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September 2022

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Recommended Citation

MSN Laboratories Private Limited, R&D Center; Srinivasan Thirumalai Rajan; Sajja Eswaraiah; M. Kishore; Seetharama Sarma Peri; Mallikarjuna Raju Koneti, "Process for the preparation of 4-(4-(4-aminophenyl) piperazin-1-yl) phenol", Technical Disclosure Commons, (September 19, 2022)
https://www.tdcommons.org/dpubs_series/5390



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Process for the preparation of 4-(4-(4-aminophenyl) piperazin-1-yl) phenol

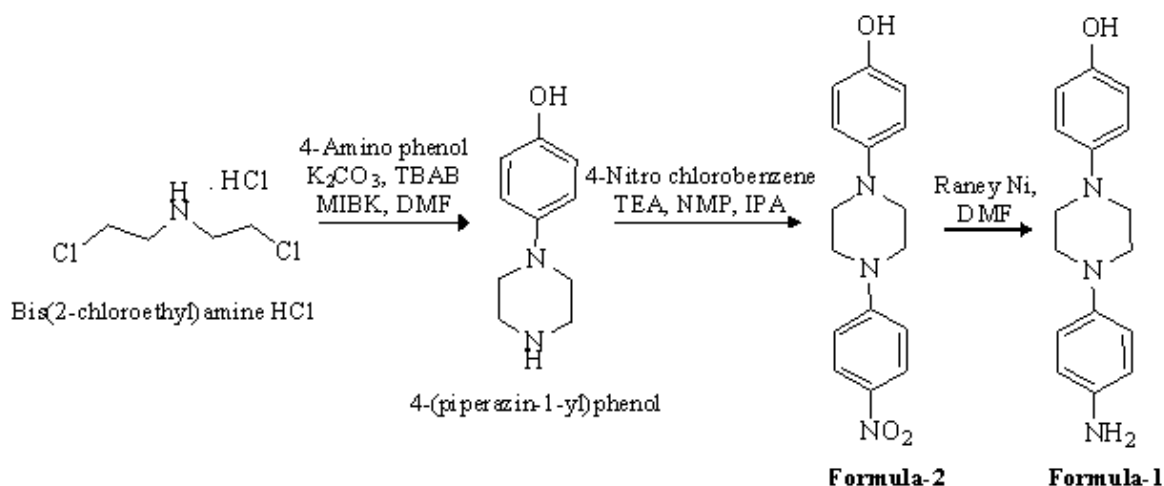
A process for the preparation of 4-(4-(4-aminophenyl)piperazin-1-yl)phenol of formula-1, which is represented by the following structural formula.



Formula-1

4-(4-(4-aminophenyl)piperazin-1-yl)phenol is a process intermediate for the preparation of triazole antifungal agent of Posaconazole, which is used to prevent serious fungal infections that can spread throughout the body in adults and children 2 years of age and older with a weakened ability to fight infection. Posaconazole delayed-release tablets are used to treat invasive aspergillosis (a serious fungal infection that begins in the lungs and spreads through the bloodstream to other organs) in adults and teenagers 13 years of age and older.

The present disclosure provides an improved process for the preparation of 4-(4-(4-aminophenyl)piperazin-1-yl)phenol with reproducibly in good purity and yield, which is schematically presented as follows.



The following examples specifies the conditions of the process for the preparation of 4-(4-(4-aminophenyl)piperazin-1-yl)phenol.

Example-1: Process for the preparation of 4-(Piperazin-1-yl)phenol.

Tetrabutylammonium bromide (87 gm) was added to the pre-cooled mixture of methyl isobutyl ketone (750 ml), 4-amino-phenol (150 gm) in dimethylformamide (150 ml) at 0-5°C and stirred the mixture for 10 minutes. Slowly potassium carbonate (760.64 gm) was added to

the mixture at 0-5°C and stirred for 10 minutes. Bis(2-chloroethyl)amine hydrochloride (318.88 gm) was slowly added to the mixture at 0-5°C and stirred for 10 minutes. Heated the mixture at 95-100°C and stirred for 8 hours. Allowed to cool the mixture to 25-30°C. Water was added to the mixture and stirred for 45 minutes at 25-30°C. Filtered the precipitated solid. Water was added to the filtered solid at 25-30°C and stirred for 30 minutes. Filtered the solid and dried to get the titled product.

Yield: 175 gm; Purity by HPLC: 96.87%

Example-2: Process for the preparation of 4-(4-(4-aminophenyl)piperazin-1-yl)phenol.

P-Nitro-chlorobenzene (105.8 gm) and Triethylamine (73.76 gm) were added to the mixture of 4-(Piperazin-1-yl)phenol (100 gm) in N-Methyl-pyrrolidone (200 ml) at 25-30°C, stirred the mixture for 10 minutes. Heated the mixture for 110-115°C and stirred for 6 hours. Allowed to cool the mixture to 25-30°C. Isopropanol (200 ml) was added to the mixture and stirred for 1 hour at 25-30°C. Cooled the mixture to 10-15°C and stirred for 1 hour. Filtered and dried the solid to obtain 4-(4-(4-nitrophenyl)piperazin-1-yl)phenol.

Dimethylformamide (1200 ml) was added to the above filtered solid of 4-(4-(4-nitrophenyl)piperazin-1-yl)phenol, which taken in autoclave vessel. Raney nickel (20 gm) in dimehtylformide was added to the mixture at 25-30°C. Appropriate hydrogen pressure was applied to the mixture. Heated the mixture to 45-50°C and stirred for 3 hours. Allowed to cool the mixture to 25-30°C. Filtered the mixture to remove raney nickel through hyflow. Water was added to the filterate at 25-30°C and stirred for 1 hour. Filtered the precipitated solid and washed with water and methanol.

Yield: 92 gm
