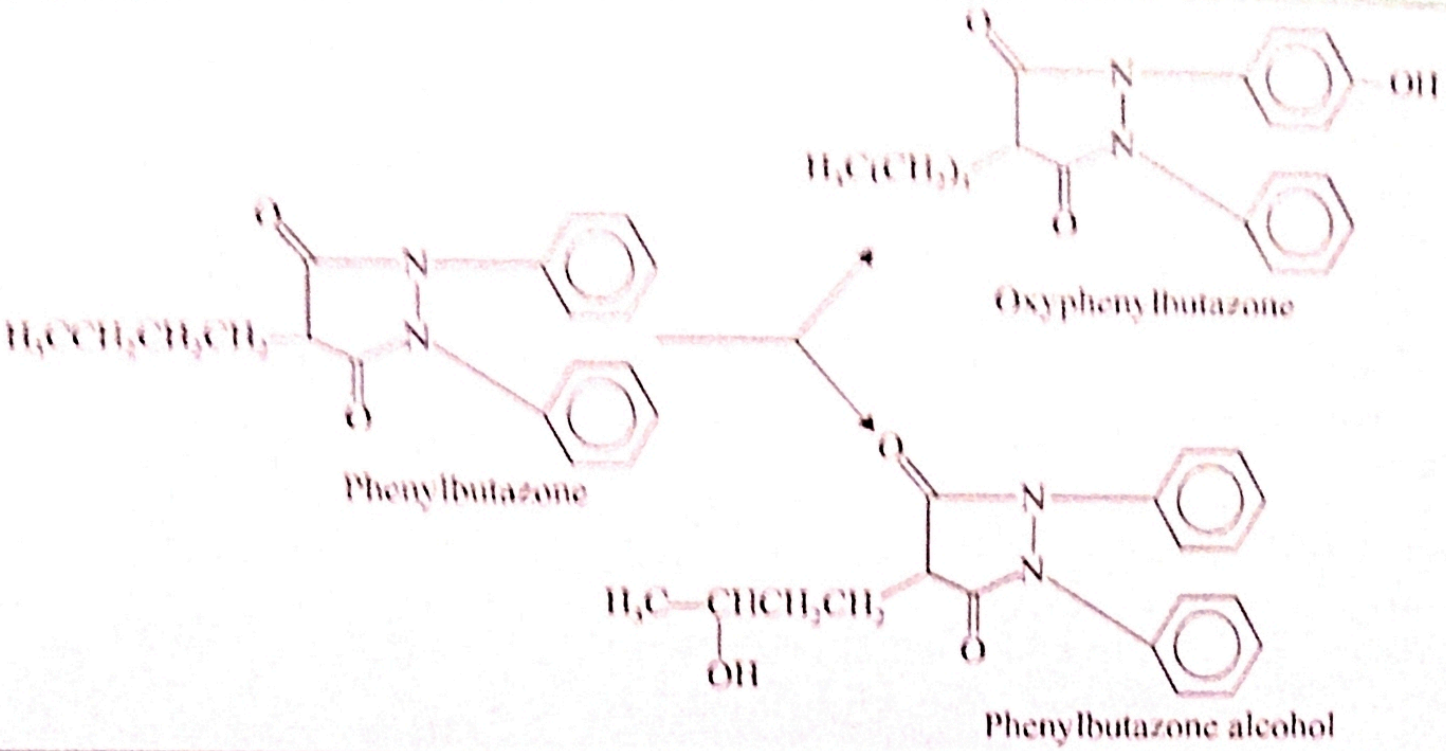

4. FACTORS GOVERNING DRUG-DESIGN

A few cardinal factors governing the efficacy towards the evaluation of **drug design** include :

(*a*) The smaller the expenditure of human and material resources involved to evolve a new drug of a particular value, the more viable is the design of the programme.

(*b*) Experimental animal and clinical screening operations of the new drugs.

(*c*) Relationships between chemical features and biolgoical properties need to be established retrospectively.

(*d*) **Quantitative structure-activity relationships (QSARs)** vary to an appreciable extent in depth and sophistication based on the nature of evaluation of structure or activity. A purposeful relation of structural variables must include steric factors, electronic features of component functional groups and, in general, the molecule as a whole.

(*e*) The trend to synthesize a huge number of newer medicinal compounds indiscriminately for exploratory evaluation still prevails which exclusively reflects the creative genuineness and conceptual functions of a highly individualized expression of novelty by a medicinal chemist.

(*f*) Introduction of functional groups in a molecule that need not essentially resemble metabolites, but are capable of undergoing bonding interactions with important functional groups of biochemical components of living organisms affords an important basis for exploration.

(*g*) Disease etiologies and various biochemical processes involved prove useful.

5. RATIONAL APPROACH TO DRUG DESIGN

A **rational approach to drug design** may be viewed from different angles, namely :

5.1. Quantum Mechanical Approach

Quantum mechanics (or **wave mechanics**) is composed of certain vital principles derived from fundamental assumptions describing the natural phenomena effectively. The properties of protons, neutrons and electrons are adequately explained under **quantum mechanics**. The electronic features of the molecules responsible for chemical alterations form the basis of drug molecule phenomena.

5.2. Molecular Orbital Approach

Based on the assumption that electrons present in molecules seem to be directly linked with orbitals engulfing the entire molecule which set forth the molecular orbital theory. The **molecular orbital approach** shows a dependence on electronic charge as evidenced by the study of three volatile inhalation anaesthetics, and also on molecular conformation as studied with respect to acetylcholine by such parameters as bond lengths and angles including torsional angles.

Molecular orbital calculations are achievable by sophisticated computers, and after meticulous interpretations of results the molecular structure in respect of structure-activity analysis is established.

5.3. Molecular Connectivity Approach

This approach establishes the presence of structural features like cyclization, unsaturation, skeletal branching, and the position and presence of heteroatom in molecules with the aid of a series of numerical indices. **For example :** an index was determined to possess a correlative factor in the SAR study of amphetamine-type hallucinogenic drugs.

Molecular connectivity approach has some definite limitations, such as : **electronegativity variance between atoms, non-distinguishable entity of *cis-trans* isomerism.**

5.4. Linear Free-Energy Approaches

This method establishes the vital link between the proper selection of physicochemical parameters with a specific biological phenomenon. However, such a correlation may not guarantee and allow a direct interpretation with regard to molecular structure, but may positively offer a possible clue towards the **selection of candidate molecules for synthesis.**

6. DRUG-DESIGN : THE METHOD OF VARIATION

Under this method a new drug molecule is developed from a **biologically active prototype.** The various **advantages** are as follows :

(*a*) At least one new compound of known activity is found.

(*b*) The new structural analogues even if not superior may be more economical.

(*c*) Identical chemical procedure is adopted and hence, considerable economy of time, library and laboratory facilities.

(*d*) Screening of a series of congener (*i.e.*, member of the same gene) gives basic information with regard to pharmacological activity.

(*e*) Similar pharmacological technique for specific screening may be used effectively.

The **cardinal objectives** of the **method of variation** are :

- To improve potency