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Quantitative Structure Activity Relationships (QSAR) study of triazole-linked chalcone and dienone hybrid compounds as antimalarial agents.

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ABSTRACT

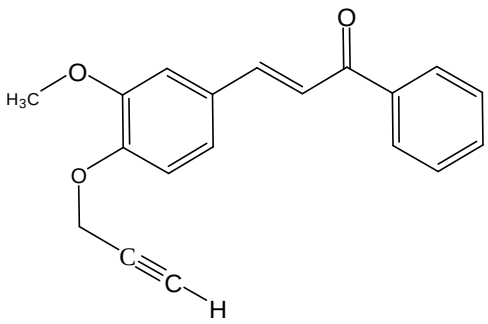
A QSAR study of triazole-linked chalcone and dienone hybrid compounds as antimalarial agents was performed with 38 (33 training + 5 test) compounds. Molecular modeling studies were performed using chemoffice 6.0 supplied by cambridgesoft. The structures were drawn using chemdraw and were converted to 3D. Energy was minimized and the lowest energy structure was used to calculate the properties. The regression analysis was carried out using a computer program called VALSTAT. The best models were selected from the various statistically significant equations. The analysis resulted in QSAR equation, which suggests that, n=32, r=0.896, r^2=0.803, adjusted squared multiple R=0.780, Standard error of estimate(s)=0.247 & validated $r^2(q^2)$ =0.642.

Keywords: Quantitative structure–activity relationships (QSAR); antimalarial activity; triazole linked chalcones; dinones hybrid compounds.

INTRODUCTION

Malaria remains one of the most widespread infectious diseases, and poses a great challenge to world health. This is underlined by staggering annual infection and mortality statistics.

Figure 1: Analogs of triazoles linked chalcones and dinones and their antimalarial activities



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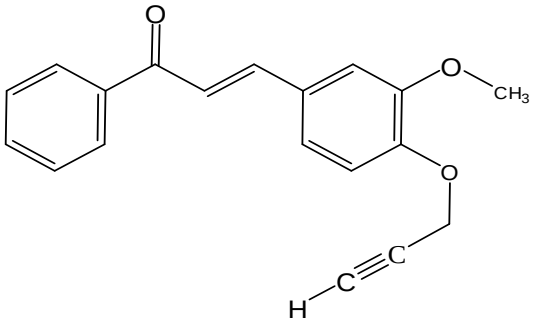

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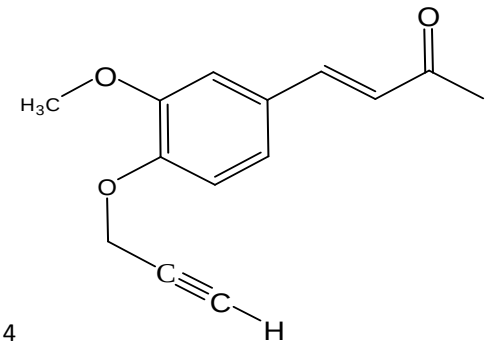

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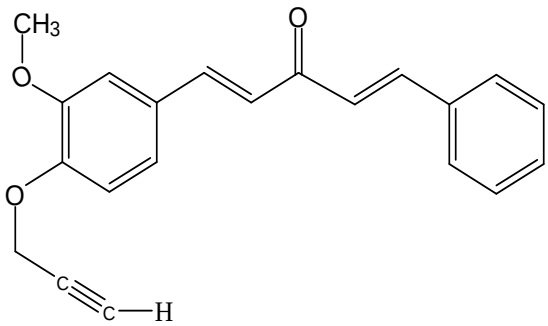

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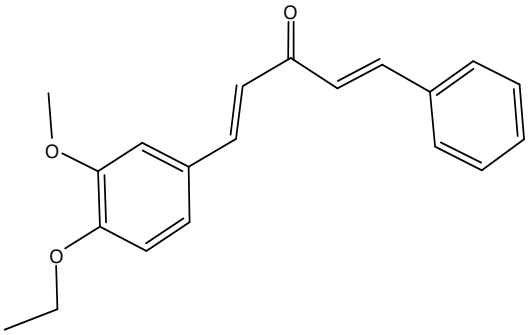

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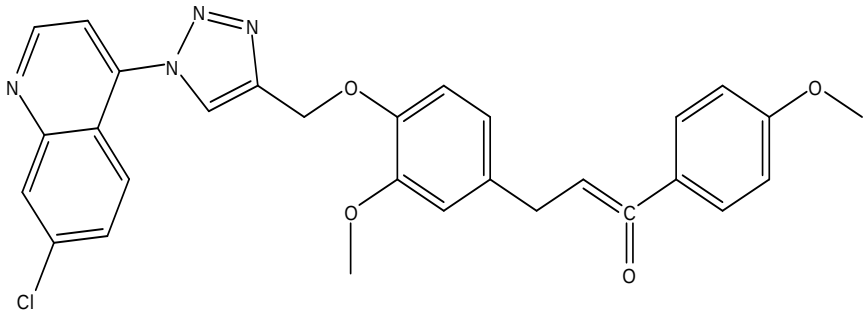


Table 1

Compound	R’	D10IC50 (µM)	Compound	R’	D10IC50 (µM)
1a	4’-OMe	9.7	**9d**		7.3
1b	2’,4’-diOMe	3.4	**9e**		3.9
1c	2’,3’,4’-triOMe	7.7	**10a**	4-F	5.2
2a	2,4-diOMe	>20	**10b**	2,4-diF	0.3
2b	2,3,4-triOMe	4.1	**10c**	2,4-diOMe	6.0
2c	2,4-diCl	3.3	**10d**	2,3,4-triOMe	7.4
2d	4-F	7.2	**10e**	2,4-diCl	4.1
2e	2,4-diF	>20	**11**	4-F	12.0
4	—	9.7	**12**	2,4-diF	0.8
5a	4’-OMe	11.8	**13a**	4’-OMe	2.8
5b	2’,4’-diOMe	5.4	**13b**	2’,4’-diOMe	1.3
5c	2’,3’,4’-triOMe	0.9	**13c**	2’,3’,4’-triOMe	1.3
5d	2,4-diCl	9.2	**13d**	2,4-diCl	1.4
5e	4-F	9.8	**13e**	4-F	1.7
5f	2,4-diF	11.9	**13f**	2,4-diF	1.4
7a	4’-OMe	2.9	**14a**	4’-OMe	3.0
7b	2’,4’-diOMe	1.5	**14b**	2’,4’-diOMe	5.1
7c	2’,3’,4’-triOMe	3.3	**14c**	2’,3’,4’-triOMe	2.5
8a	4’-OMe	0.6	**14d**	2,4-diCl	19.0
8b	2’,4’-diOMe	0.04	**14e**	4-F	9.4
8c	2’,3’,4’-triOMe	0.4	**14f**	2,4-diF	10.2
9a	2,4-diOMe	10.2	**16**		>20
9b	2,3,4-triOMe	5.4	**17**		>20
9c	2,4-diCl	3.7	**AZT**		>20

Resistance of malaria parasites to available antimalarial drugs remains a main challenge to the effective control of the disease. Varying levels of resistance to available classes of antimalarials has been reported for P. falciparum.[1,4] This has led to the adoption of combination therapies for the routine treatment of uncomplicated malaria, with particular emphasis on artemisinin-based combination therapies (ACTs).[5–7] However, recent evidence of diminished activity of artemisinins in Southeast Asia threatens this strategy.[8,9] With increasing resistance to available agents, intensive drug discovery efforts aimed at developing new antimalarial drugs or modifying existing agents are ongoing. Ideally, highly efficacious, novel antimalarial compounds will be developed to supplement available drugs.

Chalcones and dienones are structurally related compounds. Chalcones can be readily synthesized, and both naturally occurring and synthetic chalcones have been shown to exhibit notable in vivo and in vitro antimalarial activity. [10-13] AZT (Fig. 1) an antiretroviral agent approved for use in HIV infection was selected as one of the entities for hybridization to the chalcones and dienones for several reasons. Firstly, AZT is relatively hydrophilic, 30 and the resulting hybrids would therefore have enhanced aqueous solubilities and possibly improved oral bioavailability. Secondly, AZT is a nucleoside (deoxythymidine) analogue; nucleosides are biological molecules that are known to be actively transported into mammalian cells, 13 and therefore we hypothesized that linking AZT to the chalcones or dienones (7, 9 and 13) could improve oral bioavailability and facilitate delivery to intracellular sites of action. Furthermore, hybridization of the potentially antimalarial chalcones and dienones to a molecule with intrinsic anti-HIV activity might lead to the identification of molecules that exhibit both antimalarial and anti-HIV activity. The goal of quantitative structure-activity relationship (QSAR) studies are to relate the structural, chemical, physical and other properties of a compound to his biological activity. These physiochemical properties include hydrophobicity, topology, electrical properties, steric effects as well as others. The properties are described quantitatively so that a scoring function can be derived to judge the suitability of a compound as a potential therapeutic agent. These arouse our interest for establishing correlation between physicochemical properties of molecules with their biological activity. Further exploration of responsible properties may be help in development of more potent anti–microbial agents.

MATERIALS AND METHODS

The antimalarial data of triazole linked chalcones and dinones hybrid derivatives containing 38 compounds were taken from the research work of Guantai et al **(Table 1).** The biological activity data IC50 values (inhibitory concentration in µm/L) were converted to acquire negative logarithm (pIC) for QSAR analysis.

Table 2.Values of Descriptors in the final QSAR model

Comp.	BA	HOMO	log P	E14	Comp.	BA	HOMO	log P	E14
1a	5.0132	-8.6689	3.4215	3.629	**9d**	5.1366	-9.31918	2.7476	-5.95091
1b	5.4685	-8.5713	3.2951	2.3562	**9e**	5.4089	-9.46299	2.9057	-5.68754
1c	5.1135	-8.6269	3.1687	4.9552	**10a**	5.2839	-5.03773	5.5039	-0.45721
2b	5.3872	-8.82069	3.1687	5.18415	**10b**	6.5228	-8.82865	5.3572	-2.65183
2c	5.4814	-8.80685	4.6643	3.80996	**10d**	5.1307	-8.88746	5.8945	0.975189
2d	5.1426	-8.79522	3.706	5.41164	**10e**	5.3872	-9.12332	5.8663	-5.97699
4a	5.0132	-8.822	1.7442	4.6811	**11a**	4.9208	-9.257	0.7858	-6.24955
5a	4.9281	-8.63459	4.6643	7.12497	**12a**	6.0969	-8.85945	3.7464	-1.62904
5b	5.2676	-8.58499	3.7303	7.71369	**13a**	5.5528	-8.87144	2.8983	-5.60008
5c	6.0457	-8.73938	3.6039	-2.0367	**13c**	5.8866	-8.92835	2.6455	-7.92071
5d	5.0362	-8.68215	5.0995	2.33428	**13d**	5.8533	-9.27326	4.1411	-7.14217
5f	4.9244	-8.65873	4.2993	6.73712	**13e**	5.7695	-9.20086	3.1828	-5.5669
7a	5.5376	-8.55967	1.7442	-1.54957	**13f**	5.8538	-9.29836	4.1411	-7.3227
7b	5.8239	-9.00021	2.3367	-3.13799	**14a**	5.5228	-9.00715	5.8589	-2.90004
7c	5.4814	-8.89894	2.2103	-2.06197	**14b**	5.2924	-8.80557	5.7325	-5.69726
8b	7.3979	-4.92309	5.5039	0.119585	**14c**	5.602	-8.78601	5.6061	-4.92375
9a	4.9913	-8.68183	2.3367	2.66247	**14d**	4.7212	-9.00262	7.1017	-2.1597
9b	5.2676	-8.88927	2.2103	-1.31952	**14e**	5.0268	-8.95044	6.1434	-3.15274
9c	5.4317	-9.56481	3.7059	-6.0763	**14f**	4.9913	-8.9107	6.3015	-3.08551

The series was subjected to QSAR studies using CS Chem–Office Software version 2006 (Cambridge soft) [11]. Structures of all the compounds were sketched using the builder module of the program. These structures were then subjected to energy minimization using molecular mechanics (MM2) until the root mean square (RMS) gradient value became smaller than 0.1kcal/mol Å. Minimized molecules were subjected to re–optimization via Austin model–1 (AM1) method until the root mean square (RMS) gradient attained a value smaller than 0.01 kcal/mol Å using MOPAC. The descriptor values for all the molecules were calculated using "compute properties" module of program. Calculated thermodynamic descriptors included bend energy (Eb), heat of formation (Hf), total energy

(*ET*), stretch energy (*ES*), stretch bend energy (*ESB*) and torsion energy (*Etor*). Steric descriptors derived were Connolly accessible area (*CAA*), Connolly molecular area (*CMA*), Connolly solvent excluded volume (*CSEV*), exact mass (*EM*), molecular weight (*MW*), principal moment of inertia–X component (*PMIX*), principal moment of inertia–Y component (*PMIY*), principal moment of inertia–Z component (*PMIZ*), molar refractivity (*MR*) and ovality (*OVAL*) apart from this Partition coefficient calculated as *LOGP*.

Electronic descriptors such as electronic energy (*EE*), highest occupied molecular orbital energy (*HOMO*), lowest unoccupied molecular orbital energy (*LUMO*), repulsion energy (*REP*), VDW–1,4– energy (*E1,4*) and Non–1, 4–VDW energy (*Nvd*) were sequential Fischer test (*F*). The model was further validated on statistical parameter leave–one–out cross–validated square correlation coefficient (*R2 cv*), randomize biological activity data test (*Chance*) and test for outliers using Z–score value (*Zvalue*). Stepwise multiple linear regression analysis method was used to perform QSAR analysis employing in–house VALSTAT [12] program. The best model was selected on the basis of various statistical parameters such as correlation coefficient (*r*), standard error of estimation (std), F value etc.

RESULTS AND DISCUSSION

When data set was subjected to stepwise multiple linear regression analysis, in order to develop QSAR between antimalarial activity as dependent variables and physicochemical properties as independent variables, several equations were obtained.

The statistically significant equation Eq. (1) with coefficient of correlation (r^2 = 0.803) was Consider as model for antimalarial activity of triazole linked chalcones and dinones hybrids which explains for 0.612 % variance in inhibitory activity (Table 3) with low value of standard error of estimation (0.247). The model shown internal statistical significance level more than 95% as F–value =11.328

Model 1

BA= [10.1958 (± 0.545327)] +homo [0.495798(± 0.0629764)] +vdweng [-0.06345(± 0.0102468)] +logp [-0.132845(± 0.0305703)]

n=30, r=0.896158, r^2=0.803099, r^2adj=0.780379, variance=0.0612875, std=0.247563, F=35.3486
Standard Fmax value at 95% confidence=11.3282

Table 3 correlation matrix

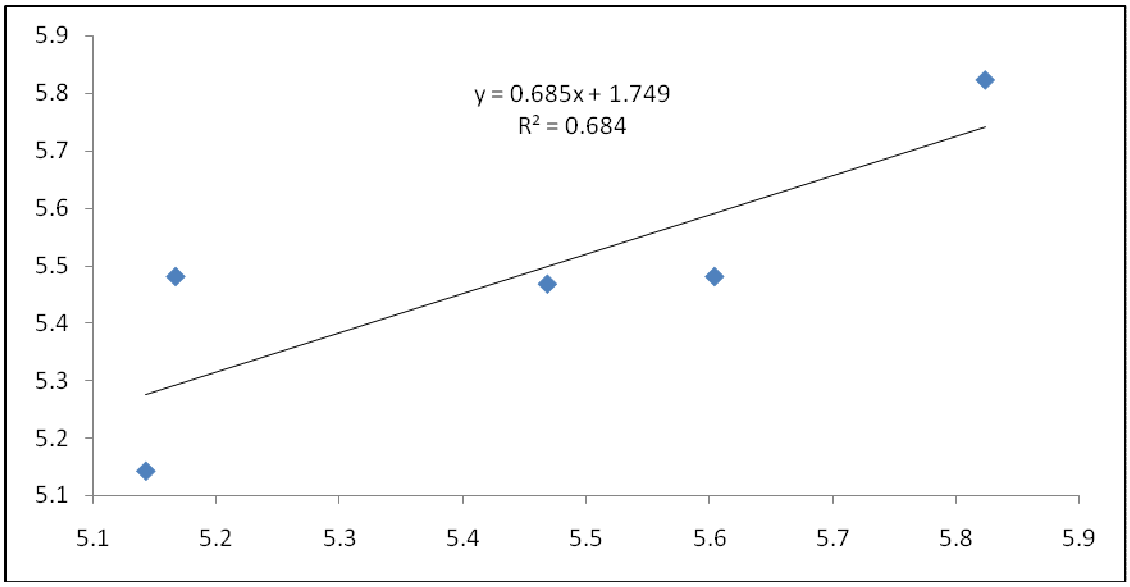
	HOMO	Vdweng	Log P
HOMO	1.00000		
vdweng	0.321931	1.000000	
Log P	0.168739	0.71088	1.0000000

The r^2-value accounts for 80.3% variance in observed activity value. Model 1 is the best equation in the QSAR study. The graph between experimental BA and predicted BA of training set compounds by using model 1 is shown in **Fig.1**. It shows that descriptor HOMO Energy (Homo), contribute positively towards antimalarial activity while VDW Energy and Log P contribute negatively towards antimalarial activity and this is the best model obtained.

Table 4 Observed vs predicted BA of the test set.

compound	BA observed	BA predicted
7c	5.60413	5.4814
2c	5.16669	5.4814
7b	5.8239	5.8239
2d	5.1426	5.1426
1b	5.4685	5.4685

Figure 2 Observed vs Predicted BA of the test set for Best Multiple Linear Regression model



CONCLUSION

The present work shows how a set of antimalarial activities of various triazole linked chalcone and dinone hybrid compounds may be treated statistically to uncover the molecular characteristics which are essential for high activity. The generated models were analyzed and validated for their statistical significance and external prediction power. The awareness and understanding of the descriptors involved in antimalarial activity of these compounds could provide a great opportunity for the ligand structures design with appropriate features, and for the explanation of the way in which these features affect the biological data upon binding to the respective receptor target. The results derived may be useful in further designing more novel antimalarial agents in series.

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