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Experimental and Computational Study of β-Aminoketone Analogues

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4.1. Introduction

Nitrogen containing molecules are significant synthetic targets owing to their wide range of applications as pharmaceutical and bioactive compounds. Mannich reaction has been one of the classical methods for the construction of nitrogenous compounds especially β-amino carbonyl compounds. These are versatile intermediates for the synthesis of β-amino alcohols or acids, which have great deal of biological significance. In the β-Aminoketones ((1-Propanones (1,3-diphenyl-3-(phenyl amino) propan-1-ones)) the formation of carbon-carbon bonds is crucial to the development of organic molecules such as medicines, biodegradable plastics and natural products. These were used as photo initiators in printing applications. These were also used as intermediates for the preparation of known keto-methylene pseudo peptides which were used as antibiotics, antibiotic enhancers or inhibitors, antioxidants *etc* **[1]**.

The β-Aminoketones are expected to act as free radical scavengers because of their structural features (**Fig.1).** The free radicals source[2]is charge transfer complex (CTC). The CTC is formed between ***n*-**electron donor and the sigma-acceptor, iodine [3].

The aim of the present work is to develop *in vitro* antioxidant property of β- Aminoketones by spectrophotometric method. The molecular modeling studies also help us to understand the various interactions between the ligand and enzyme active site in detail and there by facilitating in design of novel antioxidants. The suitable chemical environment may serve as a starting point for synthesis of cyclo-oxygenase-2 inhibitors with improved antioxidant efficacy.

4.2. Experimental Methodology

4.2.1. Antioxidant Bioassay

All the chemicals were used of analytical grade. A Systronics UV-Visible PC Based double beam spectrophotometer-2202 equipped with 1.0 cm quartz cells with a fixed slit width (2nm) was used to record the absorption spectra.

Antioxidant activity of β-Aminoketones was measured by using spectrophotometer methods. This method is based on the charge transfer complex (CTC) which is formed.

between triethyl amine and Iodine. This method is followed by measuring the maximum absorbance at 370*nm* under the optimized conditions.

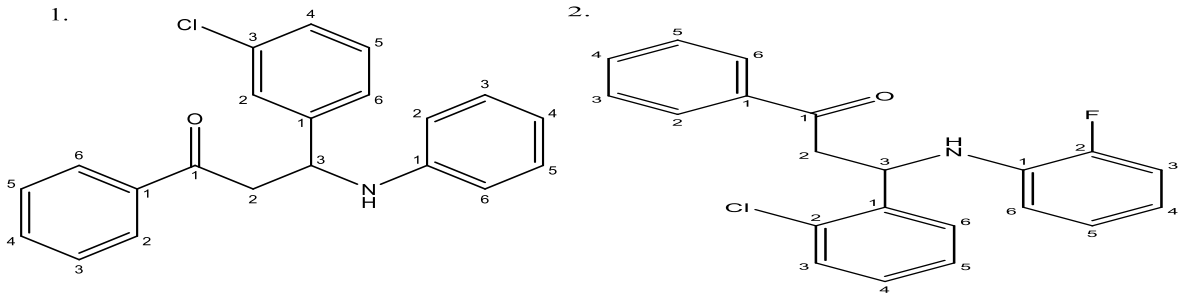
To the 10mL of 3×10^{-3}M CTC, 10mL of 10^{-3}M substituted β-Aminoketone was added. The mixture was allowed to stand for 5 min at room temperature and then the absorbance of the purple-red colored solution was measured at 370*nm*.The lower absorbance of the reaction mixture indicates higher free radical scavenging activity. The capacity of free radical scavenging activity of β-Aminoketone was calculated using the following equation:

$$\%Rs = \frac{Ai - Af}{Ai} X\ 100$$

$\mathbf{R_s}$ radical scavenging activity of β-Aminoketones, $\mathbf{A_i}$ initial absorbance of the CTC, $\mathbf{A_f}$ is the absorbance of the test/standard compound.

The optical density was recorded as decrease in intensity of purple red color of CTC. The antioxidant activity is expressed as IC_{50}. The lower IC_{50} value represents higher antioxidant activity (**Table1**) [4]. The antioxidant activity was compared with ascorbic acid, used as a standard.

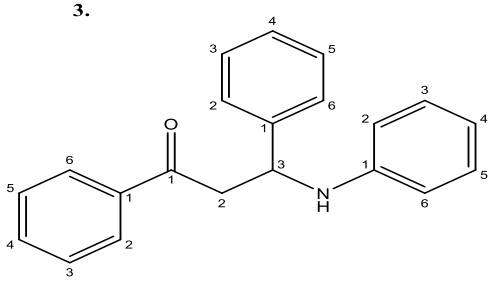
Figure 1 Structures of β-Aminoketone analogues



3-(3-chlorophenyl)-1-phenyl -3-(phenylamino)propan-1-one

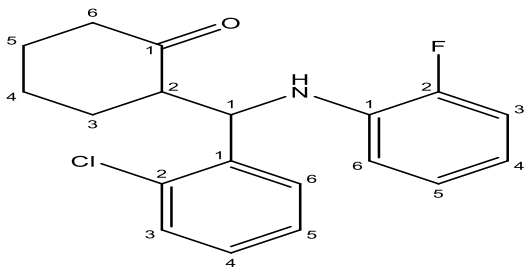
3-(2-fluorophenylamino) -3-(2-chlorophenyl)-1-phenylpropan-1-one

3.



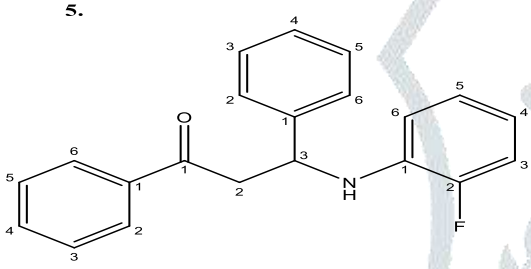
1,3-diphenyl
-3-(phenylamino)propan-1-one

4.



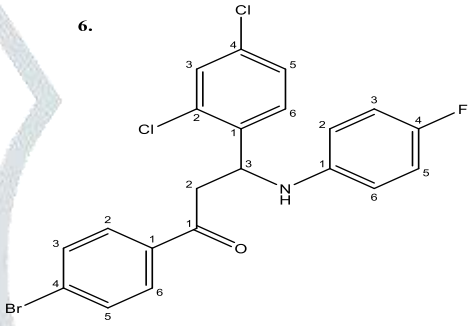
2-((2-fluorophenylamino)
(2-chlorophenyl)methyl)cyclohexanone

5.



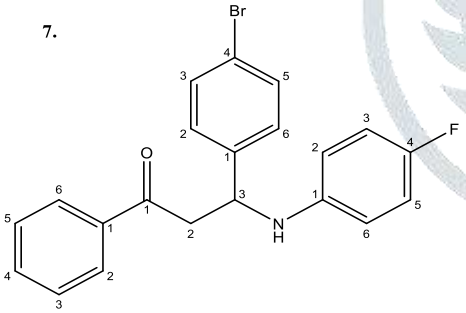
3-(2-fluorophenylamino)
-1,3-diphenylpropan-1-one

6.



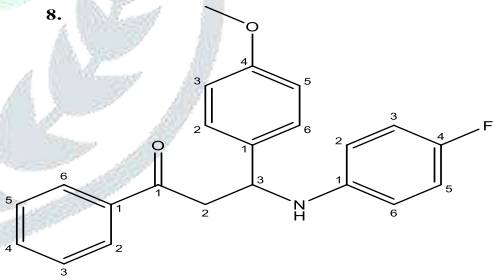
3-(4-fluorophenylamino)-1-(4-bromophenyl)
-3-(2,4-dichlorophenyl)propan-1-one

7.



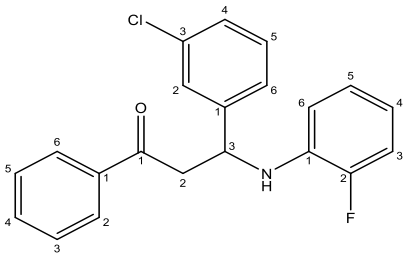
3-(4-fluorophenylamino)-3-(4-
bromophenyl)-1-phenylpropan-1-
one

8.



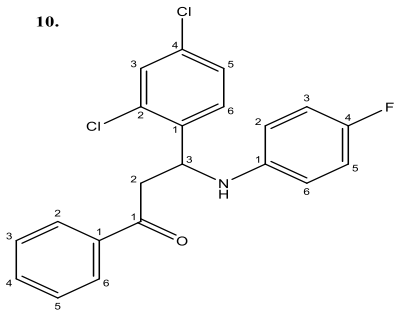
3-(4-fluorophenylamino)
-3-(4-methoxyphenyl)-1-phenylpropan-1-one

9.



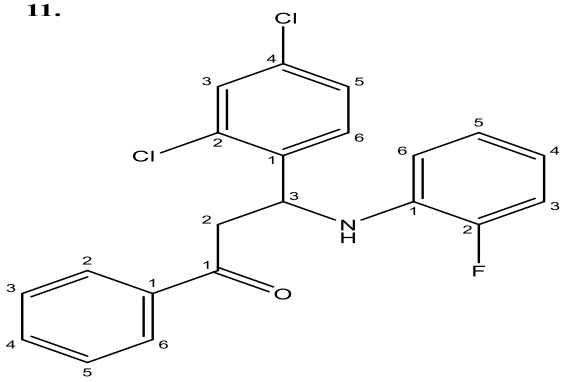
3-(2-fluorophenylamino)
-3-(3-chlorophenyl)-1-phenylpropan-1-one

10.



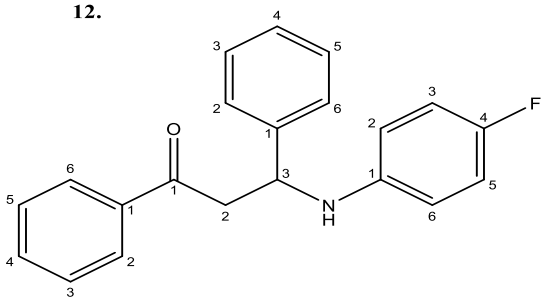
3-(4-fluorophenylamino)
-3-(2,4-dichlorophenyl)-1-phenylpropan-1-one

11.



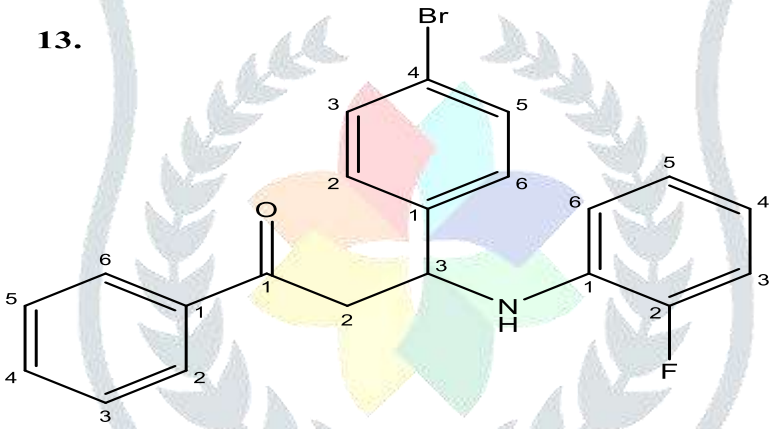
3-(2-fluorophenylamino)
-3-(2,4-dichlorophenyl)-1-phenylpropan-1-one

12.



3-(4-fluorophenylamino)
-1,3-diphenylpropan-1-one

13.



3-(2-fluorophenylamino)
-3-(4-bromophenyl)-1-phenylpropan-1-one

Table-1: Antioxidant activity of β-Aminoketone analogues.

comp	1	2	3	4	5	6	7	8	9	10	11	12	13	Ascorbic Acid(std)
$IC_{50(mM)}$	0.06	0.90	0.04	0.11	0.03	0.24	0.03	0.04	0.10	-0.19	0.03	0.02	-0.05	0.018
Act	4.20	3.04	4.36	3.95	4.46	3.62	4.48	4.38	3.97	2.30	4.46	4.68	4.30	5.20

Comp = compound, %RSA = %Radical Scavenging Activity, Act = Activity. Std = standard

4.2.2. Computational Methodology

4.2.2.1. Construction of molecular structures

A series of β-Aminoketone compounds tested for inhibitory activity was selected for the present study and the program of window Hyperchem software Inc (http://www.warezdestiny.com/free-hyp) was used in modeling studies. The molecules were generated and the energy was minimized using molecular modeling pro. The window version software SPSS10 (SPSS Software; Consulthttp://www.spss.com) was used in the regression analysis.

4.2.2.2. Calculation of quantum chemical descriptors

All of the molecular structures of the compounds were initially optimized geometrically using the semi-empirical method AM1 (Austin Model 1) and PM3 (Parameterization Model 3) [5]. The quantum chemical descriptors (variables)[6]**[7]**[8] [9] obtained for model building in this work include: energy of cation (E_{cation}), energy of anion (E_{anion}), the electron affinity (EA)(calculated from $E_{neutral}$-E_{anion}), ionization potential (IP) (calculated from E_{cation}-$E_{neutral}$),electro negativity(χ), hardness(η), softness(S), electrophilic index (ω),partition coefficient (Log P), hydration energy (HE),chemical potential(μ) and polarisability (Pol)were obtained for β-Aminoketone analogues.

4.2.3. Molecular modeling studies

QSAR technique was applied to the analogs of β-Aminoketone analogues. The appropriate descriptors or parameters for the compounds were used as independent variables.

In addition to the synthetic work, an attempt to explore docking studies on β- Amino ketone analogues was made to explain observed variance in biological activity and development of best pharmacophore activity.

4.2.3.1. GOLD Software

The GOLD2.0 (Genetic Optimization for Ligand Docking) program uses a genetic algorithm (GA) to explore the full range of ligand flexibility and the rotational flexibility of selected receptor hydrogen's [10][11]. The mechanism for ligand placement is based on fitting points. The interaction of the ligands with the receptor in the modeled complexes was investigated and observed for the fitness function ability on protein of cyclo-oxygenase-2 by using synthesized moieties.

The 3D structure of selected Protein cyclo-oxygenase-2 (4COX) was selected from PDB(Protein Data Bank) Bank RCSB with an X-ray resolution in the range of 2.90A^0 **[12](**http://www.rcsb.org/pdb).Cyclooxygenases are enzymes that take part in a complex biosynthetic cascade that results in the conversion of polyunsaturated fatty acids to prostaglandins and thromboxane(s). Their main role is to catalyze the transformation of arachidonic acid into the intermediate prostaglandin H2, which is the procursor of a variety of prostanoids with diverse and potent biological actions.COX-2 plays a major role in prostaglandin biosynthesis in inflammatory cells and in the central nervous system. Prostaglandin synthesis in these sites is a key factor in the development of inflammation and hyperalgesia. COX-2 inhibitors have analgesic and anti-inflammatory activity by blocking the transformation of arachidonic acid into prostaglandin H2 selectively. The three-step mechanism explains behind the inhibitory effects of selective COX-2 inhibitors. The first step accounts for the contact of the inhibitor with the gate of the hydrophobic channel (called the lobby region). The second step could account for the movement of the inhibitor from the lobby region to the active site of the COX enzyme. The last step probably represents repositioning of the inhibitor at the active site, which leads to strong interactions of the phenylsulfonamide or phenylsulfone group of the inhibitor and the amino acids of the side pocket. It is directly inhibition to postaglanding.

The fitness function that was implemented in GOLD consisted basically of H- bonding, complexing energy, and ligand internal energy terms. The GOLD Score was calculated by defining the site using the list of atom numbers and retaining all the other default parameters. The docking studies are frequently used to predict the binding orientations of small molecules of drug candidates to their protein targets in order to predict the affinity of the small molecules *viz*; **1-13**. A population of possible docked orientations of the ligand is set up at random. Each

member of the population is encoded as a chromosome, which contains information about the mapping of ligand H-bond atoms onto protein H-bond atoms, mapping of hydrophobic points all the conformation around flexible ligand bonds and protein OH groups. These protein-ligand complexes were prepared for docking studies by adding hydrogen atoms, removing water molecules and co-crystallized inhibitors and refined by using the SPDBV3.7[13]. Enzyme-inhibitor interactions within a radius equal to 15Å centered on reported bound inhibitors were taken into account.

4.2.3.2. *Argus Lab*

Argus Lab 4.0.1[14] was used for molecular modeling studies. This helps to visualize the binding conformations of these analogues, within the active site region of cyclo-oxygenase-2 protein.

4.2.3.3. *Auto dock*

Autodock4.0 [15] was used to estimate binding free energy and inhibition constant (K_i).

4.3. Results and Discussions

4.3.1. *Free radical scavenging activity*

Iodine itself acts as a sigma acceptor from donor, triethyl amine. The bonding type involved between these two is ***n-σ***. In the present case, the resulted CTC is evidenced by hypsochromic shift. Formation of CTC is due to excitation of electrons from orbital of donor to orbital of acceptor [16][17]. Therefore, the method is based on the reaction of ***n***- electron donors with the sigma-acceptor, iodine.

To accommodate the observed results, the following reaction mechanism is proposed:

The CTC is formed between triethyl amine as ***n***- donor (D) and iodine ($\mathbf{I_2}$) as sigma (σ)-acceptor. The CTC decomposes to give iodine free radical which in turn forms R˙radical on abstraction of hydrogen from β-Aminoketone (RH). R˙radical will then undergo further reactions which control the overall stoichiometry *i.e.*, the number of molecules Iodine reduced by RH. Mixing of iodine solution to donors resulted in decrease in intensity of color *i.e.* shifted to shorter wave length.

4.3.2. *Linear regression model analysis*

The biological activity data and the physicochemical properties IP, EA, ω, EN, η, S, LogP, HE, μ and Pol of the β-Amino ketone analogues are given in **Table2** and **Table3**. The data from these tables were subjected to regression analysis. The correlation matrices were generated with thirteen β-Amino ketone analogues**.**

Table-2: Antioxidant activities and molecular descriptors values of β-Amino ketone analogues in **AM1** method.

Compd	Obs. Act.	Eq-1		Eq-2		Molecular descriptors									
		Predicted	residual	Predicted	Residual	$IP_{(eV)}$	$EA_{(eV)}$	$EN_{(eV)}$	$\eta_{(eV)}$	$S_{(eV^{-1})}$	ω	HE (K.cal/mol)	LogP	$Pol(A^0)$	μ(eV)
1	4.20	4.13	.07	4.08	.12	7.89	0.60	4.25	3.65	.14	2.48	-5.33	3.08	38.75	-4.25
2	3.04	3.54	-.50	3.51	-.46	7.94	0.59	4.26	3.67	.14	2.48	-5.01	1.97	38.53	-4.26
3	4.36	4.41	-.05	4.37	-.01	8.09	0.51	4.30	3.79	.13	2.44	-5.48	2.79	36.70	-4.30
4	3.95	4.27	-.31	4.24	-.29	8.22	0.26	4.24	3.98	.13	2.26	-2.69	1.90	35.44	-4.24
5	4.46	4.60	-.15	4.53	-.08	7.93	-0.47	3.73	4.20	.12	1.66	-5.23	2.19	36.61	-3.73
6	3.62	3.61	.00	3.61	.01	8.02	1.00	4.51	3.51	.14	2.90	-4.22	1.80	43.09	-4.51
7	4.48	4.40	.08	4.39	.09	8.26	0.62	4.44	3.82	.13	2.58	-4.86	2.24	39.23	-4.44
8	4.38	3.92	.45	3.93	.45	8.32	0.50	4.41	3.91	.13	2.49	-6.59	1.20	39.08	-4.41
9	3.97	3.24	.73	-	-	7.76	0.40	4.08	3.68	.12	2.27	-3.82	1.97	38.53	-4.08
10	2.30	2.78	-.49	-	-	7.64	0.50	4.07	3.57	.12	2.32	-4.97	1.74	40.46	-4.07
11	4.46	4.77	-.31	4.79	-.33	8.58	0.57	4.58	4.00	.12	2.62	-4.30	1.74	40.46	-4.58
12	4.68	4.29	.39	4.26	.42	8.14	0.23	4.19	3.95	.13	2.22	-5.05	2.19	36.61	-4.19
13	4.30	4.22	.08	4.20	.10	8.17	0.61	4.39	3.78	.13	2.55	-4.81	2.24	39.23	-4.39

Table-3: Antioxidant activities and molecular descriptors values of β-Aminoketone analogues in **PM3** method.

Compd	Obs. Act.	Eq-3		Eq-4		Molecular descriptors									
		Predicted	residual	Predicted	residual	$IP_{(eV)}$	$EA_{(eV)}$	$EN_{(eV)}$	$\eta_{(eV)}$	$S_{(eV^{-1})}$	ω	HE (K.cal/mol)	LogP	Pol (A^{03})	μ(eV)
1	4.20	4.17	.03	3.95	.25	8.08	.63	4.35	3.72	.13	2.55	-5.34	3.08	38.75	-4.35
2	3.04	3.55	-.51	4.08	-.04	8.15	.38	4.26	3.88	.13	2.34	-5.04	1.97	38.53	-4.26
3	4.36	4.37	-.02	4.19	.16	8.27	.29	4.28	3.99	.13	2.30	-5.35	2.79	36.70	-4.28
4	3.95	4.15	-.19	4.28	-.33	8.47	.32	4.40	4.08	.12	2.37	-2.64	1.90	35.44	-4.40
5	4.46	3.70	.76	3.98	.48	8.14	.65	4.40	3.74	.13	2.58	-5.17	2.19	36.61	-4.40
6	3.62	3.86	-.25	3.99	-.37	8.28	1.01	4.64	3.64	.14	2.96	-4.36	1.80	43.09	-4.64
7	4.48	4.44	.04	4.23	.24	8.50	.46	4.48	4.02	.12	2.50	-4.77	2.24	39.23	-4.48
8	4.38	3.83	.54	4.30	.08	8.56	.38	4.47	4.09	.12	2.44	-6.54	1.20	39.08	-4.47
9	3.97	3.43	.54	-	-	8.09	.58	4.34	3.75	.13	2.51	-3.82	1.97	38.53	-4.34
10	2.30	3.18	-.88	-	-	8.04	.59	4.31	3.73	.13	2.50	-5.03	1.74	40.46	-4.31
11	4.46	4.46	.00	4.34	.12	8.69	.44	4.57	4.12	.12	2.53	-4.40	1.74	40.46	-4.57
12	4.68	4.20	.48	4.21	.47	8.40	.40	4.40	4.00	.13	2.42	-5.10	2.19	36.61	-4.40
13	4.30	4.84	-.54	4.37	-.07	8.72	.40	4.56	4.16	.12	2.50	-4.79	2.24	39.23	-4.56

The perusal of correlation matrix indicates that S, EA, ω and LogP were the predicted parameters from AM1 method. The enter, backward, forward, removed and stepwise regression methods are used. The regression technique was applied through the origin using these explainable parameters.

Activity = -3.713(0.692) * EA-54.516 (16.239) * **S** + 4.825(0.942)* ω +0.618(0.263)*LogP--- (1)

N = 13; R = 0.996; R^2 = 0.993; R^2adj=0.989; %EV = 99.3; SEE = 0.4228; F= 298.30; Q =2.355;

In addition, the plot of observed activity versus predicted activity was not found to be satisfactory. Hence, the predictive ability of the model is not good. **Eq.1** shows that the values of %EV are less and to improve its value, outliers (**9 & 10**) were sought and eliminated.

After the elimination of the outlier (**9&10**), a second model was developed. Overall, there is an increase in R (0.996-0.998) and %EV (99.3– 99.8) values, and a decrease in SEE (**0.4228- 0.3429**).

Activity = -3.758 (0.778) * EA-57.17 (23.379) * **S** + 4.978 (1.259) * ω +0.605 (0.261) * LogP ---------- (2)

N =11; R= 0.998; R^2= 0.996; R^2adj =0.993; %EV = 99.8; SEE = 0.3429; F =410.568; Q =2.910;

Eq.2 is an improved model since it explains the biological activity to the extent of (99.5%).

From the correlation matrix table, it reveals EA, ω,S and LogP are found to be explainable variables. A tetra-parametric QSAR equation with EA, ω, S and LogP and di-parametric QSAR equation with EA and ω were

generated in AM1 and PM3 methods respectively.

Activity = -2.971(1.083) * EA-54.54 (27.663) * S + 4.424 (1.411) * ω +0.685 (0.363) * LogP ---------- (3)
N =13; R = 0.993; R^2= 0.987; R^2adj =0.981; %EV = 98.70; SEE = 0.5601;
F = 169.019; Q = 1.7729;

Eq.3 shows that the values of % EV is less and to improve its value, outliers (**9&10**) were sought and eliminated, in addition, the plot of observed activity versus predicted activity was not found to be satisfactory. Hence, the predictive ability of the model is not good. After the elimination of the outliers (**9&10**), a second model was developed.

Activity = -2.254 (0.853) * EA+2.111 (0.179) * ω ----------(4)
N = 11; R = 0.995; R^2 = 0.990; R^2adj=0.988; %EV = 99.0; SEE = 0.4660; F = 441.942; Q =2.1351;

In an attempt to investigate the predictive potential of proposed models, the cross- validation parameters ($q^2_{cv}$and PRESS) were calculated and used. The predictive power of the equations was confirmed by leave-one-out (LOO) cross-validation method (**Table2 and Table 3)**.

Eq.3 and**4** of AM1 and PM3 methods respectively give a good q^2_{cv} value, which should be always smaller than %EV. A model is considered to be significant when q^2_{cv}=(>0.68).

Another cross-validation parameter, PRESS which is the sum of the squared differences between the actual and that predicted when the compound is omitted from the fitting process, also supports the predictive ability of **Eqs.2** and **4**. Its value decreases from **Eq.1 to Eq.3.**

The quality factor Q [18], is defined as the ratio of regression constants (R) to the standard error estimation (SEE), that is, Q = R/SEE. This indicates that the higher the value of R, and the lower the value of SEE, the higher is the magnitude of Q and the better will be the correlation. In present case, Q increases from 2.355 to 2.910 and 1.7729 to 2.1351 **(Eq. 1**
to 4).

The contributions of the physicochemical parameters are shown graphically in contribution charts (**Fig.2.** and **Fig.3**). Though the indicative parameters in AM1 are EA, S, ω and LogP the variation of Sand LogP are found to be negligible (**Table 2**). Hence, EA and ω are the main contributory factors for deciding antioxidant property. The electron affinity is characterized by the susceptibility of the compound in relation to attacks by nucleophiles. Electrophilicity is a property of atoms which signifies the energy lowering process on soaking electrons from donors. The electrophilicity index measures the stabilization in energy when the system acquires an additional electronic charge from the environment[19].The correlation between actual and predicted activity

for the compounds are shown in **Tables 2, 3** and **Figs. 4-7**.Therefore, one can conclude that electronic effects have a very important role when one is trying to understand the activity of β-Amino ketone analogues with anti-oxidant activity.

Figure 2 Plot of observed activity Vs predicted activity

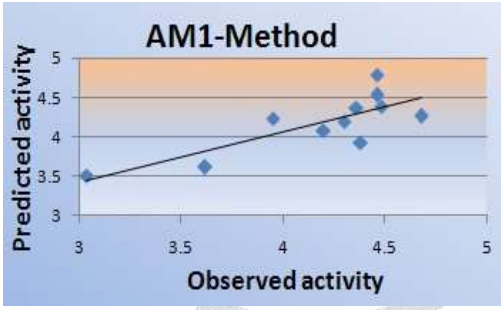


Figure 3 Plot of observed activity Vs predicted activity

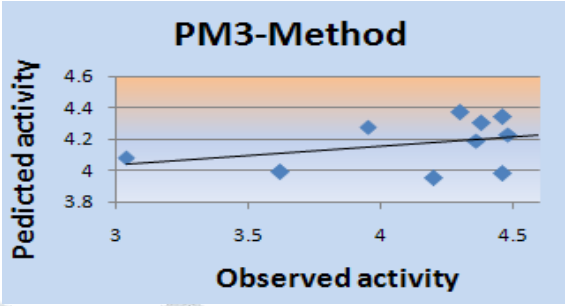


Figure 4 Plot of observed activity VsEA

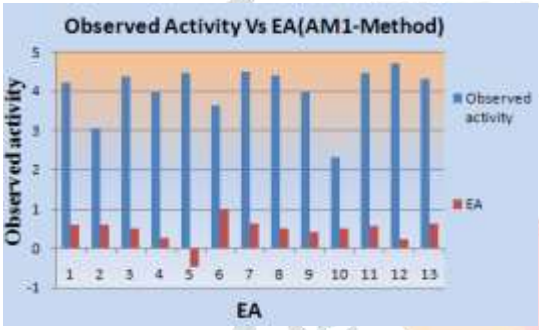


Figure 5 Plot of observed activity Vs **S**

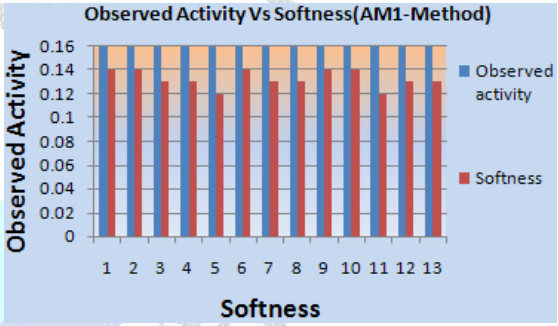


Figure 6 Plot of observed activity Vs ω

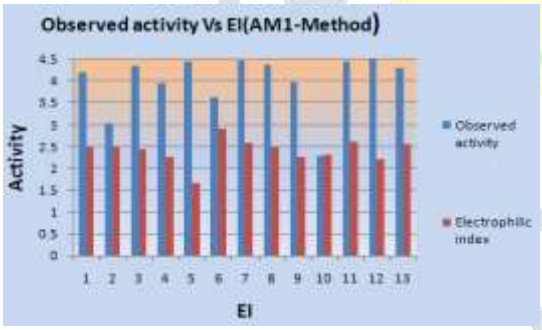


Figure 7 Plot of observed activity Vs LogP

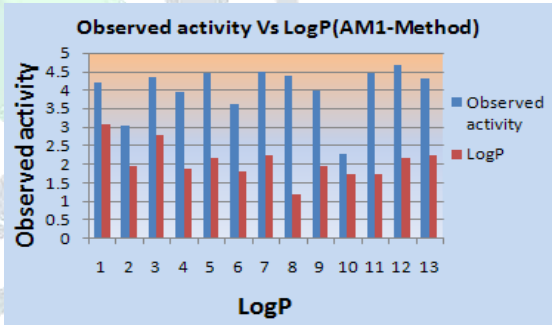


Figure 8 Plot of observed activity Vs EA

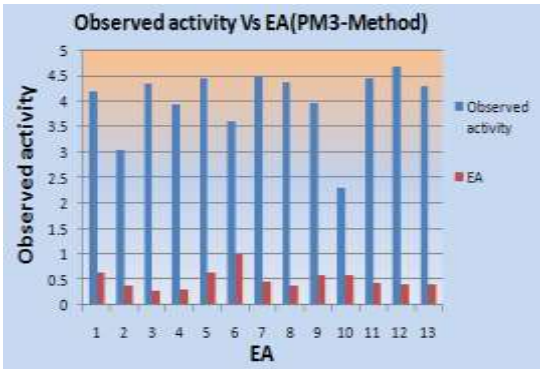
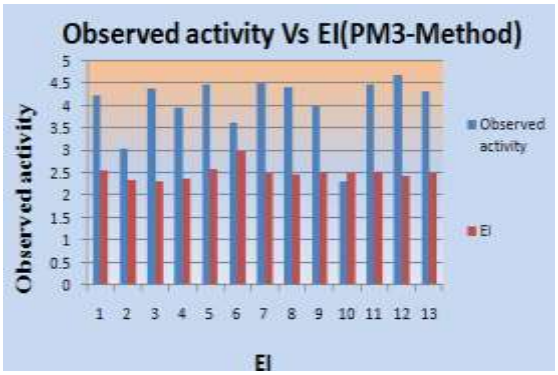


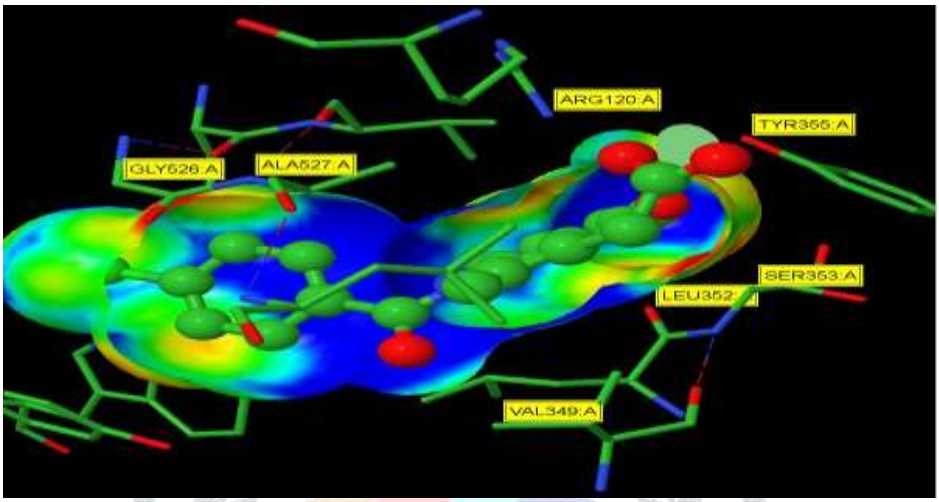
Figure 9 Plot of observed activity Vs ω



4.3.3. Docking Analysis

Among all the β-Amino ketone compounds were tested for docking study, showed good inhibitory activity values against cyclo-oxygenase-2 (**Table4**and**Table5**). The compound-**7** and **12**showed high affinities with low energy of with employed protein. It indicates the binding between 4COX and compound-1**2** indicates very good inhibition. The compounds **(1-13)** showed good inhibition with affinity ranges. In the active site of **4COX**, Thr212, Asn68, Glu67, His388, Ser 530, Tyr355, Tyr 402, Asn 382, Thr70, Glu140,
Asn144 amino acids play important role and they are shown in **Fig. 8**.

Figure 8 Active site amino acids of crystallographic protein **4COX**



The docking results from the crystal structure of cyclooxegenase-2(4COX) in the modeling study agreed well with the observed *in vitro* data, which indicated that compound-1**2** **(IC_{50}=0.020mM)** expected to be a potent inhibitor of cyclooxegenase-2.The docked score of compound-1**2** (54.19) indicates tight binding to the active site cyclooxegenase-2 and it agreed with biological activity. The high score of compound-1**2** is due to the best fitting of ligand containing electron releasing group (F) in the *para* position of aromatic ring of β-Amino ketone analogues with the cyclo-oxegenase-2 protein. The second highest score for the compound-**7** is due to electron releasing groups (F& Br) on aromatic rings of compound-**7**. The compounds **11, 5** and **3** have next highest score due to presence of electron releasing groups on aromatic ring and highest score due to *inter* molecular hydrogen bindings' with the electron releasing groups. The remaining compounds have medium gold docking score due to presence of less capacity of electron donating groups present on the aromatic ring of β-Aminoketone analogues.

Table 4 Docking values obtained from GOLD in fitness score with cyclo-oxygenase-2

Comp	Fitness	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(vdw_int)
1	57.09	0.00	46.65	0.00	-7.06
2	54.87	0.00	46.59	0.00	-9.18
3	57.57	0.00	46.05	0.00	-5.75
4	50.22	0.00	41.00	0.00	-6.16
5	**55.92**	**0.00**	**46.12**	**0.00**	**-7.49**
6	59.64	0.00	47.20	0.00	-5.27
7	**57.12**	**0.00**	**45.71**	**0.00**	**-5.73**
8	56.56	0.00	47.52	0.00	-8.78

9	58.79	0.00	47.74	0.00	-6.85
10	55.57	0.00	46.04	0.00	-7.73
11	54.31	0.00	45.35	0.00	-8.04
12	**54.19**	**0.00**	**44.56**	**0.00**	**-7.08**
13	55.88	0.00	45.95	0.00	-7.30

Table 5 Docking values obtained from GOLD in Chemscore function with cyclo- oxygenase-2 (PDB ID = 4COX)

Comp	Score	DG	S(h-bond)	S(metal)	S(lipo)	DE(clash)	DE(int)	
1	35.02	-38.69	0.00	0.00	312.12	1.89	1.78	
2	33.50	-37.24	0.00	0.00	301.18	1.84	1.90	
3	35.71	-38.48	0.00	0.00	310.29	2.09	0.68	
4	28.28	-34.29	0.00	0.00	273.27	3.85	2.17	
5	**34.66**	**-36.17**	**0.00**	**0.00**	**292.04**	**0.86**	**0.65**	
6	34.34	-43.15	0.00	0.00	351.74	4.48	4.33	
7	**34.18**	**-36.90**	**0.00**	**0.00**	**298.28**	**1.14**	**1.58**	
8	33.96	-37.41	0.00	0.00	307.11	1.78	1.67	
9	36.44	-41.42	0.00	0.00	336.92	2.15	2.83	
10	34.23	-40.63	0.00	0.00	330.17	5.61	0.79	
11	33.00	-42.18	0.00	0.00	343.42	6.23	2.95	
12	**35.80**	**-37.44**	**0.00**	**0.00**	**302.89**	**1.15**	**0.49**	
13	35.51	-40.36	0.00	0.00	327.84	2.87	1.98	

Highest Occupied Molecular Orbital(HOMO) energy and Lowest Unoccupied Molecular Orbital (LUMO) energy were constructed from of HQSAR (Hologram QSAR)**.** The theoretical calculations of molecular properties such as the maps of molecular orbitals (HOMO, LUMO), Auto dock and Argus lab binding energies showed a good correlation with antioxidant activity property (**Table 6** and **Fig.9)**. QSAR maps show positive (green) and negative (blue) contributions. The HQSAR map of compound - **5, 7** and**12**(the most potent), showed a positive contribution, indicating the importance of polar contacts to biological activity.

The energy of HOMO and LUMO are the quantum-chemical descriptors, which play an important role in chemical reactions. The delimited region for the HOMO orbital measures the electron-donor character of β-Amino ketones, and the LUMO measures the electron-acceptor character (Figure 9). The higher the energy of the HOMO the greater electron-donating ability and the lower the energy of the LUMO the lower resistant to accept electrons. The HOMO and LUMO energies also support the QSAR and docking studies (Table 6).

Table 6 HOMO, LUMO (AM1 and PM3), Auto Dock and Argus Lab energies of β- Aminoketone analogues

Compound	**AM1**		**PM3**		Auto dock B.E in K. cal/mol	Argus B.E in K cal/mol(elapsed time in seconds)
	$-\varepsilon_{HOMO\ (eV)}$	$-\varepsilon_{LUMO(eV)}$	$-\varepsilon_{HOMO(eV)}$	$-\varepsilon_{LUMO(eV)}$		
1	-8.69	-.42	-8.79	-.33	+13.04	-14.79(6)
2	-8.43	-.48	-8.59	-.54	+23.47	-13.76(7)
3	-8.59	-.34	-8.70	-.28	+5.15	-14.11(8)
4	-8.64	.02	-8.72	-.12	+3.64	-12.75(5)

5	**-8.42**	**-.35**	**-8.64**	**-.32**	**-1.25**	**-14.05(7)**
6	-8.48	-.84	-8.67	-.88	+19.62	-15.14(6)
7	**-8.73**	**-.50**	**-8.91**	**-.46**	**+20.10**	**-14.17(7)**
8	-8.60	-.39	-8.80	-.37	+20.76	-13.53(7)
9	-8.62	-.44	-8.55	-.41	+25.51	-14.67(6)
10	-8.72	-.37	-8.52	-.42	+43.15	-14.30(6)
11	-8.87	-.43	-8.92	-.32	+25.07	-15.04(7)
12	**-8.45**	**-.23**	**-8.81**	**-.40**	**+23.35**	**-13.65(6)**
13	-8.65	-.45	-9.02	-.38	+22.48	-14.91(7)

Figure 9 Best docking poses of molecule **5, 7**and **12.** HOMO, LUMO energy maps of molecule (**5,7**and**12**) and green color indicate favorable regions, while blue color indicate unfavorable region for the activity.

Best pose molecule-5 HOMO structure of molecule-5 LUMO structure of molecule-5

Best pose molecule-7HOMO structure of molecule-7LUMO structure of molecule-7

Best pose molecule-12 HOMO structure of molecule-12 LUMO structure of molecule-12

4.4. Conclusions

The antioxidant activity of β-Aminoketone analogues was determined using CTC of Iodine. In our present study, it was established the predictive QSAR models that are quite reliable to the experimental antioxidant activity of β-Aminoketone. The QSAR and molecular docking studies were performed on thirteen β-Aminoketone analogues. The best predictive AM1 model resulted in cross-validated R^2 value of 0.996, R^2adj value of 0.993 and standard error of estimate 0.2910(AM1), comprising EA, S, ω and LogP. Similarly, the best predictive PM3 model was derived with R^2 of 0.990, R^2adj of 0.988 and standard error of estimate of 0.2135, comprising EA and ω. The linear dependence of inhibitory nature on EA and ω are evident from **Figure 2**and **3** in both AM1 and

PM3 methods**.**

The electron releasing groups on aromatic ring and inter molecular hydrogen bond formation are responsible for high score in docking studies. These findings demonstrated that these compounds could be developed into novel antioxidants. QSAR equations showed good predictive performance and have ability to provide some insight into the relative importance of the individual compounds involved in determining the biologic activity or binding with receptor. Based on the bioassay and molecular modeling studies molecules**5, 7, 11**and**12** serve as an important pharmacophore for the design and development of the best antioxidant agents. Finally, it is concluded that the work presented here will play an important role in understanding the relationship between physiochemical parameters with varied structures and biological activity.

4.5. References

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