Rational design, synthesis and molecular modeling studies of novel anti-oncological alkaloids against melanoma

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[‡]Professor Alan R. Katritzky passed away10th February 2014.

Table S1 BMLR-QSAR two descriptor model for the GaLa carcinoma cell line active agents.

N=19, n=2, R^2=0.695, R^2_{cv}OO=0.570, R^2_{cv}MO=0.586, F=18.258, s^2=0.079					
Entry	ID	coefficient	s	t	Descriptor
1	0	18.986	3.118	6.090	Intercept
2	D_1	1.955	0.354	5.522	HOMO energy
3	D_2	-0.100	0.025	-3.989	Surface area for atom N
$\log(IC_{50}) = 18.986 + (1.955 \times D_1) - (0.100 \times D_2)$					

Table S2 BMLR-QSAR two descriptor model for the LuPiCi carcinoma cell line active agents.

N=19, n=2, R^2=0.689, R^2_{cv}OO=0.564, R^2_{cv}MO=0.569, F=17.702, s^2=0.119					
Entry	ID	coefficient	s	t	Descriptor
1	0	22.669	3.809	5.952	Intercept
2	D_1	2.397	0.433	5.542	HOMO energy
3	D_2	-0.114	0.031	-3.720	Surface area for atom N
$\log(IC_{50}) = 22.669 + (2.397 \times D_1) - (0.114 \times D_2)$					

Table S3 BMLR-QSAR two descriptor model for the LuCa carcinoma cell line active agents.

N=19, n=2, R^2=0.661, R^2_{cv}OO=0.540, R^2_{cv}MO=0.556, F=15.570, s^2=0.144					
Entry	ID	coefficient	s	t	Descriptor
1	0	23.802	4.228	5.629	Intercept
2	D_1	2.344	0.464	5.050	HOMO energy
3	D_2	-0.220	0.066	-3.307	HASA-2 (MOPAC PC)
$\log(IC_{50}) = 23.802 + (2.344 \times D_1) - (0.220 \times D_2)$					

Table S4 Molecular descriptor values presented in the 2D-QSAR models.

Entry	Compd.	Descriptors*								
		D_1	D_2	D_3	D_4	D_5	D_6	D_7	D_8	D_9
1	**20**	14.377	0.969	0.096	0.000	0.812	8.347	-8.714	7.915	11.645
2	**21**	14.283	0.969	0.000	0.000	0.329	8.594	-8.842	3.044	9.206
3	**22**	14.394	0.969	0.190	0.014	0.620	8.337	-8.785	6.088	10.983
4	**23**	14.391	0.969	0.093	0.000	0.620	8.356	-8.788	6.088	10.983
5	**24**	14.320	0.969	0.000	0.000	0.068	8.452	-8.926	0.609	8.078
6	**25**	14.298	0.970	0.000	0.000	0.124	8.511	-8.771	1.218	8.214
7	**26**	14.312	0.969	0.000	0.000	0.272	8.420	-8.796	2.435	9.785
8	**27**	14.421	0.973	0.000	0.000	0.205	8.471	-8.714	1.827	9.686
9	**28**	14.426	0.972	0.000	0.000	0.179	8.481	-8.8	1.827	9.921
10	**29**	14.328	0.974	0.000	0.000	1.145	8.547	-8.769	9.742	11.880
11	**30**	14.406	0.969	0.000	0.000	0.192	8.423	-8.668	1.827	8.635
12	**31**	14.359	0.970	0.000	0.000	0.137	8.669	-8.826	1.218	9.005
13	**32**	14.401	0.970	0.000	0.000	0.055	8.566	-8.804	0.609	8.358
14	**33**	14.302	0.970	0.000	0.000	0.544	8.433	-8.777	4.871	10.191
15	**34**	14.317	0.970	0.000	0.000	0.943	7.983	-8.38	7.915	11.727
16	**35**	14.381	0.968	0.000	0.000	0.639	8.040	-8.336	5.480	8.687
17	**36**	14.407	0.970	0.050	0.000	0.192	8.673	-8.768	1.827	10.149
18	**37**	14.324	0.971	0.055	0.000	0.548	8.664	-8.951	5.480	12.283
19	**38**	14.433	0.969	0.000	0.000	0.483	7.936	-8.201	4.262	11.621

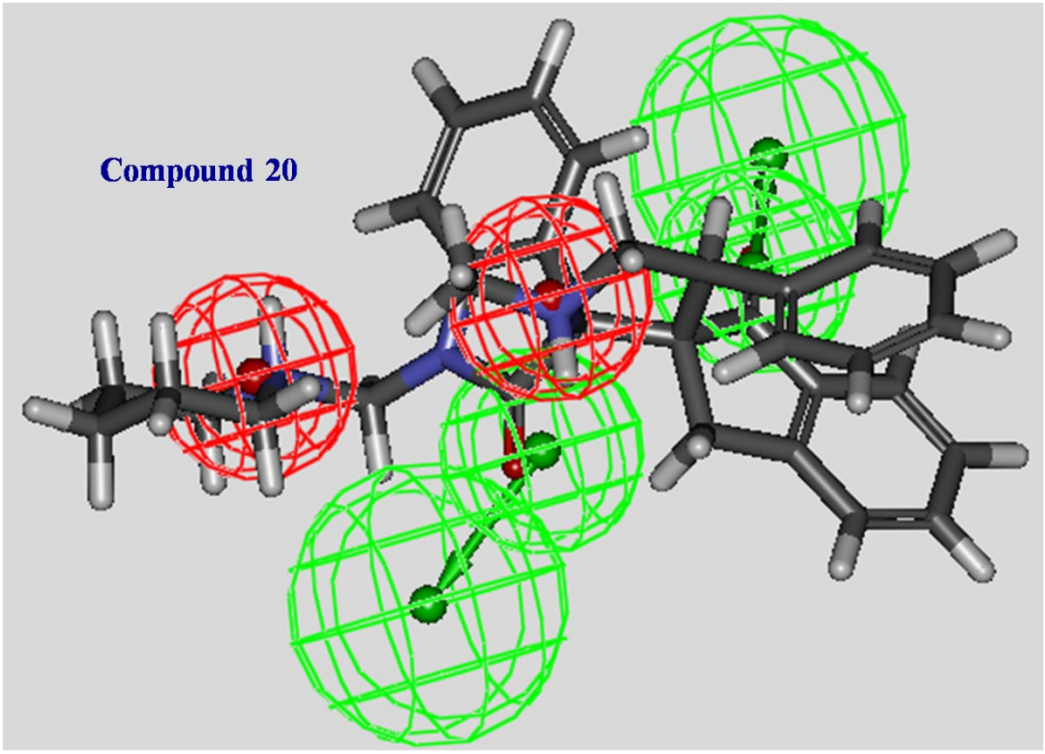
*D_1 = Min. total interaction for bond C-N, D_2 = Max. SIGMA-SIGMA bond order, D_3 = RPCS Relative positive charged SA (SAMPOS*RPCG) (Zefirov PC), D_4 = Relative number of Br atoms, D_5 = Charged surface area for atom N, D_6 = HOMO-LUMO energy gap, D_7 = HOMO energy, D_8 = Surface area for atom N, D_9 = HASA-2 (MOPAC PC).

Table S5 Descriptor of the BMLR-QSAR model for the mean IC_{50} values of the three carcinoma cell lines (GaLa, LuPiCi and LuCa) active agents.

N=19, n=3, R^2=0.799, R^2_{cv}OO=0.688, R^2_{cv}MO=0.711, F=19.912, s^2=0.069					
Entry	ID	coefficient	s	t	Descriptor
1	0	95.981	42.546	2.256	Intercept
2	D_1	7.609	1.312	5.802	Min. total interaction for bond C-N
3	D_2	-210.000	42.570	-4.933	Max. SIGMA-SIGMA bond order
4	D_3	-7.333	1.315	-5.575	RPCS Relative positive charged SA (SAMPOS*RPCG) (Zefirov PC)
$\log(IC_{50}) = 95.981 + (7.609 \times D_1) - (210.000 \times D_2) - (7.333 \times D_3)$					

Table S6 Observed and estimated/predicated values of the training set compounds **20-38** according to the BMLR-QSAR model due to mean IC_{50} values of the three carcinoma cell lines (GaLa, LuPiCi and LuCa).

Entry	Compd.	Observed IC_{50}, μM	Estimated IC_{50}, μM	Error
1	**20**	28.62	17.64	10.98
2	**21**	4.64	11.83	-7.19
3	**22**	4.41	4.88	-0.47
4	**23**	24.63	23.78	0.85
5	**24**	37.94	30.43	7.51
6	**25**	24.80	13.95	10.85
7	**26**	22.43	19.82	2.61
8	**27**	28.59	28.93	-0.34
9	**28**	35.96	36.07	-0.11
10	**29**	3.91	2.53	1.38
11	**30**	29.21	111.75	-82.54
12	**31**	26.89	35.89	-9.00
13	**32**	62.35	88.75	-26.40
14	**33**	22.26	15.38	6.88
15	**34**	19.82	20.90	-1.08
16	**35**	314.77	118.63	196.14
17	**36**	33.61	29.50	4.11
18	**37**	2.88	5.69	-2.81
19	**38**	259.90	170.83	89.07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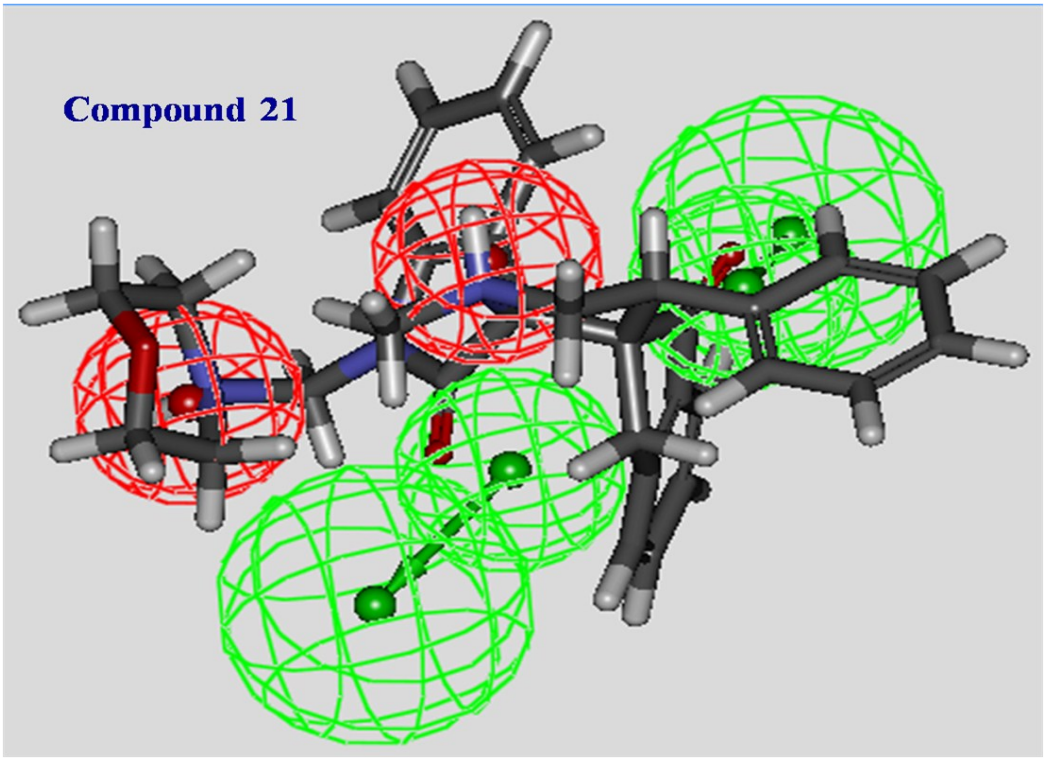
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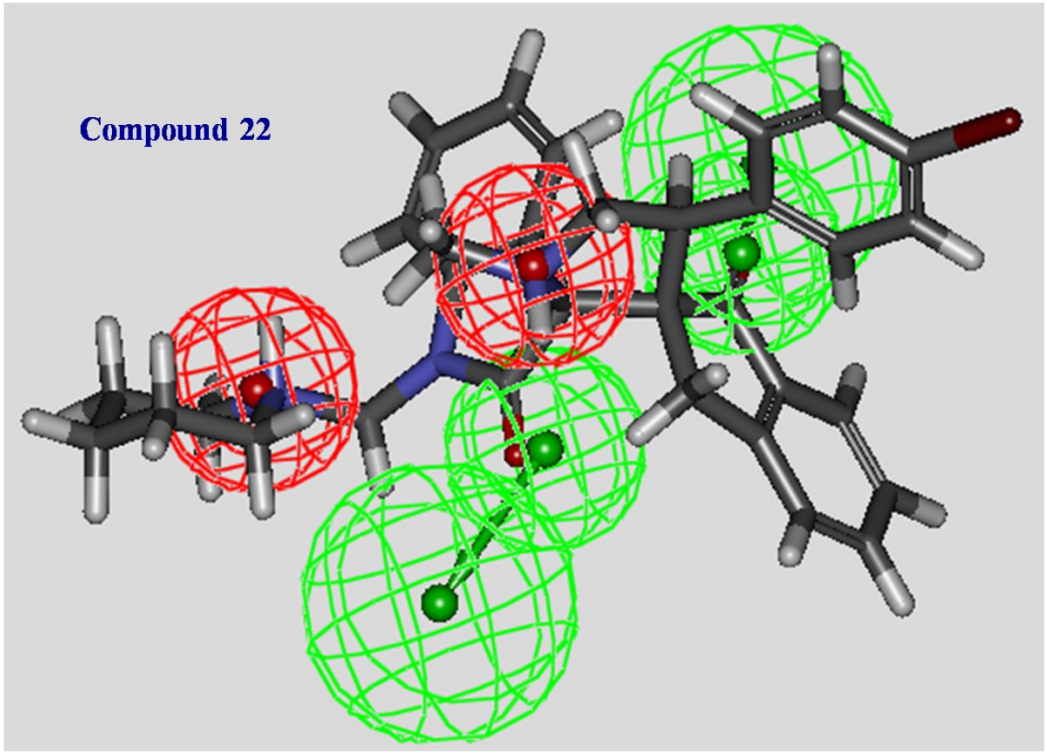
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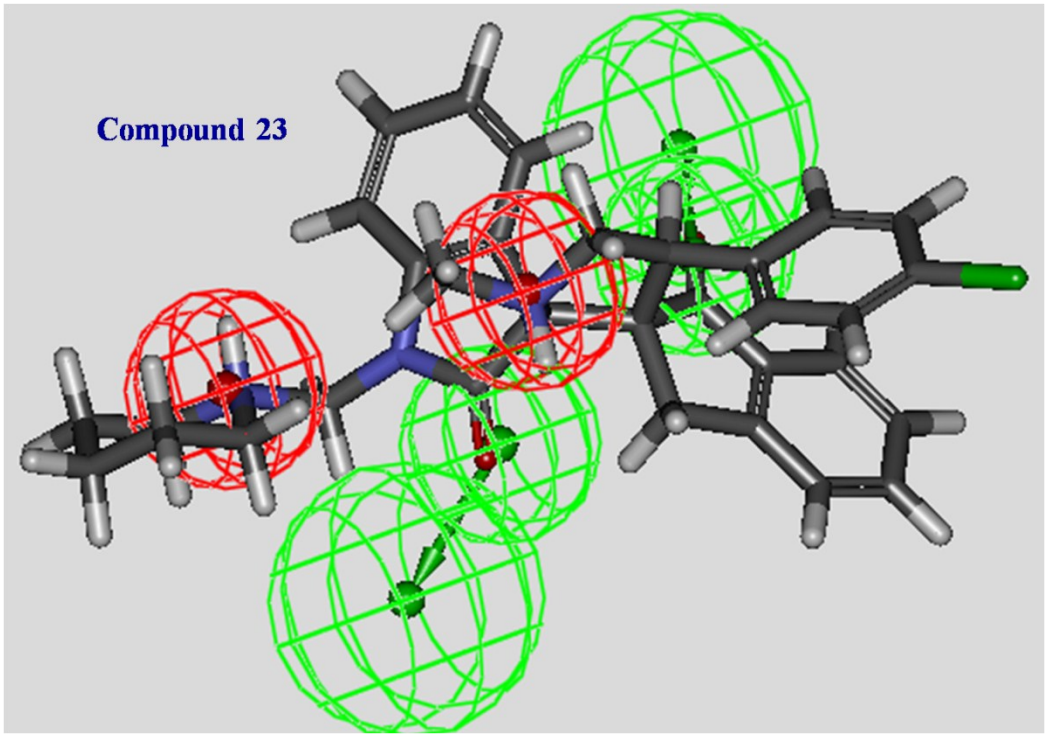
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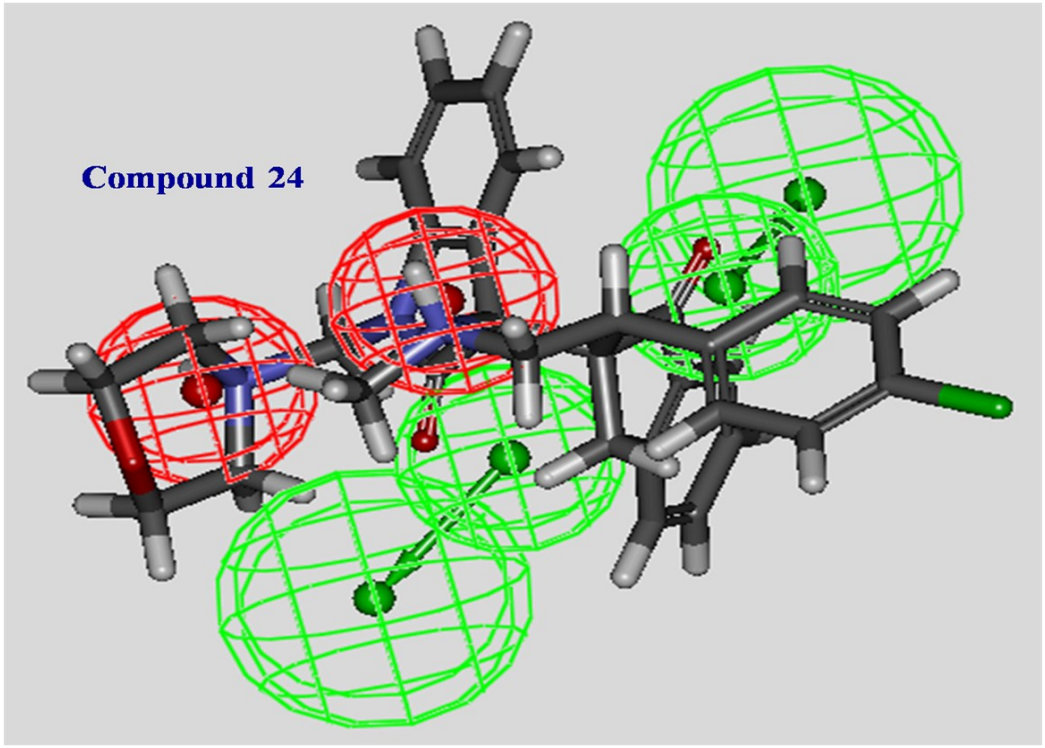
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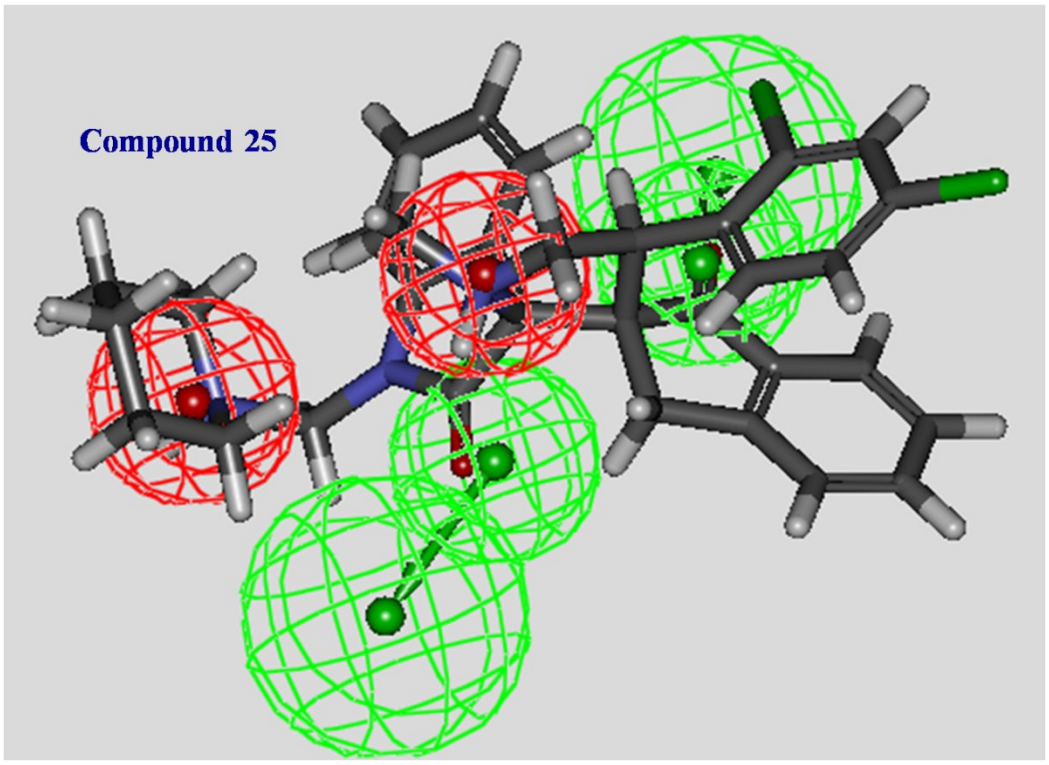
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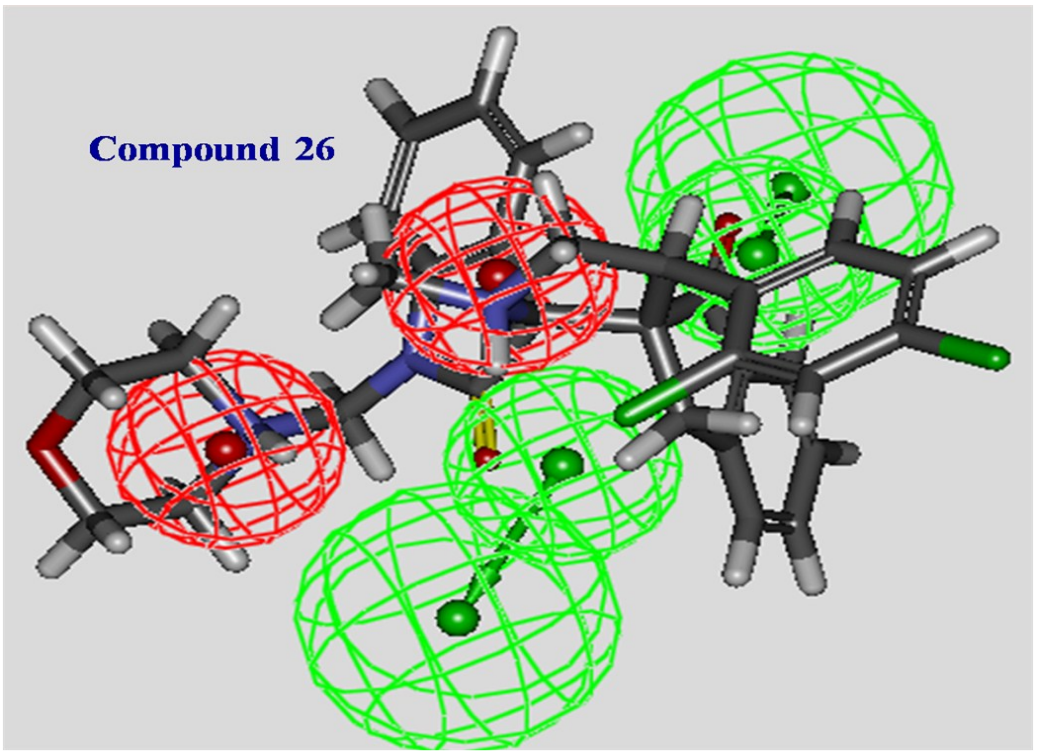
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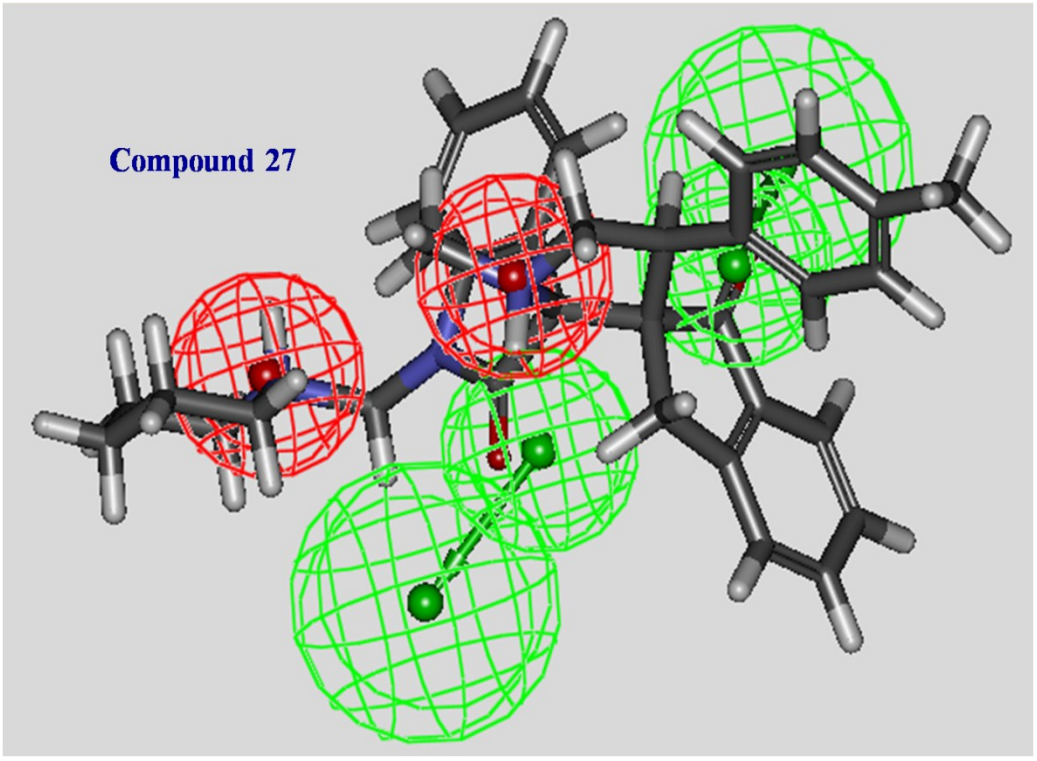
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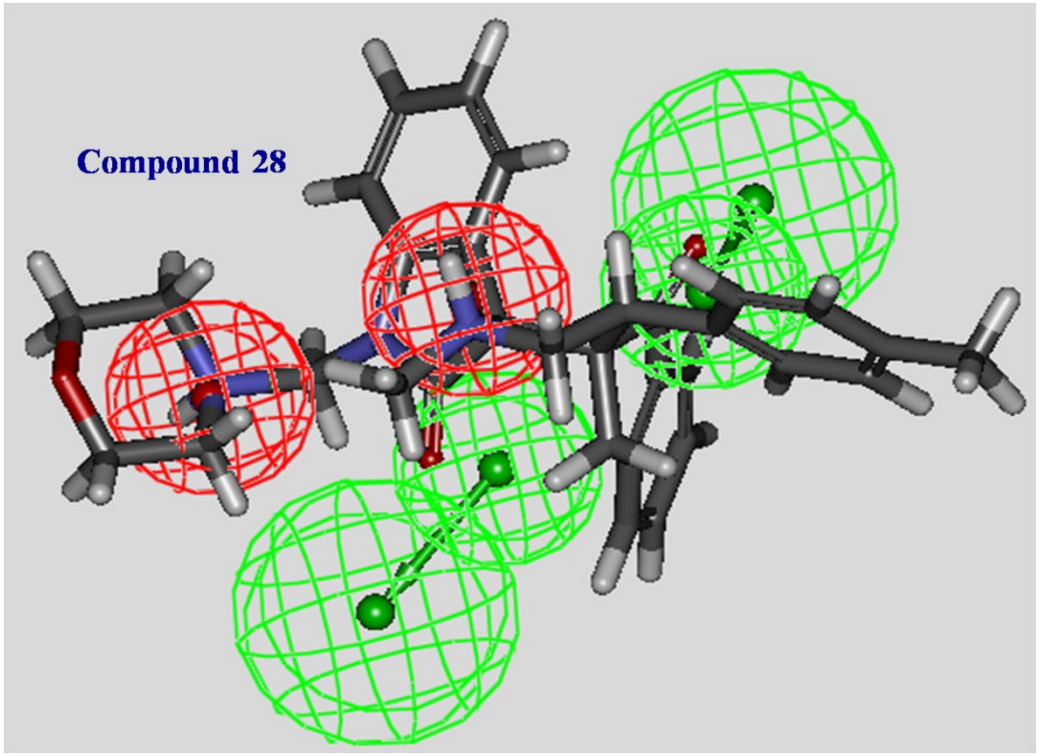
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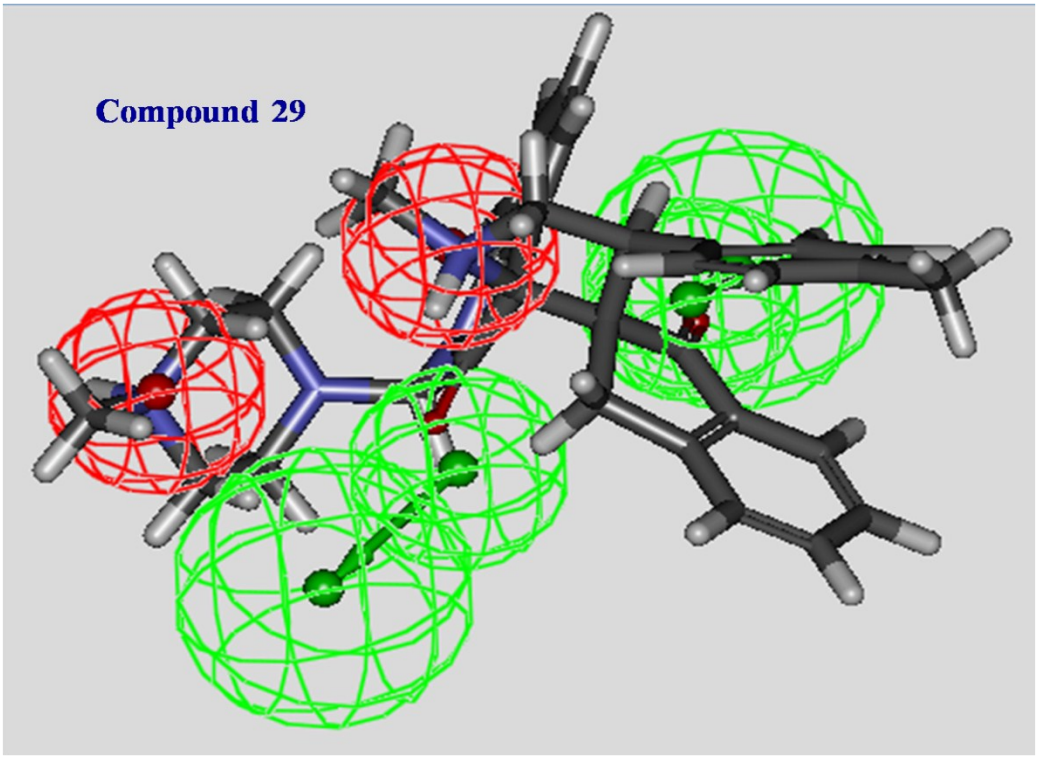
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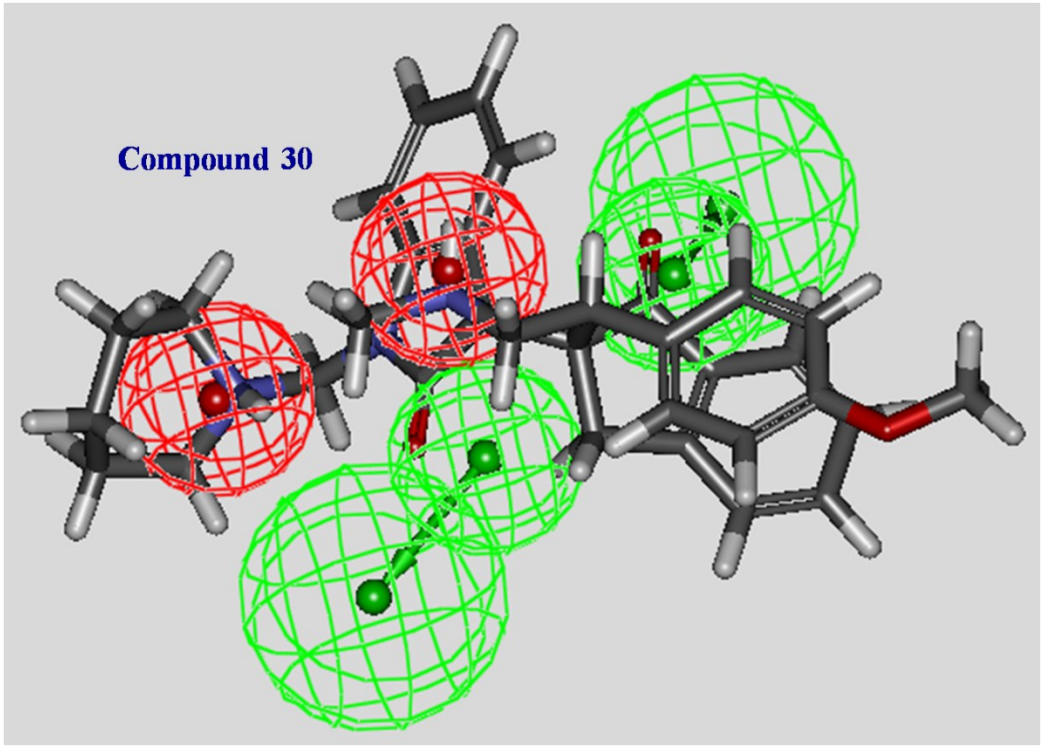
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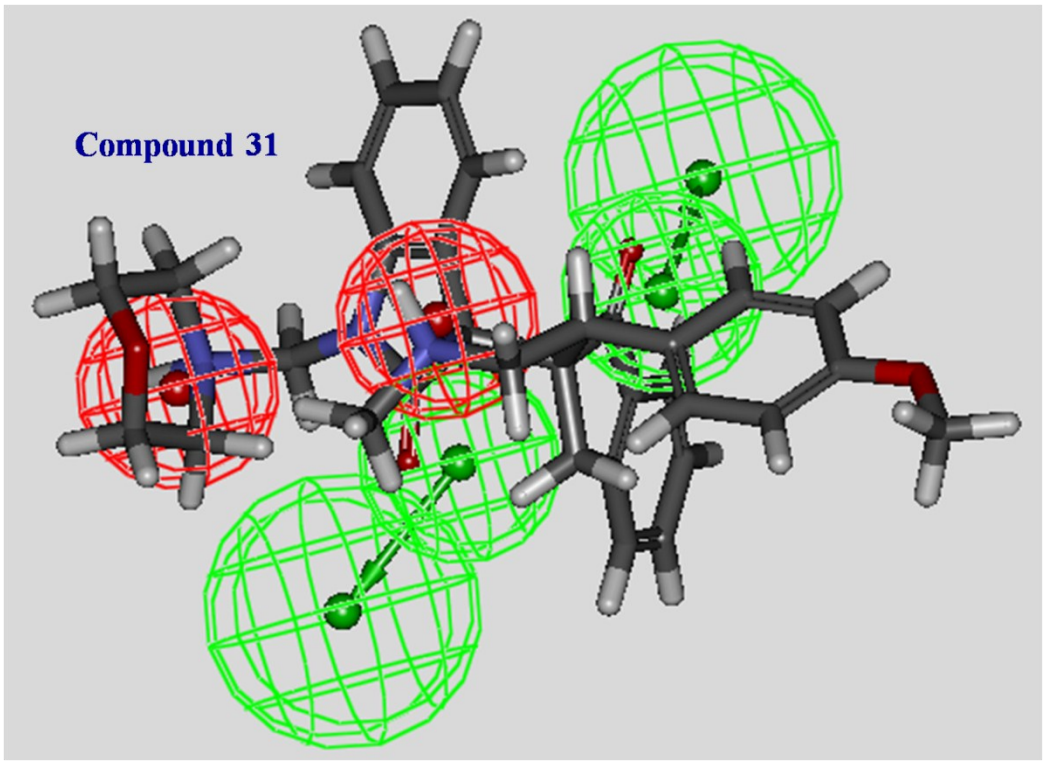
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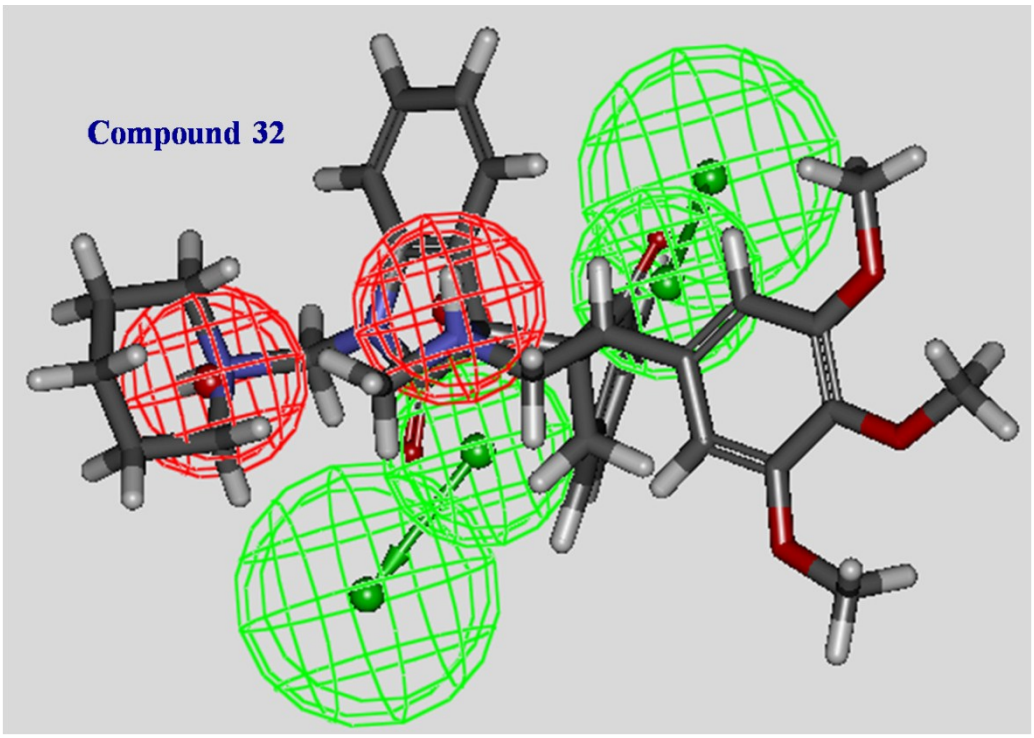
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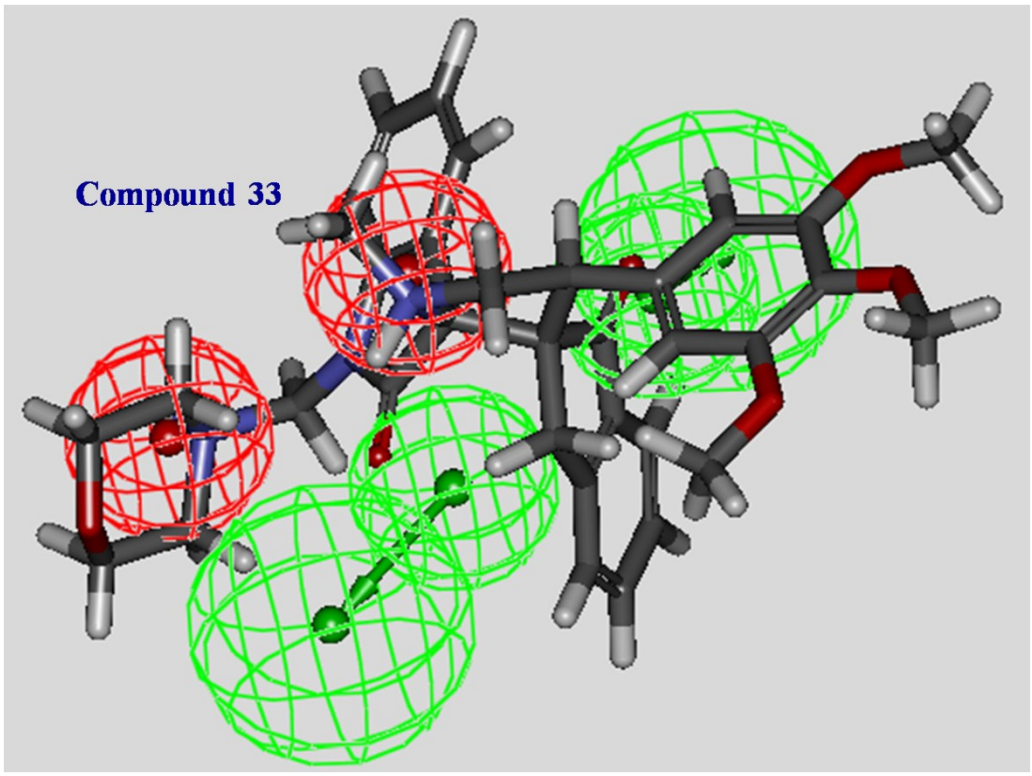
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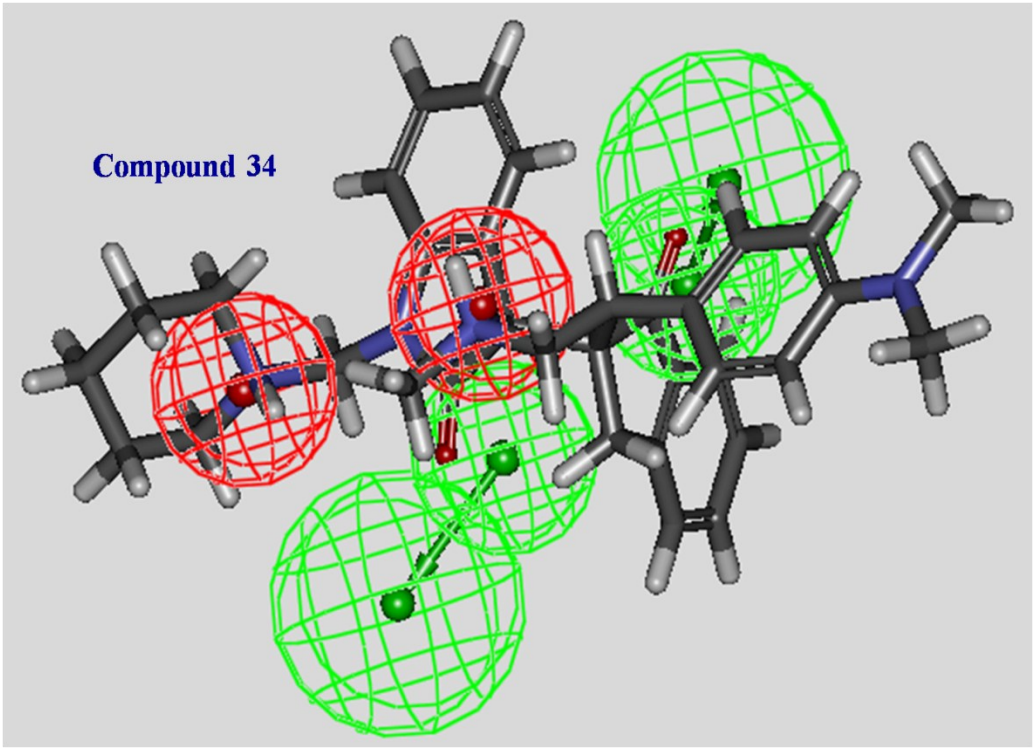
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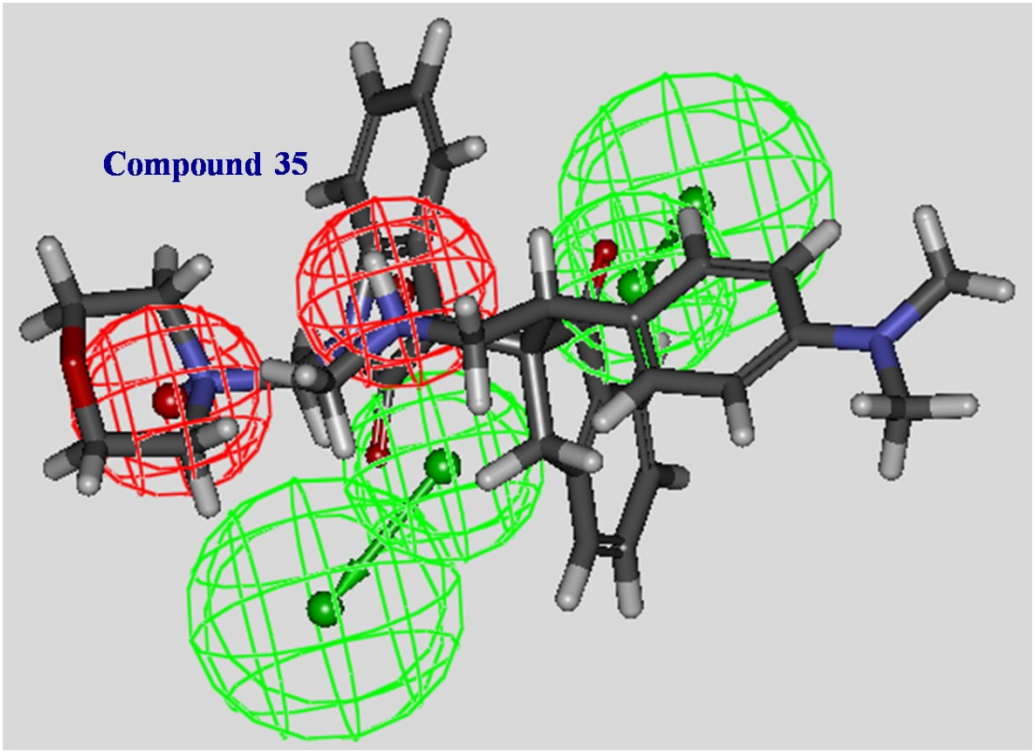
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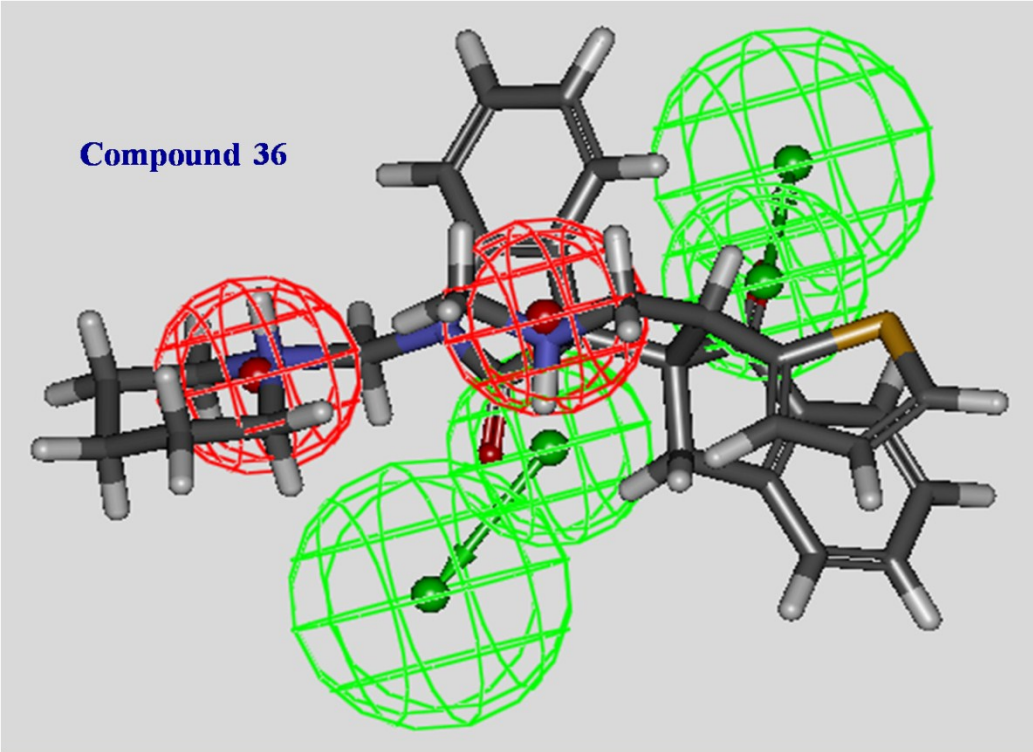
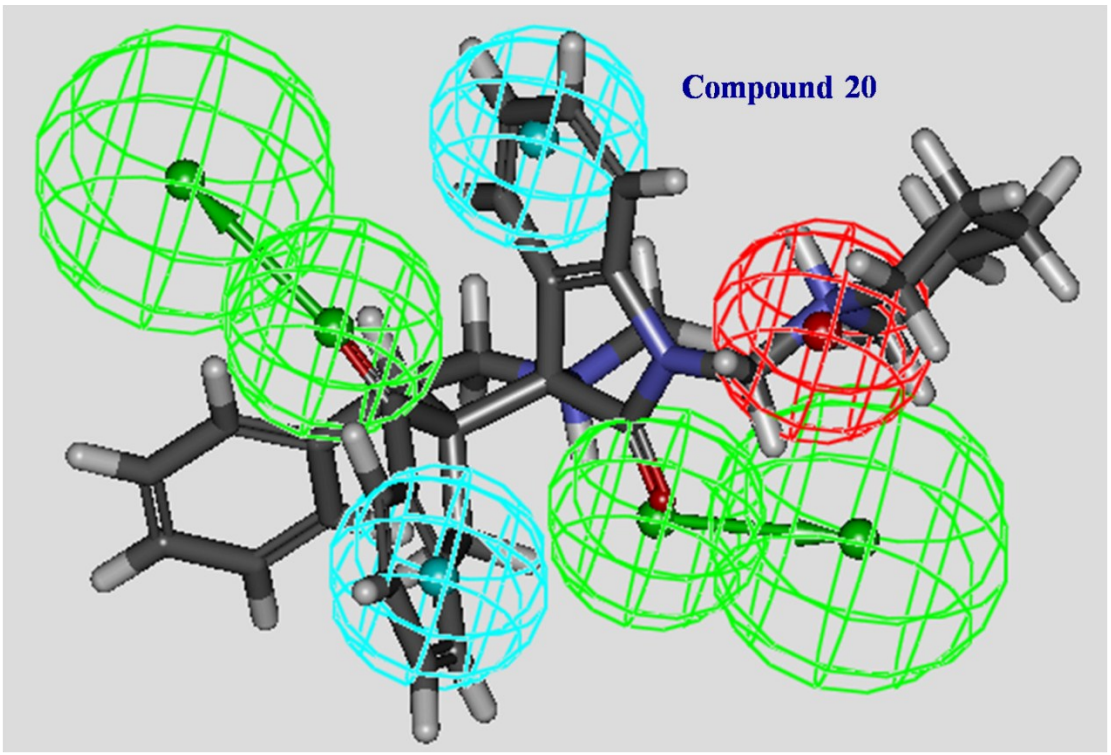


Figure S1 GaLa carcinoma cell line 3D-pharmacophore mapped on the synthesized spiro-alkaloids **20-36**.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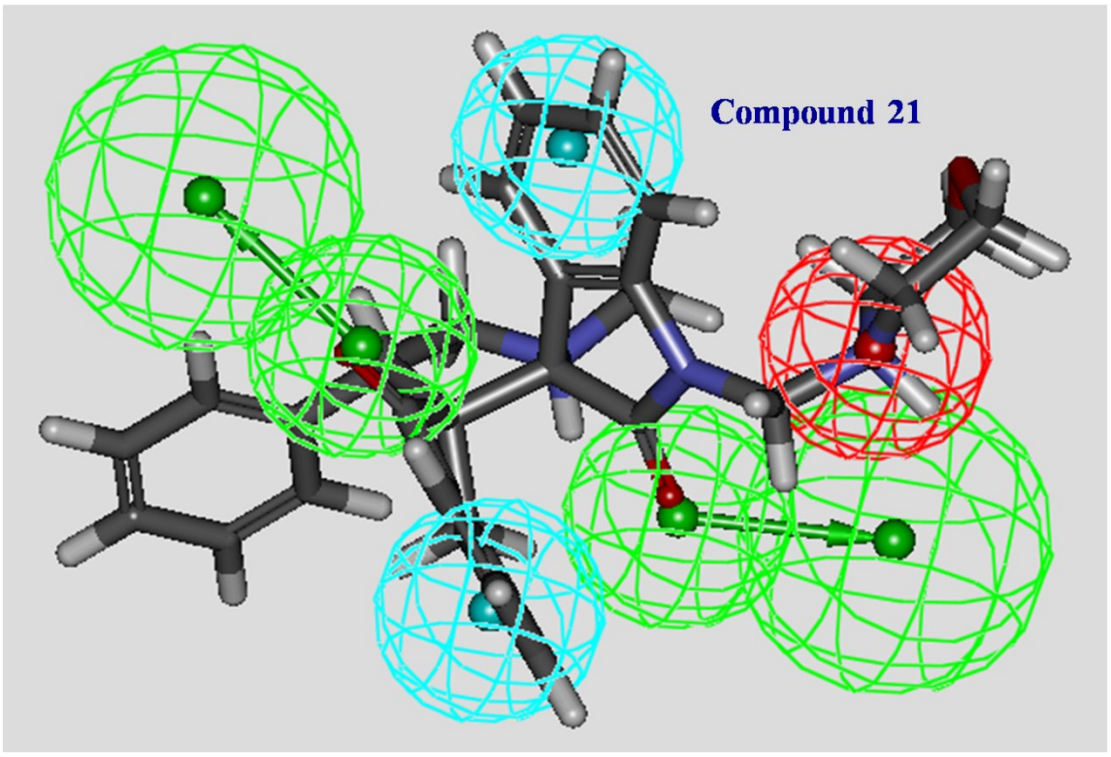
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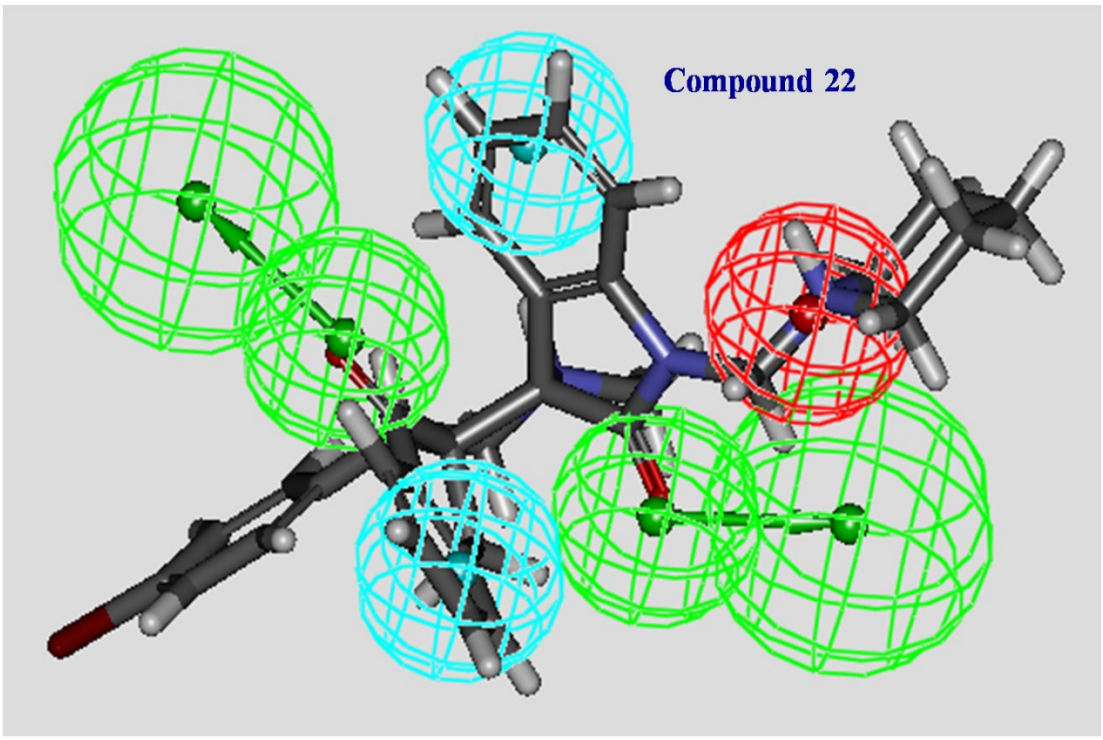
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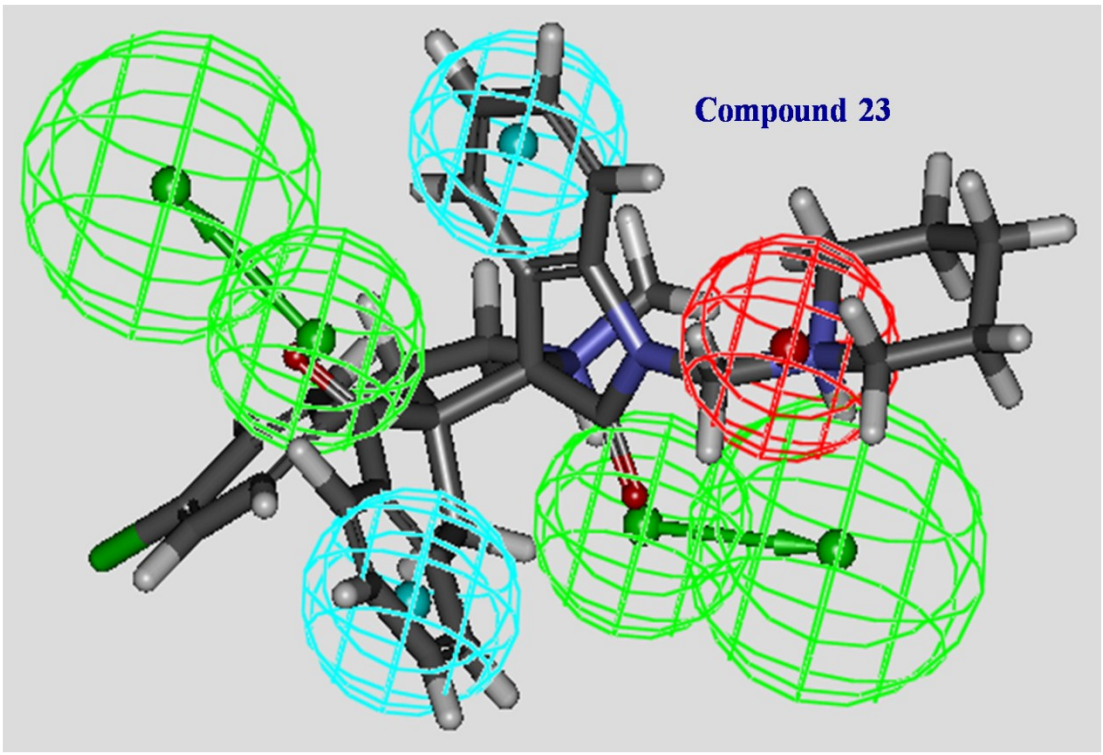
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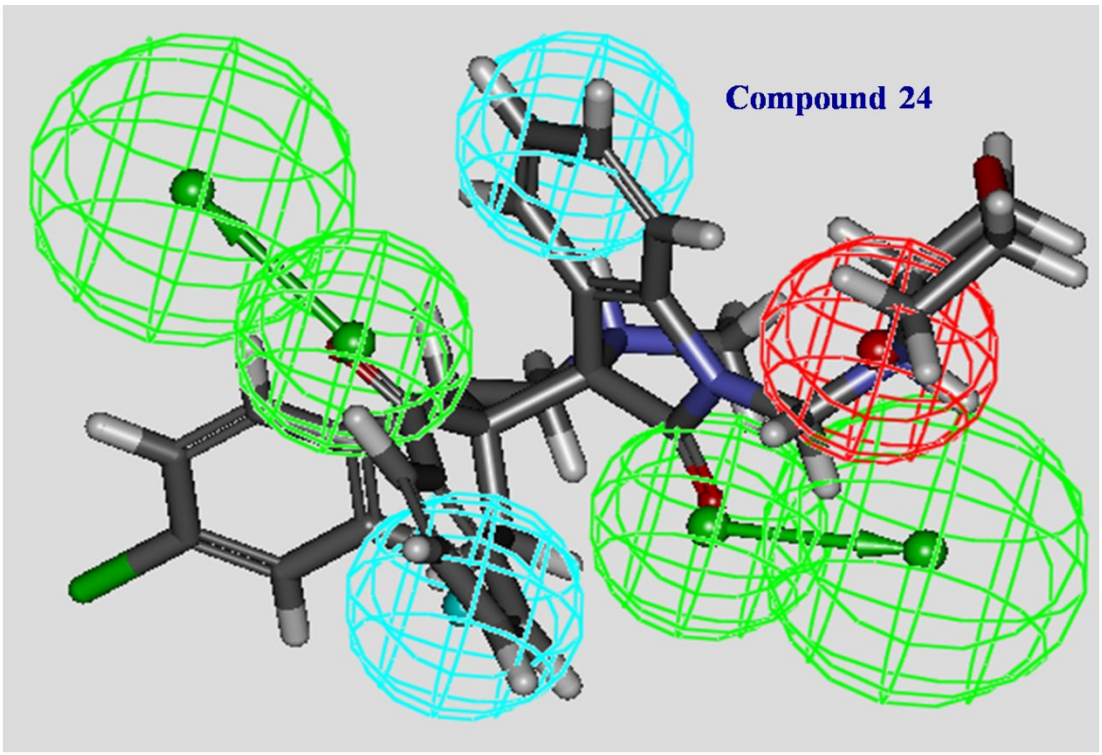
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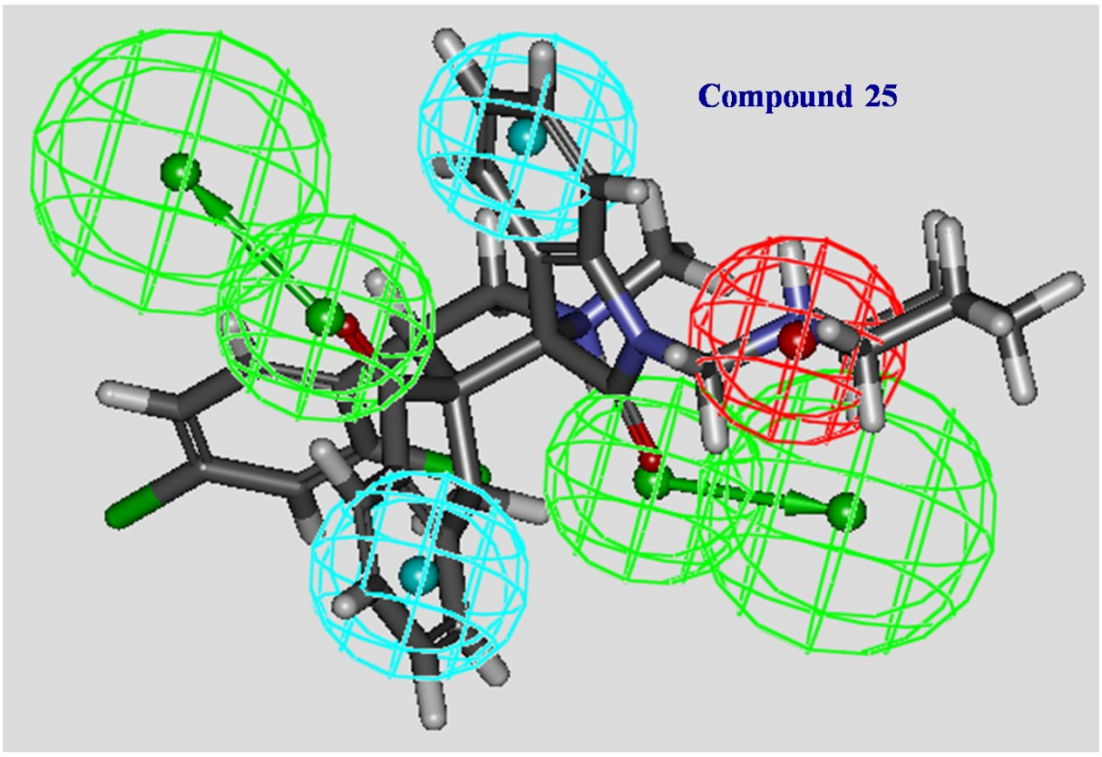
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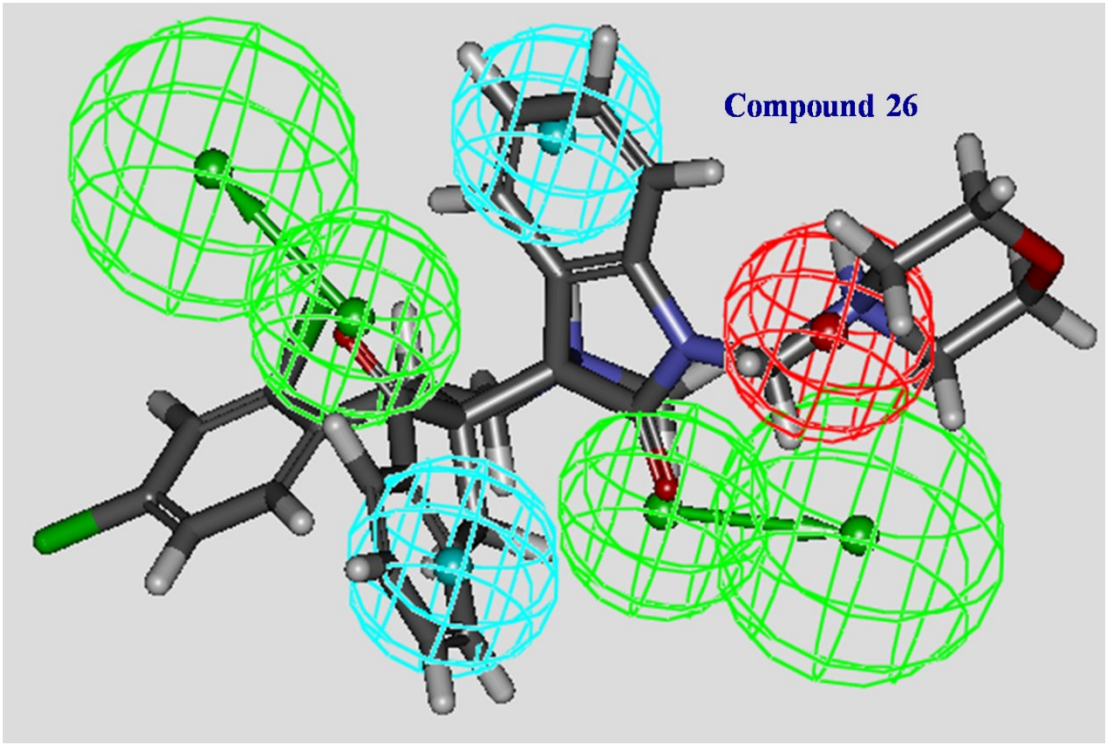
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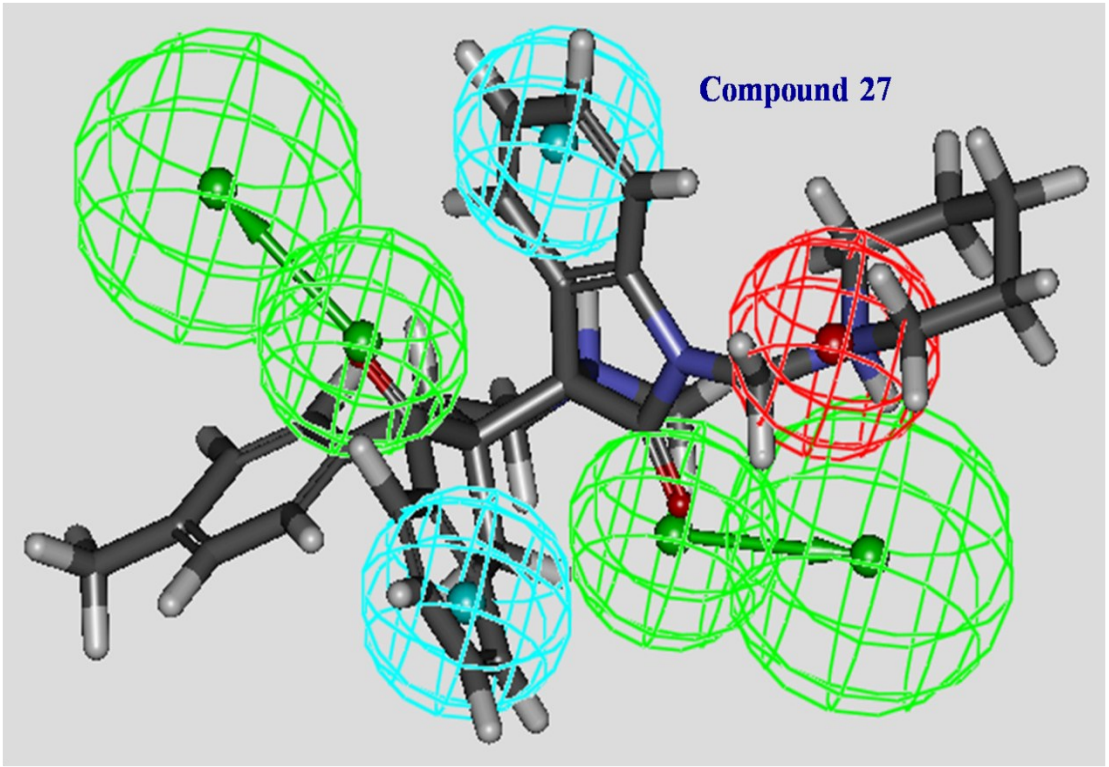
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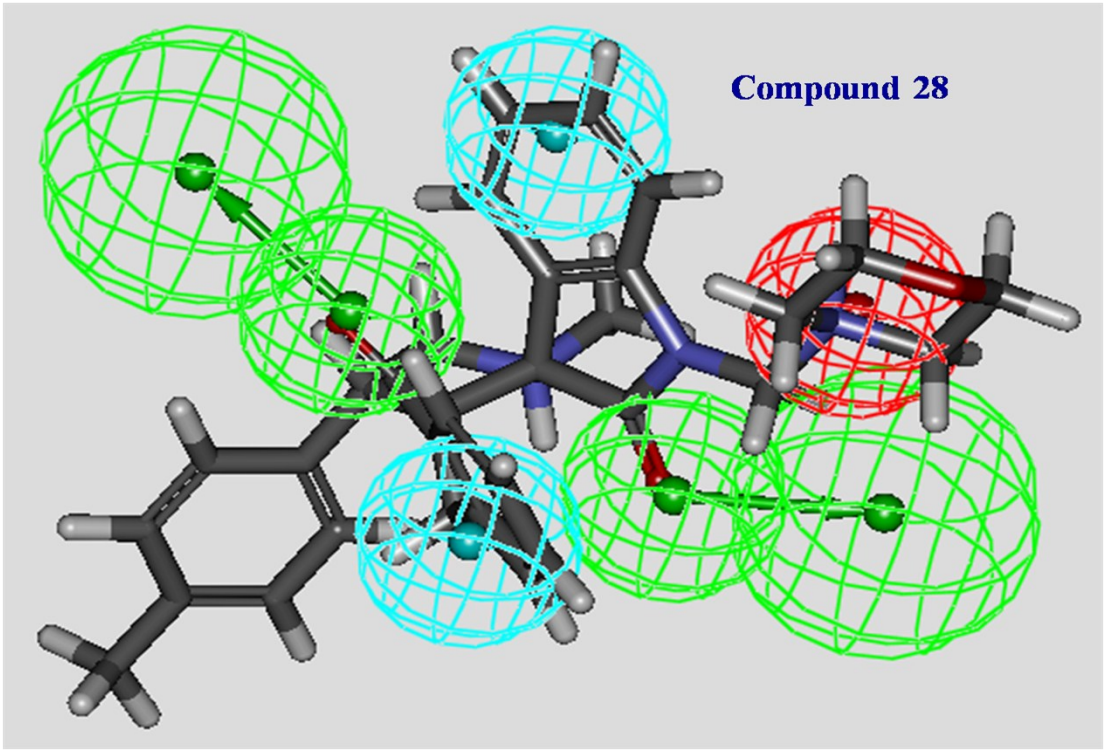
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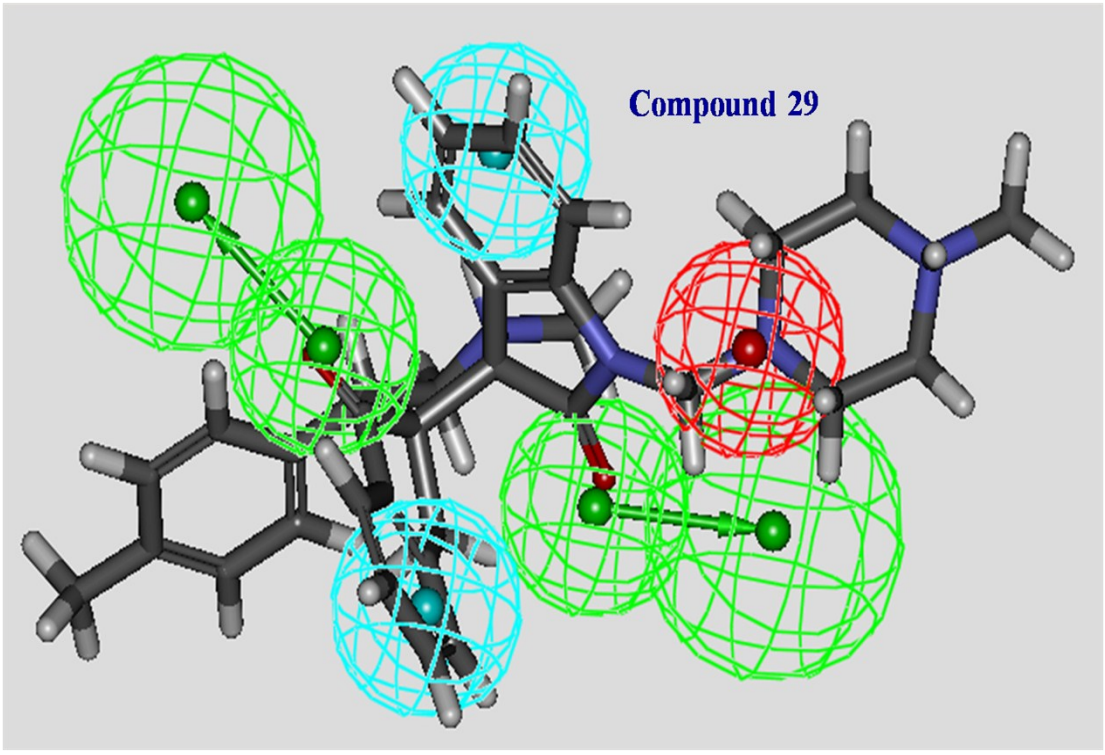
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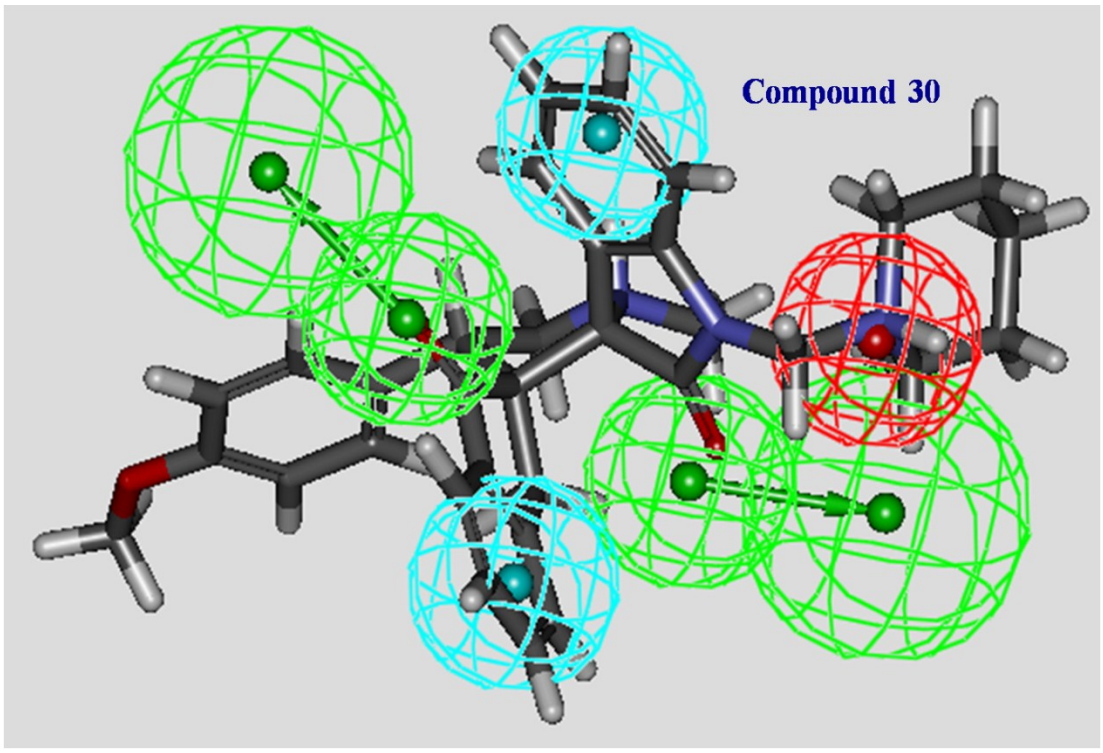
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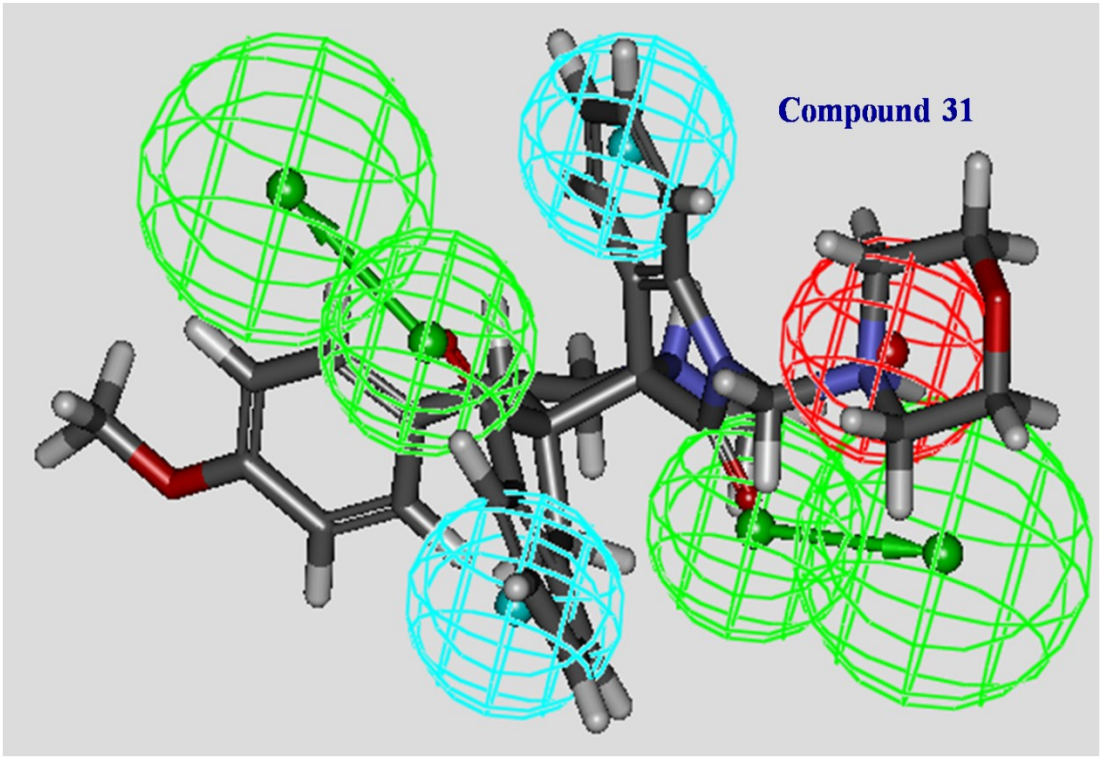
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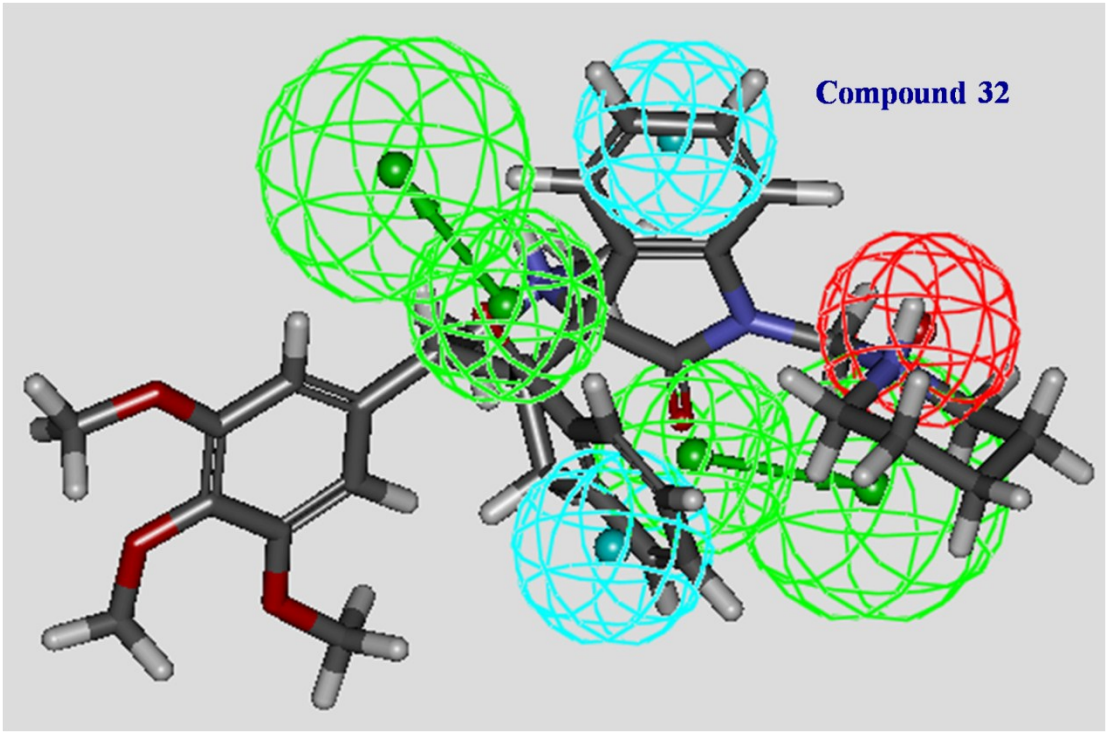
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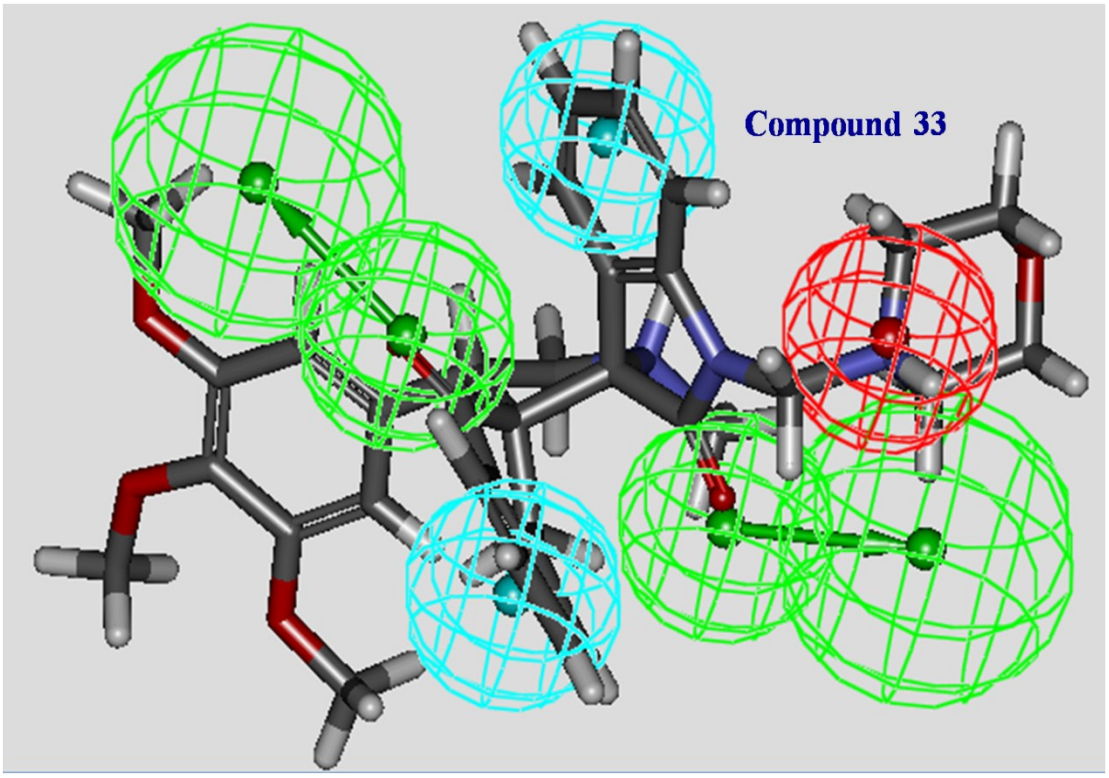
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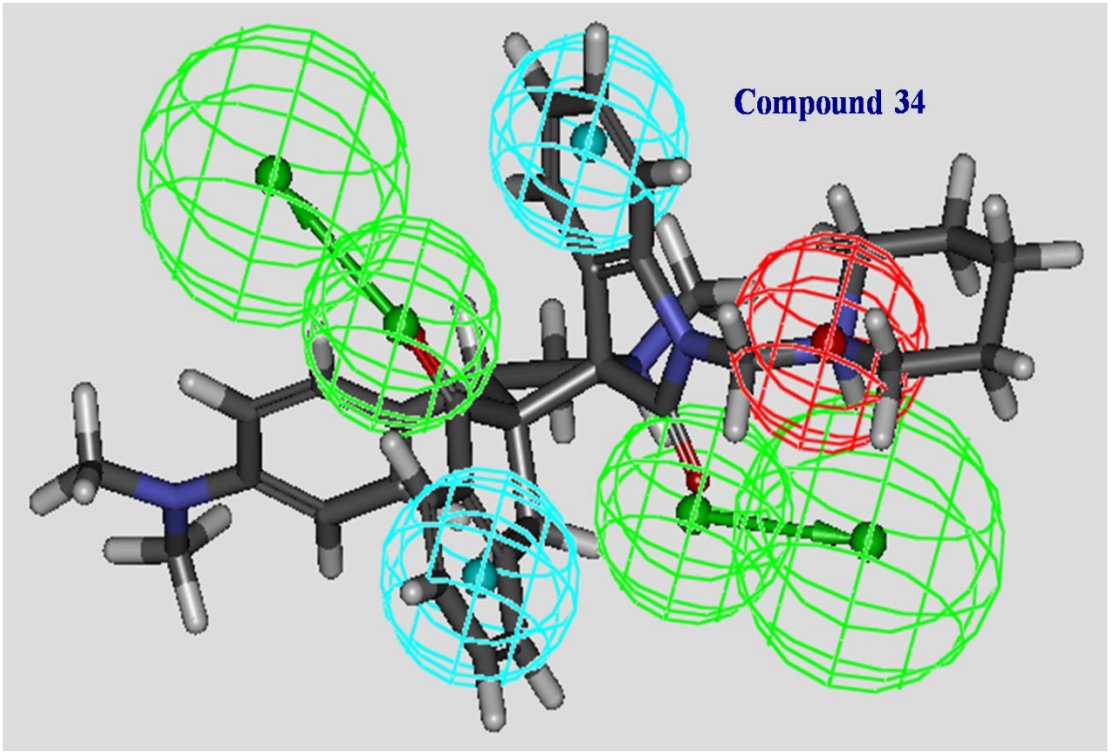
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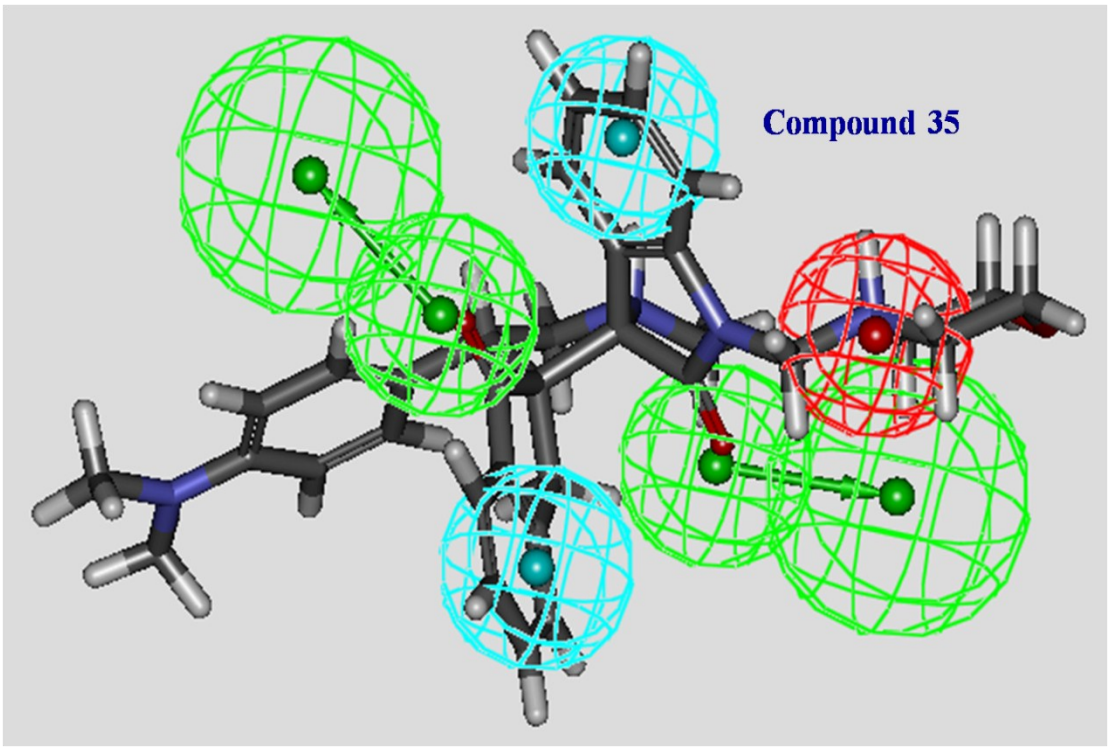
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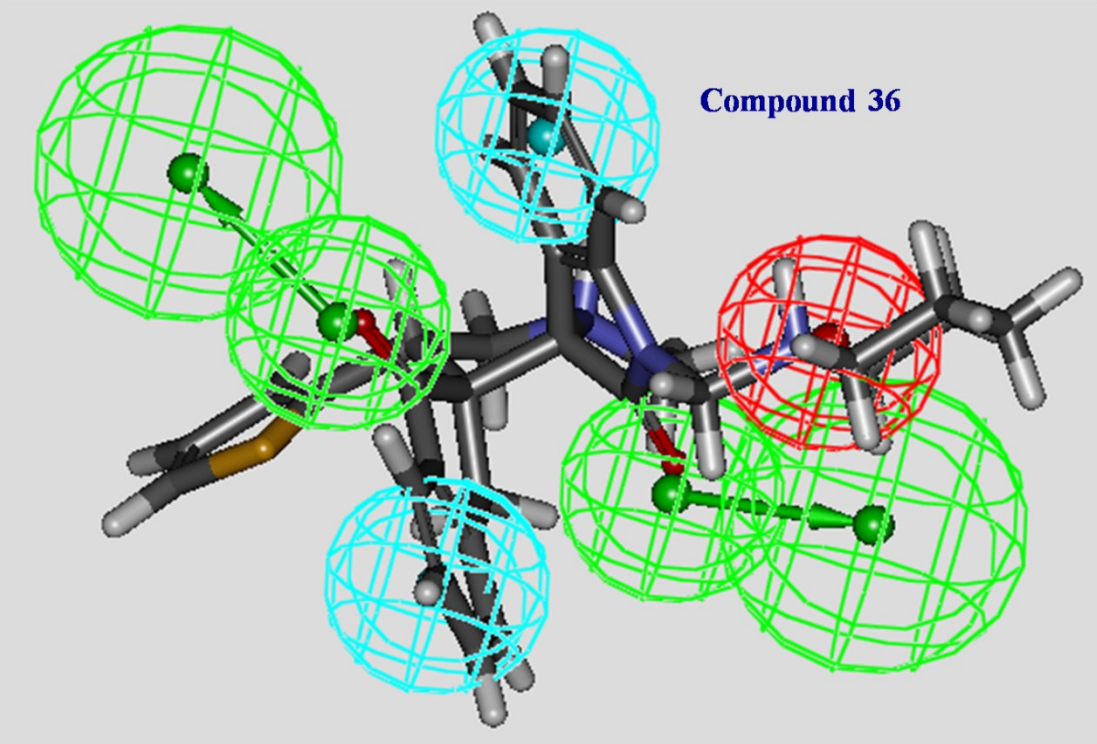
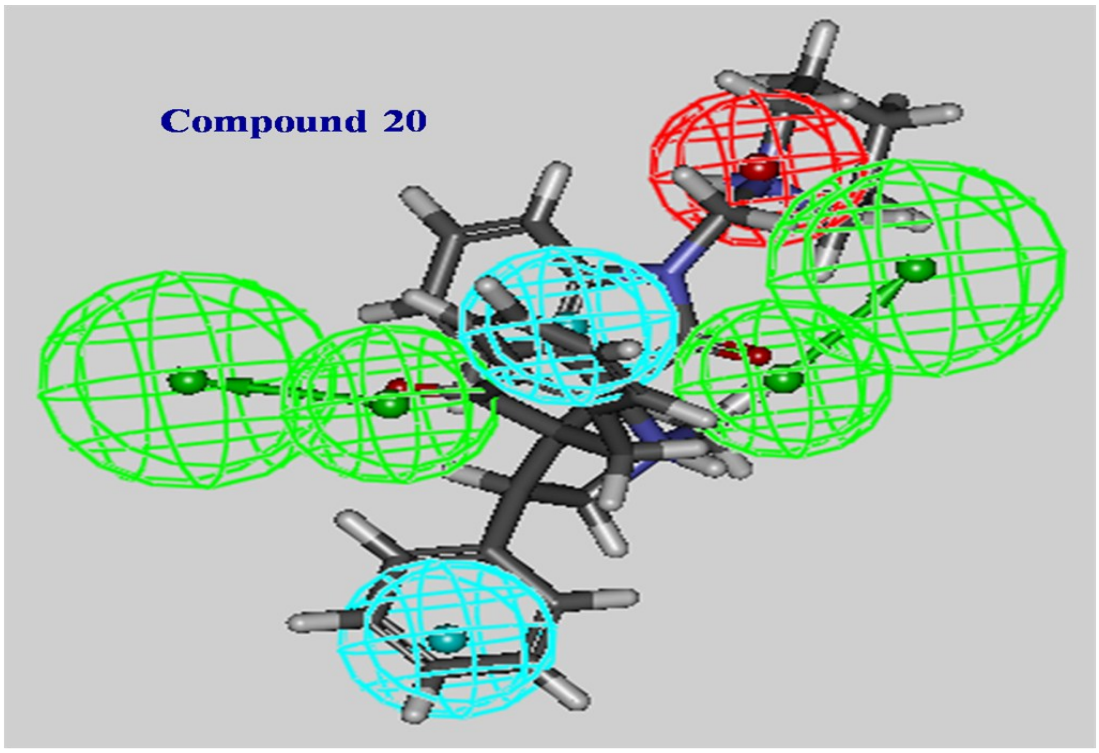


Figure S2 LuPiCi carcinoma cell line 3D-pharmacophore mapped on the synthesized spiro-alkaloids **20-36**.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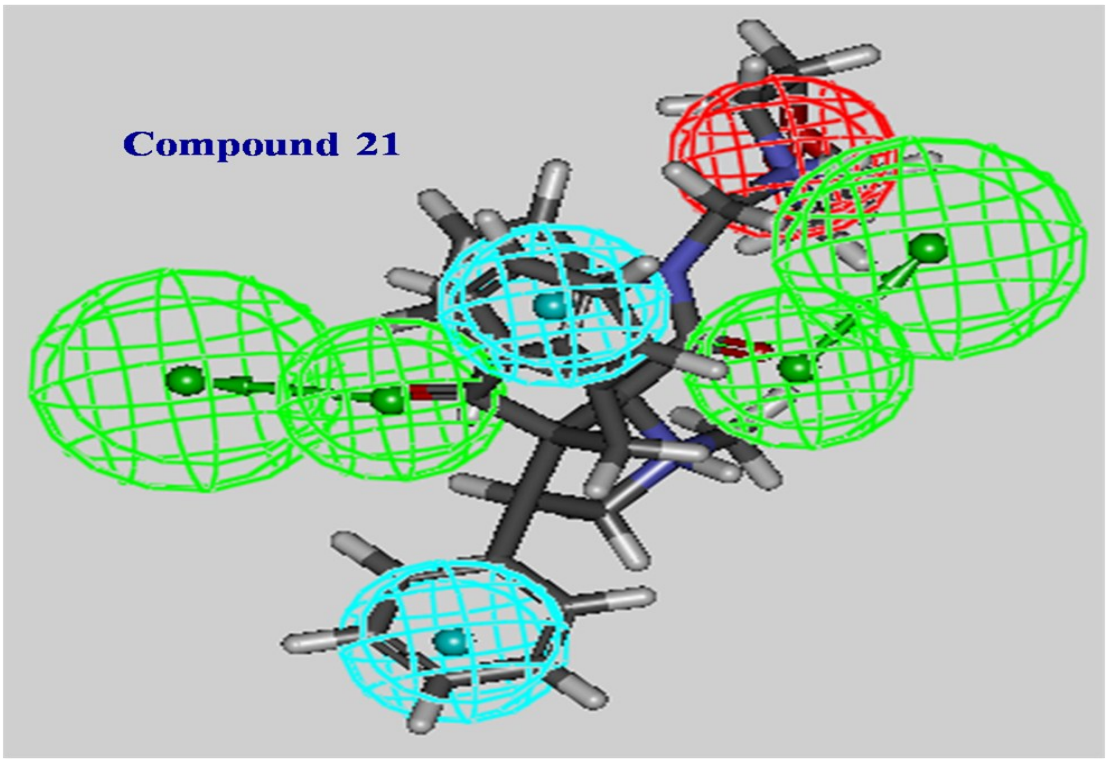
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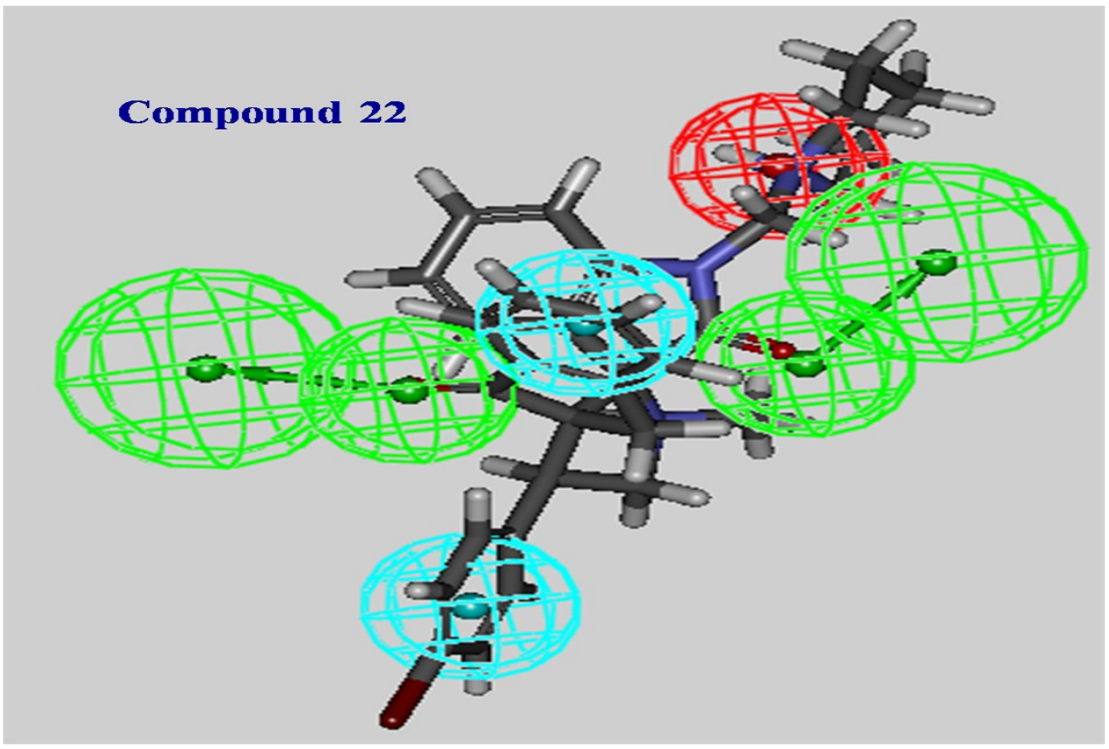
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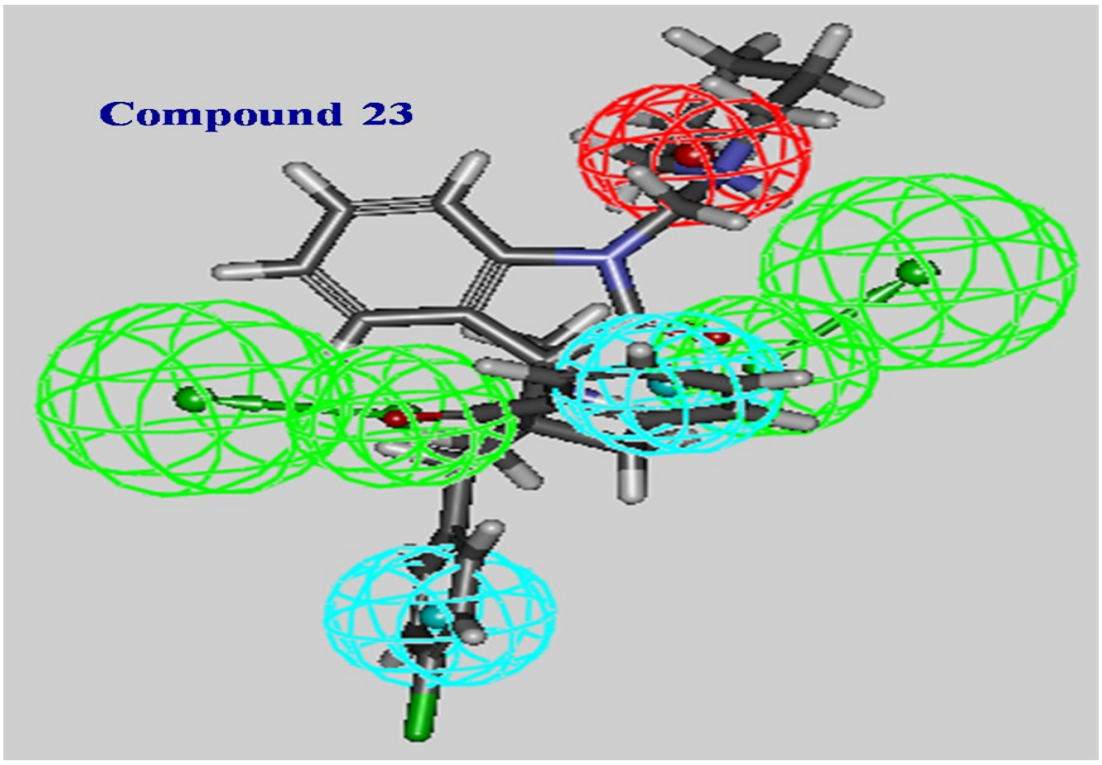
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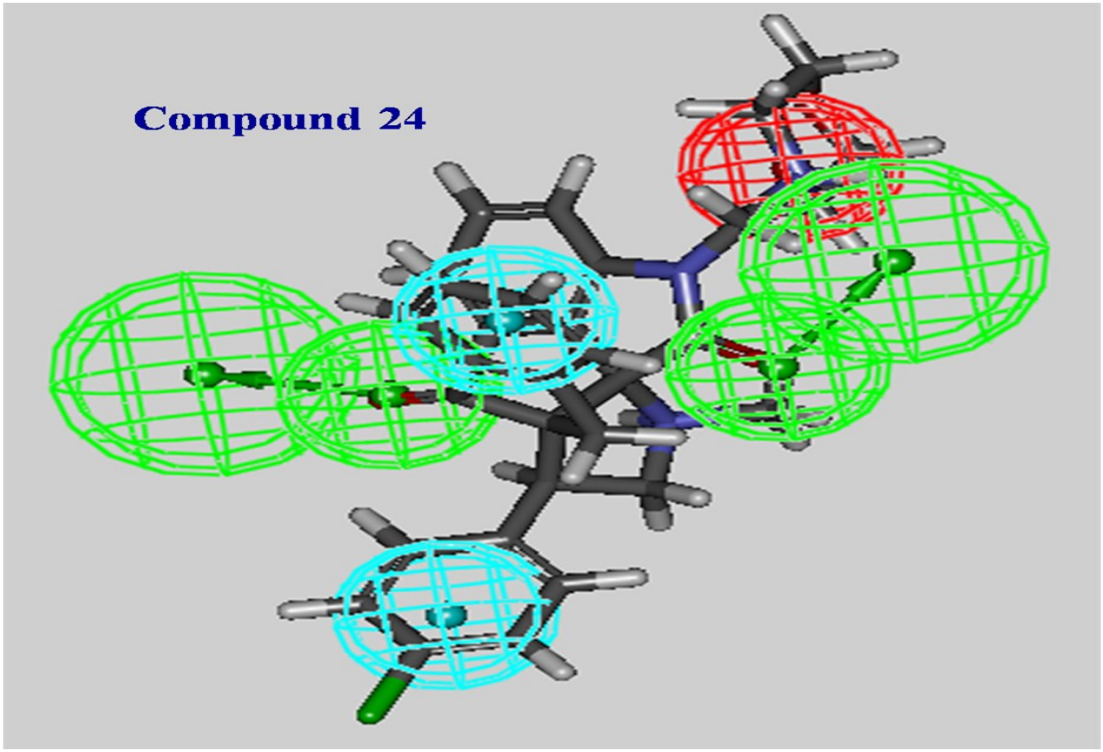
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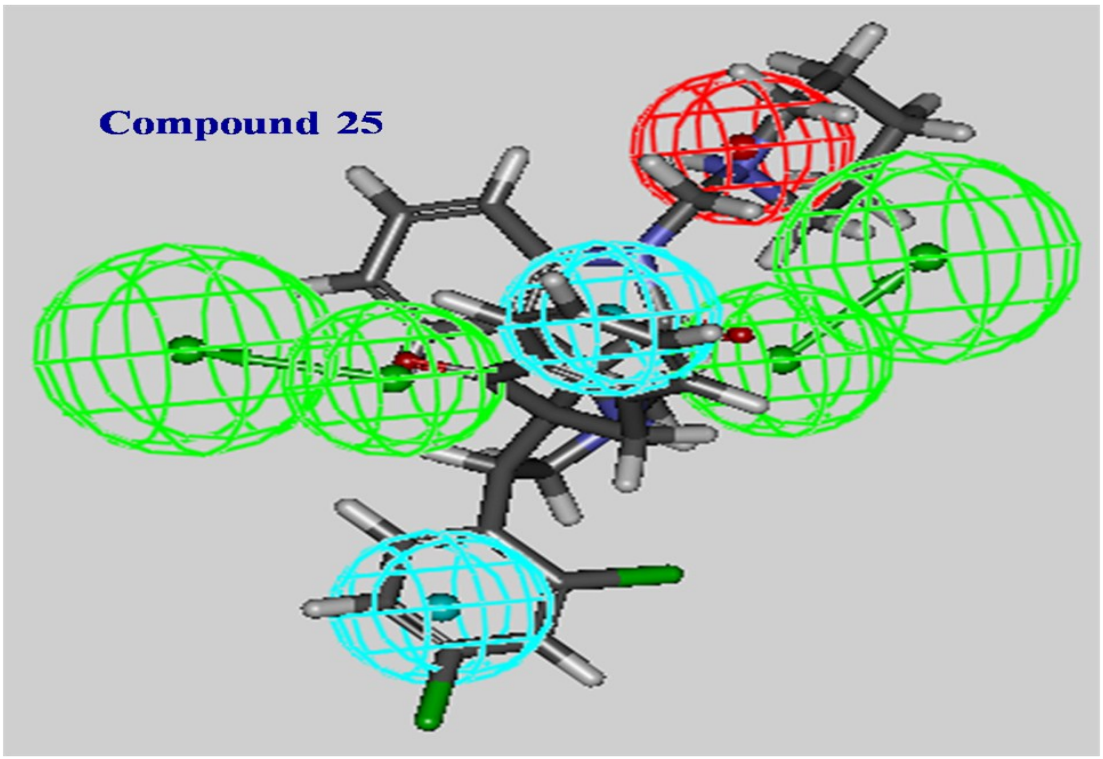
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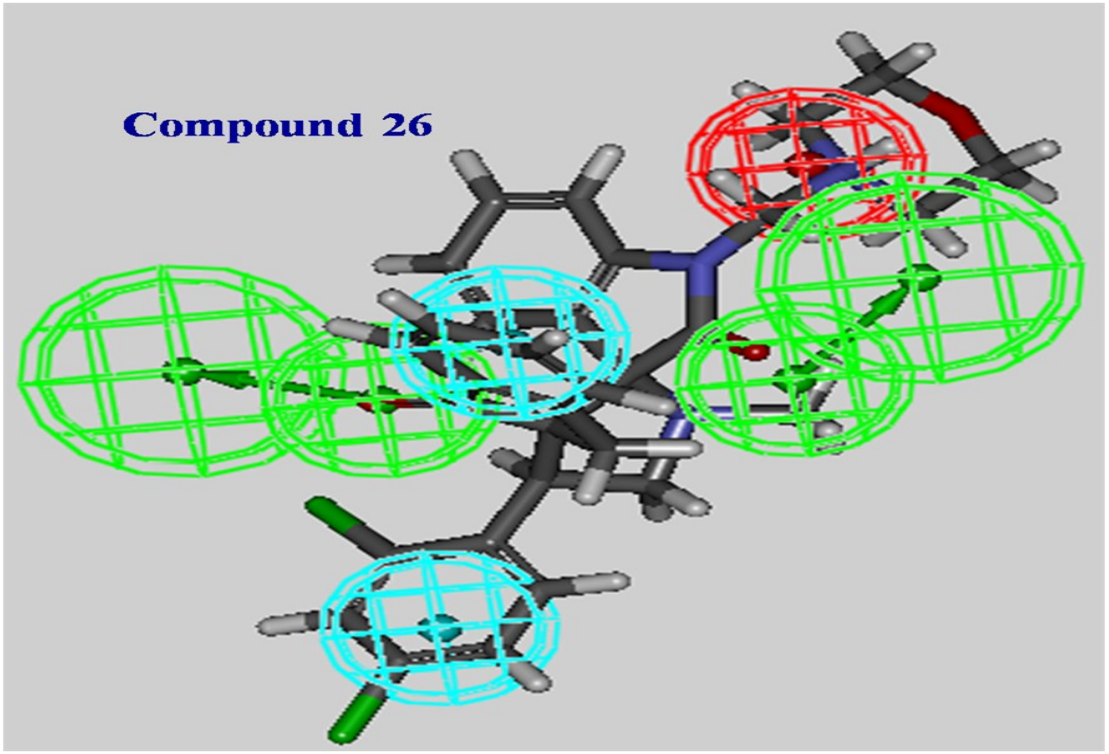
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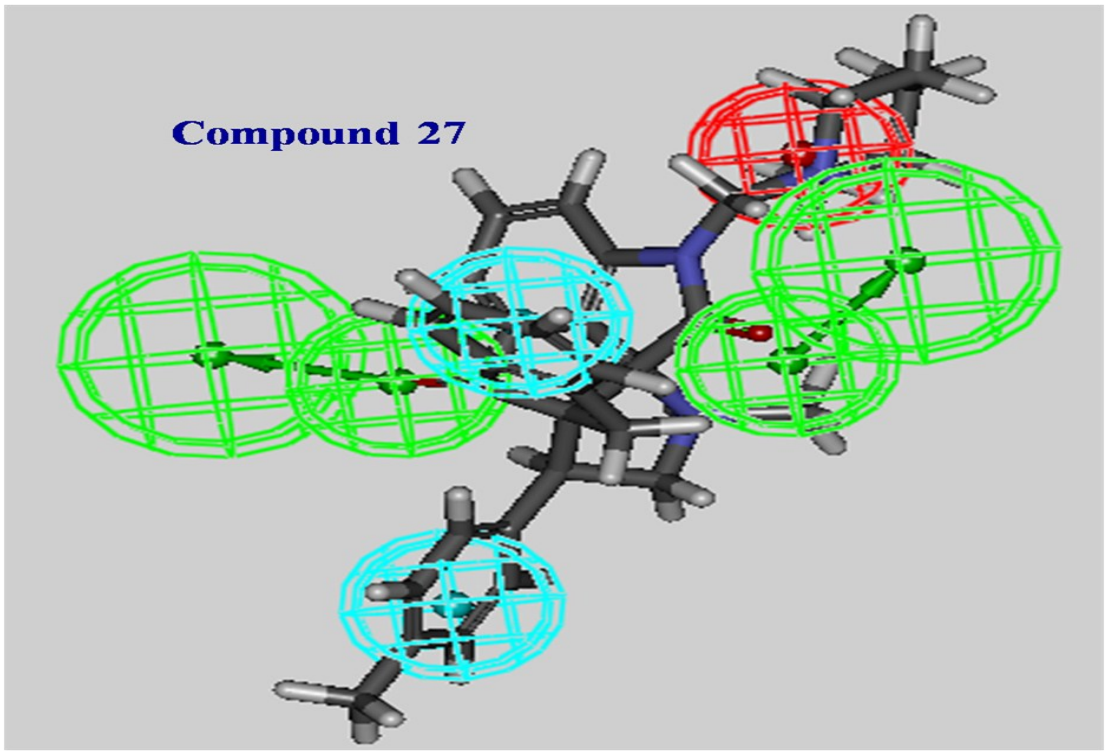
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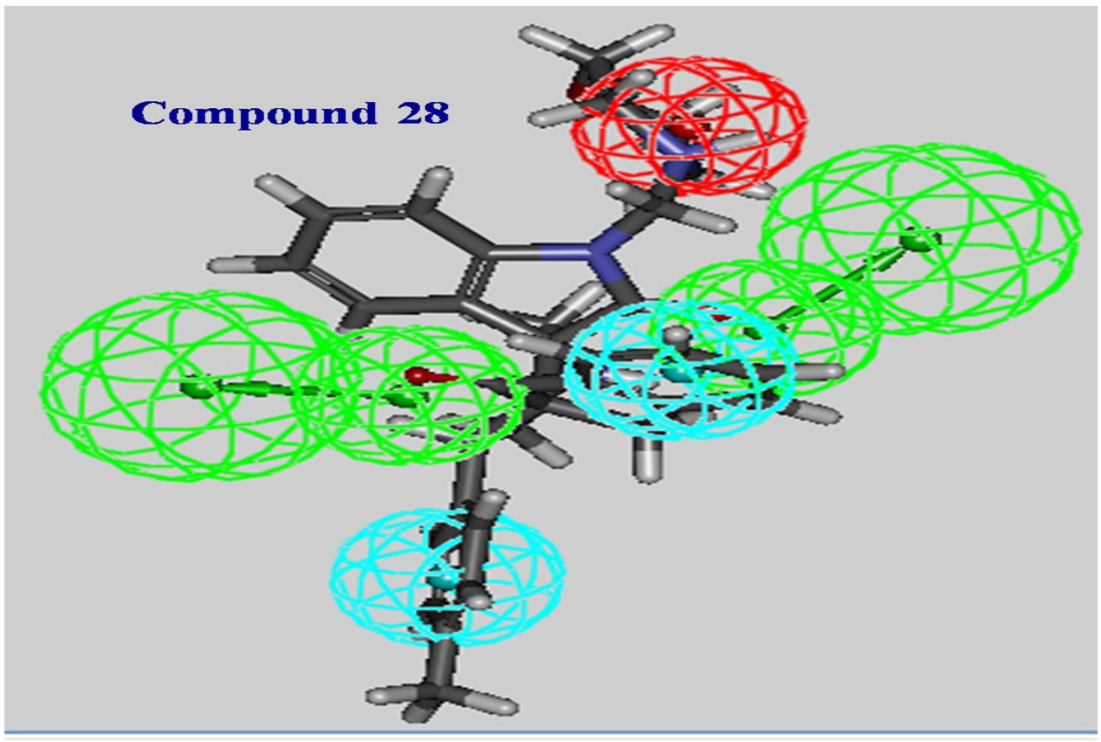
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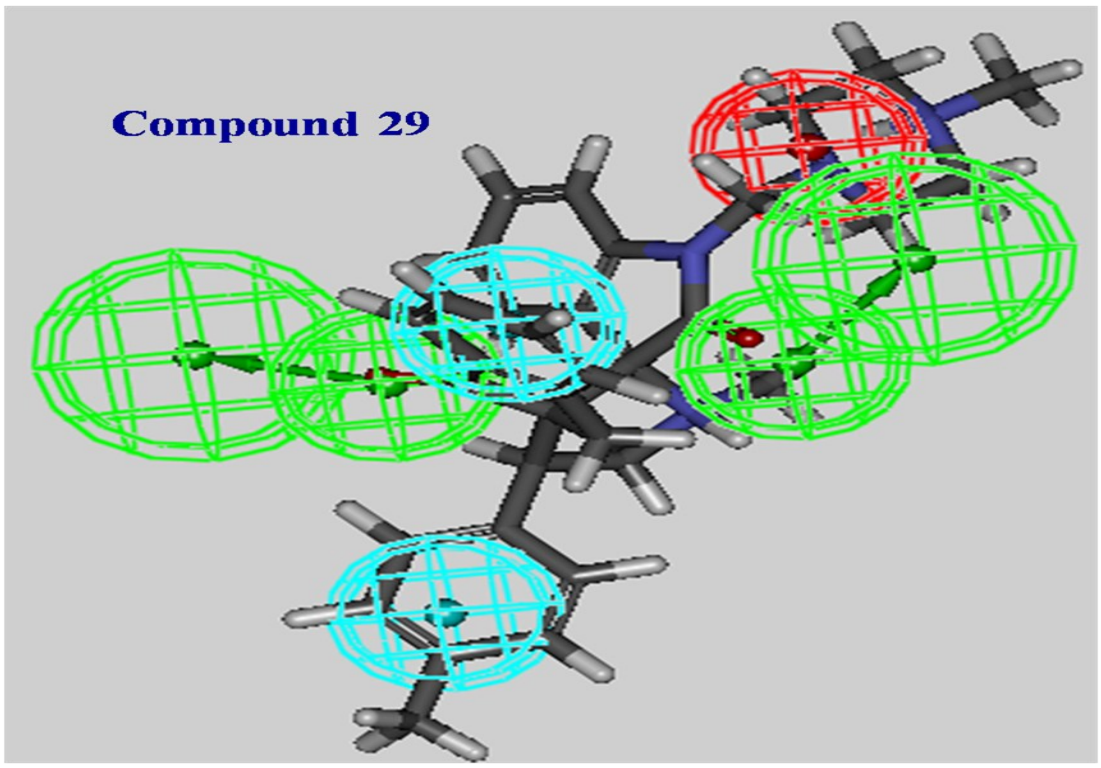
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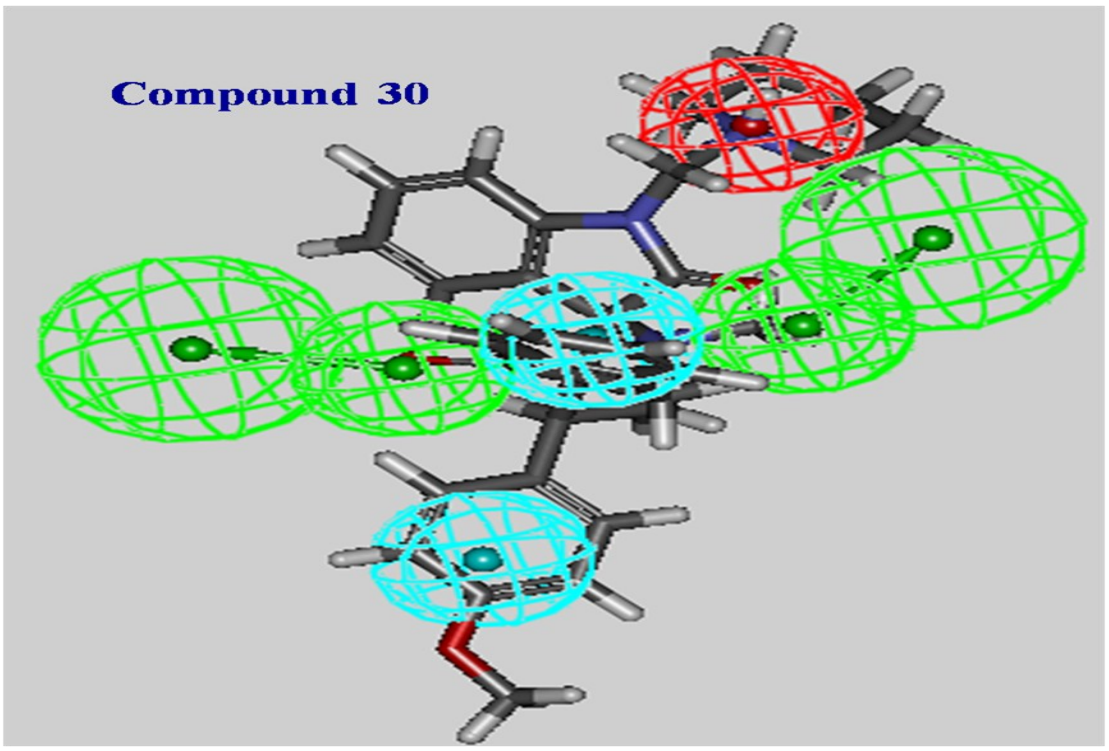
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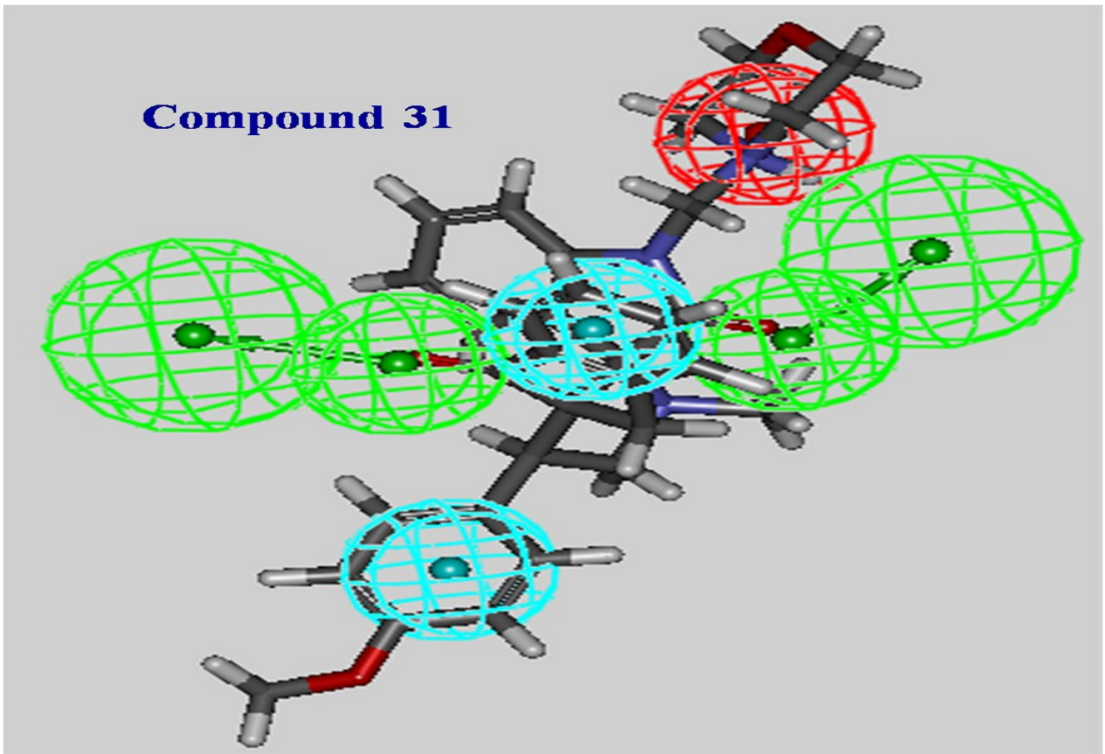
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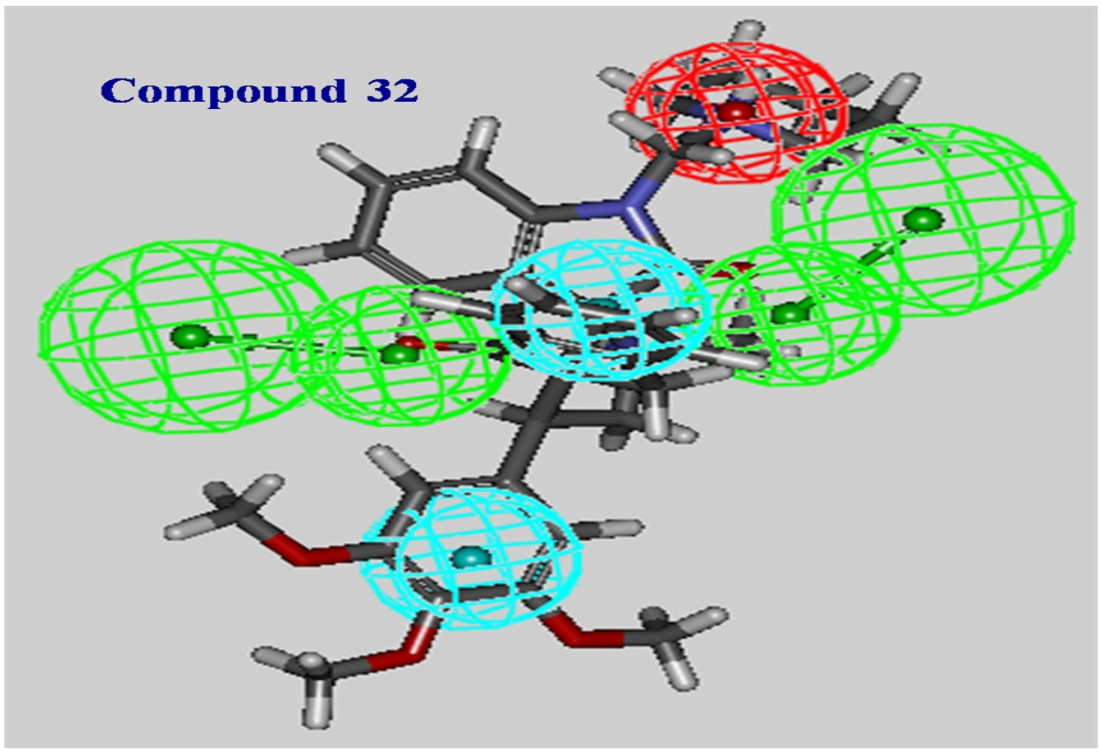
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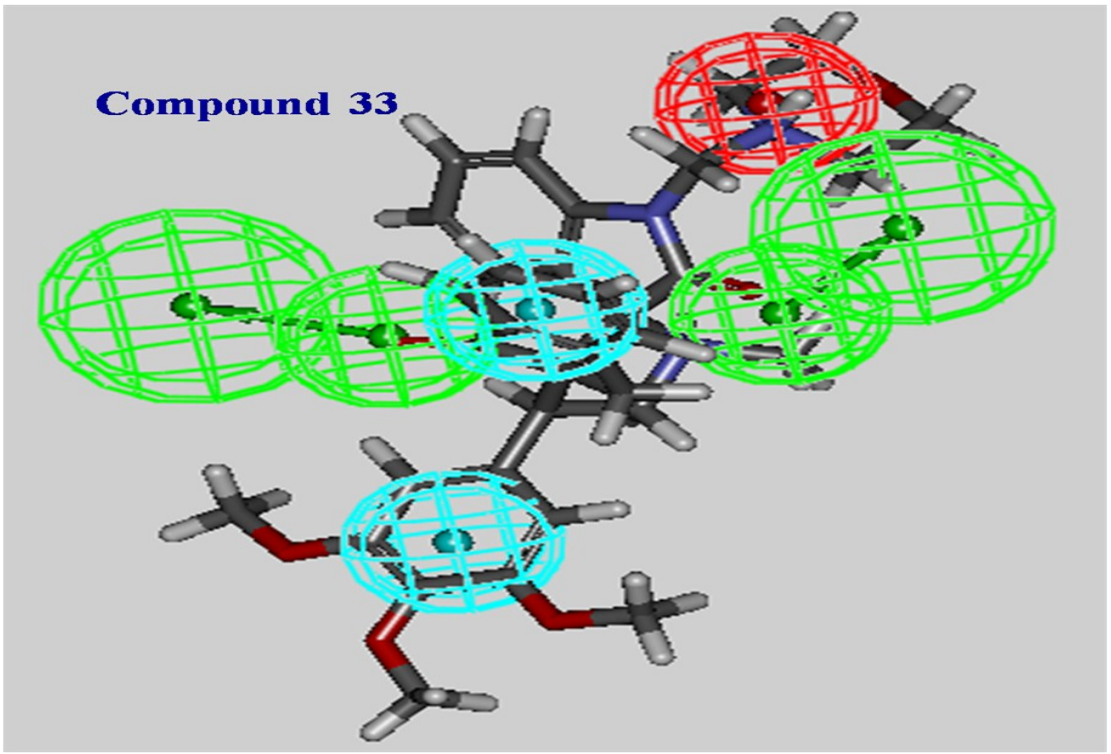
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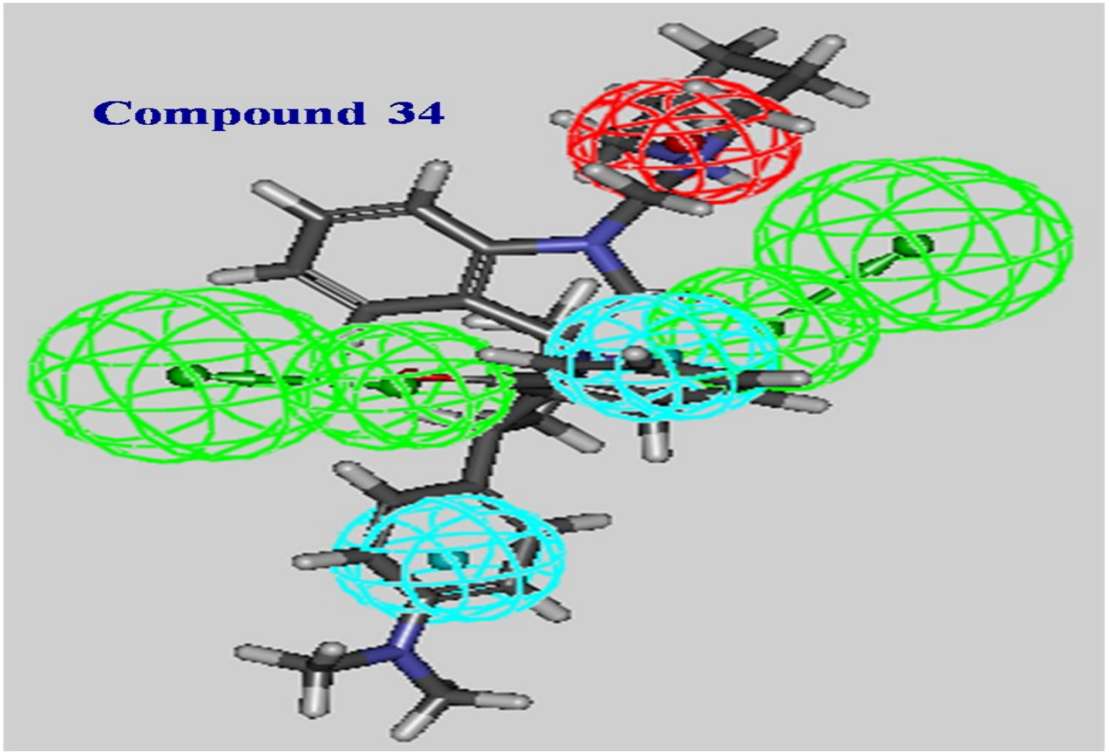
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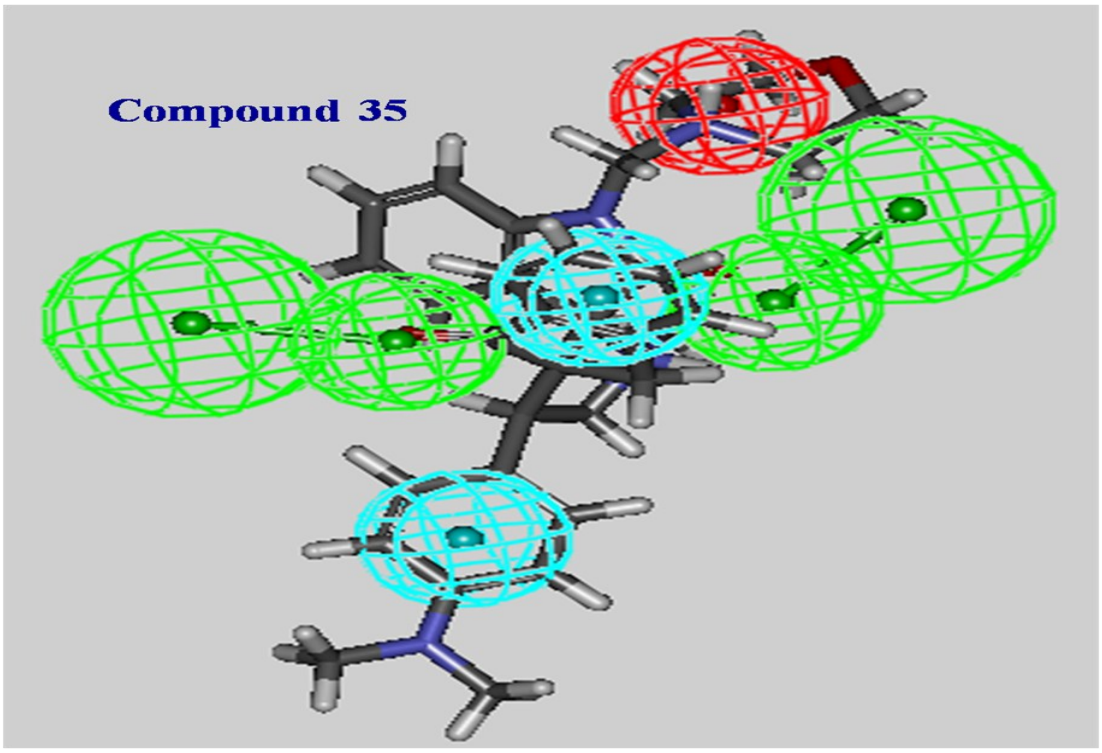
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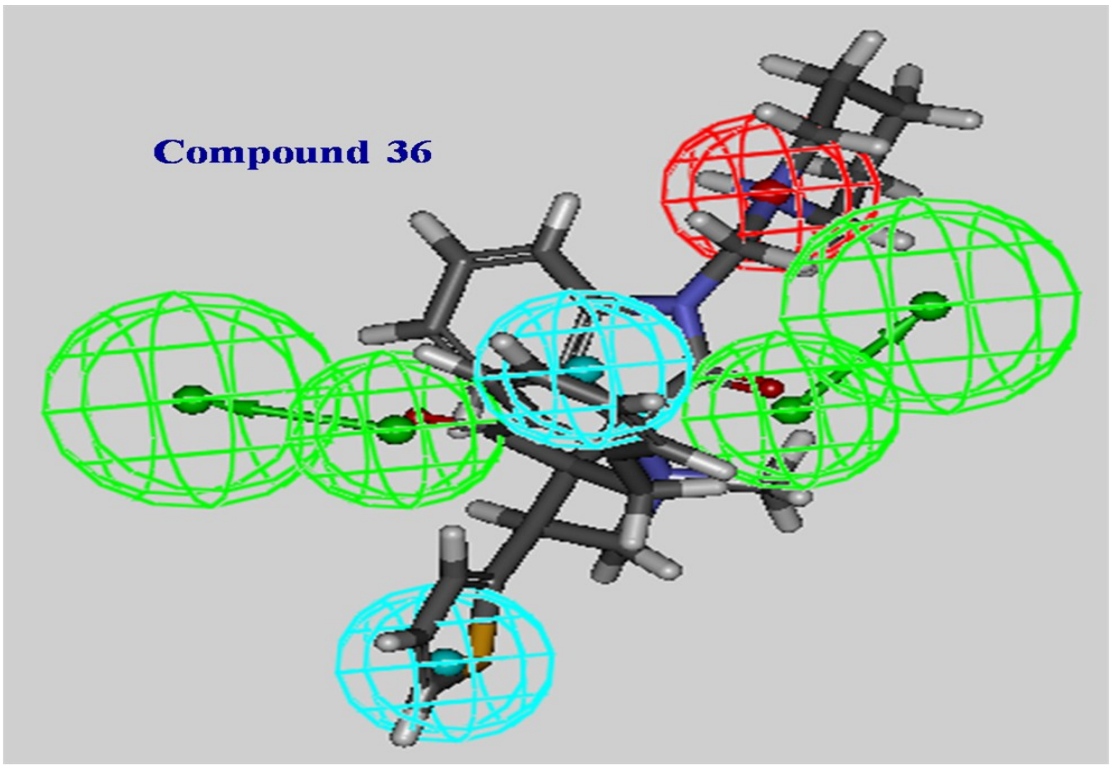

Figure S3 LuCa carcinoma cell line 3D-pharmacophore mapped on the synthesized spiro-alkaloids **20-36**.

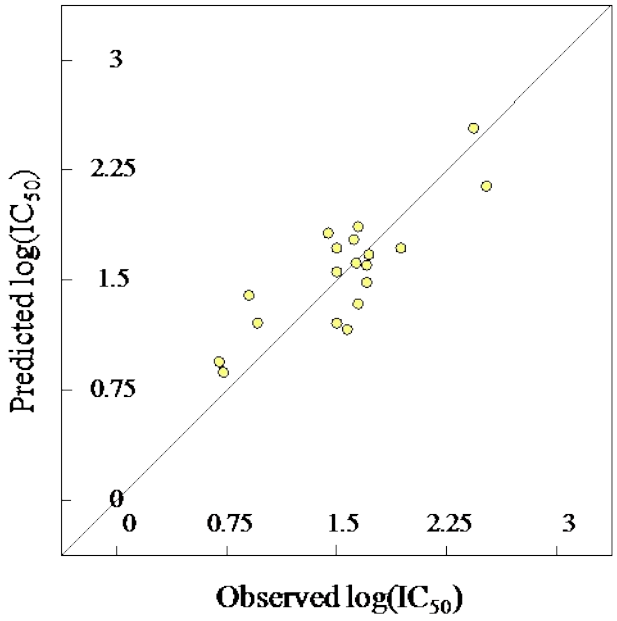

Figure S4 BMLR-QSAR model (two descriptors) plot of correlations representing the observed *vs.* predicted log(IC_{50}) values for GaLa carcinoma cell line active agents.

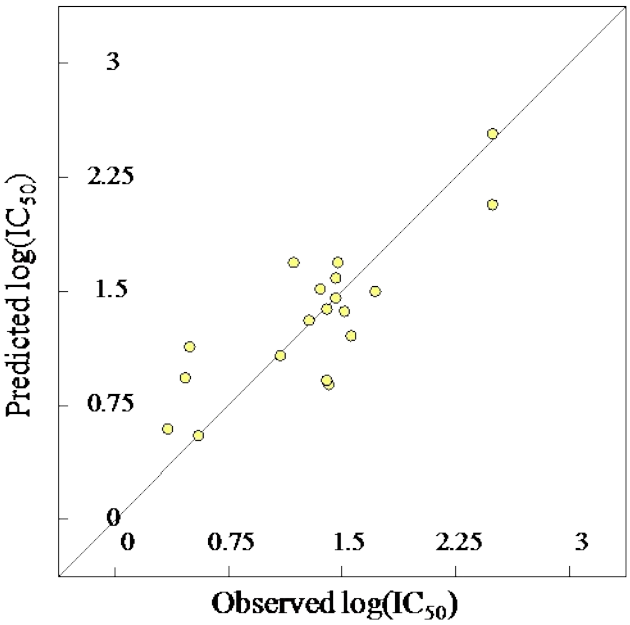

Figure S5 BMLR-QSAR model (two descriptors) plot of correlations representing the observed *vs.* predicted log(IC_{50}) values for LuPiCi carcinoma cell line active agents.

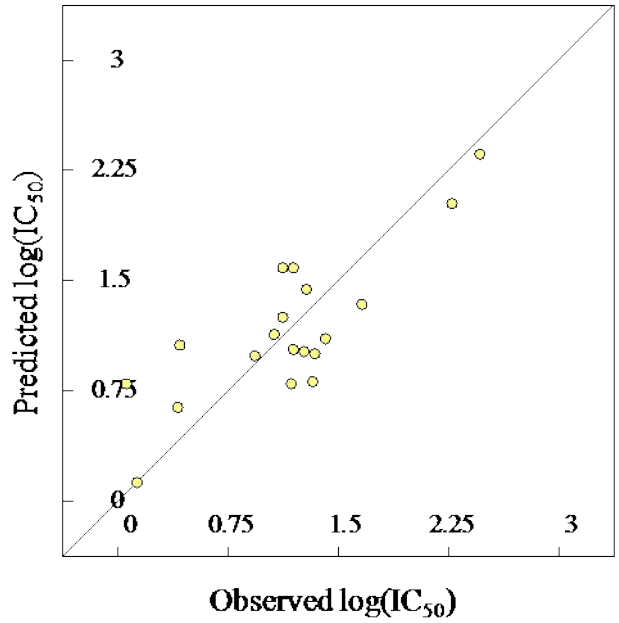

Figure S6 BMLR-QSAR model (two descriptors) plot of correlations representing the observed *vs.* predicted log(IC_{50}) values for LuCa carcinoma cell line active agents.

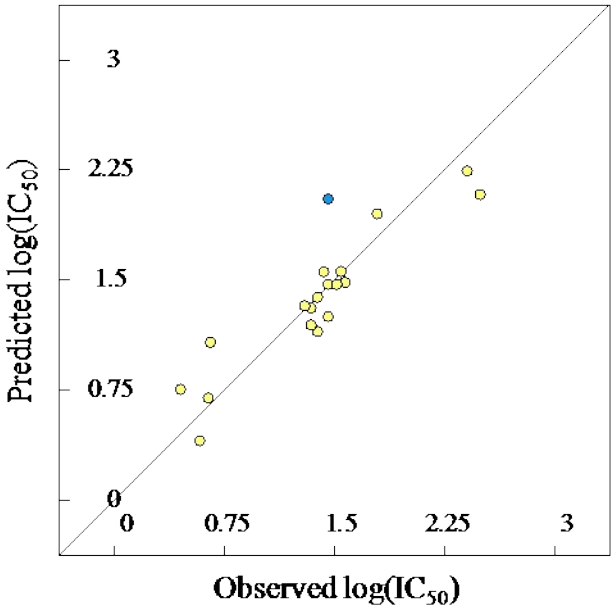

Figure S7 BMLR-QSAR model (3 descriptors) plot of correlations representing the mean observed *vs.* predicted log(IC_{50}) values of three carcinoma cell lines (GaLa, LuPiCi and LuCa) active agents (compound **11** is an outlier).