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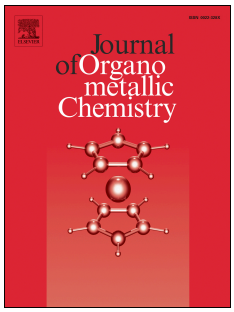

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Synthesis, characterization and antibacterial studies of schiff based 1,2,3-triazole bridged silatranes

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Abstract

A single step Cu (I) assisted click silylation reaction had been used for the synthesis of novel Schiff based 1,2,3-triazole bridged silatrane (SBTBS)-scaffolds (**5a-5f**) using polyfunctionalised Schiff based 1,2,3-triazole bridged organotriethoxysilanes (SBTBOTS) (**4a-4f**) as precursors. These compounds were synthesized in excellent yields using an economical, simple and biocompatible synthetic procedure and their structures were characterized by various spectroscopy methods such as IR, NMR (1H and 13C) and elemental analysis. The presence of different pharmacologically active segments into a single

triazole unit can result into impressive achievement in their bioactivity. So, antibacterial studies of the silatranes (**5a-5f**) were also carried out and it was observed that all the compounds showed potential antibacterial activity. The results also indicate that activity of compound **5f** is even comparable to the standard drug, cefepime.

Keywords:

Antibacterial

Click silylation

Silatrane

Trialkoxysilane

Triazole

1. Introduction

Silatranes, with general formula $X^{-}Si(OCH_2CH_2)_3N$, are intramolecular complex of silicon with triethanolamine ligand, exhibiting exclusive structure [1,2]. The unconventional trigonal bipyramidal framework of silatranes route to their high electronegativity and high dipole moment which sanction the chemisorption of these entities on the surface of cellular membranes via hydrogen interactions with equatorial oxygen atoms or by dipole-dipole interactions [3-5]. Being the atrane molecules, a feature of interest in these compounds is transannular dative bonding interaction between the silicon and the nitrogen atom which furnish some peculiar chemical properties [6]. The length of N→Si dative bond depends on electronegativity of the substituent on the silicon atom [7]. Silatranes discover multitudinous prominence advantages in catalysis, biomaterials, sol-gel, nano chemistry, agriculture, medicine and pharmacology [8].

Schiff bases, also referred as Imines, have drawn attention of scientists owing to their easy synthesis and ease of metal complexation [9]. 2-Hydroxy-1-naphthaldehyde in literature is illustrated as versatile fluorescent chemosensor building block towards a gob of cations, anions and many organic moieties. So via hybridization with primary amines and 1, 2, 3,

triazole bridged silatranyl (TBS) group, the molecule can be used as coherent fluorophore unit for a variety of analytes [10,11] as presented in Fig. 1.

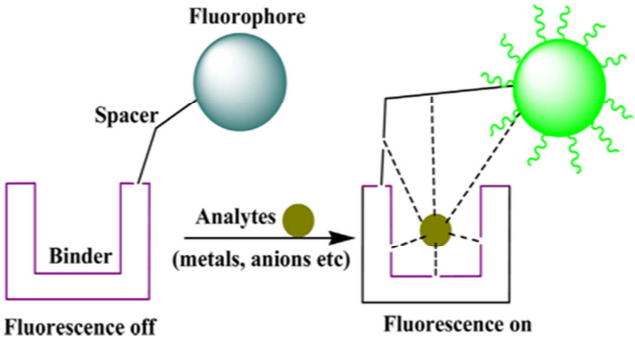


Fig. 1: Schematic representation of Schiff based 1,2,3- triazole linked silatrane as fluorescent chemosensor

The substantial, high reliability, excellent efficiency (nearly 100% yield) and fastidious reaction is the paradigm of a click procedure. Inevitably, this protocol has explored tremendously increasing application in an array of disciplines such as drug discovery and medicinal chemistry, bio-conjugation, polymer, organic chemistry, catalysts and materials science [12-15]. The pioneer effort by Cattoen and co-workers encouraged us to develop a hybrid key intermediate 1, 2, 3-triazole bridged oragnotriethoxysilanes (TBOTES) via 'Click Silylation' [16,17]. The label "Click Silylation" enclosed the powerful master plan of click and organosilicon chemistry that offer covalent congregation of smaller fragments (terminal alkynes and azide function) to TBOTES-linkers, which can further perform as an ancestral forefather for the development of efficient variegated silatranes [18,19].

Herein, we report a riveting application of click reaction in organosilicon chemistry to fabricate a library of well defined Schiff based 1,2,3-triazole bridged silatrane (SBTBS)-scaffolds, that can offer an army of imperative advantages over organotriethoxysilanes (OTS). Unlike OTS-linkers, assembled SBTBS-scaffolds are stable towards hydrolysis, oxidation and reduction and the ability of the N (3) atom of the 1,2,3-triazole, O (3) atom of the silatrane ring and N (1) atom of Schiff base segment to act as a hydrogen bond acceptor can make it an outstanding fragment in supramolecular chemistry. Further, schiff bases, 1,2,3-triazole compounds and silatranes are individually known for their antibacterial activity. Conjugation of these three potent anti-bacterial agents can have synergic effects on their individual potentials and hence the synthesized SBTBS compounds (**5a-5f**) were also

monitored against bacterial survival i.e. for their antibacterial activity against *P. aeruginosa* PAO1, *Klebsiella pneumoniae* 43816, *S. epidermidis* 3382 and *S. aureus* MRSA.

2. Experimental

2.1. Materials and methods

All the syntheses were carried out under inert dry nitrogen atmosphere using vacuum glass line. The organic solvents were dried according to standard procedures [20]. 2-Hydroxy-1-naphthaldehyde (Aldrich), Aniline (Qualigens, >99%), naphthalen-1-amine (Aldrich), 4-(phenyldiazenyl)benzenamine (CDH), 4-chlorobenzenamine (Aldrich), 4-nitrobenzenamine (Aldrich), 4-fluorobenzenamine (SDFCL), 2-methoxybenzenamine (SDFCL), propargyl bromide (80% in toluene) (Aldrich), potassium carbonate (Thomas), sodium sulphate (Finar), Bromotris (triphenylphosphine) copper(I) [CuBr(PPh3)3] (Aldrich), tetrahydrofuran (THF) (CDH), Triethylamine (Et_3N) (SDFCL), triethanolamine (CDH), KOH (CDH), Toluene (SDFCL), DMF (FINAR) were used as received. 3-azidopropyltriethoxysilane (AzPTES) was synthesized by known procedure from literature [21,22]. Infrared spectrum was obtained neat on a Thermo Scientific Fischer spectrometer. Elemental analysis was carried out on Perkin Elmer Model 2400 CHNS elemental analyzer and Thermo Scientific Flash 2000 organic elemental analyzer. Multinuclear NMR (^1H, ^{13}C) spectra were recorded on a Bruker advance II 400 and on a Jeol (AL 300 MHz) spectrometer using $CDCl_3$ as internal reference and chemical shifts were reported relative to tetramethylsilane. Melting points were uncorrected and measured in a Mel Temp II device using sealed capillaries. Mass analysis was performed on a WATERS, Q-TOF micro MASS spectrometer (ESI source with capillary voltage, 3000 V). Theoretical studies were done using density functional theory (DFT) calculations with hybrid density functional (B3LYP)/6-31+G(d) basis set level of theory.

2.2. General procedure for synthesis of schiff based alkynes (SBA) (3a-3f):- 2-(prop-2-ynyloxy)-1-naphthaldehyde (**1**) was synthesised as described in the literature from 2-hydroxy-1-naphthaldehyde [23]. Then amine (2.3 mmol) (**2a-2f**) was added to an ethanolic solution of **1** (0.5g, 2.3mmol) in a single neck round bottom flask and refluxed for 4 h followed by cooling to room temperature. The solid product was filtered and dried to obtain the yellow colored schiff bases alkynes (**3a-3f**).

2.3. General procedure for synthesis of Schiff based 1, 2, 3-triazole bridged organotriethoxysilanes (SBTBOTS)-scaffolds (4a-4f):- Under dry nitrogen atmosphere using vacuum glass line, Schiff based alkynes (1 equiv) were blended to 1:1 THF/Et_3N solvent mixture taken in a 2-neck round bottomed flask and the whole composition was mixed for 20 min at room temperature. Slow dropwise addition of AzPTES (1 equiv/alkyne function) was done followed by catalyst [$CuBr(PPh_3)_3$] (0.01 mmol/alkyne function) loading. The mixture was refluxed at 60 □ for 5h**.** The reaction was then escort to room temperature. The solvents were evaporated under reduced pressure followed by the addition of n-pentane. The reaction mixture was then filtered and quantity of filterate under reduced pressure furnished the viscous pale yellow SBTBOTS (**4a-4f**) in fantastic yield.

*2.3.1. Synthesis of (Z)-N-((2-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)benzenamine (**4a):***

The quantities used were: **3a** (0.42 g, 1.47 mmol), AzPTES (0.37 g, 1.47 mmol), Yield 96%; ^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.43 (t, 2H, J = 5.8 Hz, ─$SiCH_2$─), 1.09 (t, J = 7.3 Hz, 9H, ─$OCCH_3$), 1.76 (m, 2H, ─CCH_2C), 3.67 (m, 6H, ─OCH_2C), 4.20 (t, J = 7.6 Hz, 2H, ─NCH_2CC─), 5.35 (s, 2H, ─OCH_2Tz), 7.12– 7.81 (m, 11H), 9.13 (s, 2H, ─CH═N), 9.45 (d, J = 6.6 Hz, 1H, Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 7.6 ($SiCH_2$), 18.4 (OCH_2CH_3), 24.1 (CCH_2C), 53.8 (N_3CH_2), 58.4 (OCH_2C), 63.6 (OCH_2), 114.2─ 133.7 (Ar-C), 158.4 (CH═N).

*2.3.2. Synthesis of (Z)-N-((2-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)naphthalen-1-amine (**4b):***

The quantities used were: **3b** (0.35 g, 1.00 mmol), AzPTES (0.26 g, 1.00 mmol), Yield 93%; ^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.41 (t, 2H, J = 8 Hz, ─$SiCH_2$─), 1.07 (t, J = 7.4 Hz, 9H, ─$OCCH_3$), 1.83 (m, 2H, ─CCH_2C), 3.67 (m, 6H, ─OCH_2C), 4.20 (t, J = 6.7 Hz, 2H, ─NCH_2CC─), 5.37 (s, 2H, ─OCH_2Tz), 6.96 – 7.87 (m, 13H), 9.27 (s, 2H, ─CH═N), 9.68 (d, J = 11.6 Hz, 1H-Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 7.4 ($SiCH_2$), 18.6 (OCH_2CH_3), 22.6 (CCH_2C), 52.5 (N_3CH_2), 58.3 (OCH_2C), 63.7 (OCH_2), 112.9 ─ 134.0 (Ar-C), 158.5 (CH═N).

*2.3.3. Synthesis of (Z)-4-((E)-phenyldiazenyl)-N-((2-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)benzenamine (**4c):***

The quantities used were: **3c** (0.67 g, 1.70 mmol), AzPTES (0.42 g, 1.70 mmol), Yield 97%;

^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.48 (t, 2H, J = 11 Hz, ─$SiCH_2$─), 1.17 (t, J = 9.0 Hz, 9H, ─$OCCH_3$), 1.95 (m, 2H, ─CCH_2C), 3.70 (m, 6H, ─OCH_2C), 4.20 (t, J = 7.20 Hz, 2H, ─NCH_2CC─), 5.22 (s, 2H, ─OCH_2Tz), 7.13 – 7.53 (m, 16H), 9.25 (s, 2H, ─CH═N), 9.42 (d, J = 3.3 Hz, 1H-Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 8.4 ($SiCH_2$), 18.2 (OCH_2CH_3), 24.1 (CCH_2C), 52.5 (N_3CH_2), 58.4 (OCH_2C), 66.1 (OCH_2), 113.5 ─ 137.8 (Ar-C), 158.8 (CH═N).

*2.3.4. Synthesis of (Z)-4-nitro-N-((2-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)benzenamine (**4d**):*

The quantities used were: **3d** (0.54 g, 1.63 mmol), AzPTES (0.40 g, 1.63 mmol), Yield 98%; ^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.44 (t, 2H, J = 7.5 Hz, ─$SiCH_2$─), 1.12 (t, J = 3.6 Hz, 9H, ─$OCCH_3$), 1.76 (m, 2H, ─CCH_2C), 3.66 (m, 6H, ─OCH_2C), 4.24 (t, J = 6.90 Hz, 2H, ─NCH_2CC─), 5.36 (s, 2H, ─OCH_2Tz), 7.11 – 8.18 (m, 10H), 9.14 (s, 2H, ─CH═N), 9.44 (d, J = 8.7 Hz, 1H-Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 6.4 ($SiCH_2$), 17.2 (OCH_2CH_3), 23.1 (CCH_2C), 51.5 (N_3CH_2), 57.4 (OCH_2C), 62.4 (OCH_2), 113.1 ─ 134.1 (Ar-C), 158.3 (CH═N).

*2.3.5. Synthesis of (Z)-4-fluoro-N-((2-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)benzenamine (**4e**):*

The quantities used were: **3e** (0.50 g, 1.65 mmol), AzPTES (0.41 g, 1.65 mmol), Yield 95%; ^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.58 (t, 2H, J = 7.5 Hz, ─$SiCH_2$─), 1.09 (t, J = 6.9 Hz, 9H, ─$OCCH_3$), 1.82 (m, 2H, ─CCH_2C), 3.75 (m, 6H, ─OCH_2C), 4.21 (t, J = 9.5 Hz, 2H, ─NCH_2CC─), 5.36 (s, 2H, ─OCH_2Tz), 7.24 – 7.87 (m, 10H), 9.23 (s, 2H, ─CH═N), 9.48 (d, J = 8.1 Hz, 1H-Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 8.4 ($SiCH_2$), 17.8 (OCH_2CH_3), 23.5 (CCH_2C), 53.6 (N_3CH_2), 58.2 (OCH_2C), 62.8 (OCH_2), 123.1 ─ 134.1 (Ar-C), 158.4 (CH═N).

*2.3.6. Synthesis of (Z)-2-methoxy-N-((2-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)benzenamine (**4f**):*

The quantities used were: **3f** (0.50 g, 1.60 mmol), AzPTES (0.39 g, 1.60 mmol), Yield 94%. ^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.27 (t, 2H, J = 7.5 Hz, ─$SiCH_2$─), 1.26 (t, J = 4.8 Hz, 9H, ─$OCCH_3$), 1.78 (m, 2H, ─CCH_2C), 3.66 (m, 6H, ─OCH_2C), 3.89 (s, 3H, ─$ArOCH_3$), 4.23 (t, J = 6.3 Hz, 2H, ─NCH_2CC─), 5.36 (s, 2H, ─OCH_2Tz), 7.22 – 7.70 (m, 10H), 9.21 (s, 2H, ─CH═N), 9.48 (d, J = 8.1 Hz, 1H-Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 7.4 ($SiCH_2$), 18.2 (OCH_2CH_3), 24.6 (CCH_2C), 51.0 (N_3CH_2), 57.5 (OCH_2C), 62.8 (OCH_2), 111.8 ─ 133.4 (Ar-C), 158.6 (CH═N).

2.4. General procedure for synthesis of Schiff based 1, 2, 3-triazole bridged silatrane (SBTBS)-scaffolds (5a-5g):- In the stirred solution of triethanolamine (1 equiv) in toluene (30 ml) taken in a round bottomed flask incorporated with a dean stark equipment, SBTBOTS (1 equiv) was added drop wise followed by the addition of KOH in the catalytic amount. The mixture was refluxed for 4 h in order to remove ethanol azeotropically which was formed during the reaction. Then the solvent was removed under reduced pressure followed by addition of 15 ml hexane. The content was stirred for 24 h after which the products (**5a-5f**) segregated as yellow solid which were filtered under nitrogen atmosphere and dried with the help of vacuum.

*2.4.1. Synthesis of (Z)-N-((2-((1-(3-(2,8,9-trioxa-5-aza-1-sila-bicyclo[3.3.3]undecan-1-yl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)benzenamine (**5a):***

The quantities used were: **4a** (0.50 g, 0.9 mmol), triethanolamine (0.14 g, 0.9 mmol), Yield 89%; m. pt. 225-229 °C. Anal. Calcd for $C_{29}H_{33}N_5O_4Si$ (%): C, 64.06; H, 6.12; N, 12.88. Found (%): C, 64.13; H, 6.17; N, 12.78. IR (neat, cm−1): 571 (N → Si), 743, 1043 (Si─O), 959 (C─C), 1072, 1221 (O─CH_2), 1356 (CH_2─N), 1599 (C═N), 2884 (C═C─H). ^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.79 (t, 2H, J = 5.7 Hz, ─$SiCH_2$─), 1.76 (m, 2H, ─CCH_2C), 2.47 (t, J = 9.0 Hz, 6H, ─$OCCH_2N$), 3.43 (t, 6H, J = 5.7 Hz, ─OCH_2C), 4.34 (t, J = 6.4 Hz, 2H, ─NCH_2CC─), 5.27 (s, 2H, ─OCH_2Tz), 7.06– 7.65 (m, 11H), 9.13 (s, 2H, ─CH═N), 9.45 (d, J = 6.6 Hz, 1H, Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 8.4 ($SiCH_2$), 22.6 (CCH_2C), 52.4 (OCH_2CH_2N), 53.8 (N_3CH_2), 56.8 (OCH_2C), 67.9 (OCH_2), 121.0 ─ 133.7 (Ar-C), 158.4 (CH═N).

*2.4.2. Synthesis of (Z)-N-((2-((1-(3-(2,8,9-trioxa-5-aza-1-sila-bicyclo[3.3.3]undecan-1-yl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)naphthalen-1-amine (**5b):***

The quantities used were: **4b** (1.414 g, 2.4 mmol), triethanolamine (0.36 g, 0.9 mmol), Yield 96%; m. pt. 238-242 °C. Anal. Calcd for $C_{33}H_{35}N_5O_4Si$ (%): C, 66.75; H, 5.94; N, 11.80. Found (%): C, 66.77; H, 5.89; N, 11.68. IR (neat, cm−1): 581 (N → Si), 778, 1058 (Si─O), 929 (C─C), 1052, 1241 (O─CH_2), 1356 (CH_2─N), 1609 (C═N), 2794 (C═C─H). ^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.79 (t, 2H, J = 7.2 Hz, ─$SiCH_2$─), 1.84 (m, 2H, ─CCH_2C), 2.58 (t, J = 6.2 Hz, 6H, ─$OCCH_2N$), 3.53 (t, 6H, J = 5.7 Hz, ─OCH_2C), 4.19 (t, J = 5.8 Hz, 2H, ─NCH_2CC─), 5.38 (s, 2H, ─OCH_2Tz), 7.69– 7.89 (m, 13H), 9.31 (s, 2H, ─CH═N), 9.73 (d, J = 8.4 Hz, 1H, Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ,

ppm): 13.1 ($SiCH_2$), 26.2 (CCH_2C), 50.8 (OCH_2CH_2N), 53.3 (N_3CH_2), 57.4 (OCH_2C), 63.8 (OCH_2), 123.0 ─ 134.0 (Ar-C), 158.5 (CH═N).

*2.4.3. Synthesis of (Z)-4-((E)-phenyldiazenyl)-N-((2-((1-(3-(2,8,9-trioxa-5-aza-1-sila-bicyclo[3.3.3]undecan-1-yl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)benzenamine (**5c**):*

The quantities used were: **4c** (1.00 g, 1.50 mmol), triethanolamine (0.23 g, 1.50 mmol), Yield 91%; m. pt. 232-235 °C. Anal. Calcd for $C_{33}H_{37}N_7O_4Si$ (%): C, 64.89; H, 5.76; N, 15.14. Found (%): C, 64.73; H, 5.77; N, 15.08. IR (neat, cm−1): 572 (N → Si), 789, 1056 (Si─O), 958 (C─C), 1053, 1261 (O─CH_2), 1396 (CH_2─N), 1625 (C═N), 2812 (C═C─H).

^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.74 (t, 2H, J = 7.2 Hz, ─$SiCH_2$─), 1.29 (m, 2H, ─CCH_2C), 2.49 (t, J = 6.2 Hz, 6H, ─$OCCH_2N$), 3.42 (t, 6H, J = 5.7 Hz, ─OCH_2C), 4.16 (t, J = 5.8 Hz, 2H, ─NCH_2CC─), 5.24 (s, 2H, ─OCH_2Tz), 6.95– 7.74 (m, 16H), 9.18 (s, 2H, ─CH═N), 9.58 (d, J = 8.4 Hz, 1H, Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 8.2 ($SiCH_2$), 21.8 (CCH_2C), 53.8 (OCH_2CH_2N), 56.8 (N_3CH_2), 59.5 (OCH_2C), 67.9 (OCH_2), 121.0 ─ 133.7 (Ar-C), 158.4 (CH═N).

*2.4.4. Synthesis of (Z)-N-((2-((1-(3-(2,8,9-trioxa-5-aza-1-sila-bicyclo[3.3.3]undecan-1-yl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)-4-nitrobenzenamine (**5d**):*

The quantities used were: **4d** (0.81 g, 1.40 mmol), triethanolamine (0.21 g, 1.40 mmol), Yield 95%; m. pt. 246-215 °C. Anal. Calcd for $C_{29}H_{32}N_6O_6Si$ (%): C, 59.17; H, 5.48; N, 14.28. Found (%): C, 59.12; H, 5.27; N, 14.09. IR (neat, cm−1): 559 (N → Si), 765, 1106 (Si─O), 978 (C─C), 1087, 1361 (O─CH_2), 1348 (CH_2─N), 1648 (C═N), 2858 (C═C─H).

^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.79 (t, 2H, J = 5.1 Hz, ─$SiCH_2$─), 1.80 (m, 2H, ─CCH_2C), 2.48 (t, J = 4.8 Hz, 6H, ─$OCCH_2N$), 3.43 (t, 6H, J = 4.5 Hz, ─OCH_2C), 4.36 (t, J = 6.2 Hz, 2H, ─NCH_2CC─), 5.28 (s, 2H, ─OCH_2Tz), 7.11– 7.81 (m, 10H), 9.28 (s, 2H, ─CH═N), 9.43 (d, J = 4.4 Hz, 1H, Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 8.2 ($SiCH_2$), 23.6 (CCH_2C), 50.2 (OCH_2CH_2N), 52.4 (N_3CH_2), 56.6 (OCH_2C), 59.5 (OCH_2), 123.3 ─ 133.8 (Ar-C), 158.7 (CH═N).

*2.4.5. Synthesis of (Z)-N-((2-((1-(3-(2,8,9-trioxa-5-aza-1-sila-bicyclo[3.3.3]undecan-1-yl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)-4-fluorobenzenamine (**5e**):*

The quantities used were: **4e** (1.00 g, 1.81 mmol), triethanolamine (0.27 g, 1.81 mmol), Yield 98%; m. pt. 231-235 °C. Anal. Calcd for $C_{29}H_{32}FN_5O_4Si$ (%): C, 62.01; H, 5.74; N, 12.47. Found (%): C, 62.23; H, 5.57; N, 12.29. IR (neat, cm−1): 569 (N → Si), 768, 1096 (Si─O),

998 (C─C), 1117, 1291 (O─CH_2), 1356 (CH_2─N), 1689 (C═N), 2815 (C═C─H). ^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.41 (t, 2H, J = 9.0 Hz, ─$SiCH_2$─), 1.97 (m, 2H, ─CCH_2C), 2.80 (t, J = 6.0 Hz, 6H, ─$OCCH_2N$), 3.74 (t, 6H, J = 3.0 Hz, ─OCH_2C), 4.33 (t, J = 12.0 Hz, 2H, ─NCH_2CC─), 5.13 (s, 2H, ─OCH_2Tz), 7.13– 7.95 (m, 10H), 9.25 (s, 2H, ─CH═N), 9.51 (d, J = 4.4 Hz, 1H, Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 13.2 ($SiCH_2$), 26.3 (CCH_2C), 50.9 (OCH_2CH_2N), 53.4 (N_3CH_2), 57.4 (OCH_2C), 63.7 (OCH_2), 122.4 ─ 133.9 (Ar-C), 158.4 (CH═N). Calcd for $[M+H]^+$ 562.6; Found 562.1.

*2.4.6. Synthesis of (Z)-N-((2-((1-(3-(2,8,9-trioxa-5-aza-1-sila-bicyclo[3.3.3]undecan-1-yl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)-2-methoxybenzenamine (**5f**):*

The quantities used were: **4f** (1.00 g, 1.77 mmol), triethanolamine (0.27 g, 1.77 mmol), Yield 94%; m. pt. 239-244 °C. Anal. Calcd for $C_{30}H_{35}N_5O_5Si$ (%): C, 62.80; H, 6.12; N, 12.21. Found (%): C, 62.88; H, 5.99; N, 12.33. IR (neat, cm−1): 573 (N → Si), 786, 1065 (Si─O), 978 (C─C), 1079, 1298 (O─CH_2), 1346 (CH_2─N), 1676 (C═N), 2867 (C═C─H). ^{1}H NMR (300 MHz, CDCl3, 25 °C, δ, ppm): 0.58 (t, 2H, J = 7.7 Hz, ─$SiCH_2$─), 1.84 (m, 2H, ─CCH_2C), 2.53 (t, J = 6.9 Hz, 6H, ─$OCCH_2N$), 3.473(t, 6H, J = 8.9 Hz, ─OCH_2C), 4.36 (t, J = 10.7 Hz, 2H, ─NCH_2CC─), 5.43 (s, 2H, ─OCH_2Tz), 7.26– 7.77 (m, 10H), 8.05 (s, 2H, ─CH═N), 9.22 (d, J = 8.7 Hz, 1H, Naphthalene H). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, δ, ppm): 7.5 ($SiCH_2$), 23.6 (CCH_2C), 52.5 (OCH_2CH_2N), 56.0 (N_3CH_2), 58.8 (OCH_2C), 63.8 (OCH_2), 122.9 ─ 133.4 (Ar-C), 157.8 (CH═N).

2.5. Biological studies

2.5.1. Antibacterial assay

All the six compounds (**5a-5f**) were screened for their antibacterial activity against *P. aeruginosa* PAO1, *Klebsiella pneumoniae* 43816, *S. epidermidis* 3382 and *S. aureus* MRSA by following the well plate assay [24]. The nutrient agar was poured in petri dish (100 mm size and 4mm depth). The agar plates were then seeded with overnight broth culture, diluted to 0.5 McFarland turbidity (~ 1.5. 10^8 cells/ml). Then agar was punched to make wells of 4mm depth and 3mm diameter. A 1 mg/ml solution of all the four bacteria was loaded in separate wells and a zone of inhibition observed after overnight incubation at 37□.

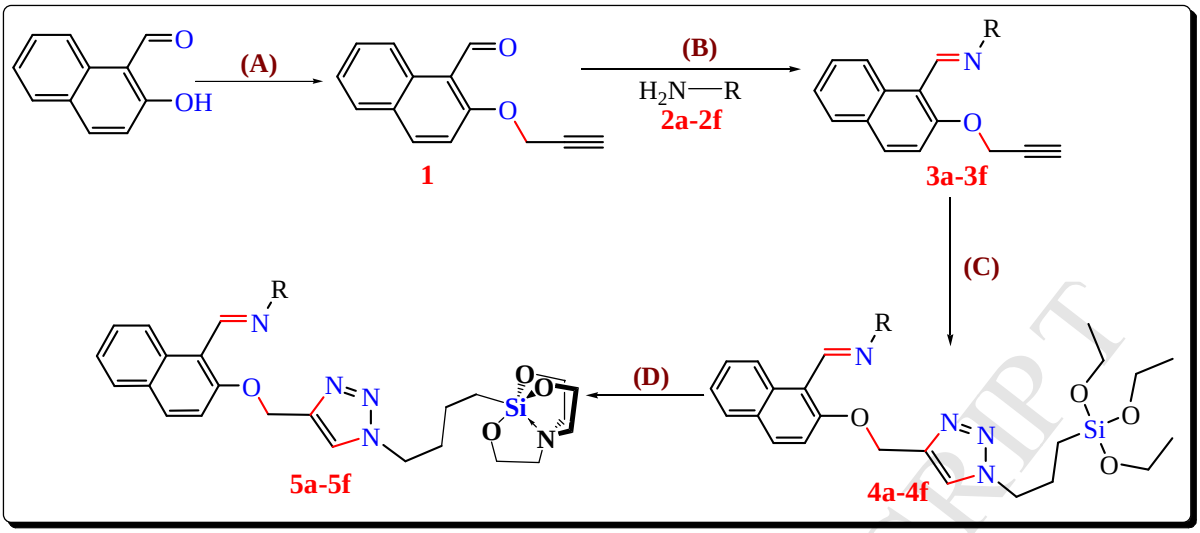
2.5.2. Minimum inhibitory concentration

For MIC assays, a stock solution of 1 mg/ml of each test compound was prepared in ethyl acetate. Further the stock solution was serially diluted in the range of 1 mg/ml to 1.65 µg/ml. Then test compounds at various concentrations were added to the nutrient broth in a 96 well microtitre plate. The different bacterial strains at 10^8 bacterial cells/ml concentrations were added to well in an assigned row. Then microtitre plate was incubated at 37□ overnight and examined for growth of the test organisms. The lowest concentration of the test compound that cleared bacterial growth in a well of the microtitre plate was taken as MIC.

3. Results and discussion

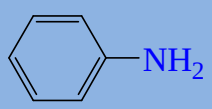
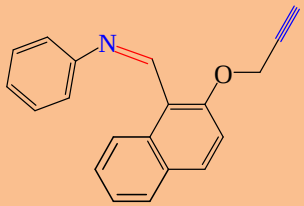
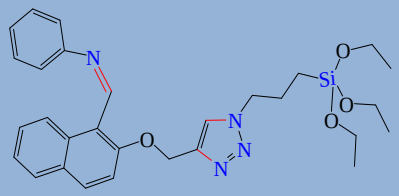
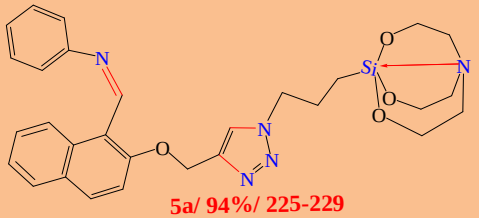
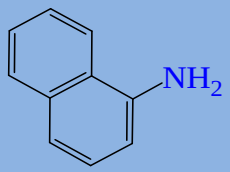
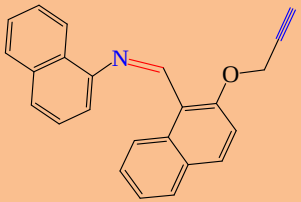
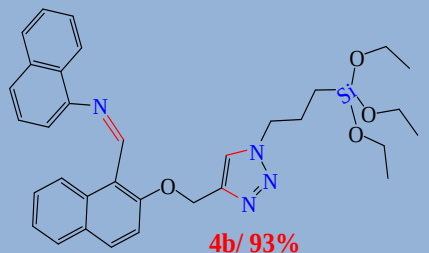
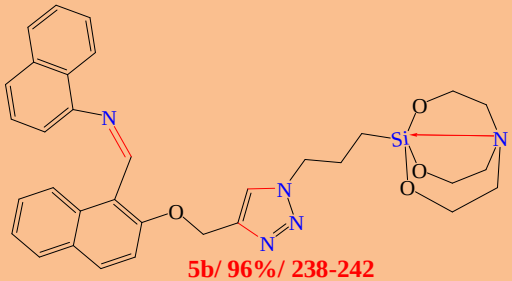
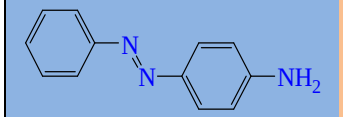
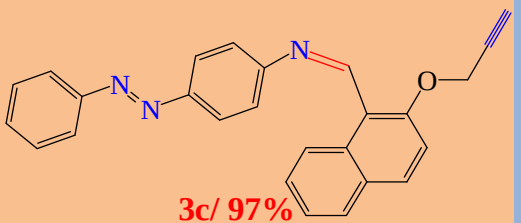
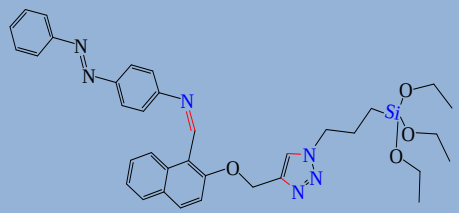
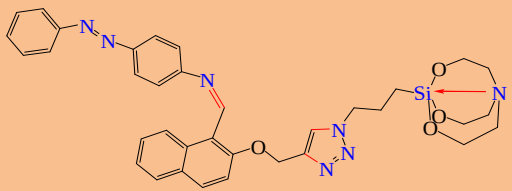
3.1. Synthesis

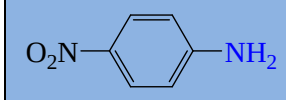
2-hydroxy-1-naphthaldehyde was used as starting ingredient for the synthesis of **SBTBOTS (4a-4f)** and **SBTBS (5a- 5f)** [Scheme 1, Table 1]. Firstly, 2-hydroxy-1-naphthaldehyde was transformed into 2-(prop-2-ynyloxy)-1-naphthaldehyde (**1**) by the reaction with propargyl bromide in DMF assisted by base K_2CO_3. Treatment of (**1**) with amines **(2a-2f)** gave Schiff based alkynes **SBA (3a-3f)**. These **SBA (3a-3f)** were then coupled with 3-AzPTES via copper-catalyzed azide–alkyne cycloaddition reaction to form Schiff based 1, 2, 3-triazole bridged triethoxysilanes (**SBTBOTS - 4a-4f).** This strategy is based on the tremendously efficient $CuBr(PPh_3)_3$–THF–Et_3N set-up. Finally, transesterification reaction of the synthesized **SBTBOTS** with triethanolamine in toluene, catalysed by KOH yielded **SBTBS** in good yields. These silatranes were observed to be hydrolytically more stable than their corresponding triethoxysilane analogues.



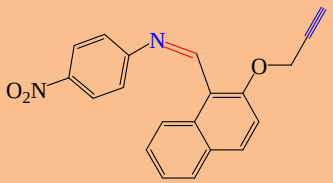
Scheme 1. (A) Propargyl bromide, K_2CO_3, DMF, 24h (B) amine **2a-2f**, ethanol, reflux, 4h, (C) AzPTES, $Cu(PPh_3)_3Br$, Et_3N, THF, 5h, 60^oC (D) Triethanolamine, KOH, toluene, 6h.

Table 1: Synthesised schiff based terminal alkynes (**3a-3f**) organotrialkoxysilanes (**4a-4f**) and silatranes (**5a-5f**).

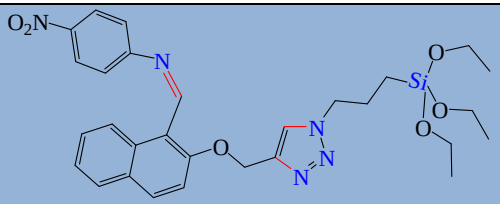
Substrate amines (2a–2f)	(SBA) (3a–3f)	(SBTBOTS) (4a–4f)/ Yield	(SBTBS) (5a–5f)/ Yield/ M.Pt. (℃)
 **2a**	 **3a/ 99%**	 **4a/ 96%**	 **5a/ 94%/ 225-229**
 **2b**	 **3b/ 95%**	 **4b/ 93%**	 **5b/ 96%/ 238-242**
 **2c**	 **3c/ 97%**	 **4c/ 97%**	 **5c/ 91%/ 232-235**



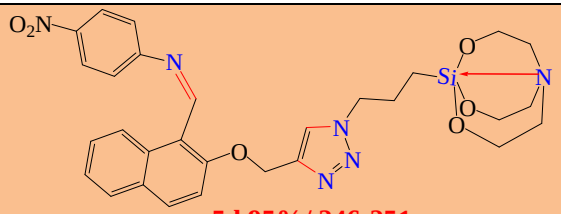
2d



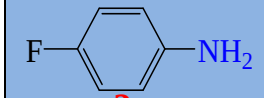
3d 98%



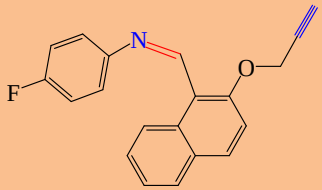
4d/ 98%



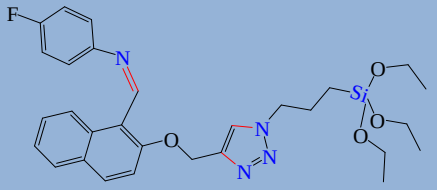
5d 95%/ 246-251



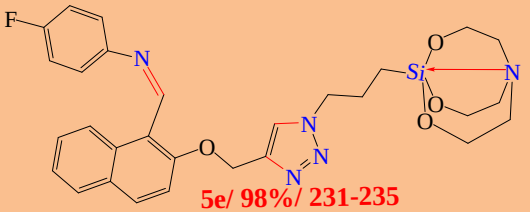
2e



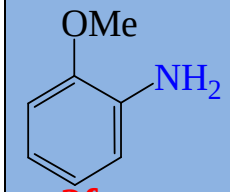
3e/ 99%



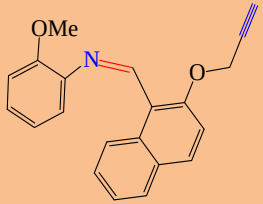
4e/ 95%



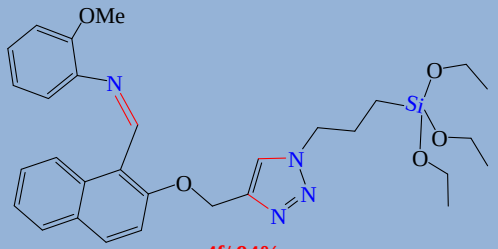
5e/ 98%/ 231-235



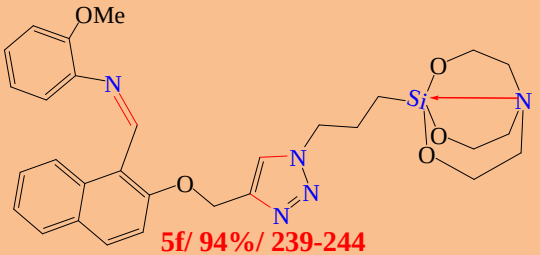
2f



3f/ 95%



4f/ 94%



5f/ 94%/ 239-244

3.2. NMR spectroscopy

^{1}H NMR spectra of **SBTBS (5a- 5f)** on enthusiastic observation revealed almost similar vogue in signals as sketched in NMR study of **SBTBOTS (4a-4f)**. All the silatranes (**5a-5f**) manifested a set of multiplets due to –CH_2 unit of propyl chain in the range of δ 1.99 – 1.78 ppm. The –OCH_2 clamped to 1, 2, 3-triazole heterocycle was extremely de-shielded which appeared at δ 5.40–5.22 ppm. The aromatic ring protons conjugated with Schiff base segment were signalled as multiplets in the region δ 8.21–7.11 ppm. The Schiff base proton ─CH═N appeared in the range of δ 9.25-9.15 ppm. The aromatic protons of Naphthalene ring signalled at δ 9.68 – 9.545 ppm. Moreover, -OCH_2CN protons of atrane ring appeared as triplet in the region δ 3.85–3.65 ppm. The NMR spectra of silatrane varied from silane by the complete disappearance of a quartet and triplet at δ 3.85–3.65 ppm and δ 1.21–1.10 ppm and origination of two new triplets with δ 3.76–3.42 due to –NCH_2CH_2O– and at δ 2.80– 2.61 due to –NCH_2CH_2O– arms of atrane ring. One more crucial shift in NMR was noticed for methylene proton of –CH_2Si in which peak switched from the maximum of δ 0.72 ppm to the minimum range of δ 0.35 ppm. Any other extra effect due to attachment of distinct moieties at ─CH═N site was negligible on other aromatic protons. In ^{13}C NMR spectra, the considerable shift was observed due to –N_3C– of 1, 2, 3-triazole as it fetched from δ 60.1–52.3 ppm to of δ 131.2–127.8 ppm. The methylene carbon of propyl chain associated to silicon atom –C–Si– materialized as the most shielded carbon atom at around δ 7.4 ppm for triethoxysilanes **4a–4f** which was displaced from δ 10–7 ppm to δ 17.3–9.5 ppm for compounds **5a–5f** designated prompting of hypervalency at silicon center. For silatranes, the –OCCN– of atrane cage framework appeared in the range δ 62.1–52.5 ppm while –OCCN– appeared at δ 51.6–46.8 ppm.

3.3. IR spectroscopy

The neat vibrational spectroscopic statistics for all compounds was recorded in the region 4000–400 cm^{-1}. All the resulting frequencies in terms of IR spectra were in fulfilment with the awaited structure of synthesized compounds. The complete clear region in the range 2180–2065 cm^{-1} authenticate complete cyclization of AzPTES and SBA (**3a–3f)** to 1, 2, 3-triazole bridged triethoxysilanes (**4a–4f)**. There were keen absorption bands in the region

3025–2799 cm^{-1} and 1670–1456 cm^{-1} that congruous to aromatic conjugation in Schiff base substituents and 1,2,3-triazole ring. The transannular bond N–Si in the silatranes **5a–5f** was signalled by the absorption bands in the region 752–525 cm^{-1}. The –CH vibrations in FTIR spectra of all triethoxysilanes **4a–4f** were depicted near 2990–2715 cm^{-1}. The CH═N segment gave sharp peak at 1648 cm^{-1}.

3.4. Biological studies

All the compounds (**5a-5f**) were screened for their antibacterial activity against gram positive and gram negative bacteria by well plate assay (Table 2). Interestingly, all of them were found positive for their activity against *K. pneumoniae* B5O55, *P. aeruginosa* PAO1, *S. aureus* MRSA and *S. epidermidis* 3382 viewed as clear zones on nutrient agar plates.

Table 2. Antibacterial activity of Schiff based 1, 2, 3-triazole linked silatranes

Bacterial agent	**MIC (µg/ml)**	**Compound**
K. pneumoniae 43816	16.5 ± 1.66	CEFEPIME
P. aeruginosa PAO1	16.5 ± 2.12	
S. aureus MRSA	3.25 ± 0.053	
S. epidermidis 3382	3.25 ± 0.027	
K. pneumoniae 43816	625 ± 26.5	CONTROL
P. aeruginosa PAO1	625 ± 53	
S. aureus MRSA	312 ± 13.25	
S. epidermidis 3382	312 ± 26.5	
K. pneumoniae 43816	106 ± 3.32	5a
P. aeruginosa PAO1	106 ± 6.75	
S. aureus MRSA	53 ± 3.32	
S. epidermidis 3382	53 ± 6.75	
*K. pneumoniae*43816	312 ± 13.25	5b
P. aeruginosa PAO1	106 ± 6.75	
S. aureus MRSA	53 ± 3.32	
S. epidermidis 3382	53 ± 3.32s	
K. pneumoniae 43816	106 ± 6.75	5c
P. aeruginosa PAO1	106 ± 13.50	
S. aureus MRSA	26.5 ± 3.32	
S. epidermidis 3382	53 ± 6.75	
K. pneumoniae 43816	106 ± 12.50	5f
P. aeruginosa PAO1	106 ± 6.75	
S. aureus MRSA	26.5± 1.66	
S. epidermidis 3382	26.5± 3.32	
*K. pneumoniae*43816	26.5± 1.66	5d
P. aeruginosa PAO1	26.5± 1.66	
S. aureus MRSA	13.25± 1.66	
S. epidermidis 3382	13.25± 3.32	

K. pneumoniae 43816	26.5± 3.32	5e
P. aeruginosa PAO1	13.25± 0.83	
S. aureus MRSA	3.25± 0.41	
S. epidermidis 3382	3.25± 0.83	

The minimum inhibitory concentration of these compounds was determined by following the method given by Balouiri *et al* [25]. The MIC of these compounds was compared to that of cefepime which is a drug of choice against gram positive as well as gram negative bacteria. By virtue of the presence of an outer membrane, Gram negative bacteria are generally more resistant towards a particular antibiotic than their Gram positive cousins [26]. Hence, all chemical compounds were found to be more effective against gram positive bacteria as compared to their gram negative cousins. For gram negative bacteria, **5d** and **5f** were seen as the drugs of choice with MIC of 26.5µg/ml and 26.5 µg/ml against *K. pneumoniae* B5O55 respectively and MIC of 26.5µg/ml and 13.25µg/ml against *P. aeruginosa* PAO1 respectively. Interestingly **5f** was highly active against *S. aureus* MRSA and *S. epidermidis* 4432 with an MIC of 3.25µg/ml each respectively. The high activity of **5f** can be due to the presence of electron donating methoxy group. Hence the activity of **5f** was comparable to the activity of cefepime and could be considered a highly potent antibacterial compound for future however, it's *in vitro* cell cytotoxicity and *in vivo* activity will determine its future use.

3.5. Theoretical studies

The structure of Schiff based 1, 2, 3-triazole linked silatrane **5a** was optimized using DFT calculations by employing B3LYP/6-31+G(d) level of theory. The optimized structure and its HOMO and LUMO orbitals are showm in figure 2.

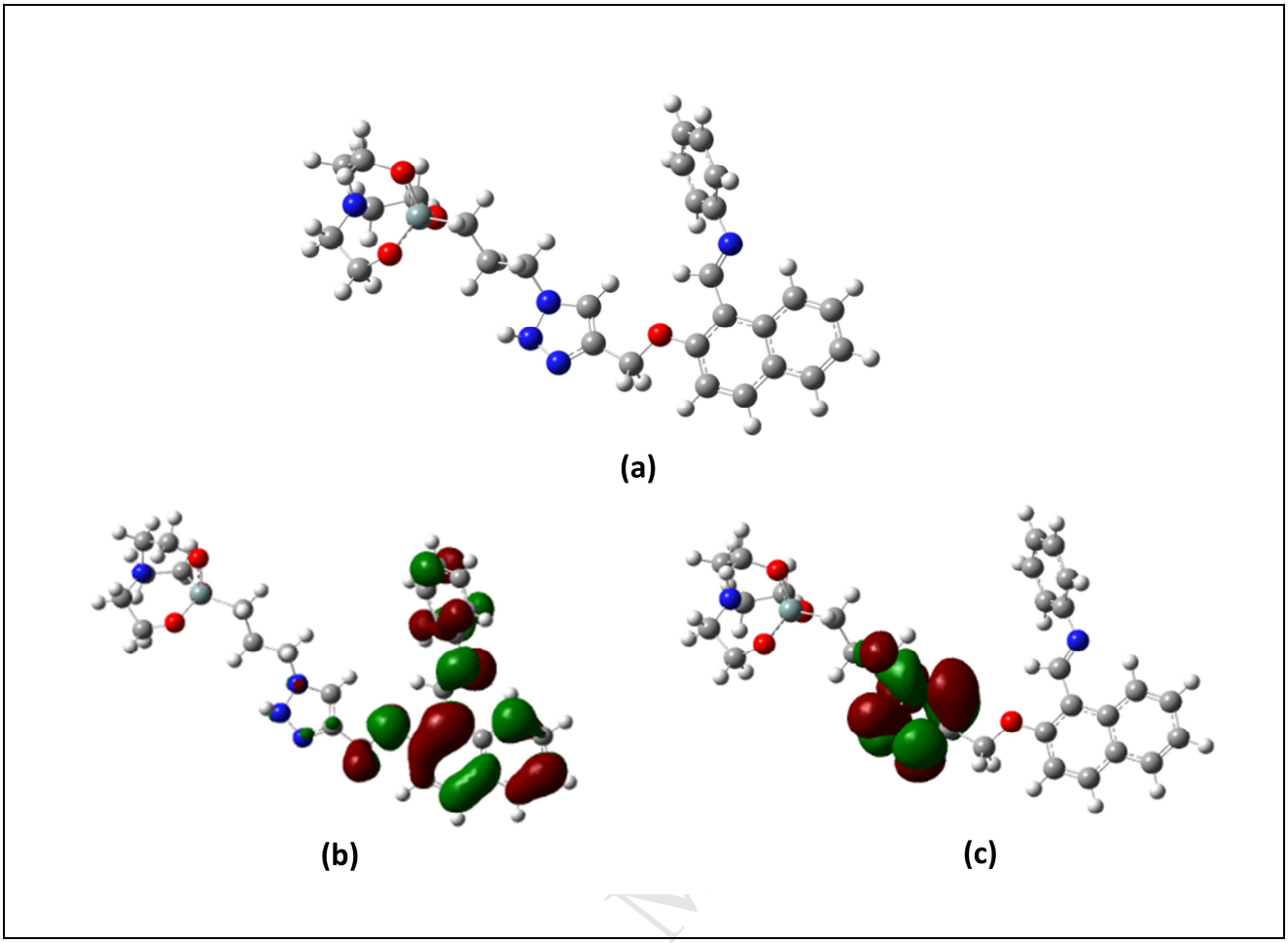


Figure 2. (a) Optimized structure of **5a** along with its (b) HOMO and (c) LUMO orbitals

4. Conclusions

2-hydroxy-1-naphthaldehyde derived SBA and organosilicon compounds were productively manufactured using an exclusive copper-catalyzed click approach. The resulting organosilatranes were characterized by IR spectroscopy, NMR (1H and 13C) spectroscopy, and elemental analysis. The synthesized compounds were applied for their use as antibacterial agents against gram positive and gram negative bacteria. The results showed that all the compounds showed significant activity but they were more effective against gram positive bacteria as compared to their gram negative counterparts. Also it was observed that the activity of compound **5f** was even comparable to the drug in use.

Acknowledgments

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Research Highlights

- Schiff based 1,2,3-triazole bridged organotriethoxysilanes (SBTBOTS) and Schiff based 1,2,3-triazole bridged silatrane (SBTBS) have synthesized.
- The synthesis has been done using Cu (I) assisted click silylation reaction.
- The synthesized silatranes were evaluated for their antibacterial activity against gram positive and gram negative bacteria