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INTERACTION STUDY OF DIMETHYLAMILAMINE OF DOPING COMPOUNDS WITH MONOMERS AS FRAMER OF MOLECULAR IMPRINTED POLYMERS (MIPS)

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The selection of functional monomers for the synthesis of dimethylamilamine (DMAA) molecular imprinting polymers (MIPs) was conducted by non-covalent interaction screening, which formed hydrogen bonding with DMAA, as the template. The analysis of the MIPs template complex was accomplished by quantum-mechanical calculations using Density Functional Theory (DFT) B3LYP with 6-311G basis set based on the Gibbs free energy and binding energy, using Gaussian software. The results revealed the monomers formed hydrogen bonding interaction and the reaction is spontaneous. Optimum binding energy indicated a stable complex formation and well-formed MIPs. The results showed the selected functional monomers, which were acid 2-acrylamide-1-ethanasulphonate (ΔG = –12.06 kcal/mol; ΔE = –27.37 kcal/mol), itaconic acid (ΔG = –11.63 kcal/mol; ΔE = –20.35 kcal/mol), methacrylic acid (ΔG = –5.22 kcal/mol; ΔE = –17.66 kcal/mol), acrylic acid (ΔG = –0.19 kcal/mol; ΔE = –11.36 kcal/mol), N– (2-hydroxyethyl) acrylamide (ΔG = –4.71 kcal/mol; ΔE = –16.66 kcal/mol), methyl 6-O-metacryloil-α-d-glucoside (ΔG = –3.86 kcal/mol; ΔE = –16.59 kcal/mol) and acrylamide (ΔG = –0.94 kcal/mol; ΔE = –12.39 kcal/mol). Theoretically, the seven functional monomers could be selected for consideration in the MIPs synthesis of DMAA with relatively good selectivity.

STUDY OF LISTERIOLYSIN O AS POTENTIAL CANDIDATE FOR BREAST CANCER VACCINE: HOMOLOGY MODELLING AND *IN SILICO* APPROACH

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Breast cancer is the most common form of malignant disease that causes deaths in non-smoking women worldwide. Estrogen receptor α (ERα) has proven to be valuable predictive and prognostic factor in the treatment of breast cancer. Therefore, inhibition of ERα has become the major strategy for prevention and treatment of the disease. The recent study showed that listeriolysin O can induce immune system, thus it can be a cancer vaccine candidate. The purpose of this study was to determine the potential candidate of breast cancer vaccine from peptides of listeriolysin O by *in-silico*. T-cell epitopes is determined by using NetCTL v1.2 and IEDB and then it was selected based on antigenicity by VaxiJen. Three-dimensional model of epitopes were designed and refined by using Modeller, I-Tasser and Rosetta, and validated by using ProSA, QMEAN and MolProbity. Validated structures were docked to H-2K^b and ERα by using DOCK v6. Stability of the best result is tested by molecular dynamics using GROMACS. Results showed that Epitope 3g and 11a have higher affinity than estrogen receptor inhibitor drug (tamoxifen) and other 20 epitopes. Epitope 11a has the highest affinity and has the hydrogen bonding with the same amino acid residues as tamoxifen. In conclusion, epitope 11a is the most potent candidate as prophylactic and therapeutic breast cancer vaccine.

IN SILICO DESIGN OF GADOLINIUM (III)-DIETHYLENE TRIAMINE PENTAACETIC ACID-FOLATE DERIVATIVE AS A CONTRAST AGENT FOR CANCER DETECTION

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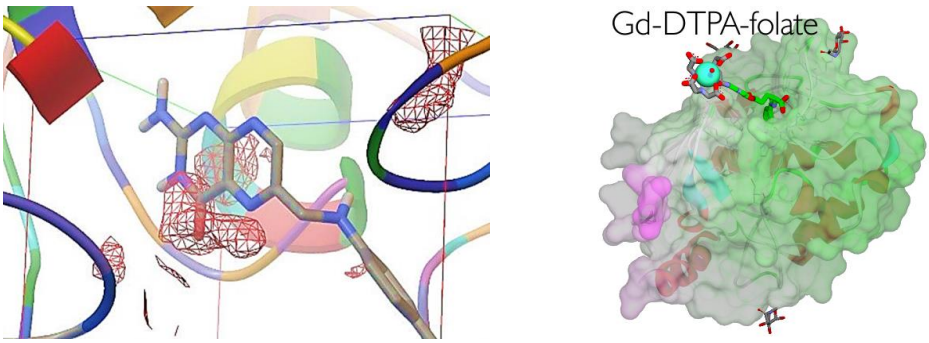
Cancer is a major health problem in the world. Early detection using Magnetic Resonance Imaging (MRI) for the presence of cancer cells could improve the successful rate of treatment. However, a selective contrast agent is required to improve the accuracy of cancer diagnosis. Many cancer cells overexpress the folate receptor alpha (FRA) on its surface. Folic acid binds to the FRA, therefore the covalently attached of folic acid to the contrast agents Gadolinium (III)-diethylene triamine pentaacetic acid (Gd-DTPA) is useful to improve the diagnostic specificity of cancer cells. This work aims to study the molecular interactions between Gd-DTPA-folate and FRA using molecular dynamics simulations and to design a derivative compound with better affinity to FRA using structure-based design method. A crystal structure of folic acid in complex with FRA was used as a template for simulations. The interaction energies were calculated using Molecular Mechanics Generalised Born Surface Area (MM/GBSA) method. As a result, Gd-DTPA-folate has a lower affinity to FRA as compared to folic acid. To improve the affinity of Gd-DTPA-folate to FRA, a derivative compound was designed based on the atomic affinity maps of the FRA binding site. An addition of a formyl group at the pterin ring of folic acid had strengthened the affinity to FRA to –60 kcal/mol, as compared to that of Gd-DTPA-folate (–42 kcal/mol). This result is expected to be useful in the development of specific contrast agent for cancer.



(a) (b)

Fig. 1: (a) Affinity map of oxygen atom (red-colored sphere) at the binding site of folate receptor alpha and (b) binding mode of interaction between Gd-DTPA-folate and folate receptor alpha.

IN SILICO STUDY OF THE STRUCTURE OF A-AMYLASE *SACCHAROMYCOPSIS FIBULIGERA* R64 MUTANT WITH INCREASED STARCH ADSORPTIVITY

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α-Amylase is one of the important enzymes for starch processing due to its wide application. It is known the starch processing requires high energy. α-Amylase with high starch adsorptivity is expected to decrease the cost of process especially during gelatinisation using high temperature. α-Amylase *Saccharomycopsis fibuligera* R64 (Sfamy R64) is a locally sourced enzyme with high amylolytic activity but low starch adsorptivity. Computer-aided molecular design has been useful to develop new protein with desired properties, e.g. to improve substrate adsorptivity by introducing surface binding site (SBS) to the structure of enzyme. This study aimed to design the mutant of Sfamy R64 with increased starch adsorptivity using computational methods. The structure of Sfamy R64 was modeled and compared to that of α-amylase *Aspergillus niger* as the positive control. Structural dynamics of enzyme were studied using molecular dynamics simulation. Enzyme's affinity on the substrate was evaluated using MM/GBSA method. The results showed that Sfamy R64 lacks of surface binding site (SBS). Furthermore, mutations of S382Y/S385W were introduced to the structure of Sfamy R64. Molecular dynamics simulation revealed that the structural behaviour of this mutant in SBS region was comparable to that of positive control. The interaction energies of positive control and the mutant towards maltose were also similar: –21.52 and –22.31 kcal/mol, respectively.

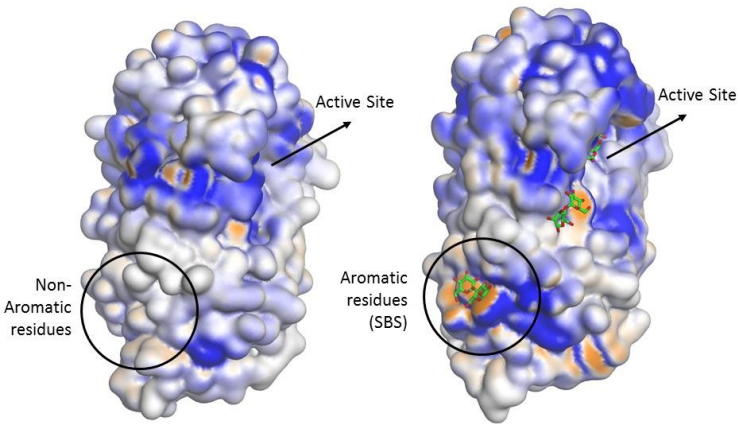

Fig. 1: Solvent surface of Sfamy R64 (left) and *A. niger* α-amylase (right) based on the aromaticity of residues (brown color = aromatic, face-side; blue color = aromatic, white color = non-aromatic).

QUANTUM MECHANICS STUDY OF CADMIUM(II)-TRIPEPTIDE COMPLEXES BY USING DOUBLE ZETA AND TRIPLE ZETA BASIS SETS

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Cadmium(II) detection in aqueous medium is an important step in the attempt to avoid human exposure to the extremely toxic metal. It is believed that one of the significant detection processes of cadmium(II) can be performed by using biosensor with the help of a tripeptide as the biological material. However, proper tripeptides for cadmium(II) detection are still unknown since there is not enough information about the interaction between cadmium(II) and the tripeptides in literature. Computational approaches such as quantum calculations can be employed to understand the electronic interaction between cadmium(II) and the tripeptides. By observing the energy change of the system, the binding energy between cadmium(II) and tripeptide can be predicted. To investigate the energy loss after forming the complex, the energy of cadmium(II), the peptide and the complex were calculated in vacuum. The procedure was repeated using Polarizable Continuum Method (PCM) in which water was chosen as the solvent. From the quantum calculations using the triple zeta basis sets in combination with Minnesota 06 (M06) functional, it can be suggested that Cysteine-Serine-Cysteine (CSC) can act as a potential tripeptide for cadmium(II) detection due to its higher tendency towards capturing the metal ions compared to the other observed 20 tripeptides, with the energy difference of –0.32 kJ/mol in the presence of water and –87.68 kJ/mol in vacuum. The results suggested that CSC peptide could serve as biological material in the cadmium(II) biosensor application.

SIRT1 ACTIVATOR: STRUCTURED-BASED PHARMACOPHORE DESIGN, MOLECULAR DOCKING, MOLECULAR DYNAMICS SIMULATION AND VIRTUAL SCREENING OF INDONESIA'S MEDICINAL PLANTS DATABASE

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In mammals, there are seven sirtuin (SIRT1–7) present. Sirtuin is a class III protein histone deacetylase family. SIRT1 is a deacetylase isoform that is nicotinamide adenine dinucleotide $(NAD)^+$ – dependent with UniProt accession code Q96EB6 (747 residues). SIRT1 activator has been implicated in diseases such as type 2 diabetes, regulating aging process, inflammation. In this research, pharmacophore models were developed using LigandScout program. Molecular docking was performed using AutoDock4 and molecular dynamics simulation using Amber12. Virtual screening was also run against an Indonesian medicinal plants database (http://herbaldb.farmasi.ui.ac.id) to find active compounds that have similar pharmacophore features with the ligand coded as 4TO, an SIRT1 activator (Protein Data Bank [PDB] ID: 4ZZI, 4ZZJ, 4ZZH). The result obtained highlighted that the best candidate for SIRT1 activator is mulberrin.

PROTON TUNNELLING IN REACTION OF BORONIC ACIDS WITH DIOLS

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Boronic acids are well known for being highly reactive towards diol containing compounds which would make them a good sensor for measuring blood glucose concentration. Various computational and experimental studies have been carried out on these molecules to understand the factors affecting their selectivity and reactivity. In this study, we use computational tools to model these molecules and calculate their thermochemical properties. The purpose of this research is to understand the effect of electronegativity on the reactivity of boronic acids towards diols. Hence, we used four different electronegative R-groups, i.e. H, I, Cl and F on boronic acid. Using the transition state theory, we calculated the rate of the reaction of boronic acid with diol. Since this reaction is dominated by proton transfer mechanism, we have speculated the probability of proton being tunnelled through the barrier. Therefore, we have also calculated the tunnelling factor for this reaction in various temperatures from 50.15 to 308.15 K. A smooth divergence from classical behaviour (linear) to quantum behaviour (curved) at 253.15 K is observed in the Arrhenius plot. This is a rather high temperature to observe quantum behaviour. A large kinetic isotope effect is also observed in all plots in the same temperature. The results of this study indicate the high tunnelling probability in this reaction which might enable us to induce tunnelling in this reaction by changing the R-group.

MOLECULAR DOCKING BASED CYTOTOXIC COMPOUND ISOLATION: A STUDY ON ONE OF BEGONIA PLANTS GROWING IN CENTRAL SULAWESI, INDONESIA

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Molecular docking based cytotoxic compound isolation has been applied to isolate the secondary metabolite from one of Begonia plants growing in Central Sulawesi, Indonesia. The structure elucidation had been performed based on nuclear magnetic resonance (NMR) spectral data to assign the compound as 2-O-β-glucopyranosil cucurbitacin D. The obtained spectral data was also in accordance with reference. The cytotoxicity test against HeLa cell lines showed moderate activity (IC_{50} of 31.88 ± 23.88 µg/ml). Molecular docking study on Epidermal Growth Factor Receptor-Tyrosine Kinase (EGFR-TK) protein by PLANTS1.2 exhibited ChemPLP score of –95.9108. Meanwhile, the native ligand (erlotinib) has a ChemPLP score of –89.1967. The calculated docking energy and binding of interaction might be correlated with the cytotoxic activity of the compound.

IN SILICO STRUCTURAL HOMOLOGY MODELING ON ENVELOPE (E) GLYCOPROTEIN OF DENGUE VIRUSES (DENV) TYPE 1–4

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Dengue infection has become global epidemic health problem. Dengue virus (DENV) is transmitted into humans by the mosquitoes *Aedes aegypti* and Aedes albopictus, via infected human blood. The specific drugs for treatment and effective vaccination for prevention of dengue infection against four types of DENV serotypes (DENV1, DENV2, DENV3 and DENV4) are currently unknown. The envelope (E) glycoprotein is responsible in viral attachment to cell surface receptors, fusion with endosomal membranes and entry into target cells, thus it is important for neutralising DENV viruses. Homology modelling on E glycoprotein of dengue viruses (DENV) Type 1–4 was constructed by using SWISS-MODEL database. The target sequence retrieved from Clustal Omega server was used to identify suitable template sequence. The homology model of three dimensional structures on E glycoprotein of each DENV serotype was evaluated and checked for quality estimation by using PROCHECK, VERIFY 3D and ERRAT server. By using PDBeFold, multiple structure alignment was done to identify similarity of each DENV serotypes models. Homology model of three dimensional structures on E glycoprotein of each DENV serotype was successfully obtained. DENV1 showed the highest quality structure while DENV2 was *vice versa*. Based on multiple structural alignments, DENV2 and DENV3 indicated the highest sequence similarity.

The structural alignment showed that DENV2 and DENV3 had the lowest RMSD score, with the score value of 1.325 and the highest Q score of 0.4433. In contrast, DENV1 and DENV4 had the highest RMSD score, with the score value of 3.146. Based on Q score result above, the lowest Q score is between DENV1 and DENV4, which is 0.193 and the highest value is between DENV2 and DENV3, which is 0.350. This means that the homology model structure of DENV2 was the most similar and closely related to the other three homology model structures of DENV serotypes.

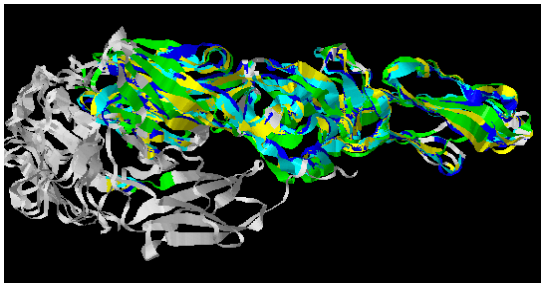

Fig. 1: Multiple structural alignments using PDBeFold. Homology model E glycoprotein of DENV1 (green), DENV2 (blue), DENV3 (light blue) and DENV4 (yellow).

In conclusion, the homology model of three dimensional structures on E glycoprotein of each DENV serotype was successfully obtained and can be used as a guiding point for further investigations on E glycoprotein of dengue viruses (DENV) Type 1–4.

MOLECULAR DOCKING OF CHALCONE DERIVATE AS A NOVEL THERAPEUTIC COMPOUND TARGETING BREAST CANCER

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Breast cancer is the most common malignancy among women in the Asian society and over the past decades its incidence rates have increased steadily. Breast cancer is a cancer caused by uncontrolled cell growth of breast tissues. One of the most common triggers of breast cancer is over expression of estrogen receptor alpha (ERα). Potential agents isolated in the form of natural compounds are among the most successful candidates for therapeutic development. In the previous study, 2',4'-dihydroxy-6-methoxy-3,5-dimethylchalcone has been isolated as an active compound from the *Eugenia aquea* leaves that has responsibility for that activity. This compound was examined for its inhibitory activity against the MCF-7 cell lines using the MTT assay and its ability to induce apoptotic mechanism by means of poly(ADP-ribose)polymerase(PARP) protein activation. The *in silico* study involved the superimposition of 2',4'-dihydroxy-6-methoxy-3,5-dimethylchalcone with tamoxifen. This compound did not have a tail chain at position 2, thus could be the cause for its activity to be lower than tamoxifen. In this study, this compound has been modified to increase selectivity and activity against the human estrogen alpha using rational drug design. The aim of this study is to find the best chalcone derivative that binds well with the estrogen receptor as a replacement for the therapy using tamoxifen. One of the efforts is modification of the structure by replacing the carbonyl group as the important pharmacophore with other possible functional groups and then determines the binding affinity of these derivatives through computer aided drug design tools. Drug design approaches used in this study were Structure-Based Drug Design (Molecular Docking) and Ligand-Based Drug Design (Pharmacophore Modelling). Characteristic interactions between tamoxifen and ERα were determined and the differences in the binding modes between tamoxifen and chalcone were observed. Tamoxifen has a hydrophobic tail that made hydrophobic interaction with the amino acids Leu525, Ala350, Trp383 and these interactions could to the high binding affinity of tamoxifen as compared to the chalcone derivatives. The pharmacophore study results showed that the compound has completed features as well as tamoxifen. Our modification of chalcone focused on the carbonyl group, because this group is absent in tamoxifen. Molecular docking was done using AutoDock 4.2, while pharmacophore modelling using LigandScout. ChalcDer1 was one of the chalcone derivatives obtained from the drug design protocol. ChalcDer1 has a free energy of binding of –10.45 kcal/mol, while tamoxifen was –11.04 kcal/mol. Amino acids that bind with ChalcDer1 were Leu525, Met343, Thr347, Leu346, Ala350, Leu349, Leu387, Glu353, Arg394, Met388 and Leu391.

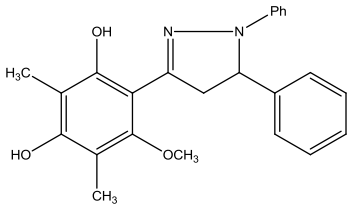

Fig. 1: ChalcDer 1.

ANTIHEPATITIS C VIRUS POTENTIAL OF MALAYSIAN FUNGAL ISOLATE CRUDE EXTRACTS

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Hepatitis C virus (HCV) is a global burden causing chronic liver diseases which effects an estimated population of 150 million worldwide. Although no vaccine is available for HCV, standard treatment procedure involves the usage of Peg-IFNα in combination with ribavirin or combination of ribavirin with either boceprevir or telaprevir. However, adverse effects are prevalent in almost half of the patients receiving the drugs. In the search for a more reliable and better antiviral drug, 110 crude extracts from various Malaysian fungal isolates were tested for the antiviral property against HCV NS3/4a protease. To the best of our knowledge, this is the first reported screening of Malaysian fungal isolates extract for HCV antiviral activity. Results from HCV protease assay kit revealed that eight of the extracts comprising methanolic and ethyl acetate fractions showed more than 95% inhibition in comparison to quercetin (positive control). An extract coded as P72 WPAA EA showed inhibition in a dose dependent manner. Further studies on the isolation and identification of the compound posing the antiviral activity are required. This study could be a benchmark for determining possible antiviral activity against other virus of the Flaviviridae family.

IDENTIFICATION OF BIOACTIVE COMPOUNDS FROM NATURAL PRODUCTS AS POTENTIAL CHOLINESTERASE INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a neurodegenerative disorder in which increasing number of nerve cells degenerate and dies along with loss in synapse. This loss of basal forebrain cholinergic cells causes a great reduction of acetylcholine, resulting in the cognitive impairment associated with AD. Acetylcholinesterase (AChE) suppression by cholinesterase inhibitors has been shown to raise the level of acetylcholine by allowing acetylcholine to have a longer duration to interact with its receptors, thus send more signals throughout the nervous system. This research aims to study and identify cholinesterase inhibitors from natural products as potential inhibitors for the AD treatment. Molecular docking of AChE enzyme with approximately 4000 compounds deposited in NADI database has been performed to blindly predict the possible molecules with the lowest binding energy for AChE inhibition. There are six plants identified from the virtual screening, three plants of them (*Clitoria ternatae, Garcinia mangostana and Centella asiatica*) were selected for the *in vitro* enzyme inhibition assay and *in vivo* animal studies. Further work on fraction isolation by high performance liquid chromatography (HPLC) will be carried out to extract and identify the bioactive compounds in the plants.

ANNOTATION AND ANALYSIS OF COMPLEX BASE INTERACTION CLUSTERS IN RIBONUCLEIC ACID THREE DIMENSIONAL STRUCTURES

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Hydrogen bonds play an important role in stabilising ribonucleic acid (RNA) three-dimensional (3D) structure. Previous studies have shown that large hydrogen bond base interactions clusters play structure stabilisation roles and may also have specific mechanistic functions such as to bind proteins or ligands. These interaction clusters may also be potential 3D motifs. Using an in house developed application, COnnection tables Graphs for Nucleic ACids (COGNAC), we annotated RNA base interaction clusters that were interconnected by at least one hydrogen bond. For this work, we focused on complex clusters that initially consisted of six bases used as search queries. The annotated clusters were classified according to the RNA structures they were found in. Our annotations include previously unreported complex base interaction clusters of 13 bases that present in a PreQ1 Class 1 riboswitch, which is the largest complex base interaction cluster we have identified thus far. The interaction of 13 bases may provide general structural stabilization to the ligand-binding site. The second largest RNA base interaction cluster of 12 bases annotated in a Lysine riboswitch may provide general structural stabilisation to the whole structure and may also be involve in temperature. The larger ribosomal RNA (rRNA) structures were found to contain complex base interaction cluster of 11 bases that may provide general structural stabilisation. It is clear that the size of the RNA structure is not necessarily an indicator of the complexity of base clusters interconnected by hydrogen bond networks that can be present.

ESSENTIAL OIL COMPOSITION OF *ACHILLEA SCHISCHKINII* SOSN. (ASTERACEAE) FROM TURKEY

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The genus *Achillea* is represented in Turkey by 42 species and most of them are used in Turkish folk medicine. Dried aerial parts of *Achillea schischkinii* Sosn., an endemic species of Turkey, collected from Elazig in Turkey were hydrodistilled to obtain an essential oil that was then analysed by gas chromatography (GC) and gas chromatography mass spectrometry (GC/MS). 59 components representing 86% of the oil were characterised 1,8-cineole (13.5%), linalool (10.5%), terpinen-4-ol (5.7%) and camphor (4.8%) being the main constituents.

COMPUTATIONAL STUDY ON REACTIVITY AND STABILITY OF COMPLEX *MESO*-TETRAKIS(1,2-DIMETHYLPYRAZOLIUM-4-YL)PORPHYRIN WITH LEAD, CADMIUM AND MERCURY

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The development of porphyrin as an analytical reagent is still growing. Porphyrin derivative compound is an important reagent candidate in analytical chemistry to be applied to separate various kinds of metal ions. Lead (Pb), cadmium (Cd) and mercury (Hg) are some examples of heavy metal which have a role as contaminants and of considerable concern because of their effect on human health such as Parkinson diseases, Alzheimer diseases and failure of several organs. The aim of this research was to study the reactivity and stability of porphyrin derivative with lead, cadmium and mercury in terms of computational study and compared with the binding constants determined by the experimental method. Interaction of meso-tetrakis (1,2-dimethylpyrazolium-4-yl)porphyrin (TDMPzP) with lead, cadmium and mercury have been performance computationally using DFT method. DFT global chemical reactivity descriptors (chemical hardness, electronic chemical potential and electrophilicity) were calculated and used to predict their relative stability and reactivity. The binding constants of the complexes were determined using UV-Vis titration method.The results show that Cd-TDMPzP has a lower energy than other complexes. The electronic chemical potential and electrophilicity of Pb-TDMPzP, Hg-TDMPzP and Cd-TDMPzP decreases, while their chemical hardness increases. The type of metalloporphyrin formation of Cd-TDMPzP is regular (planar) metalloporphyrin, while Pb-TDMPzP and Hg-TDMPzP form sitting-atop metalloporphyrins. The binding constant of Cd-TDMPzP is higher than the others. In conclusion, complex Cd-TDMPzP is the most stable and least reactive complex with the electronic chemical potential, chemical hardness and electrophilicity of –0.447, 0.052 and 1.921 eV, respectively and with the binding constant of 5.07×10^7 M^{-1}.

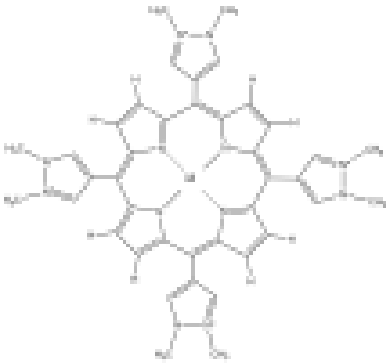

Fig. 1: Chemical structure of meso-tetrakis(1,2-dimethylpyrazolium-4-yl)porphyrin (TDMPzP) with M = H_2 (for free-base porphyrin), Pb^{2+}, Cd^{2+} and Hg^{2+}.

BIOINFORMATICS STUDY OF m.9053G>A MUTATION AT THE ATP6 GENE IN RELATION WITH TYPE 2 DIABETES MELLITUS AND CATARACT DISEASES

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Mitochondrial disease often associated with various diseases in relation with the activity of cells metabolites and the synthesis of Adenosine Triphosphate (ATP). Mutation at the mitochondrial DNA (mtDNA) is one of the causes of mitochondrial disease. The mutation of m.9053G>A at the ATP6 gene was found in patients with type 2 diabetes mellitus (DM type-2) and cataract. Therefore, this mutation is predicted to be clinical features of the two diseases. ATP6 gene encodes protein subunit of ATPase6, a part of ATP synthase, which is important in the electron transfer and proton translocation in intracellular respiration system. This study aims to investigate the mutation effect of m.9053G>A at the ATP6 gene (S176N) to the structure and function of ATPase6 using bioinformatics method. The structure of ATPase6 was constructed using homology modelling method. The crystal structure of bovine's ATP Synthase (PDB ID 5FIL) was used as a template because it has high sequence similarity (77%) and it covered 96% of the input sequence. The effect of mutation was analysed by visual inspection at the proton channel of ATPase6. It is predicted that the proton channel was disrupted due to changes of electrostatic potential along the protein surface, from partially negative charge of hydroxyl group (serine) to partially positive charge of amine group (asparagine). Further experiments, such as molecular dynamics simulation of the whole ATP synthase system is required to gain more insight into the mutation effect of m.9053G>A at the ATP6 gene.

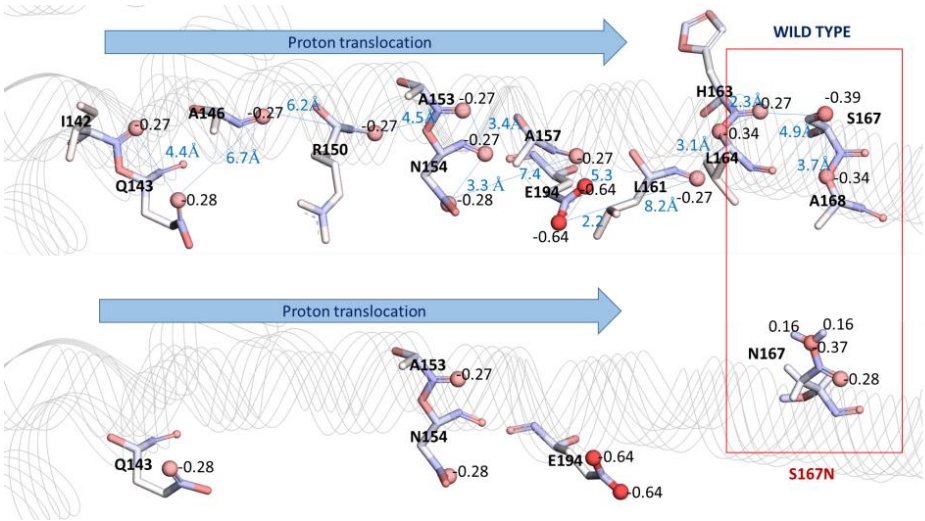

Fig. 1: Schematic of proton translocation across ATPase6. Partially positive charge of N167 is exposed on the surface of proton channel, instead of partially negative charge of S167.

DETERMINATION OF PHENOLIC COMPOUNDS OF TRIBULUS TERRESTRIS (*ZYGOPHYLLACEAE*)

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The genus *Tribulus* L. (Zygophyllaceae) known as "Çoban Çökerten, Demirdikeni" is represented by one species in Anatolia. This genus has well known biological effects, such as increasing in testosterone level, decreasing intestine weight, protection of mercury toxicity, sex reversal in fish, protecting oxidative stress, antiurolithiatic and antimicrobial effects. Its biological effects are generally attributed to saponins, flavonoids, alkaloids, glycosides and phytosteroids contents. In the present study, *Tribulus terrestris* L. was collected from Eskisehir, on August 2014. Powdered dried aerial parts and fruits were macerated with 70% methanol. The extracts were analysed by LC-MS/MS for their content of phenolic compounds. Quercetin 3-*O*-rutinoside (rutin) and quercetin dihexoside were determined to be the major compounds in the extracts. Rutin was quantified as 7.62 mg/g extract of aerial parts, whereas its content in fruits was determined to be 4.55 mg/g extract. The content of quercetin dihexoside was determined to be 7.03 mg/g herbal extract and 4.34 mg/g in the fruit extract (calculation based on rutin).

THEORETICAL EVALUATION OF THE TRIVALENT ARSENIC INTERACTION TO TRIPEPTIDES

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The interaction of trivalent arsenic, As^{3+} ion with four types of tripeptides consist of cys-cys (cysteine-cysteine) and cys-his (cysteine-histidine) combination have been determined theoretically employing the Becke three-parameter exchange and Lee-Yang-Parr correlation functionals (B3LYP) and using 6-31G(d) basis sets. Two modes of interaction have been considered: di-coordinate, involving the side chain of cysteine and histidine and tetra-coordinate, involving the side chain of cysteine and histidine and the donor's atom of middle amino acid. The optimised structures indicate that As^{3+} prefers a di-coordinate mode, bonding with side chain of cysteine and histidine. Among the complexes, it was found that tripeptides with cys-cys combination has the most stable complex with As^{3+} ion compared to cys-his combination with binding energy of 746.30 kcal/mol for As^{3+}–CFC (cysteine-phenylalanine-cysteine) and 684.80 kcal/mol for As^{3+}–CAC (cysteine-alanine-cysteine) complex. Generally, cys-cys combinations were predicted to give better interaction with As^{3+}, while the use of phenylalanine would render the peptide more flexible as compared to alanine.

A NANO CAPACITOR INVESTIGATION WITH H-BN INSULATOR

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Islamic Azad University, Tehran, Iran

In this study, we have shown the model of a nanoscale dielectric capacitor composed of edge-carboxylated carbon including carboxyl and hydroxyl functional groups as electrode plates. The thickness of two electrodes have been fixed by the ranges of 7–15 angstrom distances and separated by a few h-BN dielectrics (n = 1, 2, 3, 4 and 5) and the dielectric properties of different thickness have been studied specifically. Physical chemistry parameters including natural bond orbital (NBO), nuclear magnetic resonance (NMR), capacity, charge, voltage and energy for the model of the capacitor have been studied. The quantum and coulomb blocked effects of different h-boron nitride(BN)/grapheme oxide including heterostructures, stacks for multi dielectric properties of different (h-BN) n/grapheme oxide has been specifically studied. It could be concluded that the quantum effect has appeared in small thickness of capacitor due to number of more than three layers of h-BN, while m = 2 is the suitable layer for this capacitor.

VIRTUAL SCREENING AND ENZYMATIC ASSAY OF POTENTIAL NEURAMINIDASE INHIBITORS

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Neuraminidase (NA) activity plays an important role in the infection by influenza viruses by facilitating the release of the newly formed virions from the host cell receptor and promotes its infection to other cells or organs. With the emergence of viral resistance towards the existing NA inhibitors, the discovery of new NA inhibitors is urgently needed. In this work, docking-based virtual screening of large compounds from NCI database to rapidly select *in silico* hits to be potential NA inhibitors was carried out. A new *in vitro* method has been attempted to be developed for NA inhibition assay by utilising AlphaScreenTM technology with Alpha-1-Acid glycoprotein as a substrate. Unfortunately, this effort was unsuccessful probably due to the non-specific cleavage of sialic acid by NA. Subsequently, a traditional MUNANA assay was performed to investigate the inhibitory activities and kinetic parameters of the inhibitor compounds. Finally, the selected compounds were studied for their pharmacokinetic properties *in silico.* From the NCI database, 1541 compounds have been successfully screened and 40 *in silico* hits compounds were obtained and assayed to determine their IC50s. 10 of them demonstrated over 50% inhibition against NA and four compounds namely NSC 5069, NSC 83318, NSC 156563 and NSC 134137 were found having IC50 values of 216, 320, 571 and 673 µM, respectively. The kinetic studies showed Km value for MUNANA was 36.44 µM and Vmax for the enzymatic reaction was 551.25 RFU/min. From the Dixon plot, these four compounds appeared to competitively inhibit the neuraminidase with Ki values for NSC 5069, NSC 83318, NSC 156563 and NSC 134137 were 100.26, 204.13, 202.90 and 197.75 µM, respectively.

TO STRUGGLE THE PROBLEM OF ANTIBACTERIAL RESISTANCE: SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW 2-[(1-FURAN-2-YL)ETHYLIDENE)HYDRAZONO)]-4-PHENYLTHIAZOL-3(2*H*)-AMINE DERIVATIVES

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The treatment of infectious diseases remains an imperative issue as a result of a number of factors including arise of newer infectious diseases and growing number of multi-drug resistant microbial pathogens. Because the rate of resistance to current antimicrobial treatment has expanded seriously, the discovery of new antimicrobial agents or change for the bioactivity of the current medications is an important task. Huge numbers of the normally occurring furans have demonstrated fascinating natural activities, for example, antimicrobial activity. Also, various hydrazide–hydrazone derivatives have been asserted to have intriguing bioactivity like antibacterial activity. Furthermore; thiazole derivatives are a critical class of heterocyclic compounds. They possess a critical position in medicinal chemistry, displaying an extensive variety of bioactivities such as antibacterial and antifungal. Thus, in this study we reported the design and synthesis of some novel 2-[((1-furan-2-yl)ethylidene)hydrazono)]-4-phenylthiazol-3(2*H*)-amine derivatives (Figure 1) with moderate to high percentage yield and in a short reaction time. The synthesised compounds are identified by FT-IR, ^{1}H-NMR and mass spectroscopy. Compound 4-(3-amino)-2-[1-((2-furan-2-yl)ethylidene)hdrazono)-2,3-dihydrothiazol-4-yl]phenol showed efficacious antifungal activity. Due to the presence of free amino groups in the structure of our newly synthesised compounds, we have planned furthermore, to synthesise their Schiff base derivatives which could enhance the antimicrobial capability and help us to discover new and more effective antimicrobial agents.

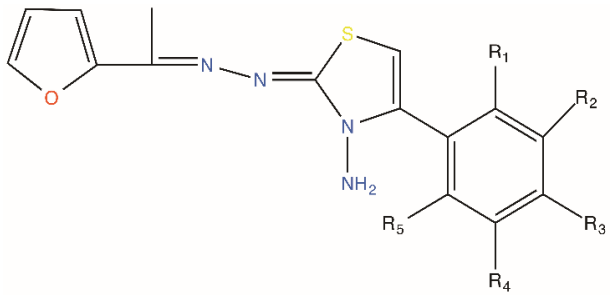

Fig. 1: General structure of newly synthesised compounds.

SYNTHESIS AND EVALUATION OF N-[1-(((3,4-DIPHENYLTHIAZOL-2(3H)-YLIDENE) AMINO)METHYL)CYCLOPENTYL]ACETAMIDE DERIVATIVES AS DUAL INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a neurodegenerative illness representing 60%–70% of dementia cases in the elderly with no current disease-altering treatment. The multi-target-coordinated ligand (MTDL) approach, in light of the "one particle, various target" worldview, has been the subject of expanding consideration by numerous exploration bunches, which have built up various mixes acting at the same time on various receptors involved in AD. In the same way, modifications in other neurotransmitter frameworks, particularly the serotonergic and dopaminergic are additionally thought to be responsible of the watched behavioural unsettling influences. Inspired by previously stated information and as a supplement of our researches on the same topic, we report herein the synthesis of some N-[1-(((3,4-diphenylthiazol-2(3H)-ylidene)amino)methyl)cyclopentyl]acetamide derivatives, by combining cyclopentyl- acetamide and thiazole moieties in single molecular structure (Figure 1) in order to investigate their ability to inhibit selectively the activity of the A and B isoforms of monoamine oxidase (MAO) and AChE enzymes since, it is demanding to find an agent that has a dual effect on both enzymes. Each one of our derivatives displayed great inhibition particularly compound N-[1-(((4-(4-methoxyphenyl)-3-phenylthiazol-2(3H)-ylidene)amino)methyl)cyclopentyl]acetamide indicated high potency (6.56 µM) reinforced with high selectivity comparable to the standard medications moclobemide. Generally, the study gave significant data to further improvement and change of medications for AD treatment.

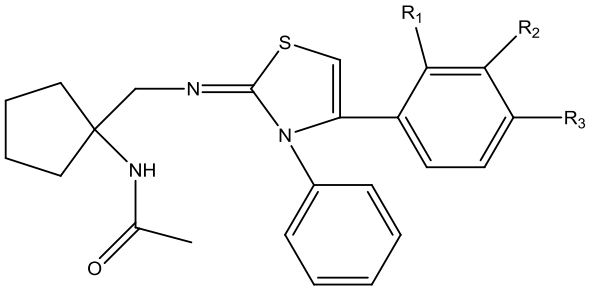

Fig. 1: General structure of newly synthesised compounds.

COMPUTATIONAL STUDY OF BUFADIENOLIDES FROM INDONESIA'S *KALANCHOE PINNATA* AS Na^+/K^+-ATPASE INHIBITOR FOR ANTICANCER AGENT

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Cancer is a leading cause of human death in the world. The identification of novel active compounds is important in the development of anticancer drugs. Indonesia with its enormous biodiversity has potential source of novel anticancer from natural compounds. The sub micromolar inhibition of bufadienolides from *Kalanchoe pinnata* on tumor cell line was reported. The proposed mechanism of its activity is through the binding of bufadienolides on Na^+/K^+-ATPase to inhibit the cell proliferation. However, the structure-activity relationship of the structural properties of bufadieolides derivatives on Na^+/K^+-ATPase inhibition has not been studied. Computational method, such as molecular docking, should be useful to investigate the binding mode of interaction between bufadienolide and Na^+/K^+-ATPase. The objectives of this study were to predict the binding pose of five bufadienolides from *K. pinnata* on Na^+/K^+-ATPase using molecular docking in comparison with a known inhibitor and to determine the important functional group of bufadieolide that is responsible for good binding. The complex structure of ligand-receptor was pre-minimised before docking. The sterical hindrance of Glu117 to the 1,3,5-ortoacetate moiety was relaxed during minimisation. The results showed that the conserved 14-OH group formed hydrogen bond with Thr797. The physicochemical properties of five bufadienolides, like Polar Surface Area (PSA) and *A* log *P*, also showed good correlation with the experimental data. It is suggested that Compound-1 has the best inhibition due to the presence of 10-CHO and 1,3,5-ortoacetate groups. These results are expected to be useful in the further development of bufadienolide-based inhibitor for anticancer.

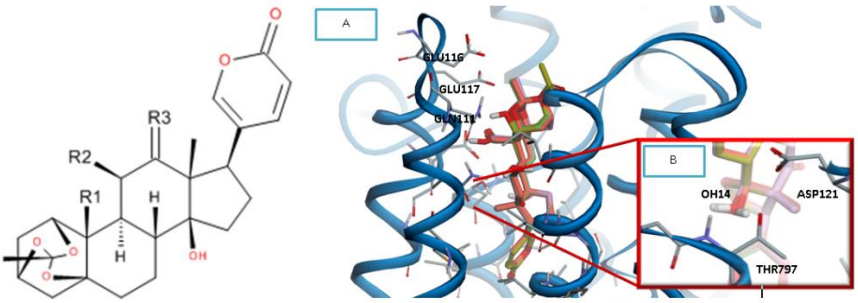

Fig. 1: Superimposition of compounds 1-5 with bufalin at the ligand binding site of NaK-ATPase. (a) Orthoacetate moeity of ligands were in close distance with Glu117 and (b) OH14 atom of all bufadienolides were potentially formed hydrogen bond with Thr797.

VIDEO VISUALISATION FOR DRUG RESISTANCE ANALYSIS FROM MOLECULAR DYNAMICS SIMULATIONS

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Molecular Dynamics Simulations are a standard way of studying the dynamic evolution of a system. The standard approach of machine learning is employed to understand the various features of the system of interacting particles. The results are analysed and some tools also allow videos of the simulations to be produced. This output is not further utilised to make the process more accessible to the researcher. We aim to develop a video visualisation tool which will help to understand easily and intuitively observe the molecular dynamics using the videos of the simulations. This is a novel attempt to apply the basic principle of computer vision and video motion analysis along with advanced features like depth perception to observe the binding sites. HIV-1 Protease Drug Resistance Analysis will be employed as the test problem and results will be verified with the previous results to see the consistency of the model proposed. The work will be based on color discrimination in an orthogonal space and multiple points of views will be observed to gauge the consistency of the tool developed. We will aim to analyse the molecular dynamics trajectories of commercial HIV-1 protease drugs, which has a different level of drug resistance, such as darunavir (level 1), lopinavir (level 3), amprenavir (level 3), indinavir (level 4) and saquinavir (level 5). All short (van der Waal's) and long (electrostatic) length interactions and desolvation energies will be studied and residues involving the binding site together with the intermolecular interactions will be investigated.

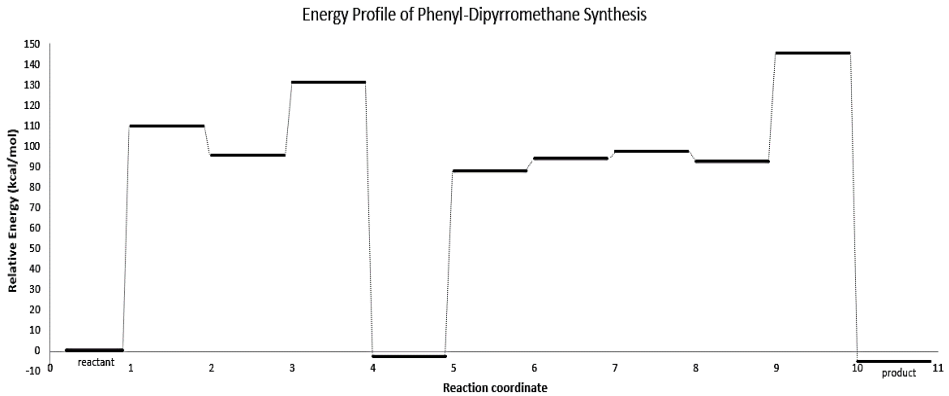

Fig. 1: Reaction pathway energy profile.

NEW BENZOTHIAZOLE-IMIDAZOLES DERIVATIVES AND THEIR ANTIPROLIFERATIVE ACTIVITY AGAINST GLIOMA (C6) AND LIVER (HEPG2) CANCER CELL LINES

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Cancer is the second leading cause of death after heart disease throughout the world. A great amount of anticancer drugs are discovered and still have been designed nowadays for cancer treatment. Today, treatments involving cytotoxic drugs are used in a widespread manner because of increasing in cancer incidence. Compounds containing imidazole and benzothiazole moieties have shown a wide range of biological properties including anticancer, antiviral, antitubercular, antimicrobial, antidiabetic and anti-inflammatory activities. These broad therapeutic properties of imidazole and benzothiazole related drugs have encouraged medicinal chemists to synthesise novel chemotherapeutic agents. According to the findings, some novel *N*-(6-substituted benzothiazol-2-yl)-2-[(4,5-dimethyl-1-((*p*-tolyl/4-nitrophenyl)amino)-1H-imidazol-2-yl)thio]acetamide derivatives (1-10) were synthesised and searched for their cytotoxic activities against C6 and HepG2 tumor cells. Among all compounds, the most active compound was determined as compound 7 whose IC_{50} value was calculated about 15.67 µg/mL through C6 tumor cell lines and also compounds 2, 4, 5, 6 were observed as good cytotoxic agents against HepG2 tumor cells. Findings about antiproliferative activity studies have encouraged the acquirement of new similar compounds in undergoing studies.

Table 1: IC_{50} values of the compounds against C6 and HepG2 tumor cell lines.

Comp.	C6	HepG2
1	27.0±1.41	50.0±5.0
2	20±2.0	26.33±1.53
3	32.67±6.43	275.0±35.36
4	22.0±3.61	29.33±1.15
5	16.33±2.31	31.67±7.23
6	19.50±2.12	28.67±1.15
7	15.67±2.52	58.33±2.89
8	>500	>500
9	24.33±4.04	>500
10	19.33±2.31	>500
Cisplatin	23.0±1.73	46.67±7.64

INSPHYL: A SYNTENY-BASED PHYLOGENETIC ANALYSIS FOR HORIZONTAL EVOLUTION

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In the era of antibiotics, the emerging diversity of antibiotics resistance in nosocomial and other infectious pathogen demands for an efficient tracking model. Genetic variation of these bacteria, however, are difficult to identify because the horizontal gene transfer (HGT) produces a high number of structural variants, most of which carries several of resistant genes. In this paper, we applied *Insphyl*, a synteny-based algorithm that detects "insertions" of DNA sequences transferred via HGT using whole genome sequences of 14 isolates obtained in s previous study of a methicillin resistant *Staphylococcus aureus* (MRSA) outbreak. The method identified a total of 373 insertions and successfully discriminated between sequence types and outbreak-related isolates. Among these variants, 20 insertions were unique to outbreak-related isolates and encoded 73 genes. Interestingly, the phylogeny and resistance of these isolates inferred by these insertions were consistent with previous analyses that used single nucleotide polymorphism (SNP)-based phylogenetics and antibiograms. This study provides a novel and efficient method of investigating the horizontal evolution of MRSA in the era of antibiotic resistance as well as important for further studies investigating the roles of the identified genes in similar infection outbreaks.

ULTRAVIOLET-VISIBLE STUDY ON ACID-BASE EQUILIBRIA OF APORPHINE ALKALOIDS FROM *ALSEODAPHNE CORNERI* AND *DEHAASIA LONGIPEDICELLATA*

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Chemical screening of the leaves and bark of *Alseodaphne corneri* and *Dehaasia longipedicellata*, belonging to the Lauraceae family were studied in detail for their alkaloidal contents. Three aporphine alkaloids: isocorydine 1, norisocorydine 2 and boldine 3 were isolated and purified using extensive chromatography techniques. Their structures were established through several spectroscopic methods: ultraviolet–visible (UV), infrared (IR), *mass* spectrometry (MS), 1D-nuclear magnetic resonance (NMR), 2D-NMR and also upon comparison with those reported in the literature. The UV-vis spectra of isocorydine 1, norisocorydine 2 and boldine 3 were studied in 2% v/v acetonitrile, at constant ionic strength (0.1 M NaCl, 35°C). The pK_a values of isocorydine 1 and norisocorydine 2 were 11.75 and 12.07, respectively. Boldine 3 gave a pK_a value of 9.16 and 10.44. Absorbance at a specific wavelength was recorded and the acidity constant (pK_a,K_a) were calculated using Basica programme.

PREDICTION OF ENZYME INHIBITION AND ANTICANCER ACTIVITY OF POTASSIUM KOETJAPATE

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Plant metabolites are currently getting interest in a cancer drug discovery area due to their complementary and moderate cytotoxicity. In this study, potassium koetjapate was developed from koetjapic acid and showed a potential antitumor potential against colon cancer. Our study showed the increased solubility of potassium koetjapate (salt of koetjapci acid) 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and molecular docking analysis were performed to determine the cytotoxicity and enzyme inhibition of potassium koetjapate. The observed 50% inhibitory concentration of potassium koetjapate was 7 µM/ml in human colon carcinoma cells (HCT) 116 cells. From the computational analysis, the tumor inhibitory was increased with the inhibition of DNA polymerase as shown by its binding energy of –8.8 kcal/mol compared to koetjapic acid with –8.4 kcal/mol. Koetjapic acid also showed lower binding energy of –8.2 kcal/mol in topoisomerase compared to in potassium koetjapate (–7.7 kcal/mol). However, both compounds showed competitive binding potential for topoisomerase and polymerase as compared to betulinic acid binding energy of –8.3 and –8.2 kcal/mol, respectively. Inhibition of these enzymes might resulted to the apoptosis of HCT 116 cells by affecting the topological process in cancer cell. In conclusion, potassium koetjapate could be a promising candidate anticancer drug with complementary effect of chemotherapeutic drugs.

BIOLOGICAL SCREENING OF VARIOUS PLANT EXTRACTS AS PROTEASE INHIBITORS AGAINST DENGUE VIRUS

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Dengue disease is a vital tropical disease which is the current public health hazard. In this research, inhibitory activities of 100 plant extracts towards dengue NS2B/NS3 protease were investigated. Plant extracts from various parts were prepared in dimethyl sulphoxide (DMSO). The results proved that some of the plant extracts such as *Syzygium polyanthum* and *Mimusops elengi* offered a significant level of NS2B/NS3 protease inhibition (93.84% and 92.14%, respectively) as compared to the standard control of quercetin in the same solvent systems. Early investigation showed that these plants contain flavonoids such as quercetin, panduratin A and 4-hydroxypanduratin A. In our docking study, quercetin showed favourable binding energy. Further isolation is necessary to identify other phytochemical compounds with anti-protease activity in *Syzygium polyanthum* and *Mimusops elengi*.

ENZYME KINETIC AND MOLECULAR DOCKING STUDIES OF NATURAL INDOLE CHOLINESTERASE INHIBITORS FROM *NAUCLEA OFFICINALIS*

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A phytochemical study on the bark and leaves of *Nauclea officinalis* has yielded nine monoterpenoid indole alkaloids: naucletine (1), angustidine (2), nauclefine (3), angustine (4), naucline (5), angustoline (6), harmane (7), 3,14-dihydroangustoline (8), strictosamide (9) and one quinoline alkaloid glycoside; pumiloside (10). All of the compounds were tested for cholinesterase inhibitory activity. All the alkaloids except for pumiloside showed strong to weak (butyrylcholinesterase) BChE inhibitory effect with IC_{50} values ranging between 1.02–168.55 µM while three compounds (angustidine, angustoline and pumiloside) showed moderate to weak (acetylcholinesterase) AChE inhibition with IC_{50} values between 21.71–261.89 µM. Angustidine was the most potent inhibitor towards both AChE and BChE. Five indole alkaloids; angustidine, angustine, nauclefine, angustoline and harmane were more potent BChE inhibitors compared to galanthamine. Angustidine was 28 times more potent as an inhibitor of BChE compared to galanthamine. Enzyme kinetic study of angustidine on BChE suggested it exhibited a mixed type of inhibition with an inhibition constant (*Ki*) of 6.12 µM. Molecular docking (MD) studies indicated that angustidine docked deep into the bottom gorge of *h*BChE, forming hydrogen bonds with Ser 198 and His 438.

QUANTITATIVE STRUCTURE-CYTOTOXICITY RELATIONSHIPS OF B-CARBOLINES

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β-Carbolines are a pharmacologically-important class of plant-derived phytochemicals and synthetic tricyclic alkaloid compounds. Recently, their derivatives are reported to exhibit potent cytotoxic activities against various cultured cancer cell lines. In this study, the capability of GRid INdependent Descriptors (GRIND-2) approach was explored to study the structural requirements needed for potent β-carbolines. Predictive three-dimensional quantitative structure-activity relationship (3D-QSAR) models using literature (model 1) and in-house (model 2) cytotoxic activity against HepG2 cancer cell line were developed. Partial least-squares (PLS) analyses of model 1 and 2 showed a squared correlation coefficient (r^2) of 0.73 and 0.95, respectively. Validation of model 1 and 2 using leave-one-out (LOO) technique resulted in cross-validation correlation coefficient (q^2) of 0.64 and 0.69, respectively. In addition, value of r^2_{pred} over 0.5 against external test sets marked the predicted capacity of the developed models. Interpretation of both models revealed the pharmacophoric importance at position 2, 6, 7 and 9 of β-carbolines.

MOLECULAR DYNAMICS SIMULATION OF α-CHYMOTRYPSIN IN DEEP EUTECTIC SOLVENT

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The use of ionic liquids as solvent for non-aqueous enzymatic reactions has been known to improve the activity and stability of biocatalysts. Previous reports showed that the use of ionic liquids not only provides a green alternative, but also increased performance of enzymes. Recently, a new class of ionic liquids known as deep eutectic solvent (DES) emerged as greener and cheaper alternative to the traditional ionic liquids. These eutectic mixtures have lower melting points while providing comparable solvent properties as traditional ionic liquids. There have has been a number of experiments showing that DES is a better solvent for enzymatic reactions when compared to the traditional ionic liquids. However, the effect of DES on the structural and dynamics properties of the enzymes has not been widely investigated. Information on how the protein structure reacts to the presence of DES on atomic level is of great interest. Herein, we report a molecular dynamics (MD) study on the stability and flexibility of α-Chymotrypsin in Choline chloride:Urea (1:2) DES mixture. The protein structure underwent MD simulations in water, choline chloride (ChCl) and choline chloride:urea (ChCl:Urea). Analysis from the last 10 ns of MD simulations showed that the protein was most stable in ChCl:Urea, followed by ChCl and least stable in water. The regions of the protein that were flexible in water was found very rigid in ChCl and ChCl:Urea. The hydrogen bonding between all components were also analysed. It was determined that the behaviour of the DES was closely similar to the ionic liquid. Apart from stabilisation of protein conformation, DES also provided more hydrogen bonding interactions to the protein, either with the hydrogen bond donor or the hydration layer on the protein surface.

2D QSAR AND MOLECULAR DOCKING STUDIES ON 1*H*-PYRROLO[2,3-*b*]PYRIDINE-5-CARBOXAMIDE DERIVATIVES AS JANUS KINASE 3 (JAK3) INHIBITOR

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Study on 2D quantitative structure-activity relationship (QSAR) and molecular docking of 1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxamide derivatives as Janus Kinase 3 (JAK3) inhibitor has been performed. A total of 13 molecular descriptors representing electronic, steric and hydrophobic parameters were selected and calculated. The developed QSAR model obtained using multi linear regression was validated by using both leave one out cross validation (q^2 = 0.69) and external test set. Based on the QSAR equation, 30 new 1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxamide derivatives were designed, seven of which have better predictive activities than the parent compound. Molecular docking was then performed for the designed compounds, which showed that critical interactions of ligands with the active site residues of JAK3 were established. This study revealed the potential of 1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxamide derivatives as immunomodulator agent targeting JAK3.

INTERACTIONS AND MOLECULAR MECHANISM OF PORPHYRIN-ACRIDINE INTERCALATION AND MINOR-GROOVE BINDING INTO DUPLEX B-DNA

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Molecular dynamics and free energy calculations in an explicit aqueous solvent are used to study the mechanism by which small molecules interact with DNA through intercalation between base pairs and at the minor groove. Initial studies have been performed on the interactions of porphyrin-acridine (PA) hybrid compounds with duplex B-DNA in previous research. We have performed free energy calculations of the interactions of four PA compounds with DNA using the molecular mechanics Poisson-Boltzmann surface area (MMPBSA) method. Also, the intercalation pathways for these PA molecules were analysed using umbrella sampling molecular dynamics simulations with the Gromacs suite of programs. Two different pathways were constructed: the first by removing the porphyrin-acridine hybrid from its intercalated state and the second by removing the molecule from its minor-groove-bound state. The DNA molecules used were hexamers d(CGATCG)2 (PDB code: 1Z3F) and d(TGATCA)2 (PDB code: 182D) that were extended to obtain dodecamers. Finally, the structure and dynamics of DNA bound to the PA molecules at the minor groove were analysed. The results show a multi-step mechanism in which the porphyrin macrocycle engages with the duplex DNA and binds at the minor groove before overcoming an energy barrier and intercalates between the DNA base pairs. Furthermore, the PA compounds were able to bind strongly to the minor groove of duplex DNA rich in AT bases and altered its conformation, extended its length and increased its curvature.

NETWORK ANALYSIS FOR THE STUDY OF SHEXIANG BAOXIN PILL FORMULA FOR TREATING CORONARY HEART DISEASE

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Traditional Chinese medicine (TCM) applies a holistic approach in treating diseases by using formulations consisting of mixture of different herbs, animal products and/or minerals. One of these formulas is Shexiang Baoxin Pill (SBP), which is widely used for cardiovascular disease such as cardiac ischemia by promoting angiogenesis and exerting cardioprotective effect in the heart. The formula is made up of seven Chinese materia medica of which only 22 bioactive compounds were used in this study. The synergistic effects of the SBP components have been examined in few metabolomics studies. However, the mode-of-actions (MOAs) of the compounds have not been clarified. In this study, the synergistic MOAs of combination of two SBP compounds were investigated to provide a simplified formula that could facilitate easier identification of putative targets and pathways, which can be challenging if they are to be tested using the present evaluation paradigm for single chemical compound. The *in silico* target prediction algorithm was used to predict the putative targets of SBP compounds. Also, a representative protein-protein interaction network of coronary heart disease (CHD) and angiogenesis was developed by

knowledge-based approach to predict the synergistic compound combinations. The network was developed based on annotated genes that were extracted from Comparative Toxicogenomics Database, Gene Ontology, Uniprot and Target Validation platform. We calculated the topological properties and the functional pathway enrichment of the representative network and mapped 191 predicted targets. The knowledge of the topological and pathway properties was then utilised to calculate synergy scores of compound combinations. We identified one compound combination, which the synergy score was comparable to two sets of compound combinations, which were previously showed synergistic effect in promoting angiogenesis. Hence, the ability of the representative network to evaluate the synergistic MOAs of compound combinations might provide a new avenue to study combination therapeutics in complex diseases.

SCREENING OF CITRUS PLANTS FOR ANTI-OBESITY PROPERTIES

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Malaysia is at an alarming rate of obesity because it ranked as the most obese country in South East Asia region that has the highest number of obesity population which can lead to death with associated high risk diseases such as cardiovascular disease, diabetes, hypertension, stroke, as well as cancer. Obesity is a result of excess dietary fat intake in the body. Pancreatic lipase is an enzyme to play a main role to hydrolyse fats into monoacylglycerol and fatty acids to be able to absorb into small intestine. One of the strategies to reduce and treat obesity is through reducing of fat absorption via pancreatic lipase inhibition. Therefore, the purpose of this study is to find potential pancreatic lipase inhibitors from natural sources, especially phytochemical compounds that help to combat obesity via reducing fat absorption. Molecular docking has been used to predict the binding energy of each ligand docked with the target receptor. In this study, chemical compounds of four Citrus families; *Citrus maxima, Citrus hystrix, Citrus microcarpa* and *Citrus aurantifolia* were docked with three dimension structure of their target receptor, a pancreatic lipase (PDB ID: 1LPB). The lowest binding energy gives a preferable result to define the compound that could be highly potential as pancreatic lipase inhibitor. Besides that, hydrogen bonding and hydrophobic interactions are the main ligand-receptor bindings that take parts in the crucial prediction. From the analyses, it was found that several ligands had shown the lowest energy docked conformation by comparing the energy with standard drug orlistat and crystal ligand inhibitor. Compounds from *Citrus aurantifolia* have scored the lowest binding energy, –9.44 kcal/mol followed by *Citrus hystrix* (–9.38 kcal/mol), *Citrus maxima* (–6.99 kcal/mol) and lastly *Citrus microcarpa* (–5.66 kcal/mol). These results were further confirmed using the methanolic extracts of the four selected citrus with pancreatic lipase inhibition assay. Our results showed that the *C. aurantifolia* has better anti-obesity properties with 86% of inhibition compared to orlistat with 98%. The other citrus plant showed 41% (*C. hystrix*), 22% (*C. maxima*) and no inhibition from the extract of *C. microcarpa*. In conclusion, virtual screening of small molecule libraries, which is a common strategy to shortlist potential inhibitors through molecular docking, would give new insights into the mechanism of pancreatic lipase inhibition and it provides that compounds from *C.aurantifolia* possible to have anti-obesity properties.

SCREENING OF SELECTED NATIVE PLANTS IN MALAYSIA FOR ANTI-OBESITY ACTIVITY

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Obesity is defined as the accumulation of fat in the body which exceeding required amount needed by the body. A person is obese when the Body Mass Index (BMI) exceeding 30 kg/m^2. Obesity is a multifactorial and heterogeneous syndrome affected from environmental factors and genetic susceptibility. The environmental factors are mainly due to daily diet. Fat-rich diet will cause excess triacylglycerol in the body. Obesity is associated to several diseases such as gallbladder disease, endocrine and metabolic disturbances, cardiovascular disease, cancer, diabetes mellitus, hypertension pulmonary disease, gout osteoarthritis and also psychological problems. The aim of this study is to find potential anti-obesity treatment from native plants in Malaysia. The strategy used to treat obesity in this study was the inhibition of pancreatic lipase. Pancreatic lipase was chosen as target enzyme because pancreatic lipase is the responsible enzyme for hydrolysis of triglyceride. After triglyceride is hydrolysed into free fatty acid and monoacylglyceride, it will be absorbed into the body. Inhibition of pancreatic lipase can prevent the triglyceride from being hydrolysed and thus excreted from the body. *In-silico* screening was carried out by screening Malaysian native plants database, Natural Product Discovery System (NADI) (www.nadi-discovery.com), via molecular docking of those plants' chemical substances against pancreatic lipase. In *in-vitro* assay, the pancreatic lipase activity was determined using a calorimetric assay approach by measuring the released of *p*-nitrophenol from *p*-nitrophenyl palmitate. Three plants with highest number of bioactive compounds potential for inhibition of pancreatic lipase were selected for *in-vitro* assay experiment. From *in-vitro* assay, crude methanol extracts of *Oryza sativa* and *Manilkara zapota* gave highest inhibitory activity, 77.65% and 65.50% inhibition, respectively. *Callophylum inophyllum* showed 7.42% inhibition. These bioactive compounds can be further tested as potential inhibitors and treatment for obesity.

ADVANTAGES OF PHARMACOMETRICS: FROM BENCH TO BEDSIDE

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Pharmacometrics involves the analysis and interpretation of data produced in pre-clinical, clinical trials and disease progress modelling. An understanding of pharmacometric modelling and simulation can give insights into the dose–concentration–effect relationship while disease progress modeling incorporates functions of natural disease progression and drug action to help understand the time course and management. *In vivo*, biomarkers such as phospho-extracellular signal–regulated kinases(ERK)/ERK intensity was used to assess the efficacy of two selected tyrosine kinase inhibitors (TKIs) in slowing/halting cyst proliferation in the kidneys of *Pkd1null*$^{+/-}$ mice. In this example, an exposure-response relationship was best described by the phospho-ERK/ERK intensity and cumulative area under the curve (cAUC) of the kidney using an Emax model. In the hospital setting,

a repeated time to event (RTTE) model was developed to describe the hazard of *Pseudomonas aeruginosa* and *Aspergillus fumigatus* positive culture events in children with cystic fibrosis by fitting a parametric hazard model. The predicted probability of having a *Pseudomonas aeruginosa* positive culture prior to the time of having a *Aspergillus fumigatus* positive culture was tested as an influence on the hazard of having an *Aspergillus fumigatus* positive culture. Other time varying (e.g. number of antibiotic therapy courses received prior the event) and time constant covariates (e.g. sex and meconium ileus) were also tested. Simulations of several doses based on the *in vivo* study for durations up to 12 weeks suggest that administration of almost 20-fold lower levels can be achieved and maintain therapeutic effects over long-term. The baseline hazard of having recurrent *Pseudomonas aeruginosa* and *Aspergillus fumigatus* positive cultures in the first five years of life of children with CF increased with time and was described by a Gompertz model. The probability of having *Pseudomonas aeruginosa* events had no detectable influence on the hazard of having *Aspergillus fumigatus* events. Parametric approach allows probability of the event to be predicted through simulation of the built hazard model. In conclusion, pharmacometrics allows the simulation of effective doses and the long-term therapeutic effect to determine first-in-human doses for clinical trials. In the case of hazard and therapy outcome, pharmacometric modelling serves as a predictor for therapy and monitoring decisions.

FINDING NEW DERIVATES CHALCONE FOR ANTI-BREAST CANCER BY USING VIRTUAL DOCKING

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Breast cancer is the most leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths. Tamoxifen is a Selective Estrogen Receptor Modulator (SERM) and the most commonly used as anti-estrogen adjuvant treatment for ER + premenopausal women. However, the risk of endometrial malignancy and hyperplasia of tamoxifen increases due to it has agonistic effect in the uterus. In our previous study, 2',4'-dihydroxy-6-methoxy-3,5-dimethylchalcon was isolated from leaves of *Eugenia aquea* and further investigations on to provide a basis for its use in breast cancer disease management. The results showed that the compound inhibited cell proliferation in a dose dependent manner with IC_{50} of 74.5 µg/mL (250 µM) and promoted apoptosis via the activation of poly(adenosine diphosphate-ribose) polymerase (PARP). However, this IC_{50} was categorised in moderate potential. Therefore, it must be effort to improve chalcone activity against breast cancer. One of the efforts is modification of structure through Computer-Aided Drug Design (CDD). Structure-Based Drug Design and Molecular Docking were employed in this study using Autodock 4.0. The aim of this study is to conduct molecular interaction of chalcone derivatives to Estrogen Receptor (ER) α. Characteristic of ERα, interaction between tamoxifen and ERα and the difference between tamoxifen and chalcone were observed. Tamoxifen has a tail of hydrophobic that made interaction hydrophobic with amino acids Leu525, Ala350, Trp383 and made affinity of interaction be higher than chalcone. The best result of this virtual docking is DerChalc10 which has a free energy of binding –12.33 kcal/mol while tamoxifen is –11.04 kcal/mol. The more the negative free binding energy is, the better the binding affinity is. Amino acid residues that bind with DerChalc10 are Met421, Leu525, Thr347, Ala350, Leu346, Leu387, Leu349, Glu353, Arg395, Met388 and Leu391.

MECHANISTIC STUDIES OF POTENTIAL ANTI-OBESITY NUTRACEUTICAL PROPERTIES IN SELECTED MALAYSIAN PLANTS

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Obesity and chronic diseases are interrelated. Higher occurrences of diseases in overweight people are the evident that obesity is the root cause for many chronic diseases. Besides physical workouts and controlled diet, anti-obesity drugs have gained immense attention and acceptance among people. Yet, nowadays there is a renewed interest in traditional medicine and an increasing demand for more drugs from plant sources. Herein, the anti-obesity activities (individually and synergistically) and their mechanisms in biological system of some Malaysian spices used as traditional medicine will be studied. The aqueous and ethanol extracts of the spices will be screened using some *in vitro* methods: anti-lipase and PTP1B assays and 3T3-L1 cell culture. Following a preliminary assay to note the changes in body weight and food intake (direct effects of any potential anti-obesity drugs) of the samples on mice, the mechanism(s) of action (MOV) of the sample that showed potential weight reducing ability will also be investigated. Lastly, virtual screening and docking techniques will be applied to validate the activity of active samples with some targets related to the mechanisms studied.

SYNTHESIS AND ANTIMICROBIAL ACTIVITY EVALUATION OF NOVEL 3,4,5-TRISUBSTITUTED 1,2,4-TRIAZOLES

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There is a continuous effort for the development of new drugs as the currently available drugs are becoming ineffective due to the drug resistance developed by pathogens. 1,2,4-Triazole ring is a prominent structure known with various biological activities of a huge number of its derivatives. It is also having consistently attracted scientific and practical interest because of their widely varying chemical properties and synthetic versatility. In the scope of this work, 2-[(5-(4-aminophenyl)-4-(4-substituted phenyl)-4*H*-1,2,4-triazol-3-yl)thio]-1-(4-substituted phenyl)ethan-1-one derivatives (1–15) and 2-[(5-(4-aminophenyl)-4-(4-substituted phenyl)-4*H*-1,2,4-triazol-3-yl)thio]-*N*-(4-substituted phenyl)acetamide derivatives (16–30) were synthesised using 4-aminobenzohydrazide as starting material. These compounds were screened for their antimicrobial activities against *B. cereus*, *S. aureus*, *E. faecalis*, *L. monocytogenes*; as gram-negative bacteria *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. typhimurium*, as yeast *C. parapsilosis*, *C. albicans*, *C. globrata*, *C. krusei*; as mold *A. niger*, *A. flavus*, *A. parasiticus*, *A. fumigatus*, *Rhizopus sp.*, *A. alternate*, *S. rolfsii* and *M. tuberculosis.* Compounds 2, 6, 7, 8 have displayed antituberculotic potential as much as standard drug, rifampin. Antibacterial and antifungal potency of these triazole compounds have found in between 144–1150 µg/mL.

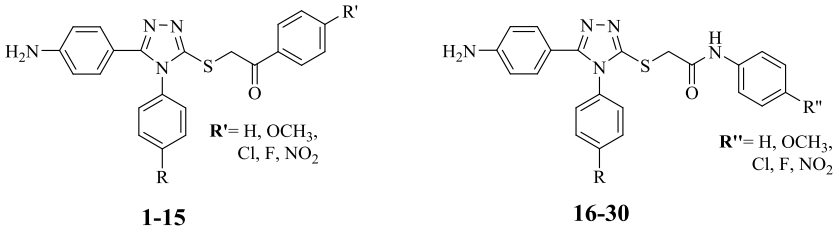

Fig. 1: The synthesised triazole compounds (1–30).

SYNTHESIS AND ANTITUBERCULAR ACTIVITY STUDIES OF SOME 3-[(4-ARYL-2-THIAZOLYL)HYDRAZONE]-1*H*-INDOL-2,3-DIONES

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Indoles, especially 1H-indole-2,3-dione (isatin) are the most prevalent heterocyclic scaffolds which have a broad spectra of medical applications such as anti-HIV, antiviral, anti-tumor, antifungal, antiangiogenic, anti-convulsant and antiparkinsonian activities. In particular, antituberculotic activity of various indole derivatives and isatin derivatives have attracted attention, in many studies. Additionally, the synthetic feasibility and extensive use of this scaffold have led medicinal chemists to this ring which has also stemmed from the interest in the biological and pharmacological properties.

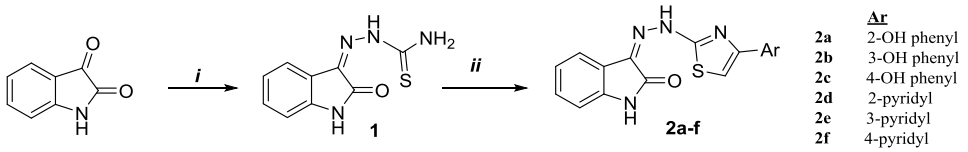

Fig. 1: Synthesis scheme of the title compounds (2a–f).

In this work, a series of 3-[(4-aryl-2-thiazolyl)hydrazone]-1*H*-indol-2,3-dione derivatives (2a–f) were designed and synthesised using isatin as starting material. The obtained thiazole compounds were screened to investigate their antituberculosis activity against *Mycobacterum tuberculosis* H37RV (ATCC 27294). Among them, two compounds 2c and 2d displayed antitubercular potential two-fold greater than standard drugs rifampin and isoniazid.

A VIRTUAL SCREENING AND MOLECULAR DYNAMICS SIMULATION STUDY OF FLAVONOID TYPE COMPOUNDS OF BAECKEIN A, C AND D FROM *BAECKEA FRUTESCENS* PLANT SPECIES ON NS2B-NS3 SERINE PROTEASE

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Dengue virus (DENV), a mosquito-borne Flavivirus, is a serious health problem with currently has no vaccine or drug treatment. NS2B-NS3 serine protease is the main target in the search for inhibitors against dengue virus. In this research work, a virtual screening of 4,000 natural compounds from NADI database was carried out to identify potent compounds for inhibiting the NS2B-NS3 serine protease function. Virtual screening results reported that the flavonoid type compounds of Baeckein A, C and D from *Baeckea frutescens* plant species are able to inhibit NS2B-NS3 serine protease activity based on the evaluation of binding free energy. The obtained complexes from virtual screening study were then subjected to a 50 ns molecular dynamics simulation study by AMBER 14.0 software program. Molecular dynamics simulation study revealed that all conformations interact with the catalytic triad residues of NS3 and C-terminus of NS2B protease. The present MD simulation confirmed the stability of the binding Baeckein C, D and A, with NS2B-NS3 protease, respectively. Finally, proposal for novel inhibitors are suggested.

MOLECULAR DOCKING AND MOLECULAR DYNAMIC STUDY OF COUMARINE, N-OXALYLGLYCINE, PYRIDINE, ORGANOSELENIUM AND ORGANOSULFUR DERIVATIVES AS INHIBITORS OF JUMONJI DOMAIN HISTON LYSINE DEMETHYLASE (KDM1A, KDM4A, KDM4C, KDM4E AND KDM5B) IN PROSTATE CANCER

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Prostate cancer is the second most common cancer in men, which approximately causes 307.000 deaths in 2012 according to International Agency for Research on Cancer World Health Organization (GLOBOCAN) report. One way of prostate cancer treatment is by inhibiting histon lysine demethylase that cause the cleavage methyl molecule from histon doesn't occur. It selectively increases the expression of several tumor suppressor genes, which role the induction of apoptosis and inhibition of angiogenesis and metastasis of cancer cells. Thus, blocking the histon lysine demethylase is an epigenetic mechanism to inhibit the cancer cells growth, especially prostate cancer. Derivative compounds of coumarine, N-oxalylglycine, organoselenium, organosulfur and pyridine have been

reported active as histon lysine demethylase inhibitors (KDM4E and KDM5B). This research aims to conduct a study of molecular docking and molecular dynamic simulation of coumarine, N-oxalylglycine, organoselenium, organosulfur and pyridine derivatives against histon lysine demetilase (KDM1A, KDM4A, KDM4C, KDM4E and KDM5B). The molecular docking of 20 compounds against five receptors histon lysine demethylase (KDM1A, KDM4A, KDM4C, KDM4E and KDM5B) showed that derivative compound of N-oxalylglycine namely (R)-3-(4-(benzyloxy)phenyl)-2-(carboxyformamido)propanoic acid and derivative compound of pyridine namely 3-(4-methoxybenzylamino)pyridine-2,4-dicarboxylic acid had the best interaction according to the binding energy (ΔG) and inhibition constants (*ki*). And the molecular dynamic simulation of those compounds complexes to five receptors histon lysine demethylase (KDM1A, KDM4A, KDM4C, KDM4E and KDM5B) for one nanosecond showed a strong interaction and low flexibility.

FLEXIBLE DOCKING ANALYSIS OF TRPV1 ANTAGONISTS, A TARGET FOR NEUROPATHIC PAIN IN DRUG DISCOVERY

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The transient receptor potential vanilloid subtype 1 (TRPV1) is a ligand-gated nonselective cation channel with high Ca^{2+} permeability. It is known to be a noticeable curative target protein for reducing pain. TRPV1 antagonists have identified as encouraging drug candidates for blocking the transmission of nociceptive signals from the periphery to the central nervous system and for alleviating other pathological states associated with this receptor. Based on the dibenzyl thiourea analogue as a lead compound, the diarylalkyl amide and furan-linked amide analogues were designed and synthesised as rat TRPV1 (rTRPV1) antagonists. We performed flexible docking study of the designed compounds with our rTRPV1 model and the results were found to be consistent with their biological activities for rTRPV1.

Moreover, the 4-methylsulfonamide derivatives were designed and synthesised as human TRPV1 (hTRPV1) antagonists. To investigate the structure-activity relationships, we carried out the flexible docking study and analysed the binding modes on our hTRPV1 homology model. The tested compounds occupied the binding site quite well and formed tight interactions via the hydrophobic and H-bonding interactions with the binding site residues. Furthermore, the additional hydrophobic group made another hydrophobic interaction. That explains why the 4-methylsulfonamide derivative with an additional hydrophobic group was much more potent in binding affinity.

EFFECTS OF Zn^{2+} METAL IONS ON THE FLEXIBILITY OF BLEG1_2437 B3 MBL ACTIVE SITE AND ITS INTERACTION WITH AMPICILLIN

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Metallo-β-lactamase (MBL) is a key enzyme used by bacterial pathogens to hydrolyse a wide range of β-lactam antibiotics. Previously, an evolutionary divergent MBL termed Bleg1_2437 from *Bacillus lehensis* G1 alkaliphile was discovered to resemble B3 subclass of metallo-β-lactamases in terms of its predicted structure. Functionally, this was later proven via enzymatic assay of Bleg1_2437 where significant antibiotics-hydrolysing activity was recorded when Zn^{2+} metal ions were present in the assay system. Although it is common knowledge that B3 MBLs require two Zn^{2+} metal ions for their catalytic activity, the nature of how these metal ions affect the structure, flexibility of B3 MBLs, particularly their active sites and interaction with antibiotics have much to be discussed about. In order to investigate the role of Zn^{2+} ions on Bleg1_2437, molecular dynamics (MD) simulation and docking were used to identify the effects of the ions on the structure, dynamics and interaction of this protein with antibiotics. The results of molecular dynamics simulations of monometal form of Bleg1_2437 suggested positive cooperation of zinc binding in the active site. Substitutions with other divalent metal ions such as Mg^{2+} and Cu^{2+} to the protein were also explored as comparisons. MD results revealed that Zn^{2+} ions stabilise Bleg1_2437 active site compared to Mg^{2+} and Cu^{2+} and give rigidity to the active site structure, enabling better interaction of substrate with the active site residues compared to other divalent metal ions. The finding of this study showed that Zn^{2+} stabilises the protein and provides rigidity to the active site structure, enabling better interaction of substrate with the active site residues compared to other divalent metal ions.

NANO DRUG DELIVERER FOR AMPICILLIN, CLAVULANIC ACID, IMIPENEM, PENICILLIN G AND TICARCILLIN

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Ampicillin belonging to the penicillin group of beta lactam antibiotics, ampicillin is able to penetrate Gram positive and some Gram-negative bacteria. Imipenem (Primaxin) is an intravenous β-lactam antibiotic discovered by Merck scientists Burton Christensen, William Leanza and Kenneth Wildonger in 1980. Ampicillin, Clavulanic acid, Imipenem, Penicillin G and Ticarcillin properties for the drug delivery with binding to SWCNNTs and SWBNNTs have been studied. Penicillin and its alteration Penicillin G or phenoxyacetic acid for Penicillin V is used for large scale production. Penicillin and other cell wall inhibitors are

primarily specific against Gram positive bacteria because of higher percentage of peptidoglycan in the cell walls of these organisms. It was the first member of the carbapenem class of antibiotics. Based on our previous works we have modeled and simulated a drug delivery system of those antibiotics. The investigation of those antibiotics in binding with single-walled carbon nanotube (SWCNT) and SWBNNTs have been studied by theoretical methods. It has been established the best structural and functional of those antibiotics. A number of computational chemistry studies carried out to understand the conformational preferences that may be attributed to stereo electronic effects. These results show the minimised structure of mentioned antibiotics with SWCNTs and SWBNNTs, calculated potential energy for important dihedral angles and the effect of temperature on geometry of optimised structure. NMR by GIAO approximation, have been applied for determination of the situation in antibiotics – SWCNT and shifting. This model provides an atomistic analysis of the antibiotics – SWCNT strategy and its implications for further investigations of drugs.

SYNTHESIS AND ANTIBACTERIAL ACTIVITY INVESTIGATION OF NEW 5-NITROFURAN DERIVATIVES

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Among many antibacterial agents, nitrofuran containing drugs such as furazolidone, nitrofurantoin nitrofurazone and furaltadone have been widely used to protect from microbic and protozoal infections especially associated with food contaminations. However, mutagenic/carcinogenic toxic effects of 5-nitrofuran skeleton were detected for both of the antimicrobial and anti-protozoal applications. Therefore, prodrug approach was suggested to increase biological activity and decrease toxicity along with improving the physico-chemical properties. For this purpose, many 5-nitrofuryl derivatives have been extensively studied in therapy against different microbial infections and these group compounds are determined producing oxidative stress into the parasite which is resulted in death of the microbe. Accordingly, six novel 4-aryl-2-[2-((5-nitrofuran-2-yl)methylene)hydrazinyl]thiazole derivatives (2a–f) were synthesised starting from 5-nitro-2-furaldehyde diacetate and using Hantzsch thiazole synthesis. The antimicrobial activity of the title compounds were screened against five gram positive bacteria *B. cereus*, *E. faecalis*, *S. aureus*, *S. epidermidis*, *L. monocytogenes* and two gram negative bacteria *E. coli* and *S. typhi*. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were calculated and compared to standard drug nitrofurazone. Compounds bearing pyridine moiety (2d, 2e) exhibited significant antibacterial activity which could be evaluated as new, promising bacteriostatic agents.

DEVELOPMENT OF A HIGH-THROUGHPUT SCREENING ASSAY AGAINST DENGUE TYPE 2 NS5 GTASE PROTEIN

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This study aims to utilise high-throughput screening (HTS) to find potential antiviral compound for Dengue Virus type 2 (DENV 2). HTS is fundamentally a testing process of various chemical compounds against a target to identify hit compounds. HTS must fulfill the characteristics of being simple, rapid, low-cost and high-efficiency. The assay's target is the dengue virus' non-structural protein 5 (NS5), which harbours a guanylyltransferase activity. This enzymatic activity is vital for the replication process of the viral genome, ensuring the virus' survival. The objective of this research is to develop a valid HTS assay against the target protein and to run a pilot screen against plant extract library. The protein NS5 GTase from DENV 2 is expressed by using the bacterial host *E. coli*. The HTS assay is in a 96-well plate format and utilises direct fluorescence from guanosine 5'-triphosphate-boron-dipyrromethene (GTP-BODIPY) to quantify the inhibition of NS5 GTase. We have succeeded in producing the target protein NS5 GTase excessively and we aim to produce a robust HTS assay against the NS5 GTase that can be used to screen a broad variation of chemical compounds and also to get hit compounds from a local plant extract library.

MYNATURE 50000 DATABASE FOR CENTRALISED NATIONAL NATURAL PRODUCT REPOSITORY FROM MALAYSIAN BIODIVERSITY

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Malaysia is one of the 12 mega-biodiversity countries of the world. An estimated 15,500 flowering plant species, soil rich in microorganisms and the vast marine organisms provide this country with huge source of potential drugs. However, to date there is no single compound from our natural products has reached the pharmaceutical market. One of the main reason for this is the absence of a systematic chemical repository as well as a facility that can meet the requirements needed by local scientists so that they could easily search, refer, exchange, share, update or contribute natural products and for screening against tropical diseases of high burden to the bottom billion. Interest in pharmaceutical databases has been continuing for more than 15 years. Developing a natural product library and chemical bank will ensure the country's natural resources can be further value added to

become pharmaceuticals and nutraceuticals. MyNature 50000, a new Malaysian natural product repository database, wish to develop and run as complete working web system with available samples of natural products and chemical agents system and currently active screening for potential anti-obesity and anti-dengue agents. This paper presents the experiences of creating the national natural product repository system MyNature 50000 which is develop to create a National Repository based on the chemical diversity of Malaysian plants and their potential as therapeutics agents. Focus of the database content is the local Malaysian plants with description of their botanical names, synonyms, sources, chemical library, extracts, fractions and compounds for drug discovery research and bioassay screening purposes. These features determine the basic system of MyNature 50000.

Fig. 1: A screen shot of MyNature 50000 database.

DOCKING STUDIES OF FLAVONOID AGLYCON OF *SOPHORA JAPONICA* L. AS ANTICANCER DRUG CANDIDATE

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Sophora Japonica Linn. is a shrub species belonging to the subfamily *Faboideae* of the pea family *Fabaceae*. Some flavonoids in *S. japonica* were discovered as prospective anticancer drug candidates. Flavonoids present in the human diet comprise many polyphenolic secondary metabolites with broad-spectrum pharmacological activities including their potential role as anticancer agents. Unfortunately, until now there is no *in silico* study of anticancer activity in flavonoid aglycone in *Sophora Japonica* Linn. Therefore, the aim of this research was to study the flavonoid aglycone of *Sophora Japonica* Linn. as anticancer candidate. Docking simulation was performed using AutoDock 4.2 involved validation of docking parameter, docking of flavonoid aglycon to a

series of cancer's receptors and analysis of docking. The receptors that have been selected are Placental aromatase (PDB ID 3S7S), CDK-2 (PDB ID 2A4L), CDK-6 (PDB ID 1XO2), VEGR (PDB ID 2OH4), Bcl2 (PDB ID 2O2F), DNA Topoisomorase I (PDB ID 1T8I), DNA Topoisomorase II (PDB ID 1ZXM), as well as Telomer G-Quadruplex receptors (PDB ID 1L1H). Validation of docking parameter was obtained from re-docking native ligand into each of those receptors and recorded RMSD was less than 2 Å. The analysis was performed by comparing the binding energy of flavonoid aglycone of *Sophora Japonica* Linn. with the binding energy of native ligand from the docking validation. The results showed that flavonoid aglycone of *Sophora Japonica* Linn. interacted with the active site of the selected cancer receptors particularly to CDK-2, CDK-6, VEGR and DNA Topoisomorase I receptors. Compounds 1, 22, 23, 34, 36, 37, 38 and 39 from a series of aglycone of *Sophora Japonica Linn.* were found to make interaction with CDK-2 receptor through hydrogen bonding with Leu83, while compounds 22, 34 and 37 showed the best interaction to CDK-6 and formed a network of hydrogen bond interaction with residues Glu99, Asp104 and Val101. Meanwhile, only compound 38 showed the best interaction to VEGR, whereas compounds 22, 38 and 39 showed interaction with DNA Topoisomerase-I binding site and formed hydrogen bond with DG12 and THR718. It is interesting to note that they have the same pattern of hydrogen bonds with the nature ligands CDK-2, CDK-6 and DNA Topoisomerase I receptor.

CoMFA AND CoMSIA STUDY OF CURCUMIN ANALOGS AS ANTIPROLIFERATIVE OF MT-4 CELL

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Cancer is the fifth highest disease (especially lungs, trachea and bronchus) that caused mortality in the world. International Agency for Cancer on Research (IARC) reported that the worldwide prevalences of cancer between 2007 to 2012 is approximately 32.6 million. Especially on 2012, it was recorded that from 14.1 million cancer patients, 8.2 million of them are now dead. Curcumin is a natural product that can be found in turmeric (*Curcuma longa* L). Biological activity of curcumin and its derivatives that have been studied are antioxidant, antibacterial, antifungal, anti-viral, anti-inflammatory and anti-angiogenic. It is also active as chemical agents against degenerative diseases such as Alzheimer, cancer and others. However the major hurdle in developing curcumin and its derivatives as a drug candidate is its low biovailability. Therefore it is neccesary to identify new curcumin analogs that have better bioacitivity and bioavailability. The aim of this research is to predict the activity of a series of curcumin analog by applying CoMFA and CoMSIA methods. Molecules of training set were prepared by optimising its geometry using DFT/3-21 G in Gaussian. Afterwards, an atom-fit alignment process was carried out in Sybyl-X. CoMFA and CoMSIA parameters were also calculated by using Sybyl-X software. The results of CoMFA study showed that r^2 = 0.985, r^2_{cv} = 0.44, standard error = 1.630 and the antiproliferative activity of curcumin analogs against MT-4 cells were more influenced by steric effect. The results of CoMSIA study showed that r^2 = 0.994, r^2_{cv} = 0.451, standard error = 1.141 and curcumin analogs as MT-4 cells growth inhibitor were contributed by hydrophobicity 30.8%, steric 9.4% and electrostatic 59.7%.

INHIBITION OF DENGUE TARGET NS2B-NS3 PROTEASE BY MALAYSIAN NATURAL PRODUCTS: A VIRTUAL SCREENING AND MOLECULAR DYNAMICS SIMULATION

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A dengue drug target, NS2B-NS3 serine protease (NS2B-NS3pro) is a prime target for the development of therapeutic agents which are not available in the market until today. In this study, a virtual screening of 4000 natural compounds from NADI database was carried out to identify potent compounds for inhibiting the NS2B-NS3 serine protease function. Virtual screening results revealed that plant with the highest number of compounds that are able to bind to NS2B-NS3 protease structure are from *Endiandra kingiana* species. The docked conformations showed that hydrophobic and hydrophilic interactions played a central role for inhibiting the protease enzyme activity. To give a better insight into the molecular interactions involved, a 50 ns molecular dynamics simulation was further conducted using NPT ensemble by using AMBER 14.0 software program for the selected natural compounds from *Endiandra kingiana* species with NS2B-NS3 protease structure. Analysis of the molecular dynamics simulation results displayed a consistent result with virtual screening study which would give useful information for the development of specific inhibitors to combat the dengue viruses.

DOCKING STUDIES OF FLAVONOID AGLYCON OF *SOPHORA JAPONICA* L. AS ANTICANCER DRUG CANDIDATE

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native ligand into each of those receptors and recorded RMSD was less than 2 Å. The analysis was performed by comparing the binding energy of flavonoid aglycone of *Sophora Japonica* Linn. with the binding energy of native ligand from the docking validation. The results showed that flavonoid aglycone of *Sophora Japonica* Linn. interacted with the active site of the selected cancer receptors particularly to CDK-2, CDK-6, VEGR and DNA Topoisomorase I receptors. Compounds 1, 22, 23, 34, 36, 37, 38 and 39 from a series of aglycone of *Sophora Japonica Linn.* were found to make interaction with CDK-2 receptor through hydrogen bonding with Leu83, while compounds 22, 34 and 37 showed the best interaction to CDK-6 and formed a network of hydrogen bond interaction with residues Glu99, Asp104 and Val101. Meanwhile, only compound 38 showed the best interaction to VEGR, whereas compounds 22, 38 and 39 showed interaction with DNA Topoisomerase-I binding site and formed hydrogen bond with DG12 and THR718. It is interesting to note that they have the same pattern of hydrogen bonds with the nature ligands CDK-2, CDK-6 and DNA Topoisomerase I receptor.

STRUCTURE BASED LIGAND DISCOVERY FOR INHIBITING RIBOFLAVIN SYNTHASE FROM *LEPTOSPIRA*

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Enzymes involved in riboflavin biosynthesis could be potential drug targets as this pathway is absence in human. Riboflavin synthase is an enzyme that catalyses the final step of riboflavin synthesis in Gram negative bacteria, a precursor molecule for synthesising the coenzymes flavin monoucleotide and flavin adenine dinucleotide. Therefore, the riboflavin synthase of locally isolated pathogenic bacterium *Leptospira* sp. was modeled using crystal structure of orthologous *E. coli* riboflavin synthase with 39% of identities as a template. The active site is located at between monomers of trimeric structure. The potential inhibitors were screened against the one million compounds in Zinc library. The docking scores ranging from –11.818 to –10.987 kcal/mol were recorded for top three hits. Molecular dynamics simulation of protein-inhibitor complex revealed that lower root mean square deviation (RMSD) for top ranked compound. Half maximal inhibitory concentration (IC_{50}) will be verified and inhibition mechanism will be postulated X-ray crystallographically.