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(54) Title: COMPOUNDS AND COMPOSITIONS FOR TREATING DISEASES ASSOCIATED WITH SERINE PROTEASE, PARTICULARLY TRYPTASE, ACTIVITY

(57) Abstract

Novel compounds, compositions and methods effective for the prevention and treatment of mast-cell mediated inflammatory disorders are described. A preferred aspect of the invention are compounds of Formula (II) in which: the dashed lines independently represent optional bonds; each R² independently

is (C₁₋₆)alkyl, (C₁₋₆)alkyloxy, halo or hydroxy; each R³ independently is (C₁₋₆)alkyl, (C₁₋₆)alkyloxy, halo or hydroxy; X³ is -C(O)- or -CR⁷R⁸-, X⁸ is -CH(R¹)_{n1}- or -C(R¹)_{n1}-, wherein R¹ is amino(N1-4)azolidinyl, amino(N1-4)azolyl, (N1-4)azolidinyl, (N1-4)azolyl, -NHC(NH)NR⁹R⁹, -C(NR⁹)R⁹, -C(NH)NHR¹⁰, -C(NH)NR¹⁰R¹⁰ or -(CR¹¹R¹¹)_nNH₂, or X⁸ is -N= or -NH(R¹)_{n1}-, wherein R¹ is -C(NR⁹)R⁹, -C(NH)NHR¹⁰ or -C(NH)NR¹⁰R¹⁰, wherein each R⁹ independently is hydrogen or (C₁₋₆)alkyl and each R¹⁰ independently is (C₁₋₆)alkyl; and X⁹ is -CH(R⁴)- or -C(R⁴)-, wherein R⁴ is -R¹², -OR¹², -N(R¹³)R¹², -SR¹², -S(O)R¹², -S(O)₂R¹², -S(O)₂N(R¹³)R¹², -N(R¹³)S(O)₂R¹², -C(O)R¹², -C(O)OR¹², -C(O)N(R¹³)R¹², -N(R¹³)C(O)R¹², -OC(O)N(R¹³)R¹², -N(R¹³)C(O)OR¹², -(CH₂)_{n4}N(R¹³)C(O)N(R¹³)R¹², -OP(O)(OR¹³)OR¹² or -C(O)N(R¹⁴)CH(COOH)R¹², or X⁹ is -N= or -N(R⁴)-, wherein R⁴ is -C(O)R¹², -C(O)OR¹², -C(O)N(R¹³)R¹², -OC(O)N(R¹³)R¹² or -C(O)N(R¹⁴)CH(COOH)R¹², wherein R¹², R¹³ and R¹⁴ are as defined in the Summary of the Invention; R⁵ is hydrogen or (C₁₋₄)alkyl, R⁶ is hydrogen or (C₁₋₄)alkyl, which alkyl optionally is substituted with one to two substituents independently selected from (C₁₋₄)alkyloxy, hydroxy and sulfo, R⁷ is hydrogen or methyl and R⁸ is hydrogen, methyl or hydroxy. The compounds, compositions and methods are effective for the prevention and treatment of inflammatory diseases associated with the respiratory tract, such as asthma and allergic rhinitis, as well as other types of immunomediated inflammatory disorders, such as rheumatoid arthritis, conjunctivitis and inflammatory bowel disease, various dermatological conditions, as well as certain viral conditions. The compounds comprise potent and selective inhibitors of the mast cell protease tryptase. The compositions for treating these conditions include oral, inhalant, topical and parenteral preparations as well as devices comprising such preparations.

