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THEORETICAL INVESTIGATIONS ON STRUCTURAL FEATURES OF SULFONYL-UREA FOR DRUG DESIGN

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ABSTRACT

Structural properties of sulfonyl-urea as active moeity are controlled by its internal structural features. The structural investigations are focused on the parameters such as bond distances inside unit cell, torsion angles and different oxidation states present together inside unit cell. All of these structural parameters play an important role in the stability of this moeity as functionalized group, which could be linked with many active groups. The visualization studies specially bond distances measurements indicated that there are three different types of N-H bonds. Furthermore, visualized XRD pattern was constructed and the fingure print peaks of sulphoyl urea, which lies at two theta ~25 with [200] muller index were compared and discussed in detail.

Key words: Sulphonyl-urea, XRD, Bond lengths, Torsion, Oxidation states.

INTRODUCTION

In the sulphonyl-urea moiety (Fig. 1) Ar and R portions of general structure provide lipophilic character whereas the -SO_2-NH-CO-NH- moiety is hydrophilic in nature. All of these functional groups are required for activity, but the lipophilic Ar and R groups account for the differences in potency (SU receptor binding), metabolism, duration, and routes of elimination[1-11].

The arylsulfonyl ureas are weak organic acids (pK_as = 5-6) and are largely ionized at physiological pH[2,3]. This ionization contributes significantly to drug potency SUR (affinity),

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extensive plasma protein binding of these agents (> 95%), and drug interactions (competitive ppb). Also, alkalinization of the urine enhances ionization and elimination (shortens half-life)[6,7,9].

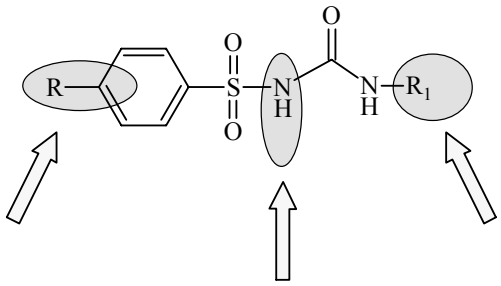

Fig. 1: Chemical structure formula of sulphonyl-urea moiety

The arylsulfonylureas products differ primarily in their relative potency and key pharmacokinetic properties. Duration of action (primarily a function of metabolism) is of primary importance because this influences the frequency of required dosing[10]. The sulfonylureas can be classified as first, second and possibly third generation agents[11,12].

EXPERIMENTAL

Structure visualization

A visualization study made is concerned by matching and comparison of experimental and theoretical data of atomic positions, bond distances, oxidation states and bond torsion on the crystal structure formed. Some of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif, or by emailing data_request @ccdc.cam.ac.uk, or by contacting ICSD-Fiz-Karlsruhe-Germany.

Structural measurements

The X-ray diffraction (XRD): Measurements were carried out at room temperature on the fine ground samples using Cu-Kα radiation source, Ni-filter and a computerized STOE diffractometer/Germany with two theta step scan technique. Rietveld and indexing of structure were made via Fullprof package and Gesas program.

RESULTS AND DISCUSSION

Fig. 1 shows the experimental XRD pattern recorded for pure urea, which is consider the main center of all sulphonyl-urea drug. The brawn circles refer to figure print peak of

highly pure urea with muller index [200], which lies at two theta value ~ 25. The matching between Fig. 1 (experimental XRD) and Fig. 2 (visualized XRD) indicated that the Fig. print peak, which lies at two theta ~ 25 is present in both patterns, which confirmed that the fitting between both patterns is present to some extent. The ratio of fitting is function in the surrounding groups around sulphonyl-urea moiety, whether these groups are small or bulk, aliphatic or aromatic.

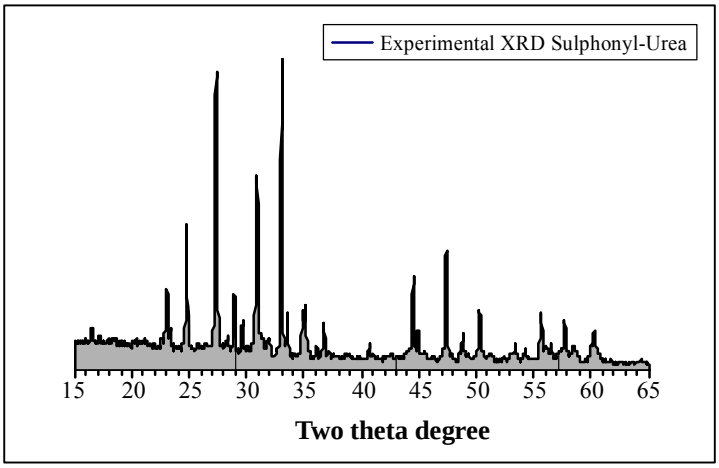

Fig. 1: XRD pattern recorded of pureurea

Fig. 2 displays visualized XRD pattern for sulphonyl urea constructed via Diamond Impact Crystal Visualizer depending upon atomic coordinates supplied from single crystal data of supphonyl-urea containing compound and pure urea (Table 1).

Table 1: Single crystal data of sulphonyl-urea containing compound

Phase data	
Formula sum	$C_4\ O_4\ N_8\ H_{16}$
Formula weight	240.222 g/mol
Crystal system	Tetragonal
Space-group	P 42/m (84)
Cell parameters	a = 5.5600 Å; c = 4.7000 Å
Cell ratio	a/b = 1.0000; b/c = 1.1830; c/a = 0.8453
Cell volume	145.29 $Å^3$

Atomic parameters								
Atom	**Ox.**	**Wyck.**	**Site**	**S.O.F.**	**x/a**	**y/b**	**z/c**	**U [Å^2]**
C1		4i	2..		0	1/2	0.32000	
O1		4i	2..		0	1/2	0.59000	
N1		8k	1		0.14000	0.64000	0.17000	
H1		8k	1		0.25000	0.75000	0.28000	
H2		8k	1		0.14000	0.64000	-0.03000	
Anisotropic displacement parameters, in Å^2								

The visualized pattern (Fig. 2) has 23 peaks. All of them is related to pure urea-moeity while Fig. 2 has lower number of peaks (18 peaks) due to the overlapping and interferences between rest structure of sulphonyl-urea with urea peaks. Although the line at two theta ~ 25 in Fig. 2 is not the most intense reflection peak but it is considered the characteristic line for urea existence phase with [200] muller index.

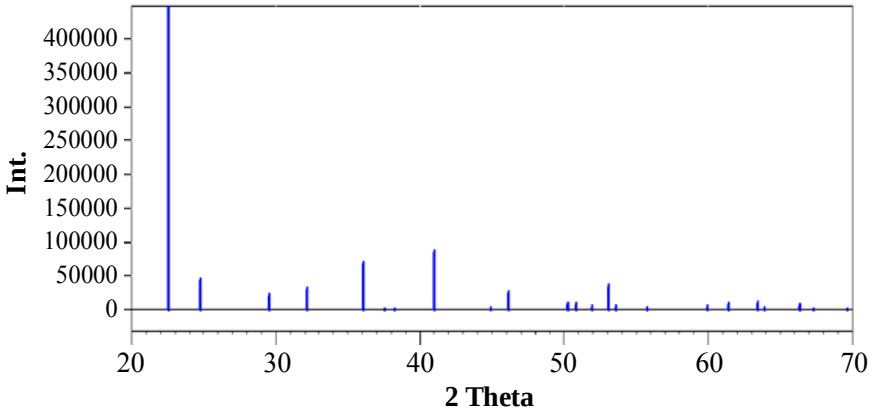

Fig. 2: Visualized XRD pattern for pure urea

There are two different types of O-H bonds such that O1-H1 bond length was found to be 2.058 Å, while O1-H2 was 2.098 Å (Table 2). It is attributed to the fact that electron density at oxygen atom is impacted sharply by inductive effects of the neighboring function groups, specially those with highly negative inductive effects as S, N, P, or halogen atoms that could be present in the drug constituents.

Table 2: Selected bond distances and lattice atomic coordinates inside unit cell of sulphonyl-urea containing drug

Atom 1	Atom 2	x/a	y/b	z/c	D1-2 Å
O1	C1	0	1/2	0.68000	0.4230
	O1	0	1/2	0.41000	0.8460
	C1	0	1/2	0.32000	1.2690
	N1	0.14000	0.64000	0.83000	1.5761
	N1	-0.14000	0.36000	0.83000	1.5761
	H1	0.25000	0.75000	0.72000	2.0585
	H1	-0.25000	0.25000	0.72000	2.0585
	H2	-0.14000	0.36000	0.97000	2.0980
	H2	0.14000	0.64000	0.97000	2.0980

CONCLUSION

(i) Varieties of oxidation states inside tetragonal unit cell of sulphonyl-urea lead to differentiation on the regular bond distances and hence, compensate lattice defects by increasing stability factor.

(ii) Nitrogen and oxygen atoms of sulphonyl-urea play important role in reinforcing lattice stability by hydrogen or other coordination bonds.

(iii) No extra torsional angles of tetragonal unit cell was noticeable. These remarks explain, why sulphonyl-urea moiety has unique and specific structural parameters as centeral moiety in most of common anti-diabetic drugs.

REFERENCES

1. UK Prospective Diabetes Study (UKPDS) Group, Lancet, 352, 9131 (1998) pp. 837-853.

2. The Diabetes Control and Complications Trial Research Group, The New England J. Med., **329**, 977-986 (19 93).

3. A. Ceriello, M. Hanefeld and L. Leiter, Arch. Inter. Med., **164(19)**, 2090-2095 (2004).

4. A. Ceriello, K. Esposito, L. Piconi, Diabetes, **57(5)**, 1349-1354 (2008).

5. M. Brownlee and I. B. Hirsch, J. Am. Med. Assoc., **295(14)**, 1707-1708 (2006).

6. J. L. Chiasson, R. G. Josse, R. Gomis, M. Hanefeld, A. Karasik and M. Laakso, J. Am. Med. Assoc., **290(4)**, 486-494 (2003).

7. R. De Caterina, Curr. Opin. Lipidol., **11(1)**, 9-23 (2000).

8. A. Ceriello, C. Taboga, L. Tonutti, Circulation, **106(10)**, 1211-1218 (2002).

9. M. Brownlee, Nature, **414**, 6865, 813-820 (2001).

10. D. Rodbard, J. Diabetes Sci. Technol., **1**, 62-71 (2007).

11. G. McGarraugh, Diabetes Technol. Therap., **11**, S17-S24 (2009).

12. H. W. Rodbard, L. Blonde, S. S. Braithwaite, Endocrine Pract., **13(1)**, 1-68 (2007).

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