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STRUCTURAL MODELING OF THE CORTISOLS CONTAINING SULFUR, SELENIUM AND TELLURIUM

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ABSTRACT

Molecular modeling of cortisol (hydrocortisone), using *Spartan* 14 software for Windows, with a good approximation corroborated the structural data previously obtained by the X-ray technique. The calculation of bond lengths and bond angles provided new structural information on the cortisols, in which sulfur, selenium and tellurium were substituted for oxygen in the keto and hydroxyl functional groups. Most of the geometric parameters obtained for cortisol and its derivatives with heavy chalcogens were similar, except for the striking elongation of the key bonds Ch-H, Ch-C and Ch = O. The cumulative effect of such changes may result in significant structural alterations in the entire molecule, resulting in a greater propensity to interact with the hormone receptor. In this way, computerized modeling of virtual compounds will be able to provide insights into the viability of further laboratory synthesis and bioactivity tests.

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INTRODUCTION

Cortisol (synthetic form known as *dexamethasone*) is a dominant glucocorticoid in humans synthesized from progesterone in the zona fasciculata of the adrenal cortex. It is believed to circulate freely, bathing all tissues and cells after release from the source of synthesis. The target cells are specialized entities, which possess specific receptor proteins, playing a key role in the mediation of hormonal response (Bohl, 2018 and Mougdil, 1988). Potency and efficacy are the two major pharmacokinetic properties of cortisol glucocorticoid matrix, which allows the replacement of a number of its constituents. For example, the C9 halogenation and C18 methylation both increase the interaction surface within the receptor pocket. These openings stimulated the continuous development of synthetic glucocorticoids with promising clinical properties, including dexamethasone and other substituted cortisols (Yuanzheng, 2014). Structure-activity relationships and effects of substitutes have been discussed in a series of papers published earlier. The active sites of the cortisol molecule (Figure. 1) are believed to be the keto group comprising the C3 atom, the C4-C5 double bond, the C11 and C17 linked OH groups, and the C20 bonded to carboxyl group (Yuanzheng, 2014). This may appear paradoxal, but data on possible substitutions by heteroatoms are limited to the above-mentioned C9 site, so that only fluorine, chloro and bromocortisols have been described (Raynor, 2007; Weeks, 1973; Weeks, 1974). As for iodocortisol, this steroid has been recently characterized as a proposed model based on computer modeling [8]. On the other hand, to the best of our knowledge, no oxygen replacements with chalcogens have been carried out in the form of real or virtual compounds. There exists a vast published material referring to the bioactive potential of sulfur and selenium for search of novel therapeutic agents and biomaterials (Devillanova, 2007). It is generally assumed that tellurium is more toxic than selenium, but this should obviously not be an obstacle to scientific research in this poorly explored area (Tiekink, 2012). It therefore seemed reasonable to proceed with structural simulations of substituted cortisols to predict the effect of chalcogen on their biochemical activity. In addition, the comparison of isolated models with their crystalline counterparts, if available, may be useful for the general understanding of the properties of real compounds in the natural milieu.

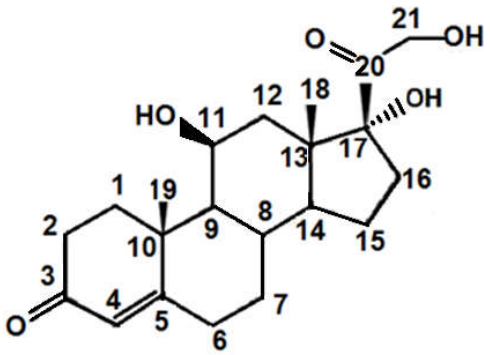

Fig. 1. Schematic representation of cortisol

MATERIALS AND METHODS

In this work, the structure of substituted cortisols were simulated employing the standard *Spartan* 14 software for Windows, which uses MMF force field. As in previous publications on the structures of virtual bioactive compounds (Nascimento, 2012), the geometry optimization was carried out in Cartesian coordinates using the Berny optimization algorithm, and adjusting the parameters until a stationary point on the potential surface was found. That means that for a small displacement the energy does not change within a certain amount, and the placements are successfully converged. It should be born in mind that no systematic energy sampling have been performed for searching conformational energy. Geometric parameters, such as interatomic distances and angles, were measured using special program features.

RESULTS AND DISCUSSION

The models obtained using the molecular modeling method are presented in Figures 2 and 3, all oriented in the same way.

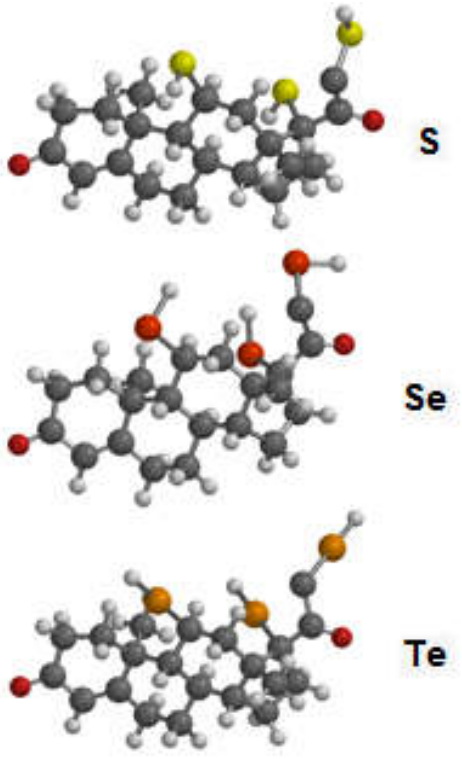

Fig. 2. Models of cortisol substituted in Ch-H groups

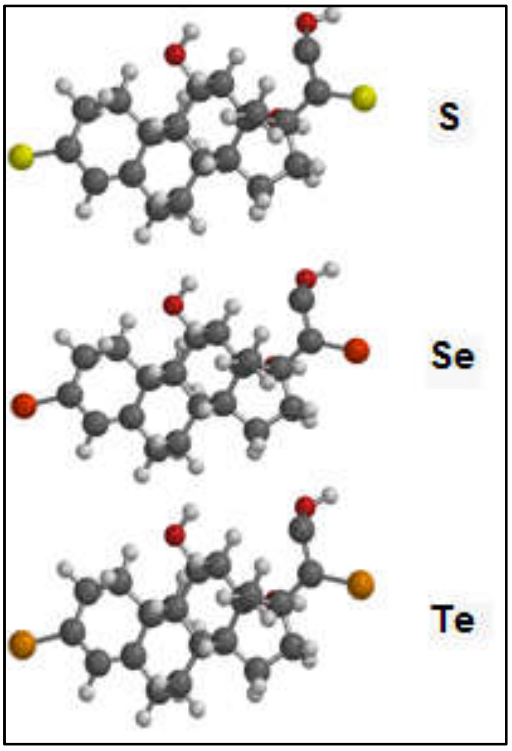

Fig. 3. Models of cortisol substituted in C = Ch groups

As for the calculated geometric parameters (bond lengths and bond angles), these are summarized in Tables 1-4. First of all, we can see (Table 1) that the set of interatomic distances calculated for cortisol molecule is almost identical to that of the structure previously refined by the X-ray technique (Castellano, 1980 and Suitchmezian, 2009).

Table 1. Calculated interatomic distances (Å) for cortisol as compared with published data

	[12]	[13]	Calculated
O – C3	1.235	1.230	1.228
C3 – C2	1.490	1.490	1.501
C2 – C1	1.523	1.499	1.522
C1 – C10	1.534	1.544	1.560
C10 – C19	1.552	1.542	1.546
C10 – C5	1.527	1.523	1.539
C5 – C4	1.355	1.342	1.345
C5 – C6	1.498	1.469	1.506
C4 – C3	1.453	1.539	1.478
C6 – C7	1.519	1.516	1.519
C7 – C8	1.535	1.539	1.542
C8 – C9	1.545	1.550	1.559
C8 – C14	1.567	1.527	1.556
C9 – Cl0	1.573	1.566	1.595
C9 – C11	1.541	1.548	1.548
O – H	-	0.890	0.973
C11 – O	1.423	1.428	1.429
C11 – C12	1.543	1.548	1.528
C12 – C13	1.530	1.529	1.535
C13 -C14	1.501	1.539	1.553
C13 – C18	1.534	1.530	1.556
C13 – C17	1.563	1.578	1.562
C14 – 15	1.506	1.533	1.544
C15 – C16	1.553	1.543	1.534
C16 – C17	1.548	1.549	1.541
C17 – O	1.430	1.425	1.431
O – H	-	0.981	0.976
C17 – C20	1.533	1.529	1.539
C20 – O	1.210	1.212	1.225
C20 – C21	1.505	1.503	1.552
C21 – O	1.410	1.415	1.343
O – H	-	0.830	0.974

Table 2. Interatomic distances (Å) calculated for S-substituted conformer with minimal potential energy (kJ/mol)

Position	Carbon				
	3	11	17	20	21
S – C3	1.682	1.228	1.228	1.228	1.228
C3 – C2	1.510	1.498	1.501	1.501	1.501
C2 – C1	1.524	1.524	1.523	1.523	1.523
C1 – C10	1.559	1.560	1.562	1.561	1.561
C10 – C19	1.547	1.547	1.546	1.546	1.546
C10 – C5	1.539	1.545	1.539	1.540	1.539
C5 – C4	1.346	1.346	1.345	1.345	1.345
C5 – C6	1.507	1.503	1.505	1.506	1.505
C4 – C3	1.484	1.476	1.478	1.478	1.478
C6 – C7	1.519	1.514	1.516	1.518	1.518
C7 – C8	1.542	1.542	1.541	1.541	1.542
C8 – C9	1.559	1.573	1.554	1.557	1.559
C8 – C14	1.555	1.554	1.553	1.555	1.555
C9 – Cl0	1.597	1.613	1.596	1.596	1.596
C9 – C11	1.548	1.563	1.547	1.547	1.548
S – H	0.973	1.341	0.974	0.973	0.973
C11 – S	1.429	1.842	1.424	1.427	1.427
C11 – C12	1.528	1.538	1.528	1.529	1.528
C12 – C13	1.535	1.535	1.542	1.537	1.535
C13 -C14	1.553	1.547	1.558	1.556	1.550
C13 – C18	1.556	1.557	1.566	1.558	1.555
C13 – C17	1.560	1.559	1.571	1.564	1.559
C14 – 15	1.542	1.544	1.548	1.544	1.544
C15 – C16	1.533	1.533	1.526	1.532	1.534
C16 – C17	1.540	1.540	1.538	1.541	1.536
C17 – S	1.431	1.431	1.851	1.438	1.431
S – H	0.976	0.976	1.340	0.978	0.975
C17 – C20	1.539	1.539	1.533	1.486	1.542
C20 – S	1.225	1.225	1.225	1.583	1.224
C20 – C21	1.552	1.551	1.558	1.563	1.553
C21 – S	1.343	1.343	1.347	1.344	1.773
S – H	0.976	0.976	0.979	0.979	1.345
Min. energy	578.56	591.62	524.43	438.05	501.96

Table 3. Angles (°) calculated for S-substituted conformer with minimal potential energy

Position	Carbon				
	C3	C11	C17	C20	C21
S – C3 – C2	120.06	122.79	122.64	122.60	122.60
S – C3 – C4	122.58	119.75	119.53	119.55	119.54
C3 – C2 – C1	109.92	110.38	110.54	110.57	110.57
C2 – C1 – C10	114.38	115.34	114.59	114.63	114.63
C1 – C10 – C19	108.41	108.22	108.77	108.58	108.57
C10 – C19 – C9	111.50	111.10	111.46	111.44	111.45
C19 – C10 – C5	108.12	108.04	107.80	107.98	107.95
C10 – C5 – C4	124.79	124.95	124.43	124.42	124.42
C5 – C4 – C3	121.40	121.93	121.89	121.88	121.88
C10 – C5 – C6	116.40	116.94	116.66	116.68	116.75
C5 – C9 – C10	109.62	110.15	110.16	109.93	109.93
C10 – C9 – C8	112.47	110.79	113.17	112.75	112.76
C9 – C8 – C7	109.43	109.64	110.76	113.96	109.71
C8 – C7 – C6	113.33	110.86	111.49	111.27	111.34
C7 – C6 – C5	110.94	110.48	110.63	110.93	110.96
C9 – C8 – C14	113.38	114.73	112.26	113.24	113.07
C8 – C14 – C15	111.70	111.75	110.97	111.44	111.87
C8 – C14 – C13	115.85	115.74	117.36	116.57	115.98
C14 – C13 – C12	111.09	110.66	113.35	111.63	111.02
H – S – C11	108.14	96.83	107.73	107.48	107.32
S – C11 – C9	111.57	116.12	111.16	110.83	110.86
S – C11 – C12	105.97	103.15	106.35	105.93	105.86
C13 – C12 – C11	116.83	117.23	117.82	116.80	116.73
C12 – C13 – C18	107.16	107.14	105.65	107.32	107.07
C18 – C13 – C14	108.78	108.78	107.05	107.60	108.69
C13 – C14 – C15	103.09	102.79	105.40	103.69	103.21
C14 – C15 – C16	107.17	107.16	107.57	107.39	107.42
C15 – C16 – C17	106.80	106.75	106.00	106.61	106.51
C18 – C13 – C17	110.55	110.45	109.36	111.69	110.95
C16 – C17 – S	107.60	107.62	108.79	107.21	107.30
H – S – C17	107.38	107.28	97.58	106.73	108.09
S – C17 – C20	108.31	108.09	105.39	106.99	109.61
C17 – C20 – S	124.70	124.61	126.40	120.91	126.03
C17 – C20 – C21	119.45	119.53	119.49	121.58	117.52
C20 – C21 – S	110.61	110.67	110.77	114.07	111.51
C21 – S – H	111.01	110.98	110.93	111.20	97.77

Some minor differences, particularly with respect to OH groups, may be due to the fact that the diffraction data are crystal-state related, so it is natural that the hydrogen bonds must be substantially modified. This means that, at least at the methodological level, these results are convergent, and *Spartan* 14 software is a suitable tool for investigating bioactive compounds. Comparisons show that, in cortisol and substitution models, the distances C - C and C = C are almost identical: 1.5 to 1.6 Å for single bonds and an invariable value of 1.345 Å for doubles matching the literature data (Allen, 1987). Since the geometric parameters for the heavier chalcogens are close, with the exception of the biologically active bonds, the full set is given in Table 2 only for the sulfur-substituted conformer. The corresponding angles for the latter are shown in Table 3. At the same time, to facilitate comparison between the most important interatomic distances, these are selected for further analysis in Tables 4-6.

Table 4. Chalcogen – hydrogen distances (Å)

Ch - H	Carbon		
	11	17	21
O	0.973	0.976	0.976
S	1.341	1.340	1.345
Se	1.509	1.510	1.513
Te	1.692	1.692	1.694

Table 5. Calcogen - carbon distances (ordinary bonds) (Å)

Ch - C	Carbon		
	11	17	21
O	1.432	1.431	1.343
S	1.842	1.851	1.873
Se	1.967	1.995	1.928
Te	2.108	2.099	2.115

Table 6. Chalcogen - carbon distances (double bonds) (Å)

Ch - C	Carbon	
	3	20
O	1.228	1.225
S	1.583	1.583
Se	1.720	1.723
Te	1.896	1.898

As can be seen from Table 4, the Ch – H bonds for either hydroxyl (attached to C11 and C17) or carbonyl (attached to C21) groups are the same for each chalcogen within a minimal margin of error. On the other hand, they increase quite dramatically from oxygen to tellurium. This growth is similar to the behavior of the corresponding bonds in other sulphides, selenides and tellurides, and therefore is not influenced by the presence of the large steroid matrix (NIST, 2018 and SBLBA, 2019). The lower electronegativity of heavy chalcogens results in their weaker attraction to the hydrogen of the adjacent cortisol molecule, so that, in the particular case of this steroid, the intermolecular Ch - H ... Ch bonds between the individual monomorphic units described by Suitchmezian *et al.* (2009), must be quite labile. In a way, this also recalls the substitution results in sufur-containing amino acids cysteine and methionine (Nascimento, 2011). Since Se – H and Te – H are the weakest bonds, so complex selenols and tellurols are stronger acids than thiols because the latter are mostly protonated. That is why selenolate and tellurate sites might be promising to react reversibly with binding domain of steroid receptor. A similar effect of electronegativity takes place when considering ordinary chalcogen-carbon distances: they grow in

the same proportion and in the same way for the carbon atoms, to which they are attached (Table 5). This, in turn, should be reflected in the conformational rearrangements of the cortisol units and, consequently, in the structure-activity relationship.

With regard to the keto groups, these bonds are more covalent than electrostatic. It may seem arbitrary to discuss the structure of molecules in a situation that, unlike biological fluids, is free of external constraints (Schmit, 1978). However, it has been shown that, at least in the crystalline structure of cortisol the molecules are linked by intermolecular hydrogen bonds between the carbonyl oxygen atoms and the hydroxyl groups (Nascimento, 2011). In fact, it is apparent from Table 6 that the Ch = C bonds are the same at both sites, but increase substantially from oxygen to tellurium. These distances are of the same order as in most structurally similar organic compounds. For example, in the case of tellurocarbonyls, the difference does not exceed 0.02 Å (Kuhn, 1993). From a practical perspective, a detailed analysis of geometric parameters is important for designing selective steroid-binding drugs (Luo, 2018).

Conclusions

Molecular modeling of cortisol (hydrocortisone) with a good approximation confirmed the structural data previously obtained by the X-ray technique for this steroid. The calculation of bond lengths and bond angles provided new structural information on the cortisol, in which sulfur, selenium and tellurium were substituted for oxygen in the keto and hydroxyl functional groups. The calculated bond lengths and bond angles of cortisol, and its derivatives with heavy chalcogens were found to be similar, except for the elongation of the key distances Ch-H, Ch-C and Ch=O bonds, in proportion to the heteroatoms ionic radii. The cumulative effect of such changes may result in significant structural alterations in the entire molecule, resulting in a greater propensity to interact with the hormone receptor. In this way, computerized modeling of virtual compounds will be able to provide insights into the viability of further laboratory synthesis and bioactivity tests.

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Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

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