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Research Article

SYNTHESIS, CHARCTERIZATION AND PHARMACOLOGICAL ACTIVITY OF ESTER PRODRUGS OF NAPROXEN

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ABSTRACT

Prodrug strategy is an established part of drug development. The present work is aimed to synthesis some novel prodrugs of Naproxen. Seven ester derivatives of Naproxen have been synthesized via acid alcohol coupling of Naproxen and alcohol derivatives in dichloromethane medium. These newly synthesized prodrugs were analyzed by NMR and IR spectroscopy. All the compounds were evaluated for anti-inflammatory activity by Carragennan Induced Rat hind Paw method and analgesic activity by acetic acid induced writhing.

Key words: GI, NSAIDs, Naproxen.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a diverse group of drugs used mainly in treatment of acute and chronic pain. But these have many side effects like effect on GI system[1], dyspepsia and low bioavailability[2]. GI side effects constitute the most frequent of all the adverse reactions of NSAIDs[3]. Major side effect is that NSAIDs could block prostaglandin synthesis[1]. Naproxen is one of the most important NSAID which is an orally administered which effect on a variety of inflammatory mediators[3]. It is an effective analgesic and anti-inflammatory agent with a good tolerability profile[3,5]. It is absorbed form the gastrointestinal tract, but like other NSAIDs it has some side effects like it affect GI system[1], dyspepsia and low bioavailability[2]. These side effects can be minimize by "Prodrug approach"

Prodrug refers to a pharmacologically inactive compound that is converted to an active drug by a metabolic transformation[8]. This bioconversion or transformation may take place during and after absorption with in the body[5-8]. It emphasizes on improving the desirable properties of drugs and decreasing the side effects[7]. Today many successful prodrugs have been developed with enhanced therapeutic efficiencies[8-11]. Prodrug approach is vary effective and helpful in decreasing the problem related with solubility, absorption, distribution, site specificity, instability, toxicity, formulation and bioavailability problem[6-10]. Among various type of prodrugs, ester and amide prodrugs are most common type[12]. In body, these prodrugs break in to parent drug and coupled moiety. Ester prodrugs synthesized by reacting carboxylic acid group and alcohol group while amide prodrugs synthesized by coupling of amine and carboxylic acid[16]. Prodrugs are frequently applied to mask polar and ionizable group of a drug molecule with the aim to improve membrane permeability and oral absorption[13]. Ester based esterase sensitive prodrug system has been used for prodrugs of acids and alcohol[8].

The result from the studies indicated that prodrugs had good chemical stability[15]. Some reports shows that the analgesics and anti inflammatory activities of ester derivatives of Naproxen have been found significant with reduction in GI toxicity. Chlorzoxazone ester prodrugs of some acidic NSAIDs induced very little irritancy in the gastric mucosa[14]. Nebumetone is a prodrug, cause fewer GI ulcer than conventional NSAIDs[5]. Diethyl carbonate prodrug of Ibuprofen and Naproxen undergo rapid transformation as compared to parent drugs. Morpholino alkyl ester of Naproxen was found more bioavailability and less irritating to gastric mucosa than parent drug.

The result from the literature survey indicated that prodrugs have good chemical stability towards hydrolysis and more bioavalailibility[12-16]. Keeping in view, the wide-ranging biological activities of Prodrugs of Naproxen, it was considered worthwhile to synthesize some new prodrugs of Naproxen of biological and pharmacological interest.

Naproxen was made to react with different alcohols, via, 2-phenylethanol and its derivatives, in presence of oxalyl chloride, in dichloromethane (DCM) at ambient temperature, by stirring on magnetic stirrer for 6-8 hrs to yield coupled products. All the products were purified using column chromatography in appropriate solvent system. Chemical structures of compounds were determined by ^{1}H NMR, and FT-IR. NMR spectra were recorded and peaks were interpreted. Animal studies were conducted with the prior approval of Institutional Animal Ethics Committee as with guidance of Committee for the Purpose of Control and Supervision of Experiments on Animal.

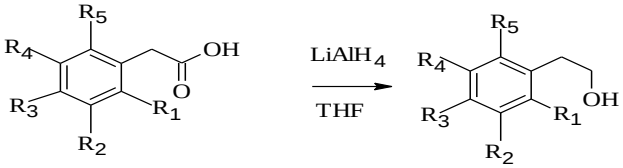
In the present study, we report the synthesis, evaluation and biological potential of ester Prodrugs of Naproxen. The alcohol derivatives choose to mask the free carboxylic group of Naproxen and Prodrugs form could show varying degree of lipofilicity and less side effects.

Objectives:

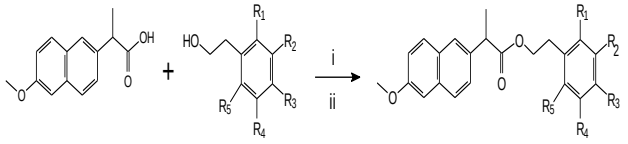
1. Design, synthesize, characterization of novel Prodrugs including Naproxen and alcohol, which could improve the physiochemical and pharmaceutical properties of drug.
2. To reduces the side effects of Naproxen by masking the free carboxlic acid group by 2-phenylethanol derivatives.

General structure and scheme of the desired Prodrug molecule -

I. SYNTHESIS OF 2-PHENYLETHANOL



II. SYNTHESIS OF PRODRUG (COUPLING OF NAPROXEN AND 2-PHENYLETHANOL)



i = Oxalyl chloride, DCM, 0°C → RT, 8 hrs

ii = DCM, 0°c → RT, 3-4 hrs

Where:

Scheme-I	R_1=H	R_2=H	R_3=H	R_4=H	R_5=H
Scheme-II	R_1=H	R_2=H	R_3=Br	R_4=H	R_5=H

Scheme-III	R_1=H	R_2=Cl	R_3=Cl	R_4=H	R_5=H
Scheme-IV	R_1=NO_2	R_2=H	R_3=H	R_4=H	R_5=H
Scheme-V	R_1=H	R_2=OCH_3	R_3= OCH_3	R_4=H	R_5=H
Scheme-VI	R_1=H	R_2=H	R_3= OCH_3	R_4=H	R_5=H
Scheme-VII	R_1= CH_3	R_2=H	R_3=H	R_4=H	R_5=H

MATERIALS AND METHODS

Chemicals and apparatus

Chemicals obtained from S.D. fine and Merck was of reagent grade used as such without further purification unless otherwise specified. Solvent used were double distilled on Rota vapor. ^{1}H NMR spectra were recorded at room temperature on a 400 MHz spectrometer from Bruker in $CDCl_3$ solution. IR were recorded with resolution 4.00 cm^{-1}

Animals

Animals were housed in-group of 5 per cage under standard laboratory conditions, temperature and humidity. All experimental procedures were carried out under standard guidelines prescribed by Committee for the Purpose of Control and Supervision of Experiments on Animal and were approved by Institutional Animal Ethics Committee.

45 Albino mice (18-22 g) five in each group were used for analgesic activity while 45

Wistar rat (120- 170 g) five in each group were used for anti-inflammatory activity.

Methods

I. Synthesis of 2-phenylethanol

To an ice-water cooled suspension of lithium aluminum hydride (380 mg, 10.0 mmol) in 5.0 ml anhydrous tetrahydrofuran(THF) , an ice-water cooled solution of carboxylic acid (2.5 mmol) in 12.5 ml anhydrous tetrahydrofuran(THF) (5ml/mol) was added at 0ºc temperature under nitrogen atmosphere and stirred the reaction mixture for 5 minutes at 0ºc. Then removed the ice-water bath and stirred reaction mixture for 4-5 hrs at room temperature. Reaction completion was checked by TLC using Ethyl acetate-Hexane (1:4) as an eluting solvent. Reaction was quenched by addition of water (10 ml). The organic compound was extracted with ethyl acetate (3x20ml). Organic layer was washed with brine (2x20ml), dried over anhydrous Na_2SO_4 and concentrated in vacuum.

Purification was done by column chromatography using Silica (100-200) in ethyl acetate-Hexane give required compounds as viscous liquids.

II. Synthesis of prodrug (coupling of Naproxen and 2-phenylethanol)

To a ice-water cooled solution of Naproxen (412 mg, 2.0 mmol) in anhydrous dichloromethane (6.0 ml, 3.0 ml/mmol), a solution of oxalyl chloride (0.26 ml, 3.4 mmol) in anhydrous dichloromethane (0.8 ml, 3.0 ml/mmol) was added dropwise at 0ºc temperature under nitrogen atmosphere and stirred the reaction mixture for 10 minutes at 0ºc. Then removed the ice-water bath and stirred reaction mixture for 8 hrs at room temperature. Evaporated the volatiles from reaction mixture on high vacuum and diluted with anhydrous dichloromethane and cooled it to 0ºc. A solution of alcohol (2.0 mmol) in anhydrous dichloromethane (6.0 ml, 3.0 ml/mmol), was then added at 0ºc, and reaction mixture was stirred at 0ºc for additional 10 minutes. Removed the ice water bath and stirred the reaction mixture for 3-4 hrs. at room temperature.

Reaction completion was checked by TLC using Ethyl acetate-Hexane (1:4) as an eluting solvent. Reaction was quenched by addition of water (10 ml). The organic compound was extracted with ethyl acetate (3x20ml). Organic layer was washed with brine (3x20ml), dried over anhydrous Na_2SO_4 and concentrated in vacuum.

Purification was done by column chromatography using Silica (100-200) in ethyl acetate-Hexane give required compounds as viscous liquids.

Study design for pharmacological study (*in vivo*) of synthesized prodrugs

Naproxen as well as the synthesized prodrugs was evaluated for anti-inflammatory and analgesic activity

a. Acetic acid – induced writhing

The animals were pretreated with drug 45 minute before induction of writhing. The drug Naproxen (100 mg/kg, i.p.) served as reference standard drug. Analgesic activity of synthesized derivatives of Naproxen (100 mg/kg, i.p.) was accessed by counting the number of writhes induced by 0.6% acetic acid (10 ml/kg i.p.). The number of writhes per animal was counted for the next 10 minutes. Percentage protection against abdominal constriction was taken as an index of analgesia.

It was calculated as:

[(Number of writhing in control group - Number of writhing in treated group) x 100] / Number of writhing in control group

b. Carragennan induced paw edema

Experimental inflammation was induced according to the method described by Winter et al. (1962). Carrageenan (0.1 ml of 1%) was injected in to the right hind paw of each rat under the planter aponeurosis. The test groups of rats were treated with Derivatives of Naproxen 100 mg/kg body weight, i.p. one hour before Carrageenan injection. At the same time the control group was administered the reference group was administered i.p. with an ethanolic solution of Naproxen at a dose of 100mg/kg body weight. The displacement technique using the plethysmometer (IITC 520, USA) immediately and 1 and 2 h did the measurements of paw volume after the injection of Carrageenan. The inhibitory activity was calculated according to the formula

Percentage inhibition = $(1- V_t / V_c)$ 100

Where V_t and V_c were edema volume in the drug treated and control groups, respectively.

RESULTS AND DISCUSSION

I. Characterization of the synthesized prodrugs

Scheme-I: Preparation of 2-phenylethyl 2-[4-(2-methylpropyl) phenyl] propanoate

^{1}H NMR (400 MHz, $CDCl_3$), δ 7.72- 7.70 (m, 2H, ArH), 7.68 (d, J=2.8, 1H, ArH), 7.40 (dd, J= 1.8, 8.5, 1H, ArH), 7.31 (d, J= 7.3, 1H, ArH), 7.23 (d, J=7.5, 2H, ArH), 7.14 (d, J= 2.5, 1H, ArH), 7.12 (dd, J= 2.4, 7.3, 1H, ArH), 7.08 (dd, J= 8.0, 9.4, 2H, ArH), 4.32-4.18 (m, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.87 (q, J= 7.1, 1H, CH*), 2.85 (dt, J=7.0, 15.9, 2H, CH_2-Ph), 1.59 (d, J=7.1, 3H, CH_3),
IR: 1733 cm^{-1} (ester)

Scheme-II: Preparation of 2-(4-bromophenyl) ethyl 2-[4-(2-methylpropyl) phenyl] propanoate

^{1}H NMR (400 MHz, $CDCl_3$), δ 7.72- 7.70 (m, 2H, ArH), 7.68 (d, J=2.8, 1H, ArH), 7.40 (dd, J= 1.8, 8.5, 1H, ArH), 7.36- 7.31 (m, 2H, ArH), 7.14 (d, J= 2.5, 1H, ArH), 7.12 (dd, J= 2.4, 7.3, 1H, ArH), 6.93 (d, J= 8.3, 2H, ArH), 4.32-4.18 (m, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.87 (q, J= 7.1, 1H, CH*), 2.80 (dt, J=5.3, 6.7, 2H, CH_2-Ph), 1.59 (d, J=7.1, 3H, CH_3),
IR: 1735 cm^{-1} (ester)

Scheme-III: Preparation of 2-(3, 4-dichlorophenyl) ethyl 2-[4-(2-methylpropyl) phenyl] propanoate

^{1}H NMR (400 MHz, $CDCl_3$), δ 7.72- 7.70 (m, 2H, ArH), 7.68 (d, J=2.8, 1H, ArH), 7.40 (dd, J= 1.8, 8.5, 1H, ArH), 7.25 (d, J= 8.2, 1H, ArH), 7.20 (d, J=2.0, 1H, ArH), 7.14 (d, J= 2.5, 1H, ArH), 7.12 (dd, J= 2.4, 7.3, 1H, ArH), 6.86 (dd, J=2.0, 8.0, 1H, ArH), 4.32-4.17 (m, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.87 (q, J= 7.1, 1H, CH*), 2.80 (dt, J=2.1, 6.5, 2H, CH_2-Ph), 1.59 (d, J=7.1, 3H, CH_3),
IR: 1736 cm^{-1} (ester)

Scheme-IV: Preparation of 2-(2-nitrophenyl) ethyl 2-[4-(2-methylpropyl) phenyl]propanoate

^{1}H NMR (400 MHz, $CDCl_3$), δ 7.92 (dd, J=1.8, 7.8, 1H, ArH), 7.72- 7.70 (m, 2H, ArH), 7.68 (d, J=2.8, 1H, ArH), 7.40 (dd, J= 1.8, 8.5, 1H, ArH), 7.35 (dt, J=1.9, 7.2, 2H, ArH), 7.14 (d, J= 2.5, 1H, ArH), 7.12 (dd, J=

2.4, 7.3, 1H, ArH), 7.09- 7.06 (m, 1H, ArH), 4.43- 4.32 (m, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.87 (q, J= 7.1, 1H, CH*), 3.17 (dt, J=6.7, 12.7, 2H, CH_2-Ph), 1.59 (d, J=7.1, 3H, CH_3),
IR: 1736 cm^{-1} (ester)

Scheme-V: Preparation of 2-(3, 4-dimethoxyphenyl) ethyl 2-[4-(2-methylpropyl) phenyl]propanoate
^{1}H NMR (400 MHz, $CDCl_3$), δ 7.72- 7.70 (m, 2H, ArH), 7.68 (d, J=2.8, 1H, ArH), 7.40 (dd, J= 1.8, 8.5, 1H, ArH), 7.14 (d, J= 2.5, 1H, ArH), 7.12 (dd, J= 2.4, 7.3, 1H, ArH), 6.75 (d, J= 8.1, 1H, ArH) 6.66 (dt, J=1.9, 6.6, 2H, ArH), 4.31-4.18 (m, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.87 (q, J= 7.1, 1H, CH*), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.82 (dt, J=6.2, 7.5, 2H, CH_2-Ph), 1.59 (d, J=7.1, 3H, CH_3),
IR: 1733 cm^{-1} (ester)

Scheme-VI: Preparation of 2-(4-methoxyphenyl) ethyl 2-[4-(2-methylpropyl) phenyl]propanoate
^{1}H NMR (400 MHz, $CDCl_3$), δ 7.72- 7.70 (m, 2H, ArH), 7.68 (d, J=2.8, 1H, ArH), 7.40 (dd, J= 1.8, 8.5, 1H, ArH), 7.14 (d, J= 2.5, 1H, ArH), 7.12 (dd, J= 2.4, 7.3, 1H, ArH), 7.00 (dd, J= 2.1, 6.7, 2H, ArH), 6.78 (dd, J= 2.1, 6.5, 2H, ArH), 4.23 (dt, J=3.2, 7.0, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.87 (q, J= 7.1, 1H, CH*), 3.78 (s, 3H, OCH_3), 2.81 (dd, J=5.5, 7.0, 2H, CH_2-Ph), 1.59 (d, J=7.1, 3H, CH_3),
IR: 1733 cm^{-1} (ester)

Scheme-VII: Preparation of 2-(2-methylphenyl) ethyl 2-[4-(2-methylpropyl) phenyl]propanoate
^{1}H NMR (400 MHz, $CDCl_3$), δ 7.72- 7.70 (m, 2H, ArH), 7.68 (d, J=2.8, 1H, ArH), 7.40 (dd, J= 1.8, 8.5, 1H, ArH), 7.14 (d, J= 2.5, 1H, ArH), 7.14- 7.09 (m, 3H, ArH), 7.05 (dd, J= 6.2, 8.8, 2H, ArH), 4.24 (t, J=7.2, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.87 (q, J= 7.1, 1H, CH*), 2.88 (dd, J=6.3, 7.4, 2H, CH_2-Ph), 2.29 (s, 3H, CH_3), 1.59 (d, J=7.1, 3H, CH_3),
IR: 1734 cm^{-1} (ester)

II. Physiochemical Properties of the Synthesized Prodrugs

Physiochemical properties of the synthesized prodrugs are shown in Table 1 and 2.

Table 1: General data for various ester prodrugs of Naproxen

Compound	Molecular Formula	Molecular Weight	Percentage Yield
Naproxen	$C_{14}H_{14}O_3$	230	-
2-phenyethanol derivative	$C_{22}H_{22}O_3$	334	78
2-(4-bromophenyl)ethanol derivative	$C_{22}H_{21}O_3Br$	413	79
2-(3, 4-dichlorophenyl) ethanol derivative	$C_{22}H_{20}O_3Cl_2$	403	80
2-(2-nitrophenyl)ethanol acid derivative	$C_{22}H_{21}O_5N$	379	86
2-(3,4-dimethoxyphenyl)ethanol derivative	$C_{24}H_{26}O_5$	394	83
2-(4-methoxyphenyl)ethanol derivative	$C_{23}H_{24}O_4$	364	85
2-(2-methylphenyl)ethanol derivative	$C_{23}H_{24}O_3$	348	88

Table 2: Solubility data for various ester prodrugs of Naproxen

Solvent	water	ethanol	chloroform	Acetone	Diethyl ether
2-phenylethanol derivative	insoluble	soluble	soluble	soluble	soluble
2-(4-bromophenyl) ethanol derivative	insoluble	soluble	soluble	soluble	soluble
2-(3, 4-dichlorophenyl) ethanol derivative	insoluble	soluble	soluble	soluble	soluble
2-(2-nitrophenyl) ethanol acid derivative	insoluble	soluble	soluble	soluble	soluble
2-(3, 4-dimethoxyphenyl) ethanol derivative	insoluble	soluble	soluble	soluble	soluble
2-(3, 4-dimethoxyphenyl) ethanol derivative	insoluble	soluble	soluble	soluble	soluble
2-(4-methoxyphenyl) ethanol derivative	insoluble	soluble	soluble	soluble	soluble
2-(2-methylphenyl) ethanol derivative	insoluble	soluble	soluble	soluble	soluble

Table 3: Table for analgesic activities by Acetic acid – induced writhings

Drug	Dose	Number of Writhes (Mean + SEM)	Percent Inhibition
Control (Ethanol)	-	38.11 ± 0.59	-
Naproxen Standard	100 mg	8.4 ± 0.78	78.01
I	100 mg	31.4± 0.86^1	17.80^0
II	100 mg	36.6 ± 0.95^2	4.71^0
III	100 mg	25.8 ± 1.18^1	32.46^1
IV	100 mg	34.6 ± 1.92^2	9.42^0
V	100 mg	22.6 ± 0.72^2	40.83^2
VI	100 mg	37.8 ± 0.78^2	10.04^0
VII	100 mg	29.4 ± 2.1^1	23.03^1

0 indicates Non significance with relative to Control, 1 indicates 0.05 < p with relative to Control, 2 indicates 0.01 < p with relative to Control

Table 4: Anti-inflammatory activies by carrageenan-induced rat paw edema

Drug	Dose	1 hr	2 hr
Control (Ethanol)	-	0.45 ± 0.012	0.62+ 0.018
Naproxen Standard	100 mg	0.18± 0.015	0.17+ 0.016
I	100 mg	0.40± 0.022^0	0.41+ 0.014^1
II	100 mg	0.48 ± 0.015^0	0.45+ 0.19^0
III	100 mg	0.31 ± 0.007^1	0.28+ 0.081^2
IV	100 mg	0.38 ± 0.011^0	0.42+ 0.018^1
V	100 mg	0.28 ± 0.015^1	0.26+ 0.021^2
VI	100 mg	0.40 ± 0.036^0	0.51+ 0.056^0
VII	100 mg	0.31 ± 0.007^2	0.35+ 0.008^2

0 indicates Non significance with relative to Control, 1 indicates 0.05 < p with relative to Control, 2 indicates 0.01 < p with relative to Control

III. Pharmacological study (*in vivo*) of synthesized prodrugs

Pharmacological study (*in vivo*) of synthesized prodrugs is shown in Table 3 and 4.

CONCLUSION

In the present study, the free acidic group of Naproxen was temporarily masked by a promoiety so as not to expose stomach's mucosa to this free carboxylic acid group. Several ester prodrugs of Naproxen were synthesized by selecting corresponding alcohols viz. 2-phenylethanol and its derivatives. The selection was done in such a manner that prodrugs with varying degree of lipophilicity could be obtained. Direct coupling was done by oxalyl chloride for preparation of these ester prodrugs. The Physicochemical data including solubility was reported in tables. All the Synthesized Prodrugs were found pharmacologically active as compared to control and were quantitatively less active than standard Naproxen.

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REFERENCES

1. John, L., Prostaglandin, NSAID,s and gastric Smucosal protection, Physiological Review, 88: 1547-1565, 2008.
2. Flower, Rod J. (2003), "The Development of Cox 2 Inhibitor." Nature Review Drug Discovery 2(3): 179-191.
3. Free encyclopedia.com.
4. Albert, A., Nature, 182:421, (1958).
5. Adis International Limited, Volume 7, Number 4, 2006, 262-266(5).
6. Dhaneshwar, S., Indian Journal of Pharmaceutical Science, 68(3), 286-294,(2006).
7. Bhosale. A. V., Agrawal, Indian Journal of Pharmaceutical Science, 68 (4), 425-431, (2006).
8. Qizhenz, Y. et al Synthesis and evolution of carbamate produrgs of S Q109 Medicinal chemistry letters (2009).
9. Mishra, S., Nucleic Acid Research Supplement, 277 (2002)
10. Rao, H.S.P., Capping Drug: Development of Prodrug, (2003)
11. Lenard. M. Nonstroidal Anti-inflammatory Drug and Phospholipids Prodrug, Gastroenterology. 990(1996).
12. Prodrug: Design and Clinical Application, Nature.com.
13. Prodrug Approach to Enhancinf the Oral Delivery of Poorly Permeable Drug by Valentino J. Stella Ahmad, Z., et al,
14. Chloroxazone ester of some NSAI Carboxylic acids, Bioorganic and Medicinal Chemistry , 17, issue 10, 3665-3670, May (2009)
15. Encyclopedia of pharmaceutical technology.
16. Prodrug of Amines, Molecules (2008), 13, 519-547.
17. Audra, L., Neltrexone Ester Prodrug Bioconversion in a human Epidermis Equivalent, (2006).
18. Guangping, W., Journal of Medicinal Chemistry, 48(1), 256-261 (2005).
19. Fang, J., Produrg Strategy for enhancing Drug Delivery via Skin, Current Drug discovery Technology, 3(3), 211-214, (2006)
20. Huang, S., Bioorganic and Medicinal Chemistry Letters, 16, 3639-3641 (2006).
21. Dhaneshwar, S., Bioorganic and Medicinal Chemistry Letters, 17(7), 1897-1902, (2007).
22. Rahman, T., Indian Journal of Pharmaceutical Science, 36 (5), 332-333, (2004).
23. Ham, H.,et al targeted Prodrug design to optimize Drug Discovery AAAPS Pharm Sci. 2000; 2 (1): article 6.