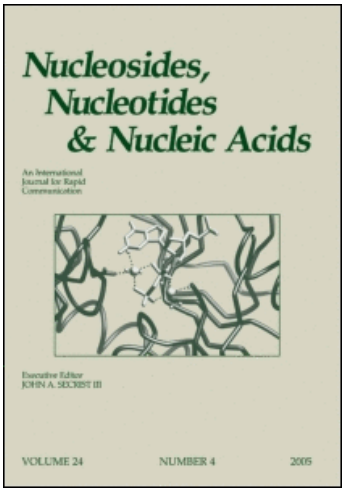

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Mineral Supported Facile Synthesis of Novel 4-Hydroxybenzoxazin-2-Thione *N*-Nucleosides

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MINERAL SUPPORTED FACILE SYNTHESIS OF NOVEL 4-HYDROXYBENZOXAZIN-2-THIONE *N*-NUCLEOSIDES

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□ *One-pot montmorillonite K-10 clay-supported reactions of substituted/unsubstituted salicylaldehyde and ribosyl/deoxyribosyl thioureas expeditiously yielded novel N-nucleosides, 4-hydroxy-3,4-dihydro-3-(β-D-ribofuranosyl or β-D-2′-deoxyribofuranosyl)-2″-benz[e]-1,3-oxazin-2-thione via cycloisomerization of aldehyde intermediate under solvent-free microwave irradiation conditions.*

Keywords One-pot; substituted salicylaldehyde; mineral-supported; microwaves; solvent-free; benzoxazin-2-thione *N*-nucleosides

INTRODUCTION

Benz[1,3]oxazine have gained recognition as they exhibit a multitude of interesting pharmacological activities viz. antibacterial, antiviral, antihelminthes, antitubercular, etc. Efavirenz (Sustiva), a benzoxazinone derivative, is a nonnucleoside reverse transcriptase inhibitor that has been approved by the U.S. Food and Drug Administration (FDA; September 17, 1998) and is presently in clinical use for the treatment of AIDS. Consequently, various benzoxazinones have been synthesized and evaluated with a view of developing more efficacious drugs than Efavirenz.[1–4] The fact that sulphur analogues of oxygen compounds display, in most cases, better biological effects is well documented.[5] Notably, most available drugs approved by FDA to treat AIDS and other viral diseases are nucleoside analogues. However, no effort has been made so far to synthesize nucleoside analogues incorporating the benzoxazinthione unit as a nucleobase, and

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therefore they appear to be attractive scaffolds to provide a chemical diverse drug-like library.

Recent years have witnessed a phenomenal growth in the application of microwave (MW) irradiation and recyclable less expensive mineral supports for organic transformations.[6–9] The application of MW irradiation in conjugation with the use of mineral supported reagents under solvent-free conditions provides an environmentally benign process with additional advantages such as enhanced reaction rates, higher yields of pure products, easier workup and considerable reduction in reaction time, all of which are eco-friendly attributes in the context of green chemistry.[10–18] Due to growing awareness about environmental legislation and environmental pollution, the development of this protocol, thus, should be welcome.

Prompted by the above reports and as a part of our research program for development of an eco-friendly synthetic protocol for pharmacologically active compounds,[19–23] we devised an original montmorillonite K-10 clay catalyzed MW activated synthesis of some hitherto unknown 4-hydroxybenzoxazin-2-thione *N*-nucleosides **3a–j** via the cycloisomerization of aldehyde intermediate **II** under solvent-free microwave irradiation conditions.

RESULTS AND DISCUSSION

This is the first example of the synthesis of 4-hydroxybenzoxazin-2-thione *N*-nucleosides. The key element in our approach is the novel utilization of salicylaldehyde as a bifunctional building block, a well documented application to the construction of various benzofused oxygen heterocycles of chemical and biological interest.[24,25]

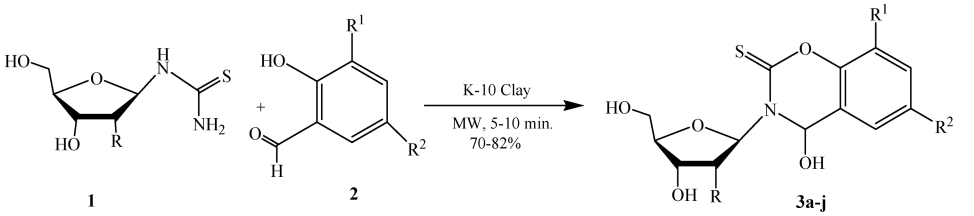
After some preliminary experimentation, it was found that the synthesis of **3a–j** can be effected starting from either salicylaldehyde **2** and ribosyl/deoxyribosyl thiourea **1** or salicylaldehyde and ribosyl/deoxyribosyl isothiocyanates. Since isothiocyanates are highly toxic, corrosive, hygroscopic, and demand special care in handling, and since the same yield is obtained, by either route, we preferred the route utilizing ribosyl/deoxyribosyl thioureas.

The present synthesis in its entirety involves intermittent irradiation of a mixture of reactants **1** and **2** and montmorillonite K-10 clay for 2 minutes in an MW oven at 600 W (Scheme 1) followed by thorough mixing for 2 minutes outside the oven. This intermittent irradiation mixing cycle was repeated for the total irradiation time specified in Table 1 to afford 4-hydroxybenzoxazin-2-thione *N*-nucleosides **3a–j** in 71–82% yields. 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 **3** (in the case of silica

TABLE 1 Mineral supported solvent-free synthesis of 4-hydroxybenzoxazin-2-thione *N*-nucleoside

	Time		Yield (%)		
Product	MW (minutes)	Thermal (hours)	MW	Thermal	m.p.(°C)
3a	7	4	72	34	136–137
3b	10	5	82	40	160–161
3c	5	4	78	37	145–146
3d	7	4	75	35	142–143
3e	6	5	77	38	149–150
3f	8	5	71	35	125–126
3g	8	5	72	37	140–141
3h	9	4	76	40	130–131
3i	8	5	70	36	127–128
3j	10	4	78	40	138–139

gel and neutral alumina). Moreover, the reactions did not take place if they were performed using the microwave without the montmorillonite K-10, either neat or in an organic solvent. This synthesis involves the conversion of ribosyl/deoxyribosyl thiourea **1** into corresponding isothiocyanate intermediate **I** (Scheme 2) was supported by trapping their *p*-tolylthiourea derivatives. When *p*-toluidine was added during the progress of reaction *p*-tolylthiourea derivatives along with **3a–j** were isolated. Isolation of the *p*-tolylthiourea derivatives clearly indicates the involvement of ribofuranosyl/deoxyribofuranosylisothiocyanate intermediate **I**. Formation of *p*-tolylthiourea derivatives was confirmed by routine characterization method.

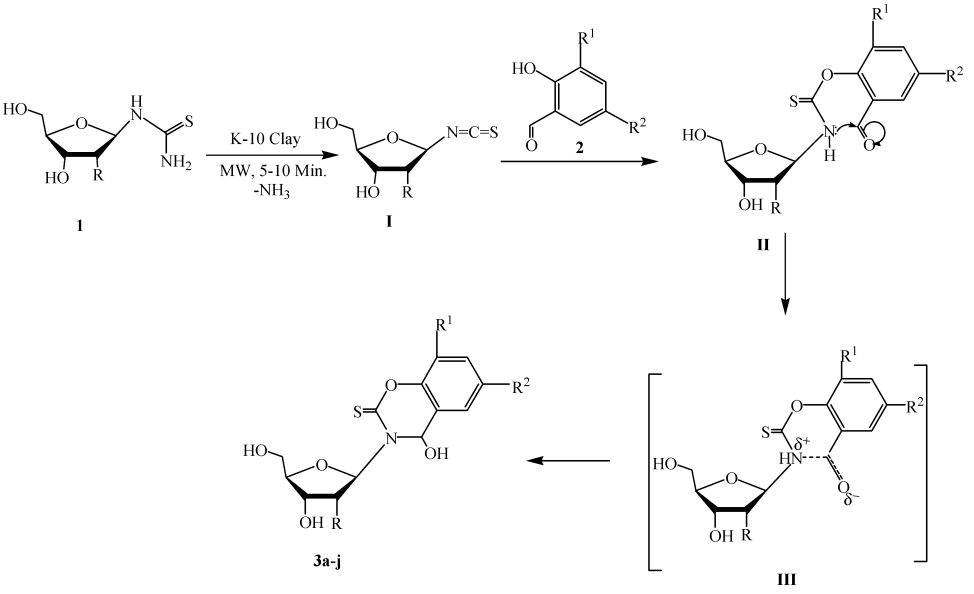


1a R= OH

1b R= H

2/3	**R**	**R^1**	**R^2**	**2/3**	**R**	**R^1**	**R^2**
a	OH	H	H	**f**	H	H	H
b	OH	H	Br	**g**	H	H	Br
c	OH	H	Cl	**h**	H	H	Cl
d	OH	OMe	H	**i**	H	OMe	H
e	OH	H	NO_2	**j**	H	H	NO_2

SCHEME 1 Mineral supported synthesis of 4-hydroxybenzoxazin-2-thione *N*-nucleosides.



SCHEME 2 Mechanism for the synthesis of 4-hydroxybenzoazin-2-thione *N*-nucleosides.

For comparison purposes, the final temperature was recorded and found to be <90°C. The reactions were also carried using a thermostated oil-bath at the same temperature (90°C) as for the MW-activated method for a longer (optimized) period of time (Table 1) 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 (Table 1). This observation can be rationalized on the basis of the formation of a dipolar activated complex **III** from an uncharged adduct in these reactions (Scheme 2) and the greater stabilization of the more dipolar activated complex by dipole-dipole interactions with the electromagnetic field of the microwaves (as compared to a actual dipolar adduct), which may reduce the activation energy ($G^{\#}$) resulting in the rate enhancement.

The structures of **3a–j** were confirmed by spectral and elemental analysis. Spectra of all the synthesized compounds showed close similarity with the spectral data for 4-substituted benz[1,3]oxazin *N*-nucleoside. ^{1}H NMR spectra of **3a–j** showed similar patterns in which their respective H-4's appeared as doublets in the δ 6.70–6.78 region with J's = 8 Hz whereas aromatic protons H-5, H-6, H-7, and H-8 appeared as doublets, doublets of doublets in the δ 7.30–8.25 region with high coupling constants of 9.0 Hz and 2.4 Hz, respectively. A broad singlet at δ 3.07–3.15, (exchangeable with D_2O) was attributed to the –OH group at C-4. Similarly, multiplets in the δ 4.09–4.67 region due to H-2′, H-3′, H-4′ and H-5′, as well as a doublet at δ 6.02–6.03 with $J_{1',2'}$ 4.2 Hz due to H-1′ and a broad singlet

at δ 6.40–6.46 (exchangeable with D_2O) due to three/two –OH groups were indicative of presence of β-D-ribo/deoxyribofuranosyl moiety in **3a–j**. In ^{13}CNMR, spectra signals in the δ 108–165 region for aromatic carbon and at δ 165–175 for $>C^{=S}$ supported that all synthesized compounds have 4-substituted benzoxazin-2-thione *N*-nucleosidic character.

In conclusion, we have developed a novel mineral supported, green, facile, high yielding synthetic protocol for preparation of potentially pharmaceutically useful 4-hydroxybenzoxazin-2-thione *N*-nucleosides starting from readily available, simple substrates under solvent-free MW irradiation conditions. This expeditious chemical transformations led to synthetically readily, manipulable product and may find application in library synthesis of such aglycon modified *N*-nucleosides.

EXPERIMENTAL

General Procedure

Melting points were determined on to an open glass capillary method and are uncorrected. All chemicals used were reagent grade and were used as received without further purification. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz on a Bruker AVANCE DPX FT spectrometer in DMSO-d_6 using TMS as an internal reference. Mass spectra were recorded on a JEOL SX-102 (FAB) mass spectrometer at 70eV. A laboratory microwave oven (Model BP 310/50) operating at 2450 MHz and power out put of 600 W was used for all the experiments. Elemental analysis were carried out using a Coleman automatic C, H and N analyzer. The progress of the reaction was monitored by TLC (Merck Silica gel). All compounds were crystallized from ethanol.

General Procedure for Synthesis of Ribofuranosyl/Deoxyribofuranosylthiourea

1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose/1,3,5-tri-*O*-acetyl-β-D-2′-deoxyribofuranose on treatment with red P and Br_2 followed by AgSCN with standard procedure[26,27] to gave 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl/3,5-di-*O*-acetyl-β-D-2′-deoxyribofuranosylisocyanate.[26,27] Isocyanates on reaction with liquid ammonia (2 ml) in benzene at 20°C for 1 hour, gave crude thiourea derivatives. The thiourea derivatives chromatographed on a 1.5-×-15 cm column with $CHCl_3$-MeOH (40:1) to gave corresponding thiourea as colorless oil, which upon drying on vaccum gave pure solid 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl/3,5-di-*O*-acetyl-β-D-2′-deoxyribofuranosyl thiourea. Deacetylation with methanolic MeONa followed by acidification with HCl gave corresponding thiourea derivatives.

*General Procedure for Synthesis of 4-Hydroxybenzoxazin-2-thione N-nucleosides (**3a–j**).* To a solution of ribosyl/deoxyribosyl thiourea **1** (5.0 mmol) and salicylaldehyde **2** (5.0 mmol) in dichloromethane (10 mL) was added

montmorillonite K-10 clay (0.50 g) with thorough mixing and the solvent then evaporated under reduced pressure. The contents were taken in a 20 mL vial and subjected to microwave irradiation for 2 minutes at 600 W. The reaction mixture was thoroughly mixed outside the microwave oven for 2 minutes and again irradiated for another 2 minutes. This irradiation-mixing cycle was repeated for the total irradiation time (Table 1). After the completion of the reaction as indicated by TLC (Hexane: AcOEt, 8:2, v/v), the product was extracted with dichloromethane (3 × 50 mL), the extract was filtered, and the filtrate was evaporated under reduced pressure to leave the crude product, which was recrystallized from ethanol to give an analytically pure **3a–j** as light yellow needles.

*3-(β-D-Ribofuranosyl)-3,4-dihydro-4-hydroxy-2*H*-benz[e]-1,3-oxazin-2-thione(**3a**).* Yield: 72% (MW), 34% (Thermal); m.p. 136–137°C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.07 (br, s, 1H, −OH-4, exchangeable with D_2O), 4.09–4.15 (m, 1H, H-4′), 4.21–4.25 (m, 3H, H-2′, −CH_2–5′), 4.64–4.67 (m, 1H, H-3′), 6.03 (d, 1H, $J_{1',2'} = 4.2$ Hz, H-1′), 6.40–6.46 (br, s, 3H, 3x OH, exchangeable with D_2O), 6.78 (d, 1H, $J_{4,OH} = 8.0$ Hz, H-4), 7.31 (d, 1H, $J_{7,8} = 9.0$ Hz, H-8), 7.91 (dd, 2H, $J_{6,7} = 9.0$ Hz, $J_{8,6} = 2.4$ Hz, H-6, H-7), 8.23 (d, 1H, $J_{5,6} = 9.0$ Hz, H-5). ^{13}C NMR (100 MHz, DMSO-d_6): δ 61.9, 70.0, 71.7, 74.8, 75.7, 76.1, 115.5, 120.9, 124.4, 128.2, 129.5, 145.0, 156.9. Anal. calcd for $C_{13}H_{15}NO_6S$ (313.33): C, 49.83; H, 4.83; N, 4.47; S, 10.23. Found: C, 49.80; H, 4.81; N, 4.45; S, 10.20. MS (FAB) *m/z*: 313 $(M+H)^+$.

*3-(β-D-Ribofuranosyl)-6-bromo-3,4-dihydro-4-hydroxy-2*H*-benz[e]-1,3-oxazin-2-thione(**3b**).* Yield: 82% (MW), 40% (Thermal); m.p. 160–161°C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.08 (br, s, 1H, -OH-4, exchangeable with D_2O), 4.09–4.15 (m, 1H, H-4′), 4.21–4.25 (m, 3H, H-2′, -CH_2–5′), 4.64–4.67 (m, 1H, H-3′), 6.03 (d, 1H, $J_{1',2'} = 4.2$ Hz, H-1′), 6.40–6.46(br, s, 3H, 3x OH, exchangeable with D_2O), 6.78 (d, 1H, $J_{4,OH} = 8.0$ Hz, H-4), 7.25 (d, 1H, $J_{7,8} = 9.0$ Hz, H-8), 7.96 (dd, 1H, $J_{7,8} = 9.0$ Hz, $J_{5,7} = 2.4$ Hz, H-7), 8.27 (d, 1H, $J_{5,7} = 2.4$ Hz, H-5). ^{13}C NMR (100 MHz, DMSO-d_6): δ 61.9, 70.0, 71.0, 74.8, 75.7, 76.1, 115.5, 117.7, 126.6, 131.5, 132.8 145.0, 155.9. Anal. calcd for $C_{13}H_{14}$ $BrNO_6S$ (392.22): C, 39.81; H, 3.60; N, 3.57; S, 8.18. Found: C, 39.78; H, 3.58; N, 3.55; S, 8.16. MS (FAB) *m/z*: 392 $(M+H)^+$.

*3-(β-D-Ribofuranosyl)-6-chloro-3,4-dihydro-4-hydroxy-2H-benz[e]-1,3-oxazin-2-thione(**3c**).* Yield: 78% (MW), 37% (Thermal); m.p. 145–146°C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.09 (br, s, 1H, -OH-4, exchangeable with D_2O), 4.09–4.15 (m, 1H, H-4′), 4.21–4.25 (m, 3H, H-2′, -CH_2–5′), 4.64–4.67 (m, 1H, H-3′), 6.03 (d, 1H, $J_{1',2'} = 4.2$ Hz, H-1′), 6.40–6.46 (br, s, 3H, 3x OH, exchangeable with D_2O), 6.78 (d, 1H, $J_{4,OH} = 8.0$ Hz, H-4), 7.26 (d, 1H, $J_{7,8} = 9.0$ Hz, H-8), 7.94 (dd, 1H, $J_{7,8} = 9.0$ Hz, $J_{5,7} = 2.4$ Hz, H-7), 8.25 (d, 1H, $J_{5,7} = 2.4$ Hz, H-5). ^{13}C NMR (100 MHz, DMSO-d_6): δ 61.9, 70.0, 71.2, 74.8, 75.7, 76.1, 116.9, 125.8, 126.2, 128.6, 129.9, 145.0, 155.0. Anal. calcd for $C_{13}H_{14}ClNO_6S$ (347.77): C, 44.90; H, 4.06; N, 4.03; S, 9.22. Found: C, 44.88; H, 4.04; N, 4.01; S, 9.20. MS (FAB) *m/z*: 347 $(M+H)^+$.

*3-(β-D-Ribofuranosyl)-3,4-dihydro-4-hydroxy-8-methoxy-2*H*-benz[e]-1,3-oxazin-2-thione(**3d**).* Yield: 75% (MW), 33% (Thermal); m.p. 142–143°C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.07 (br, s, 1H, -OH-4, exchangeable with D_2O), 4.09–4.15 (m, 1H, H-4′), 4.21–4.25 (m, 3H, H-2′, -CH_2–5′), 4.64–4.67 (m, 1H, H-3′), 6.03 (d, 1H, $J_{1',2'}$ = 4.2 Hz, H-1′), 6.40–6.46(br, s, 3H, 3x OH, exchangeable with D_2O), 6.76(d, 1H, $J_{4,OH}$ = 8.0 Hz, H-4), 3.73(s, 3H, -OCH_3), 7.24–8.25(m, 3H, H-7, H-6, H-5). ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.3, 61.9, 70.0, 72.0, 74.8, 75.7, 76.1, 113.8, 121.8, 121.9, 125.4, 142.5, 145.0, 149.0. Anal. calcd for $C_{14}H_{17}NO_7S$ (343.35): C, 48.97; H, 4.99; N, 4.08; S, 9.34. Found: C, 48.95; H, 4.96; N, 4.06; S, 9.32. MS (FAB) *m/z*: 343 $(M+H)^+$.

*3-(β-D-Ribofuranosyl)-3,4-dihydro-4-hydroxy-6-nitro-2*H*-benz[e]-1,3-oxazin-2-thione(**3e**).* Yield: 77% (MW), 38% (Thermal); m.p. 149–150°C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.07 (br, s, 1H, -OH-4, exchangeable with D_2O), 4.09–4.15 (m, 1H, H-4′), 4.21–4.25 (m, 3H, H-2′, -CH_2–5′), 4.64–4.67 (m, 1H, H-3′), 6.03 (d, 1H, $J_{1',2'}$ = 4.2 Hz, H-1′), 6.46–6.47(br, s, 3H, 3x OH, exchangeable with D_2O), 6.78 (d, 1H, $J_{4,OH}$ = 8.0 Hz, H-4), 7.32 (d, 1H, $J_{7,8}$ = 9.0 Hz, H-8), 7.96 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{5,7}$ = 2.4 Hz, H-7), 8.28 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5); ^{13}C NMR (100 MHz, DMSO-d_6): δ 61.9, 70.0, 70.7, 74.8, 75.7, 76.1, 116.4, 123.3, 124.6, 125.3, 140.8, 145.0, 163.0. Anal. calcd for $C_{13}H_{14}N_2O_8S$ (358.32): C, 43.57; H, 3.94; N, 7.82; S, 8.95. Found: C, 43.55; H, 3.92; N, 7.80; S, 8.93. MS (FAB) *m/z*: 358 $(M+H)^+$.

*3-(β-D-2-Deoxyribofuranosyl)-3,4-dihydro-4-hydroxy-2*H*-benz[e]-1,3-oxazin-2-thione(**3f**).* Yield: 71% (MW), 35% (Thermal); m.p. 125–126°C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.09 (br, s, 1H, -OH-4, exchangeable with D_2O), 2.31–2.35 (m, 2H, H-2′), 3.98–4.33 (m, 4H, H-3′, H-4′, -CH_2–5′), 6.17 (t,1H, $J_{1',2'}$ = 6.3 Hz, H-1′), 6.42–6.48 (br s, 2H, 2x OH, exchangeable with D_2O), 6.74 (d,1H, $J_{4,OH}$ = 8.2 Hz, H-4), 7.32 (d, 1H, $J_{7,8}$ = 9.0 Hz, H-8), 7.91 (dd, 2H, $J_{6,7}$ = 9.0 Hz, $J_{8,6}$ = 2.4 Hz, H-6, H-7), 8.25 (d, 1H, $J_{5,6}$ = 9.0 Hz, H-5); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.6, 60.4, 64.5, 78.9, 82.5, 85.5, 108.8, 123.0, 127.9, 129.0, 130.3, 150.3, 165.0, 170.0. Anal. calcd for $C_{13}H_{15}NO_5S$ (297.33): C, 52.51; H, 5.09; N, 4.71; S, 10.78. Found: C, 52.50; H, 5.06; N, 4.75; S, 10.76. MS (FAB) *m/z*: 297 $(M+H)^+$.

*3-(β-D-2-Deoxyribofuranosyl)-6-bromo-3,4-dihydro-4-hydroxy-2*H*-benz[e]-1,3-oxazin-2-thione(**3g**).* Yield: 72% (MW), 37% (Thermal); m.p. 140–141°C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.08 (br, s, 1H, -OH-4, exchangeable with D_2O), 2.31–2.35 (m, 2H, H-2′), 3.98–4.33 (m, 4H, H-3′, H-4′, -CH_2–5′), 6.17 (t,1H, $J_{1',2'}$ = 6.3 Hz, H-1′), 6.42–6.48 (br s, 2H, 2x OH, exchangeable with D_2O), 6.74 (d,1H, $J_{4,OH}$ = 8.2 Hz, H-4), 7.32 (d, 1H, $J_{7,8}$ = 9.0 Hz, H-8), 7.93 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{5,7}$ = 2.4 Hz, H-7), 8.26 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.6, 60.4, 64.5, 78.9, 82.5, 85.5, 122.8, 128.1, 129.5, 130.6, 150.2, 166.1, 172.9. Anal. calcd for $C_{13}H_{14}BrNO_5S$ (376.22): C, 41.50; H, 3.75; N, 3.72; S, 8.52. Found: C, 41.46; H, 3.73; N, 3.70; S, 8.50. MS (FAB) *m/z*: 374 $(M+H)^+$.

*3-(β-D-2-Deoxyribofuranosyl)-6-chloro-3,4-dihydro-4-hydroxy-2*H*-benz[e]-1,3-oxazin-2-thione(**3h**).* Yield: 76% (MW), 40% (Thermal); m.p. 130–131°C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.08 (br, s, 1H, -OH-4, exchangeable with D_2O), 2.31–2.35 (m, 2H, H-2′), 3.98–4.33 (m, 4H, H-3′, H-4′, -CH_2–5′), 6.17 (t,1H, $J_{1',2'} = 6.3$ Hz, H-1′), 6.42–6.48 (br s, 2H, 2x OH, exchangeable with D_2O), 6.74 (d,1H, $J_{4,OH} = 8.2$ Hz, H-4), 7.34 (d, 1H, $J_{7,8} = 9.0$ Hz, H-8), 7.95 (dd, 1H, $J_{7,8} = 9.0$ Hz, $J_{5,7} = 2.4$ Hz, H-7), 8.25 (d, 1H, $J_{5,7} = 2.4$ Hz, H-5); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.6, 60.4, 64.5, 78.9, 82.5, 85.5, 121.8, 127.8, 129.0, 130.1, 150.0, 165.4, 171.9. Anal. calcd for $C_{13}H_{14}ClNO_5S$ (331.77): C, 47.06; H, 4.25; N, 4.22; S, 9.66. Found: C, 47.02; H, 4.23; N, 4.18; S, 9.60. MS (FAB) *m/z*: 331 $(M+H)^+$.

*3-(β-D-2-Deoxyribofuranosyl)-3,4-dihydro-4-hydroxy-8-methoxy-2*H*-benz[e]-1,3-oxazin-2-thione(**3i**).* Yield: 70% (MW), 36% (Thermal); m.p. 127–128°C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.08 (br, s, 1H, -OH-4, exchangeable with D_2O), 2.31–2.35 (m, 2H, H-2′), 3.98–4.33 (m, 4H, H-3′, H-4′, -CH_2–5′), 6.17 (t, 1H, $J_{1',2'} = 6.3$ Hz, H-1′), 6.42–6.48 (br s, 2H, 2x OH, exchangeable with D_2O), 3.73 (s, 3H, -OCH_3), 7.24–8.25(m, 3H, H-7, H-6, H-5); ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.6, 56.3, 60.4, 64.5, 78.9, 82.5, 85.5, 113.8, 121.8, 125.0, 129.5, 149.0, 150.6, 170.0. Anal. calcd for $C_{14}H_{17}NO_6S$ (327.35): C, 51.37; H, 5.23; N, 4.28; S, 9.80. Found: C, 51.35; H, 5.20; N, 4.26; S, 9.76. MS (FAB) *m/z*: 327 $(M+H)^+$.

*3-(β-D-2-Deoxyribofuranosyl)-3,4-dihydro-4-hydroxy-6-nitro-2*H*-benz[e]-1,3-oxazin-2-thione(**3j**).* Yield: 78% (MW), 40% (Thermal); m.p. 138–139°C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.07 (br, s, 1H, -OH-4, exchangeable with D_2O), 2.31–2.35 (m, 2H, H-2′), 3.98–4.33 (m, 4H, H-3′, H-4′, -CH_2–5′), 6.17 (t, 1H, $J_{1',2'} = 6.3$ Hz, H-1′), 6.42–6.48 (br s, 2H, 2x OH, exchangeable with D_2O), 6.78 (d,1H, $J_{4,OH} = 8.2$ Hz, H-4), 7.32 (d, 1H, $J_{7,8} = 9.0$ Hz, H-8), 7.96 (dd, 1H, $J_{7,8} = 9.0$ Hz, $J_{5,7} = 2.4$ Hz, H-7), 8.28 (d, 1H, $J_{5,7} = 2.4$ Hz, H-5); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.6, 60.4, 64.5, 78.9, 82.5, 85.5, 116.3, 123.3, 124.6, 125.3, 140.8, 164.0, 176.0. Anal. calcd for $C_{13}H_{14}N_2O_7S$ (342.32): C, 45.61; H, 4.12; N, 8.18; S, 9.37. Found: C, 45.60; H, 4.10; N, 8.14; S, 9.35. MS (FAB) *m/z*: 342 $(M+H)^+$.

REFERENCES

1. Patel, M.; Ko, S.S.; McHugh, R.J., Jr, Markwalder, J.A.; Srivastava, A.S.; Cordova, B.C.; Klabe, R.M.; Erickson-Viitanen, S.; Trainor, G.L.; Seitz, S.P. Synthesis and evaluation of analogs of Efavirenz (SUSTIVA) as HIV-1 reverse transcriptase inhibitors. *Bioorg. Med. Chem. Lett.* **1999**, 9, 2805–2810.
2. Patel, M.; McHugh, R.J., Jr, Cordova, B.C.; Klabe, R.M.; Erickson-Viitanen, S.; Trainor, G.L.; Ko, S.S. Synthesis and evaluation of benzoxazinones as HIV-1 reverse transcriptase inhibitors. Analogs of Efavirenz (SUSTIVA). *Bioorg. Med. Chem. Lett.* **1999**, 9, 3221–3224.
3. Waxman, L.; Darke, P.L. The herpesvirus proteases as targets for antiviral chemotherapy. *Antivir. Chem. Chemother*, **2000**, 11, 1–22.
4. Klasek, A.; Koristek, K.; Polis, J.; Kosmrlj, J. Synthesis of novel 3-acyloxy-1,3-dihydro-2H-indol-2-ones and isomeric 4-acyl-1,4-dihydro-3,1-benzoxazin-2-ones: Double Rearrangement of 3-Hydroxyquinoline-2,4(1H,3H)-diones. *Tetrahedron* **2000**, 56, 1551–1560.

5. Hutchinson, D.W.; Masson, S. The antiviral potential of compounds containing the thiophosphoryl group. *I. R. C. S. Med. Sc.* **1986**, 14, 176–177.
6. McGee, D.P.C.; Martin, J.C.; Smee, D.F.; Verheyden, J.P.H. Synthesis and antiviral activity of the 3-deaza analogue of 9-[(1,3-dihydroxy-2-propoxy)methyl]-guanine. *Nucleosides Nucleotides* **1990**, 9, 815–826.
7. Ugi, I.; Domling, A. Multi-component reactions in organic chemistry. *Endeavour* **1994**, 18, 115–122.
8. Heck, S.; Domling, A. A versatile multi-component one-pot thiazole synthesis. *Synlett* **2000**, 424–426.
9. Kraus, G.A.; Nagy, J.O. The synthesis of amino acids by 1,3-dipolar cycloaddition of azomethine ylides. *Tetrahedron* **1985**, 41, 3537–3545.
10. Zeigler, T.; Kaisers, H.J.; Schlomer, R.; Koch, C. Passerini and Ugi reactions of benzyl and acetyl protected isocyanoglucoses. *Tetrahedron* **1999**, 55, 8397–8408.
11. Caddick, S. Microwave assisted organic reactions. *Tetrahedron* **1995**, 51, 10403–10432.
12. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. New solvent-free organic synthesis using focused microwaves. *Synthesis* **1998**, 1213–1234.
13. Varma, R.S.; Vass, A.; Dudas, J.; Solvent-free synthesis of *N*-sulfonylimines using microwave irradiation. *Tetrahedron Lett.* **1999**, 40, 4951–4954.
14. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. Microwave assisted organic synthesis—A review. *Tetrahedron* **2001**, 57, 9225–9283.
15. Perreux, L.; Loupy, A. A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic considerations. *Tetrahedron* **2001**, 57, 9199–9223.
16. Yadav, L.D.S.; Kapoor, R. *J. Org.Chem.* **2004**, 69, 8118–8120.
17. Chisem, J.; Chisem, I.C.; Rafelt, J.S.; Macquarrie, D.J.; Clark, J.H. Liquid phase oxidations using novel surface functionalised silica supported metal catalysts. *Chem. Commun.* **1997**, 2203–2204.
18. Meshram, H.M.; Sekhar, K.C.; Ganesh, Y.S.S.; Yadav, J.S. Clay catalyzed facile cyclodehydration under microwave: synthesis of 3-substituted benzofurans. *Synlett* **2000**, 1273–1275.
19. Siddiqui, I.R.; Singh, P.K.; Singh, J.; Singh, J. Synthesis and fungicidal activity of novel 4,4′-bis(2″-aryl-5″-methyl/unsubstituted-4″-oxo-thiazolidin-3″-yl) bibenzyl. *J. Agri. Food Chem.* **2003**, 51, 7062–7065.
20. Siddiqui, I.R.; Singh, P.K.; Singh, J.; Singh, J. Three-component solvent-free diastereoselective formation of oxo-thiazolidinylthiazoles under microwave irradiation. *J. Chem. Res.* **2004**, 8, 554–555.
21. Siddiqui, I.R.; Singh, P.K.; Singh, J.; Singh, J. Facile synthesis and fungicidal activity of novel 4,4′-bis[2″-(5‴-substituted rhodanin-3‴-yl)thiazol-4‴-yl]bibenzyls. *Indian J. Chem.* **2005**,44B, 2102–2106.
22. Siddiqui, I.R.; Singh, P.K.; Srivastava, V.; Singh, J. Novel clay-catalysed expeditious cyclization to bis-benzothiazepine. *Indian J. Chem.* **2005**, 44B, 2178–2182.
23. Siddiqui, I.R.; Singh, P.K.; Singh, J.; Singh, J.; Environmentally benign synthesis and fungicidal activity of heteryl analogues of bibenzyl. *Indian J. Heterocyclic Chem.* **2003**, 15, 375–378.
24. Bagnell, L.; Cablewski, T.; Strauss, C.R.; Trainor, R.W. Reactions of allyl phenyl ether in high-temperature water with conventional and microwave heating. *J. Org. Chem.* **1996**, 61, 7355–7359.
25. Varma, R.S.; Dahiya, R. An expeditious and solvent-free synthesis of 2-amino-substituted isoflav-3-enes using microwave irradiation. *J. Org. Chem.* **1998**, 63, 8038–8041.
26. Furniss, B.S.; Hannaford, A.J.; Rogers, V.; Smith, P.W.G.; Tatchell, A.R. *Vogel's Text Book of Practical Organic Chemistry, 4th ed.*, 1986, pp. 457–458.
27. Ignatova, L.A.; Shutalev, A.D.; Unkovskii, B.V.; Sinilova, N.G.; Duplishcheva, A.P. N-glycosides. V. 3-glycosyl-4-hydroxyhexahydropyrimidine-2-thiones and their acyclic glycosylthiourea precursors as stimulators of non-specific resistance to infection. *Pharmaceutical Chem. J.* **1985**, 19, 847–852.