AZAPEPTIDOMIMETICS OF MYD88 CONSENSUS PEPTIDE : SYNTHESIS AND PRELIMINARY STUDY ON THEIR EFFECTS ON IL-1-INDUCED NF-ΚB ACTIVATION

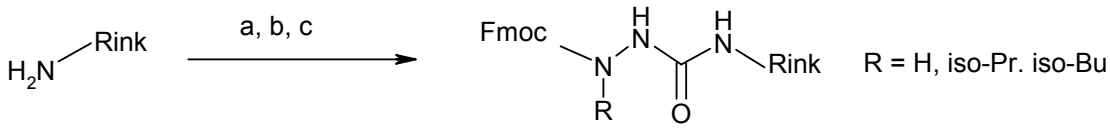
Nicola Fantò [a], Davide Vignola[a], Silvia Verì[a], Nadia Caroni[a], Ottaviano Serlupi[a], Tinti Maria Ornella[a], De Angelis Francesco[b].

[a]R&D, Sigma-Tau S.p.A., Via Pontina Km 30.400, 00040 Pomezia (Rome), Italy and [b]Chemistry Department, Chemical Engineering and Materials, University of L'Aquila, 67100 L'Aquila, Italy.

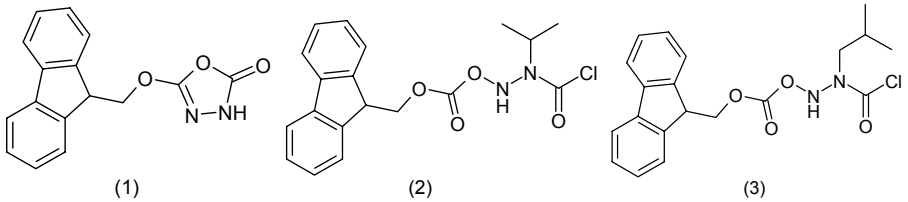
MyD88 plays a crucial role in the signalling pathways triggered by IL-1 and Toll-like receptors (TLR) in various phases of innate host defence. A crucial event in this signalling pathway is represented by dimerization of MyD88, which allows the activation of the downstream transcription factor NF-κB [1].

This work describes the synthesis of a number of azapeptidic compounds [2] structurally related to the MyD88 TIR domain consensus peptide RDVLPGT [3], and some evidence of their inhibitorial activity on IL-1 induced NF-κB activation.

The azapeptides were synthesized by Fmoc solid phase method on Rink-amide resin, using fosgene solution in toluene for azapeptide bond formation.



a) DMF, t.a., 30 min b) Piperidine 30% in DMF, t.a., 10 min c) (1) or (2) or (3), CH_2Cl_2, t.a., 90 min.



(1) (2) (3)

The aza-building blocks synthesis from tert-butyl-carbazate for the incorporation of aza-Gly, aza-Val and aza-Leu is also described.

The effect of these compounds on inhibition of IL-1-induced NF-κB activation was monitored by RGA (Reporter Gene Assay). Experimental data on some active azapeptides are also reported.

[1] Akira, S., Takeda, K.(2004) *Nature Rev. Immunol.* 4, 499-511
[2] European Patent requested n° 45785
[3] Loiarro, M., Sette, C., Gallo, G., Ciacci, A., Fantò, N., Mastroianni, D., Carminati, P., Ruggiero, V., *J.Biol. Chem.,* Papers In Press, published online ahead of print March 8, 2005, jbc.C400613200