Lead optimization in 12 months? True confessions of a chemistry team

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In 1998 GlaxoWellcome embarked upon a new enzyme-inhibitor programme. This programme featured an aggressive timeframe of seven years, from the start of medicinal chemistry through to drug launch. This period, dominated as it was by the constraints of the clinical programme, translated into a lead-optimization phase of no more than 12 months. In this article, we describe our attempts to meet this target, examining not only what we did and what worked, but also what didn't work and, most importantly, what we learnt as a result. At a time of considerable upheaval and challenge to the traditional model of drug discovery, we hope our experiences might stimulate interest, empathy and further discussion.

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In 1998 the siren call of combinatorial chemistry was proving irresistible. As a team, and coming directly from a 'traditional' medicinal chemistry project, we found the promise of combinatorial chemistry, solid-phase chemistry and stories of rapid lead-optimization (defined here as when we started with a lead to when we had achieved all the desired properties in a molecule suitable for development), fascinating. Thus, it was readily assumed that the judicious application of such technologies would usher in a new era of productivity in drug discovery.

Work culture

We were familiar with a culture of hard work and commitment to project objectives (although less so to such an immovable deadline). For the bench scientist, career progression and reward was determined primarily by personal success within the context of the team's overall performance. This could manifest itself in a strong sense of competition and ownership of individual ideas, science and chemistry. By contrast, at more senior management levels it was the fate of the project *per se* that was more closely associated with perceived performance.

Rapid lead optimization

Why this project was different

Into this environment came a project that was clearly different, in several important ways, from the usual 'top priority' programme. The single most dramatic difference was the 12-month deadline, and it is interesting to note just how readily the majority of the project team truly bought into it. In our experience, the deadline and the level of commitment to it was unprecedented and originated in the clear and absolute realisation that if we did not deliver within the narrow timeframe, then the project would fail and be terminated. This narrow timeframe would lead to considerably higher 'real world' expectation levels (often self-imposed) on scientists who had hitherto been protected from such pressure, in part, for fear of stifling creativity. The second significant aspect of the project was its high profile within the company and, in particular, the support it was allocated by resource holders. One director was quoted as saying, 'I don't mind if we waste some resource, providing we make the deadline' – a new and liberating perspective. This enabled the introduction of a 'certified project trump card' to secure resource (i.e. management would support project tasks moving to the front of any queue), which was frequently used and not without controversy. It also contributed to a strong expectation of kudos, which would accrue from meeting the challenge of the deadline. Finally, managers also openly acknowledged that this was an experiment that might fail, and this acted as a spur to a 'tell me it can't be done, and I'll try and prove you wrong'-type of attitude.

1359-6446/01/$ – see front matter PII: S1359-6446(01)01937-7

Box 1. Screening process

As a project team, we realised that the traditional 'vertical' screening cascade was simply too slow. We therefore introduced a more horizontal cascade, where compounds could be evaluated in parallel with a one-week turnaround (Fig. I). In theory, a successful compound could progress to the final screen in three weeks. Allied to this were weekly compound-progression review meetings, which included an automated recommendation (frequently ignored!) for discarding or progressing the compound. This process introduced an unprecedented energy and dynamism to the screening process, albeit placing enormous pressure levels on the screeners (Box 4).

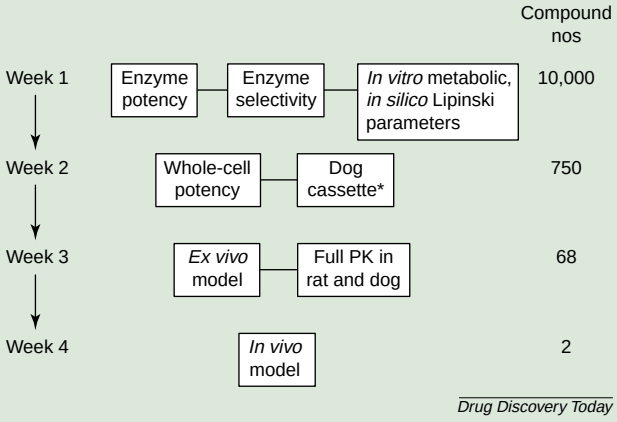

Figure I. The screening cascade, showing, horizontally, those screens that were run in parallel and, vertically, the time sequence. Abbreviation: PK, pharmacokinetics.

(*cassette dosing where multiple compounds are dosed together and evaluated simultaneously).

Initial lead optimization

Starting point

With three independent lead-optimization teams (~18–20 chemists in total), three strategies of initial lead identification were pursued:

- HTS, where we used the 'trump card' to jump the queue;
- Pharmacophore searching (constructed from published compounds);
- A 'fast-follower' programme (defined as a programme that takes as it's starting point a competitor's compound that has proven to be efficacious in the clinic) whose aim was the discovery of efficacious compounds outside the competitor's intellectual property.'

The bulk of this article is based primarily on the experiences of the team that pursued the third option, although many of these experiences were common to all teams.

Devising a lab philosophy

Having selected our starting point, our individual chemistry team then deliberately tried to frame an 'accelerated' drug discovery philosophy. A first for all of us, this was required because of the obvious need for new medicinal chemistry practices. However, it also provided an opportunity, through devising the philosophy together, to promote a higher level of commitment and ownership within the team. Some of the key points of the philosophy were:

- wherever possible, to only make what we thought would be potential development candidates with built-in 'developability' (defined as molecules containing features expected to facilitate rapid preclinical development – such as aqueous solubility – and avoiding features that might slow down development), and on a large enough scale to satisfy the screening cascade (Box 1) and also avoid time-consuming remakes.
- given the time pressures, we would concentrate on using only simple chemistry. We regarded this as a central pillar of rapid lead optimization. If the proposed synthesis of a target took more than three steps, or if there was insufficient precedent for the chemical transformation, then the target would be axed.
- we would deal with technology rather than chemistry, and use plastic rather than glass (microtitre plates rather than round-bottomed flasks). We would allow an extra two reactions per target to explore the use of new technologies, such as supported reagents and high-throughput purification, which we hoped would ultimately prove more efficient.
- we anticipated that computational techniques (such as data handling, analysis and visualization) would become increasingly central to discovery, and would require formal training and time away from the bench to ensure their successful use.
- we would seek to work much more efficiently as a team to maximize the available time for the science. Tasks such as the gathering and presentation of data, which we had all previously done for ourselves, would now be delegated to one team member, who would undertake the task on behalf of the whole team. Similarly, for meetings that we had all attended previously, we would now send one person to act as the team representative, who would then report back with the salient points.

Twelve-month medicinal chemistry 'masterplan'

Each of the three chemistry teams pursued a different drug-discovery philosophy that was reflective of their experience and the lead-identification strategy adopted. In our team, based upon perceived ease of synthesis and available SARs of our lead molecule (B-A-C-D) (Fig. 1a), we identified

three regions of the competitor molecule (B, C and D), of which modification could be expected to deliver the target profile and ensure novelty. Again, in a novel move, we attempted to formulate, in advance, a 12-month plan for the medicinal-chemistry programme, allocating fairly rigid target times for the completion of each part and making their attainment the responsibility of the team rather than of individual chemists. We envisaged modifying the B and C–D regions in two sequential iterations, thus leaving time, if necessary, to combine the knowledge from these first two iterations for a third. This translated into approximately three four-month iterations over the set 12-month period (Fig. 1b; Ref. 1).

Experimental reality

Initially, we chose to make large arrays of compounds in 96-well plates (80 compounds per plate). However, it soon became clear that, although the synthesis of large numbers of compounds was relatively straightforward (we made well over 1000 in the first three months), we were doing so without a clear idea of what constituted an acceptable purity level to generate meaningful biological data. It did not take long for us to begin to sink under a morass of often equivocal data, which proved more time-consuming to analyze than to generate. Therefore, we quickly transferred our emphasis to smaller arrays of more rigorously purified compounds (within the framework of our original planned iterations), enabling us to obtain satisfactory data and, thus, SARs in an acceptable timeframe. This decision enabled clarity of action to be re-established, although as is usual, our original plan mutated and evolved as our work continued.

As a result of our switch to smaller arrays, the first iteration was broken down into several smaller and parallel iterations, which different chemists pursued in a manner more reminiscent of traditional medicinal chemistry (Fig. 2). We began by seeking to optimize C and D: in iteration 1 (blue arrows) several approaches led to secondary mini-iterations (pink arrows), one of which led to a successful tertiary mini-iteration (orange arrows), which ultimately delivered the desired candidate. By this time we had also begun to optimize B, although this remained incomplete at the end of the programme. The third iteration was never formally begun. Throughout the programme there were several approaches that proved to be dead-ends, and ultimately these were terminated.

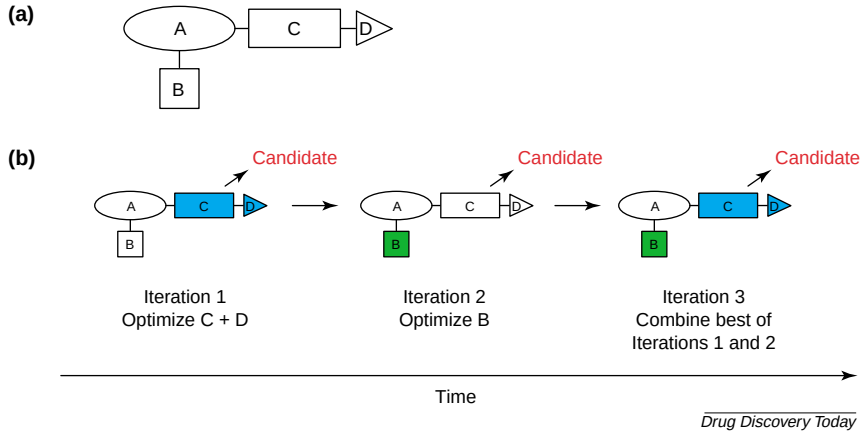

Figure 1. (a) Schematic representation of the competitor compound that provided our fast-follower opportunity, and **(b)** schematic representation of the 12-month medicinal chemistry plan.

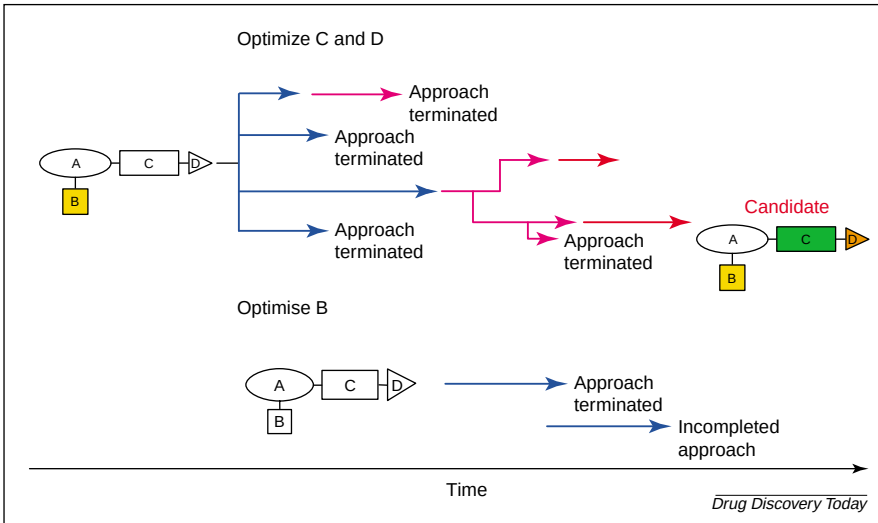

Figure 2. A schematic representation of what occurred during the 12 months of medicinal chemistry. We optimized C and D in three iterations (top of diagram). In the first iteration we followed four approaches (blue arrows). The two most promising approaches were developed further in a second iteration, also following several approaches (pink arrows). Again, the two most promising approaches were then taken to a third iteration (orange arrows), which ultimately led to the candidate. By this time we had also begun to optimize B (bottom of diagram) in an initial iteration (blue arrows). Of the two approaches followed, one was terminated and the other remained incomplete following the discovery of the candidate.

Box 2. Post-project wash up

Following completion of the project, we spent two weeks exclusively reviewing what we had done and what had and had not been successful. We had never done this before, despite most of us having been in medicinal chemistry for more than ten years, and found it to be one of the most influential and valuable exercises we had ever done. It allowed everyone to reflect and define how we had approached accelerated drug-discovery and what we might do differently next time. It allowed us to challenge dearly held principles, formulate new ones and expose behaviours that had either helped or hampered progress.

Of particular interest was:

- insight was not distributed hierarchically! Some of the most valuable comments came from more junior staff;
- we disseminated our conclusions throughout the research organization and discovered that the people who principally benefited from our conclusions were ourselves. We found, quite naturally, that our conclusions had less impact on other scientists who had not worked on this project; and
- identifying 'things we should do differently next time' that lay outside of our own control did not necessarily imply we were able, or had the influence, to implement them.

Box 3. People issues, communication and building trust

Perhaps unsurprisingly, we found it difficult to get large numbers of scientists who didn't know each other to be able to work together quickly, synergistically sharing ideas and information. There was, of course, considerable pressure to synthesize rather than hypothesize. In retrospect, however, several additional factors probably contributed. The first is that, according to personality tests, most scientists are introverts, which means they are not accustomed to meeting and quickly building relationships with lots of new people. Overcoming this takes time, which is precisely what we did not have.

The second possible contributing factor stems from people's natural tendency to look out for themselves. This is particularly true in an environment or culture where pay increases and promotions are predominantly decided on the basis of individual contribution and track record. This can increase an individual's tendency to retain ideas and a reluctance to share them. However, although people were less willing to work on ideas that were not their own, they were highly motivated and committed to making their own ideas work.

Our conclusion was that, as well as improving communication between scientists to facilitate sharing of ideas and data, the key was building trust and removing barriers between people. Some of the ways we tried to do this were through team training (for the whole project team and its component smaller teams), through social events and occasional satirical project meetings where the team and project were viewed from a comical perspective.

At the end of the day, after starting with an ambitious 'accelerated' discovery philosophy and medicinal chemistry 'masterplan', we ultimately proved successful in discovering a development candidate in 12 months. However, this was obtained by a different route from that originally envisaged, and it is that divergence, its causes and the lessons learned along the way that we will now discuss. (Note: the leads in the other chemistry teams progressed at a similar rate – the difference with this series was the more advanced starting point.)

Project review and reflections

Post-project team review

At the end of the project, a considerable amount of time was spent reviewing what we had done, both within our individual chemistry team and in terms of the project as a whole (Box 2). We explored what had worked well and what improvements could be made (Box 3). This proved an uncomfortable experience. A frequent theme in our review was the tension between being familiar with established drug-discovery processes and the belief that these would not deliver successful lead optimization in 12 months (Table 1).

When stated, many of these lessons seem obvious but they had rarely, if ever, been articulated. Of course, deriving these lessons for ourselves gave them immeasurably more impact, although no doubt they are in some ways particular to the people and the project. Furthermore, as individuals we all have to learn our own unique lessons, but some of the 'rules of thumb' we will remember in future are summarized next.

Medicinal chemistry lessons

Simpler chemistry

The complexity of the chemistry clearly varies from project to project. However, in a rapid lead-optimization environment where time is of the essence, it is worth remembering that tough chemistry voraciously devours time: avoid it if possible, but start straightaway if the medicinal chemistry rationale for the target is strong or if it opens up substantial new areas for exploration.

Application of medicinal chemistry principles

Accelerated drug discovery increases the pressure to make easier targets, which actually might not be the most appropriate targets from a medicinal chemistry perspective. Allow sufficient time to carefully design the next array – squared arrays (where two parts of the structure are varied simultaneously) are especially rich in information. Allow enough time to follow up observations. If cutting scientific corners (for example, screening compounds >90% pure), be careful and clear about what you cut and why.

Numbers and iterations

The numbers of compounds in the iteration should be dictated by the amount of time you want to spend on the iteration. Based on the view that it is the number of iterations that is important, make the minimum number of compounds (plus the serendipitous 10%) required to answer the medicinal chemistry question(s) that the iteration is asking. A lower number means easier purification, which then means better data. Higher numbers (no matter how simple) mean longer iterations. Define carefully what question(s) the iteration is asking. Make sure there is clarity amongst the group and that agreement has been reached on the question.

So much data, so little time

Throughout the project, we wrestled with the volume of data and attempts to understand what it meant. In the ongoing stampede of producing compounds and data, time for considered reflection was scarce. Chemists frequently felt that it was easier to get credit through synthesis rather than analysis, especially as computational-based analysis using new tools and software packages might not deliver tangible SARs anyway. It is crucial to invest time in finding out how to turn great screeds of data into a form that can be quickly understood and critically appraised by an audience. Periodic retreats from compound production are essential for proper data analysis and to enable time for thinking about the important non-urgent tasks (which were rarely addressed). One suggestion was to build into the programme weekly breaks every month or so for assay maintenance, data analysis, following up observations, more detailed scientific investigations and reflection.

Table 1. Some contrasts between traditional and accelerated discovery practices

Traditional practices	Accelerated practices
Monthly cycle of screening and progression of compounds	Weekly cycle
Sequential screening cascade of many stages	Parallel screening of most assays in only three stages (see Box 1)
The ease of synthesis moderately influences the acceptability of the target. The strength of the medicinal chemical rationale is paramount	The ease of synthesis is crucial; tougher chemistry requires strong medicinal chemical rationale, as it needs a higher proportion of the available resource
Emphasis on chemistry	Emphasis on technology and handling many compounds
Relatively little data, most of which can be remembered. SAR computational tools non-essential	Enormous quantities of data, which it is impossible to remember. SAR interpretation relies upon computational tools
An iterative approach with a phased introduction to building in developability and 'drug like' (e.g. Lipinski) parameters	An iterative approach, but where developability and 'drug like' (e.g. Lipinski) features are sought to be introduced from the start
More relaxed	Pressure cooker
Room for the non-passionate scientist	Motivation of the bench chemist is crucial
Less crucial to deal with people issues, which can often be side-stepped	People issues become crucial and handling them wisely is important

Box 4. Pressure

The introduction of demanding deadlines and 'real-world' pressure came as a surprise to scientists unaccustomed to such an environment. Scientific reviews and short-term intermediary deadlines accentuated the pressure. For the screeners, the weekly cycle proved remorseless and if the assay failed or required development there was a sense of letting the team down as the workload piled up. Commandeering resources for the project (often using the project 'trump card') sometimes led to team members personally facing the consequences of jumping the queue.

Because this was an unusual experience for us, we responded slowly to providing sufficient levels of psychological support to the scientists. As is usual in pressurized situations, some relationships buckled under the strain. Debate over particular scientific issues sometimes became vehicles for venting frustration and differing personal philosophies. Ultimately, however, we found that training in coping with stress and working as a team acted as pressure-release valves and provided valuable techniques for handling the strain.

Box 5. Use of solid-phase chemistry and supported reagents

During the time we ran this project (1998–2000), the concept of using solid-phase chemistry to prepare compounds for screening had gained considerable momentum. In our situation, we were acutely aware of the lead time that might be required to develop a solid-phase route to our target compounds. Therefore, we conducted an in-house straw poll on the typical lead times that chemists had experienced.

Our conclusions were that, without literature precedent, it took on average three months to make target compounds on solid phase – 25% of our time! A frequent result of this lead time was that by the time the compounds had been made, the focus of the medicinal chemistry had changed. If there was literature precedent (with accompanying experimental procedures), then the experience of others was that compounds could be made on solid phase in a much shorter timeframe, typically a month or so.

We were fortunate enough to find examples of the solid-phase chemistry we wanted to use in the literature, although after three months of effort no target compounds had been prepared and thus the work was terminated. Our conclusion was that developing solid-phase chemistry in a severely time-constrained lead-optimization process requires spare resource and plenty of luck!

The story was different with solid-supported reagents. Here, in most people's experience, if the chemistry proved successful after a short development period, then supported reagents saved time.

Lessons about people

Division of resource over particular leads

As mentioned previously, the three chemistry teams each followed separate leads. 'One series per team' had many benefits and was the most preferred option, particularly by the bench chemists, as it allowed individuality in a big project team. It also provided opportunities for ownership of a part of a series. However, in the stampede to produce compounds it was apparent, retrospectively, that there was non-optimal communication between the chemistry teams. This was clearly unsatisfactory because of missed synergies, but could be the price that has to be paid for progressing science to aggressive deadlines. The downside to the 'one series per team' approach ultimately became clear where ownership of a particular series had become deeply embedded. When flexibility was sought to adapt rapidly to changing priorities and resource levels, intransigence was found. Therefore, a change from the traditional mindset was required (see Box 3).

Box 6. Options for motivating scientists

In our experience, the factors that successfully motivated scientists in this project were unusual, and are unlikely to be frequently repeated. As a result, we have often considered what other factors might motivate scientists to pursue accelerated drug discovery. The most obvious of these is to link a major element of pay, benefits or promotion to meeting project goals within the desired timeframe. A major problem with this, however, is the likely dichotomy between the pay rises that might motivate scientists in a big pharmaceutical company (and particularly those at the bench) to radically change the way they work, and what the cost-conscious organization will be willing to pay.

There are alternatives. As an example, most chemists have a genuine interest in science and frequently conduct personal projects to which managers turn a blind eye. Reward for achieving the project goal could, therefore, include time and/or money to pursue the chemist's own research interests; in other words, a form of sabbatical. Although, on the surface, this might appear to temporarily decrease resource levels, there are substantial benefits. Such benefits are well documented elsewhere[a,b], and include refreshing the scientist's creativity, allowing people the necessary time to recharge their batteries after working to aggressive deadlines, and the potential for gaining spin-offs from interesting science. This is one example, and there are others that could, ultimately, enable the motivational reward to be tailored to the individual scientist's preference.

References

a Asenjo, M.A. *et al.* (1998) Impact of sabbatical leave on hospital and university promotions. *Med. Clin. (Barc.)* 111, 378–379

b Wilkinson, S.L. (2001) On sabbatical: a refreshing pause. *Chem. Eng. News* 79, 22–25

New roles required

It became clear that in a high-pressure, accelerated lead-optimization programme the traditional roles alone were inadequate. Many of the unique situations we encountered were derived from the size of the project group. New roles were required, and these included:

- a full-time project leader whose sole responsibility is to manage the project;
- an overall medicinal-chemistry strategy co-ordinator. This role might have resolved inflexibility and ownership issues and identified synergies across the series;
- an independent, roving, cross-series 'fertilizer', searching for SARs, overlaps and to provide links across the different chemical series;
- a molecular modeller dedicated solely to the project;
- a full-time medicinal chemist to act as the information technology expert for evaluating and providing training in new software packages for data mining and SARs;

- biologists not only responsible for meeting screening deadlines but also to develop assays and explore and understand underlying issues;
- a social co-ordinator to provide opportunities for people to build relationships. Organizing social events for 20–40 people is hard work and time consuming – it requires a persuasive cajoler!
- a representative from Human Resources to help proactively with handling stress, pressure, team building and facilitating meetings (Box 4); and
- a wise old head for support and wisdom when everything gets a bit too much!

Combinatorial chemistry

Overall, the impact of combinatorial chemistry and associated technologies for accelerated drug discovery was expected to be seismic; our experience has been more prosaic (Box 5). Reduction of these technologies to practice, constrained by the time pressures of a lead-optimization project, was a sobering exercise in what was practically realistic rather than what might be possible given more time. Our experience suggests that an equally major factor in accelerated drug discovery is discovering, introducing and gaining acceptance of new practices and new team roles.

Conclusion

The pharmaceutical industry is currently striving for unprecedented increases in drug discovery productivity. One of the practices that might achieve this is accelerated drug discovery, which has been heralded as sounding the death knell for traditional medicinal chemistry. Yet, in pioneering any new drug-discovery paradigm, the quality of science and insight clearly needs to be maintained. From our experience of lead optimization in 12 months, what seems crucial is the balance between progressing at the necessary speed and allowing sufficient time for reflection and considered decision-making.

Furthermore, we would argue that the most important factor of all is engaging the enthusiasm, energy and commitment of the bench scientist (Box 6). In our view, it is crucial that this is not regarded as being secondary in the race to embrace the latest technology and practice. Translating findings such as these into normal working practice for a project in a big pharmaceutical company could be one of the keys that unlocks the door to routine accelerated drug discovery.

Acknowledgements

We would like to thank Graham Inglis in particular for his help in preparing this article. We acknowledge the contributions of the entire project team, in particular Tony Cooper, Alan Borthwick, Lee Harrison, Geoff Clarke, Derek Demaine, Graham Inglis and Manuela Borriello. Finally, we would like to thank George Hardy, Harry Kelly and particularly Justine Lai for their critical reading of the manuscript.

References

1 Borman, S. *et al.* (1999) Reducing the time to drug discovery. *Chem. Eng. News 77*, 33–48