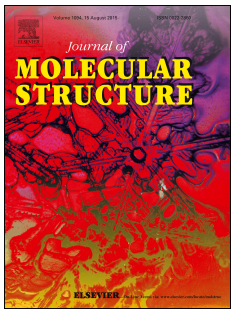
Accepted Manuscript



N-benzyl-2,7-diphenyl-1,4-diazepan-5-one analogues: Synthesis, spectral characterization, stereochemistry, crystal structure and molecular docking studies

S. Sethuvasan, P. Sugumar, M.N. Ponnuswamy, S. Ponnuswamy

PII: S0022-2860(16)30510-5

DOI: 10.1016/j.molstruc.2016.05.065

Reference: MOLSTR 22579

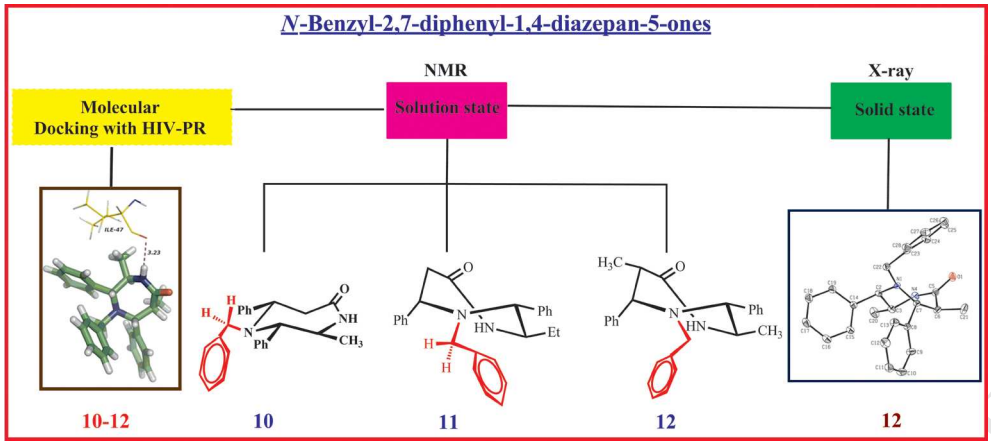
To appear in: *Journal of Molecular Structure*

Received Date: 15 April 2016

Revised Date: 15 May 2016

Accepted Date: 17 May 2016

Please cite this article as: S. Sethuvasan, P. Sugumar, M.N. Ponnuswamy, S. Ponnuswamy, *N*-benzyl-2,7-diphenyl-1,4-diazepan-5-one analogues: Synthesis, spectral characterization, stereochemistry, crystal structure and molecular docking studies, *Journal of Molecular Structure* (2016), doi: 10.1016/j.molstruc.2016.05.065.



N-Benzyl-2,7-diphenyl-1,4-diazepan-5-one analogues: Synthesis, Spectral characterization, Stereochemistry, Crystal Structure and Molecular Docking Studies

S. Sethuvasan[a], P. Sugumar[b], M. N. Ponnuswamy[b] and S. Ponnuswamy[a]*

[a]*P.G. & Research Department of Chemistry, Government Arts College (Autonomous), Coimbatore - 641 018, India.*

[b]*Centre of Advanced Study in Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai - 600 025, India.*

Abstract

Three novel *N*-benzyl-2,7-diphenyl-1,4-diazepan-5-ones **10**-**12** have been synthesized *via* two routes starting from 2,7-diphenyl-1,4-diazepan-5-ones **4**-**6** and *N*-benzyl-2,6-diphenylpiperidin-4-ones **7**-**9**. The structural characterization and conformational analysis of these synthesized compounds have been carried out using IR, mass and ^{1}H, ^{13}C, DEPT-135 and 2D (COSY and HSQC) NMR spectral techniques. The *N*-benzyldiazepan-5-one **10** is found to prefer chair conformation with equatorial orientation of alkyl and phenyl groups while *N*-benzyldiazepan-5-ones **11** & **12** prefer to adopt twist-boat conformation with phenyl rings at C-2 & C-7 occupying equatorial and pseudo-axial orientations, respectively. The single crystal X-ray structure of compound **12** has been determined which also supports the twist-boat conformation. *In silico* molecular docking study has also been performed and the results show that the compounds **10**-**12** might exhibit inhibitory activity against HIV-1 protease. All the compounds are screened for their antibacterial activity against three bacterial strains (*Staphylococcus aureus, Escherichia coli and Bacillus cereus*) and only compound **11** shows moderate activity.

Keywords: *N*-benzyldiazepan-5-ones, Chair, twist-boat, Single crystal XRD, Molecular docking

*Corresponding author: Post Graduate and Research Department of Chemistry, Government Arts College (Autonomous), Coimbatore-641 018, Tamil Nadu, India. E-mail: kspons2001@gmail

1. Introduction

Synthesis of new molecules by the fusion of two or more biologically active fragment is an important process in the fields of medicinal and pharmaceutical chemistry. A wide range of diazepines has been identified as potential drugs which are used for many therapeutic applications [1, 2]. Especially, 1,4-diazepines play a vital role in the drug industry as antimicrobial [3, 4], anti-HIV [5], psychotropic [6] and anticancer agents [7]. Furthermore, *N*-benzyl derivatives of piperidines have been found to be active against human cervical carcinoma (HeLa) cells [8]. This prompted us to synthesise a new system of *N*-benzyl-1,4-diazepan-5-ones as target molecules and to study their stereochemistry and biological activity. Very little information is available on the synthesis and stereochemistry of 1,4-diazepan-5-ones [9]. Their nitroso [10-15], ethoxycarbonyl [16] and formyl [15] derivatives prefer to exist in the flattened boat, alternate chair and twist-chair conformations in the solution state. The delocalization of nitrogen lone pair into the Π cloud results in restricted rotation about *N*-NO and *N*-CO functions which is responsible for the drastic change in the conformation of the ring and orientation of the substituents in these compounds.

The present work involves the synthesis of three new *N*-benzyl-1,4-diazepan-5-ones **10**-**12** by adopting two methods: (i) Schmidt rearrangement of piperidin-4-ones **4**-**6** followed by benzylation, (ii) benzylation of piperidin-4-ones **7**-**9** followed by Schmidt rearrangement. The characterization of compounds **10**-**12** are made with the help of IR, mass, ^{1}H, ^{1}H (D_2O), ^{13}C, DEPT-135 NMR spectra and the NMR signals are unambiguously assigned using 2D NMR (^{1}H-^{1}H COSY &^{1}H-^{13}C HSQC) spectra. The conformational analysis of compounds **10**-**12** has been carried out using NMR spectral data. In addition, the crystal structure has also been solved for compound **12** to predict the preferred conformation in the solid state using single crystal X-ray diffraction study. Furthermore, antibacterial activity and molecular docking studies with the target protein are also carried out for compounds **10**-**12**.

2. Experimental section

All chemicals were purchased from commercial suppliers and used without further purification. The melting points were taken on an electrically heated block with a calibrated thermometer and are uncorrected. The FT-IR spectra were recorded on Bruker alpha spectrometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz and 100 MHz NMR spectrometer, respectively, using $CDCl_3$ as solvent and tetramethylsilane

(TMS) as an internal reference. All chemical shifts are reported in δ units and described as being either singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), triplet (t), broad (br) and multiplet (m). Thin-layer chromatography (TLC) was performed and the progress of the reaction was monitored on a pre-coated silica gel Merck plates. Mass spectra were acquired on an EI spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 1108 CHN analyser.

All the piperidin-4-ones **1**-**3** [17], diazepan-5-ones **4**-**6** [9] and *N*-benzylpiperidin-4-ones **7**-**9** [18, 19] have been synthesized by following the reported procedures. The analytical data of *N*-benzyl-1,4-diazepan-5-ones **10**-**12** are presented in Table 1.

*2.1. General procedure for the synthesis of N-benzyl-1,4-diazepan-5-ones **10**-**12***

2.1.1 Method A

A mixture of diazepan-5-ones **4**-**6** (0.01 mol), benzyl bromide (0.015 mol, 1.78 ml) and anhydrous potassium carbonate (0.02 mol, 2.76 g) in DMF (30 ml) is stirred at room temperature for 36-48 h. To this, an excess of ice-cold water is added and extracted using dichloromethane (2×10 ml). The organic layer is washed with brine solution and dried over anhydrous Na_2SO_4. The organic layer is then concentrated in a rotary evaporator to obtain the crude product. The crude solid thus separated is purified by recrystallisation from ethanol.

2.1.2. Method B

The *N*-benzylpiperidin-4-ones **7**-**9** (5 mmol) are added to a suspension of conc. H_2SO_4 (20 ml) and dichloromethane (40 ml) at 0ºC. Then NaN_3 (sodium azide) is continuously added over a period of 3 h and the resulting mixture is stirred at RT for 1 h. The resulting solution is poured into crushed ice and alkalized with ammonia solution (20-30 ml to pH 11-12). The organic layer is separated from the water fraction, extracted with DCM (dichloromethane), dried using anhydrous Na_2SO_4 and concentrated in a rotary evaporator to obtain the crude product. The crude product thus obtained is recrystallised using ethanol.

Here, among the two methods (Methods A & B), the overall percentage of yield in method B (57-77%) is higher than that in the method A (53-61%, Table 1).

2.2. X-ray crystallography

The single crystal X-ray diffraction data were collected on a Bruker axs Kappa APEXII CCD diffractometer employing graphite-monochromatized Mo *Kα*radiation (λ =

0.71073 Å). The data were processed using the SAINT software program [20]. The structure was solved by the direct methods using SHELXS-97 and refined on F^2 by a full-matrix leasts-quares technique using the SHELXL-97 package [21, 22]. The molecular graphics plots were drawn using PLATON [23] and ORTEP-3 [24]. All H atoms were fixed geometrically and allowed to ride on their parent C atoms, with C-H distance fixed in the range 0.93-0.97 Å. The H atom displacement parameters were restricted to be 1.2Ueq for the parent atom. Crystal data and refinement details are given in Table 2. Selected bond distances, bond angles and torsion angles of the diazepan-5-one **12** are listed in Tables 3a & 3b. The molecular structure with atom-numbering and displacement ellipsoids are drawn at 30% probability level is shown in Fig. 1a. The overlapping of both the molecules present in the asymmetric unit is shown in Fig. 1b [24]. The RMSD value between the overlapped molecules is 0.272Å.

2.3. Molecular modeling study

All docking calculations were performed using the Induced Fit Docking module of the Schrödinger suite. It performs flexible protein-ligand docking and searches for favourable interactions between small ligand molecule and a typically larger receptor molecule, usually protein. Docking process is divided into three steps. Step 1 is the Initial Glide Docking, wherein protein preparation constrained refinement is carried out with a maximum of 20 poses. Step 2 involves Prime Induced Fit, wherein the side chains are optimized and refinement of residues take place if the ligand poses are within 5.0Å. Step 3 consists of the Glide redocking stage using Standard Precision (SP) mode. The best-docked structure/pose was chosen using the following three criteria: ***Glide score (G-score)*** function, ***Glide Energy*** and the number of ***residual matches (hydrogen bonds)*** with the original drug complex. All computational works were performed with various modules of Schrödinger Suite 2011 [25] using Red Hat Enterprise Linux 5.0 interface running on Pentium D workstation.

2.4. In vitro antibacterial evaluation

The minimum inhibitory concentration (MIC) of the *N*-benzyldiazepan-5-ones **10**-**12** against the three human pathogens [*Staphylococcus aureus (ATCC 25923), Escherichia coli (ATCC 25922) and Bacillus cereus (ATCC 10876)*] was analyzed by resazurin reduction assay described by Sarker *et al* [26].

2.4.1. Method to prepare resazurin dye solution

The resazurin dye solution was made by dissolving a 270 mg tablet in 40 ml of sterile distilled water. The vortex mixer was used to ensure that the resazurin solution was well dissolved and form a homogeneous solution.

2.4.2. Preparation of the activity plates

The 96 wells plates were prepared under aseptic conditions. A volume of 200 µl of compounds (1mg/ml) in 5% (v/v) dimethyl sulfoxide was pipetted out into the first row of the 96 wells plate. To all other remaining wells, 100 µl of nutrient broth was added to the bacterial cells. The serial dilutions were performed using micropipette with sterile pipette tips such that each well had 100 µl of the test material in serially descending concentrations. To all these wells 10 µl of resazurin dye solution was added. A 10 µl of bacterial suspension (5×10^6 cells/ml) was added to each well to achieve a concentration of 5×10^5 cells/ml. The commercial antibiotic, streptomycin was used as positive control in the assay plate. The plates were placed in an incubator at 37°C for 18-24 h. The color change was then observed visually. The color changes from blue to pink or colorless were recorded as a reduction of dye by the viable bacteria. The lowest concentration at which no color change occurred was taken as the MIC value.

3. Results and discussion

3.1. Chemistry

The benzylation on 1,4-diazepan-5-ones is performed by adopting two routes which are given in Scheme 1. Both the routes yielded only mono benzylated product. The *N*-benzyl-1,4-diazepan-5-ones **10**-**12** are synthesized from 1,4-diazepan-5-ones **4**-**6** and from *N*-benzylpiperidin-4-ones **7**-**9**, respectively. The *N*-benzyldiazepan-5-ones **10**-**12** are characterized using spectral and analytical data. The absence of amine NH (3292-3003 cm^{-1}) and the presence of amide NH (3184-3203 cm^{-1}) and amide CO bands (1654-1671 cm^{-1}) in their FT-IR spectra confirm the benzylation at amine nitrogen. This is further confirmed from the ^1H (D_2O) NMR spectra which show the presence of amide NH proton at 5.72-6.04 ppm. In addition, new signals appear for *N*-benzyl methylenic protons at 3.43-3.73 ppm. These CH_2 protons of **10** & **11** are diastereotopic in nature. Furthermore, the molecular ion (M^+) peaks and fragmentation patterns for the compounds **10**-**12** in their mass spectra support the formation of the products. The complete analytical data for compounds **10**-**12** are presented in Table 1.

3.2. NMR spectral assignment

The structure of *N*-benzyl-2,7-diphenyl-1,4-diazepan-5-ones **10-12** is confirmed from the IR, ^{1}H and ^{13}C NMR spectral data. DEPT-135 spectra are also recorded for all the compounds which support the assignment of ^{13}C NMR signals. The signals of the ^{1}H NMR spectra of *N*-benzyl-2,7-diphenyl-1,4-diazepan-5-ones **10-12** are assigned based on their positions, multiplicities and intensity. In addition, 2D (^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC) NMR spectra are used for the unambiguous assignment of ^{1}H & ^{13}C NMR signals and are presented in Tables 4 & 5, respectively, along with those of parent diazepan-5-ones **4-6** [10].

*3.3. Analysis of ^{1}H and ^{13}C NMR signals of compound **10***

The compound **10** has AMX and AB spin systems for the heterocyclic ring protons. The H-6a, H-6e and H-7a protons belong to the AMX spin system. The proton signal appearing at 4.24 ppm as a doublet correlates with the doublet at 3.00 ppm and a doublet of doublet at 3.17 ppm in the COSY spectrum. In fact, all the signals are expected to show doublet of doublet. However, two signals show only doublets which reveal that one of the couplings is zero due to the expected dihedral angle of 90^{o} between these vicinal protons [27]. The signal at 4.24 ppm may be assigned to H-7 proton since it correlates with other two proton signals. It shows only a doublet with the ^{3}J value of 7.6 Hz. However, the expected diaxial coupling constant would be 9-11 Hz and the decrease in diaxial coupling constant may be due to ring distortion. Further, the H-7 proton occupies the axial position and it makes an approximate angle of 90^{o} with the equatorial proton at C-6 (H-6e) which results in zero coupling ($^{3}J_{H7a,\ H6e}$=0 Hz). The equatorial proton at C-6 (H-6e) appears as doublet at 3.00 ppm and it has only a geminal coupling with H-6a ($^{2}J_{H6a,\ H6e}$ = 16.4 Hz). The doublet of doublet at 3.17 ppm is assigned to axial proton at C-6 (H-6a). The extracted coupling constant of **10-12** along with their estimated dihedral angles using DAERM (Dihedral Angle Estimation by Ratio Method) [28] are presented in Table 4 along with their parent diazepan-5-ones **4-6**.

The H-3 proton appears as a multiplet at 3.59 ppm due to its coupling with CH_3 and H-2 protons. The H-2 & H-3 protons belong to AB spin system. Thus, the doublet appearing at 3.78 ppm is assigned to H-2 benzylic proton. It has a J value of 8.4 Hz and it confirms that both the protons at C-2 and C-3 are diaxially oriented (H-2a & H-3a, respectively). Hence, the phenyl group at C-2 and the methyl group at C-3 occupy equatorial orientations. The doublet at 0.59 is assigned to CH_3 protons at C-3. Two doublets are observed for the methylenic

protons at 3.72 and 3.43 ppm. Thus, the appearance of separate signals for the CH_2 protons proves its diastereotopic nature. The aromatic protons appear between 7.14 and 7.58 ppm.

The assignment of NMR signals of compounds **11** & **12** using ^{1}H, ^{13}C NMR, and 2D NMR spectra has also been made in a similar way. The complete assignment of ^{1}H and ^{13}C NMR signals is presented in Tables 4 and 5.

*3.4. Conformational analysis of N-benzyl-2,7-diphenyl-1,4-diazepan-5-ones **10-12***

The conformational analysis of 1,4-diazepan-5-ones **4-6** has been carried out in solution and solid states. In both the states, the diazepan-5-ones **4-6** prefer to adopt a chair conformation with the equatorial orientation of bulky groups Fig. 2 [10, 14]. Further, *N*-benzylpiperidin-4-ones **7-9** are also reported to exist in a chair conformation, similar to piperidin-4-ones **1-3**, with the equatorial orientation of alkyl and aryl groups in solution and solid states [18, 19].

The preferred conformation of the *N*-benzyl-1,4-diazepan-5-ones **10-12** has been arrived by considering the vicinal coupling constants between the H-7 and H-6a & H-6e protons and between H-2 and H-3 protons. The vicinal coupling constant data ($^{3}J_{H6a,\ H7}$ and $^{3}J_{H6e,\ H7}$) are employed to estimate the dihedral angles between the vicinal protons ($\Phi_{cis}=\Phi_{H6e,H7a}$ and $\Phi_{trans}=\Phi_{H6a,H7a}$) by DAERM [28] and are used for the conformational analysis (Table 6). The appearance of Bohlmann bands (2803-2865 cm^{-1}) in the IR spectra of **10-12** indicates that atleast two axial hydrogens on carbons adjacent to the nitrogen atom are interacting with the nitrogen lone pair in the diazepanone ring [29, 30].

The seven-membered 1,4-diazepan-5-one rings are, in general, more flexible than the six-membered piperidin-4-one rings. Hence, the destabilizing strain factors (*viz.*, 1,3-diaxial interaction, *gauche* interaction, 1,4-diaxial hydrogen-alkyl interaction and bond eclipsing interaction) may force the ring to change the chair (**CE**) conformation of the parent precursors **4-6** (Fig. 2). However, the attachment of benzyl group at the ring nitrogen in the piperidin-4-ones **1-3** has not altered the chair conformation of its precursor [18, 19]. Hence, it is of interest to find out the preferred conformation of the flexible rings due to the attachment of benzyl substituent at amine nitrogen. The possible conformations for *N*-benzyl-1,4-diazepan-5-ones **10-12** are shown in Fig. 3.

*3.4.1. N-Benzyl-3-methyl-2,7-diphenyl-1,4-diazepan-5-one (**10**)*

In the chair conformation (**CE**), alkyl and aryl substituents occupy equatorial orientation. The expected vicinal coupling constants between H-2 & H-3, H-6a & H-7, and

H-6e & H-7 would be around 8-9 Hz, 10-11 Hz, and 0 Hz, respectively. The *cis* coupling ($J_{H7,\ H6e}$) constant of 0 Hz observed in the parent diazepanones **4-6** suggests a dihedral angle of ca. 90º and the *trans* dihedral angle $\Phi_{H7a,\ H6a}$ would be 159º [10]. Here, the observed coupling constant and estimated dihedral angles for compound **10** are, $J_{H2,\ H3}$= 8.4 Hz, $J_{H6a,\ H7}$= 7.6 Hz, $J_{H6e,\ H7}$= 0 Hz and $\Phi_{H7a,\ H6a}$= 161º, $\Phi_{H7a,H6e}$= 79º. Thus, the coupling constants and dihedral angles of compound **10** are similar to its parent precursor **4** ($J_{H2,\ H3}$= 7.8 Hz, $J_{H6a,\ H7}$= 10.6 Hz, $J_{H6e,H7}$= 0 Hz and $\Phi_{H7a,\ H6a}$= 159º, $\Phi_{H7a,\ H6e}$= 81º, Table 6). Hence, similar to parent diazepan-5-one **4**, compound **10** also prefers to adopt a chair conformation (**CE**) with equatorial orientation of phenyl and methyl groups (Fig. 4). Further, the possibility of the chair (**CA & TC**) and boat (**BE, BA & TB**) conformations is eliminated.

*3.4.2. N-Benzyl-2,7-diphenyl-1,4-diazepan-5-ones (**11** & **12**)*

As discussed earlier, the vicinal coupling constant and dihedral angles for the chair (**CE**) conformation is $J_{H2,\ H3}$=8-9 Hz, $J_{H6a,\ H7}$=10-11 Hz, $J_{H6e,\ H7}$=0 Hz and $\Phi_{H7,\ H6a}$ =159º, $\Phi_{H7,\ H6a}$ =90º. The extracted coupling constant and estimated dihedral angles for the compounds **11** and **12** are $J_{H2,\ H3}$=8.1-8.8 Hz, $J_{H6a,\ H7}$=8.8-10.6 Hz, $J_{H6e,\ H7}$= 2.4 Hz and $\Phi_{H7,\ H6a}$ =175º, $\Phi_{H7,\ H6e}$ =55º. Thus, the increase in the *cis* coupling constant and dihedral angle values of **11** & **12** when compared with that of the parent **5** & **6**, respectively, do not support the **CE** conformation for the compounds **11** & **12**. Hence the diazepan-5-ones **11** & **12** prefer a different conformation when compared to diazepan-5-one **10**.

In **CA** conformation, all the alkyl and aryl groups occupy axial orientations as well as the ring protons occupy equatorial orientations. The *cis* and *trans* coupling constants for benzylic protons would be expected in the range of 2-4 Hz. Further, the *cis* and *trans* dihedral angles are expected around 60º. In addition, 1,3-diaxial interaction is inevitable in **CA** which destabilizes the chair conformation and tends to move the ring towards twist (**TC & TB**) or boat (**BA & BE**) conformations. Hence, the possibility of **CA** conformation is ruled out for the compounds **11** & **12**.

The expected vicinal coupling constants in the twist-chair (**TC**) conformation are $J_{H2,\ H3}$= 9-11 Hz, $J_{H7,\ H6a}$= 4-5 Hz, $J_{H7,\ H6e}$= 2-3 Hz or $J_{H2,\ H3}$= 2-3 Hz, $J_{H7,\ H6a}$= 9-11 Hz, $J_{H7,\ H6e}$= 4-5 Hz. Here, the expected vicinal coupling constants coincide with the extracted vicinal coupling constants for compound **11** ($J_{H2,\ H3}$= 8.8 Hz, $J_{H7,\ H6a}$= 8.8 Hz & $J_{H7,\ H6e}$= 2.4 Hz). However, the twist-chair conformation does not favor a partial double-bond character at

the amide C-N bond and thus amide carbon behaves like a ketone carbon. The amide carbon signals of **11** & **12** are observed at 174-177 (δ, ppm) in their ^{13}C NMR spectra which eliminates the possibility of **TC** conformation.

The protons at C-2 and C-7 are axial and the protons at C-3 and C-6 are equatorial in the boat conformation **BA**. The expected coupling constants would be 4-5 Hz for *cis* ($J_{a,e}$) coupling and 9-10 Hz for *trans* ($J_{a,a}$) coupling. In addition, 1,3-diaxial interaction is also possible between the two phenyl groups at C-2 and C-7 which occupy axial orientation. However, in the absence of allylic strain [31], the phenyl groups need not be forced to occupy axial orientations. Thus, the diaxial coupling (8.8-10.0) observed between H-2 and H-3 for the compounds **11** and **12** eliminates the possibility for **BA** conformation.

The phenyl groups at C-2 & C-7 and alkyl groups at C-3 and C-6 are occupying equatorial and axial orientations, respectively, in **BE** conformation. Here, only *cis* coupling would be possible between H-2 & H-3. For the compounds **11** & **12**, the observed diaxial coupling constant values between H-2 and H-3 ($J_{H2, H3}$= 8.8-10.0 Hz) does not support the **BE** conformation. Furthermore, the alkyl substituent at C-3 and C-6 would feel the 1,4-diaxial hydrogen-alkyl interaction in this conformation. Thus, all these observations do not support the boat conformations with equatorial phenyl groups. Hence, the conformation **BE** is not considered further.

In the twist-boat (**TB**) conformation, the alkyl and aryl groups at C-2 & C-3 and C-6 & C-7 are equatorial, pseduo-equatorial & pseduo-axial, respectively. The extracted vicinal coupling constants for the compounds **11** and **12** (Table 6) are comparable with the expected values of **TB** conformation. The predicted **TB** conformation is further supported by the X-ray crystal structure of **12**. Hence, it is concluded that *N*-benzyl-2,7-diphenyl-1,4-diazepan-5-ones **11** and **12** prefer to adopt twist-boat conformation (**TB**) with the phenyl group at C-7 occupying pseudo-axial orientation and the phenyl group at C-2 occupying equatorial orientation (Fig. 5).

The increase in the *cis* ($J_{a,e}$) coupling constant from 0 to 2.4 Hz and decrease in *trans* ($J_{a,a}$) coupling constant from 10.7 to 8.8 Hz as well as a decrease in the *cis* dihedral angle (81→55º) and increase in *trans* dihedral angle (159→175º) between C-6 and C-7 are observed when compared with that of parent compounds **5** & **6**. This may be due to an unsymmetrical twisting of the ring which results in pseudo-axial orientation of phenyl group at C-7 and pseudo-equatorial orientation of the methyl group at C-6.

3.4.3. Shielding and deshielding effect of α, β-protons and carbons in ^{1}H and ^{13}C NMR spectra

In the ^{1}H NMR spectra, α-protons (H-2 & H-7) and β-protons (H-3, H-6a & H-6e) of **10**-**12** are less deshielded (Δδ=+ 0.04-0.56 ppm) when compared with their parent compounds **4**-**6**. The introduction of benzyl group at amine nitrogen is not influencing the α- and β-protons when compared to that of hetero conjugate groups (-NO, -CHO, -COOEt, *etc.*) [9-12]. However, significant shielding and deshielding for α & β-carbons of **10**-**12** are noted when compared to their parent compounds **4**-**6** in ^{13}C NMR spectra. Greater shielding is felt by the β-carbons (C-3 & C-6) when they are having bulky substituents at C-3 and C-6. For the compounds **10** & **11**, α-carbon C-7 is shielded (Δδ= - 2.23-2.38 ppm) and another α-carbon C-2 is deshielded (Δδ= + 1.20-2.54 ppm). The reverse is true for the compound **12** [(Δδ= -0.50 (C-2), +1.21 (C-7)]. The shielding of α-carbons can be explained by the eclipsing interaction between one of the α-carbons (C-2 or C-7) and methylenic carbon in the benzyl group at N-1. The shielding and deshielding of chemical shifts of the α- and β-protons and carbons are presented in Tables 7 & 8.

*3.5. X-ray crystal structure of compound **12***

The *N*-benzyl-1,4-diazepan-5-one **12** is crystallized with two crystallographically independent molecules in the asymmetric unit. The study on asymmetry parameters, torsion angles and least-squares planes reveals that the diazepanone ring in both the molecules adopts twist-boat conformation (Fig. 6) with puckering [32] and asymmetry parameters [33] are: q2 = 1.113(2)Å, q3 = 0.054(2)Å, φ2 = 342.02(3)° & ΔCs(C-3A) = 15.6(2)° for molecule A and q2 = 1.115(2)Å, q3 = 0.073(2)Å, φ2 = 340.02(1)° & ΔCs(C-3B)= 12.4(2)° for molecule B, respectively. The torsion angles shown in the figure (Fig. 6) are supporting the above said twist-boat conformation for both molecules (A & B).

The planar phenyl rings substituted at C-2 and C-7 positions of the diazepanone ring in both the molecules occupy equatorial orientation. The corresponding torsion angles are [C14-C2-C3-N4] 178.7(2)° & -173.1(2)° and [C5-C6-C7-C8] 145.9(2)° & 147.2(2)° for molecules A & B. The best plane of diazepanone ring orients at angles of 72.5(1)° & 80.5(1)° (Molecule A) and 56.6(1)° & 87.8(1)° (Molecule B) with respect to the two phenyl rings, respectively. The benzyl group substituted at the N-1 position of the diazepanone ring is oriented at an angle of 49.60(16)° (Molecule A) & 42.45(13)° (Molecule B), respectively.

In compound **12**, the methyl groups (C-20 & C-21) substituted at C-3 & C-6 occupy equatorial & axial orientations and the corresponding torsion angles are [N1-C2-C3-C20=] -173.5(2)° & -168.5(2)°; [C21-C6-C7-N1=] -136.1(2)° & 136.6(2)°, for molecules A & B of compound **12**, respectively. The bond lengths and bond angles are comparable with each other. The sum of the bond angles around the hetero nitrogen atoms N-1 [352.4° & 352.7°] & N-4 [359.4° & 359.7°] for molecules A & B shows that the atoms N-1 & N-4 are in sp^2 hybridized state.

3.5.1. Packing features

The packing of the molecules viewed down along the *c*-axis is shown in Fig. 7. The molecules are stabilized by N-H...O type of intermolecular interactions in addition to van der Waals forces (Table 9). The molecules at (x, y, z) and the symmetry related molecules at (1/2-x,-1/2+y,1/2-z) & (1/2-x,1/2+y,1/2-z) are linked through intermolecular N4A-H4A...O1B & N4B-H4B...O1A hydrogen bonds into cyclic centrosymmetric $R^2_2(8)$ dimers [34].

*3.6. Molecular docking studies for the compounds **10**-**12***

In this study, glide docking has been used to study the binding orientations to predict the binding affinity of the compounds **10**-**12**. The results obtained would be useful to understand the inhibitory mode of the molecule based on docking scores. This will also provide some beneficial clues in a structural modification to design new inhibitors for the treatment of HIV. The structural information and the data for the target were collected from "Protein Data Bank" (PDB ID: 1AJX) [35]. A view of the crystal structure of the compounds **10**-**12** in the HIV-1 protease active site along with hydrogen contacts is shown in Fig 8.

The disease acquired immune deficiency syndrome (AIDS) is caused by the retrovirus (HIV) human immunodeficiency virus [36]. The HIV-1 protease is essential for maturation of the virus into infectious viral particles and this enzyme is considered, as a target for drugs against AIDS [37]. HIV PR is an aspartyl protease that is functional as a dimer of two identical subunits with 99 amino acid residues [38]. Guidance in the design of inhibitors has come from the crystal structures of HIV PR complexed with different inhibitors [39]. There is a significant difference in the conformation of the protease in these inhibitor complex structures compared to the native structure [40]. The analysis of these inhibitors in complexation with the protease is presented here.

The changes in the active site area between different inhibitor HIV PR complexes are generally small (within 0.3-0.8 Å rms deviation) [41]. The amino acids Ile50/47 are symmetrically positioned and in close contacts with the inhibitors. The aspartic acids are in contact with the inhibitor, due to the asymmetric positioning of inhibitor in the active site. The conformational change of the diazepanone ring and the shift in the side chain of compounds induce the interactions with the HIV PR.

For comparison, we performed the docking studies for similar *N*-benzyl derivatives of diazepanones, namely *N*-benzyl-3-methyl-2,7-diphenyl-1,4-diazepan-5-one (**10**), *N*-benzyl-3-ethyl-2,7-diphenyl-1,4-diazepan-5-one (**11**), *N*-benzyl-3,6-dimethyl-2,7-diphenyl-1,4-diazepan-5-one (**12**) and including Co-Crystal ((4r,5s,6s,7r)-1,3-Dibenzyl-4,7-bis(phenoxymethyl)-5,6-dihydroxy-1,3 diazepan-2-one).

In compound **12**, the nitrogen and keto O atoms interact with ILE-50 at distances of 3.13 & 3.4Å. Similarly in compound **10**, the nitrogen atom in the diazepanone ring interacts with ILE-47 at 3.23Å. In compound **11**, the oxygen and nitrogen atoms in the diazepanone ring are in contact with the aspartic acids (ASP-29 and ASP-30) at distances of 2.77Å and 3.20Å.) This is due to the asymmetric positioning of inhibitor in the active site. All the *N*-benzyl-1,4-diazepan-5-ones **10**-**12** show appreciable interactions, good docking scores and glide energy. The Co-Crystal ligand also docked well at the active site and makes contact with ILE-50 and ASP-25.

The view of the *N*-benzyl-1,4-diazepan-5-ones **10**-**12** docked at the active site of the protein is shown in Fig. 8. The relevant docking scores and energy details are given in Table 10. Since the docking scores of diazepan-5-ones **10**-**12** are similar, it is difficult to judge the suitable inhibitor. However the parameters are valuable and useful to design inhibitors comprising seven-membered ring as a core structure.

3.7. Antibacterial activity

The MIC of the compounds **10**-**12** is determined visually in the resazurin dye reduction assay. The change of color of resazurin solution from blue to pink indicates that the microbial cells are viable. The enzyme oxidoreductase present inside the microbial cells converts the resazurin to resorufin which is pink in color. When the color of the dye remains blue, it indicates that there is no activity of viable cells. The compounds **10**-**12**, when added, kill the bacterial cells during incubation. This is known from the blue or purple color of dye in the respective cells. The pink color formation in the cells even after treating with test

compounds **10**-**12** or commercial drug (Streptomycin) indicates the presence of viable cells. Thus, the least dilution in which the color remains blue is taken as the MIC value of the respective compound.

The compounds **10**-**12**, tested in this assay show activity against the bacterial pathogens. The MIC values of the test material are tabulated in Table 11. Both Gram-positive and Gram-negative bacteria are susceptible to the test compounds. The results indicate that only compound **11** exhibits moderate activity and the other compounds **10** and **12** show no activity even at 100 μg/ml.

4. Conclusion

In the present study, three new *N*-benzyl-1,4-diazepan-5-ones **10**-**12** have been synthesized by following two methods and the structures are characterized using IR, mass, NMR spectral techniques. The stereochemistry has been studied for the synthesized compounds using ^{1}H and ^{13}C NMR data. The compound **10** prefers to adopt **CE** conformation whereas the compounds **11** & **12** are shown to prefer **TB** conformation with equatorial and pseudo-axial orientations phenyl rings. The X-ray crystal structure of **12** shows that it is in twist-boat conformation in solid state. *In silico* molecular docking studies are carried out for all the synthesized compounds and the results reveal that the compounds **10**-**12** are having similar binding interactions, docking score and glide energy when compared with Co-Crystal ligand. The *in vitro* antibacterial screening indicates that the compounds exhibit no activity even at 100 μg/ml and only compound **11** shows moderate activity.

Acknowledgements

SS thanks UGC, New Delhi for the award of Rajiv Gandhi National Fellowship (RGNFS). PS thanks the UGC, New Delhi for the financial support in the form of a Research Fellowship in Science for Meritorious Students. We wish to thank (SAIF) IIT, Chennai and (SIF) Vellore for NMR spectra.

Additional information

Crystallographic data (CIF and FCF) for the structure of compounds **12** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers, CCDC1453761, respectively. Copies of the data can be

obtained free of charge, on application to CCDC, 12 Union Road, CambridgeCB2 1 EZ, UK. (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).

References

[1] I.S. Weitz, M. Pellegrini, D.F. Mierke, M. Chorev, J. Org. Chem., 62 (1997) 2527-2534.

[2] I.S. Weitz, M. Pellegrini, M. Royo, D.F. Mierke, M. Chorev, Lett. Pept. Sci., 5 (1998) 83-86.

[3] M. Gopalakrishnan, P. Sureshkumar, J. Thanusu, V. Kanagarajan, R. Govindaraju, G. Jayasri, J. Enzyme Inhib. Med. Chem., 22 (2007) 709-715.

[4] N.J. Parmar, H.A. Barad, B.R. Pansuriya, S.B. Teraiya, V.K. Gupta, R. Kant, Bioorg. Med. Chem. Lett., 22 (2012) 3816-3821.

[5] L.D. Fader, R. Bethell, P. Bonneau, M. Bös, Y. Bousquet, M.G. Cordingley, R. Coulombe, P. Deroy, A. M. Faucher, A. Gagnon, N. Goudreau, C. Grand-Maître, I. Guse, O. Hucke, S.H. Kawai, J.E. Lacoste, S. Landry, C.T. Lemke, E. Malenfant, S. Mason, S. Morin, J. O'Meara, B. Simoneau, S. Titolo, C. Yoakim, Bioorg. Med. Chem. Lett., 21 (2011) 398-404.

[6] S.J. Childress, M.I. Gluckman, J. Pharm. Sci., 53 (1964) 577-590.

[7] S. Cortez-Maya, E. Cortes Cortes, S. Hernandez-Ortega, T. Ramirez Apan, A. Nieto Camacho, V.L. Irina, M. Martinez-Garcia, Anticancer Agents Med. Chem., 12 (2012) 611-618.

[8] S.D. Dindulkar, I. Bhatnagar, R.L. Gawade, V.G. Puranik, S.K. Kim, D.H. Anh, P. Parthiban, Y.T. Jeong, J. Chem. Sci., (2014) 861-873.

[9] S. Sethuvasan, P. Sugumar, V. Maheshwaran, M.N. Ponnuswamy, S. Ponnuswamy, J. Mol. Struct., 116 (2016) 188-199.

[10] U.P. Senthilkumar, R. Jeyaraman, R.W. Murray, M. Singh, J. Org. Chem., 57 (1992) 6006-6014.

[11] U. P. Senthil kumar, Conformational studies on Hexahydro-1,4-diazepines with *N*-X=Y Groups, Ph. D Thesis, Bharathidasan University, India, 1993.

[12] R. Jeyaraman, U.P. Senthilkumar, P. Bigler, J. Org. Chem., 60 (1995) 7461-7470.

[13] V. Priya, N. Shamala, M.A. Viswamitra, U.P. SenthilKumar, R. Jeyaraman, Acta Cryst., C48 (1992) 1048-1051.

[14] V. Maheshwaran, S. Sethuvasan, K. Ravichandran, S. Ponnuswamy, P. Sugumar, M.N. Ponnuswamy, Chem. Cent. J., 9 (2015) 17.

[15] S. Ponnuswamy, A. Akila, D. Kiruthiga devi, V. Maheshwaran, M.N. Ponnuswamy, J. Mol. Struct., 1110 (2016) 53-64.

[16] R. Jeyaraman, S. Ponnuswamy, J. Org. Chem., 62 (1997) 7984-7990.

[17] S.S. Ilango, S. Ponnuswamy, T. Viswanathan, Indian J. Heterocycl. Chem., 20 (2010) 17-20.

[18] S.D. Dindulkar, P. Parthiban, V.G. Puranik, Y.T. Jeong, J. Mol. Struct., 990 (2011) 44-56.

[19] S.D. Dindulkar, P. Parthiban, V.G. Puranik, Y.T. Jeong, J. Mol. Struct., 1007 (2012) 158-167.

[20] Bruker, APEX2, SAINT. Bruker AXS Inc. Madison Wisconsin, USA, (2004).

[21] G.M. Sheldrick, SADABS, University of Gottingen, Germany, (1996).

[22] G. Sheldrick, Acta Cryst., A64 (2008) 112-122.

[23] A. Spek, Acta Cryst., D65 (2009) 148-155.

[24] L. Farrugia, J. Appl. Crystallogr., 30 (1997) 565.

[25] Schrödinger, Maestro, Version 9.2, Schrödinger, LLC, New York, 2011.

[26] S.D. Sarker, L. Nahar, Y. Kumarasamy, Methods, 42 (2007) 321-324.

[27] J.W. Cooper, Spectroscopic Techniques for Organic Chemists; J.Wiley: New York, (1980) 85.

[28] K.N. Slessor, A.S. Tracey, Can. J. Chem., 49 (1971) 2874-2884.

[29] J. Skolik, P.J. Krueger, M. Wiewiorowski, Tetrahedron, 24 (1968) 5439-5456.

[30] W.F. Trager, C.M. Lee, A.H. Beckett, Tetrahedron, 23 (1967) 365-374.

[31] Y.L. Chow, C.J. Colón, J.N.S. Tam, Can. J. Chem., 46 (1968) 2821-2825.

[32] D. Cremer, J.A. Pople, J. Am. Chem. Soc., 97 (1975) 1354-1358.

[33] M. Nardelli, Acta Cryst., C39 (1983) 1141-1142.

[34] J. Bernstein, R.E. Davis, L. Shimoni, N.L. Chang, Angew Chem. Int. Ed. Engl., 34 (1995) 1555-1573.

[35] K. Bäckbro, S. Löwgren, K. Österlund, J. Atepo, T. Unge, J. Hultén, N.M. Bonham, W. Schaal, A. Karlén, A. Hallberg, J. Med. Chem., 40 (1997) 898-902.

[36] R. Gallo, P. Sarin, E. Gelmann, M. Robert-Guroff, E. Richardson, V. Kalyanaraman, D. Mann, G. Sidhu, R. Stahl, S. Zolla-Pazner, J. Leibowitch, M. Popovic, Science, 220 (1983) 865-867.

[37] C. Debouck, B.W. Metcalf, Drug Dev. Res., 21 (1990) 1-17.

[38] L.H. Pearl, W.R. Taylor, Nature, 329 (1987) 351-354.

[39] M.L. West, D.P. Fairlie, Trends Pharmacol. Sci., 16 (1995) 67-75.

[40] M.A. Navia, P.M.D. Fitzgerald, B.M. McKeever, C.T. Leu, J.C. Heimbach, W.K. Herber, I.S. Sigal, P.L. Darke, J.P. Springer, Nature, 337 (1989) 615-620.

[41] J.W. Erickson, Perspect. Drug Discovery Des., 1 (1993) 109-128.

All captions

Scheme 1

Synthesis of *N*-benzyl-2,7-diphenyl-1,4-diazepan-5-ones **10**-**12**

Figure captions

Figure 1

(a) ORTEP plot of the compound **12** with displacement ellipsoids drawn at 30% probability level

(b) The overlapping of molecules (A & B) for the compound **12** present in the asymmetric unit

Figure 2

chair conformation (**CE**) of 2,7-diphenyl-1,4-diazepan-5-ones **4**-**6**

Figure 3

Possible conformations for compounds **10**-**12**

Figure 4

Preferred conformation for compounds **10**

Figure 5

Preferred conformation for compounds **11** and **12**

Figure 6

Torsion angles for the compound **12** showing the seven-membered diazepanone ring adopts twist-boat conformation for both molecules

Figure 7

Packing of the molecules for the compound **12** viewed down on c-axis and the formation of dimer through N-H…O types of hydrogen bonds is shown in dotted lines

Figure 8

A view of the *N*-benzyl-1,4-diazepan-5-ones **10**-**12** in the protein active site showing the key hydrogen contacts

Table captions

Table 1

Analytical data of *N*-benzyl-2,7-diphenyl-1,4-diazepan-5-ones **10**-**12**

Table 2

Crystal data of *N*-benzyl-3,6-dimethyl-2,7-diphenyl-1,4-diazepan-5-one (**12**)

Table 3a

Selected bond lengths (Å) and bond angles (°) for compound **12**

Table 3b

Selected torsion angles (°) for compound **12**

Table 4

^{1}H NMR chemical shift values of *N*-benzyl-1,4-diazepan-5-ones **10**-**12** [δ (ppm)]

Table 5

^{13}C NMR chemical shift values of *N*-benzyl-1,4-diazepan-5-ones **10**-**12** [δ (ppm)]

Table 6

Coupling constants (Hz) and dihedral angles (°) of compounds **10**-**12**

Table 7

^{1}H NMR chemical shift of the α- and β-protons (Δδ, ppm) for the compounds **10**-**12**

Table 8

^{13}C NMR chemical shift of the α- and β-carbons (Δδ, ppm) for the compounds **10**-**12**

Table 9

Hydrogen-bond geometry (Å, °) for compound **12**

Table 10

Hydrogen bond interactions of *N*-benzyl-1,4-diazepan-5-ones **10**-**12** with amino acids at the active site of HIV protein

Table 11

Minimum inhibitory concentration (MIC) of compounds **10**-**12** against selected bacterial strains

Table 1

Compound	M. P. (ºC)	Yield (%)		MS m/z (M^+)	M. P. (ºC)	IR cm^{-1}		Elemental analysis Found (Calcd)%		
		Method A	Method B			amide NH	amide CO	C	H	N
10	136-138 °C	53	57	370.00	136-138 °C	3184	1654	81.30 (81.05)	6.79 (7.07)	7.36 (7.56)
11	114-116 °C	50	68	384.98	114-116 °C	3188	1656	81.44 (81.21)	7.06 (7.34)	7.10 (7.29)
12	146-148 °C	61	78	384.24	146-148 °C	3203	1671	80.90 (81.21)	7.58 (7.34)	7.07 (7.29)

Table 2

Parameters	Values
CCDC number	1453761
Empirical formula	C_{52} H_{56} N_4 O_2
Formula weight	769.01
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a = 13.944(5) Å b = 20.486(5) Å c = 16.555(5) Å β = 113.479(5) °
Volume	4338(2) $Å^3$
Z, Calculated density	4, 1.178 Mg/m^3
Absorption coefficient	0.072 mm^{-1}
F(000)	1648
Crystal size	0.21 x 0.19 x 0.16 mm
Theta range for data collection	1.62 to 28.38°
Limiting indices	-18<=h<=17, -27<=k<=27, -21<=l<=22
Reflections collected / unique	42454 / 10748 [R_{int} = 0.0363]
Completeness to θ = 28.38	98.8%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10748 / 2 / 527
Goodness-of-fit on F^2	1.015
Final R indices [I>2σ(I)]	R1 = 0.0608, wR2 = 0.1585
R indices (all data)	R1 = 0.1239, wR2 = 0.1941
Largest diff. peak and hole	0.467 and -0.206 e.$Å^{-3}$

Table 3a

Atoms	Lengths		Atoms	Angles	
	Molecule A	Molecule B		Molecule A	Molecule B
C2-N1	1.465(2)	1.470(3)	N1-C2-C3	111.20(16)	110.48(16)
C2-C3	1.527(3)	1.528(3)	N1-C2-C14	115.77(15)	115.56(18)
C2-C14	1.533(3)	1.518(3)	C3-C2-C14	113.88(16)	115.84(17)
C3-N4	1.461(3)	1.462(3)	N4-C3-C20	108.59(18)	109.05(18)
C3-C20	1.514(3)	1.516(3)	N4-C3-C2	109.31(16)	108.16(16)
C5-O1	1.229(2)	1.231(2)	C20-C3-C2	111.60(2)	112.31(18)
C5-N4	1.342(3)	1.343(3)	O1-C5-N4	122.00(2)	121.30(2)
C5-C6	1.510(3)	1.509(3)	O1-C5-C6	121.60(2)	122.60(19)
C6-C21	1.525(3)	1.514(3)	N4-C5-C6	116.28(19)	115.95(18)
C6-C7	1.552(3)	1.550(3)	C5-C6-C21	111.54(19)	112.86(18)
C7-N1	1.476(3)	1.474(2)	C5-C6-C7	112.02(17)	112.23(16)
C7-C8	1.526(3)	1.528(3)	C21-C6-C7	110.03(19)	109.65(18)
C22-N1	1.462(3)	1.451(3)	N1-C7-C8	116.64(16)	116.99(16)
			N1-C7-C6	111.91(16)	113.14(17)
			N1-C22-C23	112.78(18)	113.40(2)
			C22-N1-C2	112.91(16)	112.92(17)
			C22-N1-C7	117.13(16)	116.04(18)
			C2-N1-C7	122.41(15)	123.01(15)
			C5-N4-C3	123.46(18)	123.67(18)

Table 3b

Atoms	Angles	
	Molecule A	**Molecule B**
N1-C2-C3-N4	-53.1(2)	-48.3(2)
C14-C2-C3-N4	173.11(17)	178.69(17)
N1-C2-C3-C20	-173.44(18)	-168.49(18)
C14-C2-C3-C20	52.7(3)	58.5(3)
O1-C5-C6-C21	-9.9(3)	-10.5(3)
N4-C5-C6-C21	166.38(18)	165.0(2)
O1-C5-C6-C7	114.6(2)	113.3(2)
N4-C5-C6-C7	-69.1(2)	-71.2(2)
C5-C6-C7-N1	9.8(2)	11.9(2)
C21-C6-C7-N1	136.08(18)	136.62(19)
N1-C7-C8-C13	-74.6(3)	-64.4(3)
N1-C7-C8-C9	106.7(3)	117.5(2)
N1-C2-C14-C15	-75.2(3)	-80.8(3)
N1-C2-C14-C19	103.5(2)	99.5(2)
N1-C22-C23-C24	39.2(4)	49.1(3)
N1-C22-C23-C28	-145.3(2)	-132.2(2)
C23-C22-N1-C2	-147.2(2)	-155.57(18)
C23-C22-N1-C7	62.9(3)	53.9(3)
C14-C2-N1-C22	-49.6(3)	-58.5(2)
C3-C2-N1-C22	176.4(2)	169.52(17)
C14-C2-N1-C7	97.8(2)	90.3(2)
C3-C2-N1-C7	-36.1(3)	-41.7(2)
C8-C7-N1-C22	79.0(2)	81.3(2)
C6-C7-N1-C22	-146.68(19)	-144.61(18)
C8-C7-N1-C2	-67.5(3)	-66.2(2)
C6-C7-N1-C2	66.8(2)	67.9(2)
O1-C5-N4-C3	-163.60(19)	-164.0(2)
C6-C5-N4-C3	20.0(3)	20.5(3)
C20-C3-N4-C5	-170.44(19)	-173.3(2)
C2-C3-N4-C5	67.1(2)	64.7(3)

Table 4

Compound	H-2	H-3	H-6a	H-6e	H-7	3-CH_3	3-CH_2CH_3	6-CH_3	*N*-CH_2-Ph	NH	CONH	Aromatic protons
10	3.78 (d)	3.59 (m)	3.17 (dd)	3.00 (d)	4.24 (d)	0.59 (d)	-	-	3.72 (d) 3.43 (d)	-	5.92 (s)	7.14-7.58 (m)
4	3.70 (d)	3.82 (ddq)	3.14(dd)	2.65 (d)	4.13 (d)	0.81 (d)	-	-	-	2.07 (bs)	5.75 (bs)	7.23-7.43 (m)
11	3.85 (d)	a	3.20 (dd)	2.94 (dd)	4.31 (dd)	-	0.95 (m, CH_2) 0.71 (m, CH_3)	-	3.73 (d) a	-	5.72 (s)	7.14-7.52 (m)
5	3.77 (d)	3.65 (m)	3.15 (dd)	2.65 (d)	4.14 (d)	-	0.85 (t, CH_2) 1.12 (m, CH_3)	-	-	2.03 (s)	5.77 (bs)	7.20-7.44 (m)
12	3.69 (d)	4.25 (dq)	3.64 (q)	-	4.07 (d)	1.03 (d)	-	0.94 (d)	3.90 (dd)	-	6.04 (d)	7.08-7.34 (m)
6	3.65 (d)	3.86 (ddq)	3.08 (dq)	-	3.79 (d)	0.79 (d)	-	0.70 (d)	-	2.06 (s)	5.75 (bd)	7.20-7.40 (m)

(a) 3.53-3.48 (δ ppm) H-3 merged with H_B of *N*-CH_2-Ph

Table 5

Compound	C-2	C-3	C-5	C-6	C-7	3-CH_3	3-CH_2CH_3	6-CH_3	*N*-CH_2-Ph	Aromatic *ipso* carbons	Aromatic carbons
10	73.64	50.84	173.99	36.57	57.22	21.95	-	-	56.93	145.23, 142.70, 138.15	129.49, 128.74, 128.65, 128.29, 127.91, 127.32, 126.97, 126.47
4	71.1	54.7	175.7	47.5	59.6	19.8	-	-	-	142.1, 144.7	126.4, 127.7, 128.0, 128.6
11	71.30	56.59	174.49	38.22	58.27	-	27.00 (CH_2) 10.14 (CH_3)	-	56.92	145.13, 142.20, 138.21	129.42, 129.34, 128.81, 128.61, 128.58, 128.27, 127.74, 127.24, 126.97, 126.57
5	70.1	59.3	176.1	47.4	60.5		25.6 (CH_2) 10.1 (CH_3)		-	142.0, 144.8	126.4, 127.6, 127.7, 127.8, 128.5,
12	70.50	50.05	177.23	40.41	66.11	19.81	-	15.74	59.25	141.70, 140.14, 139.02	129.19, 128.53, 128.48, 128.17, 128.14, 127.96, 127.16, 127.07, 126.98
6	71.0	54.2	178.4	45.9	64.9	19.6	-	14.6	-	142.2, 143.2	126.7, 127.6, 127.7, 127.8, 128.0, 128.3, 128.5, 128.7

Table 6

Compound	coupling constants (Hz)				Dihedral angles (°)	
	$^{3}J_{H2,\ H3}$	$^{2}J_{H6a,\ H6e}$	$^{3}J_{H6a,\ H7}$	$^{3}J_{H6e,\ H7}$	$\Phi_{H6e,H7}$	$\Phi_{H6a,H7}$
10	8.4	16.4	7.6	0	79	161
4	7.8	14.1	10.6	0	81	159
11	8.8	16.0	8.8	2.4	55	175
5	7.8	14.1	10.7	0	81	159
12	10.0	-	9.6	-	-	-
6	8.1	-	10.6	-	-	-

Table 7

Compound	α-protons		β-protons		
	H-2	H-7	H-3	H-6a	H-6e
10	+0.08	+0.11	-0.23	+0.03	+0.35
11	+0.08	+0.17	-	+0.05	+0.28
12	+0.04	+0.28	+0.39	+0.56	-

Table 8

Compound	α-carbons		β-carbons	
	C-2	C-7	C-3	C-6
10	+2.54	-2.38	-3.86	-10.93
11	+1.20	-2.23	-2.71	-9.18
12	-0.50	+1.21	-4.15	-5.49

Table 9

D-H…A	D-H	H…A	D…A	>DHA
N4A-H4A...O1B[i]	0.86	2.15	2.946(3)	154
N4B-H4B...O1A[ii]	0.86	2.09	2.902(3)	157

Symmetry Equivalent Position

(i) 1/2-x,-1/2+y,1/2-z

(ii) 1/2-x,1/2+y,1/2-z

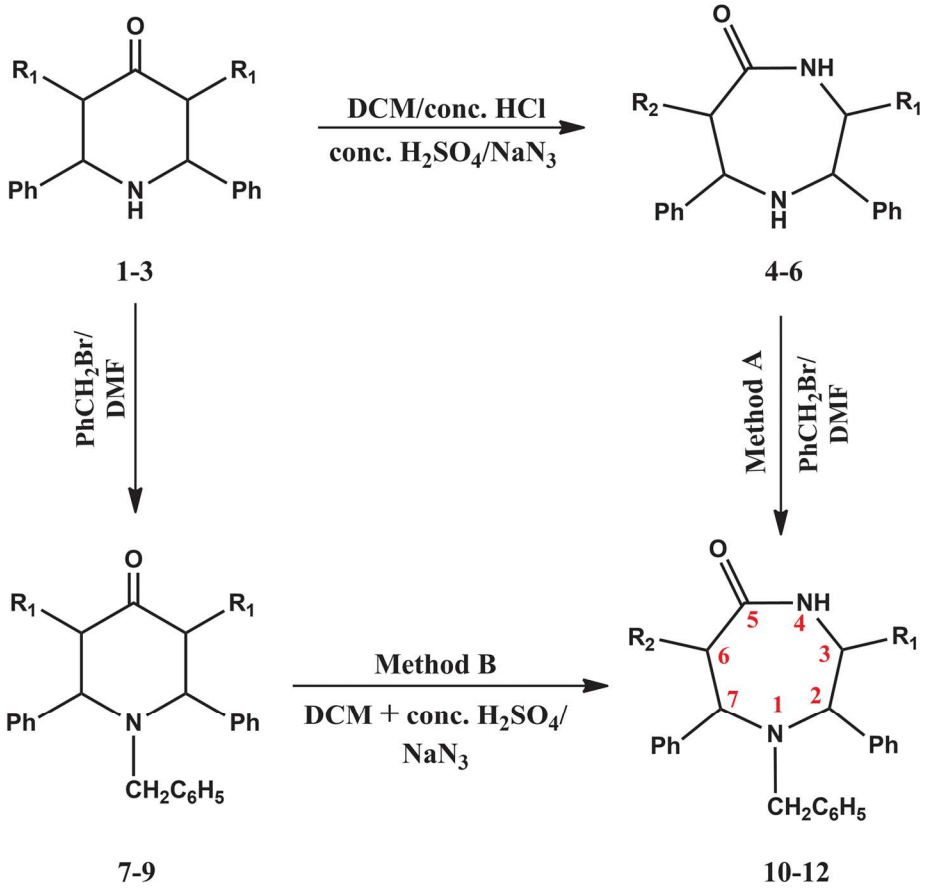
Table 10

Compound	Glide Score	Glide Energy	Interactions	Distance(Å)
12	-8.71922	-50.8854	N-H…O(ILE50)	3.1
			O…H-O(ILE50)	3.4
			N…H-O(ASP30)	3.2
11	-9.1433	-52.492	O…H-N(ASP30)	3.0
			O…H-N(ASP29)	2.8
10	-7.31637	-48.6696	N-H…O(ILE47)	3.2
			N-H…O(ILE50)	2.8
Co-Crystal	-7.70963	-59.0774	O-H…O(ASP25)	2.7
			O-H…O(ASP25)	2.7

Table 11

Compound	Minimum inhibitory concentration (MIC) µg/ml		
	Bacterial pathogens		
	Staphylococcus aureus	***Escherichia coli***	***Bacillus cereus***
10	NA	NA	NA
11	12.50	25	6.25
12	NA	NA	NA
Streptomycin	1.56	1.56	0.78

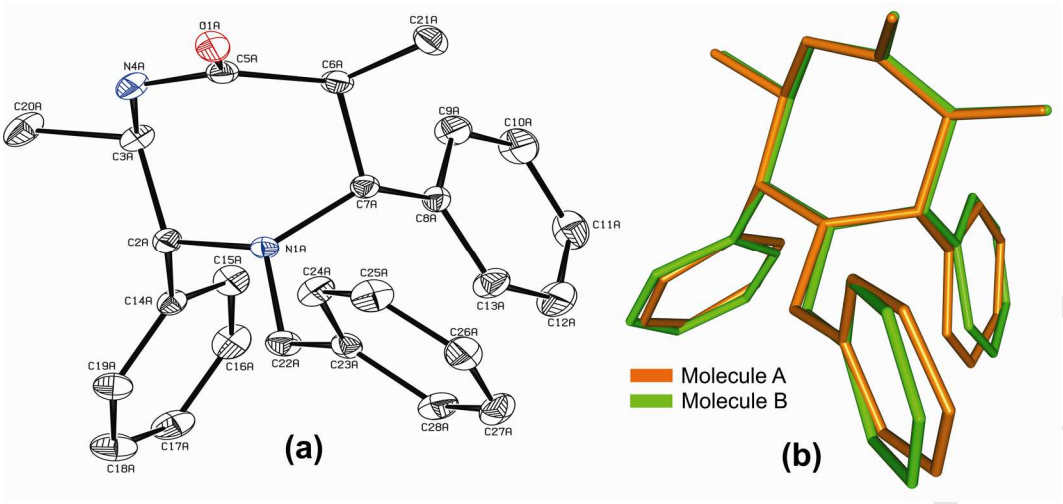
NA-No inhibition even at 100 µg/ml

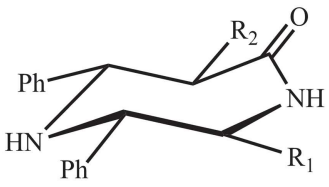


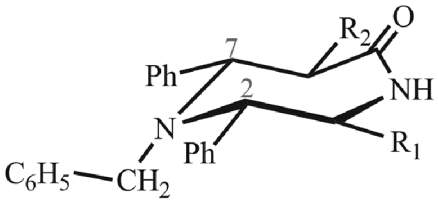
1-3 4-6

7-9 10-12

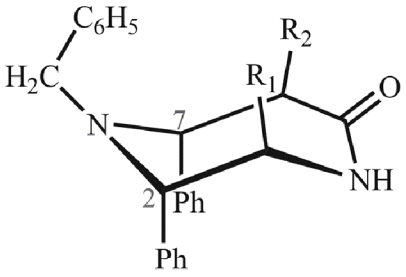
				R_1	R_2
1	4	7	10	Me	H
2	5	8	11	Et	H
3	6	9	12	Me	Me



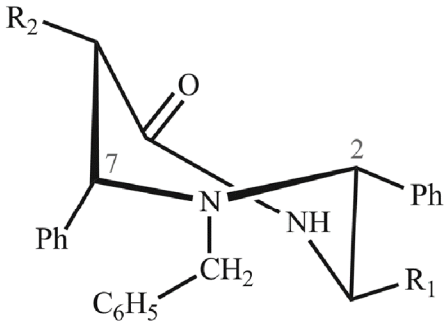




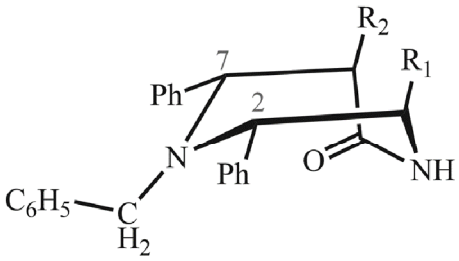
CE



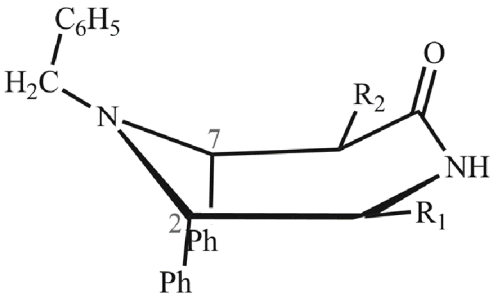
CA



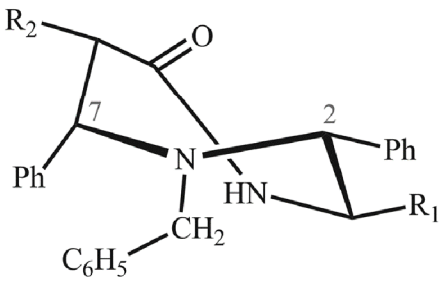
TC



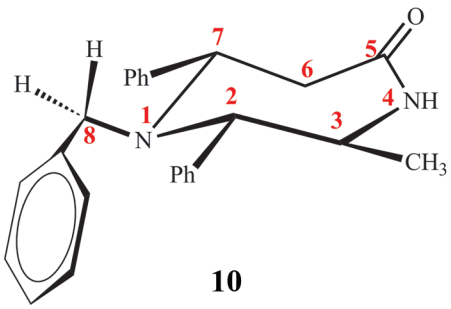
BE



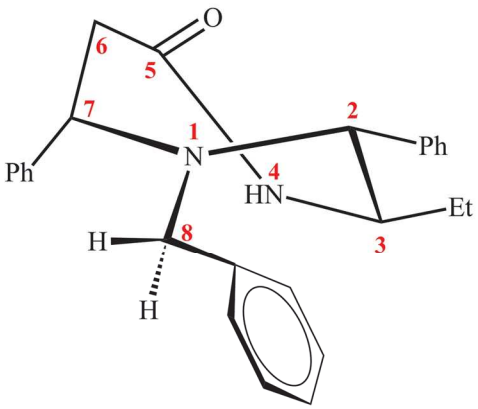
BA



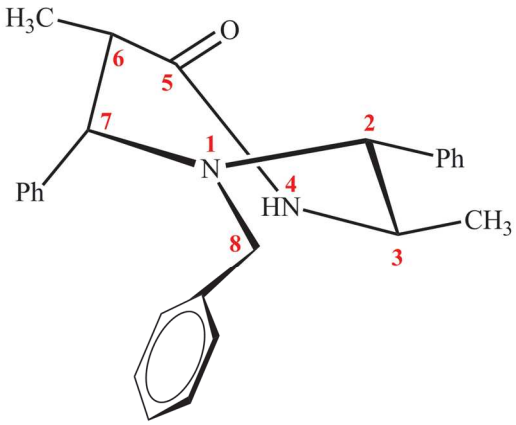
TB



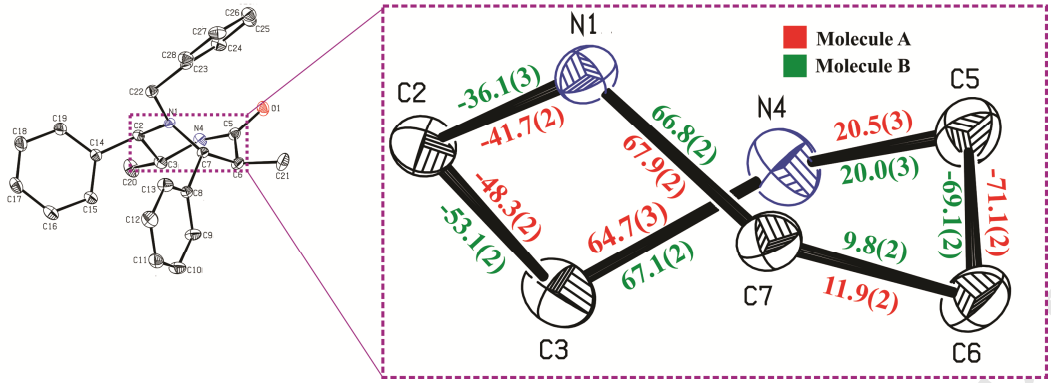
10

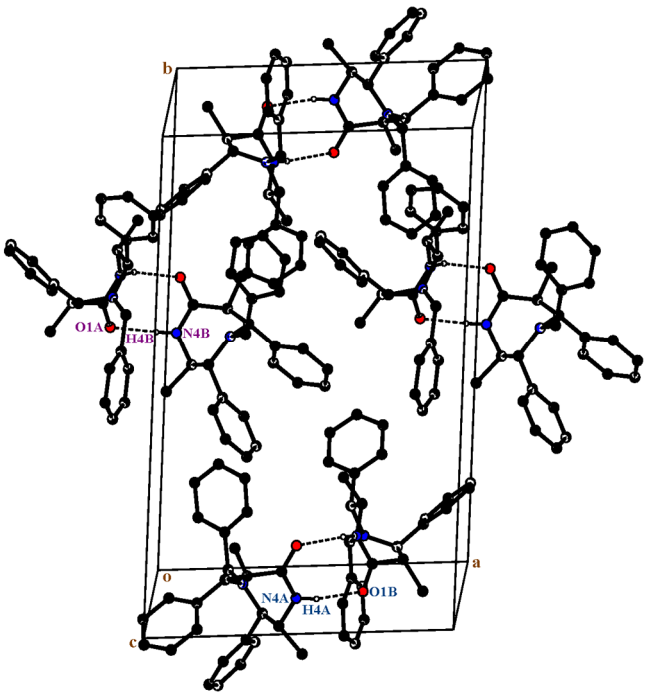


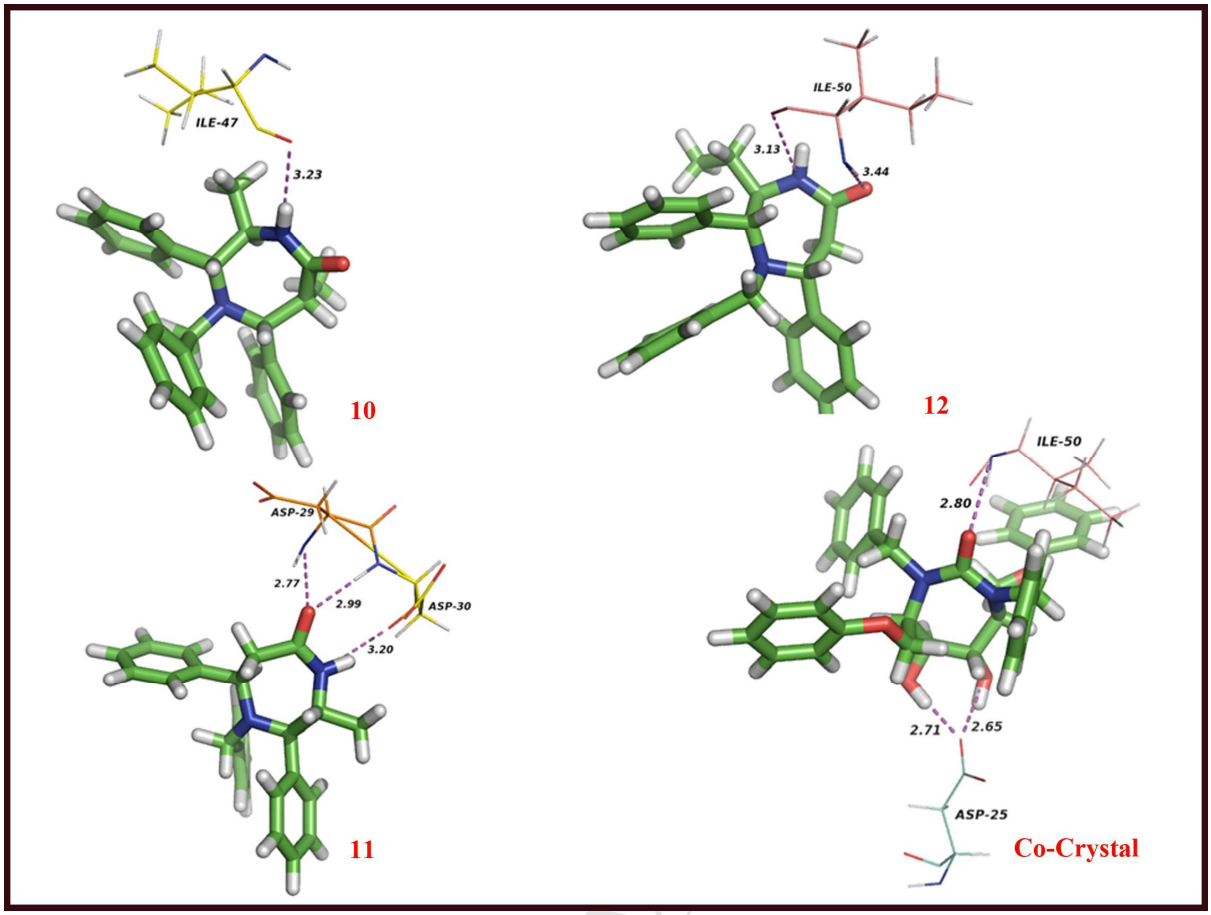
11



12







Highlights

- ✓ Three novel *N*-benzyl-1,4-diazepan-5-ones have been synthesized and characterized
- ✓ In solution state, **10** prefers **CE** conformation of the parent
- ✓ Interestingly **11** & **12** prefer twist-boat conformation
- ✓ X-ray crystal structure of **12** shows twist-boat conformation
- ✓ Docking studies confirm the binding of active compounds **10**-**12** with HIV-1 protease