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Antidepressant and Anti-Inflammatory Activities of Cationic Amphiphilic Complexes of Sulphadiazine

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Abstract- In our study we synthesized schiff' base of sulphadiazine on treating with aromatic aldehydes like para diethyl amino benzyldehyde and paradimethyl amino benzyldehyde. The synthesized schiff's bases were converted to its cationic amphiphilic bases by treating with methyl iodide. The cationic schiff bases were converted to metal complexes by treating with metals like copper chloride (CuCl2), zinc chloride (ZnCl2) and cadmium chloride (CdCl2). All the synthesized compounds were characterized by elemental analysis, IR and H1 NMR. Synthesized compounds were screened for anti-inflammatory and antidepressant activity. Copper metal complexes showed excellent anti-inflammatory activity and zinc metal complexes showed excellent anti-depressant activity.

Keywords: cationic amphiphilic bases, schiff' base, metal complexes, anti-inflammatory and antidepressant activity.

I. Introduction

An amphiphilic substance exhibits a double affinity, which can be defined from the physico-chemical point of view as a polar-apolar duality. When a single surfactant molecule exhibit both anionic and cationic dissociations it is called amphoteric or zwitterionic. Cationic amphiphilic drugs (CADs) are widely used in chronic pharmacotherapies in spite of frequently observed side effects connected with lysosomal phospholipid (PL) storage. Cationic amphiphilic drugs (CADs) represent compounds of different therapeutic classes such as antidepressants, neuroleptics, and antiarrhythmics. In acidic cellular compartments these drugs become efficiently protonated and thus trapped in, e.g. lysosomes. As a result of pHdependent ion trapping, total lysosomal drug concentrations may exceed extracellular levels by orders of magnitude. Lysosomotropic drugs may inhibit lysosomal phospholipid (PL) metabolism leading to the formation of dense cytoplasmic granules, i.e. lysosomes filled with undegraded PLs. The formation of drug-PL complexes further enhances intracellular accumulation of drugs.

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We all require iron, copper and zinc for normal brain function but metal metabolism becomes dysregulated in a variety of neurodegenerative diseases. Metals accumulate in Alzheimer's dementia and Parkinson's disease and are deficient in Menkes disease. Transition metals perform a wide range of biological functions in the brain. A common feature is their ability to exist in a variety of oxidation states and participate in redox reactions; thus copper, iron, and manganese are all catalytically active metals in a class of enzymes that sequester free radicals. It is useful to look at the common and varying functions of transition metals in the brain to better understand what mechanisms are disrupted in metal dyshomeostasis and how this may lead to cell death in diseases of the CNS (Tyszka, 2014).

Metal complexes are also known as coordination compounds, which include all metal compounds. Metal complex is a structure consisting of a central atom (or) ion (metal) bonded with anions (ligands). Compounds that contain a coordination complex are called coordination compounds. The bonding characteristics of complexes and alteration in size of the metal ion are related to thermodynamic aspects. The stability constants for the complexes formed from various metal ions and one ligand have a particular sequence (Banerjee, 2009, Shi, 2007).

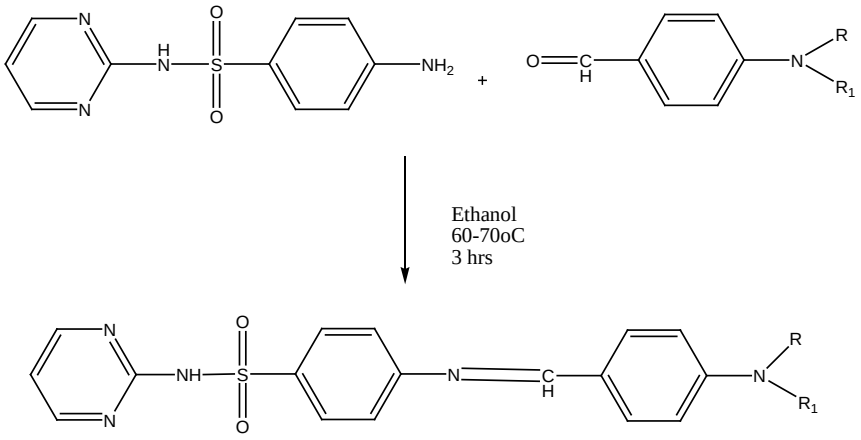
The parent sulpha drugs Sulphadiazine is a well known antibacterial in olden days. But owing to their narrow spectrum of activity and side effects, now a days their usage is limited. In our research we improved the biological activity by different synthetic modifications, In the first step by converting the parent sulpha drug in the form of Schiff base, there by generating a lone pair of electrons in a sp2 hybridized orbital in the structure leading to the derivation of and different biological properties. In the second step of synthesis the Schiff bases were converted in to their cationic amphiphiles, which may alter their pharmacokinetic profile like distribution and binding parameters. This step helped us to improve the spectrum activity from narrow spectrum to broad spectrum activity, increasing the permeability of drug molecule in brain to cross blood-brain barrier, which improves the antidepressant property, and release of cationic lipids into the macrophage cytoplasm is a necessary step for anti-inflammatory activity. In the

third step by deriving metal complexes of copper and zinc the biological properties like antidepressants and anti-inflammatory activities were strongly elucidated.

II. Materials and Methods

a) Synthesis of Schiff's Base

The Schiff's base has been synthesized by refluxing the reaction mixture of hot ethanolic solution (30 ml) of Sulphadiazine (0.01 mole) with hot ethanolic solution (30 ml) of different aromatic aldehyde (0.01 mole) for about 2-3 hours at 60-70^0 C (Fig-1). The mixture was allowed to stand over night. After that the colored solid product was filtered off, re-crystallized with ethanol and finally washed with petroleum ether. The final product was dried under reduced pressure over anhydrous calcium chloride (Panneerselvam, 2005).

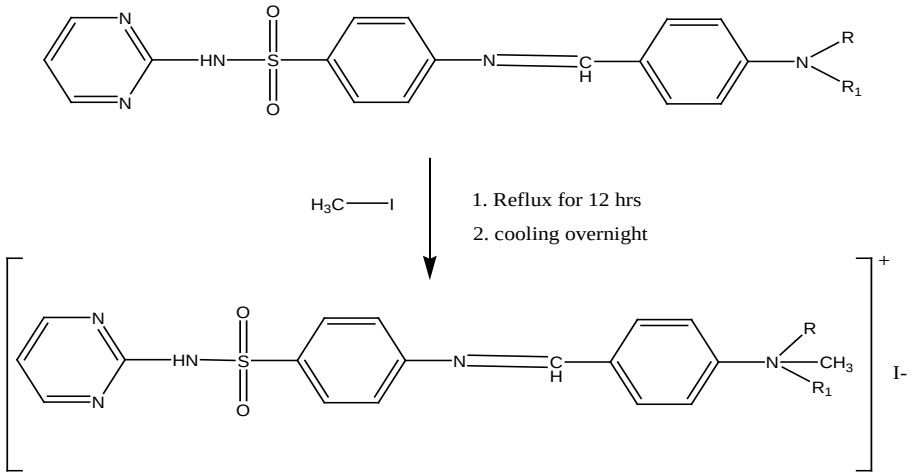


Compound A R-C_2H_5, R_1-C_2H_5
Compound B R-CH_3, R_1-CH_3

Figure 1: Scheme of synthesis of Sulphadiazine Schiff base

b) Synthesis of cationic derivative of Schiff base

Cationic derivatives of Schiff bases were obtained by direct reaction between equimolar amount of the synthesized Schiff bases and methyl iodide in 50ml ethanol (Fig-2). The reaction mixture was refluxed for 8 hours and left overnight. The precipitated products were filtered and recrystallized (Negm, 2010)

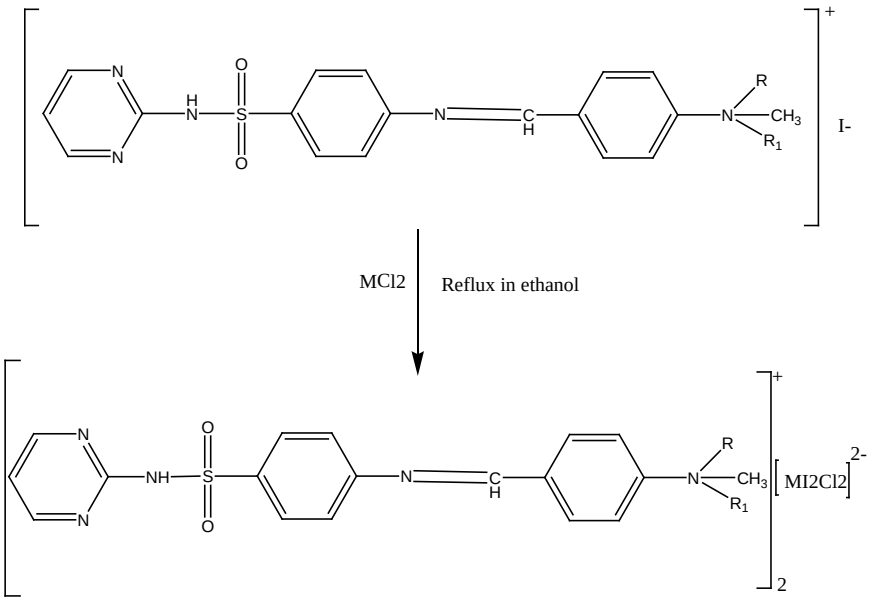


Compound A R-C_2H_5, R_1-C_2H_5
Compound B R-CH_3, R_1-CH_3

Figure 2 : Scheme of synthesis of cationic Schiff base

c) Synthesis of transition metal complexes.

Metal ion solutions of anhydrous $CuCl_2$, $ZnCl_2$ and $CdCl_2$ (0.0005 mol) in 50ml ethanol was added with synthesized cationic derivative of Schiff base separately and refluxed for 6 hours (Fig-3). The reaction mixture was left overnight to complete the precipitation of the products. The products were recrystallized with ethanol to obtain pure products (Ibotomba, 2012, Ajaykumar, 2009).



Compound A R-C_2H_5, R_1-C_2H_5
Compound B R-CH_3, R_1-CH_3
MCl_2- $CuCl_2$, $Zncl_2$ and $CdCl_2$

Figure 3 : Scheme of synthesis of cationic Schiff base

d) Determination of median lethal doses (LD50)

Animal's Swiss albino mice (20-25gm) and Male Sprague - Dawley rats (160-180) were maintained at standard diet and *ad libido.* The experiment protocol was approved from institutional ethical committee. The test compounds were dissolved in 3 % DMSO administered orally to different groups with increasing doses. Six animals were taken in each group. Mortality was determined after 24 hours of treatment. The dose, at which the 50 % mice survived, was considered as LD50 value of the compound (OECD, 2002).

Male Sprague - Dawley rats weighing 160-180 grams were divided into eight groups of six animals each. The test groups received orally 20 mg/kg of each sample. The reference group received imipramine (5 mg/kg, p.o) while the control group received vehicle (1 % CMC). Naïve rats are individually forced to swim inside a vertical Plexiglas cylinder (height : 40 cm ; diameter : 18 cm ; containing 15 cm of water maintained at 25 oC). Floating behaviour during this 5 minutes period has been determined in different groups of rats. The percentage inhibition was calculated by the formula (Kulkarni, 2010).

e) Anti depressant activity

$$\text{Percentage inhibition} = \frac{\text{Before treatment} - \text{After treatment}}{\text{Before treatment}} \times 100$$

f) Anti inflammatory activity

Swiss albino mice were divided into eight groups of six animals each. The test groups received orally 20 mg/kg of each sample. The reference group received diclofenac sodium (10 mg/kg, p.o) while the control group received vehicle (1 % CMC). All the animals should make a mark on both hind paws just beyond tibiofasial junction, so that every time the paw is dipped in mercury column up to fixed mark to ensure constant paw volume. After drug administration inject 0.1ml white egg portion to the plantar region of left paw of control as well as treated group. The right paw serve as reference non inflamed paw for comparison. The inflammation was quantitated in terms of ml i.e.

replacement of water by edema using a Plethysmometer immediately before egg white injection and then 0, 1, 2 and 3 hours after egg white injection. The percent inhibition of edema as calculated for each group with respect to its vehicle treated control group. The anti-inflammatory activity was calculated by using the relation used by

$$\% \text{ inhibition} = (Vc\text{-}Vt/Vc) \times 100$$

Whereas Vc was the average inflammation (hind paw edema) of the control group of mice at a given time, Vt was the average inflammation of the drug treated (i,e sample or reference diclofenac sodium) mice at the same time (Sathe, 2011).

g) Statistical analysis

The data were expressed as mean ±SEM. Statistical analysis was performed one-way ANOVA followed by Dunnett‟s multiple comparison test using sigma stat software (version 2.0, Jandel Scientific Inc. USA

III. Results and Discussion

a) Characterization of synthesized compounds

A1- Copper metal complex of (E)- N-(4-(diethyl, methyl amino) benzylidene)-4-(pyrimidin -2-sulfonamidyl) benzenamine.

M.F: $C_{22}H_{26}Cl_2CuI_2N_5O_2S$. M. wt: 812.8. IR (KBr) cm-1: NH bond stretching at 3400 cm-1, C=N bond stretching at 1690 cm-1, S=O stretching at 1140 cm-1, C=C stretching at 1600 and 1475 cm-1. H^1 NMR ($CDCl_3$) δ values: Multiplet at 7.44-8.38 for aromatic nucleus, singlet at 8.39 for N=CH peak, singlet at 4.0 for aromatic NH group, two triplet at 1.13 for two CH_3 groups in N-ethyl substitution, two quadret at 3.39 for two CH_2 group in N-ethyl substitution and singlet at 2.85 for N-methyl substitution. Elem Anal Calc: C, 32.51; H, 3.22; Cl, 8.72; Cu, 7.82; I, 31.2; N, 8.62; O, 3.94; S, 3.95. Elem Anal Found: C, 32.41; H, 3.32; Cl, 8.62; Cu, 7.92; I, 31.21; N, 8.60; O, 3.95; S, 3.96.

A2- Zinc metal complex of (E)- N-(4-(diethyl, methyl amino) benzylidene)-4-(pyrimidin -2-sulfonamidyl) benzenamine.

M.F: $C_{22}H_{26}Cl_2CuI_2N_5O_2SZn$. M. wt: 814.6. IR (KBr) cm-1: NH bond stretching at 3400 cm-1, C=N bond stretching at 1690 cm-1, S=O stretching at 1140 cm-1, C=C stretching at 1600 and 1475 cm-1. H^1 NMR (CDCl3) δ values: Multiplet at 7.44-8.38 for aromatic nucleus, singlet at 8.39 for N=CH peak, singlet at 4.0 for aromatic NH group, two triplet at 1.13 for two CH3 groups in N-ethyl substitution, two quadret at 3.39 for two CH2 group in N-ethyl substitution and singlet at 2.85 for N-methyl substitution. Elem Anal Calc: C, 32.44; H, 3.22; Cl, 8.70; I, 31.16; N, 8.60; O, 3.93; S, 3.94; Zn, 8.03. Elem Anal Found: C, 32.45; H, 3.23; Cl, 8.66; I, 31.14; N, 8.62; O, 3.83; S, 3.98; Zn, 8.13.

A3- Cadmium metal complex of (E)- N-(4-(diethyl, methyl amino) benzylidene)-4-(pyrimidin -2-sulfonamidyl) benzenamine.

M.F: $C_{22}H_{26}CdCl_2I_2N_5O_2S$. M.wt: 861.7. IR (KBr) cm-1: NH bond stretching at 3400 cm-1, C=N bond stretching at 1690 cm-1, S=O stretching at 1140 cm-1, C=C stretching at 1600 and 1475 cm-1. H^1 NMR (CDCl3) δ values: Multiplet at 7.44-8.38 for aromatic nucleus, singlet at 8.39 for N=CH peak, singlet at 4.0 for aromatic NH group, two triplet at 1.13 for two CH_3 groups in N-ethyl substitution, two quadret at 3.39 for two CH_2 group in N-ethyl substitution and singlet at 2.85 for N-methyl substitution. Elem Anal Calc: C, 30.67; H, 3.04; Cd, 13.05; Cl, 8.23; I, 29.46; N, 8.13; O, 3.71; S, 3.72. Elem Anal Found: C, 30.77; H, 3.14; Cd, 13.00; Cl, 8.13; I, 29.36; N, 8.03; O, 3.78; S, 3.74.

B1- Copper metal complex of (E)- N-(4-(trimethyl amino) benzylidene)-4-(pyrimidin -2-sulfonamidyl) benzenamine

M.F: C20H22Cl2CuI2N5O2S. M.wt: 784.7. IR (KBr) cm-1: NH bond stretching at 3400 cm-1, C=N bond stretching at 1690 cm-1, S=O stretching at 1140 cm-1, C=C stretching at 1600 and 1475 cm-1. H1 NMR (CDCl3) δ values: Multiplet at 7.44-8.38 for aromatic nucleus, singlet at 8.39 for N=CH peak, singlet at 4.0 for aromatic NH group and three singlet at 2.85 for three N-methyl groups. Elem Anal Calc: C, 30.61; H, 2.83; Cl, 9.04; Cu, 8.10; I, 32.34; N, 8.92; O, 4.08; S, 4.09. Elem Anal Found: C, 30.59; H, 2.81; Cl, 9.14; Cu, 8.00; I, 32.14; N, 8.82; O, 4.18; S, 4.00.

B2- Zinc metal complex of (E)- N-(4-(trimethyl amino) benzylidene)-4-(pyrimidin -2-sulfonamidyl) benzenamine

M.F: $C_{20}H_{22}Cl_2I_2N_5O_2SZn$. M.wt: 786.6. IR (KBr) cm-1: NH bond stretching at 3400 cm-1, C=N bond stretching at 1690 cm-1, S=O stretching at 1140 cm-1, C=C stretching at 1600 and 1475 cm-1. H^1 NMR (CDCl3) δ values: Multiplet at 7.44-8.38 for aromatic nucleus, singlet at 8.39 for N=CH peak, singlet at 4.0 for aromatic NH group and three singlet at 2.85 for three N-methyl groups. Elem Anal Calc: C, 30.54; H, 2.82; Cl, 9.01; I, 32.27; N, 8.90; O, 4.07; S, 4.08; Zn, 8.31. Elem Anal Found: C, 30.44; H, 2.92; Cl, 9.00; I, 32.26; N, 8.95; O, 4.17; S, 4.13; Zn, 8.21

B3- Cadmium metal complex of (E)- N-(4-(trimethyl amino) benzylidene)-4-(pyrimidin -2-sulfonamidyl) benzenamine.

M.F: $C_{20}H_{22}CdCl_2I_2N_5O_2S$. M.wt: 833.6. IR (KBr) cm-1: NH bond stretching at 3400 cm-1, C=N bond stretching at 1690 cm-1, S=O stretching at 1140 cm-1, C=C stretching at 1600 and 1475 cm-1. H^1 NMR ($CDCl_3$) δ values: Multiplet at 7.44-8.38 for aromatic nucleus, singlet at 8.39 for N=CH peak, singlet at 4.0 for aromatic NH group and three singlet at 2.85 for three N-methyl groups. Elem Anal Calc: C, 28.82; H, 2.66; Cd, 13.48; Cl, 8.51; I, 30.45; N, 8.40; O, 3.84; S, 3.85. Elem Anal Found: C, 28.92; H, 2.56; Cd, 13.42; Cl, 8.57; I, 30.40; N, 8.45; O, 3.82; S, 3.87

b) Anti inflammatory activity of synthesized compounds

Anti inflammatory activity was carried by paw oedema method using diclofenac sodium as standard. The results are given in the table-1. Currently used anti-inflammatory drugs are associated with some severe side effects. Therefore, the development of potent anti-inflammatory drugs with fewer side effects is necessary. A major factor limiting their use is gastrointestinal toxicity. In recent years, Schiff bases are widely used in formulating various types of drugs for their diversive biological activities. Metal complexes of Schiff bases have also been used as anti-inflammatory and antiarthritic agents. Anti- inflammatory of Zn (II) and Cu(II) complexes of indomethacin has been reported previously (Venugopala, 2003, Wei, 2006, Alam, 2012 & Sondhi, 2006), based on this we have evaluated anti-inflammatory activity of synthesized metal complexes. The down regulation of pro-inflammatory mediators through interaction of cationic lipids with the PKC pathway may explain this anti-inflammatory activity. Furthermore, since cationic lipids have intrinsic anti-inflammatory activity. Studies indicating that the release of cationic lipids into the macrophage cytoplasm is a necessary step for anti-inflammatory activity (Mario, 1997). Results revealed that the copper metal complexes (20mg/kg.b.wt) of Schiff bases of sulpha drugs A1, B1 showed excellent anti-inflammatory activity in carrageenan induced edema method by comparing with standard drug diclofenac sodium (10mg/kg.b.wt). It was thus confirmed that copper complexes, a unique class of potentially more therapeutically useful anti-inflammatory drugs. These results demonstrate that cationic lipids can be considered as novel anti-inflammatory agents.

Table1 : Results of *in vivo* anti inflammatory activity of metal complexes of schiff's base of Sulphadiazine

	Group	Dose	Paw volume (ml)				Difference Vc-Vt/Vc	Mean value	% anti-inflammatory activity
			0 hour	1 hour	2 hour	3 hour			
Group-I	Control	1% CMC	0.2	0.6	0.5	0.5	0.4	0.33	-
			0.2	0.6	0.6	0.7	0.4		
			0.2	0.5	0.6	0.6	0.3		
			0.2	0.5	0.6	0.7	0.3		
			0.2	0.5	0.5	0.8	0.3		
			0.2	0.5	0.7	0.8	0.3		
Group-II	Compound 1A1	(20mg/kg b.wt)	0.3	0.3	0.1	0.1	0	0.06	81***
			0.3	0.4	0.2	0.2	0.1		
			0.3	0.3	0.2	0.1	0		
			0.3	0.4	0.2	0.1	0.1		
			0.3	0.4	0.2	0.2	0.1		
			0.2	0.3	0.2	0.2	0.1		
Group-III	Compound 1A2	(20mg/kg b.wt)	0.3	0.5	0.4	0.3	0.2	0.20	39*
			0.3	0.6	0.4	0.3	0.3		
			0.3	0.5	0.4	0.3	0.2		
			0.2	0.4	0.2	0.2	0.2		
			0.3	0.4	0.3	0.2	0.1		
			0.3	0.5	0.4	0.4	0.2		
Group IV	Compound 1A3	(20mg/kg b.wt)	0.3	0.5	0.5	0.4	0.2	0.23	30*
			0.3	0.6	0.4	0.4	0.3		
			0.2	0.4	0.3	0.3	0.2		
			0.3	0.5	0.4	0.4	0.2		
			0.3	0.6	0.5	0.3	0.3		
			0.3	0.5	0.5	0.4	0.2		
Group V	Compound 1B1	(20mg/kg b.wt)	0.3	0.4	0.2	0.1	0.1	0.05	84***
			0.3	0.3	0.2	0.1	0		
			0.3	0.3	0.2	0.2	0		
			0.3	0.4	0.1	0.1	0.1		
			0.3	0.4	0.2	0.1	0.1		
			0.3	0.3	0.2	0.1	0		

Group VI	Compound 1B2	(20mg/kg b.wt)	0.3	0.5	0.4	0.4	0.2	0.18	45**
			0.3	0.6	0.5	0.2	0.3		
			0.3	0.5	0.4	0.3	0.2		
			0.3	0.4	0.2	0.1	0.1		
			0.3	0.4	0.3	0.2	0.1		
			0.3	0.5	0.4	0.4	0.2		
Group-VII	Compound 1B3	(20mg/kg b.wt)	0.3	0.6	0.4	0.4	0.3	0.26	21*
			0.3	0.7	0.5	0.5	0.4		
			0.3	0.5	0.5	0.1	0.2		
			0.3	0.4	0.7	0.2	0.1		
			0.3	0.7	0.8	0.7	0.4		
			0.3	0.5	0.7	0.4	0.2		
Group VIII	Standard Diclofenac sodium	10mg/kg	0.2	0.2	0.2	0.1	0	0.05	84***
			0.2	0.3	0.1	0.1	0.1		
			0.2	0.3	0.2	0.1	0.1		
			0.3	0.4	0.1	0.2	0.1		
			0.2	0.3	0.1	0.1	0.1		
			0.2	0.3	0.1	0.16	0.1		

n = 6. Values are expressed as ± S.E.M.

***P< 0.001, **P< 0.01, *P< 0.05, ns P > 0.05 Vs Control (One way ANOVA followed by Dunnett's test).

c) Antidepressant activity of synthesized compounds

Anti depressant activity was evaluated by force swim test method, the animals which are immobile for less time considered as active. The results are given the table-2. Results revealed that the zinc metal complexes (20mg/k.b.wt) of Schiff bases of sulpha drug A2, B2 showed excellent anti-depressant activity in reducing the duration of depressed behavior in animal models by despair swim test when compared with the standard drug Imipramine (5mg/kg.b.wt).

Table 2 : Results of *in vivo* anti depressant activity of metal complexes of schiff's base of Sulphadiazine

S.No	Treatment	Immobile response in 5 minutes		Percentage response (%)
		Before treatment	After treatment	
1	Group-I Control (1% CMC)	3.20	3.66	-
		2.86	3.14	
		3.12	3.00	
		3.56	3.66	
		3.88	3.22	
		2.88	2.86	
2	Group-II Standard (Imipramine 5mg/kg.b.wt)	3.28	1.48	65***
		3.86	1.76	
		3.42	1.34	
		3.66	0.68	
		3.18	0.86	
		3.88	1.26	
3	Group-III A1 (20mg/kg.b.wt)	3.88	1.88	51**
		4.66	1.86	
		4.12	1.96	
		2.44	1.44	
		3.72	1.63	
		3.34	1.86	
4	Group-IV A2 (20mg/kg.b.wt)	4.20	1.66	75***
		3.86	0.88	
		4.12	1.22	
		3.44	0.86	
		4.66	0.66	
		2.88	0.46	
5	Group-V A3 (20mg/kg.b.wt)	3.88	1.88	37**
		2.88	1.42	
		3.56	2.88	
		4.66	3.68	

		3.98	2.24	
		4.00	2.62	
6	Group-VI B1 (20mg/kg.b.wt)	4.20	2.61	34*
		2.86	2.02	
		3.72	1.68	
		3.48	2.82	
		3.88	2.86	
		4.88	2.92	
7	Group-VII B2 (20mg/kg.b.wt)	3.20	1.42	67***
		2.86	1.04	
		4.44	1.22	
		4.33	1.06	
		3.86	1.48	
		2.56	0.66	
8	Group-VIII B3 (20mg/kg.b.wt)	4.20	2.86	29*
		3.86	1.98	
		3.62	2.80	
		3.56	2.98	
		3.86	2.62	
		3.58	2.68	

n = 6. Values are expressed as ± S.E.M. ***P< 0.001, **P< 0.01, *P< 0.05, ns P > 0.05 Vs Control (One way ANOVA followed by Dunnett's test)

The most probable causes for depression are connected with the loss of homeostasis of the stress hormones, neurotransmitters, and disturbed trace elements levels. It has been reported that successful depression therapy can lead to zinc level normalization. It is reported that early life stress is a major risk factor for development of later depression due to affected neurogenesis in brain, especially in hippocampus. On the molecular level, these processes may be zinc-dependent via antioxidative activity changes and its influence on proper course of brain development process (Malgorzata, 2014, Chandramouli, 2012). There is an evidence for the role of mitochondrial dysfunction in the pathophysiology and treatment of neurodegenerative diseases, including mood disorders (Kato, 2000, Stork, 2005). Respiratory rate is a parameter characterizing functioning of the oxidative phosphorylation. The mitochondrial hypothesis states that impaired energy metabolism of brain cells is involved in the pathophysiology of antidepressants. The therapeutic or side effects of drugs administered in the treatment of depression may involve the targeted regulation of mitochondrial functions. In previous study it is reported that there is a direct mitochondrial targeting is involved in mechanisms of action of pharmacologically different antidepressants. Antidepressants are potent partial inhibitors of mitochondrial respiration (Jana, 2012).

IV. Conclusion

Cationic amphiphilic drugs (CADs) represent compounds of different therapeutic classes such as antidepressants, neuroleptics, and antiarrhythmics. In their neutral, lipophilic form cationic amphiphilic drug enter cells and their organelles. In acidic cellular compartments these drugs become efficiently protonated and thus trapped in, e.g. lysosomes. By increasing the permeability of drug molecule in brain to cross blood-brain barrier, which improves the antidepressant property and release of cationic lipids into the macrophage cytoplasm is a necessary step for anti-inflammatory activity.

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