SYNTHESIS, CHARACTERIZATION, MOLECULAR DOCKING OF SULPHANILAMIDE SCHIFF BASE METAL COMPLEXES AND ITS ANTIBACTERIAL, ANTI-INFLAMMATORY AND ANTI DEPRESSANT ACTIVITY

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Abstract: In our study we have a tendency to synthesized schiff' base of bactericide drug sulphanilamide on treating with aromatic aldehydes like p-diethyl amino benzyldehyde and p-dimethyl amino benzyldehyde. The synthesized schiff's bases were regenerate to its ion Schiff bases by treating with methyl group halide. The ion Schiff bases were regenerate to metal complexes by treating with metals like CuCl2, ZnCl2 and CdCl2. All the synthesized compounds were characterised by Elemental analysis, IR and ^{1}H proton magnetic resonance. Docking study was performed to know the interaction of binding sites with protein receptor using MAO-B enzymes (PDB ID: 2BK5) and COX-2 enzyme (PDB ID: 5IKR) by Virtual Screening software for Computational Drug Discovery. Synthesized metal complexes were evaluated for antibacterial, anti inflammatory and antidepressant activity. Copper metal complexes showed potent antibacterial and anti-inflammatory activity. Significant anti-depressant activity was shown for 1A2 and 1B2 zinc metal complexes**.**

Keywords: Sulphanilamide, antibacterial, anti-inflammatory, antidepressant activity

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INTRODUCTION

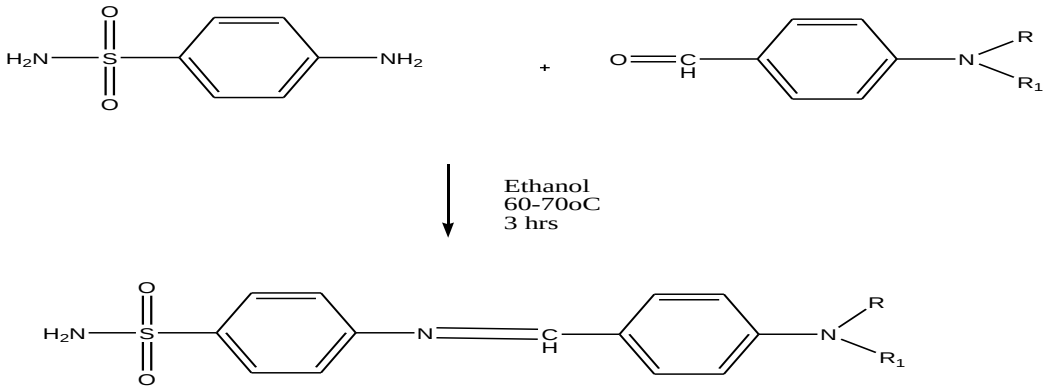
Schiff bases area unit the vital compounds within the field of healthful chemistry due to their wide selection of biological activities and industrial applications. Many studies showed that the presence of a lone combine of electrons during a sp2 hybridized orbital area unit of biological importance. Development of a replacement chemotherapeutical Schiff base could be a new space of analysis. Several studies are according relating to the biological activities of Schiff base viz. Anticancer, antibacterial drug antifungal and herbicidal activities. They conjointly function a back base for the synthesis of assorted heterocyclic compounds [1, 2]. We all need iron, copper and atomic number 30 for traditional brain perform however metal metabolism becomes dysregulated during a sort of neurodegenerative diseases. Metals accumulate in Alzheimer's {disease|Alzheimer's|Alzheimers|presenile insanity} dementia and shaking palsy and are deficient in Menkes disease. Whether or not excess metals seem as a cause or a consequence of the illness method isn't sure, however accumulation of metals have the potential to trigger cellular harm. During a healthy brain, metals ar tightly regulated. Through a sublime system of copper chaperones that taxi copper from the cell surface to specific living thing destinations, there's primarily no free copper in cells. Cellular iron isn't regulated by chaperones however rather by iron regulative proteins that orchestrate and synchronize iron uptake with iron storage to cut back the supply of free iron. In distinction to copper and iron, atomic number 30 is that the 'wild card' of brain metal metabolism as a result of not solely will it contribute to the site of key antioxidative metalloenzymes, like the Cu-Zn SOD, however it additionally exists as free atomic number 30 in some colligation vesicles and acts as a neurochemical. Once brain tissue is broken, like following a stroke, free atomic number 30 will flood the abraded areas leading to necrobiosis thanks to atomic number 30 excitotoxicity. Transition metals perform an outsized vary of biological functions at intervals the brain. a standard feature is their ability to exist during a sort of chemical reaction states and participate in reaction reactions; therefore copper, iron, and metal ar all catalytically active metals during a category of enzymes that sequester free radicals. it's helpful to appear at the common and ranging functions of transition metals within the brain to higher perceive what mechanisms ar noncontinuous in metal dyshomeostasis and the way this could cause necrobiosis in diseases of the central nervous system [3-5].

Literature review reveals that synthesized schiff's base metal complexes possess sensible medicine property. Antibacterial medicines are accepted antimicrobial agents, which are wide utilized in varied diseases. up to now

antibacterial drug metal advanced has not been synthesized. Thus we have a tendency to aim to synthesize schiff's base of antibacterial medicine with aromatic organic compound like p-diethyl amino benzyldehyde and p-dimethyl amino benzyldehyde and to make metal complexes higher than schiff's base with metals like copper, metal and metallic element.

MATERIALS AND METHODS

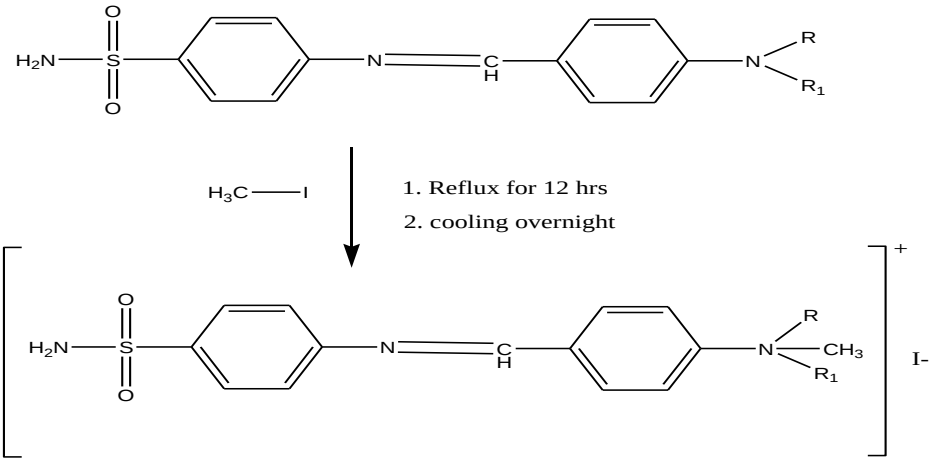
Scheme-1: (Synthesis of Sulphanilamide Schiff base)



Compound 1A **R-C_2H_5, R_1-C_2H_5**
Compound 1B **R-CH_3, R_1-CH_3**

Synthesis of Schiff's Base

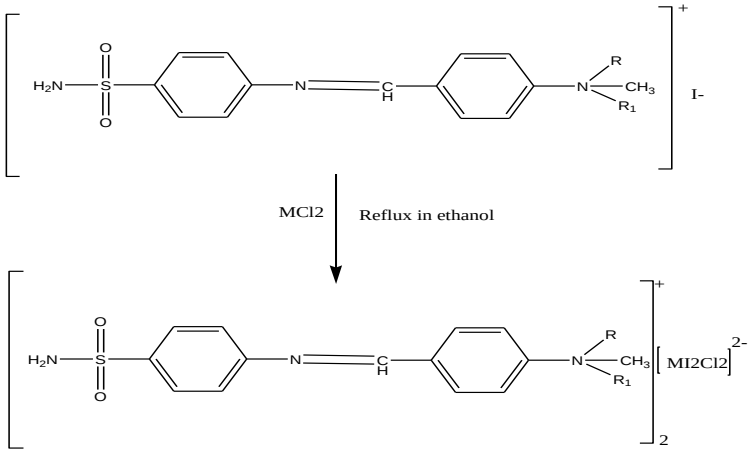
Scheme 2 (Synthesis of cationic Schiff base)



Compound 1A **R-C_2H_5, R_1-C_2H_5**
Compound 1B **R-CH_3, R_1-CH_3**

Synthesis of cationic derivative of Schiff base

Scheme 3 (Synthesis of cationic Schiff base metal complex)



Compound 1A R-C_2H_5, R_1-C_2H_5
Compound 1B R-CH_3, R_1-CH_3
MCl_2- $CuCl_2$, $Zncl_2$ and $CdCl_2$

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. The reaction mixture was left overnight to complete the precipitation of the products. The products were recrystallized with ethanol to obtain pure products.

Docking study: Docking study was performed to know the interaction of binding sites with protein receptor using MAO-B enzymes (PDB ID: 2BK5) and COX-2 enzyme (PDB ID: 5IKR) by by Virtual Screening software for Computational Drug Discovery [9].

Anti bacterial activity: Required range of Muller agar plates were ready and divided into range of quadrant.Then the plates were inoculated with acknowledged take a look at organism. Sterile discs were placed with in every quadrant.Using small measuring device ten small cubic decimeter of saturated resolution of the derivatives is applied on the individual discs.Then the plates square measure incubated at 37°C for eighteen to twenty four hrs. Once incubation for every spinoff against completely different organisms was measured and tabulated [10, 11].

Determination of median lethal doses (LD50): nimal's Swiss mice (20-25gm) and Male Sprague - Dawley rats (160-180) were maintained at customary diet and ad physical attraction. The experiment protocol was approved from institutional moral committee. LD50 values were calculable by the "acute toxicity test" as delineate elsewhere. The take a look at compounds were dissolved in three nothing DMSO administered orally to completely different teams with increasing doses. Six animals were taken in every cluster. Mortality make up my mind once twenty four hours of treatment. The dose, at that the fifty nothing mice survived, was thought of as LD50 worth of the compound [12].

Anti inflammatory activity: Swiss mice were divided into 5 teams of six animals every. The take a look at teams received orally twenty mg/kg of every sample. The reference cluster received diclofenac sodium (10 mg/kg, p.o) whereas the management cluster received vehicle (tween 80). After 1h, 0.1 mL, 1 Chronicles w/v carrageenin suspension in traditional saline was injected into the subplanatar tissue of the correct hind paw. The paw volume was measured at 30min. 1, 2,3 and 4hr once carageenan injection employing a micrometer screw gauge. The proportion inhibition of the inflammation was calculated [13].

Anti depressant activity

Male Sprague - Dawley rats consideration 160-180 grams are used. They are brought to the laboratory at least one day before the experiment and are housed one by one in makrolon cages with free access to food and water. Naïve rats are one by one forced to swim within a vertical Plexiglas. Rats placed in cylinders for the 1st time are at first extremely active, smartly swimming in circles, attempting to climb the wall or diving. Once 5-6 minutes immobility reaches a tableland wherever the rats stay immobile for around eightieth of the time. Once quarter-hour in the water the rats are removed and allowed to dry in a heated enclosure (32 c) before came back to their home cages. They are once more placed in the cylinder twenty four hours later and the total period of immobility is measured throughout a 5minute take a look at. Floating behaviour throughout this five minutes amount has been found to be duplicable in totally different teams of rats. Associate in Nursing animal is judged to be immobile whenever it remains floating passively in the water in a slightly round-backed however up-right position, its nose simply on top of the surface. take a look at medicine or commonplace are administered one hour before testing. Since experiments with the commonplace drug (Imipramine) showed that injections one,5 and twenty four previous the take a look at gave the most stable results in reducing floating these times are chosen for the experiment [14].

RESULTS AND DISCUSSION

Characterization of synthesized compounds

1A1- Copper metal complex of *(E)*- N-(4-(diethyl, methyl amino) benzylidene)-(4-sulfonamidyl) benzenamine.

M.F: $C_{18}H_{24}Cl_2CuI_2N_3O_2S$. M.wt: 732.73. IR (KBr) cm^{-1}: NH bond stretching at 3430 cm^{-1}, C=N bond stretching at 1690 cm^{-1}, S=O stretching at 1140 cm^{-1}, C=C stretching at 1640 and 1475 cm^{-1}. H^1 NMR ($CDCl_3$) δ values: Multiplet at 7.44-7.9 for aromatic nucleus, singlet at 8.63 for N=CH peak, singlet at 2.49 for NH_2 peak, two triplet at 1.33 for two CH_3 groups in N-ethyl substitution, singlet at 3.34 for N-methyl substitution. Elem Anal Calc: C, 29.42; H, 3.29;

Cl, 9.65; Cu, 8.65; I, 34.54; N, 5.72; O, 4.36; S, 4.36. Elem Anal Found: C, 28.42; H, 3.12; Cl, 9.98; Cu, 8.47; I, 34.24; N, 5.01; O, 4.28; S, 3.98.

1A2- Zinc metal complex of *(E)*- N-(4-(diethyl, methyl amino) benzylidene)-(4-sulfonamidyl) benzenamine.

M.F: $C_{18}H_{24}Cl_2I_2N_3O_2SZn$. M.wt: 736.6. IR (KBr) cm^{-1}: NH bond stretching at 3428 cm^{-1}, C=N bond stretching at 1690 cm^{-1}, S=O stretching at 1140 cm^{-1}, C=C stretching at 1670 and 1465 cm^{-1}. H^1 NMR ($CDCl_3$) δ values: Multiplet at 7.44-7.9 for aromatic nucleus, singlet at 8.63 for N=CH peak, singlet at 2.49 for NH_2 peak, two triplet at 1.33 for two CH_3 groups in N-ethyl substitution, singlet at 3.34 for N-methyl substitution. Elem Anal Calc: C, 29.35; H, 3.28; Cl, 9.63; I, 34.46; N, 5.70; O, 4.34; S, 4.35; Zn, 8.88. Elem Anal Found: C, 29.34; H, 3.29; Cl, 9.65; I, 34.02; N, 5.98; O, 4.34; S, 4.54; Zn, 8.68.

1A3- Cadmium metal complex of *(E)*- N-(4-(diethyl, methyl amino) benzylidene)-(4-sulfonamidyl) benzenamine.

M.F: $C_{18}H_{24}CdCl_2I_2N_3O_2S$. M.wt: 783.6. IR (KBr) cm^{-1}: NH bond stretching at 3412 cm^{-1}, C=N bond stretching at 1698 cm^{-1}, S=O stretching at 1143 cm^{-1}, C=C stretching at 1633 and 1485 cm^{-1}. H^1 NMR ($CDCl_3$) δ values: Multiplet at 7.44-7.9 for aromatic nucleus, singlet at 8.63for N=CH peak, singlet at 2.49 for NH_2 peak, two triplet at 1.33 for two CH_3 groups in N-ethyl substitution, singlet at 3.34 for N-methyl substitution. Elem Anal Calc: C, 27.59; H, 3.09; Cd, 14.35; Cl, 9.05; I, 32.39; N, 5.36; O, 4.08; S, 4.09. Elem Anal Found: C, 27.69; H, 3.19; Cd, 14.05; Cl, 9.15; I, 32.09; N, 5.38; O, 4.18; S, 4.00.

1B1- Copper metal complex of *(E)*- N-(4-(trimethyl amino) benzylidene)-(4-sulfonamidyl) benzenamine.

M.F: $C_{16}H_{20}Cl_2CuI_2N_3O_2S$. M.wt: 706.7. IR (KBr) cm^{-1}: NH bond stretching at 3410 cm^{-1}, C=N bond stretching at 1680 cm^{-1}, S=O stretching at 1140 cm^{-1}, C=C stretching at 1630 and 1465 cm^{-1}. H^1 NMR ($CDCl_3$) δ values: Multiplet at 7.44-7.9 for aromatic nucleus, singlet at 8.53 for N=CH peak, singlet at 2.49 for NH_2 peak, three singlet peak at 3.00 for three N-methyl groups. Elem Anal Calc: C, 27.19; H, 2.85; Cl, 10.03; Cu, 8.99; I, 35.92; N, 5.95; O, 4.53; S, 4.54. Elem Anal Found: C, 27.29; H, 2.65; Cl, 10.13; Cu, 8.89; I, 35.62; N, 5.95; O, 4.83; S, 4.64.

1B2- Zinc metal complex of *(E)*- N-(4-(trimethyl amino) benzylidene)-(4-sulfonamidyl) benzenamine.

M.F: $C_{16}H_{20}Cl_2I_2N_3O_2SZn$. M.wt: 708.5. IR (KBr) cm^{-1}: NH bond stretching at 3390 cm^{-1}, C=N bond stretching at 1670 cm^{-1}, S=O stretching at 1140 cm^{-1}, C=C stretching at 1650 and 1485 cm^{-1}. H^1 NMR ($CDCl_3$) δ values: Multiplet at 7.44-7.9 for aromatic nucleus, singlet at 8.11 for N=CH peak, singlet at 2.49 for NH_2 peak, three singlet peak at 3.02 for three N-methyl groups. Elem Anal Calc: C, 27.12; H, 2.85; Cl, 10.01; I, 35.82; N, 5.93; O, 4.52; S, 4.53; Zn, 9.23. Elem Anal Found: C, 27.14; H, 2.87; Cl, 10.11; I, 35.92; N, 5.94; O, 4.58; S, 4.47; Zn, 9.24.

1B3- Cadmium metal complex of *(E)*- N-(4-(trimethyl amino) benzylidene)-(4-sulfonamidyl)benzenamine.

M.F: $C_{16}H_{20}CdCl_2I_2N_3O_2S$. M.wt: 755.5. IR (KBr) cm^{-1}: NH bond stretching at 3425 cm^{-1}, C=N bond stretching at 1680 cm^{-1}, S=O stretching at 1150 cm^{-1}, C=C stretching at 1630 and 1465 cm^{-1}. H^1 NMR ($CDCl_3$) δ values: Multiplet at 7.44-7.9 for aromatic nucleus, singlet at 8.53 for N=CH peak, singlet at 2.49 for NH_2 peak, three singlet peak at 3.01 for three N-methyl groups. Elem Anal Calc: C, 25.43; H, 2.67; Cd, 14.88; Cl, 9.38; I, 33.59; N, 5.56; O, 4.24; S, 4.24. Elem Anal Found: C, 25.33; H, 2.47; Cd, 14.68; Cl, 9.78; I, 33.29; N, 5.88; O, 4.14; S, 4.24

Molecular Docking Studies of synthesized Schiff's base metal complexes compounds

To understand the interaction of all the synthesized compounds (1A1-1A3 and 1B1-1B3) with MAO-B enzyme and COX-2 enzyme, the crystal structure of MAO-B enzyme and COX-2 enzyme was downloaded from Protein Data Bank (PDB ID: 2BK5 and 5IKR) and the molecular docking studies were performed.

Molecular Docking Studies of synthesized Schiff's base metal complexes compounds with COX-2 enzyme (PDB ID: 5IKR).

The ligands 1B1had a -score value of −9.2 to −7.7 against COX-2 enzyme (PDB ID: 5IKR)(Table- and figure-).

Table- 1. B1 ligand with COX-2 enzyme (PDB ID: 5IKR)

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
5ikr_macro_prepared_1B1_ligand	-9.2	0	0
5ikr_macro_prepared_1B1_ligand	-8.9	28.184	27.121
5ikr_macro_prepared_1B1_ligand	-8.9	26.184	24.747
5ikr_macro_prepared_1B1_ligand	-8.5	2.982	2.542
5ikr_macro_prepared_1B1_ligand	-8.2	9.715	7.154
5ikr_macro_prepared_1B1_ligand	-7.9	13.397	11.029
5ikr_macro_prepared_1B1_ligand	-7.9	7.371	6.197
5ikr_macro_prepared_1B1_ligand	-7.9	37.156	35.609
5ikr_macro_prepared_1B1_ligand	-7.7	26.637	25.218

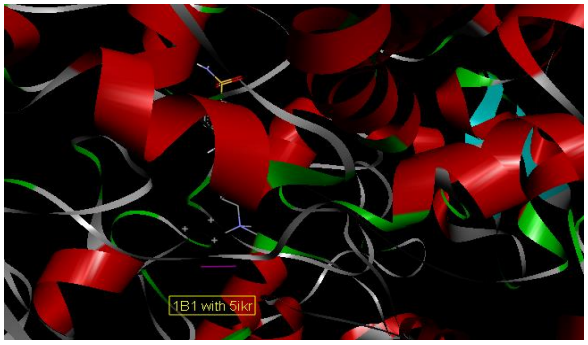


Figure 1. 1B1. ligand with COX-2 enzyme (PDB ID: 5IKR)

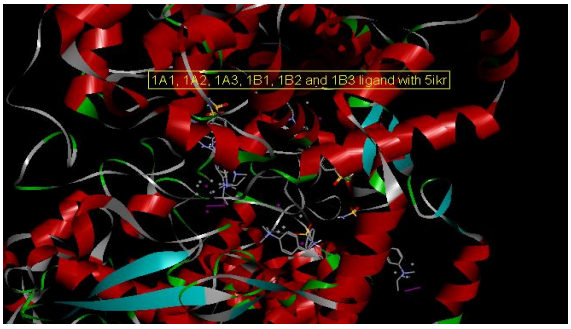


Figure 2. 1A1, 1A2,1A3, 1B1, 1B2 and 1B3 ligands withCOX-2 enzyme (PDB ID: 5IKR)

Out of all synthesized compounds 1B1 gave good score value with COX-2 enzyme than the standard. The minimum Glide energy required for the formation of complex between ligand and the receptor indicates excellent binding affinity.

Molecular Docking Studies of synthesized Schiff's base metal complexes compounds withMAO-B enzymes (PDB ID: 2BK5)

The ligands 1B2had a -score value of −8.2 to −6.8 against MAO-B enzymes (PDB ID: 2BK5)
(Table- and figure-).

Table 2. 1B2 ligand with MAO-B enzymes (PDB ID: 2BK5)

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
2bk5_macro_prepared_1B2_ligand	-8.2	0	0
2bk5_macro_prepared_1B2_ligand	-7.6	7.796	6.657
2bk5_macro_prepared_1B2_ligand	-7.1	15.7	14.044
2bk5_macro_prepared_1B2_ligand	-7.1	15.736	13.963
2bk5_macro_prepared_1B2_ligand	-6.9	48.331	45.858
2bk5_macro_prepared_1B2_ligand	-6.9	8.574	7.128
2bk5_macro_prepared_1B2_ligand	-6.9	13.854	12.857
2bk5_macro_prepared_1B2_ligand	-6.8	34.111	31.627
2bk5_macro_prepared_1B2_ligand	-6.8	15.948	14.438

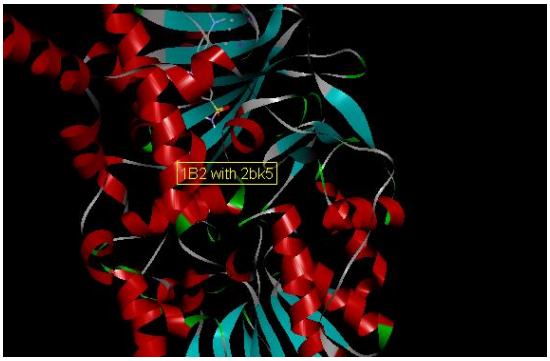


Figure 3. 1B2 ligand with MAO-B enzymes (PDB ID: 2BK5)

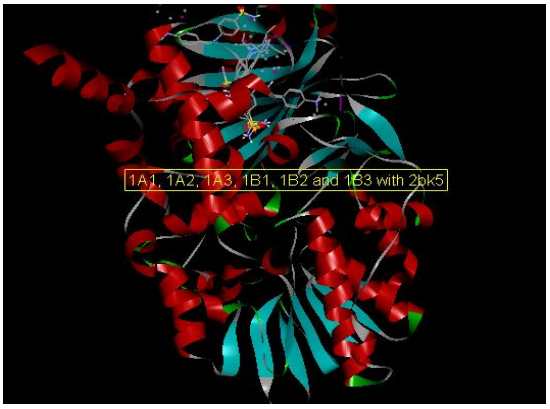


Figure 4. 1A1, 1A2,1A3, 1B1, 1B2 and 1B3 ligands with MAO-B enzymes (PDB ID: 2BK5)

Out of all synthesized compounds 1B2 gave good score value with MAO-B enzymes than the standard. The minimum Glide energy required for the formation of complex between ligand and the receptor indicates excellent binding affinity.

Antibacterial activity

Antibacterial activity was carried out by disc plate method using *B.cereus, E.coli, and P. aeruginosa* microorganism. The results are calculated and given in the table-3. The results of antibacterial activity revealed that the ligand with the Cd, Zn complexes does not exhibit antibacterial activities. However it is important to note that ligand with Cu complex exhibits potent antimicrobial activities. The Cu complex shows more activity than the Cd and Zn complex. This perhaps because of the upper stability of copper advanced than the Cd and metal advanced. The microorganisms take up metal ions on their cell walls and as a result respiration processes of cells square measure disturbed and macromolecule synthesis is blocked that is that the demand for more growth of organisms. the expansion inhibition effects of metal ions square measure goodly [15].

Table 3. Results of antibacterial activity of Schiff's base metal complexes of Sulphanilamide

S.No	Compounds	Zone of inhibition (mm)		
		B. cereus	*E. coli*	*P.aeruginosa*
1	1A1	**25**	**24**	**22**
2	1A2	25	18	24
3	1A3	21	20	20
4	1B1	20	**24**	**22**
5	1B2	22	17	18
6	1B3	19	17	19
7	Streptomycin	**24**	**24**	**21**

Anti inflammatory activity of synthesized compounds

Anti inflammatory activity was carried by paw oedema method and results shows that compound 1A1 and 1B1 at dose level of 20mg/kg.b.wt. significant activity (81 and 84 % respectively) when compared to standard diclofenac 10mg/kg.b.wt (84%). In our study results revealed that copper complexes showed potent anti-inflammatory activity but zinc complexes posses moderate anti-inflammatory activity, whereas cadmium complexes has not shown considerable activity. It was confirmed that the elevation of plasma copper-containing elements represents a physical response which can result in remission. Promotion of this physical response may be a valid approach to the treatment of the diseases with inflammatory elements. it absolutely was therefore confirmed that copper complexes, a singular category of doubtless additional therapeutically helpful for anti inflammatory medication [16].

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 and results are given the table-4. The most probable causes for depression area unit connected with the loss of physiological condition of the strain hormones, neurotransmitters, and disturbed trace components levels. It's rumored that youth stress could be a major risk issue for development of later depression because of affected maturation in brain, particularly in hippocampus. On the molecular level, these methods are also zinc-dependent via antioxidative activity changes and its influence on correct course of brain development process [17].

Table 4. Results of in vivo anti depressant activity of schiff's base metal complexes of Sulphanilamide

S.No	Treatment	Immobile response in 5 minutes		Percentage response (%)
		Before treatment	After treatment	
1	Group-I Control (1% CMC)	3.20	3.90	-
		2.86	3.14	
		3.12	3.69	
		3.00	3.22	
		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 1A1 (20mg/kg.b.wt)	2.20	1.48	43
		2.86	1.49	
		3.44	1.64	
		3.33	1.44	
		3.23	1.86	
		2.56	1.88	
4	Group-IV 1A2 (20mg/kg.b.wt)	4.20	0.96	60
		3.86	1.82	
		4.12	1.46	
		3.44	1.34	
		3.66	1.66	
		2.88	1.46	

5	Group-V 1A3 (20mg/kg.b.wt)	3.88	1.66	54
		3.66	1.33	
		3.12	0.96	
		3.44	1.44	
		3.72	1.63	
		2.34	1.86	
6	Group-VI 1B1 (20mg/kg.b.wt)	3.20	1.68	51
		2.86	1.86	
		3.72	1.66	
		3.44	0.88	
		3.88	2.86	
		2.88	0.98	
7	Group-VII 1B2 (20mg/kg.b.wt)	3.88	1.22	63
		2.86	1.42	
		3.56	0.68	
		3.66	1.68	
		3.98	1.86	
		4.00	1.22	
8	Group-IV 1B3 (20mg/kg.b.wt)	3.20	2.54	34
		3.86	2.98	
		3.62	2.04	
		3.56	1.98	
		3.88	2.64	
		2.58	1.62	

CONCLUSION

In conclusion we synthesized Schiff base by reacting Sulphamethoxazole with p-diethyl amino benzyldehyde and p-dimethyl amino benzyldehyde, six metal complexes of Schiff base by treating with $CuCl_2$, $ZnCl_2$ and $CdCl_2$. *In silico* studies results showed that docked complexes are the results of accumulative result of these interactions that are expected to own higher pharmacological activities such as anti inflammatory and anti depressant activity. Copper metal complexes 1A1 showed potent antibacterial activity against *B.cereus* and copper metal complexes 1A1 and 1B1 showed potent antibacterial activity against *E.coli* and copper metal complexes 1A1 and 1B1showed potent antibacterial activity against *P.aeruginosa* strains. Copper metal complexes 1A1 and 1B1 showed excellent anti-inflammatory activity. Significant anti-depressant activity was shown for 1A2 and 1B2 zinc metal complexes. The above 1A1, 1B1, 1A2 and 1B2 compounds activities are supported by results of *in silico* docking studies. Hence we tend to conclude that Schiff's base metal complexes offer a flexible platform for etymologizing numerous pharmacologically active medicines.

Ethical approval: NA

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Conflicts of Interest - The authors report no conflicts of interest in this work.

Author contributions: Conceptualization, Docking. All authors have read and agreed to the published version of the manuscript.

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