7th Annual Congress of International Drug Discovery Science and Technology

Shanghai, China, 22–25 October, 2009

The conference, organized by BIT Life Sciences, comprised several parallel sessions, keynote presentations and a selection of 20-minute presentations covering a range of therapeutic areas, including general medicinal chemistry, oncology, inflammation, receptors and ion channels, drug, metabolism and pharmokinetics, and fragment-based drug discovery. There were also sessions devoted to genomics, biomarkers, immunology, cell biology, molecular imaging and biochips. Supported by an exhibition of services/products and posters, the conference underlined the marked presence of Asian CROs.

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A selection of topics of current interest was presented and many of the talks discussed case studies with in-depth structure–activity relationships (SAR) and absorption, distribution, metabolism and excretion data. A brief selection of the medicinal chemistry highlights are discussed below.

Anticancer agents

Anders Poulsen (S*BIO, Singapore) presented a talk on benzimidazole-based Aurora A and B inhibitors (mitotic kinases involved in cell division), which were conceived using rational drug design by docking molecules to the ATP binding site **(Figure 1; 1)**. Molecule **2** incorporates a morpholine solubility tag to improve water solubility and activities in the low nanomolar range were achieved, as well as good pharmacokinetics for improving *in vivo* behavior [1].

G-protein-coupled receptor targets

A summary of important SARs in the development of a corticotropin-releasing factor antagonist (CRF-1), for the treatment of stress-related disorders, was described by Yuhpyng Chen (YLCPharma, USA). A high-throughput screening hit, **3,** displayed weak affinity and no CNS penetration. Lead molecule **4** gave rise to hepatoxicity in rats and dogs and was superseded by a series of arylether pyridines, **5**, which acted as antagonists in a CRH-stimulated fear-potentiated startle model in animals **(Figure 2)**. Molecules with single digit nanomolar affinity were developed, one of which is a Phase II clinical candidate. Of special note were the significant food effects associated with **5** (Y = O) in fasted versus fed dogs. The food effects were dramatically reduced by increased basicity and solubility as demonstrated in **5** (Y = NH) [2,3].

Spirocyclic melanin-concentrating hormone-1 (MCH-1) antagonists were described as potential anti-obesity agents by Takao Suzuki (Merck, Japan). The development of diarylketoxime agents, including **7,** involved removing human ether-à-go-go related gene liability and improving metabolic stability **(Figure 3)**.

Development of PDE4 inhibitors

A series of analogues for the potential treatment of chronic obstructive pulmonary disease was described by Neil Press (Novartis, UK) **(Figure 4)**. An initial oxadiazole lead, ABE-171, had poor solubility and efforts were made to disrupt crystal packing between (flat) units by the introduction of a sp^3 center in place of the benzoic acid. NVP-CPD1 had good *in vivo* properties and solubility and selectivity over other PDE isoforms and relevant binding sites (PDE4A, B, D IC_{50} = 76, 102, 9 nM, HARBS K_i = 29nM, PDE1,3,7 > 10000 nM). Moreover, NVP-CPD1 had a very long *in vivo* half-life, which was further optimized to the final clinical candidate (structure not revealed) [101].

Organ rejection/immune response & cancer

Rapamycin, an mTOR inhibitor, can be derivatized, notably at a cyclohexanol group, to yield a number of bioactive rapalogues, many of which are marketed or in development **(Figure 5)**, as described by Ming-Qiang Zhang (Roche, China, formerly of Biotica, UK). The engineered biosynthesis of a number of analogues employing fermentation and gene cassettes was also described [6].

Antibacterials

Derek Law (F2G, UK) presented a talk on antifungal agents with a novel mode of action. The piperazinyl-pyridine-containing molecule,

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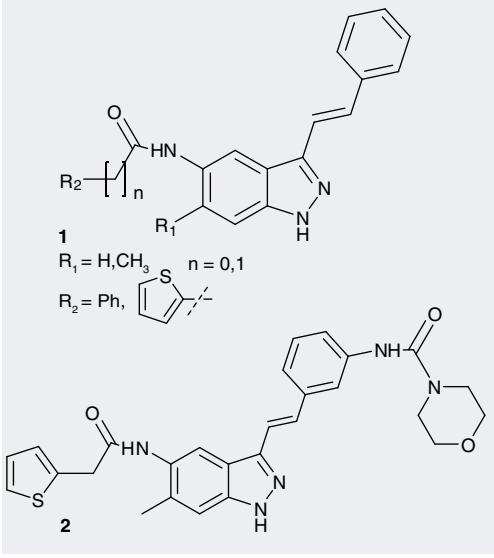

Figure 1. Aurora kinase inhibitors (S*BIO).

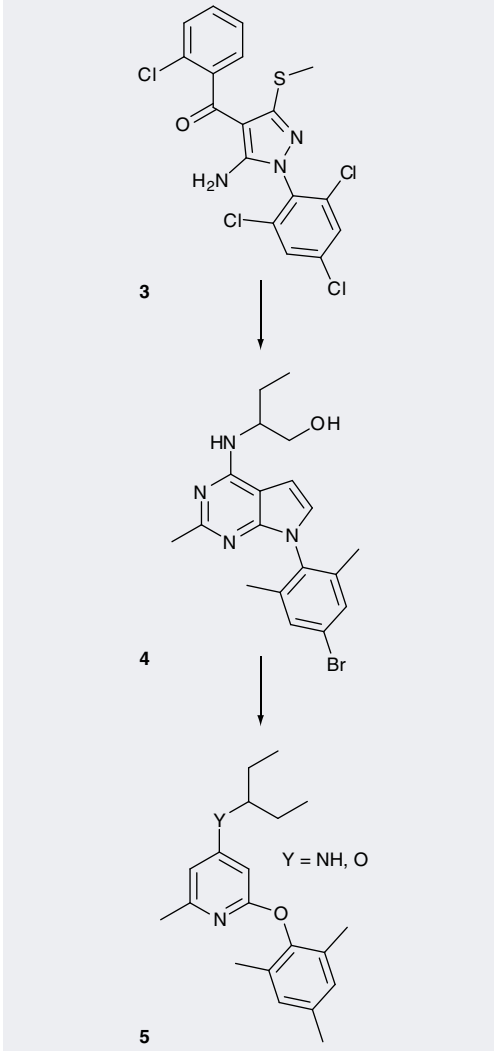

Figure 2. CRF-1 antagonists (Pfizer).

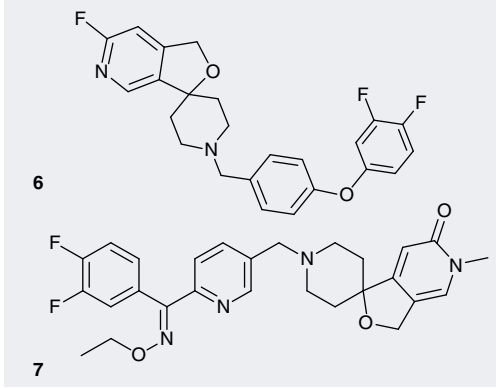

Figure 3. MCH-1 antagonists (Roche).

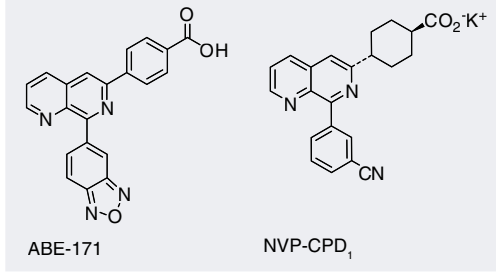

Figure 4. PDE4 inhibitors (Novartis).

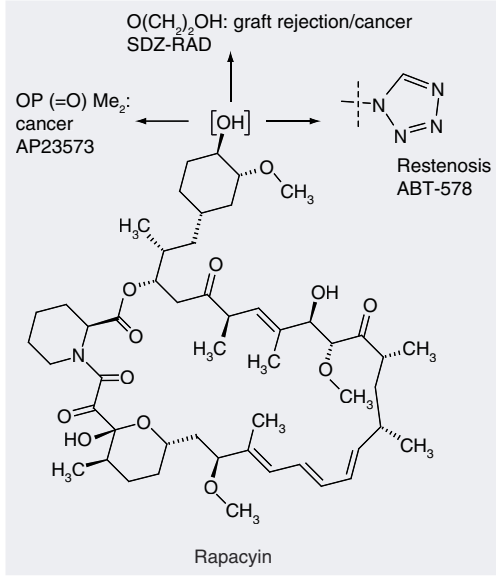

Figure 5. Rapalogues and their therapeutic targets (various companies).

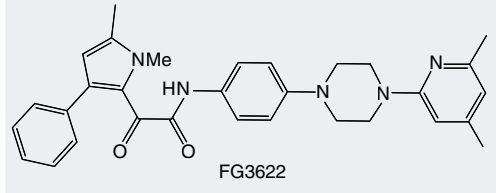

Figure 6. Antibacterial agent in Phase I clinical trials (F2G).

FG3622, acts upon bacteria that are prone to resistance including *Aspergillus* and *Fusarium* spp. **(Figure 6)**.

Looking ahead

The next conference in the series will be entitled Supporting Themes for Major Innovative Drugs, IDDST. It will be held from 23–26 October 2010 in Beijing, China.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

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