Substituted 3,6-diphenyl-7H-[1,2,4] triazolo[3,4-b] [1,3,4] Thiadiazines as Potent Inhibitors of PDE4A, PDE4B, and PDE4D

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Technology description

Phosphodiesterase 4 (PDE4) is a major cAMP-metabolizing enzyme found in immune and inflammatory cells, airway smooth muscle, and pulmonary nerves. It plays a significant role within the inflammatory responses associated with asthma and chronic obstructive pulmonary disease (COPD) and its modulation has been linked to memory enhancement and depression. Due to its widespread therapeutic potential, PDE4 inhibitors are highly sought after agents for treating numerous disease states. While several PDE4 inhibitors have already advanced into clinical settings, unfavorable side effects including emesis, nausea, and abdominal pain emphasize the need for novel chemotypes with potent and selective PDE4 inhibition.
This technology describes a series of substituted 3,6-diphenyl-7H-[1,2,4] triazolo[3,4-b] [1,3,4] thiadiazines that act as inhibitors of PDE4.

Application area

Treatment of numerous diseases associated with PDE4 including asthma, COPD, inflammatory bowel disease, and other anti-inflammatory diseases with other possible treatments including depression and psychosis.

Advantages

This core structure represents a novel chemotype within extensive classes of PDE4 inhibitors and the structure activity relationships of these PDE4 inhibitors identify key binding sites and substitutions critical to the functionality for potent PDE4 inhibition. Selectivity of this novel chemotype shows weak inhibitory potency against nine PDE isoforms excluding PDE4 and strong inhibitory potency against PDE4A, PDE4B, and PDE4D. In a selectivity comparison study, the novel chemotype performs better than the PDE4 inhibitor in clinical development. Subtype-selective PDE4 inhibitors are becoming

increasingly more important as new research shows that independent PDE isoforms have differential effects on cells.

Institution

NIH - National Institutes of Health