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Research Article

Molecular Docking and Quantitative Structure Activity Relationship (QSAR) Studies of Some Newly Synthesized Poly (Azomethine) Esters

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Molecular docking procedure is well known for the investigation of small molecules; however, for macromolecules, it has attained limited success so far. Thus, in an attempt, a series of poly (azomethine) esters was synthesized in a laboratory, and their model oligomer units were studied by computer-aided computational MOE software package to investigate, specifically, binding modes that could influence their anticancer activities. Poly (azomethine) ester (PAME) was prepared by solution phase polycondensation of a preformed Schiff base (SB) 4-((4-(4-(4-hydroxybenzylideneamino)phenoxy)phenylimino)methyl) phenol with terephthaloyl chloride (TC). Terpolymers (PAMEF, PAMEB, PAMESi, PAMEPr, and PAMEH) were synthesized by the incorporation of various moieties along with TC and SB in the main chain. Structural elucidation was carried out by spectroscopic studies and elemental analysis. Docking procedure, adopted to investigate anticancer activity, showed that material was docked in the same pocket of active site as by anticancer protein complex (PDB code: 1T69). Molecular docking along with the quantitative structure activity relationship (QSAR) investigations showed groove binding as a preferred mode between the material and double-stranded DNA (PDB ID-1BNA). Binding strength indicated worthy correlation with various physicochemical parameters of the material like hydrophobic surface area (V_{surf}), E_{HOMO}, E_{LUMO}, log P, and molar refractivity (M_R). Calculated values for the formation constant (K_f) showed good binding strength for polymer-DNA complex. Consequently, the synthesized material is expected to exhibit anticancer activities and could be studied further as anticancer drugs.

1. Introduction

Extensive use of antibiotics against microbes has diverted research to the growth of new antimicrobial agents as well as for the modification of known drugs. Cancer ranks high among all human diseases and is still in need of effective therapy [1–6]. Schiff bases are known as a versatile class of compounds that have significant properties and wide range of applications in dyes, pigments, catalysts, chemosensors, and intermediates in organic synthesis. They also exhibit applications in pharmaceutics to develop medicines such as herbicidal, antibacterial, antiviral, antifungal, anti-inflammatory, antioxidants, antimalarial, antineoplastic, anticancerous, and antitumor. In recent years, ester derivatives of aromatic Schiff bases have been reported for biological applications. Therefore, poly(Schiff base) based esters were synthesized with aliphatic and aromatic moieties to evaluate these as promising new antitumor, antioxidant, and anti-inflammatory agents using molecular docking studies [5–9]. Development of docking techniques to study

explicit interactions between newly synthesized biological material and DNA is a very promising platform for advancements in medicine and biotechnology, mainly, in the anticancer drug design area. Quantitative structure activity relationship (QSAR) approach has been widely used to design the drugs. Histone deacetylase inhibitors (HDACIs) represent a new class of compounds for the treatment of cancers. In current studies, molecular docking has been carried out on monomers with the aim of identifying their anticancer activity in human HDAC8 binding and activation [7–15].

We report, here, synthesis, structural elucidation, and molecular docking studies of some novel poly (Schiff bases). In this study, the interaction of material with the ds. DNA was carried out, wherein two types of three-molecular field descriptors (or field points) as extrema of electrostatic, steric, and hydrophobic fields are investigated and described. These field points are used to define the properties necessary for a molecule to bind in a characteristic way into a specified active site. Molecular docking simulation was used to predict the modes of interactions of the polymers with the DNA. There are reports on the molecular docking studies of nanoparticles, of metal complexes, and of their potential applications in various fields; however, the literature on the study of poly (Schiff bases) is scarce. Hence, the studies of the synthesized polymers were performed on anticancer protein complex (PDB code: 1T69) by means of Molecular Operating Environment (MOE) software (MOE, 2010.11).

2. Experimental

2.1. Materials. Terephthaloyl chloride (m.p = 43–44°C), 4-hydroxybenzalde (m.p = 112–114°C), 4,4′-oxydianiline (m.p = 188–192°C), 1,3-propanediol (211–217°C, Sigma Aldrich), 1,6-hexanediol (250°C, Sigma Aldrich), poly (dimethylsiloxane), hydroxyl-terminated ($n = 550$) (Sigma Aldrich), (1,1, 1,3,3,3-hexafluoro) bisphenol propane (160–163°C, Sigma Aldrich), and bisphenol A (158–159°C, Sigma Aldrich) were used as received. The solvents dichloromethane, ethanol (Sigma Aldrich), and dimethyl sulfoxide were purchased (Sigma Aldrich) and purified by standard reported methods for the experiments [12].

2.2. Equipment. Mel-Temp. (Mitamura Riken Kogyo Inc.) was used to determine melting point by open capillary tubes. FTIR analysis was carried out to get FTIR spectra on FTIR spectrophotometer, Perkin Elmer 1600 series. Nuclear magnetic resonance spectra were recorded on a Bruker avance 300 digital NMR solvent in DMSO-d_6, and tetramethylsilane was used as an internal standard. Elemental analyses (CHNS) were carried out on a Vaio-EL instrument. A commercial light-scattering spectrometer, BI-APD with BI9000AT digital auto correlator, was used along with a He-Ne laser (output power~400 mW at $\lambda = 638$ nm) as a light source and relevant measurements were carried out at 25 + 0.1°C.

2.3. Docking Procedure. Docking studies were carried out using MOE-Dock, Chemical Computing Group Inc. on a machine having Pentium 1.6 GHz workstation, 512 MB memory using the Windows operating system [14–18].

The crystal structure of the anticancer protein complex was taken from the Protein Data Bank (PDB id IT69) since they show the pharmacological target developing new drugs for cancer cure. DNA (PDB ID-1BNA) was used for the comprehensive study of interaction and binding mode of the material-DNA complex.

Crystal structures were edited to remove water molecules and were imported into MOE, and then, all hydrogen atoms were added to the structure with their standard geometry followed by their energy minimization using MOPAC 7.0. The resulting model was put into the systematic conformational search at default parameters with RMS gradient of 0.001 kcal/mol using Site Finder. Active sites were identified and dummy atoms were created from the resulting alpha spheres [19, 20]. The backbone and residues were kept fixed and the energy minimization was performed. Root mean square deviation (RMSD) values were used to compare the ligand between the predicted and its corresponding crystal structure. The resulting docked poses with RMSD less than 1.3 Å were clustered together. The lowest energy-minimized pose was used for further analysis.

All synthesized material was docked by the same method. Ten different conformations were chosen carefully for each compound. All other parameters were kept at their default settings. The best conformation of each compound-enzyme complex was designated based on their energy. The resulting docked complex model was then used for calculating the energy parameters using MMFF94x force field energy calculation and predicting the docked interactions at the active site.

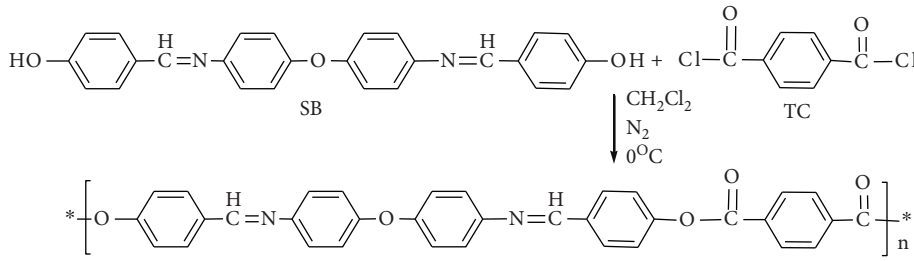
2.4. Methods

2.4.1. Synthesis of Monomers (4-((4-(4-(4-Hydroxybenzylideneamino) Phenoxy) Phenylimino) Methylphenol (SB). The Schiff base monomer (SB) 4-((4-(4-(4-hydroxybenzylideneamino) phenoxy)phenylimino) methylphenol with di-hydroxy at terminal ends was synthesized and characterized by previously reported procedure [13].

2.4.2. Synthesis of Polymer: (PAME). The polymer (PAME) was synthesized by the solution polycondensation of monomer, SB, and terephthaloyl chloride (TC) using a two-necked round-bottom flask equipped with a reflux condenser, hot plate, and magnetic stirrer and ice bath under N_2 atmosphere. SB and TC were taken in a 250 ml round-bottom flask in 100 ml dichloromethane (dried) in 1 : 1 ratio at 0°C followed by dropwise addition of 3–4 ml triethylamine. The mixture was stirred at room temperature for 24 hours and then refluxed for one hour. Yellow precipitated polymer were filtered, washed several times with water and ethanol, dried in air, and weighed [13], Scheme 1.

PAME: 538, yellow, powdered, 86%, FTIR (cm^1, KBr) 3121 (arom-CH), 1733 (C=O), 1105 (-O-), 1630 (-N=CH-). ^{1}HNMR [DMSO-d_6, deuterated dimethyl sulfoxide δ (ppm) (protonated)]: 8.4 (2H, s, azomethine), 7.47–6.9 (aromatic), 2.4 (3H, s, methyl), 2 (1H, s, alcohol), CHNS analysis, calcd; (C 75.01, H 4.45, N 5.43), found; (C 75.83, H 4.10, N 5.22).

2.4.3. Synthesis of Terpolymers (PAMEF, PAMEB, PAMEH, PAMEPr, and PAMESi). The terpolymers (TPAMEs) were



Scheme 1: Synthesis of Polymer (PAME).

formed via polycondensation of two diols and a diacid in a 150 ml round-bottom flask equipped with a reflux condenser and a hot plate with a magnetic stirrer. SB and the diol (Pr, H, Si, B, or F) were added in the flask in dried dichloromethane. Dried N_2 gas was purged into the reaction flask from the gas inlet. The reaction was carried out at 0°C in an ice bath. 4–5 ml triethylamine was added to the flask, dropwise followed by the addition of TC. The ratio for the reactants, Schiff base, diol (Pr, H, Si, B, or F), and the diacid (TC), taken was 1 : 1 : 2. The reaction mixture was stirred for 24 hours and then refluxed for 1 hour. Yellow-colored precipitated polymer was then filtered and washed many times with water to remove impurities i.e., diethyl ammonium chloride and then with ethanol to remove the impurities [13, 14], Scheme 2.

PAMEF: 742, yellow, powdered, 86%, FTIR (cm^1, KBr): 3101 (arom-CH), 1749, 1766 (C=O), 1031, 1039 (-O-), 1638, 1650(-N=CH-). ^{1}HNMR [DMSO-d_6, deuterated dimethyl sulfoxide δ (ppm) (protonated)]: 8.77 (2H, s, azomethine), 7.8–7.2 (aromatic, m), 2.6 (3H, s, methyl), 2.0 (1H, s, alcohol). CHNS analysis, calcd; (C 79.24, H 4.04, N 3.65), found; (C 79.11, H 4.08, N 3.50).

PAMEB: 748, yellow, powdered, 89%, FTIR (cm^1, KBr): 3129 (arom-CH), 1748, 1767 (C=O), 1019, 1014 (-O-), 1625, 1629 (-N=CH-).^{1}HNMR [DMSO-d_6, deuterated dimethyl sulfoxide δ (ppm) (protonated)]: 8.45 (2H, s, azomethine), 7.4–7.1 (aromatic, m), 2.3 (6H, s, methyl), 2.6 (3H, s, methyl), 2.0 (1H, s, alcohol). CHNS analysis, calcd; (C 79.61, H 4.80, N 3.74), found; (C 79.8, H 5.1, N 3.8).

PAMEH: 638, yellow, powdered, 88%, FTIR (cm^1, KBr): 3122 (arom-CH), 2019 (aliphatic-CH), 1703, 1715 (C=O), 1035, 1053 (-O-), 1652, 1651 (-N=CH-). ^{1}HNMR [DMSO-d_6, deuterated dimethyl sulfoxide δ (ppm) (protonated)]: 8.2 (2H, s, azomethine), 7.5–6.8 (aromatic, m), 2.6–2.1 (12H, m, methylene) 2.6 (3H, s, methyl), 2.2 (1H, s, alcohol). CHNS analysis; (C 75.23, H 5.33, N 4.42), found; (C 75.4, H 5.7, N 4.4).

PAMEPr: 596, yellow, powdered, 87%, FTIR (cm^1, KBr): 3151 (arom-CH), 2997 (aliphatic-CH), 1701, 1707 (C=O), 1011, 1024 (-O-), 1640, 1642 (-N=CH-). ^{1}HNMR [DMSO-d_6, deuterated dimethyl sulfoxide δ (ppm) (protonated)]: 8.4 (2H, s, azomethine), 7.2–6.7 (aromatic, m), 2.1–1.6 (m, methyl) 2.6 (3H, s, methyl), 1.9 (1H, s, alcohol).

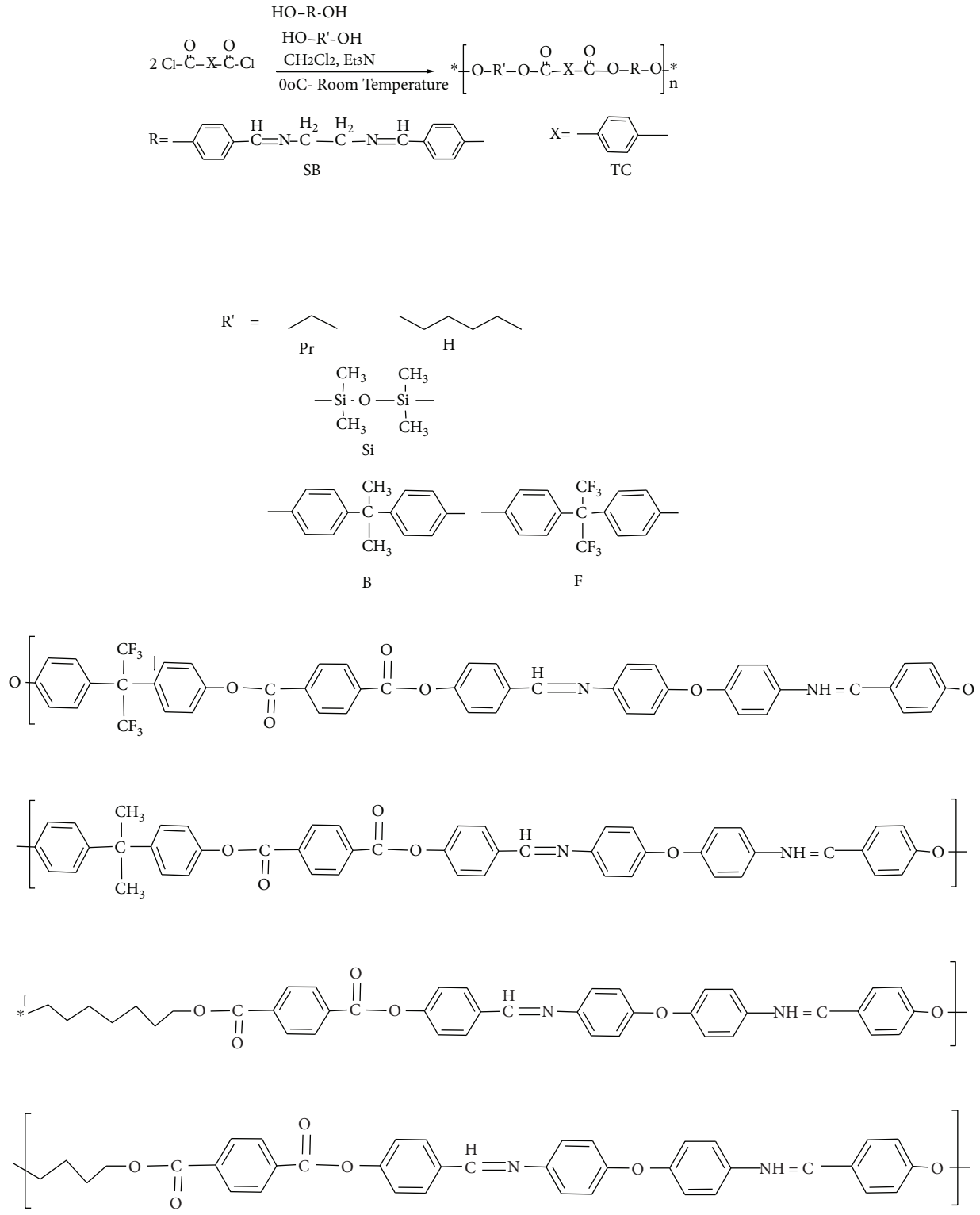
3. Results and Discussion

Schiff base (SB) which was diol-terminated, was prepared by a reported method [15]. Poly (Schiff base) ester (PAME) was prepared by a low-temperature solution polycondensation of terephthaloyl chloride (TC) and *4-((4-(4-(4-hydroxybenzylideneamino)phenoxy)phenylimino)methyl) phenol* (SB). Afterwards, five terpolymers were synthesized by incorporating different alcohols in the macrochain via one-pot three-reactant reaction in an *in situ* procedure for comparative study. The reaction was performed at atmospheric pressure and low temperature to avoid side reactions and decay of the reacting monomers [13–15].

Spectroscopic techniques, FTIR and NMR, were used to confirm the presence of different functional groups in the material (SB, PAME, PAMEF, PAMEB, PAMEH, PAMEPr, and PAMESi), and substantial changes were detected in the spectral behavior of initial reactants and final product.

The structures of the synthesized polymers were confirmed by the typical absorption peaks found at their respective frequencies. Peaks signifying absorption for (C=O) and (C-O) in ranges 1719–1755(s) cm^{-1} and 1102–1205(s) cm^{-1} individually established the presence of ester linkage in the PAME. Another peak in the region 1601–1640(s) cm^{-1} showed the presence of C=N linkage in the macrochain. The absence of broad peak in the region 3400 cm^{-1} congruent with the presence of C-Cl peak about 780–540 cm^{-1} established the occurrence of diacid groups at the ends of the macromolecules. Two similar peaks found in the ester and azomethine area in each terpolymer showed successful integration of alcohols in the parent chain. The FTIR spectra showed specific peaks related to added alcohols in addition to the peaks common in all spectra. The C-H group appeared about 3000–2900 cm^{-1} in the spectra of PAMEH and PAMEPr. The distinguishing FTIR absorption peaks for (Si-O-Si) group present in PAMESi appeared as doublet around 1020 cm^{-1} and 2900 cm^{-1}. The presence of aromatic C-H in polymers PAMEF and PAMEB was confirmed by the presence of peak around 3100 cm^{-1} indicating successful incorporation of diols in the parent chain. The presence of C-Cl in the range 780–540 cm^{-1}along with the disappearance of hydroxyl group peak in all poly (azomethine) ester and its condensation terpolymers revealed that they have acid chloride group at the terminal [14].

Structural analysis of PAME and their TPAMEs was carried out using ^{1}H NMR spectroscopy. The study was carried out after protonation of samples with *p*-toluene sulphonic-acid (dopant engineering), in solvent DMSO, using TMS as internal reference to confirm their structures. ^{1}H NMR showed the presence of all types of proton expected for the proposed structures. Signal in the range 8.3 to 8.7 ppm, common in all spectra, was attributed to the presence of HC=N proton whereas the resonance that appeared in the range



Scheme 2: Synthesis of Terpolymers (PAMEF, PAMEB, PAMEH, and PAMEPr).

6.9 to 7.9 ppm showed aromatic protons. In addition to these signals which were common in all the spectra, the polymer having aliphatic diols (PAMEPr, PAMEH) showed multiplet signal in the range 0.7 to 2.3 ppm (alip–CH). The polymer (PAMEB) showed additional signals in the range 7.0 to 8.0 ppm (aromatic structures of added diols) and 2.3 ppm (-CH_3 present in bisphenol A). PAMEF showed resonance around 7.4 to 8.1 (aromatic rings), slightly deshielded owing to the presence of electronegative F (CF_3) in the diol added. PSiol had extra resonance signals at 1.9 to 2.1 (CH_3 attached to Si).

In order to study the stoichiometry of the polymers, CHNS analysis was performed. The calculations were carried out

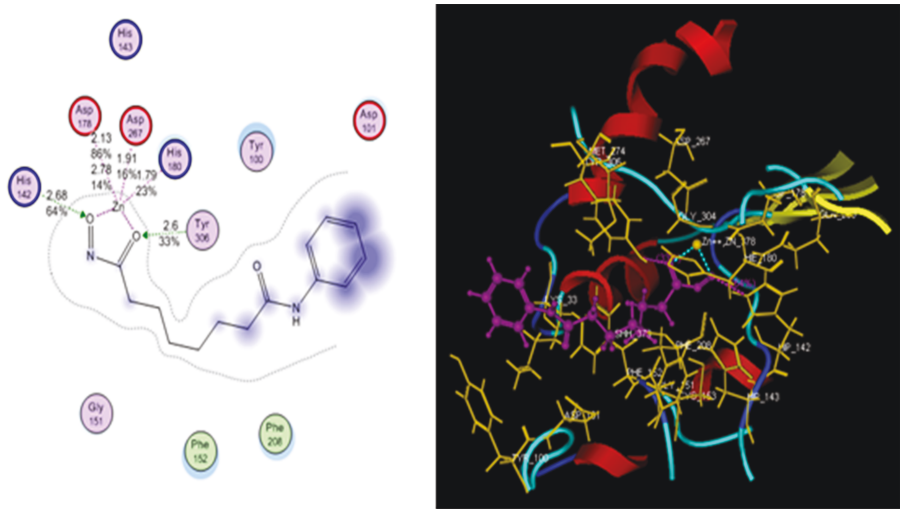


Figure 1: 2D & 3D docking pose of monomer (ball & stick) at IT69 active site, showing the H-bonding (in purple) with key contributing amino acids.

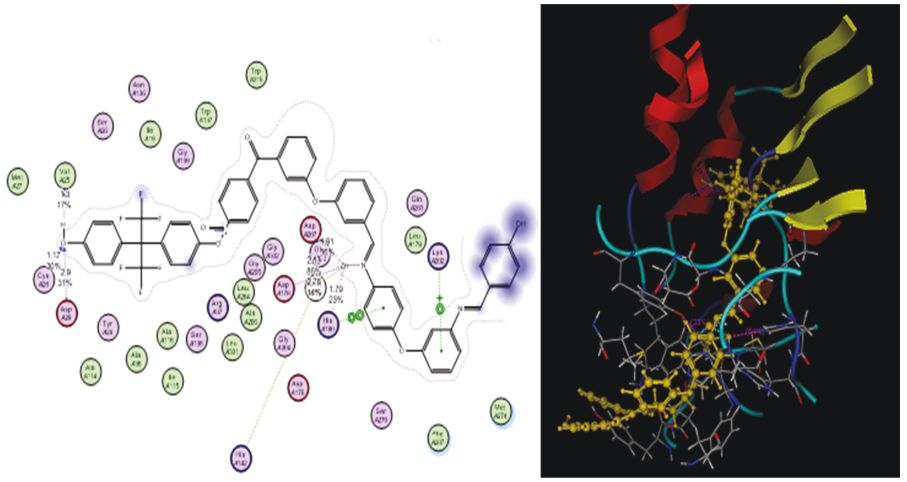


Figure 2: 2D & 3D docking pose of compound (ball & stick) at IT69 active site, showing the H-bonding, arene-π, and π-π interactions; Leu179, Lys202, Ser138, Ser276, His142, His145, Trp137, and Arg37.

based on the structure of repeat units repeated in the chains [13–16]. Data for C, H, and N contents in the material was in good agreement with the hypothetical structures [15, 16].

Molecular weight was determined by LLS and the data is given in supporting information.

3.1. Docking Results. Molecular docking is a reliable procedure which is used to predict binding poses for protein-ligand interactions. Thus, this facile study could be exploited to investigate molecular interaction and the most favorable binding site. In addition, the types of interactions based on the distance between the atoms in the amino acid and ligand could also be determined. Literature on the docking of poly (Schiff base) is scarce due to their macrostructures. In this study, we attempted to study the interactions of synthetic polymer with anticancer protein complex 1T69 and DNA (PDB ID-1BNA) by using oligomeric model compounds. In silico studies of these were expected to play a key role in order to demonstrate chemical diversity and ligand-receptor interaction of imine linkage as a part of structure, Figures 1 and 2 [17–22].

The synthesized material was docked in the active site of 1T69. Various positions of polymer chains were tried to predict the priority for binding site and mode of ligand target interactions. The best conformation for each polymer was selected based on the lowest binding energy. Binding free energy data obtained after docking procedure showed that they exhibit favorable docked complex with the target (Tables 1 and 2). The calculations were also used to predict the anticancer protein-material complex structures and to study possible interactions, based on H-bonding, π-π, and arene-π interactions, within 5 Å range. The material was found to bind in the same pocket of active site as by its actual drug which could be due to the fact that they have aromatic rings and heteroatoms, which based on literature is common to other cancer inhibitors [21, 22].

Table 1: Hydrophobic interaction of docked material with 1T69.

Polymer	His142	His143	His180	Asp168	Asp267	Phe152	Try100	Try306
PAME	+	+	+	−	+	+	+	−
PAMESi	−	−	−	−	−	−	−	−
PAMEPr	−	−	+	+	+	−	+	−
PAMEB	+	+	+	−	+	+	−	−
PAMEF	+	−	+	+	+	+	+	+
PAMEH	+	+	+	+	+	+	+	+
Cocrystallized ligand	+	+	+	+	+	+	+	+

Table 2: Binding interactions observed in 1,5-benzothiazepines with AChE.

Material	Binding energy	Distance (Å)	H-bonding Score (%)	Amino acid	Metal contact	Arene-π	π-π
PAME	−10.07	—	—	—	—	—	
PAMEPr	−7.20	1.79, 1.91	15, 17	Trp137, Ser276	Zn	Lys202, His142, His143, Arg37	
PAMEB	−6.48	1.43, 1.17, 2.9, 1.79, 1.91	23, 16	His180, Asp167	—	His142	His142
PAMEF	−7.22	1.8, 2.13, 2.78, 1.91	17, 30, 31, 16, 23	Val25, cys28, asp29, asp267, his180	Zn	Lys202	His180
PAMEH	−9.96	2.13, 2.68, 1.91, 1.79, 2.6	24, 86, 14, 19	Gly306, asp176, asp176, asp267	Zn	—	—
Cocrystallized ligand	−13.82	3.63, 1.74	86, 64, 16, 23, 33	Asp178, His142, Asp267, His180, Tyr206	Zn	—	—

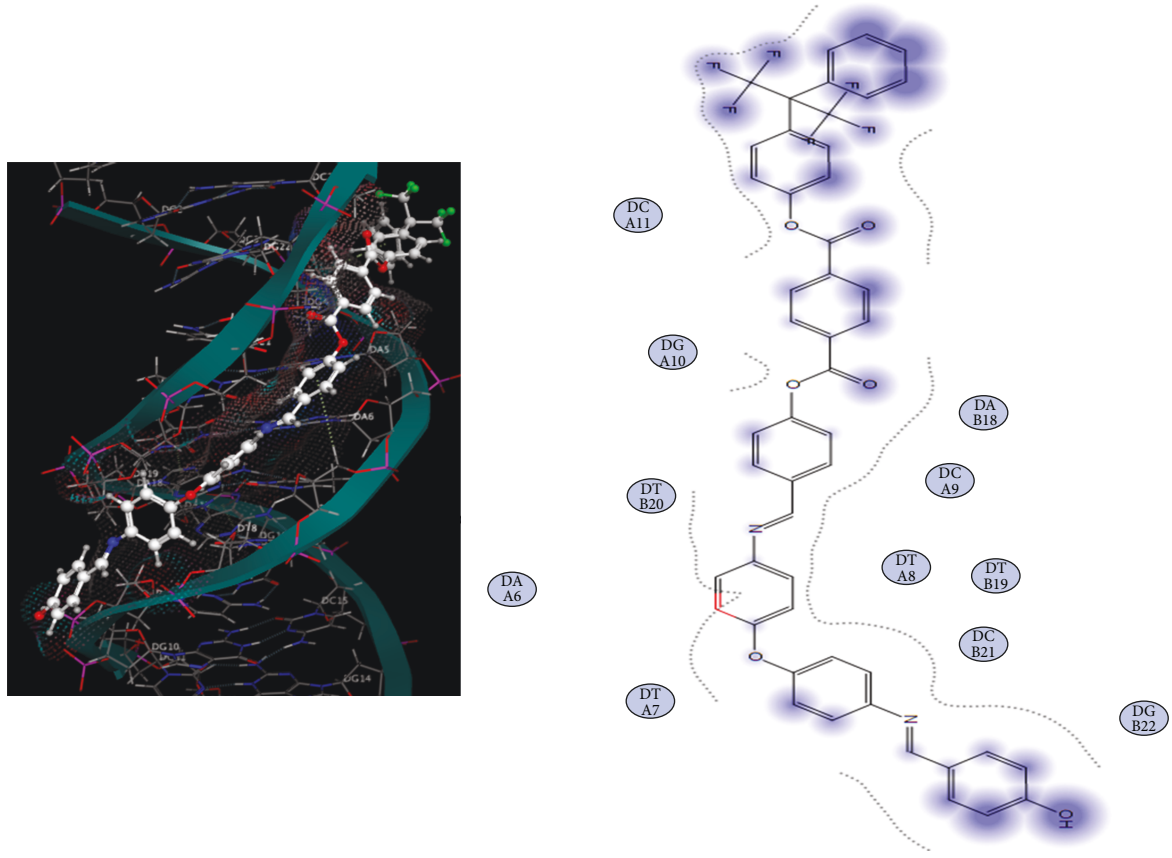
Further study was carried out to investigate polymer-DNA (PDB ID-1BNA) interactions and to explore their preferred binding mode, using MOE, Chemical Computing Inc., 2008. Binding free energy (ΔG), total energy of the complex, (E_{total}), electrostatic interactions (E_{elec}), and ionization potential (E_{IP}) between polymer and DNA were calculated on the basis of force field refinement energy calculations, Figure 3.

Numbers of both electric and molecular descriptors were also calculated with a view to find some possible correlations between the observed binding strength and these descriptors, Tables 3 and 4. A common binding mode was observed for all polymers docked to the DNA with PDB ID-1BNA. The aromatic ring of the monomer and polymers develops hydrophobic interactions with DNA base pairs. H-arene interactions are also formed between the aromatic rings of the polymers and the base pairs that are located in the entrance of the interaction site.

Groove binding was found as a preferred binding mode (in all polymers) which was selected by the external scoring function, spanning maximum number of base pairs. The energetically most favorable conformation of the docked poses (Figures 3–5) revealed that SB, PAMEF, and PAMESi fitted closely into the cavity of the targeted DNA in the minor groove within G–C rich region. There are a number of non-bonding interaction as well such as van der Waals and hydrophobic contacts operating between with DNA bases which describe the stability of groove.

3.2. Quantitative Structure Activity Relationship. For the comprehensive understanding of microscopic interactions and binding between a ligand and a receptor, a detailed analysis in SAR is important. Developing a robust model capable of predicting the property of new molecules in an objective, reliable, and precise manner is the main goal of QSAR modelling. A number of chemical parameters are reported to be responsible for their molecular interactions. The two types of molecular descriptors were calculated by Molecular Operating Environment (MOE), Chemical Computing Group, (Montreal, Canada), in order to derive a quantitative relation between binding strength of compounds and structural properties.

The plot of the electronic descriptors as independent variables against formation constant values as dependent variable is shown in Figures 6 and 7. The most important electronic parameters were energy of the frontier orbitals i.e., E_{HOMO} and E_{LUMO}. Based on frontier molecular orbital theory, the interactions between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are most important. It is generally true that an electron donor increases E_{HOMO} while an electron acceptor decreases it; therefore, compounds substituted with B have a higher E_{HOMO}. Since both E_{HOMO} and E_{LUMO} represent the electronic interactions, a good inverse relation of K_f with these two parameters was observed ($R^2 = 0.9899$). Antitumor drugs substituted with B would be having higher energy frontier orbital values and lower K_f values. Regarding a correlation of the steric parameters with binding strength (K_f), partition coefficient (log P) is representative of steric interactions, and in the present study, it showed a good correlation with K_f of all compounds. A direct correlation of K_f with log P ($R^2 = 0.6323$) was indicative of the fact



(a) (b)

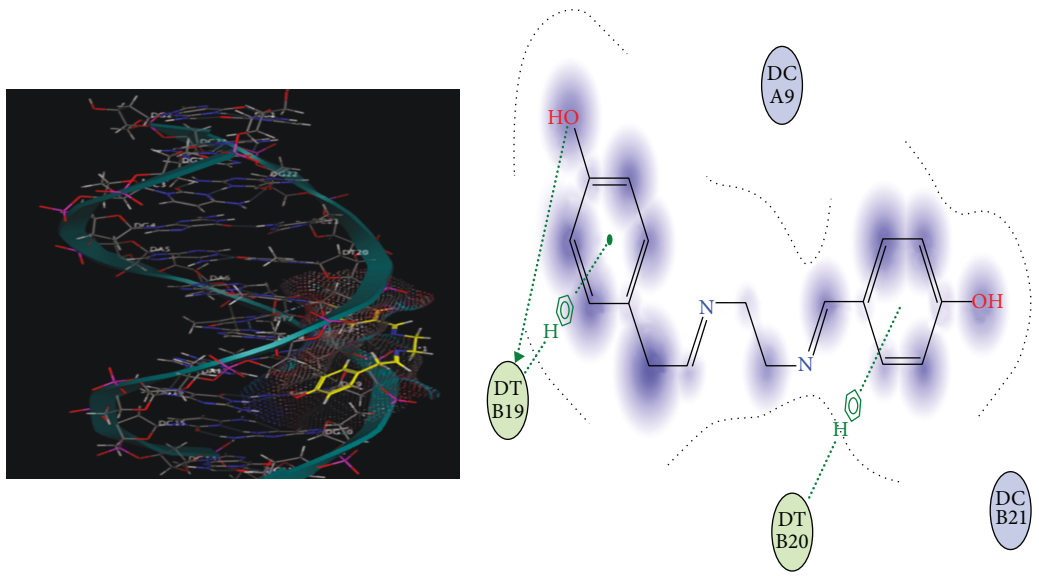
Figure 3: (a) Predicted docked pose of PAMEF polymer (labeled white) monomer with DNA. The docked conformation of the compound is shown in ball and stick representation. (b) Interaction diagrams for PAMEF. Hydrophobic interactions are shown with dotted curves. Green dotted lines represent the arene-arene interactions.

Table 3: Data set of selected electronic descriptors.

Sr. no.	Drugs	E_{HOMO} (Kcal mol^{-1})	E_{LUMO} (Kcal mol^{-1})	E_{ele} (Kcal mol^{-1})	E_{IP} (Kcal mol^{-1})	E_{Total} (Kcal mol^{-1})	K_f/M^{-1}	$-\Delta G$ (Kcal mol^{-1})
1	SB	−8.8378	−0.1785	−488902.2	8.83779	−80197.73	8.00×10^2	16.56
2	PAME	−8.8034	−1.2108	−1,187,857	8.55041	−154387.8	2.98×10^3	19.81
3	PAMEF	—	—	—	—	—	8.28×10^3	22.35
4	PAMEB	−8.6914	−1.2043	−1,846,338	8.69115	−202444.9	1.59×10^4	23.96
5	PAMEH	−8.5598	−1.1534	−1,551,449	8.55977	−183337.5	6.79×10^3	21.86
6	PAMEPr	−8.6369	−1.1435	−1,442,226	−8.62251	−176155.5	2.37×10^4	24.89
7	PAMESi	—	—	—	—	—	3.92×10^4	26.20

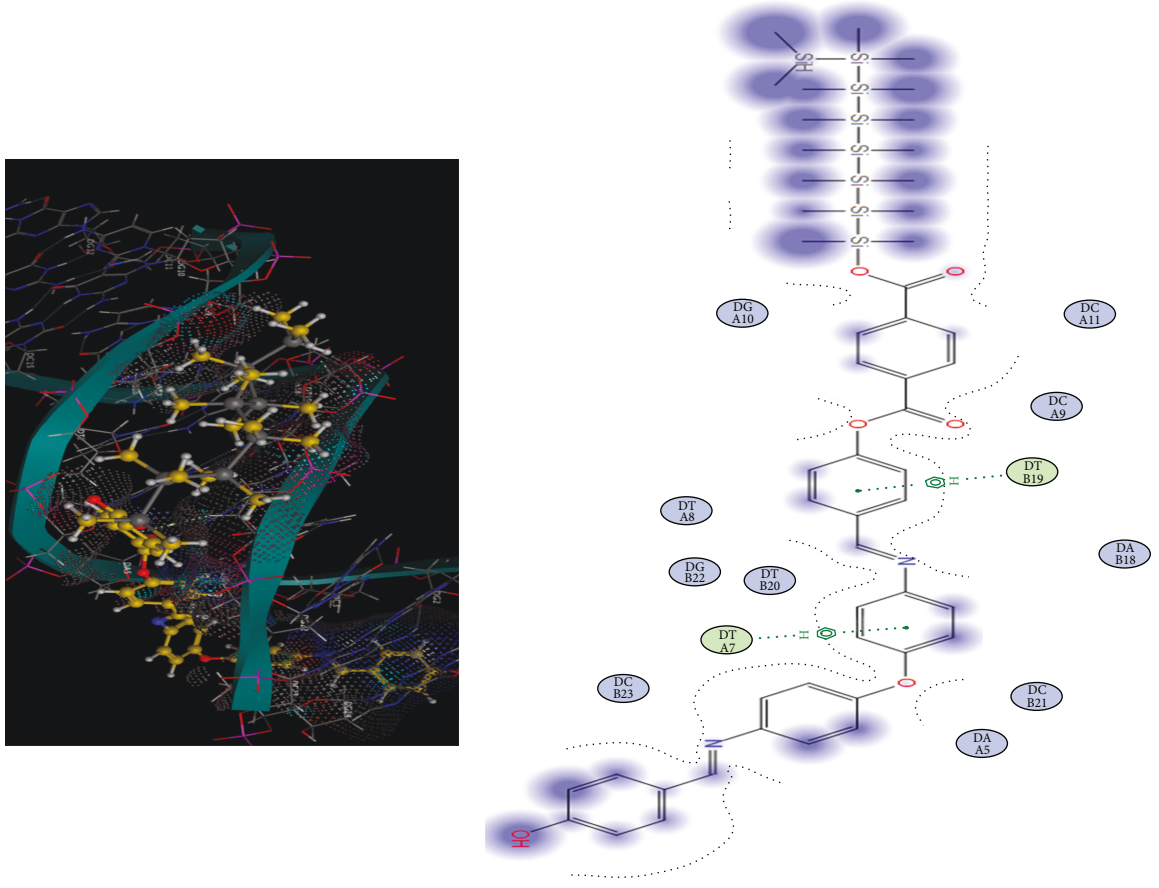
Table 4: Data set of selected steric descriptors.

Sr. no.	Drugs	log P	M_R	H_f (Kcal mol^{-1})	V_{surf}	K_f/M^{-1}	$-\Delta G$/kJ mol^{-1}
1	SB	0.6471	8.426871	−0.84934	438.25	8.00×10^2	16.56
2	PAME	0.6834	15.80061	−16.25367	768.75	2.98×10^3	19.81
3	PAMEF	0.4120	22.58593	—	985.00	8.28×10^3	22.35
4	PAMEB	0.8059	21.58178	−66.6404	945.625	1.59×10^4	23.96
5	PAMEH	0.4513	18.79636	−17.90541	818.625	6.79×10^3	21.86
6	PAMEPr	0.7000	17.85281	−50.8233	782.375	2.37×10^4	24.90
7	PAMESi	0.6013	33.10548	—	1081.25	3.92×10^4	26.20



(a) (b)

Figure 4: (a) Predicted docked pose of SB (labeled yellow) monomer with DNA. The docked conformation of the compound is shown in stick representation. (b) Interaction diagrams for SBOL. Hydrophobic interactions are shown with dotted curves. Green dotted lines represent the arene-arene interactions. Blue spheres show ligand exposure.



(a) (b)

Figure 5: (a) Predicted docked pose of PAMESi polymer (labeled yellow) monomer with DNA. The docked conformation of the compound is shown in ball and stick representation. (b) Interaction diagrams for PAMESi. Hydrophobic interactions with amino acid residues are shown with dotted curves. Green dotted lines represent the H-arene interactions.

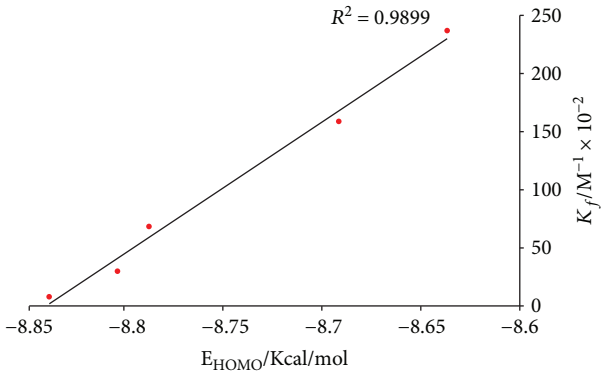


Figure 6: Plot of formation constants (K_f) vs E_{HOMO}.

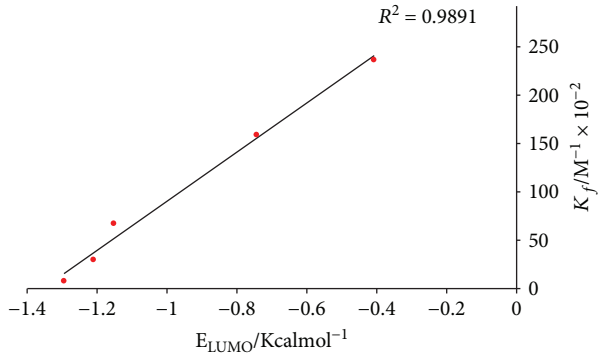


Figure 7: Plot of formation constants (K_f) vs E_{LUMO}.

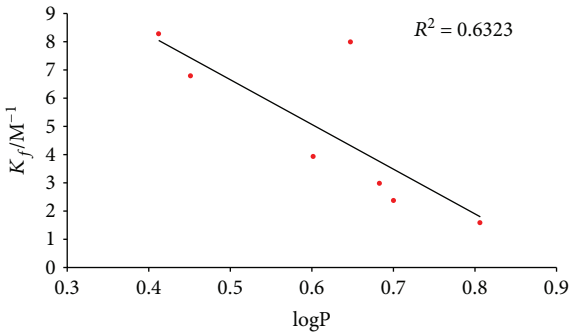


Figure 8: Plot of K_f vs partition coefficient (log P).

that drugs with a higher log P are expected to be forming stronger complex (Figures 8 and 9).

4. Conclusions

The molecular docking studies of newly synthesized poly (azomethine) esters with IT69 showed that the material binds to 1T69 with orientation and position very close to that resulting from crystallographic analysis of protein with its actual ligand. Also, it exhibits significant amounts of stabilizing interactions like H-bonding, arene-π, π-π, and hydrophobic, between the target and ligand. *In silico* studies showed that docked complexes are the results of cumulative effect of all these interactions which are expected to have

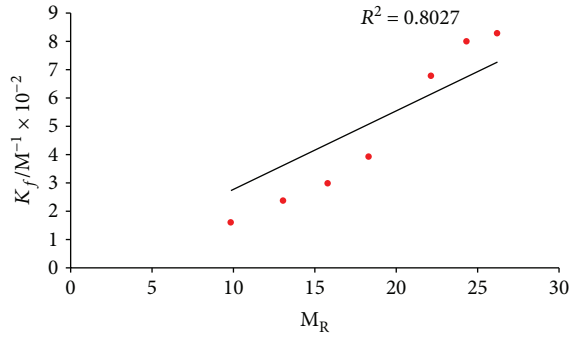


Figure 9: Plot of K_f vs molar refractivity (M_R).

better anti-lung cancer activities. The most important parameter determined from the docking results was the formation constant K_f of the complexes of polymers with DNA which could be helpful to predict the formation constant, and the interaction strength for other compounds, subsequently, is helpful to design or improve material having potential applications in anticancer drugs. Some electronic and steric descriptors were also calculated from theoretical methods, and their correlation with the formation constants were observed. The energies of HOMO exhibited an inverse relationship with K_f *whereas* steric descriptors i.e., log P and molar refractivity had a direct relationship.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Table S1: LS results of organic PAME terpolymers in DMSO at 25°C calculated by laser light-scattering technique. *(Supplementary Materials)*

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