THE LESSON OF THE LOAVES: SMALL MACHINES, BIG IMPACT IN DRUG ANALYSIS

AN INAUGURAL LECTURE,
2014/2015

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UNIVERSITY OF IBADAN

THE LESSON OF THE LOAVES: SMALL MACHINES, BIG IMPACT IN DRUG ANALYSIS

An inaugural lecture delivered at the University of Ibadan

on Thursday, 13 August, 2015

By

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The Vice-Chancellor, Deputy Vice-Chancellor (Administration), Deputy Vice-Chancellor (Academic), The Registrar and other Principal Officers, Provost of the College of Medicine, Dean of the Faculty of Pharmacy, Deans of other Faculties and Postgraduate School, Dean of Students, Distinguished Ladies and Gentlemen.

Introduction

A walk with destiny has the coloration of scheduled appointments and preventive maintenance. I saw cascade of events, dovetail into one another, in a manner reminiscent of bespoke tailors. These are my musings, as I prepare myself for this august occasion, in the month of August, 2015. I stand here today, in this famous hall, to present an inaugural lecture, less than three years from the effective date of my elevation to the grade of Professor of Pharmaceutical Chemistry, and remarkably, less than a year after the pronouncement was made. This lecture therefore has the character of an inauguration indeed. I here inaugurate the third Professorial Chair in Pharmaceutical Chemistry, in the premier university and the eleventh of such, from the Faculty of Pharmacy. The first inaugural lecture from the Department of Pharmaceutical Chemistry was also the first from the Faculty of Pharmacy. It was delivered on 16 February, 1984, by Emeritus Professor Ajibola A. Olaniyi, the indefatigable foundation Dean of the Faculty of Pharmacy, University of Ibadan, and the "Lionel Messi" of Pharmaceutical Chemistry in the nation. The second inaugural lecture was delivered on 16 June, 2011, by the first female and current Dean of the Faculty of Pharmacy, Professor Chinedum P. Babalola.

In his 1984 lecture, titled "*Pharmacy and Drugs in the Conquest of Disease*" Emeritus Professor Olaniyi wrote (Olaniyi 1984a):

> There is a lot still to be done to build an enviable Faculty of Pharmacy at Ibadan, especially in the area of research and postgraduate training. At this

stage, it might be said in the words of Sir Winston Churchill, that "this is not the end or even the beginning of the end; we have yet to reach the end of the beginning". I believe that I can speak on behalf of my colleagues that we are determined and indeed confident in our collective ability to continue to meet the challenges of the nation by contributing to the continuing development and stability of pharmacy profession in Nigeria.

With today's inaugural lecture, I believe, we are beginning to approach the "end of the beginning" and the beginning of an enviable Faculty of Pharmacy, which Olaniyi envisioned. I reckon thus, because, this is the first inaugural lecture to be delivered by a Bachelor of Pharmacy alumnus of the University of Ibadan, either in this university or anywhere else on the planet. I consider it a great privilege to be the one to give such a lecture. I have earlier been awarded the first doctorate in Pharmaceutical Chemistry from the University of Ibadan in 1998. These accomplishments are testaments to the firm resolve of the founding fathers of the Faculty of Pharmacy, which Professor Olaniyi alluded to in his inaugural lecture. As the first fully homegrown Professor, I am acquainted with the history of the Faculty. I came into the Faculty of Pharmacy by direct entry in 1986 (joined the 6th set of the B. Pharm. programme), and since then, I have never really left. I took a brief leave in December 1989, to serve a year internship at the University College Hospital, Ibadan, and later, the mandatory National Service at Vandeikya General Hospital, Vandeikya, Benue State. Since my return for M.Sc. degree in 1992, I have remained at Ibadan.

My lecture, which I titled: *"The lesson of the loaves: Small machines, big impact in drug analysis"* is a chronicle of my journey through the postgraduate training in Pharmaceutical Chemistry at Ibadan, first as a student, and later as a postgraduate teacher and researcher. I believe

inaugural lecture is in a sense, a story-telling event, and for a drug analysis expert, perhaps, a data story-telling event. The philosophy behind the research programme created by my doctorate was to design a reagent and assay technology that fuse low-cost with high-tech, such that we can have original solution options for problems in drug analysis. Such solutions are required for quality assurance of manufactured drugs, foods and dietary supplements, especially in resource-poor economies.

Drug Analysis

Drug analysis is an integral part of routine procedures in the pharmaceutical industry. From the purchase of raw materials, especially the active pharmaceutical ingredient (API) and other pharmaceutical necessities, to the production of finished drug products, systematic testing (analysis) is implemented to ascertain the quality of processes and products. The variety of delivery systems required to safely administer drugs present different challenges to the drug analyst. These challenges have to do with complexity of sample matrices. Therapeutic objectives often require that two or more API's be combined in a single dosage form. This also constitutes another level of analytical challenge, the task of multi-component analysis. At other times, the process of drug discovery warrants accurate determination of trace amounts of drugs and their metabolites in biological fluids (plasma, serum, saliva etc.), that is the task of 'trace analysis'.

In recent times, our definition of 'drugs' has shifted from traditional 'small molecules'. Many modern drugs are large 'biomolecules' (peptides and proteins), with greater structural complexities. All these realities present challenges of varying complexities to the drug analyst. In order to meet these challenges, the discipline of drug analysis has evolved over the years with techniques that can accurately deliver quantitative results when the analyte is measured. The earlier efforts required analytes in milligramme quantities, and use of simple apparatus (*classical methods*). Later efforts focused

on accurate measurement of sub-milligramme quantities in variety of matrices. This effort invariably led to the use of one instrument or the other (*instrumental methods*) (Willard et al. 1988).

Classical Methods of Analysis

Gravimetric and volumetric (titrimetry) analyses are time-honoured options in drug analysis. They have the merits of high precision and low cost. The major drawbacks are the low throughput when large numbers of samples are to be analysed, and high limit of detection, which limit their usefulness for trace analysis.

Instrumental Methods

The use of instrumentation is an exciting part of drug analysis, because of the accuracy of results obtainable, even when the analyte of interest is present in trace or ultra-trace amounts. Pharmacokinetics, the science of describing the time course of drug action, heavily relies on accurate measurement of sub-milligramme quantities of the drug in biological fluids. The popular techniques, routinely used for drug analysis, that have benefited from instrumentation are: spectroscopy, chromatography, electrochemistry, mass spectrometry and hyphenated techniques. In solving drug analysis problem, there are several important steps before and after taking measurement on an instrument.

The drug analysis problem-solving algorithm is broadly divided into three (fig. 1). First, the analyst describes the sample in order to select an appropriate method. Second, steps are taken to extract raw data from the sample and finally, the data is refined to obtain information from the sample and ultimately, knowledge is created from the whole process. Instrumentation is therefore a mere step in the middle of the entire process, with other critical steps before and after actual measurement.

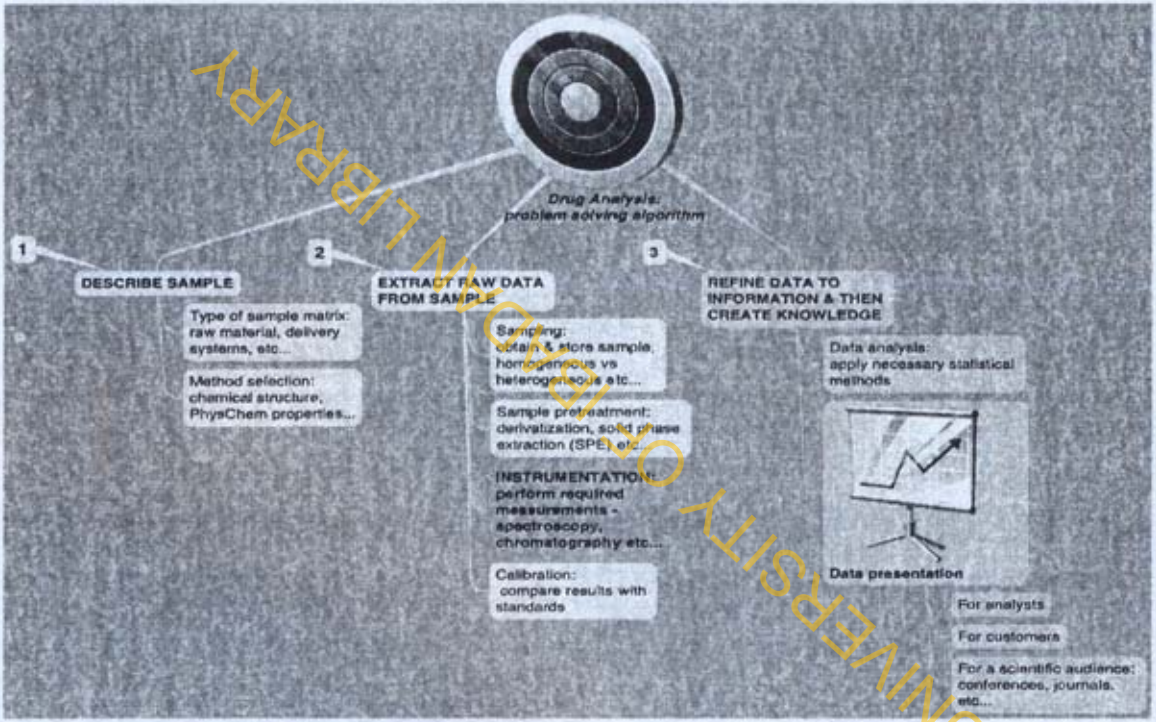


Fig. 1: Problem-solving algorithm in instrumental drug analysis.

Small Machines, Big Machines

Every analytical instrument can be divided into four basic components: (i) signal generator (ii) an input transducer (detector) (iii) an electronic signal modifier and (iv) an output transducer. Some instruments have limited signal processing capabilities, say, simple current-to-voltage conversion: these are described as "small machines". Other techniques like colorimetry, and thin layer chromatography, which rely on visualization with the naked eye or the aid of ultraviolet light for detection, fit the definition of "small machines". On the other hand, some analytical instruments are based on advanced engineering and complex microprocessors that have a variety of signal-processing capabilities. This signal-processing capabilities lead to high speed, sensitivity and resolution in drug analysis. Such instruments are described as "big machines". Examples of the 'big machines' are analytical instruments required for: capillary electrophoresis (CE), supercritical fluid chromatography (SFC), high performance thin layer chromatography (HPTLC), gas chromatography (GC), high performance liquid chromatography (HPLC), and ultra pressure liquid chromatography (UPLC). These techniques are invariably versatile, very fast and very sensitive. All these features come at a price. The hefty price tag is usually from acquisition as well as maintenance cost.

Computer-aided Analysis

The computer revolution that happened in the 1970s and the advancement in solid state integrated circuitry, have made the microprocessor technology popular in analytical instrumentation. From simple pH meters to complex mass spectrometers, microprocessors are now standard components. The use of computers in drug analysis has evolved over the years. The evolution started from "off-line" configuration, to "on-line", then "in-line", when the computer became an integral dedicated part of the packaged instrument. Further evolution led to "intra-line" configuration, where several micro-computers within a single instrument constitute subsystems of

instrument function. Hardware components include popular microprocessor-controlled robot arms, while software elements are programmes for data acquisition and processing. Additional software elements commonly include graphics display, spreadsheet analysis, artificial intelligence and expert systems (Willard et al. 1988b).

Advancement in every large scale integrated circuits has led to increasing reduction in size of instruments, with increasing signal-processing capabilities at a reduced cost. Many analytical instruments are now available with digital read out rather than the deflection meter of the previous analog devices. The "small machines" are therefore now increasingly equipped with greater software capabilities. For instance, many digital colorimeters now come with three decimal place resolution and near-spectro-photometer data-quality. Others have programmable functions that permit versatility of use. This current situation has set the stage for remarkable impact by small machines in drug analysis. The hand-held analyzer, TruScan, based on Raman Spectroscopy, is another good example of a commercially available small machine that is having a big impact in drug analysis (fig. 2). The big impact is made possible by advanced chemometrics that allows comparison of spectral data of an authentic sample, stored in a digital library in the analyzer, with the spectral data of any test sample, in order to ascertain authenticity. Both hardware and software advancement over several years have made it possible to miniaturize a spectroscopic instrument, that is found so useful in anti-counterfeiting efforts around the world ("TruScan RM Analyzer - Thermo Scientific").

(A)

(B)

Fig. 2: "Small machines" that are being applied in drug analysis with big impact: (A) programmable digital colorimeter, (B) TruScan analyzer, a hand-held drug analyzer based on Raman spectroscopy.

Source: Sherwood colorimeters, U.K. and Thermo Fisher Scientific Inc.

Molecular Probes and Assay Technologies

In addition to instrumentation, molecular probes are powerful tools in drug analysis. In order to obtain information from drug samples, several molecules with characteristic behaviours that are amenable to data acquisition are adopted in several assay technologies. This varies from chemical assays to bioassays involving microorganisms or mammalian cell-lines. Some probes are pH sensors, e.g. phenol red, exhibiting colour transition from yellow to red, with accompanying molar absorptivity changes over a pH interval of 6.8 to 8.2. Others are sensitive to redox reaction. For example, alamar blue (resazurin), is a molecular probe for monitoring cellular metabolic activity. The reagent solution contains the non-fluorescent blue-coloured molecule resazurin, which, when chemically reduced (a metabolic activity of cells), turns into the highly fluorescent red-coloured resorufin. The change in colour is accompanied by molar absorptivity change that is adaptable for absorbance measurements. On the other hand, the formation of a fluorescent product (resorufin) is also amenable to fluorescent measurements in a plate reader (fig. 3).

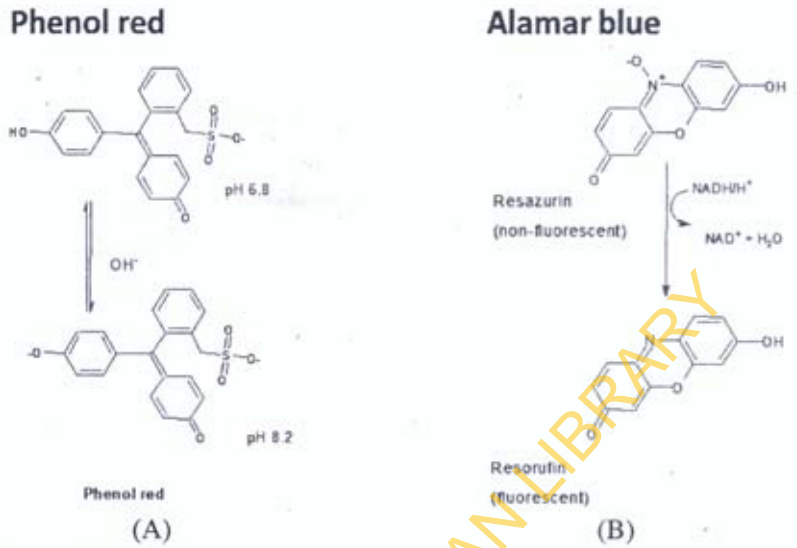


Fig. 3: Molecular behaviours that are adaptable for assay technologies (A) conversion of a (yellow) mono-anion specie of phenol red to a (red) di-anion specie of the molecule over pH interval of 6.8 to 8.2 (B) non-fluorescent specie of alamar blue (resazurin) is converted by reduction to fluorescent, red-coloured resorufin.

Assay Technologies and Bio-relevance of Results

Drug analysis often involves the use of chemical assays or bio-assays that are set up outside the living organism (*in vitro)* to simulate series of events involved in a biological process that is of interest in understanding a disease process or evaluating a pharmaceutical intervention in the biological system (*in vivo*). Over the years, reductionism became a popular paradigm in assay development. Several biological details are ignored in designing an assay, in order to obtain a simple assay that gives quick results. This oversimplification of a biological process often leads to poor *in vitro/in vivo* correlation (IVIVC). In other words, the results of many *in vitro* assays are shown to be lacking in biological relevance. The assay output does not accurately predict what is found *in vivo* for the drug under study. In order to improve this situation, there is an increasing emphasis on accounting for

greater biological details in the development of assays that are meant to have predictive value on *in vivo* realities. This paradigm shift is captured by systems biology and mathematical modelling of biological events (i.e. computational systems biology) (Kitano 2002a; Kitano 2002b).

Mathematics, Data Science, Chemometrics, Chemoinformatics, Biopharmaceutics Modelling, Predictive Science and the Pharmaceutical Industry

Mathematics

The fundamental power of mathematics makes it a powerful tool in solving many problems in drug analysis, especially the problem of bio-relevance of assay results. This fundamental power is evident in these quotes:

> The sciences do not try to explain, they hardly even try to interpret, they mainly make models. By a model is meant a mathematical construct which, with the addition of certain verbal interpretations, describes observed phenomena. The justification of such a mathematical construct is solely and precisely that it is expected to work.
>
> *John Von Neumann*

> I regard it in fact as the great advantage of the mathematical technique that it allows us to describe, by means of algebraic equations, the general character of a pattern even where we are ignorant of the numerical values which will determine its particular manifestation.
>
> *Friedrich August von Hayek*

Data Science

Data science is a set of fundamental principles that guide the extraction of knowledge from data. Data mining is the extraction of knowledge from data, via technologies that incorporate these principles. As a term, "data science" often is applied more broadly than the traditional use of "data mining," but data mining techniques provide some of the

clearest illustrations of the principles of data science (Provost and Fawcett 2013).

Chemometrics

Chemometrics can be defined as the chemical discipline that uses mathematical, statistical, and other methods employing, formal logic (a) to design or select optimal measurement procedures and experiments, and (b) to provide maximum relevant chemical information by analyzing chemical data (Massart et al. 2003).

Chemoinformatics

Chemoinformatics is concerned with the application of computational methods to tackle chemical problems with particular emphasis on the manipulation of chemical structure. A specific definition says: "Chemoinformatics is a generic term that encompasses the design, creation, organization, management, retrieval, analysis, dissemination, visualization and use of chemical information" (Leach & Gillet 2007). Chemoinformatics involves the use of a variety of techniques collectively belonging to multivariate data analysis. Examples include cluster analysis, multi-dimensional scaling, multiple linear regression and artificial neural networks.

Multiple Linear Regression

The general formula of a multiple regression is:

$$y_i = \beta_0 + \beta_1 x_{1,i} + \beta_2 x_{2,i} + \ldots + \beta_k x_{k,i} + e_i,$$

Where, y_i is the variable to be forecast and $x_{1,i},\ldots x_{k,i}$ are the k predictor variables. Each of the predictor variables must be numerical. The coefficients $\beta_1 \ldots \beta_k$ measure the effect of each predictor after taking account of the effect of all other predictors in the model. Thus, the coefficients measure the marginal effects of the predictor variables (Hyndman & Athanasopoulous 2015a).

Artificial Neural Networks

Artificial neural networks are forecasting methods that are based on simple mathematical models of the brain. They allow complex non-linear relationships between the response variable and its predictors. A neural network can be thought of as a network of "neurons" organized in layers. The predictors (or inputs) constitute the bottom layer, and the forecasts (or outputs) constitute the top layer. There may be intermediate layers made up of "hidden neurons". Each predictor has a coefficient attached to it. The coefficients attached are called "weights". The forecasts are obtained by a linear combination of the inputs. A "learning algorithm" that minimises a "cost function" such as minimum sum of squares of errors (MSE), is used to select the weights in the neural network framework (Hyndman & Athanasopoulous 2015b).

Biopharmaceutics Modelling

Biopharmaceutics modelling is a discipline that integrates physical theories of molecular behaviour, with the physiology of the gastrointestinal tract and the meaning of drug parameters, using appropriate equations and mathematical models. It is increasingly being adopted by the Pharmaceutical industry in solving drug formulation problems (Sugano 2012).

Predictive Science

Predictive science is the collective name for a network of scientific disciplines. It focuses on indicating the most likely effects and outcomes (fig. 4). Predictive science is considered a transformational opportunity for the Pharmaceutical industry, because it has started to revolutionize traditional processes involved in drug discovery and development, such that the cycle time is shorter and the risk of failure significantly reduced (Waller 2014).

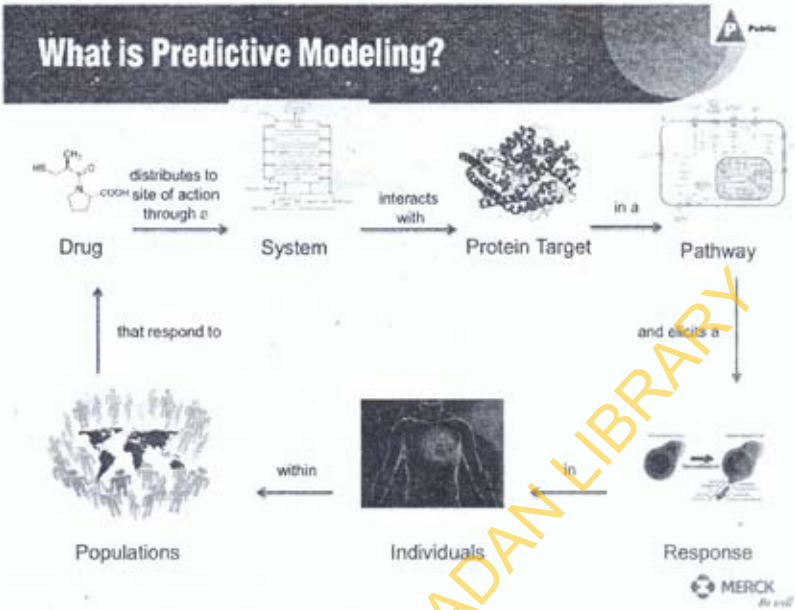


Fig. 4: Illustration of wide-ranging relevance of predictive sciences to the pharmaceutical industry. (*Every arrow in the chart represents an opportunity to develop and apply a predictive model instead of more expensive experimentation*)

Source: Waller (2014)

Starting from concepts in analytical/organic chemistry during my doctoral research, my research interests have evolved over time to become what is embodied by the field described as Chemoinformatics. In a nutshell, it involves the use of computer technologies, mathematical modelling and visualization techniques to process chemical data, leading to better data-driven decisions in diverse areas of the chemical enterprise, and drug analysis in particular.

Research Contributions from "The Idowu Lab"

Contributions to the chemical/pharmaceutical literature that have emanated from my research programmes in the University of Ibadan over the past 23 years or so are fundamental and decisive in the field of Pharmaceutical

Chemistry and drug analysis. For convenience and the constraint of time, I will present the research projects under the following headings:

(I) Reagent design and assay technologies
(II) Veterinary pharmacy and ethnopharmacology
(III) Chemoinformatics and bio-relevant assay technologies
(IV) Chemoinformatics and molecular engineering.

I. Reagent Design and Assay Technologies

Fred Sanger, the two-time Nobel Laureate in Chemistry took the first Nobel Prize in Chemistry in 1958, for the sequencing of the amino acids that make up the protein, insulin. In achieving that feat, he made a small molecule popular as analytical reagent and developed a new technique for protein analysis. 1-Fluoro-2,4-dinitrobenzene (FDNB), a dinitrophenyl compound, was used for chromophoric labelling. The "dinitrophenyl" represents a large chromophore (coloured yellow) which makes it easy to detect amino acids when the latter are tagged with this chromophore-rich reagent. Chromophoric labelling of amino acids, implemented to enhance ultraviolet detection of amino acids, some of which are devoid of chromophore, was a brilliant technique for protein analysis (Stretton 2002).

Inspired by the large molar absorptivities of dinitrophenyls, we hypothesised in 1992 that a dintrophenyl moiety and a hydrophilic carboxylic group on an aryl diazonium compound should make a versatile analytical reagent for drug analysis. The hypothesis was to produce a new aryl diazonium reagent that will be more reactive than the existing *p*-nitro benzenediazonium. The target molecule to serve as precursor to the aryl diazonium specie, is the aromatic amino acid, 4-amino-3,5-dinitrobenzoic acid (ADBA). ADBA was not commercially available at the time, so I had to find a way of synthesising it. In theory, the synthesis was supposed to be straightforward, however, in practice it was not. A proof of concept of the synthesis, and subsequent diazotisation of the amine constituted my M. Sc.

project report in 1994 (fig. 5). It was just before I completed the M.Sc. project, that Dr. Adedigbo Fasanmade, who was my project supervisor during my B. Pharm. and M.Sc. degree programmes, relocated to the United States of America for postdoctoral training. Professor Olaniyi, who was Dr. Fasanmade's project supervisor for his M.Sc. degree at the University of Ife (now Obafemi Awolowo University), graciously agreed to oversee the last stages of my M.Sc. project and allowed me to continue on the same track for my doctorate, which he supervised. I am, therefore, one of Emeritus Professor Olaniyi's academic grandchildren.

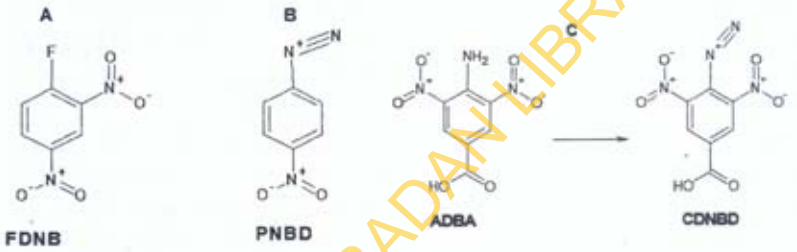


Fig. 5: Nitrophenyl reagents for chromophoric labelling: (A) Sanger's reagent (FDNB), (B) *p*-nitrobenzenediazonium (PNBD), and (C) formation of 4-carboxyl-2,6-dinitrobenzeneidazonium (CDNBD) from the aromatic amino acid (ADBA) precursor.

Synthesis of Reagent Grade 4-amino-3, 5-dinitrobenzoic Acid (ADBA)

Synthesis of ADBA was accomplished from three distinct starting materials; *p*-amino benzoic acid (PABA), 4-amino-3,5-dinitrobenzamide and *p*-anisic acid. Some of the processes required mild reaction conditions, while others were more stringent. In the end, *p*-anisic acid was favoured for routine production of ADBA, owing to a combination of percent yield and the relative safety of the process. The golden yellow compound was obtained in reagent grade purity by careful purification of the intermediate product. Potentiometric titrimetric analysis was used to determine the purity, and 100% purity was obtained (Idowu and Olaniyi 2003). The significance of this feat was attested to, when a

Japanese scientist, Masayuki Ando, independently confirmed the high purity as 99.9% by using high performance liquid chromatography (HPLC). Given the higher sensitivity of HPLC and its ability to resolve trace amounts of impurity, "three 9s" level of purity was considered significant in the eyes of Japanese scientists, considering that the sample analysed was designed, developed and produced in Ibadan, Nigeria.

Development and Evaluation of 4-carboxyl-2,6-dinitrobenzenediazonium (CDNBD) Hydrogen Sulphate

The main achievement of my doctoral research was the first-time development of a novel process of preparing the aryl diazonium ion, diazotized ADBA or 4-carboxyl-2,6-dinitrobenzenediazonium (CDNBD) hydrogen sulphate through diazotization, a popular organic unit reaction. The first aryl diazonium ion was discovered in 1858 by Peter Griess, almost one and a half century before I commenced the study. Over the years, several applications have been made of aryl diazonium ions in synthetic organic chemistry and industry. The textile, printing and cosmetics industries are the greatest beneficiaries, owing to the formation of several azo dyes through diazo coupling reaction. The prospect of a truly new and original contribution in this sphere was therefore considered slim. The fortune we had was that, the only previous attempt to diazotise ADBA in literature, reportedly failed (Elion 1923) because of the limitations of diazotization processes available at the time. ADBA is a very weakly basic aromatic amine and as such the familiar diazotization medium was unsuccessful in diazotizing it. Skilful adaptation of newer diazotization techniques since 1923 inspired the development of a process that supported quantitative application of CDNBD solution as an analytical reagent. The dinitrophenyl moiety of CDNBD facilitated its remarkable stability, which affords the use of fairly high temperature in optimising reaction conditions during application as a derivatizing reagent (Idowu et al. 2005).

Evaluation of the reagent was implemented by developing and validating colorimetric analyis of otherwise colourless

drugs after chromophoric labelling with CDNBD, via diazo coupling reaction. Several Masters of Science (M.Sc.) projects I supervised and a doctorate I co-supervised with Emeritus Professor A.A. Olaniyi, addressed the application of CDNBD to the analysis of several clinically useful drugs. The scope of work invariably involved method development and validation. In sum, successful applications were obtained with drugs that belong to certain chemical classes that readily underwent diazo coupling with CDNBD. These include mefenamic acid (Idowu et al. 2002) diclofenac (Idowu et al. 2006), aceclofenac (Aderibigbe et al. 2012a) all belonging to anthranilic acid class of non-steroidal anti-inflammatory drugs (NSAID's). Other drugs successfully analysed include: naproxen (Idowu et al. 2009), indomethacin (Adegoke et al. 2006), and propranolol (Idowu et al. 2004) all belonging to phenol ethers class. Analysis of nifedipine required a prior step of reduction of a nitro group to produce a reactive amino phenyl moiety that facilitated diazo coupling reaction (Aderibigbe et al. 2012b)

Synthesis and Lipophilicity Profiling of CDNBD-derived Azo Dyes

In addition to the use of CDNBD as a derivatizing reagent, it is equally a powerful synthetic intermediate. This is a class property for aryl diazonium ions. Part of my doctoral research and part of Dr. A.O. Adegoke's doctoral research, which I co-supervised with Emeritus Professor A.A. Olaniyi, provided comprehensive spectroscopic evidence to elucidate the structure of four new CDNBD-derived azo dyes unambiguously (Adegoke et al. 2008). The coupling components were β-naphthol (AZ-01), α-naphthol (AZ-02), naproxen (AZ-03) and nabumetone (AZ-04). This chemical library has in common, the phenyl azo hydroxynaphthalene skeleton, with sunset yellow (FD & C No. 6), which is approved for use in human foods, drugs and cosmetics. The lipophilicity profiling was implemented by using reversed phase chromatographic technique to rank them in order of overall compound lipohilicity. The structure-property-relationships (SPR) was defined by mathematical models

developed for the series, which have a predictive value on their biopharmaceutical behaviours (Idowu et al. 2007). Lipophilicity ranking follows the sequence: AZ-03 < AZ-02 < AZ-01 < AZ-04 (fig. 6)

pH Sensor

Preliminary evaluation of pH-dependent behaviour of the azo dye series revealed interesting colour-transition behaviour of some of the dyes, of which one has been developed as a pH sensor. AZ-01 exhibited colour transition from orange to violet, corresponding to pH 8 - 10. The molecule AZ-01 was branded "Nitro violet" and it has been applied as a pH sensor comparable to phenolphthalein in titrimetric analysis of weak acid versus strong base titrant (Idowu & Olaniyi 2001).

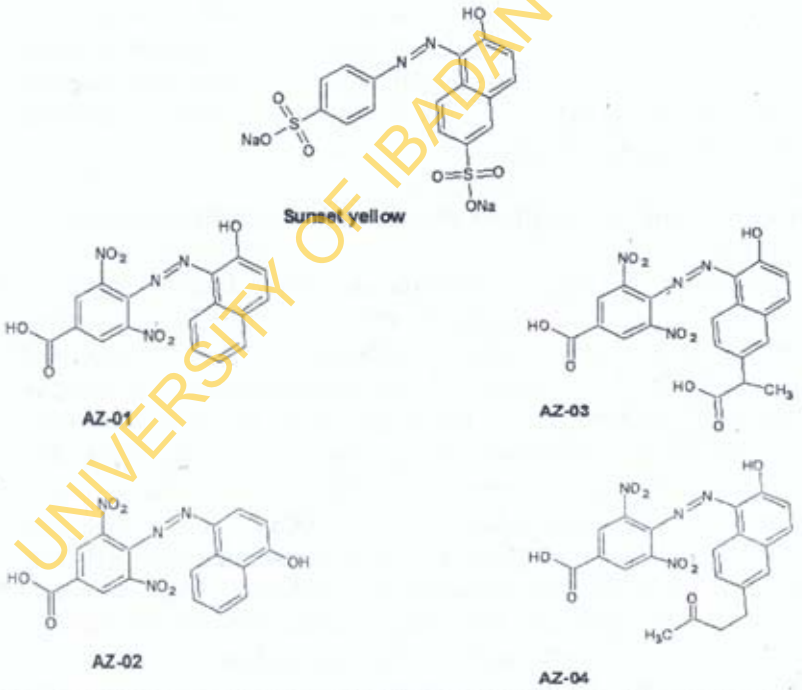


Fig. 6: Chemical structures of CDNBD-derived azo dyes and sunset yellow.

Source: Idowu et al. (2007)

A New Potential Colour Additive

Colorants are essential components of pharmaceutical delivery systems, especially paediatric formulations, where aesthetics influence the patients' willingness to accept the medication (Carter 1984). A popular example of historic significance is amaranth, while sunset yellow is an azo dye in current usage. The lipophilicity profiling of the azo dyes revealed that 4{[6-(1-carboxyethyl)-2-hydroxy -1-naphthyl] diazenyl}-3,5-dinitrobenzoic acid (AZ-03) with an additional carboxylic acid functional group in its structure, is the most hydrophilic of the series. This profile is a safety predictor, corroborating the fact that the coupling component, naproxen, is a clinically useful drug, that has survived safety scrutiny.

The "phenyl azo hydroxynaphthalene" structural moiety is common to allura red (FD & C Red No. 40) and sunset yellow (FD & C yellow No. 6), two azo dyes, out of many colour additives that require batch certification, approved for use in human cosmetics, food and drugs, by the United States Food and Drug Administration. It was desirable to implement physicochemical profiling of the new molecule, as part of documentation of its solution chemistry. This will constitute the technical data required for compilation of monograph entry on "identification". In particular, pH dependent molecular behaviours were studied (Idowu 2012). The multi-staged ionization is shown in fig. 7. The orange, unionized specie and violet, ionized specie both exhibited intense absorption, with molar absorptivities of 14,600 (490 nm) and 12,800 (550 nm) [L mol $^{-1}$ cm $^{-1}$] respectively. The degradation of AZ-03 follows pseudo first-order kinetics in alkaline medium through specific-base catalysis. It was also shown statistically, that the dye exhibits isosbestic point at 522 nm (fig. 8A and table 1). Base-catalysed degradation gave a non-linear and diagnostic rate-pH profile (fig. 8B). All these characteristics are critical to authentication of the new potential colour additive, which may be useful, after more rigorous safety testing, as colorant in liquid preparations that are either neutral or mildly acidic (i.e. pH 5 - 7), in which it exhibited greatest stability.

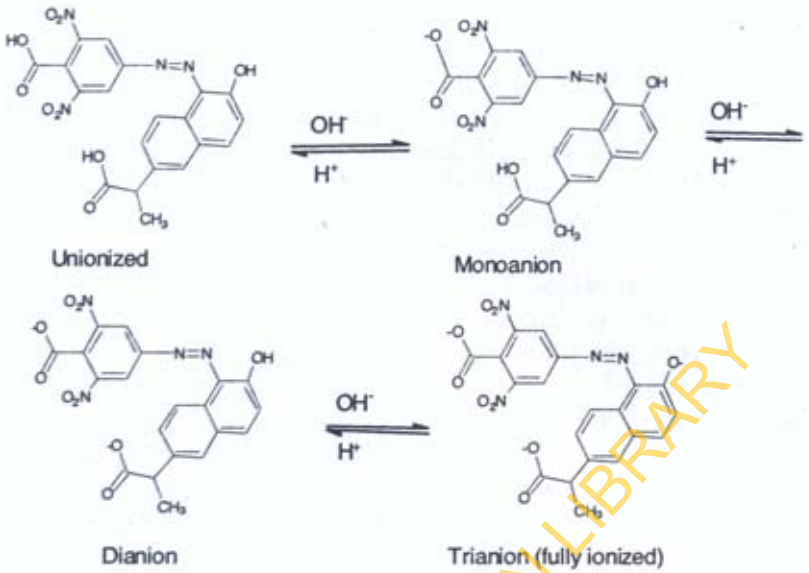


Fig. 7: Schematic representation of multiple ionisation steps in the chemical equilibrium between unionised specie (pH 7) and fully ionised specie (pH 12, trianion) of AZ-03.

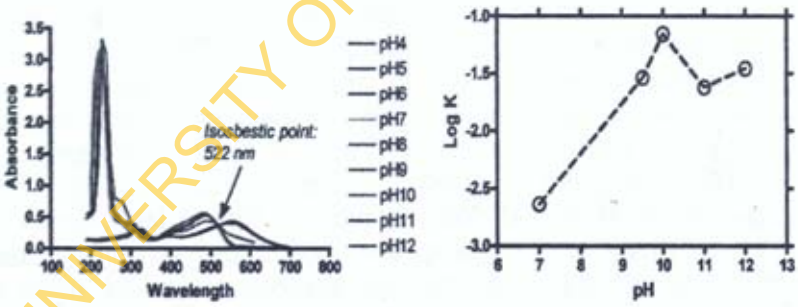


Fig. 8: Graphic display of: (A) overlaid absorption spectra of AZ-03 showing isosbestic point exists at 522 nm, and(B) non-linear, diagnostic, degradation rate-pH profile.

Table 1: Bonferroni post-test showing that Absorptivity is Statistically similar at 522 and 524 nm but statistically different at 526 and 528 nm across the three pH values (the p values at 522 nm is however about four times the Size of p value at 524 nm), supporting the choice of 522 nm as the isosbestic point

Wavelength, nm	Difference	T	p value	Summary*
pH 7 vs pH 10				
522	-0.0060	0.79	p>0.05	NS
524	-0.0020	0.26	p>0.05	NS
526	0.00	0.00	p>0.05	NS
528	0.0050	0.66	p>0.05	NS
pH 7 vs pH 11				
522	0.0090	1.2	p>0.05	NS
524	0.019	2.5	p>0.05	NS
526	0.026	3.4	p<0.01	Significant
528	0.034	4.5	p<0.001	Very significant

*NS = Not significant

Other Applications of CDNBD-derived Compounds

There are other applications of CDNBD being made by other workers around the world. Mr. Vice-Chancellor, I can reliably inform that this research programme that started in the University of Ibadan, being a platform technology, has been exported to other parts of the world. Scientists in other nations, especially in Asia have had the opportunity to apply this authentic 'made in Nigeria' scientific product. The details of that will be another story though, to be told by another man, from my department, in due season *deo volenti*. In sum, the experience with ADBA/CDNBD research programme confirms the "art of science" as enunciated in the thoughts of Jean Marie Lehn, Joint Nobel Prize Winner in Chemistry in 1987:

> Chemistry has the possibility
> To organize matter
> The ability to create new objects
> To endow matter with novel properties
> Chemistry is highly creative like art
> This is the most exciting thing
> The great fundamental power of Chemistry

We have created new molecules, with interesting and colourful behaviours, from the yellow aromatic amine, ADBA, mediated by the highly reactive, and colourless aryl diazonium intermediate; CDNBD (fig. 9).

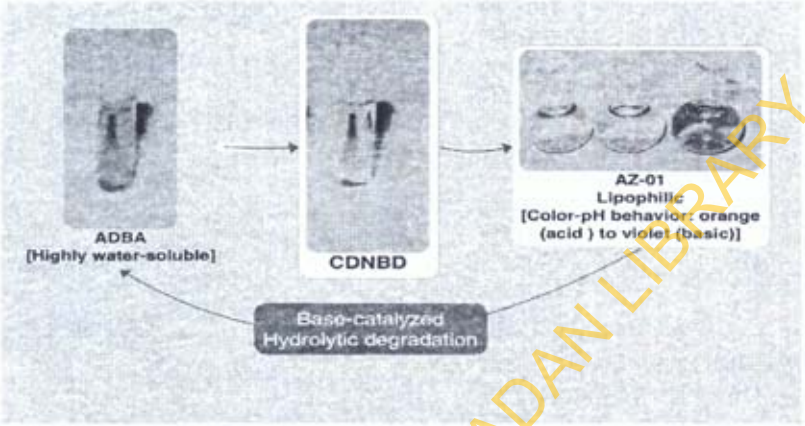


Fig. 9: The bright yellow aromatic amine is converted to the colourless reactive, CDNBD, which serves as intermediate for the synthesis of colourful azo dyes.

II. Veterinary Pharmacy and Ethnopharmacology

Anthelmintic Medicinal Plants

I have been involved in a fruitful collaboration with Veterinary Parasitologists in the University of Ibadan. Working with Professor B.O. Fagbemi and Dr. I.O. Ademola, we examined a number of medicinal plants for which there is folkloric claim of usefulness in de-worming livestock. The problem of helminthosis of livestock is an economically important problem that affects productivity of livestock farming. The global problem of resistance to anthelmintics and concerns over drug residue in livestock products require suitable alternatives. Anthelmintic phytomedicines are attractive because helminthosis is essentially a neglected disease. There are no new drugs being discovered and developed for this purpose by the big pharmaceutical companies. The leaves of *Spigelia anthelmia* (Ademola et al.

2007a), *Spondias mombin* (Ademola et al. 2005), *Nuclea latifolia* (Ademola et al. 2007b), the seed of *Leucaena leucocephala* (Ademola et al. 2005, Ademola & Idowu 2006) and the bark of *Khaya senegalensis* (Ademola et al. 2004, Ademola et al. 2009) were evaluated by *in vitro* and *in vivo* studies, to determine their effectiveness against nematodes of sheep. Chromatographic fractions of the constituents of *Leucaena leucocephala* and *Khaya senegalensis* showed evidence of possible synergism of various classes of compounds as basis of the bioactivity of the medicinal plants against helminths. Larval viability assay was used to investigate *in vitro* activity, while "feacal egg count" after treatment, relative to control experiments, was used to evaluate *in vivo* bioactivity.

Enhanced Throughput of a Screening Assay using Haemonchus placei Motility

In order to probe these plants further, with the goal of isolating active anthelmintic principles, we optimised, refined and validated a bioassay, using adult *Haemonchus placei* motility. We demonstrated that normal saline is adequate and in fact, advantageous to use as culture medium, to incubate the worms and test the effect of small molecule drugs, phytochemicals and phytomedicines. The higher solvating power of normal saline relative to phosphate buffered saline (PBS) allows wider dynamic concentration range and narrower 95% confidence limit in the method performance characteristics. Curve-fitting analysis using the sigmoidal variable slope model was adequate to quantitatively evaluate the bioactivity profile of several fractions of plant extracts representing structurally diverse active constituents. The relative potency of various extracts as determined by LC_{50} values computed from curve-fitting analysis is shown in figure 10 (Idowu et al. 2015).

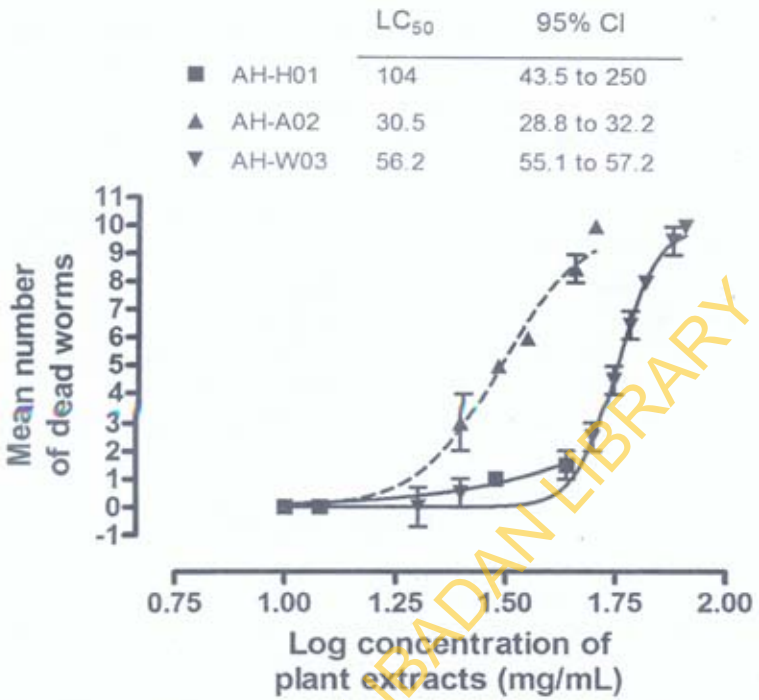


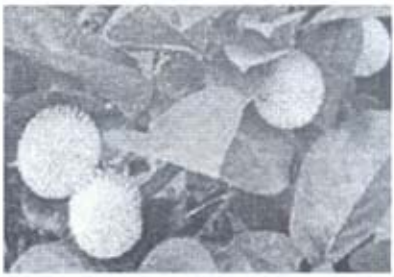
Fig. 10: Curve-fitting analysis using sigmoidal variable slope model showing the relative potency of plant extracts AH-01, AH-A02, AH-W03. AH-A02 is shown to be the most potent, with LC_{50} of 30.5 mg/mL.

Source: Idowu et al. (2015)

Phtyomedicine development from *Spondias mombin* and *Nuclea latifolia*

Sequel to the optimization and validation of an adult *H. placei* motility assay, ongoing studies are aimed at developing anthelmintic phytomedicines from the leaves of *Spondias mombin* and *Nuclea latifolia* (fig. 11). The scope of work involves isolation, purification and structure elucidation of active principles from the leaf extracts of the two plants. Subsequent to the identification of most active principles, formulations of the plant extract will be developed as possible alternative to synthetic anthelmintic.

(A) *Spondias mombin*



(B) *Nuclea latifolia*

Fig. 11: The leaves and fruit/flower of (A) *Spondias mombin* and (B) *Nuclea latifolia*.

Source: Google images

III. Chemoinformatics and Bio-relevant Assay Technologies

Physicochemical profiling of several drug parameters is critical to biopharmaceutics modelling, which is a very important discipline in modern drug development efforts. Ionization constant measurement, commonly reported as pK_a, and lipophilicity profiling, commonly reported as octanol-water partition (log P), are the two most important drug parameters. Antioxidant capacity profiling of phenolic dietary supplements is equally an existing gap of significance, given the well documented adjunctive role of antioxidant polyphenols in chemotherapy of chronic and degenerative diseases. Research in my laboratory has focused on creation of an artificial membrane as a device, possessing biomimetic attributes, for lipophilicity profiling of small molecule drugs. Secondly, a fusion of computational and experimental technologies was applied in the development of computational antioxidant capacity simulation (CAOCS), a novel framework of antioxidant capacity profiling.

Lipophilicity Profiling

The concept of partition coefficient, P, usually reported as logarithm of partition coefficient (log P), has been in use for over a century (Meyer 1899). Log P represents affinity of a

molecule or a moiety for a lipophilic environment. It is commonly measured by its distribution behaviour in a biphasic system (e.g measurement of partition coefficient in octanol/water system). This time-honoured status and wide application in the pharmaceutical industry, has bestowed the 'gold standard' label on log P as a physicochemical property and predictor of drug metabolism and pharmacokinetics (DMPK) of drug molecules, with implications for their safety and efficacy (Waring 2010, Hartmann & Schmitt 2004). The importance of physicochemical properties on permeability, absorption and bioavailability is displayed in the scheme shown in figure 12 (van de Waterbeemd 2009).

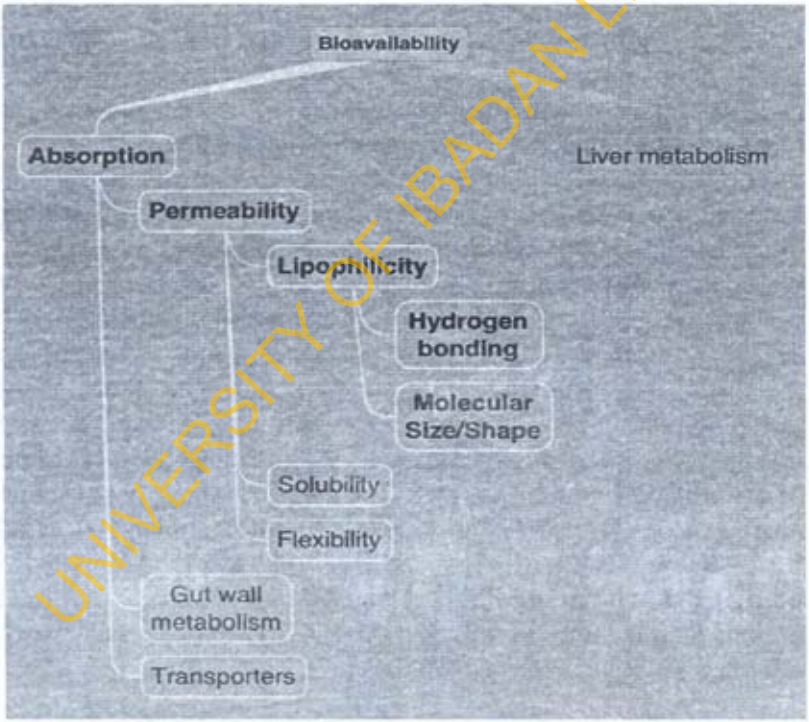


Fig. 12: Importance of physicochemical properties on permeability, absorption, and bioavailability.

Source: van de Waterbeemd (2009)

The conventional "shake-flask" method of determining log P has been criticized, however, as simplistic and tedious. This is because the complex amphiphilic chemistry of the lipoidal biological membrane is modelled by using a simple alcohol (*n*-octanol). In order to address some of the limitations of the conventional method, chromatographic techniques were developed. The reversed phase mode of thin layer chromatography (RP-TLC) and high performance liquid chromatography (RP-HPLC), using octadecylsilane (C-18) bonded phase are popular examples (Wehr 2007, Sabatka et al. 1987). Alternative sorbents are C-8 and C-3 bonded phases. In a bid to improve accuracy of simulation of biological biomembrane, a bonded phase that grafted phosphatidyl choline to silica support, was introduced as immobilized artificial membrane (IAM) (Taillardat-Bertschinger et al. 2003, Pidgeon et al. 1991). Other approaches to lipophilicity profiling utilized cell lines (e.g. Caco-2 cell lines) (Volpe 2011, Camenisch et al. 1998, Kumar et al. 2010). A cell-free model of permeability assay developed by Roche scientists, and currently being applied in the pharmaceutical industry is described as parallel artificial membrane permeability assay (PAMPA) (Avdeef 2005, Avdeef et al. 2007, Galinis-Luciani et al. 2007).

Engineered Leucaena Oil Artificial Membrane (LO-AM)

In pursuit of a bio-relevant lipophilicity profiling technology, that is, one that produces a strong correlation between *in-vitro* and *in-vivo* distribution behaviour of drug molecules, an artificial membrane was engineered from a renewable resource (Idowu et al. 2009). The lipid device was microfabricated from the refined seed oil of *L. leucocephala* (fig. 13). The lipid composition of the oil was found to be remarkably similar to the lipid composition of the biological membrane. The device operates on the principle of reversed phase planar chromatography. Data acquisition was based on solute migration and retention behaviour on the artificial membrane relative to the commercially available ODS

biomembrane model. Data analysis involved transformation of the chromatographic metric to a logarithmic function (Chromatographic R_m). Linear regression analysis of R_m and organic modifier fraction of mobile phase composition leads to the derived parameter; isocratic chromatographic hydrophobicity index (ICHI), which is the measure of lipophilicity. High water soluble drugs have high solute migration (low retention behaviour), while low water soluble drugs have low solute migration (high retention behaviour), as a result of interplay between simulated dissolution and permeation, represented by a biphasic system (fig. 14).

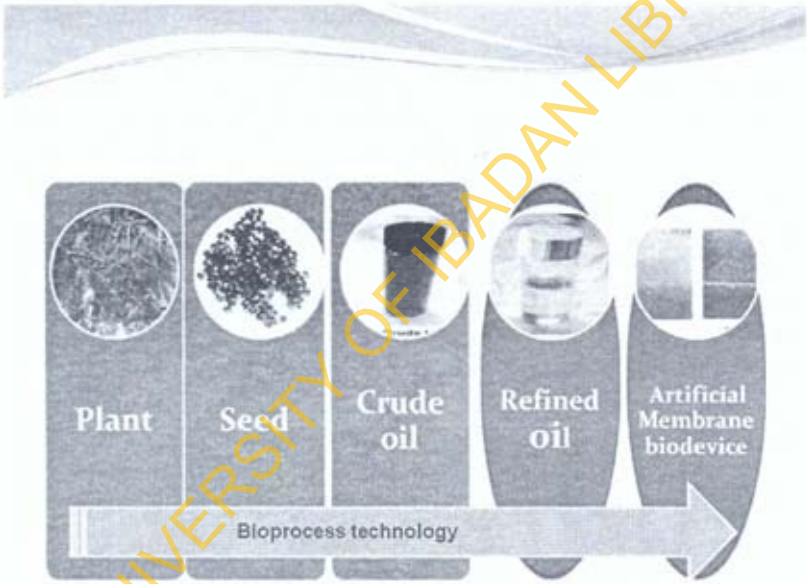


Fig. 13: Preparation of refined leucaena oil and the artificial membrane from the seeds of *Leucaena leucocephala.*

Source: Idowu et al. (2009)

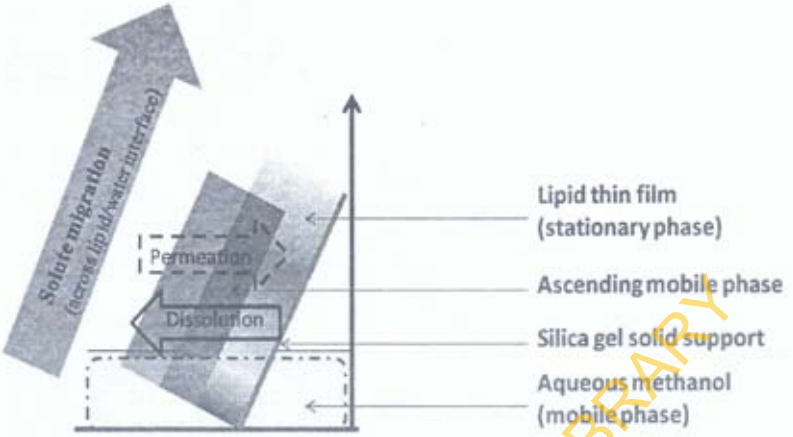


Fig. 14: Solute retention behaviour on the artificial membrane is shown as interplay of simulated dissolution and permeation in a biphasic model (the graphic is an exaggerated cross-section of the artificial membrane).

Validity analysis of the artificial membrane was the theme of the proposal I developed in collaboration with Dr. Amos Fatokun, then of Nottingham University, United Kingdom (U.K.), which was funded by Guildford Methodology Fund, a research grant awarded by the Biochemical Society, U.K., between 2011 and 2013. Ongoing study in my laboratory is exploring supportability characteristics of the new technology and practical application to lipophilicity profiling and biopharmaceutics modelling.

Antioxidant Capacity Profiling of Polyphenol and Phenol-like Dietary Supplements

Phytochemicals found in functional foods (dietary supplements) are useful for health promotion and disease prevention. Polyphenols represent a large class of these plant secondary metabolites, which are of considerable pharmaceutical and biomedical interest. Polyphenols typically exert their bioactivity through both antioxidant and non-antioxidant mechanisms. Their overall effect profile is therefore an example of polypharmacology. Antioxidant action is

important in chemoprevention of many chronic and degenerative diseases, because oxidative stress is implicated in their pathophysiology. The bio-relevant measurement of antioxidant capacity is however an elusive subject.

Antioxidant capacity profiling methodologies are based on hydrogen atom transfer (HAT) or electron transfer (ET). The more popular methodologies have been recommended for automation. These include trolox equivalent antioxidant capacity (TEAC) and oxygen radical absorbance capacity (ORAC) (Huang et al. 2002, Haytowitz & Bhagwat 2010, Zulueta et al. 2009). Some methodologies are popular in the chemical/biochemical literature, e.g. the use of a stable radical, 2, 2 - diphenyl - 1 - picryl hydrazyl (DPPH), yet the results are inconsistent and lack bio-relevance, especially because of lack of competitive kinetics in the mechanism of the reaction (Letelier et al. 2008, Sharma & Bhat 2009, Ionita 2005). Other workers have utilized cell-based assays in the search for bio-relevance (Song et al. 2010, Wolfe & Liu 2008, Wolfe & Rui 2007), yet with unsatisfactory predictive value.

It was identified that one-dimensional assays are generally inadequate to assess antioxidant capacity, such as to provide bio-relevant results. It was argued that "a reliable antioxidant protocol requires the measurement of more than one property relevant to either foods or biological systems". Two dimensional assays was recommended as a minimum requirement in order to account for membrane permeability, which is critical to disposition of the polyphenols and other antioxidant molecules, before they reach their site of action (Frankel & Meyer 2000). A technical report by the International Union of Pure and Applied Chemists (IUPAC), fairly recently, evaluated existing methods for determination of antioxidant capacity, and concluded that "...there is currently, no single antioxidant assay for food labelling because of the lack of standard quantification methods" (Apak et al. 2013). Similarly, the United States Department of Agriculture (USDA) removed the Oxygen Radical

Absorbance Capacity (ORAC) database for selected foods from their Nutrient Data Laboratory (NDL) website; "due to mounting evidence that the values indicating antioxidant capacity have no relevance to the effects of specific bioactive compounds, including polyphenols, on human health" (Nutrient Data: USDA 2010).

This recent evaluation of progress in antioxidant capacity profiling methodologies confirmed a gap still exists in bio-relevant antioxidant capacity profiling. Bio-relevant assay results are essential for quality assurance of dietary supplements and science-driven dosage regimen of dietary supplements. Safety of antioxidant preparations requires optimal dosage regimens, because of concentration-dependent cellular response that characterises antioxidant preparations (fig. 15).

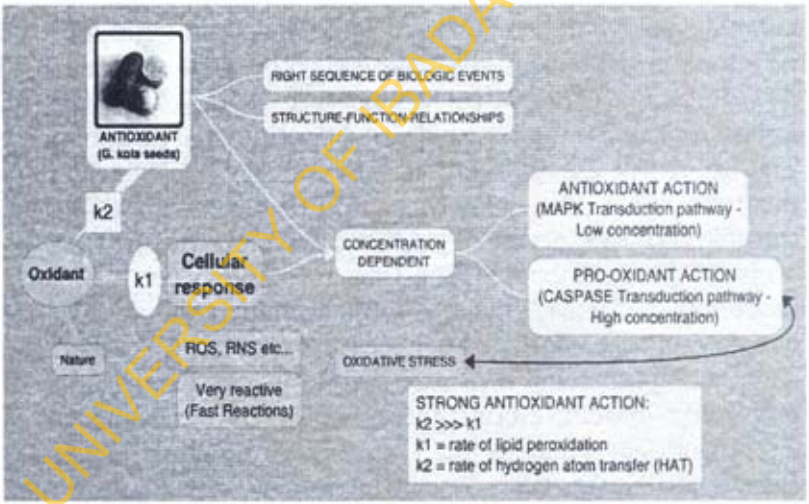


Fig. 15: Elements of a bio-relevant chemical assay. The effect of anti-oxidants in mitigating oxidative stress is a concentration-dependent cellular response. Low concentration of antioxidant is required for cell-survival. The signal transduction pathway stimulated by low concentration of antioxidants complements the HAT process that breaks the chain of peroxy radical lipid peroxidation (ROS = reactive oxygen species, RNS = reactive nitrogen species).

Computational Antioxidant Capacity Simulation (CAOCS)

> I love how mathematics allows us to see the unseeable. If we are clever enough, mathematical models can be used to gain information on things that are impossible to measure directly, which is very exciting.
>
> —*Chris Remien*

Mr. Vice-Chancellor, a new approach to antioxidant capacity profiling of polyphenols and phenol-like small molecules was developed in my laboratory, as a result of sustained systematic experimentation. A drastic departure from conventional wisdom in analytical method development for antioxidant capacity profiling led to an innovative methodology. The existing paradigm of using a free radical chemical specie as oxidant was challenged and ignored, for a new look at the task of simulating auto oxidation process and its inhibition. The novel framework I developed is an integration of computational and experimental technologies. The linear free energy relationships (LFER) theory provides a theoretic basis for simulating bio-relevant hydrogen atom transfer (HAT) kinetics through the readily accessible proton transfer (PT) kinetics. Real-time proton transfer kinetics modelling (PTKM) using nested models (mono-and bi-exponential decay), two phenolic chemosensors (phenol red and phenolphthalein) as probes and statistical identification of preferred model, constitute what is described as Computational Antioxidant Capacity Simulation (CAOCS) (Idowu 2014) (fig. 16).

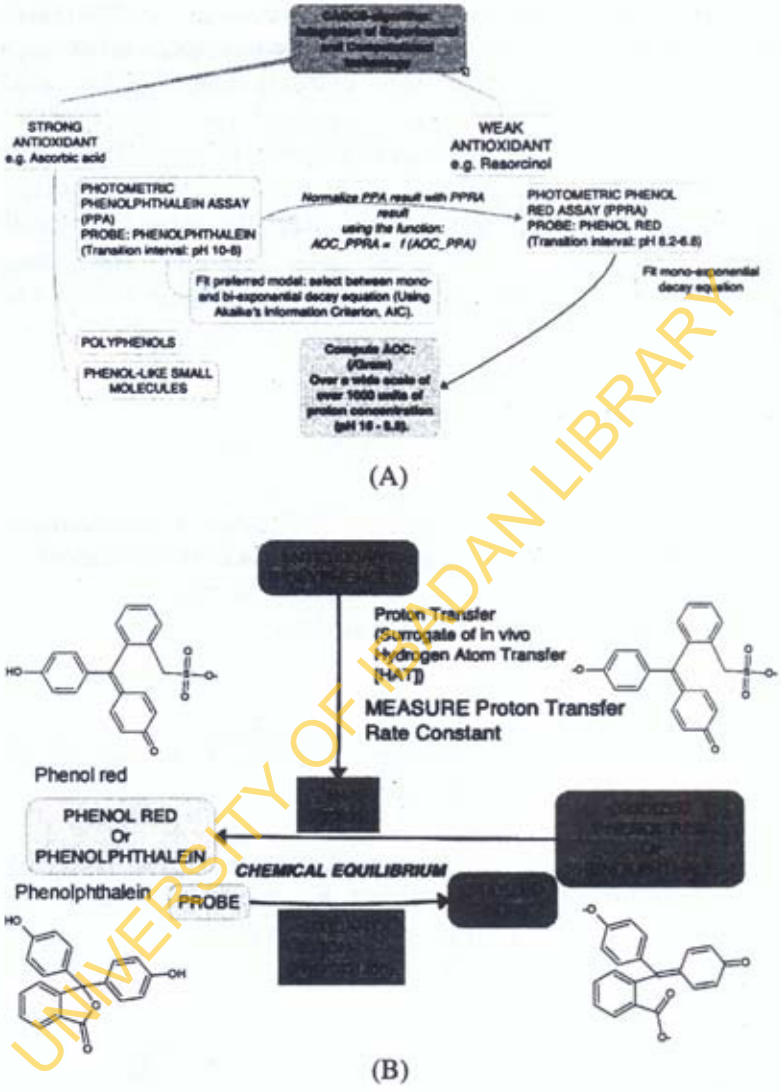


Fig. 16: Flowchart depicting; (A) the algorithm for CAOCS combining experimental with computational techniques to provide a novel methodology for AOC profiling, (B) pH-sensitive chemical equilibrium between reduced and oxidized form of probe molecules is the basis of the model system that simulates *in vivo* HAT kinetics, through readily accessible PT kinetics.

Weak antioxidant polyphenols are profiled on photometric phenol red assay (PPRA) platform, while stronger antioxidant polyphenols (e.g. *Garcinia kola* extract) and ascorbic acid (phenol-like compounds) are profiled on photometric phenolphthalein assay (PPA) platform. In order for the iteration used to model the data to converge, it was often required to remove random errors from the data by digital signal processing (DSP). The latter entails raw data transformation by using a complex multiplier (K_{cf}), before the modelling was performed (fig. 17).

(i) Bi-exponential decay model:

$$Absorbance = S_1 e^{-k_1 v} + S_2 e^{-k_2 v} + C$$

[S_1 = Span 1, S_2 = Span 2, C = Plateau, v = volume of antioxidant (titrant), k_1 and k_2 = reaction constants]

(ii) Mono-exponential decay model:

$$Absorbance = Se^{-kv} + C$$

[S= Span, k = reaction constant, v = volume of antioxidant, C = plateau]

(iii) Digital signal processing of data was performed by using a complex multiplier, K_{cf}, which is different for each data set, to filter out random error:

$$K_{cf} = \frac{\left[\sum_{i=1}^{n} A_i\right] / n}{A_i}$$

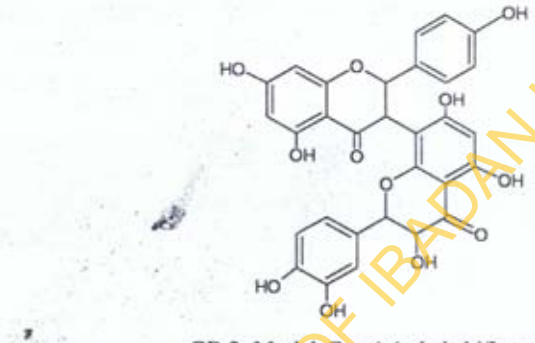
A_i = mean of initial absorbance values for each standard solution

n. = number of standard solutions that make up a family of data sets

Furthermore, results obtained on PPA platform are harmonized with the results obtained on PPRA platform by the simplified equation:

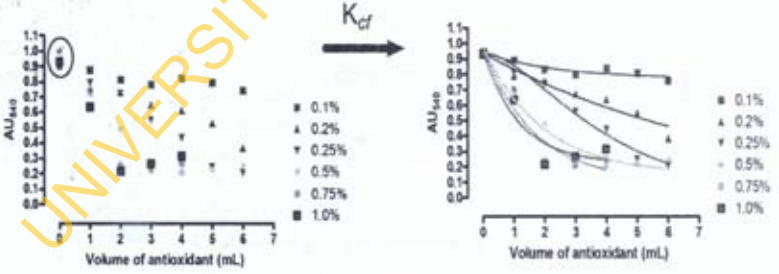
$$AOC_{PPRA} = 3.981 \times AOC_{PPA}$$

The correction factor, 3.981 is derived from the approximately 4 fold difference in the proton concentration required for data acquisition, starting from absorbance decay threshold to plateau, in PPA, relative to PPRA platform.



GB 2: Model *Garcinia kola* biflavonoid

(A)



(i) (ii)

(B)

Fig. 17: Concentration-dependent response described by bi-exponential decay equation for (A) raw data and (B) improved performance of model by using digital signal processing (DSP) to filter out random errors associated with initial values of each data set.

The computational technology output is shown to possess a signature of structure-function- relationship, and hence, a factor of bio-relevance. This was demonstrated by the excellent correlation between the antioxidant capacity metric (AOC) and the ionisation constant related parameter (pK_a) of the individual antioxidant compounds (Idowu et al. 2009, Idowu 2014) (fig. 18). The promise of this innovative methodology was attested to by Rahmat, Sotudeh-Gharebagh, Professor of Chemical Engineering, Univesity of Tehran, and Editor-in-Chief of the journal, Chemical Products and Process Modelling (De Gruyter, Germany). He remarked during the peer-review process of the first publication emanating from the studies thus:

> "We believe your article shows considerable promise..."

This promise is culminating in a bolder and more innovative strategy that is intended for the next generation of antioxidant capacity profiling methodology.

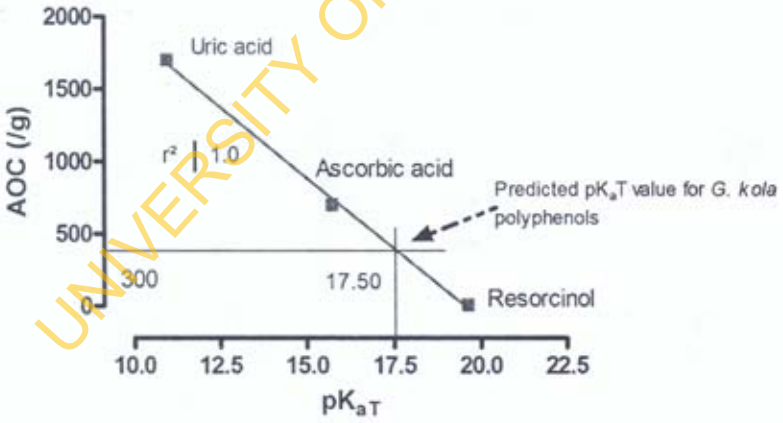


Fig. 18: Excellent correlation between a structural parameter (pK_{aT}, total pK_a) and antioxidant capacity metric (AOC), is a signature of structure-function-relationship and bio-relevance.

Next Generation Antioxidant Capacity Workflow (Next-Gen method)

We hypothesised that a two dimensional assay can be obtained by integrating surrogate of HAT and surrogate of membrane permeability (MP) as independent variables, which can be related to a response variable using appropriate mathematical models. The two dimensions critical to *in-vivo* antioxidant action are illustrated in the graphic shown in figure 19. The dependent variable is to be obtained from animal model of lipid peroxidation. A stable and reliable biomarker of lipid peroxidation will be measured for graded doses of an oxidant. Curve-fitting analysis will produce the metric that represents the relative potency of the library of study polyphenols.

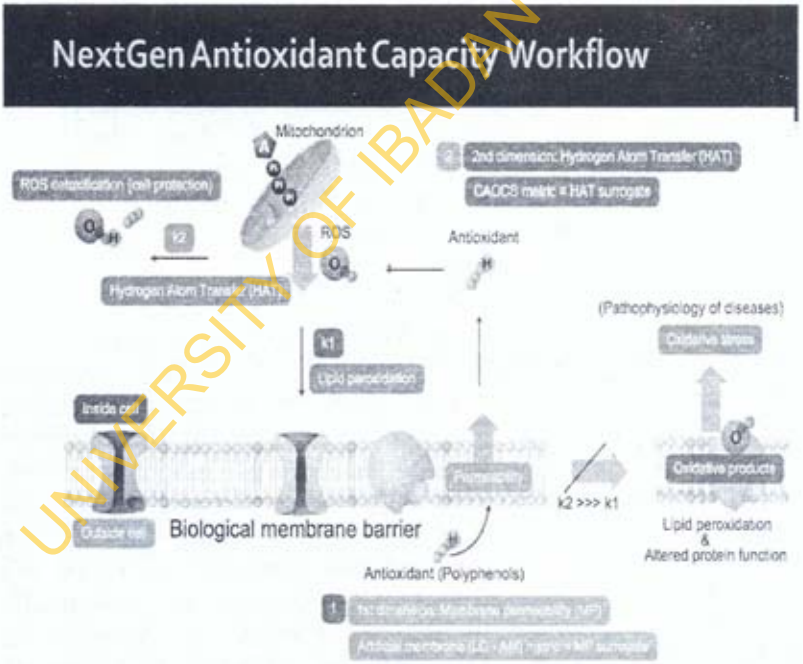


Fig. 19: Next generation antioxidant capacity workflow, highlighting the required integration of HAT and MP surrogates as predictors of response variable (animal model antioxidant action), in the quest for a bio-relevant two-dimensional assay.

In our ongoing study, the surrogates of HAT and MP will be obtained from assay platforms described above, while a preferred animal model of lipid peroxidation based on a stable and reliable biomarker is commercially available (Sapphire Bioscience, Kookaboura kit). Forecasting of bio-relevant antioxidant capacity will require model building by using artificial neural networks (ANN). It is the ultimate aim of this research to achieve the 3R's namely, (refine, reduce or replace), in the use of animals for biomedical research. The expected outcome will also provide a solution option to a problem that has been identified in the field since 2000, without a satisfactory solution 15 years after. The need for high quality research such as this, in the dietary supplement field, is attested to by Dr. Paul Coates, Director of the National Institutes of Health (NIH), Office of Dietary Supplements:

> Americans now spend about $25 billion a year on dietary supplements, yet for many of these dietary supplements, there are questions about their effectiveness and safety, hence,.....our goal of increasing high-quality scientific research to provide sound information on dietary supplements. (Coates 2010)

IV. Chemoinformatics and Molecular Engineering

The use of computational methods to tackle chemical problems, especially manipulation of structural chemical information, is applicable in diverse areas of the chemical enterprise. The use of quantitative structure activity relationships (QSAR) is a popular application in the field of drug discovery. Research in my laboratory has focused on molecular engineering, using chemoinformatics as a tool. We developed a computational methodology to statistically identify the preferred mathematical model to describe the hydrolysis of the aryl diazonium ion, CDNBD, in a strongly acidic medium. The goal of the process understanding exercise was to design, optimise and validate a process of preparing bench stable crystalline form of CDNBD, which is

a very reactive electrophile, and hence, difficult to isolate from aqueous milieu. The aryl diazonium ion was also grafted to the surface of activated charcoal, to prepare a specialty sorbent for use in sample pre-treatment, through solid phase extraction (SPE) procedure, in drug analysis.

Engineering of a Specialty Chemical: Crystalline CDNBD

Successful isolation of CDNBD as a crystalline product requires a deep understanding of the ionization equilibrium that the aryl diazonium undergoes. The main obstacle to the isolation is the high reactivity of CDNBD towards hydroxyl ion, with the consequent conversion to a chemical specie (diazotate) that cannot undergo the diazo coupling reaction, characteristic of diazonium ions. The attraction, however, is the promise of augmented stability and versatility of use. Incremental titration of buffer (pH 12.0) and distilled water was performed on three aryl diazonium ions, namely; benzenediazonium ion (BD), 4-carboxyl benzenediazonium ion (CBD), and CDNBD. The titrants thus supply hydoxyl ion [OH^-], leading to progressive hydrolysis of the aryl diazonium ions according to their reactivity (electrophilicity) (Idowu et al. 2015).

Absorbance decay signal was acquired after chromophoric labelling of instantaneous diazonium ions, while the preferred mathematical model was identified with the aid of Akaike's information criterion. The profile obtained for hydrolysis modelling of the three molecules are shown in figure 20. The high reactivity of CDNBD relative to the simpler analogues is evident in the profiles. Model parameters from the experiments constitute process variables for the synthesis of crystalline CDNBD (fig. 21). The Fourier Transform-Infra Red (FT-IR) spectra of the amine and the aryl diazonium derivative (CDNBD PF_6) are displayed in figure 22. It is shown clearly, that the N – H stretching characteristic of aromatic amines is found in ADBA, while it is absent in the aryl diazonium spectrum. In addition, the pattern of vibrational absorption in the fingerprint region distinguishes the two samples from each other. This spectroscopic evidence confirms the successful isolation of solid aryl diazonium salt, CDNBD.

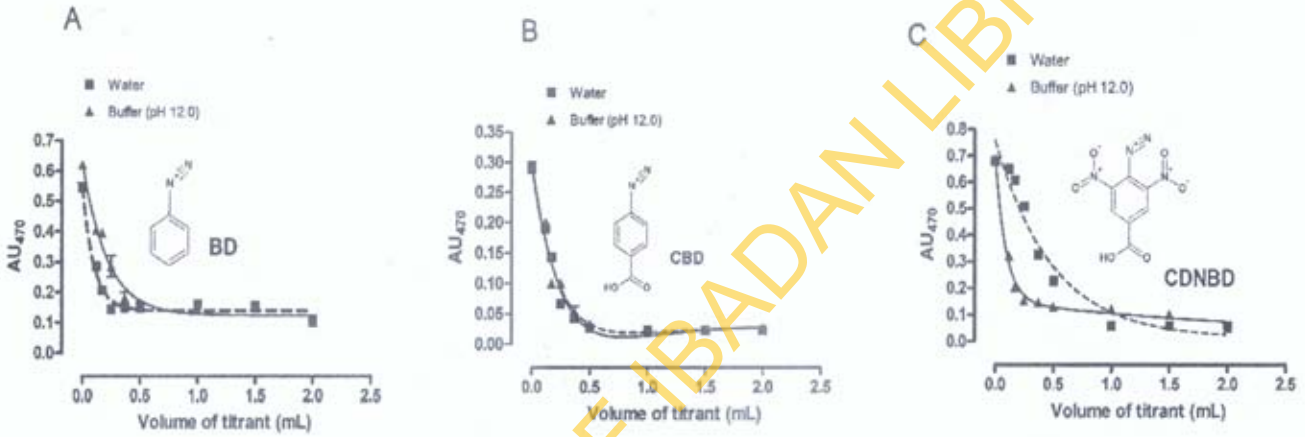


Fig. 20: Hydrolysis of benzenediazonium (BD), 4-carboxyl benzenediazonium ion (CBD), and 4-carboxyl-2,6-dinittrobenzenediazonium in (CDNBD) in response to incremental addition of water and alkaline buffer fitted to mono- and bi-exponential decay model.

Source: Idowu et al. (2015)

Fig. 21: The solid form of the aromatic amine, ADBA (yellow) and reactive CDNBD (white).

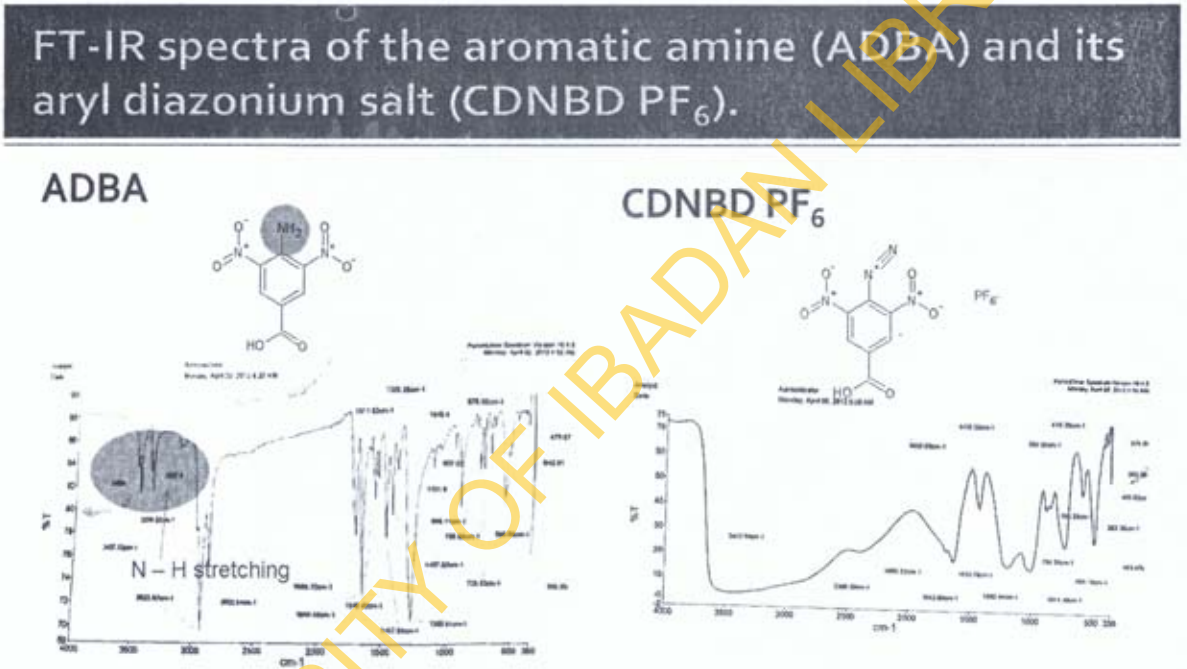
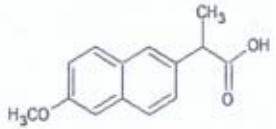


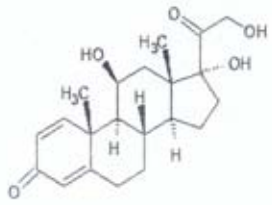
Fig. 22: FT-IR spectra of 4-amino-3,5-dinitrobenzoic acid (ADBA) and 4-carboxyl-2,6-dinitro benzenediazonium ion (CDNBD) hexafluoro-phosphate, confirms the successful isolation of the stabilised diazonium salt in solid form.

Engineering of a Specialty Sorbent: CDNBD-functionalised Activated Charcoal

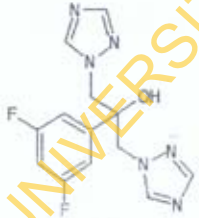
Activated charcoal is a sorbent that is put to several practical applications in drug analysis. We hypothesised that covalent grafting of CDNBD to the activated charcoal surface should permit more electrostatic interactions in addition to hydrophobic interaction. The design of an optimal sorbent material requires an optimal density of the functional moiety (CDNBD residue) on the surface. Three different formulations of varying densities of the functional moiety (AC-CDNBDs) were compared with the reference material, activated charcoal (AC). Three model compounds representing acidic (naproxen), basic (fluconazole) and neutral (prednisolone) drugs were investigated for their retention behaviour on the four sorbents (fig. 23). Data analysis was done by multidimensional scaling (MDS) (Hair et al. 2006).



Naproxen (acidic)



Prednisolone (neutral)



Fluconazole (basic)

Fig. 23: Chemical structure of model compounds: naproxen (acidic), fluconazole (basic) and prednisolone (neutral).

The elution profiles on AC-CDNBD sorbents were transformed to similarity data. Essentially, the target eluates obtained from the SPE elution chromatograms were

transformed into distances represented in multidimensional space. The chromatograms similarity data were arranged into a spatial map, with two axes. The x-axis is the number of runs of target eluates, while the y axis is the retardation factor (R_f). The similarity data was compiled by paired comparisons of each spot (target eluates) with the reference spot of the model compounds loaded on the SPE cartridge. The target eluate is defined as the 'first appearance' of each of the model drugs on the planar chromatogram (fig. 24). The axes are then interpreted in terms of objective attributes associated with them. The overall retention behaviour of the model drugs is interplay of both hydrophobic and electrostatic interactions. This MDS analysis undertaken by chromatogram perceptual mapping ultimately led to identification of the optimal design of the functionalised activated charcoal (fig. 25). These findings are documented in a recent M.Sc. Project report I supervised (Are-Daniel 2015). Ongoing study in my laboratory is exploring the applications of the optimised CDNDB-functionalised activated charcoal as a specialty sorbent for SPE applications in various drug analyses scenario.

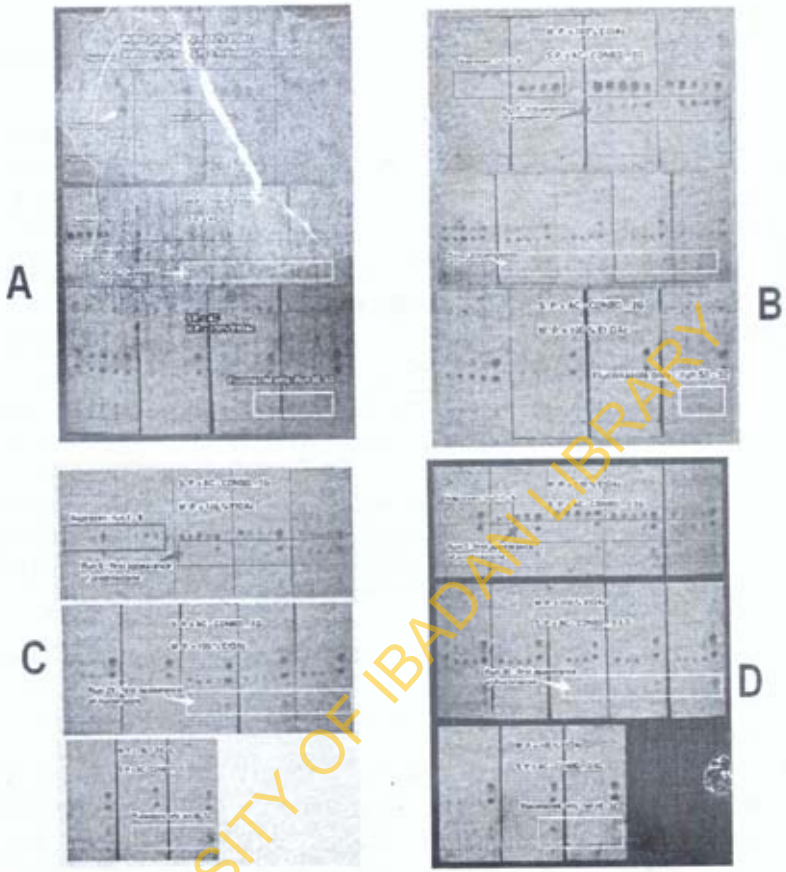


Fig. 24: Array of chromatograms of eluates from SPE cartridges packed with (A) activated charcoal (AC), (B) AC-CDNBD_2, (C) AC-CDNBD_1, (D) AC-CDNBD_0.5 sorbents loaded with a mixture of naproxen, prednisolone and fluconazole, using ethyl acetate (100 %) as eluting solvent.

Source: Idowu and Are-Daniel (2015)

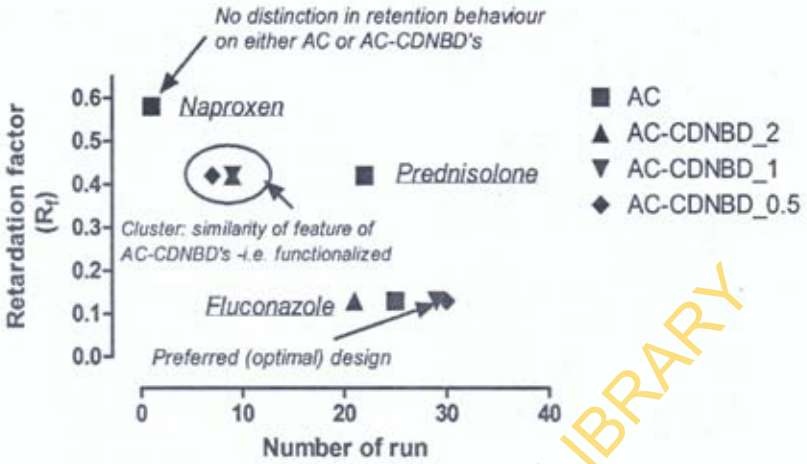


Fig. 25: Spatial map displaying the relative distances of target eluates representing similarity of surface chemistry in the three formulations of functionalised activated charcoal (relative to the reference, activated charcoal), and identification of preferred design.

Source: Idowu and Are-Daniel (2015)

The Lessons

The Lesson of Patience

The lesson of patience began early in my career. I learnt it from Mr. Khan, the Pakistani Mathematics teacher at Baptist High School Iwo, Osun State, in the 1980s. By 1985, he was elderly, perhaps in his sixties, and he had taught mathematics since he took a Bachelor's degree at age 19. Needless to say, he was an excellent and experienced teacher. He was patient in admitting me to the lower six mathematics class in 1984. I had finished my School Certificate examinations the year before, without sitting for "additional mathematics". Actually, I was interested, but, according to the teacher assigned to teach the subject at the time (who was not mathematics major), I cannot do well in it, since I was not doing well in his class. Not having a credit pass in additional mathematics meant, I did not have the prerequisite for Advanced level mathematics.

However, Mr. Khan allowed me, and put me on probation. I would continue in mathematics class, if I coped well in the first year. Due to his brilliance, patience and diligence, I did more than cope. I ranked in the second position, in the mock-examination we had in upper-six class, just before the finals. What is notable in that was the fact that I was one out of two candidates in a class of about forty, taking the unusual and unpopular combination (at that time) of "mathematics, chemistry and biology". The ability to rank higher than classmates in the traditional "mathematics, chemistry and physics" combination, without previous credit pass in "additional mathematics", was a testament to Mr. Khan's patience and diligence.

Mr. Vice-Chancellor, Sir, that experience has stayed with me up till today. It manifests in the patience I routinely take in helping my students construct their knowledge of important concepts in pharmaceutical science, while I take the role of a facilitator. It is gratifying to note, that this painstaking approach, emphasising peer-to-peer teaching, is given such a buzz in current recommendations for professional pharmacy training, the world over. "Active learning" or "Team based learning" as it is called, was practised during my Higher School Certificate training in 1984-1985. I am therefore grateful to the current Dean of the Faculty of Pharmacy, Professor Chinedum P. Babalola, for giving me the platform to lead the current transition effort of the Faculty of Pharmacy to learning in small-class format, using innovative active-learning methods.

My penchant for fundamental research requires an attitude suffused with patience. Between 1992 that I commenced my M.Sc. programme and 2002 when the first publication, documenting the successful application of CDNBD as an analytical reagent appeared, it was 10 years of hard work. From 2004, when I conceived the idea of developing a novel assay technology for antioxidant capacity profiling, to 2014 when the final documentation of the novel framework for CAOCS was published, it was another 10 years. Between 2005, when I conceived developing a strategy

for producing a bench-stable crystalline form of CDNBD, and 2015, when the methodology was published, it was another 10 years. I used to think this pace was rather slow, until I discovered, and was comforted by the outcome of a sociological research as summarised by Malcolm Gladwell, in his marvellous book, *Outliers - the story of success*. The conclusion from the studies of expertise by Gladwell (2008) says:

> the emerging picture from such studies is that ten thousand hours of practice is required to achieve the level of mastery associated with being a world-class expert - in anything

Further, it was asserted, 10 years, is roughly what it takes to put in ten thousand hours of hard practice. Gladwell found this to be true; from popular musicians, to software billionaires, and Nobel laureates. I hope this finding serves as a tonic, and anchor for the soul, for postgraduate students who are sweating it out in the laboratories. If you stay focused, it shall be well. Navigating the academic terrain and waiting for many benefits required a leverage of this lesson. "The human soul is often tortured, because we are ignorant of strategic timing", so goes an African proverb. My musings on "time" came to my aid in this respect:

> There is a twist in time,
> Ensnaring mortals in a clear divide;
> Haunted by the past,
> Fettered in the present,
> Fearful in anticipations;
> In abject haste and insecurity,
> With tortuous visions and tortured hopes,
> Forfeiting hence the future still;
>
> A glimpse of eternity calms the twist,
> For time is nothing;
> But a fragment of eternity,
> The greater will soon dissolve the lesser;

That the twist in time might cease to twist,
In the course of time, time will be no more.
—From *Potent Verses*

Mr. Vice-Chancellor, Sir, I have experienced calm in the twist of time, this awesome year, after a season of 'tortuous visions and tortured hopes'.

The Lesson of Commitment

I have experienced triumphs and setbacks on this journey. I have also attempted to meet them with equal mind. The setbacks I had to deal with, rather than the triumphs, chose the focus and topic of my inaugural lecture. I resolved not to hanker after sophisticated laboratories, with their "big machines", after I lost an opportunity to take my work to a significant milestone, in such a laboratory. Somehow, I found a way of staying grounded at doing what I could, with what I have, where I am. The outcome is a thriving research programme that has become a useful platform to train graduate students in "trace analysis" and undergraduate students in the rudiments of instrumental analysis through "chemical derivatisation technology". It is gratifying to note that over 50% of my colleagues in the Department of Pharmaceutical Chemistry, each one very brilliant in his/her own right, are individuals, whose work I had the privilege of supervising at postgraduate level, based on the research programme that emerged from the sustained effort I have described in this lecture.

In the course of my academic career, I have attempted to be authentic in my approach to work. It has not been without difficulty. I made some mistakes. To err, they say, is human. It is praiseworthy, however, that I had the chance to learn from them. Naivety of youth and sanctified stubbornness are essentially incongruent, hence, the need for a progressive knowledge of the holy. At the peak of a topsy-turvy scenario, a wise man said to me: "don't try to change yourself, if you do, you will never be able to take any giant stride", thus he provided an unexpected caution and counsel. I am grateful for that counsel. It proved true in some critical situations, some years later.

The Lesson of the Loaves

"The whole of science is nothing more than a refinement of everyday thinking"

—Albert Einstein

The idea for the title of my lecture came to me over a year before my professorship was pronounced. It came in a season of contemplation on a famous story; Christ Jesus walking on water:

> But when they saw him walking on the water, they thought he was a ghost, and screamed out. For they all saw him and they were absolutely terrified. But Jesus at once spoke quietly to them, "It's all right, it is I myself; don't be afraid!" And he climbed aboard the boat with them, and the wind dropped, but they were scared out of their wits. They had not had the sense to LEARN THE LESSON OF THE LOAVES, their minds were still in the dark.
>
> Mark. 6:49-52 (Phillips)

The "loaves" here referred to, was the "five loaves and two fish", with which he fed more than five thousand in an earlier experience. What then is the lesson of the loaves? How was it supposed to influence their reaction to a truly scary scene like "walking on water"? Whatever happened to the law of gravity? This lesson, it appears, was intended to be an illumination of the mind, intended to dispel darkness from the mind. Intended to teach the possibility of multiplication of resources, in real-time, when you thankfully embrace something that is truly insufficient. By extension, it was meant to teach the lesson, that natural laws can be temporarily suspended, to give allowance for a great deed and support obligations of honour.

Mr. Vice-Chancellor, Sir, I learnt the lesson, the lesson of the loaves. It taught me to say; "No", to despair, when I was left with ordinary tools, and a career in analytical science was

set before me. It taught me to know, that there are extraordinary potentials in ordinary tools. I can now inform this audience, that most of the works I have described in this lecture, were designed, developed and executed in laboratories at the University of Ibadan. I have used very ordinary tools, by 20th century standard, to develop world-class research programmes. In particular, digital colorimetry and thin layer chromatography are the workhorses of my laboratory!

Doris Lessing, the Nobel Laureate in Literature in 2007, was the oldest recipient of the award in that category. She was 88 at the time. The summary of her contributions, which was read at the award ceremony for the Nobel Prize, was titled: "Exposing the Extraordinary in the Ordinary". Lessing said that writing enables her to take something that is raw and unexamined and give it general significance. In the tradition of Lessing's work in literature, scientific experimentation has enabled me to take something that is "raw and unexamined" (i.e. ordinary) and give it general significance. That applies to: ADBA/CDNBD, CAOCS, and LO-AM (the artificial biomembrane). The process of developing general significance, defines a platform technology, which leads to big impact in due course. The big impact, I must say, is mediated by the fundamental power of mathematics, which a Stanford University illustrated lecture series describe as "making the invisible visible".

Professor Raji-Oyelade, distinguished professor of Comparative Literatures & Creative writing and orator of the University of Ibadan, in his 2013 inaugural lecture; "Fluent in(ter)ventions: Webs of the literary discipline" observed (Raji-Oyelade 2013):

> ... our science must humanise and our humanities be scientific. It must be repeated here that the interface of the artistic and the scientific in intellectual discourse is inevitable even in the practical project of national development.

It is my pleasure to note and firmly embrace this insightful comment. I believe my audience can now perceive, that I stand, nay, dwell, at the interface of the artistic and the scientific in intellectual discourse. Raji-Oyelade described himself as a Scholar-Poet in his lecture, a label I think most appropriate. With apologies to the orator, I wish to describe myself as a Scientist-Poet.

Recommendations

I recommend that the university management should commission the University library to help compile the "recommendations" that have been made over the past thirty years by inaugural lecturers. From the long list they come up with, five strategic recommendations should be developed to guide the engagements of the university management with policy makers and political leadership of the nation.

I prefer to lay it on the line this way, rather than compile a fresh list of "recommendations". This is because, it is my observation that the recommendations made during inaugural lectures, hitherto, hardly move out of the shelves. For instance, in his 1984 lecture, Professor Ajibola Olaniyi had this to say (Olaniyi 1984b):

> The pharmaceutical industries must be committed to, and must invest in drug research and development within the country. They must also provide facilities that will allow academic departments and research units to conduct research into the frontier areas of pharmaceutical sciences. A new interface relationship between the pharmaceutical industry, government and academic pharmaceutical research institutions must develop.

It is now over 30 years later, that "interface relationship" is almost non-existent!!!

Conclusion

It has indeed been a walk with destiny. The features of such a walk were evident in 1994. After almost three months in the United Kingdom (U.K.) without any success at unravelling the problem of poor reproducibility associated with the synthesis of ADBA, I had a clue. The clue was Beilstein, a huge resource that holds information on the most important chemical research from the 19th Century. Fortunately, a collection of Beilstein existed at the University College London (UCL), where I was a visiting scientist. It was kept in an old room, gathering dust. From Beilstein, I was ushered to an 1872 publication written in German, and a 1922 article written in French. I speak neither French nor German, so I needed translators to have access to the most relevant information to the research problem I wanted to solve.

It turned out very easy, like a walk with destiny. There was a young lady from Austria on an exchange visit to the lab I was at UCL, she helped with the translation of the German article at no cost. The wife to the technical staff I was working with speaks French, and she also helped with the translation of the article in French. Thus, it came to pass, within a week, I had a good understanding of the problem at hand, worked with the insight, and by the last week of my 3-month stay in the U.K. my purpose for coming was accomplished. I returned to Ibadan, and the Academic Staff Union of Universities (ASUU) industrial strike, which was on when I left three months earlier, was still on in January 1995. The key to my Ph.D thesis was obtained and indeed the seed for this story was quietly sown.

Mathematics has served me well and I am eternally grateful to my mathematics teachers, especially Mr. Khan. Secondary school students of all generations are told that mathematics is important. Unfortunately, they are not told why? In the mind of many, mathematics is essentially a necessary evil, fully determined to keep you out of the university if you do not befriend her. On the contrary, mathematics is important for a reason, as enunciated by two great men of science. Galileo described mathematics as "the

language in which the laws of the universe are written". Several years later, during a debate on whether studying classical language or mathematics is the better discipline for students, Josiah Willard Gibbs remarked: "mathematics is a language". Teachers of mathematics should emphasise this to secondary school students, for improved performance in mathematics. If you do not speak the language your progress will be slow and your growth stunted. Perhaps this explains, in part, our slow scientific and technological advancement as a nation.

There are other dimensions to this story, but time will fail me to get into those dimensions. Some details are outside the scope of this lecture, because they are forever classified and sealed in a folder, with a label and bold print on it; "BOJURI". It is the nature of stories. I continue to explore veterinary pharmacy in collaboration with my Veterinary Parasitologist friend in the University of Ibadan. Chemoinformatics, as a tool for bio-relevant assay and molecular engineering, also continues as research focus in my laboratory, with collaborators in Ibadan and Europe. In the days ahead, I do hope the "small-class" format and "active learning" methods of course delivery will be given a pride of place in the Faculty of Pharmacy, in a toast to the greater competence and experiential learning of students of pharmacy.

Navigating the academic terrain and training to be an expert in drug analysis has not been easy. It is akin to the ordeal of an adult Yoruba man, learning to sing in Arabic. Yet, as Charles Spurgeon famously said, and I paraphrase: "through perseverance, even the snail made it to Noah's ark". Let us all learn the lesson of the loaves, so that the smallness of our resources may cease to be a barrier to big impact, and our rising sun, cease to set at dawn.

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Finally, I want to thank God as a Scientist-Poet:

Lord, thank you for the electromagnetic radiation
Thank you so much for light that dispels darkness
For the red and blue light in photosynthesis
Thank you Lord for darkness too
You make darkness your secret place...

Thank you for the dark phase of photosynthesis,
Were it not for it, carbohydrates will be nowhere

Thank you for starch, cellulose and amylopectin
For nylon, teflon and polycarbonate
Polymers that brighten our days
Thank you for the mighty silicon too
And the revolution it has brought to us

Most of all, thank you for the light of the world...
Jesus Christ, the Son of God.

—From *Potent Verses*

Mr. Vice-Chancellor, distinguished ladies and gentlemen; This is my story, and, may God take the glory. I thank you all.

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BIODATA OF
PROFESSOR SUNDAY OLAKUNLE IDOWU

Professor Sunday Olakunle Idowu was born on 22nd September, 1968 to the family of Deacon L.A. Idowu and Deaconness T.A. Idowu of Iwo town, Osun State, Nigeria. He attended A.U.D. Primary School, Agbogbo, Iwo (1972-1975) and later, Oke-Moyo Baptist Day School, Ejigbo (1975-1978). For his secondary school education, he attended Iwo Grammar School, Iwo (1978 - 1983). He proceeded to Baptist High School, Iwo, for his Advanced level studies (1983-1985), and gained admission, by direct entry, to study Pharmacy at the University of Ibadan in 1986. He won the University Scholarship in 1987, having emerged as the Faculty Best Student at the end of 1986/87 session, an award based "purely on merit" according to the letter of award. He graduated with Bachelor of Pharmacy degree, Second Class, Upper Division, in December 1989. He was at the Department of Pharmacy, University College Hospital, Ibadan, for his internship in 1990 and served as foundation Pharmacist-in-Charge, Vandeikya General Hospital, Vandeikya, Benue State (1991 - 1992), for the mandatory National Youth Service Scheme. He returned to the University of Ibadan for M.Sc. degree in 1992 and emerged as the best student in his Pharmaceutical Chemistry class in 1994. He obtained Ph.D. in Pharmaceutical Chemistry in 1998, with accolades. Beside the record-time completion of thesis, he became the holder of the first doctorate in Pharmaceutical Chemistry to be awarded by the premier University in Nigeria. His elegant postgraduate studies furnished a new chemical entity, 4-carboxyl-2,6-dinitrobenzene diazonium (CDNBD) for routine use as derivatising reagent in instrumental chemical analysis. CDNBD has been amply demonstrated as one of the most reactive aryl diazonium ion ever documented in the chemical literature.

Professor Idowu joined the Department of Pharmaceutical Chemistry as an Assistant Lecturer on June 1, 1994, later as Lecturer II in November 1995, and was upgraded Lecturer I in December 1998. He was promoted to the grade of Senior Lecturer in 2002, Reader in 2006 and Professor in 2012.

Professor Idowu portrays a positive and revolutionary attitude towards the establishment and sustenance of research excellence, evidenced by an array of inventive research ideas he has vigorously pursued to significant milestones. His current research interest is a novel blend of bioengineering and computational modelling of chemical structural information, an aspect of the field known as Chemo-informatics. He employs process understanding, modelling and simulation to create innovative technologies for drug analysis. These works are documented in high quality journals in the field of Pharmaceutical Analysis, Chemical Engineering and Biological Engineering. He has supervised several M.Sc. research projects, co-supervised a Ph.D. thesis and currently supervising four doctoral candidates in Pharmaceutical Chemistry. He has served the University in several capacities, namely, Acting Sub-Dean (Undergraduate) in 2001, Coordinator, Department of Pharmaceutical Chemistry (2002 - 2003) and Acting Head, Department of Pharmaceutical Chemistry (2005 - 2010). He was member of Senate (2005 - 2010) and currently, member of Senate Curriculum Committee and Chairman, Curriculum Development Committee, Faculty of Pharmacy. He is an effective teacher as evidenced by opinion poll of B. Pharm. graduating class that voted him as "The most inspiring teacher" (2005) and "Most favourite teacher" (2010).

Outside the University, Professor Idowu has served as External Examiner to the Obafemi Awolowo University, Ile-Ife, for both Bachelor of Pharmacy and M.Sc. Pharmaceutical Chemistry programmes. He is a member of the Pharmaceutical Society of Nigeria (PSN), Nigerian Association of Pharmacists in Academia (NAPA) and American Chemical Society (ACS). He is a member of

Editorial Board of *African Journal of Engineering* - Chemical Engineering Subject Area - (*Hindawi Journal*, Cairo Egypt). Professor Idowu was a visiting scientist to the University College London (UCL) School of Pharmacy in 1994, funded by the British Council, and postdoctoral scientist at the Niigata University of Pharmacy and Applied Life Sciences (NUPALS), Niigata, Japan in 2004. He was awarded travel fellowship by the University of Ibadan and Solidum Pharmaceuticals Limited, Lagos, Nigeria, to attend the 4th Log P Symposium, at the Swiss Federal Institute of Technology (ETH), Zurich, Switzerland, in 2009. He won the Senate Research Grants five times (1995- 2010). International recognition of his innovative thinking came in 2011, when the Biochemical Society, United Kingdom (U. K.) awarded him and Dr. Amos Fatokun, then of Nottingham University, U. K., the Guildford Methodology Fund, for validation of a novel lipophilicity assay, which was engineered in his laboratory at the University of Ibadan.

Professor Olakunle Idowu serves as Volunteer Campus Minister, Baptist Student Fellowship, University of Ibadan; Chairman, Vision Counsel, The Vineyard Assembly, Ibadan; Serving deacon and member, Church Advisory Committee, Orita-Mefa Baptist Church, Ibadan. He is married to Foluke (nee Adeyinka), a medical practitioner, and the marriage is blessed with children.

NATIONAL ANTHEM

Arise, O compatriots
Nigeria's call obey
To serve our fatherland
With love and strength and faith
The labour of our heroes' past
Shall never be in vain
To serve with heart and might
One nation bound in freedom
Peace and unity

O God of creation
Direct our noble cause
Guide thou our leaders right
Help our youths the truth to know
In love and honesty to grow
And living just and true
Great lofty heights attain
To build a nation where peace
And justice shall reign

UNIVERSITY OF IBADAN ANTHEM

Unibadan, Fountainhead
Of true learning, deep and sound
Soothing spring for all who thirst
Bounds of knowledge to advance
Pledge to serve our cherished goals!
Self-reliance, unity
That our nation may with pride
Help to build a world that is truly free

Unibadan, first and best
Raise true minds for a noble cause
Social justice, equal chance
Greatness won with honest toil
Guide our people this to know
Wisdom's best to service turned
Help enshrine the right to learn
For a mind that knows is a mind that's free