FIRST
Pharmacy Postgraduate Symposium

ABSTRACT BOOKLET
31 AUGUST
2015

UNIVERSITY OF THE WESTERN CAPE
BELLVILLE, WESTERN CAPE, SOUTH AFRICA
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WELCOME

The organizing committee welcomes you to the launch of our first UWC School of Pharmacy Postgraduate Research Symposium. It is with great excitement that we look forward to hear about the stimulating research our peers and the School of Pharmacy are involved in. We would like to thank our senior colleagues for taking charge and carrying the beacon for the first year postgraduates and prospective bright researchers in our fourth year class. We are excited to hear every question, insight, comment and we are here to facilitate all the forthcoming and constructive discussions that emanate. We welcome you all and thank you for attending.

The sixteen contributions provide a snapshot of all the disciplines of Pharmacy from Drug Discovery, Pharmacology, Drug Delivery, Pharmacy Practice and Clinical Pharmacy.

We further wish to acknowledge the financial assistance provided by Aspen Pharmacare and thank our supervisors, the School of Pharmacy, and the University of the Western Cape. Without you this Symposium would not have been possible.

With best wishes,

Research Symposium Organizing Committee

Heather L. Moyo (Editor/Compiler), Byron Mubaiwa (Co-editor/Printing), Kudzai Mapendere (Programme), Nyashadzashwe Bepe and Mabolaeng Sekhonyana-Khetsekile (Advertising), Adeyemi Adegoke (Venue organization), Irene Denya and Tendai Samkange (Masters of Ceremony), Omolola Afolayan and Ayodeji Egunlusi (Catering), Prof. Denzil Beukes and Dr. Admire Dube (Supervisors).
MESSAGE FROM THE DIRECTOR

Dear Postgraduate, Friends and Colleagues,

On behalf of the UWC School of Pharmacy, I would like to welcome you to the 1st Pharmacy Postgraduate Symposium. We look forward to a day of highly stimulating scientific presentations and interdisciplinary interaction. We trust that this day will provide insight into research projects in the School, stimulate the exchange of fresh ideas and facilitate collaboration across discipline and departmental borders to facilitate taking research in Pharmacy to new levels of innovation and recognition.

The vision of the School of Pharmacy is ‘To be the Premier Provider of Pharmacy Education in Africa with a Global Footprint in the Pharmaceutical Sciences’ and our mission is to produce pharmacy graduates and pharmaceutical scientists equipped to respond to the pharmaceutical and healthcare needs of society by:

• Designing curricula and research programs that are contextually appropriate and internationally competitive
• Providing excellent education and training in the healthcare and pharmaceutical sciences
• Conducting nationally relevant and globally recognized research
• Instilling professionalism, social responsiveness, critical thinking, scholarly pursuit of knowledge and lifelong learning

In order for us to attain our vision and mission of leadership in teaching and global scientific recognition, research and innovation in the School will be taken to new heights and it is postgraduate studies like these presented here and symposia like this that will form the cornerstone on which we will build future success.

We look forward to your active participation.

Sarel Malan
Director, School of Pharmacy, UWC
## PROGRAMME

**UWC SCHOOL OF PHARMACY 1ST RESEARCH SYMPOSIUM**

**Monday, 31 August 2015**

**Venue: B1**

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<td>08:30</td>
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<td>09:00</td>
<td><strong>OPENING SESSION</strong>&lt;br&gt;Chair: Dr. A. Dube</td>
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<tr>
<td>09:00</td>
<td>Welcome</td>
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<td>Prof. S. Malan</td>
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<td>Prof. M. Davies-Coleman</td>
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<td>Samuel Egieyeh</td>
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<td>09:30</td>
<td>Adverse pregnancy outcomes among HIV – positive pregnant women treated with EFV – containing antiretroviral therapy in the Cape Metropole region.</td>
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<td>Mohammedmekin Mohammednur</td>
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<td>09:45</td>
<td>Formulation of a nevirapine co-crystal as a liquid dosage form.</td>
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<td>Sahana R. Injety</td>
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<td>10:00</td>
<td>Tacrine, trolox and β-carboline derivatives as lead compounds for the design and synthesis of multi-target drugs for Alzheimer’s disease therapy.</td>
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<td>Gerard A. Kenfack Teponnou</td>
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<td>10:15</td>
<td>Comparison of flavonoid profile and respiratory smooth muscle relaxant effects of <em>Artemisia afra</em> versus <em>Leonotis leonurus</em>.</td>
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<td>Tjokosela Tikiso</td>
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<td>10:30</td>
<td>Synthesis of polycyclic non-steroidal anti-inflammatory prodrugs and their biological evaluation as potential therapeutic agents in neurodegenerative disorders.</td>
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<td>Modupe K. Abaniwonda</td>
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<td>10:45</td>
<td><strong>TEA BREAK</strong></td>
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## SESSION 2

**Chairs: Frank Zindo and Mabolaeng Sekhonyana-Khetsekiile**
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<td>Rational drug therapy monitoring of type 2 diabetes mellitus at primary health care facilities in Cape Town: using glycated hemoglobin and fasting plasma glucose.</td>
<td>Khathatso Monanabela</td>
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<td>11:30</td>
<td>Hybrid molecules as inhibitors of the monoamine oxidases and caspase 3 for neurodegenerative disorders.</td>
<td>Mohsen Tavari</td>
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<td>11:45</td>
<td>Active encapsulation of diclofenac sodium into liposomes for ophthalmic preparations.</td>
<td>Evelyn N. Alonjang</td>
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<td>Oxa-pentacycloundecyl derivatives as a neuroprotective molecules.</td>
<td>Rajan Sharma</td>
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<td>12:15</td>
<td>Characterization cardiovascular effects, molecular docking and chemoinformatics analysis of compounds isolated from <em>Leonotis leonurus</em>.</td>
<td>Abd-Alkarim Sasi</td>
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<td>Synthesis and evaluation of novel coumarin-donepezil derivatives as dual acting monoamine oxidase and cholinesterase inhibitors in Alzheimer’s disease.</td>
<td>Germaine B. Foka</td>
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<td><strong>Chair: Heather Moyo + Ireen Denya</strong></td>
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<td>Solid dosage formulation of efavirenz by co-crystallization and cyclodextrin inclusion.</td>
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<td>Evaluation on the appropriateness of digoxin level monitoring at Netcare Kulis River hospital.</td>
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<td>Aspen Pharmacare</td>
<td>Dr Wai Ling Au</td>
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<td>Closing remarks</td>
<td>Dr. A. Dube</td>
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S. Egieyeh1,5, S Malan5, A. Christoffels1, J. Syce5, C. Ehrhardt2, M. Popov3, P. Gedeck4 and K. Azzaoui3

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4Novartis Institute for Tropical Disease, Singapore
5Discipline of Pharmaceutical Chemistry, School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville, 7535, Cape Town, South Africa.

Purpose:
The goal of this presentation is to highlight the role of PlasmoDB, a genomic and proteomic resource for Plasmodium, in the identification of potential cross-stage antimalarial agents that can eradicate all stages of malaria life cycle.

Methods:
A novel search strategy was used in PlasmoDB to identify genes that meet the following conditions: up-regulated across all stages of the Plasmodium falciparum (Pf) life cycle, have no orthologues in human, have significant expression level and have three dimensional (3D) crystal structures in protein data bank. The resultant cross-stage genes represented viable drug targets in Pf for in-silico drug discovery. High throughput docking (HTD) was then conducted with a commercial drug library to find hit compounds against these drug targets. Top 100,000 hits were filtered and 2000 compounds selected for in-vitro testing.

Results:
One of the cross-stage drug targets identified in Plasmodium falciparum (Pf) was Tyrosyl-tRNA ligase (3VGJ). 3VGJ is located in the cytoplasm of Pf and it is involved in protein biosynthesis, ATP binding and host cell surface receptor binding. The docking program reliably reproduces the pose of the co-crystallized ligand of 3VGJ. Selected hit compounds showed good interaction with the binding site. Initial results from in-vitro antiplasmodial assay revealed 13 highly active hits (EC50 < 1uM) from 959 compounds.

Conclusions:
This study successfully used PlasmoDB to identify genes (drug targets) that are present across all stages of the life cycle of Plasmodium falciparum (Pf). HTD identified hit compounds against one of the cross-stage drug targets, 3VGJ. In-vitro antiplasmodial assay revealed highly active hits.
Adverse pregnancy outcomes among HIV-positive pregnant women treated with efavirenz containing antiretroviral therapy in the Cape Metropole region

M.M. Mohammednur, P. Mugabo

Discipline of Pharmacology, School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville, 7535, Cape Town, South Africa.

Background:
WHO recently recommended efavirenz (EFV) use for HIV infection during pregnancy. However, safety on the use of EFV containing antiretroviral therapy during the first trimester of pregnancy is still conflicting.

Objective:
The aim of this study was to investigate adverse pregnancy outcomes among HIV-positive pregnant women who were exposed to EFV-containing HAART and determine the effect of time of initiation of therapy on adverse pregnancy outcomes.

Methods:
A retrospective comparative study was used to compare adverse pregnancy outcomes among EFV exposed vs unexposed during pregnancy. Data was extracted from patient folders and analysed using SPSS version 21.

Results and discussion:
A total of 303 folders of HIV-positive mothers were reviewed. 264 (87.1%) of them were exposed to EFV containing HAART during pregnancy; and 86 (28.4%), 23 (7.6%), 148 (48.8%), and 46 (15.2%) of them were initiated antiretroviral therapy before conception, first, second and third trimester respectively. A total of 4(1.32%) foetal abnormalities, 18(5.9%) low birth weight, 14 (4.6%) preterm delivery adverse pregnancy outcomes were observed. Most of them (31, 86.1%) were seen among EFV exposed. No association was found between foetal abnormality and low birth weight with exposure to HAART including efavirenz (p>0.05). Preterm delivery was significantly associated not only with exposure to EFV, but also with a time of initiation of antiretroviral therapy (p<0.005).

Conclusions:
More adverse pregnancy outcomes were observed among EFV exposed. However, only preterm delivery was significantly associated with EFV exposure and time of exposure.
Formulation of a nevirapine co-crystal as a liquid dosage form

S. Injety\textsuperscript{1}, H. Samsodien\textsuperscript{1}, R. Rossiter\textsuperscript{2}

\textsuperscript{1}Discipline of Pharmaceutics, School of Pharmacy, University of the Western Cape, Bellville, 7535, South Africa

\textsuperscript{2}Johnson and Johnson, 241 Main Road, Retreat, 7945, South Africa

Purpose:
A protocol was developed to select an appropriate co-former to form a nevirapine co-crystal that is suitable for formulation of suspensions. Scaling up of the chosen co-crystals was explored. Furthermore, the integrity of the co-crystal in a suspension was performed. The co-crystal suspension that was formulated was assessed for pH, viscosity and dissolution according to the standards set out in the USP 32 and compared to the branded version of the nevirapine suspension, Viramune \textregistered which is currently on the market. The suspension was characterized for particle size, zeta potential and polydispersity index.

Methods:
Co-formers suitable for nevirapine co-crystals viz. saccharin, glutaric acid, salicylic acid, rac-tartaric acid and maleic acid were characterized according to physical, chemical, pharmacological and pharmaceutical properties. A grading scale was used to select the most appropriate co-former. Upon selection of the ideal co-former for suspensions, scale-up of the nevirapine co-crystal was performed from a small scale of 350 mg to a large scale of 5 g. The identity of co-crystals was confirmed using hot stage microscopy, differential scanning calorimetry and thermogravimetric analysis. A suspension was formed and filtered. The filtrate was identified with differential scanning calorimetry and the filtered solution was identified with ultraviolet spectroscopy, to ascertain the co-crystal integrity. Quality control of the suspension was performed by measuring the pH, viscosity was measured through the Brookfield viscometer, particle size, zeta potential and polydispersity index were determined through zeta sizer. Dissolution studies were performed by USP basket II method.

Results:
In comparison to the other co-formers that could form nevirapine co-crystals, saccharin had the highest number of excellent characteristics in the physical, chemical, pharmacological and pharmaceutical properties. Nevirapine-saccharin co-crystals were prepared utilizing the slow evaporation technique. Crystals were grown using methanol as the solvent and percentage yield of the co-crystals were above 75 %. The UV and DSC of the filtrate of the suspension revealed that the co-crystal had not separated in its individual components and remained intact while in suspension form. The pH of the suspension was 8.

Conclusions:
Nevirapine-saccharin co-crystals remain intact in liquid at a pH of 8 and therefore can be used to formulate a suspension.
Tacrine, trolox and β-carboline derivatives as lead compounds for the design and synthesis of multi-target drugs for Alzheimer’s disease therapy.

G. A. Kenfack Teponnou, J. Joubert and S.F. Malan
Discipline of Pharmaceutical Chemistry, School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville, 7535, South Africa.

Purpose:
The cascade of neurotoxic events involved in the pathogenesis of Alzheimer’s disease may explain the inefficacy of currently available treatment based on acetylcholinesterase inhibitors (AChEIs - donepezil, galantamine, rivastigmine) and N-methyl-D-aspartate (NMDA) antagonists (memantine). These drugs have been designed based on the “one-molecule-one-target” paradigm and only address a single target. Conversely, the multi-target drug design strategy increasingly gains recognition.

Method:
Based on the versatile biological activities of tacrine, trolox and β-carboline derivatives and the attention they have received in the literature as lead structures for the design of multifunctional drugs for the treatment of Alzheimer’s disease, and based on the topology of the active site of AChE, we have designed tacrine-trolox and tacrine-tryptoline hybrids with various linker chain lengths. The aim with these hybrids is to provide additive or synergistic therapeutic effects that might help overcome the limitation of current anti-Alzheimer’s disease drugs. The study was rationalized by docking all structures in the active site of AChE using Molecular Operating Environment software (MOE) before proceeding with the synthesis. AChE inhibition was assessed in a UV enzyme inhibition assay using Ellman’s method. Antioxidant activities were assessed using a DPPH absorbance assay.

Results:
The hybrid compounds showed moderate to high AChE inhibitory and free radical scavenging activities, comparable or slightly higher than the reference compounds donepezil and trolox respectively. The hybrids with longer linker chain lengths (6 and 8 carbons) showed higher AChE inhibitory activity than shorter ones (2, 3, and 4 carbons). This correlates well with literature. Free radical scavenging activities however seems to be higher with shorter chain lengths.

Conclusion:
The relevance of this study is the development of novel anti-Alzheimer’s disease drugs with multi-target neuroprotective activities. Hybrid molecules that exhibit reasonable AChE inhibition and anti-oxidant activity were identified as suitable candidates for further investigation.
Comparison of flavonoid profile and respiratory smooth muscle relaxant effects of *Artemisia afra* versus *Leonotis leonurus*.

T. Tikiso, J. Syce and K. Obikeze

**Discipline of Pharmacology, School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville, 7530, Cape Town, South Africa.**

**Purpose:**
*Leonotis leonurus* and *Artemisia afra* are two of the most commonly used medicinal plants in South Africa traditionally advocated for use in asthma. These plants contain flavonoids, which are reported to have smooth muscle relaxant activity and may be responsible for the activity. The present study analyses the flavonoid profiles, levels and bronchodilatory activities of the aqueous extracts from *Leonotis leonurus* and *Artemisia afra*.

**Methods:**
Freeze-dried aqueous extracts (FDAE) of the dried leaves of the two plants were prepared. A validated HPLC assay was developed and used to identify and determine the levels of luteolin in the plant preparations. Solutions of the plant extracts were studied in the isolated guinea-pig trachea tissue preparation in the presence of carbachol, histamine and KCL. The possible mechanism of action of the two plants was determined by cumulative log dose-response curves (LDRC) for carbachol, histamine and KCL in the absence and presence of 1, 30 and 100 mg/mL solutions of the plant extracts.

**Results:**
The levels of free and total luteolin in *A. afra* FDAE (8.977 ± 0.73 µg/mL and 16.394 ± 0.884 µg/mL, respectively) were significantly more than in *L. leonurus* FDAE (0.929 ± 0.066 µg/mL and 3.093 ± 0.531 µg/mL, respectively). *L. leonurus* and *A. afra* relaxed tracheal smooth muscles contracted with histamine, KCL and carbachol in a dose dependent manner. The degree of relaxant activity of *L. leonurus* versus the three inducers of contraction (agonists) could be classified as KCL > carbachol > histamine, with EC$_{50}$ values of 9.87, 29.34 and 94.76 mg/mL respectively. The *A. afra* tracheal smooth muscle relaxant activity was categorized as carbachol > histamine > KCL, with EC$_{50}$ values of 13.93, 15.47 and 19.88 mg/ml respectively. Overall, *A. afra* which contained the higher levels of luteolin, was more potent at relaxing the guinea pig tracheal smooth muscle than *L. leonurus*.

**Conclusions:**
Aqueous solutions of *A. afra* and *L. leonurus* have potent but different degrees of bronchodilator activities that could be useful in the treatment of asthma, and these actions may be related to each plant’s luteolin (or flavonoid) levels. Moreover, it is very likely that more than one mechanism of action is involved in the tracheal smooth muscle relaxant effects of these two plants.
Synthesis of polycyclic non-steroidal anti-inflammatory prodrugs and their biological evaluation as potential therapeutic agents in neurodegenerative disorders.

M. Abaniwonda, J. Joubert
Discipline of Pharmaceutical Chemistry, School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville, 7535, Cape Town, South Africa

Purpose:
Excitotoxicity and inflammation are key propagatory mechanisms involved in the pathogenesis of neurodegenerative disorders. Non-steroidal anti-inflammatory drugs (NSAIDs) possess beneficial neuroprotective effects but their polar nature prevents them from reaching the central nervous system at therapeutic doses. Polycyclic structures such as adamantanes and pentacycloundecanes have intrinsic neuroprotective properties while serving as lipophilic scaffolds to improve the blood-brain barrier (BBB) permeability of hydrophilic compounds. This study therefore employs the prodrug approach to synthesise and evaluate novel conjugates of non-steroidal anti-inflammatory drugs and polycyclic moieties for significant neuroprotective activities.

Methods:
A series of amide and ester prodrugs incorporating cage-like structures such as amantadine or pentacycloundecanes and selected NSAIDs were synthesised. The NSAIDs were conjugated to the polycyclic moieties by esterification or amidation using activation chemistry. The prodrugs of ibuprofen, ketoprofen, naproxen and aspirin were selected based on availability of parent NSAIDs, physicochemical property of desired compounds and feasibility of synthesis. In silico blood-brain barrier permeability studies were performed on the prodrugs and the parent NSAIDs using Chemsilico Property Predictor. The novel compounds were also evaluated for antioxidant properties using DPPH+ and ABTS+ radical scavenging assays.

Results:
Preliminary studies indicates that the polycyclic prodrugs possess improved antioxidant properties compared to the parent NSAIDs as well as increased blood brain barrier (BBB) permeability as obtained from in silico BBB studies.

Conclusions:
Polycyclic structures serve as lipophilic carriers to improve the central nervous system (CNS) delivery of NSAIDs.
Rational drug therapy monitoring of type 2 diabetes mellitus at primary health care facilities in Cape Town: using glycated haemoglobin and fasting plasma glucose

K. Monanabela, M. van Huyssteen, R. Coetzee
Discipline of Pharmacy Practice, School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville, Cape Town, 7535, South Africa

Purpose:
To describe the use of glycaemic monitoring indicators in patients with type 2 diabetes mellitus treated at primary health care facilities in the Cape Town Metropolitan Region in South Africa.

Methods:
Retrospective, descriptive quantitative study design was employed. Data was obtained from the patients’ medical records in the facilities. The study included type 2 diabetes mellitus patients older than 18 years of age, who have been on treatment for a minimum of 6 months. Data analysis was done using Microsoft Excel® and SPSS version 23 was used for the statistical analysis.

Results:
The study consisted of 596 participants. Participant’s average age was 57 years, (range 29-92) and 64.3% (383) were female. Eighty six percent (513) of participants had at least one glycated haemoglobin (HbA1c) test result. Of these 72% (317) were not within the target glycaemic range. In contrast almost all participants had at least one fasting plasma glucose (FPG) test results. Of which 76% were exceeding the target FPG range. Twenty eight percent (96) of the participants who had HbA1c results outside target glycaemic range were on metformin monotherapy. While 32% (136) of the participants with FPG results outside the target range were on metformin monotherapy.

Conclusion:
Most participants had their glycaemic results outside target range regardless the monitoring tools in place, and among these uncontrolled participants 28% and 32% on HbA1c and FPG respectively were on metformin monotherapy, which indicates a need for appropriate monitoring, and better understanding of the use of HbA1c.
Hybrid molecules as inhibitors of the monoamine oxidases and caspase 3 for neurodegenerative disorders

M. Tavari, J. Joubert, and S.F. Malan
Discipline of Pharmaceutical Chemistry, School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville, 7535, Cape Town, South Africa

Purpose:
The oxidative deamination reaction catalyzed by monoamine oxidase B (MAO-B) is one of the major catabolic pathways of dopamine in the brain. Inhibition of this enzyme leads to enhanced dopaminergic neurotransmission and are currently used in the symptomatic treatment of Parkinson’s Disease (PD). Furthermore, MAO-B inhibitors may also exert neuroprotective effects by reducing the concentration of potentially hazardous by-products produced by MAO-B-catalysed dopamine oxidation. Apoptosis or programmed cell death occurs in a number of neurodegenerative disease disorders. It has been proven that inhibition of the executing enzymes, caspases-3 and -7, slows down or even stops apoptosis. Having this in mind we focused on the structures of selegiline, an irreversible inhibitor of monoamine oxidase; and 5-chlorosulfonyl isatin as a potent, non-peptide, selective inhibitor of caspase-3. Therefore we designed and synthesized multifunctional hybrid molecules acting simultaneously to halt the apoptotic neuronal breakdown process and eliminate the signs and symptoms of diseases such as PD.

Method:
The compounds were synthesized using multi-step processes and the structures and purity were confirmed by NMR and MS. Recombinant human MAO-A, MAO-B and caspase 3 enzymatic assays were performed and IC_{50} values were calculated.

Results:
The IC_{50} values indicated that the synthesized novel hybrid compounds were able to inhibit MAO-A and MAO-B and also inhibit the apoptotic initiator enzyme, caspase 3.

Conclusion:
The observation that the synthesized compounds inhibited both MAO-A, MAO-B and also showed some degree of inhibition for caspase 3, make them ideal candidates for further lead compound development and multifunctional drug design.
Active encapsulation of diclofenac sodium into liposomes for ophthalmic preparations

E. Alonjang, E. Ebrahim
Discipline of Pharmaceutics, School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville, 7535, Cape Town, South Africa

Purpose:
Liposomes as drug carriers have gained grown since their discovery in 1965 by Bangham. They have shown to improve bioavailability as they can be delivered to target site, as well as having sustained release properties. Diclofenac sodium eye drop is a sterile Nonsteroidal Anti-inflammatory Drug (NSAID). The residence time of this eye drops after being instilled is 1-2 minutes due to continuous production of tears diluting the solution amongst other factors. As a result, frequent administration (3 to 4 times a day) is needed. The only eye preparation available for diclofenac sodium is an eye drop. The investigation of encapsulation of diclofenac sodium into liposomes for ophthalmic application if successful, could present with an enhanced drug delivery and controlled release formulation. The aim of this study is to optimise active encapsulation of diclofenac sodium into liposomes. The research objectives are; to determine the critical factors that affect drug encapsulation into liposomes, to develop a protocol for active encapsulation by ion exchange method and finally to incorporate encapsulated drugs into a dosage form.

Method:
Response Surface Methodology (RSM), specifically Central Composite Design (CCD) was used to optimise active encapsulation of diclofenac sodium into liposomes. The components of liposomes being cholesterol and phostidylcholine, their concentrations and incubation time where independent variables while dependent variables were percentage encapsulation, polydispersity index (PDI) and drug release profile. Using analysis of variance (ANOVA), the interaction between the independent variable and the dependent variable were tested.

Results:
Though the independent factors had no effect on the PDI, Cholesterol had a significant effect on drug release with an R^2 of 0.9647. Incubation time showed significant effects on the responses. % Encapsulation had R^2 of 0.9927. Liposomes produced had sizes in 100nm to 205nm range with acceptable PDI of less than 0.5.

Conclusions:
Diclofenac sodium liposomes in an acceptable nano range were successfully produced by active encapsulation method. Optimization and a suitable ophthalmic dosage form for optimize preparation(s) are being explored.
Oxa-pentacycloundecyl derivatives as neuroprotective molecules

R. Sharma, J. Joubert and S.F. Malan
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Purpose:
Neurodegenerative disease is a broad term for conditions arising from progressive and irreversible deterioration of nerve cells. The etiology of neuronal death in neurodegenerative diseases is multi factorial involving different mechanisms such as excitotoxicity, oxidative stress, apoptosis, protein aggregation, neuroinflammation and loss of neurotrophic factors. Antagonism and modulation of receptors like N-methyl-D-aspartic acid (NMDA) and sigma receptors have been among key strategies for neuroprotection. In recent years polycyclic cage compounds such as adamantane and pentacycloundecane have enjoyed the attention of the research community because of their high lipophilicity and ability to cross the blood brain barrier. The purpose of this study is to use pentacycloundecane scaffolds for developing potential NMDA receptor antagonising/modulating molecules.

Method:
A series of compounds were synthesised where NO donating moieties were attached to oxa-pentacycloundecane units. Different carbon spacers from 1C to 3C’s were used between pentacycloundecyl and NO donating moiety. The nitro group attached to a phenyl group was selected as NO donating moiety. Synthesized compounds were evaluated for cytotoxicity, neuroprotection and effect on NMDA and voltage gated Ca influx.

Results:
All the designed compounds were successfully synthesised and characterised by NMR, MS and IR spectroscopic techniques. All the compounds show favourable cytotoxicity profiles and moderate to good biological activity in neuroprotection, NMDA and voltage gated Ca influx assays.

Conclusion:
The synthesised compounds comprise an ideal array of compounds to study the effect of the nitro group as NO donating moiety, ester linkage and spacer length on S-nitrosylation, calcium channel activity and NMDA receptor modulation. We envisage that these compounds may be novel leads for further development of potential neuroprotective molecules.
Characterization cardiovascular effects, molecular docking and chemoinformatics analysis of compounds isolated from *Leonotis leonurus*.

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**Purpose:**  
*Leonotis leonurus* has long been used traditionally as herbal medicine for treating several ailments including influenza, muscular cramps, skin related diseases, menstrual, antilipidemic, hyperglycaemia and hypertension. Previous studies have shown that *Leonotis leonurus* extracts have cardiovascular effects, with differences in the effects observed with different extracting solvents. Various compounds primarily terpenes have been isolated from the plant and cardiovascular effects have been reported with one diterpene. Considering the abundance of diterpenes in the plant, it is theorised that more than one diterpene in *Leonotis leonurus* is responsible for the cardiovascular activity observed with the plant extracts. The purpose of this study therefore was to investigate the cardiovascular activity of five compounds isolated from *Leonotis leonurus* extracts in the anaesthetised normotensive Wistar rats (*in-vivo*), and to study their receptor binding affinity by using Molecular Docking methods and Chemoinformatics analysis (*in-silico*).

**Methods:**  
Two compounds isolated from *Leonotis leonurus* - DC1 (0.5-40mg/kg), and DC8 (0.5-60mg/kg), were infused intravenously to anaesthetised normotensive Wistar rats, and changes to BP and HR measured via the femoral artery through a blood pressure transducer connected to a Powerlab®. The binding energy of each molecule was calculated using the molecular operating environment software. The lowest energy and highest cluster conformations of the molecules were further analysed and compared using the software of Discovery Studio.

**Results:**  
DC1 & DC8 showed statically significant increases in systolic blood pressures were observed with both compounds in normotensive rats, with no significant changes to heart rate, diastolic, and mean arterial blood pressures. In (*in-silico*) studies, all compounds showed significant binding affinity to renin, angiotensin II, angiotensin-converting enzyme, and β receptors.

**Conclusions:**  
Results suggest that DC1 and DC8 produce an increase in BP by acting as angiotensin II receptor agonists.
Synthesis and evaluation of novel coumarin-donepezil derivatives as dual acting monoamine oxidase and cholinesterase inhibitors in Alzheimer’s disease.

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Purpose:
Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterised by low acetylcholine levels in the hippocampus and cortex, causing symptoms like progressive memory loss, decline in language skills and other cognitive impairments to occur. Other causative factors of AD include oxidative stress through the process of oxidative deamination of biogenic and xenobiotic amines by monoamine oxidase-B (MAO-B), amyloid-β (Aβ) formation, and dyshomeostasis of biometals. Due to the multifactorial nature of AD, current pharmaceuticals on the market show limited therapeutic benefits and are mainly used for symptomatic relief. This study was thus aimed at synthesising a multi-target-directed-ligand able to inhibit both cholinesterase and MAO-B by using two lead compounds, one of which has cholinesterase inhibitory capacity (donepezil) and the other MAO-B inhibitory activity (coumarin).

Methods:
Four series of five compounds per series were synthesised. The first series of compounds consisted of the coumarin moiety to which 1,4-dibromo-benzene was attached. The second series represented the coumarin moiety to which a benzyl-piperidine (donepezil moiety shown to confer cholinesterase inhibitory property) was attached. The third series represented the coumarin moiety to which benzyl-piperazine was attached and the last series were compounds similar in structure to series one but without the bromine moiety. Prior to the synthesis, molecular modelling was done in order to have an idea of the binding capacity of the compounds to the active binding sites of MAO-A and B, and cholinesterases. The MAO-A and B inhibitory activity was determined using a fluorescent plate reader at an excitation of 310 nm and emission of 400 nm. The AChE and BuChE inhibitory capacity was determined using a Rayto microplate reader at an absorbance of 405 nm.

Results:
The novel compounds synthesised were confirmed by NMR and structure activity relationships could be ascertained. The MAO-B IC₅₀ values for a number of novel compounds were in the low nM range (<100 nM). The compounds showed little to no MAO-A inhibition at a 1 µM concentration, thus confirming their selectivity to MAO-B. The AChE inhibitory assay was done for all the compounds and it was observed that the presence of the bromine moiety improved the AChE inhibitory capacity. The compounds in series 3 showed the best AChE inhibition with IC₅₀ values below 10 µM. The BuChE inhibition assay is still in progress. Preliminary data showed that some of these coumarin-donepezil hybrid molecules were able to significantly inhibit both AChE and MAO-B.

Conclusion:
These novel hybrid molecules showed significant multifunctional activities. Our rational drug design approach and our underlying understanding of the multi-factorial pathology of AD combined with our molecular chemistry knowledge and approaches lead to the identification of exciting new chemical entities that can be studied further as compounds that hold potential as drug entities for the treatment of AD.
Solid dosage formulation of efavirenz by co-crystallization and cyclodextrin inclusion

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Abstract:

Efavirenz is a non-nucleoside reverse transcriptase inhibitor used as an anti-retroviral for the treatment of human immunodeficiency virus (HIV) type I. It is classified as a class II drug under the Biopharmaceutical Classification System (BCS) and exhibits a low solubility (aqueous solubility of 9.0 μg/ml) and high permeability (variable oral bioavailability).

The purpose of this study was to select the most appropriate solid derivatised form of efavirenz to improve the physical, chemical and pharmaceutical properties of the active pharmaceutical drug. To realize this purpose, co-crystallization was employed by liquid-assisted grinding and cyclodextrin inclusion was employed by kneading and freeze-drying methods. Characterization of the co-crystals and cyclodextrin complexes was achieved by hot-stage microscopy, differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FTIR), X-ray powder diffraction (XRPD) and thermogravimetric analysis.

Upon successful preparation of the newly derivatised efavirenz complex, formulation into a solid dosage form was evaluated comparable to the branded form called Stocrin®. Quality control tests according to the United States Pharmacopoeia (USP) standards were assessed such as particle size analysis, angle of repose, uniformity of mass, friability, durability, resistance to crush, disintegration and dissolution.
An assessment of the stability of the first line regimen fixed dose combination anti-retrovirals in South Africa

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Background:
South Africa has the largest antiretroviral treatment rollout programme in the world and with increasing market penetration of generic medicine in this country, there is a call for stringent quality control mechanisms following the marketing approval (post-market quality control). Unfortunately, evidence suggests that the World Health Organisation (WHO) recommendations for this aspect of quality assurance is not met by most Medicine’s Regulatory Authorities. In South Africa and many other countries this is attributed to a lack of physical and financial resources.

Aim:
This study aims to evaluate and compare the quality profile of a selected fixed-dose combination of an antiretroviral drug on tender in the public health sector with its originator counterpart.

Methods:
Samples of the tenofovir/emtricitabine/efavirenz fixed dose combination (tablet dosage forms) will be sourced from the Cape Antiretroviral Depot in the Western Cape Province. To ascertain the quality of these antiretrovirals post marketing authorisation, various quality test such as, dissolution tests, uniformity of weight tests, assay tests and impurity profile for tenofovir disoproxil fumarate according relevant pharmacopoeial specifications will be carried out.
Comparing the drug product performance of anti-infective generics and brand medicines in South Africa’s public sector

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Background:
The use of generic medicines has increased dramatically around the world in response to the escalation of economic pressure in health care – South Africa is no exception. The use of generics provides the opportunity to reduce drug cost to the government and to the patient who is the end user. Despite their increased use, the quality of generics is often met with scepticism by health care providers and patients. Most South Africans lack knowledge about generics and this has translated into negative perceptions about their quality and interchangeability with innovator brands. This study seeks to assess the quality of generic drugs using in vitro tests.

Methods:
This quantitative study assessed the quality of anti-infective generic drugs against each other and against the brand innovator using in vitro tests. Anti-infective drugs on the South African public sector, 2013-2015 tender was used as the sampling frame (N=111). Only tablet and capsule dosage forms were included. Since the tender company was identified as a potential independent variable, an exclusion criterion was a tender that was awarded to a single company, i.e. the tender was not split between 2 or more companies. All seven anti-infective drugs that were eligible for inclusion were tested using dissolution, purity, friability, content and weight uniformity in vitro tests.
Evaluation on the Appropriateness of Digoxin Level Monitoring at Netcare Kuils River Hospital.

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Purpose:
Therapeutic drug monitoring (TDM) of digoxin is monitored worldwide, but such TDM is sometimes inappropriately used. The extent and appropriateness of digoxin TDM at private health care facilities in South Africa is generally not known. The present study evaluates the exact frequency, appropriateness and effectiveness of current digoxin plasma level monitoring at Netcare Kuils River hospital and to identify the major factors contributing to inappropriate TDM.

Methods:
Appropriateness criteria of previous literature were adapted to draw up a measurement tool (questionnaire). A retrospective analysis of twenty in patients folders on digoxin treatment were randomly selected to validate the suitability of the tool at Netcare Kuils River hospital. The finalized tool will then determine the exact frequency, appropriateness and effectiveness of TDM at Netcare Kuils River hospital. A second survey will be compiled and utilized to determine and assess if the pharmacist can play a role in identifying and intervening on factors contributing to inappropriate TDM of digoxin.

Results:
Of the 20 folders assessed, an average of 84% for the appropriateness criteria were considered suitable, 83% of the information was readily available from the folders. 19% of the questions were in duplicate and 10% of the questions provided in conclusive answers.

Conclusions:
The majority of the tool was assessed as suitable to arrive at a decision on the appropriateness of the TDM. This was mainly due to combination of criteria. Some of the questions needed to be reviewed, eliminated and the scoring of the questions changed so that the measurement tool can be more suitable at Netcare Kuils River hospital.