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Chemical-quantum determination of the interaction type of leflunomide and collagen and its influence on arthritis

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***Abstract*—** *In recent years, researchers have evaluated the clinical efficacy and safety of Leflunomide (LEF) and other medications for the treatment of rheumatoid arthritis (RA). The objective of this work was chemical-quantum calculus and determination of the interaction type of LEF and collagen and its influence on arthritis. We obtained the information about the collagen of The National Center for Biotechnology Information (NCBI). It was obtained the formula of the LEF on the page of PubChem. The quantum calculations we carry out with the hyperchem software. These calculations were made in other articles already published by us. We concluded that 13 interactions of 40 calculated are significant. These 13 interactions show that only two of them are oxidant and the other 11 are reductive.*

Keywords*— *Quantum chemistry, Leflunomide, Collagen, Arthritis, Amino Acid.

I. INTRODUCTION

In recent years, researchers have evaluated the clinical efficacy and safety of LEF (figure 1) and other medications for the treatment of rheumatoid artitis (RA). In their results, they announced that, in the treatment of RA with these combinations, it presented the characteristics of remarkably lowering the levels of laboratory indices. [1-3] In other studies, it was concluded that a weekly dose of 50 mg of LEF showed similar benefits to the 10 mg daily dose of the same medication in the treatment of moderate to moderate rheumatoid arthritis. [4] We also compared the short-term efficacy of LEF and Methotrexate in the treatment of RA and did not find significant statistical differences. [5] They evaluated the clinical efficacy and safety of LEF as a new immunosuppressive medicine in lupus nephritis through a meta-analysis. LEF is a promising therapy for the treatment of lupus nephritis, mainly because of the efficacy and favorable safety profile determined by a meta-analysis. [6]

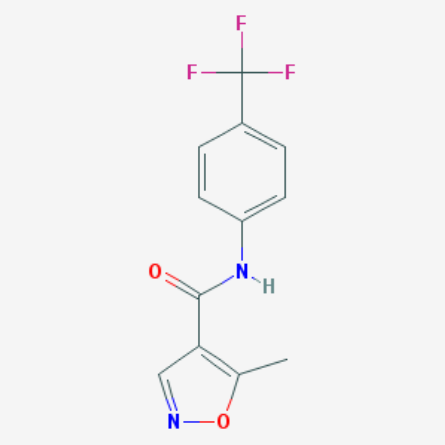

Fig.1: Leflunomide. IUPAC Name: 5-methyl-N-[4-(trifluoro methyl) phenyl]-1,2-oxazole-4-carboxamide

A proportion of patients who achieved significant clinical benefit after an adequate trial of LEF was evaluated. A significant proportion of patients, most of whom had previously failed treatment with methotrexate, were able to respond to the disease with LEF with a low risk of adverse effects, suggesting that treatment with LEF may be a reasonable and cost-effective strategy in the face of

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biological therapy. [7] It was also shown that LEF could reduce the signs and symptoms of rheumatoid arthritis (RA) with regression in structural damage. Lung involvement is one of the extra-joint manifestations of rheumatoid arthritis and can occur due to any disease itself, or with medications used in the treatment. They presented 4 cases with rheumatoid arthritis that developed pulmonary nodules with LEF therapy. [8] On the other hand, a retrospective study was carried out evaluating the side effects of LE Fin 40 patients. LEF therapy was maintained in all patients and hypoglycemia regressed at variable intervals of no more than six months. They investigated that the active metabolite of LEF A77 1726, was able to block pre-established cardiac hypertrophy in mice. Other researchers, investigated the protective effects of LEF as a new immunosuppressant, on interstitial tubule lesions in a model of diabetic nephropathy in rats. These findings suggest that LEF protects the renal lesion of diabetic rats and that it could through the inhibition of OPN / TGF-b1 (osteopontin / beta 1 growth factor) mediated by extracellular cells, matrix deposition and tubulointerstitial fibrosis, as well as its inhibition on myofibroblast epithelial tubular transdifferentiation. [9]

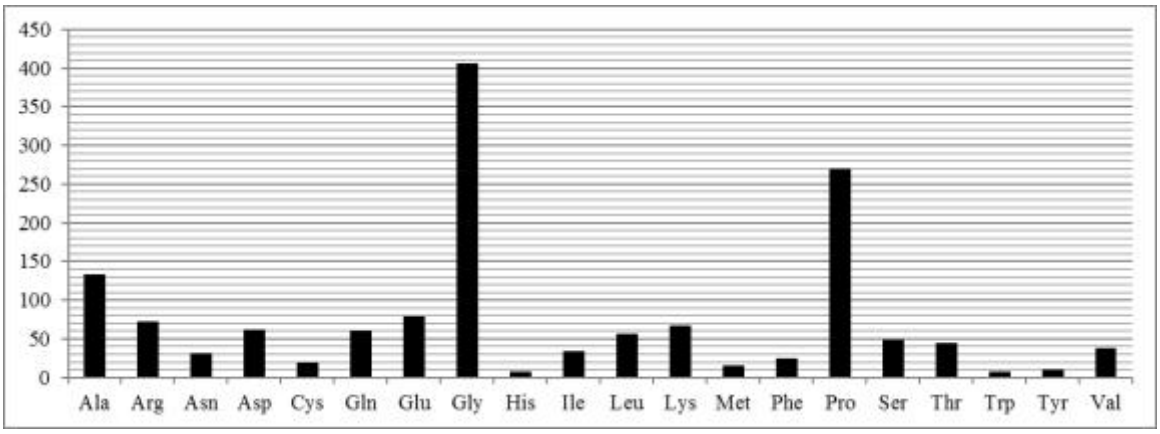

Fig.2: Graph of the amino acid content of human collagen.

Table.1: Calculation of the ETCs of the LEF in comparison with molecular oxygen and water.

No	Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
1	O_2	H_2O	-10.733	4.059	14.792	-0.038	0.171	0.209	70.775
2	O_2	LEF	-10.733	-0.484	10.249	-0.038	0.140	0.178	57.579
3	O_2	O_2	-10.733	-0.982	9.751	-0.038	0.138	0.176	55.403
4	H_2O	H_2O	-12.316	4.059	16.375	-0.127	0.171	0.298	54.950
5	H_2O	LEF	-12.316	-0.484	11.832	-0.127	0.140	0.267	44.315
6	LEF	H2O	-9.246	4.059	13.305	-0.135	0.171	0.306	43.480
7	H_2O	O_2	-12.316	-0.982	11.334	-0.127	0.138	0.265	42.770
8	LEF	LEF	-9.246	-0.484	8.762	-0.135	0.140	0.275	31.862
9	LEF	O_2	-9.246	-0.982	8.264	-0.135	0.138	0.273	30.271

The initiation and monitoring practices of rheumatologists in Australia using LEF were also evaluated. The choice of the initial dose of LEF among the Australian rheumatologists who responded varied considerably. [10] Other researchers studied the profile of side effects and survival characteristics of LEF used in a regional population of patients in New Zealand (NZ). They concluded that their studies suggest a better profile of side effects and better survival of the drug for LEF than suggested by previous studies with a survival comparable to that of methotrexate.

II. MATERIALS AN METHODS

We obtained the information about the collagen of "The National Center for Biotechnology" Information (NCBI): LOCUS CO2A1_HUMAN 1487 aa linear PRI 10-OCT-2018 DEFINITION Rec Name: Full=Collagen alpha-1(II) chain; Alt Name: Full=Alpha-1 type II collagen;

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Contains: Rec Name: Full=Collagen alpha-1(II) chain; Contains: Rec Name: Full=Chondrocalcin; Flags: Precursor. ACCESSION P02458 VERSION P02458.3 DBSOURCE Uni Prot KB: locus CO2A1_HUMAN, accession P02458; class: standard.

We obtained the formula of the LEF on the page of PubChem figure1.

In Figure 2 the graph is presented. You can see that Gly is the most abundant amino acid of all its structural composition; while Trp is the amino acid with fewer units.

In Table 1 it can be seen that the lowest value of ETC corresponds to the LEF-O_2 interaction; This means that the LEF is easily oxidized. It can also be seen that the LEF-H_2O interaction is not as deep in the quantum well; this indicates that the LEF is not very soluble in water.

Table 2 shows the calculations of two new concepts. The quantum molecular impedance is relative to water (QMIRW) and the quantum molecular conductance relative to water (QMCRW). With these two concepts, the reader will better understand the concept of ETC.

We can observe in this table 2 that the LEF-O2 interaction has almost half the value of the valence electron jump impedance of LEF towards O_2 than the jump of H_2O to another molecule of H_2O. With the conductance, the opposite happens.

The quantum calculations we carry out with the hyperchem software. These calculations were made in other articles already published by us. [11-15]

III. RESULTS AND DISCUSSIONS

We characterize human glycogen with the software model 6000. [18] Information on the sequencing of this protein was taken from the NCBI database.

Table.2: Calculation of MQIRW and MQCRW. This calculation is based on the ETCs in Table 1.

No	Reducing agent	Oxidizing agent	*MQIRW	**MQCRW
1	O_2	H_2O	1.288	0.776
2	O_2	LEF	1.048	0.954
3	O_2	O_2	1.008	0.992
4	H_2O	H_2O	1	1
5	H_2O	LEF	0.806	1.240
6	LEF	H2O	0.791	1.264
7	H_2O	O_2	0.778	1.285
8	LEF	LEF	0.580	1.725
9	LEF	O_2	0.551	1.815

**Molecular quantum impedance relative to water (MQIRW)*
***Molecular quantum conductance relative to water (MQCRW)*
The QMIRW and the QMCRW should not be confused with traditional impedance and conductance.
These concepts are similar; but, not the same.

Table.3: This table shows the 13 most likely and strongest interactions of 40 calculated.

No.	Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
13	LEF	Thr	-9.246	0.832	10.078	-0.135	0.191	0.326	30.914
12	LEF	Lys	-9.246	0.943	10.189	-0.135	0.195	0.330	30.875
11	LEF	Pro	-9.246	0.792	10.038	-0.135	0.191	0.326	30.791
10	LEF	Gln	-9.246	0.755	10.001	-0.135	0.192	0.327	30.584
9	LEF	Asn	-9.246	0.644	9.890	-0.135	0.193	0.328	30.153
8	LEF	Ser	-9.246	0.565	9.811	-0.135	0.198	0.333	29.462
7	LEF	Arg	-9.246	0.558	9.804	-0.135	0.199	0.334	29.353
6	LEF	Tyr	-9.246	0.293	9.539	-0.135	0.193	0.328	29.081
5	*LEF	*Glu	-9.246	0.438	9.684	-0.135	0.201	0.336	28.822
4	*LEF	*Met	-9.246	0.145	9.391	-0.135	0.192	0.327	28.719
3	*His	*LEF	-9.307	-0.484	8.823	-0.169	0.14	0.309	28.555
2	*LEF	*Asp	-9.246	0.420	9.666	-0.135	0.204	0.339	28.514
1	*Arg	*LEF	-9.176	-0.484	8.692	-0.165	0.14	0.305	28.499

**These interactions are the five highest and strongest probability anchor points of the 41 calculated.*

In Table 3, we can see the 13 interactions of 40 calculated. These 13 interactions show that only 2 of them are oxidant and the other 11 are reductive. The five most reliable and most probable interactions of these are

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indicated with one *. Within these five interactions are the interactions of the LEF with His and Arg in oxidizing form. Therefore, these LEF interactions are the most dangerous because they are oxidants.

IV. CONCLUSIONS

In Table 4, we summarize the most significant interactions for LEF anchors in collagen amino acids.

Table.4: Summary of the most significant interactions.

Number	AA	Units	Percentages	
1	Ala	134	9.01%	
2	Arg	72	4.84%	Oxidative anchoring (1)
3	Asn	32	2.15%	
4	Asp	62	4.17%	Reductive anchoring (2)
5	Cys	19	1.28%	
6	Gln	60	4.03%	
7	Glu	79	5.31%	Reductive anchoring (5)
8	*Gly*	*406*	*27.30%*	*Maximun Units*
9	His	8	0.54%	Reductive anchoring (3)
10	Ile	34	2.29%	
11	Leu	56	3.77%	
12	Lys	67	4.51%	
13	Met	16	1.08%	Reductive anchoring (4)
14	Phe	25	1.68%	
15	Pro	270	18.16%	
16	Ser	48	3.23%	
17	Thr	44	2.96%	
18	*Trp*	*7*	*0.47%*	*Minimun units*
19	Tyr	10	0.67%	
20	Val	38	2.56%	
	Total	1487	100.00%	

The numbers placed in parentheses indicate their position in table 3.

The research hypotheses were fulfilled. Next they are enunciated with details.

Hypothesis 1: LEF interacts with collagen through its amino acids.

Yes, these 13 of 40 interactions (Table 3) show that only two of them are oxidant and the other 11 are reductive (antioxidant).

Hypothesis 2: LEF has a positive influence on arthritis.

According to hypothesis 1. Two of 40 Interactions are oxidants, 13 of the interactions that have the lowest ETC and high to medium probability are reducing (antioxidants). Therefore, it is concluded that LEF is more beneficial than malignant.

Hypothesis 3: Quantum chemistry determines the type of interaction of LEF with the amino acids of collagen.

Yes, all interactions were calculated using the hyperchem software using the SE-PM3 method.

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