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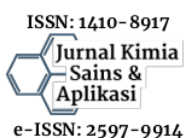
Quantitative Structure-Activity Relationship of 3-Thiocyanate-1H-Indoles Derived Compounds as Antileukemia by AM1, PM3, and RM1 Methods

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Article Info

Abstract

Cancer is a disease with fatal consequences; thus, searching for innovative compounds with anticancer properties remains an active pursuit. One of the highly promising candidates is a compound derived from 3-thiocyanato-1H-indoles. However, the number of derivative compounds is currently limited. A quantitative structure and activity relationship (QSAR) study was conducted on derivate compounds 3-thiocyanato-1H-indoles to establish equations that predict the anticancer activity of more effective derivatives. This study aims to compare the effectiveness of the AM1 (Austin Model 1), PM3 (Parameterized Model 3), and RM1 (Recife Model 1) semi-empirical methods, which are new techniques implemented in the Hyperchem version 8.0. Twenty experimental data were used, 16 derivatives of 3-thiocyanate-1H-indoles as regression compounds (fitting) and four derivates as test compounds. QSAR analysis was performed based on multiple linear regression calculations on 3-thiocyanate-1H-indoles derivative compounds by plotting IC_{50} (µM) as the dependent variable and descriptors as the independent variable. The best QSAR equation was obtained from the AM1 semiempirical calculation method with the following equation: IC_{50} = −1.705 + 0.511(Delta) + 0.346(Dipol) + 18.287(qC_9) − 0.645(Log P) + 13.952(qC_6), with n = 20; r = 0.814; r^2 = 0.662; The standard error (SE) = 1.044; Fcount/Ftable = 1.851; PRESS = 15.219.

1. Introduction

Cancer remains a significant challenge in the healthcare sector. Based on the Ministry of Health in 2020, cancer ranks as the third leading cause of death in Indonesia, following behind heart disease and stroke. Among the various types of cancer, leukemia—commonly known as blood cancer—is the prevalent type in children [1]. Leukemia arises from the excessive and uncontrolled production of white blood cells, disrupting the normal activity of other blood cells [2]. Unfortunately, due to delayed diagnosis and treatment, around 60% of children with leukemia enter medical treatment in advanced stages [3].

Current cancer treatment primarily involves chemotherapy, radiotherapy, and surgery. Researchers are actively pursuing new anticancer drug development since current anticancer agents have limitations, such as their potential to affect normal cells [4]. Conventional new drug development in the laboratory entails multiple steps such as design, synthesis, purification, and identification, which can consume time, energy, and material resources. This process can be wasteful if the

results are less efficacious than existing drugs [5, 6]. Therefore, discovering potent, safe, and selective anticancer compounds is an important aspect of developing anticancer drugs [4].

Computational chemistry has a significant role in medicinal chemistry, especially in drug design, the theoretical prediction of chemical properties, and molecule activity [7]. One of the applications of computational chemistry is the quantitative structure-activity relationship (QSAR) study [8]. This approach is beneficial as it quantitatively investigates the correlation between molecular structure and experimentally measured biological activity values [9]. Several QSAR studies have been conducted in the search for anticancer compounds, such as those utilizing the Austin model 1 (AM1) and parameterized model 3 (PM3) semi-empirical methods for the QSAR application of estradiol-derived compounds [5, 10], as well as the PM3 method for the QSAR of calanone-derived compounds [11]. Modified AM1 has also been used for calculating alkane/water partition coefficients [12], while PM3 has been used in molecular simulations [13]. Furthermore, the RM1 (Recife Model 1) method, a method used in Monte Carlo simulation [14] and available in Hyperchem version 8, is widely used for calculating the enthalpy of formation, dipole moment, net charge, ionization potential, and structure geometry [15].

Despite their use as synthesis intermediates for complex bioactive chemicals, 3-thiocyanate-1H-indoles are rarely studied [16]. 3-thiocyanate-1H-indoles are a combination of heterocyclic indoles and thiocyanate compounds, where indoles are abundant natural products with biologically active properties [17], while thiocyanate has the ability to inhibit cancer cells [18]. The 3-thiocyanate-1H-indole compound and its derivatives have been tested against human cancer HL-60, HEP-2, NCl-H292, and MCF-7 cell lines and have demonstrated good activity [4]. However, only a few derivatives of 3-thiocyanate-1H-indoles have been produced, and some of these are no anticancer activity [19]. Therefore, further studies are needed to develop better anticancer compound derivatives for use as potential drugs [20].

This study compared the semi-empirical methods of AM1, PM3, and RM1 [21]. The aim was to analyze the QSAR of 3-thiocyanate-1H-indoles derivative compounds as anticancer agents using the three methods to obtain the best mathematical equation model [22]. Semi-empirical methods offer several advantages over Ab initio, such as faster calculations, small storage space, and the ability to accurately model compounds through electronic structure calculations and experiment parameterizations [23]. Furthermore, the best QSAR equation is expected to be used for the prediction of modification of new 3-thiocyanate-1H-indoles derivatives with more potent anticancer activity.

2.   Materials and Methods

2.1.   Materials

The computer system used in this study was equipped with an Intel Core i7-9700 processor, 16 GB RAM, and Windows 10 operating system. The software included Hyperchem software version 8.0 [21] and SPSS version 25 [24]. Twenty compounds derived from 3-thiocyanato-1H-indoles and their biological activity as anticancer compounds were utilized (Figure 1) [4].
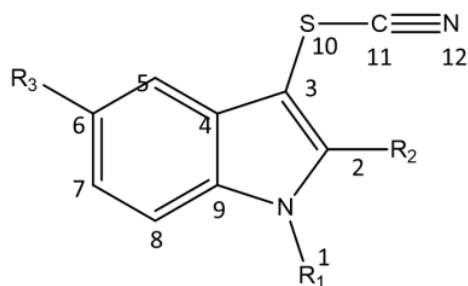
Figure 1. Structure of the parent model compound of 3-thiocyanate-1H-indoles derivatives [4]

Table 1. Fitting and test compound substituents, the IC_{50} (µM) experimental of 3-thiocyanato 1H-indoles derived compounds and the activity against HL-60 cell line [4]

Compound	R1	R2	R3	IC_{50} (µM) experiment
		Fitting compound		
2	H	H	4-Me-C_6H_4	2.53
3	H	H	OMe	5.63
5	H	H	CN	5.62
6	Ph	H	H	1.43
7	Me	H	4-Me-C_6H_4	4.05
8	4-MeO-C_6H_4	H	H	1.42
9	Me	H	H	1.54
10	4-Cl-C_6H_4	H	H	3.58
11	H	C_6H_5	H	0.63
12	H	4-Me-C_6H_4	H	2.27
13	H	4-MeO-C_6H_4	H	4.45
14	H	3CF$_3$-C_6H_4	H	0.69
15	H	4-Cl-C_6H_4	H	1.08
16	Me	C_6H_5	H	1.39
17	Me	4-Me-C_6H_4	H	1.50
20	Me	4-Cl-C_6H_4	H	1.10
		Test compound		
1	H	H	H	3.21
4	H	H	Br	3.00
18	Me	4-MeO-C_6H_4	H	1.35
19	Me	3CF$_3$-C_6H_4	H	2.56

The selection of the test compounds was based on: the smallest molecule (compound 1), the largest molecule (compound 19), the electron-withdrawing compound (compound 4), and the electron-donating compound (compound 18) (Table 1). These test compounds were expected to represent fitting compounds, and they can aid in selecting the best equation model through backward analysis, which was further tested by calculating the PRESS value [23]. The QSAR method was the Hansch method which consisted of hydrophobicity (π), electronic (σ), and steric (Es).

2.2. Structure optimization

Each 3-thiocyanate-1H-indoles derivate compound was created as a 2D structural model using the Hyperchem software. The model was then transformed into a 3D structure through the "Add H and Model Build". The structure geometry was optimized by minimizing molecular energy to attain the most stable molecular conformation. This was achieved using RHF spin pairing, lowest state, Polak-Ribiere optimization algorithm, and Root Mean Square (RMS) Gradient 0.001 kcal/Å.mol [25].

2.3. Correlation analysis

Bivariate correlation analysis was conducted using the two-tailed method and Pearson coefficient through SPSS 25 software. During this step, the correlation level between each descriptor and anticancer activity (IC_{50}) was investigated [11].

2.4. Descriptor determination

The QSAR method was Hansch method. The descriptor was composed of electrons, lipophilicity, and steric hindrance. After the optimum structure, the electrons, in this case, the charge and the dipole moment, the lipophilicity, and steric hindrance; the last two were in the QSAR properties. Determining descriptors is essential in identifying the best QSAR equation. The Hanch analysis uses electronic, steric, and hydrophobic parameters [10]. This study utilized the following descriptors as electronic parameters: atomic charge of the parent compound, hydration energy, dipole moment, HOMO, LUMO, and HOMO–LUMO energy difference (ΔE). Steric parameters included van der Waals volume (Vvdw), molecular weight (BM), and polarizability (α), while the hydrophobic parameter was the partition coefficient (Log P).

2.5. Determination of the QSAR equation

The best QSAR equation for predicting anticancer activity was determined using multilinear regression analysis. The analysis was performed by applying the backward method on 16 fitting compounds, with IC_{50} as the dependent variable and the descriptors as the independent variables. Statistical analysis was carried out on the output data of the backward analysis to select the equation model. The analysis included the correlation coefficient (r), partition coefficient (r^2), standard deviation (SD), F_{count}/F_{table}, and PRESS on four test compounds. The chosen model was then analyzed using the Enter method for all 20 compounds derived from 3-thiocyanate-1H-indoles to obtain the best QSAR equation [26]. This analysis was performed using the SPSS software.

3. Results and Discussion

3.1. Structure geometry optimization

Geometry optimization obtains the most stable molecular structure with the lowest energy and minimal atomic force [27]. This study employed three semi-empirical methods, namely AM1, PM3, and RM1 [21], to optimize the geometry of the compounds. The semi-empirical method is a type of electronic structure calculation developed based on molecular orbital theory and mathematical models. These methods simplify and approximate the computational procedure. The method involves only valence electrons in solving the Schrödinger equation, making optimization time shorter than the ab initio methods. After optimization, the compound's conformational shape differs from its original state, resulting in a broader structure due to the induction effect of electron clouds on specific atoms and groups, causing them to be further apart.

A derivative of 3-thiocyanate-1H-indoles was optimized before and after using the AM1, PM3, and RM1 methods. The total energy obtained from the AM1 method was −44065.7702998 kcal/mol, PM3 gave a total energy of −40247.4055128 kcal/mol, and RM1 resulted in a total energy of −43665.4491644 kcal/mol. This result suggests that the AM1 method gave the smallest total energy. These optimized compound structures were used to obtain data on physical and chemical properties.

3.2. Descriptor calculation results

The optimized derivative compound of 3-thiocyanate-1H-indoles was used to calculate its physicochemical characteristics. The measured values included atomic charges for qN1, qC2, qC3, qC4, qC5, qC6, qC7, qC8, qC9, qS10, qC11, qN12, hydration energy, dipole moment, HOMO, LUMO, HOMO and LUMO energy difference (ΔE) as electronic parameters. Steric parameters included van der Waals volume (Vvdw), molecular weight (BM), and polarizability (α). At the same time, the partition coefficient (Log P) was measured as a hydrophobic parameter [28].

The calculation results for the AM1, PM3, and RM1 methods are shown in Tables 2, 3, and 4, respectively. Notably, the dipole moment, partition coefficient (Log P), and net atomic charge of the C2 (qC2) show the highest trend in all three methods. For the AM1 method, the dipole moment, Log P, and qC2 were 6.265 Debye, −0.89, and 0.059 C, respectively. For the PM3 method, the dipole moment, Log P, and qC2 were 6.633 Debye, −0.89, and −0.107 C, respectively. The data for the RM1 method was 6.863 Debye for the dipole moment, −0.89 for Log P, and 0.121 C for qC2.

Table 2. Calculation data of AM1 method descriptors

Compound	Dipole	Vvdw	Hidration	log P	α	BM	qN1	qC2	qC3	qC4	qC5	qC6	qC7	qC8	qC9	qS10	qC11	qN12	HOMO	LUMO	ΔE
									Fitting compound												
2	4.462	772.49	-9.15	0.17	30.84	264.34	-0.198	-0.05	-0.383	-0.05	-0.079	-0.039	-0.1	-0.143	0.003	0.577	-0.375	-0.006	-8.144	-0.258	7.886
3	5.673	594.63	-11.29	-1.58	21.81	204.25	-0.2	-0.041	-0.392	-0.019	-0.121	0.062	-0.175	-0.109	-0.029	0.573	-0.377	0	-8.151	-0.14	8.011
5	6.977	587.99	-14.36	-0.87	21.19	199.23	-0.197	0.025	-0.42	-0.043	-0.044	-0.026	-0.082	-0.137	0.002	0.554	-0.384	-0.009	-9.278	-0.807	8.471
6	4.468	720.71	-8.36	0.12	29	250.32	-0.103	-0.05	-0.376	-0.052	-0.09	-0.142	-0.113	-0.136	0.027	0.58	-0.377	-0.001	-8.195	-0.521	7.674
7	4.883	825.15	-5.87	0.42	32.67	278.37	-0.153	-0.049	-0.383	-0.054	-0.08	-0.04	-0.101	-0.142	0.009	0.576	-0.375	-0.007	-8.066	-0.226	7.84
8	4.911	569.37	-6.68	-0.34	21.18	188.25	-0.097	-0.052	-0.377	-0.052	-0.09	-0.143	-0.113	-0.136	0.026	0.578	-0.377	-0.001	-8.18	-0.059	8.121
9	5.147	796.77	-10.05	-0.87	31.47	280.34	-0.155	-0.049	-0.383	-0.053	-0.086	-0.148	-0.11	-0.142	0.008	0.574	-0.375	-0.006	-7.969	-0.497	7.472
10	2.921	764.45	-8.01	-0.1	30.93	284.76	-0.105	-0.052	-0.371	-0.052	-0.088	-0.141	-0.111	-0.137	0.028	0.582	-0.379	0.002	-8.143	-0.75	7.393
11	4.906	715.99	-9.24	0.11	29	250.32	-0.199	0.048	-0.361	-0.064	-0.084	-0.151	-0.104	-0.148	0.016	0.582	-0.384	-0.006	-7.957	-0.766	7.191
12	5.206	767.13	-8.06	0.26	30.84	264.34	-0.2	0.051	-0.363	-0.063	-0.084	-0.151	-0.105	-0.148	0.015	0.582	-0.384	-0.007	-7.914	-0.754	7.16
13	6.265	792.7	-10.93	-0.89	31.47	280.34	-0.202	0.059	-0.368	-0.061	-0.085	-0.151	-0.105	-0.148	0.014	0.579	-0.383	-0.007	-7.874	-0.715	7.159
14	1.254	796.61	-8.56	0.68	30.56	318.32	-0.197	0.034	-0.35	-0.068	-0.082	-0.15	-0.1	-0.147	0.02	0.58	-0.385	0.003	-8.209	-1.147	7.062
15	4.148	759.41	-8.91	-0.12	30.93	284.76	-0.199	0.042	-0.356	-0.066	-0.083	-0.151	-0.102	-0.148	0.018	0.582	-0.385	-0.001	-8.056	-0.982	7.074
16	5.309	751.56	-6.89	0.35	30.84	264.34	-0.151	0.06	-0.366	-0.064	-0.085	-0.15	-0.107	-0.146	0.013	0.582	-0.388	-0.009	-7.888	-0.738	7.15
17	5.505	805.25	-5.72	0.51	32.67	278.37	-0.151	0.063	-0.368	-0.063	-0.086	-0.15	-0.107	-0.146	0.013	0.581	-0.388	-0.01	-7.846	-0.728	7.118
20	4.724	795.04	-6.57	0.13	32.76	298.79	-0.15	0.054	-0.361	-0.065	-0.084	-0.149	-0.105	-0.146	0.015	0.582	-0.388	-0.005	-7.987	-0.95	7.037
									Test compound												
1	4.751	518.25	-9.99	-0.59	19.34	174.22	-0.2	-0.05	-0.384	-0.054	-0.086	-0.148	-0.109	-0.143	0.001	0.575	-0.375	-0.005	-8.266	-0.085	8.181
4	5.833	580.79	-9.52	-0.54	21.97	253.12	-0.197	-0.05	-0.378	-0.058	-0.056	-0.187	-0.085	-0.142	0.011	0.58	-0.381	0.005	-8.441	-0.327	8.114
18	4.542	829.47	-8.6	-0.64	33.31	294.37	-0.152	0.072	-0.374	-0.06	-0.087	-0.149	-0.108	-0.145	0.012	0.577	-0.386	-0.01	-7.826	-0.688	7.138
19	7.191	830.98	-6.24	0.92	32.4	332.34	-0.15	0.045	-0.354	-0.068	-0.082	-0.149	-0.102	-0.147	0.018	0.588	-0.388	0.002	-8.099	-1.103	6.996

The PM3 method calculates a –0.107 C charge, which was negative, while the other two methods both produce positive values for qC2. This indicates that PM3 is less feasible for use, as PM3 is better suited for compounds containing transition metal atoms. The dipole moment values for all three methods were large, indicating substituents containing electronegative atoms [29]. The Log P data for all three methods are the same, indicating that the compound contains many functional groups contributing to its polarity [23].

The net atomic charge is a crucial descriptor in determining various chemical reactions and physicochemical properties of compounds. It measures intermolecular interactions and can be positive or negative, depending on the group attached to the atom. The net positive atomic charge resulted from electron-withdrawing groups, such as methoxy, which reduce the electron density. The net negative atomic charge arises from electron-contributing groups, such as methyl or alkyl groups, which increase the electron density [11]. The PM3 method calculated the atomic charge descriptors, which showed similar positive and negative charge values as those calculated by the AM1 and RM1 methods, except for qN1, which was positively charged, and qC9, which was negatively charged. The difference may be due to the

PM3 calculation method predicting that all N atoms are pyramidal, which is a weakness of the method [30].

The log P value determines the distribution of molecules in the body. A more positive log P value suggests that the compound tends to distribute in the nonpolar phase rather than the polar phase. Since the human body consists of lipid and water phases, the log P value significantly affects the diffusion process of active substances [31]. Polarizability measures a molecule's ability to form an instantaneous dipole or induce one in another molecule. Dipole attraction arises from an unsymmetrical charge distribution in the molecule, resulting in two ends with different charges. Dipole moments are crucial in drug activity, particularly in the interaction between compounds and receptor targets. If there is sufficient contact over a large area, a significant inter-dipole interaction energy can be formed. The polarizabilities obtained from the AM1, PM3, and RM1 calculations have almost the same value, indicating that the three methods are equivalent in calculating polarizability. However, the dipole moment calculation results show that the AM1 method has a relatively smaller value than PM3 and RM1.

Table 3. Calculation data of PM3 method descriptors

Compound	Dipole	Vvdw	Hidration	log P	α	BM	qN1	qC2	qC3	qC4	qC5	qC6	qC7	qC8	qC9	qS10	qC11	qN12	HOMO	LUMO	ΔE
Fitting compound																					
2	5.089	770.25	-9.12	0.17	30.84	264.34	0.323	-0.198	-0.28	-0.044	-0.065	-0.032	-0.086	-0.093	-0.181	0.394	-0.286	-0.026	-8.179	-0.268	7.911
3	6.236	596.16	-11.26	-1.58	21.81	204.25	0.321	-0.189	-0.291	-0.012	-0.112	0.078	-0.154	-0.059	-0.212	0.391	-0.289	-0.019	-8.129	-0.165	7.964
5	7.569	588.65	-14.34	-0.87	21.19	199.23	0.33	-0.137	-0.322	-0.035	-0.015	-0.021	-0.067	-0.085	-0.182	0.386	-0.303	-0.023	-9.241	-0.735	8.506
6	5.003	711.42	-8.18	0.12	29	250.32	-0.248	0.051	-0.358	-0.067	-0.052	-0.117	-0.076	-0.118	0.082	0.486	-0.152	-0.167	-8.128	-0.482	7.646
7	5.441	823.17	-5.84	0.42	32.67	278.37	0.383	-0.178	-0.28	-0.046	-0.065	-0.034	-0.086	-0.095	-0.155	0.393	-0.285	-0.027	-8.099	-0.227	7.872
8	5.823	797.09	-10.03	-0.87	31.47	280.34	0.385	-0.203	-0.269	-0.053	-0.062	-0.111	-0.087	-0.1	-0.151	0.394	-0.289	-0.021	-8.107	-0.435	7.672
9	5.732	571.74	-6.71	-0.34	21.18	188.25	0.28	-0.178	-0.28	-0.052	-0.059	-0.115	-0.084	-0.099	-0.153	0.392	-0.287	-0.023	-8.14	-0.065	8.075
10	4.356	764.6	-8.04	-0.1	30.93	284.76	0.37	-0.199	-0.263	-0.053	-0.061	-0.109	-0.084	-0.101	-0.146	0.397	-0.29	-0.018	-8.275	-0.684	7.591
11	5.423	715.8	-9.24	0.11	29	250.32	0.321	-0.12	-0.263	-0.053	-0.059	-0.115	-0.082	-0.1	-0.171	0.402	-0.305	-0.026	-8.116	-0.738	7.378
12	5.649	766.32	-8.05	0.26	30.84	264.34	0.32	-0.115	-0.265	-0.052	-0.059	-0.115	-0.082	-0.1	-0.172	0.401	-0.304	-0.027	-8.072	-0.726	7.346
13	6.633	791.81	-10.88	*-0.89*	31.47	280.34	0.316	*-0.107*	-0.27	-0.05	-0.06	-0.115	-0.083	-0.1	-0.172	0.401	-0.304	-0.027	-8.028	-0.688	7.34
14	2.172	794.38	-8.57	0.68	30.56	318.32	0.325	-0.135	-0.253	-0.056	-0.058	-0.113	-0.077	-0.1	-0.167	0.402	-0.307	-0.016	-8.368	-1.117	7.251
15	4.998	758.55	-8.9	-0.12	30.93	284.76	0.322	-0.124	-0.26	-0.054	-0.058	-0.115	-0.08	-0.1	-0.17	0.402	-0.306	-0.023	-8.21	-0.953	7.257
16	5.795	751.81	-6.89	0.35	30.84	264.34	0.29	-0.088	-0.266	-0.055	-0.059	-0.116	-0.08	-0.104	-0.157	0.4	-0.305	-0.028	-8.048	-0.702	7.346
17	5.94	804.1	-5.72	0.51	32.67	278.37	0.289	-0.084	-0.269	-0.054	-0.06	-0.116	-0.081	-0.103	-0.157	0.4	-0.305	-0.029	-8.006	-0.691	7.315
20	5.443	794.82	-6.57	0.13	32.76	298.79	0.291	-0.092	-0.263	-0.056	-0.059	-0.116	-0.079	-0.104	-0.156	0.401	-0.306	-0.025	-8.142	-0.914	7.228
Test compound																					
1	5.393	520.17	-10.02	-0.59	19.34	174.22	0.321	-0.198	-0.279	-0.05	-0.059	-0.114	-0.084	-0.097	-0.179	-0.393	-0.288	-0.023	-8.222	-0.107	8.115
4	5.948	591.7	-9.83	-0.54	21.97	253.12	0.33	-0.139	-0.326	-0.023	-0.03	-0.118	-0.075	-0.079	-0.194	0.383	-0.3	-0.028	-9.133	-0.547	8.586
18	5.055	829.02	-8.56	-0.64	33.31	294.37	0.286	-0.074	-0.275	-0.052	-0.061	-0.116	-0.082	-0.103	-0.158	0.397	-0.304	-0.029	-7.983	-0.654	7.329
19	7.759	829.09	-6.22	0.92	32.4	332.34	0.291	-0.103	-0.256	-0.059	-0.056	-0.115	-0.075	-0.105	-0.153	0.405	-0.305	-0.017	-8.256	-1.063	7.193

The HOMO-LUMO gap (ΔE) is a descriptor that measures the ease a molecular system can excite to a higher electronic state. The HOMO energy is directly linked to the ionization potential and the molecule's susceptibility to attacking electrophiles. In contrast, the LUMO energy relates to electron affinity and the molecule's vulnerability to nucleophile attack. The energy difference between the HOMO and LUMO is crucial in determining molecular stability. A large HOMO-LUMO gap (ΔE) suggests high stability and low reactivity in chemical reactions. This gap is also used to estimate the molecule's lowest excitation energy. The AM1 method produced relatively smaller ΔE values than the PM3 and RM1 methods (Table 2), indicating low stability and increased compound reactivity. Hydration energy and van der Waals volume are also considered significant in determining the biological activity of anticancer compounds, as their values vary across different compounds [21].

3.3. Correlation calculation results of descriptors with IC$_{50}$

The correlation analysis was performed using the two-tailed and Pearson correlation coefficients. The results were used to select the most suitable descriptors as independent variables for multiple linear regression (MLR) analysis. This analysis helped to determine the extent to which the independent variables (descriptors) influenced the IC50 value to construct a reliable QSAR equation. The correlation values between the descriptors and anticancer activity are presented in Table 5.

The chosen descriptor should have a significant correlation value and a significance level below 0.05 for a 95% confidence interval. Thus, the descriptors with substantial correlations for the AM1 method were ΔE, dipole, hydration, qC9, qC8, HOMO, log P, qC3, qC6, and qS10. For the PM3 method, the descriptors selected were ΔE, qC7, dipole, hydration, α, qC8, log P, qC6, BM, and qC4. Finally, the chosen descriptors for the RM1 method were ΔE, hydration, qC6, dipole, volume, log P, qC8, BM, α, and qC4.

Table 4. Calculation data of RM1 method descriptors

Compound	Dipole	Vvdw	Hydration	log P	α	BM	qN1	qC2	qC3	qC4	qC5	qC6	qC7	qC8	qC9	qS10	qC11	qN12	HOMO	LUMO	ΔE
									Fitting compound												
2	5.015	761.58	-8.88	0.17	30.84	264.34	-0.311	0.053	-0.368	-0.068	0.04	-0.059	-0.063	-0.121	0.062	0.483	-0.149	-0.173	-8.238	-0.203	8.035
3	6.092	588.77	-10.95	-1.58	21.81	204.25	-0.313	0.064	-0.379	-0.033	-0.085	0.068	-0.139	-0.087	0.028	0.479	-0.151	-0.166	-8.224	-0.108	8.116
5	7.388	581.55	-14.1	-0.87	21.19	199.23	-0.313	0.126	-0.413	-0.064	0.011	-0.084	0.039	-0.116	0.067	0.481	-0.164	-0.173	-9.365	-0.734	8.631
6	5.003	711.42	-8.18	0.12	29	250.32	-0.248	0.051	-0.358	-0.067	-0.052	-0.117	-0.076	-0.118	0.082	0.486	-0.152	-0.167	-8.291	-0.462	7.829
7	5.444	813.43	-5.64	0.42	32.67	278.37	-0.294	0.054	-0.367	-0.068	-0.04	-0.06	-0.064	-0.12	0.071	0.482	-0.149	-0.174	-8.158	-0.169	7.989
8	5.555	785.79	-9.79	-0.87	31.47	280.34	-0.242	0.049	-0.359	-0.068	-0.052	-0.118	-0.076	-0.118	0.081	0.485	-0.151	-0.168	-8.184	-0.422	7.762
9	5.718	564.24	-6.54	-0.34	21.18	188.25	-0.295	0.054	-0.369	-0.068	-0.049	-0.122	-0.075	-0.119	0.068	0.48	-0.15	-0.172	-8.267	-0.02	8.247
10	2.629	755.79	-7.84	-0.1	30.93	284.76	-0.252	0.048	-0.352	-0.067	-0.05	-0.116	-0.073	-0.119	0.083	0.49	-0.154	-0.164	-8.445	-0.754	7.691
11	5.568	708.28	-9.07	0.11	29	250.32	-0.311	0.11	-0.336	-0.08	-0.047	-0.126	-0.069	-0.125	0.073	0.489	-0.156	-0.171	-8.217	-0.698	7.519
12	5.882	760.84	-7.89	0.26	30.84	264.34	-0.311	0.113	-0.338	-0.079	-0.048	-0.126	-0.069	-0.125	0.073	0.488	-0.155	-0.172	-8.173	-0.688	7.485
13	6.863	784.62	-10.67	*-0.89*	31.47	280.34	-0.313	*0.121*	-0.342	-0.077	-0.048	-0.126	-0.07	-0.125	0.072	0.486	-0.155	-0.172	-8.122	-0.647	7.475
14	2.056	785.32	-8.37	0.68	30.56	318.32	-0.309	0.096	-0.324	-0.084	-0.046	-0.124	-0.065	-0.125	0.078	0.486	-0.155	-0.164	-8.463	-1.092	7.371
15	4.323	752.81	-8.73	-0.12	30.93	284.76	-0.31	0.1	-0.327	-0.083	-0.046	-0.125	-0.066	-0.126	0.076	0.488	-0.156	-0.166	-8.373	-0.996	7.377
16	5.477	769.77	-6.72	0.35	30.84	264.34	-0.284	0.18	-0.405	-0.049	-0.047	-0.118	-0.083	-0.11	0.05	0.479	-0.159	-0.191	-8.707	-0.418	8.289
17	5.591	820.46	-5.59	0.51	32.67	278.37	-0.284	0.183	-0.406	-0.049	-0.048	-0.118	-0.083	-0.11	0.05	0.478	-0.159	-0.192	-8.676	-0.413	8.263
20	5.217	819.42	-6.4	0.13	32.76	298.79	-0.283	0.17	-0.399	-0.051	-0.046	-0.117	-0.08	-0.11	0.051	0.48	-0.161	-0.187	-8.844	-0.709	8.135
									Test compound												
1	5.314	513.44	-9.82	-0.59	19.34	174.22	-0.313	0.054	-0.369	-0.068	-0.048	-0.122	-0.073	-0.121	0.059	0.481	-0.15	-0.171	-8.355	-0.048	8.307
4	6.7	576.8	-9.32	-0.54	21.97	253.12	-0.309	0.056	-0.365	-0.07	-0.022	-0.1	-0.053	-0.116	0.064	0.488	-0.156	-0.161	-8.566	-0.351	8.215
18	5.407	818.56	-8.34	-0.64	33.31	294.37	-0.287	0.131	-0.348	-0.072	-0.049	-0.124	-0.073	-0.123	0.068	0.483	-0.162	-0.178	-8.058	-0.628	7.43
19	7.7	819.85	-6.06	0.92	32.4	332.34	-0.286	0.106	-0.329	-0.08	-0.045	-0.124	-0.066	-0.126	0.074	0.493	-0.161	-0.167	-8.844	-1.054	7.79

Table 5. The correlation values between the anticancer activity and descriptors

AM1 method						
	Dipole	qN₁	qC₂	qC₃	qC₄	qC₅	qC₆

	Dipole	qN_1	qC_2	qC_3	qC_4	qC_5	qC_6
AM1 method							
IC_{50}	0.457	-0.264	-0.313	-0.697	0.395	0.093	0.682
	qC_7	qC_8	qC_9	qS_{10}	qC_{11}	qN_{12}	Log P
	-0.245	0.570	-0.601	-0.590	0.338	-0.001	-0.552
	Vvdw	Hidration	HOMO	LUMO	ΔE	α	BM
	-0.379	-0.560	-0.519	0.352	0.590	-0.439	-0.405
PM3 method							
	Dipole	qN_1	qC_2	qC_3	qC_4	qC_5	qC_6
IC_{50}	0.494	0.225	-0.373	-0.314	0.681	-0.061	0.705
	qC_7	qC_8	qC_9	qS_{10}	qC_{11}	qN_{12}	Log P
	-0.413	0.666	-0.292	-0.149	-0.060	0.170	-0.548
	Vvdw	Hidrasi	HOMO	LUMO	ΔE	α	BM
	-0.387	-0.555	-0.400	0.357	0.570	-0.448	-0.414
RM1 method							
	Dipole	qN_1	qC_2	qC_3	qC_4	qC_5	qC_6
IC_{50}	0.410	-0.289	-0.258	-0.279	0.312	0.133	0.629
	qC_7	qC_8	qC_9	qS_{10}	qC_{11}	qN_{12}	Log P
	0.206	0.384	-0.293	-0.142	0.099	0.244	-0.548
	Vvdw	Hidration	HOMO	LUMO	ΔE	α	BM
	-0.411	-0.547	-0.173	0.280	0.390	-0.448	-0.414

The chosen descriptor should have a significant correlation value and a significance level below 0.05 for a 95% confidence interval. Thus, the descriptors with substantial correlations for the AM1 method were ΔE, dipole, hydration, qC9, qC8, HOMO, log P, qC3, qC6, and qS10. For the PM3 method, the descriptors selected were ΔE, qC7, dipole, hydration, α, qC8, log P, qC6, BM, and qC4. Finally, the chosen descriptors for the RM1 method were ΔE, hydration, qC6, dipole, volume, log P, qC8, BM, α, and qC4.

3.4. Determination of the best equation model with multiple linear regression

Analysis using the backward method of fitting compounds resulted in developing 6, 6, and 7 QSAR equation models for AM1, PM3, and RM1, respectively (Table 6, 7, 8). The selection of the best QSAR equation requires that the correlation coefficient (r) be greater than 0.8, the Fcount value should exceed the Ftable (Fcount/Ftable>1) for a 95% confidence level, and the model should have a small standard error (SE) and a small predict the residual sum of square (PRESS) value [11].

Table 6. QSAR AM1 equation model from multiple linear regression analysis using a backward method

Model	Variable	R	r²	SE	F_{count}/F_{table}	PRESS
1	ΔE, Dipole, Hidration, qC₉, qC₈, HOMO, logP, qC₃, qC₆, qS₁₀	0.947	0.898	0.9395	4.382/4.74= 0.924	163.637
2	ΔE, Dipole, Hidration, qC₉, qC₈, HOMO, logP, qC₆, qS₁₀	0.947	0.898	0.8577	5.841/4.1= 1.424	161.876
3	ΔE, Dipole, qC₉, qC₈, HOMO, logP, qC₆, qS₁₀	0.946	0.895	0.8026	7.487/3.73= 2.221	154.696
4	ΔE, Dipole, qC₉, HOMO, logP, qC₆, qS₁₀	0.941	0.886	0.7831	8.895/3.5= 2.541	125.836
5	ΔE, Dipole, qC₉, logP, qC₆, qS₁₀	0.929	0.863	0.8113	9.411/3.37= 2.792	76.165
6	ΔE, Dipole, qC₉, logP, qC₆	0.908	0.825	0.8696	9.397/3.33= 2.821	54.746

Table 7. QSAR PM3 equation model from multiple linear regression analysis using a backward method

Model	Variable	R	r²	SE	F_{count}/F_{table}	PRESS
1	ΔE, qC₇, Dipole, Hidration, α, qC₈, logP, qC₆, BM, qC₄	0.961	0.923	0.8150	5.988/4.74= 1.255	307.388
2	ΔE, qC₇, Dipole, Hidration, polarizability, qC₈, logP, qC₆, qC₄	0.961	0.923	0.7440	7.984/4.1= 1.947	305.539
3	qC₇, Dipole, Hidration, α, qC₈, logP, qC₆, qC₄	0.961	0.923	0.6898	10.447/3.73= 2.8	309.889
4	qC₇, Dipole, Hidration, qC₈, logP, qC₆, qC₄	0.958	0.917	0.6691	12.606/3.5= 3.601	323.525
5	qC₇, Dipole, Hidration, qC₈, logP, qC₄	0.945	0.894	0.7128	12.636/3.37= 3.749	167.775
6	qC₇, Dipole, qC₈, logP, qC₄	0.932	0.869	0.7504	13.306/3.33= 3.995	114.348

Table 8. QSAR RM1 equation model from multiple linear regression analysis using a backward method

Model	Variable	R	r²	SE	F_{count}/F_{table}	PRESS
1	ΔE, Hidration, qC₆, Dipole, Volume, logP, qC₈, BM, α, qC₄	0.879	0.773	1.3981	1.704/4.74= 0.359	15.730
2	ΔE, Hidration, qC₆, Volume, logP, qC₈, BM, α, qC₄	0.879	0.773	1.2765	2.272/4.1= 0.554	17.850
3	ΔE, Hidration, qC₆, Volume, logP, qC₈, α, qC₄	0.879	0.773	1.1819	2.981/3.73= 0.799	17.943
4	ΔE, Hidration, qC₆, Volume, qC₈, α, qC₄	0.872	0.760	1.1370	3.620/3.5= 1.034	21.163
5	ΔE, Hidration, qC₆, qC₈, α, qC₄	0.834	0.695	1.2088	3.415/3.37= 1.013	10.166
6	Hidration, qC₆, qC₈, α, qC₄	0.823	0.678	1.1783	4.208/3.33= 1.263	4.135
7	Hidration, qC₆, qC₈, qC₄	0.821	0.674	1.1298	5.691/3.36= 1.693	4.719

These QSAR equation models underwent statistical testing based on the values of r, r², SE, and F [32], and the PRESS value was calculated for the four test compounds [33]. Model 6 was identified as the best for the AM1, PM3, and RM1 methods because it had an r-value in the range of 0.9, the smallest PRESS value, and the highest F_{count}/F_{table} value [34]. In selecting the QSAR equation model, the PRESS value was given significant consideration as a smaller PRESS value indicates that the calculation of compound activity prediction is closer to the experimental data. The final QSAR equation for all 3-thiocyanate-1H-indole derivative compounds was obtained using the Enter method, which analyzed the selected models from the AM1, PM3, and RM1 methods.

The results of the Enter method analysis are shown in Table 10.

Table 9. Output of AM1, PM3, and RM1 with Enter method

Model	Variable	R	r²	SE	F_{count}/F_{table}	PRESS
AM1	ΔE, Dipole, qC₉, logP, qC6	0.814	0.662	1.04484	5.481/2.96= 1.851	15.219
PM3	qC7, Dipole, qC8, logP, qC4	0.761	0.578	1.16667	3.852/2.96= 1.301	19.055
RM1	Hidration, qC6, qC8, α, qC4	0.788	0.622	1.10531	4.6/2.96= 1.554	17.103

By comparing the r, r², SE, F_{count}/F_{table}, and PRESS values, AM1 suggests the best method. Therefore, the best QSAR equation for 3-thiocyanate-1H-indoles was IC₅₀ = -1.705 + 0.511(Delta) + 0.346(Dipol) + 18.287(qC₉) − 0.645(Log P) + 13.952(qC₆), with n = 20; r = 0.814; r² = 0.662; SE = 1.044; F_{count}/F_{table} = 1.851; PRESS = 15.219. The correlation graph between predicted and experimental activities (IC₅₀) shows a slope close to 1 (Table 10, Figure 2) [26], meaning that the resulting equation can provide a good level of prediction.

Table 10. PRESS value of the final QSAR equation with Enter method

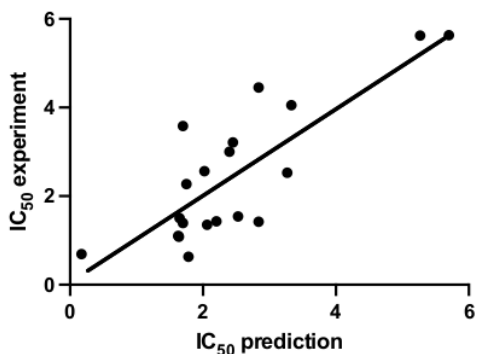| Compound	IC_{50} prediction	IC_{50} experiment	PRESS
1	2.45	3.21	0.5776
2	3.27	2.53	0.5476
3	5.70	5.63	0.0049
4	2.40	3	0.3600
5	5.27	5.62	0.1225
6	2.20	1.43	0.5929
7	3.33	4.05	0.5184
8	2.84	1.42	2.0164
9	2.53	1.54	0.9801
10	1.70	3.58	3.5344
11	1.78	0.63	1.3225
12	1.75	2.27	0.2704
13	2.84	4.45	2.5921
14	0.17	0.69	0.2704
15	1.64	1.08	0.3136
16	1.70	1.39	0.0961
17	1.65	1.5	0.0225
18	2.06	1.35	0.5041
19	2.02	2.56	0.2916
20	1.63	1.1	0.2809
Σ PRESS			15.219

Figure 2. Correlation graph between predicted and experimental activity (IC$_{50}$)

4. Conclusion

Based on the results, the RM1 semi-empirical method was the latest semi-empirical calculation method in the Hyperchem Program version 8 and unsuitable for QSAR 3-thiocyanate-1H-indoles derivative compounds. The AM1 semi-empirical method was the best for QSAR of 3-thiocyanate-1H-indoles derivative compounds compared to PM3 and RM1 methods. The AM1 semi-empirical method, obtained $r^2 = 0.662$, was a measure of the goodness of fit of a model. The standard error (SE) was 1.044.

Acknowledgment

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