Quantitative structure-activity relationships of some new beta amino-carbonyl compounds

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Hanoy K. Al-Amood, Hanan F. Al-Shamsi, and Hayat H. Abbas

Quantitative Structure-Activity Relationships of Some New Beta Amino- Carbonyl Compounds

Hanoy K. Al-Amood[1, a)] , Hanan F. Al-Shamsi[2)] And Hayat H. Abbas[1)]

[1)]*Department of Chemistry, College of Sciences, University of Basrah,Basrah,Iraq*
[2)] *Department of pharmaceutical chemistry, College of Pharmacy, University of Basrah,Basrah,Iraq*

[a)]Corresponding author: hanoy.alamood@unobasrah.edu.iq

Abstract. New compounds from the beta - aminocarbonyl groups named 3- (2,4 –dichlorophenyl)-3-((Aryl phenyl) amino)1- phenyl propan-1- one and compound 3-(benzylamino) -3- (2,4-dichlorophenyl)-1-phenylpropan -1- one, has been synthesized using a modulation method. The biological activity of the prepared compounds tested against two types of bacteria, E.coli and S. aureus, at concentration of (500) g / mL. The physical properties of beta-amino carbonyl compounds calculated using the PM3 method. The quantitative relationship between the logarithm diameter inhibition of the bacteria with some physical properties under special conditions studied. Where found an excellent relationship with the ELUMO energy, where it showed an inverse relation to the E.coli germ and was considered a predictive relationship that was able to explain the activity of the compounds very well, as well as, an inverse relation with Mulliken charge. As both attributes showed calculated hydrophobic (Clogp)H-bond acceptors, and heat of formation (ΔHf), a reverse relationship gave a good match between values measured in practice and calculated values theoretically.

Keywords: beta-amino carbonyl compounds, QSAR.

INTRODUCTION

The quantitative relationships between molecules and their properties are often "complex, not only in biological systems but also" in the physicochemical properties of compounds and many other processes. The details of the relationship between structure and effectiveness are so intricate that many assumptions and simplicity must use to make the relationship acceptable and thus be time-consuming and as an alternative to those theoretical calculations of a series of molecules with different properties are constructed. It is useful when there is a lot of information about biological mechanics, but it becomes more necessary in the absence of this information.

QSAR was developed for the first time since the beginning of the 1960s by Hansch and Fujita [1] to understand the relationships between composition and efficacy and was invaluable because it gained the ability to generate predictive models for toxicological and physiochemical processes as well as in some cases, calculation of some Absorption, Disposition, Metabolism and Excretion (ADME) that occur as soon as the drug given to the patient.

At present, it is be apply in many fields related to environmental risk assessment and drug design, due to the recognition of the importance of these results in building the ability to develop in the pharmaceutical industry, which leads to a decrease in the failure of refining processes in the drug development process, where a distinction can be made between medicinal and non-drug molecules [2] (such as drug resistance [3], toxicity prediction [4], and prediction of physicochemical properties ,such as solubility in water and fat [5], and others).

The beta-amino carbonyl compounds aroused the interest of many researchers in various fields, including the industry, where they used in the preparation of a particular ink called photoinitiators and used in three-dimensional printing [6], as well as used as intermediate compounds to produce many drugs, especially anti-cancer and anti-microbial [7,8] as well as "for use in preparing biologically active molecules [9], as well as their use in preparing enzyme inhibitors [6]. Given the "importance of these compounds and their broad applications, this has encouraged

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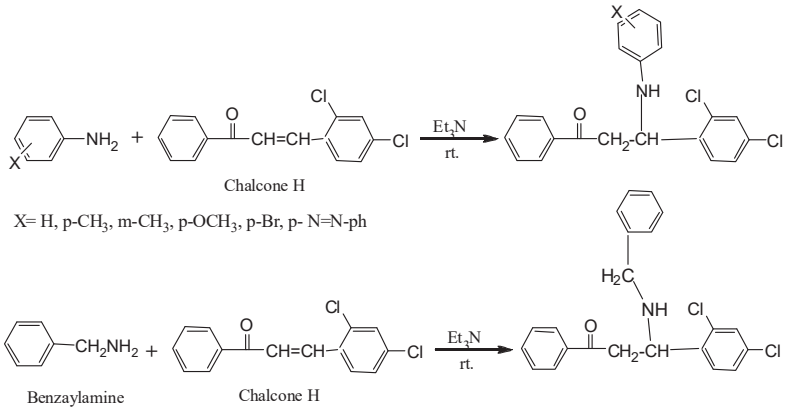
many researchers to intensify efforts to prepare beta-amino carbonyl compounds, study the effectiveness of these compounds, calculate some of their physical properties, and find the quantitative relationship between their biological efficacy and the structure in the form of an activity that is more effective for the purpose of understanding the way it works within the organism and thus trying to prepare more effective compounds.

EXPERIMENTAL

Preparation of Compounds

Seven new compounds from the beta-amino carbonyl compounds named 3- (2,4 –dichlorophenyl)-3-((X- phenyl)amino)1- phenyl propane-1- one and compound 3-(benzyl amino) -3- (2,4-dichlorophenyl)-1-phenylpropane -1- one has synthesized from the reaction of the chalcone H named [3-(2,4-dichlorophenyl)-1-(phenyl),2-propen-1-one] (10)with a series of substituted anilines where X= p-N=N-Ph, p-Br, m-CH3, p-CH3, p-OCH3 and p-H using a modulation method. (11) Scheme 1, Table 1. IR spectra for prepared compounds measured as KBr disks using Shimadzu model FT IR-8400Sspectrometer at the laboratory of the Chemistry department at Basrah University. The1H- NMR spectra recorded on a Bruker spectrometer at 400 MHz in DMSO-d6 as a solvent with TMS as an internal reference with CHN elemental analysis in Kashan University, Iran. (11)



SCHEME 1. Method of preparation compounds

TABLE 1.The Name of prepared compounds

No.	symbol	Name
1	HF_{H}	3-(2,4-dichlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one
2	$HF_{p\text{-}CH3}$	3-(2,4-dichlorophenyl)-1-phenyl-3-(p-tolylamino)propan-1-one
3	$HF_{m\text{-}CH3}$	3-(2,4-dichlorophenyl)-1-phenyl-3-(m-tolylamino)propan-1-one
4	$HF_{p\text{-}OCH3}$	3-(2,4-dichlorophenyl)-3-((4-methoxyphenyl)amino)-1-phenylpropan-1-one
5	$HF_{p\text{-}Br}$	3-((4-bromophenyl)amino)-3-(2,4-dichlorophenyl)-1-phenylpropan-1-one
6	HF_{Bz}	3-(benzylamino)-3-(2,4-dichlorophenyl)-1-phenylpropan-1-one
7	$HF_{p\text{-}N=N\text{-}Ph}$	3-(2,4-dichlorophenyl)-1-phenyl-3-((4-(phenyldiazenyl) phenyl) amino)propan-1-one

Biological Activity

The antimicrobial activity of beta-amino carbonyl compounds investigated using two bacterial species, one was Gram-negative *Escherichia coli*, and the other was Gram-positive *Staphylococcus aureus*. at (500 µg/ mL) which is used DMSO as a solvent and as a control for the hole sensitivity test [12].

Theoretical Calculations

Physical properties

Some physical properties theoretically calculated for the compounds prepared in this study using the HyperChem Professional (201) lnk program. Energy minimization for all compounds performed by the PM3 semi-empirical method with the Polark Ribier algorithm until the root-mean-square gradient of 0.1 Kcal/mol reached.

Correlation analysis

Correlation analyses of the measurements obtained from some of the physical properties of the compounds prepared in this study and the biological activity results of these compounds performed using the "Data Analysis Software" standard version MINITAB 17 lnk.

RESULTS AND DISCUSSION

The Results of Biological Activity at a Concentration (500µg \ mL)

The diameter of the inhibition zoon of the prepared compounds measured at 500µg / mL. All the compounds were given an effective biological direction of the germs *E-Coli* and *S-aureus*, as in Table

TABLE 2. The Inhibition zoon at a concentration (500 µg/mL) in mm

Compound	*E.Coli*	*S.aureus*
HF_{H}	10.0	11
$HF_{p\text{-}CH3}$	9.0	12
$HF_{m\text{-}CH3}$	10.0	12
$HF_{p\text{-}OCH3}$	0.0	13
$HF_{p\text{-}Br}$	11.0	9
HF_{Bz}	11.5	11
$HF_{p\text{-}N=N\text{-}Ph}$	15.0	14

Theoretical Calculations

Physical Properties Calculations

The physical properties of the beta-amino carbonyl compounds calculated that included the highest occupied molecular orbital energy (E_{HOMO}), the Lowest Unoccupied molecular orbital energy (E_{LUMO}), Volume, Clogp (the value of the hydrophobicity theoretically calculated) and the lipophilicity constant (π) [13], the heat of formation (ΔH_f), Polarization, refractivity index and Surface Area (Grid and Approx). Also, the number of atoms in the compound that can be hydrogen bonds with the acceptors((HB1) H-bond acceptor) [14]. Mulliken charge, which is

the sum of the charges on the carbonyl group $M_{C=O}$ and the sum of the charges on the amino group M_{N-H} and the total charges of the substituted group M_{sub}. The results listed in Tables 3 and

TABLE 3. Physicochemical properties of Beta-amino carbonyl compounds

Compounds	Surface Area (A^0)		polarization	ClogP	□□13)	ELUMO ev	EHOMO ev
	Grid	Approx.					
HF_H	607.73	517.17	40.55	5.75	0.00	-0.47725	-8.48689
$HF_{p\text{-}Me}$	619.83	547.85	42.39	6.22	0.56	-0.47950	-8.49768
$HF_{m\text{-}Me}$	626.70	548.44	42.39	6.22	0.56	-0.46424	-8.571911
HF_{OMe}	639.03	562.51	43.02	5.50	-0.02	-0.48514	-8.51072
HF_{Br}	639.12	563.07	43.18	6.54	0.86	-0.53446	-8.63199
HF_{Bz}	629.92	554.75	42.39	5.70	2.01	-0.54573	-9.18964
HF_{aza}	744.38	589.54	52.27	8.05	1.69	-1.96239	-7.55894

TABLE 4. Physicochemical properties of Beta-amino carbonyl compounds

compound	Mulliken charge				ΔHf Kcal/mol	Volume (A°)	Hydration Energy	H-bond[14] (acceptorHB1)	
	M Sub.	M NH	M C=O						
HF_H	0.104130	0.094122	0.019226	104.75	28.4413	1021.89	-5.00	4	0.05
$HF_{p\text{-}Me}$	0.253685	0.082216	0.013863	109.79	18.0408	1065.84	-4.24	4	-0.14
$HF_{m\text{-}Me}$	0.070505	0.085161	0.012537	109.79	17.7966	1065.06	-4.21	4	-0.06
HF_{OMe}	-0.052355	0.084318	0.012792	111.21	-9.8437	1091.13	-7.11	5	-0.28
HF_{Br}	-0.008309	0.099354	0.018574	112.37	35.8421	1083.09	-4.65	5	0.26
HF_{Bz}	-0.105487	-0.006200	0.008957	107.80	30.9549	1065.67	-4.72	4	-0.06
HF_{aza}	-0.025075	0.145343	0.024697	139.06	81.6506	1263.04	-11.08	6	0.33

The Quantitative Structure-Activity Relationship of the Prepared Beta-Amino Carbonyl Compounds

To understand the behaviour of the prepared compounds towards the bacteria (*E. coli* and *S-aureus*), the two studies studied the quantitative correlation between the logarithms of the bacterial inhibition diameter with some physical properties listed in Tables 2 and 3.

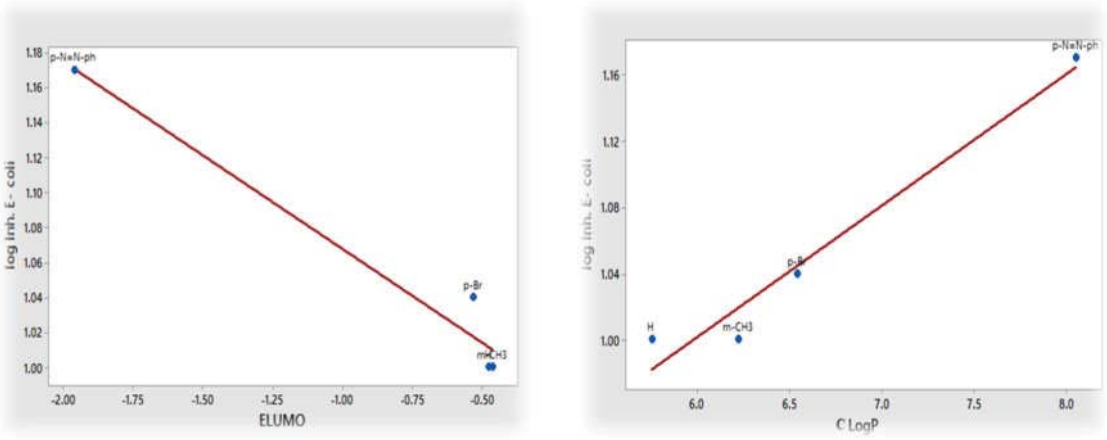
Study the correlation with logarithm of the inhibiting zoon of Escherichiacoli bacteria

We studied the relationship between the physical properties of beta-amino carbonyl compounds listed in Tables 1 and 2 and the logarithm of the inhibition zoon of bacteria *E. coli.* As we found an excellent inverse correlation with the energy of E_{LUMO} when removing the compounds ($HF_{p\text{-}Me}$, HF_{OMe} and HF_{Bz}), as in Equation 1 and Figure 1. The higher the value of the energy of the E_{LUMO} (low energy), the more effective the activity of this compound. Refers to the ability of compounds to receive the free electrons present inside the bacterial structure, and a predictive relationship has been able to explain the effectiveness of the compounds in the right way. Table 4.

$$\text{Log Inh. } E.\ coli = 0.9602 - 0.1074\ (-7.14)\ E_{LUMO} \qquad (1)$$

*n= 4, *S*= 0.0191715, r= 0. 9809, F= 50.99, P= 0.002

* Omitted HF_{Bz}, HF_{OCH3}, $HF_{p\text{-}Me}$



(a) (b)

FIGURE 1. The relationship between Log Inh. E. coli and (a) ELUMO, (b) Clogp after deletion of compounds HFp-Me, HFBz, and HFOMe

We studied the correlation with values (π) that represents the lipophilicity of substituted groups and the hydrophobic characteristics of ClogP, Equation 2, Fig. 1.b. The result was not good with the values of (π) according to Equation 3, as the conditions necessary to accept the correlation were not applied to them, while the relationship was excellent "with ClogP, and this indicates that the permeability of the compounds within the cell did not adopt the characteristics of lipophilicity of substituted groups, but rather It depended on the hydrophobic properties of the entire compound.

$$\text{Log Inh. } E.\ coli = 0.5249 + 0.0795(7.07)\ \text{ClogP} \qquad (2)$$

* n= 4, *S*= 0.0193436 , r= 0. 981 , F= 50.05 , P= 0.02

$$\text{Log Inh. } E.\ coli = 0.9699 + 0.1062\ (3.57)\ \pi \qquad (3)$$

*n= 4, *S*=0.036364 , r = 0. 93 , F= 12.73 , P= 0.07 .

* Omitted HF_{Bz}, HF_{OCH3}, $HF_{p\text{-}Me}$

H-bond acceptors and heat of formation (ΔH_f) showed good relationships after deleting the compounds ($HF_{p\text{-}Me}$, HF_{OMe}, and HF_{Bz}), as in equations 4 and 5, respectively. When the number of atoms that can form hydrogen bonds

increases, the biological activity increases, and this means an increase in the bond between the receptors and the compound, which leads to an increase in their effectiveness, Fig. 2.

Log Inh. *E. coli* = 0.5873 + 0.0809 (4.94) H-bond acceptors (4)
*n= 4 , *S*= 0.0153497 , r= 0.9612 , F= 24.45 , P= 0.04

Log Inh. *E. coli* = 0.9367 + 0.002829 (8.98) ΔH_f (5)
*n= 4 , *S*= 0.0137743 , r = 0.9878 , F= 80.66 , P= 0.012

* Omitted HF_{Bz}, HF_{OCH3}, $HF_{p\text{-}Me}$

These relationships were excellent. They gave a" good "match between the practically measured values and the theoretically calculated values from these equations. Table 5.

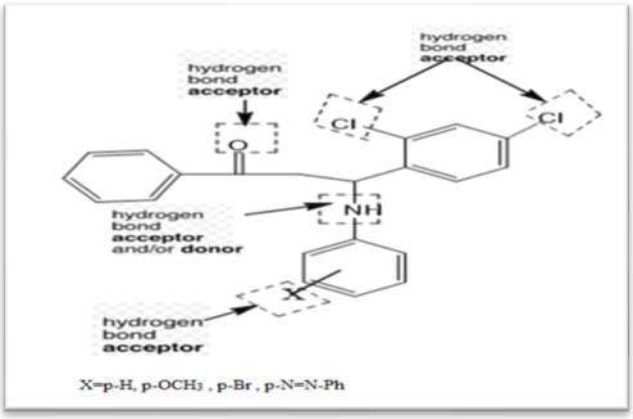


FIGURE 2. The regions of bonding of the hydrogen bonds in the prepared compounds

We found an inverse relationship with the Mulliken charge. Total charges of substituted groups for the compounds prepared in this study after removing the two compounds (HF_{OMe} and HF_{aza}), Equation 6, and the total charges on the amino group after the deletion of the compounds(HFaza, HF_{Br}, HF_{OMe}, and $HF_{p\text{-}Me}$), Equation 7. This means increasing the charge on the substituted group, as the amino group reduces the compound's effectiveness, and this is consistent with what observed in the results of Table 1. The compounds that have donor groups for electrons were less active than the compounds that have withdrawing groups. Equation 6 is a predictive equation for the effectiveness of compounds Table 5.

Log Inh. *E. coli* = 1.02976 – 0.3142 (-12.61) $M_{Sub.}$ (6)
*n= 5 , *S*= 0.0066649 , r= 0.9907 , F= 159.09 , P= 0.001.
* Omitted HF_{aza} and HF_{OMe}

Log Inh. *E. coli* = 1.05588 – 0.6220 (-12.35) M_{NH} (7)
*n= 3 , *S*= 0.0039538 , r= 0.9967 , F= 152.52 , P= 0.05
* Omitted HF_{aza}, HF_{Br} , HF_{OMe} and $HF_{p\text{-}Me}$

The relationship with the electronic effects of substituted groups (σ) Sigma in Table 3 was exponential after deleting the two compounds (HF_{OMe} and HF_{Bz}), Equation 8, that means the withdrawing electrons groups increase the effectiveness of the compounds, and this is consistent with equation 7.Withdrawing the electrons group reduces the charge on the amino group.

log Inh. *E. coli* = 1.0000 + 0.363 (3.21) σ (8)
*n=5 , *S*= 0.0457626 , r= 0.8817 , F=10.31 , P= 0.049 .
* Omitted HF_{OMe} and HF_{Bz}

TABLE 5. The values of log Inh. *E. Coli* theoretically calculated "compared to the practically measured values."

Log Inh. *E . coli* Calculated (eq no)						
Compound	**log Inh *E. coli* Observed**	**(1) E_{LUMO}**	**Clogp (2)**	**ΔH_f (5)**	**M_{sub} (6)**	**M_{NH} (7)**
HF_H	1	1.018	0.982	1.017	0.997	0.997
$HF_{p\text{-}Me}$	0.95	1.170	1.019	0.991	0.950	1.004
$HF_{m\text{-}Me}$	1	1.010	1.019	0.991	1.007	1.002
HF_{OMe}	0	1.012	0.962	0.926	1.046	1.003
HF_{Br}	1.04	1.017	1.044	1.033	1.032	0.994
HF_{Bz}	1.06	1.018	0.978	1.021	1.062	1.059
HF_{aza}	1.17	1.170	1.164	1.139	1.037	1.000

Study the correlation with logarithm of the inhibiting zoon of Staphylococcus aureus bacteria

The values of the inhibition diameter logarithm of the *S-aureus* bacteria showed a direct relationship with Clogp, surface area (grid SA), volume and the Refractive index, after deleting the two compounds (HF_{Br} and HF_{OMe}), as in the equations 9,10,11 and 12. Equations 9 and 10 are considered perfect equations. "it was able to explain the effectiveness of the compounds with high efficiency, Table 6. Fig. 3

Log Inh. *S.aurse* = 0.8024 + 0.04221 (14.74) ClogP (9)
*n= 5 , *S*= 0.0055058 , r=0.9932 , F= 217.36 , P= 0.001

Log Inh. *S.aurse* = 0.6304 + 0.000648 (4.53) S.A. grid (10)
*n= 5, *S*= 0.016877 , r= 0.9339 , F= 20.48 ,P= 0.020

Log Inh. *S.aurse* = 0.6229 + 0.000410 (5.48) volume (11)
* n= 5 , *S*= 0.0142263 , r=0.9534 , F= 30.1 ,P= 0.012

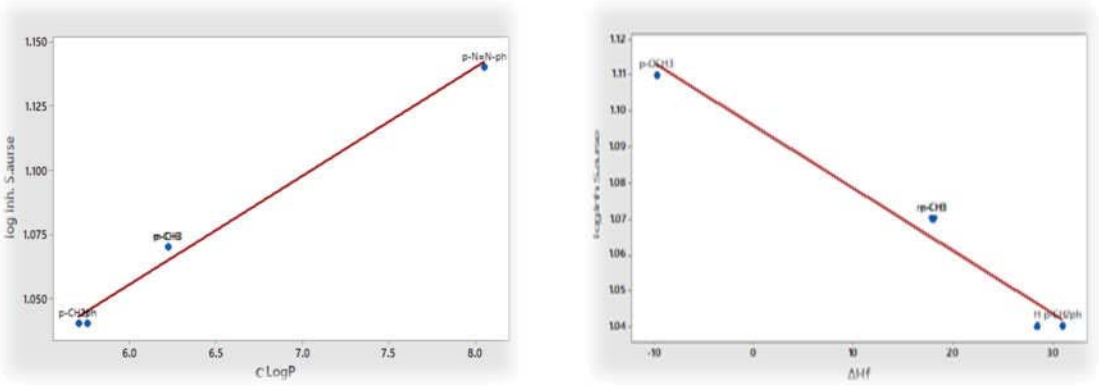
Log Inh. *S.aurse* = 0.7505 + 0.002814 (6.48) Refractive index (12)
*n= 5 , *S*= 0.0121856 , r=0.966 , F= 41.99 , P= 0.007

* Omitted HF_{OMe} and HF_{Br}

However, a negative correlation found with the heat of formation after deleting the HF_{Br} and HF_{aza} compounds Equation 19, were predicted and a predictive equation returned. Table 6, as we note that the high values of the heat formation did not explain the effectiveness results. Fig. 3.

Log Inh. *S.aurse* = 1.09589 – 0.001750 (-9.36) ΔH_f (13)
*n= 5 , S= 0.0060547 , r=0.9983 , F= 87.56 , P= 0.003 .

* Omitted HF_{aza} and HF_{Br}



(a) (b)

FIGURE 3. The relationship between Log Inh. *S.aurs.* and (a) ClogP, (b)ΔH_f after deletion of compounds

(a) HF_{OMe} and HF_{Br} (b) HF_{aza} and HF_{Br}

Inverse relationships found with the electronic effects of substituted groups σ and the proton-amine site (δ NH), after the HF_{Bz}, $HF_{Br,}$ HF_{aza} and HF_{H} compounds were omitted, Equation 14 and 15, respectively, This means that the effectiveness of the compounds depends on the amount of electronic density on the atom of the nitrogen, so the higher the charge over the group of amine (the less the charge), the more effective it is, and vice versa occurs if the charge decreases. This indicates that the bond between the compounds and the receptors is an electrostatic bond in addition to the hydrogen synergy between the electronic pair on the amino and receptor group.

$$\text{Log Inh. } S.aurse = 1.05091 - 0.2009(-5.78)\ \sigma \qquad (14)$$

*n=4 , *S*= 0.0083653 , r=0.97 , F= 33.37 , P= 0.029

*Omitted HF_{aza} HF_{Bz} and HF_{Br}

$$\text{log Inh. } S.aurse = 2.7422 - 0.2709\ (-25.38\ )\ \delta\ NH \qquad (15)$$

*n=4 , S=0.0047204 , r=0.998 , F= 644.27, p=0.002 .

*Omitted HF_{aza} HF_{Bz} and HF_{H}

TABLE. 6: The values of log Inh. *S.aruse* theoretically calculated "compared to the practically measured values

Compound	log Inh.*S.aurse* observed	log Inh.*S.aurse* Calculated (no eq)			
		Clogp (9)	S.A.grid (10)	ΔH_f (14)	δ NH (15)
HF_H	1.04	1.045	1.045	1.046	1.008
$HF_{p\text{-}Me}$	1.07	1.064	1.064	1.064	1.065
$HF_{m\text{-}Me}$	1.07	1.064	1.064	1.064	1.068
HF_{OMe}	1.11	1.034	1.034	1.113	1.114
HF_{Br}	0.95	1.078	1.078	1.033	0.951
HF_{Bz}	1.04	1.042	1.042	1.041	0.499
HF_{aza}	1.14	1.142	1.142	0.930	0.759

We notice from Tables 5 and 6 the extent of convergence between the calculated results theoretically and the results measured in practice. This means the efficiency of the chosen equations in interpreting the practical results,

and each of its equations (1), (6) and (13) Predictive equations, as these equations were able to interpret practical results with great accuracy.

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