Agonist - Any molecule that improves the activity of a different molecule; e.g., a hormone, which acts as an agonist when it binds to its receptor, thus triggering a biochemical response.

Amino acids - A group of 20 different kinds of small molecules that link together in long chains to form proteins. Often referred to as the "building blocks" of proteins. The sequence of amino acids in a protein determines the structure and function of the protein.

Analog - A drug whose structure is related to that of another drug but whose chemical and biological properties may be quite different.

Antagonist - A molecule that blocks the ability of a given chemical to bind to its receptor, preventing a biological response.

Assay - A biological test, measurement or analysis to determine whether compounds have the desired effect either in a living organism, outside an organism, or in an artificial environment.

Bioassay - Determination of the relative strength of a drug by comparing its effect on a test organism with that of a standard preparation.

Bioavailability - The percentage of drug that is detected in the systemic circulation after its administration. Losses can be attributed to an inherent lack of absorption/passage into the systemic circulation and/or to metabolic clearance. Detection of drug can be accomplished pharmacodynamically (quantification of a biological response to the drug) or pharmacokinetically (quantification of actual drug concentration). Oral bioavailability is associated with orally administered drugs.

Biotechnology - The industrial application of living organisms and/or biological techniques developed through basic research. Biotechnology products include pharmaceutical compounds and research materials.

Combinatorial chemistry (combinational chemistry or combichem) - Is used to synthesize large number of chemical compounds by combining sets of building blocks. Each newly synthesized compound's composition is slightly different from the previous one. A traditional chemist can synthesize 100-200 compounds per year. A combinatorial robotic system can produce in a year thousands or millions compounds which can be tested for potential drug candidates in a high-throughput screening process.

Combinatorial organic synthesis - A key feature of combinatorial techniques is that compound synthesis can be designed such that a range of structures can be produced simultaneously as mixtures in the same reaction vessel or individually in parallel using semi- automated synthesis. The repetitive nature of the synthetic processes involved in most combinatorial applications lends itself to automation or semi- automation. This key feature means that the bench chemist can single- handedly prepare tens, hundreds, or thousands of compounds of known structures in the time that it would take to prepare only a few pure entities by orthodox methodology.

Directed library (focused library) - Library which uses a limited number of building blocks chosen on the basis of pre-existing information or hypothesis which defines the type of functionalities deemed important to obtain a particular activity.

Drug - Any substance presented for treating, curing or preventing disease in human beings or in animals. A drug may also be used for making a medical diagnosis or for restoring, correcting, or modifying physiological functions.

Drug development process:

•Discovery: Identification of a biological, genetic or protein target linked to a particular disease; subsequent lead identification of a potential drug that interacts with the target to help cure the disease or halt its progression.

•Pre-clinical Phase: Comprehensive in vitro and animal testing of the drug

candidate to establish its target specificity, toxicity in various doses and pharmacokinetics.
•Clinical Phase I: Human trials conducted to demonstrate safety and effectiveness (efficacy); tests with paid, healthy volunteers to establish dosage, side effects and pharmacokinetics.
•Clinical Phase II: Trials with small numbers of patients conducted to identify drug performance characteristics (optimal dosing, administration, key indication).
•Clinical Phase III: Pivotal trials conducted with larger patient populations to establish efficacy and provide additional safety information.
•Approval: Data is analyzed and submitted for regulatory review. The U.S. submission to the FDA is called an NDA (New Drug Application) or BLA (Biologic License Application); the European submission to the EMEA (European Medicines Evaluation Agency) is called an MAA (Marketing Authorization Application). After stringent analysis and review of the submission, the regulatory agency provides final approval.

Drug targeting - A strategy aiming at the delivery of a compound to a particular tissue of the body.

Enzyme - A macromolecule, usually a protein, that functions as a (bio) catalyst by increasing the reaction rate. In general, an enzyme catalyzes only one reaction type (reaction selectivity) and operates on only one type of substrate (substrate selectivity). Substrate molecules are transformed at the same site (regioselectivity) and only one of a chiral substrate or of a racemate is transformed (enantioselectivity).

GPCR - G - protein coupled receptors form a large super - family of proteins composed of three major classes and more than 30 subfamilies. They are integral membrane proteins characterized by seven membrane- spanning (transmembrane; TM) regions. They are involved with signal transduction across cell membranes. Many medically and pharmacologically important proteins are included in this super-family: e.g., Acetylcholine receptors, Dopamine receptors, and Opioid receptors.

Hard drug - A nonmetabolizable compound, characterized either by high lipid solubility and accumulation in adipose tissues and organelles, or by high water solubility. In the lay press the term refers to a powerful drug of abuse such as cocaine or heroin.

High - throughput screening (HTS) - Is a tool in the discovery of pharmaceutical, chemical, and agricultural compounds. Compounds for HTS are made by either combinatorial chemistry or by synthetic chemists. During high-throughput screening (HTS) a large number of compounds are analyzed, therefore prediction of the pharmacokinetic properties of drug candidates is an important issue.

Hit - Library component with good level of desired activity.

Inhibitors - Agents that block or suppress the activity of enzymes such as proteases.

Ion channel - An integral membrane protein that provides for the regulated transport of a specific ions across a membrane.

Isosteres - Molecules or ions of similar size containing the same number of atoms and valence electrons.

Lead compound - A compound that exhibits pharmacological properties which suggest its value as a starting point for drug development.

Lead discovery - The process of identifying active new chemical entities, which by subsequent modification may be transformed into a clinically useful drug.

Lead generation - The term applied to strategies developed to identify compounds which possess a desired but non-optimized biological activity.

Lead optimization - The synthetic modification of a biologically active compound,

to fulfill stereo electronic, physicochemical, pharmacokinetic and toxicological clinical usefulness.

Ligand - A small molecule that binds specifically to a larger one; for example, a hormone is the ligand for its specific protein receptor.

Ligand design - The design of ligands using structural information about the target to which they should bind, often by attempting to maximize the energy of the interaction.

Lipid - A water-insoluble molecule which is soluble in nonpolar solvents such as ether. Divided into two classes: Saponifiable and nonsaponifiable.

Lipophilic - Capable of combining with or dissolving in lipids.

Lipophilicity - The affinity of a molecule or a moiety for a lipophilic environment. It is commonly measured by its distribution behavior in a biphasic system, either liquid-liquid (e.g., partition coefficient in 1-octanol/water) or solid/liquid (retention on reversed-phase high performance liquid chromatography (RP-HPLC) or thin-layer chromatography (TLC) system).

Lipinski's Rule of 5 - Set of criteria for predicting the oral bioavailability of a compound on the basis of simple molecular features (MolWt <= 500, clogp <= 5.0, Hbond donors <= 5, Hbond acceptors <=10, Free-rotation bonds <= 10). Often used to profile a library or virtual library with respect to the proportion of drug - like members which it contains. An algorithm, developed by Christopher A. Lipinski (of Pfizer) and colleagues, in which many of the cutoff numbers are five or multiples of five. There are actually four rules, and Pfizer has developed a additional number of criteria for adoption of lead candidates.

Macromolecule - A molecule having a molecular weight in the range of a few

thousand to many millions: proteins, nucleic acids and polysaccharides.

Mass spectrometer - A spectroscopic device in which the masses of particles, ions, and isotopes are measured. It separates isotopes according to charge and mass.

Medicinal chemistry - A chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships.

Moieties - Chemical compounds or functional groups or portions of those compounds.

Molecular modeling - A technique for the investigation of molecular structures and properties using computational chemistry and graphical visualization techniques in order to provide a plausible three-dimensional representation under a given set of circumstances.

Nanomolar - A concentration representing one billionth of a mole.

New chemical entity (NCE) - A compound not previously described in the literature.

Nuclear Magnetic Resonance (NMR) - NMR spectroscopy makes it possible to discriminate nuclei, typically protons, in different chemical environments. The electron distribution gives rise to a chemical shift of the resonance frequency. The chemical shift of a nucleus is expressed in parts per million (ppm) by its frequency, n, relative to a standard, ref, and defined as = 106 (n - ref)/o, where o is the operating frequency of the spectrometer. It is an indication of

the chemical state of the group containing the nucleus. More information is derived from the spin-spin couplings between nuclei, which give rise to multiplet patterns. Greater detail may be derived from two- or three- dimensional techniques. These use pulses of radiation at different nuclear frequencies, after which the response of the spin system is recorded as a free- induction decay (FID). Multidimensional techniques, such as COSY and NOESY, make it possible to deduce the structure of a relatively complex molecule such as a small protein (molecular weight up to 25,000).

Optimization - The process of synthesizing chemical variations, or analogs, of a lead compound, with the goal of creating those compounds with improved pharmacological properties.

Parallel synthesis - Strategy whereby sets of discrete compounds are prepared simultaneously in arrays of physically separate reaction vessels or micro compartments without interchange of intermediates during the assembly process.

Peptide - A molecule composed of two or more amino acids. Larger peptides are generally referred to as polypeptides or proteins.

Peptide bond Peptide - A planar, amide linkage between the amino group of one amino acid and the carboxyl group of another, with the elimination of a molecule of water.

Pharmacokinetics - The study of absorption, distribution, matabolism and excretion (ADME) of bioactive compounds in a higher organism.

Pharmacology - The science of studying both the mechanisms and the actions of drugs, usually in animal models of disease, to evaluate their potential therapeutic value.

Pharmacophore - A pharmacophore is the ensemble of steric and electronic

features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response. A pharmacophore does not represent a real molecule or a real association of functional groups, but a purely abstract concept that accounts for the common molecular interaction capacities of a group of compounds towards their target structure.

Potency - Refers to the concentration of an agent (drug) at which it inhibits an enzyme to a defined extent, i.e. IC50 is the concentration at which an inhibitor blocks the activity of an enzyme 50 per cent.

Privileged structure - Substructural feature which confers desirable (often drug-like) properties on compounds containing that feature. Often consists of a semi- rigid scaffold which is able to present multiple hydrophobic residues without undergoing hydrophobic collapse.

Prodrug - A chemical structure that undergoes conversion to an active drug within a biological system, such conversion usually involving metabolism.

Protease - An enzyme that hydrolyzes (breaks down a bond and adds water) proteins, especially to peptides.

Protein - A molecule composed of a long chain of amino acids. Proteins are the principal constituents of cellular material and serve as enzymes, hormones, structural elements, and antibodies. The molar mass is usually above 100,000.

Protein kinases - Enzymes that phosphorylate certain amino acid residues (most often Ser, Thr, or Tyr) in specific proteins.

Quantitative analysis - chemical determination of the amounts or proportions of constituents in a substance.

Quantitative Structure - Activity Relationships (QSAR) - Mathematical relationships linking chemical structure and pharmacological activity in a quantitative manner for a series of compounds. Methods which can be used in QSAR include various regression and pattern recognition techniques.

Receptor - A molecule within a cell or on a cell surface to which a substance (such as a hormone or a drug) selectively binds, causing a change in the activity of the cell.

Scaffold - Core portion of a molecule common to all members of a combinatorial library.

Serine protease - A family of proteases, characterized by a serine amino acid at its active site.

Solid - phase synthesis - Synthesis of compounds on a solid surface such as tiny plastic beads. In solid-phase approaches, pin or bead techniques permit the synthesis of different molecules on each pin (i.e., "one molecule- one bead"). The products of solid-phase synthesis can be cleaved from the backbone matrix for solution screening (which is essential when the screening target is a cell), or the most active molecules displayed on the polymer surface may be detected using molecular targets (receptor, enzyme, antibody) pre-tagged with a means of detection (visible color, fluorescence, radioactivity, chromophore, etc.) and then isolated and identified.

Solution phase - Solution-phase combinatorial approaches have recently become of interest as an alternative drug discovery avenue for lead discovery and optimization. The key advantages of solution-phase combinatorial approaches include an unlimited number of reactions can be used, therefore, providing maximal structural diversity, an unlimited reaction scale allows for the generation of sufficient quantities of libraries to be derived into different diverse libraries and tested in a broad range of assays, a large excess of reagents and solvents, typically required in solid-phase chemistry, are not needed in solution-phase chemistry, there is no need for linker manipulation, attachment to

and detachment from resin; therefore, the reaction sequences for library generation are shorter, soluble intermediates and final products can be obtained directly for purification and assays, it is easy to develop and monitor solution-phase reactions, and it is an efficient way for lead discovery and optimization from single-compound and complex libraries.

Spectroscopy - Is the analysis of the lines of light emitted from excited atoms as the electrons drop back through their orbitals. These lines give the energy and distances of the electronic orbitals.

Structure - Activity Relationship (SAR) - An analysis which defines the relationship between the structure of a molecule and its ability to affect a biological system.

Template - A macromolecular pattern for the synthesis of another molecule. For example, DNA is a template for RNA synthesis.

Thematic libraries synthesis - Over the past several years, combinatorial chemistry has gradually realigned itself with changing business needs. In many organizations diversity-driven library production intended to broadly cover druglike chemical space has to a large extent been replaced by thematic as well as project-directed libraries. Thematic libraries are particularly useful for a platform target-based approach to drug discovery because the control of a common biochemical theme (e.g., the use of enzyme inhibitors, peptidomimetics of receptor ligands, etc.) can often cross over providing leads in several therapeutic areas.

Three - dimensional Quantitative Structure - Activity Relationship (3D-QSAR) - The analysis of the quantitative relationship between the biological activity of a set of compounds and their spatial properties using statistical methods.

Unbiased library - Library prepared from building blocks chosen without bias towards a particular target.

Virtual library - A library which exists solely in electronic form or on paper. The building blocks required for such a library may not exist, and the chemical steps for such a library may not have been tested. These libraries are used in the design and evaluation of possible libraries.