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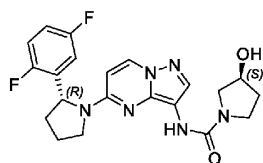
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(54) Title: PREPARATION OF (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE



Formula I

(57) Abstract: Process for preparing (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide (formula I) or a salt thereof by reacting phenyl(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3,4-dihydropyrazolo[1,5-a]pyrimidin-3-yl)carbamate or a similar derivative (formula 13) with (S)-pyrrolidin-3-ol (formula 14). Process for preparing phenyl(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3,4-dihydropyrazolo[1,5-a]pyrimidin-3-yl)carbamate (formula 13) or a similar derivative by reduction of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-nitropyrazolo[1,5-a]pyrimidine (formula 11) to (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (formula 12). Process for preparing (R)-2-(2,5-difluorophenyl)pyrrolidine(R)-2-hydroxysuccinate (formula 10) by treating (R)-N-((R)-1-(2,5-difluorophenyl)-3-(1,3-dioxan-2-yl)propyl)-2-methylpropane-2-sulfonamide (formula 19) with an acid and a reducing agent. (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide, is a tyrosin kinase (TRK) inhibitor for treating e.g. cancer.



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