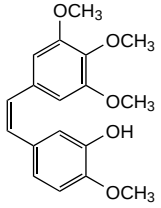
pharmacophore for this intriguing class of agent.

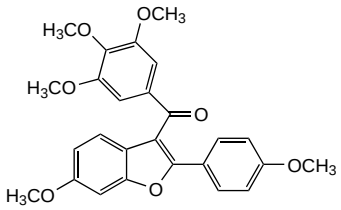
More recent studies have established that some tubulin-binding drugs selectively target the vascular system of tumours, inducing morphological changes in the endothelial cells of tumour blood vessels to occlude flow and resulting in virtually complete vascular shutdown within minutes. An example of an agent acting in this manner is combretastatin A-4 (CA4; compound **iii**), a powerful inhibitor of tubulin polymerization and a potent cytotoxin isolated from the stem wood of the South African tree *Combretum caffrum*. The disodium phosphate prodrug form of CA4 is currently undergoing clinical trials as a tumour vascular targeting agent. Two recent publications on antitumour agents structurally related to CA4, giving rise to new potent tubulin inhibitors and antimitotic agents, have appeared.



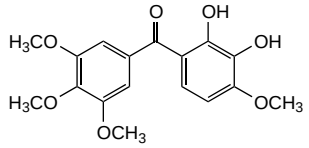
(iii)

Flynn and co-workers have described the one-pot preparation and antitumour activity of some benzo[*b*]furan and indole analogues of recently identified benzo[*b*]thiophene inhibitors of tubulin polymerization [4]. Several potent inhibitors of tubulin polymerization and colchicine binding, compared to CA4, were identified; for example, compound **iv** (IC_{50} for inhibition of tubulin polymerization = 0.41 μM, CA4 IC_{50} = 2.1 μM). In addition, tubulin inhibitors, such as **iv**, were found to be potent inhibitors of MCF-7 human breast carcinoma cell growth *in vitro* (IC_{50} = 34 nM).

Recent studies on the combretastatins have indicated the importance of the alkene *Z* geometry for inhibition of cancer-cell growth and tubulin polymerization. *Z*-Combretastatin analogues, however,

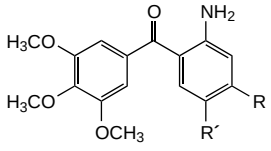


(iv)



(v)

are prone to isomerization during storage and administration; more recent studies have described the discovery of benzophenones (with the two aryl rings fixed in a quasi-*cis* orientation), such as hydroxyphenstatin (**v**), which display anticancer and antimitotic activities that are comparable to CA4 [5]. Liou and co-workers have now reported the synthesis and antitumour evaluation of related 2-aminobenzophenone derivatives [6]. Two lead compounds, **vi** and **vii**, from this new series were found with the following *in vitro* properties: inhibition of tubulin proliferation, inhibition of colchicine binding to tubulin and G_2–M phase arrest of cells. In addition, compounds **vi** and **vii** yielded 50- to 100-fold lower IC_{50} values than CA4 against Colo 205 (colon), NUGC3 (stomach) and HA22T (liver) human cancer cell lines *in vitro*.



(vi) R = OCH_3, R′ = H
(vii) R = H, R′ = OCH_3

2 West, L.M. and Northcote, P.T. (2000) Peloruside A: a potent cytotoxic macrolide isolated from the New Zealand marine sponge *Mycale sp. J. Org. Chem.* 65, 445–449

3 Hood, K.A. *et al.* (2002) Peloruside A, a novel antimitotic agent with paclitaxel-like microtubule-stabilising activity. *Cancer Res.* 62, 3356–3360

4 Flynn, B.L. *et al.* (2002) One-pot synthesis of benzo[*b*] furan and indole inhibitors of tubulin polymerisation. *J. Med. Chem.* 45, 2670–2673

5 Pettit, G.R. *et al.* (2000) Antineoplastic agents. 443. Synthesis of the cancer cell growth inhibitor hydroxyphenstatin and its sodium diphosphate prodrug. *J. Med. Chem.* 43, 2731–2737

6 Liou, J-P. *et al.* (2002) Synthesis and structure-activity relationship of 2-aminobenzophenone derivatives as antimitotic agents. *J. Med. Chem.* 45, 2556–2562

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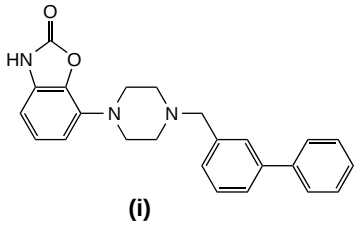
Combinatorial chemistry

Antipsychotics sharing dopamine D_2- and serotonin 5-HT_{1A}-receptor affinities

Schizophrenia is a disease of which the etiology is unknown. The disease is characterized by positive and negative symptoms: positive symptoms include hallucinations and paranoia, and the most characteristic negative symptoms are social withdrawal and flattening of the personality. Also, cognitive as well as depressive symptoms can occur. ‘Neuroleptics’ have been developed that show antipsychotic activity in the clinic. These compounds predominantly alleviate the positive symptoms by attenuating the dopaminergic neurotransmission system in the mesolimbic area of the brain. Therapy with these types of compounds is frequently accompanied by extra-pyramidal side effects (EPS) resulting from a blockade of dopaminergic activity within the motor areas of the brain. Thus, ~20% of the treated patients suffer from EPS, of which Parkinson-like symptoms is most common. There is a need for compounds that induce fewer side effects and, equally importantly, also treat the other than positive symptoms

of schizophrenia. Combining dopaminergic and serotonergic activity could be the way to develop atypical antipsychotics, those that are known to bind to the dopamine D_2 and serotonin 5-HT receptors.

Recent work has focussed on the search for compounds that share affinity for dopamine D_2 as well as serotonin 5-HT_{1A} receptors [1]. A small library of 21 compounds was synthesized in solution. The library compounds were screened for dopamine D_2 and serotonin 5-HT_{1A} receptor affinity using [^{3}H]-spiperone and 8-hydroxy-2-(di-*n*-propylamino) tetralin ([^{3}H]-8-OH-DPAT), respectively. One of the most potent compounds found was **i**, which possessed a K_i against D_2 of 2.2.nM and a K_i against 5-HT_{1A} of 9.3 nM. This work has produced an interesting set of compounds with affinity for both dopamine D_2-receptors and serotonin 5-HT_{1A}-receptors, and further work in this area is warranted.



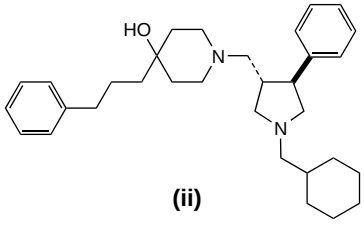
(i)

1 Feenstra, R. W. *et. al* (2001) New 1-aryl-4-(biarylmethylene)piperazines as potential atypical antipsychotics sharing dopamine D_2-receptor and serotonin 5-HT_{1A}-receptor affinities. *Bioorg. Med. Chem. Lett.* 11, 2345–2349

CCR5 antagonists

The CCR5 chemokine receptor is a member of the superfamily of seven-trans-membrane spanning G-protein coupled receptors. It has recently been discovered that the CCR5 receptor acts as a primary co-receptor, together with the cell-surface molecule CD4, for fusion then cell entry of certain HIV-1 viral strains. Compelling evidence for the role of CCR5 in HIV-1 infection comes from a study of individuals who, because of a 32 base-pair deletion in the gene for CCR5, lack functional receptor. Individuals who are homozygous for this defect are highly resistant to HIV-1 infection, whereas heterozygous individuals show significantly delayed progression to AIDS. As a result of these discoveries, many efforts to develop CCR5 antagonists have been undertaken.

A library strategy was developed with the aim of discovering novel pharmacophore elements, or novel combinations of known elements, for compounds with activity against the CCR5 receptor [2]. A library of 11,700 compounds, in mixtures of 117, was synthesized on solid phase using the Kenner sulphonamide linker. The 100 pools of 177 compounds were assayed for CCR5 affinity by measuring the ability of the mixtures to inhibit binding of ^{125}I-MIP-1α or ^{125}I-GP-120 (the HIV-1 envelop glycoprotein) to the CCR5 receptor in Chinese hamster ovary (CHO) cell membranes. Several pools were tested and found to be active. Following deconvolution of these mixtures, one of the most potent compounds isolated was **ii,** which possessed an IC_{50} value of 1 nM. This work has provided a new direction for the design of CCR5 antagonists based on the pyrrolidine scaffold with arylpropylpiperidine and aliphatic side chains. Further elaboration of this class of molecules would be worthwhile in the search for new CCR5 antagonists.



(ii)

2 Willoughby, C. A. *et. al.* (2001) Combinatorial synthesis of CCR5 antagonists. *Bioorg. Med. Chem. Lett.* 11, 3137–3141

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Profile

Calcium phosphate ceramics as carriers for bone therapeutic agents

Conventional means of administering therapeutic agents generally include oral medication, eye drops, ointments, intravenous injections and patches. However, the concept of targeted drug delivery to the site-of-action remains of major interest to improve therapeutic efficiency while producing minimum systemic side effects [1]. Considerable attention has been paid to improving drug delivery to sites dramatically limited in access, such as bone tissue [2]. Thus, because of their biological and physicochemical properties, synthetic bone substitutes have been contemplated as potential carriers for the local delivery of bioactive agents.

Calcium phosphate bone substitution materials

Although bone tissue possesses the capacity for regenerative growth, the bone repair process is impaired in many clinical and pathological situations. For example, massive bone loss caused by trauma and tumor resection, as well as deformities, requires reconstructive surgery. Therefore, there was a crucial need to develop implant technologies to promote bone healing.

Cortical and spongious bone grafts are the materials of choice for bone filling or reconstruction, but their clinical use involves some difficulties. Septic complications, viral transmission and unavailability of native bone have led to the development of synthetic bone substitutes. Among these biomaterials, macroporous calcium-phosphate (CaP) ceramics, such as hydroxyapatite (HA), β-tricalcium phosphate (β-TCP) and the HA/β–TCP association [termed biphasic calcium phosphate (BCP)] have been used clinically because their chemical composition is closely related to that of bone mineral. These ceramics are osteoconductive (act as a support for new bone formation requiring the presence of porosity) and

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