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ORIGINAL PAPER

# Towards the design of Cyclooxygenase (COX) inhibitors based on 4′,5 di-substituted biphenyl acetic acid molecules: a QSAR study with a new DFT based descriptor - nucleus independent chemical shift

**Ananda Sarkar · Golam Mostafa**

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**Abstract** Cyclooxygenase (COX) is a well-known enzyme, which converts arachidonic acid to prostaglandins $H_2$ ($PGH_2$), which are the effective mediators of inflammation. 4′, 5 di-substituted 3-biphenyl acetic acids (BPA) and several $\alpha$-methyl derivatives (MBPA) of it are widely used as powerful nonsteroidal anti-inflammatory and analgesic agents. We have chosen these activity data because the relation between the substituents and activity is not obvious and is hard to explain and also to show the superiority of DFT method. From the DFT results, various quantum chemical based descriptors were computed but the QSAR results showed that the descriptors based on frontier electron density and a new DFT based quantum chemical descriptor, nucleus independent chemical shift (NICS) are likely to be responsible for the in vitro inhibiting activity of BPA and MPBA. It has been proposed that NICS accounts for $\pi\ldots\pi$ interaction and indeed leads to a better result. To the best of our knowledge, this is the first use of NICS as a descriptor to get a better relationship to facilitate the design of COX inhibitors with potentially higher biological activity.

**Keywords** COX-inhibition · DFT-QSAR · Frontier electron density · NICS · NSAID · $\pi\ldots\pi$ interaction

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A. Sarkar
Department of Physics, APC College,
Kolkata 700131, India

G. Mostafa (✉)
Department of Physics, Jadavpur University,
Kolakata 700032, India
e-mail: mostafa@phys.jdvu.ac.in

## Introduction

Cyclooxygenase (COX) is a well-known enzyme, which converts arachidonic acid (AA, an *ω-6* PUFA) to prostaglandin $H_2$ ($PGH_2$) and subsequently to a number of other prostaglandins, which are the effective mediators of inflammation and anaphylactic reactions [1]. COX (also known as PGH synthatase) exists in two different isoforms, namely COX-1 and COX-2. COX-1 is constitutively expressed in tissues and is responsible for the physiological production of prostaglandin. COX-1 is mainly responsible for protection and maintenance of gastrointestinal tract. COX-2, the induced isoform, is responsible for the elevated production of prostaglandin during inflammation [2]. The elevated production is liable to inflammation, fever and pain. COX-2 is generally inhibited by nonsteroidal anti-inflammatory drug (NSAID), which is mostly used for fever and pain yet most abused due to its side-effects. During inhibition by NSAID, COX-1 is undesirably inhibited, producing gastrointestinal side effects. Thus the selective inhibition of COX-2 is highly desirable in the design of potential NSAID molecules [3].

QSAR is a useful technique, which mathematically relates the biological activities in terms of structural descriptors of a series of homologous molecules [4–8]. Once a correlation is established, the structure of any number of related compounds with desired properties can be predicted from this. Because the experimental determination is time-consuming and expensive, estimated values based on QSAR models are now widely used. Success of QSAR methodology is based on the reliability and the versatility of the prediction of new drug molecules and toxic molecules [4–8].

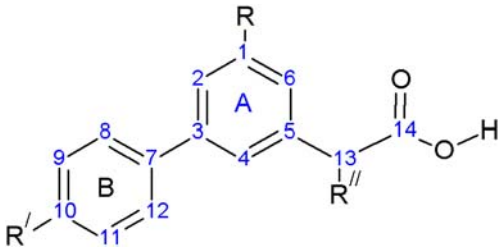
In the development of QSAR, various descriptors namely constitutional, geometrical, electrostatic, topologi-

cal and thermodynamic, have been used. Recently, quantum chemical descriptors [9] have drawn attraction as new molecular descriptors, which provide a more accurate and precise quantitative description of the geometric and electronic properties of molecules and their interactions. Though semiempirical quantum chemical methods, e.g., PM3, AM1 etc. have been used for the evaluation of quantum-mechanical descriptors for many years, the recent development of computer technology and software for electronic structure theory allows calculating quantum chemical descriptors at first principle level; such as density functional theory (DFT) [10–13]. The combination of the relatively low computational cost and the reasonable accuracy has led to the immense usefulness of the DFT based descriptors in the prediction of a broad range of the properties of atoms and molecules as well as their site selectivity.

4', 5 di-substituted 3-biphenyl acetic acids and several $\alpha$-methyl derivatives of it (Table 1) are widely used as powerful nonsteroidal anti-inflammatory and analgesic agents [14]. Although many different types of NSAID agents are reported in the literature, the search continues for more effective compounds. Though our main objective was to design NSAIDs without side effects, a careful examination of the structures reveals that there is no obvious structure property relationship for the substituents in 1, 3 and 10 positions of these molecules (Table 1). This seems interesting and DFT descriptors should give us a deeper insight to this kind of problem.

In this paper, weighted electrophilic and weighted nucleophilic frontier electron densities at position 1, 3 and 10, hybrid descriptor based on Fukui function and chemical potentials and a new descriptor, *nucleus independent chemical shift* (NICS) [15–18] were derived from the DFT

**Table 1** Molecular structure of biphenyl molecules and observed anti-inflammatory activities together with DFT-based QSAR predicted values*




| No. | Substituents | | | logCPE% | | | | |
|---|---|---|---|---|---|---|---|---|
| | R | R/ | R// | Observed | Equation 21 | | Equation 22 | |
| | | | | | Predicted | Residuals | Predicted | Residuals |
| 1 | NHAc | H | H | 0.700 | 0.71 | −0.01 | 0.81 | −0.11 |
| 2 | NHAc | MeO | H | 1.180 | 1.18 | 0.00 | 1.25 | −0.07 |
| 3 | $NH_2$ | Cl | H | 1.200 | 1.19 | 0.01 | 1.11 | 0.09 |
| 4 | H | H | H | 1.670 | 1.57 | 0.10 | 1.59 | 0.08 |
| 5 | H | MeO | H | 1.040 | 1.01 | 0.03 | 0.99 | 0.05 |
| 6 | H | Cl | H | 1.640 | 1.71 | −0.07 | 1.73 | −0.09 |
| 7 | Cl | H | H | 1.510 | 1.60 | −0.09 | 1.57 | −0.06 |
| 8 | Cl | MeO | H | 1.280 | 1.20 | 0.08 | 1.16 | 0.12 |
| 9 | Cl | Cl | H | 1.650 | 1.69 | −0.04 | 1.65 | 0.00 |
| 10 | F | H | H | 1.700 | 1.52 | 0.18 | 1.52 | 0.18 |
| 11 | F | Cl | H | 1.580 | 1.55 | 0.03 | 1.53 | 0.05 |
| 12 | H | H | Me | 1.230 | 1.35 | −0.12 | 1.37 | −0.14 |
| 13 | H | Cl | Me | 1.540 | 1.57 | −0.03 | 1.58 | −0.04 |
| 14 | Cl | MeO | Me | 0.900 | 1.05 | −0.15 | 1.02 | −0.12 |
| 15 | Cl | Cl | Me | 1.610 | 1.63 | −0.02 | 1.63 | −0.02 |
| 16 | F | H | Me | 1.490 | 1.34 | 0.15 | 1.33 | 0.16 |
| 17 | F | Cl | Me | 1.590 | 1.65 | −0.06 | 1.62 | −0.03 |
| 18 | Me | Cl | H | 1.720 | 1.71 | 0.01 | 1.77 | −0.05 |

*(Nos. are given according to DFT calculation; IUPAC No should be 7→1′, 8→2′, 9→3′, 10→4′, 11→5′, 12→6′)

calculations. These quantum chemical descriptors are employed to analyze the anti-inflammatory activity (logCPE%) of 4', 5 di-substituted 3- biphenyl acetic acids molecules to the best predictive model. To the best of our knowledge, this is the first time NICS is used as a descriptor to take account of π-interactions into QSAR models.

## Theoretical background

Among the quantum chemical descriptors chemical potential ($\mu$), hardness ($\eta$), softness (s), electrophilicity index ($\omega$), Fukui functions ($f_k^\alpha$), local softness ($s_k^\alpha$) atomic charges, molecular orbital energies, molecular polarizabilities, and frontier orbital densities are most frequently used. The chemical potential ($\mu$), hardness ($\eta$), softness (s), electrophilicity index ($\omega$) are known as global reactivity descriptors. Fukui functions ($f_k^\alpha$), local softness ($s_k^\alpha$) etc. are called local reactivity descriptors [19–23].

a) Chemical potential ($\mu$)

The chemical potential ($\mu$) has been shown to be a useful global index of reactivity in atoms, molecules and clusters. [10–13]. The "chemical potential ($\mu$)" is a measure of how much the amount of free energy of a system changes (denoted by $\partial E$) if we add or remove $\partial n_i$ number of electrons to or from the system. The analytical definition of chemical potential ($\mu$) has been provided by the density functional theory (DFT) as the partial derivative of the total energy E of an atomic or molecular system with respect to the total number of electrons N, for a constant external potential v(r)

$$\mu = \left[\frac{\partial E}{\partial N}\right]_{v(r)}. \tag{1}$$

Also $\mu$ is identified as the negative of electro negativity ($\chi$) as defined by Iczkowski and Margrave [24]

$$\chi = -\left[\frac{\partial E}{\partial N}\right]_{v(r)}. \tag{2}$$

By applying the finite difference approximation to Eq. 1, we get the operational definition of ($\mu$) as,

$$\mu = -\frac{1}{2}(IP + EA) \tag{3}$$

where, IP and EA are the ionization potential and the electron affinity of the chemical species.

According to Koopman's theorem [25], the IP is simply the eigen value of HOMO with change of sign and the EA is the eigen value of LUMO with change of sign, hence the above equation can be written as,

$$\mu = \frac{1}{2}(E_{HOMO} + E_{LUMO}). \tag{4}$$

A theoretical justification was provided from the Sanderson's Electro negativity equalization principle [26–28].

b) Fukui function

Parr and Yang [25] introduced the term Fukui Function indices which actually measures the sensitivity of a system's chemical potential to an external perturbation at a particular side or the sensitivity of the system's electron density at a particular side if an infinitesimally small number of electrons is added or excluded from the system.

$$f(r) = \left(\frac{\partial \mu}{\partial v(r)}\right)_N = \left(\frac{\partial \rho(r)}{\partial N}\right) \tag{5}$$

where $\rho(r)$ is the electron density.

In order to describe the reactivity of an atom in a molecule, it is necessary to condense the values of $f(r)$ around each atomic site into a single value ($f_k^a$) that characterize the atomic contribution in a molecule.

As $\rho(r)$ is a discontinuous function of N, Yang and Mortier [29] have proposed approximated atomic $f(r)$ indices by applying the finite difference approximation to the condensed electronic population on any atom. These can be written as;

$$f_k^+ = \rho_k(N+1)\rho_k(N) \rightarrow \text{ For Electrophilic Attacks,} \tag{6}$$

$$f_k^- = \rho_k(N) - \rho_k(N-1) \rightarrow \text{ For Electrophilic Attacks,} \tag{7}$$

$$f_k^0 = \frac{1}{2}\left(f_k^+ + f_k^-\right) \rightarrow \text{ For Radical Attacks.} \tag{8}$$

c) Local chemical potential,"Relative electrophilic chemical potential" and "Relative nucleophilic chemical potential"

In this paper we use a hybrid quantum chemical descriptor, local chemical potential, which is the modified form of the Fukui function indices. The condensed to atom variants for the atomic side "k" for electrophilic, nucleophilic, radical reactions have been defined as

$$\mu_k^+ = f_k^+\mu(\text{Suited for studies of nucleophilic attack}), \tag{9}$$

$$\mu_k^- = f_k^-\mu(\text{Suited for studies of electrophilic attack}), \tag{10}$$

$$\mu_k^0 = f_k^0\mu(\text{Suited for studies of radical attack}). \tag{11}$$

Where $\mu_k^\alpha$ are the local chemical potential, obtained simply by multiplying Fukui function indices ($f_k^\alpha$) with the global chemical potential ($\mu$).

We define relative chemical potentials as

$$\text{Relative Electrophilic chemical potential} = \left(\frac{\mu_k^-}{\mu_k^+}\right), \quad (12)$$

$$\text{Relative Nucleophilic chemical potential} = \frac{\mu_k^+}{\mu_k^-}. \quad (13)$$

The advantage of this definition is that the individual values of $\mu_k^+$ and $\mu_k^-$ are strongly influenced by the basis set or correlation effect. However, the ratio of $\mu_k^+$ and $\mu_k^-$, is expected to be less sensitive to the basis set and the correlation effect.

Obviously, the above equations give us a more definitive way of expressing electrophilic or nucleophilic attacks. If any site has $(\frac{\mu_k^+}{\mu_k^-} > \frac{\mu_k^-}{\mu_k^+})$, then this site is preferable for nucleophilic attack and if $(\frac{\mu_k^+}{\mu_k^-} < \frac{\mu_k^-}{\mu_k^+})$ then the site is preferable for electrophilic attack.

d) Hardness ($\eta$) and softness (s)

Using Koopmans' [25] theorem, hardness is defined as:

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}, \quad (14)$$

and softness

$$s = \frac{1}{2\eta}. \quad (15)$$

e) Electrophilicity index ($\omega$)

The global electrophilicity index ($\omega$) [25, 30–31] is defined in terms of chemical potential and hardness as

$$\omega = \frac{\mu^2}{2\eta}. \quad (16)$$

f) The weighted electrophilic and nucleophilic atomic frontier electron densities

The weighted electrophilic frontier electron density, $F_i^E$ and weighted nucleophilic frontier electron density, $F_i^N$ are defined as follows [9]

$$F_i^N = \frac{\sum \left(C_i^{LUMO}\right)^2}{\Delta E} \times 100 \quad (17)$$

$$F_t^E = \frac{\sum \left(C_i^{\text{HOMO}}\right)^2}{\Delta E} \times 100 \quad (18)$$

Where $C_i^{HOMO/LUMO}$ are the coefficients of the atomic orbitals of atom i in the HOMO and LUMO and $\Delta E$ is the HOMO-LUMO energy gap.

g) The nucleus-independent chemical shift (NICS)

The NICS method of estimating the aromaticity through the strength of the ring current was proposed by Schleyer *et al.* [15]. The nucleus-independent chemical shift (NICS) are obtained as the negative value of absolute magnetic shieldings NICS(0), computed at the ring centroid or NICS(1), 1 Å above the centroid, correspond to aromatic systems.

In general, the more negative the NICS, the more aromatic are the rings and conversely, positive NICS values are associated with anti-aromaticity. The system having NICS values within the range of zero is non-aromatic. NICS constitute a measure of ring current of π-aromatic system but the current strength of NICS(0) is contaminated by the ring-current of σ-bonds. Hence NICS(1) values are often considered to be better because the ring current 1 Å above the centroid is mainly constituted of π-electrons (Fig. 1). NICS(1) measures the values of π-electron ring current of the aromatic system so it can be a good descriptor mimicking π-interactions between protein and drugs. Consequently, we introduce a new quantum descriptor successfully for the first time to develop QSAR for inhibitors to COX.

## Methods and computational details

A series of 4', 5-disubstituted 3-biphenylacetic acids and several α-methyl derivatives of it were taken as study materials. The anti-inflammatory activity (LogCPE%) on SLC-SD rats using carrageenan-induced rat paw edema was taken from the literature [14] and listed in Table 1.

All the geometries of selected 18 biphenyl acetic acid derivatives have been fully optimized using the DFT

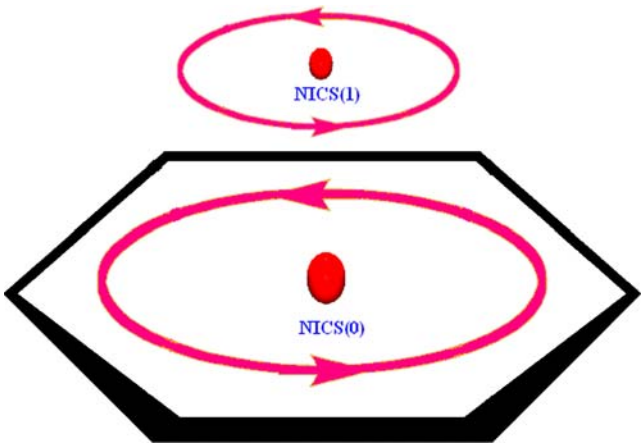



**Fig. 1** Ring current on and above 1 Å an aromatic planar moiety. The strength of the current related to NICS(0) value on the ring and NICS (1) value above 1 Å

method [19–23] with the help of Becke's three parameter hybrid density functional, B3LYP/6–31G(d,p), which include both Hartree-Fock exchange and DFT exchange correlation functional using *GAUSSIAN* 03 program [32]. The optimized geometries are characterized by harmonic-vibrational frequencies, which confirmed that the structures obtained are minimum on the potential energy surface. The coordinates and ball & stick diagram of the DFT optimized structures are given as supplementary materials. The weighted electrophilic and nucleophilic atomic frontier electron densities are calculated using Eqs. 17 and 18 respectively. The nucleus independent chemical shifts were calculated with optimized geometries of the molecules by GIAO method [32]. Standard multiple regression analyses are performed to find out the relationship between the biological activity indices and structural descriptors.

## Results and discussion

### QSAR analysis and model validation

QSAR models were derived using multiple linear regression (MLR) and the predictivity potential was determined by cross-validation methods. MLR were carried out using observed anti-inflammatory and analgesic activity as the dependent variables and various combinations of the chosen descriptors as the independent variables. The quality of the model was considered as statistically satisfactory on the basis of correlation coefficient (R), standard deviation ($\sigma$), F-statistics and T-statistics.

We know that validation is a crucial aspect of any QSAR modeling. Most of the QSAR modeling methods implement the leave-one–out (LOO) cross-validated procedure [33–34]. In this phase, 18 subsets were created according to the LOO method and the output of the removed compound was predicted for each subset. Internal predictability of the models is characterized by the cross-validated squared correlation coefficient ($q^2$) given by,

$$q^2 = 1 - \frac{\sum \left(Y_i^{pred} - Y_i^{obs}\right)^2}{\sum \left(Y_i^{obs} - Y_i^{mean}\right)^2}, \tag{19}$$

where $Y_i^{obs}$, $Y_i^{pred}$, $Y_i^{mean}$ are respectively the observed, predicted, and the observed mean values of the dependent variables; the summation runs over all compounds. The $q^2$ values are accepted as criteria of both robustness and the predictive ability of the QSAR model. Many authors consider higher $q^2>0.5$ [35–36] as an indicator that the model is highly predictive. Further, the T-test measures the statistical significance of the regression coefficients. The higher T-test values correspond to the relatively more significant regression coefficients.

To ascertain the relationship between chemical structures of the selected 18 biphenyl acetic acid derivatives and anti-inflammatory activities, we have generated various equations through different combinations of DFT descriptors including chemical potential ($\mu$), hardness ($\eta$), softness (s), electrophilicity index ($\omega$), Fukui functions ($f_k^{\alpha}$), atomic charges, molecular orbital energies, molecular polarizabilities, and frontier orbital densities keeping in mind that the number of descriptor should be as small as possible and have maximum correlation coefficient with anti-inflammatory activity (logCPE %). Out of these generated equations, the significant equation having the largest predictive power is given below:

$$\begin{gathered}\log CPE\% = -0.266 - 0.0085 f_3^N + 0.0488 f_{10}^E + 0.0429 \frac{\mu_k^+}{\mu_k^-}(k=3) \\ r^2 = 0.854 \quad q^2 = 0.776 \quad F = 27.257 \quad \sigma = 0.127\end{gathered} \tag{20}$$

where $f_3^N$, $f_{10}^E$ and $\frac{\mu_k^+}{\mu_k^-}(k=3)$ are weighted nucleophilic frontier electron densities on atom 3, weighted electrophilic frontier electron densities on atom 10 and relative nucleophilic chemical potential on atom 3, respectively. $r^2$ is the correlation coefficient, $q^2$ is the cross-validated correlation coefficient using leave-one-out (LOO) method, $\sigma$ is the standard error and F is the F-test value. Other statistical parameters are summarized in Table 2.

Interestingly, no good correlation was found with ($\mu$), hardness ($\eta$), softness (s), electrophilicity index ($\omega$), Fukui functions ($f_k^{\alpha}$), atomic charges and molecular orbital energies.

In search of a better regression model, we analyze the molecules for their activity sites. Interestingly, the HOMO and LUMO of the molecules show that the main activity sites of the molecules are clearly the aromatic rings. The HOMO and LUMO of molecule 18 with the best activity are depicted in Fig. 2a and b.

Thus, the activity of the compound should be co-operated by $\pi$-interactions. This leads us to introduce the

**Table 2** T-test values, partial correlation and uncertainties of eq. 20

| Variables | T-test values | Partial correlation with logCPE % | Uncertainties |
|---|---|---|---|
| $f_3^N$ | −2.684 | −0.583 | 0.003 |
| $f_{10}^E$ | 4.294 | 0.754 | 0.011 |
| $\frac{\mu_k^+}{\mu_k^-}(k=3)$ | 2.997 | 0.625 | 0.014 |

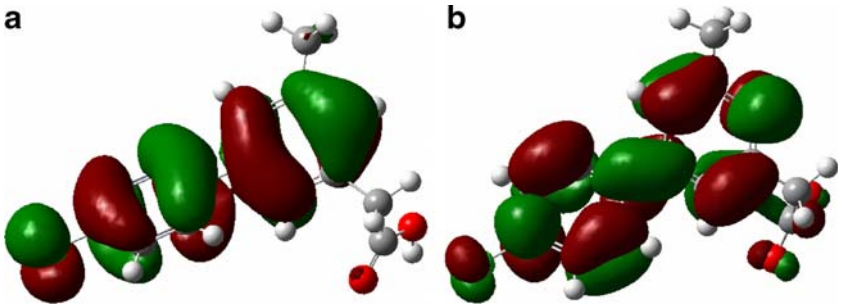



**Fig. 2** (**a**) HOMO of compound 18 and (**b**) LUMO of compound 18

NICS descriptor and the results are satisfactorily improved. It is interesting to note only A ring shows the correlation with logCPE%.

With the introduction of NICS(1) in the model,

$$\log CPE\% = 6.806 - 0.01474 f_3^N + 0.050 f_{10}^E + 0.634\,\mathrm{NICS}(1) + 0.024\frac{\mu_k^+}{\mu_k^-}(k=3)$$
$$r^2 = 0.916 \qquad q^2 = 0.867 \qquad \mathrm{F} = 35.041 \qquad \sigma = 0.100 \tag{21}$$

Other statistical parameters are given in Table 3.

In order to keep the number of independent variables as small as possible, we see T-test value as well as the partial correlation between logCPE% and $\frac{\mu_k^+}{\mu_k^-}(k=3)$ is least. Dropping the descriptor, we reached the regression equation,

$$\log \mathrm{CPE}\% = 9.762 - 0.019 f_3^N + 0.036 f_{10}^E + 0.818\,\mathrm{NICS}(1)$$
$$r^2 = 0.895 \qquad q^2 = 0.774 \qquad \mathrm{F} = 38.818 \qquad \sigma = 0.108 \tag{22}$$

Other statistical parameters are given in Table 4.

Thus the last two regression equations (Eqs. 21, 22) are not only predictive as both cross-validation and F-value are rather high but the T-test values show the descriptors taken for Eq. 22 are highly significant also. The plot of the observed versus predicted logCPE% values in Eqs. 21 and 22 of 18 BPA and MBPA compounds are depicted in Fig. 3a and b. From the above equations, it can be concluded that the negative correlation of the$f_3^N$ term indicate that the anti-inflammatory and the analgesic activity of these compounds increases with decreasing the weighted LUMO density located on atom 3 and the positive correlation of the $f_{10}^E$ term indicate that the anti-inflammatory and the analgesic activity of these compounds increases with increasing the weighted HOMO density located on atom 10. The weighted nucleophilic and electrophilic atomic frontier electron density of atoms 3 and 10 are related to the electron-accepting or electron-donating abilities. The atom at position 10 is mainly an electron-donating site, binding to the electropositive region of the receptor. The electron-accepting capacity at position 3 is to be reduced for better biological activity and binding to the electronegative region of the receptor when the NSAIDs react with the COX receptor. It is highly corroborated by Eq. 21 that relative chemical potential at atom 3 ($\frac{\mu_k^+}{\mu_k^-}(k=3)$) value has to be increased for higher biological activity.

The most interesting feature is the identification of NICS as QSAR descriptor. When frontier orbitals (HOMO & LUMO) are located on the aromatic ring, the drug receptor interactions should mediated by π…π interactions. We know that π…π interactions depend on charge distribution over the aromatic ring. An electron injecting group on the aromatic ring should make the π-lobe negative inducing an interaction with positively polarized moiety of the receptor. On the other hand, an electron withdrawing group should make the π-lobe positive, inducing an interaction with negatively polarized moiety of the receptor. In both cases, NICS value depends on the strength of the ring current over the aromatic ring. In the first case, ring current is due to presence of electrons in the π-lobe and in the second case, ring current is due to the hole in the π-lobe. Our QSAR study shows that the increment of the value of NICS depends mainly on the substituent at atom 1 but the effect

**Table 3** T-test values, partial correlation and uncertainties of Eq. 21

| Variables | T-test values | Partial correlation with logCPE % | Uncertainties |
|---|---|---|---|
| $f_3^N$ | −4.566 | −0.785 | 0.003 |
| $f_{10}^E$ | 5.569 | 0.840 | 0.009 |
| NICS(1) | 3.064 | 0.648 | 0.207 |
| $\frac{\mu_k^+}{\mu_k^-}(k=3)$ | 1.854 | 0.457 | 0.013 |

**Table 4** T-test values, partial correlation and uncertainties of Eq. 22

| Variables | T-test values | Partial correlation with logCPE % | Uncertainties |
|---|---|---|---|
| $f_3^N$ | −7.973 | −0.905 | 0.002 |
| $f_{10}^E$ | 6.697 | 0.873 | 0.005 |
| $_{NICS(1)}$ | 4.160 | 0.743 | 0.197 |

of atom 13 cannot be ignored. Interestingly, both a strong electron withdrawing group and electron injecting group should increase the ring current and hence the value of NICS. So, the effect of NICS on the activity is a cumulative effect of the substituents on atom 1 (R) and atom 13 (R"), not an individual effect. From experimental data, now we can explain the disparity on the activity data of the NSAIDs molecules.

It may be noted that the number of compounds we worked in the present work is only 18. Firstly, this is due to paucity of the available experimental dataset. Since we wanted to work on the activity data where the relation between the substituent and the biological activity is not obvious, we have taken the dataset. Secondly, despite small in number, our result shows that NICS may be a good descriptor to model π…π interaction. The other chosen quantum chemical descriptors provide stellar quantitative description in different DFT results. Thirdly, the final number of descriptors being only three, and the statistical parameter such as T-test, F-test, cross-validation being significant, our result is plausible.

## Conclusions

The current study was performed to examine the applicability of the DFT-based quantum chemical descriptors in QSAR analysis for studying the biological activity of a series of 4'', 5-disubstituted biphenyl acetic acid molecules which are known as potent nonsteroidal anti-inflammatory and analgesic agents. The DFT-based quantum chemical descriptors were obtained at the B3LYP/6–31G(d,p) level. It has been shown that the use of DFT-based quantum chemical descriptors indeed led to a better molecular insight.

The obtained QSAR results based on the DFT-based descriptors demonstrate that the biological activity was correlated linearly with weighted frontier HOMO and LUMO orbitals, relative chemical potential and NICS. From the analysis of the QSAR equation, it can be concluded that in order to get better activity, a strong electron donating/withdrawing substituent should occupy position 1 of the aromatic ring to increase NICS values and electron-accepting capacity of the atom at position 3 should be reduced and the electron donating capacity of the atom at position 10 should be increased.

It was also seen that NICS, a new DFT-based quantum chemical descriptor, indeed leads to a better result specially when there is no obvious correlation between activity and substuents. So it can be expected that our result should not only help in design of NSAIDs to inhibit COX with potentially higher biological activity but also facilitate the study of π…π interactions, which promotes drug receptor interactions.

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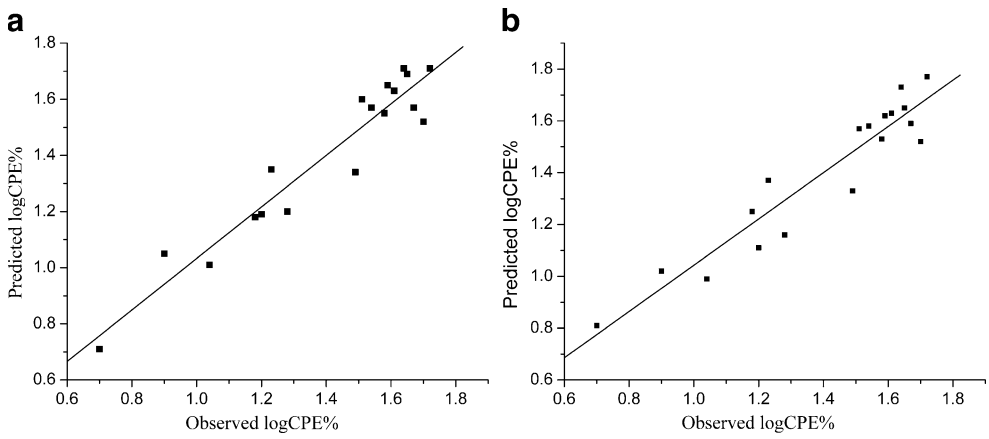


**Fig. 3** Plot of observed versus calculated anti-inflammatory activities (logCPE%) (**a**) from Eq. 21 and (**b**) from Eq. 22

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