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Original Article

A STUDY ON EFFECT OF INDOLE AS A SUBSTITUENT ON A KETO-ENOL TAUTOMER: A SYNTHETIC APPROACH ON *β*-DIKETONE

KRISHNAKUMAR K. L.[1*], MATHEW PAUL UKKEN[2], MANJU R.[3]

[1]Department of Pharmaceutical Chemistry, Acharya and BM Reddy College of Pharmacy, Chikkabanavara, Bengaluru 560107, Karnataka, India, [2]Department of Chemistry, Christ College, Irinjalakuda 680125, Kerala, India, [3]Department of Pharmaceutical Chemistry, Nirmala College of Health Science, Chalakudy 680311, Kerala, India
Email: krishnakumarkl@gmail.com

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ABSTRACT

Objective: The existence of keto-enol tautomerism in *β*-diketones can typically study by a choice of analytical technique. The position of the keto-enol equilibrium depends on a number of factors like solvent, temperature, and substituents. Here an attempt was made to examine the effect of indole, a heterocyclic moiety with the moderately high polar surface area to examine its effect on ketonisation of *β*-diketone.

Methods: The *β*-diketone studied and synthesized is a structural analog of magical drug curcumin. The structural influence of indole on ketonisation of *β*-diketone is studied to give a hypothesis on factors contributing towards ketonisation. This work involves the synthesis of 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione and the study on the single crystal structure of indole-3-carboxaldehyde, major functional component to result in the reaction. The tautomer was studied for its ability to bind with tetrahydrofolate reductase enzyme using Discovery Studio 3.5 version to differentiate the pharmacological significance of conformations.

Results: The single crystal XRD structure of this compound was deposited in Cambridge crystallographic data center bearing CCDC No.1536311. The structural characterization of synthesized ligand was carried out by using IR, Mass, ^{1}H NMR spectroscopic techniques. The docking study reveals that keto isomer found to exhibit more inhibition of the enzyme tetrahydrofolate reductase hence more pharmacologically active.

Conclusion: The experimental evidence proves that indole substitution shifted the keto-enol equilibrium towards keto form of 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione.

Keywords: Keto-enol tautomerism, *β*-diketones, 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione, Structural analog, Curcumin, Single crystal XRD, IR, Mass, ^{1}H NMR, Docking

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INTRODUCTION

Curcuminoids, the active chemical components present in Indian medicinal plant turmeric (*Curcuma Longa*, *Linn, Zingiberaceae* family) have various biological activities, including antioxidant, anti-inflammatory, anti-arthritic and anti-tumor activities [1, 2]. The potential health benefits of curcumin are limited by its poor solubility, low absorption from the gut, rapid metabolism and rapid systemic elimination [3]. Curcumin adjuvant therapy, solid dispersion, liposomal curcumin and synthetic analogs of curcumin are a few methods used to overcome these drawbacks [4]. Out of this, the synthetic analogs and their pharmacological screening are studied vastly in the past few decades [5]. The structure (fig. 1) can be related to a series of similar molecules which resulted as an attempt to synthesize synthetic curcumin of 6-aryl-5-hexene-2, 4-diones series [6, 7]. Structurally, this is *α, β*-unsaturated 1, 3-diketone with an indole substitution on its left terminal. A series of aromatic and heteroaromatic compounds were already counted under this class proved to exist in enol form [8]. The same synthetic route, when tried with 1*H*-indole-3-carboxaldehyde gave a conflict.

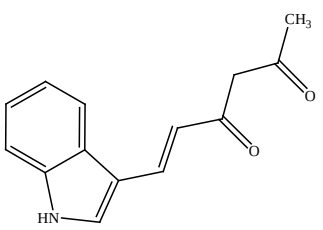

Fig. 1: Structure of 6-(1*H*-Indol-3-yl)-hex-5-ene-2, 4-dione

Normal *β*-ketones have a tendency to exist in enol, as it is more stable. This can be explained by considering the ability of enol form to contribute stable six-membered cyclic structures through hydrogen bonding as shown in structure (fig. 2). Studies suggest that the amount of Enol form decreases when a bulky alkyl substituent present at the α-position [9]. Bulky alkyl groups such as the isopropyl group or the Sec-butyl group decrease the quantity of enol form to almost 0%. The presence of an alkyl substituent on the *α*-carbon decreases the amount of enol form. The bearing of a chlorine group at the α-position increases the amount of enol form to 92%. According to Burdett and Rogers [10], the presence of electron-withdrawing groups, such as CF_3 favors the enol form. When four or more fluorine atoms are present in the molecule, the enolization is complete. Also, phenyl groups favor the enol form. The lower the polarity of the solvent, the higher is the percent of the enol form. In CCl4, 94% of the acetylacetone molecules are present in the enol form, whereas in acetonitrile this value is scaled down to 36%. The amount of enol form decreases with increasing temperatures. The NMR study of solution structures of curcumin in solvents ranging in polarity from CDCl3 to mixtures of DMSO-*d*6 in water, and in buffered aqueous DMSO-*d*6 solutions with pH values varying from 3 to 9, found that curcumin exists in solution as keto-enol tautomer, The titrimetric chloramine-T oxidative methods were used earlier for the determination of percentage of enol form of in the *β*-dicarbonyl compounds [11, 12]. The ability of these *β*-keto compounds to involve in the synthesis of medicinally active heterocyclic compounds were studied extensively in past few years [13, 14]. But when it comes to *β*-dicarbonyl compounds in the solid state, use of spectroscopic methods like ^{1}H NMR, single crystal XRD methods has to be used sensibly to distinguish the confirmation.

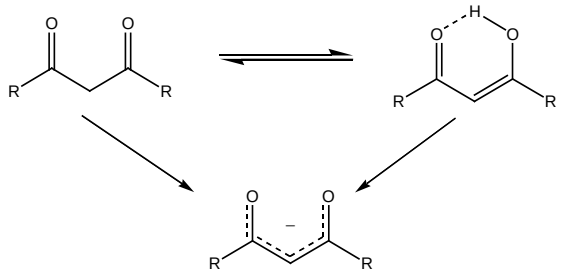

Fig. 2: Keto-enol tautomerism in *β*-ketones

It was interesting to note that indole; a bicyclic heterocyclic ring system has not reported contributing an impact on keto existence of diketone in any of this literature. This can be explored only by considering indole as a substituent on *β*-diketone, which is broadly studied for its substitution with aliphatic and aromatic groups. The available literature of substitution with benzaldehyde with the less polar surface area to vaniline with more polar surface area show the shift of equilibrium towards enolization. One such example 6-aryl-5-hexene-2, 4-diones (fig. 3) being a synthetic analog of curcumin was studied vast in previous years [15, 16].

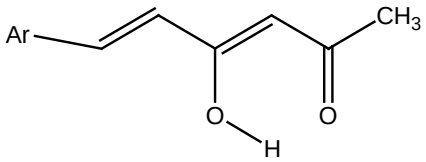

Fig. 3: Structure of 6-aryl-5-hexene-2, 4-diones

Curcumin research on synthetic analogs now turned into a stage, where researchers have to focus on identification of pharmacophore which needs to be altered for improving the efficacy as a drug candidate. There has an ongoing debate regarding *α*, *β*-unsaturated diketone system exists on curcumin as the reason for magical effect of the drug [17]. The keto-enol isomeric effect on structural pharmacophore may play an important role in binding of this analog with drug target. The relationship between tautomeric structures of curcumin and its effect on neurodegenerative diseases like Alzheimer's was the research of interest for the present [18]. So the initial efforts were taken to study the effect of indole by synthesis of 6-aryl-5-hexene-2, 4-diones using 1*H*-indole-3-carboxaldehyde. This special case captured attention while trying to synthesise a novel series of heteroaryl hexanoids using different heterocyclic aldehydes. So here focus was given on indole as a special case which demonstrated a change in structural geometry of synthetic analogs of this series. Efforts were made to study this reason by altering reaction conditions and reagent concentrations. The single crystal XRD structure of 1*H*-indole-3-carboxaldehyde is studied for its influence on bond angle and bond length on ketonisation. The ongoing research in this field suggests that proteinaceous drug receptors frequently preferentially bind a tautomer that is present in low abundance in water [19]. So the proper treatment of molecules that can tautomerize them either keto or enol form is a challenge for medicinal chemist.

Dihydrofolate reductase, one of the targets for antifolate-based drugs has been validated by researchers for the screening of pharmacological activities in related compounds [20]. The drug, which is a potent inhibitor of dihydrofolate reductase (DHFR) acts by preventing the synthesis of tetrahydro folic acid and inhibiting cell growth and multiplication. The surviving evidence from docking studies on this heated discussion of pharmacological activities of keto-enol forms favours keto form in case of curcumin [21]. The same approach on 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione, a synthetic analog of curcumin by using dihydrofolate reductase enzyme will shed light on synthetic chemist who works on modification of these analogs.

MATERIALS AND METHODS

All the chemicals utilized in this study were AR grade purchased from Sigma-Aldrich. Melting points were determined by open tube capillary method and are uncorrected. Instruments used in this investigation are UV-1601 Shimadzu recording spectrophotometer, Thermo Nicolet, Avatar 370 FTIR spectrophotometer, Jeol/Sx-102(FAB) mass spectrometer, Varian, Mercury Plus 300 MHz NMR spectrophotometer, Bruker Kappa Apex II diffractometer. The keto and enol conformations are docked using Accelrys Drug Discovery Studio 3.5. The structure of the enzyme tetrahydrofolate reductase complexes was obtained from a Protein data bank (PDB code: 7DFR) and was used for docking. The chain-A is retained and the crystal structure was cleaned by deleting the ligands and other heteroatoms. The prepared ligands were docked by using CDocker. Docking calculations were carried out using Accelrys Drug Discovery Studio (3.5version).

Experimental

Synthesis of 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione [22-24]

Acetylacetone (0.075 mol) mixed with boric oxide was suspended in dry ethyl acetate (50 ml) containing tri (sec-butyl) borate (0.1 mol). To this combination kept at about 0 °C, a solution of 1*H*-indole-3-carboxaldehyde (0. 025 mol) in dry ethyl acetate (15 ml) and n-butyl amine (0.5 ml) was added dropwise for 90 min with continuous stirring. The stirring was continued for an extra period of about 2 h and the solution was set aside all night. The reaction mixture was then stirred for about 1 h with hot (50 °C) hydrochloric acid (0.4 M, 20 ml) and extracted over and over again with ethyl acetate. The collective extracts were concentrated under vacuum and purified by column chromatography (silica gel, mesh 60-120). The yellow band developed in the lower section was recovered by successive elution with 5:1 v/v mixture of chloroform-acetone and the combined eluates on evaporation yielded 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione. Scheme of synthesis outlined below. (fig. 4) The isolated 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione was recrystallized from hot benzene to get chromatographically (TLC) pure material. The unreacted 1*H*-indole-3-carboxaldehyde was separately eluted from the reaction mixture using the same solvent system and used for crystal study.

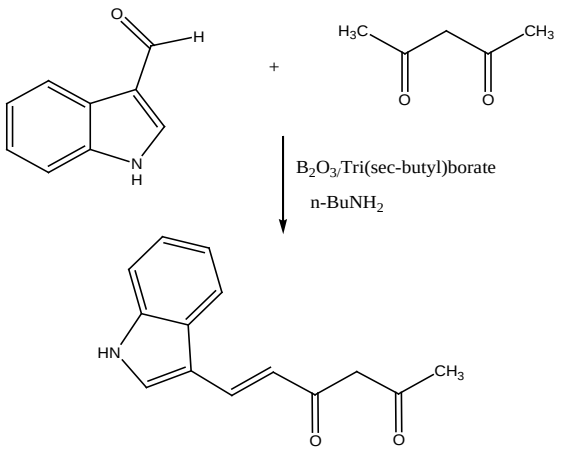

Fig. 4: Scheme of synthesis of 6-(1*H*-Indol-3-yl)-hex-5-ene-2, 4-dione

Single crystal study

The unreacted 1*H*-indole-3-carboxaldehyde was separated by column chromatographic method using 5:1 v/v mixture of chloroform-acetone from the reaction mixture and used for crystal preparation. Deep yellow plate-like crystal of 1*H*-indole-3-carboxaldehyde was prepared by crystallization of the compound from a mixture of ethanol-toluene-ethyl acetate mixture. The compound was dissolved in the solvent mixture at room temperature in a 50 ml conical flask and the mouth was closed with

cotton to allow slow evaporation of the solvent and kept aside for about 2 w when a plate-like crystal was separated. A crystal with 0.40 x 0.30 x 0.20 mm was used for obtaining X-ray diffraction data. XRD data were collected on a Bruker Kappa Apex II diffractometer. To solve the structure all crystallographic calculations were performed using Shelxl program package.

RESULTS

Characterization of 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione

The derivatives were recrystallized from hot benzene to get chromate-graphically (TLC) pure material to yield product (60%) in the yellow to orange crystalline form. The UV absorption band 280 nm, IR (ν) 1668 (C=O acetyl stretch), 1635.5 (C=O cinnamoyl stretch), 1518.8 (asymmetrical C-C-C chelate ring stretch), 1443.3 (symmetrical C-C-C chelate ring stretch), 997.2 (CH=CH stretch); 1H NMR δ 3.3 (s, 3H,-CH3), 4.9 (s, 2H,-CH2), 7.3 (td, 4H, Ar H-4, H-5, H-6, H-7, J=3.50 Hz), 7.5(d,1H, CH,-α, β-unsaturated, J=8.0 Hz), 8.1 (s,1H, Ar H-2), 8.2(d, 1H, C=CH, J=7.0 Hz,), 9.9 (s, 1H,-NH); EIMS m/z 227 [C14H13NO2]+, 170.06 [$C_{11}H_8N0$]+, 129.06 [C_9H_7N]+,117.0 [C_8H_7N]+; Accurate mass found [C14H13NO2]+: m/z 227.0, calculated for [$C_{14}H_{13}NO_2$]+; 227.09.

Crystallographic study

The ORTEP view and PLATON diagram (Shelxl program) of the molecule with the labeling of non-hydrogen atoms are shown in fig. 5 and fig. 6.

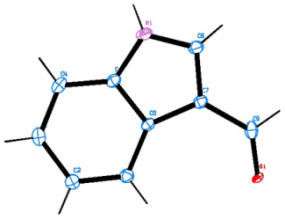

Fig. 5: 1*H*-indol-3-carboxaldehyde

Docking studies on isomer

The extent of biological activity variance on confirmations is studied by docking the keto-enol conformations against the selected enzyme dihydrofolate reductase. The amount of inhibition made by the conformations is studied by evaluating the result obtained after docking the conformations separately by using CDocker program. The CDocker energy and CDocker interaction energy were calculated. The scoring functions and hydrogen bonds formed with the surrounding amino acids are used to predict their level of inhibition on binding sites of dihydrofolate reductase receptor. The types and number of interactions between the synthesized ligand and enol confirmation were shown in fig. 8-9 (Discovery Studio 3.5, CDocker program). The CDocker energy, CDocker interaction energy for first three leads and number of hydrogen bond length are listed in table 2-3.

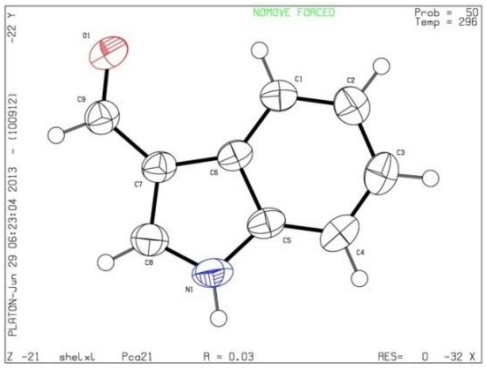

Fig. 6: 1*H*-indol-3-carboxaldehyde (PLATON)

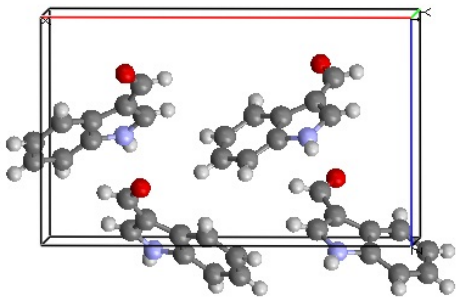

Fig. 7: Arrangement of molecule in crystal of 1*H*-indol-3-carboxaldehyde

Crystal data and structure refinement: 1*H*-indole-3-carboxaldehyde

Identification code	shelxl
Empirical formula	C_9H_7NO
Formula weight	145.16
Temperature	296(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Pca21
Unit cell dimensions	a = 14.0817(11) A alpha = 90 deg. b = 5.8006(5) A beta = 90 deg. c = 8.6895(6) A gamma = 90 deg.
Volume	709.78(10) A^3
Z, Calculated density	4, 1.358 Mg/m^3
Absorption coefficient	0.090 mm^-1
Crystal size	0.40 x 0.30 x 0.20 mm
Theta range for data collection	2.89 to 28.35 deg.
Limiting indices	-18<=h<=15,-7<=k<=7,-11<=l<=8
Reflections collected/unique	5287/1617 [R(int) = 0.0236]
Completeness to theta = 28.35	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9822 and 0.9648
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1617/1/101
Goodness-of-fit on F^2	0.549
Final R indices [I>2sigma(I)]	R1 = 0.0341, wR2 = 0.1021
R indices (all data)	R1 = 0.0422, wR2 = 0.1176
Absolute structure parameter	-1(2)
Extinction coefficient	0.048(8)
Largest diff. peak and hole	0.159 and-0.138 e. A^-3

Table 1: Bond angles and bond lengths

Atom to atom	Bond lengths [A °]	Atom to atom	Bond angles (deg)
O(1)-C(9)	1.217	C(1)-C(6)-C(5)	118.77
C(6)-C(1)	1.391	C(1)-C(6)-C(7)	134.99
C(6)-C(5)	1.404	C(5)-C(6)-C(7)	106.12
C(6)-C(7)	1.439	C(2)-C(1)-C(6)	118.71
C(1)-C(2)	1.380	C(2)-C(1)-H(1)	120.6
C(1)-H(1)	0.930	C(6)-C(1)-H(1)	120.6
C(9)-C(7)	1.423	O(1)-C(9)-C(7)	124.99
C(9)-H(9)	0.930	O(1)-C(9)-H(9)	117.5
C(7)-C(8)	1.380	C(7)-C(9)-H(9)	117.5
C(5)-C(4)	1.388	C(8)-C(7)-C(6)	106.15
C(5)-N(1)	1.377	C(8)-C(7)-C(9)	123.62
C(2)-C(3)	1.391	C(6)-C(7)-C(9)	130.20
C(2)-H(2)	0.930	C(4)-C(5)-N(1)	129.26
N(1)-C(8)	1.335	C(4)-C(5)-C(6)	122.65
N(1)-H(5)	0.860	N(1)-C(5)-C(6)	107.99
C(8)-H(8)	0.930	C(1)-C(2)-C(3)	121.23
C(3)-C(4)	1.369	C(1)-C(2)-H(2)	119.4
C(3)-H(3)	0.930	C(3)-C(2)-H(2)	119.4
C(4)-H(4)	0.930	C(8)-N(1)-C(5)	109.34

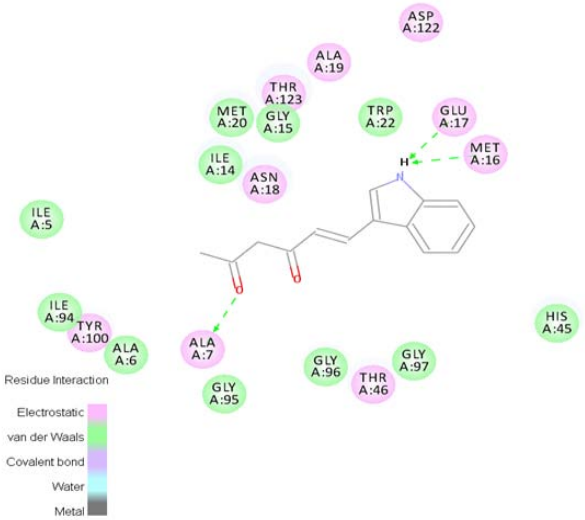

Fig. 8: Binding configuration of keto isomer

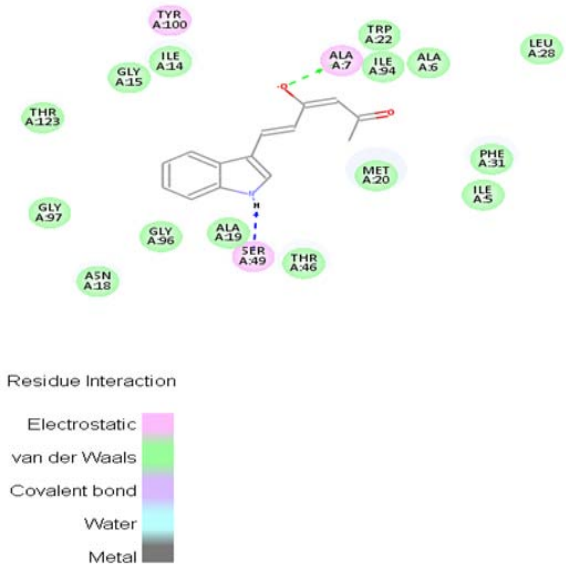

Fig. 9: Binding configuration of enol isomer

Table 2: Statistical docking results of keto isomer (discovery studio 2.5 software)

CDocker energy	CDocker interaction energy	Nature of Hydrogen bond	Distance
-31.4535	-35.2347	A: ALA7: HN-Molecule: O16	2.33905
-28.7751	-35.1325	Molecule: H30-A: MET16: O	2.48707
-28.6988	-31.5826	Molecule: H30-A: GLU17: O	2.26689

Table 3: Statistical docking results of enol isomer (discovery studio 2.5 software)

CDocker energy	CDocker interaction energy	Nature of Hydrogen bond	Distance
-28.1646	-34.8425	A: ALA7: HN-Molecule: O17	1.9063
-27.887	-35.0845	Molecule: H29-A: SER49: OG	2.30268
-27.5315	-33.8704		

DISCUSSION

The UV absorption band is very broad and shows the presence of more than one peak indicating the presence of more than one isomeric form in the ground state. The high energy band at 280 nm due to π→π* transitions of the fully conjugated system is marginally influenced by indolyl groups. The IR spectra of the diketones show the prominent band at 1635.5 assignable to the cinnamoyl ν(C=C) vibrations. The observed position and intensity of these bands indicate that the compound exhibit strong shift to keto form. A medium intensity band at 997.2 cm^{-1} in the spectra of the compounds can be assigned to the trans-CH=CH-absorption [25, 26]. The proton magnetic resonance spectra indicated that the synthetic analog existed entirely in the keto form rather than the enol form in deutero-methanol solution. The signal due to methylene carbon of keto tautomer was observed as intense peek in δ value 4.9 [27]. The mass fragmentation patterns depend mainly on the nature of groups attached to the dike to function. Elimination of O, OH, CO, $C_3HO_2^+$, CH_2=C=O (ketene), etc are characteristic of acetylacetone and related 1, 3-diketones [28]. On common practice, the *β*-diketones prefer the cis enol configuration stabilized by a strong intramolecular hydrogen bond. The information gathered from above results was found contrary to the above statement. The XRD results reveal that the crystal crystallizes in orthorhombic system with lattice parameter values, *a* =14.0817 A °, *b* =5.8006 A °, *c* =8.6895 A ° with a slight marginal difference from reported XRD values of 1H-Indole-3–carboxaldehyde [29, 30]. This ruled out the possibility of polymorphism of crystals under high-temperature reaction condition. The data obtained from single crystal XRD study of 1*H*-indol-3-carboxaldehyde used here to give evidence for keto existence. The unit cell parameters, experiment details, and refinement parameters are listed above. Analysis of bond length and bond angles (table 1) reveals that the molecule is planar with slightly tilted C=O bond with O(1)-C(9)-H(9) bond angle is 117.5 °. It was attention-grabbing to identify that, normal CHO bond is trigonal planar with angle 120 °. The O(1)-C(9) bond length was found to pretty long 1.217 A °. The comparison of XRD results of the title compound with reported aldehydes strongly suggests different geometry for 1*H*-indol-3-carboxaldehyde. Further analysis of hydrogen bonding network in the crystal pattern of 1*H*-indol-3-carboxaldehyde reveals the presence of four molecules in unit cell as shown in fig. 7 (Shelxl program).

The docking energy scores suggest that the keto form of the ligand has slightly better binding energy values in comparison with the enol isomer of 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione. But upon examining the interactions with the active binding site of the receptor, the keto isomer has a number of prominent and strong electrostatic interactions with amino acid residues like ALA: 7, TYR: 100, ASN: 18, THR: 123, ALA: 19, ASP: 122, THR: 46, GLU: 17, MET: 16. In the case of enol derivative, major interactions are of weak Van der Waals kind. Further, it is interesting to notice that the keto isomer exhibit three hydrogen bonding interactions amino acid residues in the receptor namely ALA7: HN-Molecule: O16, Molecule: H30-MET16: O and the third one with the same hydrogen atom (H: 30) in the molecule with GLU: 17. Whereas the third hydrogen bond from NH of the molecule is absent in enol isomer. Hydrogen bonds play a crucial role in defining the specificity of ligand binding. Most of the studies show that hydrogen bond and other polar interactions are playing important role in finding the proper orientation of the molecule to make maximum interactions [31]. The keto isomer was found to be more compact with three hydrogen bond interaction with amino acid residues exhibiting stronger inhibition of dihydrofolate reductase enzyme. In the enolic confirmation, the conjugated dienyl existence of molecule was thought to contribute some conformational changes in the molecule and hence steric hindrance. This steric hindrance may the reason more hydrophobic interaction and poor inhibition of enolic isomer with dihydrofolate reductase enzyme.

CONCLUSION

The results from IR band 1635.5 (C=O cinnamoyl stretch) supports the ketonic existence of 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione. This is further supported by the fact observed in ^{1}H NMR spectrum with δ value 4.9 clearly corresponds to active methylene on *α* position of the *β*-diketone system. There was no peak at δ value 15 and above clearly ruled out the chance for the existence of enolic hydrogen. The hypothesis gave here based on literature survey and experimentation highly in favor with substituent effect of indole. Electronic effects or active polar surface area of the molecule has not found to play a major role on ketonisation. The experimentation with changing reactant concentration and reaction condition has not contributed to enolization with indole-3-carboxaldehyde. Unlike other Carboxaldehyde, change in bond angle from normal trigonal 120 ° along with intermolecular hydrogen bond exists between indole-3-carboxaldehyde has found to play a major role in this context. This has added significance as the tested indole-3-carboxaldehyde used for crystal formation is extracted from reaction mixture used for preparation of 6-(1*H*-Indol-3-yl)-hex-5ene-2, 4-dione. All the available evidence in this study suggests the shift of equilibrium is more towards keto form. This equilibrium can be affected by other substitutions in the molecule. The effects of other substitution in indole and on *β*-diketone need to be studied in future. Further docking study performed on dihydrofolate reductase enzyme revealed that the keto isomer will be the best conformation with maximum binding and better predicted pharmacological activity.

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AUTHOR'S CONTRIBUTION

Krishnakumar KL: Design of work, Literature review, synthetic part, drafting the article.

Mathew Paul Ukken: Data analysis, Revision of article.

Manju R: Revision of article and interpretation of results.

CONFLICT OF INTERESTS

Declared none

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