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Research article

AN IN-SILICO EVALUATION OF SOME NOVEL CURCUMIN DERIVATIVES FOR ANTIBACTERIAL ACTIVITY AGAINST METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS*

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ABSTRACT: The multiple drug resistance in MRSA (Methicillin resistant *Staphylococcus aureus*) has become a major clinical problem worldwide. Methicillin resistance (mediated by PBP2a protein) is a serious issue limiting treatment options and necessitating the search of newer safe and effective alternative treatment regimens. Aim of the present study was to evaluate the potential of the plant product 'Curcumin' and its derivatives as effective antibacterial agents by means of insilico based studies. Computer aided drug designing is an initial platform helpful to screen novel inhibitors and has tremendous application in the development of new drugs. In the present study a series of 16 derivatives of curcumin were constructed and optimized using chemsketch software.Molecular docking was performed using the GOLD (Genetic Optimization of Ligand Docking) software which is based on genetic algorithm (GA), to study the binding orientation of these derivatives into the PBP2a structure. Derivative 10 (1E,6E)-1,7-bis(3-hydroperoxy-4-hydroxyphenyl)hepta-1,6-diene-3,5-dione) showed best docking fitness value compared to other derivatives(including Curcumin). The molecular, physicochemical, and biological properties were calculated (through molinspiration cheminformatics software) for compounds showing the best docking scores. These compounds were further subjected to toxicity predictions using the Osiris software.

Key words: MRSA, Curcumin, Docking studies, Molinspiration, Osiris software

INTRODUCTION

The introduction of penicillin in the year 1941 had greatly improved the prognosis for patients with severe staphylococcal infections, but after a few years of clinical use, resistance appeared owing to production of β-lactamases (Kirby 1944). Methicillin was designed to resist β lactamase degradation, but Methicillin Resistant *Staphylococcus aureus* (MRSA) strains were soon identified. Since then, these strains have spread worldwide (Chambers 1997). Mechanism of methicillin resistance in *Staphylococcus* is due to production of an additional non-native penicillin binding protein- PBP2a (having low affinity for β-lactams), encoded by the '*mecA*' gene (Katayama *et.al.* 2000**).** Owing to multiple drug resistance, our armamentarium against MRSA has come down to a handful of exotic drugs including Vancomycin and Teicoplanin, representing the last line of defense against MRSA. Already Vancomycin resistant *Staphylococcus aureus* (VRSA) have been reported (Applebaum 2006).

Hence the bacterial resistance to many available antibacterial agents is a growing problem, and accordingly, the development of new antibacterial agents that could overcome the resistance problem has become the subject of an ongoing research (Othman *et.al.* 2013). The last decade has also witnessed increasing intensive studies on extracts and biologically active compounds isolated from plant species used for natural therapies or herbal medicine (Rios & Recio 2005). Computer based (insilico) docking studies, molecular modeling (bioinformatics and cheminformatics) are extremely fast and cost efficient tools, useful for scientists to select the best candidates for development and for rejection of those with a low probability of success(Khan *et.al.* 2013). One such plant product with multiple therapeutic attributes is 'Curcumin'. Curcumin or diferuloylmethane with chemical formula of (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) and other curcuminoids constitute the main phytochemicals of Curcuma longa L. (Zingiberaceae family) rhizome with the common name of turmeric.

This polyphenolic compound due to a variety of biological activities has been gained significant attention of researches all over the world (Moghadamtousi *et.al.* 2014, Anand *et.al.* 2008). It is used as a food coloring agent and in traditional Indian medicine for treatment of various diseases that include biliary disorders, anorexia, cough, diabetic wounds, hepatic disorder, rheumatism, blood purification and rheumatoid arthritis (Othman *et.al.* 2013).
Several studies have shown that Curcumin has various pharmacological activities including potent antioxidant, anti-inflammatory and antiviral activities (Aggarwal *et.al.* 2003, Prusty & Das 2005) , as well as anticancer activities against different forms of cancer (Othman *et. al.* 2013).In the recent years, antibacterial activity of the plant product Curcumin against MRSA have been reported. (You *et.al.* 2003, Masroor *et.al.* 2015). However poor pharmacokinetics (of Curcumin(Ravindernath and Chandrasekara , 1980) necessitated a search for newer Curcumin analogues (Mosely et.al.2007). The use of structural analogues of Curcumin has been used as one way of improving the bioavailability of Curcumin. (Anand *et. al*., 2007)
The present study is a step in this direction.
The present in- silico study was undertaken to design, dock, evaluate the molecular properties for drug likeness, bioactivity scores and toxicity prediction of the derivatives of Curcumin, in an attempt to search a novel compound having high target selectivity, low toxicity and better bioavailability for antibacterial activity against Methicillin resistant *Staphylococcus aureus* .

METHODOLOGY

Selection and preparation of the Target

The crystal structure of Penicillin Binding Protein 2a (PBP2a) was taken from the Protein Data Bank (PDB_ID:1VQQ**)** (Figure 1). After removing the statins from the binding site, the chain A was selected for docking studies. Hydrogen atoms were added to the enzyme.

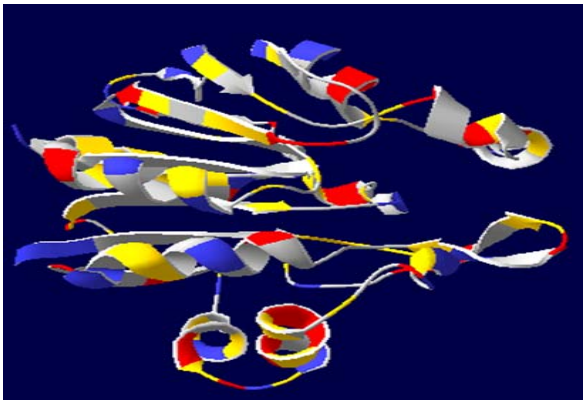

Figure 1: Structure of PBP2a

Designing of New Derivatives for Curcumin

By modifying the structure of Curcumin (Figure 2), 16 derivatives were designed for docking studies. The structures of these derivatives were constructed and optimized using ACD labs Chemsketch v 12.0. The chemical names of all these derivatives are provided in Table 1.
Structures of Curcumin and its Derivatives (Figures 2-5)

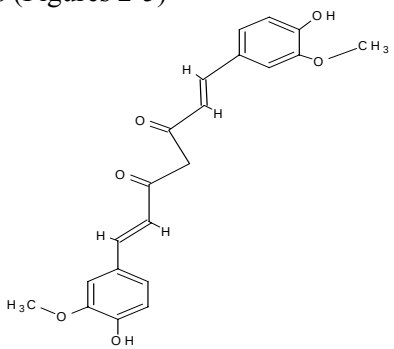

Fig.2: Curcumin (Original plant compound)
(1*E*,6*E*)-1,7-bis(4-hydroxy-3 methoxyphenyl)hepta-1,6-diene-3,5-dione

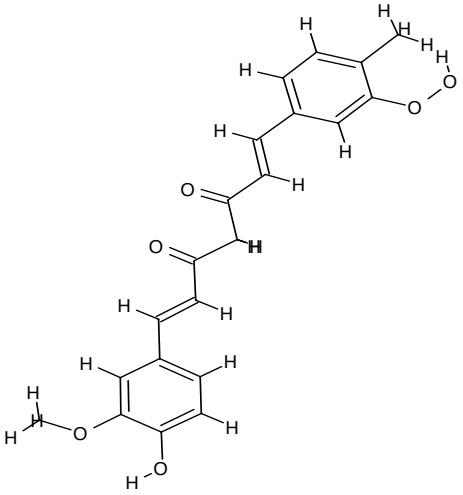

Fig.3: Curcumin 5
(1*E*,6*E*)-1-(3-hydroperoxy-4-methylphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione

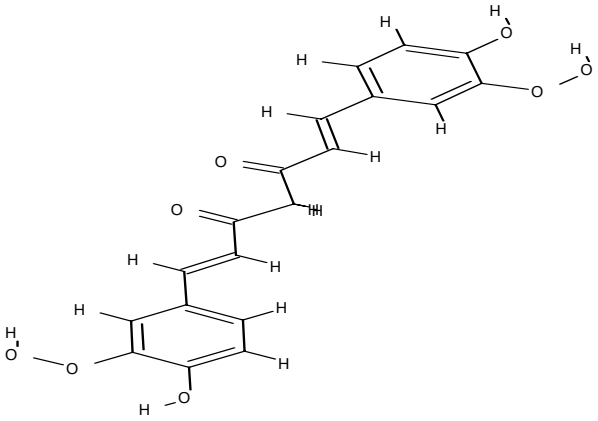

Fig. 4: Curcumin derivative 10
(1*E*,6*E*)-1,7-bis(3-hydroperoxy-4-hydroxyphenyl)hepta-1,6-diene-3,5-dione

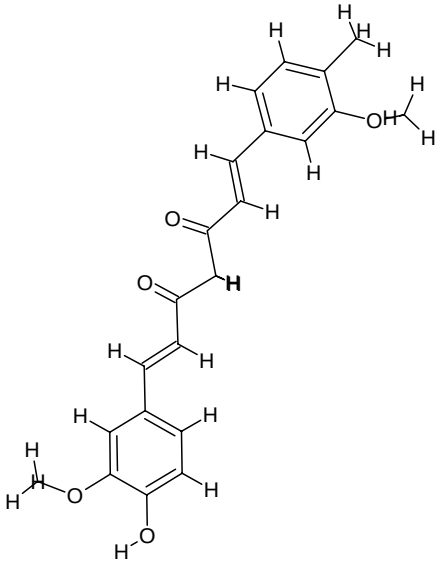

Fig. 5: Curcumin derivative 7
(1*E*,6*E*)-1-(4-hydroxy-3-methoxyphenyl)-7-(3-methoxy-4-methylphenyl)hepta-1,6-diene-3,5-dione

Table 1: Chemical Names of The Derivatives Of Curcumin

S.No	Derivative no	Chemical name
1.	Curcumin (original) or 1	(1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
2.	Curcumin 2	(1*E*,6*E*)-1-(4-hydroxy-3-methoxyphenyl)-7-(3-methoxyphenyl)hepta-1,6-diene-3,5-dione
3.	Curcumin 3	(1*E*,6*E*)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
4.	Curcumin 4	(1*E*,6*E*)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
5.	**Curcumin 5**	**(1*E*,6*E*)-1-(3-hydroperoxy-4-methylphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione**
6.	Curcumin 6	(1*E*,6*E*)-1-(3-hydroperoxy-4-hydroxyphenyl)-7-(3-methoxy-4-methylphenyl)hepta-1,6-diene-3,5-dione
7.	**Curcumin 7**	**1*E*,6*E*)-1-(4-hydroxy-3-methoxyphenyl)-7-(3-methoxy-4-methylphenyl)hepta-1,6-diene-3,5-dione**
8.	Curcumin 8	(1*E*,6*E*)-1-(3,4-dihydroxyphenyl)-7-(3-hydroperoxy-4-hydroxyphenyl)hepta-1,6-diene-3,5-dione
9.	Curcumin 9	(1*E*,6*E*)-1-(3,4-dihydroxyphenyl)-7-(3-hydroperoxy-4-hydroxyphenyl)hepta-1,6-diene-3,5-dione
10.	**Curcumin10**	**(1E,6E)-1,7-bis(3-hydroperoxy-4-hydroxyphenyl)hepta-1,6-diene-3,5-dione**
11.	Curcumin 11	(1*E*,6*E*)-1-(3-hydroperoxy-4-hydroxyphenyl)-7-(3-hydroperoxyphenyl)hepta-1,6-diene-3,5-dione
12.	Curcumin 12	(1*E*,6*E*)-1-(3,4-dihydroxyphenyl)-7-(3-hydroxyphenyl)hepta-1,6-diene-3,5-dione
13.	Curcumin 13	1*E*,6*E*)-1-(3-hydroperoxy-4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
14.	Curcumin 14	(1*E*,6*E*)-1-(3,4-dihydroxyphenyl)-7-(3-methoxyphenyl)hepta-1,6-diene-3,5-dione
15.	Curcumin 15	(1*E*,6*E*)-1-(3-hydroperoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
16.	Curcumin 16	(1*E*,6*E*)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
17.	Curcumin 17	(1*E*,6*E*)-1-(3,4-dihydroxyphenyl)-7-(3-hydroperoxy-4-methylphenyl)hepta-1,6-diene-3,5-dione

Docking Method

The binding site of PBP2a was identified using CASTp server. CASTp identifies and measures pockets and pocket mouth openings, as well as cavities. The program specifies the atoms lining
pockets, pocket openings, and buried cavities; the volume and area of pockets and cavities; and the area and circumference of mouth openings.

GOLD version 3.0.1 (Genetic Optimization of Ligand Docking) software which is based on genetic algorithm (GA) was used for molecular docking to study binding orientation of compound into the PBP2a structure. This method allows full flexibility of compounds and partial flexibility of protein .The designed derivatives were docked to the active site of the PBP2a.

The interaction of these Curcumin analogues with the active site residues are studied using molecular mechanics calculations. The parameters used for GA were population size (100), selection pressure (1.1), number of operations (10,000), number of island (1) and niche size (2).

Operator parameters for crossover, mutation and migration were set to 100, 100 and 10

respectively. Default cutoff values of 3.0 A° (dH-X) for hydrogen bonds and 6.0 A° for vanderwaals were employed. During docking, the default algorithm speed was selected and the binding site in the PBP2a was defined within a 10 A° radius with the centroid as CE atom of GLN207. The number of poses for each inhibitor was set 100, and early termination was allowed if the top three bound conformations of a compound were within 1.5A° RMSD. After docking, the individual binding poses of each compound were observed and their interactions with the protein were studied. The best and most energetically favorable conformation of each compound was selected.

Gold Score fitness function

Gold Score performs a force field based scoring function. It is made up of four components: 1. Protein-ligand hydrogen bond energy (external H-bond); 2. Protein-ligand vander waals energy (external vdw); 3.Ligand internal vander waals energy (internal vdw); 4.Ligand intramolecular

hydrogen bond energy (internal- H- bond). The external vdw score is multiplied by a factor of 1.375 when the total fitness score is computed. This is an empirical correction to encourage protein-ligand hydrophobic contact. The fitness function has been optimized for the prediction of ligand binding positions.

GoldScore = S (hb_ext) + S (vdw_ext) + S (hb_int) + S (vdw_int)

Where S (hb_ext) is the protein-ligand hydrogen bond score, S (vdw_ext) is the protein-ligand vander waals score, S (hb_int) is the score from intramolecular hydrogen bond in the ligand and S (vdw_int) is the score from intramolecular strain in the ligand.

Hence, the docking of compounds into the active site of PBP2a was performed using the GOLD software and the docking evaluations were made on the basis of GoldScore fitness functions. We preferred Gold fitness score than Chemscore fitness as Gold fitness score is marginally better than Chemscore fitness function.

ADMET Studies

The Curcumin derivatives showing the best docking scores (Figures 3-5) were used for ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) studies and physico-chemical parameters were predicted insilico by Molinspiration and Osiris software.

Smilies notations of the selected compounds were fed in the online molinspiration software (version -2014) for calculation of molecular properties (such as Log P, Total polar surface area,

Number of hydrogen bond donors and acceptors, Molecular weight, Number of atoms, Number of violations, Number of rotatable bonds and Volume) and prediction of bioactivity score for drug targets (GPCR ligands, Ion channel modulators, Kinase inhibitors, Nuclear receptor ligand ,Enzyme and Protease inhibitors). The toxicity parameters predicted were Mutagenicity, Tumorogenicity, Skin Irritation, and Reproductive Effect. Physico-chemical parameters like C log P, Solubility, Drug Likeness, Molecular Weight, and Drug Score were also predicted using Osiris property explorer software.

RESULTS AND DISCUSSION

After constructing the derivatives of Curcumin, optimizing them using chemsketch software , and having searched for the crystal model and the possible binding sites of PBP2a with CASTp server, we identified from the binding site analysis of PBP2a that, the binding pockets are identical in all chains and the largest binding pocket was taken for further docking studies.

Docking Images of Curcumin and Its Derivatives (Figure 6-9)

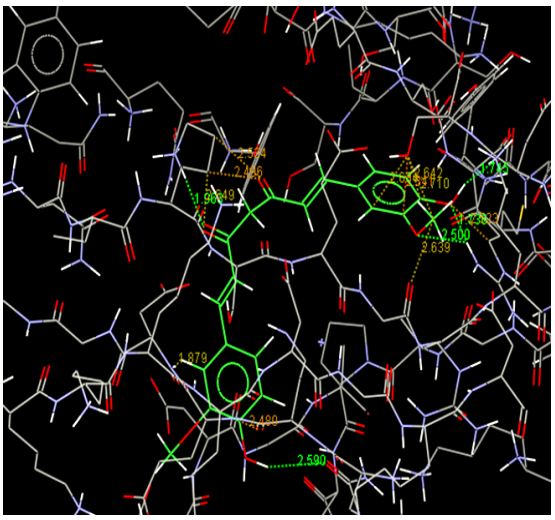

Fig. 6: Docking of Curcumin

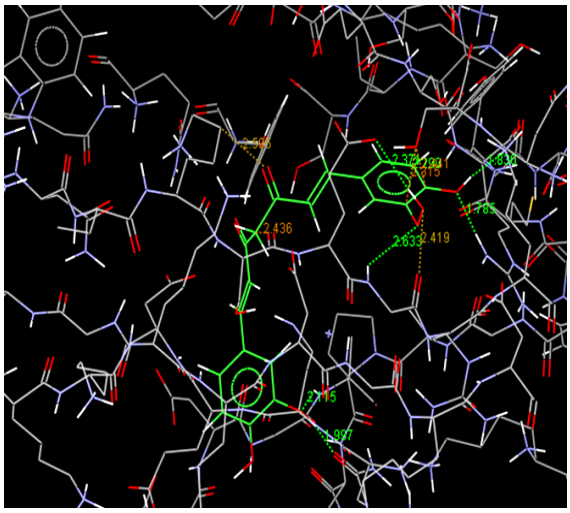

Fig. 7: Docking Image Of Derivative10

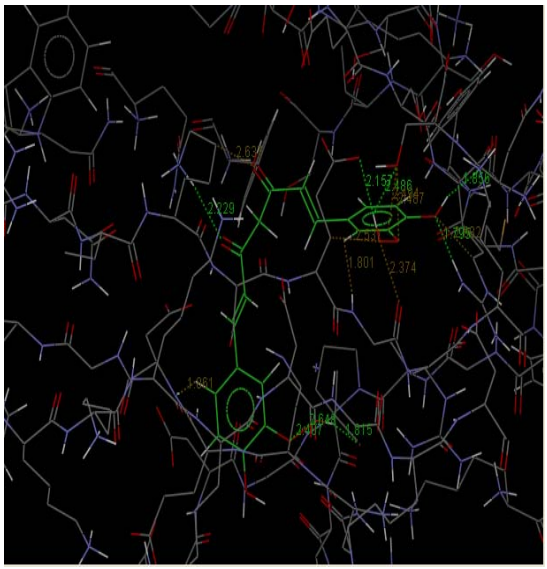

Fig. 8: Docking Image Of Derivative 5

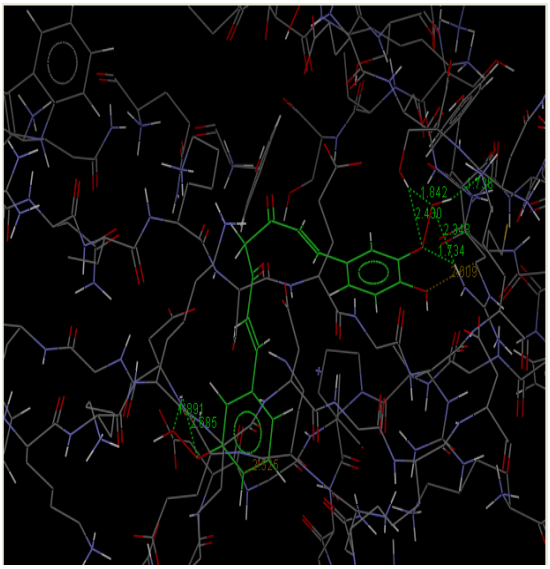

Fig.9: Docking Image Of Derivative 7

The crystal structures of PBP2a are similar and we have therefore taken 1VQQ (chain A) as representative structure for docking studies. The selected docked conformations of the PBP2a binding site are shown in Figure 6-9. The docked conformations revealed that all derivatives were located in the hydrophobic binding pocket surrounding the binuclear copper active site. In this study, all docked curcumin analogues were found to have some interaction between an oxygen atom of the compound and PBP2a. Moreover, these docked conformations also formed an H-bonding interaction with in the active site. In the binding pocket, common H-bonding interactions were formed between all docked compounds and GLY 135, GLN 137, GLN 140, HIS 143, GLU 145, GLN 145, GLN 207, ASP 209, HIS 232, THR 300, and HIS 311. In order to explain the binding of these compounds, the H-bonding interactions with the other surrounding residues in the hydrophobic binding pocket were also investigated. The docking results showed that Curcumin derivates have more affinity towards the protein than the molecule (Table 2).

Curcumin derivative 10 [(1E,6E)-1,7-bis(3-hydroperoxy-4-hydroxyphenyl)hepta-1,6-diene-3,5-dione)] showed best fitness value of 54.42, when compared to Curcumin and was higher than those of other derivatives, closely followed by derivative 5 and 7 (52.48 and 51.95, respectively). Out of the 16 derivatives, 7 derivatives showed better docking than the parent compound Curcumin. The structure of these compounds is provided in Figure 3-5. The chemical properties are tabulated in Table 3a.

Table 2: Docking Scores of Curcumin Derivatives With PBP2a

Fitness	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(in t)	Ligand name
49.94	12.67	41.58	0.00	-19.91	Curcumin
47.54	7.84	38.73	0.00	-13.55	Curcumin1
54.42	**22.08**	**32.85**	**0.00**	**-12.84**	**Curcumin10**
44.79	7.02	36.00	0.00	-11.72	Curcumin11
49.06	18.30	38.51	0.00	-22.19	Curcumin12
45.96	7.66	38.27	0.00	-14.32	Circumin13
49.02	21.16	29.76	0.00	-13.06	Curcumin14
45.55	10.32	36.55	0.00	-15.03	Curcumin15
48.96	19.97	31.41	0.00	-14.21	Curcumin16
48.95	7.45	40.03	0.00	-13.54	Curcumin17
45.74	6.75	38.05	0.00	-13.32	Curcumin2
50.60	11.25	37.21	0.00	-11.81	Curcumin3
47.67	3.13	40.63	0.00	-11.33	Curcumin4
52.48	**11.16**	**39.26**	**0.00**	**-12.66**	**Curcumin5**
50.73	8.01	43.05	0.00	-16.47	Curcumin6
51.95	**15.32**	**37.47**	**0.00**	**-14.89**	**Curcumin7**
50.50	14.67	38.33	0.00	-16.87	Curcumin8
51.25	20.84	31.33	0.00	-12.67	Curcumin9

Table 3a: Chemical Properties of Derivatives

Active Plant product and derivatives	MF	FW	COMPOSI-TION	MR Cm^3	MV (Cm^{3})	PARA CHOR (Cm^{3})	RI	ST (Dyne/cm)	DENSITY (g/cm^{3})	P (Cm^{3})	MI (Da)	NM (Da)	AM (Da)
Curcumn	$C_{21}H_{20}O_6$	368.3799	C(68.47%) H(5.47%) O(26.06%)	104.04 ±0.3	287.8 ±3.0	781.5 ±4.0	1.642 ±0.02	54.3 ±3.0	1.279 ±0.06	41.24± 0.5 10^{-24}	368.125988	368	368.3799
Derivative-10	$C_{19}H_{16}O_8$	372.32554	C(61.29%) H(4.33%) O(34.38%)	97.85 ± 0.3	249.8 ± 3.0	735.4 ±4.0	1.711 ± 0.02	75.0 ± 3.0	1.489 ± 0.06	38.79 ± 0.5 10^{-24} cm^3	372.084517	372	372.3255 Da
Derivative- 5	$C_{21}H_{20}O_6$	368.3799	C(68.47%) H(5.47%) O(26.06%)	103.89 ± 0.3	286.7 ± 3.0	781.1 ±4.0	1.644 ± 0.02	55.0 ± 3.0	1.284 ± 0.06	41.18 ± 0.5 10^{-24} cm^3	368.125988	368	368.3799 Da
Derivative -7	$C_{22}H_{22}O_5$	366.40708	C(72.12%) H(6.05%) O(21.83%)	106.99 ± 0.3 cm^3	305.7 ± 3.0 cm^3	804.2 ±4.0	1.617 ± 0.02	47.8 ± 3.0	1.198 ± 0.06	42.41 ± 0.5 10^{-24} cm^3	366.146724	366	366.4071 Da

AP= Active Plant Products, MF= Molecular Formula, FW= Formula Weight, MR= Molar Refractivity, MV = Molar Volume, RI=Refraction Index, ST = Surface Tension, DC = Dielectric Constant,MI= Monoisotropic Mass, NM = Nomimal Mass, AM Average Mass , P= Polalarizibility.

The compounds fulfilled Lipinski's rule and showed good drug likeness score (Table 3b). Lipinski's rule is widely used to determine molecular properties that are important for drug's pharmacokinetic profile in vivo.

Table 3b: Drug Likeness Score For Derivatives

COMPOUNDS	MI LOG P	TPSA	NATOMS	MW	N ON	NOHNH	NVIOLATIONS	NROTB	VOLUME
1.Curcumin	2.303	93.066	27.0	368.385	6	2	0	8	332.182
2.Derivative-10	2.063	133.522	27.0	372.329	8	4	0	8	315.095
3.Derivative-5	3.08	93.066	27.0	368.385	6	2	0	8	332.182
4.Derivative-7	3.397	72.838	27.0	366.413	5	1	0	8	340.725

According to Lipinski's rule of five (Lipinski *et.al.* 1997), a candidate molecule is more likely to be orally active if: a) the molecular weight(MW) is under 500(are easily transported, diffuse and absorbed as compared to heavy molecules), b) the calculated octanol/water partition coefficient (log P) is less than 5 (show good permeability across cell membrane.), (c) there are not more than 5 hydrogen bond donors (N 'OH' and 'NH' groups), (d) there are not more than 10 hydrogen bond acceptors (notably Oxygen and Nitrogen) and (e) No more than one number of violation (NViolations).

Total polar surface area (TPSA) was below 160 Å2 (means compound can easily bind to receptor). Numbers of rotatable bonds (NROTB) were acceptable and it is a simple topological parameter that measures molecular flexibility and is considered to be a good descriptor of oral bioavailability of drugs**.** (Veber *et.al*.2002).

These compounds were then taken for further calculation of bioactivity score (Table 3c).

Table 3c: Bioactivity Score of The Derivative

COMPOUNDS	MOLINSPI-RATION BIOACTI-VITY SCORE	GPCR LIGAND	ION CHANNEL MODU-LATOR	KINASE INHIBIT OR	NUCLEAR RECEPTOR LIGAND	PROT E-ASE INHI - BITOR	ENZYME INHI -BITOR
1.Curcumin	v2011.06	-0.06	-0.20	-0.26	0.12	-0.14	0.08
2.Derivative-10	v2011.06	0.05	-0.14	-0.24	0.19	-0.06	0.16
3.Derivative-5	v2011.06	0.02	-0.27	-0.28	0.13	-0.19	0.07
4.Derivative-7	v2011.06	-0.10	-0.28	-0.29	0.15	-0.21	0.02

The compounds under investigation showed to be biologically active molecules and can produce the physiological actions by interacting with GPCR(G Protein Coupled Receptors) ligands, nuclear receptor ligands, and inhibit protease and other enzymes.

According to the Osiris ADMET molecular property prediction results (Table 3d) though all the compounds have a good physiochemical profile, derivative 7 with high drug score and poor toxic effects qualified as a potent candidate for drug development.

Table 3d: OSIRIS ADMET Molecular Prediction Results Of the Derivatives

COMPOUNDS	MUTAGENIC	TUMORO-GENIC	IRRIT-ANT	REPRODU C-TIVE EFFECTS	C log P	SOLU-BILITY	MOL . WT	TPSA	DRUG LIKELI -NESS	DRUG SCORE
Curcumin	-	-	-	+	3.17	-3.35	382.0	93.06	-5.6	0.23
Derivative10	+	+	+	+	2.36	-5.83	386.0	133.5	-4.05	0.07
.Derivative-5	+	+	+	+	3.52	-5.54	382.0	93.06	-5.13	0.06
Derivative-7	-	-	-	-	3.71	-4.29	366.0	83.83	-5.02	0.34

CONCLUSIONS

Comparing the docking values, drug-likeliness, ADME profile and toxicity analysis of the derivatives to the parent compound Curcumin, the derivatives are found to have favourable scores thus suggesting that the problem of poor bioavailability, pharmacokinetics and solubility can be overcome by structural changes, and serve as promising lead candidates for alternative anti MRSA therapy. The docking results showed that Derivative 10 : [Chemical name : (1E,6E)-1,7-bis(3-hydroperoxy-4-hydroxyphenyl)hepta-1,6-diene-3,5-dione)] showed best docking fitness value than other derivatives including Curcumin. The study also revealed that the orientation of compounds in the PBP2a binding pocket surrounding the active site resulted in inhibition of enzyme activity. From the docking results we can conclude that these Curcumin derivatives can act as inhibitory compounds of PBP2a protein and exhibit a promising future to be developed into potent antimicrobial drugs. In silico approaches in the form of molecular, physicochemical, biological properties and toxicity analysis further increase our ability to predict and model the most relevant pharmacokinetic, metabolic and toxicity end points, helping to choose the most appropriate compound thereby accelerating the process of drug discovery. Further work on the synthesis of these Curcumin derivatives and invitro confirmation needs to be undertaken.

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