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Note

Facile synthesis of acyclic analogues of carbocyclic nucleoside as potential anti-HIV pro-drug

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Microwave induced montmorillonite K 10 clay catalyzed Michael addition of sulphur nucleophile, (4-oxo-butyl)-dithio-carbamic acid **1** to 4-arylidene-5(4*H*)-oxazolones **2a-j** followed by ring transformation of the resultant Michael adducts **3a-j** in solvent-free conditions gives **4a-j** in excellent yield. Coexistence of acidic and basic sites on surface of montmorillonite K 10 accelerates the organic reactions synergistically. The control Aldol condensation of compound **4a-j** with HCHO gives compound **5a-j**, which upon chemoselective reduction with $NaBH_4$ gives the title compound **6a-j**. This process minimizes the mechanical loss of the intermediate during the process of isolation, and thus increases the yield and decreases the cost and time.

Keywords: Michael addition, montmorillonite K 10, control aldol condensation, chemoselective reduction, microwave irradiation

Nucleosides have been playing a major role in combating tumor and viral diseases. A variety of modifications of natural nucleosides both with respect to base and sugar[1] have been made to discover novel antitumor and/ or antiviral agents[2]. Among nucleosides, carbocyclic analogues have been one of the interesting class of compounds, in which the furanose oxygen of the sugar moiety is replaced by a methylene (-CH_2-) unit, and are stable towards hydrolysis by phosphorylase. This is due to the nonglycosidic nature of the bond between the carbocyclic moiety and the heterocyclic base, which results in metabolic stability to phosphorylase. This enzyme cleaves the glycosidic bond in conventional nucleoside. Consequently, carbocyclic nucleosides display an enhance biostability[3-5]. Further, carbocyclic nucleosides like Carbovir[6] and Abacavir[7] **(Figure 1)** are of considerable interest due to their anti-tumour and anti HIV activities. Moreover, acyclic analogs of nucleosides exhibit properties, relative to their natural counterparts, which are useful in biological systems. These include increased stability toward loss of base in acidic media, a slightly higher lipophilicity and better metabolic stability toward the enzymes which cleave the glycosidic linkage of natural nucleosides.

The compounds incorporating oxazolone ring as a part of the condensed heterocyclic framework have been reported as potential fungicidal[8,9], bactericidal[10,11], herbicidal, insecticidal[12], *etc*. Further, 1,3-thiazine nucleus has been used for designing various pharmacological agents[13,14] owing to its presence in cephalosporins, which are the most common antibiotics in clinical use. Penciclovir **(Figure 1)** is an acyclic carba analogue of guanosine, and has been approved as an antiviral drug for treating diseases caused by HSV and VZV (ref.15). Since the designed title compound **6a-j** (**Scheme I**) is an acyclic carba analogue of nucleosides of 1,3-thiazine nucleobase, so apparently it may act as a potentially anti HIV active agent.

The present day industrialization has led to immense environmental deterioration. One of the chief sources of environmental pollution from the chemical industry are the organic solvents. The solvent vapours contaminate the environment/ atmosphere. The increasing awareness throughout the world has brought in a pressing need to develop an alternative synthetic approach for biologically and synthetically important compounds. This requires a new approach which will reduce the material and energy consumption, and minimize or eliminate the dispersion of harmful chemicals in the environment. The key element in the current approach is the novel utilization of oxazolone ring as a building block[16-18], a well documented application for the construction of various oxygen heterocycles of chemical and biological interest.

In view of the above facts and in continuation of the work[19-24] to develop new synthetic methodologies especially for bioactive molecules and finding simple, useful and convenient routes in heterocyclic synthesis, new facile green protocol for synthesis of potential antiviral title compounds has been developed.

Results and Discussion

It is noteworthy that all the acyclic analogues of nucleosides are new. After some preliminary experi-

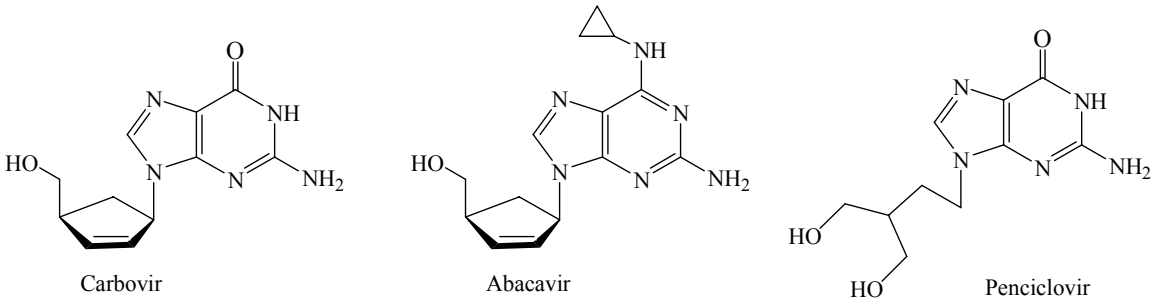
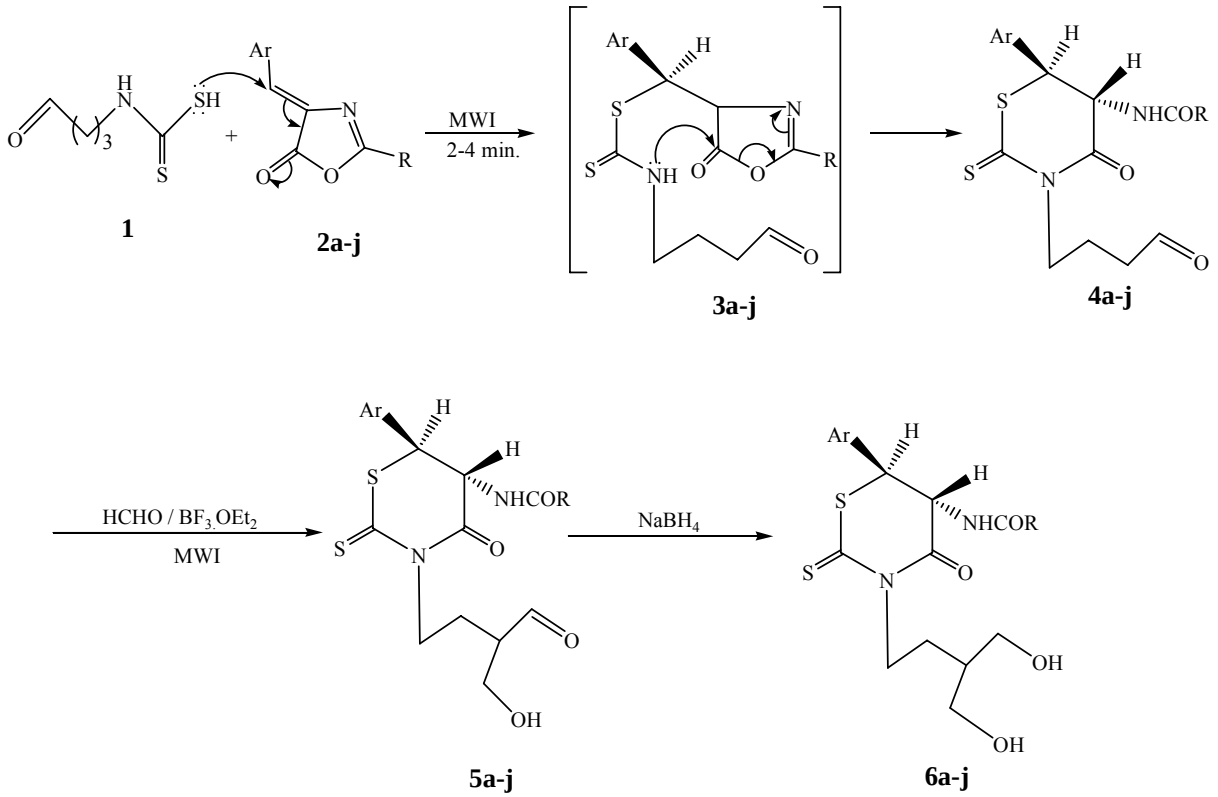


Figure 1



1 **2a-j** **3a-j** **4a-j** **5a-j** **6a-j**

2/3/4/5/6	R	Ar	2/3/4/5/6	R	Ar
a	$-CH_3$	C_6H_5-	**f**	$-CH_3$	*p*-$CH_3.C_6H_4$-
b	$-CH_3$	*p*-$CH_3O.C_6H_4$-	**g**	$-CH_3$	*o*-$CH_3O.C_6H_4$-
c	$-CH_3$	*p*-$HO.C_6H_4$-	**h**	$-CH_3$	*o*-$HO.C_6H_4$-
d	$-CH_3$	*p*-$Cl.C_6H_4$-	**i**	$-CH_3$	*o*-$Cl.C_6H_4$-
e	$-CH_3$	*p*-$NO_2.C_6H_4$-	**j**	$-CH_3$	*o*-$NO_2.C_6H_4$-

Scheme I

mentation, it was found that the synthesis of **4a-j** can be effected starting from oxazolones **2** and (4-oxo-butyl)-dithiocarbamic acid **1**. Michael addition of 4-oxo-butyl)-dithiocarbamic acid **1** on oxazolones **2**, gave intermediate **3a-j**. The key element in the present approach is that the intermediate **3a-j** were transformed into compound **4a-j** *in-situ via* cyclo-condensation without isolation and exposure of **3a-j** to the environment. Although the resulting product **4a-j** could have been formed as diastereomeric pairs,

the products could not be separated into diastereomers. It seems that *cis*-isomers, if formed, probably isomerised into the more stable *trans*-products. The ^{1}H NMR spectra of the products show distinct doublets at δ 4.66 (d, 1H, J = 7.0, S-CH-Ar) and 5.19 (d, 1H, J = 7.0, -N-CH) of 1,3-thiazene ring. So the diastereomers obtained were assigned the *trans* configuration[25,26]. This process, thus, minimizes the mechanical loss of the intermediate during the process of isolation. Coexistence of acidic and basic sites on the surface of montmorillonite K10 accelerated the organic reactions synergistically. However, the use of other mineral supports *viz*. silica gel, neutral or basic alumina was far less effective, resulting in either no reaction (in the case of basic alumina) or relatively very low yields (20-35%) of **4a-j** (in the case of silica gel and neutral alumina). Moreover, the reactions did not take place if they were performed using microwave without the montmorillonite K10, either neat or in an organic solvent. Compound **4a-j** on control aldol condensation with formaldehyde yielded **5a-j**, which on subsequent chemoselective reduction with $NaBH_4$ gave title compounds **6a-j**.

The reactions were also carried out using a thermostated oil-bath at the same temperature (90°C) as for the MW-activated method for a longer (optimized) period of time to ascertain whether the MW method improved the yield or increased conversion rates. It was found that significantly lower yields (34-40%) were obtained using oil-bath heating rather than the MW-activated method.

Experimental Section

Solvents were of reagent grade and dried using standard procedures. Melting points were determined by open glass capillary method and are uncorrected. All chemicals used were of reagent grade and were used as received without further purification. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker AVANCE DPX (400 MHz) FT spectrometer in DMSO-d_6 using TMS as an internal reference. Mass spectra were recorded on a JEOL SX-102 mass spectrometer at 70 eV. A Laboratory Microwave Oven (Model BP 310/50) operating at 2450 MHz and power output of 600 W was used for all the experiments. Elemental analyses were carried out using a Coleman automatic C, H and N analyzer. The progress of the reaction was monitored by TLC (Merck Silica gel). Column chromatography was performed over silica gel 60 (70-230 mesh). The structures of synthesized compound were confirmed by spectral and elemental analysis.

(4-oxo-butyl)-dithiocarbamic acid 1. Following the standard procedure[27], concentrated ammonia solution (20 mL) was added to CS_2 (3 mL, 50 mmole). Then 4-aminobutyraldehyde (3.48 g, 40 mmole) was added in small portions over a period of 10 min. The dithiocarbamate was allowed to stand for 3 hr and then acidified with conc HCl. The dithiocarbamic acid precipitate was filtered, washed with dry ether and dried under suction.

N-[4-Oxo-3-(4-oxo-butyl)-6-phenyl-2-thioxo-[1,3]-thiazinan-5-yl]-acetamide 4a-j

Method A (Thermal). A mixture of **1** (0.25 mole) and 4-arylidene-5(4*H*)-oxazolones[28] **2a-j** (0.25 mole) were dissolved in dioxane (30 mL) and refluxed on thermostated water-bath for the specified time (**Table I**). The completion of the reaction was checked by TLC using benzene:MeOH (7:3 v/v). The reaction-mixture was concentrated to half of its volume, cooled to RT and poured into water. The product **4a-j** thus obtained was separated by flash chromatography and purified by recrystallization from ethanol to obtain pure **4a-j**.

Method B (Microwave Irradiation). A mixture of **1** (2.5 mmole) and 4-arylidene-5(4*H*)-oxazolones[28] **2a-j** (2.5 mmole) were adsorbed on montmorillonite K-10 clay (0.5 mmole) in a 100 mL pyrex conical flask capped with a funnel and subjected to microwave irradiation for the specified time (**Table I**). The completion of the reaction was checked by TLC using benzene:MeOH (7:3 v/v). The reaction-mixture was cooled to RT and eluted with acetone (3 × 10 mL). The elute was evaporated to dryness and washed with $NaHCO_3$ (3.0% w/v) and finally with cold H_2O and dried over anhydrous $MgSO_4$. The residue on purification by silica gel column chromatography (benzene:MeOH; 8:2 v/v) furnished analytically pure **4a-j**.

Similar procedures were used with other solid supports *viz*. silica gel, neutral or basic alumina.

N-[3-(3-Hydroxymethyl-4-oxo-butyl)-4-oxo-6-phenyl-2-thioxo-[1,3]thiazinan-5-yl]-acetamide 5a-j

Method A (Thermal). Following the standard procedure[29], $BF_3{\cdot}Et_2O$ (0.01 mole) was added to a mixture of *N*-[4-oxo-3-(4-oxo-butyl)-6-phenyl-2-thioxo-[1,3]thiazinan-5-yl]-acetamide **4a-j** (0.2 mole) and HCHO (0.2 mole). The colour of the reaction-mixture changed from colourless to red-brown immediately.

Table I — Physical and spectral characterization data of compounds **4a-j, 5a-j** and **6a-j**

Compd	m.p. ºC	Yield[a] % (sec)	Yield[b] % (sec)	Yield[c] % (sec)	Yield[d] % (sec)	Yield[e] % (min)	Mol. Formula[f]	M^+ *m/z*	^{1}H NMR (δ, ppm) ($CDCl_3$)
4a	165	82 (140)	---	25 (240)	23 (190)	60 (150)	$C_{16}H_{18}N_2O_3S_2$	350	1.88 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.40 (m, 2H, -CHC=O), 3.20 (t, 2H, -NCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.08-7.21 (m, 5H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
4b	190	85 (200)	---	23 (210)	25 (230)	65 (180)	$C_{17}H_{20}N_2O_4S_2$	380	1.88 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.40 (m, 2H, -CHC=O), 3.20 (t, 2H, -NCH_2-), 3.73 (s, 3H, -OCH_3), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.72-7.01 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
4c	210	80 (230)	---	28 (260)	29 (270)	50 (200)	$C_{16}H_{18}N_2O_4S_2$	366	1.88 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.40 (m, 2H, -CHC=O), 3.20 (t, 2H, -NCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.0 (s, 1H, ArOH), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.68-6.95 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
4d	160	87 (120)	---	22 (180)	31 (190)	55 (310)	$C_{16}H_{17}ClN_2O_3S_2$	384	1.88 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.40 (m, 2H, -CHC=O), 3.20 (t, 2H, -NCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.06-7.22 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
4e	167	90 (150)	---	29 (210)	35 (170)	62 (330)	$C_{16}H_{17}N_3O_5S_2$	395	1.88 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.40 (m, 2H, -CHC=O), 3.20 (t, 2H, -NCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.38-8.14 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
4f	185	91 (170)	---	21 (270)	34 (260)	68 (350)	$C_{17}H_{20}N_2O_3S_2$	264	1.88 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3) 2.40 (m, 2H, -CHC=O), 3.20 (t, 2H, -NCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.00-7.01 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
4g	174	89 (230)	---	26 (280)	33 (250)	60 (210)	$C_{17}H_{20}N_2O_4S_2$	380	1.88 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.40 (m, 2H, -CHC=O), 3.20 (t, 2H, -NCH_2-), 3.73 (s, 3H, -OCH_3), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.72-7.01 (m, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
4h	180	81 (240)	---	27 (260)	29 (280)	63 (240)	$C_{16}H_{18}N_2O_4S_2$	366	1.88 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.40 (m, 2H, -CHC=O), 3.20 (t, 2H, -NCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.00 (s, 1H, ArOH), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.68-6.95 (m, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).

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Table I — Physical and spectral characterization data of compounds **4a-j, 5a-j** and **6a-j**—*Contd*

Compd	m.p. ºC	Yield[a] % (sec)	Yield[b] % (sec)	Yield[c] % (sec)	Yield[d] % (sec)	Yield[e] % (min)	Mol. Formula[f]	M^+ *m/z*	^{1}H NMR (δ, ppm) ($CDCl_3$)
4i	177	83 (130)	---	29 (220)	27 (170)	67 (280)	$C_{16}H_{17}ClN_2O_3S_2$	384	1.88 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.40 (m, 2H, -CHC=O), 3.20 (t, 2H, -NCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.02-7.22 (m, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
4j	163	85 (170)	---	26 (240)	26 (260)	70 (190)	$C_{16}H_{17}N_3O_5S_2$	395	1.88 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.40 (m, 2H, -CHC=O), 3.20 (t, 2H, -NCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.34-8.14 (m, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
5a	232	80 (70)	---	20 (130)	24 (140)	58 (200)	$C_{17}H_{20}N_2O_4S_2$	380	1.84 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.43 (m, 1H, -CH-C-O), 3.20 (t, 2H, -NCH_2-), 3.65 (s, 1H, -OH), 3.82 (d, 2H, -CH_2-O-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.08-7.21 (m, 5H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
5b	214	83 (90)	---	24 (160)	25 (150)	61 (210)	$C_{18}H_{22}N_2O_5S_2$	410	1.84 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.43 (m, 1H, -CH-C-O), 3.20 (t, 2H, -NCH_2-), 3.65 (s, 1H, -OH), 3.73 (s, 3H, -OCH_3), 3.82 (d, 2H, -CH_2-O-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.72-7.01 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
5c	199	80 (100)	---	23 (150)	23 (190)	65 (290)	$C_{17}H_{20}N_2O_5S_2$	396	1.84 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.43 (m, 1H, -CH-C-O), 3.20 (t, 2H, -NCH_2-), 3.65 (s, 1H, -OH), 3.82 (d, 2H, -CH_2-O-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.00 (s, 1H, -OH), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.68-6.95 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
5d	240	78 (60)	---	24 (130)	24 (120)	67 (280)	$C_{17}H_{19}ClN_2O_4S_2$	414	1.84 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.43 (m, 1H, -CH-C-O), 3.20 (t, 2H, -NCH_2-), 3.65 (s, 1H, -OH), 3.82 (d, 2H, -CH_2-O-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.06-7.22 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
5e	205	76 (170)	---	27 (240)	26 (240)	61 (270)	$C_{17}H_{19}N_3O_6S_2$	425	1.84 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.43 (m, 1H, -CH-C-O), 3.20 (t, 2H, -NCH_2-), 3.65 (s, 1H, -OH), 3.82 (d, 2H, -CH_2-O-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.38-8.14 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
5f	218	80 (170)	---	26 (220)	27 (250)	62 (310)	$C_{18}H_{22}N_2O_4S_2$	394	1.84 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.43 (m, 1H, -CH-C-O), 3.20 (t, 2H, -NCH_2-), 3.65 (s, 1H, -OH), 3.82 (d, 2H, -CH_2-O-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, -N-CH), 7.08-7.21 (dd, 5H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).

—*Contd*

Table I — Physical and spectral characterization data of compounds **4a-j, 5a-j** and **6a-j**—*Contd*

Compd	m.p. ºC	Yield[a] % (sec)	Yield[b] % (sec)	Yield[c] % (sec)	Yield[d] % (sec)	Yield[e] % (min)	Mol. Formula[f]	M^+ *m/z*	^{1}H NMR (δ, ppm) ($CDCl_3$)
5g	220	78 (130)	---	25 (240)	29 (260)	68 (340)	$C_{18}H_{22}N_2O_5S_2$	410	1.84 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.43 (m, 1H, -CH-C-O), 3.20 (t, 2H, -NCH_2-), 3.65 (s, 1H, -OH), 3.73 (s, 3H, -OCH_3), 3.82 (d, 2H, -CH_2-O-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.72-7.01 (m, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
5h	225	79 (160)	---	26 (230)	22 (250)	65 (300)	$C_{17}H_{20}N_2O_5S_2$	396	1.84 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.43 (m, 1H, -CH-C-O), 3.20 (t, 2H, -NCH_2-), 3.65 (s, 1H, -OH), 3.82 (d, 2H, -CH_2-O-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.00 (s, 1H, -OH), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.68-6.95 (m, 4H, ArH), 8.00(d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
5i	239	83 (150)	---	29 (270)	21 (230)	63 (280)	$C_{17}H_{19}ClN_2O_4S_2$	414	1.84 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.43 (m, 1H, -CH-C-O), 3.20 (t, 2H, -NCH_2-), 3.65 (s, 1H, -OH), 3.82 (d, 2H, -CH_2-O-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.02-7.22 (m, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
5j	213	76 (180)	---	21 (280)	20 (270)	60 (290)	$C_{17}H_{19}N_3O_6S_2$	425	1.84 (m, 2H -CH_2-), 2.02 (s, 3H, -$COCH_3$), 2.43 (m, 1H, -CH-C-O), 3.20 (t, 2H, -NCH_2-), 3.65 (s, 1H, -OH), 3.82 (d, 2H, -CH_2-O-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.34-8.14 (m, 4H, ArH), 8.00 (d, 1H, -CONH-), 9.72 (t, 1H, -CHO).
6a	231	---	---	---	---	70 (60)	$C_{17}H_{22}N_2O_4S_2$	382	1.51 (m, 2H -CH_2-), 1.65 (m, 1H, -CH-), 2.00 (s, 2H, -OH), 2.02 (s, 3H, -$COCH_3$), 3.20 (t, 2H, -NCH_2-), 3.49 (d, 4H, -OCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.08-7.21 (m, 5H, ArH), 8.00 (d, 1H, -CONH-)
6b	240	---	---	---	---	72 (70)	$C_{18}H_{24}N_2O_5S_2$	412	1.51 (m, 2H -CH_2-), 1.65 (m, 1H, -CH-), 2.00 (s, 2H, -OH), 2.02 (s, 3H, -$COCH_3$), 3.20 (t, 2H, -NCH_2-), 3.49 (d, 4H, -OCH_2-), 3.73 (s, 3H, -OCH_3), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.72-7.01 (dd, 4H, ArH), 8.00(d, 1H, -CONH-)
6c	211	---	---	---	---	77 (110)	$C_{17}H_{22}N_2O_5S_2$	398	1.51 (m, 2H -CH_2-), 1.65 (m, 1H, -CH-), 2.00 (s, 2H, -OH), 2.02 (s, 3H, -$COCH_3$), 3.20 (t, 2H, -NCH_2-), 3.49 (d, 4H, -OCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.00 (s, 1H, ArOH), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.68-6.95 (dd, 4H, ArH), 8.00(d, 1H, -CONH-)
6d	225	---	---	---	---	80 (60)	$C_{17}H_{21}ClN_2O_4S_2$	416	1.51 (m, 2H -CH_2-), 1.65 (m, 1H, -CH-), 2.00 (s, 2H, -OH), 2.02 (s, 3H, -$COCH_3$), 3.20 (t, 2H, -NCH_2-), 3.49 (d, 4H, -OCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.06-7.22 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-)

—*Contd*

Table I — Physical and spectral characterization data of compounds **4a-j, 5a-j** and **6a-j**—*Contd*

Compd	m.p. °C	Yield[a] % (sec)	Yield[b] % (sec)	Yield[c] % (sec)	Yield[d] % (sec)	Yield[e] % (min)	Mol. Formula[f]	M^+ *m/z*	^{1}H NMR (δ, ppm) ($CDCl_3$)
6e	235	---	---	---	---	71 (120)	$C_{17}H_{21}N_3O_6S_2$	427	1.51 (m, 2H -CH_2-), 1.65 (m, 1H, -CH-), 2.00 (s, 2H, -OH), 2.02 (s, 3H, -$COCH_3$), 3.20 (t, 2H, -NCH_2-), 3.49 (d, 4H, -OCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.38-8.14 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-)
6f	239	---	---	---	---	73 (80)	$C_{18}H_{24}N_2O_4S_2$	396	1.51 (m, 2H -CH_2-), 1.65 (m, 1H, -CH-), 2.00 (s, 2H, -OH), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3) 3.20 (t, 2H, -NCH_2-), 3.49 (d, 4H, -OCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.00-7.01 (dd, 4H, ArH), 8.00 (d, 1H, -CONH-)
6g	220	---	---	---	---	72 (110)	$C_{18}H_{24}N_2O_5S_2$	412	1.51 (m, 2H -CH_2-), 1.65 (m, 1H, -CH-), 2.00 (s, 2H, -OH), 2.02 (s, 3H, -$COCH_3$), 3.20 (t, 2H, -NCH_2-), 3.49 (d, 4H, -OCH_2-), 3.73 (s, 3H, -OCH_3), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.72-7.01 (m, 4H, ArH), 8.00 (d, 1H, -CONH-)
6h	230	---	---	---	---	70 (120)	$C_{17}H_{22}N_2O_5S_2$	398	1.51 (m, 2H -CH_2-), 1.65 (m, 1H, -CH-), 2.00 (s, 2H, -OH), 2.02 (s, 3H, -$COCH_3$), 3.20 (t, 2H, -NCH_2-), 3.49 (d, 4H, -OCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.00 (s, 1H, ArOH), 5.19 (d, 1H, *J*=7.0, -N-CH), 6.68-6.95 (m, 4H, ArH), 8.00 (d, 1H, -CONH-)
6i	236	---	---	---	---	75 (90)	$C_{17}H_{21}ClN_2O_4S_2$	416	1.51 (m, 2H -CH_2-), 1.65 (m, 1H, -CH-), 2.00 (s, 2H, -OH), 2.02 (s, 3H, -$COCH_3$), 3.20 (t, 2H, -NCH_2-), 3.49 (d, 4H, -OCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.02-7.22 (m, 4H, ArH), 8.00 (d, 1H, -CONH-)
6j	245	---	---	---	---	72 (120)	$C_{17}H_{21}N_3O_6S_2$		1.51 (m, 2H -CH_2-), 1.65 (m, 1H, -CH-), 2.00 (s, 2H, -OH), 2.02 (s, 3H, -$COCH_3$), 3.20 (t, 2H, -NCH_2-), 3.49 (d, 4H, -OCH_2-), 4.66 (d, 1H, *J*=7.0, S-CH-Ar), 5.19 (d, 1H, *J*=7.0, -N-CH), 7.38-8.14 (m, 4H, ArH), 8.00 (d, 1H, -CONH-)

[a]MWI isolated yield with montmorillonite K10 clay,
[b]MWI isolated yield with basic alumina,
[c]MWI isolated yield with neutral alumina,
[d]MWI isolated yield with silica gel,
[e]Thermal yield for the corresponding stepwise process,
[f]Satisfactory elemental microanalysis obtained C±0.1, H±0.2, N±0.3

The reaction-mixture was refluxed on thermostated water-bath for specified time (**Table I**). Et_2O (30 mL), H_2O (30 mL) were added to the reaction-mixture. The organic layer was separated and dried over anhydrous $MgSO_4$. The product was purified by flash chromatography using petroleum ether:ethyl acetate (10:1 v/v) to furnished analytically pure **5a-j**.

Method B (Microwave Irradiation). $BF_3{\cdot}Et_2O$ (0.4 mmole), *N*-[4-oxo-3-(4-oxo-butyl)-6-phenyl-2-thioxo-[1,3]thiazinan-5-yl]-acetamide **4a-j** (10 mmole) and HCHO (10 mmole) were dissolved in 20 mL Et_2O at RT. Montmorillonite K 10 clay was impregnated as solid support, so that reagents were adsorbed on the surface or in porous portion of the solid support.

Excess of Et_2O was evaporated and the reaction-mixture was taken in 100 mL pyrex conical flask capped with a funnel and subjected to microwave irradiation at 600 W for the specified time (**Table I**). The completion of the reaction was checked by TLC (silica gel). The reaction-mixture was cooled to RT and eluted with Et_2O (3 × 10 mL). The elute was washed with $NaHCO_3$ and evaporated to dryness. The residue on purification by flash chromatography using petroleum ether:ethyl acetate (10:1 v/v) to furnished analytically pure **5a-j**.

Similar procedures were used with other solid supports *viz*. silica gel, neutral or basic alumina.

***N*-[3-(4-Hydroxy-3-hydroxymethyl-butyl)-4-oxo-6-phenyl-2-thioxo[1,3]thiazinan-5-yl]-acetamide 6a-j**. *N*-[3-(3-Hydroxymethyl-4-oxo-butyl)-4-oxo-6-phenyl-2-thioxo-[1,3] thiazinan-5-yl]-acetamide **5a-j** (0.25 mmole) and 2.0 mL ethanol (95%) were taken in a 25 mL Erlenmeyer flask, and the solution cooled in an ice-bath till the temperature reached to 0-5°C. $NaBH_4$ (0.10 g) was added to the reaction-mixture cautiously with constant stirring for 10 min at RT. After the time specified (**Table I**), 4.0 mL of water and 2 mL of ether were added to the reaction-mixture to quench the reaction. The reaction flask was swirled to allow more effective mixing and the entire mixture was transferred to a large test tube and the organic and aqueous layers were allowed to separate. The aqueous layer was removed and discarded. The organic layer was washed carefully with 1.0 mL of 10% aqueous HCl to destroy any excess $NaBH_4$. Again the aqueous layer was discarded and the organic layer was washed with 1.0 mL of brine. The organic layer was then transferred to a clean centrifuge tube with the aid of a Pasteur pipette and then dried over anhydrous $MgSO_4$ for 5 min. The product was separated by chromatography over silica gel using petroleum ether:ethyl acetate (10:1 v/v) as an eluent to furnish analytically pure **6a-j**.

Conclusion

In conclusion, a novel solid supported, green, facile, high yielding, synthetic protocol has been developed for preparation of pharmaceutically useful *N*-[3-(4-hydroxy-3-hydroxymethyl-butyl)-4-oxo-6-phenyl-2-thioxo-[1,3]thiazinan-5-yl]acetamide, **6a-j** (**Scheme I**), starting from readily available, simple substrates under solvent-free conditions. This expeditious chemical transformation led to synthetically readily manipulable products and may find application in library synthesis of such aglycon modified *N*-nucleosides.

There are a number of processes in which toxic intermediates are inevitably generated, hazardous solvents are used and longer duration of reactions are involved. Accordingly, the concept disclosed here will find diverse applications in all such as well as other related processes.

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