Bioorganic & Medicinal Chemistry Letters 23 (2013) 112–116

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

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

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ARTICLE INFO

Article history:
Received 9 July 2012
Revised 13 October 2012
Accepted 2 November 2012
Available online 10 November 2012

Keywords:
Curcumin
Anticancer
Cytotoxicity
HeLa cell line
Antimalarial

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

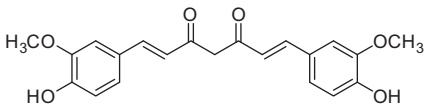

Figure 1. Structure of curcumin.

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http://dx.doi.org/10.1016/j.bmcl.2012.11.004

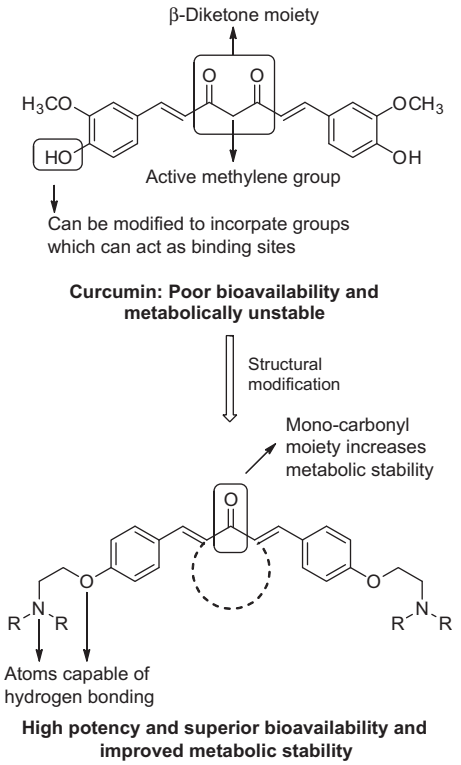


Figure 2. Modification of central β-diketone group and aryl substitution pattern.

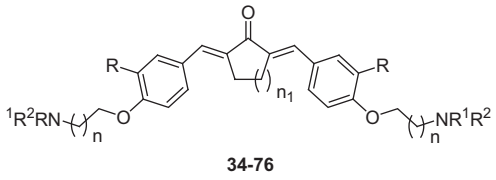


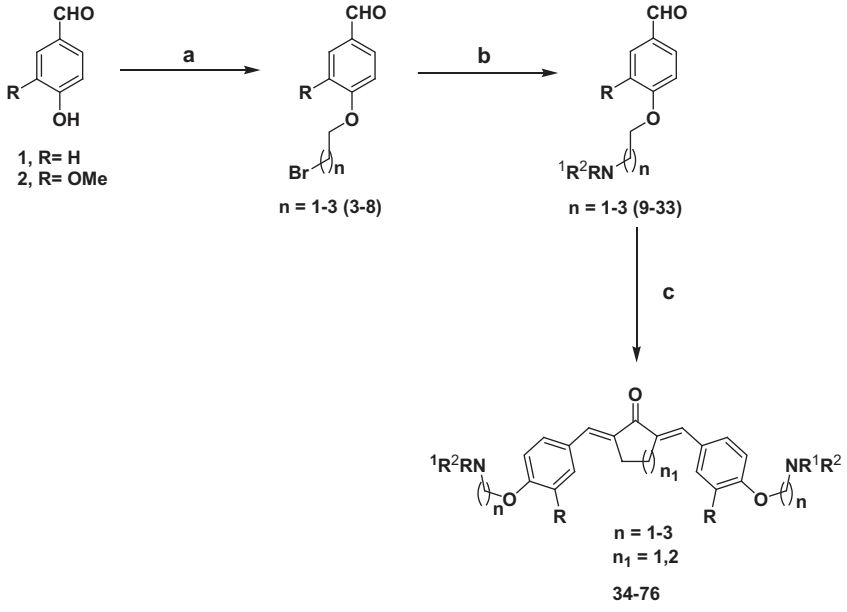
Figure 3. General structure of molecules in the present investigation.

the major skeleton of the structure. In addition, analogues were prepared by adding extra groups at two ends to examine the solubility issue (Fig. 2).

For the mono ketone part, either a five-membered ring or a six-membered ring was incorporated. The impact of rigidity was studied. For the linker on both ends, different lengths of the alkyl chain were applied to study the impact of size. For the substitution group of NR^1R^2, the following groups were used: bromo, morpholino, piperidino, dimethylamino, imidazole, 2-methyl imidazole and azepano group. The impact of the polarity and size of the substitution on two side chains was studied. Overall, a series of 43 analogues having the general structure shown in Figure 3 have been designed and prepared using one synthetic route (Scheme 1).

For the synthesis of desired monocarbonyl analogues of curcumin, commercially available starting materials *p*-hydroxy benzaldehyde (**1**) or vanillin (**2**) were reacted with an excess amount of aliphatic linear dibromoalkanes in the presence of a base (Scheme 1). The resulting aldehydes (**3**–**8**) with free bromo group at terminal position was subjected to nucleophilic substitution by different aromatic or aliphatic secondary amino functionalities to yield the corresponding amino substituted aldehydes (**9**–**33**) in high yield. The resulting compounds (**9**–**33**) were coupled with cyclopentanone or cyclohexanone in an alkaline medium in an aldol type of condensation to yield the desired curcumin analogues in good to excellent yield (70–90%) (**35**–**76**). Synthesis of analogue **34** was achieved by directly coupling cyclopentanone with 4-(2-bromoethoxy)-3-methoxybenzaldehyde (**3**) via aldol condensation.

All the synthesized compounds (Table 1) were screened for their cytotoxicity against the HeLa cancer cell line at three different concentrations. In the first screening, all compounds were tested at a concentration of 50 μM by the MTT assay. The result showed most compounds had cytotoxicity at 50 μM, and hence they were tested for the 2nd round screening at 2.5, 2 or 1 μM. Data showed that 11 compounds displayed comparable or better cytotoxicity than the control compound doxorubicin. All 11 active compounds were tested in the MTT assay with three replicated of every concentration (concentration from10 to 0.25 μM) in HeLa, PC3, DU145, KB or Molt4 cell lines. The MTT data were analyzed by curve-fitting using Sigma plotting to obtain the IC_{50} values (Table 2).



Scheme 1. Reagents and conditions: (a) aliphatic dibromoalkane, K_2CO_3, DMF, 80 °C, 1 h, 50–60%; (b) different secondary amines (HNR^1R^2), K_2CO_3, DMF, 80 °C, 6 h, 80–90%; (c) cyclic ketones, 20% (w/v) NaOH, MeOH, rt, overnight, 70–90%.