Total Synthesis of (+)-Rubellin C

Jackson A. Gartman and Uttam K. Tambar* (uttam.tambar@utsouthwestern.edu)


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Abstract: The rubellins are a family of stereochemically complex anthraquinoid heterodimers containing an unprecedented chemical scaffold. Although the rubellins have been known for over three decades, no total synthesis has been achieved since their discovery. Their topology is characterized by a 6–5–6 fused ring system, five neighboring stereocenters including a quaternary center all in a convoluted core, and an anthraquinone nucleus. The rubellin architecture has been shown to inhibit and reverse the aggregation of tau protein, a therapeutically relevant target for Alzheimer’s disease. Herein, we describe the first stereoselective synthesis of a member of the family, (+)-rubellin C, in 16 steps. Strategic disconnections allow expedient construction of stereochemical and topological intricacy in a short sequence of borylative and transition metal-catalyzed steps.

Synthesis of Novel Nitroxoline Analogs with Potent Cathespin B Exopeptidase Inhibitory Activity

Tim Van de Walle, Marina Briand, Ana Mitrović, Izidor Sosič, Stanislav Gobec, Janko Kos, Leentje Persoons, Dirk Daelemans, Steven De Jonghe, Zorica Ubiparip, Tom Desmet, Kristof Van Hecke, Sven Mangelinckx, and Matthias D’hooghe* (matthias.dhooghe@ugent.be)


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Abstract: Nitroxoline, a well-known antimicrobial agent, has been identified in several independent studies, and on different molecular targets, as a promising candidate to be repurposed for cancer treatment. One specific target of interest concerns cathepsin B, a lysosomal peptidase involved in the degradation of the extracellular matrix (ECM), leading to tumor invasion, metastasis and angiogenesis. However, dedicated optimization of the nitroxoline core is needed to actually deliver a nitroxoline-based antitumor drug candidate. Within that context, 34 novel nitroxoline analogs were synthesized and evaluated for their relative cathepsin B inhibitory activity, their antiproliferative properties and their antimicrobial activity. More than twenty analogs were shown to exert a similar or even slightly higher cathepsin B inhibitory activity compared to nitroxoline. The implemented modifications of the nitroxoline scaffold and the resulting SAR information can form an eligible basis for further optimization toward more potent cathepsin B inhibitors in the quest for a clinical nitroxoline-based antitumor agent.
Synthetic Strategies in Curcumin Chemistry Focused on Anticancer Applications
Atiruj Theppawong, Gurkirat Kaur, Vipan Kumar, John Van Camp, and Matthias D’hooghe*
(matthias.dhooghe@ugent.be)
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Abstract: In spite of having received considerable interest as a potential anticancer agent over the past two decades, curcumin has not been developed into a sturdy drug candidate yet, mainly due to the challenges imposed by its rapidly metabolizable structure, leading to bioavailability and stability issues, and its aspecific activity. To circumvent these obstacles, chemical modification of the parent scaffold has been shown to involve an eligible approach for the construction of curcuminoids with improved properties. This review article provides a compilation of curcumin modifications and the effect thereof on the anticancer activity displayed by the resulting new analogs.

Design, Synthesis, and Structure–Activity Relationship Studies of (4-Alkoxynaphthaloyl)glycinamides and Bioisosteric 1,3,4-Oxadiazoles as GPR88 Agonists
Md Toufiqur Rahman, Ann M.Decker, Tiffany L. Langston, Kelly M. Mathews, Lucas Laudermilk, Rangan Maitra, Weiya Ma, Emmanuel Darcq, Brigitte L. Kieffer, and Chunyang Jin*
(cjin@rti.org)
DOI: 10.121/acs.jmedchem.0c01581

Abstract: Increasing evidence implicates the orphan G protein-coupled receptor 88 (GPR88) in a number of striatal-associated disorders. In this study, we report the design and synthesis of a series of novel (4-alkoxynaphthaloyl)glycinamides (e.g., 31) and the corresponding 1,3,4-oxadiazole bioisosteres derived from the 2-AMPP scaffold (1) as GPR88 agonists. The 5-amino-1,3,4-oxadiazole derivatives (84, 88–90) had significantly improved potency and lower lipophilicity compared to 2-AMPP. Compound 84 had an EC₅₀ of 59 nM in the GPR88 overexpressing cell-based cAMP assay. In addition, 84 had an EC₅₀ of 942 nM in the [³⁵S]GTPγS binding assay using mouse striatal membranes but was inactive in membranes from GPR88 knockout mice, even at a concentration of 100 μM. In vivo pharmacokinetic testing of 90 in rats revealed that the 5-amino-1,3,4-oxadiazole analogues may have limited brain permeability. Taken together, these results provide the basis for further optimization to develop a suitable agonist to probe GPR88 functions in the brain.
**Chemoenzymatic Route to Stereodefined 2-(Azidophenyl)oxazolines for Click Chemistry**

Paige J. Monsen and Frederick A. Luzzio (faLuzz01@louisville.edu)


**Abstract:** Aryl-substituted esters of a racemic diprotected 2-azido-1-alkanol were submitted to the Staudinger/aza-Wittig reaction in order to assess scope and establish conditions for cyclization to the corresponding 2,4,5-trisubstituted oxazolines. Following the cyclization study, the (2R,3R)-antipode of the azidoalkanol was obtained in high ee by incubation of the corresponding racemic azidoacetate with pig liver esterase (PLE) under aqueous conditions. The p-nitrobenzoate of the enantioenriched 2-azido-1-alcohol was cyclized with triphenylphosphine/THF to give the corresponding (4R,5R)-disubstituted-2-(4-nitrophenyl) oxazoline. Selective reduction of the nitrophenyloxazoline to the corresponding aminophenyloxazoline using aluminum amalgam followed by direct azidation of the 2-(4-aminophenyl) moiety provided the corresponding (4R,5R)-2-(4-azidophenyl) oxazoline derivative. The azidophenyl oxazoline was reacted with a proven click partner 4-ethynylfluorobenzene under copper/sodium ascorbate mediation to provide the click triazole product in high yield.

**Decarboxylative Amination: Diazirines as Single and Double Electrophilic Nitrogen Transfer Reagents**

Preeti P. Chandrachud, Lukasz Wojtas, and Justin M. Lopchuk* (justin.lopchuk@moffitt.org)


**Abstract:** The ubiquity of nitrogen-containing small molecules in medicine necessitates the continued search for improved methods for C–N bond formation. Electrophilic amination often requires a disparate toolkit of reagents whose selection depends on the specific structure and functionality of the substrate to be aminated. Further, many of these reagents are challenging to handle, engage in undesired side reactions, and function only within a narrow scope. Here we report the use of diazirines as practical reagents for the decarboxylative amination of simple and complex redox-active esters. The diaziridines thus produced are readily diversifiable to amines, hydrazines, and nitrogen-containing heterocycles in one step. The reaction has also been applied in fluorous phase synthesis with a perfluorinated diazirine.
(S)-1-(Ethoxycarbonyl)ethyl(2R,5S)-2,5-dimethyl-1,3-dioxolan-4-one-2-carboxylate
R. Alan Aitken,* Oliver E. Haslett, and Alexandra M. Z. Slawin (raa@st-and.ac.uk)
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Abstract: The title compound was obtained in low yield in the condensation of ethyl pyruvate and lactic acid. Its structure is determined by NMR methods and X-ray diffraction and the mechanism for formation of this 1:2 adduct from the initial 1:1 adduct is considered.

The Stereospecific and Enantiospecific Synthesis of Indole Alkaloids which Culminated in the Ambidextrous Pictet–Spengler Reaction for the C-19 Methyl-substituted Sarpagine Family
M. Toufiqur Rahman, Ojas A. Namjoshi, James M. Cook* (capncook@uwm.edu)
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Abstract: The Pictet–Spengler reaction continues to be widely employed in the synthesis of bioactive natural products, as well as synthetic compounds containing the THIC and THIQ moieties. The asymmetric version of this reaction has been central to the enantiospecific total synthesis of >150 sarpagine/macroline/ajmaline alkaloids. The diastereospecific Pictet–Spengler reaction under thermodynamic control is crucial to the large-scale synthesis of the important tetracyclic bicyclo[3.3.1] core in >98% ee towards many indole alkaloids from this superfamily. Extensive exploration of the Pictet–Spengler reaction for the emerging class of C-19 methyl-substituted sarpagine/macroline/ajmaline alkaloids has resulted in the ambidextrous version, which has enabled access to both the natural and unnatural enantiomers of alkaloids starting with either D- or L-tryptophan, at will. Some noteworthy recent applications of the large scale Pictet–Spengler reaction in the total synthesis of sarpagine-related alkaloids and the development of the ambidextrous Pictet–Spengler reaction are described in this chapter.