IJPSR (2018), Volume 9, Issue 11 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 22 March, 2018; received in revised form, 10 June, 2018; accepted, 15 June, 2018; published 01 November, 2018

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

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Keywords:

Antibacterial, Anti-inflammatory, analgesic, Antipyretic, Mutual prodrug, Naproxen, Schiff's base

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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 Naproxen 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 Naproxen'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 prodrugs with Schiff bases having additional antibacterial activity.

INTRODUCTION: 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 **Scheme 1**.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(11).4709-15

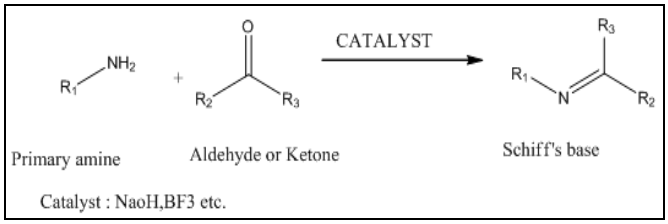
Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(11).4709-15

Naproxen belongs to the "Profens" class of NSAID's and is anti-inflammatory agent with analgesic and antipyretic activity. Generally the profens are considered being slightly "COX-1 selective"; naproxen appears to be more selective for COX-2 than other members of this series. These are used for RA, OA and as analgesics and antipyretics. Naproxens produce less GI ulceration than the salicylates, but may cause some thrombocytopenia, headache, dizziness, fluid retention, edema *etc* [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, 5, 6].



SCHEME 1: GENERAL SCHEME OF SCHIFF BASE SYNTHESIS. Where, R may be an aliphatic or an aromatic group.

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, Naproxen was obtained from Gangwal chemicals as a gift sample and used as such without purification. The Chemicals and reagents used are: 4-Amino phenol, 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). ^{1}H-NMR 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 1** and general protocol followed is as follows.

TABLE 1: LIST OF SCHIFF'S BASES SYNTHESIZED

Compound	IUPAC Nomenclature	Structure
A	4-((3,4,5-trimethoxy benzylidene) amino)phenol	
B	4-(((4-hydroxyphenyl) imino)methyl)-2-methoxyphenol	
C	4-((4-hydroxy benzylidene)amino) Phenol	
D	4-((4-chlorobenzylidene) amino)phenol	
E	4-((4-nitrobenzylidene) amino)phenol	

In a Microwave flask take 0.01 mol required aldehyde and 0.01 mol 4-amino phenol 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 4-((arylmethylene) amino) phenyl 2-(6-methoxynaphthalen-2-yl) propanoate (1): Dissolve naproxen (1mmol) in 25 ml of Dichloromethane (DCM) and let it cool to 0 °C in an ice bath. Make 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 h. Remove the ice bath and stir the

mixture for 12 h 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 **Fig. 1** [8, 9, 10]. The general scheme is represented in **Scheme 2**.

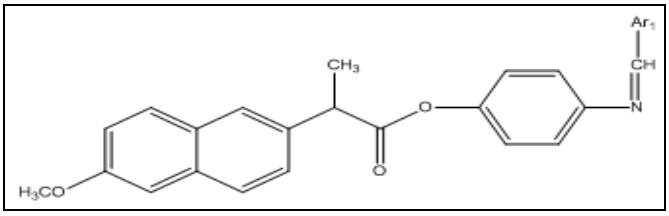
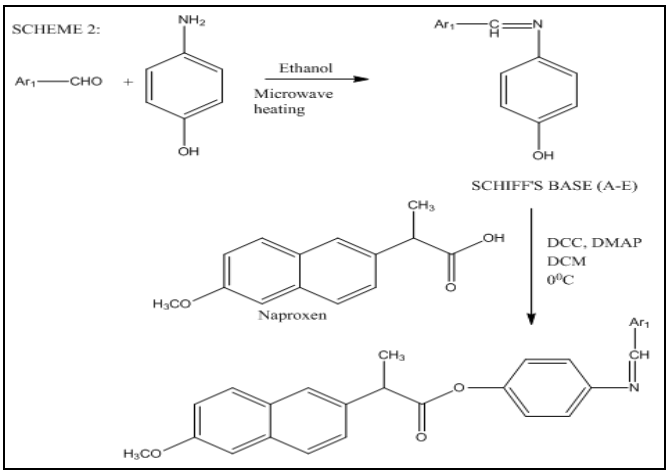


FIG. 1: STRUCTURE OF 4-((arylmethylene) amino) phenyl 2-(6-methoxynaphthalen-2-yl)propanoate(1)



SCHEME 2: GENERAL SCHEME OF SYNTHESIS OF SCHIFF BASE MUTUAL PRODRUGS OF NAPROXEN

Synthesis of 4- ((4-chlorobenzylidene) amino)phenyl 2- (6- methoxynaphthalen-2-yl) propanoate (2): Pale yellow solid; yield: 72%; m.p: 134 ºC; R_f value: 0.40 (*n*-hexane: ethyl acetate; 1:1); IR (cm^{-1}): 1749 (C=O of ester); 1691(C=N of imine); 1083; 1230 (C-O of ether); 791 (Cl str.); 1604 (Aromatic str.); ^{1}HNMR (400 MH_z; DMSO): 7.50 (d, 1H, benzylidenimin CH); 7.76 (d, 1H, benzylidenimin CH); 8.51 (s, 1H, benzylidenimin N=CH); 7.23, 7.16 (d, 1H, benzene CH); 3.86 (s, 3H, Methyl CH_3); 1.63 (d, 3H, methyl CH_3); 3.78 (q, 1H, methine CH); 7.21, 7.88, 7.86 (d, 1H, 2-Naphthalene CH); Elemental analysis: % calculated [C (73.05); H (5.00); N (3.16)]; % found [C (72.96); H(4.92); N(3.12)].

Synthesis of 4-((4-nitrobenzylidene) amino)phenyl2-(6-methoxynaphthalen-2-yl) propanoate (3): Yellow solid; yield: 68%; m.p: 92 °C; R_f value: 0.29 (*n*-hexane: ethyl acetate; 1:1); IR (cm^{-1}): 1753 (C=O of ester); 1648 (C=N of imine); 1267; 1230 (C-O of ether); 1531 (N-O str.); 1604 (Aromatic str.); ^{1}HNMR (400 MH_z; DMSO): 7.30 (d, 1H, benzylidenimin CH); 8.18 (d, 1H, benzylidenimin CH); 8.92 (s, 1H, benzylidenimin N=CH); 7.29 (d, 1H, benzene CH); 3.87 (s, 3H, methyl CH_3); 1.63 (d, 3H, methyl CH_3); 3.81 (q, 1H, methine CH); 7.26, 7.91, 7.87,7.10, 7.58 (d, 1H, 2-Naphthalene CH); Elemental analysis: % calculated [C (71.35); H (4.88); N (6.16)]; % found [C (71.13); H(4.75); N(6.09)].

Synthesis of 4- ((4-hydroxybenzylidene) amino) phenyl 2-(6-methoxynaphthalen-2-yl) propanoate (4): Buff coloured solid; Yield: 53%; m.p: 150°C; R_f value: 0.45(*n*-hexane: ethyl acetate; 1:1); IR (cm^{-1}): 1739 (C=O of ester); 1642 (C=N of imine); 1058; 1263(C-O of ether); 3352 (OH str.); 1604 (Aromatic str.); ^{1}HNMR (400 MH_z; DMSO): 7.50 (d, 1H, benzylidenimin CH); 7.76 (d, 1H, benzylidenimin CH); 8.51 (s, 1H, benzy-lidenimin N=CH); 7.23, 7.16 (d, 1H, benzene CH); 3.86 (s, 3H, methyl CH_3); 1.63 (d, 3H, methyl CH_3); 3.78 (q, 1H, methine CH); 7.21, 7.88, 7.86, 7.16, (d, 1H, 2-Naphthalene CH); 7.41, 7.43 (s, 1H, 2-Naphthalene CH); Elemental analysis: % calculated [C (76.22); H (5.45); N (3.29)]; % found [C (76.12); H(5.08); N(2.98)].

Synthesis of 4-((4-hydroxy-3-methoxybenzylidene) amino) phenyl 2-(6-methoxynaphthalen-2-yl) propanoate (5): Pale yellow solid; Yield: 48%; m.p: 142°C; R_f value: 0.42 (*n*-hexane: ethyl acetate; 1:1); IR(cm^{-1}): 1730 (C=O of ester); 1645 (C=N of imine); 1083;1263(C-O of ether); 3415 (OH str.); 1602 (Aromatic str.) ; ^{1}HNMR (400 MH_z; DMSO): 7.34 (d, 1H, benzylidenimin CH); 6.59 (d, 1H, benzylidenimin CH); 7.52 (s, 1H, benzylidenimin N=CH); 7.29 (d, 1H, benzene CH); 3.86 (s, 3H, methyl CH_3); 1.62 (d, 3H, methyl CH_3); 3.78 (q, 1H, methine CH); 7.22, 7.40, 7.43, 7.87, 7.90(d, 1H, 2-Naphthalene CH); Elemental analysis: % calculated [C (73.83); H (5.53); N (3.08)]; % found [C (73.45); H(5.42); N(3.01)].

Synthesis of 4 - ((3, 4, 5 - trimethoxybenzylidene) amino) phenyl 2- (6 - methoxynaphthalen - 2- yl) propanoate (6): Yellowish white solid; yield: 65%; m.p: 70°C; R_f value: 0.39 (*n*-hexane: ethyl acetate; 1:1); IR (cm^{-1}): 1735 (C=O of ester);

1681(C=N of imine); 1074; 1232(C-O of ether); 725, 916 (Aromatic str.); ^{1}HNMR (400 MH_z; $CDCl_3$): 7.13 (s, 1H, benzylidenimin CH); 9.83 (s, 1H, benzylidenimin N=CH); 7.27 (d, 1H, Benzene CH); 3.85 (s, 3H, methyl CH_3); 1.62 (d, 3H, methyl CH_3); 3.62 (q, 1H, methine CH); 7.70,7.72 (d, 1H, 2-Naphthalene CH); 7.40, 7.43 (s, 1H, 2-Naphthalene CH); Elemental analysis: % calculated [C (72.13); H (5.85); N (2.80)]; % found [C (72.08); H(5.78); N(2.73)]. The Final compounds synthesized are listed in **Table 2**.

TABLE 2: SCHIFF BASE MUTUAL PRODRUGS OF NAPROXEN

Compound	Ar_1	Structure
2		
3		
4		
5		
6		

Biological Screening:

Antibacterial Activity: The antibacterial activity of the synthesized compounds were evaluated *in-vitro,* antibacterial activity of different (25 µg, 50 µg, 100 µg and 200 µg) 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, 30 µl 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 37 ºC for 24 h 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, 12, 13, 14].

Antipyretic Activity:

Baker's Yeast Induced Pyrexia: (IAEC approval no: VESCOP/08/2016). 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 I: (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 Carrageenan-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 treatement (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 an electrically heated surface. The temperature is controlled for 55 °C 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 - 150 g 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 was 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 h 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 min, the animals are placed on the hot plate and the observations were recorded and at the time interval of 90, 120 and 180 min. The results of Hot plate method on rats were recorded [19, 20].

1. RESULTS AND DISCUSSION:

Antibacterial Activity: Anti-bacterial activities of the synthesized compounds were studied by the Well plate method.

TABLE 3: ANTIBACTERIAL ASSAY OF SCHIFF BASE MUTUAL PRODRUGS OF NAPROXEN

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	9	8	4	25	6	7
	50	13	12		50	9	8
	100	20	19		100	11	11
	200	23	25		200	14	18
2	25	8	5	5	25	N.O.	N.O.
	50	10	8		50	N.O.	N.O.
	100	13	10		100	9	8
	200	16	14		200	12	10
3	25	4	3	6	25	N.O.	6
	50	9	8		50	8	10
	100	13	12		100	13	13
	200	17	16		200	19	17

(Note: N.O. stands for Not Observed)

Four different concentration were selected (25µg/ml, 50 µg/ml, 100 µg/ml, 200 µg/ml) using DMSO as negative control & 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 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 4**. Aspirin, a cyclooxygenase inhibitor, at the dose of 20 mg/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 h and was maximum at 5 h after administration of carrageenan in the vehicle group.

Percent Inhibition was calculated by following formula:

$$\% \text{ Inhibition} = \frac{\text{Paw vol. of control} - \text{Paw vol. of test}}{\text{Paw vol. of control}} \times 100$$

TABLE 4: ANTI-INFLAMMATORY ACTIVITY OF SCHIFF BASE MUTUAL PRODRUGS OF NAPROXEN BY CARRAGEENAN INDUCED RAT PAW EDEMA TEST

Group	n	Dose (mg/kg)	Paw volume increase (ml)			% Inhibition		
			1 h	3 h	5 h	1 h	3 h	5 h
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	0.1266 ± 0.0113	0.2433 ± 0.0152	0.2666 ± 0.0152	62.76	64.56	66.81
3	3	20	0.1133 ± 0.0152	0.2233 ± 0.0152	0.2666 ± 0.0208	66.67	67.47	66.81
4	3	20	0.0933 ± 0.0057	0.1866 ± 0.0115	0.2366 ± 0.0152	72.55	72.82	70.54
5	3	20	0.1133 ± 0.0057	0.21 ± 0.0339	0.2533 ± 0.0347	66.67	69.41	68.46
6	3	20	0.1133 ± 0.0152	0.1966 ± 0.0115	0.2366 ± 0.0208	66.67	71.36	70.54

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 5**.

TABLE 5: ANALGESIC ACTIVITY TESTING BY HOT PLATE METHOD

Group	n	Dose (mg/kg)	Reaction time in sec at time (min) (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	3.25 ± 0.054	6.52 ± 0.075	7.8 ± 0.1	8.17 ± 0.077	7.55 ± 0.11
3	3	10	3.33 ± 0.081	6.69 ± 0.211	8.01 ± 0.093	8.45 ± 0.096	7.55 ± 0.177
4	3	10	3.3 ± 0.015	6.51 ± 0.076	7.83 ± 0.11	8.16 ± 0.09	7.55 ± 0.05
5	3	10	3.29 ± 0.115	6.37 ± 0.225	7.78 ± 0.14	8.28 ± 0.138	7.55 ± 0.17
6	3	10	3.41 ± 0.165	6.44 ± 0.269	7.54 ± 0.298	8.55 ± 0.152	7.55 ± 0.156

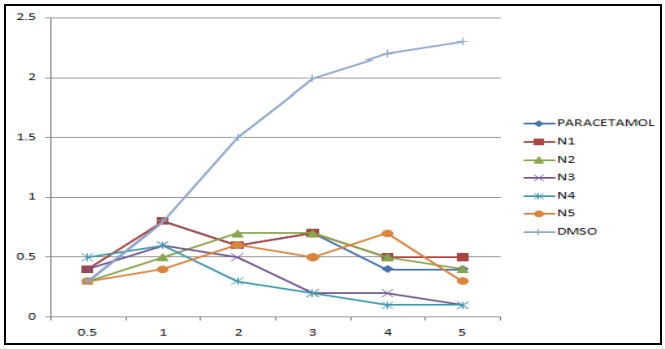


FIG. 2: ANTIPYRETIC ACTIVITY OF SCHIFF BASE MUTUAL PRODRUGS OF NAPROXEN. (X-axis: time in h; y-axis: increase in rectal temperature in °C)

Antipyretic Activity: The experimental rats showed a mean increase of about 0.64 ºC 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 **Fig. 2**.

CONCLUSION: Besides its important pharmacological activities, Naproxen 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 Naproxen 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 Naproxen mutual prodrugs.

ACKNOWLEDGEMENT: The Authors are very grateful to Gangwal chemicals for providing the gift sample required for the research.

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

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How to cite this article:
Gangrade D and Karande R: Synthesis, characterization and evaluation of Schiff's base mutual prodrugs of naproxen. Int J Pharm Sci & Res 2018; 9(11): 4709-15. doi: 10.13040/IJPSR.0975-8232.9(11).4709-15.