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Synthesis of diversely substituted adamantanes as a new class of antimicrobial agent

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Abstract 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ones are synthesized and reduced into its 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ols (**6a–m**) with $NaBH_4$ in methanol (2v), benzene (1v) mixture as the solvent system. These compounds are characterized using spectral data such as IR, ^{1}H-NMR, and ^{13}C-NMR data. These synthesized compounds are screened for their antimicrobial activity and were found to be effective anti-bacterials.

Keywords Adamantane · Adamantanol · Antimicrobial activity

Introduction

Adamantane (tricyclo[3.3.1.1^{3,7}]decane) is an important class of polycyclic compounds with a number of interesting biological properties such as anticholinergic, antimicrobial, and antiviral. Adamantane was first synthesized by Prelog in 1941 [1]. A more convenient method was found by Schleyer et al. [2]. The unique structure of adamantine is reflected in its highly unusual physical and chemical properties. The carbon skeleton of adamantane comprises a small cage structure, and because of this, adamantane and diamondoids in general are

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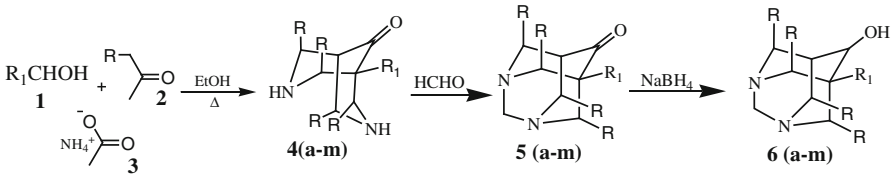
commonly known as cage hydrocarbons. Adamantane crystallizes in a face-centered cubic lattice and this is extremely unusual for an organic compound. The molecule therefore should be completely free from both angle and torsional strain. Diamantane, triamantane, and their alkyl-substituted compounds just as adamantane are also present in certain petroleum fluids. Their concentrations in these fluids are generally lower than that of adamantane and its alkyl-substituted compounds. In rare cases, tetra, penta, and hexamantanes are also found in petroleum fluids. Adamantane itself enjoys few applications since it is merely an unfunctionalized hydrocarbon. It is used in some dry-etching masks [3]. It is also used in some polymer formulations. In solid-state NMR, adamantane is a common standard for chemical shift referencing. Adamantane cannot be photoionized under atmosphere because its absorption bands lie in the vacuum-ultraviolet region of the spectrum [4]. Urotropin or 1,3,5,7-tetraazaadamantane is the best known of this class and has been used as an antigout agent in pharmacology and with various additives for the prevention and treatment of influenzas. The chemistry of adamantanes and its derivatives, particularly nitroadamantanes, is of interest for their use as high-density energetic materials [5]. Recent interest in adamantanes has extended into the area of host–guest compounds [6], combinatorial chemistry, optically active organic molecules [7], and dendritic macromolecules [8]. Tetraaryl-substituted cage hydrocarbons with tetrahedral symmetry are the potential precursors of energetic materials, dendrimers, star-shaped molecules, and molecules of interest in combinatorial chemistry [9]. The intensive progress in the adamantane chemistry was accompanied by the development of effective methods for functionalization of adamantane nucleus. Many reliable and convenient procedures for preparation of adamantane compounds have been proposed. The described methods for synthesis of trisubstituted adamantanes are well elaborated only for compounds with functional groups attached to the bridgehead positions of adamantane moiety [10, 11] and for 2,2,5-trisubstituted derivatives [12, 13]. 1,3-Diazaadamantane derivatives are of great importance as conformationally rigid analogues of pharmacologically active molecules [14, 15].

Results and discussion

Though the synthesis of 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ones and its corresponding alcohols have been reported [16–30] for a limited number of derivatives, their biological significance is not yet explored and hence in the present work 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ones were synthesized using the reports available in the literature [16–30], which in turn reduced into 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ols using $NaBH_4$; characterized using IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data and then subjected to antimicrobial evaluation against various microbial strains and the results were discussed.



Compound	R_1	R	Compound	R_1	R
5a, 6a,	-H	-Phenyl	**5h, 6h**	-H	-2-methoxyphenyl
5b, 6b	$-CH_3$	-Phenyl	**5i, 6i**	-H	-4-methoxyphenyl
5c, 6c	-H	-4-Fluorophenyl	**5j, 6j**	-H	-4-ethoxyphenyl
5d, 6d	-H	-2-Chlorophenyl	**5k, 6k**	-H	2,5-dimethoxyphenyl
5e, 6e	-H	-4-Chlorophenyl	**5l, 6l**	-H	3,4-dimethoxyphenyl
5f, 6f	-H	-4-Bromophenyl	**5m, 6m**	-H	3,4,5-trimethoxyphenyl
5g, 6g	-H	-4-Methylphenyl			

Scheme 1 Synthesis of 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-ones (**5a–m**) and its corresponding alcohols **6(a–m)**

The 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-ones **4a–m** in C_6H_6 was added with enough aq. formalin and the mixture was shaken vigorously for 15 min. The C_6H_6 layer was separated and distilled out to afford the crude 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ones (**5a–m)** (also called as 4,8,9,10-tetraaryl-1,3-diazaadamantan-6-one). The obtained crude product was recrystallized using an ethanol–benzene (4:1) mixture and the purity of the compound was checked by TLC. The compounds **5a–m** were characterized by IR, ^{1}H-NMR, and ^{13}C-NMR. Among these, the synthesis and their unambiguous chemical shift assignments of and **5a–m** (except **5c**, **5e**, **5f**, **5h**, **5l)** were already reported, and their spectral values were found to be in accord with the literature [16–21]; and hence the characterizations of remaining compounds **5c**, **5e**, **5f**, **5h**, **5l** were included in the experimental section. However, the microbial screening of all these compounds was not reported in the literature and hence all of these compounds were synthesized. Then the reagent $NaBH_4$ (dissolved in the minimum amount of water) was added to the 4,8,9,10-tetraphenyl-1,3-diazatricyclo[3.3.1.1]decan-6-ones (dissolved in methanol-benzene mixture). The mixture was refluxed for 7 h and then 6 N NaOH was added to the reaction mixture and allowed to boil for 10–20 min, then it was poured into crushed ice to afford the 4,8,9,10-tetraphenyl-1,3-diazatricyclo[3.3.1.1]decan-6-ols (**6a–m)** (Scheme 1). The obtained product was extracted with chloroform and the purity was checked by TLC. The $NaBH_4$ reduction with *iso*-propanol solvent was reported, which afford only 65 % yield, whereas the methanol-benzene solvent mixture afford more than 90 % yield. The detailed procedures are given in the experimental section. The physical and analytical data are reproduced. The products **6a–m** were characterized by IR, ^{1}H-NMR, and ^{13}C-NMR. Though some of these derivatives were already reported [16–21]; their complete chemical shift assignments were not available and hence the characterizations of **6a–m** were included in the experimental section.

The 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ols can be synthesized by two different approaches. In the first approach, 2,4,6,8-tetraaryl-3,7-diazabicyclo

Table 1 In vitro antibacterial activity of compounds **5a–m** and **6a–m**

Entry	Minimum inhibitory concentration (MIC) in μg/ml			Entry	Minimum inhibitory concentration (MIC) in μg/ml		
	Bacillus	*S. aureus*	*E. coli*		*Bacillus*	*S. aureus*	*E. coli*
Streptomycin	12.5	12.5	6.25	Streptomycin	12.5	12.5	6.25
5a	50	–	25	**6a**	12.5	12.5	100
5b	–	12.5	–	**6b**	50	100	100
5c	50	–	100	**6c**	6.25	6.25	100
5d	100	100	–	**6d**	25	100	100
5e	25	–	100	**6e**	6.25	50	50
5f	100	100	50	**6f**	6.25	6.25	–
5g	–	25	–	**6g**	100	100	–
5h	100	50	–	**6h**	–	100	100
5i	100	50	–	**6i**	100	50	100
5j	12.5	–	100	**6j**	100	25	100
5k	50	12.5	50	**6k**	6.25	–	50
5l	50	50	12.5	**6l**	100	–	–
5m	50	12.5	50	**6m**	50	–	6.25

[3.3.1]nonan-9-ones reduced into 2,4,6,8-tetraaryl-3,7-diaza bicyclo[3.3.1]nonan-9-ols using $NaBH_4$, which in turn converted into 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1] decan-6-ols using aq. formalin. In the other approach, the 2,4,6,8-tetraaryl-3, 7-diazabicyclo[3.3.1]nonan-9-ones can be converted into 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ones, which in turn reduced to 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ols using $NaBH_4$. The latter one has been already adopted and towards the earlier method here, we have attempted (the conversion of 2,4,6, 8-tetraphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**4a**) reduced into 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-ol (**5aa**) using $NaBH_4$ then into 4,8,9,10-tetraphenyl-1, 3-diazatricyclo[3.3.1.1]decan-6-ol.) and found to afford almost the same yield.

The compounds **5a–m** and **6a–m** were screened for their antibacterial activity against the three microorganisms *Bacillus,S. aureus*, and *E. coli*, and all the compounds were found to exhibit moderate activity. The minimum inhibitory concentration (MIC) values of **5a–m** and **6a–m** are given in Table 1. The compounds **5j**, **6c**, **6e**, **6f**, and **6k** exhibited better activity against *Bacillus.* The compounds **5b**, **5k**, **5m**, **6c**, and **6f** were found to exhibit better activity against *S. aureus* and **5l** and **6m** exhibited better activity against *E. coli.* In general, the compounds with fluoro, chloro, bromo, or alkoxy substituted aryls are found to exhibit better activity than the unsubstituted aryls.

Conclusions

A series of 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ones were synthesized and reduced into 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ols by sodium borohydride. The use of methanol (2v) benzene (1v) mixture as the solvent in the reduction afforded good yield. Unambiguous proton and carbon chemical shift values were assigned for these compounds and then subjected to antimicrobial evaluation and found to be an effective anti-bacterial.

Experimental

Solvents and reagents were commercially sourced and used without further purification. Melting points were taken on an Elchem Microprocessor-based DT apparatus in open capillary tubes and are uncorrected. IR spectra were obtained on an Avatar-330 FTIR spectrophotometer (Thermo Nicolet) using KBr pellets, and only noteworthy absorption levels (reciprocal centimeters) are listed. The NMR spectra were recorded on Bruker 200-, 300-, and 500-MHz spectrometer using TMS as internal standard (chemical shifts δ in ppm). Mass spectra were recorded on HRMS and LCMS by Agilent 1200 series LC and Micromass zQ spectrometer. Thin-layered chromatography (TLC) was performed on preparative plates of silica gel (s.d.fine). Visualization was made with an iodine chamber. Column chromatography was performed by using silica gel (60-120 mesh).

Representative spectral characterization of 4,8,9,10-*tetrakis*(4-bromophenyl)-1,3-diazaadamantan-6-one **(5f).**

Proton chemical shift assignment: The careful examination of proton NMR spectrum reveals that the singlet at δ 3.85 ppm integrating for two protons is due to the C-5, 7 protons, respectively. The singlets at δ 4.71 ppm and integrating for two protons represents the protons at C-4,10 and the singlet at δ 4.67 ppm and integrating for two protons represents the C-8, 9, respectively. The singlet at δ 4.34 ppm and integrating for two protons is due to the C-2 protons, respectively. The doublet at δ 6.55 ppm and δ 7.01 and integrating for four protons each with an coupling constant of 8.4 Hz is due to the aryl protons at H-4b, 10b, 4b′, 10b′ and H-4c, 10c, 4c′, 10c′. The doublet at δ 7.45 ppm and δ 7.56 and integrating for four protons each with an coupling constant of 8.4 Hz is due to the aryl protons at H-8c, 9c, 8c′, 9c′ and H-8b, 9b, 8b′, 9b′.

Carbon chemical shift assignment: The ^{13}C NMR spectrum reveals that the signal at δ 49.90 ppm corresponds to the carbons at C-5, 7 and the signal at δ 68.48 ppm corresponds to carbons at C-8, 9 respectively and the signal at δ 63.40 ppm corresponds to the carbons at C-4 and C-10 respectively. The signal at δ 67.94 ppm corresponds to the carbon at C-2 and the signal at δ 211.90 ppm corresponds to carbon at C-6 respectively and the rest of the signals appears at 132.28 (*ipso*), 130.37 (*ipso′*), 137.94 (*para*), 160.38, 136.23 (*para′*), 129.50 (*ortho*), 128.39 (*ortho′*), 121.80 (*meta*), 120.67 (*meta′*). The above discussion clearly reveals the formation of desired 4,8,9,10-tetrakis(4-bromophenyl)-1,3-diazaadamantan-6-one. In the similar way the carbon chemical shifts of other compounds has been assigned and are included in the experimental section.

4,8,9,10-*tetrakis*(4-fluorophenyl)-1,3-diazatricyclo[3.3.1.1]decan-6-one **(5c)**: Yield: 78 %, M.p., 256 °C; IR values: 1,701 cm^{-1} (C=O stretching), 3,062 cm^{-1} (Ar C–H stretching), 2,883 cm^{-1} (aliphatic C–H stretching); ^{1}H-NMR chemical shift (δ) in ppm: 4.03[s, 2H, C_5 and C_7–H], 4.93[s, 2H, C_4 and C_{10}–H], 4.85[s, 2H, C_8 and C_9–H], 4.51[s, 2H, C_2–H], 7.70, 7.12[ddd, $J = 5.9$ Hz, *ortho* and *ortho′*-H], 7.27, 6.70[t, $J = 8.7$ Hz, *meta* and *meta′*-H]; ^{13}C-NMR chemical shift (δ) in ppm: 49.88 [C_5 and C_7], 68.50 [C_8 and C_9], 63.55 [C_4 and C_{10}], 67.90 [C_2], 212.72 [C_6], 135.15, 135.11[–*ipso,* 2 carbons], 133.09, 133.13[–*ipso′*, 2 carbons], 163.65, 162.77[*para*, 2 carbons], 160.38, 159.51[*para′*, 2 carbons], 129.54, 129.64[*ortho*, 4 carbons], 128.40, 128.50[*ortho′*, 4 carbons], 113.97, 114.25[*meta*, 4 carbons], 115.85, 116.14 [*meta′*, 4 carbons].

4,8,9,10-*tetrakis*(4-chlorophenyl)-1,3-diazatricyclo[3.3.1.1]decan-6-one **(5e):** Yield: 79 %, M.p., 248 °C; IR values: 1,703 cm^{-1}(C=O stretching), 3,036 cm^{-1} (Ar C–H stretching), 2,959 cm^{-1} (aliphatic C–H stretching). ^{1}H-NMR chemical shift (δ) in ppm: 4.08[s, 2H, C_5 and C_7–H], 5.02[s, 2H, C_4 and C_{10}–H], 4.85[s, 2H, C_8 and C_9–H], 4.67[s, 2H, C_2–H], 7.34, 7.12[t, $J = 7.6$ Hz, *meta* and *meta′*-H], 7.34, 6.8[q, $J = 6.6$ Hz, *para and para′*-H]. ^{13}C-NMR chemical shift (δ) in ppm: 51.31 [C_5 and C_7], 68.67 [C_8 and C_9], 60.48 [C_4 and C_{10}], 67.57[C_2], 213.03 [C_6], 130.44[–*ipso,* 2 carbons], 129.06, 129.76[–*ipso′*, 2 carbons], [*para*, 2 carbons], 159.52, 159.91[*para′*, 2 carbons], 124.60, 126.95 [*ortho*, 4 carbons], 123.09, 124.33 [*ortho′*, 4 carbons], 116.74, 116.97 [*meta*, 4 carbons], 114.88, 115.09 [*meta′*, 4 carbons].

4,8,9,10-*tetrakis*(2-methoxyphenyl)-1,3-diazatricyclo[3.3.1.1]decan-6-one **(5h):** Yield: 70 %, M.p., 185 °C; IR values: 1,703.88 cm^{-1}(C=O stretching), 3,030 cm^{-1} (Ar C–H stretching), 2,956 cm^{-1} (aliphatic C–H stretching). ^{1}H-NMR chemical shift (δ) in ppm: 3.90[s, 2H, C_5 and C_7–H], 4.81[s, 2H, C_4 and C_{10}–H], δ 4.67[s, 2H, C_8 and C_9–H], 4.45[s, 2H, C_2–H], 7.24, 6.57[s, *ortho* and *ortho*′-H], 7.12, 6.86[d, para and para′-H]. ^{13}C-NMR chemical shift (δ) in ppm: 50.47 [C_5 and C_7], 69.23[C_8 and C_9], 64.28[C_4 and C_{10}], 68.72[C_2], 213.28 [C_6], 139.67[–*ipso,* 2 carbons], 141.21[–*ipso*′, 2 carbons], [*para*, 2 carbons], 160.34[*para*′, 2 carbons], 118.93, 120.08[*ortho*, 4 carbons], 128.17,130.08 [*ortho*′, 4 carbons], 112.14, 112.72[*meta*, 4 carbons], 113.71, 113.86[*meta*′, 4 carbons].

4,8,9,10-*tetrakis*(3,4-dimethoxyphenyl)-1,3-diazatricyclo[3.3.1.1]decan-6-one **(5l):** Yield: 70 %, M.p., 204 °C; IR values: 1,697 cm^{-1}(C=O stretching), 2,999 cm^{-1} (Ar C–H stretching), 2,933 cm^{-1} (aliphatic C–H stretching); ^{1}H-NMR chemical shift (δ) in ppm: 3.70[s, 2H, C_5 and C_7–H], 4.75[s, 2H, C_4 and C_{10}–H], 4.60[s, 2H, C_8 and C_9–H], 4.35[s, 2H, C_2–H], 6.3-7.5[m, aryl protons].

1. Representative spectral characterization of 4,8,9,10-*tetrakis*(4-bromophenyl)-1,3-diazaadamantan-6-ol (6f).

Proton chemical shift assignment: For 4,8,9,10-tetraphenyl-1,3-diazatricyclo[3.3.1.1]decan-6-ols, the compound **6f** is taken as a representative example and its chemical shift assignments have been discussed. The examination of ^{1}H NMR spectra of **6f** clearly illustrates that two sets of aryl protons are available. This indicates that all the aryl substituents are not present in the same environment. The singlet at 2.77 ppm is due to H-5, 7 couples with the doublet at 4.13 (3 Hz) ppm as well as with the triplet at 4.35 ppm (4.5 Hz). The signals at 4.10 and 4.35 ppm are due to benzylic protons at C4, C10 and C8, and C9, respectively. Based on our earlier studies, the relatively upfield benzylic signal at 4.10 [t, $J = 4.5$ Hz] ppm has been assigned to axially oriented H-8, 9 and the downfield doublet at 4.35 (with $J = 3$ Hz) is due to the H-4, 10. A singlet at 2.16 ppm integrating for one proton may be due to the –OH and the proton at H-6 appeared at 1.85 ppm. The singlet at 4.13 ppm is due to the H-2 s. The doublet at 7.52 ppm integrating for four protons is due to the *ortho* protons of aryls at C4 and C10. The doublet at 7.42 ppm integrating for four protons is due to the *meta* protons of aryl at C4 and C10. Similarly the other set of aryl protons at C8 and C9 appeared as 6.93 and 7.31 ppm. The doublet at 6.93 ppm integrating for four protons is due to the *ortho* protons of aryls at C8 and C9. The doublet at 7.31 ppm integrating for four protons is due to the *meta* protons of aryl at C8 and C9.

Carbon chemical shift assignment: The ^{13}C NMR spectrum reveals that the signal at δ 43.82 ppm corresponds to the carbons at C-5 and C-7, respectively, and the signal at δ 61.13 ppm corresponds to carbons at C-8 and C-9, respectively, and the signal at δ 58.25 ppm corresponds to the carbons at C-4 and C-10, respectively. The signal at δ 69.36 ppm corresponds to the carbon at C-2 and the signal at δ 72.31 ppm corresponds carbons at C-6, respectively, and the rest of the signals appears at 120.77 (C-4d, 10d), 121.47 (C-8d, 9d), 128.07 (C-4b, 10b, 4b′, 10b′), 128.34 (C-8c, 9c, 8c′, 9c′), 131.01 (C-4c, 10c, 4c′, 10c′), 131.97 (C-8b, 9b, 8b′, 9b′), 139.19 (C-4a, 10a), 140.09 (C-8a, 9a).

Summarized as follows: White crystalline solid; Yield: 73 %. M.p. 256-258 °C; IR (KBr, cm^{-1}): 3389 (–OH stretching), 3054 (aromatic-CH-stretching), 2801 (aliphatic-CH-stretching), 1712 (disappearance of –C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 2.19 (bs, 1H, –OH), 2.77 (s, 2H, H-5, 7), 4.07 (t, $J = 3.8$ Hz, 1H, H-6), 4.10 (s, 2H, H-8, 9), 4.13 (s, 2H, H-4, 10), 4.38 (s, 2H, H-2), 6.91 (d, $J = 8.5$ Hz, 4H, H-4b, 10b, 4b′, 10b′), 7.27 (d, $J = 8.5$ Hz, 4H, H-4c, 10c, 4c′, 10c′), 7.39 (d, $J = 8.5$ Hz, 4H, H-8c, 9c, 8c′, 9c′), 7.46 (d, $J = 8.5$ Hz, 4H, H-8b, 9b, 8b′, 9b′); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 43.82 (C-5, 7), 58.25 (C-4, 10), 61.13 (C-8, 9), 69.36 (C-2), 72.31 (C-6), 120.77 (C-4d, 10d), 121.47 (C-8d, 9d), 128.07 (C-4b, 10b, 4b′, 10b′), 128.34 (C-8c, 9c, 8c′, 9c′), 131.01 (C-4c, 10c, 4c′, 10c′), 131.97 (C-8b, 9b, 8b′, 9b′), 139.19 (C-4a, 10a), 140.09 (C-8a, 9a). HRMS: *m/z* 773.1000 (M + 4). In a similar way all other members of the series were assigned and given.

2. 4,8,9,10-tetraphenyl-1,3-diazaadamantan-6-ol (6a): White crystalline solid; Yield: 72 %. M.p. 236-238 °C; IR (KBr, cm^{-1}): 3302 (–OH stretching), 3026 (aromatic-CH-stretching), 2974 (aliphatic-CH-stretching); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.88 (bs, 1H, –OH), 2.86 (s, 2H, H-5, 7), 4.10 (t, $J = 3.4$ Hz, 1H, H-6), 4.19 (s, 2H, H-8, 9), 4.21 (s, 2H, H-4, 10), 4.54 (s, 2H, H-2), 7.03 (t, $J = 7.6$ Hz, 4H, H-4c, 10c), 7.08-7.09 (m, 6H, H-4b, 10b and 4d, 10d), 7.20 (t, $J = 7.6$ Hz, 2H, H-8d, 9d), 7.31 (t, $J = 7.6$ Hz, 4H, H-8c, 9c), 7.55 (d, $J = 7.6$ Hz, 4H, H-8b, 9b); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 44.47 (C-5, 7), 59.06 (C-4, 10), 70.05 (C-8, 9), 62.06 (C-2), 72.65 (C-6), 126.33 (C-4d, 10d), 126.51 (C-8b, 9b), 127.00 (C-4c, 10c), 127.66 (C-8d, 9d), 128.68 (C-4b, 10b), 129.00 (C-8c, 9c), 140.85 (C-4a, 10a), 141.72 (C-8a, 9a).

3. 5-methyl-4,8,9,10-tetraphenyl-1,3-diazaadamantan-6-ol (6b): White crystalline solid; Yield: 72 %; M.p. 236-238 °C; IR (KBr, cm^{-1}): 3302 (–OH stretching), 3026 (aromatic-CH-stretching), 2974 (aliphatic-CH-stretching); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.28 (bs, 1H, –OH), 1.42 (s, 3H, H-5), 4.21 (t, $J = 4.0$ Hz, 1H, H-7), 4.23 (s, 2H, H-8, 9), 4.44 (d, $J = 6.4$ Hz, 1H, H-6), 4.85 (s, 2H, H-4,10), 5.62 (s, 2H, H-2), 6.82 (t, $J = 7.4$ Hz, H-4b, 10b and 4d, 10d), 7.10 (d, $J = 7.6$ Hz, 4H, H-8c, 9c), 7.35 (t, $J = 7.4$ Hz, H-4c, 10c, H-8d, 9d), 7.58 (d, $J = 7.6$ Hz, 2H, H-8b), 7.79 (d, $J = 7.6$ Hz, 2H, H-9b); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 17.28 (C-5), 49.70 (C-7), 63.42 (C-4, 10), 68.64 (C-8, 9), 69.97 (C-2), 70.90 (C-6), 126.10 (C-4d), 126.30 (C-10d), 126.80 (C-8b), 126.92 (C-9b), 127.38 (C-4c), 128.28 (C-10c), 128.63 (C-8d, 9d), 130.54 (C-4b, 10b), 137.70 (C-8c, 9c), 138.04 (C-4a, 10a), 139.43 (C-8a, 9a).

4. 4,8,9,10-*tetrakis*(4-fluorophenyl)-1,3-diazaadamantan-6-ol (6c): White crystalline solid; Yield: 69 %. M.p. 224-226 °C; IR (KBr, cm^{-1}): 3410 (–OH stretching), 3305 (–OH stretching), 2907 (aromatic-CH-stretching), 2807 (aliphatic-CH-stretching), 1712 (disappearance of –C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.82 (bs, 1H, –OH), 2.79 (s, 2H, H-5, 7), 4.10 (t, $J = 3.8$ Hz, 1H, H-6), 4.15 (s, 2H, H-8, 9), 4.17 (s, 2H, H-4, 10), 4.42 (s, 2H, H-2), 6.82 (t, $J = 6.8$ Hz, 4H, H-8c, 9c, 8c′, 9c′), 7.00-7.03 (m, 8H, H-4b, 10b, 4b′, 10b′, 4c, 10c, 4c′, 10c′), 7.51 (q, $J = 5.5$ Hz, 4H, H-8b, 9b, 8b′, 9b′); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 44.15 (C-5, 7), 58.26 (C-4, 10), 60.94 (C-8, 9), 69.47 (C-2), 72.17 (C-6),

114.53 (C-4c, 4c′), 114.70 (C-10c, 10c′), 115.54 (C-8c, 8c′), 115.71 (C-9c, 9c′), 127.85 (C-4b, 4b′), 127.92 (C-10b, 10b′), 129.04 (C-8b, 8b′), 129.10 (C-9b, 9b′), 135.93, 135.95 (C-4a, 10a), 136.98, 137.00 (C-8a, 9a), 160.59 and 161.11 (C-4d, 10d), 162.54 and 163.06 (C-8d, 9d). HRMS: *m/z* 530.1000 (M^+).

5. 4,8,9,10-*tetrakis*(2-chlorophenyl)-1,3-diazaadamantan-6-ol (6d): White crystalline solid; Yield: 72 %. M.p. 248-250 °C; IR (KBr, cm^{-1}): 3322 (–OH stretching), 3050 (aromatic-CH-stretching), 2927 (aliphatic-CH-stretching); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.59 (bs, 1H, –OH), 3.34 (s, 2H, H-5, 7), 4.23 (s, 2H, H-8, 9), 4.38 (t, $J = 4.0$ Hz, 1H, H-6), 4.48 (s, 2H, H-4, 10), 5.12 (s, 2H, H-2), 7.04–7.09 (m, 4H, H-4c, 10c, 4c′, 10c′), 7.11 (t, $J = 7.5$ Hz, 2H, H-8c, 9c), 7.15 (dd, $J = 6.5$, 2H, H-8c′, 9c′), 7.20 (dd, $J = 6.5$, 2H, H-8b, 9b), 7.27–7.30 (m, 2H, H-4d, 10d), 7.46 (dd, $J = 6.5$, 2H, H-8d, 9d), 8.09 (d, $J = 6.5$ Hz, 2H, H-4b, 10b); HRMS: *m/z* 596.1000 (M + 2).

6. 4,8,9,10-*tetrakis*(4-chlorophenyl)-1,3-diazaadamantan-6-ol (6e): White crystalline solid; Yield: 70 %. M.p. 260-262 °C; IR (KBr, cm^{-1}): 3403 (–OH stretching), 3044 (aromatic-CH-stretching), 2891 (aliphatic-CH-stretching), 1712 (disappearance of –C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.82 (bs, 1H, –OH), 2.78 (s, 2H, H-5, 7), 4.88 (t, $J = 3.8$ Hz, 1H, H-6), 4.11 (s, 2H, H-8, 9), 4.15 (s, 2H, H-4, 10), 4.42 (s, 2H, H-2), 6.97 (d, $J = 8.5$ Hz, 4H, H-4b, 10b, 4b′, 10b′), 7.12 (d, $J = 8.5$ Hz, 4H, H-4c, 10c, 4c′, 10c′), 7.31 (d, $J = 8.5$ Hz, 4H, H-8c, 9c, 8c′, 9c′), 7.46 (d, $J = 8.5$ Hz, 4H, H-8b, 9b, 8b′, 9b′); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 43.89 (C-5, 7), 58.24 (C-4, 10), 61.06 (C-8, 9), 69.34 (C-2), 72.29 (C-6), 127.72 (C-4b, 10b, 4b′, 10b′), 128.04 (C-8b, 9b, 8b′, 9b′), 128.83 (C-4c, 10c, 4c′, 10c′), 128.99 (C-8c, 9c, 8c′, 9c′), 132.54 (C-4d, 10d), 133.39 (C-8d, 9d), 138.67 (C-4a, 10a), 139.60 (C-8a, 9a). HRMS: *m/z* 596.2634 (M + 2).

7. 4,8,9,10-*tetrakis*(4-methylphenyl)-1,3-diazaadamantan-6-ol (6g): White crystalline solid; Yield: 79 %. M.p. 216-218 °C; IR (KBr, cm^{-1}): 3377 (–OH stretching), 3057 (aromatic-CH-stretching), 2920 (aliphatic-CH-stretching); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.83 (bs, 1H, –OH), 2.89 (s, 6H, $–CH_3$), 2.91 (s, 6H, $–CH_3$), 2.77 (s, 2H, H-5, 7), 4.03 (t, $J = 3.2$ Hz, 1H, H-6), 4.16 (s, 2H, H-8, 9), 4.23 (s, 2H, H-4, 10), 4.54 (s, 2H, H-2), 6.63-6.94 (m, 8H, H-4b, 10b, 4b′, 10b′, H-4c, 10c, 4c′, 10c′), 7.14 (d, $J = 8$ Hz, 4H, H-8c, 9c, 8c′, 9c′), 7.42 (d, $J = 8$ Hz, 4H, H-8b, 9b, 8b′, 9b′); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 20.84 ($–CH_3$ carbon at C-4d, 10d), 20.98 ($–CH_3$ carbon at C-8d, 9d), 44.73 (C-4, 10), 58.69 (C-5, 7), 62.01 (C-8, 9), 69.42 (C-6), 72.69 (C-2), 126.53 (C-4b, 10b, 4b′, 10b′), 126.92 (C-8b, 9b, 8b′, 9b′), 127.62 (C-4c, 10c), 128.06 (C-4c′, 10c′), 128.33 (C-8c, 9c), 129.30 (C-8c′, 9c′), 129.68 (C-4d, 10d), 135.59 (C-8d, 9d), 136.87 (C-4a, 10a), 138.16 (C-8a, 9a). HRMS: *m/z* 514.2985 (M^+).

8. 4,8,9,10-*tetrakis*(2-methoxyphenyl)-1,3-diazaadamantan-6-ol (6h): White crystalline solid; Yield: 56 %. M.p. 208-210 °C; IR (KBr, cm^{-1}): 3420 (–OH stretching), 3070 (aromatic-CH-stretching), 2835 (aliphatic-CH-stretching); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 2.19 (bs, 1H, –OH), 3.20 (s, 2H, H-5, 7), 3.74 (s, 6H, $–OCH_3$ at 4b′, 10b′), 3.80 (s, 6H, $–OCH_3$ at 8b′, 9b′), 4.28 (t, $J = 3.2$ Hz, 1H, H-6), 4.35 (s, 2H, H-8, 9), 4.36 (s, 2H, H-4, 10), 4.98 (s, 2H, H-2), 6.58 (d, $J = 8$ Hz, 2H,

H-4b, 10b), 6.62 (d, 2H, $J = 8$ Hz, 2H, H-4d, 10d), 6.73 (t, $J = 7.4$ Hz, 2H, H-8d, 9d), 6.86 (t, $J = 7.5$ Hz, 2H, H-8c, 9c), 6.98-7.02 (m, 4H, H-4c, 10c, 4c′, 10c′), 7.35 (d, $J = 7.5$ Hz, 2H, H-8c′, 9c′), 7.88 (d, $J = 7.5$ Hz, 2H, H-8b, 9b); HRMS: *m/z* 578.3353 (M^+).

9. 4,8,9,10-*tetrakis*(4-methoxyphenyl)-1,3-diazaadamantan-6-ol (6i): White crystalline solid; Yield: 58 %. M.p. 188-190 °C; IR (KBr, cm^{-1}): 3420 (–OH stretching), 3070 (aromatic-CH-stretching), 2835 (aliphatic-CH-stretching); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.62 (bs, 1H, –OH), 2.85 (s, 2H, H-5, 7), 3.65 (s, 6H, –OCH_3 at 4d, 10d), 3.78 (s, 6H, –OCH_3 at 8d, 9d), 4.08 (t, $J = 3.8$ Hz, 1H, H-6), 4.14 (s, 2H, H-8, 9), 4.25 (s, 2H, H-4, 10), 4.53 (s, 2H, H-2), 6.65-6.78 (m, 8H, H-4b, 10b, 4b′, 10b′, 8c, 9c, 8c′, 9c′), 7.03-7.26 (m, 8H, H-4c, 10c, 4c′, 10c′, 8b, 9b, 8b′, 9b′); HRMS: *m/z* 578.1000 (M^+).

10. 4,8,9,10-*tetrakis*(4-ethoxyphenyl)-1,3-diazaadamantan-6-ol (6j): White crystalline solid; Yield: 68 %. M.p. 242-244 °C; IR (KBr, cm^{-1}): 3306 (–OH stretching), 3060 (aromatic-CH-stretching), 2880 (aliphatic-CH-stretching), 1712 (disappearance of –C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.36 (m, 12H, –CH_3, H-4d″, 10d″, –CH_3, H-8d″, 9d″), 4.02–4.04 (m, 8H, –CH_2, H-4d′, 10d′, H-8d′, 9d′), 4.46 (s, 2H, H-2), 4.92–5.03 (m, 8H, H-5, 7, H-8, 9; H-4, 10 and H-6, –OH), 6.65 (d, $J = 8.5$ Hz, 4H, H-4b, 10b, 4b′, 10b′), 6.83 (d, $J = 8.5$ Hz, 4H, H-4c, 10c, 4c′, 10c′), 6.97 (d, $J = 8.5$ Hz, 4H, H-8c, 9c, 8c′, 9c′), 7.42 (d, $J = 8.5$ Hz, 4H, H-8b, 9b, 8b′, 9b′). HRMS: *m/z* 634.1000 (M^+).

11. 4,8,9,10-*tetrakis*(2,5-dimethoxyphenyl)-1,3-diazaadamantan-6-ol (6 k): White crystalline solid; Yield: 72 %. M.p. 242-244 °C; IR (KBr, cm^{-1}): 3298 (–OH stretching), 2998 (aromatic-CH-stretching), 2834 (aliphatic-CH-stretching), 1721 (–C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.69 (bs, 1H, –OH), 3.12 (s, 2H, H-5, 7), 3.68 (s, 6H, –OCH_3, H-4b′, 10b′), 3.71 (s, 6H, –OCH_3, H-8b′, 9b′), 3.72 (s, 6H, –OCH_3, H-4c, 10c), 3.77 (s, 6H, –OCH_3, H-8c, 9c), 4.22 (t, $J = 4$ Hz, 1H, H-6), 4.30 (s, 2H, H-8, 9), 4.38 (s, 2H, H-4, 10), 4.99 (s, 2H, H-2), 6.5-6.58 (m, 8H, H-8b, 9b, 4b, 10b, 8d, 9d, 4d, 10d), 6.97 (s, 2H, H-4c′, 10c′), 7.40 (s, 2H, H-8c′, 9c′); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 38.74 (C-4, 10), 51.77 (C-8, 9), 54.12 (–OCH_3 at C-4c), 54.81(–OCH_3 carbon at C-10c), 55.29 (–OCH_3 carbon at C-8c), 55.46 (–OCH_3 carbon at C-9c), 55.72 (–OCH_3 carbon at C-4b′), 55.78(–OCH_3 carbon at C-10b′), 55.82 (–OCH_3 carbon at C-8b′), 55.91(–OCH_3 carbon at C-9b′), 56.22 (C-5, 7), 70.10 (C-6), 71.59 (C-2), 110.41 (C-4c′, 10c′, 4c′, 10c′), 111.47 (C-4d), 111.74 (C-10d), 112.17 (C-8d), 112.43 (C-9d), 113.55 (C-4b), 115.64 (C-10b), 115.82 (C-8b), 116.68 (C-9b), 130.15 (C-4a, 10a), 130.95 (C-8a, 9a), 150.52 (C-4b′, 10b′), 151.56 (C-8b′, 9b′), 152.12 (C-4c), 152.58 (C-10c), 152.89 (C-8c), 153.34 (C-9c). HRMS: *m/z* 698.3370 (M^+).

12. 4,8,9,10-*tetrakis*(3,4-dimethoxyphenyl)-1,3-diazaadamantan-6-ol (6l): White crystalline solid; Yield: 65 %. M.p. 246-248 °C; IR (KBr, cm^{-1}): 3312 (–OH stretching), 2960 (aromatic-CH-stretching), 2833 (aliphatic-CH-stretching), 1712 (disappearance of –C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.64 (bs, 1H, –OH), 2.72 (s, 2H, H-5, 7), 3.67 (s, 6H, –OCH_3 at C-4c′, 10c′), 3.82 (s, 6H, –OCH_3 at C-8d, 9d), 3.84 (s, 6H, –OCH_3 at C-4d, 10d), 3.85 (s, 6H, –OCH_3 at C-8c′, 9c′),

4.03 (t, $J = 4$ Hz, 1H, H-6), 4.09 (s, 2H, H-8, 9), 4.28 (s, 2H, H-4, 10), 4.50 (s, 2H, H-2), 6.56 (s, 2H, H-4b′, 10b′), 6.66 (d, $J = 8.0$, 2H, H-4b, 10b), 6.75 (d, $J = 8.0$, 2H, H-8c, 9c), 6.81 (d, $J = 8.0$ Hz, 2H, H-4c, 10c), 7.03 (s, 2H, H-8b′, 9b′), 7.13 (d, $J = 8.0$, 2H, H-8b, 9b). HRMS: *m/z* 698.0100 (M^+).

13. 4,8,9,10-*tetrakis*(3,4,5-trimethoxyphenyl)-1,3-diazaadamantan-6-ol (6m): White crystalline solid; Yield: 76 %. M.p. 244-246 °C; IR (KBr, cm^{-1}): 3322 (–OH stretching), 2937 (aromatic-CH-stretching), 2834 (aliphatic-CH-stretching), 1712 (disappearance of –C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 1.68 (bs, 1H, –OH), 2.87 (s, 2H, H-5, 7), 3.69 (s, 12H, $-OCH_3$ at 4c, 10c, 4c′, 10c′), 3.78 (s, 6H, $-OCH_3$ at 4d, 10d), 3.80 (s, 6H, $-OCH_3$ at 8d, 9d), 3.81 (s, 12H, $-OCH_3$ at 8c, 9c, 8c′, 9c′), 4.01 (t, $J = 3.8$ Hz, 1H, H-6), 4.09 (s, 2H, H-8, 9), 4.35 (s, 2H, H-4, 10), 4.47 (s, 2H, H-2), 6.39 (s, 4H, H-4b, 10b, 4b′, 10b′), 6.78 (s, 4H, H-8b, 9b, 8b′, 9b′); HRMS: *m/z* 818.1000 (M^+).

The spectral characterization of **2,4,6,8-tetraphenyl-3,7-diazabicyclo[3.3.1] nonan-9-ol** (**5aa**)**:**

Proton chemical shift assignment: The careful examination of ^{1}H NMR spectrum of **5aa** reveals that the singlet at δ 1.30 and 2.22 ppm integrating for one proton each is due to the NH-7 and NH-3 protons, respectively. The singlet at δ 2.63 ppm integrating for two protons represents the bridgehead protons at C-1, 5 and the singlet at δ 4.17 ppm integrating for one proton represents the proton at C-9 obtained from $NaBH_4$. The two additional singlets at δ 4.20 ppm and δ 4.31 ppm integrating two protons each represent the proton at C-6, 8. The remaining aryl region protons are exactly matching with the target molecule. The above discussion clearly reveals the formation of desired 2,4,6,8-tetraphenyl-3,7-diazabicyclo[3.3.1]nonan-9-ol (**5aa**).

Carbon chemical shift assignment: The ^{13}C NMR spectrum of **5aa** reveals that the signal at δ 48.93 ppm corresponds to the bridgehead carbons at C-1, 5 and the signals at δ 57.55 ppm and δ 61.51 ppm corresponds to the benzylic carbons at C-6, 8 and C-2, 4, respectively. The signal at δ 75.27 ppm corresponds to the carbon at C-9. The signal at δ 126.58 ppm and δ 127.25 ppm corresponds to the *p*-carbons at 6d, 8d and 2d, 4d, respectively. The rest of the signals appears at δ 126.72 (C-2b, 4b), 126.86 (C-6c, 8c), 128.14 (C-6b, 8b), 128.50 (C-2c, 4c). The signal at δ 142.38 ppm and δ 145.63 ppm corresponds to the boat and chair *ipso* carbons at C-6a, 8a and C-2a, 4a, respectively. The above discussion revealed the formation of desired 2,4,6,8-tetraphenyl-3,7-diazabicyclo[3.3.1]nonan-9-ol (**5aa**).

The 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ones (**5a–m),** 4,8,9,10-tetraaryl-1,3-diazatricyclo[3.3.1.1]decan-6-ols (**6a–m)** were evaluated for their in vitro antibacterial activity against standard pathological bacterial strains *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and *Bacillus subtilis* ATCC 29212 by agar well diffusion method (Balaji et al., 2012). Suspensions of each microorganism were prepared from their 24-h cultures to obtain approximately 10^6 colony-forming units (cfu) per milliliter for plating. DMSO was chosen as control and the compound under test was dissolved in DMSO

at a concentration of 50 μg/0.05 ml. It was aseptically transferred and applied into the cups created on the dry surface of the inoculated plates and then incubated at 37 °C overnight (~18–20 h). This assay was performed in duplicate and the mean diameters of the clear inhibition zones (mm) were recorded disregarding the single colony or a faint haze caused by the inoculums.

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