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Softness parameters based QSAR study of fluoroquinolone derivatives

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ABSTRACT

We have done QSAR analysis of C-7 derivatives of 1-Cyclopropyl-6, 8-difluoroquinolone using highest effective softness values $E_m^{\ddagger}$ and $E_n^{\ddagger}$ of hetero-atoms, quantum mechanical descriptors energy of HOMO (∈HOMO), energy of LUMO (∈LUMO), absolute hardness (), global softness (S), chemical potential (μ), electronegativity (χ) and energy descriptors heat of formation (ΔH_f^0), total energy (T_E), electronic energy (E_E), core-core repulsion (CCR) in all the possible combinations of these descriptors. QSAR model developed using chemical potential, heat of formation and total energy give very good predictive power as the regression coefficient is about 0.8. If descriptor chemical potential is replaced by electronegativity, QSAR model remains the same. We have found that five QSAR models give good predictive powers in which two give same result.

KEYWORDS

DFT;
Core-core repulsion;
Hardness;
Effective softness;
Electronic energy;
Klopman equation.

INTRODUCTION

Quinolones are a major class of antibacterial agent, which are under extensive clinical development[1]. They have an attraction because of their extremely potent activity against gram-positive and gram-negative activity, rapid bactericidal effects and low incidence of resistance development[2-4]. Among the different classes of antibacterial agents fluoroquinolones have achieved great success and aroused considerable expectations because of their broad spectrum of activity against gram-positive and gram-negative bacteria and mycobacterium[5-17]. As a result of thousands of quinolones have been synthesized in the past decade and several have been marketed and are widely used clinically[18]. These agents were characterized by excellent tissue penetration and therapeutic efficacy when used to treat infections of the genitourinary tract, respiratory tree, gastrointestinal tract, bone, and skin and soft tissues. The third and fourth generation quinolones were introduced in the 1990s. These compounds had better activity against aerobic gram-positive pathogens-particularly against the pneumococcus, including those that are penicillin-resistant and had anaerobic activity as well. The fourth-generation quinolones were the most potent against the pneumococcus and anaerobes, but retained activity against aerobic gram-negative pathogens. Moxifloxacin is the only universally available fluoroquinolone in this most potent class of compounds.

The currently available quinolones such as moxifloxacin represent major advances over the original DNA grease inhibitor. Moxifloxacin is used worldwide to treat a broad verity of bacterial infections including those in the urinary tract, respiratory system,

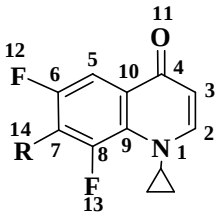

Figure 1: Fluoroquinolone derivative (1-Cyclopropyl-6,8-difluoroquinolone)

skin and soft tissue as well as those involving sexually transmitted diseases. The wide acceptance of moxifloxacin for treating infectious diseases has resulted from its broad antimicrobial spectrum, ease of oral dosing and excellent safety record.

In the wake of the anthrax terrorist attacks in the United States in 2001, ciprofloxacin received extensive media attention because it was the only drug labeled as approved by the Food and Drug Administration (FDA) for both prophylaxis and treatment of inhalation anthrax (the most serious form of the disease). However, in late October 2001, the FDA issued a notice clarifying that the antibiotic doxycycline is also approved for anthrax prophylaxis and that doxycycline and amoxicillin are also approved for treatment for all forms of anthrax. The FDA encouraged companies to update labeling of these products with this previously unspecified information

Objective

The survey of literature and browsing of internet indicates that no Quantitative Structure activity and relationship of fluoroquinolone derivatives shown in figure 1 has been studied with the softness parameters obtained by Klopman Equation[19] and Global Softness and Hardness obtained by Parr and Pearson equation[20].

Parameters such as ionization potential, electron affinity, radius and charge of atom are the essential requirements for the solution of Klopman equation[19] and have been evaluated by adopting PM3 calculation using MOPAC-2000. The values of these parameters have been substituted in Klopman equation. For the solution of Parr and Pearson equation[20], the eigen values of frontier orbitals (HOMO and LUMO) and electron density have been obtained from PM3 calculation with the help of above software. Solution of the equations provides the softness and hardness values (Local and Global) of fluoroquinolone derivatives. The quantitative structure relationship of fluoroquinolone derivatives have been studied with the effective softness, local and global Softness values, energies of HOMO and LUMO, absolute hardness, chemical potential, electronegativity, heat of formation, core-core repulsion, total energy and electronic energy.

On the basis of QSAR it has been possible to develop a principle by which the activity can be measured theoretically. Such principle has a predictive power, which makes it easy to know the activity of any fluoroquinolone derivative without performing laboratory test. The derivatives of fluoroquinolones under study are listed in TABLE 1 along with their biological activity measured in terms of Log 1/C[21-31]. Multilinear regression equations[24] have been obtained in all possible combinations of the descriptors. The correlation coefficient and cross validation coefficient has also been evaluated in order to examine the quality of relationship.

Methodology

1. Reactivity indices

We have based our QSAR study of fluoro quinolones derivatives on the following reactivity indices

1. Effective Softness Values (given by Klopman in terms of $E_n^{\ddagger}$ and $E_m^{\ddagger}$)
2. Chemical Potential (μ)
3. Absolute Hardness (η)
4. Global Softness (S)
5. Electronegativity (χ)
6. Total Energy
7. Core-core repulsion
8. Ionization Potential
9. Eigen values of HOMO
10. Eigen values of LUMO
11. Heat of formation

The evaluation of these parameters is given as below

In DFT the ground state energy of an atom or a molecule is written in terms of electron density ρ (r), and the external potential ν (r) in the form

$$E(\rho) = F(\rho) + \int dr\, \rho(r)\, \nu(r) \qquad (1)$$

Where F (ρ=T (ρ V_{ee} (ρT (ρ is the electronic kinetic energy functional, and V_{ee} (ρ is the electron-electron interaction energy functional. The minimization of the total energy, subject

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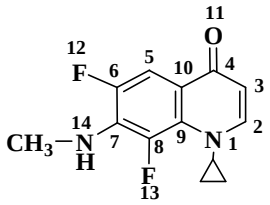
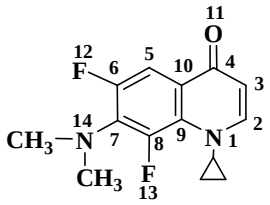
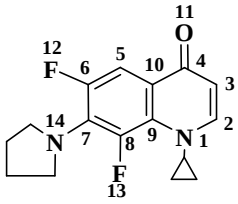
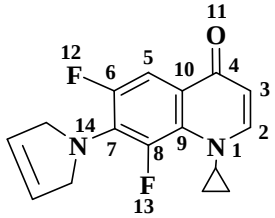
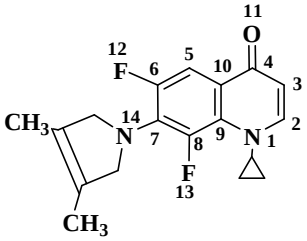
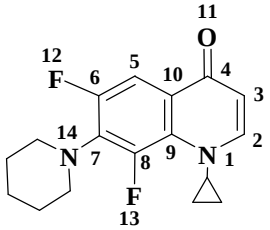
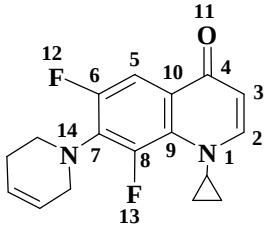
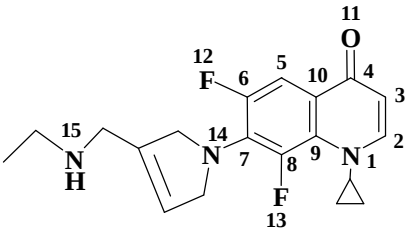
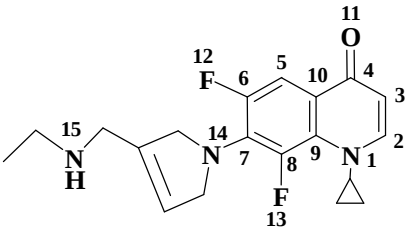
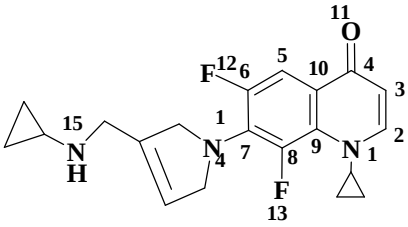
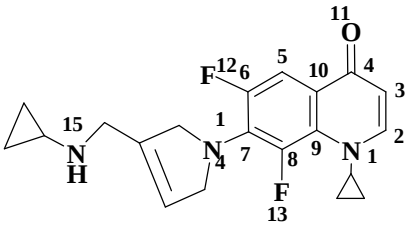
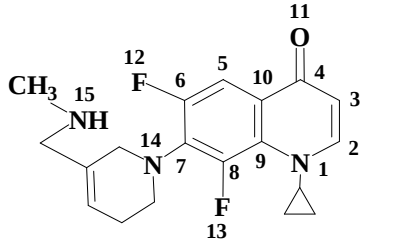
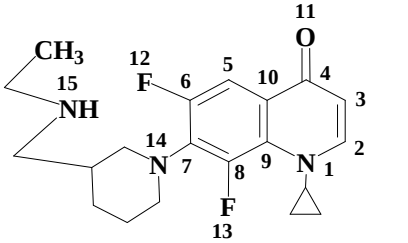
TABLE 1: Various C-7 derivatives of 1-Cyclopropyl-6, 8-difluoroquinolone alongwith there biological activity in terms of log 1/C

Compd.	Substituent at C_7	Activity in terms of log 1/C
1		6.25
2		3.125
3		0.391
4		0.781
5		0.781
6		0.781
7		1.563

Countinue in right column

Compd.	Substituent at C_7	Activity in terms of log 1/C
8		0.098
9		0.098
10		0.098
11		0.195
12		0.391
13		0.395

to the condition that the total number of electrons is fixed,

$$N = \int dr\, \rho(r) \qquad (2)$$

Leads to an Euler-Lagrange equation of the form,

$$\mu = (\partial E/\delta\rho(r))_v = v(r) + \partial F\delta\rho(r) \quad (3)$$

Where μis the chemical potential. The solution of this equation leads to the ground state density, from which one can determine the ground state energy. Parr et al define the electronegativity as the negative of chemical potential: -

$$\chi = -\mu = -(\partial E/\partial N)_v \quad (4)$$

Although the Hard and Soft Acids and Bases concept was introduced more than three decades ago by Pearson, the first unambiguous definition of Hardness and Softness was given by Parr and Pearson in early 80s. They defined global Hardness as

$$\eta = 1/2(\delta\mu/\delta N)v_{(r)} = 1/2\ (\delta^2E/\delta^2N)v_{(r)} \quad (5)$$

Where E is the total Energy, N is the number of electrons of the chemical species and $v_{(r)}$ the external potential.

The corresponding global softness S, which bears an inverse relationship with the global hardness, is defined as

$$S = 2\eta = (\partial N/\partial\mu)v_{(r)} \quad (6)$$

The operational definition of global hardness and global softness are obtained by finite difference approximation of eq-1

$$\eta = 1/2\,(IP-EA) \quad (7)$$

$$S = 1/(IP-EA) \quad (8)$$

Where IP and EA are the ionization potential and electron affinity respectively of the chemical species. According to the Koopman's theorem the IP is simply the eigen value of HOMO with change of sign and EA is the eigen value of LUMO with change of sign, therefore on this basis we can write

$$\eta = 1/2\,(\varepsilon LUMO - \varepsilon HOMO) \quad (9)$$

$$S = 1/(\varepsilon LUMO - \varepsilon HOMO) \quad (10)$$

$$\chi = 1/2\,(\varepsilon LUMO - \varepsilon HOMO) \quad (11)$$

$$\mu = 1/2\,(\varepsilon LUMO + \varepsilon HOMO) \quad (12)$$

2. Klopman equation

Beside the above global aspects the most important quantum mechanical framework of HSAB principle was first time given by G. Klopman. Who based his concept on charge and frontier orbital controlled chemical reaction and summarized the reacting species in terms of hard and soft acid and bases. For evaluation of softness values of Lewis acid and Lewis bases, he proposed the following equations-

$$E_m^{++} = IP_m a^2 (IP_m - EA_m)[\chi_r (C_r^m)^2/R_r](1-1/\epsilon)[q_r + 2b^2\chi_r (C_r^m)^2] \quad (13)$$

$$E_n^{++} = IP_n - b^2 (IP_n - EA_n) - [\chi_s (C_s^n)^2/R_s](1-1/\epsilon)[q_s - 2b^2\chi_s (C_s^n)^2] \quad (14)$$

Where $E_n^{\ddagger}$= Softness of Lewis acid, $E_m^{\ddagger}$ = Softness of a Lewis base, IP= Ionization potential of atom, EA = Electron affinity of atom, ∈ = Dielectric constant of the medium in which the reaction is carried out, R and q = Radius and charge of atom, C = Electron density, $\chi_r = q - (q-1)\sqrt{k}$ and k = 0. 75, a and b = Variational parameter defined.

as $a^2+b^2=1$

With the help of above equation Klopman calculated the softness value of a large no of cations and anions. Singh et al modified the above equation and made it applicable for neutral species. By adopting this modified method we can calculate the softness value of fluoroquinolone derivatives. For the solution of Klopman equation the essential parameters are IP, EA, R, q and C. These parameters may be calculated as follows-

3. Ionization Potential of an atom in a molecule (IP)

For the calculation of IP Dewar and Martia has proposed a fundamental equation as

$$IP = a + bq + cq^2 \quad (15)$$

Where q is valence state electronic charge derived from the hybridization state of an atom in a molecule, while a, b and c are the constants.

4. Electron affinity of an atom in a molecule (EA)

The calculation of electron affinity of an atom in molecule was main problem so for we have developed a method with the help of DFT to evaluate the electron affinity of an atom in molecule EA as follows-

Parr et al have shown that the electronegativity χ of any chemical species is equal to the negative value of chemical potential μ. Indeed it follows rigorously that.

$$\chi = -\mu = 1/2\ (I + A) \quad (16)$$

Where I and A are ionization potential and electron affinity of molecule. The equation-16 may be written as

$$A = 2\chi - I \quad (17)$$

Density Functional Theory provides a quantum mechanical justification for electronegativity. A concept used intuitively for a long time and validates Sanderson's postulates that when two or more atoms combine to form a molecule, their electronegativity gets equalized and unique electronegativity exists everywhere in a molecule. Now by putting the value of ionization potential of an atom in molecule IP in equation 17 we get electron affinity of that atom of the molecule as

$$EA = 2\chi - IP \quad (18)$$

According to Koopman's theorem the I and A are

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TABLE 2: Quantum chemical descriptors of C-7 derivatives of 1-Cyclopropyl-6, 8-difluoroquinolone

Compd.	∈HOMO	∈LUMO	η	S	μ	χ
1	-9.554	-4.274	2.64	0.189	-6.914	6.914
2	-9.792	-4.46	2.666	0.188	-7.126	7.126
3	-9.538	-4.214	2.662	0.188	-6.876	6.876
4	-9.418	-4.14	2.639	0.189	-6.779	6.779
5	-9.392	-4.4	2.496	0.2	-6.896	6.896
6	-9.474	-4.103	2.686	0.186	-6.789	6.789
7	-9.537	-4.226	2.656	0.188	-6.882	6.882
8	-9.213	-1.363	3.925	0.127	-5.288	5.288
9	-8.96	-1.019	3.971	0.126	-4.99	4.99
10	-9.004	-1.145	3.93	0.127	-5.074	5.074
11	-9.036	-1.179	3.928	0.127	-5.107	5.107
12	-7.518	-3.151	2.184	0.229	-5.335	5.335
13	-9.243	-1.387	3.928	0.127	-5.315	5.315
14	-9.074	-1.208	3.933	0.127	-5.141	5.141
15	-8.909	-1.115	3.897	0.128	-5.012	5.012
16	-9.127	-1.278	3.925	0.127	-5.203	5.203

simply the eigen value of HOMO and LUMO respectively with change in sign. Therefore from equation 16 and 18, we get,

$$EA=-(\varepsilon HOMO+\varepsilon LUMO)-(IP) \quad (19)$$

5. Charge (q) and electron density (C) of an atom in a molecule

These values have been obtained from PM3 calculation by using MOPAC-2000 software.

6. Radius of an atom (R)

The radius of atom of various elements has been taken from literature.

MATERIAL AND METHOD

In the present study we have taken a set of fluoro quinolones derivatives which are given in TABLE 1. For QSAR prediction, the 3D modeling and geometry optimization of all the compounds has been done with the help of Cache software, using PM3 Hamiltonian. The softness values in terms of $E_m^{\ddagger}$ and $E_n^{\ddagger}$ at all possible active sites of all the derivatives of fluoro quinolones have been evaluated by solving the Klopman equations. The essential requirements such as ionization potential, electron affinity, charge, electron densities etc at each site have been obtained from PM3 calculations. The Klopman equations have been solved with the help of a computer program developed by us. Since each derivative has a number of active sites, the highest $E_m^{\ddagger}$ and $E_n^{\ddagger}$ values have been chosen for QSAR study.

TABLE 3: Energy descriptors of C-7 derivatives of 1-Cyclopropyl-6, 8-difluoroquinolone

Compd.	ΔH_f^0	T_E	E_E	CCR
1	332.852	-3724.44	-19044	15319.59
2	443.141	-3837.86	-21079	17241.13
3	564.736	-4069.87	-23902.2	19832.33
4	539.289	-4070.97	-24188.5	20177.48
5	587.923	-4306.15	-27828.9	23522.72
6	555.432	-4188.91	-25148.7	20959.79
7	556.111	-4188.89	-25532.9	21344.02
8	-130.032	-4940.42	-38145.2	33204.83
9	-121.16	-4790.73	-36143.3	31352.6
10	-96.408	-5057.6	-39605.8	34548.25
11	-119.595	-4641.35	-34390.3	29748.95
12	13.227	-4754.24	-35720.6	30966.36
13	-136.071	-5089.99	-40844.1	35754.11
14	-109.773	-4759.57	-36060.8	31301.2
15	-92.511	-4923.46	-38207.4	33283.91
16	-88.81	-5175.91	-41612.2	36436.34

RESULT AND DISCUSSION

We have developed QSAR models for various C-7 derivatives of 1-Cyclopropyl-6, 8-difluoroquinolone listed in the TABLE 1 alongwith their biological activity in terms of log 1/C. Values of quantum chemical descriptors viz. energy of HOMO (∈HOMO), energy of LUMO (∈LUMO), absolute hardness (η), global softness (S), chemical potential (μ) and electronegativity (χ) of these compounds are shown in TABLE 2. Values of energy descriptors of the compounds viz. heat of formation (ΔH_f^0), total energy (T_E), electronic energy (E_E) and core-core repulsion (CCR) are given in TABLE 3. Acidic atomic softness ($E_n^{\ddagger}$) and basic atomic softness ($E_m^{\ddagger}$) of hetero-atoms of the compounds have

TABLE 4 : Atomic softness values of hetero atoms of Compound-(1)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	43.977	-9.626
N	14	108.155	-26.815
F	12	437.257	-31.909
F	13	440.548	-31.753
O	11	260.417	-21.084

En‡ is acidic atomic softness, Em‡ is basic atomic softness calculated from Klopman equations

TABLE 5: Atomic softness values of hetero atoms of compound-(2)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	50.488	7.130
N	14	100.029	-4.014
F	12	442.165	-12.544
F	13	444.629	-12.432
O	11	268.496	-2.182

En‡ is acidic atomic softness, Em‡ is basic atomic softness calculated from Klopman equations

TABLE 6: Atomic softness values of hetero atoms of Compound-(3)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	50.9579	6.71625
N	14	123.669	-10.5055
F	12	434.891	-14.2769
F	13	436.610	-14.5077
O	11	249.856	-13.7867

En‡ is acidic atomic softness, Em‡ is basic atomic softness calculated from Klopman equations

TABLE 7: Atomic softness values of hetero atoms of compound-(4)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	51.213	6.540
N	14	115.548	-8.485
F	12	433.996	-14.299
F	13	435.663	-14.522
O	11	249.941	-13.958

En‡ is acidic atomic softness, Em‡ is basic atomic softness calculated from Klopman equations

TABLE 8: Atomic softness values of hetero atoms of compound-(5)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	60.013	4.885
N	14	87.993	-1.415
F	12	434.041	-14.135
F	13	435.358	-14.311
O	11	252.904	-14.632

En‡ is acidic atomic softness, Em‡ is basic atomic softness calculated from Klopman equations

been calculated from Klopman equations and are listed in TABLES 4 to 19. Highest of softness values of each compound have been considered in developing QSAR

TABLE 9 : Atomic softness values of hetero atoms of compound-(6)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	61.508	23.062
N	14	73.185	1.867
F	12	433.866	-14.269
F	13	434.673	-14.376
O	11	249.905	-13.934

En‡ is acidic atomic softness, Em‡ is basic atomic softness calculated from Klopman equations

TABLE 10: Atomic softness values of hetero atoms of compound-(7)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	50.401	6.833
N	14	73.720	1.874
F	12	433.536	-14.090
F	13	435.714	-14.380
O	11	249.511	-13.680

En‡ is acidic atomic softness, Em‡ is basic atomic softness calculated from Klopman equations

TABLE 11 : Atomic softness values of hetero atoms of Compound-(8)

Atom	Site	$E_n^‡$	$E_m^‡$
O	11	266.476	-21.031
N	1	97.488	-6.031
N	14	117.411	-11.194
N	15	120.233	-11.954
F	12	438.724	-17.654
F	13	438.845	-17.135

En‡ is acidic atomic softness, Em‡ is basic atomic softness calculated from Klopman equations

TABLE 12: Atomic softness values of hetero atoms of compound-(9)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	98.915	-6.822
O	11	261.612	-20.057
N	14	114.933	-10.976
N	15	119.511	-12.206
F	12	438.842	-17.572
F	13	438.642	-17.544

En‡ is acidic atomic softness, Em‡ is basic atomic softness calculated from Klopman equations

TABLE 13: Atomic softness values of hetero atoms of compound-(10)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	117.873	-5.487
N	14	98.002	-6.468
O	11	267.013	-21.516
N	15	117.132	-11.438
F	12	448.651	-16.145
F	13	448.756	-16.036

En‡ is acidic atomic softness, Em‡ is basic atomic softness calculated from Klopman equations

TABLE 14: Atomic softness values of hetero atoms of compound-(11)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	112.980	-10.283
N	14	98.162	-6.461
O	11	266.979	-21.456
N	15	117.678	-11.535
F	12	439.717	-17.521
F	13	440.091	-17.574

$En^‡$ is acidic atomic softness, $Em^‡$ is basic atomic softness calculated from Klopman equations

TABLE 15: Atomic softness values of hetero atoms of compound-(12)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	74.993	-0.647
N	14	90.739	-4.400
O	11	264.153	-20.391
N	15	113.267	-10.134
F	12	440.808	-17.452
F	13	440.688	-17.435

$En^‡$ is acidic atomic softness, $Em^‡$ is basic atomic softness calculated from Klopman equations

TABLE 16: Atomic softness values of hetero atoms of compound-(13)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	116.225	-10.795
N	14	97.562	-5.970
O	11	266.504	-20.954
N	15	120.219	-11.868
F	12	439.046	-17.082
F	13	438.230	-16.969

$En^‡$ is acidic atomic softness, $Em^‡$ is basic atomic softness calculated from Klopman equations

TABLE 17: Atomic softness values of hetero atoms of compound-(14)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	114.067	-10.521
N	14	98.127	-6.404
O	11	266.936	-21.392
N	15	120.698	-12.301
F	12	439.694	-17.469
F	13	440.215	-17.542

$En^‡$ is acidic atomic softness, $Em^‡$ is basic atomic softness calculated from Klopman equations

TABLE 18: Atomic softness values of hetero atoms of compound-(15)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	112.905	-10.405
N	14	98.258	-6.623
O	11	267.012	-21.612
N	15	119.550	-12.182
F	12	439.830	-17.677
F	13	440.191	-17.727

$En^‡$ is acidic atomic softness, $Em^‡$ is basic atomic softness calculated from Klopman equations

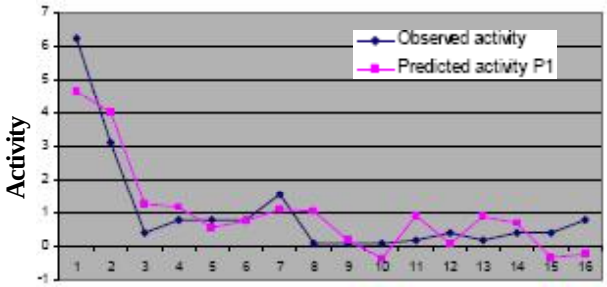
TABLE 19: Atomic softness values of hetero atoms of compound-(16)

Atom	Site	$E_n^‡$	$E_m^‡$
N	1	115.552	-10.825
N	14	97.804	-6.234
O	11	266.755	-21.245
N	15	119.693	-11.937
F	12	438.681	-17.238
F	13	439.430	-17.342

$En^‡$ is acidic atomic softness, $Em^‡$ is basic atomic softness calculated from Klopman equations

TABLE 20: Values of observed activities and predicted activities of C-7 derivatives of 1-cyclopropyl-6, 8-difluoroquinolone

Compd.	Observed activity	P1	P2	P3	P4	P5
1	6.25	4.657	4.657	4.875	4.863	4.721
2	3.125	3.989	3.989	2.451	2.456	2.568
3	0.391	1.249	1.249	1.898	1.892	1.831
4	0.781	1.168	1.168	1.838	1.85	1.846
5	0.781	0.55	0.55	1.256	1.253	1.23
6	0.781	0.768	0.768	-0.293	-0.295	-0.297
7	1.563	1.1	1.1	1.533	1.524	1.419
8	0.098	1.038	1.038	0.295	0.292	0.251
9	0.098	0.182	0.182	0.819	0.82	0.838
10	0.098	-0.364	-0.364	-0.081	-0.089	-0.2
11	0.195	0.926	0.926	1.149	1.158	1.302
12	0.391	0.07	0.07	0.18	0.188	0.308
13	0.195	0.872	0.872	-0.305	-0.301	-0.258
14	0.391	0.681	0.681	0.781	0.789	0.899
15	0.391	-0.338	-0.338	0.346	0.348	0.371
16	0.781	-0.239	-0.239	-0.432	-0.437	-0.519



Graph 1: Graph between observed activity and predicted activity P1

models because there are several hetero-atoms in each compound. MLR equations having good predictive power are given below-

$P1=-3.65289*\mu-0.0108106*\Delta H_f^0+0.00220696*T_E-8.7807$

$rCV^2=0.482981$

$r^2=0.780569$

$P2=3.65289*\chi-0.0108106\,\Delta H_f^0+0.00220696*T_E-8.7807$

$rCV^2=0.482981$

$r^2=0.780569$

$P3=-0.118016*E_m^‡-0.000232355*CCR+7.29852$

$rCV^2=0.373067$

$r^2=0.72133$

P4=-0.117229* $E_m^{\ddagger}$ +0.000217204 *E_E +7.87052
rCV^2=0.371331
r^2=0.71952
P5=-0.10571* $E_m^{\ddagger}$ +0.00336311*T_E +16.2288
rCV^2=0.365264
r^2=0.701286

The close examination of all above regression results indicates that regression models P1, P2 and P3 provide very good results. In between these five models, regression model P1 (regression between electronegativity with heat of formation and total energy) is the best model for QSAR study of the compounds. With the help of this model we can predict the activity value for any unknown compound. The following is the order of reliability of the regression models.

P1=P2 > P3 > P4 > P5

Values of predicted activities obtained from these QSAR models are given in TABLE 20. Graph between observed activity and predicted activity P1 is shown in the Graph-1.

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