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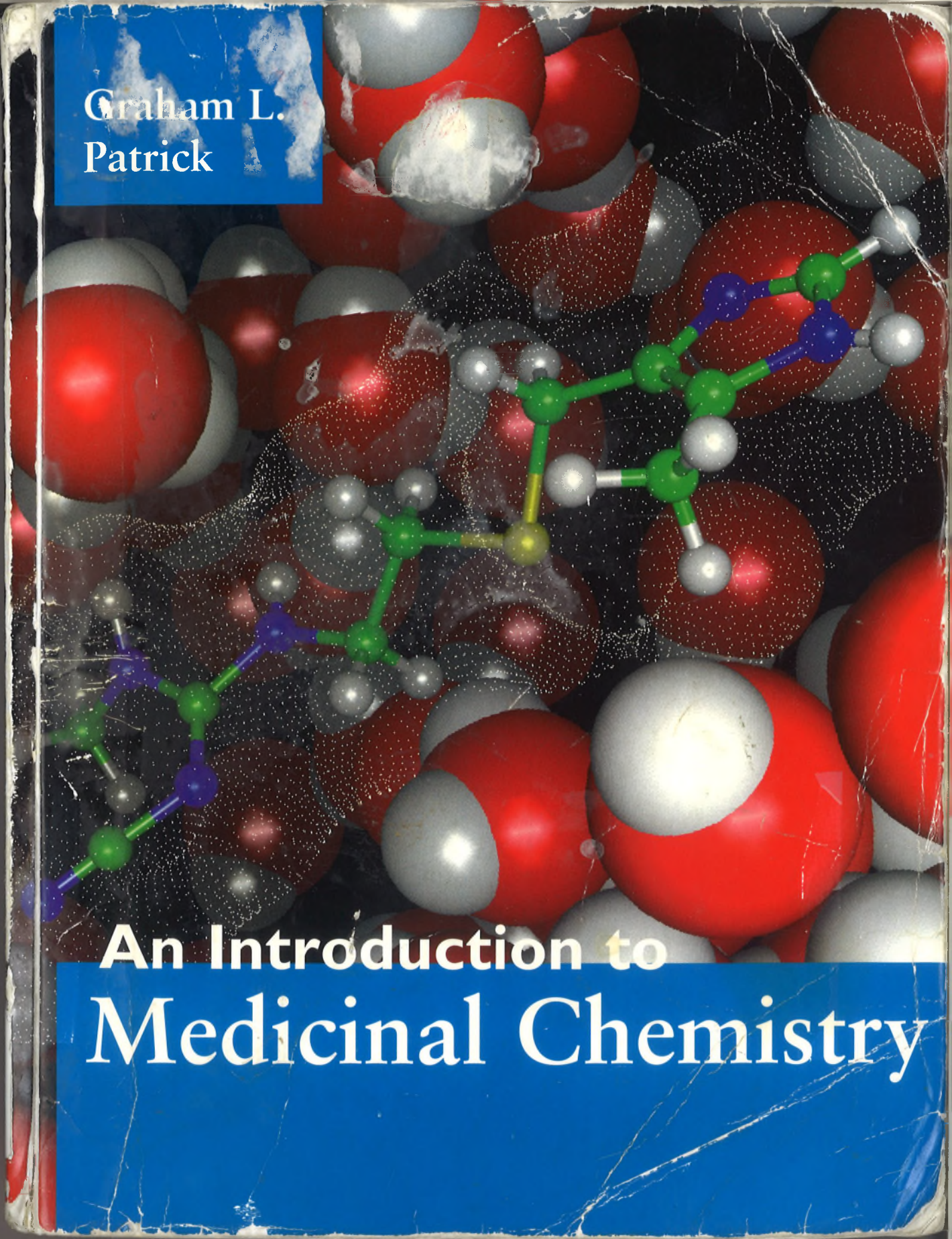

An Introduction to Medicinal Chemistry

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7 • Drug development

For several thousand years, man has used herbs and potions as medicines, but it is only since the mid-nineteenth century that serious efforts were made to isolate and purify the active principles of these remedies. Since then, a large variety of biologically active compounds have been obtained and their structures determined (e.g. morphine from opium, cocaine from coca leaves, quinine from the bark of the cinchona tree).

These natural products became the lead compounds for a major synthetic effort where chemists made literally thousands of analogues in an attempt to improve on what Nature had provided. The vast majority of this work was carried out with no real design or reason, but out of the results came an appreciation of certain tactics which generally worked. A pattern for drug development evolved. This chapter attempts to show what that pattern is and the useful tactics which can be employed for developing drugs.

Nowadays, the development of a novel drug from natural sources might follow the following pattern.

- Screening of natural compounds for biological activity.
- Isolation and purification of the active principle.
- Determination of structure.
- Structure–activity relationships (SARs).
- Synthesis of analogues.
- Receptor theories.
- Design and synthesis of novel drug structures.

7.1 *Screening of natural products*

The screening of natural products became highly popular following the discovery of penicillin from a mould. Plants, fungi, and bacterial strains were collected from all round the world in an effort to find other metabolites with useful biological activities. This led in particular to an impressive arsenal of antibacterial agents (Chapter 9).

Screening of natural products from plant and microbial sources continues today in

the never-ending quest to find new lead compounds. In recent years, organisms from marine sources have given novel compounds with interesting biological activity and this is a field likely to expand.

7.2 *Isolation and purification*

The ease with which the active principle can be isolated and purified depends very much on the structure, stability, and quantity of the compound.

Penicillin proved a difficult compound to isolate and purify. Although Fleming recognized the antibiotic qualities of penicillin and its remarkable non-toxic nature to man, he disregarded it as a useful drug since it appeared too unstable. He could isolate it in solution, but whenever he tried to remove the solvent, the drug was destroyed. Now that we know the structure of penicillin (Chapter 9), its instability under the purification procedures of the day is understandable and it was not until the development of a new procedure called freeze-drying that a successful isolation of penicillin was achieved.

Other advances in isolation techniques have occurred since those days and in particular in the field of chromatography. There are now a variety of chromatographic techniques available to help in the isolation and purification of a natural product.

7.3 *Structure determination*

In the past, determining the structure of a new compound was a major hurdle to overcome. It is sometimes hard for present-day chemists to appreciate how difficult structure determinations were before the days of NMR and IR spectroscopy. A novel structure which may now take a week's work to determine would have provided two or three decades of work in the past. For example, the microanalysis of cholesterol was carried out in 1888 to get its molecular formula, but its chemical structure was not fully established until an X-ray crystallographic study was carried out in 1932.

Structures had to be degraded to simpler compounds, which were further degraded to recognizable fragments. From these scraps of evidence, possible structures were proposed, but the only sure way of proving the theory was to synthesize these structures and to compare their chemical and physical properties with those of the natural compound or its degradation products.

Today, structure determination is a relatively straightforward process and it is only when the natural product is obtained in minute quantities that a full synthesis is required to establish its structure.

In cases where there is not enough sample for an IR or NMR analysis, mass spectroscopy can be helpful. The fragmentation pattern can give useful clues about

the structure, but it does not, however, prove the structure. A full synthesis is still required as final proof.

Vinblastine (Fig. 7.1), an alkaloid used against advanced teratomas and lymphomas, is an example of how complex the structures of natural products can be. However, analytical skills and instruments have advanced to such an extent that even this structure is relatively simple compared to some of the natural product structures being studied today.

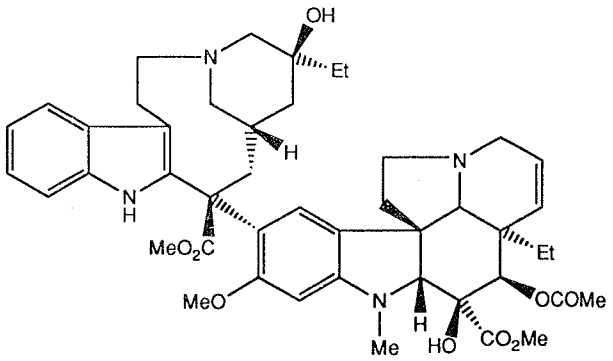

Fig. 7.1 Vinblastine.

7.4 *Structure–activity relationships*

Once the structure of a biologically active compound is known, the medicinal chemist is ready to move on to study the structure–activity relationships of the compound.

The aim of such a study is to discover which parts of the molecule are important to biological activity and which are not. The chemist makes a selected number of compounds, which vary slightly from the original molecule, and studies what effect that has on the biological activity.

One could imagine the drug as a chemical knight entering the depths of a forest (the body) in order to make battle with an unseen dragon (the body's affliction) (Fig. 7.2). The knight (Sir Drugalot) is armed with a large variety of weapons and armour, but since his battle with the dragon goes unseen, it is impossible to tell which weapon he uses or whether his armour is essential to his survival. We only know of his success if he returns unscathed with the dragon slain. If the knight declines to reveal how he slew the dragon, then the only way to find out how he did it would be to remove some of his weapons and armour and to send him in against other dragons to see if he can still succeed.

As far as a drug is concerned, the weapons and armour are the various chemical functional groups present in the structure, which can bind to the receptor or enzyme. We have to be able to recognize these functional groups and determine which ones are important.

Let us imagine that we have isolated a natural product with the structure shown in Fig. 7.3. We shall name it Glipine. There are a variety of groups present in the structure and the diagram shows the potential bonding interactions which are possible with a receptor.

It is unlikely that all of these interactions take place, so we have to identify those which do. By synthesizing compounds (such as the examples shown in Fig. 7.4) where

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