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Research Article

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ANALGESIS POTENTIAL OF NOVEL PRODRUGS OF NAPROXEN

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ABSTRACT

Non-steroidal anti-inflammatory drugs are mostly prescribed drugs for patients with inflammatory conditions, but their efficacy is offset by a significant incidence of gastrointestinal (GI) side effects. A series of novel prodrugs of naproxen have been synthesized and evaluated for analgesic potential. The results indicate good analgesic activity.

Keywords: Naproxen, Prodrug, Glucose, Amino acids and analgesic potential.

INTRODUCTION

The new prodrug approach for the designing and synthesis of nonsteroidal anti-inflammatory drugs (NSAIDs) have been given much attention by medicinal chemists, especially in the past years. As we known, NSAIDs are among the most widely used prescribed and over the counter (OTC) medications. Naproxen [(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid] is non-steroidal anti-inflammatory drug with analgesic, antipyretic properties and is frequently used for the treatment of rheumatoid arthritis and osteoarthritis[1,2]. Upon oral administration, the drug forms crystals that coat the digestive mucus. Due to its acidity and low solubility, these crystals are dissolved slowly and results in irritation and damage to the stomach walls, which on prolonged use can lead to the formation of ulcerations in the mucus[3]. The undesired GI irritation principally limits the clinical utility of most of the conventional NSAIDs. The main causes of NSAID-induced gastropathy are reduced mucosal cytoprotective prostaglandin (PG) levels, increased gastric acidity and increased gastric motility. The increased gastric motility of the drug leads to a reduced mucosal blood flow, hypoxia and destruction of the mucous bicarbonate barrier, which prevents back diffusion of pepsin and hydrogen ions from the lumen into the mucosal membrane[4]. The GI side effects produced by NSAIDs are generally caused by two different mechanisms: a direct contact mechanism on the GI mucosa through oral dose and a generalized systemic action appearing after intravenous dosing[5].

The prodrug concept involves delivering the drug by doing its chemical modification the bioreversible form in order to change its pharmaceutical and pharmacokinetic properties[6]. In recent years, much attention has been focused on the development of prodrugs of non-steroidal anti-inflammatory drugs (NSAIDs) in order to depress their gastrointestinal (GI) side effects.

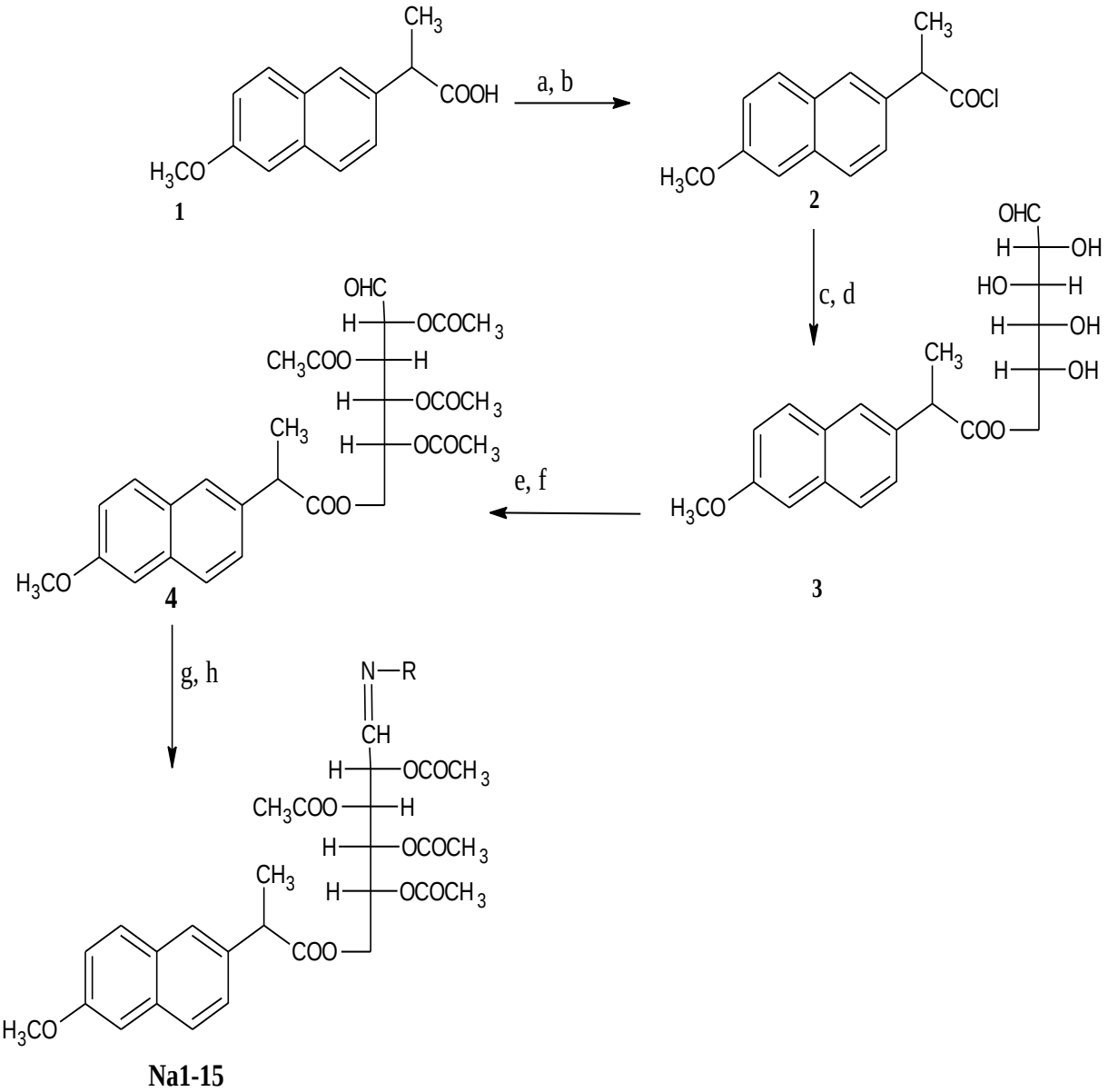
The esterification of NSIADs, however results in reduced GI toxicities. As we know ester being pharmacologically inactive *per se* readily hydrolyzed following their absorption to release the parent acid in the blood. The esters should also possess desirable physicochemical properties such as aqueous solubility and lipophilicity[5]. Carrier linked prodrugs are formed by combining an existing drug with a compound known as a carrier, which gives the desired chemical and biological properties to the resulting compound. The link between the drug and carrier is a functional group that can be metabolized in the body. Moreover, if the carrier is a natural product in case of prodrugs

than it can be *in vivo* degraded to small non-toxic and non-immunogenic fragments[7].

Various prodrugs of naproxen synthesized in the form of esters and amide. Although considerable research has been carried out designing prodrugs of naproxen with reduced GI toxicity, however no one seems to be an ideal and hence there is a need to develop newer prodrugs with better pharmaceutical and pharmacological profile[8].

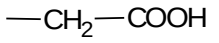
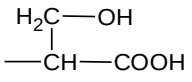
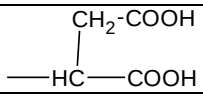
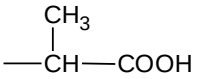
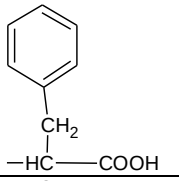
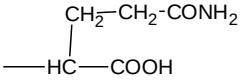
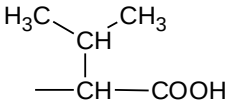
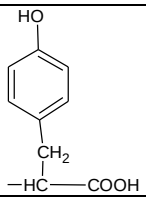
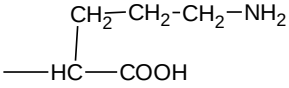
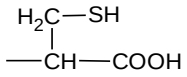
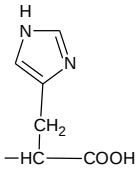
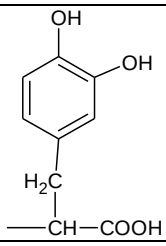
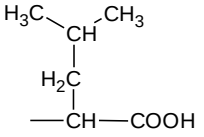
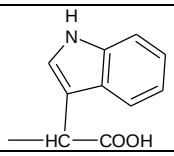
From the previous studies of β-D-glucopyranosyl derivative of ibuprofen, have found that the prodrugs possess increased analgesic and anti-inflammatory activity with reduction in gastrointestinal toxicity.

The present studies were undertaken in order to minimize the ulcerogenic potential of naproxen and to render it water soluble properties through glucosidation and Schiff base formation for better absorption and sustained release. We thought to modify the structure of naproxen by making the ester with glucose and further modifying it to a Schiff's base by reaction of the glucosyl derivative with differ[rent amino acids. The specially designed prodrug was with expected advantage of afford gastric protection by [1] by temporarily masking the acidic carboxylic group until absorption, [2] inhibition of gastric secretion[9].



Scheme. 1: Synthetic route of Naproxen Prodrugs, reagents and reaction conditions: (a) $SOCl_2$; (b) Benzene; (c) Glucose; (d) Pyridine; (e) $(CH_3CO)_2$; (f) $ZnCl_2$; (g) R; (h) Alcohol

Compound	R	Compound	R	Compound	R

Na1		Na6		Na12	
Na2		Na7		Na13	
Na3		Na8		Na14	
Na4		Na9		Na15	
Na5		Na10			

PHARMACOLOGICAL ACTIVITY

Evaluation of Analgesic Activity

The experimental protocol was approved by Institutional Animal Ethics Committee. The analgesic activity was assessed by tail immersion method[10].

- ✓ Animals: The study was carried out on healthy Swiss Albino mice weighing between 25-30g of either sex. The mice were selected and divided by randomization into 17 groups. Each group was having six mice. All the animals were fasted for 18 h prior to the commencement of experiment but water was provided ad libitum.
- ✓ Drugs and dose: All the doses of standard (naproxen) and test drugs (Na1-15) were prepared in 0.5% w/v tween 80 which served as drug vehicle.
- ✓ Control group: Control group of animal received 0.5% w/v tween 80 (10ml/Kg) alone
- ✓ Standard group: Standard group of animals received naproxen (50 mg/Kg) alone
- ✓ Test group: Test group of animals received dose of 50 mg/Kg of test compound (Na1-15) alone.
- ✓ Route of administration: The control, standard and test drugs were given by oral route to mice.
- ✓ Procedure

  The lower 5 cm portion of the tail is marked. This part of the tail is immersed in a cup of freshly filled water of exactly 55^0C and the tail-withdrawal reflex was taken as initial reading. After the administration of the control, standard and test drugs, the tail-withdrawal reflex of the mice was taken at 30, 60 90 and 120 min intervals.

RESULT AND DISCUSSION

Analgesic activity

The analgesic activity was carried out by tail immersion method. The results of analgesic activity of naproxen and its prodrugs were reported in table **1**. Na1, Na2, Na3, Na4, Na5, Na7, Na8, Na9, Na10, Na11, Na12, Na13, Na14 and Na15 showed good activity as compared to naproxen. Naproxen and its prodrugs significantly protect ($p<0.01$) writhing response induced by acetic acid as compared to control.

Table 1: Analgesic activity of naproxen and its prodrugs

Treatment	Dose (mg/Kg)	Latency Period (min)				% Protection			
		30	60	90	120	30	60	90	120
Control	-	1.7±0.3	1.7±0.3	1.7±0.3	1.7±0.3	-	-	-	-
Naproxen	50.00	9.3±0.4	13.5±0.6	14.5±0.5	14.7±0.2	447.0	694.1	752.9	764.7
Na1	62.8	6.0±0.8$^{\Delta}$	12.2±1.0$^{\Delta}$	13.8±0.8$^{\Delta\Delta}$	7.3±1.0$^{\Delta}$	252.9	617.6	711.7	329.4
Na2	63.2	3.0±0.8$^{\Delta\Delta}$	2.7±0.5$^{\Delta\Delta}$	4.5±1.1$^{\Delta}$	6.2±2. $^{\Delta}$	76.4	58.8	164.7	264.7
Na3	66.0	12.8±1.8$^{\Delta}$	12.3±1.4$^{\Delta\Delta}$	6.3±2.3$^{\Delta}$	7.5±2. $^{\Delta}$	652.9	623.5	270.5	341.1
Na4	66.4	7.0±0.6$^{\Delta\Delta}$	12.2±0.8$^{\Delta}$	14.5±0.3$^{\Delta}$	13.7±0.6$^{\Delta}$	311.7	617.6	752.9	705.8
Na5	67.4	6.5±1.1$^{\Delta}$	7.0±1.2$^{\Delta\Delta}$	10.5±2.1$^{\Delta\Delta}$	8.0±2.3$^{\Delta\Delta}$	282.3	311.7	517.6	370.5
Na6	66.2	5.7±1.1$^{\Delta}$	9.5±1.6$^{\Delta}$	10.8±2.2$^{\Delta}$	11.2±2.3$^{\Delta}$	235.2	458.8	535.2	558.8
Na7	67.8	5.8±0.6$^{\Delta}$	13.8±0.6$^{\Delta}$	14.5±0.34$^{\Delta}$	13.7±0.6$^{\Delta}$	241.1	711.7	752.9	705.8
Na8	69.4	12.5±1.9$^{\Delta}$	13.2±1.8$^{\Delta}$	13.2±1.8$^{\Delta}$	13.2±1.5$^{\Delta}$	635.2	676.4	676.4	676.4
Na9	67.0	7.8±0.5$^{\Delta}$	13.2±0.9$^{\Delta}$	12.0±2.0$^{\Delta\Delta}$	6.2±1.7$^{\Delta\Delta}$	358.8	676.4	605.8	264.7
Na10	71.9	2.8±0.4$^{\Delta}$	3.0±0.4$^{\Delta\Delta}$	4.3±1.1$^{\Delta}$	7.7±1.3$^{\Delta}$	64.7	76.4	152.9	352.9
Na11	67.6	7.0±1.7$^{\Delta}$	11.2±1.7$^{\Delta}$	9.5±1.5$^{\Delta}$	8.5±2.5$^{\Delta}$	311.7	558.8	458.8	400
Na12	68.9	3.7±0.4$^{\Delta}$	10.7±0.9$^{\Delta}$	13.5±0.8$^{\Delta}$	14.0±0.5$^{\Delta}$	117.6	529.4	694.1	723.5
Na13	64.7	6.0±1.1$^{\Delta}$	8.5±2.0$^{\Delta}$	11.3±2.2$^{\Delta}$	10.3±2.3$^{\Delta}$	252.9	400	564.7	505.8
Na14	71.7	4.2±0.3$^{\Delta}$	9.0±1.6$^{\Delta}$	13.2±0.8$^{\Delta}$	14.2±0.4$^{\Delta}$	147.0	429.4	676.4	735.2
Na15	69.6	4.5±0.4$^{\Delta}$	12.2±0.9$^{\Delta}$	14.0±0.5$^{\Delta}$	14.2±0.4$^{\Delta}$	164.7	617.6	723.5	735.2

Values expressed as Mean **±** SEM and are in seconds.
n = 6 animals; *p < 0. 01 as compared to control
$^{\Delta}$p < 0.05; $^{\Delta\Delta}$p < 0.01 as compared to naproxen

Statistical analysis

All the results were expressed as Mean ± Standard error (SEM). Data was analyzed using one-way ANOVA followed by Dunnett: Compare all vs. control. p-value < 0.01 were considered as statistically significant.

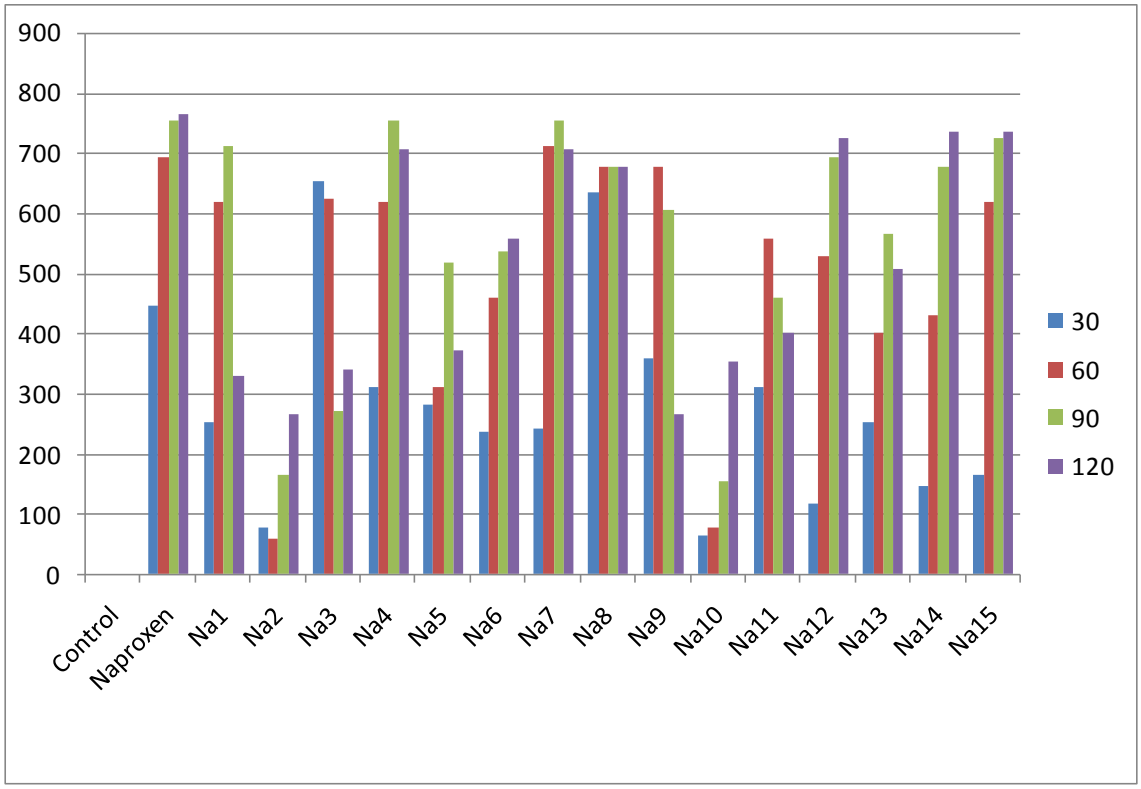


Chart. 1: % Protection by the synthesized compounds

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