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Schiff Base Derivative of Aldehydes with Diamino Compound and their Anti-Inflammatory Activity

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Abstract

A Schiff base is a ketone or aldehyde nitrogen analog in which the group between carbon and oxygen is substituted by the group C = N -R. Schiff's bases are commonly used compounds which interrelate through azomethine nitrogen with metal ions and they have applications in many fields including biological, analytical and inorganic chemistry. Schiff's bases are used in organic synthesis as coloring agent, as catalysts, as intermediates and also as polymer stabilizer. Schiff bases also exhibited anti-inflammatory activities. Bis-salicaldihyde synthesized using methanolic solution of salicylaldehyde which was reacted with ethylene diamine for 15 minutes at room temperature. The resulting compound was then characterized by melting point and pharmacological activities were done. Acute toxicity of the compound was also carried out. Studies were performed on albino mice on three different doses (50, 100 and 150 mg).Results revealed that bis-salisaldehyde have no toxicity upto 1000 mg dose, and have anti-inflammatory effects.

1. INTRODUCTION

Inflammation has acquired the attention of global research due to its implication in both human and animal diseases. Inflammatory abnormalities are considered as a giant group of disorders that trigger a huge variety of human diseases [1]. Inflammation is a crucial aspect of host response that escorts to infection, and is requisite to keep healthy condition against microbial infections. However, excessive inflammation may contribute to acute or chronic human diseases. Acne vulgaris, asthma, glomerulonephritis, hypersensitivities, coeliac disease, chronic prostatitis, inflammatory bowel diseases, rheumatoid arthritis, sarcoidosis, pelvic inflammatory disease, reperfusion injury, transplant rejection, autoimmune diseases, interstitial cystitis and vasculitis are some examples of disorders associated with inflammation [2-3]. Non-steroidal anti-inflammatory drugs (NSAIDs) were the first group that was used to treat inflammatory diseases. Commonly used anti-inflammatory drugs such as NSAIDs are associated with some adverse effects such as myocardial infarction, congestive heart failure, nausea/vomiting, dyspepsia, gastric ulceration/bleeding, diarrhoea hypertension and salt and fluid retention [4]. The NSAIDs may also cause renal failure when used in combination with some diuretic and ACE inhibitors (triple whammy effect), nephrotic syndrome, interstitial nephritis, acute tubular necrosis and acute renal failure [5]. NSAIDs may also be causing analgesic nephropathy when used in combination with phenacetin and/or paracetamol, photosensitivity, premature birth, hepatotoxicity, raised liver enzymes, hyperkalaemia, bronchospasm, rash and allergy, headache, dizziness, confusion. NSAIDs have been extensively used for the treatment of minor pain and for the management of oedema and tissue damage resulting from inflammatory joint disease (arthritis) [6-7].

Due to the limitations and adverse effects of existing anti-inflammatory drugs, there is an urgent need to develop novel therapeutic agents with enhanced efficacy and safety. Schiff bases, characterized by the azomethine (-CH=N-) functional group, have gained considerable attention in medicinal chemistry due to their broad-spectrum biological activities [8]. These compounds are known to interact with biological systems through their azomethine nitrogen, which plays a crucial role in metal coordination, enzyme inhibition, and receptor binding [4]. Schiff bases have demonstrated significant pharmacological effects, including antibacterial, antifungal, antiviral, anticancer, anticonvulsant, antihypertensive, and anti-inflammatory activities. The versatility of Schiff bases makes them attractive candidates for drug development [9].

Structurally, Schiff bases are synthesized by the condensation of primary amines with aldehydes or ketones, and their biological activity is largely influenced by the nature of the substituents attached to the azomethine moiety [10-11]. The introduction of electron-donating or electron-withdrawing groups in Schiff base derivatives can enhance their pharmacological properties by modulating lipophilicity, electronic distribution, and metal chelation capabilities. Additionally, Schiff bases containing heterocyclic nuclei, such as pyrazol-3-one, thiazolidinone, and imidazole, have been extensively investigated for their therapeutic applications [12-13].

In this study, Schiff base derivatives were synthesized using selected aldehydes and diamino compounds to evaluate their therapeutic potential. The incorporation of the pyrazol-3-one nucleus and azomethine linkage may enhance interactions with biological targets involved in inflammation. Pyrazol-3-one derivatives are known for their anti-inflammatory activities, making them promising candidates for the development of safer and more effective anti-inflammatory agents.

2. MATERIALS AND METHODS

2.1. CHEMICAL AND INSTRUMENT

The synthesis of the Schiff base compound was conducted in the Chemistry

Laboratory of the Department of Pharmacy, Sarhad University of Science and Information Technology, Peshawar**,** under the supervision ofProfessor Dr. Nazar ul Islam. The chemicals used in the synthesis included salicylaldehyde (Sigma-Aldrich, Germany), which was dissolved in methanol (Merck, Germany), and ethylene diamine (Sigma-Aldrich, UK), which was dissolved in ethanol (Merck, Germany). The reaction was performed at room temperature using standard laboratory glassware, following protocols established for Schiff base synthesis The reaction was carried out in a round-bottom flask (Pyrex, USA), which served as the primary reaction vessel. A water bath (Memmert, Germany) was used to control the temperature during cooling. Filtration was performed using a funnel and filter paper (Whatman No. 1, GE Healthcare, UK), while graduated beakers and pipettes (Eppendorf, Germany) were employed for precise measurement of reagents. In in vivo studies, various chemicals were used to assess the pharmacological activities of the synthesized Schiff base. These included dimethyl sulfoxide (DMSO) (Sigma-Aldrich, USA) and Tween 80 (Merck, Germany) as solvents, normal saline (B. Braun, Germany) as a control vehicle, and tramadol (Pfizer, USA), diclofenac sodium (Novartis, Switzerland), histamine (Sigma-Aldrich, France), carrageenan (Sigma-Aldrich, USA), Brewer's yeast (Merck, Germany), paracetamol (GSK, UK), and acetic acid (Sigma-Aldrich, Germany) for experimental assays.

2.2. SYNTHESIS

The synthesized compound was prepared through the condensation reaction between aldehyde and diamine to form a Schiff base. Generally, Schiff bases are synthesized by the reaction of primary amines with aldehydes in the presence of an organic solvent such as methanol. In this reaction, the amino group of ethylene diamine reacts with the carbonyl group of salicylaldehyde, resulting in the formation of an imine linkage (-C=N-) with the elimination of a water molecule [14]. The reaction scheme involved the condensation of aldehydes with diamino compounds to produce Schiff bases according to the following generalized reaction:

$$R{-}CHO + H_2N(CH_2)NH_2 \rightarrow H_2N(CH_2)N{=}CHR + H_2O$$

2.3. Breeding of experimental Animals:

The experimental study involved albino mice weighing 18–30 g, which were housed under standard conditions with regulated temperature (22 ± 2°C), humidity (55 ± 5%), and a 12-hour light-dark cycle**.** The animals were kept in stainless steel cages (Tecniplast, Italy) with soft wood shavingsas bedding and were provided with a standard pellet diet(Envigo, UK) and water ad libitum [15] (OECD, 2001). These conditions ensured compliance with international laboratory animal handling guidelines (OECD, 2001) [16].

2.4 Acute Toxicity:

Many tests are available for determining the effects of drugs on CNS activity and physiological functions. The acute toxicity of the synthesized compound was determined by the method described by Irwin. Albino mice of either sex, having weight of 24-30g were selected for study. The solution of the test compound was prepared in 3% DMSO and 2% tween 80 and adding 95% normal saline to it. [17-18].

2.5 Anti-inflammatory activity:

2.5.1 Carrageenan-induced paw edema in mice:

There are many methods for induction of edema in mice describe in literatures, but edema induced by carrageenan is most commonly used method for determination of acute inflammation [19]. Induction of inflammation by carrageenan is biphasic edema. Histamine and bradykinins are detected in first phase while prostaglandins detected in second phase. First phase edema is of low intensity while second phase edema has pronounced edema and develops after 24 h with maximal effect between 48 and 72 h [20-21].

Experimental protocols:

Animals were grouped and all the animals were fasted overnight, only water was given to them.

Group-I (control): Carrageenan (1% w/v suspension) was injected in the right hind foot.

Group-II (standard): This group receive diclofenac sodium at a dose of 5 mg/ kg body weight intraperitoneally (i.p).

Groups-III-V (compound treatments): Test samples will be given to this group at dose of 50, 100 & 150mg/ kg body weight i.p. respectively.

2.5.2 Histamine induced edema:

Local edema can be induced by subcutaneous injection of histamine (0.1%) in the hind paw of mice [22].

2.6 Statistical Analysis

All experimental data were expressed as mean ± standard error of mean (SEM) for six animals in each group (n=6). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test for multiple comparisons between the treated groups and the vehicle-treated control group. The differences were considered statistically significant at $p<0.05$. In the graphical presentation of data, *$p<0.05$, **$p<0.01$, and ***$p<0.001$ indicated significant differences compared with the vehicle-treated group [23].

3 RESULTS

3.1. Acute Toxicity

Studies of acute toxicity of Bis-salicyldehyde did not produce any significant change in the behaviour of animals like lack of convulsion, respiratory distress, writhing, changes in reflex activity and death. In one of the 20 animals from group V receiving 1000 mg 0f Bissalicydehyde, a slight increase in irritability and writhing was observed. All other 19 animals were healthy after 24 hours. No death was observed [24].

Animals were divided into 5 groups, each group containing 4 animals (n=4). All animals were weighed before starting of activity and then test compound was administered according to body weight in different doses described in the table no.1. After administration of test compound to four groups and normal saline to control group, behavioral changes were observed at 0 (immediately after injection), 30 and 60 minutes and then after 24 hours. Each animal was observed for the presence or absence of any behavioral symptoms and physiological changes and number of deaths were noticed.

Table no. 1. Acute toxicity.

GROUP	VEHICLE	DOSE (mg/kg)
1	Normal Saline	10 ml
2	Test Compound	300
3	Test Compound	500
4	Test Compound	700
5	Test Compound	1000

3.2.Carrageenan-induced paw edema

The study of the acute anti-inflammatory test showed that Bis-salicylaldehyde produced a significant (P=0.018) reduction at 3 h in Carrageenan induced paw edema when compared to the control group. This anti-inflammatory effect is comparable to that produced by tramadol Fig 1.

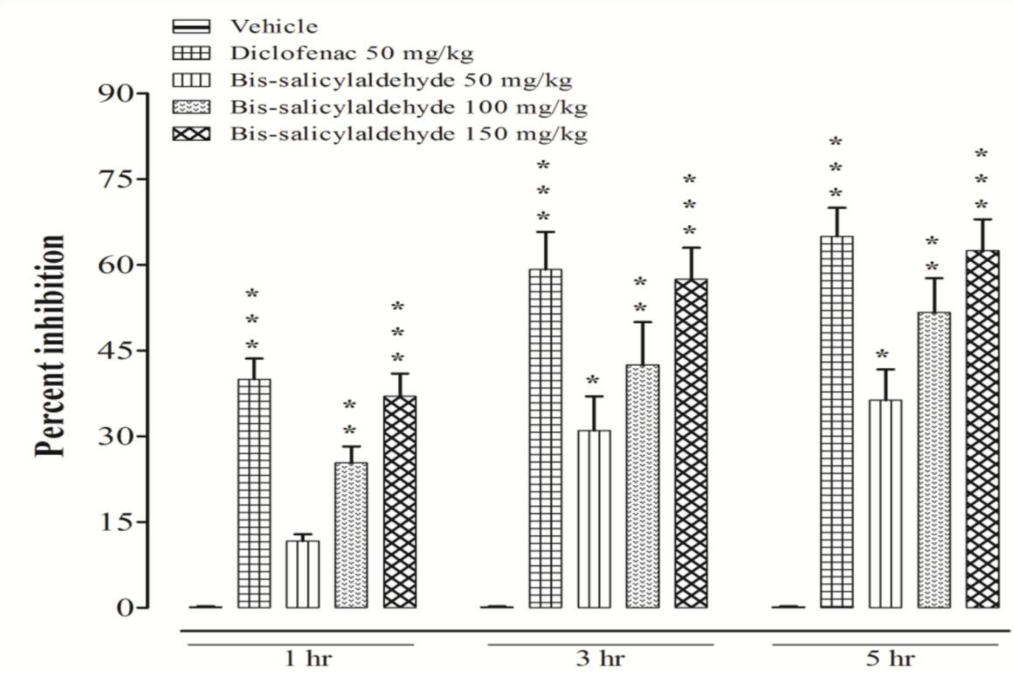

Figure 1: Anti-inflammatory effect of the Bis-salicylaldehyde on the carrageenan-induced paw edema in the mice. Bars show percent inhibition mean ± SEM and data were analyzed by one-way ANOVA followed by Dunnett posthoc test (n=6). *p<0.05, **p<0.01, and ***p<0.001 compared with the vehicle treated mice.

Table No. 2. Careegenan induced paw edema

	ehi c le	Di clo fe na c 50 mg /kg	Bis sal icy lde h yd e 50 mg /kg	Bis sal icy lde h yd e 10 0 mg /kg	Bis sal icy lde h yd e 15 0 mg /kg	ehi c le	Di clo fe na c 50 mg /kg	Bis sal icy lde h yd e 50 mg /kg	Bis sal icy lde h yd e 10 0 mg /kg	Bis sal icy lde h yd e 15 0 mg /kg	ehi cle	Di clo fe na c 50 mg /kg	Bis sal icy lde h yd e 50 mg /kg	Bis sal icy lde h yd e 50 mg /kg	Bis sal icy lde h yd e 50 mg /kg
ean …	.20 0 0	0.0 0	1.6 7	5.3 3	7.0 0	.20 0 0	9.1 8	1.0 0	2.5 0	7.5 0	.20 00	5.0 0	6.3 3	1.6 7	2.5 0
td. evi ati on	.10 0 0	.24 5	.08 2	.03 3	.65 7	.10 0 0	1.4 4	.48 5	0.6 1	.77 8	.10 00	.07 1	.29 2	0.4 1	.77 8

td. Err or	.05 7 74	.60 6	.20 2	.90 6	.00 0	.05 7 74	.60 6	.00 0	.50 0	.50 0	.05 77 4	.00 0	.36 4	.00 9	.50 0

3.3. Histamine-induced paw edema

Injecting histamine in the paw of mice produced a local edema with maximal rate detected within 1 h after injection and thereafter declined to the end of the experiment. Intraperitoneal injections of Bis-salicylaldehyde at doses of 100 and 150 mg/kg, but not at a dose of 50 mg/kg, significantly decreased 1, 2 and 3 h paw thickness induced by histamine ($F_{(3,80)} = 23.636$, $p<0.05$) (Figure 2).

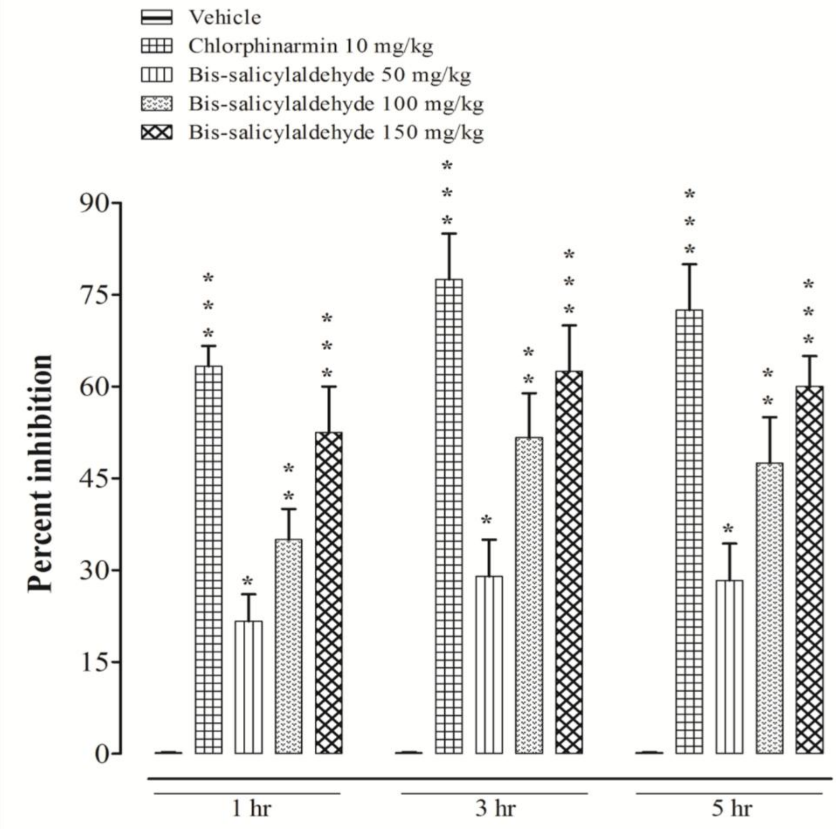

Figure 2: Anti-inflammatory effect of the Bis-salicylaldehyde on the histamineinduced paw edema in the mice. Bars depict percent inhibition mean ± SEM and data were analyzed by one-way ANOVA followed by Dunnett posthoc test (n=6). *p<0.05, **p<0.01, and ***p<0.001 compared with the vehicle treated mice.

Table. No. 3. Histamine induced paw edema

	eh i cl e	hlor phin ar ami ne 0mg /kg	Bi ss ali cy ld e hy de 50 m g/ kg	issal icyl de yde 100 mg/ kg	issal icyl de yde 150 mg/ kg	eh i cl e	hlor phin ar ami ne 0mg /kg	Bi ss ali cy ld e hy de 50 m g/ kg	issal icyl de yde 100 mg/ kg	issal icyl de yde 150 mg/ kg	ehi cl e …	hlor phin ar ami ne 0mg /kg	Bi ss ali cy ld e hy de 50 m g/ kg	Bi ss ali cy ld e hy de 50 m g/ kg	Bi ss ali cy ld e hy de 50 m g/ kg
ea n …	.2 0 00	3.33	1. 67	5.00	2.50	.2 0 00	7.50	9. 00	1.67	2.50	.20 00	2.50	8. 33	7. 50	0. 00
td. evi at ion	.1 0 00	.709	.6 38	.660	0.61	.1 0 00	0.61	.4 85	2.58	0.61	.10 00	0.61	0. 41	0. 61	.0 71
td. Er ror	.0 5 74	.330	.4 10	.000	.500	.0 5 74	.500	.0 00	.265	.500	.05 77 4	.500	.0 09	.5 00	.0 00

4. DISCUSSION

According to research done on pharmacological activities, it has been shown that Schiff bases have anti-inflammatory activities. Furthermore, Ceramella et al. (2022) studied this broad spectrum of biological applications, confirming that the incorporation of azomethine systems successfully yields anti-inflammatory properties. This is the first report regarding anti-inflammatory effect of Schiff's bases compound known as Bis-salicylaldehyde, according to our knowledge. Present studies confirmed that Bis-salicylaldehyde has noticeable anti-inflammatory properties with a reasonable safety profile [25].

The synthesis of a Schiff base from a ketone or aldehyde is a reversible reaction which usually occurs under catalysis of base or acid or by heating [26]. Generally, the formation of Schiff base is completed by removing water or separating item, or both, many of Schiff bases can be hydrolyzed by aqueous acid or base back to their old form. Sandhu et al. (2023) studied this structural condensation pathway, demonstrating how primary amines react with active carbonyl substrates to generate reversible azomethine linkages. Schiff's bases are commonly used compounds which interrelate through azomethine nitrogen with metal ions and they have applications in many fields including biological, analytical and inorganic chemistry [27]. This coordination capacity was further documented by K. Joshi (2022), who reported this behavior as an effective pathway where the basic imine nitrogen serves as a vital ligand for complexation in both analytical and biological chemistry fields [28].

Schiff's bases are used in organic synthesis as coloring agent, as catalysts, as intermediates and also as polymer stabilizers. Unver & Bektas (2018) reported this structural versatility, noting that azomethine derivatives are heavily exploited across synthetic chemistry due to their remarkable molecular stability and chemical adaptability [29].

Aldehydes and Ketones revealed anti-inflammatory activity. Bis-salicyldehyde might have anti-inflammatory effect due to presence of aldehyde group in its structure. Due to presence of isolated aldehydes, Bis-salicyldehyde have significant pharmacological activities as previous data on Schiff bases have been shown that this class of compound have inflammation relieving effect [30]. This is congruent with investigations by Arora et al. (2021), who studied this correlation and verified that aldehyde-derived Schiff bases serve as efficient chemical skeletons that actively reduce somatic pain and localized inflammatory swelling [31]. The observed activity might be due to the presence of active pharmacological metabolite that interfere with release of prostaglandins. Medetalibeyoğlu, Manap et al. (2025) reported this phenomenon in azomethine derivatives, observing that the metabolic cleavage or structural interaction of Schiff base complexes actively limits pro-inflammatory prostanoid discharge.

The acceptable preliminary screening test for anti-inflammatory action is carrageenan induced paw edema. Edema produced due to carrageenan is a two-phase process [32]. In the first phase due to release of serotonin, histamine and bradykinin, edema develops while in the second phase COX enzyme play key role in producing edema. Posadas et al. (2004) studied this biphasic inflammatory development, confirming that early-stage cellular swelling transitions into a prolonged COX-2 dependent cascade over subsequent hours. This enzyme is considered to be an identified target for a variety of anti-inflammatory drugs such as diclofenac sodium [33], which inhibit paw edema produced by injecting carrageenan. Therefore, for comparison three standards were used. Bis-salicylaldehyde significantly ($p < 0.001$) inhibited later phase paw edema as a same pattern to diclofenac sodium, whose action is inhibiting inflammatory mediators by blocking cyclooxygenase enzyme. Halici et al. (2007) reported this comparative baseline profile, proving how standard non-steroidal anti-inflammatory agents downregulate downstream prostanoid pathways to significantly alleviate local paw volume [28]. Although the exact mechanism of action is not clear, it is possible that, the anti-inflammatory activity produced by Bis-salicylaldehyde could be due to the inhibition of the synthesis, and release of inflammatory mediators [34]. Therefore we tested Bis-salicylaldehyde against histamine induced paw edema in mice. Results showed that the compound significantly reduced histamine induced edema with maximum protection observed at the peak of the vascular response window. Henriques et al. (1987) studied this focused autacoid model, demonstrating that tracking localized thickness alterations reveals immediate anti-histaminic and capillary stabilizing capabilities [35]. Histamine is an important mediator of inflammation. These results are in concordance with reported literature for other Schiff bases which possesses, analgesic, anti-inflammatory, and antipyretic properties. The inhibition of inflammation by Schiff bases could be attributed to the presence of active constituents. This metabolic action aligns with studies by Murtaza et al. (2017), who reported this phenomenon in novel imine systems and verified that azomethine linkages act as highly effective pharmacophores to interrupt both early autacoid release and systemic prostaglandin synthesis. Due to presence of aldehydes and ketones in the other Schiff's bases compounds, its effect against COX enzyme, supplemented the anti-inflammatoryactivities of our test compound and confirmed its medicinal use as an anti-inflammatory agent.

5. CONCLUSION

This study possesses a significant importance in the development of a new drug which permits us to predict that bis-salicyldihyde is a new drug anti-inflammatoryeffects. In-vivo studies showed vital anti- inflammatory effects. This drug may have not common side effects which are produced by using traditional NSAIDs which minimize economic burden and also improves patient compliance. The current study possesses a base for development of new drug which require detail pharmacological study. Moreover, Bis-salicyldihyde may further be evaluated for its nephrotoxic, hepatotoxic and ulcerogenic effects, as new molecule for treatment of inflammatory conditions.

CONFLICT OF INTEREST

The authors have No conflict of interest in this research work.

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