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Singlet Oxygen: Toxicity and Therapeutic Properties

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Key words: Singlet oxygen, toxicity, therapeutic properties

The organic, biological and medicinal chemistry of molecular oxygen, in its ground and excited (Δg, $^1O_2$) states, is of extraordinary interest (1-4). Oxygen plays an important role in aging, damage to materials in the environment, cellular pathology (for example the damage following stroke or heart attack) and in many other areas (5). In this presentation, a short overview of the key issues of sensitized photooxidations in organic biological and medicinal systems will be attempted.

$$\text{Sens} \xrightarrow{h\nu} {}^*\text{Sens} \xrightarrow{O_2} {}^1O_2$$

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New Opportunities for the Treatment of Pain and Inflammation: The Endocannabinoid System and Inhibitors of Phospholipase A_2

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Key words: Pan, inflammation, endocannabinoid system, phospholipase A_2 inhibitors

The interest in new treatments for pain and inflammation has been recently increased, because current therapies have been associated with undesirable side effects and, in various cases (e.g. neuropathic pain), have been proved unsuccessful. This presentation

will focus on the opportunities provided by the endocannabinoid system and inhibitors of phospholipase A_2 (PLA_2) for the development of new medications for pain and inflammation. Five proteins involved in the endocannabinoid system, namely CB_1 and CB_2 receptors, anandamide transporter, fatty acid amide hydrolase (FAAH) and monoglyceride lipase (MGL) are excellent potential targets. In our lab we have designed and synthesized the first inhibitors of MGL. On the other hand, we have designed and synthesized novel inhibitors of human GIVA PLA_2, which may regulate the production of arachidonic acid and PGE_2 in cells and demonstrate potent *in vivo* anti-inflammatory and analgesic activities.

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Apolipoprotein A-I Peptide Models as Probes for Developing Atheroprotective Agents

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Key words: Apolipoprotein A-I, peptide models, atheroprotective agents

The inverse relationship between plasma levels of high density lipoprotein (HDL) and the risk of atherosclerosis and coronary artery disease has been attributed to several HDL functions, including antioxidant and antiinflammatory effects. An important role in these effects plays the apolipoprotein content of HDL, especially apolipoprotein A-I (apoA-I). With the aim to develop atheroprotective agents, we report on the design, synthesis, conformational analysis and biological effects of four amphipathic α-helix apoA-I peptide models:

Ac-ESK(Palm)KELSKSW^{10}SEM^{13}LKEK(Palm)SKS-NH_2 (1),
Ac-ESK(Palm)KELSKSM^{10}SEW^{13}LKEK(Palm)SKS-NH_2 (2),
Ac-FKEFSKSMSEWFKEF-NH_2 (3),
Ac-FKEFSKSASEWFKEF-NH_2 (4)

where Glu and Lys residues constitute the hydrophilic face, while Met, Phe, Leu, Trp as well as Palmitoyl-groups the spatially segregated hydrophobic phase of the amphipathic α-helix. Met could serve as additional oxidant-scavenger for protecting LDL from irreversible oxidative damage and Trp as intrinsic fluorescence probe. The syntheses of the apoA-I peptide models were carried out following the Fmoc-strategy and an orthogonal protection system. The helical characteristics of the apoA-I peptide models in their reconstituted form in POPC, DMPC, DMPG were studied by CD spectroscopy. The ability of the apoA-I

peptide models to inhibit Cu^{2+}-induced oxidation of the low-density lipoprotein (LDL) *in vitro*, and to prevent the oxidation induced inactivation of the LDL-associated platelet-activating factor acetylhydrolase (PAF-AH) at different concentrations were investigated and their atheroprotective role is discussed.

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Efficient Syntheses of Polyaminotetrazoles as Lead Compounds for the Development of Polyamine-Based Pharmaceuticals

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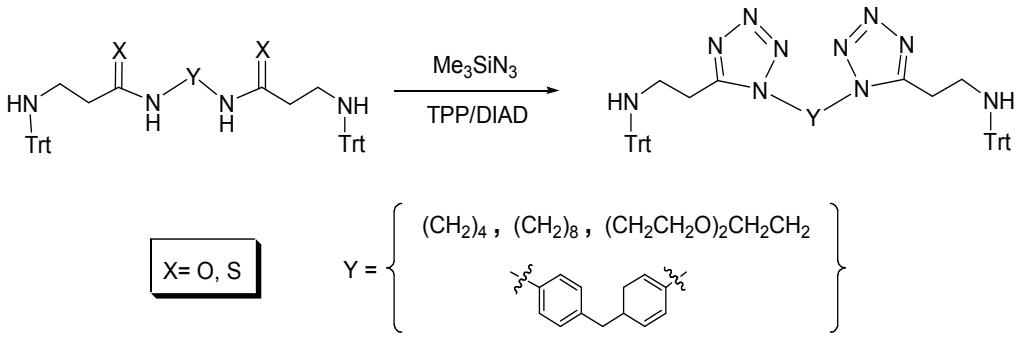
Key words: Polyaminotetrazoles, synthesis, polyamine-based pharmaceuticals



5-Substituted-1*H*-tetrazoles and 1,5-disubstituted-tetrazoles are often used as metabolism-resistant isosteric replacements for carboxylic acids and as *cis* amide bond surrogates, respectively, in SAR-driven analog synthesis in medicinal chemistry (1-3). Although a variety of synthetic tetrazole-containing biologically active substances are described in the current literature there are no examples of polyamine-based tetrazoles. We have developed a general methodology that provides easy access to linear 5-aminoalkyl-1*H*-tetrazoles and polyamines incorporating tetrazole units in their skeleton, by activating, where necessary, secondary amide bonds through thionation toward their reaction with azidotrimethylsilane under Mitsunobu reaction conditions (4).

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Pharmacokinetic Studies in Rodents for the Discovery of New Drugs by Liquid Chromatography Tandem Mass Spectrometry (Lc-Ms-Ms)

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Key words: New drugs, pharmacokinetics studies, Lc-Mc-Ms, rodents

A typical medicinal chemistry program generates numerous new leads that require further characterization in order to guide investigators (chemists) towards the synthesis of analogues that are more *drug like*. One of our main objectives is to aid medicinal chemists through our expertise in state of the art bioanalytical techniques such as tandem mass spectrometry coupled with pilot *in vivo* studies in rodents. Rapid answers can be obtained to questions of bioavailability, plasma clearance, brain penetration and overall tissue distribution, all critical components of the drug discovery process. We have elected an example of a potent cyclic peptide in order to demonstrate how LC-MS-MS can be employed towards sensitive measurements of peptide in rat plasma and how an extension of the approach allows the measurement of peptide in rat brain following intravenous administration. The type of information obtained from those studies is crucial for the *in vivo* pharmacologic evaluation of new chemical entities and can lead to the design of molecules with improved pharmacokinetic properties.

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Ground-Hemlock, *Taxus Canadensis*, as a Source of Paclitaxel

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Key words: *Taxus Canadensis*, paclitaxel

Paclitaxel, a naturally derived anti-cancer drug, was discovered by scientists at the National Cancer Institute (NCI) in the 1960's. By 1983 the first human trials of the compound's antitumour activity began and in 1991 Bristol-Myers Squibb (BMS) secured the rights from NCI to produce and develop the drug.

The original source of paclitaxel was the bark of the pacific yew (*Taxus brevifolia),* which was limited in availability and unlikely to meet the projected needs for the drug which was approved for ovarian and breast cancer therapy.

Attention turned to the common ornamental plant, the English yew (*Taxus bacccata*) from which a compound, 10-deacetylbaccatin III or 10-DAB, a close chemical relative of paclitaxel, could be obtained and was convertible by semi-synthesis, on a commercial basis, to the anti-cancer agent.

In the early 1990's interest in finding other sources of paclitaxel (value ~US $600,000 per kg, at that time) rapidly developed and it was soon learned that ground hemlock (*Taxus canadensis*), a common shrub in the eastern North American forests, contained substantial quantities of paclitaxel as well as 10-DAB, however the major "taxane" component of ground-hemlock proved to be another close relative of paclitaxel namely 13-acetyl-9-dihydrobaccatin III or DHB.

An efficient, three-step chemical transformation of the relatively abundant 13-acetyl-9-dihydrobaccatin III (DHB) into 10-deacetylbaccatin III (10-DAB), the established paclitaxel semi-synthesis precursor, will be presented.

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Research and Development of Anticancer Drugs

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Key words: Anticancer drugs, R&D

In the last decades our knowledge has greatly increased in regard to the structure, synthesis and mechanism of action of compounds with anticancer activity. Research and

development of anticancer drugs is a lengthy process, taking over 12 years and requiring hundreds of millions Euros, from the identification of a suitable drug target to the introduction of a new medicine. Following resolution of intellectual property issues and successful initial *in vitro* experiments, a new compound undergoes *in vitro* toxicity screening on a variety of tumour cell lines. Only 2% of the tested entities continue to *in vivo* animal experiments, where the biodistribution, toxicity and efficacy are determined. Only 1-2 out of 10,000 new molecules successfully complete this stage of development and are considered for testing in humans. Phase I and II clinical trials are conducted with a limited number of patients to determine safety, dosage and effectiveness. Following this, Phase III studies are initiated, with larger number of patients typically in a multicentre/multinational setting, where the safety is confirmed and the efficacy of the new treatment is determined as compared with existing therapies. Only 20% of the new compounds, which enter clinical development, successfully reach the market, where research continuous through Phase IV clinical trials and pharmacovigillance procedures.

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Role of Harp on the Growth of Glioblastoma Cells

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Key words: Glioblastoma cells, harp

Heparin affin regulatory peptide (HARP) seems to be involved in the progression of brain tumors, such as the glioblastoma multiforme, with mechanisms yet to be elucidated. Glioblastoma multiforme is the most aggressive malignant glioma and among the highly angiogenesis-dependent tumors. In this study, we tried to determine the role of HARP in glioblastoma multiforme, using antisense strategy to inhibit the endogenously expressed HARP in C6 glioma cells. Reduction of HARP protein in C6 cells affected proliferation rate and anchorage-independent growth of these cells, increased tumor-induced angiogenesis *in vitro* and *in vivo* and vascular endothelial growth factor (VEGF) mRNA levels. Conclusively, HARP seems to have a significant effect on tumor growth and angiogenesis induced by C6 glioma cells.

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