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Araştırma Makalesi / Research Paper

QSAR Studies on Anticancer Activities of Some Imidazole and Imidazo [1,2-a] Pyrazine Derivatives

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ABSTRACT

In this study, the correlations between the anticancer activities (i.e., concentration of growth inhibition of 50% on 66 human tumor cell lines by National Cancer Institute (NCI) were used as log(1/C) values) and some physicochemical parameters (i.e., hydrophobic parameters, clogP, π, electronic parameters, σ, $\mathcal{F}$, and steric parameters, E_s, MR) were investigated. Additionally, the remarkable correlations were reported between biological activity and π, $\mathcal{F}$, MR values for imidazole derivatives similar to between biological activity and clogP, E_s, values for imidazo[1,2-a]pyrazine derivatives.

Keywords: imidazo[1,2-a]pyrazine, pyrazino[1,2-a]benzimidazole, anticancer activity, quantitative structure-activity of relationship (QSAR), Hansch analysis methods

Bazı İmidazol ve İmidazo[1,2-a] Pirazin Türevlerinin Antikanser Aktiviteleri Üzerine QSAR Çalışmaları

ÖZ

Bu çalışmada, antikanser etkiler (Amerika Ulusal Kanser Enstitüsü (NCI) tarafından, 66 kanserli hücrede yapılmış olan büyüme testlerinden alınan Log(1/C) değerleri) ile bazı fizikokimyasal parametreler (hidrofobik parametreler olarak clogP, π, elektronik parametreler olarak σ, $\mathcal{F}$, ve sterik parametreler olarak, E_s, MR) arasındaki korelasyonlar incelenmiştir. Buna göre, imidazol türevleri için, biyolojik etki ile π, $\mathcal{F}$, MR parametreleri arasında ve benzer şekilde, imidazo[1,2-a]pirazin türevleri için, biyolojik etki ile clogP, E_s parametreleri arasında önemli miktarda korelasyon olduğu rapor edilmiştir.

Anahtar Kelimeler: İmidazo[1,2-a]pirazin, pirazino[1,2-a]benzimidazol, antikanser etki, kantitatif yapı-etki ilişkileri (QSAR), Hansch analiz metodu.

INTRODUCTION

The imidazo[1,2-a]pyrazines and pyrazino[1,2-a]benzimidazoles were synthesized in our laboratory previously and tested for cytotoxic effects by National Cancer Institute (NCI) (Demirayak et al., 2002; Demirayak ve Kayagil, 2005; Demirayak et al., 2011; Kayağil ve Demirayak 2011). It was revealed that they behave as remarkable anticancer activities (Brown, 2001; Contour-Galcera et al., 2001; Prevost et al., 2003; Thurieau et al., 2000, 2002). Furthermore, imidazo[1,2-a]pyrazines were also denoted to display chemiluminescent effect as *Luciferin* and to attract attention (Toshio et al., 1968; Mccapra and Roth, 1972; Barraclough et al., 1993; Adamczyk et al., 2003).

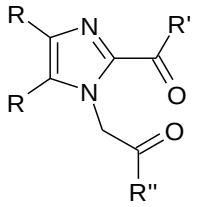
Structure-activity relationship (SAR) published by Crum-Brown and Fraser in 1968 has still been employed. Effects of drugs separated as structurally specific and nonspecific can change with the variation of their physicochemical parameters. The structurally specific drugs are susceptible especially to small modifications in the chemical structure because of the fact that the drugs are interacted with a receptor or an enzyme (Silverman, 2004).

The selected compounds in all our studies were studied based on their structure and separated as imidazole and imidazo[1,2-a]pyrazine derivatives. In this suggested study, the substituted imidazoles including benzimidazoles and imidazo[1,2-a]pyrazines consisting of pyrazino[1,2-a]benzimidazoles were separately evaluated. Each substance was used to investigate a structure and calculate to its physicochemical parameters according to its substitution. QSAR was studied based on the biological activity values used as log(1/C) and also it was studied based on the physicochemical parameters of the selected substances. Therefore, Hansch Linear and Nonlinear Analysis Methods (Hansch et al., 1973, 1977, 1995; Hansch & Leo, 1995; Kubinyi, 1993; Leo et al., 1971, 1975; Taft, 1952) were used for all the compounds in presented study.

MATERIAL AND METHOD

QSAR Studies

The compounds used in the study and their biological data were obtained from our previous studies. The imidazoles (Demirayak et al., 2002, 2011; Kayağil & Demirayak, 2011), **1-19**, were shown in Fig. 1. and Table 1. Their biological data and physicochemical parameters were given in Table 2. The imidazo[1,2-a]pyrazines (Demirayak et al., 2002; Demirayak & Kayagil, 2005; Kayağil & Demirayak, 2011), **20-49**, were shown in Fig. 2. and Table 3. Their biological data and physicochemical parameters were given in Table 4. Synthesis protocols and spectral data of the compounds were examined previously (Demirayak et al., 2002, 2011; Demirayak ve Kayagil, 2005; Kayağil ve Demirayak, 2011).



1-19

Fig. 1. Imidazoles

Table 1. Imidazoles

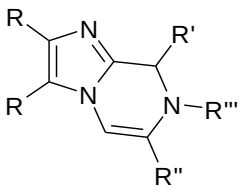
Comp.	R	R'	R''
1	-C_6H_4-4-Me	-C_6H_5	-C_6H_4-4-OMe
2	-C_6H_4-4-Me	-C_6H_5	-C_6H_4-4-Cl
3	-C_6H_4-4-OMe	-C_6H_5	-C_6H_5
4	-C_6H_4-4-OMe	-C_6H_5	-C_6H_4-4-OMe
5	-C_6H_4-4-OMe	-C_6H_5	-C_6H_4-4-Cl
6	-C_6H_4-4-Cl	-C_6H_4-4-Cl	-C_6H_5
7	-CH=CH-CH=CH-	-C_6H_5	-C_6H_5
8	-CH=CH-CH=CH-	-C_6H_5	-C_6H_4-4-OMe
9	-CH=CH-CH=CH-	-C_6H_5	-C_6H_4-4-F
10	-CH=CH-CH=CH-	-C_6H_5	-C_6H_4-4-Cl
11	-CH=CH-CH=CH-	-C_6H_4-4-OMe	-C_6H_4-4-OMe

12	-CH=CH-CH=CH-	-C_6H_4-4-OMe	-C_6H_4-4-Cl
13	-CH=CH-CH=CH-	-C_6H_4-4-Cl	-C_6H_4-4-OMe
14	-CH=CH-CH=CH-	-CH_2-CH=CH-C_6H_3-3,4-Cl_2	-C_6H_5
15	-CH=CH-CH=CH-	-CH_2-CH=CH-C_6H_4-4-Cl	-C_6H_4-4-Cl
16	-CH=CH-CH=CH-	-CH_2-CH=CH-Fur	-C_6H_4-4-OMe
17	-CH=CH-CH=CH-	-CH_2-CH=CH-Fur	-C_6H_4-4-Cl
18	-CH=CH-CH=CH-	-CH_2-CH=CH-Thi	-C_6H_4-4-Me
19	-CH=CH-CH=CH-	-CH_2-CH=CH-Thi	-C_6H_4-4-Cl

Fur: Fur-2-yl, Me: Methyl, Thi: Thien-2-yl

Table 2. Biological data and physicochemical parameters of imidazoles

Comp.	$Log(1/C)_{obsv}$	clogP	π	σ	$\mathcal{F}$	E_s	MR
1	4.10	5.90	8.94	- 0.65	0.50	- 7.07	117.52
2	4.01	6.62	9.67	- 0.15	0.65	- 7.49	115.68
3	4.02	5.17	7.80	- 0.58	0.76	- 5.14	115.12
4	4.09	5.06	7.78	- 0.85	1.02	- 5.69	121.96
5	4.01	5.78	8.51	- 0.35	1.27	- 6.11	120.12
6	4.02	7.22	9.97	0.65	1.51	- 6.95	116.44
7	4.15	3.49	5.24	0.02	0.19	- 7.70	68.19
8	5.54	3.39	5.22	- 0.25	0.45	- 8.25	75.03
9	5.27	3.55	5.38	0.08	0.66	- 8.16	68.08
10	5.25	4.11	5.95	0.25	0.64	- 8.67	73.19
11	5.51	3.28	5.20	- 0.52	0.71	- 8.80	81.87
12	5.46	4.00	5.93	- 0.02	0.86	- 9.22	80.03
13	5.01	4.00	5.93	- 0.02	0.86	- 9.22	80.03
14	4.64	4.98	7.48	0.60	1.08	- 12.48	88.15
15	4.81	4.98	7.48	0.46	1.08	- 12.48	88.15
16	4.50	2.75	4.63	- 0.73	0.55	- 12.71	77.30
17	4.75	3.47	5.36	- 0.23	0.70	- 13.13	75.46
18	4.42	3.91	6.27	- 0.11	0.24	- 13.92	81.45
19	4.73	4.21	6.42	0.29	0.69	- 13.65	81.83



20-49

Fig. 2. Imidazo[1,2-a]pyrazines.

Table 3. Imidazo[1,2-a]pyrazines.

Comp.	R	R'	R''	R'''
20	-H	-C_6H_4-4-OMe	-C_6H_4-4-Me	-
21	-H	-C_6H_4-4-Cl	-C_6H_5	-
22	-H	-C_6H_4-4-Cl	-C_6H_4-4-Me	-
23	-H	-C_6H_4-4-Cl	-C_6H_4-4-OMe	-
24	-H	-C_6H_4-4-Cl	-C_6H_4-4-Cl	-
25	-C_6H_4-4-OMe	-C_6H_5	-C_6H_5	-
26	-C_6H_4-4-Cl	-C_6H_5	-C_6H_5	-
27	-C_6H_4-4-Cl	-C_6H_4-4-Cl	-C_6H_5	-
28	-CH=CH-CH=CH-	=CH_2	-C_6H_5	-C_6H_5
29	-CH=CH-CH=CH-	=CH_2	-C_6H_5	-C_6H_4-4-Me
30	-CH=CH-CH=CH-	=CH_2	-C_6H_5	-C_6H_4-4-OMe
31	-CH=CH-CH=CH-	=CH_2	-C_6H_5	-C_6H_4-4-Cl
32	-CH=CH-CH=CH-	=CH_2	-C_6H_5	-C_6H_4-4-NO_2
33	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-Me	-C_6H_5
34	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-Me	-C_6H_4-4-Me
35	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-Me	-C_6H_4-4-OMe
36	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-OMe	-C_6H_5
37	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-OMe	-C_6H_4-4-OMe
38	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-Cl	-C_6H_5
39	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-Cl	-C_6H_4-4-OMe
40	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-OMe	-C_6H_4-4-O-CH_2-CH_2-Pip
41	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-Cl	-C_6H_4-4-O-CH_2-CH_2-Pip
42	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-OMe	-C_6H_4-4-O-CH_2-CH_2-Mor
43	-CH=CH-CH=CH-	=CH_2	-C_6H_4-4-Cl	-C_6H_4-4-O-CH_2-CH_2-Mor
44	-CH=CH-CH=CH-	-CH_2-CH=CH-C_6H_3-3,4-Cl_2	-C_6H_5	-
45	-CH=CH-CH=CH-	-CH_2-CH=CH-C_6H_4-4-Cl	-C_6H_4-4-Cl	-
46	-CH=CH-CH=CH-	-CH_2-CH=CH-Fur	-C_6H_4-4-Me	-
47	-CH=CH-CH=CH-	-CH_2-CH=CH-Fur	-C_6H_4-4-Cl	-
48	-CH=CH-CH=CH-	-CH_2-CH=CH-Thi	-C_6H_4-4-OMe	-
49	-CH=CH-CH=CH-	-CH_2-CH=CH-Thi	-C_6H_4-4-Cl	-

Fur: Fur-2-yl, Me: Methyl, Mor: Morpholine-4-yl, Pip: Piperidine-1-yl, Thi: Thien-2-yl

Table 4. Biological data and physicochemical parameters of imidazo[1,2-a]pyrazines

Comp.	$Log(1/C)_{obsv}$	ClogP	π	σ	$\mathcal{F}$	E_s	MR
20	5.25	3.92	4.46	- 0.46	0.38	- 3.69	63.21
21	5.10	4.32	4.63	0.21	0.57	- 2.99	56.75
22	6.29	4.63	5.19	0.04	0.53	- 4.11	61.37
23	5.07	4.21	4.61	- 0.06	0.83	- 3.54	63.59
24	4.88	4.93	5.34	0.44	0.98	- 3.96	61.75
25	4.08	6.98	7.80	- 0.58	0.84	- 5.14	115.12
26	4.00	8.41	9.26	0.42	1.14	- 5.98	111.44

27	4.42	9.03	9.97	0.65	1.55	- 6.95	116.44
28	4.37	5.45	5.80	- 0.15	0.15	- 9.52	72.81
29	4.27	5.77	6.36	- 0.32	0.11	- 10.64	77.43
30	4.72	5.35	5.78	- 0.42	0.41	- 10.07	79.65
31	4.50	6.07	6.51	0.08	0.56	- 10.49	77.81
32	5.14	5.32	5.52	0.63	0.82	- 12.04	79.14
33	5.42	5.77	6.36	- 0.32	0.11	- 10.64	77.43
34	4.54	6.08	6.92	- 0.49	0.07	- 11.76	82.05
35	4.47	5.66	6.34	- 0.59	0.37	- 11.19	84.27
36	5.17	5.35	5.78	- 0.42	0.41	- 10.07	79.65
37	4.75	5.24	5.76	- 0.69	0.67	- 10.62	86.49
38	4.82	6.07	6.51	0.08	0.56	- 10.49	77.81
39	5.02	5.96	6.49	- 0.19	0.82	- 11.04	84.65
40	4.90	6.06	4.85	- 0.20	0.55	- 12.02	93.19
41	4.62	6.78	5.58	0.30	0.70	- 12.64	91.35
42	4.72	5.57	3.43	- 0.65	0.55	- 11.65	90.30
43	4.59	4.85	4.16	- 0.15	0.70	- 12.07	88.46
44	4.28	6.93	6.77	0.46	1.08	- 13.53	89.18
45	4.02	6.93	6.77	0.46	1.08	- 13.53	89.18
46	4.18	5.12	5.21	- 0.63	0.25	- 15.43	76.11
47	4.45	5.42	5.36	- 0.23	0.70	- 15.28	76.49
48	4.41	5.44	5.69	- 0.21	0.54	- 15.38	84.70
49	4.14	6.16	6.42	0.29	0.69	- 15.80	82.86

The aim of this study is to find the relationship between the anticancer activities and some physicochemical parameters. The calculated clogP and Hansch Aromatic Substituent Constants, π, as hydrophobic parameters, Hammett Substituent Constants, σ, and Swain-Lupton Substituent Constants, $\mathcal{F}$, as electronic effects, Taft Steric Constants, E_s, and Molecular Refractivity, MR, as steric parameters were selected in this study. The values of logP were calculated by using Hansch's clogP (Leo et al., 1971; 1975; Hansch & Leo, 1995). The values of π, σ, $\mathcal{F}$, and MR were calculated by adding π, σ, $\mathcal{F}$, and MR values of the substituents (Hansch et al., 1973; 1977; 1995; Hansch & Leo, 1995; Kubinyi, 1993; Leo et al., 1971; 1975;) 1-,2-,4- and 5- aryl/allyl groups for the imidazoles and 2-,3-,6-,7- and 8- aryl/alkyl/allyl groups for the imidazo[1,2-a]pyrazines. Taft Steric Constants, E_s, were calculated similar to the compounds (Taft, 1952).

The correlation matrix amongst regression parameters were shown in Table 5 for imidazoles and in Table 6 for imidazo[1,2-a]pyrazines, respectively. The multi regression was applied on log(1/C) values with physicochemical parameters. Hansch Linear and Nonlinear Analysis Methods were employed as shown below (in turn in order Eqs. (1), (2)). Accordingly, the many equations were obtained for both imidazoles (Eqs. (3)-(16)) and imidazo[1,2-a]pyrazines (Eqs. (17)-(22)). Since any correct correlation amongst the values was not found for both imidazoles and imidazo[1,2-a]pyrazines when Nonlinear Hansch Equation (Eqs. (2)) was used, $clogP^2$ and π^2 values were not shown on Tables and Equations in this suggested study. The six parameters used on regression analysis were processed one by one and collected according to parameter type. The similar parameters in hydrophobic, electronic and steric were not employed together. The regression analyses were carried out with Office-Excel Correlation and Regression Analyses Package.

General Equations for Hansch Analysis Methods

$$Log(1/C) = k_1.clogP\ (\pi) + k_2.\ \sigma\ (Ŧ) + k_3.E_s\ (MR) + k_0 \quad (1)$$

$$Log(1/C) = k_1.clogP\ (\pi) - k_2.clogP^2\ (\pi^2) + k_3.\ \sigma\ (Ŧ) + k_4.E_s\ (MR) + k_0 \quad (2)$$

Equations For Imidazoles

$$Log(1/C) = -0.301\ (\pm0.085)\ \mathbf{clogP} + 6.007\ (\pm0.397) \quad (3)$$
$$r = 0.652 \quad s = 0.438$$

$$Log(1/C) = -0.238\ (\pm0.061)\ \pi + 6.263\ (\pm0.423) \quad (4)$$
$$r = 0.690 \quad s = 0.418$$

$$Log(1/C) = -0.021\ (\pm0.005)\ \mathbf{MR} + 6.545\ (\pm0.440) \quad (5)$$
$$r = 0.731 \quad s = 0.394$$

$$Log(1/C) = -0.392\ (\pm0.102)\ \mathbf{clogP} + 0.561\ (\pm0.376)\ Ŧ + 5.994\ (\pm0.383) \quad (6)$$
$$r = 0.704 \quad s = 0.423$$

$$Log(1/C) = -0.306\ (\pm0.098)\ \mathbf{clogP} + 0.001\ (\pm0.042)\ \mathbf{E_s} + 6.015\ (\pm0.718) \quad (7)$$
$$r = 0.652 \quad s = 0.451$$

$$Log(1/C) = -0.046\ (\pm0.152)\ \mathbf{clogP} - 0.019\ (\pm0.009)\ \mathbf{MR} + 6.532\ (\pm0.454) \quad (8)$$
$$r = 0.732 \quad s = 0.405$$

$$Log(1/C) = -0.297\ (\pm0.071)\ \pi + 0.520\ (\pm0.348)\ Ŧ + 6.272\ (\pm0.408) \quad (9)$$
$$r = 0.735 \quad s = 0.404$$

$$Log(1/C) = -0.238\ (\pm0.069)\ \pi + 0.001\ (\pm0.039)\ \mathbf{E_s} + 6.277\ (\pm0.717) \quad (10)$$
$$r = 0.690 \quad s = 0.431$$

$$Log(1/C) = -0.064\ (\pm0.129)\ \pi - 0.016\ (\pm0.011)\ \mathbf{MR} + 6.550\ (\pm0.450) \quad (11)$$
$$r = 0.735 \quad s = 0.403$$

$$Log(1/C) = 0.469\ (\pm0.318)\ Ŧ - 0.025\ (\pm0.005)\ \mathbf{MR} + 6.563\ (\pm0.426) \quad (12)$$
$$r = 0.768 \quad s = 0.381$$

$$Log(1/C) = -0.398\ (\pm0.116)\ \mathbf{clogP} + 0.565\ (\pm0.390)\ Ŧ - 0.005\ (\pm0.041)\ \mathbf{E_s} + 6.063\ (\pm0.695) \quad (13)$$
$$r = 0.704 \quad s = 0.436$$

$$Log(1/C) = -0.136\ (\pm0.154)\ \mathbf{clogP} + 0.574\ (\pm0.342)\ Ŧ - 0.019\ (\pm0.009)\ \mathbf{MR} + 6.526\ (\pm0.431) \quad (14)$$
$$r = 0.781 \quad s = 0.384$$

$$Log(1/C) = -0.299\ (\pm0.079)\ \pi + 0.521\ (\pm0.360)\ Ŧ - 0.003\ (\pm0.038)\ \mathbf{E_s} + 6.310\ (\pm0.694) \quad (15)$$
$$r = 0.735 \quad s = 0.417$$

$$\mathbf{Log(1/C)} = -0.118\ (\pm0.127)\ \pi + 0.547\ (\pm0.331)\ Ŧ - 0.017\ (\pm0.010)\ \mathbf{MR} + 6.575\ (\pm0.428) \quad (16)$$
$$\mathbf{r = 0.782} \quad s = 0.383$$

Equations For Imidazo[1,2-a]pyrazines

$$Log(1/C) = -0.248\ (\pm0.069)\ \mathbf{clogP} + 6.120\ (\pm0.409) \quad (17)$$
$$r = 0.559 \quad s = 0.415$$

$$Log(1/C) = -0.020\ (\pm0.005)\ \mathbf{MR} + 6.299\ (\pm0.441) \quad (18)$$
$$r = 0.574 \quad s = 0.409$$

$$\mathbf{Log(1/C)} = -0.220\ (\pm0.065)\ \mathbf{clogP} + 0.046\ (\pm0.019)\ \mathbf{E_s} + 6.424\ (\pm0.397) \quad (19)$$
$$\mathbf{r = 0.661} \quad s = 0.382$$

$$Log(1/C) = -0.111\ (\pm0.135)\ \mathbf{clogP} - 0.012\ (\pm0.010)\ \mathbf{MR} + 6.336\ (\pm0.446) \quad (20)$$
$$r = 0.589 \quad s = 0.412$$

$$Log(1/C) = -0.169\ (\pm0.054)\ \pi + 0.060\ (\pm0.019)\ \mathbf{E_s} + 6.302\ (\pm0.387) \quad (21)$$
$$r = 0.643 \quad s = 0.390$$

$$Log(1/C) = -0.039\ (\pm0.076)\ \pi - 0.017\ (\pm0.007)\ \mathbf{MR} + 6.331\ (\pm0.451) \quad (22)$$
$$r = 0.580 \quad s = 0.415$$

Anticancer Activity

The cytotoxic and/or growth inhibitory effects of the compounds were evaluated in vitro against approximately sixty six human tumor cell lines derived from nine neoplastic diseases namely; Leukaemia (L), Non-Small Cell Lung Cancer (NSCLC), Colon Cancer (CC), Central Nervous System Cancer (CNSC), Melanoma (M), Ovarian Cancer (OC), Renal Cancer (RC), Prostate Cancer (PC), Breast Cancer (BC). The evaluation

of anticancer activity was performed at the National Cancer Institute (NCI) of Bethesda, USA, following the in vitro screening program, which is based upon the use of multiple panels of 66 human tumor cell lines against which our compounds were tested at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8} M. The percentage growth was evaluated spectrophotometrically versus controls not treated with test agents. A 48 h continuous drug exposure protocol was followed and a sulforhodamine B (SRB) protein assay was used to estimate cell viability of growth (Boyd, 1989). Antilog of the mean graph midpoint (MG-MID) values was used as biological data.

RESULT AND DISCUSSION

In this study, the many equations was formed for both imidazoles and imidazo[1,2-a]pyrazines. The relationships between biological activity and physicochemical parameters were investigated by multiple regression analyses and statistically significant equations. In these equations, r is the correlation coefficient, s is the standard deviation. The equations in which their correlation coefficient values were lower than 0.5, were not taken in this study. In addition, if the sign of the correlation between log 1/C and physicochemical parameters was not same with correlation matrix shown in both Table 5 and Table 6, these equations including these parameters were discarded. In statistical evaluations, it is necessary that the sign of correlation should be same. Therefore, the equations including electronic parameter, σ, were not employed for imidazoles. The equations including electronic parameters, σ, and Ŧ, were not used for imidazo[1,2-a]pyrazines. In all equations, there is no correlation between coefficients and standard deviations.

The higher correlation was reported between biological activity and hydrophobic parameters, clogP, and π, with electronic parameter, Ŧ, and with steric parameter, MR, for imidazoles. On the other hand, the higher correlation was reported between biological activity and hydrophobic parameters, clogP, and, π, with steric parameter, MR, for imidazo[1,2-a]pyrazines. Eqs. (16) was selected as imidazole equation owing to the fact that r value is higher than the others, in Fig. 1. Similarly, Eqs. (19) was selected as imidazo[1,2-a]pyrazine equation, in Fig. 2. The results calculated according to selected equations were given in Table 7 for imidazoles and in Table 8 for imidazo[1,2-a]pyrazines, respectively.

Table 5. The correlation matrix amongst regression parameters for imidazoles.

	$Log(1/C)_{obsv}$	clogP	π	σ	Ŧ	E_s	MR
$Log(1/C)_{obsv}$	1						
clogP	- 0,652	1					
π	- 0.690	0.993	1				
σ	0.181	0.209	0.133	1			
Ŧ	- 0.178	0.599	0.562	0.331	1		
E_s	- 0.293	0.453	0.431	- 0.346	0.220	1	
MR	- 0.731	0.856	0.892	- 0.283	0.520	0.576	1

Table 6. The correlation matrix amongst regression parameters for imidazo[1,2-a]pyrazines.

	$Log(1/C)_{obsv}$	clogP	π	σ	Ŧ	E_s	MR
$Log(1/C)_{obsv}$	1						
clogP	- 0,559	1					
π	- 0.444	0.864	1				
σ	- 0.059	0.417	0.364	1			
Ŧ	- 0.225	0.557	0.452	0.684	1		
E_s	0.443	- 0.173	0.049	0.106	0.174	1	
MR	- 0.574	0.860	0.667	0.091	0.490	0.221	1

Table 7. The observed and calculated activity values for imidazoles.

Comp.	$Log(1/C)_{obsv}$ NCI	$Log(1/C)_{calc}$ Eq.114
1 [4]	4.10	4.02
2 [4]	4.01	3.97
3 [4]	4.02	4.10
4 [4]	4.09	4.00
5 [4]	4.01	4.10
6 [4]	4.02	4.07
7 [3]	4.15	4.05
8 [3]	5.54	5.59
9 [3]	5.27	5.35
10 [3]	5.25	5.17
11 [3]	5.51	5.62
12 [3]	5.46	5.65
13 [3]	5.01	5.08
14 [1]	4.64	4.65
15 [1]	4.81	4.78
16 [1]	4.50	4.59
17 [1]	4.75	4.77
18 [1]	4.42	4.25
19 [1]	4.73	4.61

CONCLUSIONS

It was seen that anticancer activity was decreased by aryl groups on 4- and 5- positions of imidazole, **1-6**. When the 1,2-butadienyl was on the above positions, the structure was called as benzimidazole, **7-19**. In this case, the activity was increased. When substituted aryl groups, including methoxy and chloride were on the 1- and 2- positions of benzimidazole, the activity was more effective.

On the other hand, imidazo[1,2-a]pyrazines with 2- and 3- position empty, **20-24**, were more effective based on the activity. In addition, in these compounds, methoxy and chloride were also very important. In addition to methoxy and chloride, methyl was also important in these compounds. QSAR studies reveal that benzimidazoles with methoxy and/or chloride substituted aryl groups placed especially on 1- and 2- positions were effective with respect to others. Furthermore, pyrazino[1,2-a]benzimidazoles with methyl, methoxy and chloride placed on 6-, 7- and 8- positions were more effective than the others. When all the compounds, **1-49**, were examined, it was seen that the 6,8-diarylimidazo[1,2-a]pyrazine derivatives were more effective.

Table 8. The observed and calculated activity values for imidazo[1,2-a]pyrazines.

Comp.	$Log(1/C)_{obsv}$ NCI	$Log(1/C)_{calc}$ Eq.203
20 [2]	5.25	5.18
21 [2]	5.10	5.16
22 [2]	6.29	5.99
23 [2]	5.07	5.14
24 [2]	4.88	4.82
25 [4]	4.08	3.90
26 [4]	4.00	4.04
27 [4]	4.42	4.44
28 [1]	4.37	4.22
29 [1]	4.27	4.10
30 [1]	4.72	4.64
31 [1]	4.50	4.41
32 [1]	5.14	5.21
33 [1]	5.42	5.64
34 [1]	4.54	4.77
35 [1]	4.47	4.48
36 [1]	5.17	5.34
37 [1]	4.75	4.64
38 [1]	4.82	4.81
39 [1]	5.02	5.18
40 [1]	4.90	5.10
41 [1]	4.62	4.64
42 [1]	4.72	4.85
43 [1]	4.59	4.65
44 [1]	4.28	4.48
45 [1]	4.02	4.08
46 [1]	4.18	4.23
47 [1]	4.45	4.77
48 [1]	4.41	4.77
49 [1]	4.14	4.64

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