

COVER IMAGE

Chemical probes provide important tools for dynamically interrogating biological systems and for investigating potential drug targets. In this issue we feature a collection of Commentaries and Review Articles that highlight recent advances and future directions in the field.

On the cover, we highlight three research papers in this issue that describe advances in chemical probe research: using new biochemical assays, Bradner *et al.* discover unexpected selectivity within current HDAC inhibitors and develop a true pan-HDAC inhibitor (p238); Kokel *et al.* describe a method for identifying neuroactive molecules and predicting their mode of action through behavioral zebrafish assays (p231); and Bracha *et al.* use a combination of RNAi, metabolomics and chemical probes to uncover metabolic enzymes that regulate myoblast differentiation (p202). Cover image by Katie Vicari, based on artwork provided by Sigrid Hart (phylogenetic trees), Randall Peterson (zebrafish images) and Felice Frankel (cell images).

Corrected after print 18 March 2010.

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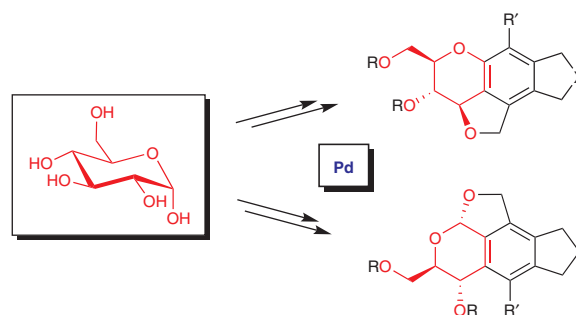
BRIEF COMMUNICATIONS

199 Domino access to highly substituted chromans and isochromans from carbohydrates

M Leibelng, D C Koester, M Pawliczek, S C Schild & D B Werz

Pd-catalyzed domino reactions have been shown to stitch together chemical groups to form more complex scaffolds. Now these methods are used in a diversity-oriented synthesis approach to make intricate natural product-like structures using simple sugars as starting materials.

► N&V p174

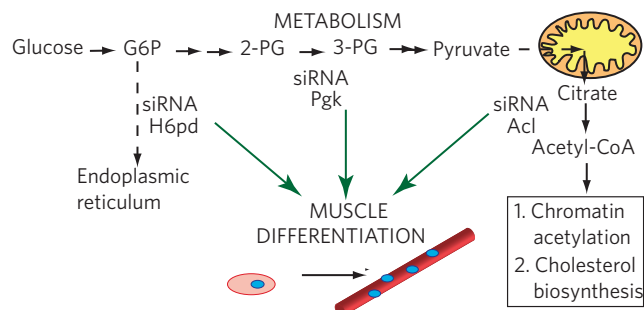


202 Carbon metabolism-mediated myogenic differentiation

A L Bracha, A Ramanathan, S Huang, D E Ingber & S L Schreiber

Differentiation of mouse myoblasts is coordinated with glycolysis, calcium/calcineurin signaling, chromatin acetylation and cholesterol biosynthesis. This is consistent with profiling of the intracellular metabolites that accompany myogenic differentiation and points to new targets for cancer differentiation therapy of rhabdomyosarcoma.

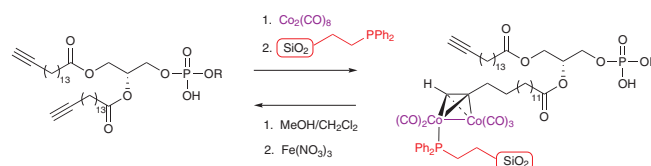
► N&V p176



205 Capture and release of alkyne-derivatized glycerophospholipids using cobalt chemistry

S B Milne, K A Tallman, R Serwa, C A Rouzer, M D Armstrong, L J Marnett, C M Lukehart, N A Porter & H A Brown

Reversible cobalt complexation of alkynes is a critical step in some chemical transformations. New research shows this reaction can be used to specifically retrieve modified lipids from complex cellular mixtures, simplifying tracking and providing insights into lipid metabolism.

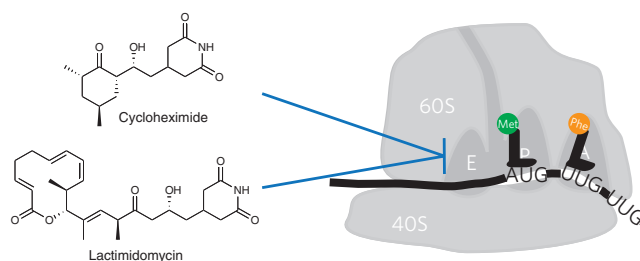


ARTICLES

209 Inhibition of eukaryotic translation elongation by cycloheximide and lactimidomycin

T Schneider-Poetsch, J Ju, D E Elyer, Y Dang, S Bhat, W C Merrick, R Green, B Shen & J O Liu

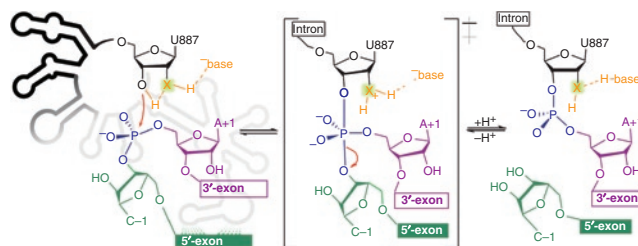
Cycloheximide is a natural product that cell biologists have used for decades as a tool to arrest protein synthesis in eukaryotes. Biochemical data now refine our mechanistic view of how cycloheximide and structurally related analogs inhibit translational elongation.



218 The 2'-OH group at the group II intron terminus acts as a proton shuttle

M Roitzsch, O Fedorova & A M Pyle

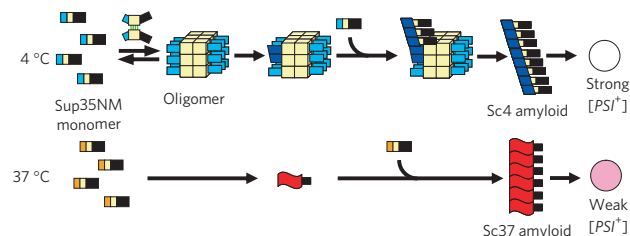
Group II introns can act as mobile genomic elements and integrate into genomic DNA through reverse splicing. A selective nucleotide modification approach was used to show that the 2'-hydroxyl at the ribozyme 3' terminus plays a catalytic role as a proton shuttle during reverse splicing.



225 Differences in prion strain conformations result from non-native interactions in a nucleus

Y Ohhashi, K Ito, B H Toyama, J S Weissman & M Tanaka

The prion strain phenomenon states that distinct amyloid conformations with different toxicity phenotypes and heritable states can arise from a single polypeptide. The decision about conformation is made at the level of the initial nucleus, where different nuclei will lead to different conformations.

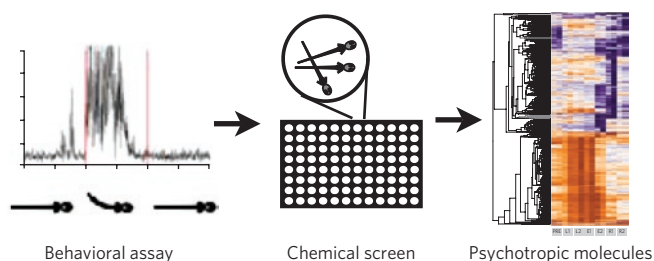


231 Rapid behavior-based identification of neuroactive small molecules in the zebrafish

D Kokel, J Bryan, C Laggner, R White, C Y J Cheung, R Mateus, D Healey, S Kim, A A Werdich, S J Haggarty, C A MacRae, B Shoichet & R T Peterson

Despite the need for new psychoactive drugs, there are few robust approaches for discovering novel neuroactive molecules. Development of a behavior-based, high-throughput screen in zebrafish led to the discovery of molecules with neurological effects. Translating the complex behavioral phenotypes elicited by compounds into a simple barcode enabled identification of their mechanism of action.

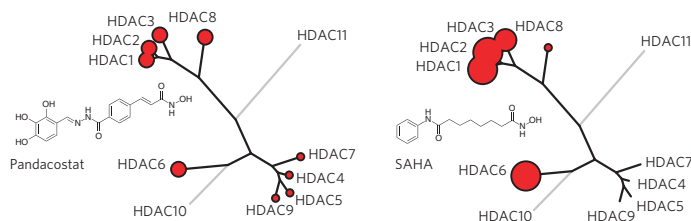
► N&V p172



238 Chemical phylogenetics of histone deacetylases

J E Bradner, N West, M L Grachan, E F Greenberg, S J Haggarty, T Warnow & R Mazitschek

In contrast to perceived nonselectivity, biochemical profiling reveals that currently available HDAC inhibitors predominantly inhibit only class I and IIb HDAC enzymes. A new pan-selective inhibitor, obtained by screening a focused library, provides an important tool for studying class IIa HDACs.



244 CORRIGENDA AND ERRATA

CLASSIFIEDS

See the back pages

ERRATUM

Cover caption

Nat. Chem. Biol. **6** (2010); published online 12 February 2010; corrected after print 18 March 2010

In the version of this cover caption initially published, Sigrid Hart's name was misspelled. The error has been corrected in the HTML and PDF versions of the cover caption.