

# DAY 1

Keynote Forum



EuroSciCon Congress on

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## PROTEIN BINDING TO TETRACYCLINES: INHIBITOR, REGULATOR, SUBSTRATE

**Winfried Hinrichs**

University of Greifswald, Germany

**T**his review will give a short overview on structural biology of tetracyclines. The group of tetracycline are one of the "big four" of antibiotic compounds. Tetracyclines block the bacterial protein synthesis by binding to the ribosomal 30S subunit. Crystal structure analyses of proteins that mediate resistance against the drug belong to a widespread efflux mechanism (Tet repressor controlled) and a chemical inactivation by a flavin monooxygenase (TetX). Non-antibiotic properties are also well known: tetracyclines interfere with inflammatory mechanisms by inhibiting Phospholipase A2. All these tetracycline binding proteins are characterized at atomic resolution. The tetracycline can act as a regulatory compound but is also a substrate or inhibitor for enzymatic mechanisms. The conclusion is that tetracyclines are an example for side effects of drugs that are more interesting than the obvious mode of action.



### Biography

Winfried Hinrichs studied Chemistry and completed his PhD in 1983 at the University of Hamburg followed by Postdoctoral studies at the Rijksuniversiteit Leiden in 1984/5. He joined the group of Wolfram Saenger at the Free University of Berlin and expanded his crystallographic expertise to bio-crystallography (1986-1999). After a sabbatical in Strasbourg (IGBMC, Dino Moras) in 1998/99, he became a Full Professor in Biochemistry focused on Structural Biology at the University Of Greifswald, Germany. He was the Director of the Institute Of Biochemistry in 2008-2014 and retired in 2016. He has published about 120 papers in reputed journals and is serving as Topical Editor for *Biochemistry of Chemtexts*.

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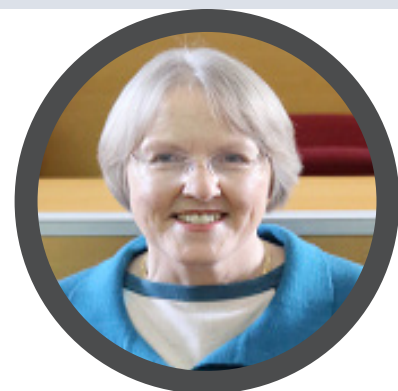
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## KINETICS, INHIBITION AND DRUG DESIGN FOR MONOAMINE OXIDASES

**Rona R Ramsay**

University of St Andrews, Scotland, UK

**M**onoamine oxidase (MAO) has been a drug target for 60 years, particularly to treat neuropsychiatric disorders. The flavin-containing monoamine oxidases (MAO A and MAO B) located on the outer membrane of mitochondria oxidise neurotransmitter amines and generates hydrogen peroxide. In the brain, inhibition of MAO increases neurotransmitter levels, alleviating depression or helping compensate for cell loss in neurodegeneration. In the periphery, MAO activity is essential for protection against biogenic amines. MAO also metabolizes many amine drugs, an important factor in pharmacokinetics. Kinetic studies of the two forms of MAO (MAO A and MAO B) have revealed that ligands bind differently to the oxidized and reduced forms, and have facilitated design of selective inhibitors. This presentation will summarize the structure and function of MAO and its inhibition by current drugs. Most successful drugs are irreversible inhibitors that inactivate MAO by forming a flavin adduct, so that activity *in vivo* is recovered only by new protein synthesis. Recent data that resolves the controversial structure of adduct will be presented, along with steady-state and stopped-flow kinetics of adduct formation. Going forward, computational methodologies, medicinal chemistry, and enzymology facilitate structure-based drug design for new multi-target compounds that inhibit not only MAO, but also other targets where binding might prevent neurodegeneration in one multi-target compound.



### Biography

Rona R Ramsay has pursued her Research in Enzymology in Cambridge, California and St Andrews (where she has lectured for 23 years), focusing on mitochondrial enzymes, investigating how these enzymes work and how they are regulated, techniques of kinetic analysis, spectroscopy, structural determination, inhibitor studies, and molecular biology are combined with molecular modelling to elucidate mechanism and guide drug discovery. Her historic works include the discovery of the carnitine carrier and the regulation of carnitine acyltransferases in fatty acid metabolism; the metabolism of the neurotoxin MPTP and identification of Complex I in the respiratory chain as the target of MPP+ toxicity; and the kinetics of iron-sulfur proteins and of flavoenzymes. Her Current research focusses on monoamine oxidases involves collaborations with medicinal chemists and neuropharmacologists to identify new multi-target molecules against neurodegenerative diseases. ORCID ID: [orcid.org/0000-0003-1535-4904](https://orcid.org/0000-0003-1535-4904).

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