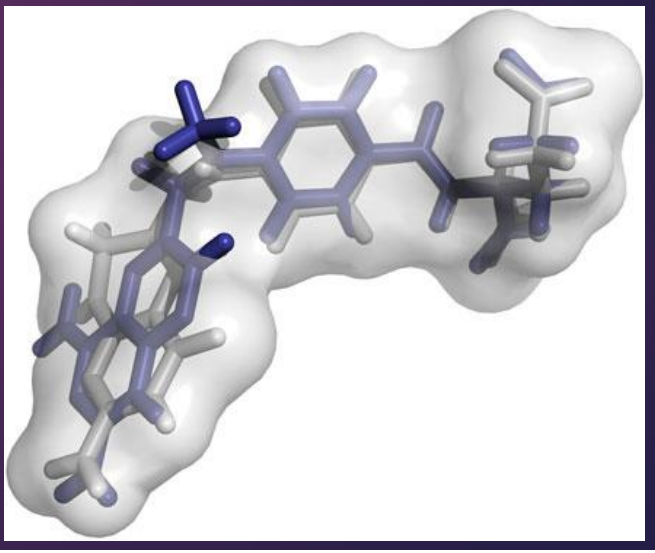
COMPUTER AIDED DRUG DESIGN (CADD) AND DEVELOPMENT METHODS



DRUG DEVELOPMENT

- Drug development is a challenging path
- Today, the causes of many diseases (rheumatoid arthritis, cancer, mental diseases, etc.) are not fully explained and it is even more difficult to develop medicines for these diseases.
- Only 1 out of 10,000 molecules synthesized can be used as a drug.
- It is quite costly.
- It takes a long time.

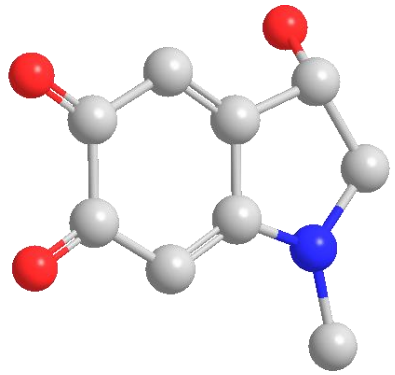
RATIONAL DRUG DESIGN

- For all these reasons, it is now necessary to design drugs in a rational way.

- Understanding of several physiological and biochemical mechanisms and their relation to diseases at the molecular level, clarification of some receptors and structures have contributed to the development of computer-aided drug design methods.

COMPUTER-AIDED DRUG DESIGN

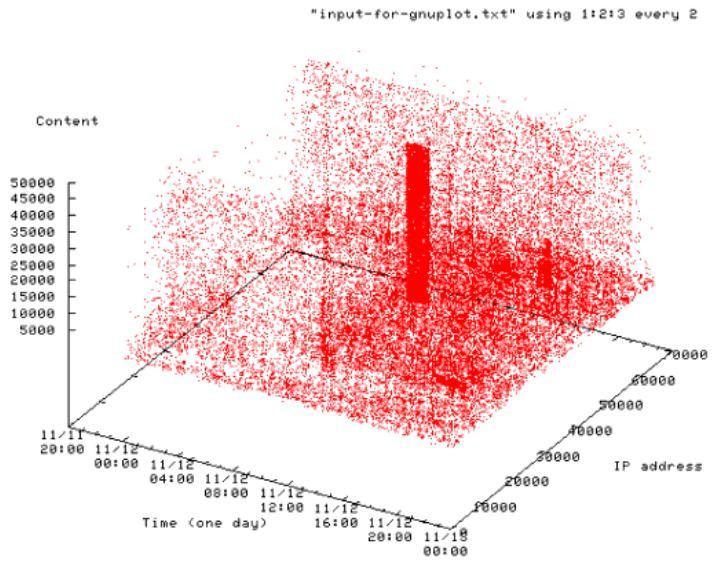
- Quantitative structure activity relationship (QSAR)



- Molecular modeling studies

QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS (QSAR)

- A QSAR is a mathematical relationship between a **biological activity of a molecular system** and **its geometric and chemical characteristics**.



QSAR

- The first study to identify the relationships between chemical structure and biological activity has been done in France in 1863. (A. Cros)
- According to this study,

"As the solubility of water in some of the investigated alcohols decreases, the toxic effects on the mammals are increased".

QSAR's goal

- Designing a new compound that can exert better effect using the structure-effect relationship analysis equation developed over a series of compounds,
- Reducing the toxicity of an existing compound,
- Optimize to be the leader with the optimum lipophilic property to pass a selected barrier (e.g. blood-brain barrier)

Biological Responses Used in QSAR Studies

- **Affinity data:** substrate or receptor binding
- **Rate constants:** association, dissociation
- **Inhibition constants:** IC50, enzyme inhibition values
- **Pharmacokinetic parameters:** absorption, distribution, metabolism, excretion
- ***In vitro* and *in vivo* biological activity data**
- **Pharmacodynamic data of drugs** (drug-receptor interaction)
- **Toxic effect parameters**

Parameters

- Parameters used in QSAR studies are constants that are used to quantitatively describe **intramolecular forces**, **activities such as transportation, distribution** that provide drug receptor interaction.

Physicochemical Parameters Used in Structure-effect Studies

PHYSICOCHEMICAL PARAMETERS	SYMBOL
LIPOPHILIC (HYDROPHOBIC) PARAMETERS	
Partition Coefficient	Log P, $(\log P)^2$
π-Substituent Constant	π, $(\pi)^2$
Chromatography Distribution Coefficient (Liquid-liquid)	R_M
Hydrophobic Fragmental Constant	f
ELECTRONIC PARAMETERS	
Ionization Constant	pK_a
Sigma Aromatic Substituent Constant	σ_m , σ_m
Modification σ Aromatic Substituent Constants	σ^+, σ^-, σ_1, σ_R, σ^o
Sigma Aliphatic Substituent Constant	σ^*
Substituent Resonance Effect	*R*
Substituent Inductive Effect	*F*

Physicochemical Parameters Used in Structure-effect Studies

PHYSICOCHEMICAL PARAMETERS	SYMBOL
QUANTUM MECHANICAL PARAMETERS	
Atomic σ Elektron Charge	q^{σ} , Q^{σ}
Atomic π Elektron Charge	q^{π} , Q^{π}
Nucleophilic Delocalization State	S_r^{N}
Electrophilic Delocalization State	S_r^{E}
Energy of Lowest Unoccupied Molecular Orbital, “electrophilicity“	E_{LUMO}
Energy of Highest Occupied Molecular Orbital, “nucleophilicity“	E_{HOMO}
STERIC PARAMETERS	
Steric Substituent Constant	E_S
Molar Volume	MV
Molar Refractivity Substituent Constant	MR
Molecular Weight	MW
Van der Waals Radii	R
Sterimol Width and Length Parameters	L, B_1-B_4

Structural Parameters (Indicator)

- The structural parameter is used if any position in the molecular structures of the chemical compounds does not include a sufficient number of substituent substitutions.
- Structural parameters are determined to be "1" or "0", respectively, depending on the presence or absence of the molecular substituent being analyzed.

Lipophilic Property

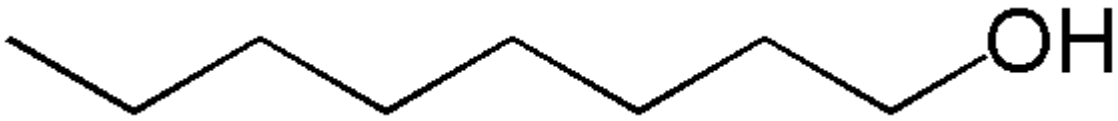
- The most used physicochemical property in QSAR studies are lipophilic property.
- Lipophilicity can be defined as the dispersion between water and oil phase.
- Parameters showing this distribution;
  - Log P
  - R_M

Log P = Partition Coefficient

- It is a parameter that expresses the concentration of the chemical compound distributed between the lipid-water layers. For this purpose, it was found that the most suitable solvent system is 1-octanol / water.
- As the water, the buffer solution is prepared to imitate the physiological pH (pH = 7.4).

Why 1-Octanol

- 1-octanol, due to the long alkyl chain and the polar hydroxyl (OH) group, carries a hydrophobic tail and a polar head. So, it forms a good example of cell membrane lipids.
- The OH group it carries has a receptor and donor property in the formation of hydrogen bonds and can interact with a wide variety of polar groups.
- It has low vapor pressure. This allows the measurements to be repeated.
- It has a broad range of UV transmittance and facilitates the quantitative determination of many compounds dissolved therein.



Partition Coefficient (Log P) Calculation

1- Fragmentation Method and Theoretical Log P Calculation

- Includes the theoretical calculation of the hydrophobic constant (Log P) value of the molecule, taking advantage of the sum of the hydrophobic action values of various atomic and atomic groups (various fragments) calculated by Hanch et al.

As the form of mathematical expression, the following symbols and expressions are used.

- fb = Single bond between fragments of straight chain
- *fb* = Single bond between fragments of ring
- fcbr = Branched chain
- fgbr = Branched group (used in case of polar fragments instead of H atoms in the structure)
- f_{ϕ} = A fragment attached to an aromatic ring
- $f_{\phi\phi}$ = A fragment attached to two aromatic rings

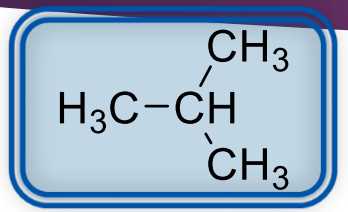
Regulated Fragment Constants

$f_H = 0.225$ $f_{CH3} = 0.89$ $f_{CH2} = f_{CH3} - f_H = 0.66$ $f_{CH} = f_{CH2} - f_H = 0.43$ $f_C = f_{CH} - f_H = 0.20$	$f_b = -0.12$ single bond (between fragments of straight chain) $f_b = -0.09$ single bond (between fragments of ring) $f_{cbr} = -0.13$ (branched chain) $f_{gbr} = -0.22$ (branched group)

Fragment	f	f_{ϕ}	$f_{\phi\phi}$
- Br	0.20	1.09	
- Cl	0.06	0.94	
- F	-0.38	0.37	
- I	0.60	1.35	
- $N(CH_3)_2$	-2.16	-1.17	-1.29
- NO_2	-1.26	-0.02	
- O -	-1.81	-0.57	0.53
- S -	-0.79	0.03	0.77
- NH -	-2.11	-1.03	-0.18
- NH_2 -	-1.54	-1.00	
- OH	-1.64	-0.40	
-CN	-1.28	-0.34	
-C (=O)$N(CH_3)_2$	-3.20	-2.82	-2.09
-C (=O)NH	-2.71	-1.81	-1.06
-C_6H_5	1.90		

Examples -1:

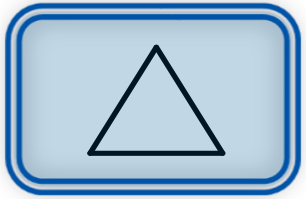
- **Isobutane**



$3\ f_{CH3} + 1 f_{CH} + 2\ f_b + f_{cbr} = 3(0.89) + (0.43) + 2(-0.12) + (-0.13) = 2.86$

(found log P : 2.76)

- **Cyclopropane**



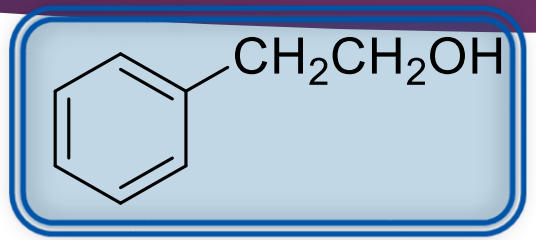
$3\ f_{CH2} + 2\ f_b = 3(0.66) + 2(-0.09) = 1.80$

(found log P : 1.72)

Note: f_b is used for every single bond after the first C-C bond.

Examples -2:

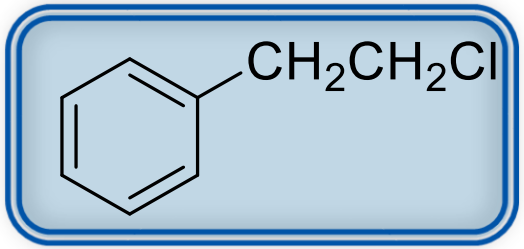
- **2-phenylethanol**



$f_{C6H5} + 2\, f_{CH2} + f_{OH} + 2\, f_b = (1.90) + 2\,(0.66) + \quad (-1.64) + 2\,(-0.12) = 1.34$

(found log P : 1.36)

- **(2-chloroethyl) benzene**

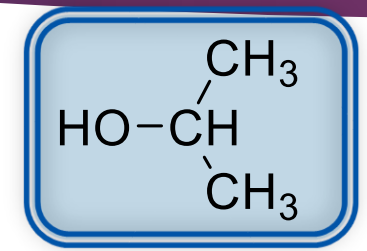


$f_{C6H5} + 2\, f_{CH2} + f_{Cl} + 2\, f_b = (1.90) + 2(0.66) + (0.06) + 2(-0.12) = 3.04$

(found log P : 2.95)

Examples -3:

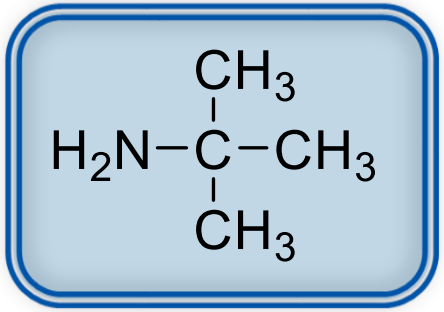
- **Isopropyl alcohol**



$2\,f_{CH3} + 1\,f_{CH} + f_{OH} + 2f_b + f_{gbr} = 2(0.89) + (0.43) + (-1.64) + 2(-0.12) + (-0.22) = 0.11$

(found log P : 0.05)

- **tert-Butylamine**

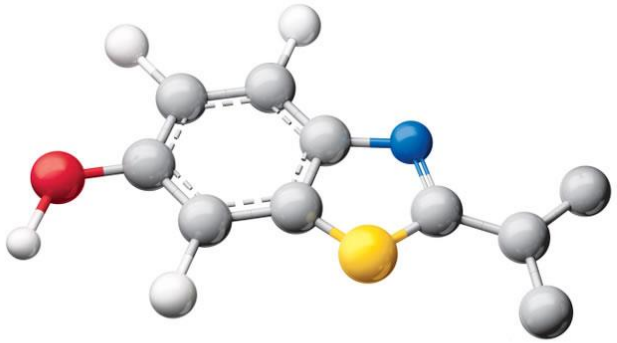


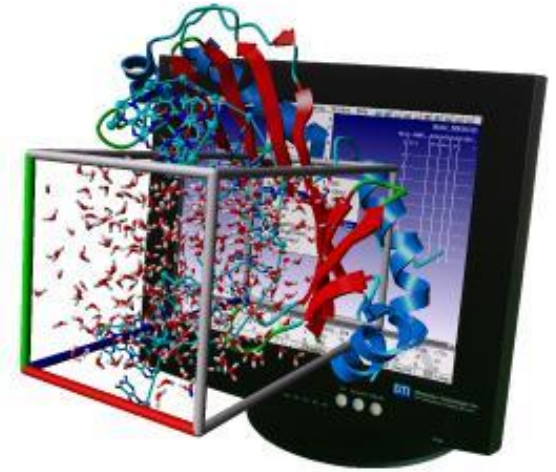
$3\,f_{CH3} + 1\,f_C + f_{NH2} + 3\,f_b + 2\,f_{gbr} = 3(0.89) + (0.20) + (-1.54) + 3(-0.12) + 2(-0.22) = 0.53$

(found log P : 0.40)

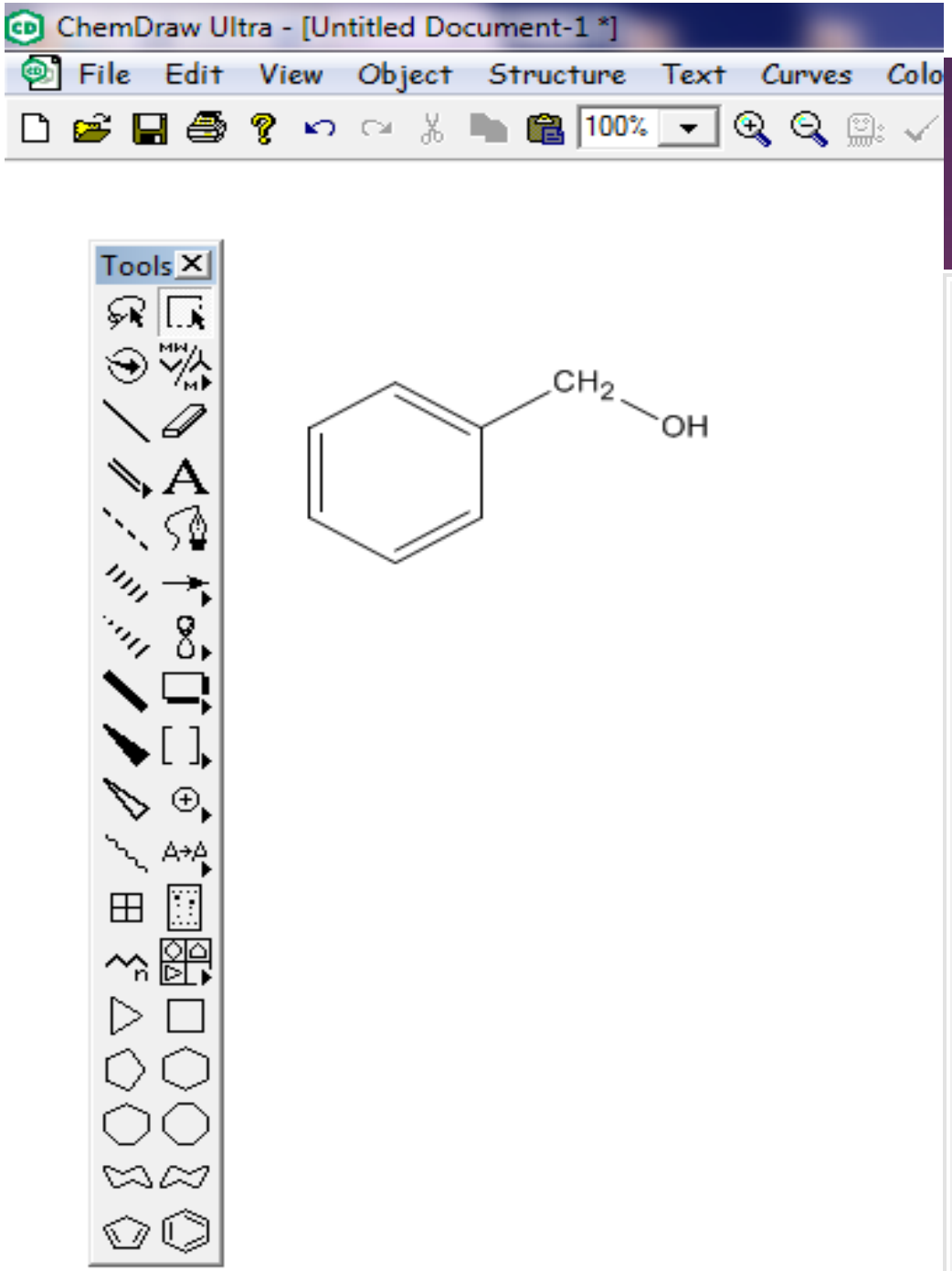
2- LogP Calculation Using Computer Programs

- Using the ChemSketch drawing program of ACD (Advanced Chemistry Development) / Labs, molecules can be drawn and the Log P values can be calculated from the hydrophobic parameters using Log P mod.





Distribution Coefficient Calculation on the Computer Using ChemDraw Ultra Program



3-Calculation of Log P Value by Experimental Method

1-Octanol solution

(saturated with buffer solution)

Buffer solution

(saturated with 1-octanol)

hazırlanır.

Buffer Solution contains;

- potassium dihydrogen phosphate,
- Disodium hydrogen phosphate.$12H_2O$

Experimental Procedure:

- The compound to be determined by the distribution coefficient is weighed to about 10 mg and is completed 50 ml with 1-octanol. A çözeltisi
- 10 ml of this solution is taken and 10 ml of buffer solution is added. It is stirred for 1 hour in a water bath at 37ºC (body temperature).
- At the end of this period 1-octanol and water layers are separated.
- Take 1 ml of the octanol layer and complete 20 ml with 1-octanol. The absorbance value (y1) of the maximum wavelength of this solution in the UV spectrum taken between 190-400 nm is determined.

Preparation of standard solutions and calibration curve

- 1 ml of solution **(A)** prepared at the beginning of the experiment is transferred to 3 volumetric flask.
- The volumetric flasks are completed 20, 30 and 40 ml separately with 1-octanol.
- The absorbance values **(y)** of the standard solutions prepared are read in the maximum wavelength at 190-400 nm in the UV spectra.
- Two separate studies can be performed using the absorbance values obtained.

1-Regression analysis method

$$y = ax + b$$

Prepared at various concentrations, standard solutions' absorbance values

These solutions' concentration values

The a and b values found are substituted in the following equation.

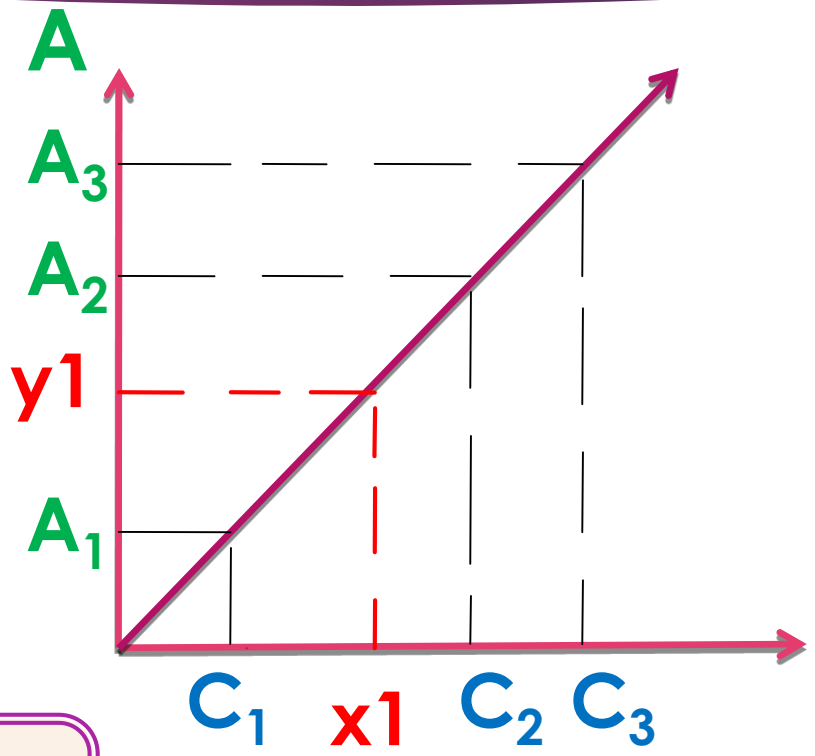
$$y_1 = ax_1 + b$$

UV absorbance value of the standard

The concentration of compound remaining in the octanol layer is found

2-Graphical Method

Measured absorbance values



20 ml: A1-C1
30 ml: A2-C2
40 ml: A3-C3

Concentration values of standard solution

$$\log P = \log \frac{\text{Amount, passed into octanol}}{\text{Amount, passed into water}}$$

Example:

5 mg of aspirin was dissolved in 50 ml of 1-octanol, from which 25 ml was taken and mixed with an equal volume of buffer solution for one hour at 37° C in a erlenmeyer with stopper. At the end of the period, 1 ml of 1 octanol layer was taken and was completed 10 ml in volumetric flask and the absorbance value was 0.4320 in UV. Calculate the Log P value of the aspirin.

(Mw=180, a=9723.57, b= -0.07243)

Solution:

(Mw=180, a=9723.57, b= - 0.07243)
(Absorbance value: 0,4320)

y = ax + b ⟶ 0,4320 = 9723,57**x** + (-0,07243)

x = 5,188.10^{-5} (the amount remaining in octanol)
1/10 diluted concentration

5,188.10^{-5} x10 = 5,188.10^{-4} **(actual concentration remaining in octanol)**

$$M = \frac{n}{V} = \frac{M/MA}{V} = \frac{5*10^{-3}/180}{50*10^{-3}} = 5{,}55 * 10^{-4}$$ **(starting amount)**

5,56.10^{-4} - 5,188.10^{-4} =0,372.10^{-4} **(Amount, passed into water)**

$$\log P = \log \frac{\text{Amount, passed into octanol}}{\text{Amount, passed into water}} = \log \frac{5{,}188 \,.\, 10^{-4}}{0{,}372 \,.\, 10^{-4}} = 1{,}14$$

Calculation of R_M

- They are used to roughly predict the lipophilic properties of the compounds.
- In the R_M assay using the thin layer chromatography (TLC) method it is believed that 1-octanol-saturated plates represent the lipid phase in the organism.
- R_M value is calculated from Rf values.

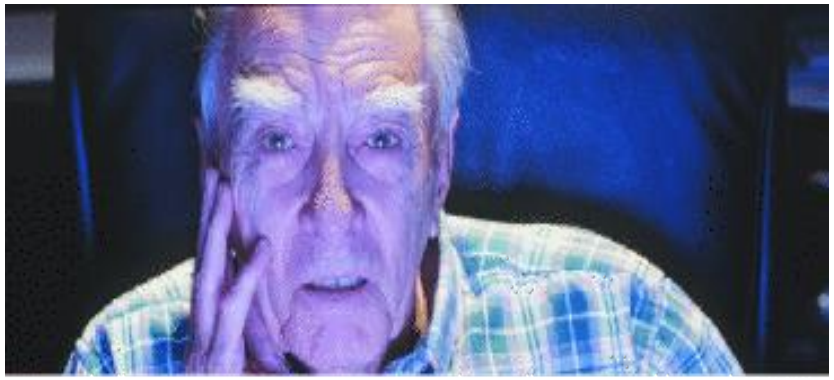
$$R_M = \log (1/Rf - 1)$$

Structure-Activity Relationships (QSAR) Analysis

- In the 1960s, two separate quantitative structure activity relationship analysis methods were developed.
- They were developed by Hansch and Fujita, Free and Wilson.
- Quantitative structure-activity relationships (QSAR) are the mathematical methods for describing the relationships between molecular properties of chemical compounds **(structural / physicochemical properties)** and biological activities.

Hansch Analysis Method

- Hansch developed the following formula, expressing that the observed biological effects of the compounds in a homologous series in the method of analysis are a function of the physicochemical properties of these compounds.


Hansch

biological effect = f (hydrophobic) + f (electronic) + f (steric) + c (constant)

Log 1 / C = Logarithmic biological effect

Independent variables of physicochemical parameters

$$Y \text{ (biological activity)} = k_o + k_1X_1 + k_2X_2 + \ldots + k_nX_n$$

The constant (correlation constant) indicating the contribution of the unexplained residue to the biological activity

The constants (regression coefficients) that define (+) or (-) contribution of physicochemical properties to biological activity

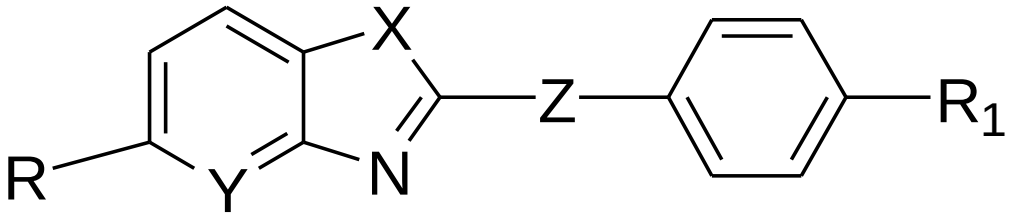
- **Regression processing:** Correlates the relationship between dependent Y variables (biological activity) and independent X variables (physicochemical parameters) with the least squares method, yielding the most appropriate model in the statistical direction and allowing the QSAR analysis to be resolved.

- **Objective:** To determine the correlation equation that quantitative structure-effect relationships provides adequately and the best solution.

- **Correlation Coefficient (R or R^2):** Provides statistical information on which model is compatible and valid. The less the difference between the observed and the calculated biological effect values of the analyzed compounds, the closer the R is to 1.
- **R^2** : Indicates the percentage of this harmony identified.
- **Standard deviation or error:** Indicates whether the model in which the correlation equation emerges corresponds to the statistically. As this value approaches zero, the value of R increases.
- **Fisher Test:** Indicates to what degree the model is statistically valid. Statistically the model is considered valid and reliable if p> 95% contains a value above the table probability limits.

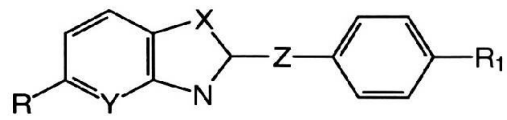
QSAR Application

A series of 2,5-disubstituted benzimidazole, benzoxazole and 2-substituted oxazolo (4,5-b) pyridine derivatives have been synthesized and tested in vitro against *K. pneumoniae*. The quantitative structure-effect relationships (QSAR) of the compounds are explained by applying the **Hansch analysis method** using the obtained activity results.



I = X: NH, Y: CH, Z: CH_2 or
II = X: O, Y: CH, Z: CH_2 or
III = X: O, Y: N, Z: -

Tablo 4.3. 2,5-Disübstitüe benzimidazol, benzoksazol ve 2-sübstitüe oksazolo (4,5-b) piridin türevleri ve eşitlik 1'de kullanılan parametreler



Bileşik	R	R_1	X	Y	Z	$H_{ACCEPT,R}$	F_R	I_X	I_Y	I_Z	MIC (μg/ml)	Gözlenen[a]	Hesaplanan[b]	Artan
1	H	H	O	CH	-	0	0.00	0	0	0	12.5	4.1936	4.2445	-0.0509
2	H	OCH_3	O	CH	-	0	0.00	0	0	0	12.5	4.2557	4.2445	0.0112
3	H	$C(CH_3)_3$	O	CH	-	0	0.00	0	0	0	12.5	4.3033	4.2445	0.0588
4	H	NH_2	O	CH	-	0	0.00	0	0	0	12.5	4.2538	4.2445	-0.0187
5	H	$NHCH_3$	O	CH	-	0	0.00	0	0	0	12.5	4.2538	4.2445	0.0093
6	Cl	CH_3	O	CH	-	0	0.41	0	0	0	25	3.9889	4.0491	-0.0602
7	Cl	C_2H_5	O	CH	-	0	0.41	0	0	0	25	4.0132	4.0491	-0.0359
8	Cl	$C(CH_3)_3$	O	CH	-	0	0.41	0	0	0	25	4.0580	4.0491	0.0089
9	Cl	$NHCOCH_3$	O	CH	-	0	0.41	0	0	0	25	4.0595	4.0491	0.0104
10	Cl	$NHCH_3$	O	CH	-	0	0.41	0	0	0	25	4.0148	4.0191	-0.0343
11	Cl	Cl	O	CH	-	0	0.41	0	0	0	25	4.0238	4.0191	-0.0253
12	Cl	NO_2	O	CH	-	0	0.41	0	0	0	25	4.0624	4.0191	0.0133
13	NO_2	H	O	CH	-	1	0.67	0	0	0	12.5	4.2837	4.3253	-0.0416
14	NO_2	CH_3	O	CH	-	1	0.67	0	0	0	12.5	4.3083	4.3253	-0.0170
15	NO_2	$C(CH_3)_3$	O	CH	-	1	0.67	0	0	0	12.5	4.3718	4.3253	0.0495
16	NO_2	NH_2	O	CH	-	1	0.67	0	0	0	12.5	4.3100	4.3253	-0.0153
17	NO_2	Cl	O	CH	-	1	0.67	0	0	0	12.5	4.3418	4.3253	0.0165
18	NO_2	Br	O	CH	-	1	0.67	0	0	0	12.5	4.4070	4.3253	0.0817
19	NH_2	H	O	CH	-	1	0.02	0	0	0	6.25	4.5269	4.6351	-0.1082
20	NH_2	C_2H_5	O	CH	-	1	0.02	0	0	0	6.25	4.6060	4.6351	-0.0291
21	NH_2	NO_2	O	CH	-	1	0.02	0	0	0	6.25	4.6142	4.6351	-0.0209
22	NH_2	Br	O	CH	-	1	0.02	0	0	0	6.25	4.7197	4.6351	0.0846

23	NH_2	F	O	CH	-	1	0.02	0	0	0	6.25	4.6296	4.6351	-0.0055
24	NH_2	$N(CH_3)_2$	O	CH	-	1	0.02	0	0	0	6.25	4.6313	4.6351	-0.0038
25	CH_3	CH_3	O	CH	-	0	-0.04	0	0	0	12.5	4.2519	4.2636	-0.0117
26	CH_3	C_2H_5	O	CH	-	0	-0.04	0	0	0	12.5	4.2783	4.2636	0.0147
27	CH_3	OCH_3	O	CH	-	0	-0.04	0	0	0	12.5	4.2819	4.2636	0.0183
28	CH_3	F	O	CH	-	0	-0.04	0	0	0	12.5	4.2595	4.2636	-0.0041
29	CH_3	$NHCOCH_3$	O	CH	-	0	-0.04	0	0	0	12.5	4.2874	4.2636	0.0238
30	CH_3	$NHCH_3$	O	CH	-	0	-0.04	0	0	0	12.5	4.2801	4.2636	0.0165
31	CH_3	$N(CH_3)_2$	O	CH	-	0	-0.04	0	0	0	12.5	4.3050	4.2636	0.0414
32	H	CH_3	O	N	-	0	0.00	0	1	0	6.25	4.5298	4.5763	-0.0465
33	H	C_2H_5	O	N	-	0	0.00	0	1	0	6.25	4.5584	4.5763	-0.0179
34	H	$C(CH_3)_3$	O	N	-	0	0.00	0	1	0	6.25	4.6090	4.5763	0.0327
35	H	OCH_3	O	N	-	0	0.00	0	1	0	6.25	4.5622	4.5763	-0.0141
36	H	OC_2H_5	O	N	-	0	0.00	0	1	0	6.25	4.5883	4.5763	0.0120
37	H	NH_2	O	N	-	0	0.00	0	1	0	6.25	4.5319	4.5763	-0.0444
38	H	NO_2	O	N	-	0	0.00	0	1	0	6.25	4.5763	4.5763	0.0137
39	H	Cl	O	N	-	0	0.00	0	1	0	6.25	4.5703	4.5763	-0.0060
40	H	Br	O	N	-	0	0.00	0	1	0	6.25	4.6471	4.5763	0.0708
41	H	H	O	CH	CH_2	0	0.00	0	0	1	6.25	4.5282	4.5918	-0.0636
42	H	OCH_3	O	CH	CH_2	0	0.00	0	0	1	6.25	4.5865	4.5918	-0.0053
43	H	Br	O	CH	CH_2	0	0.00	0	0	1	6.25	4.6672	4.5918	0.0754
44	H	Cl	O	CH	CH_2	0	0.00	0	0	1	6.25	4.5945	4.5918	0.0027
45	H	NO_2	O	CH	CH_2	0	0.00	0	0	1	6.25	4.6129	4.5918	0.0211
46	NO_2	H	O	CH	CH_2	1	0.67	0	0	1	6.25	4.6130	4.6725	-0.0595
47	NO_2	OCH_3	O	CH	CH_2	1	0.67	0	0	1	6.25	4.6610	4.6725	-0.0115
48	NO_2	Br	O	CH	CH_2	1	0.67	0	0	1	6.25	4.7300	4.6725	0.0055
49	NO_2	Cl	O	CH	CH_2	1	0.67	0	0	1	6.25	4.6680	4.6725	-0.0045
50	NO_2	NO_2	O	CH	CH_2	1	0.67	0	0	1	6.25	4.6840	4.6725	0.0115
51	NO_2	NO_2	NH	CH	CH_2	1	0.67	1	0	1	12.5	4.373	4.3641	0.0132
52	NO_2	OCH_3	NH	CH	CH_2	1	0.67	1	0	1	12.5	4.3549	4.3641	-0.0092
53	NO_2	OC_2H_5	NH	CH	CH_2	1	0.67	1	0	1	12.5	4.3159	4.3641	0.0118
54	CH_3	CH_3	NH	CH	CH_2	0	-0.04	1	0	1	12.5	4.2760	4.3023	-0.0263

55	CH_3	OCH_3	NH	CH	CH_2	0	-0.04	1	0	1	12.5	4.3045	4.3023	0.0022
56	CH_3	OC_2H_5	NH	CH	CH_2	0	-0.04	1	0	1	12.5	4.2869	4.3023	-0.0154
57	H	CH_3	NH	CH	-	0	0.00	1	0	0	25	3.9201	3.9361	0.0160
58	H	OCH_3	NH	CH	-	0	0.00	1	0	0	25	3.9523	3.9361	0.0162
59	CH_3	OCH_3	NH	CH	-	0	-0.04	1	0	0	25	3.9786	3.9551	0.0235

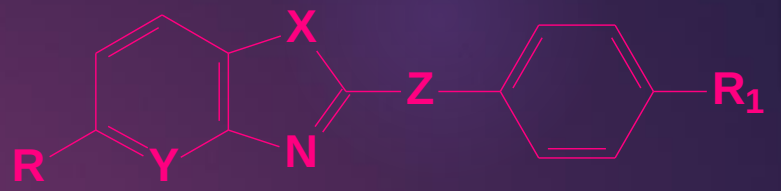
[a] log 1 / C.
[b]Eşitlik 4.1. kullanılarak

Eşitlik no.	Eşitlik 4.1.	n	R^2	s	F	
4	$\log 1 / C = 0.196(+-0.058)H_{ACCEPRT,R} + 4.315$	59	0.17	0.21	11	
5	$\log 1 / C = 0.274(+-0.051)H_{ACCEPRT,R} + 0.340(+-0.067)I_Y + 4.237$	59	0.43	0.18	21	
6 7	$\log 1 / C = 0.245(+-0.043)H_{ACCEPRT,R} + 0.398(+-0.058)I_Y$ $+0.219(+-0.046)I_Z + 4.178$	59	0.60	0.15	27	
8	$\log 1 / C = 0.415(+-0.042)H_{ACCEPRT,R} + 0.371(+-0.044)I_Y +$ $0.252(+-0.035)I_Z - 0.443(+-0.068)F_R + 4.205$	59	0.77	0.11	46	
9	$\log 1 / C = 0.400(+-0.015)H_{ACCEPRT,R} + 0.332(+-0.015)I_Y +$ $0.347(+-0.013)I_Z - 0.477(+-0.024)F_R - 0.308(+-0.015)I_X +$ 4.245	59	0.97	0.04	393	$p < 0.001$

- **Log 1/C** = 0,400(±0,015)$H_{ACCEPT,\ R}$ + 0,332(±0,015)I_Y + 0,347 (± 0,013)I_Z – 0,477(±0,024)F_R – 0,308(±0,015)I_X + 4,245

- The most appropriate correlation (linear relationship) was obtained with the equations, R^2 = 97% and s = 0.004.

When the equality is examined,



$$\text{Log } 1/C = 0{,}400(\pm 0{,}015)H_{ACCEPT,\ R} + 0{,}332(\pm 0{,}015)I_Y + 0{,}347\ (\pm\ 0{,}013)I_Z - 0{,}477(\pm 0{,}024)F_R - 0{,}308(\pm 0{,}015)I_X + 4{,}245$$

- The R group is important for biological activity,
- The substituents in the hydrogen trapping group (H_{ACCEPT}) in the R group increase the activity,
- The presence of substituents having the negative field effect (F_R) of the R groups increases activity,
- IX, IY, IZ are also determinants for activity,
- IX, NH reduces activity, O increases activity,
- IY, N increases activity,
- IZ methylene group is important, it increases activity.
- There is no obvious statistical effect of group R1.

Result

- The 2-benzyl oxazolo (4,5-b) pyridine derivatives which have a negative field effect at R are more effective.
- This work will lead to the synthesis of compounds which we have found to be more effective.