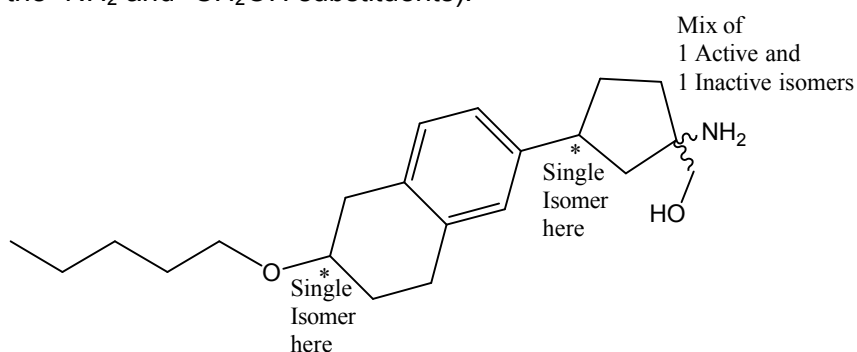


European Patent Application No. 15756772.8 - 1501 (3183242)
Regional Phase of PCT Application PCT/US2015/046005
Bristol-Myers Squibb Company

Experimental Report

The compounds of Examples 11-14 each contain three stereocenters (see structure below). In each case, they are a single isomer at the far left and also a single isomer at the point of attachment of the cyclopentane bond to the aryl ring. However, they are mixtures of isomers at the far right stereocenter (i.e. the point of attachment of the -NH₂ and -CH₂OH substituents).



This is important because only one of the isomers at that stereocenter is efficiently converted to the active phosphorylated form. Consequently, only half of the material contributes meaningfully to the observed lymphocyte reductions.

Therefore, although Examples 11-14 were dosed at 2 mg/kg for this study, the effective dose of the active isomer in each example was approximately 1 mg/kg. In contrast, Example 703 was the active isomer at far right stereocenter.

Examples 11-14 and Comparative Example 703 were tested in the Blood Lymphocyte Reduction Assay in mice.

Examples 11-14 administered to mice at an effective dose of 1 mg/kg (adjusted for active isomer) showed lymphocyte reductions of 61 to 84%. In comparison, Comparative Example 703 administered to mice at a dose of 1 mg/kg (active isomer only), showed a lymphocyte reduction of 52%, shown in the Table below:

Compound	Lymphocyte Reduction at 24 hr	Dose	Dose (Adjusted for active isomer)	Comments
Comparative Example 703	52%	1 mg/kg	1 mg/kg	Contains only active 1 <i>R</i> isomer
Example 11	84%	2 mg/kg	1 mg/kg	Contains 50% inactive 1 <i>S</i> isomer
Example 12	61%	2 mg/kg	1 mg/kg	Contains 50% inactive 1 <i>S</i> isomer
Example 13	83%	2 mg/kg	1 mg/kg	Contains 50% inactive 1 <i>S</i> isomer
Example 14	81%	2 mg/kg	1 mg/kg	Contains 50% inactive 1 <i>S</i> isomer