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Study on interaction between carbon nanotubes (CNTs) as nano carrier for loading and delivery of Methotrexate

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ABSTRACT: The Methotrexate delivery by carbon nanotubes (CNTs) and the structural changes of drug combination upon the carbon nanotubes and bio thermodynamic of the drug have been studied by molecular computational methods. Computational molecular methods have been fulfilled by molecular mechanics methods with four force field, and semi empirical with all methods. We investigate different parameters such as total energy, potential energy and kinetic energy and time of simulations are 10 ns. In this research, solvent effects on the relative energies and structural properties of single-walled carbon nanotubes surrounded by water and gas were revealed by Monte Carlo simulation. Calculation and geometrical optimization in different temperature (292,298,310 and 315 kelvin) were conducted via Monte Carlo method (Amber, Bio+, MM+ and OPLS). The semi-empirical calculations such as total energy, binding energy, isolated atomic energy, electronic energy, core–core interaction and heat of formation in AM1,PM3, MNDO and CNDO for Methotrexate and CNT- Methotrexate complex. Analysis of methotrexate and its interaction with CNTs show that, this carrier can be utilized to improve the activities of this anti-cancer drug.

Keywords: *Carbon nanotubes,Methotrexate, Monte Carlo, Semi-empirical*

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INTRODUCTION

Methotrexate (MTX), formyl known as amethopterin with molecular formula $C_{20}H_{22}N_8O_5$ uses in cancer field are in Breast cancer, Head and Neck cancer (Catimel, 1996, Clavel, *et al.,* 1994), (Abramowicz, 2003), lung cancer (Manrow, *et al.,* 2014), lymphomas (Wei Guo, *et al.,* 1999) and osteosarcoma (Ervin and Canellos, 1980). In Autoimmune therapy it is used in Psoriasis (Sabiqa Haider, *et al.,* 2014), Rheumatoid Arthritis (Weinblatt, *et al.,* 1985, Williams, *et al.,* 1985, Andersen, *et al.,* 1985, Furst, 1997)and Crohn's disease (Parker, *et al.,* 2010)Carbon nanotubes (CNTs) and their fantastic structure such as high surface area, high thermal conductivity, stability, electronic properties, and unique physicochemical properties enable the covalent and noncovalent introduction of several pharmaceutically relevant

entities (Madadi Mahani, 2017). CNTs can be binded with different functional groups to carry several moieties together for targeting, imaging, and therapy (Prato, *et al.,* 2008).

Adsorption of these drugs into or onto the CNTs is based on two kinds of forces: covalent and non-covalent force. Many small polymeric anticancer agents as well as the large ones, can be adsorbed non-covalently onto the surface of pristine CNTs. Forces that rule such adsorption are the hydrophobic and π-π stacking interactions between the chains of the adsorbed molecules and the surface of CNTs.

Since many anticancer drugs are in nature hydrophobic or have hydrophobic moieties, the hydrophobic forces are the main moving forces for the loading of such drugs into or onto CNTs (Zhang, *et al.,*2011, Jia, *et al.,*2007, Lucente-Schultz,*et al.,*2009). Covalent functionalization gives the more safe conjunction of functional molecules. CNTs can be oxidase, giving CNTs hydrophilic groups as OH, COOH, and so on. Strong acid solution treatment can create defects in the side walls of CNTs, and the carboxylic acid groups are generated at the deficiency point, mainly on the open ends (Zhang, *et al.,*2011, Prato, *et al.,*2008, Jain, *et al.,*2009).

MATERIAL AND METHODS

In this study molecular mechanic methods were discussed. For this purpose HyperChem 8.0.8 Software and used Molecular mechanic calculations and semi empirical method. HyperChem is a sophisticated molecular modeling environment that is known for its quality, Flexibility, and the ease of use. 3Dembodiment with quantum calculations, molecular mechanics, and dynamics are other capability of this tool (Shahmasoorian,*et al.,*2014, Jafari-Dehkordi, *et al.,*2015).

The drug with its CNT in two forms of single and multi-walled was investigated by HyperChem software in some step. The first one contains: choosing the “file” from top of the menu, then we chose the main file with “pdb” or “mol” format, after that we have the molecule with 3D structure. For computation of molecular mechanic after choosing one of the four force field (mm+, bio+, amber, opls), from the menu bar we usage of Mont-Carlo simulation method issurrounded environment by water and gas with different temperature based on Kelvin degree (292,298,310,315).

Three important parameters such as total energy, potential energy and kinetic energy in time of simulations 10 ns were also investigated data we carry out from Monte-Carlo simulation. In semi empirical methods (Am1, Pm3, Cndo, Indo, Mndo, Mndo3, Rm1, Zindo/1, Zindo/Tndo) the vibration analysis of molecules is the best described using a quantum mechanical approach that was obtained Safi (Najafabadi, *et al.,*2015).

RESULT AND DISCUSSION

Following calculations of energy parameters in Molecular Mechanic and Semi empirical methods that have been done by Mont Carlo in different temperatures and subsequently some results have

been accrued. In these result most of the energy parameters were discussed in 310 Kelvin means the temperature which the molecules are in the most stable condition in the body (Mackerell, *et al.,*2004, Weiner, *et al.,*1984).

In Fig. 1 as itis shown, for methotrexate and its disconnected nanotubes in 310 k as normal body temperature our energy parameters such as potential energy, at 100th step are in the minimum measure of its own. It can be obtained that these macro molecules are stable in that specific temperature(Safi Najafabadi, *et al.,*2015).

For amber force field like what happened in bio, in 310 k energy parameters decrease with a slight slope till 100th step in Fig. 2, Fig. 3 and Fig. 4 in 298k at 100th step, the molecules especially methotrexate with no nanotube has the lowest measure. In Fig. 5, connected methotrexate to multi-walled nanotube in 298k, there is minimum potential energy for amber, bio and opls force field. Beside total energy in four forces field goes down by decreasing temperature. In the position of the drug connected with single-walled nanotube as it appeared in Fig. 6, potential and total energy parameters at 315k in amber force field have the lowest energy as the same as bio at 298k. In mm+, potential energy at 292,310,315 kelvin temperatures has the same measure 176.66 kcal/mol. Fig. 7 in semi empirical methods at the state of methotrexate with no connection, and in present of single walled CNTs, the stable energy is in CNDO, and in presence of multi-walled nanotube it's in INDOs. As it comes up for multi-walled CNTs connection INDOs and for single-walled connection CNDO are our significant points Fig. 8.

Table 1. Methotrexate + MWCNT and SWCNT in mm+ force field.

T(k)	Time	Methotrexate			MWCNT+Methotrexate			SWCNT+Methotrexate		
		Ekin	Epot	Etot	Ekin	Epot	Etot	Ekin	Epot	Etot
292	0	47.8714	253.8778	301.7493	220.2087	3020.056	3240.265	124.4658	176.667	301.1327
	10		133.8843	181.7558		2290.981	2511.19		229.1993	353.6651
	20		89.44203	137.3135		1923.092	2143.3		244.1516	368.6174
	30		78.19187	126.0633		1678.19	1898.399		257.9489	382.4146
	40		78.12519	125.9966		1495.667	1715.876		263.6913	388.157
	50		71.3339	118.0801		1403.181	1623.39		263.895	388.3608
	60		68.15643	116.0279		1308.207	1528.415		269.988	394.4537
	70		67.59957	118.8041		1251.516	1471.724		260.5034	384.9692
	80		70.93266	118.8041		1218.592	1438.801		276.7293	401.195
	90		65.42273	113.2942		1208.091	1428.3		273.8559	398.3217
	100		65.41149	113.2829		1182.521	1402.73		280.1278	404.5935
298	o	48.8551	253.8778	302.7329	237.5539	4715.45		127.0233	176.667	303.6902
	10		133.8843	182.7395		3371.858	3609.411		239.0536	366.0769
	20		92.35922	141.2143		2631.362	2868.916		245.7932	372.8165
	30		86.45959	135.3147		2268.442	2505.996		261.9941	389.0174
	40		71.44696	120.3021		2061.774	2299.328		267.5436	394.5669
	50		70.8588	119.7139		1811.556	2049.109		263.8907	390.914
	60		69.02903	117.8841		1674.205	1911.759		272.3273	399.3506
	70		67.56025	116.4154		1587.338	1824.892		273.524	400.5473
	80		64.54689	113.402		1513.266	1750.82		287.6044	414.6277
	90		73.79354	122.6487		1471.836	1709.39		298.2906	425.3139
	100		66.18423	115.0393		1425.257	1662.811		283.4104	410.4337
310	o	50.8224	253.8778	304.7002	233.7832	4715.455	4949.238	127.0233	176.667	308.8053
	10		134.3073	185.1297		3408.55	3642.333		230.6119	362.7502
	20		92.70034	143.5228		2736.76	2970.543		253.1865	385.3248
	30		81.22876	132.0512		2299.68	2533.463		266.1312	398.2695
	40		87.94112	138.7635		2014.759	2248.542		262.0359	394.1742
	50		81.08414	131.9066		1808.807	2042.591		254.254	386.3923
	60		83.12156	133.944		1646.961	1880.744		260.8551	392.9935
	70		76.02121	126.8436		1551.964	1785.747		270.0337	402.172
	80		70.69282	121.5152		1484.714	1718.497		274.5958	406.7341
	90		76.89871	127.7211		1460.991	1694.774		270.351	402.4893
	100		65.48385	116.3063		1414.244	1648.027		275.9854	408.1237
315	o	51.6421	253.8778	305.52	237.5539	4715.455	4953.009	134.2696	176.667	310.9365
	10		126.4297	178.0718		3371.858	3609.411		253.5927	387.8623
	20		93.85239	145.4945		2723.978	2961.532		248.1009	382.3705
	30		86.37851	138.0207		2332.639	2570.192		265.4673	399.7369
	40		77.98895	129.6311		2017.291	2254.845		284.0892	418.3587
	50		71.66372	123.3059		1811.556	2049.109		269.721	403.9906
	60		67.99835	119.6405		1674.205	1911.759		273.6769	407.9465
	70		68.92126	120.5634		1587.338	1824.892		287.3524	421.622
	80		63.10832	114.7505		1513.266	1750.82		277.3258	411.5953
	90		63.20374	114.8459		1471.836	1709.39		296.1207	430.3903
	100		69.56616	121.2083		1425.257	1662.811		294.9138	429.1834

Table 2. Methotrexate+MWCNT and SWCNT in amber force field.

T(k)	Time	Methotrexate			MWCNT+Methotrexate			SWCNT+Methotrexate		
		Ekin	Epot	Etot	Ekin	Epot	Etot	Ekin	Epot	Etot
292	0	47.8714	253.8778	301.7493	220.2087	23924.98	24145.19	124.4658	682.0958	806.5615
	10		133.8843	181.7558		9112.606	9332.814		609.9294	734.3951
	20		89.44203	137.3135		5942.364	6162.572		567.0329	691.4987
	30		78.19187	126.0633		4471.996	4692.204		541.0595	665.5252
	40		78.12519	125.9966		3564.769	3784.977		537.2962	661.762
	50		71.3339	118.0801		3035.213	3255.422		523.6469	648.1126
	60		68.15643	116.0279		2623.631	2843.84		501.8349	626.3007
	70		67.59957	115.471		2352.457	2572.666		496.1718	620.6376
	80		70.93266	118.8041		2167.892	2388.1		494.8682	619.3339
	90		65.42273	113.2942		2071.461	2291.669		484.4522	608.918
	100		65.41149	113.2829		1996.355	2216.563		485.2608	609.7266
298	0	48.8551	253.8778	302.7329	224.7335	12539.8	12764.53	127.0233	682.0958	809.119
	10		133.8843	182.7395		4849.939	5074.673		630.9181	757.9414
	20		92.35922	141.2143		2983.225	3207.958		581.6002	708.6235
	30		86.45959	135.3147		2400.493	2625.227		571.3514	698.3747
	40		71.44696	120.3021		1997.792	2222.526		543.0788	670.1021
	50		70.8588	119.7139		1779.13	2003.863		511.6664	638.6896
	60		69.02903	117.8841		1611.093	1835.826		512.2122	639.2354
	70		67.56025	116.4154		1611.093	1835.826		525.5055	652.5288
	80		64.54689	113.402		1482.44	1707.174		494.4547	621.478
	90		73.79354	122.6487		1370.354	1595.088		500.6085	627.6318
	100		66.18423	115.0393		1331.884	1556.618		487.8537	614.877
310	0	50.8224	253.8778	304.7002	233.7832	5988.453	12773.58	477.6044	682.0958	814.2341
	10		134.3073	185.1297		5754.67	5988.453		629.5863	761.7246
	20		92.70034	143.5228		2885.011	3118.794		593.0995	725.2378
	30		81.22876	132.0512		2191.519	2425.302		573.3921	705.5304
	40		87.94112	138.7635		1874.318	2108.102		543.0407	675.179
	50		81.08414	131.9066		1691.816	1925.599		518.1672	650.3056
	60		83.12156	133.944		1551.297	1785.08		512.5079	644.6462
	70		76.02121	126.8436		1469.911	1703.694		498.3329	630.4712
	80		70.69282	121.5152		1380.986	1614.769		496.0482	628.1866
	90		76.89871	127.7211		1356.367	1356.367		471.3577	603.496
	100		65.48385	116.3063		1345.495	1579.278		4678268	599.9651
315	0	51.6421	253.8778	305.52	237.5539	12539.8	12777.35	134.2696	460.6778	594.9474
	10		126.4297	178.0718		4791.753	5029.307		438.1522	572.4218
	20		93.85239	145.4945		2958.129	3195.683		389.4296	523.6992
	30		86.37851	138.0207		2269.93	2507.484		353.9921	488.2616
	40		77.98895	129.6311		1967.44	2204.994		335.1624	469.432
	50		71.66372	123.3059		1743.537	1981.091		320.5159	454.7855
	60		67.99835	119.6405		1605.064	1842.618		304.4091	438.6786
	70		68.92126	120.5634		1516.187	1753.741		305.5586	439.8282
	80		63.10832	114.7505		1436.759	1674.313		301.3422	435.6118
	90		63.20374	114.8459		1403.366	1640.92		302.6555	436.9251
	100		69.56616	121.2083		1334.909	1572.463		292.8391	427.1087

Table 3. Calculation of methotrexate by semi empirical methods.

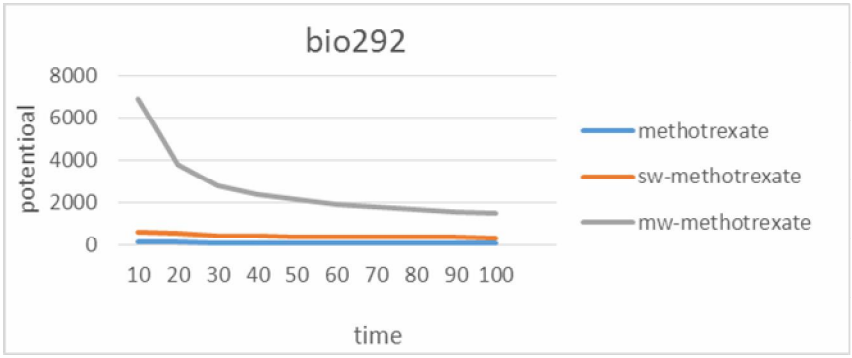
Method **and Energy**	**AM1**	**CNDO**	**PM3**	**INDO**	**MNDOd**	**Mndo3**	**Mndo**	**Rm1**	**ZINDO1**	**Zindos**	**Tndo**
Total energy	-140913.0463	-215887.0952	-126076.6191	-207532.1101	-141282.7323	-137222.9414	-141282.7325	-140106.3702	-197512.1929	-162411.5807	-214238.1168
Binding energy	-5618.863731	-17355.88155	-5702.165602	-16393.00866	-5641.965929	-5776.625027	-5641.96622	-4812.187688	-16566.32997	-26194.05966	-15706.90313
Isolated energy	-135294.1826	198531.2136	-120374.4535	-191139.1014	-135640.7663	-131446.3163	-135640.7663	-135294.1826	-180945.8629	-136217.521	-198531.2136
Electronic energy	-1119437.367	-1269139.889	-1095601.085	-1260784.904	-1120638.434	-1100609.712	-1120638.434	-1118314.234	-1250764.987	-1038512.757	-1267490.911
Core-core interaction	978524.3204	1053252.794	969524.4658	1053252.794	979355.7019	963386.7707	979355.7019	978207.8637	1053252.794	876101.1767	1053252.794
Heat of formation	146.9752687	-11590.04255	63.6733977	-10627.16966	123.8730712	-10.7860268	123.8727796	953.651312	-10800.49097	-20428.22066	-9941.064128

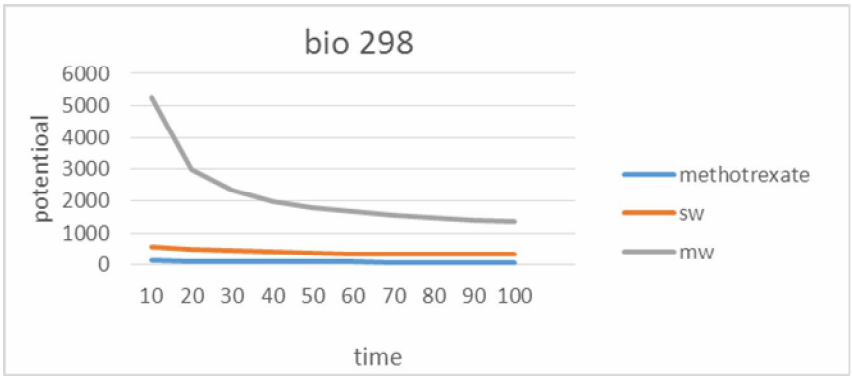
Table 4. Calculation of SWCNT+Methotrexate by semi empirical methods.

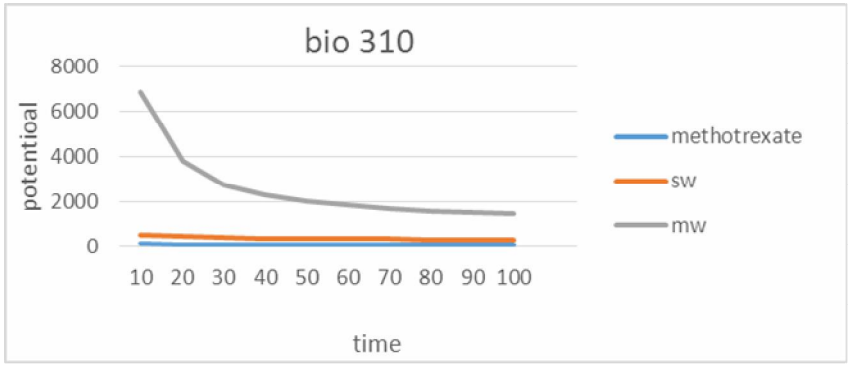
***Method and* Energy**	**AM1**	**CNDO**	**PM3**	**INDO**	**MNDOd**	**Mndo3**	**Mndo**	**Rm1**	**ZINDO1**	**Zindos**	**Tndo**
Total energy	-357920.1224	-544770.8622	-327842.5507	-248375.7242	-358107.5385	995775.2983	-358107.5385	-353220.8385	-486076.1713	-417072.0759	-531798.9779
Binding energy	-17819.16946	-61285.80612	-17959.07176	217323.6306	-17994.84756	1330202.692	-17994.84756	-13119.88554	-45932.17152	-72667.89429	-48313.92184
Isolated energy	-340100.9529	-483485.056	-309883.4789	-465699.3548	-340112.691	-334427.3935	-340112.691	-340100.9529	-440143.9998	-344404.1816	-483485.056
Electronic energy	-6308612.016	-6761150.965	-6240721.169	-6464755.827	-6310602.412	-4896947.19	-6310602.412	-6302907.133	-6702456.274	-6048507.159	-6748179.08
Core-core interaction	5950691.894	6216380.103	5912878.619	6216380.103	5952494.874	5892722.488	5952494.874	5949686.294	6216380.103	5631435.083	6216380.103
Heat of formation	1084.381538	-42382.25512	944.4792375	236227.1816	908.7034369	1349106.243	908.7034369	5783.665463	-27028.62052	-53764.34329	-29410.37084

Table 5. Calculation of MWCNT+Methotrexate by semi empirical methods.

***Method* and Energy**	**AM1**	**CNDO**	**PM3**	**INDO**	**MNDOd**	**Mndo3**	**Mndo**	**Rm1**	**ZINDO1**
Total energy	3333739.673	3583783.263	3203109.925	3724215.462	3256594.36	3199426.367	3256594.36	3252805.261	3820181.941
Binding energy	3929849.089	4423460.622	3749879.685	4533115.134	3852296.956	3787580.107	3852296.956	3848914.677	4584323.612
Isolated energy	-596109.4159	-839677.359	-546769.7607	-808899.6715	-595702.5968	-588153.7399	-595702.5968	-596109.4159	-764141.6709
Electronic energy	-15025398	-15544819.03	-15039434.37	-15404386.83	-15108097.05	-14988652.79	-15108097.05	-15103573.18	-15308420.35
Core-core interaction	18359137.67	19128602.3	18242544.29	19128602.3	18364691.41	18188079.16	18364691.41	18356378.44	19128602.3
Heat of formation	3965174.78	4458786.313	3785205.376	4568440.825	3887622.647	3822905.798	3887622.647	3884240.368	4619649.303







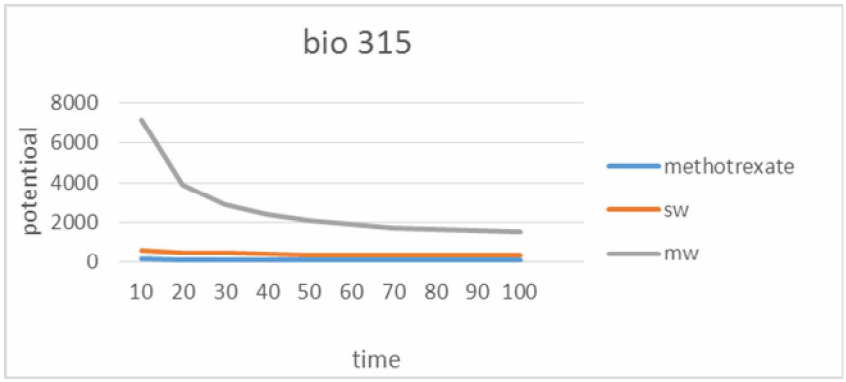


Fig. 1. Methotrexate+MWCNT and SWCNT in Bio force field by Molecular Mechanics methods.

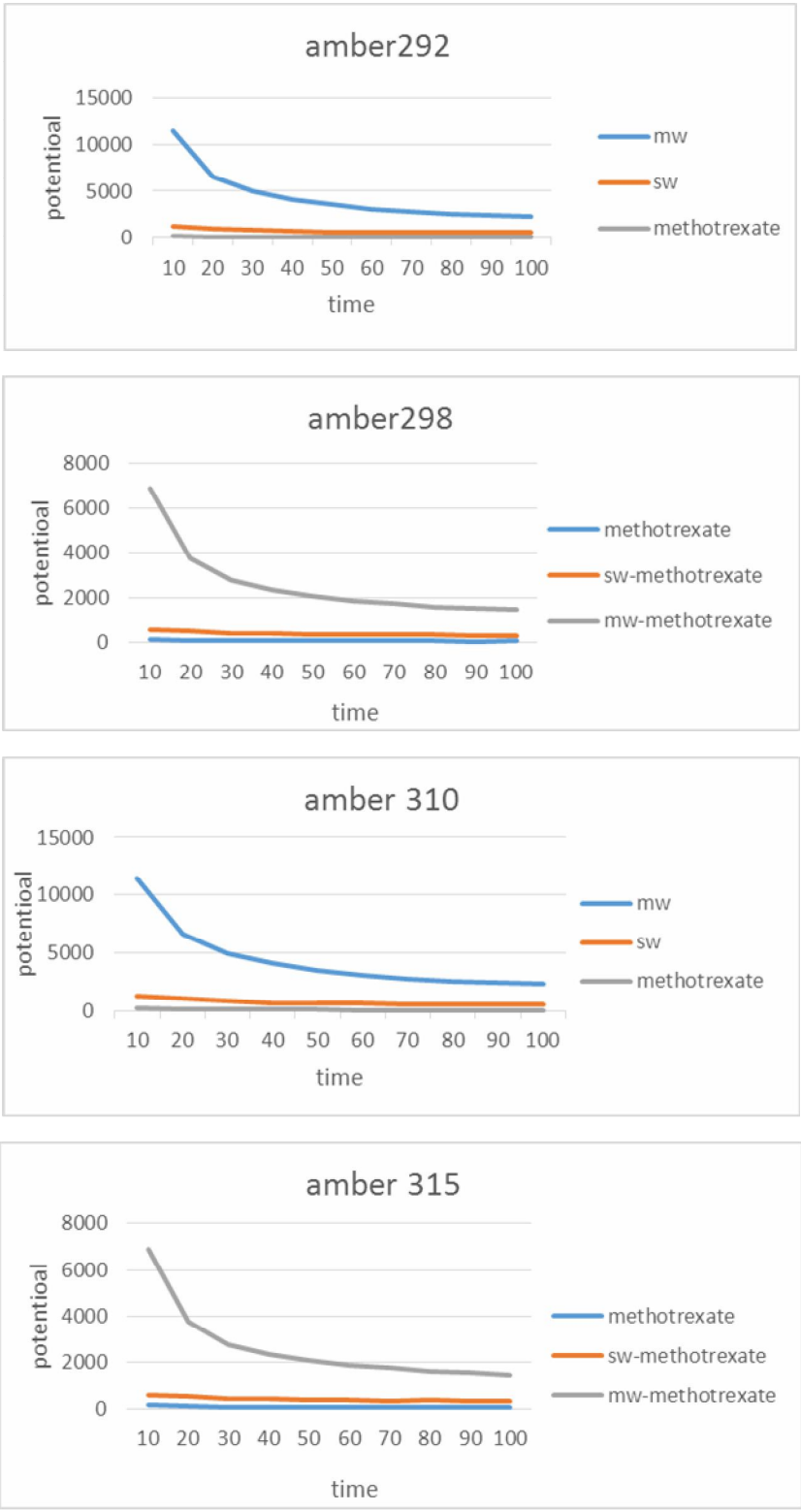


Fig. 2. Methotrexate+MWCNT and SWCNT in Amber force field by Molecular Mechanics methods.

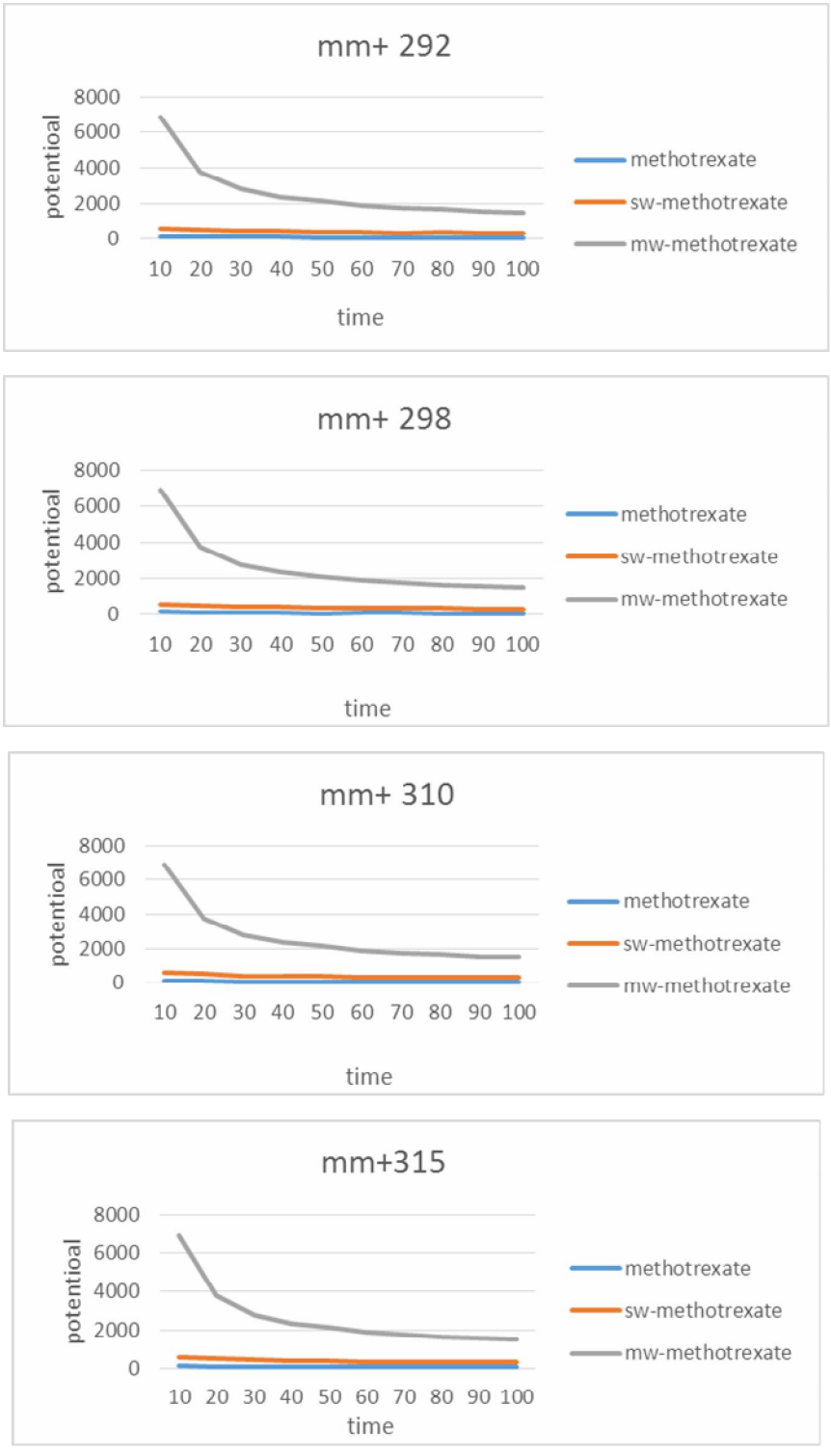


Fig. 3. Methotrexate+MWCNT and SWCNT in MM+ force field by Molecular Mechanics methods.

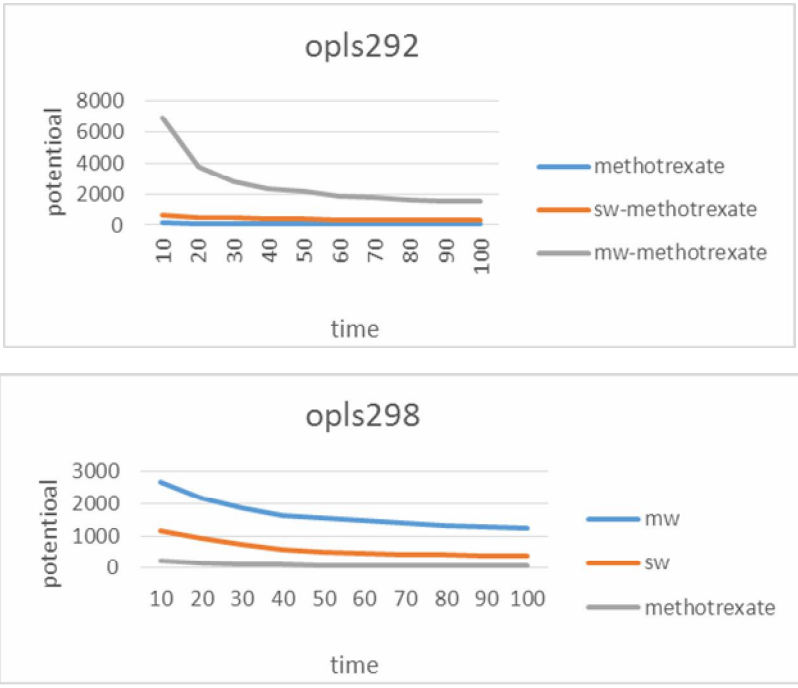


Fig. 4. Methotrexate+MWCNT and SWCNT in Opls force field by Molecular Mechanics methods.

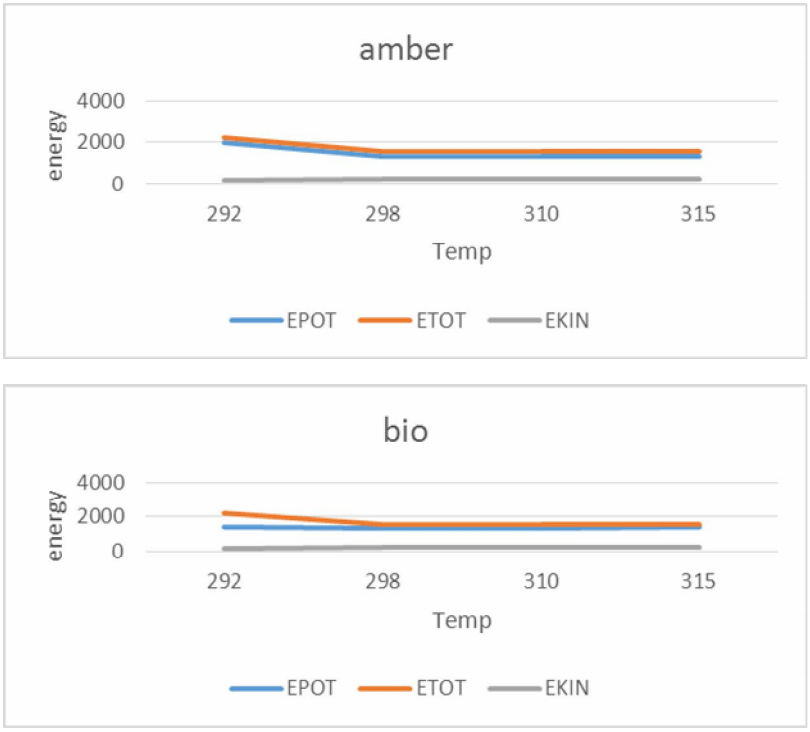


Fig. 5a. Methotrexate+MWCNT in Bio & Amber Force Field by Molecular Mechanics methods.

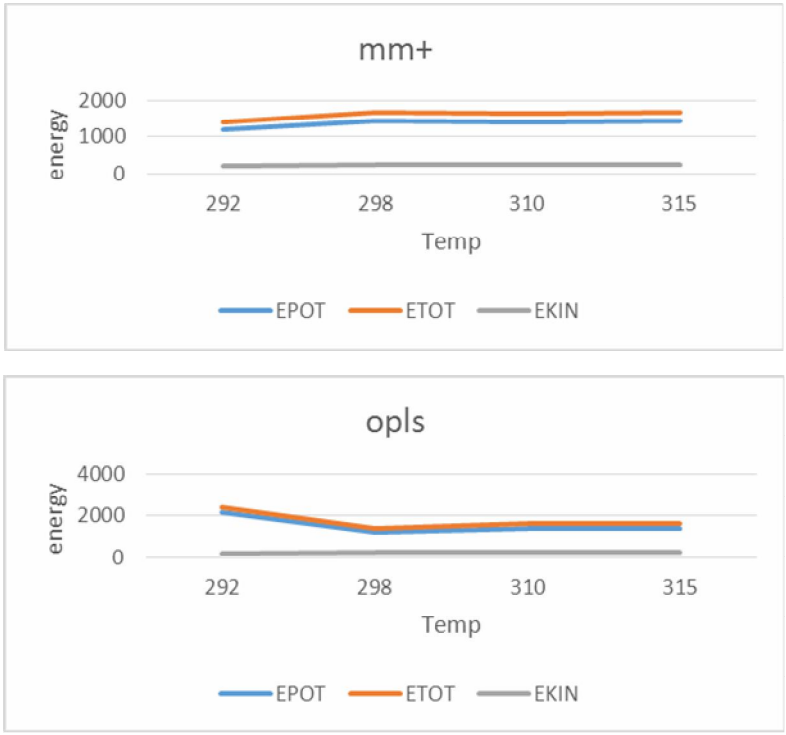


Fig. 5b. Methotrexate+MWCNT in Opls & Mm+ Force Field by Molecular Mechanics methods.

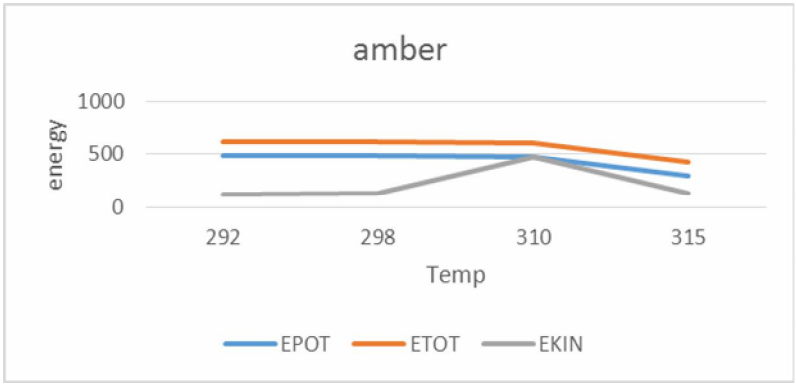


Fig. 6a. Methotrexate+SWCNT in Amber Force Field by Molecular Mechanics methods

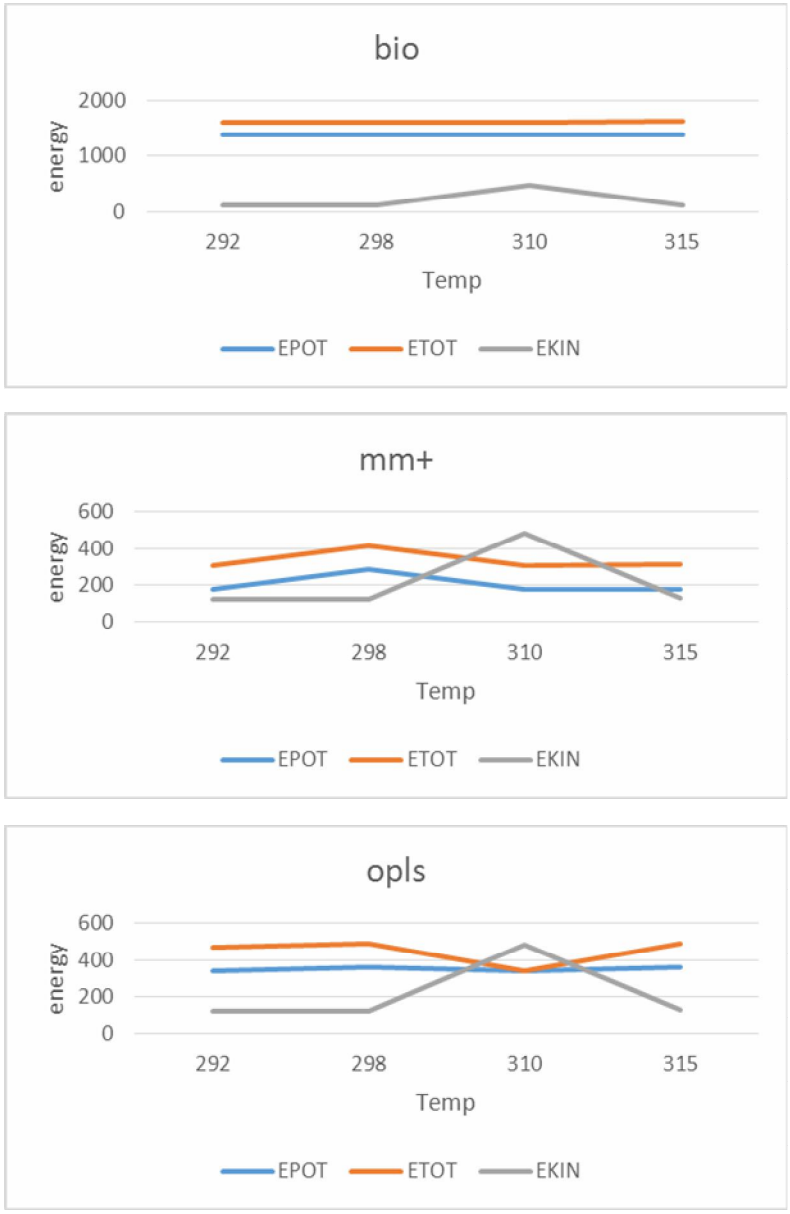


Fig. 6b. Methotrexate+SWCNT in Bio & Opls & Mm+ Force Field by Molecular Mechanics methods.

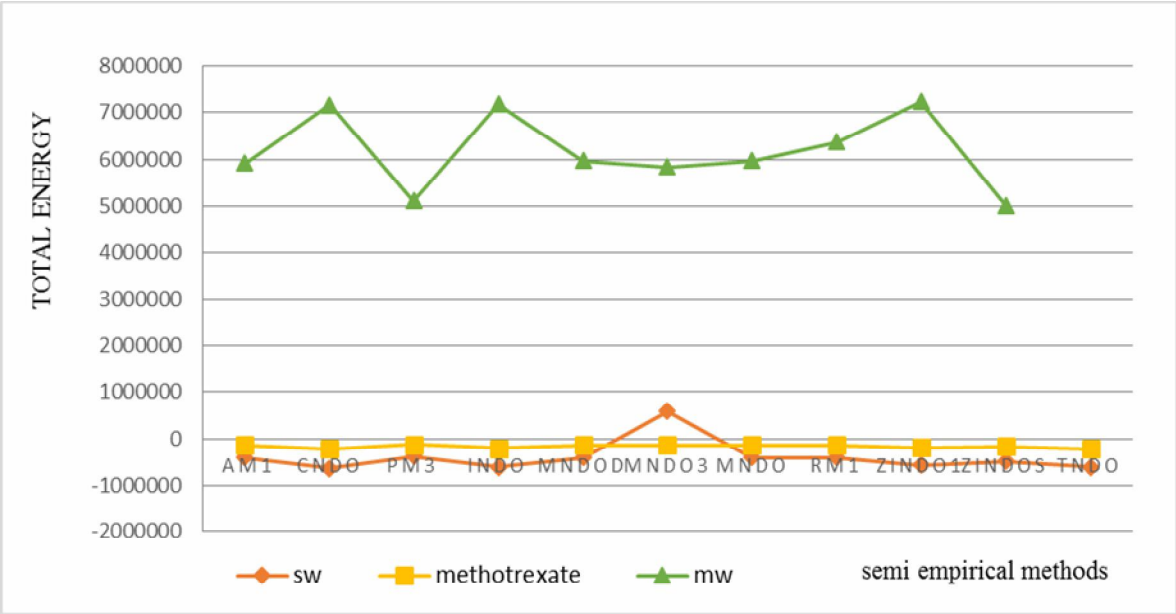


Fig. 7. Methotrexate, Methotrexate+SWCNT and Methotrexate+MWCNT in semi empirical methods.

Table 9. Comparison Epot in Mm+, at 310k.

Time step	MWCNT + Methotrexate	SWCNT + Methotrexate
0	4715.455	176.667
10	3371.858	239.0536
20	2631.362	245.7932
30	2268.442	261.9941
40	2061.774	267.5436
50	1811.556	263.8907
60	1674.205	272.3273
70	1587.338	273.524
80	1513.266	287.6044
90	1471.836	298.2906
100	1425.257	283.4104

Table 10. Comparison Epot in mm, at 310k.

Time step	MWCNT+ Methotrexate	SWCNT + Methotrexate
0	5988.453	682.0958
10	5754.67	629.5863
20	2885.011	593.0995
30	2191.519	573.3921
40	1874.318	543.0407
50	1691.816	518.1672
60	1551.297	512.5079
70	1469.911	498.3329
80	1380.986	496.0482
90	1356.367	471.3577
100	1345.495	467.8268

Table 11. Comparison Epot in Mm+, at 298k. Table12. Comparison Epot in amber at 298k.

Time step	MWCNT+ Methotrexate	SWCNT + Methotrexate
0	4715.455	176.667
10	3371.858	239.0536
20	2631.362	245.7932
30	2268.442	261.9941
40	2061.774	267.5436
50	1811.556	263.8907
60	1674.205	272.3273
70	1587.338	273.524
80	1513.266	287.6044
90	1471.836	298.2906
100	1425.257	283.4104

Time step	MWCNT+ Methotrexate	SWCNT + Methotrexate
0	12539.8	682.0958
10	4849.939	630.9181
20	2983.225	581.6002
30	2400.493	571.3514
40	1997.792	543.0788
50	1779.13	511.6664
60	1611.093	512.2122
70	1611.093	525.5055
80	1482.44	494.4547
90	1370.354	500.6085
100	1331.884	487.8537

CONCLUSIONS

In this study all energy parameters found out theoretically by Mont Carlo software. The results obtained that in vacuum environment, at our two remarkable temperature (310 and 298 kelvin) in position of methotrexate connected to multi-walled CNTs in mm+ and amber force field, as it shown above at the beginning system has great potential energy but the more steps are going forward less potential energy calculated. It means that the complex is more stable at those temperatures however the single-walled form got less stability by steps progressing in mm+ force field (Tables 9 & 11).

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