

Peptides in Łódź

(story about fascination of unnatural
amino-acids)

Zbigniew J. Kamiński
Institute of Organic Chemistry
Łódź University of Technology

Polish Peptide Symposium
Jastrzębia Góra 3-7 Sept. 2017

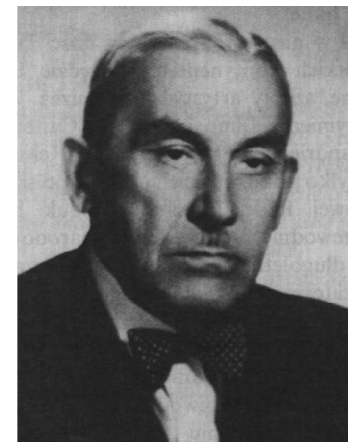
ZJK1
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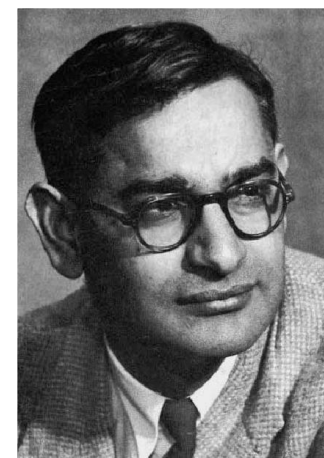
Prof. Mirosław Leplawy

Prof. George W. Kenner

Prof. Jan Michalski



Prof. Osman Achmatowicz



Prof. Gobind Khorana

Slajd 2

- ZJK2** To fill the gap, prof O. Achmatowicz arranged post-doc position to bright minded scientist dr Jan Michalski in Cambridge in the group of His good friend prof. Gobind Khorana to participate in the project focused on how nucleic acid base are coding sequences of amino-acids.
ZJK; 2017-11-13
- ZJK3** Prof. J. Michalski, after coming back to Lodz started research on nucleic acids, so in order to ignite research on peptides, the next young, bright scientist, dr Mirosław T. Leplawey, was sent to England, this time to Liverpool, to prof. George Wallace Kenner, the peptide offspring of Khorana group.
ZJK; 2017-11-22
- ZJK4** The Kenners doubts was as follow: "OK, if triplet of nucleic bases are coding sequence of proteinogenic amino-acids, so what about unnatural amino-acids which are identified in natural products? Could we synthesize proteins with unnatural amino-acids residues?
ZJK; 2017-11-13
- ZJK5** And dr M.T.Leplawy starting His research in Liverpool presented that synthesis of peptides from unnatural amino-acids is possible.Difficult task but affordable in experienced hands.

ZJK; 2017-11-22
- ZJK1** Story begin when Prof Osman Achmatowicz (Dean of Faculty of Chemistry) realized that nucleic acids and peptides are emerging area of organic chemistry, but in Poland without tradition and basic experience .
ZJK; 2017-11-13



Polish Visitor Wears Mr. Bisset's Kilt!

NOT a member of the Celtic Congress but a Polish Chemistry graduate. Dr. Thomas Leplawy, of Lodz, Poland, undertaking research at Liverpool University was one of 14 foreign students invited to the Island for the Easter vacation by the Douglas Rotary Club.

The Dr. was staying with the Rev. J. Duffield, M.A., at the Vicarage, Onchan, along with a Dutch student Hans Kortegaas who is studying economics. The reason for the Dr.'s Highland apparel is that during the holiday he and Mr. Kortegaas were entertained by Rotarian A. R. Bisset, a staunch Scot. Dr. Leplawy was fascinated by Mr. Bisset's regalia and it was an extra treat when he was invited to don the outfit . . . which he kept on for the remainder of the day!



Slajd 3

ZJK6

The post-doc from the other side of iron-curtain was a surprise and a hot news presented in a local media. Nevertheless, polish guest was treated with a little bit nonchalance until... as dr. Lepawy mentioned...they learned that I am better tennis player then all my colleges. This teach them respect also to my research.

ZJK; 2017-11-13

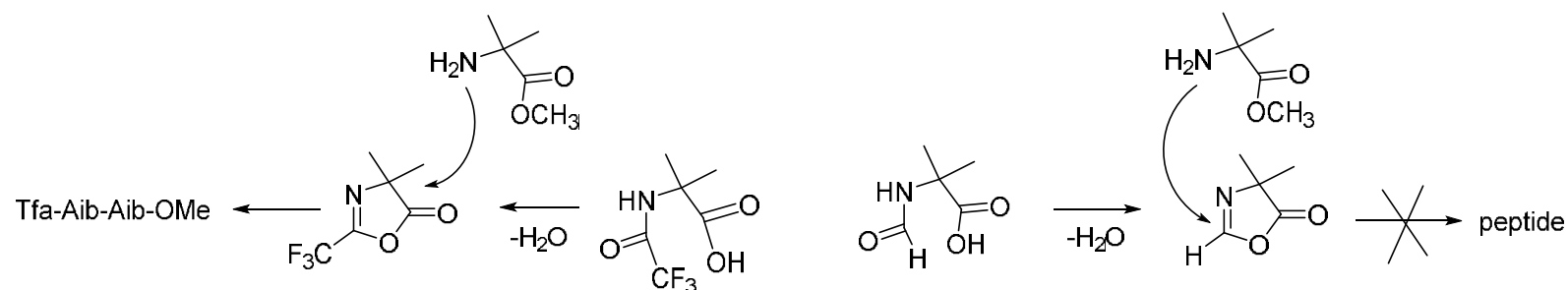


Peptides—XI: Synthesis of peptides derived from alpha-methylalanine

M.T. Leplawy ¹, D.S. Jones, G.W. Kenner, R.C. Sheppard

Abstract

Union of α -methylalanyl residues in a peptide chain is severely sterically hindered. This hindrance can be overcome by employing either the mixed anhydride (I) of pivalic acid and benzyloxycarbonyl- α -methylalanine or, more generally, oxazolones (II), including 4,4-dimethyl-2-trifluoromethyloxazolone (II; R = CF₃). 4,4-Dimethyloxazolone (II; R = H) has been obtained in solution and characterized by its infra-red spectrum; it is attacked by α -methylalanine methyl ester at the methine group, in contrast to the normal reaction with cyclohexylamine at the carbonyl group.

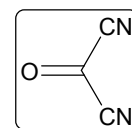
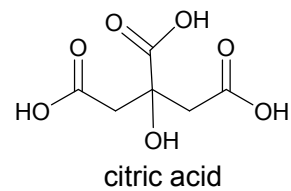
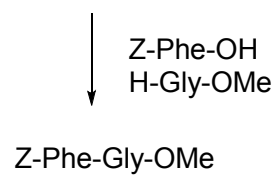
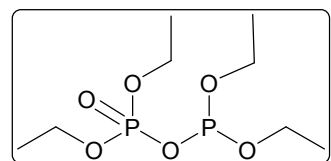


Slajd 4

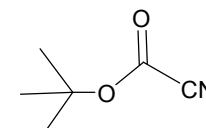
ZJK7

And indeed, dr Leplawy correctly diagnosed and resolved the crucial synthetic problem caused by steric hindrance typical for incorporation of α,α -disubstituted amino-acid into the peptide chain. The manuscript published in Tetrahedron, presenting His research results became one of the most often cited classic papers dedicated to Aib peptides. Of course, dr Leplawy come back to Poland infected with this strange disease -fascination to unnatural objects.

ZJK; 2017-11-22



carbonyl cyanide



M. Leplawy, W. Stec. *Acad. Polon. Ser. Sci. Chim* **1964**, (12), 21.

PhD Thesis: J. Zabrocki.
 New methods in peptide synthesis, **1975**.

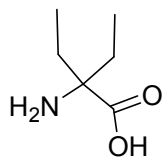
PhD Thesis: K. Kociołek
 Reactions of carbonyl cyanide with ketones, **1975**

Slajd 5

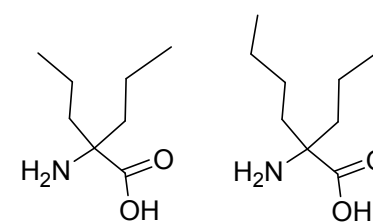
ZJK8

Soon after return of docent M.T. Leplawy to Łódź it has been found that fascination with unnatural amino-acids is infectious and transmittable to PhD students. Thus, even the classic search for the new coupling method based on application of mixed phosphoric acid anhydrides and new protective group focused on the bunch of alfa,alfa-disubstituted amino-acids.

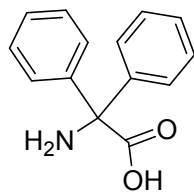
ZJK; 2017-11-13



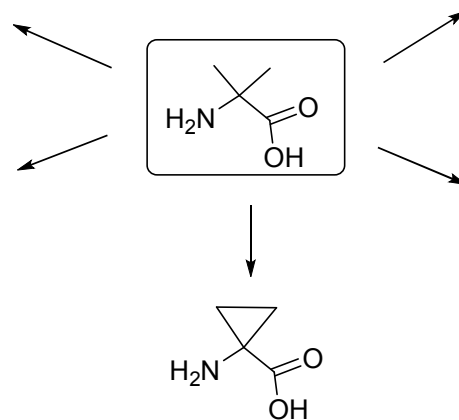
PhD Thesis: **A. S. Redlinski**, Synthesis of peptides derived from α,α -dialkyl- α -aminoacids, **1975**,



PhD Thesis: **K. Kaczmarek**, Chemical, stereochemical and biological consequences of incorporation of α,α -diethylglycine into peptide chain, **1988**



MSc Thesis: **Z. Kaminski**,
An attempts to synthesis of peptides derived from diphenylglycine, **1970**



PhD Thesis: **U. Grzegorzewska**, Aminocycloalkanopenicillines and their activity against selected bacteria strains, **1972**.

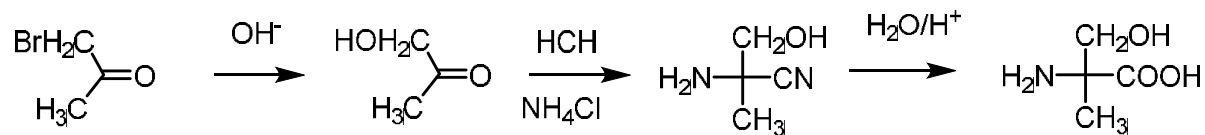
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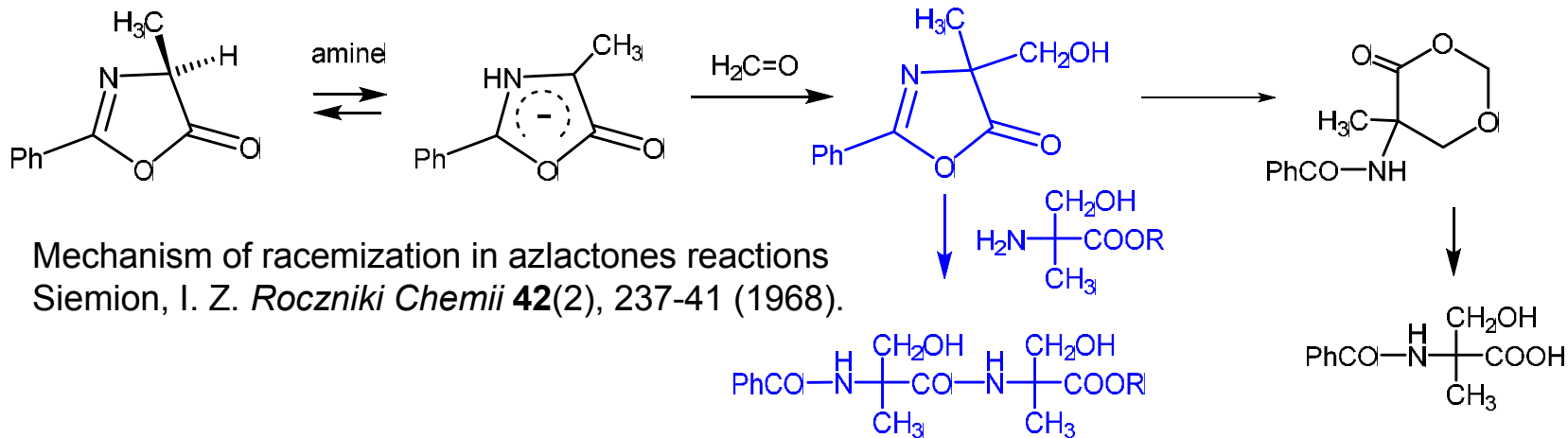
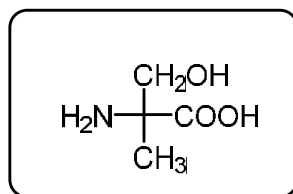
Soon, one by one PhD theses dedicated to linear or cyclic di-substituted amino-acids were successfully finalized. Only MSc Z. Kamiński complained, that it is possible to prepare alpha, alpha-diphenylglycine tetrapeptide by application of Ritter reaction, but according to his opinion there is no future for peptide synthesis in concentrated sulphuric acid. Docent M. T. Leplawy accepted this opinion and proposed the new generation of interesting amino-acids.

ZJK; 2017-11-13

ZJK10
ZJK11
ZJK12



Zielinski N.D; Dengin E| *Chem. Ber.* **55**, 3354 (1922)



Slajd 7

- ZJK10** Fantastic. The proposed alfa-methylserine was sterically hindered (without any doubts), but also chiral and with functional group in the side chain. Of course, it was not commercially available.
ZJK; 2017-11-13
- ZJK11** In the literature there is described by Zelinski and Dengin rather tedious and not very promising approach to alfa-methylserine. But the help came from Wrocław. Prof. I. Z. Siemion reported that oxazolone derived from N-benzoilalanine in the basic media is prone to racemization due to formation of appropriate oxazolone anion. The imagination prompted the next step involving condensation with formaldehyde leading to hydroxymethylated oxazolone (blue printed) and then according to classic method described by M.T. Leplawy to appropriate peptides. Unfortunately, the isolated product was not expected oxazolone, but was identified as 4-oxo-1,3-dioxane.
ZJK; 2017-11-13
- ZJK12** Fortunately, 4-oxo-1,3-dioxane degraded smoothly to alpha-hydroxymethylserine or its N-protected derivatives useful for separation on enantiomere and preparation of building blocks necessary for incorporation of alpha-hydroxymethylserine into the peptide chain.
ZJK; 2017-11-13

DSc: Aleksandra Olma
„Wpływ aminokwasów amfifilowych
na właściwości peptydów biologicznie aktywnych „
(2000) Politechnika Łódzka

PhD: Bartłomiej Koźniewski,
“Enzymatyczny rozdział enancjomerów
pochodnych α -podstawionych seryn”
(2016) Politechnika Łódzka

PhD: Aleksandra Olma
„Synteza α -hydroksymetylo-
aminokwasów oraz ich peptydów„
(1980) Politechnika Łódzka

PhD: Joanna Katarzyńska
“4-Alkilopseudoproliny jako bloki
budulcowe peptydów. Aspekty
syntetyczne i strukturalne”
(2004) Politechnika Łódzka

PhD: Urszula SŁomczyńska
“ α -Hydroksymetylowanie
aminokwasów i peptydów”
(1981) Politechnika Łódzka

PhD: Zbigniew J. Kamiński,
“ α -Hydroksymetylowanie
aminokwasów i peptydów”
(1976) Politechnika Łódzka

PhD: Marcin Stasiak,
“Konsekwencje chemiczne, strukturalne i
biologiczne inkorporacji alfa-
hydroksymetyloseryny w łańcuch peptydowy”
(1999) Politechnika Łódzka

Mechanism of racemization in azlactones reactions
Siemion, Ignacy Z. *Roczniki Chemii* 42(2), 237-41 (1968).

Slajd 8

ZJK13

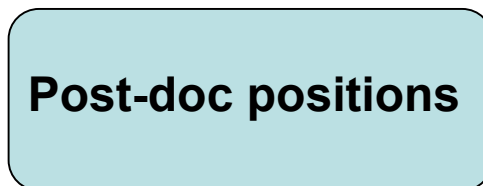
Hydroxymethylation procedure was found general and in hands of skilful chemists was successfully applied in the syntheses of other hydroxymethylated amino-acids. The researches in most cases was honored by PhD or DSc titles.

ZJK; 2017-11-13

prof. **G.R. Marshall**
St. Louis, USA
J. Zabrocki,
K. Kociołek
U Słomczyńska
A. Redliński
K. Kaczmarek
A. Olma
M. Leplawy
T. Leplawy

prof. **M, Mannig**
Toledo, USA
A. Olma

prof. **G. Barany**
Mineapolis, USA
U. Słomczyńska



Prof. **J. Pita**
Baltimore, USA
K. Kociołek

Prof. **G.W. Kenner**
Liverpool, England
Z. Kamiński

Slajd 9

ZJK14

All doctors from Lelawy's group leave Łódź and joined excellent laboratories in USA or England as post-docs.

ZJK; 2017-11-13

ZJK15

„Marshall's Plan” for peptides in Łódź



Slajd 10

ZJK15

The most successful was the so called "Marshall Plan".

Most of peptide chemists got training in St. Luis School of Medicine in laboratory of prof G.R Marshall.

ZJK; 2017-11-13

ZJK16



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ZJK16

Prof. MT Leplawy and dr J. Zabrocki in St Louis,
ZJK; 2017-11-13

ZJK17

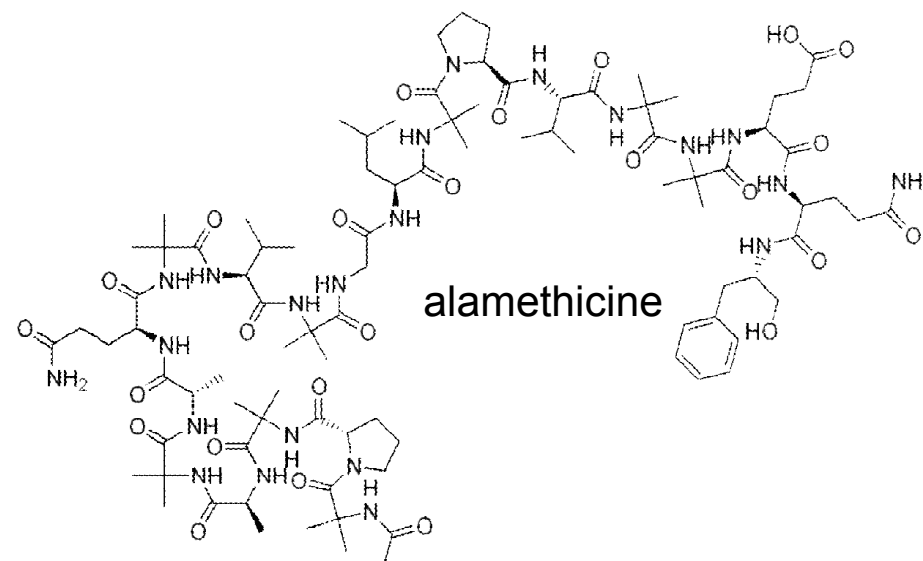


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ZJK17

Picknick in the prof. Marshall's garden.

ZJK; 2017-11-13



Proc. Natl. Acad. Sci. USA
Vol. 87, pp. 487–491, January 1990
Biophysics

Factors governing helical preference of peptides containing multiple α,α -dialkyl amino acids

[α -helix/ α -aminoisobutyric acid (α -methylalanine)/emerimicin/peptaibol/x-ray crystallography]

GARLAND R. MARSHALL*[†], EDWARD E. HODGKIN*, DAVID A. LANGS[‡], G. DAVID SMITH[‡],
JANUSZ ZABROCKI[§], AND MIROSLAW T. LEPLAWY[§]

*Department of Pharmacology, Washington University School of Medicine, Saint Louis, MO 63110; [†]Medical Foundation of Buffalo, Inc., Buffalo, NY 14203; and [§]Institute of Organic Chemistry, Politechnika, 90-924 Lodz, Poland

Communicated by Isabella L. Karle, June 22, 1989 (received for review July 28, 1988)

Slajd 13

ZJK18

Cooperation with prof. G.R. Marshall group was coordinated by dr J. Zabrocki. The most spectacular achievements were synthesis of peptaibol antibiotics, studies of conformational effects caused by two alpha substituents and also studies on surrogates of s-cis conformation of peptide bonds (tetrazole etc).

ZJK; 2017-11-13



Zabrocki, J.; Smith, G.D.; Dunbar, J.B., Jr.; Iijima, H.; Marshall, G.R.
„Conformational mimicry. 1,5-Disubstituted tetrazole ring as a surrogate for the cis amide bond”, *J. Am. Chem. Soc.* (1988), 110(17), 5875-80.

Marshall G R; Clark J D; Dunbar J B Jr; Smith G D; Zabrocki J; Redlinski A S; Leplawy M T
Conformational effects of chiral alpha,alpha-dialkyl amino acids. I. C-terminal tetrapeptides of emerimicin containing alpha-ethylalanine”, *Int. J. Peptide Protein Res.* (1988), 32(6), 544-55.

Slomczynska, U.; Zabrocki, J.; Kaczmarek, K.; Leplawy, M.T.; Beusen, D.D.; Marshall, G.R.
„Facilitated synthesis of peptaibols: alamethicin via enzymic segment condensation”
Biopolymers (1992), 32(11), 1461-70.

Slomczynska, U.; Beusen, D.D.; Zabrocki, J.; Kociolek, K.; Redlinski, A.; Reusser, F.; Hutton, W.C.;
Leplawy, M.T.; Marshall, G.R. „Emerimicins III and IV and their ethylalanine¹² epimers. Facilitated
chemical-enzymatic synthesis and a qualitative evaluation of their solution structures”
J. Am. Chem. Soc. (1992), 114(11), 4095-106.

Zabrocki, J.; Dunbar, J.B., Jr.; Marshall, K.W.; Toth, M.V.; Marshall, G.R.
„Conformational mimicry. Synthesis and incorporation of 1,5-disubstituted tetrazole dipeptide analogs
into peptides with preservation of chiral integrity: bradykinin”, *J.Org.Chem.* (1992), 57(1), 202-9.

Beusen D D; Zabrocki J; Slomczynska U; Head R D; Kao J L; Marshall G R
„Conformational mimicry: synthesis and solution conformation of a cyclic somatostatin hexapeptide
containing a tetrazole cis amide bond surrogate”, *Biopolymers* (1995), 36(2), 181-200.

Slajd 14

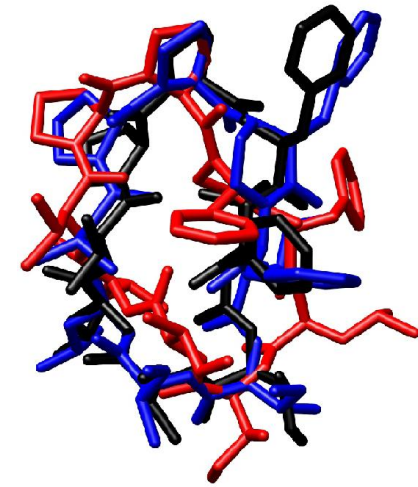
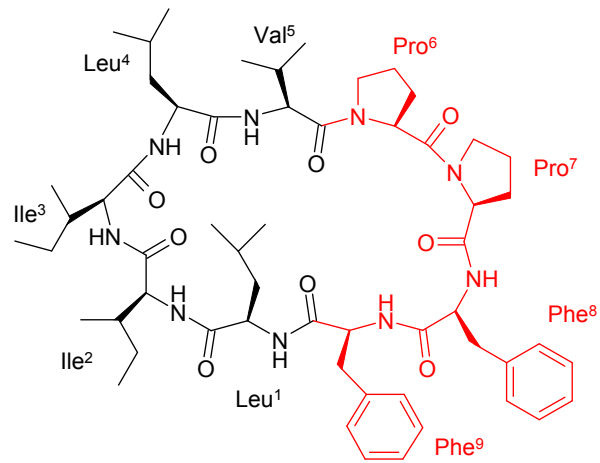
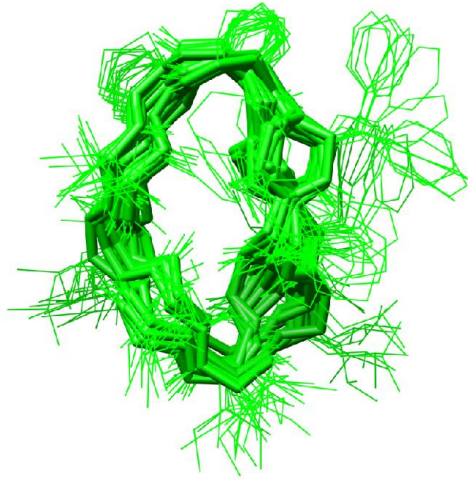
ZJK19

Finally, cooperation gave several valuable publications presented in excellent journals.

ZJK; 2017-11-22

ZJK27

Cyclolinopeptid A



Slajd 15

ZJK27

As well as inspiration to the new research areas.

ZJK; 2017-11-21



SCIENTIFIC REPORTS

OPEN

Ligand selectivity in tachykinin and natalisin neuropeptidergic systems of the honey bee parasitic mite *Varroa destructor*

Received: 17 August 2015
Accepted: 13 November 2015
Published: 28 January 2016

Hongbo Jiang^{1,2}, Donghun Kim¹, Sharon Dobesh¹, Jay D. Evans³, Ronald J. Nachman⁴, Krzysztof Kaczmarek^{4,5}, Janusz Zabrocki^{4,5} & Yoonseong Park¹

The varroa mite, *Varroa destructor*, is a devastating ectoparasite of the honey bees *Apis mellifera* and *A. cerana*. Control of these mites in beehives is a challenge in part due to the lack of toxic agents that are specific to mites and not to the host honey bee. In searching for a specific toxic target of varroa mites, we investigated two closely related neuropeptidergic systems, tachykinin-related peptide (TRP) and natalisin (NTL), and their respective receptors. Honey bees lack both NTL and the NTL receptor in their genome sequences, providing the rationale for investigating these receptors to understand their specificities to various ligands. We characterized the receptors for NTL and TRP of *V. destructor* (VdNTL-R and VdTRP-R, respectively) and for TRP of *A. mellifera* (AmTRP-R) in a heterologous reporter assay system to determine the activities of various ligands including TRP/NTL peptides and peptidomimetics. Although we found that AmTRP-R is highly promiscuous, activated by various ligands including two VdNTL peptides when a total of 36 ligands were tested, we serendipitously found that peptides carrying the C-terminal motif -FWxxRamide are highly specific to VdTRP-R. This motif can serve as a seed sequence for designing a VdTRP-R-specific agonist.

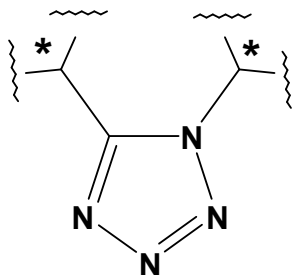
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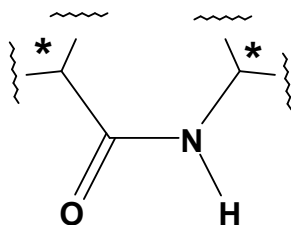
As well as inspiration to the research in still other areas in cooperation with prof. R.J. Nachman.

ZJK; 2017-11-22

Cis peptide bond surrogate

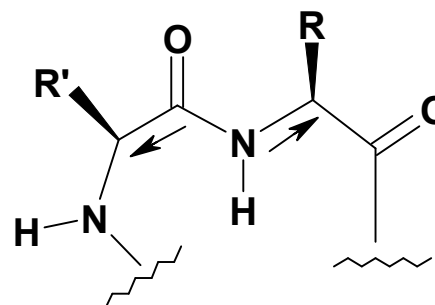
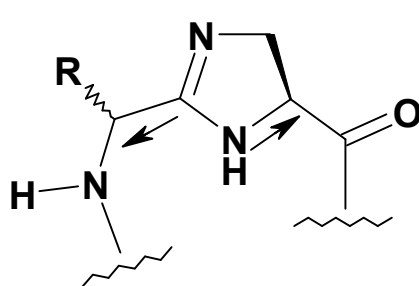


TETRAZOLE



4-AMINOPYROGLUTAMIC ACID

Trans peptide bond surrogate



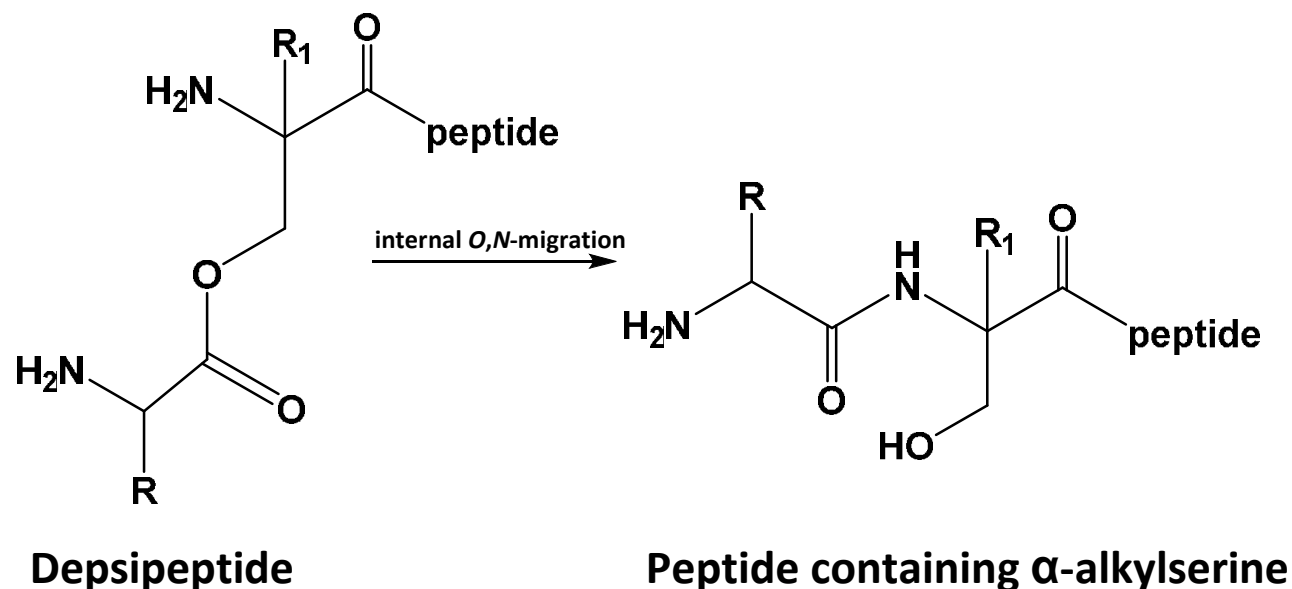
Slajd 17

ZJK28

including modification of the peptide bond.

ZJK; 2017-11-21

O-ACYL ISOPEPTIDE METHOD IN PEPTIDE SYNTHESIS



BIVALENT LIGANDS OF OPIOID RECEPTORS, ANALOGS OF BIPHALIN AND DIMERIC DERMORPHIN ANALOGS CONTAINING AMPHIPHILIC α -ALKYLSERINES OR β^3 -HOMO-AMINO ACIDS

Frączak O, Lasota A, Leśniak A., Lipkowski A.W, **Olma A.** The biological consequences of replacing D-Ala in biphalin with amphiphilic α -alkylserines. *Chem. Biol. Drug Des.* 2014 84, 199-205

Frączak O, Lasota A., Leśniak A., Lipkowski AW, **Olma A.** Kosson P., Muchowska A, Lipkowski A.W, Olma A. Biphalin analogues containing β^3 -homo-amino acids at the 4,4' positions. *Peptides* **2015**; 66, 13–18

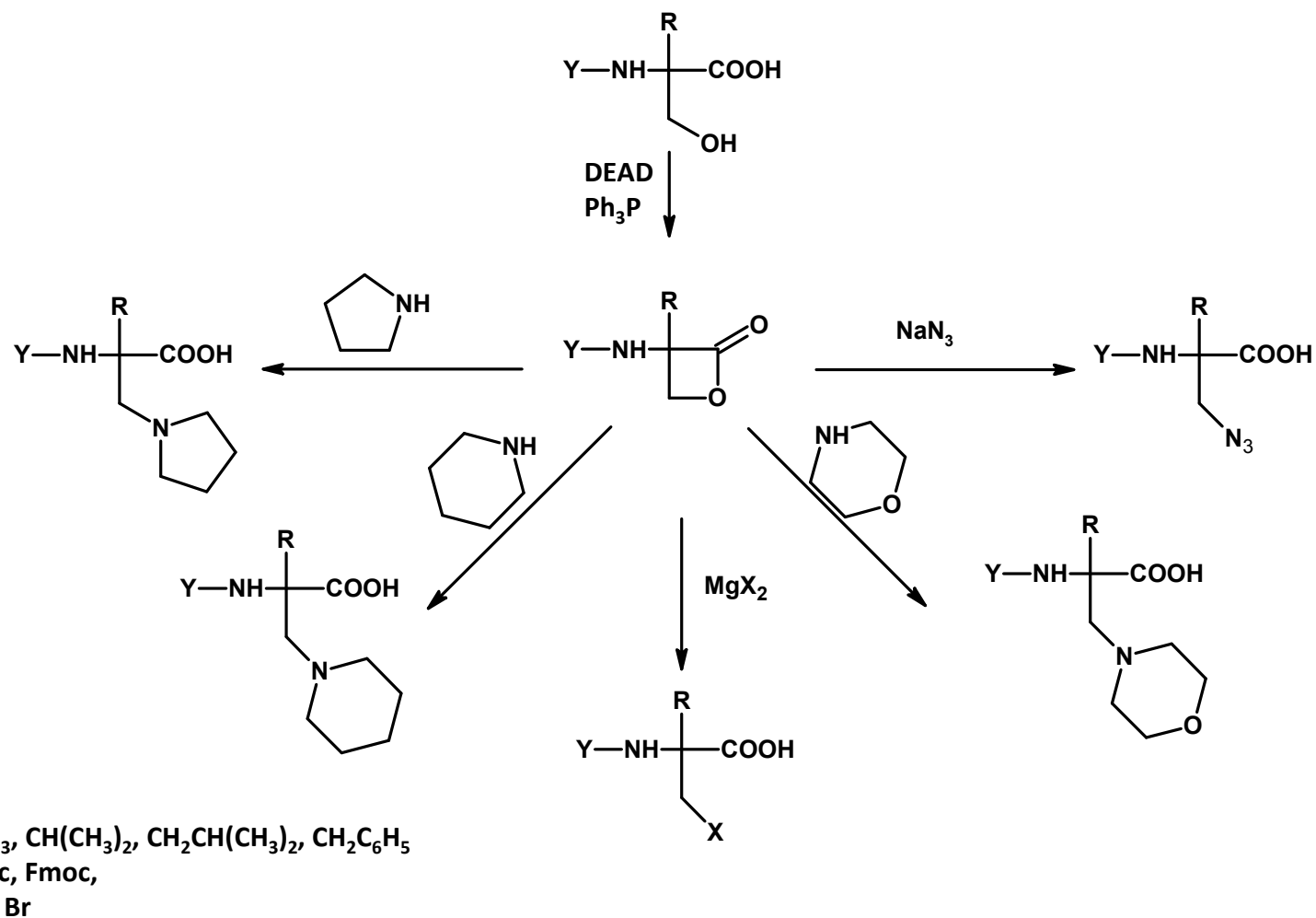
Frączak O., Lasota A., Tymecka D., Kosson O., Muchowska A., Misicka A., **Olma A.**, Synthesis, binding affinities and metabolic stability of dimeric dermorphin analogs modified with β^3 -homo-amino acids. *J. Pept. Sci.*, **2016**; 22: 222–227

Slajd 18

ZJK21

Post-doc position of dr A. Olma in Laboratory of M. Manning gave her excellent back-ground knowledge of peptide synthesis. This suited well in the many, very ambitious projects focused on studies biological effects caused by the presence of hydroxymethylated amino-acid residue in bioactive peptides.

ZJK; 2017-11-22

Transformation of α -alkylserines into α -alkyl- β -substituted alanines

Olma A. Kudaj A. *Tetrahedron Lett.*, **2005**, 46: 6239, Kudaj A. Olma A. *Tetrahedron Lett.*, **2007**, 48: 6794; Kudaj A., Olma A. *Tetrahedron Lett.*, **2008**, 49: 6445-6447; Olma A., Lasota A., Kudaj A., *Amino Acids*, **2012**, 42(6):2525-8

Lasota A., Frączak O., Leśniak A., Muchowska A., Lipkowski A.W. Nowakowski M., Ejchart A. *Olma A. J. Pept. Sci.*, **2015**, 21: 120–125; Lasota A., Frączak O., Muchowska A., Nowakowski M., Maciejczyk M., Ejchart A., *Olma A. Chem. Biol. Drug Des.*, **2016**, 87:824-832; Maciejczyk M., Lasota A., Frączak O, Kosson P, Misicka A., Nowakowski M., Ejchart A. *Olma A. J. Pept. Sci.*, **2016** 22, 545-551

Slajd 19

ZJK20

Very elegant achievement of prof. A. Olma involved transformation of hydroxymethyl group into many other functions including azides.

ZJK; 2017-11-13

ZJK22



Slajd 20

ZJK22

Dr Z.J. Kamiński as post-doc joined prof. G.W. Kenner's group at the University of Liverpool and participated in solution phase synthesis of lysozyme analogue. But this time, unnatural amino-acids introduced into the synthesized protein molecule demonstrated the dark face. Prepared analogue was found inactive, and what is worst, attempts to resolve the structure-activity relations were so frustrating, that prof. G.W. Kenner brake down, passed away, and left his research group unattended.

ZJK; 2017-11-22

Overview

The concept of superactive esters

Could peptide synthesis be improved by inventing superactive esters?

ZBIGNIEW J. KAMIŃSKI

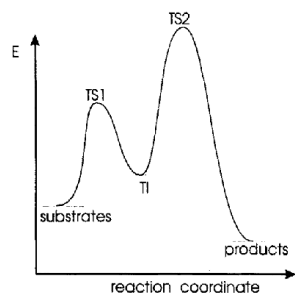


FIGURE 2
Reaction profile for the stepwise $A_N^+D_N^+$ mechanism of acylation by means of active esters.

active esters

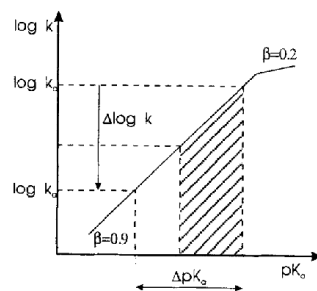


FIGURE 3
Bronsted relation: $\log k = f(pK_a)$ for active esters. ($\beta = 0.7-0.9$).

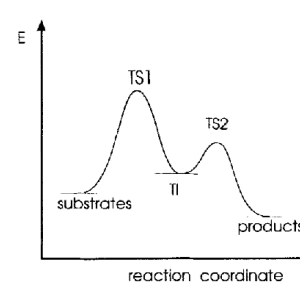


FIGURE 4
Reaction profile for the $A_N^+D_N$ or $A_N^+D_N+$ mechanism expected for superactive esters.

superactive esters

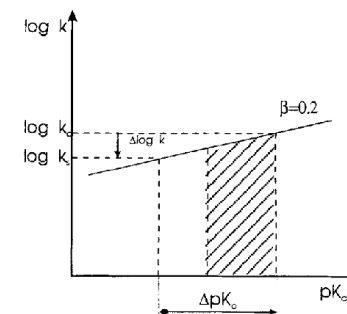


FIGURE 5
Bronsted relation $\log k = f(pK_a)$ for superactive esters ($\beta = 0.3$).

ACKNOWLEDGEMENT

The author thanks to Prof. R. Bodalski and Dr. P. Paneth for discussion of the manuscript.

This paper is dedicated to Prof. M.T. Leplawy on occasion of his 70th birthday.

Slajd 21

ZJK23

So, the post-doc training in Liverpool was not flourishing with excellent papers, but it was a lesson of humility granted to all involved in syntheses of non-typical objects.

ZJK; 2017-11-22

ZJK24

And everything started from beginning presenting hypothesis, that many synthetic problems could be resolved by designing "superactive" esters. According to the presented hypothesis this could be achieved, if formation of tetrahedral intermediate is rate limiting step, but transition state of its decay is lowered by synchronous, highly thermodynamically favorable additional process.

ZJK; 2017-11-14

TABLE 1

Geometry of the ester linkage; C(O)—OR' and C(O)O—R' bond lengths of selected esters RCO—O—R' (50–54)

	R'	Bond length (Å)		Ref.
		RCO—OR'	RCOO—R'	
1.	Alkyl esters (average)	1.340	1.451	(51)
2.	CH ₂ = CH	1.327	1.375	(55)
3.	Aryl esters (average)	1.368	1.402	(51)
4.	4-O ₂ N-C ₆ H ₄ (3)	1.362	1.393	(51)
5.	C ₆ F ₅	1.352	1.390	(54)
6.	Triazine ester (1)	1.379	1.384	(51)

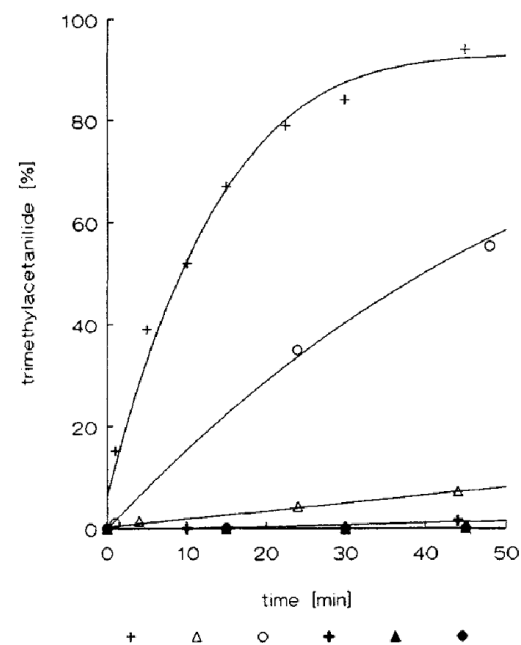
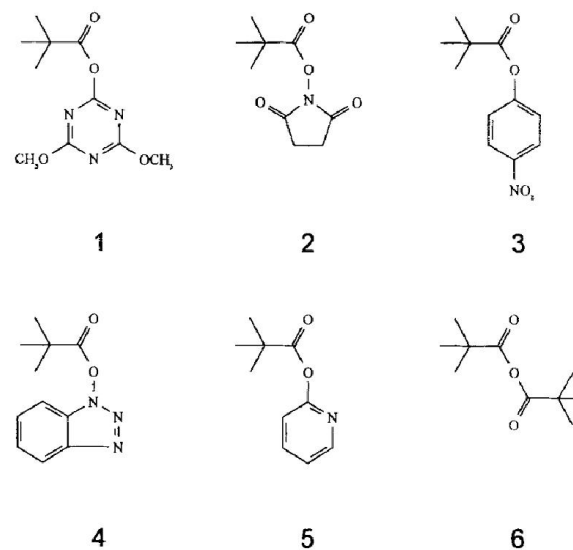
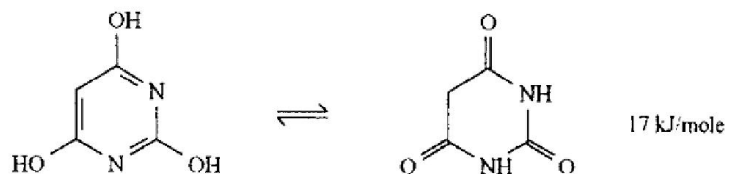
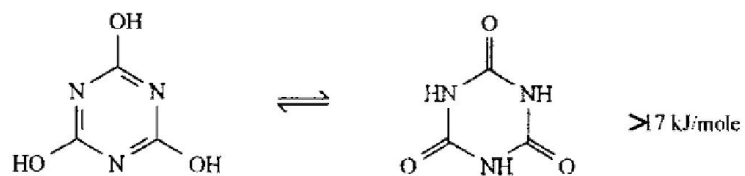


FIGURE 9

Relative rate of aniline trimethylacetylation (concentration of acylating reagent; 0.5 mol/L; aniline 5 mol/L; temperature 65 °C) in acetonitrile-d₃ solutions monitored by ¹H-NMR spectroscopy. Acylating reagents: 1 (+); 2 (Δ); 3 (O); 4 (●); 5 (+); 6 (▲).



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ZJK29

The studies has been undertaken in Łódź to confirme the hypothesis postulating existence of "superactive esters" .

ZJK; 2017-11-22

Kamiński Z.J.

"2-Chloro-4,6-disubstituted-1,3,5-triazines. A Novel Group of Condensing Reagents"
Tetrahedron Lett. 26, 2901-2904, (1985).

Kamiński, Z.J.

"2-Chloro-4,6-dimethoxy-1,3,5-triazine. A new Coupling reagent for Peptide Synthesis"
Synthesis (10), 917-920, (1987).

Kamiński Z.J.

"A new reaction of 2-chloro-4,6-dimethoxy-(diaryloxy)-1,3,5-triazines with carboxylic acids leading to hitherto unknown 2-acyloxy-4,6-dimethoxy-(diaryloxy)-1,3,5-triazines,,,"
J. prakt. Chem. 332, 579-581, (1990).

Kamiński Z.J., Paneth P., O'Leary M.,

"Nitrogen Kinetic Isotope Effects on the Acylation of Aniline"
J. Org. Chem. 56. 5716-5719, (1991).

Kaminski Z.J.

"Concept of superactive esters. Could the peptide synthesis be improved by inventing superactive esters"
Int. J. Peptide Protein Res. 43, 312-319, (1994)

Kamiński, Z.J.; Paneth, P.; Rudziński, J.

"A Study on Activation of Carboxylic Acids by Means of 2-Chloro-4,6-dimethoxy-1,3,5-triazine and 2-chloro-4,6-diphenoxy-1,3,5-triazine",
J. Org. Chem. 63, 4248-4255 (1998).

Kamiński, Z.J.

"Triazine-Based Condensing Reagents"
Biopolymers. 55, (2) 140-165 (2000).

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ZJK25

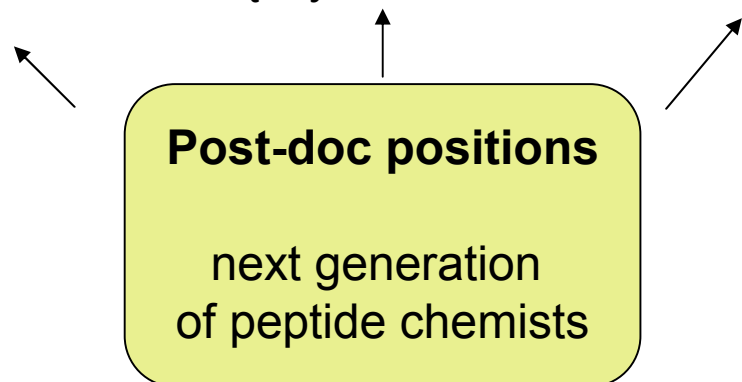
Surprisingly, the hypothesis was correct one. "Superactive" esters were designed, prepared, isolated and unambiguously identified as new, previously not described derivatives of 1,3,5-triazine. The predicted mechanism was confirmed by studies of kinetic isotope effects.

ZJK; 2017-11-14

prof. **A. M. Papini**
Florence, Italy
B. Kolesińska

prof. **H. Strasdeit**
Hohenheim, Germany
J. Frączyk

prof. **D. Seebach**
ETH Zurich, Swiss
B. Kolesińska



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ZJK26

And the next generation of peptide chemists came. Dr Beata Kolesińska got excellent post doc position in Florence under supervision of prof Anna Maria Papini and in ETH Zurich under supervision of prof Dieter Seebach. In Zurich she was infected with fascination to beta-amino-acids. Dr Justyna Frączyk joined the group of prof Henry Strasdeit at the University of Hohenheim.

ZJK; 2017-11-22

Kamiński Z.J.; **Kolesińska B.**; Kolesińska J.; Sabatino G.; Chell, M.; Rovero P.; Błaszczak M.; Główska M. L.; Papini A.M.

„N-Triazinylammonium tetrafluoroborates. A New Generation of Efficient Coupling Reagents Useful for Peptide Synthesis”

J. Am. Chem. Soc., **127**(48); 16912-16920 (2005).



Kolesińska B.; Kamiński Z.J.,

„The umpolung of substituent effect in nucleophilic aromatic substitution. A new approach to the synthesis of *N,N*-disubstituted melamines (triazine triskelions) under mild reaction conditions”

Tetrahedron, **65** 3573–3576 (2009).

Kolesińska B., Kamiński Z.J.

„Design, synthesis and application of enantioselective coupling reagent with a traceless chiral auxiliary”
Org. Lett., **11** (3), 765-768 (2009).

Kolesińska B.; Kasperowicz K.; Sochacki M.; Mazur A.; Jankowski S.; Kamiński Z.J.

„The design, synthesis and application of a chiral coupling reagent derived from strychnine for the enantioselective activation of the carboxylic group:

Tetrahedron Lett. **51**, 20-22 (2010)

Jastrzabek, K.G.; Subiros-Funosas, R.; Albericio, F.; **Kolesinska B.**; Kaminski, Z.J.

„4-(4,6-Di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylmorpholinium Tetrafluoroborate. Triazine-Based Coupling Reagents Designed for Coupling Sterically Hindered Substrates”

J. Org. Chem., **76**, 4506–4513 (2011),

Kolesinska B.; Rozniakowski K.K.; Fraczyk J.; Relich J.; Papini A.M.; Kaminski Z.J.

“The Effect of Counterion and Tertiary Amine on the Efficiency of *N*-Triazinylammonium Sulfonates in Solution and Solid-Phase Peptide Synthesis”

EurJOC, **2015**, 401–408;

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ZJK30

Both contibuted substantially to develope new, stable triazine reagents.

ZJK; 2017-11-21



COMMUNICATION

Visible-Light Microscopic Discovery of Up to 150 μm Long Helical Amyloid Fibrils Built of the Dodecapeptide H-(Val-Ala-Leu)₄-OH and of Decapeptides Derived from Insulin

by Monika Świontek^{a)†}, Zbigniew J. Kamiński^{a)}, Beata Kolesińska^{*a)}, and Dieter Seebach^{*b)}

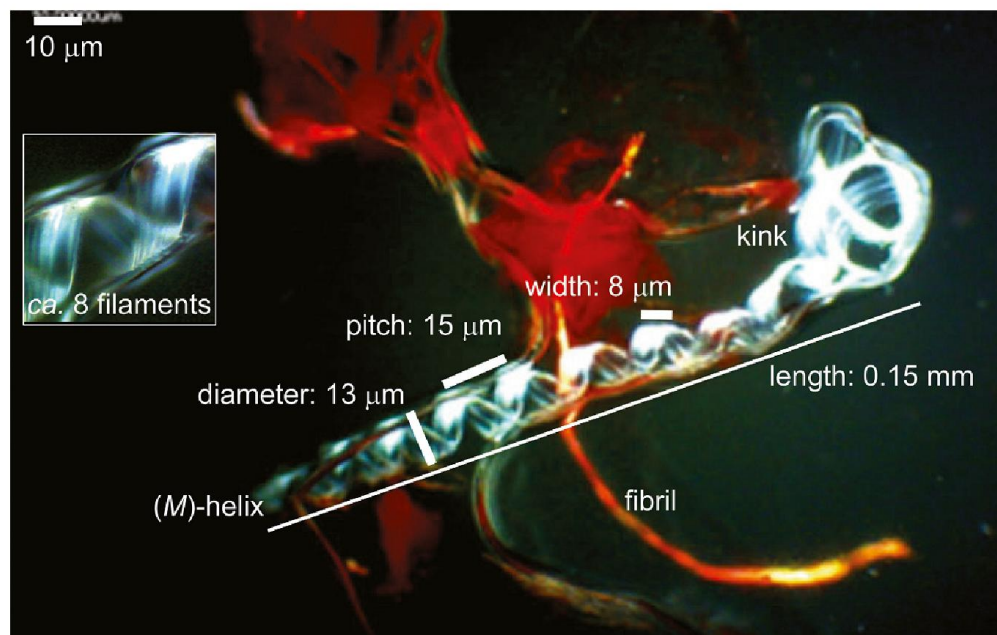


Fig. 2. Microscopy under polarized light of Congo-red-stained aggregates of the peptide H-(Val-Ala-Leu)₄-OH (2). The picture was obtained after an incubation time of 14 days; for details, see accompanying text and *Footnote 3*. The insert of one enlarged helix pitch shows the filaments of which the twisted tape is composed.

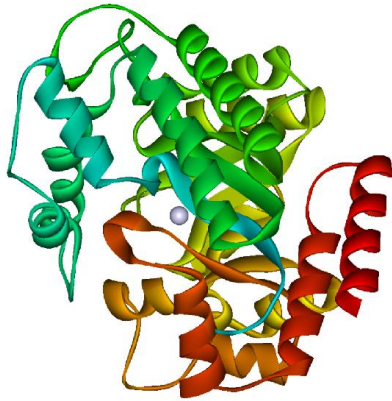
Slajd 26

ZJK31

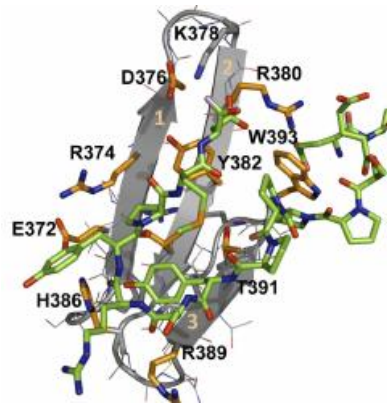
But also developed brand new area of peptide chemistry: peptides with beta-amino-acids residues, cell penetrating peptides, peptide aggregation, molecular mimicry and others.

ZJK; 2017-11-22

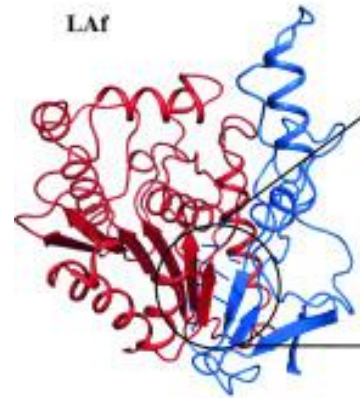
Immunological System and Molecular Mimicry



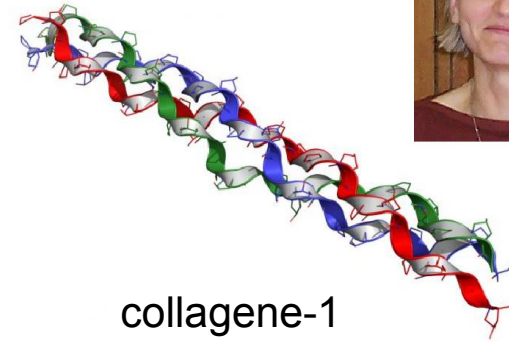
adenozyne deaminase



NEDD4L (ubiquitin ligase)



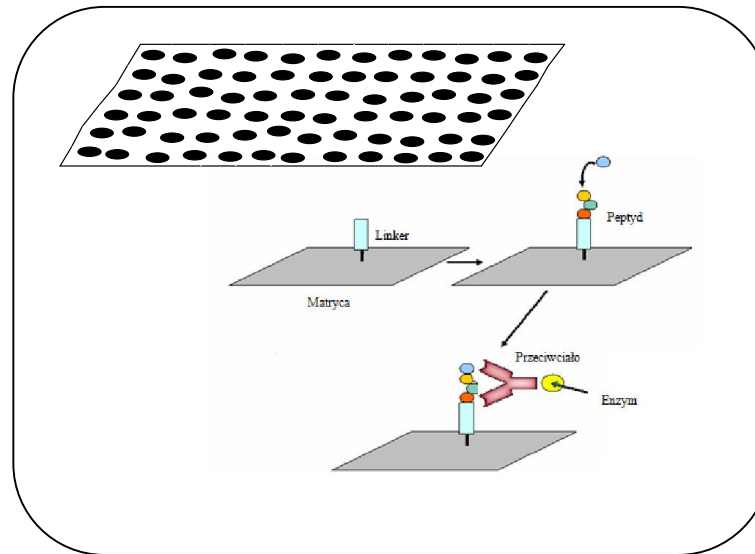
LAF-4



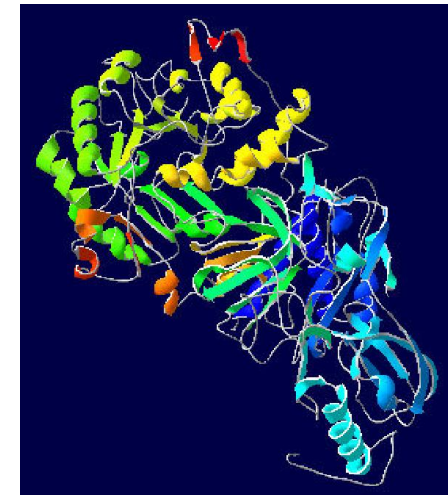
collagene-1



actin



rheumatoid arthritis, atherosclerotic diseases



Ureases:
H. Pylori,
Proteus mirabilis,
Staphylococcus,
Klebsiella,
Canavalia ensiformis,

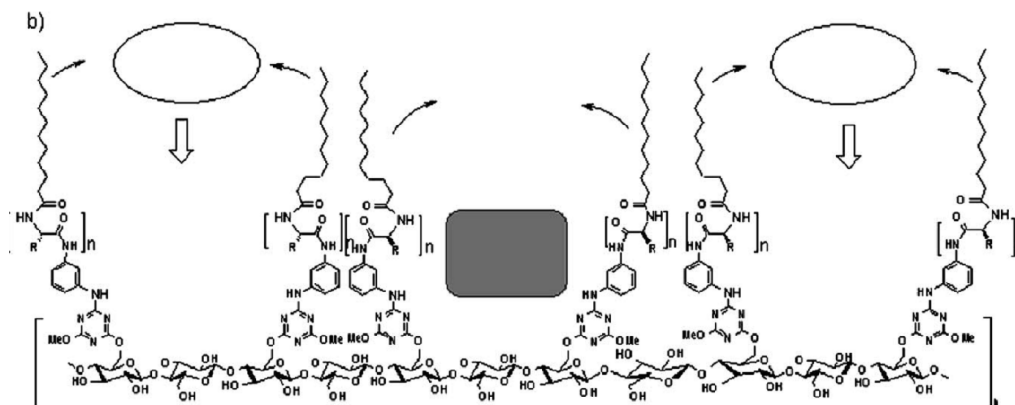
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ZJK32

Prof Beata Kolesińska is developing systematic studies on molecular mimicry between human proteins and proteins of pathogenic microorganisms.

Her other research are is focused on self-organization of peptides and proteins.

ZJK; 2017-11-21

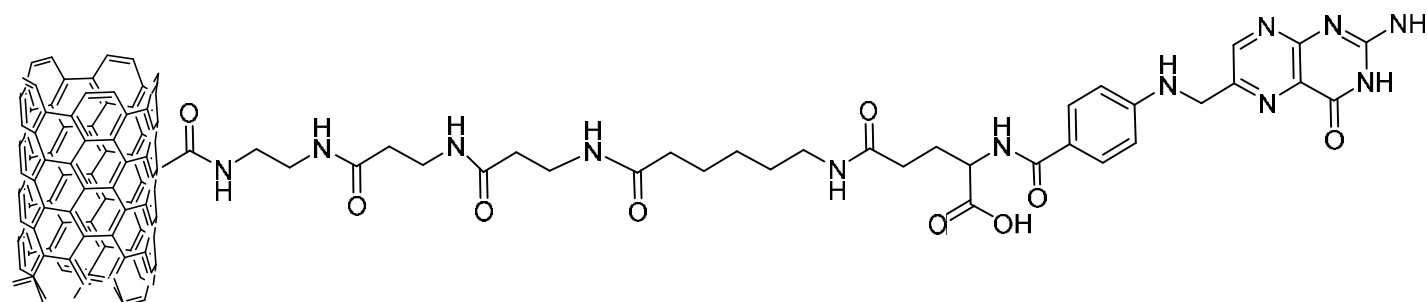


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Combinatorial Chemistry & High Throughput Screening, 2013, 16, 562-571

***N*-Lipidated Oligopeptides Immobilized on Cellulose as New Type of Organocatalysts**

Justyna Fraczyk, Beata Kolesinska and Zbigniew J. Kaminski*



Carbon nanotubes functionalized with folic acid attached via biomimetic peptide linker.

Fraczyk J, Walczak M, Szymanski L, Kolacinski Z, Wrzosek H, Majsterek I, Przybylowska-Sygut K, Kaminski ZJ;
Nanomedicine 2017, 12(18), 2161–2182.

ZJK33

The research area of dr Justyna Frączyk is focused on surface modification of materials by attachment of peptides to form molecular receptors and catalytically active chemzymes.

The surface modified materials include cellulose, silica, metal oxides, and nanomaterials: carbon nanotubes, nanodiamonds etc. In this case the unnatural motif arises from incorporation of the solid supports as crucial fragments determining functionality of peptides.

ZJK; 2017-11-22

**and this is not the end,
I presume**

**because peptides
with unnatural components
are fascinating indeed**

