

CHEMISTRY AND EARLY DEVELOPMENT SUPPORT

Medicinal Chemistry and Early Development

OUR CAPABILITIES, SKILLS AND EXPERTISE

PEOPLE

— Key strengths in communication and project management developed through the successful delivery of >100 projects
— Talented pool of scientists with broad experience in the life science industry

CHEMISTRY SUPPORT

— State-of-the-art chemistry and analytical platform including: ▶ Parallel synthesisers (Radley) ▶ Microwave synthesisers (Biotage) ▶ Parr hydrogenators and autoclaves ▶ Combiflash systems (Teledyne-Isco) ▶ Flash chromatography systems ▶ Reaction capability between -78° C to +250° C
— Expertise in the multi-step synthesis (mg to multi-gm) of: ▶ Metabolites and standards ▶ Natural product-like heterocyclic scaffolds ▶ Building blocks, intermediates and impurities

— Parallel multi-step synthesis of analogues on a large scale

OXETANONE BUILDING BLOCKS

— Evotec has optimised the process for the large scale synthesis of 3-Oxetanone and its derivatives
— Using these building blocks as starting points or intermediates can significantly accelerate your medicinal chemistry projects
— Over 70 derivatives are available on request in mg to kg quantities using validated routes

EARLY CHEMISTRY DEVELOPMENT

— Process research and development: ▶ Route scouting ▶ Optimisation of process from 100 gm to multiple kg ▶ Development of non-infringing routes for

Evotec is capable of providing cost efficient chemistry capacity whilst leveraging leading capabilities and scientific know-how. In addition, Evotec's project management and problem solving culture, developed through 15 years of delivering high quality services, will ensure we deliver on promises.

Evotec's offering include:

- Medicinal chemistry support
- Custom synthesis
- Oxetanone building blocks and derivatives
- Early chemistry development
- Analytical services

active pharmaceutical ingredients (APIs)
▶ Process compliance to SHE
— Scale-up and non-GMP production of intermediates and APIs up to 25 kg

ANALYTICAL SERVICES

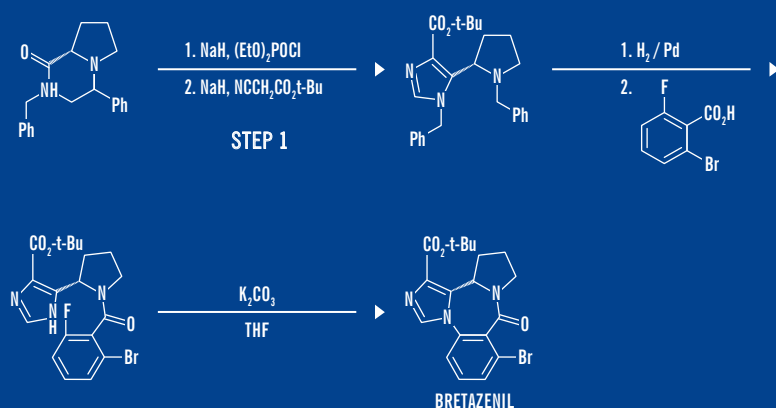
— State-of-the-art analytical chemistry platform including: ▶ FT NMR 400 MHz-Multinuclear (Bruker) ▶ HPLC and LC MS/MS systems (Thermo, Agilent, Waters) ▶ GC (Varian)
— Structure determination and elucidation
— Method development and validation
— Impurity profiling and characterisation
— Analytical testing of: ▶ Active pharmaceutical ingredients (APIs) and bulk drug Intermediates ▶ Finished dosage forms ▶ Forced degradation as per GMP requirements

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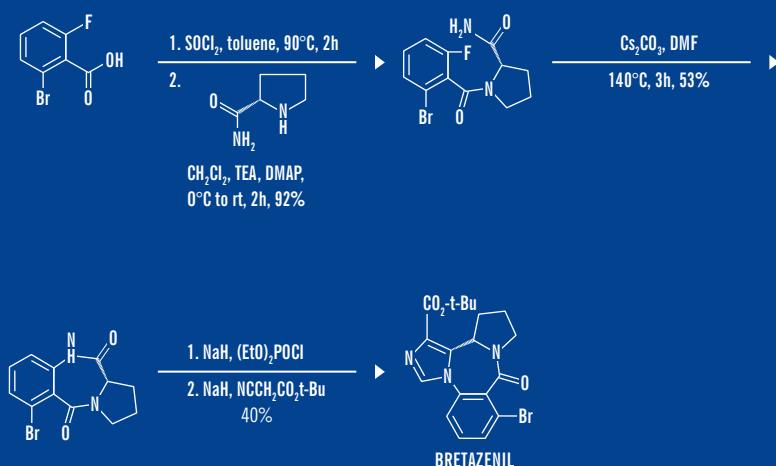
Case studies: Expertise in synthetic chemistry and problem solving capabilities are key to our success. In addition, project management and validated processes ensure we successfully deliver on promises

SYNTHESIS OF REFERENCE COMPOUND: BRETAZENIL

— Challenges in Step 1: Poor yields and irreproducible results, original route was dropped



— Alternative route designed and implemented

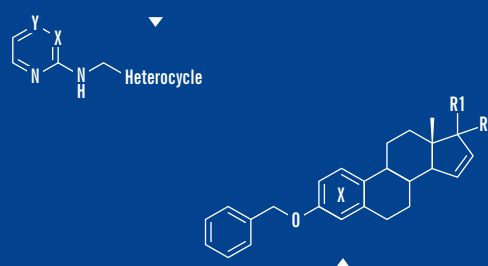


— Challenges in final purification were resolved by using a combination of chromatography and recrystallisation techniques

— Delivered 10 gm of Bretazenil with purity >95% and >98% as determined by ¹H NMR and HPLC respectively

ROUTE DEVELOPMENT AND SCALE-UP: SOME SUCCESS STORIES

— Synthesised >6 kg
— Purity >95% HPLC and ¹H NMR
— Six step synthesis including CBz protection, NaBH₄ reduction and debenzylation



— Synthesised 25 kg
— Purity >95% HPLC and ¹H NMR
— Five step synthesis including ketalisation, bromination and elimination

OXETANONE AND DERIVATIVES: A KEY BUILDING BLOCK IN YOUR SYNTHETIC STRATEGY

— Oxetanone and over 70 derivatives are available on request using validated routes. Some examples:

