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Synthesis, Characterization, Biological Activity, and DFT-Reactivity Assessment of Mn(II), Co(II), and Cu(II) Complexes of a New N_2O Tridentate Schiff Base[1]

M. S. Engin, S. Demir, Ş. Direkel, S. Eymur, S. Çay*, and A. Güder

Giresun University, Giresun, 28200 Turkey
**e-mail: seydahmet.cay@giresun.edu.tr*

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Abstract—Three new homoleptic Schiff base: metal(II) complexes, bis{2-[(pyridin-2-yl) methylene-amino] naphthoxometal(II)} [$M(npa)_2$], (M = Mn(II) (**1**), Co(II) (**2**), Cu(II) (**3**), npa is monoanion of 2-[(pyridin-2-yl)methyleneamino]naphthol), have been prepared and characterized by elemental analyses, FT–IR, ^1H and ^{13}C NMR, and HR-MS-TOF. Antimicrobial activity of the title compounds was tested against six standart bacteria and two standart fungi isolates by microdilution broth assay with Alamar Blue Dye. Biological activity of the complexes has been estimated by using Fukui reactivity indices and frontier molecular orbitals in the framework of conceptual density functional theory.

Keywords: N_2O Schiff bases, 2-picolylamine, antimicrobial activity, Schiff base, metal(II) complexes, reactivity descriptors

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Synthesis of versatile Schiff base compounds and corresponding metal complexes has been of certain challenge for coordination chemists. Presence of both hard/borderline oxygen/nitrogen and soft sulphur donor atoms facilitates coordination of such ligands almost with all metal species bearing stable complexes. Antibacterial, antifungal, antitumor, anti-inflammatory and antipyretic properties of the complexes have been extensively studied [1–8]. Tridentate metal complexes of Schiff bases with N_2O, NO_2, N_2S, and NSO chromophores demonstrate remarkable biological activities [1, 2, 9, 10], essentially within the concept of Tweedy's chelation theory and Overton's correlation [11, 12] between the increment of biological activity of free ligand and complexation with metal ion. Tridentate Schiff bases that contain heterocyclic nitrogen among donor sets enhance biological activities [1, 3, 4, 6, 7]. No studies of antimicrobial acitivity of metal complexes prepared from tridentate *o*-hydroxysalicylaldehyde Schiff bases containing pyridine moiety have been carried out. Only structural characterization and DNA binding studies of 2-picolylamine derivated N_2O Schiff base-metal complexes were presented [13–16]. In the current study, analogous Mn(II), Co(II), and Cu(II) complexes of the flexible Schiff base were synthesized by condensation of 2-picolylamine with 2-hydroxynaphthaldehyde. Their antibacterial and antifungal properties were tested. The Alamar Blue (resazurin) Assay was used for testing proliferation and cytotoxicity in lymphocytes and other cell lines [17]. Non-toxic for cells over long incubation time Alamar Blue is an oxidation-reduction indicator that changes colour from dark blue to bright pink in the presence of bacterial viability as a response to chemical reduction of a growth medium [18-20]. The complexes reported herein were studied *in vitro* against the selected six different standart bacteria: *Staphylococcus aureus* (Methicillin Susceptible) ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Haemophilus influenzae* ATCC 40247, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Pseudomonas aeruginosa* ATCC 27853, and the selected two standart fungi; *Candida albicans* ATCC 14053 and *Candida parapsilosis* ATCC 22019. Reactivity of the complexes was qualitatively assessed by the concepts of Frontier molecular orbitals and Fukui reactivity descriptors that are strictly defined by several approximations in DFT framework. The reactivity orders of the complexes were represented by FMO gaps and Fukui indexes.

[1] The text was submitted by the authors in English.

EXPERIMENTAL

Materials and methods. CHN analysis was carried out on a Costech ECS 4010 CHNS elementel analyser (U.S.A). FT-IR spectra were recorded on a Bruker IFS 66/S, FRA 106/S, Hyperion 1000, Ramanscope II spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ on a Bruker Avance III 400 mHz spectrometer using TMS as the internal standard. HR-MS spectra were measured on a Agilent LC/MS-TOF spectrometer for solutions in acetonitrile.

Synthesis of 2-{[(pyridin-2-yl)methyleneamino]-naphthol}. 2-Hydroxynaphthaldehyde (0.690 g, 4 mmol) and 2-picolylamine (0.438 g, 4 mmol) were dissolved in ethanol (15 mL) and the reaction mixture was refluxed at 70°C for 3 h. The resulting faint orange solution was filtered off while hot, cooled down to room temperature and stored for crystallization. Well-formed coarse crystals precipitated from the solution within one day were filtered off, washed with small amount of cold ethanol and dried in the air. Yield 90%, mp 85–87°C. IR spectrum, ν, cm^{-1}: 1618 (C=N); 1534 (C=C); 3053 $(C–H)_{arom}$; 3303 (O–H). ^{1}H NMR spectrum, δ, ppm: 4.97 s (2H, C<u>H</u>$_2$N), 7.00 s (1H, ArH), 7.23–7.32 m (2H, ArH), 7.39 d (*J* = 8 Hz, 1H, ArH), 7.48 t (*J* = 8 Hz, 1H, ArH), 7.66 d (*J* = 8 Hz, 1H, ArH), 7.70–7.77 m (2H, ArH), 7.96 d (*J* = 4 Hz, 1H, ArH), 8.63 d (*J* = 8 Hz, 1H, ArH), 9.04 s (1H, C<u>H</u>N), 14.83 s (1H, O<u>H</u>). ^{13}C NMR spectrum, δ, ppm: 59.7, 107.4, 118.3, 121.8, 122.8, 123.0, 123.8, 126.6, 128.0, 129.2, 133.5, 136.9, 137.1, 149.7, 156.8, 159.7, 173.8. Calculated, %: C 77.84; N 10.68; H 5.38. Found, %: C 77.65; N 10.50; 4.75.

Synthesis of the complexes. Metal complexes of npa were prepared by reacting a metal(II) perchlorate with the Schiff base solutions as above prepared without further purification. For the synthesis of each complex, metal(II) perchlorate hexahydrate (2 mmol) was dissolved in 10 mL of ethanol and the solution was added dropwise to a stirred solution of npa (2 mmol) and the mixture was stirred for 1 h at room temperature. The obtained precipitate (orange for **1**, brick red for **2** and dark blue for **3**) was filtered off, washed with cold ethanol and dried in the air. Yields, %: 57 (**1**), 65 (**2**), 47 (**3**). Complex **1**: Yield 57%. IR spectrum, ν, cm^{-1}: 1620, ν(C=N); 1539, ν(C=C); 3050, $\nu(C–H)_{arom}$ Found, %: C 69.15; N 9.25; 3.62. $C_{34}H_{26}N_4O_2Mn$. Calculated, %): 70.71; N 9.70; H 4.54. Complex **2**: Yield 65%. IR spectrum, ν, cm^{-1}: 1620, ν (C=N); 1539, ν(C=C); 3050, $\nu(C–H)_{arom}$ Found, %: C 69.77; N 9.13; H 3.87. $C_{34}H_{26}N_4OCo$. Calculated, %: C 70.22; N 9.63; H 4.51. Complex **3**: IR spectrum, ν, cm^{-1}: 1620, ν(C=N); 1542, ν(C=C); 3070, $\nu(C–H)_{arom}$. Found, %: C 68.82; N 9.17; 4.02. $C_{34}H_{26}N_4O_2Cu$. Calculated, %: C 69.67; N 9.56; H 4.47.

Biological Study

Preparation of standart bacteria and fungi isolates. The complexes **1, 2,** and **3** were screened *in vitro* against *Staphylococcus aureus* (MSSA) ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Haemophilus influenzae* ATCC 40247, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603 and *Pseudomonas aeruginosa* ATCC 27853. Standard bacteria isolates were obtained from the American Type Culture Collection. The *in vitro* antifungal activity of the complexes was evaluated against selected two standart fungi isolates: *Candida albicans* ATCC 14053 and *Candida parapsilosis* ATCC 22019 (Fungal isolates were obtained from the American Type Culture Collection). Six different standart bacterial isolates were stored at -80°C and then exposed to room temperature and vitalized by passaging into Blood Agar medium (Merck) and Eosin Methylene Blue (EMB, Merck) Agar medium with testing their purity. Similarly, fungal isolates were vitalized in Sabouraud Dextrose Agar (SDA, Merck) followed by purity control. Bacteria and fungi colonies were taken into sterile glass tubes containing 2 mL Mueller–Hinton Broth (MHB, Merck) medium for bacteria and 2 mL Sabouraud Dextrose Broth (SDB, Merck) medium for fungi and proliferations were incubated by overnight storing in incubator at 37°C. McFarland 0.5 standards were used as turbidity standards in preparation of suspensions of standart bacterial isolates in the range of 10^7 –10^8 cfu per mL in MHB. The amount of final inoculums for performing the antibacterial assay were 10^5 cfu/mL. Same procedure was applied to fungal isolates in SDB medium.

Preparation of the test compounds and Alamar Blue Dye. The compounds **1, 2,** and **3** were dissolved in 10% DMSO, that had no inhibition effect on the tested microorganisms, to obtain 50 mg/mL stock solution. The stock solutions were filtered by 0.45 diametered membrane filter and sterilization was ensured by collecting into a sterile tube. Powder Alamar Blue Dye (Sigma–Aldrich, USA) was used as the indicator stain for detection of antimicrobial activity. The Alamar Blue stock solution (prepared by dissolving 270 mg resazurin in 40 mL of sterile distilled water) was filtered by 0.45 diametered membrane filter and collected into a sterile tube.

Determination of MIC of the compounds. Antibacterial and antifungal activities of the complexes were determined by microdilution broth assay [21] with Alamar Blue Dye. The *in vitro* antimicrobial activity of the complexes was tested in MHB for bacteria and in SDB for fungi by the two fold serial dilution method [21]. The minimum inhibitory concentration (MIC) was adjusted by two fold serial dilution of the tested compounds at descending concentrations ranging from 10.0 to 5.120 μg/mL, in MHB medium containing 10% DMSO and in a sterile 96-well round bottomed microplate. Upon reaching the final volume of 100 μL per well, bacteria inoculum suspension was added to each well containing diluted compounds. The latter two wells were used as negative (the compound and Alamar Blue dye) and positive controls (standart bacterial isolates and Alamar Blue dye), respectively. Alamar Blue dye of 20 μL was added to each well after 20 h incubation at 37°C. The plate was incubated again with Alamar Blue dye for 4 h at 37°C. Well-defined color change from pink to red in the well after incubation was attributed to positive bacterial growth while blue color indicated absence of viability. The MICs corresponding to the greatest dilution of a compound did not show color shift. The same procedure applied for antibacterial study was also followed for antifungal activity tests. The MICs were recorded after 24 h incubation of bacteria and fungi. Amikacin and Amphotericin B were used as standards for bacteria and fungi studies, respectively. All tests mentioned were duplicated.

Computational protocol. Biological activity of molecular species are somewhat associated with their chemical reactivity [22–25]. Fukui functions (*f*), together with molecular electrostatic potential (MEP) are among the popular fundemental reactivity descriptors that are quantitatively applied to chemical reactivity of molecules within the concept of density functional theory [26]. Fukui function is the measure of differential change in electron density (ρ) of a molecule or atom with respect to infinitesimal change of electron number (*N*) at the constraint of a constant external potential (*v*) namely, at a fixed geometry. In this context, these descriptors give information about site reactivities within molecules through the use of electron density.

Since electron density is a discontinuous property with respect to *N* finite difference approximation proposed for definite explanation of the descriptors of a system was introduced elsewhere with the following definitions:

$$\begin{aligned} f^{+}_{v,N}(r) &= \rho_{v,N+1}(r) - \rho_{v,N}(r), \\ f^{-}_{v,N}(r) &= \rho_{v,N}(r) - \rho_{v,N-1}(r), \\ f^{0}(r) &= 1/2[\rho_{v,N+1}(r) - \rho_{v,N-1}(r). \end{aligned} \tag{1}$$

Positive *f* value (f^+) maximized at any region or atom of a molecule is measured by the electron density change upon addition of an electron and denotes to most favorable site for nucleophilic attack of the molecule while negative *f* value (f^-) is measured by the change upon subtraction of an electron and denotes to most suitable site for electrophilic attack. f^0 Termed as dual descriptor [27–30] and approximated to be an average of the former two terms is the measure of radical attack. The Fukui function is computed as the functional derivative of chemical potential (μ) perturbed by *v:*

$$f(r) = \left[\frac{\delta\mu}{\delta v(r)}\right]_N. \tag{2}$$

Within density functional-B3LYP framework, exchange correlation has not derivative discontinuity and μ is equal to orbital energies [31–34].

$$\begin{aligned} \mu^{+} &= E_{\mathrm{LUMO}}, \\ \mu^{-} &= E_{\mathrm{HOMO}}. \end{aligned} \tag{3}$$

In this context, f^+ is strictly equal to LUMO density or energy while f^- is equal to HOMO density or energy.

$$\begin{aligned} f^{+}_{v,N}(r) &= |\phi^{\mathrm{LUMO}}_{v,N}(r)|^2 = \rho^{\mathrm{LUMO}}_{v,N}(r), \\ f^{-}_{v,N}(r) &= |\phi^{\mathrm{HOMO}}_{v,N}(r)|^2 = \rho^{\mathrm{HOMO}}_{v,N}(r), \\ f_{v,N}(r) &= \phi^{\mathrm{LUMO}}_{v,N}(r) - \phi^{\mathrm{HOMO}}_{v,N}(r)^2 = \rho^{\mathrm{LUMO}}_{v,N}(r) - \rho^{\mathrm{HOMO}}_{v,N}(r). \end{aligned} \tag{4}$$

In most cases such as reactivity studies in atomic level, the use of condensed Fukui functions as the reduced form of the functions to atomic scale is more convenient. For an atom *k*, the condensed Fukui functions are following:

$$\begin{aligned} f^{+} &= q_k(N+1) - q_k(N), \\ f^{-} &= q_k(N) - q_k(N-1), \\ f^{0} &= 1/2[q_k(N+1) - q_k(N-1)]. \end{aligned} \tag{5}$$

Here q_k is the electronic population of atom k in the molecule under consideration.

Calculation of Fukui indices is rational for more elaborate interpretation of reactivities of the complexes in terms of conceptual DFT. For this purpose, SPE

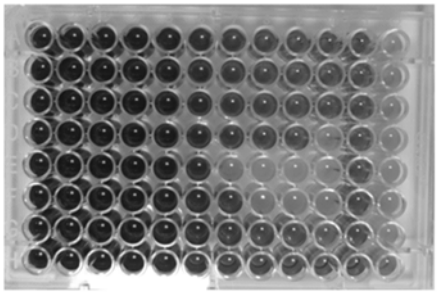

Fig. 1. Antibacterial and antifungal activity (microplate of **2**).

analyses including spin densities were performed using 6-31G(d,p) double zeta basis set at the equilibrium geometries of the complexes optimized at B3LYP/3-21G level. In case of the study reported herein, it is not possible for one to illustrate the regioselectivities of the complexes in atomic scale through condensed Fukui functions in such molecular resolution. But it is inevitable to use Fukui indices from Eqs. (1) and (3). Hence SPE calculations of cationic, anionic and neutral forms of the complexes, related to (N – 1), N, and (N + 1) systems respectively, were performed. Subsequently total SCF densities, natural population analysis (NPA) data for FMOs were extracted from output files. The obtained isosurfaces and 3D contourplots of the complexes were utilized for their biological activities.

RESULTS AND DISCUSSION

Stoichiometries of the complexes were confirmed by weight loss determination. The complexes were insoluble in water or nonpolar organic solvents but soluble in DMF and DMSO.

Characterization of Hnpa. IR spectra of the Schiff base contained an imine band at 1618 cm^{-1} and ^1H NMR spectrum exhibited the singlet at 9.04 ppm of the imine proton. Singlet of the $ArCH_2N$ methylene protons appeared at 4.97 ppm. ^{13}C NMR spectrum demonstrated imine carbon signal at 173.8 ppm and methylene carbon at δ = 59.5 ppm.

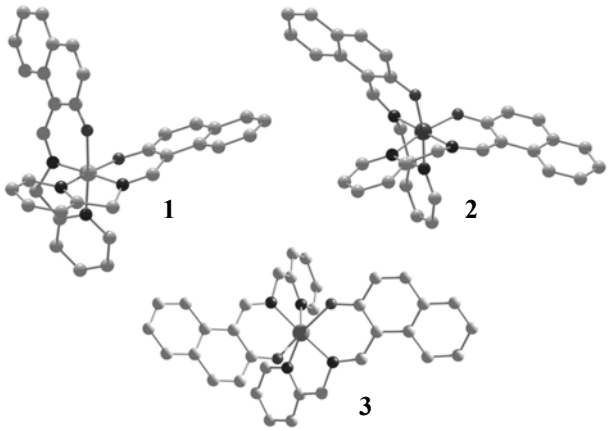

Fig. 2. Optimized structures of the complexes **1–3**.

HR-MS/TOF. TOF-MS spectra of compounds **1, 2,** and **3** exhibited the corresponding distinctive molecular signals.

Biological studies. *Antibacterial and antifungal activities.* The complexes were tested against pathogenic fungal isolates such as *C. albicans* and *C. Parapsilosis* (Table 1). Their MIC values were compared with the amphotericin B standard antifungal drug. MICs were assessed by microdilution broth assay. Antibacterial and antifungal activities assessed with Alamar Blue dye are shown in Fig. 4. Antimicrobial activity of the synthesized compounds in each microplate was evaluated in the first six row for bacteria and in the other two rows for fungi with negative control in 11th wells and positive control in 12th well (Fig. 1).

The most effective antibacterial activity among the complexes was identified for the compound **2.**

Table 1. The antimicrobial activities of the complexes

Complexes	*S.aureus* ATCC 25923	*E.faecalis* ATCC 29212	*H.influenza* ATCC 40247	*E.coli* ATCC 25922	*K.pneumoniae* ATCC 700603	*P.aeruginosa* ATCC 27853	*C.albicans* ATCC 14053	*C.parapsilosis* ATCC 22019
1	640	20	20	1280	2560	1280	1280	160
2	<10	<10	<10	20	160	80	20	<10
3	320	80	160	320	1280	2560	320	320

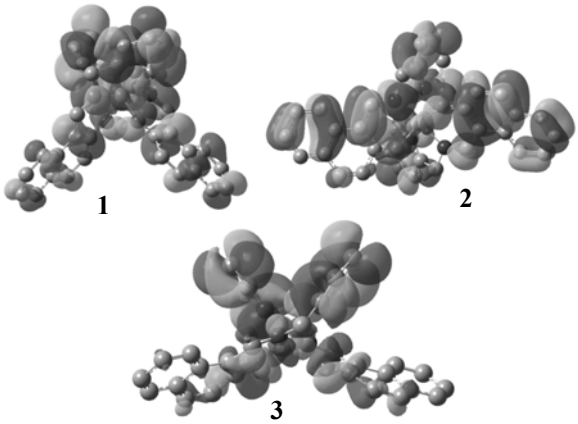

Fig. 3. 3D contourplots of HOMO-LUMO gaps for the complexes.

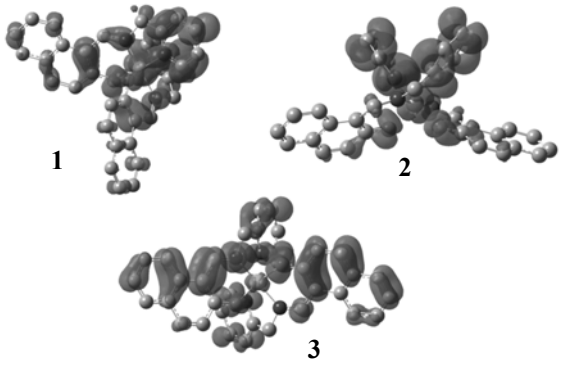

Fig. 4. Squared isosurfaces of f^0 for the complexes with the isovalues of 0.001 a.u.

Similarly, the most and the least effective antifungal activities among the complexes were exhibited by **2** and **1** respectively.

The highest antibacterial activity was observed for *E. faecalis* (MIC 10–80 μg/mL) while the lowest one was observed for *K. pneumoniae* (MIC: 40–2560 μg/mL). As a general trend, the complexes exhibited more effective activity towards *C. parapsilosis* relative to *C. albicans*.

Conceptual density functional view to reactivities of the complexes. Initial geometries of the complexes for optimization were randomly constructed partly utilizing experimental spectroscopic data. The optimized structures (Fig. 2) were approved as local minima by subsequently performed frequency analyses. Although the values of Fukui functions reasonably depend on the population analyses method and the combination of basis functions used, 6-311G (2d,p) basis set was arbitrarily chosen as sufficiently polarized and large basis set for the NPA analyses of the optimized structures of the complexes within tolerable computational expense. For definition of the descriptors according to finite differences method, populations of valence shell spin orbitals from NPA data were used since the use of spin orbitals for these open-shell systems was reasonable.

Nature of reactivity and reactive sites of the complexes towards bacteria and fungi under study was exactly uncertain either nucleophilic or electrophilic. Therefore the most reasonable approach to predict the reactive sites of the complexes was to elucidate gap values and isosurfaces and 3D contourplots of dual descriptors that were actually combinations of the indices for both nucleophilic and electrophilic attacks. A reasonable difference of the gap value of **2** from the others fairly demonstrated its highest reactivitiy in terms of HOMO-LUMO gaps (Fig. 3). Isosurfaces obtained from squares of HOMO-LUMO difference densities of the complexes yielding f^0 are presented in Fig. 4. Distribution of f^0 was populated intensely on picolylamine sides in **1** and **2** while it was more delocalized over naphthaldimine sides in **3.** Hence it could be deduced (Fig. 4) that higher delocalization of f^0 in **3** made it more stable and less reactive. The large energy gap for **3** (Table 2) also confirmed such statement. The proximities of gap values of **1** and **2** were also confirmed by their similar f^0 distributions (Figs. 3 and 4). Isosurfaces f^0 of the complexes

Table 2. Energy gaps and condensed-to-atom Fukui indices of the complexes

Energy gap calculated using HOMO-LUMO differences					Condensed-to-atom Fukui indices, for the atoms in brackets				
molecule	f^+	f^-	f^0	$E_{HOMO–LUMO}$, eV	molecule	f^+	f^-	f^0	$E_{HOMO–LUMO}$, eV
1	–	–	–	4.9829	Mn (**1**)	0.19526	0.14200	0.229000	–
2	–	–	–	4.4709	Co (**2**)	0.00071	0.26275	0.071330	–
3	–	–	–	6.4700	Cu (**3**)	0.30861	0.01930	0.163955	–

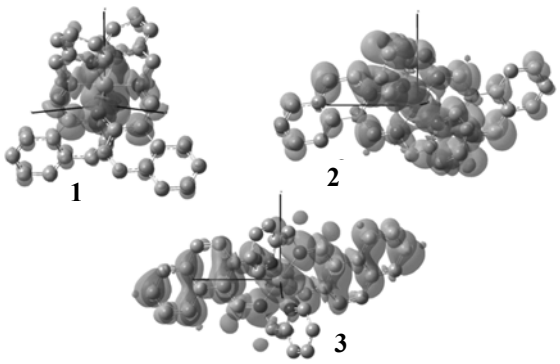

Fig. 5. Isosurfaces f^0 of the complexes from difference spin densities with the isovalues of 0.02 a.u.

calculated from the differences of the spin densities are presented in Fig. 5. The blue regions indicate the sites favoring nucleophilic attack while the purple regions indicate the sites for electrophilic attack. The predominance of purple in **2** indicated the electrophilic nature of it and by contrast, these of blue in both **1** and **3** indicated their nucleophilic nature**.** Besides the highest f^- value for Co (Table 2) the data implied indirectly the common oxidation tendency of the metal.

CONCLUSIONS

Three analogous complexes of a tridentate flexible Schiff base ligand have been prepared and characterized by spectroscopic methods. The compounds were screened against the selected six bacteria and two fungi. Several compounds demonstrated antimicrobial activity and upon further studies, those can be evaluated as new therapeutic agent against bacteria and fungi. Reactivity of the compounds towards the organisms considered have been tested by computing local Fukui functions including dual descriptor. Compulsorily, the reactivities have been conjectured to be either nucleophilic or electrophilic in order to be assessed within the concept of reactivitity indexes. The results were in good accordance with the experimental data.

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