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New unsymmetrically substituted triazacyclohexanes: Synthesis, characterisation, antimicrobial properties and DFT study

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ABSTRACT

New five unsymmetrically substituted 1,3,5-triazacyclohexanes compounds, carrying aliphatic as well as aromatic substituent, were synthesized and structural analyses were performed by FTIR, ^{1}H NMR and single crystal X-ray techniques. Experimental research was complemented by quantum mechanical calculations. The present triazacyclohexane rings adopt a chair conformation by both R_1 substituents in axial positions and R_2 group in an equatorial form. Further, all compounds were screened for their anti-bacterial and anti-fungal properties. By revealing further insight into triazacyclohexanes systems, the data theoretically predicted and experimentally obtained in current research may be helpful guide for the medicinal chemists.

1. Introduction

Synthesis of 1,3,5-triazacyclohexanes (TAC) from primary amines and formaldehyde has been known for over a century [1]. Different triazines were synthesized according to the procedure described earlier [2]. TAC are subject to some structural researchers considering their use in the industrial chemistry. TAC can be employed as ligand for new complexes worked as catalyst in the polymerization and trimerization of olefines [3]. Further, the interest in TAC as ligand seems to growing rapidly [4–8].

Conformational effect of non-bonding electrons is a feature of heterocyclic chemistry [9]. Heterocyclic nucleus in TAC is expected to prefer a chair conformation. For the substituent orientation, four distinct types can be postulated, namely eee, eea, eaa and aaa (e: equatorial and a: axial). They have axial repulsions involving substituent and/or lone pairs of electrons on nitrogen atoms [10]. Conformations of 1,3,5-trialkyl-1,3,5-triazacyclohexanes in solution were analysed by dipole moment measurement and NMR. The former suggested varying amounts of eee, eea and eaa forms [10,11]. X-ray researchers for 1,3,5-tricyclohexyl compounds established that they adopt eea conformation [12]. 1,3,5-triaryl-1,3,5-triazacyclohexanes prefer the diaxial–equatorial form in the solid state, thus avoiding 1,3-diaxial lone-pair repulsions [5,13–15].

In the present research, the new five unsymmetrically substituted 1,3,5-triazacyclohexanes compounds (1a-5a) were synthesized and their structures were confirmed via FTIR and ^{1}H NMR. Structures of 1,3-bis(p-bromophenyl)-5-ethyl-1,3,5-triazinane (1a), 1,3-bis(p-bromophenyl)-5-butyl-1,3,5-triazinane (2a) and 1,3-bis(p-bromophenyl)-5-cyclohexyl-1,3,5-triazinane (3a) were determined by single crystal X-ray technique. Hydrogen bonding interactions and antimicrobial properties of the compounds were also investigated. Further, DFT (B3LYP functional and 6-31G(d) basis set) was used to support structural and spectroscopic data of 1a-3a compounds.

2. Experimental

2.1. Synthesis

Unsymmetrically substituted triazacyclohexanes were prepared from the condensation reaction between aromatic or aliphatic

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amine (1), aliphatic or aromatic amine (2) with formaline (3) with [2:1:3] stoichiometric ratio (Fig. 1a and Table SI1; SI: Supplementary Information). They were obtained according to the literature methods [5–8,10–12,16]. All chemicals used were purchased from Aldrich and employed without further purification.

2.1.1. 1,3-bis(p-bromophenyl)-5-ethyl-1,3,5-triazinane (1a)

Ethylamine 70% in water (0.555 ml, 10 mmol) and p-bromoaniline (3.44 g, 20 mmol) were dissolved in ethanol (10 ml) and an aqueous solution of formaldehyde in water (37%, 5.4 ml, 72 mmol) was added under stirring. The reaction mixture was kept at room temperature for one day. Resulting precipitate was filtered and dried to yield the required product (3.35 g, 78.82%). Purity of the compound was confirmed by TLC (Rf = 0.34, Chloroforme/Petroleum Ether (7/3)) and m.p = 99 °C. ^{1}H NMR (ppm): 1.1 (t, J = 7.2 Hz, 3H, -CH_3), 2.6 (q, J = 7.1 Hz, 2H, -CH_2-), 4.3 (s, 4H, -N(Et)CH_2N(Ar)-), 4.7 (s, 2H, -N(Ar)CH_2N(Ar)), 6.9 (d, J = 9 Hz, 4H, Ar), 7.4 (d, J = 9 Hz, 4H, Ar).

2.1.2. 1,3-bis(p-bromophenyl)-5-butyl-1,3,5-triazinane (2a)

n-butylamie (0.4956 ml, 5 mmol) and p-bromoaniline (1.72 g, 10 mmol) were dissolved in ethanol (10 ml) and the solution of formaldehyde in water (37%, 2.52 ml, 36 mmol) was added under stirring. Similar processes were performed to yield the required product (1.6832 g, 74.28%). Purity of the compound was confirmed by TLC (Rf = 0.40, Chloroforme/Petroleum Ether (7/3)) and m.p = 110 °C. ^{1}H NMR (ppm): 0.8 (t, J = 7.3 Hz 3H, -CH_3 (butyl)), 1.17–1.38 (m, 4H, -CH_2-(butyl)), 2.5 (t, 2H, -CH_2-(butyl)), 4.2 (s, 4H, R–NCH_2N(Ar)), 4.6 (s, 2H, (Ar)NCH_2N(Ar)), 6.8 (d, J = 9.1 Hz, 2H), 7.3 (d, J = 9.0 Hz, 2H).

2.1.3. 1,3-bis(p-bromophenyl)-5-cyclohexyl-1,3,5-triazinane (3a)

Cyclohexylamine (0.57 ml, 5 mmol) and p-bromoaniline (1.72 g, 10 mmol) were dissolved in ethanol (10 ml). An aqueous solution of formaldehyde in water (37%, 2.52 ml, 36 mmol) was added under stirring. Similar steps were applied to yield the required product (1.83 g, 76.44%). Compound's purity was confirmed by TLC (Rf = 0.36, Chloroforme/Petroleum Ether (7/3)) and m.p = 166 °C. ^{1}H NMR (ppm): 1.48 (m, 10H, -CH_2-(cyclohexyl)), 2.5 (m, 1H, N–CH-(cyclohexyl)), 4.21 (s, 4H, -(cyclohexyl)NCH_2N(Ar)), 4.61 (s, 2H, -N(Ar)CH_2N(Ar)), 6.8 (m, 4H, Ar), 7.25 (m, 4H, Ar).

2.1.4. 1,3-bis(p-chlorobenzyl)-5-bromophenyl-1,3,5-triazacyclohexane (4a)

p-chlorobenzylamie 98% (1.215 ml, 10 mmol) and p-bromoaniline (0.86 g, 5 mmol) were dissolved in ethanol (10 ml). The aqueous solution of formaldehyde in water (37%, 2.52 ml, 36 mmol) was added under stirring. Similar processes were performed to yield the required product (3.675 g, 90.42%). It's purity was confirmed by TLC (Rf = 0.92, Chloroforme/Petroleum Ether (7/3)) and m.p = 102 °C. ^{1}H NMR (ppm): 1.5 (s, 2H (N–CH_2-Ar)), 3.5 (s, 4H R–NCH_2N(Ar)), 4.1 (s, 2H (Ar)NCH_2N(Ar)), 6.6 (d, J = 9.1 Hz, 2H Ar–Br) 7.1 (d, J = 8.6 Hz, 2H Ar–Br), 7.2 (d, J = 1.6 Hz, 2H Ar–Cl), 7.2 (d, J = 1.6 Hz, 2H Ar–Cl).

2.1.5. 1-(p-bromophenyl)-3,5-dicyclohexyl-1,3,5-triazinane (5a)

n-hexylamie (0.655 ml, 5 mmol) and p-bromoaniline (1.72 g, 5 mmol) were dissolved in ethanol (10 ml). An aqueous solution of

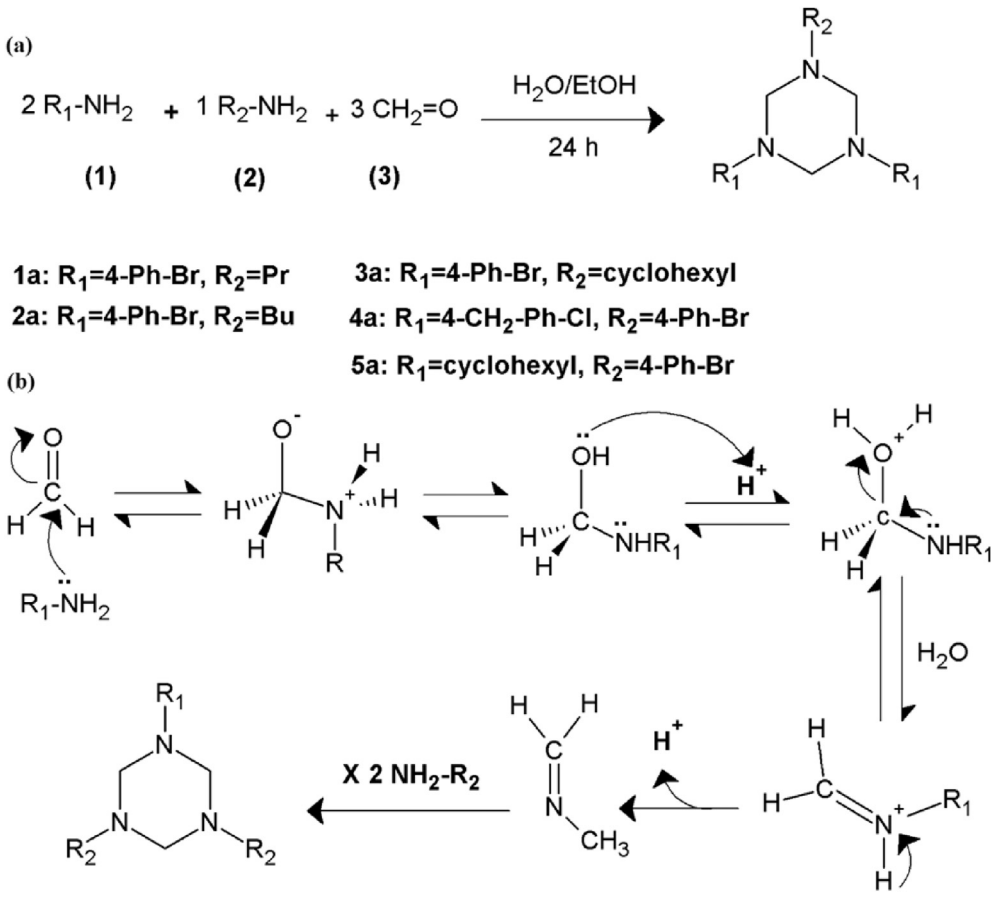

Fig. 1. (a) Synthesis reaction of 1a-5a. (b) Mechanism of interaction to obtain 1a-5a.

formaldehyde in water (37%, 2.52 ml, 36 mmol) was added under stirring. Similar steps were applied to yield the required product (1.3122 g, 54.53%). Purity of the compound was confirmed by TLC (Rf = 0.38, Chloroforme/Petroleum Ether (7/3)) and m.p = 63 °C. ^{1}H NMR (ppm): 0.8 (t, J = 6.7 Hz 3H, -CH_3 (hexyl)), 1.2–1.4 (m, 8H, -CH_2-(hexyl)), 2.5 (m, 2H, -CH_2-(hexyl)), 4.2 (s, 4H, R–NCH_2N(Ar)), 4.6 (s, 2H, (Ar)NCH_2N(Ar)), 6.8 (d, J = 8.9 Hz, 2H), 7.3 (d, J = 9.0 Hz, 2H).

2.2. Spectroscopic measurements

FT-IR spectra were reported by a Frontier spectrometer in the region of 4000–400 cm^{-1}, performing KBr technique at a resolution of 2 cm^{-1}. ^{1}H NMR spectra were recorded by a Bruker DRX spectrometer (300 MHz) in $CDCl_3$. Chemical shifts were referred to TMS by the residual signals from the solvent.

X-ray diffraction intensity was collected at 273 K for 1a and 150 K for 2a-3a using an Oxford Diffraction Xcalibur, Atlas, Gemini ultra-diffractometer with Mo Kα radiation (λ = 0.71073 Å) for 1a-2a and Cu Kα radiation (λ = 1.54180 Å) for 3a, equipped with the required cooling. The unit cell determination and data reduction were performed by CrysAlis [17] on the full set of data. Calculations were carried out by WinGX [18]. Crystal structure was solved by direct methods with SIR2004 [19] and refined by full-matrix least-squares against F^2 using all data (SHELX97) [20]. All non-H atoms were modelled with anisotropic displacement parameters. H atoms attached to –CH_3 and –CH_2 were located in difference Fourier maps refined as riding atoms with distances constraints of methyl C–H = 0.96 Å and [U_{iso}(H) = 1.5 U_{eq}(C,N)]. Aromatic H atoms were positioned geometrically and were allowed to ride on their parent C atoms with C–H = 0.93 Å and and U_{iso}(H) = 1.2U_{eq}(C). Crystal structure was visualized by ORTEP3 [21] and MERCURY [22]. Analyses were also performed by PLATON [23].

2.3. Antimicrobial activity

1a-5a were screened in vitro for anti-bacterial and anti-fungal properties against *Escherichia coli, Salmonella typhi, Staphylococcus aureus, Bacillus subtilis* at 200, 300, 400, 500 μg/ml concentrations and *Aspergillus niger* at 100, 200, 300, 400 μg/ml, respectively, by cup plate agar diffusion method [24]. Concentrations were chosen after determining minimum inhibitory concentrations (MIC) of each compound. The solvent used was dmso further diluted with water. Müller-Hinton and Sabouraud agars were used as the growth medium for bacterial and fungal species correspondingly. Furthermore, dmso was employed as a control for all type of microorganisms. Control indicated no activity against the strains of microorganisms. Results were obtained after 48 h of incubation at 35 °C and 28–30 °C for anti-bacterial and anti-fungal tests, respectively. They were compared with standard drugs *penicillin and greseofulvin* for anti-bacterial and anti-fungal activities, measuring the zone of inhibition in mm.

3. Computational method

Computations were performed by Gaussian 09 [25]. GaussView 5.0.8 was employed for geometrical and spectroscopic illustrations [26]. Starting geometries of 1a-3a (eaa chair conformation) for the calculations were taken from X-ray refinement data (Fig. 2). They were optimized, without imposing symmetry, by B3LYP functional with 6–31G(d) basis set. To confirm the nature of the ground state structure, the calculation of harmonic vibrational frequencies was conducted by the same functional and basis sets, and then they were scaled by 0.9613 [27]. Frontier molecular orbital energies of 1a-3a were also computed together with some electronic properties such as electrical band gap or chemical hardness by the same level.

4. Results and discussion

4.1. Synthesis

Five unsymmetrically substituted triazacyclohexanes (1a-5a) were prepared from the condensation reaction of R_1-NH_2 and R_2-NH_2 with formaldehyde (Fig. 1a). All compounds were obtained with high yield, 54.53–90.42%, as colourless and stable at room temperature (Table SI1). The interaction mechanism is production of Schiff base, which polymerize to give unsymmetrically substituted triazacyclohexanes (Fig. 1b).

4.2. Structural analysis

Molecular structures and atom-labeling schemes for 1a-3a are shown in Fig. 2. Crystal and refinement data for the compounds are given in Table 1. CCDC 1048029 (1a), 1048031 (2a) and 1048030 (3a) contain supplementary crystallographic data for the compounds. 1a crystallizes in monoclinic, $P2_1/c$ space group. Its asymmetric unit contains one 1,3-bis(p-bromophenyl)-5-ethyl-1,3,5-triazinane molecule, a = 6.0380 (4) Å, b = 14.0469 (9) Å, c = 20.423 (17) Å and β = 97.235 (7)°. 2a crystallizes in orthorhombic Pcmn space group with half molecule of 1,3-bis(p-bromophenyl)-5-butyl-1,3,5-triazacyclohexane in the asymmetric unit cell. Further, 3a crystallizes in monoclinic $P2_1/n$ space group with one molecule of 1,3-bis(p-bromophenyl)-5-cyclohexyl-1,3,5-triazacyclohexane in the asymmetric unit cell. All compounds crystallize with 4 molecules in the unit cell.

Each molecule prefers the eaa chair conformation by diaxial repulsion. Analogue positions were also reported for previous unsymmetrically substituted triazacyclohexanes [6–8]. In the triazacyclohexane ring for 1a, C2N1C6N5 and C6N5C4N3 torsion angles are 53.8° (56.4°) and 59.2° (56.3°), the mean is 56.5° (56.4°). Computed values have been given in the parenthesis. For the 2a compound, C2N1C6N1 and C2N3C2N1 torsion angles are 54.8° (53.9°) and 62.2° (57.6°), the mean is 58.5° (55.8°). Similarly, for 3a, C6N1C2N3 and C6N5C4N3 angles 53.0° (53.8°) and 59.7° (57.6°), the average is 56.4° (55.7°). CH_2–N bond lengths (C6–N1, C4–N5) are 1.443 Å (1.449 Å) and 1.465 Å (1.450 Å), the mean is 1.454 Å (1.450 Å) for 1a. C2–N1 and C6–N1 bond lengths are 1.455 Å (1.454 Å) and 1.461 Å (1.468 Å), the average is 1.458 Å (1.461 Å) for 2a. Turning to 3a, C4–N3 and C6–N5 bond lengths are 1.450 Å (1.454 Å) and 1.470 Å (1.472 Å), the mean is 1.460 Å (1.463 Å). Similar values (1.441–1.464 Å) were reported for the previous studies [5–8]. CH_2–N–CH_2 (C4N5C6 and C2N3C4) bond angles of 1a are 107° (108°) 110.4° (110.6°), the mean is 108.7° (109.3°). C2N3C2^i and C2N1C6 angles of 2a are 107.2° (109.2°) and 109.6° (110.1°), the average is 108.4° (109.7°). C4N5C6 and C2N3C4 bond angles of 3a 107.3° (108.4°) and 110.7° (110.3°), the mean is 109.0° (109.4°). Some selected structural parameters of the compounds are given in Table SI2. Theoretical parameters given in parenthesis for CH_2–N bond lengths, CH_2–N–CH_2 bond angles and torsion angles of the triazacyclohexane ring are also in good agreement with the experimentally observed values.

All N atoms have distinctly pyramidal geometry with aryl and alkyl N–C bonds inclined at 31.06–33.84° and 49.82–63.46° to their respective CH_2–N–CH_2 planes correspondingly (Table 2). Nitrogen atoms of aliphatic amines are associated with larger out-of-plane than nitrogens of aromatic amines. Previous studies also indicated that the corresponding out-of-plane angle of aryl N–C is 37.5–42.2° in aniline [28], 27.0° in N,N-dimethylaniline [29] and 36.9–37.4° in p-fluoro aniline [30] whereas the alkyl N–C is

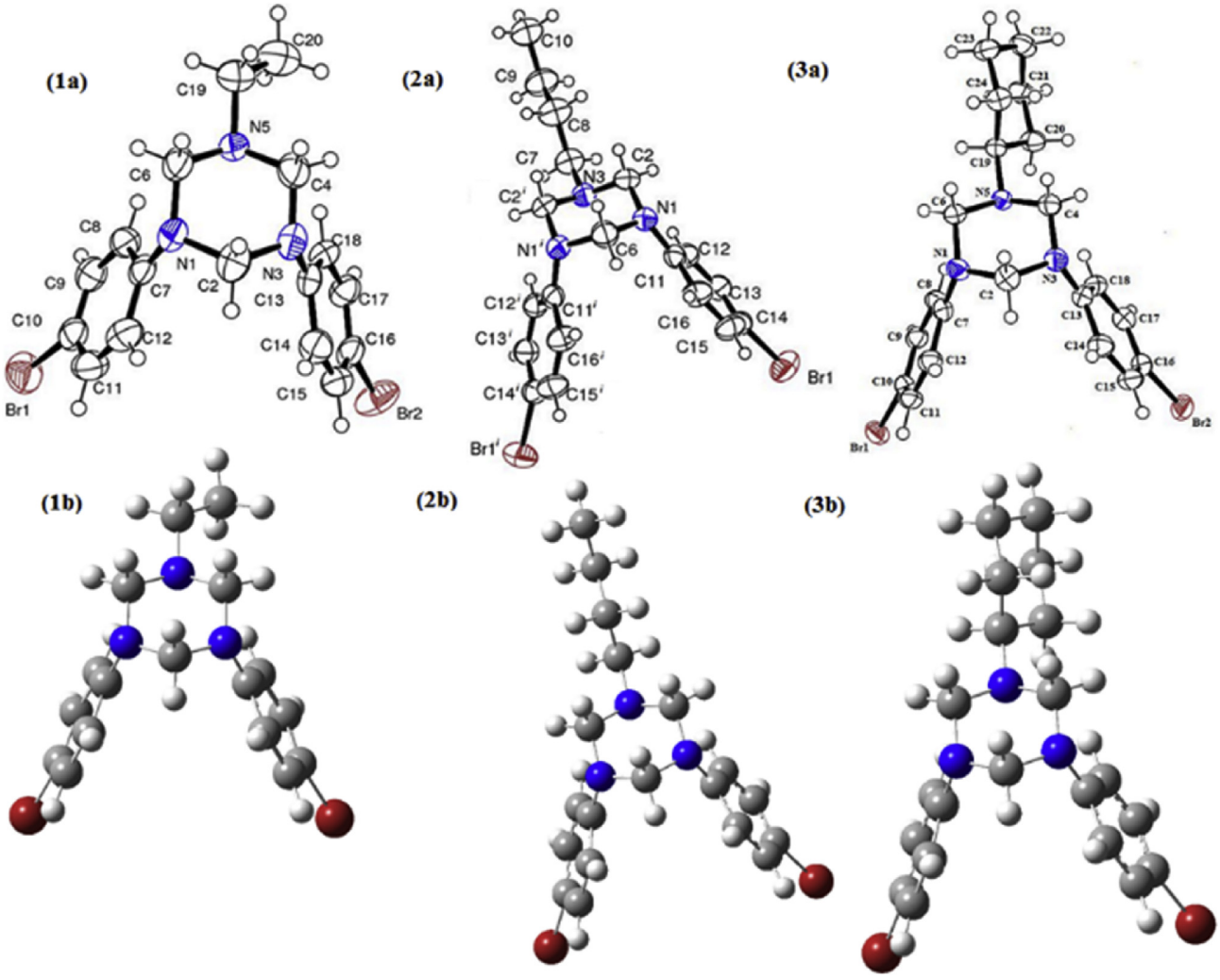

Fig. 2. Molecular structures of 1a-3a, with the atom-labelling schemes. Displacement ellipsoids are drawn at the 50% probability level. Optimized (1b-3b) structure of the compounds.

46.1–52.2° in cyclohexylamine [12]. The corresponding angle for a tetrahedral arrangement is 54.7°. The axial N–C bonds in compounds are consequently between outwards by 21–24° from ideal chair form while alkyl N–C bonds are between outwards by 5–9°. As seen from Table 2, the angle θ for 2a is in the range of 64.14–64.30°, indicating that the dihedral angle between the N atom lone-pair orbital and aromatic π orbitals [29]. For 1a, it is 56.43–63.03°and the dihedral angle of lone-pair/π-orbital is 27–34°. However, for 3a (alkyl = cyclohexyl) it is 51.5–56.54° and the dihedral angle for lone-pair/π-orbital is increased to 33–39°. In the absence of steric effects, this angle would be expected to be 0° to provide maximum overlap. Nitrogen and bromo atoms deviate from the phenyl by 0.126 Å - 7.73° and 0.013 Å - 1.69°, giving out-of-plane angle of 5.11–7.76° range (mean 6.43°) for the aryl C–N bonds and 0.39–5.09° range (mean 2.94°) for the aryl C–Br bonds, respectively. Molecular orbital computation of aniline gave a non-planar equilibrium geometry with the C(Aryl)-N bond inclined at 2.4° to the aromatic plane [31].

For 3a, in the cyclohexyl rings, the CCC angles range from 109.4° (110.3°) to 111.6° (111.7°) and the mean is 110.5° (111.2°). The smallest position belongs to directly bonded to the triaza heterocycle (C19), and it indicates that a steric effect is involved. Although HCH angles of cyclohexyl group, 108.0° (107.0°), are subject to fairly large errors, the mean value of 107.0° (106.5°) is undoubtedly significantly smaller than tetrahedral. C–C bond lengths are 1.514 Å (1.535 Å) - 1.531 Å (1.548 Å) and the average is 1.522 Å (1.539 Å). The eleven C–H bonds of cyclohexyl group range from 0.97 Å (1.096 Å) to 0.98 Å (1.101 Å) and the mean length, 0.98 Å (1.099 Å), is the customary 0.1 Å, shorter than C–H internuclear distances determined by spectroscopy or neutron diffraction methods. In their crystal structures, molecules are stacked in alternating layers along the b axis (Fig. 3). As seen from Table 3, intramolecular C–H···N hydrogen bonds may be effective in the stabilization of the structures of 1a-3a.

4.3. Vibrational analysis

1a, 2a and 3a molecules consist of 41, 47 and 51 atoms, so they have 117, 135 and 147 normal vibrational modes. They belong to the point group C_1 with only identity symmetry operation. FT-IR spectra are performed to analysed the chemical bonding and structures (Figure SI1). The characteristic and strong bands experimentally observed have been discussed in here. In the high vibrational region, vibrations observed at 3027, 2976, 2933 and 3036, 2956, 2927 cm^{-1} are attributed to aromatic CH, aliphatic CH_3, CH_2 stretching vibrations of 1a and 2a, respectively, which is

Table 1
Crystal data and structure refinement for 1a-3a.

Crystal data	1a	2a	3a
Empirical formula	C_{17} H_{19} Br_2N_3	C_{19} H_{23} Br_2N_3	C_{21} H_{25} Br_2N_3
Formula weight (g/mol)	425.17	453.22	479.26
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1/c$	Pcmn	$P2_1/n$
Unit cell dimensions (Å,°)			
a	6.0380 (4)	5.8328(4)	6.1854 (10)
b	14.0469	14.2772 (10)	21.2260 (10)
c	20.423	22.9148 (13)	15.0526 (10)
β	97.235 (7)	90	92.944 (10)
Volume (Å^3)	1718.4 (2)	1908.3 (2)	1973.67 (11)
Z	4	4	4
F(000)	848	911.9	967.8
D (mg/m^3)	1.643	1.580	1.610
Wavelength (Mo Kα),Å	0.71073	0.71073	1.54180
Shape, Color	Block, colourless	Block, colourless	Block, colourless
Crystal size (mm^3)	0.009 × 0.012 × 0.019	0.300 × 0.543 × 0.622	0.039 × 0.110 × 0.430
θ_{max}-θ_{min} (°)	29.6–2.9	28.9–3.6	66.9–3.6
μ (mm^{-1})	4.717	4.253	5.274
Temperature (K)	293	293	150
Refinement Method	F^2	F^2	F^2
Least-squares matrix	Full	Full	Full
R[$F^2 > 2\sigma(F^2)$]	0.0464	0.0464	0.0469
wR(F^2)	0.0981	0.1202	0.0567
Measured reflections	8755	6447	9670
Independent reflections	2335	2335	4682
Reflections with $I > 2\sigma(I)$	2398	1389	2906
R_{int}	0.028	0.040	0.046
h	−7 → 8	−7 → 5	−5 → 7
k	−17 → 18	−12 → 18	−25 → 23
L	−16 → 27	−31 → 30	−17 → 17
H atom	constrained refinement	constrained refinement	constrained refinement
W	1/[σ2(F_o^2) + (0.0195 P)2 + 1.4080 P]	1/[σ2(F_o^2) + (0.0336 P)2 + 0546 P]	1/[σ2(F_o^2) + (0.0794 P)2 + 1.0096 P]
$\Delta_{\rho max}$ (e A^{-3})	0.55	0.53	0.86
$\Delta_{\rho min}$ (e A^{-3})	−0.64	−0.51	−0.46

Table 2
Conformational details for 1a-3a.

Compound		θ; between planes *dagj* and *aghijkl* γ; between band *a-g* and plane *fab* ζ; between band *a-g* and plane *ghijkl*		
		θ(°)	γ (°)	ζ (°)
1a	N-5 equatorial	–	54.29	–
	N-1 axial	56.43	32.68	7.76
	N-3 axial	63.03	33.09	5.11
2a	N-5 equatorial	–	63.46	–
	N-1 axial	64.14	33.43	5.75
	N-3 axial	64.30	33.43	5.62
3a	N-5 equatorial	–	49.82	–
	N-1 axial	51.50	31.06	5.50
	N-3 axial	56.54	33.84	6.27

theoretically calculated as 3073, 2941, 2879 cm^{-1} and 3073, 2926, 2909 cm^{-1}. However, aliphatic CH_2 stretching band of 3a are observed at 2924 (2919) cm^{-1}. Absorption bands observed at 1586 (1586), 1585 (1586) and 1586 (1586) cm^{-1} are the ν(C=C) of the six-membered aromatic system of 1a-3a. The CN amine III stretching vibrations for 1a and 2a are observed at 1356 (1355) and 1357 (1350) cm^{-1} while the related band of 3a is reported as 1367 (1366) cm^{-1}. The CN ph-NR2 bands of 1a and 3a are reported as 1270 (1261) and 1280 (1274) cm^{-1}. IR spectra show strong stretching bands at 520 (542), 518 (543) and 520 (549) cm^{-1} for the C–Br bond of 1a.-3a, respectively. These bands are observed in the expected regions and similar patterns were reported earlier [5,16]. The theoretically calculated and scaled values of these modes discussed have been also given in parenthesis. Experimental data are also in good agreement with the theoretical values. All computed vibrational frequencies are tabulated in Table SI3.

Similarly, characteristic stretching bands of 4a and 5a have been reported as 2916-2936 cm^{-1} (aliphatic CH_2), 3010-3036 cm^{-1} (CH aromatic), 1590-1625 cm^{-1} (ring aromatic), 1265-1380 cm^{-1} (CN, ph-NR_2), 1310-1360 cm^{-1} (CN amine III), 500-600 cm^{-1} (C–Br), 600-830 cm^{-1} (C–Cl) and 2952 cm^{-1} (aliphatic CH_3), 2923 cm^{-1} (aliphatic CH_2), 3014 cm^{-1} (CH aromatic), 1589 cm^{-1} (ring aromatic), 1380 cm^{-1} (CN ph-NR_2), 1300 cm^{-1} (CN amine III), 522 cm^{-1} (C–Br) correspondingly.

4.4. Antimicrobial activity

It is expected that these compounds exhibit high biological activity since they contain CN group and halogen Br atom as pharmacophore. Values of MIC observed for all the synthesized compounds are presented in Table 4. Antibacterial screening results give that 4a shows promising activity while the others show poor activities against *Escherichia coli*. 3a and 4a show good and high activities against *Salmonella typhi* and *Staphylococcus areus*. 2a, however, gives low activity against *Staphylococcus areus*. Further, as seen from Table 4, all compounds are inactive against *Fusirium moneliforme*. 1a, 2a and 3a show inhibitory effects against *Aspergillus flavus, Aspergillus niger* and *Pencillium chrysogenum* correspondingly while 4a and 5a indicate inhibitory effects against all of them, and *Aspergillus flavus* and *Pencillium chrysogenum*.

4.5. Electronic properties

It is reported in literature that dipole moment and some electronic properties such as electrical band gap may be related to

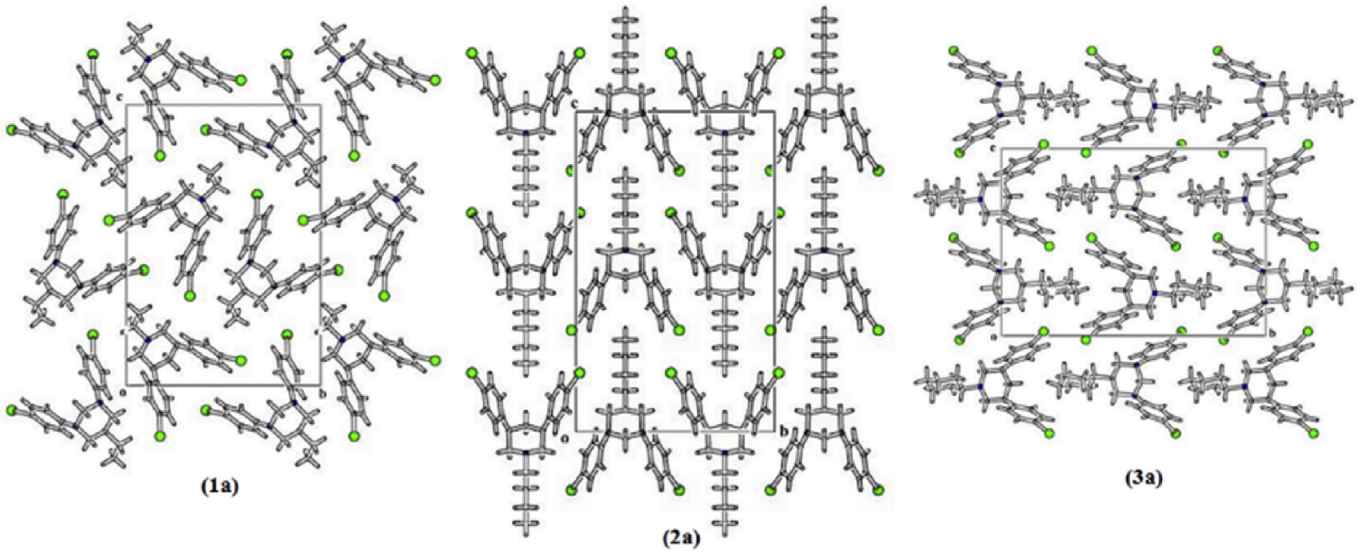

Fig. 3. Packing diagrams of 1a-3a along the b axis.

Table 3
Hydrogen bond geometry (A°,°) of 1a-3a.

D-H … A	D-H	H … A	D … A	D-H … A
1a				
C8–H8···N5^{i}	0.930	2.736	3.279(4)	118.16
C18–H18··· N5^{i}	0.930	2.839	3.340(4)	115.00
2a				
C12–H12···N5^{i}	0.930	2.809	3.300(6)	114.12
3a				
C8–H8···N5^{i}	0.930	2.705	3.266(4)	119.57
C18–H18···N5^{i}	0.930	2.829	3.359(5)	117.30
C17–H17···N3^{ii}	0.930	2.866	3.534(5)	129.79
C9–H9···N1^{ii}	0.930	2.867	3.527(5)	128.94

Symmetry codes: (i) x, y, z and (ii) x-1, +y, +z.

biological activity [32]. Therefore, we have investigated some parameters and they are summarised in Table 5. Further, density of state (DOS) spectra, molecular frontier orbitals and electrostatic potential surfaces (EPS) of 1a-3a are given in Fig. 4, Figures SI2 and SI3. Spectra were created by Gaussian curves of unit height and full width at half maximum (FWHM) of 0.3 eV. Density graphs of frontier orbitals were plotted by a contour value of 0.02.

Table 5
Energetic parameters of 1a-3a.

Parameter	1a	2a	3a
Dipole moment (D)	5.123	5.488	5.582
HOMO (eV)	−5.330	−5.296	−5.272
LUMO (eV)	−0.384	−0.359	−0.343
Gap (eV)	4.946	4.937	4.929
Chemical hardness (eV)	2.473	2.468	2.464
Electrophilicity index (eV)	1.650	1.619	1.599
Electronegativity (eV)	2.857	2.827	2.807

Molecular orbital energies, gaps and dipole moments are sufficient for the compounds to be biologically active when compared with the organic compounds previously synthesized in literature [32,33]. Compounds 1a-3a have large dipole moment as 5.123, 5.488 and 5.582 D which is an essential criterion for drug-receptor interaction [34]. In all compounds, HOMO is delocalized on almost all atoms of R_1 substituents (4-Ph-Br) together with N-R_1 region while LUMO is delocalized on almost all atoms of R_1 substituents (4-Ph-Br) except Br halogen atoms and without N-R_1 region. Antibacterial activity of the compound is a function of their LUMO which measures the electrophilicity of the compound. The

Table 4
Anti-bacterial and anti-fungal screening results of 1a-5a.

Compound	*Salmonella Typhi*	*Bacillus Subtilus*	*Staphylococcus Areus*	*Escherichia Coli*
1a	10	11	18	10
2a	10	11	13	8
3a	13	12	21	10
4a	20	19	26	16
5a	11	16	14	9
Penicillin	25	17	40	18
Dmso	No	No	No	No
Compound	*Aspergillus Flavus*	*Aspergillus Niger*	*Fusirium Moneliforme*	*Pencillium Chrysogenum*
1a	−	+	+	+
2a	+	−	+	+
3a	+	+	+	−
4a	−	−	+	−
5a	−	+	+	−
Greseofulvin	−	−	−	−
Control	+	+	+	+

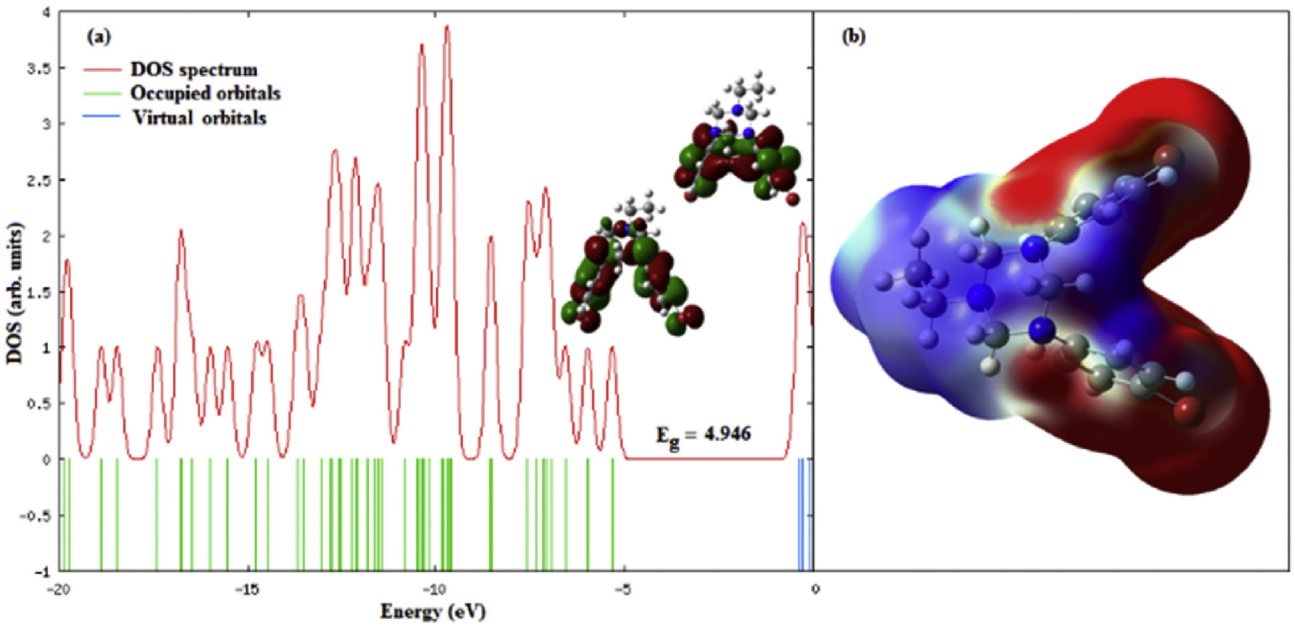

Fig. 4. (a) DOS spectrum and molecular frontier orbitals of 1a. (b) EPS diagram of 1a.

compound with low LUMO energy is more capable to accept electrons than those with higher LUMO energy, and thus a high activity requires a low electrophilicity. It was theoretically found that the compound 3a has lower electrophilicity index than 1a and 2a. These theoretical results are in good agreement with the experimental data for the compounds 1a-3a.

Electrical band gap of 1a-3a decreases gradually by the size of substituent whereas dipole moment follows opposite trend (Table 5). Electrical band gaps are about 4.9 eV which is sufficiently large to meet the viability criterion [35]. Values of the chemical hardness, electrophilicity index and electronegativity indicate same trend with electrical band gap. Electrostatic potential maps enable to visualize the charge distributions for compounds. Surfaces are defined by the 0.0004 electrons/b^3 con-tour of the electronic density. Color ranges (in a.u.) are more positive than 0.017 for blue and more negative than −0.017 for red. Areas of low and high potentials, red and blue, are characterized by an abundance of electrons and a relative absence of electrons, respectively. Therefore, the lowest electrostatic potential area corresponds to the greatest electron concentration area. The results indicate that the compounds have analogues potential features and red areas seem as the most probable candidates as active sites for the compounds (Fig. 4 and Figure SI2).

5. Conclusions

In summary, the new five unsymmetrically substituted triazacyclohexanes were prepared between two amines and formaldehyde. FT-IR and ^{1}H NMR analyses of the compounds were reported and the solid-state structures of some compounds were determined by single crystal X-ray. They were also supported by the quantum mechanical calculations. 1a-3a compounds adopt the eaa chair conformation. All compounds showed an activity against the strains of microorganisms used. 4a having bromo halogens as pharmacophore is exhibited an antimicrobial activity proving probably the relation between structure and activity. Electrical band gaps and dipole moments are sufficient for the compounds to be biologically active such as viability and drug-receptor interaction criterions correspondingly.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.molstruc.2016.09.060.

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