Compounds for Drug Therapy that Target ABCG2

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Technology description

Methods and novel compounds have been developed which inhibit cancer-associated transporter proteins. These methods and compounds treat or prevent the onset of cancer-associated transporter protein-mediated disease. Specifically, this invention provides novel pyrazolo[1,5-a]pyrimidine efflux inhibitors that are selective toward ABCG2 over ABCB1.

Background

Chemotherapy is currently one of the most effective ways to treat metastatic cancers. However, the treatment effectiveness of these chemicals is often impeded by the body' s defense mechanism to foreign intrusion. Specifically, three major subfamilies (ABCB, ABCC, and ABCG) of the ABC transporter superfamily are related to human multidrug resistance (MDR) and influence oral absorption and disposition of a wide variety of drugs, and as a result their expression levels have important consequences for susceptibility to drug-induced side effects, interactions, and treatment efficacy. Although a large number of compounds have been identified possessing ABC transporter inhibitory properties, only a few of these agents are appropriate candidates for clinical use as MDR reversing agents. Dual treatment with ABC transporter inhibitors in conjunction with chemotherapeutics is a common treatment strategy to circumvent MDR in cancers. However, the failures of current classes provide ample justification for identifying new classes of inhibitors to improve the outcome in cancer chemotherapy. ABC efflux transporter inhibition is now in its third generation with the majority of focus still on ABCB1. Although there is significant progress with ABCB1 inhibitors, similar progress has not been made with ABCG2 inhibitors, though its relevance as a clinical target has been well documented. In addition, specificity to one ABC transporter (ie. ABCB1 vs ABCG2) has not been well explored. Recent work demonstrated the differential cross-reactivity of inhibitors across ABCB1, ABCC1, and ABCG2 transporters of drugs like cyclosporine or verapamil. Cross-reactivity of both these inhibitors across all three transporters could help explain severe toxicity effects. Such interactions can be quite complex, since the array of substrate/non-substrate and inhibitor/non-inhibitor is further clouded by the possibility of multiple interaction sites and unwarranted cytotoxicity. Thus specificity to one ABC transporter over another, especially ABCB1, might better be used to demonstrate inhibitory potential of a new chemical entity.

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Application area

Potential for better chemotherapy results in battling cancer
Potential for inhibition of multidrug resistance toward chemotherapeutic drugs
Potential development of inhibitors that are selective toward ABCG2 over ABCB1
ABC G2 is really directed at solid tumors (e.g. breast, prostate and lung), while ABC B1 is not (it is mostly an issue in leukemia or blood tumors). ABC G2 inhibitors have not been extensively looked at in solid tumors and these hold promise.

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