The Facile Syntheses of 2,3-Dihydro-1*H*-1,5-benzodiazepines and Their Ribofuranosides

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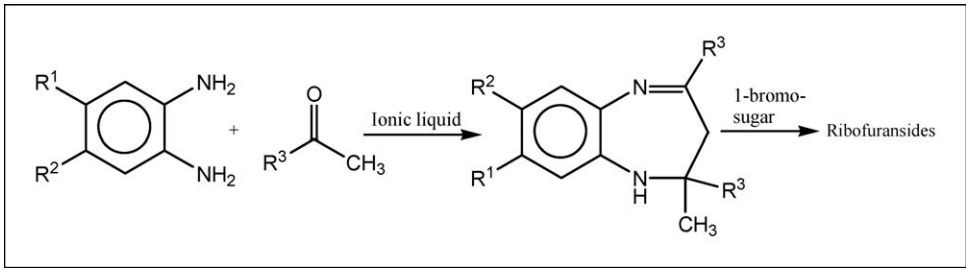

The facile syntheses of 2,3-dihydro-1*H*-benzodiazepines containing heterocyclic moieties and their ribofuranosides have been accomplished in ionic liquids at ambient temperature. The characterization of all these compounds has been done unambiguously by IR, ^{1}H NMR, ^{13}C NMR, GC-MS spectroscopy, and elemental analysis.

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INTRODUCTION

The 1,5-Benzodiazepines have attracted tremendous attention due to their diversified medicinal properties [1–4], *e.g.* analgesic, hypnotic, sedative, antianxiety, anticonvulsant, antidepressant, and anti-inflammatory activities. These derivatives have also been used in viral infections and cardiovasulcar disorders [5]. Commercial applications of this heterocyclic system as dyes for acrylic fibres and in photography have also been reported [6].

These derivatives also act as key intermediates for the synthesis of fused ring derivatives [7], viz., triazolo-, oxadiazolo-, oxazino-, furano-, and pyrido- benzodiazepines.

A survey of the literature reveals that the synthesis of 1,5-benzodiazepines involves the condensation of *o*-phenylenediamine with β-haloketones [8], α,β-unsaturated carbonyl compounds [9] or ketones in the presence of BF_3-etherate [10], polyphosphoric acid or SiO_2 [11], $NaBH_4$ [12], MgO-$POCl_3$ [13], $InBr_3$ [14], $InCl_3$ [15], ionic liquids [16], Amberlyst [17] or zinc montmorillonite [18], etc.

The chemistry of nucleosides has been an active area of research in academia and in industry as it has demonstrated significant importance in cancer and viral therapy [19]. Also, protected nucleosides serve as building blocks for the synthesis of oligonucleotides, which has been used as probes for diagnostic purposes [20] and in antisense therapeutics [21]. The antisense oligonucleotides and siRNA have been extensively employed in selective inhibition of gene expression [22]. To our knowledge, only scanty information is available in regard to the synthesis of 1,5-benzodiazepine derivatives containing heterocyclic moieties, their spiro derivatives [23] and nucleosides. Furthermore, the reported methods are associated with several drawbacks, such as expensive reagents, drastic reaction conditions, extended reaction times, formation of the side products, unsatisfactory yields, complex experimental procedures, and involving the use of environmentally black listed solvents, *e.g.* *N*,*N*-dimethylformamide, *N*-methylpyrrolidine, *etc*.

In view of our continuous interest in the synthesis of nucleosides [24] and the only report on ionic liquid promoted lipase catalysed synthesis of nucleosides [25], we have developed a facile synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines containing heterocyclic moieties and their spiro derivatives at ambient temperature in environmentally benign ionic liquid (IL). These derivatives could be subsequently transformed to their ribofuranosides in the same pot under mild conditions.

RESULTS AND DISCUSSION

In our strategy, we first attempted the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines containing heterocyclic moieties/spiro derivatives from the reaction between *o*-phenylenediamine and an heterocyclic ketone(s) in an IL, *viz*. 1,3-di-*n*-butylimidazolium bromide [BBIM]Br, 1,3-di-*n*-butylimidazolium tetrafluoroborate [BBIM]BF_4, 1,3-di-*n*-butylimidazolium hexafluorophosphate [BBIM]PF_6, 1-methoxyethyl-3-methylimidazolium trifluoroacetate [MOEMIM]TFA, and 1-

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methoxyethyl-3-methylimidazolium mesylates [MOEMIM]Ms at ambient temperature (28 ± 2°). The reaction afforded 2,3-dihydro-1*H*-1,5-benzodiazepine containing heterocyclic moieties or their spiro derivatives in excellent yields (Table 1).

The chracterization of the compounds **3a-k** have been carried out by IR, ^{1}H NMR, ^{13}C NMR, GC-MS spectroscopy and elemental analysis.

A plausible mechanism of the reaction appears to involve nucleophilic attack of *o*-phenylenediamine on the carbonyl carbon of the heterocyclic ketone to generate diaminoalcohol followed by loss of water to afford diimine intermediate **A**. The latter may undergo 1,3-hydrogen shift to yield isomeric imine-enamine intermediate **B**, which on cyclization affords 2,3-dihydro-1*H*-1,5-benzodiazepines/spiro compounds *via* dipolar intermediate (Scheme 1).

To devise our goal of designing a one pot synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepiene ribofuranosides **4a-k**, the solubility of the compounds **3a** and **3j** was checked in ionic liquids by dissolving till saturation in 1 mL of IL. These data are summarized in Table 2.

The data presented in Table 2 suggest that the compounds **3a** and **3j** show better solubility in [MOEMIM]Ms, [MOEMIM]TFA, which may therefore be used for ribofuranosylation. This may be attributed due to the ability of oxygenated cation to hydrogen bond with -NH of the 1,5-benzodiazepine.

In a one-pot synthesis of 1,5-benzodiazepine ribofuranosides, *o*-phenylenediame (entry 1 Table 1) was first reacted with heterocyclic ketone **2a** in [MOEMIM]TFA, the progress of the reaction being monitored by TLC. After completion of the reaction, the sugar, viz., β-D-ribofuranose-1-bromo-2,3,5-tribenzoate was added and the contents were further stirred. After workup compound **4a** was obtained in 92% yield. On carrying out this reaction in [MOEMIM]Ms, **4a** was obtained in 80% yield (Scheme 2).

These investigations suggest that [MOEMIM]TFA is a better protocol for the synthesis of compounds **4a**, which is in consonance with the earlier report [26]. Same method was employed for the synthesis of ribofuranosides **4a-k**.

The compounds **4a-k** have been characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR, GC-MS spectroscopy, and elemental analysis.

We also checked the recyclability of the ionic liquid [MOEMIM]TFA for one pot synthesis of compound **4a** from *o*-phenylenediameine, and heterocyclic ketone **2a** as described earlier. The results of the recyclability are shown in Table 3, which suggest that the yield of the compound **4a** decreases by 5.6 and 10%, respectively in first and second recycling of [MOEMIM]TFA. However, in the third cycle, the decrease in yield was significant.

SUMMARY

In summary, a facile one pot synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepine derivatives containing heterocyclic moieties, their spiro derivatives and their ribofuranosides have been developed at ambient temperature in environmentally benign ionic liquids(s). [MOEMIM]TFA was found to be a better solvent for this purpose. The simplicity of the procedure, easy recovery and reuse of the reaction media *viz*. ionic liquid make this methodology a convenient, efficient, economic, and attractive.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR spectrometer using KBr pellets. ^{1}H NMR spectra were recorded on a JEOL AL-300 MHz NMR spectrometer in $CDCl_3$ using TMS as an internal standard (chemical shift in δ ppm). ^{13}C NMR spectra were recorded on a JEOL AL-75 MHz NMR spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were measured on HP 5890 GC-MS (70eV.EI). The purity of the products was checked by TLC using silica gel 60F 254 aluminium sheets and visualization was accomplished by iodine/UV light. Ionic liquids were prepared by reported methods [27,28]. All reagents were used as obtained commercially.

Synthesis of 2,3-dihydro-1H-1,5-benzodiazepines (3a-k). *o*-Phenylenediamine (0.005 mol) and heterocyclic ketone (0.010 mol) were added to IL (0.015 mol). The contents were stirred magnetically at room temperature (28 ± 2°C). The progress of the reaction was monitored by TLC using silica gel 60F 254 aluminum sheet in pet.ether/EtOAc 7:3. Upon completion of the reaction, water (20 mL) was added to it. The organic compound was then extracted with EtOAc (2 × 15 mL). The combined organic layer was distilled under reduced pressure (10 mmHg) at 50°C to afford compounds **3a-k**. All these products were further purified by column chromatography on silica gel 60–120 mesh by eluting with pet.ether-EtOAc (7:3).

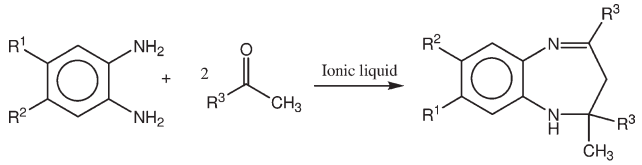
2,4-Di(2′-Furyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3a). Solid, mp = 152–153°C; R_f = 0.45 (pet.ether - ethyl acetate = 7:3); ^{1}H NMR δ : 1.69 (s, 3H, —CH_3), 2.90 (d, J = 13.2 Hz, 1H, methylene), 3.05 (d, J = 13.2 Hz, 1H methylene), 3.40 (s, 1H, NH), 6.46 (d, J = 2.2 Hz, 1H, Furyl), 6.64 (d, J = 3.0 Hz, 1H, Furyl), 6.90–7.03 (m, 2H, 1H furyl and 1H phenyl), 7.10–7.15 (m, 1H, phenyl), 7.28 (d, J = 2.8 Hz, 1H, phenyl), 7.40 (d, J = 3.0 Hz, 1H, phenyl), 7.51 (d, J = 1.4 Hz, 1H, furyl), 7.60 (d, J = 3.0 Hz, 1H, Furyl), 7.78 (d, J = 1.4 Hz, 1H, Furyl); ^{13}C NMR δ : 28.80, 39.60, 71.40, 105.10, 110.62, 112.10, 113.72, 122.55, 123.15, 126.50, 128.45, 137.70, 141.30, 142.00, 146.10, 154.10, 158.50, 159.90; IR (KBr cm^{-1}) ν: 3320, 3040, 2970, 1640; GC-MS : M^+, 292.

2,4-Di(2′-thiophenyl)-2-methyl-2,3-dihydro-1H,1,5-benzodiazepine (3b). Solid, mp = 104–105°C; R_f = 0.48 (pet.ether - ethyl acetate = 7:3); ^{1}H NMR δ : 1.80 (s, 3H, CH_3), 2.95 (d, J = 13.8 Hz, 1H, methylene), 3.05 (d, J = 13.8 Hz, 1H, methylene), 3.60 (s, 1H, NH), 6.60–6.70 (m, 2H, 1H thiophenyl

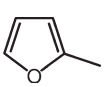
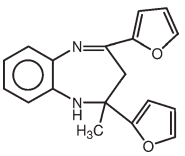
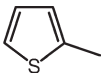
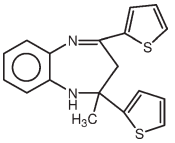
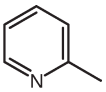
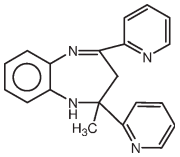
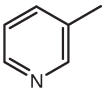
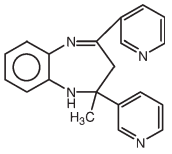
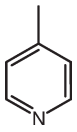
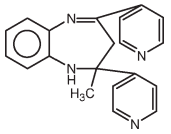
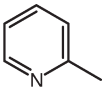
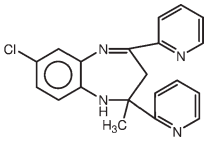
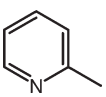
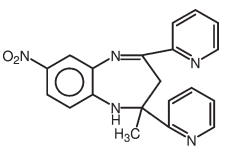
and 1H phenyl), 6.75 (dd, J = 1.4 Hz, 1H, Phenyl), 6.80–6.85 (m, 2H, 1H thiophenyl and 1H phenyl), 6.92–6.98 (m, 2H, 1H thiophenyl and 1H phenyl), 7.05 (dd, J = 1.3 Hz, 1H, thiophenyl), 7.29 (d, J = 1.5 Hz, 1H, thiophenyl), 7.37 (d, J = 3.0 Hz, 1H, Thiophenyl); ^{13}C NMR δ : 31.10, 44.82, 73.10, 106.45, 111.20, 113.80, 114.60, 122.10, 124.20, 127.78,

Table 1

Synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines.

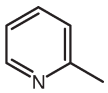
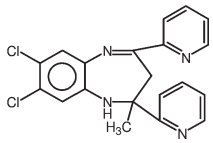
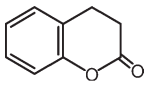
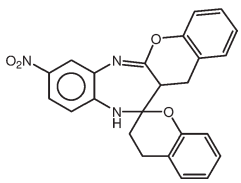
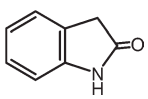
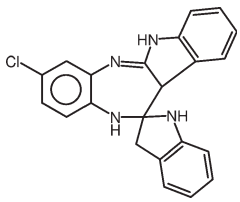
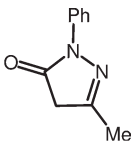
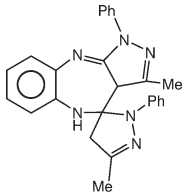


1 **2** **3**

Entry	Compd.	OPD R^1	OPD R^2	R^3	Product	Yield of 1,5-bezodiazepines (%)/time (h) [BBIM]Br	[BBIM]BF_4	[BBIM]PF_6	[MOEMIM]TFA	[MOEMIM]Ms
1	**3a**	H	H			85/7.5	87/6.5	90/5.5	92/4.5	80/4.5
2	**3b**	H	H			80/7.0	85/6.0	87/5.5	90/5.0	90/5.5
3	**3c**	H	H			78/6.5	83/6.0	85/5.5	94/5.0	90/5.5
4	**3d**	H	H			80/7.0	82/6.5	86/6.0	92/5.0	88/5.5
5	**3e**	H	H			82/7.0	85/6.5	85/6.0	94/5.0	90/5.5
6	**3f**	H	Cl			78/7.0	83/6.5	86/6.0	90/5.0	88/5.5
7	**3g**	H	NO_2			73/7.0	79/6.5	82/6.0	85/5.0	80/5.5

(*Continued*)

Table 1
(*Continued*)

Entry	Compd.	OPD R^1	OPD R^2	R^3	Product	Yield of 1,5-bezodiazepines (%)/time (h) [BBIM]Br	[BBIM]BF_4	[BBIM]PF_6	[MOEMIM]TFA	[MOEMIM]Ms
8	**3h**	Cl	Cl			63/7.5	69/7.0	72/6.5	79/5.5	75/6.5
9	**3i**	H	NO_2			67/7.5	72/7.0	75/6.5	80/5.5	76/6.5
10	**3j**	H	Cl			75/7.0	78/6.5	80/6.5	82/5.5	76/6.0
11	**3k**	H	H			75/7.5	77/6.5	82/6.5	90/5.0	85/6.0

128.20, 128.50, 130.48, 137.50, 141.40, 147.95, 153.78, 162.80; IR (KBr, cm^{-1}) ν : 3325, 3040, 2970, 1625; GC-MS : M^+, 324.

2,4-Di(2′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3c). Solid, mp = 162°C; R_f = 0.46 (pet.ether - ethyl acetate = 7:3); ^{1}H NMR δ : 1.82 (s, 3H, CH_3), 2.91 (d, J = 13.2 Hz, 1H, methylene), 3.05 (d, J = 13.2 Hz, 1H, Mehtylene), 3.40 (s, 1H, NH), 6.80 (m, 1H, phenyl), 6.90 (m, 1H, phenyl), 6.95 (d, J = 3.0 Hz, 1H, phenyl), 7.24 (dd, J = 3.4 Hz, 1H, pyridyl), 7.46 (d, J = 3.0 Hz, 1H, phenyl), 7.55 (d, J = 3.4 Hz, 1H, pyridyl), 7.66 (dd, J = 3.4 Hz, 1H, pyridyl), 7.83 (t, J = 4.9 Hz, 1H, pyridyl), 7.86 (dd, J = 7.0 Hz, 1H, pyridyl), 8.63 (d, J = 7.2 Hz, 1H, pyridyl), 8.68(d, J = 4.6 Hz, 1H, pyridyl), 8.80 (d, J = 4.6 Hz, 1H, pyridyl); ^{13}C NMR δ : 31.15, 37.05, 73.25, 119.65, 120.68, 121.30, 123.95, 124.08, 126.56, 128.55, 128.80, 135.90, 136.00, 138.90, 139.15, 147.80, 148.26, 156.30, 165.15, 167.20; IR (KBr, cm^{-1}) ν : 3315, 3015, 2970, 1635; GC-MS : M^+, 314.

2,4-Di(3′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3d). Solid, mp = 168°C; R_f = 0.42 (pet.ether - ethylacetate = 7:3); ^{1}H NMR δ : 1.82 (s, 3H, CH_3), 2.98 (d, J = 13.2 Hz, 1H, methylene), 3.08 (d, J = 13.2 Hz, 1H, methylene), 3.50 (s, 1H, NH) 6.85–6.90 (m, 1H, phenyl), 6.95–6.98 (m, 1H, phenyl), 7.30 (t, J = 3.6 Hz, 1H, pyridyl), 7.35 (d, J = 1.8 Hz, 1H, phenyl), 7.40 (dd, J = 3.0 Hz, 1H, phenyl), 7.50 (s, 1H, pyridyl), 7.55 (d, J = 1.8 Hz, 1H, pyridyl), 7.80 (t, J = 3.4 Hz, 1H, pyridyl), 7.96 (s, 1H, pyridyl), 8.20 (d, J = 7.0 Hz, 1H, pyridyl), 8.71 (d, J = 1.8 Hz, 1H, pyridyl), 8.80 (d, J = 1.8 Hz, 1H pyridyl); ^{13}C NMR δ : 29.70, 42.70, 72.50, 121.45, 122.05, 122.95, 127.00, 128.80, 133.30, 133.45, 133.92, 134.10, 137.28, 139.40, 142.15, 147.35, 148.40, 150.45, 161.42, 164.60; IR (KBr, cm^{-1}) ν : 3320, 3020, 2980, 1640; GC-MS : M^+, 314.

2,4-Di(4′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3e). Solid, mp = 170°C; R_f = 0.44 (pet.ether - ethyl acetate = 7:3); ^{1}H NMR δ : 1.89 (s, 3H, CH_3), 2.90 (d, J = 13.4 Hz, 1H, methylene), 3.17 (d, J = 13.4 Hz, 1H, methylene), 3.81 (s, 1H, NH), 6.90 (dd, J = 1.3 Hz, 1H, phenyl), 6.98 (dd, J = 1.3 Hz, 1H, Phenyl), 7.13 (d, J = 1.3 Hz, 1H phenyl), 7.25 (d, J = 1.3 Hz, 1H, phenyl), 7.30 (d, J = 1.75 Hz, 1H, pyridyl), 7.48 (d, J = 2.10 Hz, 1H, pyridyl), 7.75 (d, J = 2.4Hz, 1H, pyridyl), 7.98 (d, J = 1.5 Hz, 1H, pyridyl), 8.10 (d, J = 1.5 Hz, 1H, pyridyl), 8.28 (d, J = 1.4 Hz, 1H, pyridyl), 8.70 (d, J = 1.75 Hz, 1H, pyridyl), 8.80 (d, J = 2.15 Hz, 1H, pyridyl); ^{13}C NMR δ : 29.76, 42.80, 72.60, 121.40, 122.07, 122.90, 127.02, 128.75, 133.20, 133.40, 133.85, 134.10. 137.25, 139.40, 147.30, 148.10, 148.30, 150.40, 161.45, 164.60; IR (KBr, cm^{-1}) ν: 3310, 3010, 2965, 1630; GC-MS : M^+, 314.

7-Chloro-2,4-di(2′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3f). Solid, mp = 161°C; R_f = 0.48 (pet.ether - ethyl acetate = 7:3); ^{1}H NMR δ : 1.82 (s, 3H, CH_3), 2.83 (d, J = 13.0 Hz, 1H, methylene), 3.24 (d, J = 13.0 Hz, 1H, methylene),

Scheme 1

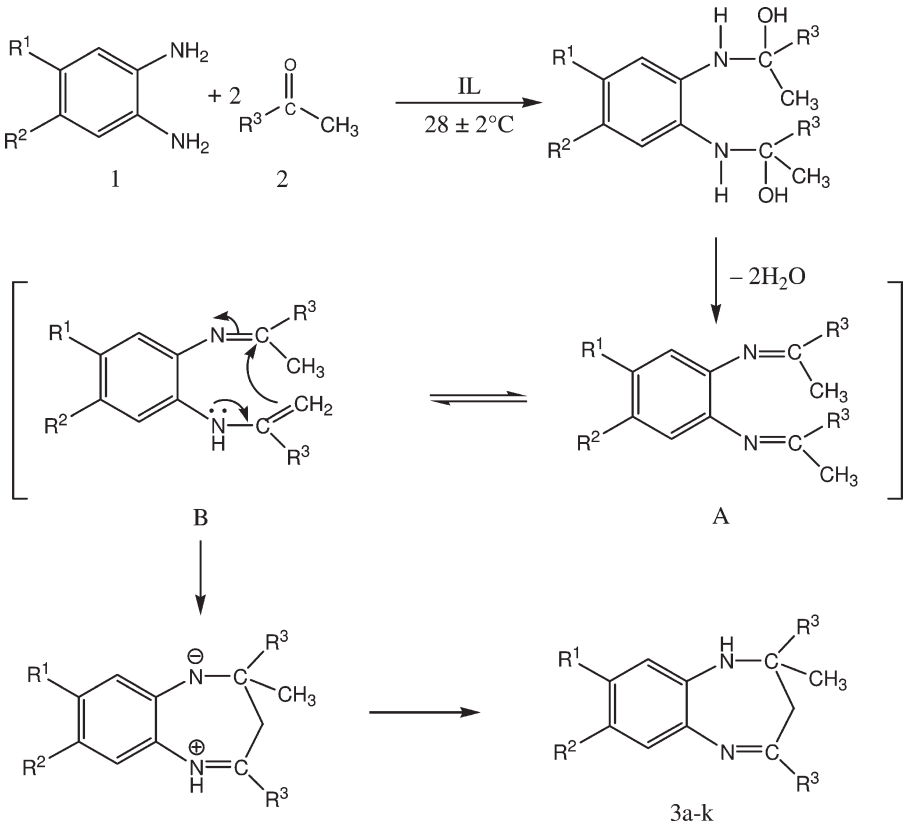


Table 2

Solubility analysis of compounds in ionic liquids (mg mL^{-1}), room temperature (22°C).

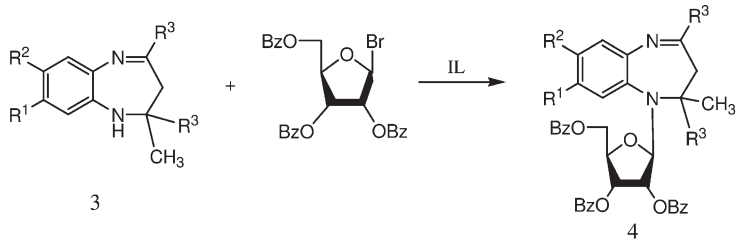
	Solubility (mg mL^{-1})				
Compounds	[BBIM]Br	[BBIM]BF_4	[BBIM]PF_6	[MOEMIM]TFA	[MOEMIM]MS
3a	40	120	290	390	370
3j	75	115	275	400	380

3.76 (s, 1H, NH), 7.02–7.06 (m, 2H, 1H pyridyl and 1H phenyl), 7.15–7.20 (m, 2H, 1H pyridyl and 1H phenyl), 7.28–7.30 (m, 2H, 1H pyridyl and 1H phenyl), 7.50 (t, J = 2.8 Hz, 1H, pyridyl), 7.86 (t, J = 1.2 Hz, 1H, pyridyl), 8.60 (dd, J = 1.65 Hz, 1H, pyridyl), 8.68 (d, J = 1.8 Hz, 1H, pyridyl), 8.70 (d, J = 2.10 Hz, 1, pyridyl); ^{13}C NMR δ : 31.28, 37.56, 73.50, 121.97, 122.46, 122.73, 124.38, 126.45, 127.14, 128.02, 130.45, 131.67, 136.46, 137.68, 140.21, 148.10, 148.31, 148.49, 156.31, 167.04; IR (KBr, cm^{-1}) ν : 3280, 3050, 2970, 1620; GC-MS : M^+, 349.

7-Nitro-2,4-di(2′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3g). Deep red solid, mp = 141°C; R_f = 0.42 (pet.ether - ethyl acetate = 7:3); ^{1}H NMR δ : 1.88 (s, 3H, CH_3), 2.92 (d, J = 13.8 Hz, 1H, methylene), 3.26 (d, J = 13.8 Hz, 1H, methylene), 3.28 (s, 1H, NH), 6.42 (s, 1H, phenyl), 6.56 (d, J = 1.8 Hz, 1H, phenyl), 7.10 (d, J = 1.8 Hz, 1H, phenyl), 7.25 (dd, J = 1.3 Hz, 1H, pyridyl), 7.30–7.36 (m, 2H, pyridyl), 7.55 (d, J = 1.9 Hz, 1H, pyridyl), 7.61 (dd, J = 1.3 Hz, 1H, pyridyl), 8.16 (d, J = 1.8 Hz, 1H, pyridyl), 8.65 (d, J = 1.95 Hz, 1H, pyridyl), 8.70 (d, J = 2.2 Hz, 1H, pyridyl); ^{13}C NMR δ : 32.10, 36.50, 75.10, 114.40, 117.20, 122.52, 124.10, 124.20, 125.90, 127.20, 129.10, 130.88, 135.70, 136.10, 138.40, 149.08, 149.90, 152.60, 163.38, 164.60; IR (KBr, cm^{-1}) ν : 3325, 3140, 2940, 1620. Anal. Calcd for $C_{20}H_{17}N_5O_2$: C, 66.82; H, 4.77; N, 19.49. Found : C, 66.85; H, 4.80; N, 19.47.

7,8-Dichloro-2,4-di(2′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3h). Deep brown solid, mp = 110°C; R_f = 0.46 (pet.ether - ethyl acetate = 7:3); ^{1}H NMR δ: 1.53 (s, 3H, –CH_3), 2.90 (d, J = 13.2 Hz, 1H, methylene), 3.02 (d, J = 13.2 Hz, 1H, methylene), 4.10 (s, 1H, NH), 7.00 (s, 1H, phenyl), 7.32 (d, J = 1.70 Hz, 1H, pyridyl), 7.38 (d, J = 2.9 Hz, 1H, pyridyl), 7.58 (d, J = 2.8 Hz, 1H, pyridyl), 7.64 (d, J = 2.9 Hz, 1H, pyridyl), 7.77 (dd, J = 1.70 Hz, 1H, pyridyl), 7.80 (s, 1H, phenyl), 8.63 (d, J = 1.90 Hz, 1H, pyridyl), 8.84 (d, J = 2.10 Hz, 1H, pyridyl), 8.90 (d, J = 1.70 Hz, 1H, pyridyl); ^{13}C NMR δ : 31.52, 37.52, 77.10, 119.56, 123.40, 124.79, 129.51, 130.08, 130.21, 136.06, 136.57, 137.31, 138.53,

Scheme 2



Ribofuranoside	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k
Time (h) taken (for one pot syntheses)	7.5	7.0	7.5	7.5	7.0	7.5	7.5	7.5	8.5	8.5	9.0

Table 3

Recyclability studies of [MOEMIM]TFA for the synthesis of compound **4a**.

No. of cycles	Yield (%)/time (h)
0	90/3.0
1	85/3.0
2	81/3.0
3	78/3.5

138.97, 145.43, 148.33, 148.46, 156.10, 164.67, 168.53; IR (KBr, cm^{-1}) ν : 3310, 3050, 2940, 1620. Anal. Calcd for $C_{20}H_{16}N_4Cl_2$: C, 62.64; H, 4.20; N, 14.61. Found : C, 62.66; H, 4.18; N, 14.64.

7-Nitro-2-spiro(2′-chromane)-3″,4″-dihydrochromano[2,3-c]-2,3-dihydro-1H-1,5-benzodiazepine (3i). Dark brown solid, mp = 137°C; R_f = 0.47 (pet.ether - ethyl acetate = 7:3); ^{1}H NMR δ: 2.62 (d, *J* = 13.20 Hz, 1H, methylene), 2.68 (t, *J* = 12.4 Hz, 1H, methine), 2.70 (d, *J* = 13.20 Hz, 1H, methylene), 2.75 (t, *J* = 12.4 Hz, 2H, methylene), 2.90 (t, *J* = 13.4 Hz, 2H, methylene), 3.58 (s, 1H, NH), 6.60 (d, *J* = 2.4 Hz, 1H, cromanyl), 6.84 (dd, *J* = 2.1 Hz, 2H, chromanyl), 6.87 (dd, *J* = 1.8 Hz, 2H, cromanyl), 6.89 (d, 1.8 Hz, 1H, cromanyl), 7.07 (t, *J* = 2.1 Hz, 1H, cromanyl), 7.10 (t, *J* = 1.8 Hz, 1H, cromanyl), 7.20 (d, *J* = 2.1 Hz, 1H, phenyl), 7.24 (s, 1H, phenyl), 7.26 (d, *J* = 2.1 Hz, 1H, phenyl); ^{13}C NMR δ : 15.70, 20.20, 20.43, 47.20, 81.40, 113.30, 114.10, 120.90, 122.10, 123.70, 124.10, 125.10, 126.35, 126.65, 127.10, 128.90, 129.10, 129.75, 137.90, 138.90, 147.70, 157.10, 158.90, 164.10; IR (KBr, cm^{-1}) ν : 3510, 3405, 2905, 1620. Anal. Calcd for $C_{24}H_{19}N_3O_4$: C, 69.71; H, 4.63; N, 10.16. Found : C, 69.74; H, 4.65; N, 10.13.

7-Chloro-2-spiro(2′-indoline)-indolino[2,3-c]-2,3-dihydro-1H-1,5-benzodiazepine (3j). Dark brown solid, mp = 158°C; R_f = 0.48 (pet.ether - ethylacetate = 7:3); ^{1}H NMR δ : 2.60 (s, 1H, methine), 2.68 (d, *J* = 13.20 Hz, 1H, methylene), 2.80 (d, *J* = 13.20; 1H, methylene), 3.50 (s, 1H, NH), 3.60 (s, 1H, NH), 3.80 (s, 1H, NH), 6.33 (d, *J* = 2.10 Hz, 1H, indolinyl), 6.38 (dd, *J* = 2.2 Hz, 2H, indolinyl), 6.87 (t, *J* = 2.3 Hz, 1H, indolinyl), 6.89 (t, *J* = 3.04 Hz, 1H, indolinyl), 6.96 (d, *J* = 2.0 Hz, 1H, indolinyl), 6.98 (dd, *J* = 1.8 Hz, 1H, indolinyl), 7.01 (d, *J* = 1.8 Hz, 1H, indolinyl), 7.33 (d, *J* = 2.0 Hz, 1H, phenyl), 7.71 (s, 1H, phenyl), 7.74 (d, *J* = 2.2 Hz, 1H, phenyl); ^{13}C NMR δ : 52.10, 53.40, 54.20, 70.20, 72.10, 76.10, 108.20, 109.41, 109.61, 110.19, 112.28, 112.48, 117.30, 118.20, 122.30, 125.20, 127.44, 132.70, 137.36, 143.25, 143.38, 177.09. IR (KBr, cm^{-1}) ν : 3520, 3410, 2910, 1640. Anal. Calcd for $C_{22}H_{17}N_4Cl$: C, 70.84; H, 4.59; N, 15.03. Found : C, 70.87; H, 4.55; N, 15.05.

2-Spiro[5(3-methyl-1-phenylpyrazoline)]-3″-methyl-1″-phenyl pyrazolino[4,5-c]-2,3-dihydro-1H-1,5-benzodiazepine (3k). Brown solid, mp = 142°C; R_f = 0.46 (pet.ether - ethyl acetate = 7:3); ^{1}H NMR δ : 0.90 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.10 (s, 1H, methine), 2.60 (s, 2H, methylene), 3.70 (s, 1H, NH), 6.40–6.60 (m, 8H, phenyl), 6.90–7.02 (m, 3H, phenyl), 7.10–7.18 (m, 3H, phenyl); ^{13}C NMR δ : 20.20, 21.50, 34.60, 42.40, 48.30, 54.30, 74.20, 110.90, 112.50, 113.60, 115.20, 116.10, 117.20, 122.20, 125.60, 127.60, 128.20, 129.10, 131.20, 132.80, 136.10 137.10, 141.20, 143.50, 146.70, 156.60; IR (KBr, cm^{-1}) ν : 3520, 3400, 2905, 1640. Anal. Calcd for $C_{26}H_{24}N_6$: C, 74.25; H, 5.75; N, 19.99. Found : C, 74.28, H, 5.72, N, 19.97.

Synthesis of 2,3,5-β-D-ribofuranose-1-bromo-2,3,5-tribenzoate. This has been synthesized by reported method [29].

Synthesis of 2,3-dihydro-1,5-benzodiazepine ribofuranosides (4a-k). After completion of the reaction between OPD and heterocyclic ketone (monitored by TLC), 2,3,5-β-D-ribofuranose-1-bromo-2,3,5-tribenzoate equivalent to 1.1 mole of compound **3** was added to the reaction mixture. The contents were further stirred magnetically, till completion of the reaction (checked by TLC). The ribofuranoside was extracted with ethyl acetate (2 × 15 mL). The solvent was removed by distillation under reduced pressure and the product **4** so obtained was chromatographed over silica gel (60–120 mesh) column by eluting with pet.ether-EtOAc (7:3) to afford pure ribofuranosides.

2,4-Di(2′-furyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4a). Solid, mp = 146–148°C; R_f = 0.35 (pet.ether - ethyl acetate - 8:2); yield 86%; ^{1}H NMR δ : 1.69 (s, 3H, –CH_3), 2.90 (d, *J* = 7.2 Hz, 1H, methylene), 3.05 (d, *J* = 7.2 Hz, 1H, methylene), 4.38 (d, *J* = 7.4 Hz, 2H, C_5''sugar), 4.89–4.93 (m, 3H, C_2'', C_3'', and C_4'' sugar), 6.60 (d, *J* = 8.4 Hz, 1H, C_1'' sugar), 6.85–7.25 (m, 10H, 4H phenyl and 6H furyl), 7.35–8.15 (m, 15H, OBz); ^{13}C NMR δ : 28.40, 39.20, 45.60, 65.75, 68.90, 69.10, 70.0, 86.40, 105.10, 110.21, 112.40, 113.55, 119.25, 122.50, 123.10, 127.60, 128.45, 129.70, 130.25, 132.85, 133.40, 138.08, 164.65, 167.00; IR (KBr, cm^{-1}) ν : 3050, 1750, 1660, 1595. GC-MS : M^+, 736.

2,4-Di(2′-thiophenyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4b). Solid, mp = 142–144°C; R_f = 0.38 (pet.ether - ethyl acetate = 8:2); yield 90%; ^{1}H NMR δ : 1.65 (s, 3H, CH_3), 2.85 (d, *J* = 7.2

Hz, 1H, methylene), 3.0 (d, J = 7.2 1H, methylene), 4.37 (d, J = 7.4 Hz, 2H, C_5'' sugar), 4.87–4.92, (m, 3H, C_2'', C_3'' & C_4'' sugar), 6.70 (d, J = 8.4 Hz, 1H, C_1''), 6.75–7.28 (m, 10H, 4H phenyl and 6H thiopenyl), 7.38–8.02 (m, 15H, OBz); ^{13}C NMR δ : 28.20, 39.10, 45.40, 65.75, 68.95, 69.10, 70.01, 86.40, 105.08, 110.20, 112.40, 113.50, 119.25, 122.40, 123.00, 127.65, 128.45, 129.70, 130.55, 132.80, 133.45, 138.00, 164.55, 167.00; IR (KBr, cm^{-1}) ν : 3040, 1760, 1665, 1590. Anal. Calcd for $C_{44}H_{36}N_2O_7S_2$: C, 68.71; H, 4.72; N, 3.64. Found : 68.74; H, 4.75; N, 3.60.

2,4-Di(2′-pyridyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4c). Solid, mp = 134°C; R_f = 0.36 (pet.ether - ethylacetate = 8:2); yield 88%; ^{1}H NMR δ : 1.78 (s, 3H, –CH_3), 2.95 (d, J = 7.4 Hz, 1H, methylene), 3.10 (d, J = 7.4 Hz, 1H, methylene), 4.40 (d, J = 7.4 Hz, 2H, C_5'' sugar), 4.90–4.95 (m, 3H, C_2'', C_3'' and C_4'' sugar), 6.80 (d, J = 8.4 Hz, 1H, C_1'', sugar), 6.95–7.20 (m, 4H, phenyl), 7.35–8.59 (m, 23H, 15H OBz and 8H pyridyl); ^{13}C NMR δ : 29.50, 40.20, 46.40, 65.70, 68.90, 69.15, 70.10, 86.45, 113.85, 119.80, 120.75, 123.50, 127.95, 128.40, 128.55, 129.75, 130.50, 132.78, 133.65, 136.10, 139.45, 149.10, 163.48, 164.65, 167.00; IR (KBr, cm^{-1}) ν : 3015, 1750, 1635, 1590. Anal. Calcd for $C_{48}H_{38}N_4O_7$: C, 72.79; H, 5.05; N 7.38. Found : 72.81; H, 5.02; N, 7.42.

2,4-Di(3′-pyridyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4d). Solid, mp = 138°C; R_f = 0.40 (pet.ether - ethyl acetate = 8:2); yield; 89%; ^{1}H NMR δ : 1.75 (s, 3H, –CH_3); 2.94 (d, J = 7.4 Hz, 1H, methylene), 3.08 (d, J = 7.4 Hz, 1H, methylene), 4.39 (d, J = 7.4 Hz, 2H, C_5'' sugar), 4.89–4.93 (m, 3H, C_2'', C_3'' & C_4'' sugar), 6.78 (d, J = 8.4 Hz, 1H, C_1'' sugar), 6.98–7.20 (m, 4H, phenyl), 7.30–8.64 (m, 23H, 15H OBz & 8H pyridyl); ^{13}C NMR δ : 29.42, 40.01, 46.25, 65.50, 68.91, 69.10, 70.01, 86.45, 113.85, 119.80, 120.75, 123.44, 127.85, 128.40, 128.55, 129.60, 130.55, 132.74, 133.65, 136.00, 139.45, 149.10, 163.25, 164.55, 167.00; IR (KBr, cm^{-1}) ν : 3020, 1745, 1640, 1595, GC-MS; M^+, 758.

2,4-Di(4′-pyridyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4e). Solid, mp = 144°C; R_f = 0.39 (pet.ether - ethyl acetate = 8:2); yield 90%; ^{1}H NMR δ : 1.72 (s, 3H, –CH_3), 2.92 (d, J = 7.2 Hz, 1H, methylene), 3.05 (d, J = 7.2 Hz, 1H, methylene), 4.37 (d, J = 7.4 Hz, 2H, C_5'' sugar), 4.87–4.92 (m, 3H, C2″, C3″, and C4″ sugar), 6.82 (d, J = 8.2 Hz, 1H, C_1' sugar), 6.92–7.25 (m, 4H, phenyl), 7.35–8.60 (m, 23H, 15H OBz and 8H pyridyl); ^{13}C NMR δ : 29.20, 40.10, 46.15, 65.45, 68.90, 69.10, 70.01, 86.45. 113.80. 119.80, 120.65, 123.32, 127.75, 128.42, 128.65, 129.55, 130.45, 132.60, 133.55, 136.25, 139.35, 149.05, 163.15, 164.20. 167.00; IR (KBr, cm^{-1}) ν : 3020, 1745, 1640, 1590. Anal. Calcd for $C_{46}H_{38}N_4O_7$: C, 72.79; H, 5.05; N, 7.38. Found : C, 72.81; H, 5.02; N, 7.40.

7-Chloro-2,4-di(2′-pyridyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4f). Solid, mp = 149°C; R_f = 0.38 (pet.ether - ethyl acetate = 8:2); yield 80%; ^{1}H NMR δ : 1.78 (s, 3H, –CH_3), 2.95 (d, J = 7.2 Hz, 1H, methylene), 3.08 (d, J = 7.2 Hz, 1H, methylene), 4.42 (d, J = 7.4 Hz, 2H, C_5'' sugar), 4.89–4.95 (m, 3H, C_2'', C_3'', and C_4'' sugar), 6.80 (d, J = 8.2 Hz, 1H C_1'' sugar); 7.02–7.25 (m, 3H, phenyl), 7.40–8.70 (m, 23H, 15H OBz & 8H pyridyl), ^{13}C NMR δ : 29.50, 40.25, 46.45, 65.70, 68.92, 69.10, 70.01, 86.45, 117.22, 119.75, 120.90, 124.25, 128.42, 128.85, 129.76, 130.55, 131.72, 132.85, 133.25, 136.45, 139.44, 149.32, 163.55, 164.65, 167.00; IR (KBr, cm^{-1}) ν : 3040, 1750, 1620, 1590. Anal. Calcd for $C_{46}H_{37}O_7Cl$: C, 69.63; H, 4.70; N, 7.06. Found : C, 69.65; H, 4.67; N, 7. 09.

7-Nitro-2,4-di(2′-pyridyl)-2-methyl-1-(2″,3″.5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4g). Solid, mp = 149°C; R_f = 0.44 (pet.ether - ethyl acetate = 8:2); yield 78%; ^{1}H NMR δ : 1.78 (s, 3H, –CH_3), 2.98 (d, J = 7.4 Hz, 1H, methylene), 3.10 (d, J = 7.4 Hz, 1H, methylene), 4.45 (d, J = 8.2 Hz, 2H, C_5'' sugar), 4.88–4.96 (m, 3H, C_2'', C_3'' and C_4'' sugar), 6.82 (d, J = 8.4 Hz, 1H, C_1'' sugar), 7.10–7.30 (m, 3H, phenyl), 7.38–8.65 (m, 23H, 15H OBz and 8H pyridyl); ^{13}C NMR δ : 29.65, 40.32, 46.53, 65.75, 68.92, 69.25, 70.01, 86.45, 118.42, 120.00, 121.25, 124.64, 128.45, 128.88, 129.75, 130.50, 131.92, 132.85, 133.22, 136.45, 139.65, 149.32, 163.65, 164.60, 167.00; IR (KBr, cm^{-1}) ν : 3130, 1760, 1640, 1595. Anal. Calcd for $C_{46}H_{37}N_4O_9$: C, 68.72; H, 4.64; N, 8.71. Found : C, 68.75; H, 4.67; N 8.68.

7,8-Dichloro-2,4-di(2′-pyridyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4h). Solid, mp. = 136°C; R_f = 0.42 (pet.ether - ethyl acetate = 8:2); yield 75%; ^{1}H NMR δ : 1.80 (s, 3H, CH_3), 2.98 (d, J = 7.4 Hz, 1H, methylene), 3.12 (d, J = 7.4 Hz, 1H, methylene), 4.48 (d, J = 8.2 Hz, 2H, C_5'' sugar), 4.88–4.99 (m, 3H, C_2'', C_3'', and C_4'' sugar), 6.85 (d, J = 8.2 Hz, 1H, C_1'' sugar), 7.35–8.75 (m, 25H, 15H OBz, 2H phenyl and 8H pyridyl); ^{13}C NMR δ : 29.66, 40.48, 46.65, 65.75, 68.90, 69.25, 70.01, 86.45, 124.22, 124.45, 128.80, 129.75, 130.52 131.95, 132.66, 132.84, 133.25, 136.40, 139.65, 149.35, 163.60, 164.50, 167.00; IR (KBr. cm^{-1}) ν : 3090, 1763, 1765, 1625, 1590. Anal. Calcd for $C_{46}H_{36}N_4O_7Cl_2$: C, 66.72; H, 4.38; N, 6.77. Found : C, 66.75; H, 4.40, N, 6.75.

7-Nitro-2-spiro(2′-chromane)-3″,4″-dihydrochromano[2,3-c]-1-(2‴, 3‴,5‴-tri-o-benzoyl -β-D-rifuranosyl)-2,3-dihydro-1,5-benzodiazepine (4i). Solid, mp = 152–154°C; R_f = 0.47 (pet.ether - ethyl acetate = 8:2); yield 75%; ^{1}H NMR δ : 2.35 (t, J = 12.4 Hz, 2H, methylene), 2.50 (t, J = 12.4 Hz, 2H, methylene), 2.62 (d, J = 12.2 Hz, 2H, methylene), 2.68 (t, J = 13.20 Hz, 1H, methine), 4.35 (d, J = 7.2 Hz, 2H, C_5''' sugar), 4.78–4.90 (m, 3H, C_2''',C_3''', and C_4''' sugar), 6.78 (d, J = 8.2 Hz, 1H, C_1''' sugar), 6.85–7.30 (m, 11H, 3H phenyl and 8H chromanyl), 7.38–8.20 (m, 15H, OBz); ^{13}C NMR δ : 25.40, 27.95, 41.90, 45.55, 46.65, 65.72, 68.92, 69.22, 70.00, 86.42, 118.45, 120.42, 120.95, 124.65, 128.42, 128.85, 129.70, 130.55, 131.75, 132.66, 133.25, 136.42, 139.55, 149.32, 163.50, 164.66, 167.00; IR (KBr, cm^{-1}) ν : 2920, 1750, 1630, 1595. Anal. Calcd for $C_{50}H_{39}N_3O_{11}$: C, 69.99; H, 4.58; N, 4.90. Found : C, 69.72; H, 4.60 N, 4.87.

7-Chloro-2-spiro(2′-indoline)-indolino[2,3-c]-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-N,N-di(2″,3″,5″-tri-o-benzoyl-β-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4j). Solid, mp = 158°C; R_f = 0.43 (pet.ether - ethyl acetate = 8:2); yield 77%; ^{1}H NMR δ : 2.50 (s, 2H, methylene), 2.70 (s, 1H, methine), 4.37 (d, J = 7.4 Hz, 6H, 3 × C_5'' sugar) 4.80–4.93 (m, 9H, 3 × C_2'', C_3'', and C_4'' sugar), 6.80 (d, J = 8.2 Hz, 3H, 3 × C_1'' sugar), 6.90–7.25 (m, 11H, 3H phenyl and 8H indolinyl), 7.35–8.40 (m, 45H, 3 × OBz); ^{13}C NMR δ : 27.95, 45.60, 52.50, 65.70, 68.90, 69.21, 70.01, 86.45, 118.45, 120.22, 124.65, 128.42, 128.85, 129.70, 130.50, 131.75, 132.66, 133.20, 136.45, 139.55, 149.30, 163.45, 165.65, 167.00; IR (KBr, cm^{-1}) ν : 2915, 1760, 1620, 1592. Anal.

Calcd for $C_{100}H_{77}N_4O_{21}$: C, 71.87; H, 4.64; N, 3.35. Found : C, 71.90; H, 4.62, 3.38.

2-Spiro[5-(3-methyl-1′-phenylpyrazoline)]-3″-methyl-1″-phenylpyrazolino[4,5-c]-1-(2‴,3‴,5‴-tri-o-benzoyl-β-D-ribofuranosyl) -2,3-dihydro-1,5-benzodiazepine (4k). Solid, mp = 154–156°C; R_f = 0.37 (pet.ether - ethyl acetate = 8:2); yield 85%, ^{1}H NMR δ : 1.85 (s, 3H, —CH_3), 1.88 (s, 3H, —CH_3), 2.40 (s, 2H, methylene), 2.50 (s, 1H, methine), 4.36 (d, J = 7.2 Hz, 2H, $C_5‴$ sugar), 4.80–4.92 (m, 3H, $C_2‴$, $C_3‴$, and $C_4‴$ sugar), 6.60–7.10 (m, 15H, 14H phenyl, and 1H $C_1‴$ sugar), 7.25–8.30 (m, 15H, OBz); ^{13}C NMR δ : 27.90, 41.45, 45.62, 51.40, 51.65, 65.72, 68.92, 69.20, 70.01, 86.45, 113.50, 119.52, 123.25, 127.62, 128.45, 129.72, 130.55, 132.84, 133.45, 138.00, 162.62, 162.68, 164.65, 170.00; IR (KBr, cm^{-1}) ν : 2910, 1760, 1625. Anal. Calcd for $C_{55}H_{44}N_6O_7$: C, 72.19; H, 5.13; N, 9.72. Found : C, 72.22; H, 5.15, N, 9.70.

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