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Research Article

A Schiff base molecule based on phenanthrene: structural characterisation and DNA binding capabilities

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ABSTRACT

A new phenanthren based Schiff base compound (**PBS**) was synthesized by the condensation reaction of phenanthrene-9-carbaldehyde and 4-aminophenol. The structure of the compound was characterized by FTIR, $^{1}H(^{13}C)$ NMR and elementel analysis. Through a single crystal X-ray diffraction investigation, the compound's crystal structure was identified. The X-ray crystallographic data revealed that the phenanthrene and phenol rings are approximately perpendicular with respect to each other. Molecules in the structure are connected to one another by phenol-imine hydrogen bonds [O1-H·····N1] forming supramolecular hydrogen bond chains. Moreover, the phenanthrene fused ring system are involved in π-π stacking interactions with the same sections of the adjacent molecules (head to tail manner). The double-stranded fish sperm DNA (dsFS-DNA) binding properties of the compound was investigated by spectrophotometric, fluorimetric and viscosity methods. According to the spectral data, the interacts of the compound with DNA in groove binding mode with a binding constant (K_b: 4.6 ×10^4 M^{-1}). The fact that the viscosity of the dsFS-DNA did not significantly change when the compound PBS was present suggesting non-intercalative binding of the compound with DNA.

Keywords: Phenanthrene, azomethine, XRD structure, DNA interaction.

Fenantren bazlı bir Schiff bazı bileşiğinin yapısal karakterizasyonu ve DNA bağlama özellikleri

ÖZ

Fenantren-9-karbaldehit ve 4-aminofenolün kondenzasyon reaksiyonu ile fenantren bazlı yeni bir Schiff baz bileşiği (PBS) sentezlenmiştir. Bileşiğin yapısı FTIR, $^{1}H(^{13}C)$ NMR ve elementel analizi ile karakterize edildi. Bileşiğin kristal yapısı, tek kristal X-ışını kırınım deneyi ile belirlendi. X-ışını kristalografik verileri, fenantren ve fenol halkalarının birbirine göre yaklaşık olarak dik olduğunu ortaya çıkardı. Yapıda moleküller, moleküller arası fenol-imin hidrojen bağları [O1-H·····N1] ile bağlanır ve supramoleküler hidrojen bağ zincirleri oluşturur. Ayrıca fenantren halka sistemi, komşu moleküllerin aynı bölümleri ile π-π istifleme etkil (baş-kuruk) etkileşimlerinde yer alır. Bileşiğin çift sarmallı balık sperm DNA'sına (dsFS-DNA) bağlanma özellikleri spektrofotometrik, florimetrik ve viskosimetrik yöntemlerle araştırılmıştır. Spektral veriler, bileşiğin, önemli bağlanma sabiti (K_b: 4.6 x 10^4 M^{-1}) ile oluk bağlanma modunda DNA ile etkileşime girdiğini göstermiştir. Bileşik PBS'nin varlığında, dsFS-DNA'nın viskozitesi önemli bir değişiklik gözlenmemesi, bileşiğin dsFS-DNA ile interkalatif olmayan bağlanma modunda etkileşime girdiğini göstermektedir.

Anahtar Kelimeler: Fenantren, Schiff bazı, kristal yapı, DNA bağlama özellikleri.

1. INTRODUCTION

We still deal with problems and the inefficiency of current medications despite the availability of numerous cancer treatment agents.[1] It is extremely difficult to find possible new chemotherapeutics with increased efficacy and fewer adverse effects.[2,3] One of the most key aspects for therapeutic discovery in the battle against cancer is DNA.[4,5] DNA intercalating compounds are anticipated to reversibly bind DNA and interfere with crucial cancer cell processes like transcription and replication.[6] DNA intercalating substances frequently have polar properties that allow hydrogen bonding interactions with nucleic acids, as well as planar polycyclic aromatic rings (like

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anthracene and phenanthrene) that aid in the compound's ability to settle between base pairs of DNA.[7,8]

Schiff bases are a basic category of organic compounds and can be prepared from the reaction of aldehyde or ketones with primary amines.[9] Numerous biological activities, such as those against cancer, bacteria, malaria, viruses, and fungi, are present in Schiff base compounds.[10–12] In this study, a Schiff base compound labelled as PBS (Figure 1) containing phenanthrene group was synthesized. It was aimed to provide a dual functionality consisting of hydrophilic hydroxyl groups and planar phenanthrene group in the synthesized compound. The synthesized compound was expected to show a high affinity for the hydrophobic and hydrophilic regions of the DNA molecule. FTIR, NMR, and elemental analysis techniques were used to characterize the generated Schiff base compound's molecular structure. Additionally, the compound's single crystals were formed, and a single crystal X-ray diffraction investigation revealed its structural structure. UV-Vis absorption, florescence, and viscosity experiments were used to assess the produced substance's DNA binding capabilities.

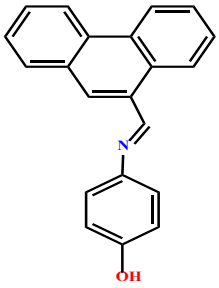

Figure 1. Structure of the phenanthrene-Schiff base compound

2. MATERIALS AND METHODS

2.1. Chemicals

All reagents (4-aminophenol and phenanthrene-9-carbaldehyde) and solvents used in the synthesis were purchased from companies and used as received.

2.2. Physical measurements

Using an LECO CHNS 932, elemental analyses (C, H, and N) were carried out. Using KBr disc (4000-400 cm^1), FTIR spectra were acquired using a Perkin Elmer Spectrum 400 FT-IR spectrophotometer. A Perkin Elmer Lambda 45 spectrophotometer was used to record the compounds' absorption spectra in DMSO solution (10^{-5} M). TMS was employed as the internal standard while 1H/13C NMR spectra in CDCl3 were collected on a Bruker 400 MHz equipment. On a Bruker APEX 2 CCD diffractometer, single crystal X-ray diffraction data for the molecular compound phenanthrene Schiff-based were obtained using Mo- K radiation (= 0.71073) at 293(2) K. Data reduction was done using Bruker SAINT.[13] Using Olex2,[14] SHELXT was used to solve and SHELXL to refine the structure.[15,16] The structure of compound PBS was determined using the direct technique and all of the reflections on F2. The carbon and oxygen hydrogen atoms were positioned correctly using a riding model.

2.3. Synthesis of [(E)-4-((phenanthren-9-ylmethylene)amino)phenol] (PSB)

Absolute ethanol (20 mL) was used to dissolve phenanthrene-9-carbaldehyde (2 mmol), which then underwent a 10-minute reflux process. To the refluxing solution, 4-aminophenol (2 mmol) in absolute ethanol (10 mL) was added. The clear, yellow reaction mixture was then refluxed for an additional four hours and cooled to room temperature. Yellow-colored precipitates that formed after cooling were filtered and air dried.

Chemical Formula: $C_{21}H_{15}NO$. Molecular weight: 297.36 g/mol. Yield: 82%. Colour: Yellow. FTIR (ATR, cm^{-1}) 3005, 2915, 1607, 1503, 1442, 1367, 1273, 1232, 1105, 968, 913, 815, 735, 716, 573, 519. Elemental analyses found (calculated for $C_{21}H_{15}NO$) %: C, 84.73(84.82); H, 4.86(5.08); N, 4.66(4.71). ^{1}H NMR ($CDCl_3$, ppm): 9.65 (b, OH, 1H), 8.80 and 8.76 (d, $CH_{phenanthrene}$, 2H), 8.51 (s, CH=N, 1H), 8.38 (s, $CH_{phenanthrene}$, 1H), 8.17-7.60 (m, $CH_{phenanthrene}$, 6H), 7.30(d, CH_{phenol}, 2H), 6.98(d, CH_{phenol}, 2H). ^{13}C NMR: 162.3(CH=N), 157.3, 144.2, 134.2, 133.8, 132.8, 132.5, 131.0, 130.2, 128.7, 127.3, 126.8, 126.2, 124.2, 123.5, 122.6, 118.3, 116.4.

2.4. DNA binding studies

2.4.1. Absorption spectral measurements

The interactions between double-stranded fish sperm DNA (dsFS-DNA) and synthesized Schiff base compound (PBS) were investigated by UV-Vis spectroscopic titrations according to our previous studies.[17,18] For this, the The substance (PBS) had a UV-Vis absorption spectrum alteration in DMSO (2.0 10-5 M), containing Tris-HCl buffer, pH = 7.0) with increasing amount of double-stranded fish sperm DNA (dsFS-DNA) were recorded in the range of 240-600 nm range. The absorption spectral change of the compound was examined to be able to examine the binding properties of the compound with DNA. Using the Benesi-Hildebrand equation (1), [dsDNA]/(εa–εf) versus [dsDNA] a linear association was seen when the data was plotted.

$$[dsDNA]/(\varepsilon a-\varepsilon f)=[dsDNA]/(\varepsilon b-\varepsilon f)+1/K_b(\varepsilon b-\varepsilon f) \quad (1)$$

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where f is a compound's extinction coefficient in its free form, b is a compound's extinction coefficient in its fully bound form, [dsDNA] is a compound's concentration in base pairs, and a represents the apparent extinction coefficient calculated from Aobds/[Ligands or complexes]: K_b is the binding constant which was calculated from the slope of the line drawn between [dsDNA]/(εa – εf) and [dsDNA].

2.4.2. Competitive binding studies

Ethidium bromide (EB) is a flat molecule and DNA intercalating agent. EB shows weak emissive in its free form, yet its emission intensity dramatically increases when it is attached to DNA.[19,20] When there are competitive intercalating agent, EB complex's DNA emission intensity decreases (emission quenching) due to the displacement of EB from DNA-EB complex. Most of the time, competitive binding via intercalation is blamed for the DNA-EB complex's emission intensity quenching. In our study, dsFS-DNA (75 µM) solution was treated with EB (5 µM) in Tris-HCl buffer and then increasing amount of the Schiff base compound (0-30 µM in DMSO) were added. The solutions' emission spectra were then measured between 560-760 nm (l_{exc}: 526 nm). The decrease of the emission intensity was examined and the putting out constants (K_{sv}) was obtained from the Stern-Volmer equation (2).

$$F_0/F = 1 + K_{SV}[Q] \quad (2)$$

When there is no Schiff base complex present, F0: DNA-EB emission intensity, *F*: emission intensity of DNA-EB in the presence of the Schiff base compound and [Q]: the total concentration of the Schiff base compound.

2.4.3. Viscosity measurements

Binds to DNA interaction of the compound (PBS) was also studied by measurement of viscosity. Rising amounts of the Schiff-based molecule and the dsFS-DNA solution's viscosity was recorded on an Ostwald viscometer at 25 ± 0.1 °C. The relative viscosity for dsFS-DNA in absence (h_0) and presence (h) of the synthesized compounds was obtained.[21] The relative viscosity $(h/h_0)^{1/3}$ versus 1/R were then plotted. where R: concentration of dsFS-DNA/concentration of the Schiff base compound (PBS).

3. RESULTS AND DISCUSSION

The condensation reaction was used in this study to create a new Schiff base compound with a high yield and purity from phenanthrene-9-carbaldehyde and 4-aminophenol. FTIR, NMR and micro analyses (C, H and N) were used to elucidate the compound's structure. The experimental elemental analysis results are in good agreement with the theoretical estimates of the suggested compound's structure, supporting the sample's purity. The FTIR spectrum of the compound was obtained and the spectroscopic data are provided in the experimental part. In the spectrum of the compound, a broad band 3000-3100 cm^{-1} can be assigned to the phenolic group n(O-H) stretching's. The relatively weak peaks at around 2900 cm^{-1} are due to the n(C-H) stretching's. The imine bond n(C=N) stretching's was observed at 1607 cm^{-1} as relatively sharp peak.[22,23] The emergence of imine bond stretching's in the FTIR spectrum provides evidence that the Schiff base complex has formed. In Figure 1, the compound's FTIR spectrum is presented.

In order to further investigate the structure of the compound, The compound's $^1H(^{13}C)$ NMR spectra were collected in $CDCl_3$ and the NMR data with peak assignments are displayed in the experimental part. In the ^1H NMR spectrum of the compound, a broad peak at 9.65 ppm is due to the phenolic proton.[24] Two doublet peaks at 8.80 and 8.76 ppm are assigned to the phenanthrene protons. The imine bond proton of the compound is shown as a singlet peak at 8.51 ppm.[25] Multiplet and overlapped peaks at 8.17-7.60 ppm are due to the phenanthrene protons. In the spectrum of the compound, two doublet peaks at 7.30 and 6.98 ppm are due to the phenolic C-H protons. The integration values of proton signals support the compound's suggested structure. The ^{13}C NMR spectrum of the compound shows a peak at 162.3 ppm which is attributed to the imine bond carbon atom. The remaining carbon atom signals are displayed between 157.3 and 116.4 ppm. The compound's NMR spectra showed that the sample contains no major organic impurities.

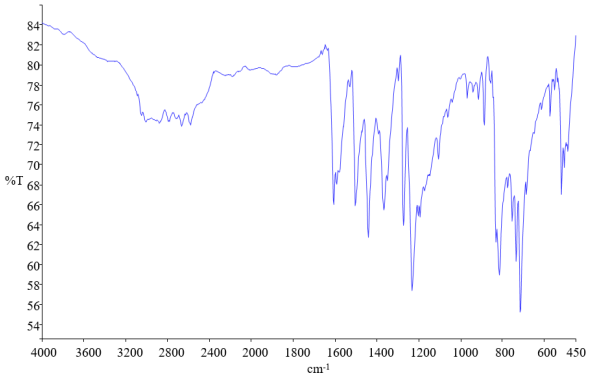

Figure 2. FTIR spectrum of the phenanthrene-Schiff base compound (PBS)

3.1.Crystal structure of the phenanthrene-Schiff base compound (PBS)

Re-crystallization of ethanol solution of the compound produced single crystals of the compound. By using a single crystal XRD investigation, the compound's crystal structure was identified. The compound's X-ray

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crystallographic information is provided in Table 1. The monoclinic unit cell and P21/n space group were used to solve the structure of the phenanthrene-Schiff base complex with the final refinement value of 0.0421(R_1). The thermal ellipsoid plot of the structure is displayed in Figure 3a In the structure of the compound, phenanthrene and phenol rings are linked by an imine bond (C=N) linkage. The C7-N1 imine bond distance is 1.2715(19) Å showing a characteristic imine bond distance. In the structure, the phenanthrene and phenol rings are almost perpendicular with respect to each other with the dihedral angle of 79.49º. In the structure of the compound, the phenolic group of a molecule makes an intermolecular hydrogen bond [O1-H·····N1] with the imine nitrogen atom of a neighbouring molecule under symmetry operation of -1/2+x,3/2-y,1/2+z. The phenol-imine intermolecular hydrogen bond contacts form a hydrogen bond chain as shown in Figure 3b. The compound's crystal structure was also further stabilized by anticipated stacking interactions π stacking contacts. The flat surface of the phenanthrene fused ring system allows the π-stacking interactions with the neighbouring molecules. Molecules are linked by phenanthroline-phenanthroline head to tail π-π stacking interactions along the *a* axis as shown in Figure 3c.

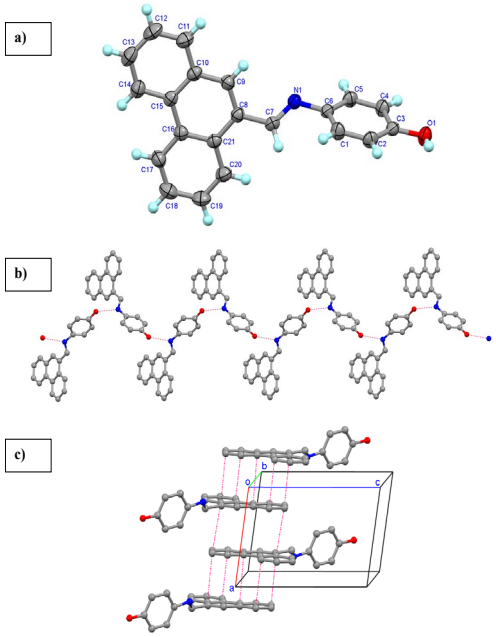

Figure 3 a) Thermal ellipsoid plot (50% probability) of the compound (PBS) with atom numbering. b) hydrogen bond contacts. c) Packing plot showing π-π stacking interactions.

Table 1. X-ray crystallographic data for the compound (PBS)

Empirical formula	$C_{21}H_{15}NO$	β/°	98.455(3)
Formula weight	297.34	γ/°	90
Temperature/K	293(2)	Volume/Å^3	1485.43(8)
Crystal system	Monoclinic	Z	4
Space group	$P2_1/n$	Reflections collected	4714
a/Å	7.1024(2)	Independent reflections	2925 [R_{int} = 0.0155, R_{sigma} = 0.0317]
b/Å	20.9464(6)	Final R indexes [I>=2σ (I)]	R_1 = 0.0421, wR_2 = 0.0970
c/Å	10.0945(3)	Final R indexes [all data]	R_1 = 0.0550, wR_2 = 0.1087
α/°	90		

3.2. Electronic absorption properties

In DMSO solution (10^{-5} M), UV-Vis absorption characteristics of the compound were examined. The absorption spectrum of the compound was taken in the range of 240-640 nm. In the spectrum shown in Figure 4, two absorption bands were observed at 240-440 nm range. The first and more intense peak was observed at 250-290 nm range (l_{max}: 260 nm). The relatively broader absorption band was seen at 300-430 nm range (l_{max}: 364 nm). The absorption bands in the UV-Vis spectrum can be assigned to the π-π* electronic transition due to the π-electrons in the structure of the compound.

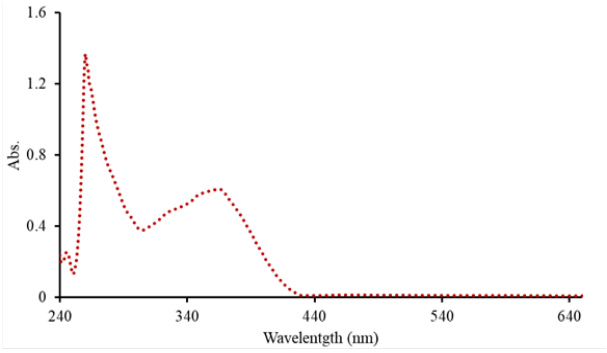

Figure 4. Absorption spectrum of the compound in DMSO (10^{-5} M).

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3.3. DNA binding studies

DNA is the main target for the most chemotherapy agents of cancer. A huge number of compounds have prepared for the targeting of DNA.[26] To ascertain the impact of the DNA targeting of new drug candidates, the interactions/binding between the drug candidate molecule and DNA should be investigated.[27] The DNA binding agents bind to DNA covalent and non-covalent interactions and the latter one is focus of the many DNA targeting studies.[28] Intercalation between base pairs, groove bonding, and electrostatic interactions are examples of non-covalent interactions between DNA and binding substances.[28,29] The dsFS-DNA (fish sperm double-stranded DNA) binding properties of the phenanthrene based Schiff base compound (PBS) was investigated by UV-Vis absorption measurements. UV-Vis absorption spectra of the compound (PBS) in DMSO: TRIS–HCl buffer solution (2.0 ×10-5 M) were recorded in presence of incremental addition of dsFS-DNA (100-1000 µl, 1.78 × 10−4 M). UV-Vis absorption spectral change of the compound in the presence of PBS is shown in Figure 5.

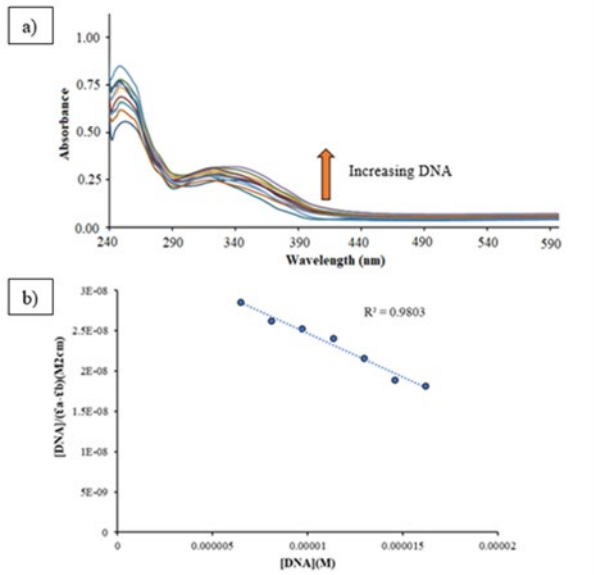

Figure 5. a) Absorption spectra of PSB, in 2 mM Tris–HCl/2 mM NaCl buffer at pH 7.0 in the presence of incremental the addition of dsFS-DNA. b) Plot of [DNA]/Ɛa–Ɛf) vs. [DNA] for the titration of PBS with dsFS-DNA (0-1000 µM).

The compound PBS showed two absorption bands in the range of 240-440 nm. In the presence of DNA, the first absorption band at 240-290 nm range did not show considerable red or blue shift yet the absorption values increased with the gradual addition of DNA (hyperchromic effect). Addition of DNA causes noticeable change in the absorption band at 290-400 nm range. The presence of DNA resulted in a sight red shift accompanied by higher absorption values (hyperchromic effect). The spectral change of the compound PBS in the presence of DNA is indicative of the interactions between the compound and DNA. Using the absorption band at 290-400 nm range, binding constant (Kb) was found to be 4.6 ×104 M-1 from the linear plot [dsDNA]/(εa–εf) versus [dsDNA] (Figure. 5). DNA binding constant of the compound Kb falls within the range of groove binding agents.[30]

Ethidium bromide (EB) are used as a probe of DNA secondary structure and it intercalates into the double-stranded DNA.[31] Although free EB shows weak fluorescence properties in the range of 560-760 nm (lexc: 526 nm), the insertion of EB into DNA base pair causes dramatic increase in the emission intensity.[32] In the presence of a competitive compound, DNA binding competition is expected. The DNA binding competition can visualize by measuring the emission spectra of DNA-EB complex. The emission of the DNA-EB complex is usually quenched in the presence of a competitor molecule. The DNA-EB complex's emission band is being quenched and this is often assigned to the replacement EB form DNA-EB with the competitor molecule, the excited state energy transfer, or the conformational change of DNA. The emission spectra of the DNA-EB complex [dsFS-DNA: 75 µM), EB: 5 µM in Tris-HCl buffer] recorded in the presence of increasing amount of the Schiff base compound (PBS) (0-30 µM in DMSO). It was observed that the emission band of DNA-EB complex at 560-760 nm (lexc: 526 nm) was gradually quenched by the addition of the Schiff base compound. By using the Stern-Volmer equation, Io/I versus [PBS] plot was drawn (Figure 6) and linearity was observed. From slope of this plot, quenching constant (Ksv) was found to be 2.42 × 104 M-1. The obtained Ksv suggests non-intercalative binding interactions between the synthesized compound and DNA.

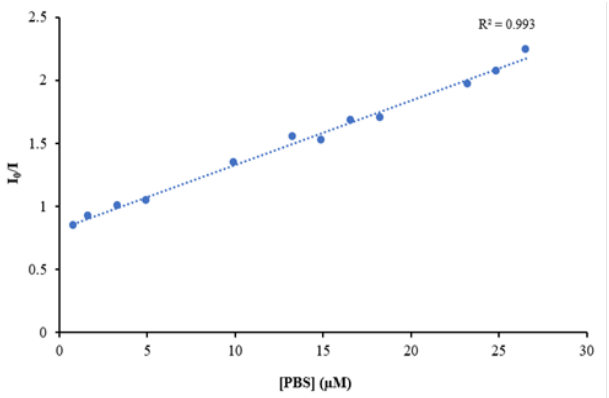

Figure 5. Stern-Volmer plot (I_o/I versus [PBS]) of fluorescence titrations of DNA-EB complex HDSB with PBS. (λ_{exc}: 526 nm).

The interaction between the synthesized phenanthrene based Schiff base compound (PBS) and DNA was further examined by viscosity measurements. When an

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intercalation agent is applied, viscosity of the DNA solution rises. The DNA length and viscosity are increased when an intercalating molecule binds to the spaces between DNA base pairs. Viscosity of dsFS-DNA solution (50 mM) in the presence of incremental addition of PBS (keeping DNA concentration constant) was recorded and the relative viscosity of dsFS-DNA is shown in Figure 7.

The presence of various concentration of PBS did not cause dramatic change in the viscosity of dsFS-DNA which suggests the non-intercalative binding mode between PBS and dsFS-DNA.[21]

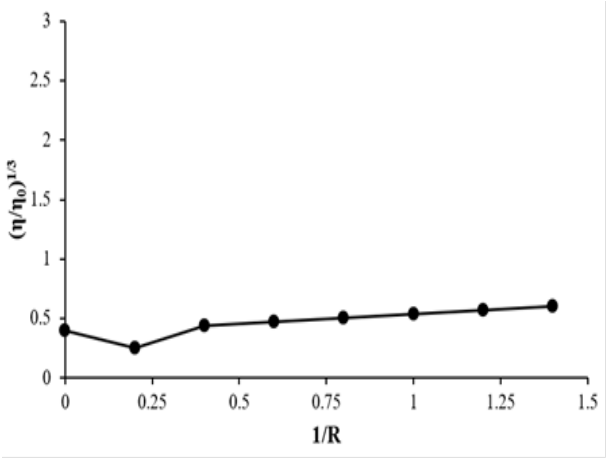

Figure 6. The relative viscosity change of dsFS-DNA (50 µM) with various concentration of the Schiff base compound.

4. CONCLUSIONS

A new phenanthrene based Schiff base compound (PSB) was prepared and its structure was characterized. The compound's crystal structure was clarified by a single crystal XRD investigation. Crystal structure of the compound was stabilised by intermolecular hydrogen bond contacts and π-π stackings. The DNA binding properties of the compound was investigated by spectrophotometric, fluorimetric and viscosity methods. The UV-Vis spectrometric data revealed that the compound has considerable binding affinity to DNA with binding constant (K_b) of 4.6×10^4 M^{-1}. The spectral and viscosity data showed that the compound interacts with double strand DNA *via* non-intercalative groove binding mode.

Conflict of interests

I declares that there is no a conflict of interest with any institute, person, company, etc.

Appendix A. Supplementary data

The cif file for single crystal XRD data was deposited to Cambridge Crystallographic Data Centre with CCDC number of 2194269.

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