B.Sc.(Hons) Pharm. Sci
Computational Chemistry

PROJECT DESCRIPTIONS

Fourth Year Students

Agonist Drug Design at the Farnesoid X (FXR) Receptor

Julia Agius

Metabolic Syndrome is a highly prevalent disease. FXR agonists such as feroline decrease serum triglycerides, cholesterol and hyperglycaemia. Feroline was superimposed in LigandScout onto Tschimgine, a FXR agonist described in pdb ID 5IAW. A consensus pharmacophore was modelled and used to query the ZincPharmer databases and 311 lead-like molecules were identified. These were docked into a FXR protomol modelled in SYBYL-X and the highest affinity structures were identified for further optimisation

Drug Design at the Glucocorticoid Receptor Alpha (GRα)

Andrew Aquilina

Glucocorticoid research aims to keep the immunosuppressant and anti-inflammatory effects of traditional drugs without their collateral effects. The study used dexamethasone and novel GRα agonist- Compound 21 to try to create an average pharmacophore in LigandScout and to identify analogous structures from the ZincPharmer database. The structural diversity between the 2 molecules precluded the creation of a consensus pharmacophore. The use of the Compound 21 pharmacophore to query the ZincPharmer database resulted in 123 lead like hit structures which must be ranked in order of GRa affinity.

Drug Design at the 8-oxoguanine DNA glycosylase (OGG1) receptor

Katarina Maria Bugeja

The OGG1 receptor is a target for management of inflammatory conditions such as COPD and asthma. This study aimed to identify OGG1 modulators using virtual screening. Two OGG1 antagonists- TH9525 AND TH5487 were used to create a consensus pharmacophore in LigandScout. This which was read into the ZincPharmer database where 300 Rule of 3 compliant hits were identified. Their affinity for a modelled OGG1 receptor protomol will be calculated and the highest affinity structures will be proposed for optimisation

Design of Novel Benzimidazole Hybrid Structures Capable of Simultaneous Peroxisome Proliferator Activated Receptorγ/Angiotensin Receptor (PPARγ/ATR) Modulation

Matthias Borg

Dual PPARγ/ATR agonists have potential in the management of metabolic syndrome. This study used the hybrid benzimidazole HTR-04, and olemsartan and telmisartan to model a consensus pharmacophore in LigandScout. This was used to query the ZincPharmer database and 1468 lead-like molecules were identified. The affinity of these molecules for the modelled PPARg and the ATR protomols will be quantified and the optimal structures identified for optimisation

Agonist-Based Drug Design at the Vitamin D (VDR) Receptor

Bettina Camilleri

Vitamin D, and its agonist analogs are used in the management of hyperproliferative diseases. Many analogs cause hypercalcaemia. TX522 (pdb ID 1TXI) is a VDR agonist that does not cause this effect. It was used, with a second agonist (pdb ID 1IE9), to generate a consensus pharmacophore in LigandScout. This was submitted as a query to ZincPharmer for the identification of similar structures where 47 lead-like molecules were identified. Of these, the structures with the highest affinity for the VDR protomol will be targeted for further optimisation.

Drug Design at the Protein tyrosine phosphatase 1B (PTP1B) Receptor

Rachel Callus

The PTP1B receptor is a validated target for Type 2 Diabetes management. The modelling of uncharged bromophenols yielded high affinity inhibitors. The flagship molecule LXQ46 was modelled in Sybyl and superimposed in LigandScout onto a Bicyclic Thiophene inhibitor (pdb ID 2AZR) and an average pharmacophore was created. This was read into ZincPharmer for lead structure identification. 1678 lead-like hit structures were consequently identified and will be docked into the PTP1B receptor protomol. The highest affinity structures will be further optimised.

Drug Design at the Pregnane X Receptor (PXR)

Maria Martina Cutajar

The PXR mediates drug-drug interactions. Drug-drug interactions decrease therapeutic efficacy implying clinical potential for PXR antagonists. This study probed the PXR receptor and modelled small molecule modulators using virtual screening. A pharmacophoric structure of the PXR antagonist GSK002 was modelled in Ligandscout and used to query the Zincpharmer database to identify analogous lead-like structures (n = 391). These will now be sequentially docked into the PXR protomol (modelled in Sybyl-X) and the highest affinity structures will be selected for optimisation.

Drug Design at The Trypanothione Reductase (TR) Enzyme Using the Kukoamine Scaffold as a Lead

Aisha Diyab

The natural antihypertensive agent, kukoamine A, a bis (trihydro-cinnamoyl) spermidine derivative, was identified as a TR inhibitor- the target for the management of trypanosimiasis. Its structure was modelled in Sybyl and used together with that of the TR inhibitor quinacrine mustard (pdb ID 1GXF) to model pharmacophores which were used in virtual screening at the ZincPharmer database. Only quinacrine mustard yielded lead-like hit structures (n = 18). These were docked into the TR protomol, and the structures with the highest affinity were proposed for optimisation.

Drug Design at the IL-1 receptor-associated kinase (IRAK) Receptor

Justine Decelis

The IRAK4 receptor has been found to be over-expressed in many melanomas and is an important mediator in rheumatoid arthritis. This study used the scaffold of the experimental inhibitors- CA-4948 (PDB ID 7C2V) and FJ9 (PDB ID 7C2W) to model separate pharmacophores in LigandScout. These were read into ZincPharmer for the identification of lead-like structures with potential to inhibit IRAK4. 44 hit molecules were obtained exclusively from the FJ9 pharmacophore. These will be docked into the IRAK protomol and the highest affinity structures will be identified for optimisation

Antagonist Drug Design at the Farnesoid X (FXR) Receptor

Jade Marie Falzon

Evidence shows that FXR antagonism has a role in the management of hepatic disorders associated with bile secretion. Suvanine, a marine sponge extract, has FXR antagonist activity. Suvanine was modelled in Sybyl and was used with the antagonist molecule described in pdbID 4OIV to model an average pharmacophore in LigandScout that was used to identify analogous structures in ZincPharmer. A total of 568 Rule of 3 compliant molecules were identified. These will be docked sequentially into a modelled FXR protomol, and the highest affinity structures will be identified for optimisation.

Drug Design at the Lactate Dehydrogenase (LDe) Enzyme

Natalia Ferris

LDe inhibition results in a hypotensive effect. The flavonoid myricetin is a newly identified inhibitor. Its structure was extracted from pdb ID 5YUN. It was superimposed onto the LDe pyrazine inhibitor described in pdb ID 4M49 to simulate bioactivity. The pharmacophore of the superimposed myricetin was modelled in LigandScout and submitted to ZincPharmer. 300 lead-like hits were retrieved, and this cohort of lead-like structures was docked into a modelled LDe protomol. Their affinity was calculated, and the best structures identified for optimisation.

Drug Design at the Oestrogen receptor (ER) using Propyl Gallate as a Lead

Michaela Mifsud

The ER, a breast cancer mediator, binds to antagonist xeno-oestrogens or endocrine disruptors such as propyl gallate. This was modelled in Sybyl and used to model consensus pharmacophores with raloxifene and 4-hydroxytamoxifen (pdb IDs 1ERR & 3ERT respectively) separately in LigandScout. A consensus pharmacophore was also modelled after superimposing raloxifene and 4-hydroxytamoxyfen. The 3 consensus were read separately into ZincPharmer for lead like Rule of 3 compliant hit structure identification. No hits were identified. The propyl gallate scaffold will be used in a de novo approach.

Drug Design at the Cannabinoid 1 (CB1) Receptor

Michael Laferla

Rimonabant, a CB1 antagonist, is useful in reducing tobacco and narcotic dependence. In this study its structure was extracted from pdb ID 6AJI. It was superimposed in LigandScout onto AM6538- a small molecule CB1 antagonist described in pdb ID 5TGZ and a consensus pharmacophore was modelled. This was submitted as a query to ZincPharmer with the application of filters compliant with the Rule of 3. No lead-like hit analogs were identified. This consensus pharmacophore will now be used in a de novo approach.

Drug Design at the E Coli DNA Gyrase

Maria Portelli

DNA gyrase is vital in bacterial DNA compaction and an important target for inhibitors. Myricetin, a flavonoid, has been shown to be a DNA gyrase inhibitor. It was modelled in Sybyl and its pharmacophore, together with that of the benzothiazole inhibitor described in pdb ID 5L3J. These were submitted to ZincPharmer with filters for lead likeness. The benzothiazole inhibitor produced a total of 1,440 hit structures. These were docked into a modelled DNA gyrase protomol and the optimal molecules were identified.

Drug Design at the Constitutive Androstane (CAR)Receptor

Gianluca Muscat

CAR agonism is of clinical utility in the treatment of cholestasis. The agonist 2-phenyl-3,4-dihydroquinazolin-4-one scaffold was superimposed in LigandScout onto 3 of its analogs and a consensus pharmacophore was modelled. A pharmacophore of Androstenol (pdb ID 1XNX) was also modelled and used for screening on ZincPharmer. 608 Lipinski rule compliant hits were identified from both pharmacophores. These were docked into a CAR protomol modelled in SYBYL-X and the highest affinity structures were identified for further optimisation.

Drug Design at the leucine-rich repeat kinase (LRRK2) Receptor

Shanice Marie Spiteri

LRRK2 activation is associated with Parkinson's disease. It is a target for novel drug design aimed to mitigate the condition. Some LRRK2 inhibitors such as that described in pdb ID 5OQ7 are currently undergoing Phase 1 trials. This inhibitor scaffold was used to model a pharmacophore which was submitted as a query at the ZincPharmer database. Rule of 3 compliant lead-like hits were sought. No hit molecules conforming to these inclusion criteria were identified. This inhibitor scaffold will be used in a *de novo* approach.

Drug Design at the Aldose Reductase (AR) Receptor

Etienne Xiberras

AR, through its conversion to sorbitol, drives the complications of diabetes. Quercitin and quercitirin have AR antagonist properties. Their pharmacophoric structures were modelled in Sybyl and used to model an average pharmacophore with the small molecule inhibitor in pdb ID 2FZD. After the modelling of an average pharmacophore virtual screening using both this and the individual pharmacophores as lead molecules at the ZincPharmer database. When filters for lead-likeness were applied, no hit structures could be retrieved. The lead scaffolds will now be utilised in a *de novo* approach.

Antagonist-Based Drug Design at the Vitamin D (VDR) Receptor

Kristy Xuereb

VDR hyperactivity is associated with cholestasis, depression and cardiac dysfunction. Angiotensin receptor blockers, specifically telmisartan, are potent VDR antagonists. This study used telmisartan (pdb ID 3VN2) and adamantyl- a Vitamin D analog (pdb ID 2ZMJ) to model individual pharmacophores in LigandScout. These were read sequentially into ZincPharmer. Only the TLS501 pharmacophore produced a single hit structure with a molecular weight of 400. It was docked into a modelled VDR protomol and its binding affinity calculated. The hit molecule will be further analysed and optimised.

Drug Design at the Dihydroorotate Dehydrogenase (DHODH) receptor using the Teriflunomide scaffold as a Lead

Paula Zammit

Mouse studies show that DHODH inhibition is a novel route for the treatment of epilepsy. Teriflunomide, used in Multiple Sclerosis is a potent inhibitor with poor intra-cerebral penetration. Its scaffold (pdb ID 1D3H) was used together with that of its biaryl analog (PDB ID 3U20) to model a consensus pharmacophore which was read into ZincPharmer for the identification of more non-polar analogs. 353 lead-like hit structures were identified. After the DHODH protomol was modelled in Sybyl-X, the hits were docked into it, and the highest affinity structures were identified for optimisation.