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# A Monte Carlo simulation study of vinblastine and vincristine as clinical drugs

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## ABSTRACT

In this study, Monte Carlo statistical mechanical simulations for vinblastine and vincristine were carried out in standard manner using the Metropolis sampling technique in canonical (T, V, N) ensemble., Geometrical optimizations of vinblastine and vincristine were carried out with the HF method coupled to 6-31G(d) basis sets for all atoms. Simulation was done by four force fields of $MM^+$, $BIO^+$, AMBER and OPLS. Some important energy parameters such as Potential Energy and Total Energy in ten different simulating temperatures (300, 302, 304, 306, 308, 310, 312, 314, 316 and 318 Kelvin) were used for computation.

**Keywords:** Vinblastine; Vincristine; Monte Carlo

## INTRODUCTION

The vinca alkaloids are a subset of drugs derived from the Madagascar periwinkle plant. They were discovered in the 1950's by Canadian scientists, Robert Noble and Charles Beer [1, 2]. Vinca alkaloids have been found to control diabetes, high blood pressure, and are the drugs that have even been used as disinfectants. There are four major vinca alkaloids (vinblastine, vinorelbine, vincristine, and vindesine) that are applied in clinical usages [3].

The vinca alkaloids are cytotoxics so that they halt the division of cells and cause cell death. During cell division, vinca alkaloid molecules bind to the building blocks of a protein called tubulin and prevent from its formation. Tubulin protein normally works in cells to create "spindle fibers," (also called microtubules). These microtubules provide cells with both the structure and flexibility they need to divide and replicate. Without microtubules, cells cannot divide. The vinca alkaloid's mechanism in a nutshell: by occupying tubulin's building block structure, vinca alkaloids inhibit cancer cells division. The antitumor activity of vinblastine is ascribed to primarily inhibition of mitosis at metaphase through its interaction with tubulin. Vinblastine

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binds to the microtubular proteins of the mitotic spindle causes microtubule crystallization so that mitotic arrest or cell death [4, 5].

Vincristine's inhibition of microtubule formation is especially powerful. Dynamic character of tubulin protein is the reason for this fact. Its long chain of building blocks is always growing in some places and breaking in others. The less contiguous parts of a tubulin molecule have pieces only two building blocks long, called dimers. Vincristine has a high affinity for tubulin dimers, and the reaction between vincristine and the dimers is rapidly reversible. That means a vincristine molecule will attach to a dimer at one site, break off, and then reattach at another site. This keeps two sites per dimer "poisoned" and unable to reassemble into the protein. So vincristine's ability to destabilize tubulin is especially good [6, 7].

The aim of this work is to understand molecular mechanic of vinblastine and vincristine drugs, which will be useful for designing anticancer drugs.

# THEORETICAL

### *Background and Computational Methods*

The Monte Carlo method was invented by scientists working on the atomic bomb in the 1940s, who named it for the city in Monaco famed for its casinos and games of chance. Its core idea is to use random samples of parameters or inputs to explore the behavior of a complex system or process [8]. Molecular mechanic simulation method are especially useful in studying systems with a large number of coupled degrees of freedom, such as liquids disordered materials, strongly coupled solids and cellular structures.

Simulation refers to methods aimed at generating a representative sampling of a system at a finite temperature [9]. Monte Carlo (MC) methods are a class of computational algorithms that rely on repeated random sampling to compute their results.

The systems can be studied in the coarse-grained or *ab initio* frameworks depending on the desired accuracy. Computer simulations allow us to monitor the local environment of a particular molecule to see if some chemical reaction is happening for instance. We can also conduct thought experiments when the physical experiments are not feasible, for instance breaking bonds, introducing impurities at specific sites, changing the local/global structure, or introducing external fields. Biological systems such as proteins [10] membranes [11], images of cancer [12], are being studied by means of computer simulations.

Thermodynamic averages of molecular properties can be determined from MC methods, as can minimum energy structures. MC simulations require only the ability to evaluate the energy of the system, which may be advantageous if calculating the first derivative is difficult or time- consuming. Furthermore, since only a single particle is moved in each step, only the energy changes associated with this move must be calculated, not the total energy for the whole system. A disadvantage of MC methods is the lack of the time dimension and atomic velocities, and they are not suitable for studying time-dependent phenomena or properties depending on momentum.

Geometrical optimizations of vinblastine and vincristine were carried out with the HF method coupled to 6-31G(d) basis sets for all atoms. Simulation was done in $MM^{+}$, $BIO^{+}$, AMBER and OPLS force fields. Some important energy parameters such as Potential Energy and Total Energy in ten different simulating temperatures (300, 302, 304, 306, 308,

310, 312, 314, 316 and 318 Kelvin) were used for computation.

## RESULTS AND DISCUSSION

Monte Carlo statistical mechanical simulations were carried out in standard manner using the Metropolis sampling technique [13] in canonical (T, V, N) ensemble.

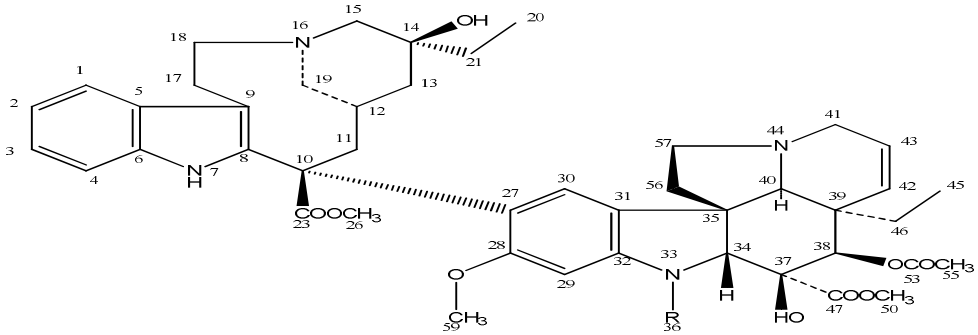
The two compounds are very similar in the structure and molecular structure of vinblastine and vincristine has been presented in scheme 1.

The main purpose is to find for the lowest energy, in which the molecule is in its most stable state. In this study AMBER, $MM^{+}$, $BIO^{+}$ and OPLS force fields were chosen. The total Potential Energy is the sum of mentioned contribution interactions based on the force fields. Therefore, force fields are a series of functional energy parameters that evaluate performance and calculate the Potential Energy of molecule in various positions of its constituent atoms and bonds [14, 15].

In this work, we have determined all possible potential and total energy of vinblastine and in vincristine by Monte Carlo method at 300, 302, 304, 306,308,310,312,314,316, and 318 K. The obtained valuable data for thermodynamic parameters (E potential, E total), analyzed under the different simulation procedure, various temperatures values every 10 ps span are listed in tables. Calculations of potential energy and total energy were performed by four force fields (AMBER, $BIO^{+}$, $MM^{+}$ and OPLS). For example, the results obtained by AMBER and $MM^{+}$ for vinblastine and vincristine have been tabulated as tables 1-4.

**Table 1.** Calculated potential energy for vinblastine, belong to AMBER force field at ten different temperature

| Potential Energy (Kcal/mol) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Method | AMBER/ Monte Carlo | | | | | | | | | |
| Time (PS) | 300 | 302 | 304 | 306 | 308 | 310 | 312 | 314 | 316 | 318 |
| 10 | 50449000 | 53512342 | 53512342 | 53512342 | 53128563 | 52690522 | 52806650 | 52806650 | 52806651 | 52806650 |
| 20 | 1314905.8 | 1626318.6 | 1626318.6 | 1785355.3 | 1204928.9 | 1787593.5 | 2115727.6 | 2115727.6 | 2094548.3 | 2127119.6 |
| 30 | 271681.5 | 189228.57 | 189522.42 | 105404.19 | 163599.14 | 165276.17 | 116559.33 | 116262.21 | 217476.76 | 270463.7 |
| 40 | 52361.15 | 29296.18 | 37555.35 | 21771.44 | 28030.01 | 35234.38 | 18926.18 | 23716.78 | 43225.02 | 62895.78 |
| 50 | 13874.383 | 8497.899 | 10712.909 | 8287.879 | 7107.155 | 8711.508 | 8189.063 | 7894.82 | 11596.633 | 16761.794 |
| 60 | 6035.871 | 4427.751 | 5305.803 | 4684.934 | 4082.47 | 4404.972 | 4590.423 | 4416.86 | 4773.3 | 5101.984 |
| 70 | 2658.939 | 3458.772 | 3628.05 | 3561.057 | 3091.596 | 3166.71 | 3482.746 | 3371.445 | 3144.896 | 3418.002 |
| 80 | 2018.184 | 2980.936 | 2950.486 | 2871.28 | 2612.269 | 2720.612 | 2756.059 | 2844.769 | 2472.099 | 2707.019 |
| 90 | 1604.06 | 2608.213 | 2570.094 | 2488.824 | 2243.976 | 2475.265 | 2199.5 | 2568.873 | 1946.18 | 2265.44 |
| 100 | 1288.7445 | 2293.1791 | 2301.0309 | 2252.82 | 1903.6555 | 2263.2345 | 1756.3964 | 2332.8191 | 1582.1818 | 1831.39818 |



**Scheme 1.** Molecular structure of vinblastine and vincristine (Vincristine: R= CHO; Vinblastine: R= $CH_3$).

**Table 2.** Calculated potential energy for vinblastine, belong to MM+ force field at ten different temperature

| Potential Energy (Kcal/mol) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Method | MM+/ Monte Carlo | | | | | | | | | |
| Time (PS) | 300 | 302 | 304 | 306 | 308 | 310 | 312 | 314 | 316 | 318 |
| 10 | 4534.575 | 4534.575 | 4518.281 | 4537.923 | 4557.658 | 4406.06 | 4393.835 | 4393.835 | 4394.035 | 4382.339 |
| 20 | 3141.478 | 3118.733 | 3138.051 | 3011.141 | 2919.735 | 2892.965 | 2962.516 | 2962.516 | 2891.541 | 2913.151 |
| 30 | 2338.082 | 2294.103 | 2298.376 | 2156.649 | 2122.811 | 2072.862 | 2164.998 | 2164.998 | 2103.993 | 2177.182 |
| 40 | 1753.396 | 1795.26 | 1737.617 | 1644.85 | 1766.982 | 1628.7 | 1729.651 | 1729.651 | 1703.937 | 1678.862 |
| 50 | 1378.158 | 1369.994 | 1345.728 | 1240.39 | 1483.564 | 1346.885 | 1381.282 | 1379.448 | 1443.559 | 1357.129 |
| 60 | 1118.115 | 1057.000 | 1142.777 | 975.0752 | 1306.345 | 1145.577 | 1092.2192 | 1109.6975 | 1146.613 | 1085.6503 |
| 70 | 899.4439 | 839.9989 | 979.0861 | 809.4138 | 1120.114 | 971.6776 | 880.545 | 874.4816 | 981.1758 | 931.5397 |
| 80 | 736.228 | 700.2869 | 741.6991 | 688.4232 | 899.2035 | 852.353 | 763.7964 | 747.9081 | 838.3322 | 790.2792 |
| 90 | 633.1893 | 626.3875 | 628.5347 | 612.8694 | 721.9906 | 719.4925 | 665.6212 | 654.7784 | 742.1789 | 667.0155 |
| 100 | 550.19736 | 558.6757 | 573.32891 | 562.37427 | 624.42518 | 666.90045 | 580.88282 | 564.29009 | 647.041545 | 585.594727 |

Comparisons of potential energy levels in different temperatures are displayed in Figs. 1a- 1d for vinblastine and 2a- 2d for vincristine. The energy plots versus time steps for four force fields have been illustrated in figure 2a-2d and 3a-3d. The plots show the same behavior for four methods at all 10 temperature intervals.

According to results observed in tables 1 and 2 and figs 1 for vinblastine potential energy in different time steps and various force fields shows that maximum quantity observed in 310 K in OPLS force field and minimum quantity observed in 300 K, 550.19 Kcal/mol in MM+ force field. According to results observed in tables 3 and 4 and figs 2 for vincristine potential energy in different time steps and various force fields shows that maximum quantity observed in 310 K in AMBER force field and minimum quantity observed in 310 K, 278.51 Kcal/mol in MM+ force field.

According to results observed in tables 5 and fig. 3 for vinblastine total energy in different temperature and various force fields shows that maximum quantity observed in 308 K, 2526.39 Kcal/mol in OPLS method.

According to results observed in tables 6 and fig. 4 for vincristine total energy in different temperature and various force fields shows that maximum quantity observed in 306 K, 570.447 Kcal/mol in BIO+ method.

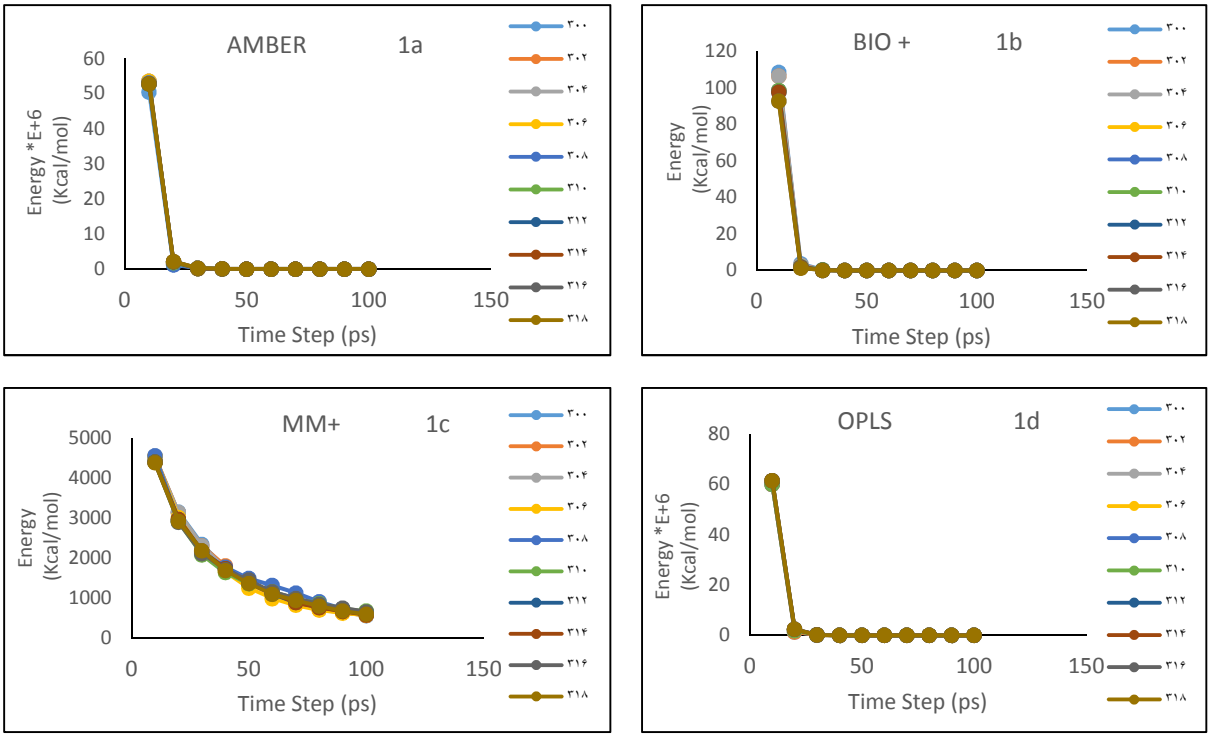



**Fig. 1.** The graphs of vinblastine potential energy belong to a) AMBER b) $BIO^{+}$, c) $MM^{+}$, d) OPLS force fields.

**Table 3.** Calculated potential energy for vincristine, belong to AMBER force field at ten different temperature

| Potential Energy (Kcal/mol) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Method | AMBER/ Monte Carlo | | | | | | | | | |
| Time (PS) | 300 | 302 | 304 | 306 | 308 | 310 | 312 | 314 | 316 | 318 |
| 10 | 66669750 | 66671240 | 66671240 | 66671240 | 66671240 | 81036240 | 70086826 | 70075328 | 70075328 | 58988803 |
| 20 | 3200478.3 | 4887313.4 | 4887313.8 | 4887313.9 | 3814583.8 | 5311674.9 | 969475.5 | 924610.3 | 924609.5 | 177970.3 |
| 30 | 70518.05 | 58130.19 | 331198.4 | 70424.57 | 60196.7 | 65283.15 | 66477.72 | 39605.25 | 39520.64 | 7816.392 |
| 40 | 5442.965 | 3206.117 | 158067.4 | 6133.808 | 5069.302 | 6810.503 | 8880.389 | 4711.518 | 3892.231 | 1888.933 |
| 50 | 1933.352 | 1047.783 | 718566 | 1465.579 | 1354.736 | 1779.538 | 1911.726 | 1801.541 | 1556.908 | 981.6114 |
| 60 | 1159.876 | 669.871 | 488821.1 | 926.0091 | 724.1822 | 919.1727 | 1109.991 | 1048.303 | 956.0189 | 705.5823 |
| 70 | 860.7192 | 523.628 | 499640.3 | 616.8188 | 498.0776 | 666.7751 | 695.2647 | 727.495 | 683.5751 | 543.4913 |
| 80 | 619.9293 | 455.3749 | 375344.2 | 488.0953 | 430.2659 | 542.5169 | 504.1217 | 576.4321 | 543.4305 | 460.7368 |
| 90 | 470.1542 | 403.445 | 396553.9 | 418.8983 | 404.8856 | 471.2364 | 428.6849 | 487.3585 | 474.307 | 430.5735 |
| 100 | 404.9508 | 383.0372 | 368279.55 | 381.96991 | 382.40409 | 424.43782 | 400.20609 | 427.94445 | 443.43745 | 400.167 |

**Table 4.** calculated potential energy for vincristine, belong to $MM^{+}$ force field at ten different temperature

| Potential Energy (Kcal/mol) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Method | $MM^{+}$/ Monte Carlo | | | | | | | | | |
| Time (PS) | 300 | 302 | 304 | 306 | 308 | 310 | 312 | 314 | 316 | 318 |
| 10 | 1811.181 | 1825.863 | 1774.751 | 1774.751 | 1774.751 | 1781.948 | 1781.948 | 1791.754 | 1791.754 | 1786.094 |
| 20 | 1172.071 | 1196.137 | 1068.278 | 1069.0069 | 1079.8519 | 1144.8081 | 1088.374 | 1128.662 | 1128.6629 | 1094.697 |
| 30 | 774.9873 | 805.4633 | 688.3277 | 691.7222 | 725.0924 | 699.1269 | 687.7324 | 739.8002 | 752.2391 | 701.8544 |
| 40 | 558.8123 | 545.9983 | 514.4215 | 518.433 | 554.1168 | 510.242 | 498.7968 | 551.805 | 555.8914 | 529.5489 |
| 50 | 464.0144 | 427.0653 | 426.5527 | 441.7188 | 469.7542 | 416.2247 | 430.5498 | 459.9416 | 446.453 | 447.3894 |
| 60 | 401.0245 | 375.6622 | 378.397 | 388.0903 | 420.5896 | 361.8982 | 382.0928 | 396.2465 | 395.9465 | 398.4633 |
| 70 | 372.1776 | 335.9098 | 349.9951 | 362.4731 | 382.0106 | 329.2889 | 349.4232 | 349.6155 | 352.1546 | 371.3351 |
| 80 | 345.6443 | 322.6189 | 332.1923 | 339.363 | 355.0489 | 309.4171 | 328.8694 | 312.5646 | 342.5879 | 342.5787 |
| 90 | 316.2172 | 308.121 | 309.9506 | 329.2566 | 327.4962 | 288.6556 | 321.3545 | 303.098 | 323.4118 | 322.2277 |
| 100 | 305.6673 | 294.8295 | 293.7925 | 306.93409 | 307.82491 | 278.51809 | 306.16309 | 287.0697 | 310.96718 | 318.11172 |

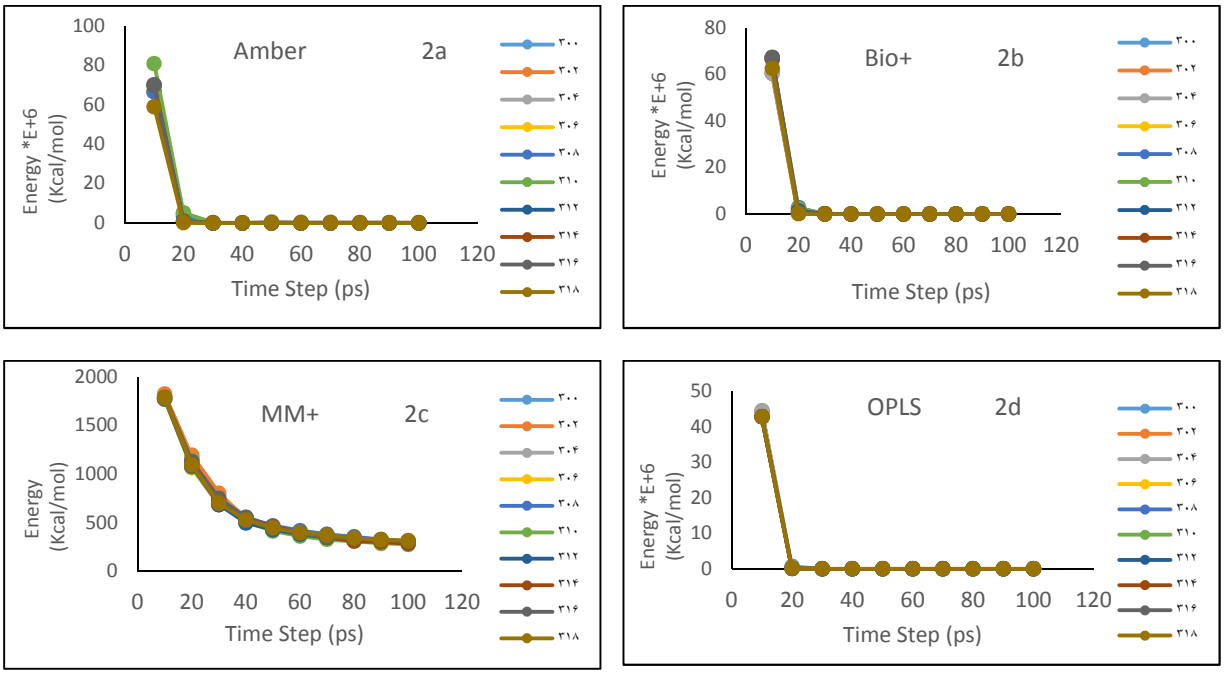



**Fig. 2.** The graphs of vincristine potential energy belong to a) AMBER b) $BIO^{+}$, c) $MM^{+}$, d) OPLS force fields.

**Table 5**. Computed total energy (kcal/ mol) for vinblastine, belong to AMBER, $MM^{+}$, $BIO^{+}$ and OPLS force fields under ten different temperature

| Total Energy (Kcal/mol) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Method | 300 | 302 | 304 | 306 | 308 | 310 | 312 | 314 | 316 | 318 |
| AMBER | 1283.59 | 2271.41 | 2307.07 | 2228.64 | 1817.02 | 2288.61 | 1718.96 | 2322.42 | 1527.61 | 1770.11 |
| OPLS | 2164.13 | 2136.51 | 1893.53 | 2272.42 | 2526.39 | 1877.34 | 2032.83 | 2142.88 | 2135.64 | 2111.96 |
| $MM^{+}$ | 630.38 | 628.254 | 650.87 | 644.359 | 702.702 | 756.339 | 655.522 | 648.057 | 707.722 | 667.406 |
| $BIO^{+}$ | 1792.13 | 2495.95 | 1744.98 | 1844.41 | 1259.92 | 1430.14 | 1967.26 | 1445.2 | 1483.22 | 1613.85 |

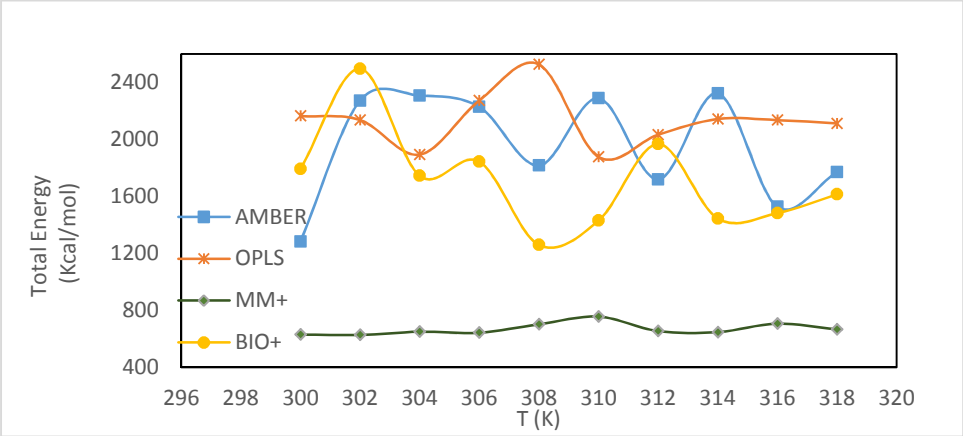



**Fig. 3.** The graphs of vinblastine Total Energy.

**Table 6.** Computed total energy (kcal/ mol) for vincristine, belong to AMBER, $MM^{+}$, $BIO^{+}$ and OPLS force fields under ten different temperature

| Total Energy (Kcal/mol) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Method | 300 | 302 | 304 | 306 | 308 | 310 | 312 | 314 | 316 | 318 |
| AMBER | 489.792 | 483.865 | 504.532 | 482.932 | 483.375 | 534.712 | 502.087 | 525.551 | 537.601 | 505.981 |
| OPLS | 452.847 | 471.442 | 445.115 | 469.3 | 430.017 | 436.682 | 445.061 | 460.554 | 454.705 | 435.433 |
| $MM^{+}$ | 416.127 | 404.437 | 394.893 | 401.57 | 414.904 | 381.269 | 411.173 | 387.991 | 420.581 | 425.974 |
| $BIO^{+}$ | 545.059 | 547.836 | 550.403 | 570.447 | 552.624 | 555.436 | 517.037 | 572.967 | 562.428 | 570.926 |

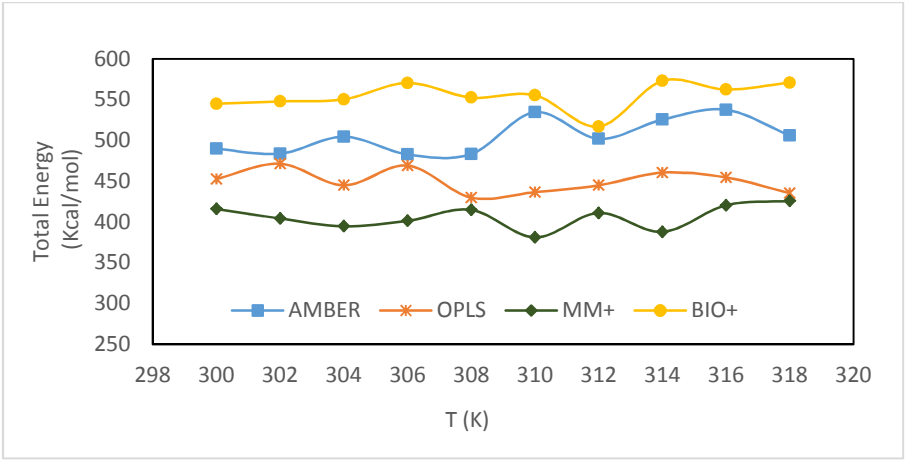



**Fig. 4.** The graphs of vincristine Total Energy.

## CONCLUSIONS

Performance of the Molecular Mechanic investigation of vincristine and vinblastine gave the potential energy and total energy by Monte Carlo method in different temperature. The study showed that the system has the different level of energy and the different stability which is caused by the forces from inside the system. The best spatial conformity which means the highest stability level or the lowest level of energy was found. Also, it is obvious from the above diagrams that maximum amount of potential energy is related to 312K, OPLS method for vinblastine and 310K,

AMBER method for vincristine. The highest level of total energy observed in OPLS method for vinblastine and $BIO^+$ for vincristine. So with considering high amount of total energy, there will be minimum stability in this method.

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