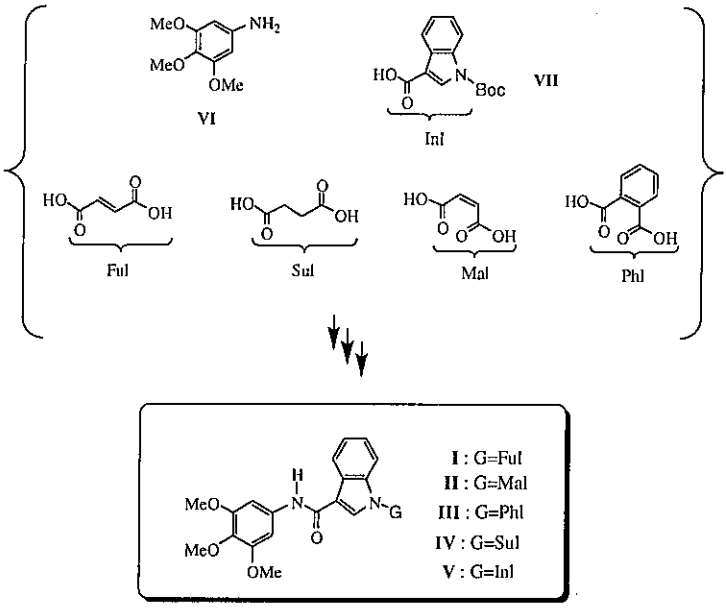
No 43

Synthetic Studies Towards the Development of a Novel Class of Analogs of the Pharmacologically Important Retinoid Acitretin

G. Magoulas and D. Papaioannou
Department of Chemistry, University of Patras, Greece

The novel acitretin-type retinoids *I-V* have been obtained by combining, in liquid or on solid phase, 3,4,5-trimethoxyaniline (*VI*), *N*-Boc-protected indole-3-carboxylic acid (*VII*) and suitable derivatives of the dicarboxylic acids fumaric, succinic, maleic and phthalic.



No 44

New synthetic Analogues of Oxytocin with Modifications in the *C*-terminal Region: Structure-Activity Relationships

G. Papageorgiou[1], M. Fragiadaki[1], G. Pairas[1], V. Magafa[1], J. Slaninová[2] and P. Cordopatis[1]
[1]Department of Pharmacy, University of Patras, GR-26504, Patras, Greece; [2]Department of Peptide Biochemistry, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of Czech Republic, Flemingovo square 2, Prague 6, CZ-166-10, Czech Republic

Oxytocin (OT), is a cyclic nonapeptide that is structurally similar to vasopressin, differing by only two amino acids. It is synthesized as a larger precursor molecule in cell bodies of the paraventricular nucleus and to a lesser extent, the supraoptic nucleus in the hypothalamus. The precursor is rapidly broken down to the active hormone and its neyrophysin, by proteolysis, packaged into secretory granules, as an oxytocin-neyrophysin complex and secreted from nerve endings, that terminate primarily in the posterior pituitary gland (neyrohypophysis). In addition, oxytocin-ergic neurons that

are known to regulate the autonomic nervous system, project to regions of the hypothalamus, brainstem and spinal cord. Oxytocin stimulates, both, the frequency and force of uterine contractions. Furthermore, is involved in several physiological functions, as milk ejection, vascular and cardiac relaxation and it seems that Oxytocin plays a role in sexual, maternal and social behavior. Hundreds of synthetic oxytocin anlogues have been the subject of extensive pharmacological investigations.

The design of OT antagonists has been mainly based on data from structure-activity studies. Observations in bibliography suggested that the *C*-terminal tripeptide sequence and especially the proper orientation of the *C*-terminal glycine carboxamide appears to be critical for obtaining oxytocin analogues with high potency. Furthermore, the configuration and the hydrophobicity of the aromatic amino acid in position 2 are important for the antagonistic activity. On the basis of these findings, we set out the synthesis of new oxytocin analogues containing mercapto-propionic- acid (Mpa) in position 1, D-Tyr(OEt)-OH and D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic-acid (D-Tic) in position 2, the α-helix inducing amino acid 2-aminoisobutyric-acid (Aib) in positions 7 and 9 and D or L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic-acid (Tic) in position 7.

The analogues were synthesized by Fmoc/Bu^t solid phase methodology utilizing a 2-chlorotrityl-chloride resin as solid support bearing a Rink-Bernatowitz linker to provide the peptide amide. Electro-spray MS was in agreement with the expected results. From the preliminary biological assays the new analogues were characterized as antagonists.

No 45

Synthesis and Characterization of the Gallium(III) Complex of a Bleomycin Analogue, with Potential Antitumor Activity

Manessi[1], I. Chadjistamatis[1], C. Raptopoulou[2] and T. Zafiropoulos[1]
[1]Department of chemistry, University of Patras, Patra, Greece; [2]Materials Science, National Center for Scientific Research *Demokritos*, Athens, Greece

The bleomycins (BLMs) comprise a family of glycopeptide antitumor antibiotics that act by damaging DNA through formation of an activated complex of bleomycin, Fe(III) and oxygen. When "activated BLM" initiates DNA degradation, H_4' is removed from deoxyribose and C_4' is exposed to attack by endogenous O_2. "Activated BLM" can be formed from bleomycin, Fe(II) and O_2 as well as through routes involving Fe(III) and peroxides or superoxide. Since gallium(III) resembles iron(III) in certain respects (e.g., ionic radii: 62 and 65 ppm respectively) and since gallium salts have shown antitumor activity, the Ga^{III}-BLM complex could also have similar activity. The Ga(III) complex of a designed ligand LH_2, N-(2-(4-imidazolyl)ethyl)pyridine-2-carboxamide, that mimics the metal-binding portion of bleomycin has been isolated and characterized by spectroscopic techniques. Reaction of the peptide ligand LH_2 with $(Et_4N)[GaCl_4]$ in ethanol affords the gallium (III) complex $[Ga(LH)_2]Cl{\cdot}2H_2O$, which will be tested for its activity in tumor cells.

No 46

Solid Phase Synthesis of Peptide C-Terminal Thioesters by Fmoc-*t*Bu Chemistry for Application in Native Chemical Ligation

S. Goulas and D. Gatos
Department of Chemistry, University of Patras, Greece

Peptide C-terminal thioesters are key intermediates in a variety of applications, most notably the recently developed native chemical ligation method. The technique of native chemical ligation has enabled the total chemical synthesis of proteins with molecular weights far in excess of those achievable by SPPS and convergent peptide synthesis. The method involves the conden-

sation of two unprotected peptide segments, one bearing a C-terminal thioester and the other an N-terminal cysteine residue, to afford a protein with a native amide linkage at the site of ligation. So far thioesters have been prepared mostly by the use of the least prevalent Boc/Bzl method. We report here a novel method for the solid phase synthesis of thioesters by Fmoc/tBu method.

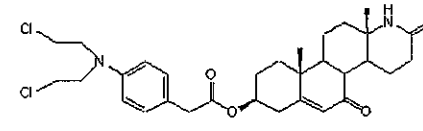
No 47

A Study of the Conformational Properties of 3β-hydroxy-17α-aza-D-homo-5-androsten-7,17-dione-4-N,N-bis(2-chloroethyl)amino-phenylacetate and its Thermal Effects on Membrane Bilayers

A. Kapou[1,2], T. Mavromoustakos[2], S. Golic[3] and S. Nikolaropoulos[1]

[1]Laboratory of Pharmaceutical Chemistry, Department of Pharmacy, University of Patras, Greece; [2]Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, Athens, Greece; [3]National Institute of Chemistry, Ljubljana, Slovenia

3β-hydroxy-17α-aza-D-homo-5-androsten-7,17-dione-4-N,N-bis (2-chloroethyl) amino-phenylacetate (*I*) belongs to a category of promising candidate anticancer compounds. Compound *I* combines a steroidal with an alkylating pharmacophore segment and it has proved highly effective in several *in vitro* and *in vivo* experiments that simulate leukaemia in humans, producing less toxicity than the corresponding alkylating agent alone. Aiming to explore the mechanism of action of *I* and its analogs, we studied two major parameters that designate the action of drugs; (i) physicochemical parameters that govern drug-membrane interactions and (ii) stereoelectronic parameters that govern pharmacophore properties. *Differencial Scanning Calorimetry* (*DSC*) is the method of choice to study the thermal effects of different compounds on model lipoidal bilayers, comprising a biological membrane permeability model. Thus, we conducted several DSC experiments on *I* and its synthetic precursors and we propose a physicochemical explanation for the increased activity of *I* when compared to 4-N,N-bis(2-chloroethyl) aminophenylacetic acid. The dependence of anticancer activity on the structural features of such compounds can be studied with the use of Structure-Activity Relationships (QSAR, classical or 3D). Aiming to develop a 3D-QSAR model in the near future, we proceeded to the conformational analysis of *I* using *2D-NMR* and *Molecular Modeling*. The proposed conformation(s) will be used as conformation-template(s) for the analysis of a series of *I*'s congeners by means of 3D-QSAR.



No 48

a_2-Adrenergic Receptors (AR) Activate MAPK in Renal Proximal Tubule Cells

O.K. Mastrogianni, A. Lymperopoulos, S. Taraviras and C. Flordellis

Dept. of Pharmacology, Medical School, University of Patras, Greece

a_2 ARs are an eterogenous class of receptors comprising 3 subtypes (a_{2a}, a_{2b}, a_{2c}) encoded by distinct genes and having different pharmacological properties, chromosomal localization, tissue distribution and possibly signal transduction properties. All 3 subtypes had been found to be expressed in the human and rat kidney but their

precise expression and their specific physiological role in renal function remains unclear.

The a_{2b} subtype specifically, which is expressed principally in the proximal tubular cells, had been demonstrated to be of great importance for the mediation of the regulatory actions of catecholamines on gleomerular filtration and Na^+ and water excrission and renin release.

The proximal tubule stimulation of a_2 ARs increases Na^+/HCO_3^- reabsorption by activating the Na^+/H^+ exchangion type 3 isoform which is expressed in the brush border membrane of the tubular cells. Furthermore, reabsorption of di/tripeptides in the proximal tubule is controlled by two systems of transport PEPT-1 and PEPT-2.

Recent studies in some epithelial cellular systems expressing these transporters have shown that stimulation of a_2 ARs activates transepithelial transport of antibiotics by PEPT-1. The purpose of the present research project is to investigate the mechanism by which a_2 ARs activates these transport systems. To this, we have been using LLC-PK1 cells permanently cotransfected with the a_{2b} human AR and the transporter PEPT-1 or PEPT-2. Ligand binding experiment had shown substantional level of expression (1pmol/mg of proteins). As a first step, we have been investigating the activation of MAPK activity by a_2ARs. Stimulation of these cells by UK 14.304 caused an increased ERK1/2 phosphorylation which correlated with enhanced MAPK activity and nuclear translocation. MAPK activation was inhibited by pertussis toxin and partially by pretreatment of the cells with the PI3kinase inhibitor LY 294002. Additional studies will be necessary to clarify the role of MAPK stimulation in the activation of the transporters PEPT-1 and PEPT-2, given the pharmacological importance of these two molecules as they are responsible for the reabsorption of a series of drugs, including β-lactam antibiotics and iostatic molecules like AZT.

No 49

Structural Studies and Sequence Homology Investigations of Agonist and Antagonist Peptides of the Guinea Pig Myelin Basic Protein (MBP) Epitope 74-85: Implication for Structure-Function Relationships

A.G. Tzakos[1], P. Fuchs[2], N.A.J. van Nuland[2], A. Troganis[3], T. Tselios[4], S. Deraos[4], J. Matsoukas[4], I.P. Gerothanassis[1] and A.M.J.J. Bonvin[2]

[1]Department of Chemistry, Section of Organic Chemistry and Biochemistry, University of Ioannina, Ioannina GR-45110, Greece; [2]Bijvoet Center for Biomolecular Research, Department of NMR Spectroscopy, Padualaan 8, 3584 CH Utrecht, the Netherlands; [3]Department of Biological Applications and Technologies, University of Ioannina, GR-45110, Greece; [4]Department of Chemistry, University of Patras, Patras 265 00, Greece

Experimental autoimmune encephalomyelitis (EAE), an animal model of Multiple Sclerosis, is induced in susceptible animals by immunodominant determinants of myelin basic protein (MBP) (1). In order to characterize the molecular features of antigenic sites, which are important for designing EAE suppressing molecules, we report structural studies, based on NMR experimental data in conjunction with molecular dynamic simulations, of the potent linear dodecapeptide epitope of the guinea pig MBP, Gln^{74}-Lys^{75}-Ser^{76}-Gln^{77}-Arg^{78}-Ser^{79}-Gln^{80}-Asp^{81}-Glu^{82}-Asn^{83}-Pro^{84}-Val^{85} (MBP_{74-85}), and its antagonist analogue $Ala^{81}MBP_{74-85}$ (2). The two peptides, exhibit significantly different side-chain and backbone conformations in both H_2O and DMSO solutions. The agonist MBP_{74-85} adopts a compact conformation due to electrostatic interactions of Arg^{78} with the side-chains of Asp^{81} and Glu^{82}. Arg^{78} is, therefore, "locked" in a well-defined conformation, perpendicular to the peptide backbone that is easily accessible for the action of enzymes (3). These electrostatic interactions are, however, absent in the case of the antagonist Ala^{81} MBP_{74-85}, resulting in a high flexibility of the side-chain of Arg^{78}. Sequence alignment of the two analogues with several species of MBP suggests the critical role for the positively charged residue Arg^{78}, first, in the stabilization of the local microdomains (epitopes) of the integral protein; second, in a number of post-translational

modifications relevant to multiple sclerosis, such as the conversion of charged arginine residues to uncharged citruline; third, in the formation of the trimolecular T-cell receptor (TCR) –MBP_{74-85} –MHC II complex (3).

1. Tompkins T.A., Moscarello M.A.: *Arch. Biochem. Biophys. 302*: 476-483 (1993)
2. Tselios T., Probert L., Daliani I., Matsoukas E., Troganis A., Gerothanassis I.P., Mavromoustakos T., Moore G.J., Matsoukas J.M.: *J. Med. Chem. 42*: 1170-1177 (1999)
3. Tzakos A., Fuchs P., van Nuland N, Troganis A., Tselios T., Deraos S., Matsoukas J., Gerothanassis I. and Bonvin A., *J. Med. Chem., submitted., 2003*

No 50

Interactions of the Toxin Paralysin β-Ala-Tyr with Phospholipid Bilayers

I. Kyrikou[1,2], C. Poulos[2] and T. Mavromoustakos[1]

[1]Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, Vas. Constantinou 48, Athens 11635, Greece; [2]Department of Chemistry, University of Patras, GR-26500, Patras, Greece

A toxin from the larvae of the gray flesh fly Neobelleria Bullata (i.e. paralysin β-Ala-Tyr) is known to have biological activity. Since it causes reduced locomotory activity, paralysis and fast death, it is suggested that it acts on the nervous system. It is also hypothesized that paralysins interfere with some neurotransmitter receptors with drastic changes in bio-electrical activity as a result. Because the interactions of both the β-Ala-Tyr and glutamate have the same effect on the nervous system it is believed that both bind onto the same receptor, the metabotropic Glu-receptor, and that the dipeptide is an antagonist. To examine if β-Ala-Tyr affects membrane bilayers we applied a combination of DSC and solid state NMR spectroscopy. Such studies may propose if the dipeptide favors extracellular versus intracellular action on the receptor. It will also shed some light on the role of the membrane in the dipeptide: receptor interactions.

No 51

Design and Synthesis of Linear and Cyclic Analogues of Human Myelin Basic Protein mbp_{87-99} Epitope: Stability and HLA-binding Studies

G. Deraos[1], T. Tselios[1], S. Deraos[1], H. Kalbacher[2] and J. Matsoukas[1]

[1]Department of Chemistry, University of Patras, 26500 Patras, Greece; [2]Department of Biochemistry, University of Tübingen, Germany

Multiple sclerosis (MS) is a chronic specific CD4+T-cell mediated disease of the central nervous system (CNS) characterized by local T cell and macrophage infiltrates, demyelination and loss of neurologic function [1-3]. Susceptibility to multiple sclerosis (MS) is associated with certain MHC class II haplotypes, including HLA-DR2. Two DRB chains, DRB5*0101 and DRB1*1501, are co-expressed in the HLA-DR2 haplotype, resulting in the formation of two functional cell surface heterodimers, HLA-DR2a (DRA*0101, DRB5*0101) and HLA-DR2b (DRA*0101, DRB1*1501). Both isotypes can present an immunodominant peptide of myelin basic protein (MBP 84-102) to MBPspecific T cells from MS patients [4,5]. Candidate autoantigens include constituents of the myelin sheath such as Myelin Basic Protein (MBP) and Proteolipid Protein (PLP). Modern approaches towards the therapeutical management of MS involve the design and use of peptide analogues of disease-associated myelin epitopes to induce peripheral T cell tolerance.

In the present report, we designed and synthesized a linear [Ala^{91}, Ala^{96}] MBP_{87-99} and a cyclic peptide analogue cyclo(87-99) [Ala^{91}, Ala^{96}] MBP_{87-99} based on the human myelin basic protein epitope (MBP_{87-99}) (Val^{87}-His-Phe-Phe-Lys^{91}-Asn-Ile-Val-Thr-Pro^{96}-Arg-Thr-Pro^{99}) [6]. Structure-activity studies have shown that Lys^{91} and Pro^{96} residues are important for encephalitogenicity. These analogues were tested for their

resistance to hydrolysis using Proteases such as Cathepsin D, AEP, Lysosomal fraction. Furthermore, the analogues were tested for HLA-alleles binding using HLA-DR2, DR4. Cyclic analogue cyclo(87-99) [Ala^{91}, Ala^{96}] MBP_{87-99} was stable in proteases like Cathepsin D, AEP, Lysosomal fraction and binding assays demonstrate the very good binding in HLA-DR2 and HLA-DR4 alleles. As a control we used linear MBP_{83-99} epitope [7].

References

1. Martin R., McFarland H., and McFarlin D.: Immunological aspects of demyelinating diseases. *Ann. Rev. Immunol. 10*: 153-187 (1992)
2. Steinman L.: 1996. Multiple sclerosis: a coordinated immunological attack against myelin in the central nervous system. *Cell 85*: 299-302 (1996)
3. Hafler D.A., Weiner H.L.: Immunologic mechanisms and therapy in multiple sclerosis. *Immunol. Rev. 144*: 75-107 (1995)
4. Spielman R.S., Nathenson N.: The genetics of susceptibility to multiple sclerosis. *Epidemiol. Rev. 4*: 45 (1982)
5. Hillert J., Kall T., Vrethem M., Fredrikson S., Ohlson M., Olerup O.: The HLA-Dw2 haplotype segregates closely with multiple sclerosis in multiplex families. *J. Neuroimmunol. 50*: 95 (1994)
6. Tselios T., Apostolopoulos V., Daliani I., Deraos S., Grdadolnik S., Mavromoustakos T., Melachrinou M., Thymianou S., Probert L., Mouzaki A., Matsoukas J.: Antagonistic effects of human cyclic MBP(87-99) altered peptide ligands in experimental allergic encephalomyelitis and human T-cell proliferation. *J. Med. Chem.* 45: 275-283 (2002)
7. Beck H., Schwarz G., Schroter C.J., Deeg M., Baier D., Stevanovic S., Weber E., Driessen C., Kalbacher H., Cathepsin S.: An asparagine-specific endoprotease dominate the proteolytic processing of human myelin basic protein in vitro. *Eur. J. Immunol.* : 3726-36 (2001)

No 52

Total Syntheses of Crowned Polyamines from Simple, Commercially Available, Building Blocks

N. Tsiakopoulos and D. Papaioannou
Department of Chemistry, University of Patras, Greece

Total syntheses of crown ethers bearing polyamine moieties, e.g *I-III*, have been effected using commercially available linear amino acids, like β-alanine (*βAla*) and γ-aminobutyric acid (*γAba*), epichlorohydrin (*EPH*) and polyethylene glycols, e.g. DEG and TREG, as building blocks.

No 53

Design and Synthesis of New Analogues of Leuprolide

A. Zompra, G.A. Spyroulias, V. Magafa, G. Pairas and P. Cordopatis
Department of Pharmacy, University of Patras, GR-26504 Patras, Hellas

The hypothalamic Luteinizing Hormone-Releasing Hormone (LHRH) (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2) plays a central role in the biology of reproduction and synthetic LHRH analogues have been proven valuable in the treatment of a wide variety of endocrinological and nonendocrinological disorders. Agonistic analogues of LHRH, represented by Leuprolide ([$DLeu^6$, $desGly^{10}$]-LHRH-ethylamide), have been widely used in oncology and gynaecology for nearly two decades. In this study, we report an improved synthesis of new analogues of LHRH and we present the conformational analysis in solution of the (i) LHRH, (ii) Leuprolide and (iii) an analogue namely [Aib^6, $desGly^{10}$]-LHRH-NHEt. Studies performed in order to gain valuable insights on bioactive conformation and use these for the design of new analogues. The structural criteria for the synthesis of the new analogues of LHRH were on the basis that most of the superagonists usually incorporate a D-amino acid substituting for Gly in position 6 and an *N*-ethylamide instead of the terminal Gly-NH_2 in position 10 (Fujino modification). These chemical modifications decrease the susceptibility of the peptide to proteolytic degradation and lead to peptides with high binding affinity to the receptor of LHRH. Additionally, according to NMR experiments and physicochemical studies, these engineered changes enhance the bioactive β-turn conformation at the region Tyr^5–Gly^6–Leu^7–Arg^8 of LHRH. The synthesized analogues of LHRH bear the Fujino modification while Gly^6 has been also substituted by α,α-dialkyl amino acids. Peptide synthesis has been performed through solid phase chemistry on a [3-((Ethyl-Fmoc-amino)-methyl)-1-

indol-1-yl]-acetyl AM resin via Fmoc/^{t}Bu methodology. Conformational analysis has been performed using NMR spectroscopy and structural Molecular Dynamics. Refinement of structural models has been achieved through energy minimization of the calculated structures. After analyses of peptides conformation, the tendency of molecules to form a *U*-shape fold it is revealed.

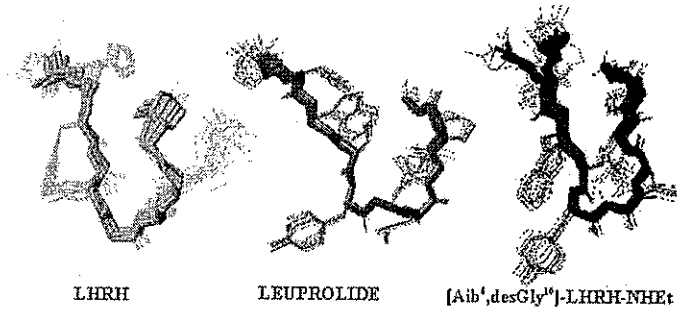


Figure 1. The best 20 models for the LHRH (left), Leuprolide (center) and [Aib^6, desGly^{10}]-LHRH-NHEt (right).

No 54

Production of Egg–Yolk (Polyclonal) Antibodies to the Phenyl n–Methylcarbamate Group of Pesticides in order to Immobilize them into Immunoaffinity Columns

K. Prousalis and T. Tsegenidis
Department of Chemistry, University of Patras, Greece

A great number of considerably efficient analytical and clean–up procedures, based on monoclonal or polyclonal antibodies, have been developed in the field of pesticide residue analysis, in the last twenty years. ELISA is considered to be a very powerful tool for the simple and fast determination of selected pesticides, in complex matrices. Biosensors are small, easy to carry equipments, containing antibodies to organic pollutants. A lot of biosensors have been constructed for in-field, instant concentration measurements, of toxic agrochemicals, especially in waters (rivers etc). Immunosorbent materials consist of antibodies immobilized on an appropriate support material (commonly CNBr activated Sepharose). Columns or cartridges, filled with immunosorbents, are widely used for the selective clean - up of extracts containing pesticide residues, prior to chromatographic determination. A common immunoaffinity clean-up procedure involves three basic steps:

(i) loading the extract containing the analyte onto the column, the compound of interest is retained on the solid-phase,

(ii) washing the column (usually with water), all interfering substances are removed from the column,

(iii) elution with small volume of suitable solvent or buffer, the analyte is quantitevely recovered in a solution ready for instrumental analysis.

The aim of this work is the production of IgY (egg–yolk) antibodies to a group of widely used pesticides: the N–methylcarbamates. Haptens and their BSA conjugates are being synthesized. The immunization of laying–hens by those conjugates will lead to the production of specific polyclonal antibodies. The latter will be isolated from the yolk of the eggs and separated into various groups using immunoaffinity chromatography. Their affinity towards selected carbamates will be tested. Those who exhibit high selectivity to the analytes will be immobilized to suitable solid – phases, so as to form immunosorbents.

IgY technology is non invasive by means of collecting eggs instead of bleeding an animal in order to isolate the immunoglobulins out of its serum. The fact that it lessens the pain of animals should be a reason enough for adopting it. Moreover, this technology has lower cost, is much more simpler and offers large quantities of polyclonal antibodies compared to IgG antibody production by rabbits or sheeps.

No 55

Novel Hybrid Imidazole-based Compounds Against Hypertension and Other Cardiovascular Diseases

N. Giatas[1], P. Roumelioti[1], A. Zoga[2], M. Anastasopoulou[1], D. Vlahakos[2] and J. Matsoukas[1]

[1]Department of Chemistry, University of Patras, Patra, Greece; [2]Onassis Cardiac Surgery Center, Athens, Greece

Hypertension is a common disease and a known risk factor for ischemic heart disease, stroke, peripheral vascular disease, retinopathy and renal failure. There are 2 major neurohormonal systems that regulate cardiovascular function, including smooth muscle tone: the renin-angiotensin system (RAS) and the sympathetic nervous system (SNS). The most recent class of RAS blockers is the non-peptide AII receptor antagonists that have been developed and found in clinical trials to be effective and very well tolerated. This is an important issue because by improving compliance a much higher percentage of hypertensive patients could achieve good blood pressure control and decrease the risk for cardiovascular and renal complications. There are 2 major components involved in SNS function: vasomotor neurons, which regulate vascular resistance, and lumbosacral neurons, which modulate lower urinary tract outlet resistance. Almost all vasomotor nerves are adrenergic. Alpha 1 adrenergic blockers, alpha 2 adrenergic agonists and beta blockers are widely used in the treatment of high blood pressure, certain irregular heart rhythms, chest pain associated with insufficient oxygen delivery to the heart and heart failure. Novel, potent, non-peptide hybrid compounds have been synthesized in our laboratory combining the most important pharmacological characteristics of both the AT1 antagonists and the SNS suppressants. The synthetic strategy involves a new, novel and high-yield method. The synthesized compounds could selectively block angiotensin II and at the same time act as SNS suppressants. These novel compounds are proprietary new drugs, which have potential applications in the treatment of hypertension, congestive heart failure, diabetic nephropathy and other cardiovascular diseases.