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MERIT OF INDOLE β-DIKETONATES AS SCAFFOLDS IN DRUG DISCOVERY-AN *IN SILICO* APPROACH USING DISCOVERY STUDIO

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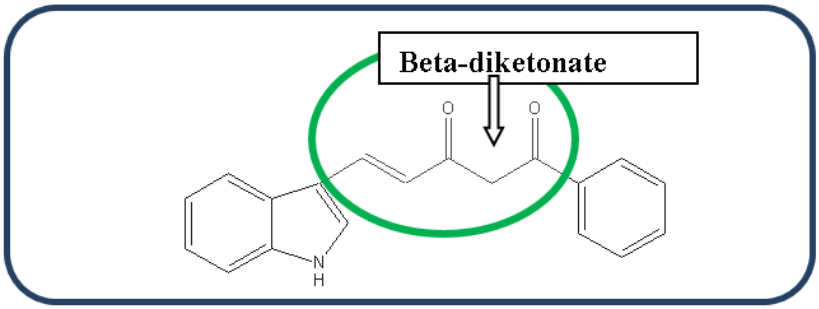
Abstract

From a medicinal chemist's viewpoint, two scaffolds can be diverse, if they are built up via different synthetic routes. Synthetic curcumin is one of such scaffold studied and synthesized extensively in different part of word. Though many analogues were patented, major pitfalls in curcumin chemistry without a significant therapeutic agent requires attention. The existing multi directional studies in the last forty-plus years with diverse curcumin templates are to be analyzed to find out the most suitable scaffold among them. It is a high time to investigate, test and hypotheses in silico prior to costly random experimental implementation of synthetic curcumin. The diverse approach existed in SAR based synthesis and the existing numerous synthetic approaches should be streamlined for reducing the time and expense involved in bringing products to market. So, this study focuses on collection and in silico screening of existing templates of "curcumin research" for cyto toxicity receptor binding. It further continues with identification and enlightenment on highly disputed pharmacophore in curcumin, which is responsible for high potential cytotoxic action. The aim of curcumin scaffold hoping is to synthesis structurally novel compound from the identified templates by in silico method and to explore the core structures ability to bind with the most suitable receptor. The second part of work is on modifying synthetic route, which make it appropriate for synthesizing the series of compounds from most eligible drug candidate. At the same time, parallel to these acute toxicity studies of these sequences of compound was conducted in the aim of bringing a safe analogue. Curcumin research, which turned out to be one of the preferred subjects for organic, inorganic chemists should need a direction. By this scaffold hoping and in silico analysis on available synthetic analogues for a given target will definitely give light on ability of these diverse compounds to bind on same receptor. The in vivo and in vitro studies help in exploring the effect of modification on pharmacophore features of identified eligible drug candidate. Scaffold hopping will be an excellent method to be experimented in this juncture of curcumin research

Key Words: *In silico* screening, Curcumin analogue, Receptor binding, Scaffold hoping,

INTRODUCTION

Various studies have revealed that curcumin modulates abundant targets. These include the growth factors, growth factor receptors, transcription factors, cytokines, enzymes, and genes regulating apoptosis. During the last decade, synthetic modifications of curcumin, which were meant at enhancing its bioactivities, have been intensively considered. However, few of these studies were paid attention on the improvement of its pharmacokinetic profiles. Some of the studies suggested that the stability and bioavailability of curcumin could be enhanced by deleting the *β*-diketone moiety (1,3). In contrast to that the present study focused on pharmacological significance of this moiety in binding with drug receptors. The cyclooxygenases (COX-2) are in charge for the conversion of arachidonic acid to prostaglandins (PGs), and their metabolites occupy a critical role in multiple physiologic and pathophysiological processes. Numerous numbers of literatures already explained the expression of COX-2 in human cancers (2). The ultimate goal of cancer treatment is to specifically prevent such over expressed enzymes that can bring changes in cell replication. The synthetic analogue (Structure-**1**) of curcumin bearing the *β*-diketone system was studied for its inhibitive properties against the cyclooxygenases enzyme (4,5).



(*E*)-5-(1*H*-indol-3-yl)-1-phenylpent-4-ene-1,3-dione

Structure 1: Indole analogue of synthetic Curcumin

The above indole substituted ligand was selected from library of fifty heterocyclic derivatives of 5-hetero aryl-1-phenyl-4-pentene-1,3-diones (6,7). The ligand was prepared by B_2O_3 mediated condensation of different heterocyclic aldehydes with benzoyl acetone (10,11). Further scaffold hoping for this identified derivative was carried out by *in silico* screening of different conformations of this ligand with the COX-2 enzyme. Discovery studio 2.0 was used for the comparative docking studies on the projected molecule.

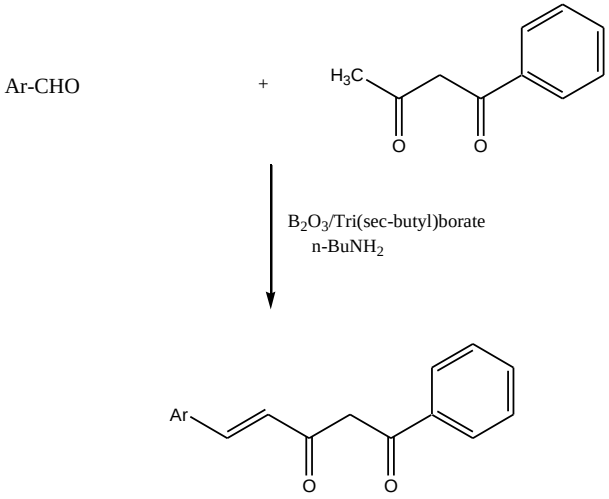
Materials & Methods

The chemicals required were obtained from Lancaster, Sigma and Aldrich chemical suppliers. Commercial solvents were distilled and used for synthesis. Solvents purified by methods recommended by Weissberger were employed for physical and physiochemical measurements. To build the COX-2 homology model, a BLASTp algorithm against Protein Data Bank (PDB) was used to carry out the sequence homology searches. Crystal structure of *Mus musculus* cyclooxygenase 2 (PDB ID: 1PXX) was taken as a template to build homology model (8,9). The Modeller 9v7 program was employed to generate the 3D models of COX-2. The optimized model was subjected to quality assessment with respect to its geometry and energy and then subjected to molecular docking.

Experimental

Synthesis of 5-(1*H*-Indolyl-3-yl)-1-phenyl-pent-4-ene-1,3-dione

The compounds were prepared by the Claisen-Schmidt condensation (10,11,12) of indole-3-carboxaldehyde with benzoyl acetone as reported. Benzoyl acetone (0.005 mol) mixed with boric oxide (0.005 mol) and dry ethyl acetate (5 ml) was stirred for *ca.* 1 h. The stirring was further continued for 1 h with slow addition of a solution of aromatic aldehyde (0.005 mol) in dry ethyl acetate (5 mL), followed by tri-(sec-butyl) borate (0.01 mol) and n-butylamine (0.05 mL). After stirring for an additional period of *ca.*3 h, the solution was set aside overnight. Hot *ca*. 60°C hydrochloric acid (0.4 M, 7.5 mL) was then added to the reaction mixture and again stirred for *ca* .1 h, and extracted with ethyl acetate, the combined extracts were concentrated and the residual paste obtained was stirred with hydrochloric acid (2M, 10 mL). The separated solid product was collected, washed with water, ethanol and dried under reduced pressure. The method followed as per **scheme-1** was crystallized using hot benzene to obtain chromatographically pure ligand.



Scheme-1-Synthesis of 5-hetero aryl-1-phenyl-4-pentene-1,3-dione

Docking of ligand with COX-2

COX2 protein was cleaned by standardizing atom orders, ordering the bonds, protein naming, alternate conformations, adding incomplete residues and modifying hydrogen with clean protein tool. COX2 protein was prepared by a Prepare Protein Protocol and energy was minimized. 3D protein structure of COX2 docked with prepared ligand of **5**-(1*H*-Indolyl-3-yl)-1-phenyl-pent-4-ene-1,3-dione. After docking experiments, the ten poses viewed by Dock Sore (DS) viewer. Hydrogen bond interactions and docking score was sequenced and recorded and given in **table-1**.

Results & Discussion

The docked ligand was found to have three hydrogen bond interactions to the COX-2 receptor. The amino acids like tyrosine A:355, arginine A:120, arginine A:513 was found to involve in hydrogen bond with the *β*-diketone system of ligand. The docking interaction of ligand with COX-2 is given in figure-1 and 2.

Pose_number	Cdocker_energy	Cdocker_interaction_energy
1	7.17606	20.7565
2	6.97322	21.1109
3	6.97322	21.1109
4	6.97322	21.1109
5	6.91148	24.5108
6	6.90191	21.5024
7	6.90191	21.5024
8	6.90191	21.5024
9	6.76898	21.0765
10	6.76898	21.0765

Table-1. Dock score

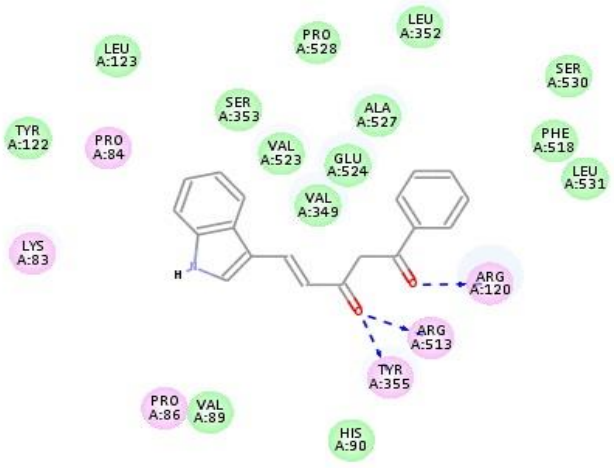


Figure-1. 2D structure of docking with receptor

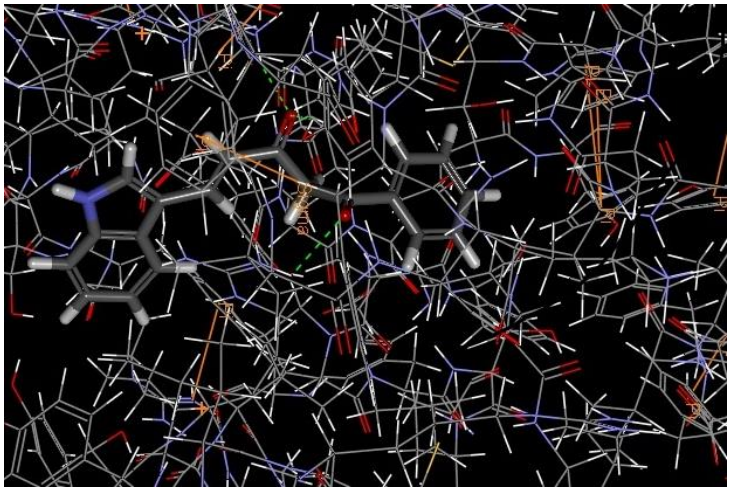


Figure-2. 3D structure of Hydrogen bond interactions.

Conclusion

Our molecular docking score and amino acid residual interaction through hydrogen bond with diketone oxygen atom is clear indication of *β*-diketone as the pharmacophore in this molecule. This particular analogue shown better scores than the enol isomer of the ligand ruled out the reason of α, β-unsaturation next to the keto group as the reason for pharmacological significance of curcumin analogues. The docking energy values and distance of hydrogen bonds with amino acid residues are in agreement with considering this particular ligand as a active lead compound. Curcumin chemist should now aim at considering *β*-diketone as the most interesting scaffold and need to study the effect of substitution on aryl and hetero aryl rings on the docking score.

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