Supporting Information for

Synthesis of the NK1 Receptor Antagonist GW597599. Part 2:

Development of a Scalable Route to a Key Chirally Pure

Arylpiperazine

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Process Safety Evaluation

The chemical method for the preparation of the intermediate **14** was assessed in order to ensure safe scale up on pilot plants. Previous experience on the same kind of reactions suggested that the main factors to keep under control were the possible presence of diborane gas in the vent lines and the handling of the large amount of hydrogen generated during this process, so that gas ignition and potential explosions are avoided.

The process was tested in a reaction calorimeter which was modified to acquire data about the generation of gaseous species. The gas stream emitted from the top of the condenser of the reaction calorimeter was directed through a thermal mass flow meter with the aim of measuring the rate of gas generation at any time during the process. The gas stream leaving the flow meter was then diverted to a mass spectrometer in order to derive a semi-quantitative estimation of the gas stream composition.

This study has shown that the three main operations – addition of the solution of **13** to NaBH₄ in tetrahydrofuran, addition of BF₃·THF and addition of methanol – were associated with both heat and gas evolutions. During all of these additions, the rates of heat and gas output were effectively dependent on the rate of dosing. As a result the rate of reaction was so fast that at any time the reaction could have been stopped simply by pausing the addition.

With an input of 1 kilogram of **13**, experimental data allowed to calculate that *ca.* 95 litres of gas evolved during the addition of the solution of **13** to the suspension of NaBH₄, *ca.* 160 litres of gas evolved during the addition of BF₃·THF and *ca.* 390 litres of gas evolved during the addition of methanol.

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The analysis of the gas stream composition indicated that the main component was hydrogen, with a variable amount of solvent carried over. Diborane gas was always under the limit of detection of the equipment and so we postulated that it was not present in the gas stream during this process.

From these data it is concluded that the pilot plant equipment could cope with this level of hydrogen generation and the proposed process was deemed to be scalable with only minor adjustments to the rates of dosing.

Figure 1 Plot of the rate of gas generation associated to the addition of the solution of compound **13** to the suspension of NaBH_4 in tetrahydrofuran.

Figure 2 Plot of the rate of gas generation associated to the addition of the complex $\text{BF}_3 \cdot \text{THF}$.

Figure 3 Plot of the rate of gas generation associated to the addition of methanol.

Chiral HPLC of (2S)-2-(4-fluoro-2-methylphenyl)piperazine dihydrochloride salt 14