Introduction

- Medicinal chemistry is the branch of science which explains design & production of compounds that can be used for prevention, treatment or cure of human & animal diseases.
- It includes study of already existing drugs of their biological properties & their SAR.
- As per IUPAC:-
- It concerns discovery, development, identification & interpretation of mode of action of biologically active compounds at molecular level.

Introduction

- Medicinal chemistry is a discipline at the intersection of chemistry & pharmacology that involves identification, synthesis & development of new chemical entities that are suitable for medical or pharmaceutical use.
- Medicinal chemistry is an interdisciplinary science combining variety of subjects such as organic chemistry, phytochemistry, pharmacology, toxicology, molecular biology, biochemistry, computational chemistry, physical chemistry & statistics.
- It also includes the study of existing drugs, their pharmacological properties, toxic effects & their quantitative structure-activity relationships (QSAR).

Drugs

- Definition:- All chemicals other than food that affect living processes.
- If it effects helps body then drug is medicine.
- If causes harmful effects on body, it is poison.
- The same chemical can be medicine as well as poison depending on conditions of use & person using it.
- "Medicinal agents used for diagnosis, prevention, treatment of symptoms & cure of diseases."
- All drugs have potential for producing more than one response. Some adverse drug responses which are unavoidable are appearing at therapeutic doses are termed as Side Effects, but Adverse drug effects appearing at extreme drug doses are described as Toxic Effects.

Classification of Drugs

- By origin:- Sources of drugs
- Natural:-
  - Plants:- Vincristine, taxol, digoxin, quinine, reserpine
  - Animals:- Gonadotropins, heparin, insulin
  - Minerals:- Cisplastin anticancer agent
  - Micro-organisms:-Penicillin, streptomycin, tetracycline
  - Marines:- Ziconotide (Prialt), cone snail toxin to treat severe neurotic pain; bryo-statin-like compounds as anticancer agent.
- Semisynthetic:- 6-APA from fungus *Penicillium chrysogenum.*
- Biosynthetic:- Biosynthetic human insulin, hepatitis vaccine.
- Synthetic:- Aspirin, paracetamol. Most widely used due to inexpensiveness, ease of quality control, mass production & therapeutic efficacy.

Classification of Drugs

- By action:- Asthma
- By Therapeutic Use:- It affects normal dynamic processes of the body. Eg. Cardiovascular Agents i.e., Antihypertensive, anti-anginals, anti-arrythmics, vasodilators.
- By Site of Drug Action:- Eg. Cocaine, alcohol
- By Chemical structure:- or functional groups such as hydrocarbons, alcohols, acids, phenols.

Process of Drug Discovery

- Discovery:- The initial step of drug discovery involves the identification of new active compounds, often called hits or leads, which are found by screening many compounds of synthetic or natural sources for their targeted biological properties.
- More often, the hits use to come from synthetic sources, such as historical compound collections & combinatorial chemistry.

Process of Drug Discovery

- Optimization:- The second step involves further chemical alterations on SAR basis to enhance the biological & physicochemical properties of a given candidate compound library.
- Chemical modifications can improve binding property & interaction (pharmacophores) of drug candidate compounds, their affinities & pharmacokinetics or indeed their reactivity & stability during their metabolic degradation.
- As per IUPAC:-
- Pharmacophore is the ensemble of steric & electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure & to trigger (or to block) its biological response.

Process of Drug Discovery

- Among the methods that have contributed to the quantitative metabolic prediction, a recent example is substrate product occurrence ratio calculator (SPORCalc).
- The identified pharmacophore plays an important role in finding the lead compounds, which exhibit the most potency, the best pharmacokinetics & least toxicity.

Process of Drug Discovery

- The QSAR molecular modeling tools, such as comparative molecular field analysis (CoMFA) & comparative molecular similarity index analysis (CoMSIA), which leads to tabulated data & first- & second-order equations.
- Among the theories related to these, the most relevant being Hansch's analysis that involves Hammett electronic parameters, steric parameters & log P (lipophilicity) parameters.
- Development:- Final step involves rendering the lead compounds that are suitable for use in the clinical trials after their successful pharmacodynamic optimization in clinical trials, the optimization of the synthetic route for bulk production & the preparation of a suitable drug formulation.

History & Development of Medicinal Chemistry

- Many years ago people used a wide range of natural products for medicinal purpose. These products obtained from animals, vegetables & mineral sources were sometimes very effective. But many of the products were found to be toxic & it is interesting note that the Greeks used the same word pharmakon for body poisons & medicinal products. Literature about the ancient remedies was not readily available for use until the invention of the printing press in the 15^{th} century.

History & Development of Medicinal Chemistry

- The therapeutic properties of plants were described by the Ancient Greeks & by the Romans & are recorded in the writings of Hippocrates, Dioscorides, Pliny & Galenus.
- Some metals & metal salts were also used at this time (metal-based drugs, eg. Cisplastin-Anticancer agent).
- In the middle ages various 'Materia Medica' & pharmacopeias brought together traditional uses of plants.
- Exploration in the seventeenth & eighteenth centuries led to the addition of a number of useful tropical plants to those of European origin.

History & Development of Medicinal Chemistry

- General anesthetics were introduced in surgery from 1842 onwards, diethyl ether (1842), nitrous oxide (1845) & chloroform (1847).
- Antiseptics such as iodine (1839) & phenol (1860) also made an important contribution to the success of surgery.
- The hypnotic activity of chloral (trichloroethanal) (1869) was also reported.
- Many of the developments after the 1860s arose from the synthesis of compounds specifically for their medicinal action.
- Although use of willow bark as a pain killer was known to the herbalists, the analgesic activity of its constituent salicin & of salicylic acid were developed in the 1860s & 1870s.

History & Development of Medicinal Chemistry

- p-Hydroxyacetanilide (paracetamol) & phenacetin (1886) were also recognized as pain killers.
- Acetylation of salicylic acid to reduce its deleterious effect on the stomach led to the introduction of aspirin in 1899. However it mode of action was not established until 1971.

History & Development of Medicinal Chemistry

- In the 19th century, extraction procedures & pure isolated entities (i. e. pure form of substances, such as alkaloids, carbohydrates, etc.) were reported to be in existence. Some of the isolated compounds were proved to be satisfactory as therapeutic agents. The majority of the plant or natural products were believed to be too toxic, such as morphine (1805) & cocaine, which was extensively prescribed by physicians.

History & Development of Medicinal Chemistry

- Various modifications of the dialkylamino esters of aromatic acids modelled on part of the structure of cocaine led to benzocaine (1892) & procaine (1905).
- The barbiturates, veronal (1903) & phenobarbital (1911) were introduced as sleeping tablets.
- Once ideas of chemical structure were formulated in the mid-ninteenth century, the first theories of the relationships between chemical structure & biological activity began to emerge.
- Thus Crum-Brown & Fraser (1869) noted that a 'relationship exists between the physiological action of a substance & its chemical composition' leading to the idea that cells can respond to the signals from specific molecules.

History & Development of Medicinal Chemistry

- In the search of finding less toxic medicines than these, on the basis of natural sources, resulted in the introduction of synthetic substances such as drugs in the late 19th century. These improvements were based on the structures of known biologically active compounds, now referred to as 'leads'. By adopting this approach, structurally related compounds were developed for the targeted activity. These lead-related compounds are refereed to as analogues.

History & Development of Medicinal Chemistry

- In 1910, Paul Enrlich & Saccachiro Hata synthesized the first synthetic drug, Arsphenamine, by combining synthesis with reliable biological screening & evaluation procedures. At the beginning of 19^{th} century, Enrlich recognized the fact that expected biological & toxic properties of drugs were important in their screening. He demonstrated that the more effective drug showed a greater selectivity for target microorganism than its host. Consequently, to compare the effectiveness of different compounds, he expressed drug selectivity by a term known as chemotherapeutic index, which he defined as follows:
- Chemotherapeutic index = Minimum effective dose/Maximum tolerable dose

History & Development of Medicinal Chemistry

- On the basic of this concept, over 600 structurally related arsenic compounds were tested & catalogued in terms of the therapeutic index by Paul & Hata. This has led to discovery of Arsphenamine (Salvarsan, Hoechst, German) in 1909, that could cure mice infected with syphilis. This drug was found to be effective in humans, but it must be used with extreme care, as it is very toxic. However, it was replaced by penicillin in mid-1940s.

History & Development of Medicinal Chemistry

- Enrlich' method of approach is still one of the basic techniques used to design & evaluate new drugs in medicinal chemistry. Recently, chemotherapeutic index has been updated to take into account the variability of individuals & is how defined as its reciprocal, therapeutic index or ratio.
- Therapeutic index = LD_{50}/ED_{50}
- Where LD_{50} is lethal dose that is required to kill 50% of the test animals or microorganisms & ED_{50}

Is the effective dose that is required to produce a therapeutic response in 50% of the test animals or microorganisms. However, the therapeutic index values can only be used as a limited guide of relative usefulness for the different compounds.

History & Development of Medicinal Chemistry

- Apart from this, serendipity has played a large part in the discovery of drugs. For example, the development of penicillin by Florey & Chain was possible only because of Alexander Fleming, who noted the inhibition of *Staphylococcus* by *Penicillium notatum*. Despite our increases knowledge base, it is still necessary to pick a correct starting point for an investigation, if a successful outcome is to be achieved. However, modern techniques, such as computerized molecular docking & combinatorial chemistry introduced in 1970s & 1990s, respectively, are likely to reduce the number of intuitive discoveries.

History & Development of Medicinal Chemistry

- The action of acetylcholine on nerve tissue has been recognized in the late 19th century. Barger & Dale (1910) examined the response of various tissues to acetylcholine agonists & showed that there were different receptor sub-types; some responding to muscarine & others to nicotine.
- The 1920s & 1930s saw the recognition of vitamin deficiency diseases & the elucidation of the structure of various vitamins.
- It was also a period in which there was exposure of many Europeans to tropical diseases.
- The iodinated quinolines such as entero-vioform were introduced to combat amoebic dysentery & complex dyestuff derivatives such as suramin & germanin were developed in the 1920s to treat sleeping sickness.

History & Development of Medicinal Chemistry

- Synthetic anti-malarials such as pamaquine (1926), mepacrine (1932) & later chloroquine (1943) & paludrine (1946) were introduced as quinine replacements.
- In 1935 Domagk observed the anti-bacterial action of the sulfonamide dyestuff, prontosil red, from which the important family of sulphonamide anti-bacterial agents were developed.
- In 1940-1941 Chain, Florey & Heaton isolated benzylpenicillin. After considerable chemical work, the beta-lactam structure for the penicillins was established.

History & Development of Medicinal Chemistry

- The structures of steroid hormones were established in the 1930s & 1940s. The discovery in 1949 of the beneficial effect of cortisone in alleviating the inflammation associated with rheumatism provided the stimulus for synthetic activity in this area.
- A number of anti-inflammatory semi-synthetic corticosteroids such as prednisolone, betamethasone & triamcinolone became available in the late 1950s & 1960s.
- A number of developments took place in the 1960s, which had been introduced as a sedative, when used by pregnant women, led to the birth of deformed children.
- The logical development during the 1960s of histamine antagonists for the treatment of peptic ulcers led to cimetidine (1976) & then ranitidine (1981).

History & Development of Medicinal Chemistry

- Adrenaline (epinephrine) was the first substance to be recognized as a hormone (1901). The adrenergic receptors were divided in the alpha & beta receptors by Ahlquist in 1948 based on their responses to selective agonists, eg., isoprenaline.
- The beta receptors were subsequently subdivided by Lands. This, together with an understanding of the metabolism of adrenalin (epinephrine) led to the discovery of salbutamol (1976) as a selective beta2 agonist in the treatment of asthma.

History & Development of Medicinal Chemistry

- Medicinal chemistry has revolutionized the treatment of mental disease during the second half of the 20th century. An increasing understanding of the role of various neurotransmitters in the brain has played an important part in this.
- A number of anti-depressants & anti-psychotic agents were developed in the 1950s including phenothiazine & chlorpromazine.
- The discovery in 1950 that a dopamine deficiency was associated with the neurodegenerative disease known as Parkinson's disease, led to various strategies to overcome this dopamine deficiency.
- A significant step forward came in 1959 when methods for the commercial isolation of the 6-APA core of the penicillins were developed. This permitted the synthesis of a range of semi-synthetic penicillins with enhanced stability & activity.
- Methicillin, ampicillin & amoxycillin were introduced in 1960, 1961 & 1964 respectively.

History & Development of Medicinal Chemistry

- The related cephalosporin beta lactum antibiotics, cephaloridine, cephaloxin & cefaclor were introduced in 1964, 1067 & 1974 respectively.
- Inhibition of the sterol component of the fungal cell wall has provided the basis of the action of a family of antifungal agents known as the azoles. These include micoconazole (1972), ketoconazole (1980) & fluconazole (1988).

History & Development of Medicinal Chemistry

- The identification of the viral origin of HIV-AIDs in 1983 led to the introduction of azidothymidine (AZT) in 1987 to combat this disease.
- More recently (1999) zanamavir (Relenzas) & oseltamivie (Tamiflus) have been developed for the treatment of 'flu'.
- The impact of genomics on medicine & the recognition of genetic differences associated not only with specific diseases but also with the susceptibility to disease are likely to lead to significant new treatments & refinements of older treatments.
- While many of these may involve the surgical introduction of particular cells, their ultimate success will retain a medicinal chemistry input. The diagnostic test for many of these conditions also requires the skill of the medicinal chemist.

References

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