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Detailed Quantum Mechanical QSAR Analysis of Certain Aminopyrimidoisoquinolinequinones with Anticancer Activity

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Abstract

A detailed quantum mechanical analysis of electronic disposition of five aminopyrimidoisoquinolinequinones (APIQs) was performed after extraction of this subset of compounds from a larger data set of APIQs via a reported clustering methodology (Elfaki, *et al.* 2020). Both semi empirical PM3 method and DFT quantum mechanical methods were used to calculate global and local quantum mechanical descriptors (QMDs) to define the electronic environment of these molecules in attempt to rationalize their observed anticancer response variability. The biological response is the anticancer activity against human gastric adenocarcenoma (AGS) cell line. The correlation matrix between the calculated global electronic descriptors and biological activity demonstrated that the global dipole moment gives the highest correlation. The local electronic environment was analysed by The Mullikan charges (MC) and Fukui functions for N-5, C-6, C-8 in addition to the N atom of phenylamino side group at C-8. MCs furnished no useful information as each of these atoms had almost identical MC values for all the five compounds with exception of C-6 which gave varied values. Regressing MCs of C-6 against the response traces 60% of the latter variability. As C-6 is an extra annular methyl carbon adjacent to N-5 in isoquinoline residue of APIQ, we reasoned that the chemical reactivities of 4 out of the 5 APIQs might be due to a Chichibabin-type tautomerism implying a possible alkylation aspect in their mechanism of action. The corresponding Fukui functions (f^-, f^+ and f^0) showed a considerable consistency with the patterns of chemical reactivity exhibited by this small set of APIQs.

Keywords

APIQs, DFT, Semi Empirical PM3, Global and Local Quantum Mechanical

Descriptors

1. Introduction

Physicochemical properties and structural features of chemical compounds control their biological activities [1]. For example, the ability of a molecule to cross cell membranes or dissolve in fatty tissues is closely related to its lipophilicity [2]. Likewise, ability of a molecule to form stable complexes and/or react with biological molecules is directed by its electronic distribution [3]. Quantum mechanical descriptors (QMD) such as the energy of the highest occupied molecular orbital ε_{HOMO}, the energy of the lowest unoccupied molecular orbital ε_{LUMO}, electronegativity (χ), hardness (η), softness (S), electrophilicity index (ω) have been used in the elucidation of the chemical reactivity [4] [5]. QMD can be divided into two kinds: global descriptors which describe whole molecule such as electrophilic index and dipole moment and local descriptors which describe parts of molecule such as Mullikan atomic charge and Fukui function [6]. Density functional theory (DFT) beside semi empirical PM3 method has been used fairly successful in elucidation of molecular properties and chemical reactivity [7]. In the present study, we report a detailed quantum mechanical study of electronic dispositions of five aminopyrimidoisoquinolinequinones (APIQs) [8] which cluster together when a larger data set of congeneric 27 APIQs was subjected regression clustering as previously reported by our group [9]. Both semi empirical PM3 method and DFT methods were used to calculate several global and local QMDs for these compounds in attempt to rationalize and explain the variability of biological response as a consequence of electronic environment.

2. Material and Method

Software:

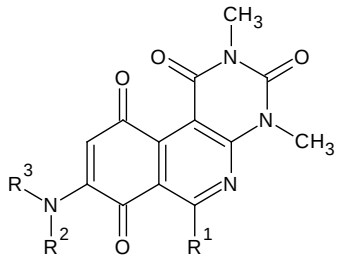
Gaussian 5.0.8 was used to draw/optimize of structures and for DFT calculation of Fukui functions basis set 3 - 21 G and B3LYP method [10]. Arguslab 4 and Molecular Operation Environment (MOE) 2008 softwares were used to calculate Mullikan charge and global descriptors [11]. Statistical analysis was performed using Microsoft Excel 2010 program.

Data set:

The biological activity used in the present study is the anticancer activities of compounds 5, 17, 18, 19 and 23 which are extracted from a larger data set through a reported clustering procedure [9]. We maintain the original numbering as appeared in the previous paper. The cancer cell line used is human gastric adenocarcenoma (AGS) cell line. Biological response is expressed as the inhibitory concentration of 50% of the subjects IC_{50}. The structures and biological activities of the APIQ's are shown in **Table 1**.

Figure 1 shows the optimized chemical structures of molecules.

Table 1. Structures and biological responses of APIQs.



No	R^1	R^2	R^3	IC_{50} (μM)
5	H	H	*p*-MeO-Ph-	2.8
17	Me	H	*p*-HO-Ph-	3.3
18	Me	H	*p*-MeO-Ph-	5.5
19	Me	H	*p*-F-Ph-	1
23	Me	H	2,5-diMeO-Ph-	31.7

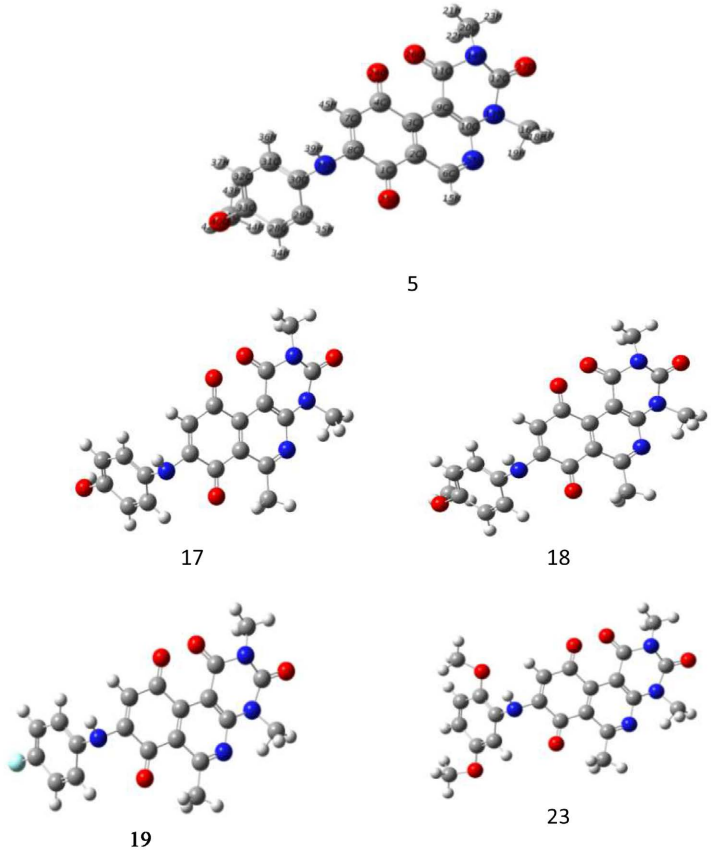


Figure 1. Optimized chemical structure of the APIQs (colored balls represent to: black (C), red (O), blue (N), yellow greenish (F) and white is (H)).

3. Results and Discussion

Global electronic descriptors

Table 2 contains the most significant global electronic descriptors of the five

APIQs under study. Table 3 shows the correlation matrix between these descriptors including the response.

The correlation matrix between the global electronic descriptors and biological activity, demonstrates that the global dipole moment gives the highest correlation. The QSAR equation can be written as the following:

$$IC_{50} = 0.3255\,\text{dipo} + 1.9086 \quad (1)$$

$$n = 5,\ R^2 = 0.88,\ s = 4.9,\ F = 23.8$$

It is clear from the data in Table 3 that dipole moment explains up to 88% the variability of the response while electrophilicity index explains up to 86%. These two descriptors are collinear (property spaces overlap to the extent of 72%). The unexplained variability by them combined amount to 16%. This could be attributed to communal effect of the rest of descriptors on variability.

It should be noted that there is a high collinearity between GAP and the electrophilicity index. Molecule 23 has the highest GAP (0.525) with the highest ω (1.731254) whereas molecule 18 has the lowest GAP (0.038) with the lowest ω (0.083993).Thus GAP explains the same variability as ω. GAP is pictorially rendered in Figure 2 to get a feel of the cause of partitioning of this particular set of molecules in one and the same cluster.

Table 2. Global electronic descriptors of the five APIQs molecules.

Comp.	ε_{HOMO} (eV)	ε_{LUMO} (eV)	η (eV)	s (eV)	χ (eV)	GAP (eV)	dip (debye)	ω
5	3.073	3.316	0.121	4.122	−3.195	0.242	1.115	0.619086
17	2.797	2.846	0.024	20.149	−2.822	0.049	3.161	0.049628
18	2.931	2.969	0.019	25.908	−2.950	0.038	2.772	0.038597
19	2.436	2.549	0.056	8.858	−2.492	0.112	4.464	0.112882
23	3.367	3.892	0.262	1.902	−3.630	0.525	12.45	1.731254

Table 3. Correlation matrix among the global electronic descriptors and IC_{50}.

	ε_{HOMO}	ε_{LUMO}	η	S	X	GAP	dipole	ω	AGS
ε_{HOMO}	1								
ε_{LUMO}	0.93	1							
Ƞ	0.57	0.81	1						
S	0.12	0.30	0.65	1					
X	0.97	0.98	0.72	0.22	1				
GAP	0.57	0.81	1	0.65	0.72	1			
dipo	0.27	0.44	0.66	0.22	0.37	0.66	1		
ω	0.64	0.85	0.98	0.54	0.77	0.98	0.72	1	
IC_{50}	0.60	0.75	0.78	0.21	0.70	0.78	0.88	0.86	1

Local electronic descriptors

The local environment may be considered by looking at certain atoms around the molecule. We considered N-5, C-6 and C-8 in addition to the nitrogen atom of phenylamino side group at C-8.

Using the PM3 semi-empirical method, the value of Mullikan charge MC remain the same for all these atoms except for C-6 (Table 4), where a significant linear correlation was discerned ($R^2 = 0.6$) with the logarithm of the IC_{50} as depicted in Figure 3.

This shows that this carbon is active in spite of its full valence through its presence in the aromatic ring system in addition to its bonding to methyl group. The reason for this is not far-fetched; The presence of a methyl group adjacent

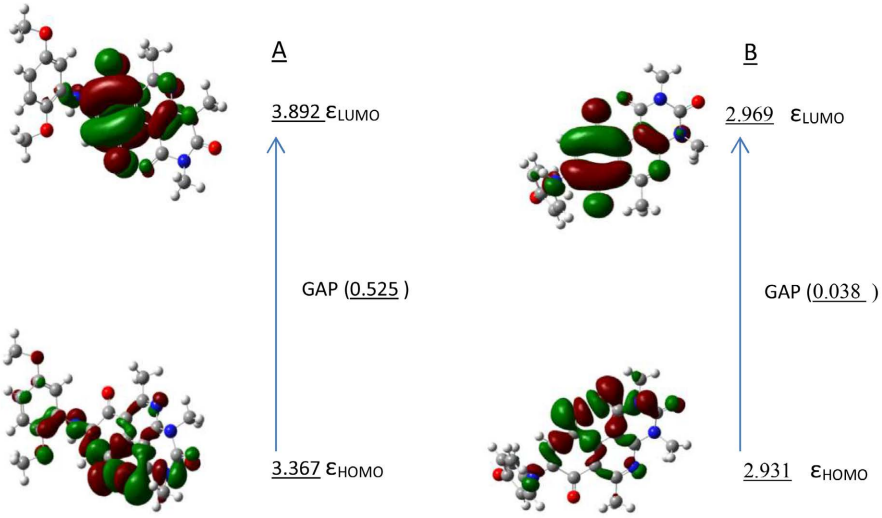


Figure 2. Illustrated ε_{HOMO}, ε_{LUMO} and GAP for molecules 23 (A) and 18 (B).

Table 4. Mullikan charges of N-5, C-6, C-8 and N-amino using PM3 method.

Comp.	N-5	C-6	C-8	N-amino
5	4.9998	2.1548	−4.0002	−3
17	4.9978	3.4735	−4	−3
18	4.9999	4.1069	−4.0001	−3
19	4.9979	2.1318	−4.0001	−3
23	4.9999	3.477	−4.0002	−3

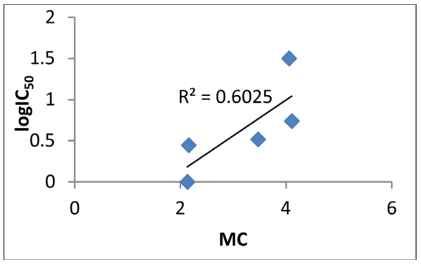


Figure 3. Correlation matrix between MC (C-6) and $logIC_{50}$.

to the nitrogen of the pyridine part of the chromophore may cause a Chichibabin-type tautomerism to occur in the following manner [12]*:*

This tautomerism imparts a chemical reactivity which traces the variability of the biological activity to the extent of 60%. Moreover, there an additional element to add to the reactivity which the generation of an enamine scaffold *in situ* [13]. This opens a whole perspective of chemical reactivity which might even suggest alkylation aspect of the mechanism of action of this particular group of APIQs.

To get a more accurate picture of the above mentioned argument, we used DFT method to calculate the following Fukui functions: forward Fukui function f^+, backward Fukui function f^- and neutral Fukui function f^0 for nucleophilic, electrophilic and radical attacks respectively. These functions are calculated as follows [14]:

For nucleophilic attack:

$$f^+ = q_a\left(N_{el}+1\right) - qa\left(N_{el}\right) \tag{2}$$

For electrophilic attack:

$$f^- = q_a\left(N_{el}\right) - qa\left(N_{el}-1\right) \tag{3}$$

For radical attack:

$$f^0 = q_a\left(N_{el}+1\right) - qa\left(N_{el}-1\right)/2 \tag{4}$$

In these equations q_a is the atomic charge (evaluated from Mullikan population analysis) at the jth atomic site in the neutral (N), anionic ($N+1$) or cationic ($N-1$) chemical species. We calculated Fukui function for our 5 APIQs and the results are summarized in **Table 5**.

We correlated Fukui functions for atoms N-5, C-6, C-8 and N-atom of 8-phenylamino side group each with the response. The outcomes (as R^2) of these correlations are summarized in **Figure 4**.

Upon examining the value of R^2 summarized in **Figure 4**, the following remarks could be made:

- *N*-5: it is apparent that this atom is prone to nucleophilic attack, *i.e.*, it is an electron deficient atom or an electrophilic site. This is to be expected as tuatomer b generated by Chichibabin-type tautomerism (**Figure 5**) contains a secondary amino group with a free lone pair of electron which could easily

Table 5. Calculated Fukui functions for N-5, C-6, C-8 and N-atom of 8-phenylamino side group.

Molecules	IC_{50} (μM)	C-6			C-8			N-5			N-phenyl		
		F^+	F^-	F^0	F^+	F^-	F^0	F^+	F^-	F^0	F^+	F^-	F^0
5	2.8	0.026	0.028	0.027	0.032	0.047	0.039	0.026	0.039	0.033	0.028	0.014	0.021
17	3.3	0.015	0.019	0.017	0.032	0.046	0.039	0.026	0.037	0.031	0.028	0.014	0.021
18	5.5	0.015	0.019	0.017	0.032	0.046	0.039	0.026	0.037	0.031	0.028	0.014	0.021
19	1	0.015	0.019	0.017	0.032	0.046	0.039	0.026	0.037	0.031	0.027	0.014	0.02
23	31.7	0.014	0.019	0.016	0.026	0.046	0.036	0.024	0.034	0.030	0.025	0.012	0.018

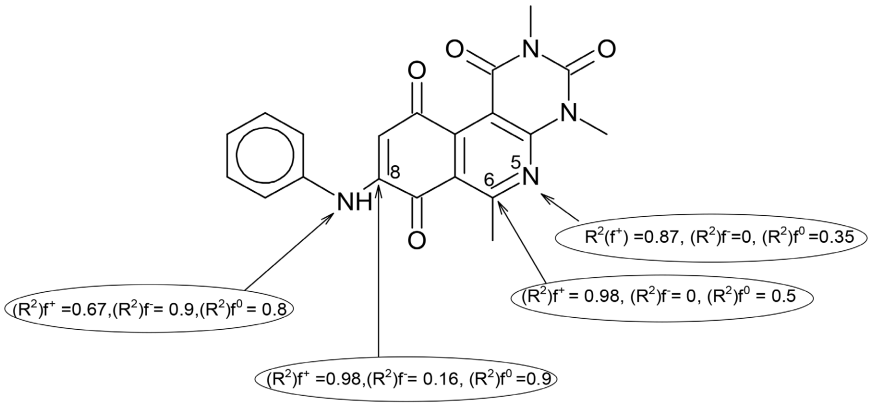


Figure 4. R^2 for the correlation between Fukui functions of N-5, C-6, C-8 and N-phenylamino atoms and IC_{50}.

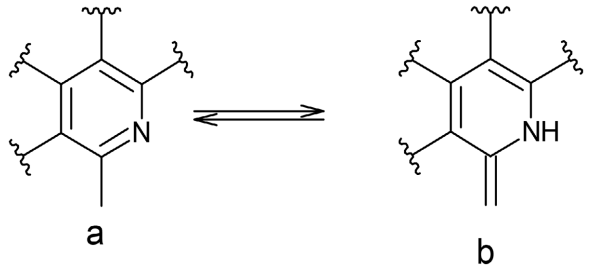


Figure 5. Chichibaben-type tautomerism of the methyl pyridine ring of isoquinoline scaffold of APIQs.

be protonated to enhance nucleophilic attack as already indicated in **Figure 5**.

- *C*-6: also exhibits similar behavior because of the presence of electrophilic N-5 atom which withdraws electron density from it. Reviewing the value of Fukui functions for the five APIQs shows that compound 5 in which there is no methyl group at C-6 has the highest f^+ value indicative that this position is open to nucleophilic attack to a degree of forming a full-fledge covalent bond, moreover, it is well-known that isoquinoline nucleus undergoes nucleophilic aromatic substitution at position 1 in pyridine ring which correspond to C-6 in isoquinoline [15]. While the other four compounds, owing to the covalent bond to the methyl group, might enter into an electrostatic interaction with electron rich center in the receptor. Thus we can say that the enamine in tautomer b (**Figure 5**) is complimentary with an electrophilic pocket in the receptor.
- *C*-8: Upon concentrating on C-8 and we notice the R^2 values for f^+ and f^0 = 0.98 and 0.9 respectively. This is easily justifiable by noting that this atom is a part of α,β-unsaturated carbonyl system and may constitute a Michael acceptor [16], **Figure 6**, which represents an electron deficient site. The same electron deficient site is attractive for free radicals which give justification of the high value of f^0.
- *N-phenyl group*: As for the N atom of 8-phenylamino group the R^2 value of f^- and f^+ of 0.9 and 0.67 respectively may indicate a protonation equilibrium as such (**Figure 7**):

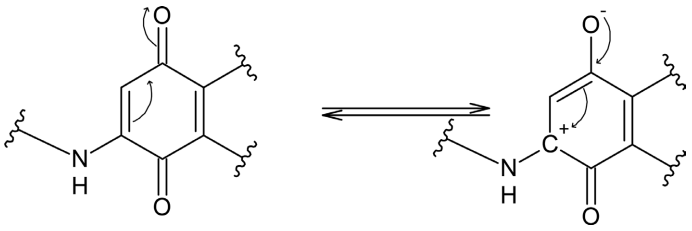


Figure 6. Michel acceptor at C-8 atom.

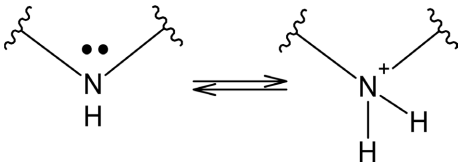


Figure 7. Equilibrium between protonated and electron lone pair of N-phenyl.

4. Conclusion

The variability in chemical reactivity for present set of APIQ (five molecules) has been studied using global and local descriptors. Dipole moment, as a global descriptor, demonstrated a high correlation with the biological activity. The Mullikan charge for C-6, as a local descriptor, showed that this carbon atom is active in spite of its full valence through its presence in an aromatic ring system in addition to its bonding to a methyl group as presence of methyl group adjacent to the nitrogen of the pyridine part of the chromophore may cause a Chichibabin-type rearrangement. The correlation between IC_{50} and Fukui functions for atoms N-5, C-6, C-8 and N-atom of 8-phenylamino side group is consistent with variation in chemical behavior for each atom.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary Material

calculation of electronic global descriptors

comp	H	L	η	S	X	I	A	μ	DN	GAP	dipo
5	3.073826	3.316397	0.121286	8.245009	-3.19511	-3.07383	-3.3164	3.195112	-26.3437	0.242571	1.1156
17	2.797199	2.846827	0.024814	40.29983	-2.82201	-2.7972	-2.84683	2.822013	-113.727	0.049628	3.1619
18	2.93106	2.969657	0.019299	51.8175	-2.95036	-2.93106	-2.96966	2.950359	-152.88	0.038597	2.7723
19	2.436342	2.549224	0.056441	17.71762	-2.49278	-2.43634	-2.54922	2.492783	-44.1662	0.112882	4.464
23	3.367261	3.892795	0.262767	3.805653	-3.63003	-3.36726	-3.8928	3.630028	-13.8146	0.525534	12.4501

calculation of fuqui functions

C-6

comp	mol.0	mol.+1	mol.-1	f+	f-	f0
5	0.166277	0.192568	0.137904	0.026291	0.028373	0.027332
17	0.367922	0.383025	0.348301	0.015103	0.019621	0.017362
18	0.367994	0.383052	-0.0267	0.015058	0.394691	0.204875
19	0.368371	0.38363	0.34871	0.015259	0.019661	0.01746
23	0.367285	0.381132	0.347861	0.013847	0.019424	-0.17401

C-33

comp	mol.0	mol.+1	mol.-1	f+	f-	f0
5	0.254879	0.272333	0.238764	0.017454	0.016115	0.016785
17	0.235202	0.250254	0.220677	0.015052	0.014525	0.014789
18	0.254883	0.271276	0.000493	0.016393	0.25439	0.135392
19	0.297029	0.31437	0.279042	0.017341	0.017987	0.017664
23	0.280688	0.017883	0.268233	-0.26281	0.012455	-0.12518
23	0.293693	0.054672	0.288383	-0.23902	0.00531	-0.11686

negativity-atom

comp	mol.0	mol.+1	mol.-1	f+	f-	f0
5	-0.52074	-0.50593	-0.53305	0.014809	0.012305	0.013557
17	-0.59283	-0.57514	-0.60864	0.017685	0.015811	0.016748
18	-0.52075	-0.50681	0.000053	0.013933	-0.5208	-0.25343
19	-0.28632	-0.26553	-0.30558	0.02079	0.019267	0.020029
23	-0.54197	0.034341	-0.52836	0.576308	-0.01361	0.281349
23	-0.52262	0.034557	-0.52709	0.557178	0.004468	0.280823

O-orient. For NH2-posi.28

comp	mol.0	mol.+1	mol.-1	f+	f-	f0
5	-0.1767	0.059448	-0.17154	0.236149	-0.00516	-0.05605
17	-0.17696	0.055945	-0.17216	0.232903	-0.0048	-0.05811
18	-0.17675	-0.17344	-0.00024	0.003311	-0.17652	-0.08684
19	-0.1715	-0.1682	-0.16697	0.003299	-0.00453	-0.16759
23	-0.20432	0.001395	0.037626	0.205712	-0.24194	0.019511

O-orient. For NH2-posi.30-31

comp	mol.0	mol.+1	mol.-1	f+	f-	f0
5	-0.1969	0.003768	-0.19882	0.200671	-0.20067	-0.09753
17	-0.19734	0.001971	-0.19942	0.199314	-0.19931	-0.09873
18	-0.19686	-0.19168	0.001898	0.005184	-0.00518	-0.09489
19	-0.192	-0.18689	-0.19447	0.005111	-0.00511	-0.19068
23	-0.20432	0.001395	0.037626	0.205712	-0.20571	0.019511

quinone atom(O-23)

comp	mol.0	mol.+1	mol.-1	f+	f-	fo
5	-0.39614	-0.31907	-0.50287	0.077069	0.106731	-0.41097
17	-0.39546	-0.31933	-0.5012	0.076138	0.105739	-0.41026
18	-0.39538	0.466833	-0.50098	0.862211	0.105606	-0.01708
19	-0.39442	-0.3181	-0.50037	0.076319	0.10595	-0.40924
23	-0.39788	-0.32772	-0.50316	0.070161	0.105279	-0.41544

quinone atom(C-1)

comp	mol.0	mol.+1	mol.-1	f+	f-	f0
5	0.39997	0.432956	0.359576	0.032986	0.040394	0.07338
17	0.399069	0.432154	0.35974	0.033085	0.039329	0.072414
18	0.399166	-0.08121	0.35989	-0.48037	0.039276	-0.4411
19	0.39966	0.433084	0.360411	0.033424	0.039249	0.072673
23	0.396245	0.427937	0.356156	0.031692	0.040089	0.071781

N-12

comp	mol.0	mol.+1	mol.-1	f+	f-	f0
5	-0.55753	-0.53081	-0.59691	0.02672	0.039372	0.033046
17	-0.60537	-0.57952	-0.64249	0.025846	0.037119	0.031483
18	-0.60543	-0.57964	-0.64245	0.025785	0.037027	0.031406
19	-0.60513	-0.57905	-0.64212	0.026078	0.036989	0.031534
23	-0.60683	-0.58275	-0.64431	0.024074	0.037486	0.03078

C-8

comp	mol 0	mol+1	mol-1	f+	f-	f0
5	0.162464	0.194268	0.115143	0.031804	0.047321	0.039563
17	0.170314	0.202084	0.124458	0.03177	0.045856	0.038813
18	0.170324	0.202239	0.124203	0.031915	0.046121	0.039018
19	0.170132	0.202781	0.123997	0.032649	0.046135	0.039392
23	0.160496	0.187238	0.11468	0.026742	0.045816	0.036279

N-phenylamino group

comp	mol 0	mol+1	mol-1	f+	f-	f0
5	-0.65282	-0.62394	-0.66705	0.028881	0.01423	0.021556
17	-0.65354	-0.62584	-0.66774	0.027698	0.014204	0.020951
18	-0.65368	-0.62599	-0.66773	0.027692	0.014051	0.020872
19	-0.65329	-0.62634	-0.6673	0.026947	0.014011	0.020479
23	-0.64996	-0.62461	-0.66224	0.025355	0.012278	0.018817

C-30 C phenyl ring attached to amino

comp	mol 0	mol+1	mol-1	f+	f-	f0
5	0.164578	0.151272	0.186279	-0.01331	-0.0217	-0.0175
17	0.164201	0.150358	0.185434	-0.01384	-0.02123	-0.01754
18	0.164776	0.15062	0.186281	-0.01416	-0.02151	-0.01783
19	0.162211	0.147815	0.183133	-0.0144	-0.02092	-0.01766
23	0.116466	0.110302	0.138089	-0.00616	-0.02162	-0.01389

C-5 adjacent tocarbony group

comp	mol 0	mol+1	mol-1	f+	f-	f0
5	-0.19195	-0.17746	-0.23196	0.014494	0.040008	0.027251
17	-0.19107	-0.17709	-0.23178	0.013979	0.040713	0.027346
18	-0.19096	-0.17703	-0.23171	0.013929	0.040758	0.027344
19	-0.19016	-0.17611	-0.23139	0.014056	0.041232	0.027644
23	-0.19019	-0.17648	-0.23266	0.013708	0.042465	0.028087

C-side chain

comp	mol 0	mol+1	mol-1	f+	f-	f0
5	0	0	0	0	0	0
17	-0.59799	-0.59927	-0.59363	-0.00128	-0.00436	-0.00282
18	-0.59806	-0.59932	-0.59371	-0.00127	-0.00435	-0.00281
19	-0.59811	-0.59938	-0.59374	-0.00127	-0.00437	-0.00282
23	-0.59784	-0.59909	-0.59356	-0.00124	-0.00428	-0.00276

calculation of Mulican charg for different atoms in different positions

11C 0	0.166277	11C 0	0.367922	11C 0	0.367994	11C 0	0.368371	11C 0	0.367285
33C 0	0.254879	32C 0	0.235202	32C 0	0.254883	32C 0	0.297029	27C 0	0.280688
400 0	-0.52074	390 0	-0.59283	390 0	-0.52075	44F 0	-0.28632	30C 0	0.293693
11C+1	0.192568	11C +1	0.383025	11C +1	0.383052	11C +1	0.38363	430 0	-0.54197
33C+1	0.272333	32C +1	0.250254	32C +1	0.271276	32C +1	0.31437	440 0	-0.52262
400+1	-0.50593	390 +1	-0.57514	390 +1	-0.50681	44F +1	-0.26553	11C +1	-0.00017
11C-1	0.137904	11C -1	0.348301	11C -1	-0.0267	11C -1	0.34871	27C +1	0.017883
33C-1	0.238764	32C -1	0.220677	32C -1	0.000493	32C -1	0.279042	30C +1	0.054672
400-1	-0.53305	390 -1	-0.60864	390 -1	0.000053	44F -1	-0.30558	430 +1	0.034341
								440 +1	0.034557
orientation 5		orientation 17		orientation 18		orientation 19		11C -1	0.347861
28C 0	-0.20312	27C 0	-0.20197	27C 0	-0.20314	27C 0	-0.22323	27C -1	0.268233
29C 0	-0.1767	28C0	-0.17696	28C0	-0.17675	28C0	-0.1715	30C -1	0.288383
31C 0	-0.1969	30C 0	-0.19734	30C 0	-0.19686	30C 0	-0.192	430 -1	-0.52836
32C 0	-0.19296	31C 0	-0.1915	31C 0	-0.19287	31C 0	-0.22246	440 -1	-0.52709
28C +1	0.03958	27C +1	0.038844	27C +1	-0.19423	27C +1	-0.21367		
29C +1	0.059448	28C+1	0.055945	28C+1	-0.17344	28C+1	-0.1682		
31C +1	0.003768	30C+1	0.001971	30C+1	-0.19168	30C +1	-0.18689		
32C +1	0.049822	31C +1	0.050071	31C +1	-0.18418	31C +1	-0.21321		
28C -1	-0.21288	27C -1	-0.21199	27C -1	0.000133	27C -1	-0.23375	orientation 23	
29C -1	-0.17154	28C-1	-0.17216	28C-1	-0.00024	28C-1	-0.16697	28C 0	-0.20432
31C -1	-0.19882	30C-1	-0.19942	30C-1	0.001898	30C -1	-0.19447	31C 0	-0.21248
32C -1	-0.20019	31C -1	-0.1992	31C -1	-0.00011	31C -1	-0.23051	32C 0	-0.21884
								28C +1	0.001395
								31C +1	-0.01438
5 quinone-atom		17 quinone-atom		18 quinone-atom		19 quinone-atom		32C +1	0.025557
O-24-0	-0.39614	O-23-0	-0.39546	O-23-0	-0.39538	O-23-0	-0.39442		
O-25-0	-0.449	O-24-0	-0.4561	O-24-0	-0.45614	O-24-0	-0.45704	28C -1	0.037626
C-1 0	0.41737	C-1 0	0.423672	C-1 0	0.423777	C-1 0	0.424086	31C -1	-0.03154
C-4 0	0.39997	C-4 0	0.399069	C-4 0	0.399166	C-4 0	0.39966	32C -1	-0.04746
O-24-+1	-0.31907	O-23+1	-0.31933	O-23+1	0.466833	O-23+1	-0.3181		
O-25-+1	-0.39559	O-24+1	-0.4056	O-24+1	-0.01739	O-24+1	-0.40576	23 quinone-atom	
C-1 +1	0.431707	C-1 +1	0.437066	C-1 +1	0.011417	C-1 +1	0.43755	O-23-0	-0.39788
C-4 +1	0.432956	C-4 +1	0.432154	C-4 +1	-0.08121	C-4 +1	0.433084	O-24-0	-0.45776
O-24--1	-0.50287	O-23-1	-0.5012	O-23-1	-0.50098	O-23-1	-0.50037	C-1 0	0.423431
O-25--1	-0.55897	O-24-1	-0.56145	O-24-1	-0.56152	O-24-1	-0.5624	C-4 0	0.396245
C-1 -1	0.365548	C-1 -1	0.37358	C-1 -1	0.373717	C-1 -1	0.373952	O-23+1	-0.32772
C-4 -1	0.359576	C-4 -1	0.35974	C-4 -1	0.35989	C-4 -1	0.360411	O-24+1	-0.41333
								C-1 +1	0.435507
								C-4 +1	0.427937
N-isoquinoline								O-23-1	-0.50316
N-12-0	-0.55753	N-12-0	-0.60537	N-12-0	-0.60543	N-12-0	-0.60513	O-24-1	-0.56279
N-12+1	-0.53081	N-12+1	-0.57952	N-12+1	-0.57964	N-12+1	-0.57905	C-1 -1	0.374086
N-12-1	-0.59691	N-12-1	-0.64249	N-12-1	-0.64245	N-12-1	-0.64212	C-4 -1	0.356156
								N-12-0	-0.60683
								N-12+1	-0.58275
								N-12-1	-0.64431