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A THEORETICAL STUDY ON BASICITY BEHAVIOUR OF SOME 4-AMINOQUINAZOLINE DERIVATIVES

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ABSTRACT

The acidity constants (K_a) of five 6-substitue-4-aminoquinazoline compounds were determined theoretically. The gas and aqueous phase geometries and possible tautomeric forms were defined with full geometry optimization by using B3LYP/6-31G(d) method for the 4-aminoquinazoline derivatives. It was found that most stable forms are amino form and the first protonation occurs at the ring nitrogen atom N1.

Keywords: Protonation, DFT calculation, Aminoquinazoline derivatives, Tautomerism.

BAZI 4-AMİNOKİNAZOLİN TÜREVLERİNİN BAZLIK DAVRANIŞLARI ÜZERİNE TEORİK BİR ÇALIŞMA

ÖZ

Bazı 6-substitue-4-aminokinazolin bileşiklerinin asitlik sabitleri teorik olarak incelenmiştir. 6-substitue-4-aminokinazolin türevleri için gaz ve sıvı faz geometrileri ve olası tatomerik formları tam geometri optimizasyonu ile birlikte B3LYP/6-31G(d) yöntemi kullanılarak tanımlanmıştır. En kararlı formun amino formu olduğu ve ilk protonlanmanın halka azot atomunda (N1) olduğu bulunmuştur.

Anahtar Kelimeler: Protonlanma, DFT hesaplaması, Aminokinazolin türevleri, Tautomerizm.

1. INTRODUCTION

Some aminoquinazoline derivatives were effective as antitumour, antimutagenic, anti-inflammatory, anti-microbial, antihypertensive, and anti-bacterial agents (Liu et al. 2006; Rosowsky et al. 1999; Gangjee et al. 1995; Abouzid and Shouman 2008; Cakici et al. 2010; Harris et al. 1990). Furthermore some of them were found to be highly selective inhibitors of tyrosine kinase (Zielinski and Kudelko 2005; Fry et al. 1994; Traxler et al. 1996; Myers et al. 1997) and dihydrofolate reductase enzymes (Hynes et al. 1991). Many researchers have already reported their research results of experimental studies on the bioactivities of aminoquinazoline derivatives (Liu et al. 2007; Kawakami et al. 2011; Okano et al. 2009; McLuskey et al. 2004).

The knowledge of acidity constants of organic molecules is very important in the chemical and pharmaceutical industries (Hemmateenejad et al. 2010; Alizadeh et al. 2010) and the acid-base interactions of some aminoquinazoline derivatives were studied experimentally (Zielinski and Kudelko 2000a, 2000b, 2005). We now report on theoretically calculated acid dissociation constant (K_a) and energy values for possible tautomer forms of some 6-substitue-4-aminoquinazoline derivatives. The obtained results were evaluated by searching a possible correlation with the experimental results in the literature (Zielinski and Kudelko 2005).

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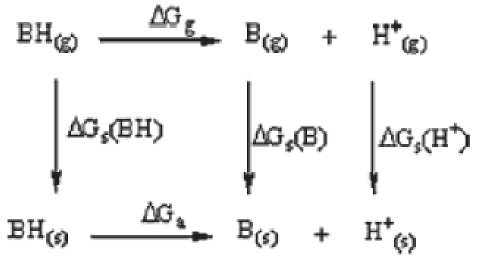
2. COMPUTATIONAL METHODS

Nowadays both microscopic and macroscopic theoretical methods are available for the estimation of solvation free energies. Therefore it is possible, in principle, to determine theoretical relative or absolute acidity constants (K_a) using the thermodynamic cycle and Eq. 2.1. Scheme 1 shows the interrelationship between the thermodynamic parameters of gas and solution phases.



Scheme 1. Interrelationship between the gas phase and solution phase thermodynamic parameters.

The acidity constant (K_a) can be computed by using Eq. 2.1 and Eq. 2.2. The Eq. 2.2 is rearranged form of Eq. 2.1.

$$\Delta G_a = -RT \ln K_a \qquad (2.1)$$

$$pK_a = \Delta G_a / 2.303RT \qquad (2.2)$$

The *ab initio* calculations of the absolute pK_a values can be done by using Eq.2.3 in which ΔG_g and $\Delta G_a = \Delta G_s(B) - \Delta G_s(BH) + \Delta G_s(H^+)$ are the gas phase and solvation free energies of the ionization and ΔG_ss are solvation free energies of base and acid.

$$pK_a = [\Delta G_g + \Delta G_a] / 2.303\ RT \qquad (2.3)$$

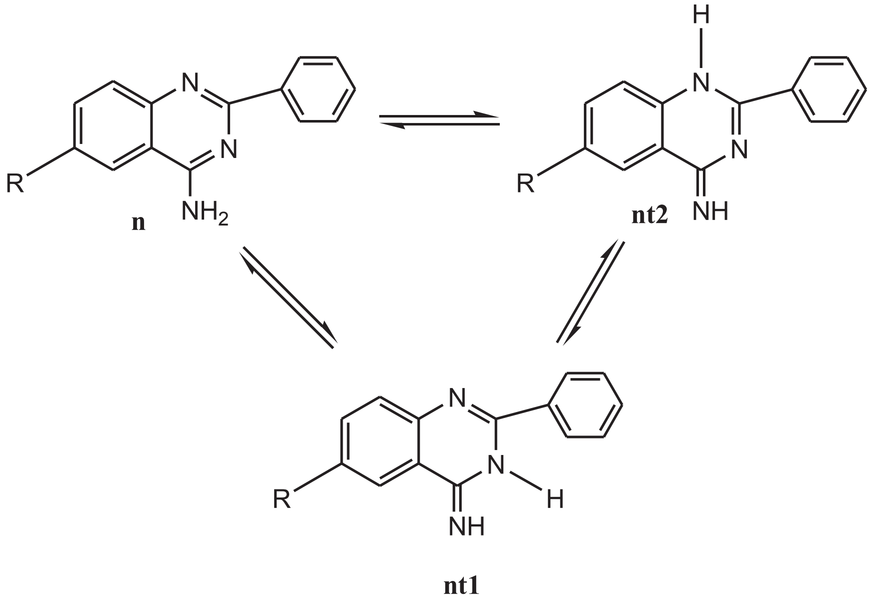
In the present work, density functional geometry DFT(B3LYP/6-31G(d) optimization was performed using Gaussian 03W program (Frisch et al. 2003). After geometry optimization the vibration spectrum was evaluated to check that no imaginary frequency is present. Integral equation formalism model (IEF-PCM) for solvation and United Atom Topological Model (UAHF) for molecular cavity were used for aqueous phase calculations. The total energies were given in Hartree using the conversion factor 1 Hartree =627.5095 kcal/mol. The value of $\Delta G_s(H^+)$ -274 kcal/mol has been used for pK_a calculation.

3. RESULTS AND DISCUSSION

3.1 Tautomerism

The possible tautomeric forms and energy values of the studied molecules were given in Scheme 2 and Table 1.

n	R
1	H
2	CH_3
3	OCH_3
4	Br
5	Cl



Scheme 2. Possible tautomeric forms of the studied molecules.

Table 1. B3LYP/6-31G(d) calculated gas phase energy values of the possible tautomeric forms

Tautomeric form	E_T (hartree)	G_T (hartree)
1	**-704.181**	**-704.220**
1t1	-704.163	-704.203
1t2	-704.159	-704.199
2	**-743.471**	**-743.513**
2t1	-743.454	-743.496
2t2	-743.450	-743.494
3	**-818.671**	**-818.714**
3t1	-818.654	-818.697
3t2	-818.650	-818.693
4	**-3275.295**	**-3275.338**
4t1	-3275.277	-3275.320
4t2	-3275.273	-3275.316
5	**-1163.786**	**-1163.827**
5t1	-1163.768	-1163.810
5t2	-1163.764	-1163.806

E_T=E+Zero Point Energy
G_T=Thermal Free Energy

As it can be seen from the Table 1, tautomeric forms **1**, **2**, **3**, **4** and **5** have the lowest energies and more stable than **t1** and **t2** forms. Similar results have been found experimentally in the literature (Zielinsky and Kudelko 2000a, 2000b). These most stable forms were used further calculations and discussions.

3.2 Basicity

The DFT calculated thermal and solvation free energy (ΔG_g and ΔG_s) values of the neutral molecules and their protonated cations were depicted in Table 2. Possible protonation patterns for studied molecules are shown in Scheme 3.

The studied molecules have three nitrogen atoms which are labeled with N1, N2 and N3. The N1 and N2 are ring nitrogen atom and N3 belongs to NH_2 substituent (Figure 1).

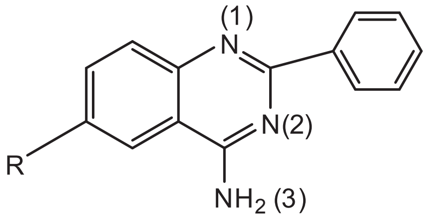
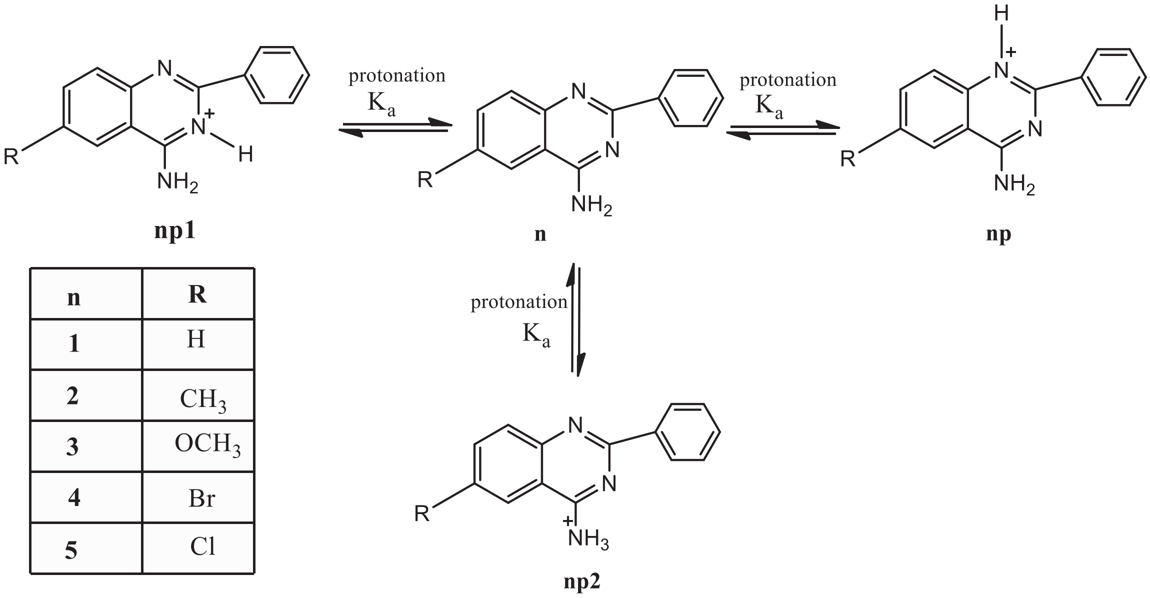


Figure 1. Numbering figure of the nitrogens.



n	R
1	H
2	CH_3
3	OCH_3
4	Br
5	Cl

Scheme 3. Possible protonation patterns of the studied molecules.

The N1 atom protonations were found to yield more stable forms than other nitrogen protonations at the studied molecules (Table 2). The calculated acidity constant values were observed very close to experimental values at N1 atom than other nitrogens as well. The highest and lowest calculated pK_a values of protonation on N1 atom have been found 5.59 and 3.75 for 6-methyl-4-aminoquinazoline and 6-bromo-4-aminoquinazoline, respectively.

B3LYP/ 6-31G(d) method $pK_{a(N1\ prot.)}$: $-CH_3$ > -H > $-OCH_3$ > -Cl > -Br
5.59 > 5.45 > 5.27 > 3.79 > 3.75

→ decreasing basicity

We have attempted to correlate the experimental pK_a values (Zielinski and Kudelko 2005) with calculated pK_a values and observed that the best fit occured with N1 protonation. The highest regression value was determined as 73% for N1 protonation of the studied molecules (Figure 2). The regression value for N2 protonation is 64% and these forms are not more stable than N1 protonated ones (Table 2). N2 protonation needs approximately 9 kcal/mol and 7 kcal/mol more energy at gas and water phase than N1 protonation, respectively. The regression on N1 protonation increase to %93 without **2**. This molecule has a methyl group at 6 position and gives electrons to ring inductively. Other substituents are methoxy, bromine and chlorine and these substituents give electrons to ring via mesomeric effect. Because of this the molecules **1**, **3**, **4** and **5** have similar protonation mechanism.

Table 2. Aqueous phase and gas phase B3LYP/6-31G(d) calculated thermal and solvation free energies, investigated compounds at 298K.

Compound	R	Thermal Free Energy Gg kcal/mol	Solvation Free Energy $\Delta G_{s(B)}$ kcal/mol	Thermal Free Energy $Gg_{(BH^+)}$ kcal/mol	Solvation Free Energy $\Delta G_{s(BH^+)}$ (kcal/mol	[a]$\delta\Delta G$ (kcal/mol)	[b]$pK_{a(calc.)}$	[c]$pK_{a(exp.)}$
1	H	-441904.9497	-6.99			281.433	5.45	5.44
1p	H			-442147.083	-46.29			
1	H	-441904.9497	-6.99			278.024	2.95	
1p1	H			-442137.8335	-52.13			
1	H	-441904.9497	-6.99			259.281	-10.79	
1p2	H			-442112.6811	-58.54			
2	6-CH_3	-466561.7275	-7.11			281.624	5.59	5.16
2p	6-CH_3			-466805.5212	-44.94			
2	6-CH_3	-466561.7275	-7.11			278.183	3.07	
2p1	6-CH_3			-466796.3006	-50.72			
2	6-CH_3	-466561.7275	-7.11			260.603	-9.82	
2p2	6-CH_3			-466771.2310	-58.21			
3	6-OCH_3	-513750.5266	-9.03			281.181	5.27	5.33
3p	6-OCH_3			-513994.7376	-46.00			
3	6-OCH_3	-513750.5266	-9.03			279.917	4.34	
3p1	6-OCH_3			-513989.3000	-50.17			
3	6-OCH_3	-513750.5266	-9.03			261.862	-8.90	
3p2	6-OCH_3			-513963.2988	-58.12			
4	6-Br	-2055305.597	-7.09			279.118	3.75	4.78
4p	6-Br			-2055544.185	-47.62			
4	6-Br	-2055305.597	-7.09			275.989	1.46	
4p1	6-Br			-2055535.2462	-53.43			
4	6-Br	-2055305.597	-7.09			260.236	-10.09	
4p2	6-Br			-2055510.5329	-62.39			
5	6-Cl	-730312.7612	-6.97			279.166	3.79	4.98
5p	6-Cl			-730550.9976	-47.90			
5	6-Cl	-730312.7612	-6.97			276.030	1.49	
5p1	6-Cl			-730542.0807	-53.68			
5	6-Cl	-730312.7612	-6.97			260.338	-10.02	
5p2	6-Cl			-730517.3795	-62.69			

[a]$\delta\Delta G$= (Gg- $Gg_{(BH^+)}$) + ($G_{s(B)}$. $\Delta G_{s(BH^+)}$) [b]pK_a calculated from $pK_a = [\Delta G_g + \Delta G_a] / 2.303\ RT$, [c]$pK_{a\,(expt.)}$ were taken from ref.(Kudelko;2005)

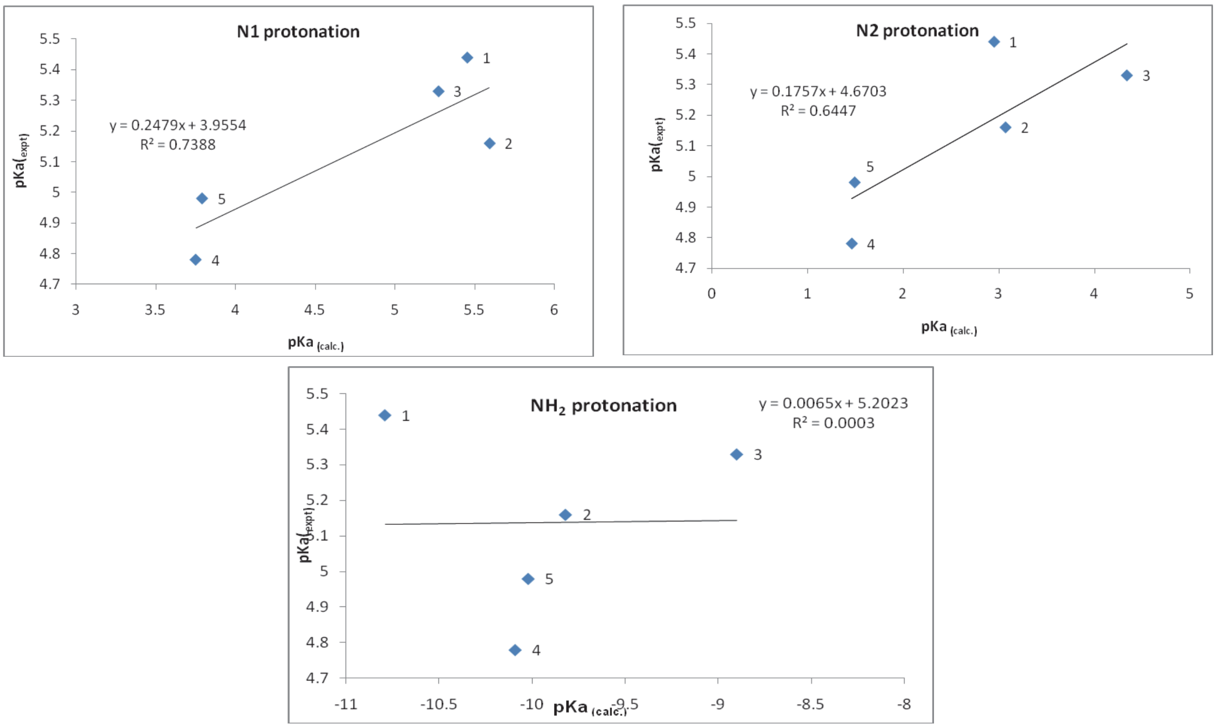


Figure 2. Correlation graphics between experimental and calculated acidity constants.

CONCLUSION

The correlation searches between the experimental and DFT calculated acidity constants of five 6-substitue-4-aminoquinazolines have given acceptable results. The regression analysis, energy values and calculated acidity constants indicate that the N1 atom protonation more likely than the other two nitrogen protonations in aqueous phase.

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REFERENCES

Abouzid, K. and Shouman,S.(2008). Design, synthesis and in vitro antitumor activity of 4-aminoquinoline and 4-aminoquinazoline derivatives targeting EGFR tyrosine kinase. *Bioorganic& Medicinal Chemistry* 16, 7543-7551.

Alizadeh, K., Rezaei, B. and Maddah, B. (2010). Spectrophotometric determination of aqueous acidity constants of three azo dyes. *Central European Journal of Chemistry* 8(2), 392-395.

Cakici, M., Catir, M., Karabuga, S., Kilic, H., Ulukanli, S., Gulluce, M. and Orhan, F. (2010). Synthesis and biological evaluation of (S)-4-aminoquinazoline alcohols. *Tetrahedron:Asymmetry* 21, 2027-2031.

Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Montgomery, Jr J.A., Vreven, T., Kudin, K.N., Burant, J.C., Millam, J.M., Iyengar, S.S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G.A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J.E., Hratchian, H.P., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cami, R., Pomelli, C., Ochterski, J.W., Ayala, P.Y., Morokuma, K., Voth, G.A., Salvador, P., Dannenberg, J.J., Zakrzewski, V.G., Dapprich, S., Daniels, A.D., Strain, M.C., Farkas, O., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Ortiz, J.V., Cui, Q., Baboul, A.G., Clifford, S., Cioslowski, J., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Gonzalez, C. and Pople, J.A. (2004). Gaussian 03; Gaussian, Inc., Wallingford CT.

Fry, D.W., Kraker, A.J., McMichael, A., Ambroso, L.A., Nelson, J.M., Leopold, W.R., Connors, R.W. and Bridges, A.J. (1994). A spesific inhibitor of the epidermal growth factor receptor tyrosine kinase. *Science* 265, 1093-1095.

Gangjee, A., Zaveri, N., Kothare, M. and Queener, S.F. (1995). Nonclassical 2,4-diamino-6-(aminomethyl)-5, 6, 7, 8-tetrahydroquinazoline antifolates: synthesis and biological activities. *Journal of Medicinal Chemistry* 38, 3660-3668.

Harris, N.V., Smith, C. and Bowden, K. (1990). Antifolate and antibacterial activities of 5-substituted 2,4-diaminoquinazolines. *Journal of Medicinal Chemistry* 33, 434-444.

Hemmateenejad, B., Emami, L. and Sharghi, H. (2010). Multi-wavelength spectrophotometric determination of acidity constant of some newly synthesized Schiff bases and their QSPR study. *Spectrochimica Acta Part A* 75, 340-346.

Hynes, J.B., Tomazic, A., Kumar, A., Kumar, V. and Freisheim, J.H. (1991). Inhibition of human dihydrofolate reductase by 2,4-diaminoquinazolines bearing simple substituents on the aromatic ring. *Journal of Heterocyclic Chemistry* 28, 1981-1986.

Kawakami, J.K., Martinez, Y., Sasaki, B., Harris, M., Kurata, W.E. and Lau, A.F. (2011). Investigation of a novel molecular descriptor for the lead optimization of 4-aminoquinazolines as vascular endothelial growth factor receptor-2-inhibitors: application for quantitative structure-activity relationship analysis in lead optimization. *Bioorganic& Medicinal Chemistry Letters* 21 1371-1375.

Liu, G., Yang, S., Song, B., Xue, W., Hu, D., Jin, L. and Lu, P. (2006). Microwave assisted synthesis of N-arylheterocyclic substituted-4-aminoquinazoline derivatives. *Molecules* 11, 272-278.

Liu, G. Hu, D.Y., Jin, L.H., Song, B.A., Yang, S., Liu, P.S., Bhadury, P.S., Ma, Y., Luo, H. and Zhou, X. (2007). Synthesis and bioactivities of 6,7,8-trimethoxy-N-aryl-4-aminoquinazoline derivatives. *Bioorganic& Medicinal Chemistry* 15, 6608-6617.

McLuskey, K., Gibellini, F., Carvalho, P., Avery, M.A. and Hunter, W.N. (2004). Inhibition of Leishmania major pteridine reductase by 2,4,6- triaminoquinazoline: structure of the NADPH ternary complex. *Acta Crystallographica D* 60, 1780-1785.

Myers, M.R., Setzer, N.N., Spada, A.P., Person, P.E., Ly, C.Q., Maguire, M.P., Zulli, A.L., Cheney, D.L., Zilberstein, A., Johson, S.E., Franks, C.F. and Mitchell, K.J. (1997). The synthesis and sar of new 4-(N-alkyl-N-phenyl)amino-6,7-dimethoxyquinazolines and 4-(N-alkyl-N-phenyl)aminopyrazole [3,4-d]pyrimidines, inhibitors of CSF-1R tyrosine kinase activity. *Bioorganic& Medicinal Chemistry Letters* 7(4), 421-424.

Okano, M., Mito, J., Maruyama, Y., Masuda, H., Niwa, T., Nakagawa, S., Nakumura, Y. and Matsuura, A. (2009). Discovery and structure-activity relationships of 4-aminoquinazoline derivatives, a novel class of opioid receptor like-1 (ORL1) antagonists. *Bioorganic& Medicinal Chemistry* 17, 119-132.

Rosowsky, A., Papoulis, A., Forsch, R.A. and Queener, S.F. (1999). Synthesis and antiparasitic and antitumor activity of 2,4-diamino-6-(arylmethyl)-5,6,7,8-tetrahydroquinazoline anologues of pritrexim. *Journal of Medicinal Chemistry* 42, 1007-1017.

Traxler, P.M., Furet, P., Melt, H., Buchdunger, E., Meyer, T. and Lydon, N. (1996). 4-(Phenylamino)pyrrolopyrimidines: potent and selective, ATP site directed inhibitors of the EGF-receptor protein tyrosine kinase. *Journal of Medicinal Chemistry* 39, 2285-2292.

Zielinski, W. and Kudelko, A. (2000a). Concerning the basicity of 4-dimethylaminoquinazoline derivatives. *Monatshefte für Chemie* 131, 733-738.

Zielinski, W. and Kudelko, A. (2000b). Synthesis and basicity of 4-amino-2-phenylquinazolines. *Monatshefte für Chemie* 131, 895-899.

Zielinski, W. and Kudelko, A. (2005). Acid base interactions in some isoquinoline and quinazoline amino derivatives. *Arkivoc* v, 66-82.