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Solubility and thermodynamics of 4-(4-ethoxyphenyl)-5-(3,4,5-trimethoxybenzoyl)-3,4-dihydropyrimidin-2(1*H*)-one in various pure solvents at different temperatures

Faiyaz Shakeel [a,*], Mashooq A. Bhat [b], Nazrul Haq [a]

[a] Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia
[b] Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

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ABSTRACT

Dihydropyrimidine derivatives have great potential in the treatment of various kinds of cancers. The main problem associated with these medicines is the poor solubility of these drugs in an aqueous media. Hence, in the current research work, the solubility of dihydropyrimidine derivative i.e. 4-(4-ethoxyphenyl)-5-(3,4,5-trimethoxybenzoyl)-3,4-dihydropyrimidin-2(1*H*)-one [coded as DHP-5] was measured in twelve different pure solvents such as water, methanol, ethanol, 1-butanol, 2-butanol, isopropyl alcohol (IPA), ethylene glycol (EG), propylene glycol (PG), ethyl acetate (EA), dimethyl sulfoxide (DMSO), polyethylene glycol-400 (PEG-400) and Carbitol® at five different temperatures and atmospheric pressure. Experimental solubilities (expressed as mole fraction) of DHP-5 were fitted and correlated with Van't Hoff and Apelblat models. The solubilities (expressed as mole fraction) of DHP-5 at $T = 318.15$ K were observed highest in PEG-400 (1.21×10^{-2}) followed by DMSO (9.96×10^{-3}), Carbitol® (6.24×10^{-3}), EA (3.45×10^{-3}), 1-butanol (1.46×10^{-3}), 2-butanol (1.45×10^{-3}), PG (1.33×10^{-3}), IPA (1.13×10^{-3}), EG (1.07×10^{-3}), ethanol (8.02×10^{-4}), methanol (5.77×10^{-4}) and water (2.54×10^{-5}) and similar trend was observed at all five different temperatures investigated. Apparent thermodynamic analysis indicated that the dissolution behavior of DHP-5 was spontaneous, endothermic and entropy-driven in all pure solvents investigated.

1. Introduction

Heterocyclic compounds have been reported to have great importance in life due to the presence of their structure subunits in several natural products such as hormones, vitamins and antibiotics [1–3]. These compounds have considerable attention in design and synthesis of biologically active molecules [4,5]. Pyrimidines and dihydropyrimidines are heterocyclic compounds which have been reported to have several therapeutic activities such as analgesic, antipyretic, anti-inflammatory, antiviral, antifungal, antibacterial, antileishmanial, antihypertensive, antidiabetic, antiallergic, anticonvulsant, antioxidant, diuretic, anti-HIV, herbicidal and anticancer activities [6–21]. Nevertheless, dosage form design/formulation development of these derivatives is limited due to their toxic effects and weak solubilization power in water. The IUPAC name of dihydropyrimidine derivative investigated in this work is 4-(4-ethoxyphenyl)-5-(3,4,5-trimethoxybenzoyl)-3,4-dihydropyrimidin-2(1*H*)-one [coded as DHP-5]. This novel compound was obtained as a slightly yellow semi-crystalline solid with the molecular formula and molar mass of $C_{22}H_{24}N_2O_6$ and 412.28 g mol^{-1}, respectively (Fig. 1). This novel compound (DHP-5) was found to show great antitumor activities against breast cancer cells MCF-7 and colon cancer cells LOVO both in vitro as well as in vivo [22]. However, this compound was found to be poorly soluble in water due to which its formulation development was difficult [23–25]. The solubility data of new chemical entities and existing drugs in pure solvents are important in their purification, recrystallization, drug discovery processes and formulation development [23–27]. Hence, it is important to measure the solubility of DHP-5 in various aqueous and organic solvents. The commonly used solvents for solubilization of drugs have been reported as ethanol, water, propylene glycol (PG) and polyethylene glycol-400 (PEG-400) [26,27]. The solubility data of pyrimidine and dihydropyrimidine are poorly reported in literature so far. The solubilities and apparent thermodynamic function of

* Corresponding author.
E-mail address: faiyazs@fastmail.fm (F. Shakeel).

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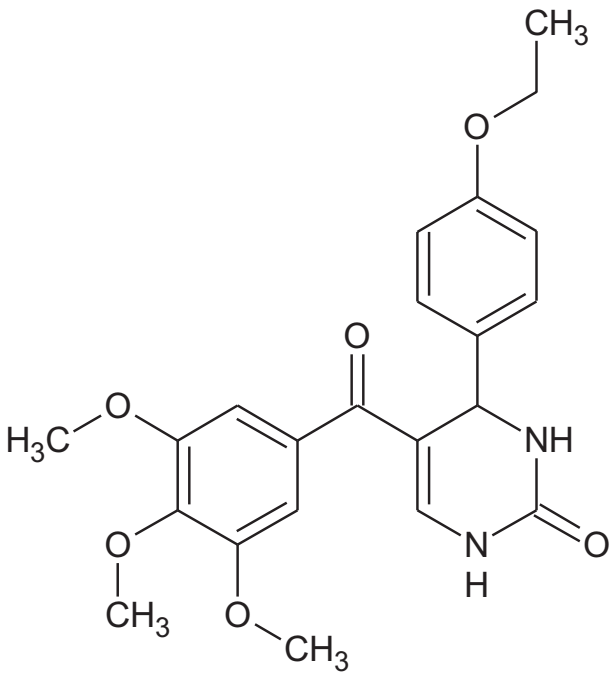

Fig. 1. Molecular structure of DHP-5 (molar mass: 412.28 g mol^{-1}).

DHP-5 in any aqueous or organic solvent or their mixture have not been reported in literature so far. Hence, in the current research work, the solubilities (expressed as mole fractions) of DHP-5 in twelve different pure solvents such as water, methanol, ethanol, Carbitol®, PEG-400, PG, ethylene glycol (EG), isopropanol (IPA), ethyl acetate (EA), 1-butanol, 2-butanol and dimethyl sulfoxide (DMSO) were determined at temperatures $T =$ (298.15 to 318.15) K and pressure $p = 0.1$ MPa. Apparent thermodynamic analysis of solubilities of novel anticancer compound DHP-5 was carried out using Van't Hoff and Krug et al. analyses. The solubility values of DHP-5 obtained in this work could be useful in several processes such as recrystallization, purification, preformulation studies and formulation development of DHP-5.

2. Experimental

2.1. Materials

DHP-5 was synthesized and characterized in the Laboratory of Pharmaceutical Chemistry, King Saud University, Riyadh, Saudi Arabia. Methyl alcohol (IUPAC name: methanol), ethyl alcohol (IUPAC name: ethanol), 1-butyl alcohol (IUPAC name: 1-butanol), 2-butyl alcohol (IUPAC name: 2-butanol), IPA (IUPAC name: isopropanol) and Carbitol® (IUPAC name: diethylene glycol monoethyl ether) were obtained from Sigma Aldrich (St. Louis, MO). PEG-400 (IUPAC name: polyethylene glycol-400), PG (IUPAC name: 1,2-propanediol), EA (IUPAC name: ethyl acetate), DMSO (IUPAC name: dimethyl sulfoxide) and EG (IUPAC name: 1,2-ethanediol) were obtained from Fluka Chemica (Buchs, Switzerland). Water was obtained from a water purification unit in the laboratory. The details about materials used in this work are presented in supplementary Table 1 (Table S1).

2.2. Synthesis, characterization and identification of compound DHP-5

The synthesis of compound DHP-5 was carried out in a single step. Enaminone was reacted with *p*-ethoxybenzaldehyde and urea in presence of acetic acid to yield the compound DHP-5. The synthesized compound DHP-5 was characterized in terms of yield, purity, melting point, FT-IR spectra, GC–MS spectra, ^{1}H NMR spectra, ^{13}C NMR spectra and elemental analyses [22]. The yield and melting point of compound DHP-5 were recorded as 60% and (168 to 170) ^{0}C, respectively. The purity of DHP-5 was confirmed by elemental analysis and thin layer chromatography. The structure elucidation of compound DHP-5 was based on FT-IR spectra, GC–MS spectra, ^{1}H NMR spectra, ^{13}C NMR spectra and elemental analyses. FT-IR spectra of compound DHP-5 are shown in supporting information Fig. 1 (Fig. S1). The characteristics FT-IR peaks of compound DHP-5 were appeared at 3411 cm^{-1} (N—H), 2938 cm^{-1} (ArC-H), 1696 cm^{-1} (C═O), 1648 cm^{-1} (C═O), 1618 cm^{-1} (C═C) and 1126 cm^{-1} (C—O). GC–MS spectra of compound DHP-5 are shown in Fig. S2 which also supported the FT-IR results. ^{1}H NMR spectra of compound DHP-5 are shown in Fig. S3. In the ^{1}H NMR spectra, the signals of the individual protons of the compounds were verified on the basis of multiplicity, chemical shifts and coupling constant. The compound showed the D_2O exchangeable broad singlet at 8.8 ppm and 9.5 ppm corresponding to NH protons. ^{13}C NMR spectra of compound DHP-5 are shown in Fig. S4 which also supported its spectral identification. The results of elemental analyses are listed in Table S2. The mass fractions (%) of C, H and N were similar with their calculated mass fractions. Overall, analytical and spectral data of the compound DHP-5 were in good agreement with the composition of the synthesized compound.

2.3. Analyses of DHP-5

The amount of DHP-5 present in solubility samples was analyzed with the help of reversed phase high performance liquid chromatography (HPLC) equipped with ultra-violet (UV) detector (HPLC-UV) at the wavelength of 300 nm. This analysis was performed at 298.15 K using HPLC system (Waters, USA). The chromatographic conditions and column used in this work were same as described in analyses of bergenin in solubility samples [28]. The combination of ethanol:methanol (50:50% v/v) was utilized as the mobile phase in this work. The elution of DHP-5 was performed at a flow rate of 1.0 mL min^{-1} at the wavelength of 300 nm. The calibration curve was plotted between the concentration of DHP-5 and measured HPLC area. The calibration curve was observed linear in the range of $(1-100)$ μg g^{-1} with coefficient of determination (R^2) value of 0.9993. The equation of regressed line was obtained as $y = 19{,}258 \times + 7734.3$; in which x is the concentration of DHP-5 and y is the measured HPLC area. The proposed analytical method was validated for the linearity, accuracy, precision, sensitivity and specificity.

2.4. Measurement of DHP-5 solubility

The solubility of DHP-5 in twelve different pure solvents was determined with the help of an isothermal method [29]. The experiments were performed at five different temperature i.e. $T =$ (298.15 to 318.15) K and $p = 0.1$ MPa. The excess amount of DHP-5 was added in known quantities of each pure solvent in triplicates. The sample mixtures were transferred to biological shaker (Julabo, PA) at 100 rpm for 3 days. After equilibrium reached (preliminary studies were carried out to optimize an equilibrium time), each sample mixture was taken out from the shaker and allowed to settle solid DHP-5 particles for the period of 24 h [28]. After 24 h settling of solid DHP-5 particles, supernatants were taken, diluted with mobile phase and subjected for the quantification of DHP-5 content by HPLC-UV method described above at the wavelength of 300 nm. The experimental solubilities (expressed as mole fraction) of DHP-5 (x_e) were calculated by using the standard formula reported in literature [26,27].

3. Results and discussion

3.1. Experimental solubility data of DHP-5

Measured x_e values of DHP-5 in twelve different pure solvents at $T =$ (298.15 to 318.15) K and $p = 0.1$ MPa are listed in Table 1.

Table 1
Experimental solubilities (x_e, expressed as mole fraction) of DHP-5 in different pure solvents (S) at temperatures T = (298.15 to 318.15) K and pressure p = 0.1 MPa[a].

	x_e				
S	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K	T = 318.15 K
Water	7.87×10^{-6}	1.09×10^{-5}	1.51×10^{-5}	2.02×10^{-5}	2.54×10^{-5}
Ethanol	2.94×10^{-4}	4.02×10^{-4}	5.16×10^{-4}	6.54×10^{-4}	8.02×10^{-4}
IPA	4.69×10^{-4}	6.19×10^{-4}	7.72×10^{-4}	9.58×10^{-4}	1.13×10^{-3}
EG	3.97×10^{-4}	5.43×10^{-4}	6.97×10^{-4}	8.66×10^{-4}	1.07×10^{-3}
(*RS*)-PG	5.04×10^{-4}	6.82×10^{-4}	8.70×10^{-4}	1.07×10^{-3}	1.33×10^{-3}
PEG-400	5.21×10^{-3}	6.75×10^{-3}	8.31×10^{-3}	1.03×10^{-2}	1.21×10^{-2}
Carbitol	3.01×10^{-3}	3.67×10^{-3}	4.41×10^{-3}	5.19×10^{-3}	6.24×10^{-3}
1-Butanol	6.72×10^{-4}	8.59×10^{-4}	1.05×10^{-3}	1.25×10^{-3}	1.46×10^{-3}
(*RS*)-2-Butanol	6.70×10^{-4}	8.55×10^{-4}	1.04×10^{-3}	1.24×10^{-3}	1.45×10^{-3}
EA	1.43×10^{-3}	1.74×10^{-3}	2.22×10^{-3}	2.86×10^{-3}	3.45×10^{-3}
DMSO	5.47×10^{-3}	6.50×10^{-3}	7.54×10^{-3}	8.79×10^{-3}	9.96×10^{-3}
Methanol	2.52×10^{-4}	3.28×10^{-4}	4.07×10^{-4}	4.90×10^{-4}	5.77×10^{-4}

[a] The standard uncertainties u are $u(T)$ = 0.10 K, $u(p)$ = 0.003 MPa and $u_r(x_e)$ = 1.20%.

Literature solubilities of DHP-5 in any of the investigated solvents have not been reported and hence literature comparison was not made in this work. It was observed that the x_e values of DHP-5 were increasing with the rise in temperature in each pure solvent investigated. The x_e values of DHP-5 at T = 318.15 K were observed highest in PEG-400 (1.21×10^{-2}) followed by DMSO (9.96×10^{-3}), Carbitol® (6.24×10^{-3}), EA (3.45×10^{-3}), 1-butanol (1.46×10^{-3}), 2-butanol (1.45×10^{-3}), PG (1.33×10^{-3}), IPA (1.13×10^{-3}), EG (1.07×10^{-3}), ethanol (8.02×10^{-4}), methanol (5.77×10^{-4}) and water (2.54×10^{-5}) and similar trend was observed at all five different temperatures investigated. The x_e values of DHP-5 in PEG-400, DMSO and Carbitol® were significantly higher in comparison with its x_e values in other pure solvents studied. For nonpolar solutes such as DHP-5, the solubility is inversely proportional to the dielectric constant/polarity of the solvent. The highest x_e values of DHP-5 were observed in PEG-400 that could be probably due to higher molar mass and lower dielectric constant/polarity of PEG-400 in comparison with pure water [28]. The x_e values of DHP-5 in DMSO were lower than its x_e values in PEG-400. This observation was due to lower molar mass and higher dielectric constant/polarity of DMSO in comparison with PEG-400. Therefore, the x_e values of solute depend not only on dielectric constant/polarity but also on molecular structure and molar mass of the solvent. The solubility values of DHP-5 obtained in the current research work could be really useful in several processes such as recrystallization, purification, preformulation studies and formulation development of DHP-5.

3.2. Correlation of x_e values of DHP-5

The x_e values of DHP-5 obtained in this work were correlated with semiempirical mathematical models such as Apelblat and Van't Hoff models [28,30,31]. The Apelblat solubility (x^{Apl}) of DHP-5 was calculated using Eq. (1) as reported in literature [30,31]:

$$\ln x^{Apl} = A + \frac{B}{T} + C \ln (T) \quad (1)$$

In which, T is already defined and the symbols A, B and C are the parameters/coefficients of Apelblat model. Apelblat parameters were determined by multivariate regression analysis of x_e values of DHP-5 presented in Table 1 [25]. The correlation between x_e and x^{Apl} values of DHP-5 was performed by the calculation of root mean square deviations (*RMSD*). The *RMSD* values were determined by using its standard formula presented in our previous article [27].

The graphical correlation between natural logarithmic x_e and x^{Apl} values of DHP-5 in each pure solvent against 1/T is shown in Fig. 2. These results indicated good graphical correlation between natural logarithmic x_e and x^{Apl} values of DHP-5 (Fig. 2). The resulting data of this correlation are listed in Table 2. The *RMSD* values in twelve different pure solvents were obtained in the range of (0.44 to 1.72) %. The *RMSD* value was observed highest in EA (1.72%) followed by PG, water, EG, PEG-400, ethanol, IPA, 1-butanol, Carbitol®, 2-butanol, methanol and DMSO. However, the R^2 values for DHP-5 were obtained in the range of 0.9974 to 0.9999. The observed *RMSD* and R^2 values for DHP-5 indicated good correlation of x_e values of DHP-5 with Apelblat model.

The Van't Hoff model solubility ($x^{van't}$) of DHP-5 was calculated using Eq. (2) as reported in literature [28]:

$$\ln x^{van't} = a + \frac{b}{T} \quad (2)$$

In which, the symbols a and b are the coefficients/model parameters of Van't Hoff model. The parameters a and b were determined by plotting ln x_e values of DHP-5 against 1/T.

The correlations between x_e and $x^{van't}$ values of DHP-5 was performed using *RMSD* values [27].

The graphical correlation between natural logarithmic x_e and $x^{van't}$ values of DHP-5 in each solvent against 1/T was recorded similar as discussed for Apelblat correlation and hence Figure is not reported for this correlation. The resulting data of this correlation are listed in Table 3. The *RMSD* values in twelve different pure solvents were recorded as (0.57 to 2.27) %. The *RMSD* value for DHP-5 was recorded highest in EG (2.27%) and IPA (2.27%) followed by methanol, water, ethanol, PG, 1-butanol, PEG-400, 2-butanol, EA, DMSO and Carbitol®. The R^2 values for DHP-5 were obtained in the range of 0.9941 to 0.9995. The obtained *RMSD* and R^2 values for DHP-5 again indicated good correlation of x_e values of DHP-5 with Van't Hoff model.

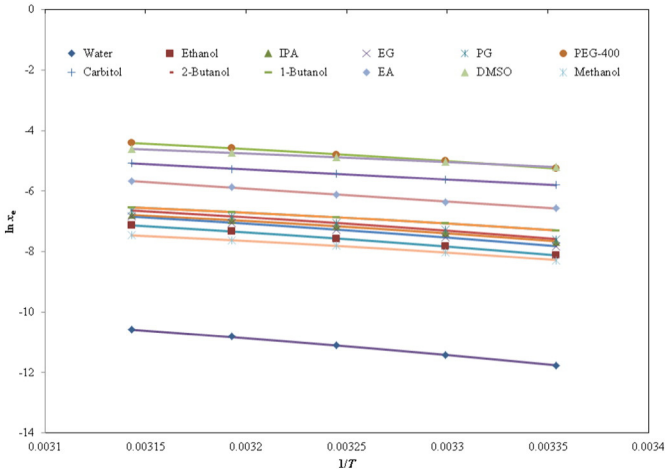

Fig. 2. Correlation of experimental logarithmic solubilities (ln x_e) of DHP-5 with Apelblat model in twelve different pure solvents against 1/T; symbols represent the experimental logarithmic solubilities of DHP-5 while the solid lines represent the logarithmic solubilities calculated by Apelblat model.

Table 2
Apelblat parameters (A, B and C), R^2 and *RMSD* (%) for DHP-5 in different pure solvents (*S*).

S	*A*	*B*	*C*	R^2	*RMSD* (%)
Water	610.41	−33,167.30	−89.67	0.9999	1.07
Ethanol	583.18	−31,015.00	−85.52	0.9990	0.73
(*RS*)-PG	524.95	−28,158.40	−76.89	0.9984	1.08
PEG-400	480.66	−25,605.90	−70.21	0.9990	0.87
Carbitol	−13.31	−2549.03	2.82	0.9994	0.59
EG	545.48	−29,215.70	−79.91	0.9985	0.93
IPA	581.26	−30,437.40	−85.44	0.9991	0.62
1-Butanol	521.77	−27,262.50	−76.81	0.9990	0.60
(*RS*)-2-Butanol	507.74	−26,620.80	−74.72	0.9991	0.57
EA	−64.09	−992.54	50.19	0.9974	1.72
DMSO	197.06	−11,651.60	−28.64	0.9996	0.44
Methanol	623.42	−32,165.80	−91.93	0.9990	0.45

3.3. Apparent thermodynamic analyses for DHP-5 dissolution

Apparent thermodynamic analyses were carried out to determine the dissolution behavior of DHP-5 in twelve different pure solvents. Apparent thermodynamic analyses were performed by the calculation of three thermodynamic parameters such as standard dissolution enthalpy ($\Delta_{sol}H^0$), standard Gibbs energy ($\Delta_{sol}G^0$) and standard entropy ($\Delta_{sol}S^0$). The $\Delta_{sol}H^0$ values for the dissolution behavior of DHP-5 in each solvent were determined at mean harmonic temperature (T_{hm}) using Van't Hoff analyses with the help of Eq. (3) [32,33]:

$$\left(\frac{\partial \ln x_e}{\partial\left({}^{1}/_{T}-{}^{1}/_{T_{hm}}\right)}\right)_P = -\frac{\Delta_{sol}H^0}{R} \tag{3}$$

In this way, the $\Delta_{sol}H^0$ values for DHP-5 dissolution were determined by plotting ln x_e values of DHP-5 against ${}^{1}/_{T}-{}^{1}/_{T_{hm}}$. These Van't Hoff plots were observed as linear with R^2 values in the range of 0.9951 to 0.9995.

The $\Delta_{sol}G^0$ values for dissolution behavior of DHP-5 were also determined at T_{hm} by using the approach of Krug et al. analyses [34]. The $\Delta_{sol}S^0$ values for dissolution behavior of DHP-5 were determined with the help of the combined principles of Van't Hoff and Krug et al. analyses [32–34].

The resulting data of apparent thermodynamic analyses along with R^2 values for the dissolution behavior of DHP-5 in twelve different pure solvents are shown in Table 4.

From the apparent thermodynamic analyses of DHP-5 (Table 4), it can be seen that the $\Delta_{sol}H^0$ values for DHP-5 dissolution in twelve different pure solvents were recorded as positive values in the range of (23.7 to 46.6) kJ mol^{-1}. The $\Delta_{sol}H^0$ value for the dissolution behavior of DHP-5 was recorded highest in pure water (46.6 kJ mol^{-1}) followed by ethanol (39.3 kJ mol^{-1}), EG (38.7 kJ mol^{-1}), PG (37.6 kJ mol^{-1}), EA (35.5 kJ mol^{-1}), IPA (34.7 kJ mol^{-1}), PEG-400 (33.5 kJ mol^{-1}), methanol (32.5 kJ mol^{-1}), 2-butanol (30.4 kJ mol^{-1}), 1-butanol (30.4 kJ mol^{-1}), Carbitol® (28.4 kJ mol^{-1}) and DMSO (23.7 kJ mol^{-1}). In general, the $\Delta_{sol}H^0$ values for DHP-5 dissolution were recorded lower for pure solvents with higher x_e values such as DMSO and Carbitol®. However, the $\Delta_{sol}H^0$ values for DHP-5 dissolution were recorded higher for pure solvents with lower x_e values such as water, ethanol, EG and PG. The $\Delta_{sol}G^0$ values for dissolution behavior of DHP-5 in twelve different pure solvents were also recorded as positive values in the range of (12.3 to 28.5) kJ mol^{-1}. The $\Delta_{sol}G^0$ value for dissolution behavior of DHP-5 was also recorded highest in water (28.5 kJ mol^{-1}) followed by methanol (20.0 kJ mol^{-1}), ethanol (19.4 kJ mol^{-1}), EG (18.6 kJ mol^{-1}), IPA (18.4 kJ mol^{-1}), PG (18.1 kJ mol^{-1}), 1-butanol (17.6 kJ mol^{-1}), 2-butanol (17.6 kJ mol^{-1}), EA (15.6 kJ mol^{-1}), Carbitol® (13.9 kJ mol^{-1}), DMSO (12.5 kJ mol^{-1}) and PEG-400 (12.3 kJ mol^{-1}). These results of $\Delta_{sol}G^0$ for dissolution behavior of DHP-5 were in good agreement with results experimental solubilities of DHP-5 in twelve different pure solvents. The results of apparent thermodynamic analyses in terms of $\Delta_{sol}H^0$ and $\Delta_{sol}G^0$s in all pure solvents indicated spontaneous and endothermic dissolution of DHP-5 in all pure solvents investigated. The lower values of $\Delta_{sol}H^0$ and $\Delta_{sol}G^0$s in DMSO, PEG-400 and Carbitol® indicated that relatively lower energies are required for solubilization of DHP-5 in DMSO, PEG-400 and Carbitol® in comparison with other solvents investigated. The $\Delta_{sol}S^0$ values for dissolution behavior of DHP-5 in twelve different pure solvents were also observed as positive values in the range of (36.3 to 68.9) J mol^{-1} K^{-1} which indicated an entropy-driven dissolution of DHP-5 in all pure solvents investigated. The positive values of $\Delta_{sol}H^0$ in all twelve different pure solvents were possible due to strong molecular interactions between DHP-5-solvent molecules in comparison with weak molecular interactions between DHP-5-DHP-5 and solvent-solvent molecules [28,35].

Table 3
Van't Hoff model parameters (*a* and *b*), R^2 and *RMSD* (%) for DHP-5 in different pure solvents (*S*).

S	*a*	*b*	R^2	*RMSD* (%)
Water	7.10	−5617.00	0.9975	2.16
Ethanol	7.78	−4738.70	0.9962	2.14
(*RS*)-PG	7.64	−4535.60	0.9959	2.06
PEG-400	8.29	−4034.90	0.9963	1.84
Carbitol	5.67	−3422.20	0.9995	0.57
EG	7.84	−4664.30	0.9960	2.27
IPA	6.39	−4184.20	0.9954	2.27
1-Butanol	5.00	−3662.60	0.9951	1.98
(*RS*)-2-Butanol	4.99	−3661.10	0.9954	1.81
EA	7.79	−4282.70	0.9972	1.71
DMSO	4.37	−2854.20	0.9987	0.75
Methanol	4.87	−3917.10	0.9941	2.21

Table 4
Apparent thermodynamic quantities ($\Delta_{sol}H^0$, $\Delta_{sol}G^0$ and $\Delta_{sol}S^0$) and R^2 values for dissolution of DHP-5 in different pure solvents (*S*)[a].

S	$\Delta_{sol}H^0$/kJ mol^{-1}	$\Delta_{sol}G^0$/kJ mol^{-1}	$\Delta_{sol}S^0$/J mol^{-1} K^{-1}	R^2
Water	46.6	28.5	58.9	0.9975
Ethanol	39.3	19.4	64.7	0.9962
(*RS*)-PG	37.6	18.1	65.5	0.9960
PEG-400	33.5	12.3	68.9	0.9963
Carbitol	28.4	13.9	47.1	0.9995
EG	38.7	18.6	65.1	0.9960
IPA	34.7	18.4	53.1	0.9955
1-Butanol	30.4	17.6	41.5	0.9951
(*RS*)-2-Butanol	30.4	17.6	41.4	0.9954
EA	35.5	15.6	64.7	0.9972
DMSO	23.7	12.5	36.3	0.9988
Methanol	32.5	20.00	40.5	0.9942

[a] The relative uncertainties are $u(\Delta_{sol}H^0) = 0.68$ kJ mol^{-1}, $u(\Delta_{sol}G^0) = 0.22$ kJ mol^{-1} and $u(\Delta_{sol}S^0) = 1.65$ J mol^{-1} K^{-1}.

4. Conclusion

The mole fraction solubilities of an anticancer compound DHP-5 in twelve different pure solvents were determined at $T = (298.15$ to $318.15)$ K and $p = 0.1$ MPa. The solubilities of DHP-5 were found to be increasing with the rise in temperature in all twelve different pure solvents investigated. The correlation and curve fitting results indicated good correlation of experimental solubility data of DHP-5 with Van't Hoff and Apelblat models. The mole fraction solubility of DHP-5 was observed highest in PEG-400 followed by DMSO, Carbitol®, EA, 1-butanol, 2-butanol, PG, IPA, EG, ethanol, methanol and water at all five different temperatures investigated. The results of apparent thermodynamic analyses of solubility data of DHP-5 indicated spontaneous, endothermic and entropy-driven dissolution behavior of DHP-5 in all twelve different pure solvents investigated.

Conflict of interest

The authors state that they do not have any conflict of interest associated with this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.molliq.2016.10.047.

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