Cyclopentenone: a special moiety for anticancer drug design

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The conjugate cyclopent-en-one chemical group is a special moiety for anticancer drugs. Studies on cyclopentenone prostaglandins, clavulones and other compounds have revealed its mechanism of action and a wide spectrum of intracellular targets, ranging from nuclear factors to mitochondria. The introduction of the cyclopentenone moiety into molecules, such as jasmonates and chalcones, has been shown to boost their anticancer potential. In this work, reviewing pertinent up-to-date literature, we have pointed out potentially effective cyclopentenone-bearing compounds for anticancer clinical research and inspiring relationships for future drug design. In particular, it appears that the addition of cyclopentenone groups to target-orienting molecules, in order to inactivate specific proteins in cells, could be a helpful general strategy for the development of novel therapeutic molecules. *Anti-Cancer Drugs* **17:1017–1022**

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Introduction

The conjugate cyclopent-en-one (CP) chemical group is an essential pharmacophore of anticancer molecules, such as CP prostaglandins (PGs) (CPPGs) [1] and clavulones [2]. It is also responsible for the antiviral [3] and differentiating properties [4] of simple model compounds, such as cyclopent-2-en-1-one (2CP) or 4-cyclopentene-1,3-dione (4CP).

From a biochemical point of view, the α,β-unsaturated carbonyl group of CP is an electrophilic center susceptible to undergoing addition reactions with nucleophiles, such as free sulfhydryl groups of reduced glutathione (GSH) or cysteine residues in proteins (Fig. 1). Alkylation of crucial cysteine residues can result in a loss of function of the targeted proteins [1]. As the α,β-unsaturated carbonyl group is a 'soft' electrophile, alkylation of weaker nucleophilic sites located in other macromolecules, such as DNA, is much less likely [5].

The CP chemical group can react with a spectrum of cellular targets, including various nuclear factors and still undefined targets on cancer cell mitochondria. Moieties other than CP are important in directing the CP reactivity toward different targets (Table 1).

When introduced in anticancer molecules, the CP pharmacophore can increase their potency. This has been shown, for instance, in studies about chalcones [6] and jasmonates [7]. In particular, for methyl jasmonate, a new agent that targets cancer cell mitochondria [8], the introduction of the CP moiety increases its antiproliferative potential by a factor of 29 [9] (Fig. 2).

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Structure–function relationships, reviewed in this paper, have led us to point out interesting anticancer molecules for future clinical settings and inspiring relationships for future anticancer drug design.

Studies on prostaglandins

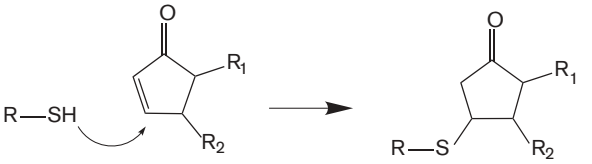
Much of what is known about structure–function relationships of compounds bearing the CP chemical moiety, as a pharmacophore, is due to studies on CPPGs: PGA_1, PGA_2, PGJ_2 and some of their metabolites such as 15-deoxy-$\Delta^{12,14}$-PGJ_2 (15d-PGJ_2), Δ^{12}-PGJ_2 and Δ^7-PGA_1.

The chemical reactivity of CP, rather than hormonal activity of the prostanoid nucleus, is essential for their pharmacological properties [10]. In fact (i) other prostaglandins, that do not have the CP group, do not show a similar range of biological activities [5], (ii) conjugation of the CP group with glutathione (GSH) eliminates CPPGs activity [10–13]; and (iii) many, if not all, of their biological activities are mimicked by the simple model compound 2CP itself, although at 30- to 100-fold higher concentrations [13].

CPPGs show antineoplastic, anti-inflammatory and antiviral properties [1]. The CP chemical group is essential for all these activities. A variety of molecular targets are involved (Table 1).

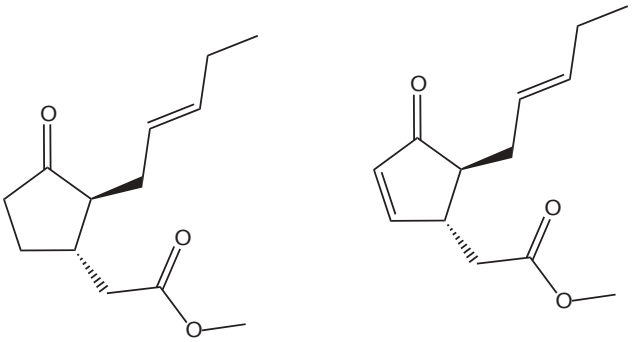
CPPGs' ability to induce cell cycle arrest and apoptosis is strongly dependant on the cell type and treatment conditions. CPPGs have been shown to induce growth arrest of human and murine tumor cells in the G_1 phase

Fig. 1



Chemical reactivity of the cyclopentenone pharmacophore with a generic thiol compound. Exposed cysteine residues in proteins exhibit this type of reactivity.

Fig. 2



Introducing a cyclopentenone, chemical moiety into the structure of methyl jasmonate (left structure), a 29-fold more potent anticancer molecule has been obtained (right structure) [9]. This strategy could be useful for novel anticancer drug design. Other examples are already known in the literature (see text).

of the cell cycle at sub-toxic doses [14,15]. Under these conditions, cell cycle arrest is correlated with down-regulation of several proteins that positively regulate cell cycle progression, such as the autocrine growth factor insulin-like growth factor-1 (IGF-1) and cyclin D1, and up-regulation of $p21^{CIP1/WAF1}$, which inhibits cell cycle progression [16]. At higher concentrations, CPPGs cause cell death rather than growth arrest in G_1. Cell death is often due to apoptosis [12,17–19], even if cases of non-apoptotic cell death associated with arrest in the S phase have been reported [20].

CPPG-induced apoptosis is also due to the inactivation of the transcription factor nuclear factor-κB (NF-κB), which has potent antiapoptotic activity. Elucidation of the molecular mechanism for repression of NF-κB activity by 15d-PGJ_2 has revealed that two target protein cysteine residues are involved. One of these is located in the activation loop of IκB kinase, which is required for NF-κB activation, and the other is located in the DNA-binding domain of NF-κB [21,22].

CPPGs of the J series inhibit the ubiquitin isopeptidase activity of the proteasome pathway thanks to their CP group that confers the ability to impair the conformation, the phosphorylation and the transcriptional activity of the p53 tumor suppressor with potency and efficacy. CPPGs of the J series are more effective inhibitors than representative members of the A series [23].

CPPGs can act in concert with traditional chemotherapy and radiotherapy. Kikuchi *et al.* [24], for instance, observed that PGD_2, Δ12-PGJ_2, and Δ7-PGA_1 are able to increase the inhibitory effect of cisplatin on the growth of human ovarian cancer cells in nude mice. Synergistic cytotoxic interactions between Δ^{12}-PGJ_2 and both ionizing radiation and cisplatin have also been reported [25]. This synergy has been observed in a variety of tumor cell lines and a decrease of about 10-fold in the dose of cisplatin or ionizing radiation required to kill 50% of the tumor cells has been observed. The synergy is probably due to the fact that ionizing radiation and cisplatin both induce DNA damage, whereas the CPPGs target specific cellular proteins.

The NF-κB transcription factor is a major target involved in the anti-inflammatory action of CPPGs. In addition, CPPGs can affect immune cells, such as dendritic cells and lymphocytes, that are indirect contributors of inflammation. In dendritic cells, they can induce caspase activation and apoptosis by a peroxisome proliferator-activated receptor-γ-dependant and -independent mechanism. Mature dendritic cells show enhanced susceptibility as compared with immature dendritic cells [26]. Lymphocyte-induced apoptosis is independent of peroxisome proliferator-activated receptor-γ and concomitant with the activation of the mitochondrial apoptotic pathway, in the absence of external death receptor signaling [27].

CPPG antiviral activity depends on a variety of molecular processes. PGA_1 and Δ^{12}-PGJ_2, for instance, inhibit the replication of vesicular stomatitis virus and a Sendai virus by selective inhibition of viral protein synthesis and interference with viral protein glycosylation and maturation. A hypothesis that the selective inhibition of viral protein synthesis is related to the induction of heat shock protein 70 synthesis has been advanced [28]. In other cases, CPPGs block virus replication in human cells without inhibition of the viral protein synthesis, but inhibiting a late event in virus replication, such as protein assembly and maturation of virions [29]. PGA_1 and PGJ_2 inhibit the replication of HIV-1 in acutely infected human cells without interfering with virus uncoating or reverse transcription, or with the accumulation of viral DNA. Instead, these two compounds appear to specifically inhibit accumulation of viral mRNA [30,31]. As NF-κB plays a key role in the activation of HIV-1 transcription and NF-κB is a major target for CPPGs, it is

Table 1 Growth-related and stress-induced factors known to be regulated by CP-bearing compounds

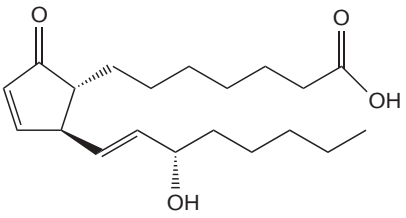
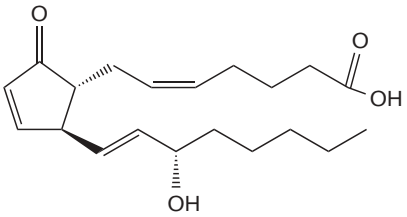
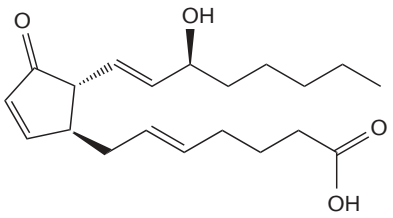
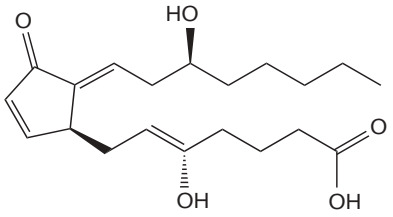
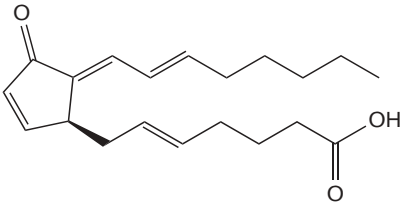
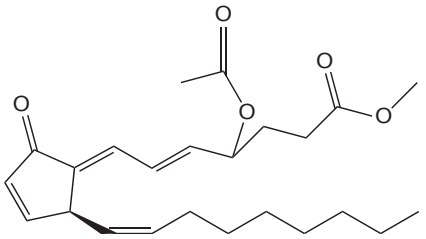
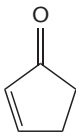
PGA_1		HSP70 $p^{21CIP1/WAF1}$ heme oxygenase IGF-I NF-κB PPAR-γ
PGA_2		HSP70 Gadd153 $p21^{CIP1/WAF1}$ c-Fos Egr-1 γ-Glutamylcysteine synthetase c-Myc N-Myc cyclin D1 CDk4 IGF-I NF-κB PPAR-γ
PGJ_2		HSP70 p21CIP1/WAF1 ubiquitin (UbB and C) IGF-I NF-κB PPAR-γ
Δ^{12}-PGJ_2		HSP70 GRP78 protein disulfide isomerase heme oxygenase c-Myc
15d-PGJ_2		HSP70 glutathione S-transferase

Table 1 *Continued*

Clavulone II		cyclin D1 Bax Mcl 1 Bid
2CP		NF-κB cyclin D1 IGF-I Waf1 HSP70

All these compounds are very interesting anticancer agents. Despite their biochemical reactivity and anticancer potential mainly due to their shared CP chemical moiety, their structures and cellular targets are different (see text). CP, cyclopentenone; PG, prostaglandin; HSP, heat shock protein 70; NF-κB, nuclear factor-κB; PPAR-γ; peroxisome proliferator-activated receptor-γ.

reasonable to predict that it might also be responsible for CPPG repression of HIV-1 transcription [1].

Despite the wide range of antitumor activities, CPPGs have not yet been tested in clinical settings. This is mainly due to in-vivo drug delivery-related difficulties. In fact, CPPGs are water insoluble and vehicles for intravenous administration are needed. Liposome suspension formulations are under investigation [32]. In addition, their reactivity toward cysteine residues and GSH greatly challenges their possibility to reach distant targets through systemic circulation. Nonetheless, direct injective administration of 15d-PGJ_2 in mice has been recently performed with success [33].

Studies on 2-cyclopenten-1-one

2CP has usually served as a simple model compound for studying the biological activity of more complex molecules, including CPPGs, and a number of other natural and synthetic agents [34,35]. Interestingly, many, if not all, of the biological activities of CPPGs are mimicked by 2CP itself.

2CP, for instance, has an antiviral activity similar to that of CPPGs against both DNA and RNA viruses, due to selective induction of heat shock protein 70 expression in human cells, through cycloheximide-sensitive activation of heat shock transcription factor 1 [3].

Only a few studies, so far, have specifically addressed the effect of 2CP alone on growing cells and the targets for its activity (Table 1), but evidence for an antiproliferative potential is strong. 2CP dose-dependently reduces cell viability and significantly induces apoptosis in human umbilical endothelial cells with as low a concentration as 0.25 μmol/l [36]. 2CP functions as a differentiating agent for MCF-7 breast cancer cells. 2CP causes cell cycle arrest in G_1 and down-regulates cyclin D1 gene expression in these cells. Further results have indicated that CP represses cyclin D1 promoter activity and that the element that mediates this effect is located in the core promoter [4]. CP inhibits NF-κB activity, although at concentrations approximately 100-fold higher than 15d-PGJ_1 [21]. Interestingly and paradoxically, however, 2CP is superior to 15d-PGJ_2 as an agent against the human breast cancer cell line (MCF-7) *in vitro*. In fact, 2CP does not induce expression of heme oxygenase-1, an activity that confers an unwanted sort of cytoprotective or antiapoptotic effect to 15d-PGJ_2 at low concentrations [37].

As other en-ones without a cyclic structure, e.g. curcumin, show antitumor activity [38], the question of the importance of the cyclic structure for CP anticancer activity has been raised. Bui and Strauss [13] have addressed this issue by studying the effects of CPPGs and related simpler compounds, which contain a five-membered ring system, on stress-induced IGF-1 and Waf1 gene expression. They reported that 2CP, but not cyclopentane or cyclopentene, represses IGF-1 and induces Waf1 gene expression, demonstrating the requirement for the α,β-unsaturated carbonyl group for regulation of the two genes. The di-one compound 4CP,

which has two potentially reactive carbons rather than one, is considerably more potent than 2CP in repressing IGF-1 gene expression ($IC_{50} = 30\,\mu mol/l$ for 4CP as compared with $167\,\mu mol/l$ for 2CP). Additional results indicate that diethyl maleate, which has two α,β-unsaturated carbonyls in a non-cyclic configuration, also represses IGF-1 gene expression and induces Waf1 gene expression, although with less potency ($IC_{50} = 214\,\mu mol/l$). Thus, the cyclic structure apparently strengthens the en-one effect [13]. Preclinical applications of 2CP, 4CP or similar compounds have not been published thus far. Nevertheless, thanks to their very low toxicity profile, these simple compounds appear interesting candidates for future anticancer applications.

Studies on clavulones

The CP chemical group is involved in the pharmacological activity of marine prostanoid clavulones. Recently, a biological examination of purified compounds obtained from a combinatorial cross-conjugated en-one library based on the structure of clavulones has revealed that, among clavulone-like compounds, those bearing the CP group have a cytotoxicity comparable to the best performing chemotherapeutics [2]. Preclinical settings with these strong cytotoxic clavulones are underway.

Targets of CP reactivity in clavulones are mainly mitochondrial (Table 1). Clavulone II triggers apoptotic signaling in human acute promyelocytic leukemia HL-60 cells, with an early induction of phosphatidylserine externalization, mitochondrial dysfunction, and alteration of the cell cycle. Clavulone II induces the disruption of mitochondrial membrane potential and activation of caspase-8, caspase-9 and caspase-3 in a time- and concentration-dependent manner. The effect of higher clavulone II concentrations can be accompanied by the up-regulation of Bax, down-regulation of Mcl-1 and cleavage of Bid. Low concentrations of clavulone II induce the antiproliferative effect through the down-regulation of cyclin D1 expression and G_1 arrest of the cell cycle [39].

Potentiating existing molecules

The introduction of CP chemical groups in the structure of anticancer molecules, such as jasmonates and chalcones, has been shown to increase their efficacy.

Jasmonates are regulator molecules of plant growth and differentiation, and have been shown to induce differentiation also in several human cancer cell lines. They are considered very promising differentiating inducers to control acute myelogenous leukemia, as prolonged exposure to relatively low concentrations of jasmonates induces growth arrest and re-differentiation of acute myelogenous leukemia cells in a mitogen-activated protein kinase-dependant way [9]. Higher concentrations of methyl jasmonate can instead induce perturbation of cancer cell mitochondria, leading to the release of cytochrome *c* and eventual cell death. A most important characteristic of jasmonates is their ability to selectively kill cancer cells while sparing normal cells [7]. Introduction of a double bond at the 4,5-position of methyl jasmonate (Fig. 2) greatly enhances methyl jasmonate antitumor activity. The synthetic methyl-4,5-didehydro-jasmonate, in fact, is approximately 29-fold more active than methyl jasmonate [9]. Preclinical evaluations of jasmonates with leukemia models in mice have given very encouraging results [7].

Chalcones, in particular combretastatin (COA) analogs, have established clinical efficacy as antimitotic and tubulin-binding agents. COA-4 phosphate also causes selective damage to tumor vasculature [40]. In a phase II clinical setting for COA-4 in late-stage non-small cell lung cancer, the drug has been reported to prolong survival to almost a year [41]. CP derivatives of COA demonstrate a remarkable enhanced cytotoxic activity against a variety of human cancer cell lines representing cancer of the colon, pancreas, larynx, ovary, duodenum, kidney, oral cavity, prostate, lung, endothelial cells and leukemias. COA CP derivatives show strong cytotoxicity, with IC_{50} values in the very low nanograms per milliliter range. Preliminary in-vivo evaluation have shown that, when administered at 40 mg/day in mice with Lewis lung carcinoma, these compounds inhibit the growth of a tumor mass with an efficacy comparable to that of etoposide, but with lower toxicity effects [6].

Conclusions

Today, available CP-bearing compounds, mainly CPPGs and clavulones, but also falconensones [42], zerumbone [43] and others, are interesting anticancer molecules, already under study. 2CP, 4CP and similar simple compounds, despite their lack of specificity, but a very low toxicity profile, appear to be additional interesting candidates for anticancer strategies. Finally, the CP chemical group could be a useful moiety for anticancer drug design. In fact, directing its wide-spectrum reactivity by means of specific chemical structures, it could be possible to target and inactivate specific proteins in cancer cells.

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