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pharmaceutics
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Supramolecular chemistry of cyclodextrins and their inclusion complexes containing bioactive guest compounds

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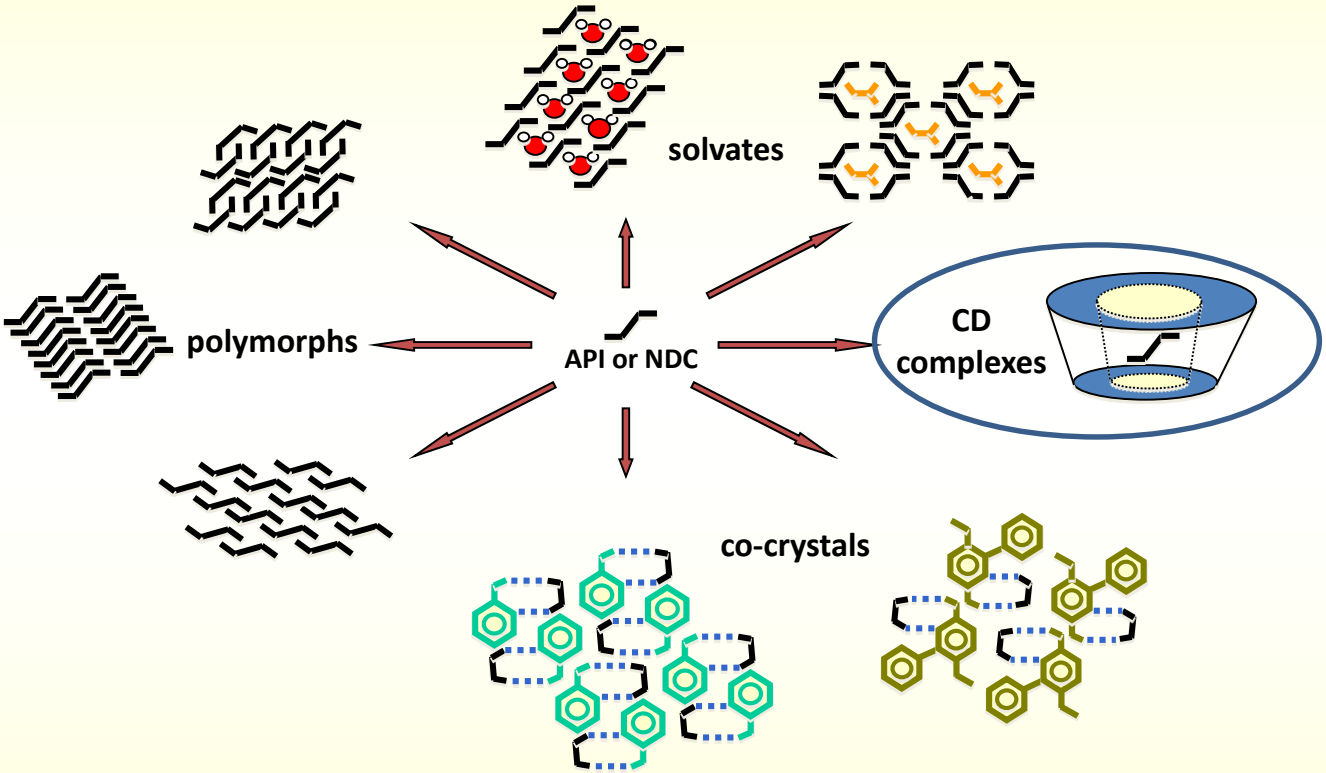
Supramolecular Derivatives of Bioactive Compounds



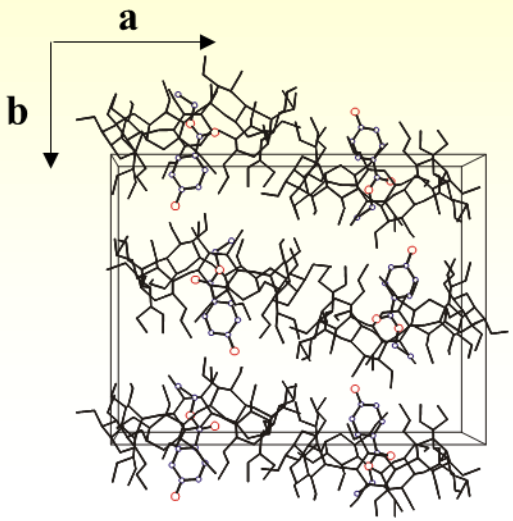
Centre for Supramolecular Chemistry Research,
Department of Chemistry, University of Cape Town, South Africa

Merits of single crystal X-ray analysis for CD complexes

- **Provides *unequivocal identity of* molecular structures of the host, guest and water molecules and their spatial relationships**
- **Reveals the *role of water molecules* in the complexation process and/or its significance in complex**
- **Permits the computation a *simulated* ('computed') PXRD pattern**
- **Provides *substantiating data* for patent registrations**
- **Every crystalline CD-drug complex is structurally unique and consequently displays distinct pharmaceutically relevant properties**

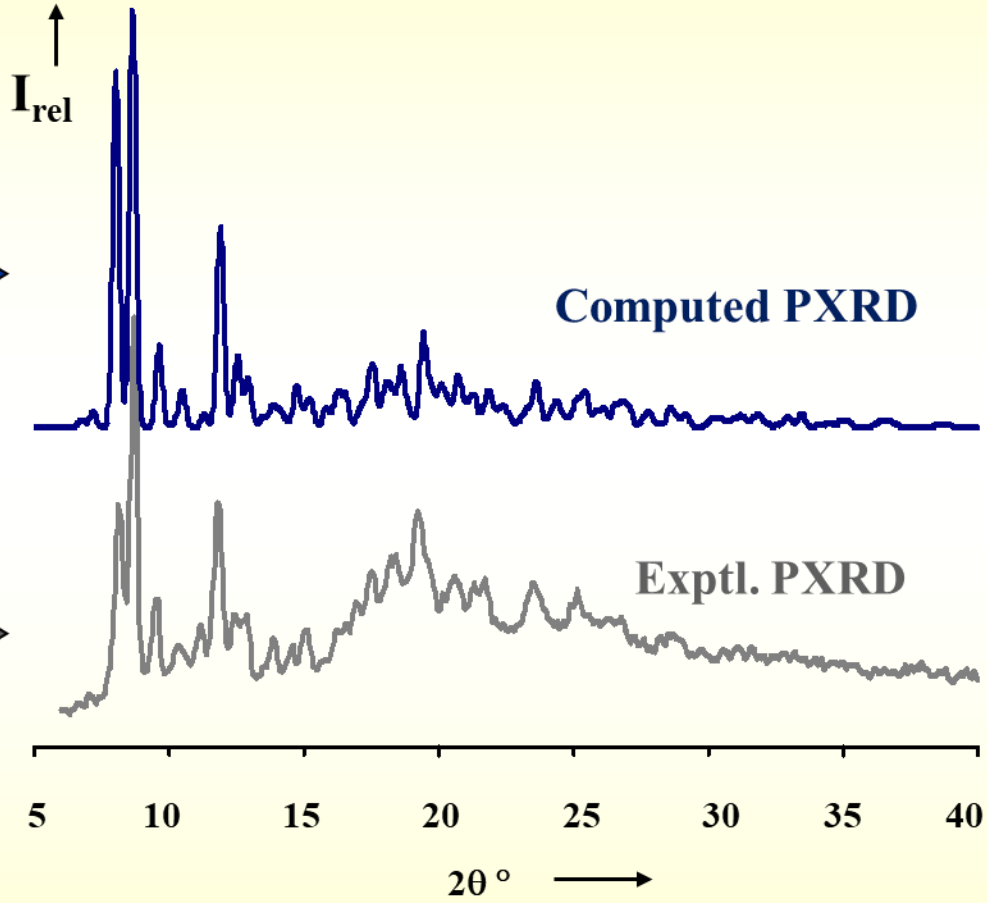
FOR MEDICINAL APPLICATIONS, SINGLE CRYSTAL XRD IS "AN UNEQUIVOCAL METHOD OF SOLID FORM IDENTIFICATION, PREFERRED BY THE FDA… "

Utility of single-crystal data to generate a PXRD pattern



known crystal structure

kneaded/co-precipitated material



Close correspondence proves that the single crystal selected for X-ray analysis is the same phase as the bulk material, but the experimental sample is not 100% crystalline.

Utility of Powder X-ray Diffraction (PXRD) for verifying complex formation between a cyclodextrin and a guest

based on the known tendency for CD-complexes

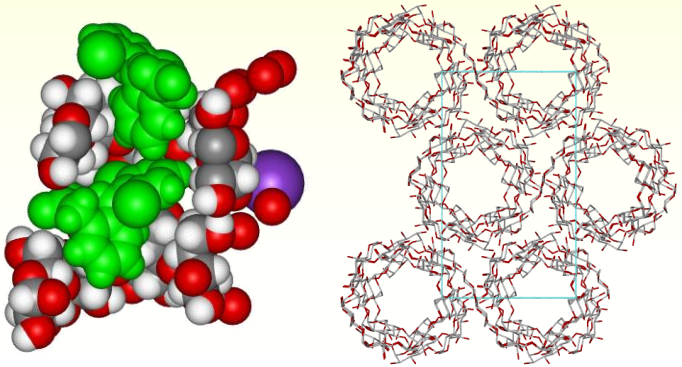
to crystallize in well-defined isostructural families,

each being characterized by a distinctive PXRD profile

Identification of a new complex isostructural series

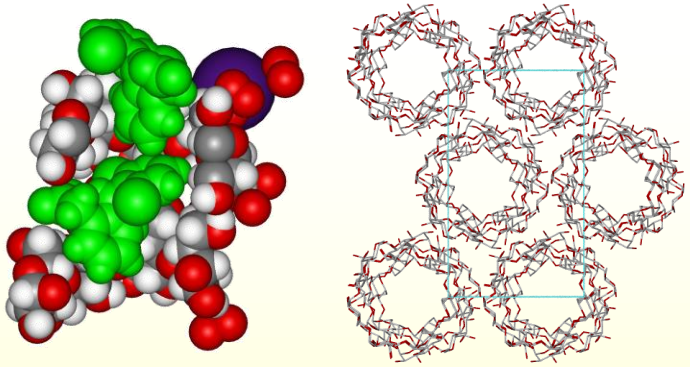
Diclofenac potassium - β-CD complex

$C_{42}H_{70}O_{35} \bullet C_{14}H_{10}Cl_2NO_2^- K^+ \bullet 10H_2O$

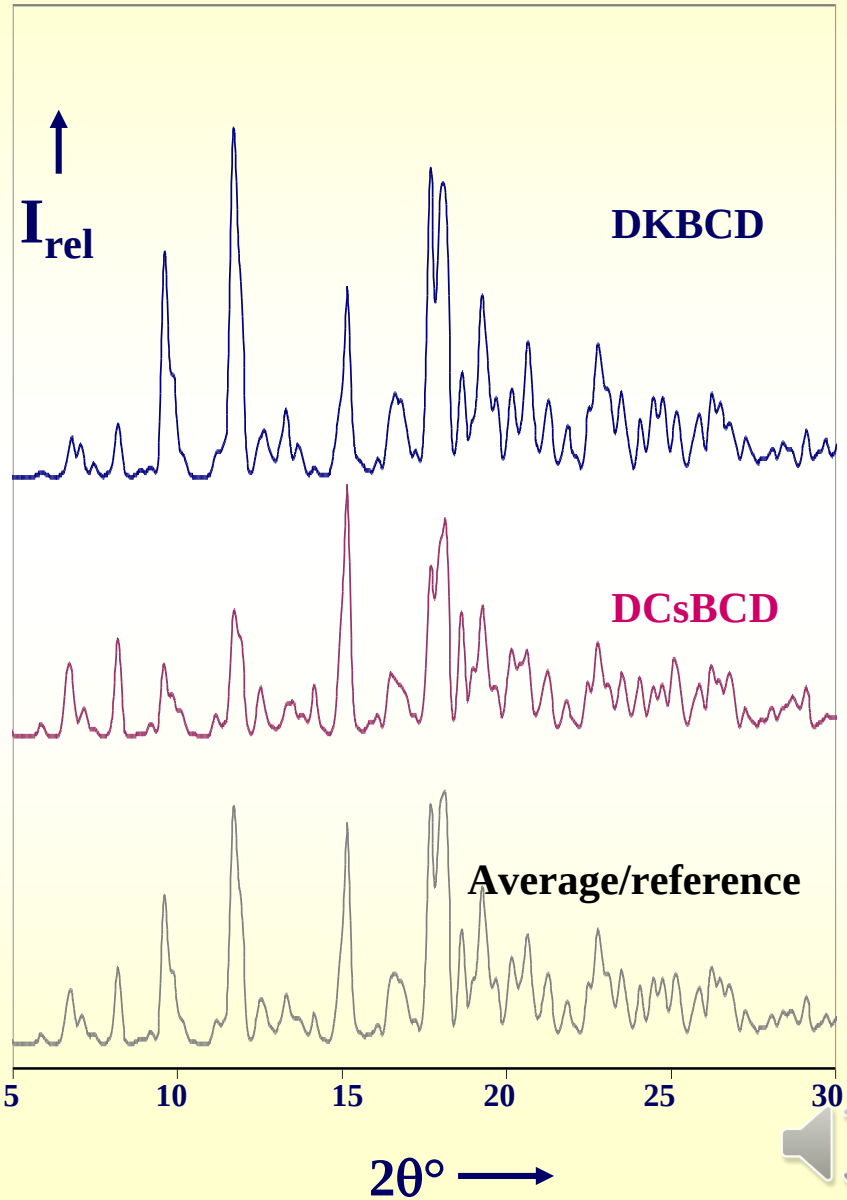


Diclofenac caesium - β-CD complex

$C_{42}H_{70}O_{35} \bullet C_{14}H_{10}Cl_2NO_2^- Cs^+ \bullet 9H_2O$



SINGLE CRYSTAL X-RAY STRUCTURES



Inclusion of (±)-α-Lipoamide in native and methylated cyclodextrins

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Department of Chemistry,

University of Cape Town, Rondebosch 7701, South Africa

Introduction:

(±)-α-Lipoamide is a bioactive compound and is converted to unbound lipoic acid within the body. This compound is of interest for its use as nutritional supplement and as therapeutic agent. It is an antioxidant with a wide range of potential uses, including administration as an antiretroviral agent and is currently used in the clinical treatment of diabetic neuropathy. The utility of this compound is drastically hindered by its poor solubility profile and thermal and metabolic stabilities.[1-3]

Aim:

The aim was to make use of supramolecular methods to alter the physicochemical properties of this compound without modifying its biological activity. Cyclodextrin (CD) inclusion complexation was the method of choice as it has many proven examples of improving stability and/or solubility of the included guest molecules.

Results:

The melting point of racemic 1,2-Dithiolane-3-pentanamide (α-lipoamide; α-LA) found in literature is 124-126 °C and the experimental equilibrium solubility of the compound in the absence of cyclodextrins at 25 °C was measured as 3.1×10^{-3} M in water.[4]

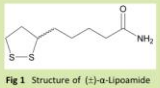


Fig 1 Structure of (±)-α-Lipoamide

Fig 2 Hot stage microscopy (HSM) images of an inclusion complex of (±)-α-Lipoamide with permethylated α-CD [(hexakis (2,3,6-tri-*O*-methyl)-α-CD; TRIMEA; TMA].

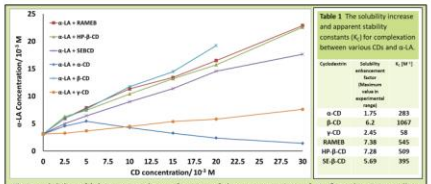


Table 1 The solubility increase and apparent stability constants (K_1) for complexation between various CDs and α-LA.

Cyclodextrin	Solubility enhancement factor (Maximum value in experimental range)	K_1 [M⁻¹]
α-CD	1.75	283
β-CD	6.2	1067
γ-CD	2.45	58
RAMEB	7.38	545
HP-β-CD	7.28	509
SE-β-CD	5.69	395

Fig 5 Solubility of (±)-α-Lipoamide as a function of the concentrations of α-, β- and γ-CD as well as the derivatised CDs namely, Hydroxypropyl-β-CD (HP-β-CD), Sulfobutyl ether β-CD (SEBCD) and randomly methylated β-CD (RAMEB) at 25 °C.

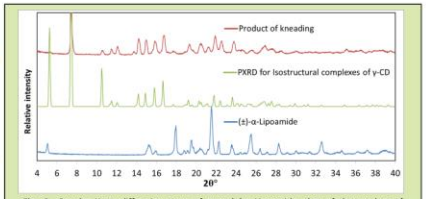


Fig 3 Powder X-ray diffraction trace of pure (±)-α-Lipoamide, that of the product of kneading it with γ-CD, and that of a known isostructural γ-CD inclusion complex.

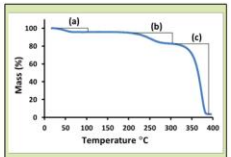


Fig 4 A representative Thermal Gravimetric Analysis result of an inclusion complex of (±)-α-Lipoamide with TRIMEA. The stepped weight losses correspond with water loss (a) guest loss (b) and (c) host loss at a host:guest:water ratio of 1:1:2.

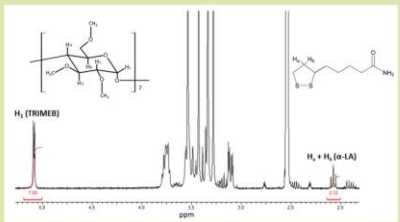


Fig 6 Partial ^{1}H NMR spectrum of an (±)-α-Lipoamide complex with (heptakis(2,3,6-tri-*O*-methyl)-β-CD (TMB)) confirming 1:1 host-guest stoichiometry.

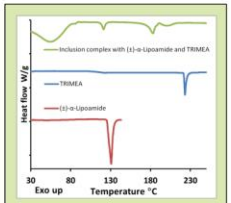


Fig 7 A representative Differential Scanning Calorimetry result showing traces of (±)-α-Lipoamide, TRIMEA and that of a complex of the two.

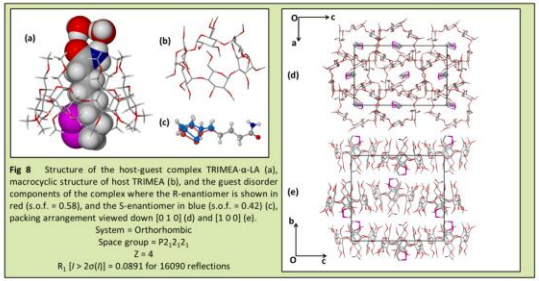


Fig 8 Structure of the host-guest complex TRIMEA-α-LA (a), macrocyclic structure of host TRIMEA (b), and the guest disorder components of the complex where the R-enantiomer is shown in red (s.o.f. = 0.58), and the S-enantiomer in blue (s.o.f. = 0.42) (c), packing arrangement viewed down [0 1 0] (d) and [1 0 0] (e).
System = Orthorhombic
Space group = $P2_12_12_1$
$Z = 4$
R_1 [$I > 2\sigma(I)$] = 0.0891 for 16090 reflections

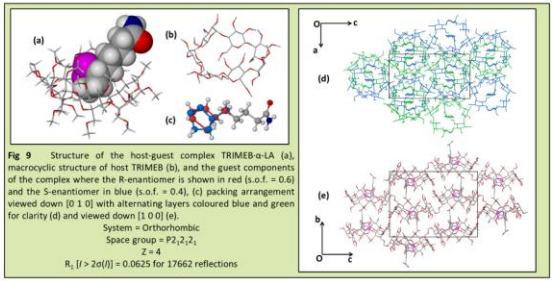
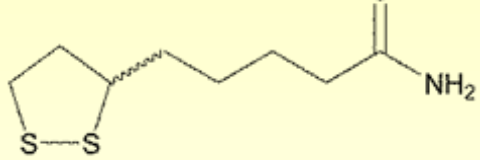


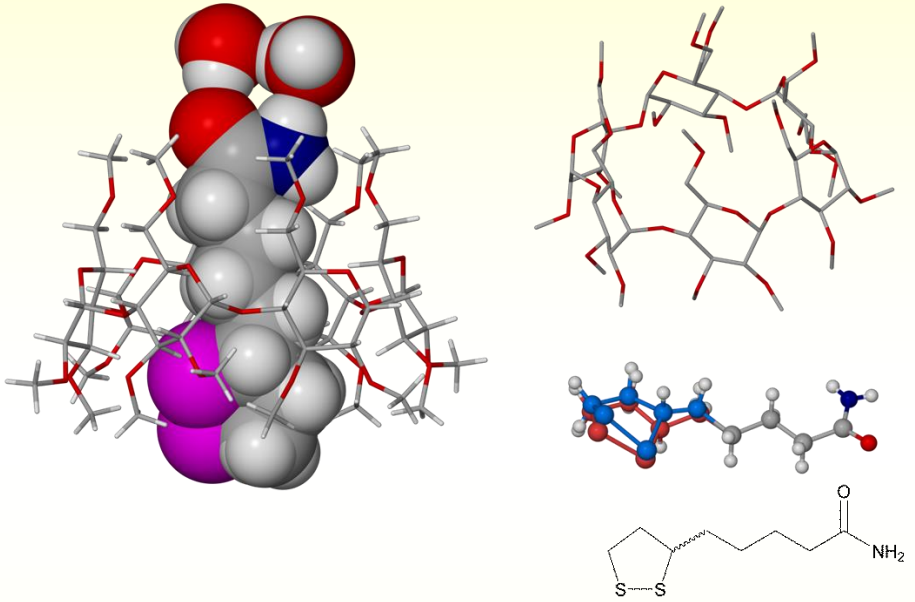
Fig 9 Structure of the host-guest complex TRIMEB-α-LA (a), macrocyclic structure of host TRIMEB (b), and the guest components of the complex where the R-enantiomer is shown in red (s.o.f. = 0.6) and the S-enantiomer in blue (s.o.f. = 0.4), (c) packing arrangement viewed down [0 1 0] with alternating layers coloured blue and green for clarity (d) and viewed down [1 0 0] (e).
System = Orthorhombic
Space group = $P2_12_12_1$
$Z = 4$
R_1 [$I > 2\sigma(I)$] = 0.0625 for 17662 reflections



α-Lipoamide

Much more than X-ray diffraction is required to characterize a CD or a CD complex comprehensively.

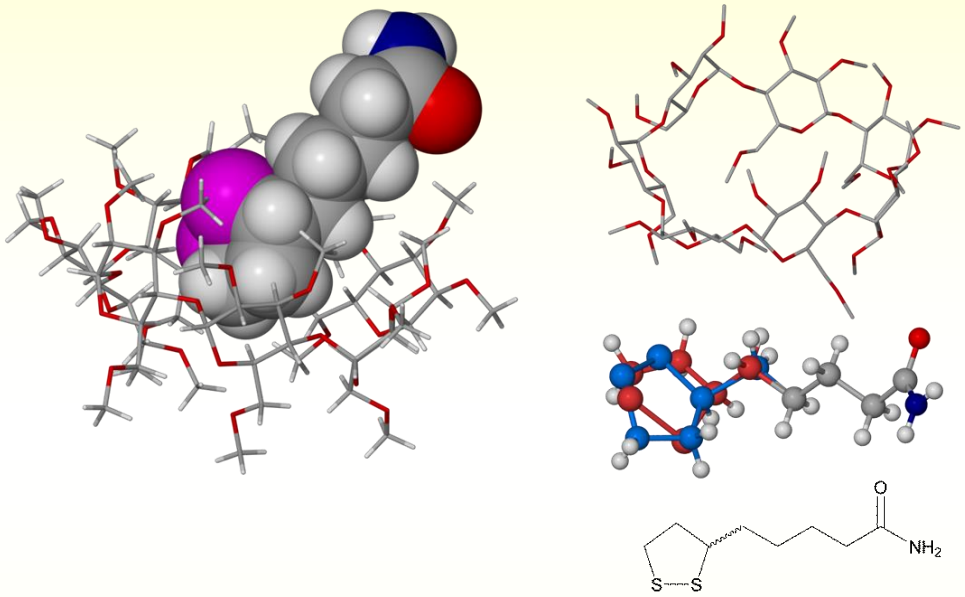
Single crystal X-ray structures of α-Lipoamide complexes with methylated CDs – *contrasting guest inclusion modes*



TRIMEA·α-LA

Orthorhombic , space group $P2_12_12_1$,
R1 [I > 2σ(I)] = 0.089 for 16090 reflections

R-enantiomer red (s.o.f. = 0.58),
S-enantiomer in blue (s.o.f. = 0.42)



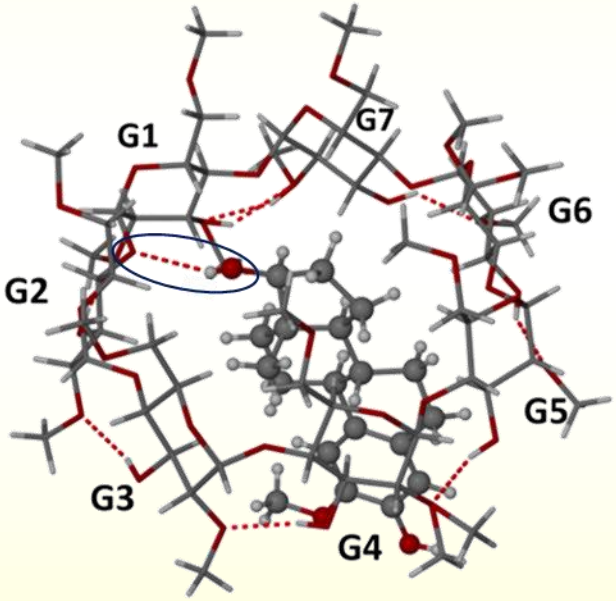
TRIMEB·α-LA

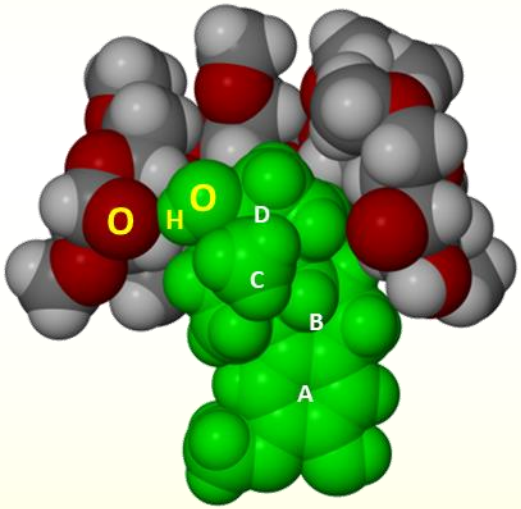
Orthorhombic , space group $P2_12_12_1$,
R1 [I > 2σ(I)] = 0.063 for 17662 reflections

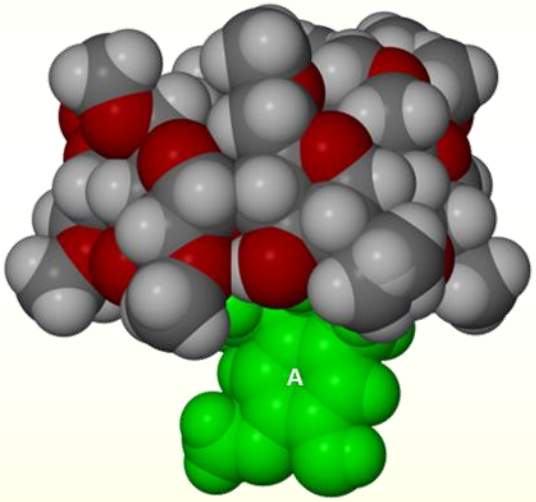
R-enantiomer red (s.o.f. = 0.60),
S-enantiomer blue (s.o.f. = 0.40)

Inclusion of anticancer agent 2-methoxyestradiol in DIMEB

First X-ray crystal structure of a CD-steroid complex



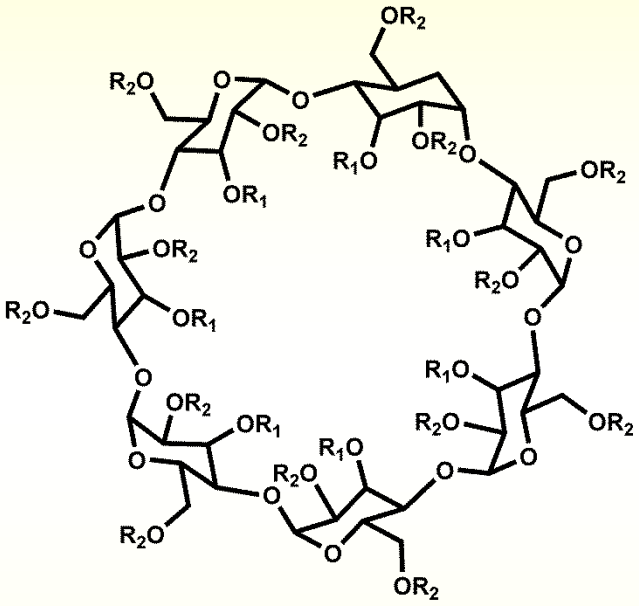




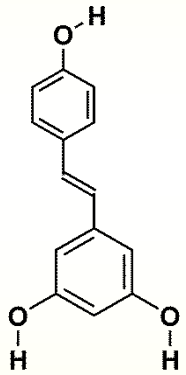
M.R. Caira, S.A. Bourne, H. Samsodien, V.J. Smith.
***Beilstein Journal of Organic Chemistry*, 2015, 11, 2616.**

The role of water in CD complexes

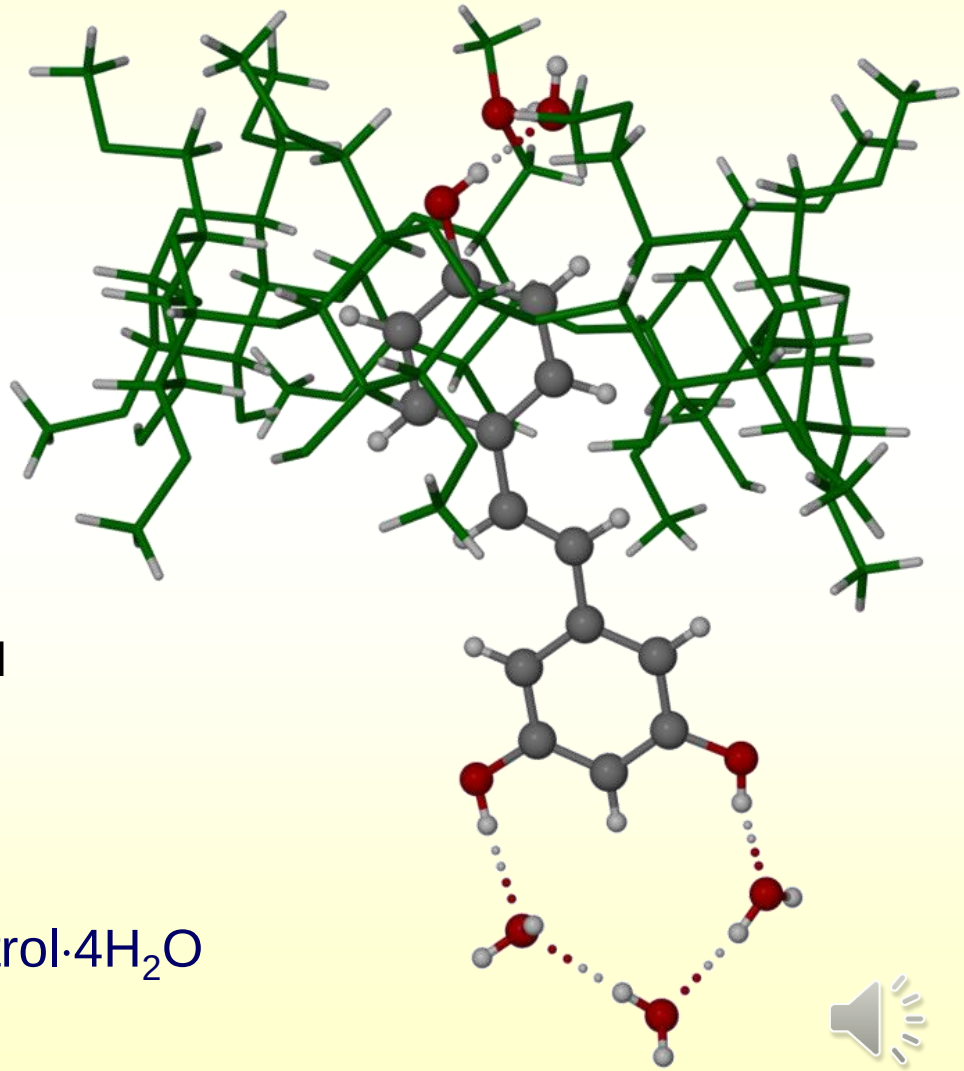
(b) Solvating hydrophilic functional groups



‘DIMEB’: R_1 = H, R_2 = Me



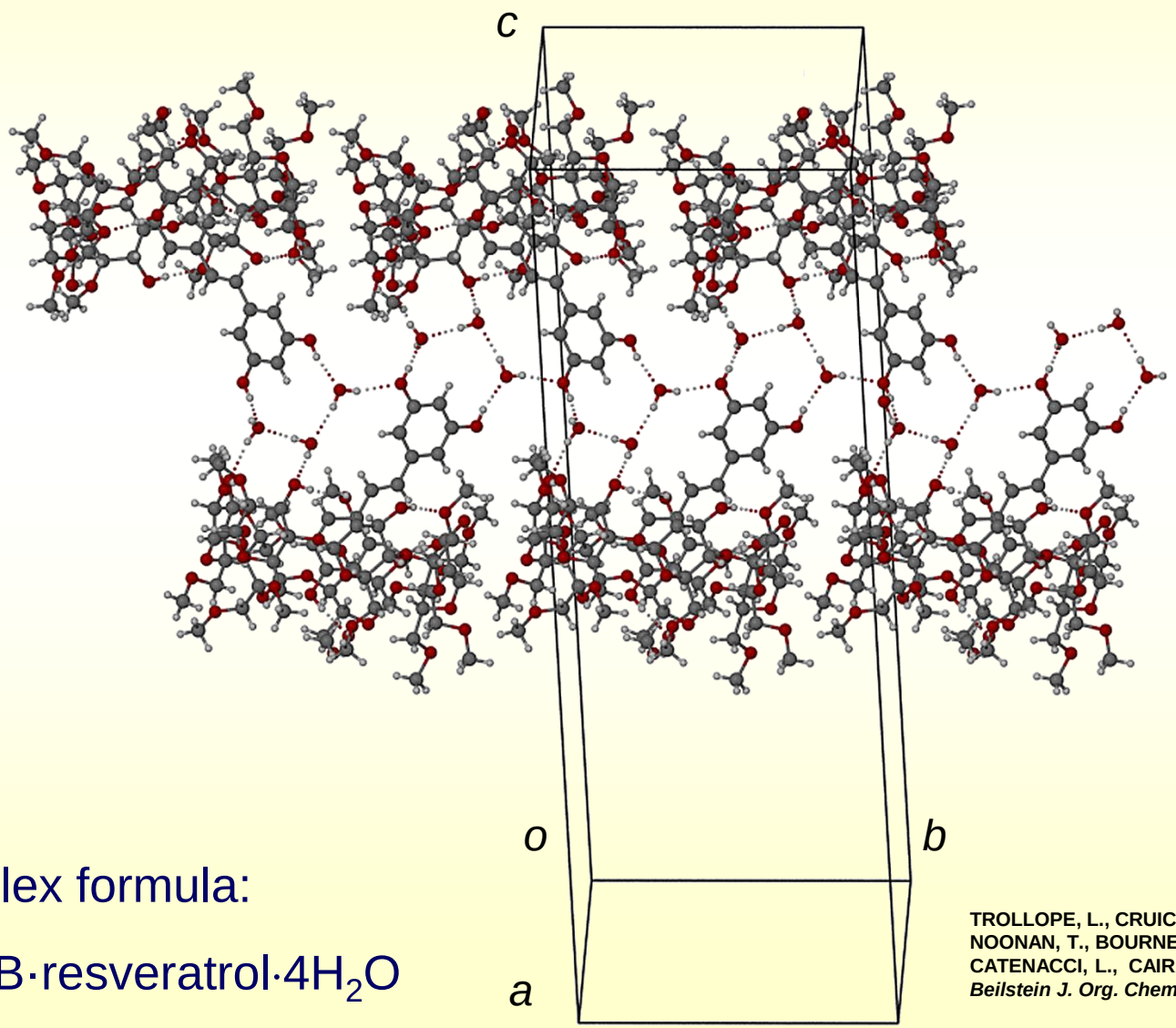
resveratrol



Complex formula: DIMEB·resveratrol·4H_2O

The role of water in CD complexes

Propagating layers *via* extended hydrogen bonding

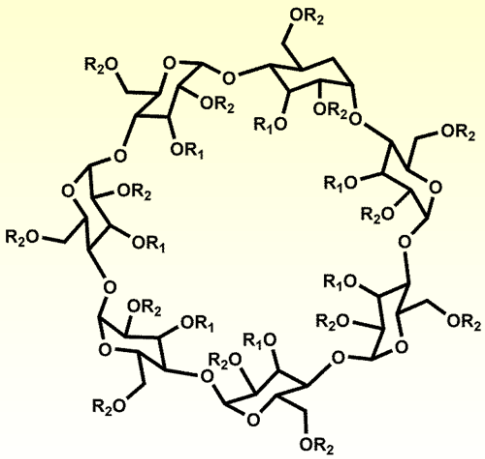


Complex formula:

DIMEB·resveratrol·4H_2O

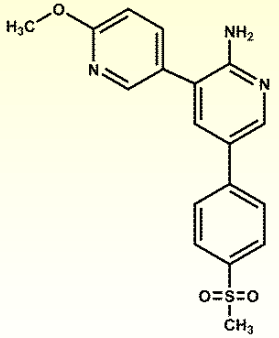
TROLLOPE, L., CRUICKSHANK, D.L., NOONAN, T., BOURNE, S.A., SORRENTI, M. CATENACCI, L., CAIRA, M.R.
Beilstein J. Org. Chem. 2014, *10,* 3136–3151.

Inclusion of a potent antimalarial drug candidate MMP in DIMEB

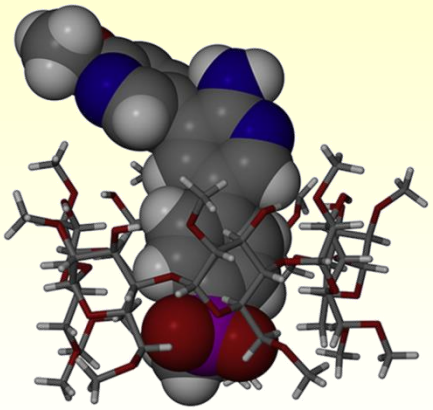


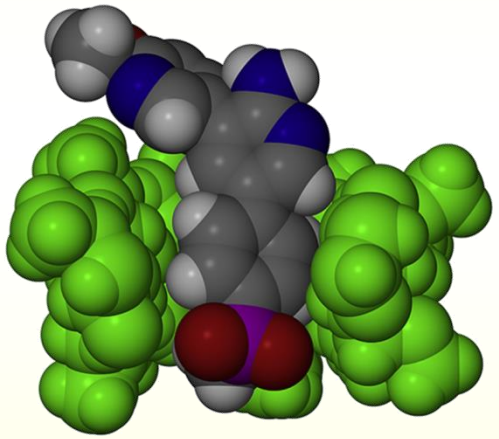
'DIMEB': R_1 = H, R_2 = Me

+



MMP





DIMEB·MMP·2H_2O

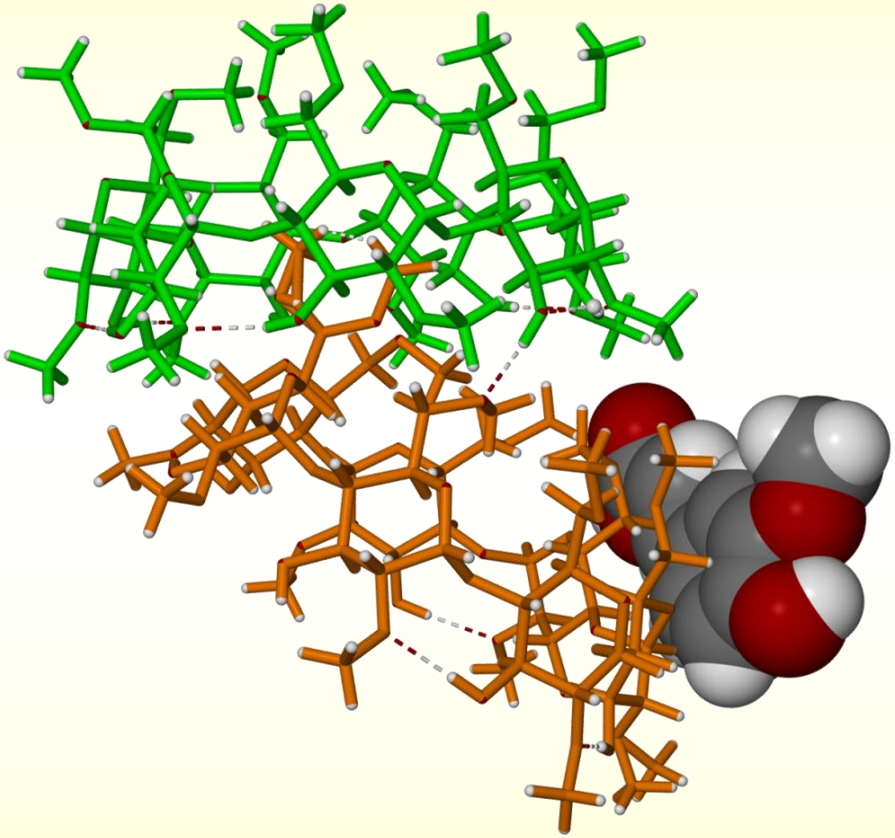
"Preliminary results from a PK study using C57BL/6 mice indicated that the inclusion complex DIMEB·MMP·2H_2O effected a somewhat slower release of the bioactive compound and an increase in its apparent half-life, whereas an efficacy study using mice infected with P. berghei indicated that the antimalarial activity due to MMP in complexed form was more than double that of MMP alone at a dose of 3 mg/kg.

However, more extensive in vivo PK studies to rationalize the improvement in in vivo efficacy are ongoing. A full account of the methodology and results of PK and efficacy studies will be published elsewhere".

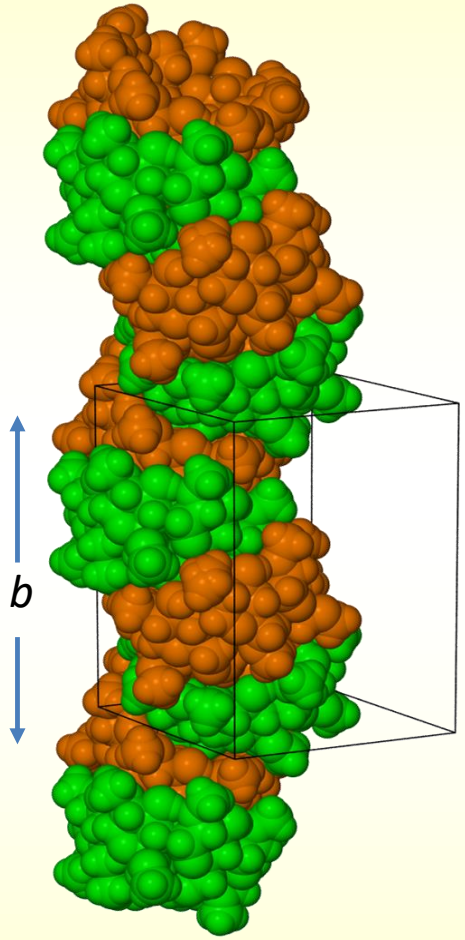
(Based on N. Strydom, L. Wiesner, unpublished data, 2016).

L.M. JOSEPH, K. CHIBALE, M.R. CAIRA. Preparation and physicochemical characterization of an inclusion complex between dimethylated β-cyclodextrin and a drug lead from a new class of orally active antimalarial 3,5-diaryl-2-aminopyridines. *J. Pharm. Sci.*, 2016, *105*, 3344-3350.

X-ray structure of a '*non-inclusion*' complex* between DIMEB and guest ferulic acid



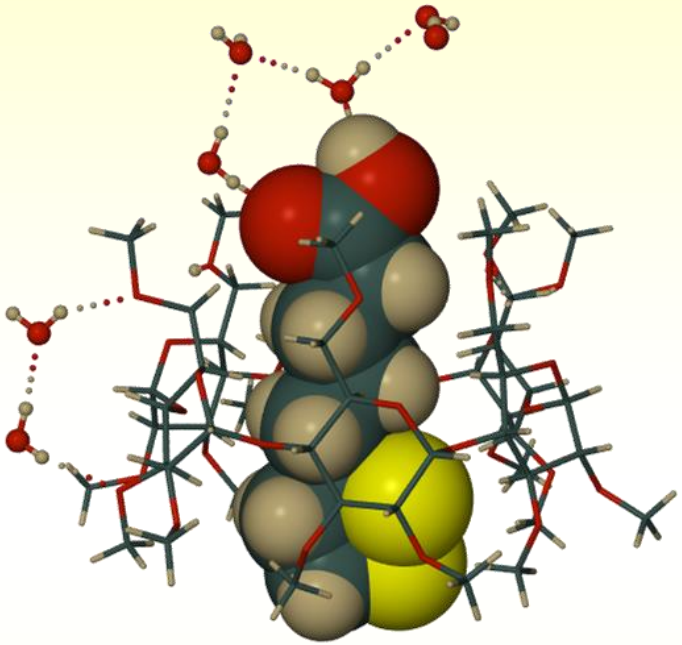
2:1 host-guest complex;
guest molecule *not* included in CD cavity



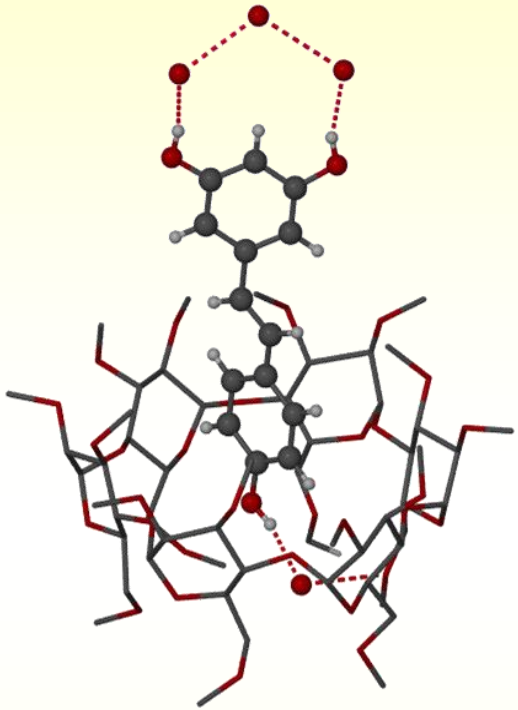
Spiral column of self-included DMB molecules

*A paper by L. Hunt, S.A. Bourne and M.R Caira describing this phenomenon has been submitted to the journal Biomolecules (Nov 2020)

On-going studies with antioxidants



(*R*)-lipoic acid – CD complex



trans-resveratrol – CD complex

Pterostilbene: *IECP 2020 Sciforum Conference Proceedings Paper:*

Inclusion of pterostilbene in natural cyclodextrins: complex preparation and solid-state characterization

Laura Catenacci, Milena Sorrenti, Maria Cristina Bonferoni, Alexios I. Vicatos and Mino R. Caira

Prof Kelly Chibale (Director: H3-D Drug Discovery and Development Centre)

Research support

National Research Foundation (Pretoria)
University of Cape Town Research Committee

CSCR group

Co-supervisor Susan Bourne and the MSc and PhD students who contributed to the reported results

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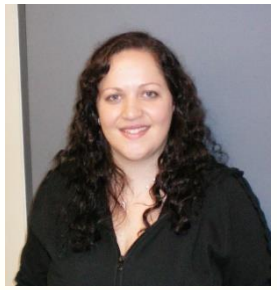
Laurelle Joseph

Buntubonke Mzondo

Susan Bourne



Lee Hunt

Dyanne Cruickshank

Halima Samsodien

Terence Noonan

Alexios Vicatos