IJPAC
© Global Research Publications

Vol. 14 • Nos. 1-2 • January-June, 2019
pp. 17-23

# Synthesis and Characterization of Substituted-fluoro and Azido $2^1$, $3^1$-dideoxy Guanosine Nucleosides and Screening of their Antiviral Activity Against Corn Virus

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**ABSTRACT:** In a quest for novel antiviral nucleoside, a series of new antiviral compounds have been synthesised. All the synthesised compounds have been well characterised by their elemental analysis, IR and 1H NMR data. IR spectra in KBr were recorded on a Perkin - Elmer 881 and 993 infrared spectrophotameter vmax (cm-1),1H NMR spectra were re-corded on Varian EM - 360 (60 MHz) or Perkin - Elmer R - 32 (90 MHz) spectrometer in DMSO - d6; CDCl3 plus DMSO - d6 using TMS inter-nal reference; chemical shifts are expressed in d (ppm).Melting points were determined by open glass capillary method and are uncorrected.

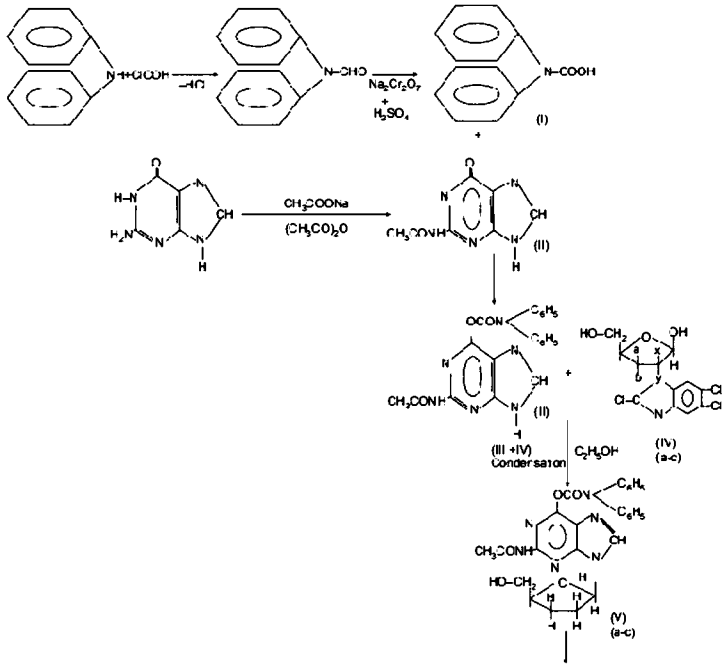
***Keywords:*** antiviral , nucleosides, guanisine,

## Introduction

New guanosine nucleoside analogues having substitution at $2^1$ and $3^1$ position were synthesized . In the present study, we investigated the possibility of antiviral action by these nucleoside against corn virus.

1. synthetic route for $3^1$-fluoro and $3^1$-azido $2^1$, $3^1$ dideoxy guanosine

## Preparation of $3^1$-fluoro and $3^1$-azido $2^1$, $3^1$-dideoxy Guanosine

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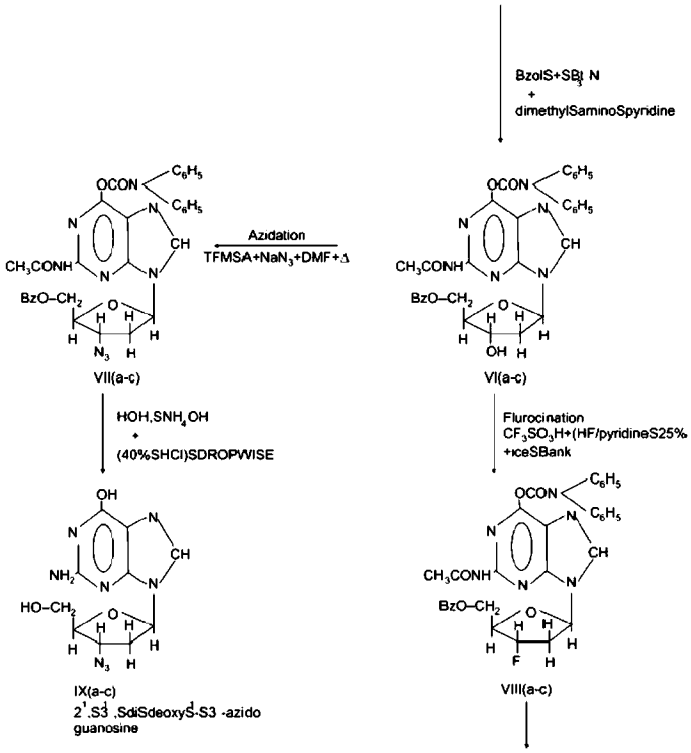
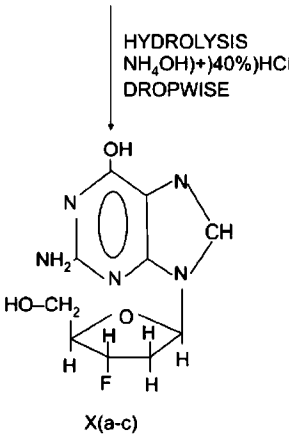


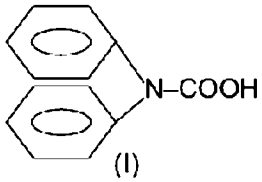




IVa)X=H, Y=H a=H,b=OH (Deoxy)ribose)

IVb)X=H, Y=OH a=H,b=OH (Ribose)

IVc)X=H, Y=OH a=OH,b=H (Xylose)

## 1. Preparation of N – N - Diphenyl Formic Acid




(I)

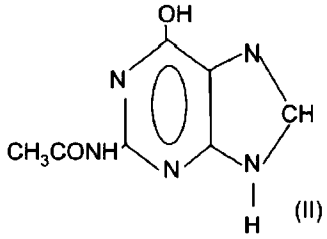
0.985 ml (0.005 mole) of diphenyl amine and 15 g of NaOH were taken in 250 ml. conical flask. 70 ml water was added in the conical flask. (HCOOH + NaCl ——> HCOCl + NaOH). Cork the flask and vigorous shaking was done for about 1 hour. Pour the contents onto 250 gm of crushed ice crystals of respective compounds N – N - diphenyl formaldehyde were obtained and recrystastalization was done by hot alcohol.

ib) 0.02 mole 3.94 g of N- N- diphenyl formaldehyde obtained in the step la was taken in 250 ml conical flask along with 2.45 g of solid $K_2Cr_2O_7$, 10 ml of $H_2O$ and 5 ml of concentrated $H_2SO_4$ (AR). Heat the contents up to boiling point. After cooling pour the contents into cold water and the producty was filtered.

**Yield (%)= 64%**

**M.P. (°C)= 106°C**

## 2. Preparation of 2 – N - Accetyl Guanine



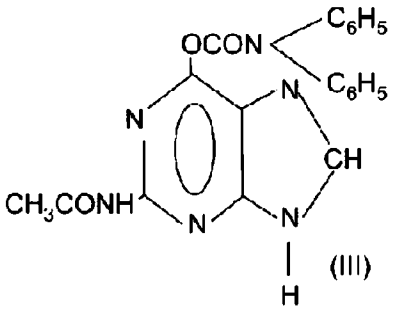

(II)

0.01 mole (1.51 g) of guanine, 2 ml (0.02 mole) of acetic anhydride and 0.02 mole (1.2 ml) glacial acetic and were taken in 200 ml round bottom flask. After refluxing the contents for about 15 minutes, contents was poured into the beaker containing ice cold water. Crystals of 2-N-acetyl guanine were obtained and recrystallised by methyl alcohol.

**Yield (%) = 60%**

**M.P. (°C) = 123°C**

## 3. Preparation of 2 – *N* -acetyl - 6 - 0 - Diphenyl Carbamoyl Guanine



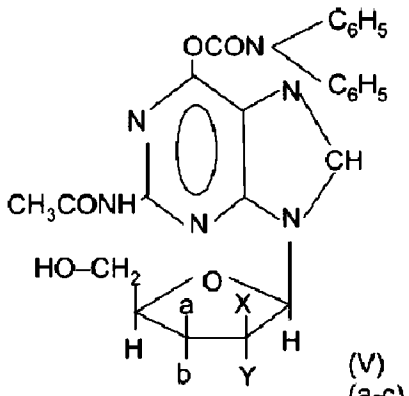

(III)

0.75 g (0.005 mole) of N - acetyl guanine and 1.06 g of N – N - diphenyl formic acid were ground together in 25 ml dioxan and solution was acidified by some drops of 5N - HCl (AR) to get homogeneous solution and reaction mixture was refluxed for 1 hour and when it was concentrated to half of its volume, it was cooled and poured into ice cold water to get desired product and recrystallisation was done by methyl alcohol.

**Yield (%) = 60%**

**M.P. (°C) = 148°C**

## 4. Preparation of 2 – N – Acetyl – 6 – O – Diphenyl Carbamoyl – 2[1] – Deoxy Guanosine




(V)
(a-c)

(V-a)x=H,y=H,
a=H,b=OH,
(V-b)x=H,y=OH,
a=H,B=OH,
(V-c)x=H,y=OH,
a=OH,B=H.

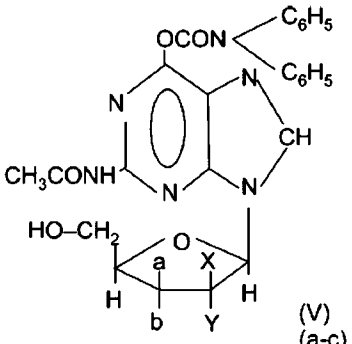
0.001 mole (0.388 g) of 2 – *N* – accetyl – 6 – 0 - disphenyl carbamoyl guanine and 0.001 mole (0.134 gm) of deoxyribose were dissolved in the minimum amount of $C_2H_5OH$ in 200 ml round bottom flask and solution was refluxed for 5 hours with occasional shaking. The reaction mixture when became half of it's volume, was cooled and poured onto crushed ice in a beaker to get the crystals of desired nucleoside (Va) and recrystallisation was done by methyl alcohol.

Similarly,

compounds 2 – *N* – acetyl – 6 – 0 - diphenyl carbomoyl ($1^1$-ribofuranosyl) guanine (Vb), and 2 – *N* – acetyl – 6 – 0 - diphenyl carbamoyl ($1^1$ - xylofuranosyl) guanine (Vc), were prepared.

| **Yield (%)** | **Va** | **Vb** | **Vc** |
|---|---|---|---|
| | 56% | 54% | 60% |
| **M.P. (°C)** | 182°C | 186°C | 185°C |

**5. Preparation of 2 – N – Acetyl – 6 – 0 - Diphenyl Carbamoyl (2¹ – Deoxy – 5¹ – Benzoyl – β – D – Ribofuranosyl) Guanine**




(V)
(a-c)

(V-a)x=H,y=H,
a=H,b=OH,
(V-b)x=H,y=OH,
a=H,B=OH,
(V-c)x=H,y=OH,
a=OH,B=H.

0.001 mole (0.504 g) of compound Va and 0.001 mole (1.5 ml) of benzoyl chloride, 2 ml acetone were taken in 100 ml flask. Now 10 ml of aqueous solution of NaOH was added gradually with constant stirring. Contents were poured into ice cold water contained in a beaker white crystalline product was obtained.

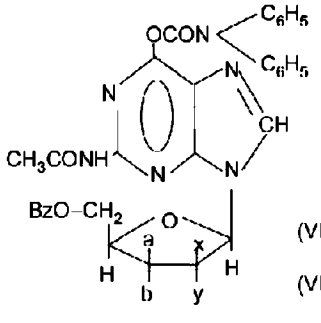
Similarly,

2–*N*–acetyl–6–0- diphenylcarbamoyl (5¹ - benzoyl – β – D - ribo furanosyl) guanine (VIb),

2–*N*–acetyl–6–0- diphenylcarbamoyl (5¹ - benzoyl – β – D – xylofuranosyl) guanine (VIc) were obtained.

| **Yield (%)** | **VIa** | **VIb** | **VIc** |
|---|---|---|---|
| | 60% | 56% | 62% |
| **M.P. (°C)** | 210°C | 218°C | 216°C |

**6. Preparation Of (3¹ – Azido – 2¹, 3¹ – Dideoxy 5¹ – Benzoyl Furanosyl) – 2 – *N– Acetyl– 6 – 0 - Diphenyl Carbamoyl Guanosine (Vii A-c)***




(VII)
(a-c)

(VII-a) x=H,y=H,
a=H,b=$N_3$,
(VII-b) x=H,y=OH,
a=H,b=$N_3$,
(VII-c) x=H,y=OH,
a=OH,b=$N_3$.

0.001 mole (0.608 g) of 5¹ ben zoylated nucleoside (VIa) and 0.001 mole (0.065 g) of NaN3 were ground together and then taken in a round bottom flask. To this N – N - dimethyl formamide (DMF) was added along with some drops of trifluoromethanesulphonic anhydride and contents were shaken for half an hour at room temperature and then mixture was poured into ice cold water to get crystals of the 3¹ -azido derivative of nucleoside.

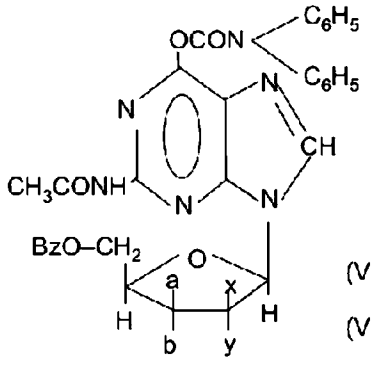
In the same manner

(3¹ -azido – 3¹ – dideoxy – β – D ribofuranosyl) – 2 – *N* – acetyl – 6 – 0 – diphenyl carbamoyl guanosine (VIIb) and

(3¹ – azido – 5¹ -benzoyl – β – D – xylofuranosyl) – 2 – *N* – acetyl – 6 – 0 - diphenyl carbamoyl guanosine (VIIc) were prepared.

| **Yield (%)** | **VIIa** | **VIIb** | **VIIc** |
|---|---|---|---|
| | 64% | 51% | 56% |
| **M.P.(°C)** | 234°C | 230°C | 238°C |

**7. Preparation of (3¹ – Fluoro – 2¹, 3¹ - Dideoxy – 5¹ – Benzoyl - B – D – Ribofuranosyl) – 2 – N – Acetyl – 6 – 0 – Diphenyl Carbamoyl Guanosine (Viii A-c)**




VIII (a-c)

(VIII-a) x=H,y=H,
a=H,b=F,
(VIII-b) x=H,y=OH,
a=H,b=F,
($V_I$II-c) x=H,y=OH,
a=OH,b=F.

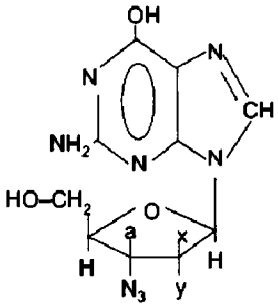
0.005 mole (0.34 g) of benzoylated nucleoside (VIa) was mixed with HF/pyridine (25%) mixture on ice bath and tertiary butyl nitrite (1.8 ml/15.0 m. mole) was added in it. After stirring for one hour the solution was allowed to warm up to room temperature where it was kept for 12 hours (over night) and after this, it was dilute with chloroform (200 ml) and was poured slowly into $NaHCO_3$ solution (100 ml). The organic layer was washed with water (100 ml) dry over anhydrous $MgSO_4$ in desiccators and evaporate it to dryness white solid of 2- fluorinated nucleoside (VIIIa) was obtained.

In the same manner

($3^1$ – fluoro - $2^1$, $3^1$ – dideoxy – $5^1$ – benzoyl – β – D – xylofuranosyl) – 2 – *N* – acetyl – 6 – 0 – diphenyl guanosine (VIIIb) and

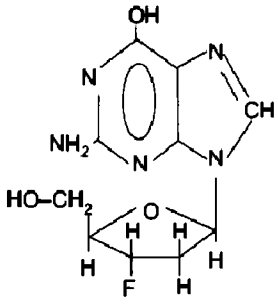
($3^1$ – fluoro – $2^1$, $3^1$ – dideoxy – $5^1$ – benzoyl – β – D – xylofuranosyl) – 2 – *N* - acetyl – 6 – 0 – diphenyl guanosine (VIIIc) were prepared.

**8. Preparation of $2^1$, $3^1$ - Dideoxy – 1 – ( β – D - Deoxy Ribofuranosyl) –$3^1$ – Azido Guanosine (IX A-C) and $2^1$, $3^1$ - Dideoxy – 1 – ( β – D - Deoxy Ribofuranosyl) –$3^1$ – Fluoro Guanosine (X A-C)**




IX (a-c)
$2^1$, $3^1$-di-deoxy-$3^1$-azido guanasine

(IX-a) x=H,y=H, a=H,b=$N_3$,
(IX-b) x=H,y=OH, a=H,b=$N_3$.
(IX-c) x=H,y=OH, a=OH,b=$N_3$.




X (a-c)
$2^1$, $3^1$-di-deoxy-$3^1$-fluoro guanasine

(X-a) x=H,y=H, a=H,b=F,
(X-b) x=H,y=OH, a=H,b=F.
(X-c) x=H,y=OH, a=OH,b=F.

Compound (VIIa) & compound (VIIIa) (0.005 mole) 0.30 gm & (0.3216 mole) 0.316 gm were taken in the separate round bottom flash and 15 ml $NH_4OH$ and ethanol 8 ml were added in the flask and refluxed for one hour then the mixture was cooled and acidified with dil HCl. The product were filtered washed with cold water and recrystallised with organic solvent.

In the same manner,

$3^1$ – deoxy – $3^1$ – azido – 1 – ( β – D – ribofuranosyl) guanosine (IX – b);

$3^1$ – deoxy – $3^1$ – azido – 1 – ( β – D – xylofuranosyl) guanosine (IX – c);

$3^1$ – deoxy – $3^1$ – azido – 1 – ( β – D – ribofuranosyl) guanosine (X – b);

$3^1$ – deoxy – $3^1$ – azido – 1 – ( β – D – xylofuranosyl) guanosine (X – c);

were prepared.

**Yield % IXa IXb IXc**

60% 68% 52%

**M.P. (°C)** 227°C 229°C 232°C

**Yield % Xa Xb Xc**

56% 51% 54%

**M.P. (°C)** 236°C 234°C 232°C

**Table 5**

| CompoundNo. | Yield(%) | M.P.(°C) | MolecularFormula | (calc.) Found% C H N |
|---|---|---|---|---|
| III | 60% | 148°C | $C_{20}H_{16}O_3N_6$ | (61.8, 4.1, 21.0)61.2, 4.0, 21.2 |
| Va | 56% | 182°C | $C_{25}H_{24}O_6H_6$ | (59.5, 4.7, 16.6)59.3, 4.5, 16.6 |
| Vb | 54% | 186°C | $C_{25}H_{24}O_7N_6$ | (57.6, 4.6, 16.1)57.6, 4.1, 16.1 |
| Vc | 60% | 185°C | $C_{25}H_{24}O_7N_6$ | (57.6, 4.6, 16.1)57.5, 4.3, 16.0 |
| VIa | 6% | 210°C | $C_{32}H_{28}O_7N_6$ | (63.1, 4.6, 13.8)63.4, 4.4, 13.7 |
| VIb | 56% | 218°C | $C_{32}H_{28}O_8N_6$ | (61.5, 4.1, 13.4)61.5, 4.3, 13.6 |
| VIc | 62% | 216°C | $C_{32}H_{28}O_8N_6$ | (61.5, 4.1, 13.4)61.1, 4.2, 13.6 |
| VIIa | 64% | 234°C | $C_{32}H_{27}O_6N_9$ | (60.6, 4.2, 19.9)60.3, 4.2, 19.8 |
| VIIb | 51% | 230°C | $C_{32}H_{27}O_7N_9$ | (59.1, 4.1, 19.4)59.2, 4.3, 19.6 |
| VIIc | 56% | 238°C | $C_{32}H_{27}O_7N_9$ | (59.1, 4.1, 19.4)59.4, 4.0, 19.3 |
| VIIIa | 72% | 240°C | $C_{32}H_{27}O_6N_6F$ | (64.0, 4.5, 14.0)64.1, 4.4, 14.2 |

*Contd.*

| CompoundNo. | Yield(%) | M.P.(°C) | MolecularFormula | (calc.) Found% C H N |
|---|---|---|---|---|
| VIIIb | 68% | 248°C | $C_{32}H_{27}O_7N_6F$ | (62.3, 4.3, 13.6)62.4, 4.2, 13.5 |
| VIIIc | 74% | 249°C | $C_{32}H_{27}O_7N_6F$ | (62.3, 4.3, 13.6)62.4, 4.1, 13.5 |
| IXa | 60% | 227°C | $C_{10}H_{12}O_3N_8$ | (43.7, 4.3, 40.8)43.5, 4.3, 40.7 |
| IXb | 68% | 229°C | $C_{10}H_{11}O_4N_8$ | (39.0, 3.5, 36.4)39.1, 3.4, 36.2 |
| IXc | 52% | 232°C | $C_{10}H_{11}O_4N_8$ | (39.0, 3.5, 36.4)39.1, 3.6, 36.3 |
| Xa | 56% | 236°C | $C_{10}H_{12}O_3N_5F$ | (46.3, 4.6, 27.0)46.2, 4.5, 27.2 |
| Xb | 51% | 234°C | $C_{10}H_{12}O_4N_5F$ | (43.6, 4.3, 25.5)43.5, 4.2, 25.4 |
| Xc | 54% | 232°C | $C_{10}H_{12}O_4N_5F$ | (43.6, 4.3, 25.5)43.4, 4.5, 25.5 |

**Table 6**

| Compound No. | I.R. (KBr)n Cm–1 | 1HNMR($CDCl_3$–$\delta_6$)d, J, (Hz) |
|---|---|---|
| Va | 3181 (N–H)16922 (>CO)1572 (C=C) | 7.21-7.84 (10H, m, ArH),8.7-8.8 (bs, 1-H, N–H),4.71 (1H, J=6.5, $1^1$-H),5.80 (2H, br, s, 2XOH),3.71-3.84 (4H, m, $2^1$, $3^1$, $4^1$-H),3.51-3.63 (2H, m, $5^1$-H) |
| Vb | 3178 (N–H)1680 (>CO)1558 (C=C) | 7.14-7.32 (10H, m, ArH),8.8-8.9 (br, s, 1-H, N–H),4.84 (1H, J=6.5, $1^1$-H),5.26 (3H, br, s, 3XOH),3.74-3.98 (3H, m, 21, 31, 41-H),3.61-3.62 (2H, m, 51-H) |
| Vc | 3179 (N–H)1690 (>CO)1565 (C=C) | 7.26-7.38 (10H, m, ArH),8.5-8.7 (br, s, 1H, N–H),4.71 (1H, J=6.0, $1^1$-H),5.74 (3H, br, s, 3XOH),3.71-7.86 (3H, m, $2^1$, $3^1$, $4^1$-H)3.59-3.61 (2H, m, 51-H) |
| VIa | 3179 (N–H)1698 (>CO)1562 (C=C) | 7.03-7.61 (15H, m, Arh),8.4-8.6 (bs, 1H, N–H),4.70- (1H, J=6.6, $1^1$-H),5.10 (1H, br, s, 1XOH),3.68-3.79 (NH, m, $2^1$, $3^1$, $4^1$-H),3.52-3.61 (2H, m, 51-H) |
| VIb | 3098 (N–H)1685 (>CO)1549 (C=C) | 7.64-7.98 (15H, m, ArH),8.1-8.6 (br, s, H, N–H),4.64 (1H, J=6.9, $1^1$-H5.64 (2H, br, s, 2XOH),3.64-4.19 (3H, m, $2^1$, $3^1$, $4^1$-H),3.5-3.62 (2H, m, 51-H) |
| VIc | 3089 (N–H)1680 (>CO)1541 (C=C) | 7.14-7.56 (15H, m, ArH),8.9-9.0 (br, s, 1H, N–H),4.14 (1H, J=6.1, $1^1$-H),5.19–(2H, br, s, 2XOH),3.61-3.98 (3H, m, $2^1$, $3^1$, $4^1$-H,3.41 (2H, m51-H) |
| VIIa | 3165 (N–H)1685 (>CO)1556 (C=C) | 7.12-7.84 (15H, m, ArH),8.1-8.4 (br, s, 1H, N–H),4.24 (1H, d, J=6.0, 11-H),3.81-4.53 (4H, m, 21, 31, 41-H),3.91-4.09 (2H, m, 51-H) |
| VIIb | 3172 (N–H)1680 (>CO)1565 (C=C) | 7.4-8.1 (15H, m, ArH),8.0-8.3 (1H, br, s, N–H),4.26 (1H, d, J=6.4, $1^1$-H),3.19 (3H, m, $2^1$, $3^1$, $4^1$-H),5.86 (1H, br, s, 1XOH) |
| VIIIa | 3160 (N–H)1682 (>CO)1550 (C=C) | 7.63-7.98 (15H, m, ArH),8.1-8.4 (1H, br, s, N–H),4.64 (1H, J=6.4, $1^1$-H),3.36-3.49 (4H, m, $2^1$, $3^1$, $4^1$-H),3.64-4.0 (2H, m, 51-H) |
| VIIIb | 3165 (N–H)1681 (>CO)1558 (C=C) | 7.26-7.79 (15H, m, ArH),8.6-8.8 (1H, br, s, N–H),4.16 (1H, J=6.9, 11-H),3.34-3.59 (3H, m, $2^1$, $3^1$, $4^1$-H),3.64-3.98 (2H, m, 51-H) |
| IXa | 3159 (N–H)1556 (C=C) | 8.4-8.9 (2H, br, s, N–H),4.16 (1H, J=6.4, $1^1$-H),3.61-3.96 (4H, m, $2^1$, $3^1$, $4^1$-H),3.64-3.71 (2H, m, 51-H),5.16 (1H, br, 1XOH) |

*Contd.*

| Compound No. | I.R. (KBr)n Cm–1 | 1HNMR($CDCl_3$–$\delta_6$)d, J, (Hz) |
|---|---|---|
| IXb | 3162 (N–H)1550 (C=C) | 8.1-8.6 (2H, br, s-N–H),4.28 (1H, J=6.0, $1^1$-H),3.94-4.18 (3H, m, $2^1$, $3^1$, $4^1$-H),3.81-3.914 (2H, m, 51-H5.11-5.26 (2H, br, s, 2XOH) |
| IXc | 3160 (N–H)1552 (C=C) | 8.4-9.0 (2H, br, s, N–H),4.16 (1H, J=6.0, $1^1$-H),3.69-4.20 (3H, m, $2^1$, $3^1$, $4^1$-H),3.74-3.79 (2H, m, 61-H),5.21-5.39 (2H, br, s, 2XOH) |
| Xa | 3150 (N–H))1562 (C=C) | 8.1-8.6 (2H, br, s, N–H),3.59-3.68 (4H, m, $2^1$, $3^1$, $4^1$-H4.29 (1H, J=6.0, $1^1$-H),3.64-3.89 (2H, m, 51-H),5.60 (1H, br, s, 1XOHC–51) |
| Xb | 3165 (N–H)1554 (C=C) | 8.4-8.8 (2H, br, s, N–H),3.46-3.84 (3H, m, $2^1$, $3^1$, $4^1$-H),3.61-3.78 (2H, m, $5^1$-H), 5.80 (1H, br, s, 1XOHC-51) |
| Xc | 3165 (N–H)1556 (C=C) | 8.16-8.47 (2H, br, s, N–H),3.49-3.76 (3H, m, $2^1$, $3^1$, $4^1$-H),3.56-3.71 (2H, m, $5^1$-H),5.74 (1H, br, s, 1XOH, C–51) |

## RESULT AND DISCUSSION

The synthesis of nucleosides was achieved by the sequence of reactions shown in the synthetic scheme. This study shows the synthesis of new guanosine nucleoside analogues having the base moiety was located at either 2' or 3' – sugar carbon. Systematic synthetic modifications on heterocyclic moiety in these molecules give rise to structurally diverse nucleoside analogues showing antiviral activity. These compounds exerted antiviral activity against corn virus (from moderate to high) at different concentrations.

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