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# Synthesis of pyrazole acrylic acid based oxadiazole and amide derivatives as antimalarial and anticancer agents

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ABSTRACT

Depravity of malaria in terms of morbidity and mortality in human beings makes it a major health issue in tropical and subtropical areas of the globe. Drug counterfeiting and non-adherence to the treatment regimen have significantly contributed to development and spread of multidrug resistance that has highlighted the need for development of novel and more efficient antimalarial drugs. Complexity associated with cancer disease and prevalence of diversified cell populations vindicates highly specific treatment options for treatment of cancer. Resistance to these anticancer agents has posed a great hindrance in successful treatment of cancer. Pondering this ongoing situation, it was speculated to develop novel compounds targeting malaria and cancer. Moving on the same aisle, we synthesized pyrazole acrylic acid based oxadiazole and amide derivatives using multi-step reaction pathways (**6a–x; 6a′–h′**). Schizont maturation inhibition assay was employed to determine antimalarial potential. Compound **6v** emerged as the most potent antimalarial agent targeting falcipain-2 enzyme. Anticancer activity was done using sulforhodamine B assay. Compounds **6b′** and **6g′** demonstrated promising results against all the tested cell lines. Further, Microscopic view clearly indicated formation of apoptotic bodies, chromatin condensation, shrinkage of cells and bleb formation. Validation of the results was achieved using molecular docking studies. From the obtained results, it was observed that cyclization (oxadiazole) favored antimalarial activity while non-cyclized compounds (amides) emerged as better anticancer agents.



## 1. Introduction

In view of emerging and spreading resistance to the current therapies, novel antimalarials are on high demand. Malaria, caused by *Plasmodia* parasites has emerged as a serious issue imposing its fatal effects on human health [1]. 212 million cases of malaria across the globe have been inventoried in the World Malaria Report, 2016 [2], making it a world health crisis of paramount urgency [3]. However, in the absence of any effective and approved vaccine targeting malaria, clinicians rely totally on the chemotherapeutic agents for curbing this menace [4], despite the fact that all the agents introduced to mankind have developed resistance over the span of past 20–25 years [5].

Amongst different potential targets for curbing malaria, cysteine protease falcipain-2 (Fig. 1) of *Plasmodium falciparum* (*P. falciparum*) is one of the most extensively studied targets [6]. During the life cycle of malaria parasite, erythrocytic phase is accountable for symptoms in humans. Thereby, development of drugs targeting erythrocytic phase is the main focus [7]. During intraerythrocytic phase, the parasites utilize different proteases bringing about hydrolysis of hemoglobin in the acidic food vacuole leading to the generation of amino acids required for parasite protein

*Abbreviations:* HOBt, hydroxybenzotriazole; EDCl, 1-ethyl-3-(3-dimethylamino propyl)carbodiimide; DMF, *N-N*-dimethyl formamide; s, singlet; 5-FU, 5-fluorouracil; *P. falciparum*, *Plasmodium falciparum*; SI, Selectivity Index; TLC, Thin Layer Chromatography; IR, infra-red; NMR, Nuclear Magnetic Resonance; TMS, tetramethylsilane; *J*, Coupling Constant; DMF, dimethyl formamide; $POCl_3$, Phosphorus Oxychloride; NCI, National Cancer Institute; SRB, sulforhodamine B; DAPI, 4′-6-diamidino-2-phenylindole; RI, Resistance Index; SP, Standard Precision; ESI, Electrospray Ionization.

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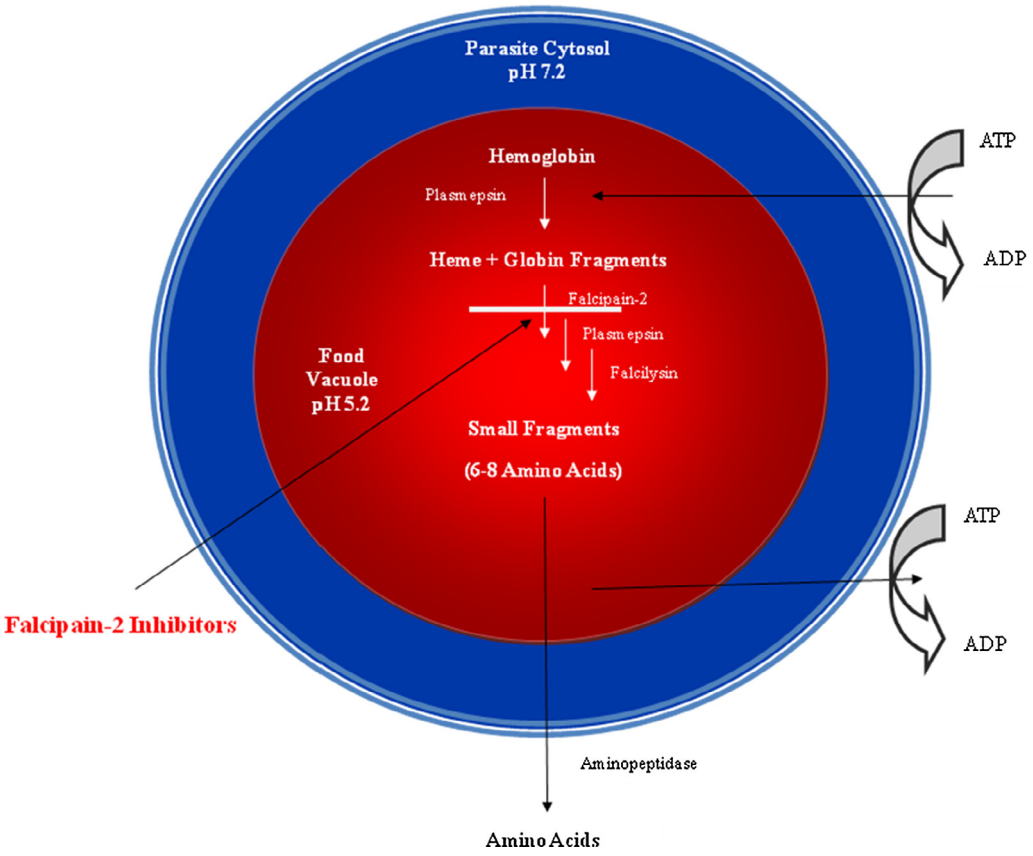


**Fig. 1.** Mechanism of action of Falcipain-2 Inhibitors.

synthesis [8]. Falcipain-2 is one of the key enzymes involved in this digestion. Treatment with falcipain-2 inhibitors leads to accumulation of undigested hemoglobin in the swollen food vacuole, hence resulting in blockage of parasite development [9,10].

Cancer is known to encompass a broad spectrum of diseases in which host cells flee their normal cell cycle regulation and show the hallmark of uncontrollable proliferation. This particular phenomenon can be linked to a number of factors like gender, ethnicity, age of onset and lifestyle. However, this can also be associated with cellular transformation linked to viral infection, chemical or radiation exposure or the reason may be spontaneous in nature [11]. Combination of surgery and/or radiotherapy is the most opted therapeutic option by clinicians for treatment of cancer [12]. Failure in cancer chemotherapy is generally observed due to development of multi-drug resistance, a condition where cancer cells become resistant to structurally unrelated chemotherapeutic agents. Another reason is poor patient compliance which arises due to clinical systemic toxicity, which is generally observed in bone marrow, GI tract and hair [13,14].

Pyrazole and 1,3,4-oxadiazole derivatives are well known to possess versatile biological activities like anticancer [15,16], antimicrobial [17,18], analgesic, anti-inflammatory [17,19], antitubercular [17,20] etc. Pyrazole based compounds are well reported in the literature as antimalarial agents (**A** and **B**) [21,22]. This moiety is also traceable in a number of anticancer agents like encorafenib (**C**), crizotinib (**D**) and pyrazofurin (**E**) [17,23,24]. 1,3,4-oxadiazole is well known to exhibit potent antimalarial (**F** and **G**) [25,26] and anticancer (**H** & **I**) activities [27,28]. Amide linkage can be seen in the literature as an important linker present in different molecules exhibiting antimalarial (**J**) [29] and anticancer activity (**K**, **L** and **M**) [30,31,32] (Fig. 2).

In the prevailing scenario, development of new efficient therapeutics for the treatment of malaria and cancer is an important venture. Strategy that is gaining popularity in the field of drug discovery is development of single chemical entities containing a combination of pharmacophores with significant biological activities [33,34]. In the present study, pyrazole acrylic acids were linked to different substituted benzohydrazides in the presence of a cyclization agent, $POCl_3$ to get oxadiazole derivatives (Scheme 1). These compounds were evaluated for antimalarial and anticancer activities. Further, pyrazole acrylic acids and benzohydrazides were coupled in the presence of coupling agents, Hydroxybenzotriazole (HOBt) and 1-Ethyl-3-(3-dimethylamino propyl)carbodiimide (EDCl), leading to the formation of amide linkage (Scheme 2) between these two (Fig. 3). These compounds were also tested for antimalarial and anticancer activities.

## 2. Results and discussion

### 2.1. Chemistry

Multi-step reactions were employed to obtain the requisite compounds for Schemes 1 and 2**.** The difference in the two schemes lies in the final step of coupling the acrylic acid derivatives with different benzohydrazides. First step involved an addition reaction between substituted acetophenone derivatives and phenylhydrazine. Consequent to this, Vilsmeier-Haack reaction was employed which involved formylation of the aromatic compound using *N*-*N*-dimethyl formamide (DMF) as an acylating agent in the presence of activating agent, $POCl_3$. The reaction took place *via* the formation of Vilsmeier complex, also referred to as Vilsmeier reagent [35]. Derivatives of pyrazole carbaldehydes were