WALTER SISULU UNIVERSITY

PROFESSOR OF ORGANIC CHEMISTRY

EXECUTIVE DEAN OF THE FACULTY OF SCIENCE, ENGINEERING AND TECHNOLOGY

TOPIC

PHOTODYNAMIC THERAPY FOR THE DEVELOPING WORLD

BY

SP SONGCA

DATE

14 SEPTEMBER 2010

VENUE

WALTER SISULU AUDITORIUM 500 AT NELSON MANDELA DRIVE

Professor S P Songca is an organic chemist with vast research experience spanning over two decades. His main research interests include spectroscopic analytical techniques, the use of laboratory in the teaching of science, synthesis and evaluation of amphiphilic porphyrins for use in photodynamic therapy, synthesis, funcctionalization, and characterization of magnetic iron oxide-gold core-shell nano-particles, nanotechnology and dermographic and biochemical aspects of human geophagia. Some major projects he is involved with include synthesis of p-phenyl linked poprhyrins oligomers for use in Photodynamic Therapy, organometalic reactions and compounds of oligopyrroles with two, three and four pyrrole rings mediated by methylene bridges, construction of chemokine plasmid expression vectors as biological adjuvants to augment immune responses, effects of antidiabetic medicinal plant *Clausena Anisata* on selected carbohydrate metabolizing enzymes, and extraction, isolation and characterization of antibacterial compounds from *Rhus Leptodictya*, and geophagia in South Africa, Botswana and Swaziland. Prof SP Songca has also received several research grants in excess of R15 000 500.00. Some of the grants include R 986,000.00 in 1998 from South African National research Foundation (NRF) for Institutional Research Development, R1,095,000.00 in 1998 from NRF for Equipment Programme, R116,000.00 in 2003 from NRF for Economic Growth and International Competitiveness, R162,500.00 in 2003 from NRF for Education for the Knowledge Era, R1675000.00 in 2007 from NRF for National Equipment Program, and R6000 000.00 from SAAVI in 2006 for Collaborative Research Project with NICD. Professor Songca has published more than 35 conference and Journal articles in both local and international Journals and Conferences. He is actively involved in student supervision and has graduated more than 14 post graduate students, is currently supervising another 14, three of whom are PhDs, six MSc and five Honors. Prof Songca also has several years of experience in lecturing in Higher Institutions of learning including the universities of Transkei, Cape Town, Zululand, South Africa, Limpopo and Walter Sisulu from 1983 until now. He has had several positions of responsibility some of which are; head of department for Science and Mathematics at Marelane High School in Bizana, Vice Dean of Science, University of Transkei, Deputy Dean of Science, University of Limpopo, Medunsa Campus, HOD of Chemistry Department in Transkei and Zululand and Universities of Limpopo, and Director of the School of Physical and Mineral Sciences, University of Limpopo. Presently Prof Songca is the Executive Dean, Faculty of Science, Engineering and Technology, Walter Sisulu University. Prof Songca belongs to several Professional bodies among which are the South African Chemical Institute, The Royal Society of Chemistry, International Society of Optical Engineering, and Society of Porphyrins and Phthalocyanines. Prof Songca is actively involved in community activities and serves as Non-executive director and board member in the Eastern Cape Parks Board, Non-executive director and board member of the Eastern Cape Information Technology Initiative, Evaluator Research Proposals For NRF and MRC medical research council. He is also a reviewer for several Journals. Prof Songca is the Country Coordinator for South Africa responsible for Physical Sciences in the project on Geophagia in South Africa, Botswana and Swaziland and the chairperson of the national eSkills Research Networks – an initiative of the eSkills Intitute. He is the son of Caleb and Joyce Songca with six siblings and is married to Reverend Nokulunga Patricia Songca.

Inaugural Lecture Protocol

Chancellor

Members of Council

Vice Chancellor Sir

Deputy Vice Chancellor – Academic Affairs and Research

Deputy Vice Chancellor – Planning, Quality Assurance and Development

Registrar

Executive Deans

Deputy Deans

Directors of Schools

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Students and student leaders

Members of the University Community

Distinguished Guests

Friends and relatives

Ladies and gentlemen

It is an honor and rare privilege for me to be standing here in front of you delivering this inaugural lecture as a scientist. I belong to the group of scientists known as organic chemists. Later on in my professional life I practiced to become what is known as a medicinal chemist – a chemist that practices the chemistry that deals with chemical compounds used in medicine.

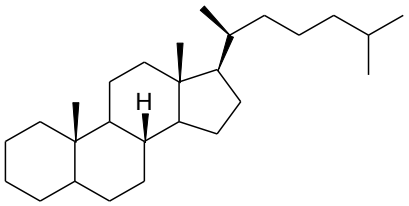
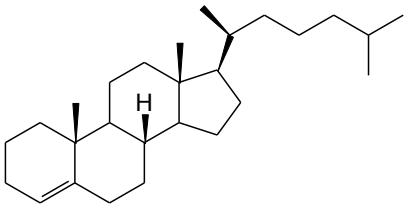
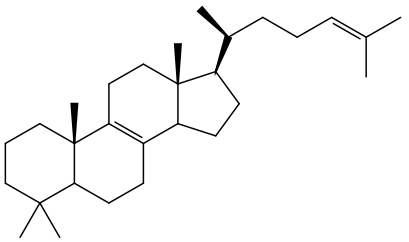
1 Biographical Information

Born in the small Eastern Pondoland town of Lusikisiki I was raised by late parents Caleb and Joyce Songca with six siblings: Nantoe, Siphakamise, Popi, Dzanana, Sizwe and Maxolwanele. My parents wanted me to become a medical doctor because of the tremendous wealth that medical doctors commanded in those days – perhaps even today; a wish I unfortunately resisted, dreaming from a very early age of one day becoming a scientist. I used to read science novels and as I grew up, moved on to watch many a science fiction movie, a past time I still enjoy whenever I get the chance. I saw science as an avenue for doing much good. My grand father, an all time role model of mine was a missionary evangelist and minister of the Apostolic Faith Mission church. He travelled from the home base of my clan at Mhlakulo in Tsolo to the Eastern Pondoland, with my grandmother and one child, the elder brother to my dad, evangelizing and establishing many churches along the way. His missionary route went through Libode past Enyandeni great place across the Mzimvubu river, past Port St. Johns and finally he settled at Mzizangwa in Lusikisiki where he established the headquarters of the Eastern Pondoloand mission of the church, a place I remember so fondly. He was a great man. He was blessed with seven other children including my dad. My dad, a teacher by training apparently carried the same explorer's gene and he started many new schools in the eastern Pondoland and as the first black school board secretary, earned himself the nic-name of "uNobhala" among his peers. I am the third child and the second son. At school I immediately loved learning and books especially English literature, and I used to read newspapers after my dad had discarded them and tell the news articles and stories to my friends as early as standard 6, a feat in my days.

My passion for learning earned me very good positions and I progressed well. I was not very clever, but I worked very hard and loved learning. I was hungry for knowledge and for the ability to learn on my own. I went through rote learning, mimicry and many other modes until I resolved to extract understanding from the words of the authors of textbooks, novels and other literature. I read Mathematics, Biology, Physical Science including the modern day discipline of Physics and Chemistry, English, Afrikaans and Xhosa. Because my parents were extremely nomadic I attended primary schools at St. Andrews in Lusikisiki, St. Georges in Mount Frere, Blythswood in Nqamakwe and Lourdes in Mzimkulu, secondary and high schools at Mfundisweni High School in Flagstaff and finally at Mqikela High School in Lusikisiki, where I completed my senior certificate, obtaining it without endorsement in the first attempt and with endorsement in the second. I moved to Mthatha where I enrolled at the newly established University of Transkei for a BSc. Degree, which I obtained in three years, majoring in Mathematics and Chemistry. I continued with the BSc. Honours which I obtained after two years due to a re-examination that I had to take in Inorganic Chemistry as well as a course in Advanced Analytical Chemistry which I had to take at the University of the Witwatersrand. This is where I met a colleague and friend of mine Prof. Nakani who mentored me in Wits life and other areas while he was doing his PhD there. I then went to work as a teacher at Marelane High School where I taught only for one year, fleeing at the end of that year after realizing clearly that one needs training as a teacher in order to teach. I was head hunted by my former Inorganic Chemistry Professor, Prof. Louie Du Preez to join the department of Chemistry as a laboratory assistant. I was promptly promoted to junior lecturer after passing the Inorganic Chemistry module and therefore completing the BSc. Honours degree. I immediately enrolled for the MSc degree in organic

chemistry with the University of Transkei under the supervision of Prof. Piacenza. My research was concerned with the synthesis of 2,3-dihydroxy steroid compounds including, cholestanes, cholest-4-enes and lanostenes and their 2,3-dihydroxy epimerization reactions. I never completed this work because my head of department, Prof. Rutherford organized a British Council scholarship for me to go to the United Kingdom to do my MSc. as a result of which I moved to London in September of 1989 where I enrolled for MSc in chemical research at Queen Mary and Westfield College, one of the many colleges of the University of London.

Table 1: Cholestanes, cholest-4-enes, lanostenes.

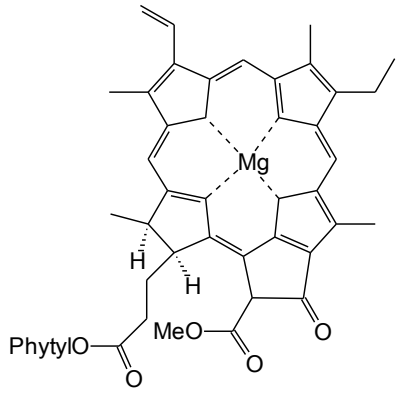
#	Structure	Name	Reference
1		Cholestanes	Unpublished work
2		cholest-4-enes	Unpublished work
3		lanostenes	Unpublished work

During my last days as a teacher at Marelane High School, I met a beautiful young lady in Mthatha – a saleslady at her family's business Mandlakamoya, where I had spotted a music system that I wanted to buy. I married her eight months later. It was not until some 24 months later that I returned and bought the music system. My wife of 27 years is Nokulunga Songca (nee Silinga), a minister of religion in the Methodist Church of Southern Africa. What started as a wild fire in 1983 has now settled to be a warm glow of ambers with no signs of fading. To God be the glory. The music system still occupies one corner from where it perfumes our house with the graceful melodies of classical and gospel music.

My wife joined me in London in December 1989 where we would remain for the next five years. Supported by the University of Transkei and the British Council for one year, followed by Luthuli Memorial Trust and finally United Nations Education and Training Programme for Southern Africa, I waded through my studies towards my MSc followed by my PhD, interluded by a seven months stint back at the University of Transkei. I would like to briefly outline some important details of my support by the Luthuli Memorial Trust and subsequently the United Nations Education and Training Programme for

Southern Africa. The Luthuli Memorial Trust policy was to provide South Africans with sponsorship for only one degree so as to spread the resources widely and support as many South Africans as possible. Luthuli Memorial Trust therefore offered to sponsor my wife towards her degree in English Literature and Communication. She persuaded them to rather continue sponsoring me with the funds that were ear-marked for her support, to which they reluctantly agreed. When the funds ran out and while Luthuli Memorial Trust was looking for alternative support for us, she worked for the Hard Hat Café at Canary Wharf in the Isle of Dogs in order to support us and she continued to do so until I completed my studies. What a supporter! What a wife! I am where I am today because of that selfless dedication and support.

Table 2: Structure of Chlorophyl a.

#	Structure	Name	Reference
4		Chlorophyl a	Woodward et al, 1990

I was introduced to the chemistry of porphyrins and phthalocyanines and to photodynamic therapy, one area of application of these compounds for the first time by Professor Raymond Bonnet, my supervisor. Prof. Bonnet was a student of Prof. Woodward, well known in Organic Chemistry literature for the Woodward-Hoffman rules featured in electrocyclic reactions, who first described the total synthesis of chlorophyll-a. After the passing of Prof. Woodward, Prof. Bonnett my PhD supervisor and his peers collected all the research note books, the published and unpublished works of Prof. Woodward and put together the total synthesis of chlorophyll-a 1, one of the greatest milestone applications of oligopyrrole chemistry. This article contains some of the contributing works to the founding of the prestigious journal Tetrahedron and it describes the total synthesis of chlorophyll-a starting from Knorr's pyrrole synthesis and includes more than forty six stages required to reach the target molecule.

2 What is photodynamic therapy?

Photodynamic therapy has been defined as the combined effect of a photosensitizing drug and light to produce biological damage of therapeutic value, under conditions where neither the light nor the drug operating alone have any effect (2). The approach has aroused considerable interest in scientific, medical and commercial circles in recent years, partly because it is conceptually very exciting, but also because there is no doubt that it works exceptionally well in destroying malignant or otherwise problematic tissue. The basis for PDT lies with two remarkable properties of the photosensitizing drugs

that are used in the approach - their preferential accumulation in some tissue types notably cancer tissue and the subsequent light triggered toxicity of the photosensitizing drugs used (3).

3 How does photodynamic therapy work?

The patient is injected intravenously with a suitable preparation of the drug and confined to the dark. A period of time is allowed for the drug to accumulate preferentially in cancer tissue. The period varies from drug to drug, from as little as 3 hrs, to more than 72 hrs. After this period, due to its inherent preferential localization, most of the drug is in the cancer tissue. The differential in drug concentration between cancer tissue and the rest of the body varies from drug to drug, from as low as 6:1 to more than 20:1. Due to its inherently low toxicity in the dark, at this stage the drug is harmless to both tumour and interstitial tissue. A suitable dose of light is then administered. This presents little challenge for external cancers. For internal ones, optic fibre light delivery and guidance devices are often used. Because of its photosensitizing effect, the drug then turns toxic and drug rich tissue is destroyed immediately. Cancer tissue destruction persists without affecting drug deficient tissue. Some time is allowed for the drug to be completely cleared from the body after which the patient is allowed back into environments of normal lighting (4). This is illustrated diagrammatically in figure 1.

Figure 1 (a): Practical administration of Photodynamic therapy

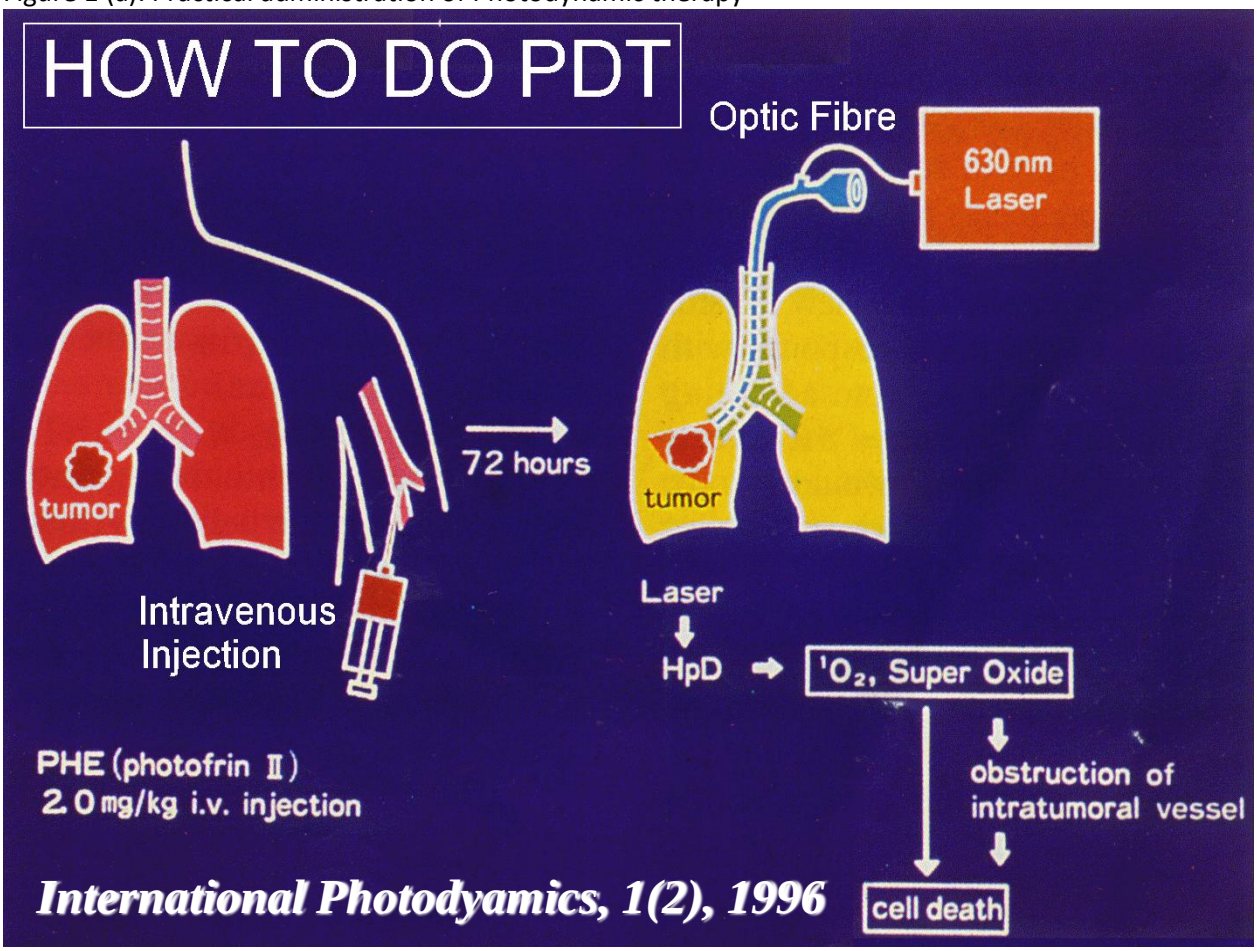
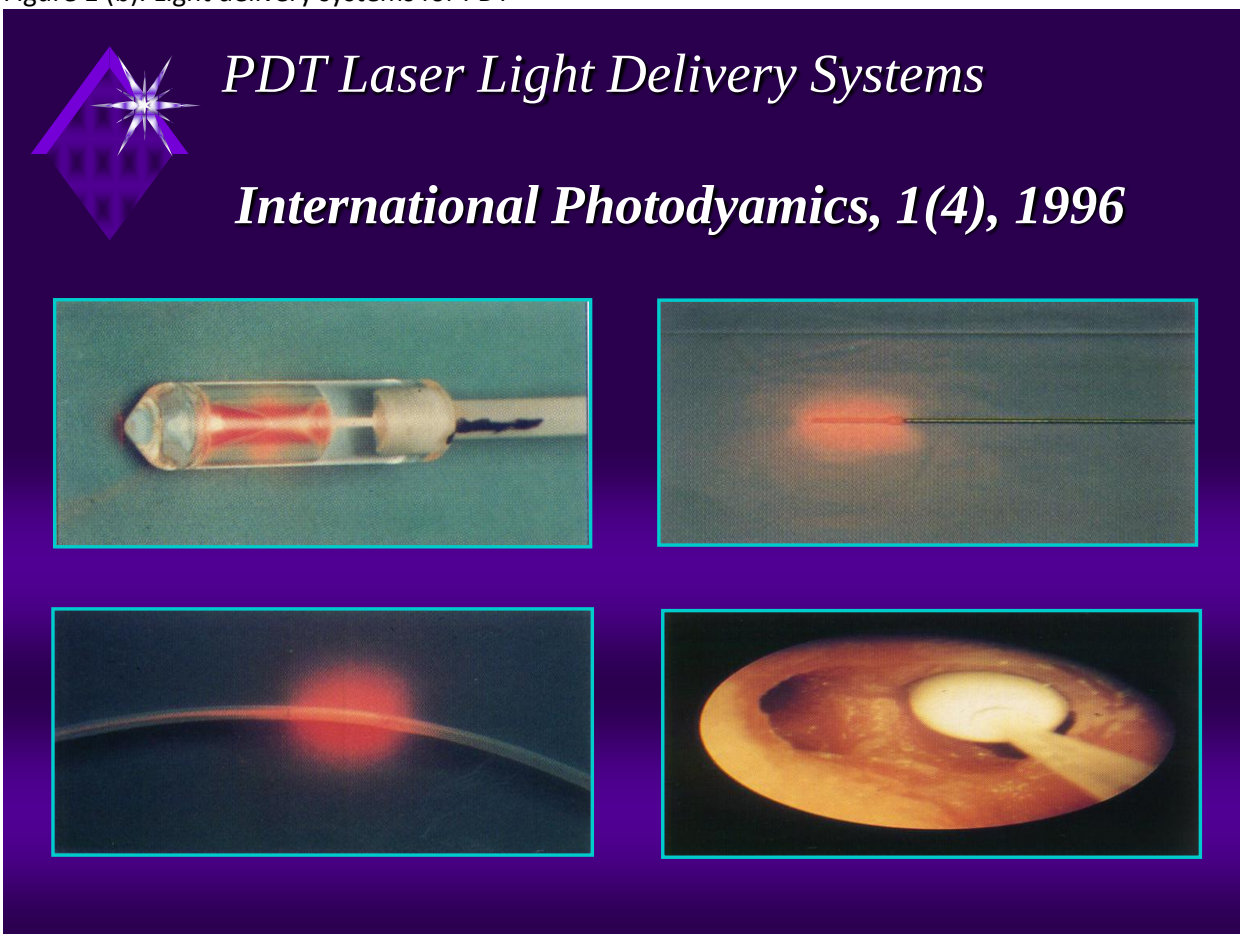


Figure 1 (b): Light delivery systems for PDT



Cancer tissue destruction is achieved because the drug absorbs the energy of light and transfers it to molecular oxygen, generating singlet oxygen, a highly reactive species, which causes biological damage (5). The extremely short lifetime of singlet oxygen within the biological environment means that the treatment is highly localized, without systemic side effects (6). For this reason, PDT can be especially effective in disease sites close to vital organs, such as in cancers of the head, neck, and the brain (7). Although necrosis has been recognized as the major photodynamic response, apoptosis is now well described in PDT (8).

5 Does **photodynamic therapy** work?

PDT was first demonstrated by what can be described as a foolhardy experiment by Meyer-Betz in 1913. He injected himself with 200mg of haematoporphyrin and observed his reaction to visible light. The result was that all exposed surfaces became swollen with visible reddening of the skin for several weeks (9). On the other hand selective tumour localisation of haematoporphyrin derivative was first demonstrated by Lipson and Baldes in 1961 (10). It was not until later, in 1972, that the two ideas i.e. the photodynamic effect and tumour localisation, were put together. Thus the possibility that a porphyrin could be used to photosensitise the preferential degradation of tumour tissue was demonstrated. Diamond showed that in the presence of haematoporphyrin, tumour cells are destroyed

by continued irradiation (11). Subsequently, it was shown that it is haematoporphyrin oligomers, which occur as impurities in commercial haematoporphyrin, rather than haematoporphyrin itself, which is effective in causing photodegradation of tumour tissue (12). Experiments of this kind on human beings were first carried out in 1976 by Kelly and Snell (13). Although the question of whether PDT does work in clearing actual tumors persisted for a long time, it has been laid to rest by the gradual adoption in the clinic where irrefutable evidence accumulated over many years shows that it actually does (see figure 2).

Figure 2: Before and after treatment pictures showing that **photodynamic therapy** does work.

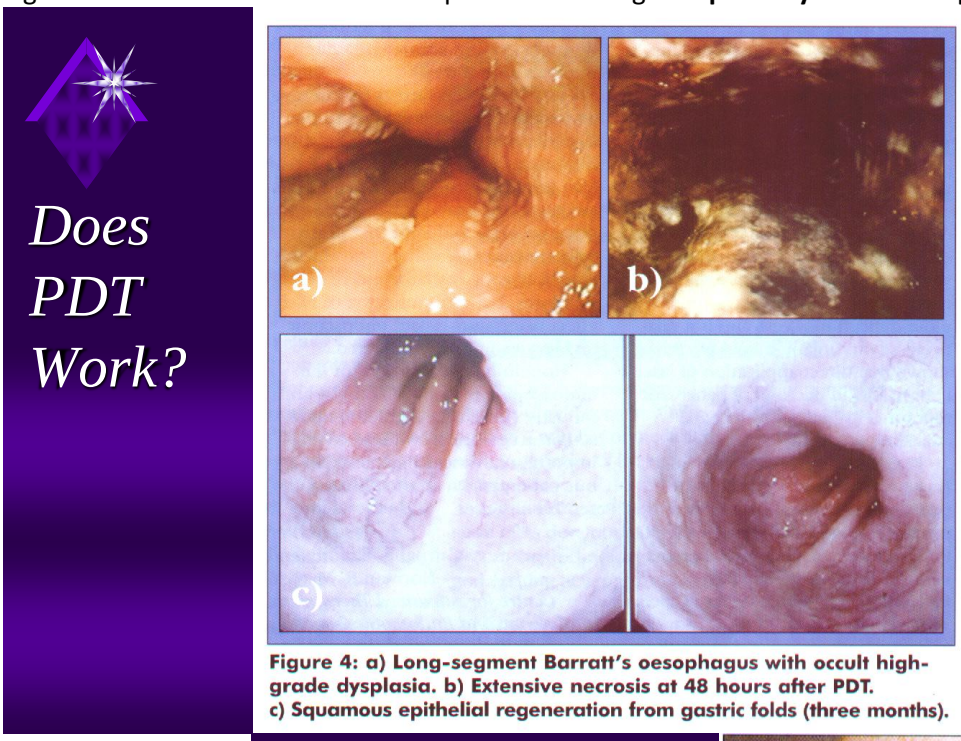


Figure 4: a) Long-segment Barratt's oesophagus with occult high-grade dysplasia. b) Extensive necrosis at 48 hours after PDT. c) Squamous epithelial regeneration from gastric folds (three months).

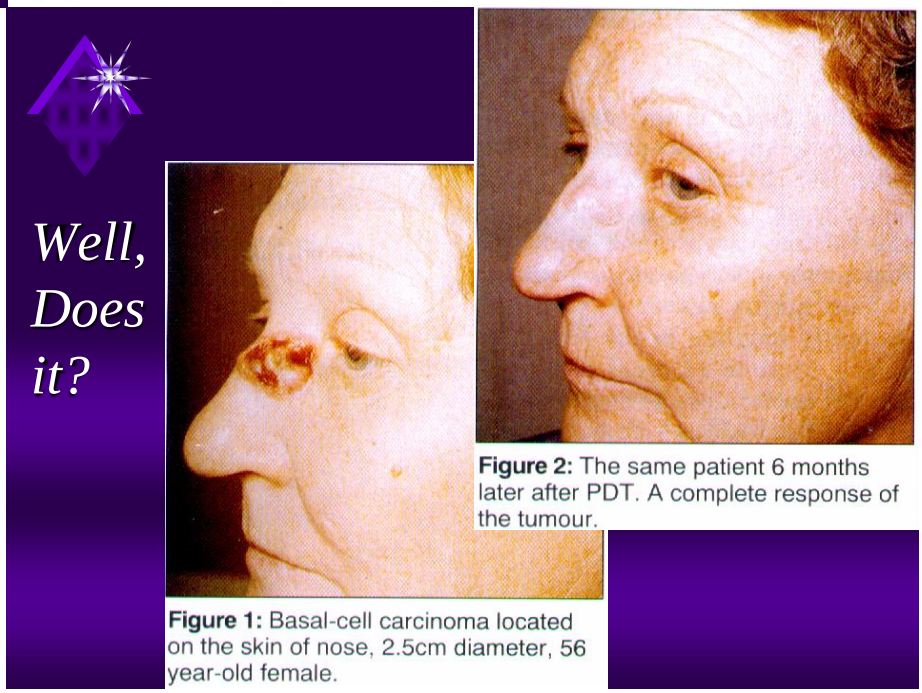


Figure 2: The same patient 6 months later after PDT. A complete response of the tumour.

Figure 1: Basal-cell carcinoma located on the skin of nose, 2.5cm diameter, 56 year-old female.

The evidence is overwhelming

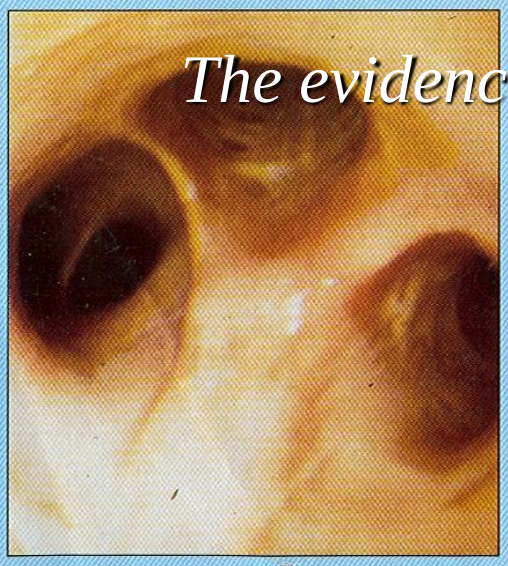


Figure 2a: Bronchoscopic findings of 78 year old male with a nodular squamous cell carcinoma, 0.5 cm x 0.5 cm in size in right upper bronchus. Roentgenographic examinations were negative.

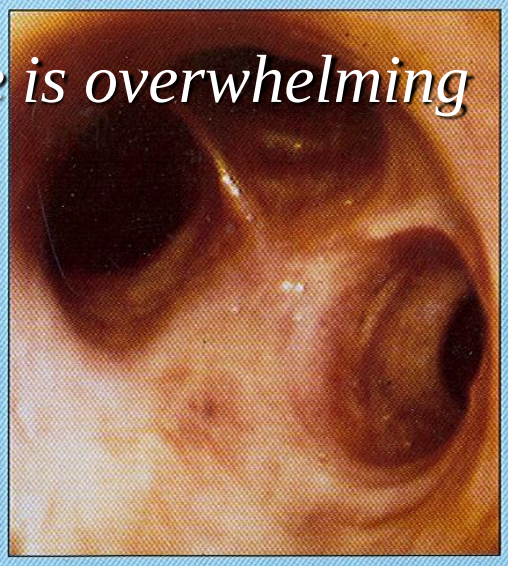


Figure 2b The same site 2 months after PDT. Complete remission was obtained.

PDT works exceptionally well

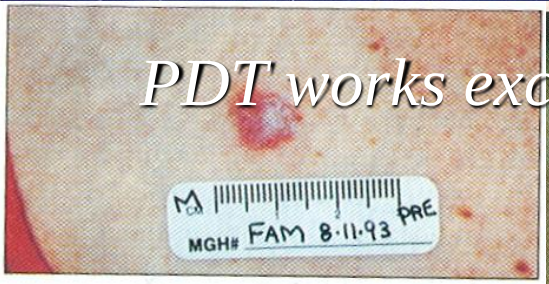


Figure 3a. *In situ* squamous cell carcinoma in an immunosuppressed kidney transplant patient before treatment.

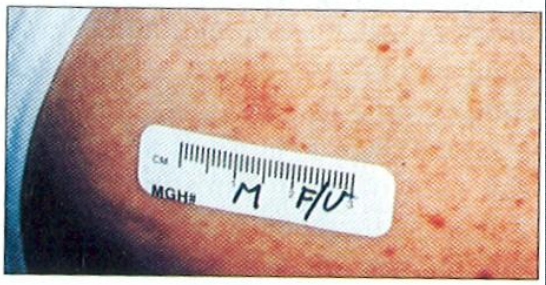
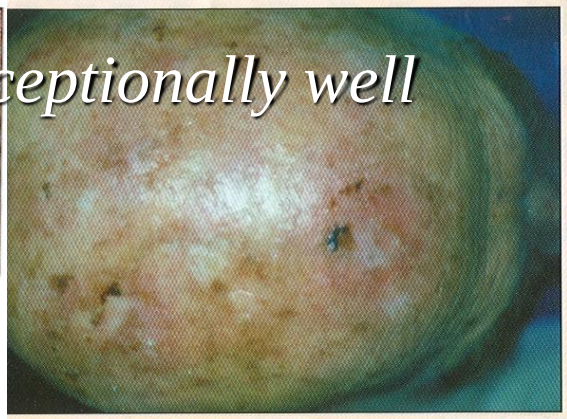


Figure 3b. The same tumour after four treatments with 20% topical ALA. Complete remission was obtained.



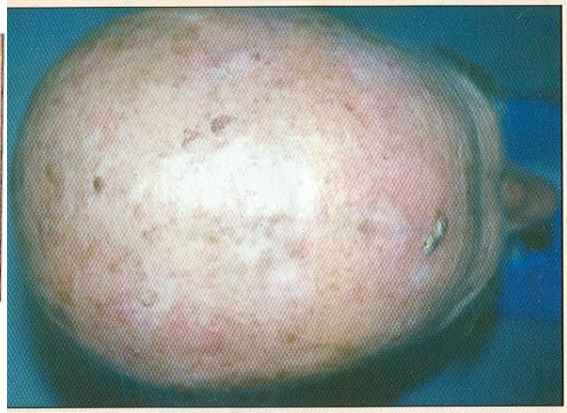
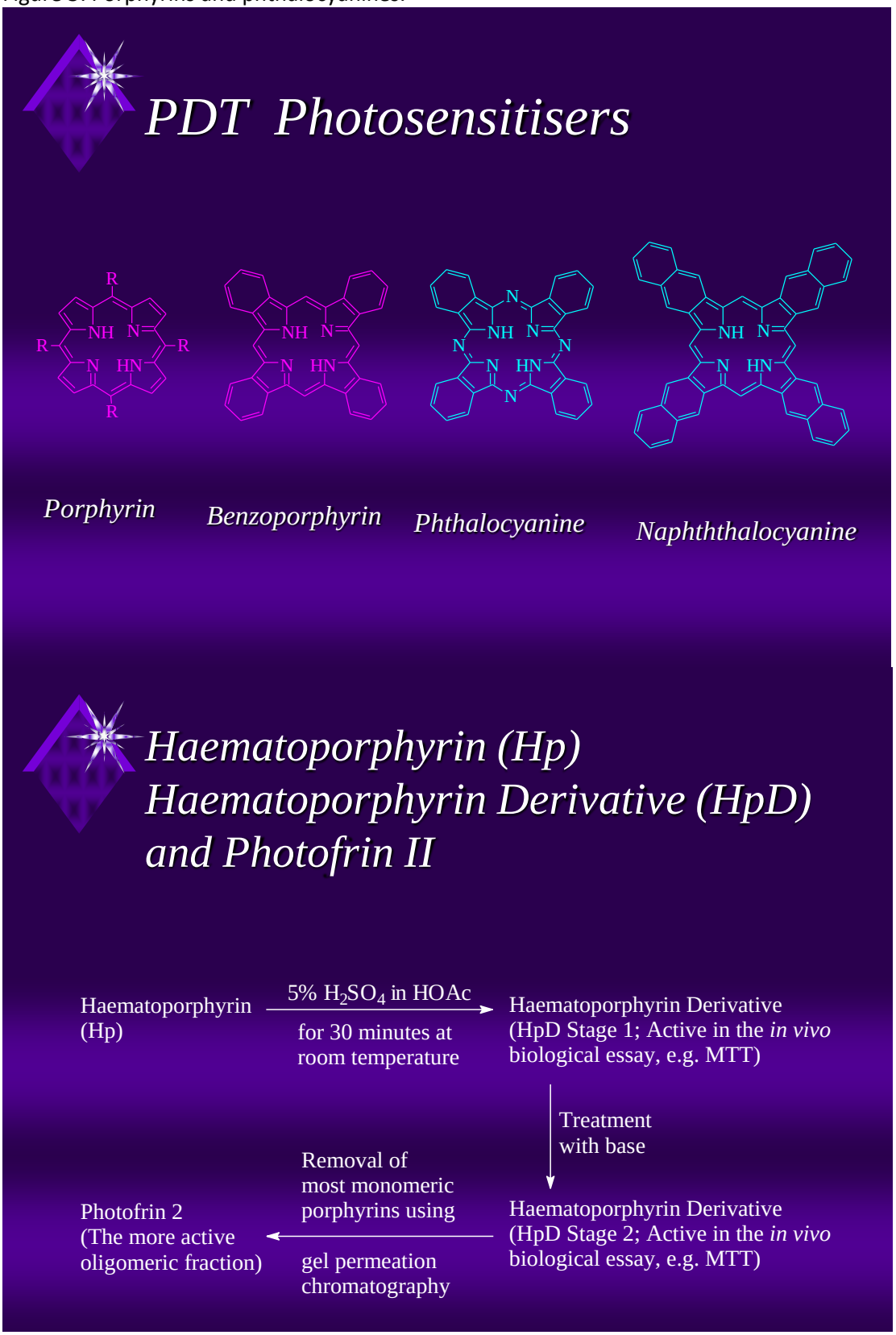


Figure 3: Porphyrins and phthalocyanines.

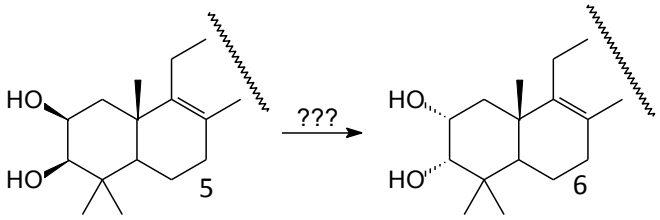


6 Photodynamic Therapy Drugs

PDT drugs belong to the unique family of macrocyclic porphyrin, and phthalocyanine type of compounds (14). A number of drugs have been licensed for use in PDT (15). Photofrin currently enjoys the widest approval, in a number of countries, including Canada, Denmark, France, Finland, Germany, Iceland, Italy, Japan, Netherlands, United Kingdom, and the USA, for a variety of cancers, including lung, oesophageal, bladder, gastric, cervical, skin, and brain cancer (16). Photofrin belongs to the first generation of PDT drugs in that it is a mixture of a number of porphyrin compounds, oligomers that are derived from haematoporphyrin, and its composition is not stable (17) as shown in figure 3.

7 New direction in research

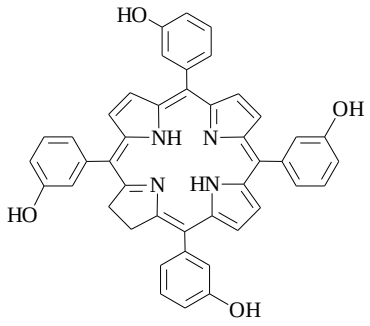
This took me on a new direction in so far as my research was concerned. After several years of researching steroids for no apparent direct benefit to human kind except for curiosity to find out if one could do epimerization reactions without ring opening and closure, I am suddenly confronted with fantastic molecules that could transform the landscape for the palliative management of cancer! I loved the molecules, I loved the applications and for the first time I was faced with the reality of my life-long dream of doing science for the sake of doing good for human kind. I was thankfull and I grabbed the opportunity with all my front legs and some of the hind ones. To this day I am still a photodynamic therapy scientist although I have expanded my basic research in drug development to include prospecting medicinal plants with a view to discovering plant based remedies for human sicknesses.



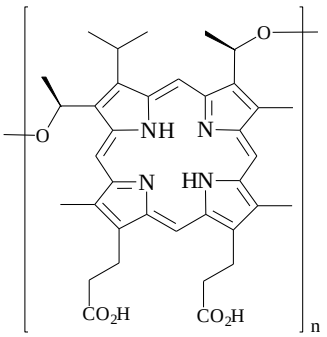
Equation 1

My first encounter with these molecules was such a lovely experience that together with a Turkish and a Spanish scientist we decided to pose with the molecular content of the drug preparation known as Foscan as our supervisor took the picture. Foscan was commissioned by Scotia Pharmaceuticals from our research group and is used to treat head and neck cancers in Europe and Canada. Other second generation drugs now in use apart from Foscan from Scotia (18), include Visudyne from QLT (19), Lutex from Pharmacyclics (20), Pc4 from Case Western Reserve (21), Purlytin from Miravant (22), NPe6 from Nippon (23), HPPH from Roswell Park Cancer Institute (24), and amino laevulinic acid from DUSA (25). A number of second generation drugs are under development including boronated porphyrins, which will be used in boron neutron capture therapy (26). Our group was involved in developing variants of the Foscan type of porphyrins. However in our case these were solubilized in hydroxylic media by fluorination and by other means in order to establish drugs that are cleared quickly from the body (27).

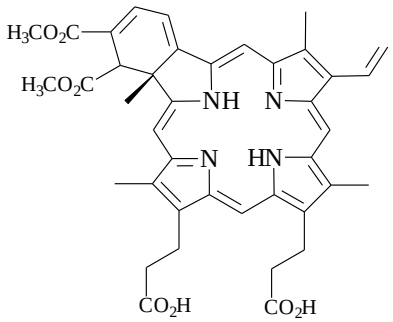
Figure 4: Structures of the leading second generation drugs now in use.



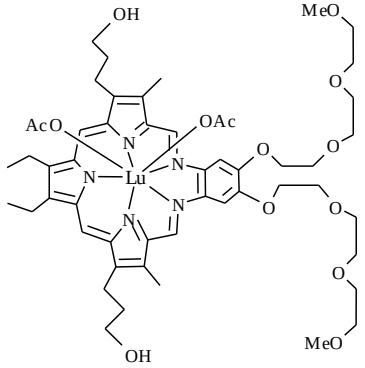
Foscan (Scotia)



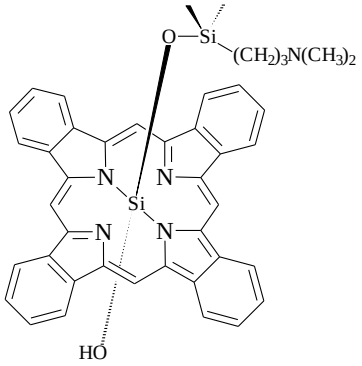
Photofrin (Axcan)



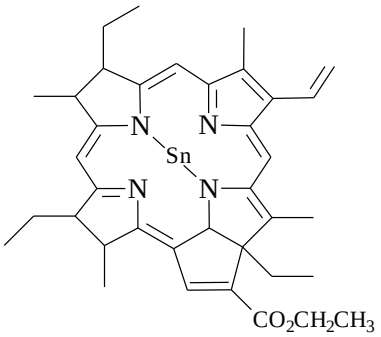
Visudyne (QLT)



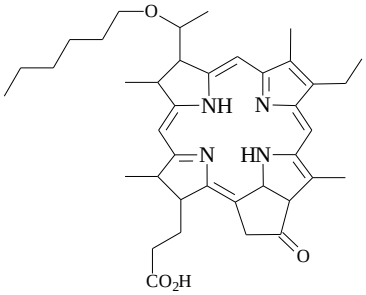
Lutex (Pharmacyclics)



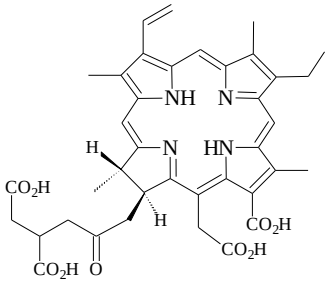
Pc4 (Case Western Reserve)



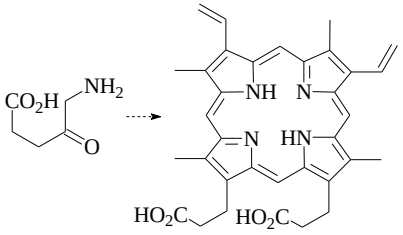
Purlytin (Miravant)



HPPH (Roswell Park Cancer Institute)

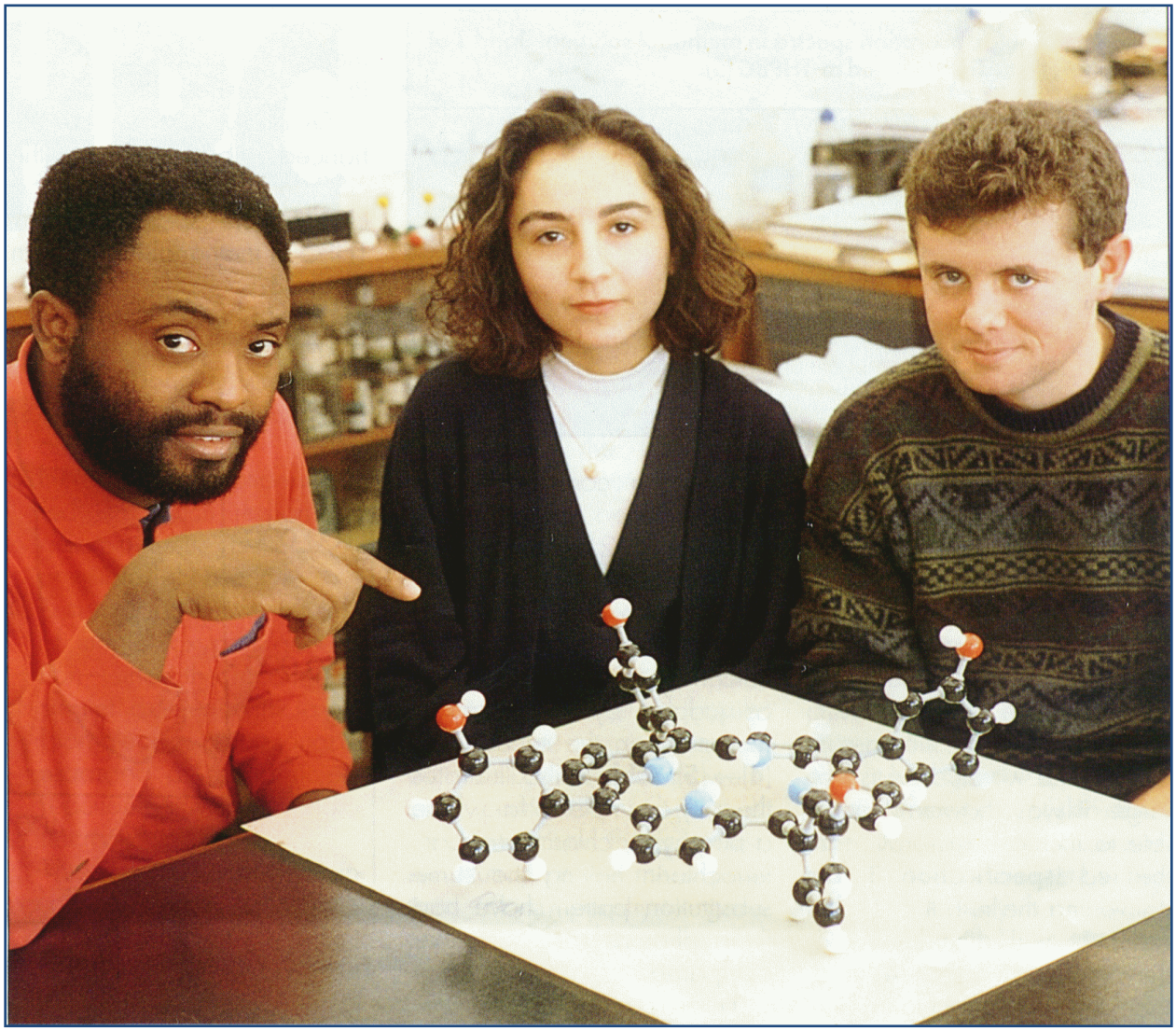


NPe_6 (Nippon Petrochemicals)



Levulan (DUSA)

Figure 5: The porphyrinic molecular content of Foscan.

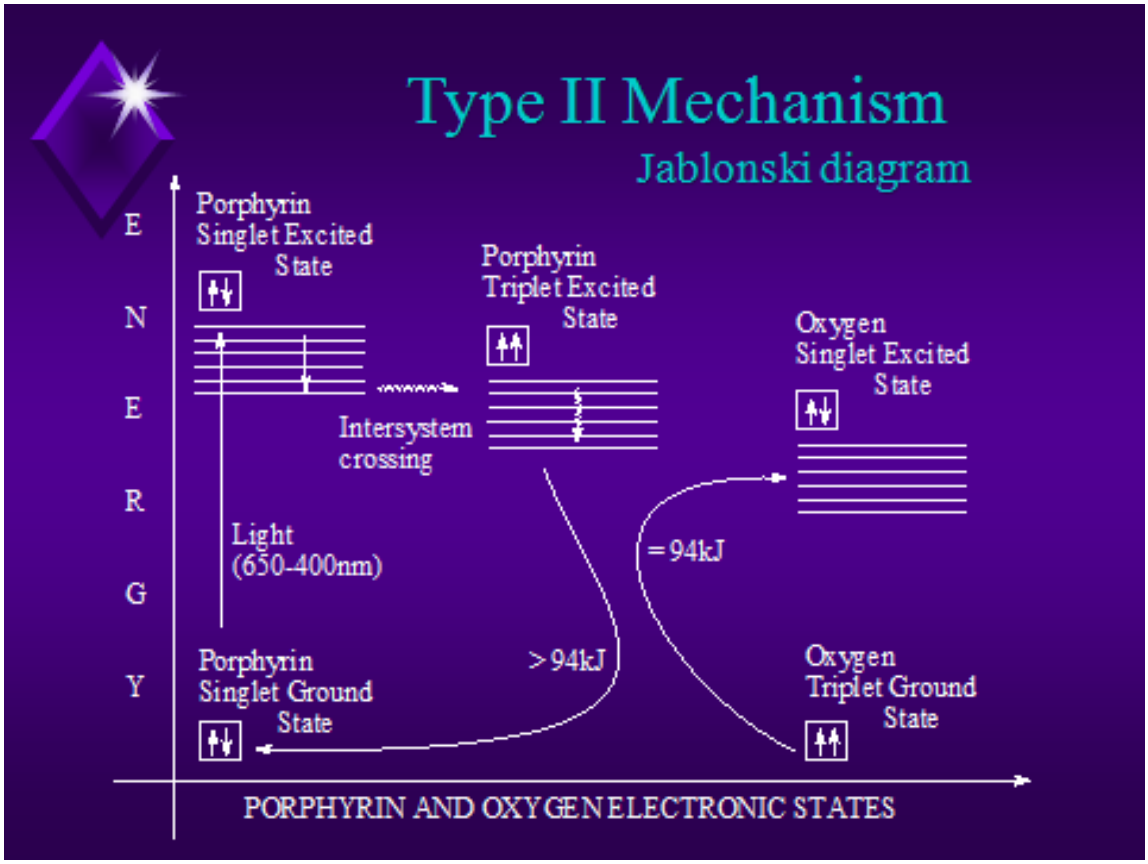


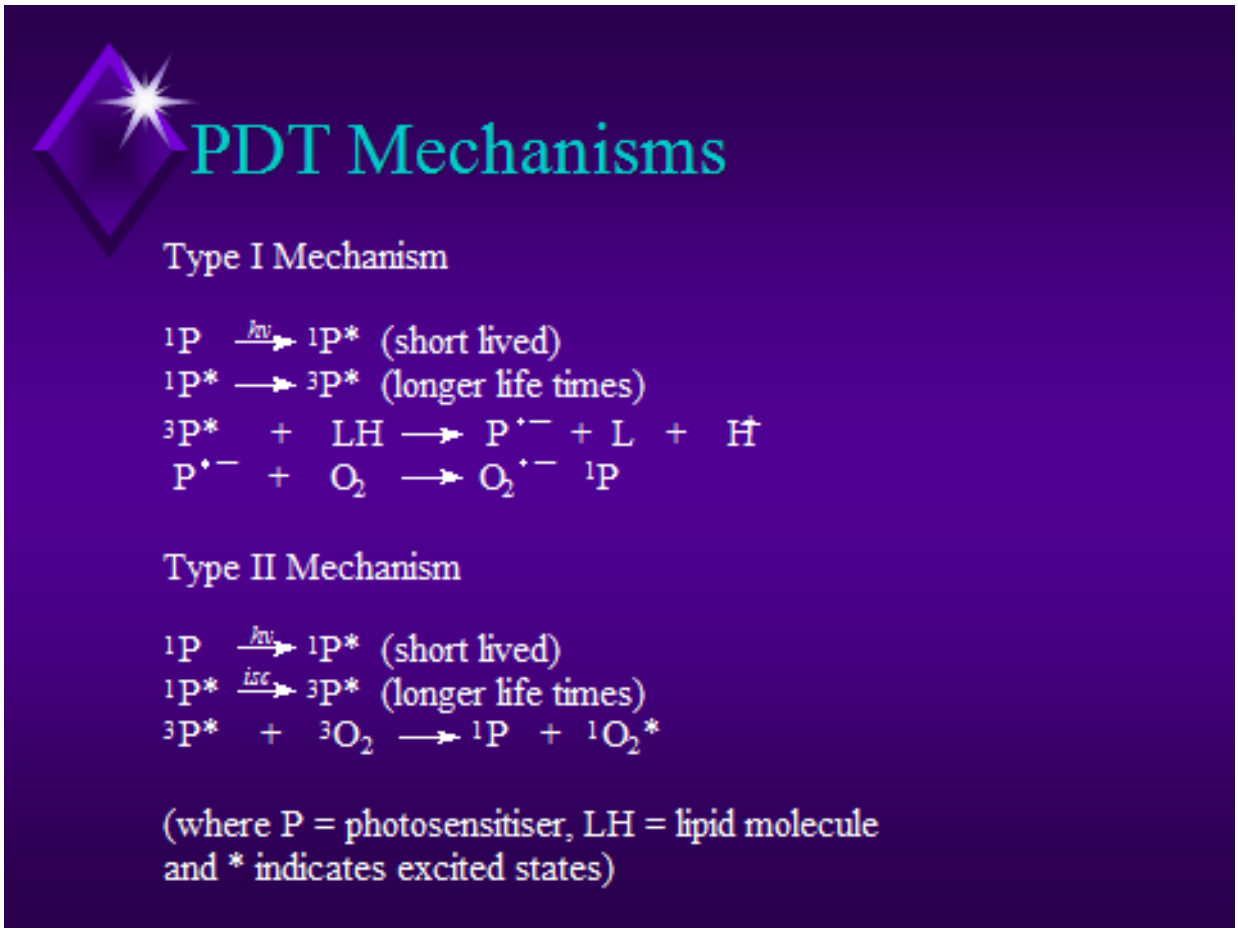
Some of the desirable features of second generation drugs, include lack of toxicity in the dark, selective uptake by cancer tissue, and short-term retention to avoid the persistence of photosensitivity. Other important features include a triplet energy greater than 94kJ/mol, intermediate lipid water partition coefficient, pure single chemical compounds, and light absorption in the red or far red part of the visible spectrum. The last feature derives from the high depth of penetration of tissue by radiation in the red region of the spectrum and beyond, and it is being used as a design feature for third generation drugs (28). There are a number of third generation photosensitisers in experimental stages. One group of these has two chromophores; one chromophore rapidly picks up two photons in the infrared region of the light spectrum and converts them into a single photon. This photon is then absorbed by the sensitiser's second porphyrinic chromophore. Such sensitisers are expected to be able to generate singlet oxygen from the triplet state of the porphyrinic chromophore of the photosensitiser, even though infrared excitation is being used. Experiments on this work are currently underway (29).

8 **The photophysical mechanism of** photodynamic therapy

Perhaps there is a need to go a little deeper into the photophysical mechanisms of PDT. If you find this boring just skip it, it won't mind. There are two mechanisms that have been described for PDT, namely PDT type I and PDT type II. PDT type I mechanism involves the photo-excitation of the photosensitiser from its singlet ground state to its first singlet excited state, followed by intersystem crossing to the triplet excited state. This is followed by direct interaction of the porphyrin with cell membrane components to generate porphyrin anionic radicals which rapidly react with oxygen to generate toxic superoxide radicals. Type II mechanism involves the photo-excitation of the photosensitiser from its singlet ground state to its first singlet excited state, followed by intersystem crossing to the triplet excited state. This is followed by photosensitisation of triplet ground state oxygen to give singlet excited state oxygen. Singlet excited state oxygen causes chemical degradation of a variety of biological systems (30, 31). Unsaturated lipids, cholesterol, and certain amino acid side chains in proteins, as potential targets of singlet oxygen, are important membrane components (32). Photochemical damage to these membrane components may lead to the inhibition of membrane bound enzymes, and to the interference with membrane transport and this could result in impairment of the vital membrane permeability barriers (31, 33) and to subsequent cell death by necrosis. It may also trigger the chain of events that lead to apoptosis. These are illustrated in figure 6.

Figure 6: Photodynamic therapy type I and type II mechanisms.





9 Drug development.

Foscan was a marvel to me and has since inspired my research to design photodynamic drug molecular systems that are based on the Foscan type template. What were the challenges with Foscan? Bonnett et al (34) and Berenbaum et al (35) had described a series of Foscan type molecules and studied their biological and photophysical features. These were hydrophobic molecules that were found to be hard to dissolve in water and therefore difficult to administer intravenously – although with the advent of liposomal encapsulation technology the problem of intravenous administration of hydrophobic drugs has largely been solved, leaving the problem of clearance from the body after PDT as a main challenge. Our initial attempt at solubilizing these compounds in hydroxylic media was rewarded with a reduction of the partition coefficients from 6.0×10^4 to 3.0×10^4 (36). How was this accomplished? Derivatives of the series of the porphyrins reported by Berenbaum et al and Bonnet et al with fluorine atoms adjacent to the hydroxyl groups were prepared. This was done in order to solubilize the hydroxyl groups using the electron withdrawing effects of the fluorine atoms. The effect was minimal as measured using the partition coefficients which decreased by roughly 50% (see figure 7).

Figure 7: Solubilization of tetrahydroxyphenylporphyrins with fluorine.

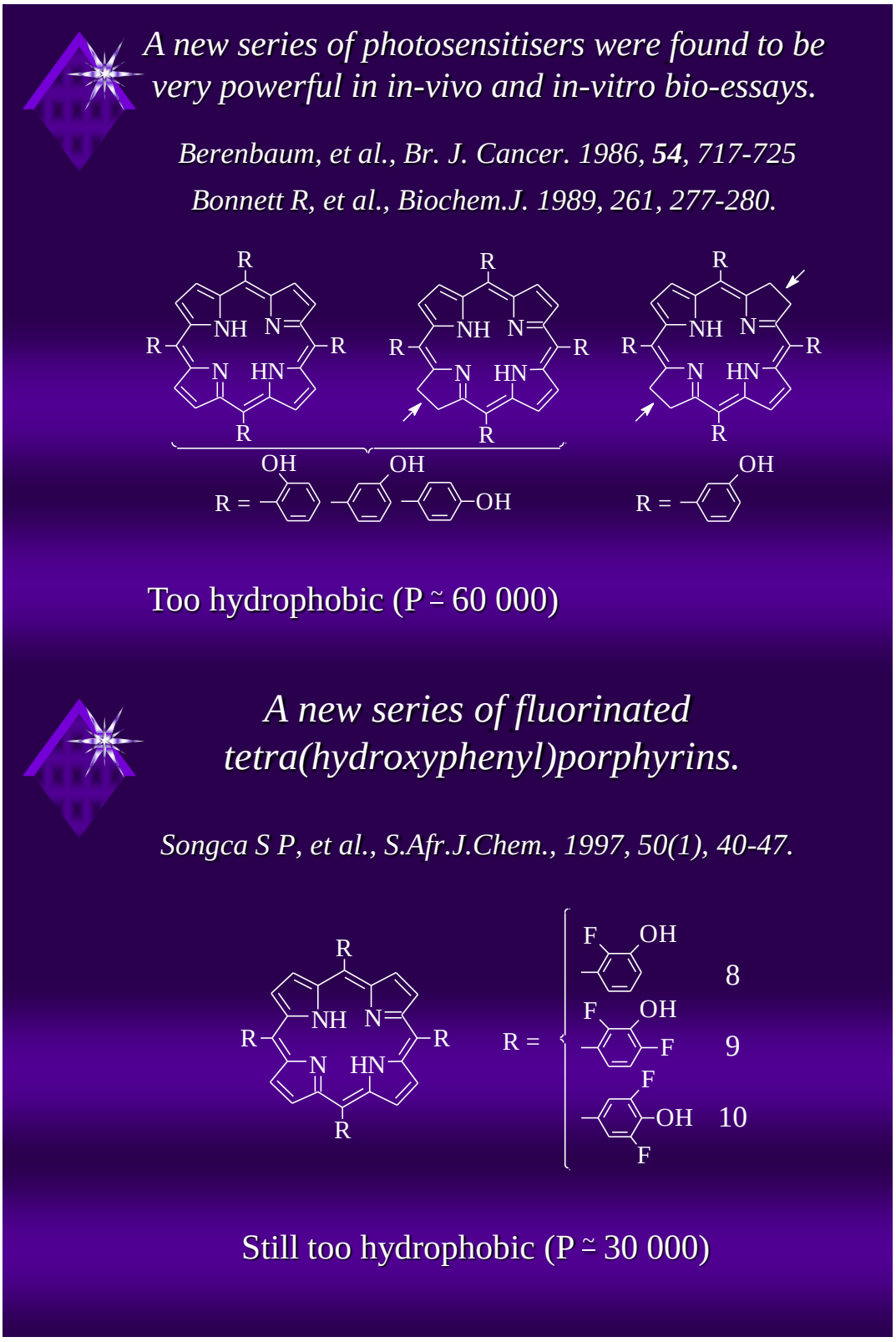
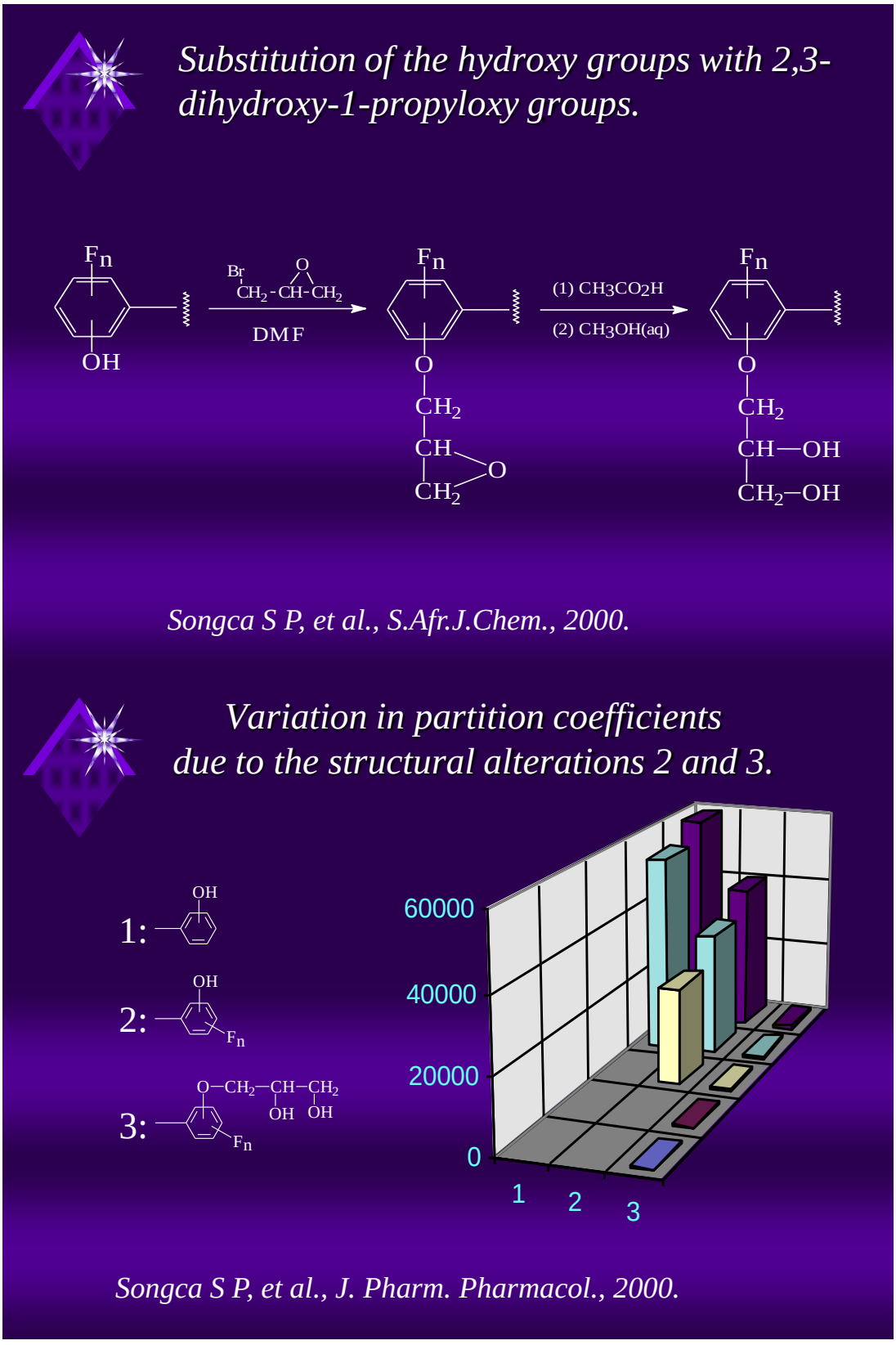


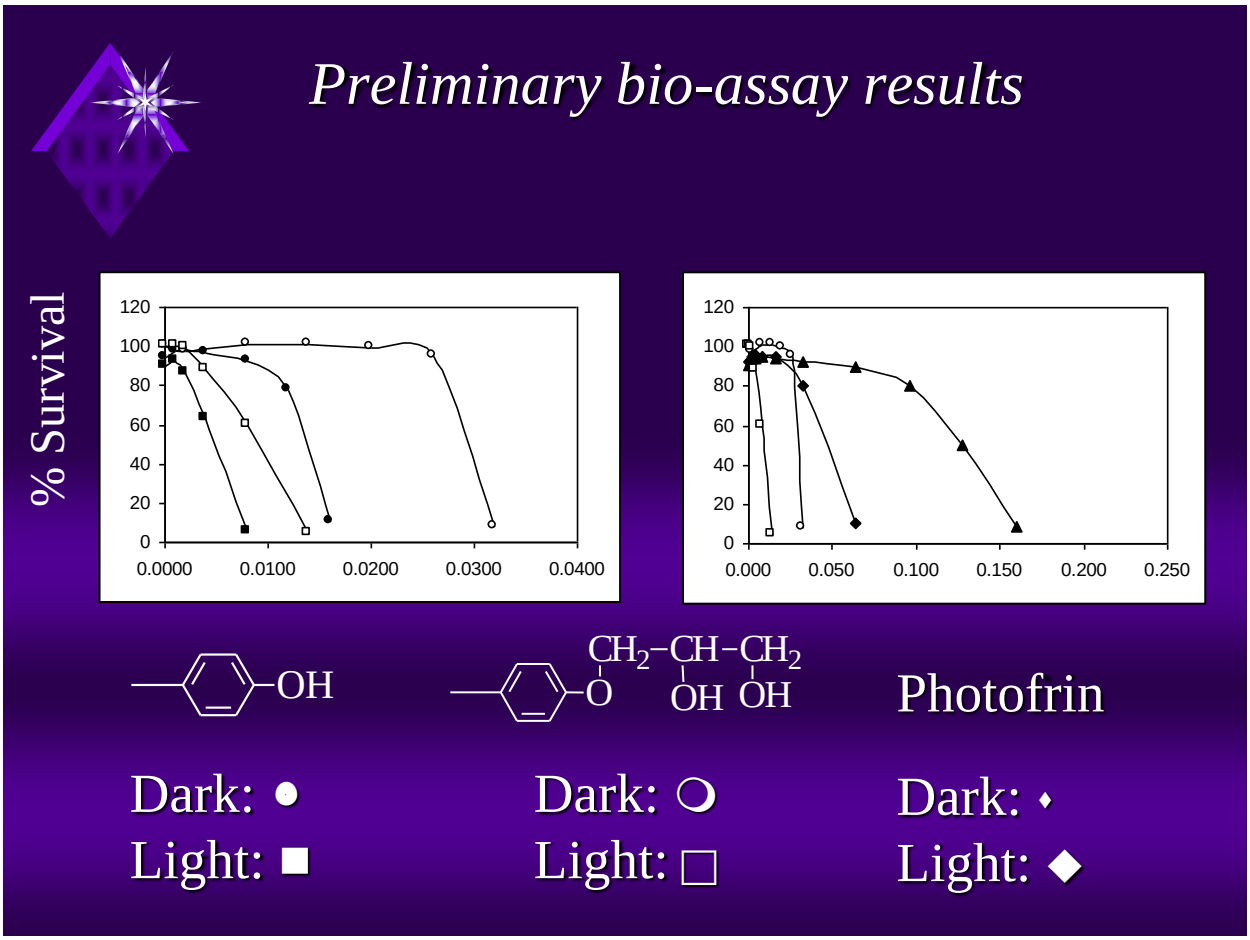
Figure 8: Solubilization of tetrahydroxyphenylporphyrins with 2,3-dihydroxy-1-propyloxy groups.



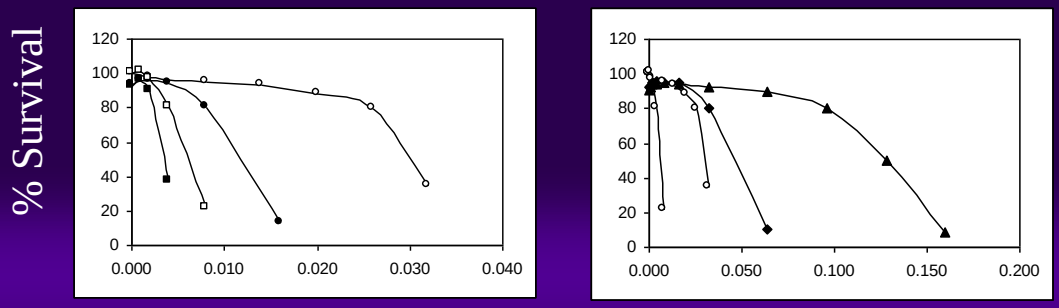
Subsequent to this the hydroxyl groups were converted to 2,3-dihydroxy-1-propyloxy groups using nucleophilic substitution with epibromohydrin followed by base catalysed hydrolytic epoxy ring opening to give tetrakis(2,3-dihydroxy-1-propyloxyphenyl)porphyrins, compounds with eight rather than four hydroxyl groups. The partition coefficients decreased by nearly two orders of magnitude!

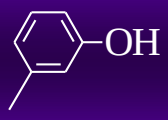
This method of solubilization appeared to have worked much better than that of the solubilization using adjacent fluorination. What was not clear was how good the porphyrins solubilized in this way were, in destroying cancer cells *in vivo* and how well they would work in destroying cancer cells *in vitro*. The biological activities of the series of compounds reported by Berenbaum *et al* and Bonnett *et al* were compared to that of Photofrin, to those of the fluorinated compounds as well as to those of the 2,3-dihydroxy-1-propyloxy substituted compounds testing their cell destruction using the cell colony survival method. The 2,3-dihydroxy-1-propyloxy substituted compounds showed the highest biological activity. ^{19}FNMR was used to measure tissue distribution of the fluorinated porphyrins *in vitro* using tumor implanted rats. When compared to the brain, abdomen, thoracic cavity, the highest concentration of porphyrins was found in the implanted tumor (see figure 9). This result was consistant with the preferential tumor localization of this type of tetra(hydroxyphenyl)porphyrin.

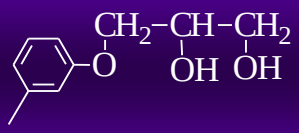
Figure 9: Biological activities and tissue distribution studies



Preliminary bio-assay results





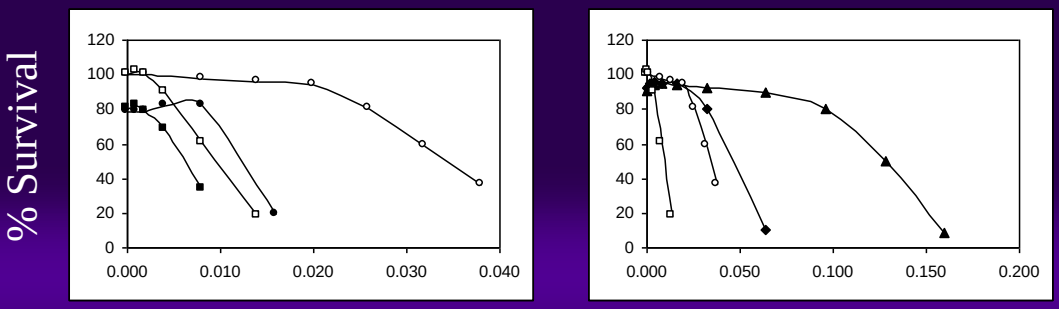


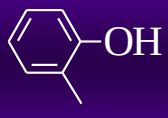
Photofrin

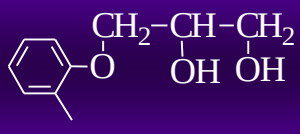
Dark: ● Dark: ❍ Dark: ♦

Light: ■ Light: □ Light: ◆

Preliminary bio-assay results







Photofrin

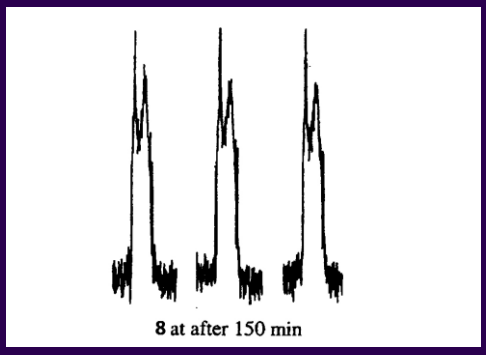
Dark: ● Dark: ❍ Dark: ♦

Light: ■ Light: □ Light: ◆

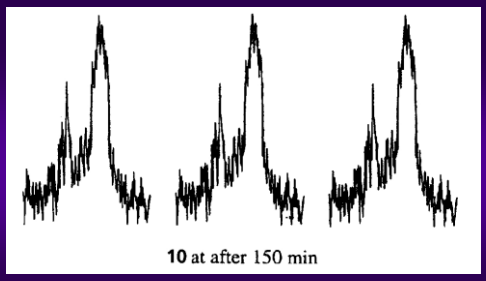
19F-NMR tumour detection using the fluorinated tetra(hydroxyphenyl)porphyrins.

Songca S P, J.Pharm. Pharmacol., 2001, 53, 1469-1476.

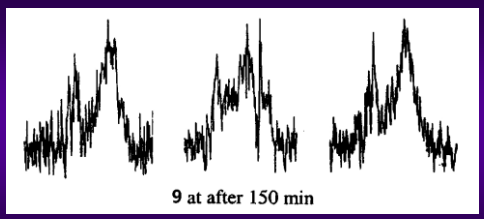
Porphyrin	8	9	10
Implanted tumour	19	5	10
Abdomen	0.5	0.6	1.5
Thoracic cavity	0.5	0.9	1.3
Brain	2.0	1.6	1.8



8 at after 150 min



10 at after 150 min



9 at after 150 min

10 Photodynamic therapy is ideal for the developing world

By now I was hooked. I had tasted porphyrin chemistry and applications in photodynamic therapy and I had become a photodynamic therapy scientist. Something still bothered me though. The uptake of the technology at the clinic was very slow. What was the problem? Was it the technology transfer tactics used or the lack thereof? Clinicians were very skeptical, particularly those in the developing world where the technology was needed the most. In an article that appeared in Photodynamics International, photodynamic therapy was commended as the most suitable method for cancer therapy in the developing world (36). It is cost effective and simple to use. Unlike chemotherapy, no special training is required for nurses, no post treatment course in intensive care. No engineer, computerised dosimetry computations, or additional costs for isotope re-treatment are required, as in radiotherapy. There are no blood transfusions, or sophisticated operating theatres, as in surgery. Ironically it is in the developing world that there appears to be very little awareness of and access to PDT. Cancer sufferers are thus limited to chemotherapy, radiotherapy, and surgery, procedures that are relatively complex and costly, without distinctive advantage in cure or palliation. It is possible that the low level of clinical practice in PDT in the developing world is related to the low level of articulation of what is admittedly a relatively new modality. However, this slow emergence of clinical practice in PDT when compared to advances in its developmental research was also observed in the developed world in the last century.

I had another challenge now. I wanted to popularize photodynamic therapy in the clinic particularly in the developing world. I bought subscription to Photodynamics International and I read it. By now I had completed my PhD and had returned to South Africa where I resumed my duties as a junior lecturer at the University of Transkei. I was later promoted to the position of associate Professor in organic chemistry. After five years, I took a sabbatical at the University of Cape Town, where I was hosted by the Liver Research Unit located at Groote Schuur Hospital as a visiting Professor and by the department of Chemistry where my research laboratory was located. The clinicians that I worked with at Groote Schuur Hospital were very sympathetic, even more skeptical. I wrote an article to promote and popularize PDT and submitted it to the South African Medical Journal for publication. The article remained under review for more than eighteen months before it was finally rejected. The local clinicians had spoken. I was sad but I decided to continue the fight. I needed to collaborate with bold boundary smashing clinicians.

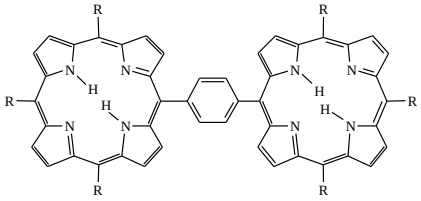
11 What is the appropriate technology transfer approach?

In the mean time, photodynamic therapy was advancing. The journal of porphyrins and phthalocyanines and the associated international conference on porphyrins and phthalocyanines had been established and had both become an overnight success. More than 30% of these two media were preoccupied with photodynamic therapy and its new and emerging modalities. Photodynamic therapy was emerging as a treatment of new diseases other than cancer for which it was originally developed and had become known. Management of age related macular degeneration with Visudyne is a case in point. Now here was an example of the kind of technology transfer tactics that may be required to break the stalemate between clinicians and photodynamic therapy drug development scientists in the developing world. Visudyne was developed under a collaboration between Prof. Dolphin and two very bold lady clinicians who saw an opportunity and took it. Until then there was no established treatment of AMD. However when the patient is intravenously injected with Visudyne, there is significant occlusion of the choroidal neovascularization and this has been confirmed by fluorescein angiography. The treatment has now been refined and accepted by most clinics in the developed world. Needless to say Prof. Dolphin and the two very bold ladies have become overnight celebrities for the discovery.

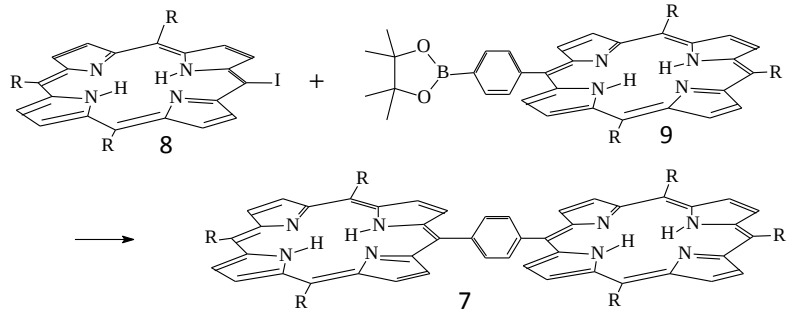
12 My students are enjoying photodynamic therapy research

Research in photodynamic therapy has attracted a wide range of studentships in my group. One student has chosen to explore the oligomerization of tetra(hydroxyphenyl)porphyrins. The impetus for this derives from the documented enhancement of photodynamic activity associated with oligomerization. It was first recognized with the constituents of Photofrin, a multi component mixture consisting of a variety of monomers dimmers and other oligomers linked by carbon to carbon and carbon to oxygen ether and ester linkages. Upon chemical separation of the monomeric fraction of Photofrin from its oligomeric fraction, it was found that the monomeric fraction had no photodynamic activity but the oligomeric fraction retained photodynamic activity. Upon further testing it was found that all types of oligomers, whether linked by carbon to carbon, carbon to oxygen ether or ester linkages retained photodynamic activity. Mr. Isaac Masilela, one of the MSc students at the University of Limpopo, Medunsa Campus, has made significant strides in preparing dimmers of tetra(hydroxyphenyl)porphyrins.

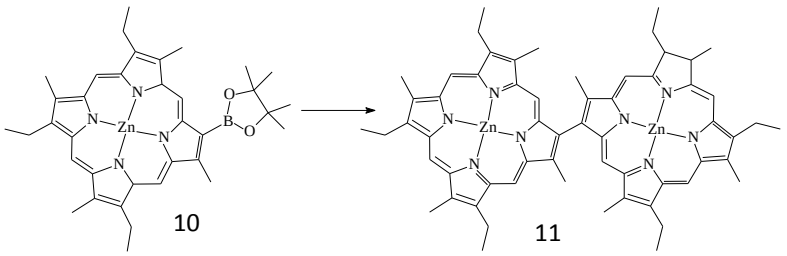
Table 3: Tetra(hydroxyphenyl)porphyrinic dimers.

#	Structure	Name	Reference
7		Phenylene linked dimer of tetra(phenyl)porphyrin R = Phen	Songca and Masilela (2006)

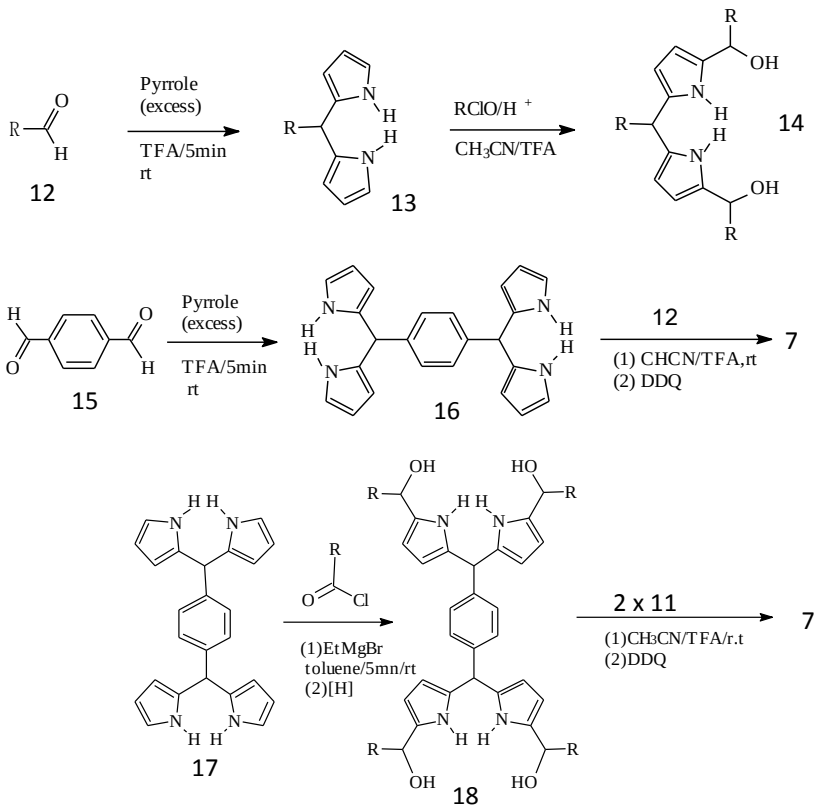
His approach was derived from the methodology of Yu and Lindsey (37). He demonstrated application of an approach for the preparation of phenylene linked porphyrin dimers 7 from terephthaldehyde 13. Two porphyrin units are constructed on each side of the molecule, from the reaction of each carboxaldehyde group. The reaction sequence starts with condensation of terephthaldehyde with excess pyrrole to give 1,4-bisdipyrrylmethylbenzene 16. A similar reaction of excess pyrrole with benzaldehyde gives dipyrrylmethylbenzene 13. This is followed by Friedel-Crafts reaction with benzoyl chloride at position 1 and 9 of the dipyrrylmethylbenzene 13 to give a dicarbonyl product, which is reduced to give the corresponding dicarbinol 18. Condensation of 18 with 13 gives the dimmer 7. These reactions were demonstrated with the synthesis of three phenylene linked dimers, two of which have not been reported previously. Yu and Lindsey performed these reactions and compared them to the corresponding Suzuki coupling (38) of the as prepared porphyrinic monomers and found them to be far superior in terms of cost and yield.



Equation 2



Equation 3



Equation 4

Equation 5

Equation 6

Figure 10 (a): NMR spectroscopic evidence of the intermediates in equation 6

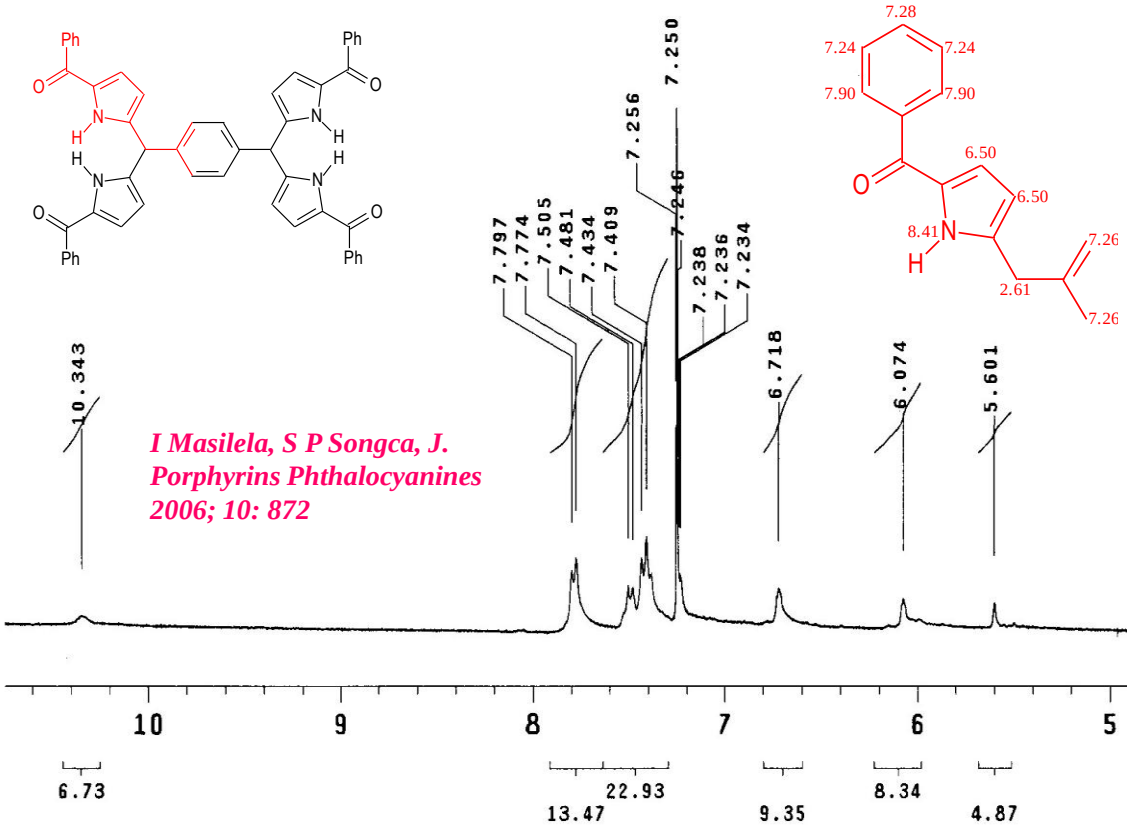
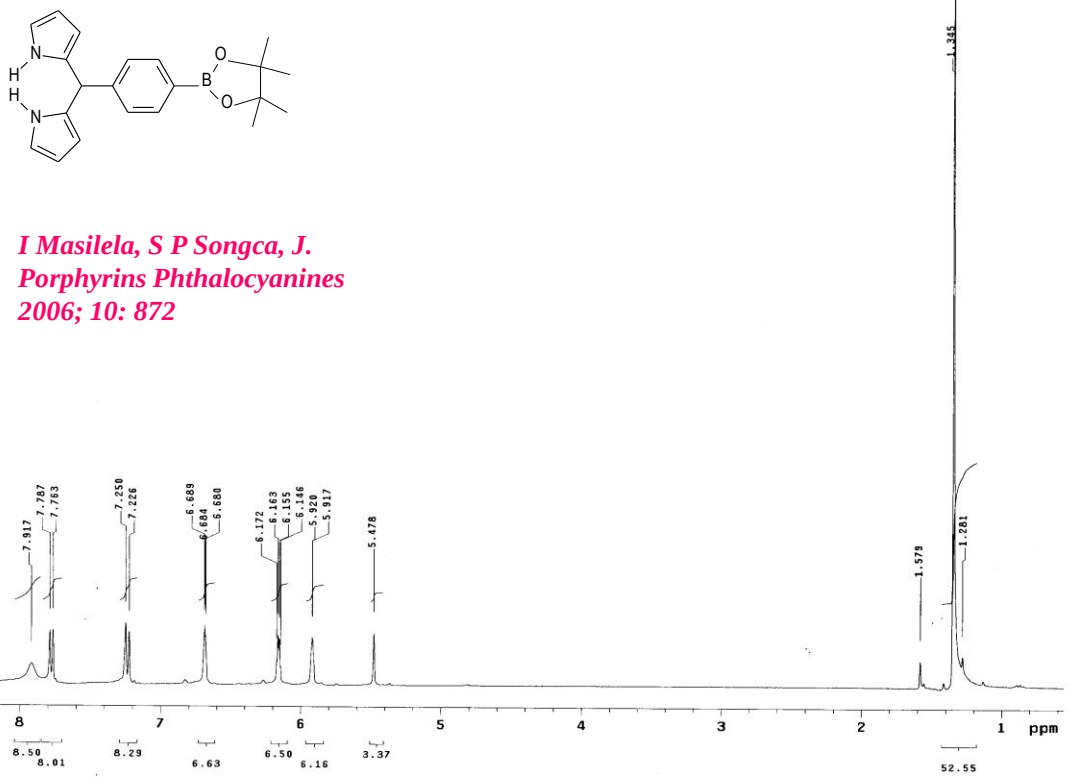
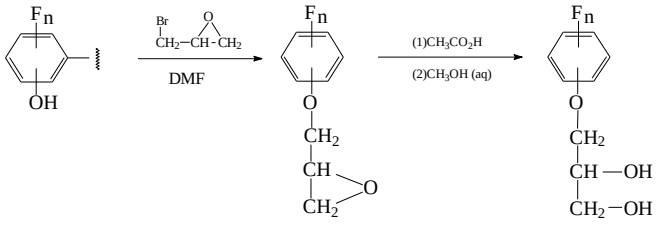


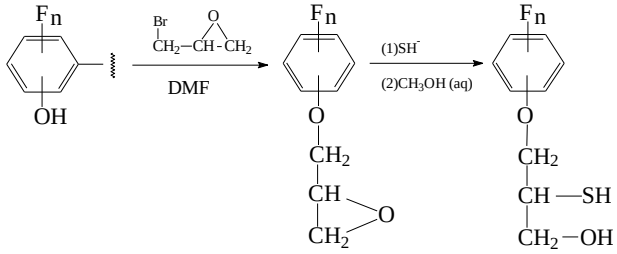
Figure 10 (b): NMR spectroscopic evidence of the intermediates in equation 2



The work of Dr. Mbatha who prepared a series of 5,10,15,20-tetra(hydroxyphenyl)porphyrins and 5,10,15,20-tetrakis(2,3-dihydroxy-1-propyloxyphenyl)porphyrin and tested them as part of his studies towards MSc was described in section 9. This work was continued by Mr. Makhubela, a PhD student registered at the University of Limpopo, Medunsa campus. In his enthusiasm he branched out to prepare derivatives 5,10,15,20-tetrakis(2,3-dihydroxy-1-propyloxyphenyl)porphyrin compounds in which some of the hydroxyl groups are replaced with thiol groups.



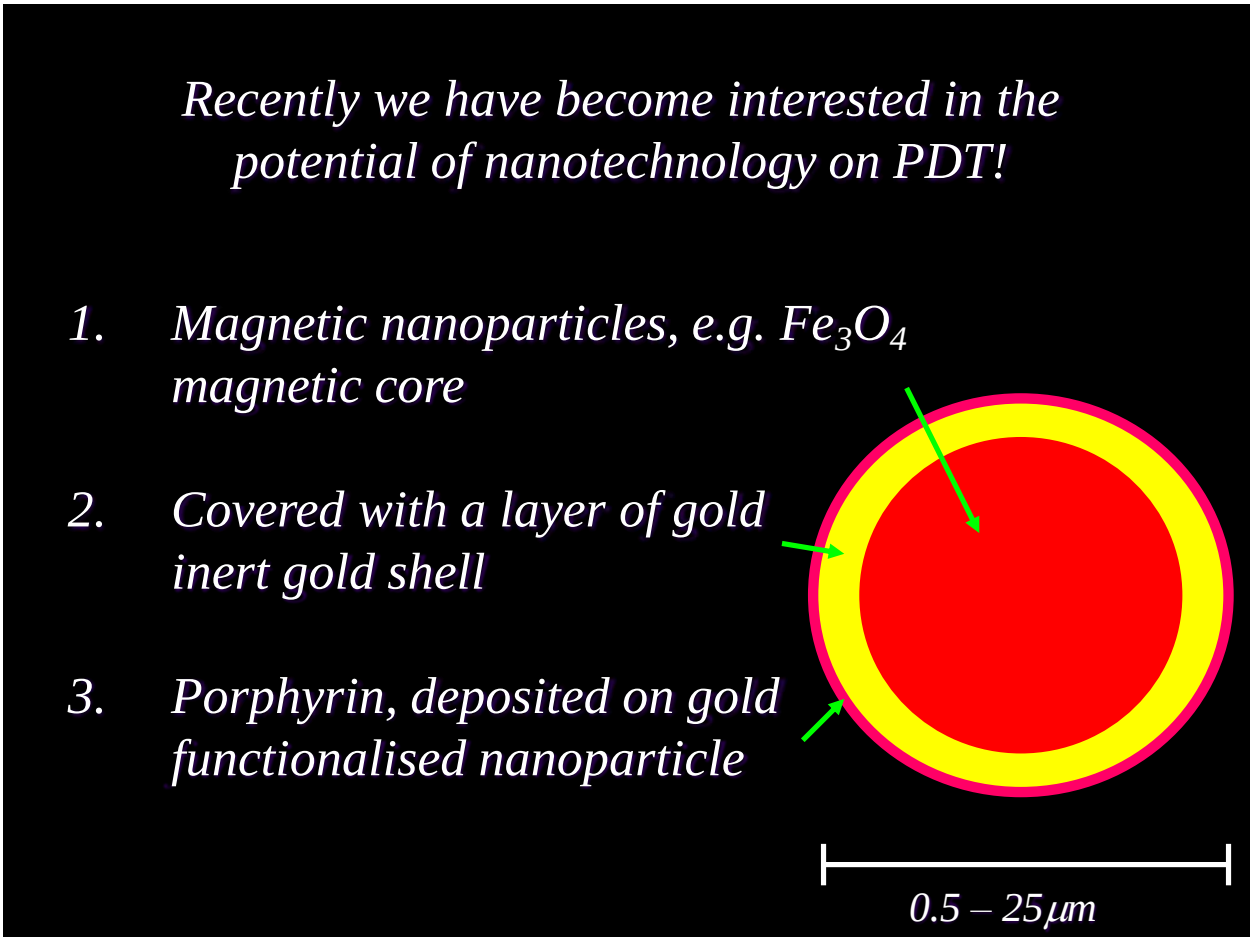
Equation 7



Equation 8

13 Can the delivery of porphyrins to cancerous tissue be improved?

Recently we have started to explore the possibility of improving photodynamic therapy by using better delivery systems and applying it in conjunction with magnetic hyperthermia. We have postulated that by depositing porphyrin compounds on gold coated superparamagnetic iron oxide nanoparticles, it is possible to magnetically enhance their delivery to tumour tissue by magnetic control. This postulate has two assumptions. Firstly it is assumed that the porphyrin compounds deposited on gold coated superparamagnetic iron oxide nanoparticles will retain the inherent tumor localization thus drag the nanoparticles to the tumor tissue. Secondly it is assumed that the gold coated superparamagnetic iron oxide nanoparticles with deposited porphyrin compounds will retain their magnetic susceptibility. When a magnet is place on or near the tumor tissue, the nanoparticles will drag the deposited porphyrin compounds tumor tissue. We further postulate that the porphyrin compounds deposited on gold coated superparamagnetic iron oxide nanoparticles will retain their photodynamic activity so that once tumor localization is achieved and light of the correct wavelength is delivered, the tumor will be destroyed.



Hypothesis 1

Iron oxide – gold, core – shell nanoparticles can be prepared and characterized.

Oligomeric porphyrins can be deposited on the gold surface of iron oxide-gold magnetic nanoparticles using the Au-S covalent bonding.

The deposition of oligomeric porphyrins on the surface of iron oxide-gold magnetic nanoparticles can be characterized with FTIR and other spectroscopic techniques.

Hypothesis 2

"Porphyrin dragging nanoparticle"

Because the porphyrins deposited in this way are expected to preferentially localise in tumour tissue this should lead to preferential tumour localisation of the iron oxide-gold magnetic nanoparticles on which they are deposited.

*"**Nanoparticle dragging Porphyrin"***

In addition because the nanoparticles are magnetic, they can be localised magnetically in any part of the body.

Hypothesis 3

Photodynamic therapy can be used to preferentially destroy the tumour tissue.

A combination of magnetic hyperthermia and photodynamic therapy can be used to preferentially destroy the tumour tissue.

The last hypothesis is that upon application of an oscillating magnetic field with the correct frequency of oscillation, the gold coated superparamagnetic iron oxide nanoparticles with deposited porphyrin compounds will be agitated and thus increase the temperature of the tumour relative to non-agitated tissue, thus destroying the tumor tissue. This is the essence of magnetic hyperthermia.

Adeolu Eshilokun has devoted his work to this research. The aim of this study is to prepare novel porphyrin compounds with thiolated side chains. The thiolated side chains are then used to anchor the porphyrins on the gold surface of the gold coated superparamagnetic iron oxide nanoparticles. The aim is also to evaluate the efficacy and potency of these compounds in cancerous tumor imaging, photodynamic therapy and a combination of photodynamic therapy and magnetic hyperthermia. In this regard novel thiolated porphyrinic compounds have been prepared and characterized. The gold coated superparamagnetic iron oxide nanoparticles have also been prepared and characterized.

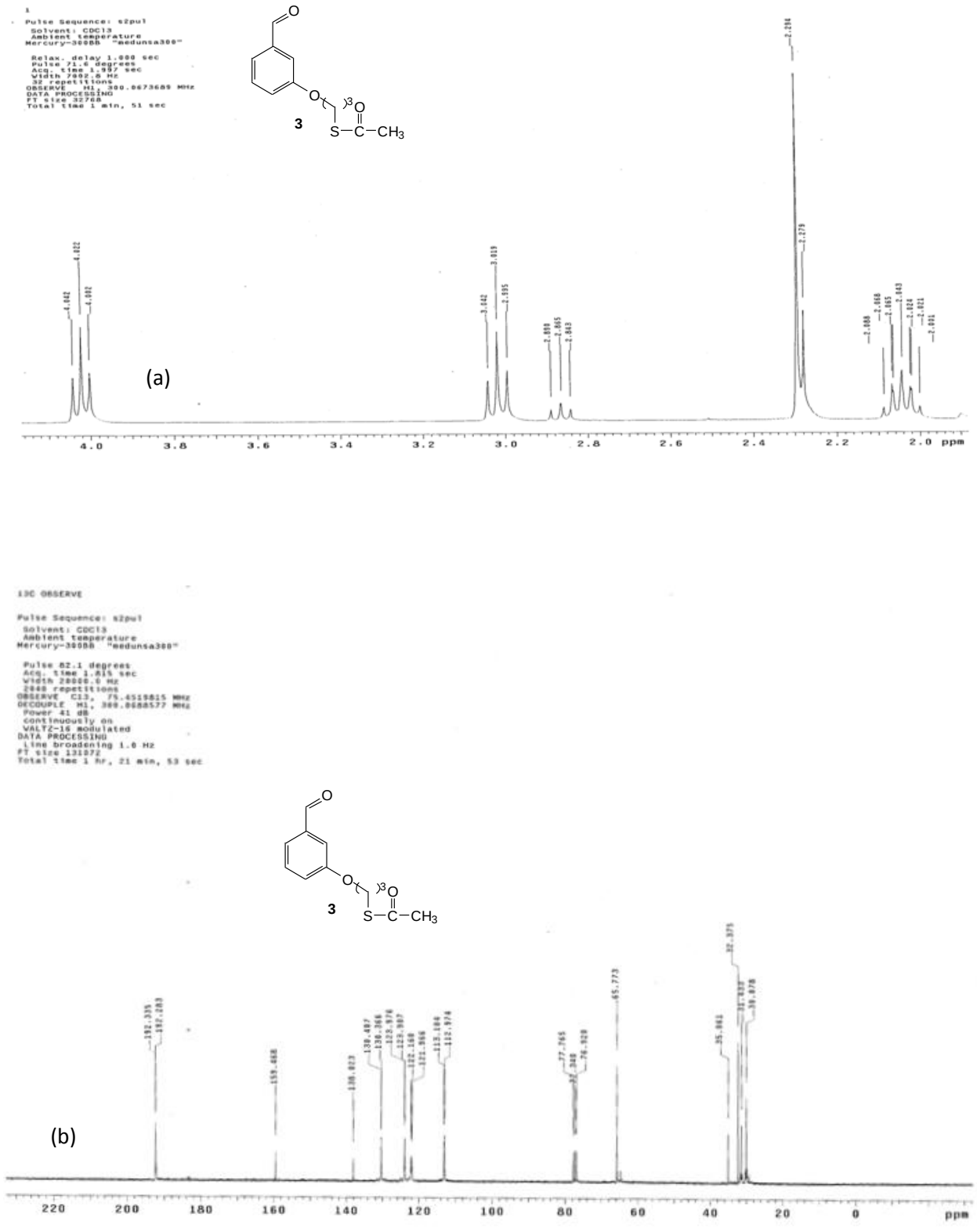


Figure 11: ^{1}HNMR (a) and ^{13}CNMR (b) spectra of the benzaldehyde precusor with thiolated side chains

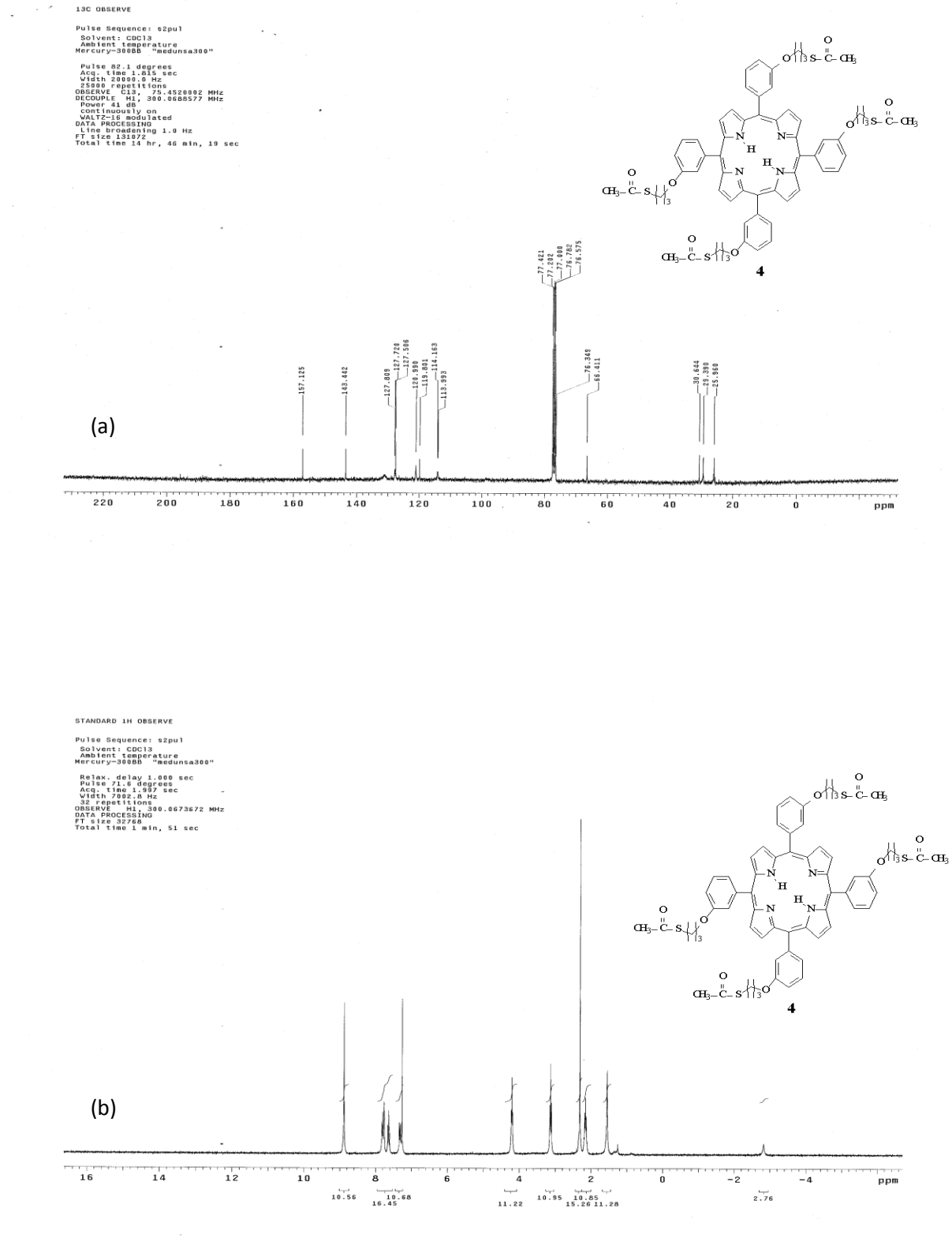


Figure 12: ^{1}HNMR (a) and ^{13}CNMR (b) spectra of the porphyrin compound with thiolated side chains

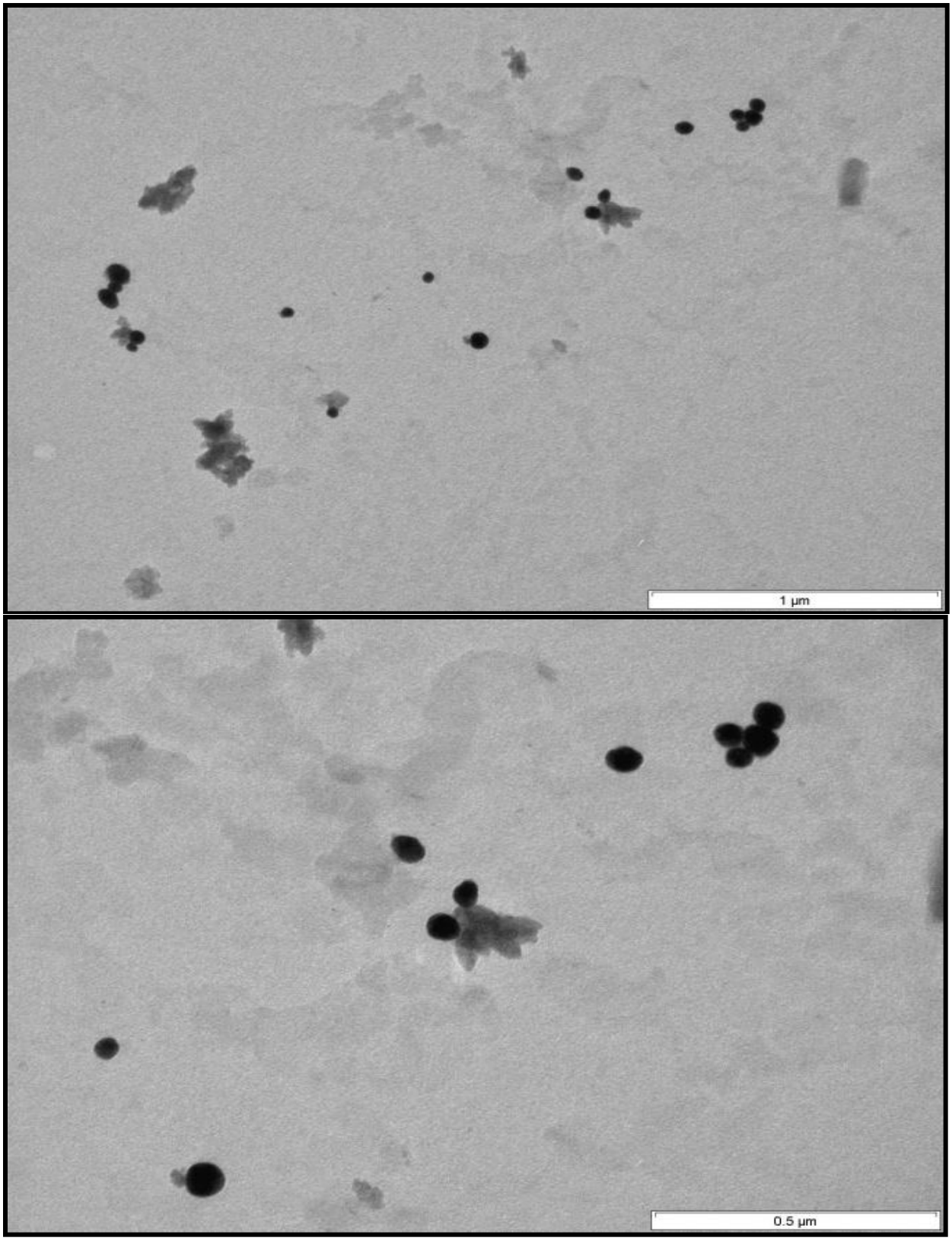


Figure 13: Electron microscopy of the gold coated superparamagnetic iron oxide nanoparticles.

14 Epilogue

It has been a long journey fraught with challenges but decorated with many rewards. I have stopped to smell the roses. Photodynamic therapy has made many gains but suffered many retreats. The porphyrin chemist and photodynamic therapy scientist has aged with some grace but survives. The future of porphyrins, phthalocyanines and photodynamic therapy looks very good. The developed world has embraced the technology in the clinic and is reaping the rewards. The developing world has remained stubbornly skeptical and cancer sufferers can only rely on traditional approaches for palliative care. Special collaborations with clinicians may the hope for photodynamic therapy and cancer sufferers. Interestingly most of the clinical trials for new photodynamic therapy modalities take place in Africa. One of the main sites the clinical trials for Foscan was Groote Schoor Hospital in Cape Town and this research showed that Foscan was a particularly good photosensitiser for head and neck cancer.

I could not have made it without my partner, friend, wife and personal chaplain, Reverend Nokulunga Songca. Her commitment to things that count as opposed to those that can be counted has become my motto in life. I journeyed with her through many tough times. When I was doing my MSc degree at the University of Transkei she was always on her knees praying for me. She has continued this tradition till this day. This is something I do not take for granted. This is something I immensely value in my life. It is no wonder to me that the revelation that I would complete the rest of my higher training abroad was given to her long before the award of the British Council and Luthuli Memorial Trust scholarships.

To God be the glory

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