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Relationship between Electronic Structure and Cytotoxic Activity of Dopamine and 3-Benzazepine Derivatives

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Abstract. *A structure-activity relationship of dopamine and 3-benzazepine derivatives is discussed, using theoretically calculated results. In order to clearly divide dopamines and 3-benzazepines into a strongly active and a weakly active group, the CC_{50}, two different dipole moments ($\mu_{ESP\text{-}G}$ and $\mu_{ESP\text{-}W}$) and heat of formation (ΔH_f) of dopamine **[1-13]** and 3-benzazepine derivatives **[14-23]** were separately calculated in two states of gas-phase and water-solution by the COSMO/PM3 method. It was found that ten derivatives **[1-3, 9, 12-13** and **20-23]** (CC_{50}: 0.056 to 2.5 mM) showed the strongest cytotoxic activity with small $\Delta\Delta H_f$ values, whereas thirteen derivatives **[4-8, 10-11, 14-19]** (CC_{50}: > 3.6 mM) showed the weakest cytotoxic activity with large $\Delta\Delta H_f$ values.*

3-Benzazepines possess a wide range of interesting biological activities such as reverse transcriptase inhibition, an antimicrobial effect, cytotoxic activity, adrenoreceptor antagonism, binding to the phencyclidine site of the *N*-methyl-D-aspartate (NMDA) receptor and alteration of lipophilicity (1). The benzazepines also showed an inhibitory effect on the functions of natural killer (NK) cells including granular lymphocytes and monocytes (2). 3-Benzazepines **[20, 21, 22]** exhibited an antimicrobial effect, F'lac plasmid elimination activity and antibody-dependent cellular cytotoxicity (ADCC). Interestingly, one compound, **[23]**, could inhibit the antiplasmid effect of promethazine (a phenothiazine derivative), when compared to the control (promethazine alone) on plasmid curing effect (3). Three 7, 8-dihydroxy-3-benzazepines **[20-22]**, having the ability to generate radicals, were cytotoxic to the human promyelotic leukaemia HL-60 cells (4). Some 3-benzazepine derivatives showed an antagonist activity at the peripheral postjunctional α-2 adrenoreceptors (5). The unsubstituted 3-benzazepine had a considerable affinity for the phencyclidine binding site of the *N*-methyl-D-aspartate (NMDA) receptor (6). The alteration of the lipophilicity of 3-benzazepines themselves did not affect their pharmacokinetics, however, the pharmacokinetics of secondary amines may differ from the tertiary amines (7). The quantum chemical calculations of 3-benzazepines have been correlated to (a) the accessory π-binding site in a location complementary to a suitably oriented aromatic ring, (b) the effects on D-1 and D-2 D-A receptors, (c) the effects on the 2-phenyldopamine, (d) the exceptional D-1 agonist potency and (e) the D-2 agonist activity, using the calculation parameters (8). The D-1 D-A binding activity has been correlated with the calculated torsion angle of the biphenyl portion of these molecules. Then, a good D-1 dopamine binding has been observed when the aromatic rings approach coplanarity, which means that a poor binding occurs when the aromatic rings are orthogonal (9). The *N*-methyl 3-benzazepines retained the good D-2 agonist potency, but the substitution of *N*-methyl groups converted the D-1 agonist activity to antagonist activity (10).

Based on the above quantum-chemical calculations and their association with the biological activities of 3-benzazepines, the purpose of this paper was to reveal any relationship between a molecular orbital calculation with 3-benzazepine and dopamine derivatives.

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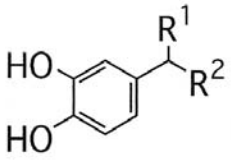
Key Words: Dopamines, 3-benzazepines, dipole moment (μ).

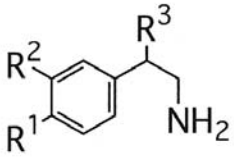
Materials and Methods

Chemicals. Thirteen dopamines **[1-13]** and ten 3-benzazepine derivatives **[14-23]** were synthesized as described previously (11, 12) (Figure 1).

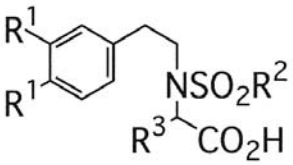
Dopamine derivatives



1: R^1=H, R^2=CH_2NH_2
2: R^1=OH, R^2=CH_2NH_2
3: R^1=H, R^2=CO_2H
4: R^1=OH, R^2=CO_2H

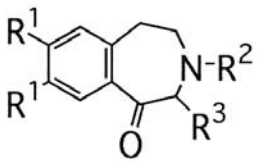


5: R^1=OH, R^2=OMe,R^3=H
6: R^1=OH, R^2=OMe,R^3=OH
13: R^1=R^2=OMe, R^3=H

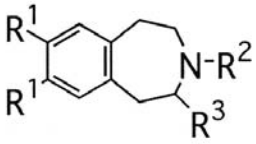


7: R^1=OMe, R^2=Me, R^3=Me
8: R^1=OMe, R^2=CF_3, R^3=Me
9: R^1=H, R^2=CF_3,R^3=H
10: R^1=OMe, R^2=CF_3, R^3=H
11: R^1=OMe, R^2=CF_3, R^3=$CHMe_2$
12: R^1=OMe, R^2=CF_3, R^3=Ph

3-Benzazepine derivatives



14: R^1=OMe, R^2=Ms, R^3=Me
15: R^1=OMe, R^2=Tf, R^3=Me
16: R^1=H, R^2=Tf, R^3=H
17: R^1=OMe, R^2=Tf, R^3=H
18: R^1=OMe, R^2=Tf, R^3=$CHMe_2$
19: R^1=OMe, R^2=Tf, R^3=Ph



20: R^1=OH, R^2=H, R^3=CF_3
21: R^1=OH, R^2=Me, R^3=CF_3
22: R^1=OH, R^2=H, R^3=H
23: R^1=OMe, R^2=H, R^3=CF_3

Figure 1. *Structures of compounds* ***[1-23]****. Abbreviation: Me=CH_3; Ms=SO_2CH_3; Tf=SO_2CF_3.*

Table I. *Cytotoxic activity and estimated cytotoxic activity, $\Delta\Delta H_f$,dipole moment (μ) and I_{OH} of compounds* ***[1-23]*** *in gas-phase and water-solution by the PM3 method.*

Compound No	CC_{50}		$\Delta\Delta H_f$ (in KJ/mol)	μ (in D units)		I_{OH}
	obs.[mM]	calc.[a)]		μ_{ESP-G}	μ_{ESP-W}	
1	0.11	0.11	52.3	1.72	3.08	1
2	0.23	0.28	66.9	2.10	2.70	1
3	0.79	0.77	80.8	1.81	5.37	1
4	>10	2.02	144.1	4.14	8.54	1
5	6.4	2.12	62.5	1.95	3.02	0
6	7.6	2.48	91.6	2.16	2.62	0
7	>10	5.44	261.3	3.77	7.73	0
8	3.6	3.53	144.7	3.42	5.27	0
9	2.4	4.25	185.0	5.26	6.64	0
10	6.2	3.88	166.9	2.91	5.63	0
11	9.6	4.29	250.8	3.30	4.35	0
12	0.43	3.27	130.7	3.42	4.75	0
13	2.0	1.73	48.0	1.06	1.37	0
14	>10	4.94	221.8	4.98	8.17	0
15	>10	4.75	222.3	5.35	6.45	0
16	6.4	3.43	188.8	5.28	7.04	0
17	>10	5.39	251.5	5.54	8.45	0
18	>10	4.71	217.5	4.95	6.67	0
19	>10	4.84	229.1	4.45	6.37	0
20	0.084	0.12	91.6	2.17	2.65	1
21	0.086	0.06	89.8	2.01	2.47	1
22	0.056	0.02	75.9	0.82	1.46	1
23	2.5	2.50	92.6	1.59	2.65	0

a) Estimated from equation 1.

Theoretical calculations. The molecular orbital calculation by parametric method 3 (PM3) was performed with application of the winMOPAC program (13). The geometries of compounds **[1-23]** were optimized with respect to all geometrical parameters using the Broyden-Fletcher-Goldfrab-Shanno algorithm incorporated in the program. The geometries of compounds **[1-23]** in water-solution were compared with those in gases by the conductor-like screening model (COSMO) and electrostatic potential (ESP) calculations. The COSMO procedure generates a conducting polygonal surface around the system at van der Waal's distance. The number of the geometrical segments per atom (NSPA) was 60 and the dielectric constant 78.4 at 25°C (water). The values of dipole moment (μ) in the gas-phase and in the water-solution of compounds **[1-23]** were calculated by the ESP/PM3 and COSMO/PM3 methods. For this calculation, an IBM aptiva E47 personal computer was used.

Results and Discussion

Cytotoxicity. Millimolar concentrations of dopamines **[1-13]** and 3-benzazepines **[14-23]** were cytotoxic to HL-60 cells. Among dopamines, the cytotoxic activity of **[1]** was the greatest (CC_{50}=0.11 mM), followed by **[2]** (CC_{50}=0.23 mM) and **[12]** (CC_{50}=0.43 mM). These thirteen dopamines could be separated into two groups: less active dopamine derivatives (**[4-11]**, **[13]**) and highly active dopamines ([**1-3, 12**]) (Table I). Among 3-benzazepines, the cytotoxic activity of **[22]** was the greatest (CC_{50}=0.056 mM), followed by **[20]** (CC_{50}=0.084 mM) and **[21]** (CC_{50}=0.086 mM) (Table I). Simililary, the ten 3-benzazepines could also be separated into two groups: less active **[2,3,4**, 5-tetrahydro-3-benzazepinones **[14-19]** and highly active 2,3,4,5-tetrahydro-3-benzazepines **[20-23]**.

By the results of CC_{50}, we introduce physicochemical parameter I_{OH}, The present study demonstrated that, first, dopamines and 3-benzazepines having two *ortho* phenolic OH groups in the catechol skeleton (dopamines **[1-3]** and 3-benzazepines **[20-23]**) were cytotoxic (I_{OH}=1) and second, those without the OH group in the benzene ring (dopamines **[7-13]**, 3-benzazepines **[14-19]** and **[23]**) had much lower cytotoxic activity (I_{OH} =0).

Partition coefficient logP has been used as an index for the structure-activity relationship analysis for new drug design. A stereohydrophobic parameter dGW was obtained by the PM3 method. The dGWs were defined from their free-energy changes for the association in the aqueous

solution and in the vacuum (14). The structure-activity relationship analysis revealed that hydrophobicity of whole molecule ($\Delta\Delta H_f$), existence of two ortho phenolic OH groups (I_{OH}) and dipole moment (μ) might control the cytotoxic activity. Here, we discuss the relationship between the cytotoxic activity and individual quantitative structure-activity relationship (QSAR) parameters. Table I shows the cytotoxic activity (CC_{50}), dipole moment (μ) and $\Delta\Delta H_f$ of compounds **[1-23]** by using the PM3 calculation method. Two types of dipole moment were calculated by this method.

Relationship between cytotoxic activity and $\Delta\Delta H_f$. Several reports have been published on predicting logP by molecular orbital calculations for a soluble molecule. Recently, we have reported a QSAR between cytotoxic activity and three QSAR electronic parameters of $\Delta\Delta H_f$, I_{OH} and $\mu_{ESP\text{-}G}$ of 3-benzazepine derivatives **[14-23]** (15). Consequently, the following correlation equation 1 was obtained.

$CC_{50} = -2.85 + 0.0718 \times \Delta\Delta H_f - 1.87 \times I_{OH} - 0.816 \times \mu_{ESP\text{-}G}$ (equation 1)

The correlation coefficient (r^2) and F value were calculated to be 0.999 and 150313, respectively. However, the multiple linear-regression analysis for dopamines **[1-13]** using the above equation 1 could not correlate with the three QSAR parameters of $\Delta\Delta H_f$, I_{OH} and $\mu_{ESP\text{-}G}$. The correlation coefficient (r^2) and F value were calculated to be 0.38 and 5.45, respectively. Therefore, we repeated the optimization of geometry for dopamines **[1-13]** with step1 ($\omega 1$) = 30°, point 12 and step 2 ($\omega 2$) = 30°, point 12 (Figure 2). The differences between heat of formation in gas-phase and in water-solution ($\Delta\Delta H_f$) are shown in Table I. Among dopamines, the derivatives with smaller $\Delta\Delta H_f$ (**[1]** ($\Delta\Delta H_f$ = 52.3 KJ/mol; CC_{50} = 0.11 mM), **[2]** ($\Delta\Delta H_f$ = 66.9 KJ/mol; CC_{50} = 0.23 mM), **[3]** ($\Delta\Delta H_f$ = 80.8 KJ/mol; CC_{50} = 0.79 mM) and **[13]** ($\Delta\Delta H_f$ = 48.0 KJ/mol; CC_{50} = 2.0 mM) were more cytotoxic than compounds **[4, 6-11]** with larger $\Delta\Delta H_f$ (Table I). Compounds with smaller $\Delta\Delta H_f$ (**[20]** ($\Delta\Delta H_f$ = 91.63 KJ/mol; CC_{50} = 0.084 mM), **[21]** ($\Delta\Delta H_f$ = 89.79 KJ/mol; CC_{50} = 0.086 mM), **[22]** ($\Delta\Delta H_f$ = 75.87 KJ/mol; CC_{50} = 0.056 mM) and **[23]** ($\Delta\Delta H_f$ = 92.55 KJ/mol; CC_{50} = 2.5 mM) were more cytotoxic than compounds **[14-19]** with larger $\Delta\Delta H_f$ (Table I). This suggests a positive relationship between $\Delta\Delta H_f$ and cytotoxic activity.

Relationship between cytotoxic activity and dipole moments. The dipole moment (μ) was used to determine the interaction of two molecules with different dipoles. Table I shows the dipole moment (μ) of compounds **[1-23]** in gas-phase and water-solution, calculated by the PM3 method. Two types of dipole moment were calculated by the PM3 method. The values of $\mu_{ESP\text{-}G}$ and $\mu_{ESP\text{-}W}$ were evaluated from the point charge calculated by ESP calculations in the gas-phase and in the water-solution, respectively. The values of $\mu_{ESP\text{-}W}$ were calculated by the COSMO/PM3 method. Interestingly, among dopamine derivatives **[1-13]**, four derivatives **[1-3, 13]** showed strong cytotoxic activity (CC_{50} < 2.5 mM) with smaller $\mu_{ESP\text{-}G}$ values of 1.72 D, 2.10 D, 1.81 D and 1.06 D, respectively. On the other hand, three dopamines **[4, 7, 11]** showed weak cytotoxic activity (CC_{50} > 9.6 mM) with larger $\mu_{ESP\text{-}G}$ values of 4.14 D, 3.77 D and 3.30 D, respectively. A similar tendency was also found for the calculated $\mu_{ESP\text{-}W}$. Among ten 3-benzazepines **[14-23]**, four 3-benzazepines **[20-23]** showed strong cytotoxic activity (CC_{50} < 2.5 mM) and lower $\mu_{ESP\text{-}G}$ values of 2.17 D, 2.01 D, 0.82 D and 1.59 D, respectively. On the other hand, six 3-benzazepines **[14-19]** showed the weak cytotoxic activity (CC_{50} > 6.4 mM) and higher $\mu_{ESP\text{-}G}$ values of 4.98 D, 5.35 D, 5.28 D, 5.54 D, 4.95 D and 4.45 D, respectively. A similar tendency was also found for the calculated $\mu_{ESP\text{-}W}$. This result suggests a positive relationship between the calculated dipole moments and the cytotoxic activity.

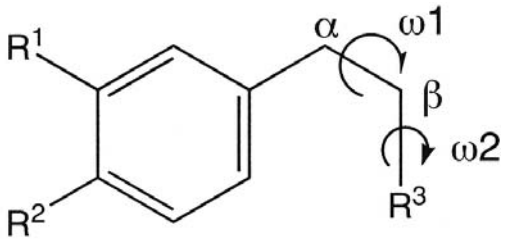


Figure 2. *Definitions of the rotational angles of the side chains around the α-β bond and β-γ bond.*

Structure-activity relationship analysis between CC_{50} and electronic properties. In order to obtain a quantitative correlation between cytotoxic activity and electronic property, we calculated the coefficient of the multiple determination and F value. The structure-activity relationship analysis revealed that the hydrophobicity of whole molecule ($\Delta\Delta H_f$), the existence of two ortho phenolic OH groups (I_{OH}) and dipole moment (μ) might greatly contribute to the cytotoxic activity. The correlation coefficients (r^2) between CC_{50} values for seven compounds **[1, 2, 3, 20, 21, 22, 23]** and three electronic parameters of $\Delta\Delta H_f$, I_{OH} and $\mu_{ESP\text{-}W}$ were calculated to be 0.99 for seven compounds. The F value for seven compounds was 845.1. Then, since the F values of these seven compounds for this orbital model were larger than the five percent critical value, the hypothesis is acceptable and the following equation 2 is proposed:

$CC_{50} = 0.900 + 0.0141 \times \Delta\Delta H_f - 1.87 \times I_{OH} + 0.112 \times \mu_{ESP\text{-}W}$ (equation 2)

The CC_{50} values estimated from equation 2 are shown in Table I. The present study suggests the application of theoretical calculation such as dipole moments and $\Delta\Delta H_f$ to the prediction of the cytotoxic activity of dopamine and 3-benzazepine derivatives.

References

1 Winstock J, Hieble JP and Wilson JW: The chemistry and pharmacology of 3-benzazepines. Drugs Future *10*: 645-96, 1985.

2 Berek L, Petri IB, Varga E, Molnar J, Kawase M, Saito S and Motohashi N: Immunomodulating effect of 2,3,4,5-tetrahydro-1H-3-benzazepines (a new class of non-nucleoside inhibitors of reverse transcriptase). Int J Antimicrob Agents *14*: 221-224, 2000.

3 Motohashi N, Kawase M, Saito S, Miskolci C, Berek L and Molnar J: Plasmid elimination and immunomodulation by 3-benzazepines *in vitro*. Anticancer Res *19*: 5075-5078, 1999.

4 Kawase M, Saito S and Motohashi N: Chemistry and biological activity of new 3-benzazepines. Int J Antimicrob Agents *14*: 193-201, 2000.

5 Daly RN, Sulpizio AC, Levitt B, DeMarinis RM, Regan JW, Ruffolo RR and Hieble JP: Evidence for heterogeneity between pre- and postjunctional alpha-2 adrenoceptors using 9-substituted 3-benzazepines. J Pharmacol Exp Ther *247*: 122-128, 1988.

6 Wunsch B, Nerdinger S, Bauschke G and Hofner G: Noncompetitive NMDA antagonists: a novel synthesis of 1-phenyltetrahydro-3-benzazepines. Arch Pharm (Weinheim) *330*: 211-4, 1997.

7 Gombar CT, Demarinis RM, Wise M and Mico BA: Pharmacokinetics of a series of 6-chloro-2,3,4,5-tetrahydro-3-substituted-1H-3-benzazepines in rats. Determination of quantitative structure-pharmacokinetic relationships. Drug Metab Dispos *16*: 367-372, 1988.

8 Weinstock J, Oh HJ, DeBrosse CW, Eggleston DS, Wise M, Flaim KE, Gessner GW, Sawyer JL and Kaiser C: Synthesis, conformation, and dopaminergic activity of 5, 6-ethano-bridged derivatives of selective dopaminergic 3-benzazepines. J Med Chem *30*: 1303-1308, 1987.

9 Ladd DL, Weinstock J, Wise M, Gessner GW, Sawyer JL and Flaim KE: Synthesis and dopaminergic binding of 2-aryldopamine analogues: phenethylamines, 3-benzazepines, and 9-(aminomethyl)fluorenes. J Med Chem *29*: 1904-1912, 1986.

10 Ross ST, Franz RG, Wilson JW, Brenner M, DeMarinis RM, Hieble JP and Sarau HM: Dopamine receptor agonists: 3-allyl-6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol and a series of related 3-benzazepines. J Med Chem *29*: 733-740, 1986.

11 Kawase M, Motohashi N, Niwa M and Nozaki M: Use of the triflamide group for Friedel-Crafts acylation of *N*-(β-phenethyl)amino acids to 3-benzazepine derivatives. Heterocycles *45*: 1121-9,1997.

12 Kawase M, Niwa M, Nozaki M and Motohashi N: Synthesis of 2-trifluoromethyl-2,3,4,5-tetrahydro-1H-3-benazepine derivatives. Heterocycles *48*: 555-60,1998.

13 PM3 semi-emprical MO calculations were performed by MOPAC version 6 on an IBM aptiva E47 personal computer.

14 Ohkura K and Hori H: Analysis of structure-permeability correlation of nitrophenol analoges in newborn rat abdominal skin using semiempirical molecular orbital calculation. Bioorg Med Chem *7*: 309-314, 1998.

15 Kawase M, Motohashi N, Kurihara T, Inagaki M, Satoh K and Sakagami H: Relationship between radical intensity and cytotoxic activity of dopamine-related compounds. Anticancer Res *18*: 1069-1074, 1998.

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