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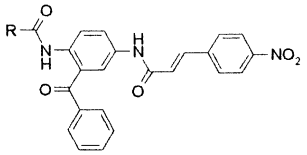
Non-thiol Farnesyltransferase Inhibitors: *N*-(4-Acylamino-3-benzoylphenyl)-4-nitrocinnamic Acid Amides

Jacek Sakowski,[a] Isabel Sattler[b] and Martin Schlitzer[a]

[a]*Institut für Pharmazeutische Chemie, Philipps-Universität Marburg, Marbacher Weg 6, D-35032 Marburg, Germany*
[b]*Hans-Knöll-Institut für Naturstoff-Forschung e.V., Beutenbergstraβe 11, D-07745, Jena, Germany*

We have developed a 4-nitrocinnamoyl substituted benzophenone as a novel non-thiol farnesyltransferase inhibitor. Replacement of the *p*-tolyl moiety of our initial lead structure by different *para* and *ortho* substituted phenyl residues as well as by 1-naphthyl resulted in derivatives with considerably enhanced activity displaying IC_{50} values between 42 and 52 nM. These compounds represent novel, readily accessible non-thiol farnesyltransferase inhibitors being more active than the corresponding thiol-containing analogues.

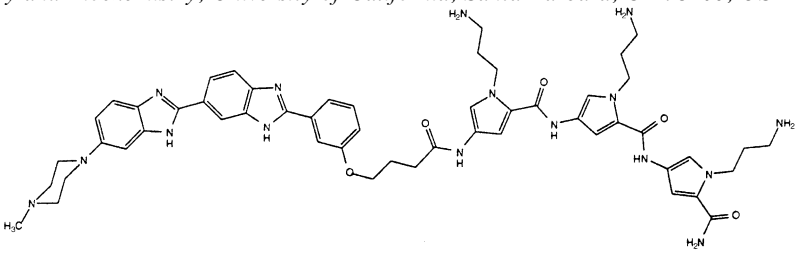


Bioorg. Med. Chem. 10 (2002) 241

Recognition of Nine Base Pair Sequences in the Minor Groove of DNA at Subpicomolar Concentrations by a Novel Microgonotropen

Alexander L. Satz and Thomas C. Bruice

Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106, USA



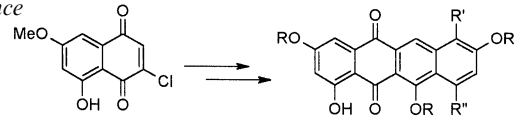
Bioorg. Med. Chem. 10 (2002) 253

Synthesis and Cytotoxic Activity of Tetracenomycin D and of Saintopin Analogues

Philippe Martin,[a] Stéphane Rodier,[a] Martine Mondon,[a] Brigitte Renoux,[a] Bruno Pfeiffer,[b] Pierre Renard,[b] Alain Pierré[c] and Jean-Pierre Gesson[a]

[a]*Laboratoire de Synthèse et Réactivité des Substances Naturelles, Université de Poitiers et CNRS, 40 avenue du Recteur Pineau, 86022 Poitiers, France*
[b]*ADIR, 1 rue Carle Hébert, 92415 Courbevoie Cedex, France*
[c]*Institut de Recherche Servier, 11 rue des Moulineaux, 92450 Suresnes, France*

Analogues of saintopin (R = R′ = H, R″ = OH) and of tetracenomycin D (R = R′ = H, R″ = Me) have been prepared and their cytotoxicity activity against L1210 has been evaluated.

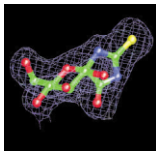


Bioorg. Med. Chem. 10 (2002) 261

Kinetic and Crystallographic Studies of Glucopyranosylidene Spirothiohydantoin Binding to Glycogen Phosphorylase B

Nikos G. Oikonomakos,[a] Vicky T. Skamnaki,[a] Erzsébet Ösz,[b] László Szilágyi,[b] László Somsák,[b] Tibor Docsa,[c] Béla Tóth[c] and Pál Gergely[c]

[a]*Institute of Biological Research and Biotechnology, The National Hellenic Research Foundation, 48 Vas. Constantinou Avenue, Athens 11635, Greece*
[b]*Department of Organic Chemistry, University of Debrecen, POB 20, H-4010 Debrecen, Hungary*
[c]*Department of Medical Chemistry, Medicaland Health Science Centre, University of Debrecen, H-4026 Debrecen, Bem ter 18/B, Hungary*



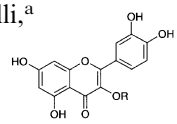
Electron density map of glucopyranosylidene thiohydantoin bound to glycogen phosphorylase b.

Bioorg. Med. Chem. 10 (2002) 269

Antimicrobial and Anti-Lipase Activity of Quercetin and Its C2–C16 3-*O*-Acyl-Esters

Maria Teresa Gatto,[a] Serena Falcocchio,[a] Eleonora Grippa,[a] Gabriela Mazzanti,[a] Lucia Battinelli,[a] Giovanni Nicolosi,[b] Daniela Lambusta[b] and Luciano Saso[a]

[a]*Department of Pharmacology of Natural Substances and General Physiology, University of Rome "La Sapienza", P.le Aldo Moro 5, 00185 Rome, Italy*
[b]*Istituto CNR per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico, Via del Santuario 110, 95028 Valverde (CT), Italy*



	R
1	Acetyl
2	Butyryl
3	Iso-Butyryl
4	Caproyl
5	Decanoyl
6	Lauroyl
7	Myristoyl
8	Palmitoyl

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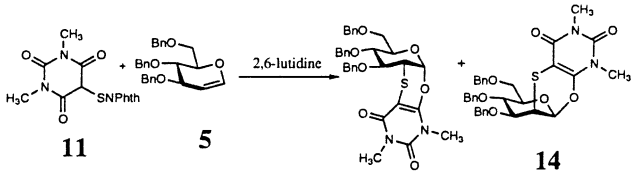
The Synthesis and Biological Evaluation of Novel Bridging Nucleoside Analogues

Cecilia H. Marzabadi,[a] Richard W. Franck[a] and Raymond F. Schinazi[b]

[a]*Department of Chemistry, Hunter College-CUNY, 695 Park Avenue, New York, NY 10021, USA*
[b]*Veterans Affairs Medical Center and Department of Pediatrics, Emory University School of Medicine, 1670 Clairmont Road, Decatur, GA 30033, USA*



11 **5** **13** **14**

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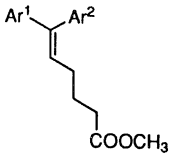
Synthesis of Alkenyldiarylmethane (ADAM) Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors with Non-Identical Aromatic Rings

Guozhang Xu,[a] Tracy L. Hartman,[b] Heather Wargo,[b] Jim A. Turpin,[b] Robert W. Buckheit, Jr.[b] and Mark Cushman[a]

[a]*Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907, USA*
[b]*Infectious Disease Research Department, Southern Research Institute, 431 Aviation Way, Frederick, MD 21701, USA*

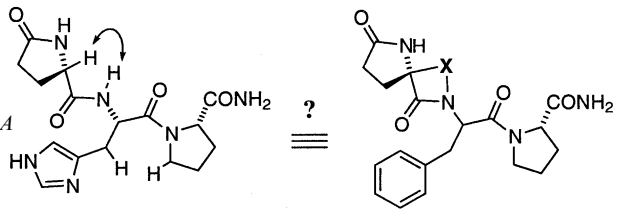


Bioorg. Med. Chem. 10 (2002) 291

Conformationally Restricted TRH Analogues: Constraining the Pyroglutamate Region

Jill C. Simpson,[a] Chris Ho,[b] E.F. Berkley Shands,[c] Marvin C. Gershengorn,[d,e] Garland R. Marshall[b] and Kevin D. Moeller[a]

[a]*Department of Chemistry, Department of Molecular Biology and Pharmacology, Washington University, St. Louis, MO 63130, USA*
[b]*Center for Molecular Design, Washington University, St. Louis, MO 63130, USA*
[c]*Department of Computer Science, Washington University, St. Louis, MO 63130, USA*
[d]*Division of Molecular Medicine, Department of Medicine, Cornell University Medical College, New York, NY 10021, USA*
[e]*The New York Hospital, New York, NY 10021, USA*



1. TRH

2. X= CH=CH, CH_2CH_2, or $CH_2CH_2CH_2$

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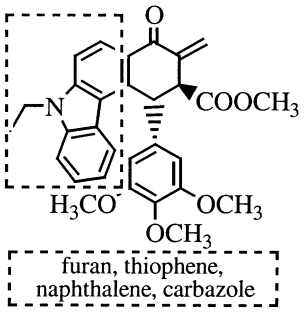
Synthesis and Cytotoxic Activities of Analogues of Thuriferic Acid

Blanca Madrigal,[a] Pilar Puebla,[a] Angel Ramos,[a] Rafael Peláez,[a] Dolores Grávalos,[b] Esther Caballero[a] and Manuel Medarde[a]

[a]*Laboratorio de Química Orgánica y Farmacéutica, Facultad de Farmacia. Campus Miguel de Unamuno, 37007-Salamanca, Spain*
[b]*Instituto BioMar, La Calera 3, 28760-Tres Cantos (Madrid), Spain*

New heterocyclic and polycyclic analogues of the natural lignan thuriferic acid have been synthesised. All of them are cytotoxic against several cancer cell lines, although they lack the 1,3-benzodioxole system of podophyllotoxin and related cytotoxic lignans. Differences in the conformational preferences of thuriferic acid and these analogues are explained by the increasing steric interactions between the A–B ring system and E-ring (3,4,5-trimethoxyphenyl).



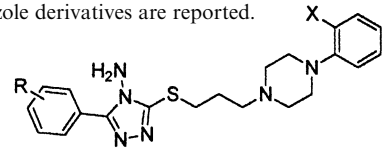
Bioorg. Med. Chem. 10 (2002) 313

[1,2,4]Triazole Derivatives as 5-HT_{1A} Serotonin Receptor Ligands

Maria Concetta Sarvà,[a] Giuseppe Romeo,[a] Francesco Guerrera,[a] Mariangela Siracusa,[a] Loredana Salerno,[a] Filippo Russo,[a] Alfredo Cagnotto,[b] Mara Goegan[b] and Tiziana Mennini[b]

[a]*Dipartimento di Scienze Farmaceutiche, Università di Catania, viale A. Doria 6, 95125 Catania, Italy*
[b]*Istituto di Ricerche Farmacologiche "Mario Negri", via Eritrea 62, 20157 Milan, Italy*

Synthesis and binding affinities for the 5-HT_{1A} versus the α_1-adrenergic receptor of new [1,2,4]triazole derivatives are reported.



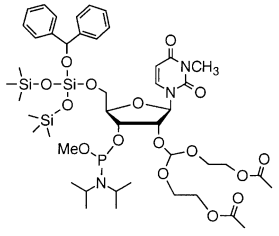
Bioorg. Med. Chem. 10 (2002) 325

Synthesis of a 3-Methyluridine Phosphoramidite to Investigate the Role of Methylation in a Ribosomal RNA Hairpin

Helen M.-P. Chui,[a] May Meroueh,[a] Stephen A. Scaringe[b] and Christine S. Chow[a]

[a]*Department of Chemistry, Wayne State University, Detroit, MI 48202, USA*
[b]*Dharmacon Research Inc., Lafayette, CO 80026, USA*

A m^3U amidite was synthesized and employed to generate 19-nt hairpin RNAs representing the 1920 region of *Escherichia coli* 23S rRNA. Biophysical studies were carried out to determine the effects of methylation on RNA structure.



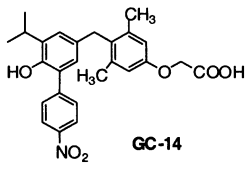
Bioorg. Med. Chem. 10 (2002) 333

Synthesis and Biological Activity of Novel Thyroid Hormone Analogues: 5′-Aryl Substituted GC-1 Derivatives

Grazia Chiellini,[a] Ngoc-Ha Nguyen,[a] James W. Apriletti,[b] John D. Baxter[b] and Thomas S. Scanlan[a]

[a]*Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco, CA 94143-0446, USA*
[b]*Metabolic Research Unit, University of California, San Francisco, CA 94143-0540, USA*

A new series of 5′-substituted thyroid hormone analogues has been prepared. All of the compounds in the series function as T_3 agonists, with the exception of one compound, **GC-14**. **GC-14** in competition experiments with T_3, is able to antagonize T_3 activation in a dose-dependent manner.



GC-14

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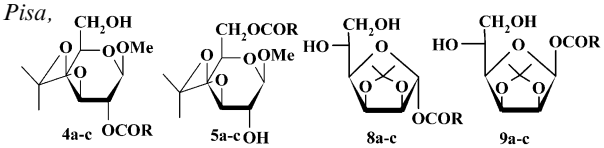
Preparation and Evaluation of the In Vitro Erythroid Differentiation Induction Properties of Some Esters of Methyl 3,4-*O*-Isopropylidene-β-D-galactopyranoside and 2,3-*O*-Isopropylidene-D-mannofuranose

Giorgio Catelani,[a] Felicia D'Andrea,[a] Ettore Mastrorilli,[a] Nicoletta Bianchi,[b] Cristiano Chiarabelli,[b] Monica Borgatti,[b] Dino Martello[b] and Roberto Gambari[b,*]

[a]*Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno, 33-56126, Pisa, Italy*
[b]*Dipartimento di Biochimica e Biologia Molecolare, Università di Ferrara, Via L. Borsari, 46-44100, Ferrara, Italy*

Glycide esters **4a–c**, **5a–c**, **8a–c** and **9a–c** were synthesized and in vitro tested as erythroid inducers toward K562 human leukemic cells. Compounds **5b**, **5c**, **8b**, **8c** and **9c** exhibit a high biological activity and could be proposed as possible erythroid differentiation agents.



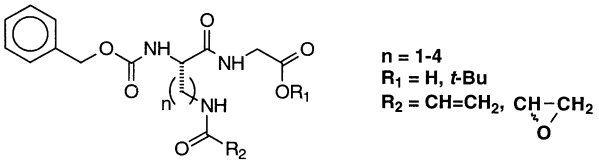
Bioorg. Med. Chem. 10 (2002) 355

Synthesis of Dipeptide-Bound Epoxides and α,β-Unsaturated Amides as Potential Irreversible Transglutaminase Inhibitors

Pierre de Macédo, Claudio Marrano and Jeffrey W. Keillor

Département de chimie, Université de Montréal, C.P. 6128, Succursale Centre-ville, Montréal, Québec, Canada H3C 3J7

The synthesis of 24 irreversible transglutaminase inhibitors is reported.



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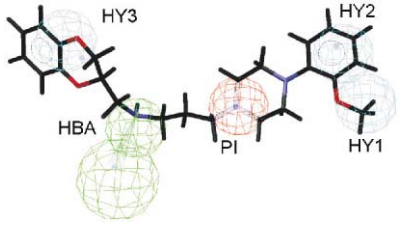
Synthesis and Biological Activity of New 1,4-Benzodioxan-arylpiperazine Derivatives. Further Validation of a Pharmacophore Model for α_1-Adrenoceptor Antagonists

Roberta Barbaro,[a] Laura Betti,[b] Maurizio Botta,[c] Federico Corelli,[c] Gino Giannaccini,[b] Laura Maccari,[c] Fabrizio Manetti,[c] Giovannella Strappaghetti[a] and Stefano Corsano[a]

[a]*Istituto di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo 1, 06123 Perugia, Italy*
[b]*Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Università di Pisa, Via Bonanno 6, 56126 Pisa, Italy*
[c]*Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via A. Moro, 53100 Siena, Italy*

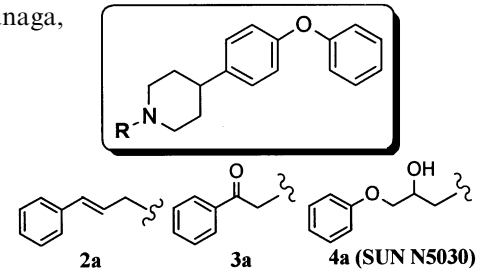


Bioorg. Med. Chem. 10 (2002) 371

Synthesis and Biological Evaluation of New 4-Arylpiperidines and 4-Aryl-4-piperidinols: Dual Na^+ and Ca^{2+} Channel Blockers with Reduced Affinity for Dopamine D_2 Receptors

Hirokazu Annoura, Kyoko Nakanishi, Mayumi Uesugi, Atsuko Fukunaga, Seiichi Imajo, Atsuko Miyajima, Yoshiko Tamura-Horikawa and Shigeki Tamura

Suntory Biomedical Research Limited, 1-1-1, Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka 618–8503, Japan



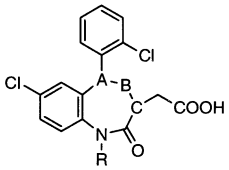
Bioorg. Med. Chem. 10 (2002) 385

Syntheses of Fused Heterocyclic Compounds and Their Inhibitory Activities for Squalene Synthase

Takashi Miki, Masakuni Kori, Akira Fujishima, Hiroshi Mabuchi, Ryu-ichi Tozawa, Masahira Nakamura, Yasuo Sugiyama and Hidefumi Yukimasa

Takeda Chemical Industries, Ltd. Pharmaceutical Research Division; 2-17-85, Juso-Honmachi, Yodogawa-ku, Osaka 532-8686, Japan

A variety of fused heterocyclic compounds were synthesized and evaluated for squalene synthase inhibitory activity. The 4,1-benzoxazepine nucleus is optimal template. Comparison of the X-ray structures of these compounds suggests that orientation of the 5 (or 6)-phenyl group is important for activity.



A-B-C = CH–O–CH, CH–S–CH, CH–CH_2–N, C = N–CH, CH–NH–CH, CH–CH_2–CH, CH–CH_2O–CH, etc.

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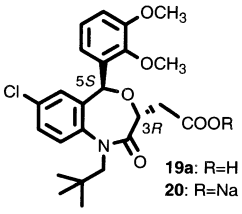
Novel 4,1-Benzoxazepine Derivatives with Potent Squalene Synthase Inhibitory Activities

Takashi Miki, Masakuni Kori, Hiroshi Mabuchi, Hiroshi Banno, Ryu-ichi Tozawa, Masahira Nakamura, Shigekazu Itokawa, Yasuo Sugiyama and Hidefumi Yukimasa

Takeda Chemical Industries, Ltd. Pharmaceutical Research Division, 2-17-85, Juso-Honmachi, Yodogawa-ku, Osaka 532-8686, Japan

Novel 4,1-benzoxazepine derivatives were prepared and evaluated for squalene synthase inhibitory activity. The (3*R*,5*S*)-enantiomer **19a** exhibited potent activity, while the (3*S*,5*R*)-enantiomer exhibited the modest inhibitory activity. Compound **20** (sodium salt of **19a**) markedly decreased plasma cholesterol in marmosets.

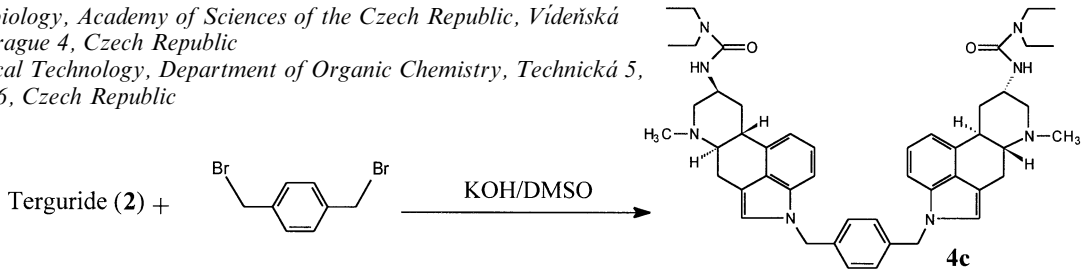


Bioorg. Med. Chem. 10 (2002) 415

Clustered Ergot Alkaloids Modulate Cell-mediated Cytotoxicity

Vladimír Křen,[a] Anna Fišerová,[a] Lenka Weignerová,[a] Ivan Stibor,[b] Petr Halada,[a] Věra Přikrylová,[a] Petr Sedmera[a] and Miloslav Pospíšil[a]

[a]*Institute of Microbiology, Academy of Sciences of the Czech Republic, Vídeňská 1083, CZ 142 20 Prague 4, Czech Republic*
[b]*Institute of Chemical Technology, Department of Organic Chemistry, Technická 5, CZ 166 10 Prague 6, Czech Republic*



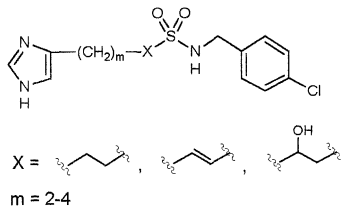
Bioorg. Med. Chem. 10 (2002) 425

ω-(Imidazol-4-yl)alkane-1-sulfonamides: A New Series of Potent Histamine H_3 Receptor Antagonists

Matthew J. Tozer, Ildiko M. Buck, Tracey Cooke, S. Barret Kalindjian, Michael J. Pether and Katherine I. M. Steel

The James Black Foundation, 68 Half Moon Lane, Dulwich, London, SE24 9JE, UK

ω-(1*H*-Imidazol-4-yl)alkane-1-sulfonamides, ω-(1*H*-imidazol-4-yl)alk-1-ene-1-sulfonamides and 2-hydroxy-ω-(1*H*-imidazol-4-yl)alkane-1-sulfonamides were prepared and found to be potent histamine H_3 receptor antagonists.

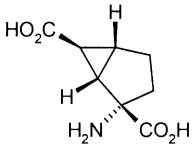


Bioorg. Med. Chem. 10 (2002) 433

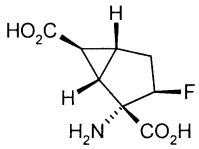
Stereoselective Synthesis of 2-Amino-3-fluoro Bicyclo[3.1.0]hexane-2,6-dicarboxylic Acid

Concepción Pedregal[a] and William Prowse[b]

[a]*Centro de Investigación Lilly, SA, Avda. de la Industria, 30, 28108, Alcobendas, Madrid, Spain*
[b]*Lilly Research Centre Ltd., Windlesham, Surrey GU20 6PH, UK*



(+) 4 (LY354740)



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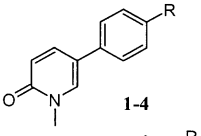
Bioorg. Med. Chem. 10 (2002) 437

5-Phenyl Substituted 1-Methyl-2-pyridones and 4′-Substituted Biphenyl-4-carboxylic Acids. Synthesis and Evaluation as Inhibitors of Steroid-5α-reductase Type 1 and 2

Franck Picard, Tobias Schulz and Rolf W. Hartmann

8.5 Pharmaceutical and Medicinal Chemistry, Saarland University, PO Box 15 11 50, D-66041 Saarbrücken, Germany

The synthesis of 18 title compounds designed as steroidomimetic inhibitors of 5α-reductase is described. They showed a wide variety of inhibitory activities toward human and rat isozymes 1 and 2.



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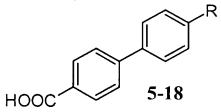

5-18

R : -CON< , -COAlkyl

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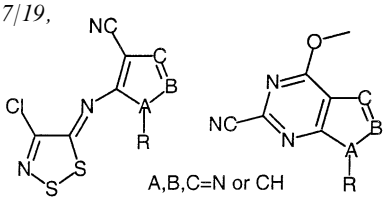
Antimicrobial and Antitumor Activity of *N*-Heteroimmine-1,2,3-dithiazoles and Their Transformation in Triazolo-, Imidazo-, and Pyrazolopirimidines

Pier Giovanni Baraldi,[a] Maria Giovanna Pavani,[a] Maria del Carmen Nuñez,[a] Patrizia Brigidi,[b] Beatrice Vitali,[b] Roberto Gambari[c] and Romeo Romagnoli[a]

[a]*Dipartimento di Scienze Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 17/19, 44100 Ferrara, Italy*
[b]*Dipartimento di Scienze Farmaceutiche, Via Belmeloro, 40126 Bologna, Italy*
[c]*Dipartimento di Biochimica e Biologia Molecolare, Università di Ferrara, Via L. Borsari 46, 44100 Ferrara, Italy*

A series of 4-chloro-5-heteroimmine-1,2,3-dithiazoles has been evaluated for their antibacterial, antifungal and antitumor activity. The subsequent cyclization with sodium methoxide in boiling methanol furnished pyrazolo, imidazole and triazole-pyrimidines.



A,B,C=N or CH

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A Mercapto Analogue of 5′-Noraristeromycin

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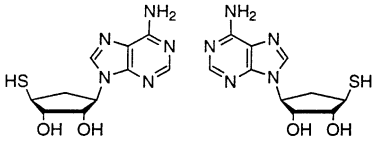

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