Patent Highlights

A snapshot of noteworthy recent developments in the patent literature of relevance to pharmaceutical and medical research and development.

WO/2014/194519

Imidazole derivatives and methods for use thereof for improving pharmacokinetics of drug

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Keywords: • biological availability
• cytochrome P-450 CYP3A inhibitors
• HIV protease inhibitors • ritonavir

Ritonavir is an inhibitor of the human immunodeficiency virus protease, but the primary reasons for including it in many highly active antiretroviral therapy regimens is that it blocks cytochrome P450 3A4 and P-glycoprotein drug transporters, acting as a pharmacokinetic enhancer for many other anti-HIV drugs (including protease inhibitors) that are hepatically metabolized through this route [1,2]. However, ritonavir is associated with hepatotoxicity, hyperlipidemia and unfavorable gastrointestinal effects. The invention presents imidazole compounds that have IC_{50} values for CYP3A4 in the low nanomolar range (lower than ritonavir [3]) while other pharmacologically relevant liver cytochromes are essentially unaffected, their IC_{50} values being higher by at least three orders of magnitude. When fasted male Han–Wistar rats were co-dosed with 10 mg/kg oral dose of a compound of the invention and 10 mg/kg of atazanavir (the HIV protease inhibitor in Bristol–Myers Squibb's Reyataz), mean ata-

zanavir exposure was 1.5- to 8.2-fold higher, and mean plasma drug concentrations were 1.1- to 117-fold higher, at 8 h post-dose compared with the same dose of atazanavir alone. Whether the compounds of the invention have HIV protease inhibitor activity is not disclosed.

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Novel pyrrole compounds with silicon incorporation

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Keywords: • BM-212 • organosilicon compounds • piperazines • pyrroles • tuberculosis

Among the new antimycobacterial agents that have been developed to address the problem of multidrug resistant varieties of tuberculosis, pyrrole derivatives related to the prototypical 1,5-bis(4-chlorophenyl)-2-methyl-3-(4-methylpiperazin-1-yl)methyl-1H-pyrrole (BM-212) [4] appear to show potent and selective activities. 1,5-Diaryl-2-ethyl pyrroles derived from this progenitor compound [5] have been used as templates to design new azasilinane agents. Silicon-containing analogs are expected to have better pharmacokinetic and pharmacodynamic properties and they also may have better cell-wall penetrating capability [6]. Their

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minimum inhibitory concentrations for growth of a virulent strain of *Mycobacterium tuberculosis* are mostly in the lower ng/ml range while the values for BM-212 and rifampicin are 0.7 and 0.25 µg/ml; and 0.125–0.5 µg/ml for 1,5-diphenylpyrroles not containing silicium [7]. Sila analogs of established drugs can have quite distinct metabolic fates [8], making this approach – which has not been reported for tuberculosis drugs so far – seem very worthwhile.

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Pyrazolopyridine derivatives for use in the treatment of bladder cancer

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Keywords: • fibroblast growth factor receptor 3
• urinary bladder neoplasms

A very strong correlation exists between the expression of mutated forms of fibroblast growth factor receptor-3 (FGF-R3) and low-grade bladder carcinomas [9]. The most common mutation is Ser249Cys, which results in a ligand-independent constitutive dimerization of the receptor that permanently activates the intracellular kinase signaling pathways, and also in increased expression of the receptor. FGF-R3 inhibitors such as the benzimidazole-quinolinone dovitinib (Novartis) are being investigated to address this target [10,11], which is also present in many non-urothelial cancers. However, dovitinib was not robustly successful in clinical trials for other cancers, and it has a tendency toward drug accumulation. Sanofi is now trying pyrazolo[3,4-b]pyridines that inhibit the amount of intracellular ATP in TCC97–7 bladder cancer cells (which overexpress FGF-R3 with the Ser249Cys mutation) by more than 20% at 1 or 10 µM. If this does not seem very impressive, one has to consider that such drugs might be intended for intravesical instillation (the standard procedure for chemotherapy of nonmuscle invasive bladder cancer with mitomycin B or attenuated *Bacillus Calmette–Guerin* in combination with transurethral resection of the cancer). With only the patient's urine to dilute the drug and limited systemic exposure, it might be possible to apply sufficiently high concentrations to the residual tumor area. Dovitinib, which Novartis has in a Phase II study (NCT01732107) [42] for *Bacillus Calmette–Guerin*-refractory urothelial carcinoma, is administered orally (500 mg in a 5 days on, 2 days off dosing schedule).

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Menin-MLL inhibitors and methods of use thereof

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Keywords: • leukemia, biphenotypic, acute
• myeloid-lymphoid leukemia protein
• proto-oncogene proteins

Mixed lineage leukemia is a heterogeneous group of acute myeloid and lymphoblastic leukemias bearing features of more than one hematopoietic cell lineage. A common feature of these molecularly and immunologically diverse leukemias, which account for about 80% of pediatric acute leukemia cases, is the translocation and frame fusion of the *MLL* gene on chromosome 11q23 [12]. More than 60 fusion partner genes have been identified. Diverse as the resulting oncoproteins are, they retain the *MLL* *N*-terminal domain which contains the motifs binding menin, a tumor repressor protein; their leukemogenic activity depends on this interaction [13]. The structural basis for the rational design of such small molecule inhibitors has only recently become available [14,15]. The present invention provides compounds (predominantly *N*-propylpiperidin-4-yl diphenylmethanols) that inhibit the menin–MLL interaction, as shown by a fluorescence polarization assay using a fluorescein-labeled 12-amino acid *MLL*-derived peptide which binds menin with nanomolar affinity. The compound's IC_{50} values for competitive displacement of the peptide were typically in the micromolar range.

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A method of increasing GiPCR signaling in the cells of a scoliotic subject

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Keywords: • antigens, CD44 • integrin $\alpha_5\beta_1$
• osteopontin • scoliosis

At a prevalence of 4% in the adolescent population, idiopathic scoliosis is the most common orthopedic condition requiring surgery in this age group, with bracing or surgical correction as the standard treatments [16]. Could this condition become a target for pharmacological therapy? This is not as far fetched as it seems at first sight. The inventors had shown (in WO/2008/119170) that plasma levels of osteopontin, a multifunctional cytokine, are elevated in patients with idiopathic scoliosis and in mice forced to assume

a bipedal posture (a well established animal model of this disease). To investigate whether the relationship is pathognomonic, the inventors used strains of osteopontin- and CD44-deficient mice with a C57Bl/6J background. Such animals are known for impaired osteoclast motility and resorptive activity [17]. The invention shows that osteopontin reduces G-protein-coupled receptor signaling via $\alpha_5\beta_1$ integrin interference, probably by sequestering Gi proteins and/or inactivating them after their phosphorylation. Depletion of CD44 exacerbates the inhibitory effect of osteopontin. Hyaluronic acid, a known CD44 ligand with a higher binding affinity than osteopontin [18], further potentiates the osteopontin effect in a dose-dependent manner. By competing against osteopontin at the CD44 binding site, hyaluronic acid increases osteopontin bioavailability to bind $\alpha_5\beta_1$ integrin and to inhibit receptor signaling. Finally, the present invention shows that the presence of a mutation in CD44 further decreases G-protein-coupled receptor signaling in osteoblasts of scoliotic subjects. The inventors have described a diagnostic assay developed on the basis of these insights [19], and the group published additional work after the application's priority date [20].

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New macrocyclic amidinourea derivatives, methods of preparation and uses thereof as chitinase inhibitors

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Keywords: • candida • chitinase • macrocyclic compounds

The preferred first-line therapy against *Candida* spp. infections relies on azoles, such as fluconazole and voriconazole, and polyenes, such as amphotericin B. Mammals do not synthesize or utilize chitin, which is an essential component of fungal cell walls. This makes inhibitors of chitinase (which is essential for fungal cell replication and differentiation [21]) a particularly attractive alternative for the design of new agents that avoid the increasing multidrug resistance of pathogenic fungi. Building on their earlier work that created macrocyclic amidinourea chitinase inhibitors [22], the inventors have now improved the series for higher activity and a more versatile synthetic pathway. The compounds were tested against 116 clinical isolates of seven different *Candida* species from various body sites, and also against *Candida albicans* and *Candida glabrata* strains carrying known mutations that confer resistance to azole antifungals. Four of the new com-

pounds had minimal inhibitory concentration values in the low $\mu\text{g/ml}$ range against fluconazole-resistant strains; compound 17 was slightly superior to voriconazole when used against *C. albicans* strains. For the companion peer review paper see [23].

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Agonists of DDAH1 for treating endothelial dysfunction

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Keywords: • amidohydrolases
• DDAH-1 protein • hypertension • portal • microRNAs
• nitric oxide

The two isoforms of dimethylarginine dimethylaminohydrolase (DDAH), a ubiquitous mammalian enzyme, remove methylarginines which are generated during protein degradation and inhibit the production of nitric oxide synthase [24,25]. The inventors have found that expression of DDAH1, which drives over 90% of the metabolism of asymmetric dimethylarginine, is significantly reduced in bile duct ligated rats (an established model of liver cirrhosis) on the mRNA level, through post-transcriptional regulation by miRNAs 128 and 219. Inhibiting the binding of these miRNAs to their respective targets in the 3' untranslated region of the DDAH1 messenger leads to increased DDAH1 protein synthesis, decreased asymmetric dimethylarginine levels, increased endothelial nitric oxide synthase activity and (as a consequence of nitric oxide action) to a significant lowering of the increased portal pressure. Other conditions characterized by endothelial dysfunction should also be responsive. Obviously, the 'DDAH1 agonists' also have to be nucleic acids, with or without chemical modifications. For example, they may have the sequence of the 52 basepair region of the DDAH1 3'UTR or a fragment thereof, comprising one or both binding sites for miR-219 (GACAATC) and miR-128 (CACTGT). - In hypoxia, the role of these two miRNAs appears to be taken by miR-21, which may be of significance in pulmonary hypertension [26,27].

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1-Sulfonyl piperidine derivatives as modulators of prokineticin receptors

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Keywords: • intercellular signaling peptides and proteins • PKR1 protein • mouse

Prokineticins are cysteine-rich regulatory peptides that act via two highly conserved G-protein-coupled receptors, PKR1 and PKR2 which are broadly expressed in peripheral tissues [28,29]. This leads to phospholipase C activation, inositol phosphate production and calcium mobilization, and activation of the MAPK pathway. Prokineticins regulate gut motility, neurogenesis, circadian rhythms, nociception, hematopoiesis and immune responses; the potential therapeutic range of receptor modulators is correspondingly broad. In an assay based on RBL2H3 cells expressing human PKR1 receptors and measuring the change in intracellular calcium levels induced by Gq-mediated increase in inositol triphosphate, most of the *N*-sulfonylpiperidine PKR antagonists of this invention had IC₅₀ values in the high nanomolar range. Prokineticin receptors are unusual targets, but certainly not unheard of: for guanidine-based PKR1 antagonists see [30]; for 1,3,5-triazin-4,6-diones, see [31].

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Difluoroethyl-oxazole substituted bridges spiro[2.4]heptane derivatives as ALX receptor agonists

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Keywords: • inflammation • receptors, lipoxin • spiro compounds

ALXR (also formyl peptide receptor-2, FPR-2) is a G-protein-coupled receptor that binds the glucocorticoid-inducible pro-resolution factor annexin A1 and the lipid metabolite, lipoxin A4 with high affinity and increases arachidonic acid production, resulting in potent anti-inflammatory action [32,33]. Actelion has already disclosed bridged spiro[2.4]heptane ALXR agonists in WO/2010/134014, WO/2012/066488, WO/2013/171694 and WO/2013/171687; the company now continues this series of highly chiral molecules, hoping to identify leads for the treatment of obstructive airway diseases, allergic conditions, inflammatory cardiovascular and neurological disorders, retroviral infections and pain. Alzheimer's disease is also identified as a target condition, but here lipoxin might be a double-edged sword: the pathogenic relevance of the inflammatory microglial response that is seen around amyloid plaques remains controversial. It is possible that the Aβ(1–42)-induced dysfunction of inflammation resolution in microglia contributes to the disease [34]. Allergan has disclosed closely related ALXR agonists in WO2011/163502

and WO/2013/009543; this might reflect intense competition, or an undisclosed cooperation.

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Labeled protein kinase G-I-α-binding compounds and their use in imaging and quantifying pain

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Keywords: • chronic pain • cyclic GMP-dependent protein kinase type I • ganglia • molecular imaging • spinal

With no objective tools to quantify the type and severity of chronic pain, physicians have to rely on patient testimony to identify whether the pain originates from the periphery or the CNS, to match the type of analgesic and its dose to the intensity of the pain, and to distinguish actual chronic pain from psychiatric symptoms and simulation attempts. The inventors have resorted to a family of balanol analogs, disclosed by Columbia University in 2007 (see US8846742), that selectively bind to a chronic pain-specific, activated form of protein kinase G-I that is expressed in involved dorsal root ganglia. Balanol has been characterized as a potent ATP-competitive inhibitor of protein kinases A and C [35], and is a key determinant of spinal synaptic potentiation [36]. Preferred is *N*-((3R,4R)-4-(4-(2-fluoro-3-methoxy-6-propoxybenzyl)benzamide)pyrrolidin-3-yl)-1H-indazole-5-carboxamide (NOP-46) which is labeled with a PET tracer (fluorine-18 or carbon-11). Besides being helpful for the pain specialists with access to PET imaging, this could have extremely attractive applications in analgesic drug development where animal models currently rely on behavioral expression of pain. The inventors mention a rat model for allodynia from neuroma, but do not disclose data or images. There seems to be no peer review literature on the NOP series of compounds.

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IDO inhibitors

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MeSH Keywords: • immunomodulation • indoleamine-pyrrole 2,3-dioxygenase • neoplasms

Indoleamine-2,3-deoxygenase (IDO), an interferon-γ-induced tryptophan-degrading enzyme which catalyzes the initial, rate-limiting step in the conver-

sion of tryptophan to *N*-formylkynurenine but also degrades serotonin and melatonin, has been known for 40 years. It is overexpressed in many human tumors, and is implicated in neuropsychiatric disorders, autoimmune diseases, infections and cataract. Because kynurenine participates in the mechanism of tumor immune tolerance, IDO inhibition has been considered a strategy for indirect immunotherapy for cancer [37,38], but the enzyme has been slow to become a pharmacological target. The compound of the invention are mostly (tolylureido) biphenyls, obviously part of a large library building effort that has produced the related compounds disclosed in WO/2015/006520, WO/2014/150677 and WO/2014/150646. In May 2014 Bristol-Myers Squibb announced a clinical trial collaboration to evaluate a combination regimen of its investigational PD-1 immune checkpoint inhibitor, nivolumab, and Incyte's oral IDO-1 inhibitor, INCB24360 in a Phase I/II study for diverse types of solid tumors. Clearly, we are seeing only the beginning of a strategy that involves this new type of small molecule immunomodulators.

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Antiviral compounds, pharmaceutical compositions, and methods and use thereof

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Keywords: • immunomodulation • pattern recognition • receptors • RNA helicases • RNA viruses

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Shifting the focus of antiviral drug development away from the targeting of viral proteins to enhancing of the host's innate antiviral immune response is an interesting strategy for which the retinoic acid-inducible gene-I (RIG-I) pathway could offer an avenue. Together with toll-like receptors and C-type lectins, RIG-I receptors make up the innate pathogen pattern recognition system [39]. In hepatitis B virus infection, RIG-I functions as a virus sensor activating innate signaling, and to counteract viral polymerase in human hepatocytes [40]. Other RNA viruses, especially influenza, could also be targeted; not only as a therapy but also to increase the efficacy of vaccines [41]. Two hits from the isoflavone library presented in this invention, KIN100 and KIN101 were highly active against hepatitis C virus, respiratory syncytial virus, dengue virus and encephalomyocarditis virus; KIN269 exhibited an even broader activity spectrum, and was active in mouse models of influenza and coronavirus infections. The inventors consider these compounds to be leads for QSAR-based optimization, which should provide agents with nanomolar or picomolar potency.

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<https://clinicaltrials.gov/ct2/show/NCT01732107>