Drugs Originating from the Screening of Organic Chemicals

The previous chapter dealt with a variety of drugs that can trace their origins to the screening of synthetic dyes for chemotherapeutic activity. Even more drugs have been discovered through the screening of other synthetic compounds.

Screening has been used both to discover drug prototypes and to find improved analogues of other compounds that exhibit useful activity but require enhancement in some manner. Examples of the latter process can be found throughout this book, but the present chapter is concerned solely with the discovery of drug prototypes through screening and their subsequent development to provide therapeutic agents.

CLASSICAL ANTIHISTAMINES

After the presence of histamine in the body had been established there was considerable interest in its physiological role. Daniel Bovet at the Pasteur Institute realised that antagonists of acetylcholine and adrenaline, e.g. atropine and ergotamine, had made it possible for physiologists to investigate and understand their actions. Since no antagonist of histamine existed, Bovet screened compounds that had previously been synthesised at the Institute and found that certain adrenaline analogues and antagonists diminished the action of histamine on the guinea pig intestine. However, when the most promising of these, piperoxan, was injected into live guinea pigs it failed to protect them against the otherwise lethal bronchoconstrictive action of histamine administered by the intrajugular route.

On examining similar compounds prepared at the Institute, Bovet and Anne-Marie Staub found Ernest Fourneau’s compound 929F to be the most potent histamine antagonist yet tested on the guinea pig intestine. When it was administered to guinea pigs, it consistently protected them against the otherwise lethal bronchoconstrictive action of histamine. Compound 1167F, in which the oxygen atom was replaced by nitrogen, was also effective.

Staub investigated several more compounds and proceeded to define the molecular requirements for antihistaminic activity, with remarkable accuracy. Unfortunately, none of the compounds examined were safe enough for human administration. It was not until 1941...
that phenbenzamine was found suitable for clinical use after Mosnier had synthesised 24 analogues of 1571F at the Rhône-Poulenc laboratories in Paris.\textsuperscript{5} 

![Chemical structures of phenbenzamine, mepyramine, tripelennamine, cyclizine, and hydroxyzine.]

Two years after the introduction of phenbenzamine, Bovet and his colleagues published their studies on the closely related mepyramine, in which a pyridine ring replaced one of the benzene rings.\textsuperscript{6} This alteration was probably introduced because of the experience Rhône-Poulenc had acquired from their British subsidiary, May and Baker, who had developed sulfapyridine. Researchers at Ciba Pharmaceuticals in Summit, New Jersey, synthesised tripelennamine, which differed only in the absence of the methoxyl group attached to the benzene ring.\textsuperscript{7} 

![Chemical structures of cyclizine and hydroxyzine.]

The American division of Burroughs Wellcome developed cyclizine, a long-acting antihistamine in which the amino group was derived from piperazine instead of dimethylamine.\textsuperscript{8} In the clinic it proved to be a useful anti-emetic drug, achieving the notable distinction of being selected by the US National Aeronautic and Space Agency for use as a space sickness remedy on the first manned flight to the moon. The related hydroxyzine is an antihistamine that has also been used as a minor tranquilliser.\textsuperscript{9} 

During the Second World War, Rhône-Poulenc followed up Ehrlich’s demonstration of antimalarial activity with methylene blue by investigating phenothiazines. This line of research was abandoned after negative results were obtained, but Bernard Halpern and René Ducrot realised that one of the phenothiazines synthesised by Paul Charpentier was an analogue of phenbenzamine in which its two benzene rings were bridged by a sulfur atom. When tested, it proved to be an antihistamine and was given the name ‘fenethazine’.

![Chemical structures of fenethazine and promethazine.]

Promethazine, a derivative of fenethazine synthesised in 1946, had an extra methyl group on the dimethylaminoethyl side chain and turned out to be highly potent and a very long-acting antihistamine.\textsuperscript{10} Charpentier had intended to place the methyl group on the adjacent carbon atom. Had he succeeded, the compound would not have been as successful. It was marketed as an antihistamine, but its ability to cause prolonged central depression also led to its use as a non-prescription hypnotic.
Aminoalkyl Ether Antihistamines

Diphenhydramine was one of several compounds designed to be antispasmodics by George Rieveschl, an assistant professor at the University of Cincinnati. It was synthesised in 1943 by Fred Huber, one of his research students. Parke, Davis and Company tested the new compounds on the guinea pig ileum and found diphenhydramine to be a highly potent antispasmodic. Extensive testing revealed not only that it had an exceptionally high safety margin but also that it was a potent antihistamine. Parke, Davis bought the patent rights from Rieveschl, granting him a 5% royalty on all sales for the next 17 years while the patent lasted. Rieveschl joined Parke, Davis and became Director of Research in 1947, in which role he was responsible for the development of the very similar antihistamine known as ‘orphenadrine’. Both compounds had atropine-like anticholinergic effects, which were more marked in orphenadrine and resulted in its use in the treatment of Parkinson’s disease. In an attempt to develop an analogue of orphenadrine with reduced side effects, the Riker Company synthesised nefopam in 1966. At first, this was thought to be a centrally acting muscle relaxant, but was later shown to be an analgesic. It is used in the management of moderate pain.

Antihistamines became immensely popular during the late 1940s, being hailed in some quarters as miracle drugs! Although their principal use was in the control of certain conditions such as hay fever or urticaria, they were initially believed to be of value for a wide range of ailments, including the common cold. Leading pharmaceutical manufacturers competed vigorously to develop new antihistamines, resulting in the introduction of a plethora of new drugs with little to choose between them, none being free of the tendency to cause drowsiness.

G.D. Searle and Company, a family-owned Chicago pharmaceutical distributor, broke new ground by introducing a formulation of diphenhydramine designed to minimise drowsiness by formulating it with a mild stimulant, namely 8-chlorotheophylline. The resulting salt, dimenhydrinate, did not prevent drowsiness, but it became one of the most profitable antihistamines on the market after it was found to have an unexpected therapeutic action. Samples had been sent to the allergy clinic at Johns Hopkins University in Baltimore for evaluation by Leslie Gay and Paul Carliner. They administered dimenhydrinate to a patient suffering from urticaria. She then discovered that when travelling on a streetcar after having swallowed the drug, she was not car sick – for the first time in years! Tests on other patients who suffered from travel sickness confirmed the apparent value of dimenhydrinate. The matter was reported to Searle, who organised an ambitious clinical trial. On 27 November 1947, the General Ballou sailed from New York to Bremerhaven in Germany. The crossing was particularly rough, yet only 4% of the troops on board who received the drug were sick, in contrast to a quarter of the others who received a placebo. Furthermore, all but 17 of 389 sick soldiers recovered within a couple of hours of receiving dimenhydrinate. Unlike earlier remedies such as hyoscine, the only significant side effect was drowsiness. Searle quickly exploited this before their rivals began to discover that other antihistamines were also effective against motion sickness.
Monoaminopropyl Antihistamines

Research workers at the Schering Corporation realised that all the potent antihistamines contained two aromatic rings joined to either a nitrogen or an oxygen atom. They therefore synthesised a new series in which these rings were instead attached to a carbon atom as this had roughly similar atomic dimensions, being an example of isosteric replacement of an atom. This led to the development of the long-acting antihistamines pheniramine, brompheniramine and chlorpheniramine in 1948, the latter two being more potent.16

A similar approach was adopted around the same time, at the Wellcome Research Laboratories in England, although a few years passed before triprolidine was marketed.17

Merck introduced a cyclic analogue of pheniramine known as cyproheptadine.18 It had similar properties to chlorpheniramine, but was also of some value in the prophylaxis of migraine due to its ability to act as a 5-HT2 antagonist. It is now reserved for refractory cases of migraine. Pizotifen proved to be better than cyproheptadine in the prophylactic treatment of migraine.19,20

The Schering–Plough Corporation developed azatadine as a potential non-sedating antihistamine.21 A pre-clinical behavioural test on cats indicated an absence of central activity, but azatadine turned out to be a typical potent sedating antihistamine when administered to human volunteers.

Non-sedating Antihistamines

Richardson–Merrell chemists synthesised terfenadine in 1973 as a potential tranquilliser, but found it to be inactive as it did not enter the central nervous system. Pharmacologist Richard Kinsolving noticed that it had a resemblance to diphenhydramine and it was tested and then found to be an antihistamine that did not cause sedation.22 Clinical trials confirmed that terfenadine was the first non-sedating antihistamine to have been discovered.
In 1992, the US Food and Drug Administration issued a warning that some patients who took terfenadine might develop a life-threatening ventricular arrhythmia called ‘torsades de pointes’. Use of the drug was ruled out in patients with liver disease as it was not being efficiently metabolised. This problem was overcome when the active metabolite, fexofenadine, was introduced.23

Despite the fact that it had taken almost 40 years to discover a non-sedating antihistamine, several more were introduced soon after the launch of terfenadine. Wellcome marketed a derivative of tripolidine known as ‘acrivastine’ which was developed as a non-sedating antihistamine by incorporating an ionisable side chain to reduce central nervous system penetration.24

Frank Villani at Schering–Plough synthesised potential antihistamines designed to antagonise both histamine H1 and H2 receptors. He hoped that these might have useful anti-ulcer properties. He began by making analogues of azatadine in which the basicity of the piperidine ring nitrogen was reduced by the formation of urea, sulfonamide and carbamate derivatives. The resulting compounds failed to exhibit histamine H2 blocking activity. However, when the ethyl carbamate ester was later screened it had no effect on the central nervous system. Further investigation confirmed that it was a non-sedating antihistamine.25 Attempts were then made to find a longer-acting analogue. When a chlorine atom was placed at the 8-position of the ring system to reduce oxidative metabolism, it increased the duration of action in human volunteers from under 8 hours to permit once-daily medication. Unexpectedly, this modification also increased potency by a factor of four.26 This new 8-chloro analogue was also active when given by mouth. It received the approved name of ‘loratadine’, and was marketed as a non-sedating antihistamine.

**Antipsychotic Agents**

The phenothiazine tranquillisers were developed as a consequence of studies initiated at the Sidi Abdallah Hospital near Bizerte, Tunisia, in April 1949 by Henri Laborit, a French Navy
surgeon who had been one of the first to use antihistamines to pre-medicate patients undergoing surgery. His concern about the traumatic effects of surgical shock led him to consider the possibility that antihistamines might prevent the capillary hyperpermeability caused by histamine release in patients in shock. He therefore incorporated mepyramine and promethazine in the mixture of drugs he was administering. Over an 8 month period it then became apparent to Laborit that the antihistamines had unusual central actions which were contributing to the antishock action. The mood of his patients had improved and, particularly in the case of promethazine, they were less anxious and required less morphine. An army psychiatrist confirmed this effect of the drug, but matters rested there for the time being.

On being transferred to the Val-de-Grâce Military Hospital in Paris, Laborit took the opportunity to investigate the central effects of antihistamines in more detail. In collaboration with the anaesthetist Pierre Huguenard, he was able to show that they lowered body temperature and so reduced basal metabolism to produce a reduction in the amount of anaesthetic required during operations. This, in turn, lowered the risk of shock, so once more Laborit turned his attention to the effects of pre-medication on shock. He now experimented with a ‘lytic cocktail’ of drugs to cool the bodies of patients wrapped in ice bags even further.

Laborit visited the manufacturer of promethazine, the Specia Laboratories of Rhône–Poulec at Vitry-sur-Seine, near Paris, and described his work. In the autumn of 1950 they began a search for a drug that would have an action on the central nervous system that met Laborit’s requirements. Simone Courvoisier screened phenothiazines that Paul Charpentier had synthesised as potential antihistamines, investigating those that were previously rejected because of sedating effects. When the fenethazine analogue now known as promazine proved most interesting despite its low level of antihistaminic activity, Charpentier synthesised analogues of it. One of them was chlorpromazine, a chlorinated derivative prepared in December 1950. It was passed to Courvoisier who identified its outstanding activity and low toxicity.

In the spring of 1951, samples of chlorpromazine were given to Laborit. He confirmed that it was indeed the agent he had long sought. After completing appropriate animal tests, he incorporated the new drug into a ‘lytic cocktail’ in combination with promethazine and the fenethazine analogue known as ethazine for use on patients undergoing surgery. Before long, he observed that not only did they fare better both during and after their operations, due to the antishock action, but they also seemed relaxed and unconcerned with what was happening to them during the normally stressful pre-operative period. The significance of this was not lost on Laborit. He persuaded his psychiatric colleagues at the Val-de-Grâce Hospital to test the mixture on psychotic patients. On 19 January 1952 Joseph Hamon, the Director of the Neuropsychiatric Service, assisted by Jean Paraire and Jean Velluz, began to treat a manic patient who was decidedly agitated until he was given his first injection. At once, he became calm and remained so for several hours. It was recognised that the mixture of drugs was palliative rather than curative, but this did not stop the release of the patient from hospital three weeks later. However, the psychiatrists at the Val-de-Grâce Hospital did not observe the full effects of chlorpromazine as it was only one component of a mixture, with the dose duly modified to take account of the other two central depressants, promethazine and pethidine. Consequently, they soon abandoned the mixture and returned to using electroshock therapy on their patients.

On learning of the effects of the mixture containing chlorpromazine, Pierre Deniker of the Sainte Anne Hospital in Paris requested samples of chlorpromazine from Rhône–Poulec for a detailed study of its psychopharmacological action when administered without other drugs.
He and his senior colleague Jean Delay conducted a clinical trial on 38 patients, soon confirming its outstanding value as a tranquilliser for manic, agitated and psychotic patients. Chlorpromazine was found to be a relatively sedating antipsychotic drug, but unlike the then popular sedatives (i.e. central depressant drugs such as hypnotics administered in subhypnotic doses) it did not aggravate disorders of wakeful consciousness. Indeed, mental confusion was alleviated. In schizophrenic patients, chlorpromazine produced a diminution in aggressiveness, agitation and delusion. Particularly characteristic of chlorpromazine was its effect on the central control of movement whereby a type of akinesia, or psychomotor indifference, was induced in patients. This led Delay and Deniker in 1955 to introduce the term ‘neuroleptic’ to describe any antipsychotic drug with this effect.

Chlorpromazine was marketed in France by Rhône-Poulenc in the autumn of 1952. The early observations by French psychiatrists and others became generally accepted, with the result that psychiatry was transformed and psychotic patients were released from the restraints of straight-jackets and locked wards. They were not cured, but the phenothiazines controlled their behaviour. Some critics believe that physical restraint had simply been substituted by chemical restraint. That view remains a minority one. As with all other drugs, problems occurred when insufficient care was taken with their administration. A discussion of these here is inappropriate, but considering that millions of patients have received these drugs, their record is impressive.

The remarkable success of chlorpromazine stimulated rival manufacturers to introduce analogues of it. Many of these compounds had a different substituent incorporated in place of the chlorine atom attached at position 2 of the phenothiazine ring. This was motivated not merely by a desire to circumvent the Rhône-Poulenc patents, but also by a belief that potency was influenced by the electron-withdrawing power of the substituent, a view that has not been upheld. Typical variants included acetyl, methoxyl, nitrile, trifluoromethyl, thioalkyl and dialkylsulfonamide groups. The differences between the scores of phenothiazine tranquillisers that have been introduced into the clinic are less significant than the variability in patient response to any single drug.

The Rhône-Poulenc researchers found that more potent analogues could be obtained by replacing the dimethylamine function on the side chain of chlorpromazine with a piperazine group. This increased side effects involving dopaminergic extrapyramidal pathways in the nervous system, leading to a Parkinson’s disease-like tremor in some patients. This may have been a direct consequence of the reduction of anticholinergic activity arising from the use of smaller doses than for chlorpromazine. Anticholinergic drugs are actually used to treat phenothiazine-induced extrapyramidal tremor. There is, however, a benefit from the diminished anticholinergic response in patients treated with the piperazine compounds, namely that they are less sedating. For this reason they are preferred to other phenothiazines for the prevention and treatment of nausea. The first of the piperazine compounds to be marketed was prochlorperazine.

Drugs Originating from the Screening of Organic Chemicals

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- Chlorpromazine
- Fluphenazine
- Prochlorperazine
- Thioridazine
- Chlorprothixene
Fluphenazine had a very similar activity to prochlorperazine, but as it had an alcohol function in the side chain, it was also formulated as either the enanthate (i.e. heptanoate) or decanoate ester in an oily depot injection. This was injected every 14–28 days for the long-term control of psychotic behaviour. In contrast to fluphenazine, thioridazine had a low potency. However, its anticholinergic activity helped to counter extrapyramidal tremor and was an important advantage for elderly patients. This was to some extent offset by an increased risk of hypotension.

In 1958, Petersen and his colleagues, working with the Danish firm H. Lundbeck, published their first report on the thioxanthenes, a new series of tranquillisers in which the nitrogen of the phenothiazine ring had been isosterically replaced by a carbon atom. As these tricyclic compounds had strong chemical similarities to the phenothiazine tranquillisers, it is hardly surprising that their therapeutic activity proved to be similar. The first member of the series to be introduced underwent a clinical trial with 70 patients in 1958 and was marketed the following year with the approved name of chlorprothixene. Lundbeck introduced clopenthixol three years later after clinical evaluation had shown it to be a better antipsychotic agent than chlorprothixene. It was a mixture of cis and trans isomers. The active cis isomer was introduced into the clinic as zuclopenthixol. The acetate ester was also developed for depot medication.

Reports of persistent abnormal facial movements among patients who had taken chlorpromazine began to be published within five years of its introduction. The condition was termed ‘tardive dyskinesia’. Lawsuits were brought against companies that marketed the drug. Once it was realised that related drugs could also cause tardive dyskinesia, companies were discouraged from developing new tranquillisers.

Anxiolytic Drugs

Early in 1954 at the laboratories of Hoffmann–LaRoche in Nutley, New Jersey, Leo Sternbach decided to reinvestigate some tricyclic compounds he had synthesised about 20 years earlier at the University of Cracow as part of his post-doctoral studies on dyestuffs. He had in mind the tricyclic nature of chlorpromazine, which had just been discovered, and he believed that the introduction of a basic side chain into his own compounds might create derivatives with a degree of overall similarity to it. He prepared around 40 new compounds by reacting his key intermediate, an alkyl halide, with a variety of secondary amines selected to confer structural analogy with the tricyclics then being patented. When these compounds were submitted to Lowell Randall for screening for muscle relaxant, sedative and anticonvulsant properties, they were all found to be inactive. Renewed chemical studies then revealed that the tricyclic system of the key synthetic intermediate was not that of a benzheptoxdiazine, as had been believed, but was instead a quinazoline-3-oxide. This seemed to account for the lack of biological activity in the derivatives synthesised from this intermediate. The last compound Sternbach had prepared remained untested until a year and a half later, when a colleague who was tidying up the laboratory suggested it should be sent for screening. Sternbach agreed, and a few days later Randall informed him that his compound appeared to approach the activity of chlorpromazine as a tranquilliser. Furthermore, it had a low level of acute toxicity and was free from significant side effects. This report engendered considerable excitement and raised
the obvious question of why only this single compound was active. The answer was soon found when Sternbach reinvestigated its chemistry. It became clear that by using the primary amine methylamine in the last stage of the synthesis, the reaction had followed a different pathway (ring enlargement) from that undergone when secondary amines had been employed. The product formed was a benzodiazepine.\textsuperscript{45,46} Sternbach filed a US patent application for this new tranquilliser, chlordiazepoxide, in May 1958. The initial clinical studies were conducted on 16,000 patients before it was granted approval by the US Food and Drug Administration in 1960. Thousands of benzodiazepines have been synthesised since then, of which several are still used throughout the world as anti-anxiety agents and hypnotics. While they can be of value in patients whose anxiety interferes with their work, leisure and personal relationships, the benzodiazepines have been widely misused in the treatment of the most trivial symptoms of stress. Dependence and tolerance occur after prolonged use. This has recently resulted in litigation brought by patients who have suffered from dependence on benzodiazepines.

\begin{figure}
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\includegraphics[width=\textwidth]{benzodiazepines.png}
\caption{Benzodiazepines}
\end{figure}

Because chlordiazepoxide was not designed to be a benzodiazepine, certain features of its chemical structure were superfluous, notably the basic side chain and the \(N\)-oxide function. Simpler analogues were found, the first of these being synthesised in 1959 and marketed four years later as diazepam.\textsuperscript{47} It had more pronounced muscle relaxant properties than chlordiazepoxide and a half-life of one to two days as it was slowly cleared from the body.

Benzodiazepines were used for treating chronic anxiety states. Some of them, including diazepam, formed an active metabolite such as nordiazepam or something similar, which was responsible for their effects. Unfortunately, nordiazepam took from two to five days before being cleared from the body, hence its concentration gradually built up as more doses were taken. Recognition of this led to the introduction of benzodiazepines that did not form this type of active metabolite or which were rapidly eliminated. Examples of this include oxazepam,\textsuperscript{48} itself a metabolite of diazepam, and lorazepam.\textsuperscript{49} As these are alcohols, they are glucuronidated in the liver and quickly eliminated by the kidneys.

\begin{figure}
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\includegraphics[width=\textwidth]{benzodiazepines2.png}
\caption{Benzodiazepines 2}
\end{figure}

Flumazenil was synthesised in 1979.\textsuperscript{50} The replacement of a phenyl group by a carbonyl removed most of the typical sedative and anxiolytic activity, but as it still fitted the benzodiazepine receptor flumazenil acted as an antagonist when a moderate dose was
administered. It has been used to reverse the sedation produced by benzodiazepines, either when given as medication during short surgical procedures or in overdosage by drug abusers.

Seeking a product with which to enter the growing market in psychotropic drugs, the Tanabe Seiyaku Company of Japan prepared analogues of an antidepressant called thiazesim, in which a hydroxyl group or an \(O\)-acyl group was introduced at the 3-position of the benzothiazepine ring system. This manoeuvre had been instituted in the knowledge that the presence of a hydroxyl group in the equivalent position of diazepam had produced a more potent drug that did not accumulate in the body, e.g. oxazepam and lorazepam. When fully evaluated, these 3-substituted 1,5-benzothiazepines lacked sufficient novelty for them to be marketed. However, routine screening revealed that the 3-\(O\)-acyl benzothiazepines exerted a strong coronary vasodilator effect in the anaesthetised dog at dose levels that produced minimal central effects. Analogues were synthesised and it was established that introduction of a methyl or methoxy group at the 4-position of the benzene ring enhanced potency. Diltiazem was then found to have good oral absorption coupled with high efficacy and low toxicity. As it was a racemic mixture, its isomers were examined. As the dextro isomer possessed all the vasodilating activity, it was selected for clinical evaluation after it was fully evaluated by pharmacologists who demonstrated that it had a papaverine-like vasodilating action on the coronary artery and antagonised calcium ion flow across cardiac muscle membrane stores. The novelty of this action resulted in diltiazem being the first coronary vasodilator to be described as a ‘calcium antagonist’. The anti-arrhythmic activity also observed was due to the fact that there are fast and slow calcium channels, and diltiazem not only blocks calcium transport through the slow channels but also delays their recovery.

Diltiazem is now used in the treatment of angina and a slow-acting formulation is available for patients with hypertension who respond poorly to beta-blockers.

**Hypnotic Benzodiazepines**

Among the earliest chemical modifications effected on the benzodiazepine nucleus was the introduction of the nitro group, as this offered chemists an opportunity of subsequent structural variation. Several nitro compounds were prepared by Sternbach and his colleagues, of which nitrazepam proved to be much more potent than chlordiazepoxide in both mice and cats. Subsequent investigations showed that sleep could be induced by larger doses that were well below the toxic threshold. Indeed, so wide was the margin of safety that self-poisoning with nitrazepam was most unlikely to occur. This safety factor alone ensured worldwide acceptance of this new hypnotic. However, nitrazepam had a half-life of around 26 hours and so persisted in the body long enough to cause a hangover effect when patients awakened.
Temazepam was developed by Wyeth Laboratories in Radnor, Pennsylvania, and became a very popular hypnotic because there was no hangover effect.\textsuperscript{49} It was more susceptible than nitrazepam to metabolic deactivation in the liver, with a half-life of 8–10 hours, and no active metabolite formed. Unfortunately, temazepam was widely abused as an illicit recreational drug. Other short-acting hypnotics that were introduced include lormetazepam\textsuperscript{54} and loprazolam\textsuperscript{55}.

Midazolam was a short-acting anxiolytic agent developed by Hoffmann–LaRoche.\textsuperscript{56} Formulated as the hydrochloride salt, it is the only water-soluble benzodiazepine available for injection. When injected it has a half-life of about 1–3 hours and produced amnesia for a period of about 10 minutes after administration. It is also given continuously by the intravenous route in order to sedate patients undergoing intensive care.

**Tricyclic Antidepressants**

The recognition of the tranquillising properties of chlorpromazine in the mid-1950s led psychiatrists to test it and its analogues in a variety of clinical conditions. Roland Kuhn of the Cantonal Psychiatric Clinic, Munsterlingen, Switzerland, noticed that chlorpromazine produced effects that reminded him of those he had observed when testing an antihistamine that had been sent to him by Geigy for testing as a hypnotic. On that occasion, Kuhn had suggested further studies would be worth while, but this suggestion was ignored. This time, a long letter he wrote to Geigy was taken seriously, especially as the antihistamine had a striking structural resemblance to chlorpromazine. He received further samples of the antihistamine, code-named G22150. While it was soon found to have interesting properties, it had too many side effects. Geigy then sent Kuhn samples of imipramine, an analogue of G22150 with a side chain identical to that of chlorpromazine.\textsuperscript{57,58} Kuhn thoroughly evaluated imipramine in a variety of psychiatric conditions. Early in 1956, it was administered to several patients suffering from endogenous depressions. After only three patients had been treated, it became clear that this new tricyclic compound had unique properties. A letter sent to Geigy at the beginning of February that year referred to the pronounced antidepressant activity of the new drug. At the Second International Congress of Psychiatry, held in Zurich 7 months later, an audience of a dozen people heard the first public disclosure of this major advance. A subsequent publication caught the attention of a wider audience.\textsuperscript{59,60} Since then, imipramine has been administered to millions of patients with impressive results.
Rival companies responded by introducing their own antidepressants, which had similar activity to imipramine. For example, trimipramine was synthesised as an analogue of trimeprazine at the Rhône–Poulenc laboratories, while clomipramine was introduced by Smith, Kline and French.

The recognition of the antidepressant action of imipramine revealed that minor structural alterations in the central ring of phenothiazine tranquillisers could radically change their pharmacological profile. This stimulated medicinal chemists to synthesise novel tricyclic compounds. As has been seen, replacement of the nitrogen atom in the central ring of chlorpromazine led to the introduction of the thioxanthenes as tranquillisers in 1958. Similarly, replacement of the sulfur atom in the thioxanthene system resulted in the first of the dibenzocycloheptadienes, namely amitriptyline, which was synthesised by several groups in 1960. One of the first was Merck Sharp & Dohme Research Laboratories, who also prepared nortriptyline. Both resembled imipramine insofar as they were antidepressants rather than tranquillisers, but were noticeably less stimulating. This has made them more suitable than imipramine for treating agitated, anxious patients who were also depressed.

Analogues of amitriptyline include doxepin, in which a carbon atom in the central ring is replaced by oxygen. It has a similar clinical profile to amitriptyline, but may be somewhat less cardiotoxic in overdosage. Dosulepin is similar in its activity.
In 1958, researchers at the Wander Research Institute in Basle synthesised analogues of imipramine in which one or more heteroatoms replaced carbon atoms in the central ring. Particularly interesting from a pharmacological point of view were several amidines, including the antidepressants amoxapine and clozapine. Amoxapine had very similar antidepressant properties to imipramine, but clozapine proved to be an antipsychotic drug. However, it was atypical insofar as it did not produce extrapyramidal side effects and was of value in patients who had failed to respond to treatment with other antipsychotic drugs. It was marketed in Switzerland and Austria in 1972, but a high incidence of agranulocytosis was observed during a clinical trial in Finland three years later. This resulted in the use of clozapine being severely restricted. However, in 1988 a major study by John Kane of Hillside Hospital in Glen Oaks, New York, revealed the outstanding activity of clozapine in the treatment of schizophrenics who had not responded to therapy with conventional antipsychotic drugs. It became more frequently prescribed thereafter.

When Lilly researchers examined the effect of replacing either of the benzene rings in clozapine with a thiophen ring, they found four compounds worthy of further study. Only one of these proved to be safe enough for human studies. It was marketed under the name ‘olanzapine’ in 1996 as a safer alternative to clozapine. Quetiapine is a similar atypical antipsychotic drug.

Carbamazepine was synthesised by Walter Schindler at the Geigy laboratories in Basle in 1953 when the company was investigating analogues of chlorpromazine. It was only some years later that its anticonvulsant properties were recognised. The first clinical study was not carried out until 1963, and it seems to have taken longer than most anticonvulsants to become established in clinical practice. Carbamazepine is now considered to be as effective as phenytoin in the control of partial and tonic–clonic seizures.

**Selective Serotonin Reuptake Inhibitors**

During the 1960s, Swiss psychiatrist Paul Kielholz differentiated tricyclic antipressants for clinical application on the basis of whether they possessed the ability to sedate, stimulate drive or improve the mood of patients. At that time there was a broad consensus that the tricyclic antidepressants acted by inhibiting the reuptake of norepinephrine back into the neurones from which it was released, thereby elevating the level of the hormone. By the end of the decade, however, there was mounting evidence that the reuptake of 5-HT was also blocked. The first to associate the thinking of Kielholz with the biochemical advances were the Russians Izyaslav Lapin and Gregory Oxenkrug of Bekhterev’s Psychoneurological Research Institute in Leningrad. In 1969, they suggested that increased serotonergic activity in the brain involving tryptophan and its metabolites, including 5-HT, accounted for the mood-elevation effect of antidepressants, while increased noradrenergic activity was responsible for the motor
and energising effects. Several groups of researchers followed this up by seeking selective serotonin reuptake inhibitors (SSRIs).

At the Karolinska Institutute, Arvid Carlsson examined the effects of antihistamines on both 5-HT and norepinephrine uptake in tissues. Although most had mixed activity, diphenhydramine affected only 5-HT uptake. In collaboration with Peder Berntsson and Hans Corrodi of Aktiebolaget Hassle, based in Gothenburg and part of Astra, Carlsson quickly developed a pheniramine analogue as a potent SSRI in the spring of 1971. Several years later it was marketed in Europe as zimelidine in 1982, but was withdrawn by Astra the following year because ten cases of the Guillaine–Barre syndrome had been reported out of 200,000 prescriptions. This neurological disorder was characterised by progressive muscular weakness. Fortunately, a slow recovery over a period of months occurred in all patients once medication had ceased.

The second SSRI to be marketed in Europe also had to be withdrawn shortly after its introduction, this time because it produced agranulocytopenia in a few patients. The drug was an antihistamine analogue called indalpine, developed by Gerard Le Fur and his colleagues at Fournier Frères, a company that became part of Rhône–Poulenc.

The next SSRI to be introduced was fluvoxamine. It remained on the market without encountering the problems faced by its predecessors. However, during early trials concern was expressed over the number of patients who committed suicide before the drug had exerted its beneficial action. Similar concerns have been raised about other SSRIs, despite their main advantage over tricyclic antidepressants being their enhanced safety margin when deliberate overdoses are consumed. This issue is highly contentious and is being examined in the law courts.

Several other SSRIs were subsequently marketed, including one that has become a household name. Bryan Molloy of Eli Lilly made analogues of diphenhydramine for Robert Rathbun and Richard Kattau to screen for inhibition of norepinephrine and 5-HT uptake.
They found \(N\)-methyl-phenoxyphenylpropylamine to be twice as potent at inhibiting uptake of 5-HT as it was at inhibiting norepinephrine uptake, so a series of analogues of it were synthesised. This resulted in the discovery of fluoxetine as an SSRI. Eli Lilly marketed it in 1988. Since then, it has become the most frequently prescribed antidepressant drug. It was especially popular in the United States under its proprietary name of Prozac\textsuperscript{®}.

**ANTIFIBRINOLYTIC DRUGS**

S. Okamoto set up a screening programme to find antifibrinolytic drugs that could be used to stop haemorrhage. Among the 400 or so compounds he tested were basic amino acids that were found to have some activity, the most effective being lysine.

\[
\text{lysine} \quad \begin{array}{c}
\text{H}_2\text{N} \\
\text{COOH}
\end{array} \\
\text{\textit{\alpha}-aminocaproic acid} \quad \begin{array}{c}
\text{H}_2\text{N} \\
\text{COOH}
\end{array} \\
\text{tranexamic acid}
\]

Since lysine had inadequate potency for clinical applications, analogues of it were examined. This led to the discovery in 1957 that removal of the \(\alpha\)-amino group greatly enhanced activity, \(\varepsilon\)-aminocaproic acid being ten times as potent as lysine.\textsuperscript{79} Further investigation showed that it was an inhibitor of plasminogen activation. It was introduced into the clinic as a haemostatic agent, but was superseded by tranexamic acid.

When Okamoto and his colleagues screened a large number of analogues of \(\varepsilon\)-aminocaproic acid they discovered that the distance between the carboxylic and amino groups was critical, as was the nature of the linkage between them. After finding that a benzene ring could be used as a linkage, a cyclohexane ring was shown to be even more potent. The most potent compound was tranexamic acid, so named because it was a \textit{trans} isomer.\textsuperscript{80} The \textit{cis} isomer was inactive as the amino and carboxylic groups were positioned too close to each other. Tranexamic was introduced to stop haemorrhage during surgery.

**NON-STEROIDAL ANTI-INFLAMMATORY DRUGS**

During the 1950s, it became widely recognised that the long-term use of corticosteroids in rheumatoid arthritis caused serious problems that were inherent in the nature of the medication. In 1955, Stewart Adams at the Boots Pure Drug Company laboratories in Nottingham established a screen to find a safe, orally active anti-inflammatory agent. This involved ultraviolet (UV) irradiation of the backs of guinea pigs 30 minutes after they had received a test compound by mouth. Adams had established that this procedure reliably indicated the ability of aspirin to reduce inflammation and could be used to test alternatives to it in the search for a more potent compound with fewer side effects.

The chemist working with Adams was John Nicholson. Both were convinced that the presence of a carboxylic acid group was responsible for the anti-inflammatory activity of aspirin and some of its analogues. Adams screened phenylacetic and phenoxyacetic acids previously made by the company as potential herbicides. After 2-(4'-ethylphenoxy)propionic acid proved to be several times as potent as aspirin, more than 200 aryloxyalkanoic acids were synthesised and tested.\textsuperscript{81} Eventually, 2-(4'-phenylphenoxy)propionic acid emerged as a candidate for clinical investigation. Its ethyl ester was preferred since it was expected to cause less gastric irritancy. However, when put on clinical trial in 1960 it turned out to be
inactive in patients with rheumatoid arthritis. Significantly, its analgesic and antipyretic effects were feeble. This led to a decision that all active test compounds should in future be tested for analgesic and antipyretic as well as anti-inflammatory activity.

[Chemical structures of 2-(4'-ethylphenoxy)propionic acid and 2-(4'-phenylphenoxy)propionic acid]

Attention was now switched to 4-alkylphenyl and biphenylalkanoic acids. Approximately 450 more compounds were synthesised and screened. Two of these were examined in the clinic, but produced rashes in patients. Finally, ibufenac was found to exhibit more than four times the potency of aspirin. After an early clinic trial gave encouraging results, it was marketed in 1966. However, it had to be withdrawn soon after when evidence of an unacceptable incidence of jaundice appeared.

Ibuprofen was selected as an acceptable alternative to ibufenac after animal studies confirmed that it did not accumulate in the liver or produce ulcers in dogs, as had some similar compounds. It proved to be a safe, effective anti-inflammatory agent with analgesic and antipyretic properties and was marketed in 1969. Ibuprofen became widely prescribed throughout the world in the wake of increasing concern about the hazard of gastric bleeding caused by aspirin. Such was its relative safety that in 1983 it became available in the United Kingdom as a non-prescription analgesic on account of its having the lowest overall rate of reporting of suspected adverse reactions among the non-steroidal anti-inflammatory agents, some 20 million prescriptions having been issued over the preceding 15 years.

Among the 600 compounds screened by Adams before the introduction of ibuprofen were several 4-biphenylalkanoic acids. These proved to be highly potent anti-inflammatory agents, but were abandoned in favour of the less-potent phenylalkanoic acids that were at that time believed to be less toxic. After the introduction of ibuprofen these acids were again investigated, resulting in the introduction of flurbiprofen. Although it turned out to be 5–10 times as potent as ibuprofen, this did not confer any significant therapeutic advantage. The indications for its use are identical to those for ibuprofen.
Rival manufacturers quickly developed analogues of ibuprofen. Syntex introduced naproxen, which was twice as potent as ibuprofen and had a longer duration of action, allowing twice-daily dosing.\(^8\) Beecham Pharmaceuticals developed the related nabumetone as a prodrug that rapidly underwent metabolic activation in the liver to form the acid.\(^7\) Their intention had been to minimise the inhibition of prostaglandin synthesis in the stomach and so reduce gastric irritation, but this would only have been relevant if that inhibition had been a local rather than a systemic effect. Rhône-Poulenc marketed ketoprofen, which was about ten times as potent as ibuprofen and had a longer duration of action.\(^8\) Fenoprofen was introduced by Lilly.\(^9\) It had a similar duration of action to ibuprofen but was 2–3 times as potent.

A number of other non-steroidal anti-inflammatory acids were marketed in the 1970s and 1980s. Among them was benoxaprofen, which was developed at the Lilly Research Centre in Surrey, England.\(^9\) When it was launched in the United Kingdom in March 1980, benoxaprofen was promoted as an anti-arthritic agent that could be taken as a single daily dose because of its resistance to metabolic degradation. At the time, this was considered helpful in ensuring good patient compliance. There were also anecdotal reports of dramatic improvements in the condition of seriously crippled patients.

In February 1982, Hugh Taggart at Queen’s University in Belfast reported the deaths of five elderly patients who had received benoxaprofen.\(^9\) Urgent enquiries ensued and the UK Committee on Safety of Medicines withdrew the Product Licence in August of that year, amid intense media coverage. By that time, 83 fatalities had occurred among three-quarters of a million patients in the United Kingdom who had taken the drug. Most had died from renal or hepatic failure.

The 15th International Congress of Rheumatology held in Paris in June 1981 had been told that benoxaprofen was slowly excreted, its biological half-life being as long as four days in elderly patients. Earlier reports had indicated that the half-life was 33 hours in humans, justifying the convenience of once-daily dosage. The implications of a more prolonged half-life in elderly patients had not then been obvious. It is with the benefit of hindsight that they certainly are now. The issue relates to the question of toxicity, for it is only if a drug is relatively toxic that a problem arises from its accumulation in patients with poor renal function. Although reports of photosensitivity and nail damage had been received, benoxaprofen was not at that time thought to be any more toxic than other non-steroidal anti-inflammatory agents.

The outcome of this tragic affair would have been different if more information about the effects of benoxaprofen in elderly people had been available. The manufacturer had mentioned the need for dosage reduction in a pamphlet issued three months after the Paris Symposium, but this seems to have been generally overlooked. Only 52 patients over the age of 65 had received the drug in clinical trials, but this was not exceptional since it was not expected that elderly patients should be recruited specifically for such trials. Lessons were learned from this affair, not least being the importance of an exemplary level of vigilance required from both manufacturers and licensing authorities. Furthermore, there is now recognition that elderly patients should not be prescribed long-acting drugs when alternatives are available.
Selective COX-2 Inhibitors

In 1991, Dan Simmons and his colleagues at Brigham Young University in Utah discovered that there was a second type of cyclooxygenase enzyme inhibited by aspirin and the non-steroidal anti-inflammatory agents. This COX-2 was principally involved in producing prostaglandins during inflammation, whereas COX-1 was involved in routine physiological processes such as platelet aggregation. Pharmaceutical companies immediately recognised the implications and began seeking selective COX-2 inhibitors that would be free from the side effects of existing anti-inflammatory drugs that all lacked selectivity.

G.D. Searle launched a screening programme that was to test over 2500 compounds. These were at first screened against cloned COX-2 enzyme, but it was found that an assay in rodents was more reliable. Around 10% of the compounds were selected for further screening, from which seven emerged as potential drug candidates and were examined in several species of animals. A compound from the company’s agrochemical library of compounds turned out to be both a selective COX-2 inhibitor and an anti-inflammatory agent. It was marketed in 1999 with the approved name of ‘celecoxib’. It was hoped that it would produce a lower incidence of side effects than other anti-inflammatory drugs.

Rival companies introduced several more selective COX-2 inhibitors during the next few years. One of these, rofecoxib, was suddenly withdrawn in 2004 after Merck had conducted a study that revealed that patients taking their product faced a higher risk of heart attacks and stroke than those on a placebo.

ETHAMBUTOL

In the course of an extensive screening programme, researchers at Lederle Laboratories discovered that N,N'-diisopropylethylenediamine had antituberculosis activity comparable with that of isoniazid. The sole drawback was its greater toxicity.

An extensive series of analogues was synthesised, culminating in the development of ethambutol, which was reported in 1961 to be a particularly promising drug. This early promise was fulfilled and ethambutol is still used in combination with other agents. The main problem with it is that visual side effects occur and thus patients require to be regularly monitored while receiving treatment.

LEVAMISOLE

The Janssen Research Laboratory at Beerse in Belgium initiated an extensive screening programme in which 2721 novel heterocyclic compounds were tested for anthelmintic activity.
against three types of parasitic worms before an aminothiazole derivative, R6438, was found to be effective in chickens and sheep.

Its failure in mice and rats pointed to the possibility that it had to undergo metabolic conversion to an active drug that was only formed in some animals. All the metabolites were then isolated and synthesised. R8141 was the only active one, but was difficult to produce and, in addition, was unstable in water. A large series of its analogues was synthesised, of which one met all the requirements for possible clinical application. This was given the approved name of ‘tetramisole’, but it was its laevo isomer that was selected for medicinal use since it was several times more potent, yet no more toxic. It is employed under the name ‘levamisole’ as an ascaricide to eliminate the common roundworm.

PYRANTEL

In the mid-1950s, Pfizer researchers at Groton, Connecticut, established a screening programme to find new anthelmintic agents. In order to widen the score of the screens, laboratory mice were inoculated with three different organisms, namely the tapeworm *Hymenolepis nana*, the nematode *Nematospiroides dubius* and the pinworm *Syphacia obvelata*. Out of a large number of compounds submitted for screening, only compound I emerged with any evidence of activity. When administered by mouth to sheep, it had little activity, probably because it hydrolysed to the compounds from which it had been synthesised, namely 2-thienylthiol and 2-imidazolidone.

Analogue

Analogues of compound I designed to resist hydrolysis were synthesised at the Pfizer research centre in Sandwich, England. An early advance came when a methylene group replaced the sulfur atom in the bridge between the two rings to give a compound that was active against a variety of roundworms that infested sheep. As this compound was toxic, analogues were synthesised. Optimal activity against a variety of nematodes was obtained by enlarging the imidazoline to a tetrahydropyrimidine ring, as in pyrantel. This was an orally active broad-spectrum anthelmintic that was effective against roundworms, hookworms and threadworms in both humans and animals.

Oxantel was one of several analogues of pyrantel that were prepared in order to examine the relationship between aromatic ring substitution and anthelmintic potency. It had only one-tenth of the activity of pyrantel in the mouse screen against *N. dubius*, but was active against the tapeworm *H. nana*, unlike pyrantel. When tested in dogs with whipworm infestation, it was also active. This activity against whipworm infection compensated for its narrow spectrum of anthelmintic activity, and became the principal clinical application.

NIFEDIPINE

Because 1,4-dihydropyridines played an important role in biochemical processes yet had never been investigated pharmacologically, the medicinal chemistry group at the Bayer laboratories...
submitted a variety of these for screening. After some of these compounds were found to exhibit a measurable effect on cardiac output, more than 2000 analogues were synthesised and screened. In 1967, Friedrich Bossert and Wulf Vater applied for a South African patent in which they claimed that nifedipine possessed marked coronary vasodilating activity.

Further investigations revealed that nifedipine selectively blocked calcium channels in the conductive cells of the heart and vascular smooth muscle, thereby inhibiting the entry of ionised calcium and its release from intracellular stores. Since calcium was required for membrane depolarisation and muscle contraction, nifedipine relaxed smooth muscle both in the myocardium and in the walls of blood vessels. The outcome of this was dilation of the coronary vessels and a fall in vascular resistance, with a consequent reduction of cardiac afterload, work and oxygen consumption. As this was of major importance in the treatment of vascular disorders such as angina and hypertension, nifedipine was marketed in 1975.

Several analogues of nifedipine have been developed which have a longer duration of action and hence are less likely to cause fluctuations in blood pressure and reflex tachycardia, e.g. felodipine and amlodipine. Nimodipine had a high specificity for calcium channels in cerebral blood vessels and hence was able to increase cerebral blood flow without decreasing blood pressure. This made it valuable in the prevention of cerebral arterial spasm after subarachnoid haemorrhage.

CARMUSTINE

In 1955, following a decade of remarkable progress in the sphere of cancer chemotherapy in the United States, Congress allocated large sums of money to set up a screening programme run by the Cancer Chemotherapy National Service Center (CCNSC), which was part of the National Cancer Institute. The first contracts were awarded to four screening centres that confidentially tested large numbers of compounds submitted by academic and industrial researchers. By the end of the decade, these centres were testing around a thousand chemicals each month against animal tumours.

In 1959, researchers at the Wisconsin Alumni Research Foundation discovered that 1-methyl-1-nitroso-3-nitroguanidine (MNNG), an intermediate used by organic chemists to prepare the unstable alkylating agent diazomethane, had antileukaemic activity in mice. Unfortunately, human trials were disappointing. Nevertheless, when Thomas Johnston, George McCaleb and John Montgomery at the Southern Research Institute in Birmingham, Alabama, were notified by the CCNSC of the activity of MNNG, they immediately began an evaluation of related compounds as there was considerable concern that half of the long-term survivors among children who received combination chemotherapy for acute leukaemia were
dying from meningeal leukaemia. They found that an alternative compound used in the
synthesis of diazomethane, namely 1-methyl-1-nitrosourea (MNU), was more active than
MNNG. As it was also more lipophilic, they believed it would penetrate the central nervous
system and so be effective in meningeal leukaemia. After preliminary tests in animals injected
intracerebrally with leukaemic cells, MNU was investigated further by the National Cancer
Institute.107 While this was taking place, analogues of MNU were synthesised and tested at the
Southern Research Institute. The researchers there believed that the antileukaemic activity was
due to MNU decomposing into diazomethane hydroxide, a powerful alkylating agent.
Attempts were therefore made to find a more active biological alkylating agent by replacing
the N-methyl group with similar groups that would produce diazoalkyl hydroxides with
different activity profiles. This led to the synthesis of carmustine.108 When it was tested in mice
injected with L-1210 leukaemic cells, not only was it the most active of 23 compounds
submitted for evaluation and far superior to MNU but it was also the first to cure such
mice.109 An early clinical trial confirmed the value of carmustine.110

As expected, carmustine penetrated into the central nervous system because of its high lipid
solubility. It controlled meningeal leukaemia in some children, but as this soon became
preventable by irradiating the cranium at the outset of acute lymphocytic leukaemia
treatment, this application of carmustine became redundant. It is instead used to treat brain
tumours, advanced Hodgkin’s disease, lymphomas and myelomas. Because of its alkylating
activity, local tissue damage would be caused if it were taken by mouth or injected
intramuscularly. Hence carmustine is given intravenously so that immediate dilution by blood
occurs. Lomustine, which was also developed at the Southern Research Institute, can be taken
by mouth.111

PRAZIQUANTEL

In 1972, a screening programme at the Bayer Institute for Chemotherapy in Wuppertal
revealed anthelmintic activity in novel pyrazinoisoquinolines that had been synthesised in the
laboratories of E. Merck and Company of Darmstadt in the course of a joint project between
these two German companies. Praziquantel was selected from over 400 compounds for further
investigation. It exhibited outstanding efficacy against all known intestinal cestode infections
in humans, as well as a great many in animals.112

Further studies revealed not only that a single oral dose was capable of eradicating these
infections but also that praziquantel was highly effective against schistosomiasis and a variety
of other parasitic infections.113 It became the first drug to receive World Health Organization
approval for use in mass eradication programmes aimed at eliminating a broad range of parasitic infections.

MILRINONE

At the Sterling–Winthrop Research Institute in Rensselaer, New York, a screening programme was established in order to find inotropic compounds with cardiotonic activity similar to that of the cardiac glycosides. Amrinone was discovered to be among the most active of the compounds capable of increasing the contractility of cardiac muscle. In addition, it has a useful vasodilating action. These properties were found to be due to its ability to act as a selective phosphodiesterase inhibitor in cardiac and vascular muscle, raising intracellular levels of cAMP. This resulted in an increase in calcium levels, which accounted for the increased force of cardiac contraction. As it had little effect on heart rate, amrinone was suitable for use as a cardiac muscle stimulant in congestive heart failure. However, the Sterling–Winthrop researchers found milrinone to be many times more potent, so it was preferred for clinical use.

Several other companies sought selective phosphodiesterase inhibitors, enoximone being developed at the Merrell Dow Research Center in Cincinnati after it was discovered that imidazole had some activity. It was less potent than milrinone.

NAFTIFINE

Naftifine was found to be an antifungal agent during screening at the Sandoz Research Institute in Vienna. It was shown to have a novel mode of action which involved blocking the synthesis of ergosterol by inhibiting squalene oxidase, but it was only suitable for topical use.

Over a thousand analogues of naftifine were prepared in order to establish the requirements for optimal antifungal activity. From this, acetylenic allylamines were selected for special attention, resulting in the development of terbinafine as an orally active antifungal agent with significantly greater activity than naftifine.

PROPOFOL

At the Alderley Edge laboratories of ICI (now AstraZeneca), screening in mice for potential anaesthetics revealed the anaesthetic activity of 2,6-diethylphenol.
Roger James and J.B. Glen then prepared and examined further alkyl-substituted sterically hindered phenols in order to optimise activity in this series. They found that it was necessary to strike a balance between the minimum steric hindrance providing adequate potency and excessive steric crowding, which caused loss of anaesthetic activity. In addition, lipophilicity had to be limited in order to avoid slower kinetics through binding to plasma proteins. The most active compounds were di-sec-alkyl substituted and had 6 to 8 carbon atoms in the side chains. Propofol was the only compound among those studied that emerged with a satisfactory profile when evaluated as an intravenous anaesthetic. It is now widely used.

**ANGIOTENSIN II ANTAGONISTS**

Angiotensin II is a powerful hypertensive agent because it binds to receptors known as AT₁ and AT₂ to cause vasoconstriction. Using these receptors as a target for high throughput screening (HTS), the Japanese company Takeda tested a vast number of compounds and obtained a ‘hit’. Analogues of this were then prepared by DuPont chemists in order to find a compound that was selective for the AT₁ receptor. This was given the approved name of ‘losartan’ and was introduced into the clinic in 1993.

Unlike the ACE inhibitors, losartan and its analogues do not cause the breakdown of bradykinin, hence patients do not experience the unwelcome dry cough caused by ACE inhibitors. In general, the clinical value of angiotensin II antagonists matches that of the ACE inhibitors.
Several other angiotensin II antagonists have been introduced, including eprosartan, candesartan, irbesartan, valsartan, olmesartan and telmisartan. Even a superficial glance at their chemical structures shows that they are derived from either losartan or the lead compound from HTS that led to its development. This reveals the pattern of drug development by rival companies that will be seen when future drugs derived from HTS are introduced.

**IMATINIB**

In 1973 at the University of Chicago, Janet Rowley established that the missing portion of chromosome 22, the ‘Philadelphia chromosome’, had translocated to chromosome 9 in patients with chronic myelogenous leukaemia (CML). During the next decade it was confirmed that one gene from each chromosome (Bcr in chromosome 22, Abl in chromosome 9) fused to form a new gene, designated Bcr–Abl. This gene produced the rogue protein that caused CML. David Baltimore and his colleagues at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, reported that this protein was a tyrosine kinase enzyme. In the early 1990s, the Swiss company Ciba-Geigy became interested in the possibility of designing an inhibitor of the enzyme. Using high throughput screening of the company’s small molecule libraries, a 2-phenylaminopyrimidine emerged as a weak inhibitor of several protein kinases that could serve as a lead for further development. Introduction of a methyl at the 6-position and of a benzamide on the phenyl ring enhanced inhibitory activity towards Abl. A promising inhibitor ultimately emerged from this work, but it lacked water solubility and oral bioavailability was poor. These difficulties were overcome by attaching an N-methylpiperazine to form imatinib.

Imatinib appears to be giving encouraging results as a highly selective chemotherapeutic agent for the treatment of CML. Among untreated patients who receive imatinib, around 60% respond to treatment and experience few side effects. There have been no long-term studies yet, but it is clear that this is the first drug that can treat cancer by targeting a protein that causes the disease. Several companies are currently investigating other protein kinase inhibitors.

**REFERENCES**


57. US Pat. 1951: 2554736 (to Geigy).


