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Correlation of pazopanib solubility in (ethyl acetate + ethanol) and (ethyl acetate + 2-propanol) cosolvent mixtures at different temperatures using different mathematical models

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SUMMARY

Objectives: To evaluate the predictive capacity and relevance of six mathematical models for correlating Pazopanib solubility in ethyl acetate + ethanol and ethyl acetate + 2-propanol cosolvent mixtures. **Methods:** A Python-based computational framework using nonlinear optimization algorithms (Levenberg-Marquardt) was employed to fit van't Hoff, Buchowski-Ksiazczak (λh), Apelblat, van't Hoff-Yaws, Wilson, and NRTL models to experimental data ranging from 288.15 K to 328.15 K. **Results:** Although three-parameter models (Apelblat and van't Hoff-Yaws) yielded nearly perfect statistical fits (R^2 ≈0.9999), they suffered from severe multicollinearity and coefficients lacking physical significance. Two-parameter semi-empirical models, particularly van't Hoff and λh, demonstrated greater stability and thermodynamic consistency. Activity coefficient-based models (Wilson and NRTL) exhibited severe numerical instability and an order-of-magnitude increase in residual errors. **Conclusions:** For industrial design and solubility prediction, the van't Hoff and Buchowski-Ksiazczak models are technically superior due to their parsimony and statistical robustness, whereas activity-based models prove unreliable for this specific system.

***Keywords*:** Solubility; pazopanib; cosolvency; mathematical models; thermodynamics.

RESUMEN

Correlación de la solubilidad de pazopanib en mezclas de cosolventes (acetato de etilo + etanol) y (acetato de etilo + 2-propanol) a diferentes temperaturas utilizando diferentes modelos matemáticos

Objetivo: Evaluar la capacidad predictiva y pertinencia de seis modelos matemáticos para correlacionar la solubilidad de Pazopanib en mezclas cosolventes de acetato de etilo con etanol y 2-propanol. **Métodos**: Se empleó un marco computacional en Python utilizando algoritmos de optimización no lineal (Levenberg-Marquardt) para ajustar los modelos de van't Hoff, Buchowski-Ksiazczak (λh), Apelblat, van't Hoff-Yaws, Wilson y NRTL a datos experimentales entre 288.15 K y 328.15 K. **Resultados**: Los modelos de tres parámetros (Apelblat y van't Hoff-Yaws) alcanzaron ajustes estadísticos superiores ($R^2 \approx 0.9999$), aunque presentaron multicolinealidad severa y coeficientes sin significado físico. Los modelos de dos parámetros, especialmente van't Hoff y λh, mostraron mayor estabilidad y consistencia termodinámica. Los modelos basados en coeficientes de actividad (Wilson y NRTL) exhibieron inestabilidad numérica y errores significativamente mayores, evidenciados en el análisis de residuales. Conclusiones: Para fines de diseño industrial y predicción, los modelos de van't Hoff y Buchowski-Ksiazczak son técnicamente superiores debido a su parsimonia y robustez estadística, mientras que los modelos de tres parámetros y de coeficientes de actividad resultan poco fiables para la caracterización termodinámica de este sistema.

***Palabras clave*:** Solubilidad; pazopanib; cosolvencia; modelos matemáticos; termodinámica.

RESUMO

Correlação da solubilidade do pazopanibe em misturas de cossolventes (acetato de etila + etanol) e (acetato de etila + 2-propanol) em diferentes temperaturas usando diferentes modelos matemáticos

Objetivos: Avaliar a capacidade preditiva e a pertinência de seis modelos matemáticos para correlacionar a solubilidade do Pazopanibe em misturas cossolventes de acetato de etila com etanol e 2-propanol. **Métodos:** Utilizou-se uma estrutura computacional em Python com algoritmos de otimização não linear (Levenberg-Marquardt) para ajustar os modelos de van't Hoff, Buchowski-Ksiazczak (λh) Apelblat, van't Hoff-Yaws, Wilson e NRTL a dados experimentais entre 288,15 K e 328,15 K. **Resultados**: Os modelos de três parâmetros (Apelblat e van't Hoff-Yaws) apresentaram os melhores ajustes estatísticos ($R^2 \approx 0,9999$), porém exibiram problemas de multicolinearidade e falta de significado físico em seus coeficientes. Os modelos semiempíricos de dois parâmetros, especialmente van't Hoff e λh demonstraram maior estabilidade e consistência termodinâmica. Os modelos baseados em coeficientes de atividade (Wilson e NRTL) mostraram instabilidade numérica grave e parâmetros sem validade física. **Conclusões:** Para fins de projeto industrial, os modelos de van't Hoff e Buchowski-Ksiazczak são superiores devido à sua parcimônia e estabilidade estatística, sendo os mais recomendados para a predição da solubilidade neste sistema

***Palavras-chave*:** Solubilidade; pazopanibe; cosolvência; modelos matemáticos; termodinâmica.

1. INTRODUCTION

Solubility stands as one of the most critical physicochemical properties in the design and development of pharmaceutical products, as it directly influences fundamental industrial processes such as formulation, preformulation, purification, and quantification of active ingredients [1-4]. This property has a direct impact on the drug's performance and its ability to achieve the desired therapeutic effect within the body [5, 6]. However, the experimental determination of solubility requires rigorous processes that demand a significant amount of resources, both in terms of time and raw materials [7, 8]. In this context, the use of mathematical models has become an essential strategy, as it allows for the estimation of solubility under conditions different from experimental ones based on a limited number of data points, thus optimizing research resources [9-12].

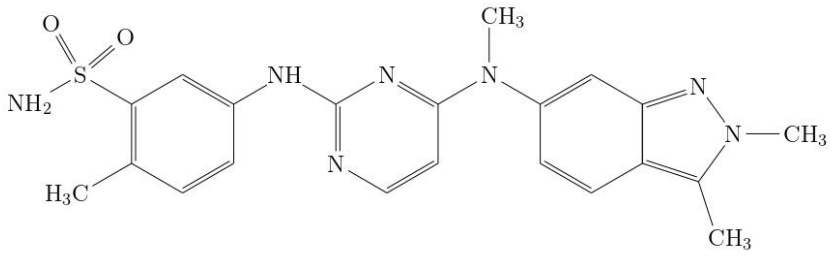

Figure 1. Molecular structure of Pazopanib.

Pazopanib [IUPAC name 5-({4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]pyrimidin-2-yl}amino)-2-methylbenzenesulfonamide (CAS: 444731-52-6), and chemical formula $C_{21}H_{23}N_7O_2S$ see Fig. 1], is a drug of significant therapeutic relevance [13-15]. Although the solubility of various drugs has been widely studied, current research related to new pharmaceutical forms and solvent systems remains necessary to promote greater pharmacological efficiency and more stable formulations [16, 17]. The use of cosolvent mixtures, such as ethyl acetate with alcohols (ethanol and 2-propanol), represents a viable alternative in the industry due to their safety profiles and solvation capacity [18-22]. Therefore, the availability of solubility data and accurate correlation models in these systems is of great industrial and academic relevance [23-27]. For the analysis and correlation of solubility data, scientific literature offers diverse theoretical approaches. Generally, most models relate solubility to one or two independent variables, the most common being temperature and cosolvent composition [28-30]. Among the models describing solubility dependence on temperature, classical thermodynamic equations are prominent [31-35]. The van't Hoff model relates the variation in solubility to the change in temperature, assuming a constant enthalpy of solution [30, 34]. On the other hand, models such as van't Hoff-Yaws and the Apelblat equation account for deviations from linearity in van't Hoff plots, incorporating terms that address the influence of temperature on heat capacity changes (ΔC_p) and solution non-idealities [30, 36, 37]. Likewise, the Buchowski–Ksiazczak (λh) model describes solid-liquid equilibrium through expressions that consider immiscibility in the solid state and negligible effects of pressure changes [38]. Additionally, to understand molecular interactions and the behavior of excess Gibbs energy (g^E) as a function of mixture composition, models based on the concept of local composition are employed. The Wilson equation, proposed in 1963, allows for expressing excess Gibbs energy in multicomponent systems and is useful for indicating deviations from ideality through its adjustable parameters [39, 40]. Similarly, the NRTL (Non-Random Two Liquid) model, developed by Renon and Prausnitz, is applicable to both miscible and partially miscible systems and describes excess Gibbs energy based on energy interaction parameters and non-randomness factors [39, 41, 42]. The purpose of providing background information and a solid theoretical framework is to supply the context essential for understanding the significance of the research question within the broader field of study. Consequently, and given the need for efficient predictive tools, the objective of this research was to evaluate the pertinence and predictive capability of six mathematical models (van't Hoff, Buchowski–Ksiazczak λh, van't Hoff-Yaws, Apelblat, Wilson, and NRTL) in correlating the solubility of Pazopanib in cosolvent mixtures of (ethyl acetate + ethanol) and (ethyl acetate + 2-propanol) [43]. The aim is to identify the most efficient model or group of models in terms of mathematical simplicity and correlation power for their application in industrial processes.

2. METHODOLOGY

Solubility data correlation and thermodynamic parameter estimation were conducted using a computational framework developed in Python (v3.x) and executed within the Google Colab cloud-based research environment. This approach enabled the integration of nonlinear optimization algorithms with high-performance numerical and statistical computing libraries.

2.1. Algorithmic Implementation and Libraries

The core data processing relied on the NumPy and Pandas libraries for vector manipulation and the structuring of experimental datasets (T, x_{Exp} Matplotlib and Seaborn were employed to visualize solubility trends and goodness-of-fit. Nonlinear regression was performed using the SciPy library (optimize module). Specifically, the curve-fit function, utilizing the Levenberg-Marquardt (LM) algorithm, was employed. This iterative technique combines the advantages of gradient descent and Gauss-Newton methods, facilitating convergence toward the global minimum of the objective function defined as the weighted sum of squared residuals between experimental and predicted solubility values.

2.2. Evaluated Thermodynamic Models

The correlative capability of six distinct mathematical models was evaluated, encompassing semi-empirical equations, empirical equations, and models based on activity coefficients. The models implemented were: van't Hoff Model [22, 44-47], van't Hoff-Yaws [30], Non-linear van't Hoff–Grant [48], Buchowski-Ksiazczak (λh) model [38], NRTL (Non-Random Two-Liquid) [49-52] and Wilson [40].

2.3. Optimization Strategy and Statistical Validation

To ensure the robustness of the fitted parameters, an automated routine was implemented to execute the following steps for each isotherm or dataset: *i)* Parameter Initialization: Definition of initial guesses based on the underlying physics of the problem to avoid local minimum during optimization. *ii)* Fit Iteration: Minimization of the loss function using the LM algorithm until a predefined convergence tolerance is reached. *iii)* Uncertainty Calculation: Estimation of standard errors for the fitted parameters by deriving the covariance matrix of the fit.

To assess the quality of the fit and select the most suitable model, rigorous statistical metrics were calculated for each system: R-squared, Root Mean Square Error (RMSE), mean absolute error (MAE), Bias of an estimator, Relative Accuracy, Index of Agreement (d), and KGE.

3. RESULTS AND DISCUSSION

Figure 2 presents the solubility of pazopanib in {ethyl acetate + ethanol} and {ethyl acetate + n-propanol} cosolvent mixtures, based on data reported by Shi *et al.* [43]. The data exhibit temperature-dependent behavior, characterized by an increase in the mole fraction of pazopanib as the temperature rises within the range of 288.15 K to 328.15 K. The arrangement of the upper curves, corresponding to the higher-temperature isotherms, unequivocally confirms the endothermic nature of the dissolution process ($\Delta_{soln}H > 0$) [53-56]. This implies that the system requires thermal energy input to overcome the lattice energy barrier inherent to the drug's crys-

talline structure. From a compositional perspective, the solubility profile deviates from linearity, demonstrating a marked cosolvency phenomenon wherein the synergistic interaction of the mixture exceeds the solvation capacities of the pure components.

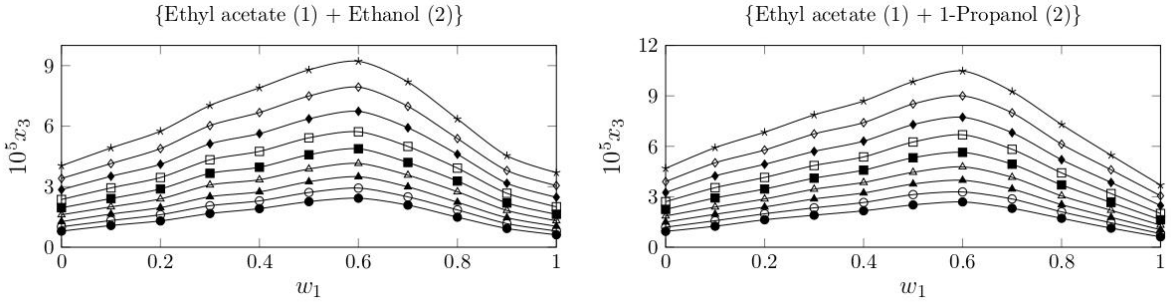

Figure 2. Solubility of pazopanib in cosolvent mixtures {Ethyl acetate + Ethanol} and {Ethyl acetate + n-Propanol} from 288.15 K (●) to 329.15 K (*).

In both studied systems, solubility maxima ($x_{3,max}$) are located in an intermediate composition region rich in ethyl acetate, specifically around a mass fraction of w_1=0.6. A comparison of solubility magnitudes reveals that the system comprising ethyl acetate and 1-propanol exhibits higher thermodynamic efficiency, reaching solubility values near $10.5 \cdot 10^{-5}$ in mole fraction at 328.15 K, slightly surpassing the maximum of $9.2 \cdot 10^{-5}$ obtained with the ethanolic system under the same conditions. To elucidate this behavior from thermodynamic and molecular perspectives, it is imperative to correlate the chemical structure of pazopanib a complex molecule featuring multiple hydrogen bond donor and acceptor centers, as well as extensive hydrophobic zones with the physicochemical properties of the solvents, using Hildebrand solubility parameters (δ) [57-59]. An analysis of the pure component values (δ_3 = 27.8 MPa$^{1/2}$, δ_{EtAc} = 18.2 MPa$^{1/2}$, δ_{EtOH} =26.1 MPa$^{1/2}$, and δ_{PrOH} = 24.9 MPa$^{1/2}$ [1]) suggests an apparent contradiction regarding the classical rule of similarity. Theoretically, pure ethanol should be the optimal solvent due to the numerical proximity of its parameter to that of the solute ($\Delta\delta$ = 1.7 MPa$^{1/2}$). However, experimental evidence shows that the addition of ethyl acetate maximizes solubility, despite shifting the mixture's solubility parameter further from that of the drug ($\Delta\delta$ = 9.6 MPa$^{1/2}$). This discrepancy indicates that the total solubility parameter is insufficient to describe the system, necessitating a decomposition of interactions into dispersion, polarity, and hydrogen bonding components, alongside entropic considerations [60, 61]. The underlying mechanism of this synergistic cosolvency lies in the ability of ethyl acetate, a polar aprotic solvent, to act as a structure-breaking agent within the self-association networks characteristic of alcohols (protic solvents). By disrupting the rigid alcohol structure, ethyl acetate increases system entropy and reduces the energy cost of cavitation required to accommodate the solute molecule [62]. This process frees up the alcohol hydroxyl groups to establish specific hydrogen bond interactions with the nitrogen atoms and sulfonamide groups of pazopanib. Simultaneously, ethyl acetate efficiently solvates the aromatic rings and lipophilic regions of the drug via London dispersion and dipole-dipole forces, achieving an optimal energy balance in the mixture at $w_1 \approx 0.6$. Finally, the superior performance of the 1-propanol system over the ethanol system is attributed to steric and hydrophobic factors. The longer alkyl chain of 1-propanol confers greater lipophilic character and conformational flexibility. These properties favor Van der Waals interactions with the carbon backbone of pazopanib and provide greater free volume for molecular accommodation, thereby compensating for the difference in global solubility parameters.

3.1. Mathematical Assessment of Solubility

One of the most versatile tools for process optimization is mathematical modeling, which allows making approximations under different conditions than experimental ones [9, 63].

Mathematical models to correlate drug solubility in cosolvent systems can be classified into two groups [64-66]: the models that work as a function of the cosolvent composition and the models that work as a function of temperature. In the former, the most used models are Yalkowsky-Roseman-van´t Hoff [67, 68], Wilson [39], Modified Wilson [69], NRTL [39], and Extended Hildebrand [23, 70, 71]. In the latter [72, 73], the most used models are, Apelblat [74] and Buchowski-Ksiazczak λh [75, 76] and van't Hoff–Yaws model [77]. The latter models have a significant predictive potential whenever the data to predict are to interpolate.

Hence, the experimental solubility data were correlated with the models, van´t Hoff (Equation (13)), Apelblat (Equation (14)), Buchowski-Ksiazczak λh (Equation (15)), van't Hoff–Yaws (Equation (16)), NRTL (Equation (17)), Wilson (Equation (18)), and Modified Wilson (Equation (19)).

$$\ln x_{3,1+2} = A + BT^{-1} \tag{1}$$

$$\ln x_{3,1+2} = A + BT^{-1} + CT^{-2} \tag{2}$$

$$\ln x_{3,1+2} = A + BT^{-1} + C \ln T \tag{3}$$

$$\ln[1 + \lambda(1 - x_3)x_3] = \lambda h(T^{-1} - T_m^{-1}) \tag{4}$$

Here, the parameters A, B, C, D, λ, and h are coefficients for each of the models; T is the temperature (in K); $x_{3,1+2}$ is the solubility of Pazopanib in the cosolvent mixture; $x_{3,1}$ is the solubility in {Ethyl acetate + Ethanol} and {Ethyl acetate + Propanol}; $x_{3,2}$ is the solubility of Pazopanib in water; and w_1 is the mass fraction of Ethyl acetate in (Ethyl acetate + Ethanol) and (Ethyl acetate + Propanol) free of solute (component 3).

$$\ln \gamma_3 = (x_2\tau_{23}G_{23} + x_1\tau_{13}G_{13})(x_3 + x_2G_{23} + x_3G_{13})^{-1} - x_3(x_2\tau_{23}G_{23} + x_1\tau_{13}G_{13})(x_3 + x_2G_{23} + x_3G_{13})^{-2} + x_2G_{32}(x_3G_{32} + x_2 + x_1G_{12})^{-1}[\tau_{32} - (x_3\tau_{32}G_{32} + x_1\tau_{12}G_{12})(x_3G_{32} + x_2 + x_1G_{12})^{-1}] + x_1G_{31}(x_3G_{31} + x_2G_{21} + x_1)^{-1}[\tau_{31} - (x_3\tau_{31}G_{31} + x_2\tau_{21}G_{21})(x_3G_{31} + x_2G_{31} + x_1)^{-1}] \tag{5}$$

$$\ln \gamma_3 = 1 - \ln(x_3 + x_2\Lambda_{32} + x_1\Lambda_{31}) - [(x_3(x_3 + x_2\Lambda_{32} + x_1\Lambda_{31})^{-1}) + (x_2\Lambda_{23}(x_3\Lambda_{23} + x_2 + x_1\Lambda_{21})^{-1}) + (x_1\Lambda_{13}(x_3\Lambda_{13} + x_2\Lambda_{12} + x_1)^{-1})] \tag{6}$$

Where, γ_3 is the activity parameter of Pazopanib; and τ, G and Λ are model parameters.

Regarding the NRTL model, G is a dimensionless interaction parameter, which depends on the energy interaction parameter, g, and the nonrandomness factor, α. The NRTL model contains three parameters, but the reduction of experimental data for several binary systems indicates that α varies from 0.20 up to 0.47; when experimental data are few, α value is usually settled arbitrarily as $\alpha = 0.3$. Therefore:

$$G_{ij} = e^{(-\alpha_{ij}\tau_{ij})};\ \alpha_{ij} = \alpha_{ji} = 0.3 \tag{7}$$

Table 1. Parameters of the Apelblat model

w_1	Ethyl acetate (1) + Ethanol (2)			Ethyl acetate (1) + n-Propanol (2)		
	A	*B*	*C*	*A*	*B*	*C*
1.0	32 ±29	–5556 ±1352	–4.46 ±4.30	32 ±29	–5556 ±1352	–4.47 ±4.31
0.9	22 ±36	–4676 ±1714	–3.16 ±5.47	35 ±19	–5265 ±909	–5.01 ±2.90
0.8	48 ±23	–5606 ±1091	–7.09 ±3.49	–29 ±21	–2050 ±1002	4.45 ±3.20
0.7	–75 ±14	255 ±664	11.34 ±2.12	45 ±20	–5288 ±972	–6.61 ±3.11
0.6	–44 ±14	–1100 ±685	6.62 ±2.19	33 ±23	–4707 ±1065	–4.95 ±3.41
0.5	–58 ±11	–497 ±535	8.79 ±1.71	49 ±20	–5446 ±934	–7.30 ±2.99
0.4	–73 ±18	52 ±842	11.10 ±2.69	–2.2 ±31	–3119 ±1457	0.42 ±4.67
0.3	58 ±25	–6033 ±1197	–8.61 ±3.83	14 ±29	–3937 ±1370	–2.02 ±4.38
0.2	11 ±8	–3998 ±381	–1.60 ±1.22	–23 ±17	–2304 ±829	3.59 ±2.65
0.1	19 ±19	–4459 ±912	–2.78 ±2.92	80 ±11	–7271 ±534	–11.68 ±1.71
0.0	102 ±26	–8440 ±1217	–15.02 ±3.88	13 ±41	–4286 ±1927	–1.78 ±6.15

Table 2. Parameters of the Buchowski–Ksiazaczak λh model

w_1	Ethyl acetate (1) + Ethanol (2)		Ethyl acetate (1) + n-Propanol (2)	
	λ	*h*	λ	*h*
1.0	0.0101 ±0.0005	414677 ±15615	0.0101 ±0.0005	414677 ±15615
0.9	0.0065 ±0.0003	571349 ±18370	0.0074 ±0.0003	499033 ±16532
0.8	0.0059 ±0.0002	576254 ±18497	0.0067 ±0.0002	509159 ±10651
0.7	0.0059 ±0.0002	543353 ±16788	0.0069 ±0.0003	467321 ±15371
0.6	0.0058 ±0.0002	533611 ±12041	0.0072 ±0.0003	441324 ±15139
0.5	0.0061 ±0.0001	521702 ±10167	0.0067 ±0.0003	469673 ±18767
0.4	0.0068 ±0.0003	490770 ±18570	0.0064 ±0.0002	502064 ±11717
0.3	0.0064 ±0.0002	531465 ±10950	0.0066 ±0.0002	505638 ±13031
0.2	0.0061 ±0.0001	576229 ±3937	0.0061 ±0.0001	555557 ±9536
0.1	0.0059 ±0.0002	611476 ±13040	0.0078 ±0.0004	468150 ±18551
0.0	0.0067 ±0.0003	573928 ±22061	0.0070 ±0.0002	537043 ±1369

Table 3. Parameters of the van't Hoff-Yaws model

w_1	Ethyl acetate (1) + Ethanol (2)			Ethyl acetate (1) + n-Propanol (2)		
	A	B	C	A	B	C
1.0	0.844 ±1.773	–3129 ±1110	–162716 ±173727	0.84 ±1.77	–3129 ±1110	–162716 ±173727
0.9	–1.443 ±1.864	–2014 ±1165	–260930 ±181883	0.46 ±1.34	–3113 ±835	–86191 ±130423
0.8	–2.844 ±1.676	–1209 ±1046	–337875 ±163054	2.83 ±1.70	–4630 ±1063	188374 ±165724
0.7	6.172 ±0.711	–6762 ±443	541438 ±69079	–2.43 ±0.98	–1373 ±607	–288133 ±94691
0.6	4.130 ±1.094	–5518 ±681	365800 ±106109	–2.87 ±1.42	–1077 ±885	–324161 ±137841
0.5	4.642 ±0.571	–5805 ±356	399443 ±55436	–2.76 ±1.03	–1179 ±643	–309028 ±100202
0.4	6.059 ±0.843	–6604 ±526	497434 ±81962	1.27 ±1.53	–3700 ±954	70528 ±148666
0.3	–3.348 ±1.216	–854 ±758	–389055 ±118246	–0.67 ±1.3	–2491 ±824	–127839 ±128442
0.2	0.217 ±0.448	–3071 ±279	–66792 ±43611	2.70 ±1.17	–4594 ±728	184172 ±113583
0.1	–0.973 ±1.255	–2346 ±784	–193347 ±122337	–4.28 ±0.60	–131 ±375	–544321 ±58542

0.0	–5.665 ±1.212	617 ±757	–681957 ±118325	0.84 ±2.10	–3382 ±1318	–54394 ±205778

Table 4. Parameters of the van't Hoff model

w_1	Ethyl acetate (1) + Ethanol (2)		Ethyl acetate (1) + n-Propanol (2)	
	A	*B*	*A*	*B*
1.0	2.46 ±0.07	–4154 ±23	2.46 ±0.07	–4154 ±23
0.9	1.23 ±0.09	–3686 ±27	1.38 ±0.06	–3668 ±19
0.8	0.66 ±0.08	–3387 ±26	0.96 ±0.06	–3440 ±20
0.7	0.62 ±0.11	–3290 ±34	0.53 ±0.08	–3220 ±24
0.6	0.36 ±0.07	–3168 ±21	0.47 ±0.07	–3160 ±21
0.5	0.55 ±0.08	–3247 ±26	0.42 ±0.08	–3165 ±25
0.4	0.98 ±0.11	–3421 ±34	0.55 ±0.07	–3249 ±23
0.3	0.62 ±0.09	–3339 ±30	0.62 ±0.07	–3305 ±22
0.2	0.89 ±0.02	–3497 ±7	0.85 ±0.05	–3426 ±16
0.1	1.02 ±0.05	–3587 ±16	1.29 ±0.11	–3615 ±33
0.0	1.28 ±0.14	–3737 ±45	1.39 ±0.09	–3729 ±30

3.2. Statistical Evaluation of Pazopanib Solubility Model Fit

Examination of the regression coefficients and their respective standard uncertainties reveals a distinct dichotomy between the mathematical fitting capability and the thermodynamic robustness of the employed models. While the two-parameter models demonstrate consistency, the three-parameter models exhibit severe statistical pathologies.

An analysis of Table 1, corresponding to the Apelblat model (Equation 3), identifies a critical phenomenon of multicollinearity and a lack of statistical significance in the coefficients. Specifically, for the (Ethyl Acetate + Ethanol) cosolvent mixture at a mass fraction of $w_1 = 0.4$, parameter *A* is reported as 52 with a standard uncertainty of ±842. A standard deviation exceeding the nominal parameter value by a factor of more than 16 indicates that this coefficient is statistically indistinguishable from zero [78, 79].

This behavior recurs in parameter *C* for the same mixture (while 11.10±2.69 appears stable, it contrasts with $w_1 = 0.7$, where *C* = 11.34±2.12 is paired with a *B* value of 255±664). Such instability suggests that, within the studied temperature range (288.15 K – 328.15 K), the solubility curvature is not sufficiently pronounced to decouple the effects of the $1/T$ and $\ln(T)$ terms. Physically, this precludes the confident use of parameter *C* to estimate the variation in the isobaric solution heat capacity (ΔC_p), as these values are artifacts of the numerical fitting rather than intrinsic system properties.

An analogous, and perhaps more pronounced, situation is observed in Table 3 with the van't Hoff-Yaws model (Equation 2). For pure ethyl acetate ($w_1 = 1.0$), parameter *C* presents a value of -162,716 with an uncertainty of ±173,727. The fact that the confidence interval includes zero confirms that including this third parameter contributes no statistically significant information compared to a simple linear model. Furthermore, the erratic fluctuation in the signs and magnitudes of *C* across the cosolvent composition (oscillating between massive positive and negative values, e.g., 541,438 at $w_1 = 0.7$) lacks phenomenological justification, confirming an overfitting of the experimental data. In contrast, the two-parameter models exhibit superior statistical stability, rendering them more reliable for process engineering interpolations.

In Table 2, the Buchowski-Ksiazczak model (Equation 4) displays well-behaved parameters. Parameter λ, theoretically related to the inverse of the melting temperature and non-

ideality, oscillates within a coherent range (0.0058 – 0.0101). The associated uncertainties are consistently low (e.g., for $w_1 = 0.6$ in EA+EtOH, $\lambda = 0.0058 \pm 0.0002$), representing a relative error of less than 4%. Parameter *h*, related to the process enthalpy, also exhibits smooth trends with composition, devoid of the abrupt jumps observed in the three-term models.

Finally, Table 4 summarizes the parameters of the van't Hoff model (Equation 1). This model presents the greatest statistical robustness. The *B* coefficients are consistently negative (between -3100 and -4200), thermodynamically confirming the endothermic nature of the dissolution process ($\Delta_{soln}H > 0$) across the entire studied composition range. The magnitude of the uncertainties in *B* (typically ±20–30) is very low compared to the parameter value (approximately 0.7% relative error), validating the linearity of the ln x_3 vs $1/T$ plots within the working temperature interval.

From an applied thermodynamics perspective, although the Apelblat and van't Hoff-Yaws models may offer marginally superior correlation coefficients due to their greater mathematical flexibility, their parameters lack physical reliability in this specific system due to high cross-correlation and excessive standard errors. For the purposes of design, simulation, and solubility prediction of Pazopanib in these mixtures, the van't Hoff and Buchowski-Ksiazczak models are technically superior due to their parsimony and statistical stability.

Table 5. Parameters of the NRTL model

Ethyl acetate (1) + Ethanol (2)						
T	$\tau(1.2)$	$\tau(1.3)$	$\tau(2.1)$	$\tau(2.3)$	$\tau(3.1)$	$\tau(3.2)$
288.15	–0.9 ±315	22 ±1.0	0.9 ±283	19 ±0.5	–4.7 ±0.10	–4.5± 0.05
293.15	–0.9 ±286	22 ±0.8	0.9 ±258	19 ±0.4	–4.7 ±0.07	–4.5 ±0.05
298.15	–0.9 ±248	21 ±0.7	0.9 ±225	19 ±0.4	–4.6 ±0.07	–4.4 ±0.04
303.15	–0.8 ±236	21 ±0.5	0.8 ±215	19 ±0.5	–4.6 ±0.04	–4.4 ±0.05
308.15	–0.8 ±334	20 ±0.9	0.9 ±304	18 ±0.6	–4.5 ±0.08	–4.3 ±0.07
313.15	–0.9 ±400	20 ±1.1	0.9 ±365	18 ±0.9	–4.5 ±0.10	–4.3 ±0.10
318.15	–0.9 ±411	19 ±1.2	0.9 ±376	18 ±1.0	–4.4 ±0.11	–4.2 ±0.12
323.15	–0.9 ±359	19 ±1.1	0.9 ±329	17 ±1.1	–4.4 ±0.11	–4.2 ±0.12
328.15	–0.8 ±325	19 ±0.9	0.8 ±298	17 ±1.0	–4.3 ±0.09	–4.1 ±0.12
Ethyl acetate (1) + n-Propanol (2)						
T	$\tau(1.2)$	$\tau(1.3)$	$\tau(2.1)$	$\tau(2.3)$	$\tau(3.1)$	$\tau(3.2)$
288.15	–1.3 ±298	23 ±1.257	1.3 ±276	21 ±0.4	–4.8 ±0.11	–4.6 ±0.04
293.15	–1.3 ±197	23 ±0.597	1.3 ±183	21 ±0.5	–4.8 ±0.05	–4.6 ±0.05
298.15	–1.3 ±230	22 ±0.749	1.3 ±214	20 ±0.6	–4.7 ±0.07	–4.5 ±0.06
303.15	–1.2 ±43	22. ±0.225	1.2 ±40	20 ±0.4	–4.8 ±0.02	–4.5 ±0.04
308.15	–1.2 ±62	21 ±0.168	1.2 ±58	19 ±0.5	–4.6 ±0.02	–4.4 ±0.05
313.15	–1.2 ±124	21 ±0.257	1.2 ±116	19 ±0.6	–4.6 ±0.02	–4.4 ±0.06
318.15	–1.3 ±112	20 ±0.223	1.3 ±106	19 ±0.7	–4.5 ±0.02	–4.4 ±0.07
323.15	–1.4 ±36	20 ±0.157	1.4 ±34	18 ± 0.4	–4.5 ±0.02	–4.3± 0.04
328.15	–1.4 ±50	20 ±0.118	1.4 ±47	18 ± 0.5	–4.4 ±0.01	–4.3 ±0.05

Table 6. Parameters of the Wilson model*

Ethyl acetate (1) + Ethanol (2)						
T	$\Lambda(1.2)$	$\Lambda(1.3)$	$\Lambda(2.1)$	$\Lambda(2.3)$	$\Lambda(3.1)$	$\Lambda(3.2)$
288.15	1.7 ±16	–16 ±1473	0.8 ±3	–16 ±1553	e	i
293.15	A	2.4 ±387	1.6 ±0.4	–2.6 ±0.35	0.019 ±7	4.4 ±1.646
298.15	0.5 ±5080	0.810 ±4065	2.1 ±13239	–1.4 ±4066	0.060 ±245	0.80 ±327
303.15	1.5 ±0.6	8 ±0.002	0.7 ±0.3	8.6 ±0.00	F	J

Ethyl acetate (1) + Ethanol (2)						
T	$\Lambda(1.2)$	$\Lambda(1.3)$	$\Lambda(2.1)$	$\Lambda(2.3)$	$\Lambda(3.1)$	$\Lambda(3.2)$
308.15	4.1 ± 1	–2.16 ±0.19	D	0.26 ±0.96	1.25 ±0.24	0.16 ±0.15
313.15	1.8 ±24	–11 ±1334	0.8 ±40	–11 ±1252	G	i
318.15	B	1.03 ±6	1.5 ±0.3	–2.4 ±0.20	0.060 ±0.406	2.49 ±0.54
323.15	1.7 ±20	–10 ±1010	0.8 ±36	–10 ±1040	H	J
328.15	c	0.871 ±9	1.4 ±0.5	–2.4 ±0.48	0.070 ±0.68	2.26 ±1.12
Ethyl acetate (1) + n-Propanol (2)						
T	$\Lambda(1.2)$	$\Lambda(1.3)$	$\Lambda(2.1)$	$\Lambda(2.3)$	$\Lambda(3.1)$	$\Lambda(3.2)$
288.15	1.6 ±15	–17 ±1512	0.8 ±25	–17 ±2565	b	j
293.15	1.6 ±1.54	9 ±0.01	0.6 ±0.6	9 ±0.00	c	k
298.15	3.6 ±1.12	–2.2 ±0.23	a	0.5 ±0.52	1.3 ±0.3	0.11 ±0.01
303.15	1.6 ±15	–14 ±1140	0.9 ±24	–13 ±1656	d	l
308.15	1.3 ±1.33	8 ±0.01	0.8 ±0.8	8 ±0.00	e	m
313.15	1.6 ±14	–12 ±877	0.9 ±22	–12 ±1510	f	n
318.15	1.5 ±14	–11 ±786	0.9 ±23	–11 ±1653	g	o
323.15	1.4 ±1.12	7 ±0.01	0.7 ±0.6	7 ±0.00	h	p
328.15	0.1 ±0.43	7 ±0.00	10 ±43	7 ±0.07	i	q

*During parameter estimation using the NRTL and Wilson models, outliers were encountered and are explicitly reported to ensure traceability. These extreme values correspond to numerical combinations explored by the fitting algorithm during optimization but exhibit no physical or statistical consistency with the system behavior. Consequently, they are interpreted as artifacts of the computational procedure. For the {Ethyl acetate + Ethanol} system a: -5930941 ± 22832613482885, b: -27634735 ± 9484331741220, c: -9796882 ± 22427860978166, d: -61200472 ± 361300445093403, e: 2773595 ± 4084281212, f: -0.0000007 ± 0.0000004, g: 25866 ± 34536277, h: 6395 ± 6461476, i: 3244987 ± 5040591118, j: 0.0000009 ± 0.0000005, k: 28619 ± 35836119, l: 6870 ± 7154591 and {Ethyl acetate + Propanol} system a: -127870089 ± 585190773392122, b: 5577126 ± 8430842586, c: 0.0000008 ± 0.00000093, d: 221074 ± 252057277, e: 0.0000013 ± 0.00000177, f: 49904 ± 43814756, g: 19284.113 ± 15176362.438, h: -0.0000025 ± 0.00000241, i: 0.000000005 ± 0.00007834, j: 6114146.082 ± 15677258858.414, k: 0.00000067 ± 0.0000002, l: 235868.212 ± 390641891.605, m: 0.00000161 ± 0.0000009, n: 51973.958 ± 78521827.394, o: 19562.308 ± 32344175.713, p: 0.00000231 ± 0.0000015, q: 0.00000014 ± 0.0008210.

Analysis of the parameter results for the NRTL and Wilson models reveals severe issues regarding parameter identifiability and numerical stability. These issues compromise the physical thermodynamic validity of the obtained parameters, despite the models exhibiting high global statistical correlations (as suggested by the r^2 values reported in previous sections). Table 5 summarizes the dimensionless energy interaction parameters (τ_{ij}) for the Non-Random Two-Liquid (NRTL) model. A critical dichotomy is observed between the solvent-solvent and solute-solvent parameters. The solvent-solvent interactions (τ_{12} and τ_{21}) show statistical insignificance, evidenced by disproportionate uncertainty in the parameters describing the interaction between Ethyl Acetate (1) and the alcohol (2). For example, in the mixture with Ethanol at 288.15 K, a value of τ_{12} = -0.9±315 is reported. A standard deviation more than 300 times greater than the nominal parameter value indicates that this coefficient lacks statistical significance. Mathematically, this suggests that the objective function (minimization of solubility error) is extremely insensitive to changes in solvent-cosolvent interactions, or that the error surface is remarkably flat in that dimension. Conversely, an analysis of the solute parameters (Component 3) involving Pazopanib (τ_{13}, τ_{31}, τ_{23}, τ_{32}) shows considerably smaller standard deviations (e.g., τ_{31} = -4.7±0.095). This is physically consistent, as the solubility of the solid (the dependent

variable) is highly sensitive to how the model describes the solute's affinity for the solvents. However, the magnitude of τ_{13} (approx. 22–23) compared to τ_{31} (approx. -4.7) suggests a strong asymmetry in molecular interactions, which is typical of solutions with significant differences in molecular size and polarity. Although the parameters vary with temperature, the magnitude of the propagated experimental error (±300 or more) makes it impossible to establish a reliable thermodynamic trend (such as the derivation of excess enthalpy, H^E) from the thermal dependence of these τ parameters.

This disproportionate uncertainty (e.g., τ_{12}= -0.9 ±315) stems from a high insensitivity of the objective function regarding solvent-cosolvent interactions when fitting solely to solute solubility data. Consequently, these specific parameters lack statistical significance, as the standard deviation's magnitude renders the coefficients indistinguishable from zero, indicating that the error surface is remarkably flat in these dimensions.

Analysis of Table 6 reveals a massive failure in the non-linear regression process for the Wilson model. The presented results lack physical meaning and are purely numerical artifacts of the optimization algorithm (Levenberg-Marquardt) [80]. Numerical divergence and mathematical artifacts are likely present, as evidenced by extremely large values for certain parameters (e.g., a: $-1.27 \cdot 10^{14}$ or d: $-6.12 \cdot 10^{14}$) [81, 82]. This indicates that the algorithm did not converge to a physical minimum but rather diverged toward infinite values or stagnated in spurious local minima. In the context of the Wilson equation, interaction parameters of this magnitude would imply exponential terms ($\Lambda ij = e^{-\Lambda ij/RT}$) that are effectively zero or infinite, a thermodynamic impossibility for miscible systems. Even for values not marked as outliers, the uncertainties are unacceptable. For example, for (Ethyl Acetate + Ethanol) at 298.15 K, the reported value is Λ_{13}= 2.1±13239. A relative error of 630,000% confirms that the model is over-parameterized relative to the available data. The Wilson model requires the simultaneous estimation of multiple interaction pairs in a ternary system; however, with data limited solely to the solubility of Component 3 (and lacking binary vapor-liquid equilibrium data for the solvent mixture), the model suffers from severe multicollinearity. Consequently, the values fluctuate violently with temperature without a physical pattern (e.g., Λ_{21} shifts from 1.7 to 2.4, then to 0.5, and finally to 4.1 over 5 K intervals). This violates the thermodynamic principle regarding the continuity of free energy functions with respect to temperature.

The severe over-parameterization of the Wilson model, combined with the absence of experimental binary vapor-liquid equilibrium data for the solvent mixture, triggers a massive failure in the non-linear regression process. This lack of data prevents the correct segregation of molecular interaction pairs, forcing the algorithm to produce numerical artifacts that fluctuate erratically with temperature, thereby violating the thermodynamic principle of continuity in free energy functions.

Thus, from a thermodynamic perspective, the parameters reported in Tables 5 and 6 must not be used for predicting thermodynamic properties (such as infinite dilution activity coefficients or enthalpies of mixing). The observed phenomenon is a classic case of "Error Compensation" in multivariable regression. The mathematical algorithm forced a fit for the solubility curve by assigning random, enormous values to solvent-solvent interaction parameters (which have little impact on the solid fit) to marginally minimize the residual error. Therefore, the presented Wilson model is thermodynamically invalid despite its numerical curve-fitting capability.

Table 7 presents the validation of the six mathematical models evaluated (Apelblat, Buchowski-Ksiazczak, van't Hoff, van't Hoff-Yaws, NRTL, and Wilson) as applied to two cosolvent systems: {Ethyl acetate + Ethanol} and {Ethyl acetate + 1-Propanol}. The analysis is based on seven goodness-of-fit and error metrics. The Coefficient of Determination (R^2) exhibits values close to 1 for all models in both systems, ranging from 0.9906 to 0.9999. Most models exceed the threshold of $R^2 > 0.999$, indicating that they explain more than 99.9% of the variability observed in the experimental solubility data (x_3). This suggests that the relationship between solubility, temperature, and cosolvent composition is adequately captured by the proposed mathematical structures.

Table 7. Validation of the six mathematical models evaluated

Cosolvent mixture	Model	R^2	RMSE	MAE	Bias	Relative Accuracy	Index of Agreement (d)	KGE
Ethyl acetate (1) + Ethanol (2)	Apelblat	0.9999	1.39×10^{-7}	1.06×10^{-7}	8.28×10^{-9}	0.9962	0.9999	0.9996
	Buchowski	0.9998	2.94×10^{-7}	2.23×10^{-7}	-7.1×10^{-9}	0.9930	0.9999	0.9979
	van't Hoff	0.9998	2.55×10^{-7}	2.06×10^{-7}	9.48×10^{-9}	0.9922	0.9999	0.9991
	van't Hoff-Yaws	0.9999	1.33×10^{-7}	1.04×10^{-7}	5.81×10^{-10}	0.9963	0.9999	0.9999
	NRTL	0.9997	4.19×10^{-7}	2.87×10^{-7}	6.82×10^{-9}	0.9919	0.9999	0.9988
	Wilson	0.9906	2.19×10^{-6}	$1.5E\times10^{-6}$	$-1E\times10^{-7}$	0.9659	0.9976	0.9832
Ethyl acetate (1) + Propanol (2)	Apelblat	0.9999	2×10^{-7}	1.6×10^{-7}	1.14×10^{-8}	0.9951	0.9999	0.999
	Buchowski	0.9998	3.03×10^{-7}	2.41×10^{-7}	-4.8×10^{-8}	0.9930	0.9999	0.9972
	van't Hoff	0.9999	2.54×10^{-7}	1.99×10^{-7}	9.19×10^{-9}	0.9933	0.9999	0.9992
	van't Hoff-Yaws	0.9999	1.88×10^{-7}	1.52×10^{-7}	1.28×10^{-9}	0.9952	0.9999	0.9999
	NRTL	0.9997	3.54×10^{-7}	2.69×10^{-7}	7.87×10^{-9}	0.9921	0.9999	0.9986
	Wilson	0.9949	1.41×10^{-6}	8.39×10^{-7}	-7×10^{-8}	0.9702	0.9987	0.9901

The Apelblat and van't Hoff-Yaws models achieve a nearly perfect R^2 of 0.9999 in both systems. This is statistically expected, as both are three-parameter models that incorporate logarithmic or quadratic terms to correct for deviations from linearity in the $\ln x_3$ vs. $1/T$ relationship, offering greater flexibility to fit data curvature. Regarding the Wilson model, it presents the lowest values (0.9949 and 0.9906); while statistically acceptable, this denotes a slightly inferior capacity to model this specific system compared to the semi-empirical equations.

Regarding the magnitude of error analysis, the Root Mean Square Error (RMSE) and Mean Absolute Error (MAE) metrics are reported on a mole fraction scale (10^{-7}), confirming the precision of the fits. When analyzing error minimization for the system containing Ethanol, the van't Hoff-Yaws model presents the lowest error (RMSE = $1.33\cdot10^{-7}$), followed very closely by the Apelblat model (RMSE $\approx 1\cdot10^{-7}$). The consistency between metrics—specifically the relationship where RMSE > MAE—is maintained in almost all cases. This is typical, as the RMSE penalizes large errors (outliers) more heavily. Bias is negligible for all models, with values ranging between 10^{-8} and 10^{-10}. Furthermore, the bias results indicate an absence of systematic error, given that values close to zero demonstrate that no model systematically overestimates

or underestimates solubility across the entire temperature range; errors are random and evenly distributed around the predictions.

The van't Hoff-Yaws model shows the lowest absolute bias ($5.811 \cdot 10^{-10}$ for Ethanol), reinforcing its position as the most mathematically robust model for this dataset.

In analyzing Predictive Efficiency (KGE, Index of Agreement, Relative Accuracy), the Kling-Gupta Efficiency (KGE)—which combines correlation, variability, and bias—confirms the superiority of the three-parameter models. Apelblat and van't Hoff-Yaws achieve KGE values of 0.9996 – 0.9999, indicating a nearly perfect simulation of experimental reality. regarding the Index of Agreement (d) [83], all models achieve an index of $d \approx 0.999$, except for Wilson, which decreases slightly to 0.997–0.998. This validates the utility of all proposed models for industrial prediction purposes. Thus, from a strictly statistical perspective, the analysis of Table 7 leads to the conclusion that the van't Hoff-Yaws and Apelblat models are statistically indistinguishable and superior to the others.

Figures 3, 4, and 5 corroborate a robust validation of the fit quality for the six mathematical models studied (van't Hoff, van't Hoff-Yaws, Buchowski-Ksiazczak, Apelblat, Wilson, and NRTL) regarding the experimental solubility data of Pazopanib.

Regarding the Linearity and Global Goodness-of-Fit Analysis (Figure 3), the plots allow for a visual evaluation of the deviation from the identity line ($y=x$), which represents the perfect model. High collinearity is observed in most models, with points adhering strictly to the main diagonal [84]. This indicates Coefficients of Determination (R^2) close to unity, suggesting that the variance explained by the models is very high. Consequently, the Apelblat and van't Hoff-Yaws models exhibit the least dispersion perpendicular to the identity line, confirming their superior capacity to capture both the central tendency and subtle variations in the data throughout the entire range of temperatures and compositions. Conversely, the Wilson model presents visibly greater dispersion, particularly in the regions of medium and high solubility ($6.0 - 10.0 \cdot 10^{-5}$). This systematic deviation (a "fanning effect") suggests that the Wilson model, which is based on activity coefficients, struggles to reproduce the solubility curvature with the same precision as the empirical temperature models in this specific system. Although he NRTL model performs better than Wilson, it shows marginally higher dispersion than the Apelblat and Yaws models.

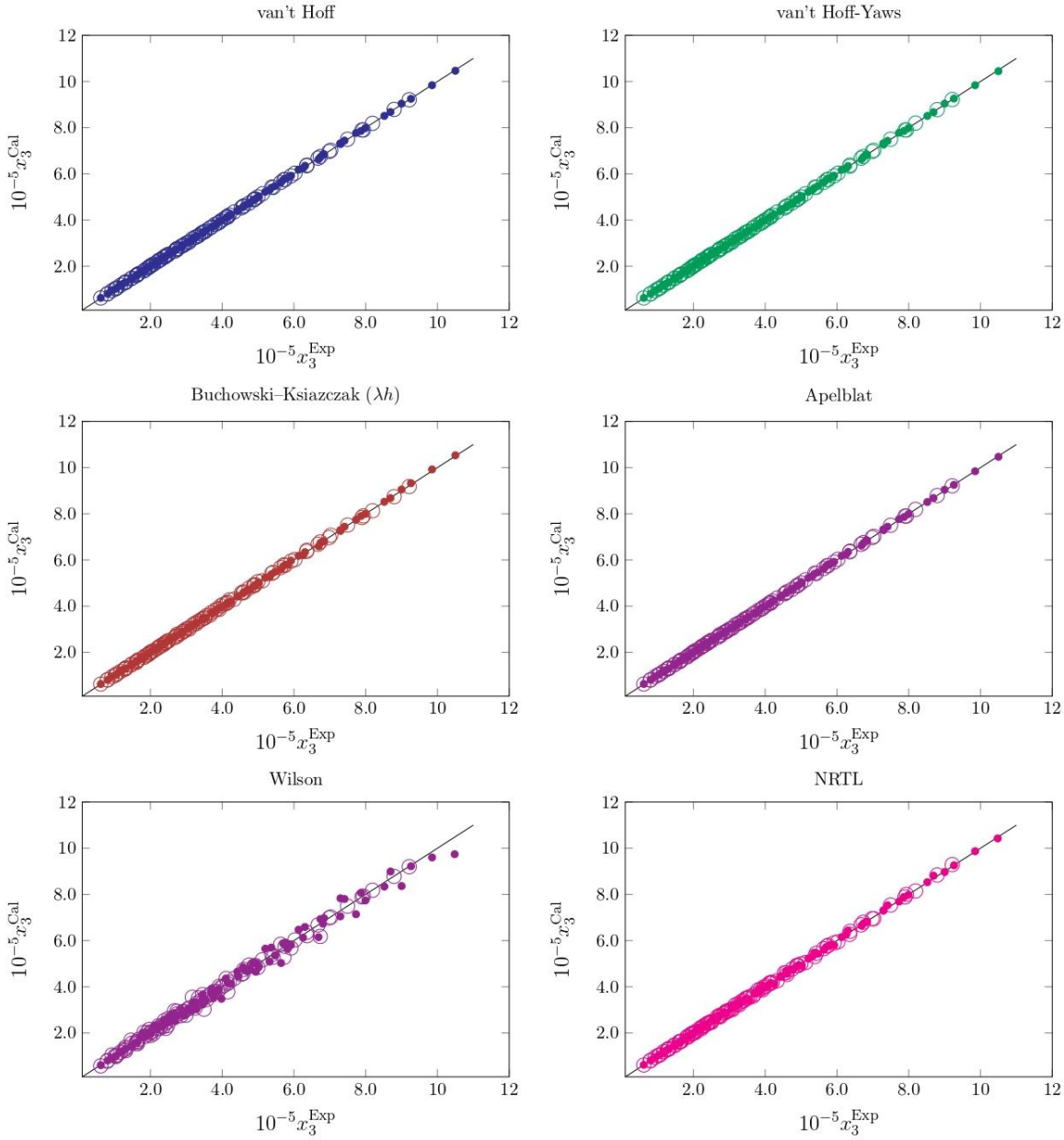

Figure 3. Experimental solubility data versus predicted solubility of Pazopanib (3) in {Ethyl acetate + Ethanol} (●) and {Ethyl acetate + Propanol} (o) cosolvent mixtures.

Despite achieving high global statistical correlations ($R^2 > 0.99$), the NRTL and Wilson models remain unreliable for predicting advanced thermodynamic properties such as activity coefficients or mixing enthalpies in this system. This discrepancy arises from 'Error Compensation', where the mathematical algorithm achieves a numerical fit by assigning physically impossible values to interaction parameters to minimize residual error. Therefore, these models serve only as numerical curve-fitting tools and lack physical validity for broader thermodynamic characterization.

A comparative analysis of error magnitude (Figure 4), based on the Root Mean Square Error (RMSE), enables a quantitative assessment of model precision. The Wilson model acts as a performance outlier, exhibiting significantly higher RMSE values compared to the other models. Specifically, these values approach $1.0 \cdot 10^{-7}$ when the visual scale is adjusted, or appear an order of magnitude higher based on the previously discussed tables. This statistically confirms that the Wilson model yields the poorest fit within the set. Regarding sensitivity to the

cosolvent system, the Buchowski-Ksiazczak model displays a notable discrepancy between the errors associated with the ethanol system (open circles) and the 1-propanol system (filled circles). The error is substantially higher for the ethanol system, suggesting that the λh assumption is less robust in describing solute-solvent interactions involving the shorter alkyl chain. This behavior likely stems from specific solvation effects that remain uncaptured by this two-parameter model. Conversely, the Apelblat and Yaws models present the lowest RMSE values. Crucially, they demonstrate consistency across both cosolvent systems—evidenced by the minimal distance between the open and filled circles—indicating mathematical robustness independent of the specific alcohol used.

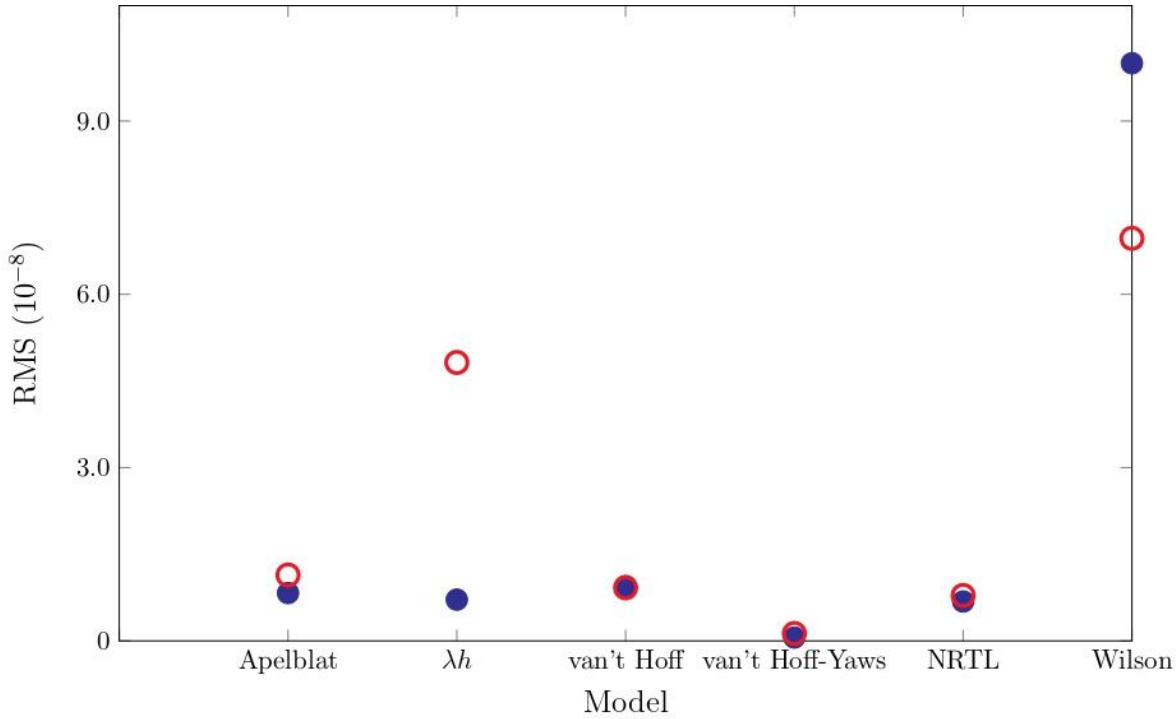

Figure 4. Root Mean Square of models (Ethyl acetate + Ethanol} (o) and {Ethyl acetate + Propanol} (●) cosolvent mixtures).

Figure 5 presents the residual and homoscedasticity analysis. As the most critical diagnostic tool, it illustrates the distribution of residuals as a function of calculated solubility. Notably, the Wilson model exhibits residuals that are an order of magnitude larger than those of the other models evaluated. Furthermore, the point distribution is non-random; it displays clear patterns and clustering, which is indicative of systematic bias. Consequently, the model fails structurally to capture the physics of the system, leaving significant information within the residuals.

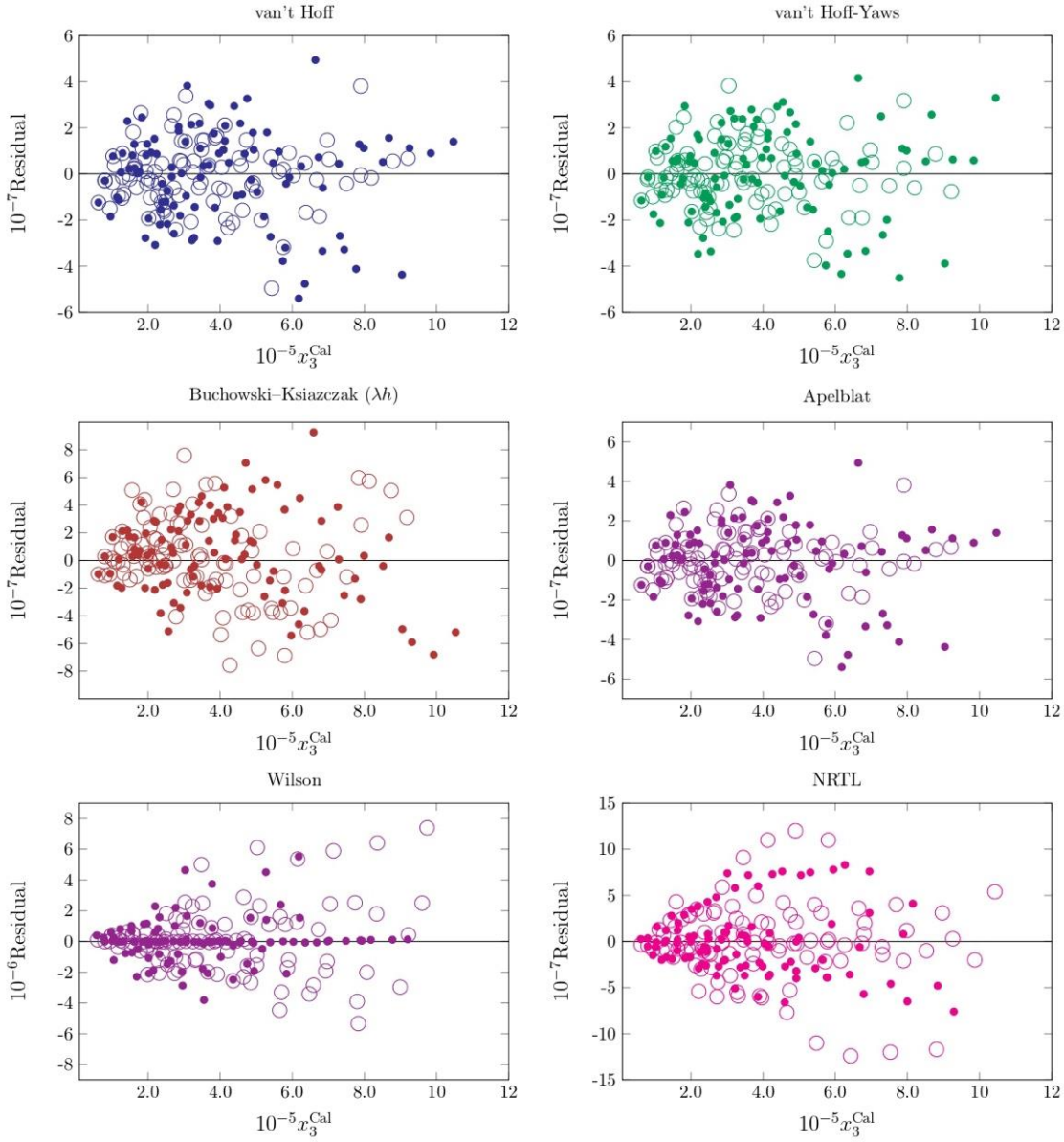

Figure 5. Residuals versus fits plot ({Ethyl acetate + Ethanol} (o) and {Ethyl acetate + Propanol} (●) cosolvent mixtures).

The plots for the Buchowski-Ksiazczak and NRTL models show a slight "cone" pattern or outward expansion to the right, indicating heteroscedasticity; specifically, the error variance increases as the magnitude of solubility increases. While this phenomenon is common in solubility data, an ideal model should minimize it.

Conversely, the Apelblat and van't Hoff-Yaws models exhibit a stochastic distribution. The residuals for these two models demonstrate ideal statistical behavior: a "cloud" of points distributed randomly around the zero line (white noise), devoid of curvature patterns or obvious trends. This validates that the additional terms in these equations ($C\ln T$ or CT^{-2}) effectively capture the non-linearity of the solubility-temperature relationship, confining the residuals to random experimental error.

The residual distribution, (Figure 6), show the varying degrees of thermodynamic robustness and numerical stability among the six evaluated models. A primary observation is the significant scale disparity between the Wilson model and the other candidates. While the residuals for the Apelblat, van't Hoff-Yaws, NRTL, and semi-empirical models are constrained

to a factor of 10^{-7}, the Wilson model exhibits a dispersion an order of magnitude larger, reaching the 10^{-6} scale. This quantitative divergence aligns with the assessment of the Wilson model's severe over-parameterization and the lack of binary data, which results in numerical instability and a failure to capture the underlying physics of the Pazopanib solubility curve.

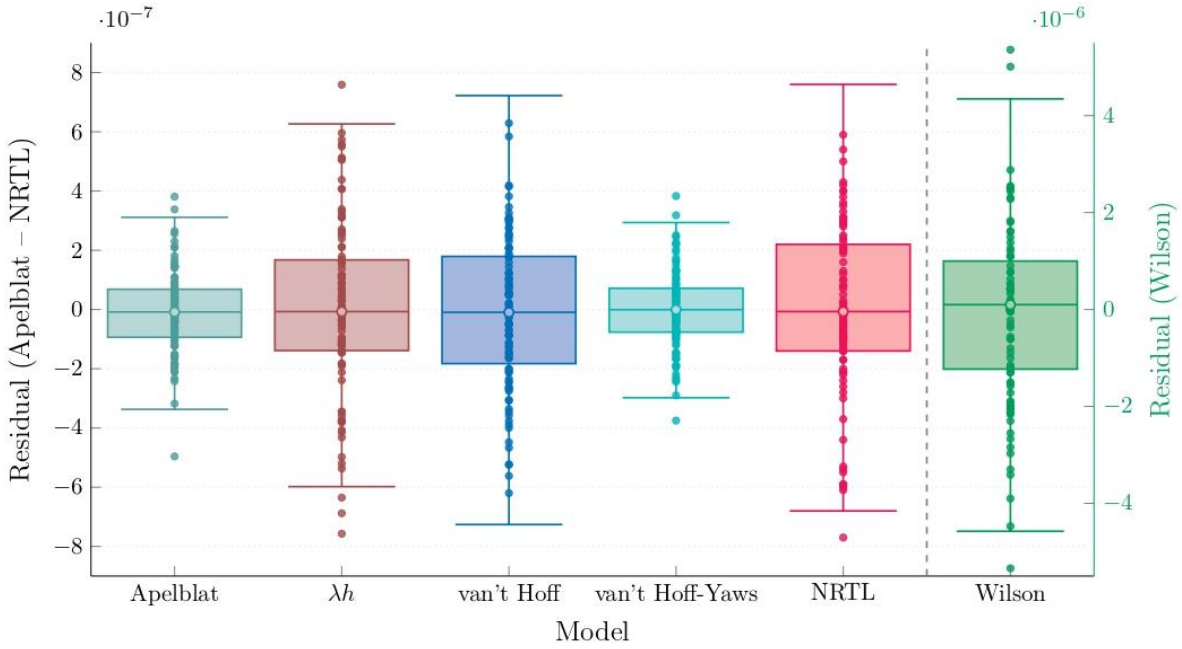

Figure 6. Comparative distribution of solubility residuals for the six evaluated mathematical models. The primary y-axis (left) represents the residuals for the Apelblat, *λh*, van't Hoff, van't Hoff-Yaws, and NRTL models on a scale of 10^{-7}. The secondary y-axis (right) denotes the residuals for the Wilson model on a scale of 10^{-6}.

The three-parameter empirical models, specifically Apelblat and van't Hoff-Yaws, demonstrate the highest precision, characterized by the narrowest interquartile ranges and the most compact distribution of individual data points around the zero-residual line. This suggests that their mathematical flexibility effectively absorbs the non-linearity of the temperature-solubility relationship. However, as noted in the discussion of multicollinearity, this superior statistical fit does not necessarily translate to physical validity, as the coefficients in these models often lack thermodynamic meaning and suffer from high cross-correlation. In contrast, the NRTL and *λh* models show a broader spread and a higher frequency of outliers, which reflects the previously identified heteroscedasticity, where error variance increases with solubility magnitude

Furthermore, the NRTL model, despite having a lower scale than Wilson, displays significant dispersion compared to the purely temperature-dependent models. This observation supports the concerns regarding the solvent–solvent interaction parameters (τ_{12} and τ_{21}) which exhibit disproportionate standard deviations and render the model statistically insignificant for certain interaction pairs. The large distribution of residuals in NRTL and Wilson, coupled with the "Error Compensation" identified in the regression process, confirms that while these activity-coefficient-based models can be forced into a numerical fit, they do not possess the parsimony or stability required for reliable thermodynamic prediction of properties like mix-

ing enthalpies or activity coefficients. Consequently, the statistical evidence reinforces the conclusion that the two-parameter van't Hoff and λh models offer the best balance of simplicity and thermodynamic consistency for industrial application.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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