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In This Issue

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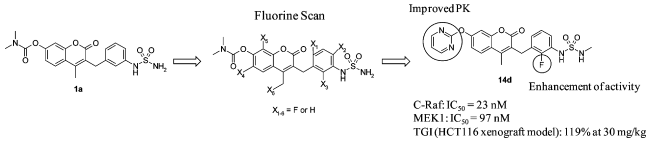
## FLUORINE SCANNING FOR BIOACTIVITY

Gene mutations for proteins along the RAS/RAF/MEK/ERK pathway have been identified in a range of tumor bodies. This pathway has been shown to be activated in cutaneous melanomas, thyroid, colonic, and ovarian carcinomas and some sarcomas. Thus, inhibitors of this pathway have been highly desirable and are continually in development, while some have progressed to clinical trials.

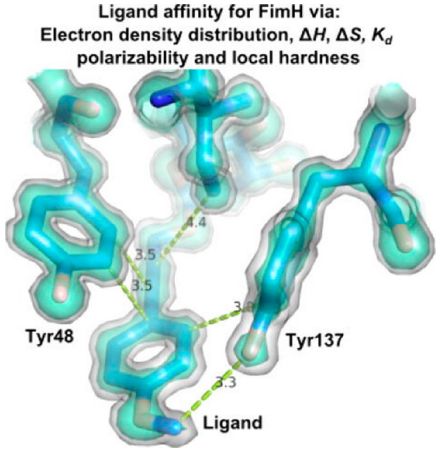
Fluorine substitutions of a lead compound are one of the most utilized modifications during lead optimizations, with ~20% of marketed drugs containing fluorine atoms. In this issue, Hyohdoh et al. (DOI: 10.1021/ml4002419) describes a late stage nonselective fluorination of previously reported key intermediates and lead structures with Raf/MEK inhibitory activity. The authors were able to obtain a larger set of monofluorinated compounds with comparable physiochemical properties to the nonfluorinated lead structure. The fluorine scanning strategy helped identify the best site for fluorine with respect to bioactivity.




## REACTIVITY DESCRIPTORS TO CALCULATE INTERACTION ENERGIES

Uro- and enteropathogenic *Escherichia coli* stick to epithelial linings by the binding of the fimbrial adhesin FimH to high-mannosylated receptors and can cause a sequel of infections and inflammations. Bacterial antibiotic resistance calls for alternative treatments of cystitis and Crohn's disease.

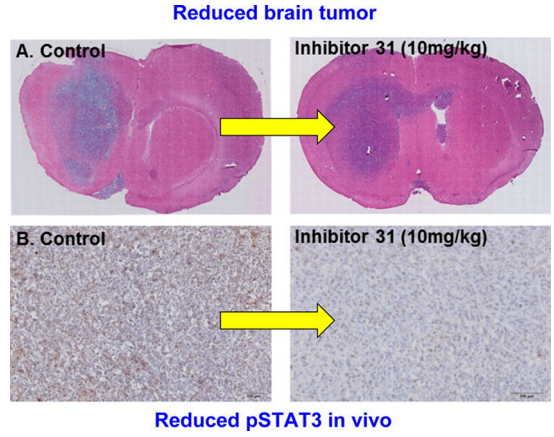
Here, Roos et al. (DOI: 10.1021/ml400269v) demonstrates that local hardness and polarizability are valuable tools in calculating interaction energies by evaluating these reactivity descriptors in predicting ligand affinity in the tyrosine gate of FimH. These descriptors can thus be used for a better identification of therapeutically promising FimH antagonists, provide insights to the search for new treatments of urinary tract infections, and are valuable tools for rapid drug design.




## INHIBITOR OF GLIOBLASTOMA BRAIN CANCER STEM CELLS

Glioblastoma (GBM) is thought to be the most aggressive and lethal of brain cancers, having a median survival after treatment of approximately 15 months. Brain tumors have been shown to contain subpopulations of brain tumor stem cells (BTSCs) that are clonogenic, self-renewal, multipotent, and tumorigenic. Thus, BTSCs require new therapeutic approaches to effectively eliminate in order to improve the outcome of GBM.

Haftchenary et al. (DOI: 10.1021/ml4003138) describe the identification of the potent, nonphosphorylated, direct-binding inhibitors of Signal Transducer and Activator of Transcription 3 (STAT3) SH2 domain. STAT3 gene is shown to be abnormally active in GBM and thus critically important in mediating tumor growth and therapeutic resistance. One compound displayed the highest STAT3 binding affinity, effectively suppressing STAT3 phosphorylation at nanomolar concentrations.

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