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SYNTHESIS AND BIOLOGICAL EVALUATION OF COPPER (II) COMPLEXES OF SULPHONYL UREAS DERIVATIVES

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ABSTRACT
A series of Cu (II) complexes of sulphonyl urea derivatives were synthesized and the structures of the newly synthesized compounds were confirmed by FT-IR and 1H NMR spectral studies. All new derivatives **5(a-d)** were screened for their *in vivo* hypoglycemic activities, it has been found that Cu (II) complexes of sulphonyl urea showed remarkable activity than the parent sulphonyl urea derivatives.

KEY WORDS
Cu (II) complexes, sulphonyl urea derivatives, hypoglycemic activity

INTRODUCTION
Diabetes mellitus[1] is a clinical syndrome characterized by hyperglycemia due to absolute (type I) or relative (type II)[2] deficiency of insulin. In both type I (IDDM) and type II (NIDDM) diabetes, [3] the actions of insulin are almost impaired by insensitivity of target tissue. It is characterized by both tissue insulin resistance and an insulin secretary defect. Diabetes mellitus in now recognized as a serious global health problem[4] as it has broken the age barrier and appears even in younger people. [5]
Noninsulin dependent diabetes mellitus (NIDDM) is much more common than IDDM, NIDDM is increasing exponentially worldwide and inviting major health problems from its complications.[6, 7]Various classes of drugs are now available for the controlling of type II diabetes mellitus such as sulphonyl urea, biguanides, a-glucosidase inhibitors, 2,4-thiazolidinediones and traditional herbal drugs. [8,9]
The sulphonyl urea derivatives have been categorized as first and second generation drugs in these second generation drugs are more potent.[10-12]Sulphonyl urea derivatives and its analogous have been reported to possess excellent biological activities.[13,14]Therefore, sulphonyl urea derivatives are proved to be a useful starting material for physiologically or pharmacological product.
Furthermore, it has been reported that the biological activity of metal complexes is more potent and less toxic as compared to the free ligand. [14,15]In light of these finding, it is

supposed that the introduction of Cu (II) metal to sulphonyl urea moiety may produce derivatives with considerable hypoglycemic activity.

EXPERIMENTAL

The progress of each reaction was monitored by thin layer chromatography (TLC) by n-hexane:ethyl acetate solvent system. Starting compound acetanilide is of Sigma Aldrich make. Melting points were uncorrected taken in an open capillary tube on a Stuart melting point apparatus. The IR spectra of the compounds were recorded on Shimadzu FTIR Spectrometer with KBr pellets. PMR spectrums were recorded on Bruker Avance 400 MHz NMR Spectrometer.

General procedure for the synthesis of 4-acetamidobenzene-1-sulfonyl chloride (2)

A mixture of acetanilide (0.148mole) and chlorosulphonic acid (0.77 mole) was refluxed for 1 hour. After the completion of a reaction (monitored by TLC), the reaction mixture was poured over crushed ice to afford a white crystallized product **(2)**was filtered and dried.

General procedure for the synthesis of 4-acetamidobenzene-1 sulphonamide (3).

4-acetamidobenzene-1-sulfonyl chloride **(2)** was mixed with 14 ml ammonia solution and 14 ml of water. The content of the flask was heated at 80°C for 15 minutes. The 4-acetamidobenzene-1-sulfonyl chloride **(2)** converted into a pasty suspension of corresponding sulphonamide **(3)**. The suspension was cooled in ice and then dil. H_2SO_4 is added until the mixture was just acidic to cango-red, then formed product**(3)** was filtered and dried.

General procedure for the synthesis of sulphonyl urea derivatives 5(a-d)

A mixture of 4-acetamidobenzene-1 sulphonamide **(3)**(0.005 mole), various substituted phenyl isothiocynate **(4)** (0.005 mole) and potassium carbonate (0.50 mole) in acetone 10 mL was refluxed for 5 h. The progress of the reaction was checked using TLC technique. After completion of reaction, the solvent was removed under vacuum and solid mass was poured in ice-cool water. It was then neutralized with acetic acid obtained solid filtered, washed it with ice cold water, dried and recrystallized by ethyl alcohol to afford the target compounds **5(a-d)**.

General procedure for the synthesis of preparation of metal Complexes 5(a-d)*

Metal Complexes were synthesized by employing various methods[16]. In the present work, the metal complexes of Cu (II) with different sulphonyl urea derivatives were synthesized[15] by refluxing the ethanol solution of metal chloride in 1:2 molar ratios. The reaction mixture was refluxed for 3-4 hours. On cooling, the precipitate formed was separated by filtration and washed with cold ethanol followed by petroleum ether and dried over anhydrous $CaCl_2$ in vacuum.

Table 1: Preliminary data of the sulphonyl urea derivatives **5(a-d)**

Entry	Molecular formula	Molecular weight	Color	m. p. (°C)	Practical Yield (%)
5a	$C_{15}H_{15}N_3O_3S_2$	349.4279	White	167-168	66
5b	$C_{16}H_{17}N_3O_3S_2$	363.4545	White	181-183	64
5c	$C_{15}H_{14}N_4O_5S_2$	394.4255	White	178-181	67
5d	$C_{15}H_{14}BrN_3O_3S_2$	428.324	White	198-199	88

Table 2: Preliminary data of the metal complexes **5(a-d)***

Entry	Metal Complex	Color	M. P. / Decomposition temp. in °C
5a*	Cu(II)- $C_{15}H_{15}N_3O_3S_2$	Faint blue	> 250°C
5b*	Cu(II)- $C_{16}H_{17}N_3O_3S_2$	Faint blue	216°C
5c*	Cu(II)- $C_{15}H_{14}N_4O_5S_2$	Faint gray	198°C
5d*	Cu(II)- $C_{15}H_{14}BrN_3O_3S_2$	Shining blue	> 250°C

Table 3: Comparison of IR Spectra of the Derivatives with metal complexes

Derivatives/ Complex	SO_2 cm^{-1}	C=S cm^{-1}	C-S cm^{-1}	C=N cm^{-1}	C-N cm^{-1}
5a	1118-1163	1163	-	-	1244
5a*	1118-1161	-	684	1595	-
5b	1158	1423-1479	-	-	1269
5b*	1160	-	738	1606-1637	-
5c	1147	1269	-	-	1319
5c*	1143	-	740	1531-1600	-
5d	1128	1184	-	-	1309
5d*	1126	-	761	1531-1602	-

Hypoglycemic Activity

Assessment of the antidiabetic activity was done according to Alloxin induced diabetes method[17]. Metformin hydrochloride was taken as reference drug. Body weight of each animal in all 10 groups was measured one week before the study. After one week animals were again weighted for fixing the dose of alloxin. Dose of alloxin is given by intraperitoneal route. Blood glucose levels of all animals were measured after 48hrs. Then the dose of compounds was given for 15 days by oral route. After 15 days of compound dosage the glucose levels in blood of each rat was measured and the results were noted.

Selection of animal species

Healthy young albino rats of either sex weighing between 150 to 220gms (8 to 12 weeks old) were used for acute toxicity study to determine LD_{50} of various extracts. Totally there were ten groups, each groups consists of five animals.

Housing and Feeding Condition

The temperature in the experimental room was around 25°C. Lightening was artificial, the sequence being 12 hours dark, 12 hours light. The conventional laboratory diet was feeded, with an unlimited supply of drinking water.

Preparation of doses

All the doses were prepared by dissolving 1mg of respective ligand and its complexes in 1ml DMSO and in 1ml Saline solution.

Administration of doses

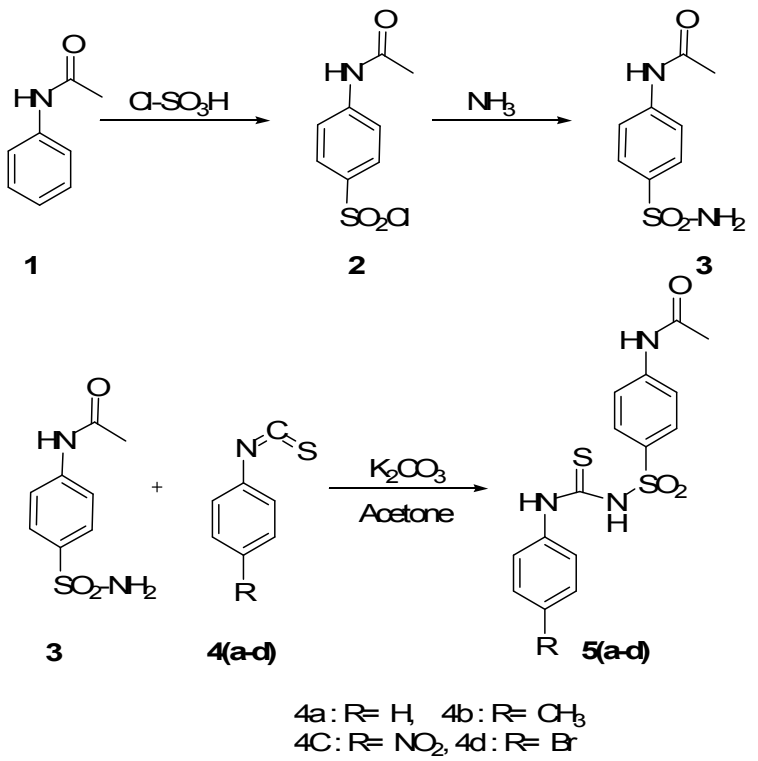
The test substances were administered in a single dose by using feeding tube. After fasting for 3-4 hours, rats were weighted and the test substance administered.

Number of animals and dose levels

In each steps five animals were used. Since there was no information on the substance to be tested (i.e. compounds), starting dose was selected to be 25mg/kg body weight. As it showed no death, the next dose was selected as 50 mg/kg body weight. Finally 47.57kg body weight was considered as the toxic dose and one seventh of this dose was taken as experimental dose for antidiabetic studies.

RESULTS AND DISCUSSION

Sulhonyl urea derivatives were synthesized from acetanilide (**1**), which on treatment with chlorosulphonic acid gave 4-acetamidobenzene-1-sulfonyl chloride **(2),** in which addition of ammonia gaves 4-acetamidobenzene-1sulphonamide**(3).** The 4-acetamidobenzene-1sulphonamide**(3)**treated with various substituted phenyl isothiocynate **4(a-d)** gives target compounds in good yields. The chemistry of target compounds is quoted in **Scheme 1.**



Scheme 1: Synthesis of sulphonyl urea derivatives **5 (a-d)**

The spectra of the metal complexes **5(a-d)** in the area are broad and diffused. The broadening may be the result of the overlap of the bands due to ν(OH) of coordinated water molecules which appears as a broad band between 3200-3600 cm^{-1} [18, 19] The synthesized ligands contain C-N linkage, whose frequencies are expected to be in the range of 1200-1400 cm^{-1}. [18]A peak in the region 1244-1319 cm^{-1} for all the four ligands, has been observed and is assigned to the ν (C-N). In all the metal complexes under study, this band is shifted to higher frequency region and found to appear in the range of 1531-1637cm^{-1}. Such an up shift clearly indicated the involvement of nitrogen in co-ordination with metal atom. [20] M-S stretching vibrations have been observed in the lower region of M-N vibrations i.e. in the range of 200-600cm^{-1}.
In the present study M-S vibrations were in the range of 205-532 cm^{-1}.The infrared spectra of the ligand and their metal complexes provide vital information about the bonding. The spectra of complexes exhibit strong absorption bands in the range 1500-1600 cm^{-1}. This absorption is associated with the stretching vibration of C=N. The -OH absorption band in the ligands are observed in the region 3200-3600 cm^{-1}. This sharp band has disappeared in capacity indicating its involvement in the bond formation process. IR spectrum of ligand **5a** shows characteristic absorption due to -C=S at 1163 and at 1244–1319 cm^{-1} due to C-N stretching vibrations. The IR spectrum of complex **5a*** synthesized from ligand **5a** confirms the formation of complex. It clearly indicates the presence of -C=N and C-S bond because -C=N absorption was observed at 1595cm^{-1} and absorption at 684 cm^{-1} due to the presence of C-S. IR spectrum of ligand **5b** shows characteristic absorption due to C=S at 1423-1479 cm^{-1} and C-N stretching at 1269cm^{-1}. The IR spectrum of complex **5b*** synthesized from ligand **5b**confirms the formation of complex and indicates the presence of C=N and C-S bond because C=N absorption was observed at 1606-1637cm^{-1} and C-S absorption at 738 cm^{-1}.IR spectrum of ligand **5c** shows absorption at 1269 cm^{-1} due to C=S and at 1319 cm^{-1} due to C-N

bond. The IR spectrum of complex **5c*** synthesized from ligand **5c** confirms the formation of complex. It indicates the presence of -C=N and C-S bond because C=N absorption takes place at 1531-1600 cm^{-1} and C-S absorption at 740 cm^{-1} respectively.

The ^{1}H NMR spectra of the some representative metal complexes were recorded. However due to the presence of a metal ion, proton resonance was not expected to take place, and only broad peak were observed in the spectra. Hence the formation of complex was confirmed by comparison data obtained from ligand and the complex.

Hypoglycemic Activity Evaluation Study

The synthesized compounds were screened *in vivo* studies for their hypoglycemic activity. The assessment of the activity was done according to Alloxin induced diabetes method. Metformin hydrochloride was taken as reference drug.

It was found that some of sulphonyl urea derivatives and their complexes have shown promising antidiabetic activity compared to the standard metformin hydrochloride. Out of which ligand **5b**, complex **5C*** and complex **5d*** have shown significant activity. It has been found that the complexes shown higher antidiabetic activity than the ligands.

Table 4: Antidiabetic activity of ligands and their complexes

Normal	**104**	**121**	**119**	**111**	**95**	**550/5=110**	
Normal	**98**	**110**	**112**	**102**	**87**	**509/5=101.8**	**8.2**
Alloxin	210	225	200	198	196	1029/5=205.8	
Ligand 5a	195	205	185	176	180	941/5=188.2	17.6
Alloxin	192	201	205	213	220	1031/5=206.2	
Complex 5a*	172	176	187	195	199	929/5=185.8	20.4
Alloxin	240	225	238	228	232	1163/5=232.6	
Ligand 5b	205	198	204	206	196	1009/5=201.8	30.8
Alloxin	190	175	180	205	200	950/5=190.00	
Complex 5b*	168	160	163	182	180	853/5=170.6	19.4
Alloxin	208	210	217	209	211	1055/5=211.00	
Ligand 5c	192	190	200	190	193	965/5=193.00	18.00
Alloxin	185	190	210	205	190	985/5=197.00	
Complex 5c*	155	158	175	180	170	830/5=167.6	29.4
Alloxin	235	228	225	230	228	1146/5=229.2	
Ligand 5d	220	216	218	215	212	1081/5=216.2	13.00
Alloxin	230	215	200	215	225	1085/5=217.00	
Complex 5d	203	185	175	180	192	935/5=187.00	30.00
Alloxin	218	230	222	225	215	1110/5=222.00	
Metformin hydrocholoride	**178**	**193**	**184**	**184**	**172**	**911/5=182.2**	**39.8**

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