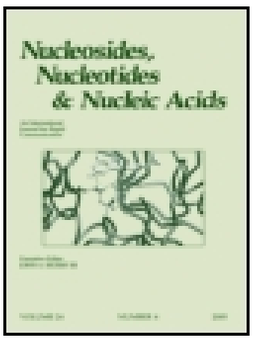

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SYNTHESIS OF 3'-O^2-(AZAHETEROCYCLE)-THYMIDINES

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ABSTRACT : The synthesis of 3'-O^2-(azaheterocycle)-thymidines is presented from 1-thia-3-aza-1,3-butadiene precursors (*N*-thioacylamidines). A variety of heterocycles is accessible using the dienic, the electrophilic or the nucleophilic reactivity of these thia-azabutadiene systems. 3'-O^2-(azaheterocycle)-thymidine analogues are regarded as potential substrates to interfere with the DNA-polymerization process.

Key Words: 3'-modified thymidine, thioacylamidines, thioacylimines, 4*H*-1,3-thiazines, thiazoles, thiazol-2-ine, 1-thia-3-azabutadienes.

Original nucleoside analogues have aroused considerable interest since sugar-modified derivatives having potential antiviral and antitumour effects were discovered.[1] In the hope of elucidating and/or finding better therapeutic agents, a wide variety of 3'-modified dideoxynucleoside analogues have been prepared.[2] They either act as enzyme inhibitors or as chain terminators of viral DNA-polymerization due to the lack of 3'-hydroxyl group.[3] Modified nucleosides with nucleobase analogue or tethered original

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heterocycle at the sugar moiety, have aroused new attention.[4] The discovery of TSAO [2',5'-bis-O-(*tert*-butyldimethylsilyl)-β-D-ribofuranosidyl]-3'-spiro-5'-(4"-amino-1",2"-oxathiole-2",2" dioxide) thymidine derivatives,[5] regarded as the first HIV-1 reverse transcriptase (RT), specific inhibitors interacting at non-substrate binding sites of the HIV-1 reverse transcriptase (RT), has elicited new class of 3'-heterocyle nucleoside analogues which behave like nonnucleoside RT substrates.[6]

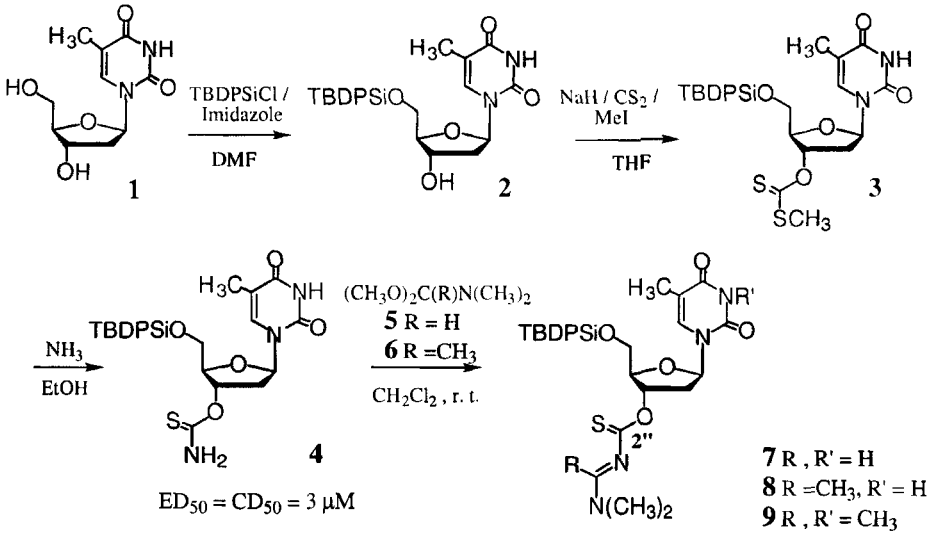
With respect to the previous studies carried out in our laboratory, *N*-thioacylamidine derivatives (1-thia-3-aza-1,3-butadienes) possessing dienic,[7a-h] electrophilic[7i-j] and nucleophilic characters,[7k-l] have been regarded as promising intermediates to produce various five and six membered heterocycles with structural analogie with natural nucleobases. These thia-azaheterodienes can be introduced either at the anomeric position of the pentafuranoside[8] or at the 3'-positions of deoxynucleosides to give original modified nucleosides by heterocyclisation. In order to illustrate the latter purpose, the synthesis of two 3'-(*N*-thioacylamidine)-thymidines is presented and the easy access to 3'-O^2-[(4-methyl)-1,3-thiazolyl]-thymidine and 3'-O^2-[(5,6-*bis*-methoxycarbonyl-4-dimethylamino)-4*H*-1,3-thiazinyl]-thymidine from these heterodiene precursors is discussed. The biological activity of these nucleoside analogues was evaluated as potential anti-HIV agents.

Results and Discussion

As starting material for the preparation of the 3'-O^2-(*N*-thioacylamidine)-thymidines, the 3'-O^2- thiocarbamoyl-thymidine **4** was synthesized in four steps from the thymidine **1** (Scheme 1). The protection of the primary hydroxyl of **1** was achieved using the *tert*-butyldiphenylsilylchloride in *N,N*-dimethylformamide, in the presence of imidazole,[9] to give the 5'-silyloxy thymidine **2** in 80% yield. The treatment of **2** with carbon disulphide and sodium hydride in tetrahydrofuran, followed by the addition of methyl iodide, afforded the methyl xanthate **3** in 75% yield.[10] Then, the reaction of **3** with ammonia in ethanol yielded the thiocarbamoyl-thymidine **4** in 95%.

The access to the *N*-thioacylamidines **7** and **8** was achieved by condensation of the precursor **4** with *N,N*-dimethylformamide dimethyl acetal **5** and *N,N*-dimethylacetamide dimethyl acetal **6**, respectively[7c-h]. The 1-thia-3-aza-1,3-butadiene **7** and its C4 methylated analogue **8** were isolated in 95% and 90% yield, respectively, when the reactions were runned in methylene chloride at room temperature. Addition of the dimethylacetal **6** in excess, at higher temperature, in a toluene solution of **4** induced subsequent N^3-methylation of the nucleobase to afford a mixture of **8** (55% yield) and methylated thymidine **9** in 20% yield.

The electrophilic properties of the *N*-thioacylamidine **8** were emphazised by the synthesis of five membered heterocycles. Nucleophile addition of sulphoxonium ylide,[11]

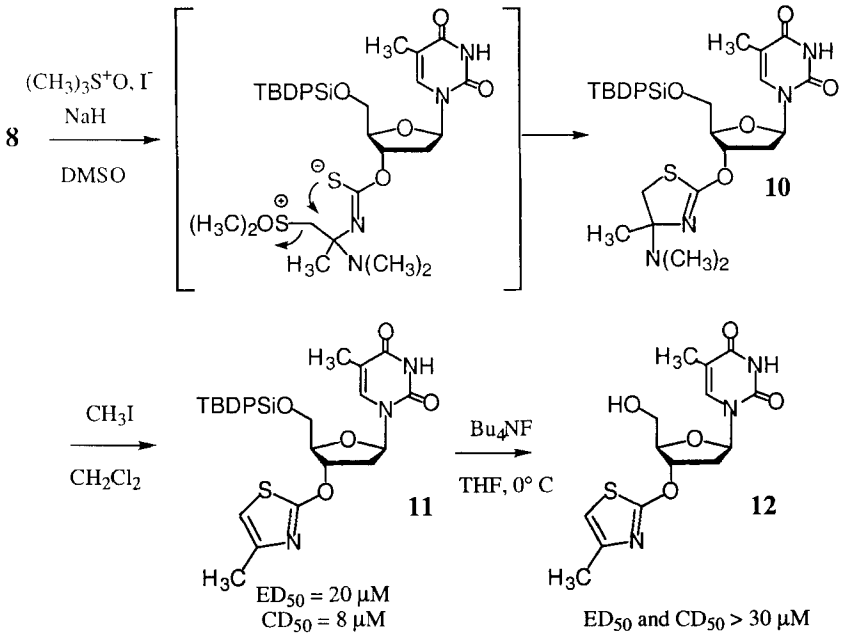


Scheme 1

generated *in situ* by the treatment of trimethylsulphoxonium iodide with one equivalent of sodium hydride in the dimethylsulphoxide, occurred at the C^4 centre of the *N*-thioacylamidine **8** (Scheme 2). The cyclisation step, resulting from the intramolecular substitution of the sulphoxide leaving group, furnished a mixture of diastereomers 3'-O^2-(thiazol-2-ine)-thymidine **10** in 95% yield. Aromatization of the thiazol-2-ine **10** into thiazole heterocycle **11** was achieved in 60% yield by quaternization of the dimethylamino group using methyl iodide in methylene chloride.[7j] The deprotection of 5'-silyloxy function was carried out with tetrabutylammonium fluoride trihydrate (Bu_4NF, $3H_2O$) in tetrahydrofuran yielded the desilylated thymidine **12** in 65%.

One of the most interesting properties of the 3'-O^2-(*N*-thioacylamidine)-thymidines concerns their ability to react as 4π–diene intermediates in the presence of electron deficient partners.[7h] The synthesis of the 3'-O^2-[2-(5,6-*bis*-methoxycarbonyl)-4*H*-1,3-thiazinyl)-thymidine **13** from **7** was chosen to emphazised the behaviour of the heterodiene in a [4 + 2] cycloaddition reaction (Scheme 3).

The addition of dimethylacetylene dicarboxylate (DMAD) to a solution of **7** carried out in refluxing methylene chloride afforded the diastereomers 4*H*-1,3-thiazine **13a** and **13b** in 95% yield. Both isomers were purified by flash chromatography on silica gel and isolated in the same ratio (**13a /13b** = 1/1). It seems that under a thermal activation, no facial selectivity was induced in the presence of a chiral auxiliary at the C^2 position of the thia-azaheterodiene skeleton involved in the Diels-Alder reaction. Deprotosylilation of the



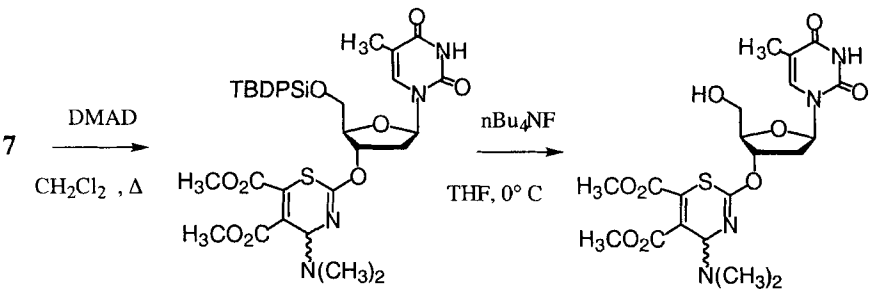
Scheme 2

intermediates **13a** and **13b**, as described above, gave the corresponding 3'-*O*2-(4*H*-1,3-thiazinyl)-thymidine analogues **14a** and **14b**, respectively, in 70% yields.

The synthesis of functionalized 4*H*-1,3-thiazine heterocycles allows us to envisage further modifications which could be of interest in the research of new isothymidine analogues. Indeed, the ester groups could be easily transformed into acid, alcohol, amide or amine functions which could be helpful in the research of HIV RT inhibitors. Furthermore, cyclic regression leading to the extrusion of the sulfur atom from the 4*H*-1,3-thiazines, through electrochemical process,[12] could be also investigated to produce original functionalized pyrrole heterocycles.

Biological Activity :

Compounds **4**, **11**, **12** and **14 (a,b)** were selected for the evaluation of their potential anti-HIV activity. The biological activity of these compounds was measured on CEM4 lymphocytic cell lines infected with HIV-1 (Lai strain). Two parameters were studied, the cytotoxicity and the anti-viral activity. To estimate the antiviral activity of these compounds we measured the inhibition of the reverse transcriptase (RT) activity in culture supernatants using the SPA RT assay and to determine the cytotoxicity these compounds we studied the inhibition of the cellular viability using the MTT dosage.[13] AZT (obtained



Scheme 3

from Sigma) was included in this assay (on day 5 post-infection, AZT exhibited a CD_{50} equal to 5μM and a ED_{50} equal to 0.019μM). Values of the CD_{50} and the ED_{50} of the compounds evaluated are included in the respective schemes.

At day five post-infection, compound **4** exhibited a CD_{50} and an ED_{50} at same doses (# 3μM). In order to get more insight into the biological activity of this set of compound and eventually to discriminate what part of these molecules is responsible for the induction of cytotoxicity and/or anti-viral activity, we have further evaluated the biological activity of compounds **11** and **12**. Removal of the *tert*-butyldiphenylsilyl moiety (**11** *vs* **12**) resulted in the lost of the cytotoxicity observed with compound **4**. Furthermore it appears that the presence of a thiazole ring induces a weak anti-viral activity (compound **11**). But the removal of the *tert*-butyldiphenylsilyl group leads to the lost of the weak anti-viral activity observed without appearance of a cytotoxicity.

Compounds **14a** and **14b** showed a weak anti-viral activity (ED_{50}~20μM and ~30μM respectively) without association of significant cytotoxic activity at concentration up to 30μM (CD_{50} > 30μM) indicating that in this series both the anti-HIV activity and the cytotoxicity could be dependent on the exact nature of the heterocycle.

Additional investigations are needed to determine whether the incorporation of the other heterocycle could increased the anti-HIV activity of these thymidine derivatives.

As a result of these preliminary investigations, we have synthesized a new type of ambiphilic heterodienes (1-thia-3-aza-1,3-butadienes) at the 3'-position of the thymidine, which have been already shown as versatile building blocks to acced to a range of five and six membered heterocyles.[7] This strategy could be easily extended to the other purine or pyrimidine nucleosides. While no significant anti-HIV activity was enregistrated, this class

of compounds should be of interest in other range of DNA and RNA viruses or in the context of "Base Addition Sequencing Scheme" (BASS).[14] Indeed, the introduction of spectroscopically distinct and aqueous labile functionality at the 3'-position of the nucleoside is reasonably envisageable from the 3'-O^2-(*N*-heteroacylamidine)- and/or 3'-O^2-(thia-azaheterocycle) nucleoside precursors.

EXPERIMENTAL

^1H NMR and ^{13} C NMR spectra were recorded on a Bruker spectrometer ARX 400 ; chemical shifts are expressed in parts per million (ppm) referenced to residual chloroform. Coupling constants (J) are given in hertz (Hz). Multiplicities are recorded as s (singlet), d (doublet), t (triplet) and m (multiplet or massif). Mass spectra, m/z (% base peak), were recorded on Hewlett Packard 5989A and LSIMS HMRS were taken by a ZabSpecETOF mass spectrometer. All solvents were freshly distilled prior to use by standard methods.[15] Flash chromatography was performed on silica-gel Merck 60 230-400 mesh. All compounds were fully identified by ^1H, ^{13}C NMR 400MHz and HRMS mass spectrum analysis.[16] They are spectrometrically pure but thermally too unstable to provide correct elemental analyses.

5'-*O*-*tert*-butyldiphenylsilyl-3'-O^2(methythio)thiocarbonyl-thymidine (3)

A solution of 5'-*O*-*tert*-butyldiphenylsilyl-thymidine **2** (720 mg, 1.5 mmol) dissolved in THF (2 mL) was added to a suspension of NaH (60%) (100mg, 2.5 mmol) in THF (8 mL) at 0°C. After 15 min. of stirring, CS_2 (0.27 mL, 4.5 mmol) was added and after supplementary 1 h., MeI (0.14 mL, 1.8 mmol) was introduced in the solution. The reaction was allowed to warm to room temperature over 1 h. before the solution was diluted with CH_2Cl_2 (50 mL) and washed with brine (2x100mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The chromatography of the crude product gave **3** in 75 % yield. Rf 0.7 (EtOAc : light petroleum 1 : 1).^1H NMR δ ppm: 1.10 (s, 9H, $C(CH_3)_3$), 1.62 (s, 3H, C^5-CH_3), 2.19 (m, $^2J_{H2'a-H2'b}$ = 14.0Hz, $^3J_{H2'a-H1'}$ = 9.3Hz, $^3J_{H2'a-H3'}$ = 6.2Hz, 1H, $H^{2'a}$), 2.58 (s, 3H, SCH_3), 2.66 (dd, $^2J_{H2'a-H2'b}$ = 14Hz, $^3J_{H2'b-H1'}$ = 5.2Hz, 1H , $H^{2'b}$), 4.02 (dd, $^2J_{H5'a-H5'b}$ = 11.5Hz, $^3J_{H5'a-H4'}$ = 1.8Hz, 1H, $H^{5'a}$), 4.08 (dd, $^2J_{H5'a-H5'b}$ = 11.5Hz, $^3J_{H5'b-H4'}$ = 2.1Hz, 1H, $H^{5'b}$), 4.28 (m, 1H, $H^{4'}$), 6.16 (m, 1H, $H^{3'}$), 6.48 (dd, $^3J_{H2'a-H1'}$ = 9.3Hz, $^3J_{H2'b-H1'}$ = 5.2Hz, 1H, $H^{1'}$), 7.40 (m, 6H, H^{Ar}), 7.56 (s, 1H, H^6), 7.67 (m, 4H, H^{Ar}), 9.35 (s, 1H, NH); ^{13}C NMR δ ppm : 12.0 (C^5-$\underline{C}H_3$), 19.3 ($\underline{C}(CH_3)_3$ and SCH_3), 26.9 ($C(\underline{C}H_3)_3$), 38.1 ($C^{2'}$), 64.3 ($C^{5'}$), 83.4 ($C^{3'}$), 84.5 ($C^{1'}$), 84.8 ($C^{4'}$), 111.6 (C^5), 128.0, 130.1, 130.2, 131.8, 132.7, 135.2 and 135.6 (C^{Ar}), 135.3 (C^6), 150.5 (C^2), 163.7 (C^4), 215.0 (C=S). IR cm^{-1} (KBr): 3395, 3071, 1700, 1696. SM m/z (CI, NH_3): 571 (MH^+).

5'-*O*-*tert*-butyldiphenylsilyl-3'-O^2-thiocarbamoyl-thymidine (4)

Xanthate **3** (860 mg, 1.5 mmol) dissolved in EtOH (20 mL) was treated under gaseous ammonia while stirring for 1 h. The flux of ammonia was stopped and the solution was stirred for a further 3 h. Gaseous ammonia was removed and the solution was concentrated under reduced pressure. The compound **4** was isolated as a white powder in 95% yield and used with no further purification. Rf 0.1 (EtOAc : light petroleum 1 : 1). ^{1}H NMR δ ppm (DMSO *D6*): 1.02 (s, 9H, C(CH$_3$)$_3$), 1.46 (s, 3H, C^5-CH$_3$), 2.41 (m, 2H, H$^{2'a}$ and H$^{2'b}$), 3.94 (dd, $^2J_{H}$5'a-$_H$5'b = 11.2Hz, $^3J_{H}$5'a-$_H$4' = 2.6Hz, 1H, H$^{5'a}$), 4.01 (dd, $^2J_{H}$5'a-$_H$5'b = 11.2Hz, $^3J_{H}$5'b-$_H$4' = 3.2Hz, 1H, H$^{5'b}$), 4.15 (m, 1H, H$^{4'}$), 5.90 (m, 1H, H$^{3'}$), 6.25 (dd, ^{3}J = 8.7Hz, ^{3}J = 5.8Hz, 1H, H$^{1'}$), 7.41 (m, 7H , H^{Ar} and H^6), 7.65 (m, 4H, H^{Ar}), 8.66 (s, 1H, NH), 8,98 (s, 1H, NH), 11.17 (s, 1H, NH); ^{13}C NMR δ ppm (DMSO *D6*): 11.9 (C^5-CH$_3$), 19.0 (C(CH$_3$)$_3$), 26.8 (C(CH$_3$)$_3$), 37.2 (C$^{2'}$), 64.4 (C$^{5'}$), 79.6 (C$^{3'}$), 83.6 (C$^{1'}$), 84.2 (C$^{4'}$), 111.6 (C^5), 128.2, 130.2, 130.3, 132.2, 132.9, 135.0 and 135.3 (C^{Ar}), 134.9 (C^6), 150.5 (C^2), 163.7 (C^4), 190.0 (C=S). IR cm^{-1} (KBr): 3434, 3304, 3198, 3071, 1700, 1663, 1614. SM m/z (CI, NH$_3$): 540 (MH+). SM m/z (I%) (EI): 405 (59), 199 (71), 165 (33), 163 (36), 135 (41), 81 (100), 59 (38). HRMS (M+H)+ Calcd for $C_{27}H_{34}N_3O_5SiS$: 540.1988, found 540.1992.

5'-*O*-*tert*-butyldiphenylsilyl-3'-O^2-[(4-dimethylamino)-1-thia-3-aza-1,3-butadienyl]-thymidine (7)

N,*N*-dimethylformamide dimethylacetal (0.05 mL, 0.37 mmol) was added dropwise to a suspension of thiocarbamate **4** (180 mg, 0.33 mmol) in CH_2Cl_2 (5 mL). After 1 h. of stirring the solution was concentrated under reduced pressure. The residue was purified by chromatography to give **7** as a white foam in 95 % yield. Rf 0.36 (EtOAc).^{1}H NMR δ ppm: 1.14 (s, 9H, C(CH$_3$)$_3$), 1.57 (d, ^{4}J = 1Hz, 3H, C^5-CH$_3$), 2.37 (ddd, $^2J_{H}$2'a-$_H$2b' = 13.8Hz, $^3J_{H}$2'a-$_H$1' = 9.3Hz, $^3J_{H}$2'a-$_H$3' = 6.3Hz, 1H, H$^{2'a}$), 2.70 (dd, $^2J_{H}$2'a-$_H$2'b =13.8Hz, $^3J_{H}$2'b-$_H$1' = 5.3Hz, 1H, H$^{2'b}$), 3.14 (s, 3H, N-CH$_3$), 3.24 (s, 3H, N-CH$_3$), 4.04 (dd, $^2J_{H}$5'a-$_H$5'b = 11.4Hz, $^3J_{H}$5'a-$_H$4' = 1.7Hz, 1H, H$^{5'a}$), 4.16 (dd, $^2J_{H}$5'a-$_H$5'b = 11.4Hz, $^3J_{H}$5'b-$_H$4' = 2.1Hz, 1H, H$^{5'b}$), 4.33 (m, 1H, H$^{4'}$), 6.10 (m, 1H, H$^{3'}$), 6.53 (dd, $^3J_{H}$2'a-$_H$1' = 9.3Hz, $^3J_{H}$2'b-$_H$1' = 5.3Hz, 1H, H$^{1'}$), 7.40 (m, 6H, H^{Ar}), 7.60 (q, ^{4}J = 1Hz, 1H, H^6), 7.71 (m, 4H, H^{Ar}), 8.67 (s, 1H, NH), 8.74 (s, 1H, H$^{4''}$); ^{13}C NMR δ ppm: 11.9 (C^5-CH$_3$), 19.3 (C(CH$_3$)$_3$), 27.0 (C(CH$_3$)$_3$), 36.5 (N-CH$_3$), 37.2 (C$^{2'}$), 42.0 (N-CH$_3$), 64.7 (C$^{5'}$), 80.7 (C$^{3'}$), 84.7 (C$^{1'}$), 85.3 (C$^{4'}$), 111.2 (C^5), 127.9, 128.0, 130.0, 130.1, 132.0, 133.0, 135.2 and 135.6 (C^{Ar}), 135.2 (C^6), 150.2 (C^2), 163.7 (C^4), 164.3 (C$^{4''}$), 204.0 (C=S). IR cm^{-1} (KBr) : 3454, 3048, 1695, 1625, 1614. SM m/z (I%) (EI): 405 (19), 279 (35), 199 (25), 135 (22), 133 (48), 115 (36), 99 (100), 81 (54). HRMS (M+H)+ Calcd for $C_{30}H_{39}N_4O_5SiS$: 595.2410, found 595.2468.

5'-*O*-*tert*-butyldiphenylsilyl-3'-O^2-[(4-dimethylamino)-1-thia-3-aza-1,3-pentadienyl]-thymidine (8)

N,N-dimethylacetamide dimethylacetal (0.24 mL, 1.67 mmol) was added dropwise to a suspension of thiocarbamate **4** (450 mg, 0.83 mmol) in CH_2Cl_2 (10 mL). After 12 h. of stirring the solution was concentrated under reduced pressure. The residue was purified by chromatography to give **8** as a white foam in 90 % yield. Rf 0.30 (EtOAc). ^1H NMR δ ppm: 1.03 (s, 9H, $C(CH_3)_3$), 1.49 (s, 3H, C^5-CH_3), 2.27 (ddd, $^2J_{H}$2'a-$_H$2b' = 13.7Hz, $^3J_{H}$2'a-$_H$1' = 9.2Hz, $^3J_{H}$2'a-$_H$3' = 6.2Hz, 1H, $H^{2'a}$), 2.34 (s, 3H, $C^{4"}$-CH_3), 2.55 (dd, $^2J_{H}$2'a-$_H$2'b =13.7Hz, $^3J_{H}$2'b-$_H$1' = 5.3Hz, 1H, $H^{2'b}$), 3.03 (s, 3H, N-CH_3), 3.06 (s, 3H, N-CH_3), 3.96 (dd, $^2J_{H}$5'a-$_H$5'b = 11.3Hz, $^3J_{H}$5'a-$_H$4' = 1.5Hz, 1H, $H^{5'a}$), 4.09 (dd, $^2J_{H}$5'a-$_H$5'b = 11.3Hz, $^3J_{H}$5'b-$_H$4' = 2.0Hz, 1H , $H^{5'b}$), 4.24 (m, 1H, $H^{4'}$), 5.88 (m, 1H, $H^{3'}$), 6.42 (dd, $^3J_{H}$2'a-$_H$1' = 9.2Hz, $^3J_{H}$2'b-$_H$1' = 5.3Hz, 1H, $H^{1'}$), 7.32 (m, 6H, H^{Ar}), 7.52 (s, 1H, H^6), 7.62 (m, 4H, H^{Ar}), 9.20 (s, 1H, NH); ^{13}C NMR δ ppm : 11.8 (C^5-$\underline{C}H_3$), 17.9 ($C^{4"}$-$\underline{C}H_3$), 19.3 ($\underline{C}(CH_3)_3$), 26.9 ($C(\underline{C}H_3)_3$), 38.5 ($C^{2'}$), 38.8 (N-CH_3), 38.9 (N-CH_3), 64.7 ($C^{5'}$), 80.2 ($C^{3'}$), 84.6 ($C^{1'}$), 85.6 ($C^{4'}$), 111.2 (C^5), 127.9, 128.0, 129.9, 130.0, 132.0, 133.0, 135.1 and 135.6 (C^{Ar}), 135.1 (C^6), 150.4 (C^2), 163.9 (C^4), 165.8 ($C^{4"}$), 195.1 (C=S). IR cm^{-1} (KBr) : 3420, 2932, 1708, 1698, 1644, 1634. SM m/z (I%) (EI) : 406 (29), 405 (100), 279 (36), 199 (74), 165 (23), 163 (34), 135 (29), 81 (61). HRMS (M+H)+ Calcd for $C_{31}H_{41}N_4O_5SiS$: 609.2567, found 609.2549.

5'-*O*-*tert*-butyldiphenylsilyl-3'-O^2-[(4-dimethylamino)-1-thia-3-aza-1,3-pentadienyl]-N^3-methyl-thymidine (9)

N,N-dimethylacetamide dimethylacetal (0.13 mL, 0.91 mmol) was added dropwise to a suspension of thiocarbamate **4** (450 mg, 0.83 mmol) in anhydrous toluene (10 mL). The mixture was refluxed for 12 h. and the solution was concentrated under reduced pressure. The residue was purified by chromatography to give **8** (55%) and **9** as a white foam in 20 % yield. Rf 0.4 (EtOAc : light petroleum 9 : 1). ^1H NMR δ ppm: 1.02 (s, 9H, $C(CH_3)_3$), 1.53 (d, ^3J = 1Hz, 3H, C^5-CH_3), 2.26 (m, $^2J_{H2'a-H2b}$ = 13.8Hz, ^3J H2'a-H1' = 9.2Hz, 1H, $H^{2'a}$), 2.35 (s, 3H, $C^{4"}$-CH_3), 2.57 (dd, $^2J_{H2'a-H2'b}$ =13.8Hz, ^3J H2'b-H1' = 5.3Hz, 1H, $H^{2'b}$), 3.03 (s, 3H, N-CH_3), 3.06 (s, 3H, N-CH_3), 3.26 (s, 3H, N^3-CH_3), 3.95 (dd, $^2J_{H5'a-H5'b}$ = 11.4Hz, $^3J_{H5'a-H4'}$ = 1.8Hz, 1H, $H^{5'a}$), 4.07 (dd, $^2J_{H5'a-H5'b}$ = 11.3Hz, $^3J_{H5'b-H4'}$ = 2.0Hz, 1H, $H^{5'b}$), 4.25 (m, 1H, $H^{4'}$), 5.85 (m, 1H, $H^{3'}$), 6.45 (dd, $^3J_{H2'a-H1'}$ = 9.2Hz, $^3J_{H2'b-H1'}$ = 5.3Hz, 1H, $H^{1'}$), 7.33 (m , 6H, H^{Ar}), 7.52 (d, ^3J = 1Hz, 1H, H^6), 7.62 (m, 4H, H^{Ar}); ^{13}C NMR δ ppm: 12.6 (C^5-$\underline{C}H_3$), 17.8 ($C^{4"}$-$\underline{C}H_3$), 19.2 ($\underline{C}(CH_3)_3$), 26.8 ($C(\underline{C}H_3)_3$), 27.7 (N^3-$\underline{C}H_3$), 38.5 ($C^{2'}$), 38.7 (N-$\underline{C}H_3$), 38.9 (N-$\underline{C}H_3$), 64.6 ($C^{5'}$), 80.2 ($C^{3'}$), 85.4 ($C^{1'}$), 85.5 ($C^{4'}$), 110.1 (C^5), 127.8, 129.9, 130.0, 132.0, 132.9, 133.0, 135.1 and 135.6 (C^{Ar} and C^6), 150.9 (C^2), 163.5 (C^4), 165.9 ($C^{4"}$), 195.0 (C=S). IR cm^{-1} (KBr) : 3067, 2932,

2857, 1702, 1697, 1618. SM m/z (I%) (EI): 419 (14), 279 (59), 199 (100), 197 (24), 179 (20), 173 (27), 163 (21), 140 (28), 135 (37), 81 (70), 77 (21), 57 (32), 55 (40), 44 (37).

5'-*O*-*tert*-butyldiphenylsilyl-3'-O^2-[(4-dimethylamino-4-methyl)-1,3-thiazol-2-inyl]-thymidine (10)

Sodium hydride (2.65 mmol) was added to a solution of trimethylsulphoxonium iodide (583 mg, 2.65 mmol) dissolved in DMSO (15 mL) under argon. The heterodiene **8** (802 mg, 1.32 mmol) was added to the solution after 1h. of stirring at room temperature. The reaction mixture was stirred overnight and the solution was diluted with EtOAc (60 mL) and washed with water (3x60 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the crude product gave the diastereoisomers **10** isolated as a white powder in 95% yield. Rf 0.10 (EtOAc : light petroleum 6 : 4).^{1}H NMR δ ppm : 1.10 (m, 18H, 2xC$(CH_3)_3$), 1.38 and 1.44 (2s, 2x3H, 2xC$^{4"}$-CH_3) , 1.57 and 1.60 (2s, 2x3H, 2xC^5-CH_3), 2.18 and 2.31 (2s, 12H, 2xN$(CH_3)_2$), 2.29 (m, 2x1H, 2xH$^{2'a}$), 2.61 (dd, ^{2}J = 13.8Hz, ^{3}J = 5.1Hz, 2x1H, 2xH$^{2'b}$), 3.20 and 3.23 (2d, ^{2}J = 11.7Hz, ^{2}J = 11.9Hz, 2x1H, 2xH$^{5"a}$), 3.58 and 3.60 (2d, ^{2}J = 11.7Hz, ^{2}J = 11.9Hz, 2x1H, 2xH$^{5"b}$), 4.04 (m, 2x2H, 2xH$^{5'a}$ and H$^{5'b}$), 4.24 and 4.29 (m, 2x1H, 2xH$^{4'}$), 5.51 (m, 2x1H, 2xH$^{3'}$), 6.46 (m , 2x1H , 2xH$^{1'}$), 7.42 (m, 2x6H, H^{Ar}), 7.50 and 7.56 (2s, 2x1H, 2xH^6), 7.67 (m, 2x4H, H^{Ar}), 9.90 (m, 2x1H , 2xNH); ^{13}C NMR δ ppm : 11.9 (C^5-$\underline{C}H_3$), 19.3 ($\underline{C}(CH_3)_3$), 25.4 and 25.9 (C$^{4"}$-$\underline{C}H_3$), 26.9 (C($\underline{C}H_3)_3$), 38.1 (C$^{2'}$), 39.0 (N$(CH_3)_2$), 42.7 and 43.3 (C$^{5"}$), 64.1 (C$^{5'}$), 80.7 and 80.9 (C$^{3'}$), 84.2 and 84.3 (C$^{1'}$), 84.6 and 84.9 (C$^{4'}$), 93.6 (C$^{4"}$), 111.3 (C^5), 127.9, 129.9, 130.0, 132.0, 132.8 and 132.9, 135.1 and 135.4 (C^{Ar}), 134.8 (C^6), 150.6 (C^2), 163.2 (C^4), 164.0 (C$^{2"}$). IR cm^{-1} (KBr) : 3400, 1703, 1692, 1626. SM m/z (I%) (EI): 520 (24), 405 (29), 279 (33), 199 (39), 197 (23), 165 (48), 135 (52), 115 (22), 51 (100). HRMS (M+H)$^+$ Calcd for $C_{32}H_{43}N_4O_5SiS$: 623.2723, found 623.2731.

5'-*O*-*tert*-butyldiphenylsilyl-3'-O^2-[(4-methyl)-1,3-thiazolyl]-thymidine (11)

Methyl iodide (0.2 mL, 3.27 mmol) was added dropwise to a solution of thiazoline **10** (680mg, 1.09 mmol) dissolved in CH_2Cl_2 (5 mL). After 24 h. of stirring at room temperature, the reaction mixture was diluted in CH_2Cl_2 and washed with brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the crude product gave the compound **11** as a white powder (60 %). Rf 0.75 (EtOAc : light petroleum 6 : 4). ^{1}H NMR δ ppm (DMSO D_6) : 1.12 (s, 9H, C$(CH_3)_3$), 1.62 (s, 3H, C^5-CH_3), 2.19 (d, ^{4}J = 0.8Hz; 3H, C$^{4"}$-CH_3), 2.32 (ddd, $^2J_{H2'a\text{-}H2b'}$ = 14.0Hz, $^3J_{H2'a\text{-}H1'}$ = 9.3Hz, $^3J_{H2'a\text{-}H3'}$ = 6.4Hz, 1H, H$^{2'a}$), 2.61 (dd, $^2J_{H2'a\text{-}H2'b}$ =14.0Hz, $^3J_{H2'b\text{-}H1'}$ = 5.2Hz, 1H, H$^{2'b}$), 4.03 (dd, $^2J_{H5'a\text{-}H5'b}$ =

11.4Hz, $^3J_{H5'a-H4'}$ = 1.8Hz, 1H, $H^{5'a}$), 4.16 (dd, $^2J_{H5'a-H5'b}$ = 11.4Hz, $^3J_{H5'b-H4'}$ = 2.2Hz, 1H, $H^{5'b}$), 4.30 (m, 1H, $H^{4'}$), 5.69 (m, 1H, $H^{3'}$), 6.24 (d, ^4J = 0.8Hz, 1H, $H^{5''}$), 6.46 (dd, $^3J_{H2'a-H1'}$ = 9.3Hz, $^3J_{H2'b-H1'}$ = 5.2Hz, 1H, $H^{1'}$), 7.41 (m, 6H, H^{Ar}), 7.56 (s, 1H, H^6), 7.70 (m, 4H, H^{Ar}), 9.06 (s, 1H, NH); ^{13}C NMR δ ppm (DMSO *D6*): 12.0 (C^5-$\underline{C}H_3$), 17.6 ($C^{4''}$-$\underline{C}H_3$), 19.4 ($\underline{C}(CH_3)_3$), 27.0 ($C(\underline{C}H_3)_3$), 38.3 ($C^{2'}$), 64.3 ($C^{5'}$), 81.1 ($C^{3'}$), 84.4 ($C^{1'}$), 85.1 ($C^{4'}$), 105.6 ($C^{5''}$), 111.3 (C^5), 128.0, 130.0, 130.1, 132.2 and 132.9 (C^{Ar} , 135.0 (C^6), 135.2 and 135.5 (C^{Ar}), 146.8 ($C^{4''}$), 150.4 (C^2), 163.7 (C^4), 172.2 ($C^{2''}$). IR cm-1 (KBr): 3435, 2905, 1711, 1695, 1689. SM m/z (CI, NH_3) : 578 (MH+). SM m/z (I%) (EI) : 520 (27), 405 (43), 387 (20), 327 (20), 307 (20), 279 (43), 199 (36), 197 (24), 165 (55), 135 (56), 122 (21), 115 (23), 81 (100). HRMS (M+H)+ Calcd for $C_{30}H_{36}N_3O_5SiS$: 578.2145, found 578.2125.

3'-*O*^{2}-[(4-methyl)-1,3-thiazolyl]-thymidine (12)

Tetrabutylammonium fluoride trihydrate (164 mg, 0.52 mmol) was added under argon to a solution of thiazole **11** (300 mg, 0.52 mmol) in dry THF (10 mL) cooled to 0°C. The reaction mixture was stirred at 0°C, until T.L.C. indicated complete desilylation (1.5 h.). The solution was diluted with CH_2Cl_2 (50 mL) then washed with NH_4Cl 5% (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the crude product gave the desilylated compound **12** as a white powder in 65 % yield. Rf 0.20 (EtOAc : light petroleum 6 : 4). ^1H NMR δ ppm (DMSO *D6*) : 1.25 (s, 1H, NH), 1.78 (d, ^4J = 1Hz, 3H, C^5-CH_3), 2.18 (d, ^4J = 1Hz, 3H, $C^{4''}$-CH_3), 2.40 (m, 2H, $H^{2'a}$ and $H^{2'b}$), 3.70 (m , 2H , $H^{5'a}$ and $H^{5'b}$), 4.15 (m , 1H , $H^{4'}$), 5.24 (t , ^3J = 5Hz ; 1H , OH), 5.44 (m, 1H, $H^{3'}$), 6.21 (dd, ^3J = 6.0Hz, ^3J = 8.5Hz, 1H , $H^{1'}$), 6.63 (d, ^4J = 1Hz, 1H, $H^{5''}$), 7.75 (d, ^4J = 1Hz, 1H, H^6); ^{13}C NMR δ ppm (DMSO *D6*) : 12.3 (C^5-$\underline{C}H_3$), 17.4 ($C^{4''}$-$\underline{C}H_3$), 36.7 ($C^{2'}$), 61.3 ($C^{5'}$), 81.9 ($C^{3'}$), 83.7 ($C^{1'}$), 84.4 $C^{4'}$), 106.5 ($C^{5''}$), 109.7 (C^5), 135.8 (C^6), 146.2 ($C^{4''}$), 150.4 (C^2), 163.7 (C^4 , 174.8 ($C^{2''}$). IR cm-1 (KBr) : 3209, 3173, 1710, 1664, 1650. SM m/z (CI, NH_3): 340 (MH+). SM m/z (I%) (EI) : 225 (79), 127 (69), 116 (49), 115 (30), 99 (32), 81 (29), 71 (21), 69 (100), 55 (22).

5'-*O*-*tert*-butyldiphenylsilyl-3'-*O*^{2}-[(5,6-*bis*-methoxycarbonyl-4-dimethyl-amino)-4*H*-1,3-thiazinyl]-thymidine (13)

Dimethyl acetylenedicarboxylate (0.125 mL, 1.01 mmol) was added to a solution of heterodiene **7** (200 mg, 0.336 mmol) in CH_2Cl_2 (5 mL). The solution was stirred at reflux until T.L.C. showed complete disappearance of **7**, then reaction mixture was cooled to room temperature and concentrated under reduced pressure. Chromatography of the crude product on silica gel allowed the separation of the two diastereoisomers of **13** in 95 % yield (**13a** : **13b** 1 : 1). Rf 0.50 and 0.55 (EtOAc : light petroleum 1 : 1). ^1H NMR δ ppm : first eluted **13a:** 1.03 (s, 9H, $C(CH_3)_3$), 1.54 (d, ^4J = 0.8Hz, 3H, C^5-CH_3), 2.02 (s, 6H, $N(CH_3)_2$), 2.24 (ddd, $^2J_{H2'a-H2b'}$ =14.1Hz, $^3J_{H2'a-H1'}$ = 9.4Hz,

$^3J_{H2'a-H3'}$ = 6.2Hz, 1H, $H^{2'a}$), 2.53 (dd, $^2J_{H2'a-H2'b}$=14.1Hz, $^3J_{H2'b-H1'}$ = 5.2Hz, 1H, $H^{2'b}$), 3.74 (s, 3H, CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 3.93 (dd, $^2J_{H5'a-H5'b}$ = 11.4Hz, $^3J_{H5'a-H4'}$ = 1.9Hz, 1H , $H^{5'a}$, 3.98 (dd, $^2J_{H5'a-H5'b}$ = 11.4Hz, $^3J_{H5'b-H4'}$ = 1.5Hz, 1H, $H^{5'b}$), 4.17 (m, 1H, $H^{4'}$), 5.38 (s, 1H, $H^{4''}$), 5.54 (m, 1H, $H^{3'}$), 6.39 (dd, $^3J_{H2'a-H1'}$ = 9.4Hz, $^3J_{H2'b-H1'}$ = 5.2Hz, 1H, $H^{1'}$), 7.36 (m, 6H, H^{Ar}), 7.50 (d, ^4J = 0.8Hz, 1H, H^6), 7.58 (m, 4H, H^{Ar}), 9.33 (s, 1H, NH) - second eluted **13b:** 1.03 (s, 9H, $C(CH_3)_3$), 1.47 (d, ^4J = 1Hz , 3H, C^5-CH_3), 2.14 (s, 6H, $N(CH_3)_2$), 2.24 (ddd, $^2J_{H2'a-H2b'}$ = 13.9Hz, $^3J_{H2'a-H1'}$ = 9.3Hz, $^3J_{H2'a-H3'}$ = 6.3Hz, 1H, $H^{2'a}$), 2.50 (dd, $^2J_{H2'a-H2'b}$ =13.9Hz, $^3J_{H2'b-H1'}$ = 5.2Hz, 1H, $H^{2'b}$), 3.73 (s, 3H, CO_2CH_3), 3.75 (s, 3H, CO_2CH_3), 3.89 (dd, $^2J_{H5'a-H5'b}$ = 11.3Hz, $^3J_{H5'a-H4'}$ = 2Hz, 1H, $H^{5'a}$), 3.95 (dd, $^2J_{H5'a-H5'b}$ = 11.3Hz, $^3J_{H5'b-H4'}$ = 1.8Hz, 1H , $H^{5'b}$), 4.16 (m, 1H, $H^{4'}$), 5.41 (s, 1H, $H^{4''}$), 5.52 (m, 1H, H^3), 6.36 (dd, $^3J_{H2'a-H1'}$ = 9.3Hz, $^3J_{H2'b-H1'}$ = 5.2Hz, 1H, $H^{1'}$), 7.36 (m, 6H, H^{Ar}), 7.43 (d, ^4J = 1Hz, 1H, H^6), 7.56 (m, 4H, H^{Ar}), 9.53 (s, 1H, NH); ^{13}C NMR δ ppm : **13a:** 11.9 (C^5-$\underline{C}H_3$), 19.3 ($\underline{C}(CH_3)_3$), 26.9 ($C(\underline{C}H_3)_3$), 38.1 ($C^{2'}$), 39.9 (N-$(CH_3)_2$), 52.7 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 64.3 ($C^{5'}$), 78.4 ($C^{3'}$), 78.7 ($C^{4''}$), 84.5 ($C^{1'}$), 84.7 ($C^{4'}$), 111.5 (C^5), 127.4 and 129.2 ($C^{5''}$ and $C^{6''}$), 128.0, 130.1, 130.2, 131.9 and 132.6, 135.1 and 135.5 (C^{Ar}), 134.8 (C^6), 150.4 (C^2), 152.7 (CO), 162.3, 163.8 and 167.0 (C^4, $C^{2''}$ and CO). - **13b:** 11.8 (C^5-$\underline{C}H_3$), 19.3 ($\underline{C}(CH_3)_3$), 26.9 ($C(\underline{C}H_3)_3$), 38.0 ($C^{2'}$), 39.8 (N-$(CH_3)_2$), 52.7 ($CO_2\underline{C}H_3$), 53.2 ($CO_2\underline{C}H_3$), 64.0 ($C^{5'}$), 78.1 ($C^{3'}$), 78.5 ($C^{4''}$), 84.2 ($C^{1'}$), 84.5 ($C^{4'}$), 111.4 (C^5), 127.5 and 129 ($C^{5''}$ and $C^{6''}$), 127.9, 130.0, 130.1 and 132.0, 135.0 and 135.4 (C^{Ar}), 134.8 (C^6), 150.4 (C^2), 152.6 (CO), 162.2, 163.9 and 167.8 (C^4, $C^{2''}$ and CO). IR cm^{-1} (KBr): 3454, 3073, 1736, 1722, 1664. SM m/z (I%) (EI): 405 (34), 279 (100), 173 (40), 81 (47).

3'-O^2-[(5,6-*bis*-methoxycarbonyl-4-dimethylamino)-4*H*-1,3-thiazinyl]-thymidine (14)

Tetrabutylammonium fluoride trihydrate (50 mg, 0.16 mmol) was added under argon to a solution of **13a** or **13b** (120 mg, 0,16 mmol) dissolved in dry THF (15 mL) at 0°C. The reaction mixture was stirred at 0°C. until T.L.C. indicated complete desilylation (1.5 h.). The solution was diluted with CH_2Cl_2 (50 mL) then washed with NH_4Cl 5% (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduce pressure. Chromatography of the crude product gave the desilylated compounds **14a** or **14b** isolated as a white powder in 70 % yield. Rf 0.20 (EtOAc : light petroleum 8 : 2). **14a:** ^1H NMR δ ppm : 1.91 (s, 3H, C^5-CH_3), 2.28 (s, 6H, $N(CH_3)_2$), 2.50 (m, 2H, $H^{2'a}$ and $H^{2'b}$), 3.82 (s, 3H, CO_2CH_3), 3.84 (s, 3H, CO_2CH_3), 3.91 (m, 2H, $H^{5'a}$ and $H^{5'b}$), 4.24 (m, 1H, $H^{4'}$), 5.50 (m, 1H, $H^{3'}$), 5.56 (s, 1H, $H^{4''}$), 6.21 (dd,

$^3J_{H2'a-H1'}$ = 8.0Hz, $^3J_{H2'b-H1'}$ = 6.4Hz, 1H , $H^{1'}$), 7.38 (s, 1H, H^6); ^{13}C NMR δ ppm : 12.4 (C^5-$\underline{C}H_3$), 37.1 ($C^{2'}$), 39.9 (N-$(CH_3)_2$), 52.8 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 62.3 ($C^{5'}$), 78.2 ($C^{3'}$), 78.6 ($C^{4''}$), 84.8 ($C^{4'}$), 86.6 ($C^{1'}$), 111.3 (C^5), 127.5 and 129.1 ($C^{5''}$ and $C^{6''}$), 136.7 (C^6), 150.5 (C^2), 152.9 (CO), 162.3, 163.9 and 167.0 (C^4, $C^{2''}$ and CO). - **14b:** ^1H NMR δ ppm (DMSO *D6*): 1.77 (s, 3H, C^5-CH_3), 2.19 (s, 6H, $N(CH_3)_2$), 2.34 (m, 2H, $H^{2'a}$ and $H^{2'b}$), 3.68 (m, 2H, $H^{5'a}$ and $H^{5'b}$), 3.71 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 4.11 (m, 1H, $H^{4'}$), 5.24 (t, ^3J = 5,0Hz, 3H, OH), 5.47 (m, 1H, $H^{3'}$), 5.51 (s, 1H, $H^{4''}$), 6.18 (dd, $^3J_{H2'a-H1'}$ = 9.0Hz, $^3J_{H2'b-H1'}$ = 5.8Hz, 1H, $H^{1'}$), 7.75 (s, 1H, H^6), 11.3 (s, 1H, NH); ^{13}C NMR δ ppm (DMSO *D6*) : 11.7 (C^5-$\underline{C}H_3$), 35.9 ($C^{2'}$), 39.7 (N-$(CH_3)_2$), 52.2 ($CO_2\underline{C}H_3$), 53.2 ($CO_2\underline{C}H_3$), 60.9 ($C^{5'}$), 77.6 ($C^{4''}$), 78.5 ($C^{3'}$), 83.0 ($C^{1'}$), 83.9 ($C^{4'}$), 109.2 (C^5), 126.5 and 128.5 ($C^{5''}$ and $C^{6''}$), 135.5 (C^6), 149.9 and 150.8 (C^2 and CO), 161.5, 163.1 and 165,7 (C^4, $C^{2''}$ and CO). IR cm^{-1} (KBr) : 3385, 3269, 1726, 1699. SM m/z (CI, NH_3) : 499 (MH+). SM m/z (I%) (EI) : 231 (85), 199 (44), 172 (100), 141 (32), 140 (30), 129 (34), 126 (25), 113 (23), 112 (25), 98 (24), 84 (22), 80 (24), 72 (26), 69 (77). HRMS $(M+H)^+$ Calcd for $C_{20}H_{27}N_4O_9S$: 499.1499, found 499.1508.

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