REVIEW

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A classification of drug substances according to their mechanism of action

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Different classification systems for therapeutic agents exist. The most commonly used one is the ATC Code (ATC: Anatomy, Therapeutic properties, Chemical, pharmacological properties). Here, an alternative classification system (TCAT: Target – Chemistry – Anatomy – Therapy) is proposed which refers to the molecular mechanism of action or rather, target. The main subgroups of targets are: enzymes; substrates, metabolies, proteins; receptors; ion channels; transporter molecules and systems; nucleic acids, ribosomes; physicochemical mechanisms; antigen-antibody reactions; unknown targets. This target-oriented approach may be particularly useful in teaching advanced medicinal chemistry.

1. The organization of pharmaceuticals

"Over 50,000 different medications exist – and your pharmacist knows them all." This slogan has recently been used by ABDA (Federal Union of German Associations of Pharmacists) to promote the public image of pharmacists in Germany. As it may be, the knowledge of such a vast number of products can only be mastered with the help of an excellent system of classification – a virtual filing cabinet similar to the physical ones familiar to us from the local pharmacy.

From a pharmaceutical standpoint there are many different criteria which can be used to classify a certain type of medication: Alphabetical order, type of formulation, the frequency with which it is prescribed or recommended, price, refundibility, prescription or non-prescription medication, etc.

If a classification of the active pharmaceutical ingredients is undertaken, numerous possibilities are revealed, as well. At the end of the 19th century, Ernst Schmidt (1845–1921), director of the Department of Pharmaceutical Chemisty at the Philipps-University in Marburg, authored "A Detailed Textbook of Pharmaceutical Chemistry" in which he proposed that the study of pharmaceutical chemistry and, thus, drug substances belonged to the science of "pure" chemistry. Consequently, the first volume of his work was entitled "Inorganic Chemistry" and was followed by a further volume, "Organic Chemistry". According to Schmidt, drug substances were to be classified the same as other chemical entities; by nature of their primary elements, functional moieties or organic substance class. Recently, the idea of classifying drug substances strictly according to their chemical constitution or structure has been revived. Numerous databases now attempt to gather and organize information on existing or potential drug substances according to their chemical structure and diversity. The objective is to create substance "libraries", which contain pertinent information about possible ligands for new targets (e.g. an enzyme or receptor) of clinical interest (Schneider 2002; Goodnow et al. 2003), and more importantly, to understand the systematics of molecular recognition (ligand-receptor) (Hendlich et al. 2003; Gohlke and Klebe 2002).

Another older criterion for classifying drug substances is the division of natural and synthetic substances into different groups. The modern-day version of this practice is exemplified in the differentiation between "antibiotics" and "chemotherapeutics", still used in the German "Rote Liste", a compilation of medications. In other cases, chemical properties are purposely used as an exclusion criterion for a class of substances, such as in the example of the "non-steroidal anti-inflammatory drugs" (NSAID). Sometimes it is simply easier to classify something for what it is *not* rather than for what it *is*.

2. The ATC system

Currently, the most commonly used classification system for drug substances is the ATC system (Schwabe 1995). It was introduced in 1976 by the Nordic Council on Medicines as a method to carry out drug utilization studies throughout Scandinavia. In 1981, the World Health Organization recommended the use of the ATC classification for all global drug utilization studies and in 1982 founded the WHO Collaborating Centre for Drugs Statistics Methodology in Oslo to establish and develop the method. The ATC system categorizes drug substances at five different levels according to ⇒ the organ or system on which they act (**a**natomy) ⇒ **t**herapeutic properties ⇒ and **c**hemical, pharmacological properties. The first level is comprised of the main anatomical groups, while the second level contains the pharmacologically relevant therapeutic subgroup. The third level consists of the pharmacological subgroup and the fourth the chemical subgroup. The fifth level represents the chemical substance (= the actual drug entity). Substances

with multiple effects and different therapeutic indications can be found more than once within the system. The ATC system is used routinely within the current university pharmacy curriculum. For example, the well-known German textbook "Mutschler – Drug Actions" (Mutschler et al. 2001) organizes its content according to the system. Each subject is introduced by the organ upon which an effect is shown, followed by the therapeutic effect, the mechanism of activity and finally the chemical substance class.

3. Alternative to ATC: TCAT

The progress achieved within the past few decades in deciphering the biochemical mechanism of activity of drug substances and investigating the structure of biological systems has been accompanied by a deeper understanding of how drug substances act at a molecular level. This greater knowledge of how drugs interact with the body (mechanisms of action, drug-target interactions) has not only narrowed the gap between the disciplines (i.e. pharmaceutical chemistry, pharmacology, and molecular biology), but has also led to the reduction of established drug doses and inspired the development of newer, highly specific drug substances for a known mechanism of action. A preoccupation with the molecular details has sometimes, however, resulted in a tendency to focus only on this one aspect of the drug's effect. For example, cumulative evidence is now suggesting that the proven influence of certain psychopharmaceuticals on neurotransmitter metabolism has little to do with the treatment of schizophrenia or the effectiveness of the drug for this indication (Hyman and Fenton 2003).

Nonetheless, a categorization of drug substances according to their *molecular mechanism of action* has advantages. Similar to the ATC system, such a "taxonomy" also requires a hierarchy of levels. However, in this case, the first level is not grouped according to an anatomical parameter (e.g. sympathetic nerve system, CNS, kidneys, etc.), but rather a "micro-anatomical" characteristic; namely, the biochemical structure with which the substance interacts. In the place of a physiological functional unit would be a type of reaction; for example "Ezetimib: Inhibition of cholesterine absorption".

The term "mechanism of action" itself implies an inherent classification according to the dynamics of drug substance effects at the molecular level. However, the fact that most drug substances do not undergo covalent interactions with their molecular partners and the dynamics of these interactions are often unknown – existing usually only as speculative models – makes the categorization of substances according to their reactive and conformation-dependent processes unproductive at the moment. "Mechanism of action" must, therefore, be placed in quotations; for practical purposes the term can currently only be used to describe static targets. The definition of the target, or more specifically the biochemical functional unit, is a decisive factor for a classification. For example, is a target a type of receptor "only" or does it include the process of action and inactivation of the effector, as well? Should an entire signal transduction pathway be defined or only specific relevant segments of the pathway? Is an entire ribosome the target or rather a specific type of subunit? Could even one molecule – such as a single ribosomal RNA – be considered a target? The actual depth of detail used to define the target is primarily dependent upon the amount of knowledge available about the target and its interactions with a drug. Yet even if the target structure has already been elucidated, it may still be that the molecular effect of the drug cannot be fully described by the interactions with i.e. one target protein alone. For instance, antibacterial oxazolidinones interact with 23S-rRNA, tRNA, and two polypeptides, ultimately leading to an inhibition of protein synthesis. In this case, a description of the mechanism of action which only includes interactions with the 23S-rRNA target would be too narrowly defined. Especially in situations where the dynamics of the drug substance stimulate or inhibit a biological process, it is necessary to move away from the descriptions of single proteins, receptors, etc., and view the entire signal chain as the target.

The following mechanisms of action exemplify dynamic (process) mechanisms of drug action:

– (non-)covalent modifications of the active center (e.g. acetylation of bacterial transpeptidases by beta-lactam antibiotics);
– allosteric modulations (e.g. benzodiazepines/GABA-receptors);
– substrate modifications (e.g. vancomycin);
– molecules requiring activation (pharmacodynamic prodrugs in contrast to pharmacokinetic prodrugs, e.g. paracetamol);
– instances of modifications of a substrate or cofactor (e.g. asparaginase that depletes tumor cells of asparagine; isoniazide that is "inadvertently" activated by the Mycobacteria leading to an inactive covalently modified NADH; vancomycin that binds to the building block bacteria use for the construction of the murein saccculus).

However, as already mentioned, our current knowledge of the molecular dynamics of the effect of most drug substances is still too patchy to lay the foundation for even a somewhat complete "dynamics" classification system.

A further criterion required for the categorization of drug substances according to their target is the anatomical localization of the target. This is essential for a differentiation between substances with the same biochemical target, yet a different organ specificity (example: nifedipine and verapamil are both L type calcium channel inhibitors; the former interacts primarily with vascular calcium channels and the latter with cardial calcium channels).

In view of these observations, we propose an alternative classification system based upon the following hierarchy:
Target – **C**hemistry – **A**natomy – **T**herapy (the TCAT system).

The contents of the following tables represent our attempt to classify the most relevant drug substances currently available, as well as all new developments within the past three years. Within the frame of this discourse it should be noted that the development of a classification system somewhere in between the ATC and TCAT systems is also conceivable. In this case, the primary classification criterion would be the type of cell in which a substance acts, rather that the anatomical or the biochemical functional unit (representing a compromise between the two systems). Such a system could be very useful for certain substances; however, it shall not be pursued further here.

4. The universe of drug targets

How many targets exist in total? This is a question of great interest to all those developing new medications. An attempt to find the answer is being carried out by searching the human genome for new targets. At the present, the only information that can be read from the genome is the protein code, which means that the results of our current analyses are at best an estimation for the number of exist-

ing proteins. This is limiting, as even splice variants cannot be detected in this manner, let alone dynamic aspects, such as transient gene expression and the complex interactions between proteins.

At the time when 100,000 genes – more specifically, protein coding gene sequences – were estimated to exist, a hypothesis was made as to the number of molecular targets "hit" by the entire collection of drug substances available on the market. The lowly sum of 482 was identified (Drews and Ryser 1997). Later, the hypothesis was revised to include approximately 8,000 targets of pharmacological interest, of which nearly 5,000 could be potentially "hit" by normal drug substances, nearly 2,400 by antibodies and approximately 800 by protein pharmaceuticals (Burgess and Golden 2002).

A different count came to the conclusion that all currently used drugs hit 399 non-redundant molecular targets belonging to a mere 130 protein families. These numbers are based upon ligand binding studies. Approximately 3,000 targets for low molecular weight drugs were predicted to exist based on extrapolations from the number of currently identified genes within the human genome (Hopkins and Groom 2002).

So what should one believe? Obviously, the target universe is a space of as yet unknown extension.

5. How did our list originate?

In order to produce a list of drugs useful for a pharmaceutical curriculum, we began by sorting substances according to their target. Then we decided which of the biochemical structures would be most suitable as the primary criteria (the "T" in TCAT). The following were devised:

- Enzymes
- Substrates
- Receptors
- Ion channels
- Transport molecules
- Nucleic acids
- Ribosomes
- Miscellaneous: Physicochemical mechanisms
- Antigen-antibody reactions
- Unknown mechanisms of activity
- (Hormones and hormonal pathways)
- (Vitamines)

These represent the major groups in the first level.

The next level in the hierarchy must then include "all" enzymes, receptors, etc. that have been identified as plausible targets for drug substances. We proceeded by sorting the following drugs into their corresponding target groups (enzymes, receptors, etc.):

– all substances included in the 13th "Selection of Essential Drugs" published by the WHO (WHO 2002), excluding the categories: Vitamines, minerals, oxygen as a narcotic gas, diagnostics, all drugs used for substitution therapy, such as hormones, contraceptives;

– all newly developed drugs from the past three years (Pharmazeutische Zeitung 2003);

– drugs approved by FDA or EMEA in 2004 (Frantz 2004) with new mechanism of action, again excluding substitution therapeuticals;

– targets listed by Drews and Ryser 1997.

We checked the resulting list against the compilation of receptors that was produced for nomenclature purposes (Alexander et al. 2001), and further supplemented the list using the current edition of "Mutschler – Drug Actions" (Mutschler et al. 2001).

In this way, the list included only those targets relevant for the effect of drugs currently on the market. New targets and mechanisms of action were not listed if a corresponding drug interacting with that target has not been marketed yet. Drugs currently undergoing clinical trials have been excluded for the sake of briefness and also due to the numerous status fluctuations of such drugs.

A subdivision of the major groups according to the "anatomy" (cell type or physiological functional unit within which the target is located and acted upon by the drug) and the substance class has been carried out only briefly for the purpose of simplicity. The main focus has been given to the classification of the substance according to its biochemical target.

A categorization going into further detail will not be undertaken within the scope of this article; for example, transporter proteins have been subclassified in great detail (Saier 1999; Goldberg et al. 2003). This should be reserved for the appropriate textbook.

The categorization presented here shuns the difficult, yet important aspect of target validation; whether an observed molecular reaction is actually responsible for the clinical effect of a drug or is only an insignificant side effect. For example, it has been widely discussed whether the inhibition of the COX enzymes is fully responsible for the anti-inflammatory and analgetic effects of COX inhibitors. The ongoing search for a neuropeptide Y (ant)agonist may also be futile, because the inhibition or stimulation of this system does not produce the desired effects. Phospholipase inhibitors should supposedly show a similar *in vivo* effect to the COX inhibitors, which inhibit a downstream enzyme, yet they don't. The list goes on and on.

One could argue, using numerous examples as evidence, that the metabolism of a drug substance is too complex a system to be understood in its entirety. However, science cannot function without hypotheses and classifications, and expert information material on new drug entities is not considered complete without the inclusion of a putative mechanism of action (illustrated with the mandatory colorful cartoons). One could even gain the impression that in this day and age an effective drug compound has no chance of approval by the regulatory agencies without even a postulated mechanism of activity. This seems to be a rather contraproductive tendency in light of the many drug substances that have provided alleviance for so many conditions without a clear knowledge of their mechanism of action. In other words, would it be wise to obstruct the development of new and promising drug compounds just because the mechanism of action is not fully understood? Of course, it would always be optimal if the mechanism of action could be elucidated. However, the *clinical* proof of principle is and remains the relevant aim and criterion.

A categorization of compounds according to their mechanism of action will inevitably lead to a group of leftover drugs with a proven clinical effectiveness, but an unknown molecular target. Such compounds can, if at all, only hypothetically be classified within the selected major groups. The ATC classification system, with its systematical categorization according to therapeutic aspects (e.g. "analgetics"), does not have this problem as every substance in the list shows – or is claimed to show – a therapeutic effect.

It will also happen, as with the ATC system, that certain drug substances will appear more than once in the list. Indeed, it will most likely happen more often than in the ATC system, due to the fact that some drug effects are based on the synergistic effects of more than one mechanism of action.

6. Which classification system is best suited for a pharmaceutical curriculum?

While we were developing our lists, we gained the impression that the ATC system is better suited for a study of drug substances when the emphasis is placed on their *therapeutic use*. The ATC system is more descriptive and, therefore, easier to learn. Further, there are no compounds that cannot be classified within the ATC system, because every compound displays at least one therapeutic indication and effect. On the other hand, a classification according to the molecular mechanism of action, as in our TCAT system, is more useful and meaningful in cases where the primary interest is geared towards the development of drug substances and the elucidation of their molecular interactions with the body. One could conclude that ATC is more appropriate for the subjects of pharmacology and clinical pharmacy, whereas TCAT is more useful when teaching medicinal chemistry. The question remains as to whether it is wise to confront pharmacy students in the short period of their last two years of university education with two different classification systems. From a didactical perspective, it would most likely be more prudent to remain by the ATC system, but within the framework of the medicinal chemisty curriculum place emphasis upon the "C" in ATC, i.e. the "chemistry of drug effects" (= molecular mechanisms of action). In this case, a certain overlap between the subject material taught in the (molecular) pharmacology and pharmaceutical biology courses is to be expected. This, however, could be of great benefit to both the students and lecturers, if a collegial consensus among the lecturers could be reached, in which a desired (semi-) redundance ("repetitio est mater studiorum") by important drug compounds is agreed upon and the remaining less important compounds or therapeutical classes are divided amongst the faculties ("repetitio non semper placet").

Table: Drugs classified according to their targets (TCAT system)

ENZYMES	
OXIDOREDUCTASES	
Aldehyde dehydrogenase	Disulfiram
Monoamine oxidases	
MAO_A	Tranylcypromine Moclobemide
MAO_B	Tranylcypromine
Cyclooxygenases	
Cyclooxygenase-1	Acetylsalicylic acid, Profens Paracetamol (as N-(4-hydroxyphenyl)-arachidonylamide)
Cyclooxygenase-2	Acetylsalicylic acid, Profens, Coxibs, Paracetamol (as N-(4-hydroxyphenyl)-arachidonylamide)
Diamine oxidase increased release	Heparin
Vitamin K epoxide reductase	Warfarin Phenprocoumon
Aromatase	Exemestane
Lanosterol demethylase	Azole antifungals
Lipoxygenases 5-Lipoxygenase	Mesalazine Zileuton
Thyroidal peroxidase	Thiouracils
Iodothyronine-5′ deiodinase	Propylthiouracil
HMG-CoA reductase	Statins
5α-Testosteron reductase	Finasteride, Dutasteride
Dihydrofolate reductase (bacterial)	Trimethoprim
Dihydrofolate reductase (human)	Methotrexate
Dihydrofolate reductase (parasitic)	Proguanil
Enoyl reductase (mycobacterial)	Isoniazid, Ethionamide Protionamide Pyrazinamide
Xanthine oxidase	Allopurinol
TRANSFERASES	
Protein kinase C inhibitors	Miltefosine
Bacterial peptidyl transferase	Chloramphenicol
Catecholamin-O-methyltransferase inhibitors	Entacapone

Table: (continued)

TRANSFERASES (cont.)	
RNA polymerase (bacterial)	Ansamycin
Reverse transcriptases (viral)	
competitive inhibitors	Abacavir, Zidovudine
allosteric inhibitors	Efavirenz, Nevirapine
DNA polymerases	Acyclovir Valgancyclovir; Suramin
Transaminases	
GABA transaminase	
inhibitors	Valproic acid Vigabatrin
Tyrosine kinases	
PDGF-R-, ABL- und KIT-receptor tyrosine kinases	
inhibitors	Imatinib
HYDROLASES	
Esterases	
Acetylcholinesterase	
inhibitors	Physostigmine Neostigmine, Galantamine
reactivators	Obidoxime, Pralidoxime
Phosphodiesterases	Caffein
Phosphodiesterase-5 inhibitors	Sildenafil
Glycosidases	
α-Glycosidases, viral	
inhibitors	Zanamivir, Oseltamivir
α-Glycosidases, human	
inhibitors	Miglitol
Lipases	
Lipoprotein lipase	
effectors	Fibrates
Gastrointestinal lipases	
inhibitors	Orlistat
Proteases	
Aspartyl proteases	
Viral aspartyl proteases	Saquinavir, Indinavir
Serin proteases	
Bacterial serin proteases	
direct inhibitors	Beta lactams
indirect inhibitors	Glycopeptides
Lactamases	
inhibitors	Sulbactam
hAntithrombin	
activators	Heparin-Na
hPlasminogen	
activators	Streptokinase
Trypsin, Kallikrein	Aprotinin
Coagulation factors	
activators	Factor IX complex Factor VIII
Faktor Xa inhibitor	Fondaparinux
Metalloproteases	
hAngiotensin converting enzyme	
inhibitors	Captopril
Human renal dehydropeptidase	
inhibitors	Cilastatin
Carboxypeptidase A (Zn)	
inhibitors	Penicillamine
Vasopeptidase (a neutral endopeptidase)	Omapatrilat
Phosphatases	
Calcineurin	
inhibitors	Ciclosporin Tacrolimus Pimecrolimus
Inositol polyphosphate phosphatase	
inhibitors	Lithium ions
Phosphorylases	
Bacterial C55-lipidphosphate dephosphorylase	
inhibitors	Bacitracin

Table: (continued)

LYASES	
DOPA decarboxylase	Carbidopa
Carboanhydrase	Acetazolamide
Histidine decarboxylase	Tritoqualine
Ornithine decarboxylase	Eflornithine
ISOMERASES	
Alanine racemase	D-Cycloserine
DNA gyrases	
bacterial DNA gyrases	Quinolones, Floxacins
Topoisomerases	
Topoisomerase II	Etoposide, Doxorubicin Daunorubicin
LIGASES (= SYNTHASES)	
Dihydropteroate synthase	Sulfonamides
Thymidylate synthase (fungal and human)	Fluorouracil
Thymidylate synthase (human)	Methotrexate
Kinases	
Phosphofructokinase inhibitors	Antimony compounds
an intracellular kinase	Sirolimus (= Rapamycin) complexed with an FK506-binding protein
Haem polymerase (Plasmodium)	Chloroquine, Primaquine Quinines, Mefloquine
1,3-β-D-Glucansynthase (fungi)	
inhibitors (non-competitive)	Caspofungin
Glucosylceramide synthase	
inhibitors	Miglustat
Substrates, Metabolites, Proteins	
Asparagine	Asparaginase
Urate	Rasburicase (an urate oxidase)
VAMP-Synaptobrevin, SNAP25, Syntaxin	light chain of the botulinum neurotoxin (Zn-endopeptidase)
RECEPTORS	
DIRECT LIGAND-GATED ION CHANNEL RECEPTORS	
$GABA_A$ receptors	
Barbiturate binding site	
agonists	Barbiturate
Benzodiazepine binding site	
agonists	Diazepam
antagonists	Flumazenil
Acetylcholine receptors	
Nicotinic receptors	
agonists	Pyrantel (by Angiostrongylus), Levamisole
antagonists	
stabilizing	Alcuronium
depolarizing	Suxamethonium
Glutamate receptors (ionotrope)	
NMDA subtype	
antagonists	Memantine
expression modulators	Acamprosate
Phencyclidine binding site	
antagonists	Ketamine
G-PROTEIN COUPLED RECEPTORS	
Acetylcholine receptors	
Muscarinic receptors	
Muscarine receptor subtypes	
agonists	Pilocarpine
antagonists	Atropine, Tropicamide, Ipratropiumbromide, Biperidene, Tiotropiumbromide

Table: (continued)

G-PROTEIN COUPLED RECEPTORS (cont.)	
Adenosine receptors	
antagonists	Caffein, Theophylline
Adrenoceptors	
agonists	Adrenaline, Noradrenaline, Ephedrine
α-Adrenoceptors	
α_1- & α_2-receptors	
agonists	Xylometazoline
α_1-receptors	
antagonists	Prazosine, Ergotamine
α_2-receptors, central	
antagonists	Methyldopa
β-Adrenoceptors	
antagonists	Isoprenaline
β_1-receptors	
antagonists	Propranolol, Atenolol
β_2-receptors	
agonists	Salbutamol
antagonists	Propranolol
Angiotensin receptors	
AT_1-receptors	
antagonists	Sartans
Cannabis receptors	
CB_1- & CB_2-receptors	
agonists	Dronabinol
Cysteinyl-leukotriene receptors	
antagonists	Montelukast
Dopamine receptors	
Dopamine receptor subtypes	
direct agonists	Dopamine, Levodopa
D_2-, D_3-, D_4-agonists	Apomorphine
antagonists	Metoclopramide, Ergometrine, Chlorpromazine, Fluphenazine
D2-antagonists	Haloperidol, Ziprasidone
Endothelin receptors (ET_A, ET_B)	
ET-1	
antagonists	Bosentan
$GABA_B$ receptors	
antagonists	Baclofen
Glucagon receptors	
agonists	Glucagon
Histamine receptors	
Histamine receptor subtypes	
H_1-antagonists	Diphenhydramine, Cetirizine, Loratadine, Ebastine
H_2-antagonists	Cimetidine, Ranitidine
Opioid receptors	
agonists	Morphine, Pethidine, Codeine, Loperamide
partial agonists	Buprenorphine
antagonists	Naltrexon
partial antagonists	Buprenorphine
Neurokinin receptors	
NK receptor subtypes	
NK1 receptors	
antagonists	Aprepitant
Prostanoid receptors	
agonists	Misoprostol, Sulprostone, Iloprost
antagonists	Bimatoprost
Serotonine receptors	
Serotonine receptor subtypes	
(partial) agonists	Ergometrine, Ergotamine
$5\text{-}HT_{1B/1D}$	
agonists	Triptans
$5\text{-}HT_2$	
antagonists	Quetiapine
$5\text{-}HT_{2A}$	
antagonists	Ziprasidone
$5\text{-}HT_3$	
antagonists	Ondansetrone

Table: (continued)

G-PROTEIN COUPLED RECEPTORS (cont.)	
Vanilloide receptors	
agonists	Paracetamol (N-(4-hydroxyphenyl)-arachidonylamide)
Vasopressin receptors	
agonists	Vasopressin
V_2-agonists	Desmopressin
OT-agonists	Oxytocin
antagonists	
OT-antagonists	Atosiban
INTERLEUKINE RECEPTORS	
IL-1 receptors	
antagonists	Anakinra
RECEPTORS ASSOCIATED WITH A TYROSINE KINASE	
Insulin receptor	
direct agonists	Insulin
sensitizers	Glitazone, Biguanides
INTRACELLULAR RECEPTORS	
Steroid hormone receptors	
Mineralcorticoid receptors	
agonists	Aldosterone et. al.
antagonists	Spironolactone
Glucocorticoid receptors	
agonists	Glucocorticoids
Gestagen receptors	
agonists	Gestagens
Estrogen receptors	
agonists	Estrogens
(partial) antagonists	Clomifene
antagonists	Tamoxifene
downregulators	Fulvestrant
Androgen receptors	
agonists	Testosterone
Vitamin D hormone receptors	
agonists	Vitamin D & analogs
ACTH receptors	
agonists	Tetracosactide
Cytosolic guanylate cyclases	
NO donors	
via reductive biotransformation	Nitric acid esters
non-enzymatic	Molsidomine, Nitroprusside-Na
INTRANUCLEAR RECEPTORS	
Thyroid hormone receptors	L-Thyroxine
ION CHANNELS	
VOLTAGE-DEPENDENT CA CHANNELS	
general	Carbamazepine, Oxcarbazepine, Lamotrigine
in Schistosoma sp.	
inhibitors	Praziquantel
L-type channels	
inhibitors	Nifidipine, Verapamil, Lercanidipine
T-type channels	
inhibitors	Succinimides
K CHANNELS	
K channel openers	Sulfonylurea, Nateglinide
NA CHANNELS	
epithelial Na channels (ENaC)	
inhibitors	Quinidine, Procainamide, Lidocaine, Bupivacaine, Amiloride
voltage-dependent Na channels	Carbamazepine, Phenytoine, Topiramate, Valproic adic

Table: (continued)

Cl CHANNELS	
Cl channel opener (parasites)	Ivermectin
Inhibitors (mast cells)	Cromoglycic acid
$Na^+/K^+/Cl^-$ COTRANSPORTERS	
Inhibitors	Diuretic sulfonamides
Na^+ NEUROTRANSMITTER COTRANSPORTERS (SAIER 1999; GOLDBERG ET AL. 2003)	
Inhibitors	Clomipramine, Amitryptiline, Fluoxetine, Reboxetine, Dopamine, Tiagabine
NaCl TRANSPORTERS	
Inhibitors	Diuretic thiazides
Na^+/H^+ ANTIPORTERS	
	Triamterene, Amiloride
PROTON PUMPS	
Mg^{2+}-dependent ATPase inhibitor	Reserpine
Ca^{2+}-dependent ATPase (PfATP6;Plasmodia) inhibitors	Artemisinine & derivatives
H^+/K^+-ATPase inhibitors	Omeprazole
Na^+/K^+ ATPASE	
Inhibitors	Cardiac glycosides
NUCLEIC ACIDS	
DNA AND RNA	
Alkylation	Cisplatin, Cyclophosphamide, Chlorambucile, Chlormethine, Dacarbazine
Intercalation	Doxorubicin, Daunorubicin, Bleomycin
Strand breaks	Nitroimidazoles
False base pairs	Azathioprine, Mercaptopurine, Cytarabine, Idoxuridine, Adefovir-dipivoxil
RNA	
rRNA	
16S-rRNA	Aminoglycoside antiinfectives
23S-rRNA	Makrolide antiinfectives
23S-rRNA/tRNA/2-polypeptide complex	Oxazolidinone antiinfectives
SPINDLE	
Inhibition of development	Vinca alkaloids
Inhibition of desaggregation	Taxanes
INHIBITION OF MITOSIS	
	Colchicine
RIBOSOMES	
As soon as information becomes available as to which proteins or which RNA sequence a compound binds to, it will be added to this section	
30S SUBUNIT (BACTERIAL)	
	Tetracyclines
50S SUBUNIT (BACTERIAL)	
	Lincosamides, Quinupristin-Dalfopristin

Table: (continued)

PHYSICOCHEMICAL MECHANISMS	
Acid binding	Magnesium hydroxide, Aluminum hydroxide
Adsorptive	Activated charcoal
Adstringent	Bismuth compounds
Surface active substances	Simeticone, Chlorhexidine, Chloroxylene
on cell membranes	Coal tar
from fungi	Nystatin, Amphotericin B
Mucosal irritation	Anthrones, Anthraquinones
Osmotically acitve	Lactulose, Dextran 70, Polygeline, Glucose, Elektrolyte solutions, Mannitol
Water binding	Urea, Ethanol
UV absorbant	p-Amino-benzoic acid derivatives
Reflective	Zinc oxide, Titanium dioxide
	Tannines, Polyphenoles; Dithranol; Polyvidon iodide; Silver nitrate, Hypochlorite, Permanganate, Benzoylperoxide; Nitroimidazoles, Nitrofuranes; Temoporfin (mainly via singlet oxygen; cytostatic drug), Verteporfin (mainly via singlet oxygen; ophthalmic drug)
Reductive	
reduces disulfide bridges	D-Penicillamine, N-Acetyl-cysteine
Complexing agents	Al^{3+}, Arsenic compounds
Salt formation	Sevelamer
Modification of tertiary structure	Enfuvirtide (from glycoprotein 41)
ANTIGEN-ANTIBODY REACTIONS	
Sera, vaccines	
Immune modulators	Pegfilgastrim, pegylated Interferon-α2, Glatirameracetat
Monoklonale antibodies	Alemtuzumab, Etanercept, Trastuzumab
UNKNOWN MECHANISM OF ACTION	
	Alendronate (osteoclast inhibitor)
	Ambroxol (stimulates mucus production)
	4-Aminosalicylic acid
	Arsenic trioxide (cytostatic drug)
	Beclaplermin (wound treatment)
	Bexarotene (cytostatic drug)
	Bupropion (smoking cessation)
	Chloral hydrate
	Clofazimine
	Dactinomycin (RNA synthesis inhibitor)
	Dapsone (folic acid synthesis)
	Diethyl carbamazine
	Diethyl ether
	Diloxanide
	Dinitric oxide
	Ethambutol
	Ezetimib (cholesterol absorbtion inhibitor)
	Gentian violet
	Ginkgolides
	Griseofulvin (Ann Dermatol Venereol. 2001 Dec;128(12):1317−25)
	Halofantrine, Limefantrine (anti-malaria drug; prevents haem polymerization)
	Halothane
	Hydrazinophthalazine
	Levetiracetam (antiepileptic drug)
	Mebendazole
	Methyl-(5-amino-4-oxopentanoate) (cytostatic drug)
	Niclosamide
	Pentamidine
	Podophyllotoxin
	Procarbazine
	Selenium sulfide

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