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Activity of substituted thiophene sulfonamides against malarial and mammalian cyclin dependent protein kinases

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ABSTRACT

Cyclin dependent protein kinases (CDKs) are pursued as drug targets for several eukaryotic pathogens. In this study, we identified thiophene and benzene sulfonamides as potent inhibitors of Pfmrk, a *Plasmodium falciparum* CDK with sequence homology to human CDK7. Several of the compounds demonstrated inhibitor selectivity for CDK7 over CDK1, CDK2, and CDK6. The compounds are moderate antimalarial agents against drug resistant parasites and possess encouraging in vitro therapeutic indices as determined against human cell lines. One particular sub-class of compounds, bromohydrosulfonylacetamides, was specific for Pfmrk with IC_{50} values in the sub-micromolar range. These compounds represent the most potent Pfmrk inhibitors reported and provide support for further characterization and derivation as potential antimalarial agents.

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Cyclin dependent protein kinases (CDKs) are highly conserved regulators of cell cycle control among most eukaryotic organisms.[1] Multiple mechanisms regulate the activity CDKs to ensure the precise and ordered progression of the mitotic cell cycle. When these mechanisms fail, uncontrolled growth can result in neoplasticity. Interestingly, a few mammalian cells and eukaryotic single cell organisms grow and differentiate via an alternate mitotic cell cycle known as endoreduplication, in which multiple rounds of DNA synthesis occurs in the absence of mitosis or cytokinesis.[2] The primary difference between a mitotic cell cycle and an endocycle depends on the timing and alternation between CDK activation and inactivation.[3] Some cancer cells can exit the normal mitotic cell cycle and undergo an endocycle process in an effort to escape drug pressure and/or develop resistance.[4] This implication of a direct role in cell cycle progression, differentiation and development of drug resistance make CDKs attractive drug targets. In fact, there are currently 11 compounds in various stages of clinical develop for the treatment of cancer.[5] CDKs are also pursued as drug targets for the development of anti-infective agents against fungal, viral, and protozoan infections. *Plasmodium falciparum* is a protozoan intracellular parasite that is responsible for approximately two million malaria-related deaths annually.[6] In the absence of an effective vaccine, antimalarial drugs must be prescribed for treatment and prophylaxis. *P. falciparum* has developed resistance to most of the antimalarial drugs currently in use today at an alarming rate and therefore new drugs are urgently needed. It is expected that target-based approaches may introduce novel chemotypes into the antimalarial drug development pipeline.

Several plasmodial CDKs have been identified and among these, PfPK5 and Pfmrk have been pursued as antimalarial drug targets.[7,8] PfPK5 shares significant sequence homology with CDK1 and is believed to play a role in DNA synthesis.[9,10] Pfmrk shares similarities with human CDK7 by virtue of its sequence similarity, substrate specificity and effector molecule binding (cyclin H and MAT1).[11–13] Pfmrk is localized to the nucleus where it is believed to play a role in either DNA replication or transcriptional control.[14] Direct comparison, however, of the cell cycle-dependent functions of plasmodial and human CDKs is difficult since the malaria cell cycle operates under the confines of an endomitotic cycle (schizogony) however it is likely that CDKs play a key regulatory role in the malaria cell cycle.[15,16] The identification of inhibitors for Pfmrk and PfPK5 has been aided by crystal structures, QSAR pharmacophores and molecular docking approaches.[17–20]

In the search for inhibitors against malarial CDKs, selectivity must be addressed to avoid toxicity associated with cross-reactivity with human CDKs. Reports have demonstrated that inhibitors can be developed that are selective for malarial CDKs. Differences in the architecture of the active sites provide opportunities to design selective malarial CDK inhibitors. Several unique amino

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acids occupy the active site of Pfmrk that is believed to dictate a specific inhibitor profile. Many of the broad-spectrum CDK inhibitors that are commercially available fail to inhibit Pfmrk.[18,21] Using a QSAR pharmacophore specific for Pfmrk,[19] several chemotypes, (oxindoles, chalcones, tryptanthrins, and phenyl-quinolinones), have been identified as inhibitors.[22–24] Compounds in these chemical classes demonstrate selectivity for Pfmrk over human and additional plasmodial CDKs.

In this study, we explore the Pfmrk inhibiting properties of several sulfonamides. Previous reports demonstrated that isoquinoline sulfonamides are weak Pfmrk inhibitors and that variation within the quinoline moiety influences Pfmrk inhibition.[21] In this study, we investigate additional sulfonamides, which contain substituted moieties of thiophene (Fig. 1) and benzene (Fig. 2). These compounds were tested for inhibition of Pfmrk using an in vitro kinase assay as previously reported.[23] As shown in Table 1, many of these compounds inhibit Pfmrk at low to sub-micromolar concentrations. This is the first reported class of compounds with this level of potency against Pfmrk. Although we grouped these compounds into separate chemical classes, three compounds have the sulfonamide linker replaced with a carbamoylformamide linker (**1**), formylacetohydrazide linker (**2**), or an aminoacetonitrile linker

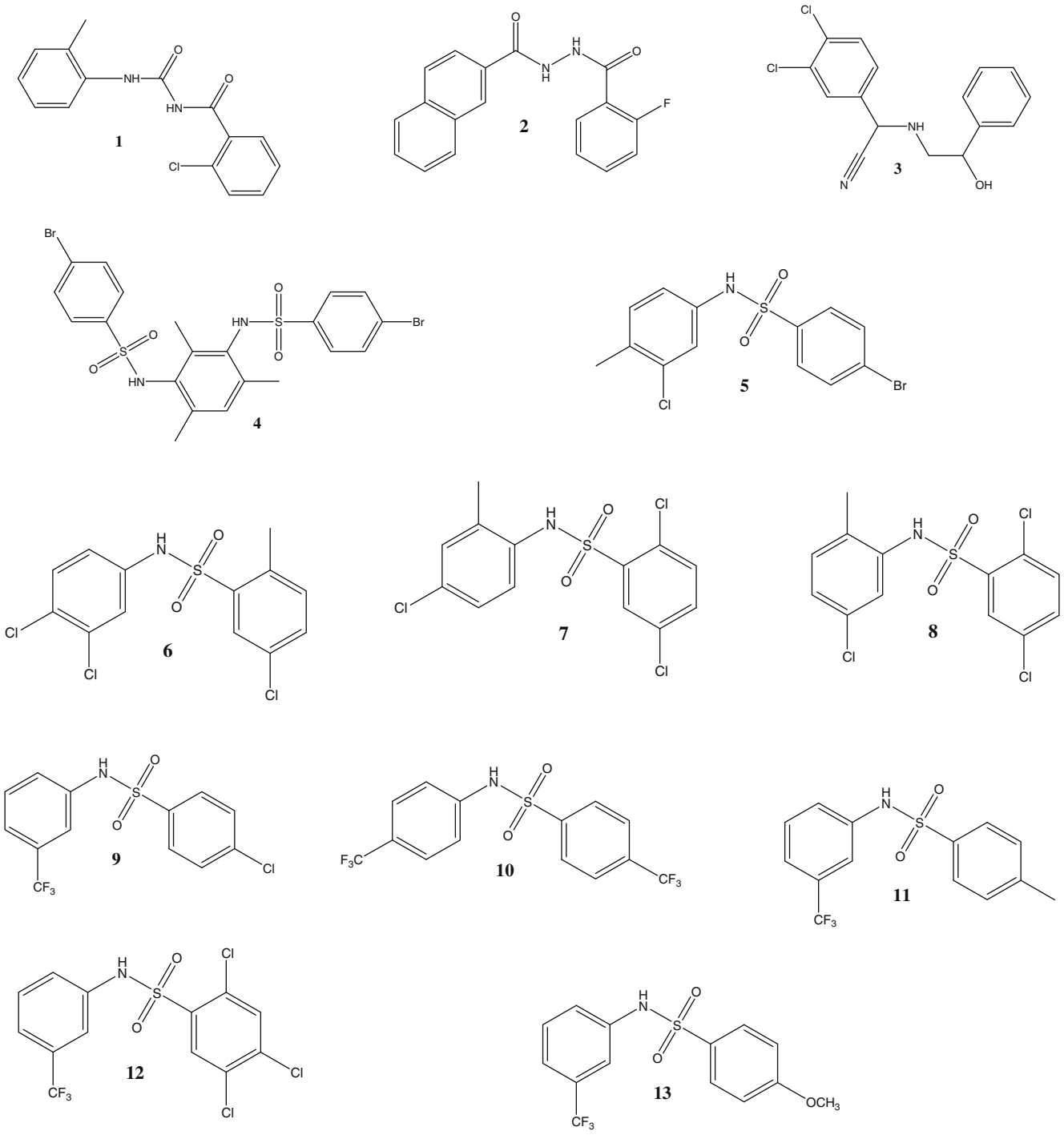

Figure 1. Structures of benzyl-sulfonamides.