Research Article

QSAR and Docking Studies of Synthesized Diarylsulfonylurea Chalcone Hybrids as Anti-Inflammatory Agents

Bharat Kumar Bugata*, Kaladhar DSVGK
Dept of Biochemistry & Bioinformatics, GIS, GITAM University, Visakhapatnam, India.
***Corresponding author's E-mail:** bharatgitam@gmail.com

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ABSTRACT

The synthesis of a series of Diarylsulfonyl ureas Chalcone Hybrids is used to be evaluated for their anti-inflammatory activity using *in silico* methods. The activity of Diarylsulfonylurea Chalcone Hybrids using 2D Qsar and docking studies (Hex and igemDock) has been not reported till now. In the present studies, QSAR properties has shown higher molecular surface with 4e followed by 4u, 4c, 4i and 4d. Parameters like Volume, Refractivity, Polarizability and Mass has obtained more for 4y, Hydration energy is more with logP and less for 4m. The most five preferable structures (4f, 4g, 4m, 4u and 4v) having least minimization energies with docked structural comparison using hex v6.3. The five preferable structures (4a, 4b, 4e, 4s and 4y) has least minimization energies with the active binding sites and docked Structural Comparison using iGEMDOCK. Hence the proposed work has shown good anti-inflammatory activity with Synthesized Diarylsulfonylurea Chalcone Hybrids using *in silico* studies.

Keywords: Anti-inflammatory activity, Docking, QSAR, Synthesized Diarylsulfonylurea Chalcone Hybrids.

INTRODUCTION

Chalcones, a new class of glycosidase (α-glucosidase, α-amylase, and β-amylase) inhibitors acts against α-glucosidase shows non-competitive inhibition.[1] The effect of chalcones on serum glucose-lowering in hyperglycemic-normal rats highlighting novel compounds with strong anti-hyperglycemic properties.[2] Chalcones, considered as the precursors of flavonoids and isoflavonoids, area unit galore in edible plants, and have conjointly been shown to show a various array of medical specialty activities.[3]

Chalcones represent a vital cluster of the polyphenolic family, which incorporates an outsized variety of present molecules. This family possesses a stimulating spectrum of biological activities, as well as antioxidative, medication, medicament, anticancer, cytotoxic, and immunosuppressive potential.[4] Conversion of the difluorinated chalcones to difluorinated propanediones seems to provide better protection against inflammation.[5] The substitution of an aryl group of chalcone by a heterocyclic quinoline group would enhance the biological activity.[6]

The sulfonylurea, inhibits eosinophil survival in a manner similar to lidocaine.[7] Sulfonylurea's include several medications that act on β-cells to increase insulin release.[8] Diarylsulfonylurea (DSU) is a novel anticancer agent because of its unique DSU chemical structure, broad-spectrum antisolid-tumor activity in preclinical models.[9] DSUs with exceptionally broad-spectrum activity against syngeneic rodent solid tumors *in vivo* is described.[10]

Quantitative structure activity relationship (QSAR) approach is better for designing new drugs when the target is not known or if there are multiple targets.[11] The anticancer result of chalcones derivatives and new QSARs are able to facilitate within the understanding of the role of chalcones and of their analogues on cancer.[12] From the QSAR studies, Pharmacophores has been established for coming up with novel medication molecules.[13]

Sulfonylurea were the only drugs used to stimulate insulin secretion in patients with type 2 diabetes.[14] A need for rapid and efficient computational methods capable of differentiating compounds with acceptable biopharmaceutical and QSAR properties.[15]

Methodology

A series of new Diarylsulfonylurea-Chalcone hybrids compounds (4A-4y) has been studied by QSAR through Hyperchem v5.1 software. The compounds synthesized by Bharat *et al,* 2013 has been analyzed for anti-inflammatory activity through *in vitro* studies.[16]

Figure 1: Diarylsulfonylurea-chalcone bioactive pharmacophores

Protein related to anti-inflammatory activity of 5-LOX inhibitor has been retrieved from PDB (3V99) and has been used as receptor. Various ligands have been designed using Chemdraw ultra v10.0 and the 3D models are subjects to energy minimization using molecular

mechanics (MM2) with Chem3D ultra v10.0. The energy minimized structures are considered as ligands for docking.

Hex v6.3 and iGEMDOCK v2.1 are the free software that has good Protein-Ligand activity. The minimum energy obtained during docking process will be the good ligand. Lower the energy higher will be the stable and effective molecule.

Table 1: Diarylsulfonylurea-chalcone hybrids compounds (4A-4Y)

Compound	R	Yield [a] (%)	Molecular weight (g)	Molecular formula	M.p. (°C)
4a	C_6H_5	97	420	$C_{23}H_{20}N_2O_4S$	151.3
4b	4-MeC_6H_4	89	434	$C_{24}H_{22}N_2O_4S$	233.8
4c	4-$NMe_2C_6H_4$	88	463	$C_{25}H_{25}N_3O_4S$	150.5
4d	2,4-di$OMeC_6H_3$	84	480	$C_{25}H_{24}N_2O_6S$	163.3
4e	3,4, 5-tri$OMeC_6H_2$	88	510	$C_{26}H_{26}N_2O_7S$	198.6
4f	2-OHC_6H_4	86	436	$C_{23}H_{20}N_2O_5S$	258.9
4g	3-OHC_6H_4	82	436	$C_{23}H_{20}N_2O_5S$	185.2
4h	4-OHC_6H_4	89	436	$C_{23}H_{20}N_2O_5S$	185.7
4i	3-OEt,4-OHC_6H_3	89	480	$C_{25}H_{24}N_2O_6S$	174.3
4j	3-OMe,4-OHC_6H_3	93	466	$C_{24}H_{22}N_2O_6S$	178.6
4k	2-$NO_2C_6H_4$	86	465	$C_{23}H_{19}N_3O_6S$	231.8
4l	3-$NO_2C_6H_4$	89	465	$C_{23}H_{19}N_3O_6S$	172.2
4m	5-OH,2-$NO_2C_6H_3$	85	481	$C_{23}H_{19}N_3O_7S$	166.2
4n	3-FC_6H_4	84	438	$C_{23}H_{19}FN_2O_4S$	183.5
4o	4-FC_6H_4	87	438	$C_{23}H_{19}FN_2O_4S$	150.3
4p	2-ClC_6H_4	88	454	$C_{23}H_{19}ClN_2O_4S$	244.5
4q	4-ClC_6H_4	92	454	$C_{23}H_{19}ClN_2O_4S$	227.5
4r	2,4-diClC_6H_3	85	489	$C_{23}H_{18}Cl_2N_2O_4S$	220.5
4s	3-BrC_6H_4	84	499	$C_{23}H_{19}BrN_2O_4S$	214.2
4t	4-BrC_6H_4	81	499	$C_{23}H_{19}BrN_2O_4S$	244.2
4u	4-Allyl-OC_6H_4	85	476	$C_{26}H_{24}N_2O_5S$	162.2
4v	Phenylethene-yl	94	446	$C_{25}H_{22}N_2O_4S$	178.3
4w	Pyridin-3-yl	86	421	$C_{22}H_{19}N_3O_4S$	231.8
4x	Pyridin-4-yl	89	421	$C_{22}H_{19}N_3O_4S$	188.0
4y	Anthracen-9-yl	93	520	$C_{31}H_{24}N_2O_4S$	174.4

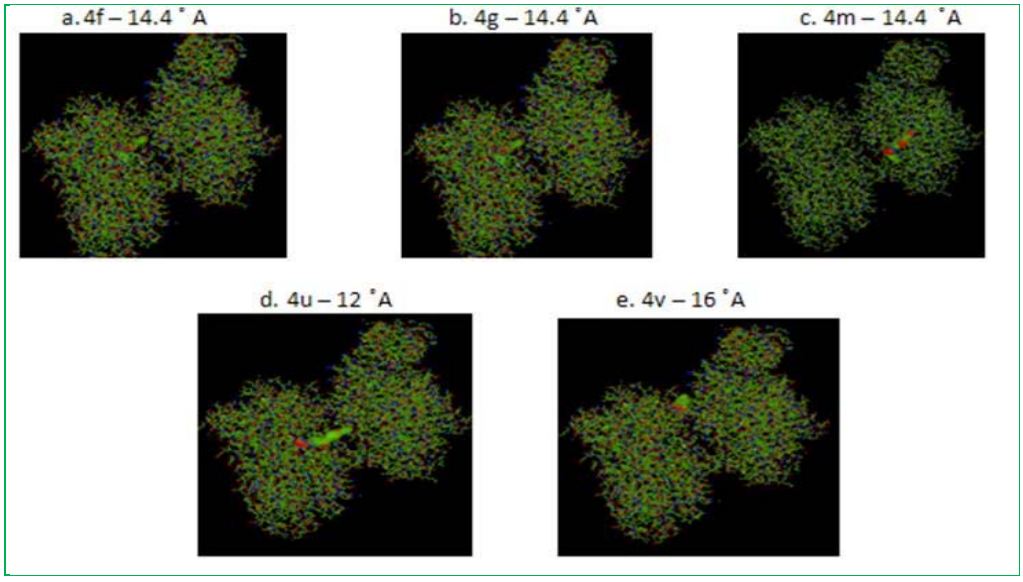

Figure 2: Docked structures for anti-inflammation using Hex

Table 2: QSAR Properties

Partial Charges (in electrons)	Approx Surface Area (in A^2 units)	Grid (in A^2 units)	Volume (in A^3 units)	Hydration energy (in Kcal/mol)	log P Values	Refractivity (in A°units)	Polarizabality (in A°units)	Mass (in amu)
4a	629.80	689.96	1166.97	-10.63	1.48	129.14	42.75	420.48
4b	678.45	726.67	1231.06	-9.40	1.64	133.42	44.58	434.51
4c	**740.86**	774.76	1315.39	-9.54	0.54	142.76	47.77	463.55
4d	**715.32**	757.98	1309.36	-12.42	-0.50	141.89	47.69	480.54
4e	**762.34**	**815.04**	1395.15	-13.64	-1.50	148.26	50.17	510.56
4f	641.46	712.66	1200.19	-15.02	0.46	130.74	43.39	436.48
4g	656.86	713.54	1202.22	-17.38	0.46	130.74	43.39	436.48
4h	650.18	709.46	1201.00	-17.48	0.46	130.74	43.39	436.48
4i	**717.79**	779.07	1322.5	-15.36	-0.19	141.87	47.69	480.54
4j	681.81	742.20	1263.48	-16.73	-0.53	137.12	45.86	466.51
4k	666.59	725.29	1232.38	-14.35	-1.26	134.85	44.59	465.48
4l	619.86	680.17	1149.00	-14.12	-1.26	134.85	44.59	465.48
4m	670.91	728.00	1239.80	**-20.89**	**-2.29**	136.46	45.23	481.48
4n	651.05	700.62	1186.69	-10.33	0.88	129.27	42.66	438.47
4o	647.20	700.93	1186.69	-10.31	0.88	129.27	42.66	438.47
4p	658.60	709.79	1211.30	-10.35	1.26	133.85	44.68	454.93
4q	670.75	721.43	1220.83	-10.26	1.26	133.85	44.68	454.93
4r	680.39	721.34	1241.28	-10.02	1.04	138.57	46.61	489.37
4s	686.55	735.01	1243.89	-10.32	1.54	136.67	45.38	499.38
4t	679.90	733.48	1240.84	-10.24	1.54	136.67	45.38	499.38
4u	**750.54**	802.97	1351.33	-13.04	1.23	144.68	48.70	476.55
4v	694.70	754.38	1271.25	-11.20	2.02	139.46	46.23	446.52
4w	619.52	691.50	1163.98	-12.33	0.14	125.64	42.04	421.47
4x	616.28	685.23	1156.57	-12.26	0.01	125.57	42.04	421.47
4y	686.12	806.06	**1406.52**	-11.35	1.63	**165.53**	**55.11**	**520.60**

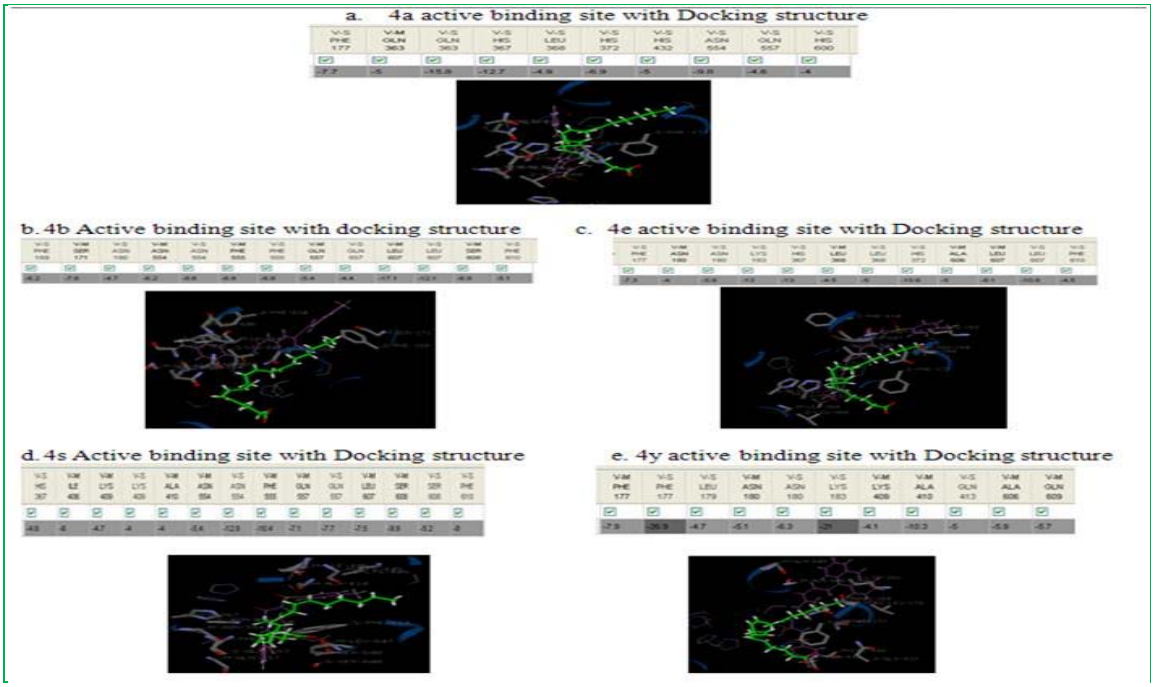

Figure 3: Docked structures for anti-inflammation using iGEMDOCK

RESULTS

Various ligands designed have been used to know the molecular parameters for the second generation drug discovery. QSAR properties provide the molecular parameters that have stability and activity of a ligand.

Table 2 shown higher molecular surface with 4e followed by 4u, 4c, 4i and 4d. QSAR parameters like Volume, Refractivity, Polarizability and Mass are obtained more for 4y. Hydration energy is more and log P less for 4m.

Hex dock software using compounds (4A →4Y) has been conducted in the present work. The most five preferable structures (4f, 4g, 4m, 4u and 4v) having least minimization energies in molecular studies with the docked structural comparison is provide in Table 3 and Figure 2.

Table 3: Best molecules for anti-inflammation using Hex

S.No.	Energy Minimization
4f	-313.18
4g	-330.58
4m	-310.04
4u	-316.57
4v	-310.38

iGEMDOCK Software Using Compounds (4A →4Y) has been conducted. The five preferable structures (4a, 4b, 4e, 4s and 4y) having least minimization energies in molecular studies with the active binding sites & Docked Structural Comparison has been shown in Table 4 and Figure 3. Based on distance, 4u (12˚A) has shown good result compares to other synthesized compounds.

Table 4: Anti-inflammation compounds using iGEMDOCK

S.No	Energy Minimization
4a	-199.55
4b	-124.64
4e	-129.25
4s	-127.47
4y	-123.55

DISCUSSION

Anti-inflammation is the property of the diseases that links to the pathways of aging diseases.[17] A substance that reduces inflammation linked to Diabetes, cancer, etc are anti-inflammatory compounds used to reduce the risk of age related diseases.

Chalcones were regularly synthesized to guage their restrictive effects on the activation of mast cells and neutrophils and the inhibitory effect on phlogist-induced hind-paw edema in mice. A series of chalcones and related compounds were prepared by Claisen-Schmidt condensation of appropriate acetophenones with appropriate aromatic aldehyde and the anti-inflammatory activities of these synthetic compounds were studied on inhibitory effects on the activation of mast cells and neutrophils.[18]

Chalcones and their derivatives were previously synthesized and evaluated for their anti-inflammatory activity. *In vitro*, chalcones inhibited degranulation and 5-lipoxygenase in human neutrophils.[19] The process of degranulation of mast cells and neutrophils contributed to inflammatory diseases. Activation of microglial cells and macrophages is believed to worry in inflammatory, infectious and chronic diseases of the central nervous system. Combining the potent inhibition of chemical mediators free by the degranulation of mast cells or neutrophils and from the activated microglial cells or macrophages, might cause a promising antiinflammatory agent for the treatment of peripheral and central inflammation.[20]

Chalcone derivatives have a potential role in modulating the inflammatory process.[21] The α,β-unsaturated organic compound moiety in each 2',4',6'-Tris(methoxymethoxy) chalcone (TMMC) and chalcones might be vital in mediating this impact. to research the structural needs of TMMC derivatives for medication effects.[22] Methyl and hydroxy substituted chalcones were found to be cytotoxic in vitro whereas only hydroxy substituted chalcones could reduce ascites tumour in animals.[23]

Scientific investigations on the bioavailability of chalcones from food sources are limited but variety of synthetic chalcones (SCs) has been reported to possess a wide range of pharmaceutically important biological activities. Plethora of literature has accumulated in the recent years suggesting the role of chalcones and its derivatives as an anti-inflammatory, anticancer, and antioxidant agents.[24] Chalcones have also been reported as inhibitors of angiogenesis, because the process of angiogenesis (formation of new blood vessels) is proved to be crucial for the survival and proliferation of solid tumors. Arresting the angiogenesis process has been considered as a potential target for the development of anticancer drugs.[25]

Chalcones square measure ready by condensation Aryl ketones with aromatic aldehydes in presence of appropriate condensation agents. They endure a spread of chemical reactions and square measure found helpful in synthesis of kind of heterocyclic compounds. Chalcones are used as intermediate for the preparations of compounds having therapeutic value.[26] Chalcones exert their cytoprotective actions via activation of specific transcriptional factors and upregulation of endogenous defensive pathways, like phase II enzymes and therefore the stress macromolecule protoheme oxygenase-1 (HO-1).[27]

QSAR study discovered that the presence of electron-withdrawing teams in B-ring and electron-donating teams in A-ring of chalcones was necessary for inhibition of LPS-induced IL-6 expression.[28] Naringenin chalcone inhibited the assembly of TNF-α, MCP-1, and gas (NO) by LPS-stimulated RAW 264 macrophages in

a very dose-dependent manner. Co-culture of 3T3-L1 adipocytes and RAW 264 macrophages markedly magnified the assembly of TNF-α, MCP-1, and NO compared with the management cultures; but treatment with naringenin chalcone dose-dependently inhibited the assembly of those proinflammatory mediators.[29] The potent synthesized structure 2′,5′-dihydroxychaclones have anti-inflammatory drug effects.

The potent repressive result of 2′,5′-dihydroxy-dihydrochaclones on NO production in LPS-activated scavenger cell, in all probability through the suppression of iNOS supermolecule expression, is planned to be helpful for the relief of septic shock.[30] chalcones in inflammation that controls both the immune system and tumorigenesis. Chronic subclinical inflammation is a part of insulin resistance syndrome. Drugs which are effective in dampening such subclinical inflammation may provide protection against development of diabetic complications, which may be reflected partly as a protection provided by drug in experimental models of inflammation.[31]

Inflammatory pathways are shown to mediate the survival, proliferation, invasion, ontogeny and metastasis of tumors.[32] QSAR may be a helpful suggests that for maximizing the efficiency of a brand new lead compound. Within the lead optimization part of the artificial project, numerous QSAR procedures with the help of computer-technology can be planned. The QSAR procedures are supported physical organic ideas and involve calculation operations. Since inflammation may be a complicated development involving interrelationships between body substance and cellular reactions through variety of inflammatory mediators.[33] The developed QSAR model approach models provide pertinent information into the physiochemical properties governing the investigated biological properties.[34]

Mono- and di-O-prenylated chalcone derivatives designed on the basis of a homology derived molecular model of 5-lipoxygenase (5-LOX). The compounds were docked into 5-LOX active site and the binding characteristics.[35] The usefulness of computational chemistry to the pharmaceutical (and chemical) industry depends on its ability to provide knowledge about the structure and properties of substances and the transformations they undergo. The complexness of realistic model calculations and therefore the time-critical nature of the results need superior computing to discover and test ideas for novel compounds that will be useful in therapeutic intervention.

In computational experiments, chemists use molecular modeling programs, computer graphics and databases of 2D and 3D molecular structures to explore chemical structures and physical properties. The goal of computational of computational chemistry is to enhance the creative process of solving molecular level problems in chemistry.[36]

CONCLUSION

The present QSAR and docking studies diarylsulfonyl ureas chalcone hybrids can be considered as anti-inflammatory compounds. Further analysis has to be conducted showing anti-cancer and anti-D2M activities that are related to ageing diseases.

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