Structure and physicochemical properties in relation to drug action

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In this review, classification of drugs, chemical structure, and biological activity, examples of pharmacological activities of some structural moieties, bioisosterism, physicochemical properties in relation to drug action, drug–receptor theory, acid–base chemistry in formulation and biodistribution of the drug, quantitative structure–activity relationship, and molecular docking are briefly presented with examples.

Keywords:
bioisosterism, drug distribution, molecular modeling, pharmacological effects, physicochemical properties

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Introduction

Classification of drugs

Drugs are chemical molecules that may be arranged and classified according to their medical use into the following: (a) drugs that act on the various physiological functions of the body, which can be grouped together as pharmacodynamic agents, for example sedatives, analgesics, antipyretic and antirheumatic agents, antipsychotic, antihistaminic and antiallergic drugs, anti-inflammatory agents, diuretics, cardiovascular agents and drugs acting on the heart, and adrenergic and cholinergic agents and drugs acting on the gastrointestinal tract (GIT), etc., (b) central nervous system (CNS) Agents, for example antidepressant drugs, anesthetic, hypnotic drugs, etc., (c) drugs that are used to fight pathogenic organisms can be grouped together as chemotherapeutic agents, for example sulfonamides, antibiotics, anti-infective agents, antimicrobial, antiamoebic, antifungal agents, antiviral agents, anticancer agents, antimalarial agents, etc., and (d) supplement agents, for example vitamins, dietary supplements, etc. [1,2].

In general, the chemical structure of any drug profoundly affects both its pharmacodynamic and pharmacokinetic properties, irrespective of the subclass that drug belongs to. In the following sections, we will discuss the impact of the structural features of the drugs on the pharmacological actions, illustrated with many examples from various drug families.

Chemical structure and biological activity

Pharmacological activities of important structural moieties

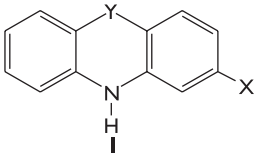
Correlating the structural and functional properties of a wide variety of natural products, it has become clear that particular common pharmacophoric units of these molecules are essential for certain pharmacological actions that they share. This observation was used as a guiding principle in designing analogues with improved specificity and lowered toxicity [1,2].

It has been found that several structural units and fragments have been associated with particular types of pharmacological activity. Some of these structural moieties with pharmacological activities are presented in Table 1.

Bioisosterism

The synthesis of structural analogues of a certain compound or drug has been carried out by substitution of an atom or group of atoms in the parent compound for another with similar electronic and steric characteristics. The rationale behind this procedure is the principle called bioisosterism [48]. The isosters should be isoelectric, that is should have the same total charge. Examples of such pairs of isosters are CO and NO_2, CO_2 and N_2O, N_3– and NCO–, and CH_2N_2 and CH_2 = CO. In the aromatic ring system, the vinylene group (–CH = CH–) of benzene, the sulfur of thiophene (–S–), and nitrogen (–N =) of pyridine are examples of isosteric groups [49].

Among the heterocyclic ring systems, the interchange of –O– or –S– by –NH– or $–CH_2–$ is a common practice and examples can be found among tranquilizers and antidepressants as indicated by the chemical structure of the compound (**I**) [1,2].



(I) X= Cl, F
Y= O, S, CH_2

The bioisosterism has been applied to the corresponding derivatives of benzene and thiophene, respectively, whereas furan and pyrrole do not show a close resemblance to benzene [1,2].

A close steric similarity for thiophene and benzene derivatives has been explained in terms of hybridization in the sulfur atom, which allows participation of the pd2 orbital [48].

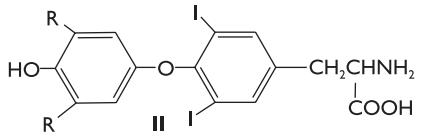
According to the definition of bioisosterism, groups such as halogens, OH, NH_2, and CH_3 can be interchanged in isosters with retention of biological activity. Examples of such molecules are found in thyromimetic compounds (Levothyroxine, **IIa**), which is used in replacement therapy of decreased thyroid function [50], and compounds with antihistaminic activities (Tripelenamine, **III**) [51].

Table 1 Pharmacological activities of some structural moieties

Type of structure	Chemical group	Example of drug compound	Mode of action	Pharmacological activities
R–COOH	Acids	Propionic acid [3]	(a)	Fungistatic
R–CH(OH)–COOH		Chaulmogric acid [4]	(b)	Mycobacteriostatic
HO–Ar–COOH		Mandelic acid [4]	(c)	Bacteriostatic
		Salicylic acid (aspirin) [5]	(d)	Antipyretic, antirheumatic
R–OH	Alcohols	Benzyl alcohol [6]	(e)	Local anesthetic
		Ethyl alcohol [7]	(f)	Sedative, excitant
		2-Propanol [8]	(g)	Anticonvulsant
		Propranolol [9]	(h)	Antihypertensive
$R–CONH_2$	Amides	Hydantoin [10]	(i)	Anticonvulsant
		Procainamide [11]	(j)	Cardiotonic
		Nikethamide [12]	(k)	Analeptic
		Lidocaine [13]	(e)	Local anesthetic
		Lisergic acid-diethyl-Amide [14]	(l)	Psychotomimetic
$R_2–NH(CH_2)_2–Cl$	Amines	Dibenamine [15]	(m)	Sympatholytic
$RN(CH_2CH_2Cl)_2$		Nitrogen mustard [16]	(n)	Anticancer
RNHCl		Chlorpromazine [17]	(l)	Antipsychotic
Heterocyclic amines		Chloroquine [18]	(o)	Antimalarial
ArC(OH)CR–NHR		Phenethylamine [19]	(p)	Pressor
$R_2CHO(CH_2)_2–_NR2$		Amphetamine [20]	(q)	Central nervous system stimulant
		Serotonin [21]	(r)	Neuromodulator
		Diphenhydramine [22]	(s)	Antihistaminic
$ArCH(OH)(CH_2)n\text{-}NR_2$	Amino alcohols	Nor-epinephrine [23]	(p)	Vasopressor
		Ephedrine [24]	(l)	Sympathomimatic
		Quinine [25]	(o)	Antimalarial
$Ar_2C(COR)(CH_2)_2–_NR2$	Amino ketone	Methadone [26]	(t)	Analgesic
N^+R_4	Ammonium compounds	Tetraethylammonium [27]	(u)	Depressor
		Acetylcholine [28]	(v)	Cholinergic
		Hexamethonium [29]	Nicotinic acetylcholine receptor antagonist	
$H_2N–Ar–COR$	Esters	Benzocaine [30]	(e)	Local anesthetic
R_2O	Ethers	Ethyl ether [31]	(g)	Anesthetic
RNHC = NHNHR	Guanidine	Chloroguanide [32]	(o)	Antimalarial
		Guanethidine [33]	(w)	Antihypertensive
R–Cl	Halogenated compounds	Ethyl chloride [34]	Because of its lipid solubility and halogenated property	Antihelmintic
$CHCl_3$Iodinated compounds		Chloroform [35]	(g)	AnestheticRadiopaque
Fluoro compounds		Fluorocorticoids [36]	Class of steroidal hormone	Anti-inflammatory
R–H	Hydrocarbons	Cyclopropane [37]	(g)	Anesthetic
(HO)–Ar–COR	Ketones	Acetophenone [38]	(f)	Sedative
		Phenyl-indandione [39]	produces a Prothrombopenia	Anticoagulant
		Ketosteroids [40]	Class of steroidal hormone	Hormonal analogue
$Ar–NO_2$	Nitro compounds	Chloamphenicol [41]	(y)	Bactericidal
		Nitrofurans [42]	(y)	Antibiotic

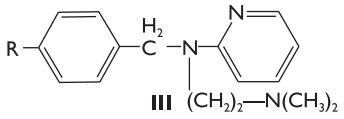
ONNHCONHR	Nitrosocompounds	Nitrosoureas [43]	(b)	Antineoplastic
Ar–OH	Phenols	Estradiol [44]	(z)	Estrogenic
		Amodiaquine [32]	(o)	Antimalarial
		Guaicol [45]	(a′)	Expectorant
		Hexylresorcinol [46]	Acts on nematode cuticle	Antihelmintic
RNHCONHR¢	Ureas and Ureidens	Barbiturates [47]	(f)	Hypnotic
		Hydantoins [10]	(i)	Anticonvulsant

(a) Used as a food preservative, it prevents mycotoxin generation, (b) it is a growth enzyme inhibitor, (c) a urease inhibitor, (d) a prostaglandins synthesis inhibitor, (e) it has a possible effect on the boundary lipids membrane bilayer around the Na^+ channel, (f) has evaporative refrigerant action, (g) is a Na^+ channel blocker, (h) a prototypical β adrenergic receptor antagonist, (i) a direct blocker of the ionotropic glutamate receptor, (j) blocks the Na^+ channel in the SA node and ventricles, (k) is a stimulant that acts mainly on the respiratory cycle, it is directly excited in the medulla oblongata respiratory center, (l) is an NMDA (dopamine receptor) antagonist, (m) an adrenergic blocking agent, (n) a DNA alkylating agent, (o) a DNA interchelating agent, (p) an α1 adrenergic receptor agonist, (q) enters nerve terminals and displaces neurotransmitter molecules (nor-adrenaline, dopamine) from storage areas within the nerve terminal, (r) is a blocking dopamine receptor, (s) a first-generation H1 antagonist, (t) an opioid agonist, (u) a ganglionic blocking agent, (v) a neuromuscular blocking agent, (w) reduces the release of catecholamine, (y) is a protein synthesis-inhibiting agent, (z) regulates gene transcription, which leads to the formation of mRNA that interacts with ribosomes to produce specific proteins that express the effect of estradiol on the target cell, and (a′) is an irritant to the gastric vagal receptor and recruits efferent parasympathetic reflexes that induce glandular exocytosis of a less viscous mucus mixture.



II

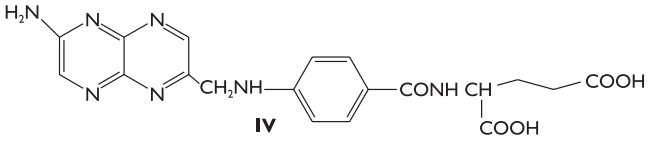
IIa, R=I, IIb, R= C(CH$_3$)$_3$



III

III, R=H, IIIb, R=OCH$_3$

The isosteric comparison of –OH, NH_2, and –SH has been rationalized on their ability to donate electrons and also to form hydrogen bonds. The antagonistic activity of $–NH_2$ and OH has been reported among the derivatives of pteroylglutamic acid (PGA, **IV**) [52].



IV

Physicochemical properties in relation to drug action

In general, when a drug molecule enters the body, it will interact with one or more biopolymers found in the extracellular fluid, in the cell membrane, and within cells [53]. The type and the extent of this interaction will depend on the kind and number of chemically reactive functional groups and the polarity of the drug molecule [54]. The drug–protein interaction does not involve covalent bonds that are relatively stable at body temperatures. Instead, weak forces such as ionic bonds, hydrogen bonds, Van der Waals forces, dipole–ion, and dipole–dipole forces are involved. The partition coefficient *P*, produced because of the presence of drug through lipid membranes/water system found in the body, is given by $P = [\text{drug}]_{\text{lipid}}/[\text{drug}]_{\text{water}}$, the Hansch equation. A biological response is produced by the interaction of a drug with a functional or an organized group of molecules, which may be called the biological receptor site. Table 2 shows the types of chemical bonds.

Table 2 Types of chemical bonds

Bond type	Bond strength (kcal/mol)	Example
Covalent	40–140	CH_3OH
Reinforced ionic	10	fx4
Ionic	5	$R_4N^+–I^-$
Hydrogen	1–7	$^-OH–O$ =
Ion–dipole	1–7	$R_4N^+–:NR_3$
Dipole–dipole	1–7	O = C–:NR_3
Van der Waals	0.5–1	$C^-–C^+$
Hydrophobic	1	See the Hydrophobic bond section

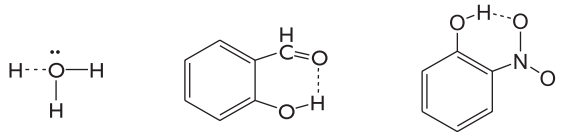
The hydrophobic bond

This is a concept used to explain attractive interactions between nonpolar regions of the receptor and the drug. Explanations such as the isopropyl moiety of the drug fits into a hydrophobic cleft on the receptor composed of the hydrocarbon side chains of the amino acids valine, isoleucine, and leucine are commonly used to explain why a nonpolar substituent at a particular position on the drug molecule is important for activity. Also, the polypeptide chain is considered to be the primary level of protein structure and the folding of the polypeptide chains into a specified structure maintained through hydrogen bonding interactions (intramolecular) [55].

Hydrogen bond

Among the secondary forces, hydrogen bonding that occurs over short distances (2.5–2.7 Å) is one of

the most important forces that affects the physical property of the compound. The important hydrogen bonding groups are –OH, –NH, which can form either intermolecular or intramolecular hydrogen bonds. Some examples are water, salicylic acid, and *o*-nitrophenol. The antipyretic and antirheumatic effects of salicylic acid are because of its prostaglandin synthase-inhibitory effect.



Chelation

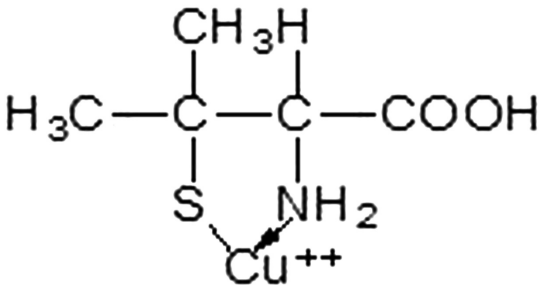
The compounds that are obtained by donating electrons to a metal ion with the formation of a ring structure are called chelates (e.g. copper-chelate) (Fig. 1); the compounds capable of forming a ring structure with a metal are termed ligands. In this example, the ligand is a mercaptoamino acid that donates electrons to the Cu^{2+} ion [56].

Chelation can be used for sequestration of metal ions [57], stabilization of drugs [58], and elimination of toxic metals from intact organisms [57] and also for improvement of metal absorption. An important example of chelating agents is the radioactive transition state artificial metal, technetium (^{99m}Tc), for albumin injection used as radiotracers in diagnostic nuclear medicine practice [59].

Surface activity

Four different types of surface-active agents can be recognized: (a) anionic compounds, for example salt of bile acids, salts of sulfate or phosphate esters of alcohols and salts of sulfonic acids; (b) cationic compounds, for example high-molecular-weight aliphatic amines and quaternary ammonium derivatives; (c) nonionic compounds, for example polyoxyethylene ethers and glycol esters of fatty acids; and (d) amphoteric surfactants [60].

Figure 1



Cu-chelate.

The surface-active molecules can be formed at the surface of water or at the interface of polar and nonpolar liquids with the nonpolar portion of the molecule oriented toward the nonpolar liquid and the polar groups toward the polar liquids. Three different types of forces are involved in the orientations of surface-active molecules, namely, Van der Waals, hydrogen bonds, and ion dipoles [1,2].

Charge transfer interaction

In these interactions, electrons are not fully transferred; rather, electron density is distributed between molecules the same way as in covalent bond. The molecule that accepts electron density is called the acceptor and the molecule that donates electron density is called the donor [1,2]. The charge transfer interactions are weak in comparison with the covalent bonding because each of the molecules involved in the interaction already has its primary valence requirements satisfied. The commonly known examples of charge transfer complexes are aromatic molecules. The contribution of charge transfer interactions toward drug activity has been determined in terms of molecular orbital calculations. The calculations of the energy for the highest occupied molecular orbital and the lowest empty one of actinomycin and of various purines have shown them to be in accordance with the observed electron-accepting and electron-donating properties of the respective compounds. The interactions of Cu, Pd, and Ni chelates of 8-hydroxyquinoline with various electron acceptors support charge transfer as a possible mechanism of action of these compounds [1,2].

Drug–receptor theory

The drugs produce their effects by complexing to an enzyme or a protein through a hydrophobic group, where the biological counterpart of the complex is called a biophase or a receptor [1,2]. It was assumed that under equilibrium conditions, although the concentration of the drug in the biophase and in the extracellular fluids is different, their escaping tendency in each phase would be the same [1,2].

The overall pharmacological action of a particular drug is because of the contribution of hydrophobic, electronic, and steric factors between the drug and its receptor.

Drug–receptor complex

Following administration into the biological system, a drug must pass through many barriers, survive alternate sites of attachment and storage, and avoid significant metabolic destruction before it reaches

the site of action, usually a receptor on or in the cell [61]. At the receptor, the following equilibrium usually holds:

Drug + receptor *f* drug-receptor complex → pharmacologic response.

The ideal drug molecule will enter the systemic circulation, pass through the lipid barriers, and finally make contact with the receptor in an equilibrium process. A good ability to fit the receptor favors binding and the desired pharmacological response. In contrast, a poor fit favors the reverse reaction and the drug will be expected to dissociate from the receptor and re-enter the systemic circulation to be excreted (Fig. 2).

Many variables contribute toward a drug's binding to the receptor. These include the molecule, the three-dimensional shape of the molecule, and consequently the type of chemical bonding involved in the binding of the drug to the receptor.

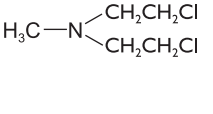
Most drugs that belong to the same pharmacological class have certain structural features in common. For example, the barbiturates act as CNS depressants by bonding to a specific receptor: hydantoins act on CNS receptors [10], producing an anticonvulsant response; benzodiazepines combine with the γ-aminobutyric acid receptors, resulting in anxiolytic activity [62]; penicillin and cephalosporin inhibit enzymes required to construct the bacterial cell wall; and tetracycline acts on bacterial ribosomes [1,2].

Drug–receptor covalent bond

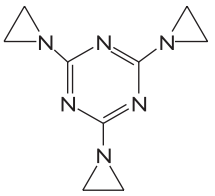
Covalent bond formation between a drug and a receptor is the basis of Baker's concept of active site-directed irreversible inhibition [63].

The following three examples for a drug–receptor covalent bond are known:

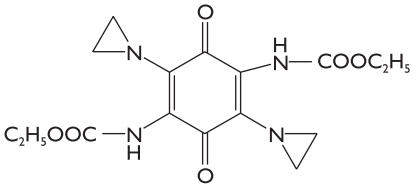
The alkylating agents: antitumor agents such as β-haloalkylamines, 'nitrogen mustards', or aromatic nitrogen alkylating agents, for example triethylene melamine and diazoquone [64,65].



Nitrogen mustard

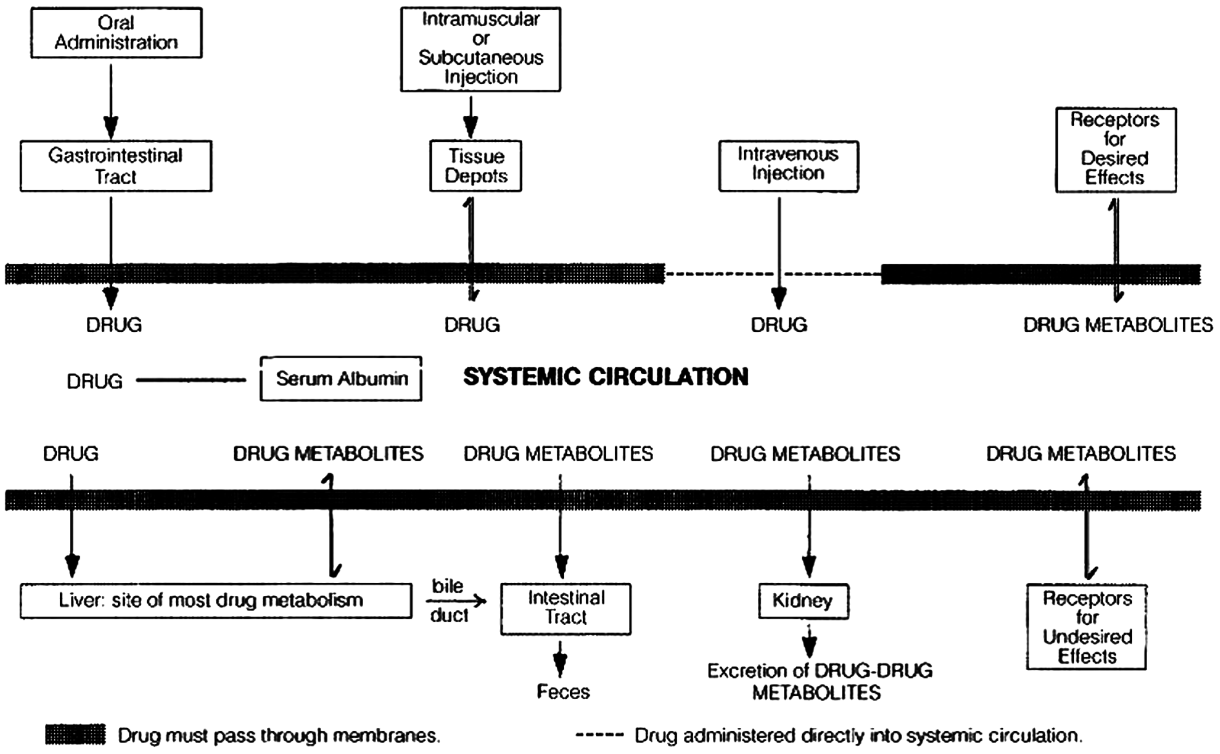


Triethylene Melamine



Diazquone

Figure 2

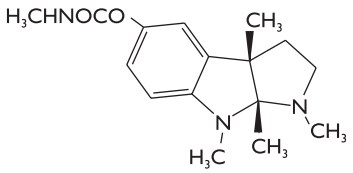


Summary of drug distribution [1,2].

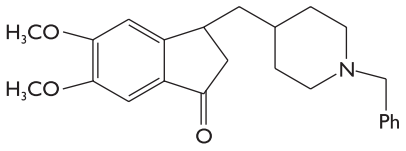
The alkylation of nucleic acid (DNA) or proteins involves a substitution reaction in which a nucleophilic atom (nu) of the biopolymer replaces a leaving group from the alkylating agent.

Nu – H + alkyl – Y → alkyl – nu + H^+ ++ Y^-.

(ii) Inhibitors of acetylcholine esterase, such as physostigmine and donepezil for the treatment of Alzheimer's disease [66,67].

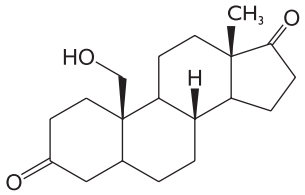


Physostigmine



Donapezil

(iii) The aromatase inhibitors: 4-hydroxy androstenedione (**4-HA**) [68,69].



4-HA

When a pharmacological agent forms a covalent bond with a receptor, the cell must destroy the receptor, or, in the case of alkylating agents, the cell would be replaced, ideally with a normal cell. In other words, the usual use of drugs in medical treatment calls for the drug's effect to last for a finite period of time. If the patient does not tolerate the drug well, it is even more important that the agent dissociate from the receptor and be excreted from the body [1,2].

Drug distribution

Oral administration

The drug must go into solution to pass through the gastrointestinal mucosa. Even drugs administered as true solutions may not remain in solution as they enter the acidic stomach and then pass into the alkaline intestinal tract. Unless the drug is intended to act locally in the GIT, it will have to pass through the gastrointestinal mucosal barrier into venous circulation to reach the site of the receptor. The drug's route involves distribution of partitional between the aqueous environment of the GIT, the lipid bilayer cell membrane of the mucosal cells, possibly the aqueous interior of the mucosal cells, the lipid bilayer membranes on the venous side of the GIT, and the aqueous environment of the venous circulation.

Parenteral administration

Many times, there will be therapeutic advantages to bypassing the intestinal barrier by using parenteral (injectable) dosage forms. Intravenous administration places the drug directly into the circulatory system, where it will be distributed rapidly throughout the body, including tissue depots and the liver, where biotransformations occur, in addition to the receptors. Drug distribution is summarized in Figure 2.

Drug transport

Membranes in the body

In order for a drug to reach its site of action, it must pass through a number of complex membranes. Membranes play an important role in determining the manner in which drugs are distributed or in some cases may serve as the site of action. Plasma membrane surrounding the individual cells seems to be similar for a wide variety of tissues. It is considered to consist of two layers of lipid molecules oriented with their water-soluble polar groups facing outward and their nonpolar groups held together on the inside by Van der Waals forces [70]. The lipids include lecithin, sphingomyelin, cephalin, and cholesterol [70]. The bimolecular layers of phospholipids and intrinsic globular proteins are considered to be stabilized by a layer of unfolded protein molecules [70].

Drug transport

Drugs can pass through membranes by (a) simple diffusion: majority of drug substances pass through membranes by simple diffusion; the rate of transport depends on the solubility of the drug in lipid or lipid/water partition coefficient [71]. Most of the drugs are weak electrolytes and exist in aqueous solutions as a mixture of ionized and unionized forms [71]. The cell membranes are permeable to the lipid-soluble unionized forms of the weak acids and weak bases, and at equilibrium, the concentration of the unionized form is identical on the two sides of the membrane [71]. The lipid solubility of the ionized form of the drug is low and the passage across the membrane is negligible. The fraction of the total drug present in the ionized form is given by the dissociation constant, which is expressed for both acids and bases as a pK_a. The relationship between pK_a and the concentration of ionized and unionized drug is given by Henderson– Hasselbalch equations:

For weak acids: $pK_a = pH + \log \frac{C_u}{C_i}$, (1)

For weak bases: $pK_a = pH + \log \frac{C_u}{C_i}$, (2)

where C_u and Ci are the concentrations of unionized and ionized forms of the drug, respectively. Because the ionized form of a weakly acidic and basic drug does not penetrate the lipid membrane, its concentration in each compartment in the body is a function of the pK_a of the compound and the pH in the compartment.

Filtration

It has been suggested that the lipoprotein membrane is not continuous, but punctured by a series of water-filled pores whose effective radius is about 4 Åand therefore small drug molecules can be transported by pore filtration [1,2].

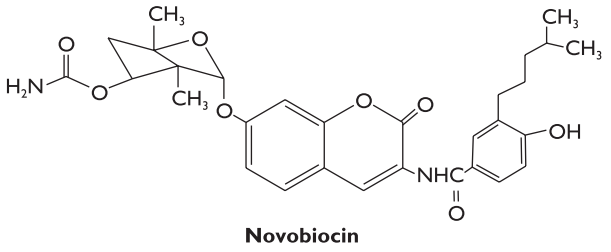
Specialized transport

It has been proposed that certain organic and inorganic ions as well as certain large lipid insoluble molecules such as monopolysacharides can be transported by special carriers. The ions or molecules to be transported become attached to the carrier at one surface of the membrane and are released at the other surface while the carrier returns to the original surface to complete the cycle; the process is called special transport. However, if the substrate molecule is moved against a concentration gradient, energy will be needed and the process is called active transport [72]. For example, 5-fluoro- and 5-bromouracils are transported by active transport [73].

Drug absorption

When a drug is administered by different routes such as (a) oral administration, (b) parenteral administration, for example intravenous, intramuscular, subcutaneous, intraspinal, or intracerebral, and so on, it can produce its characteristic pharmacological properties only when a sufficient number of molecules reach its particular site when the response is triggered. Following its administration, its concentration in the body is governed by four processes: absorption, distribution, metabolism, and excretion.

The rate of drug absorption will be influenced by the properties of the dosage, which in turn is influenced by particle size because the dissolution rate is directly related to the surface area of the drug exposed to the medium in which it dissolves [74]. The chemical nature of the drug also influences the dissolution rate. For example, the salt of a weak acid dissolves faster than the weak acid itself as in the amorphous antibacterial agent, novobiocin, which dissolves more readily than its crystalline form and produces an adequate concentration in the plasma. [75,76].

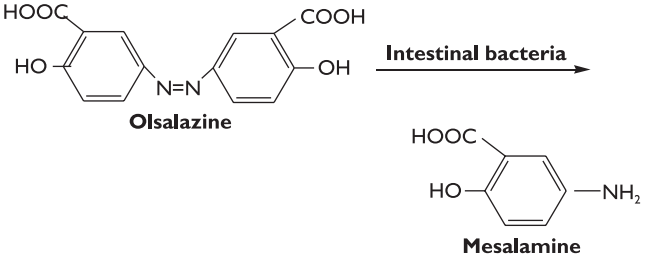


Novobiocin

Oral administration

As shown in Fig. 2, the drug must go into solution to pass through the GIT mucosa. Even drugs administered as true solutions may not remain in solution as they enter the acidic stomach and then pass into the alkaline intestinal tract. Any compound passing through the GIT will encounter a large number and variety of digestive and bacterial enzymes, which theoretically can degrade the drug molecule. Chemical modification is used to a limited extent to facilitate a drug reaching its desired target. An example is olsalazine, a prodrug used in the treatment of ulcerative colitis.

Olsalazine is a dimer of the pharmacologically active mesalamine (5-amino salicylic acid), which is not effective orally because it is metabolized to inactive forms before reaching the colon [77]. The dimeric form passes through a significant portion of the intestinal tract before being cleaved by the intestinal bacteria into two equivalents of mesalamine [77]. In practice, a new drug entity under investigation will likely be dropped from further consideration if it cannot survive in the intestinal tract or if its oral bioavailability is low, necessitating parenteral dosage forms only.



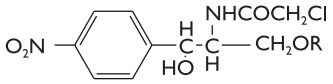
Olsalazine

Mesalamine

In contrast, these same digestive enzymes serve as activators of prodrugs. Chloramphenicol is water soluble enough (2.5 mg/ml) to come into contact with the taste receptors on the tongue, producing an unpalatable bitterness [78]. To mask this bitter taste, the palmitic acid moiety is added as an ester of chloramphenicol's primary alcohol. This reduces the parent drug's water solubility (1.05 mg/ml) enough so that it can be formulated as a suspension that passes

over the bitter taste receptors on the tongue [78]. Once in the intestinal tract, the ester linkage is hydrolyzed by the digestive esterases into the active antibiotic and the very common dietary fatty acid palmitic acid [78].

Olsalazine and chlorampenicol palmitate are examples of prodrugs, that is compounds that are inactive in their native form but are easily metabolized to the active agents.



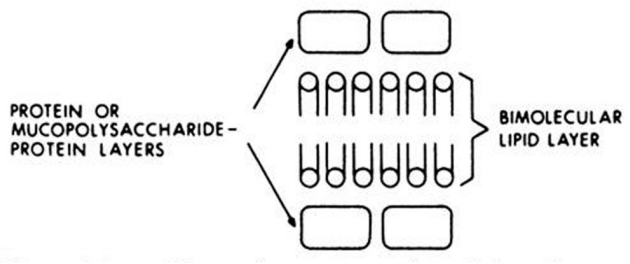
Chloramphenicol, R=H
Chloramphenicol palmitate, R= $CO(CH_2)_{14}CH_3$

Unless the drug is intended to act locally in the GIT, it will have to pass through the GIT mucosal barrier into venous circulation to reach the receptor site. The drug's route involves distribution or portioning between the aqueous environment of the GIT, the lipid bilayer cell membrane of the mucosal cells, possible the aqueous interior of the mucosal cells, the lipid bilayer membranes on the venous side of the GIT, and the aqueous environment of the venous circulation [1,2]. The drug's passage through the mucosal cells can be passive or active. Part of the lipid membranes is a series of channels that form, disappear, and reform. There are receptors that move compounds into the cell by a process called (pinocytosis) [1,2]. Drugs that resemble a normal metabolic precursor or an intermediate may be actively transported into the cell by the same system that transports the endogenous compound. However, most drug molecules are too large to enter the cell by an active transport mechanism through the passages. The latter, many times, pass into the patient's circulatory system by passive diffusion (Fig. 3).

Parenteral administration

Subcutaneous and intramuscular injections slow distribution of the drug because it must diffuse from the site of injection into systemic circulation. These parenteral routes produce a depot in the tissue (Fig. 2), from which the drug must reach the blood or lymph.

Figure 3



Schematic representation of the cell membrane [1,2].

Once in systemic circulation, the drug will undergo the same distributive phenomena as orally and intravenously administered agents before reaching the target receptor. In general, the same factors that control the drug's passage through the gastrointestinal mucosa will also determine the rate of movement out of the tissue depot.

Excretion

The main route of excretion of a drug and its metabolites is through the kidney. For some drugs, entrohepatic circulation (Fig. 2), in which the drug re-enters the intestinal tract from the liver through the bile duct, can be an important part of the agent's distribution in the body and route of excretion. Either the drug or the drug metabolite can re-enter systemic circulation by passing once again through the intestinal mucosa. A portion of either may also be excreted in the feces. Also, drugs and their metabolites can be excreted in a nursing mother's milk [1,2].

Drug metabolism

Types of metabolic conversions

The chemical reactions of drugs and other organic substances that occur in the body are classified into (a) oxidation reactions, (b) reduction reactions, and (c) replacement reactions (hydrolysis, acetylation, methylation, and conjugation reactions). The metabolic pathways that involve the transformation of specific grouping in a substrate molecule are known as phase reactions [76]. Drug metabolism occurs in two phases. Intermediate pharmacologically active metabolites are usually produced by phase I reactions. The products from the phase I chemistry are converted into inactive water-soluble end products by phase II reactions (conjugation reactions) [79].

Oxidation

This is normally the first step involved in the drug metabolism unless the drug has such functional groups such as –OH, –SH, $–NH_2$, and –COOH, which are capable of conjugation. A complex of nonspecific microsomal enzymes present in the liver catalyzes metabolic oxidation of a large variety of many compounds (endogenous substances such as steroid hormones and exogenous substances such as drugs and pollutants). The most important enzyme involved in this type of oxidation is cytochrome P-450 [80].

Reduction

Metabolic reductions are carried out by the enzyme system, which makes use of sodium dihydrogen phosphate (NADPH) as a hydrogen donor [81].

Hydrolysis

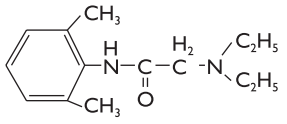
Esterases such as pseudocholine esterase present in plasma will catalyze the hydrolysis reactions of drug substances [1,2].

Conjugation reactions

In the case of drugs containing groups such as –OH, –SH, –NH2, and –COOH, conjugation with glucuronic acid, sulfate, amino acids, and peptides is the major pathway for metabolic elimination [82].

In human drug metabolism, the main conjugation reactions occur through conjugation to glucuronic acid, sulfate, or glutathione [82]. Obviously, drugs that are bound to serum protein or show favorable partitioning into tissue depots will be metabolized and excreted more slowly for the reasons discussed above.

All substances in the circulatory system, including drugs, metabolites, and nutrients, will pass through the liver. Most molecules absorbed from the GIT enter the portal vein and are initially transported to the liver. A significant proportion of a drug will partition or be transported into the hepatocyte, where it may be metabolized by hepatic enzymes to inactive chemicals during the initial trip through the liver by what is known as the first-pass effect [83]. Lidocaine, a local anesthetic antiarrhythmic agent, is a classic example of the significance of the first-pass effect. It is metabolized during its initial passage through the liver; therefore, its oral administration is impractical [83].



Lidocaine

Acid–base properties

Most drugs can be classified as acids or bases as a large number of drugs can behave as either acids or bases as they circulate in the patient in different dosage forms and end up in systemic circulation. A drug's acid–base properties can considerably influence its biodistribution and partitioning characteristics. For the definition of acids and bases, the model used in pharmacy and biochemistry was developed independently by Lowry and Bronsted. An acid is a proton donor and a base is a proton acceptor.

Acid-conjugate base

Representative examples of pharmaceutically important acidic drugs are listed in Table 3. Each acid, or proton donor, yields a conjugate base. Conjugate bases range from the chloride ion (reaction a), which does not accept a proton in aqueous media, to ephedrine (reaction h), which is an excellent proton acceptor.

Base-conjugate acid

The Bronsted–Lowry theory defines a base as a molecule that accepts a proton [1,2]. The product resulting from the addition of a proton to the base is the conjugate acid. Pharmaceutically important bases are listed in Table 4. There are a variety of structures, including the easily recognizable base sodium hydroxide (reaction a); the basic component of an important physiological buffer, sodium monohydrogen phosphate (reaction b), which is also the conjugate base of dihydrogen phosphate

Table 3 Examples of acids

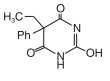
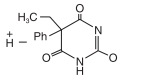
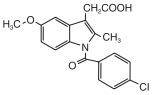
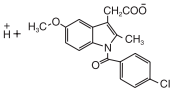
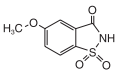
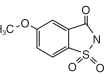
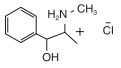
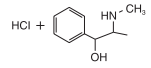
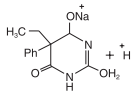
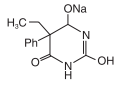
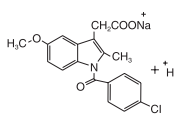
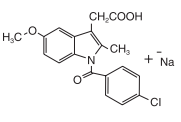
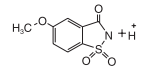
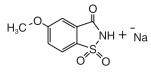
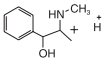
Reaction	Acid name	Acid structure	→	H^+ + conjugate base
(a)		HCl	→	$H^+ + Cl^-$
(b)	Sodium dihydrogen phosphate	NaH_2PO_4	→	$H^+ + NaHPO_4$
(c)	Ammonium chloride	NH_4Cl	→	$H^+ + NH_3(Cl)^-$
(d)	Acetic acid	CH_3COOH	→	$H^+ + CH_3COO^-$
(e)	Phenobarbital		→	
(f)	Indomethacin		→	
(g)	Saccharin		→	
(h)	Ephedrine HCl		→	

Table 4 Examples of bases

Reaction	Base name	Base + H^+	→	Conjugate acid
(a)	Sodium Hydroxide	$NaOH + H^+$	→	$H_2O + Na^+$
(b)	Sodium monohydrogen phosphate	$Na_2HPO_4 + H^+$	→	$H^+ + NaHPO_4$
(c)	Ammonia	$NH_3 + H^+$	→	NH_4^+
(d)	Sodium acetate	$CH_3COONa + H^-$	→	$Na^+ + CH_3COOH$
(e)	Phenobarbital		→	
(f)	Indomethacin		→	
(g)	Saccharin		→	
(h)	Ephedrine HCl		→	

(reaction b in Table 3); ammonia (reaction c), which is also the conjugate base of the ammonium cation (reaction c in Table 3); sodium acetate (reaction d), which is also the conjugate base of acetic acid (reaction d in Table 3); the enolate form of phenobarbital (reaction e), which is also the conjugate base of phenobarbital (reaction e in Table 3); the carboxylate form of indomethacine (reaction f), which is also the conjugate base of indomethacine (reaction f in Table 3); the imidate form of saccharin (reaction g), which is also the conjugate base of saccharin (reaction g in Table 3); and the amine ephedrine (reaction h), which is the conjugate base of ephedrine HCl (reaction h in Table 3).

All these reactions presented in Tables 3 and 4 can be rewritten as complete acid–base reactions as follows:

Acid + base *f* conjugate acid + conjugate base,

$HA + HOH \; f \; H_3O^+ + A^-$.

The equilibrium constant $K_{eq} = \dfrac{[H_3^+O]\,[A^-]}{[HA]\,[H_2O]}$.

In a dilute solution of a weak acid, the molar concentration of water

$$[H_2O] = \frac{\text{Weight of 11}}{\text{Molecular weight}} = 55.5 \text{ mol/1},$$

$$K_a = K_{eq}\,[H_2O] = {}_{eq}\,(55.5) = \frac{[H_3^+O]\,[A^-]}{[HA]^+}.$$

Since

p*K*a = –log*K*a and pH = –log $[H_3O]^+$.

The pH will be calculated according to the following equation:

$$pH = pKa + \log\frac{[A^-]}{[HA]}. \qquad (3)$$

It is now common to express the basisity of a chemical in terms of pK_a using the following equation:

$$pKa = pKb - 14. \qquad (4)$$

Examples of calculations requiring the pK_a (a): to determine the ratio of ephedrine to ephedrine. HCl (pK_a 9.6) in the intestinal tract at pH 8.07. Using Eq. (4) we obtain

$$8.0 = 9.6 + \log\frac{[\text{ephedrine}]}{[\text{ephedrine HCl}]} = -1.6,$$

$$\frac{[\text{ephedrine}]}{[\text{ephedrine HCl}]} = 0.025.$$

The number whose log is -1.6 is 0.025, meaning that there are 25 parts ephedrine for every 1000 parts ephedrine HCl in the intestinal tract whose environment is pH 8.0.

To determine the pH of a buffer containing 0.1 mol/l AcOH (pK_a 4.8) and 0.08 mol/l AcONa. Using Eq. (4) we obtain

$$pH = 4.8 + \log\frac{0.08}{0.1} = 4.7 .$$

Statistical prediction of pharmacological activity

Quantitative structure–activity relationship

Just as mathematical modeling is used to explain and model many chemical processes, it has also been used to quantify the effect of a structural change on a defined pharmacological response. This would meet three goals in drug design: (a) to predict biological activity in untested compounds; (b) to define the structural requirements required for a good fit between the drug molecule and the receptor; and (c) to design a test set of compounds to maximize the amount of information on structural requirements for activity from a minimum number of compounds tested. This aspect of medicinal chemistry is commonly referred to as quantitative structure–activity relationship [1,2]. The partition coefficient has become the most important physical chemical measurement for quantitative structure–activity relationship studies using the following equation:

$$\log BR = a(\text{physical chemical property}) + c. \qquad (5)$$

where Eq. (5) is an equation of straight line, where BR = a defined pharmacological response usually expressed in millimoles such as the inhibitory constant K_i, the effective dose in 50% of the subjects (ED50), the lethal dose in 50% of the subjects (LD_{50}), or the minimum inhibitory concentration. It is common to express the biological response as a reciprocal, 1/BR or 1/C, where *a* = = the regression coefficient or slope of the straight line; and *c* = the intercept term on the y axis (when the physical chemical property, *P* = zero). *P* is the partition coefficient. ED_{50} is the amount of drug needed to obtain the defined pharmacological response. If the $ED_{50}$of a drug A is 1 mmol and $ED_{50}$of drug B is 2 mmol; drug A is twice as potent as drug B. In other words, the smaller the ED_{50}(or ED_{90}, LD_{50}, minimum inhibitory concentration, etc.), the more potent the substance being tested.

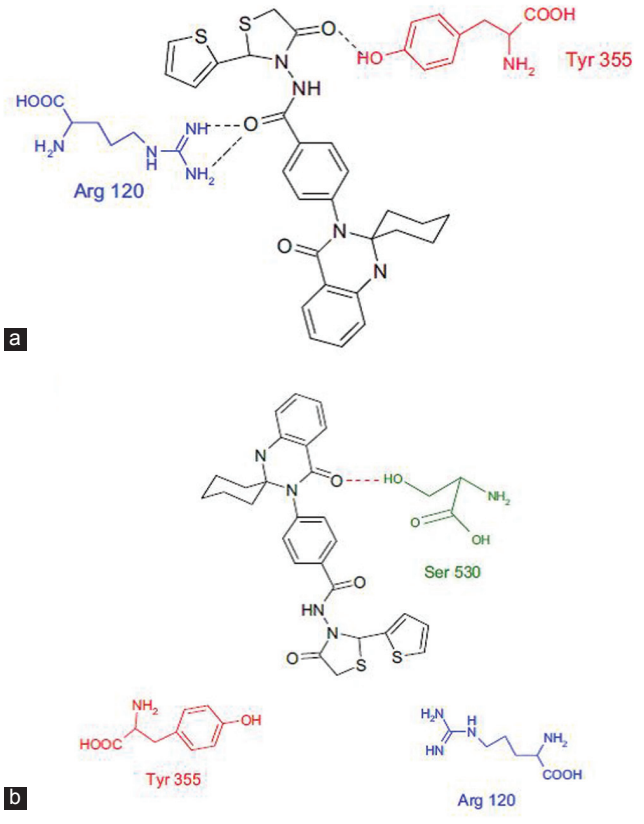
Molecular modeling (computer-aided drug design)

The low cost of powerful desktop computers enables design of the molecule on the bases of an estimated

fit onto a receptor or has similar spatial characteristics found in the prototypical lead compound. This assumes that the molecular structure of the receptor and the geometry of its active site for a reasonable estimation of the three-dimensional shape besides the databases containing the three-dimensional coordinates of the chemicals must be known in detail to predict the ligand (drug)–receptor interactions. The initial receptor model was based on a rigid lock-and-key concept, with a drug (key) fitting into a receptor (lock). It has been used to explain why certain structural attributes produce a predictable pharmacological action assuming that both the drug and the receptor can have considerable flexibility [84]. Molecular graphics, using programs that calculate the preferred conformations of drug and receptor, show that a receptor can undergo an adjustment in three-dimensional structure when the drug makes contact. In other words, the drug docks with the receptor [85].

Recently, we synthesized several spiro (quinazoline-cyclohexane)-4(3*H*)-ones to be tested for their anti-inflammatory and analgesic activities in rats. Molecular docking of some representative examples of the new compounds into COX-2 enzyme has been carried out as shown in Figures 4–6. Compound XVIb, which has the highest anti-inflammatory effect, has the nearest root mean square deviation value to that of indomethacin [58]. It was found that compound XVIb has two best conformations in which it can interact with the Arg 120 $–NH_2$ group and the Tyr 355 –OH group (Fig. 4a), and with the Ser 355 –OH group (Fig. 4b) [86].

Figure 4



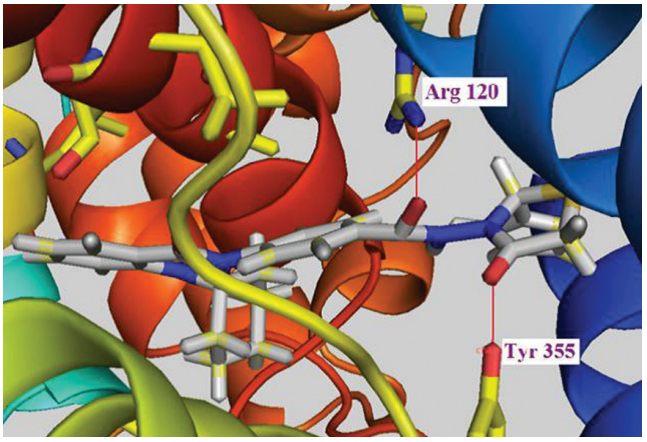
(a) Possible interactions of compound **XVIb** with Arg 120 and Tyr 355.

Possible hydrogen bond formation with –OH of Ser 530

Another example for molecular docking studies has been reported recently by us [87]. It has been found that several newly synthesized pyridine sulfonamide-thiazolidinones and their C-nucleosides showed considerable cytotoxic effect against the breast carcinoma cell line MCF-7 and the cervix carcinoma cell line HELA [87]. Autodock molecular docking into protein tyrosine kinase (PTK) has been carried out for lead optimization of the compounds in study as potential PTK inhibitors (Figs. 7 and 8).

The molecular docking study showed the binding affinities of the synthesized 2-[(2*S*,3*R*,4*R*)1-(1,2,3,4-tetrahydroxy butyl)]-3-[4-[(pyridin-2-ylamino) sulfonyl] phenyl]thiazolidin-4-one (3*a*), *N*-(*o*-hydroxy-*p*-methoxyphenylarylidene)-imino-4-[(pyridin-2-ylamino)sulfonyl]benzenes (4*c*), *N*-(indol-3-ylarylidene)-imino-4-[(pyridin-2-ylamino)sulfonyl] benzenes (4*e*), and 2-(indol-3-yl)-3-[4-[(pyridin-2-ylamino)-sulfonyl]phenyl]thiazolidin-4-ones (5*e*) into PTK, where compounds (4*c*,*e*) showed the highest binding free energies, being (ΔGb: 8.99 and 10.81 kcal/mol, respectively), with 1–3 hydrogen bonds with Lys623, Cys673, and Asp810 mainly through their sulfamoyl moiety. Compound 3a showed poor binding affinity, with binding free energy being (ΔGb: 5.43 kcal/mol), which predicts its weak biological antitumor activity.

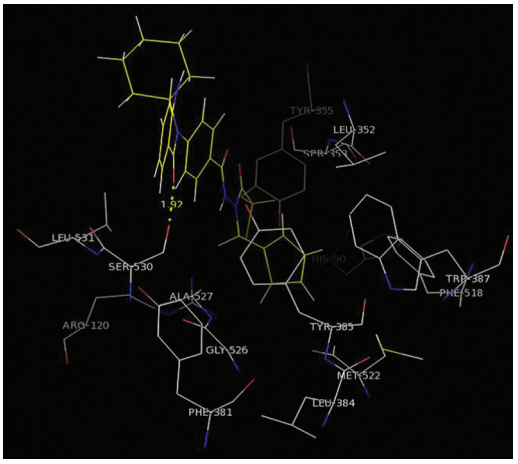
Figure 5



Compound **XVIb** (in stick) and how it fits into the pocket. The protein is presented as a cartoon and colored as a spectrum.

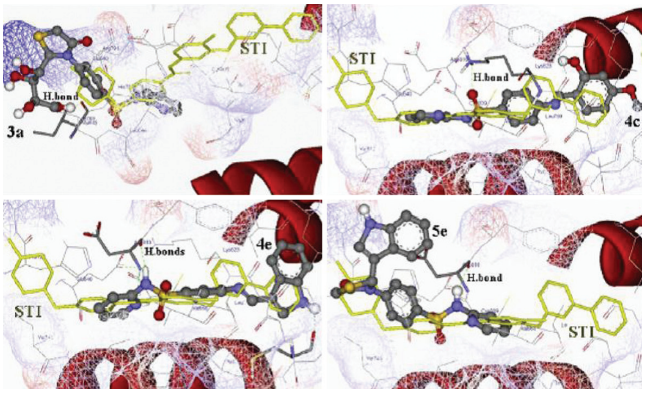
Finally, to search for new candidates for the treatment of breast cancer and encouraged by the critical role of poly (ADP-ribose) polymerase-1 enzyme inhibitors as potentiators of the antitumor activity of DNA-damaging drugs [88] and ionizing radiation and as single-agent drugs in breast cancer [89], it seemed of interest to synthesize novel series of spiro [quinazoline-2,1′-cyclohexane] derivatives that were subjected to in-vitro anticancer screening against the breast adenocarcinoma cell line (MCF-7) and the most active compounds were further subjected to a PARP-1 inhibitory enzyme assay. Moreover, docking of the most biologically active synthesized compounds into the active site of the PARP-1 enzyme was performed using Swiss PDB Viewer software, Swiss institute of bioinformatics, Switzerland in order to calculate the binding free energy and to correlate the docking results with the biological results. Most of the docked compounds showed good binding free energy that ranged from (−25.05 to −37.31 kJ/mol), which represents good stability compared with the reference ligand 3SMI (−29.38 kJ/mol). High negative values were estimated for compound 3-[2-[1-(1,2,3,4-tetrahydroxybutyl)]-4-oxo-2*H*,4*H*-benzo[*e*][1,3]thiazin-3-yl]-spiro[(2*H*,3*H*)-quinazoline-2,1′-cyclohexan]-4(1*H*)-one, the most active PARP-1 inhibitor (IC_{50} = 1.45 μmol/l) with promising cytotoxic activity (IC_{50} = 26.70 μmol/l). As shown in (Fig. 9), the compound shows better insertion and more stable complex through mediation of two hydrogen bonds between its quinazoline-4-CO and sugar-OH with amino acids Ser 1607 and Tyr 1620 [90].

Figure 6



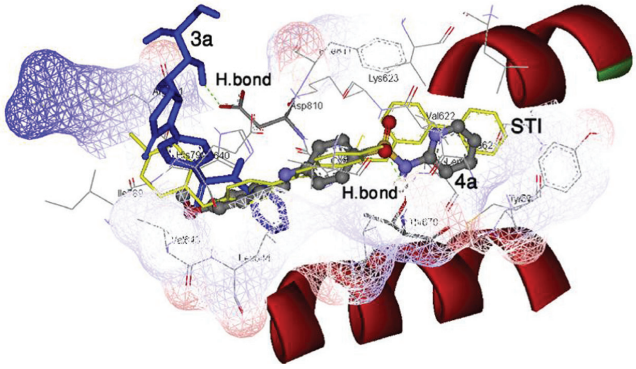
Distance between –CO of the quinazoline ring and the –OH group of **XVIb**.

Figure 7



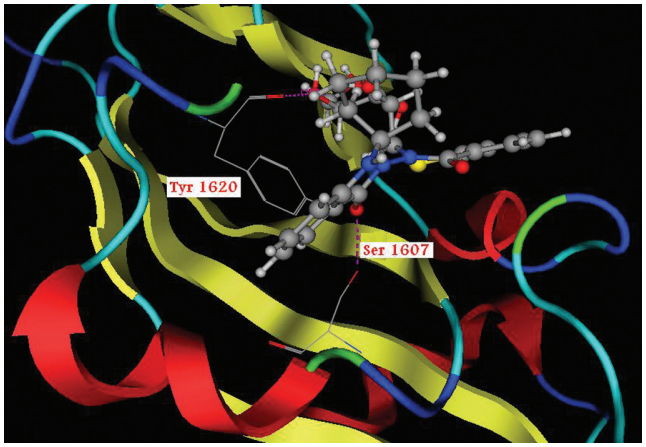
Comparative binding affinities of compounds (**3a, 4c, 4e,** and **5e**; colored by element, ball and stick) into PTK, where compounds **4c, 4e** showed the highest binding energy with 1–3 hydrogen bonds through interaction with Lys623, Cys673, and Asp810 mainly through their sulfamoyl moiety. The binding pocket of PTK is shown in a transparent solid surface with labeled amino acids and the STI ligand is shown as a yellow line. The settled hydrogen bonds are shown as green dotted lines.

Figure 8



Differential binding affinities of compounds (**3b**; blue, stick) and (**4a**; ball and stick) into PTK, where compounds **4a** showed a higher binding energy, being (ΔGb: 9.07 kcal/mol). Compound **3b** yielded (ΔGb 5.90 kcal/mol). The binding pocket of PTK is shown in wire mesh view with labeled amino acids and the STI ligand as a yellow line. The settled hydrogen bonds are shown as green dotted lines.

Figure 9



Three-dimensional possible interaction between quinazoline-4-CO and sugar-OH of the tested compound with the amino acids Ser 1607 and Tyr 1620 of the enzyme-active site.

Conclusion

One of the goals is to design drugs that will interact with receptors as specific tissues. There are several ways to do this, including (a) searching for structures that show specificity for the target receptor that will produce the desired pharmacological response while decreasing the affinity for undesired receptors that produce adverse response using recent techniques such as molecular modeling. In the field of molecular modeling, docking is a method that predicts the preferred orientation of organic compounds inside a target macromolecule to form a stable complex. It results in the study of protein–ligand interaction properties such as binding energy, affinity, and geometry complementarity, (b) altering the molecule, which in turn can alter the biodistribution, and (c) the still experimental approach of attaching the drug to a monoclonal antibody that will bind to a specific tissue antigenic for the antibody. Biodistribution can be altered by changing the drug's solubility, enhancing its ability to resist being metabolized, altering the formulation or physical characteristics of the drug, and changing the route of administration.

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Conflicts of interest

There are no conflicts of interest.

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