"Molecular dynamics simulation studies of matrix metalloproteinases MMP2 and MMP9 and computer aided drug designing using phytochemicals as their potential inhibitors"

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In

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CERTIFICATE

This is to certify that the M. Tech. dissertation entitled **"Molecular dynamics simulation studies of matrix metalloproteinases MMP2 and MMP9 and computer aided drug designing using phytochemicals as their potential inhibitors"**, submitted by **SAMRIDHI (2K11/BIO/22)** in partial fulfilment of the requirement for the award of the degree of Master of Technology, Delhi Technological University (Formerly Delhi College of Engineering, University of Delhi), is an authentic record of the candidate's own work carried out by her under my guidance.

The information and data enclosed in this dissertation is original and has not been submitted elsewhere for honouring of any other degree.

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DECLARATION

I, Samridhi, student of M.tech - Bioinformatics here by declare that the thesis titled **"Molecular dynamics simulation studies of matrix metalloproteinases MMP2 and MMP9 and computer aided drug designing using phytochemicals as their potential inhibitors"** which is submitted by me to the Department of Biotechnology, Delhi Technological University, bawana, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology has not previously formed the basis for the award of any Degree, Diploma, Associateship, Fellowship or other similar title or recognition. This work of mine is carried out at Bioinformatics Institute of India, Noida, U. P.

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CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF GRAPHS

LIST OF ABBREVIATIONS

- B-FGF - Basic fibroblast growth factor
- ECM - Extracellular matrix
- EGF- Epidermal growth factor
- EMMPRIN - Extracellular matrix metalloproteinase inducer
- EMT - Epithelial to mesenchymal transition
- HB-EGF - Heparin binding-epidermal growth factor
- IGFBP - Insulin-like growth factor binding proteins
- IGFs - Insulin-like growth factors
- LN - Lymph nodes
- MMPIs - Matrix metalloproteinases inhibitors
- MMPs - Matrix metalloproteinases
- MT-MMPs - Membrane-type matrix metalloproteinases
- NSCLC - Non–small-cell lung cancer
- TIMP-2 - Tissue inhibitor of metalloproteinases 2
- TNF-α - Tumor necrosis factor- α
- VEGF- Vascular endothelial growth factor

"Molecular dynamics simulation studies of matrix metalloproteinases MMP2 and MMP9 and computer aided drug designing using phytochemicals as their potential inhibitors"

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ABSTRACT

Matrix metalloproteinases (MMPs), also designated matrixins, hydrolyze components of the extracellular matrix. These proteinases play a central role in many biological processes, such as embryogenesis, normal tissue remodeling, wound healing, and angiogenesis, and in diseases such as atheroma, arthritis, cancer, and tissue ulceration (Visse *et al.*,2003). MMPs, especially those capable of cleaving type IV basement membrane collagen (MMP-2 and -9) were considered to be ideal targets for drug development.Two gelatinases, MMP-2 (72-kDa gelatinase) and MMP-9 (92-kDa gelatinase), are key proteinases governing the degradation of basement membrane collagen types IV and V, as well as different types of gelatine. These two share structural and catalytic similarities; however, their gene expression is differentially regulated, partly due to the distinct structure of the regulatory elements and promoters in their genes. In contrast to MMP-9, whose expression has been implicated in renal development, macrophage differentiation, atherosclerosis, inflammation, rheumatoid arthritis, and tumor invasion, MMP-2 usually is expressed constitutively.In this study natural compounds from medicinal plants were used for drug designing for MMP2 and MMP9. Molecular dynamics simulation showed structures of MMP2 and MMP9 to be stable. Natural compound library was screened for both the targets. Screenedout ligands with low binding energy were selected. A pharmacophore model was generated from the selected ligands to ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with specific biological target structures "MMP9 and MMP2" and to block their biological response. Four pharmacophore feature pattern were obtained for MMP9: (a) one hydrophobic feature (b) three hydrogen bond acceptor, for MMP2: (a) two hydrogen bond donor (b) two hydrogen bond acceptor and for MMP2 and MMP9: (a) one hydrogen bond donor (b) three hydrogen bond acceptor. Natural compounds with minimum binding energy and good druglike properties were selected. Gentiopicroside and16R,19E-isositsirikine could be predicted to be the potential drug against MMP9 and MMP2 respectively**.** Rhamnetin, Irilin-D and Febrifugine could be predicted to be the potential drug against both MMP9 and MMP2.

INTRODUCTION

The matrix metalloproteinases (MMPs) are a family of structurally related zinc - containing endopeptidases that mediate the breakdown of connective tissue macromolecules. The mammalian MMP family is composed of at least 20 enzymes, classically divided into four sub-groups on the basis of substrate specificity and domain structure: the collagenases, the stromelysins, the gelatinases and the membrane-type MMPs. Because of their central role in re-modelling connective tissue, both as part of normal physiological growth and repair, and as part of disease processes, there has been substantial interest in these proteins as targets for therapeutic intervention in a wide range of degenerative and inflammatory diseases, such as arthritis and atherosclerosis, as well as in cancer. It was in the context of cell movement in malignancy that the gelatinases MMP2 and MMP9 were described, through their ability to degrade basement membranes as well as other matrix components. Whilst the importance of the MMP family in the pathogenesis of arthritis and cancer has been well documented over many years, it is only relatively recently that MMPs and their inhibitors have been shown to be important in connective tissue re-modelling in diseases of the cardiovascular system, such as atherosclerosis (Rowsell *et al.*,2002).

Various members of the MMP family have been shown to be expressed in atherosclerotic lesions of various types, but MMP9 is seen consistently in inflammatory atherosclerotic lesions, typically expressed by lipid-laden macrophages. Evidence from histological investigations and molecular genetic studies implicates MMP9 over-expression in the vascular re-modelling events preceding plaque rupture, the most common cause of acute myocardial infarction. More recently, animal studies have shown that a reduction of MMP9 activity, either by genetic manipulation or through pharmacological intervention, has an impact on ventricular re-modelling following infarction. Thus, MMP9 activity may represent a key mechanism in the pathogenesis of heart failure (Rowsell *et al.*,2002).

Due to the complexity of their contributions to normal physiological processes, broad-spectrum inhibition of the MMPs has led to unintended side effects during clinical trials. Therefore, the development of MMP inhibitors (MMPIs) with increased specificity for unique MMP targets has been the focus of much recent research at the industrial level and in academia.

Medicinal plants can be used for the treatment of MMPs related diseases. Phytochemical constituents of these medicinal plants could be used to as inhibitors of MMPs. Medicinal plants are various plants used in herbalism and thought by some to have medicinal properties. Few plants or their phytochemical constituents have been proven to have medicinal effects by rigorous science or have been approved by regulatory agencies such as the United States Food and Drug Administration or European Food Safety Authority.

Natural product library generated by the phytochemicals from medicinal plants could be virtual screened to get the desired druglike molecule which would be used as a drug against matrix metalloproteinases MMP9 and MMP2.

REVIEW OF LITERATURE

Matrix metalloproteases (MMPs) are a multigene family of zinc-dependent endopeptidases that share a similar structure and which collectively, have the capacity to degrade virtually every component of the extracellular matrix (ECM). Common properties of the MMPs include the requirement of zinc in their catalytic site for activity and their synthesis as inactive zymogens that generally need to be proteolytically cleaved to be active. Normally the MMPs are expressed only when and where needed for tissue remodeling that accompanies various processes such as during embryonic development, wound healing, uterine and mammary involution, cartilage-to-bone transition during ossification, and trophoblast invasion into the endometrial stoma during placenta development. However, aberrant expression of various MMPs has been correlated with pathological conditions, such as periodontitis, rheumatoid arthritis, and tumor cell invasion and metastasis (Rundhaug *et al.*, 2003). There are eight distinct structural classes of MMPs: five are secreted and three are membrane-type MMPs (MT-MMPs). Many of the extracellular signalling events that regulate cell behaviour occur at or near the cell membrane and are regulated by pericellular proteolysis. The MT-MMPs are covalently linked to the cell membrane, which is the most obvious way of tethering MMP activity to the cell membrane. The secreted MMPs can, however, also localize to the cell surface by binding to integrins or to CD44 or through interactions with cell-surface associated heparan sulphate proteoglycans, collagen type IV or the extracellular matrix metalloproteinase inducer (EMMPRIN) (Egeblad *et al.*,2002). Based on their substrate specificity, MMPs have been divided into distinct subclasses: collagenases, gelatinases, stromelysins, and matrilysins. The minimal domain structure consists of a signal peptide, prodomain, and catalytic domain. The propeptide domain contains a conserved cysteine residue (the “cysteine switch”) that coordinates to the catalytic zinc to maintain inactivity. The gelatinases (MMP-2 and -9) contain inserts that resemble collagen-binding type II repeats of fibronectin within their catalytic domains in addition to the simple hemopexin domain structure.

STRUCTURE OF MATRIX METALLOPROTEINASES

The MMPs are multidomain enzymes, which contain at least a prodomain and a catalytic domain (except for MMP- 23). The most complex MMP structures available to date is the structure of proMMP-1 including prodomain, catalytic domain, linker and hemopexin domain and of proMMP-2, which contains additionally three fibronectin type-II repeats (Jozic *et al.*,2004).

The catalytic domain

The catalytic domain of all MMPs is similar in showing a shallow active-site cleft notched into the front surface and separating the smaller ‘lower subdomain’ from the larger ‘upper subdomain’ This cleft extends horizontally across the molecule and would bind a peptide substrate from left to right. The upper subdomain encompasses a characteristic five-stranded, highly twisted β-sheet, flanked by three surface loops on its convex side and by two long

regular α-helices on its concave side. Four of the five β-strands are aligned in a parallel fashion, only the cleft-sided 'edge strand' IV runs in opposite direction. The chain passes β strand sI, α-helix hA, β-strand sII, sIII, before entering the so-called S-loop, which is fixed via the 'structural zinc' (Z2) and one of three bound calcium ions (Ca1) to the underlying β-sheet. This S-loop extends into the cleft-sided 'bulge', which continues into the anti-parallel edge strand, forming a segment of prime importance for binding of peptidic substrates and inhibitors via main chain hydrogen bonds. The end of the sII-sIII connecting segments together with the sIV-sV connecting loop sandwiches another calcium ion (Ca2). After strand sV, the chain passes through the large open sV-hB loop, another segment of high variability and a source of specificity within the MMP family, before entering the long horizontally extending 'active-site helix' hB. This helix provides the first and the second His of the metzincin characteristic zinc binding (Z1) motif (His218 and His222, using the proenzyme nomenclature of MMP-1) together with the 'catalytic' Glu (Glu219). Then the chain bends down, provides the third zinc ligand (His228), terminates the metzincin motif with the 1.4-tight 'Met-turn' and forms the lower substrate interaction surface of the primed sites with the segment Pro238- Ser239-Tyr240 (wall-forming segment, forming the outerwall of the S1'-pocket). The domain is completed by the following specificity loop and helix hC (Butler *et al.*,2004).

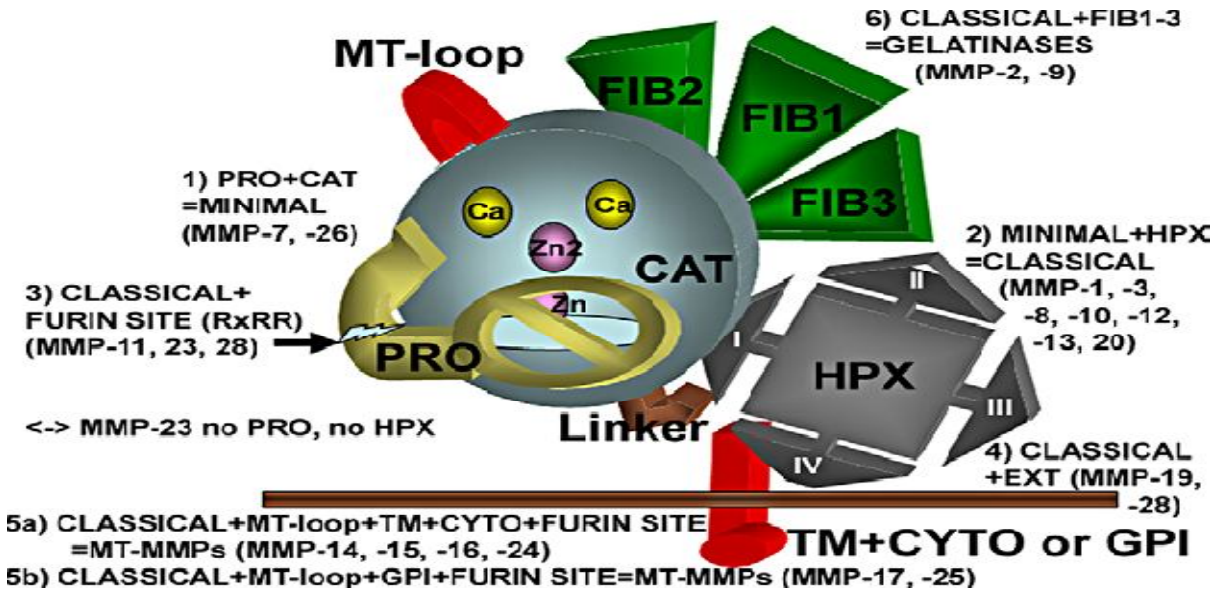


FIG-1: SCHEMATIC REPRESENTATION OF THE DOMAIN STRUCTURE OF HUMAN MMP FAMILY MEMBERS:THE CATALYTIC (CAT) DOMAIN IN SHOWN WITH THE TWO ZINCS (PINK) AND TWO CALCIUM IONS (YELLOW). THE PRODOMAIN (PRO) IN DARK YELLOW BLOCKS THE ACTIVE SITE.A LINKER PEPTIDE (LINKER) CONNECTS THE CATALYTIC AND THE HEMOPEXIN-LIKE (HPX) DOMAIN. SOME CLASSICAL MMPS SHOW AN EXTENSION (EXT) AT THE C-TERMINUS WHICH IS NOT A MEMBRANE ANCHOR. THE MT-MMPS (MT-LOOP) SHOW A MEMBRANE-ANCHOR THAT IS EITHER BE A TRANSMEMBRANE (TM) HELIX WITH SMALL CYTOPLASMIC PART (CYTO) OR A GPI-ANCHOR(GPI) (Maskos, K. 2005).

Metal site geometries

Besides the catalytic zinc, all MMP catalytic domains possess another zinc ion, the so-called structural zinc, and one to three calcium ions (Bode *et al*,2004). The structural zinc is liganded in a tetrahedral coordination sphere made up by His168,Asp170, His183 and His196 (Z2) and seems to be more tightly bound than the catalytic zinc. The first and thus probably most tightly bound calcium ion (C1) packs the second part of the S-shaped loop against the side-chain carboxylate groups of a conserved Asp-Glu couple pointing upward from strand sV. The second calcium ion (C2) is sandwiched between the sVI-sV loop and strand sIII coordinated in an octahedral manner by three carbonyl groups, one carboxylate oxygen of the invariant Asp194 and a water molecule. The loop following strand Sv encircles another calcium atom (C3) in MMP-1, -3, -7, -9, -10 and -12, which is bound through the carbonyl groups of residues 199 and 201 together with the carboxylate oxygens of Glu/Asp199 and Asp124 and two water molecules in a pentagonal bipyrmid. The Asp124 seems to be the critical determinant for the presence of this third calcium site (Maskos, K. 2005).

Specificity determinants

The upper rim of the active-site is formed by the so-called bulge-edge segment and the second half of the S-loop, while the lower rim is constituted by the third zinc-binding imidazole and the so-called S1'wall-forming segment. In sum, this arrangement leads to a relatively flat surface putting up the nonprimed sites and a clear cleft accommodating the primed sites. Most of the inhibitors bind only to the primed sites inserting into the cleft- like surface under the formation of a beta-sheet with the bulge edge segment on top and the S1'wall-forming segment below. The side chain in P1' position is the critical determinant for the affinity of inhibitors and also for the cleavage of substrates. Further clear substrate determinants that could be determined via substrate and inhibitor work are the S3, S2, S1, and S2' subsites. The P3 residue, which is always Pro in collagen cleavage sites, touches the mainly hydrophobic S3 pocket. The S2 subsite is located on top of the third active site zinc ligand (His228) and is shallow in most MMPs. It's size and polarity mostly depends on the residue in position 227. Longer side chains in P1 elongate along His183 and the residue in position 180, which can vary from Ser to Phe. A P2' side chain will become squeezed between the bulge rim and the middle residue in the Pro-Xaa-Tyr240 wall-forming segment (Lang *et al.*,2004).

The prodomain

So far, prodomain containing structures have been published for MMP-1, -2, -3 and -9. This domain exhibits an egg-like shape attached with its rounded side to the active site cleft of the catalytic domain. In proMMP-1, -3 and -9, the first 12, 11 and 9 residues are disordered, respectively, while the corresponding N-terminus of MMP-2 is fixed through mainly hydrophobic interactions with the third fibronectin type-II repeat. The prodomain essentially consists of three helices that are arranged nearly perpendicular to each other and connected via rather flexible and proteolysis susceptible loops. In case of MMP-1 and MMP-2, the loop between helix H1 and helix H2 (bait region) contains the region of the first activation cleavage (EKRRN in proMMP-1 and SCN*LF in proMMP- 2). This first cleavage is supposed to destabilize the threehelix bundle of the MMP prodomains. The most likely

reasons for the presence of structure in this loop in proMMP-2 are the six residue shorter loop and the presence of a disulfide bridge in this region compared to the other three proMMPs. An almost invariant P90-R-C-G-V-P-D loop (switch loop) covers the active site which ends at the 99/100 cleavage site, the beginning of the active enzyme. The prodomain is bound in the substrate binding sites P3' to P2 and forms five main chain hydrogen bonds but runs in opposite direction as a substrate would do. Due to the coordination of the active site zinc by Cys92 and the salt bridge between Arg91 and Asp96, the S1' and S2' pockets are not filled by the switch loop (Maskos, K. 2005).

The hemopexin-like domain

The hemopexin-like domain in MMPs has the shape of an oblate ellipsoidal disc. The polypeptide chain is essentially organized in four β-sheets (blades), which are numbered I–IV in their order of appearance and arranged almost symmetrically around a central channel giving rise to a four-bladed propeller. At the entrance of the central channel (defined by the direction of the β-strands) three aspartates and one glutamate form an acidic patch. These side chains form salt bridges to neighboring β-strands while the carbonyl groups (at distances of 2.1–2.5 Å), which face the tunnel center, together with two water molecules bind a calcium ion in an octahedral conformation in many structures (Jozic *et al.*,2004). In the center of this tunnel, there are indications for a tetragonally coordinated chloride ion bound by four main chain amide groups. The same amino acids may additionally coordinate a Na+ or a calcium ion with their carbonyl oxygens at typical distances (2.3–2.6 Å).

The hinge region

The hinge-region in MMPs is a segment of 15–65 amino acids. It is of critical importance for the stability of the enzyme and also for the degradation of complex substrates such as fibrillar collagen by collagenases which require the concerted action of the catalytic and the hemopexin domain (Chung *et al.*,2004). Recently, it has been shown that also the hinge region itself can contribute to the collagen binding and unwinding and its breakdown (Tam *et al.*,2004).

The fibronectin type II repeats

The three individual consecutive repeats that form the fibronectin-like domain of MMP-2 (also named Col-1, -2, -3 domains) have been solved by NMR. Spectral perturbations induced by a peptide mimicking the collagen consensus sequence, (Pro-Pro-Gly), indicated interactions mainly with exposed aromatic residues around the central Arg34 (fibronectin type-II repeat nomenclature of MMP-2). In accordance with the crystal structure of proMMP-2 that showed interaction of the prodomain segment 33–42 of proMMP- 2 only with Col-3 the propensity of this propeptide segment to interact with the three individual repeats (Col-1 to -3) at the PPG6 interaction sites. In the proenzyme structure, these contacts mainly involve Ile35, Phe37 and Asp40 of the propeptide (Maskos, K. 2005).

REGULATION OF MATRIX METALLOPROTEINASE ACTIVITY

The MMPs are synthesized as inactive ZYMOGENS (pro-MMPs). They are kept inactive by an interaction between a cysteine-sulphydryl group in the propeptide domain and the zinc ion bound to the catalytic domain: activation requires proteolytic removal of the propeptide prodomain. MMP-2 is activated at the cell surface through a unique multistep pathway that involves MMP-14 (MT1-MMP) and the tissue inhibitor of metalloproteinases 2 (TIMP-2) TIMP-2 binds MMP-14 at its amino terminus and pro-MMP-2 at its carboxyl terminus, which allows an adjacent, non-inhibited MMP-14 to cleave the bound pro-MMP-2.MMP-14 does not fully activate MMP-2 and another, already activated, MMP-2 is required to remove a residual portion of the MMP-2 propeptide. MMP activity is tightly controlled by endogenous inhibitors. The main inhibitor of MMPs in tissue fluids is α2-macroglobulin, an abundant plasma protein. α2-macroglobulin binds to MMPs and the α2-macroglobulin–MMP complex then binds to a scavenger receptor and is irreversibly cleared by endocytosis. In a similar way to α2-macroglobulin, thrombospondin-2 forms a complex with MMP-2 and facilitates scavenger-receptor-mediated endocytosis and clearance. By contrast, thrombospondin-1 binds to pro-MMP-2 and -9 and directly inhibits their activation. Curiously, thrombospondin-1 has also been reported to increase MMP-2 and -9 activation (Egeblad *et al.*,2002).

FUNCTIONAL ROLES OF MMP IN CANCER

Proteolysis of Extra cellular matrix (ECM)

In most organs, the principle components of the ECM are collagens and numerous other proteins including laminin, entactin, and proteoglycans that make up the basement membrane. Tumor cells overexpress proteases and/or induce expression of these enzymes in neighboring stromal cells in order to degrade the basement membrane and invade the surrounding tissue. Several MMPs have been implicated in the ECM degradation associated with tumor growth and angiogenesis. This proteolytic activity is also required for a cancer cell to invade a nearby blood vessel (intravasation) and then extravasate at a distant location and invade the distant tissue in order to seed a new metastatic site (Roy *et al.*, 2009).

Modulation of Cell Adhesion, Migration, and Epithelial to Mesenchymal Transition

ECM degradation products display unique biologic properties that can trigger a variety of cellular signals. For example, cleavage of collagen IV and laminin-5 generates cryptic peptides that can in turn promote migration of tumor cells. MMP substrates include non-ECM molecules, ranging from growth factor precursors and cell surface adhesion molecules to angiogenic inhibitor precursors. E-cadherin is cleaved leading to the release of soluble E-cadherin and the disruption of cell-cell interactions leading to disruption of cell adhesion and increase in migration. In addition, several integrins can serve as substrates for MMPs. MMPs have also been implicated in the epithelial to mesenchymal transition (EMT), a hallmark of cancer progression to metastasis.During EMT, tumor cells acquire migratory characteristics and more readily invade into surrounding tissues and metastasize to secondary sites. Activation of growth factors and cleavage of adhesion molecules are some of the proposed mechanisms underlying MMP induced EMT (Roy *et al.*, 2009).

Regulation of Cytokines and Receptors

Recent studies point to an emerging role for MMPs in modulating aspects of immunity and inflammation during tumorigenesis (Noel *et al.*,2008). Cytokine signaling is an integral aspect of inflammation. A variety of cytokines, cytokine receptors, and chemokines have been found to undergo MMP-mediated cleavage. In breast cancer, MMP-9 expression is upregulated in tumor-associated stromal cells including neutrophils, macrophages, and lymphocytes and may play a role in tumor-associated inflammation (Roy *et al.*, 2009).

Regulation of Growth Factors and Receptors

Several members of the MMP can regulate cellular proliferation by modulating the bioavailability of growth factors or cell-surface receptors. For example, the bioavailability of insulin-like growth factors (IGFs) is mainly regulated by IGF binding proteins (IGFBP). MMP-1, -2 and -3, cleave IGFBP-3, while IGFBP-1 is a substrate for MMP-11. Ligands for several growth factor receptors are processed by MMP family members. Chief among them are the epidermal growth factor (EGF) receptor ligands: heparin-binding EGF (HB-EGF), amphiregulin, betacellulin, heregulin, and epiregulin. Normally, signaling via the EGF receptor (EGFR) pathway is tightly controlled. In cancer, as a consequence of increased shedding of active EGFR ligands and induction of constitutively active EGFR kinases, signaling through these pathways is upregulated, resulting in uncontrolled proliferation, migration, and survival of cancer cells. MMPs have been shown to promote angiogenesis through their release of angiogenic factors stored in the ECM such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF). Stroma-derived MMP-9 can facilitate the liberation of ECM-sequestered VEGF during tumor angiogenesis (Ongusaha *et al.*,2004).

Role in Tumor-Associated Angiogenesis

Angiogenesis is a complex process by which new blood vessels are formed from existing vessels; it involves multiple interactions between endothelial cells, surrounding pericytes, and smooth muscle cells, ECM, and angiogenic cytokines/ growth factors. The multiple steps include degradation of the basement membrane surrounding an existing vessel, migration and proliferation of endothelial cells into the new space, maturation, differentiation, and adherence of the endothelial cells to each other, and lumen formation. Angiogenesis can be initiated by the release of proangiogenic factors (*e.g.*VEGF, b-FGF, and tumor necrosis factor α) from inflammatory cells, mast cells, macrophages, or tumor cells. These factors bind to their respective cell-surface receptors on endothelial cells, leading to their activation, which includes the induction of cell proliferation, increased expression of cell adhesion molecules (*e.g.*, integrins α1β1,α2β1, α5β1, and αvβ3; *T*-shaped receptors), secretion of MMPs, and increased migration and invasion. b-FGF is mitogenic for many cell types including endothelial cells, and, although it does not have a conventional signal peptide for secretion, it can be found sequestered in the ECM bound to heparan-sulfate-containing proteoglycans, where it is released by ECM-degrading enzymes. b-FGF induces cell proliferation, protease

production, chemotaxis, and modulates integrin expression in endothelial cells (Rundhaug *et al.*,2003).

VEGF is a potent mitogen and chemoattractant for endothelial cells and induces the release of MMP-2, MMP-9, and MT1-MMP by endothelial cells. In addition, VEGF, also known as vascular permeability factor, induces vascular permeability, which allows leakage of plasma proteins, such as fibronectin and other clotting proteins. Activation of the clotting system results in deposition of fibrin in the provisional stroma. Fibronectin and fibrin then bind and activate their integrin receptors (α5β1 and αvβ3) on activated endothelial cells. The integrin αvβ3 localizes to the tips of endothelial cells in sprouting vessels, and its expression is reduced on mature vessels. Interestingly, αvβ3 integrin has also been shown to bind MMP-2, which may participate in its activation and serve to localize it to the surface of invading endothelial cells. More recent reports suggest αvβ3 integrin may actually have antiangiogenic effects as a receptor for endogenous angiogenesis inhibitors, thrombospondins, tumstatin, and the isolated hemopexin domain of MMP-2, and by down-regulating expression of the VEGF receptor, VEGFR-2. Ligand binding to integrins initiates intracellular signaling, which promotes. TGFα, released from bound ECM and activated by MMPs, is a potent chemoattractant for monocytes and macrophages, and stimulates their production of proangiogenic factors, b-FGF, tumor necrosis factor-α, and interleukin-1α. TGFα also induces the expression of MMP-2 and -9, and PDGF-A and –B by endothelial cells and down-regulates TIMP expression. Mechanical/shear stress on extruding endothelial cells also induces expression and secretion of PDGF-B. PDGF-BB homodimer acts as an autocrine growth factor for endothelial cells as well as stimulating chemotaxis, proliferation, and the differentiation of pericytes and smooth muscle cells required for vessel maturation. Contact between endothelial cells and pericytes further induces TGFα expression. TGFα also contributes to vessel maturation/stabilization by stimulating the secretion of chondroitin sulfate, the principle ECM component between endothelial and smooth muscle cells, by smooth muscle cells.

MMPs contribute to angiogenesis not only by degrading basement membrane and other ECM components, allowing en-dothelial cells to detach and migrate into new tissue, but also by releasing ECM-bound proangiogenic factors (b-FGF, VEGF, and TGFα). In addition, MMP degradation of ECM components generates fragments with now-accessible integrin binding sites, triggering integrin intracellular signaling. By directly binding to αvβ3, MMP-2 may itself initiate integrin signaling and thereby contribute to endothelial cell survival and proliferation. However, MMPs also are able to generate endogenous angiogenesis inhibitors from larger precursors: cleavage of plasminogen by MMPs releases angiostatin; endostatin is the COOH terminal fragment of the basement membrane collagen XVIII, which can be generated by cleavage by cathepsins and MMPs; and generation of the hemopexin domain of MMP-2 from MMP-2 may be through autocatalysis. Thus, the MMPs have both pro- and antiangiogenic functions. On the whole, however, MMPs are required for angiogenesis, and MMPIs have been shown to inhibit angiogenesis in animal models (Rundhaug *et al.*,2003).

MMP2 and MMP9 AS BIOMARKERS OF CANCER

One of the more promising and exciting applications of MMPs in human cancers is as potential cancer biomarkers, both diagnostic and prognostic.

Breast Cancer

Evidence is emerging that members of the MMP family can serve not only as potential markers for diagnosis and prognosis, early detection, and risk assessment, but also as indicators of tumor recurrence, metastatic spread, and response to primary and adjuvant therapy for breast cancer. MMP-9 levels in tumor tissue as well as serum, plasma, and urine are significantly elevated in patients with breast cancer (Wu *et al.*,2008). Recently, efforts have focused on the use of MMPs potential biomarkers of early breast cancer. Studies indicate that urinary MMP-9 in addition to being predictive markers for breast cancer, may also prove useful as noninvasive breast cancer risk assessment tools (Pories *et al.*,2008).

Metastatic breast cancer involves the regional lymph nodes (LN) and liver or bone resulting in significant morbidity. Several independent studies have used circulating MMP-9 activity to predict metastatic spread of disease as well as to monitor patient response to primary and adjuvant therapy and to evaluate outcome. High levels of serum MMP-9 and TIMP-1 are associated with increased incidence of LN metastasis and decreased relapse-free and overall survival rates. MMPs may also be useful in predicting therapeutic efficacy (Roy *et al.*, 2009).

Pancreatic Cancer

Nowhere is the need more urgent for sensitive and specific biomarkers for early diagnosis and to screen high-risk patients than in pancreatic cancer. This disease is extremely difficult to diagnose in its early stages due to a lack of specific symptoms and the limitations of current diagnostic methods. Several studies have evaluated differentially expressed biomarkers for pancreatic cancer using tissue, blood, or pancreatic juice. Serum and tissue levels of MMP-9 are significantly higher in patients with pancreatic ductal adenocarcinoma than in patients with chronic pancreatitis and healthy controls (Tian *et al.*,2008). MMP-2 levels are upregulated in the pancreatic juice of patients with cancer (100%) as compared with patients with chronic pancreatitis (2%) or normal controls (0%).

Lung Cancer

Several studies have reported that plasma and/or serum levels of MMP-9 and TIMP-1 are elevated in patient with stage III or IV lung cancer whencompared with those in patients with nonmalignant lung diseases (Koc *et al.*,2006). Retrospective studies of non–small-cell lung cancer (NSCLC) tissue found that MMP-7 expression was higher in squamous cell carcinomas than in adenocarcinomas and correlated with significantly lower overall survival in patients (Liu *et al.*,2007).

Bladder Cancer

As is expected, a majority of the biomarker studies in patients with bladder cancer have focused on urine. Studies have shown that urinary MMP-2 and MMP-9 levels correlate with presence of bladder cancer as well as stage and grade of disease. The identification of several MMP species in urine from patients with primary tumors in the bladder and prostate including MMP-2, MMP-9, MMP-9/neutrophil gelatinase-associated lipocalin complex and MMP-9 dimer (Roy *et al.*,2008). The difference in detection of MMP species in the urine of the two types of cancers studied may serve as a tumor-specific fingerprint that can indicate both the presence of a tumor as well as its location. Increased levels of MMP-9 and MMP-2 in urine correlate with increased expression of these proteases in bladder tumor tissue as well.

Colorectal Cancer

MMP-2 and MMP-9 have been studied as potential prognostic biomarkers of colorectal cancer. Elevated plasma MMP-2 levels have also been shown to correlate with lymph node metastasis (Langenskiold *et al.*,2005). These MMPs may not be prognostic markers for tumor recurrence, however, since plasma proMMP-2 and -9 activities did not correlate with disease relapse after surgery (Waas *et al.*,2005).

Ovarian Cancer

MMP-2, -9, and -14 are among the most studied MMPs as biomarkers for ovarian cancer. MMP-9 activity in tissue extracts was significantly increased in advanced ovarian cancers (International Federation of Gynecology and Obstetrics stage III) compared with benign tumors and was found to be an independent prognosticator of poor survival. In another study of invasive epithelial ovarian cancer, high stromal expressions of MMP-9 and -14 were significantly correlated with cancer progression and were independent prognostic markers. Correlation with ovarian cancer progression has also been reported for MMP-2 and elevated levels of MMP-2 in cancer cells of peritoneal implants were associated with a significant risk of death in stage III ovarian carcinomas (Perigny *et al.*,2008). Importantly, the cellular source of MMPs must be considered when evaluating MMPs as ovarian cancer biomarkers. Strong MMP-9 levels in cancer cells were associated with longer survival whereas strong stromal MMP-9 was associated with shorter survival, suggesting a dual role for MMP-9 during ovarian cancer progression (Sillanpaa *et al.*,2007).

Prostate Cancer

MMP-2, -9, -15, and -26 expression in tissue or serum have been positively correlated with prostate cancer. Among these MMPs, the activities of plasma MMP-2 and -9 increased significantly in metastatic prostate cancer. In addition, increased urinary MMP-9 activity has been shown to distinguish between prostate and other types of cancer (eg, bladder cancer) (Roy *et al.*,2008). MMPs can also be combined with other markers to increase their predictive capability.

Brain Tumors

Elevated tissue levels of MMP-2 and MMP-9 have been reported in aggressive brain tumors. Positive MMP-2 expression in tissue was also associated with shorter survival in patients with malignant brain tumors. Both latent and activated forms of MMP-2 and MMP-9 have been detected in the cerebrospinal fluid of patients with brain tumors. In studies of primary glial tumors and other CNS tumors, have recently shown that detection of MMP-2, MMP-9, MMP-9/neutrophil gelatinase-associated lipocalin complex, and/or VEGF in the urine predicted disease status and therapeutic efficiency of patients with brain cancer (Smith *et al.*,2008). Importantly, these studies showed that the upregulation of MMP-2 and -9 in the source tumor tissue was also reflected in CSF as well as in urine of these patients.

MMPS AS THERAPEUTIC TARGETS

Given the important roles thatMMPsplay in tumor growth, metastasis, and the dysregulated angiogenesis that drives them, there has been significant attention paid to the development of clinically useful antagonists of this enzyme family. There are a number of matrix metalloproteinase inhibitors (MMPIs) that are currently being tested in all three phases of clinical trials against a variety of human cancers (Robins *et al.*,2008). The promise of this therapeutic approach has yet to be realized and the academic, pharmaceutical, and biotechnology arenas continue to debate the potential issues underlying the lack of therapeutic success in cancer treatment.

METHODOLOGY

Data set for this insilico study included:

(A)STRUCTURES OF MMP2 AND MMP9

Crystal structures of both matrix metalloproteinases were taken from RCSB PDB.
MMP2-PDB ID: 1Q1B
MMP9-PDB ID: 1GKC
And visualised by UCSF Chimera visualisation software.

RCSB PROTEIN DATA BANK

The **Protein Data Bank** (**PDB**) is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. (See also crystallographic database.) The data, typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists from around the world, are freely accessible on the Internet via the websites of its member organisations (PDBe, PDBj, and RCSB). The PDB is overseen by an organization called the Worldwide Protein Data Bank, wwPDB.

The PDB is a key resource in areas of structural biology, such as structural genomics. Most major scientific journals, and some funding agencies, such as the NIH in the USA, now require scientists to submit their structure data to the PDB. If the contents of the PDB are thought of as primary data, then there are hundreds of derived (i.e., secondary) databases that categorize the data differently. For example, both SCOP and CATH categorize structures according to type of structure and assumed evolutionary relations; GO categorize structures based on genes.

UCSF Chimera: visualisation software

UCSF Chimera is a highly extensible program for interactive visualization and analysis of molecular structures and related data, including density maps, supramolecular assemblies, sequence alignments, docking results, trajectories, and conformational ensembles. High-quality images and animations can be generated.

(B)MOLECULAR DYNAMICS SIMULATION

A computational method which describes equilibrium and dynamics properties of a biological system. Generates configurations of the system by integration of Newton's laws of motion – calculate the time dependence of the molecular system.Generates information at the microscopic level –atomic positions and velocities.Connects structure and function by providing additional information to X-ray crystallography and NMR. Molecular dynamics simulation of both the targets MMP9 and MMP2 was done using gromacs.

TOOL: GROMACS

GROMACS simulates molecular dynamics. It is primarily designed for biochemical molecules like proteins and lipids that have many complicated bonded interactions, but since it is extremely fast at calculating the nonbonded interactions (that usually dominate simulations) it is also used for research on non-biological systems, e.g. polymers. GROMACS is user-friendly, with topologies, parameter files, and error messages written in clear text format. There is a lot of consistency checking, but no scripting language: all programs use a simple interface with command line options for input and output files.

(C)CHEMOINFORMATICS

Chemoinformatics is the mixing of those information resources to transform data into information and information into knowledge for the intended purpose of making better decisions faster in the area of drug lead identification and optimization.

(C1)NATURAL COMPOUNDS LIBRARY GENERATION: Chemical structures of constituents from medicinal plants were taken from chemical databases to generate a natural compound library:

- CHEMSPIDER(chemical database)
- ChEMBL - European Bioinformatics Institute
- Chemical Entities of Biological Interest (*ChEBI*)

CHEMSPIDER (chemical database)

ChemSpider is a free chemical compound search system maintained by the Royal Society of Chemistry that has indexed chemical structures by "reading" images in patents and other documents throughout the web. It then "tags" the chemical structure data with a number of chemical identifiers and chemical properties.

ChemSpider relies on both open access sources (such as regulatory lists) and closed, for-profit commercial sources for the data it indexes. One of its partners for patent content is the SureChem database.

ChemSpider provides free chemical structure and even sub-structure searches, as well as searches by other identifiers such as IUPAC chemical name, SMILES codes, and InChI codes. Available options for search forms include:

- Simple Search - Search by Systematic Name, Synonym, Trade Name, Registry Number, SMILES, InChI or CSID. Additional filter options available (Sinlge/Multi-component, Isotopically Labeled, Additional Filters)

- Structure Search - Convert identifier to structure, load structure, or draw structure in structure-drawing tool. Search options include Exact, Substructure, or Similarity, with additional options available depending on selected search type. Additional filter options available (Sinlge/Multi-component, Isotopically Labeled, Additional Filters)
- Advanced Search - Search by Structure, Identifier, Elements, Properties, Calculated Properties, Data Source/Type/Focused Library, LASSO Similarity. Additional filter options available (Sinlge/Multi-component, Isotopically Labeled, Additional Filters)
- Ligand screening (available in Advanced Search options)
- Chemical elements (available in Advanced Search options)
- Intrinsic properties (available in Advanced Search options)
- Predicted properties (available in Advanced Search options)
- Data slice (available in Advanced Search options)

CHEMBL - EUROPEAN BIOINFORMATICS INSTITUTE (chemical database)

ChEMBL is a database of bioactive drug-like small molecules, it contains 2-D structures, calculated properties (e.g. logP, Molecular Weight, Lipinski Parameters, etc.) and abstracted bioactivities (e.g. binding constants, pharmacology and ADMET data).The data is abstracted and curated from the primary scientific literature, and cover a significant fraction of the SAR and discovery of modern drugs.

CHEMICAL ENTITIES OF BIOLOGICAL INTEREST (*CHEBI*) (chemical database)

Chemical Entities of Biological Interest (ChEBI) is a freely available dictionary of molecular entities focused on 'small' chemical compounds. The molecular entities in question are either natural products or synthetic products used to intervene in the processes of living organisms. Genome-encoded macromolecules (nucleic acids, proteins and peptides derived from proteins by cleavage) are not as a rule included in ChEBI. In addition to molecular entities, ChEBI contains groups (parts of molecular entities) and classes of entities. ChEBI includes an ontological classification, whereby the relationships between molecular entities or classes of entities and their parents and/or children are specified.

TABLE:1 NATURAL COMPOUND LIBRARY

	LIGANDS	PLANTS
1.	(-)-1-(s)-norcoclaurine	*Nelumbo nucifera*
2.	(-)Beta-santalene	*Santalum album*
3.	(-)-Centrolobol	*Viscum album var. meridianum*
4.	(-)-Cubebin	*Blumea balsamifera, Boswellia sacra, Cubeb*
5.	(-)-Epicatechin-3-o-gallate	*Phyllanthus, Callicarpa americana*
6.	(-)-Matairesinol	*Forsythia, Arctium lappa, Berchemia lineata*
7.	(+)-3-beta-acetoxy-a-muurolene	*Boesenbergia rotunda*
8.	(+)-Anwulignan	*Kadsura longepedunculata*
9.	(+)-Aromadendrin	*Chromolaena odorata, Berchemia lineata, Berchemia lineate, Artemesiaa*
10.	(+)-Dihydromyricetin	*Cedrus deodera*
11.	(+)-Epiafzelechin	*Cassia fistula*
12.	(+)-Gallocatechin	*Phyllanthus*
13.	(+)-Morelloflavone	*Selaginella*
14.	(+)-Nootkatone	*Juniperus communis*
15.	(+)-Swainsonine	*Ipomea*
16.	(+)Thujopsene	*Juniperus communis*
17.	(1R)-1-ethoxyethyl-2-o-ethyl-a-d-glucopyranoside	*Cardiospermum halicacabum*
18.	(2s)-2-amino-2-phenylethanol	*Castanea sativa*
19.	(2z)-3-(4-hydroxy-3,5-dimethoxyphenyl)acrylaldehyde	*Castanea sativa*
20.	(E)-Alpha-bisabolene	*Bunium persicum, Angelica glauca, Ranunculaceae, Juniperus communis, Marrubium vulgare,Nigella sativa, Schisandra chinesis, Tunisian ruta chalepensis*
21.	(R)-Coclaurine	*Nelumbo nucifera*
22.	(S)-Cheilanthifoline	*Corydalis ternata*
23.	1,2,3,4-tetrakis-o-(3,4,5-trihydroxybenzoyl)-a-d-glucopyranose	*Castanea sativa*
24.	1,2,6-trigalloylglucose	*Castanea sativa*
25.	1,3-didenzylurea	*Cocos nucifera*
26.	1,5-anhydro-d-allitol	*Celery*
27.	14-deoxy-11,12-didehydroandrographolide	*Andrographis paniculata*
28.	16-hydroxytabersonine	*Catharanthus*
29.	16R,19E-isositsirikine	*Catharanthus roseus*
30.	1-deoxy-1-[methyl(octanoyl)amino]-d-allitol	*Celery*
31.	1-dodecanol	*Ruta graveolens*
32.	1-isopropyl-2-methoxy-4-methylbenzene	*Blumea*

33.	1-phenyl-3-(p-nitrophenyl)-2,3-dibromopropan-1-one	*Boesenbergia rotunda*
34.	1-triacontanol	*Argyreia nervosa*
35.	2-(4-hydroxyphenyl)ethyl-a-d-glucopyranoside	*Cardiospermum halicacabum*
36.	2-(dimethylamino)propiophenone	*Boesenbergia rotunda*
37.	2-(ethylamino)-1-phenylpropan-1-one	*Boesenbergia rotunda*
38.	2,3-diethylpyrazine	*Annonaceae*
39.	2,4,5-trimethoxybenzaldehyde	*Acorus calamus*
40.	2,4-dihydroxychalcone	*Chrysanthemum indicum*
41.	2,5-dimethyl para anisaldehyde	*Chrysanthemum*
42.	2,6-dimethoxybenzoquinone	*Berchemia lineata*
43.	2-[(2s)-2-oxiranyl]ethyl-a-d-glucopyranoside	*Cardiospermum halicacabum*
44.	2-acetamido-1,5-anhydro-2-deoxy-d-allitol	*Celery*
45.	2-acetythiolphene	*Annonaceae*
46.	2-amino-3-phenyl-propionic acid	*Colocasia esculenta*
47.	2-amino-4-methyl-pentanoic acid	*Colocasia esculenta*
48.	2-benzoxazolinones	*Calceolaria thyrsiflora Graham*
49.	2-bromopropiophenone	*Boesenbergia rotunda*
50.	2-ethyl-3-methylmaleimide	*Vallisneria spiralis*
51.	2-furancarboxaldehyde	*Colocasia esculenta*
52.	2-furanmethanol	*Colocasia esculenta*
53.	2-hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone	*Boesenbergia rotunda*
54.	2-methyl-3-phenylpropanoate	*Boesenbergia rotunda*
55.	2-methyltryptoline	*Anadenanthera colubrina*
56.	2-nonyne	*Ammi visnagin*
57.	2-phenylethyl acetate	*Ranunculaceae,Alstonia boonei, Castanea sativa*
58.	2-propanone,1-hydroxy	*Tripterygium wilfordii*
59.	3-(dimethylamino)-1-(4-methoxyphenyl)-1-propanone hydrochloride	*Boesenbergia rotunda*
60.	3-benzylidene camphor	*Cinnamomum camphora*
61.	3-epimaslinic acid	*Centella asiatica*
62.	3-geranyl-4-hydroxybenzoate	*Boesenbergia rotunda*
63.	3-methoxy-4-hydroxypropiophenone	*Boesenbergia rotunda*
64.	3-nitro-4-anisaldehyde	*Aquilaria sinensis*
65.	3-nitropropiophenone	*Boesenbergia rotunda*
66.	3-thujanol	*Artimesia dracunculus*
67.	4-(aminomethyl)-2-methoxyphenol	*Centaurea*
68.	4-[(1s)-1-amino-2-hydroxyethyl]-5-chloro-2-methoxyphenol	*Centaurea*
69.	4-amino-2-methoxyphenol	*Centaurea*
70.	4-aminopropiophenone	*Boesenbergia rotunda*
71.	4-anisic acid	*Aquilaria sinensis*
72.	4-benzyloxy-propiophenone	*Boesenbergia rotunda*
73.	4'-bromopropiophenone	*Boesenbergia rotunda*
74.	4H-pyran-4-one-2,3-dihydro-3,5-dihydroxy-6-methyl	*Cardiospermum halicacabum*

75.	4-hydroxyphenylacetic acid	*Convolvulus arvensis*
76.	4-methoxycinnamonitrile	*Cinnamomum cassia,*
77.	4-methoxyglucobrassicin	*Capparis spinosa*
78.	4'-methoxypropiophenone	*Boesenbergia rotunda*
79.	4-methylpropiophenone	*Boesenbergia rotunda*
80.	4-o-methyl-d-glucuronic acid	*Gum arabic*
81.	4'-phenylpropiophenone	*Boesenbergia rotunda*
82.	5,7,3',4',5-pentahydroxyflavone	*Balanites, Chrysanthemum Morifolium, Nelumbo nucifera, Amaranthus spinosus*
83.	5-htp(5-hydroxytryptophan)	*Griffonia simplicifolia*
84.	5-hydroxy-4,7dimethoxyy-flavone	*Chrysanthemum*
85.	5-methoxy-n-methyltryptamine	*Anadenanthera colubrina*
86.	5-o-methyl-embelin	*Embelia ribes burm*
87.	8,11-octadecadienoic acid	*Colocasia esculenta, Osmanthus fragrans*
88.	8-methoxypsoralen	*Angelica archangelica, Fresh celery (Apium graveolens), Ruta chalepensis*
89.	9,12,15-octadecatrienoic acid	*Artemisia capillaris, colocasia esculenta*
90.	9-octadecenoic acid	*Castanea sativa*
91.	Abrine	*Abrus precatorius*
92.	Acacetin	*Chrysanthemum morifolium, Clerodendrum infortunatum, Peperomia pellucida, Aquilaria sinensis, Red propolis, Peperomia pellucida*
93.	Acacetin-7-neohesperidoside	*Chrysanthemum morifolium, Calendula officinalis*
94.	Acetic acid-geranyl ester	*Acorus calamus*
95.	Acetyl eugenol	*Chenopodium album*
96.	Aesculetin	*Convolvulus arvensis, Ipomoea, Kalimeris indica, Lonicera japonica*
97.	Ajmalicine	*Catharanthus, Rauwolfia serpentina*
98.	Alangimarckine	*Alangium salvifolium*
99.	Allantoic acid	*Desmodium caudatum*
100.	Allocimene-A	*Xylopia aethiopica and Annona senegalensis*
101.	Allyl cinnamate	*Cinnamomum cassia*
102.	Aloe emodin	*Kalimeris indica, Berchemia lineata*
103.	Alpha-aminopropiophenone	*Boesenbergia rotunda*
104.	Alpha-bergamotene	*Alpinia galangal*
105.	Alpha-cadrene	*Trichilia connaroides*
106.	Alpha-campholenaldehyde	*Boesenbergia rotunda*
107.	Alpha-crocin	*Gardenia jasminoides*
108.	Alpha-eleostearic acid	*Momordica dioica Roxb.*
109.	Alpha-guaiene	*Callicarpa, Crassocephalum Crepidioides, Osmanthus fragrans,*

		Eaglewood
110.	Alpha-himachalene	*Copaifera, Cedrus deodera, Crassocephalum crepidioides, Juniperus communis, Pimpinella anisum*
111.	Alpha-ionol	*Osmanthus fragrans*
112.	Alpha-methyl-trans-cinnaamate	*Centella asiatica, Cinnamon, Curcuma amada roxb, Fresh celery (Apium graveolens), Red propolis*
113.	Alpha-phellandrene	*Cannabis, Citrullus colocynthis, Crassocephalum crepidioides, Juniperus communis, Kaempferia, Lobelia pyrami-dalis, Myrtus communis, Nigella arvensis, Ruta chalepensis*
114.	Alpha-santalol	*Santalum album*
115.	Alpha-terpineol acetate	*Artemisia absinthium, Basil , Betula,Blumea balsamifera, Blumea megacephala, Bunium persicum, Calendula officinalis,Ranunculaceae, Cinnamon, Chenopodium album, Kaempferia, Myrtus communis, Osmanthus fragrans*
116.	Alpha-thujone	*Matricaria chamomilla, Marrubium vulgare, Artimesia dracunculus*
117.	Alpinetin	*Boesenbergia rotunda*
118.	Amentoflavone	*Selaginella*
119.	Amfepramone	*Boesenbergia rotunda*
120.	Ampelopsin-F	*Trema orientalis*
121.	Amygdalin	*Citrullus, Citrullus colocynthis*
122.	Anagalligenin-A	*Anagallis arvensis*
123.	Anemone-purple-anthocyanin-3	*Anemone*
124.	Angoroside-A	*Scrophularia ningpoensis*
125.	Angoroside-C	*Scrophularia ningpoensis*
126.	Apigenin	*Callicarpa, cannabis, Centella asiatica, Chamomile, Clerodendrum infortunatum, Colocasia esculenta Hamelia patens, Lonicera japonica, Vitex agnus-castus, Peperomia pellu ida, Red propolis, Scutellaria lateriflora*
127.	Apigenin-7-glucoside	*Chamomile*
128.	Apiol	*Peperomia pellucida*
129.	Arbutin	*Arctostaphylos uva-ursi*
130.	Arcitiin	*Forsythia, arctium lappa, Trachelospermum jasminoides*
131.	Arecatannin-B1	*Areca nut*
132.	Asarone-1	*Acorus calamus linn, Cissus*

		Quadrangularis
133.	Asarone-2	*Acorus calamus linn cissus Quadrangularis,*
134.	Asiatic acid	*Centella asiatica*
135.	Asiaticoside	*Centella asiatica, Jacaranda mimosaefolia*
136.	Astragalin	*Cornus kousa, Hedera helix, Phyllanthus*
137.	Astragaloside	*Astragalus propinquus*
138.	Atrovirinone	*Garcinia atroviridis*
139.	Atrovirisidone	*Garcinia atroviridis*
140.	Auroxanthin	*Physalis alkekengi*
141.	Avenasterol	*Centratherum anthelminticum*
142.	Bacopasaponin-C	*Bacopa monniera*
143.	Bacopaside-I	*Bacopa monniera*
144.	Bacopaside-II	*Bacopa monniera*
145.	Bacoside-A	*Bacopa monniera*
146.	Bacoside-A3	*Bacopa monniera*
147.	Bacoside-B	*Bacopa monniera*
148.	Baicalein	*Scutellaria lateriflora*
149.	Baicalin	*Scutellaria lateriflora*
150.	Balanophonin	*Embelia ribes burm*
151.	Barbaloin	*Aloe vera tourn*
152.	Bayogenin	*Centella asiatica, Hedera helix*
153.	Behenic acid	*Convolvulus arvensis*
154.	Benzyl-beta-d-glucopyranoside	*Cardiospermum halicacabum*
155.	Berberine	*Anamitra cocculus, Argemone mexicana, Tinospora cordifolia, Coscinium fenestratum*
156.	Bergapten	*Ammi majus, Angelica archangelica, Balanites, Fresh celery (Apium graveolens), Ruta chalepensis*
157.	Beta-amyrin	*Alstonia boonei, Callicarpa, Careya Arborea, Convolvulus arvensis, Capsicum annuum*
158.	Beta-chamigrene	*Trichilia connaroides*
159.	Beta-citronellol	*B. rotunda, Betula, Chenopodium album, Marrubium vulgare, Schisandra chinesis*
160.	Beta-cubebennne	*Cubeb*
161.	Beta-d-glucuronic acid	*Althaea officinalis*
162.	Beta-elemene	*Ageratum fastigiatum, Matricaria chamomilla, Callicarpa, Cannabis, Chamomile, Chromolaena odorata, Hedera helix,Juniperus communis, Kaempferia, Nigella arvensis, Schisandra chinesis*
163.	Beta-glucogallin	*Phyllanthus niruri*
164.	Beta-sesquiphellandrene	*Artemesiaaaa*

165.	Beta-sitosterol	*Alstonia boonei, Argyreia nervosa, Astragalus, Balanites, Callicarpa, Careya arborea, Cedrus deodera, Convolvulus arvensis, Desmos chinensis, Hedera helix, Hyoscyamus niger, Hypoxis hemerocallidea, Jatropha curcas, Kadsura longepedunculata, Kalimeris indica, Magnolia denudata, Ophiopogon japonicus, Parthenocissus quinquefolia, Uncaria tomentosa, Tagetes erecta ,Capsicum annuum, Phyllanthus, Fresh celery (Apium graveolens), Rubus crataegifolius, Schisandra chinesis, Scrophularia ningpoensis, Trifolium pratense*
166.	Beta-thujaplicine	*Artimesia dracunculus*
167.	Beta-thujone	*Artimesia dracunculus*
168.	Betaine	*Astragalus*
169.	Betanin	*Boerhavia erecta*
170	Betulinic acid	*Alstonia boonei, Bacopa monniera, Betula, Callicarpa, Careya arborea, Centella asiatica, Ipomoea, Jacaranda mimosaefolia, Viscum album var. meridianum*
171.	Bicyclogermacrene	*Artemisia absinthium, Artemisia dracunculus, Callicarpa, Chromolaena odorata, Nigella Arvensis, annonaceae*
172.	Biochanin-A	*Trifolium pratense, Cassia fistula*
173.	Bis(2-ethylbutyl) phthalate	*Cistanche deserticola*
174.	Bis[2-(2-butoxyethoxy)ethyl] phthalate	*Cistanche deserticola*
175.	Bis[2-(2-ethoxyethoxy)ethyl] phthalate	*Cistanche deserticola*
176.	Bisabolene	*Alpinia galanga willd, Cannabis, Juniperus communis, Marrubium vulgare, Nigella sativa, Schisandra chinesis,Ttunisian,Ruta chalepensis*
177.	Bisabolol	*Artemisia dracunculus, Matricaria Chamomilla, Chamomile, Juniperus communis, Kaempferia, Catharanthus roseus, Annonaceae*
178.	BSSG(β-Sitosterol glucoside)	*Hypoxis hemerocallidea*
179.	Bufotennin	*Ammi visnagin*
180.	Butanoic acid,2-methyl-3-oxo-ethyl ester	*Colocasia esculenta*
181.	Butanoic acid-4-hydroxy	*Colocasia esculenta*
182.	Butylidenephthalide	*Colocasia esculenta*
183.	Cadinol	*Calendula officinalis, Callicarpa, Centella asiatica, Crassocephalum*

		crepidioides
184.	Caffeic acid	*B. rotunda, Chamomile, Chrysanthemum morifolium, Convolvulus arvensis, Colocasia esculenta, Curcuma amada roxb, Hedera helix, Ipomoea, Myrtus communis, Sanicula europaea*
185.	Calamenene	*Rotundus, Acorus calamus, Astragalus propinquus*
186.	Calycosin	*Trifolium pratense*
187.	Campesterol	*Aquilaria crassna, Callicarpa, Hedera helix, Uncaria tomentosa, Peperomia pellucid,Althaea officinalis*
188.	Canavanine	*Sutherlandia frutescens, Astragalus propinquus*
189.	Cannabigerol	*Cannabis*
190.	Car-3-ene	*Artemisia dracunculus, Cannabis, Curcuma amada roxb, Juniperus communis, Myrtus communis, Boesenbergia rotunda*
191.	Carbamic acid-ethyl-phenyl-ester	*Cardiospermum halicacabum*
192.	Carbamic acid-n-hydroxy-phenyl-ester	*Cardiospermum halicacabum*
193.	Carvacrol-methyl-ether	*Annonaceae, Artemesiaaaa*
194.	Carvone	*Artemisia absinthium, Basil , Boswellia sacra, Citrullus Colocynthis, Kaempferia*
195.	Casticin	*Vitex agnus-castus*
196.	Catalpol	*Buddleja cordata*
197.	Celastrol	*Tripterygium regelii*
198.	Chalepin	*Ruta chalepensis*
199.	Chamazulene	*Artemisia absinthium, Artemisia dracunculus, Chamomile, Artimesia dracunculus*
200.	Chanoclavine	*Argyreia speciosa, Argyreia nervosa*
201.	Chanoclavine-I-aldehyde	*Argyreia nervosa, Argyreia speciosa*
202.	Chelerythrine	*Argemone mexicana, Ardisia japonica*
203.	Chlorogenic acid	*B. rotunda, Centella asiatica, Chamomile, Chrysanthemum morifolium, Convolvulus arvensis, Colocasia esculenta, Hedera helix, Rhodiola*
204.	Chrysin	*Red propolis*
205.	Chrysoriol	*Red propolis, Ardisia japonica*
206.	Cinnamonitrile-3,4-dimethoxy	*Cinnamomum cassia*
207.	Cinnamonitrile-p-dimethylamino	*Cinnamomum cassia*
208.	Cinnyl cinnamate	*Populus balsamifer*

209.	Cis-isoelemicin	*Nutmeg*
210.	Cis-jasmone	*Catharanthus roseus, Artemisia*
211.	Cis-leucosceptoside-A	*Rehmannia glutinosa*
212.	Cis-martynoside	*Rehmannia glutinosa*
213.	Cis-sabinol	*Artemisia*
214.	Cis-sabinyl acetate	*Calendula officinalis*
215.	Cistanoside-C	*Callicarpa, Callicarpa americana*
216.	Cistanoside-E	*Callicarpa*
217.	Cistanoside-F	*Callicarpa*
218.	Citronella	*B. rotunda, Betula, Chenopodium album, Marrubium vulgare, Schisandra chinesis*
219.	Citronellol	*B. rotunda, Betula, Chenopodium album, Marrubium vulgare, Schisandra chinesis*
220.	Cleomiscosin-A	*Embelia ribes burm*
221.	Columbamine	*Anamitra cocculus, Argemone Mexicana, Coscinium fenestratum*
222.	Conduritol	*Gymnema sylvestre*
223.	Coniferyl aldehyde	*Antiaris toxicaria*
224.	Coumarin	*Butea monosperma*
225.	Crocetin	*Gardenia jasminoides*
226.	Cubebin	*Boswellia sacra, cubeb*
227.	Cucurbitacin-B	*Trichosanthes cucumerina, Curcuma amada, Curcuma longa*
228.	Cumin aldehyde	*Bunium persicum, Artemesia*
229.	Cuminol	*Artemesia*
230.	Curcumene	*Curcuma amada, Curcuma longa*
231.	Curcuphenol	*Callicarpa, Rutachalepensis, Curcuma longa*
232.	Cuspareine	*Anemone chinensis*
233.	Cusparine	*Anemone chinensis*
234.	Cyclohexanamine-n-3-butenyl-n-methyl	*Cardiospermum halicacabum*
235.	D-(-)mannitol	*Bacopa monniera, Ichnocarpus frutescens*
236.	Daidzein	*Trifolium pratense*
237.	D-allitol	*Fresh celery (Apium graveolens)*
238.	Daucosterol	*Aralia cordata thunb., Desmos hinensis, Hyoscyamus niger, Jatropha curcas, Ophiopogon Japonicus tagetes erecta, Arctium lappa, Rubus crataegifolius, Schisandra chinesis, Viscum album var. meridianum, Embelia ribes burm*
239.	Decussatin	*Trema orientalis*
240.	Demethoxycucurmin	*Curcuma longa*
241.	Dibutyl phthalate	*Aquilaria crassna, Cissus quadrangularis, Aquilaria sinensis*

242.	Dichloro-p-cymene-(1,10)-phenanthroline-5-maleimide	*Vallisneria spiralis*
243.	Didodecyl phthalate	*Alstonia venenata*
244.	Dihydrocapsaicin	*Capsicum annuum*
245.	Dillapiole	*Artemesiaaaa*
246.	Diosmetin	*Chrysanthemum morifolium*
247.	DMT	*Anadenanthera colubrina*
248.	D-pinitol	*Sutherlandia frutescens*
249.	D-quercitol	*Gymnema sylvestre*
250.	Dulcin	*Pithecellobium dulce benth*
251.	Dyclonine	*Boesenbergia rotunda*
252.	Echitamine	*Alstonia boonei*
253.	E-decalactone	*Echinophora platyloba, Cocos nucifera*
254.	Elemicin	*Artemisia dracunculus, Chenopodium album, Nutmeg,*
255.	Ellagic acid	*Myriophyllum spicatum, Myrtus communis*
256.	Elymoclavine	*Ipomea*
257.	Ephedrine	*Ephedra sinica*
258.	Epi-afzelechin	*Cassia fistula*
259.	Epicatechin	*Boerhavia erecta,Ccassia fistula, Colocasia esculenta, Camellia sinensis, Phyllanthus, Trema orientalis*
260.	Epigallocatechin-gallate	*Camellia sinensis, Phyllanthus, Berchemia lineata*
261.	Epipinoresinol	*Embelia ribes burm*
262.	Episterol	*Alangium salviifolium*
263.	Epi-taxifolin	*Berchemia lineata*
264.	Epsilon-viniferin	*Parthenocissus quinquefolia*
265.	Eremoligenol	*Myrica gale*
266.	Ergostine	*Ipomea*
267.	Eriodictyol	*Berchemia lineata, Scutellaria lateriflora, Viscum album var. meridianum*
268.	Eriodictyol-7-neohesperidoside	*Berchemia lineata, Scutellaria lateriflora, Viscum album var. meridianum, Calendula officinalis*
269.	Erucic acid	*Salvia hispanica*
270.	Esculetin-4-carboxylic acid-ethyl-ester	*Convolvulus arvensis*
271.	Esculetin-4-carboxylic acid-methyl ester	*Convolvulus arvensis*
272.	Estragole	*Nigella sativa, Pimpinella anisum*
273.	Ethyl cinnamate	*Cinnamomum cassia, Chenopodium album*
274.	Ethyl salicylate	*Betula*
275.	Ethyl-2-methyl-3-oxo-3-phenylpropanoate	*Boesenbergia rotunda*
276.	Ethyl-4-o-alpha-d-glucopyranosyl-a-d-glucopyranoside	*Cardiospermum halicacabum*

277.	Ethyl-alpha-d-glucopyranoside	*Cardiospermum halicacabum*
278.	Eugenol	*Acorus calamus , Callicarpa, Cinnamon, Nutmeg, Osmanthus fragrans*
279.	Eugenol cinnamate	*Cinnamomum cassia*
280.	Eupatorin-5-methyl ether	*Chrysanthemum*
281.	Falcarindiol	*Aralia cordata*
282.	Farnesol	*Artemisia dracunculus, chamomile, Juniperus communis, Trichilia connaroides*
283.	Febrifugine	*Dichroa febrifuga*
284.	Fenchone	*Cannabis*
285.	Fenchyl acetate	*Alpinia nigra*
286.	Ferulic acid	*Cedrus deodera, Convolvulus arvensis, Curcuma amada roxb, Red propolis*
287.	Festuclavine	*Argyreia speciosa, Ipomoea, Argyreia nervosa*
288.	Festuclavine(+)	*Argyreia speciosa, Ipomoea, Argyreia nervosa*
289.	Fisetin	*Ephedra sinica*
290.	Flavokawaine-B	*Piper methysticum*
291.	Formic acid	*Colocasia esculenta*
292.	Formic acid-2-propenyl ester	*Colocasia esculenta*
293.	Galangin	*Alpinia galanga willd, Red propolis*
294.	Gallic acid	*Citrullus colocynthis, Colocasia esculenta, Curcuma amada roxb, Myriophyllum spicatum, Myrtus communis, Tagetes erecta, Rhus glabra, Red propolis, Castanea sativa*
295.	Gallotannin	*Arctostaphylos uva-ursi*
296.	Gamma-curcumene	*Curcuma amada, Curcuma longa*
297.	Gamma-fagarine	*Argentine*
298.	Gamma-guaiene	*Callicarpa, Crassocephalum crepidioides, Osmanthus fragrans*
299.	Gamma-terpinene	*Angelica glauca*
300.	Genistein	*Trifolium pratense, Flemingia macrophylla, Trifolium repens*
301.	Genkwanin	*Chrysanthemum indicum, Aquilaria sinensis,*
302.	Gentiopicroside	*Centaurium erythraea, Frasera caroliniensis*
303.	Gentisic acid	*Convolvulus arvensis, Curcuma amada roxb*
304.	Geraniin	*Phyllanthus*
305.	Geraniol	*Artemisia absinthium, Basil, Betula, Calendula officinalis, Chamomile, Juniperus communis, Marrubium*

		vulgare, Myrtus communis, Schisandra chinesis, Boesenbergia rotunda
306.	Geranyl formate	*B. rotunda, Marrubium vulgare, Balanites aegyptiaca*
307.	Geranyl isovalerate	*Artemisia absinthium, Centaureaaustro-anatolica*
308.	Germacrene	*Nigella sativa, Balanites aegyptiaca*
309.	Germacrene-D	*Ageratum fastigiatum, Annona senegalensis, Artemisia absinthium, Basil, Blumea balsamifera, Boswellia sacra, Matricaria chamomilla, Angelica glauca, Caesalpina pulcherrima, Calendula officinalis, Callicarpa, chamomile, Chromolaena odorata, Hedera helix, Juniperus communis, Kaempferia, Marrubium vulgare*
310.	Glucoputranjivin	*Sisymbrium officinale*
311.	Glucuronic acid	*Gum arabic*
312.	Glutinol	*Kalanchoe pinnata*
313.	Glyceryl palmitate	*Kalimeris indica*
314.	Gomisin-A	*Schisandra chinesis*
315.	Gomisin-N	*Schisandra chinesis*
316.	Grossamide	*Cannabis, Hyoscyamus niger, Embelia ribes burm*
317.	Guaiazulene	*Artemisia dracunculus, Matricaria chamomilla, Rhododendron Tomentosum*
318.	Guiaol	*Aquilaria crassna, Crassocephalum crepidioides, Aquilaria sinensis*
319.	Harpagide	*Scrophularia ningpoensis*
320.	Harpagide-7-acetyl	*Scrophularia ningpoensis*
321.	Harpagoside	*Scrophularia ningpoensis, Verbascum thapsus*
322.	Heleurine	*Heliotropium*
323.	Heliotrine	*Heliotropium*
324.	Heneicosane	*Betula*
325.	Henisol	*Ageratum fastigiatum*
326.	Hentriacontan-16-one	*Gymnema sylvestre*
327.	Hentriacontane	*Aquilaria sinensis*
328.	Hentriacontanol	*Paspalum scrobiculatum*
329.	Herniarin	*Chamomile*
330.	Hesperetin	*Colocasia esculenta, Red propolis, Crataegus*
331.	Hexadecanoic acid	*Cardiospermum halicacabum*
332.	Hexadecanoic acid-2-chloro-1-(chloromethyl)ethyl esteracid	*Cardiospermum halicacabum*
333.	Hexadecanoic acid-ethyl ester	*Cardiospermum halicacabum*

334.	Hexadecanoic acid-methyl ester	*Cardiospermum halicacabum*
335.	Hinokiflavone	*Selaginella*
336.	Hinokinin	*Phyllanthus*
337.	Hispidulin	*Centipeda minima*
338.	Homocapsaicin	*Capsicum annuum,Cannabis*
339.	Homoeriodictyol	*Viscum album var. meridianum*
340.	Homoplantaginin	*Scrophularia ningpoensis*
341.	Homovanillyl alcohol	*Capsicum annuum, Cannabis*
342.	Humulene oxide	*Eaglewood*
343.	Hydnocarpin-D	*Lonicera japonica.*
344.	Hydroxytyrosol	*Olea europaea*
345.	Hyperoside	*Colocasia esculenta, Crataegus*
346.	Hypophyllanthin	*Phyllanthus*
347.	Icariside	*Nelumbo nucifera, Saraca asoca*
348.	Indicine-n-oxide	*Heliotropium*
349.	Inokosterone	*Apamarga*
350.	Irilin-D	*Chenopodium rubrum*
351.	Isochlorogenic acid	*Centella asiatica*
352.	Isocolumbin	*Tinospora cordifolia*
353.	Iso-formononetin	*Astragalus propinquus*
354.	Iso-liquiritigenin	*Hydnocarpus hainainanensis, Areca catechu,Celery*
355.	Isomitraphylline	*Uncaria tomentosa*
356.	Isoorientin	*Colocasia esculenta, Eleusine corocana*
357.	Isopulegol acetate	*Tunisian,Ruta chalepensis, Artemisia*
358.	Iso-quercitrin-6-acetate	*Phyllanthus, Ardisia japonica*
359.	Isorhamnetin	*Calendula officinalis, Chrysanthemum indicum, Red propolis, Boerhavia erecta*
360.	Isorhamnetin-3-o-rutinoside	*Boerhavia erecta, Calendula officinalis, Nelumbo nucifera*
361.	Iso-rhamnetin-3-o-neo-hesperidoside	*Calendula officinalis*
362.	Iso-silybin-a	*Silybum marianum*
363.	Isovitexin-2-o-beta-d-glucoside	*Eleusine corocana*
364.	Jatrorrhizine	*Argemone mexicana, Tinospora cordifolia, Coscinium fenestratum*
365.	Kaempferide	*Alpinia galanga willd, Red propolis,*
366.	Kaempferitrin	*Citrullus colocynthis, Tagetes erecta*
367.	Kaempferol	*Argyreia speciosa, Argyreia nervosa, B. rotunda ,Cannabis, Cassia fistula, Centella asiatica, Convolvulus arvensis, Cornus kousa, Hedera helix, Myrtus communis, Red propolis*
368.	Kaempferol-3-o-rutinoside	*Hedera helix, Balanites aegyptiaca*
369.	Karakoline	*Aconite*
370.	Kaurenoic acid	*Montanoa tomentosa*

371.	Kukoamine-A	*Lycium barbarum*
372.	Kumatakenin	*Astragalus propinquus*
373.	Lanosterol	*Typha elephantina Roxb*
374.	Lariciresinol	*Forsythia, Callicarpa Americana, Saraca asoca*
375.	L-α-terpineol	*Artemisia absinthium, Basil , Betula, Blumea balsamifera, Blumea megacephala, Bunium persicum, Calendula officinalis, Ranunculaceae,Ccinnamon, Chenopodium album, Kaempferia, Myrtus communis, Osmanthus fragrans*
376.	L-β-bisabolene	*Bunium persicum, Angelica glauca, Ranunculaceae, Juniperus communis, Marrubium vulgare, Nigella sativa, Schisandra chinesis, Tunisian,Ruta chalepensis*
377.	Leachianone-G	*Desmodium caudatum*
378.	Leonurine	*Leptospermum scoparium*
379.	Ligustilide	*Celery*
380.	Lilac aldehyde	*Artemisia*
381.	Linalool	*Ammi visnaga, Annona senegalensis, Aralia cachemirica decne, Artemisia absinthium, B. rotunda, Basil , Betula, Blumea megacephala, Artemisia dracunculus, Matricaria chamomilla, Ranunculaceae, Cannabis, Chamomile,Chenopodium album, Crassocephalum crepidioides, Colocasia esculenta, Heracleum persicum, Juniperus communis, Kaempferia, Myrtus communis, Osmanthus fragrans, Trichilia connaroides*
382.	Liquiritigenin	*Hydnocarpus hainainanensis, Areca catechu,Celery*
383.	Loganin	*Alstonia boonei, Strychnos nux-vomica*
384.	Lotaustralin	*Rhodiola rosea*
385.	Lucenin-1	*Eleusine corocana*
386.	Luteolin	*Callicarpa, cannabis, Chamomile, Colocasia esculenta, Lonicera japonica, Nelumbo nucifera, Ophiopogon japonicus, Vitex agnus-castus, Aquilaria sinensis, Scutellaria lateriflora*
387.	Luteolin-4-glucoside	*Bacopa monniera, Lonicera japonica.*

388.	Luteolin-7-B-D-glucopyranoside	*Bacopa monniera, Lonicera japonica.*
389.	Lyoniside	*Saraca asoca*
390.	Lysergol	*Argyreia speciosa, Ipomoea, Argyreia nervosa, Ardisia japonica*
391.	Madecassoside	*Centella asiatica*
392.	Magniferin	*Ipomea*
393.	Malvalic acid	*Cassia fistula*
394.	Marmesin	*Ammi majus, Balanites*
395.	Maslinic acid	*Jacaranda mimosaefolia, Nelumbo nucifera*
396.	Medicagenic acid	*Kalimeris indica*
397.	Megastigmatrienone	*Colocasia esculenta, Osmanthus fragrans*
398.	Methcathinone	*Boesenbergia rotunda*
399.	Methyl anthranilate	*Ranunculaceae, Catharanthus roseus*
400.	Methyl cinnamate	*B. rotunda, Ranunculaceae, Cinnamomum cassia, Alpinia galanga*
401.	Methyl eugenol	*Ranunculaceae, Myrtus communis, Nutmeg, Red propolis, Artimesia dracunculus*
402.	Methyl gallate	*Rhus glabra*
403.	Methyl isoeugenol	*Nutmeg, Acorus calamus*
404.	Methyl jasmonate	*Catharanthus roseus*
405.	Methyl linoleate	*Argyreia speciosa, Osmanthus fragrans, Ardisia japonica*
406.	Methyl palmitate	*Argyreia speciosa,Chamomile, Ardisia japonica*
407.	Methyl stearate	*Argyreia speciosa, Ardisia japonica*
408.	Methyl-3,4-dimethoxycinnamate	*Ipomea*
409.	Methyl-3-phenylpropanoate	*Boesenbergia rotunda*
410.	Methyl-5-eicosenoate	*Ardisia japonica*
411.	Methyl-anthranilate	*Castanea sativa*
412.	Methylbutyl-2-methylbutanoate	*Ipomea*
413.	Methylephedrine	*Ephedra sinica*
414.	Miquelianin	*Nelumbo nucifera*
415.	Mitraphylline	*Uncaria tomentosa, Mitragyna speciosa*
416.	Mulberroside-F	*Hydnocarpus hainainanensis, Antiaris toxicaria*
417.	Muzigadial	*Warburgia salutaris*
418.	Myrcene	*Ammi visnaga, Annona senegalensis, Aralia cachemirica decne, Artemisia Absinthium, B. rotunda, Boswellia sacra, Artemisia dracunculus, Matricaria chamomilla, Bunium persicum, Caesalpina pulcherrima,*

		Cannabis, Celery, Chenopodium album, Crassocephalum crepidioides, Juniperus communis, Kaempferia, Lobelia pyrami-dalis, Myrtus communis, Nigella arvensis, Nigella sativa ,Nutmeg, Osmanthus fragrans, Tunisian Ruta chalepensis, Trichilia connaroides
419.	Myricetin	*Centella asiatica, Red propolis*
420.	Myristicin	*Heracleum persicum, Nutmeg, Boesenbergia rotunda*
421.	Myristoleic acid	*Ardisia japonica*
422.	Naphthopyrone	*Coleus forskohlii Briq.*
423.	Naringenin	*Chamomile, Colocasia esculenta, Berchemia lineata, Scutellaria lateriflora, Viscum album var. meridianum, Berchemia lineata*
424.	Naringin	*B. rotunda*
425.	Naringin dihydrochalcone	*Boesenbergia rotunda*
426.	Narirutin	*Hamelia patens*
427.	Neoglucobrassicin	*Capparis spinosa*
428.	Neohesperidose	*Calendula officinalis*
429.	Nepitrin	*Scrophularia ningpoensis*
430.	Nerol	*Caesalpinia pulcherrima*
431.	Nerolidol	*B. rotunda, Calendula officinalis, Chamomile, Cinnamon, Heracleum persicum,Juniperus communis, Osmanthus fragrans, Artemesia*
432.	Nerolidyl acetate	*Rhododendron tomentosum*
433.	Nimbin	*Azadirachta indica*
434.	Niranthin	*Phyllanthus*
435.	N-methylephedrone	*Boesenbergia rotunda*
436.	Nobiletin	*Jatropha curcas*
437.	Nonacosane	*Colocasia esculenta*
438.	Nonacosane -10,15 diol	*Colocasia esculenta*
439.	Nonacosane -10-ol	*Colocasia esculenta*
440.	Nonanal	*Artemesiaaaa*
441.	Nopinone	*Callicarpa americana*
442.	N-tritriacontane	*Vitex negundo*
443.	Occidentalol -I	*Trichilia connaroides*
444.	Occidentalol -II	*trichilia connaroides*
445.	Ocimene	*Xylopia aethiopica and Annona senegalensis*
446.	O -coumaric acid	*Centella asiatica, Colocasia esculenta, Red propolis*
447.	O -methoxy cinnamaldehyde	*Cinnamomum cassia*
448.	Ononin	*astragalus, astragalus propinquus*
449.	Ophiopogonin -C	*Trifolium pratense, Ophiopogon*

		japonicus
450.	Orientin	*Cannabis, Colocasia esculenta, Eleusine corocana*
451.	Paclobutraazol	*Mangifera indica*
452.	Palmatin	*Tinospora cordifolia ,Anamirta cocculus*
453.	Palmatine	*Tinospora cordifolia, Anamirta cocculus*
454.	Patchouli alcohol	*Osmanthus fragrans*
455.	Patuletin	*Centella asiatica, Myrtus communis*
456.	P-coumaric acid	*B. rotunda, Centella asiatica, Colocasia esculenta, Curcuma amada roxb, Hedera helix, Red propolis*
457.	P-cresol-methyl ether	*B. rotunda, Centella asiatica, Colocasia esculenta, Curcuma amada roxb, Hedera helix, Red propolis*
458.	Pentagalloyl glucose	*Castanea sativa*
459.	Pentatriacontane	*Vitex negundo*
460.	Peperomin -B	*Peperomia pellucida*
461.	Pericyclivine	*Catharanthus roseus*
462.	Perilla aldehyde	*Blumea megacephala, Kaempferia, Annonaceae, Blumea*
463.	Perilla ketone	*Lobelia pyrami-dalis*
464.	Perillaldehyde	*Blumea*
465.	Peruviol	*Artemesia*
466.	Petunidin	*Callicarpa americana*
467.	P-fluoropropiophenone	*Boesenbergia rotunda*
468.	Phenylacetaldehyde	*Catharanthus*
469.	Phenylethyl alcohol	*Catharanthus*
470.	Phloretin	*Boesenbergia rotunda*
471.	Phloridzin	*Boesenbergia rotunda*
472.	P-hydroxybenzoic acid	*Centella asiatica, Convolvulus arvensis, Hydnocarpus hainainanensis*
473.	Phyllanthin	*Phyllanthus*
474.	Phylloquinone	*Calendula officinalis*
475.	Phytol	*Artemisia capillaris, Basil , Betula, callicarpa, Cardiospermum halicacabum, Chamomile, Cissus quadrangularis ,Tunisian, Ruta chalepensis*
476.	Phytosterol	*Caesalpinia bonduc, Althaea officinalis*
477.	Piceatannol	*Cissus quadrangularis, Parthenocissus quinquefolia*
478.	Piceid	*Parthenocissus quinquefolia*
479.	Picralinal	*Alstonia boonei*

480.	Pinocarvone	*Annonaceae*
481.	Pinocembrin	*B. rotunda, Boesenbergia rotunda, Red propolis*
482.	Pinocembrin chalcone	*Boesenbergia rotunda*
483.	Pinocembrin -7-methyl-ether	*Boesenbergia rotunda*
484.	Piperine	*Piper longum*
485.	Piperlongumine	*Piper longum*
486.	Piperlonguminine	*Piper longum*
487.	Plastoquinone	*Calendula officinalis*
488.	Plumbagin	*Plumbago zeylanica*
489.	P-menthone	*Centaurium erythraea*
490.	P -methoxybenzylacetone	*Aquilaria sinensis*
491.	Polydatin	*Rubus crataegifolius*
492.	Pomolic acid	*Callicarpa, Centella asiatica, Heracleum persicum*
493.	Pop	*Boesenbergia rotunda*
494.	Pratensein	*Trifolium pratense*
495.	Primulaverin	*Pithecellobium dulce benth*
496.	Procyanidin -B2	*Cassia fistula*
497.	Propanoic acid	*Colocasia esculenta*
498.	Propanoi c acid-2-oxo-methyl ester	*Colocasia esculenta*
499.	Propiophenone	*B. rotunda*
500.	Propiophenone -2-amino-4'-hydroxy	*Boesenbergia rotunda*
501.	Propiophenone -4'-fluoro-3-(4-phenylpiperidino)-hydrochloride	*Boesenbergia rotunda*
502.	Protocatechualdehyde	*Castanea sativa*
503.	Protocatechuic acid	*Convolvulus arvensis, Curcuma amada roxb, Hedera helix, Kalimeris indica, Castanea sativa*
504.	Prunasin	*Prunus avium*
505.	Prunetin	*Flemingia macrophylla*
506.	Pseudo -strychnine	*Strychnos nux-vomica*
507.	Psoralen	*Angelica archangelica,Fresh celery (Apium graveolens),Ruta chalepensis*
508.	Pulegone	*Tunisian,Ruta chalepensis, Artemisia*
509.	Putrescine	*Heliotropium*
510.	Quercetin -3,4'-diglucoside	*Amaranthus spinosus*
511.	Quercetin -3-arabinoglucoside	*Amaranthus spinosus*
512.	Quercetin -3-glucoside	*Balanites, Chrysanthemum morifolium, Nelumbo nucifera, Amaranthus spinosus*
513.	Quercitrin	*Phyllanthus, Ardisia japonica*
514.	Quinazolone	*Dichroa febrifuga*
515.	Quinic acid	*Chrysanthemum*
516.	Rapanone	*Heliotropium*
517.	Raubasine	*Catharanthus, Rauwolfia serpentine, Mitragyna speciosa*

518.	Resveratrol	*Parthenocissus quinquefolia, Areca catechu*
519.	Reticuline	*Argemone Mexicana, ardisia japonica*
520.	Rhamnetin	*Red propolis, Ipomea*
521.	Rhamnocitrin	*Ipomea*
522.	Rhein	*Cassia fistula*
523.	Rhoifolin	*Lonicera japonica*
524.	Ricinoleic acid	*Castanea sativa*
525.	Robustaflavone	*Selaginella*
526.	Rosarin	*Rhodiola rosea*
527.	Rosavin	*Rhodiola*
528.	Rosiridin	*Rhodiola*
529.	Rosmarinic acid	*Hamelia patens, Sanicula europaea*
530.	Rutacridone epoxide	*Ruta graveolens*
531.	Sabinene	*Calendula officinalis, Cubeb*
532.	Safrole	*Nutmeg, Pimpinella anisum*
533.	Sakuranetin	*Red propolis, Boesenbergia rotunda*
534.	Salidroside	*Rhodiola, rhodiola rosea*
535.	Salvigenin	*Chenopodium rubrum*
536.	Santolina alcohol	*Santolina alcohol*
537.	Sativene	*Juniperus communis*
538.	Scholaricinne	*Alstonia boonei*
539.	Scholarine	*Alstonia boonei*
540.	Scoparone	*Artemisia capillaries, Ipomea*
541.	Scopoletin	*Argyreia speciosa, Ipomoea, Myrtus communis, Ardisia japonica*
542.	Scopolin	*Hedera helix, Ipomea*
543.	Scutellarin	*Citrus macroptera, Clerodendrum infortunatum*
544.	Sedanolide	*Celery*
545.	Sinensetin	*Orthosiphon stamineus*
546.	Senkyunolide -C	*Celery*
547.	sennoside-B	*Cassia fistula*
548.	Shyobunone	*Acorus calamus*
549.	Sigmasta -4-22diene-3-one	*Anagallis arvensis*
550.	Sinapic aldehyde	*Castanea sativa*
551.	Sitosterol palmitate	*Tinospora cordifolia*
552.	Smilagenin	*Sarasaparilla*
553.	Solavetivone	*Lycium barbarum*
554.	Sophoricoside	*Styphnolobium japonicum*
555.	Soyasaponin -I	*Astragalus propinquus*
556.	Spermidine	*Heliotropium*
557.	Squalene	*Cardiospermum halicacabum, Colocasia esculenta, Capsicum annuum, Alstonia venenata*
558.	Sterculic acid	*Cassia fistula*
559.	Stigmasterol	*Aalstonia boonei, Aralia cordata thunb, Bacopa monniera,Callicarpa,*

		Convolvulus arvensis, hedera helix, kalimeris indica, uncaria tomentosa, *peperomia pellucida*
560.	Stigmasteryl acetate	*alstonia boonei, aralia cordata thunb, bacopa monniera, callicarpa, convolvulus arvensis, Hedera helix, Kalimeris indica, Uncaria tomentosa, Peperomia pellucida*
561.	Stilbene	*Boswellia papyriferai*
562.	Suberic acid	*Vernonia galamensis*
563.	Subsessiline	*Voacanga africana*
564.	Succinic acid	*Desmos chinensis, Kalimeris indica, Fresh celery (Apium graveolens).*
565.	Sudan -III	*Gardenia jasminoides*
566.	Sulfurien	*Butea monosperma*
567.	Supinidine	*Heliotropium*
568.	Supinine	*Heliotropium*
569.	Swertiamarin	*Centaurium erythraea, Frasera caroliniensis,*
570.	Syringaldehyde	*Castanea sativa*
571.	Syringic acid	*Aristolochia fangchi, Balanites, Callicarpa,Convolvulus arvensis, Curcuma amada roxb, Kalimeris indica*
572.	Tabersonine	*Voacanga africana, Catharanthus*
573.	Taraxerol	*Careya arborea, Ipomoea, Jatropha curcas*
574.	Tartaric acid	*Gymnema sylvestre*
575.	Tembetarine	*Tinospora cordifolia*
576.	Tephrosin	*Millettia pachycarpa*
577.	Terpinolene	*Artemisia dracunculus, Celery, Chromolaena odorata, Cinnamon, Crassocephalum crepidioides, Heracleum persicum, Juniperus communis, Nigella arvensis, Nutmeg, Annonaceae*
578.	Terpinyl acetate	*Amomum subulatum penne*
579.	Tetrahydrocurcumin	*Curcuma amada, Curcuma longa*
580.	Theobromine	*Ichnocarpus frutescens*
581.	Theophylline	*Ichnocarpus frutescens*
582.	Thuj -3-en-10-al	*Annonaceae*
583.	Thuja -2,4(10)-diene	*Annonaceae*
584.	Thujene	*Ammi visnaga, Annona senegalensis, Aralia cachemirica decn., Arnica montana, Boswellia sacra, Angelica glauca, Calendula officinalis, Caesalpina pulcherrima, Cannab Chenopodium album, Celery, Cinnamon, Crassocephalum*

		crepidioides,Jjuniperus communis, Kaempferia, Nigella arvensis
585.	Thymol	*Ammi visnaga, Arnica montana, Artemisia absinthium, Artemisia dracunculus, Matricaria chamomilla, Chenopodium album, Heracleum persicum, Juniperus communis, Kaempferia, Nigella sativa, Schisandra chinesis, Ammi visnagin*
586.	Tiliroside	*Ipomea*
587.	Tolperisone	*Boesenbergia rotunda*
588.	Tormentic acid	*Rubus crataegifolius*
589.	Trachelanthimidine	*Heliotropium*
590.	Trachelogenin	*Ipomea*
591.	Trans -4-methoxycinnamaldehyde	*Cinnamomum cassia,*
592.	Trans -5-o-(4-coumaroyl)-d-quinic acid	*Amaranthus spinosus*
593.	Trans -carveol	*Heracleum persicum, Juniperus communis, myrtus communis*
594.	Transcinnamic acid	*Centella asiatica, Cinnamon, Curcuma amada roxb, Fresh celery (Apium graveolens), Red propolis*
594.	Triacontanol cerotate	*Marselia quadrifolia*
595.	Tricine	*Chrysanthemum indicum, Eleusine corocana*
596.	Trifoliol	*Trifolium repens*
597.	Trigonelline	*Trigonella foenum-graecum*
598.	Triptolide	*Tripterygium wilfordii*
599.	Tubuloside -E	*Callicarpa americana*
600.	Turmerone	*Curcuma longa*
601.	Tussilagone	*Tussilago farfara*
602.	Umbelliferone	*Calendula officinalis, Chamomile, Convolvulus arvensis, Ipomoea, Trifolium repens*
603.	Umckalin	*Datura stramonium*
604.	Uncarine -E	*Ucaria tomentosa*
605.	Uniconazole	*Arabidopsis*
606.	Ursolic acid	*Alstonia boonei, Callicarpa, Centella asiatica, Colocasia esculenta, Rubus crataegifolius, Schisandra chinesis*
607.	Uvaol	*Gardenia jasminoides, Arctostaphylos uva-ursi*
608.	Valencene	*Callicarpa, Cyperus, Montanoa tomentosa, Annonaceae*
609.	Valoneic acid	*Castanea sativa*
610.	Vanillic acid	*Balanites, Callicarpa, Centella asiatica, Convolvulus arvensis,*

		Hyoscyamus niger
611.	Vanillic aldehyde	*Castanea sativa*
612.	Vanillyl alcohol	*Castanea sativa*
613.	Veraguensin	*Magnolia denudata*
614.	Veratrole alcohol	*Callicarpa americana*
615.	Vernolic acid	*Centratherum anthelminticum*
616.	Viridiflorol	*Ageratum fastigiatum, Matricaria chamomilla, Callicarpa, Heracleum persicum*
617.	Vitexin	*Cannabis, Colocasia esculenta, Eleusine corocana*
618.	Voacamidine	*Voacanga africana*
619.	Vobasine	*Voacanga africana*
620.	Vobtusine	*Voacanga africana*
621.	Volemitol	*Pithecellobium dulce benth*
622.	Wedelolactone	*Eclipta alba ,Wedelia calendulacea*
623.	W-hydroxy-iso-dillapiole	*Artemesiaaaa*
624.	Wogonin	*Hydnocarpus hainainanensis, Antiaris toxicaria*
625.	Worenine	*Ardisia japonica*
626.	Wuweizisu -C	*Schisandra chinesis*
627.	Xanthotoxin	*Ammi majus, Angelica archangelica, Ruta chalepensis*
628.	Zeatin	*Hypoxis radix*

(Aggarwal *et al.*, 2006; Garodia *et al.*, 2007; Gupta *et al*., 2009; Meena *et al*., 2009; Mehrotra *et al*., 2007)

(D)VIRTUAL SCREENING

Virtual screening uses computer-based methods to discover new ligands on the basis of biological structures. Natural compound library generated above was screened against the target structures matrix metalloproteinases MMP9 and MMP2.

TOOL: PYRX - VIRTUAL SCREENING TOOL

PyRx is a Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. PyRx enables Medicinal Chemists to run Virtual Screening form any platform and helps users in every step of this process - from data preparation to job submission and analysis of the results. PyRx wizard features easy-to-use user interface and chemical spreadsheet like functionality that makes it a valuable tool for Rational Drug Design.

(C2)MOLECULAR PROPERTIES OF CHEMICAL COMPOUNDS

Molecular property and bioactivity of screenedout natural compound library was predicted by molinspiration calculation of molecular properties and prediction of bioactivity server. It helps to predict drug-like compounds from a library of compounds depending upon the molecular property and bioactivity of compounds.

MOLINSPIRATION CHEMOINFORMATICS : calculation of molecular properties and prediction of bioactivity server

Molinspiration supports internet chemistry community by offering free on-line services for calculation of important molecular properties (logP, polar surface area, number of hydrogen bond donors and acceptors and others), as well as prediction of bioactivity score for the most important drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors).

LogP (octanol/water partition coefficient): LogP is calculated by the methodology as a sum of fragment-based contributions and correction factors. Method is very robust and is able to process practically all organic, and most organometallic molecules.

Molecular Polar Surface Area TPSA: TPSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood-brain barrier penetration.

"Rule of 5" Properties : is set of simple molecular descriptors used by Lipinski in formulating his "Rule of 5". The rule states, that most "drug-like" molecules have logP <= 5, molecular weight <= 500, number of hydrogen bond acceptors <= 10, and number of hydrogen bond donors <= 5. Molecules violating more than one of these rules may have problems with bioavailability. The rule is called "Rule of 5", because the border values are 5, 500, 2*5, and 5.

Number of Rotatable Bonds – nrotb: This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs. Rotatable bond is defined as any single non-ring bond, bounded to nonterminal heavy (i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier.

(E)PHARMACOPHORE MODEL

A pharmacophore model from the selected ligands having low binding energy and druglike properties was generated for matrix metalloproteinases MMP2 and MMP9. A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response. Pharmacophore modeling is a powerful method to rapidly identify new potential drugs. For the numerous therapeutically relevant drug targets with undetermined active site geometries, pharmacophore modeling provides an effective mechanism for virtual screening. Using proven pharmacophore methods, researchers can achieve astounding results from limited data.

TOOL:LIGANDSCOUT

LigandScout takes a macromolecular structure, containing a bound ligand and identifies the key features on the ligand which are interacting with points on the protein. These, complete with a series of excluded volume features defining the shape of the active site, are automatically detected by the software and are merged into the pharmacophore.

Pharmacophores can also be created from ligands in the absence of a protein structure, but no excluded volumes are included in the output pharmacophore and the directionality of donor/acceptor groups is excluded where there may be ambiguity in positioning. The software allows alignment of either a set of ligand molecules, or of a set of pharmacophores.

Pharmacophores can be merged to create both all-encompassing consensus pharmacophores, containing all features of all input pharmacophores, or shared feature pharmacophores, which only extract the features that are common to all members of the input set of pharmacophores to allow identification of common binding modes.

(F)DOCKING

Above selected phytochemicals were docked agaist matrix metalloproteinases MMP2 and MMP9.Docking is a process, in which 2 molecules fit or dock together in a three dimensional space. Docking explores ways in which a target protein molecule and another molecule, such as drugs fit together. It predicts the optimal configuration and energy between the two molecules. It changes the orientations of molecules to maximize their interactions and minimize the total energy of interaction. The best binding pose has the minimal binding energy.

TOOL: MOLEGRO VIRTUAL DOCKER

Molegro Virtual Docker (MVD) is an integrated environment for studying and predicting how ligands interact with macromolecules. The identification of ligand binding modes is done by iteratively evaluating a number of candidate solutions (ligand conformations) and estimating the energy of their interactions with the macromolecule. The highest scoring solutions are returned for further analysis. MVD requires a three-dimensional structure of both protein and ligand (usually derived from X-ray/NMR experiments or homology modeling). MVD performs flexible ligand docking, so the optimal geometry of the ligand will be determined during the docking.

Computer aided drug designing is being extensively used to identify potential treatment for a number of diseases. There are numerous bioinformatics tools available which can be used to establish newer drugs for various diseases. Some of these tools were used in this study, to establish potential drugs for the treatment of diseases caused by matrix metalloproteinases MMP-2 and MMP-9. However, in-vitro and in-vivo studies are essential to verify the results obtained by using computer aided drug designing.

RESULTS

(A)MOLECULAR DYNAMICS SIMULATIONS OF MMP9

(1)MMP9-ENERGY MINIMIZATION

Steepest descents converged to $f_{max} < 1000$(minimum energy defined)

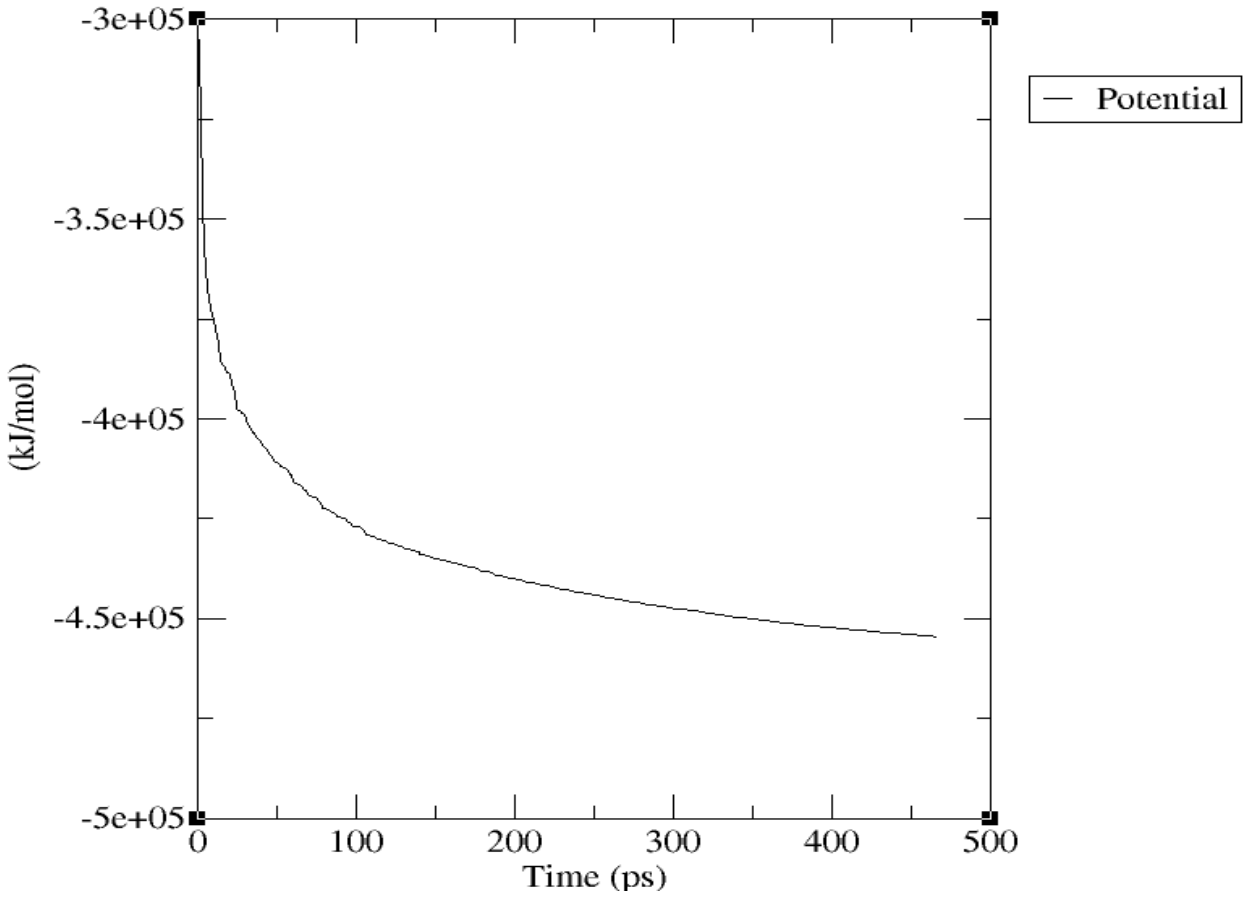
Potential energy: -4.5452447e+05

Maximum force: 9.3448706e+02 on atom 1079

E_{pot} was negative and target F_{max} was not greater than 1000 kJ mol^{-1} nm^{-1} (minimum energy defined) so the structure of MMP9 was stable.

TABLE-2: POTENTIAL ENERGY (MMP9)

Energy	Average	Err. Est.	Rmsd	Tot -drift
Potential	-435519	9300	22125.5	-61809.8 (kj/mol)



GRAPH-1: POTENTIAL ENERGY (MMP9)

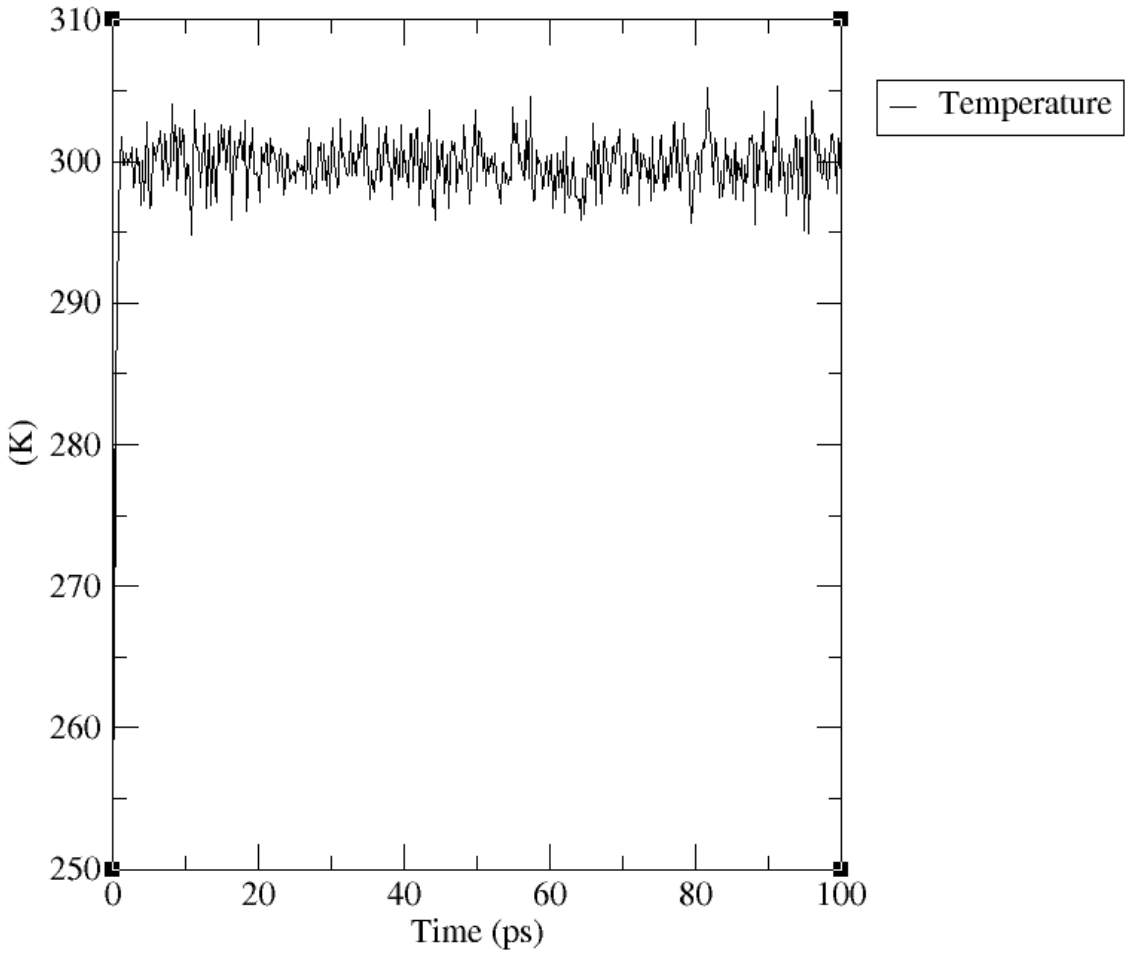
(2) MMP9-EQUILIBRATION

(2A)MMP9-TEMPERATURE

From the plot below, it is clear that the temperature of the system quickly reaches the target value (300 K), and remains stable over the remainder of the equilibration.

TABLE-3: TEMPERATURE (MMP9)

Energy	Average	Err. Est.	Rmsd	Tot -drift
temperature	299.684	0.22	4.01561	1.34663(k)



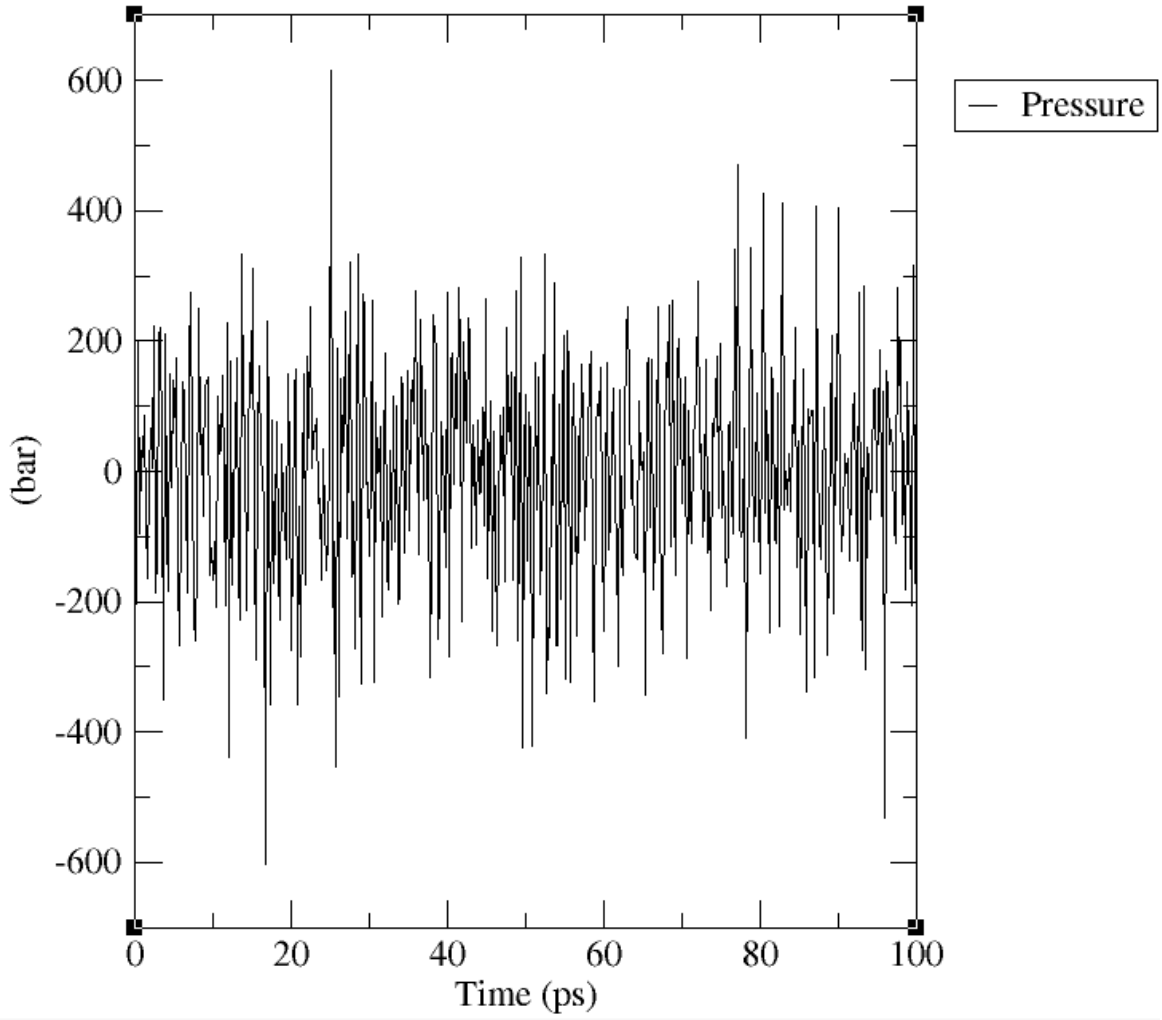
GRAPH-2: TEMPERATURE (MMP9)

(2B)MMP9-PRESSURE

The pressure value fluctuates widely over the course of the 100-ps equilibration phase, but this behavior is not unexpected.Over the course of the equilibration, the average value of the pressure is 0.92 bar.

TABLE-4: PRESSURE (MMP9)

Energy	Average	Err. Est.	Rmsd	Tot -drift
Pressure	0.920889	0.23	163.059	-0.743242 (bar)



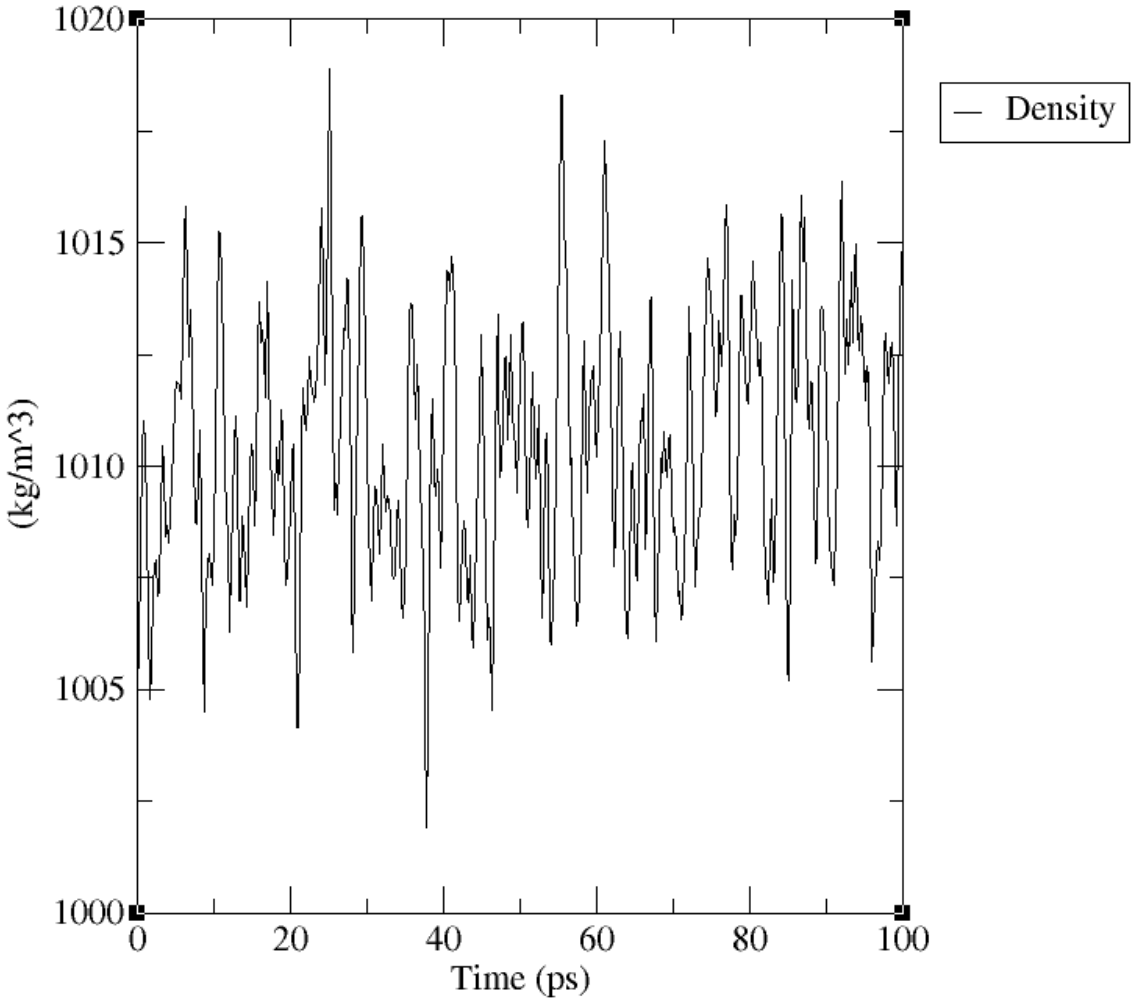
GRAPH-3: PRESSURE (MMP9)

(2C)MMP9-DENSITY

The average value over the course of 100 ps is 1010.47 kg m^{-3}, close to the experimental value of 1000 kg m^{-3}.The density values are very stable over time, indicating that the system is well-equilibrated now with respect to pressure and density.

TABLE-5: DENSITY (MMP9)

Energy	Average	Err. Est.	Rmsd	Tot -drift
Density	1010.47	0.27	2.75122	1.80483(kg/m^3)

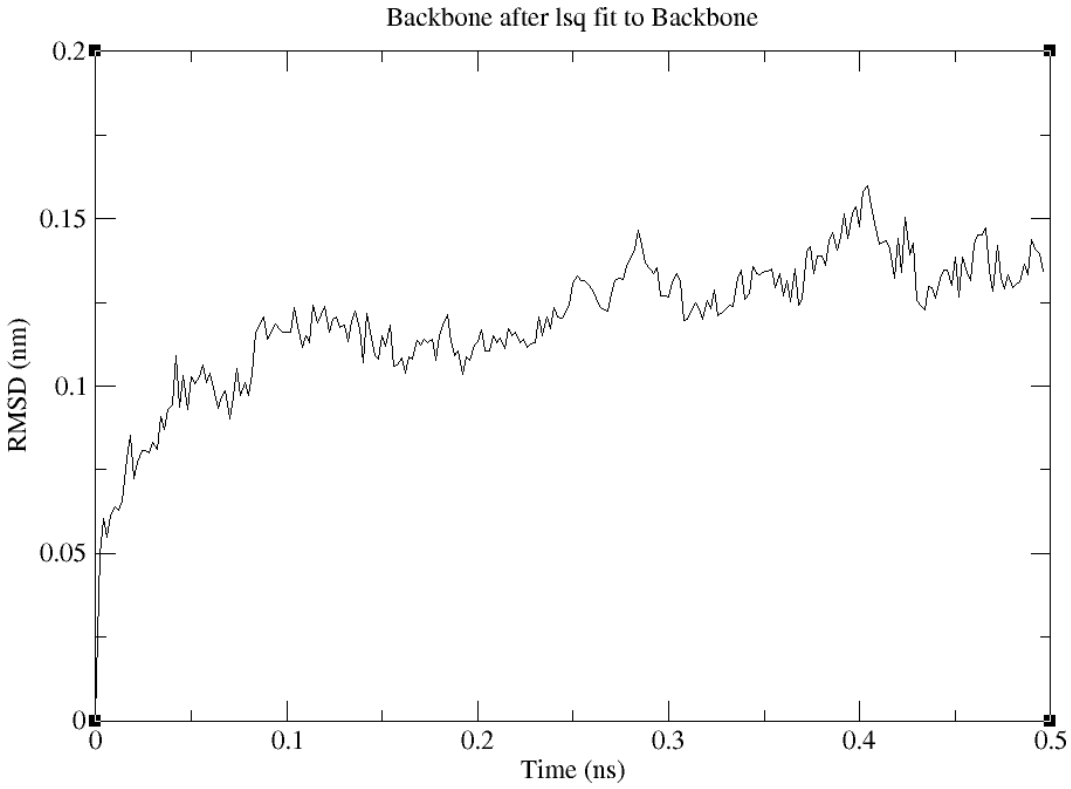


GRAPH-4: DENSITY (MMP9)

(3)MMP9 - RMSD (*root-mean-square deviation)*

The output plot below, shows the RMSD relative to the structure present in the minimized, equilibrated system.

This plot shows the RMSD levels off to ~0.125 nm (1.25 Å), indicating that the structure is stable.

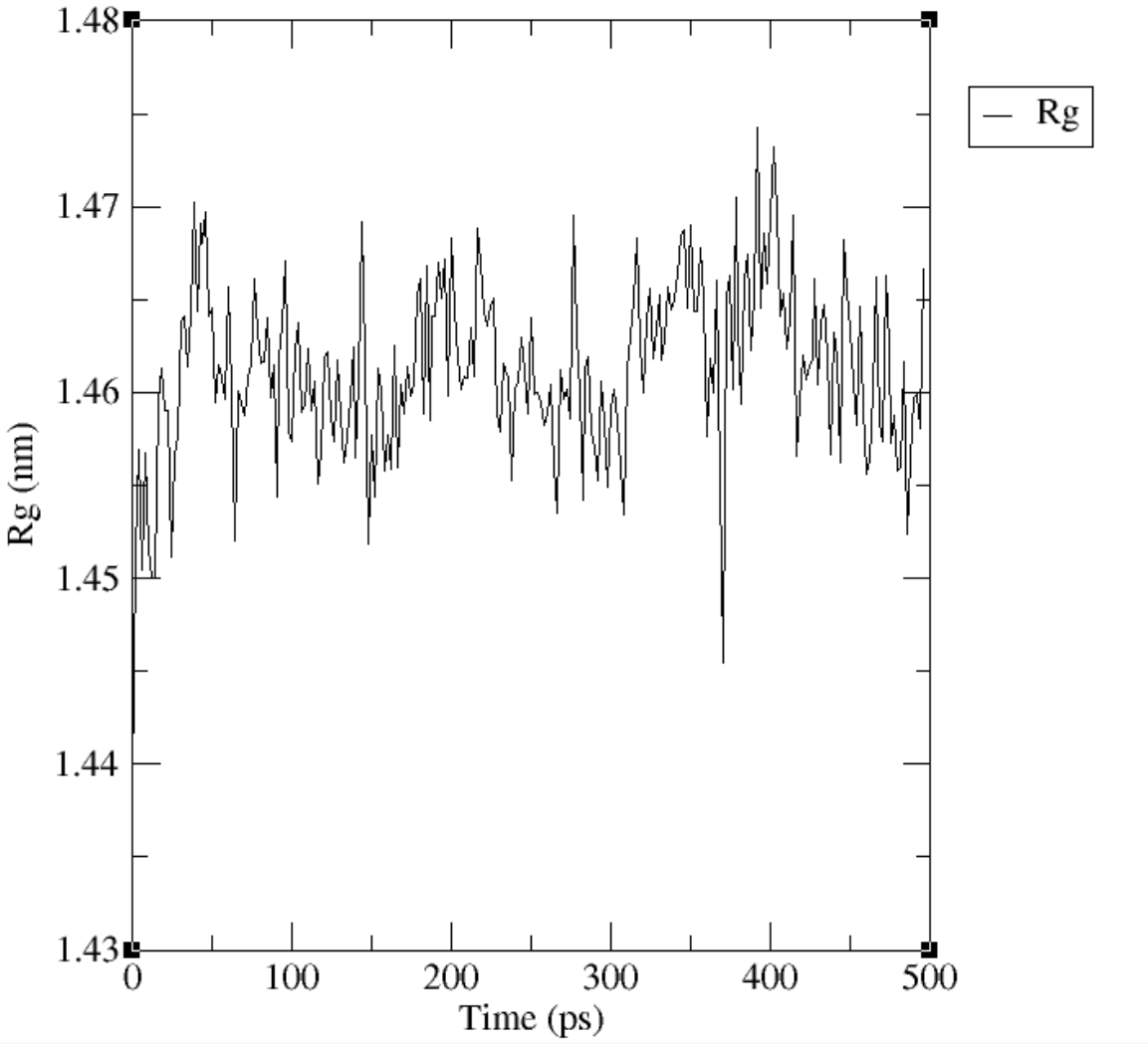


GRAPH-5: ROOT-MEAN-SQUARE DEVIATION-RMSD (MMP9)

(4)MMP9-RADIUS OF GYRATION

If a protein is stably folded, it will likely maintain a relatively steady value of R_g. If a protein unfolds, its R_g will change over time.

From the graph below, it is shown that reasonably variant R_g values,but it shows average 1.46nm so that the protein remains stable,in its compact (folded) form over the course of 0.5ns at 300k. So the protein "MMP9" was stable during molecular dynamic simulations.



GRAPH-6: RADIUS OF GYRATION (MMP9)

(B)MOLECULAR DYNAMICS SIMULATIONS OF MMP2

(1).MMP2-ENERGY MINIMIZATION

Steepest descents converged to f_{max} <1000(minimum energy defined)

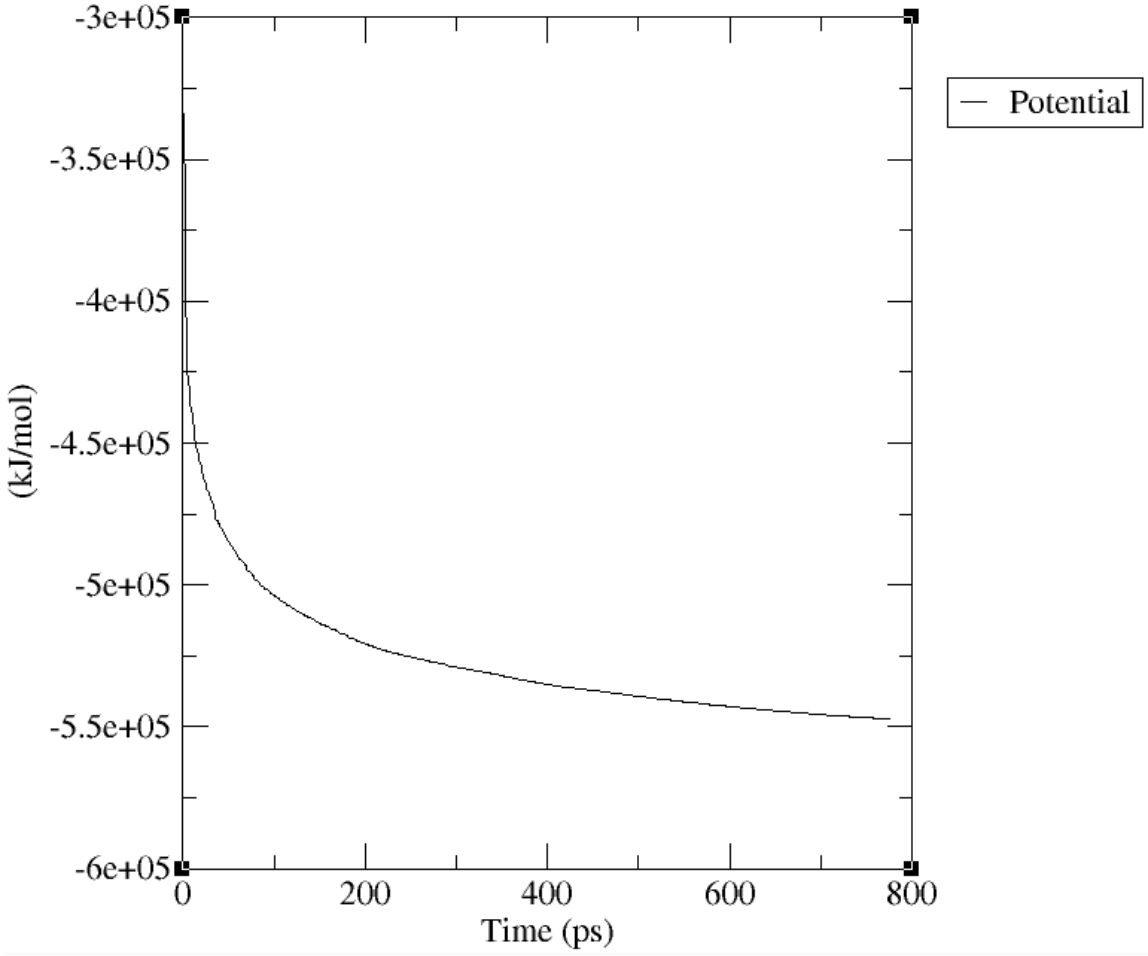
Potential energy: -5.4730019e+05

Maximum force: 8.8860901e+02 on atom 1441

E_{pot} was negative and target F_{max} was not greater than 1000 kJ mol^{-1} nm^{-1} (minimum energy defined) so the structure of MMP2 was stable.

TABLE-6: POTENTIAL ENERGY(MMP2)

Energy	Average	Err. Est.	Rmsd	Tot -drift
Potential	-525813	11000	26160.1	-70970.9 (kj/mol)



GRAPH-7: POTENTIAL ENERGY (MMP2)

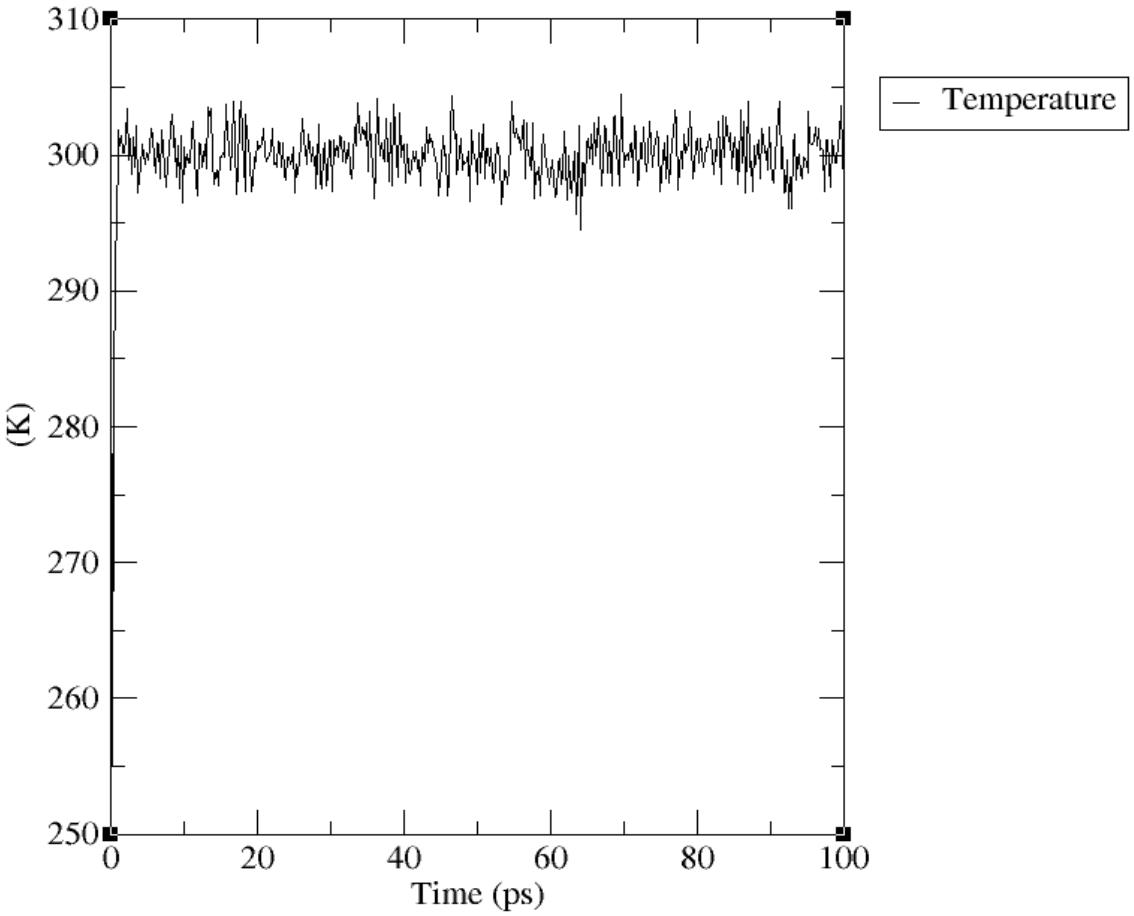
(2) MMP2-EQUILIBRATION

(2A)MMP2-TEMPERATURE

From the plot below, it is clear that the temperature of the system quickly reaches the target value (300 K), and remains stable over the remainder of the equilibration.

TABLE-7: TEMPERATURE (MMP2)

Energy	Average	Err. Est.	Rmsd	Tot -drift
Temperature	299.774	0.23	4.3567	1.27993(k)



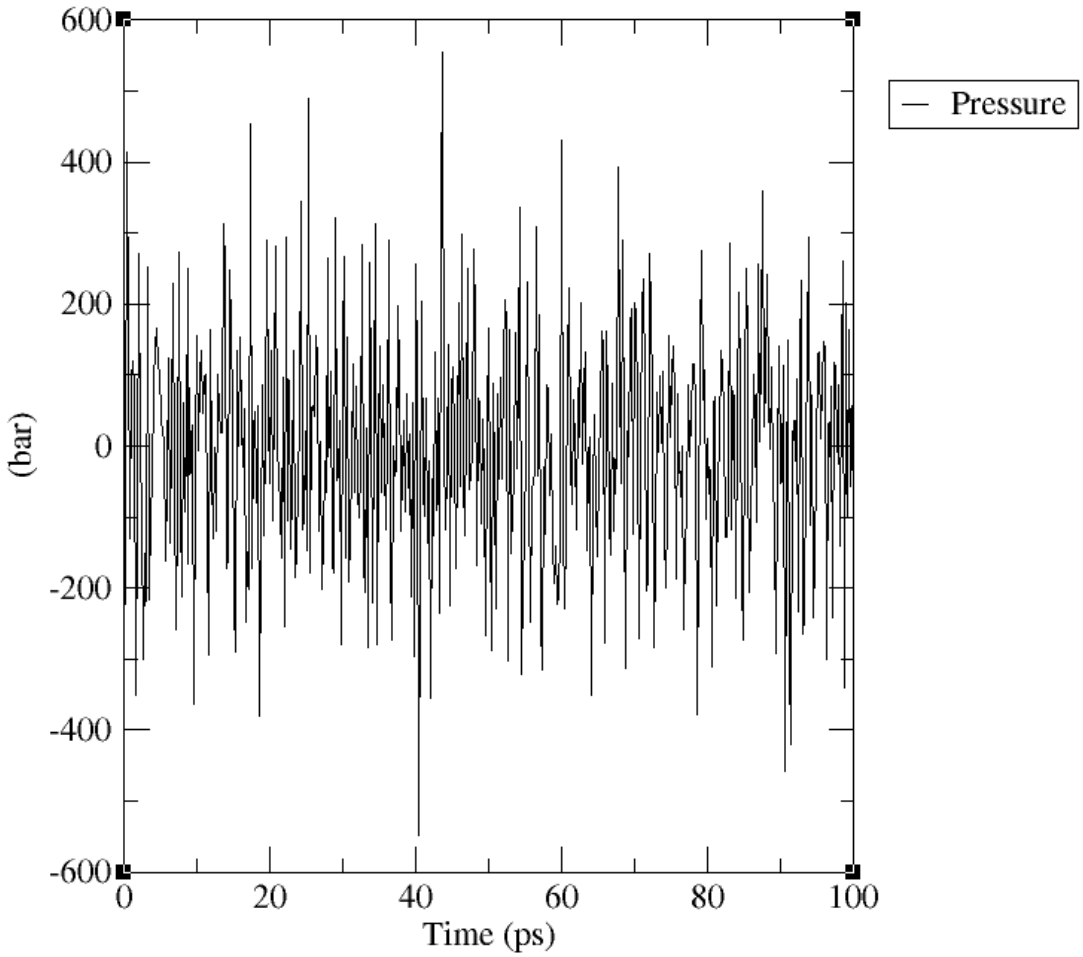
GRAPH-8: TEMPERATURE (MMP2)

(2B)MMP2-PRESSURE

The pressure value fluctuates widely over the course of the 100-ps equilibration phase, but this behaviour is not unexpected. Over the course of the equilibration, the average value of the pressure is 0.91 bar.

TABLE-8: PRESSURE (MMP2)

Energy	Average	Err. Est.	Rmsd	Tot -drift
Pressure	0.914411	0.61	166.439	-0.799075 (bar)



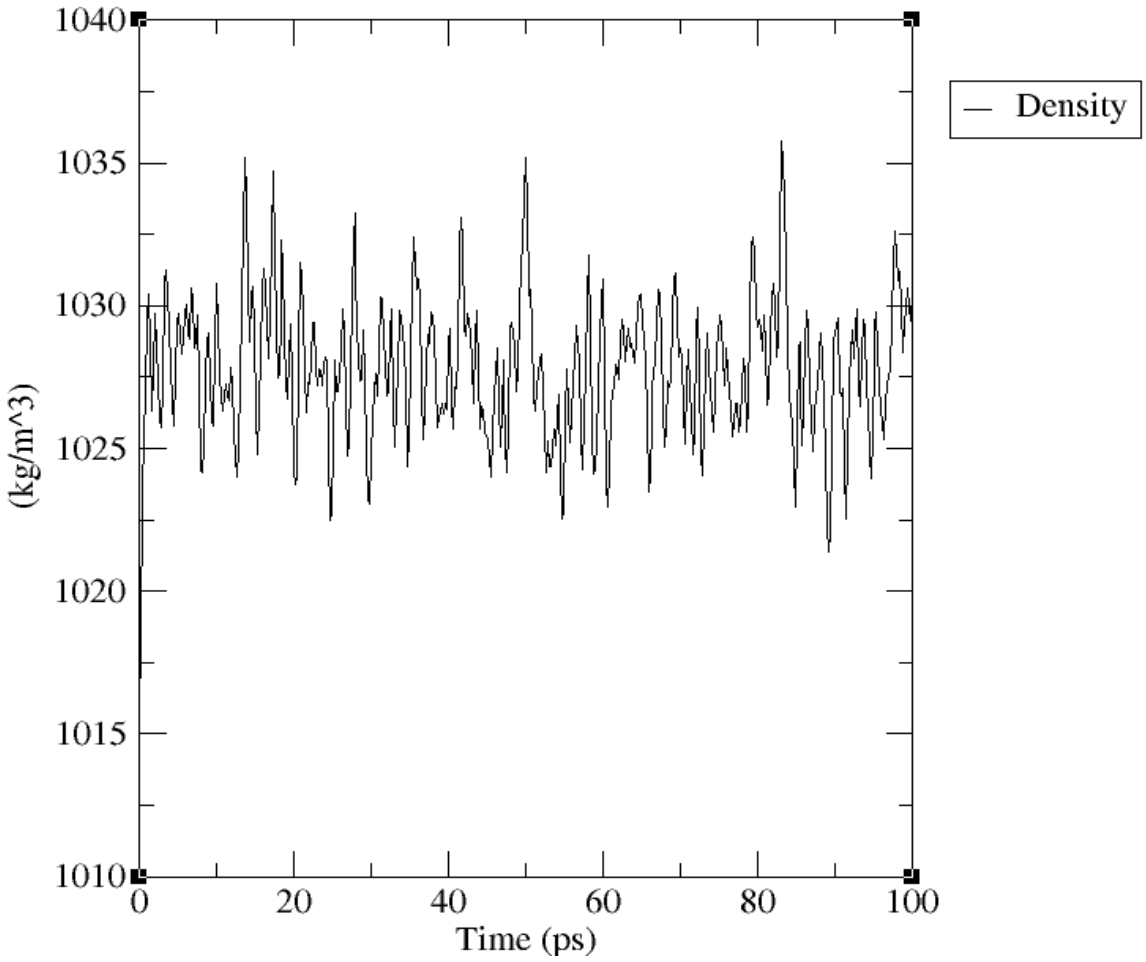
GRAPH-9: PRESSURE (MMP2)

(2C)MMP2-DENSITY

The average value over the course of 100 ps is 1027.83 kgm^{-3}, close to the experimental value of 1000 kg m^{-3}.The density values are very stable over time, indicating that the system is well-equilibrated now with respect to pressure and density.

TABLE-9: DENSITY (MMP2)

Energy	Average	Err. Est.	Rmsd	Tot -drift
Density	1027.83	0.13	2.39542	-0.191919 (kg/m^3)

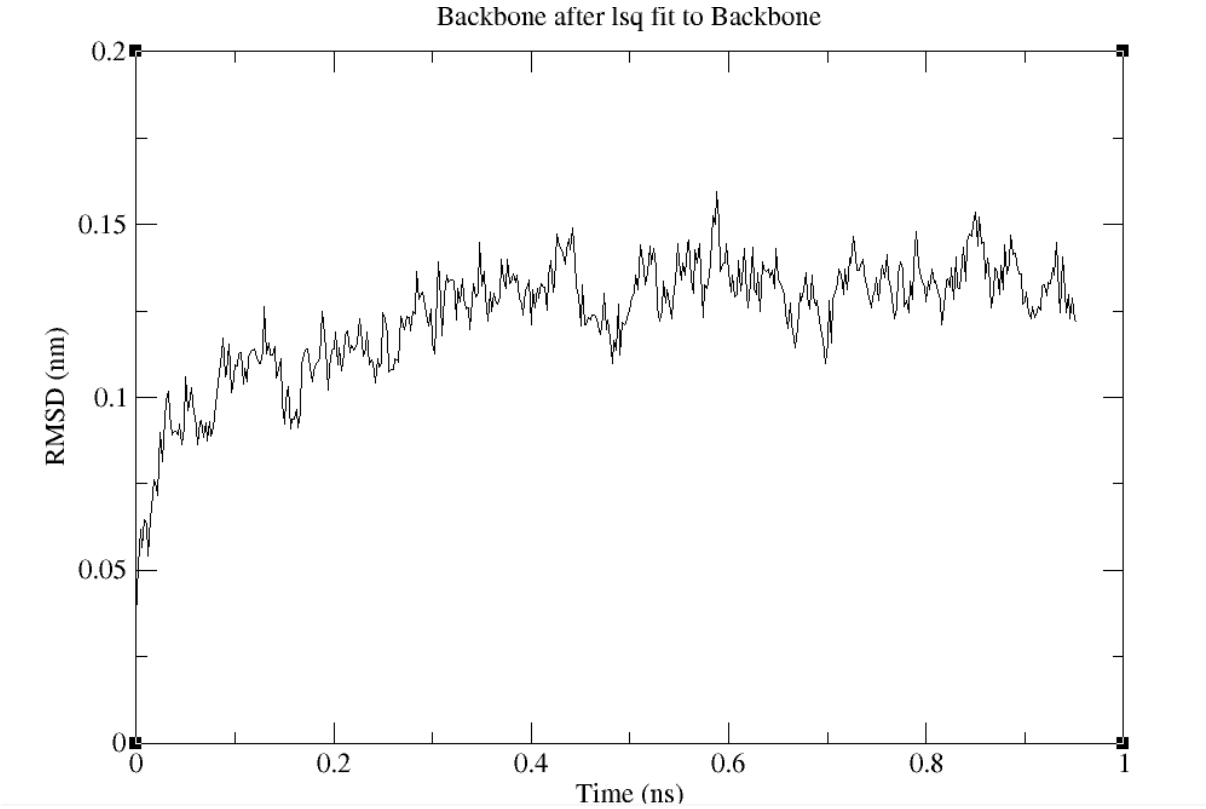


GRAPH-10: DENSITY (MMP2)

(3)MMP2-RMSD(*root-mean-square deviation)*

The output plot below, shows the RMSD relative to the structure present in the minimized, equilibrated system.

This plot shows the RMSD levels off to ~0.125 nm (1.25 Å), indicating that the structure is stable.

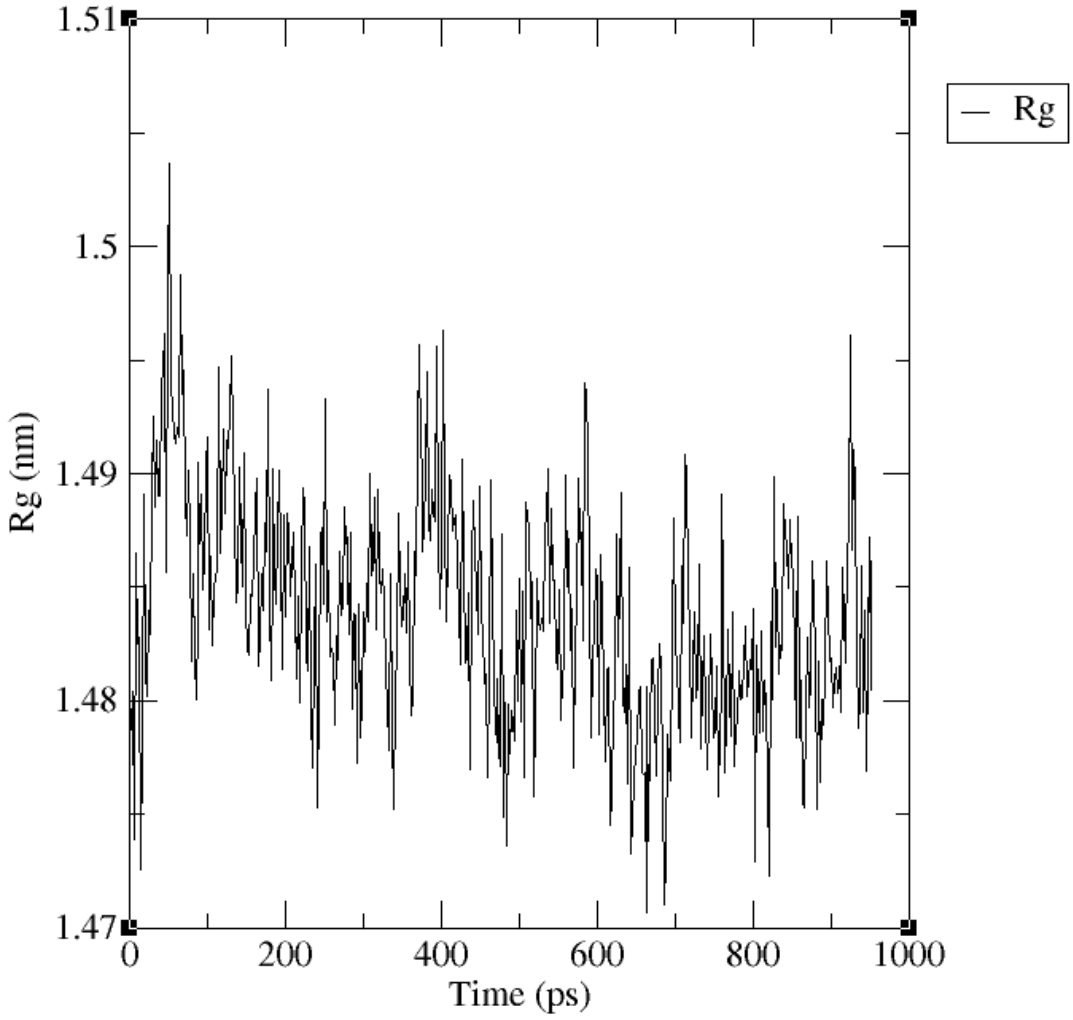


GRAPH-11: ROOT-MEAN-SQUARE DEVIATION- RMSD (MMP2)

(4)MMP2-RADIUS OF GYRATION

If a protein is stably folded, it will likely maintain a relatively steady value of R_g. If a protein unfolds, its R_g will change over time.

From the graph below, it is shown that reasonably variant R_g values,but it shows average 1.485nm so that the protein remains stable,in its compact (folded) form over the course of 1ns at 300k. So the protein "MMP9" was stable during molecular dynamic simulations



GRAPH-12: RADIUS OF GYRATION (MMP2)

(C)VIRTUAL SCREENING

All the natural compounds from medicinal plants were screened for matrix metalloproteinases MMP2 and MMP9 and compounds having binding energy within the range of "10-14" were taken as the final screenedout ligands. As the binding energy within this range is considered as stable for the docked structure.

TABLE-10: SCREENED OUT LIGANDS FOR MMP9

	LIGANDS	BINDING ENERGY
1.	(-)-1-(S)-Norcoclaurine	-10.4
2.	(-)-Centrolobol	-10.3
3.	1,2,6-Trigalloylglucose	-13.3
4.	1-phenyl-3-(p-nitrophenyl)-2,3-dibromopropan-1-one	-12.5
5.	4-Benzyloxy-propiophenone	-12.4
6.	5,7,3',4',5-PENTAHYDROXYFLAVONE	-12.4
7.	5-htp (5-hydroxytryptophan)	-10.4
8.	5-hydroxy,4,7-dimethoxyy-flavone	-11.3
9.	Acacetin	-11.4
10.	Alpinetin	-11.1
11.	Amygdalin	-10.1
12.	Anemone purple anthocyanin-3	-11.0
13.	Astragalin	-12.1
14.	Baicalein	-13.0
15.	Betanin	-10.0
16.	Bisabolol	-10.1
17.	Catalpol	-14.3
18.	Chrysoriol	-12.0
20.	Cinnyl Cinnamate	-13.8
21.	Cis-Martynoside	-14.1
22.	Cubebin	-13.7
23.	Cusparine	-11.5
24.	Daidzein	-12.6
25.	Decussatin	-10.8
26.	Demethoxycucurmin	-10.3
27.	Dibutyl phthalate	-11.2
28.	Eriodictyol	-12.1
29.	Gallotannin	-13.5
30.	Genistein	-12.8
31.	Genkwanin	-11.6
33.	Gentiopicroside	-12.4
33.	Geraniin	-14.0
34.	Guaiol	-10.7

35.	Harpagide-7-acetyl	-13.4
36.	Hesperetin	-12.0
37.	Hinokinin	-10.5
38.	Homoeriodictyol	-12.0
39.	Icariside	-14.3
40.	Isochlorogenic acid	-10.0
41.	Isorhamnetin	-14.1
42.	Iso-Rhamnetin-3-O-neo-hesperidoside	-13.3
43.	Isorhamnetin-3-O-rutinoside	-12.0
44.	Kaempferol-3-O-rutinoside	-12.3
45.	Liquiritigenin	-11.7
46.	Luteolin-4-glucoside	-14.0
47.	Neohesperidose	-11.7
48.	Occidentalol-II	-10.1
49.	Petunidin	-11.4
50.	Phloretin	-12.8
51.	Phloridzin	-12.3
52.	Piceatannol	-10.2
53.	Pinocembrin-7-methyl-ether	-11.2
54.	Pinocembrin-chalcone	-10.3
55.	Piperine	-10.4
56.	Polydatin	-10.0
57.	Pratensein	-10.2
58.	Propiophenone,4'-fluoro-3-(4-phenylpiperidino)-hydrochloride	-11.3
59.	Prunasin	-10.0
60.	Prunetin	-10.1
61.	Phylloquinone	-10.4
62.	Resveratrol	-11.8
63.	Reticuline	-13.2
64.	Rhamnocitrin	-11.0
65.	Robustaflavone	-11.2
66.	Rosavin	-10.1
67.	Sakuranetin	-11.4
68.	Salidroside	-13.2
69.	Salvigenin	-11.2
70.	Seninsetin	-10.3
71.	Sudan III	-11.6
72.	Sulfurien	-10.9
73.	Swertiamarin	-13.4
74.	Tetrahydrocurcumin	-10.4
75.	Tiliroside	-10.5
76.	Tolperisone	-10.0
77.	Tubuloside E	-11.4
78.	Valencene	-10.0
79.	Viridiflorol	-10.1
80.	Wogonin	-13.0

TABLE-11: SCREENEDOUT LIGANDS FOR MMP2

	LIGANDS	BINDING ENERGY
1.	16R,19E-isositsirikine	-12.3
2.	Ajmalicine	-14.0
3.	Alpha-crocin	-10.6
4.	Berberine	-10.3
5.	Chelerythrine	-11.4
6.	Cis-Leucosceptoside-A	-12.5
7.	Daucosterol	-10.7
8.	Iso-Silybin-A	-13.1
9.	Luteolin-7-b-D-Glucopyranoside	-14.0
10.	Matairesinol	-10.4
11.	Mulberroside -F	-10.6
12.	Nobiletin	-10.3
13.	Ononin	-11.3
14.	Pericyclivine	-11.5
15.	Pseudo -Strychnine	-10.1
16.	Scholaricinne	-14.1

TABLE-12: SCREENEDOUT LIGANDS FOR MMP2 AND MMP9

	LIGANDS	BINDING ENERGY	
		MMP9	MMP2
1.	(-)-Epicatechin-3-O-gallate	-11.8	-11.5
2.	(+)-Anwulignan	-10.8	-10.3
3.	(+)-aromadendrin	-11.5	-11.1
4.	(+)-Gallocatechin	-11.6	-11.0
5.	(+)-morelloflavone	-10.4	-10.3
6.	(+)-Nootkatone	-10.4	-10.1
7.	1,2,3,4-Tetrakis-O-(3,4,5-trihydroxybenzoyl)-a-D-glucopyranose	-14.3	-14.2
8.	4'-Phenylpropiophenone	-11.8	-11.3
9.	Acacetin-7-neohesperidoside	-14.0	-13.6
10.	Aloe emodin	-13.1	-12.9
11.	Amentoflavone	-13.5	-13.1
12.	Ampelopsin-F	-10.2	-10.3
13.	Angoroside -C	-12.3	-12.0
14.	Apigenin-7-glucoside	-10.3	-10.0
15.	Arecatannin-B1	-10.2	-10.0
16.	Baicalin	-12.5	-12.4
17.	Barbaloin	-10.0	-10.3
18.	Bicyclogermacrene	-11.4	-11.2
19.	Biochanin-A	-10.9	-10.6
20.	Calycosin	-11.0	-11.0
21.	Chrysin	-12.6	-12.1
22.	Cistanoside-C	-12.5	-12.4
23.	Cuspareine	-11.1	-10.7

24.	Diosmetin	-13.4	-12.9
25.	Ellagic acid	-13.0	-12.7
26.	Epi -Afzelechin	-11.3	-10.9
27.	Epigallocatechin_gallate	-11.7	-11.4
28.	Epi -Taxifolin	-12.1	-11.6
29.	Ergostine	-10.6	-11.1
30.	Eupatorin-5-methyl-ether	-10.7	-10.4
31.	ε -viniferin	-13.2	-13.8
32.	Febrifugine	-11.6	-11.6
33.	Fisetin	-12.9	-12.4
34.	Galangin	-11.1	-11.0
35.	Grossamide	-11.6	-11.3
36.	Hydnocarpin -D	-10.9	-10.4
37.	Hyperoside	-12.5	-12.1
38.	Irilin-D	-11.4	-11.1
39.	Iso-Formononetin	-10.9	-10.7
40.	Iso-Quercitrin-6-acetate	-11.7	-11.3
41.	Isorhamnetin-3-0-rutinoside	-12.0	-11.7
42.	Lariciresinol	-11.3	-10.8
43.	Marmesin	-10.5	-10.3
44.	Miquelianin	-12.3	-12.3
45.	Naphthopyrone	-10.7	-10.5
46.	Naringenin	-12.9	-12.4
47.	Naringin	-14.4	-14.3
48.	Occidentalol-I	-10.3	-10.6
49.	Paclobutraazol	-12.8	-12.3
50.	Pentagalloyl-glucose	-13.3	-12.9
51.	Piceid	-11.2	-10.9
52.	Picralinal	-10.3	-10.2
53.	Pinocembrin	-12.6	-12.1
54.	Quercetin-3-arabinoglucoside	-12.5	-12.1
55.	Quercetin-3-glucoside	-11.5	-11.4
56.	Quercitrin	-13.0	-12.6
57.	Rhamnetin	-11.1	-10.7
58.	Rhein	-13.5	-13.2
59.	Rhoifolin	-14.3	-14.2
60.	Scutellarin	-12.7	-12.7
61.	Shyobunone	-11.5	-11.3
62.	Sitosterol palmitate	-12.2	-11.7
63.	Trachelogenin	-10.8	-10.4
64.	Uniconazole	-13.1	-13.2
65.	Veraguensin	-10.7	-10.2
66.	Vitexin	-11.0	-10.7
67.	Worenine	-10.1	-10.3
68.	Xanthotoxin	-10.6	-10.3

(D)MOLECULAR PROPERTY PREDICTION OF LIGANDS

Molecular properties of ligands were predicted to check druglike properties of a ligand so that it can be considered as a drug molecule if it satisfies all the druglike properties. **LIPINSKI RULES** evaluate druglikeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans.

LIPINSKI RULES

1. Log p: lipophilicity of ligand should not be greater than 5.

2. Molecular weight: should not be greater than 500 daltons.

3. Hydrogen bond donor: should not be greater than 5.

4. Hydrogen bond acceptor: should not be greater than 10.

Log s: The aquous solubility of a compound significantly affects its absorption and distribution characteristics. Typically, a low solubility goes along with a bad absorption and therefore the general aim is to avoid poorly soluble compounds. logS value should be greater than -4.

TABLE-13: MOLECULAR PROPERTIES OF SCREENEDOUT LIGANDS FOR MMP9

LIGANDS	LOGP	TPSA	MW	nATOMS	nON	nOHNH	nVIOLATIONS	nROTB	LOGS
(-)-1-(S)-Norcoclaurine	2.005	72.711	271.316	20	4	4	0	2	-3.06
(-)-Centrolobol	4.129	60.684	300.398	22	3	3	0	8	-3.94
1,2,6-Trigalloylglucose	-1.069	329.48	636.471	45	18	12	3	13	-2.79
1-phenyl-3-(p-nitrophenyl)-2,3-dibromopropan-1-one	4.461	62.895	413.065	21	4	0	0	5	-5.89
4-Benzyloxy-propiophenone	3.99	26.305	240.302	18	2	0	0	5	-4.73
5,7,3',4',5-pentahydroxyflavone	1.683	131.35	302.238	22	7	5	0	1	-2.39
5-htp (5-hydroxytryptophan)	-1.583	99.341	220.228	16	5	5	0	3	-1.78
5-hydroxy,4,7-dimethoxyy-flavone	3.535	68.907	298.294	22	5	1	0	3	-3.29

Acacetin	2.999	79.901	284.267	21	5	2	0	2	-3.7
Alpinetin	2.664	55.767	270.284	20	4	1	0	2	-3.45
Amygdalin	-2.366	202.32	457.432	32	12	7	2	7	-1.11
Anemone purple anthocyanin-3	-4.513	539.05	1274.082	90	33	19	3	21	-3.25
Astragalin	0.125	190.27	448.38	32	11	7	2	4	2.45
Baicalein	2.682	90.895	270.24	20	5	3	0	1	-2.98
Betanin	-4.906	247.10	550.473	39	15	8	3	8	-4.13
Bisabolol	4.679	20.228	222.372	16	1	1	0	4	-3.48
Catalpol	-2.813	161.59	362.331	25	10	6	1	4	-0.19
Chrysoriol	2.282	100.12	300.266	22	6	3	0	2	-3.16
Cinnyl Cinnamate	4.877	26.305	264.324	20	2	0	0	6	-5.5
Cis - Martynoside	0.166	223.30	652.646	46	15	7	3	13	-3.1
Cubebin	3.63	66.398	356.374	26	6	1	0	4	-3.88
Cusparine	4.56	40.594	307.349	23	4	0	0	4	-4.57
Daidzein	2.559	70.667	254.241	19	4	2	0	1	-3.28
Decussatin	3.132	78.141	302.282	22	6	1	0	3	-3.51
Demethoxycucurmin	3.23	86.989	338.359	25	5	3	0	6	-4.7
Dibutyl phthalate	4.429	52.61	278.348	20	4	0	0	10	-4.67
Eriodictyol	1.628	107.21	288.255	21	6	4	0	1	-2.9
Gallotannin	0.643	310.65	636.471	45	18	11	3	10	-2.74
Genistein	2.268	90.895	270.24	20	5	3	0	1	-3.08
Genkwanin	2.653	75.995	286.283	21	5	2	0	2	-3.51
Gentiopicroside	-0.895	134.91	356.327	25	9	4	0	4	-1.35
Geraniin	-0.775	450.25	952.648	68	27	14	3	3	-2.23
Guaiol	3.824	20.228	222.372	16	1	1	0	1	-3.45
Harpagide-7-acetyl	-2.24	175.37	406.384	28	11	6	2	5	-0.94
Hesperetin	1.935	96.223	302.282	22	6	3	0	2	-3.34
Hinokinin	3.017	63.241	354.358	26	6	0	0	4	-4.59
Homoeriodictyol	1.935	96.223	302.282	22	6	3	0	2	-3.36
Icariside	-0.104	210.50	464.379	33	12	8	2	4	-2.32
Isochlorogenic acid	1.424	211.27	516.455	37	12	7	3	9	-3.61
Isorhamnetin	1.99	120.35	316.265	23	7	4	0	2	-2.65
Iso-Rhamnetin-3-O-neo-hesperidoside	-0.756	258.43	624.548	44	16	9	3	7	-2.23
Kaempferol-3-O-rutinoside	-0.574	249.19	594.522	42	15	9	3	6	-2.29
Liquiritigenin	2.2	66.761	256.257	19	4	2	0	1	-3.28

Luteolin-4-glucoside	-0.042	190.27	448.38	32	11	7	2	4	-2.64
Neohesperidose	-3.342	169.29	326.298	22	10	7	1	3	0.17
Occidentalol-II	3.983	173.97	574.582	42	10	6	2	3	-4.61
Petunidin	-0.73	121.54	317.273	23	7	5	0	2	-3.29
Phloretin	2.656	97.983	274.272	20	5	4	0	4	-3.32
Phloridzin	0.401	177.13	436.413	13	10	7	1	7	-2.56
Piceatannol	2.497	80.912	244.246	18	4	4	0	2	-3.4
Pinocembrin-7-methyl-ether	3.132	55.767	270.284	20	4	1	0	2	-3.44
Pinocembrin-chalcone	3.165	77.755	256.257	19	4	3	0	3	-3.4
piperine	3.332	38.777	285.343	21	4	0	0	3	-3.28
Polydatin	1.199	139.83	390.388	28	8	6	1	5	-2.71
Pratensein	2.086	100.12	300.266	22	6	3	0	2	-3.32
Propiophenone,4'-fluoro-3-(4-phenylpiperidino)-hydrochloride	4.395	20.309	311.4	23	2	0	0	5	-4.87
Prunasin	-0.659	123.17	295.291	21	7	4	0	4	-1.02
Prunetin	2.804	79.901	284.267	21	5	2	0	2	-3.48
Phylloquinone	8.803	34.142	450.707	33	2	0	1	14	-6.88
Resveratrol	2.986	60.684	228.247	17	3	3	0	2	-3.52
Reticuline	2.375	62.162	329.396	24	5	2	0	4	-3.28
Rhamnocitrin	2.708	100.12	300.266	22	6	3	0	2	-3.58
Robustaflavone	5.16	181.79	538.464	40	10	6	3	3	-4.89
Rosavin	-0.955	158.30	428.434	30	10	6	1	7	-1.77
Sakuranetin	2.653	75.995	286.283	21	5	2	0	2	-3.51
Salidroside	-0.701	119.60	300.307	21	7	5	0	5	-1.36
Salvigenin	3.322	78.141	328.32	24	6	1	0	4	-4.19
Seninsetin	3.188	76.381	372.373	27	7	0	0	6	-4.64
Sudan III	7.214	69.684	352.397	27	5	1	1	4	-5.17
Sulfurien	1.763	90.895	270.24	20	5	3	0	1	-3.44
Swertiamarin	-1.656	155.14	374.342	26	10	5	0	4	-0.95
Tetrahydrocurcumin	2.244	93.066	372.417	27	6	2	0	10	-4.82
Tiliroside	2.491	216.58	594.525	43	13	7	3	8	-3.52
Tolperisone	3.593	20.309	245.366	18	2	0	0	1	-3.17
Tubuloside E	0.745	231.14	650.63	46	15	7	3	13	-3.11
Valencene	5.006	0	204.357	15	0	0	1	1	-4.85
Viridiflorol	4.073	20.228	222.372	16	1	1	0	0	-4.72
Wogonin	2.958	79.901	284.267	21	5	2	0	2	-3.36

TABLE-14: MOLECULAR PROPERTIES OF SCREENEDOUT LIGANDS FOR MMP2

LIGANDS	LOGP	TPSA	MW	nATOMS	nON	nOHNH	nVIOLATIONS	nROTB	LOGS
16R,19E-isositsirikine	3.29	65.562	354.45	26	5	2	0	4	-3.18
Ajmalicine	3.414	54.568	352.434	26	5	1	0	2	-3.54
Alpha-crocin	-2.199	391.20	976.972	68	24	14	3	20	-3.24
Berberine	0.196	40.821	336.367	25	5	0	0	2	-6.02
Chelerythrine	0.797	40.821	332.335	25	5	0	0	0	-6.28
Cis-Leucosceptoside-A	-0.141	234.29	638.619	45	15	8	3	12	-2.92
Daucosterol	7.152	99.38	576.859	41	6	4	2	1	-5.31
Iso-Silybin-A	1.465	155.14	482.441	35	10	5	0	4	-3.72
Luteolin-7-b-D-Glucopyranoside	0.187	190.27	448.38	32	11	7	2	4	-2.4
Matairesinol	1.915	85.229	358.39	26	6	2	0	2	-4.47
Mulberroside -F	-0.927	232.12	566.512	40	14	9	3	7	-2.42
Nobiletin	3.37	85.615	402.399	29	8	0	0	7	-4.64
Ononin	-0.472	129.59	324.285	23	8	4	0	2	-1.39
Pericyclivine	3.771	45.334	322.408	24	4	1	0	2	-3.35
Pseudo - Strychnine	1.263	53.009	350.418	26	5	1	0	0	-1.9
Scholaricinne	2.424	82.026	356.422	26	6	3	0	3	-2.19

TABLE-15: MOLECULAR PROPERTIES OF SCREENEDOUT LIGANDS FOR MMP2 AND MMP9

LIGANDS	LOGP	TPSA	MW	nATOMS	nON	nOHNH	nVIOLATIONS	nROTB	LOGS
(-)Epicatechin-3-O-gallate	2.537	177.13	442.376	32	10	7	1	4	-4.0
(+)Anwulignan	4.642	47.93	328.408	24	4	1	0	6	-5.06
(+)aromadendrin	1.201	107.21	288.255	21	6	4	0	1	-2.47
(+)Gallocatechin	1.077	130.60	306.27	22	7	6	1	1	-2.55
(+)morelloflavone	3.873	198.11	556.479	41	11	7	3	3	4.56
(+)Nootkatone	3.667	17.071	218.34	16	1	0	0	1	-3.88

1,2,3,4-Tetrakis-O-(3,4,5-trihydroxybenzoyl)-a-D-glucopyranose	1.593	377.41	788.576	56	22	13	3	13	-2.92
4'Phenylpropiophenone	4.134	17.071	210.276	16	1	0	0	3	4.53
Acacetin-7-neohesperidoside	0.513	217.97	592.55	42	14	7	3	7	-2.41
Aloe emodin	2.424	94.826	270.24	20	5	3	0	1	-2.95
amentoflavone	5.16	181.79	538.464	40	10	6	3	3	-4.87
Ampelopsin-F	4.599	121.36	454.478	34	6	6	1	2	-4.88
Angoroside -C	-1.114	282.22	784.761	55	19	9	3	15	-2.74
Apigenin-7-glucoside	0.676	170.04	432.381	31	10	6	1	4	-2.45
Arecatannin-B1	3.585	331.12	866.781	63	18	15	3	5	-3.55
Baicalin	0.545	187.11	446.364	32	11	6	2	4	-2.41
barbaloin	0.176	167.90	418.398	30	9	7	1	3	-2.2
Bicyclogermacrene	5.294	0	204.357	15	0	0	1	0	-4.39
Biochanin-A	2.804	79.901	284.267	21	5	2	0	2	-3.46
Calycosin	2.377	79.901	284.267	21	5	2	0	2	-3.53
Chrysin	2.943	70.667	254.241	19	4	2	0	1	-3.38
Cistanoside-C	-0.141	234.29	638.619	45	15	8	3	12	-2.95
Cuspareine	4.506	21.706	311.425	23	3	0	0	5	-4.45
Diosmetin	2.282	100.12	300.266	22	6	3	0	2	-3.34
Ellagic acid	0.943	141.33	302.194	22	8	4	0	0	-2.57
Epi -Afzelechin	1.858	90.146	274.272	20	5	4	0	1	-2.77
Epigallocatechin-gallate	2.245	197.36	458.375	33	11	8	2	4	-3.8
Epi -Taxifolin	0.712	127.44	304.254	22	7	5	0	1	-2.42
Ergostine	2.58	118.20	595.7	44	10	3	1	5	-3.46
Eupatorin-5-methyl-ether	2.881	87.375	358.346	26	7	1	0	5	-4.12
ε -viniferin	4.768	110.37	454.478	34	6	5	0	4	-5.28
Febrifugine	0.022	84.223	301.346	22	6	2	0	4	-2.86
Fisetin	1.974	111.12	286.239	21	6	4	0	1	-3.28
Galangin	2.651	90.895	270.24	20	5	3	0	1	-3.36
Grossamide	4.05	146.58	624.69	46	10	5	1	12	-1.35
Hydnocarpin – D	2.727	138.82	464.426	34	9	4	0	4	-4.59
Hyperoside	-0.364	210.50	464.379	33	12	8	2	4	-2.38
Irilin-D	1.794	120.35	316.265	23	7	4	0	2	-1.51
Iso-Formononetin	3.095	59.673	268.268	20	4	1	0	2	-3.83

Iso-Quercitrin-6-acetate	0.34	216.58	506.416	36	13	7	3	6	-2.55
Isorhamnetin-3-0-rutinoside	-0.756	258.43	624.548	44	16	9	3	7	-2.35
Lariciresinol	2.331	88.386	360.406	26	6	3	0	6	-4.24
Marmesin	2.18	59.673	246.262	18	4	1	0	1	-2.71
Miquelianin	-0.487	227.57	478.362	34	13	8	2	4	-2.3
Naphthopyrone	2.977	30.211	196.205	15	2	0	0	0	-3.39
Naringenin	2.117	86.989	272.256	20	5	3	0	1	-3.11
Naringin	-0.369	225.06	580.539	41	14	8	3	6	-2.16
Occidentalol-I	4.359	173.97	588.609	43	10	6	2	3	-4.68
Paclobutraazol	2.986	50.946	293.798	20	4	1	0	5	-3.45
Pentagalloyl-glucose	2.761	444.17	940.681	67	26	15	3	16	-3.14
Piceid	1.199	139.83	390.388	38	8	6	1	5	-2.71
Picralinal	2.613	67.875	366.417	27	6	1	0	3	-2.19
Pinocembrin	2.596	66.761	256.257	19	4	2	0	1	-3.14
Quercetin-3-arabinoglucoside	-1.644	269.42	596.494	42	16	10	3	6	-2.18
Quercetin-3-glucoside	0.157	210.50	464.379	33	12	8	2	5	-2.04
Quercitrin	0.644	190.27	448.38	32	11	7	2	3	-2.4
Rhamnetin	2.219	120.35	316.265	23	7	4	0	2	-3.33
Rhein	2.997	111.89	284.223	21	6	3	0	1	-3.12
Rhoifolin	-0.023	228.97	578.523	41	14	8	3	6	-2.36
Scutellarin	0.065	207.34	462.363	33	12	7	2	4	-2.22
Shyobunone	4.953	17.071	220.356	16	1	0	0	3	-4.67
Sitosterol palmitate	10.25	26.305	653.133	47	2	0	2	22	-8.04
Trachelogenin	1.278	94.463	388.416	28	7	2	0	7	-4.05
Uniconazole	3.275	50.946	291.782	20	4	1	0	4	-3.62
Veraguensin	4.108	46.17	372.461	27	5	0	0	6	-5.26
Vitexin	0.518	181.04	432.381	31	10	7	1	3	-2.4
Worenine	0.618	40.821	334.351	25	5	0	0	0	-5.64
Xanthotoxin	2.276	52.585	216.192	16	4	0	0	1	-5.64

(E)BIOLOGICAL ACTIVITY PREDICTION OF LIGANDS

Bioactivity prediction is done for calculation of druglikeness score towards GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors and other enzyme targets. Pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others.

TABLE-16: BIOLOGICAL ACTIVITY OF SCREENEDOUT LIGANDS FOR MMP9

LIGANDS	GPCR LIGAND	ION CHANNEL MODULATOR	KINASE INHIBITOR	NUCLEAR RECEPTOR LIGAND	PROTEASE INHIBITOR	ENZYME INHIBITOR
(-)-1-(S)-Norcoclaurine	0.25	0.23	-0.24	-0.15	-0.04	0.16
(-)-Centrolobol	0.3	0.28	0.06	0.42	0.25	0.37
1,2,6-Trigalloylglucose	-0.31	-0.8	-0.63	-0.5	-0.13	-0.31
1-phenyl-3-(p-nitrophenyl)-2,3-dibromopropan-1-one	-0.46	-0.48	-0.4	-0.34	-0.52	-0.32
4-Benzyloxy-propiophenone	-0.25	-0.12	-0.43	-0.13	-0.32	-0.09
5,7,3',4',5-pentahydroxyflavone	-0.01	-0.06	0.28	0.35	-0.17	0.3
5-htp (5-hydroxytryptophan)	0.42	0.59	0.04	0.07	0.18	0.53
5-hydroxy,4,7-dimethoxyy-flavone	-0.07	-0.17	0.16	0.29	-0.21	0.17
Acacetin	-0.08	-0.16	0.17	0.33	-0.25	0.2
Alpinetin	0.02	-0.23	-0.28	0.33	-0.16	0.17
Amygdalin	0.24	0.02	0.03	-0.11	0.19	0.44
Anemone purple anthocyanin-3	-5.01	-5.31	-5.33	-5.25	-4.9	-4.97
Astragalin	0.05	-0.05	0.1	0.2	-0.05	0.41
Baicalein	-0.12	-0.18	0.19	0.17	-0.35	0.26
Betanin	0.16	-0.18	-0.38	-0.1	0.0	0.3
Bisabolol	-0.06	0.26	-0.78	0.37	-0.38	0.43
Catalpol	0.34	0.2	0.04	0.27	0.46	0.63
Chrysoriol	0.05	-0.14	0.25	0.32	-0.26	0.21
Cinnyl Cinnamate	-0.16	-0.08	-0.29	0.1	-0.3	0
Cis -Martynoside	-0.16	-0.82	-0.51	-0.49	-0.06	-0.21
Cubebin	0.32	0.03	-0.03	0.18	0.37	0.25
Cusparine	0.23	-0.07	0.22	0.02	-0.06	0.16
Daidzein	-0.31	-0.64	-0.2	0.04	-0.83	0.02
Decussatin	-0.16	-0.18	-0.01	0.23	-0.28	0.18
Demethoxycucurmin	-0.08	-0.41	-0.11	0.03	-0.09	0.15
Dibutyl phthalate	-0.16	-0.09	-0.27	-0.12	-0.25	-0.07

Eriodictyol	0.07	-0.2	-0.22	0.46	-0.09	0.21
Gallotannin	-0.19	-0.71	-0.47	-0.48	-0.08	-0.22
Genistein	-0.22	-0.54	-0.06	0.23	-0.68	0.13
Genkwanin	0.02	-0.26	-0.25	0.4	-0.12	0.16
Gentiopicroside	0.0	0.13	-0.45	-0.06	-0.02	0.37
Geraniin	-3.6	-4.14	-4.19	-4.03	-3.32	-3.65
Guaiol	-0.21	-0.13	-0.89	0.17	-0.17	0.07
Harpagide-7-acetyl	0.31	0.31	-0.06	0.23	0.37	0.53
Hesperetin	0.04	-0.26	-0.2	0.38	-0.13	0.16
Hinokinin	0.24	-0.07	-0.06	0.03	0.12	0.18
Homoeriodictyol	0.04	-0.26	-0.2	0.38	-0.13	0.16
Icariside	0.02	-0.09	0.18	0.22	-0.07	0.44
Isochlorogenic acid	0.18	0.03	-0.02	0.46	0.13	0.37
Isorhamnetin	-0.1	-0.26	0.25	0.28	-0.3	0.22
Iso-Rhamnetin-3-O-neo-hesperidoside	-0.11	-0.69	-0.25	-0.32	-0.1	0.03
Kaempferol-3-O-rutinoside	-0.01	-0.43	-0.09	-0.17	-0.04	0.18
Liquiritigenin	0.03	-0.32	-0.39	0.31	-0.21	0.17
Luteolin-4-glucoside	0.1	-0.01	0.18	0.28	-0.02	0.43
Neohesperidose	0.19	0.06	-0.07	-0.2	0.2	0.53
Occidentalol-II	0.05	-0.32	-0.21	0.08	-0.02	0.1
Petunidin	-0.15	-0.17	0.03	0.01	-0.29	-0.01
Phloretin	0.03	0.19	-0.17	0.27	-0.03	0.28
Phloridzin	0.17	0.17	-0.09	0.26	0.14	0.44
Phylloquinone	0.05	-0.12	-0.1	0.17	-0.04	0.3
Piceatannol	-0.11	0.05	-0.11	0.08	-0.34	0.07
Pinocembrin-7-methyl-ether	-0.03	-0.29	-0.32	0.3	-0.17	0.14
Pinocembrin-chalcone	-0.15	0.03	-0.26	0.04	-0.27	0.13
Piperine	0.15	-0.18	-0.13	-0.13	-0.1	0.04
Polydatin	0.14	0.07	0.02	0.21	0.05	0.34
Pratensein	-0.19	-0.56	0.02	0.22	-0.65	0.09
Propiophenone,4'-fluoro-3-(4-phenylpiperidino)-hydrochloride	0.16	0.03	-0.06	0.04	-0.09	-0.03
Prunasin	0.26	0.03	-0.03	-0.07	0.21	0.6
Prunetin	-0.23	-0.59	-0.06	0.23	-0.66	0.07
Resveratrol	-0.2	0.02	-0.2	0.01	-0.42	0.02
Reticuline	0.28	0.14	-0.15	-0.19	-0.02	0.04
Rhamnocitrin	-0.12	-0.28	0.19	0.3	-0.28	0.2
Robustaflavone	0.1	-0.19	0.12	0.26	-0.03	0.09
Rosavin	0.13	0.13	-0.08	-0.08	0.02	0.34
Sakuranetin	0.02	-0.26	-0.25	0.4	-0.12	0.16
Salidroside	0.35	0.29	0.13	0.06	0.19	0.59
Salvigenin	-0.11	-0.27	0.16	0.13	-0.29	0.11
Seninsetin	-0.08	-0.15	0.14	0.1	-0.2	0.1

Sudan III	0.06	-0.1	0.04	-0.26	-0.04	0.06
Sulfurien	-1.18	-1.26	-0.52	-0.56	-1.21	0.0
Swertiamarin	0.17	0.26	-0.22	0.04	0.26	0.43
Tetrahydrocurcumin	0.05	-0.04	-0.23	0.12	0.0	0.13
Tiliroside	-0.1	-0.6	-0.24	-0.07	-0.09	0.05
Tolperisone	-0.03	-0.1	-0.5	-0.37	-0.29	-0.15
Tubuloside E	-0.11	-0.8	-0.53	-0.46	0.0	-0.15
Valencene	-0.31	-0.22	-1.28	0.41	-0.79	0.26
Viridiflorol	-0.5	-0.29	-0.82	-0.22	-0.48	-0.13
Wogonin	-0.14	0.0	0.13	0.13	-0.31	0.23

TABLE-17: BIOLOGICAL ACTIVITY OF SCREENEDOUT LIGANDS FOR MMP2

LIGANDS	GPCR LIGAND	ION CHANNEL MODULATOR	KINASE INHIBITOR	NUCLEAR RECEPTOR LIGAND	PROTEASE INHIBITOR	ENZYME INHIBITOR
16R,19E-isositsirikine	0.42	0.23	-0.21	-0.02	-0.13	0.11
Ajmalicine	0.42	0.35	-0.38	-0.22	-0.2	-0.05
Alpha-crocin	-3.54	-4.02	-3.98	-3.93	-3.24	-3.57
Berberine	-0.11	0.71	-0.27	-0.78	-0.35	0.82
Chelerythrine	-0.03	0.5	0.17	-0.76	-0.14	0.54
Cis-Leucosceptoside-A	-0.09	-0.7	-0.41	-0.38	-0.02	-0.11
Daucosterol	0.15	-0.21	-0.47	0.33	0.11	0.41
Iso-Silybin-A	0.07	-0.05	0.01	0.16	0.02	0.23
Luteolin-7-b-D-Glucopyranoside	0.09	-0.02	0.15	0.27	-0.01	0.42
Matairesinol	0.23	-0.02	0.0	0.13	0.1	0.21
Mulberroside -F	0.05	-0.28	-0.01	0.11	-0.02	0.2
Nobiletin	-0.13	-0.04	0.09	0.0	-0.22	0.11
Ononin	0.01	-0.18	-0.24	-0.1	-0.2	0.41
Pericyclivine	0.62	0.39	-0.24	-0.05	-0.19	0.01
Pseudo -Strychnine	0.32	0.26	-0.65	-0.05	0.12	-0.05
Scholaricinne	0.43	0.16	-0.34	0.17	0.12	0.1

TABLE-18: BIOLOGICAL ACTIVITY OF SCREENEDOUT LIGANDS FOR MMP2 AND MMP9

LIGANDS	GPCR LIGAND	ION CHANNEL MODULATOR	KINASE INHIBITOR	NUCLEAR RECEPTOR LIGAND	PROTEASE INHIBITOR	ENZYME INHIBITOR
(-)-Epicatechin-3-O-gallate	0.17	0.02	0.05	0.34	0.13	0.25
(+)-Anwulignan	0.0	-0.04	-0.1	-0.04	-0.07	0.05
(+)-aromadendrin	0.05	0.03	-0.07	0.26	0.03	0.29
(+)-Gallocatechin	0.40	0.14	0.14	0.57	0.29	0.49
(+)-morelloflavone	0.01	-0.44	0.08	0.38	-0.11	0.13
(+)-Nootkatone	-0.4	-0.31	-1.73	0.66	-0.58	0.34
1,2,3,4-Tetrakis-O-(3,4,5-trihydroxybenzoyl)-α-d-glucopyranose	-1.54	-2.74	-2.28	-2.38	-1.1	-1.88
4'Phenylpropiophenone	-0.36	-0.11	-0.49	-0.32	-0.51	-0.13
Acacetin-7-neohesperidoside	0.01	-0.47	-0.11	-0.11	0.0	0.17
Aloe emodin	-0.02	0.02	0.12	0.24	0.04	0.38
amentoflavone	0.07	-0.16	0.19	0.21	0.06	0.1
Ampelopsin-F	0.12	0.09	-0.11	0.25	-0.05	0.06
Angoroside -C	-1.33	-2.48	-2.06	-2.11	-0.93	-1.6
Apigenin-7-glucoside	0.1	-0.01	0.15	0.31	0.02	0.43
Arecatannin-B1	-2.81	-3.6	-3.45	-3.31	-2.25	-3.11
Baicalin	0.07	-0.1	0.0	0.3	-0.05	0.42
Barbaloin	0.18	0.08	0.14	0.33	0.08	0.35
Bicyclogermacrene	-0.75	-0.69	-1.11	-0.65	-0.88	-0.16
Biochanin-A	-0.23	-0.59	-0.06	0.23	-0.66	0.07
Calycosin	-0.25	-0.65	-0.08	0.06	-0.78	0.01
Chrysin	-0.11	-0.08	0.15	0.3	-0.30	0.26
Cistanoside-C	-0.09	-0.70	-0.41	-0.38	-0.02	-0.11
Cuspareine	0.20	0.03	-0.01	-0.06	0.0	0.0
Diosmetin	-0.05	-0.14	0.25	0.32	-0.26	0.21
Ellagic acid	-0.29	-0.27	-0.01	0.11	-0.18	0.17
Epi -Afzelechin	0.38	0.15	0.05	0.57	0.25	0.47
Epigallocatechin-gallate	0.16	0.02	0.06	0.33	0.13	0.25
Epi -Taxifolin	0.09	0.03	-0.04	0.29	0.05	0.29
Ergostine	0.65	-0.42	-0.36	-0.51	0.22	-0.18
Eupatorin-5-methyl-ether	-0.05	-0.11	0.18	0.18	-0.2	0.16
ε -viniferin	0.18	-0.02	-0.02	0.2	-0.04	0.2

Febrifugine	0.21	-0.02	-0.1	-0.48	0.35	0.41
Fisetin	-0.11	-0.27	0.18	0.2	-0.36	0.2
Galangin	-0.13	-0.21	0.19	0.28	-0.32	0.28
Grossamide	-0.04	-0.9	-0.71	-0.59	-0.18	-0.34
Hydnocarpin -D	0.13	-0.09	0.24	0.36	-0.03	0.32
Hyperoside	0.06	-0.04	0.13	0.2	-0.06	0.42
Irilin-D	-0.22	-0.63	0.01	0.07	-0.68	0.05
Iso-Formononetin	-0.3	-0.69	-0.19	0.05	-0.8	-0.02
Iso-Quercitrin-6-acetate	0.01	-0.09	0.02	0.17	-0.06	0.37
Isorhamnetin-3-o-rutinoside	-0.12	-0.66	-0.23	-0.36	-0.13	0.02
Lariciresinol	0.18	-0.2	-0.08	0.19	-0.03	0.23
Marmesin	-0.42	-0.57	-0.82	-0.2	-0.61	0.21
Miquelianin	0.08	-0.06	-0.01	0.33	-0.05	0.42
Naphthopyrone	-0.47	-0.17	-0.61	-0.51	-0.9	0.04
Naringenin	0.03	-0.2	-0.26	0.42	-0.12	0.21
Naringin	0.11	-0.4	-0.24	0.04	0.09	0.24
Occidentalol-I	0.01	-0.49	-0.31	0.03	-0.07	0.02
Paclobutraazol	0.08	-0.22	-0.37	-0.23	-0.05	0.09
Pentagalloyl-glucose	-3.52	-4.06	-3.97	-4.03	-3.15	-3.65
Piceid	0.14	0.07	0.02	0.21	0.05	0.34
Picralinal	0.11	0.07	-0.4	0.23	0.13	0.13
Pinocembrin	0.0	-0.2	-0.32	0.37	-0.17	0.21
Quercetin-3-arabinoglucoside	0.0	-0.41	-0.1	-0.17	-0.07	0.2
Quercetin-3-glucoside	0.07	-0.11	0.08	0.01	-0.08	0.47
Quercitrin	-0.01	-0.08	0.08	0.17	-0.06	0.37
Rhamnetin	-0.11	-0.27	0.21	0.27	-0.27	0.2
Rhein	-0.08	-0.1	0.01	0.29	-0.06	0.28
Rhoifolin	0.07	-0.35	-0.03	0.01	0.03	0.26
Scutellarin	0.08	-0.09	0.01	0.33	-0.05	0.41
Shyobunone	-0.46	-0.17	-1.25	0.21	-0.24	0.16
Sitosterol palmitate	-0.28	-0.97	-1.03	-0.24	-0.13	-0.28
Trachelogenin	0.24	0.05	-0.07	0.27	0.08	0.20
Uniconazole	-0.01	-0.08	-0.31	-0.2	-0.24	0.41
Veraguensin	0.03	-0.19	-0.18	0.11	-0.14	0.04
Vitexin	0.13	-0.14	0.19	0.23	0.03	0.46
Worenine	-0.04	0.64	-0.32	-0.77	-0.35	0.52
Xanthotoxin	-0.68	-0.12	-0.76	-0.8	-0.91	-0.15

(F) SELECTION OF LIGANDS

Ligands showing molecular properties and bioactivity score that satisfy all the criteriaof a good drug like compound (LIPINSKI RULE) were selected for further research to get a good quality drug against the selected targets matrix metalloproteinases MMP9 and MMP2.

TABLE-19: LIGANDS SELECTED FOR MMP9

1.	(-)-1-(S)-Norcoclaurine
2.	(-)-Centrolobol
3.	5,7,3',4',5- pentahydroxyflavone
4.	5-htp (5-hydroxytryptophan)
5.	5-hydroxy,4,7-dimethoxyy-flavone
6.	Acacetin
7.	Alpinetin
8.	Baicalein
9.	Bisabolol
10.	Chrysoriol
11.	Cubebin
12.	Daidzein
13.	Decussatin
14.	Eriodictyol
15.	Genistein
16.	Genkwanin
17.	Gentiopicroside
18.	Guaiol
19.	Hesperetin
20.	Homoeriodictyol
21.	Isorhamnetin
22.	Liquiritigenin
23.	Petunidin
24.	Phloretin
25.	Piceatannol
26.	Pinocembrin-7-methyl-ether
27.	Pinocembrin-chalcone
28.	Piperine
29.	Pratensein
30.	Prunasin
31.	Prunetin
32.	Resveratrol
33.	Reticuline
34.	Rhamnocitrin
35.	Sakuranetin
36.	Salidroside
37.	Sulfurien
38.	Swertiamarin
39.	Tolperisone
40.	Wogonin

TABLE-20: LIGANDS SELECTED FOR MMP2

1.	16R,19E-isositsirikine
2.	Ajmalicine
3.	Iso-Silybin-A
4.	Ononin
5.	Pericyclivine
6.	Pseudo -Strychnine
7.	Scholaricinne

TABLE-21: LIGANDS SELECTED FOR MMP2 AND MMP9

1.	(+)-aromadendrin
2.	(+)-Nootkatone
3.	Aloe emodin
4.	Biochanin-A
5.	Calycosin
6.	Chrysin
7.	Diosmetin
8.	Ellagic acid
9.	Epi -Afzelechin
10.	Epi -Taxifolin
11.	Febrifugine
12.	Fisetin
13.	Galangin
14.	Irilin-D
15.	Iso-Formononetin
16.	Marmesin
17.	Naphthopyrone
18.	Naringenin
19.	Paclobutraazol
20.	Picralinal
21.	Pinocembrin
22.	Rhamnetin
23.	Rhein
24.	Uniconazole

(G)PHARMACOPHORE

From the above selected ligands a pharmacophore model was generated to predict a minimum necessary structure the molecules must possess in order to bind to the same receptor or target.

MMP9: PHARMACOPHORE MODEL

All the ligands showing stable binding energy and good drug like properties were selected to build a pharmacophore model which fits best to the target MMP9. Four pharmacophore feature pattern were obtained for MMP9: (a) hydrophobic feature (yellow in table-22) (b) 3 hydrogen bond acceptor (red in table-22).

TABLE-22: PHARMACOPHORE FEATURE PATTERN FOR MMP9

	Active		Name	Type	Feature Pattern
1	☑		C:\Users\ownre\Desktop\mmp9\Prunasin.pdb	Test	
2	☑		C:\Users\ownre\Desktop\mmp2&9\Swertiamarin....	Training	
3	☑		C:\Users\ownre\Desktop\mmp2&9\wogonin.pdb	Training	
4	☑		C:\Users\ownre\Desktop\mmp2&9\Baicalein.pdb	Training	
5	☑		C:\Users\ownre\Desktop\mmp9\Pinocembrin ch...	Test	
6	☑		C:\Users\ownre\Desktop\mmp2&9\hesperetin.pdb	Test	
7	☑		C:\Users\ownre\Desktop\mmp2&9\Salidroside.pdb	Training	
8	☑		C:\Users\ownre\Desktop\mmp2&9\Gentiopicrosi...	Test	
9	☑		C:\Users\ownre\Desktop\mmp2&9\isorhamnetin...	Test	
10	☑		C:\Users\ownre\Desktop\mmp2&9\alpinetin.pdb	Test	
11	☑		C:\Users\ownre\Desktop\mmp2&9\5,7,3',4',5 PE...	Test	
12	☑		C:\Users\ownre\Desktop\mmp2&9\Pinocembrin...	Test	
	Active		Name	Type	Feature Pattern
13	☑		C:\Users\ownre\Desktop\mmp2&9\acacetin.pdb	Test	
14	☑		C:\Users\ownre\Desktop\mmp2&9\sakuranetin.p...	Test	
15	☑		C:\Users\ownre\Desktop\mmp2&9\5 hydroxy ,4,7...	Test	
16	☑		C:\Users\ownre\Desktop\mmp2&9\Homoeriodic...	Test	
17	☑		C:\Users\ownre\Desktop\mmp2&9\Eriodictyol.pdb	Test	
18	☑		C:\Users\ownre\Desktop\mmp2&9\Chrysoriol.pdb	Test	
19	☑		C:\Users\ownre\Desktop\mmp9\prunetin.pdb	Test	
20	☑		C:\Users\ownre\Desktop\mmp2&9\genistein.pdb	Test	
21	☑		C:\Users\ownre\Desktop\mmp9\(-)-1-(S)-Norcoc...	Test	
22	☑		C:\Users\ownre\Desktop\mmp2&9\genkwanin.p...	Test	
23	☑		C:\Users\ownre\Desktop\mmp2&9\rhamnocitrin....	Test	
24	☑		C:\Users\ownre\Desktop\mmp2&9\Petunidin.pdb	Test	
	Active		Name	Type	Feature Pattern
25	☑		C:\Users\ownre\Desktop\mmp2&9\Reticuline.pdb	Test	
26	☑		C:\Users\ownre\Desktop\mmp9\pratensein.pdb	Test	
27	☑		C:\Users\ownre\Desktop\mmp2&9\decussatin.pdb	Test	
28	☑		C:\Users\ownre\Desktop\mmp9\piceatannol.pdb	Test	
29	☑		C:\Users\ownre\Desktop\mmp2&9\resveratrol.pdb	Test	
30	☑		C:\Users\ownre\Desktop\mmp2&9\liquiritigenin....	Test	
31	☑		C:\Users\ownre\Desktop\mmp2&9\Phloretin.pdb	Test	
32	☑		C:\Users\ownre\Desktop\mmp9\piperine.pdb	Test	
33	☑		C:\Users\ownre\Desktop\mmp2&9\daidzein.pdb	Test	
34	☑		C:\Users\ownre\Desktop\mmp9\Tolperisone.pdb	Test	
35	☑		C:\Users\ownre\Desktop\mmp2&9\sulfurien.pdb	Test	
36	☑		C:\Users\ownre\Desktop\mmp9\guaiol.pdb	Test	
37	☑		C:\Users\ownre\Desktop\mmp2&9\cubebin.pdb	Test	
38	☑		C:\Users\ownre\Desktop\mmp9\(-)-Centrolobol....	Test	
39	☑		C:\Users\ownre\Desktop\mmp9\bisabolol.pdb	Ignored	

Yellow: hydrophobic feature ; red: hydrogen bond aceptor

FIG-2: HYDROPHOBIC FEATURE OF PHARMACOPHORE FOR MMP9: feature highlighted in bright yellow colour.

FIG-3: HYDROGEN BOND ACCEPTOR-1 FEATURE OF PHARMACOPHORE FOR MMP9: feature highlighted in bright yellow colour.

FIG-4: HYDROGEN BOND ACCEPTOR-2 FEATURE OF PHARMACOPHORE FOR MMP9: feature highlighted in bright yellow colour.

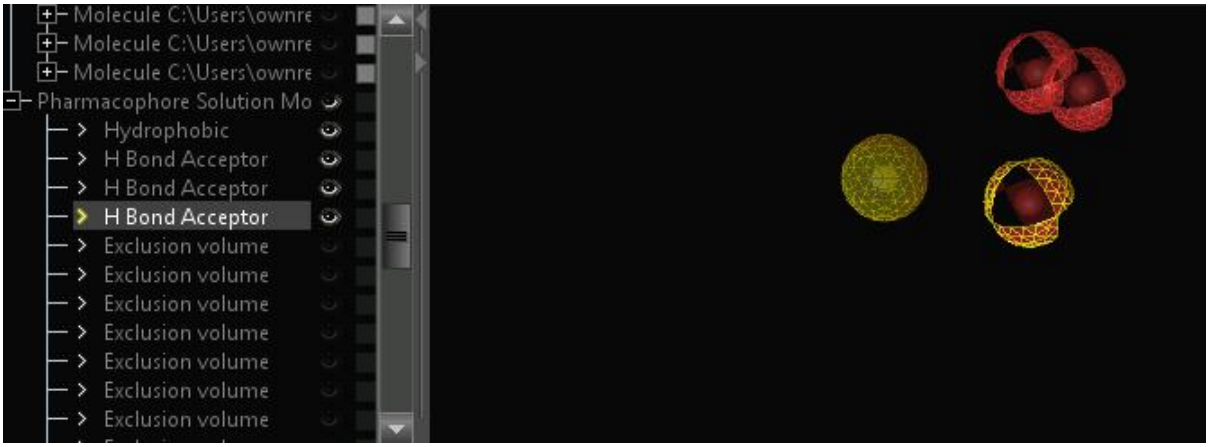


FIG-5: HYDROGEN BOND ACCEPTOR-3 FEATURE OF PHARMACOPHORE FOR MMP9: feature highlighted in bright yellow colour.

(1)PRUNASIN: It has highest pharmacophore fit score: 47,3900 and has all four pharmacophore features:(a) hydrophobic feature(yellow) (b)3 hydrogen bond acceptor(red).

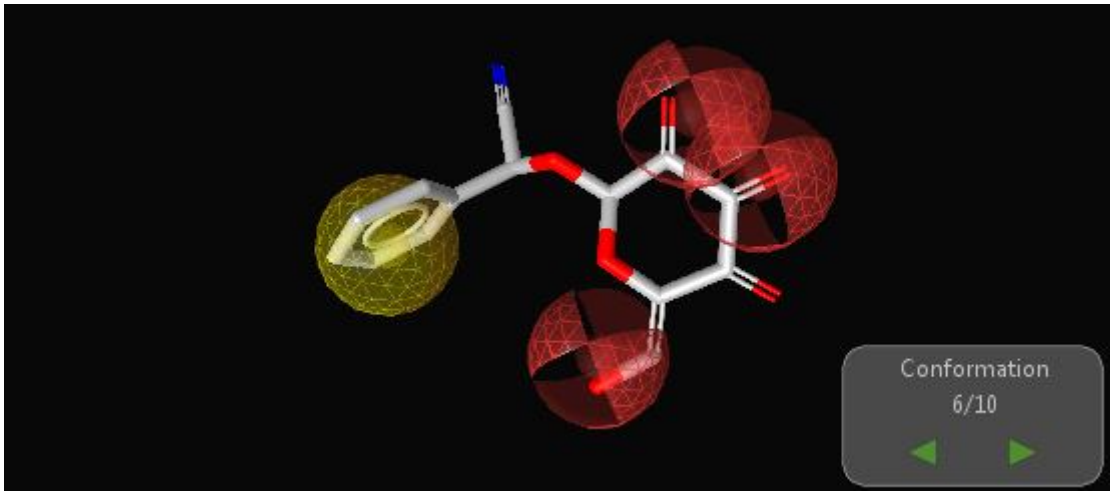


FIG-6A: PRUNASIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

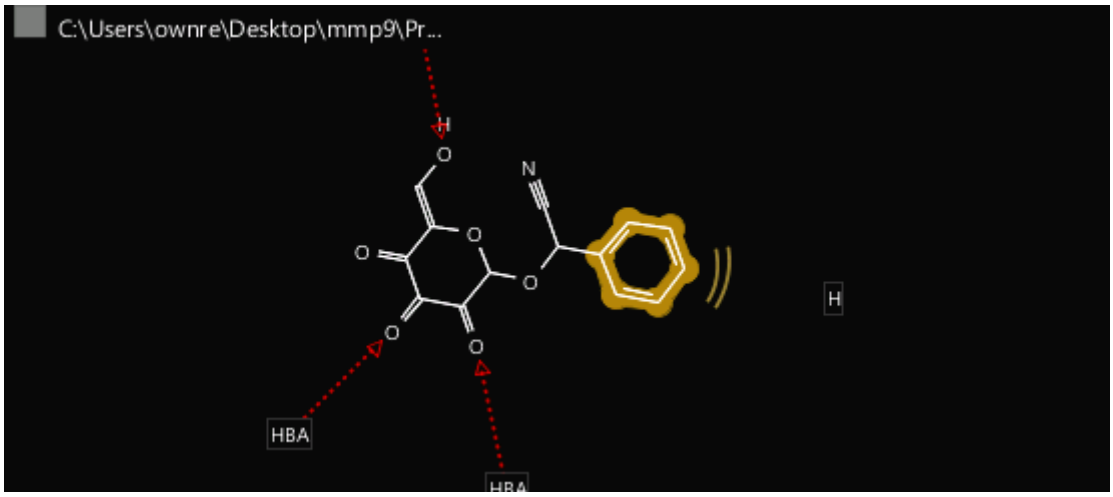


FIG-6B: PRUNASIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(2) SWERTIAMARIN: Swertiamarin has second highest pharmacophore fit score: 47,3800 and has all four pharmacophore features:(a) hydrophobic feature(yellow) (b)3 hydrogen bond acceptor(red).

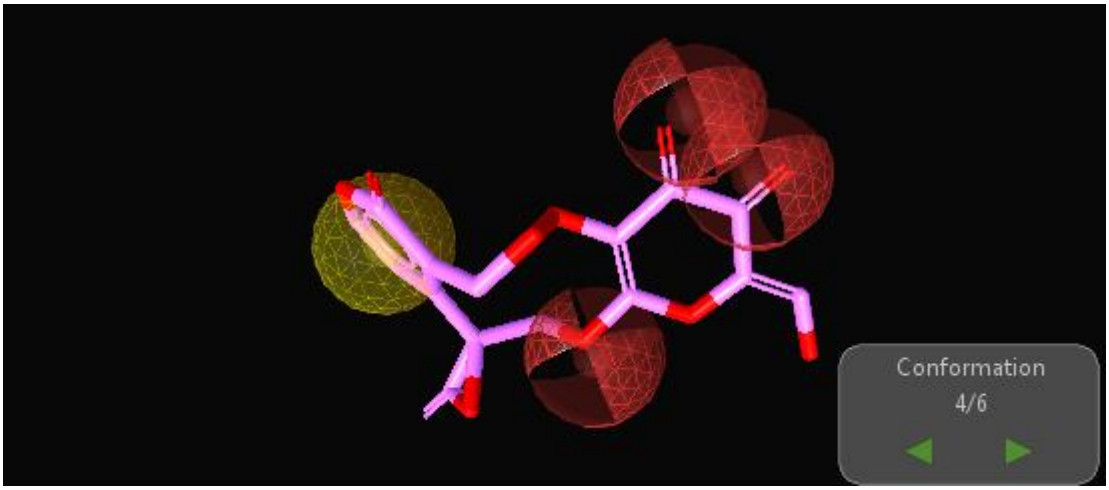


FIG-7A: SWERTIAMARIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

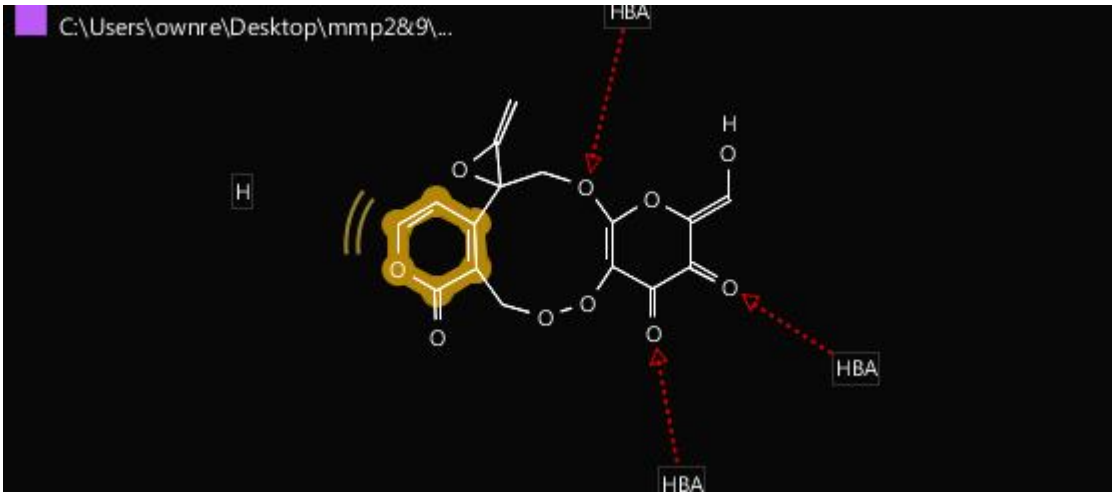


FIG-7B: SWERTIAMARIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(3)WOGONIN: wogonin has third highest pharmacophore fit score: 46,8600 and has all four pharmacophore features:(a) hydrophobic feature(yellow) (b)3 hydrogen bond acceptor(red).

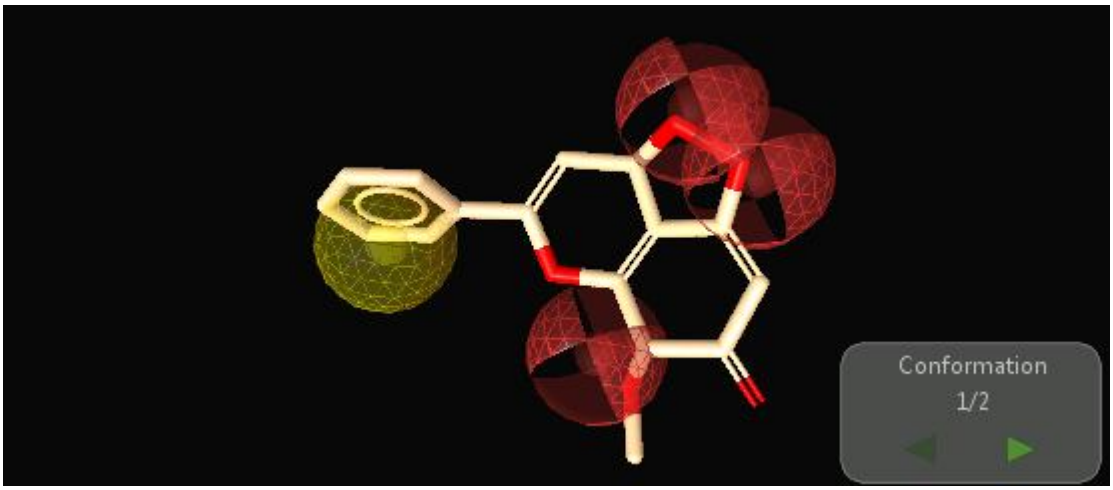


FIG-8A: WOGONIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

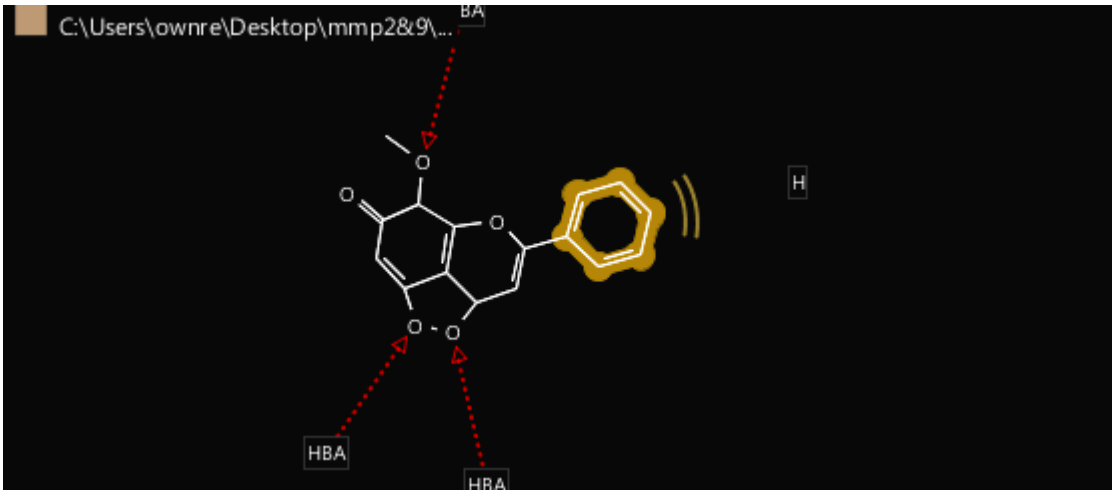


FIG-8B: WOGONIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(4) BAICALEIN: Baiclein has pharmacophore fit score: 46,7900 and has all four pharmacophore features:(a) hydrophobic feature(yellow) (b)3 hydrogen bond acceptor(red).

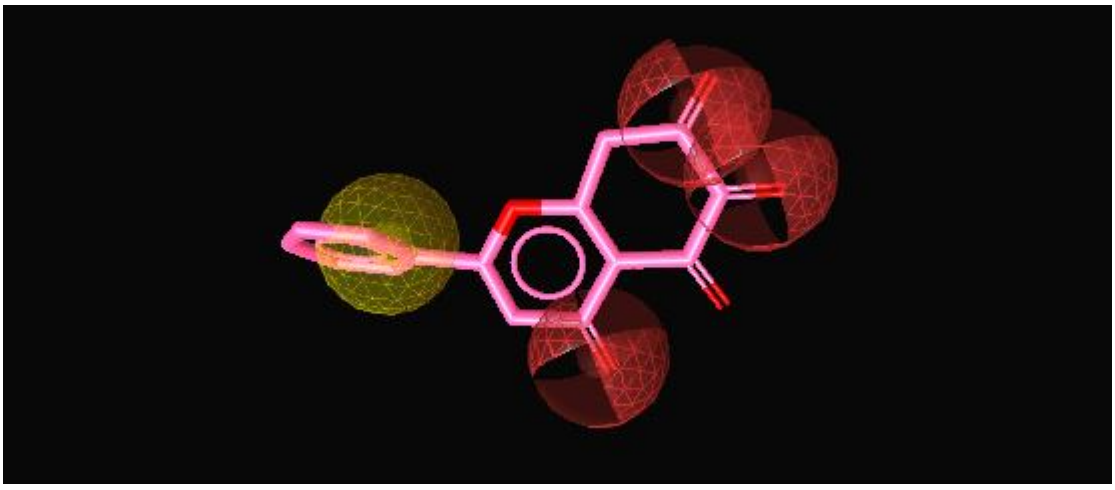


FIG-9A: BAICALEIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

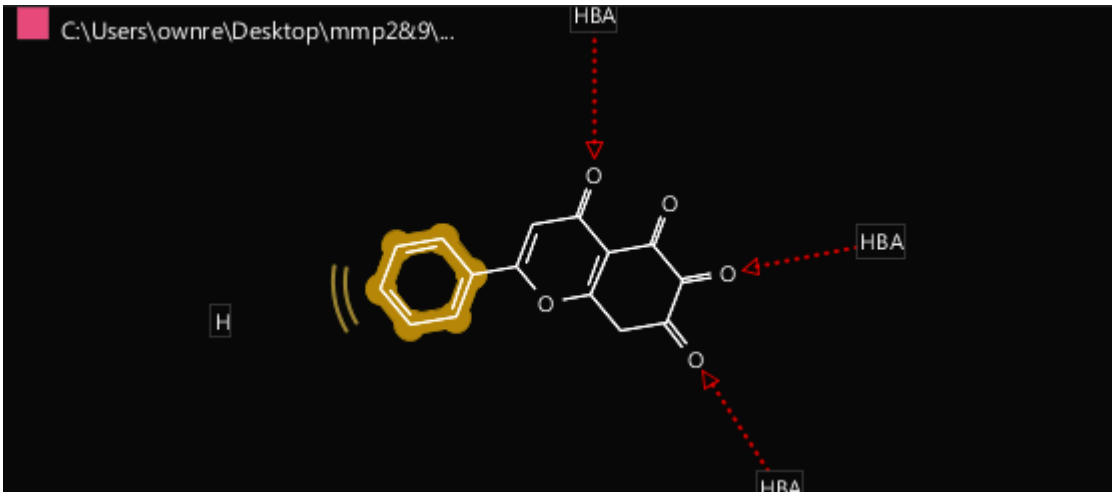


FIG-9B: BAICALEIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(5)PINOCEMBRIN-CHALCONE: Pinocembrin-chalcone has pharmacophore fit score: 46,7500 and has all four pharmacophore features:(a) hydrophobic feature(yellow) (b)3 hydrogen bond acceptor(red).

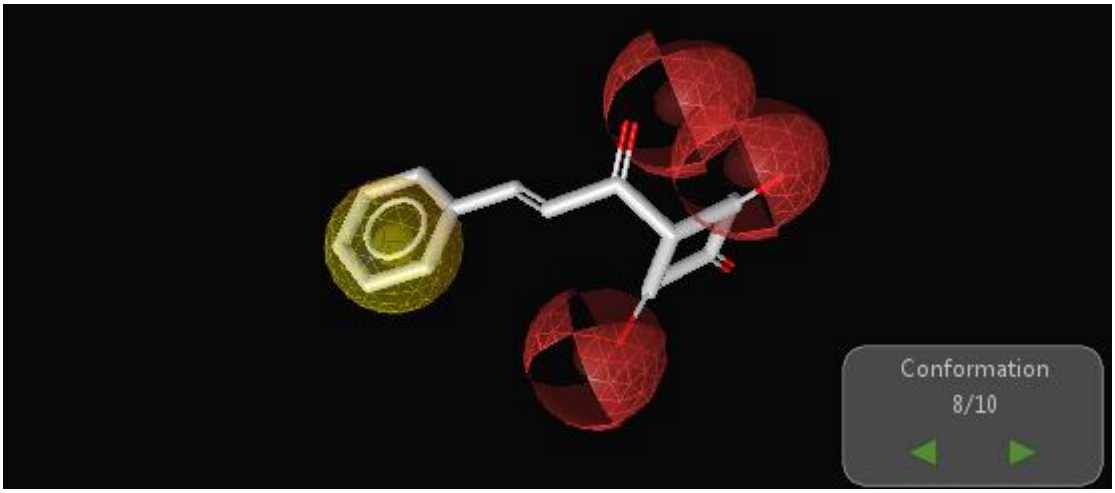


FIG-10A : PINOCEMBRIN-CHALCONE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

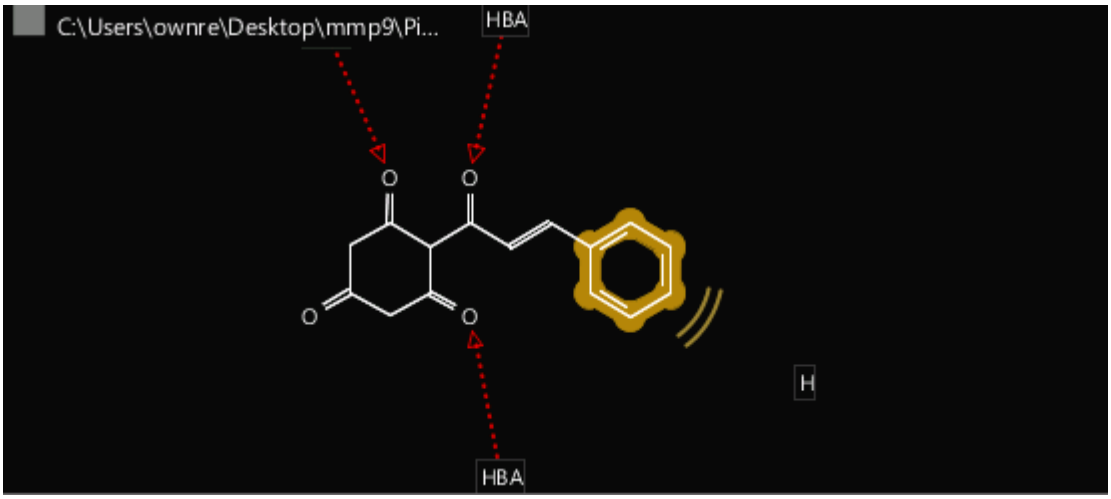


FIG-10B : PINOCEMBRIN-CHALCONE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(6)HESPERETIN: Hesperetin has pharmacophore fit score: 46,7000 and has all four pharmacophore features:(a) hydrophobic feature(yellow) (b)3 hydrogen bond acceptor(red).

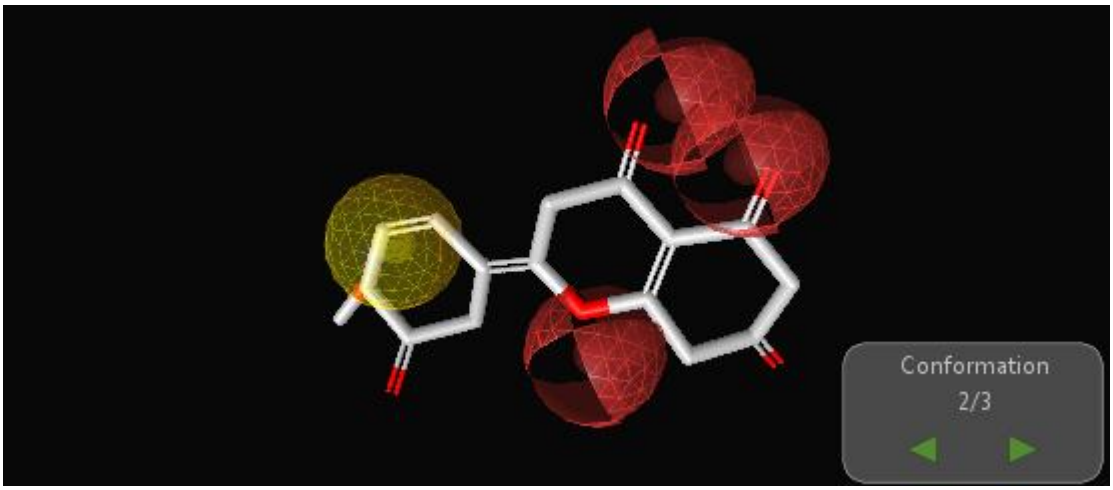


FIG-11A : HESPERETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

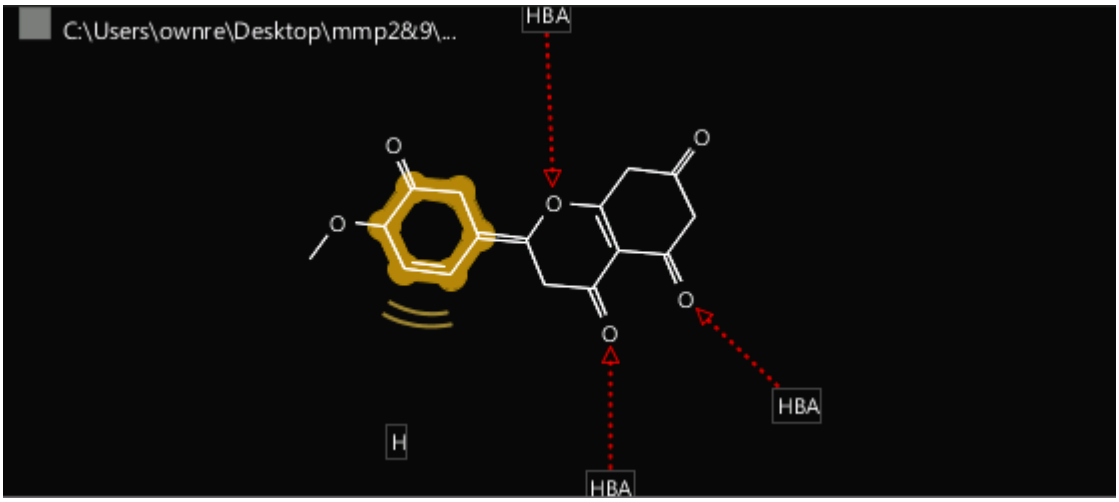


FIG11-B : HESPERETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(7)SALIDROSIDE: Salidroside has pharmacophore fit score: 46,4000 and has all four pharmacophore features:(a) hydrophobic feature(yellow) (b)3 hydrogen bond acceptor(red).

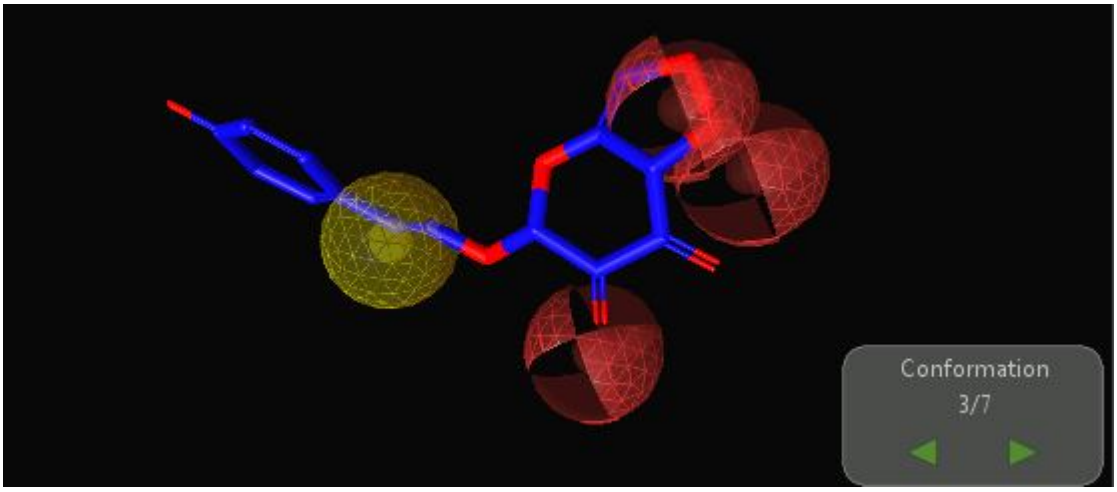


FIG-12A : SALIDROSIDE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

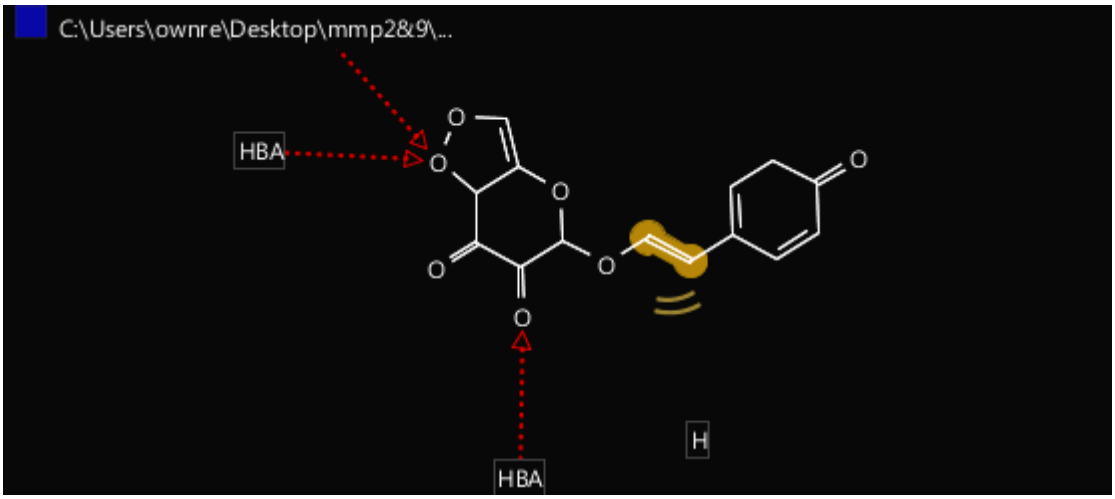


FIG-12B : SALIDROSIDE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(8)GENTIOPICROSIDE: Gentiopicroside has pharmacophore fit score: 46,2400 and has all four pharmacophore features:(a) hydrophobic feature(yellow) (b)3 hydrogen bond acceptor(red).

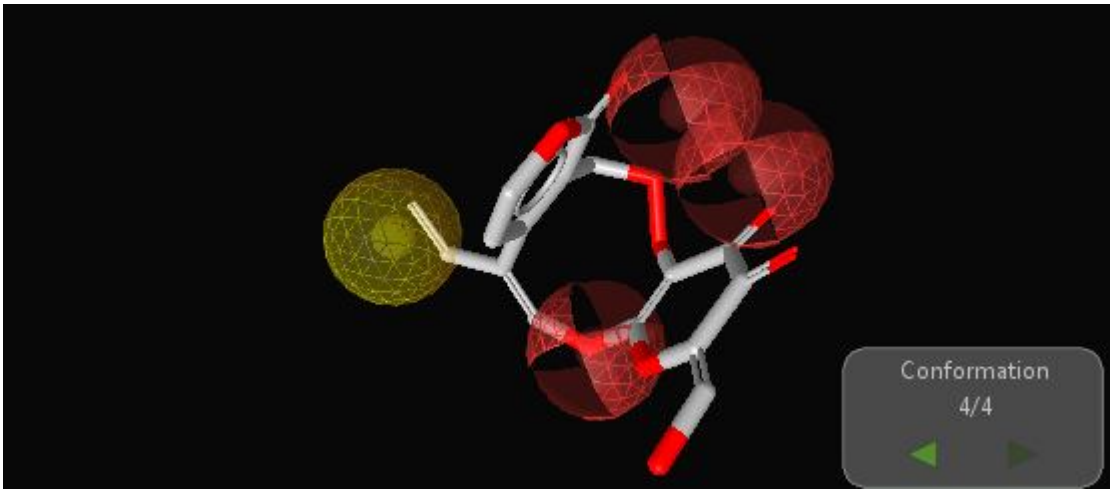


FIG-13A: GENTIOPICROSIDE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

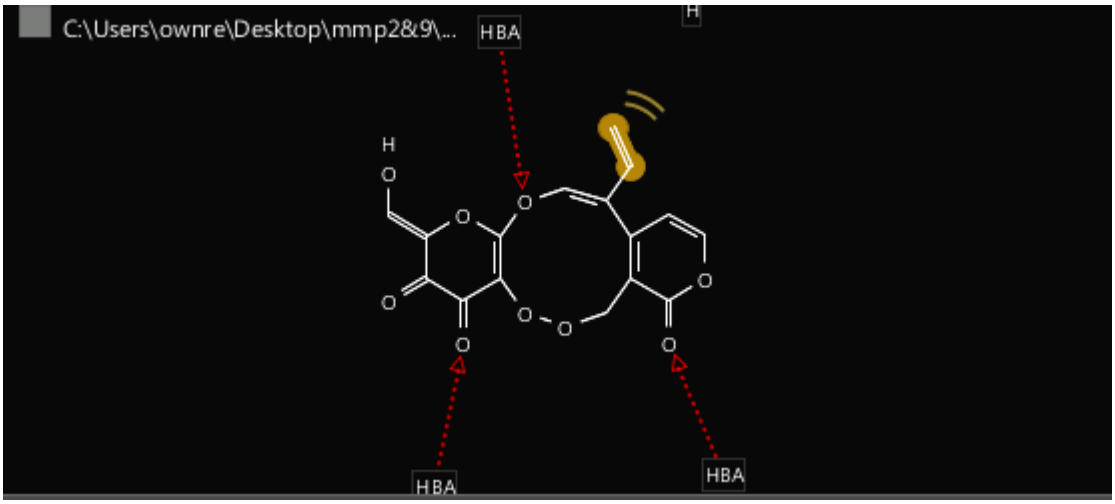


FIG-13B: GENTIOPICROSIDE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(9)5-HTP: 5-htp has pharmacophore fit score: 38,4200 and has three pharmacophore features: (a)3 hydrogen bond acceptor(red).

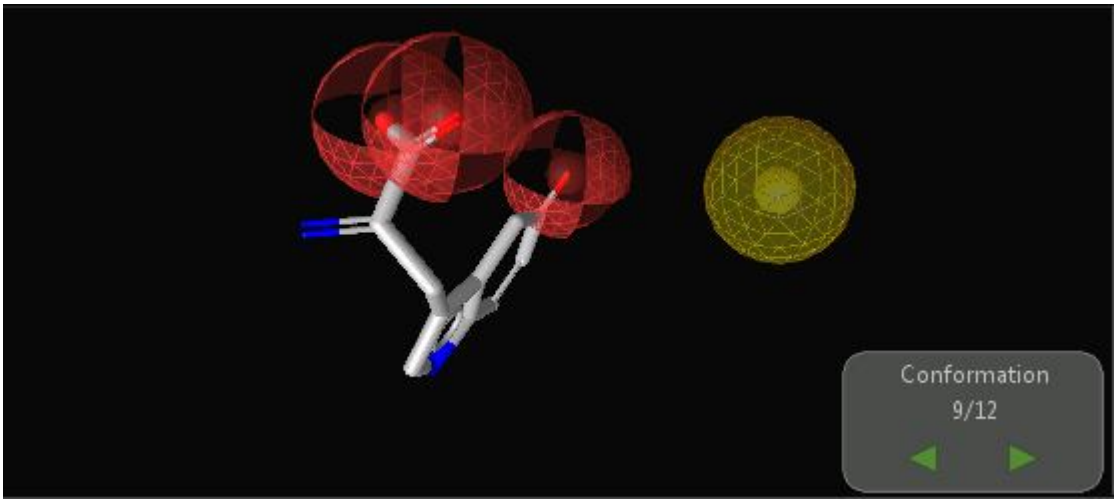


FIG-14A: 5 HTP: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

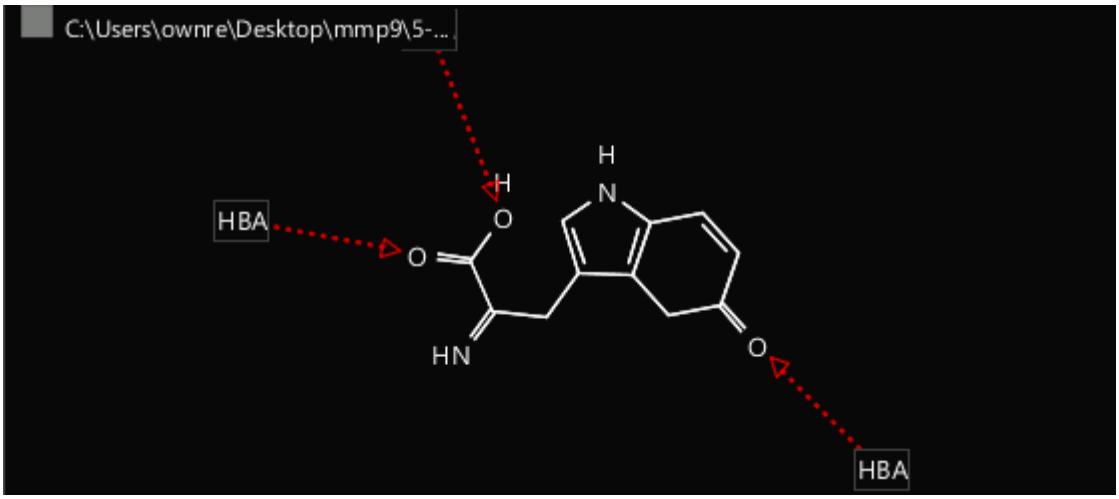


FIG-14B: 5 HTP: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(10)ISORHAMNETIN: Isorhamnetin has pharmacophore fit score: 38,0400 and has three pharmacophore features: (a)3 hydrogen bond acceptor(red).

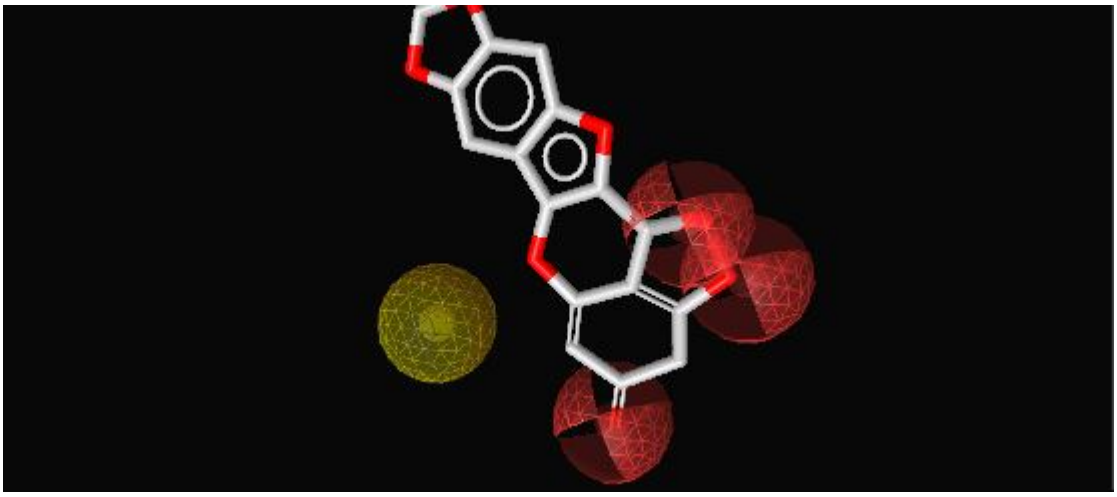


FIG-15A: ISORHAMNETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

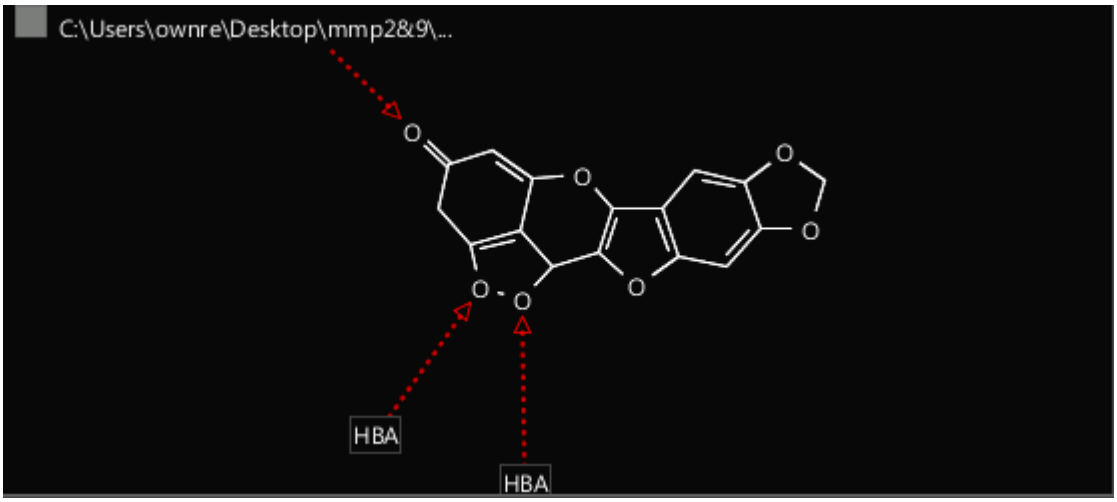


FIG-15B: ISORHAMNETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(11) ALPINETIN: Alpinetin has pharmacophore fit score: 37,7700 and has three pharmacophore features: (a) hydrophobic feature(yellow) (b)2 hydrogen bond acceptor(red).

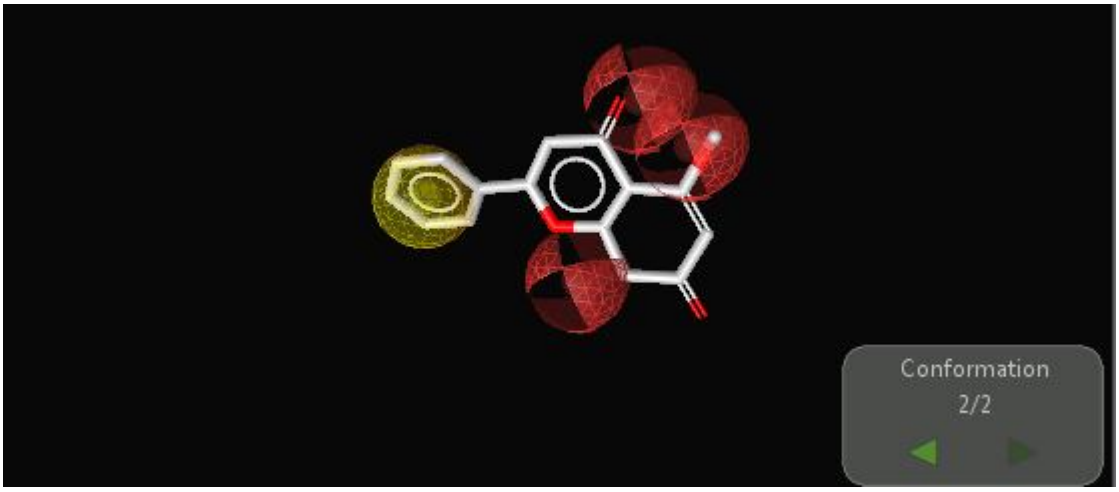


FIG-16A: ALPINETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

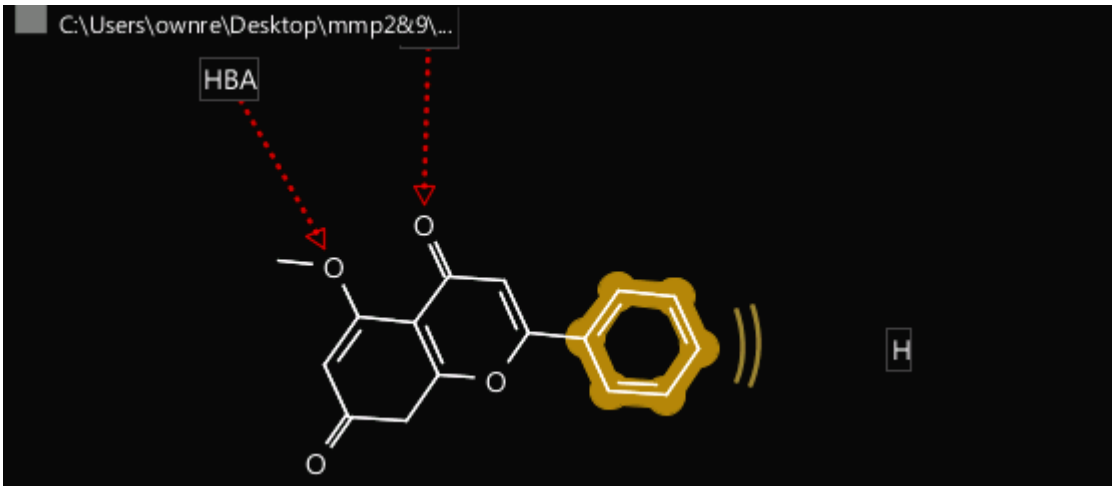


FIG-16B: ALPINETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(12) 5,7,3',4',5- PENTAHYDROXYFLAVONE: 5,7,3',4',5- pentahydroxyflavone has pharmacophore fit score: 37,7000 and has three pharmacophore features: (a)3 hydrogen bond acceptor(red).

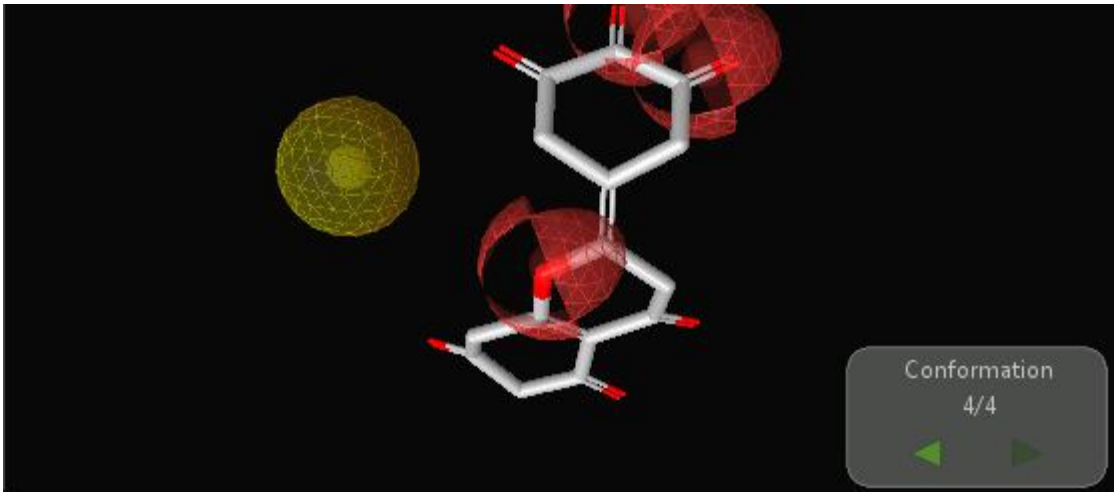


FIG-17A: 5,7,3',4',5- PENTAHYDROXYFLAVONE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

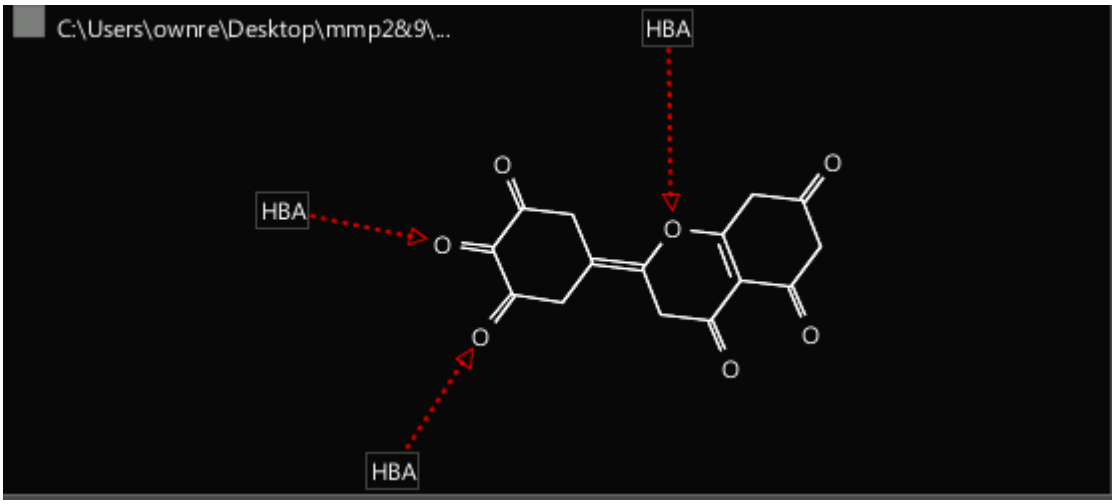


FIG-17B: 5,7,3',4',5- PENTAHYDROXYFLAVONE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(13) PINOCEMBRIN-7-METHYL-ETHER: Pinocembrin-7-methyl-ether has pharmacophore fit score: 37,6800 and has three pharmacophore features: (a) hydrophobic feature(yellow) (b)2 hydrogen bond acceptor(red).

FIG-18A: PINOCEMBRIN-7-METHYL-ETHER: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

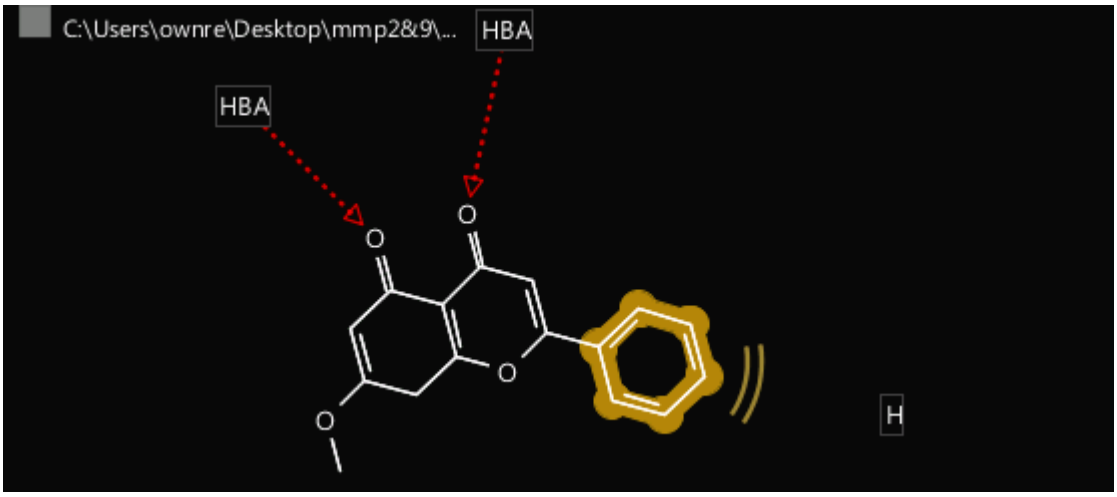


FIG-18B: PINOCEMBRIN-7-METHYL-ETHER: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(14) ACACETIN: Acacetin has pharmacophore fit score: 37,6200 and has three pharmacophore features: (a) hydrophobic feature(yellow) (b)2 hydrogen bond acceptor(red).

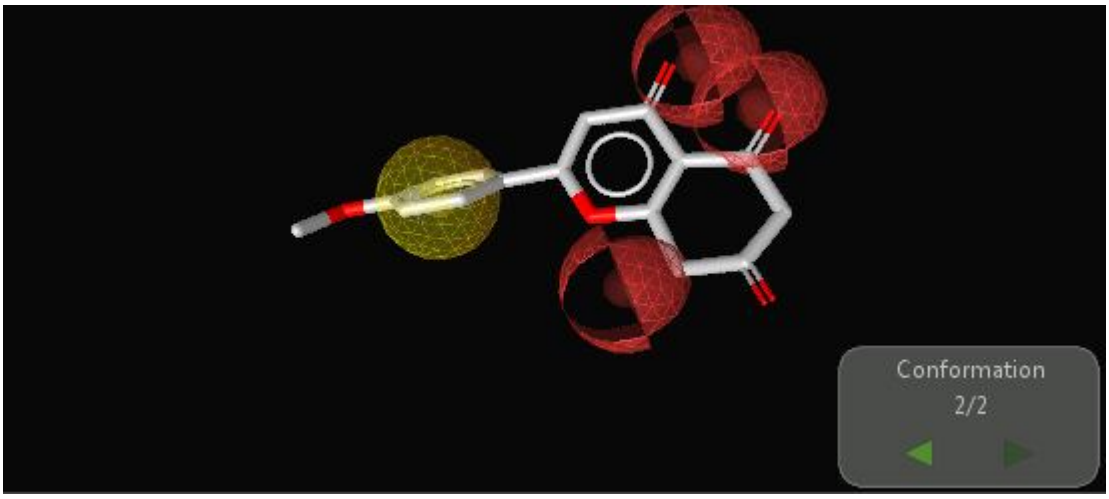


FIG-19A: ACACETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

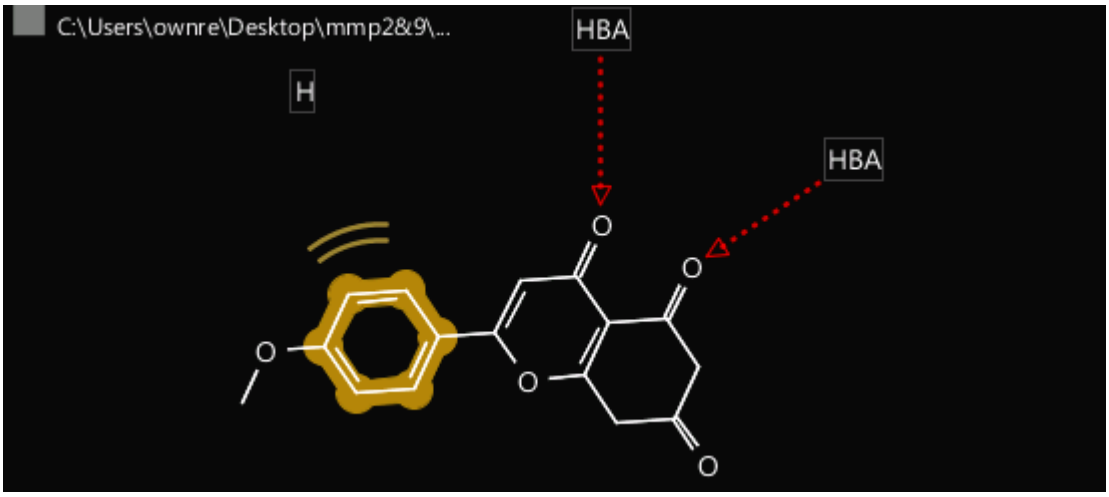


FIG-19B: ACACETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(15) SAKURANETIN: Sakuranetin has pharmacophore fit score: 37,6200 and has three pharmacophore features: (a) hydrophobic feature(yellow) (b)2 hydrogen bond acceptor(red).

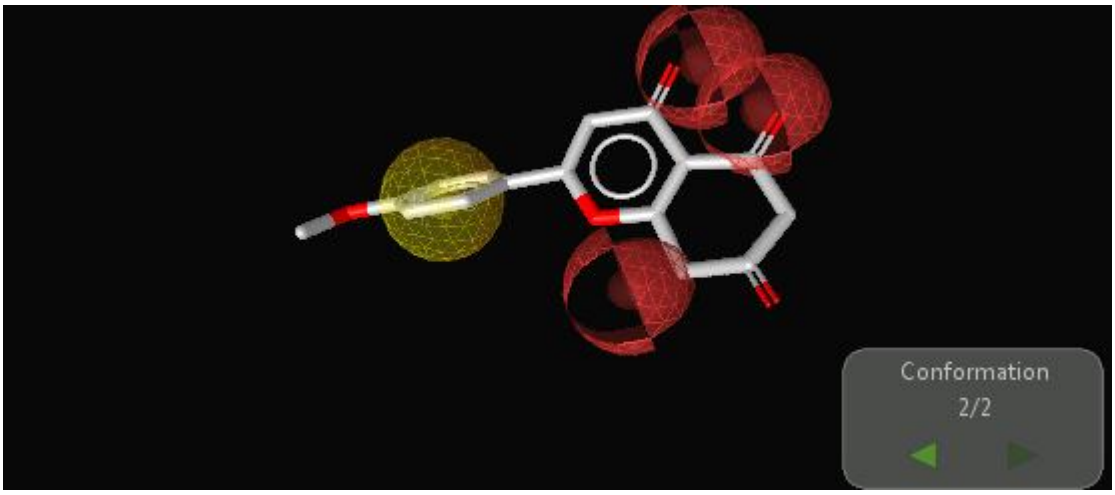


FIG-20A: SAKURANETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

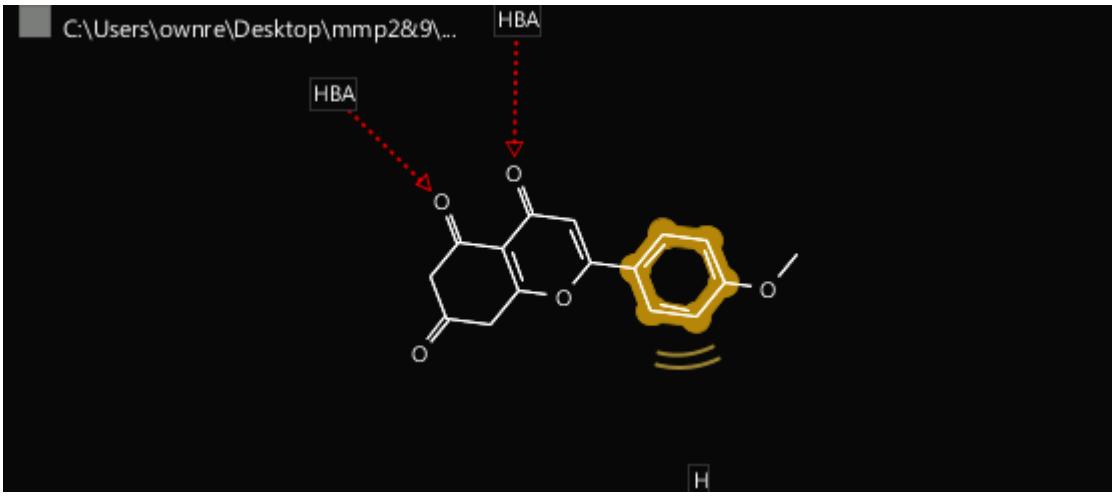


FIG-20B: SAKURANETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(16) 5-HYDROXY,4,7-DIMETHOXYY-FLAVONE: 5-hydroxy,4,7-dimethoxy flavone has pharmacophore fit score: 37,6000 and has three pharmacophore features: (a) hydrophobic feature(yellow) (b)2 hydrogen bond acceptor(red).

FIG-21A: 5-HYDROXY,4,7-DIMETHOXYY-FLAVONE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

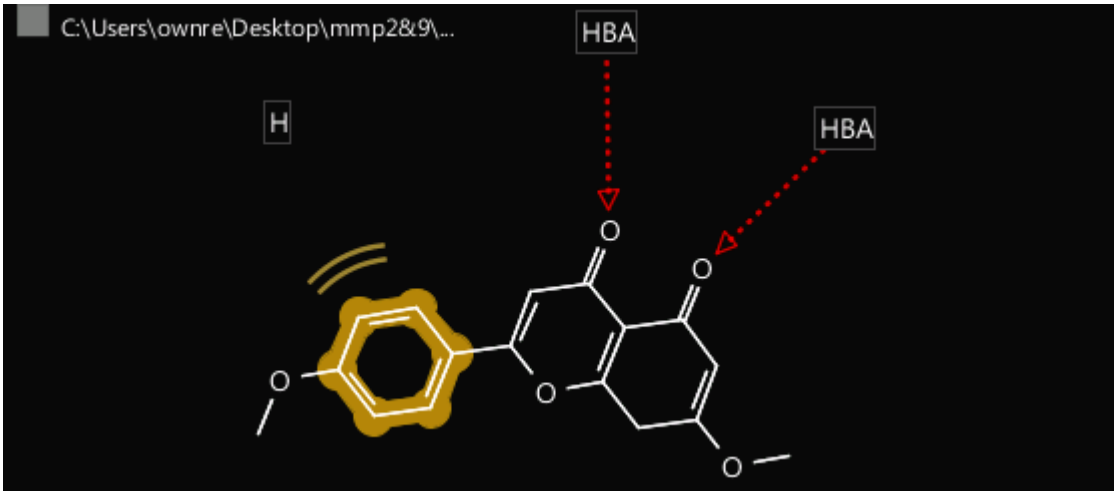


FIG-21B: 5-HYDROXY,4,7-DIMETHOXYY-FLAVONE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(17) HOMOERIODICTYOL: Homoeriodictyol has pharmacophore fit score: 37,5400 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

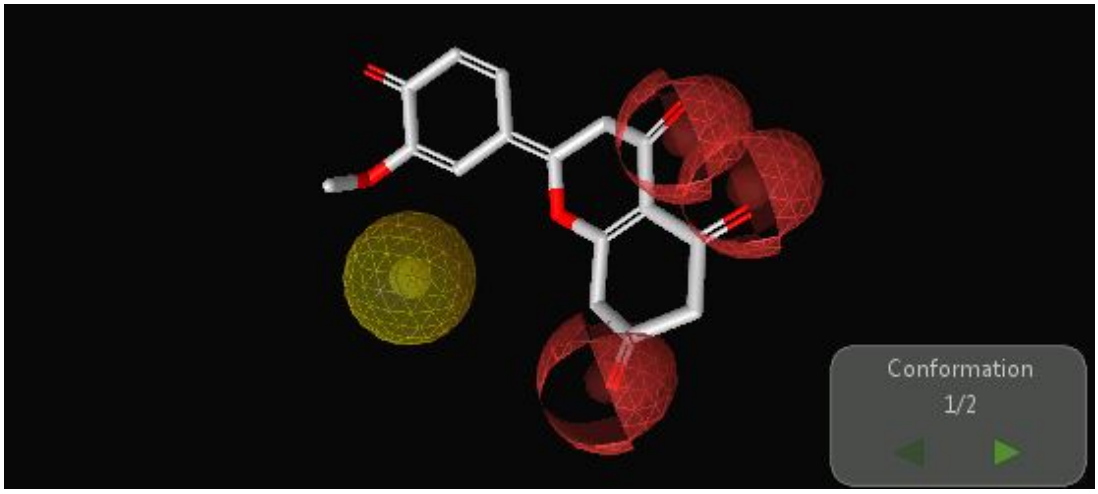


FIG-22A: HOMOERIODICTYOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

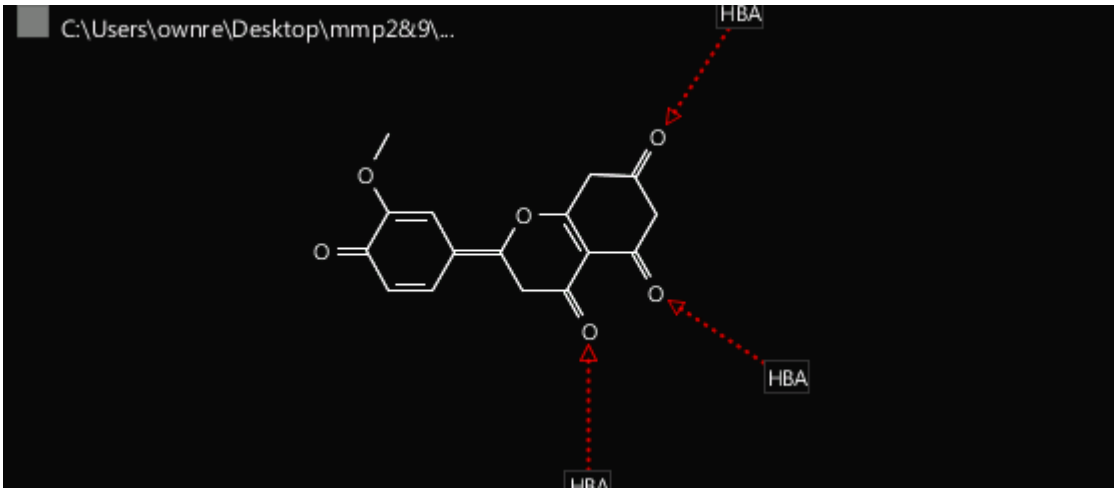


FIG-22B: HOMOERIODICTYOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(18) ERIODICTYOL: Eriodictyol has pharmacophore fit score: 37,5400 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

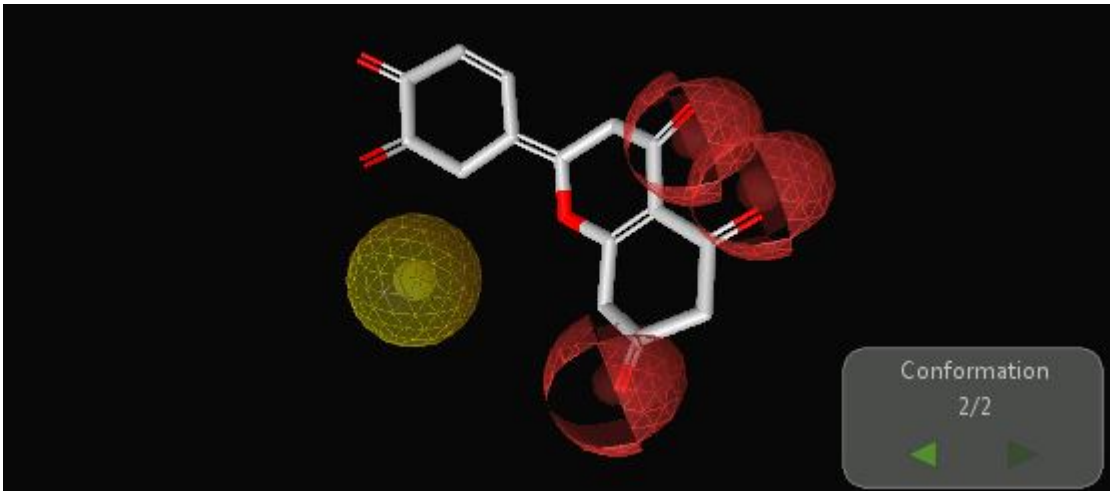


FIG-23A: ERIODICTYOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

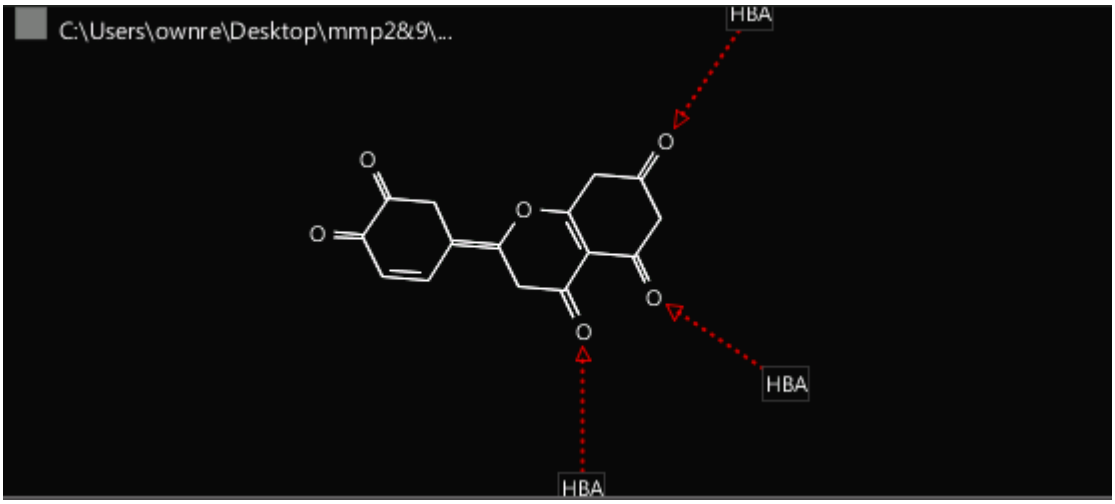


FIG-23B: ERIODICTYOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(19) CHRYSORIOL: Chrysoriol has pharmacophore fit score: 37,5400 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

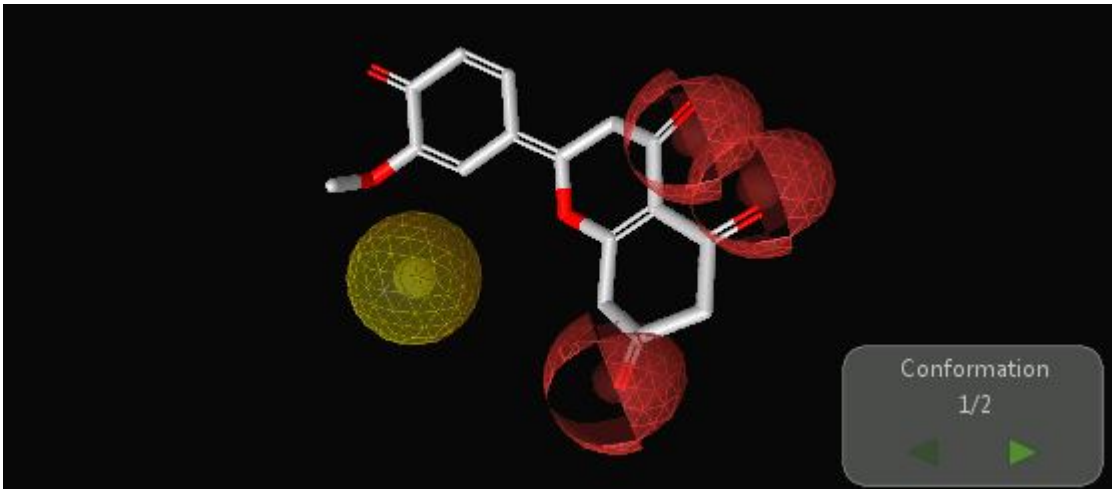


FIG-24A: CHRYSORIOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

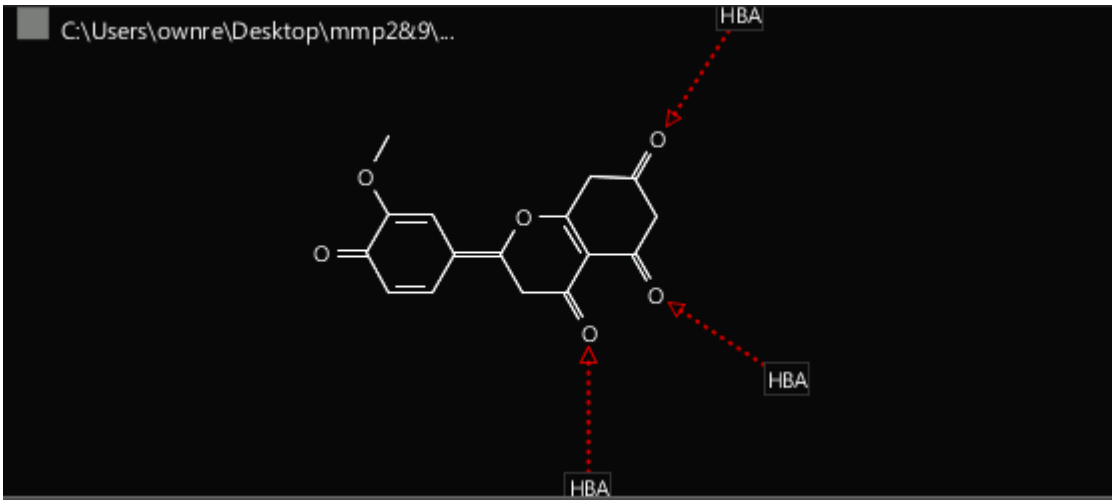


FIG-24B: CHRYSORIOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(20)PRUNETIN: Prunetin has pharmacophore fit score: 37,5200 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

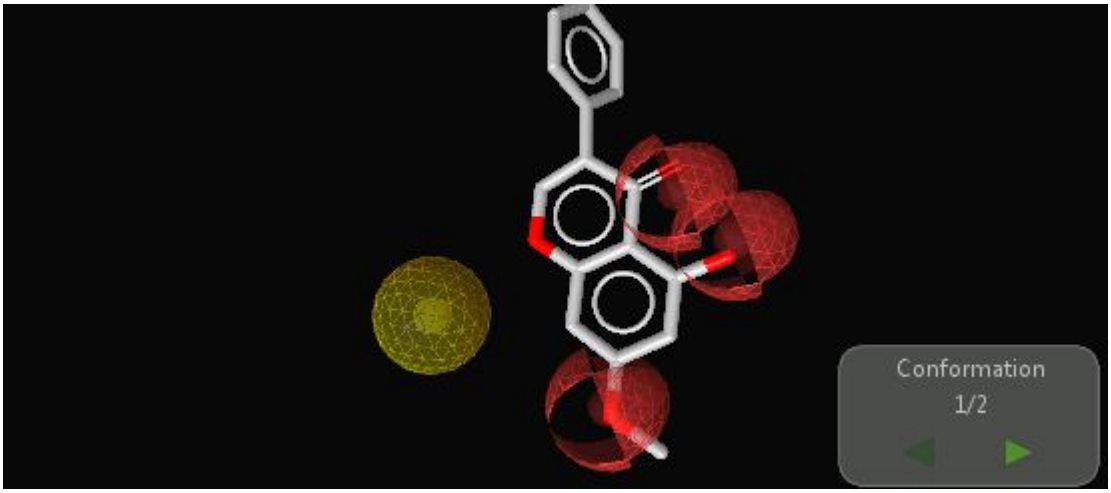


FIG-25A: PRUNETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

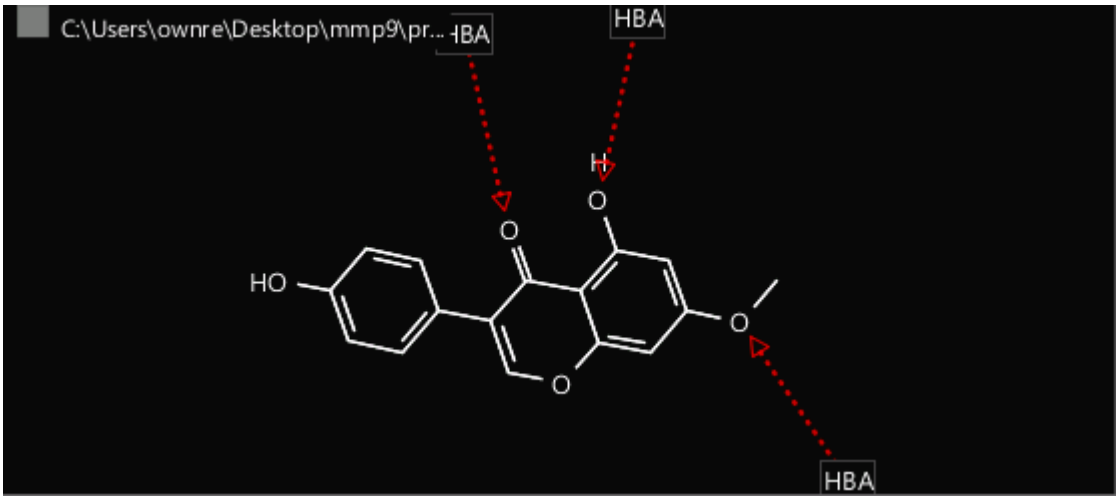


FIG-25B: PRUNETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(21) GENISTEIN: Genistein has pharmacophore fit score: 37,5100 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

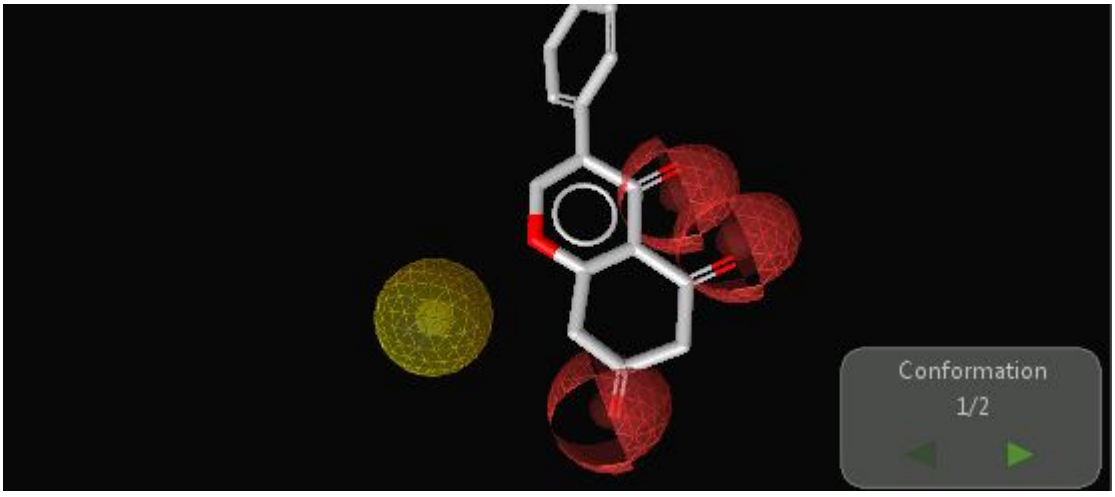


FIG-26A: GENISTEIN:SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

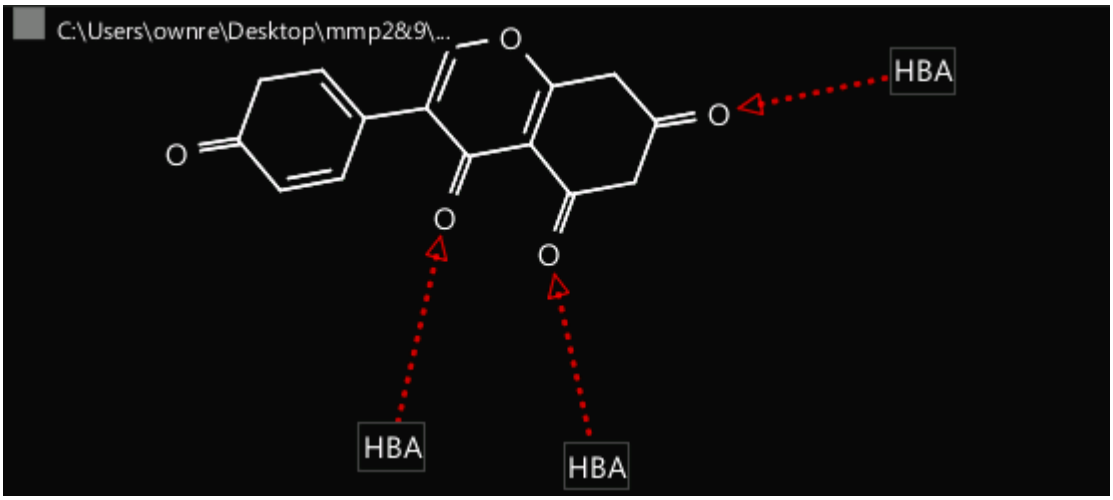


FIG-26B: GENISTEIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(22) (-)-1-(S)-NORCOCLAURINE: (-)-1-(s)-norcoclaurine has pharmacophore fit score: 37,4700 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

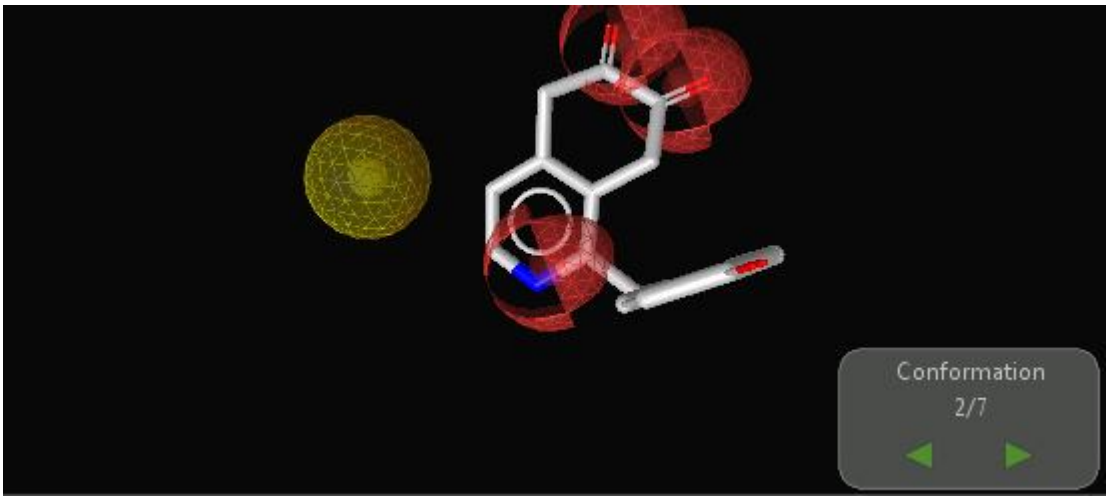


FIG-27A: (-)-1-(S)-NORCOCLAURINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

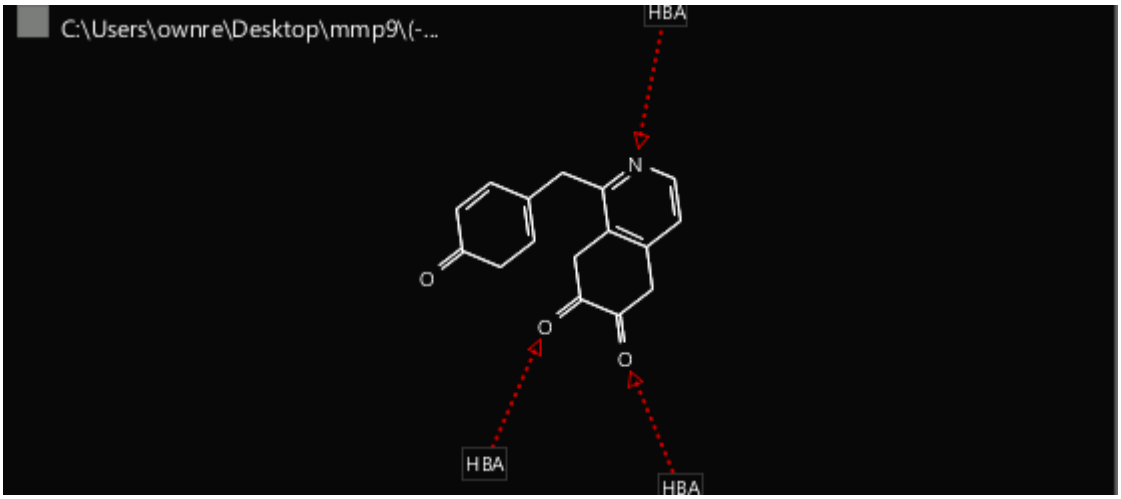


FIG27-B: (-)-1-(S)-NORCOCLAURINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(23) GENKWANIN: Genkwanin has pharmacophore fit score: 37,3000 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

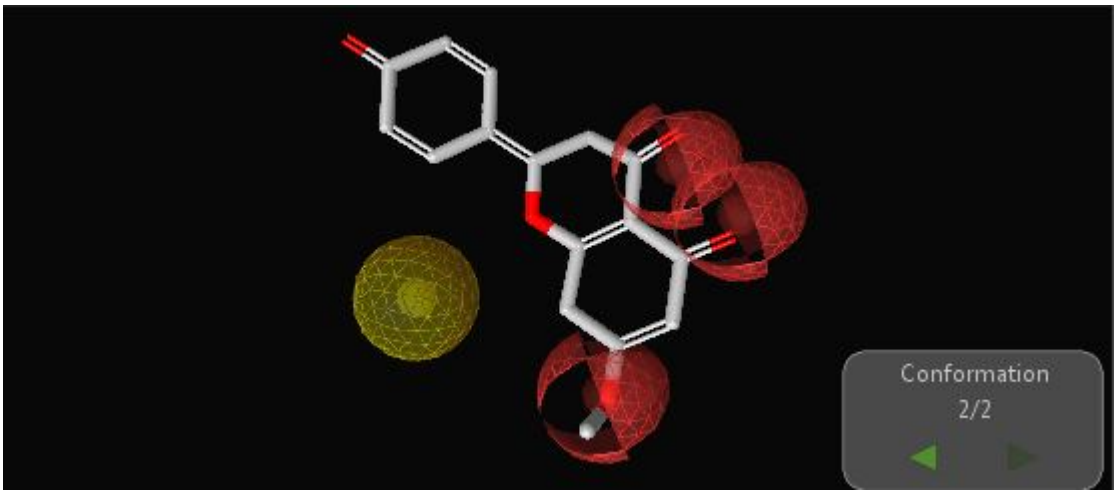


FIG-28A: GENKWANIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

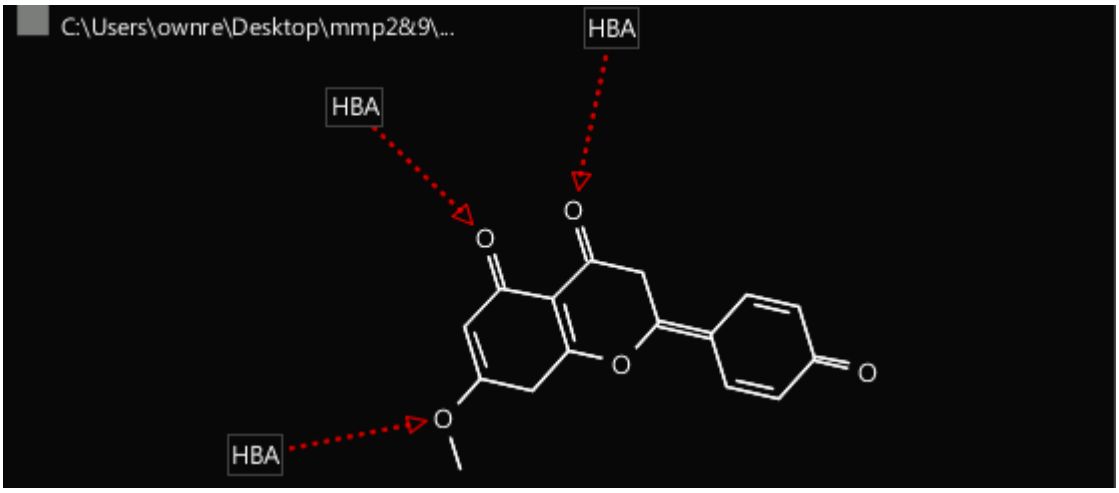


FIG-28B: GENKWANIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(24)RHAMNOCITRIN: Rhamnocitrin has pharmacophore fit score: 37,2700 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

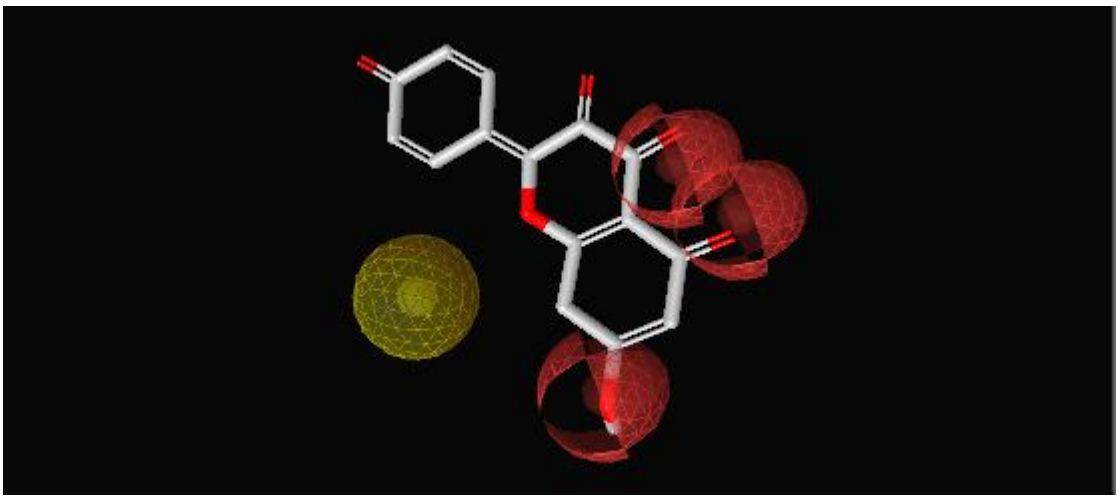


FIG-29A: RHAMNOCITRIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

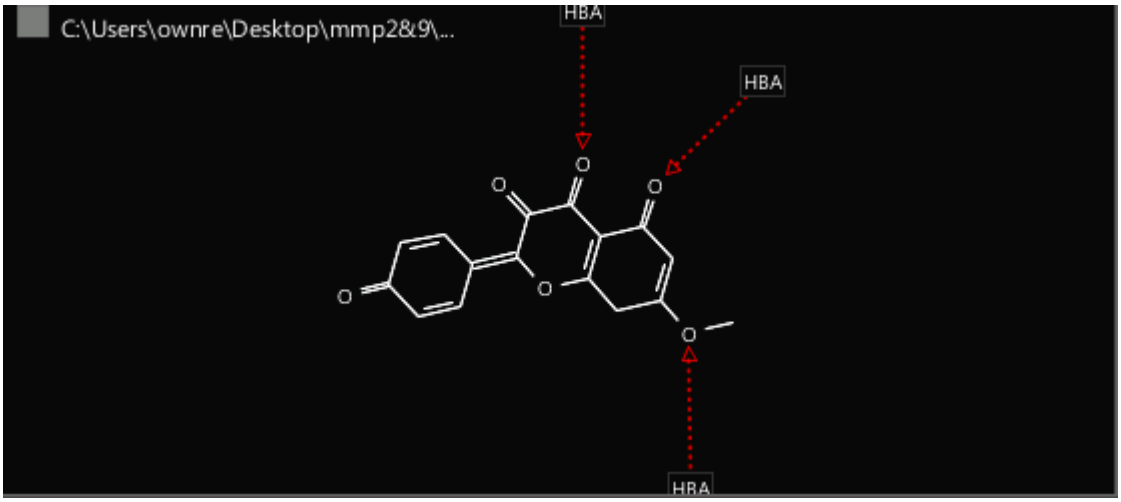


FIG29-B: RHAMNOCITRIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(25) PETUNIDIN: Petunidin has pharmacophore fit score: 37,1800 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

FIG-30A: PETUNIDIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

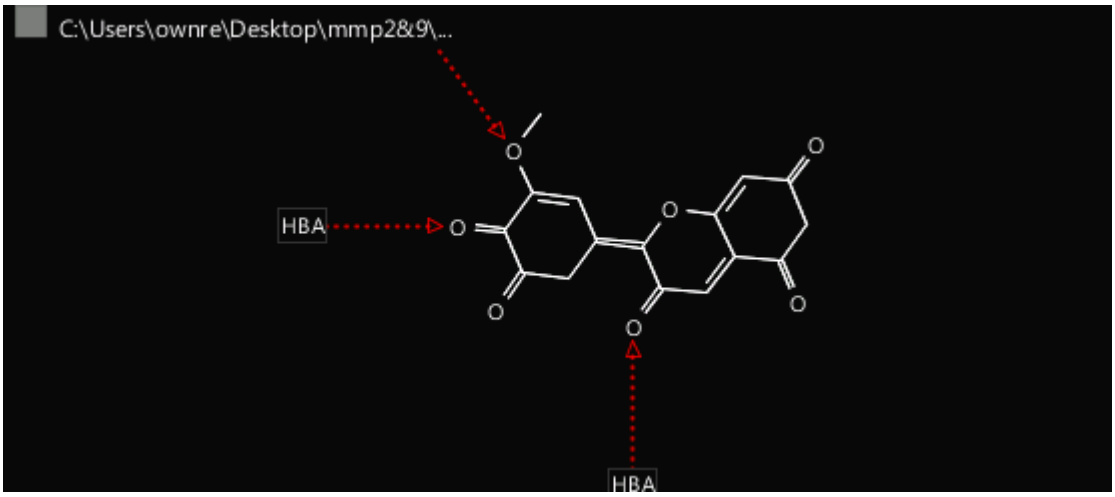


FIG-30B: PETUNIDIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(26)RETICULINE: Reticuline has pharmacophore fit score: 37,1600 and has three pharmacophore features: (a) hydrophobic feature(yellow) (b)2 hydrogen bond acceptor(red).

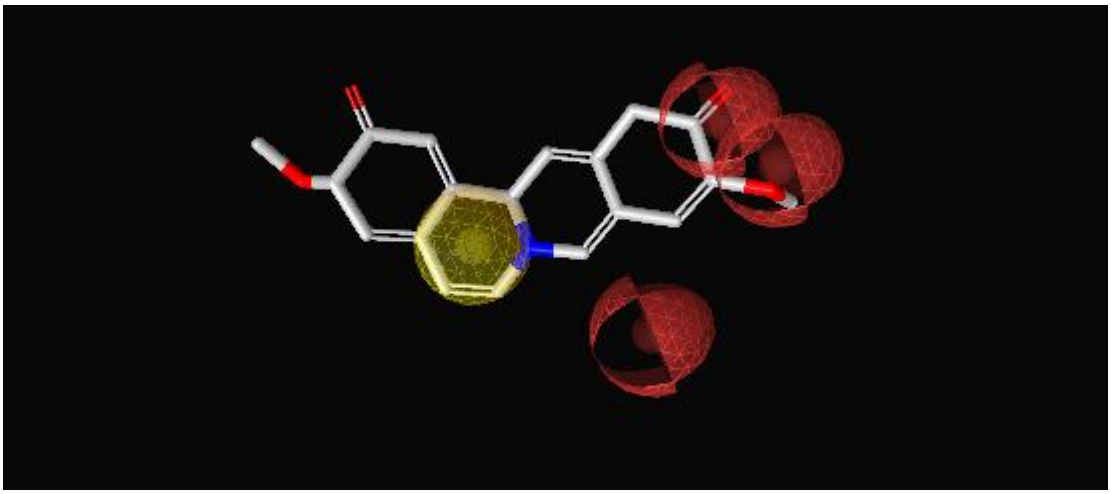


FIG-31A: RETICULINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

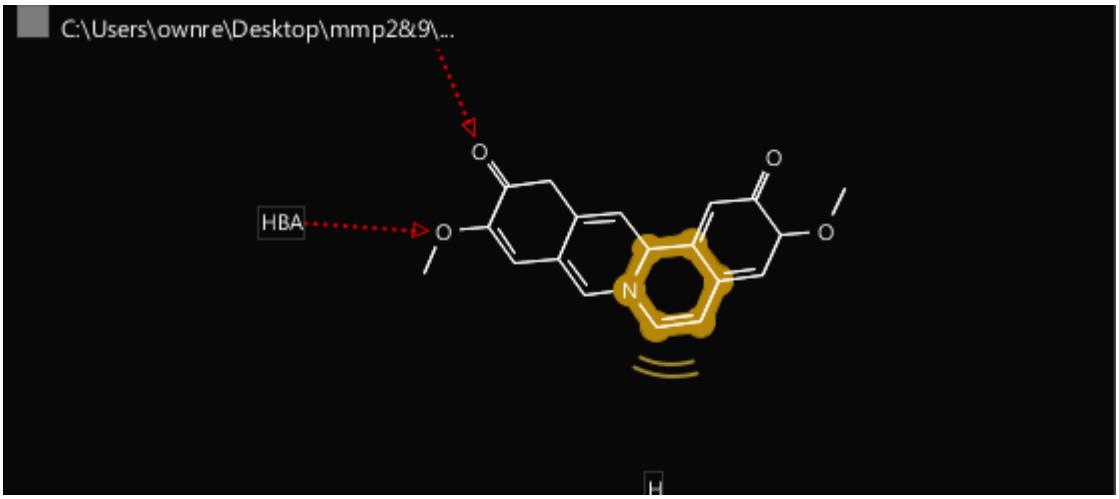


FIG31-B: RETICULINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(27): PRATENSEIN: Pratensin has pharmacophore fit score: 37,0300 and has three pharmacophore features: (a) hydrophobic feature(yellow) (b)2 hydrogen bond acceptor(red).

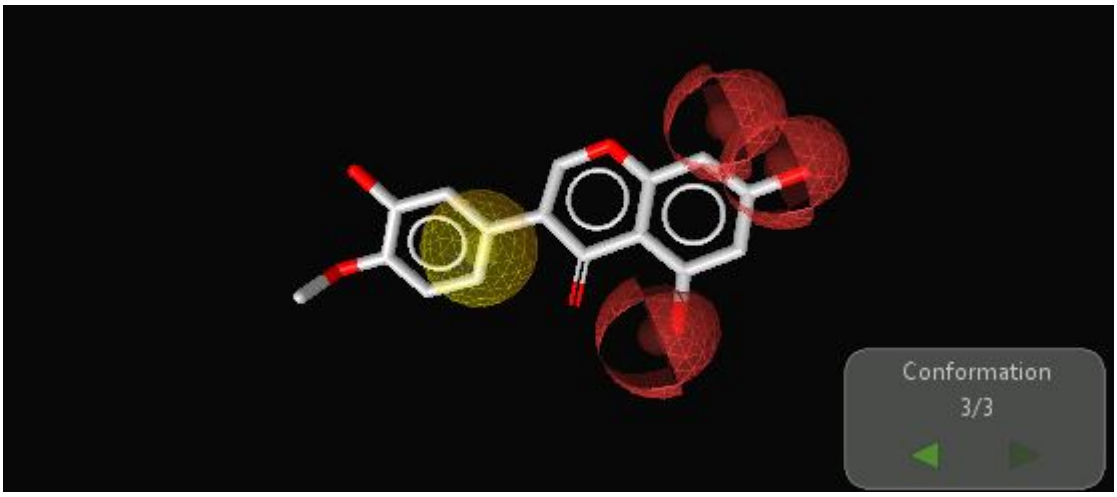


FIG-32A: PRATENSEIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

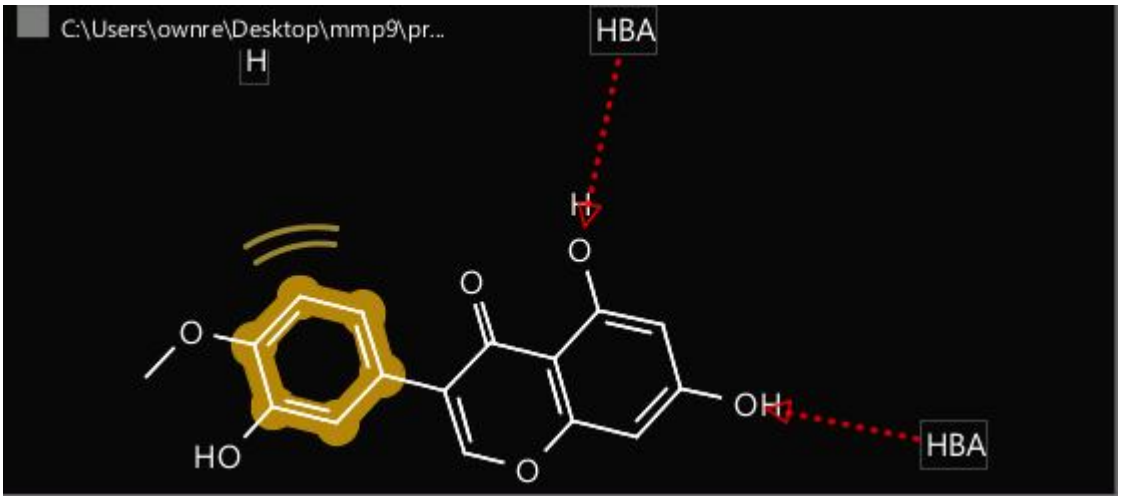


FIG-32B: PRATENSEIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(28) DECUSSATIN: has pharmacophore fit score: 36,3800 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

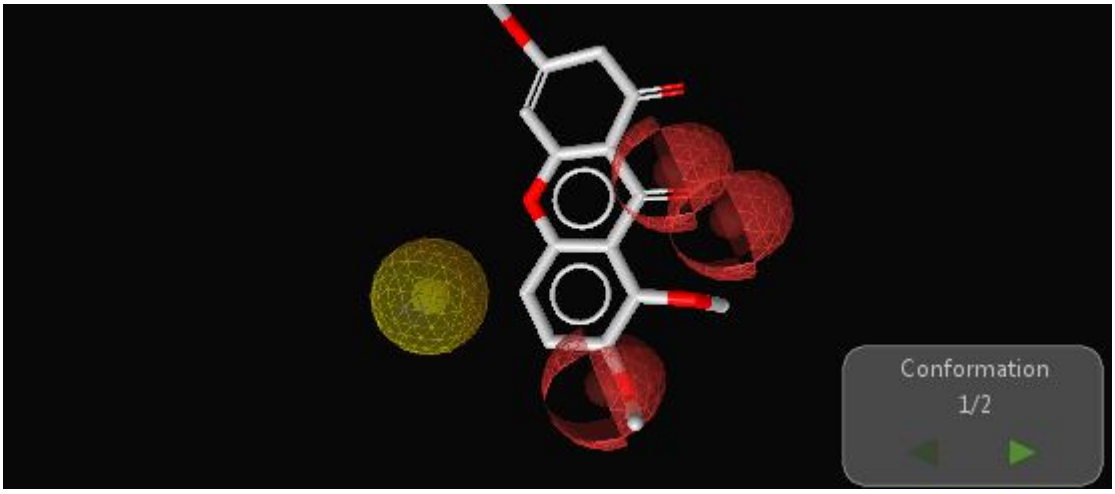


FIG-33A: DECUSSATIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

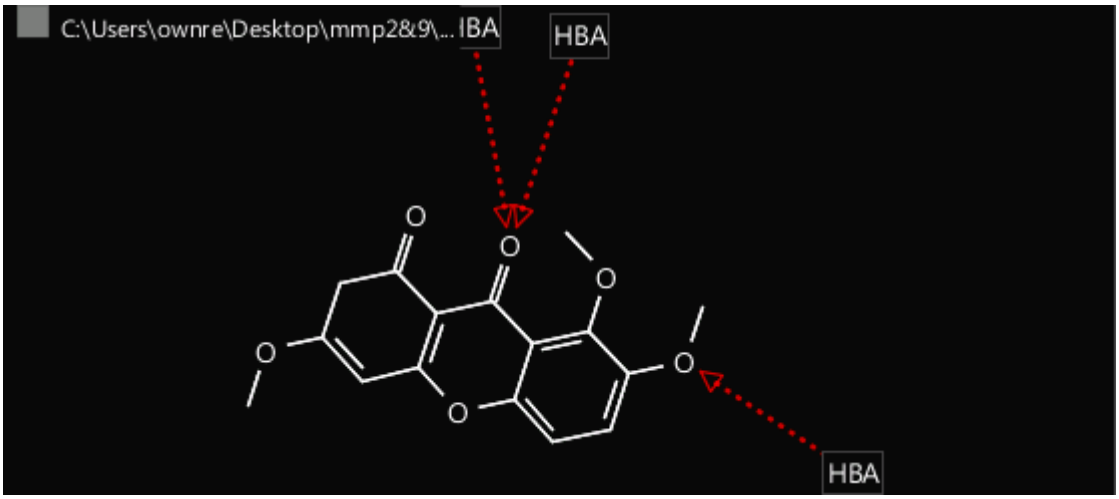


FIG-33B: DECUSSATIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(29) PICEATANNOL: Piceatannol has pharmacophore fit score: 36,3100 and has three pharmacophore features: (a) hydrophobic feature(yellow) (b)2 hydrogen bond acceptor(red).

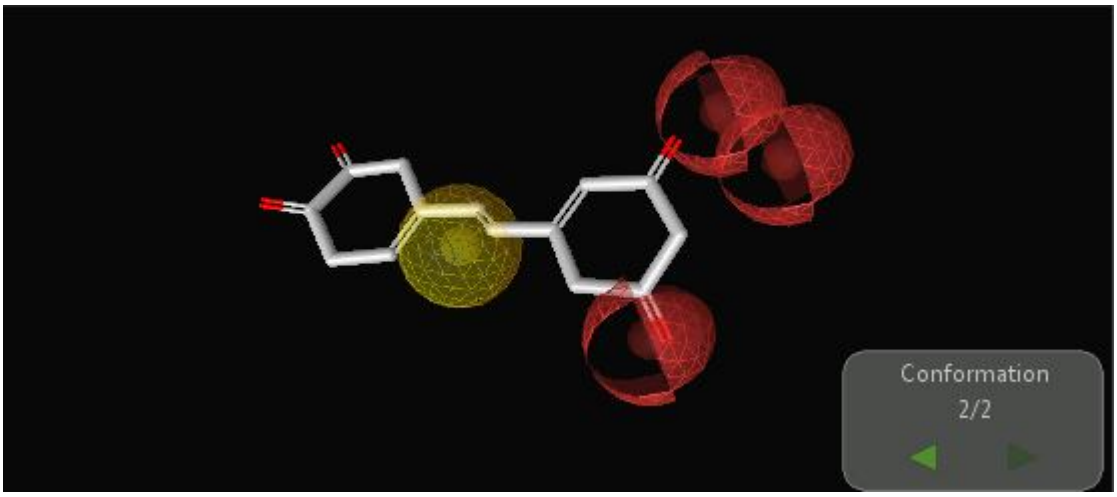


FIG-34A: PICEATANNOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

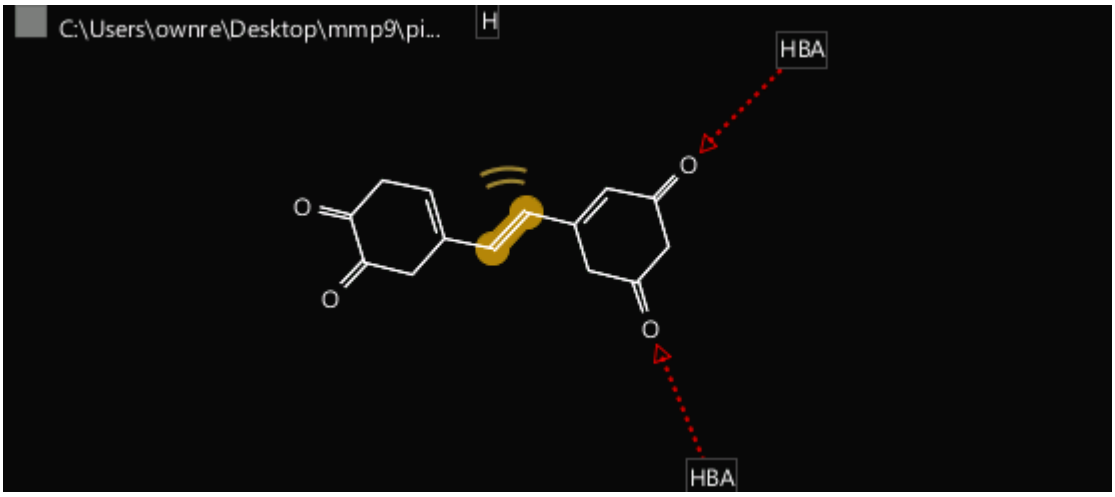


FIG-34B: PICEATANNOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(30) RESVERATROL: Resveratrol has pharmacophore fit score: 36,2800 and has three pharmacophore features: (a) hydrophobic feature(yellow) (b)2 hydrogen bond acceptor(red).

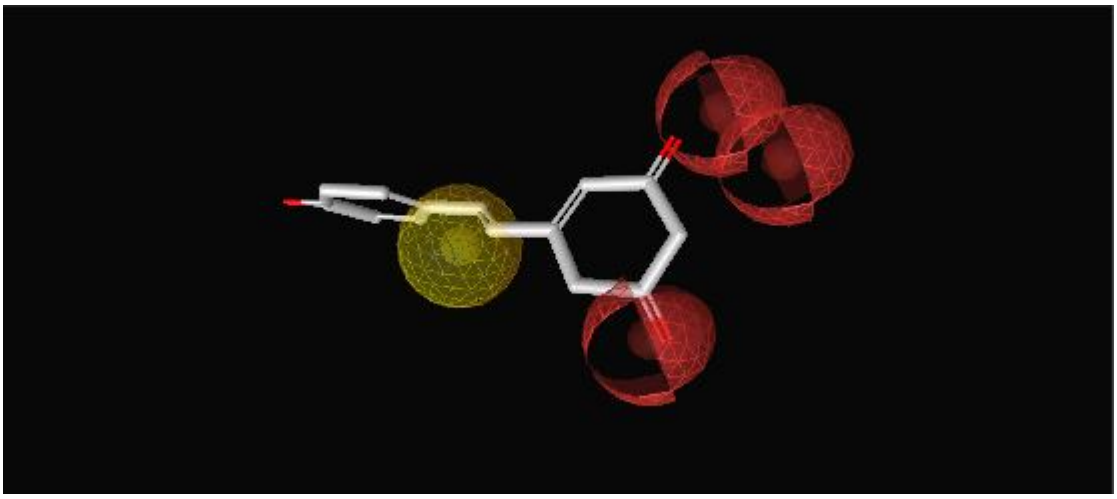


FIG35-A: RESVERATROL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

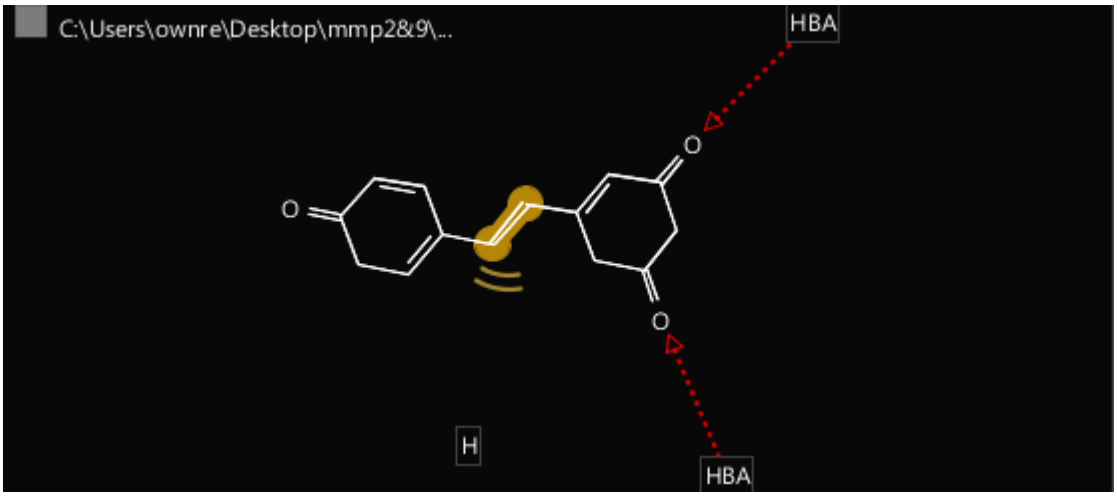


FIG-35B: RESVERATROL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(31)LIQUIRITIGENIN: Liquiritigenin has pharmacophore fit score: 36,2600 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

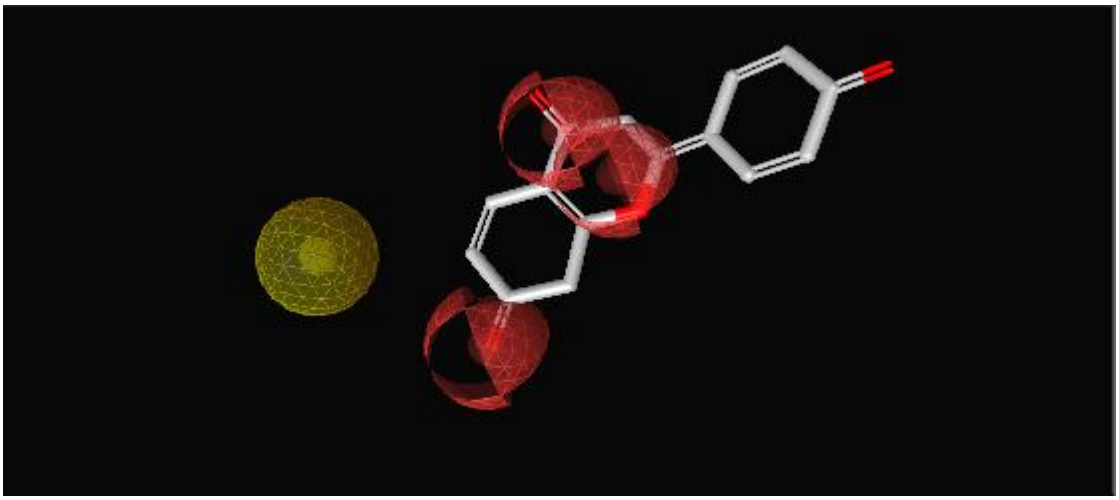


FIG-36A: LIQUIRITIGENIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

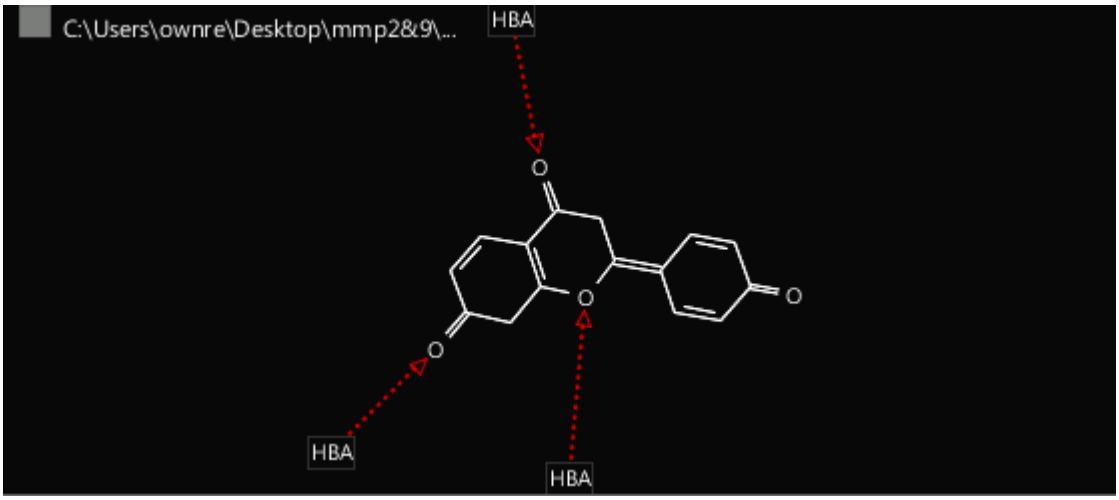


FIG-36B: LIQUIRITIGENIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(32)PHLORETIN: Phloretin has pharmacophore fit score: 36,2300 and has three pharmacophore features: (a) 3 hydrogen bond acceptor(red).

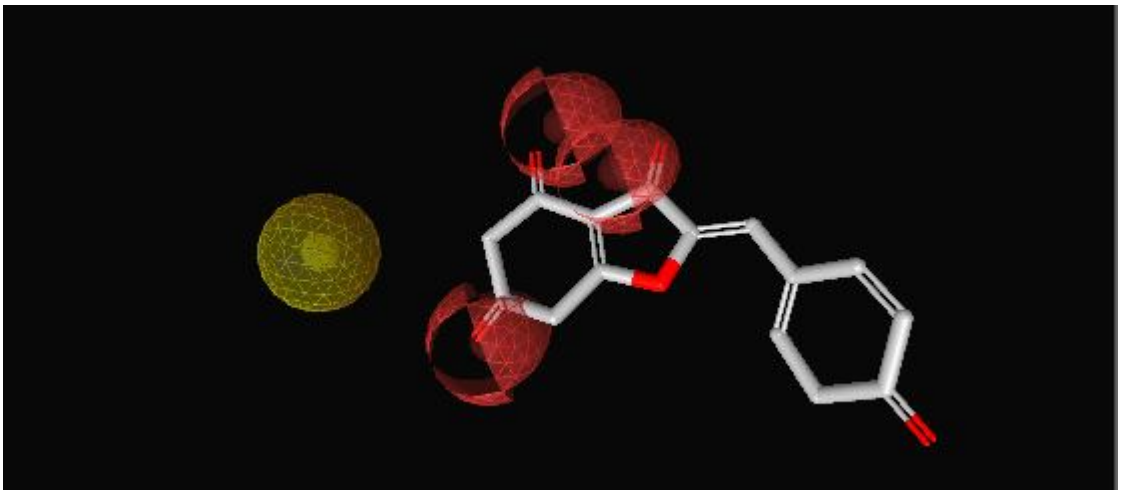


FIG-37A: PHLORETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

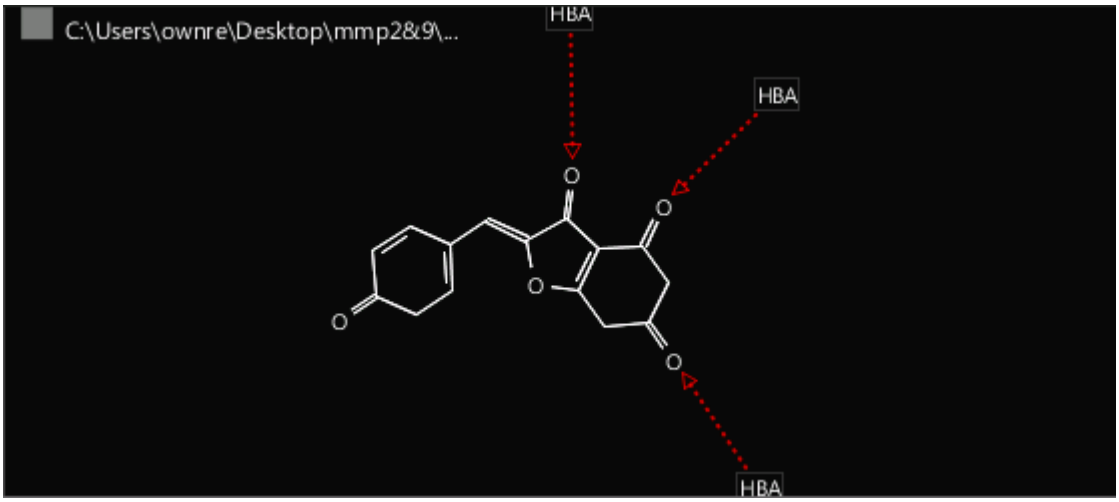


FIG-37B: PHLORETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(33) PIPERINE: Piperine has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands.

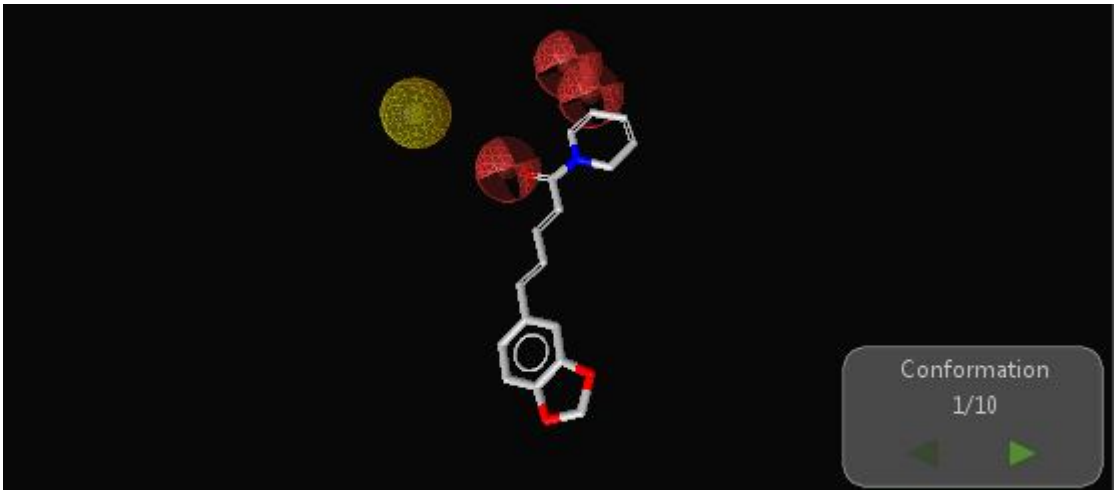


FIG-38A: PIPERINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

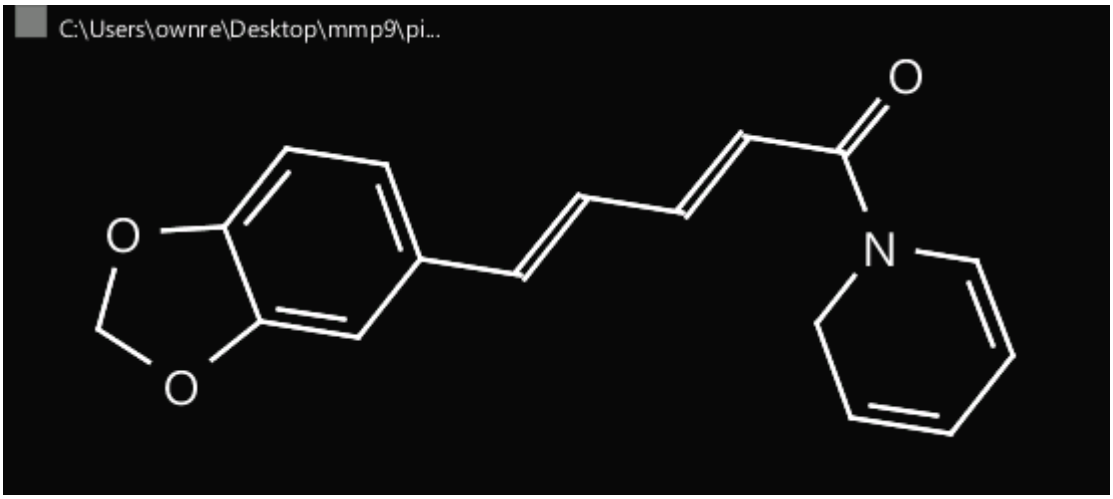


FIG-38B: PIPERINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(34) DAIDZEIN: Daidzein has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands

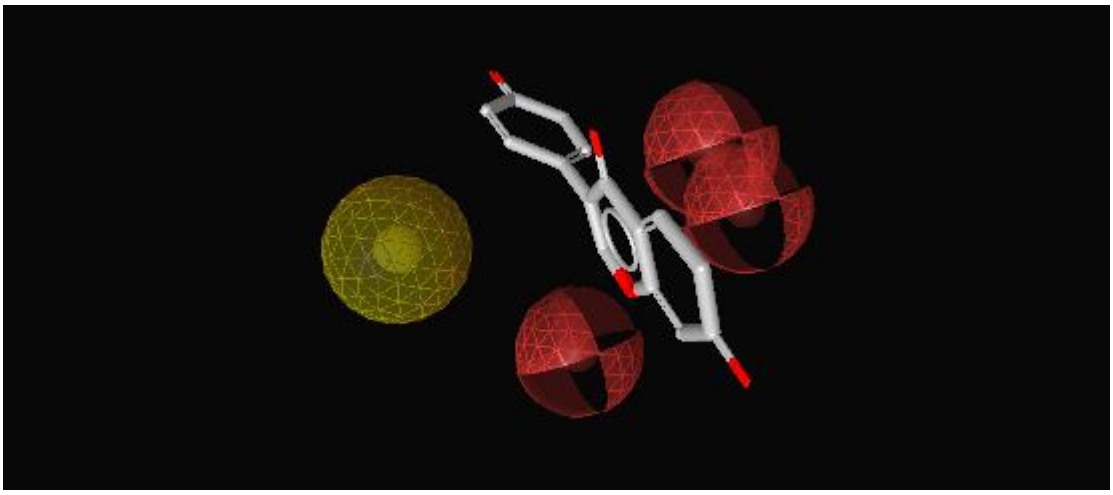


FIG-39A: DAIDZEIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

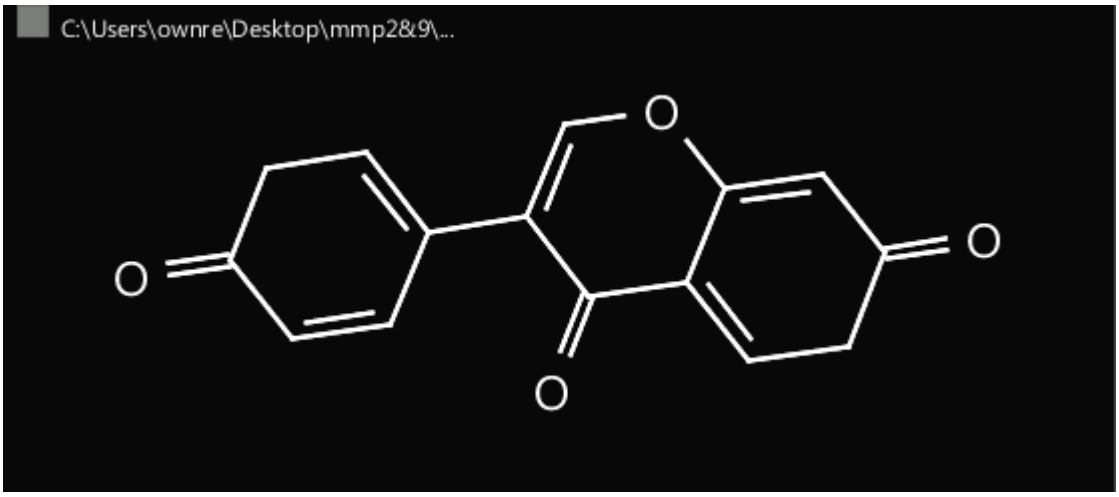


FIG-39B: DAIDZEIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(35) TOLPERISONE: Tolperisone has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands

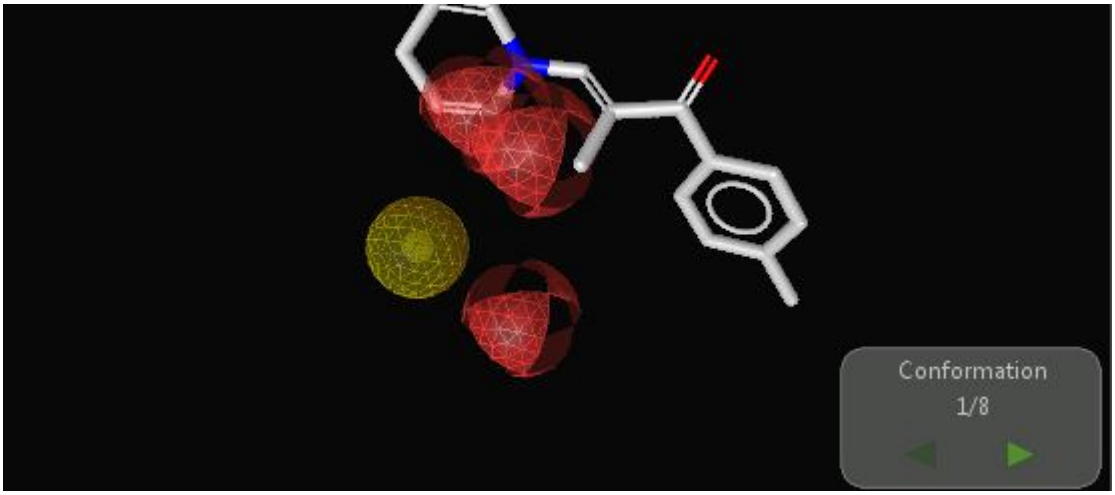


FIG-40A: TOLPERISONE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

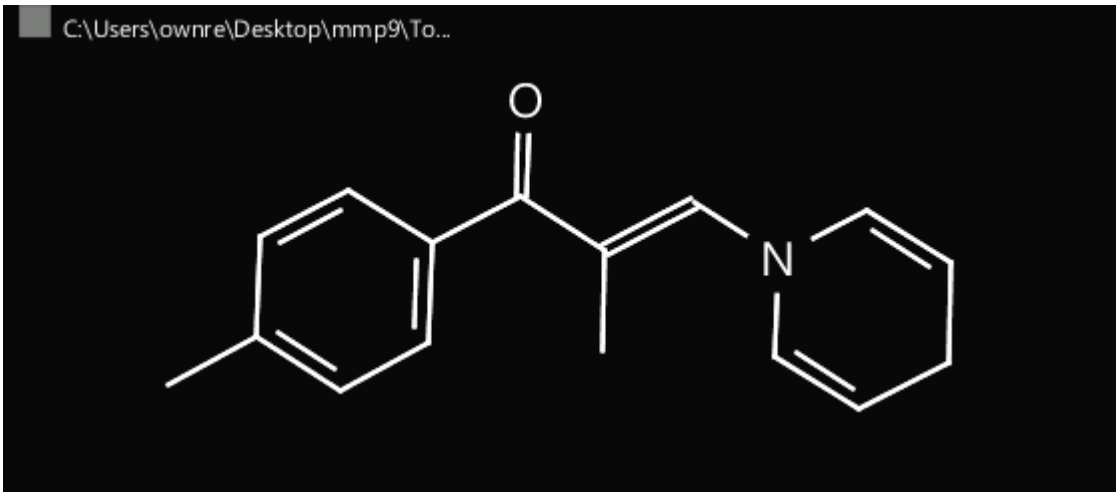


FIG-40B: TOLPERISONE:SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(36) SULFURIEN: Sulfurien has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands

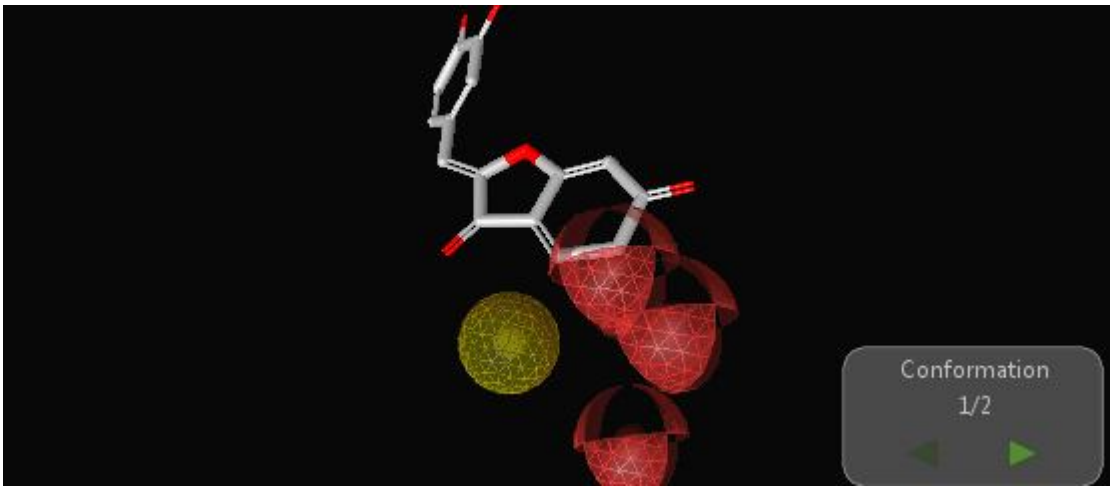


FIG-41A: SULFURIEN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

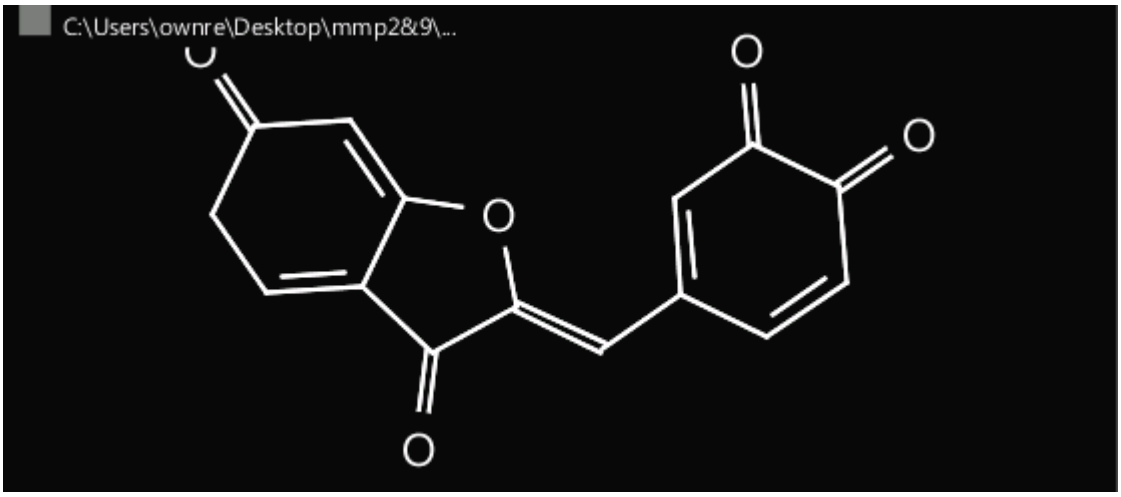


FIG-41B: SULFURIEN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(37) GUAIOL: Guaiol has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands

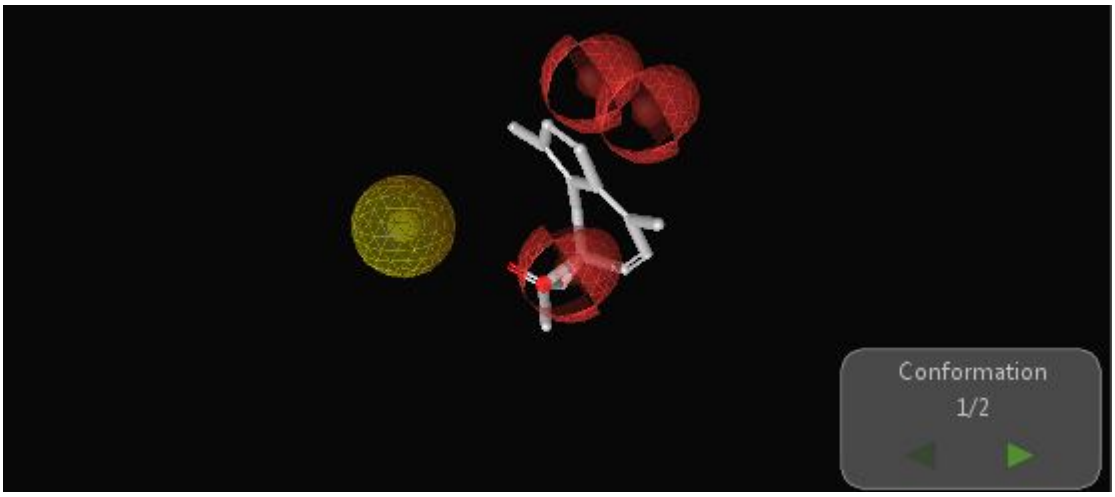


FIG-42A: GUAIOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

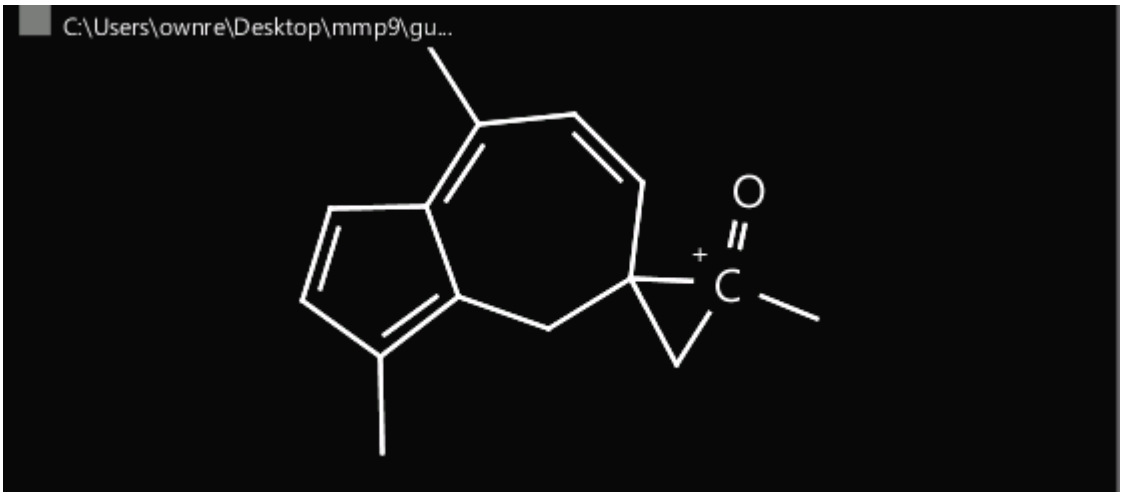


FIG-42B: GUAIOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(38)CUBEBIN: Cubebin has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands

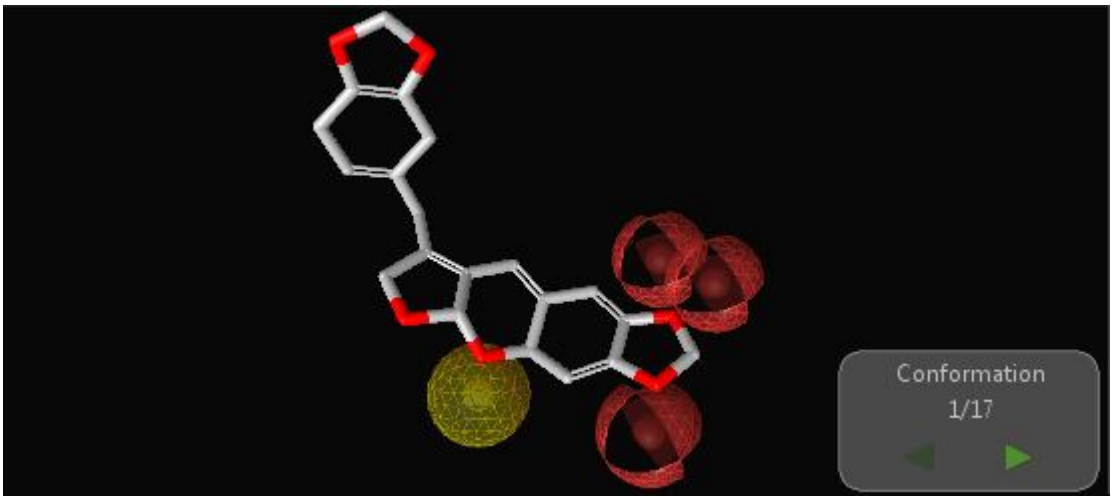


FIG-43A: CUBEBIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

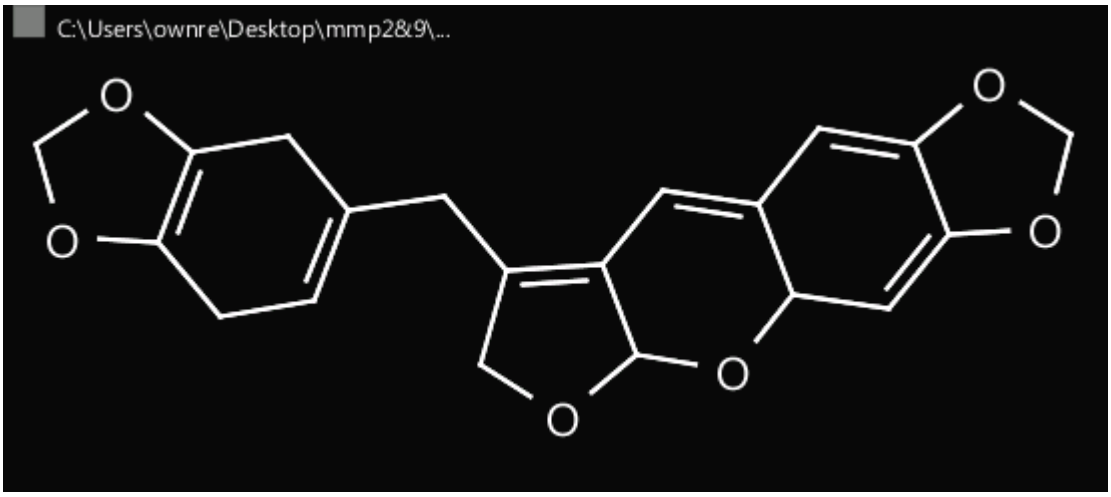


FIG-43B: CUBEBIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(39): (-)-CENTROLOBOL: (-)-Centrolobol has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligand.

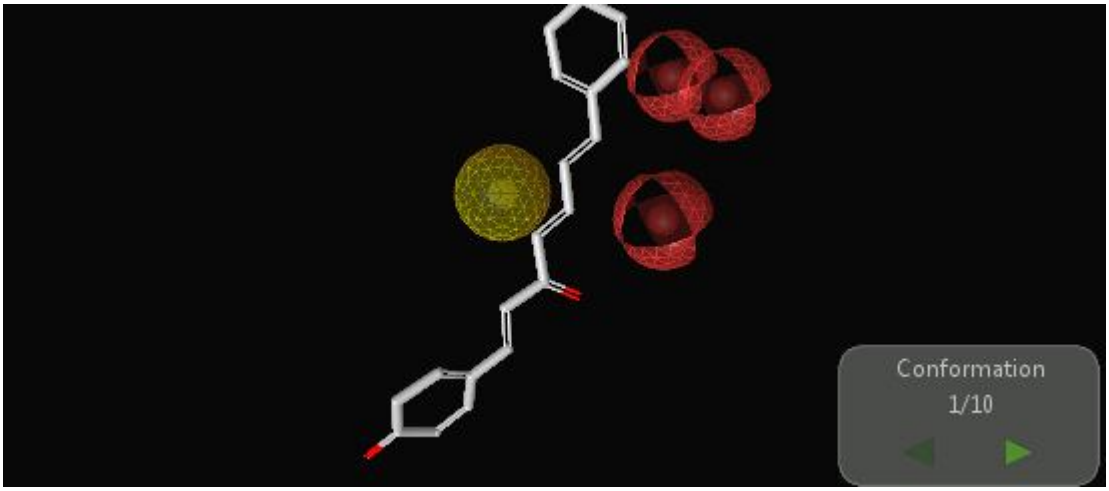


FIG-44A: (-)-CENTROLOBOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

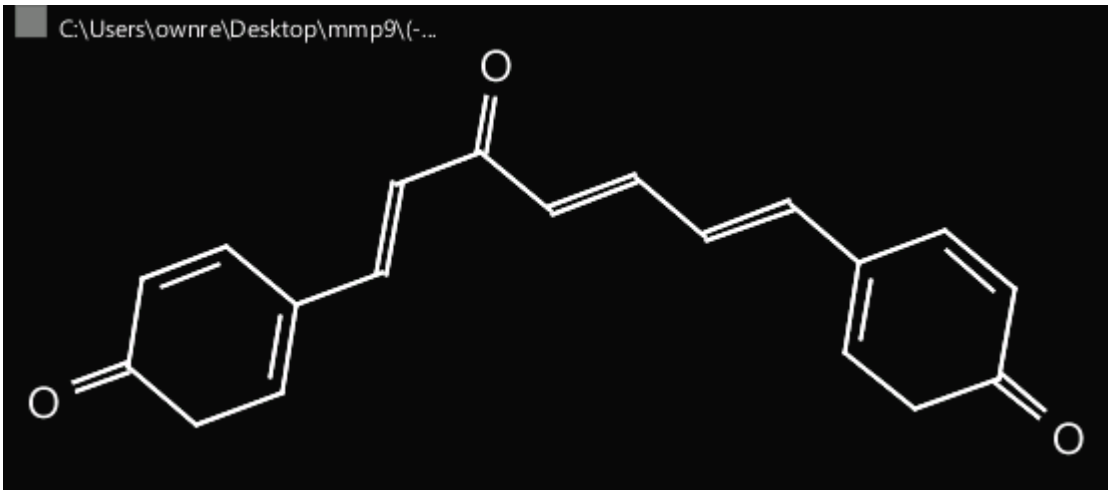


FIG-44B: (-)-CENTROLOBOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(40) BISABOLOL: Bisabolol has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands

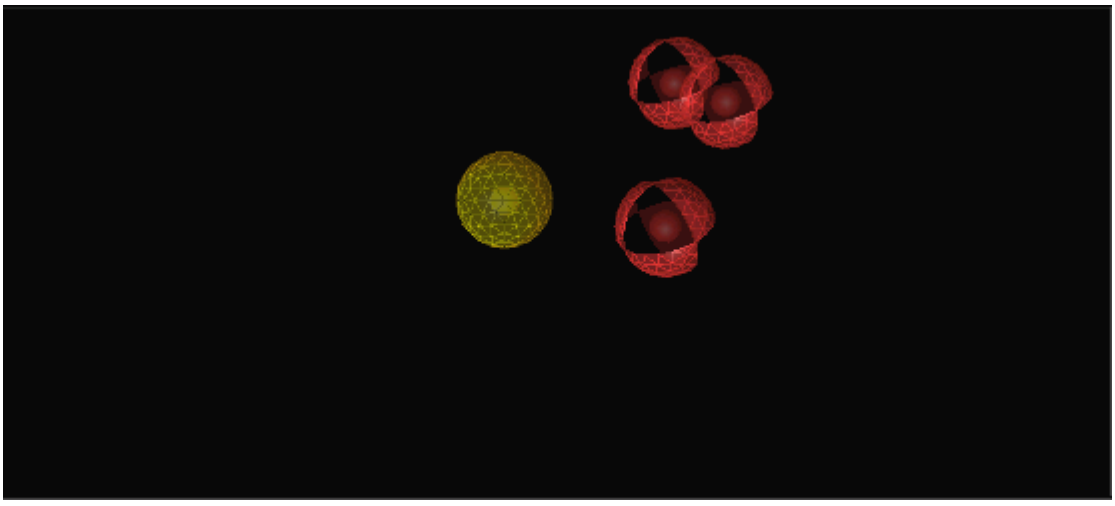


FIG-45A: BISABOLOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

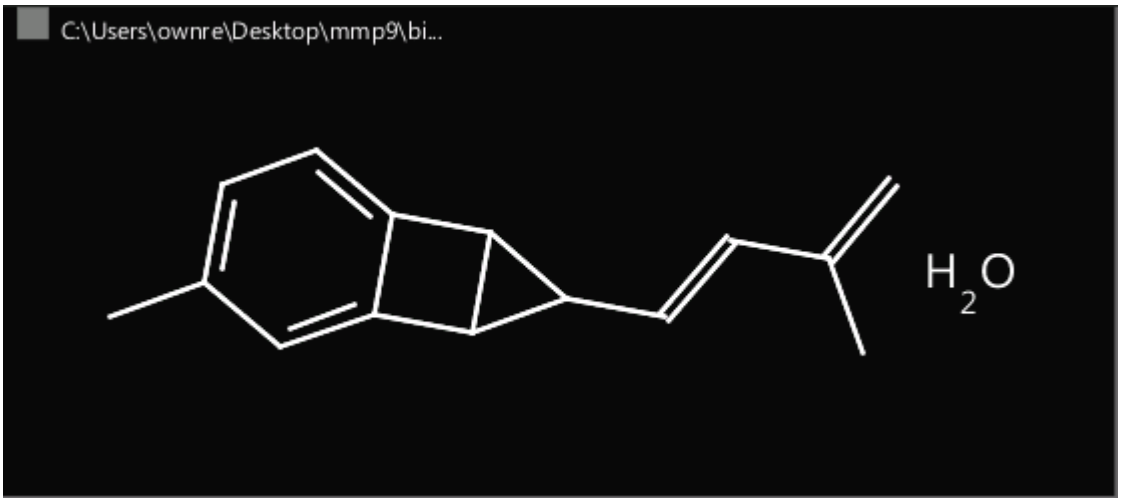


FIG45-B: BISABOLOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

MMP2: PHARMACOPHORE MODEL

All the ligands showing stable binding energy and good drug like properties were selected to build a pharmacophore model which fits best to the target MMP2. Four pharmacophore feature pattern were obtained for MMP2: (a) 2 hydrogen bond donor(green in table-23) (b) 2 hydrogen bond acceptor(red in table-23)

TABLE-23: PHARMACOPHORE FEATURE PATTERN FOR MMP2

	Active		Name	Type	Feature Pattern
1	▪		C:\Users\ownre\Desktop\mmp2\Ajmalicine.pdb	Training	
2	▪		C:\Users\ownre\Desktop\mmp2&9\Uso-Silybin A...	Training	
3	▪		C:\Users\ownre\Desktop\mmp2\Lscholaricinne.pdb	Training	
4	▪		C:\Users\ownre\Desktop\mmp2&9\anonin.pdb	Test	
5	▪		C:\Users\ownre\Desktop\mmp2\pseudo-Strychni...	Test	
6	▪		C:\Users\ownre\Desktop\mmp2&9\16R,19E-isosit...	Test	
7	▪		C:\Users\ownre\Desktop\mmp2&9\penicyclivine...	Test	

Red: hydrogen bond acceptor ; green: hydrogen bond donor

FIG-46: HYDROGEN BOND ACCEPTOR-1 FEATURE OF PHARMACOPHORE FOR MMP2: feature highlighted in bright yellow colour.

FIG-47: HYDROGEN BOND ACCEPTOR-2 FEATURE OF PHARMACOPHORE FOR MMP2: feature highlighted in bright yellow colour.

FIG-48: HYDROGEN BOND DONOR-1 FEATURE OF PHARMACOPHORE FOR MMP2: feature highlighted in bright yellow colour.

FIG-49: HYDROGEN BOND DONOR-2 FEATURE OF PHARMACOPHORE FOR MMP2: feature highlighted in bright yellow colour.

(1) AJMALICINE: Ajmalicine has highest pharmacophore fit score: 46,4500 and has pharmacophore features: (a)2 hydrogen bond donor(green) (b)2 hydrogen bond acceptor(red)

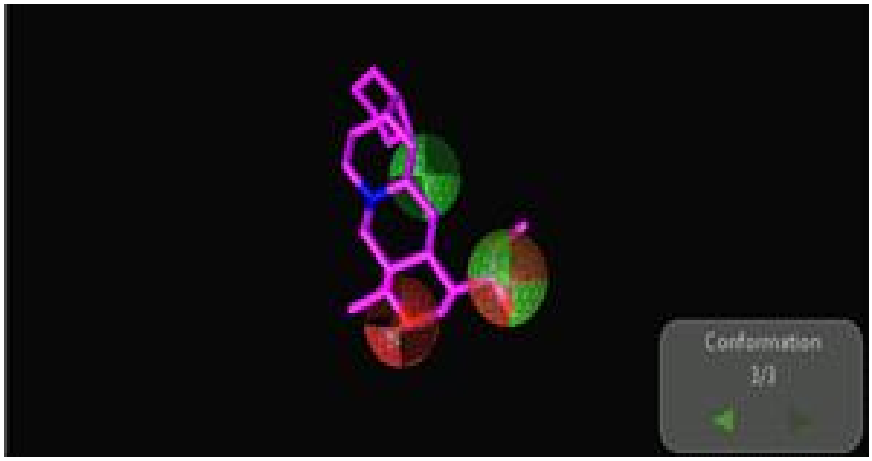


FIG-50A: AJMALICINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

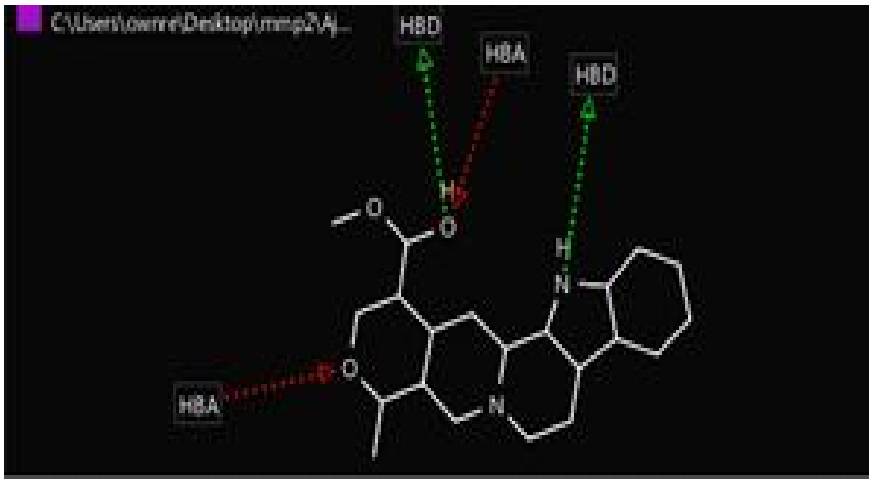


FIG-50B: AJMALICINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(2)ISO-SILYBIN-A: Iso-silybin has pharmacophore fit score: 46,4500 and has pharmacophore features: (a)2 hydrogen bond donor(green) (b)2 hydrogen bond acceptor(red)

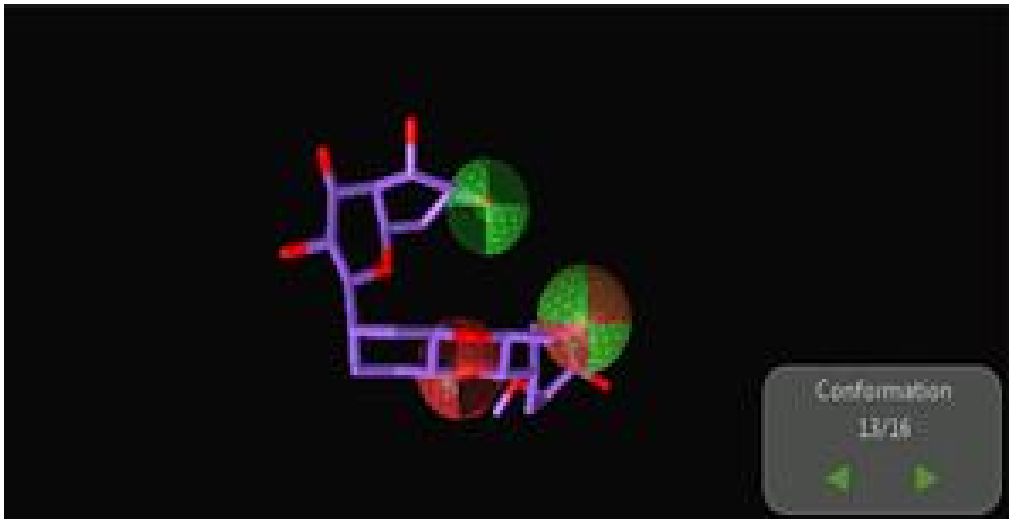


FIG-51A: ISO-SILYBIN-A: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

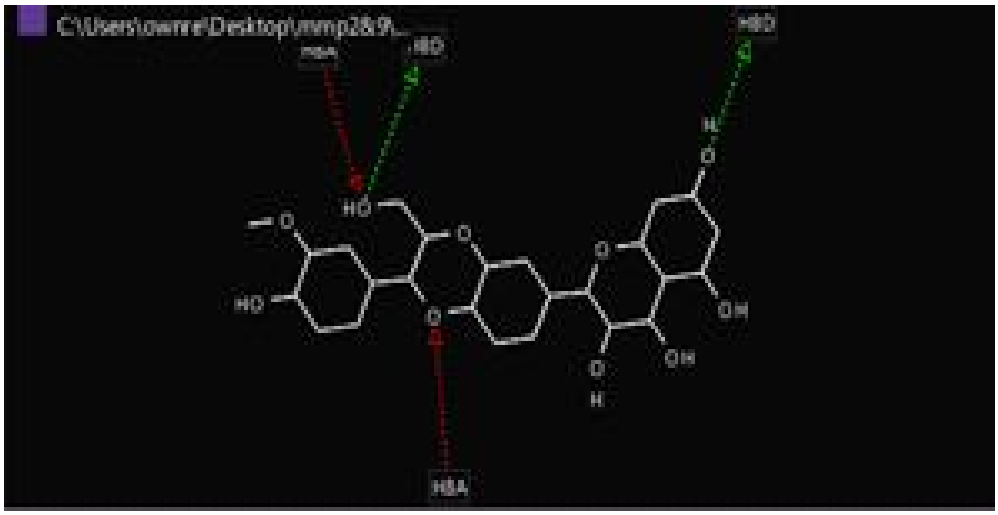


FIG-51B: ISO-SILYBIN-A: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(3)SCHOLARICINNE: Scholaricinne has pharmacophore fit score: 46,4600 and has pharmacophore features: **(a)2 hydrogen bond donor(green) (b)2 hydrogen bond acceptor(red)**

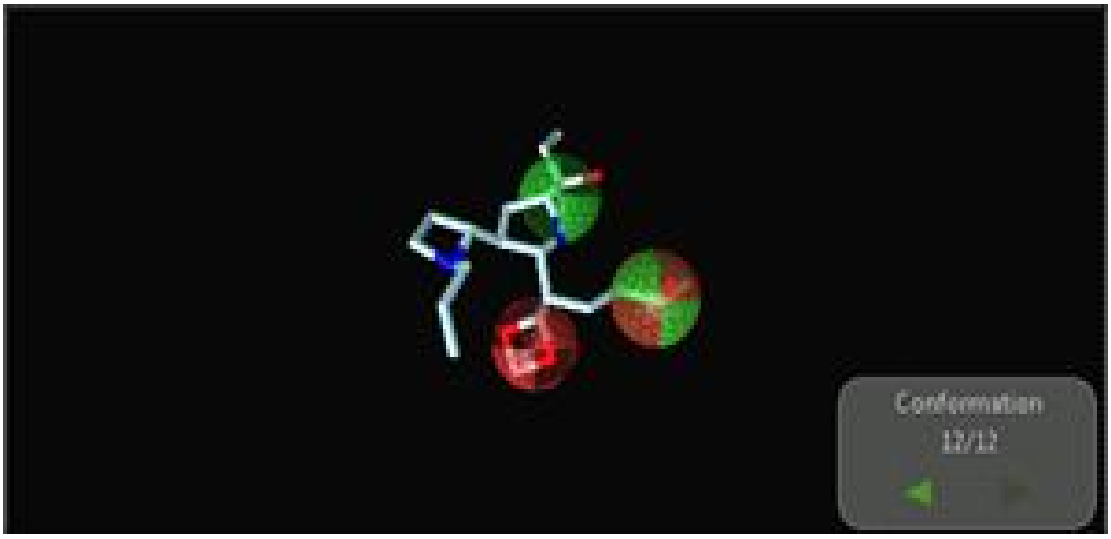


FIG-52A: SCHOLARICINNE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

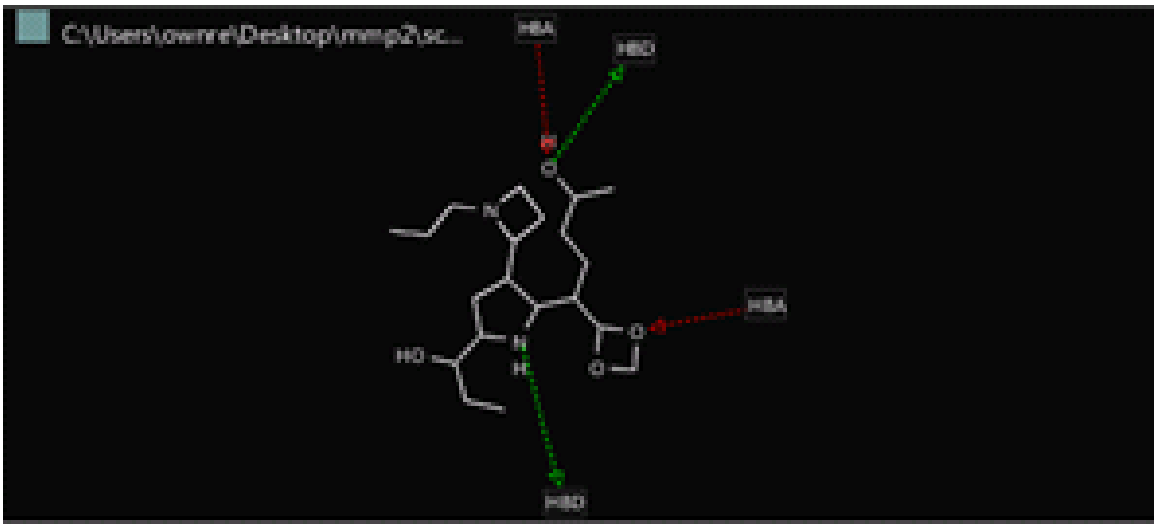


FIG-52B: SCHOLARICINNE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(4)ONONIN: Ononin has pharmacophore fit score: 46,4300 and has pharmacophore features: **(a)2 hydrogen bond donor(green) (b)2 hydrogen bond acceptor(red)**

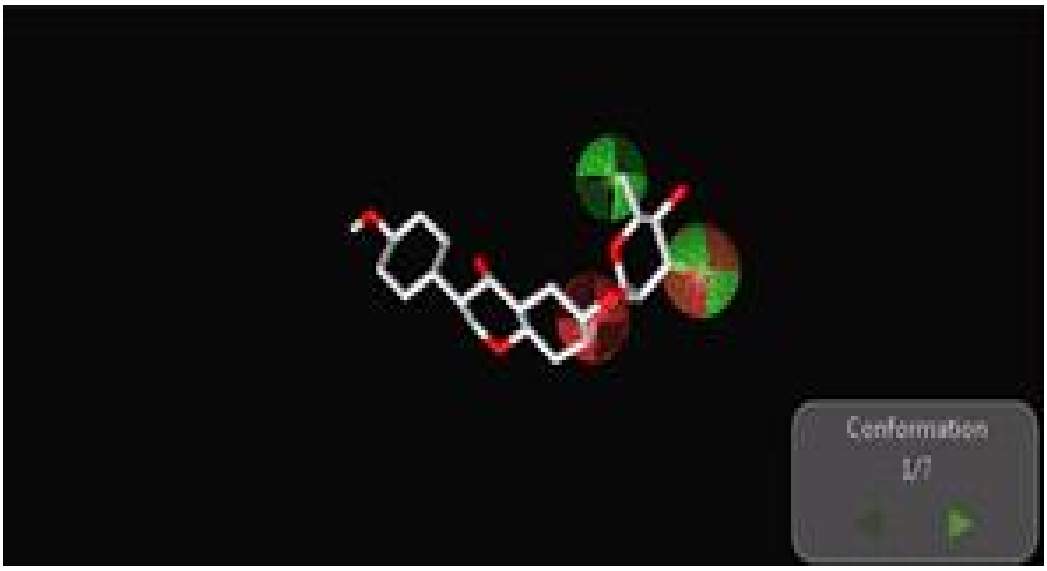


FIG-53A:ONONIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

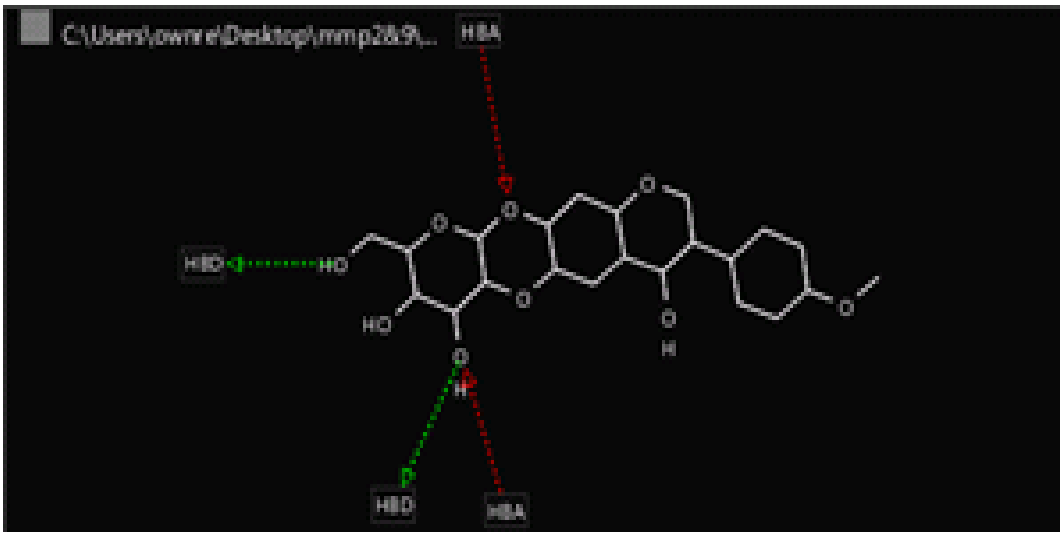


FIG-53B:ONONIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(5) PSEUDO STRYCHNINE: Pseudo-strychnine has pharmacophore fit score: 46,0400 and has pharmacophore features: **(a)2 hydrogen bond donor(green) (b)2 hydrogen bond acceptor(red)**

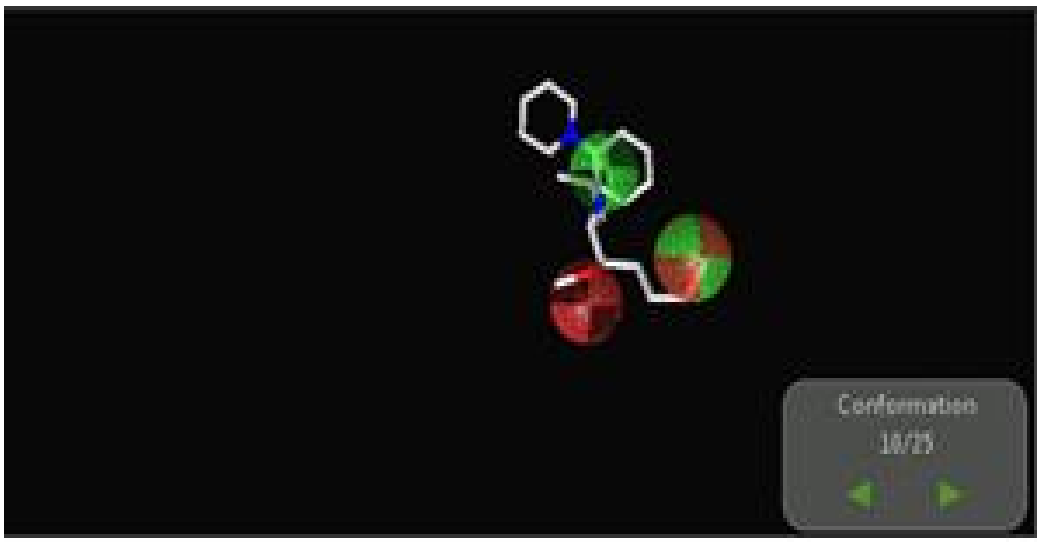


FIG-54A: PSEUDO STRYCHNINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

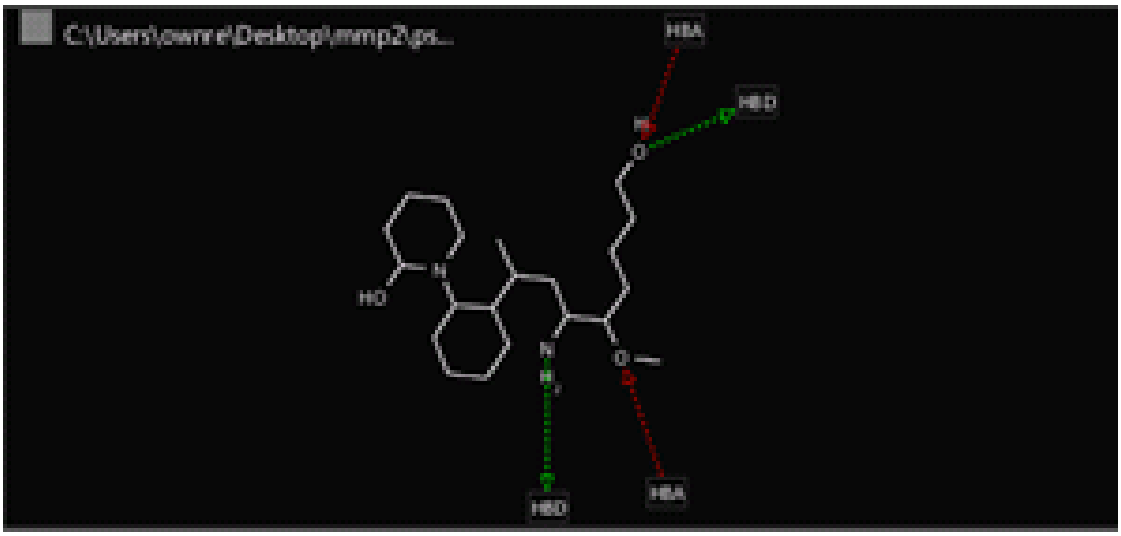


FIG-54B: PSEUDO STRYCHNINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(6)16R,19E-ISOSITSIRIKINE: 16R,19E-isositsirikine has pharmacophore fit score: 0.0 and has no pharmacophore features.It has no shared feature of pharmacophore compared to the other ligands for this pharmacophore model.

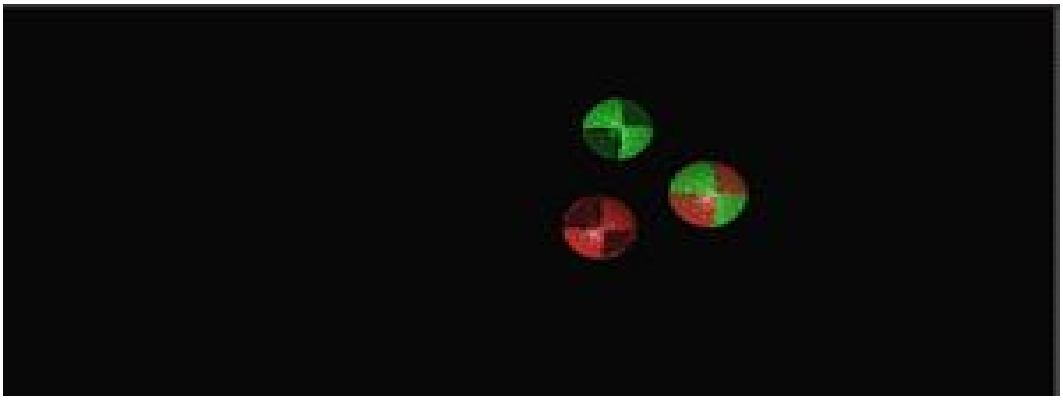


FIG-55A: 16R,19E-ISOSITSIRIKIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

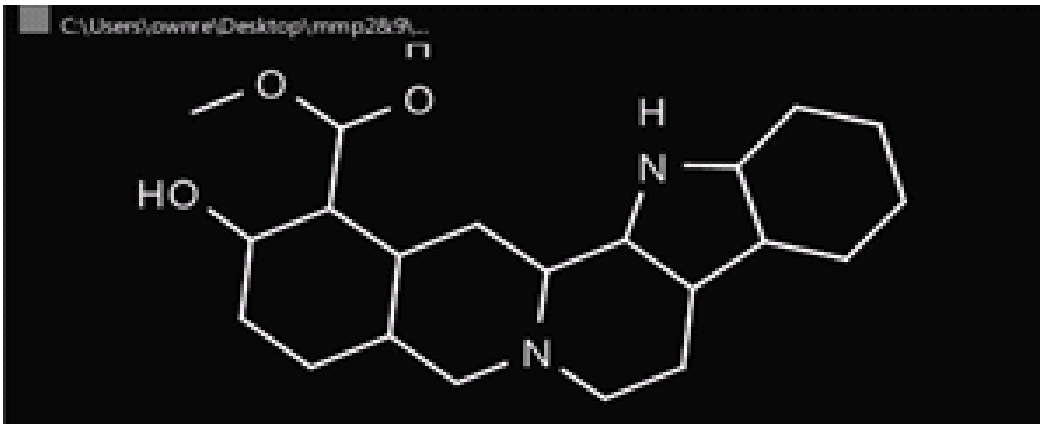


FIG-55B: 16R,19E-ISOSITSIRIKIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(7)PERICYCLIVINE: Pericyclivine has pharmacophore fit score: 0.0 and has no pharmacophore features.It has no shared feature of pharmacophore compared to the other ligands for this pharmacophore model.

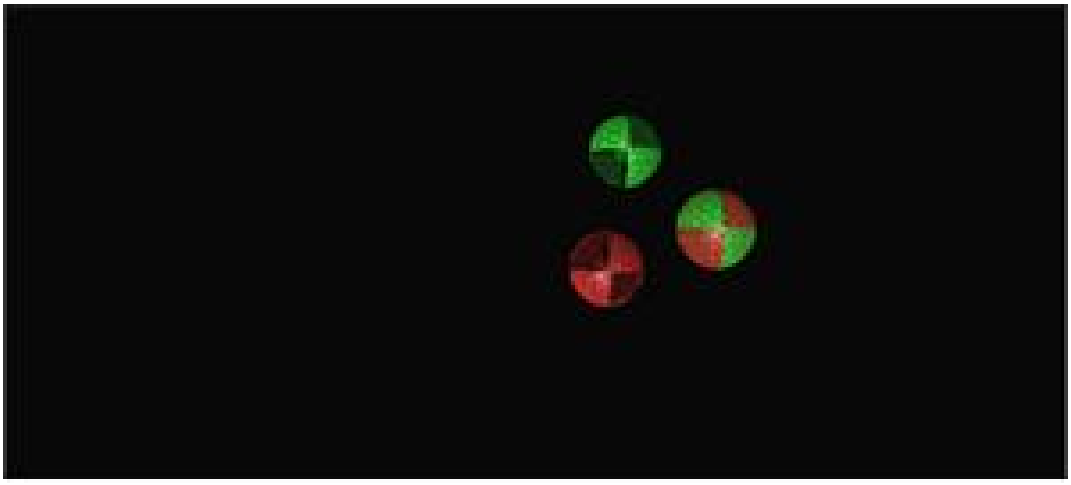


FIG-56A: PERICYCLIVINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

FIG-56B: PERICYCLIVINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

MMP2 AND MMP9: PHARMACOPHORE MODEL

All the ligands showing stable binding and good drug like properties were selected to build a pharmacophore model which fits best to the targets MMP9 and MMP2. Four pharmacophore feature pattern were obtained for MMP2 and MMP9: (a) 1 hydrogen bond donor(green in table-24) (b) 3 hydrogen bond acceptor(red in table-24)

TABLE-24: PHARMACOPHORE FEATURE PATTERN FOR MMP2 AND MMP9

	Active		Name	Type	Feature Pattern
1	✓		C:\Users\ownre\Desktop\mmp2&9\uniconazole....	Test	
2	✓		C:\Users\ownre\Desktop\mmp2&9\Febrifugine.p...	Test	
3	✓		C:\Users\ownre\Desktop\mmp2&9\paclobutraaz...	Test	
4	✓		C:\Users\ownre\Desktop\mmp2&9\naphthopyro...	Test	
5	✓		C:\Users\ownre\Desktop\mmp2&9\picralinal.pdb	Test	
6	✓		C:\Users\ownre\Desktop\mmp2&9\biochanin A....	Test	
7	✓		C:\Users\ownre\Desktop\mmp2&9\iso-Formono...	Test	
8	✓		C:\Users\ownre\Desktop\mmp2&9\aloe emodin....	Training	
9	✓		C:\Users\ownre\Desktop\mmp2&9\diosmetin.pdb	Training	
10	✓		C:\Users\ownre\Desktop\mmp2&9\ellagic cid.pdb	Test	
11	✓		C:\Users\ownre\Desktop\mmp2&9\irilin D.pdb	Test	
12	✓		C:\Users\ownre\Desktop\mmp2&9\marmesin.pdb	Test	
	Active		Name	Type	Feature Pattern
13	✓		C:\Users\ownre\Desktop\mmp2&9\calycosin.pdb	Test	
14	✓		C:\Users\ownre\Desktop\mmp2&9\rhein.pdb	Training	
15	✓		C:\Users\ownre\Desktop\mmp2&9\Rhamnetin.p...	Test	
16	✓		C:\Users\ownre\Desktop\mmp2&9\epi-Taxifolin....	Test	
17	✓		C:\Users\ownre\Desktop\mmp2&9\(+)-aromade...	Test	
18	✓		C:\Users\ownre\Desktop\mmp2&9\galangin.pdb	Test	
19	✓		C:\Users\ownre\Desktop\mmp2&9\fisetin.pdb	Test	
20	✓		C:\Users\ownre\Desktop\mmp2&9\chrysin.pdb	Test	
21	✓		C:\Users\ownre\Desktop\mmp2&9\naringenin.pdb	Test	
22	✓		C:\Users\ownre\Desktop\mmp2&9\pinocembrin....	Test	
23	✓		C:\Users\ownre\Desktop\mmp2&9\epi-Afzelechi...	Test	
24	✓		C:\Users\ownre\Desktop\mmp2&9\(+)-Nootkato...	Ignored	

Red: hydrogen bond acceptor ; green: hydrogen bond donor

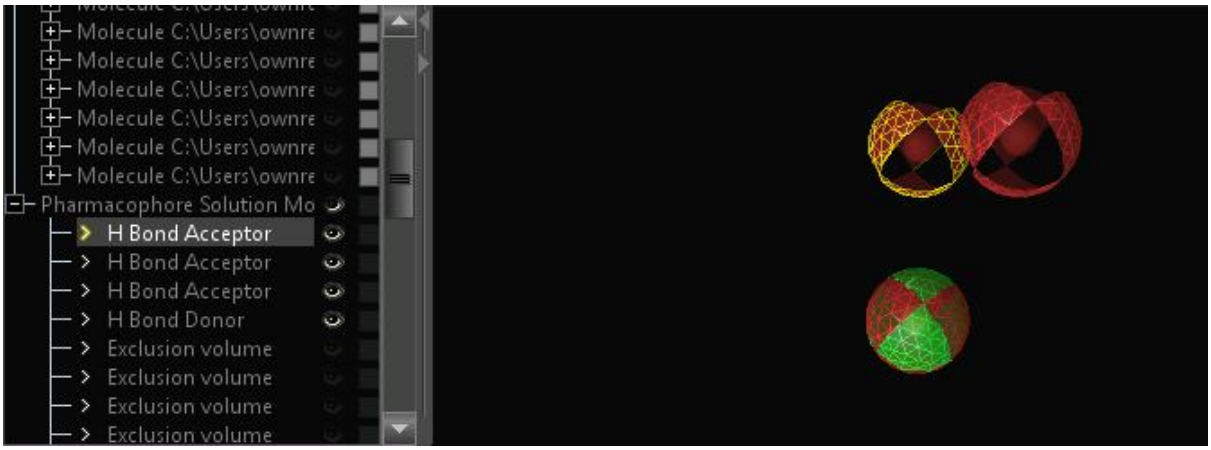


FIG-57: HYDROGEN BOND ACCEPTOR1 FEATURE OF PHARMACOPHORE FOR MMP2 AND MMP9 : feature highlighted in bright yellow colour.

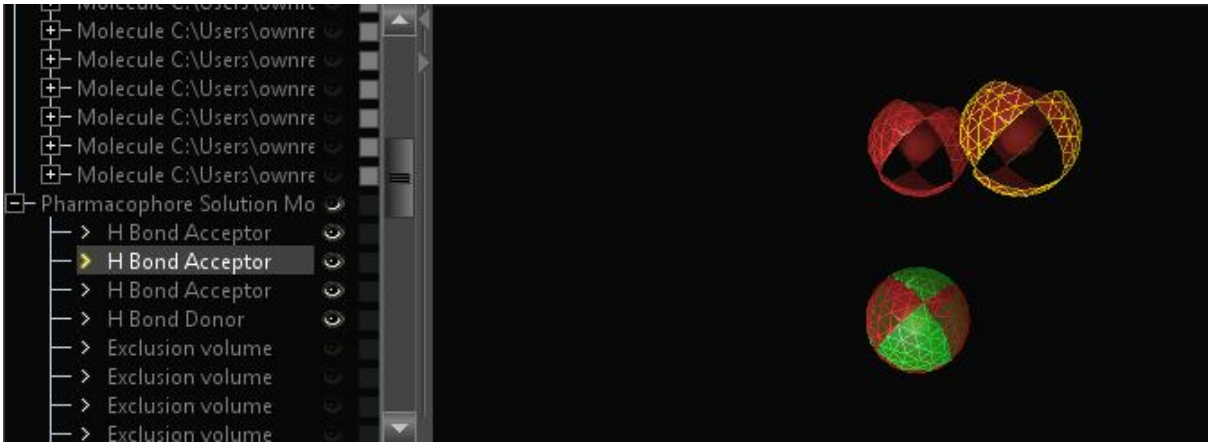


FIG-58: HYDROGEN BOND ACCEPTOR2 FEATURE OF PHARMACOPHORE FOR MMP2 AND MMP9 : feature highlighted in bright yellow colour

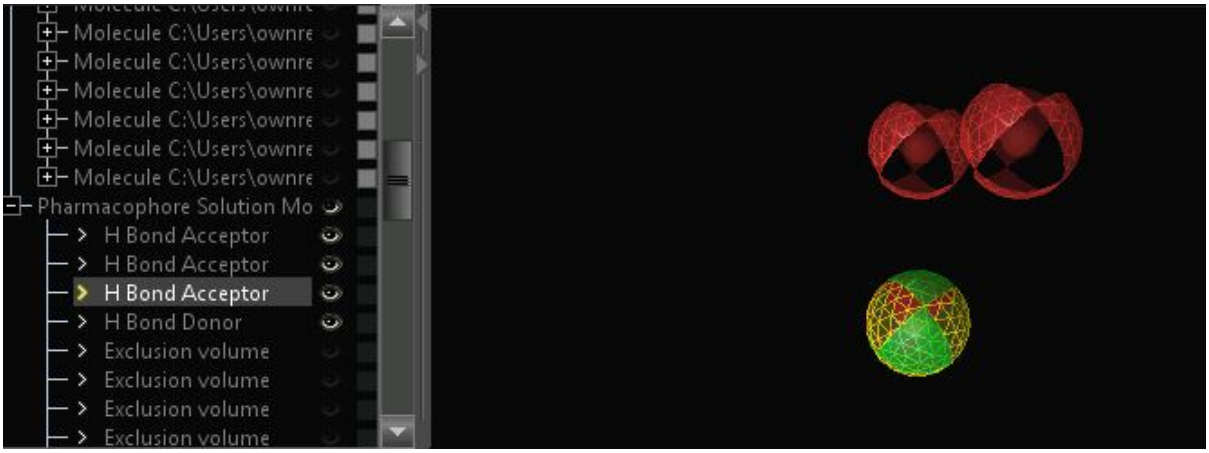


FIG-59: HYDROGEN BOND ACCEPTOR3 FEATURE OF PHARMACOPHORE FOR MMP2 AND MMP9: feature highlighted in bright yellow colour

FIG-60: HYDROGEN BOND DONOR FEATURE OF PHARMACOPHORE FOR MMP2 AND MMP9: feature highlighted in bright yellow colour

(1)PINOCEMBRIN: Pinocembrin has pharmacophore fit score: 48,5600 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

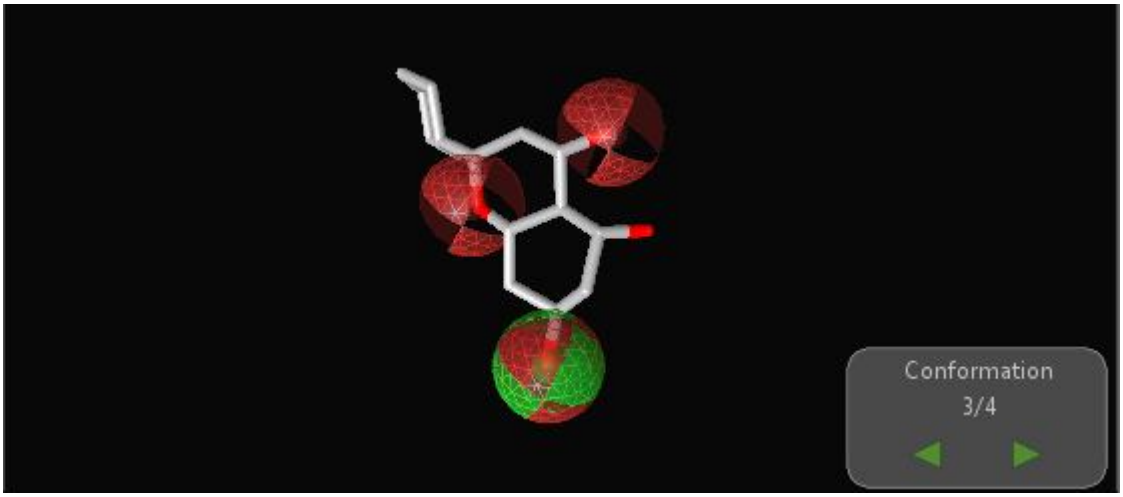


FIG61A: PINOCEMBRIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

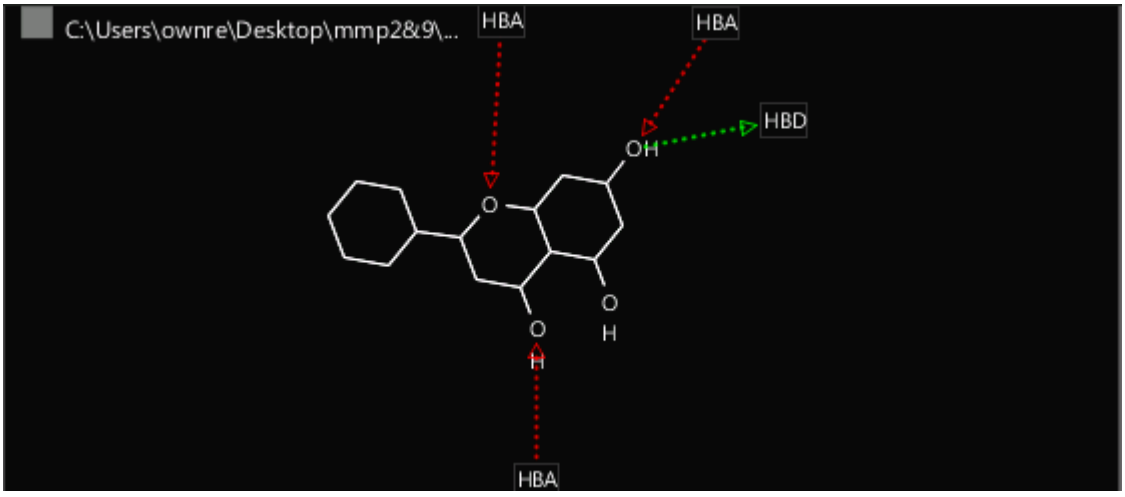


FIG-61B: PINOCEMBRIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(2) NARINGENIN: Naringenin has pharmacophore fit score: 48,5600 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

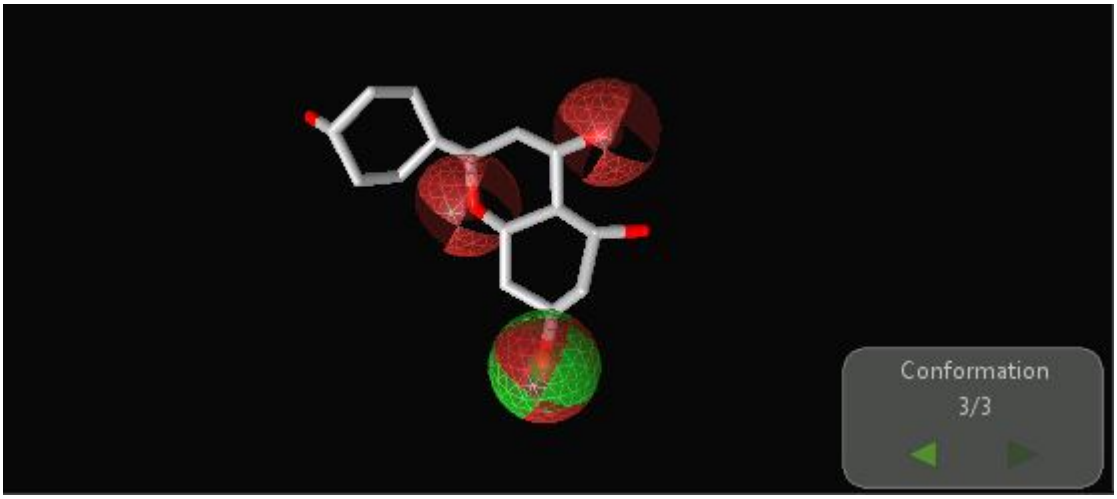


FIG-62A: NARINGENIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

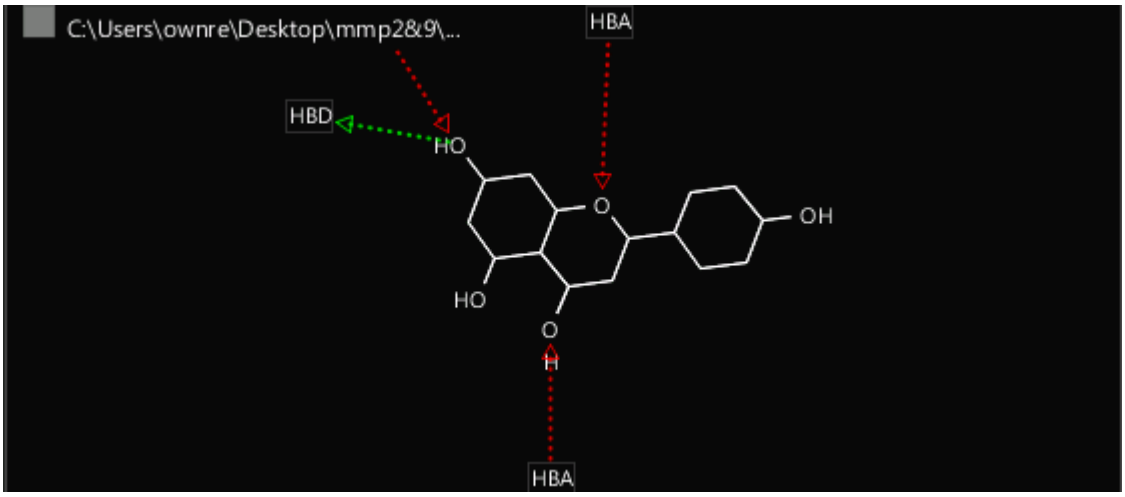


FIG-62B: NARINGENIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(3)CHRYSIN: Chrysin has pharmacophore fit score: 48,5600 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

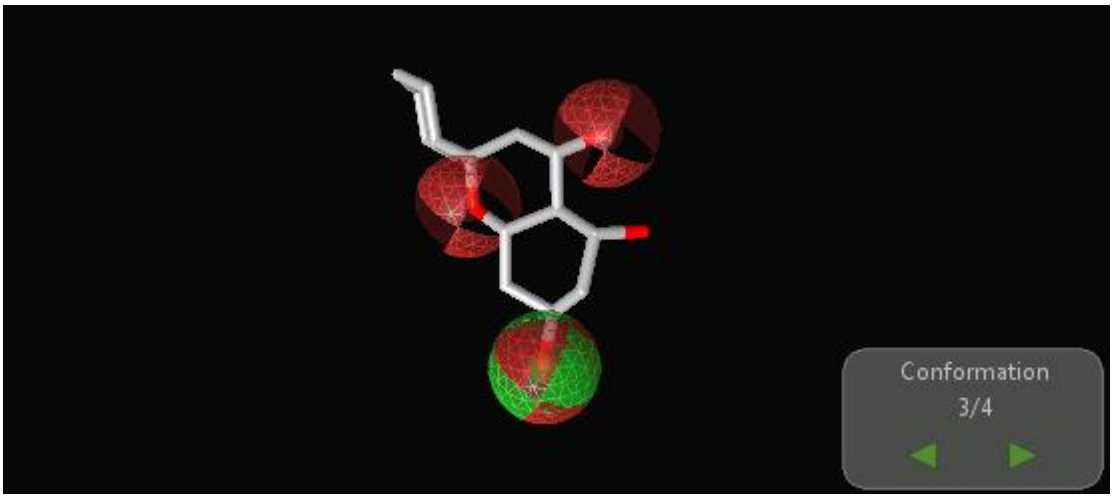


FIG-63A: CHRYSIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

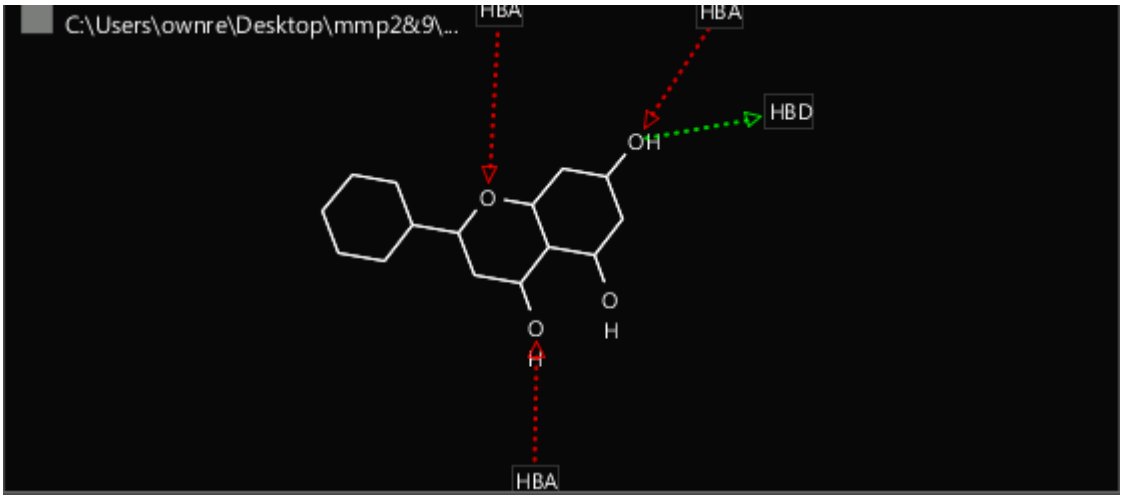


FIG-63B:CHRYSIN:SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(4)FISETIN: Fisetin has pharmacophore fit score: 48,5600 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

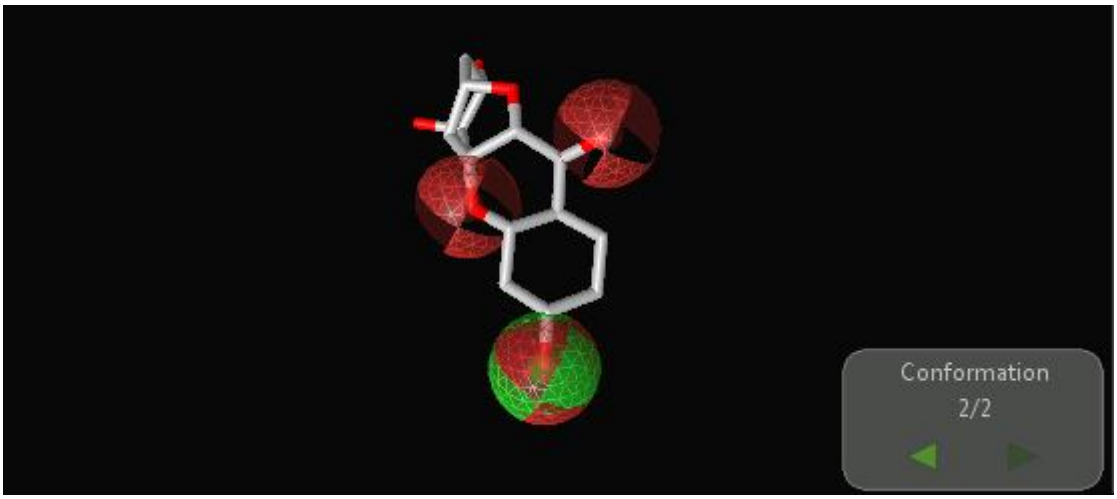


FIG-64A: FISETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

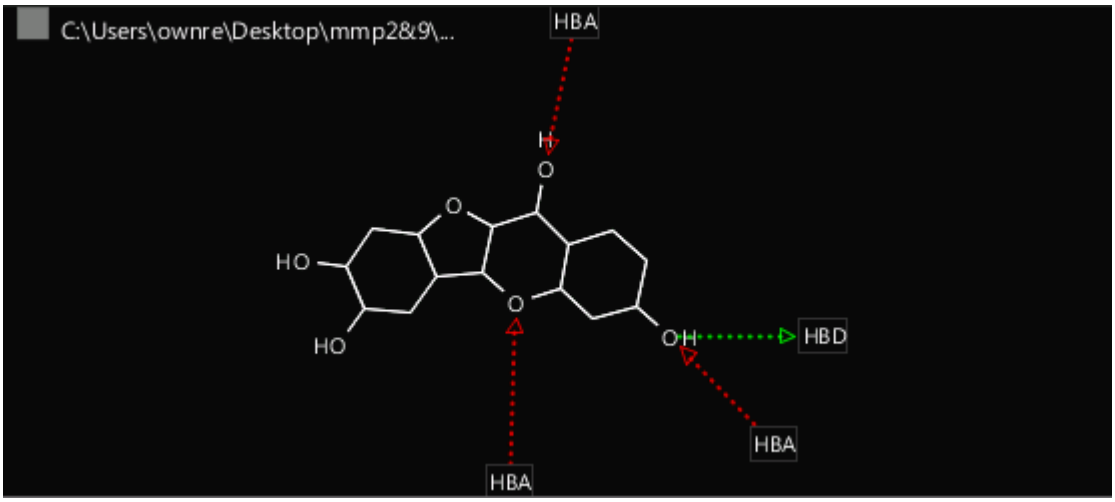


FIG-64B: FISETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(5)GALANGIN: Galangin has pharmacophore fit score: 48,4800 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

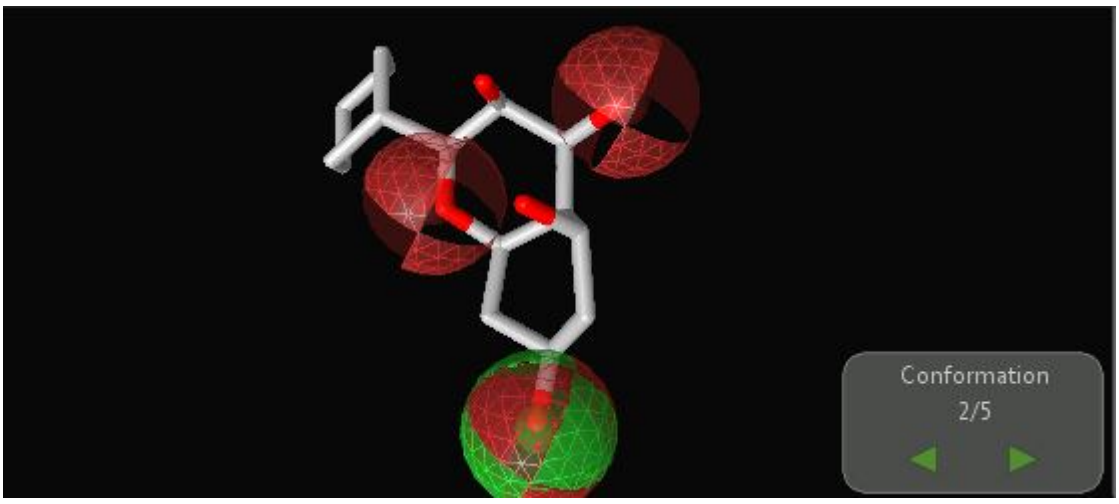


FIG-65A: GALANGIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

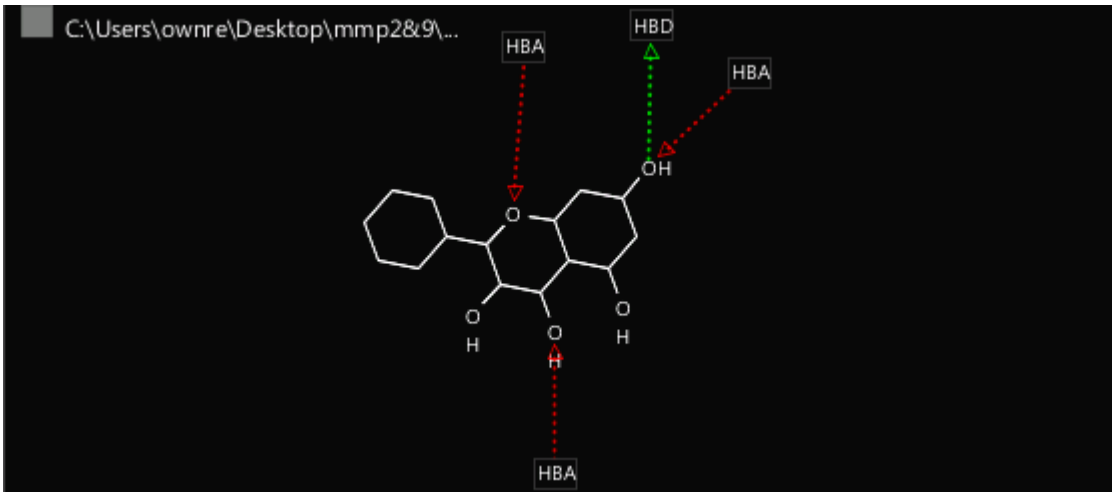


FIG-65B: GALANGIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(6) (+)-AROMADENDRIN: (+)-Aromadendrin has pharmacophore fit score: 48,4800 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

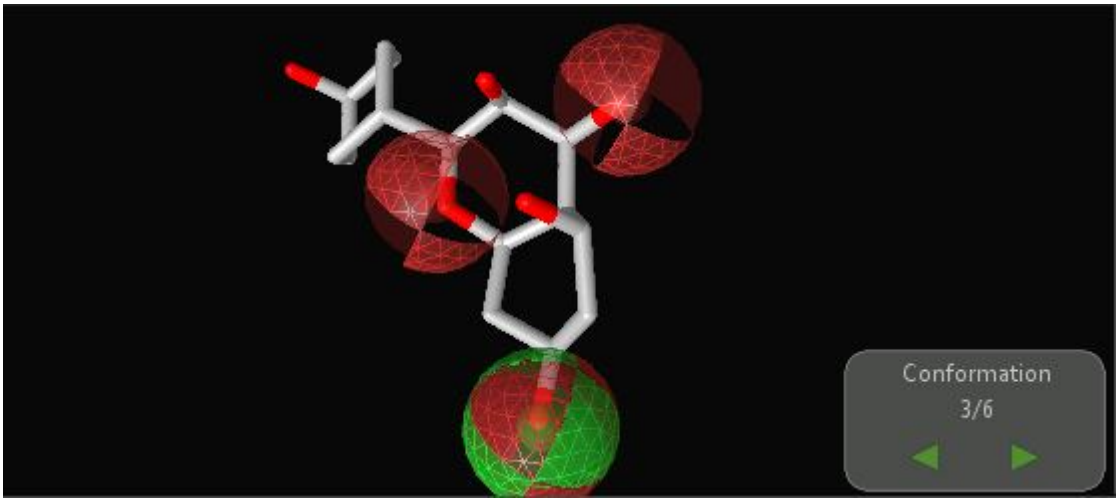


FIG-66A: (+)-AROMADENDRIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

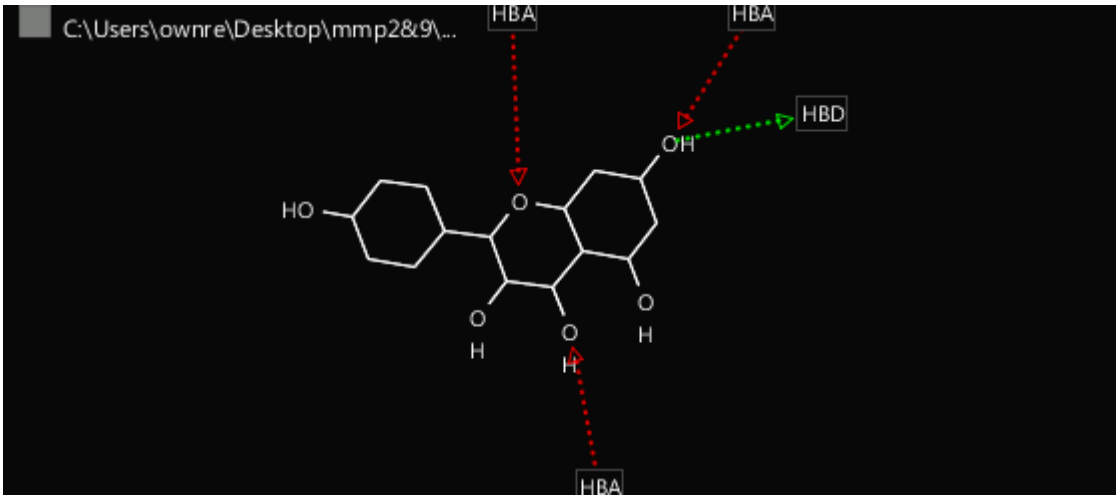


FIG-66B: (+)-AROMADENDRIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(7)EPI-TAXIFOLIN: Epi-taxifolin has pharmacophore fit score: 48,4300 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

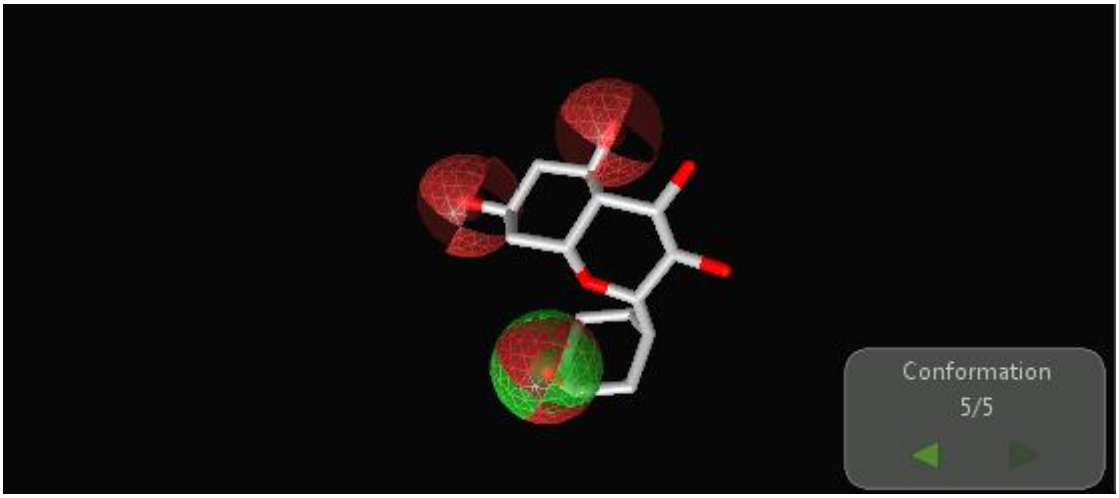


FIG-67A: EPI-TAXIFOLIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

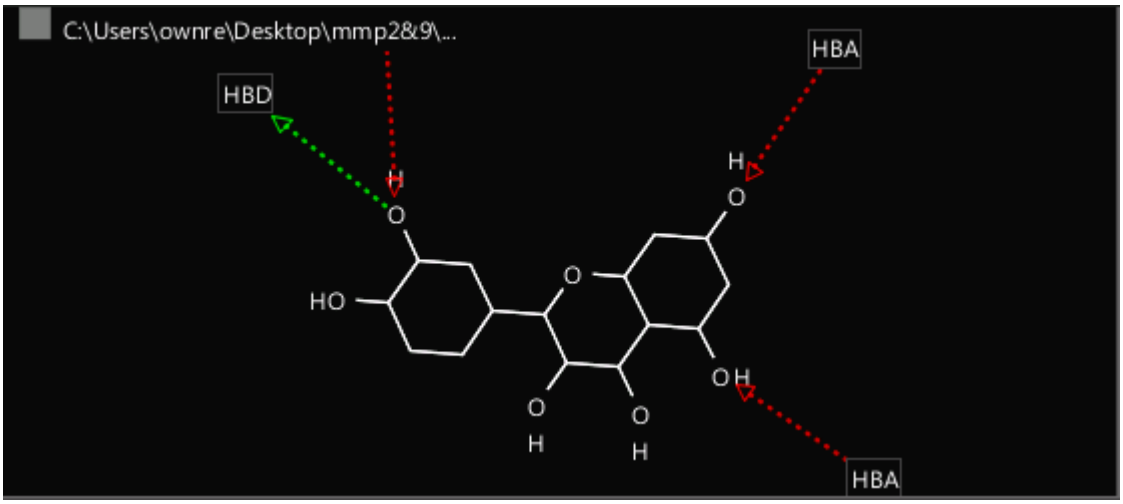


FIG-67B: EPI-TAXIFOLIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(8)RHAMNETIN: Rhamnetin has pharmacophore fit score: 48,2900 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

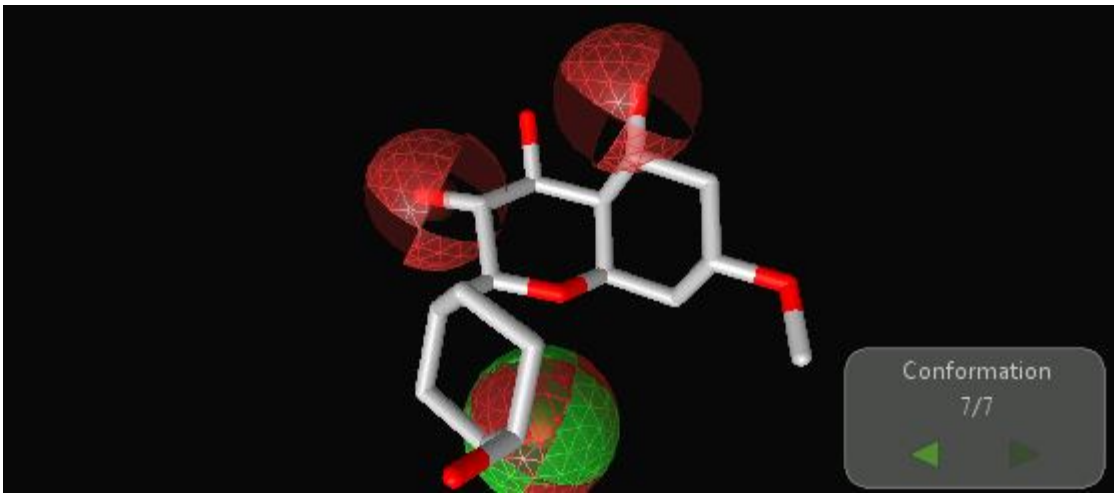


FIG-68A:RHAMNETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

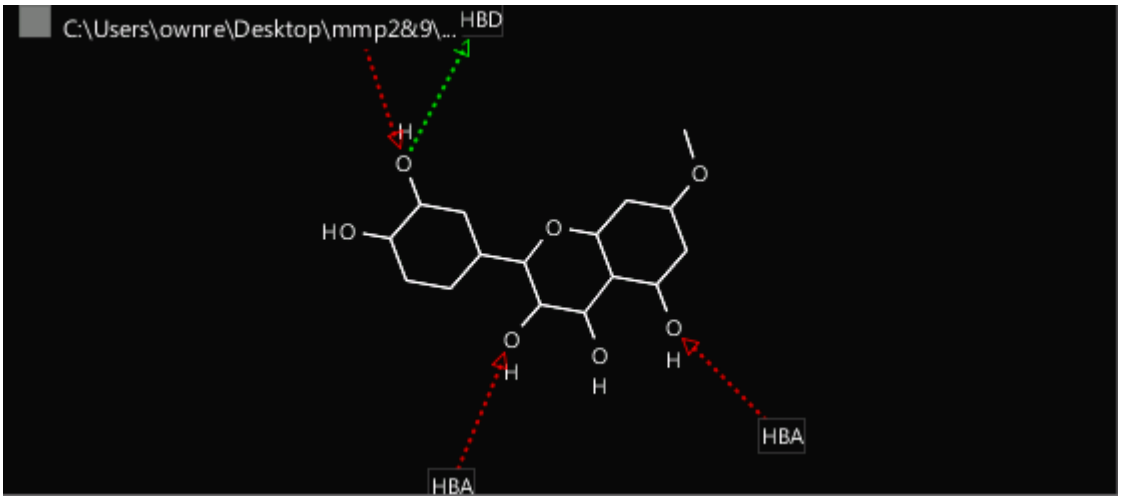


FIG-68B:RHAMNETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(9)RHEIN: Rhein has pharmacophore fit score: 48,2300 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

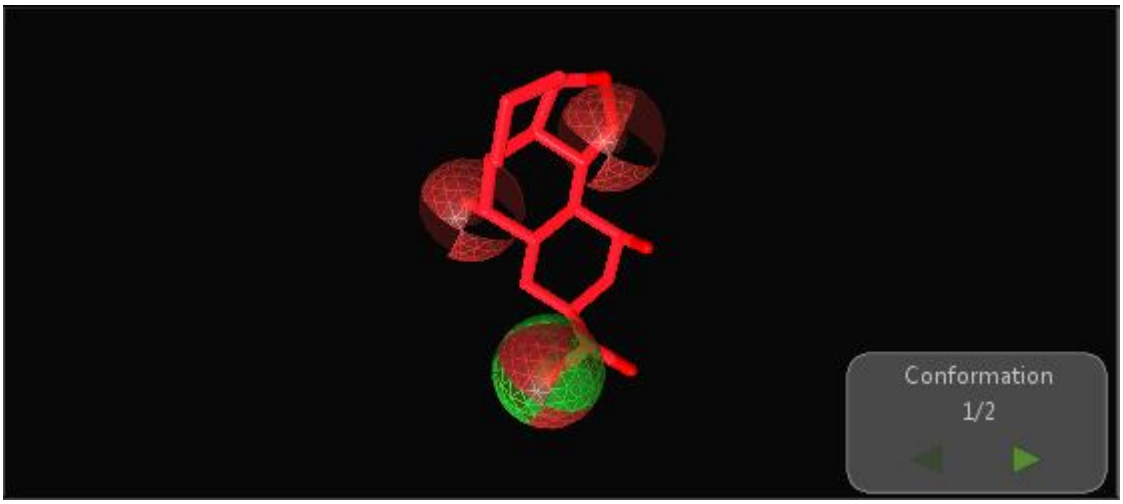


FIG-69A: RHEIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

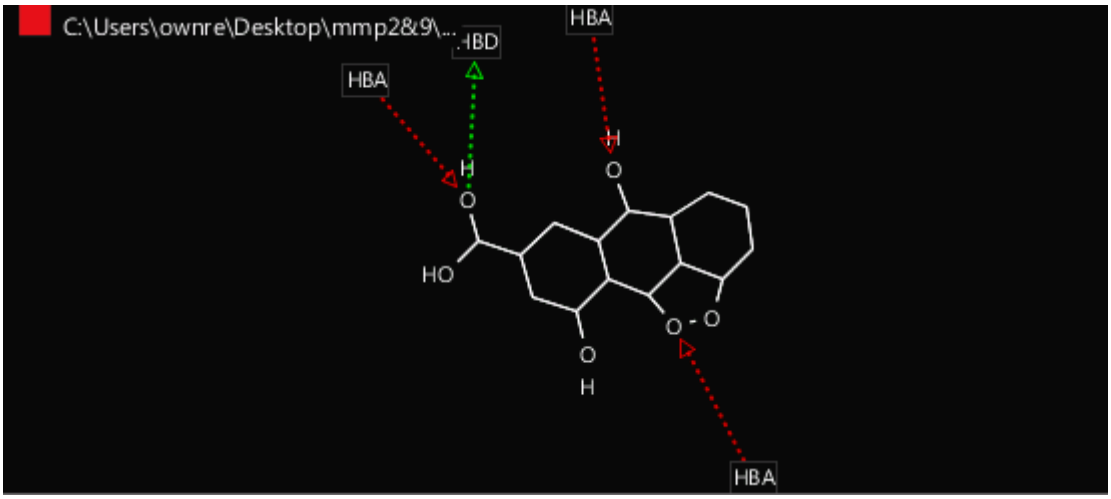


FIG-69B: RHEIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(10) CALYCOSIN: Calycosin has pharmacophore fit score: 48,1300 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

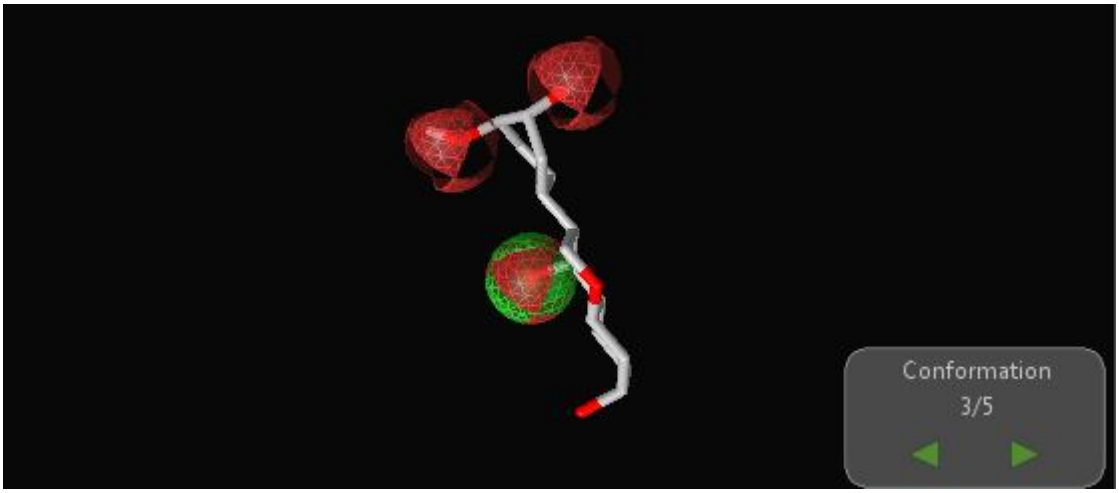


FIG-70A: CALYCOSIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

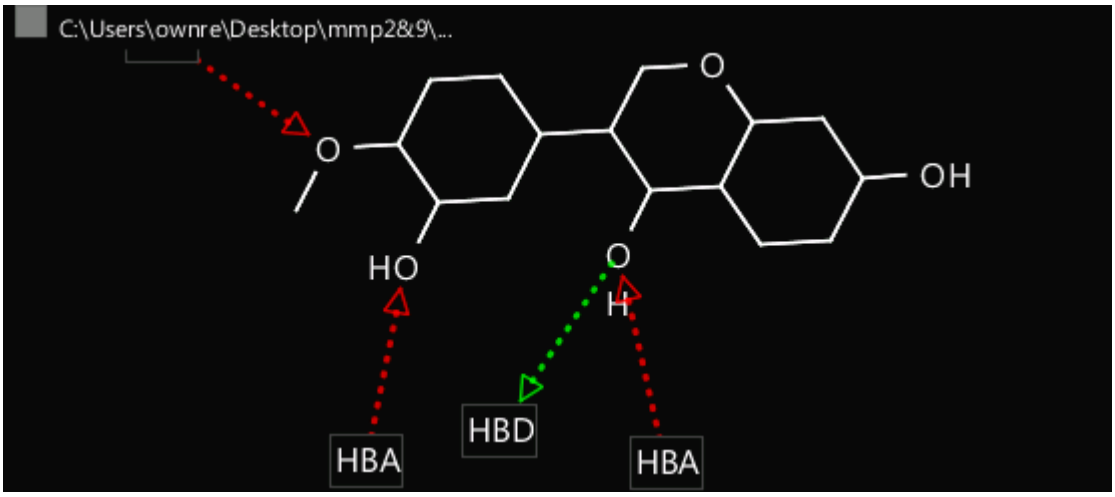


FIG-70B: CALYCOSIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(11)MARMESIN: has pharmacophore fit score: 48,0500 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red)

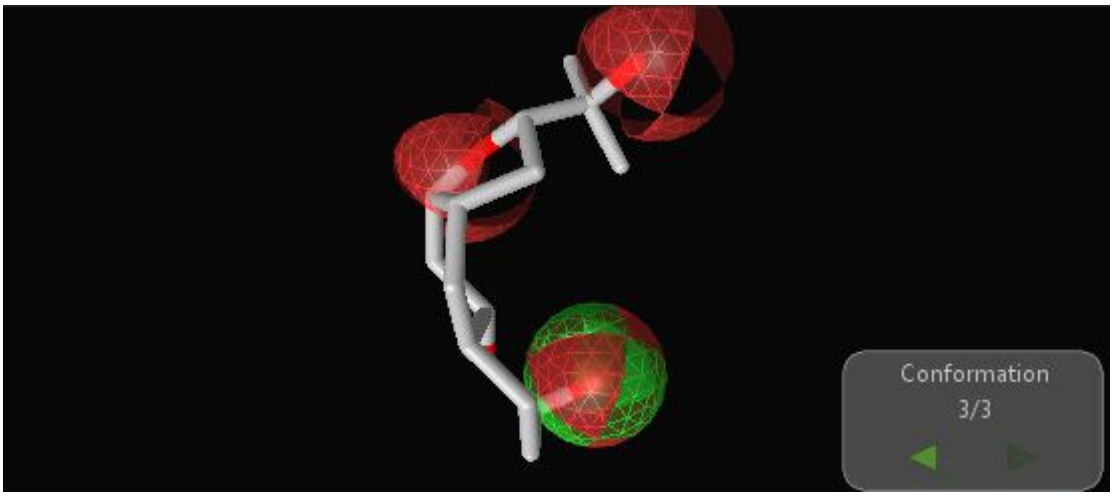


FIG-71A: MARMESIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

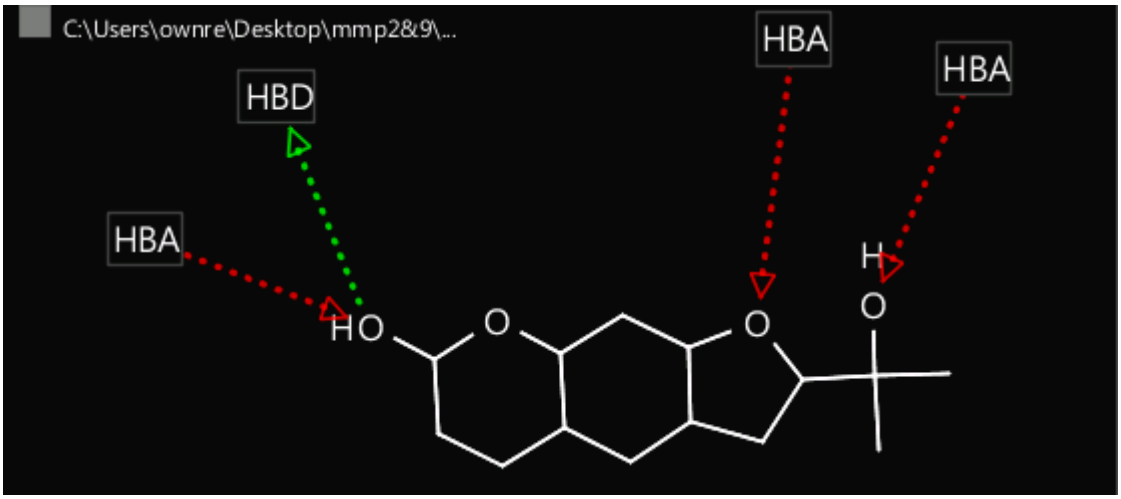


FIG-71B: MARMESIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(12) IRILIN-D: Irilin-D has pharmacophore fit score: 47,9100 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red) .

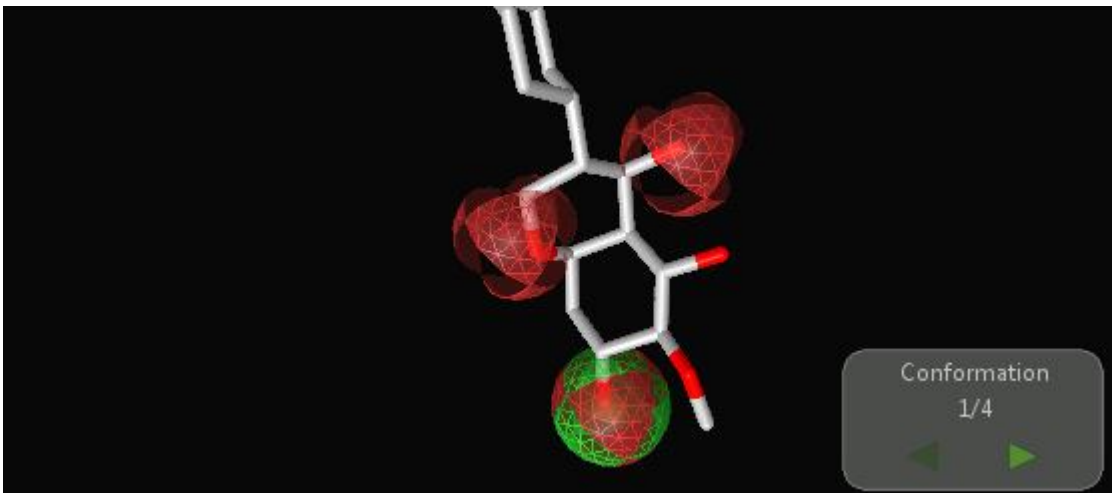


FIG-72A: IRILIN-D: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

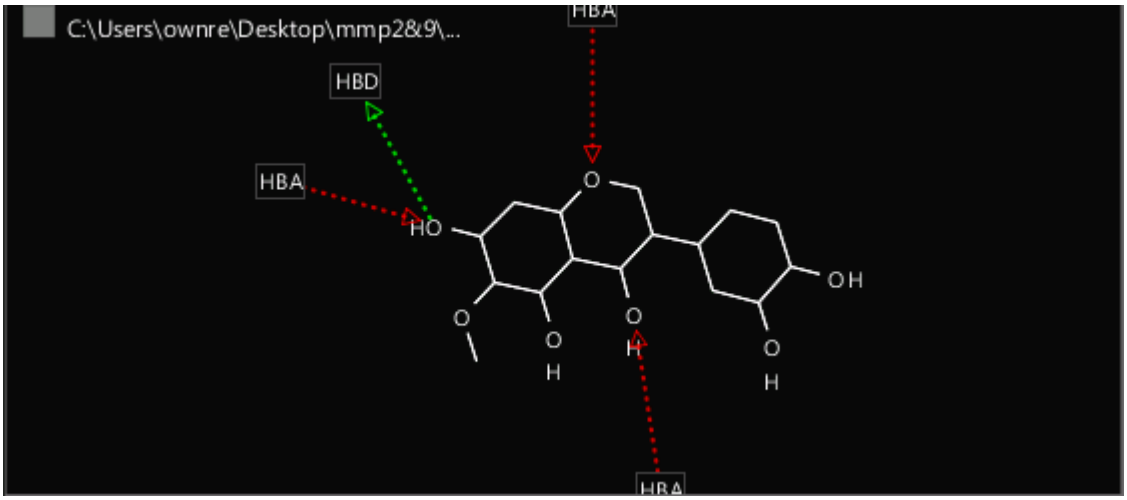


FIG-72B: IRILIN-D: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(13)ELLAGIC ACID: Ellagic acid has pharmacophore fit score: 47,8500 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

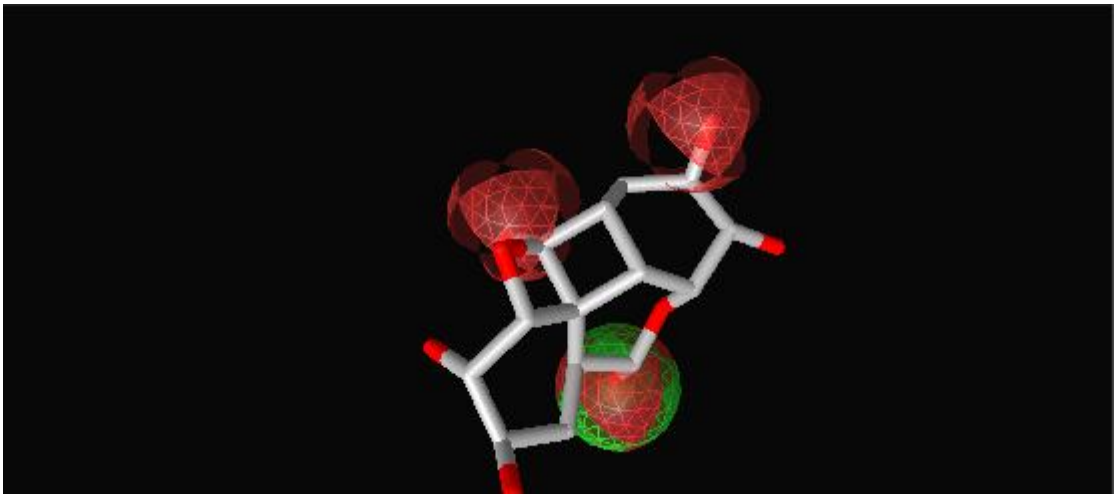


FIG-73A: ELLAGIC-ACID:SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

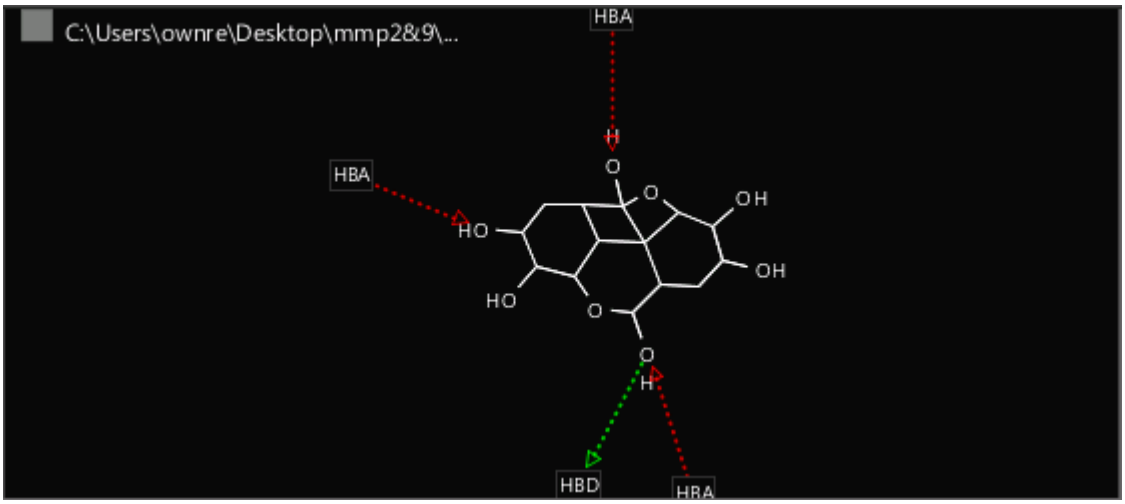


FIG-73B: ELLAGIC-ACID: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(14)DIOSMETIN: Diosmetin has pharmacophore fit score: 47,8400 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

FIG-74A: DIOSMETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

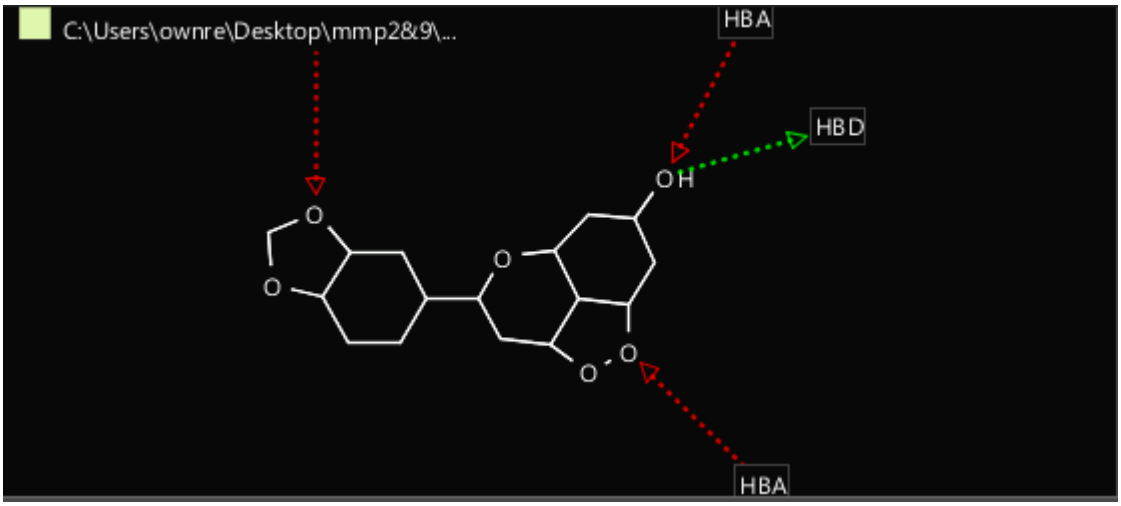


FIG-74B: DIOSMETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(15)ALOE EMODIN: Aloe emodin has pharmacophore fit score: 47,1300 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

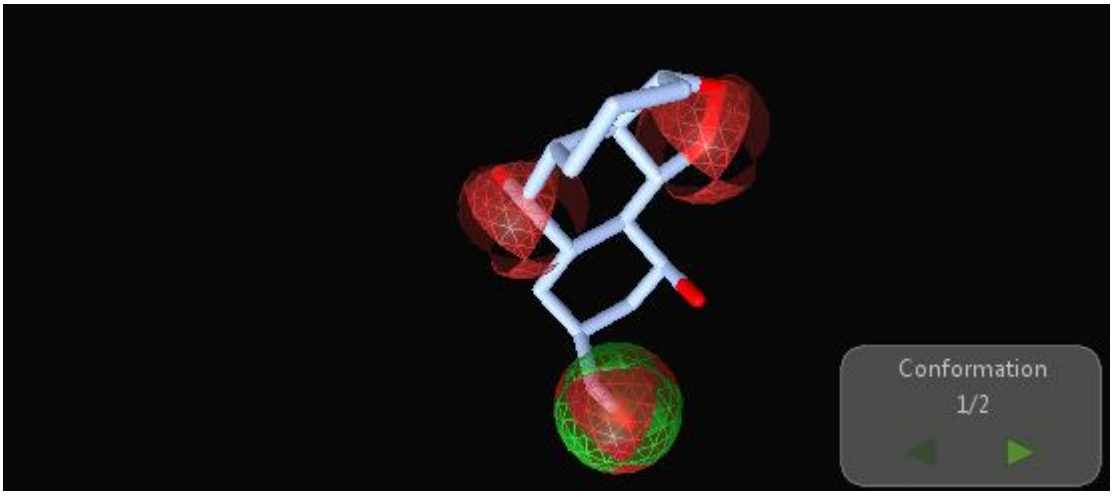


FIG-75A: ALOE EMODIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

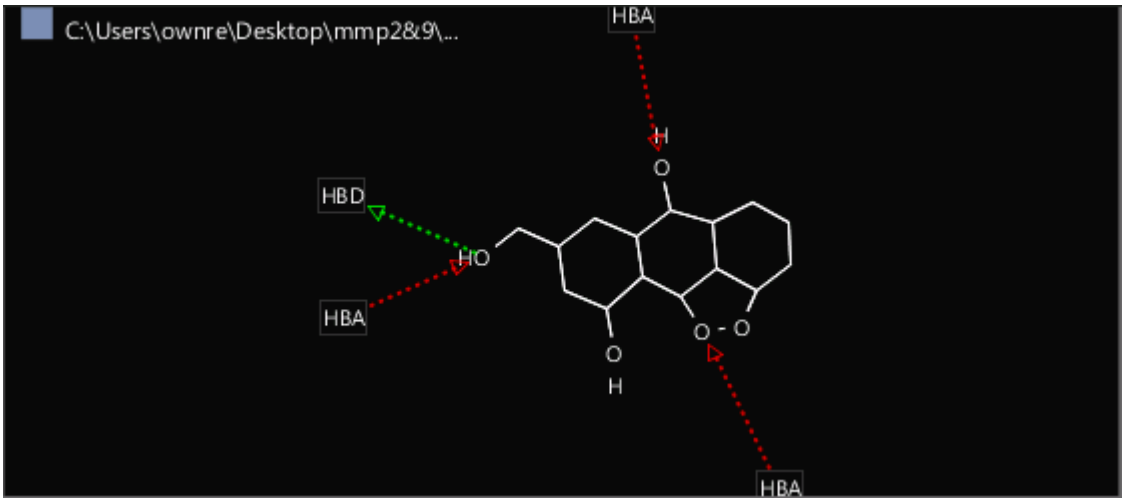


FIG-75B: ALOE EMODIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(16) ISO-FORMONONETIN: Iso-formononetin has pharmacophore fit score: 47,0800 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red).

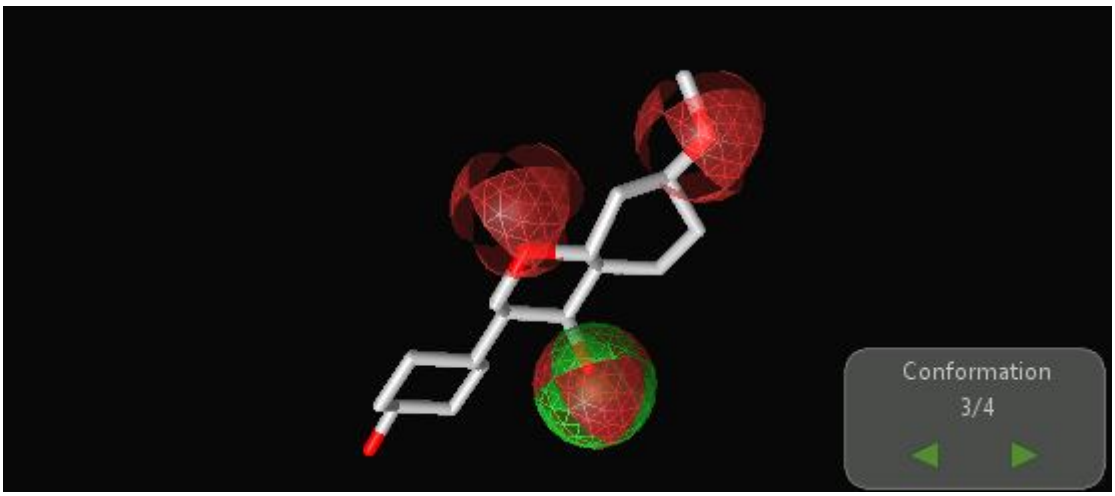


FIG-76A: ISO-FORMONONETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

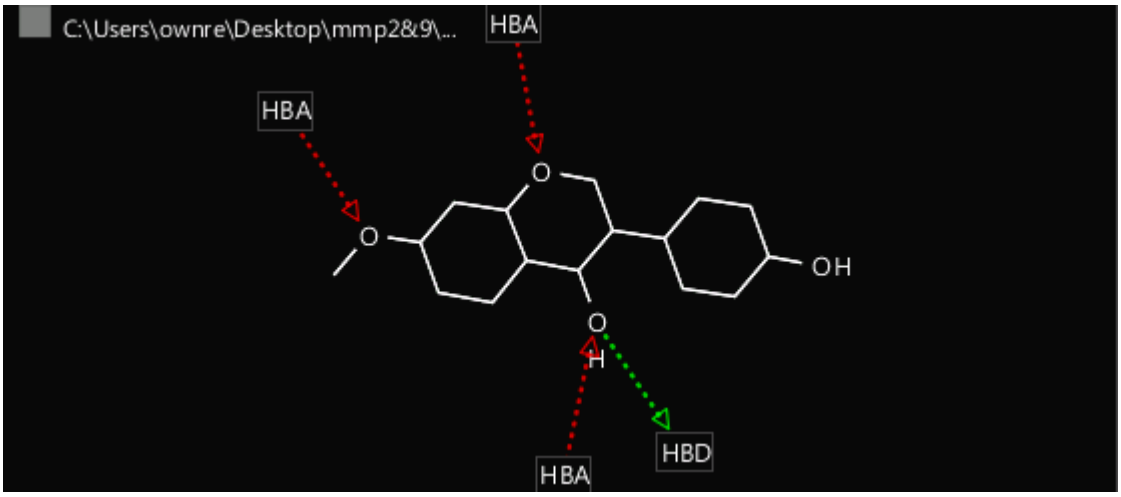


FIG-76B: ISO-FORMONONETIN: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(17) BIOCHANIN-A: Biochanin-A has pharmacophore fit score: 46,3300 and has all four pharmacophore features: (a)1 hydrogen bond donor(green) (b)3 hydrogen bond acceptor(red.)

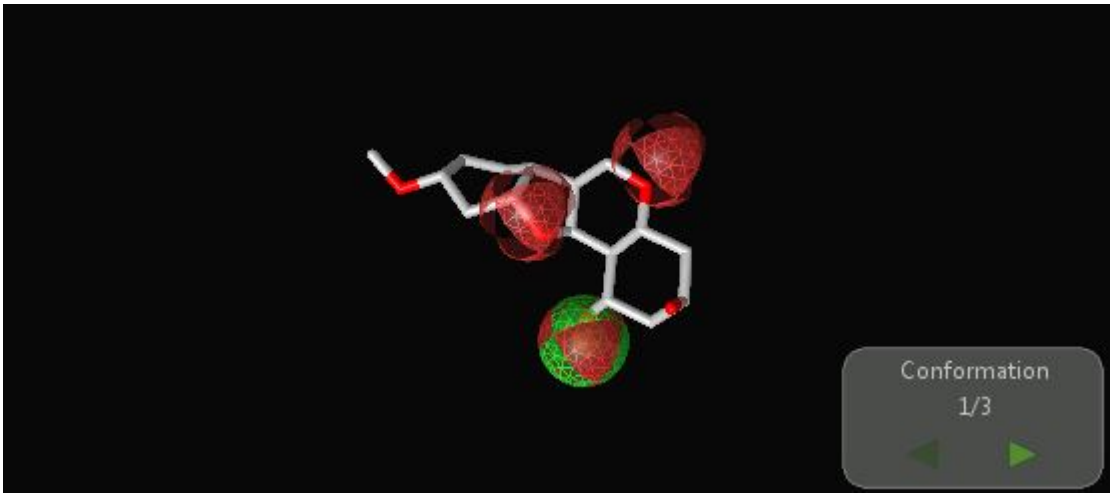


FIG-77A: BIOCHAININ -A: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

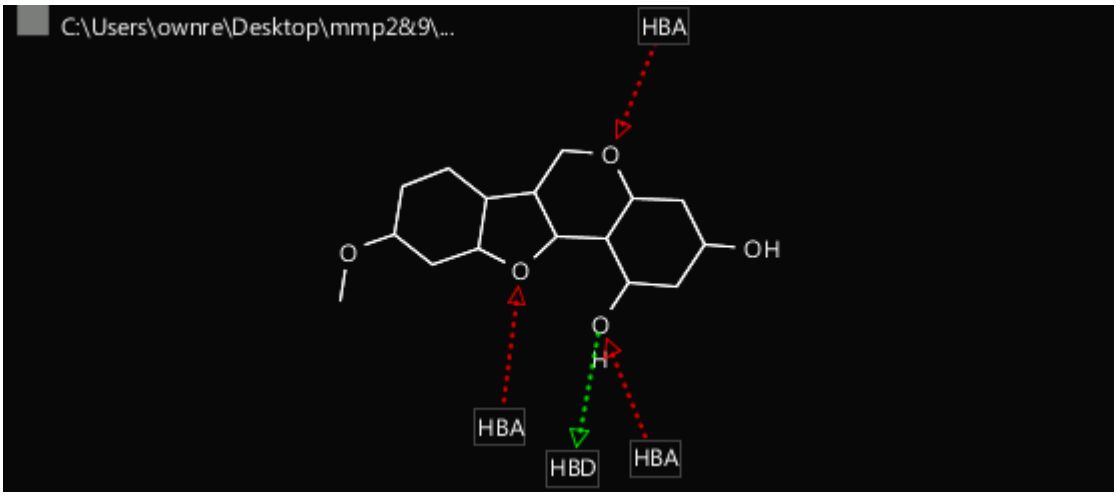


FIG77-B: BIOCHAININ -A: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(18) PICRALINAL: Picralinal has pharmacophore fit score: 38,1800 and has three pharmacophore features: (a)1 hydrogen bond donor(green) (b)2 hydrogen bond acceptor(red)

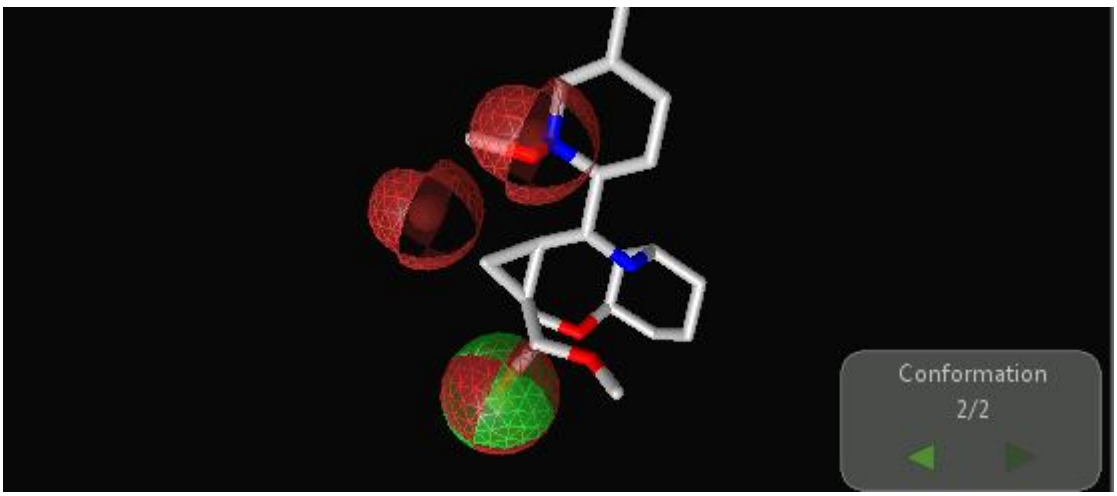


FIG-78A: PICRALINAL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

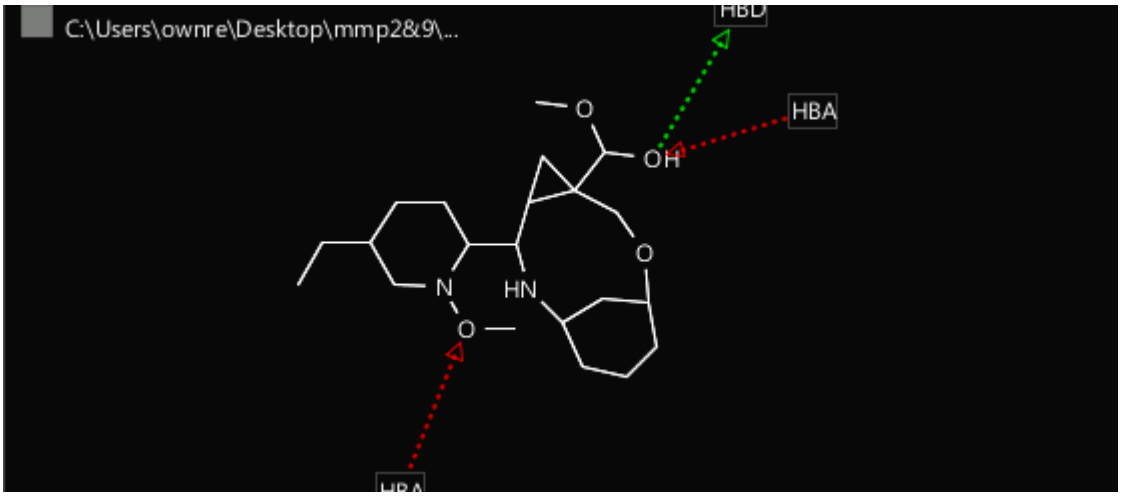


FIG-78B: PICRALINAL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(19) NAPHTHOPYRONE: Naphthopyrone has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands for this pharmacophore model.

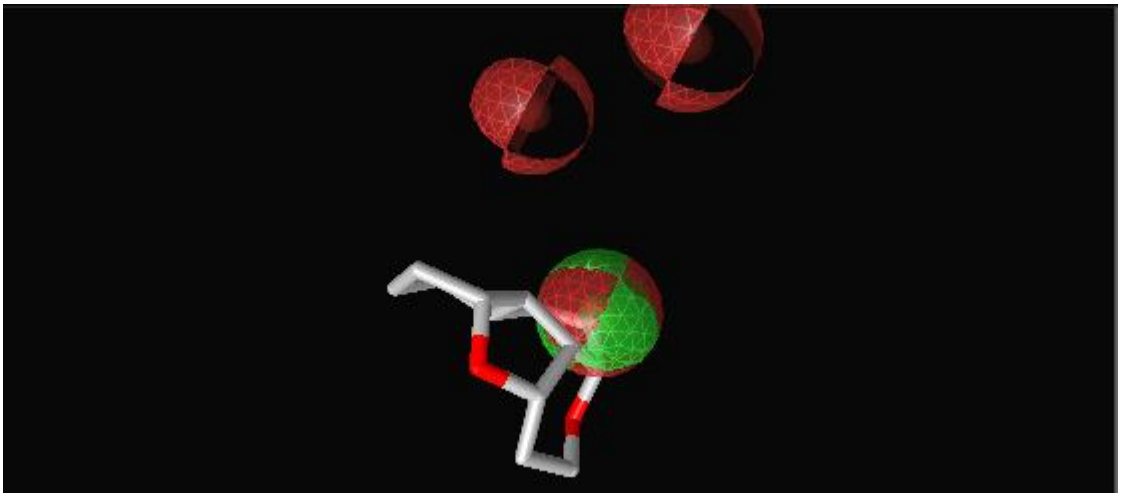


FIG79-A: NAPHTHOPYRON : SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

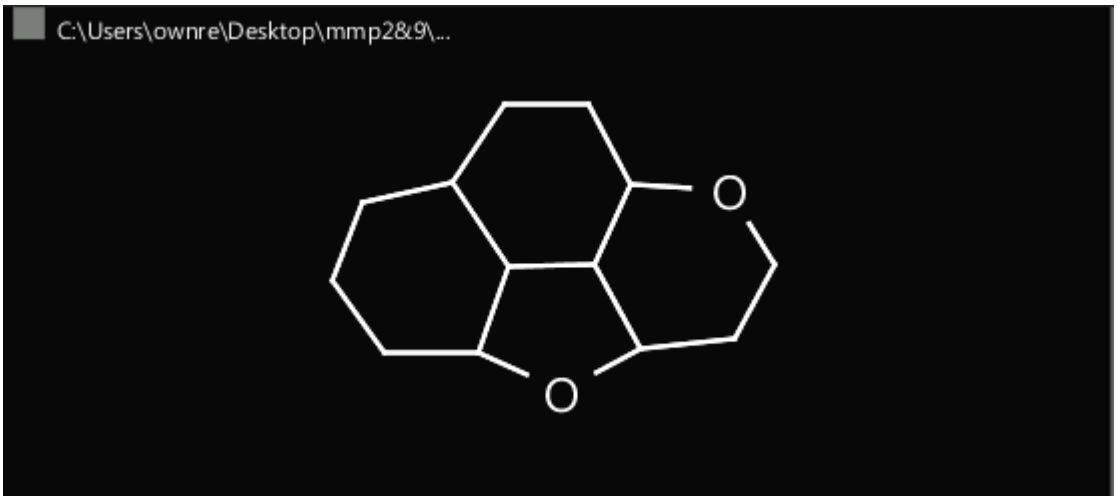


FIG79-B: NAPHTHOPYRONE : SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(20) PACLOBUTRAAZOL: Paclobutraazol has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands for this pharmacophore model.

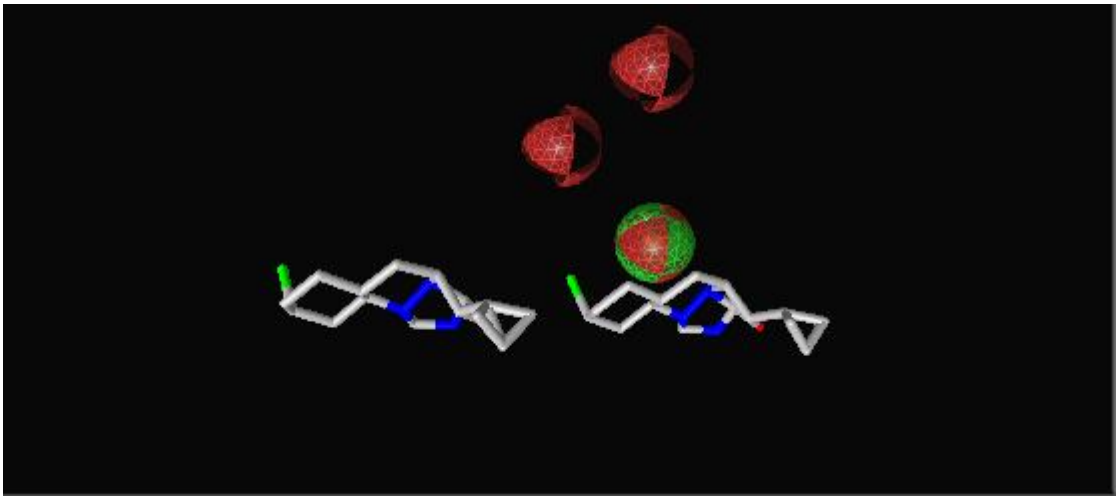


FIG-80A: PACLOBUTRAAZOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

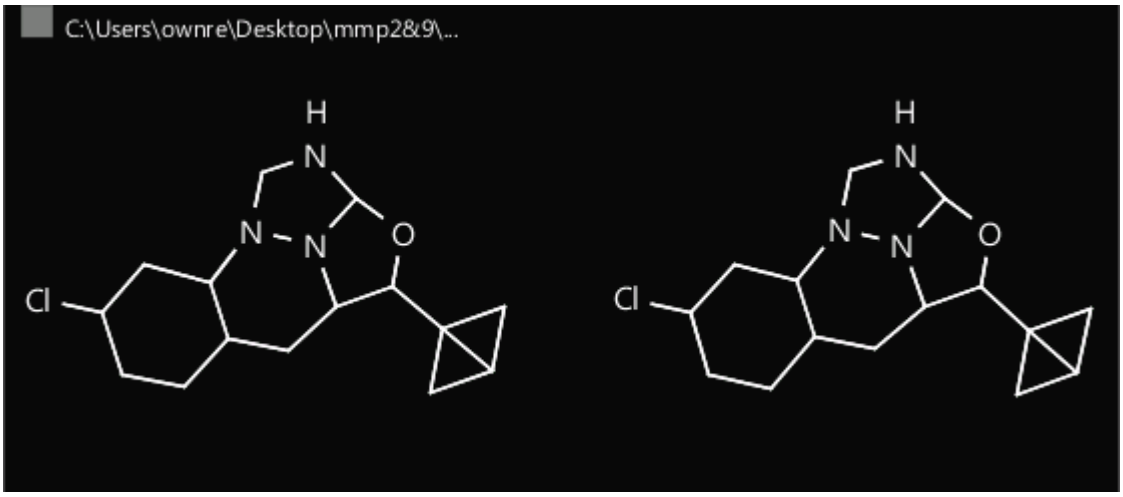


FIG-80B: PACLOBUTRAAZOL: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(21) FEBRIFUGINE: Febrifugine has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands for this pharmacophore model.

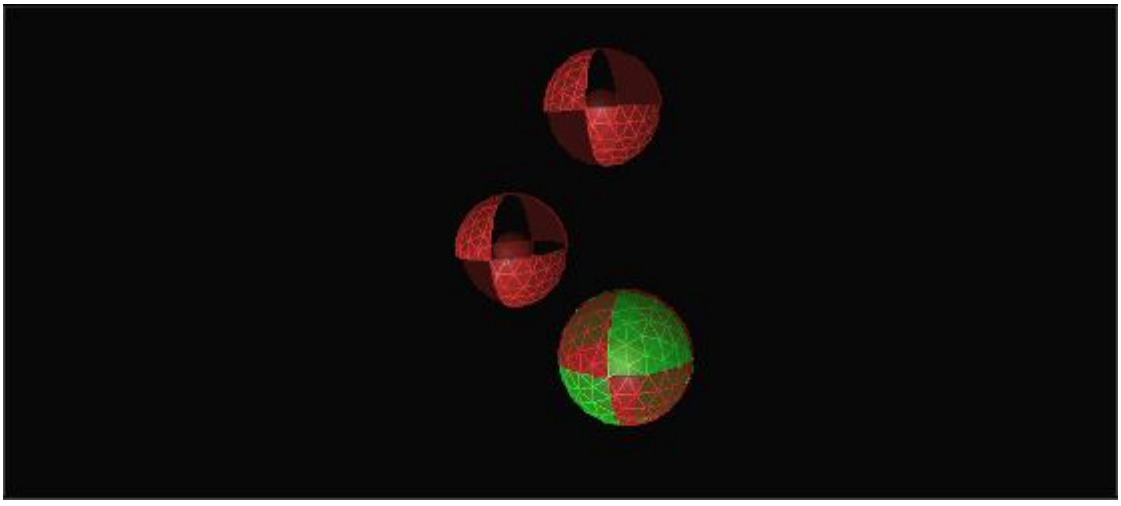


FIG-81A: FEBRIFUGINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

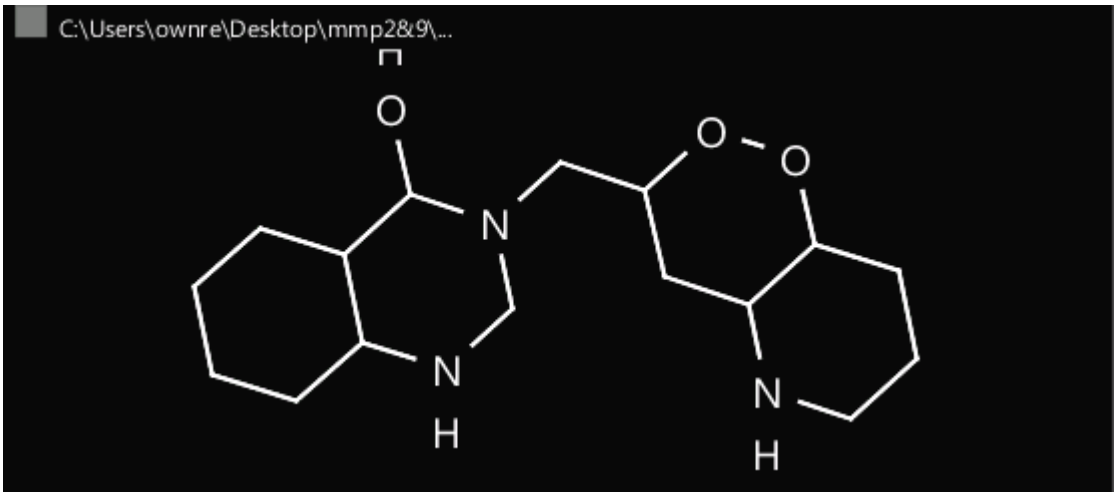


FIG81-B: FEBRIFUGINE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(22) UNICONAZOLE: Uniconazole has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands for this pharmacophore model.

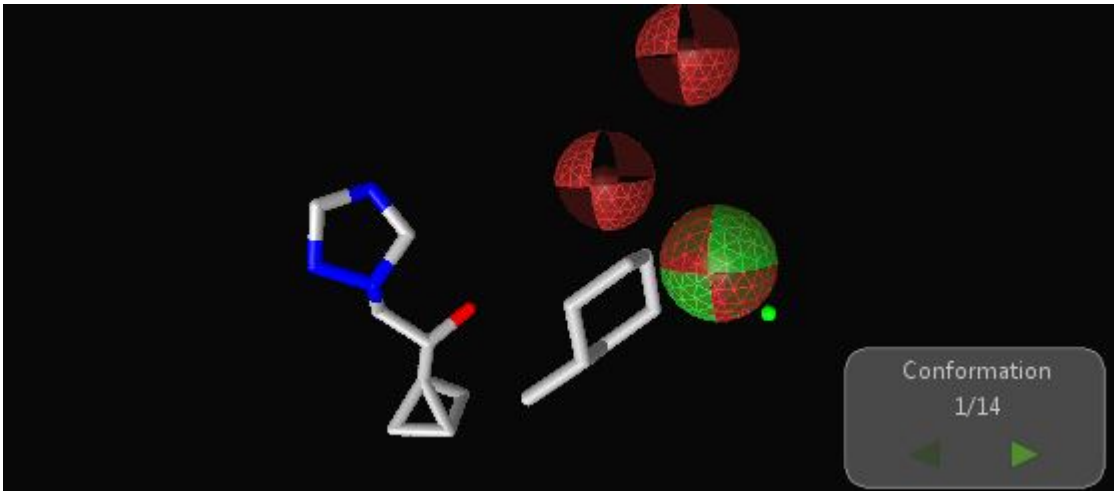


FIG-82A: UNICONAZOLE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

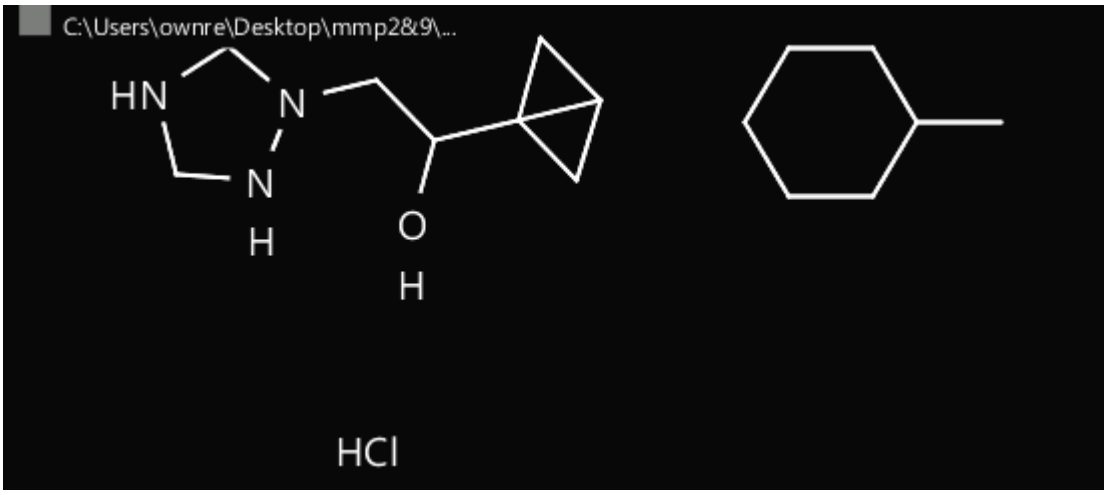


FIG-82B: UNICONAZOLE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(23) (+)-NOOTKATONE: (+)-Nootkatone has pharmacophore fit score: 0.0 and has no pharmacophore features. It has no shared feature of pharmacophore compared to the other ligands for this pharmacophore model.

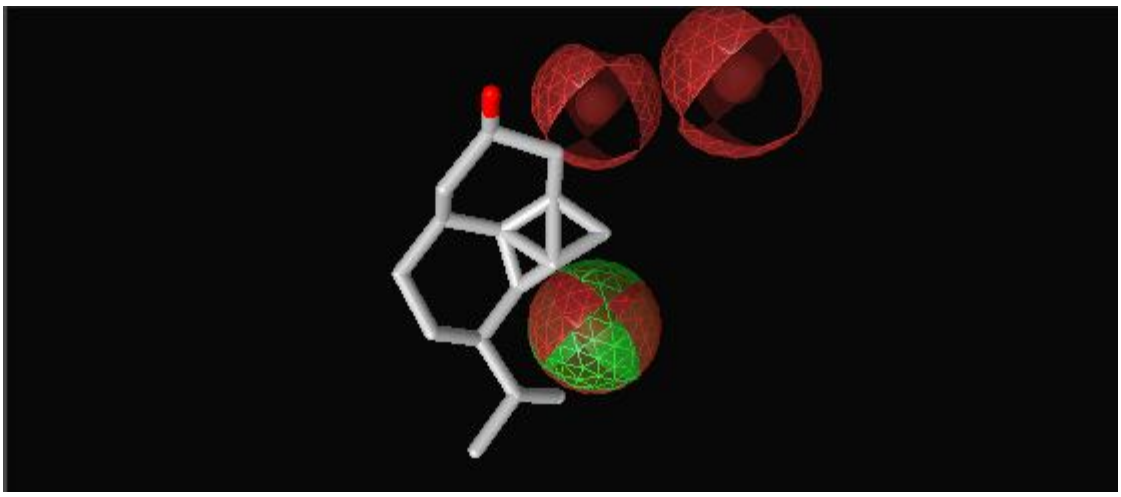


FIG-83A: (+)-NOOTKATONE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

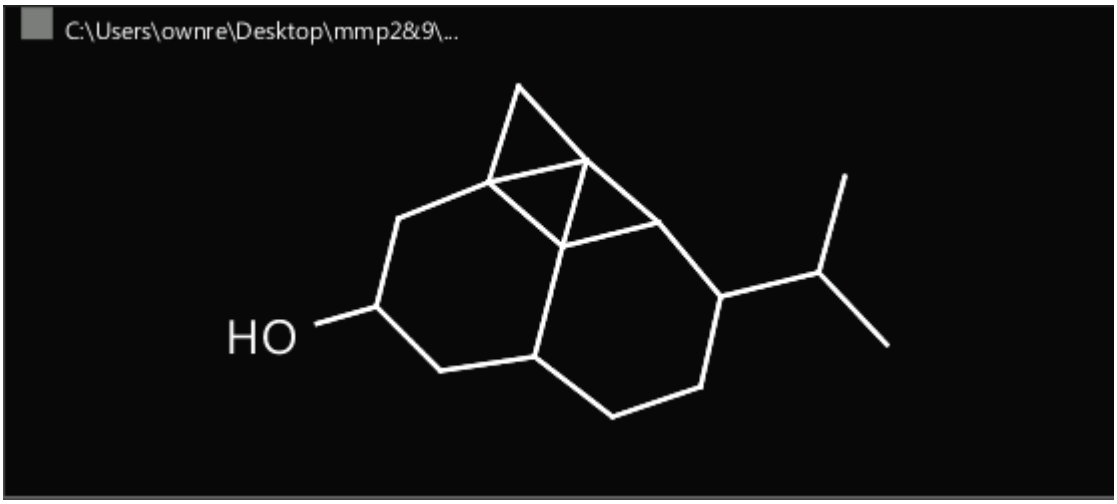


FIG-83B: (+)-NOOTKATONE: SHARED FEATURE PHARMACOPHORE (BEST CONFORMATION)

(H)DOCKING

All the ligands selected above for pharmacophore model generation were docked to the targets matrix metalloproteinases MMP2 and MMP9. Hydrogen bonds and hydrophobic interactions are mainly involved in the binding stability of docked structures. Binding stability of docked structures were determined by predicting hydrogen bonds and hydrophobic interactions from ligandmap of the software molegro virtual docker.

TABLE-25:DOCKING RESULTS OF MMP-9

	LIGANDS	MOLDOCKSCORE	HYDROPHOBIC INTERACTIONS	HYDROGEN BONDS
1.	(-)-1-(S)-Norcoclaurine	-195.269	Ala 417 Arg 424	
2.	(-)-Centrolobol	-119.583	His 401 Glu 402 Ala 417	Leu 188
3.	5,7,3',4',5-pentahydroxyflavone	-206.844	Ala 417 Met 422 Arg 424	

4.	5-htp	-122.901		Arg 424
5.	5-hydroxy,4,7-dimethoxyy-flavone	-137.515	Leu 418 Arg 424	
6.	Acacetin	-141.568	His 401 Arg 424	
7.	Alpinetin	-137.179	Ala 417 Met 422	
8.	Baicalein	-201.485	Met 422	
9.	Bisabolol	-156.128	Met 422	
10.	Chrysoriol	-211.901	Ala 417 Met 422	
11.	Cubebin	-128.862	Met 422 Arg 424	Leu188 Ala 189
12.	Daidzein	-164.190	Arg 424	
13.	Decussatin	-206.678	Met 422	
14.	Eriodictyol	-106.784	Ala 417 Tyr 423 Arg 424	
15.	Genistein	-175.038	Arg 424	
16.	Genkwanin	-137.323	His 401 Ala 417 Met 422	
17.	Gentiopicroside	-236.394	Leu 397 Ala 417 Met 422 Arg 424	
18.	Guaiol	-155.308	Ala 417 Met 422	
19.	Hesperetin	-126.498	Ala 417 Leu 418 Met 422	Arg 424
20.	Homoeriodictyol	-122.311	His 401 Ala 417 Met 422	
21.	Isorhamnetin	-220.525	Ala 417 Met 422	
22.	Liquiritigenin	-120.330	Val 398 His 401 Ala 417 Met 422 Arg 424	
23.	Petunidin	-105.798	Leu 418	Leu 188 Ala 189
24.	Phloretin	-160.031	Ala 417 Arg 424	
25.	Piceatannol	-173.471	Ala 417	
26.	Pinocembrin-7-	-177.071	Met 422	

	methyl-ether		Arg 424	
27.	Pinocembrin-chalcone	-137.447	His 401	
28.	piperine	-191.125	Arg 424	
29.	Pratensein	-159.695	His 401 Leu 418 Tyr 420	Ala 189 Glu 402 Met 422 Arg 424
30.	Prunasin	817.675	Ala 417 Met 422 Arg 424	Leu418 Tyr 420
31.	Prunetin	-155.637	His 401 Ala 417 Leu 418 Tyr 420 Arg 424	Ala 189 Met 422
32.	Resveratrol	-146.774	Ala 417 Met 422	
33.	Reticuline	-233.788	Ala 417 Arg 424	
34.	Rhamnocitrin	-209.549	Met 422 Arg 424	
35.	Sakuranetin	-136.852	Leu 397 Leu 418 Met 422	Arg 424
36.	Salidroside	-162.367	Arg 424	
37.	Sulfurien	-145.670	Ala 417 Met 422 Arg 424	
38.	Swertiamarin	-138.152	His 401 Met 422 Tyr 423	
39.	Tolperisone	-177.122	Ala 417 Met 422	
40.	Wogonin	-212.314	Ala 417 Met 422	

TOP 3 DOCKED STRUCTURE OF MMP9

Top 3 docked structures with minimum and stable binding energy of phytochemicals with the target MMP9 were selected.

(A)Gentiopicroside: MOLDOCKSCORE: -236.394

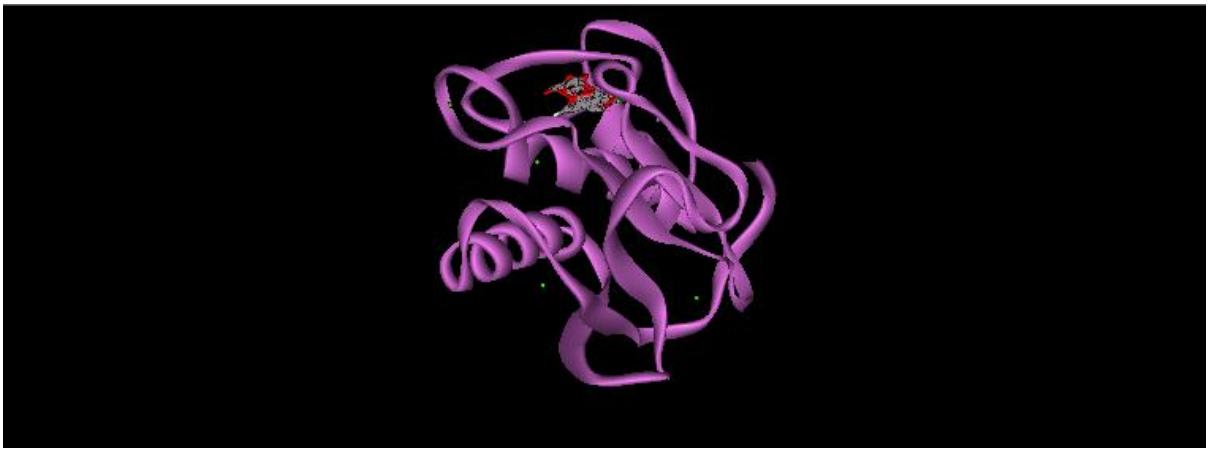


FIG-84A: DOCKED STRUCTURE OF MMP9 WITH GENTIOPICROSIDE: Purple colour ribbon represents the target protein-MMP9 and red and grey colour represents the lead compound-Gentiopicroside

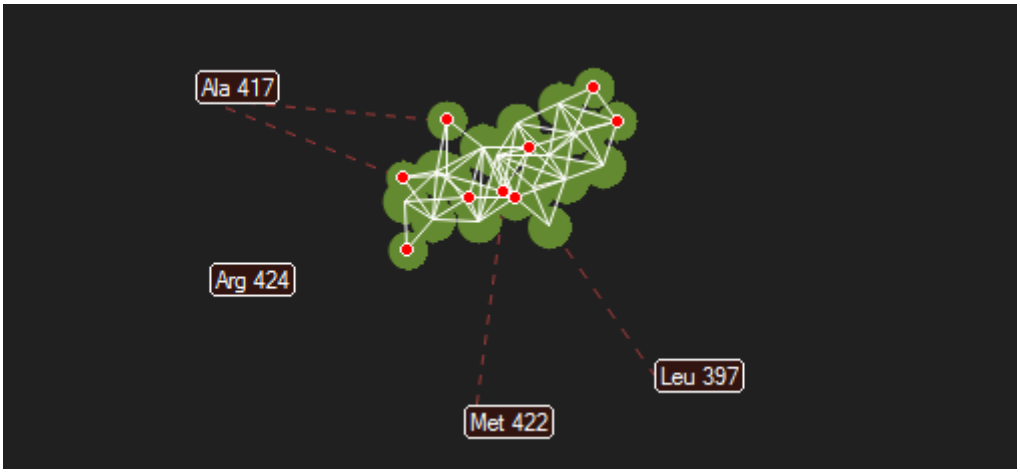


FIG-84B: LIGAND MAP: SHOWING INTERACTIONS OF GENTIOPICROSIDE WITH MMP9

(B)Reticuline: MOLDOCKSCORE: -233.788

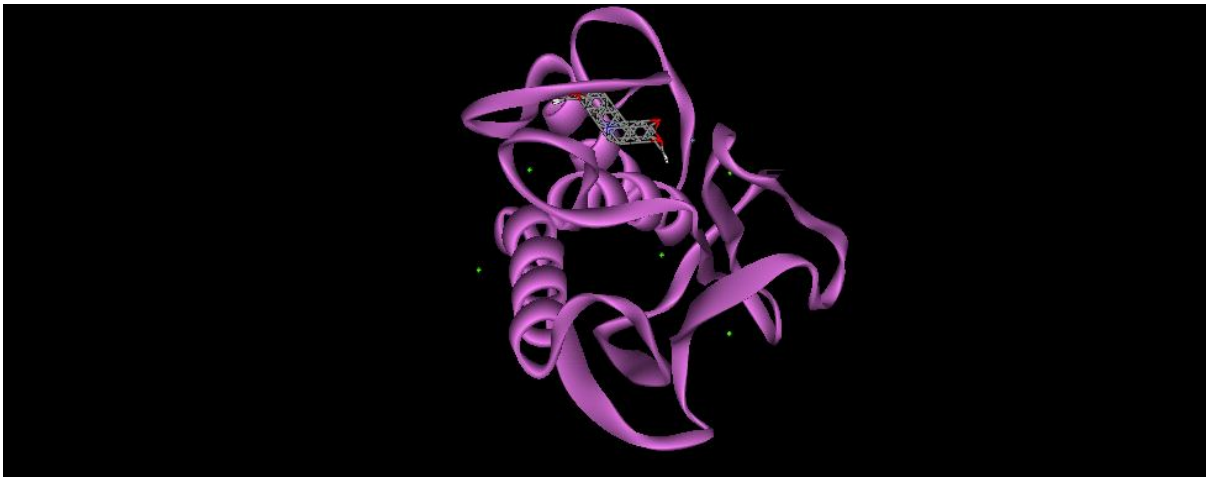


FIG-85A: DOCKED STRUCTURE OF MMP9 WITH RETICULINE: Purple colour ribbon represents the target protein-MMP9 and red and grey colour represents the lead compound- reticuline

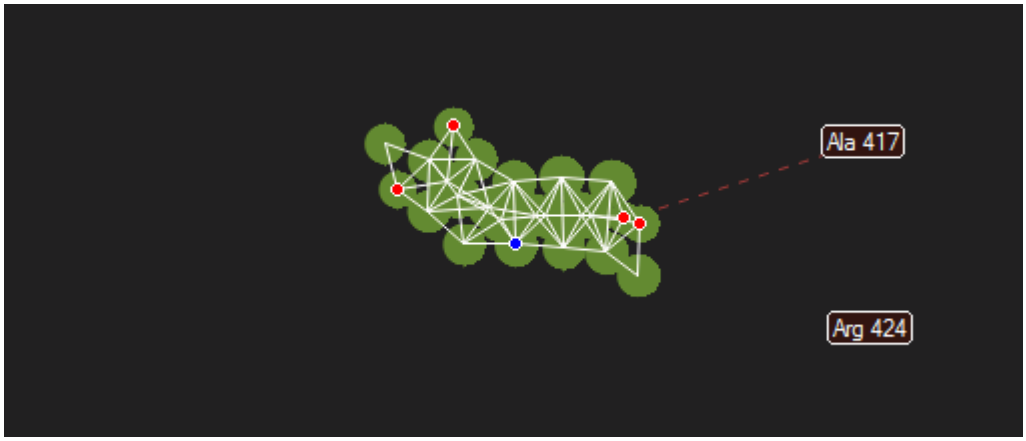


FIG-85B: LIGAND MAP: SHOWING INTERACTIONS OF RETICULINE WITH MMP9

(C)Isorhamnetin: MOLDOCKSCORE: -220.525

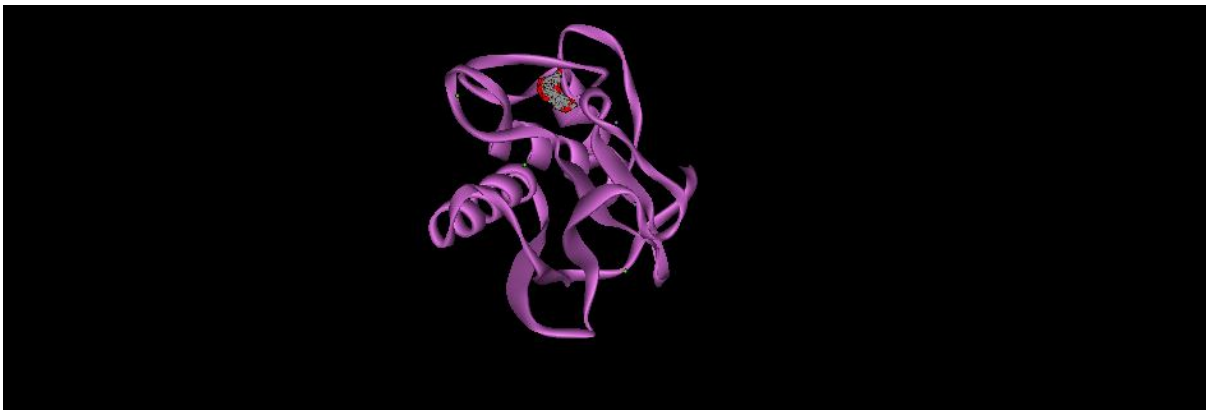


FIG-86A: DOCKED STRUCTURE OF MMP9 WITH ISORHAMNETIN: Purple colour ribbon represents the target protein-MMP9 and red and grey colour represents the lead compound-Isorhamnetin

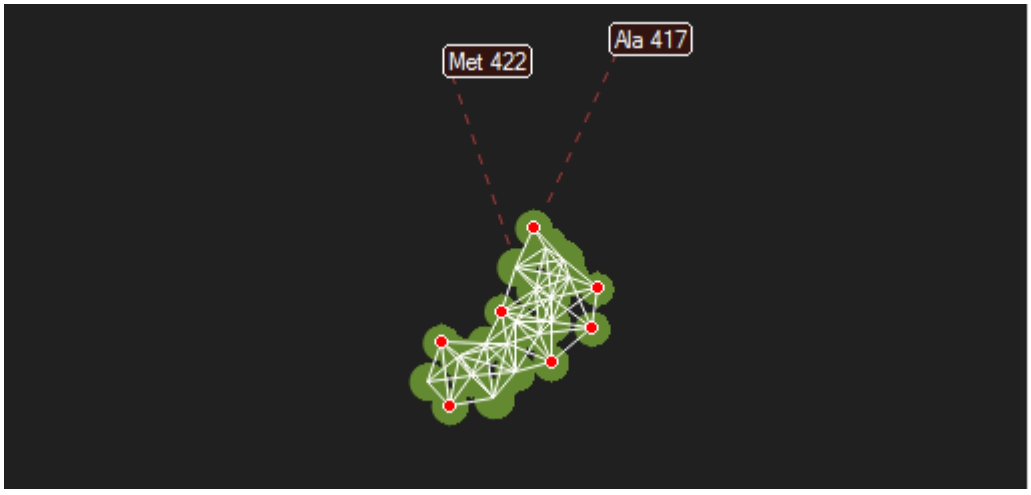


FIG-86B: LIGAND MAP:SHOWING INTERACTIONS OF ISORHANETIN WITH MMP9

TABLE-26:DOCKING RESULTS OF MMP-2

	LIGANDS	MOLDOCKSCORE	HYDROPHOBIC INTERACTIONS	HYDROGEN BONDS
1.	16R,19E-isositsirikine	-215.015	Ala 217 Ile 222	
2.	Ajmalicine	-192.297	Leu 197 Leu 218 Ile 222 Tyr 223	
3.	Iso-Silybin-A	38.9838	Gly 162 Leu 164 His 201 Ile 222	The 227
4.	Ononin	-159.192	Ala 165 Leu 197 His 201 Gly 216 Pro 221 Ile 222 Phe 232	Glu 202 Ala 217 Ala 220 Pro 221
5.	Pericyclivine	-166.677	Ala 217 Ile 222	Thr 227
6.	Pseudo -Strychnine	-32.4783	Leu 197 Val 198 Ala 217 Leu 218 Ala 220 Ile 222 Thr 223	Ala 220
7.	Scholaricinne	-184.769	Leu 197 His 201 Ala 217 Leu 218 Ile 222	

TOP 3 DOCKED STRUCTURE OF MMP2

Top 3 docked structures with minimum and stable binding energy of phytochemicals with the target MMP2 were selected.

(A) 16R,19E-isositsirikine: MOLDOCK SCORE: -215.015

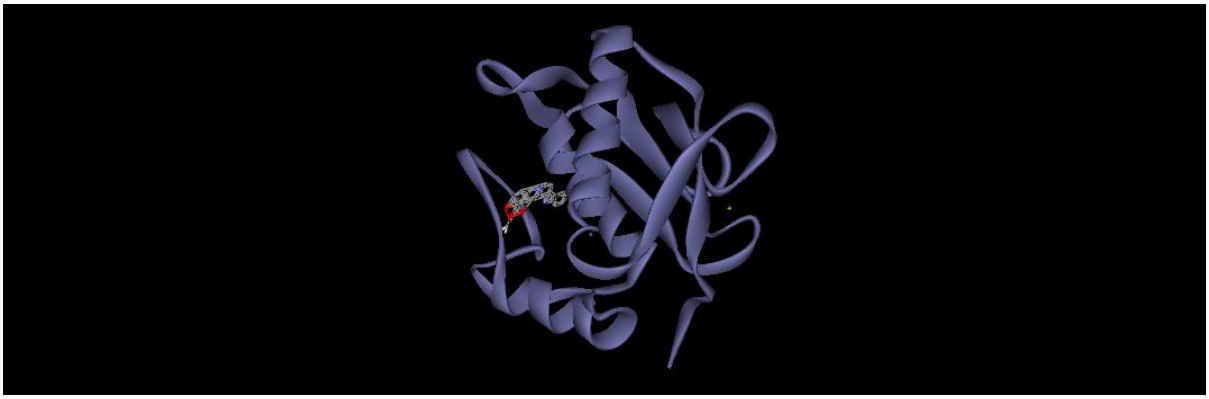


FIG-87A: DOCKED STRUCTURE OF MMP2 WITH 16R,19E-ISOSITSIRIKINE:blue colour ribbon represents the target protein-MMP2 and red and grey colour represents the lead compound-16R,19E-isositsirikine

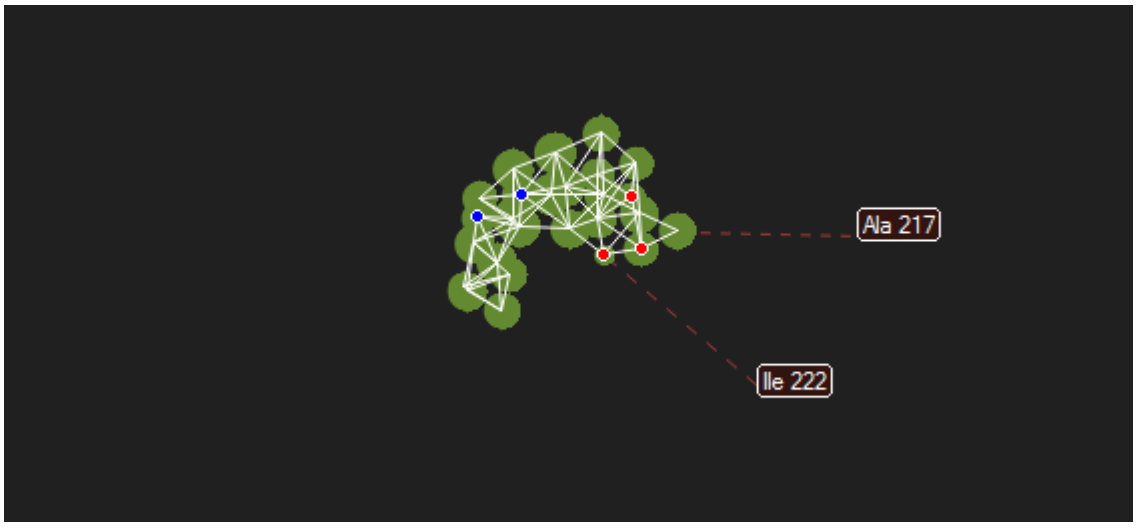


FIG-87B: LIGAND MAP: SHOWING INTERACTIONS OF 16R,19E-ISOSITSIRIKINE WITH MMP2

(B)Ajmalicine: MOLDOCKSCORE: -192.297

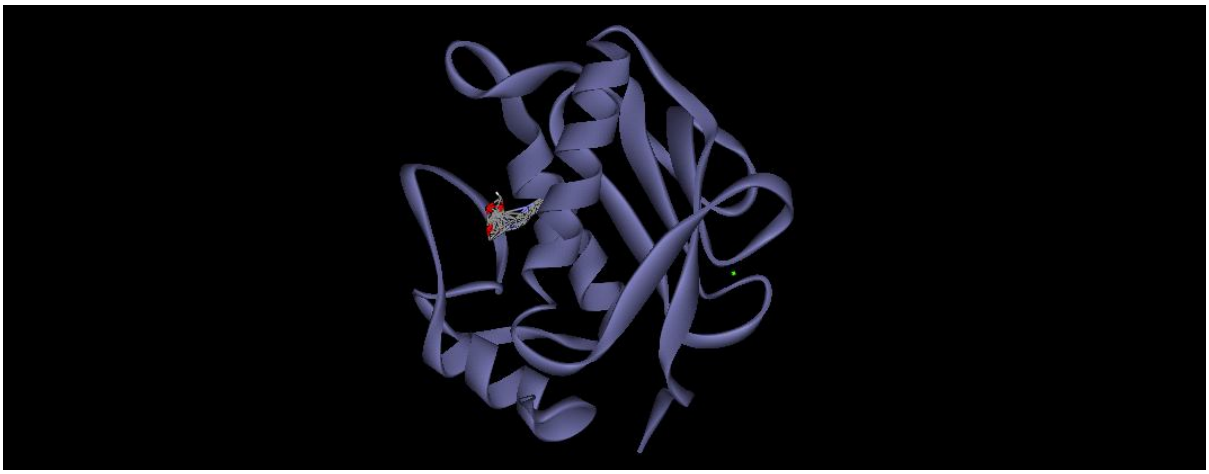


FIG-88A: DOCKED STRUCTURE OF MMP2 WITH AJMALICINE:blue colour ribbon represents the target protein-MMP2 and red and grey colour represents the lead compound- Ajmalicine

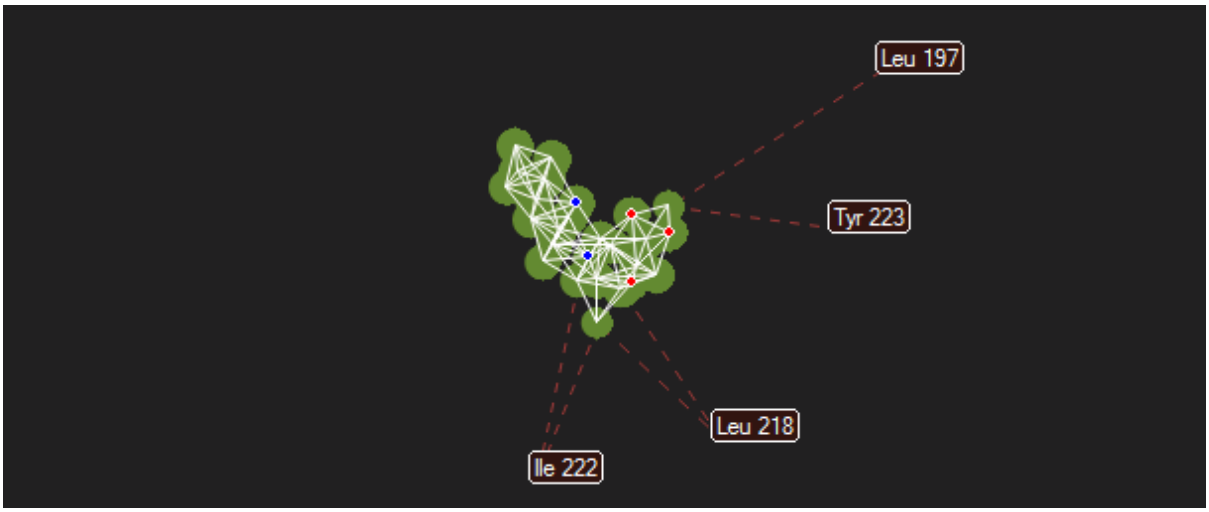


FIG-88B: LIGAND MAP: SHOWING INTERACTIONS OF AJMALICINE WITH MMP2

(C)Scholaricinne: MOLDOCKSCORE: -184.769

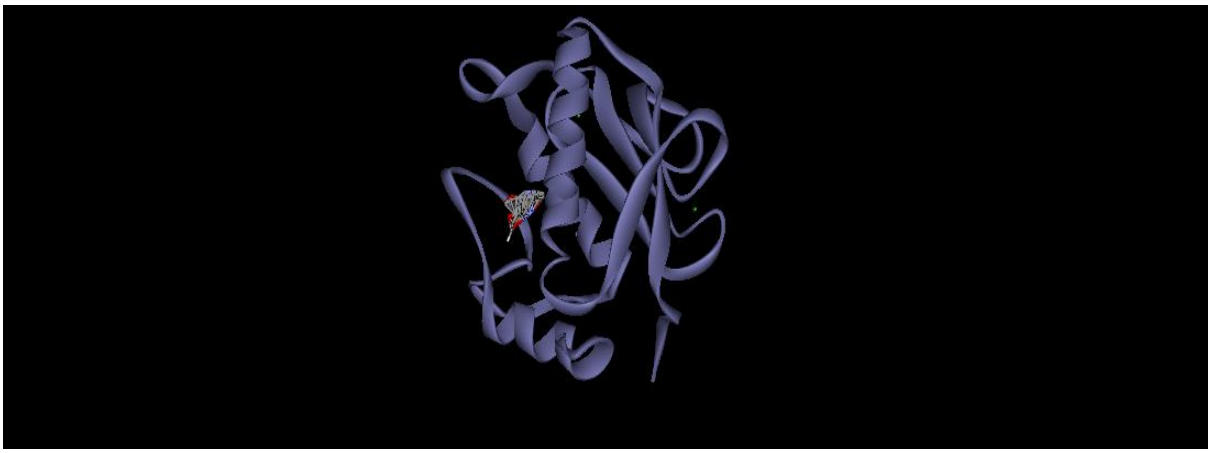


FIG-89A: DOCKED STRUCTURE OF MMP2 WITH SCHOLARICINNE:blue colour ribbon represents the target protein-MMP2 and red and grey colour represents the lead compound-Scholaricinne

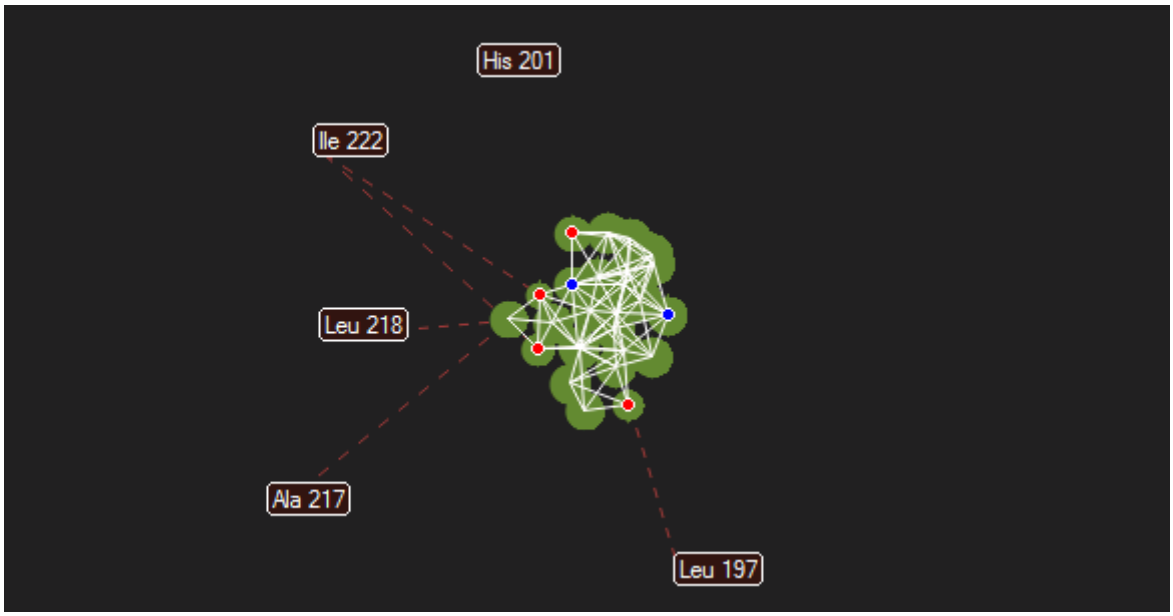


FIG-89B: LIGAND MAP: SHOWING INTERACTIONS OF SCHOLARICINNE WITH MMP2

TABLE-27:DOCKING RESULTS OF MMP-9 AND MMP2

	LIGANDS	TARGET	MOLDOCKSCORE	HYDROPHOBIC INTERACTIONS	HYDROGEN BONDS
1.	(+)-aromadendrin	MMP9	-132.160	Ala 417 Arg 424	
		MMP2	-110.957	His 201 Pro 221	
2.	(+)-Nootkatone	MMP9	-152.830		Arg 424
		MMP2	-141.560	Ile 222	
3.	Aloe emodin	MMP9	-193.126	Leu 418 Met 422 Arg 424	
		MMP2	-179.175	Val 198	
4.	Biochanin-A	MMP9	-199.857	Met 422 Arg 424	
		MMP2	-184.222	Ile 222 Tyr 223	
5.	Calycosin	MMP9	-198.974	Ala 417 Met 422	
		MMP2	-186.722		Leu 164 Ala 165
6.	Chrysin	MMP9	-191.723	Met 422	
		MMP2	-175.119	His 201	
7.	Diosmetin	MMP9	-198.125	Ala 417 Met 422 Arg 424	
		MMP2	-183.107	His 201	
8.	Ellagic acid	MMP9	-167.888	Leu 397 Arg 424	
		MMP2	-155.202	Val 198 Leu 218 Tyr 223	
9.	Epi -Afzelechin	MMP9	-131.372		
		MMP2	-109.628	Leu 164 Pro 221	
10.	Epi -Taxifolin	MMP9	-115.202	Leu 188 Ala 189 Met 422	
		MMP2	-106.948	Ile 222	
11.	Febrifugine	MMP9	-207.866	Tyr 420	
		MMP2	-188.355	Ile 222	
12.	Fisetin	MMP9	2.13392		
		MMP2	-170.523	His 201	
13.	Galangin	MMP9	-192.915	Val 398 Met 422	

		MMP2	-174.02	Val 198 Ile 222 Tyr 223	
14.	Irilin-D	MMP9	-215.133	Leu 418 Met 422	
		MMP2	-199.271	Leu 164 Val 198	Leu 164 Ala 165
15.	Iso-Formononetin	MMP9	-190.001	Leu 418 Met 422 Arg 424	
		MMP2	-178.285		Leu 164 Ala 165
16.	Marmesin	MMP9	-143.022		Ala 189 Glu 402 Arg 424
		MMP2	-131.447		Ala 165 Thr 227
17.	Naphthopyrone	MMP9	-142.205	His 401	
		MMP2	-133.511	His 201	
18.	Naringenin	MMP9	-175.124	Ala 417 Met 422	
		MMP2	-160.998	Val 198 His 201	
19.	Paclobutraazol	MMP9	-182.361	Ala 417 Met 422	Arg 424
		MMP2	-161.481	His 201 Ala 220	
20.	Picralinal	MMP9	-97.3566	Leu 397 Pro 415 Ala 417 Leu 418 Tyr 420 Met 422 Arg 424 Thr 426 Pro 430	Ala 417 Arg 424
		MMP2	-161.481	Ile 222	
21.	Pinocembrin	MMP9	-191.735	Met 422	
		MMP2	-175.114	His 201	
22.	Rhamnetin	MMP9	-217.386	Ala 417 Met 422 Arg 424	
		MMP2	-197.890	Val 198 Ile 222	
23.	Rhein	MMP9	-202.976	Val 398 His 401 Ala 417 Tyr 420 Tyr 423	

		MMP2	-189.155	Val 198	
24.	Uniconazole	MMP9	-192.580	Leu 418 Met 422	
		MMP2	-177.102		

TOP 3 DOCKED STRUCTURES OF BOTH MMP2 AND MMP9

Top 3 docked structures with minimum and stable binding energy of phytochemicals with both the targets MMP9 and MMP2 were selected.

(A1)Rhamnetin: MMP9: MOLDOCKSCORE: -217.386

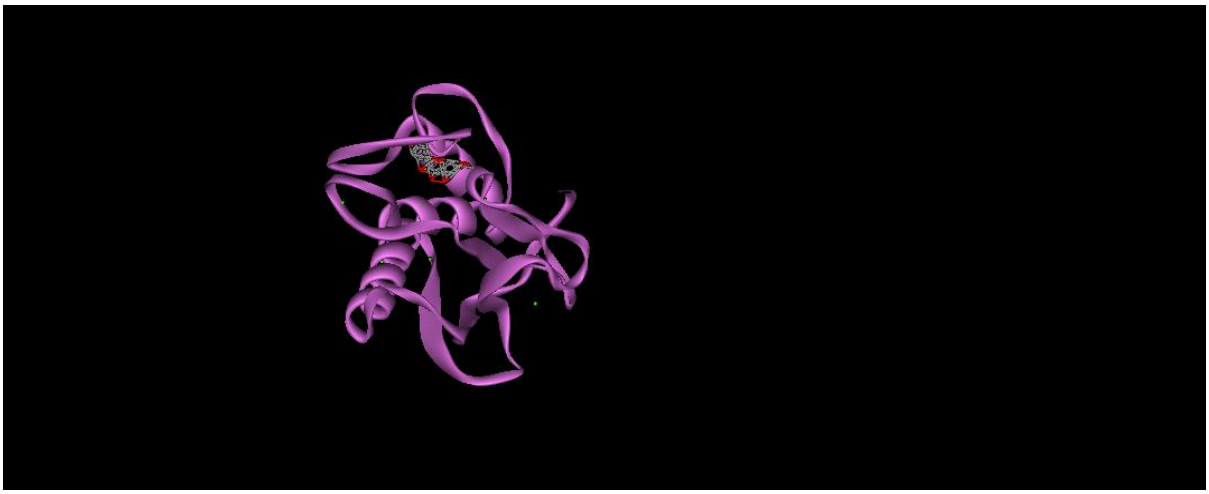


FIG-90A: DOCKED STRUCTURE OF MMP9 WITH RHAMNETIN:purple colour ribbon represents the target protein-MMP9 and red and grey colour represents the lead compound- rhamnetin

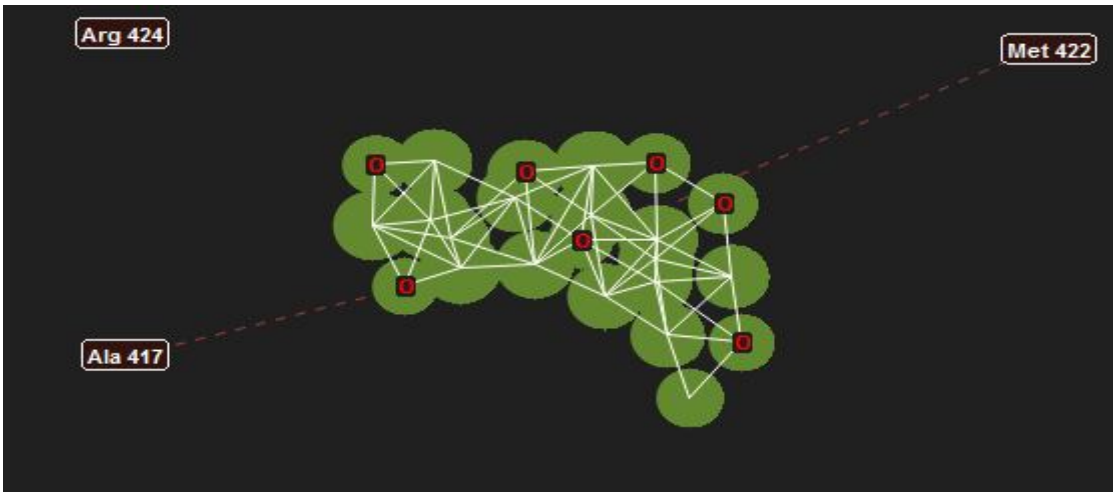


FIG-90B: LIGAND MAP: SHOWING INTERACTIONS OF RHAMNETIN WITH MMP9

(A2)Rhamnetin: MMP2: MOLDOCKSCORE: -197.890

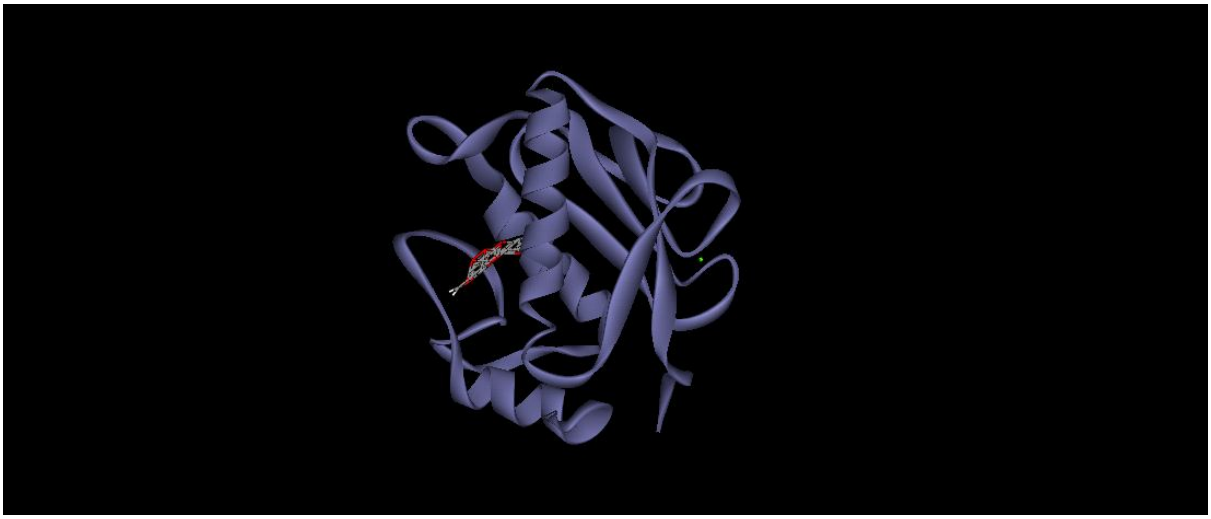


FIG-91A: DOCKED STRUCTURE OF MMP2 WITH RHAMNETIN: blue colour ribbon represents the target protein-MMP2 and red and grey colour represents the lead compound- rhamnetin

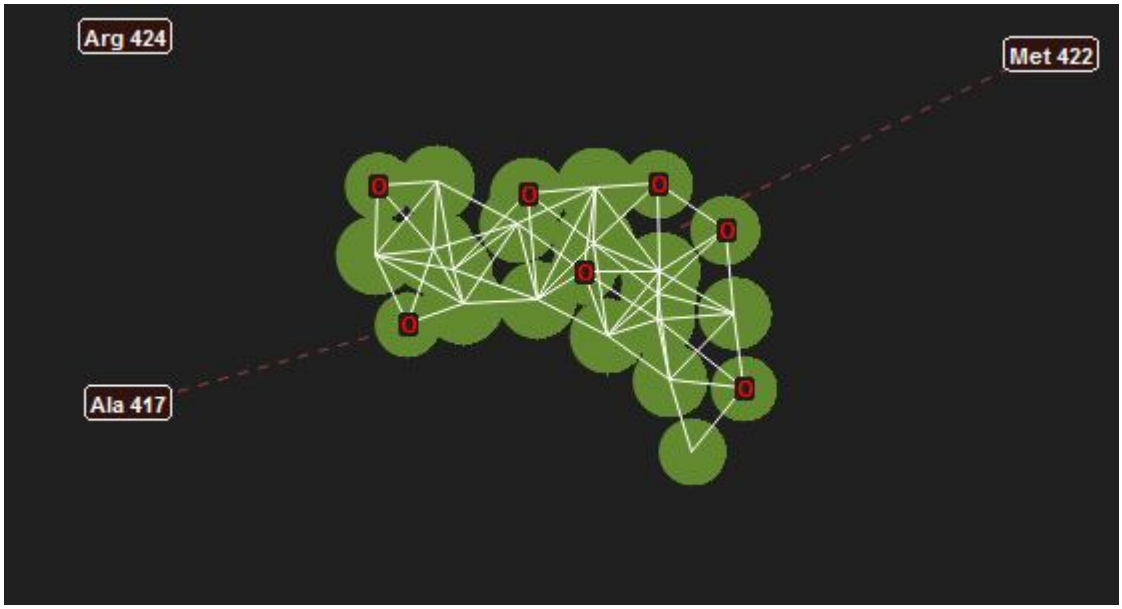


FIG-91B: LIGAND MAP: SHOWING INTERACTIONS OF RHAMNETIN WITH MMP2

(B1) Irilin-D: MMP9: MOLDOCKSCORE : -215.133

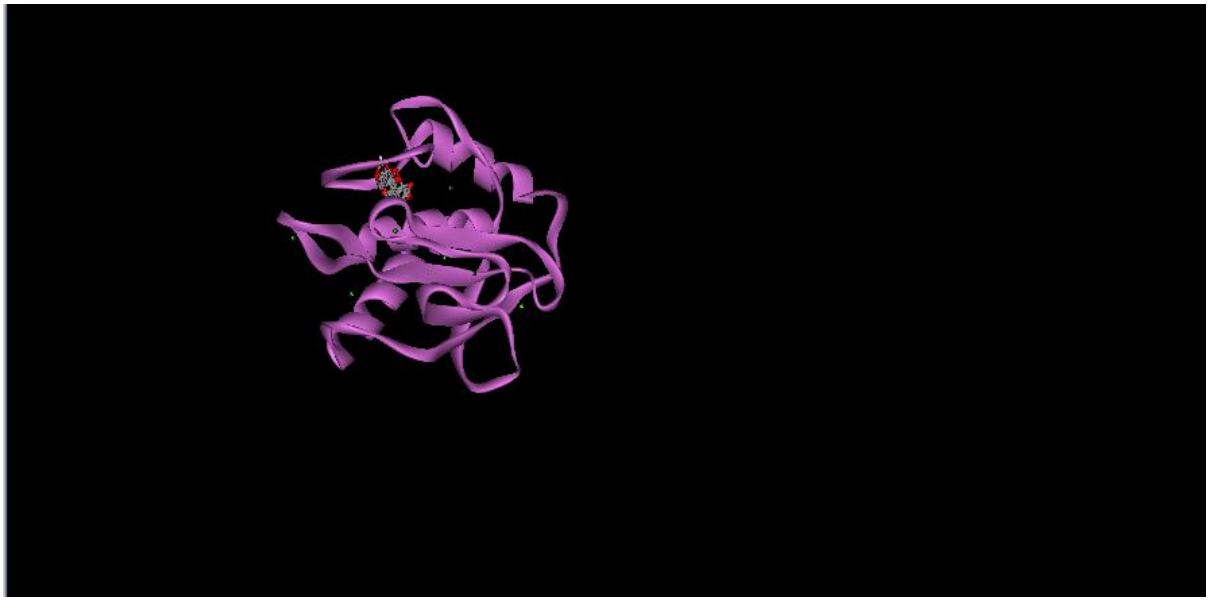


FIG-92: DOCKED STRUCTURE OF MMP9 WITH IRILIN-D:purple colour ribbon represents the target protein-MMP9 and red and grey colour represents the lead compound- Irilin-D

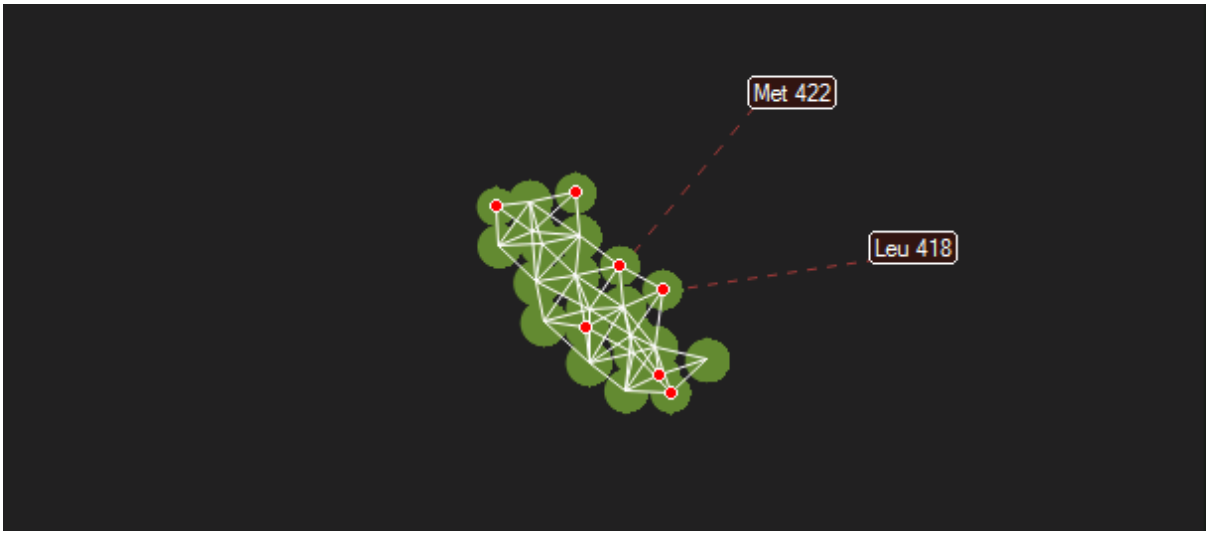


FIG-92: LIGAND MAP:SHOWING INTERACTIONS OF IRILIN-D WITH MMP9

(B2)Irilin-D: MMP2: MOLDOCKSCORE : -199.271

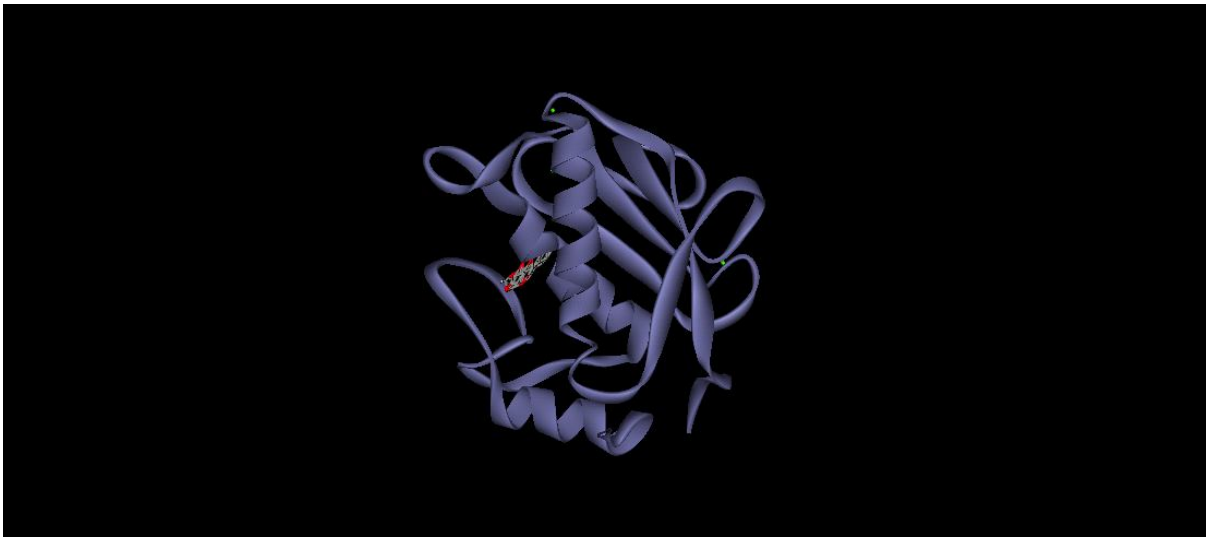


FIG-93A: DOCKED STRUCTURE OF MMP2 WITH IRILIN-D:purple colour ribbon represents the target protein-MMP2 and red and grey colour represents the lead compound- Irilin-D

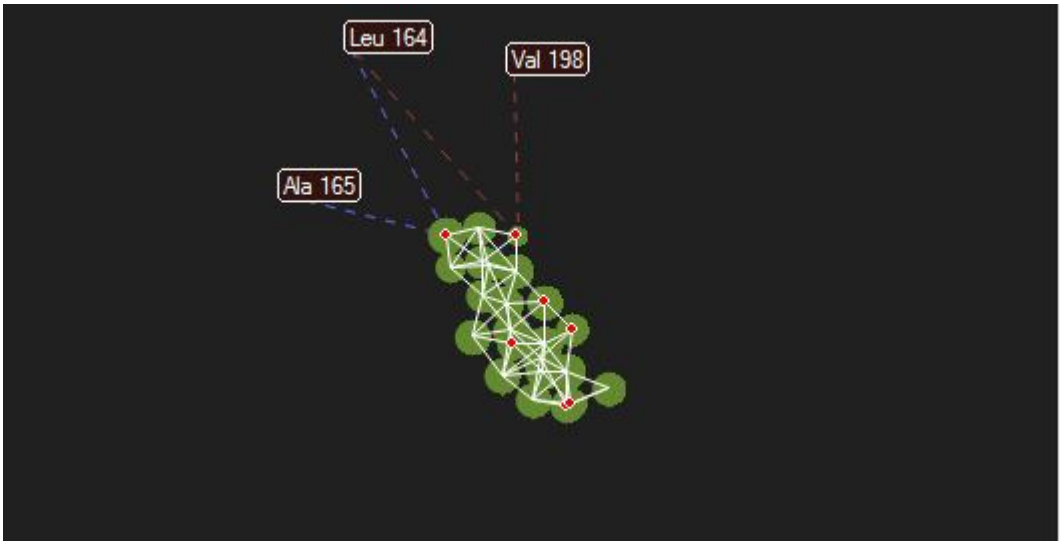


FIG-93A: LIGAND MAP:SHOWING INTERACTIONS OF IRILIN-D WITH MMP2

(C1) Febrifugine: MMP9: MOLDOCKSCORE: -207.866

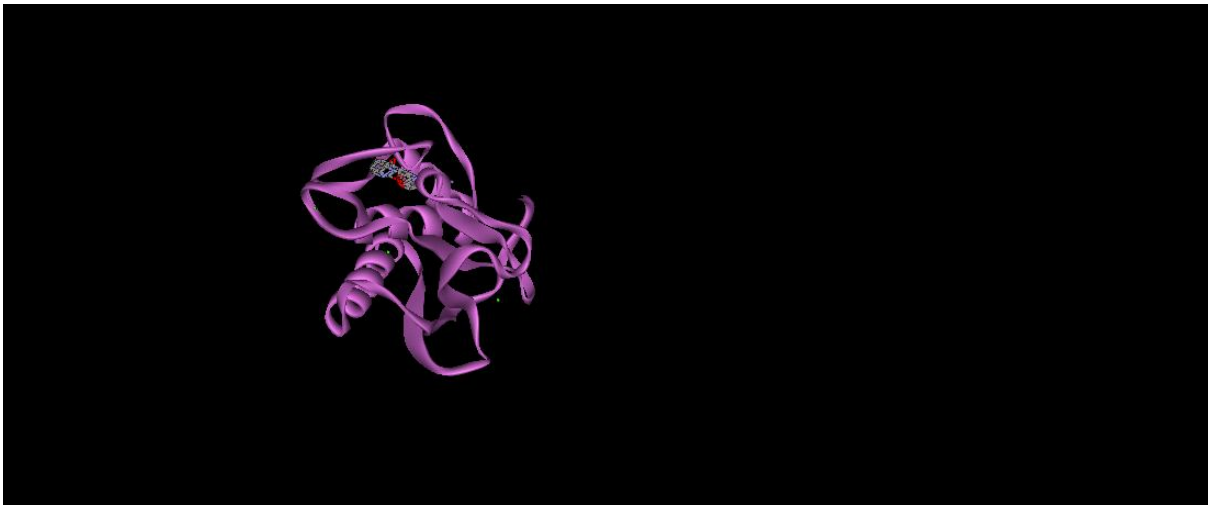


FIG-94A: DOCKED STRUCTURE OF MMP9 WITH FEBRIFUGINE:purple colour ribbon represents the target protein-MMP9 and red and grey colour represents the lead compound- Febrifugine

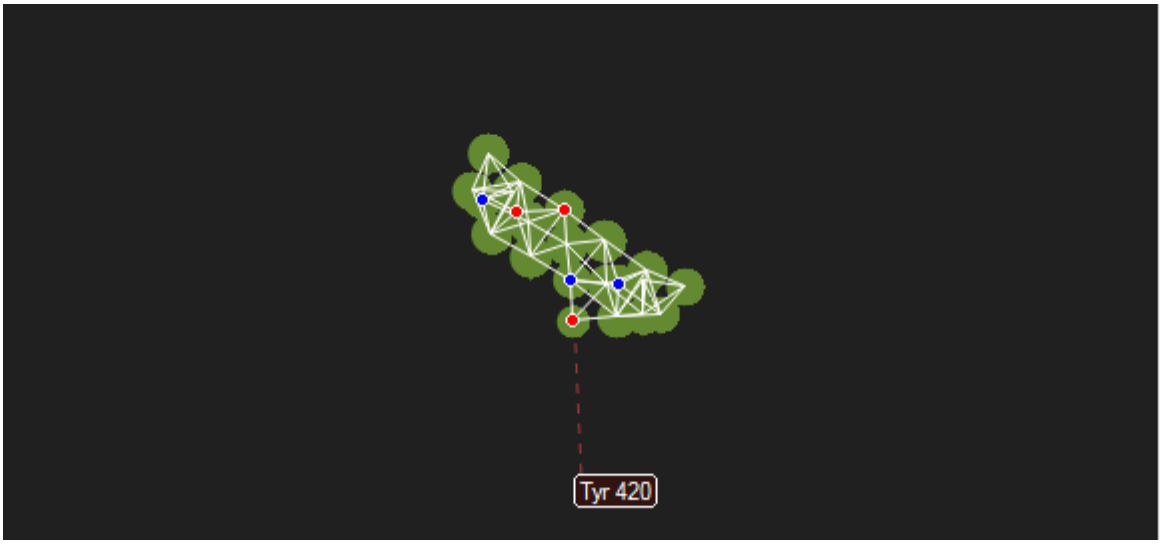


FIG-94B: LIGAND MAP:SHOWING INTERACTIONS OF FEBRIFUGINE WITH MMP9

(C2)Febrifugine: MMP2: MOLDOCKSCORE: -188.355

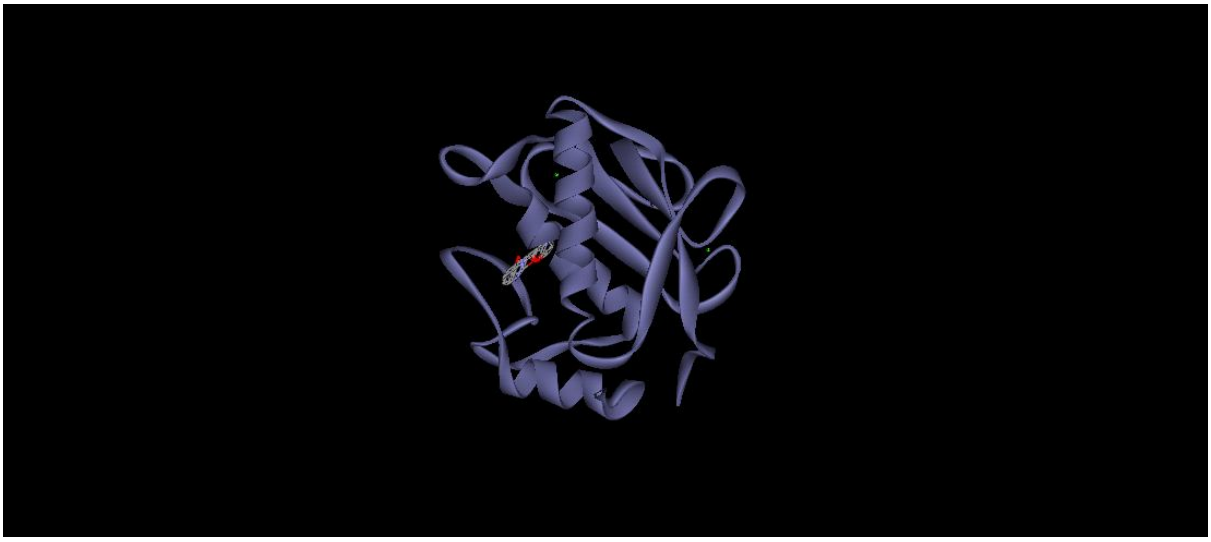


FIG-95A: DOCKED STRUCTURE OF MMP2 WITH FEBRIFUGINE: blue colour ribbon represents the target protein-MMP2 and red and grey colour represents the lead compound- Febrifugine

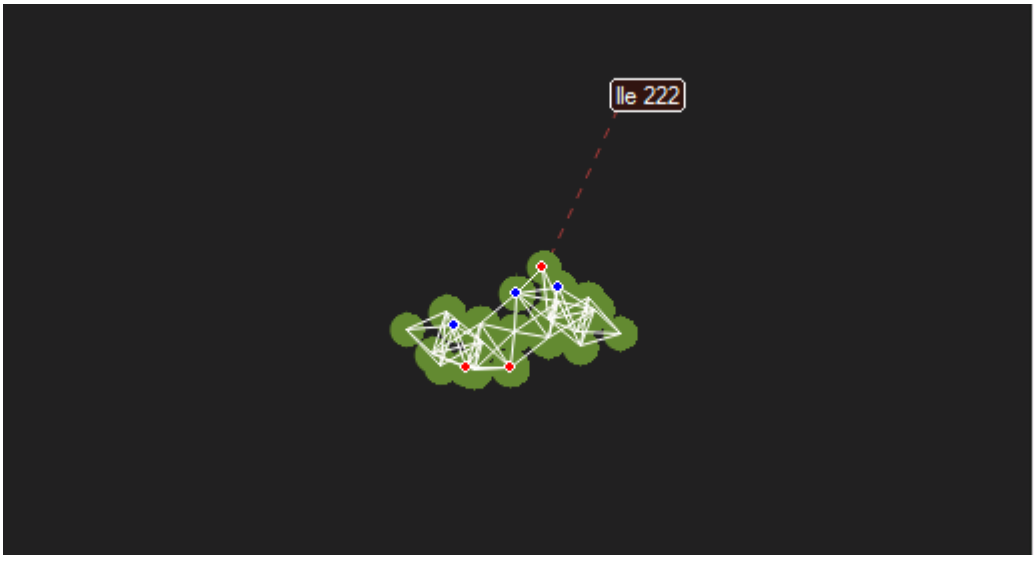


FIG-95B: LIGAND MAP:SHOWING INTERACTIONS OF FEBRIFUGINE WITH MMP2

DISCUSSION

This is an in-silico study, and using various bioinformatics tools, stability and compactness of the targets matrix metalloproteinases MMP9 and MMP2 was checked by molecular dynamics simulation. A natural compounds library of 628 phytochemicals from medicinal plants was generated and virtually screened against both the targets MMP9 and MMP2. Screenedout phytochemicals having binding energy of range "-10 to -14" were selected. Drug like properties of selected phytochemicals were predicted. Selected phytochemicals having good drug like properties were taken further. Pharmacophore models were generated for both the targets matrix metalloproteinases MMP9 and MMP2. Four pharmacophore feature pattern were obtained for MMP9:(a) one hydrophobic feature (b) three hydrogen bond acceptor,for MMP2: (a) two hydrogen bond donor (b) two hydrogen bond acceptor and for MMP2 and MMP9: (a) one hydrogen bond donor (b) three hydrogen bond acceptor.

Successful docking of the three dimensional structure of protein matrix metalloproteinases MMP9 and MMP2 with the selected phytochemicals were obtained. Phytochemicals having druglike properties and lowest binding energy against the target MMP9 were gentiopicroside (moldockscore:-236.394), reticuline (moldockscore:-233.788) and isorhamnetin (moldockscore:-220.525), against the target MMP2 were 16R,19E-isositsirikine (moldockscore:-215.015), Ajmalicine (moldockscore:-192.297) and Scholaricinne (moldockscore:-184.769) and against both the targets MMP9 and MMP2 were Rhamnetin (MMP9: moldockscore:-217.386, MMP2: moldockscore:-197.890), Irilin-D (MMP9: moldockscore:-215.133, MMP2: moldockscore:-199.271) and Febrifugine (MMP9: moldockscore:-207.866, MMP2: moldockscore:-188.355).

This suggests that potential drugs for treatment of MMP9 could be gentiopicroside (chemical constituent *of Centaurium erythraea* and *Frasera caroliniensis*), reticuline (chemical constituent of *Argemone Mexicana* and *ardisia japonica*) and isorhamnetin (chemical constituent of *Calendula officinalis, Chrysanthemum indicum, Red propolis* and *Boerhavia erecta*), of MMP2 could be 16R,19E-isositsirikine (chemical constituent of *Catharanthus roseus*), Ajmalicine (chemical constituent of *Catharanthus, Rauwolfia serpentine*) and Scholaricinne (chemical constituent of *Alstonia boonei*) and of both MMP2 and MMP9 could be rhamnetin (chemical constituent of *Red propolis* and *Ipome*), irilin-D (chemical constituent of *Chenopodium rubrum*) and febrifugine (chemical constituent of *Dichroa febrifuga*).Further in-vitro studies need to be done to establish the efficacy of these phytochemicals against both the targets matrix metalloproteinases MMP9 and MMP2. In this study, it was tried to establish potential treatment of MMP9 and MMP2 related diseases specially cancer, using phytochemicals from medicinal plants using bioinformatics tools. Gentiopicroside from plants *Centaurium erythraea* and *Frasera caroliniensis* and 16R,19E-isositsirikine from plant *Catharanthus roseus* can be used as potential drugs against MMP9 and MMP2 respectively. Rhamnetin from plants *Red propolis* and *Ipome* can be used as a potential drug against both MMP2 and MMP9. As stated earlier, further in-vitro and in-vivo studies could be undertaken to prove the same.

CONCLUSION AND FUTURE PERSPECTIVE

MMPs (a multigenic family of proteolytic, zinc-dependent enzymes), displaying multidomain structures and substrate specificities, are involved in both the turnover and degradation of ECM proteins, processing, activation, or deactivation of a variety of soluble factors. Based on their substrate specificity and domain organization, MMPs may be classified as collagenases, gelatinases, stromelysins, membrane type, matrilysins, and other MMPs. MMPs have attracted more attention because of their roles in diseases. They are believed to participate in embryonic development, arthritis, angiogenesis, morphogenesis, reproduction, tissue resorption and remodeling, tumor growth, progression, invasion, metastasis through breakdown of ECM, cell surface proteins, processing growth factors, cytokines, and chemokines (Sekhon, BS. 2010).

Structural analyses have also led to the design of potent synthetic matrixin inhibitors, some of which have exhibited efficacy in animal models of cancer and arthritis, but unfortunately, clinical trials have shown no significant benefit. Such discrepancies may be due to the fact that the trials were conducted on patients with advanced stages of disease. Other possibilities are that the inhibitor concentration reached in vivo was insufficient to inhibit target enzymes in the tissue or that nontarget enzymes were inhibited.

The design of specific inhibitors for these metalloproteinases is an important future challenge. Such inhibitors are useful not only for gaining insights into the biological roles of MMPs but also for the development of therapeutic interventions for diseases associated with unbalanced ECM degradation.

In this insilico study matrix metalloproteinases MMP2 and MMP9 were selected due their involvement in causing various types of cancer: breast cancer, pancreatic cancer, lung cancer, bladder cancer, colorectal cancer, ovarian cancer, prostate cancer and brain tumor. Human MMPs are generally composed of three domains: the N-terminal propeptide domain, the protease or catalytic domain and the C-terminal, hemopexinlike domain. The structural features most critical in determining MMP substrate specificity and thereby inhibitor specificity are contained within the catalytic domain, although the hemopexin domain is required for binding the triple-helical collagen substrate (Rowsell *et al.*,2002).

The two gelatinases MMP9 and MMP2 contain an additional domain composed of an excursion of three tandem fibronectin repeats from within the zinc-binding catalytic domain. Hydrophobic pockets in the fibronectin domains are likely to be responsible for gelatine binding. The structure of the catalytic domain of human MMP9 (without the fibronectin repeats) consists of a five-stranded β-sheet and three α-helices, as found for other MMPs. The catalytic centre is composed of the active-site zinc ion, co-ordinated by three histidine residues (401, 405 and 411) and the essential glutamic acid residue (402).The conformations of surface loops within the catalytic domains of various MMPs show the largest structural differences (as seen for MMP9 and MMP2).The structures of MMP9 and MMP2 are highly

similar; the main differences occur in the S1 subsite or selectivity pocket. Residues 425–431 in MMP9 (427–433 for MMP2, numbered as for the intact MMP2) form a loop that deviates from the equivalent loop in the MMP2 structures. Thus, both the structural and sequence variability of the S1 loops and the nature of the bound ligand contribute to the observed overall size and shape of the S1 pockets in the different MMPs. A main determinant of the shape of the pocket is the size and orientation of the residue at the end of the pocket (MMP2, Thr426; MMP9, Arg424) (Rowsell *et al.*,2002).

Molecular dynamics simulation was performed to predict the stability and compactness of the structure of matrix metalloproteinases MMP2 and MMP9. The structures were predicted to be stable. Phytochemicals were used to prepare a natural compound library and virtually screened to find a natural potential drug against matrix metalloproteinases MMP2 and MMP9. Screenedout phytochemicals having binding energy of range "-10 to -14" were selected. Drug-like properties of selected phytochemicals were predicted by Lipinski rule of five.Phytochemicals having good drug-like properties were taken further. Pharmacophore models were generated to determine the functional groups necessary for binding of ligands to both the targets matrix metalloproteinases MMP9 and MMP2. Four pharmacophore feature pattern were obtained for MMP9:(a) one hydrophobic feature (b) three hydrogen bond acceptor, for MMP2: (a) two hydrogen bond donor (b) two hydrogen bond acceptor and for both MMP2 and MMP9: (a) one hydrogen bond donor (b) three hydrogen bond acceptor. Selected phytochemicals were docked to the targets matrix metalloproteinases MMP2 and MMP9 to get binding energy and interactions between them. Phytochemicals having minimal binding energy and good hydrophobic interactions for their docked structures were predicted to be the potential drug against the targets matrix metalloproteinases MMP2 and MMP9.

Phytochemicals that could be potential drugs against the target MMP9 are gentiopicroside (chemical constituent *of Centaurium erythraea* and *Frasera caroliniensis*), reticuline (chemical constituent of *Argemone Mexicana* and *ardisia japonica*) and isorhamnetin (chemical constituent of *Calendula officinalis, Chrysanthemum indicum, Red propolis* and *Boerhavia erecta*), against the target MMP2 are 16R,19E-isositsirikine (chemical constituent of *Catharanthus roseus*), Ajmalicine (chemical constituent of *Catharanthus, Rauwolfia serpentine*) and Scholaricinne (chemical constituent of *Alstonia boonei*), and against both the targets MMP2 and MMP9 are rhamnetin (chemical constituent of *Red propolis* and *Ipome*), irilin-D (chemical constituent of *Chenopodium rubrum*) and febrifugine (chemical constituent of *Dichroa febrifuga*).

Further in-vitro studies need to be done to establish the efficacy of these phytochemicals against both the targets matrix metalloproteinases MMP9 and MMP2. For further research structures of these phytochemicals could be manipulated, by arranging the functional groups in three dimensional structure of the pharmacophore model generated in this insilico study, to increase the stability and to minimize the binding energy of the ligand-target complex to design more specific potential drug against the targets matrix metalloproteinases MMP2 and MMP9 with minimal side effects. So new drugs against the cancer could be designed to eradicate this deadly disease.

REFERENCES

- Aggarwal, BB; Ichikawa, H; Garodia, P; Weerasinghe, P; Sethi, G; Bhatt, ID; Pandey, MK; Shishodia, S. and Nair, MG. (2006). From traditional Ayurvedic medicine to modern medicine: identification of therapeutic targets for suppression of inflammation and cancer. Expert Opin. Ther. Targets. ***10(1),*** 87-118.
- Bode, W. and Maskos, K. Matrix metalloproteinases.(2004) in: A. Messerschmidt,W. Bode, M. Cygler (Eds.), Handbook of Metalloproteins, JohnWiley & Sons, Chichester, England. 130–147.
- Butler, GS; Tam, EM. and Overall C. (2004). The canonical methionine 392 of matrix metalloproteinase 2 (gelatinase A) is not required for catalytic efficiency or structural integrity. J. Biol. Chem. ***279***, 15615–15620.
- Chung, L; Dinakarpandian, D; Yoshida, N; Fields, JL; Fields, GB; Visse, R.(2004). Collagenase unwinds triple-helical collagen prior to peptide bond hydrolysis. EMBO J. **23**, 3020–3030.
- Egeblad, M. and Werb, Z. (2002. New functions for the matrix metalloproteinases in cancer progression. Nature reviews. ***2***, 161-174.
- Garodia, P; Ichikawa, H; Malani, N; Sethi, G; Aggarwal, BB. (2007). From Ancient Medicine to Modern Medicine: Ayurvedic Concepts of Health and Their Role in Inflammation and Cancer. Journal of the Society for Integrative Oncology. ***5***, 1-14.
- Gupta, M. and Shaw, BP. (2009). Uses of medicinal plants in panchkarma ayurvedic therapy.indian journal of traditional knowledge. ***8(3)*** ,372-378.
- Jozic, D; Bourenkov, G; Lim, NH; Visse, R; Nagase, H; Bode, W. (2004). X-ray structure of human proMMP-1: new insights into procollagenase activation and collagen binding. J. Biol. Chem. Epub.Dec 15.
- Koc, M; Ediger, D; Budak, F. (2006). Matrix metalloproteinase-9 (MMP-9) elevated in serum but not in bronchial lavage fluid in patients with lung cancer. Tumori. ***92***, 149-154.
- Lang, R; Braun, M; Sounni, NE; Noel, A; Frankenne, F; Foidart, J.M. (2004). Crystal structure of the catalytic domain of MMP-16/MT3- MMP: characterization of MT-MMP specific features. J. Mol. Biol. ***336***, 213–225.

- Langenskiold, M; Holmdahl, L; Falk, P. (2005). Increased plasma MMP-2 protein expression in lymph node-positive patients with colorectal cancer. Int J Colorectal Dis ***20***, 245-252.
- Liu, D; Nakano, J; Ishikawa S. (2007). Overexpression of matrix metalloproteinase-7 (MMP-7) correlates with tumor proliferation, and a poor prognosis in non-small cell lung cancer. Lung Cancer. ***58***, 384-391.
- Maskos, K. (2005). Crystal structures of MMPs in complex with physiological and pharmacological inhibitors. Biochimie. ***87***, 249–263.
- Meena, AK; Bansal, P; Kumar, S. (2009). Plants-herbal wealth as a potential source of ayurvedic drugs. Asian Journal of Traditional Medicine. ***4(4),*** 152-170.
- Mehrotra, NN; Ojha, SK. and Tandon, S. (2007). Drug Development for Cardiovascular Diseases from Ayurvedic Plants. Current R&D Highlights, Jan.-Mar, 1-89.
- Noel, A; Jost, M; Maquoi, E. (2008). Matrix metalloproteinases at cancer tumor-host interface. Semin Cell Dev Biol. ***19***, 52-60.
- Ongusaha, PP; Kwak, JC; Zwible, AJ. (2004). HB-EGF is a potent inducer of tumor growth and angiogenesis. Cancer Res. ***64***, 5283-5290.
- Perigny, M; Bairati, I; Harvey, I. (2008). Role of immunohistochemical overexpression of matrix metalloproteinases MMP-2 and MMP-11 in the prognosis of death by ovarian cancer. Am J Clin Pathol. ***129***, 226-231.
- Pories, SE; Zurakowski, D; Roy, R. (2008). Urinary metalloproteinases: Noninvasive biomarkers for breast cancer risk assessment. Cancer Epidemiol Biomarkers Prev ***17***, 1034-1042.
- Robins, HI; Neill, A; Gilbert, M. (2008). Effect of dalteparin and radiation on survival and thromboembolic events in glioblastoma multiforme: A phase II ECOG trial. Cancer Chemother Pharmacol. ***62***, 227-233.
- Rowsell, S; Hawtin, P; Minshull, CA; Brockbank, MV; Barratt, DG; McPheat, WL; Waterson, D; Henney, AM. and Pauptit, RA. (2002). Crystal Structure of Human MMP9 in Complex with a Reverse Hydroxamate Inhibitor. J. Mol. Biol. ***319***, 173–181.
- Roy, R; Louis, G; Loughlin, KR. (2008). Tumorspecific urinary matrix metalloproteinase fingerprinting: Identification of high molecular weight urinary matri metalloproteinase species. Clin Cancer Res. ***14***, 6610-6617.

- Roy, R; Yang, J. and Moses, MA. (2009). Matrix Metalloproteinases As Novel Biomarkers and Potential Therapeutic Targets in Human Cancer J Clin Oncol. ***27***, 5287-5297.
- Rundhaug, JE. (2003). Matrix Metalloproteinases, Angiogenesis, and Cancer. Clinical Cancer Research. ***9***, 551–554.
- Sekhon, BS. (2010). Matrix metalloproteinases – an overview, dove press Research and Reports in Biology. ***1***, 1–20.
- Sillanpaa, S; Anttila, M; Voutilainen, K. (2007). Prognostic significance of matrix metalloproteinase-9(MMP-9) in epithelial ovarian cancer. Gynecol Oncol. ***104***, 296-303.
- Smith, ER; Zurakowski, D; Saad, A. (2008). Urinary biomarkers predict brain tumor presence and response to therapy. Clin Cancer Res. ***14***, 2378-2386.
- Tam, EM; Moore, TR; Butler, GS; Overall, CM. (2004). Characterization of the distinct collagen binding and cleavage mechanisms of matrix metalloproteinase 2 and 14 (gelatinaseA and MT1-MMP): the differential roles of the MMP hemopexin C domains and the MMP-2 fibronectin type II modules in collagen triple helicase activities. J.Biol. Chem. ***279***, 43336–43344.
- Tian, M; Cui, YZ; Song, GH. (2008). Proteomic analysis identifies MMP-9, DJ-1 and A1BG as overexpressed proteins in pancreatic juice from pancreatic ductal adenocarcinoma patients. BMC Cancer. ***241***, 1-11.
- Visse, R; Nagase, H. (2003). Matrix Metalloproteinases and Tissue Inhibitors of Metalloproteinases : Structure, Function, and Biochemistry. Circ Res. ***92***, 827-839.
- Waas, ET; Wobbes, T; Lomme RM. (2005). Plasma gelatinase activity does not reflect disease activity after operation for colorectal cancer. Oncology. ***68***,256-262.
- Wu, ZS; Wu, Q; Yang, JH. (2008). Prognostic significance of MMP-9 and TIMP-1 serum and tissue expression in breast cancer. Int J Cancer. ***122***, 2050-2056.

APPENDIX

RESULTS OF VIRTUAL SCREENING OF NATURAL COMPOUND LIBRARY.

TABLE-28: BINDING ENERGY OF NATURAL COMPOUND LIBRARY TO THE TARGETS MATRIX METALLOPROTEINASES MMP2 AND MMP9

S.NO	LIGANDS	BINDING ENERGY	
		MMP9	MMP2
1.	(-)-1-(S)-NORCOCLAURINE	-10.4	-9.9
2.	(-)BETA-SANTALENE	-8.0	-7.2
3.	(-)-CENTROLOBOL	-10.3	-9.6
4.	(-)-CUBEBIN	-9.7	-9.5
5.	(-)-EPICATECHIN-3-O-GALLATE	-11.8	-11.5
6.	(-)-MATAIRESINOL	-8.7	-8.4
7.	(+)-3B-ACETOXY-A-MUUROLENE	-2.7	-2.7
8.	(+)-ANWULIGNAN	-10.8	-10.3
9.	(+)-AROMADENDRIN	-11.5	-11.1
10.	(+)-DIHYDROMYRICETIN	-8.6	-8.2
11.	(+)-EPIAFZELECHIN	-8.9	-8.9
12.	(+)-GALLOCATECHIN	-11.6	-11.0
13.	(+)-MORELLOFLAVONE	-10.4	-10.3
14.	(+)-NOOTKATONE	-10.4	-10.1
15.	(+)-SWAINSONINE	-7.4	-7.3
16.	(+)THUJOPSENE	-6.4	-5.8
17.	(1R)-1-ETHOXYETHYL-2-O-ETHYL-A-D-GLUCOPYRANOSIDE	-6.6	-7.2
18.	(2S)-2-AMINO-2-PHENYLETHANOL	-7.4	-7.4
19.	(2Z)-3-(4-HYDROXY-3,5-DIMETHOXYPHENYL)ACRYLALDEHYDE	-6.9	-7.0
20.	(E)-A-BISABOLENE	-8.6	-8.2
21.	(R)-COCLAURINE	-8.7	-9.0
22.	(S)-CHEILANTHIFOLINE	-8.9	-9.6
23.	1,2,3,4-TETRAKIS-O-(3,4,5-TRIHYDROXYBENZOYL)-A-D-GLUCOPYRANOSE	-14.3	-14.2
24.	1,2,6-TRIGALLOYLGLUCOSE	-13.3	-12.6
25.	1,3-DIDENZYLUREA	-9.6	-9.1
26.	1,5-ANHYDRO-D-ALLITOL	-6.2	-6.1
27.	14-DEOXY	-16.4	-15.2
28.	16-HYDROXYTABERSONINE	-7.3	-7.8
29.	16R,19E-ISOSITSIRIKINE	-11.9	-12.3
30.	1-DEOXY-1-[METHYL(OCTANOYL)AMINO]-D-ALLITOL	-8.5	-8.5
31.	1-DODECANOL	-6.0	-5.9
32.	1-ISOPROPYL-2-METHOXY-4-METHYLBENZENE	-7.5	-7.3

33.	1-PHENYL-3-(P-NITROPHENYL)-2,3-DIBROMOPROPAN-1-ONE	-12.5	-11.4
34.	1-TRIACONTANOL	-5.9	-5.8
35.	2-(4-HYDROXYPHENYL)ETHYL-A-D-GLUCOPYRANOSIDE	-9.8	-9.1
36.	2-(DIMETHYLAMINO)PROPIOPHENONE	-7.1	-6.4
37.	2-(ETHYLAMINO)-1-PHENYLPROPAN-1-ONE	-7.3	-6.8
38.	2,3-DIETHYLPYRAZINE	-7.0	-6.9
39.	2,4,5-TRIMETHOXYBENZALDEHYDE	-6.2	-5.8
40.	2,4-DIHYDROXYCHALCONE	-9.7	-9.2
41.	2,5-DIMETHYL PARA ANISALDEHYDE	-7.5	-7.1
42.	2,6-DIMETHOXYBENZOQUINONE	-6.6	-6.2
43.	2-[(2S)-2-OXIRANYL]ETHYL-A-D-GLUCOPYRANOSIDE	-7.7	-7.4
44.	2-ACETAMIDO-1,5-ANHYDRO-2-DEOXY-D-ALLITOL	-6.8	-6.8
45.	2-ACETYTHIOLPHENE	-5.7	-5.7
46.	2-AMINO-3-PHENYL-PROPIONIC ACID	-6.9	-6.8
47.	2-AMINO-4-METHYL-PENTANOIC ACID	-5.4	-5.1
48.	2-BENZOXAZOLINONES	-7.1	-7.0
49.	2-BROMOPROPIOPHENONE	-7.7	-7.6
50.	2-ETHYL-3-METHYLMALEIMIDE	-7.1	-6.8
51.	2-FURANCARBOXALDEHYDE	-5.0	-4.6
52.	2-FURANMETHANOL	-4.9	-4.8
53.	2-HYDROXY-4'-(2-HYDROXYETHOXY)-2-METHYLPROPIOPHENONE	-9.0	-8.5
54.	2-METHYL-3-PHENYLPROPANOATE	-8.5	-8.1
55.	2-METHYLTRYPTOLINE	-9.8	-9.2
56.	2-NONYNE	-5.7	-5.6
57.	2-PHENYLETHYL ACETATE	-7.2	-6.9
58.	2-PROPANONE,1-HYDROXY	-3.7	-3.7
59.	3-(DIMETHYLAMINO)-1-(4-METHOXYPHENYL)-1-PROPANONE HYDROCHLORIDE	-7.4	-7.1
60.	3-BENZYLIDENE CAMPHOR	-5.3	-5.2
61.	3-EPIMASLINIC ACID	-7.4	-8.4
62.	3-GERANYL-4-HYDROXYBENZOATE	-8.6	-8.3
63.	3-METHOXY-4-HYDROXYPROPIOPHENONE	-7.4	-7.0
64.	3-NITRO-4-ANISALDEHYDE	-7.2	-6.8
65.	3-NITROPROPIOPHENONE	-7.8	-7.7
66.	3-THUJANOL	-8.2	-8.0
67.	4-(AMINOMETHYL)-2-METHOXYPHENOL	-6.6	-6.2
68.	4-[(1S)-1-AMINO-2-HYDROXYETHYL]-5-CHLORO-2-METHOXYPHENOL	-6.9	-6.6
69.	4-AMINO-2-METHOXYPHENOL	-6.4	-6.1
70.	4-AMINOPROPIOPHENONE	-7.1	-6.7
71.	4-ANISIC ACID	-6.5	-6.2
72.	4-BENZYLOXY-PROPIOPHENONE	-12.4	11.8
73.	4'-BROMOPROPIOPHENONE	-8.1	-7.9
74.	4H-PYRAN-4-ONE-2,3-DIHYDRO-3,5-	-6.3	-6.1

	DIHYDROXY-6-METHYL		
75.	4-HYDROXYPHENYLACETIC ACID	-6.9	-6.5
76.	4-METHOXYCINNAMONITRILE	-7.2	-6.9
77.	4-METHOXYGLUCOBRASSICIN	-7.7	-7.3
78.	4'-METHOXYPROPIOPHENONE	-7.2	-6.8
79.	4-METHYLPROPIOPHENONE	-7.3	-7.2
80.	4-O-METHYL-D-GLUCURONIC ACID	-7.0	-6.6
81.	4'-PHENYLPROPIOPHENONE	-11.8	-11.3
82.	5,7,3',4',5-PENTAHYDROXYFLAVONE	-12.4	-11.1
83.	5-HTP	-10.4	-9.8
84.	5-HYDROXY-4,7DIMETHOXYY-FLAVONE	-11.3	-10.2
85.	5-METHOXY-N-METHYLTRYPTAMINE	-8.2	-7.8
86.	5-O-METHYL-EMBELIN	-7.1	-7.3
87.	8,11-OCTADECADIENOIC ACID	-6.6	-6.3
88.	8-METHOXYPSORALEN	-6.4	-8.3
89.	9,12,15-OCTADECATRIENOIC ACID	-6.9	-7.1
90.	9-OCTADECENOIC ACID	-6.4	-6.8
91.	A-AMINOPROPIOPHENONE	-7.0	-6.5
92.	A-BERGAMOTENE	-6.1	-6.5
93.	ABRINE	-8.7	-8.5
94.	ACACETIN	-11.4	-10.8
95.	ACACETIN-7-NEOHESPERIDOSIDE	-14.0	-13.6
96.	ACETIC ACID-GERANYL ESTER	-7.0	-6.6
97.	ACETYL EUGENOL	-6.4	-6.8
98.	A-ELEOSTEARIC ACID	-7.4	-6.9
99.	AESCULETIN	-8.7	-8.5
100.	A-GUAIENE	-6.4	-7.0
101.	AJMALICINE	-15.7	-14.0
102.	ALANGIMARCKINE	-8.6	-8.6
103.	ALLANTOIC ACID	-7.5	-7.3
104.	ALLOCIMENE-A	-6.2	-6.1
105.	ALLYL CINNAMATE	-7.4	-7.1
106.	ALOE EMODIN	-13.1	-12.9
107.	ALPHA-CADRENE	-5.9	-7.1
108.	ALPHA-CAMPHOLENALDEHYDE	-5.3	-5.0
109.	ALPHA-CROCIN	-8.6	-10.6
110.	ALPHA-HIMACHALENE	-6.3	-6.1
111.	ALPHA-IONOL	-6.0	-6.7
112.	ALPHA-METHYL-TRANS-CINNAAMATE	-8.3	-8.1
113.	ALPHA-PHELLANDRENE	-7.2	-7.1
114.	ALPHA-SANTALOL	-6.5	-5.4
115.	ALPHA-THUJONE	-8.2	-8.0
116.	ALPINETIN	-11.1	-10.4
117.	AMENTOFLAVONE	-13.5	-13.1
118.	AMFEPRAMONE	-7.1	-6.9
119.	AMPELOPSIN-F	-10.2	-10.3
120.	AMYGDALIN	-10.1	-9.5
121.	ANAGALLIGENIN-A	-7.4	-8.3

122.	ANEMONE-PURPLE-ANTHOCYANIN-3	-11.0	-8.5
123.	ANGOROSIDE-A	-6.9	-6.6
124.	ANGOROSIDE-C	-12.3	12.0
125.	APIGENIN	-9.5	-8.8
126.	APIGENIN-7-GLUCOSIDE	-10.3	-10.0
127.	APIOL	-6.3	-6.3
128.	ARBUTIN	-8.8	-8.7
129.	ARCITIIN	-15.6	16.1
130.	ARECATANNIN-B1	-10.2	10.0
131.	ASARONE-1	-5.8	-5.6
132.	ASARONE-2	-8.7	-8.1
133.	ASIATIC ACID	-7.2	-8.1
134.	ASIATICOSIDE	-18.3	-17.0
135.	ASTRAGALIN	-12.1	-11.7
136.	ASTRAGALOSIDE	-18.4	-22.8
137.	A-TERPINEOL ACETATE	-9.9	-9.4
138.	ATROVIRINONE	-7.5	-8.2
139.	ATROVIRISIDONE	-8.5	-8.8
140.	AUROXANTHIN	-6.9	-9.4
141.	AVENASTEROL	-15.0	-14.2
142.	BACOPASAPONIN-C	-7.5	-7.2
143.	BACOPASIDE-I	-8.6	-8.4
144.	BACOPASIDE-II	-7.9	-7.9
145.	BACOSIDE-A	-8.1	-9.0
146.	BACOSIDE-A3	-8.0	-7.1
147.	BACOSIDE-B	-7.2	-8.9
148.	BAICALEIN	-13.0	-12.3
149.	BAICALIN	-12.5	12.4
150.	BALANOPHONIN	-8.1	-7.7
151.	BARBALOIN	-10.0	-10.3
152.	BAYOGENIN	-7.2	-7.6
153.	BEHENIC ACID	-7.3	-7.1
154.	BENZYL-BETA-D-GLUCOPYRANOSIDE	-9.5	-9.1
155.	BERBERINE	-9.0	-10.3
156.	BERGAPTEN	-6.7	-7.5
157.	BETA-AMYRIN	-7.8	-8.5
158.	BETA-CHAMIGRENE	-5.8	-5.9
159.	BETA-CITRONELLOL	-6.4	-6.1
160.	BETA-CUBEBENNNE	-6.5	-6.8
161.	BETA-D-GLUCURONIC ACID	-6.3	-6.4
162.	BETA-ELEMENE	-6.1	-6.3
163.	BETAINE	-14.6	-15.9
164.	BETANIN	-10.0	-8.3
165.	BETA-SITOSTEROL	-7.7	-7.6
166.	BETA-THUJAPLICINE	-8.0	-7.7
167.	BETA-THUJONE	-8.2	-8.0
168.	BETULINIC ACID	-7.4	-7.6
169.	B-GLUCOGALLIN	-10.7	-10.2

170.	BICYCLOGERMACRENE	-11.4	-11.2
171.	BIOCHANIN-A	-10.9	-10.6
172.	BIS(2-ETHYLBUTYL) PHTHALATE	-8.7	-8.3
173.	BIS[2-(2-BUTOXYETHOXY)ETHYL] PHTHALATE	-8.4	-7.8
174.	BIS[2-(2-ETHOXYETHOXY)ETHYL] PHTHALATE	-8.4	-7.7
175.	BISABOLENE	-6.9	-6.9
176.	BISABOLOL	-10.1	-9.6
177.	B-SESQUIPHELLANDRENE	-8.6	-8.3
178.	BSSG(BETA-SITOSTEROL GLUCOSIDE)	-14.3	-15.0
179.	BUFOTENNIN	-8.6	-7.9
180.	BUTANOIC ACID,2-METHYL-3-OXO-ETHYL ESTER	-5.4	-5.2
181.	BUTANOIC ACID-4-HYDROXY	-4.4	-4.0
182.	BUTYLIDENEPHTHALIDE	-8.4	-8.4
183.	CADINOL	-5.7	-5.6
184.	CAFFEIC ACID	-8.8	-8.4
185.	CALAMENENE	-7.5	-7.8
186.	CALYCOSIN	-11.0	-11.0
187.	CAMPESTEROL	-15.7	-14.7
188.	CANAVANINE	-6.2	-5.9
189.	CANNABIGEROL	-9.3	-9.0
190.	CAR-3-ENE	-5.7	-6.1
191.	CARBAMIC ACID-ETHYL-PHENYL-ESTER	-7.2	-6.7
192.	CARBAMIC ACID-N-HYDROXY-PHENYL-ESTER	-7.5	-7.1
193.	CARVACROL-METHYL-ETHER	-2.2	-2.1
194.	CARVONE	-7.9	-7.5
195.	CASTICIN	-8.7	-8.4
196.	CATALPOL	-14.3	-13.4
197.	CELASTROL	-7.3	-7.8
198.	CHALEPIN	-8.6	-8.7
199.	CHAMAZULENE	-9.3	-8.1
200.	CHANOCLAVINE	-7.2	-7.1
201.	CHANOCLAVINE-I-ALDEHYDE	-7.3	-7.2
202.	CHELERYTHRINE	-9.3	-11.4
203.	CHLOROGENIC ACID	-9.4	-9.6
204.	CHRYSIN	-12.6	-12.1
205.	CHRYSORIOL	-12.0	-11.2
206.	CINNAMONITRILE-3,4-DIMETHOXY	-6.9	-6.6
207.	CINNAMONITRILE-P-DIMETHYLAMINO	-7.5	-7.3
208.	CINNYL CINNAMATE	-13.8	-13.0
209.	CIS-ISOELEMICIN	-6.3	-6.0
210.	CIS-JASMONE	-7.4	-7.3
211.	CIS-LEUCOSCEPTOSIDE-A	-11.1	-12.5
212.	CIS-MARTYNOSIDE	-14.1	-13.2
213.	CIS-SABINOL	-8.2	-8.0
214.	CIS-SABINYL ACETATE	-9.7	-9.3
215.	CISTANOSIDE-C	-12.5	-12.4
216.	CISTANOSIDE-E	-9.4	-9.1

217.	CISTANOSIDE-F	-6.9	-6.6
218.	CITRONELLA	-6.2	-5.9
219.	CITRONELLOL	-6.7	-6.3
220.	CLEOMISCOSIN-A	-8.4	-8.2
221.	COLUMBAMINE	-10.9	-14.5
222.	CONDURITOL	-6.3	-5.7
223.	CONIFERYL ALDEHYDE	-7.0	-6.8
224.	COUMARIN	-7.7	-7.6
225.	CROCETIN	-8.8	-8.1
226.	CUBEBIN	-13.7	-12.4
227.	CUCURBITACIN-B	-9.5	-9.4
228.	CUMIN ALDEHYDE	-8.2	-7.9
229.	CUMINOL	-8.2	-8.0
230.	CURCUMENE	-8.6	-8.2
231.	CURCUPHENOL	-8.4	-7.9
232.	CUSPAREINE	-11.1	-10.7
233.	CUSPARINE	-11.5	-10.6
234.	CYCLOHEXANAMINE-N-3-BUTENYL-N-METHYL	-7.0	-6.8
235.	D-(-)MANNITOL	-5.5	-5.2
236.	DAIDZEIN	-12.6	-11.9
237.	D-ALLITOL	-5.6	-5.4
238.	DAUCOSTEROL	-9.7	-10.7
239.	DECUSSATIN	-10.8	-10.2
240.	DEMETHOXYCUCURMIN	-10.3	-9.4
241.	DIBUTYL PHTHALATE	-11.2	-10.4
242.	DICHLORO-P-CYMENE-(1,10)-PHENANTHROLINE-5-MALEIMIDE	-6.5	-6.6
243.	DIDODECYL PHTHALATE	-9.0	-8.0
244.	DIHYDROCAPSAICIN	-9.1	-8.4
245.	DILLAPIOLE	-7.0	-7.4
246.	DIOSMETIN	-13.4	-12.9
247.	DMT	-8.1	-7.8
248.	D-PINITOL	-6.3	-6.0
249.	D-QUERCITOL	-6.6	-6.6
250.	DULCIN	-7.0	-7.0
251.	DYCLONINE	-9.1	-8.6
252.	ECHITAMINE	-3.2	-3.2
253.	E-DECALACTONE	-7.3	-7.3
254.	ELEMICIN	-6.5	-6.0
255.	ELLAGIC ACID	-13.0	-12.7
256.	ELYMOCLAVINE	-7.1	-7.9
257.	EPHEDRINE	-7.0	-6.7
258.	EPI-AFZELECHIN	-11.3	-10.9
259.	EPICATECHIN	-9.3	-8.7
260.	EPIGALLOCATECHIN-GALLATE	-11.7	-11.4
261.	EPIPINORESINOL	-6.8	-8.3
262.	EPISTEROL	-8.0	-8.7
263.	EPI-TAXIFOLIN	-12.1	-11.6

264.	EPSILON-VINIFERIN	-13.2	-13.8
265.	EREMOLIGENOL	-9.6	-8.1
266.	ERGOSTINE	-10.6	-11.1
267.	ERIODICTYOL	-12.1	-11.7
268.	ERIODICTYOL-7-NEOHESPERIDOSIDE	-14.5	-14.7
269.	ERUCIC ACID	-7.2	-7.1
270.	ESCULETIN-4-CARBOXYLIC ACID-ETHYL-ESTER	-8.1	-7.5
271.	ESCULETIN-4-CARBOXYLIC ACID-METHYL ESTER	-8.4	-7.8
272.	ESTRAGOLE	-6.7	-6.5
273.	ETHYL CINNAMATE	-7.2	-6.9
274.	ETHYL SALICYLATE	-7.0	-6.9
275.	ETHYL-2-METHYL-3-OXO-3-PHENYLPROPANOATE	-7.9	-7.4
276.	ETHYL-4-O-A-D-GLUCOPYRANOSYL-A-D-GLUCOPYRANOSIDE	-7.3	-8.1
277.	ETHYL-A-D-GLUCOPYRANOSIDE	-6.9	-6.6
278.	EUGENOL	-6.6	-6.2
279.	EUGENOL CINNAMATE	-9.6	-9.2
280.	EUPATORIN-5-METHYL ETHER	-10.7	-10.4
281.	FALCARINDIOL	-7.8	-7.2
282.	FARNESOL	-7.4	-7.1
283.	FEBRIFUGINE	-11.6	-11.6
284.	FENCHONE	-5.8	-5.2
285.	FENCHYL ACETATE	-6.0	-5.6
286.	FERULIC ACID	-9.3	-8.9
287.	FESTUCLAVINE	-7.0	-7.9
288.	FESTUCLAVINE(+)	-7.0	-7.9
289.	FISETIN	-12.9	-12.4
290.	FLAVOKAWAINE-B	-8.1	-8.3
291.	FORMIC ACID	-2.7	-2.6
292.	FORMIC ACID-2-PROPENYL ESTER	-3.8	-3.6
293.	GALANGIN	-11.1	-11.0
294.	GALLIC ACID	-7.7	-7.7
295.	GALLOTANNIN	-13.5	-12.9
296.	GAMMA-CURCUMENE	-8.2	-7.9
297.	GAMMA-FAGARINE	-6.9	-7.2
298.	GAMMA-GUAIENE	-6.2	-7.1
299.	GAMMA-TERPINENE	-7.0	-6.7
300.	GENISTEIN	-12.8	-12.2
301.	GENKWANIN	-11.6	-10.2
302.	GENTIOPICROSIDE	-12.4	-11.0
303.	GENTISIC ACID	-7.4	-7.5
304.	GERANIIN	-14.0	-13.4
305.	GERANIOL	-6.6	-6.2
306.	GERANYL FORMATE	-6.5	-6.3
307.	GERANYL ISOVALERATE	-7.1	-7.2
308.	GERMACRENE	-8.5	-8.0

309.	GERMACRENE-D	-6.0	-6.2
310.	GLUCOPUTRANJIVIN	-6.6	-6.7
311.	GLUCURONIC ACID	-5.8	-5.6
312.	GLUTINOL	-8.2	-8.3
313.	GLYCERYL PALMITATE	-9.4	-9.1
314.	GOMISIN-A	-6.0	-5.9
315.	GOMISIN-N	-6.5	-6.7
316.	GROSSAMIDE	-11.6	-11.3
317.	GUAIAZULENE	-9.9	-8.2
318.	GUIAOL	-10.7	-9.4
319.	HARPAGIDE	-6.3	-6.5
320.	HARPAGIDE-7-ACETYL	-13.4	-12.1
321.	HARPAGOSIDE	-8.9	-8.4
322.	HELEURINE	-6.7	-6.4
323.	HELIOTRINE	-7.6	-6.9
324.	HENEICOSANE	-7.0	-6.8
325.	HENISOL	-6.4	-6.1
326.	HENTRIACONTAN-16-ONE	-6.3	-6.1
327.	HENTRIACONTANE	-5.8	-5.9
328.	HENTRIACONTANOL	-7.4	-6.9
329.	HERNIARIN	-8.5	-8.0
330.	HESPERETIN	-12.0	-10.9
331.	HEXADECANOIC ACID	-6.0	-6.3
332.	HEXADECANOIC ACID-2-CHLORO-1-(CHLOROMETHYL)ETHYL ESTERACID	-7.6	-7.6
333.	HEXADECANOIC ACID-ETHYL ESTER	-7.1	-6.9
334.	HEXADECANOIC ACID-METHYL ESTER	-5.9	-6.1
335.	HINOKIFLAVONE	-18.0	-16.9
336.	HINOKININ	-10.5	-9.9
337.	HISPIDULIN	-9.1	-8.9
338.	HOMOCAPSAICIN	-9.1	-8.5
339.	HOMOERIODICTYOL	-12.0	-11.2
340.	HOMOPLANTAGININ	-8.5	-9.5
341.	HOMOVANILLYL ALCOHOL	-7.0	-6.6
342.	HUMULENE OXIDE	-7.2	-7.6
343.	HYDNOCARPIN-D	-13.9	-13.4
344.	HYDROXYTYROSOL	-6.7	-6.6
345.	HYPEROSIDE	-12.5	-12.1
346.	HYPOPHYLLANTHIN	-6.8	-6.9
347.	ICARISIDE	-14.3	-13.3
348.	INDICINE-N-OXIDE	-7.0	-6.6
349.	INOKOSTERONE	-7.2	-8.0
350.	IRILIN-D	-11.4	-11.1
351.	ISOCHLOROGENIC ACID	-10.0	-9.3
352.	ISOCOLUMBIN	-7.6	-7.7
353.	ISO-FORMONONETIN	-10.9	-10.7
354.	ISO-LIQUIRITIGENIN	-9.2	-8.5
355.	ISOMITRAPHYLLINE	-7.3	-7.2

356.	ISOORIENTIN	-8.7	-9.5
357.	ISOPULEGOL ACETATE	-7.0	-6.6
358.	ISO-QUERCITRIN-6-ACETATE	-11.7	-11.3
359.	ISORHAMNETIN	-14.1	-13.2
360.	ISORHAMNETIN-3-0-RUTINOSIDE	-12.0	-11.7
361.	ISO-RHAMNETIN-3-O-NEO-HESPERIDOSIDE	-13.3	-12.5
362.	ISO-SILYBIN-A	-12.5	-13.1
363.	ISOVITEXIN-2-O-BETA-D-GLUCOSIDE	-8.4	-8.6
364.	JATRORRHIZINE	-8.3	-9.1
365.	KAEMPFERIDE	-8.9	-8.5
366.	KAEMPFERITRIN	-14.6	-13.8
367.	KAEMPFEROL	-8.7	-8.3
368.	KAEMPFEROL-3-O-RUTINOSIDE	-12.3	-11.7
369.	KARAKOLINE	-6.8	-7.5
370.	KAURENOIC ACID	-7.3	-6.7
371.	KUKOAMINE-A	-8.1	-7.7
372.	KUMATAKENIN	-9.8	-9.5
373.	LANOSTEROL	-7.4	-9.2
374.	LARICIRESINOL	-11.3	-10.8
375.	L-A-TERPINEOL	-8.2	-7.9
376.	L-B-BISABOLENE	-8.2	-8.6
377.	LEACHIANONE-G	-8.9	-8.7
378.	LEONURINE	-8.7	-8.0
379.	LIGUSTILIDE	-8.4	-8.4
380.	LILAC ALDEHYDE	-6.0	-5.8
381.	LINALOOL	-6.1	-6.3
382.	LIQUIRITIGENIN	-11.7	-10.4
383.	LOGANIN	-9.2	-8.7
384.	LOTAUSTRALIN	-9.6	-9.0
385.	LUCENIN2	-8.4	-7.6
386.	LUTEOLIN	-9.8	-9.3
387.	LUTEOLIN-4-GLUCOSIDE	-14.0	-12.8
388.	LUTEOLIN-7-B-D-GLUCOPYRANOSIDE	-15.9	-14.0
389.	LYONISIDE	-7.7	-8.4
390.	LYSERGOL	-7.1	-8.0
391.	MADECASSOSIDE	-9.3	-8.9
392.	MAGNIFERIN	-7.6	-9.7
393.	MALVALIC ACID	-6.6	-6.8
394.	MARMESIN	-10.5	-10.3
395.	MASLINIC ACID	-7.5	-8.0
396.	MEDICAGENIC ACID	-7.3	-7.8
397.	MEGASTIGMATRIENONE	-5.8	-6.2
398.	METHCATHINONE	-7.0	-6.7
399.	METHYL ANTHRANILATE	-7.8	-7.5
400.	METHYL CINNAMATE	-8.7	-8.3
401.	METHYL EUGENOL	-8.2	-7.9
402.	METHYL GALLATE	-7.2	-7.0
403.	METHYL ISOEUGENOL	-9.4	-9.2

404.	METHYL JASMONATE	-7.7	-7.3
405.	METHYL LINOLEATE	-7.2	-7.0
406.	METHYL PALMITATE	-7.2	-6.8
407.	METHYL STEARATE	-7.3	-6.9
408.	METHYL-3,4-DIMETHOXYCINNAMATE	-7.4	-6.8
409.	METHYL-3-PHENYLPROPANOATE	-7.0	-6.6
410.	METHYL-5-EICOSENOATE	-8.8	-8.0
411.	METHYL-ANTHRANILATE	-7.8	-7.5
412.	METHYLBUTYL-2-METHYLBUTANOATE	-6.4	-6.0
413.	METHYLEPHEDRINE	-7.5	-7.3
414.	MIQUELIANIN	-12.3	-12.3
415.	MITRAPHYLLINE	-7.0	-6.7
416.	MULBERROSIDE-F	-9.2	-10.6
417.	MUZIGADIAL	-6.1	-6.0
418.	MYRCENE	-6.2	-6.1
419.	MYRICETIN	-8.6	-8.2
420.	MYRISTICIN	-7.8	-7.0
421.	MYRISTOLEIC ACID	-7.2	-6.7
422.	NAPHTHOPYRONE	-10.7	-10.5
423.	NARINGENIN	-12.9	-12.4
424.	NARINGIN	-14.4	-14.3
425.	NARINGIN DIHYDROCHALCONE	-8.6	-8.7
426.	NARIRUTIN	-16.2	-15.4
427.	NEOGLUCOBRASSICIN	-7.9	-7.7
428.	NEOHESPERIDOSE	-11.7	-10.3
429.	NEPITRIN	-9.3	-9.8
430.	NEROL	-6.2	-5.9
431.	NEROLIDOL	-8.2	-8.1
432.	NEROLIDYL ACETATE	-6.0	-7.1
433.	NIMBIN	-2.6	-2.6
434.	NIRANTHIN	-7.5	-6.6
435.	N-METHYLEPHEDRONE	-7.5	-7.3
436.	NOBILETIN	-9.6	-10.3
437.	NONACOSANE	-7.3	-7.2
438.	NONACOSANE-10,15 DIOL	-8.5	-8.5
439.	NONACOSANE-10-OL	-8.5	-8.3
440.	NONANAL	-5.6	-5.5
441.	NOPINONE	-2.7	-2.7
442.	N-TRITRIACONTANE	-7.6	-7.1
443.	OCCIDENTALOL-I	-10.3	-10.6
444.	OCCIDENTALOL-II	-10.1	-8.9
445.	OCIMENE	-6.2	-6.1
446.	O-COUMARIC ACID	-7.5	-7.1
447.	O-METHOXY CINNAMALDEHYDE	-6.9	-6.5
448.	ONONIN	-10.3	-11.3
449.	OPHIOPOGONIN-C	-9.0	-7.1
450.	ORIENTIN	-8.4	-8.3
451.	PACLOBUTRAAZOL	-12.8	-12.3

452.	PALMATIN	-7.4	-8.1
453.	PALMATINE	-7.4	-7.4
454.	PATCHOULI ALCOHOL	-5.9	-5.7
455.	PATULETIN	-8.8	-9.1
456.	P-COUMARIC ACID	-7.1	-6.9
457.	P-CRESOL-METHYL ETHER	-2.1	-2.1
458.	PENTAGALLOYL GLUCOSE	-13.3	-12.9
459.	PENTATRIACONTANE	-7.6	-7.1
460.	PEPEROMIN-B	-6.8	-6.6
461.	PERICYCLIVINE	-10.8	-11.5
462.	PERILLA ALDEHYDE	-7.3	-7.0
463.	PERILLA KETONE	-6.6	-6.2
464.	PERILLALDEHYDE	-7.3	-7.0
465.	PERUVIOL	-8.5	-8.1
466.	PETUNIDIN	-11.4	-10.8
467.	P-FLUOROPROPIOPHENONE	-7.1	-6.8
468.	PHENYLACETALDEHYDE	-6.9	-6.8
469.	PHENYLETHYL ALCOHOL	-6.0	-5.8
470.	PHLORETIN	-12.8	-12.1
471.	PHLORIDZIN	-12.3	-11.5
472.	P-HYDROXYBENZOIC ACID	-6.3	-6.2
473.	PHYLLANTHIN	-7.2	-6.5
474.	PHYLLOQUINONE	-10.4	-9.7
475.	PHYTOL	-6.9	-7.1
476.	PHYTOSTEROL	-21.1	-20.1
477.	PICEATANNOL	-10.3	-9.2
478.	PICEID	-11.2	-10.9
479.	PICRALINAL	-10.3	-10.2
480.	PINOCARVONE	-7.0	-6.5
481.	PINOCEMBRIN	-12.6	-12.1
482.	PINOCEMBRIN CHALCONE	-10.3	-9.1
483.	PINOCEMBRIN-7-METHYL-ETHER	-11.2	-10.2
484.	PIPERINE	-10.4	-9.8
485.	PIPERLONGUMINE	-8.8	-8.6
486.	PIPERLONGUMININE	-9.2	-9.0
487.	PLASTOQUINONE	-8.6	-6.2
488.	PLUMBAGIN	-9.1	-9.1
489.	P-MENTHONE	-7.7	-7.4
490.	P-METHOXYBENZYLACETONE	-7.5	-7.0
491.	POLYDATIN	-10.0	-9.0
492.	POMOLIC ACID	-22.9	-21.7
493.	POP	-7.0	-6.8
494.	PRATENSEIN	-10.2	-9.3
495.	PRIMULAVERIN	-8.6	-7.6
496.	PROCYANIDIN-B2	-8.9	-8.0
497.	PROPANOIC ACID	-3.6	-3.6
498.	PROPANOIC ACID-2-OXO-METHYL ESTER	-4.1	-4.2
499.	PROPIOPHENONE	-7.6	-7.3

500.	PROPIOPHENONE-2-AMINO-4'-HYDROXY	-7.3	-6.8
501.	PROPIOPHENONE-4'-FLUORO-3-(4-PHENYLPIPERIDINO)-HYDROCHLORIDE	-11.3	-10.4
502.	PROTOCATECHUALDEHYDE	-6.9	-6.8
503.	PROTOCATECHUIC ACID	-7.2	-7.0
504.	PRUNASIN	-9.9	-9.1
505.	PRUNETIN	-10.1	-9.5
506.	PSEUDO-STRYCHNINE	-9.8	-10.1
507.	PSORALEN	-9.7	-9.3
508.	PULEGONE	-7.7	-7.4
509.	PUTRESCINE	-4.0	-3.8
510.	QUERCETIN-3,4'-DIGLUCOSIDE	-15.1	-14.6
511.	QUERCETIN-3-ARABINOGLUCOSIDE	-12.5	-12.1
512.	QUERCETIN-3-GLUCOSIDE	-11.5	-11.4
513.	QUERCITRIN	-13.0	-12.6
514.	QUINAZOLONE	-7.9	-7.7
515.	QUINIC ACID	-7.4	-7.0
516.	RAPANONE	-7.4	-7.3
517.	RAUBASINE	-7.6	-9.4
518.	RESVERATROL	-11.8	-11.0
519.	RETICULINE	-13.2	-11.7
520.	RHAMNETIN	-11.1	-10.7
521.	RHAMNOCITRIN	-11.0	-10.4
522.	RHEIN	-13.5	-13.2
523.	RHOIFOLIN	-14.3	-14.2
524.	RICINOLEIC ACID	-7.3	-7.2
525.	ROBUSTAFLAVONE	-11.2	-10.2
526.	ROSARIN	-9.8	-8.9
527.	ROSAVIN	-10.1	-9.3
528.	ROSIRIDIN	-8.0	-8.0
529.	ROSMARINIC ACID	-9.5	-9.1
530.	RUTACRIDONE EPOXIDE	-7.8	-8.4
531.	SABINENE	-7.7	-7.8
532.	SAFROLE	-7.4	-7.0
533.	SAKURANETIN	-11.4	-10.8
534.	SALIDROSIDE	-13.2	-11.9
535.	SALVIGENIN	-11.2	-10.3
536.	SANTOLINA ALCOHOL	-8.1	-7.9
537.	SATIVENE	-6.2	-5.7
538.	SCHOLARICINNE	-15.6	-14.1
539.	SCHOLARINE	-0.9	-1.0
540.	SCOPARONE	-8.4	-7.7
541.	SCOPOLETIN	-7.9	-7.5
542.	SCOPOLIN	-9.2	-9.0
543.	SCUTELLARIN	-12.7	-12.7
544.	SEDANOLIDE	-8.4	-8.4
545.	SENINSETIN	-10.3	-9.8
546.	SENKYUNOLIDE-C	-8.5	-7.9

547.	SENNOSIDE-B	-16.2	-16.0
548.	SHYOBUNONE	-11.5	-11.3
549.	SIGMASTA-4-22DIENE-3-ONE	-7.8	-8.8
550.	SINAPIC ALDEHYDE	-6.1	-6.1
551.	SITOSTEROL PALMITATE	-12.2	-11.7
552.	SMILAGENIN	-8.2	-8.2
553.	SOLAVETIVONE	-6.2	-7.1
554.	SOPHORICOSIDE	-18.3	-16.7
555.	SOYASAPONIN-I	-7.8	-7.7
556.	SPERMIDINE	-5.1	-4.9
557.	SQUALENE	-8.5	-8.3
558.	STERCULIC ACID	-6.7	-6.6
559.	STIGMASTEROL	-8.1	-8.8
560.	STIGMASTERYL ACETATE	-7.8	-8.9
561.	STILBENE	-9.0	-8.6
562.	SUBERIC ACID	-8.3	-7.8
563.	SUBSESSILINE	-7.5	-7.2
564.	SUCCINIC ACID	-5.4	-5.4
565.	SUDAN-III	-11.6	-10.8
566.	SULFURIEN	-10.9	-10.2
567.	SUPINIDINE	-5.5	-5.3
568.	SUPININE	-6.6	-6.6
569.	SWERTIAMARIN	-13.4	-11.4
570.	SYRINGALDEHYDE	-6.6	-6.2
571.	SYRINGIC ACID	-6.9	-6.3
572.	TABERSONINE	-7.5	-7.8
573.	TARAXEROL	-8.1	-8.0
574.	TARTARIC ACID	-6.1	-6.1
575.	TEMBETARINE	-8.6	-8.8
576.	TEPHROSIN	-7.4	-8.6
577.	TERPINOLENE	-7.3	-7.1
578.	TERPINYL ACETATE	-9.9	-9.4
579.	TETRAHYDROCURCUMIN	-9.5	-10.4
580.	THEOBROMINE	-8.0	-7.8
581.	THEOPHYLLINE	-7.9	-7.6
582.	THUJ-3-EN-10-AL	-7.8	-7.6
583.	THUJA-2,4(10)-DIENE	-7.8	-7.7
584.	THUJENE	-7.8	-7.7
585.	THYMOL	-7.0	-7.1
586.	TILIROSIDE	-10.5	-9.9
587.	TOLPERISONE	-10.0	-9.3
588.	TORMENTIC ACID	-23.2	-21.5
589.	TRACHELANTHIMIDINE	-5.4	-5.2
590.	TRACHELOGENIN	-10.8	-10.4
591.	TRANS-4-METHOXYCINNAMALDEHYDE	-6.9	-6.6
592.	TRANS-5-O-(4-COUMAROYL)-D-QUINIC ACID	-8.8	-8.7
593.	TRANS-CARVEOL	-7.7	-7.6
594.	TRANSCINNAMIC ACID	-7.0	-6.6

594.	TRIACONTANOL CEROTATE	-3.3	-3.3
595.	TRICINE	-7.6	-7.6
596.	TRIFOLIOL	-8.7	-9.2
597.	TRIGONELLINE	-6.6	-6.4
598.	TRIPTOLIDE	-7.8	-9.1
599.	TUBULOSIDE-E	-11.4	-10.8
600.	TURMERONE	-9.0	-8.3
601.	TUSSILAGONE	-7.7	-6.7
602.	UMBELLIFERONE	-8.5	-8.2
603.	UMCKALIN	-8.0	-7.7
604.	UNCARINE-E	-7.9	-8.1
605.	UNICONAZOLE	-13.1	-13.2
606.	URSOLIC ACID	-7.8	-8.4
607.	UVAOL	-22.0	-20.8
608.	VALENCENE	-10.0	-9.9
609.	VALONEIC ACID	-9.4	-9.3
610.	VANILLIC ACID	-6.1	-6.5
611.	VANILLIC ALDEHYDE	-7.4	-7.3
612.	VANILLYL ALCOHOL	-6.7	-6.4
613.	VERAGUENSIN	-10.7	-10.2
614.	VERATROLE ALCOHOL	-8.1	-7.8
615.	VERNOLIC ACID	-7.5	-7.4
616.	VIRIDIFLOROL	-10.1	-8.9
617.	VITEXIN	-11.0	-10.7
618.	VOACAMIDINE	-7.0	-7.3
619.	VOBASINE	-6.8	-6.7
620.	VOBTUSINE	-15.1	-14.5
621.	VOLEMITOL	-6.1	-5.7
622.	WEDELOLACTONE	-7.6	-9.2
623.	W-HYDROXY-ISO-DILLAPIOLE	-6.9	-7.1
624.	WOGONIN	-13.0	-12.1
625.	WORENINE	-10.1	-10.3
626.	WUWEIZISU-C	-7.3	-6.8
627.	XANTHOTOXIN	-10.6	-10.3
628.	ZEATIN	-9.8	-9.4