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A New Approach to Rapid Parallel Development for Four Neurokinin Antagonists. Part 1.

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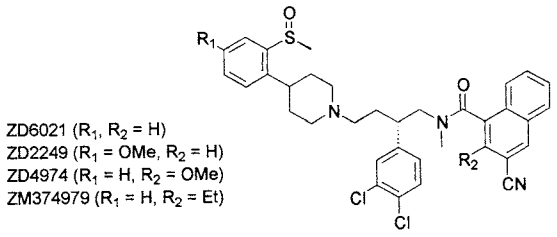
Abstract:

A new approach to the rapid parallel development and scale-up of four neurokinin antagonists is presented. An analysis of the factors affecting scale-up revealed that only process safety and robustness were essential. Other factors could be ignored if we focused only on rapid short-term delivery rather than longer-term development. An acceptance of the use of Research chemistry routes in combination with automation and experimental design techniques further expedited this approach. We were able to deliver 1-kg quantities of each compound for clinical trials within 6−7 months from the start of lab work.

Introduction

In the past few years at AstraZeneca there has been an active research and development programme investigating neurokinin antagonists for the potential treatment of asthma, depression, and urinary incontinence, amongst other therapeutic areas.[1] The desired approach for this project was to evaluate a series of four structurally related compounds in preliminary toxicity and clinical studies, to select the best compound for further development. The structures of the compounds are shown below:



This placed an unusual request on our Process R&D (PR&D) Department of requiring approximately 1 kg of each compound as quickly as possible, focusing on rapid short-term delivery rather than longer-term process development. We present a series of papers in which we describe the following aspects of this work:

- A new approach (for our group) to rapid parallel scale-up,[2] developed specifically for this series of compounds, which allowed resource to focus only on the key deliverables of the first 1-kg campaign. This concept paper describes the philosophy behind this approach and illustrates it with examples from across the series of compounds.
- Application of this approach to a key fragment, cyano acid, used in the manufacture of ZD6021 and ZD2249, including an alternative philosophy towards environmental, safety and yield aspects.[3]
- A more detailed study of the final-stage coupling reactions which are common to all compounds in the series.[4]
- New route research and preliminary development for the cyano acid subunit in this series which was identified early in the programme as a definite requirement should any compounds require further scale-up.[5]
- Further application of this approach to the methoxy sulfoxide fragment of ZD2249, including some challenging issues we encountered in scaling up the route used by our Research colleagues.[6]
- Our approach to the issue of hindered rotation and resulting atropisomerism for the later compounds in this series (ZD4974 and ZM374979). During this work we discovered an interesting, mild and selective transformation of methoxynaphthyl to alkylnaphthyl compounds which will also be reported.[7]

Further papers related to other fragments and compounds in the series may be published at a later date (probably in this journal).

Overall Approach for Rapid Parallel Development. The following approach was taken in deciding how to undertake the overall project and where to focus our efforts:

- Could the Research[2] route and processes be operated on up to 100-L scale to make the first 1 kg of drug substance?

(1) Bernstein, P. R.; Aharony, D.; Albert, J. S.; Andisik, D.; Barthlow, H. G.; Bialecki, R.; Davenport, T.; Dedinas, R. F.; Dembofsky, B. T.; Koether, G.; Kosmider, B. J.; Kirkland, K.; Ohnmacht, C. J.; Potts, W.; Rumsey, W. L.; Shen, L.; Shenvi, A.; Sherwood, S.; Stollman, D.; Russell, K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2769 and references therein. Albert, J. S.; Aharony, D.; Andisik, D.; Barthlow, H.; Bernstein, P.; Bialecki, R. A.; Dedinas, R.; Dembofsky, B. T.; Hill, D.; Kirkland, K.; Koether, G. M.; Kosmider, B. J.; Ohnmacht, C.; Palmer, W.; Potts, W.; Rumsey, W.; Russell, K.; Shen, L.; Shenvi, A.; Sherwood, S.; Warwick, P. J. *J. Med. Chem.* **2002**, *45*, 3972.

(2) This approach was named "Project Discovery" in ex-Zeneca, but this term has not been used here, in part because the medicinal chemistry departments are now referred to as Discovery Chemistry. To avoid possible confusion, the Medicinal Chemistry/Discovery Department is referred to throughout this paper as the Research Department.

(3) Moseley, J. D.; Moss, W. O.; Welham, M. J.; Ancell, C. L.; Banister, J.; Bowden, S. A.; Norton, G.; Young, M. J. *Org. Process Res. Dev.* **2003**, *7*, pp 58−66.

(4) Parker, J. S.; Bowden, S. A.; Firkin, C. R.; Moseley, J. D.; Murray, P. M.; Welham, M. J.; Wisedale, R.; Young, M. J.; Moss, W. O. *Org. Process Res. Dev.* **2003**, *7*, pp 67−73.

(5) Ashworth, I.; Bowden, M. C.; Dembofsky, B.; Levin, D.; Moss, W. O.; Robinson, E.; Szczur, N.; Virica, J. *Org. Process Res. Dev.* **2003**, *7*, 74−81.

(6) Bowden, S. A.; Burke, J. N.; Gray, F.; McKown, S.; Moseley, J. D.; Moss, W. O.; Murray, P. M.; Welham, M. J. *Org. Process Res. Dev.* Manuscript in preparation.

(7) Parker, J. S.; Smith, N. A.; Welham, M. J.; Moss, W. O. *Org. Process Res. Dev.* Manuscript in preparation.

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If so, we focused on the minimum work to deliver that; if not, we sought to develop alternatives.

- Were any processes or routes suitable for the first manufacture but unsuitable for further scale-up? If so, we planned to undertake longer-term process research and development, at a time appropriate for supply of future requirements.[5]
- Were there any common intermediates? If so, we aimed to develop processes suitable for pilot-plant manufacture and manufacture ~10 kg of intermediate. Out-sourcing to a contractor could also be considered as an alternative manufacturing option at this point.
- We also sought to maximise the use of automation techniques such as factorial experimental design (FED) and our Zymark robot, which, unrelated to this project, was becoming available at the time.

Detailed Approach of Rapid Parallel Development. We reviewed in detail our traditional approach to the development of new compounds related to the first point above. The approach previously taken was to identify the appropriate route for development, ideally for long-term manufacture, and then undertake process research and development with several long-term goals in mind. The factors considered when developing these goals were typically the following: environment, health, manufacturability, output, process safety, quality, robustness, yield, and cost. An analysis of each of these factors was undertaken to decide whether it was still necessary to consider each one in the short term. This analysis concluded that only two factors, process safety and robustness, were important to maximise the chance of successful delivery of 1 kg of drug. Clearly, process safety could not be compromised, and an understanding of potential chemical hazard issues was required in all cases where there was any concern. We also decided that due to the unoptimised nature of these rapidly developed processes, it was essential to be able to demonstrate a level of process robustness; the rate of development required for this project would not tolerate delays.

Focus on Safety and Robustness. To focus on the two key factors of safety and robustness, a structured approach to development was adopted. The key issue of safety was addressed by close liaison with our Large Scale Laboratory (LSL)[8] and Hazards Group at the start of work on each compound, to ensure that key safety issues were highlighted and that appropriate work was undertaken. Safety was maintained as the top priority throughout all lab work and LSL manufacture. Experimental hazard analysis was undertaken when deemed necessary, and some processes were modified to improve safety, for example by eliminating all-in reactions and using controlled additions.

(8) The Macclesfield LSL is a cGMP manufacturing facility for synthesis of bulk drug for clinical studies and uses all glass vessels. It is typically where the first significant scale-up of a process occurs and commonly delivers tens of kilograms of intermediates and kilograms of bulk drug. It consists of a range of glass reactors 10−100 L in scale, fully contained, with other ancillary equipment in fume cupboards. Operating ranges vary from −78 to +130 °C. Atmospheric hydrogenations can be performed, and a 20-L rotary evaporator is available for distillations if required. Product is generally isolated as a solid on Nutsches. AstraZeneca has several other LSLs at different sites which operate in a similar fashion.

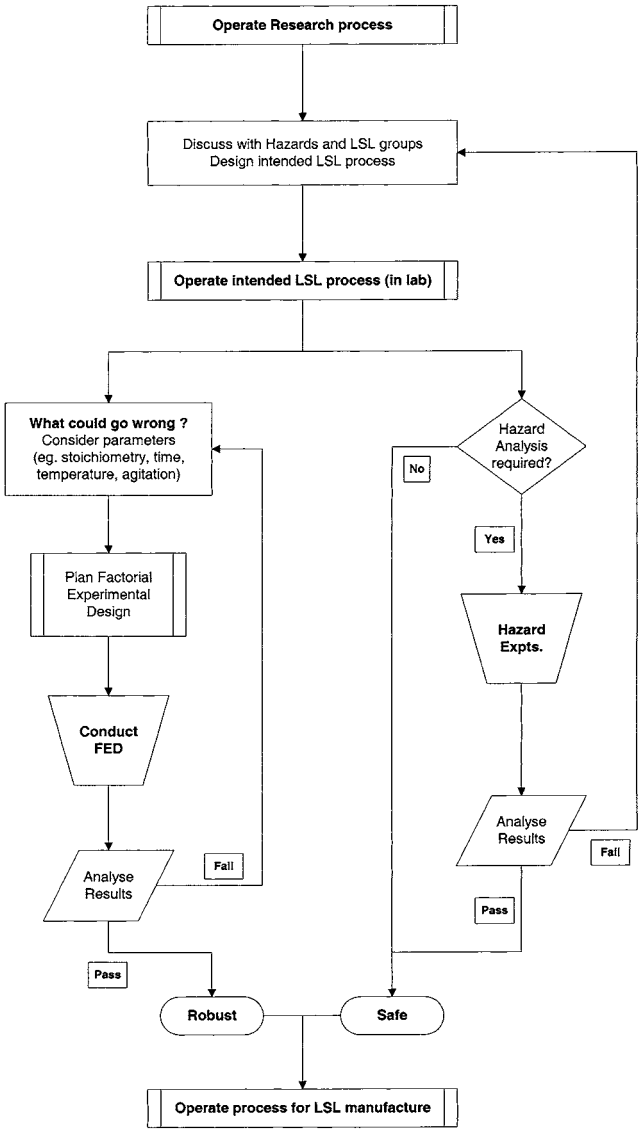


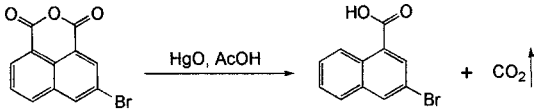
Figure 1.

The issue of process robustness was addressed by identifying the key factors in each process and considering the impact of varying them. A structured technique was used for this process, aimed at identifying all variables and then prioritising them. Following this analysis, experimental work was undertaken to demonstrate robustness, making use of FED and automation as much as possible. A schematic representation of this approach is given in Figure 1.

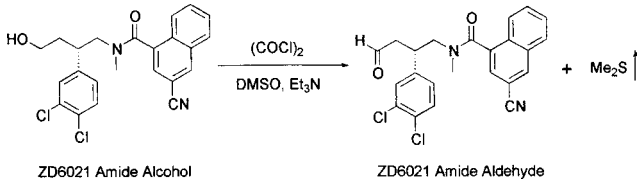
By using this approach it was possible to demonstrate that a process was safe and robust in a relatively short time (typically 4−6 weeks, but in some cases less than 2 weeks). Despite other factors being unoptimised, it was then considered acceptable to scale up the process. In fact, we judged that most Research reaction conditions could be transferred to the LSL without too much problem. Most of our own lab work was actually spent on reducing volumes, developing isolation procedures, and generally simplifying the work-up procedures.

Examples of Approach Applied to Other Factors. We decided the other factors would require little or no development if we were only considering the short-term view. The

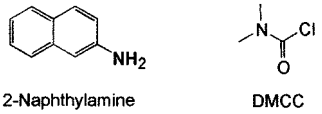
availability of the LSL provided a high degree of containment and flexibility, which we considered would allow us to overcome several potential concerns. Specifically, environmental concerns could be put aside for the short term. For example, we made the potentially controversial decision to use HgO in the ZD6021 bromo acid stage, even though this could not be considered for pilot-plant manufacture, let alone full-scale production. We judged that the high degree of containment in the LSL made this acceptable, and small-scale specialist disposal was not prohibitively expensive for the quantities in question. This reaction was also subject to an extensive FED investigation on the Zymark robot, as discussed in the following contribution.[3]



A second example was the Swern oxidation[9] used for all compounds in the series. This resulted in the stoichiometric generation of dimethyl sulphide (DMS) which required scrubbing. Again, this could be contained in the LSL environment, and the scrubbing was accommodated.[4]

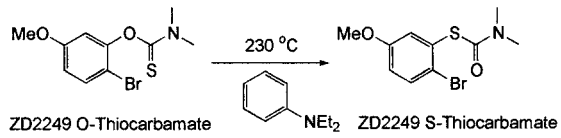


We made few concessions to health in the toxicity of the reagents we were prepared to consider, again judging that the LSL containment and procedures were good on both points. The use of HgO and generation of DMS as a byproduct, with appropriate handling, illustrated this point. There were two exceptions, however. We rejected immediately any possible synthetic routes to ZD6021 cyano acid generated from 2-naphthylamine (as had our Research colleagues)[1] or where this known human carcinogen[10] might occur as an impurity in the synthesis (e.g., via the nitro or diazo derivatives).[11]



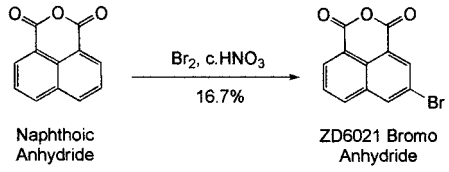
The first coupling reaction of ZD6021 amide alcohol and cyano acid was achieved via the acid chloride, in which the known animal carcinogen[10] dimethyl carbamoyl chloride (DMCC) is formed. After this, we investigated alternative coupling conditions; however, we met with mixed success as discussed in a following contribution.[4] In the longer term, we would certainly have reviewed other reagents and sought alternatives in some cases.

Manufacturability, by which we mean the ability to scale-up, was given some consideration, but generally we were able to accommodate the majority of Research-based processes with little major alteration in the LSL, again due to its inherent flexibility. The Swern oxidations, requiring −78 °C, and the Newman−Kwart rearrangement,[12] requiring 230 °C for the *S*-thiocarbamate stage of ZD2249,[6] were notable successes. Interestingly, this was also a stage in which the Research reaction conditions required little modification once the high temperature was known to be viable. More effort went into improving the dilute workup conditions, and by cutting down the volumes, a simplified workup procedure was developed, which in the plant increased the yield from 60 to 90%.



The silver sulfate-mediated bromination[13] of naphthoic anhydride was thought to be inoperable in the LSL, but this was a rare exception (see below). However, other reagents or procedures were used successfully (e.g., BH_3·pyridine complex,[4] Grignard reagents,[4,6,7] and Kagan asymmetric oxidations[6,14]).

Output and yield did receive some belated attention, as we found that material supply rapidly became an issue for the later stages of each compound. From ZD2249 onwards, we planned on overages in the manufacture to support lab work, but we never found a satisfactory answer to this problem. We had determined to force through the Research route despite its low efficiency for some stages, and accepting the bromination of naphthoic anhydride in 16.7% yield as the first step in the cyano acid synthesis was our most obvious example.

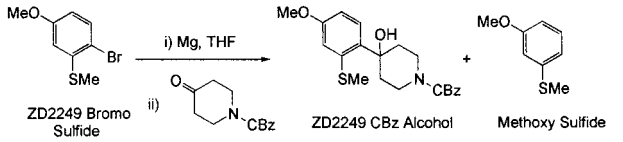


Fortunately, the remainder of the synthesis to cyano acid was relatively efficient.[3] Towards the end of each manufacture, it became essential to focus some effort in this area to meet the targets in some cases, notably ZD2249.

Quality was also given a low priority, which may appear somewhat surprising. In fact, the quality criteria of 95% still had to be met, but we made provision for the use of large-

(9) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(10) Irving Sax, N. *Dangerous Properties of Industrial Materials*, 5th ed.; Van Nostrand Reinhold Company: New York, 1979.
(11) *EH40/2002 Occupational Exposure Limits*; HSE Books: Norwich, UK, 2002. Manufacture of 2-naphthylamine is prohibited under Regulation 4(1) of the *Control of Substances Hazardous to Health (COSHH) Regulations*, 1999.
(12) Newman, S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980. Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 3410.
(13) Mitchell, W. J.; Topsom, R. D.; Vaughan, J. *J. Chem. Soc.* **1962**, 2526
(14) Kagan, H. B. Asymmetric Oxidation of Sulfides. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 203−226.

scale chromatography[15] if we failed to achieve the desired target. This was a new development for us. Both ZD6021 and ZD2249 avoided chromatography at the pure stage at some cost to yield, but the other two final compounds were both purified by chromatography, and quality was much superior as a result.[4] Chromatography was also necessary for an earlier intermediate of ZD2249 to remove both an impurity and a byproduct (methoxy sulfide). It took 3−4 weeks to purify enough material (3.5 kg) in seven runs from three batches of CBz alcohol and required a herculanean effort from the LSL to support this endeavour. Although this did achieve the desired result of quality and quantity required without delaying the project, it is doubtful we would repeat such efforts on another stage.



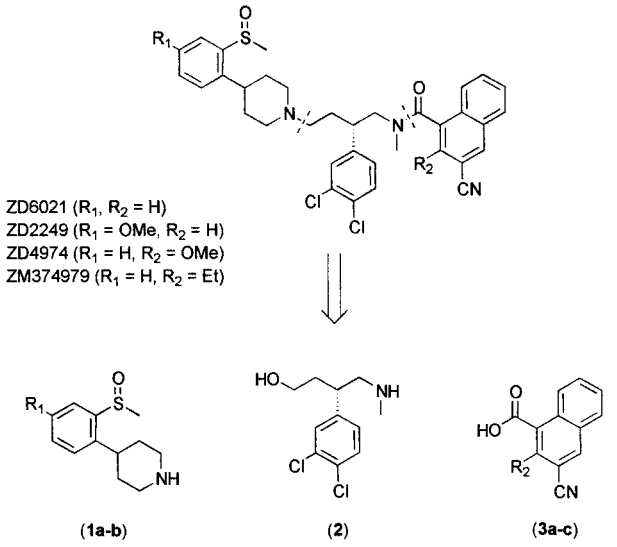
Last, we expended no effort in reducing long-term costs (although we were not greatly troubled by any expensive raw materials or intermediates on this project). We debated the use of stoichiometric silver sulfate in the ZD6021 bromo anhydride process,[13] which would have entailed significant costs at full scale, but quickly decided that this should not deter us from 1-kg manufacture (in fact, we did not pursue this process for other reasons).[3]

In summary, all long-term considerations other than process safety and robustness could be sacrificed or postponed. Alternatively, they could be ameliorated by the use of budget (e.g., disposal costs) or technology (e.g., chromatography).

Approach to Subunit Synthesis and Assembly for Neurokinin Project. The Research routes were convergent and retrosynthetic analysis showed that all four compounds were susceptible to two simple disconnections which led to three subunits (**1**, **2**, and **3**) as shown in Scheme 1. It was decided in the first case to adopt this route for the manufacture of ZD6021, and this strategy was then used successfully for all other compounds in the series.

Pip Sulfoxide Fragments. The pip sulfoxide fragment (**1a**) was common to three out of the four compounds and had previously been made on a pilot-plant scale for an earlier development compound (ZD7944). Details of the route (but not scale-up) have been published elsewhere.[16] Scale-up details may be published in future. The manufacture of the methoxy sulfoxide (**1b**) required an entirely different route, and its synthesis is reported in a subsequent paper.[6]

Scheme 1



***N*-Methylamine Fragment.** This fragment (**2**) was an intermediate common to the whole series, for which preparation has been published by another group.[17] Some modifications to the published route were made, and the processes were successfully scaled up to pilot-plant scale to make 12 kg of *N*-methylamine as the fumarate salt. This was also an example of a key intermediate that was successfully outsourced to supply larger quantities. This work may be published in the future.

Cyano Acid Fragments. The simple structure of the cyano acid unit (**3a**) required for ZD6021 and ZD2249 disguises the fact that 1,3-disubstituted naphthalenes are difficult to make. Synthesis of this molecule is the subject of two subsequent contributions in this issue.[3,5] Synthesis of the trisubstituted naphthalenes (**3b**) and (**3c**) will be covered in the contribution focusing on ZD4974 and ZM374979, where the feature of atropisomerism (due to the additional substitution) will be of key interest.[7]

Subunit Assembly. The same reaction sequence was used for the subunit assembly of each compound. This involved coupling the *N*-methylamine (**2**) and appropriate naphthoic acid portion (**3a**−**c**), then performing a Swern oxidation and reductive amination to introduce the appropriate piperidine (**1a**−**b**). Details of the Swern oxidation and successive chemistry are discussed in the subsequent contribution for the two later compounds in the series, since the processes were optimised for these compounds.[4]

(15) Chromatography was performed on polypropylene Nutsches of 32- or 42-cm diameter, extended to about 70-cm depth and specially manufactured for this purpose. The base of the Nutshche had a paper filter covered in a layer of sand onto which the silica "column" was loaded as a slurry, with another layer of sand on top. Standard flash chromatography silica gel was used (230−400 mesh), with as little as 10−14 times the mass used compared to that of the crude material in some cases, but more if needed, depending on the chromatographic separation. The crude products were loaded in the minimum of solvent, and vacuum was used to pull through aliquots of solvent from below without allowing the column to dry out. Solvents were then removed on a large rotary evaporator.

(16) Shenvi, A. B.; Aharony, D.; Brown, F. J.; Buckner, C. K.; Campbell, J. B.; Dedinas, R. F.; Gero, T. W.; Green, R. C.; Jacobs, R. T.; Kusner, E. J.; Miller, S. C.; Ohnmacht, C.; Palmer, W.; Smith, R.; Steelman, G.; Ulatowski, T.; Veale, C.; Walsh, S. *Abstracts of Papers, Part 1*, 214th National Meeting of the American Chemical Society, Las Vegas, NV, September 7−11; American Chemical Society: Washington, DC, 1997; pp MEDI 264.

(17) Emonds-Alt, X.; Goulaouic, P.; Proletto, V.; van Broeck, D. Eur. Pat. 0 474 561. Miller, S. C.; PCT Int. Appl. WO 95/15961.

Review of Learning from this New Approach. This new project approach provided us with the opportunity to undertake a fundamental review of our approach to process development and initial scale-up, by shifting the focus from long-term development to short-term delivery. The following key learning points were identified:

- A key aspect discovered early on was the need for a greater level of analytical support and particularly a fast turnaround of results specifically from LC−MS and metals analysis. This was readily resolved.
- More time and support were also required from the Hazards Group since they were required to assess a larger number of less well-developed processes. Early discussions with this group proved to be critical in providing an early warning of potentially problematic stages. We faced no insuperable issues on this project, but it was accepted that, had one arisen, a delay would have been inevitable since we could not compromise in this area.
- The structured FED approach to finding parameter ranges and the use of automation became a regular feature of the project. FED was particularly useful for defining a robust reaction space within which to operate. Both techniques have continued to be routinely used on subsequent projects, more commonly in optimizing parameter ranges but also in other areas.
- Kepner−Tregoe analysis was also used routinely on these projects to help tackle particular issues, most often in problem analysis but also with decision analysis. Later, potential problem analysis was also employed prophylactically.
- Chromatography was used successfully on the large scale, particularly for the bulk drug compounds themselves. Its use for earlier intermediates such as ZD2249 CBz alcohol was demanding, and since then, more suitable and dedicated equipment has become available at several sites.
- The traditional process development approach of working with crystalline intermediates was not overlooked. For example, for the remaining three compounds, the *N*-methylamine (**2**) was isolated and handled as the fumarate salt. This led to improved analysis, handling, and final product quality.
- Finally, intermediate supply remained a problem throughout the project. Ironically, the pace of lab work required several if not all stages to be worked on simultaneously and made great demands on the limited materials available. Use of the robot and FED performed on tube scale went some way to maximizing learning from the small quantities of material initially available. Scaling up unoptimised processes in the lab is rarely successful without some development. After experience from ZD6021, contingencies were built into the ZD2249 project to pull material during the manufacture to support lab work which was partially successful. Later compounds were less problematic, largely because the key intermediates were becoming available in much larger quantities after repeat or pilot-plant manufactures (e.g., *N*-methylamine). A satisfactory solution to this problem was never fully achieved. A better option might now use the new "scaling out" technologies.

Conclusions

Under the project remit, four compounds in the neurokinin programme were delivered at the 1-kg scale within the time set (6−7 months each) and of suitable quality for toxicity and preliminary clinical testing. The total project time fell over 14 calendar months, which showed that a high level of parallel processing was achieved. For a specific example, ZD2249 required 22 chemical steps and delivered ∼1 kg of bulk drug in 6 months from the start of lab work. A compound of this complexity (e.g., ZD7944)[16] would previously have required 12−18 months from start of lab work to the first delivery of bulk drug. Most stages were developed within 4−6 weeks, with more than half developed within 5 weeks, and the shortest being 2 weeks in some of cases. A review of the ZD2249 project revealed that lab work had indeed focused primarily on process safety issues and robustness, although in the case of ZD2249, quality had also been a significant factor. Other issues, however, had received only minimal attention as intended, and no work was driven by cost.

Overall, about 80 separate stages were successfully accommodated in the LSL between 20- and 100-L scale without incident, indicating that the processes were safe. Only three batches were put aside out of about 190 (due to poor impurity profile), indicating that the processes were also robust. In focusing lab work only on the key aspects identified as essential for the first campaign, several reagents, reaction conditions, and operations were performed which would not have been considered appropriate previously. This expedient approach greatly speeded up the development process without compromising safety and allowed us to meet our target of first delivery for clinical studies in around 6 months for each compound.

Acknowledgment

Laboratory development was performed at Avlon by Claire Ancell, Sharon Bowden, Kate Firkin, Fiona Gray, Laura Harnett, Paul Murray, Jeremy Parker, Bharti Patel, Simon Preston, Neil Smith, Matt Welham, Richard Wisedale, and Maureen Young. Danny Levin and his team at Huddersfield provided additional specific laboratory development work for cyano acid (**3a**).[5] Manufacture was performed in the Macclesfield LSL by John Banister, Nigel Burke, Steve Knight, Steve McKown, Glenn Norton, and Kevin Vare. Hazard studies were provided by Steve Hallam and Paul Gillespie from Process Safety Group, Blackley. Analytical support was performed at Avlon by Steve Baldwin, Nathalie Roberts, and Matt Young and later, additionally at Macclesfield by Kate Arnot, George Kirk, Matt Ling, and Anne Williams. Colleagues in Research at Wilmington, DE, also provided much useful advice, in particular Peter Bernstein, Cy Ohnmacht, Ashok Shenvi, and Jim Hulsizer and his team.

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