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SYNTHESIS, CHARACTERIZATION AND EVALUATION OF SCHIFF's BASE MUTUAL PRODRUGS OF PIROXICAM

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ABSTRACT

Background: A Schiff base, a pharmacologically privileged scaffold and a nitrogen analog of an aldehyde or ketone in which the C=O group is replaced by C=N-R group. Mutual prodrug is a Carrier linked Prodrug consist of two pharmacologically active substances together in a single moiety. **Objective:** The goal of the study is to synthesize combined form of the various Schiff's bases with Piroxicam for enhanced biological and pharmacological activity. **Methods:** Various conventional as well as green methods are incorporated for synthesis of Schiff's bases whereas; simple shaking method is adapted for mutual prodrug synthesis. Biological evaluation was done according to literature. **Results and conclusion:** Besides Piroxicam's important pharmacological activities, it possesses severe side effects due to certain functional groups present in it. Thus, Derivatization method was incorporated to shun the side effects of the drug by synthesizing its Mutual prod rugs with Schiff bases having additional antibacterial activity.

KEYWORDS

Antibacterial, Anti-inflammatory, Analgesic, Antipyretic, Mutual prodrug, Piroxicam and Schiff's base etc.

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INTRODUCTON

A Schiff base, named after Hugo Schiff, is synonymous with azomethine, is a pharmacologically privileged scaffold. A Schiff's base is a nitrogen analog of an aldehyde or ketone in which the C=O group is replaced by C=N-R group. Schiff's bases are an important class of compounds in organic chemistry and are useful in making carbon-nitrogen bond. The imine or azomethine group present in their structure is critical to their biological activity[1]. They are usually formed by condensation of primary amine with the

carbonyl compound according to the following scheme as shown in Figure No.1.

Where, R may be an aliphatic or an aromatic group.

Oxicams such as Piroxicam are characterized by the 4-hydroxybenzothiazine heterocycle. The acidity of the oxicams is attributed to the 4-OH with the enolate anion being stabilized by intramolecular H-bonding to the amide N-H group. Also, the presence of the carboxamide substituent at the 3-position of the benzothiazine ring contributes toward acidity by stabilizing the negative charge formed during ionization (resonance stabilization). Oxicams are primarily ionized at physiologic pH and acidity is required for COX inhibitory activity[2,3].

Mutual prodrug is a Carrier linked Prodrug consist of two pharmacologically active substances together in a single moiety. Two pharmacologically active agents combined together so that each acts as a carrier for the other agent and vice versa. The Parent drug may lack some additional biological effects which can be incorporated by the carrier selected, thus ensuring some additional advantage. Site specificity of a parent drug can be improved by using a carrier drug which may target the drug to specific organ or tissues. The carrier drug may be used to overcome some side effects of the parent drugs as well[4-6].

EXPERIMENTAL SECTION

MATERIALS

All the chemicals and reagents were of AR grade as well as LR grade and used without further purification. The starting materials were obtained from Loba Chemie, Piroxicam was obtained from Ramdev chemicals pvt. Ltd. as a gift sample and used as such without purification. The Chemicals and reagents used are: 4-Amino benzoic acid, 4-chloro beanzaldehyde, 4-hydroxy benzaldehyde, 4-nitro benzaldehyde, Vanillin, 3, 4, 5-trimethoxy benzaldehyde, Ethanol, Dimethyl amino pyridine(DMAP), Dicyclohexyl carbodiimide (DCC), Dichloro methane (DCM), Ethyl acetate, n-Hexane.

Instrumentation

Melting points of all the synthesized compounds were checked in capillary tubes by using a melting point apparatus (VEEGO melting point apparatus). All the compounds were characterized by FT-IR spectrometer (IR-Affinity, Shimadzu) using ATR correction method. Quantification of compounds was done using UV-spectrophotometer (UV-1800, Shimadzu). Plasma separation in hydrolysis studies was done using Micro centrifuge (RM-12, REMI). 1HNMR spectra were obtained from 400MHz instrument (Bruker Advance II 400 NMR Spectrometer) and chemical shifts were measured as parts per million (ppm) downfield from Dimethyl sulfoxide (DMSO) as internal standard.

Methodology

General procedure for synthesis of Schiff's bases

Solvent less method (Green method/ Microwave method) was carried out to synthesize the required Schiff's bases (A-E) shown in Table No.1 and general protocol followed is as follows:

In a Microwave flask take 0.01 mol required aldehyde and 0.01 mol 4-amino benzoic acid as amine in very less amount of solvent i.e. about 15-20 ml of ethanol. Put reaction for heating in microwave synthesizer at power level 2(i.e. 170 watt) for appropriate time interval of about 3-5 min. After completion of reaction pour reaction contents into 20-30 ml ice cold water and stir vigorously over a magnetic stirrer. Filter the contents and recrystallize in ethanol[7].

General procedure for synthesis of 2-methyl-1, 1-dioxido-3-(pyridin-2-ylcarbamoyl)-2H-benzo[e] [1, 2] thiazin-4-yl 4-((argiomethylene) amino) benzoate (1)

Dissolve Piroxicam (1mmol) in 25 ml of Dichloromethane (DCM) and let it cool to 0°C in an ice bath. Make a solutions of DCC (1mmol), DMAP (0.1mmol) and Schiff's base (1mmol) in 25 ml DCM each. Add all the above solutions to the Naproxen portion in 250 ml RBF at 0°C and the reaction mixture is stirred at 0°C for 1 hour. Remove the ice bath and stir the mixture for 12 hrs at room temperature. The reaction mixture was filtered and the filtrate was concentrated in a vacuum (in vacuo). Wash the residue with 25ml 5% sodium bicarbonate solution. Separate the Organic layer from aqueous layer and dried over $MgSO_4$ to give final compound (1) as shown in Figure No.3[8-

[10]. The general scheme is represented in Figure No.2

Synthesis of 2-methyl-1, 1-dioxido-3-(pyridin-2-ylcarbamoyl)-2H-benzo[e] [1, 2] thiazin-4-yl 4-((4-nitrobenzylidene) amino) benzoate (2)

Pale yellow solid; Yield: 63% ; m.p: 244ºC ; R_f value: 0.41(n-Hexane: Ethyl acetate; 1:1); IR(cm^{-1}): 1757 (C=O of ester); 1632 (C=N of imine); 727 (Cl str.); 771-914 (Aromatic str.); 1676 (C=O of amide); 1128 (S=O of SO2); ^{1}HNMR (400 MH_z; DMSO): 9.99 (s, 1H, Sec. Amide NH); 7.51 (d, 1H, Benzylidenimin CH); 7.79 (d, 1H, Benzylidenimin CH); 8.39 (s, 1H, Benzylidenimin N=CH); 7.44, 7.68, 7.81, 8.18 (d, 1H, Benzene CH); 2.54 (q, 3H, Methyl CH_3); 8.06, 6.57 (d, 1H, 2-pyridine); 6.59,7.56(t, 1H, 2-pyredine) Elemental analysis: % Calculated [C (60.79); H (3.69); N (9.78); O (13.96); S (5.60); Cl (6.19)]; % Found [C (60.67); H (3.56); N (9.71); O (13.80); S (5.51); Cl (6.02)].

Synthesis of 2-methyl-1, 1-dioxido-3-(pyridin-2-ylcarbamoyl)-2H-benzo[e] [1, 2] thiazin-4-yl 4-((4-nitrobenzylidene) amino) benzoate (3)

Yellow solid; Yield: 71% ; m.p: 224ºC ; R_f value: 0.38(n-Hexane: Ethyl acetate; 1:1); IR (cm^{-1}): 1759 (C=O of ester); 1637 (C=N of imine); 1373,1529 (NO2 str.); 773-937 (Aromatic str.); 1708 (C=O of amide); 1197 (S=O of SO2); ^{1}HNMR (400 MH_z; DMSO): 8.78 (s,1H,Sec.amideNH); 8.32(d,1H,BenzylideniminCH); 8.15(d,1H, BenzylideniminCH); 8.37 (s,1H, Benzylidenimin N=CH); 8.04(d,1H,2-pyridine); 6.57(d,1H, 2-pyridine); 6.59(t,1H, 2pyridine);7.83(t,1H, 2-pyridine); 2.54 (q,3H,Methyl CH3); 7.41;8.19;7.81;7.67 (1,d,BenzeneCH); 7.65,7.34 (t,1H,BenzeneCH) Elemental analysis: % Calculated [C (59.69); H (3.63); N (12.00); O (19.19); S (5.49)]; % Found [C (59.55); H (3.58); N (11.89); O (19.03); S (5.40)].

Synthesis of 2-methyl-1, 1-dioxido-3-(pyridin-2-ylcarbamoyl)-2H-benzo[e] [1, 2] thiazin-4-yl 4-((4-hydroxybenzylidene) amino) benzoate (4)

Yellow solid; Yield: 57% ; m.p: 248ºC ; R_f value: 0.33(n-Hexane: Ethyl acetate; 1:1); IR(cm^{-1}): 1735 (C=O of ester); 1637(C=N of imine); 3628 (OH str.); 788-916(Aromatic str.); 1681 (C=O of amide); 1128 (S=O of SO2); ^{1}HNMR (400 MH_z; DMSO): 8.24(s,1H,Sec.amideNH); 6.85(d,1H,BenzylideniminCH); 7.64(d,1H, Benzylidenimin CH); 8.21(s,1H, Benzylidenimin N=CH); 8.09(d,1H,2-pyridine); 6.57(d,1H, 2-pyridine); 6.59 (t,1H, 2pyridine); 7.55(t,1H, 2-pyridine); 2.54(q,3H,Methyl CH3); 7.57;8.22;7.65;7.67 (1,d,BenzeneCH); 7.59,7.56 (t,1H,BenzeneCH) ; 4.25 (s,1H,Aromatic C-OH) Elemental analysis: %Calculated [C (62.81); H (4.00); N (10.10); O (17.31); S (5.78)]; % Found [C (62.70); H (3.87); N (10.02); O (17.13); S (5.66)].

Synthesis of 2-methyl-1, 1-dioxido-3-(pyridin-2-ylcarbamoyl)-2H-benzo[e] [1, 2] thiazin-4-yl 4-((4-hydroxy-3-methoxybenzylidene) amino) benzoate (5)

Yellow solid; Yield: 42% ; m.p: 190ºC ; R_f value: 0.39(n-Hexane: Ethyl acetate; 1:1); IR (cm^{-1}): 1735 (C=O of ester); 1637(C=N of imine); 3641 (OH str.); 729-937(Aromatic str.); 1696 (C=O of amide); 1128 (S=O of SO2); 1097,1236 (CO str of ether) ^{1}HNMR (400 MH_z; DMSO): 9.18 (s,1H,Sec.amideNH); 7.01 (d,1H,BenzylideniminCH); 7.33(d,1H, Benzylidenimin CH); 8.41(s,1H, Benzylidenimin N=CH); 8.14 (d,1H,2-pyridine); 6.55(d,1H, 2-pyridine); 6.63(t,1H, 2pyridine); 2.48(q,3H,Methyl CH3); 7.44;8.14;7.81;7.68 (1,d,BenzeneCH); 7.51,7.34 (t,1H,BenzeneCH); 5.34 (s,1H,Aromatic C-OH); 3.83(s,3H,Methyl O-CH3) Elemental analysis: %Calculated [C (61.64); H (4.14); N (9.58); O (19.16); S (5.48)]; % Found [C (61.55); H (4.03); N (9.45); O (19.08); S (5.34)].

Synthesis of 2-methyl-1, 1-dioxido-3-(pyridin-2-ylcarbamoyl)-2H-benzo[e] [1, 2] thiazin-4-yl 4-((3, 4, 5-trimethoxybenzylidene) amino) benzoate (6)

Yellow solid; Yield: 67% ; m.p: 76ºC ; R_f value: 0.37 (n-Hexane: Ethyl acetate; 1:1); IR (cm^{-1}): 1759 (C=O of ester); 1641 (C=N of imine); 725-937 (Aromatic str.); 1695 (C=O of amide); 1128 (S=O of SO2); 1047,1240 (CO str of ether) ^{1}HNMR (400 MH_z; DMSO): 8.59 (s,1H,Sec.amideNH); 7.17 (d,1H,BenzylideniminCH); 8.38 (s,1H, Benzylidenimin N=CH); 8.09 (d,1H,2-pyridine); 6.57 (d,1H, 2-pyridine); 6.59 (t,1H, 2pyridine); 2.54 (q,3H,Methyl CH3); 7.44;8.14;7.81;7.68

(1,d,BenzeneCH); 7.51,7.34 (t,1H,BenzeneCH) ; 3.87 (s,3H,Methyl O-CH3)

Elemental analysis: %Calculated [C (61.14); H (4.49); N (8.91); O (20.36); S (5.10)]; % Found [C (60.98); H (4.35); N (8.78); O (20.13); S (4.96)].

The Final compounds synthesized are listed in table No.2.

BIOLOGICAL SCREENING

Antibacterial activity

The antibacterial activity of the synthesized compounds were evaluated *in vitro,* antibacterial activity of different (25µg, 50µg, 100µg and 200µg) concentrations of test compounds were tested against gram positive bacteria *B. subtilis* and gram negative bacteria E.coli The inoculated sterilized nutrient agar media was poured into petri dishes and allowed to solidify. 6mm wells were made on the agar surface, into each of these wells, 30µl of the test compound with different concentrations /reference standard/control was added by using a micropipette. Norfloxacin was used as standard reference and DMSO was used as a control (solvent) which did not possess any inhibition zone. The plates were incubated at 37ºC for 24 hours for bacterial activity. The zone of inhibition was calculated by measuring the diameter of the inhibition zone around the well (in mm) including the well diameter. The readings were taken in three different fixed directions in all 3 replicates and the average values were tabulated. And the inhibition zones were calculated and recorded[11-14].

Antipyretic activity

Baker's yeast induced pyrexia

Rats were divided into four groups (n = 3). The animals were set in their cages individually throughout the experiment. Rectal temperature was measured with a lubricated Omron Thermometer probe inserted into the rectum. Rectal temperature was measured every 15 min for each 5 h and recorded manually at specified intervals. To minimize the stress response of the animals to the lightly restrained condition, made a careful handling and performed two sets of acclimatizing training in the cage for 2 days before starting the experiments. Fever was induced by intraperitoneal injection of baker yeast 135 mg/kg, which induced a sustained increase in

Rectal temperature for 5 h. Paracetamol and other test compounds, reverted baker yeast-induced fever. The test compounds and Paracetamol was administered 1 h after injecting yeast.

Group 1: (Control) only yeast was injected and continuously temperature was monitored and recorded at specified interval for 5 h.

Group II: received 2.5 % DMSO (0.5 ml) was given orally 1 h after administering yeast.

Group III: Test compounds (20 mg/kg) dissolve in DMSO (0.5 ml) was administered orally 1 h after administering yeast.

Group IV: Paracetamol (150 mg/kg) was given orally 1 h after administering yeast[15,16].

Anti-inflammatory activity:

The Anti-inflammatory activity was evaluated by using Carrageen an-induced Rat paw edema method. Rats weighing 150-200 grams were divided in three groups of three animals each. Group I serves as control without using drug, Group II received ASP 20 mg/kg, group III receives prodrug, where the dose was molecularly equivalent to ASP. The drug was given Intraperitoneal to the animal by 0.5% of sodium CMC and each animal received a dose of 1ml. 30 min. after administration of the drug, each animal receives an injection of 0.1 ml of Carrageenan by sub-plantar route in its left hind paw. The measurement of left hind paw volume was carried out using plethysmometer before any treatment (V_0) and in any interval (V_t) after the administration of drugs. All the results were expressed as Mean ± S.E.M[17,18].

Analgesic activity

Hot plate method

The paws of rats are very sensitive to heat at temperatures which are not damaging the skin. The responses are jumping, withdrawal of the paws and licking of the paws. The hot plate, which is commercially available, consists of a electrically heated surface. The temperature is controlled for 55° to 56 °C. This can be a copper plate or a heated glass surface. The animals are placed on the hot plate and the time until either licking or jumping occurs is recorded by a stop-watch. Swiss albino

rats weighing between 100-150g were used for evaluation of analgesic activity; in each group three albino rats were kept. A solution of Ibuprofen (dose-100mg/kg/10ml) was prepared in normal saline water. Test solution of prodrugs were prepared (10mg/kg/10ml) Wistar albino rats were divided into three different groups each containing three animals, the animals were marked individually. Food was withdrawn 12 hours prior to drug administration till completion of experiment. The animals were weighed and numbered appropriately. The test and standard drugs were given orally. After 60 minutes, the animals are placed on the hot plate and the observations were recorded and at the time interval of 90, 120 and 180 minutes. The results of Hot plate method on rats were recorded[19,20].

RESULTS AND DISCUSSION

Antibacterial activity

Anti-bacterial activities of the synthesized compounds were studied by the Well plate method. Four different concentration were selected (25µg/ml, 50 µg/ml, 100 µg/ml, 200µg/ml) using DMSO as negative control and Norfloxacin as positive control. The zone of inhibition was measured against *B. subtilis* (Gram positive) and *E. coli* (Gram negative) in mm and the results are presented in Table No.3.

Anti-inflammatory activity

The inhibitory activity on carrageenan induced rat hind paw edema, caused by the subplanatar administration of NSAID's mutual prodrugs, at various assessment times after carrageenan injection are shown in Table No.4. Aspirin, a cyclooxygenase inhibitor, at the dose of 20mg/kg body weight exhibited significant edema inhibition. NSAID's mutual prodrugs at doses equivalent to that of aspirin also possessed significant inhibitory effect on carrageenan induced paw edema at all recorded times. This increase was observed at minimum 1 hr. and was maximum at 5hr. after administration of carrageenan in the vehicle group. Percent Inhibition was calculated by following formula:

% Inhibition = [Paw vol. of control – Paw vol. of test] / Paw vol. of control x 100

Analgesic activity

The Hot plate is useful in the elucidating centrally mediated responses, which focuses mainly on changes above the spinal cord level. All the test and standard drugs significantly reduce the pain as compare to the control group and results are shown in Table No.5.

Antipyretic activity

The experimental rats showed a mean increase of about 0.64 ℃ in rectal temperature 1 h after Backer's yeast injection (135 mg/kg, i.p). The test compound produced significant antipyretic activity at 2, 3, 4 and 5 h. Test compounds and the reference drug Paracetamol (150 mg/kg) showed significant antipyretic activity throughout the observation period up to 5 h. Antipyretic activity results are represented in Figure No.4.

Table No.1: List of Schiff's bases synthesized

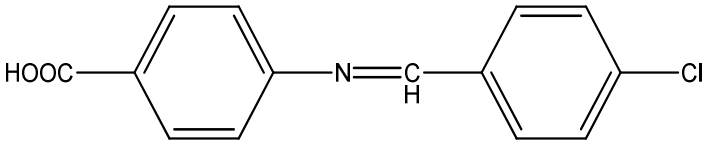
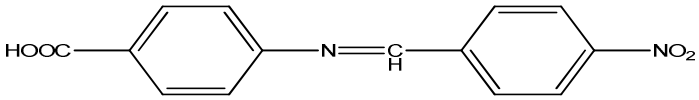
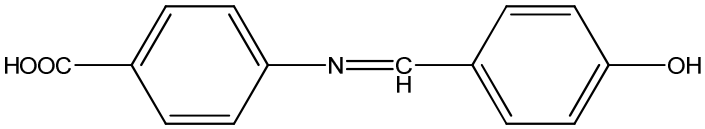
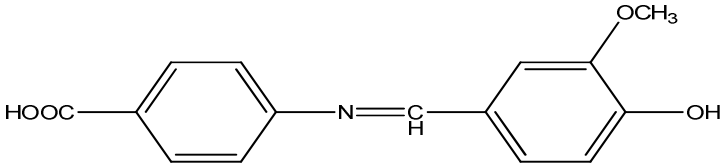
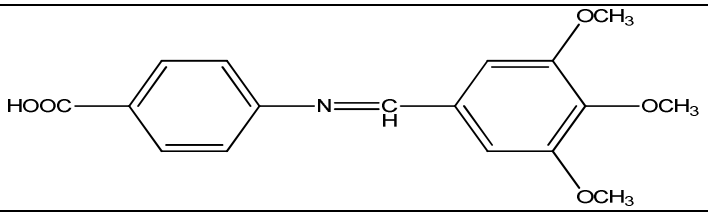
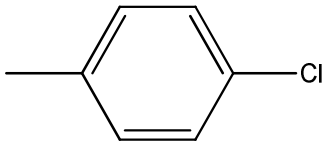
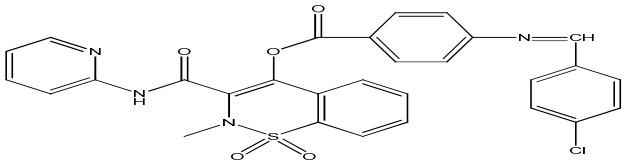
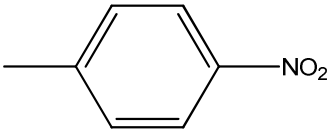
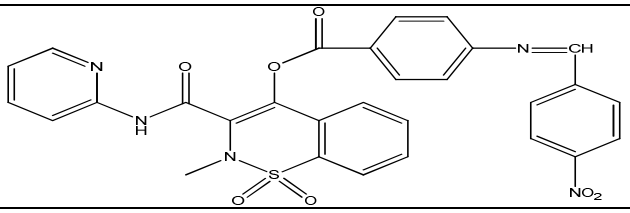
COMPOUND	IUPAC NOMENCLATURE	STRUCTURE
A	4-((4-chlorobenzylidene) amino) benzoic acid	
B	4-((4-nitrobenzylidene) amino)benzoic acid	
C	4-((4-hydroxybenzylidene) amino)benzoic acid	
D	4-((4-hydroxy-3-methoxybenzylidene) amino)benzoic acid	
E	4-((3,4,5-trimethoxybenzylidene) amino)benzoic acid	

Table No.2: Schiff base mutual prodrugs of Piroxicam

Compound	Ar_1	Structure
2		
3		

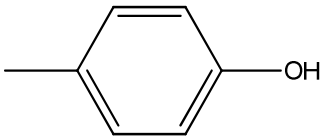
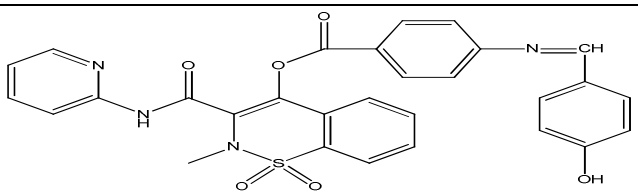
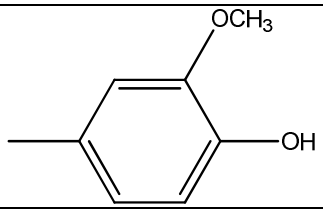
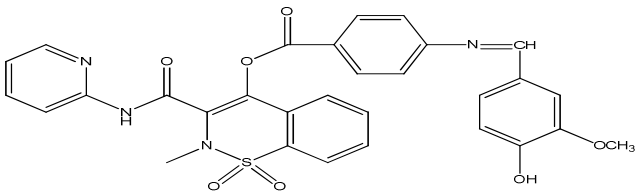
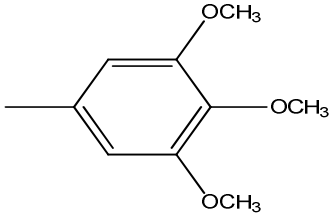
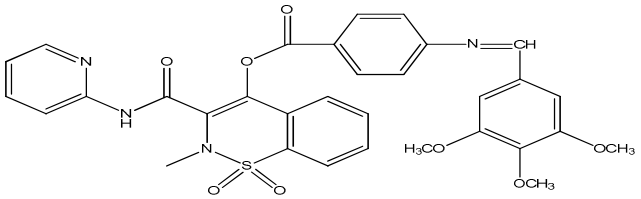
4		
5		
6		

Table No.3: Antibacterial assay of Schiff base mutual prodrugs of Piroxicam

Compound	Concentration of Compound in µg/ml	Zone of inhibition in mm		Compound	Concentration of Compound in µg/ml	Zone of inhibition in mm	
		E.coli	B.subtilis			E.coli	B.subtilis
Norfloxacin	25		8	4	25		6
	50		12		50		6
	100		19		100		12
	200		25		200		13
2	25		9	5	25		10
	50		11		50		11
	100		16		100		22
	200		18		200		23
3	25		11	6	25		7
	50		12		50		9
	100		17		100		12
	200		19		200		15

Table No.4: Anti-inflammatory activity of Schiff base mutual prodrugs of Piroxicam by Carrageenan Induced Rat Paw Edema test

GROUP	n	DOSE (mg/kg)	PAW VOLUME INCREASE (ml)			% INHIBITION		
			1 Hr	3 Hr	5 Hr	1 Hr	3 Hr	5 Hr
Control	3	-	0.34 ± 0.01732	0.6866 ± 0.0152	0.8033 ± 0.0152	-	-	-
Aspirin	3	20	0.1066 ± 0.005774	0.23 ± 0.0001	0.288 ± 0.001	68.64	66.50	64.14
2	3	20	0.13 ± 0.01	0.2533 ± 0.0152	0.2966 ± 0.0152	61.76	63.10	63.07
3	3	20	0.13 ± 0.01	0.27 ± 0.01	0.3066 ± 0.0152	61.76	60.67	61.83
4	3	20	0.12 ± 0.02	0.23 ± 0.02	0.2766 ± 0.0305	64.70	66.50	65.56
	3	20	0.1133 ± 0.0152	0.21 ± 0.0339	0.2533 ± 0.0351	66.67	69.41	68.46
6	3	20	0.12 ± 0.0173	0.2333 ± 0.0251	0.2533 ± 0.0351	64.70	66.02	68.46

Table No.5: Analgesic activity testing by HOT PLATE method

GROUP	n	DOSE (mg/kg)	Reaction time in seconds at time (minutes) (mean ± sem)				
			0	60	90	120	180
Control	3	-	3.2 ± 0.07	3.24 ± 0.04	4.06 ± 0.152	3.55 ± 0.0452	3.91 ± 0.07
Ibuprofen	3	100	3.35 ± 0.060	6.66 ± 0.06	7.84 ± 0.06	8.28 ± 0.04	7.82 ± 0.067
2	3	10	3.33 ± 0.081	6.63 ± 0.062	7.86 ± 0.249	8.24 ± 0.266	7.94 ± 0.290
3	3	10	3.42 ± 0.040	7.78 ± 0.184	8.16 ± 0.296	8.57 ± 0.274	8.10 ± 0.293
4	3	10	3.25 ± 0.054	7.41 ± 0.297	8.28 ± 0.328	8.64 ± 0.314	8.19 ± 0.293
5	3	10	3.17 ± 0.040	6.69 ± 0.211	7.86 ± 0.249	8.28 ± 0.04	8.24 ± 0.266
6	3	10	3.24 ± 0.039	6.37 ± 0.225	7.8 ± 0.1	8.16 ± 0.09	7.55 ± 0.17

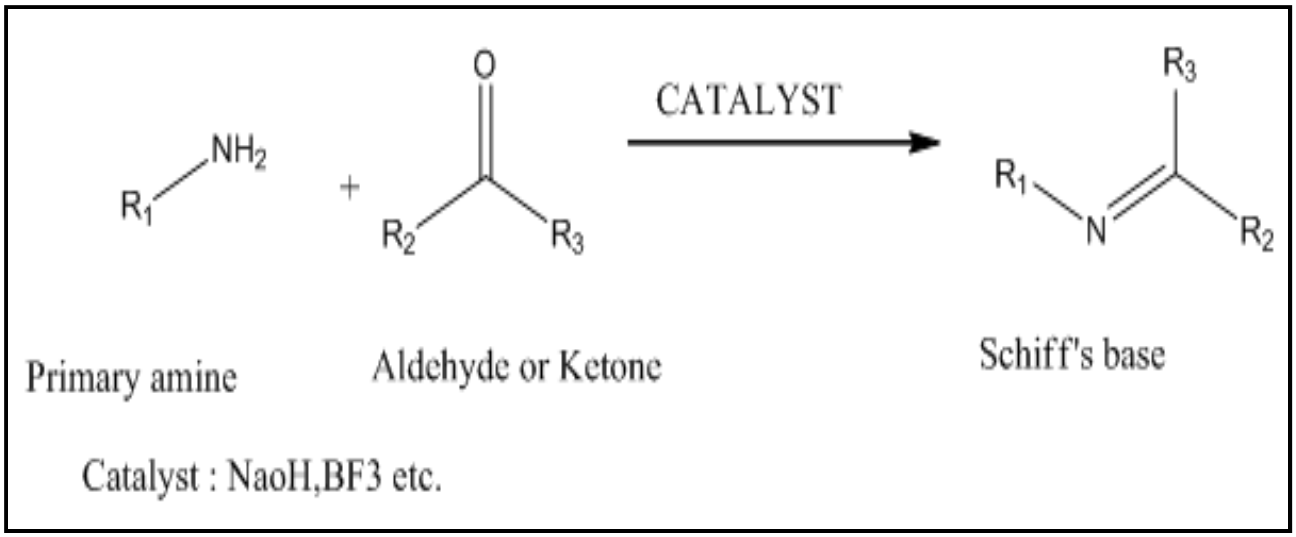


Figure No.1: General Scheme of Schiff base Synthesis

Scheme of synthesis

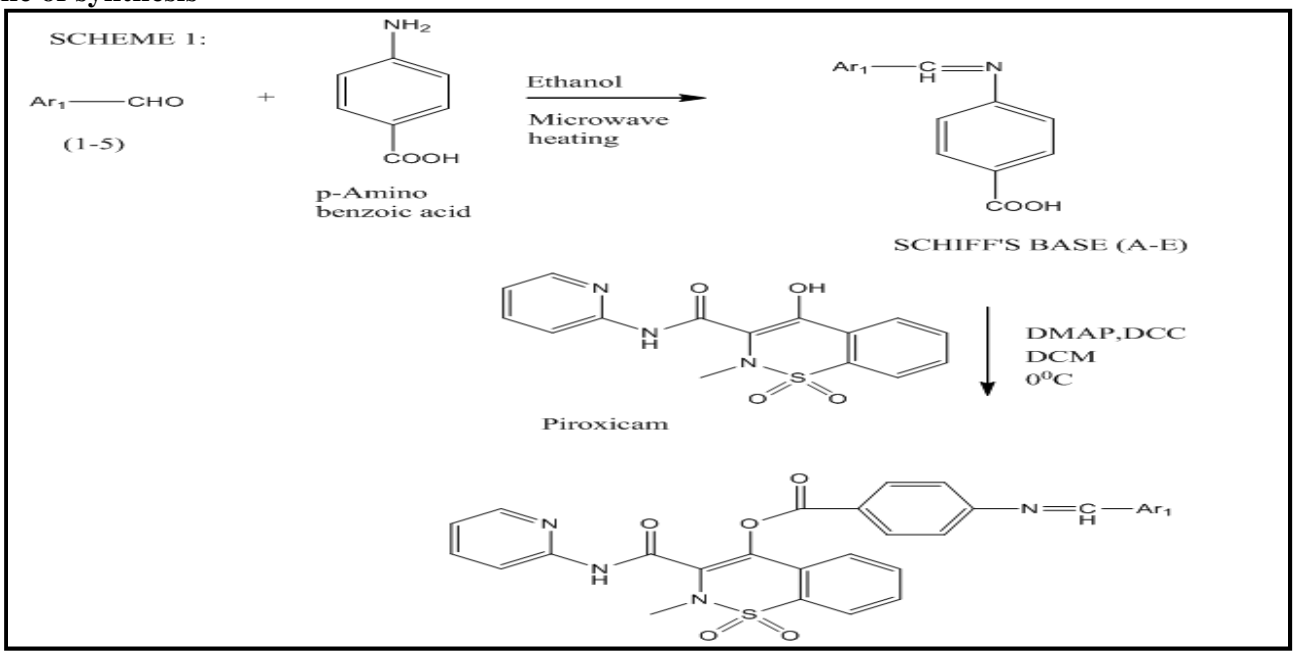


Figure No.2: General Scheme of synthesis of Schiff base mutual prodrugs of Piroxicam

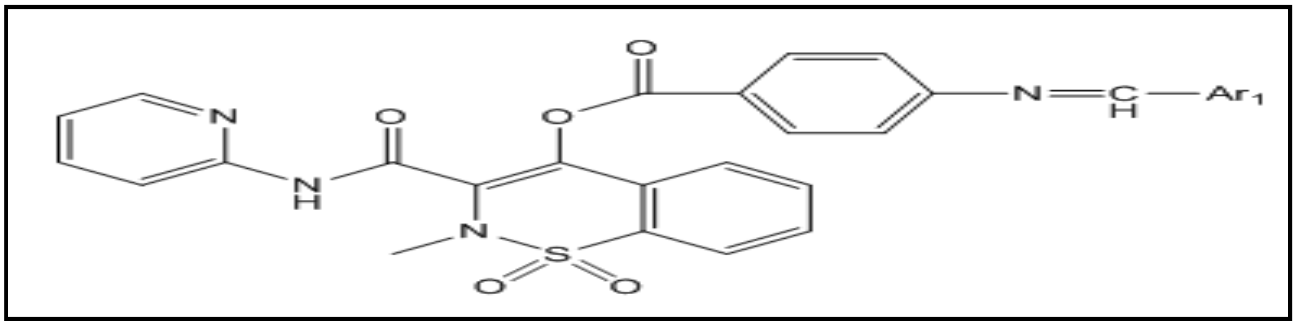


Figure No.3: Structure of 2-methyl-1, 1-dioxido-3-(pyridin-2-ylcarbamoyl)-2H-benzo[e] [1, 2] thiazin-4-yl 4-((argiomethylene) amino) benzoate (1)

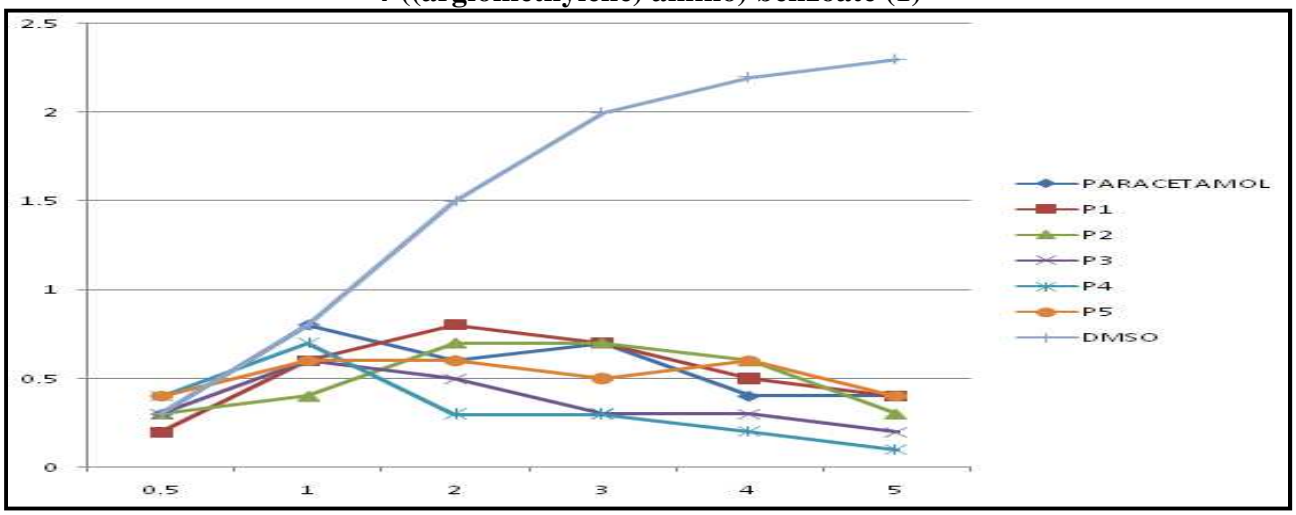


Figure No.4: Antipyretic activity of Schiff base mutual prodrugs of Piroxicam (x-axis: time in hours; y-axis: increase in rectal temperature in °C)

CONCLUSION

Besides its important pharmacological activities, Piroxicam possesses severe side effects due to acidic functional group present in it. Thus, Derivatization method was incorporated to shun the side effects of the drug by synthesizing its Mutual prodrugs with Schiff bases. Mutual prodrugs of Piroxicam with Schiff's bases were synthesized as Schiff's bases were found to possess good anti-bacterial activity. Compounds thus evaluated for their antibacterial effect and all of them found to be fairly active against E.coli and B.subtilis. The synthesized compounds were proceed for physical characterization also its IR, NMR, Elemental analysis confirm the anticipated structure. All of the compounds showed good Anti-inflammatory, Analgesic and Anti-pyretic activity as Piroxicam mutual prodrugs.

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CONFLICT OF INTREST

The authors declare that there is no conflict of interests regarding the publication of this article.

BIBLIOGRAPHY

1. Azhar S, Najam-ul-haq M, Atif M, Khan S A L I, Maalik A, Alam F *et al.* Recent Pharmacological Advancements in Schiff Bases : A Review, *Acta Pol Pharm - Drug Res Drug Res,* 71(4), 2014, 531-5.
2. Tripathi K D. "Essential Of Medical Pharmacology", *Jaypee Publication,* 6th Edition 2004.

3. Bell S, Conklin G, Childress S J. *Am. Chem. Soc.,* 85(2), 1963, 2868.
4. Silverman R B. The organic chemistry of drug design and drug action, *Academic press publisher New delhi,* 3rd Edition, 2014, 423-459.
5. Supriya Shirke *et al.* Prodrug design: an overview, *Int J Pharm Chem Biol Sci*, 1(5), 2015, 232-241.
6. Datar P, Tejashree Shendge. Design, Synthesis and Stability Studies of Mutual Prodrugs of NSAID's, *Chem Inform*, 1(1), 2015, 1-8.
7. Abirami M, Nadaraj V. Synthesis of Schiff Base under Solvent-free Condition : As a Green Approach, *Int J ChemTech Res,* 6(4), 2014, 2534-8.
8. Dhokchawle B, Tauro S K M. Synthesis, spectral studies, hydrolysis kinetics and pharmacodynamic profile of mefenamic acid prodrugs, *Der Pharma Chem*, 3(6), 2014, 347-353.
9. Somani R, Chavan A M D. Synthesis and pharmacological evaluation of antiinflammatory mutual amide prodrugs, *Indian J Pharm Sci*, 3(75), 2013, 353-357.
10. Omar T N A. Synthesis and Preliminary Pharmacological Evaluation of Esters and Amides Derivatives of Naproxen as Potential Anti-Inflammatory Agents, *Iraqi J Pharm Sci,* 22(1), 2013, 120-7.
11. Asif M. A Review on Anticancer and Antimicrobial Activity of Tetrafluoroquinolone Compounds, *Ann Med Chem Res,* 1(1), 2014, 1-10.
12. Shumaila K, Shagufta K, Sultan N A N. Synthesis of Ibuprofen Derivatives with Improved Antibacterial Activity, *Asian J Chem*, 27(9), 2015, 3259-3262.
13. El-Agamey A G A, Attaia A, Abo A. *Arch. Appl. Sci. Res,* 4(3), 2012, 1339.
14. Asif Hussain, Ahmed A S A. Synthesis and biological evaluation of a mutual prodrug of norfloxacin and fenbufen, *J Taibah Univ Med Sci*, 11(3), 2016, 277-281.
15. Ahmad R, Asad M, Siddiqui Z N. Evaluation of Antipyretic and Antinociceptive Potential of New Heterocyclic Derivatives of 3-Formyl-4-Hydroxycoumarin In Rats, *Int Res J Pharm Appl Sci (IRJPAS),* 3(5), 2013, 253-9.
16. Jaya Prithi peesa, Yalavarthi P, Rasheed A. A perspective review on role of novel NSAID prodrugs in management of acute inflammation, *Journal of acute disease,* 5(5), 2016, 364-381.
17. Paliwal M, Jain S. Synthesis and Biological Evaluation of Mutual Prodrugs of 2- {[3-(Trifluoromethyl) Phenyl] Amino} Benzoic Acid, *Int J Pharma Bio Sci,* 6(1), 2015, 12-25.
18. Walsangikar S, Bhatia N. Synthesis and Evaluation of Mutual Prodrug of Aspirin and Chlorzoxazone, *J Pharm Sci Innov,* 2(2), 2013, 35-40.
19. Ruchita, Sucheta, Nanda S, Pathak D. Analgesic Prodrugs for Combating their Side-Effects: Rational Approach, *Curr Drug Deliv,* 14(1), 2017, 16-26.
20. N S. Recent Approach on Synthesis Characterization and Evaluation of Some Analgesic and AntiInflammatory Drugs, *Org Med Chem*, 4(3), 2017, 1-5.

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