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Graphical Abstracts/J. Fluorine Chem. 129 (2008) 725–729

J. Fluorine Chem., 129 (2008) 731

Use of fluorinated functionality in enzyme inhibitor development: Mechanistic and analytical advantages

David B. Berkowitz, Kannan R. Karukurichi, Roberto de la Salud-Bea, David L. Nelson, Christopher D. McCune

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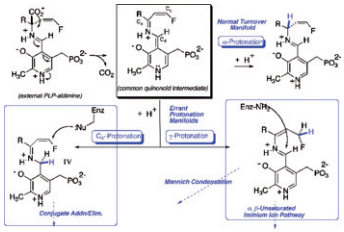
Incorporation of fluorinated functionality into enzyme inhibitor design allows for the calculated re-routing of mechanistic intermediates. The "bio-orthogonality" of the 19-F isotope provides a built-in analytical tool by which to follow the mechanistic course of such fluorinated inhibitors.



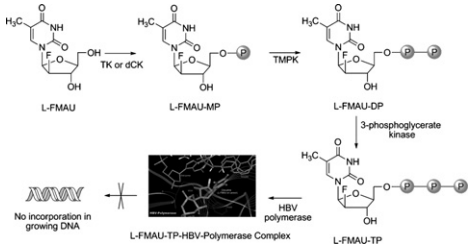
J. Fluorine Chem., 129 (2008) 743

Fluorinated nucleosides: Synthesis and biological implication

Peng Liu, Ashoke Sharon, Chung K. Chu

The University of Georgia, College of Pharmacy, Athens, GA 30602, USA

A number of important pharmaceuticals have been discovered based on fluorinated analogs of biologically active nucleosides. The introduction of fluorine at an appropriate position has modulated and/or improved the pharmacological properties of nucleosides. The present review deals with the synthetic methodology, structural and biological implication of carbohydrate-modified fluoronucleosides.



J. Fluorine Chem., 129 (2008) 767

Synthesis of Ψ[CH(R_F)NH]Gly-peptides: The dramatic effect of a single fluorine atom on the diastereocontrol of the key aza-Michael reaction

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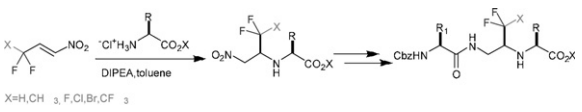
[b]*C.N.R-Istituto di Chimica del Riconoscimento Molecolare, Sezione "A. Quilico", via Mancinelli 7, I-20131 Milano, Italy*



We describe in full-detail the synthesis of new ψ[CH(R_F)NH]-peptidomimetics, having different fluoroalkyl groups R_F, as peptide bond surrogates. A key step in the synthesis is a stereoselective aza-Michael addition of chiral α-amino acid esters to β-fluoroalkyl-α-nitroethenes. The diastereoselection of the process was influenced by the electronegativity, rather than by the steric bulk, of the fluorinated residue R_F in the β-position of the nitroalkene acceptors. Replacement of a single F atom of R_F by a hydrogen or methyl group brings about a dramatic drop of stereocontrol, whereas Br, Cl and CF_3, albeit bulkier than F, provide inferior results in terms of stereocontrol. A mechanistic hypothesis is provided.

doi:10.1016/S0022-1139(08)00251-0

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Gem-difluorination in superacid: The dramatic role of halonium ions

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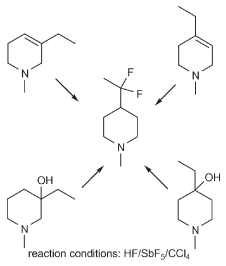

In HF/SbF_5, in the presence of CCl_4 or NBS, unsaturated or hydroxylated piperidines yield difluoroanalogues in good yields. The ability to perform hydride abstraction on chloroderivatives, and the ability to form bridged bromonium ions from unsaturated substrates seem to completely influence the reaction course. Some aspects of the mechanism were clarified by DFT calculations.

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Practical syntheses of 4-fluoroprolines

Mukund S. Chorghade[a], Debendra K. Mohapatra[b], Gokarneswar Sahoo[b], Mukund K. Gurjar[b], Manish V. Mandlecha[c], Nitin Bhoite[c], Santosh Moghe[c], Ronald T. Raines[d]

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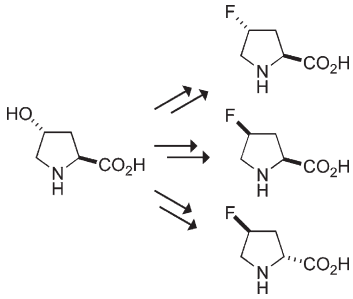
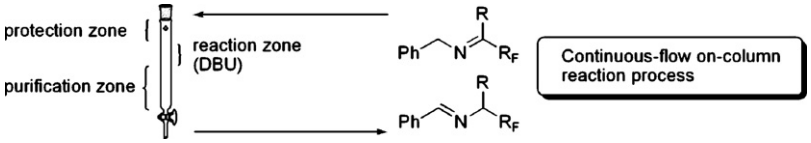
[b]*National Chemical Laboratory, Pune, India*
[c]*THINQ Pharma–CRO, Mumbai, India*
[d]*Departments of Biochemistry and Chemistry, University of Wisconsin–Madison, Madison, WI 53706, USA*



Routes have been developed for the economical, process-scale synthesis of the 2*S*,4*R*, 2*S*,4*S*, and 2*R*,4*S* diastereomers of 4-fluoroproline.

J. Fluorine Chem., 129 (2008) 785

First example of continuous-flow reaction conditions for biomimetic reductive amination of fluorine-containing carbonyl compounds



Vadim A. Soloshonok[a,b], Taizo Ono[a]

[a]*National Institute of Advanced Industrial Science and Technology (AIST), 2266 Anagahora, Shimoshidami, Moriyama-ku, Nagoya, Aichi 463-8560, Japan*
[b]*Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK 73019, United States*

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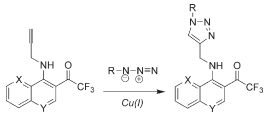
Copper catalyzed 1,3-dipolar cycloaddition reaction of azides with *N*-(2-trifluoroacetylaryl)propargylamines. A mild entry to novel 1, 4-disubstituted-[1,2,3]-triazole derivatives



Jean-Florent Lamarque[a], Christophe Lamarque[a], Sandrine Lassara[a], Maurice Médebielle[a], Jérome Molette[a], Emilie David[b], Stéphane Pellet-Rostaing[b], Marc Lemaire[b], Etsuji Okada[c], Dai Shibata[d], Guillaume Pilet[e]

[a]*Université de Lyon, Université Claude Bernard Lyon 1 (UCBL), Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), Laboratoire de Synthèse de Biomolécules (LSB), UMR 5246 CNRS-UCBL-INSA Lyon-CPE Lyon, Bâtiment Chevreul, 43 bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France*
[b]*Université de Lyon, Université Claude Bernard Lyon 1 (UCBL), Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), Laboratoire de Catalyse et Synthèse Organique (CASO), UMR 5246 CNRS-UCBL-INSA Lyon-CPE Lyon, Bâtiment 308 CPE Lyon, 43 bd du 11 Novembre 1918, 69616 Villeurbanne Cedex, France*
[c]*Department of Chemical Science and Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan*
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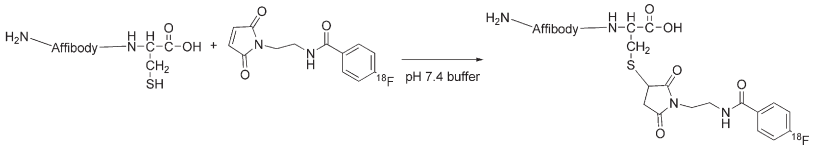
Radiolabeling of HER2-specific Affibody® molecule with F-18

Dale O. Kiesewetter[a], Gabriela Krämer-Marek[b], Ying Ma[a], Jacek Capala[b]

[a]*Positron Emission Tomography Radiochemistry Group, NIBIB, Bethesda, MD 20892, United States*
[b]*Radiation Oncology Branch, NCI, NIH, Bethesda, MD 20892, United States*



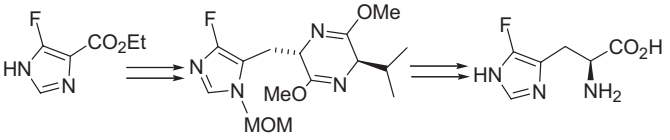
The optimization of the conjugation of Affibody® molecule with *N*-[2-(4-[^{18}F]fluorobenzamido)ethyl]maleimide to produce a PET imaging agent for HER2-expressing tumors is described.

J. Fluorine Chem., 129 (2008) 807

An enantioselective synthesis of (*S*)-4-fluorohistidine

Jan Hajduch, John C. Cramer, Kenneth L. Kirk

Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, DHHS, Bethesda, MD 20892, United States



(*S*)-4-Fluorohistidine was synthesized by diastereoselective alkylation of a MOM-protected 4-fluoro-5-bromomethyl imidazole.

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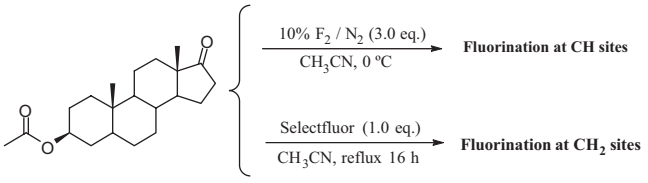
Elemental fluorine. Part 22. [For Part 21, see R.D. Chambers, G. Sandford, J. Trmcic, T. Okazoe, Org. Proc. Res. Dev. (in press)] Fluorination of 3β-acetoxy-5α-androstan-17-one using fluorine and Selectfluor®



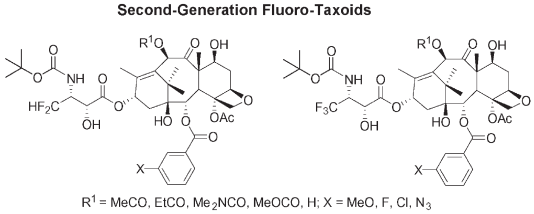
Richard D. Chambers[a], Takashi Nakano[a], Mandy Parsons[a], Graham Sandford[a], Andrei S. Batsanov[b], Judith A.K. Howard[b]

[a]*Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK*
[b]*Chemical Crystallography Group, Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK*

Fluorination of 3β-acetoxy-5α-androstan-17-one by elemental fluorine gives products arising from fluorination at tertiary CH sites whereas Selectfluor gives products derived from fluorination of CH_2 sites.

J. Fluorine Chem., 129 (2008) 817

Syntheses and structure–activity relationships of novel 3′-difluoromethyl and 3′-trifluoromethyl-taxoids



Larissa V. Kuznetsova[a], Antonella Pepe[a], Ioana M. Ungureanu[a], Paula Pera[c], Ralph J. Bernacki[c], Iwao Ojima[ab]

[a]*Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, United States*
[b]*Institute of Chemical Biology & Drug Discovery, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, United States*
[c]*Department of Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Institute, Elm and Carlton Streets, Buffalo, NY 14263, United States*

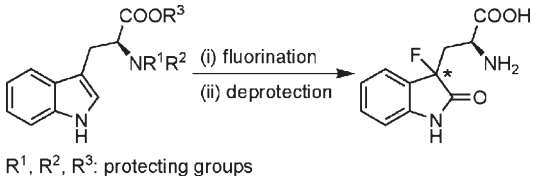
Novel 3′-difluoromethyl-taxoids and 3′-trifluoromethyl-taxoids were synthesized and evaluated for their *in vitro* cytotoxicities against human breast, non-small cell lung, and colon cancer cell lines. These second-generation fluoro-taxoids exhibit two orders of magnitude higher potency than paclitaxel against multidrug-resistant cancer cell lines. Structure–activity relationship of these highly potent fluoro-taxoids is discussed.

J. Fluorine Chem., 129 (2008) 829

Synthetic studies of 3-(3-fluorooxindol-3-yl)-L-alanine

Tomoya Fujiwara[a], Bin Yin[a], Meixiang Jin[a], Kenneth L. Kirk[b], Yoshio Takeuchi[a]

[a]*Graduate School of Medicine and Pharmaceutical Sciences for Research, University of Toyama, Sugitani 2630, Toyama 930-0194, Japan*
[b]*Laboratory of Bioorganic Chemistry, National Institute of Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, DHHS, Bethesda, MD 20892, USA*



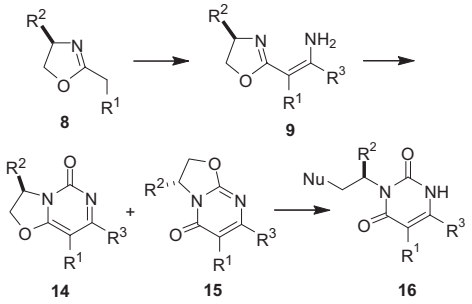
J. Fluorine Chem., 129 (2008) 836

An efficient synthesis of uracil derivatives from 2-alkyl-Δ^2-oxazolines and nitriles

Santos Fustero[a,b], Juan F. Sanz-Cervera[a,b], Salvador Mérida[a], Raquel Román[a], Salvador Villanova[a], Carmen Ramírez de Arellano[a]

[a]*Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain*
[b]*Centro de Investigación Príncipe Felipe, E-46013 Valencia, Spain*

The synthesis of both fluorinated and non-flurinated uracil derivatives is described.



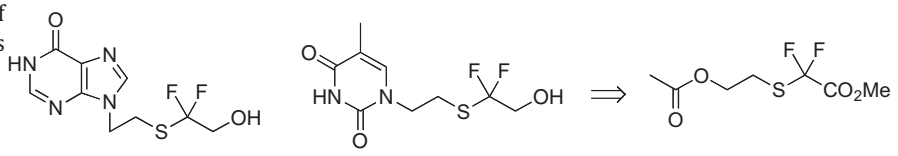
J. Fluorine Chem., 129 (2008) 848

Synthesis and biological evaluation of fluorinated acyclothionucleosides

Sonia Gouault-Bironneau, Aboubacary Sène, Jean-Marie Catel, Thierry Lequeux

Laboratoire de Chimie Moléculaire et Thio-organique, ENSICAEN, Université de Caen Basse-Normandie, CNRS-UMR 6507, 6 boulevard du Maréchal Juin, 14050 Caen, France

The synthesis and the biological activity of *gem*-difluoro-acythioclonucleoside analogues are reported.



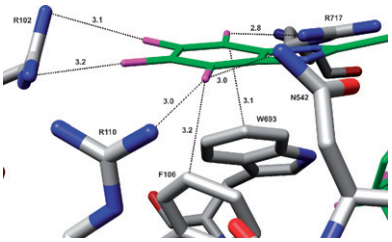
J. Fluorine Chem., 129 (2008) 852

A fluorine scan of non-peptidic inhibitors of neprilysin: Fluorophobic and fluorophilic regions in an enzyme active site

Martin Morgenthaler[a], Johannes D. Aebi[b], Fiona Grüninger[b], Daniel Mona[b], Björn Wagner[b], Manfred Kansy[b], François Diederich[a]

[a]*Laboratorium für Organische Chemie, ETH Zürich HCI, Hönggerberg, CH-8093 Zürich, Switzerland*
[b]*Pharmaceuticals Division, Discovery Chemistry, F. Hoffmann-La Roche AG, CH-4070 Basel, Switzerland*

A series of fluorinated inhibitors of the metalloprotease neprilysin (NEP) was prepared. The arginine-rich protein environment around the central platform of the inhibitor was found to tolerate fluorine substituents well, whereas fluorination of ligand fragments filling the S1' pocket led to significantly lower binding affinities.

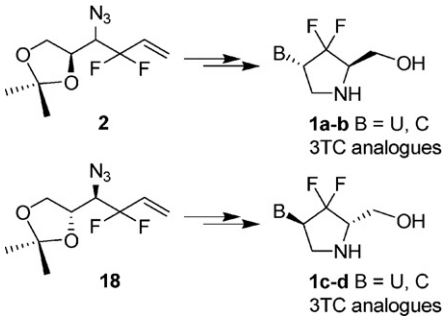


J. Fluorine Chem., 129 (2008) 866

Synthesis of 2′,3′-dideoxy-6′,6′-difluoro-3′-azanucleosides

Xuyi Yue[a], Xiao-Long Qiu[a], Feng-Ling Qing[a,b]

[a]*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*
[b]*College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China*

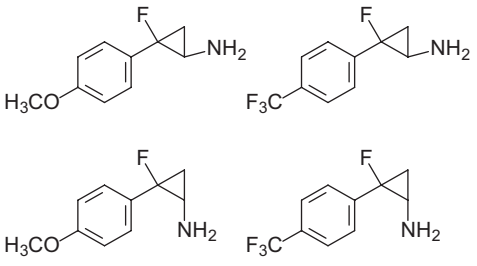


J. Fluorine Chem., 129 (2008) 875

Fluorinated phenylcyclopropylamines. Part 6. Effects of electron withdrawing or donating aryl substituents on the inhibition of tyramine oxidase from *Arthrobacter* sp. by diastereomeric 2-aryl-2-fluoro-cyclopropylamines

Svenja Hruschka[a], Shinichi Yoshida[b], Kenneth L. Kirk[c], Günter Haufe[a]

[a]*Organisch-Chemisches Institut and International NRW Graduate School of Chemistry, Universität Münster, Corrensstr. 40, D-48149 Münster, Germany*
[b]*Tottori Institute of Industrial Technology, Tottori 689-1112, Japan*
[c]*Laboratory of Bioorganic Chemistry, National Institute of Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892, USA*



Diastereomeric 2-aryl-2-fluorocyclopropylamines with electron-donating or electron withdrawing groups such as methox- or trifluoromethyl groups in the aromatic ring are investigated as tyramine oxidase inhibitors.

J. Fluorine Chem., 129 (2008) 881

Synthesis of fluorinated analogues of the neurosteroid $GABA_A$ receptor antagonist, 17-PA

Gildas Deniau[a], Keith T. Sillar[b], David O'Hagan[a]

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[b]*School of Biology, Bute Building, University of St-Andrews, St-Andrews, Fife KY16 9TS, Scotland KY16 9ST, UK*