Design, Synthesis, Drug-Likeness And In Silico Prediction of Polycyclic Aromatic Schiff Base Tethered Organosilatrane

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Abstract

The present article includes the generation of aromatic Schiff base tethered organosilatrane via two step synthetic pathways starting from anthracene-10-carbaldehyde and 1H-indole-3-carbaldehyde. The synthesis was achieved by employing condensation reaction followed by transesterification methodology. The prepared organosilatrane containing aromatic schiff based ligands were structurally authenticated using spectroscopic techniques such as FT-IR, NMR and mass analysis. The prepared compounds were also scrutinized for in silico physiochemical properties via Molinspiration and ADMET software and the results revealed their good biological potential for drug discovery.

1. Introduction

Silatrane is made up of two words; 'sila' and 'atrané' where 'sila' originates from silicon and 'atrané' signifies a group of tricyclic caged heterocycles containing transannular dative bond between nitrogen and a heteroatom ring [1–3]. Therefore, a tricyclic ring structured molecule bearing silicon as heteroatom is known as silatrane. Alternatively silatrane, with general formula $N[(CR_1R_2)_nO]_3SiR$, can be considered as hypervalent silicon species surrounded by three oxygen atoms and an exocyclic substrate. It includes three heterocyclic caged structures with triethanolamine and transannular bond between nitrogen and silicon atom [4]. These pentacoordinated compounds acquire distorted trigonal bipyramidal geometry around silicon atom. The transannular dative bond between nitrogen and silicon is the feature of interest on account of its uniqueness of molecular structure, architectural beauty and peculiar stereoelectronic and chemical properties [5–10]. The strength (bond length) of transannular dative bond ($N \rightarrow Si$) depends upon exocyclic substrate attached to the silicon atom. Nevertheless, in general, the bond length of $N \rightarrow Si$ lies between 1.965 Å and 2.24 Å except in the complexes of silatrane with noble metals. Two configurations of silatrane exist with respect to nitrogen atom; exo and endo configurations where interatomic distance ($N \rightarrow Si$) in exo and endo are 2.35–2.45 Å and 2.9–3.0 Å respectively [11–12]. The practical applications of silatrane can be seen in various fields such as in medicine, it is employed as anticancer, antimicrobial, anti-inflammatory and anti-tumour agents and affects the germination rate of barley seeds in field of agriculture [13–20]. Further, owing to hydrolytically stable nature, it regulates the hydrolysis rate and condensation processes in the field of sol-gel processes. Moreover, silatrane is also used as adhesive promoter and strong reducing agent for conversion in organic synthesis [21–32].

Schiff bases are generated by the condensation reaction between primary amines and aldehydes. This is an important class of compounds chiefly due to their ease of preparation, structural diversity, good solubility, redox, magnetic, spectral, and catalytic properties in common solvents. The imine group in them can bind to the transition metal ions easily because of the presence of lone pair on nitrogen atom. Numerous Schiff bases of aromatic compounds are well known for biological and chemosensing applications as per earlier reports [33–36]. Anthracene, consisting of three fused benzene rings, is a component of coal tar and is employed for the production of the dyes such as red dye alizarin while indole is a nitrogen-based heterocyclic scaffold whose compounds are most significant owing to their biological and pharmaceutical activities. Anthracene and indole are polycyclic aromatic molecules whose

photophysical properties have been found to be easily tuned via structural modifications. The tunability of anthracene and indole makes them for use in luminescent devices, such as photoprobes and organic light emitting diodes. In this present work, we have synthesized aromatic Schiff base tethered organosilatrane using anthracene and indole carboxyaldehyde as starting materials which can reveal remarkable significance in various research fields.

2. Experimental Section

2.1. Material and methods

The synthesis was carried out under high vacuum using schlenk apparatus under inert atmosphere. The solvents were obtained from commercial sources and were used after drying. Anthracene-10-carbaldehyde and 1H-indole-3-carbaldehyde were used as received from Sigma-Aldrich. The neat FT-IR spectra were traced by using Thermo Scientific NICOLET IS50 spectrophotometer. NMR spectrum [^1H (400 MHz) and ^{13}C (100 MHz)] were outlined via multinuclear FT NMR spectrometer model Avance-II (Bruker). The mass spectral data was recorded on WATERS, Q-TOF micro MASS spectrometer (ESI source having capillary voltage, 3000 V).

2.2. Synthesis and Characterization

2.2.1. General procedure for synthesis of silanes and silatrane

Aromatic aldehydes (1 equi) were dissolved in toluene (20ml) and stirred for 10-15 min under the nitrogen atmosphere by using Schlenk apparatus. Later N^1 -(3-(triethoxysilyl) propyl) ethane-1, 2-diamine (1 equi) was added under same condition and refluxed the reaction mixture for 4h at 100°C. The solvent was evaporated under high vacuum and organosilanes were obtained as oily liquid. Further the organosilanes (1equi.) were dissolved in toluene containing potassium hydroxide in a catalytic amount. To this solution, addition of triethanolamine under the nitrogen atmosphere was done followed by stirring for 10-15 min at room temperature. This reaction mixture was refluxed for 4 h at 100°C that results the removal of ethanol azeotropically which was formed as byproduct. Subsequently, the reaction mixture was kept at room temperature and the solvent was evaporated under high vacuum followed by the addition of hexane (2ml). The solvent was decanted off to get the desired product.

(Z)-N1-(3-(2,8,9-trioxa-5-aza-1-sila-bicyclo[3.3.3]undecan-1-yl)propyl)-N2-(anthracen-10-ylmethylene)ethane-1,2-diamine (6a)

Anal. Calcd. for $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_3\text{Si}$: C, 67.35; H, 7.17; N, 9.06. Found: C, 67.11; H, 7.08; N, 8.99. ^1H NMR (400 MHz, CDCl_3) δ 8.54 (s, 1H), 8.41 – 8.29 (m, 1H), 8.18 – 7.82 (m, 3H), 7.54 – 7.39 (m, 4H), 7.31 (d, J = 1.4 Hz, 1H), 3.54 (d, J = 5.4 Hz, 6H), 3.45 – 3.40 (m, 2H), 2.80 – 2.77 (m, 2H), 2.63 – 2.57 (m, 2H), 2.49 – 2.45 (m, 6H), 1.26 (t, J = 2.8 Hz, 2H), 0.93 – 0.80 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 133.59, 131.34, 128.23,

127.22, 126.37, 119.44, 77.30, 77.25, 77.05, 76.79, 67.45, 65.84, 60.29, 59.12, 57.76, 56.96, 56.82, 51.08, 50.84, 15.27, 1.01, 0.00.

(Z)-N1-((1H-indol-3-yl)methylene)-N2-(3-(2,8,9-trioxa-5-aza-1-sila-bicyclo[3.3.3]undecan-1-yl)propyl)ethane-1,2-diamine (6b)

Anal. Calcd. for C₂₀H₃₀N₄O₃Si: C, 59.67; H, 7.51; N, 13.92. Found: C, 59.45; H, 7.40; N, 13.89. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.38 (dd, *J* = 21.2, 8.1 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 19.8 Hz, 1H), 3.98 (s, 1H), 3.61 (s, 6H), 3.48 (q, *J* = 7.0 Hz, 2H), 2.80 (d, *J* = 6.2 Hz, 2H), 2.53 (s, 6H), 1.63 (dd, *J* = 6.9, 3.4 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 2H), 0.89 – 0.84 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 135.72, 128.29, 127.87, 126.39, 124.05, 123.15, 121.85, 121.55, 120.67, 120.00, 119.67, 119.31, 118.35, 116.01, 109.96, 103.40, 77.29, 77.24, 77.04, 76.79, 59.09, 57.81, 57.71, 56.93, 51.15, 31.59, 29.31, 23.87, 22.05, 15.27, 14.11, 12.78, 8.77, 1.02, 0.00.

(Z)-N1-(anthracen-10-ylmethylene)-N2-(3-(3,7,10-trimethyl-2,8,9-trioxa-5-aza-1-sila-bicyclo[3.3.3]undecan-1-yl)propyl)ethane-1,2-diamine (7a)

Anal. Calcd. for C₂₉H₃₉N₃O₃Si: C, 68.87; H, 7.77; N, 8.31. Found: C, 68.69; H, 7.62; N, 8.22. ¹H NMR (400 MHz, CDCl₃) δ 8.51 (s, 1H), 8.33 (q, *J* = 6.4, 4.5 Hz, 1H), 8.05 – 7.91 (m, 2H), 7.86 – 7.76 (m, 1H), 7.60 – 7.39 (m, 5H), 3.97 – 3.87 (m, 3H), 3.23 – 3.10 (m, 2H), 2.83 – 2.76 (m, 2H), 2.56 – 2.41 (m, 6H), 2.27 – 2.18 (m, 2H), 1.24 (d, *J* = 14.2 Hz, 2H), 1.11 – 1.07 (m, 9H), 0.45 – 0.34 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 134.14, 130.74, 127.25, 125.80, 106.85, 77.28, 77.23, 77.02, 76.77, 67.68, 66.22, 65.61, 65.52, 20.73, 20.48, 20.41, 20.31, 0.79, 0.01.

(Z)-N1-((1H-indol-3-yl)methylene)-N2-(3-(3,7,10-trimethyl-2,8,9-trioxa-5-aza-1-sila-bicyclo[3.3.3]undecan-1-yl)propyl)ethane-1,2-diamine (7b)

Anal. Calcd. for C₂₃H₃₆N₄O₃Si: C, 62.13; H, 8.16; N, 12.60. Found: C, 61.95; H, 8.07; N, 12.49. ¹H NMR (400 MHz, DMSO) δ 7.54 (s, 1H), 7.36 (dd, *J* = 22.5, 8.3 Hz, 2H), 7.02 – 6.88 (m, 2H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.70 (s, 1H), 3.68 – 3.64 (m, 3H), 2.62 (s, 2H), 2.37 (t, *J* = 10.1 Hz, 6H), 2.21 (d, *J* = 12.4 Hz, 2H), 1.58 (d, *J* = 18.8 Hz, 4H), 1.00 (d, *J* = 7.2 Hz, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 131.85, 131.62, 129.51, 129.09, 128.90, 127.71, 125.35, 77.42, 77.31, 77.10, 76.79, 59.12, 50.73, 32.95, 23.50, 21.98, 9.71, 1.08.

3. Results And Discussion

3.1. Synthesis and characterization

Two steps synthetic procedure has been followed for the synthesis of organosilatrane which is based on the condensation and transesterification reaction (Scheme 1). In the first step, equimolar mixture of aromatic aldehydes (**1**) and N¹-(3-(triethoxysilyl) propyl) ethane-1,2-diamine (**2**) were dissolved in toluene and the reaction mixture was made to undergo condensation reaction to afford the organosilanes. In the

next step, organosilanes were mixed with tripodal ligands (**4** and **5**) in equimolar ratio using toluene as solvent to undergo transesterification reaction and potassium hydroxide was also employed in catalytic amount to give the organosilatrane. The solvent was evaporated under pressure to isolate the hydrolytically stable desired products (Table 1).

Table 1: Synthesized organosilatrane

The structures of organosilatrane were validated by IR, NMR and mass spectroscopy. In the IR spectroscopy of all synthesized compound, characteristics peaks were observed for Schiff base (C=N) in the region of 1600-1650 cm^{-1} , for Si-O bond in the region of 1000-1100 cm^{-1} and for transannular bond between nitrogen and silicon ($\text{Si} \cdots \text{N}$), band lies between 500-550 cm^{-1} . Similarly, NMR spectra also showed the signal in accordance to synthesized structure. The signal appearing for OCH_2 and NCH_2 was present for **6a** and **6b** at $\delta = 3.53$ -3.65 ppm and 2.40-2.60 ppm respectively. These two signals present in equal intensity indicated the formation of silatranyl cage of the prepared compounds. Similarly, the signal was demonstrated for OCH, OCCH_3 and NCH_2 for **7a** and **7b** lies at $\delta = 3.65$ -3.95 ppm, 1.00-1.30 ppm and 2.30-2.50 ppm respectively. Additionally, the aromatic protons and Schiff base proton of **6a-6b** and **7a-7b** were also observed in the region 6.50-8.00 ppm. In ^{13}C NMR spectrum, the carbon next to silicon was seen in shielded region at around $\delta = 20$ ppm. Further, the spectra displayed the signal at around 50 ppm and 60 ppm for NCH_2 and OCH_2 of atrane cage (**6a-6b** and **7a-7b**). The mass spectra of the synthesized organosilatrane showed molecular ion peak confirming their formation.

3.2 Physiochemical Properties

There are numerous chemical methodologies for synthesizing drugs but several drug molecules are toxic in nature and have poor physiochemical properties. Hence, to examine the drug bioavailability of compounds, there are factors affecting parameters for physiochemical properties of drug such as number of rotational bonds, lipophilicity, polar surface area and hydrogen bond donating or accepting power which has been analysed by computational method. These methods involved web server such as MOLINSPIRATION (<http://www.molinspiration.com>) and PreADMET (<http://preadmet.bmrbc.org>) for

study of physiochemical properties for the synthesized compounds [37]. Drug-likeness in synthesized compounds can be evaluated by using the Lipinski's 'rule of five' [38]. According to this rule, drug molecules should complete some basic condition of molecular properties such as number of hydrogen bond donor (HBD) < 5, molecular weight < 500, number of hydrogen bond acceptors (HBA) < 10 and octanol-water partition coefficient (logP) < 5 for productive results. Most of the prepared organosilatrane followed the Lipinski's 'rule of five' as shown in table 2. Moreover, there are some more parameters like number of rotatable bonds (n-ROTB) and polar surface area (PSA) for calculation of bioavailability of drug molecule. This rule articulates that the compounds with low oral bioavailability have n-ROTB >140 and PSA > 140.

Table 2 In silico physicochemical properties of Polycyclic aromatic Schiff base tethered silatrane (6-7)

Comp. ID	M.W.	miLogP	PSA	n-ONACCEPTOR	n-OHNDONAR	nRotB	Lipinski's Violations
Rule	<500	<5		≤10	≤5	<15	≤1
6a	463.65	3.42	55.33	6	1	8	0
7a	505.74	4.51	55.33	6	1	8	1
6b	402.57	1.28	71.12	7	2	8	0
7b	444.65	2.37	71.12	7	2	8	0

The bioactivity score of GPCR ligands, ion channel modulators (ICM), enzyme inhibitor (EI), protease inhibitor (PI), kinase inhibitor (KI) and nuclear receptor ligand (NRL) of the synthesized compounds has been shown in table 3. Greater the value of bioactivity score, probability of compounds to be active will be higher. Hence, compounds having bioactivity score greater than 0.00 is likely to have biological activity, value 0.50 to 0.00 are moderately active and if the score is lower than 0.50 it is presumed to be inactive [39]. All organosilatrane were active on GPCR ligands, kinase inhibitor, protease inhibitor and enzyme inhibitor. Further, all the synthesized compounds (6-7) were moderately active on nuclear receptor ligands. Except 7a as moderate, all the prepared compounds were active on ion channel modulator.

Table 3: The bioactivity score of Polycyclic aromatic Schiff base tethered silatrane (6-7)

Comp. ID	GPCR	ICM	NRL	KI	PI	EI
6a	0.11	0.03	-0.32	0.08	0.03	0.28
7a	0.09	-0.02	-0.35	0.02	0.03	0.24
6b	0.30	0.09	-0.33	0.21	0.01	0.36
7b	0.26	0.07	-0.37	0.12	0.01	0.31

Pharmacokinetic properties like toxicity, metabolism, absorption, excretion and distribution examines the results of drug for the body. ADMET model is an open source for collection of information about drug invention and developmental stages from published reports in high quality dataset. Earlier steps of ADMET calculation predict the range for lead molecules which can assist to save time and expenditure in experimental prediction including worse profile. Therefore, the synthesized compounds were examined for pharmacokinetic assessment to calculate the drug's beneficial absorption (table 4). The strength of drugs to cardiovascular system depends upon the oral absorption which alternatively depends on the activities of various factors like transporters, membrane permeability and drug metabolizing enzymes [40-41]. The degree of transportation via gastro-intestinal tract (GIT) wall is calculated through human intestinal absorption (HIA) factor that assists in determination of absorption viability of a drug via the small intestine. ADMET calculations demonstrated that the compounds consisting of HIA values > 70% are best absorbed compounds. HIA values for the synthesized compounds were lying between the ranges of 93.22-97.66 which suggests the tremendous absorption behaviour.

Table 4. Pharmacokinetic descriptors of Polycyclic aromatic Schiff base tethered silatranes (6-7)

Compound	Caco-2Cell Permeability (nm s ⁻¹)	BBB	HIA	MDCK (nm s ⁻¹)	Plasma Protein Binding (%)	Skin Permeability (log Kp)
6a	22.21	0.11	97.58	88.24	66.43	-2.99
7a	22.24	1.03	97.66	69.09	74.99	-2.52
6b	21.88	0.47	93.23	90.45	25.94	-4.60
7b	21.94	0.93	93.70	23.23	45.80	-4.94

Blood brain barrier (BBB) is another significant parameter for drug's permeability and acts as physiological wall to regulate the passage of compounds via blood to brain [42]. This factor played an important role in pharmaceutical domain because of holding a property of brain protection, central nervous system (CNS) active molecules must cross it and the CNS inactive molecule do not allow to cross it. Thus as per the BBB value shown in table 4, the prepared compounds are adequate absorber since the value lying between 0.1-1. Further, plasma protein binding (PPB) is one of the most important factors for drug distribution which influences the drug's biological half life by the binding capacity with albumin present in blood. Therefore, binding affinity of drugs with blood plasma manipulates the dosage and bioavailability of drug. The binding part of synthesized drugs with plasma protein (PPB) was calculated which comes out to be less than 90% that indicates the compounds will less bind to plasma protein and makes the drug availability for diffusion and transportation through cell membranes to enable its interaction with target [43]. Caco-2 and MDCK (MadinDarbey Canine Kidney) cell models were employed for evaluating the drug cell absorption. Caco-2 cell line is a thin layer human bladder epithelial

cancer cell line that works as an imitator for paracellular flow of compounds through the intestinal mucosa. This model has two significance; simplicity and reproducibility which supports in accessing the oral absorption of potential drug candidate. MDCK cells can also be employed for scrutiny of fast membrane permeability [44-45]. The calculated value of Caco-2 and MDCK for compounds showed satisfactory results for epithelial permeability. The other parameter which is used for measuring the transdermal delivery of drugs is known as skin permeability denoted as log K_p by the following equation (1)

$$K_p = K_m \cdot D/h \quad (1)$$

where K_m denotes as distribution coefficient between stratum corneum and vehicle. D and h are the average diffusion coefficient (cm²/h) and thickness of skin (cm) respectively. The estimated skin permeability values for designed compounds lies in the range of 2.5194- 4.9434. This calculated result of physio-chemical properties for designed compounds (6-7) reveals that values are in acceptable range as expected and so, the synthesized compounds fulfils the conditions for well-behaved drug molecule.

4. Conclusion

In this work, aromatic Schiff base linked organosilatrane have been synthesized. A two step pathway was employed for the synthesis of designed molecules and the condensation and transesterification methodologies gave good yields of the desired compounds. The structures of prepared organosilatrane were characterized by spectroscopic techniques such as FT-IR, NMR and Mass spectroscopy. Organosilatrane were also examined for *in silico* physiochemical properties with the help of Molinspiration and ADMET software for examining their biological potential. The results showed that the generated compounds have the potential to be used for drug discovery.

Declarations

There is no conflict of interest.

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Scheme

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