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PATENT HIGHLIGHT

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Antiparasitic Compounds May Potentially Treat Malaria and Other Parasitic Diseases

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Title: Compounds and Compositions for the Treatment of Parasitic Diseases

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Disease Area: Malaria and other parasitic diseases **Biological Target:** Protozoan parasites such as Plasmodium genus and Leishmania genus

Summary: The invention in this patent application relates to imidazo[1,2-a]pyrazine derivatives represented generally by formula (I). These compounds possess antiparasitic activities and may be useful in the treatment of diseases caused by protozoan parasites such as malaria.

Many infectious diseases such as malaria, leishmaniasis, and chagas are caused by protozoan parasites. These are vector-borne parasitic diseases that are transmitted by arthropod vectors (such as specific mosquitos or flies).

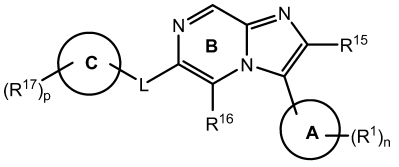
Malaria is transmitted to humans by the bite of female Anopheles mosquitos. According to the World Health Organization (WHO) data, there were about 219 million cases of malaria resulting in 660,000 deaths worldwide in 2010. Most Malaria deaths occur in children under the age of 5. Malaria is caused by four protozoan parasites of the genus Plasmodium: *Plasmodium falciparum*; *Plasmodium vivax*; *Plasmodium ovale*; and *Plasmodium malaria*. The deadliest malaria parasite is *Plasmodium falciparum*; it has acquired resistance against nearly all available antimalarial drugs with the exception of the artemisinin derivatives.

Leishmaniasis is another protozoan parasitic disease. It is caused by the genus Leishmania and is transmitted by the bite of female sand flies. While the number of cases is much smaller than malaria, it is spread over 88 countries. Visceral leishmaniasis (or kala-azar) caused by the parasite Leishmania donovani can be fatal if left untreated. Sodium stibogluconate (Pentostam) and meglumine antimoniate (Giucantim) are two leading drugs for treatment of visceral leishmaniasis. Not only do the parasites develop resistance to them but the treatment is also long and painful and may cause undesirable side effects.

The African trypanosomiasis (sleeping sickness) is caused by the Trypanosoma genus and is transmitted by tsetse fly bites. Chagas (American trypanosomiasis) is another human parasitic disease found on the American continent caused by *Trypanosoma cruzi* and is transmitted by blood-sucking insects. Chagas occurs in two stages: an early acute stage and a late chronic stage that develops over many years. Chronic infections may cause dementia, damage to the heart muscle, dilation of the digestive tract, and weight loss, and it is often fatal if left untreated. The two drugs nifurtimox and benznidazole are used in the treatment of chagas. However, they have to be administered for a long time causing many undesired side effects and may develop drug resistance.

Thus, there is a great need for the discovery and development of novel compounds that possess antiparasitic activities and can be used for the treatment of malaria and other parasitic diseases. The compounds described in this patent application may potentially address this need.

Important Compound Classes:



Formula (I)

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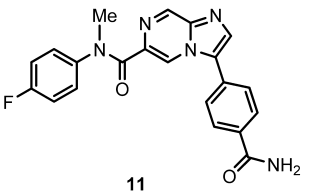
Key Structures: The inventors reported the structures of 503 examples of formula (I) including the following representative structures:



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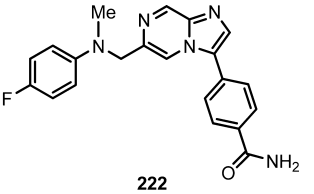

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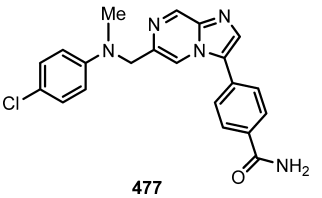

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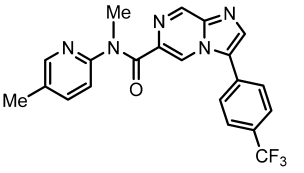

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Biological Assay: The inventors reported the following biological assays to evaluate the compounds of the invention:

- Assay for *P. falciparum* Proliferation in Infected Human Blood Cells
- Assay for Proliferation of Parasite in Infected Liver Cells

Biological Data: Biological data were reported for all compounds in the first assay and for 13 examples in the second assay. Representative data from both assays are listed in the following table:

Example	Inhibitory Efficacy of Compounds of the Invention in delaying P. falciparum Proliferation in Infected Human Blood Cells	Inhibitory Efficacy of Compounds of the Invention in delaying the Proliferation of P. yoelli Sporozolte in Infected Liver Cells
	EC_{50} (nM)	EC_{50} (nM)
11	74	56
222	30	7
477	9	11
491	199	1108

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2. Fueller, F.; Jehle, B.; Putzker, K.; Lewis, J. D.; Krauth-Siegel, R. L. *J. Biol. Chem.* **2012**, *287* (12), 8792−8802.
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Notes

The authors declare no competing financial interest.