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Chemical Reactivity and Skin Sensitization Studies on a Series of Chloro- and Fluoropyrroles—A Computational Approach

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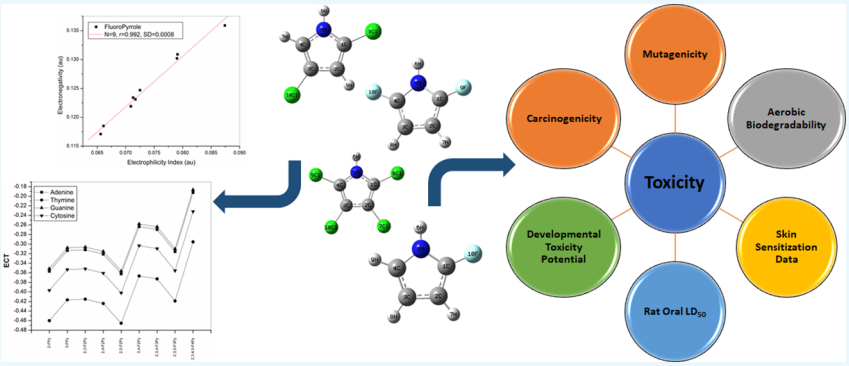

ABSTRACT: Global density functional descriptors analysis on a series of chloro- and fluoropyrroles provide vital data concerning their overall biochemical activities. In this study, a comprehensive investigation is presented for a series of chloro- and fluoropyrroles using DFT-based descriptors to elucidate physicochemical properties and their relevance to reactivity, charge transfer, site selectivity, and toxicity. Electrophilicity-based charge transfer (ECT) descriptor reveals the fact that chloro- and fluoropyrroles act as electron donors during their interaction with DNA bases. The local descriptor, namely, multiphilic descriptor conveys the activeness of specific sites in chloro- and fluoropyrroles. Further, Toxicity Prediction Komputer Assisted Technology (TOPKAT) studies on carcinogenicity bioassays using four rodent models provide the interesting fact that chloro- and fluoropyrroles exhibit a strong skin sensitization effect in these species.

1. INTRODUCTION

Global and local activities of molecules were analyzed in detail with density functional (DF) descriptors, viz., chemical hardness, chemical potential, electrophilicity index, Fukui functions (FF), and local philicities.[1−3] Computational analysis has been utilized to study the properties of known materials and to foresee those of yet unidentified ones.[4−6] The importance of electrophilicity index in reactivity and structure-based activity/toxicity studies has been extensively deliberated.[7−10] Recently, the importance of nucleic acid (NA)-based interaction studies to model bioactivity and toxicity has been effectively explained using QSAR and structural descriptors.[11]

Pyrrole derivatives are nitrogen-containing heterocyclic compounds with a five-membered ring that are extensively found in a variety of natural and synthetic chemicals with useful bioactivities. Pyrrole derivatives have been used in a variety of applications, pharmaceutics,[12−14] antibacterial,[15−17] antiviral,[18,19] anti-inflammatory,[20−22] analgesic,[23] anti-cancer,[24,25] antihyperlipidemic,[26] and antihyperglycemic medicines,[27,28] in addition to their biological action.

Several biologically active compounds with useful properties such as antipsychotic, anticancer, and antimalarial were obtained with various pharmacophores combination in a pyrrole ring system.[29] Direct functionalization on electron-rich heteroaromatic compound, namely, the pyrroles via catalytic and noncatalytic methods were presented in a recent review.[30] The possibility of developing densely functionalized pyrroles from inexpensive and commonly obtainable carbohydrates has been discussed.[31]

Polypyrrole (PPy) has drawn distinct attention due to its conductivity and other prospective applications.[32,33] The electrical conductivity of PPy is due to charge transport as well as the leaping of carriers.[34−36] Hence, study of monomers, which are the building blocks of these polymers, has become

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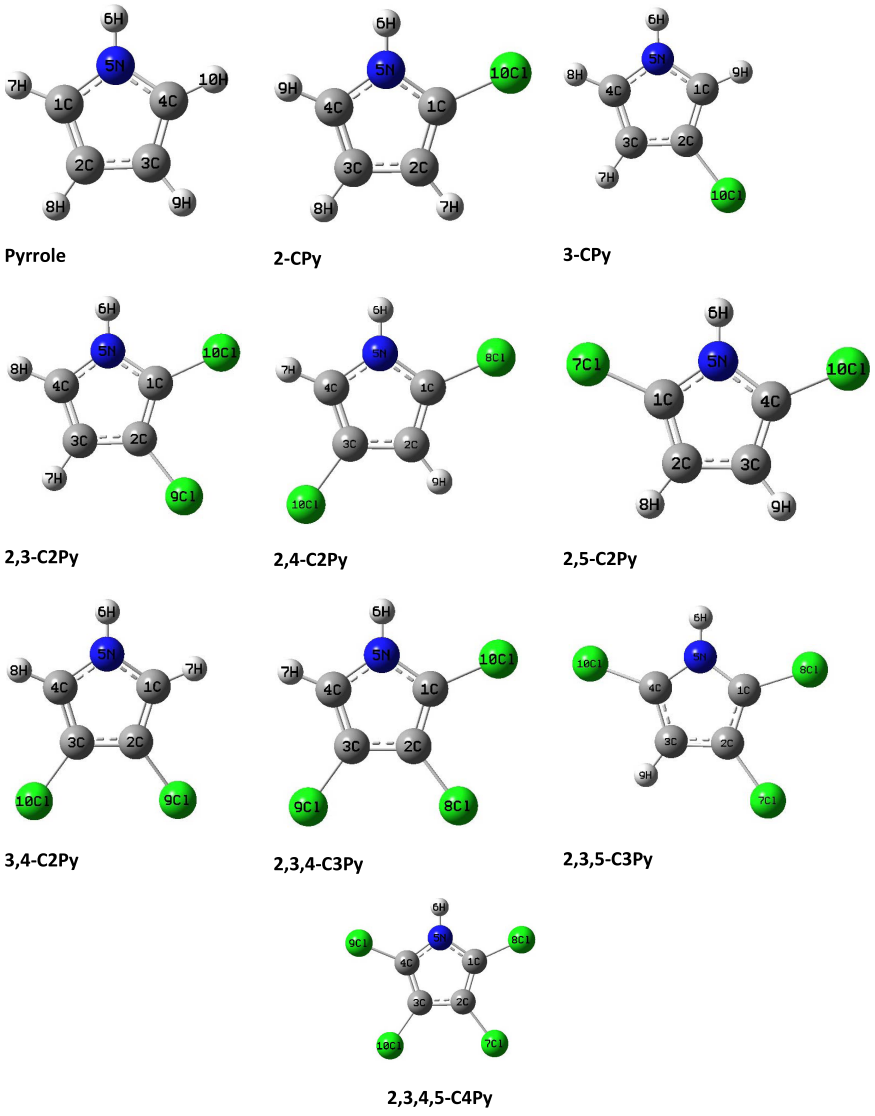

Figure 1. Optimized structures of chloropyrroles with atom specification.

an interesting research field. It is fascinating to note that the pyrrole fragment is a part of many biotic systems.[37] They are also important components in the production of alkaloids and artificial heterocycles.[38] Greater attention has been directed toward the production and application of pyrrole derivatives as dyes.[39] Furthermore, pyrroles have been claimed to be used in organic semiconductors.[40,41] Immunogenicity levels of PPy-based materials have been reported to be equivalent to those of other FDA-approved biomaterials.[42] As a result, researchers have used PPy-containing composites to regenerate electro-active tissues as an alternative to conventional treatments for clinical disorders. Biocompatible polypyrrole (PPy) can be chemically modified to facilitate biomolecule conjugation. Access to this class of chemicals has received a lot of research interest because of their wide range of applications. Recently, electronic, structural, and other related properties of chlorine-substituted pyrroles (CPy) and fluorine-substituted pyrroles (FPy) were studied using DFT-based investigation.[43,44]

In the present work, efforts have been made to probe the energetics, global reactivity, charge transfer, and site selectivity of a series of chloro- and fluoropyrroles using various DF descriptors that is important to understand and predict the toxicity of these compounds. Such work has not been attempted on the selected series of compounds in any of the known previous studies. Further, for the first time, the utility of the TOPKAT (Toxicity Prediction Komputer Assisted Technology)[45−48] NTP (National Toxicology Program) carcinogenicity module for the selected molecules has been evaluated by determining the system's ability to predict the results of rodent carcinogenicity bioassays.

2. THEORETICAL BACKGROUND

Chemical potential (μ) and hardness (η) are given[49−51] as

$$\mu = \frac{E_{\mathrm{LUMO}} + E_{\mathrm{HOMO}}}{2} \tag{1}$$

and

$$\eta = \frac{E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}}}{2} \tag{2}$$

where E_{LUMO} and E_{HOMO} are the energies of the lowest unoccupied molecular orbital and the highest occupied molecular orbital, respectively.

Fukui functions in the condensed form are defined as[52]

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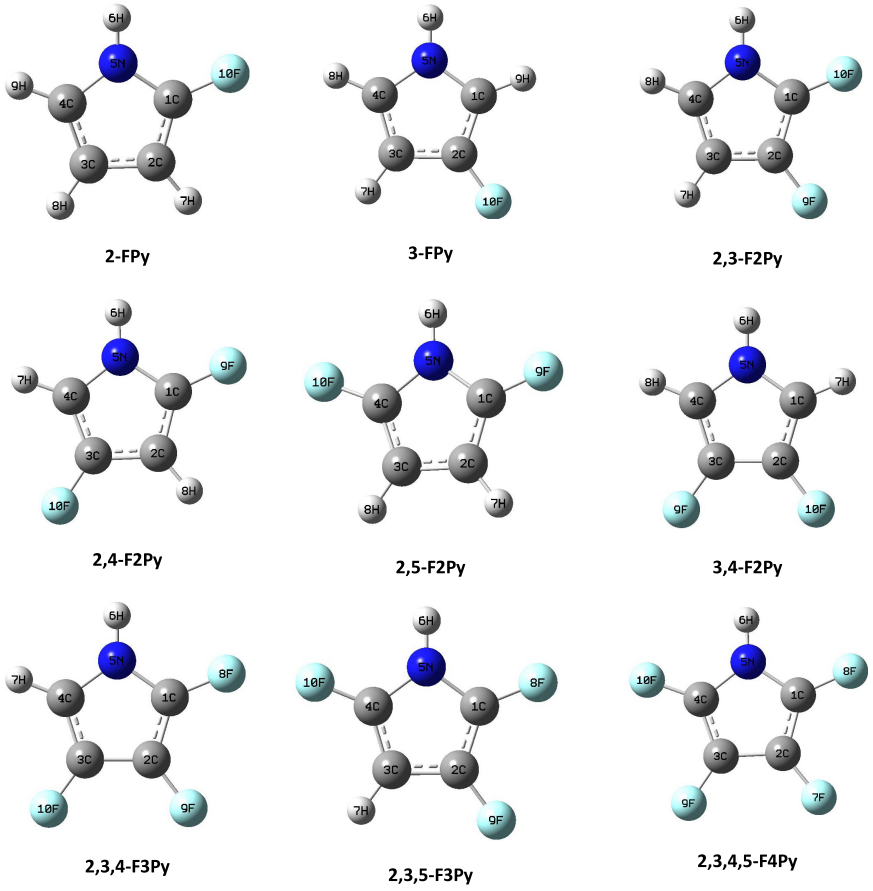

Figure 2. Optimized structures of fluoropyrroles with atom specification.

Table 1. Energetics of Pyrrole and Chloropyrroles Calculated with the B3LYP/6−311++G Method**[a]

molecule	energy, E (hartree)	zero-point energy, ZPE (kcal/mol)	ΔE	ΔE_0	enthalpy, H (hartree)	ΔH
pyrrole	−210.23058	51.56			−210.14349	
2-CPy	−669.84952	45.68	0.51	0.42	−669.77069	0.43
3-CPy	−669.85034	45.78	0.00	0.00	−669.77138	0.00
2,3-C2Py	−1129.46697	39.88	0.76	0.87	−1129.39620	0.85
2,4-C2Py	−1129.46818	39.77	0.00	0.00	−1129.39756	0.00
2,5-C2Py	−1129.46719	39.70	0.62	0.55	−1129.39665	0.57
3,4-C2Py	−1129.46717	39.96	0.64	0.82	−1129.39632	0.78
2,3,4-C3Py	−1589.08314	33.94	0.35	0.48	−1589.02056	0.45
2,3,5-C3Py	−1589.08369	33.81	0.00	0.00	−1589.02127	0.00
2,3,4,5-C4Py	−2048.69809	27.89			−2048.64374	

[a]Relative energy (ΔE), relative energy including ZPE (ΔE_0), and relative enthalpy (ΔH) are in kcal/mol.

Table 2. Energetics of Fluoropyrroles Calculated with the B3LYP/6−311++G Method**[a]

molecule	energy, E (hartree)	zero-point energy, ZPE (kcal/mol)	ΔE	ΔE_0	enthalpy, H (hartree)	ΔH
2-FPy	−309.49151	46.44	0.00	0.00	−309.41177	0.00
3-FPy	−309.49125	46.52	0.16	0.24	−309.41141	0.22
2,3-F2Py	−408.74667	41.44	3.04	3.14	−408.67402	3.15
2,4-F2Py	−408.75152	41.34	0.00	0.00	−408.67904	0.00
2,5-F2Py	−408.75053	41.31	0.62	0.60	−408.67807	0.61
3,4-F2Py	−408.74665	41.55	3.05	3.27	−408.67387	3.25
2,3,4-F3Py	−508.00153	36.33	1.92	2.06	−507.93599	2.04
2,3,5-F3Py	−508.00458	36.19	0.00	0.00	−507.93924	0.00
2,3,4,5-F4Py	−607.25370	31.20			−607.19527	

[a]Relative energy (ΔE), relative energy including ZPE (ΔE_0), and relative enthalpy (ΔH) are in kcal/mol.

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$$f_k^+ = q_k(N+1) - q_k(N)$$
$$f_k^- = q_k(N) - q_k(N-1)$$
$$f_k^0 = (f_k^+ + f_k^-)/2 \quad (3)$$

where $q_k(N)$, $q_k(N+1)$, and $q_k(N-1)$ are the electronic population of the N, $N+1$, and $N-1$ electron systems, respectively, and f_k^+, f_k^-, and f_k^0 are condensed-to-atom Fukui functions for the nucleophilic, electrophilic, and radical attacks, respectively.

Index of electrophilicity, ω, is defined by[53]

$$\omega = \frac{\mu^2}{2\eta} \quad (4)$$

A multiphilic descriptor is known by[54]

$$\Delta\omega_k = [\omega_k^+ - \omega_k^-] = \omega[f_k^+ - f_k^-] = \omega[\Delta f_k] \quad (5)$$

Table 3. Global Parameters (in au) Calculated from the B3LYP/6−311++G ** Method for Chloropyrroles

molecule	chemical potential (μ)	chemical hardness (η)	electrophilicity index (ω)
pyrrole	−0.1154	0.1031	0.0646
2-CPy	−0.1180	0.1043	0.0667
3-CPy	−0.1234	0.1040	0.0732
2,3-C2Py	−0.1248	0.1043	0.0747
2,4-C2Py	−0.1254	0.1054	0.0746
2,5-C2Py	−0.1192	0.1061	0.0670
3,4-C2Py	−0.1315	0.1049	0.0824
2,3,4-C3Py	−0.1329	0.1039	0.0850
2,3,5-C3Py	−0.1285	0.1032	0.0800
2,3,4,5-C4Py	−0.1384	0.0985	0.0972
adenine	−0.1469	0.0994	0.1085
thymine	−0.1574	0.0996	0.1244
guanine	−0.1368	0.0929	0.1007
cytosine	−0.1477	0.0973	0.1120

Table 4. Global Parameters (in au) Calculated from the B3LYP/6−311++G Method for Fluoropyrroles**

molecule	chemical potential (μ)	chemical hardness (η)	electrophilicity index (ω)
2-FPy	−0.1170	0.1044	0.0656
3-FPy	−0.1219	0.1047	0.0710
2,3-F2Py	−0.1231	0.1056	0.0718
2,4-F2Py	−0.1233	0.1066	0.0713
2,5-F2Py	−0.1185	0.1062	0.0661
3,4-F2Py	−0.1302	0.1072	0.0791
2,3,4-F3Py	−0.1309	0.1083	0.0791
2,3,5-F3Py	−0.1247	0.1073	0.0725
2,3,4,5-F4Py	−0.1359	0.1057	0.0874

Table 5. TOPKAT-Based NTP Carcinogenicity of Male Mouse (CMM) and Female Mouse (CFM) for Pyrroles/Chloropyrroles Showing Calculated Probability and Discriminant Score

	CMM		CFM	
molecule	calculated probability	discriminant score	calculated probability	discriminant score
2,3,4,5-C4Py	0.614	0.883	0.631	1.831
2,3,4-C3Py	0.613	0.669	0.597	1.102
2,3,5-C3Py	0.613	0.669	0.606	1.422
2,3-C2Py	0.614	0.956	0.619	1.640
2,4-C2Py	0.614	1.042	0.622	1.680
2,5-C2Py	0.614	0.867	0.630	1.814
2-CPy	0.612	1.537	0.608	1.451
3,4-C2Py	0.650	2.045	0.608	1.455
3-CPy	0.659	2.175	0.606	1.418
pyrrole	0.672	2.366	0.599	1.220

The fractional number of electrons, transferred from system A to system B, represented by the global interaction parameter ΔN is given by[55]

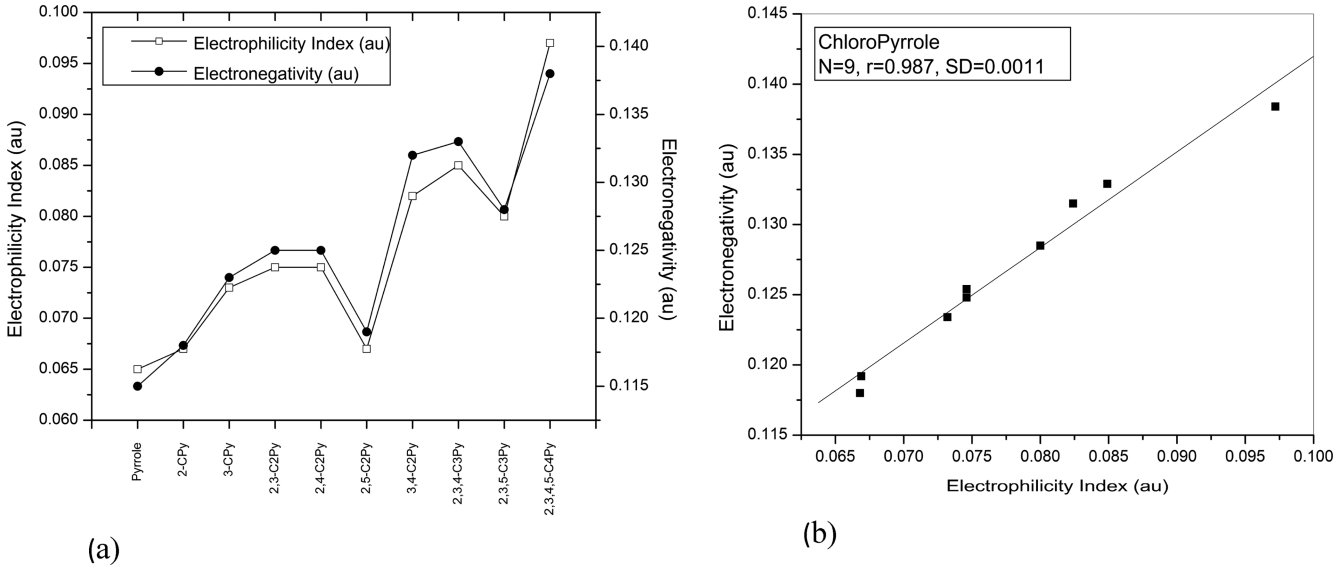

Figure 3. (a, b) Plots between global parameters electrophilicity index (au) and electronegativity (au) for chloropyrroles showing a high correlation (r) value of 0.987.

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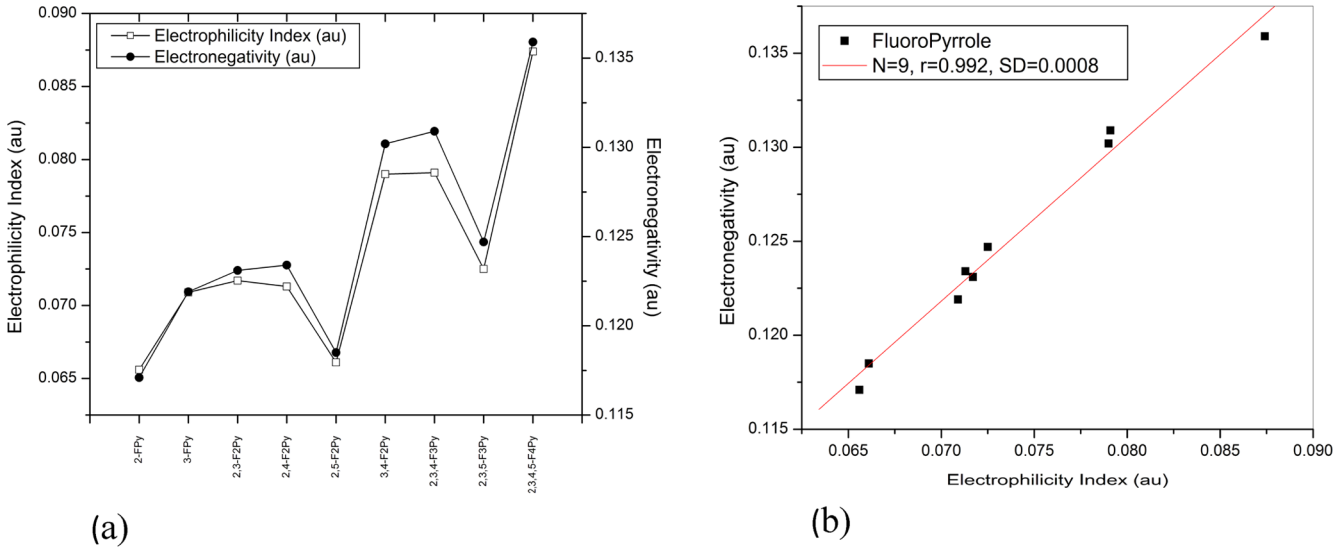

Figure 4. (a, b) Plots between global parameters electrophilicity index (au) and electronegativity (au) for fluoropyrroles showing a correlation (r) value of 0.992.

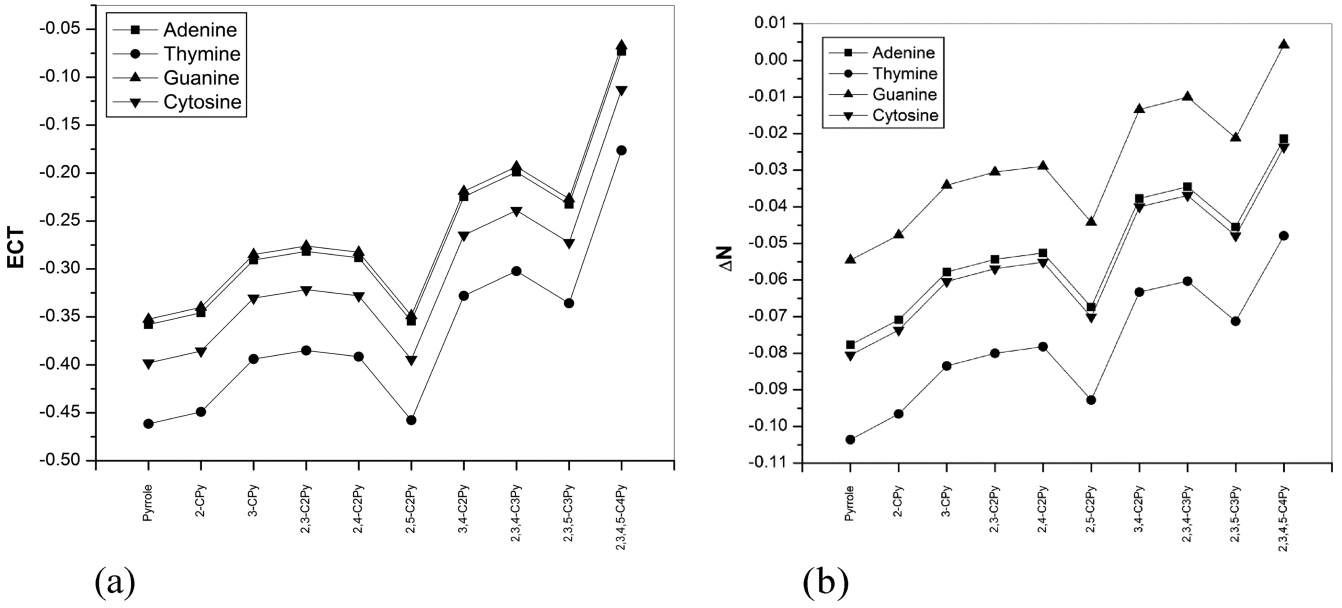

Figure 5. Interaction of chloropyrroles with DNA bases based on (a) electrophilicity-based charge transfer (ECT) and (b) charge transfer (ΔN) showing maximum for thymine base.

$$\Delta N = \frac{\mu_B - \mu_A}{2(\eta_A + \eta_B)} \quad (6)$$

where μ_A, μ_B and η_A, η_B are the chemical potentials and chemical hardness of systems A and B, respectively.

The maximum electronic charge ΔN_{max}[53]

$$\Delta N_{max} = 2\omega/\chi = 2\omega X \quad (7)$$

where $X = 1/\chi$, with χ $(= -\mu)$ being the electronegativity of the system.

Electrophilicity-based charge transfer (ECT) is specified by[56]

$$ECT = (\Delta N_{max})_A - (\Delta N_{max})_B = 2[\omega_A X_A - \omega_B X_B] \quad (8)$$

3. RESULTS AND DISCUSSION

The numberings of the atom for the selected optimized pyrroles are displayed in Figures 1 and 2.

3.1. Energetics of Chloro- and Fluoropyrroles. The energies and thermodynamic (enthalpy H) parameters of all chloropyrroles alongside pyrrole are exhibited (Table 1). The relative energies are calculated separately for mono-, di-, tri-, and tetra-substitutions. The relative energy ΔE represents the extent of molecular stability. 3-CPy showed better stability than 2-CPy with a 0.51 kcal/mol energy difference. Among dichloropyrroles, 2,3-C2Py is 0.76 kcal/mol less stable than 2,4-C2Py. Similarly, 2,3,5-C3Py is the most stable isomer and 2,3,4-C3Py is the least stable isomer among trichloropyrrole with an energy difference of 0.35 kcal/mol.

The calculated energies and thermodynamic measure (enthalpy) of all fluoropyrroles are presented in Table 2. For

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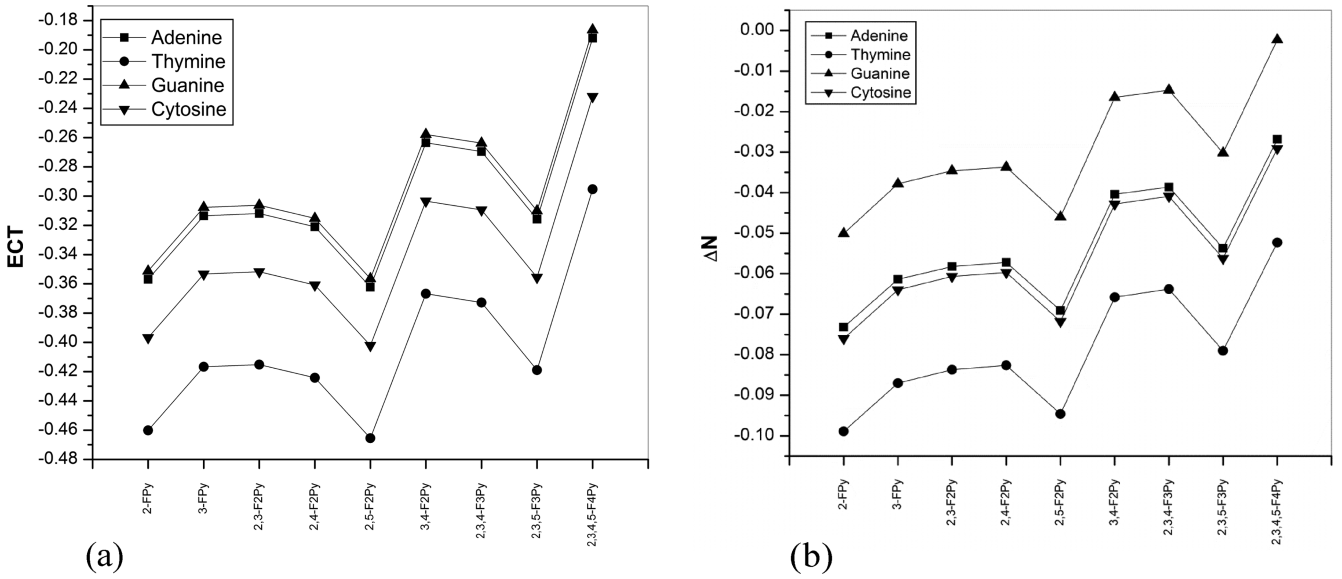

Figure 6. Interaction of fluoropyrroles with DNA bases based on (a) electrophilicity-based charge transfer (ECT) and (b) charge transfer (ΔN) showing maximum for thymine and minimum for guanine base.

Table 6. TOPKAT-Based NTP Carcinogenicity Male Rat (CMR) and Female Rat (CFR) for Pyrroles/Chloropyrroles Showing Calculated Probability and Discriminant Score

	CMR		CFR	
molecule	calculated probability	discriminant score	calculated probability	discriminant score
2,3,4,5-C4Py	0.599	−0.435	0.519	−0.084
2,3,4-C3Py	0.540	−1.861	0.502	−0.722
2,3,5-C3Py	0.593	−0.608	0.502	−0.722
2,3-C2Py	0.588	−0.731	0.507	−0.527
2,4-C2Py	0.572	−1.121	0.507	−0.527
2,5-C2Py	0.617	0.032	0.515	−0.252
2-CPy	0.577	−1.004	0.509	−0.475
3,4-C2Py	0.604	−0.325	0.510	−0.435
3-CPy	0.575	−1.058	0.501	−0.750
pyrrole	0.629	0.380	0.515	−0.240

Table 7. TOPKAT-Based Aerobic Biodegradability (AB) and Developmental Toxicity Potential (DTP) Data for Pyrroles/Chloropyrroles Showing Calculated Probability and Discriminant Score

	AB		DTP	
molecule	calculated probability	discriminant score	calculated probability	discriminant score
2,3,4,5-C4Py	0.161	−8.578	0.453	−2.673
2,3,4-C3Py	0.142	−9.383	0.467	−2.249
2,3,5-C3Py	0.133	−9.828	0.431	−3.371
2,3-C2Py	0.135	−9.741	0.433	−3.300
2,4-C2Py	0.138	−9.574	0.466	−2.273
2,5-C2Py	0.209	−6.861	0.435	−3.245
2-CPy	0.217	−6.608	0.407	−4.178
3,4-C2Py	0.203	−7.069	0.515	−0.882
3-CPy	0.210	−6.817	0.525	−0.609
pyrrole	0.463	−0.578	0.484	−1.740

monofluoropyrroles, the stability of 2-FPy is higher than 3-FPy by 0.16 kcal/mol. For difluoropyrroles, 3.05 kcal/mol is the difference in energy between the most (2,4-F2Py) and least (3,4-C2Py) stable isomers. Similarly, 2,3,5-F3Py is the most stable isomer and 2,3,4-F3Py is the least stable isomer among trifluoropyrrole with an energy difference of 1.92 kcal/mol.

Further, the thermodynamic parameters H and ΔH for chloropyrroles and fluoropyrroles vary in a similar trend to E and ΔE, respectively. These parameters are useful in explaining the molecular features of chloro- and fluoropyrroles in the gas phase. The lower values for relative energy (ΔE) and enthalpy (ΔH) for the isomers of CPy are an indication of the fact that they are closer in their stability and thermodynamic property.

3.2. Global Descriptors of Chloro- and Fluoropyrroles. The estimated values of global reactivity descriptors for pyrrole and chloropyrroles are represented in Table 3 and 4. Figure 3a illustrates the plot of ω versus χ of pyrrole and chloropyrroles.

A direct proportionality between the values of ω and χ is observed; ω and χ increase with an increase in the number of Cl addition with the exception of 2,5-C2Py and 2,3,5-C3Py showing a slight drop in their values. The values of ω and χ are minimal for pyrrole (least reactive) and maximal for 2,3,4,5-C4Py (highly reactive). 2,3,4,5-C4Py also has a minimal hardness satisfying the principle of minimum electrophilicity.[57] A high correlation (r) of 0.987 happens between ω and χ (Figure 3b).

The assessed parameters for fluoropyrroles are shown in Table 4. Figure 4a displays the plot of ω versus χ of fluoropyrroles. Fluoropyrroles show a similar trend for ω and χ to chloropyrrole but with F atom addition. 2,5-F2Py and 2,3,5-F3Py are exceptions showing a slight drop in their values. Further, 2-FPy is the least reactive molecule, and 2,3,4,5-C4Py is a highly reactive molecule. A better correlation (r = 0.992) exists between ω and χ (Figure 4b).

3.3. Charge Transfer Analysis of Chloro- and Fluoropyrroles. ECT has been utilized to understand the interaction characteristics of pyrrole/chloropyrroles (System A) with DNA bases (System B) (Figure 5a). It is interesting to

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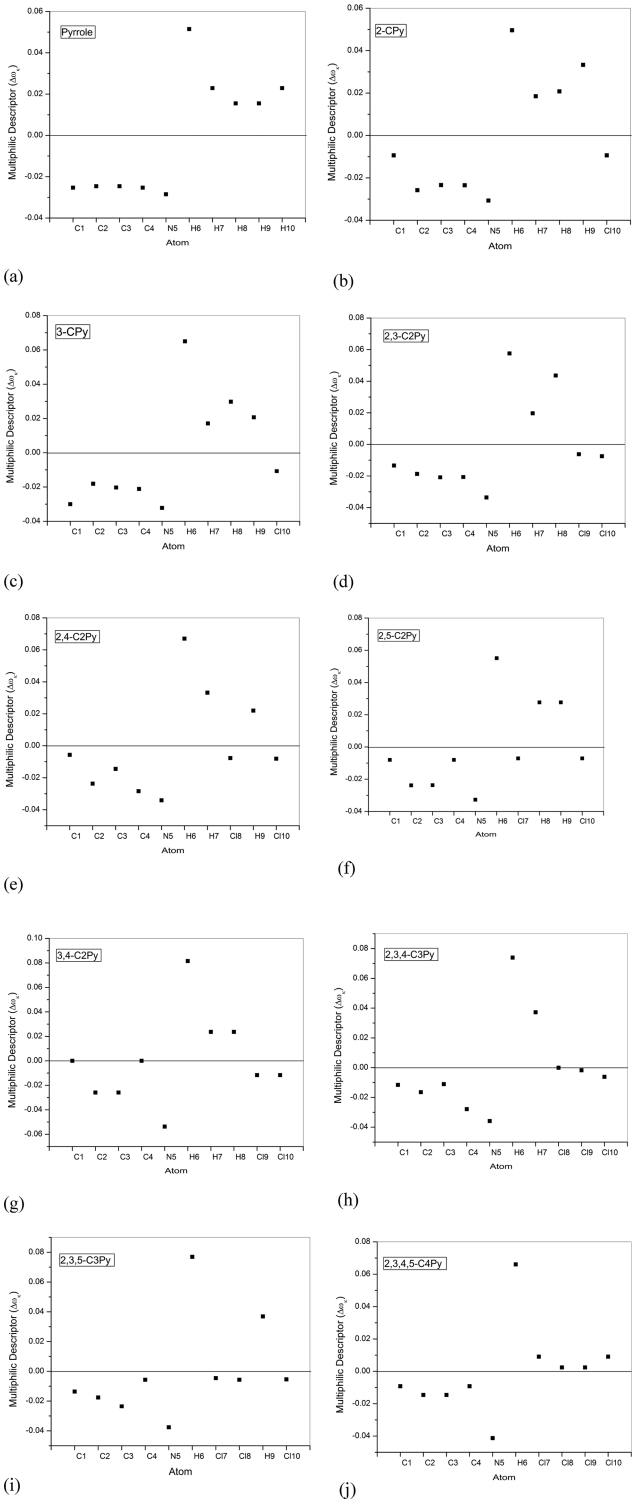

Figure 7. (a–j) Multiphilic descriptors ($\Delta\omega_k$) for atoms in pyrrole/chloropyrroles. N_5 position in pyrrole is susceptible to electrophilic attack (EAK) with a value of −0.028, and H_6 site is better toward nucleophilic attack (NAK) with a value of 0.051.

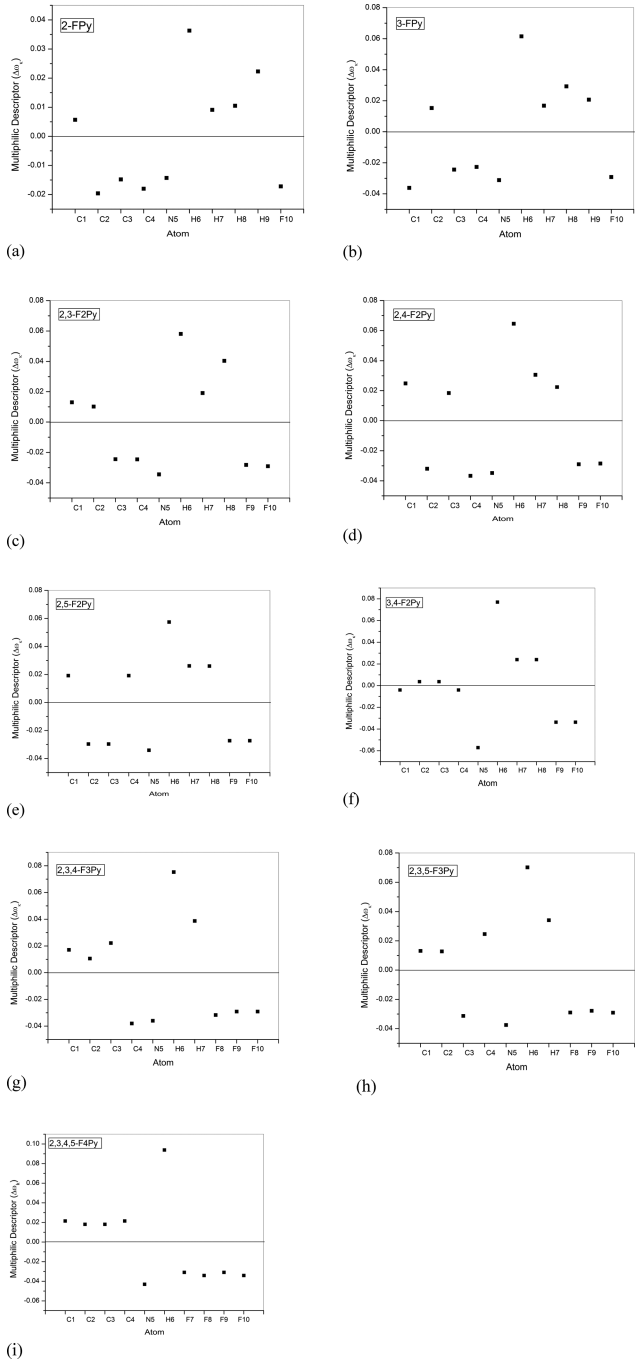

Figure 8. (a–i) Multiphilic descriptors ($\Delta\omega_k$) for atoms in fluoropyrroles. H_6 site has preference toward nucleophilic attack (NAK), whereas fluorine and N_5 sites to have preference to electrophilic attack (EAK).

note that pyrrole/chloropyrroles turn into donor of electrons with all DNA bases. It can be observed that all chloropyrroles have less interaction with guanine and maximum interaction with thymine among the selected DNA bases. A similar trend is exhibited by ΔN-based interaction studies (Figure 5b) for chloropyrroles supporting our ECT results.

It is important to note a similar trend between fluoropyrroles and DNA bases like chloropyrroles (Figure 6a). The electron-donating nature of fluoropyrroles is minimal with guanine and maximum with thymine. Interestingly, an identical trend is presented by ΔN (Figure 6b) for fluoropyrroles supporting our ECT-based outcome.

3.4. Chloro- and Fluoropyrroles with Multiphilic descriptor. Figure 7a–j highlights the multiphilic descriptor ($\Delta\omega_k$) for pyrrole/chloropyrroles. The N_5 position in pyrrole is extra susceptible to electrophilic attack (EAK) with a value of −0.028, and H_6 site shows better preference toward

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Table 8. TOPKAT-Based Rat Oral LD_{50} ($RO\text{-}LD_{50}$), Skin Sensitization Data (SSD), and Mutagenicity Data (MD) for Pyrroles/Chloropyrroles Showing Calculated Probability and Discriminant Score

	$RO\text{-}LD_{50}$	SSD		MD	
molecule	calculated probability (g/kg)	calculated probability	discriminant score	calculated probability	discriminant score
2,3,4,5-C4Py	0.303	0.769	−0.452	0.685	−2.356
2,3,4-C3Py	0.165	0.759	−0.666	0.656	−3.347
2,3,5-C3Py	0.227	0.762	−0.614	0.644	−3.734
2,3-C2Py	0.145	0.755	−0.748	0.682	−2.460
2,4-C2Py	0.177	0.755	−0.748	0.601	−5.020
2,5-C2Py	0.228	0.749	−0.880	0.684	−2.373
2-CPy	0.304	0.738	−1.094	0.701	−1.713
3,4-C2Py	0.178	0.753	−0.801	0.672	−2.807
3-CPy	0.185	0.745	−0.962	0.629	−4.199
pyrrole	0.567	0.711	−1.589	0.715	−1.124

Table 9. TOPKAT-Based NTP Carcinogenicity of Male Mouse (CMM) and Female Mouse (CFM) for Fluoropyrroles Showing Calculated Probability and Discriminant Score

	CMM		CFM	
molecule	calculated probability	discriminant score	calculated probability	discriminant score
2,3,4,5-F4Py	0.613	0.639	0.622	1.684
2,3,4-F3Py	0.610	0.370	0.607	1.445
2,3,5-F3Py	0.610	0.370	0.622	1.684
2,3-F2Py	0.614	0.980	0.619	1.642
2,4-F2Py	0.613	0.749	0.619	1.642
2,5-F2Py	0.613	0.749	0.634	1.882
2-FPy	0.613	1.453	0.619	1.642
3,4-F2Py	0.614	1.225	0.611	1.504
3-FPy	0.617	1.601	0.611	1.504

Table 10. TOPKAT-Based NTP Carcinogenicity Male Rat (CMR) and Female Rat (CFR) for Fluoropyrroles Showing Calculated Probability and Discriminant Score

	CMR		CFR	
molecule	calculated probability	discriminant score	calculated probability	discriminant score
2,3,4,5-F4Py	0.637	0.641	0.509	−0.463
2,3,4-F3Py	0.602	−0.355	0.509	−0.463
2,3,5-F3Py	0.627	0.338	0.509	−0.463
2,3-F2Py	0.599	−0.452	0.501	−0.750
2,4-F2Py	0.599	−0.452	0.501	−0.750
2,5-F2Py	0.624	0.241	0.509	−0.475
2-FPy	0.610	−0.149	0.509	−0.452
3,4-F2Py	0.614	−0.046	0.501	−0.750
3-FPy	0.624	0.256	0.502	−0.727

nucleophilic attack (NAK) with a value of 0.051. It is interesting to notice that for all chloropyrroles, N_5 site is more inclined to EAK and H_6 site has a better preference to NAK. Another interesting detail is that chlorine site in chloropyrroles is prone to EAK except for 2,3,4,5-C4Py, where they prefer NAK.

The multiphilic descriptor ($\Delta\omega_k$) for the fluoropyrroles is presented (Figure 8a−i). It is intriguing to take note of the fact

Table 11. TOPKAT-Based Aerobic Biodegradability (AB) and Developmental Toxicity Potential (DTP) Data for Fluoropyrroles Showing Calculated Probability and Discriminant Score

	AB		DTP	
molecule	calculated probability	discriminant score	calculated probability	discriminant score
2,3,4,5-F4Py	0.334	−3.418	0.535	−0.329
2,3,4-F3Py	0.342	−3.223	0.538	−0.259
2,3,5-F3Py	0.324	−3.668	0.549	0.030
2,3-F2Py	0.350	−3.048	0.525	−0.618
2,4-F2Py	0.350	−3.048	0.538	−0.259
2,5-F2Py	0.347	−3.114	0.541	−0.172
2-FPy	0.374	−2.486	0.497	−1.382
3,4-F2Py	0.367	−2.644	0.538	−0.259
3-FPy	0.370	−2.581	0.528	−0.535

that for all fluoropyrroles, H_6 site has preference toward NAK, and fluorine sites to EAK. Another point is that N_5 site is prone to EAK. Further, C_4 site has preference toward EAK for 2,4-F2Py and 2,3,4-F3Py. Hence, the susceptible atomic positions have been identified with multiphilic descriptor.

3.5. Toxicity Analysis on Chloro- and Fluoropyrroles.

While DF descriptors delineated the stability, reactivity, site activeness, and nature of charge transfer with DNA bases, TOPKAT has been utilized to analyze the toxicity of the selected systems. The results of the National Toxicology Program's carcinogenicity bioassays using four rodent models constitute a separate database in TOPKAT. Therefore, the predictions made by TOPKAT on a single chemical can differ greatly among the four rodent models because each prediction is dependent on a different base of experimental data. The toxicity profiles for all of the chlorine-substituted pyrroles (CPy) were extensively studied by TOPKAT 6.2 and are tabulated in Tables 5−8.

From Table 5, studies on male mouse and female mouse showed no sign of carcinogenicity for selected chloropyrroles, with probability ranging from 0.612 to 0.672 and from 0.597 to 0.631, respectively. The computed probability values of 0.540−0.629 for the NTP carcinogenicity call (male rat) model and 0.501−0.519 for NTP carcinogenicity call (female rat) model (Table 6), which is below 0.70, and discriminant scores in the negative range imply that they are noncarcinogens. Table 7 illustrates the computed probabilities for the aerobic

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Table 12. TOPKAT-Based Rat Oral LD_{50} (RO-LD_{50}), Skin Sensitization Data (SSD), and Mutagenicity Data (MD) for Fluoropyrroles Showing Calculated Probability and Discriminant Score

	RO-LD_{50}	SSD		MD	
molecule	calculated probability (g/kg)	calculated probability	discriminant score	calculated probability	discriminant score
2,3,4,5-F4Py	0.105	0.753	−0.801	0.721	−1.755
2,3,4-F3Py	0.075	0.753	−0.801	0.730	−0.864
2,3,5-F3Py	0.101	0.755	−0.748	0.720	−1.820
2,3-F2Py	0.064	0.745	−0.962	0.743	0.224
2,4-F2Py	0.073	0.745	−0.962	0.715	−2.306
2,5-F2Py	0.074	0.738	−1.094	0.719	−1.893
2-FPy	0.102	0.729	−1.264	0.731	−0.777
3,4-F2Py	0.080	0.742	−1.014	0.722	−1.682
3-FPy	0.079	0.736	−1.132	0.695	−3.941

biodegradability and developmental toxicity potential (DTP) model. The computed probability range for aerobic biodegradability is 0.133−0.463 and 0.407−0.525 for the developmental toxicity potential model, which is much lesser and does not produce a positive response. The computed probabilities for rat oral LD_{50}, skin sensitization, and mutagenicity model are shown in Table 8. With 0.145−0.567 g/kg, the rat oral LD_{50} values fall in optimum prediction space (OPS) for all compounds. The computed probability for the skin sensitization model falls within the range of 0.711−0.769, which is greater than 0.70 and possesses a strong sensitization effect. However, with probability values between 0.601 and 0.715 from the Ames mutagenicity model, the selected chloropyrrole is likely to produce a nonmutagenic effect.

The toxicity profiles for the fluorine-substituted pyrroles (FPy) were studied by TOPKAT 6.2 and are tabulated in Tables 9−12.

Table 9 shows that like chloropyrroles, fluoropyrroles also show no sign of carcinogenicity toward male mouse and female mouse. The computed probability values for FPy derivatives range from 0.599 to 0.637 for the NTP carcinogenicity call (male rat) model and from 0.501 to 0.509 for NTP carcinogenicity call (female rat) model are represented in Table 10.

The discriminant scores in the negative range and low probability values imply that they are not carcinogenic. Table 11 illustrates the computed probabilities for the aerobic biodegradability and developmental toxicity potential (DTP) model.

The computed probability ranges for aerobic biodegradability are 0.324−0.374 and 0.497−0.549 for the developmental toxicity potential model, which is much lesser than 0.70 and does not produce a positive response. The computed probabilities for rat oral LD_{50}, skin sensitization, and mutagenicity model are shown in Table 12. With 0.064−0.105 g/kg, the rat oral LD_{50} value gets in optimum prediction space (OPS) for selected systems.

The computed probability for skin sensitization model is in the range of 0.729−0.755, which is greater than 0.70 and possesses a strong sensitization effect. However, for Ames mutagenicity model, the computed probability varies from 0.695 to 0.743. Hence, most of the selected molecules exhibit nonmutagenic effect except 2,3-F2Py, which has a positive discriminant score and may act as a mutagen.

4. CONCLUSIONS

The stability, reactivity, and site selectivity on pyrrole, chloropyrroles, and fluoropyrroles have been analyzed based on the density functional theory-based computational approach. Computed electrophilicity index descriptor identified the least and the most reactive among the selected series of compounds. The chemical reactivity of chloropyrroles (fluoropyrroles) depends on chlorine (fluorine) position in the molecule. The usefulness of ECT in understanding the electron-donating capacity of chloropyrroles (fluoropyrroles) during its encounter with DNA bases has been successfully examined. The preferred site for EAK and NAK in chloropyrroles (fluoropyrroles) has also been identified using the multiphilic descriptor. Further, TOPKAT-based NTP studies showed a significant skin sensitization effect but no carcinogenicity and mutagenicity effect for the selected systems. The present work has indicated that these molecules need to be examined further in the way of their impact on the biological environment in the future for their safe employment in some applications.

5. COMPUTATIONAL DETAILS

The geometries of pyrrole, chloropyrroles, and fluoropyrroles along with DNA bases are optimized using B3LYP/6−311++G**[58−60] available in *Gaussian 16* suite of programs.[61] Frequency calculations confirmed the minimum-energy structures. The numberings of the atom for the selected optimized pyrroles are displayed in Figures 1 and 2. The index of electrophilicity is computed using eq 4. ECT is computed using eq 8. The natural population analysis (NPA)[62] is used for obtaining condensed FF. Then, the multiphilic descriptor ($\Delta\omega_k$) is calculated using eq 5. A library of CPy and FPy molecules are subjected to the toxicity prediction module (TOPKAT v6.2) in the chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) protocol.[45−48]

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Notes

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