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ARAŞTIRMA MAKALESİ / **RESEARCH ARTICLE**

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MULTIVARIATE SAR STUDIES ON SOME NOVEL DRUG PRECURSOR BENZOTHIAZOLINONE DERIVATIVES

ABSTRACT

Multivariate structure-activity relationships of new modeled thirty two antinociceptive active benzothiazolinone derivatives have been investigated by using two different chemometrics methods, principal component analysis (PCA) and hierarchical cluster analysis (HCA), for rating biological activities. Twenty Molecular descriptors, which indicate electronic, termochemical and hydrophobic properties of molecules, are calculated by means of Austin Model (AM1) and density functional theory (DFT). The PCA and HCA methods are applied with polarizability (α), electrophilic index (ω) and heat of formation in aqueous phase ($HOF_{Aqueous}$). The results are found quite efficient to classify the thirty two compounds in two groups to be active and inactive. The correlation matrix and variable weight have been used to explain of relationships between calculated physicochemical parameters of molecules. Adding F and OCH_3 substituents to main ring of the investigated compounds and lengthening in alkyl group located on piperazine changes the biological activity.

Keywords: NSAI drug, Benzothiazolinone, Multivariate SAR, Principal component analysis (PCA), Hierarchical cluster analysis (HCA).

BAZI YENİ İLAÇ ÖNCÜSÜ BENZOTİYAZOLİNON TÜREVLERİ ÜZERİNE ÇOK DEĞİŞKENLİ SAR ÇALIŞMALARI

ÖZ

Yeni modellenen analjezik aktif otuziki benzotiyazolinon türevinin çok değişkenli yapı-aktivite ilişkileri iki farklı kemometric metot olan temel bileşen analizi (PCA) ve hiyerarşik kümeleme analizi (HCA) kullanılarak incelendi. Moleküllerin elektronik, termokimyasal ve hidrofobik özelliklerini tanımlayan yirmi moleküler tanımlayıcı Austin Modeli (AM1) ve yoğunluk fonksiyonel teorisi (DFT) kullanılarak hesaplandı. HCA ve PCA metotları sıvı fazdaki ($HOF_{Sıvı}$) polarizebilite (α), elektrofilik indis (ω) ve oluşum ısısı ile uygulanır. Sonuçlar otuziki molekülü aktifve inaktif olarak iki grupta sınıflandırmak için oldukça etkili bulundu. Korelasyon matrisi ve değişken ağırlığı moleküllerin hesaplanan fizikokimyasal parametreleri arasındaki ilişkileri açıklamak için kullanıldı. İncelenen bileşiklerin ana halkasına F ve OCH_3 sübstitüentlerin eklenmesi ve piperazin üzerindeki alkil gurubunun uzaması biyolojik aktiviteyi değiştir.

Anahtar Kelimeler: NSAI ilaç, Benzotiyazolinon, Çok değişkenli SAR, Temel bileşen analizi (PCA), Hiyerarşik kümeleme analizi (HCA).

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1. INTRODUCTION

Benzothiazolinone derivatives are considered as very important groups of non steroidal anti-inflammatory drugs. These derivatives have different type of biological activity such as antibacterial, anticonvulsive, diuretic, antihistaminic and antiarithmic (Şimşek, R., et al., 1995; Gvozdjakova, A. and Zemanova, M., 1984; Vanderberk, J. and Kennis, L.E.J., 1976; Uçar, H., et al., 1997; Diouf, D., et al., 1993; Çakır, B., et al. 1997; Antonova, A., 1998; Engel, W., et al., 1982; Fujisavata Pharmaceutical Co., Ltd, 1971) Some compounds are obtained having analgesic and anti-inflammatory activities by considering [2(3*H*)-benzothiazolon–3-yl]acetamide derivatives (Ferreira, S.H., et al., 1995).

The physicochemical properties and molecular structures of biological active compounds have attributed very important attitudes in biological medium. Research for quantitative relationship between physicochemical properties, structural and conformational properties and biological activity is a subject of QSAR/QSPR and SAR. These relationships facilitate to understand and explain the most effective parameters in drug design and development of new biologically active compounds exhibiting desirable properties. Thus, structure-activity relationship (SAR) studies have been established to be helpful in elucidating of drug properties of several kinds of compounds (Arroio, A., et al., 2004; Vendrame, R., et al., 2002; Camargo, A.J., et al., 2002; Ferreira, M.M.C., 2002; Lameira, J. and Medeiros, I.G., 2006). It is reported that benzothiazolinone derivatives have antinociceptive activity to different grades Önkol, T., et al., 2012). We reported different structure-activity relationships of thirty two benzothiazolinone molecules in the earlier studies (Gülseven Sıdır, Y., et al.,2011; Öğretir, C., et al., 2008-2010; Gülseven Sıdır, Y. and Sıdır, İ., 2013). The SAR defined by using chemometric methods (PCA and HCA) of the investigated compounds have not been previously reported in the literature. Besides, rating the biological activity of molecules and relationship between calculated parameters have been investigated by chemometric methods. Thus, we have aimed to investigate benzothiazolinone molecules as having antinociceptive activity by establishing the relationship between structure and activity for a set of benzothiazolinone derivatives in this study. Molecular descriptors of novel drug precursors are generally correlated with biological activity and this correlation study is named as structure-activity relationships (SAR) (Arroio, A., et al., 2004; Vendrame, R., et al., 2002; Camargo, A.J., et al., 2002).

2. METHODOLOGY

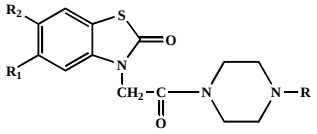
2.1. Quantum Chemical Calculations

Biological activity of a drug is defined to be based on three different molecular properties like electronic, steric and hydrophobic parameters. Calculated physicochemical parameters in the present work are dipole moment (μ), polarizability (α), HOMO (Highest Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital), ionization potential (IP) and electron affinity (EA) according to Koopmans' theorem, electronegativity (χ), molecular hardness (η), molecular softness (S), electrophilic index (ω), octanol-water partition coefficient (log *P*), molar refractivity (MR) and heat of formation (HOF). Octanol-water partition coefficient (log *P*) plays particularly a vital role in physicochemical, environmental and biological processes through it determines transport phenomena in vivo such as the blood-brain membrane barrier. Thus, a total of twenty molecular descriptors were calculated for each of the studied molecules. The chosen calculated descriptors represent different sources of chemical information in terms of electronic, hydrophobic and steric features of the compounds (King, F.D., 1997).

Molecular structures of benzothiazolinone derivatives are listed in Table 1. Investigated benzothiazolinone derivatives have a lot of free-rotational bonds which change conformational stability. In this work, we have performed conformational stability analysis for obtaining the lowest energy structure. Firstly, the lowest energy structures were calculated by using HF/3-21G method in Spartan 08W software (Spartan08, 2006). Afterwards, molecular structures with the lowest energy of each molecule were optimized by using B3LYP method in Gaussian03W software (Gaussian03W, 2004) Their fundamental vibrations were controlled whether molecular structures were true minima. Gaussian03W output files give directly the μ, α, HOMO and LUMO values and some of the molecular parameters. Some of the other parameters (IP, EA, χ, η, S and ω) were derived from these results. Octanol-water partition coefficient (log *P*), molar refractivity (MR) and heat of formation

(HOF) parameters were calculated by CS ChemOffice2004 software. The Austin model-1 (AM1) method was used for re-optimization the studied molecules using MOPAC (Dewar, M.J.S., et al., 1985). Gas Phase and aqueous phase heat of formations were calculated by AM1 method with CAChe 6.1 software (CAChe WorkSystem Pro, Version 6.1.12, 2004).

Table 1.The molecular structures and classifications in terms of analgesic activity of investigated molecules.



Molecule number	R_1	R_2	R	Activity
1	H	H	CH_3	Inactive
2	H	H	C_2H_5	Active
3	H	H	$CH(CH_3)_2$	Inactive
4	H	H	$CH_2CH_2CH_2CH_3$	Active
5	H	4-$CH_3C_6H_5CO$	CH_3	Inactive
6	H	4-$CH_3C_6H_5CO$	C_2H_5	Inactive
7	H	4-$CH_3C_6H_5CO$	$CH(CH_3)_2$	Inactive
8	H	4-$CH_3C_6H_5C$	$CH_2CH_2CH_2CH_3$	Inactive
9	H	4- FC_6H_5CO	CH_3	Active
10	H	4- FC_6H_5CO	C_2H_5	Active
11	H	4- FC_6H_5CO	$CH(CH_3)_2$	Active
12	H	4- FC_6H_5CO	$CH_2CH_2CH_2CH_3$	Active
13	H	4- $CH_3OC_6H_5CO$	CH_3	Active
14	H	4- $CH_3OC_6H_5CO$	C_2H_5	Active
15	H	4- $CH_3OC_6H_5CO$	$CH(CH_3)_2$	Active
16	H	4- $CH_3OC_6H_5CO$	$CH_2CH_2CH_2CH_3$	Active
17	Cl	H	CH_3	Inactive
18	Cl	H	C_2H_5	Inactive
19	Cl	H	$CH(CH_3)_2$	Inactive
20	Cl	H	$CH_2CH_2CH_2CH_3$	Active
21	Cl	4-$CH_3C_6H_5CO$	CH_3	Inactive
22	Cl	4-$CH_3C_6H_5CO$	C_2H_5	Inactive
23	Cl	4-$CH_3C_6H_5CO$	$CH(CH_3)_2$	Inactive
24	Cl	4-$CH_3C_6H_5CO$	$CH_2CH_2CH_2CH_3$	Inactive
25	Cl	4- FC_6H_5CO	CH_3	Active
26	Cl	4- FC_6H_5CO	C_2H_5	Active
27	Cl	4- FC_6H_5CO	$CH(CH_3)_2$	Active
28	Cl	4- FC_6H_5CO	$CH_2CH_2CH_2CH_3$	Active
29	Cl	4- $CH_3OC_6H_5CO$	CH_3	Active
30	Cl	4- $CH_3OC_6H_5CO$	C_2H_5	Active
31	Cl	4- $CH_3OC_6H_5CO$	$CH(CH_3)_2$	Active
32	Cl	4- $CH_3OC_6H_5CO$	$CH_2CH_2CH_2CH_3$	Active

Molecular structures of benzothiazolinone derivatives are listed in Table 1. Investigated benzothiazolinone derivatives have a lot of free-rotational bonds which change conformational stability. In this work, we have performed conformational stability analysis for obtaining the lowest energy structure. Firstly, the lowest energy structures were calculated by using HF/3-21G method in Spartan 08W software (Spartan08, 2006). Afterwards, molecular structures with the lowest energy of each molecule were optimized by using B3LYP method in Gaussian03W software (Gaussian03W, 2004) Their fundamental vibrations were controlled whether molecular structures were true minima. Gaussian03W output files give directly the μ, α, HOMO and LUMO values and some of the molecular parameters. Some of the other parameters (IP, EA, χ, η, S and ω) were derived from these results. Octanol-water partition coefficient (log *P*), molar refractivity (MR) and heat of formation (HOF) parameters were calculated by CS ChemOffice2004 software. The Austin Model-1 (AM1) method was used for re-optimization the studied molecules using MOPAC (Dewar, M.J.S., et al., 1985). Gas phase and aqueous phase heat of formations were calculated by AM1 method with CAChe 6.1 software (CAChe WorkSystem Pro, Version 6.1.12, 2004).

2.2. The Statistic Calculations

The physicochemical parameters are correlated with the biological activity through the use of two different methods: principal component

analysis (PCA), which is useful form of computational analysis for correlation of biological activity and molecular structure, and hierarchical cluster analysis (HCA). The correlation matrix expounds relationships between calculated physicochemical parameters of the molecules. It is desirable to apply different methods to the same problem in SAR.

The PCA is a multivariate statistical technique whose essential object is to reduce the dimension of a data set that presents a large number of interrelated variables. This is achieved by transforming to a new set of variables, called the Principal Components (PCs). They are uncorrelated and ordered so that the first PCs retain most of the variation present in all of the original variables (Wold, S., et al., 1987, Mackiewicz, A. and Ratajczak, W., 1993; Rusu, M., et al., 1999; Sarbu, et al., 2001; Sarbu, C., et al., 2002; Jolliffe, T., 1986).

The HCA technique examines the distances between the samples in a data set and represents this information as a two-dimensional plot called dendogram. It is informative for examining the dendogram in conjunction with PCA since it gives similar information in different forms. In HCA, each point forms an only cluster initially and then the similarity matrix is analyzed. The most similar points are grouped forming one cluster and the process is repeated until the whole points belong to any group (Kowalski, B.R. and Bender, C.F., 1972). The PCA, HCA and correlation matrix used in this work were performed by using the SPSS 15.0 software (SPSS 15.0 for Windows, 1989-2006).

3. Results and Discussion

3.1. The Correlation Matrix and Selection of Molecular Variables

The calculated physicochemical parameters of thirty two benzothiazolinone derivatives are thought from references (Gülseven Sıdır, Y., et al.,2011; Öğretir, C., et al., 2008-2010; Gülseven Sıdır, Y. and Sıdır, İ., 2013). The correlation matrix of physicochemical parameters and variance weights are listed in Table 2.

The correlation matrix is worthwhile for marking redundancies or interrelationships among the variables. This is fulfilled through an analysis of the correlation matrix of biological or chemical properties (Richon, A.B., 1997). It is shown in Table 2 that calculated molecular descriptors of studied molecules are correlated to each other. The correlation coefficients are above 0.70, in that case, two variables are found directly proportional to each other. If the correlation coefficients are above -0.70, it can be said that, two variables are inversely proportional to each other. It can be shown in Table 2 that the log *P* values are well correlated with entropy, MR, S and C_v. The polarizabilities of the studied molecules linearly depend on log *P*, MR, and C_v. In that, the polarizabilities values of molecules can partially effect to biological activity. MR parameter is correlated with S, Entropy and C_v parameters. The correlation between E_{LUMO} and η is very good due to 0.944 correlation value. Both E_{LUMO} and η values determine to reactivity of biological medium. The EA values are linearly exchanging with C_v and Entropy. As seen in Table 2, hyperpolarizabilities of investigated molecules change as inversely proportional with ΔE, E_{LUMO}, χ and η parameters. The bigger η gives rise to less biological activity. HOF values (both gaseous phase and aqueous phase) of molecules are found inversely correlated with log *P*. α, V_m and S have linear relationships between these three molecular parameters. In that, when V_m is increasing, α is increasing (S.M. Smith, et al., 2004).

Firstly, molecular variables of benzothiazolinone derivatives are auto-scaled, producing new molecular variables with a mean of 0 and a standard deviation of 1. Thus, molecular properties could be compared to each other on the same scale. Secondly, variance weight and correlation matrix of molecular variable were calculated. Third, eight variables in Table 2 are selected due to having values above 8 for the variance weights. Finally, we have selected in three molecular variables dissociated as inactive and active derivatives having high correlation coefficients (above 0.8) to each other of variables in correlation matrix. These variables are α, ω and $HOF_{Aqueous}$.

Table 2. The variance weights and correlation matrix of physicochemical parameters of the investigated molecules

	α	μ	E_{HOMO}	E_{LUMO}	ΔE	q-	qH+	V_m	IP	EA	χ	η	S	ω	log*P*	MR	HOF_{Aqua}	HOF_{Gas}	S_e	C_v	*Variance weights*
α	1	0.48	-0.21	-0.87	-0.87	0.27	0.07	0.78	0.21	0.87	-0.80	-0.86	0.85	-0.47	0.81	0.98	-0.72	-0.67	0.97	0.97	2150.593
μ		1	-0.08	-0.36	-0.36	0.65	0.43	0.41	0.08	0.36	-0.33	-0.36	0.32	-0.30	0.33	0.43	-0.28	-0.27	0.45	0.43	3.774
E_{HOMO}			1	0.38	0.05	-0.25	-0.15	-0.07	-1.00	-0.38	0.60	0.05	-0.03	0.27	-0.00	-0.18	0.39	0.38	-0.17	-0.20	0.027
E_{LUMO}				1	0.94	-0.24	-0.13	-0.67	-0.38	-1.00	0.96	0.94	-0.93	0.51	-0.74	-0.88	0.70	0.66	-0.84	-0.85	0.253
ΔE					1	-0.17	-0.09	-0.70	-0.05	-0.94	0.82	1.00	-0.99	0.45	-0.80	-0.88	0.61	0.58	-0.84	-0.85	0.217
q-						1	0.59	0.31	0.25	0.24	-0.28	-0.17	0.13	-0.35	0.08	0.26	-0.17	-0.15	0.27	0.26	0.000
qH+							1	0.18	0.15	0.13	-0.16	-0.10	0.02	-0.43	-0.04	0.05	-0.04	-0.03	0.03	0.05	0.000
V_m								1	0.07	0.67	-0.60	-0.70	0.69	-0.53	0.68	0.79	-0.59	-0.56	0.80	0.79	1409.101
IP									1	0.38	-0.60	-0.05	0.03	-0.27	0.00	0.18	-0.39	-0.38	0.17	0.20	0.027
EA										1	-0.96	-0.94	0.93	-0.51	0.74	0.88	-0.70	-0.66	0.84	0.85	0.253
χ											1	0.82	-0.80	0.51	-0.64	-0.80	0.71	0.68	-0.76	-0.79	0.086
η												1	-0.99	0.45	-0.80	-0.88	0.61	0.57	-0.84	-0.85	0.054
S_e													1	-0.42	0.81	0.86	-0.60	-0.57	0.82	0.83	0.002
ω														1	-0.44	-0.47	0.33	0.32	-0.47	-0.47	8.343
log*P*															1	0.88	-0.55	-0.53	0.88	0.87	0.717
MR																1	-0.70	-0.66	0.99	0.99	269.066
HOF_{Aqua}																	1	0.99	-0.70	-0.72	503.668
HOF_{Gas}																		1	-0.66	-0.68	441.481
S_e																			1	0.99	482.116
C_v																				1	231.283

<α>=Molecular polarizability, μ=Dipole moment, E_{HOMO}=High-occupied molecular orbital energy, E_{LUMO}=Lowest-unoccupied molecular orbital energy, V_m=Molecular volume, IP=Ionization potential, EA=Electron affinity, χ=Electronegativity, η=Chemical hardness, S=Chemical softness, ω=Electrophilic index, MR=Molar refractivity, HOF=Heat of formation, S_e=Entropy, C_v: J. Mol^{-1}. K^{-1} , Entropy: J. Mol^{-1}. K^{-1}.

The physicochemical of parameters molecules 1-32 have been given from ref. (Gülseven Sıdır, Y., et al.,2011; Öğretir, C., et al., 2008-2010; Gülseven Sıdır, Y. and Sıdır, İ., 2013).

Table 3. The PC1 and PC2 values for selected variable

Selected Variable	PC1	PC2
R_3	-0,516	0,355
Q_1	-0,474	0,245
A	0,452	0,486
Log *P*	0,029	0,753
MR	0,551	0,104

3.2. Principal Component Analysis (PCA)

The PCA analysis for thirty two molecules and first three principal components (PCs) values are listed in Table 3 and 4, respectively. PC1 vs. PC2 score plots for both three variables (physiochemical parameters) and thirty two molecules are depicted in Figures 1 and 2, respectively.

Table 3. Variance percentage for the PCs.

Principal Component	Percentage	Total Percentage
PC1	67.89	67.89
PC2	23.33	91.22
PC3	8.775	100.00

It can be seen in Table 3 that the first three principal components (PCs) are explained as 100 % to many results of total variance of the data set. Thus, values of PC1, PC2 and PC3 are found to be 67.89 %, 23.33 % and 8.77 %, respectively. In that, almost all of the variances are explained by the first three PCs and their score plot is a reliable representation of the spatial distribution of the points for the data sets. As can be seen from Figures 1 and 2, benzothiazolinone derivatives are branched in two groups according to biological activity as the fact that are active and inactive. Activities of these groups are classificated according to PCs values. The PC1 values found to below 0.7 indicate inactive molecules whereas the molecules whose PC1 values in above 0.7 indicate active molecules. We can say that PC1 is responsible to allocate as inactive (M1, M3, M5-8, M13, M17-19, M21-24) and active (M2, M4, M9-16, M20, M25-30 and M32) compounds. As can be seen in Figure 1, α, ω and $HOF_{Aqueous}$ variables have high PC1 loadings. PC1 which is the most responsible discrimination among the active and inactive molecules is expressed with below equation;

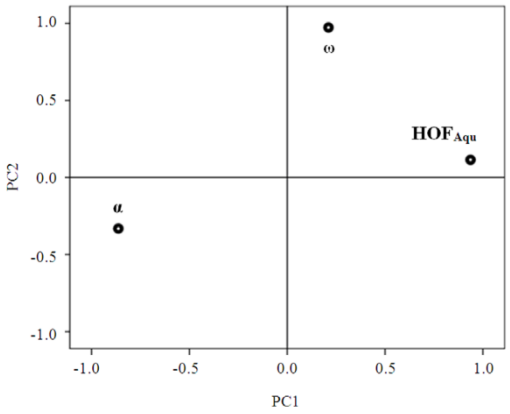


Figure 1. PC1 vs. PC2 plots for calculated physicochemical parameters of the investigated molecules.

Table 4. PCA scores of the studied molecules.

Compounds	PC1	PC2
M1	0.697	0.717
M2	0.712	0.702
M3	0.676	0.737
M4	0.726	0.688
M5	0.661	0.75
M6	0.669	0.743
M7	0.674	0.739
M8	0.687	0.727
M9	0.733	0.68
M10	0.735	0.678
M11	0.740	0.673
M12	0.754	0.656
M13	0.716	0.698
M14	0.721	0.693
M15	0.721	0.693
M16	0.730	0.683
M17	0.678	0.735
M18	0.686	0.728
M19	0.689	0.725
M20	0.708	0.707
M21	0.666	0.746
M22	0.671	0.742
M23	0.685	0.729
M24	0.691	0.723
M25	0.737	0.676
M26	0.740	0.673
M27	0.739	0.674
M28	0.749	0.663
M29	0.720	0.694
M30	0.721	0.693
M31	0.719	0.695
M32	0.732	0.681

$$PC1=-0.863\alpha+0.211\omega+0.937HOF_{Aqueous} \quad (1)$$
$$PC2=-0.331\alpha+0.937\omega+0.115\ HOF_{Aqueous} \quad (2)$$

If the PC1 and PC2 values have above from 7 values; in that case, active molecules can be obtained. In Eq. (1) and (2), ω has very higher values, while α must be comparatively in acceptable lower values. In addition, it must have lower values (near to zero) ($HOF_{Aqueous}$) because heat of formation in aqueous phase have minus sign. Thus, we can say that analgesic activities of investigated molecules have partly been controlled by ω, α and $HOF_{Aqueous}$ expect for steric hindrance, inductive effects and mesomeric effects. These observations affirm with early other research paper to antinociceptive activities compared with aspirin of these molecules (Önkol, T., et al., 2012).

Higher electrophilic index: This parameter is a measure of reactivity of molecules and a compound having electrophilic properties loves electrons. The more electrophilic index value of a compound is great, the more biological activity is high. But, this parameter in some cases has scaled toxicity of compounds, also.

HOF Aqueous values near to zero: This parameter is a measure of energy to formation in aqueous medium of compound. If this parameter' value is close to zero, the reactivity in biological medium increase.

Suitable Lower Polarizability: Polarizability controls the reactivity level of a compound when reactivity changes. Polarizability of investigated molecules is found in allowable lower value.

It can be seen from both Figure 2 and reported work, M5 molecules has not analgesic activity, while M28 molecule is analgesic active (Önkol, T., et al., 2012). Molecule M28 carries butyl, Cl and 4-FC_6H_5CO substituents at R_1, R_2 and R, respectively. These substituents give rise to gain biological activity of the molecule. Moreover, it is observed that 4-FC_6H_5CO and 4-$CH_3OC_6H_5CO$ substituents in R_2 position effect largely the analgesic activity of M9-M16 and M25-M32 molecules.

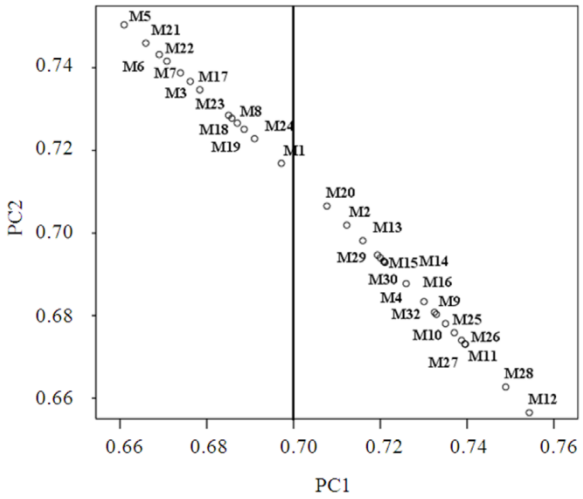


Figure 2. PC1 vs. PC2 score plot of the investigated molecules.

3.3. Hierarchical Cluster Analysis (HCA)

The HCA has been used to determine the cluster samples with similarity and the distance among the samples in two dimensional plots (dendogram). HCAs score plot of investigated molecules are depicted in Figure 3.

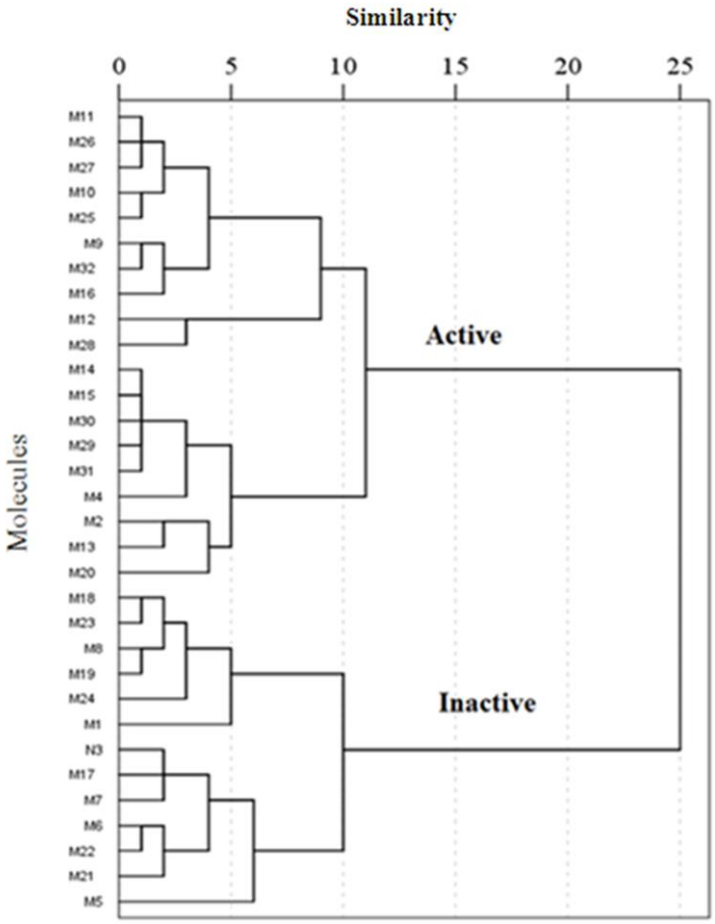


Figure 3. HCA plot of the investigated molecules

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This work is dedicated to the memory of our colleague Dear Prof. Dr. Cemil Öğretir, who passed away on January 19, 2011.

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