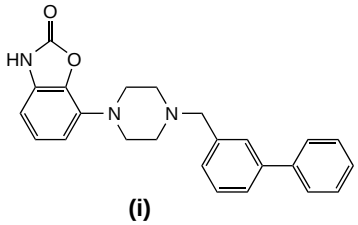
of schizophrenia. Combining dopaminergic and serotonergic activity could be the way to develop atypical antipsychotics, those that are known to bind to the dopamine $D_2$ and serotonin 5-HT receptors.

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.



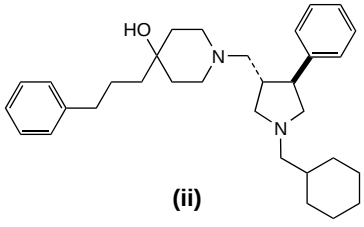

**(i)**

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)**

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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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resorbable (degradable through chemical and cellular processes) as illustrated in Fig. 1. They are also biocompatible – they do not induce adverse local tissue reactions, immunogenicity or systemic toxicity.

In the past decade, these biomaterials have been marketed and approved for use in humans as bone substitutes. Various presentations are currently used in orthopaedic and maxillo-facial surgery, such as wedges, blocks or granules (Fig. 1). Because of their bone substitution properties, CaP ceramics have naturally been considered as a potential matrix for the development of a bioactive drug-delivery system (DDS) in bone sites [3].

*Association of CaP ceramics with therapeutic agents*

The conventional CaP ceramic manufacturing process involves consolidation of powder by isostatic pressure followed by a sintering step (T >1000°C) to achieve fusion of particles of the material. Heating is necessary to strengthen the material but unfortunately prevents mixing of therapeutic agents with CaP before consolidation. To overcome this problem, therapeutic agents have been loaded on CaP ceramics after consolidation by adsorption through electrostatic interactions and reversible binding simply by incubating the ceramic block in a solution containing the drug. In addition, an innovative process, called 'dynamic compaction', to consolidate CaP powder without the use of external heating, has recently been patented [4]. In this process, compaction is achieved by a shockwave produced by piston impact on the surface of CaP powders and subsequent consolidation by localized interparticle melting [5,6].

*Pharmacokinetic profile of drug released from CaP ceramics*

The drug release pattern from homogeneous drug-loaded solid matrix generally follows the square root of time relationship [7]:

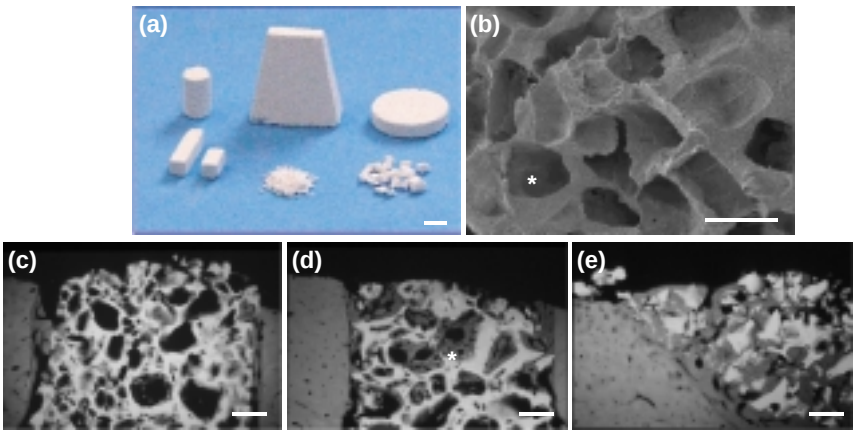


**Figure 1.** Macroporous biphasic calcium phosphate (BCP) ceramic. Macroscopic observation of: **(a)** Macroporous BCP ceramics (granules, pellet, wedge, cylinder and blocks). Scanning electron microscopy observation of BCP ceramic blocks, **(b)** before (* macropores 200–500 μm in diameter), **(c)** after2 weeks, **(d)** after 4 weeks (* newly-formed bone inside macropores), **(e)** and after 30 weeks of implantation in bone defects (dog femur) illustrating the progressive process of ceramic bone replacement. Ceramic appears in lighter grey, bone in darker grey and soft tissues in black. Scale bars: **(a)** 5 mm, **(b–e)** 500 μm.

$$M_t = A\, M_o\, [\, C_s\, (D_i\, \varepsilon/\tau)\, (2C_d - \varepsilon C_s) t\, ]^{1/2}$$
$$K = A\, M_o\, [\, C_s\, (D_i\, \varepsilon/\tau)\, (2C_d - \varepsilon C_s)]^{1/2}$$

where $M_t$ is the amount of drug released from the matrix at time *t*, K the Higuchi release rate constant, $M_o$ the total amount of drug loaded, A the matrix surface area, $D_i$ the drug diffusion coefficient, $C_s$ the drug solubility, $C_d$ the drug concentration, $\tau$ the matrix tortuosity, and $\varepsilon$ the matrix porosity. The linear pattern for the square root of time obtained with CaP ceramic systems [8] indicates that initial release involves a first-order diffusion-controlled mechanism, as originally described by Higuchi *et al.* [9]. However, this theoretical analysis of the release rate of drugs dispersed in solid matrices concerns cases in which solid drug particles are dispersed in a homogeneous matrix. In this case, matrix acts as a diffusional support from which drugs are released by the leaching action of penetrating solvent. This description does not seem to be totally appropriate to a drug solution adsorbed onto a solid degradable CaP matrix. Finally, even if drug release appears too complex to be described by a simple diffusion mechanism (with respect to the Higuchi equation), pharmacokinetics of drug release from CaP ceramic is also dependent on matrix tortuosity and porosity. Both of these ceramic parameters are affected by the precipitation–dissolution process of CaP, which occurs when such ceramics are immersed in release solution or under the influence of the ceramic resorption–degradation process in bone sites. Thus, drug release *in vivo* is under the influence of both a diffusion mechanism and the ceramic resorption–degradation process. A precise knowledge of ceramic dissolution and resorption properties is therefore of importance to provide clinicians with a valuable CaP ceramic DDS for bone sites.

*Therapeutic applications of CaP ceramic-based DDSs*

Preclinical and clinical trials have shown that CaP ceramics were able to induce new bone formation leading to their total replacement by lamellar bone. However, osteoconductivity of CaP ceramics does not yet enable large bone defects to be filled. At present, one approach to improve the ceramic bone

replacement consists of associating an osteogenic factor with the material. In this attempt, growth factors, such as transforming growth factor [10], platelet-derived growth factor [11], bone morphogenetic proteins [12], growth hormone [8] and insulin-like growth factor-1 [13] have been investigated successfully. These promising results have encouraged the scientific community to consider CaP ceramics as supports for the release of other molecules that are potentially implicated in the local treatment of bone pathologies, such as infections, bone tumors and pathological bone loss.

Therapy of bone infections (osteomyelitis) could easily last two years because of the poor accessibility of the infection site by common systemically administered antibiotics. This is mainly because bones are moderately perfused organs and because of a reduced blood supply associated with the formation of diffusional barriers in the infected bone tissues. Therefore, to improve therapy, resorbable CaP materials have been contemplated as potential carriers for antibiotics. They release effective drug amounts at the site of infection for several months and the systemic drug concentration remains low. Among the various antibiotics, vancomycin [14] and gentamycin have been extensively investigated and proved efficacy in human osteomyelitis [15].

A major attempt in treating bone and soft tissue tumors is to maintain local long acting and effective high concentrations of a chemotherapeutic drug at the site of tumors and, at the same time, producing minimum systemic side effects. Porous CaP ceramics have been demonstrated to be an efficient form of local DDS for methotrexate or *cis*-platinum and successfully used in the clinical treatment of mice osteosarcoma [16]. CaP ceramic could therefore have a major role in cancer chemotherapy in reducing the recurrence of tumors without the risk of systemic toxicity.

Osteoarticular disorders associated with increased osteoclastic bone resorption (as observed in osteoporosis, Paget's disease, bone lytic tumors, periodontal disease, and so on) often lead to pathological fractures. They are widely treated by systemic administration of bisphosphonates, which are potent inhibitors of osteoclast activity. Association of CaP materials with bisphosphonates would enable an increase in the efficiency of bisphosphonate by being locally released and decreasing significant secondary effects (nephrotoxicity) observed after systemic treatments. In this objective, ceramic hydroxyapatite implants have been used in dental surgery. Denissen *et al.* [17] reported that bisphosphonates could be beneficial in preventing alveolar bone destruction associated with natural and experimental periodontal disease and demonstrated the efficiency of bisphosphonate-complexed hydroxyapatite implants on the repair of alveolar bone.

### *Conclusions*

Bone diseases are in close relationship with population aging processes and, therefore, their treatments are a great challenge for the scientific community. The development of a bone-targeted bioactive DDS using a bone substitute provides an attractive and efficient approach to the treatment of bone pathologies, not only from clinical and scientific viewpoints but also at a social and economical level. Of course, the therapeutic window for CaP ceramic DDSs is mainly based on *in vitro* results and animal studies do not always extend well to human situations; however, this could be a good starting point for clinical trials. In addition, the approval of sustained release systems, such as those described here, could make the development of important innovative therapeutic-based strategies for the management of chronic bone affections (bone-forming protein [18] or gene transfer [19]) possible in the near future.

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