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Research Article

DESIGN AND MOLECULAR MODELING STUDIES OF NOVEL BENZIMADAZOLE DERIVATIVES

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ABSTRACT: In this present study, Molecular docking studies were performed to 12 novel derivatives of Benzimidazole. And the interaction between ligand and receptor were brought in focus some important interaction at the molecular level. The synthesized compounds were estimated for "Binding Free Energy", Vander wall's energy, Electrostatic Energy, Total Intermolecular Energy and Interaction surface of the ligand and protein. A novel substituted benzimadazole derivatives were designed and docked into the active site of cycloxagenase I further studies have been carried out to know affinity, orientation and binding mode.
KEYWORDS: Benzimadazole, Biniding affinity, Molecular Docking

INTRODUCTION

Cyclooxygenase[1] (**COX**) is an enzyme that is responsible for formation of important biological mediators called prostanoids, including prostaglandins, prostacyclin and thromboxane. Pharmacological inhibition of *COX* can provide relief from the symptoms of inflammation and pain. Non-steroidal anti-inflammatory drugs, such as aspirin and ibuprofen, exert their effects through inhibition of COX. The names "prostaglandin synthase (PHS)" and "prostaglandin endoperoxidesynthetase (PES)" are still used to refer to COX.

FUNCTION

COX converts arachidonic acid (AA, an ω-6 PUFA) to prostaglandin H_2 (PGH_2), the precursor of the series-2 prostanoids. The enzyme contains two active sites: a heme with peroxidase activity, responsible for the reduction of PGG_2 to PGH_2, and a cyclooxygenase site, where arachidonic acid is converted into the hydroperoxyendoperoxide prostaglandin

G_2 (PGG_2). The reaction proceeds through H atom abstraction from arachidonic acid by a tyrosine radical generated by the peroxidase active site. Two O_2 molecules then react with the arachidonic acid radical, yielding PGG_2.

At present, three *COX* isoenzymes are known: *COX-1*, *COX-2*, and *COX-3*. *COX-3* is a splice variant of COX-1, which retains intron one and has aframeshift mutation; thus some prefer the name *COX-1b* or *COX-1 variant* (*COX-1v*).[3]

Different tissues express varying levels of *COX-1* and *COX-2*. Although both enzymes act basically in the same fashion, selective inhibition can make a difference in terms of side-effects. *COX-1* is considered a constitutive enzyme, being found in most mammalian cells. *COX-2*, on the other hand, is undetectable in most normal tissues. It is an inducible enzyme, becoming abundant in activated macrophages and other cells at sites of inflammation. More recently, it has been shown to be upregulated in various carcinomas and to have a central role in tumorigenesis.

Both COX-1 and -2 (also known as PGHS-1 and -2) also oxygenate two other essential fatty acids – DGLA (ω-6) and EPA (ω-3) – to give the series-1 and series-3 prostanoids, which are less inflammatory than those of series-2. DGLA and EPA are competitive inhibitors with AA for the COX pathways. This inhibition is a major mode of action in the way that dietary sources of DGLA and EPA (e.g., borage, fish oil) reduce inflammation.[4]

PHARMACOLOGY

In terms of their molecular biology, *COX-1* and *COX-2* are of similar molecular weight, approximately 70 and 72 kDa, respectively, and having 65% amino acid sequence homology and near-identical catalytic sites. The most significant difference between the isoenzymes, which allows for selective inhibition, is the substitution of isoleucine at position 523 in*COX-1* with valine in *COX-2*. The smaller Val_{523} residue in *COX-2* allows access to ahydrophobic side-pocket in the enzyme (which Ile_{523} sterically hinders). Drug molecules, such as DuP-697 and the coxibs derived from it, bind to this alternative site and are considered to be selective inhibitors of *COX-2*[2].

Newer NSAIDs

Selectivity for *COX-2* is the main feature of celecoxib, rofecoxib, and other members of this drug class. Because COX-2 is usually specific to inflamed tissue, there is much less gastric irritation associated with COX-2 inhibitors, with a decreased risk of peptic ulceration. The selectivity of COX-2 does not seem to

negate other side-effects of NSAIDs, most notably an increased risk of renal failure, and there is evidence that indicates an increase in the risk for heart attack, thrombosis, and stroke through an increase of thromboxane unbalanced by prostacyclin (which is reduced by COX-2 inhibition). Rofecoxib (brand name Vioxx) was withdrawn in 2004 because of such concerns. Some other COX-2 selective NSAIDs, such as celecoxib, and etoricoxib, are still on the market.

Natural COX inhibition

Culinary mushrooms, like Maitake, may be able to partially inhibit *COX-1* and *COX-2*[3].

A variety of flavonoids have been found to inhibit COX-2[4,5].

Cardiovascular side-effects of COX inhibitors

COX-2 inhibitors have been found to increase the risk of atherothrombosis even with short-term use. A 2006 analysis of 138 randomised trials and almost 150 000 participants[8] showed that selective *COX-2* inhibitors are associated with a moderately increased risk of vascular events, mainly due to a twofold increased risk ofmyocardial infarction, and also that high-dose regimens of some traditional NSAIDs such as diclofenac and ibuprofen are associated with a similar increase in risk of vascular events.

MEDICINAL USES:

NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. Research continues into their potential for prevention of colorectal cancer, and treatment of other conditions, such as cancer and cardiovascular disease.

NSAIDs are generally indicated for the symptomatic relief of the following conditions:[3]

- Rheumatoid arthritis[4]
- Osteoarthritis
- Inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
- Acute gout
- Dysmenorrhoea (menstrual pain)
- Metastatic bone pain
- Headache and migraine
- Postoperative pain
- Mild-to-moderate pain due to inflammation and tissue injury
- Pyrexia (fever)
- Ileus
- Renal colic
- They are also given to neonate infants whose ductusarteriosus is not closed within 24 hours of birth

Aspirin, the only NSAID able to irreversibly inhibit COX-1, is also indicated for inhibition of platelet aggregation. This is useful in the management of arterial thrombosis and prevention of adverse cardiovascular events. Aspirin inhibits platelet aggregation by inhibiting the action of thromboxane A_2.

In 2001 NSAIDs accounted for 70,000,000 prescriptions and 30 billion over-the-counter doses sold annually in the United States.

MODULE 1: LIGAND GENERTOR

As a step towards drug design studies, tweleve novel benzimidazole derivatives were synthesized and the results were communicated elsewhere and these structures are drawn using Marvin sketch and these structures were cleaned by 3D cleaning method in Marvin sketch.

MODULE 2: RECEPTOR REPARTION

The enzyme cycloxagenase-I were obtained from Brookhaven protein bank and code is 1EQH. Then the enzyme is structurally corrected using Pymol.

Binding Site Preparations : Active sites for enzyme COX I were identified using Q site finder. These active sites are used to prepare binding sites for ligand interaction.

EXPERIMENTAL:

Novel benzimidazole derivatives were drawn using Marvin sketch and these structure were cleaned using 3D clean method in Marvin sketch and these ligands are imported into Flexx . And COX I obtained from PDB were also imported intoflexx. Novel benzimadazole derivatives were docked with enzyme cox I (1EQH) and the results were tabulated in table1.

TABLE 1:

s.no	***Est.Free energy of binding***	***Est.inhibitionconstant,ki***	***Vdw+Hbond desolv energy***	***Elaetrostatic energy***	***Total Intermolec.Energy***	***Frequency***	***Interat surface***
1	***-8.53kcal/mol***	***562.51nM***	***-9.40kcal/mol***	***-0.01kcal/mol***	***-9.41kcal/mol***	***100%***	***686.293***
2	***-6.72kcal/mol***	***-11.78nM***	***-6.97kcalmol***	***-0.06kcal/mol***	***-7.02kcal/mol***	***50%***	***512.038***
3	***-7.92kcal/mol***	***1.57 µ M***	***-8.91kcal/mol***	***-0.01kcal/mol***	***-8.91kcal/mol***	***50%***	***617.011***
4	***-7.06kcal/mol***	***6.72µM***	***-7.56kcal/mol***	***-0.03kcal/mol***	***-7.58kcal/mol***	***100%***	***511.266***

5	*-8.50kcal/mol*	*587.33nM*	*-9.05kcal/mol*	*-0.03kcal/mol*	*-9.09kcal/mol*	*100%*	*595.929*
6	*-7.37kcal/mol*	*3.93µM*	*-8.91kcal/mol*	*-0.03kcal/mol*	*-8.53kcal/mol*	*50%*	*638.977*
7	*-6.97kcal/mol*	*7.84µM*	*-7.89kcal/mol*	*+0.01kal/mol*	*-7.88kcal/mol*	*50%*	*833.728*
8	*8.55kcal/mol*	*541.37nM*	*-9.91kcal/mol*	*-0.01kcal/mol*	*-9.20kcal/mol*	*100%*	*632.208*
9	*-5.45kcal mol*	*101.49µM*	*-6.02kcal/mol*	*+0.01kcal/mol*	*-6.01kcal/mol*	*50%*	*815.233*
10	*-8.98kcal/mol*	*262.02nM*	*-9.74kcal/mol*	*-0.01kcal/mol*	*-9.75kcal.mol*	*50%*	*660.485*
11	*-10.56kcal/mol*	*18.11nM*	*-11.20kcal/mol*	*+0.00Kcal/mol*	*-11.20kcal/mol*	*50%*	*752.435*
12	*-9.08kcal/mol*	*219.83nM*	*-10.78kcal/mol*	*-0.03kcal/mol*	*-10.81kcal/mol*	*50%*	*755.946*

RESULTS AND DISCUSSION

Molecular docking studies were performed to all 12 novel derivatives of Benzimidazole. And the interaction between ligand and receptor were brought in focus some important interaction at the molecular level. The synthesized compounds were estimated for "Binding Free Energy", Vander wall's energy, Electrostatic Energy, Total Intermolecular Energy and Interaction surface of the ligand and protein. Among the synthesized compounds, Compound 11 has highest binding free energy of 10.56 -k Cal, and compounds 12,10,8,5,1 has higher binding energy than the standard indomethacin binding energy is-8.45 k cal/mol. Vander walls force and hydrophobic force are responsible forming stable ligand and receptor complex. Compound 11 has the highest vander walls force of -11.20 k cal/mol due to this the compound 11 forms most stable complex when compared to other novelbenzimadazole derivatives.

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