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QSAR STUDIES ON PPARγ AGONIST 2- ALKOXYDIHYDROCINNAMATES WHICH USE AS LEAD MOLECULE FOR THE SYNTHESIS OF NEW COMPOUNDS TO TREAT DIABETES AND NEUROLOGICAL DISORDER

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ABSTRACT: Quantitative Structure-Activity Relationships (QSAR) is based on the assumption that the activity of a certain chemical compound is related to its structure. More precisely, this approach says that the activity or the property is related to the chemical structure through a certain mathematical algorithm or rule. Quantitative structure-activity relationship (QSAR) analysis used to understand the structural factors responsible for PPAR-γ agonistic activity of some 2-Alkoxydihydrocinnamates. Several pharmacophore-based models indicated the importance of steric, hydrophobic, and hydrogen bond acceptor groups to agonistic activity.

INTRODUCTION: QSAR is the one technique which is helpful to optimize the lead molecule and identifying drug targets via Bioinformatics tools. They can be used to analyze the target structure for the possible binding site, generate candidate molecules, and check for their drug-likeness. Docks these molecules with the target rank them according to their binding affinity and further optimize the molecules improve binding characteristics. Development of Peroxisome proliferators' gamma (PPARγ) Agonist molecules using a combination of Bioinformatics tools like QSAR and docking provides a faster, cost-effective, and reliable methodology.

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These tools have now become an integral part of lead discovery, SAR development, and lead optimization. Inflammation, mitochondria dysfunction, and oxidative stress play major roles in Parkinson's disease (PD), where the primary pathology is the significant loss of dopaminergic neurons in the substantianigra (SN). Current methods used to treat PD focus mainly on replacing dopamine in the nigrostriatal system. However, with time, these methods fail and worsen the symptoms of the disease.

This implies there is more to the treatment of PD than just restoring dopamine or the dopaminergic neurons, and that a broader spectrum of factors must be changed to restore environmental homeostasis. Pharmacological agents that can protect against progressive neuronal degeneration, increase the level of dopamine in the nigrostriatal system, or restore the dopaminergic system offers various avenues for the treatment of PD are drugs that reduce inflammation, restore mitochondrial

function, or scavenge free radicals have also been shown to offer neuroprotection in various animal models of PD.

The activation of peroxisome proliferator receptor–gamma PPARγ has been associated with altering insulin sensitivity, increasing dopamine, inhibiting inflammation, altering mitochondrial bioenergetics, and reducing oxidative stress - a variety of factors that are altered in PD. Therefore, PPARγ activation may offer a new, clinically relevant treatment approach to neuroinflammation and PD related neurodegeneration. Peroxisome Proliferator-Activated Receptors (PPARs) belong to the nuclear receptor family, which are to be defined as transcription factors activated by ligands (some of the fatty acids and their lipids metabolites).

Identified in 1990 as a response to the Peroxisome Proliferation, their role in the control of lipids and lipoproteins metabolism, glucose homeostasis, as well as in the case of cell differentiation has been observed [1]. Recently it has been demonstrated that they interfere in the development of tumor process, in the control of the inflammatory response, and of the associated disorders [2, 3]. The research results (on both humans and animals), clearly demonstrate that molecules derived from TZD family (troglitazone, pioglitazone, rosiglitazone), are capable of correcting significant insulin resistance *in-vivo*. There were proposed few hypotheses for explaining how PPARγ activation with TZD may improve insulin resistance. These hypotheses do not exclude one another. PPARγ activation involves adipocytes differentiation and fatty acid storage in adipose tissue (diminishing circulant lipids, which allow the muscle a higher sensitivity to insulin). Gaining weight at animals treated with TZD comes in favor of these hypotheses.

Other versions would be that PPARγ activation modifies the expression and adipocyte protein secretion like leptine and TNF-α, which may play a role in insulin-resistance [4]. Though there are few human data in favor of this mechanism, it is not excluded for the adipocytes to produce other factors, not yet identified, under the control of PPARγ. It is also possible that encoded genes of the proteins involved in insulin action to be target PPARγ genes and their transcriptional activation through TZD to increase the action of insulin in cells. Due to these hypotheses, there are data which demonstrate that PPARγ activation with rosiglitazone enhances the anti-lipolitic effect of insulin in the cells.

So, it is probable that PPARγ is one of the action mechanism actors of insulin in adipocytes. Recently, it has been postulated the PPARγ role in the inflammatory process and atherosclerosis [8]. PPARγ expression has been emphasized in the spleen, human monocytes, and backbone precursor cells. PPARγ expression is notably increased in rat activated macrophages, and the treatment with TZD inhibits the production induced by activating markers. In human activated monocytes, PPARγ agonists inhibit the production of the pro-inflammatory cytokines: TNF-α, IL-1, IL-6 [5, 6].

These effects may interfere in atherosclerosis, at the level of atheroma where the activated macrophage products (MMP-9 gelatinase, IL-1, TNF alpha) play an important role. Other studies suggest that PPARγ may interfere with apoptosis and that this function could be used against the proliferation of different tumor cells which strongly express PPARγ (colon, prostate) [7, 8, 9]. In the vascular wall, PPARs interfere with chemotaxis and cell adhesion of monocytes, T lymphocytes, and eosinocytes. In the human endothelial cells, TZD inhibits monocytes chemotactic protein-1 (MCP-1) transcription, a protein which plays a major role in the initiation of atherosclerotic inflammatory process [10].

MATERIALS AND METHODS: The series of compounds which was subjected to QSAR analysis was 2- alkoxy dihydro cinnamates [11], the series is listed in **Table 1**. In this table, EC_{50} value (µM) refers to the concentration of compounds required to activate 50% of the receptors.

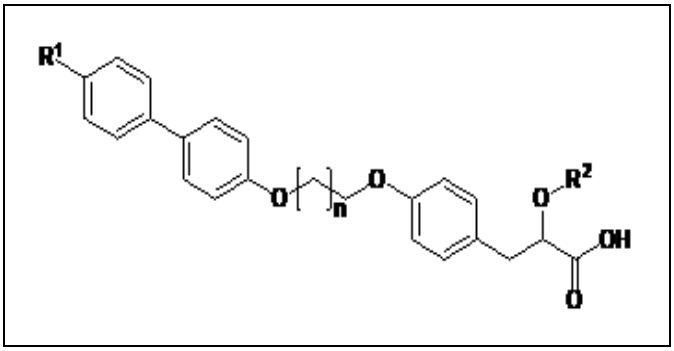

FIG. 1: ALKOXYDIHYDROCINNAMATES DERIVATIVE

During QSAR study, the value of EC_{50} (µM) was converted to –log EC_{50} (M) to bring out better linear correlations and reduce clustering of compounds during the generation of regression lines.

TABLE 1: FUNCTIONAL ACTIVITY AND *IN-VITRO* DATA FOR COMPOUNDS 1A-1M

Compound	R_1	R_2	n	EC_{50} (µM)
1a	H	Me	2	0.89
1b	H	Et	2	2.57
1c	H	Cyclopentyl	2	6.31
1d	F	Me	2	0.38
1e	F	Et	2	1.23
1f	F	Cyclopentyl	2	6.46
1g	Et	Me	2	0.14
1h	Et	Et	2	0.15
1i	Et	Cyclopentyl	2	2.24
1j	H	Et	3	1.58
1k	H	Cyclopentyl	3	3.8
1l	Br	Me	2	1.69
1m	Br	Et	2	0.76

Multiple linear regression (MLR) analysis was adopted for the QSAR study using Hansch approach. A self-generated software, kindly gifted by prof. S.P. Gupta (Chemistry group, BITS, Pilani) was utilized for generating QSAR equation, which provides a correlation coefficient (*r*), standard deviation (*s*), and the ratio between the variance of calculated and observed activities (*F)*. The figures in the parentheses are 95% confidence interval, and *n* is the number of data points. The software also gives the inter-correlation matrix among the descriptors. Van der Waal's volume (Vw) was calculated using the classical procedure

RESULTS AND DISCUSSION: We correlated the activity of 2-alkoxy dihydro cinnamate derivatives **Table 1** with various physicochemical, electronic, and steric parameters. After many trials, Equation (1) was found to be promising.

-logEC_{50} (M)) = 1.789 (1.335) R_1Vw -1.627 (0.906) R_2Vw + 6.325(0.549)

n = 13
r = 0.864
s = 0.273
F = 14.673.....1

Compound	R_1 Vw	R_2 Vw	Obsd. -EC_{50}	Calcd. -EC_{50}	Calcd. residual	L-O-O	L-O-O residual
1a	0.056	0.245	6.050	6.027	0.023	6.019	0.030
1b	0.056	0.399	5.590	5.776	-0.186	5.811	-0.221
1c	0.056	0.757	5.190	5.194	-0.004	5.195	-0.005
1d	0.115	0.245	6.420	6.133	0.287	6.062	0.357
1e	0.115	0.399	5.910	5.882	0.028	5.878	0.031
1f	0.115	0.757	5.180	5.299	-0.119	5.337	-0.157
1g	0.399	0.245	6.850	6.641	0.209	6.547	0.302
1h	0.399	0.399	6.820	6.390	0.430	6.241	0.578
1i	0.399	0.757	5.640	5.808	-0.168	5.959	-0.319
1j	0.056	0.399	5.800	5.776	0.024	5.771	0.028
1k	0.056	0.757	5.420	5.194	0.226	5.109	0.310
1l	0.287	0.245	5.770	6.440	-0.670	6.594	-0.824
1m	0.287	0.399	6.110	6.190	-0.080	6.200	-0.090

Then standard deviation was multiplied by factor 2, It was observed that amongst 13 data points, only one point having calculated a residual value which was outside 2*s* range, this indicates that three outliers are present in the models. After removing them, a new equation was generated with the same parameters as in equation 1. The resulting equation 2 is as follows

-logEC_{50} (M) = 2.053 (0.899) R_1Vw - 1.921(0.625)R_2 Vw + 6.476(0.375)
n = 12
r = 0.950
s = 0.177
F = 41.371 2
R^2= 0.90
Q^2= 0.807

CONCLUSION: In equation 2, the positive contribution of the steric parameter (Vw) at position 1 indicates the presence of the bulkier group at this position is involved in the steric interaction with the receptor.

Thus, the new substituents at this position should be bulky with high R_1 Vw. While at position 2 the contribution of van der Waal's volume (R_2Vw), is negative, thus to avoid the steric hindrance on the receptor, the substituent should be small with low van der Waal's volume (Vw).

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CONFLICT OF INTEREST: Nil

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