SYNTHESIS OF PYRIMIDINE NUCLEOSIDE ANALOGUES

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Abstract

The uracil and thymine nucleoside analogues (11) and (12) were obtained *via* reaction of diacetone glucose (1) with dimethyl sulphoxide and acetic anhydride to give diacetone glucose-3-ulose derivative (2). Reaction of compound (2) with dimethylmalonate under PTC (Phase Transfer Catalyst) yielded the malonate compound (3), which was converted to the 3-*C*-nitromethyl-3-*C*-dimethylmalonyl derivative (4), upon treatment with nitromethane in presence of sodium methoxide. The isopropylidene at 5, 6-position was removed with acetic acid followed by periodate oxidation and borohydride reduction to give the ribo derivative (6). The 5-hydroxy group was protected with benzoyl group using benzoyl chloride to give the 5-benzoate derivative (7). Treatment of compound (7) with mixture of acetic acid, acetic anhydride and few drops of sulfuric acid to gave the 1, 2-di-*O*-acetylated compound (8). When compound (8) was allowed to react with silylated thymine and uracil, compounds (9) and (10) were obtained. Deprotection of compounds (9) and (10) under basic condition yield the new pyrimidine nucleoside analogues (11) and (12).

Introduction

The discovery of nucleosides organic chemistry have been actively involved in the synthesis of nucleoside analogues (NA) in order to selectively interfere with such life important process as (DNA) and (RNA) synthesis and to aid in the elucidation of biosynthesis pathways[1]. The methods of nucleoside analogues synthesis have been treated in a number of reviews and monographs[2-5]. Over the years nucleoside analogues have been found to display a wide range of biological activities such as antitumer[6,7], antiviral[8,9] and antibacteril[10] activities. Thus modified nucleoside have been useful in understanding mutagenesis and biological pathways as will as developing pharmaceuticals, which has promoted the need for synthetic methods to modify naturally occurring nucleoside for study[11-17] . This stimulated my interest for synthesis of new nucleoside analogues.

Results and Discussion

I reported here a method for synthesis of pyrimidine nucleoside analogues. Compounds (1) and (2) were synthesized according to literature[18,19]. Thus it has been found that compound 1,2:5,6 –di-*O*-isopropylidene-α-D-glucofuranos-3-ulose (2) reacted with dimethylmalonate under (PTC) to give the malonate derivative (3) (56.71 % yield) as syrup.

The structure of compound (3) was established based on the data of IR, ^{1}H-NMR spectra and elemental analysis (Tables 1 and 2). The IR spectrum of this compound showed a band of –OH and ester groups. While their ^{1}H-NMR spectrum revealed the signal of hydroxyl group, four signals of methyl groups for isopropylidene and the signal of dimethylmalonyl (Tables 1 and 2).

The compound (4) could be obtained *via* elimination of water from position three between sugar and dimethylmalonyl for compound (3) in presence of sodium methoxide under heat condition to give the intermediate containing exo ethylenic bond[20], followed by Michael addition of nitro methane immediately as a nucleophile (Scheme). The IR spectrum of this compound showed a band of -CH_2NO_2, while a band of -OH disappeared and the ^{1}H-NMR spectrum showed a signal of -CH_2NO_2 proton (Tables 1 and 2).

The isopropylidene at 5, 6-positions for compound (4) was removed by hydrolysis with acetic acid[21] (60 %) to afford the diol compound (5) (70.82 % yield) as syrup. The IR spectrum of this compound showed a band of hydroxyl groups and ^{1}H-NMR spectrum revealed the signal of hydroxyl groups with disappearance of the two -CH_3 signals (Tables 1 and 2).

Oxidation of compound (5) with sodium periodat in ethanol gave aldehyde as intermediate followed by reduction immediately with sodium borohydride to give compound (6) (47.63 % yield) as syrup (Scheme). The structure of compound (6) was established based on the data of IR, ^{1}H-NMR spectra and elemental analysis
(Tables 1 and 2).

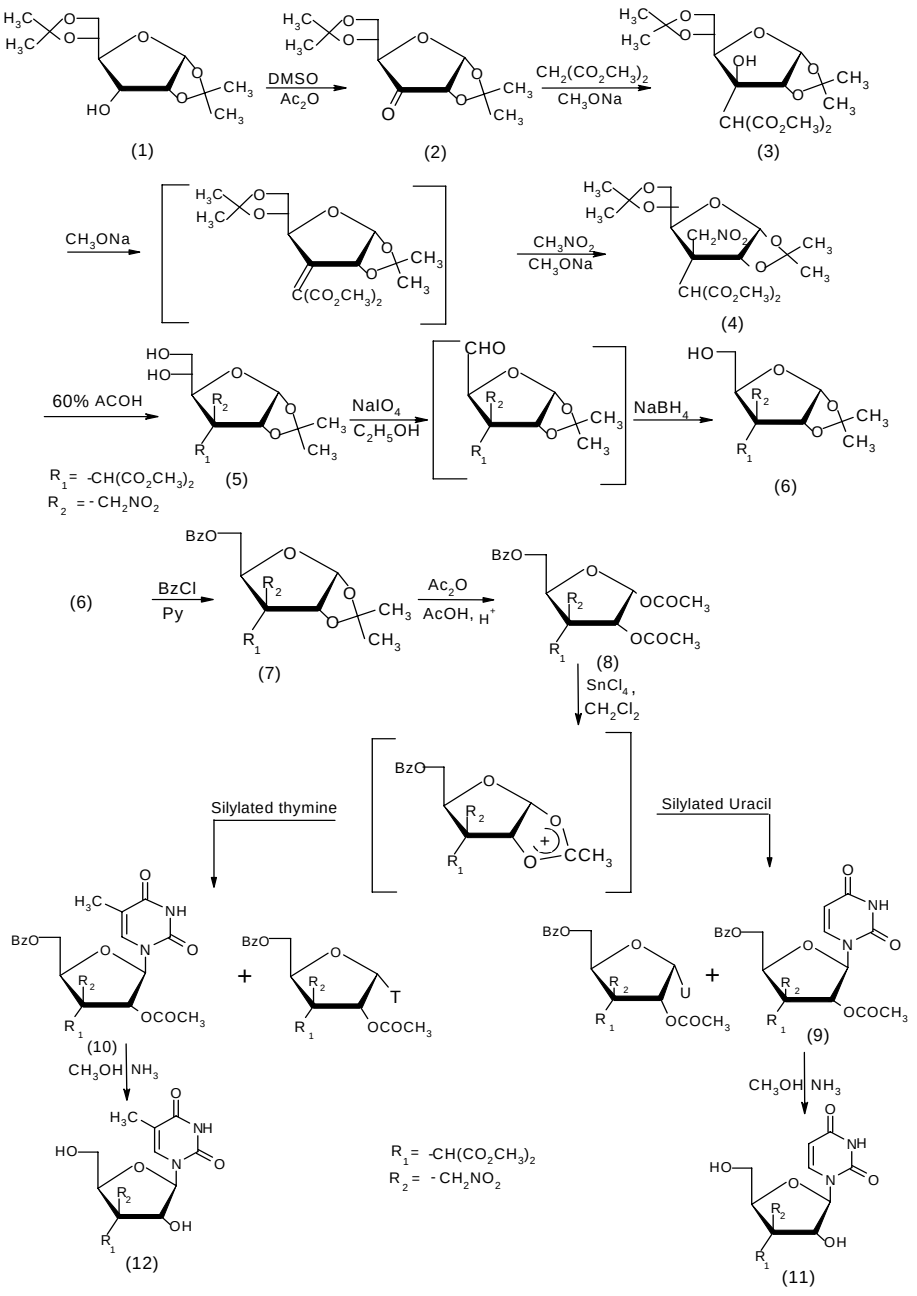
Protection of the primary hydroxyl group at five position was achieved by treatment of compound (6) with benzoyl chloride in a mixture of anhydrous pyridine and benzene to give the benzoate derivative (7) (54.43 % yield) as syrup. The IR spectrum of this compound showed a bands of aromatic with disappearance a hydroxyl group band and the ^{1}H-NMR spectrum revealed the signal of aromatic protons (Table 2).

The isopropylidine group at 1, 2 -position of compound (7) was removed and protected by using a mixture of concentrated acetic acid, acetic anhydride and sulfuric acid (1:1: 0.05 v / v) to afford the 1, 2-di-*O*-acetylated compound (8) (64.02 % yield) as syrup. The ^{1}H-NMR spectrum revealed the signal for two -CH_3 of acetyl groups (Table 2).

Synthesis of pyrimidine nucleoside analogues (9) and (10) from compound (8) were obtained *via* modified Hilbert- Johnson procedure using simple Friedel-Crafts catalyst. The reaction involves the conversion of the protected sugar into the reactive intermediate (electrophilic, 1,2-acetyloxonium ion), the formation of (1,2 acetyloxonium ion) determinate the exclusive formation of the β–anomer[22,23].

Reaction of compound (8) with the silylated uracil and thymine in dichloromethane and the presence of anhydrous stannic chloride $SnCl_4$ as a Lewis acid to give the protected uracil and thymine nucleoside analogues as syrup with the regeneration of the catalyst. The syrup was purified on silica gel column chromatography to give β -anomers (9) (54.79 %) and (10) (48.88 % yield) as major products and α - anomers as minor products (Scheme).

The structure of compounds (9) and (10) was established based on the data of IR, ^{1}H-NMR spectra and elemental analysis (Tables 1 and 2). When compounds (9) and (10) were allowed to react with methanolic ammonia[24], the new unprotected pyrimidine nucleoside analogues (11) and (12) were obtained. The IR spectra of these compounds showed bands of hydroxyl and imide groups, and the ^{1}H-NMR spectra showed disappearance of the signals of the protected groups (Table 2).


DMSO
Ac2O
CH2(CO2CH3)2
CH3ONa
(1)
(2)
(3)
CH3ONa
CH3NO2
CH3ONa
(4)
60% ACOH
NaIO4
C2H5OH
NaBH4
R1= -CH(CO2CH3)2
R2 = - CH2NO2
(5)
(6)
BzCl
Py
Ac2O
AcOH, H+
(7)
(8)
SnCl4 ,
CH2Cl2
Silylated thymine
Silylated Uracil
(10)
(9)
CH3OH NH3
(12)
(11)
R1= -CH(CO2CH3)2
R2 = - CH2NO2

(Scheme)

Experimental procedure

Infrared spectra were recorded using Shimadzu-408 (Nujol or thin film). ^{1}H-NMR spectra were recorded on Varian Em 390-90 MHz, Gemini 200 and Brucker WP-80 spectrometer using $CDCl_3$ as a solvent and $(Me)_4Si$ as internal standard. Chemical shifts are expressed as δ ppm. Elemental analyses were preformed at the Micro analytical Center of Cairo University using Perkin Elemer 2400 CHN elemental analyzer. TLC was preformed on aluminum plates coated with 0.25 mm layer of silica gel f_{245} (fluka). Compound was detected by iodine vapors. Some synthesized compounds were purified by column chromatography using silica gel about (60-120) mesh. Solvent and liquid reagents used in experimental procedure were dried by anhydrous $MgSO_4$ and $CaCl_2$. Solvents were removed under reduced pressure using rotary evaporator.

Synthesis of 3-hydroxy-3-*C*-dimethylmalonyl-1, 2:5, 6-di –*O*-isoprop- ylidene-α-D-glucofuranos (3).

Compound 1,2 : 5,6 – di -*O*- isopropylidene-α-D-glucofuranos –3-ulose (2), (70 gm, 271 mmol) was dissolved in benzene (150 ml) and a solution of (0.5 N) sodium hydroxide (50 ml); followed by addition of dimethylmalonate (35 ml, 265 mmol) and (2.8 gm, 8.69 mmol) from tertiary butyl ammonium bromide as catalyst, after stirring for 18 hours at 30 ^{0}C, tlc showed that the reaction was completed. The benzene layer was separated and the aqueous layer was extracted with benzene (2 x 30 ml), the combined benzene extracts were dried over anhydrous $MgSO_4$ and was evaporated under reduced pressure to give compound (3) (60 gm, 56.71 %) as syrup.

Synthesis of 3-deoxy-3-*C*-dimethylmalonyl-3-*C*-nitromethyl-1,2:5,6-di-*O*-isopropylidene-α-D-ribo-hexofuranose (4).

Compound (3) (58 gm, 148 mmol) was dissolved in absolute methanol (120 ml), sodium methoxide (9 gm, 166 mmol), followed by addition of nitromethane (10 ml, 163 mmol). The reaction mixture was stirred at 40 ^{0}C. TLC (Benzene:ethyl acetate, 10:1) showed that the reaction was completed after 20 hours, the mixture was neutralized and the solvent was evaporated to a small residue and partitioned between chloroform and water. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed to give compound (4) (44 gm, 68.32 %) as syrup.

Synthesis of 3-deoxy-3-*C*-dimethylmalonyl-1,2-*O*-isopropylidene-3-*C*-nitromethyl-α-D-ribo-hexofuranose (5).

Compound (4) (42 gm, 96.9 mmol) was dissolved in acetic acid (80 ml, 60 %), the mixture was stirred for 22 hours at room temperature. The

solution was evaporated under reduced pressure and the resulting residue was co evaporated with toluene
(2 x 50 ml) to give compound (5) (27 gm, 70.82 % yield) as syrup.

Synthesis of 3-deoxy-3-*C*-dimethylmalonyl-1,2-*O*-isopropylidene-3-*C*-nitromethyl-α-D-ribofuranose (6).

Compound (5) (25 gm, 63.6 mmol) was dissolved in ethanol (100 ml), followed by addition of sodium periodate (14 gm, 64.8 mmol). The solution had been stirred at room temperature. TLC (Benzene:ethyl acetate10:1) showed that the reaction was complete after 1 hour. Ethylene glycol (4 ml) was added and the solution was stirred for 5 minutes. The resulting aldehyde sugar was immediately reduced by addition of sodium borohydride (2.4 gm, 64.8 mmol), and stirred for 45 minutes. The solid residue was removed by filtration and the filtrate was extracted with chloroform (3 x 50 ml), dried over anhydrous $MgSO_4$ and the solvent was removed to give compound (6) (11 gm, 47.63 % yield) as syrup.

Synthesis of 5-*O*-benzoyl–3-deoxy-3-*C*-dimethylmalonyl-1,2-*O*-isopropylidene-3-*C*-nitromethyl-α-D-ribo-furanose (7).

The compound (6) (10 gm, 27.5 mmol) was dissolved in a mixture of anhydrous pyridine (10 ml) and benzene (40 ml), the mixture was cooled to 0 ^{0}C, followed by addition of benzoyl chloride (4.0 ml, 28.46 mmol), and the resulting mixture was stirred for 20 hours at room temperature. The mixture was poured onto cooled water (50 ml) and extracted with chloroform (3x40 ml), the organic layer was separated then dried over anhydrous $MgSO_4$, filtrated and concentrated under reduced pressure. Traces of pyridine were removed by co evaporation with dry toluene (3 x 10 ml) to afford syrup. This syrup was purified on a silica gel column chromatography eluted with (Benzene:ethyl acetate,10:1) mixture to give compound (7) (7.0 gm, 54.43 % yield) as syrup.

Synthesis of 3-deoxy-3-*C*- dimethylmalonyl-3-*C*-nitromethyl -1,2-di-*O*-acetyl-α-D-ribo- furanose (8).

Compound (7) (6.0 gm, 12.8 mmol) was dissolved in acetic acid (20 ml), acetic anhydride (20 ml) and sulfuric acid (0.01 ml). The resulting solution was stirred for 12 hours at room temperature. The reaction mixture was poured onto water (50 ml) and extracted with chloroform (3x40 ml); the organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to afford syrup. This syrup was purified on a silica gel column chromatography eluted with mixture of

(Benzene: ethyl acetate, 10:1) to give compound (9) (4.2 gm, 64.02 % yield) as syrup.

Synthesis of-1(5′-*O*-Benzoyl-3′-deoxy-3′-*C*-diethylmalonyl-3′-*C*-nitromethyl-2′-*O*-acetyl-*β*-D-ribofuranosyl) uracil (9).

Compound (8) (2.0 gm, 3.9 mmol) and silylated uracil (2.0 gm, 7.8 mmol) was dissolved in anhydrous dichloromethane (20 ml) and anhydrous stannic chloride (0.09 ml). The mixture was stirred at 35 ^{0}C, which time, tlc (benzene: ethyl acetate, 10:1) showed that the reaction was completed after 13 hours. The reaction mixture was poured onto (40 ml) water and extracted with dichloromethane (3 x 30 ml). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated to afford syrup. This syrup product was purified on a silica gel column chromatography using (chloroform: acetone, 10:1) as an eluent to give two different fractions as syrup the first one compound (9) (1.2 gm, 54.79 %) as*β*-anomer and the second as *α*- anomer (0.1 gm, 4.56 %).

Synthesis of 1(2′-*O*-acetyl –3′-deoxy-3′-*C*-diethylmalonyl-3′-*C*-nitromethyl -*β*-D-ribofuranosyl) thymine (10).

The acetylated sugar (8) (2.0 gm, 3.9 mmol) and silylated thymine (2 gm, 7.4 mmol) was dissolved in anhydrous dichloromethane (25 ml) and anhydrous stannic chloride (0.09 ml); the mixture was stirred at 35 ^{0}C for 15 hours to afford the syrup.

This syrup purified on a silica gel column using (chloroform: acetone, 10:1) as eluent to give two different fraction as syrup, the first one compound (10) (1.1 gm, 48.88 % yield) as *β*-anomer and the second *as α*- anomer (0.14 gm, 6.22 %yield).

Synthesis of 1(3′-deoxy-3′-*C*-diethylmalonyl- 3′-*C*-nitromethyl-*β*-D-ribofuranosyl) uracil and thymine (11) and (12).

A solution of (9) (0.8 gm, 1.4 mmol) in methanolic ammonia (50 ml) was stirred at room temperature. TLC showed that the reaction was completed after 18 hours and then evaporated to dryness. The residue was purified on a silica gel column chromatography using (chloroform: ethanol, 10:1) as an eluent to give compound (11) (0.3 gm, 50.84 % yield) as a syrup.

For preparation of thymine nucleoside analogue (12) from compound (10) (0.7 gm, 1.2 mmol) in methanolic ammonia (50 ml) was stirred at room temperature at the same conditions to give compound (12) (0.26 gm, 50.00 % yield) as a syrup.

Conclusion

According to the literature of nucleoside analogues compounds, we expect biological activity for our derivative. For future study we recommend a biological study and bio-assay for these compounds.

Table, 1. Characterization Data of the Newly Synthesized Compounds.

Comp. No	Molecular formula	Yield (%)	Elemental analysis, Calculate / Found (%)		
			C	H	N
3	$C_{17}H_{26}O_{10}$	56.71	52.30 52.39	6.66 6.69	-
4	$C_{18}H_{27}NO_{11}$	68.32	49.88 49.96	6.23 6.26	3.23 3.30
5	$C_{15}H_{23}NO_{11}$	70.82	45.80 45.87	5.85 5.90	3.56 3.61
6	$C_{14}H_{21}NO_{10}$	47.63	46.28 46.31	5.78 6.81	3.85 3.92
7	$C_{21}H_{25}NO_{11}$	54.43	53.96 54.01	5.35 5.39	2.99 3.06
8	$C_{22}H_{25}NO_{13}$	64.02	51.66 51.70	4.89 4.92	2.73 2.80
9	$C_{24}H_{25}N_3O_{13}$	54.79	51.24 51.31	4.44 4.48	7.29 7.37
10	$C_{25}H_{27}N_3O_{13}$	48.88	52.08 52.17	4.68 4.72	7.11 7.19
11	$C_{15}H_{19}N_3O_{11}$	50.84	43.26 43.30	4.56 4.61	9.85 9.91
12	$C_{16}H_{21}N_3O_{11}$	50.00	44.65 44.70	4.88 4.92	9.53 9.60

(Table, 2). IR (cm^{-1}) and ^{1}H-NMR (δ ppm) of the Newly Synthesized Compounds.

Comp	IR (cm^{-1})	^{1}H-NMR, ($CDCl_3$) δ ppm
3	3400 for hydroxyl group; 2950, 2850 (aliphatic, C-H); 1720	1.6 -1.8 (12H, 4s, 4 -CH_3 isopropylidene); 2.8 (1H, s, -CH- malonate); 3.0 (6H, s, 2-CH_3

	for ester groups (-CO_2CH_3).	malonate); 3.9 (H, s, -OH); 4.9-6.0 (5H, m, H-2, H-4, H-5, H-6^a, H -6^b) and 6.1(1H, d, H-1).
4	2850, 2950 (aliphatic, C-H); 1725 for ester groups (-CO_2CH_3); and 1535 for nitro group.	1.4-1.6 (12H, 4s, 4-CH_3 isopropylidene); 2.6 (1H, s, -CH malonate); 3.1 (6H, s, 2-CH_3 malonate); 3.8 (2H, s, -CH_2NO2); 4.8-5.9 (5H, m, H-2, H-4, H-5, H-6^a, H-6^b) and 6.1(1H, d, H-1)
5	3400 for hydroxyl groups; 2950, 2850 (aliphatic, C-H); 1720 for ester groups and 1530 for nitro group.	1.5, 1.6 (6H, 2s, 2 -CH_3 iso); 2.5 (1H, s, -CH-, malo); 3.1 (6H, s, 2 -CH_3, malo); 3.8 (2H, s, -CH_2,NO_2); 4.0 (2H, s, 2 –OH); 4.8-5.9 (5H, m, H-2, H-4, H-5, H-6^a, H-6^b); 6.1(1H, d, H-1).
6	3400 for hydroxyl group; 2950, 2850 (aliphatic, C-H); 1715 for ester groups and 1530 for nitro group.	1.7, 1.9 (6H, 2s, 2 -CH_3, iso); 2.7 (1H, s, -CH-, malo); 3.2 (6H, s, 2 -CH_3, malo); 3.5 (2H, s, -CH_2NO_2); 4.1 (1H, s, -OH); 4.6-6.0 (4H, m, H-2, H-4, H-5^a, H-5^b) and 6.1(1H, d, H1).
7	3020 (aromatic, C-H); 2950, 2850 (aliphatic,C-H); 1710 for ester groups; 1600, 1580 (aromatic, C=C) and 1535 for nitro group.	1.4, 1.5 (6H, 2s, 2 -CH_3, iso); 2.7 (1H, s, -CH-, malo); 3.0 (6H, s, 2 -CH_3, malo); 3.7 (1H, s, -CH_2NO_2); 4.7-5.8 (4H, m, H-2, H-4, H5^a, H5^b); 6.0 (1H, d, H1) and 7.0-8.1(5H, m, aromatic protons).
8	3020 (aromatic, C-H); 2950, 2850 (aliphatic, C-H); 1715, 1685 for ester groups; 1600, 1570 for (aromatic, C=C) and 1530 for nitro group.	2.1, 2.2 (6H, 2s, 2 -$COCH_3$); 2.8 (1H, s, -CH-, malo); 3.1 (6H, s, 2-CH_3, malo); 3.7 (2H, s, -CH_2 NO_2); 4.6-5.8 (4H, m, H-2, H-4, H-5^a, H-5^b); 6.1 (1H, d, H-1) and 7.0-8.2 (5H, m, aromatic protons).
9	3300 (-NH-); 3020 (aromatic, C-H); 2950, 2850 (aliphatic, C-H); 1720, 1680 for	2.2 (3H, s, -$COCH_3$); 2.7 (1H, s, -CH-, malo); 3.2 (6H, s, 2 -CH_3,malo); 3.8 (2H, s, -CH_2NO_2); 4.6-5.7 (4H, m, H-2, H-4, H-5^a, H-

	carbonyl groups; 1590, 1575 for (aromatic, C=C) and 1530 for nitro group.	5^{b}); 6.2-6.7 (3H, m, H-$1^{/}$ and H-5, H-6) and 7.1-8.3 (6H, m, br, aromatic protons and amid NH).
10	3300 (-NH-); 3020 (aromatic, C- H); 2950, 2850 (aliphatic, C-H); 1710, 1690 for carbonyl groups; 1590, 1570 for (aromatic, C=C) and 1535 for nitro group.	2.0 (3H, s, -$COCH_3$); 2.5 (3H, s, -CH_3 on base); 2.8 (1H, s, -CH- malo); 3.3 (6H, s, 2 -CH_3,malo); 3.7 (2H, s, -CH_2NO_2); 4.6-5.8 (4H, m, H-$2^{/}$, H-$4^{/}$, H-$5^{/a}$, H$5^{/b}$); 6.2-6.8 (1H, m, H-$1^{/}$ and H6 on base); 7.0-8.4 (6H, m, br, aromatic protons and amid, -NH-).
11	3450, 3300 (-OH and -NH-); 2950, 2850 (aliphatic, C-H); 1715, 1700 for carbonyl groups; 1570 for (C=C) and 1530 for nitro group.	2.9 (1H, s, -CH, malo); 3.1 (6H, s, 2 -CH_3, malo); 3.8 (2H, s, -$CH_2 NO_2$); 4.0 (2H, s, 2 -OH); 4.5-5.8 (4H, m, H-$2^{/}$, H-$4^{/}$, H-$5^{/a}$, H-$5^{/b}$); 6.2-6.8 (1H, m, H-$1^{/}$ and H5, H6) and 8.0-8.5 (1H, s, br, amid, -NH-).
12	3500, 3300 (-OH and -NH-); 2950, 2850 (aliphatic,C-H); 1715, 1690 for carbonyl groups, 1560 for (C=C) and 1530 for nitro group.	2.4 (3H, s, -CH_3 on base); 2.8 (1H, s, -CH- malo); 3.2 (6H , s, 2 -CH_3 malo); 3.7 (2H, s, -$CH_2 NO_2$); 4.1 (2H, s, 2 -OH); 4.8-5.8 (4H, m, H-$2^{/}$, H-$4^{/}$, H-$5^{/a}$, H-$5^{/b}$); 6.0-6.9 (3H, m, H-$1^{/}$ and H-6 on base) and 8.0-8.8 (1H, s, br, -NH- amid)

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