RHODES UNIVERSITY

Pharmacophore modelling, 3D-QSAR and ADME prediction for drug design in cardiovascular biology

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Acknowledgements

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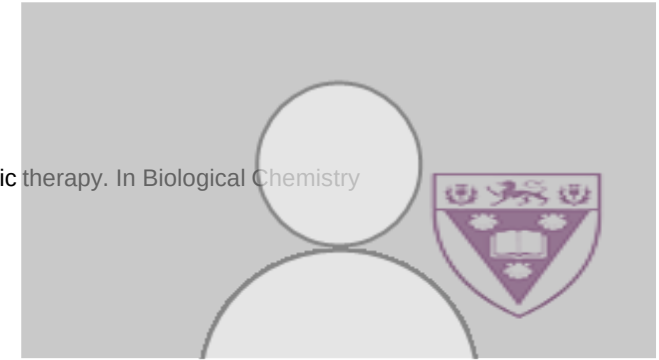
Introduction

- The world health organization (WHO) reported a pandemic in 2020, which resulted in deaths of many people caused by corona virus.
- The recent researches shows that patients with cardiovascular diseases are more at risk of the corona virus regardless of age and gender.
- High cholesterol in the blood increase the risk of cardiovascular diseases such as coronary heart disease and peripheral arterial disease.
- High cholesterol builds up in the arteries and the build up is known as atherosclerosis.
- There is the reduction of blood flow which results in cardiovascular disease which can lead to heart attack and stroke.

Belter, A., Skupinska, M., Giel-Pietraszuk, M., Grabarkiewicz, T., Rychlewski, L., & Barciszewski, J. (2011). Squalene monooxygenase-A target for hypercholesterolemic therapy. In Biological Chemistry (Vol. 392, Issue 12, pp. 1053–1075

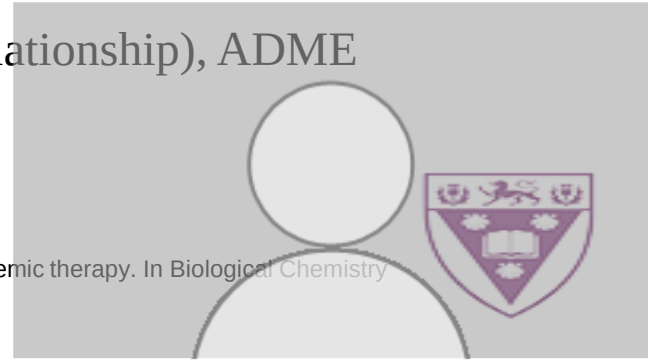


Introduction

- Statins are drugs used to lower cholesterol.
- The lipid hypothesis developed in 1976 by Hillary Newland
- They are inhibitors of HMG-CoA reductase, the rate limiting enzyme of cholesterol, they are used to cure cardiovascular diseases
- They block a substance that the body use to make cholesterol and lower the low-density lipoprotein (LDL)
- Moreover, they reduce the platelet activity and prevents the build-up on the arteries.
- Side effects of statins are muscle weakness, memory problems, joint or bone pain, cramps and stiffness, muscle aches and pain and tiring easily.

Aims of project

- Design or discover new drugs that can be used to lower cholesterol using drug repurposing.
- We employ the pharmacophore modelling, 3D-QSAR(Quantitative structure activity relationship), ADME (Absorption, Distribution, Metabolism and Excretion.



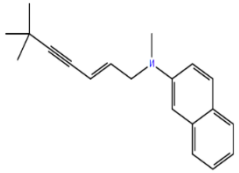
https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1

Asteur, U. L., & Schneider, G. (n.d.). Lecture 1 Pharmacophores & Molecular Similarity. W ww.darwin-online.org.uk

Belter, A., Skupinska, M., Giel-Pietraszuk, M., Grabarkiewicz, T., Rychlewski, L., & Barciszewski, J. (2011). Squalene monooxygenase-A target for hypercholesterolemic therapy. In Biological Chemistry (Vol. 392, Issue 12, pp. 1053–1075)..

Dataset

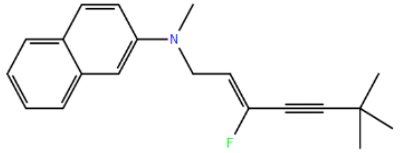
Anticholesterolemic squalene monooxygenase inhibitors from garlic extract



Terbinafine

$IC_{50} = 45$ nM

$pIC_{50} = 7{,}347$ M



SDZ SBA 586

$IC_{50} = 50\ nM$

$pIC_{50} = 7{,}301\ M$

TNSA

$IC_{50} = > 400\ \mu M$

$\mathrm{p}IC_{50} = 3{,}3979\ M$

Preparation of ligands

A database of 106 compounds were obtained from (Agnieszka Belter et al,.2011) and used for the project.

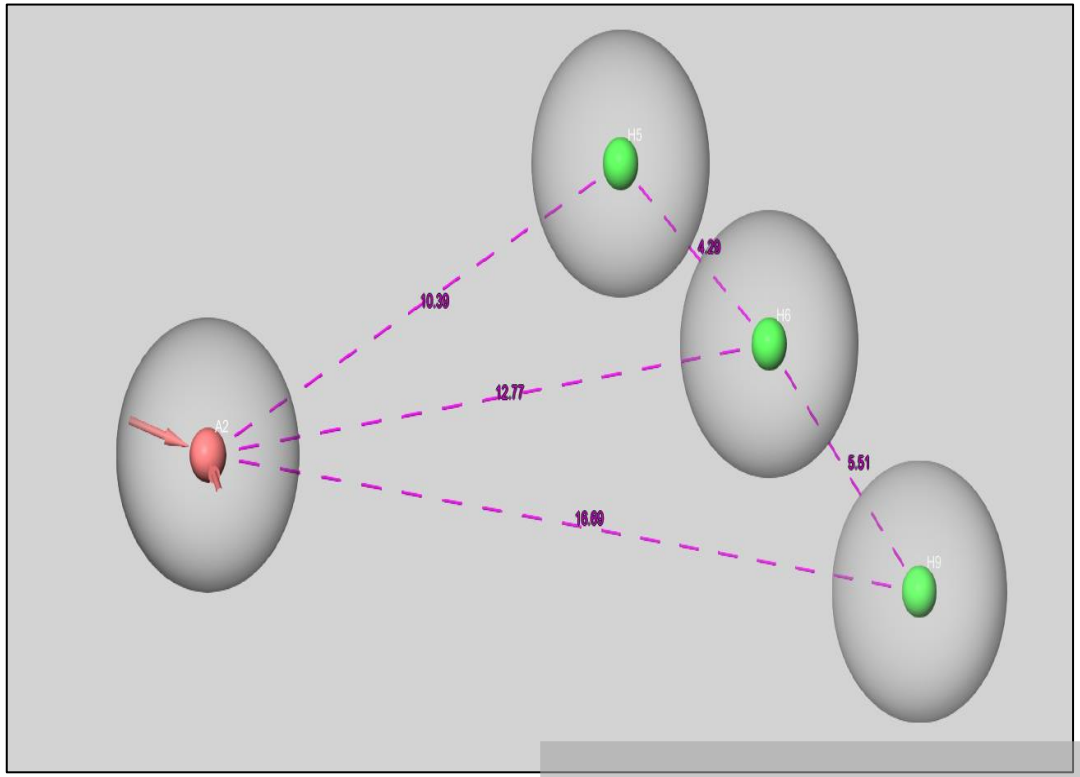
Abe, I., Seki, T., Umehara, K., Miyase, T., Noguchi, H., Sakakibara, J. and Ono, T., 2000. Green tea polyphenols: novel and potent inhibitors of squalene epoxidase. Biochemical and biophysical research communications, 268(3), pp.767-771.

Pharmacophore generation

A pharmacophore model is an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger or block its biological response, this is the definition as stated by IUPAC. (Kunal Roy et al.,2015).

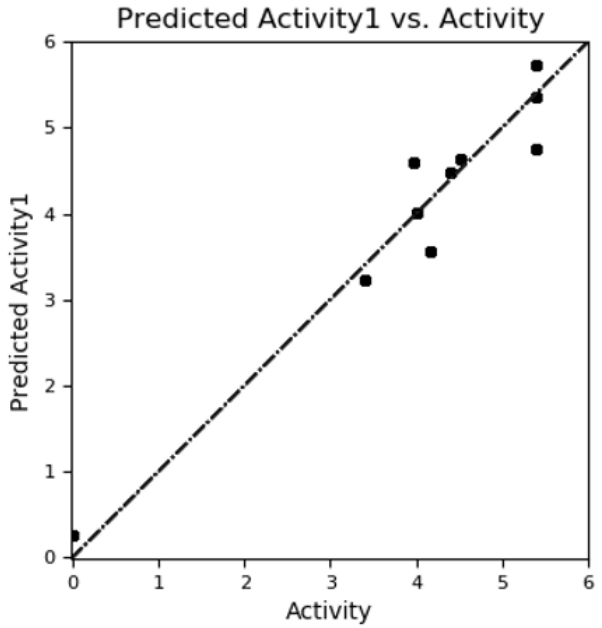
Pharmacophore	Survival Score	Site Score	Vector Score	Volume Score	Phase Hypo Score
AHHH_1	3,994	0,574	0,921	0,464	0,852
AHHH_2	3,954	0,479	0,903	0,407	0,849
AHHH_3	3,953	0,622	0,868	0,388	0,847
AHHH_4	3,919	0,634	0,863	0,358	0,847
AHHH_5	3,907	0,468	0,968	0,418	0,846
DHHH_1	3,879	0,568	0,951	0,461	0,845
AHHH_6	3,863	0,645	0,884	0,382	0,844
AHHH_7	3,851	0,577	0,833	0,370	0,843
AHHH_8	3,843	0,615	0,900	0,413	0,842
DHHH_2	3,854	0,585	0,969	0,442	0,832

A: Hydroogen bond acceptor; **H**: Hydrophobic, **D**: Hydrogen bond donor



The pharmacophoric model **AHHH_1** with distances in Å. The pink sphere with arrow, hydrogen bond acceptor, green (A), green sphere, hydrophobe

3D-QSAR and ADME-T results



Plot of actual value activity vs. predicted value activity of external training set

SD	R^2	R^2 *Scramble*	R^2 *CV*	F	P	Stability	RMSE	Q^2	Pearson-r
0.3116	0.9718	0.9358	-0.0587	206.8	7.08e-06	-0.000951	0.64	0.2091	1.0000

SD : Standard deviation of regression, R^2 **:** Regression coefficient, R^2 *CV* **:** Cross validation R-Squared, **F :** Variance ratio of model to the observed activity variance, **P**: Significance level of variance, **RMSE**: Root mean square error , Q^2**:** Cross validated coefficient

3.3 Physicochemical properties and ADME-T profile

Physicochemical properties	TNSA75	TNSA82	TNSA78
Mol MW	250.423	412.553	402.659
DonorHB	1.000	0.000	1.000
AccptHB	1.700	0.000	3.400
Log P	-3.563	-13.312	-6.048
PSA	22.799	0.000	33.098

Conclusion

In summary, by employing the combined in-vitro and in-vivo approach the insights into the structural framework of the compounds of squalene monooxygenase were investigated and provided in detailed by the atom based 3D-QSAR. Conclusively, there is a high chance that squalene could be replace the old targets in hypercholesterolemia therapy

Ganjoo, A., & Prabhakar, C. (2019). In silico structural anatomization of spleen tyrosine kinase inhibitors: Pharmacophore modeling, 3D QSAR analysis and molecular docking studies. Journal of Molecular Structure, 1189, 102–111

M. F. Khan, G. Verma, W. Akhtar et al., “Pharmacophore modeling, 3D-QSAR, docking study and ADME prediction of acyl 1, 3, 4-thiadiazole amides and sulfonamides as antitubulin agents,” Arabian Journal of Chemistry, vol. 12, no. 8, pp.