Presents

3rd UWC School of Pharmacy Postgraduate Research Symposium

02 OCTOBER 2017

SCHOOL OF PHARMACY, UNIVERSITY OF THE WESTERN CAPE, ROBERT SOBUKWE ROAD, BELLVILLE, CAPE TOWN 7535, SOUTH AFRICA

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Welcome

Dear guests, participants, staff members and students,

A very warm welcome to the 3rd UWC School of Pharmacy Postgraduate Symposium. We wish everyone an exhilarating, comfortable and intellectually stimulating time in this symposium. As in previous years, presentations will cover a complete spectrum of pharmaceutical research, from drug discovery and development, through pharmacological assessment, development of novel drug development technologies to assessing service-learning needs and optimizing therapy in a clinical setting. We trust that this symposium will re-invigorate everyone and allow us to showcase the value of scientific research by reporting exciting new trends and important advances Science.

We wish to express our gratitude to our sponsor, Aspen Pharmacare, without whom this event would not have been possible. We would also like to thank the staff members who offered advice, and especially acknowledge Ms Benita van Rooyen and Mr Brian Minnis for their support.

On behalf of the organizing committee, we thank you for helping to make this important milestone in the development to our scientific endeavours in science a great success, and wish everyone a very successful and stimulating stay in this symposium.

Sincerely,

Postgraduate Symposium Committee:

Achmat Kamies (abstracts), Bjorn Martin (abstracts), Zaahirah Mukaddam (catering), Lovetone Musakwa (venue), Sheunopa Mzezewa (venue), Julian Sheldon (chair)

Academic Advisors:

Professor Denzil Beukes and Dr Admire Dube
Message from the Director

Dear Postgraduates, Friends and Colleagues,

On behalf of the UWC School of Pharmacy, I would like to welcome you to the 3rd Pharmacy Postgraduate Symposium. We look forward to a day of stimulating scientific presentations and interdisciplinary interaction. This day will provide insight into research projects in the School, stimulate the exchange of ideas and facilitate collaboration across discipline and departmental borders to facilitate taking research in Pharmacy to new levels of innovation and recognition.

We are working and moving towards our vision; to be the Premier Provider of Pharmacy Education in Africa with a Global Footprint in the Pharmaceutical Sciences and our mission; to produce graduates and pharmaceutical scientists equipped to respond to the pharmaceutical and healthcare needs of society. This is done by providing the appropriate education and training and conducting research that is nationally relevant and globally recognized.

Postgraduate studies like these presented here and symposia like these form the cornerstone on which we build the future success of the School and attain our vision and mission of leadership in learning and global recognition for research and innovation. We look forward to your active participation.

Sarel Malan

Director, School of Pharmacy, UWC
# Agenda

**3rd Annual Post Graduate Symposium 02 October 2017**

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## Session 1

**Chairs:** Achmat Kamies & Julian Sheldon

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**Chairs:** Bjorn Martin & Sheunopa Mzezewa

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*Chairs: Zene Damonze & Marilyne Umugiraneza*

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**END OF PROGRAMME**
Formulations and characterization of pcl nanoparticles encapsulating rifapentine

Alkassim Ahmed, Admire Dube, Kenechukwu Obikeze

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

Introduction: Tuberculosis (TB) is one of the world’s deadliest communicable diseases, and as of 2015 the world health organisation [WHO] reported an estimated worldwide incidence of 10.4 million and death toll of 1.4 million. Although effective treatment for the disease is available, the currently recommended treatment for the new cases of the drug susceptible TB consists of a six-month regimen of four first line drugs. The poor absorption of these anti-TB drugs with increased risk of resistance, and poor permeability into infected macrophages result in the long treatment schedule and increased chances of resistance. Rifapentine is one of the new drugs used in the treatment of tuberculosis. However, some pharmacokinetics challenges, including poor absorption and a high affinity for plasma proteins, associated with the use of the drug affect its pharmacodynamics. Nanotechnology drug delivery system offer a promising solution to enhance drug kinetics by nano- encapsulation. This approach significantly contributes to higher bioavailability, as well as improving other kinetics parameters, minimizing TB drug resistance, decrease treatment duration and reduce number of [doses]. PCL is one of the most promising polymers for controlled and site specific drug delivery. It is known for its biodegradability and favourable toxicity profile. The objective is to encapsulate rifapentine in PCL nanoparticles in order to improve the pharmacokinetics of the drug.

Methods: The single emulsion solvent evaporation technique was used to synthesise o/w [PCL] rifapentine loaded [NPs] using polyvinyl alcohol [PVA] as a surfactant. Characterisation of NPs for particle size, [PDI] and [ZP] was done using [DLS] and particle shape was determined by [SEM]. UV-VIS spectroscopy was used to determine rifapentine loading and release in [PBS pH 7.4 at 37°C].

Results: The z-average size of the nanoparticles was found to be 351.3±10.3nm. All NPs formulated were relatively monodisperse, with the PDI less than 0.4. ZP values were less than -30mv. 0.0069 of the drug was encapsulated.

Conclusions: Having successfully formulated NPs with good physicochemical properties, the NPs are suitable for delivery and can be used for further pharmacokinetics studies in animals.

Keywords: Tuberculosis, rifapentine, PCL nanoparticles.
First-in-class ‘green’ gold nanoparticles with methodical release properties — Sargassum incisifolium’s nanocarrier

Byron Mubaiwa1,2. Edith Antunes1,3, Denzil R. Beukes1,2.

1Marine BioDiscovery Research Group, 2School of Pharmacy, 2Department of Chemistry, University of the Western Cape, Robert Sobukwe Road, Bellville, Cape Town, 7535, South Africa

Introduction: The long standing goal for medicinal care is for medicines to work as efficient, targeted in vivo ‘machines’ without systemic toxicity. This is especially for conditions where selective toxicity is difficult to achieve, such as cancer therapy. Nanotechnology, a robust field of our times, has aspects of which some of these difficulties can and are being addressed. Nanomaterials such as gold nanoparticles, have been identified as multifunctional platforms to carry bioactives, and are thought to be vehicles capable to deliver them in a way as to improve efficiency and selectivity. This technology has inevitably converged with natural products in a parallel drive to use less toxic chemicals and energy, to produce products that are biologically and ecologically friendly—the so called greener practices. Marine algae are one of three major natural biomasses used to prepare ‘green’ nanoparticles, and this study is centralized around marine brown alga based, Sargassum incisifolium gold nanoparticles.

Methods:

Result: Using various specification Sargassum gold nanoparticles; the nanoconstruct prepared from between 20–40 mg of extract, appeared to bind an optimum amount of bioactive and consequently release it over 72 hours—to a plateau of up to 90% of total expected metabolite.

Conclusions: A ‘first in class’ nanocarrier assembled from the aqueous extract of a naturally obtained marine alga, Sargassum incisifolium {obeying some green synthetic practices}, was presented here—the functionalized ‘green’ gold nanoparticle. The controlled, methodical and repeatable nature of the release, reveals a potential nano-drug carrier; capable of carrying small molecules in a biological system and binding them for sufficient time to reach their target. Slowing down in vitro molecule release and further understanding the pH-responsiveness of the nanoparticles, would be a future direction to take.

Keywords: Nanomedicines, Small-molecule-delivery, Brown Marine Algae, Metallic Nanomaterials.
Antimicrobial discovery from South African marine algae

Edmund R Mabande1,2, Marilize Le Roes-Hill3, John J. Bolton4, Nicole Sibuyi5, Mervin Meyer5, Denzil R Beukes1,2

1Marine Biodiscovery Research Group, 2School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville, South Africa.
3Biocatalysis and Technical Biology Research Group, Institute of Biomedical and Microbial Biotechnology, Cape Peninsula University of Technology, Bellville 7535, South Africa,
4Department of Biological Sciences, University of Cape Town, Rondebosch, 7701, South Africa,
5Department of Biotechnology, University of the Western Cape, Robert Sobukwe Road, Bellville, South Africa

Introduction: Antimicrobials are chemical compounds that destroy or inhibit the growth of microorganisms. The development of (antimicrobial) drug resistance and slow pace of new antibiotic discovery is one of the major health challenges facing the world today. There is therefore a crucial need to discover and develop new antimicrobial agents. In this study we explore the potential of marine algae as a source of new antibiotics.

Methods: Crude organic extracts and chromatographic fractions obtained from small scale extraction of 17 different marine algae were used to prepare a pre-fractionated library that would be tested against several disease causing microorganisms. The activity of the prefractionated library and purified compounds was determined against a panel of drug resistant microorganisms namely Acinetobacter baumannii ATCCBA-1605, Enterococcus faecalis ATCC 51299, Escherichia coli ATCC 25922, Staphylococcus aureus subsp. aureus ATCC 33591 and Candida albicans ATCC 24433. Cytotoxicity tests of 50-selected library extracts and isolated compounds were also done. Based on its antimicrobial activity and interesting chemical profile, the seaweed Plocamium sp. was selected for further study. Plocamium metabolites were purified using preparative chromatography as well as normal phase HPLC. The structures of purified compounds were determined from spectroscopic data e.g. NMR.

Results: A small library of 153 fractions was generated from collections of South African marine algae. Pre-fractionated crude extracts showed excellent antimicrobial activity against all microbes but particularly against Staphylococcus aureus. Three new halogenated monoterpenes were isolated and their structures determined. The compounds were generally active against the gram-positive bacteria and the yeast. Compounds were relatively non-toxic to the human cell lines.

Conclusion: Three novel, antimicrobial halogenated monoterpenes were isolated from a Plocamium sp. Antimicrobial activity of crude fractions was excellent but that of isolated compounds was not as great as anticipated possibly due to their highly non-polar nature.

Keywords: Antimicrobial, natural products, marine algae, halogenated monoterpenes, cytotoxicity, drug resistant, bioautography, HPLC, structural elucidation
Evaluation of angiotensin converting enzyme inhibitory activity of 
Centella asiatica leaves extract

Emmanuel Ichoku, Kenechukwu Obikeze

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

Introduction: Angiotensin Converting enzyme inhibitors (ACEIs) have been established as one of the major therapeutic agent in the treatment of hypertension and diabetic nephropathy. Over the years, studies have been conducted on plants of natural origin to identify new ACEI compounds. Centella asiatica commonly known as Gotu Kola, is traditionally used for wound healing, improving memory concentration and venous insufficiency in South Africa. Claims have been made about the anti-hypertensive effect of C. asiatica but few studies have been conducted to validate such claims. The purpose of this study was to identify and evaluate ACE inhibitory activity of the leaves extracts of the plant.

Method: Plant Extraction- 2 kg of Dried Centella leaves powder was macerated in ethanol (99%) and distilled water for 24 hours, Extracts were filtered, evaporated and freeze dried to yield ethanol and aqueous extracts respectively. ACE activity- AssayACE inhibition by the extracts was evaluated according to the modified method of Wanasundara et al., 2002). Fluorescence of OPA bound to enzyme-cleaved HHL on a fluorescence plate reader at 355nm excitation, 535nm emission was used to determine ACE inhibitory effect of different concentrations (50, 100 and 200mg/ml) of each extract. Enalapril was used as positive control and sodium borate buffer as negative control.

Results: Both Extracts showed inhibitory activity, with ethanolic extract showing the highest inhibitions at 98% (50mg/ml) and 99.37% (200mg/ml) respectively, and aqueous extract at 35.09% (50mg/ml) and 93.56% (200mg/ml). IC50 value for ethanolic and aqueous extracts were determined at 75.63 and 96.34 mg/ml respectively.

Conclusion: Ethanolic extract of Centella Asiatica consistently showed a significant high inhibition activity when compared to the aqueous extract indicating ACEI activity. Further studies will be conducted on the ethanolic extract to identify which compound or group of compounds shows activity.

Keywords: Angiotensin Converting Enzyme inhibitor, Centella asiatica, Gotu Kola, Asiatic Pennywort, In vitro Assay, hypertension.
Effect of particle size on the antibacterial activity of gold nanoparticles

Ephraim Maphasa, Mervin Meyer and Admire Dube

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

Introduction: Antibiotic-resistant bacteria have become a major global challenge. Killing of antibiotic-resistant bacteria requires a high dose of expensive drugs, which possess negative side effects to the infected individuals. Spherical gold nanoparticles (sAuNPs) have been reported to exert antibacterial activity against a number of gram positive and gram-negative bacteria. However, there is still uncertainty regarding the antibacterial activity of sAuNPs. In this study, it was hypothesized that AuNPs will show a size- and concentration-dependent antibacterial activity against selected gram positive (+) and gram negative (-) bacteria.

Methods: sAuNPs were synthesized using citrate reduction. The size of each NP was examined using the Malvern Zetasizer Nano-ZS90 instrument. The morphology of the NPs was determined using HR-TEM. The stability of the NPs in both dH₂O and LB media was also determined at 4°C and at 37°C. The bacterial growth inhibiting activity of each AuNP was examined using the broth micro-dilution and Alamar blue.

Results: The hydrodynamic sizes of the AuNPs were 62.7 ± 4.6 nm (AuNP 1), 33.68 ± 1.68 nm (AuNP 2) and 24.49 ± 0.05 nm (AuNP 3). All these NPs were relatively monodispersed with PDI values of 0.545 ± 0.05, 0.398 ± 1.0 and 0.259 ± 0.09, respectively. The NPs were prone to aggregation when introduced to nutrient media. Nevertheless, The NP clusters showed activity against E. coli.

Conclusions: The sAuNPs formed clusters in LB media. These clusters showed a time-and concentration-dependent growth inhibiting activity against E. coli when compared to S. aureus and MRSA. Therefore, the results indicated that the sAuNP clusters had more growth inhibiting activity against gram-negative bacteria. Clusters of AuNP 1 showed more effective at inhibiting the growth of the selected bacteria.

Keywords: Antimicrobial-resistance, Escherichia coli, Bacterial growth inhibition Gold nanoparticles, Methicillin-resistant Staphylococcus aureus and Staphylococcus aureus.
Optimising diabetes management at a public sector primary health care clinic in Cape Town

Farhaana Sonday, Angeni Bheeki, Mea Van Huyssteen

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

Introduction: Diabetic patients are often prescribed medicine therapies which are not in accordance with standard treatment guidelines (STGs). In such situations, medicine related problems (MRPs) are inevitable. The pharmacist’s role in medicine therapy management (MTM) for diabetes is underutilized in public sector health care facilities.

Methods: An evaluation study design with a case study approach was implemented over 8 months at a community day centre. The pharmacist/researcher trained in therapeutics assessed prescriber adherence to STGs in the management of stable diabetic patients. Pharmacist-led recommendation(s) were noted on a label which was attached onto the diabetic patient folder to prompt prescriber action at the patient follow-up consultation. Ethics approval was obtained from the University of the Western Cape (MB/16/4/11) and the Department of Health (WC_2016RP43_75).

Results: Retrospective prescriptions evaluations from 109 diabetic patient folders led to the identification of 453 MRPs that prompted pharmacist-led recommendations. The most frequent MRP identified related to prescribers not requesting laboratory tests (69%) for medicine efficacy monitoring and overlooking patient body mass index calculations (81%) for medicine dose calculations. Overall, one-quarter (27%) of the pharmacist’s recommendations was accepted by prescribing staff. The indiscriminate prescribing of aspirin (15%) in diabetic patients needs attention.

Conclusions: Prescriber uptake of pharmacist’s therapeutic recommendations is novel in public sector primary care facilities. Prescription monitoring and evaluation is crucial to optimise rational medicine use at facilities. Pharmacist-led workshops advocating a multidisciplinary team approach in the management of diabetic patients at primary health care facilities should be instituted.

Keywords: diabetes; medicine related problems; medicine therapy management; pharmacist-led recommendations; multidisciplinary team
Polycyclic propargylamine derivatives as multitargeted neuroprotective agents.

Frank T. Zindo, Sarel F. Malan and Jacques Joubert

School of Pharmacy, University of the Western Cape, Private Bag X17, Bellville 7535

Introduction: The multifactorial pathogenesis of neurodegenerative diseases remains a hindrance to the successful design of an ‘ultimate’ drug that can potentially confer sufficient neuroprotection. We previously reported polycyclic propargylamine derivatives to exhibit in vitro anti-apoptotic activity. The compounds however showed little to no inhibitory activity on the L-type voltage gated calcium channels (VGCC’s), N-methyl-D-aspartate (NMDA) receptors as well as the monoamine oxidase B (MAO-B) enzyme. These target sites are some of the main targets for existing treatment options. We have therefore designed a new series of propargylamine derivatives with the intent of improving activity on these vital drug target sites.

Methods: The new series of compounds carry the propargylamine functional group conjugated to various polycyclic cage moieties. The series design was guided by computer simulated docking studies performed on the Molecular Operating Environment® (MOE) software to predict potential binding interactions with the MAO-B enzyme active site. Using the polycyclic cage moiety as a scaffold, the new compounds were synthesized by virtue of SN2 nucleophilic substitution reactions to afford 12 propargylamine-derived compounds. These compounds will be assayed for in vitro cell viability, neuroprotection, VGCC, NMDA receptor and MAO-A and -B inhibitory activity.

Results: Cell viability studies were performed on SH-SY5Y human neuroblastoma cells using the 1-methyl-4-phenyl pyridinium (MPP+) induced neurotoxicity method at test compound concentrations of 10 µM, 50 µM and 100 µM. The results show that treatment with test compound at 10 µM did not significantly affect cell viability. More biological work on neuroprotection, VGCC, NMDA receptors and MAO-A and -B inhibition assays is currently underway. The results from these assays will give a broader activity profile of the novel series of propargylamine derivatives.

Conclusion: Compounds that render such multimechanistic activity have great potential to serve as future analogues for the treatment and management of neurodegenerative disorders.

Keywords: Neurodegeneration, Multitargets, Propargylamine, Molecular Modelling
The development and application of state-of-the-art ICP-MS methods for routine testing of clinical development and commercial drug product and pharmaceutical components for elemental impurities

*Heather Moyo*¹, *Eberhard König*², *Christoph Meyer*², *Marcel Jegge*²

¹Department of Pharmaceutical Chemistry, School of Pharmacy, University of the Western Cape, Bellville, Cape Town 7535
²Elemental Impurities Center of Excellence, QC-AS&T, Novartis Technical Operations
Novartis Pharma Stein AG, Stein, Switzerland

**Introduction:** ICH Q3D is a new global guideline which requires the routine testing of elemental impurities in drug products used in clinical development and in commercial supply. The Novartis Technical Operations network consisting of more than 67 production sites invested in 7 Centers of Excellence (CoE) for ICP-MS laboratories one of which is being established in Stein. This ICP-MS lab is being developed and will need to go into routine operation. For this, the lab needs to be set up and analytical method development is required. Of particular concern was repeatedly reported copper level incompatibility when matrices containing sodium are sent for testing at an external laboratory. It falls on Novartis to ensure that the sources of these samples comply by the time the new regulation comes into play. In addition, it is required that risk assessments making use of Quality by Design approaches be compiled for commercial products and for products used in clinical development. To this end, a cross-industry effort at sharing non-proprietary information was established and a review of the data gathered thus far was prepared for publication. The information in the coalition database can be used in the risk assessments based on conclusions reached from the gathered data.

**Methods:** Experimental use of ICP-MS, Data mining

**Results:** Compliance of matrices that contain sodium was achieved with the use of ICP-MS on kinetic energy discrimination (KED) mode. Mined excipients have the highest quantities of elemental impurities. More samples are needed for 23% of the excipients in the coalition database to enable a credible preliminary analysis of the results to determine their associated toxicological risk. Risk determination goes beyond the data offered on paper for some excipients. The analytical chemist must use their discretion depending on application and the actual amount used in practice to make a determination as to the risk of such excipients, for example, colorants.

**Conclusions:** ICP-MS on KED mode will be used to ensure compliance of pharmaceuticals and pharmaceutical components which contain sodium at NTO, Stein. Information gathered and consolidated during the data-mining process on the coalition database will be used to compile risk assessments for pharmaceuticals and pharmaceutical components. The review of the coalition database has been arranged into 3 different presentations: an internal one to be used for training of associates, an external one to inform industry partners on findings and recommendations, and one for the database host company, Lhasa Limited, with feedback and recommendations.

**Keywords:** Elemental impurities, Worst-case toxicological outcome, permitted daily exposure limits, Inductively-coupled plasma mass spectrometry (ICP-MS), Compliance, Quality by Design, Data-mining, Risk assessments
Indole derivatives as multifunctional agents for Alzheimer’s disease

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Introduction: Alzheimer’s disease (AD) is one of many diseases that can be classified as a neurodegenerative disorder and is ranked as the leading cause of death among the elderly. The pathology of AD and other neurodegenerative disorders involves multiple steps leading to neuronal cell death. Current treatment options include cholinesterase- and monoamine oxidase-B inhibitors, calcium channel blockers and NMDA receptor antagonists. These treatment options, however, only alleviate the symptoms of these disorders and are devoid of any neuroprotective and/or neurorestorative properties that are needed for disease modifying effect. The result is a shift in research towards the design and discovery of multi-target compounds. This study is thus based on this one-drug-multiple-target paradigm and aims to produce a new series of indole derivatives with multifunctional activities. We hypothesize that these compounds will serve as dual cholinesterase and monoamine oxidase inhibitors and possess superior activity compared to existing anti-Alzheimer’s drugs.

Methods: The synthesis of the compounds was carried out by nucleophilic substitution of an acyl chloride to the indole ring followed by the substitution of propargylamine moiety at position 1. Eight compounds were successfully synthesized and characterised. Thereafter in vitro assays were carried out on four enzymes (MAO-A, MAO-B, acetyl- and butyrylcholinesterase) to ascertain the inhibitory capacity of the compounds. Molecular modelling was carried out using MOE to visualise binding interactions in the enzymes. The results showed that the compounds occupied the active sites of the enzymes and had interactions with significant amino acids.

Results: MAO and cholinesterase inhibitory activities were tested at various concentrations with clorgyline, rasagiline and tacrine as reference compounds. All the compounds showed satisfactory inhibition of both enzymes. The results of a chemical stability test showed that 6 is more stable than the carbamate linked compound 8. This compound can thus be considered for optimisation and perhaps development as a multipotent drug molecule against AD.

Conclusions: AD poses an enormous socio-economic burden on society and it is critical that research identifies compounds that are able to slow down or halt the progression of AD. This study identified novel multifunctional agents with potential neuroprotective properties that may be considered as new lead compounds/drug candidates against AD.
The effectiveness of using pictograms on medicine labels: a comparative study in community health centres in Cape Town

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Introduction: Inappropriate medicine labelling contributes to poor interpretation and improper use, which could adversely affect patient health outcomes. In developing countries, pictograms on medicine labels support patients’ ability to read, understand and recall information. This comparative study examined patient interpretation of ‘routine text-only instructions’ versus ‘text and pictogram’ medicine labels on oral rehydration (OR) pre-packed dry ingredients.

Method: Community health centres (n=4) from Tygerberg sub-district were recruited. Participants (n=132) located in the paediatric section’s waiting area were either shown an OR medicine label which is routinely used (control group, n=65) or one containing both text and pictogram instructions (experimental group, n= 67). Each participant had to answer six questions about OR preparation and use. These responses were recorded and rated for accuracy by comparing the participant’s answer to the actual information on the relevant label. Ethics approval was obtained from the University of the Western Cape (BM/16/3/01) and Cape Town City Health (WC_2016RP38_657).

Results: Of the six label-specific questions participants from the experimental group were able to give more accurate answers for four of the questions as compared to the control group. The most significant difference between the two groups were recorded for the question that could be read from a single pictogram (p=0.00) on the experimental group’s label. Almost two-thirds of the experimental group (64%) indicated that they did not find it difficult to understand the text and pictogram label, compared to a third of the control group’s (32%) response to the routine label.

Conclusion: Pictograms on medicine labels are an effective tool to reinforce understanding of medicine use instructions. Medicine labels with pictograms should be encouraged at public health facilities. Pictograms for other commonly used medication should be investigated.

Keywords: Medication label, oral rehydration therapy, pictogram.
Synthesis and evaluation of fluorescently linked polycyclic cage derivatives for application in neurodegenerative disorders

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Introduction: Neurodegenerative disorders are usually chronic in nature and characterized by the gradual, progressive loss of neurons in specific areas of the central nervous system (CNS), more precisely the brain. Examples of these diseases include Alzheimer's (AD) and Parkinson's disease (PD). Most of these are incurable with a range of signs and symptoms usually leading to functional limitations. They affect the quality of daily life of both the individuals suffering from the disorder and their families. Worldwide approximately 47 million people live with dementia, and it is expected to increase to more than 131 million by 2050, meaning it has a huge socio-economic impact. The pathology of neurodegenerative disorders involves multiple steps leading to neuronal cell damage or death. Current treatment options for these diseases include calcium channel blockers and N-methyl-D-aspartate receptor NMDA receptor antagonists, cholinesterase and monoamine oxidase-B inhibitors. These however only result in symptomatic relief, and are devoid of any neuroprotective and/or neurorestorative properties. Furthermore, fluorescent imaging techniques can be used to visualise degradation of the CNS and also help visualise the distribution of drugs in the CNS. This can help with early detection and more effective treatment of these disorders.

Method: The synthetic procedure involved conjugating fluorescent ligands to polycyclic cages via substitution reactions. Structural elucidation was carried out using analytical techniques NMR, MS, and IR. NMDA and voltage gated calcium channel assays are being carried out and finally, fluorescent imaging studies will be done using an IVIS Spectrum device.

Results: The compounds have been successfully synthesised and confirmed by NMR and IR. The biological assays are currently being done, while fluorescent imaging will be the final step.

Conclusion: Neurodegenerative diseases pose an enormous socio-economic burden on society, thus studies improving not only the understanding, but also our ability to treat these diseases are crucial. This study will identify novel fluorescent agents with potential neuroprotective properties that may be considered as new lead compounds or fluorescent imaging tools that may find application in neurodegenerative studies.
Integrating complementary and alternative medicines into pharmacy practice: identifying challenges in meeting professional responsibilities and training needs

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Introduction: Community pharmacies are popular suppliers of complementary and alternative medicines (CAMs) and pharmacists encounter requests from consumers for information on them. The purpose of this study was to assess the extent to which community pharmacists, and final year pharmacy students at the University of the Western Cape (UWC), are able to meet professional obligations with respect to CAMs.

Method: Data was collected through semi-structured interviews with nine practicing community pharmacists in the Cape Metropole, a questionnaire and knowledge test on CAMs conducted with fourth year pharmacy students at the UWC, and an electronic survey implemented nationally with practicing community pharmacists.

Results: Interviews with pharmacists revealed that the majority (>65%) reported sufficient or extensive knowledge on health supplements. In contrast, the majority (> 65%), indicated that they had minimal or no knowledge on herbal medicines and homeopathic preparations. Results from student surveys reflect that majority (between 60-85%) of students had either no knowledge or that their knowledge was minimal and insufficient to advise and counsel patients on the use CAMs. The national electronic survey results revealed that most significant barrier experienced by pharmacists in meeting their professional responsibilities, was the lack of knowledge and confidence on CAMs. Majority of pharmacists (90%) indicated that their undergraduate training was insufficient to prepare them to meet the professional responsibilities with respect to CAMs.

Conclusion: The results of this study revealed that the education and training on CAMs have been insufficient to prepare pharmacists and pharmacy students to meet the professional responsibilities expected of a pharmacist. There is a need for training to be addressed to prepare pharmacists to meet consumer requirements for information and guidance on the use of CAM products.
Hygroscopic starch polymer of *Ipomoea batatas*: A novel tablet excipient in high-dose formulations?

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**Introduction**: Natural starch polymers have been explored and used as excipients in the pharmaceutical industry due to their low toxicity, low cost and availability. The choice of excipient is particularly critical for high-dose formulations due to the necessity to optimize the quantity utilized. It is important to keep the size of tablet small and acceptable for swallowing in spite of the increased drug load.

**Methods**: The analytical and mechanical evaluations of the hygroscopic starch polymer derived from *Ipomoea batatas* as a tablet binder and filler/disintegrant were carried out in comparison with starch 1500 (maize starch BP) in paracetamol high-dose formulation. Preparations of the polymer as extragranular excipient and as binder at varying concentrations of 2.5, 5.0 and 7.5% w/w were used to produce the granules by wet granulation method and compressed into tablets at 26.25KN. The analytical evaluation of the starch polymer/paracetamol solid system was obtained by FTIR, DSC and TGA, while the mechanical strengths and drug release properties of the designed tablets were assessed using RC/FR ratio, RCFR/DT ratio and dissolution rate.

**Results**: Notable chemical incompatibilities were observed between the starch polymer and paracetamol when large amounts of the polymer (≥30%w/w) were used. However, smaller quantities of 5% w/w and less do not produce incompatibilities.

**Conclusions**: Hygroscopic *Ipomoea batatas* starch polymer was found to compared well with maize starch BP as binder and filler/disintegrant when used in small quantities at the percentage by weight specified (≤5% w/w). The polymer is thus only suitable for use in high dose formulations that do not require large quantities of excipients.

**Keywords**: Hygroscopic *Ipomoea batatas*, starch polymer, high-dose formulation.
Isolation and structural characterization of cytotoxic secondary metabolites from South African *Ircinia* and *Latrunculia* sponges

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**Introduction:** Cancer is a major health problem worldwide and it occupies one of the top positions as cause a death in most countries. The use of natural products as chemotherapeutic agents is well established, however, many of the currently available drugs are associated with undesirable side effects and high toxicity. Furthermore, the development of drug resistant cancers makes the search for anticancer lead compounds a priority. Historically, researchers have mainly focused on terrestrial organisms for drug discovery leaving the marine environment an untapped source of new anticancer drug leads. Marine sponges of the genus *Ircinia* and South African Latrunculid sponge are known to produce potent cytotoxic natural products. In this study we investigated the chemical constituents of a newly collected *Ircinia* and Latrunculid sponges from the coasts of South Africa and their cytotoxicity.

**Method:** The 2 sponge samples; *Ircinia* and Latrunculid sponges, were exhaustively extracted with methanol and methanol/dichloromethane 1:1 and organic extracts were concentrated under reduced pressure. *Ircinia* sponge extract was subsequently chromatographed on HP20SS, silica gel and normal phase HPLC to give a mixture of geometric isomers variabilin and strobilinin. In case of Latrunculid sponge, the organic extract was separated using modified Kupchan separation method to get 3 fractions, MeOH, CHCl₃ and hexane fractions. MeOH extract was further separated on SepPak C18 column chromatography with gradient elution followed by C18 reversed phase HPLC to give tsitsikammamine A and tsitsikammamine A N₁₈-oxime. Structure elucidation of the compounds was done by thorough analysis of their 1D and 2D NMR data and by comparison with literature. Cytotoxic activity of the three compounds was performed using WST-1 antiproliferation assay on 4 cell lines; MCF-7, PC-3, U-87 and HEK-293.

**Results:** A mixture of geometric isomers furanosesterpenes was isolated from Ircinia sponge and were identified as variabilin and strobilinin. From Latrunculid sponge, tsitsikammamine A and tsitsikammamine A N₁₈-oxime were isolated. The tsitsikammamines showed potent cytotoxicity effects against all 4 cell lines with IC₅₀ as low as 1.5µg/ml and 5.6µmg/ml for tsitsikammamine A and tsitsikammamine A N₁₈-oxime respectively while variabilin/stroblinin had the least activity and only showed less than 50% cell viability on HEK-293 cell line with IC₅₀ of 11.9µg/ml.

**Conclusion:** secondary metabolites were successfully isolated from Ircinia and Latrunculid sponges and these metabolites showed potent cytotoxicity effects against MCF-7, HEK-293, PC-3 and U-87 cell lines.

**Keywords:** *Ircinia* sp., Latrunculid sponges, marine natural products, tsitsikammamines, furanosesterpenes, cancer, cytotoxicity.
A pharmacy perspective on the epidemiology of antimicrobial drugs in the Kuilsriver area to treat infections.

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Introduction: Antimicrobial drugs have a pivotal role worldwide in preventing infections and treating infectious diseases. The challenge that lies in the health sector is to maintain antimicrobials’ effectiveness by using them appropriately (P.Matsoso 2015). The aim of this study is to investigate the epidemiology of antimicrobial drugs and factors that lead to the inappropriate use of antimicrobials in the private sector from a pharmacy perspective.

Methods: This was a cross-section study design where two different questionnaires were used to collect data for analysis. Patients’ questionnaires aimed at collecting data on their health history, antimicrobial knowledge and psychosocial factors. The Unisolve questionnaires aimed at collecting data on patients’, prescribers’ and antimicrobial drugs information.

Results: One hundred and thirty-two respondents were included in the first part of the study and 65.9% of the respondents received antimicrobial agents without a prior diagnostic test done to conclude presence of an infection, while only 34.1% reported that diagnostic tests were done. A total of 24.2% of the respondents knew what antimicrobial agents that had been prescribed while 75.8% had no idea. Sixty respondents reported on, keeping antimicrobial drugs for future use (33.3%), throwing away leftovers (61.7%), while 5% kept for other ailments. The second part of the study had five hundred and three patients included and results showed that dentist, general practitioners and specialist prescribed antimicrobial drugs inappropriately in (17.2%, 42.9%, and 34.1%) of each group’s total prescriptions respectively.

Conclusions: Epidemiology studies proved to be useful tools to judge appropriateness of antimicrobials use amongst patients and prescribers and to determine factors affecting inappropriate use. This study showed that both patients and prescribers use antimicrobial drugs inappropriately.

Keywords: Antimicrobial drugs, epidemiology, cross-section study
Novel Adamantane-Chloroquinolin Conjugates to overcome *Plasmodium falciparum* chloroquine resistance

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**Introduction**: Malaria poses devastating health and socioeconomic outcomes on global health, especially among pregnant women and children below the age of 5 in endemic areas. This is made worse by *Plasmodium falciparum* resistance to available antimalarials, especially chloroquine (CQ), which was the drug of choice for many years against blood stage malaria. CQ resistance is mostly associated with mutations in the *P. falciparum* chloroquine resistance transporter (PfCQRT) protein localized in the parasitic digestive vacuole (DV) membrane. It enhances CQ efflux out of the DV and reduces its accumulation at its site of action. Consequently, there is need for continued research for a more effective therapeutic drug to solve this problem of CQ resistance. The aim of this study was to synthesize novel adamantane-chloroquinolin (AD-CQ) conjugates as potentially improved ‘reversed chloroquine’ compounds to overcome *P. falciparum* CQ resistance.

**Methods**: The AD-CQ conjugates consisted of the CQ-like 4-aminoquinoline pharmacophore conjugated to an adamantane moiety via an alkyl linker. Firstly, the CQ-like nucleus was conjugated to alkyl linkers of different chain lengths by nucleophilic substitution reactions to generate the aminoquinoline (ACQ) intermediates. These compounds were then used for the synthesis of the novel AD-CQ conjugates in series 1 and 2. Series 1 compounds were synthesized by conjugation of an adamantane diketone and appropriate ACQ intermediates via reductive amination followed by transannular cyclization. Series 2 compounds were synthesized by direct conjugation between 2-adamantone and ACQ intermediates. The novel conjugates were structurally confirmed by NMR, IR and MS and subjected to in vitro MTT and pLDH assays to evaluate their cytotoxic and antimalarial activity against CQ*S* and CQ*R* strains of the *P. falciparum* parasite respectively.

**Results**: All the novel AD-CQ compounds were non-toxic (CHO IC<sub>50</sub> = 37860 – 279420 nM) and some of the conjugates exhibited potent antimalarial activity in vitro, superior to CQ against the CQ*R* strain and thus overcame *P. falciparum* CQ resistance. Compound 5, 6 and 9 were highly active compounds on both CQ*S* and CQ*R* strains (IC<sub>50</sub> < 100 nM). Compound 5 showed the lowest resistance index (RI = 2.11) with good activity against the CQ*R* strain (IC<sub>50</sub> = 98.92 nM) and was identified as the most promising novel AD-CQ conjugate. Its ability to retain activity in the CQ*R* strain was 18-fold better than that of CQ. The adamantane moiety, especially the aza-adamantanol, was shown to be a significant *P. falciparum* CQ resistance reversal agent compared to the previously used structurally related compounds.

**Conclusions**: The 4-aminoquinoline pharmacophore is still a viable class for optimisation to generate new antimalarial compounds. The hybridization of adamantane moieties as reversal agents to a 4-aminoquinoline nucleus produced improved reversed CQ molecules that overcame *P. falciparum* CQ resistance in vitro.
Influence of HIV status and age on cycloserine clearance in multidrug-resistant tuberculosis patients

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Introduction: Despite the high rate of adherence to anti-tuberculosis medication by patients, the emergence of multidrug-resistant tuberculosis (MDR-TB) still occurs. Literature implicates pharmacokinetic variability in anti-tuberculosis drugs as one of the main causes of the emergence of MDR-TB. The objective of this study was to describe the population pharmacokinetics (PPK) of cycloserine and determine the factors affecting its clearance.

Methods: This non-randomised clinical study involved 30 MDR-TB patients admitted to Brewelskloof Hospital in Worcester and were in the intensive phase of treatment for at least 2 weeks. Blood samples were collected at baseline, 1, 2, 3, 4, 8, 16 and 24 hours after witnessing drug intake. Plasma concentrations were determined using a validated LC-MS/MS method. Population pharmacokinetic parameters were estimated by employing non-linear mixed effects modelling executed in Monolix 2016R1 software.

Results: A total of 146 plasma samples from 30 patients were included in the analysis. A 2-compartment model with first-order elimination best described pharmacokinetic profiles of cycloserine. The PPK parameters estimated were $K_a$ (absorption constant), $C_l$ (central clearance), $V_1$ (central volume), $Q$ (inter-compartmental clearance) and $V_2$ (peripheral volume), 0.03 h$^{-1}$, 45.5 L/h, 36.7 L, 4.33 L/h and 22 L, respectively. Being HIV positive and old decreased cycloserine clearance ($C_l$), $\beta = -0.687$ and $-0.688$, respectively. The inter-individual variation in $K_a$ was 87.8% and in $C_l$ was 40.6%. $V_1$ had the largest inter-individual variation with 103%.

Conclusions: Cycloserine clearance is affected by HIV status and old age in MDR-TB patients. We propose a cycloserine dose adjustment in this population of patients or preferably individualised dosing.

Keywords: Cycloserine, MDR-TB, population pharmacokinetics, HIV.
Evaluation of the protein corona of human serum albumin on polycaprolactone and poly(lactic-co-glycolic) acid nanoparticles

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Introduction: Nanotechnology is a concept of high potential in many applications in modern science yet suffers a great limitation known as protein corona; layers of proteins forming on the surface of nanoparticles (NP) by covalent bonds, forming two layers, hard corona (bound to the surface of nanoparticle) and soft corona (a layer of protein exchange with surrounding proteins due to their abundance). This soft corona confers dynamic changes on the surface and determines NP characteristics as this layer may inhibit or promote cell association. Overall understanding of this complex can enable prediction of resulting biological response and biodistribution of NP. This study is attempting to predict and quantify interaction of human serum albumin proteins with PCL and PLGA nanoparticles using proteomics. Currently we do not know the specific proteins forming the corona of PCL and PLGA NPs. However, understanding this interaction in future we can use one of these NPs to load drug to lower the affinity on the drug to human blood plasma for latent tuberculosis treatment.

Methods: Protein binding study of Polycaprolactone (PCL), Polylactic acid (PLA) and Poly(Lactic-co-glycolic) Acid (PLGA) was done using UV spectroscopy and Fourier Transformation Infrared Spectroscopy (FTIR). The emulsion-solvent evaporation technique was used to synthesize PCL and PLGA nanoparticles based on low affinity for the drug. Dynamic light scattering and Scanning Electron Microscopy (SEM) were used to evaluate particle size, zeta potential and shape. Proteomic study on protein interaction with nanoparticle surface was studied using gel electrophoresis and these proteins from Human Serum Albumin will later be identified with Matrix-assisted laser desorption/ionization-Time of flight mass spectrometry (MALDI-TOF).

Results: The z-average size of the PCL is 384.4 ± 12.80 nm, Polydispersity index 0.169 ± 0.05 and Zeta potential -14.86 ± -2.49 (mV). The z-average size for PLGA is 434.0 ± 83.08 nm, Polydispersity index 0.262 ± 0.07, and Zeta potential -6.17 ± -3.03 (mV). SEM results showed spherical particles of approximately 200 nm size. One-dimensional SDS gel electrophoresis showed that protein corona forms around particles being a soft and hard corona.

Conclusions: Proteins from human serum albumin bind to PCL and PLGA nanoparticles forming a soft and hard corona. Next set of studies will identify these proteins using MALDI-TOF mass spectrometry.

Keywords: Tuberculosis, Polymer, PCL, Nanoparticles, Protein Corona.
Isolation and structural characterisation of marine natural products with anti-mycobacterium activity

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Introduction: Tuberculosis (TB) is an airborne bacterial infection caused by *Mycobacterium tuberculosis*. An estimated one-third of the world population is reported to have been latently infected by *M. tuberculosis*. Furthermore, the approximate mortality rate from active TB is about three million annually. Current drug treatment poses several challenges including toxic side-effects and drug resistance. There is, therefore a need for new drugs for the treatment of this infectious disease. Marine natural products offer unique and chemically diverse compounds which serve as antibacterial leads. However, few studies have explored the use of marine natural products in the treatment of TB. Hence, this study aims to discover new and effective anti-mycobacterial leads from marine natural products.

Methods: A polymerase chain reaction (PCR) amplification of the 16S ribosomal RNA gene from 3 marine bacterial isolates was performed. The amplicons were sent for sequencing and the obtained nucleotide sequences blasted against the NCBI 16S ribosomal RNA database for identification of the 3 isolates. For initial bioassay test, sloppy-agar overlay activity test against *Mycobacterium smegmatis* was performed. Following activity testing, the isolates were grown for 14 days in a 250 mL GYM streptomycetes medium to enable production of secondary metabolites. The pellet was separated from the cell culture by centrifugation. The supernatant was treated with ethyl acetate. The ethyl acetate extracts were dried in a rotary evaporation and the dried samples reconstituted in dimethyl sulfoxide and analysed by ¹H NMR spectroscopy. Thereafter, promising lead extracts were fractionated by C18-Reversed phase silica gel column chromatography. Subsequently, the fractions were tested for inhibitory activity against *Mycobacterium smegmatis* using the well diffusion assay technique.

Results: The bacterial isolates were identified as *Paenibacillus glucanolyticus*, *Vibrio pomeroyi* and *Vibrio splendidus*. The sloppy-agar overlay activity tests of the bacterial isolates showed inhibitory activity towards *Mycobacterium smegmatis*. The ethyl acetate treated extracts findings following ¹H NMR spectroscopy showed presence of aromatic leads. The collected fractionated samples also inhibited the growth of *Mycobacterium smegmatis* following the well diffusion assay.

Conclusions: Marine bacterial isolates were identified. Inhibitory activity properties of the isolates were demonstrated using sloppy-agar overlay technique. Promising leads were extracted and isolated from the bacterial isolates. Lastly, the fractionated leads exhibit anti-mycobacterial activity against *Mycobacterium smegmatis*.

Keywords: anti-mycobacterial; marine natural products; *Mycobacterium smegmatis*; secondary metabolites
Moving towards social accountability in pharmacy education: What is the role of the community?

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Introduction: The University of the Western Cape (UWC), School of Pharmacy has embedded service-learning in the undergraduate curriculum in an attempt to align activities with the social accountability values. Third year pharmacy students are expected to provide pharmaceutical services for a week per semester at community healthcare centres located across the Cape Town Metropole region. This study explored the experiences and opinions of the service-learning in Pharmacy (SLiP) programme from a community perspective.

Methods: The study was qualitative and explorative in design underpinned by a participatory research approach. Community representatives were recruited via a key informant who is associated with the community health forum structure, formally embedded in the provincial health system. Data were collected through semi-structured interviews and focus group discussions and were audio-recorded, transcribed and thematically analysed.

Results: Themes were identified from two interviews with the key informant and two focus group discussions with community health forum representatives. The community noted the positive attitudes and professionalism which students displayed during their service experience. Systemic barriers such as depersonalised dispensing at the pharmacy window, long patient waiting time and poor logistical practices led to inadequate pharmacotherapeutic approaches in chronic disease management. Such barriers overcame attempts towards meaningful engagement between pharmacists, pharmacy students and patients. The community suggested that greater student participation in patient group education is needed and re-iterated that the short duration of SLiP at the community health centre was inadequate to develop advocacy skills aimed at quality service provision.

Conclusions: These results highlight the silo approach which still divides pharmacy education and practice. Collaborative efforts between the health system, pharmacy schools and the community are crucial in realigning activities towards systemic interdependence.

Keywords: Pharmacy curriculum, service-learning in pharmacy, social accountability
Introduction: Tenofovir disoproxil fumarate (TDF) and Zidovudine (AZT) are both nucleotide and nucleoside analogue reverse transcriptase inhibitors (NRTIs), respectively. They are used in the management and prevention of the Human Immunodeficiency Virus (HIV) infection. These drugs are faced with delivery challenges such as low intestinal permeability and extensive first pass liver metabolism for TDF and AZT, respectively. Their use may also be limited by dose-dependent adverse effects, which may result in treatment failure when patients become non-compliant and non-adherent to their prescribed antiretroviral (ARV) regimen. Nano-formulations have become a focal point in the pharmaceutical industry for their drug delivery abilities, and capability to modify a drug’s plasma exposure via sustained release or cell targeting. This can further reduce toxicities and adverse effects associated with these therapeutics. The aim of this study was to formulate polymeric nanoparticles of TDF and AZT as a means to improve bioavailability via improved intestinal permeability, and avoidance of first pass effect by improving lymphatic uptake. Improved bioavailability of the drug may also result in use of lower doses and so a decrease in dose-dependent toxicity.

Methods: Nanoparticles were prepared using a modified version of the double emulsion (water-in-oil-in-water) solvent evaporation and diffusion method. Two ratios of PLGA (50:50 and 85:15) were used to prepare four formulations. The physico-chemical and pharmaceutical properties of the formulations were assessed.

Results: Nanoparticles ranging in size from 103 to 160 nm were successfully formulated, with polydispersity index of 0.3 to 4. The zeta potential of the particles was -19.1 after washing. Maximum encapsulation efficiency was calculated as 46.62%.

Conclusions: Nanoparticles of relatively small sizes were formulated. Their average size and polydispersity index indicated homogeneity of the particles, which would enhance intestinal absorption, and by implication reduce dose-dependent adverse effects further studies are required to improve encapsulation efficacy.

Keywords: Tenofovir disoproxil fumarate, zidovudine, nanoparticles, water-in-oil-in-water double emulsion.
Towards the synthesis of cyclopent[b]indole derivatives of indanocine as antiproliferative agents

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Introduction: Indanocine (1) is an antimitotic compound which displays potent activity against a range of cancer cells (mean GI<sub>50</sub> < 20 nM). In the current study we wished to explore the synthesis and cytotoxic activity of a series of cyclopent[b]indole derivatives (2). Although the cyclopent[b]indole scaffold is not common in nature it is present in the antimitotic natural products nostodione A (3).

Methods: A series of 10 different cyclopent[b]indoles were synthesised as follows. Commercially available 2-carboethoxycyclopentanone was initially hydrolyzed under mild conditions to afford the free carboxyate which was reacted with the diazonium salt of aniline at 0-4 °C to give the phenylhydrazone. Cyclization of phenylhydrazone using 1.8 M H2SO4 afforded the indole.

Results: Compounds were synthesised in yields ranging between 50 and 65% after purification. The methoxy substituted phenylhydrazone appear to be much less stable and gave the final indole in about 28% yield. The structures of all synthesised compounds were fully characterized by 1H and 13C NMR spectroscopy. The 13C NMR spectrum showed the expected eleven carbon signals of the cyclopent[b]indole core structure, including a carbonyl signal at δC (195ppm).

Conclusion: Cyclopent[b]indoles were synthesised in moderate yields in three steps. Further elaboration of the cyclopent[b]indole via Aldol condensation of substituted benzaldehydes and their biological activity assessment is in progress

Keywords: Indanocine, cyclopent[b]indole, antiproliferative activity.
Formulation and evaluation of the biocompatibility of chitosan-dextran nanoparticles using a blood brain barrier model

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Introduction: Central nervous system (CNS) bacterial infections are a therapeutic challenge, due to insufficient drug penetration to the CNS as a result of the blood brain barrier (BBB). Moreover, the surge of multidrug resistant strains of gram-negative CNS infections (such as those arising from klebsiella pneumonia, Pseudomonas aeruginosa and Acinetobacter species) has propagated the use of neurotoxic and nephrotoxic ‘last line of defense drug’ polymyxin E Colistin. The BBB is highly specialized, metabolically active, selectively permeable barrier that regulates the movement of exo-and-endogenous molecules into and out of the brain parenchyma. Hence, large hydrophilic antibacterial drugs like Colistin exhibit poor penetration into the CNS. Chitosan based NPs (NP) have been proposed as drug delivery systems across the BBB as they have the ability to encapsulate poorly soluble drugs and may be efficiently taken up by endothelial cells. Moreover, chitosan has been implicated in modulating the tight junction (TJ) paracellular permeability thus potentially facilitating drug transportation. Chitosan itself is a natural polymer extracted from exoskeleton of crustaceans like shrimp and chitin that has been deemed to be biodegradable and biocompatible. However, although not directly toxic, CS’s modulation of TJ may prove to have sub-lethal toxicity on the BBB. Hence elucidating the biocompatible nature of CS-based NPs may be pharmaceutically significant. This study focused on the developing a chitosan-dextran (CS-DS) nano drug delivery system to encapsulate colistin in order to assess the interaction of CS-DS NP on in vitro BBB model. This was achieved through preparing DS-CS NPs through electrostatically interaction using polyelectrolytic complexation (PEC) with the aim of obtaining small, monodisperse, negatively charged NPs. We hypothesized that encapsulation of colistin on into DS-CS NPs would decrease the innate neurotoxic effects of colistin on BBB.

Methods: The NP physicochemical properties (hydrodynamic diameter (nm), zeta-potential (mV) and poly-disparity index (PDI) were obtained through manipulation of the charge index during PEC. The charge index was expressed as the number of negatively charged DS sulphate groups to positively charged CS amine groups. The NPs were spontaneously formed when varying volumes of DS were pipetted into CS (the reaction was allowed to commence for 10 min at 1000 rpm magnetic agitation). The indirect incorporation method was utilized to encapsulate colistin into the NP (EE). Subsequently, the concentration of colistin encapsulated was determined by measuring the absorbance of the supernatant against a calibration curve (established using ultra-violet light spectroscopy, uv-vis). The stability of the physicochemical properties of NP was established by exposing the NP to biological milieu. The NPs were incubated in serum free and serum containing Dulbecco’s Modified Eagle’s medium as well as phosphate buffered saline (37 °C FOR 10, 30 and 60 mins). Cell viability studies using trypan blue exclusion method were performed by exposing confluent mouse brain endothelial cell monolayer to 9.6 µg/ml of empty and colistin loaded NP as well as free colistin. After which, the transendothelial electrical resistance across the endothelial monolayer was measured for all exposures (using the Ohm Millicell-ERS®-Electrical
Resistance System). Finally, the topographical localization of the NPs was analyzed using scanning electron microscopy.

**Results:** Dynamic light scattering characterization of the NP revealed that (1) charge index had a dual effect on the physicochemical properties of the NP. An increase in charge index divided NP into positively charged NP with large hydrodynamic diameters versus negatively charged NP with small hydrodynamic diameters. This was observed as an increase in the charge index correlated to a statistically significant decrease in particle hydrodynamic diameter. This was observed between the range of the lowest charge index value 0.03 (551 ± 84.05 nm) to the highest charge index value 43.5 (144.4 ± 10.89 nm) (P < 0.0001). Additionally, As the charge index increased from 0.03 to 43.5, the net charge of the particles significantly decreased from a highly positive zeta potential of 61.27 ± 7.27 mV to negative zeta potential of -54.77 ± 23.29 mV (P<0.0001). (2) the NP were unstable in biological media, DS-CS np’s exposed to serum free DMEM were significantly larger than the control (1342.67 ± 203.56 nm, 146.43 ± 17.38 nm respectively, P<0.01). This was also true for PBS (1673.6 ± 169.33, 160.26 ± 7.56 nm respectively, P<0.0001). However, the PDI values suggested that the samples were too polydisperse to denote accurate reflection on NP hydrodynamic diameters in biological media. Uv-vis analysis showed that the EE of the NPs was 24%. Cell viability studies showed bend cells treated with 9, 6 µg/ml of colistin had significant increase in cellular toxicity (46.5 ± 9.63 %). However, colistin loaded and empty NPs showed no toxicity. No effects on BBB tautness when measurement paracellular permeability based were observed. Furthermore, the topographical interaction of CS-DS np bend5 showed a structurally intact and healthy monolayer versus an unhealthy monolayer due to treatment with colistin.

**Conclusions:** Evaluation of DS-CS NPs showed remarkable neuroprotective effect. CS NPs had a protective effect on the BBB by mitigating the toxicity imposed by free drug colistin, thus providing a basis of biocompatible BBB drug delivery system.

**Keywords:** CNS infections, BBB, drug delivery system, CS-DS NP, colistin, toxicity, biocompatibility