5. An Approach to Computer-Aided Drug Design: A Trial to Design a New Antiinflammatory Agent

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1. Introduction

Paul Ehrlich's achivement in 1909 of the discovery of a specific cure for syphilis had a profound effect on drug research. Ehrlich and his colleagues made over 600 compounds in an attempt to find a cure for trypanosomiasis. Although the 606th compound was inactive against trypanosomes, Ehrlich's co-worker, S. Hata, tried it on syphilis because of the superficial similarities between trypanosomes and spirohetes. It worked and the drug, *Salvarsan* became famous.

Occasionally new drugs are found by accident. More frequently they are developed as part of an organized effort to discover new ways to treat specific diseases. The traditional way to discover new drugs has been to screen a large number of synthetic chemical compounds or natural products for desirable effects. Although this approach for the development of new pharmaceutical agents has been successful in the past, we have reached the point where it is becoming much less effective.[1,2]

It is estimated that over 5,000,000 perfectly identified chemical substances are described in the current scientific literature. To this number approximately 100,000 new compounds are added every year. Up to now, more than 20,000 sulfonamides, 40,000 potential tuberculostatics, 120,000 potential antimalarials, 900,000 potential antineoplastics and others have been screened. Of which about 4,000 compounds were/are used as drug, and no chemical can be said to cure truely cancer. The probability to find out a new drug is decreasing rapidly. Also, the introduction of new drug into therapeutics is now very expensive. In most countries, the cost of new active ingredient, from is ideation in the researcher's minds until is introduction on the market, ranges from $ 10 million to $ 100 million. The genesis of new drug took about 9 to 13 years.[3] Some efforts to reduce the cost and time were evolved consequently.

Computer-aided drug design has come of age. All the world's major pharmaceutical companies and many in agrochemicals and materials have invested heavily in the area. The combination of theoretical calculation and graphics display is providing tools for deciding which molecules to synthesize for specific roles. The rapid developments in computational science are accelerating the growth. It must be noticed that most of new drugs which are introduced to the market today were developed under the direct or indirect aids of these researches.[1,2,4-7]

However computer-aided drug design itself is not everything. No drug can be designed from nothing. There must be a large number of basic scientific data set which include not only physicochemical parameters but also biological and other informations. There must be researcher's own inspiration to manipulate them, and the correct idea.

To try drug design, some cost is needed such as expensive computer system and softwares which are capable of real-time graphics and certain essential calculations, *etc.*[8] There is an urgent need to establish the research programs in this field, but we cannot say there are sufficient efforts for those in Korea now.

2. The Concept of New Drug

2-1. New chemicals

New chemicals which have more than needed potency of effects, or reduced toxicity, *etc.*

2-2. Known chemicals

Redicovery of known chemicals *via*

Alteration of the drug pharmacokinetics in vivo to enhance its absorption, distribution, biotransformation, and excretion, in other words, enhancement of drug bioavailibility.

*Improvement of stability and solubility properties.

*Adjunct to pharmaceutical formulation.

*Decreased toxicity and adverse reactions.

*Increased site specificity.

*Increased duration of pharmacological effects, *etc.*

3. Methods of New Drug Development

(Rationally directed) random screening with synthetic chemical compounds.

The traditional way to find out new drug *via*

*ring closure or opening.

*formation of lower or higer homologues.

*introduction of double bonds.

*introduction of chiral center.

*introduction, removal or replacement of bulky group.

*isosteric substitution.

*change of position or orientaion of certain groups.

*introduction of alkylating moieties.

*modification toward inhibition or promotion of various electronic states,

3-1. Extraction from natural sources

Our planet shelters approximately 600,000 vegetable species, but less than 10% of them have been studied scientifically under the chemical or pharmacological aspects.[3] It is hoped, therefore, that the therapeutic armamentarium will be gradually enriched with new drugs obtained from planets as a consequences of investigations in this field.

3-2. Rediscovey of Known compound via optimization of effects

*Targeting

*Prodrug

*Bioprecursor

3-3. Indirect approaches from other basic researches

Biochemical, pharmacological researches are making a great advances. The success of basic sciences may provide a new idea for the therapeutic concepts, thus may induce a new drug development.

3-4. Computer-aided drug design

Approaches from QSAR (Quantitative Structure Activity Relationship)

Biological Activity=f(physicochemical properties)

Based upon Hansch equation,[9] the contribution of each substituted group on the biological effect of the compounds are calculated, regressed and compared. If the results are accepted as significant ones, the optimal group can be chosen.[1,4,10,11]

$$\log 1/C_i = a\sigma_i + bEs_i + c\pi_i dMR_i + e + \cdots$$

1) Choose the reference compound.
2) Synthesize analogues having various substituents (20-30 molecules).
3) Test activites.
4) Perform regression for the selected parameters
5) If optimal parameters were found, model the molecules.
6) Synthesize the proposed moleules (2-5 molecuies).
7) Test activities again.
8) Perform regression again, figure out the optimal structure.
9) Synthesize and test.

3-5. Approaches from receptor (binding space) modeling

The basis for this insight is the concept of pharmacophore, i.e. those features common to a set of drugs acting on the same receptor which are responsible for recognition and transduction of the appropriate response. In other words, we can assume a unique three-dimensional pattern of electron density in the receptor which may bind with the ligands. The lock-and-key or induced-fit model may be used to figure out the necessary spatial distribution of the bindig region.[12-17]

1) Collection of the structural data set.
2) Conformation analysis (in solid state, and solution state).
3) Molecular energy state calculations (rotational energy, electrostatic energy, *etc.*).
4) Pattern analysis, figure out pharmacophore.
5) Receptor (binding space) modeling.
6) Binding mode determination.
7) Designing the optimal molecule.
8) Synthesize, test.

3-6. Direct simulation from the known receptor structure

If we know the three-dimensional structure of the receptor, direct simulation of the ensemble of the receptor with varous ligands are possible. By now, over 400 protein structures have determined by X-ray diffraction technique. Several

mode of interaction between the important macromolecules and ligands were reported.[19,20]

4. Requirements for Computer-Aided Drug Design

4-1. Three dimensional structural data of certain drug analogues

*The results of X-ray crystallography and/or NMR.

*(The Cambridge structural database[21])

*Any other structural informations

*Any other structural informations

4-2. Physicochemical data

*pKa, partition coefficient, solubility, *etc.*

4-3. Pharmacological data

*Potency, efficacy, adverse effects

Table I—Some Software Packages Used Frequently in Drug Design

AMBER	--molecular mechanics and dynamics
CAMSEQ	--molecular mechanics and display
CHEMLAB	--molecular mechanics, quantum mechanics, and molecular display
CHEM-X	--molecular mechanics, dynamics and display
DISCOVER	--molecular mechanics and dynamics
INSIGHT	--molecular display
FRODO	--molecular display
GRAMPS	--general graphical display system
HYDRA	--molecular mechanics, dynamics and molecular display
MACRO-MODEL	--molecular mechanics and molecular display
MIDAS	--molecular display
MMS	--molecular display
SYBYL	--molecular mechanics and moleular display
MENDYL	--macromolecular mechanics and molecular display

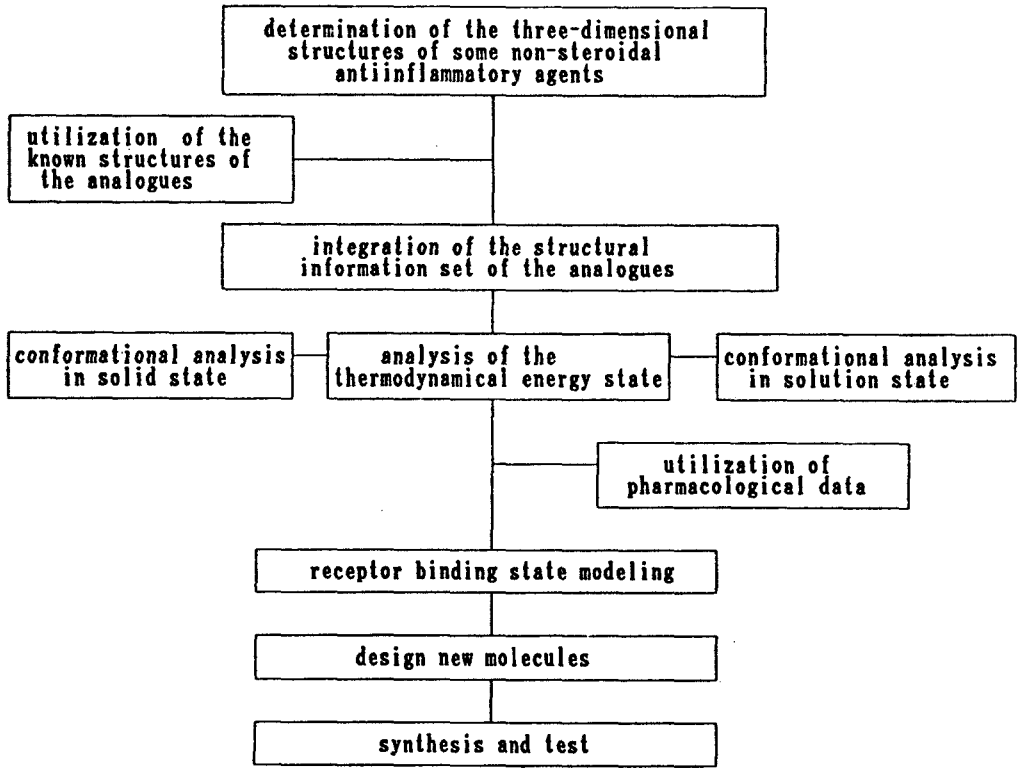

Figure 1—The flow chart of the trial to design new antiinflammatory agent.

4-4. Computer system

*Large memory, fast speed machine with peripherals like color-graphic display, plotter, *etc.*

*Which is capable of real-time graphics and needed calculations

4-5. Softwares

*Softwares to display three-dimensional molecular stuctures freely

*Softwares to calculate the molecular energy state such as molecular mechanics, dynamics, quantum mechanics, and statistical mechanics

*Statistical analysing programs

5. A Trial to Design a New Antiinflammatory Agent

5-1. Determination of three-dimensional structures of some non-steroidal antiinflammatory agent

We have determined the crystal structures of some non-steroidal antiinflammatory agents such as naproxen, alclofenac, fenbufen, cinmetacin, tenoxicam, naproxen sodium etc. by X-ray diffraction technique.[22-27] The three-dimensional structures of some other antiinflammatory agents which were not determined yet are under investigation.

Collection of other structural informations of the analogues

5-2. Conformational analysis

The conformation of the drug analogues in crystal and solution state should be analysed. By NOE and/or COSY techniques of NMR, the conformation of the molecules in solution state may be determined.[28,29] The thermodynamical energy states and barriers are calculated using the appropriate molecular mechanics softwares.

5-3. Receptor (binding space) modeling

Comparing the structural informations of each molecule, one can figure out the essential spatial distribution of the binding space of the receptor.

Design optimal molecules

Synthesize and test

Reconstruction of the three-dimensional binding space

Design, synthesize and test again

References

1) C. Hansch and J.M. Blaney; The New Look to QSAR, In *"Drug Design: Fact or Fantasy ? "*, G. Jolles and K.R.H. Wooldridge Ed., Academic Press, London, 1984, p. 185
2) C.L. Prost and T.J. Perun; Introduction to Computer-Aided Drug Design, In *"Computer-Aided Drug Design, Methods and Application"*, T.J. Perun and C.L. Propst Ed., Marcel Dekker Inc., New York, 1989, p. 2
3) A. Koplkovas; Develoment of drugs, In *"Essentials of Medicinal Chemistry"* 2ed., A. Kopolkova Ed., Wiley, New York, 1988, p. 53
4) T. Fujita; The Role of QSAR, In *"Drug Design: Fact of Fantasy ? "*, G. Jolles and K.R.H. Wooldridge Ed., Academic Press, London, 1984, p. 19
5) H. Weinstein and R. Osman; Interaction Mechanisms at Biological Targets: Implicatons for Design of Serotonin Receptor Ligands, In *"Computer-Aided Molecular Design"*, W.G. Richards Ed., IBM Technical Servies, 1989, p. 105
6) M.J. Wyvratt and A.A. Patchet; Recent Developments in the Design of Angiotensin-converting enzyme inhibitiors, *Med. Res. Rev.*, **5**, 583 (1985)
7) V.N. Balaji, J.S. Dixon, D.H. Smith, R. Venkataraghavan and K.C. Murdock; Design of Anticancer Drus Modeling Techniques, In "Macromolecular Structure and Specificity: Compouter-Assisted Modeling and Application", B. Venkataraghavan and R.J. Feldmann Ed., The New York Academy of Sciences, New York, 1985, p. 140
8) R. Langridge, T.E. Ferrin, I.D. Kuntz and M.L. Connolly; Real-Time Color Graphics in Studies of Molecular Interactions, *Science*, **221**, 661 (1981)
9) C. Hansch; On the Structure of Medicinal Chemistry, *J. Med. Chem.*, **19**(1) 1 (1976)
10) R. Franke; Extrathemodynamic Approach to Quantitative Structure-Activity Analysis (Hansch Analysis), In *"Pharmacochemistry Library, Vol. 7, Theoretical Drug Design Methods"*, R. Franke Ed., Elsevier, Amsterdam, 1984, p. 25
11) P. Moser, A. Sallmann and I. Weissenberg; Synthesis and Quantitative Structure-Activity Relationships of Diclofenac Analogues, *J. Med. Chem.*

33(9), 2359 (1990)

12) D.G. Hangauer; Computer-Aided Design and Evaluation of Angiotensin-Converting Enzyme Inhibitors, In "*Computer-Aided Drug Design, Methods and Applications*", T.J. Perun and G.L. Propst Ed., Marcel Dekker Inc., New York, 1989, p. 253
13) R.A. Scherrer; In "*Antiinframmatory Agents: Chemistry and Pharmacology, Vol. 1*", R.A. Scherrer and M.W. Whitehouse Ed., Academic Press, New York, 1974, p. 29
14) P. Gund and T.Y. Shen; A Model for the Prostaglandin Synthetase Cyclooxygenation Site and Its Inhibition by Antiinflammatory Arylacetic Acids, *J. Med. Chem.*, **20**(9), 1146 (1977)
15) R.A. Appleton and K. Brown; Conformational Requirements at the Prostaglandin Cyclooxygenase Receptor Site: A Template for Designing Nonsteroidal Antiinflammatory Drugs, *Prostaglandins*, **18**(1), 29 (1979)
16) R. Nicholson *et al.*; *J. Pharm. Pharmcol.*, **34** Suppl., 106 (1982)
17) T.A. Andra, S.W. Dietich, W.J. Murray, P.A. Kollman and E.C. Jorgensen; A Model for Thyroid Hormone-Receptor Interactions, *J. Med. Chem.*, **22**(3), 221 (1979)
18) R. Armi, U. Heinemann, M. Maslowska, R. Tokuoka and W. Saenger, *Acta Crysta.*, **B43**, 548 (1987)
19) C. Hansch, R. Li, J.M. Blaney and R. Langridge; Comparison of the Inhibition of *Escherichia coli* and *Lactobacillus casei* Dihydrofolate Reductase by 2, 4-Diamino-5-(substituted benzyl) pyrimidines, *J. Med. Chem.*, **25**, 774 (1982)
20) K. Zakrzewska and R. Lavery; Theoretical Studies of Groove-Binding Drugs with DNA, In "*Computer-Aided Molecular Design*", W.G. Richards Ed., IBM Technical Services, 1989, p. 129
21) Allen F.H., Bellard S., Brice M.D., Cartwrigh B.A., Doubleday A., Higgs H., Hummelink T., Hummelink-Peters B.G., Kennard O., Motherwells W.D. S., Rodgers J.R. and Watson D.G.; The Cambridge Crystallographic Data Center; Computer-based Search, Ritrieval, Analysis and Display of Information, *Acta Cryst.* **B35**, 2331 (1979)
22) Y.B. Kim, S.J. Kim, and J.H. Koo: Refinement of the Structure of Alclofenac, 4-Allyloxy-3-chlorophenylacetic acid ($C_{11}H_{11}O_3Cl$)., *Arch. Pharm. Res.*, **9**(4), 223 (1986)
23) Y.B. Kim, I.Y. Park, and Y.H. Park: The Crystal Structure of Fenbufen, 3-(4-Biphenylylcarbonyl) propionic acid ($C_{16}H_{14}O_3$), A Non-steroidal Antiinflammatory Agent., *Arch. Pharm. Res.*, **11**(2), 127 (1988)
24) Y.B. Kim, I.Y. Park, and Y.H. Park: The Crystal Structure of Cinmetacin ($C_{21}H_{19}NO_4$), A Non-steroidal Antiinflammatory agent., *Arch. Pharm. Res.*, **12**(1), 52 (1989)
25) Y.B. Kim, H.J. Song, and I.Y. Park: Refinement of the Structure of (+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid., *Arch. Pharm. Res.*, **10**(4), 232 (1987)
26) Unpublished results.
27) Y.B. Kim, I.Y. Park, and W.R. Lah: The Crystal Structure of Naproxen Sodium, ($C_{14}H_{13}O_3Na$), A Non-steroidal Antiinflammatory Agent., *Arch. Pharm. Res.*, **13**(2), 166 (1990)
28) G.M. Clore, M. Nilges and A.M. Gronenborn; Determination of Three-Dimensional Structures of Proteins in Solutions by Dynamic Simulated Annealing with Interproton Distances Derived From Nuclear Magnetic Resonance Spectroscopy, In, "*Computer-Aided Molecular Design*", W.G. Richards Ed., IBM Technical Services, 1989, p. 203
29) A. Bax; Chemical Shift Correlation Spectroscopy, In "*Two-Dimensional Nuclear Magnetic Resonance in Liquids*", A. Bax Ed., D. Reidel Publishing Co., Dordracht, p. 50 (1984)