Grid Potential Analysis and Docking Studies on a Dataset of N-Arylsulfonyl-3-AcetylIndoles as Anti-HIV Agent

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A grid potential analysis employing the **AutoGPA** module in **MOE2009.10** was performed on a dataset of **42 molecules of N-arylsulfonyl-3-acetylindoles** as **anti-HIV agent**. The molecular docking simulations were also employed to position the inhibitors to their binding site to determine the most appropriate binding mode for different conformations of molecule. The uniqueness of AutoGPA module is that, it automatically builds the 3D-QSAR model on the pharmacophore based molecular alignment. The best AutoGPA 3D-QSAR model obtained in the present study gives the **cross-validated q^2 value** of **0.588** and **r^2pred value** of **0.701** among the fifty six 3D-QSAR model developed. Furthermore, the **steric** and **electrostatic contour maps** for AutoGPA model along with the 3D structure of protein (binding residue of active site) inlaid were obtained to better understand the structural requirements against HIV and interaction between binding residues of protein and inhibitors. The study shows that **hydrophobic** and **hydrogen bonding potential groups** are favorable for optimization of parent nucleus for better activity.

Background

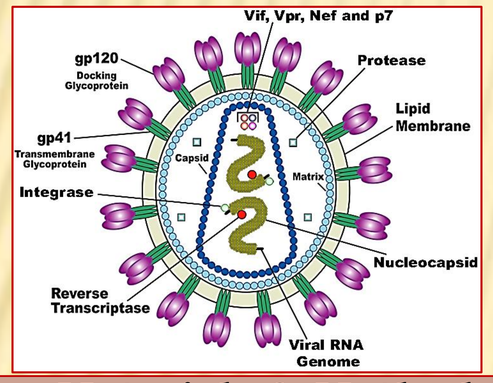
AIDS: Leading Global public health threat

Flaws of current therapy:

- Low oral bioavailability
- Development of drug-resistant HIV strains
- Long term toxicity

Challenges:

- Discovery & Development of new antiretroviral drugs with reduced toxicity
- Enhanced potency
- Different mechanism of action & better resistance profile
- Reduced prevalence of adverse drug-drug interactions



Materials & Methods

Data taken from literature: Synthesis & anti-HIV-1 activity of some N-arylsulfonyl-3-acetylindoles in vitro

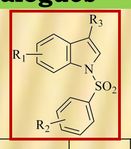
Source: Bioorganic & Medicinal Chemistry Letters; 20(2010):3534-3536

Compounds: 42 compounds of N-arylsulfonyl-3-acetylindoles active against C8166 cells (EC_{50} activity)

Computational Methods:

Molecular Modeling: MOE2009.10 and SYBYL 8.0

Table: Structure & activity (pEC_{50}) of N-arylsulfonyl-3-acetylindole analogues



Cmpd No.	R_1	R_2	R_3	Activity pEC50 (M)	Surflex Docking Score
01*	H	H	H	6.032	3.3769
02	H	4-CH_3	H	4.874	3.9371
03*	H	3-NO_2	H	6.131	5.1782
04	H	3-NO_2, 4-Cl	H	6.420	4.8127
05*	H	4-Br	H	4.690	3.5419
06*	H	4-Cl	H	4.909	4.0570
07	5-NO_2	4-Br	H	4.203	4.3979
08	5-NO_2	H	H	5.318	3.6853
09	5-NO_2	4-CH_3	H	4.580	4.0788
10	6-CH_3	H	H	6.051	4.0956
11	6-CH_3	4-Br	H	4.859	4.9591
12*	6-CH_3	3-NO_2	H	6.585	3.9074
13	6-CH_3	4-CH_3	H	5.523	4.9370
14	6-CH_3	4-C_2H_5	H	5.089	5.9300
15*	6-CH_3	4-Cl	H	6.143	4.4550
16	5-CN	4-CH_3	H	4.198	3.9453
17	5-CN	4-Br	H	4.158	2.9797
18	5-CN	H	H	5.491	3.8609
19	5-CN	4-Cl	H	4.305	3.7107
20	5-CN	3-NO_2	H	4.394	5.0225
21	5-CN	4-C_2H_5	H	5.381	4.7412
22	H	H	$COCH_3$	5.572	6.3285
23*	H	4-CH_3	$COCH_3$	4.507	5.7842
24*	H	3-NO_2	$COCH_3$	5.674	5.5133
25	H	3-NO_2, 4-Cl	$COCH_3$	5.465	5.2328
26	H	4-Br	$COCH_3$	4.093	5.6113
27	H	4-Cl	$COCH_3$	4.054	3.8191
28*	5-NO_2	4-Br	$COCH_3$	4.264	4.8947
29*	5-NO_2	H	$COCH_3$	4.339	4.6456
30	5-NO_2	4-CH_3	$COCH_3$	3.688	4.9212
31	6-CH_3	H	$COCH_3$	6.444	4.3350
32	6-CH_3	4-Br	$COCH_3$	5.368	6.2735
33	6-CH_3	3-NO_2	$COCH_3$	5.991	6.2671
34	6-CH_3	4-CH_3	$COCH_3$	4.859	4.5898
35	**6-CH_3**	**4-C_2H_5**	**$COCH_3$**	**6.886**	**7.3071**
36	6-CH_3	4-Cl	$COCH_3$	5.257	5.5371
37*	5-CN	4-CH_3	$COCH_3$	4.114	4.7752
38	5-CN	4-Br	$COCH_3$	3.697	3.9379
39	5-CN	H	$COCH_3$	4.240	4.7317
40	5-CN	4-Cl	$COCH_3$	4.264	5.1451
41	5-CN	3-NO_2	$COCH_3$	4.811	5.0174
42	5-CN	4-C_2H_5	$COCH_3$	4.516	6.8591

*Test Set

Grid Potential Analysis Workflow

Structure generation & minimization within MOE using MMFF94x force field & associated partial charge

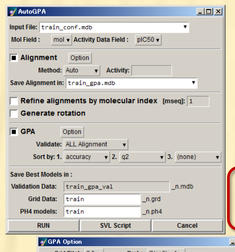
Data set division on activity ranking

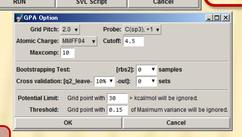
Test Set

Training Set

Conformation generation

Conformation generation of Training set (conf. import)





Ph4-based alignment (Pharmacophore elucidation)

Generate 3D-QSAR models for all alignments (GPA): Grid Potential Analysis

Rank models by predictive q^2

Best model (s)

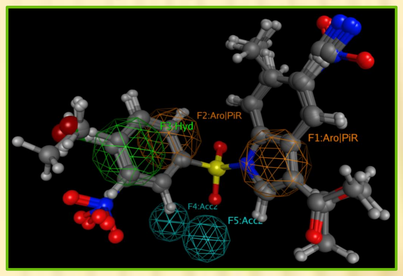
Pharmacophore + 3D-QSAR

+ Allowable Space

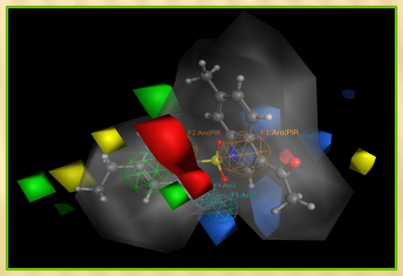
AutoGPA model

Grid Potential Analysis Contour plots

Pharmacophore alignment of training set

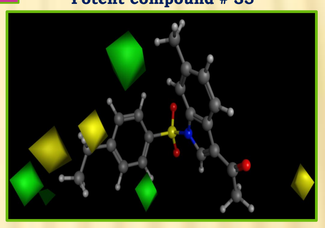


AutoGPA model of (cmpd:35) potent compound

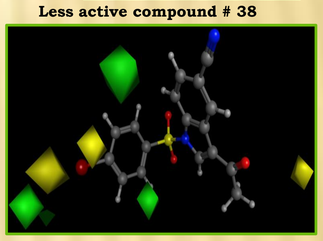


Steric Contours

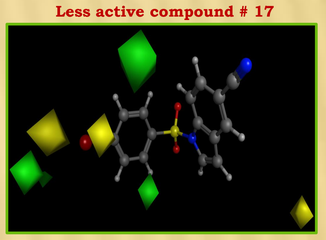
Potent compound # 35



Less active compound # 38

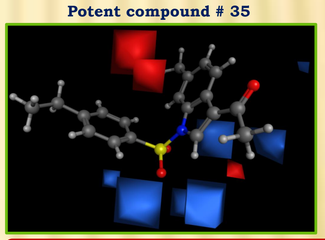


Less active compound # 17



Electrostatic Contours

Potent compound # 35



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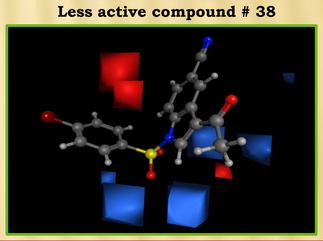

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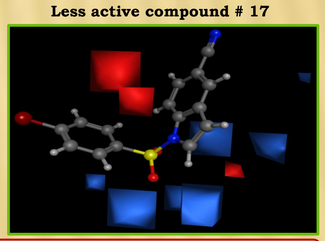
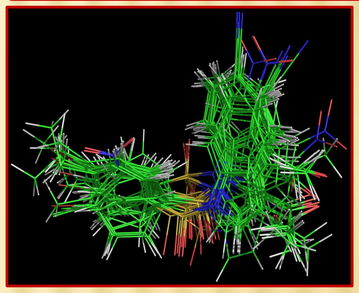
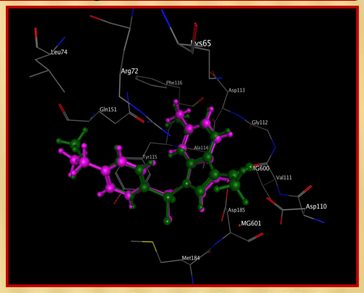


Molecular Docking Analysis

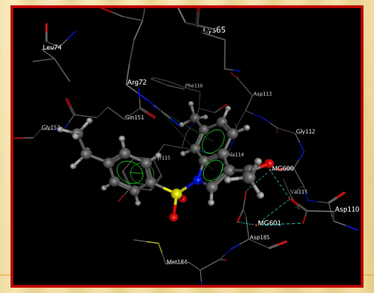


Superimposition of all docked molecule

PBD ID: 1RTD

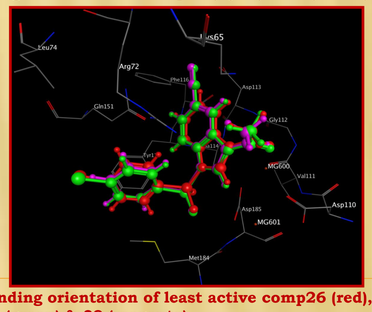


Binding orientation of comp14 (Cyan) & 35 (Green)



Ligand-interaction diagram for most potent ligand (comp35) which has best docking pose

Binding site amino acids:
Lys65, Arg72, Leu74, Asp110, Val111, Gly112, Asp113, Ala114,Tyr115, Phe116,Gln151, Gly152, Met184, Asp185

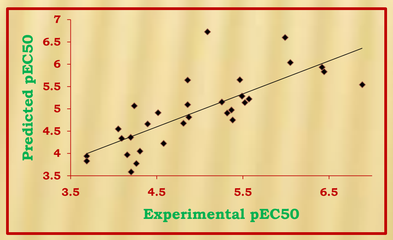


Binding orientation of least active comp26 (red), 38 (green) & 39 (magenta)

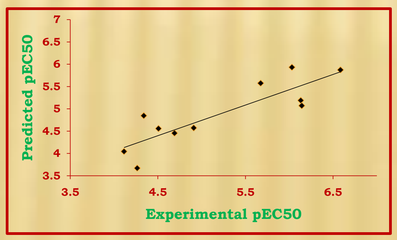
Results & Discussion

Statistical Data for AutoGPA model

PLS statistics	AutoGPA model
q^2	0.588
r^2	0.833
MSE	0.113
r^2_{pred}	0.701
maxcomp	10
r^2_m	0.732
Contribution	
Steric:	0.202
Electrostatic:	0.798



(a)



(b)

Experimental and Predicted activity (pEC50) for training (a) & test set (b) data

Conclusion

- Grid Potential analysis results concluded that hydrophobic substituent at R_1 & R_3 position provides better inhibition in the data set, whereas presence of hydrogen bonding groups at R_3 position further enhances the activity.
- Molecular Docking results are well accordance with grid potential analysis results which further supported the results obtained from 3D-QSAR analysis.

References

1. Comparative molecular field analysis (CoMFA).1. Effect of shape on binding of steriods to carrier proteins. Richard D. Cramer, David E. Patterson, Jeffrey D. Bunce, J. Am. Chem. Soc., 1988, 110, 5959-5967
2. AutoGPA: A novel 3D-QSAR method based on grid potential analysis and pharmacophore alignment. Naoyuki ASAKAWA, Seiichi KOBAYASHI, Junichi GOTO, Noriaki HIRAYAMA Poster presentation at InCoB 2011 and 1st ISCB-Asia Joint Conference (http://www.incob2011.org).

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