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Published in the Slovak Republic  
European Journal of Molecular Biotechnology  
Has been issued since 2013.  
E-ISSN: 2409-1332  
2019, 7(1): 8-16

DOI: 10.13187/ejmb.2019.1.8  
[www.ejournal8.com](http://www.ejournal8.com)



## Regioselectivite and Reactivity of the Pyridinein Nucleophilic Substitution Reaction: DFT Study

M. El idrissi <sup>a, \*</sup>

<sup>a</sup>Chouaïb Doukkali University, El Jadida, Morocco

### Abstract

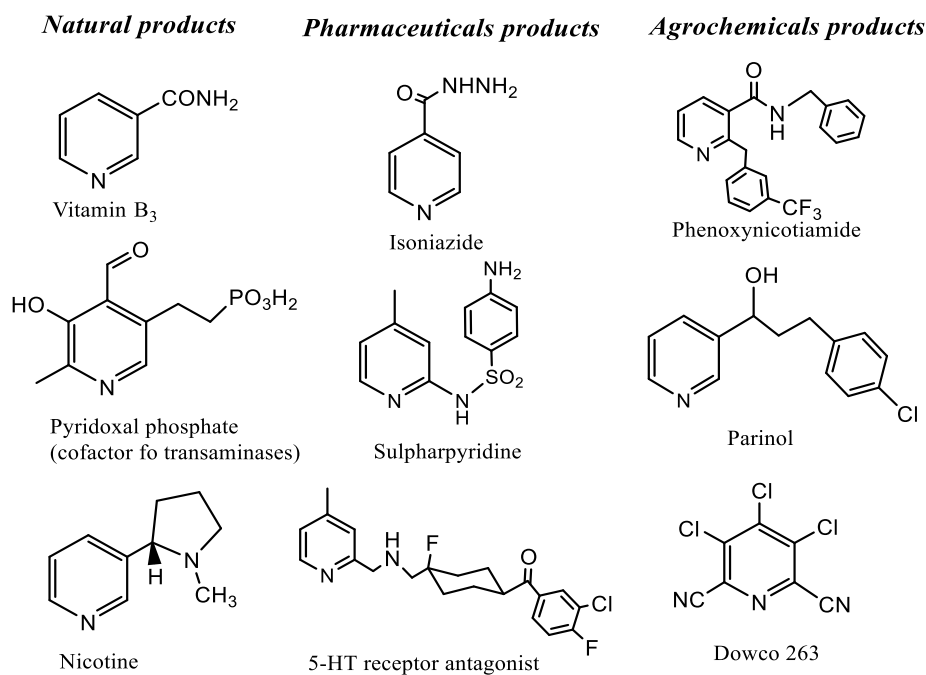
In this work, we theoretically studied the regioselectivity experimentally observed in the substitution reactions between pyridine and nucleophile (KOH, NaNH<sub>2</sub> and EtMgX). This work was done using the DFT method at the B3LYP/6-31G (d) level. The analysis of the OMF, ESP and the reactivity indices derived from the DFT confirm the regioisomeric path of these reactions. The analysis of the energies of the products shows that these substitution reactions favor the regioselectivity, moreover we examined the pyridine like catalyst in the reaction alkylation, and our study shows that pyridine is a good catalyst for esterification reactions. The results obtained are in agreement with the experimental data.

**Keywords:** Density Functional Theory, Pyridine, Becke 3-Parameter Lee-Yang-Parr, Frontier Molecular Orbital, The global DFT indices, Parr functions.

### 1. Introduction

The chemistry of heterocyclic products is one of the most complex branches of organic chemistry (Boukiss et al., 2017). It is even exciting for, its theoretical proposition, for the variety of its synthetic procedures, and for the pharmacological and industrial connotation of heterocyclic products (Arrieta et al., 2007; Aucagne et al., 2007; Wang et al., 2012; Zaki et al., 2017). A field of such importance and essential complexity should be made as gladly accessible as possible, and to be short of a current detailed and comprehensive presentation of heterocyclic chemistry is so fervently felt. It is the aim of the present series to fill this gap by specialist presentations of variety branches of heterocyclic chemistry. Pyridine is a limpid, slightly yellowish liquid with an unpleasant and penetrating odor (sour, putrid and fish-like). Pyridine derivatives such as Vitamin B<sub>3</sub>, Vitamin B<sub>6</sub> (Figure 1) and pyridoxal phosphate which is an essential coenzyme in a significant number of amino acid reactions (transaminations, decarboxylations and racemisations).

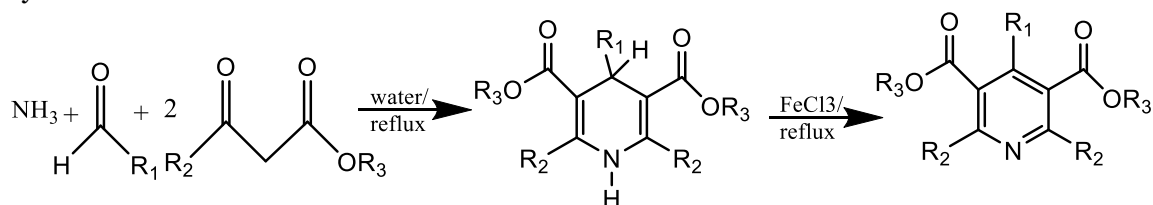
\* Corresponding author  
E-mail addresses: [idrissi\\_82@hotmail.fr](mailto:idrissi_82@hotmail.fr) (M. El idrissi)



**Fig. 1.** Pyridine and pyridine derivatives

Pyridines (or azines) are organic compounds widely used in agrochemicals and pharmaceuticals (Davis et al., 2005). Pyridines are used to make drugs, insecticides, herbicides, dyes, paints, disinfectants and explosives. Pyridines also have the function of a catalyst in certain chemical reactions such as condensation or halogenation (introduction of halogen atoms in a reaction) (Corma, 1995). Pyridine is also widely used as an organic solvent; it is also used to denature the commercial ethanol used for the same purpose. It is also used in the manufacture of many pharmaceutical products, rubber and as a waterproofing, bactericidal and insecticide.

Pyridine is prepared by the method of synthesis of Hantzsch (Hantzsch, 1981; Henry, 2004), that is a reaction between an aldehyde, with two equivalents of  $\beta$ -keto ester and a nitrogen donor makes it possible to obtain a dihydropyridine which by oxidation (by HNO<sub>3</sub>, Ce (IV) or a quinone), the solvent utilized may be water or ethanol (Figure 3). Pyridines can be extracted from bone tars (Dippel animal oils) by the action of dilute sulfuric acid. After evaporation, it is taken up with sodium hydroxide and distilled.



**Fig. 2.** The method of synthesis of Hantzsch

Our aim in this work is to present a theoretical study of substitution reactions of the pyridine and compared the results of our computations with experimental outcomes obtainable in the literature.

## 2. Computational methods

DFT computations were carried out using the B3LYP functional (Yanai et al., 2004), together with the standard 6-31(d) basis set (Yanai et al., 1982). The optimizations have been realized using the Bery analytical gradient optimization method. All computations have been shown with the Gaussian 09 suite of programs (Frisch et al., 2009). The global electrophilicity index (Parr et al., 2009)  $\omega$ , was given by the following expression  $\omega = \frac{\mu^2}{2\eta}$ , in terms of the electronic chemical

potential  $\mu$  and the chemical hardness  $\eta$ . Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO,  $\varepsilon_H$  and  $\varepsilon_L$  as  $\mu = \frac{\varepsilon_H + \varepsilon_L}{2}$  and  $\eta = \varepsilon_H - \varepsilon_L$ , respectively. The empirical nucleophilicity index  $N$  (Domingo et al., 2008; Domingo, Pérez 2011), based on the HOMO energies obtained within the Kohn-Sham (Kohn, Sham, 1965), and defined as  $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$ . the nucleophilicity was referred to tetracyanoethylene (TCE). This choice allowed us to handle conveniently a nucleophilicity scale of positive values. Electrophilic  $P_k^+$  and nucleophilic  $P_k^-$  Par functions were obtained through analysis of the Mulliken atomic spin density (ASD) of the radical anion and radical cation of the reagents. The local electrophilicity and the local nucleophilicity indices were evaluated using the following expressions  $\omega_k = \omega P_k^+$  and  $N_k = N P_k^-$  (Ourhriss et al., 2018; El Haib et al., 2018; Ourhriss et al., 2017; El Idrissi et al., 2017; Zeroual et al., 2017a; Zeroual et al., 2017b; Zeroual et al., 2017c; Zeroual et al., 2017d; Zoubir et al., 2017a; Zoubir et al., 2017b; Zoubir et al., 2017c; Zeroual et al., 2017; Zeroual et al., 2017; El Idrissi et al., 2017; Zoubir et al., 2016; Zeroual et al., 2016; El Idrissi et al., 2016; Zeroual et al., 2015a; Zeroual et al., 2015b; Zeroual et al., 2015c; Zeroual et al., 2015d; Zeroual et al., 2015e; Zeroual et al., 2015f; Zeroual et al., 2015g; Zeroual et al., 2015h; Barhoumi et al., 2015; Ryachi et al., 2015; Zeroual et al., 2014a; ; Zeroual et al., 2014b; ; Zeroual et al., 2014c; El Idrissi et al., 2013). The stationary points were characterized by frequency computations in order to verify that TSs have one and only one imaginary frequency. Intrinsic reaction coordinate (IRC) (Fukui, 1970) pathways were traced to verify the connectivity between minima and associated TSs.

### 3. Results and discussion

The current theoretical study has been divided in seven parts: (1) an examination of the conceptual DFT indices of the reagents involved in electrophilic and nucleophilic substitution reaction of pyridine with KOH, NaNH<sub>2</sub> and dichloromethane. (2) Next, the investigation of the HOMO, LUMO and ESP of the reagents. (3) Then, thermodynamic examination of these reactions to understand the regioselectivity observed. (4) After that, the theoretical study of reaction between pyridine and EtMgX, (5) Moreover, scrutinizing a pyridine as a catalyst in acylation reactions, (6) in addition, the theoretical study of aromatic electrophilic substitution of pyridine. (7) Finally, Thermodynamic study of the electrophilic substitution reaction of pyridin-2-amine.

#### 3.1 The conceptual DFT indices of the reagents involved in substitution reaction of pyridine with KOH and NaNH<sub>2</sub>

The global DFT indices, namely the electronic chemical potential  $\mu$ , chemical hardness  $\eta$ , electrophilicity  $\omega$  and nucleophilicity  $N$ , are given in Table 1.

**Table 1.** B3LYP/6-31G(d) chemical hardness, electronic chemical potential, electrophilicity, nucleophilicity in eV, of the pyridine, KOH and NaNH<sub>2</sub> there total energies

	$\eta$	$\mu$	$\omega$	$N$	$\Delta N_{max}$	Energy
Pyridine	6.26	-3.74	1.11	2.65	0.59	-248.284973
KOH	2.42	-2.54	1.33	5.77	1.04	-675.7130626
NaNH <sub>2</sub>	2.29	-2.76	1.67	5.61	1.20	- 218.2212268

The electronic chemical potential of pyridine, -3.74 eV, is higher than that of acetic dichloromethane, -4.43 eV, indicating that along a polar reaction the global electron density transfer (GEDT) will flux from the pyridine framework towards the dichloromethane. The electrophilicity  $\omega$  and nucleophilicity  $N$  indices of the simplest pyridine are 1.11 and 2.65 eV, being classified on the borderline of marginal electrophiles and as a strong nucleophile within the electrophilicity and nucleophilicity scales. On the other hand, dichloromethane has a global electrophilicity  $\omega$  index of 1.22 eV and a nucleophilicity  $N$  index of 1.10 eV, being classified as a strong electrophile and as a marginal nucleophile.

Consequently, it is expected that the , dichloromethane participates as a good electrophile towards the strong nucleophilic pyridine.

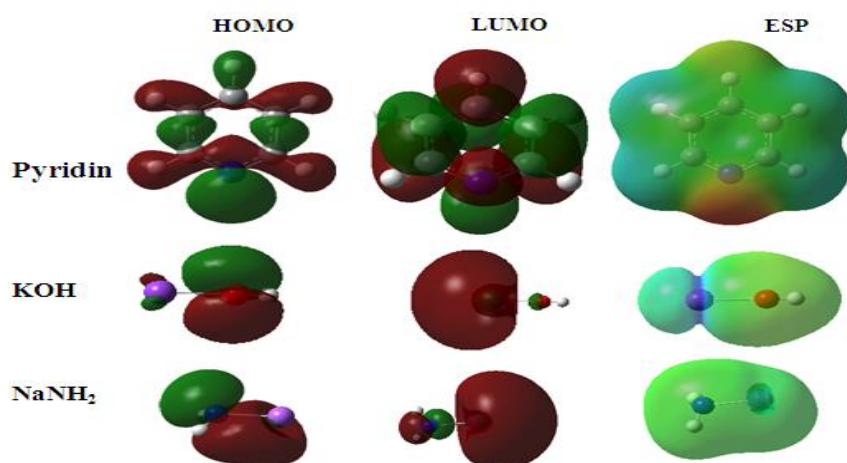
Other hand the electronic chemical potential of KOH and NaNH<sub>2</sub>, -2.42, -2.76 eV, are higher than that of pyridine, -3.74 eV, indicating that along a polar reaction the global electron density transfer) will flux from the KOH and NaNH<sub>2</sub> framework towards the pyridine. The electrophilicity  $\omega$  and nucleophilicity N indices of the simplest KOH and NaNH<sub>2</sub> are 1.33, 1.67 and 5.77, 5.61 eV, being classified on the borderline of marginal electrophiles and as a strong nucleophile within the electrophilicity and nucleophilicity scales.

Consequently, it is expected that the , pyridine participates as a good electrophile towards the strong nucleophilic KOH and NaNH<sub>2</sub>.

### 3.2 The analyze of the HOMO, LUMO and ESP of the reagents

As the non-symmetric reagents, the preliminary two-center interaction involving the most electrophilic center of the electrophile and the most nucleophilic center of the nucleophile.

To pinpoint the actives regions of these reagents, we have illustrated in Figure 3 the density of the HOMO, LUMO orbital and ESP of the reagents.

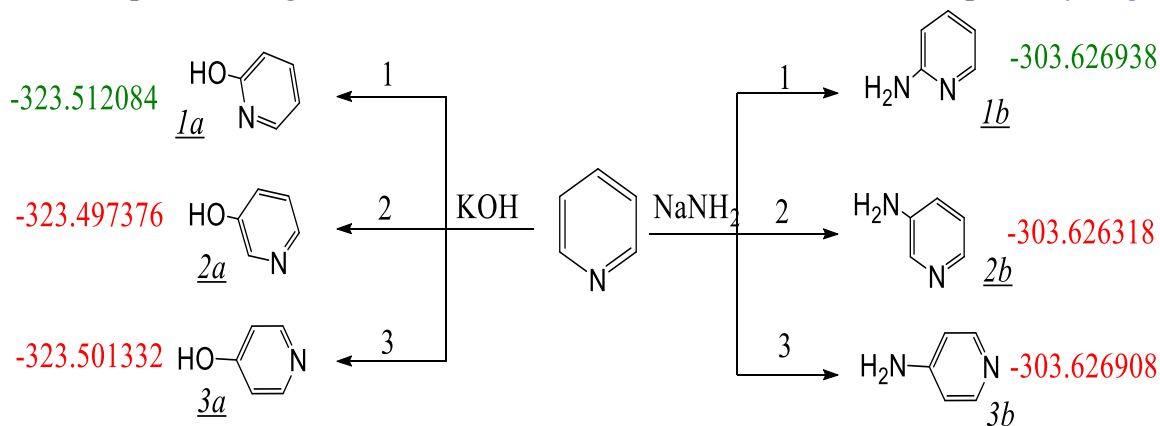


**Fig. 3.** The density of the HOMO, LUMO orbital and ESP of the reagents

According to the density of the HOMO orbital of the reagents, we find that the HOMO orbital is located on the nitrogen atom and para carbon atom of pyridine, for the KOH, NaNH<sub>2</sub> and DCM molecules is located respectively on the oxygen atom, the nitrogen atom and the atom of chlorine. This result is confirmed by EPS these centers possess a red color what to indicate that these centers carry a negative charge.

### 3.3 Thermodynamic Study of the substitution reaction of pyridine with KOH and NaNH<sub>2</sub>

Due to the asymmetry of the pyridine, the substitutions reactions between pyridine and nucleophiles (KOH and NaOH) can take place along three regioisomeric pathways, the ortho, the meta and para, leading to the formation of the 1a, 2a, 3a, 1b, 2b and 3b, respectively (Figure 4).

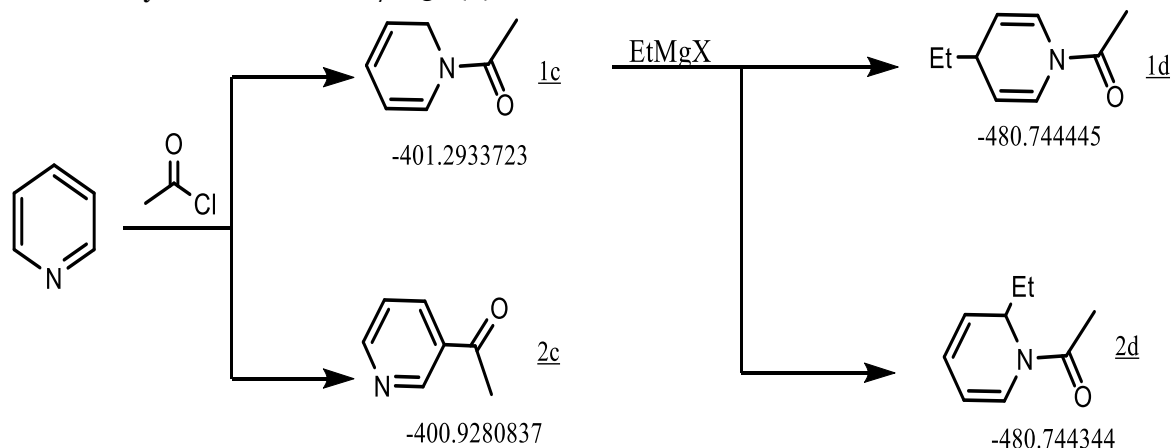


**Fig. 4.** Studied competitive regioisomeric channels associated with the substitutions reactions between pyridine and nucleophiles (KOH and NaOH). (energies in Atomic Unit)

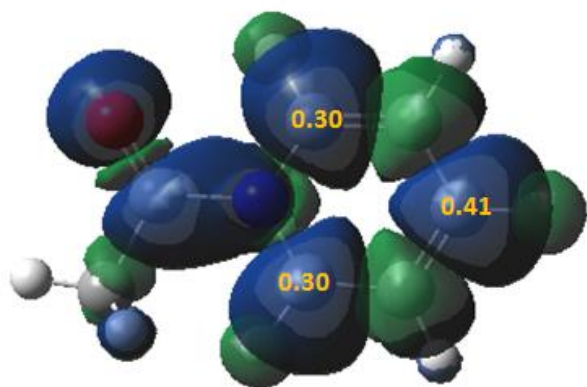
The gas phase formations of the products 1a, 2a, 3a, 1b, 2b and 3b are: -323.512084 (1a), -323.497376 (2a), -323.501332 (3a) -303.626938 (1b), -303.626318 (2b) and -303.626908 (3b) A.U. The conclusion can be drawn from these energy results, the formation of the products 1a and 1b are favored in good agreement.

### 3.4 Understanding the regioselectivity in reaction between pyridine and EtMgX

Electrophilic aromatic substitutions are difficult to realize because pyridine is less reactive than benzene. In this part we study the reaction between pyridine and acetyl chloride, after that we study the reaction between the product obtained and EtMgCl to examine the regioselectivity experimentally observed. In Figure 5, we show the reaction paths and the energies of the products obtained by the method DFT/6-31 (d).



**Fig. 5.** Studied competitive regioisomeric channels associated with the substitutions reactions of pyridine (energies in Atomic Unit)



**Fig. 6.** 3D representations of the ASD of the radical cation the electrophilic  $P_k^+$  Parr functions 1-acetylpyridin-1-ium

The energy of the product 1c. (-401.2933723) is lower than the product energy 2c (-400.9280837), which shows that the product 1c is thermodynamically favorable, moreover the energy of the product 1d is (-480.744445) is lower than the energy of the product 2d (-481.744344) which shows that the product 2d is thermodynamically favorable. In Figure 7 we have illustrated the electrophilic functions of Parr of the product 1c, according to this figure we find that the value of electrophilic functions of Parr in the carbon atom 4 is greater than the value at the carbon atom 1, which confirms that the nucleophilic attack is favorable in the carbon 4.

### 3.5 Pyridine as a catalyst in acylation reactions

The central principle of catalysis lies in the fact that the active sites are indeed involved in the intermediate stages of the reaction, but that they are regenerated at the end of the process, thus

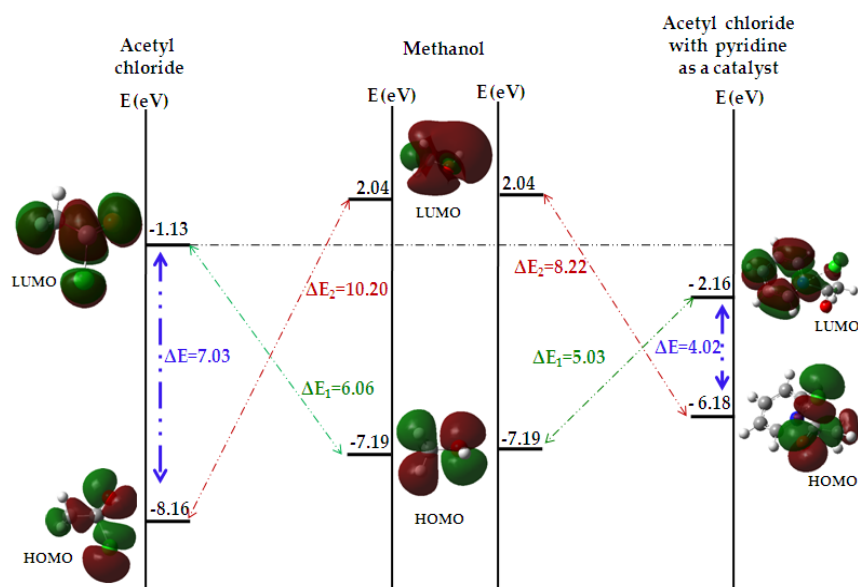


recovering their initial characteristics, the catalyst is therefore not consumed during the reaction: it can thus be used in limited quantities and act efficiently for long periods without the need for replacement. In this section, we examined the effect of pyridine as catalysts on the esterification reaction between methanol and Acetyl chloride.

We have reassembled in Table 2 the energy of the HOMO, LUMO orbital and the energy gap between the two frontiers orbital of the methanol, acetyl chloride and acetyl chloride with pyridine, and in Figure 7 we have illustrated the maps of the HOMO, LUMO orbital and the energy gap between the two orbital.

**Table 2** B3LYP/6-311G(d) the energy of the HOMO, LUMO orbital and the energy gap between the two frontiers orbital of the two partners

	Methanol	Acetyl chloride	Acetyl chloride + pyridine
HOMO	-7.19	-8.16	-2.16
LUMO	2.04	-1.13	-6.18
$ E_{Methanol}^{HOMO} - E_{Acetyl}^{LUMO} $	-----	6.06	5.03
$ E_{Methanol}^{LUMO} - E_{Acetyl}^{HOMO} $	-----	10.20	8.22



**Fig. 7.** 3D representations of the HOMO, LUMO of methanol acetyl chloride and acetyl chloride with pyridine

We note from Table 2 and Figure 7 that the energy gap between the HOMO and LUMO orbital of the reagents without pyridine as a catalyst is of order:  $\Delta E_1 = 6.06$ ,  $\Delta E_2 = 1.20$  and  $\Delta E = 7.03$ . When pyridine is used as a catalyst, the difference becomes of order:  $\Delta E_1 = 5.03$ ,  $\Delta E_2 = 8.22$  and  $\Delta E = 4.02$ . Therefore the presence of pyridine as a catalyst promotes esterification reactions in good agreement with experimental observations.

#### 4. Conclusion

In this chapter, we have discussed the regioselectivity of the substitution reactions between pyridine and KOH,  $\text{NaNH}_2$  and  $\text{EtMgX}$ , this work was done using within Density Functional Theory at the B3LYP / 6-31G (d) level. Analysis of the conceptual DFT indices indicates that these reactions are highly regioselective, in addition our study shows that pyridine is a good catalyst for esterification reactions.

## 5. Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper. Also, they declare that this paper or part of it has not been published elsewhere.

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