Purpose
Cannabinoïd receptors have gained increasing attention as drug targets for developing potential therapeutic ligands. Our purpose is to discover new CB2 ligands with novel chemical structure and potential therapeutic uses.

Methods
1. Within an in vitro high-throughput screening research program to discover novel CB2-selective ligands, N-(4-chlorophenethyl)-4-methyl-N-tosylbenzenesulfonamide (10) was identified as a novel chemotype with selective CB2 activity (CB2 Ki = 192 nM, selectivity index of 26-fold).
2. On the basis of this promising result, we considered 10 as a lead compound and conducted further medicinal chemistry structure–activity relationship (SAR) studies.
3. Four series of compounds were designed, synthesized, and tested in competition binding activities on both CB2 and CB1 receptors. The representative compounds were also examined in cAMP assays, with the aim of evaluating their functionality.
4. Three compounds were selected as top candidates to be evaluated against RANKL-induced osteoclast differentiation on RAW 264.7 cells. Meanwhile, to examine whether the impaired osteoclastogenesis is due to the decrease in viability of the precursor cells, the cytotoxicity profile of these compounds upon osteoclast precursors RAW 264.7 were investigated by a standard MTT assay.
5. 3D QSAR studies were carried out for the synthesized analogues to correlate structural and experimental data for further SAR studies.

Results
Four sets of triaryl ligands (46 compounds) were designed and synthesized for further structural modifications and led to the identification of eight compounds as potent and selective CB2 inverse agonists with high binding affinity (CB2 Ki < 10 nM). Especially, compound 57 exhibited the strongest binding affinity on the CB2 receptor (CB2 Ki of 0.5 nM) and the best selectivity over the CB1 receptor (selectivity index of 2594).
Importantly, 57 also showed potent inhibitory activity on osteoclast formation, and it was confirmed by a cell viability assay that the inhibition effects were not derived from the cytotoxicity.
Finally, 3D QSAR studies confirmed our SAR findings that three bulky groups play an important role for CB2 receptor binding affinity.

Conclusion
Newly discovered compound 57 offers an attractive starting point for further optimization and is a promising antiosteoporosis agent.