Thalidomide Analogs

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Technology description

Summary

Inflammatory processes associated with the over-production of cytokines, particularly of tumor necrosis factor-alpha (TNF-alpha), accompany numerous neurodegenerative diseases, such as Alzheimer's disease and ALS, in addition to numerous common systemic conditions, such as rheumatoid arthritis, septic shock, graft-versus-host disease, Crohn's disease and erythema nodosum leprosum (ENL). TNF-alpha has been validated as a drug target with the development of the inhibitors Enbril (Amgen, Thousand Oaks, CA/Wyeth, Princeton, NJ) and Remicade (Centocor, Malvern, PA/ Schering-Plough, Orange, NJ) as prescription medications for rheumatoid arthritis. Both, however, are large macromolecules and hence are expensive to produce, require direct intravenous or subcutaneous injection, and have negligible brain access. The classical orally active drug, thalidomide (N-alpha-phthalimidoglutarimide), a glutamic acid derivative, is being increasingly used in the clinical management of a wide spectrum of immunologically mediated and infectious diseases, and cancers. Its clinical value in treating ENL derives from its TNF-alpha inhibitory activity. Specifically, it inhibits TNF-alpha protein expression at the post-transcriptional level by facilitating turnover of the mRNA (Sampaio et al., 1991 & 1993; Moreira et al., 1993). More recent research has shown similar inhibitory action of COX2 protein expression (Fujita et al., 2001). These actions are mediated post-transcriptionally via AU-rich elements found in the 3N untranslated regions (3N-UTRs) of each mRNA (Kruys et al., 1994; Chen et al., 1995). Thalidomide's anti-angiogenesis activity derives from its inhibitory actions on basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) (D'Amato et al., 1994; Figg et al., 2002). The agent, additionally, acts as an inhibitor of the transcription factor, NFkB and a co-stimulator of both CD8+ and CD4+ T cells (Haslett et al., 1998). However, the action of thalidomide to lower TNF-alpha levels and inhibit angiogenesis is not particularly potent and it therefore represents an interesting lead compound for medicinal chemistry.
Novel structural modification of thalidomide was achieved towards the discovery of original and potent isosteric analogues. The present invention relates to thalidomide analogues and, in particular, thiothalidomides (sulfur-containing thalidomide analogues), methods of synthesizing the analogues, and methods for using the analogues to modulate TNF-alpha and angiogenesis activities in a subject. Disclosed analogues potently inhibited TNF-alpha secretion, compared to thalidomide, via post-

transcriptional mechanisms that decreased TNF-alpha mRNA stability via its 3N-UTR (Zhu et al., 2003). Actions to inhibit angiogenesis were determined in widely accepted ex vivo assays.

Institution

NIH - National Institutes of Health