An Efficient Chemical Synthesis of Nicotinamide Riboside (NAR) and Analogues

Bioorg. Med. Chem. Lett. 12 (2002) 1135

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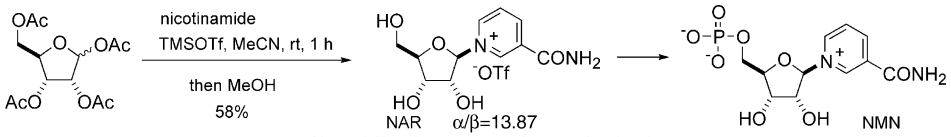


2'- and 3'-epimers were also synthesized.

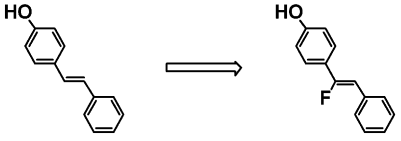
Design and Synthesis of Lignostilbene-α,β-dioxygenase Inhibitors

Bioorg. Med. Chem. Lett. 12 (2002) 1139

Sun-young Han,[a,b] Hiroki Inoue,[c] Tamami Terada,[c] Shigehiro Kamoda,[d] Yoshimasa Saburi,[c] Katsuhiko Sekimata,[a,b] Tamio Saito,[e] Masatomo Kobayashi,[e] Kazuo Shinozaki,[e] Shigeo Yoshida[a] and Tadao Asami[a,*]

[a]*RIKEN, Hirosawa 2-1, Wako, Saitama 351-0198, Japan,* [b]*Department of Biological and Environmental Sciences, Graduate School of Science and Engineering, Saitama University, Saitama 338-8570, Japan,* [c]*Department of Biomaterial Sciences, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo 113-0032, Japan,* [d]*University Forest in Hokkaido, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Hokkaido 079-1561, Japan,* [e]*RIKEN Tsukuba Institute, Koyadai 3-1-1, Tsukuba, Ibaraki 305-0074, Japan*

Lignostilbene-α,β-dioxygenase cleaves the olefinic double bond of phenolic stilbenes by a mechanism similar to that of 9-*cis*-epoxycarotenoid dioxygenase, a key enzyme in abscisic acid biosynthesis. Several analogues of stilbene were designed and synthesized, and their efficacy as inhibitors of lignostilbene-α,β-dioxygenase was examined. The compound (*Z*)-1-(4-hydroxyphenyl)-1-fluoro-2-phenylethene (**2**) was found to be a potent inhibitor of this enzyme with an IC_{50} of 3 μM.



4-hydroxystilbene (**2**)

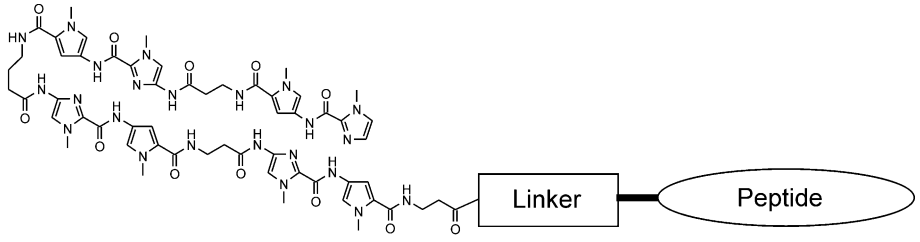
A Practical Approach to the Synthesis of Hairpin Polyamide–Peptide Conjugates Through the Use of a Safety-Catch Linker

Bioorg. Med. Chem. Lett. 12 (2002) 1143

Daniela Fattori, Olaf Kinzel, Paolo Ingallinella, Elisabetta Bianchi and Antonello Pessi*

Istituto di Ricerche di Biologia Molecolare P. Angeletti (IRBM), Via Pontina Km 30.600, 00040 Pomezia, Rome, Italy

The use of a safety-catch linker allowed for the rapid synthesis of hairpin polyamide–peptide conjugates, containing an additional linker element.



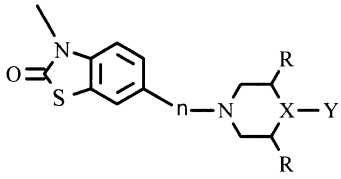
Synthesis and Pharmacological Evaluation of 6-Piperidino- and 6-Piperazinoalkyl-2(3*H*)-benzothiazolones as Mixed σ/5-HT_{1A} Ligands

Bioorg. Med. Chem. Lett. 12 (2002) 1149

Ange Mouithys-Mickalad,[a,*] Jacques H. Poupaert,[b] Santi Spampinato[c] and Daniel Lesieur[a]

[a]*Institut de Chimie Pharmaceutique Albert Lespagnol, Université de Lille 2, 3, rue du Professeur Laguesse, F-59006 Lille, France*
[b]*Ecole de Pharmacie, Université Catholique de Louvain, Avenue E. Mounier 73, B-1200 Bruxelles, Belgium*
[c]*Dipartimento di Farmacologia, Facoltà di Farmacia, Università degli Studi di Bologna, 48 via Irnerio, I-40126 Bologna, Italy*

The synthesis of 6-piperidino and 6-piperazinoalkyl-2(3*H*)-benzothiazolones is reported. Most of them exhibit high affinity at σ and/or 5-HT_{1A} receptors.



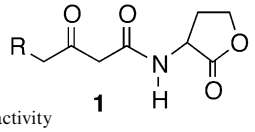
n = 2, 4 ; X = N, CH ; R = H, CH_3
Y = C_6H_5-, $C_6H_5CH_2$-, 2,4 or 3,4-$Cl_2C_6H_5CH_2$-

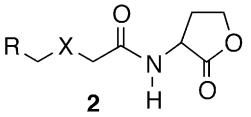
Bioorg. Med. Chem. Lett. 12 (2002) 1153

New Synthetic Analogues of *N*-Acyl Homoserine Lactones as Agonists or Antagonists of Transcriptional Regulators Involved in Bacterial Quorum Sensing

Sylvie Reverchon,[a,*] Bernard Chantegrel,[b] Christian Deshayes,[b] Alain Doutheau[b] and Nicole Cotte-Pattat[a]

[a]*Unité de Microbiologie et Génétique CNRS-INSA-UCB UMR 5122, INSA, Batiment Louis Pasteur, 11 Avenue Jean Capelle, 69621 Villeurbanne, France*
[b]*Laboratoire de Chimie Organique, INSA, Batiment Jules Verne, 17 Avenue Jean Capelle, 69621 Villeurbanne, France*





R = Alk, Ar X = CH_2, O, S

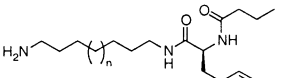
A series of novel synthetic *N*-acyl-homoserine lactone analogues of type **1** or **2** has been evaluated for both their inducing activity and their ability to competitively inhibit the action of 3-oxo-hexanoyl-L-homoserine lactone, the natural inducer of bioluminescence in the bacterium *Vibrio fischeri*. In the newly synthesized analogues, the extremity of the acyl chain was modified by introducing ramified alkyl, cycloalkyl or aryl substituents at the C-4 position. Most of the analogues bearing either acyclic or cyclic alkyl substituents showed inducing activity. In contrast, the phenyl substituted analogues displayed significant antagonist activity. We hypothesized that the antagonist activity of the phenyl compounds may result from the interaction between the aryl group and aromatic amino acids of the LuxR receptor, preventing it from adopting the active dimeric form.

Bioorg. Med. Chem. Lett. 12 (2002) 1159

Solid-Phase Synthesis and Pharmacological Evaluation of Analogues of PhTX-12—A Potent and Selective Nicotinic Acetylcholine Receptor Antagonist

Kristian Strømgaard,[a,*] Ian R. Mellor,[b] Kim Andersen,[c] Ioana Neagoe,[b] Florentina Pluteanu,[b] Peter N. R. Usherwood,[b] Povl Krogsgaard-Larsen[a] and Jerzy W. Jaroszewski[a]

[a]*Department of Medicinal Chemistry and NeuroScience PharmaBiotec Research Center, Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark*
[b]*Division of Molecular Toxicology, School of Life and Environmental Sciences, University of Nottingham, University Park, Nottingham NG7 2RD, UK*
[c]*Department of Combinatorial Chemistry, Medicinal Chemistry Research, H. Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark*



PhTX-7 (n=1) PhTX-10 (n=4)
PhTX-8 (n=2) PhTX-11 (n=5)
PhTX-9 (n=3) PhTX-12 (n=6)

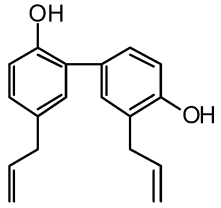
Truncated analogues of PhTX-12 were synthesized using solid-phase methodologies and characterized at the nAChR by in vitro electrophysiology. PhTX-11 was a potent, voltage-independent antagonist of nAChR.

Bioorg. Med. Chem. Lett. 12 (2002) 1163

Neurotrophic Activity of Honokiol on the Cultures of Fetal Rat Cortical Neurons

Yoshiyasu Fukuyama,[a,*] Kousuke Nakade,[a] Yuka Minoshima,[a] Ritsuko Yokoyama,[a] Haifeng Zhai[a] and Yasuhide Mitsumoto[b]

[a]*Institute of Pharmacognosy, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan*
[b]*Neurodegenerative Disease Research Group, Second Institute of New Drug Research, Otsuka Pharmaceutical Co. Ltd., Tokushima 771-0192, Japan*



1

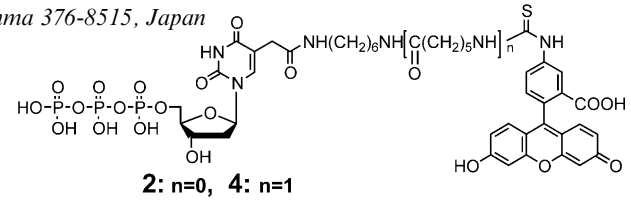
Honokiol (**1**) exhibits a neurotrophic activity in the primary cultures of rat cortical neurons and its trophic effect on neurons is comparable to bFGF.

Bioorg. Med. Chem. Lett. 12 (2002) 1167

Enzymatic Synthesis of Labeled DNA by PCR Using New Fluorescent Thymidine Nucleotide Analogue and Superthermophilic KOD Dash DNA Polymerase

Tsutomu Obayashi, Mohammed M. Masud, Akiko N. Ozaki, Hiroaki Ozaki, Masayasu Kuwahara and Hiroaki Sawai*

Department of Applied Chemistry, Gunma University, Kiryu, Gunma 376-8515, Japan



2: n=0, **4**: n=1

Triphosphate of a new fluorescent-labeled thymidine analogue was incorporated as a substrate for PCR using KOD Dash DNA polymerase forming the corresponding fluorescent-labeled DNA which is useful for a DNA probe.

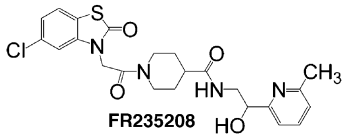
Bioorg. Med. Chem. Lett. 12 (2002) 1171

Novel Potent Antagonists of Human Neuropeptide Y Y5 Receptor (I): 2-Oxobenzothiazolin-3-acetic Acid Derivatives

Seiichiro Tabuchi,[a] Hiromichi Itani,[a] Yoshihiko Sakata,[b] Hiroko Oohashi[b] and Yoshinari Satoh[a,*]

[a]*Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan*
[b]*Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan*

Novel 5-chloro-2-oxobenzothiazolin-3-acetic acid derivatives were synthesized and showed high affinity for the NPY-Y5 receptors.



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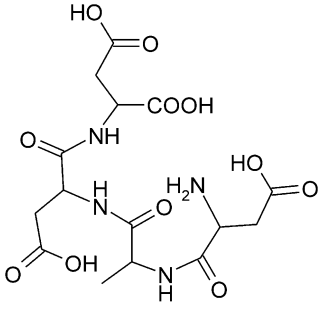
Bioorg. Med. Chem. Lett. 12 (2002) 1177

Carbonic Anhydrase Activators: Human Isozyme II is Strongly Activated by Oligopeptides Incorporating the Carboxyterminal Sequence of the Bicarbonate Anion Exchanger AE1

Andrea Scozzafava and Claudiu T. Supuran*

Università degli Studi di Firenze, Dipartimento di Chimica, Laboratorio di Chimica Bioinorganica, Rm. 188, Via della Lastruccia, 3, I-50019 Sesto Fiorentino (Firenze), Italy



Bioorg. Med. Chem. Lett. 12 (2002) 1181

Novel Bicyclic Lactam Inhibitors of Thrombin: Highly Potent and Selective Inhibitors

Yves St-Denis,[a] Sophie Lévesque,[a,*] Benoit Bachand,[a] Jeremy J. Edmunds,[b] Lorraine Leblond,[a] Patrice Préville,[a] Micheline Tarazi,[a] Peter D. Winocour[a] and M. Arshad Siddiqui[a]

[a]*Shire BioChem., 275 Armand-Frappier Blvd., Laval, Québec, Canada H7V 4A7*
[b]*Pfizer Global Research and Development, Ann Arbor, MI 48105, USA*

The potency and selectivity of a previous series of low molecular weight thrombin inhibitors were improved through modifications of the P1 and P3 residues. Introduction of diphenyl substituted sulfonamides in the P3 moiety led to highly efficacious compounds. By correctly selecting the combination of P1 and P3 residues, high levels of potency, selectivity and in vivo efficacy were obtained.

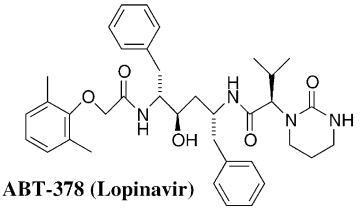
Bioorg. Med. Chem. Lett. 12 (2002) 1185

Synthesis and Structure–Activity Relationships of a Novel Series of HIV-1 Protease Inhibitors Encompassing ABT-378 (Lopinavir)

Hing L. Sham,* David A. Betebenner, Xiaoqi Chen, Ayda Saldivar, Sudthida Vasavanonda, Dale J. Kempf, Jacob J. Plattner and Daniel W. Norbeck

Pharmaceutical Discovery, D47B, Building AP-10, Abbott Laboratories, Abbott Park, IL 60064-6101, USA

Structure–activity relationships of analogues at the P2′ site of ABT-378 are reported.



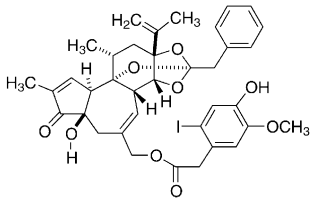
ABT-378 (Lopinavir)

Bioorg. Med. Chem. Lett. 12 (2002) 1189

Synthesis and In Vitro Evaluation of a Novel Iodinated Resiniferatoxin Derivative that is an Agonist at the Human Vanilloid VR1 Receptor

Mark E. McDonnell,[a] Sui-Po Zhang,[a] Adrienne E. Dubin[b] and Scott L. Dax[a,*]

[a]*Johnson & Johnson Pharmaceutical Research and Development, Welsh and McKean Roads, Spring House, PA 19477, USA*
[b]*Johnson & Johnson Pharmaceutical Research and Development, 3210 Merryfield Row, San Diego, CA 92121, USA*



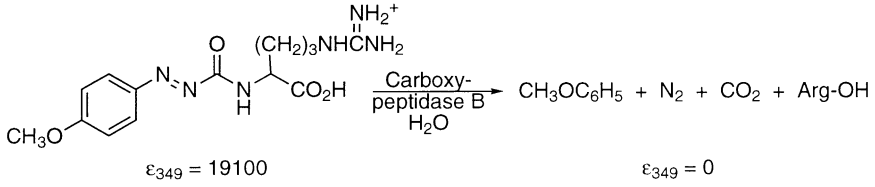
The 2-iodo-4-hydroxy-5-methoxyphenylacetic acid ester of resiniferinol **5** was synthesized and displayed high affinity binding ($K_i = 0.71$ nM) for the hVR1 receptor and functioned as a partial agonist.

Bioorg. Med. Chem. Lett. 12 (2002) 1193

Anisylazoformylarginine: A Superior Assay Substrate for Carboxypeptidase B Type Enzymes

William L. Mock* and Daniel J. Stanford

Department of Chemistry, University of Illinois at Chicago, Chicago, IL 60607-7061, USA

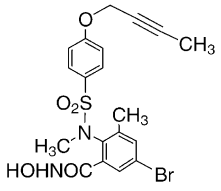


Bioorg. Med. Chem. Lett. 12 (2002) 1195

Anthranilate Sulfonamide Hydroxamate TACE Inhibitors. Part 1: Structure-Based Design of Novel Acetylenic P1′ Groups

James M. Chen,[a,*] Guixian Jin,[a] Amy Sung[b] and Jeremy I. Levin[a,*]

[a]*Wyeth-Ayerst Research, 401N. Middletown Road, Pearl River, NY 10965, USA*
[b]*Wyeth-Ayerst Research, PO Box CN-8000, Princeton, NJ 08543, USA*



6b

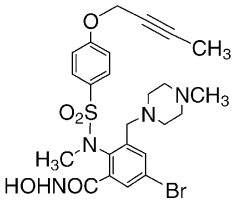
The structure-based design of potent sulfonamide hydroxamate TACE inhibitors bearing novel acetylenic P1′ groups has led to compounds with excellent in vitro potency against TACE and selectivity over MMP-1, exemplified by butynyl ether **6b**.

Bioorg. Med. Chem. Lett. 12 (2002) 1199

Anthranilate Sulfonamide Hydroxamate TACE Inhibitors. Part 2: SAR of the Acetylenic P1′ Group

J. I. Levin,[a,*] J. M. Chen,[a] M. T. Du,[a] F. C. Nelson,[a] L. M. Killar,[b] S. Skala,[b] A. Sung,[b] G. Jin,[a] R. Cowling,[a] D. Barone,[c] C. J. March,[c] K. M. Mohler,[c] R. A. Black[c] and J. S. Skotnicki[a]

[a]*Wyeth-Ayerst Research, 401N. Middletown Road, Pearl River, NY 10965, USA*
[b]*Wyeth-Ayerst Research, PO Box CN-8000, Princeton, NJ 08543, USA*
[c]*Immunex Corporation, Seattle, WA 98101, USA*



4t

Compound **4t**, a potent and selective inhibitor of TACE, in vitro and in vivo, has been identified.

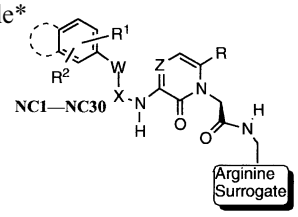
Bioorg. Med. Chem. Lett. 12 (2002) 1203

Non-Covalent Thrombin Inhibitors Featuring P_3-Heterocycles with P_1-Monocyclic Arginine Surrogates

John E. Reiner, Daniel V. Siev, Gian-Luca Araldi, Jingrong Jean Cui, Jonathan Z. Ho, Komandla Malla Reddy, Lala Mamedova, Phong H. Vu, Kuen-Shan S. Lee, Nathaniel K. Minami, Tony S. Gibson, Susanne M. Anderson, Annette E. Bradbury, Thomas G. Nolan and J. Edward Semple*

Department of Medicinal Chemistry, Corvas International, Inc., 3030 Science Park Road, San Diego, CA 92121, USA

The design, synthesis, and biological activity of novel, achiral, non-covalent thrombin inhibitors **NC1**–**NC30** will be disclosed that feature three classes of monocyclic P_1-arginine surrogates: (1) (hetero)aromatic amidines, amines and hydroxyamidines, (2) 2-aminopyrazines, and (3) 2-aminopyrimidines and 2-aminotetrahydropyrimidines.



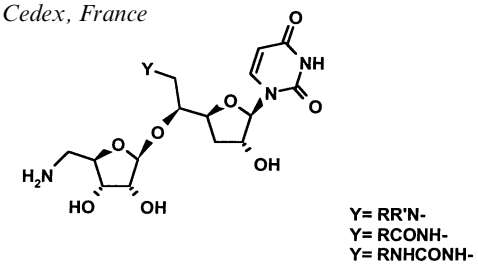
Bioorg. Med. Chem. Lett. 12 (2002) 1209

Synthesis of Sub-Micromolar Inhibitors of MraY by Exploring the Region Originally Occupied by the Diazepanone Ring in the Liposidomycin Structure

C. Dini,* S. Didier-Laurent, N. Drochon, S. Feteanu, J. C. Guillot, F. Monti, E. Uridat, J. Zhang and J. Aszodi

Aventis Pharma, Paris Research Centre, 102 route de Noisy, 93235 Romainville Cedex, France

The synthesis and inhibitory activity against MraY of a series of simplified analogues of Liposidomycins are described. These compounds were mainly obtained by performing parallel synthesis in the 6′-position of a scaffold that gathers key features found necessary for the binding to MraY. Thus, inhibitory activity was improved from 5300 to 140 nM. This improvement was correlated with the length and lipophilicity of substituents, but was found to be independent of the nature of the chemical bond generated. In addition, some of these inhibitors presented encouraging antibacterial activities.



Bioorg. Med. Chem. Lett. 12 (2002) 1215

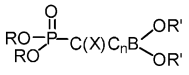
Novel Matrix Metallo-Proteinase (MMP-2) Phosphonoboronate Inhibitors

Inna Pergament,[a] Reuven Reich[b] and Morris Srebnik[a,*]

[a]*Department of Medicinal Chemistry and Natural Products, Hebrew University in Jerusalem, POB 12065, Jerusalem 91120, Israel*

[b]*Department of Pharmacology, School of Pharmacy, Hebrew University in Jerusalem, POB 12065, Jerusalem 91120, Israel*

The SAR of a group of novel phosphonoboronate MMP-2 inhibitors is reported.



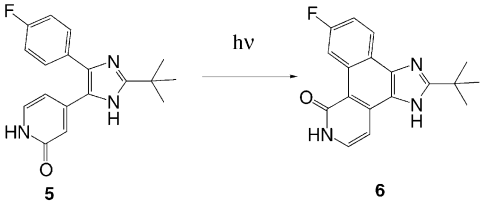
Bioorg. Med. Chem. Lett. 12 (2002) 1219

Photochemical Preparation of a Pyridone Containing Tetracycle: A Jak Protein Kinase Inhibitor

James E. Thompson,* Rose M. Cubbon, Richard T. Cummings, Linda S. Wicker, Robert Frankshun, Barry R. Cunningham, Patricia M. Cameron, Peter T. Meinke, Nigel Liverton, Youmin Weng and Julie A. DeMartino

Merck Research Laboratories, Merck & Co., 80M-127, PO Box 2000, Rahway, NJ 07065-0900, USA

Pyridone **5** was found to be a potent Jak protein kinase inhibitor after photochemical cyclization to **6**.



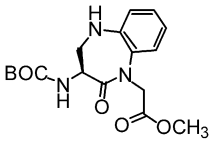
Bioorg. Med. Chem. Lett. 12 (2002) 1225

A Practical Synthesis of (*S*) 3-*tert*-Butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-1,5-benzodiazepine-1-acetic Acid Methyl Ester as a Conformationally Restricted Dipeptido-Mimetic for Caspase-1 (ICE) Inhibitors

David J. Lauffer* and Michael D. Mullican

Vertex Pharmaceuticals, Inc., 130 Waverly Street, Cambridge, MA 02139-4211, USA

A simple and versatile method for the synthesis of (S) 3-*tert*-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-1,5-benzodiazepine-1-acetic acid methyl ester (**4**), a dipeptide mimetic, has been developed. The regioselective functionalization of the N1 and N5 ring nitrogens and the C3 amino group is demonstrated in the synthesis of an interleukin-1β converting enzyme inhibitor.



4

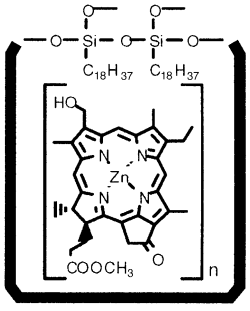
Bioorg. Med. Chem. Lett. 12 (2002) 1229

Self-Assembly of Synthetic Zinc Chlorins in a Silicate Micelle Prepared by Sol-Gel Process

Yoshitaka Saga,[a] Tomohiro Miyatake[b] and Hitoshi Tamiaki[a,*]

[a]*Department of Bioscience and Biotechnology, Faculty of Science and Engineering, Ritsumeikan University, Kusatsu, Shiga 525-8577, Japan*
[b]*Department of Materials Chemistry, Faculty of Science and Technology, Ryukoku University, Otsu, Shiga 520-2194, Japan*

Silicate microcapsules including self-aggregates of zinc chlorins were prepared as a novel model of extramembrenous light-harvesting antennae of green photosyntheic bacteria.



Bioorg. Med. Chem. Lett. 12 (2002) 1233

Amino Acid Derived Sulfonamide Hydroxamates as Inhibitors of Procollagen C-Proteinase. Part 2: Solid-Phase Optimization of Side Chains

Sharon M. Dankwardt,* Sarah C. Abbot, Chris A. Broka, Robert L. Martin, Christine S. Chan, Eric B. Springman, Harold E. Van Wart and Keith A. M. Walker

Roche Bioscience, Inflammatory and Viral Diseases Unit, 3401Hillview Ave, Palo Alto, CA 94304, USA

The solid-phase synthesis of these potent inhibitors of procollagen C-proteinase (PCP) is presented.