NEWS & ANALYSIS

...highlighting the latest news and research in medicinal chemistry from academia and industry

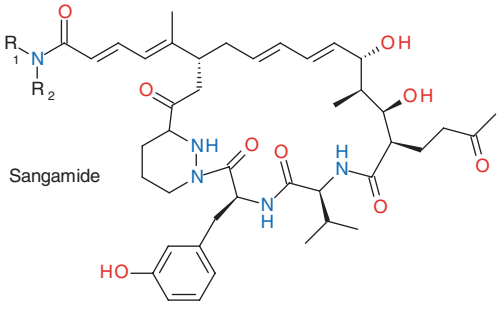
New compound class under investigation for HCV drug

A collaboration between researchers in academia and industry in the UK, China, Belgium and the USA has uncovered a potential new starting point for the discovery of novel HCV drugs. The works demonstrates that derivatives of sangamide show both *in vitro* and *in vivo* inhibition of the virus.

"...the group wanted to study a new compound class in order to improve the possibility of oral administration, reducing immunosuppressive activity and have greater potency against HCV."

Sangamide is a derivative of sanglifehrin A, a polyketide natural product from the *Streptomyces* sp. that binds to cyclophilin. This protein acts as a peptidyl-prolyl isomerase that catalyzes the *cis–trans* isomerization of the peptide bond preceding prolyl residues, an important process for HCV replication. While recent research regarding cyclophilin inhibitors, such as alisporivir, have been derived cyclosporine A, the group wanted to study a new compound class in order to improve the possibility of oral administration, reducing immunosuppressive activity and have greater potency against HCV.

The group first confirmed the mechanism of action, demonstrating that the sangamides investigated inhibited the interaction between the CypA and the HCV NS5A proteins using an *in vitro* model. Following this, the group studied the stability of the analogs of sangamide using phosphate buffered saline, human liver microsomes, mouse liver microsomes and human hepatocytes. While $t_{1/2}$ values for microsome stability were variable (ranging from 1 to 37 min), hepatocyte stability was much better.



When compared to cyclosporine A derivatives, including alisporivir, the sangamide compounds showed reduced immunosuppressant activity in human mixed lymphocyte reactions, with observed IC_{50} values being much higher than those reported for alisporivir. The researchers demonstrated (using a mouse model 10 mg/kg per os and 1 mg/kg intravenous dosing) that the pharmacokinetics of the sangamide compounds was suitable for a once-daily regime.

"When compared to cyclosporine A derivatives ... the sangamide compounds showed reduced immunosuppressant activity in human mixed lymphocyte reactions..."

One of the problems relating to the development of cyclosporine A analogs is that they inhibit the xenbiotic transporter MDR1/P-glycoprotein. Using MDCK MDR-1-expressing cell lines, the sangamide compounds showed no inhibition of this protein.

Of the 16 compounds investigated, the group have chosen the sangamide derivative with the $-O(CH_2)_4-$ spanning the R_1 and R_2 positions for further optimization.

Written by Isaac Bruce, Commissioning Editor.

Source: Moss SJ, Bobardt M, Leyssen P *et al.* Sangamides, a new class of cyclophilin-inhibiting host-targeted antivirals for treatment of HCV infection. *Med. Chem. Commun.* doi:10.1039/C1MD00227A (2011) (Epub ahead of print).

CONTENTS

FUTURE SCIENCE part of fsg

Trans-Pacific academia–industry agreement for the development of neurological therapeutics

The Japanese pharmaceutical company Eisai and John Hopkins University (USA) have announced that they are to work together on neurological drug-discovery projects. The collaboration hopes to utilize the drug-discovery strengths of teams at Eisai along with the translational expertise from researchers at John Hopkins University's Brain Science Institute in order to develop innovative therapeutics for a range of complaints.

> *"Eisai have a strong history in collaborating with academic institutions in the area of neurology."*

Eisai have a strong history in collaborating with academic institutions in the area of neurology. For over 20 years the company has worked with University College London (UK), a partnership that has entered a new phase this year with biomarker research relating to neuroinflammation, neurovascular/mitochondria, and proteostasis being undertaken. Kyoto University (Japan) has been developing non-human primate models with the pharmaceutical company in recent years also.

> *"Eisai will be allowed access to John Hopkins University's research regarding novel neurological therapeutic targets in return for them providing the university with its compound libraries."*

The Brain Institute at John Hopkins University will add Eisai to Biogen Idec, Johnson & Johnson and Helsinn Healthcare as its industrial partners. Since its official launch in 2007, the institute has awarded over US$13 million and boasts among its current drug-discovery project work relating to Mas-related G-protein coupled receptor activation for the treatment of pain and inhibition of glutamate carboxypeptidase II as a novel treatment for peripheral neuropathies.

The collaboration will be in accordance with Eisai's 'Open Innovation Model', where Eisai will be allowed access to John Hopkins University's research regarding novel neurological therapeutic targets in return for them providing the university with its compound libraries. Eisai will provide John Hopkins University with upfront and milestone payments for any successful compound that will be licensed as well as royalties on future sales.

Written by Isaac Bruce, Commissioning Editor. Source: Eisai press release: www.eisai.com/news/news201171.html

Water washes away lock and key model

A team of researchers form Harvard University (USA), led by George Whitesides, has published its work relating to the hydrophobic effect in drug–target interactions. The paper concludes that there is not one single hydrophobic interaction but instead a distribution of hydrophobic effects.

> *"…results support the hypothesis that structured water molecules … determine the thermodynamics of binding of these ligands at the active site of the protein."*

The lock and key analogy, which has long been used by researchers studying drug interactions, states that the thermodynamically favorable interactions between non-polar surfaces in aqueous solutions are the most important component of drug binding. However, this assumption has mostly been developed from studies partitioning non-polar molecules in octanol (or other hydrophobic liquids) and water, which are entropically driven interactions.

Whitesides and his colleagues studied hydrophobic binding on human carbonic anhydrase II, measuring changes in enthalpy, entropy and Gibbs free energy when ligands were bound to the enzyme and when they were partitioned between octanol and water. In the octanol–water system, entropy again was the major factor, however, in the ligand–enzyme system, it was enthalpy that was the larger contribution due to the breaking down of hydrogen bonding in the surrounding water.

The article concludes that the, "results support the hypothesis that structured water molecules – including both the molecules of water displaced by the ligands and those reorganized upon ligand binding – determine the thermodynamics of binding of these ligands at the active site of the protein. Hydrophobic effects in various contexts have different structural and thermodynamic origins, although all may be manifestations of the differences in characteristics of bulk water and water close to hydrophobic surfaces."

Written by Isaac Bruce, Commissioning Editor. Source: Snyder PW, Mecinovic J, Moustakas DT *et al.* Mechanism of the hydrophobic effect in the biomolecular recognition of arylsulfonamides by carbonic anhydrase. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1114107108 (2011) (Epub ahead of print).

Generic company joins Medicines Patent Pool

Aurobindo Pharma, the India-based producer of generic drugs, has entered an agreement with the Medicines Patent Pool; a deal that both parties hope will increase the speed at which anti-HIV medication can be reached by those in the developing world.

> *"Competition from generic producers has been one of the most powerful tools to reduce drug prices."*

"We are excited about both the public health and business opportunities provided by the Patent Pool licences. Aurobindo looks forward to increasing its manufacture of HIV-related products, and expanding its work to cover promising new treatments, for the millions of people living with HIV across the globe," PV Ramaprasad Reddy, chairman of Aurobindo, stated in the Medicines Patent Pool press release.

The company will produce emtricitabine, cobicistat, elvitegravir and the fixed-dose combination of these medicines known as the Quad (a combination of the three and tenofovir), which were licensed to the pool by Gilead in July 2011. Aurobindo has decided to take advantage of a key provision negotiated by the Medicines Patent Pool in order for it to provide and sell tenofovir to multiple countries without paying royalties. The Indian company does have success in producing generic drugs for HIV patients, most notably fixed-dose combinations and formulations for pediatrtics.

Denis Broun, executive director of UNITAID said that the organization, "welcomes this new agreement, which will increase the number of manufacturers of new products to treat HIV infections. Competition from generic producers has been one of the most powerful tools to reduce drug prices. This agreement shows that generic manufacturers believe in the Patent Pool, and this is good news for people living with HIV across the developing world who will be able to access affordable, quality medicines."

Written by Isaac Bruce, Commissioning Editor. Source: Medicines Patent Pool press release: www.medicinespatentpool.org/NEWS-ROOM/News-from-the-Pool/Generics-Join-the-Pool

New findings regarding targeting the mTOR signaling pathway

Michele Pagano and her team of researchers from New York University's Cancer Institute (USA) have published the findings resulting from their work with members of the Howard Hughes Medical Institute (USA) and the Lautenberg Center for General and Tumor Immunology (Hebrew University, Israel) into a potential new target for anti-cancer treatments. The CK1 enzyme, the group claims, could be targeted in cancer cells created owing to the malfunction in the mTOR signaling pathway.

The researchers studied multi-protein complexes as well as protein regulators in cancer cells. Their findings demonstrated that the complex $SCF^{\beta TrCP}$ (Skp1, Cullin1 and F-box protein) has a significant role in cancer. The complex aids in the removal of an inhibitor of the mTOR pathway, DEPTOR. Ubiquitin ligase complexes with $SCF^{\beta TrCP}$ are responsible for the cell's removal of unwanted proteins and inhibiting these complexes block cancer cell proliferation. CK1, the researchers revealed, is needed for $SCF^{\beta TrCP}$ to promote DEPTOR degradation.

A pharmacologic inhibitor of CK1 was tested by the researchers and shown to stabilize the levels of DEPTOR in cancer cells; whereas, other known inhibitors of other proteins had no effect. The group believes that these findings can be used in the development of more effective CK1 cancer treatments.

Written by Isaac Bruce, Commissioning Editor. Source: Duan S, Skaar JR, Kuchay S *et al.* mTOR generates an auto-amplification loop by triggering the βTrCP- and CK1α-dependent degradation of DEPTOR. *Mol. Cell* 44(2), 317–324 (2011).

The editorial team welcomes suggestions for timely, relevant items for inclusion in the news. If you have newsworthy information, please contact:

Gino D'Oca, Managing Commissioning Editor, *Future Medicinal Chemistry*,
Future Science Ltd, Unitec House, 2 Albert Place, London, N3 1QB, UK
Tel.: +44 (0)20 8371 6090
Fax: +44 (0)20 8343 2313
E-mail: g.doca@future-science.com