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Synthesis and Characterization of 2-substituted - 5, 6–Dichloro Benzimidazole Antiviral Isonucleosides and their Antiviral Activity Against Corn Virus

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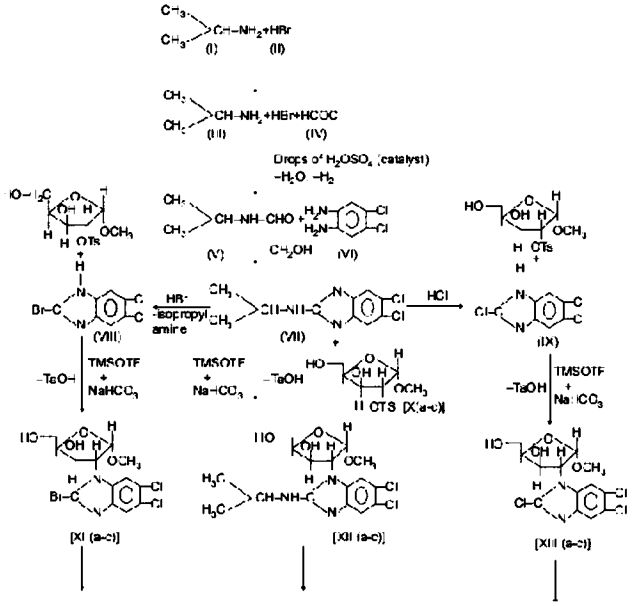
ABSTRACT: In a quest for novel antiviral nucleoside, a series of new antiviral compounds have been synthesised. All the synthesised compounds have been well characterised by their elemental analysis, IR and 1H NMR data. IR spectra in KBr were recorded on a Perkin - Elmer 881 and 993 infrared spectrophotameter 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.

Introduction: in iso-nucleosides the base moiety is located at either 2'or 3' – sugar carbon. Therefore iso-nucleoside attracted much attention owing to their chemical and enzymatic stability and potential antiviral activities .The rationale behind the synthesis of iso-nucleosides is that even with the transposition of heterocyclic base to the 2' or 3' – position, the spatial arrangement between the base and the 5' hydroxyl group is maintained. Moreover the new glycosidic bond is more stable towards hydrolysis than its conventional counterpart.

Keywords: nucleosides , isonucleosides, benzimidazole, antiviral

2-substituted - 5, 6–Dichloro benzimidazole synthetic Scheme For -2[1]- Isonucleosides



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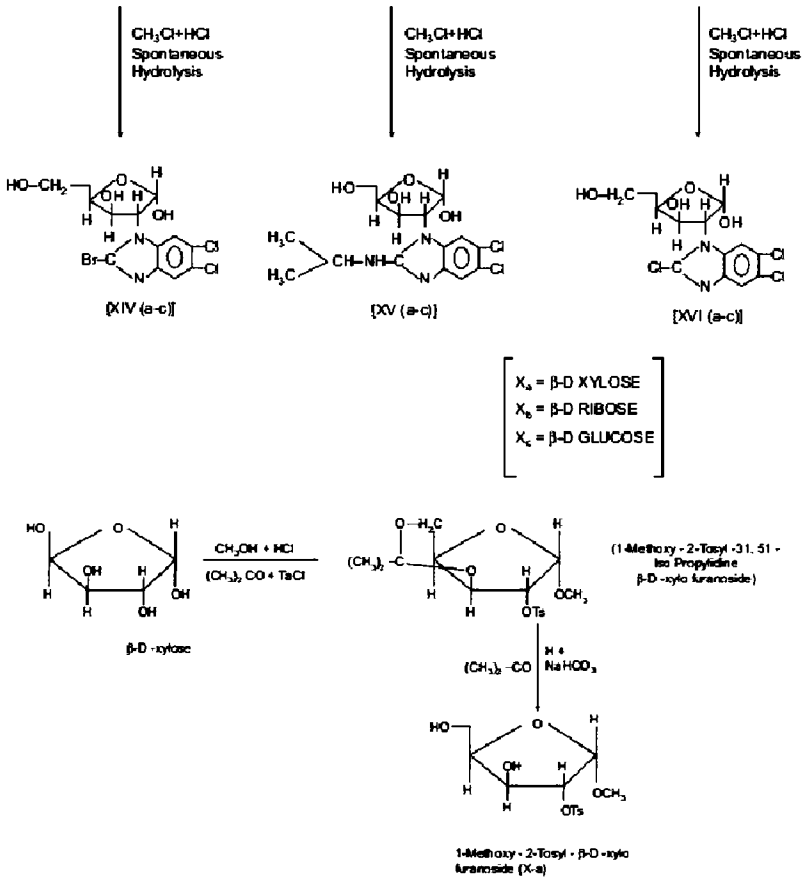
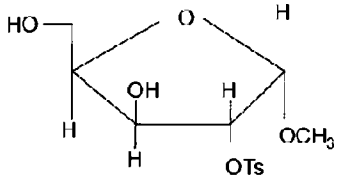


1. Preparation of 5, 6- dichloro - 2 - (*N* - isopropyl amino) – 1 - *H* - benzimidazole as given in series.(published)

2. Preparation of 1^1 - methoxy – 2^1 - tosyl β - xylofuranoside (X-a)



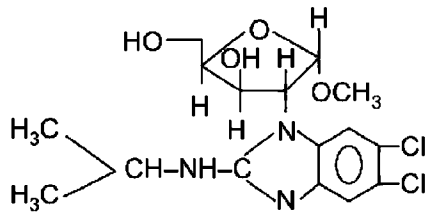
1-Methoxy - 2- Tosyl - β-D -xylo furanoside (X-a)

1.5 gm (0.01 mole) of xylose was dissolved in 10ml acetone in 200 ml round bottom flask along with 2-3 ml HCl (AR) and mixture was refluxed for 15 minutes. This 2.5 ml CH3OH and 2 ml TsCl in 10 ml pyridine were added and reaction mixture was heated on water bath for half an hour and then refluxed for half an hour with occasional shaking 10 ml saturated $NaHCO_3$ was added and mixture was heated. The mixture then heated again for 15 minutes and poured on to 250 ml ice of cold water taken in a 500 ml beaker. The crystals of compound (X-a) were obtained and then recrystallised by ethanol.

Similarly 1^1-methoxy – 2^1 - tosyl – β – D - ribofuranoside (Xb) and 1^1 - methoxy - 2^1 - tosyl – β – D - glucopyranoside (X c) were prepared.

Compound No.	Xa	Xb	Xc
Yields (%)=	60%	52%	58%
M.P. (°C)=	175-178°C	152-155°C	197-200°C

3. Preparation Of 5, 6 - Dichloro – 2 – *N* - Isopropylo – 1 – *H* - (β – D - 1^1 - Methoxy Xylofuranosyl) Benzimidazole



A mixture of 11 - methoxy – 21 – tosyl – β – D -

xylofuranoside 0.01 mole (3.18 g) and 5, 6 - dichloro (2 – ***N*** - isopropyl amino) – 1 - ***H*** - benzimidazole 0.01 mole (2.449) with 0.25 g (0.001 mole) of 12 were dissolved in a minimum amount of dioxan and reation mixture was refluxed for 2 hours. After cooling the reaction mixture was poured into aqueous solution of (0.27 g = 0.001 mole) sodiumthiosulphate to remove excess of iodine. The desired product (XII a) so obtained was filtered, washed with water and recrystalised with ethanol.

Similarly,

5, 6 – dichloro – 2 - (***N*** - isopropyl amino) – 1 – ***H*** - (β – D - 1^1 methoxy ribofuransoyl) benzimidazole (XII b).

5, 6 – dichloro – 2 - (***N*** - isopropyl amino) – 1 – ***H*** - (β – D - 1^1 methoxy glucopyransoyl glucopyransoyl) benzimidazole (XII c).

2 – bromo – 5, 6 - dichloro - 1 – ***H*** - (β – D - 1^1 - methoxy xylo furanosyl) benzimidazole (XI a)

2 – bromo – 5, 6 – dichloro - 1 - ***H*** - (β - D - 1^1 - methoxy ribo furanosyl) benzimidazole (XI-b)17

2 - bromo - 5, 6 - dicloro - 1 - ***H*** - (β - D - 1^1 - methoxy gluco pyranosyl) benzimidazole (XI-c)

2, 5, 6 - trichloro - 1 - ***H*** - (β - D - 1^1 - methoxy xylofuranosyl) benzimidazole (XIII a)

2, 5, 6 - trichloro - 1 - ***H*** - (β - D - 1^1 - methoxy xylofuranosyl) benzimidazole (XIII b)

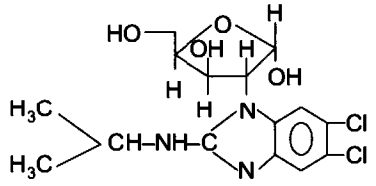
2, 5, 6 - trichloro - 1 ***H*** - (β - D - 1^1 - methoxy glucopyronosyl) benzimidazole (XIII c)

were prepared.

The Yields, melting points, molecular formulae and elemental analysis of the compound (mentioned above) are given in the table (3) and their IR and 1H NMR Spectral are given in the table (4).

4. Preparation of 2, 6 - dichloro - 1 - *H* - (2 - isopropyl amino) (β - D - xylofuranosyl) benzimidazole - 2^1 - isonucleoside (XV)

5, 6 - dichloro - 1 - *H* - (2 - isopropyl amino) (β – D - 1^1 methoxy xylofuranosyl) benzimidazole (0.01 mole) 3.9 g, 10 ml CH3OH and 0.19 ml solution of sodium methoxide (0.1 g Na + 20 ml CH3OH) were taken in a flask. The mixture was allowed to stand for one hour with occasional shaking. The solution was neutralized by adding dil HCl. The product thus obtained was filtered off and recrystallisation was done by ethanol. By employing the same procedure following compound:



[XV(a-c)]

5, 6 - dichloro - 1 - ***H*** - (2 - isoproyl amino) (β - D - ribo furanosyl benzimidazole - 2^1 - isonucleoside (XV-b)

5, 6 - dichloro - 1 - ***H*** - (2 - isopropyl amino) (β - D - glucopyranosyl) benzimidazole - 2^1 - isonucleoside (XV-c)

2 - bromo - 5, 6 - dichloro - 1 - ***H*** - (β - D - xylofuranosyl) benzimidazole - 2^1 - isonucleoside (XIV a)

2 - bromo - 5, 6 - dichloro - 1 - ***H*** - (β - D - ribofuranosyl) benzimidazole - 2^1 - isonucleoside (XIVb)

2 - bromo - 5, 6 - dichloro - 1 - ***H*** - (β - D - glucopyranosyl) benzimidazole - 2^1 - isonucleoside (XIVc)

2, 5, 6 - trichloro - 1 - ***H*** - (β - D - xylofuranosyl) benzimidazole - 2 - isonucleoside (XVIa)

2, 5, 6 - trichloro - 1 - ***H*** - (β - D - ribofuranosyl) benzimidazole - 2^1 - isonucleoside (XVIb)

2, 5, 6 - trichloro - 1 - ***H*** - (β - D - glucopyranosyl) benzimidazole - 2^1 - isonucleoside (XVIc)

were prepared.

The yields, M.P. (°C), molecular formulae and elemental analysis of the above mentioned compounds are given in table (3) and their IR & 1H-NMR spectral data are given in table (4).

Table 3: Yields, melting points, molecular formulae and elemental analysis of compounds (VII-XVI)

CompoundNo.	Yield(%)	M.P.(°C)	MolecularFormula	(calc.) Found% C H N
VII	65%	171-173°C	$C_{10}H_{11}N_3C_{12}$	(49.1, 4.5, 17.2)49.1, 4.3, 17.1
VIII	64%	169-170°C	$C_7H_3N_2C_{12}Br$	(31.5, 1.1, 5.2)31.6, 1.0, 5.6
IX	68%	165-167°C	$C_7H_3N_2C_{13}$	(37.8, 1.3, 6.3)37.7, 1.3, 6.4
XIa	74%	254-257°C	$C_{13}H_{13}O_4C_{12}BrN_2$	(14.5, 3.3, 7.2)14.3, 3.2, 7.5
XIb	68%	248-249°C	$C_{13}H_{13}O_4N_2C_{12}Br$	(14.5, 3.3, 7.2)14.4, 3..1, 7.2
XIc	61%	269-271°C	$C_{14}H_{17}O_5N_2C_{12}Br$	(37.8, 3.8, 6.3)37.4, 3.5, 6.4
XIIa	69%	262-265°C	$C_{16}H_{21}O_4N_3C_{12}$	(49.2, 5.3, 10.7)49.2, 5.1, 10.8
XIIb	57%	259-261°C	$C_{16}H_{21}O_4N_3C_{12}$	(49.2, 5.3, 10.7)49.1, 5.4, 10.8
XIIc	64%	274-276°C	$C_{17}H_{23}O_5N_3C_{12}$	(48.5, 5.4, 10.0)48.4, 5.1, 10.2
XIIIa	52%	248-250°C	$C_{13}H_{13}O_4N_2C_{13}$	(42.4, 3.5, 7.6)42.3, 3.5, 7.1
XIIIb	68%	243-245°C	$C_{13}H_{13}O_4N_2C_{13}$	(42.4, 3.5, 7.6)42.3, 3.4, 7.4
XIIIc	66%	251-253°C	$C_{14}H_{15}O_5N_2C_{13}$	(42.2, 3.7, 7.0)42.2, 3.9, 7.1
XIVa	59%	231-232°C	$C_{12}H_{11}O_4N_2C_{12}Br$	(36.1, 2.7, 7.0)36.0, 2.8, 7.2
XIVb	60%	224-2026°C	$C_{12}H_{11}O_4N_2C_{12}Br$	(36.1, 2.7, 7.0)36.2, 2.8, 7.1
XIVc	65%	252-254°C	$C_{13}H_{13}O_4N_2C_{12}Br$	(37.8, 3.1, 6.7)37.6, 3.1, 6.4
XVa	64%	250-252°C	$C_{15}H_{19}O_4N_3C_{12}$	(47.8, 5.0, 11.1)47.7, 6.0, 11.2
XVb	68%	263-265°C	$C_{15}H_{19}O_4N_3C_{12}$	(47.8, 5.0, 11.1)47.6, 5.2, 11.1
XVc	67%	270-273°C	$C_{16}H_{21}O_5N_3C_{12}$	(47.2, 5.1, 10.3)47.5, 5.1, 10.4
XVIa	54%	233-235°C	$C_{12}H_{11}O_4N_2C_{13}$	(40.7, 3.1, 7.9)40.3, 3.1, 7.5
XVIb	60%	248-249°C	$C_{12}H_{11}O_4N_2C_{13}$	(40.7, 3.1, 7.9)40.9, 3.2, 7.4
XVIc	63%	249-250°C	$C_{12}H_{11}O_4N_2C_{13}$	(40.6, 3.3, 7.3)40.4, 3.2, 7.4

Table 4 Spectroscopic Data of Compounds VII-XVIc

Compound No.	I.R. (KBr)n Cm–1	1HNMR($CDCl_3$–d_6) δ , J, (Hz)
VII	1627 (C=N)1560 (C=C)3345 (N–H)	9.14 (1H, s, -NH),7.1-7.14 (2H, ArH),2.1-2.4 (d, 6H-2Me),2.8 (Sep, 1H, –CH)
VIII	1628 (C=N)1560 (C=C)3340 (N–H)	7.5-7.6 (2H, ArH),9.4 (1H, s, -NH),2.1-2.3 (d, 6H, –2Me),2.5 (Sep, 1H, –CH),
IX	1627 (C=N)1559 (C=C)3342 (N–H)	7.2-7.5 (2H, Arh),9.4 (1H, s, -NH),2.2-2.5 (d, 6H-2Me),2.8 (Sep, 1H, -CH)
XIa	1630 (C=N)1550 (C=C)3342 (N–H)	7.4-7.6 (2H, Arh),9.3 (1H, s, -NH),6.7 (1H-J=6.8 1–H),5.5-5.4 (2H, 21-H, 41-H),5.1 (1H, 31-H),5.2 (2H, m, 2XOH),2.2-2.3 (3H, d, OMe)
XIb	1628 (C=N)1558 (C=C)3340 (N–H)	7.4-7.8 (2H, ArH),8.9 (1H, s, –H),6.4 (1H-J=7.0 11 -H),5.6-5.8 (2H, 21-H, 41-H),5.7 (1H, 31-H),3.8-4.0 (2H, 51-H),5.5-5.6 (2H, m, 2XOH),2.1-2.2 (3H, d, OMe)
XIc	1640 (C=N)1554 (C=C)3346 (N–H)	7.8-8.4 (2H, Arh),8.1 (1H, s, -NH),6.2 (1H, J=6.8 1-H),4.8-5.0 (3H, 21, 31, 41-H),3.63-3.66 (2H, m, 61-H),5.36 (br, s, 3H, 3XOH)
XIIa	1629 (C=N)1549 (C=C)3345 (N–H)	7.1-7.4 (2H, Arh),9.0 (1H, NH),2.8 (1H, sep, -CH),2.6 (6H, d, 2Me),4.9-5.1 (3H, m, 21, 31, 41-H),4.4 (1H, J=7.5, 11-H),4.2-4.3 (2H, m, 51-H),2.2-2.4 (3H, d, OCH3)
XIIc	1629 (C=N)1558 (C=C)3344 (N–H)	7.3-7.9 (2H, Arh),8.6 (1H, s, NH),2.3 (6H, d, 2-Me),2.6 (1H, Sep, -CH),3.7-3.9 (3H, m, 21, 31, 51-H),3.8 (1H, m, 41-H),5.1 (3H, br, s, 3XOH),2.0-2.4 (3H, d, -OCH3)
XIIIa	1624 (C=N)1552 (C=C)3340 (N–H)	7.2-8.0 (2H, Arh),8.6 (1H, s, NH),4.7-5.6 (3H, m, 21, 31, 41-H),4.2 (1H, J=8.0, 11-H),4.5-4.6 (2H, m, 51-H),2.2-2.6 (3H, d, -OCH3)

XIIIb	1624 (C=N)1554 (C=C)3338 (N–H)	7.1-7.5 (2H, Arh),8.1 (1H, s, NH),4.3-5.1 (3H, m, 21, 31, 41-H),3.8 (1H, J=8.0, 11-H),4.5-4.8 (2H, m, 51-H),2.1-2.6 (3H, d, -OCH3)
XIIIc	1628 (C=N)1559 (C=C)3340 (N–H)	7.5-8.3 (2H, Arh),8.4 (1H, NH),3.5-3.8 (3H, m, 21, 31, 51-H),4.1 (1H, m, 41-H),3.0-3.4 (2H, m, 61-H),5.4 (3H, br, 3XOH),2.1-2.6 (3H, d, -OCH3)
XIVa	1632 (C=N)1565 (C=C)3340 (N–H)	7.3-7.7 (2H, ArH),8.9 (1H, s, NH),5.1-5.5 (3H, m, 21, 31, 41-H),6.4 (1H, J=8.0, 11-H),3.8-4.5 (2H, m, 51-H),5.9-6.3 (3H, m, 3XOH)
XIVb	1630 (C=N)1556 (C=C)3342 (N–H)	7.5-8.1 (2H, ArH),8.5 (1H, s, NH),6.1 (1H, J=6.8, 11-H),5.1-5.6 (3H, m, 21, 31, 41-H),3.0-4.9 (2H, m, 51-H),5.2-6.1 (3H, m, 3XOH)
XIVc	1638 (C=N)1556 (C=C)3338 (N–H)	7.1-7.4 (2H, ArH),8.0 (1H, s, NH),6.4 (1H, J=8.0, 11-H),5.1-5.4 (4H, m, 21, 31, 41, 51-H),3.1-4.6 (2H, m, 61-H),5.5-6.3 (4H, br, s, 4X-OH)
XVa	1630 (C=N)1547 (C=C)3341 (N–H)	7.3-7.6 (2H, ArH),8.2 (1H, s, NH),2.9 (1H, sep, CH),2.3 (6H, d, 2Me),6.1 (1H, J=7.5, 11-H),5.4-5.9 (3H, m, 21, 31, 41-H),3.2-3.8 (2H, 51-H),5.9-6.5 (3H, m, 3X-OH)

Result and Discussion

The synthesis of iso-nucleosides was achieved by the sequence of reactions shown in figure 1. This study shows the synthesis of new types of iso-nucleosides analogues having the base moiety was located at either 2'or 3' – sugar carbon Systematic synthetic modifications on hetero-cyclic moiety in these molecules give rise to structurally diverse iso- nucleoside analogues showing antiviral activity. These compounds exerted antiviral activity against corn virus (from moderate to high) at different concentrations

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