NEW AGE

Fourth Edition

# Medicinal Chemistry

Ashutosh Kar

NEW AGE INTERNATIONAL PUBLISHERS

## 6. REVERSE DESIGNING

Interestingly, **reverse designing** has come into being by virtue of the introduction of *two* extremely important scientific discoveries, namely : (*a*) **High Throughput Screening**, and (*b*) **Combinatorial Chemistry**.

### 6.1. High Throughput Screening

Biological testing procedures may be adopted profusely and automated meticulously in an extremely innovated process known widely as **high throughput screening**, that could be able to carry out the normal, rapid, and precise testing scores of newly designed chemical structures all and sundry at a time. It is, however, pertinent to mention here that in several occasions it is absolutely feasible as well as possible to make use of the enormous fruitful advantages of various well-known **gene-cloning methodologies**. In this manner, one has to first and foremost **clone the desired receptor**, and subsequently measure the **binding phenomenon** of the **newly synthesized drug molecules** to the corresponding **cloned receptor**.

### 6.2. Combinatorial Chemistry

Even with the advent of a plethora of such widely accepted and practised methodologies as : Superb statistical methods, traditional synthetic techniques, and time-tested biological screening procedures, invariably prove to be very expensive and sometimes trun out to be non-productive in nature at the end. In fact, the tremendous stress and strain of this sort of cumbersome testing procedures ultimately led to the enterprising technique commonly known as **combinatorial chemistry**. Interestingly, it overwhelmingly makes use of comprehensive and extended libraries of chemical functional moieties which specifically interact either with a '**base molecule**' or with a '**parent molecule**' in a highly systematic small quantum of well-defined purely synthetic stepwise procedures.

Baum and Borman* (1996) postulated that '**combinatorial chemistry**' refers to a particular sophisticated method of minimizing the effective cost of drug discovery whereby the following *three* cardinal objectives may be accomplished with utmost satisfaction and fruitful results, namely :

(*a*) to determine altogether '**new leads**'

(*b*) to find newer '**prototype drug molecules**', and

(*c*) to **refine and optimize the QSAR**.

**Salient Features :** The various *salient features* of '**combinatorial chemistry**' are as enumerated under :

(1) **Chemical diversity of products :** Useful libraries of '**reactive**' chemical functional moieties invariably give rise to the **chemical diversity of products** which shall be duly screened for respective biological activity.

(2) Chemistry involved is not only graceful and stylish but also comparatively simple, whereby a few '**same reactions**' could suffice in yielding thousands of **drug molecules** in a specific congeneric series.

*Baum R and Borman S : *Chem. Engg. News.*, **74** : 28, 1996.

(3) Invariably, one makes use of the **solid-state synthetic techniques** to allow the **desired growth of drug molecules** upon **polymer support**.

(4) The '**chemical reactions**' involved in (2) and (3) above must fulfil *three* vital and important criteria, such as : (*i*) clean reaction, (*ii*) reproducible reaction, and (*iii*) high yielding reaction.

(5) '**Robotics**' have been employed profusely to cut down the '**effective cost of synthesis**' drastically.

In a rather broader perspective towards the ever increasing and eternal (never-ending) search for newer '**drug molecules**' *i.e.*, chemical entities that essentially requires specific and noteworthy biological characterstic feature do require *two* kinds of approaches, for instance :

(*a*) **Rational Designing :** It is considered to be the most '**popular technique**' by virtue of the fact that it bears a **direct relationship** along with a **methodical stepwise development** of the creative genius and wisdom of a **medicinal chemist** to explore and exploit the **Lock-and Key Model** with respect to the **ligand-receptor docking**.

**Rational designing** usually encounters the following *three* obstacles and hinderances, such as :

(*i*) **limitations***. *e.g.*, conformational flexibilities for both ligand and receptor,

(*ii*) **conformers****. *i.e.*, binding with higher-energy conformers.

(*iii*) **active conformers*****. *i.e.*, influence of salt and water concentration upon the active conformers.

However, all the aforesaid *three* obstacles have been duly taken care of and adequately attended to, with an aim to design a '**drug**' that could mimick vividly the same in an ***in vitro* model.**

(*b*) **Reverse Designing.** Essentially involves the grouping together and searching**** of functionally and structurallly identical chemical entities***** by making use of common and biologically effective motif, termed as **pharmacophore******, which is specifically found either in the **corporate** or **commercial** database. Importantly, at every articulated step carried out meticulously in the **intricate discovery phenomenon** one has to heavily depend upon the manipulative skill(s) related to **CADD**, which provides an extra mileage plus meritorious advantage in **data-processing** into several vital and relevant informations for future analysis in **drug design**.

The elaborated and comprehensive '**Flow Chart**' has been dipicted in Figure 3.11 that evidently depicts the *two* above cited processes *viz.*, **rational designing** and **reverse designing** together with the latest well-known ***in silico* techniques (in box)** that are employed very commonly in various processes associated with **drug design**.

---

*Jorgensen WL., *Science*, **254** : 954, 1991.

**Oshiro CM *et al.* : *J Comput Aided Mol Des.*, **9** : 113, 1995.

***Wlodek ST *et al.* : *Protein Sc.*, **7**, 573, 1998.

****Giller VJ and Johnsen AP : In : **Designing Bioactive Molecules : Three Dimensional Techniques and Applications**, Martin YC and Willen P (Eds.) : **AM. Chem. Soc**, Washington DC, 1997.

*****Martin YC, *J. Med Chem.*, **35** : 2145, 1992.

******Schneider G *et al.* : *Angew Chem Int Ed Engl.* **38**, 2894, 1999.

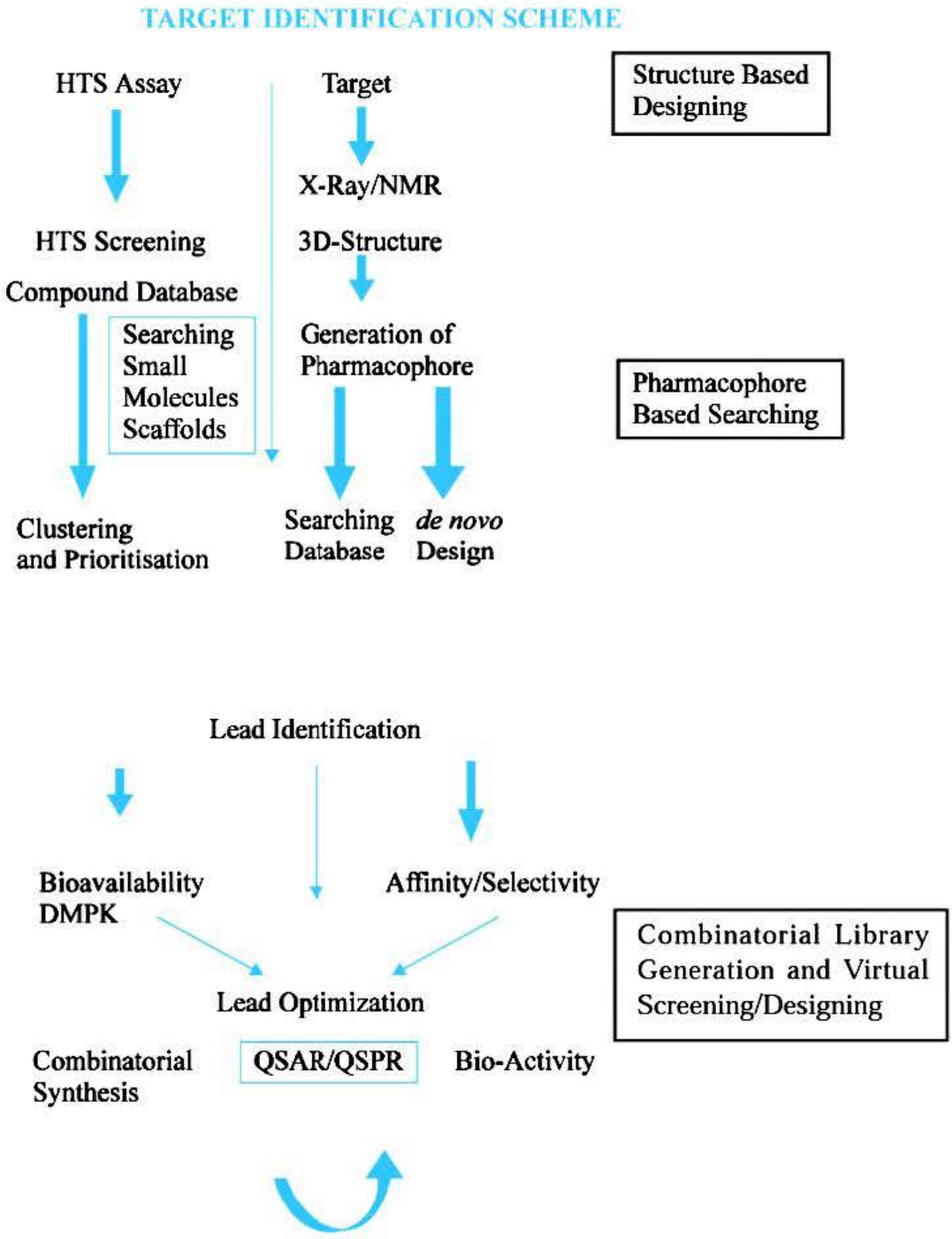


**Fig. 3.11. Flow Chart of Rational Designing and Reverse Designing plus *in silico* Techniques Used in Drug Designing Method**

**[In Silico Techniques are shown in Boxes *viz,* structure-based designing ; Pharmacophore-based designing ; and combinatorial Library generation and virtual screening/designing]**