, 3H, CH_3-TEMPO), 1.00 (s, 6H, 2 CH_3's-TEMPO). ^{13}C-NMR($CDCl_3$); δ 164.2, 150.4, 139.1, 109.3, 83.6, 75.4, 71.3, 69.3, 61.3, 59.8, 55.7, 45.4, 34.0, 25.9, 21.8, 20.4, 12.3. IR(KBr); 3186, 2974, 2940, 1706, 1676, 1466, 1376, 1297, 1262, 1097 cm^{-1}. HRMS: $(M + Na)^+$ calcd. for $C_{20}H_{33}N_3O_5Na$; 418.2318. Found; 418.2310.

1-{1-Isobutoxy-2-[(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yl)oxy]ethyl}-5-methyl-pyrimidine-2,4-(1H,3H)-dione (7). HPLC (75% MeOH/25% H_2O) ret. time = 5.70 min. ^{1}H-NMR($CDCl_3$); δ 9.31 (s, 1H, NH), 7.28 (s, 1H, vinylic H), 5.78 (t, 1H, J = 4.4, CH), 3.95 (d, 2H, J = 5.1, CH_2), 3.41 (ddd, 1H, CH-TEMPO), 3.31 (s, 3H, OCH_3), 3.25 (d, 2H, J = 6.3, CH_2), 1.95 (s, 3H, Thy-CH_3), 1.91–1.81 (m, 3H, CH + CH_2-TEMPO), 1.35 (dd, 2H, CH_2), 1.18 (s, 3H, CH_3-TEMPO), 1.14 (s, 3H, CH_3-TEMPO), 1.11 (s, 3H, CH_3-TEMPO), 1.08 (s, 3H, CH_3-TEMPO), 0.92 (d, 6H, J = 6.6, CH(CH_3)$_3$). ^{13}C-NMR($CDCl_3$); δ 163.0, 149.9, 134.8, 109.2, 81.4, 75.3, 74.6, 70.2, 58.9, 54.5, 43.2, 31.6, 26.9, 19.7, 17.9, 17.8, 11.2. IR(KBr); 3176, 3053, 2971, 1681, 1645, 1468, 1375, 1260, 1100, 1069 cm^{-1}. HRMS: $(M+H)^+$ calcd. for $C_{21}H_{38}N_3O_5$; 412.2811. Found; 412.2802.

1-{1-(9H-carbazol-9-yl)-2-[(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yl)oxy]ethyl}5-methylpyrimidine-2,4-(1H,3H)-dione (9). HPLC (80% MeOH/20% H_2O) ret. time = 6.76 min. ^{1}H-NMR($CDCl_3$); δ 9.79 (s, 1H, NH), 8.07 (d, 2H, J = 7.7, arom.), 7.70 (d, 2H, J = 8.5, arom.), 7.49 (t, 2H, J = 7.3, arom.), 7.30 (t, 3H, J = 7.7, CH + arom.), 7.24 (s, 1H, Thy. vinylic), 4.92 (t, 1H, J = 7.5, CH), 4.78 (dd, 1H, CH), 3.41 (ddd, 1H, CH-TEMPO), 3.31 (s, 3H, OCH_3), 1.87(dd, 2H, CH_2-TEMPO), 1.78 (s, 3H, Thy-CH_3), 1.38 (dd, 2H, CH_2-TEMPO), 1.19 (s, 3H, CH_3-TEMPO), 1.13 (s, 3H, CH_3-TEMPO), 1.08 (s, 3H, CH_3-TEMPO), 1.07 (s, 3H, CH_3-TEMPO). ^{13}C-NMR($CDCl_3$); δ 163.8, 150.8, 139.8, 136.2, 126.7, 124.1, 120.8, 120.5, 111.8, 110.2, 75.7, 71.4, 64.8, 60.5, 60.4, 55.8, 44.5, 33.0, 21.0, 12.7. IR(KBr); 3514, 3179, 3058, 2975, 2937, 1686, 1449, 1376, 1327, 1257, 1214, 1092 cm^{-1}. HRMS: $(M+H)^+$ calcd. for $C_{29}H_{37}N_4O_4$; 505.2815. Found; 505.2799.

5-Methyl-1-{2-[(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yl)oxy]-1-(2-oxoazepan-1-yl)ethyl}pyrimidine-2,4-(1H,3H)-dione (10). HPLC (65% MeOH/35% H_2O) ret. time = 4.86 min. ^{1}H-NMR($CDCl_3$); δ 10.10 (s, 1H, NH), 7.52 (s, 1H, Thy. vinylic), 5.76 (t, 1H, CH), 4.40 (t, 2H, J = 7.3, CH_2), 3.62 (m, 2H, CH_2), 3.41 (ddd, 1H, CH-TEMPO), 3.32 (s, 3H, OCH_3), 2.54 (quintet, 2H, CH_2), 1.91 (s, 3H, Thy. CH_3), 1.86 (m, 2H, CH_2), 1.71 (brd. s. 6H, 3 CH_2's), 1.36 (m, 2H, CH_2), 1.21 (s, 3H, CH_3-TEMPO), 1.13 (s, 6H, 2 CH_3's-TEMPO), 1.06 (s, 3H, CH_3-TEMPO). ^{13}C-NMR($CDCl_3$); δ 177.9, 164.5,

151.5, 140.9, 109.4, 73.6, 71.4, 70.9, 60.2, 60.1, 55.8, 49.8, 44.4, 37.8, 33.2, 32.9, 29.7, 28.9, 23.3, 21.1, 20.9, 12.4. IR(KBr); 3490, 3186, 2976, 2935, 1686, 1466, 1362, 1258, 1190, 1096 cm^{-1}. HRMS: $(M + Na)^+$ calcd. for $C_{23}H_{38}N_4O_5Na$; 473.2740. Found; 473.2729.

5-Fluoro-1-{3-[(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yloxy]tetrahydrofuran-2-yl}pyrimidine-2,4-(1H,3H)-dione (11). HPLC (55% MeOH/45% H_2O) ret. time = 7.14 min. ^{1}H-NMR($CDCl_3$,$DMSO_{d6}$ mix); δ 9.77 (brd. s, 1H, NH), 7.38 (d, 1H, J_{HF} = 6.2, vinylic H), 6.25 (d, 1H, J = 5.8, CH), 4.77 (dt, 1H, J = 6.2, CH), 4.21 (dd, 1H, J = 5.2, CH), 3.83 (dd, 1H, J = 5.6, CH), 3.39 (ddd, 1H, CH-TEMPO), 3.31 (s, 3H, OCH_3), 2.31 (dd, 2H, CH_2), 1.85 (dd, 2H, CH_2), 1.37 (dd, 2H, CH_2), 1.20 (s, 6H, 2 CH_3-TEMPO), 1.04 (s, 3H, CH_3-TEMPO), 0.98 (s, 3H, CH_3-TEMPO). ^{13}C-NMR($CDCl_3$,$DMSO_{d6}$ mix); δ 157.5 (d, J_{CF} = 25.4), 149.4, 139.7 (d, J_{CF} = 234.3), 125.7 (d, J_{CF} = 33.2), 83.7, 82.9, 71.1, 65.9, 61.0, 59.4, 55.7, 44.8, 34.4, 33.3, 31.9, 21.3, 21.1. IR(KBr); 3170, 3060, 2976, 1720, 1704, 1658, 1474, 1402, 1362, 1261, 1090 cm^{-1}. HRMS: $(M + Na)^+$ calcd. for $C_{18}H_{28}N_3O_5FNa$; 408.1911. Found; 408.1933.

5-Fluoro-1-{3-[(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yl)oxy]tetrahydro-2H-pyran-2-yl}pyrimidine-2,4-(1H,3H)-dione (13). HPLC (70% MeOH/30% H_2O) ret. time = 4.27 min. ^{1}H-NMR($CDCl_3$); δ 9.33 (brd. s, 1H, NH), 7.72 (d, 1H, J_{HF} = 6.2, vinylic CH), 5.58 (d, 1H, J = 1.8, CH), 4.29 (dt, 1H, CH), 3.72 (dd, 1H, CH), 3.42 (ddd, 1H, CH-TEMPO), 3.31 (s, 3H, OCH_3), 2.55 (dd, 1H, CH), 1.92–1.63 (brd. m, 5H, CH_2+ CH_2+ CH), 1.49–1.38 (brd. m, 3H, CH_2+ CH), 1.34 (s, 3H, CH_3-TEMPO), 1.27 (s, 3H, CH_3-TEMPO), 1.15 (s, 3H, CH_3-TEMPO), 1.05 (s, 3H, CH_3-TEMPO). ^{13}C-NMR($CDCl_3$); δ 156.8 (d, J_{CF} = 25.4), 148.6, 139.7 (d, J_{CF} = 234.4), 127.5 (d, J_{CF} = 33.2), 98.8, 83.9, 79.5, 71.2, 61.3, 59.9, 55.7, 45.4, 34.8, 33.8, 32.5, 25.6, 24.5, 20.2. IR(KBr); 3427, 3198, 2975, 2939, 1720, 1664, 1466, 1377, 1362, 1259, 1099 cm^{-1}. HRMS: $(M+Na)^+$ calcd. for $C_{19}H_{30}N_3O_5FNa$; 422.2067. Found; 422.2063.

5-Fluoro-1-{1-isobutoxy-2-[(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yl)oxy]ethyl}-pyrimidine-2,4-(1H,3H)-dione (12). HPLC (75% MeOH/25% H_2O) ret. time = 5.10 min. ^{1}H-NMR($CDCl_3$); δ 9.71 (brd. s, 1H, NH), 7.54 (d, 1H, J_{HF} = 5.9, vinylic CH), 5.75 (dd, 1H, CH), 3.96 (d, 2H, J = 4.4, CH_2), 3.42 (ddd, 1H, CH-TEMPO), 3.32 (s, 3H, OCH_3), 3.28 (d, 2H, J = 6.6, CH_2), 1.93–1.82 (m, 5H, $2CH_2$'s + CH), 1.36 (dd, 2H, CH_2), 1.19 (s, dd, 4H, CH_3-TEMPO + CH), 1.13 (s, 6H, 2 CH_3-TEMPO), 1.09 (s, 3H, CH_3-TEMPO), 0.93 (d, 6H, J = 6.6, $CH(CH_3)_2$). ^{13}C-NMR($CDCl_3$); δ 157.1 (d, J_{CF} = 27.3), 149.6, 140.5 (d, J_{CF} = 236.3), 124.6 (d, J_{CF} = 33.2), 83.5, 76.3, 71.5, 60.4, 60.3, 55.8, 44.4, 32.9, 28.3, 21.1, 19.1, 19.0. IR(KBr); 3194, 3072, 2974, 1723, 1667, 1470, 1385, 1256, 1099, 1075 cm^{-1}. HRMS: $(M + Na)^+$ calcd. for $C_{20}H_{34}N_3O_5FNa$; 438.2380. Found; 438.2379.

1-{1-(9H-Carbazol-9-yl)-2-[(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yl)oxy]ethyl}-5-fluoropyrimidine-2,4-(1H,3H)-dione (14). HPLC (80% MeOH/20% H_2O) ret. time = 5.66 min. ^{1}H-NMR($CDCl_3$); δ 10.26 (brd. s, 1H, NH), 8.03 (d, 2H, J = 7.7, aromatic CH), 7.66 (d, 2H, J = 8.4, arom. CH), 7.47 (s,d, 3H, arom. CH + vinylic CH), 7.31 (d, dd, 3H, arom. CH + CH), 4.92 (dd, 1H, CH), 4.76 (dd, 1H, CH), 3.42 (ddd, 1H, CH-TEMPO), 3.31 (s, 3H, OCH_3), 1.86 (dd, 2H, CH_2), 1.39 (m, 2H, CH_2), 1.20 (s, 3H, CH_3-TEMPO), 1.15 (s, 3H, CH_3-TEMPO), 1.09 (s, 6H, 2

CH_3's-TEMPO). ^{13}C-NMR($CDCl_3$); δ 156.9 (d, J_{CF} = 25.4), 149.4, 140.6 (d, J_{CF} = 240.2), 139.5, 126.9, 124.7 (d, J_{CF} = 33.2), 124.1, 121.1, 120.6, 110.1. IR(KBr); 3186, 3063, 2974, 2938, 1707, 1669, 1449, 1376, 1324, 1254, 1219, 1090 cm^{-1}. HRMS: $(M + Na)^+$ calcd. for $C_{28}H_{33}N_4O_4FNa$; 509.2564. Found; 509.2576.

N-(1-{3-[(2,2,6,6-Tetramethyl-4-methoxypiperidin-1-yl)oxy]tetrahydrofuran-2-yl}-2-oxo-1,2-dihydropyrimidine-4-yl)benzamide (16). HPLC (70% MeOH/30% H_2O) ret. time = 5.87 min. ^{1}H-NMR($DMSO_{d6}$); δ 10.11 (brd. s, 1H, NH), 8.02 (d, 2H, J = 7.0, aromatic CH), 7.82 (d, 1H, J = 7.4, vinylic CH), 7.63–7.48 (t,d, 4H, vinylic CH + aromatic CH), 6.32 (d, 1H, J = 5.5, CH), 4.85 (ddd, 1H, J = 5.4, CH), 4.25 (dt, 1H, J = 7.4, CH), 3.97 (dt, 1H, J = 7.0, CH), 3.36 (ddd, 1H, CH-TEMPO), 3.27 (s, 3H, OCH_3), 2.47 (dt, 1H, J = 5.9, CH), 2.29 (dt, 1H, J = 6.3, CH), 1.90–1.72 (m, 2H, 2 CH's), 1.38–1.27 (dd, 2H, CH_2), 1.23 (s, 3H, CH_3-TEMPO), 1.19 (s, 3H, CH_3-TEMPO), 1.00 (s, 3H, CH_3-TEMPO), 0.89 (s, 3H, CH_3-TEMPO). ^{13}C-NMR($DMSO_{d6}$); δ 167.0, 162.7, 155.1, 145.7, 133.2, 132.8, 128.6, 128.1, 95.9, 85.9, 78.7, 81.6, 71.1, 66.6, 61.2, 59.4, 55.6, 45.0, 34.3, 33.6, 31.3, 21.4, 21.1. IR(KBr); 3440, 3195, 2977, 2935, 1687, 1661, 1627, 1556, 1487, 1395, 1301, 1258, 1090 cm^{-1}. HRMS: $(M + Na)^+$ calcd. for $C_{25}H_{34}N_4O_5Na$; 493.2427. Found; 493.2413.

N-(1-{3-[(2,2,6,6-Tetramethyl-4-methoxypiperidin-1-yl)oxy]tetrahydro-2H-pyran-2-yl}-2-oxo-1,2-dihydropyrimidine-4-yl)benzamide (17). HPLC (80% MeOH/20% H_2O) ret. time = 4.65 min. ^{1}H-NMR($CDCl_3$); δ 8.74 (brd. s, 1H, NH), 8.06 (d, 1H, J = 7.7, vinylic H), 7.91 (d, 2H, J = 8.8, aromatic CH), 7.65–7.49 (t,d, 4H, Vinylic H + aromatic), 5.76 (d, 1H, J = 2.2, CH), 4.36 (ddd, 1H, CH), 4.21 (dt, 1H, CH), 3.74 (dt, 1H, CH), 3.37 (ddd, 1H, CH-TEMPO), 3.28 (s, 3H, OCH_3), 2.54 (dt, 1H, CH), 2.15–2.04 (dt, 1H, CH), 1.82–1.88 (dt, 1H, CH), 1.72–1.65 (dd, 2H, 2 CH), 1.49–1.28 (dd,dt, 3H, CH + CH_2), 1.27 (s, 3H, CH_3-TEMPO), 1.14 (s, 3H, CH_3-TEMPO), 0.98 (s, 3H, CH_3-TEMPO), 0.90 (s, 3H, CH_3-TEMPO). ^{13}C-NMR($CDCl_3$); δ 166.6, 161.8, 154.5, 147.6, 133.2, 133.1, 129.0, 127.5, 95.8, 85.3, 73.5, 71.3, 69.4, 61.3, 59.9, 55.7, 45.6, 33.9, 25.5, 22.2, 20.5. IR(KBr); 3449, 2974, 2936, 1699, 1663, 1621, 1560, 1485, 1390, 1317, 1258, 1098 cm^{-1}. HRMS: $(M + H)^+$ calcd. for $C_{26}H_{37}N_4O_5$ 485.2754. Found; 485.2758.

N-(1-{1-Isobutoxy-2-[(2,2,6,6,-tetramethyl-4-methoxypiperidin-1-yl)oxy]ethyl}-2-oxo-1,2-dihydropyrimidine-4-yl)benzamide (15). HPLC (80% MeOH/20% H_2O) ret. time = 6.94 min. ^{1}H-NMR($CDCl_3$); δ 9.05 (brd. s, 1H, NH), 7.96–7.92 (s,d, 3H, aromatic + vinylic H), 7.60–7.48 (d,t, 4H, aromatic + vinylic H), 5.92 (dd, 1H, J = 3.3, CH), 4.02 (dd, 2H, CH_2), 3.41 (ddd, 1H, CH-TEMPO), 3.31 (s, 3H, OCH_3), 3.29–3.24 (m, 3H, CH + CH_2), 1.94–1.83 (dd,d, 3H, CH + CH_2), 1.34 (dd, 1H, CH_2), 1.24 (s, 3H, CH_3-TEMPO), 1.15 (s, 3H, CH_3-TEMPO), 1.09 (s, 3H, CH_3-TEMPO), 1.07 (s, 3H, CH_3-TEMPO), 0.94 (dd, 6H, $CH(CH_3)_3$). ^{13}C-NMR($CDCl_3$); δ 162.2, 155.1, 145.1, 133.1, 128.8, 127.6, 96.4, 84.7, 76.4, 71.4, 60.3, 60.2, 55.6, 44.4, 32.8, 28.2, 21.1, 21.0, 19.0. IR(KBr); 3391, 2972, 1669, 1623, 1558, 1487, 1382, 1299, 1257, 1098 cm^{-1}. HRMS: $(M + H)^+$ calcd. for $C_{27}H_{41}N_4O_5$; 501.3077. Found; 501.3062.

N-(1-{1-(2-Oxoazepan-1-yl)-2-{(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yl)oxy]ethyl}-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide (18). HPLC (70% MeOH/30% H_2O) ret. time = 6.91 min [as an inseparable mixture of isomers]

^{1}H-NMR($CDCl_3$); δ 9.23 (brd. s, 1H, NH), 8.10 (d, 1H, J = 7.6, vinylic CH), 7.99 (d, 2H, J = 7.6, aromatic CH), 7.62–7.43 (s,t, 4H, vinylic CH + aromatic CH), 5.89 (dd, 1H, J = 3.4, CH), 6.13 (dd, 1H, CH), 4.55 (ddd, 1H, CH), 4.42 (ddd, 1H, CH), 3.91 (ddd, 1H, CH), 3.72 (ddd, 1H, CH), 3.41 (ddd, 1H, CH), 3.31 (s, 3H, OCH_3), 2.52 (ddd, 2H, CH_2), 1.86 (ddd, 2H, CH_2), 1.70 (dd,ddd, 6H, 3 CH_2's), 1.35 (ddd, 2H, CH_2), 1.22 (s, 3H, CH_3-TEMPO), 1.13 (s, 6H, 2 CH_3's-TEMPO), 1.05 (s, 3H, CH_3-TEMPO). ^{13}C-NMR($CDCl_3$); δ 179.4, 177.9, 176.4, 162.5, 155.7, 149.6, 133.1, 133.0, 128.8, 127.9, 95.9, 73.1, 72.7, 71.4, 60.3, 60.1, 55.8, 50.4, 44.5, 37.9, 33.1, 29.7, 28.9, 23.2, 21.1. IR(KBr); 3273, 2974, 2934, 1660, 1624, 1560, 1483, 1314, 1256, 1096 cm^{-1}. HRMS: $(M + Na)^+$ calcd. for $C_{29}H_{41}N_5O_5Na$; 562.3005. Found; 562.3002.

1-[4-Hydroxy-5-(hydroxymethyl)-3-(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yloxy)-tetrahydrofuran-2-yl]-5-methylpyrimidine-2,4-(1H,3H)-dione (22). HPLC (40% MeOH/60% H_2O) ret. time = 6.53 min. IR(KBr); 3448, 2977, 2939, 1686, 1474, 1379, 1274, 1090, 1050 cm^{-1}. ^{1}H-NMR($DMSO_{d6}$); δ 11.35 (s, 1H, NH), 7.39 (s, 1H, vinylic H), 6.31 (d, 1H, J = 7.0, H_1'), 5.21 (d, 1H, J = 6.2, $C_3'OH$), 4.99 (dd, 1H, J = 4.0, $C_5'OH$), 4.48 (t, 1H, 36.1, H_2'), 4.26 (dd, 1H, J = 6.6, H_3'), 3.55–3.45 (dd,dd,dd, 3H, H_4' + $2H_5'$), 3.18 (s, 3H, 4-OCH_3), 1.78 (s, 3H, CH_3), 1.27, 1.07, 0.97, 0.84 (4s, 12H, 4 CH_3's), 1.21–1.10 (dd,dd,dd, 5H, CH + $2CH_2$'s), ^{13}C-NMR($DMSO_{d6}$); δ 163.54, 150.46, 138.80, 107.96, 88.38, 81.69,73.20,70.49,60.42,59.58, 54.95, 44.58, 44.52, 33.89, 32.63, 20.76, 20.39, 11.86. HRMS: $(M + Na)^+$ calcd. for $C_{20}H_{33}N_3O_7Na$ 450.2216. Found; 450.2206.

5-Fluoro-1-[4-hydroxy-5(hydroxymethyl)-3-(2,2,6,6-tetramethyl-4-methoxypiperidin-1-yloxy)tetrahydrofuran-2-yl]pyrimidine-2,4-(1H,3H)-dione (21). HPLC (40% MeOH/60% H_2O) ret. time = 5.64 min. IR(KBr); 3448, 2977, 2941, 1707, 1475, 1364, 1269, 1087, 1046 cm^{-1}. ^{1}H-NMR($DMSO_{d6}$); δ 11.96 (s, 1H, NH), 7.95 (d, 1H, J = 7.0, vinylic H), 6.31 (d, 1H, J = 6.6, H_1'), 5.23 (d, 1H, J = 5.7, $C_3'OH$), 5.10 (t, 1H, J = 3.5, $C_5'OH$), 4.52 (dd, 1H, J = 6.0, H_2'), 4.28 (dd, 1H, J = 6.6, H_3'), 3.71–3.50 (dd,ddd, 3H, H_4' + 2 H_5'), 3.19 (s, 3H, 4-OCH_3), 1.27, 1.10, 0.98, 0.89 (4s, 12H, 4 CH_3's), 1.22–1.15 (dd,dd,dd, 5H, CH + $2CH_2$'s). ^{13}C-NMR($DMSO_{d6}$); δ 156.70 (d, J_{CF} = 25.4), 148.94, 139.06 (d, J_{CF} = 30.4), 126.91 (d, J_{CF} = 35.2), 88.12, 81.99, 72.45, 70.49, 60.50, 59.32, 54.92, 44.49, 33.72, 32.57, 20.85, 20.36. HRMS: $(M + Na)^+$ calcd. for $C_{19}H_{30}N_3O_7FNa$; 454.1965. Found; 454.1955.

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