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EMERGING ANTI-INFLAMMATORY POTENTIALS OF SOME NOVEL SCHIFF'S BASE DERIVATIVES OF 3, 4-DIOXYMETHYLENE ACETOPHENONE

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ABSTRACT

Introduction: Inflammation represents a physical challenge to the human by offering acute pain, edema, redness, and bodily discomfort. The area of drug discovery is a continuous process for designing and fabricating better non-steroidal anti-inflammation drugs (NSAIDs). However, they suffer from abundant side-effects such as bleeding in GIT, stomach pain, heartburn, etc. **Objective:** Based on the path of new drug discovery, the present investigation aimed at exploration of anti-inflammatory potential of two Schiff's base containing 3, 4-dioxymethylene based compounds. **Materials and Methods:** (*Z*)-4-(2-aminoethyl)-*N*-(1-(benzo[d][1,3]dioxol-5-yl)ethylidene)aniline **(3)** (at 100 mg/kg b.w.) and (*Z*)-*N*-(1-(benzo[d][1,3]dioxol-5-yl)ethylidene)-4-(2-(methylamino)ethyl)aniline **(5)** (at 100 mg/kg b.w.) were screened for edema reducing potentials using carrageenan-induced paw edema method with comparison to the standard drug indomethacin (at 10 mg/kg b.w.). **Results and Discussion:** The molecule **(3)** exhibited % edema reduction of 14.88%, 27.64%, and 38.24%, respectively at 1 hr, 2 hr, and 3 hr. The compound **(5)** demonstrated % edema reduction of 20.53%, 31.49%, and 44.13%, respectively at first hr, second hr, and third hr. The synthesized Schiff's base molecules expressed noteworthy activity as compared to indomethacin (standard drug). **Conclusion:** The present research represented the importance of Schiff's base containing 3,4-dioxymethylene hybrid compounds and will open new avenues in pharmacotherapeutics. The study will also motivate the researchers across the globe in developing still better molecules with better therapeutic index.

Keywords: 3, 4-dioxymethylene, Acetophenone, Anti-inflammatory, Edema, Schiff's base, Synthesis.

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INTRODUCTION

3,4-dioxymethylene based compounds have demonstrated several pharmacological potentials in medicinal chemistry. A number of analogs and hybrids have been developed based on this scaffold which has demonstrated multifarious therapeutic perspectives such as organotin (IV) derivatives of 6-nitrophenylpropenoic acid (anti-cancer activity), [1] aryloxypropanolamines (anti-hyperglycemic activity), [2] amphetamines (neuropsychopharmacological activity), [3] β-styrene (triple negative breast cancer inhibitory potential and NLRP3 inhibitor), [4] [5] organotin (IV) derivatives of phenylacetic acid (anti-tumor activity), [6] etc.

Schiff's base is the compound which comprises of C=N (azomethine) component which is synthesized by the condensation of NH_2 (primary amines) and C=O (carbonyl group) with the elimination of a single water molecule. [7] The compound exhibit numerous biological activities like anti-inflammatory, [8] anti-oxidant, [9] anti-diabetic, [10] anti-cancer, [11] etc.

Inflammation represents a physical challenge to the human by offering acute pain, edema, redness, and bodily discomfort. [12] From the last several decades, researches took place in developing potential non-steroidal anti-inflammation drugs (NSAIDs) and studying their possible mechanism(s) of action. [13] However, they suffer from abundant side-effects such as bleeding in GIT, stomach pain, heartburn, etc. [14] The thrust area of drug discovery is a never-ending and continuous process for designing and fabricating better analogs. [15] Based on the path of new drug discovery, the present investigation aimed at exploration of anti-inflammatory potential of two Schiff's base containing 3,4-dioxymethylene based compounds; (*Z*)-4-(2-aminoethyl)-*N*-(1-(benzo[d][1,3]

dioxol-5-yl)ethylidene)aniline **(3)** and (*Z*)-*N*-(1-(benzo[d][1,3] dioxol-5-yl)ethylidene)-4-(2-(methylamino)ethyl)aniline **(5)** using carrageenan-induced paw edema method with comparison to the standard drug indomethacin.

MATERIALS AND METHODS

Chemicals and Instrumentation

All chemicals and analytical grade reagents were procured from Sigma Aldrich, Germany. The chemical reaction progress was supervised using the Merck® pre-coated silica gel-G TLC plates. The elemental composition of the compounds was determined using CHN analyzer (PerkinElmer Elemental Analyzer 2400 instrument). The structure of the final compounds was established using the sophisticated spectroscopic techniques like Fourier Transformed Infrared Spectroscopy (Shimadzu® IRAffinity-1 instrument) and the readings were expressed in cm^{-1}, ^{1}H-NMR Spectroscopy (Bruker Avance-II instrument) was calibrated using tetramethylsilane (internal standard) and the readings were expressed in ppm, and Mass Spectroscopy (MICROMASS Q-TOF instrument) was recorded.

Animals

The carrageenan-induced paw edema method was performed on Swiss albino rats of age 5-7 weeks and having body weight 140-210 g, after obtaining permission from Department Ethical Committee and by following the guidelines of CPCSEA (1389/a/10/CPCSEA). The experimental animals were kept in the departmental animal house under a controlled environment (temperature 25–26ºC, humidity 55–65%, 12 hr cycles of light and dark). The rodents were given free access to water and fed with standard rodent pellets.

Synthesis of target compounds

The novel Schiff's base compounds **(3)** and **(5)** were synthesized from the 3,4-dioxymethylene containing starting material, 1-(benzo[d][1,3]dioxol-5-yl)ethanone **(1)**. For the synthesis of novel molecules, the carbonyl part of the acetophenone group made electrophilic attack with the nucleophilic amine part of the reactants; 4-(2-aminoethyl)aniline **(2)** and 4-(2-(methylamino)ethyl)aniline **(4)** to form azomethine (Schiff's base) components. **Figure 1** represents the synthetic pathway.

Synthetic protocol for (Z)-N-(1-(benzo[d][1,3]dioxol-5-yl)ethylidene)(substituted)aniline

In a round bottom flask, equimolar quantity (0.01 M) of ethanolic solution of 1-(benzo[d][1,3]dioxol-5-yl)ethanone **(1)** and 4-(2-aminoethyl)aniline **(2)** or 4-(2-(methylamino)ethyl)aniline **(4)** were made to refluxed for 6 hr duration in the presence of glacial acetic acid (7-8 drops). The reaction content was cooled in crushed ice to precipitate the final product. The obtained products were washed with water, dried, and recrystallized suitably. [16]

(Z)-4-(2-aminoethyl)-N-(1-(benzo[d][1,3]dioxol-5-yl)ethylidene)aniline **(3)**

64% yield; FTIR (KBr) υ (cm^{-1}): 3338 (-NH_2, stretching), 3124 (-NH, stretching), 3031 (C-H, aromatic), 1675 (C=N, azomethine), 1612 (C=C, aromatic), 1578 (-NH, bending), 1455 (-CH_2, bending), 1313 (C-N, stretching), 1251 (C-O); ^{1}H NMR (δ, ppm, $CDCl_3$): 6.9-7.6 (Aromatic, 7H), 5.81 (1, 2H), 5.39 (11, Amine, 2H), 3.03 (9, 2H), 2.75 (10, 2H), 2.11 (5, Methyl, 3H). MS: M^+ 282. Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 71.79; H, 6.14; N, 9.36

(Z)-N-(1-(benzo[d][1,3]dioxol-5-yl)ethylidene)-4-(2-(methylamino)ethyl)aniline **(5)**

73% yield; FTIR (KBr) υ (cm^{-1}): 3177 (-NH, stretching), 3051 (C-H, aromatic), 1686 (C=N, azomethine), 1623 (C=C, aromatic), 1593 (-NH, bending), 1474 (-CH_2, bending), 1349 (C-N, stretching), 1262 (C-O); ^{1}H NMR (δ, ppm, $CDCl_3$): 6.7-7.5 (Aromatic, 7H), 5.93 (1, 2H), 3.43 (12, Methyl, 3H), 2.88 (9, 2H), 2.56 (10, 2H), 2.19 (5, Methyl, 3H), 1.98 (11, Amine, 1H). MS: M^+ 296. Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.21; H, 6.38; N, 9.12.

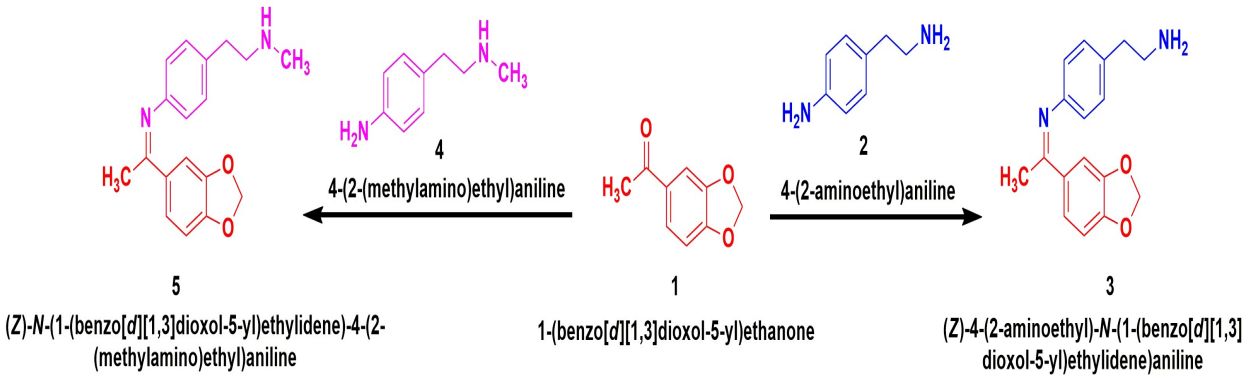

Figure 1: Protocol for the synthesis of novel Schiff's base compounds of 3,4-dioxymethylene.

Acute toxicity studies

The highest therapeutic dose of the compounds was determined in accordance to the OECD protocol at an escalating dose in the range of 25-500 mg/kg. The *in vivo* safety limit was computed based on the LD_{50} values. [17]

Anti-inflammatory screening

The anti-inflammatory activity of the fabricated compounds was screened using carrageenan-induced paw edema method. Before the commencement of the study, the rats were fasted overnight and fed with 5 mL distilled water through the oral route. The above step was performed to remove or reduce the differences during the experimental study. The rats in the experimental group received 100 mg/kg b.w. of the compounds (in saline solution) an hour before the commencement of the study. The inflammation was produced by injecting 1% carrageenan solution at the subplanter region of the right hind paw. The rats in the control group received saline solution with a few drops of solubilizer. The rat paw thickness was estimated by determining the disparities between the width of the injected paws and the non-injected paws by utilizing the mercury digital micrometer for the duration of 3 hrs with 1 hr interval. Indomethacin (10 mg/kg b.w.) was utilized as the standard drug. [18] The formula for the calculation of percentage (%) inhibition of edema:

$$\textbf{\% inhibition} = \frac{Ic - It}{Ic}$$

where, Ic and It represented the mean increase in paw circumference in control and treated groups.

Statistical treatment

The anti-inflammatory results were analyzed statistically by ANOVA method (one-way) followed by the Dunnett's multiple comparisons test. The P value < 0.01 was considered statistically significant.

RESULTS AND DISCUSSION

Chemistry

The spectroscopic techniques supported the formation of the Schiff's base analogs. The disappearance of the carbonyl group of 3,4-dioxymethylene acetophenone in the FT-IR spectrum at 1731 cm^{-1} ascertained the formation of the compounds. In addition to it, the FT-IR spectra of both the compounds displayed the presence of the azomethine moiety (1675 cm^{-1} for **3** and 1686 cm^{-1} for **5**) which assured further confirmation of the molecules. Both the fabricated analogs were differentiated by the variation in the primary and secondary amines where, in the compound **3**, a primary amine was predominantly observed at 3338 cm^{-1} along with a secondary amine at 3124 cm^{-1}, respectively in the FT-IR spectra. In contrast to it, the FT-IR spectrum of the compound **5** presented only a secondary amine. The ^{1}H-NMR spectra clearly differentiated both the compounds as evidenced from the –NH- part in the aliphatic component, where it was seen at 5.39 ppm for compound **3** and 1.98 ppm for compound **5**. The aliphatic component in both the compounds was further confirmed by the spectral peak at 1455 cm^{-1} and 1474 cm^{-1} which represented the $–CH_2-$ groups. The proton-NMR spectra also supported the presence of the aliphatic component in both the compounds as seen from peak in the range 2 ppm to 3 ppm. The methyl group linked with the azomethine part in both the compounds was principally seen in ^{1}H-NMR spectra at 2.1 ppm to 2.2 ppm. The aromatic ring was confirmed from the peaks ranged from 6.4-7.6 ppm. Moreover, the C=C and C-H stretching of the aromatic rings were detected in the FT-IR spectra. The 3,4-dioxymethylene component was assured from the C-O stretching in the FT-IR for both the analogs at 1251 cm^{-1} and 1262 cm^{-1}, respectively. Furthermore, the proton-NMR presented C-H peak of the 3,4-dioxymethylene component at 5.81 ppm and 5.93 ppm, respectively. The mass spectra showed the presence of base peaks corresponding to the molecular mass of the compounds. A number of fragment peaks were seen principally in the spectra. The CHN analyses additionally confirmed the formation of the proposed compounds as observed from the values of the practical percentage of the elements.

Acute toxicity study

The molecules **(3)** and **(5)** presented no such toxic effects over the tested range of 25-500 mg/kg and the anti-inflammatory screening was performed at a dose of 100 mg/kg b.w.

Anti-inflammatory activity

Both the tested molecules **(3)** and **(5)** expressed noteworthy edema reducing activity as compared to indomethacin (the standard drug). The compound **(5)** demonstrated higher *in vivo* anti-inflammatory potential than compound **(3)** with % edema reduction of 20.53%, 31.49%, and 44.13%, respectively at first hr, second hr, and third hr. The molecule **(3)** exhibited % edema reduction of 14.88%, 27.64%, and 38.24%, respectively at 1 hr, 2 hr, and 3 hr. One of the reasons for the better activity of the compound **(5)** may be due to higher lipophiicty of the compound which facilitates better penetration to the molecular targets. Both the compounds are believed to demonstrate anti-inflammatory activity by inhibition of the key inflammatory mediators like cyclooxygenase-1/2 (COX-1/2) and lipoxygenase (LOX).

Table 1: Exploration of *in vivo* anti-inflammatory activity of Schiff's base compounds of 3,4-dioxymethylene.

Group	Percentage (%) inhibition of edema		
	1 hr	**2 hr**	**3 hr**
5	20.53± 2.81*	31.49±1.68**	44.13± 2.97**
3	14.88±1.53**	27.64 ± 2.41*	38.24± 1.72**
Indomethacin	45.17±1.27**	63.93± .33**	77.71± 1.19**

n = 6; ED_{50} of 100 mg/kg b.w. in male adult albino mice; P < 0.01

CONCLUSION

The current investigation highlighted the anti-inflammatory potential of the two synthesized Schiff's base molecules **(3)** and **(5)** where the compounds expressed noteworthy activity as compared to indomethacin (standard drug) with 38.24% and 44.13% edema reducing potential after 3 hrs. However, no such structure-activity-relationships (SARs) can be predicted from this study, some knowledge of anti-inflammatory expression can be derived from this study. The present research represented the importance of Schiff's base containing 3, 4-dioxymethylene hybrid compounds and will open new avenues in pharmacotherapeutics. The study will also motivate the researchers across the globe in developing still better molecules with better therapeutic index.

CONFLICT OF INTEREST

None of the author has any conflict of interest in the context of this work.

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