

FROM SYNTHETIC METHODOLOGY  
TO MAKING MOLECULES WITH A MISSION –  
A RESEARCH SUMMARY OF THE FIRST 10 YEARS

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*From synthetic methodology to making molecules with a mission –  
a research summary of the first 10 years*

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## ABOUT THE AUTHOR

Willem van Otterlo was born in Amsterdam, The Netherlands. As a child he moved to Southern Africa and received his primary and secondary schooling in Windhoek, Namibia, and Johannesburg, South Africa. In 1989 he started his BSc and in 1999 he graduated with a PhD that involved the synthesis of analogues of the michellamines. The PhD was performed under the mentorship of Profs CB de Koning and JP Michael at the School of Chemistry, University of the Witwatersrand (WITS), Johannesburg. He then spent two years in the research group of Prof. Stephen Hanessian (University of Montreal, Quebec, Canada) as a postdoctoral fellow, involved in projects focused on medicinal chemistry and synthesis utilising peptide-based building blocks. In 2001 he returned to his *alma mater* to take up a lecturing position and initiated a research programme involving the application of organometallic reagents to the synthesis of small benzo-fused molecules, eventually attaining the rank of Associate Professor. In July 2008 he joined Prof. Dr Herbert Waldmann's Chemical Biology group at the Max Planck Institute, Dortmund, as a von Humboldt (Georg-Forster) Research Fellow for a sabbatical year to learn more about the interaction between chemistry and biology. He then took up the Chair of Organic Chemistry at Stellenbosch University, Western Cape. Since June 2010 he has been striving to nurture a team environment at the Department of Chemistry and Polymer Sciences so that organic and medicinal chemistry research can be performed in collaboration with talented colleagues. His current research interests are focused on the synthesis of small molecules with potential bioactivity, particularly molecules based on natural templates such as pancratistatin, podophyllotoxin, colchicine and purpurogallin, as well as research focused on the design of better ligands for enzymes (kinases and phosphatases) and nuclear receptors (estrogen receptor).

## ACKNOWLEDGEMENTS

I would like to make it clear from the onset that the progress in my research career has been entirely dependent on numerous mentors, colleagues, friends and family members – without their input and support it simply would not have been possible to be successful as an academic! I would like to firstly thank the academic ‘giants’ on whose shoulders I now stand and with many of whom I am still looking forward to fruitful collaborations and social interactions. They include Prof. Charles de Koning (mentor and friend), Prof. Jo Michael, Prof. Neil Coville, Prof. Dr Hans-Gunter Schmalz and Prof. Dr Herbert Waldmann. Other role models in the South African community that I would like to acknowledge are Prof. Ivan Green and Prof. Mike Davies-Coleman. I also gratefully acknowledge a number of academics from the ‘next generation’ who have been wonderful to work with, to learn from and to plunge forward into new research adventures with; they include Prof. Alexander Kornienko, Prof. Dr Daniel Rauh, Prof. Ivo Hümmelgen and Prof. Patrick Arbuthnot. I would like to thank my new colleagues at the Department of Chemistry and Polymer Sciences at Stellenbosch University for their welcome – in particular my new organic and medicinal chemistry sojourners Dr Stephen Pelly, Dr Gareth Arnott, Dr Margaret Blackie and Dr Maritha le Roux. Dr Pelly is also gratefully acknowledged for help with preparing the protein structures in this summary. Finally, in terms of research, it would be seriously amiss not to acknowledge the postdoctoral fellows and the undergraduate and postgraduate students with whom I have had many enjoyable research interactions; again, without their hard work very little would have been achieved. Lastly, I would like to thank my immediate family and friends – particularly Lara, Mikaela and Saskia van Otterlo – for their love, understanding and support; it is not always plain sailing being married to, or being the daughters of, a ‘nutty professor’....

## DEDICATION

*To my mother, Alida van Otterlo-Bekker (1940–2007) – my  
quiet, and yet most fervent, supporter*

## IMPORTANT NOTE REGARDING RESEARCH SUMMARY AND REFERENCES

It is imperative to note that the essence of modern research is summarised in the word 'collaboration'. It should thus be taken to heart that the work described here, while described as being 'my' research achievement, has been performed in collaboration with numerous other worthy contributors, be they academics or students. In particular, my former colleagues at WITS, particularly Profs de Koning, Coville and Michael, deserve much of the acclaim; it is due to their support during my time at WITS that I was able to oversee any research at all, and they have my deepest thanks for their team spirit. Furthermore, while compiling this summary it quickly became obvious that I would not be able to do justice to the other phenomenal researchers active in the scientific areas that we have been involved in. Due to space limitations I have therefore only listed publications to which we have contributed, and I humbly apologise for not being able to cite all the seminal work in the literature. The reader should thus be aware that our work forms a 'brick in the wall of science' and that the references in our actual papers give due credit to the other researchers involved.

# FROM SYNTHETIC METHODOLOGY TO MAKING MOLECULES WITH A MISSION – A RESEARCH SUMMARY OF THE FIRST 10 YEARS

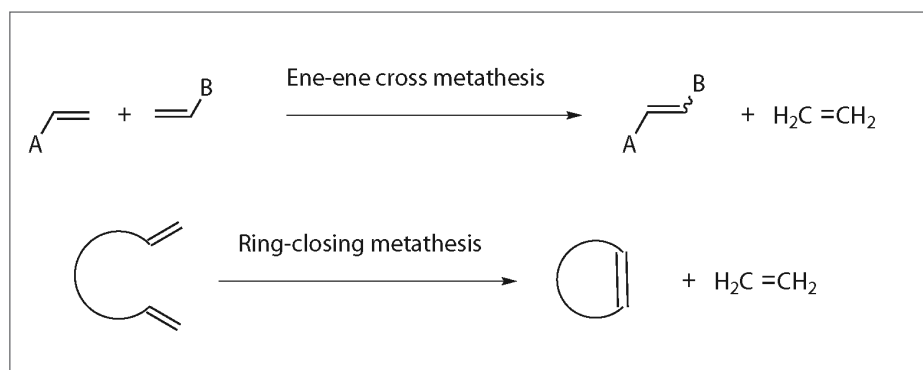
## INTRODUCTION

On joining WITS as a lecturer in June 2001, my fascination with a new synthetic ‘methodology-on-the-block’, namely metal-catalysed metathesis, was already in place. The synthetic methodology research work from our group based on this theme and performed in the formative years of my research career will be described in the first part of this summary. This will be followed by our adventures into the synthesis of functional molecules, in other words molecules created for a particular objective, be it application in nanomaterials, medicinal chemistry or biological systems.

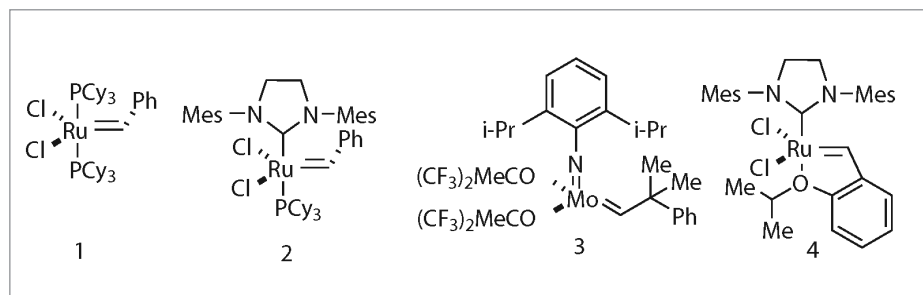
## APPLICATIONS OF METATHESIS, ISOMERISATIONS AND OTHER REACTIONS TO THE SYNTHESIS OF BENZO-FUSED COMPOUNDS

To an organic chemist the term ‘metathesis’ brings to mind the interaction of two alkenes, two alkynes or an alkene with an alkyne to generate new unsaturated

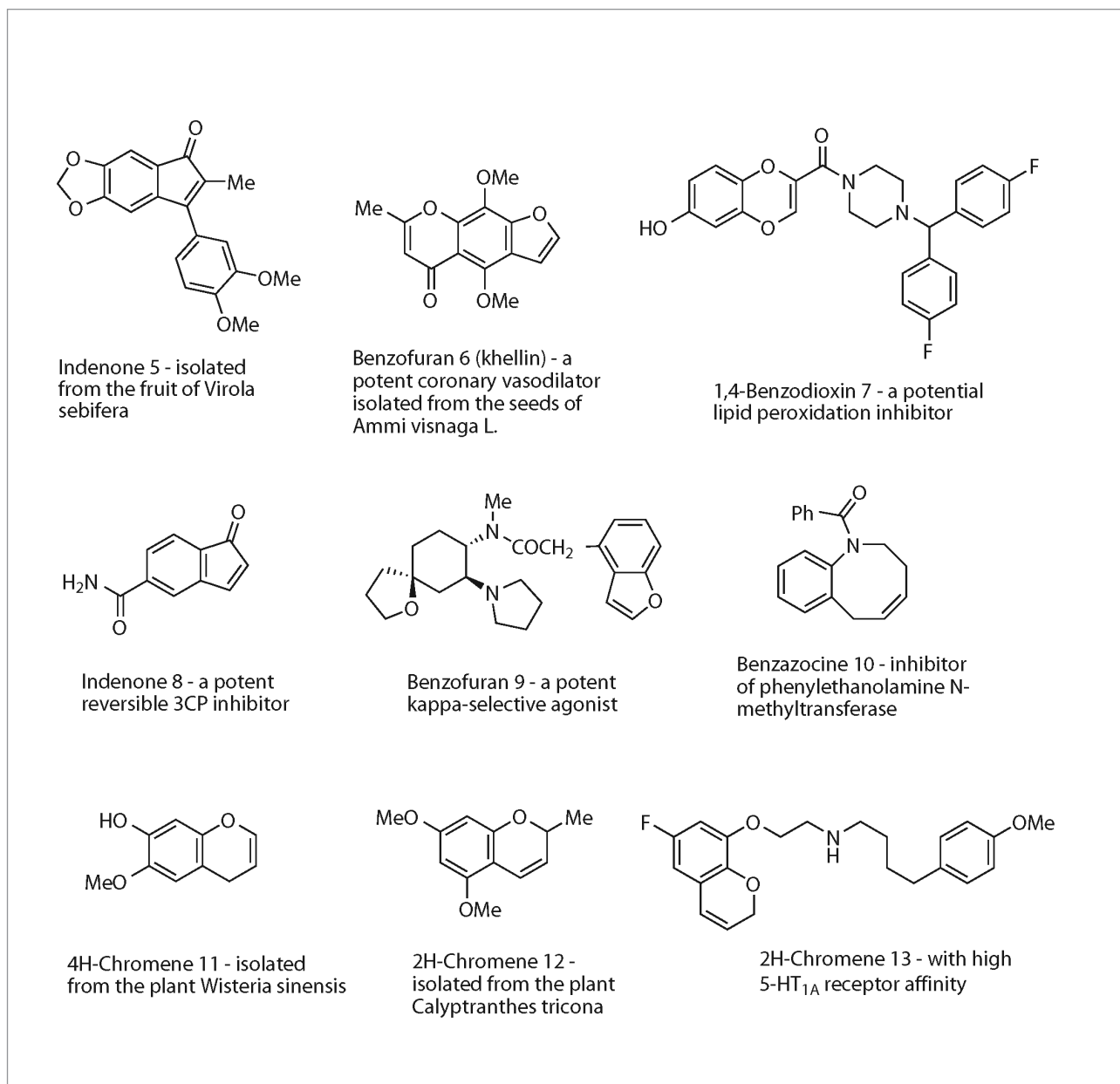
substrates, as demonstrated by the two examples of ene-ene-cross metathesis (CM) and ring-closing metathesis (RCM) shown in **Scheme 1**. Of particular interest has been RCM, which results in carbo- or heterocycles with an internal unsaturated bond (see **Scheme 1**). Over the past two decades the advances in the field of metathesis have been facilitated by the development of modern metal-carbene catalysts, exemplified by the Grubbs first and second generation ruthenium catalysts (**1** and **2**, respectively), the Schrock molybdenum catalyst **3** and the ruthenium Hoveyda-Grubbs catalyst **4**, as depicted in **Figure 1** (for an exhaustive list of reviews on the topic of metathesis see reference<sup>1</sup>). As an aside, the metathesis pioneers Grubbs, Schrock and Chauvin received the Nobel Prize for chemistry (2005) due to their fundamental contributions to metathesis chemistry. I distinctly remember my initial interest of applying this methodology to a target group of so-called benzo-fused heterocycles, molecules in which an interest had been born during my PhD days.



**Scheme 1**



**Figure 1:** Examples of modern catalysts used in metathesis



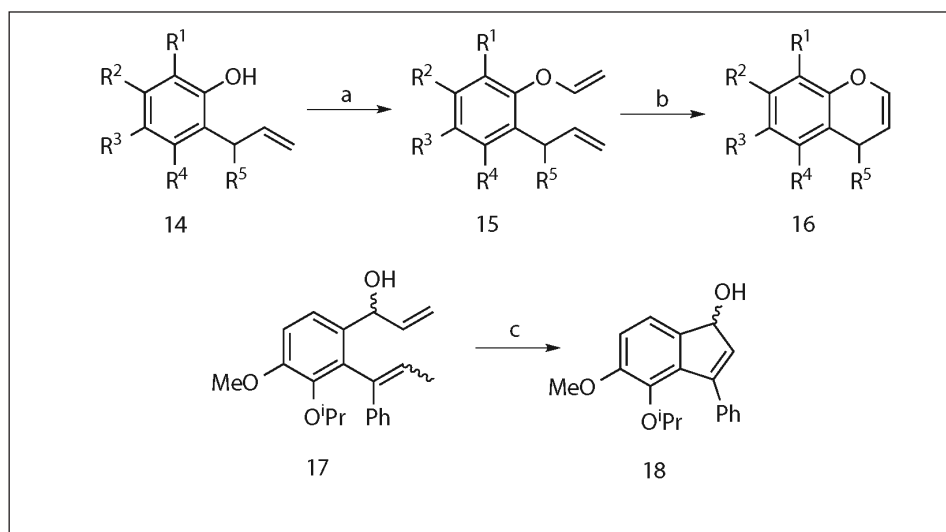
**Figure 2:** Examples of benzo-fused, bioactive and naturally occurring compounds

The reason for our fascination with the benzo-fused classes of compounds is that they are frequently found as structural motifs in natural products and as a consequence in pharmaceutically relevant synthetic compounds. It is because of these characteristics that benzannulated compounds are often referred to as 'privileged scaffolds'. **Figure 2** shows a very limited number of natural products and bioactive compounds (**5–13**), all with aromatic rings fused to heterocyclic rings of varying size and containing different heteroatoms.

In 2003, our first research work was published, which described a metathetic synthetic approach to the

synthesis of a number of substituted chromenes **16**, a naphthalene, a naphthol and an indenol **18** (see **Scheme 2**).<sup>2</sup> This paper set the scene for a solid number of other publications from our group as it became clear that the methodology had broad applicability to the synthesis of benzo-fused compounds. Of interest was that the synthesis of the chromenes required a vinylation, followed by a metathesis reaction involving a vinyl ether functional group. This work represented one of the early examples of the successful metathesis reaction on an electron-rich *O*-vinyl alkene (for extension of this work to both *2H*- and *4H*-chromenes see reference<sup>3</sup>).

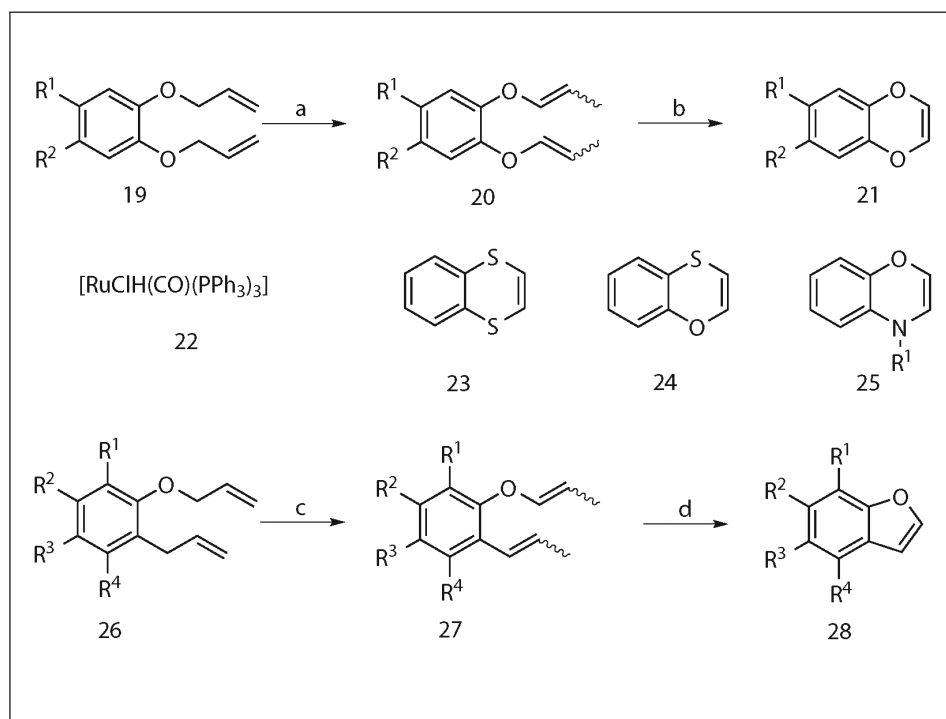




**Scheme 2:** Conditions and yields: (a)  $\text{Cu}(\text{OAc})_2$ ,  $\text{Sn}(\text{vinyl})_4$ ,  $\text{MeCN}$ ,  $\text{O}_2$  (98–99%); (b) **2** (5 mol %), toluene (80–98%); (c) **2** (5 mol %),  $\text{CH}_2\text{Cl}_2$  (67%).

This paper was followed in the same year by work describing the metathesis of more examples involving vinyloxy groups – this time being introduced by a ruthenium-catalysed isomerisation process of an allyl functional group using ruthenium hydride complex **22** (see **Scheme 3**).<sup>4</sup> These initial results utilised the *bis*-isomerisation of 1,2-*bis*-allyloxybenzenes **19**, followed by RCM of substrate **20** to afford substituted benzo[1,4]dioxins **21** in excellent yields over the two steps. The isomerisation-RCM protocol could even be performed in a one-pot manner in which the metathesis catalyst was added after the isomerisation process was deemed complete. In addition, the *bis*-isomerisation of allyl-2-

(allyloxy)benzene **26**, followed by introduction of the Grubbs second generation catalyst **2**, also afforded the benzofuran skeleton **28** (via the *bis*-isomerised compound **27**). Of interest is that both these observations led to full papers describing the synthesis of a range of substituted benzo[1,4]dioxins<sup>5</sup> and benzofurans,<sup>6</sup> highlighting the applicability of this approach to these versatile benzannulated heterocycles. Subsequently, it was even proven that the isomerisation-RCM approach was tolerant of *S,S*-, *S,O*- and *N,O*-*bis*-allylbenzenes, thereby affording the benzodithiin **23**, 1,4-benzoxathiin **24** and 4*H*-1,4-benzoxazine **25** cores, respectively.<sup>5</sup>

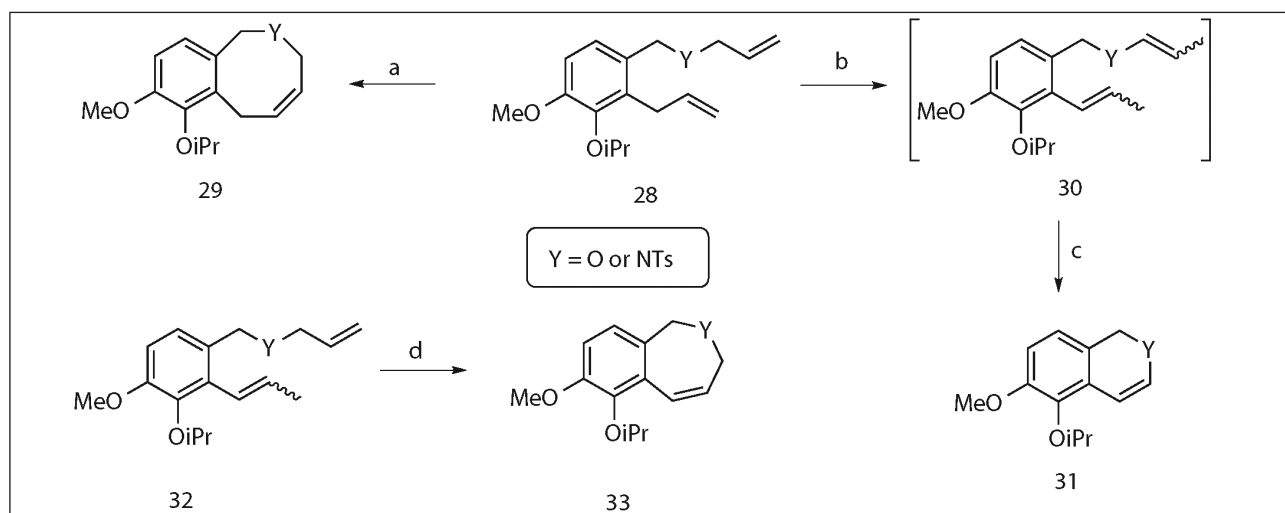


**Scheme 3:** Conditions and yields: (a) **22** (1 mol %), toluene- $d_8$  or toluene, 65–100 °C; (b) **2** (5 mol %), toluene- $d_8$  or toluene, 65–80 °C (~70% over two steps); (c) **22** (5 mol %), toluene or  $\text{CH}_2\text{Cl}_2$  (54%-quantitative); (d) **2** (5 mol %), toluene (20%-quantitative).

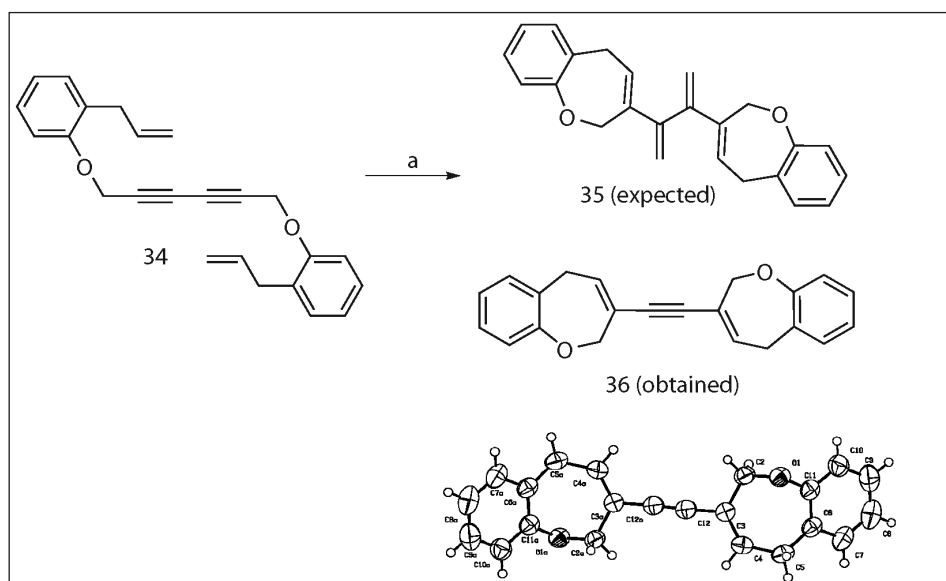
Since the application of an RCM or isomerisation-RCM approach for the synthesis of benzo-fused compounds with small ring sizes (5 and 6) had been very successful, the approach was applied to larger benzannulated heterocycles. **Scheme 4** demonstrates how the appropriate application of the isomerisation and RCM methodologies readily afforded 6-, 7- and 8-membered ring systems (i.e. compounds **31**, **33** and **29**, respectively), irrespective of whether the heteroatom in the ring was oxygen or nitrogen.<sup>7</sup> Later this concept was extended to other aromatic systems<sup>8</sup> that included the pyridine ring,<sup>9</sup> as well as to extensions of other heterocycles such as the 2-benzazocine ring.<sup>10</sup> Of interest is that the latter paper represents one of the first examples in which compounds from our laboratory were tested for their anti-cancer cytotoxicity, paving the

way for more bioactivity-inspired synthetic endeavours yet to follow.

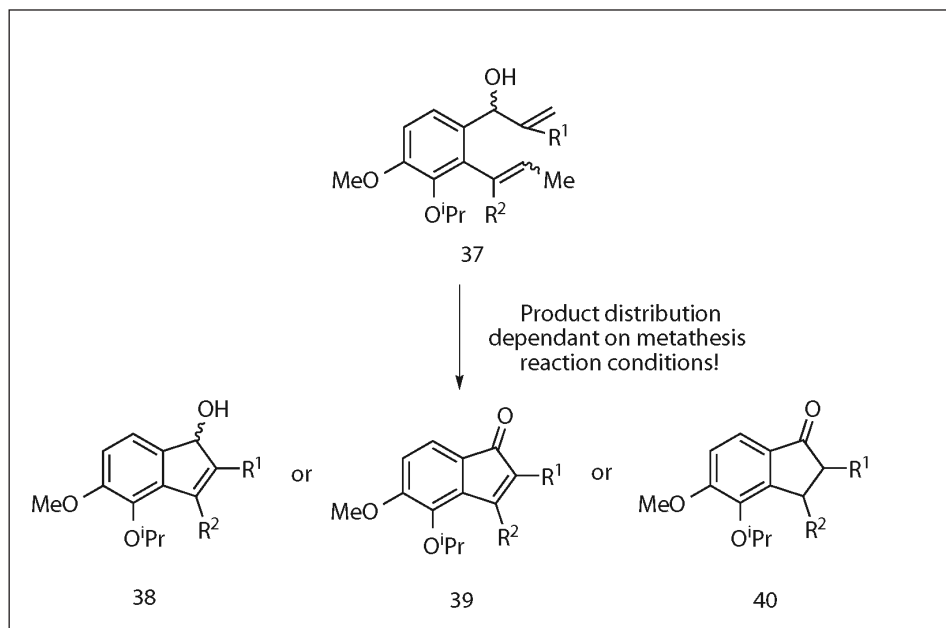
When working in a new field, there are often surprises awaiting the research student in the laboratory, surprises that can of course be of synthetic value (in the sciences this type of unexpected discovery is often referred to as being due to 'serendipity and the prepared mind'). The first unusual reaction occurred during the proposed synthesis of dimeric benzo-fused systems using another variant of the metathetic arsenal, viz. ene-yne metathesis. In contrast to our expectations, instead of the expected product **35**, compound **36** was isolated (see **Scheme 5**).<sup>11</sup> This turned out to represent the first reported example of a metallotropic [1,3]-shift in 1,3-diyne, mediated specifically by a ruthenium carbene.



**Scheme 4:** Conditions and yields: (a) **2** (5 mol %), toluene, 60 °C, 1 h, (52%-quantitative); (b) **22** (5 mol %), toluene, 80 °C; (c) **2** (5 mol %), toluene, 60–110 °C, 1 h, (52%-quantitative over two steps); (d) **2** (5 mol %), toluene, 60–80 °C, 2–4 h, (64%-quantitative).



**Scheme 5:** Conditions and yields: (a) **2** (6 mol % x 2), toluene, 80 °C, ethylene atmosphere (1 atm.), **35**, 0%, **36**, 54%. Single crystal X-ray structure shown for **36**.

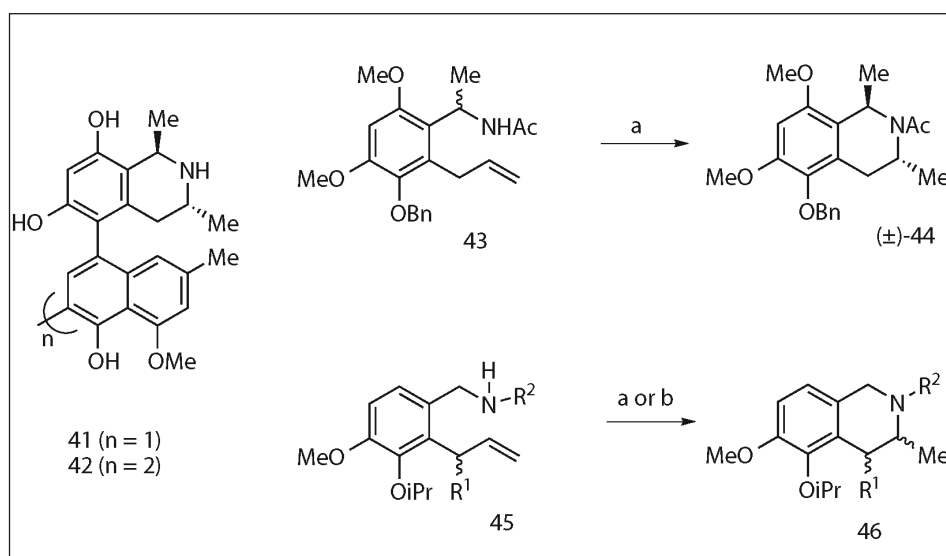


**Scheme 6**

A second example involving unexpected results returns to the synthesis of small benzo-fused molecules. During attempts to synthesise substituted indenols, it became apparent that by simply moderating the reaction conditions, the product distribution could be shifted to afford indenols **38**, indenones **39** or, even in some cases, indanones **40** (see **Scheme 6**).<sup>12,13</sup> These results were due to the conversion of the Grubbs carbene into a ruthenium-hydrido species under the harsher high temperature conditions employed, facilitating the catalysis of dehydrogenative oxidations and redox isomerisations required for the formation of compounds of types **39** and **40**.

Last in this section on synthetic methodology applied in our laboratories, the synthesis of substituted tetrahydroisoquinolines (THIQs) by a different route

will be described. THIQs are also considered privileged structures, with many natural products containing this motif. See for instance the naphthylisoquinoline alkaloids, korupensamine **B 41** and michellamine **B 42** in **Scheme 7** (analogues of these very compounds being the subject of my PhD thesis.<sup>14-17</sup> In addition, research performed during my postdoctoral fellowship in Montreal, Quebec, Canada,<sup>18</sup> and during various collaborations on THIQs and imbedded THIQs is also part of the reason for the interest in the THIQ framework).<sup>19,20</sup> While the application of an isomerisation-RCM approach to afford substituted unsaturated THIQs was unfortunately unreliable,<sup>21</sup> the application of a reductive mercuration-hydroamination (i.e. **43** → **44**) or an *n*-butyllithium-mediated hydroamination approach (i.e. **45** → **46**) was far more successful.<sup>22,23</sup>



**Scheme 7:** Conditions and yields: (a)  $\text{Hg}(\text{OAc})_2$ , THF- $\text{H}_2\text{O}$  (1/1), rt, 18 h; then aq. NaOH,  $\text{NaBH}_4$ , 0 °C to rt, 18 h (63–90%); (b) *n*-BuLi (2 x 16 mol %), rt, 6 h, then 60 °C, 18 h (62–87%).

In conclusion to this section, it is evident that our approaches to the synthesis of small benzo-fused systems have been successful, in particular the application of the isomerisation-RCM methodologies. For additional examples of our work in this area, including collaborative work, see the following references:<sup>21,24-26</sup> Furthermore, from ongoing work presented in the literature it is also clear that these types of reaction will continue to enhance the chemist's ability to synthesise even more interesting benzannulated heterocyclic systems. The potential of this reaction was highlighted when we (Prof. Charles de Koning and I) were honoured in receiving an invitation to prepare a comprehensive review article entitled 'Metathesis in the synthesis of aromatic compounds' for the prestigious journal *Chemical Reviews*.<sup>1</sup> It is thus envisaged that although much of the present research in our laboratories is orientated toward medicinal chemistry (i.e. the synthesis of compounds with postulated bioactivity) and chemical biology (i.e. the synthesis of molecules as probes in biological systems), the application of the metathesis methodology as a synthetic strategy will always remain prominent in our research.

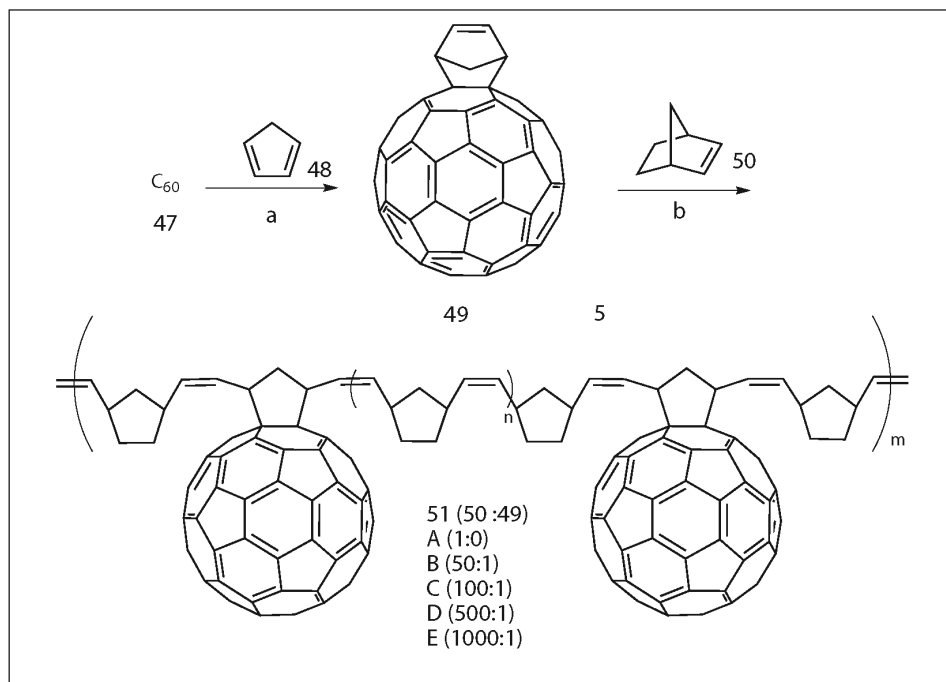
## APPLIED ORGANIC SYNTHETIC CHEMISTRY: MOLECULES WITH A MISSION

As mentioned in the conclusion of the last section, while a considerable portion of our research time during the last 10 years has been invested in the development of novel approaches to the synthesis of interesting compound structures, in recent years the desire to make molecules that actually 'do stuff' has become even stronger. In this section of the research

summary, applications of the molecules made in our laboratory will be described. This will include brief descriptions of the synthesis of functionalised carbon materials and macrostructures such as lipoplexes, the synthesis of compounds with anti-cancer activity based on designs from nature and, finally, the design and synthesis of compounds to specifically interact with the active sites of biological receptors and enzymes.

## FUNCTIONALISED ORGANIC CARBONACEOUS MATERIALS

The discovery and production of carbonaceous materials such as fullerenes, nanotubes and carbon spheres has made a major contribution to advances in the field of nanotechnology, i.e. the control of structure on a very small size scale, leading to materials with varied and valuable properties. Our contribution to this particular area of research has been aimed at the functionalisation of these carbon-based materials using organic chemistry to obtain compounds that may find application in materials chemistry, in particular for devices such as solar cells and sensors. The work, done in conjunction with Prof. N Coville (WITS, CATOMAT group), has recently resulted in a number of publications, the first involving the metathetic preparation of a polymer containing covalently bound fullerene **51** (see **Scheme 8**)<sup>27</sup> and the second utilising metals supported on carbon spheres as catalysts for organic transformations.<sup>28</sup> In the last two years, Prof. I Hümmulgen (Federal University of Paraná, Curitiba, Brazil) has applied some of the synthesised materials in nanoscale devices to obtain hydrostatic pressure sensors,<sup>29</sup> vapour sensors<sup>30</sup> for ethanol, methanol and toluene, and finally components for simple write-once-read-many-times (WORM) memory devices.<sup>31</sup>

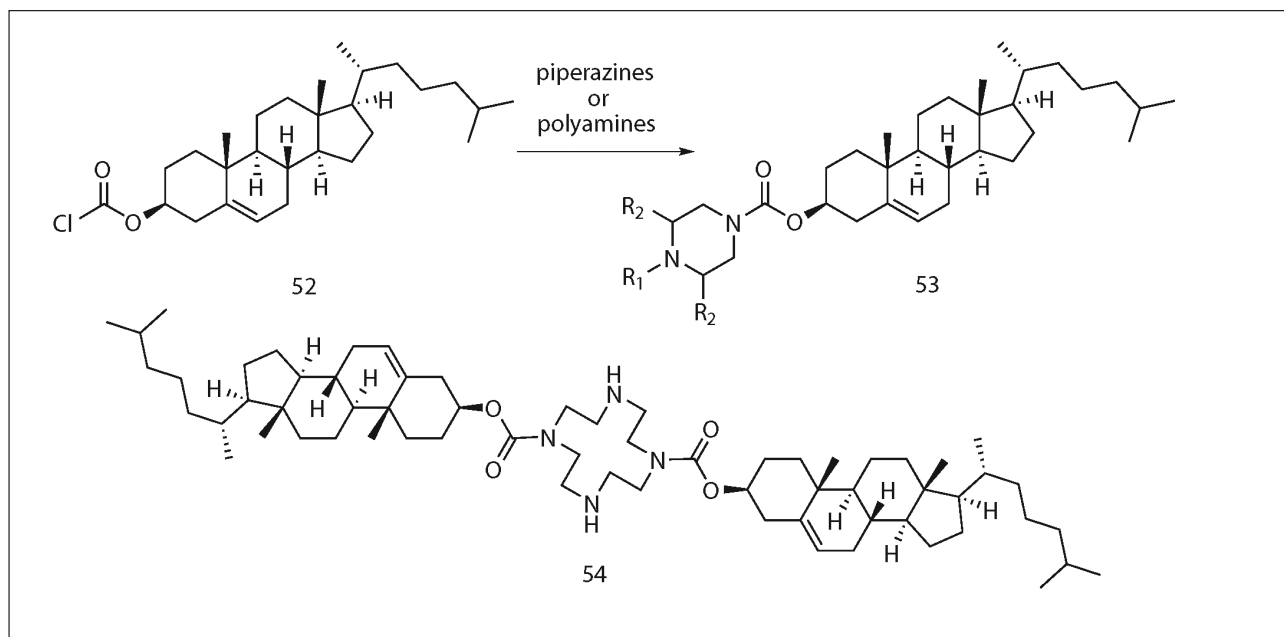


**Scheme 8:** Conditions and yields: (a) Toluene, rt, 45 min., (52%); (b) **2** (catalytic), xylene, rt, 1 h (83–93 mass %).

## SYNTHESIS OF COMPONENTS FOR LIPOPLEXES UTILISED IN GENE TRANSFER AGENTS

Over the last few years we have also been involved in a fruitful collaboration with Prof. P Arbutnot (Anti-viral Gene Therapy Research Unit, WITS), involving the synthesis of novel cholesterol-based components of nucleic acid-transporting lipoplexes for the potential treatment of hepatitis B. Lipoplexes are nano-sized macrostructures held together by intermolecular forces

and have the potential to be important vehicles for drug delivery due to a number of advantages. Recently, the first publications on this work have described the design of novel piperazine- and macrocyclic amine-cholesterol derivatives (see for instance piperazine derivative **53** and cyclen-bis-cholesterol derivative **54** in **Scheme 9**) as key components for lipoplex formulation,<sup>32,33</sup> as well as their application in a novel gene therapy approach for the treatment of hepatitis B, an important disease in the South African context.<sup>34</sup>

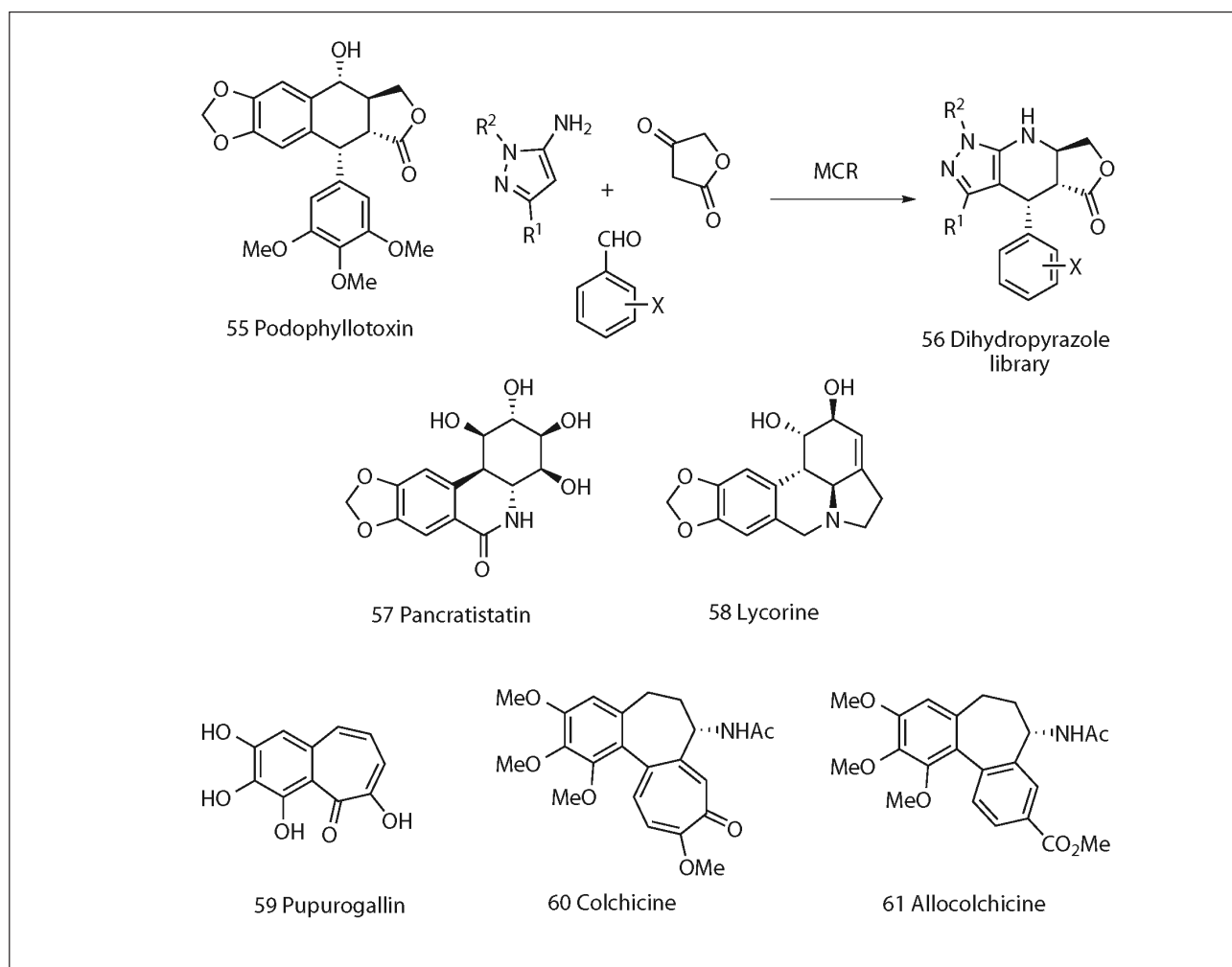


**Scheme 9**

## THE SYNTHESIS OF NATURAL-PRODUCT-INSPIRED COMPOUNDS AS ANTI-CANCER AGENTS

The animal and plant kingdoms abound with examples of compounds that have wonderful arrays of biological activities. It would thus be foolish not to utilise these compounds as inspiration for the design of 'easier-to-synthesise' analogues with focused activities and fewer off-target interactions (i.e. with fewer side effects). With this in mind, we have been involved in a number of collaborations – between synthetic chemists, molecular modellers, biochemists and structural biologists – with the specific aim of finding molecules with anti-cancer properties. For instance, an international collaboration with Prof. A Kornienko (New Mexico Institute of Technology and Mining) has involved the

design and synthesis of analogues, **56**, of the cytotoxic natural product podophyllotoxin **55**. These analogues were synthesised in *one step* by a multi-component reaction (see **Scheme 10**), and this research has recently culminated in a publication.<sup>35</sup> The remarkable aspect of this work is that many of the compounds thus synthesised were at least as potent as the natural product; indeed, some analogues were even more active. In collaboration with the same American group, open-chain analogues of a potent, naturally occurring carboisostyryl named pancratistatin **57** have also been reported.<sup>36</sup> Furthermore, work based on the natural products lycorine **58**,<sup>37</sup> purpurogallin **59**, colchicine **60**, allicolchicine **61** and others is ongoing, with exciting results indicating that the medicinal chemistry strategies based on these compounds could result in 'hit compounds' worth further pharmaceutical investigation.

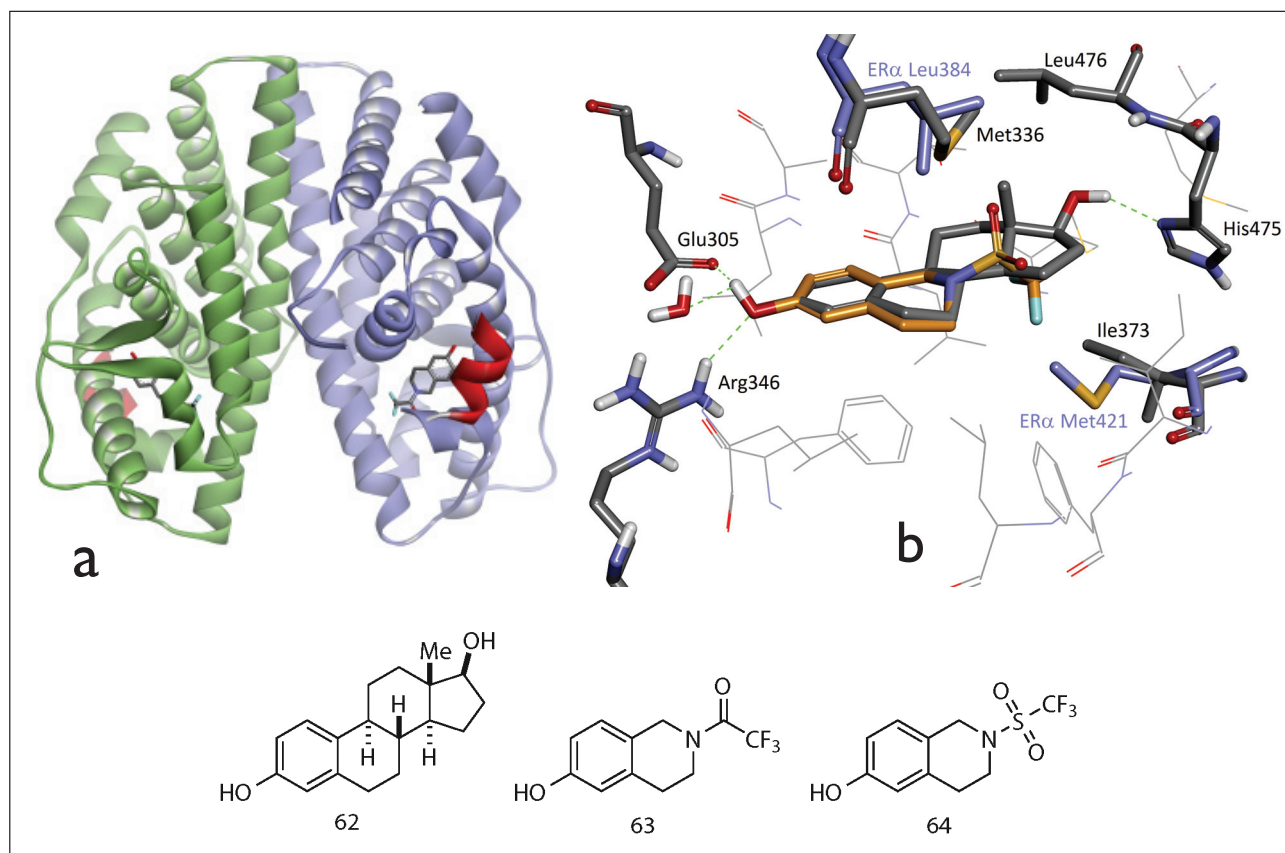


**Scheme 10**

## THE DESIGN AND SYNTHESIS OF SMALL MOLECULES DESIGNED TO INTERACT WITH BIOMOLECULAR ENTITIES

The indistinct intersection between the areas of chemistry and biology had always been of interest to me,<sup>38-40</sup> and in 2009 I had the privilege to work with a world leader in the area of ‘chemical biology’ – Prof. H Waldmann – during a sabbatical stay at the Max Planck Institute of Molecular Physiology in Dortmund (Germany) as a von Humboldt (Georg-Forster) Research Fellow. During this year I was able to immerse myself in a fascinating set of laboratories where the worlds of synthetic organic chemistry, biochemistry, computational chemistry and biology were collaborating in a symbiosis dedicated to understanding problems in the domain of chemical biology. In one of the ongoing projects, I was fortunately able to synthesise a set of compounds (see for instance compounds **63** and **64** in **Figure 3**) required to support the premise presented in a (mostly) computational paper<sup>41</sup> describing methodology

to traverse ‘chemical space’, thereby highlighting the value of organic synthesis in confirming hypotheses. (If I had to describe the essence of being an organic chemist it would probably be ‘We make – therefore we are.’) The scope of the compounds synthesised for this project was recently extended to present additional evidence for the suitability of the THIQ scaffold being a motif for the design of estrogen receptor (ER) modulators.<sup>42</sup> The ERs belong to the superfamily of nuclear receptors, and of interest is that there are two subtypes of ER (ER $\alpha$  and ER $\beta$ ), each with unique tissue distribution patterns and transcriptional properties. A significant challenge in medicinal chemistry has been the identification of selective ER $\beta$  modulators for the development of potential novel tissue and cell-selective drug candidates that could be applied in the treatment of cancer and inflammatory diseases. Of note is that this project is still the topic of collaborative research with the Technical University of Eindhoven (Prof. L Brunsveld), with the Chemical Genomics Center of the Max Planck Society, Dortmund (Dr. C Ottmann), and with a colleague at Stellenbosch University (Dr SC Pelly for computational modelling investigations).

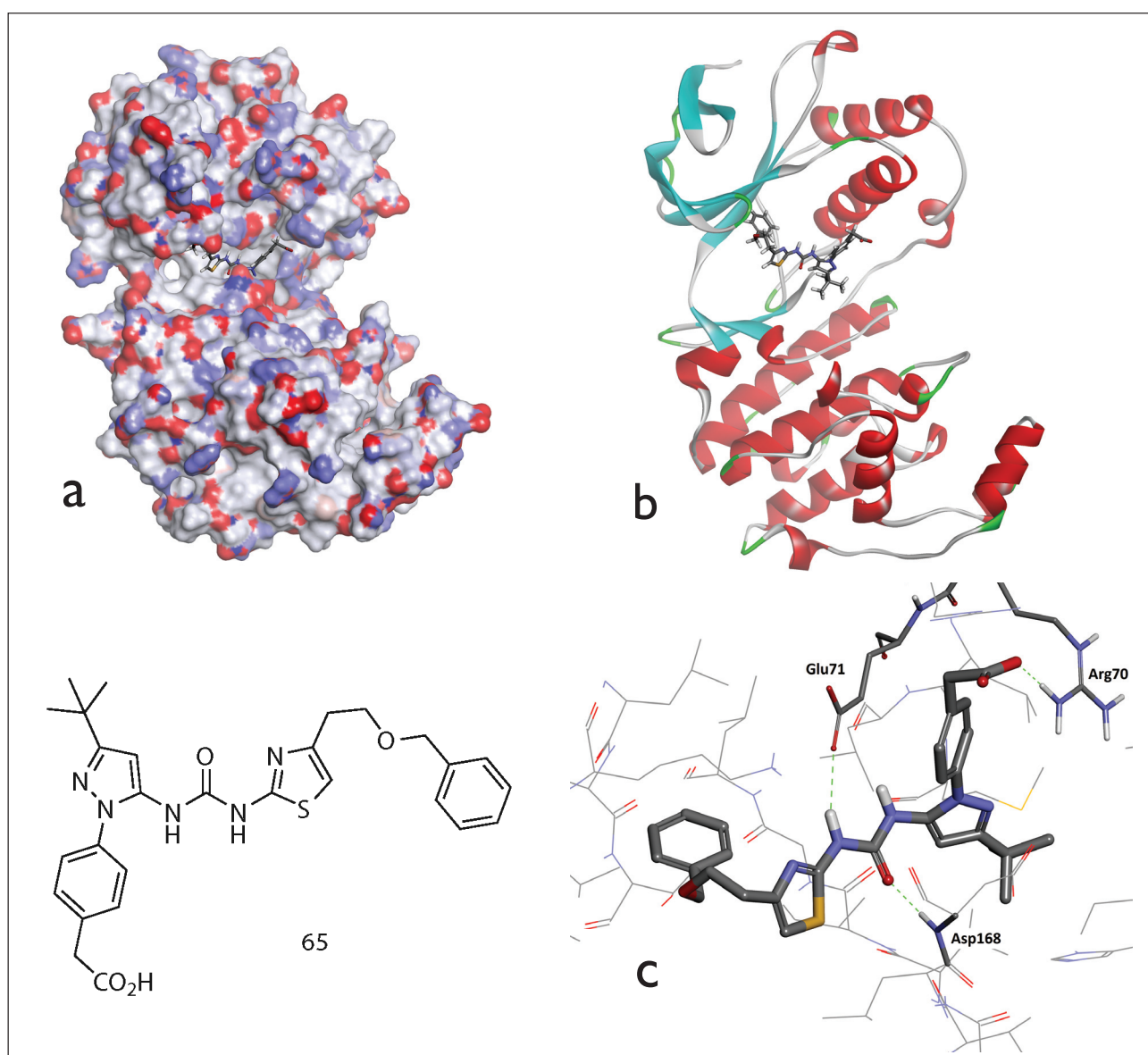


**Figure 3:** (a) General structural fold of the ER $\beta$  LBD bound to fragment **63** in complex with an SRC-1 box 2 peptide (red); (b) The crystal structure of compound **64** with the ER $\beta$  LBD (grey) and overlaid with ER $\beta$  LBD - estradiol **62** (magenta; PDB 3DT3). Only key residues are shown for simplicity.



During my time at the Max Planck Institute, Dortmund, I was also very fortunate to engage with an up-and-coming research leader, Prof. Dr D Rauh (Technical University of Dortmund), who is passionately involved in research focused on kinases and phosphatases – important proteins responsible for the transfer of phosphate groups in biostructures and ultimately dictating crucial cellular processes such as cell differentiation and apoptosis. An enriching time in his laboratories involved learning about the importance of kinase deregulations and the resultant impact on cells and cancer processes,<sup>43</sup> as well as the importance of having descriptive assay systems to evaluate small molecule interactions with actual target proteins.<sup>44</sup> Other work involved the study of actual examples of proteins implicated in human

oncology (there are more than 500 kinases in the human ‘kinome’). For instance, a small library of thiazole-based compounds was synthesised, based on a design proposed to allow interactions with the p38 mitogen-activated protein (MAP) kinase active site. The molecules were found to display good activity in an enzyme-based screen, and the binding mode of these molecules to p38a was examined by protein X-ray crystallography, a very valuable technique for medicinal chemistry.<sup>45</sup> See for instance the X-ray crystal structure of compound **65** in the active site of p38 MAP kinase (**Figure 4**). Further collaborations, involving other topical kinases, are currently underway with the Rauh research group, and we are optimistic that the results of these studies will make important contributions to the field.



**Figure 4:** General structure of p38 MAP kinase in (a) surface charge representation and (b) ribbon structure, both with compound **65** in the active site; (c) Crystal structure of **65** in active site of p38 MAP kinase with only key residues shown for simplicity.



## CONCLUSIONS AND A LOOK INTO THE FUTURE

It should be evident from this research 'summary' that during the course of my career, the beauty of molecular interactions between small molecules and much larger biological systems has become an ever-increasing fascination for me. It is in this place between the worlds of biology and chemistry that the almost overwhelming complexity of multiple yet breathtakingly simple intermolecular interactions responsible for vast cascades of bioresponses continues to pose fresh challenges to scientists attempting to unravel the secrets of biological life. As a result, this area of research has brought together many weird and wonderful scientific bedfellows, including researchers from biological, physical, computational, medicinal, pharmaceutical and, of course, chemical backgrounds; over the last few years I have therefore been privileged to have interacted with many incredible researchers, and for this I am thankful. Many of these researchers are working on the cutting edge of their disciplines, and their work has the potential to benefit humanity and the wonderful world we live

in. It is against this picture of complexity that I feel organic chemistry still has the potential to play one of the most important roles in the understanding of how these biological systems function. Amidst the intricacy of the tertiary and quaternary structures of protein 'behemoths', the ability to add one carbon to another is still a wonderful skill to possess. The power to synthesise small molecules of defined structure in a flask, molecules containing functional groups so arranged as to be able to interact specifically with proteins hundreds of times their size, is still of incalculable value to many research projects. I am thus tremendously looking forward to the challenges before our research group – be it the summons to solve a particular tricky synthetic transformation in the laboratory or the challenge to come up with a small molecule with the ability to modulate a complex biomolecule. It is thus with little doubt that I feel our research will continue to benefit from the application of hardcore organic synthetic chemistry to find answers to the questions of our day and age – be it the enigmas concerning the issues of energy or materials or the conundrums in medicine concerning HIV/Aids, hepatitis, tuberculosis or cancer.

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