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The Chemistry Behind the Cure: Organic Chemistry in Drug Design and Action

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ABSTRACT

The living systems are, at their core, extraordinarily sophisticated organic chemistry laboratories. Every biological process including DNA replication, enzyme catalysis, signal transduction, metabolism is executed through the same functional-group chemistry taught in an introductory organic course: nucleophiles attacking electrophiles, acids donating protons to bases, electrons flowing through conjugated systems. This review examines how organic chemistry principles explain the structure and behaviour of biomolecules, how biological catalysis mirrors and inspires laboratory reactivity, and how this shared chemical language is exploited across the drug development pipeline right from target identification and hit discovery to lead optimization, pharmacokinetics, and clinical translation. The boundary between "organic chemistry" and "biology" is, in a real sense, artificial. Carbohydrates, lipids, proteins, and nucleic acids are organic molecules governed by the same rules of bonding, stereochemistry, and reactivity as any small molecule on a laboratory bench. What makes biological chemistry distinctive is not a different set of rules but an extraordinary degree of control: enzymes accelerate reactions by many times precisely organizing functional groups in three-dimensional space, and biological systems achieve levels of chemo-, regio-, and stereoselectivity that synthetic chemists still strive to match. Drug development sits directly at this interface. A drug is, definitionally, a small organic molecule (or increasingly, a biologic) designed to intervene in a biological process using organic-chemical logic like binding a receptor through hydrogen bonds and van der Waals contacts, inhibiting an enzyme by mimicking its transition state, or undergoing metabolic transformation that activates or deactivates the compound. This review traces that logic from the fundamental organic chemistry of biomolecules through to its application in modern drug discovery.

1. Introduction

Medicinal chemistry occupies the intersection of chemical and life sciences, encompassing the processes of drug discovery, molecular design, and compound synthesis for clinical application. According to world health organization the essential medicines are those that satisfy the priority health care needs of the population [1].

The work of medicinal chemistry includes several interconnected tasks like extracting active ingredients from natural sources or synthesize them, study their interaction with biological targets and also to track its metabolism [2]. Simultaneous advancements in organic chemistry, biochemistry, pharmacology, molecular biology, and computational sciences have collectively accelerated the progress of modern drug discovery. The genomics which is the study of an organism's full set of genes and proteomics which is the study of the proteins have become key tools for identifying new drug targets, often by comparing newly found genes or proteins to ones already characterized [3]. The rational drug design built on these tools is now a major focus across pharmaceutical companies, biotech firms, universities, and research institutes. The Organic chemistry sits at the centre of this work [4].

The organic chemistry provides both the conceptual framework and the practical toolkit that turn a biological insight into an actual molecule [5]. The rational drug design begins with an understanding of a disease-relevant target which is typically either a protein, enzyme, receptor, or nucleic acid [6].

Organic chemistry serves as the structural foundation for rational drug design, enabling chemists to construct molecules whose precise geometry and functional groups allow them to interact selectively with a given biological target. The concepts such as bond angles, stereochemistry, functional group reactivity, and conformational flexibility all come from

organic chemistry, and they determine whether a candidate molecule will fit snugly into a binding site or fail to engage it at all [7].

Rather than functioning merely as a descriptive tool for molecular architecture, organic chemistry serves as the enabling engine for the multi-step synthesis of therapeutic agents. Following lead identification, medicinal chemists leverage synthetic strategies to assemble the target molecule, optimize its scaffold, and synthesize structural analogues [2, 8]. This precise manipulation of functional groups including methyl-to-ethyl bio isosteric swaps, halogenation, and ring-size modulation underpins the execution of structure-activity relationship (SAR) profiling [9]. Every change is observed carefully. It has capability to affect potential selectivity, toxicity and utility. It provides feedback in drug designing process towards an optimized compound.

Organic chemistry also shapes a drug's pharmacokinetic behaviour like how it is absorbed, distributed, metabolized and excreted (ADME) [10].

The physicochemical properties like lipophilicity, polarity, molecular weight, and hydrogen-bonding capacity, all rooted in organic structure, influence whether a compound can cross cell membranes, survive first-pass metabolism in the liver, or reach its target tissue in sufficient concentration [11]. The medicinal chemists routinely apply guidelines such as Lipinski's Rule of Five, which are grounded entirely in organic-chemical descriptors, to predict a compound's likelihood of oral bioavailability early in the design process [12].

The synthesis of small drug molecule candidates remains the backbone of modern days drug discovery. They are synthesized by medicinal chemists, many of whom were originally trained as organic chemists. Finally, organic chemistry is what makes drug candidates scalable [13].

A compound that shows promise in early biological assays required eventually be synthesized in far larger quantities that is from milligram amounts used in initial screening to kilogram batches needed for animal studies and, ultimately, clinical trials [14].

The rational drug designing has always been a challenging process. Despite significant advances in computational modelling and target-based screening, it continues to pose considerable challenges, owing to the

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complex interplay between molecular structure, biological activity, and pharmacokinetic behaviour; within this framework, organic chemistry serves as an indispensable discipline, providing the synthetic and mechanistic foundation required to design, optimize, and manufacture viable drug candidates [15].

In this way, organic chemistry isn't just a supporting discipline in rational drug design, it is the mechanism through which biological targets are translated into physical molecules, therapeutic hypotheses are tested through structural modification, and pharmacological ambition is turned into something that can actually be manufactured and administered to patients [16].

2. Non-Rational Approaches to Drug Discovery: A Historical Perspective

Well before scientific instruments like the microscope or the modern clinical trial existed, people were already grappling with the same fundamental questions that continue to shape medicine today: what causes illness, and how might it be cured? The history of early medicine isn't a single, linear story. It is a mosaic of distinct traditions that developed independently, including those of Mesopotamia, Egypt, India, China, and Greece, each one confronting disease using the knowledge and reasoning available within its own culture [17].

While medicinal chemistry as a formal field has taken shape gradually over time, its roots stretch back thousands of years. From the earliest periods of human history, people turned to nature itself for healing it includes herbs, roots, tree bark, and berries. Drawing on their inherent therapeutic qualities to combat disease long before any organized scientific framework existed [18].

Long before the tools of modern chemistry existed, healers across China, India, the Andes, the Middle East, and Europe identified plants whose extracts relieved fever, pain, inflammation, and hypertension. The earliest documented medicine reported are as follows.

2.1 The Roots of *Dichroa febrifuga*

The root of *Dichroa febrifuga*, known in Chinese medicine as chang shan, was used for centuries to treat malarial fevers. Twentieth-century pharmacological investigation confirmed that crude extracts of the root were active against malaria parasites, and researchers subsequently isolated a family of alkaloids from the plant, the most active of which was later named Febrifugine Fig. 1 [19]. Febrifugine and its analogs remain of pharmacological interest today, more than two thousand years after chang shan first entered Chinese medical use, though the compound's side effects have limited its direct clinical adoption.

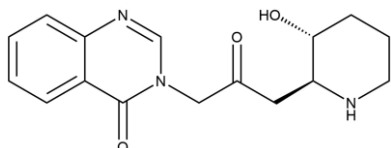


Fig. 1 Chemical structure of febrifugine

2.2 The Stem of *Ephedra sinica*

The dried stem of *Ephedra sinica*, has a documented history in Chinese medicine stretching back thousands of years, where it was used to induce perspiration and to relieve asthma, colds, and nasal congestion [20].

It is now known to contain two active constituents, 1) *Ephedrine*: It is drug that is used as a stimulant, appetite suppressant, decongestant and hypertensive agent. 2) *Pseudoephedrine*: It is used as a nasal/sinus decongestant and stimulant (pseudoephedrine hydrochloride). The plant's active alkaloid, ephedrine (Fig. 2), was first isolated and characterized by the Japanese chemist Nagayoshi Nagai in 1885, but its significance went largely unrecognized for several decades.

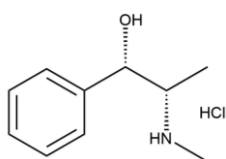


Fig. 2 Chemical structure of pseudoephedrine hydrochloride

In the 1920s, pharmacologists Ko Kuei Chen and Carl Schmidt at Peking Union Medical College rediscovered ephedrine, demonstrated that its

physiological effects paralleled those of adrenaline, and showed that, unlike adrenaline, it could be taken orally with a longer duration of action. This work introduced ephedrine to Western medicine as a treatment for asthma and established the closely related compound pseudoephedrine as a nasal decongestant still used in over-the-counter remedies today [21].

2.3 The Opium Poppy: Morphine and Codeine

The analgesic properties of the opium poppy, *Papaver somniferum*, were recorded as early as the third century BC by the Greek botanist Theophrastus, and the tenth-century Persian physician Rhazes later recommended opium preparations for pain, cough, and mental disturbance [22]. Opium remained in use as a crude preparation for centuries before the German pharmacist Friedrich Sertürner isolated its principal active alkaloid in 1804 and 1805, naming it morphium after the Greek god of dreams, a name later revised to morphine shown in Fig. 3a.

Sertürner's work is generally regarded as the first isolation of a medicinal alkaloid from a plant, and it launched the systematic chemical study of plant alkaloids as a distinct branch of pharmaceutical science [23]. A related alkaloid, codeine shown in Fig. 3b, was isolated from opium in 1832 and went on to become a widely used cough suppressant and mild analgesic [24].

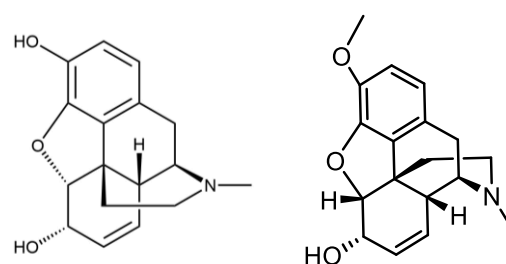


Fig. 3 Chemical structure of a) morphine and b) codeine

2.4 Henbane and Scopolamine: Sedative to "Truth Serum"

Henbane (*Hyoscyamus niger*) has been used since antiquity as a sedative and hallucinogen, with documented use dating back to the Ebers Papyrus and continuing through Greek, Roman, and medieval European practice [25]. Its active alkaloid, scopolamine (Fig. 4) was employed in early twentieth-century obstetrics, combined with morphine, to produce a state of sedated amnesia during childbirth known as "twilight sleep". Physicians observed that women in this state answered questions with unusual candor, an observation that led obstetrician Robert House to propose scopolamine as an interrogation aid in the 1920s [26]. The drug's brief career as a so-called truth serum was later abandoned once controlled studies failed to confirm that it reliably prevented deception scopolamine remains in clinical use today.

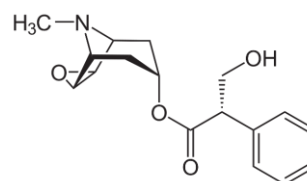


Fig. 4 Chemical structure of scopolamine

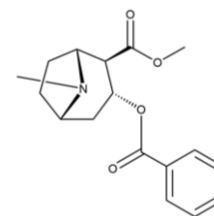


Fig. 5 Chemical structure of cocaine

2.5 Coca and Cocaine: Andean Stimulant to Isolated Alkaloid

Chewing of coca leaves in the Andean highlands' dates back thousands of years, with archaeological evidence of the practice found in Peru and Chile. The Inca regarded the plant as sacred, restricted its use to nobility and favoured classes, and relied on it to combat fatigue, hunger, and the effects of high altitude; silver miners and long-distance runners chewed the leaves for endurance [27]. The alkaloid responsible for these stimulant effects was isolated by German chemists in the mid-nineteenth century, first by Friedrich Gaedcke in 1855 and again, more definitively, by Albert

Niemann, who named the compound cocaine (Fig. 5). Once isolated, cocaine moved rapidly into Western medicine and popular culture as a stimulant and local anesthetic before its addictive potential led to strict regulation [28].

2.6 *Rauwolfia serpentina* and Reserpine: Ayurvedic Root to Antihypertensive

The root of *Rauwolfia serpentina*, known in India as sarpagandha, has been used in ayurvedic and folk medicine for centuries to treat conditions ranging from insomnia and insanity to snakebite and hypertension [29]. Indian researchers Sen and Bose published early clinical reports on the plant's use for hypertension and insanity in the 1930s and 1940s, but the plant remained largely unknown in Western medicine until 1949, when a case series drew international attention. Reserpine, the principal active alkaloid, was isolated from the root in 1952, and clinical researcher Robert Wallace Wilkins subsequently established its effectiveness as an antihypertensive agent, marking a milestone in the pharmacological treatment of high blood pressure [30].

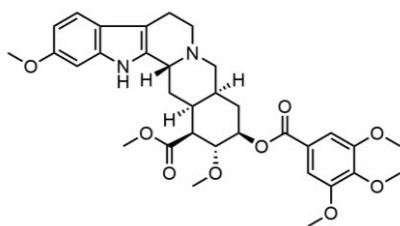
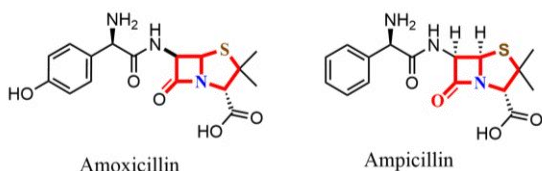


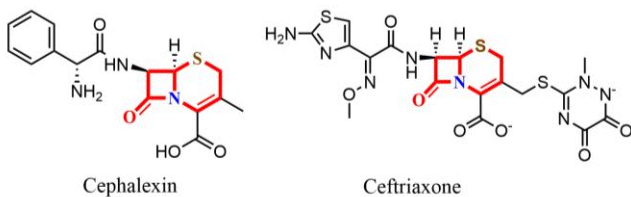
Fig. 6 Chemical structure of reserpine

The alkaloids reviewed here, febrifugine, ephedrine, morphine, codeine, scopolamine, cocaine, reserpine (Fig. 6) all trace back to plants that traditional healer in China, India, the Andes, and the Mediterranean world identified centuries or millennia before modern chemistry existed. Their subsequent isolation and pharmacological characterization transformed folk remedies into precisely dosed, mechanistically understood medicines, several of which remain in clinical use today. This history underscores both the depth of traditional ethnobotanical knowledge and the essential role that chemical isolation and pharmacological testing play in converting that knowledge into modern medicine.

Penicillins



Cephalosporins



Carbapenems

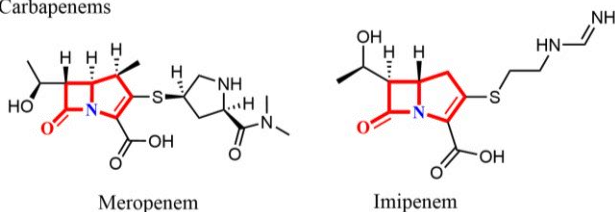


Fig. 7 Structures of penicillins, cephalosporins and carbapenem antibiotics

3. Rational Drug Discovery: An Organic Chemistry Perspective

3.1 Antibacterial Drugs

3.1.1 Organic Chemistry of Beta-Lactam Antibiotics

The β -lactam antibiotics are one of the most widely used classes of antimicrobial drugs. This class includes penicillins, cephalosporins,

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carbapenems etc. are shown in Fig. 7. The penicillins, cephalosporins, and carbapenems all have in common the β -lactam ring and are known collectively as β -lactam antibiotics. The penicillins, cephalosporins and carbapenems are bactericidal [31].

The post facto analysis suggests that penicillin actually mimics the structure of acyl-D-alanyl-D-alanine as it is involved in cross-link formation [32] (Fig. 8). They are ideal drugs as they help inhibiting an enzyme essential for bacterial growth which do not exist in animals namely peptidoglycan transpeptidase [33].

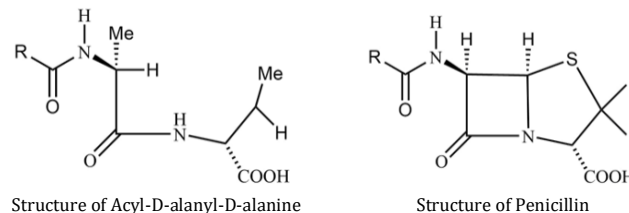


Fig. 8 Comparison of structure of acyl-D-alanyl-D-alanine with penicillin

3.1.1.1 Action of Mechanism

Step 1: The transpeptidase enzyme catalyses the cross-linking of the peptidoglycan to form the bacterial cell wall. The possible organic reaction mechanism is shown in step wise manner.

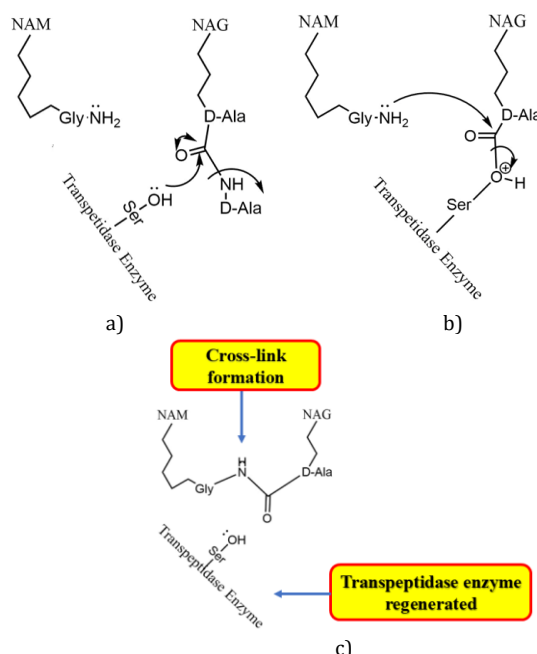


Fig. 9 a) Nucleophilic attack of enzyme b) initiation of cross-linkage and c) cross-link formation and enzyme regeneration

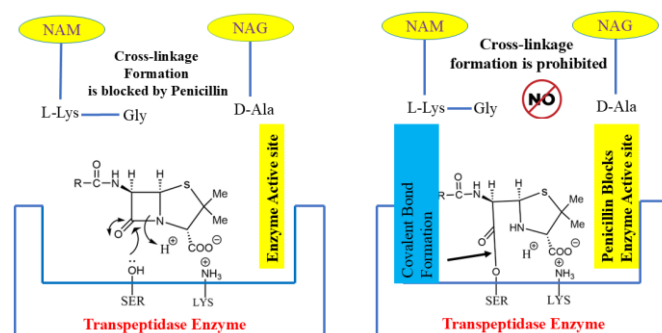


Fig. 10 a) Penicillin molecule mimics the acyl-D-alanyl-D-alanine structure and it occupies an active site of transpeptidase enzyme. b) Inhibitory action of penicillin blocking the active site of transpeptidase enzyme and preventing cross-link formation resulting in weakening of bacterial cell wall

The process is initiated with the attack of -OH group of serine from transpeptidase enzyme on carbonyl carbon of D-alanine. Fig. 9a. This results in the formation of bond between transpeptidase enzyme and D-alanine Fig. 9b. Now the carbonyl carbon atom of D-alanine is susceptible to another nucleophilic attack from -NH₂ group of glycine amino acid from another adjacent chain as shown in Fig. 9c. This results in the formation of

cross-linkage between two different but adjacent chains and the transpeptidase enzyme is regenerated for further cross-link formation.

Step II: The second step is the enzyme inhibitory action of penicillin drug molecule. The penicillin molecule mimics the acyl-D-alanyl-D-alanine structure and it occupies an active site of transpeptidase enzyme. The possible organic reaction mechanism involves a nucleophilic attack from -OH group of serine on a susceptible carbonyl carbon of β -lactam ring of penicillin drug molecule which is key interacting site. It is shown in Fig. 10a. The strong covalent bond formation results in irreversible enzyme inhibition. The unavailability of enzyme active site for acyl-D-alanyl-D-alanine creates an inhibitory action for cross-link formation in cell wall. A possible inhibitory action of penicillin where it binds and blocks enzyme active site is shown in Fig. 10b. This results in weakening of bacterial cell wall.

3.1.2 Organic Chemistry of Non- β -Lactam Antibiotics

3.1.2.1 Fluoroquinolones

Fluoroquinolones continue to rank among the most clinically significant classes of antibacterial drugs, employed in managing a broad spectrum of bacterial infections spanning respiratory tract infections, bloodstream infections, gynaecological infections, sexually transmitted infections, prostatitis, spontaneous bacterial peritonitis, urinary tract infections, various skin, bone, and soft tissue infections, as well as community-acquired pneumonia [34].

Fluoroquinolones such as ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin (Fig. 11) could exert the antibacterial activity through binding to type II bacterial topoisomerase enzymes, DNA gyrase and topoisomerase IV [35].

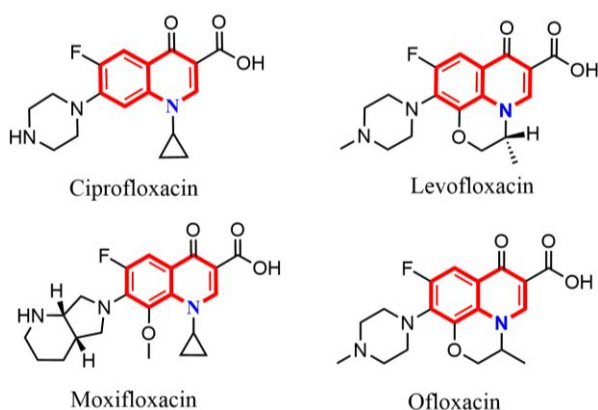


Fig. 11 Chemical structures of fluoroquinolones

The common feature of DNA strand cleavage by attack of active-site tyrosine residue of enzyme. The possible nucleophilic attack occurs via phenolic hydroxyl group on phosphorus atom in the DNA backbone. This results in the formation of possible covalent adduct which is shown in Fig. 12. The enzyme temporarily holds the broken strand ends to prevent genome fragmentation while structural changes occur. Quinolone binds and inhibits enzyme and prevents bacterial growth [36].

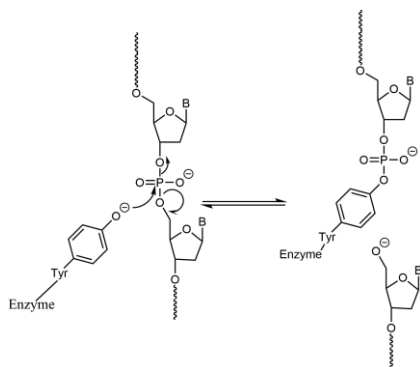


Fig. 12 Enzyme catalysed DNA strand cleavage

3.1.2.2 Tetracycline

Tetracycline as shown in Fig. 13 belongs to the bacterial aromatic polyketide family, and its four fused rings (the "tetra-cycle" that gives the class its name) are assembled biosynthetically by a type II polyketide synthase, which builds the poly- β -ketone backbone through successive decarboxylative condensation of malonyl-CoA extender units, followed by

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modifications by cyclases, oxygenases, and transferases [37]. Tetracycline exerts its antibacterial effect by inhibiting bacterial protein synthesis, targeting the bacterial ribosome selectively over the eukaryotic one [38]. Tetracyclines passively diffuse through pores in the bacterial membrane and accumulate intracellularly to act on the ribosome, where they prevent attachment of aminoacyl-tRNA to the 30S ribosomal subunit in a reversible fashion to stop protein synthesis [39].

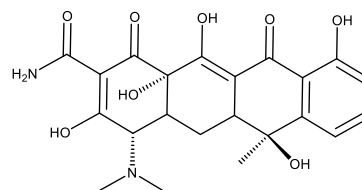


Fig. 13 Chemical structure of tetracycline

The organic chemistry of tetracycline's core scaffold is not incidental. The mechanism strongly depends on metal chelation, and specifically through carbon atoms bearing the enolic/ketone system, phenolic hydroxyls, and carbonyl amide system [40].

3.2 Antihypertensive Drugs

3.2.1 ACE Inhibitor

ACE inhibitors (Angiotensin-Converting Enzyme inhibitors) are a class of drugs used mainly to treat hypertension, heart failure, and to provide renal protection (especially in diabetic nephropathy). ACE is a zinc metalloprotease (enzyme) that converts angiotensin I (inactive) into angiotensin II (a potent vasoconstrictor), and also breaks down bradykinin (a vasodilator) [41].

Captopril structure shown in Fig. 14 is an ACE (angiotensin-converting enzyme) inhibitor used to treat hypertension and heart failure. It was one of the first orally active ACE inhibitors, developed in the 1970s [42]. The overall scaffold is a peptidomimetic. It structurally resembles a dipeptide analogue of the C-terminal Ala-Pro sequence of angiotensin I, allowing it to competitively occupy the ACE active site. Captopril's structure is built from two key fragments joined by an amide bond:

- Proline ring: It is a five-membered pyrrolidine ring bearing a carboxylic acid group (-COOH) at the α -carbon. This mimics the C-terminal proline found in angiotensin I, the natural substrate of ACE.
- A thiol group (-SH): at the terminal carbon is the key pharmacophore.
- A methyl branch at the α -carbon adjacent to the carbonyl.

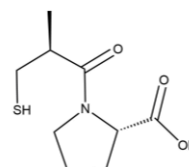


Fig. 14 Chemical structure of captopril

3.2.2 Renin Inhibitors

Renin is an aspartyl protease enzyme that occupies a pivotal, rate-limiting position at the very apex of the Renin-Angiotensin-Aldosterone System (RAAS), the principal physiological cascade governing blood pressure homeostasis, fluid balance, and electrolyte regulation [43].

Renin is initially synthesized as an inactive precursor, pre-prorenin, which undergoes proteolytic cleavage to form prorenin, and subsequently to the active enzyme, renin, through removal of a 43-amino acid pro-segment. Structurally, renin is a two-domain, bilobal aspartyl protease with a deep active-site cleft situated between the N- and C-terminal domains [44]. Renin's well-characterized crystal structure (e.g., PDB entries such as 2REN, 1HRN, 3VCM) has made it a favourable target for structure-based drug design and molecular docking studies [45].

3.2.2.1 Mechanism of Action in the RAAS Cascade

Renin catalyses the first and rate-limiting step of the RAAS cascade: the cleavage of the N-terminal decapeptide from angiotensinogen (a glycoprotein synthesized primarily by the liver) to generate angiotensin I, an inactive decapeptide. Angiotensin I is subsequently converted to the biologically active octapeptide angiotensin II by angiotensin-converting enzyme (ACE), primarily in the pulmonary vascular endothelium. Angiotensin II exerts its hypertensive effects collectively through direct vasoconstriction, stimulation of aldosterone secretion from the adrenal cortex and promotion of vascular and cardiac hypertrophy over the long term.

The drug molecule aliskiren shown in Fig. 15 retains a 4-hydroxy-5-amino octanamide backbone. All four stereo-centers are critical. Renin's chiral active site is highly stereospecific and even single stereo-center inversion likely to reduce binding affinity drastically.

The terminal carbamoyl-methyl-propyl-amide group is polar which engages residues near the enzyme surface improving binding and contributing to aqueous solubility [46].

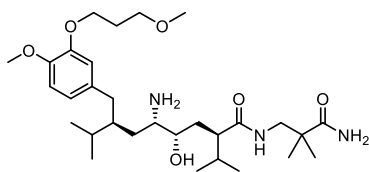


Fig. 15 Chemical structure of aliskiren

3.3 Analgesics

Analgesics are a class of drugs used to relieve pain without causing loss of consciousness, commonly known as painkillers. They work through various mechanisms depending on their type: non-opioid analgesics (like NSAIDs such as aspirin and ibuprofen) primarily inhibit the cyclooxygenase (COX) enzymes, reducing prostaglandin synthesis and thereby decreasing inflammation and pain sensitivity at the site of injury, while also providing antipyretic effects [47].

3.3.1 COX Inhibitor: Aspirin Drug

Aspirin (acetylsalicylic acid) relieves pain primarily by inhibiting the enzyme cyclooxygenase (COX). Step-by-step pathway of action of aspirin shown in Fig. 16 [48]. Step I: Tissue injury/inflammation makes cell membranes to release arachidonic acid; Step II: COX enzymes convert arachidonic acid into prostaglandins; Step III: Prostaglandins make nerve endings more sensitive to other pain mediators like bradykinin and histamine; Step IV: Aspirin irreversibly acetylates a serine residue on COX enzyme's active site and blocks prostaglandin synthesis shown in Fig. 17 [49].

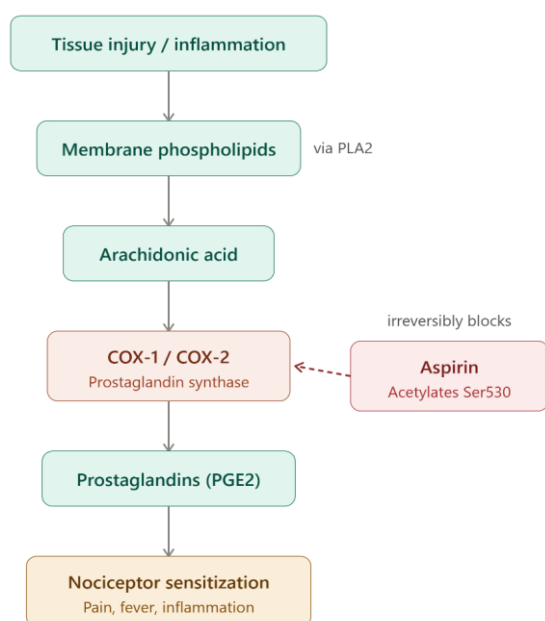


Fig. 16 COX enzyme inhibitor action of aspirin

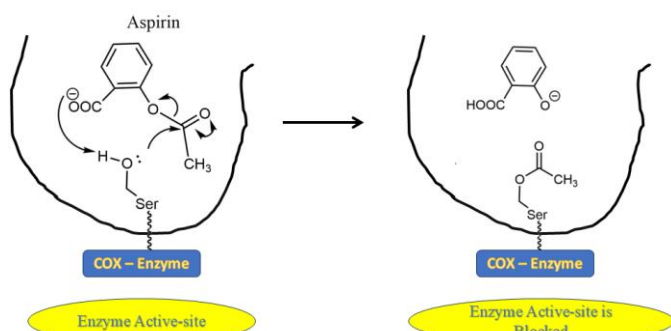


Fig. 17 Acetylation of serine residue and inhibition of COX enzyme by drug aspirin

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3.3.2 COX Enzyme Inhibitor: Diclofenac Drug

Diclofenac drug molecule exerts its analgesic, anti-inflammatory, and antipyretic effects primarily by non-selectively inhibiting the cyclooxygenase enzymes, COX-1 and COX-2, though it shows a modest preference for COX-2 [50].

Its carboxylic acid group forms hydrogen bonds with the arginine residue at the apex of the COX active site. The interactions seen with most other carboxylic acid-containing NSAIDs. While its dichlorophenyl ring occupies the hydrophobic channel, sterically blocking arachidonic acid from accessing the catalytic site, as shown in Fig. 18. This process halts and reduces the production of prostaglandins, which normally sensitize peripheral nociceptors, promote vasodilation and vascular permeability at inflamed sites, thereby lowering pain perception and suppressing local inflammation, while reduced hypothalamic prostaglandin levels further account for its antipyretic action [51].

Diclofenac has also been reported to exert a modest inhibitory effect on the lipoygenase pathway, limiting leukotriene formation, which may contribute an additional dimension to its anti-inflammatory profile beyond classical COX inhibition alone [52].

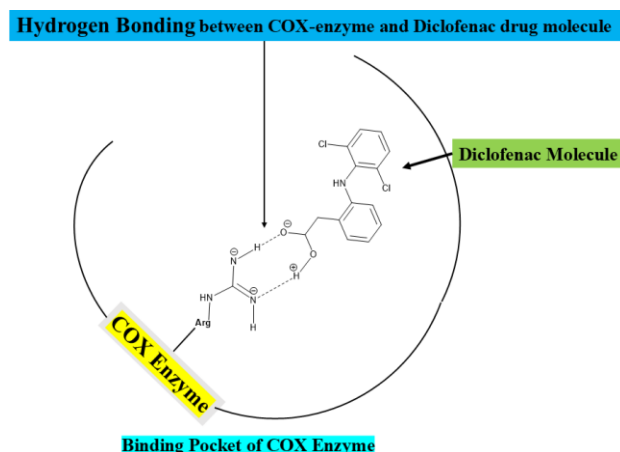


Fig. 18 Possible diclofenac drug molecule in binding pocket of COX-enzyme

3.4 Anticancer Drugs

3.4.1 DNA Alkylating Agents: Sulphur Mustard Drugs

The DNA-alkylating agents represent one of the oldest and most widely used classes of chemotherapeutic drugs, originating from the observation of myelosuppressive effects of sulphur mustard gas in World War I soldiers, which led to the development of nitrogen mustards as the first clinically used anticancer alkylating agents in the 1940s [53]. The possible organic reaction mechanism followed by these drugs involves following steps:

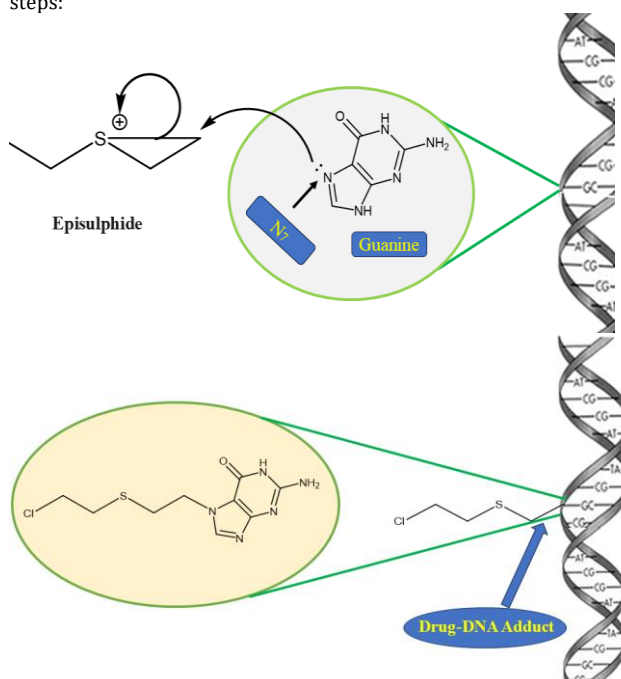


Fig. 19 a) Formation of episulphide b) nucleophilic attack by guanine nitrogen on Episulphide c) formation of drug-DNA adduct

Step I: Formation of episulphide by neighbouring group participation Fig.19a. The lone pair of sulphur atom attacks through neighbouring group participation on neighbouring carbon atom which contains chlorine as a leaving group. This results in the formation of episulphide or episulphonium ion which is now susceptible to attack by guanine-DNA.

Step II: The nucleophilic attack from N-7 position of guanine-DNA takes place shown in Fig. 19b. In DNA actually the most nucleophilic part is the bases. The nitrogen bases are nucleophiles. Out of these nucleophiles' guanine has a very strong nucleophilic nitrogen in the form of imidazole because guanine is imidazole fused pyrimidine. This imidazole nitrogen called N₇ is the most nucleophilic part.

Step III: A covalent bond is formed between guanine and drug. This forms a covalent adducts which results in intra-strand and inter-strand cross-links shown in Fig. 19c.

These cross-links prevent proper DNA strand separation during replication and transcription process, this triggers DNA damage response pathways, cell cycle arrests and ultimately apoptosis particularly in rapidly dividing malignant cells.

The sulphur mustards are too toxic for systemic use; this foundational neighbouring group participation (NGP) mechanism directly inspired the development of nitrogen mustards (like mechlorethamine and chlorambucil). Nitrogen mustards utilize an aziridinium (nitrogen-based) intermediate which resembles the structure to the episulphide (or episulphonium ion) to target rapidly dividing cancer cells [54].

3.4.2 DNA Alkylating Agents: Nitrogen Mustard Drugs

Nitrogen mustard drugs represent one of the earliest and most important classes of alkylating anticancer agents, tracing their origin to the toxic effects of sulphur mustard which were observed in World War I and World War II soldiers [55]. The recently approved nitrogen mustard drugs are as shown in Fig. 20. They are bifunctional alkylating agent (nitrogen mustard) that exerts its cytotoxic effect through DNA cross-linking [56].

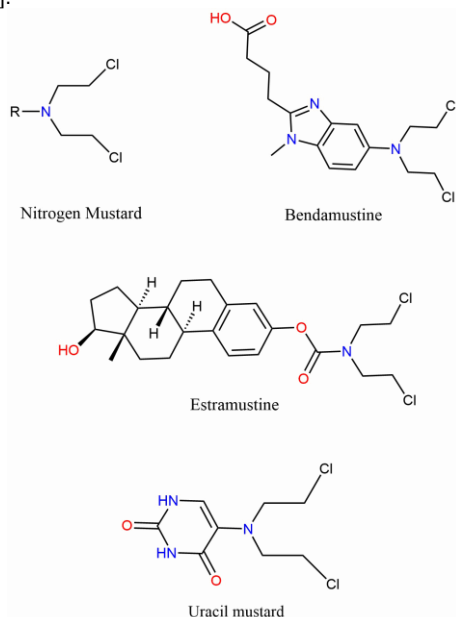


Fig. 20 Chemical structures of nitrogen mustard drugs

The organic reaction mechanism of mechlorethamine is as follows:

Step 1: Formation of an Aziridinium Ion: The bis (2-chloroethyl) amine group of mechlorethamine undergoes intramolecular cyclization or neighbouring group participation, where a chlorine atom is displaced by the adjacent nitrogen lone pair, forming a highly reactive, strained aziridinium ring [57] intermediate as shown in Fig. 21a.

Step 2: Nucleophilic Attack by DNA: The N₇ position of guanine (a highly nucleophilic site due to the electron-rich imidazole ring) attacks the electrophilic carbon of the aziridinium ring, opening the ring and forming a covalent alkyl linkage between the drug and the DNA base [58] as shown in Fig. 21b.

Step 3: Formation of the Second Aziridinium Ion and Cross-Linking: Mechlorethamine is bifunctional (bearing two chloroethyl arms), the process repeats on the second arm, forming a second aziridinium ion that reacts with a guanine N₇ on the opposite DNA strand (or a nearby position on the same strand) [59] Fig. 21c.

This results in a covalent cross-link between two guanine bases, most often on opposite strands of the DNA double helix, physically linking the two strands together.

<https://doi.org/10.30799/jacs.284.26120504>

Cytotoxic consequence of this cross-linking prevents DNA strand separation during replication and transcription, blocking DNA synthesis and RNA transcription. The cell recognizes this damage as irreparable, triggering apoptosis, particularly in rapidly dividing malignant T-lymphocytes [60].

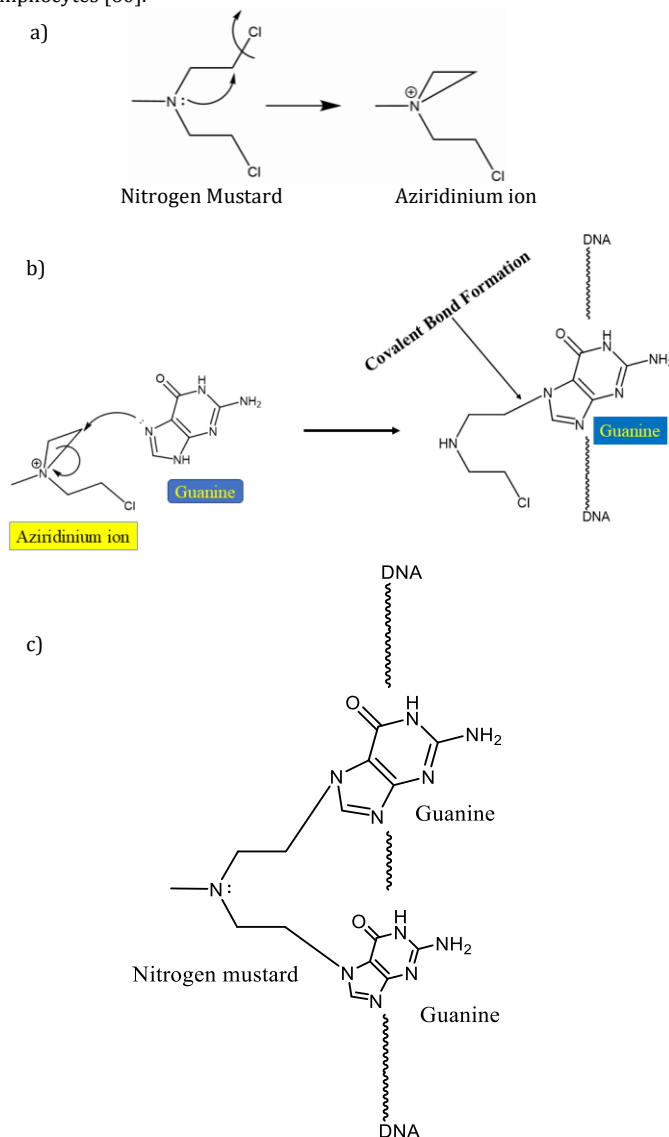


Fig. 21 a) Formation of aziridinium ion, b) formation of drug-DNA adduct and c) cross-link formation

4. Conclusion

The journey of a simple organic molecule to a life-saving medicine illustrates one of chemistry's most profound contributions to human health. As this review has shown, the principles of organic chemistry like functional group reactivity, stereochemistry, molecular geometry, and non-covalent interactions are not merely academic abstractions but the very foundation upon which rational drug design is built.

This review underscores the indispensable role of organic chemistry in elucidating the molecular basis of drug action across diverse therapeutic classes, demonstrating that pharmacological efficacy is ultimately governed by precise, structurally-defined chemical interactions between drug molecules and their biological targets. Across β -lactam antibacterials, the strained four-membered ring system was shown to be the chemical linchpin of activity, undergoing nucleophilic acyl substitution by the serine hydroxyl of penicillin-binding proteins to irreversibly acylate and inactivate the transpeptidase enzyme, thereby disrupting bacterial cell wall biosynthesis; in contrast, non- β -lactam antibacterials illustrated that antimicrobial action need not depend on ring strain-driven electrophilicity alone, instead exploiting alternative organic mechanisms such as DNA gyrase inhibition, protein synthesis interference, or membrane-targeted disruption, reflecting the chemical versatility available to medicinal chemists in circumventing resistance mechanisms like β -lactamase-mediated hydrolysis. In the domain of antihypertensive therapy, ACE inhibitors exemplified the strategic use of a zinc-chelating functional

group, most notably the sulfhydryl or carboxyl moiety, to competitively occupy the active site of a zinc metalloprotease, while renin inhibitors such as aliskiren demonstrated a more sophisticated application of transition-state analog chemistry, wherein a non-hydrolysable dihydroxyethylene-derived pharmacophore was rationally engineered to mimic the tetrahedral gem-diol transition state of aspartyl protease catalysis, achieving potent and selective inhibition without the metabolic liabilities of earlier peptidic candidates. The analgesic agents examined, aspirin and diclofenac, further reinforced the centrality of nucleophilic acyl substitution and hydrogen-bonding chemistry in enzyme inhibition, with aspirin's irreversible acetylation of the serine residue within cyclooxygenase active sites and diclofenac's carboxylate-mediated hydrogen bonding to Tyr385/Ser530 both illustrating how subtle differences in functional group positioning and binding mode can distinguish reversible from irreversible inhibition, and selective from non-selective enzyme engagement. Finally, the anticancer alkylating agents, sulfur mustard and its therapeutically repurposed nitrogen mustard derivatives, revealed one of the most chemically elegant yet biologically consequential mechanisms: the intramolecular neighbouring-group participation that generates a highly electrophilic aziridinium ion, capable of sequential nucleophilic attack by guanine N7 positions on DNA to form cytotoxic interstrand cross-links, a mechanism whose origins in wartime chemical toxicology paradoxically gave rise to the foundation of modern cancer chemotherapy.

Collectively, these diverse case studies affirm that rational drug design and mechanistic pharmacology are fundamentally rooted in organic reaction principles, including nucleophilic substitution, electrophilic reactivity, hydrogen bonding, stereochemical specificity, and transition-state stabilization. A deep understanding of these organic chemical foundations not only clarifies how existing drugs exert their therapeutic effects but also provides a rational framework for the continued design of next-generation therapeutics. As drug discovery increasingly integrates computational and structure-based design methodologies, the organic chemistry principles reviewed here will remain foundational, bridging classical mechanistic understanding with modern rational therapeutic innovation. The process of drug discovery continues to evolve. It is increasingly guided by structural biology, computer-aided design, and a deeper understanding of biomolecular interactions but organic chemistry will remain the indispensable language through which the next generation of cures is written. Ultimately, behind every effective medicine lies not magic, but molecules which are precisely designed, synthesized, and optimized through the enduring principles of organic chemistry.

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