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Synthesis, antimalarial activity and cytotoxic potential of new monocarbonyl analogues of curcumin

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ABSTRACT

A series of novel monocarbonyl analogues of curcumin have been designed, synthesized and tested for their activity against Molt4, HeLa, PC3, DU145 and KB cancer cell lines. Six of the analogues showed potent cytotoxicity towards these cell lines with IC_{50} values below 1 μM, which is better than doxorubicin, a US FDA approved drug. Several analogues were also found to be active against both CQ-resistant (W2 clone) and CQ-sensitive (D6) strains of *Plasmodium falciparum* in an in-vitro antimalarial screening. This level of activity warrants further investigation of the compounds for development as anticancer and antimalarial agents.

Natural products have played a vital role in the drug discovery process and approximately 67% of the drugs in the clinical market today are inspired by or derived from natural sources.[1] Curcumin (diferuloylmethane, Fig. 1), isolated from the rhizome of turmeric (Curcuma longa Linn.), is one of such natural compounds, which has been a subject of intense study for many decades.[2] Turmeric has been used since ancient time in South Asian subcontinents particularly in India and China as a dietary pigment, essential spice, and it has also been used in the traditional medicine as an antiseptic, anti-inflammatory and wound-healing agent.[3] Curcumin is also known for its anti-inflammatory, antioxidant, antimicrobial, antiviral, antiangiogenic, chemopreventative, chemotherapeutic and anticancer activities.[4] Recently, curcumin was also explored for its antimalarial activity against both chloroquine (CQ)-sensitive and chloroquine (CQ)-resistance strains of *Plasmodium falciparum*.[5] It has also shown hepato-protective and nephro-protective,[6] thrombosis suppressing,[7] myocardial infarction protective,[8] anti-hypoglycemic,[9] and anti-rheumatic[10] activities, and exhibited decreased tumorigenesis in many organs when tested in vivo.[2,11]

In vitro studies demonstrated that curcumin has potent cytotoxicity towards many cell lines derived from leukemia,[12] cervical cancer,[13] colorectal carcinoma,[14] prostate cancer[15] and human breast cancer cells.[16] However, limited clinical efficacy such as poor solubility, bioavailability and absorption as well as rapid metabolism have been major problems associated with curcumin.[17]

Detailed pharmacological studies conducted on curcumin demonstrates that the β-diketone functionality of curcumin is a substrate for liver aldoketo reductases and this may be one of the reasons for the rapid metabolism of curcumin in vivo.[18] The mono carbonyl analogues of the curcumin have been designed and synthesized in anticipation that the in vivo metabolic stability of these analogues can be improved and some of these compounds have shown very good anticancer activity.[19] Structure–activity relationship studies conducted on these compounds revealed that the heteroaromatic core in these compounds correlated with high anti-proliferative and anti-inflammatory activities.[20] Therefore, as a part of our ongoing programme towards the development of medicinally important molecules,[21] we became interested in modifying the structure of the curcumin by changing the β-diketone structure to mono carbonyl with rigid ring, while retaining

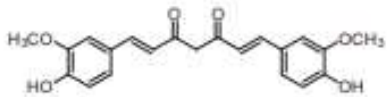

Figure 1. Structure of curcumin.

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