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Antioxidant properties of ethenyl indole: DPPH assay and TDDFT studies†

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A series of ethenyl indoles (*e.g.* 3-(4-substituted phenylethenyl-*E*)-N–H-indole) with various donor or acceptor substituents have been synthesized and their antioxidant properties have been studied. Ethenyl indoles exhibit antioxidant activity in a substituent dependent manner. Ethenyls bearing strong electron withdrawing substituents show weak or no antioxidant activity, whereas ethenyls with electron donating substituents exhibit antioxidant properties comparable to vitamin E. It can be seen from a plot of the percentage of inhibition *versus* the antioxidant concentration, that the hydroxy substituted ethenyl indole exhibits good antioxidant properties (50% inhibition concentration (IC_{50}) ~ 24 μM) as compared to the other ethenyls (IC_{50}: 30–63 μM) and that it is comparable to vitamin E (IC_{50} ~ 26 μM). The results are also supported by the computational data obtained through time dependent density functional theory (TDDFT) calculations. From the TDDFT and antioxidant study, it was shown that there is a correlation between the highest occupied molecular orbital (HOMO)–lowest unoccupied molecular orbital (LUMO) energy, the ground state dipole moment, optical band gap, bond dissociation enthalpy and the ionization potential of the ethenyls with the antioxidant properties. A possible hydrogen and/or electron and proton transfer mechanism is suggested for the quenching of the free radical.

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1. Introduction

In biological systems such as cells, tissues and bio-molecules, antioxidants prevent oxidative damage by acting as scavengers to reactive oxygen species (ROS).[1–5] Vitamin C and vitamin E are well known non-enzymatic antioxidants within normal cells that interact directly with radicals such as hydroxyl and peroxyl intermediates and help to minimize the consequences of lipid peroxidation in membranes. There are several natural antioxidants that help reduce the risk of ROS induced human diseases such as heart, neurodegenerative, cancer, chronic and age related degenerative diseases.[2,3] Natural antioxidants are more suitable compared to synthetic antioxidants. However, natural antioxidants have their own merits and demerits such as a lack of water solubility and average antioxidant activity. Most antioxidants are lipid-soluble with a lower absorption capacity, such as vitamin E, carotenoids, and lipoic acid. Thus, newer synthetic antioxidants with higher antioxidant properties are highly warranted. Many synthetic antioxidants that have been developed recently exhibit good antioxidant properties.[6–10] For example, stilbenoids and their derivatives, show remarkably high antioxidant activities.[11–16] Some of the synthetic antioxidants such as butylated hydroxy phenyl derivatives BHA, BHT, TBHQ are used as food preservatives,[17] dihydroquinoline ethoxyquin[18] is used in the rubber industry, and organochalcogen compounds are used in biological and other industrial applications.[19] Heterocyclic compounds, in particular, are the most important class of molecule that show a wide range of medicinal properties. Compounds based on the indole moiety are very limited, but exhibit good anti-oxidation activities with a 50% inhibition concentration (IC_{50}) approximately 25 μM.[20,21] The practical applications of indoles and pyrroles are heavily centered in pharmaceutical area and thus many indole based compounds have been synthesized in an effort to find substances with useful activity in biological systems.[22–25] For example, carbazole-based compounds exhibit radical scavenging properties (IC_{50}: 42 μM) as well as being potential candidates for anticancer activities.[22] 3-Indolyl-chromene derivatives exhibit antioxidant properties comparable to vitamin C (IC_{50}: 10–15 μM)[23] and indole-based ethylenophanes show radical scavenging properties similar to those of vitamin E (IC_{50}: 28 μM).[24] Another indole derivative has been found to be a powerful antioxidant towards suspensions of graphene oxide.[25] Thus, in a continuation of stilbene research, the antioxidant activity and its mechanism for a series of donor and acceptor substituted ethenyl indoles was investigated, as shown in Fig. 1. The results are also supported by computational data using time dependent density functional theory (TDDFT).

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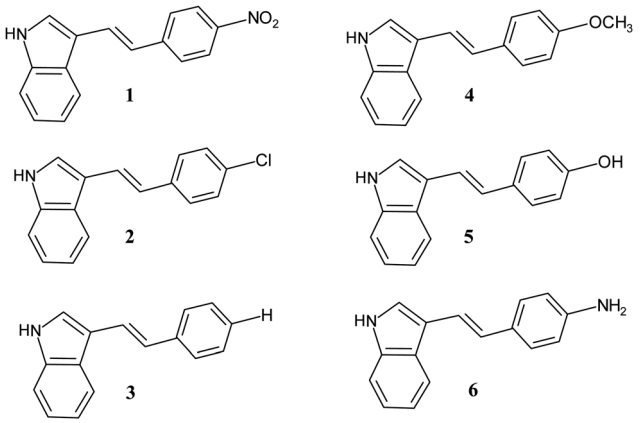


Fig. 1 Structure of compounds **1–6**, the antioxidant properties of which were evaluated.

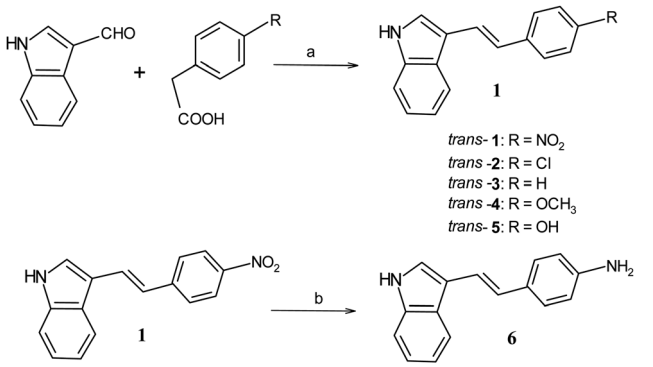


Fig. 2 Synthetic routes and reaction conditions used to obtain the ethenyl indoles: (a) pyridine, piperidine, 100 °C, reflux 8 h and (b) $FeSO_4$, aqueous NH_3, ethanol, 100 °C, 3 h.

2. Experimental

2.1 Materials and analytical equipment

The starting materials and reagents for the synthesis of the ethenyl indoles were received from local suppliers (M/s. Sisco Research Laboratory). Compounds were synthesized using a Carousel 6 plus reaction station, made by Radleys. Synthetic compounds were characterized through UV-visible (UV-Vis) spectroscopy, Fourier-transform infrared (FTIR) spectroscopy, ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR, gas chromatography–mass spectrometry (GC–MS) and carbon hydrogen and nitrogen (CHN) analysis. The absorption spectra were measured on a PerkinElmer Lambda 750 UV/VIS/near-infrared (NIR) spectrophotometer and the fluorescence spectra were measured on a PerkinElmer LS-55 fluorescence spectrophotometer using a red photomultiplier tubes (PMT) detector system. The FTIR spectra in the KBr discs were recorded on an Impact Nicolet-400 spectrophotometer. The ^{1}H and ^{13}C NMR spectra, in $CDCl_3$ as a solvent and using tetramethylsilane (TMS) as an internal standard, were recorded on a JEOL 500 MHz FTNMR instrument. The GC–MS spectra were recorded on a GCD 1800A Hewlett Packard GC–mass spectrometer. CHN analyses were performed on a Theoquest CE instrument 1112 series CHNS auto analyzer. Melting points were determined on a Lab India melting point apparatus. For spectroscopic studies, UV grade solvents were used.

2.2 Synthesis of compounds 1–6

The substituted *p*-phenyl ethenyl-*E*-indoles (**1–5**) were synthesized by the condensation of the *p*-substituted phenyl acetic acid with the corresponding 3-formylindole (2 : 1 molar ratio) in the presence of a pyridine–piperidine mixture as described previously[26–35] and the synthetic routes shown in Fig. 2 were followed to obtain compound **1**. 3-Formyl indole (1.45 g, 0.01 mol) was added to freshly distilled pyridine (10 mL), piperidine (0.6 mL) and *p*-nitrophenyl acetic acid (3.62 g, 0.02 mol) in a round bottom flask fitted with a reflux condenser. The reaction mixture was heated at 100 °C for 8 h. The progress of the reaction was monitored using thin layer chromatography. The reaction mixture was cooled to room temperature, poured into ice-cold water and treated with 100 mL of diluted hydrochloric acid to remove the excess pyridine from the reaction mixture. A brick red colored product was extracted in dichloromethane and purified by column chromatography using 2–5% ethyl acetate in petroleum ether as the eluting solvent, the desired compound was obtained in 31% yield. Compound **6** was obtained through the reduction reaction of **1**. For this purpose, ethenyl indole **1** in ethanol was refluxed in the presence of aqueous ferrous sulfate and ammonia solution at 100 °C for 3 h, as shown in Fig. 2. The products were purified by column chromatography using 2–10% ethyl acetate in petroleum ether (60–80 °C) as the eluting solvent. The compounds were characterized using UV-Vis, FTIR, ^{1}H NMR and ^{13}C NMR, GC-MS and CHN analysis.

2.3 Methods used for antioxidant studies

The antioxidant studies of ethenyl indoles **1–6** were performed using a 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay.[36,37] For this purpose, varying concentrations of the ethenyl compound (0 to 400 μM) were added to a 100 μM concentration of the DPPH solution and the quenching of the absorbance at 517 nm of the DPPH radical was monitored at regular time intervals (0–45 min). The quenching of the DPPH solution with standard antioxidants (*e.g.* ascorbic acid, vitamin E) was also used as a positive control. All of the experiments were performed in triplicate and the average absorbance was measured for calculating the percentage of inhibition using eqn (1).

$$\%\ \text{Inhibition of the DPPH free radical} = [(A_{\text{blank}} - A_{\text{sample}})/(A_{\text{blank}})] \times 100 \quad (1)$$

In which A_{blank} represents the absorbance of the DPPH radical in the absence of a sample, and A_{sample} is the absorbance of the DPPH radical in the presence of varying concentrations of sample. The radical inhibition concentration (IC_{50}) of the ethenyls was calculated from the plot of the percentage inhibition *versus* the sample concentration.

2.4 Method for calculating the bond dissociation enthalpy, ionization potential, proton affinity, proton dissociation enthalpy and electron transfer enthalpy

Many types of anti-oxidation mechanisms are suggested in the literature,[38–41] such as hydrogen atom transfer (HAT), single electron transfer (SET) or single electron transfer followed by proton transfer (SET-PT), sequential proton loss and electron transfer (SPLET) and so forth. It is noteworthy that the anti-oxidation mechanism is very complex and therefore both thermodynamic as well as kinetic studies can provide complete information, as reported recently for the trolox molecule that follows the HT, SET or SPLET mechanism based on the reacting environment and the pH conditions.[39] In such mechanisms, the quenching of the free radical occurs through either hydrogen atom transfer[38–40] or electron transfer followed by a proton transfer mechanism[38,39,41] (Scheme 1). Thus, thermodynamic parameters, such as the bond dissociation enthalpy (BDE), ionization potential (IP), proton affinity (PA), proton dissociation enthalpy (PDE) and electron transfer enthalpy (ETE), provide the most valuable information for determining the antioxidant capacity of a molecule.

The BDE, IP, PA, PDE and ETE of the ethenyl indoles were calculated using TDDFT. For this purpose, various structures (neutral, free radical, cationic radical and anion) of the ethenyl indoles were optimized using the Avogadro and ORCA version 4.0 program package.[42] The energy of the molecule was calculated using the Becke's three parameter hybrid exchange–correlation, B3LYP/def2-SVP basis set.[43] The density functional theory (DFT) and B3LYP predicted bond dissociation energies are the most reliable and comparable as compared to other computational methods, as shown from the previously published literature.[44–47] The BDE, IP, PA, PDE and ETE of the molecules were calculated using eqn (2)–(6).

$$\mathrm{BDE} = E_{\mathrm{Ar–X^{\bullet}}} + E_{\mathrm{H^{\bullet}}} - E_{\mathrm{Ar–XH}} \quad (2)$$

In which $E_{\mathrm{Ar–XH}}$, $E_{\mathrm{Ar–X^{\bullet}}}$, and $E_{\mathrm{H^{\bullet}}}$ are the enthalpies of the Ar–XH, Ar–X$^{\bullet}$ radical, and hydrogen radical, respectively as described previously.[33]

$$\mathrm{IP} = E_{\mathrm{Ar–X^{\bullet+}H}} - E_{\mathrm{Ar–XH}} \quad (3)$$

In which $E_{\mathrm{Ar–XH}}$, and $E_{\mathrm{Ar–X^{\bullet+}H}}$ are the enthalpies of the Ar–XH, Ar–X$^{\bullet+}$H cationic radical.[34]

$$\mathrm{PA} = E_{\mathrm{Ar–X^{-}}} + E_{\mathrm{H}}^{+} - E_{\mathrm{ArXH}} \quad (4)$$

In which $E_{\mathrm{Ar–X^{-}}}$, E_{H}^{+} and $E_{\mathrm{Ar–XH}}$ are the enthalpies of the anion Ar–X^{-}, H^{+}, Ar–XH.

$$\mathrm{PDE} = E_{\mathrm{Ar–X^{\bullet}}} + E_{\mathrm{H}}^{+} - E_{\mathrm{ArX^{\bullet+}H}} \quad (5)$$

In which $E_{\mathrm{Ar–X^{\bullet}}}$, E_{H}^{+} and $E_{\mathrm{ArX^{\bullet+}H}}$ are the enthalpies of the radical Ar–X$^{\bullet}$, H^{+}, Ar–X$^{\bullet+}$H cationic radical.

$$\mathrm{ETE} = E_{\mathrm{Ar–X^{\bullet}}} + E_{\mathrm{e}}^{-} - E_{\mathrm{Ar–X^{-}}} \quad (6)$$

In which $E_{\mathrm{Ar–X^{\bullet}}}$, $E_{\mathrm{e^{-}}}$ and $E_{\mathrm{Ar–X^{-}}}$ are the enthalpies of the radical Ar–X$^{\bullet}$, electron (e^{-}), Ar–X^{-} anion.

The difference in the energy, ΔBDE, ΔIP, ΔPA, ΔPDE and ΔETE were calculated with respect to vitamin E using eqn (7)–(11).

$$\Delta\mathrm{BDE} = \mathrm{BDE} - \mathrm{BDE}_{\mathrm{vitamin\ E}} \quad (7)$$

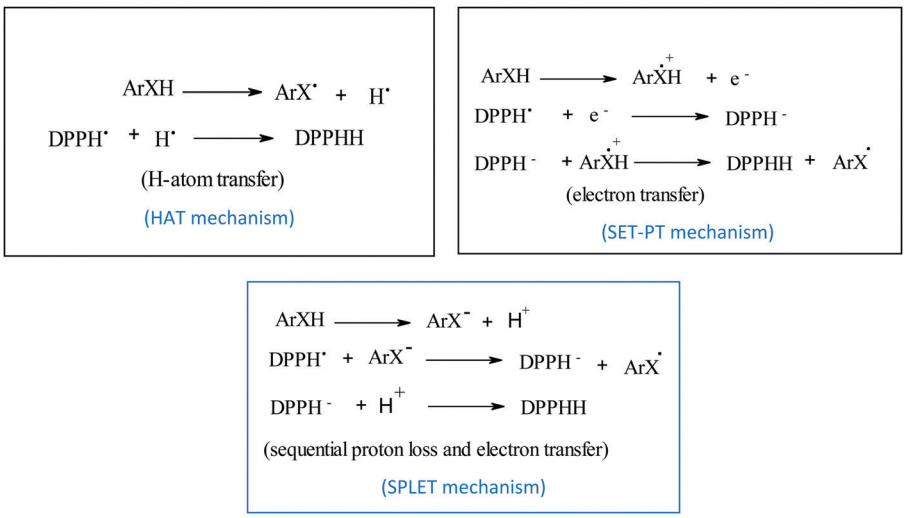
$$\Delta\mathrm{IP} = \mathrm{IP} - \mathrm{IP}_{\mathrm{vitamin\ E}} \quad (8)$$

$$\Delta\mathrm{PA} = \mathrm{PA} - \mathrm{PA}_{\mathrm{vitamin\ E}} \quad (9)$$

$$\Delta\mathrm{PDE} = \mathrm{PDE} - \mathrm{PDE}_{\mathrm{vitamin\ E}} \quad (10)$$

$$\Delta\mathrm{ETE} = \mathrm{ETE} - \mathrm{ETE}_{\mathrm{vitamin\ E}} \quad (11)$$

The TDDFT method was validated using standard compounds, such as 2,4,6-tri-*tert*-butylphenol, for which a BDE of 81.24 kcal mol^{-1} has been reported experimentally elsewhere.[48–50] Similarly, the computed energy of the hydrogen radical, ($E_{\mathrm{H^{\bullet}}}$) is −13.547 eV (−312.32 kcal mol^{-1} and −0.497 a.u.), the ΔBDE for resveratrol and 4-hydroxy stilbene



Scheme 1 Antioxidant mechanism through H-atom transfer, electron transfer or sequential proton loss and electron transfer followed by a proton transfer mechanism.

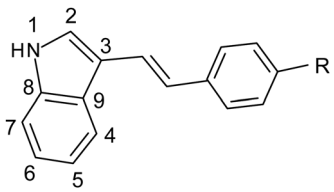
with respect to phenol is well matched with the value reported in the literature[48] and is comparable to our experimental and theoretical results.

2.5 Method for TDDFT

For the calculation of the computational parameters, the ORCA *ab initio* quantum chemical software package was used.[42] For this purpose, TDDFT[46,47] has been used for the calculation of the ground state dipole moment, the absorption wavelength maximum ($\lambda_{abs\,max}$), the vertical excitation energy and the oscillator strength (*f*) using functional B3LYP with a def2 SVP basis set.[43] The minimized geometry was further confirmed by vibrational analysis, resulting in no imaginary frequencies. This geometry is used as the input for further calculations to obtain the frontier molecular orbitals (FMOs), single-point TDDFT studies (first 10 vertical singlet–singlet transitions) were used to obtain the UV-Vis spectra using a B3LYP functional and a def2 SVP basis set. The software multiwfn 3.6 was employed to simulate the major portion of the absorption spectrum.

3. Results and discussion

3.1 Synthesis and characterization of indolic ethenyls 1–6



The *trans*-olefins of **1–6** were obtained through the condensation reaction as shown in Fig. 2, with a reasonable yield (24–56%). All of the compounds were characterized using ^{1}H NMR, ^{13}C NMR, FTIR, MS (EI+ method) and CHN analysis. In ^{1}H NMR, the two doublet peaks for the olefin protons appear near δ 7.1 and 7.2 with a *J* coupling constant of *J* = 15.8–16.5 Hz corresponding to the *trans*-isomer for **4–6**. In the case of compound **1–2**, the two doublet peaks appear close to δ 7.3 and δ 7.5 (*J* = 15.8–16.5 Hz). Similarly, the indole ring protons such as –C_5–H and C_6–H appear as a multiplate near δ 7.1–7.2, –C_2–H appears as a singlet near δ 7.3–7.4, –C_4–H as a doublet at δ 7.9 (*J* = 7.5–8.2 Hz) and –C_7–H as a doublet at δ 8.0 (*J* = 6.2–7.5 Hz). In FTIR, the indole N–Hst appears close to 3370 cm^{-1}. The C–Hst appears close to 3040 cm^{-1} and C=Cst appears in between 1620–1636 cm^{-1}. Similarly, the aromatic C=Cst and C–Cst appear close to 1520, 1488, 1455, and 1400 cm^{-1}. For compound **1**, the N=O symmetrical and asymmetrical stretching frequency appeared at 1330 and 1520 cm^{-1}. In compound **4**, the O–Cst of the methoxy appeared at 1244 cm^{-1}. For compound **5**, a broad peak at 3126 cm^{-1} corresponding to the O–Hst is observed. For compound **6**, two sharp peaks appeared at 3394 and 3341 cm^{-1} corresponding to the primary amine group. This confirmed the presence of the functional group in the respective olefin compounds. Details of the characterization data (^{1}H and ^{13}C NMR, FTIR, CHN, GC-MS) are provided in the ESI† (Fig. S1–S6).

3.2 Antioxidant properties of ethenyl indole using the DPPH assay

The antioxidant properties of compounds **1–6** were studied using a DPPH assay, in which the DPPH free radical changes its color from purple to yellow upon the quenching of the radical in the presence of an antioxidant (*e.g.* ethenyl indoles, **1–6**). The decrease in the absorbance of the DPPH radical was monitored at 517 nm in methanol (Fig. 3) and the plot of the percentage of inhibition *versus* antioxidant concentration was drawn (Fig. 4). It can be seen that except for the nitro substituted ethenyl, all of the other ethenyls exhibit antioxidant properties. The hydroxy (*e.g.* phenolic group) substituted ethenyl indole (**5**) exhibits better antioxidant properties with an IC_{50} of approximately 24 μM compared to the other ethenyls **2–4** and **6** (IC_{50}: 30–63 μM) and comparable to those of vitamin E (IC_{50} ∼ 26 μM).

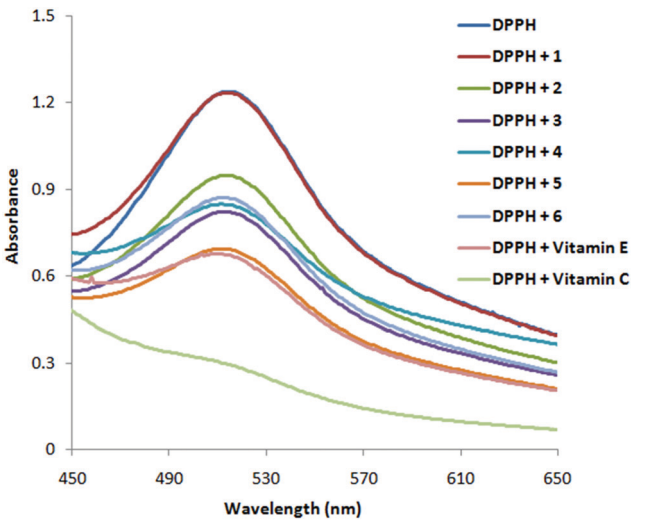


Fig. 3 Typical absorption spectra of 100 μM of the DPPH radical alone and in presence of a 25 μM concentration of ethenyl indoles **1–6**, vitamin E and vitamin C.

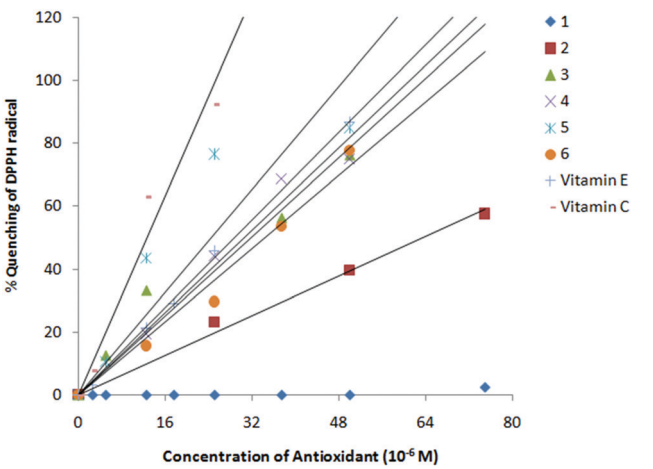


Fig. 4 A plot of the percentage of quenching of the DPPH radical *versus* the concentration of the natural antioxidants and ethenyl indoles **1–6**.

Upon replacement of the hydroxy group with a methoxy in compound **5**, a slight decrease in the radical quenching, but a similar IC_{50} value, is observed. This suggest that the anti-oxidation in this molecule could be caused by the hydrogen atom transfer of the indolic NH and/or electron transfer followed by the proton transfer mechanism. On the other hand, in the presence of an electron withdrawing substituent, the antioxidant activity of the ethenyl indole is decreased. For example, as compared to **3** (IC_{50}: 31 μM), the radical quenching activity of compound **2**, which has an electron withdrawing chloro substituent (*e.g.* Cl), is reduced further (IC_{50}: 63 μM). Ethenyl **1**, which has a nitro substituent, does not show any antioxidant activity. On the other hand, ethenyl with a donating substituent exhibits good antioxidant properties. Thus, the antioxidant activities could be caused by hydrogen atom transfer and/or electron transfer followed by a proton transfer mechanism in a substituent dependent manner. In order to understand the antioxidant properties in detail, the optical properties of these molecules were determined using absorption, fluorescence and TDDFT.

3.3 Absorption and fluorescence properties of ethenyl 1–6

The absorption and fluorescence spectra of **1–6** were recorded in methanol (Table 1 and Fig. 5 and 6). For all the compounds, the extinction coefficient (ε) lies between 10 000–30 000 M^{-1} cm^{-1},

Table 1 IC_{50} values of the indolic ethenyls (**1–6**) for the DPPH radical in methanol

Compounds	λ_{abs} [a] (nm)	λ_{em} [a] (nm)	ε (M^{-1} cm^{-1})	Band gap using Tauc plot	IC_{50} (μM)	R^2
1	413	590	23900	2.37	—	—
2	335	395	18 800	3.24	63	0.99
3	327	396	10 800	3.31	31	0.96
4	327	404	17 800	3.30	30	0.98
5	322	390	24 400	3.30	24	0.88
6	324	405	12 200	3.24	34	0.98

[a] Vitamin E (IC_{50}, 26 μM), ascorbic acid (vitamin C) (IC_{50}, 12 μM).

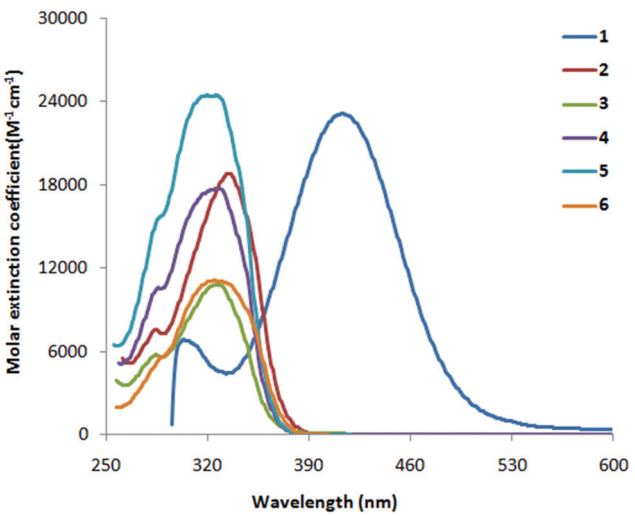


Fig. 5 Absorption spectra of compounds **1–6** in methanol.

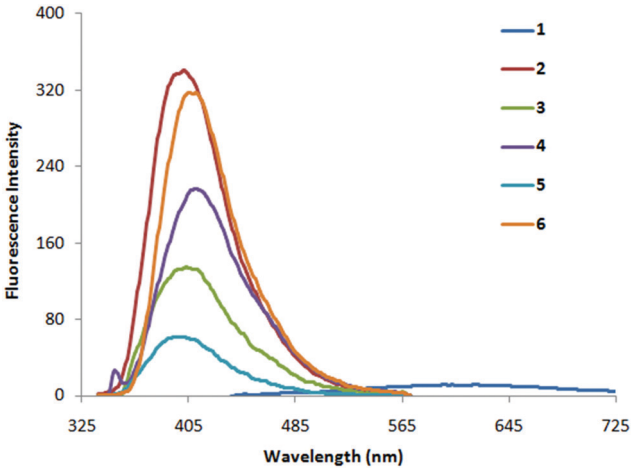
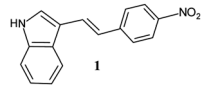
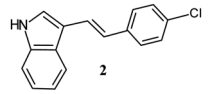
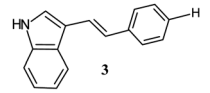
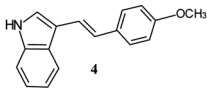
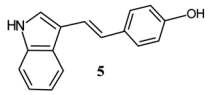
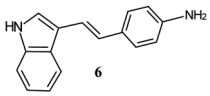


Fig. 6 Fluorescence spectra of compounds **1–6** in methanol.

which indicates a π → π* nature for the transition. It can be seen that the absorption wavelength maximum (λ_{abs}) and fluorescence wavelength maximum (λ_{em}) are sensitive to the substituent. Upon increasing the electron withdrawing capacity of the substituent, a red shift in the λ_{abs} and λ_{em} is observed and a maximum of 86 nm in the λ_{abs} and 194 nm in the λ_{em} was observed for **1**, whereas for **2–6**, a minimal red shift was observed. Using a Tauc plot (Fig. S7, ESI†), the optical band gap of ethenyl indole was determined using the absorption spectrum in methanol and using the TDDFT method (Fig. S8–S11, ESI†). It was found that for **1**, the optical band gap was 1.06 eV lower as compared to other ethenyls. The large red shift and low optical band gap suggest the involvement of a charge transfer state for **1** with a strong electron withdrawing nitro group. Also, ethenyl **1** is electron deficient in nature. The ground state dipole moments of ethenyls **1–6** were computed using the TDDFT method and the excited state dipole moments were calculated using a Lippert–Mataga plot (Fig. S11–S13, ESI†). The ground state dipole moment of **1** is 8.39 Debye with a small optical band gap of 2.37 eV as compared to the other ethenyls (Table 2 and Fig. S12, ESI†). Similarly, the change in the excited state dipole moment for **1** is large compared to **2–6** (for **1**: ∼15 Debye and 6–9 Debye for **2–6**) (Table S1 and Fig. S13, ESI†). The optical band gap of vitamin E is 5.17 eV and ethenyls **2–6** are comparable (TDDFT: 3.82–3.79 eV; Tauc plot: 3.24–3.31 eV). On the other hand, compound **1** has an optical band gap that is 0.8 eV lower (TDDFT: 3.06 eV; Tauc plot: 2.37 eV) as compared to **2–6**. Similarly, the ground state dipole moments of vitamin E, compound **4** and **5** are 0.80–1.37 Debye (vitamin E: 0.80 Debye, **4**: 1.05 Debye, **5**: 1.37 Debye), whereas the dipole moment of compound **6** is a little larger (2.44 Debye). Therefore, the dipole moment is increased with the increasing electron withdrawing nature of the substituent (**1**-NO_2: 8.39 Debye, **2**-Cl: 3.99 Debye, **3**-H: 2.57 Debye). Interestingly, the antioxidant efficacy is decreased with the increasing electron withdrawing nature of the *p*-phenyl substitution. The order of the antioxidant capacity is vitamin E ∼ **5**-OH ∼ **4**-OCH_3 > **3**-H ∼ **6**-NH_2 > **2**-Cl > **1**-NO_2. This indicates an inverse relationship between

Table 2 TDDFT computed, ground state dipole moment (μ_g), optical band gap, BDE and IP of the indolic ethenyls (**1–6**)

Compound	μ_g (Debye)	Optical band gap (eV)	BDE (kcal mol^{-1})	ΔBDE (kcal mol^{-1})	IP (kcal mol^{-1})	ΔIP (kcal mol^{-1})
Vitamin E (IC_{50}: 26 μM)	0.80	5.17	82.97 (–OH)	0	157.43	0
 **1** (IC_{50}: Nil)	8.39	3.05	103.39 (–NH)	20.42	161.05	3.62
 **2** (IC_{50}: 63 μM)	3.99	3.82	97.65 (–NH)	14.68	151.44	−5.99
 **3** (IC_{50}: 31 μM)	2.57	3.86	96.11 (–NH)	13.14	150.31	−7.12
 **4** (IC_{50}: 30 μM)	1.05	3.84	97.17 (–NH)	14.20	144.36	−13.07
 **5** (IC50: 24 μM)	1.37	3.85	98.44 (–NH) 94.10 (–OH)	15.47 11.13	145.38	−12.05
 **6** (IC_{50}: 34 μM)	2.44	3.79	95.79 (–NH) 105.38 ($–NH_2$)	12.82 22.41	140.10	−17.33

the antioxidant capacity and the dipole moment of the compound (Table 2 and Fig. S12, ESI†). Similarly, it is shown that compound **1**, with a smaller optical band gap (2.37 eV), does not show antioxidant activity, whereas compounds **3–5** with optical band gaps of approximately ∼3.30 eV exhibit an antioxidant activity that is comparable to that of vitamin E.

3.4 TDDFT studies of the ethenyl indoles (1–6)

In recent years, TDDFT studies have been carried out to understand anti-oxidation mechanisms in detail. Such activities can be determined by calculating the chemical properties such as the BDE, IP, PA, PDE and ETE of the antioxidants. In many biological systems, the antioxidant properties of the phenolic compounds (Ar–OH) are dependent upon the stability of the phenoxyl radical (Ar–O$^{\bullet}$) and act through proton transfer mechanism.[40,44,51–58] It is known that phenol- or tryptophan-like antioxidants act *via* a H atom transfer mechanism owing to them having low BDEs.[41,59] It is also known that these molecules have the smallest BDE owing to the resonance or intramolecular hydrogen bonding within the molecule and hence, exhibit a larger antioxidant activity.[41,59] Similarly, resveratrol-like antioxidants work through the electron transfer mechanism owing to their small IP values and negative ΔIP values as compared to phenol and its related compounds.[47] Thus, TDDFT computation was carried out on the ethenyl indoles (**1–6**) and various parameters such as the BDE, IP, PA, PDE and ETE were calculated, as shown in Tables 2 and 3.

The BDE is a very important thermodynamic parameter, which is used to characterize the ability of a compound to undergo a homolytic reaction. For ethenyl indoles, the BDEs of indolic NH, aniline NH and phenol OH are 96, 105 and 94 kcal mol^{-1} respectively. Thus, the BDE of the aniline NH bond is 10 kcal mol^{-1} higher compared to that of the indolyl NH bond. The BDE of the indolyl NH bond is increased further in the presence of an electron withdrawing substituent (NO_2, Cl), whereas the BDE is reduced in the presence of an electron donating substituent (NH_2, OH, OCH_3). The highest BDE of 103 kcal mol^{-1} for nitro compound **1** and the lowest BDE of 95 kcal mol^{-1} for amine **6** were found. This indicates that the electron withdrawing group stabilizes the ethenyl indole and destabilizes its free radical, whereas an electron donating group destabilizes the neutral molecule and stabilizes the radical through the delocalization of unpaired electrons, which is well known in other reported amine compounds.[58] Recently the radical quenching activities of the hydroxy spiroselenuranes were shown to have similar results. In these molecules, the electron withdrawing benzamide ring reduced the antiradical activity, whereas the electron donating aniline ring increased the antioxidant properties owing to the stabilization of the free radical.[60] Similarly, in ethoxyquin, and dihydroquinoline compounds, the extensive delocalization of the aminyl radical leads to a lower BDE (∼81 kcal mol^{-1}) and exhibits better antioxidant properties compared to those of α-tocopherol.[61,62] Thus, thermodynamic compounds with lower BDE values may

Table 3 TDDFT computed, PDE, PA, and ETE of the indolic ethenyls (**1–6**)

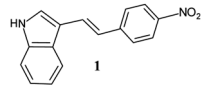
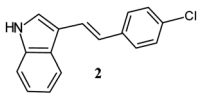
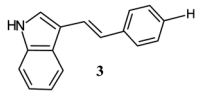
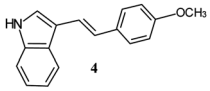
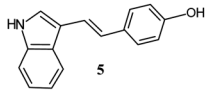
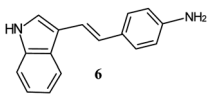
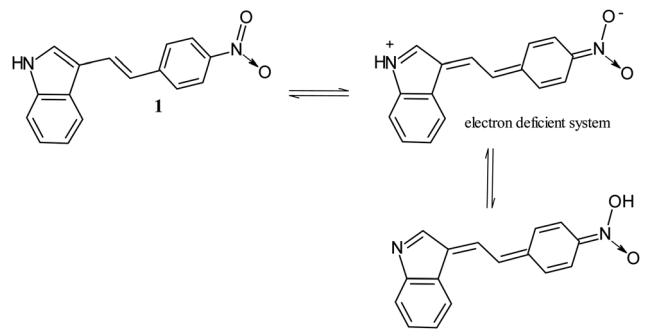
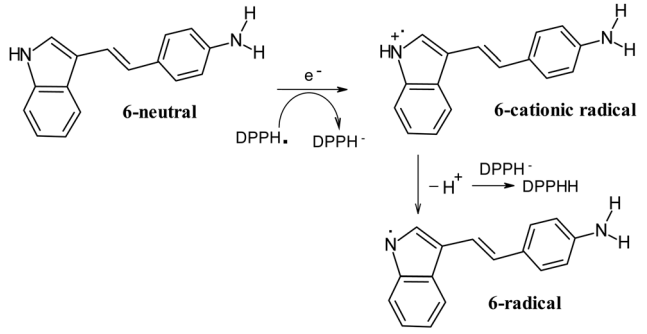
Compound	PDE (kcal mol^{-1})	ΔPDE (kcal mol^{-1})	PA (kcal mol^{-1})	ΔPA (kcal mol^{-1})	ETE (kcal mol^{-1})	ΔETE (kcal mol^{-1})
Vitamin E (IC_{50}: 26 μM)	236.37	0	365.34	0	29.19	0
 **1** (IC_{50}: Nil)	253.18	16.81	349.93	−15.40	63.54	34.35
 **2** (IC_{50}: 63 μM)	257.05	20.68	354.61	−10.72	53.12	23.93
 **3** (IC_{50}: 31 μM)	256.63	20.26	355.95	−9.38	50.24	21.05
 **4** (IC_{50}: 30 μM)	263.64	27.27	359.92	−5.41	47.34	18.15
 **5** (IC_{50}: 24 μM)	263.90 259.56	27.53 23.19	361.69 363.84	−3.64 −1.49	46.83 40.35	17.64 11.16
 **6** (IC_{50}: 34 μM)	266.52 276.11	30.15 39.74	362.41 390.30	−2.92 +24.96	43.46 25.16	14.27 −4.03

exhibit higher antioxidant activity. In the case of ethenyl indoles, the antioxidant activity is increased with the increasing donating ability of the substituent with a lower BDE. Thus, the antioxidant activity in ethenyl indoles could be a result of a thermodynamically controlled HAT mechanism. Nitro compound **1** does not show any activity. This could be a result of the formation of an electron delocalized charge transfer resonating structure (Scheme 2), which is unable to donate a hydrogen or electron. This type of inactivity is found in organotellurium compounds that rapidly convert to a product which cannot act as a hydrogen donor or electron donor to a peroxy radical.[63]



Scheme 2 The lack of antioxidant activity in ethenyl indole (**1**) is a result of the charge transfer and formation of a stable electron deficient resonating structure.

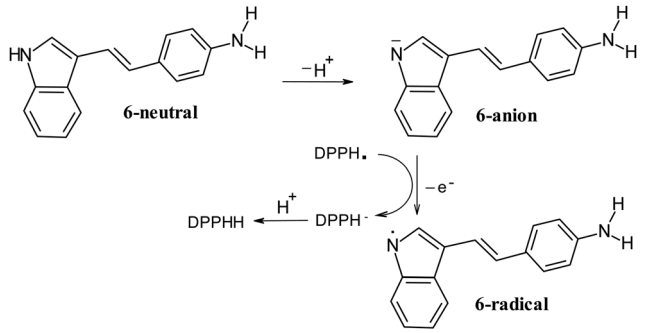
For the SET-PT mechanism, the IP and the highest occupied molecular orbital (HOMO) energy represent the electron donating capability of an antioxidant. It is known that the electron withdrawing substituent stabilizes the neutral molecule, which leads to a lower HOMO energy (more negative) and destabilizes the radical and the radical cation, which results in an increase in the IP energy.[59,64] On the other hand, the electron donating substituent stabilizes the radical and the radical cation and destabilizes the neutral molecule, which results in a higher HOMO energy (less negative) and a decrease in the IP values.[59,65,66] In the present ethenyl indoles, a higher IP of 161 kcal mol^{-1} for the nitro compound **1** and a lower IP of 140 kcal mol^{-1} for the amino compound **6** was found. Upon increasing the donating ability of the substituent, the IP is decreased with the increasing HOMO energy. The IP order is NO_2 > Cl > H > OCH_3 ~ OH > NH_2. The smaller IP value in the presence of a donating substituent could be a result of the stabilization of the cationic free radical through a mesomeric effect. There is a correlation between the HOMO and LUMO energies of the compounds and the antioxidant efficacy. The lowest unoccupied molecular orbital (LUMO), as well as the HOMO energy, is gradually decreased (more negative) with the increasing electron withdrawing nature of the substituent and the highest negative HOMO–LUMO energy was computed for **1** (HOMO: −5.51 eV, LUMO: −2.46 eV). On the other hand, the highest HOMO energy was computed for the hydroxy (**5**) and amino compound (**6**) (HOMO: −4.62 eV, LUMO: −0.83 eV).



Scheme 3 Antioxidant properties of ethenyl indole (**6**) through a SET-PT mechanism *via* a cationic radical intermediate.

As the HOMO is related to the ionization energy, a larger HOMO energy for a molecule leads to a favorable ionization process and thus, favors the anti-oxidation process (Fig. S10, ESI†). Similarly, ethenyl indole with a large optical band gap exhibits better antioxidant properties (Fig. S11, ESI†). The involvement of the electron delocalization in molecule **1** leads to a smaller optical band gap with a large ground state dipole moment (μ_g) and the molecule is electron deficient in nature, (**1**-NO_2 substitution, μ_g: 8.39 Debye). This molecule exhibits no antioxidant activity (Fig. S12, ESI†). The HOMO and LUMO energy and the optical band gap of the neutral (NH), cationic (NH+), free radical ($N^{\bullet}$) and anion (N^{-}) groups of the ethenyls were computed (Fig. S13–S15, ESI†). It can be seen that the HOMO and LUMO energy of the neutral and free radical species are comparable (difference 0.2–0.4 eV). The cationic radical species are more stable by 4 eV as compared to the neutral ethenyl indole. Thus, ethenyl indole with a donating substituent can easily give an electron and exhibits better antioxidant properties through the SET-PT mechanism (Scheme 3).

The other possible mechanism is the SPLET *via* the anionic intermediate, as shown in Scheme 4. In this mechanism the role of PA, the reaction enthalpy, is important. The PA of indolic NH, phenyl amine NH and phenol OH were found to be 362, 390 and 363 kcal mol^{-1} respectively. It is well known that the electron donating group increases the PA, whereas the electron withdrawing group decreases the PA.[59,67] The highest PA of 362 kcal mol^{-1} for indolic NH and 390 kcal mol^{-1} for phenyl NH was found for the amino compound **6** and a lower PA of 349 kcal mol^{-1} was found for the nitro compound **1**. The ethenyl indole with NO_2 substitution shows the largest decrease in PA by 11 kcal mol^{-1}. The increasing order of PA energy is as follows: **6** > **5** > **4** > **3** > **2** > **1** and the antioxidant capacity is in the reverse order IC_{50} (*e.g.* **5** > **6** > **4** > **3** > **2** > **1**). Thus, if any anion is generated through proton abstraction by following the SPLET mechanism (Scheme 4), then the indolyl anion could be further stabilized in the presence of an electron withdrawing substituent with a consequent decrease in the PA and an increased in the antioxidant activity. However, in the present ethenyl the antioxidant activity is enhanced in the presence of an electron donating substituent. Thus, the SPLET pathway can be ruled out.



Scheme 4 Antioxidant properties of ethenyl indole (**6**) through proton loss followed by an electron and proton transfer *via* the anionic intermediate, a less favorable mechanism.

The PDE and ETE also provide useful information for the later step in the SET-PT and SPLET mechanisms respectively[68,69] (Schemes 3 and 4). Thus, the substituent dependent BDE, PA, IP, PDE and ETE energy data can provide further insights into the preferred thermodynamic mechanism for the antioxidant activity for ethenyl indole. The PDE and ETE were determined and are shown in Table 2.

The highest PDE of 276 kcal mol^{-1} for the cationic phenyl amine radical and 266 kcal mol^{-1} for the cationic indolic NH radical were found for the strong electron donating amine compound **6**, whereas the lowest PDE of 253 kcal mol^{-1} for the cationic indolic NH radical was found for the strong electron withdrawing nitro compound **1**. This is because the electron donating substituent stabilizes the radical cation more as compared to the electron withdrawing group. Thus, the PDE is larger for the ethenyl with a strong electron donating amine substituent and it requires a higher energy for the dissociation of the proton from the radical cation intermediate. Similarly, the lowest ETE of 43 kcal mol^{-1} for the indolic anion, and 25 kcal mol^{-1} for the phenyl amine anion were found for compound **6**, whereas the highest ETE of 63 kcal mol^{-1} was found for the nitro compound **1**. It is known that a more stabilized anion requires a higher energy to transfer the electron to the free radical.[59,68,69]

Thus, in the presence of an electron-withdrawing substituent, the indolic ethenyl shows a higher BDE, IP and ETE, whereas a higher PA and PDE is found in the presence of an electron-donating substituent. For all the ethenyl indoles, the BDE is lower compared to the IP and PA energy, and thus, these compounds can follow the thermodynamically controlled HAT mechanism. It is also worth mentioning that single electron transfer followed by proton transfer (SET-PT) could also be a possible mechanism as per the experimental results on the antioxidant activity. The amine and hydroxy compounds have a lower IP energy owing to the formation of a more stable cationic radical and thus, exhibit better antioxidant properties. On the other hand, the SPLET mechanism is a preferred thermodynamic process for the electron withdrawing substituent. However, the nitro substituted ethenyl indole does not show any antioxidant activity and the chloro substituted ethenyl indole shows a lower activity and therefore the SPLET mechanism can be ruled out.

4. Conclusion

In summary, ethenyl indoles with various donors or acceptor substituents were synthesized and their substituent dependent antioxidant activity was studied using a DPPH assay and the TDDFT method.

The ethenyl indole with an electron withdrawing nitro compound does not show antioxidant properties owing to charge transfer and the electron deficient system. Ethenyl with a moderate electron withdrawing chloro substituted compound show a reduced activity, whereas ethenyls with an electron donating substituent (OCH_3, OH, NH_2) show antioxidant properties comparable to those of vitamin E. From the experimental and computed BDE, IP and PA values of the ethenyl indoles, it is suggested that these compounds prefer HAT as well as the SET-PT for the radical quenching process. The nature of the substitution also plays an important role in determining the antioxidant activities. Overall, the present indole-based donor and acceptor ethenyls exhibit substituent dependent antioxidant activity, which is interesting. As the anti-oxidation mechanism is very complex, kinetic studies on these molecules can provide further insights into the mechanism of action in detail. These experimental and computational results, however, provide a new direction for designing and developing novel molecules with efficient antioxidant properties.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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