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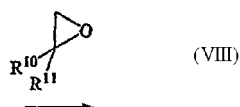
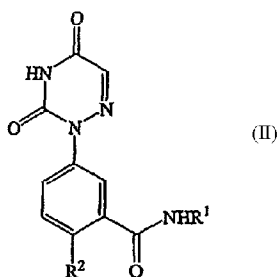
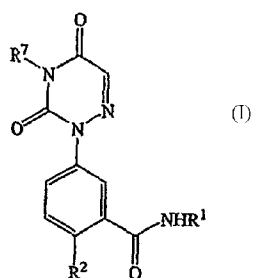
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(54) Title: METHOD FOR PREPARING 5-[4-(2-HYDROXY-ETHYL)-3,5-DIOXO-4,5-DIHYDRO-3H-[1,2,4]-TRIAZIN-2-YL]BENZAMIDE DERIVATIVES WITH P2X7 INHIBITING ACTIVITY BY REACTION OF THE DERIVATIVE UNSUBSTITUTED IN 4-POSITION OF THE TRIAZINE WITH AN OXIRAN IN THE PRESENCE OF A LEWIS ACID



(57) Abstract: The present invention relates to methods of preparing compounds of formula (I), R^7 is $-CH_2-C(R^{10}R^{11})-OH$, wherein R^{10} and R^{11} are independently selected from the group consisting of: hydrogen, phenyl, and (C_1-C_6) alkyl optionally substituted with one to three halos, hydroxy, $-CN$, (C_1-C_6) alkoxy, $((C_1-C_6)alkyl)_n-N$, $(C_1-C_6)alkyl-(C=O)-$, $(C_3-C_8)cycloalkyl-(C=O)-$, 5 or 6-membered heterocycloalkyl- $(C=O)-$, phenyl- $(C=O)-$, naphthyl- $(C=O)-$, 5- or 6-membered heteroaryl- $(C=O)-$, $(C_1-C_6)alkyl-(C=O)O-$, $(C_1-C_6)alkyl-O(C=O)-$, $(C_3-C_8)cycloalkyl$, phenyl, naphthyl, 5 or 6-membered heterocycloalkyl, and 5- or 6-membered heteroaryl; or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 and R^4 have any of the values as defined in the specification. Wherein said method comprises reacting a compound of formula (II) with a compound of formula (VIII) in the presence of at least one Lewis acid. The compounds are useful as agents in the treatment of diseases, including inflammatory diseases such as rheumatoid arthritis. Also provided are compositions of crystalline 2-Chloro-N-(1-hydroxy-cycloheptylmethyl)-5-[4-(2R-hydroxy-3-methoxy-propyl)-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl]-benzamide comprising less than 2.5% residual organic solvent, and methods for preparing said compositions. Further provided are methods for crystallizing 2-Chloro-N-(1-hydroxy-cycloheptylmethyl)-5-[4-(2R-hydroxy-3-methoxy-propyl)-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl]-benzamide.



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