Chapter – 2

AIM OF THE PRESENT WORK

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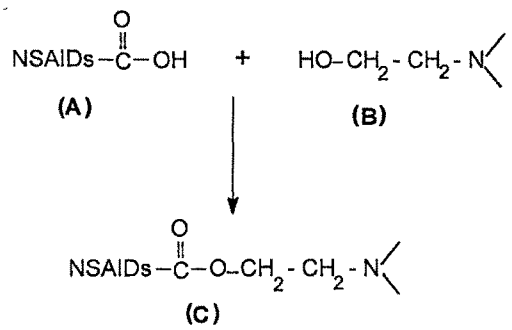
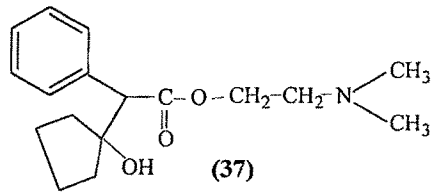
Survey of literature quite clearly indicated that a majority of researchers have simply blocked the free carboxylic group present in NSAIDs into ester or amide functionality thereby, converting the biologically active NSAIDs into inactive prodrugs. We thought of moving a step ahead whereby, we would be able to block the free carboxylic group present in NSAIDs into ester functionality, like other workers, and at the same time convert the NSAIDs through this chemical modification into anticholinergic compounds. In other words, this approach involved, modifying the NSAIDs chemically into anticholinergic agents. Once modified, the molecules would exhibit anticholinergic actions in the GIT and after absorption from GIT into the blood, the temporarily modified compounds would be chemically/enzymatically cleaved into the parent NSAIDs, free to show their original inherent anti-inflammatory and analgesic activity.

The above planned idea could be realized if we could convert the carboxylic group present in NSAIDs to N,N-disubstitutedaminoethyl ester functional group. These compounds then, would resemble structurally to the aminoethylalcohol ester class of potent anticholinergic agents. A terminal tertiary 'Nitrogen', with an ethylene bridge between the ester carbonyl group and the terminal 'Nitrogen', and the presence of bulky groups at the carboxyl terminal are the structural requirements[93] for a compound of aminoalcohol ester class of anticholinergics. These structural requirements are also satisfied by our designed esters. The rationale behind this drug design is based on the expected advantage that besides blocking the carboxyl group temporarily, the existence of anticholinergic activity in these intact esters would further aid in decreasing the GI toxicity by decreasing the gastric acid secretions and peristaltic movements.

Hence, the present work was undertaken with the aim of synthesizing the N,N-disubstituted aminoethyl ester derivatives (**C**) of some clinically used NSAIDs, which would decrease the local GI irritation by two different mechanisms. The ionisable free carboxylic group would be blocked, as is the case with normal esters. In addition to this, it was hypothesized that this type of aminoesters (**C**) could possess anticholinergic activity as they have structural resemblance with the aminoalcohol ester class of anticholinergic drugs, e.g. cyclopentolate **(37).** The above designed esters can be seen

to satisfy the requirements for possessing the anticholinergic activity and hence, were expected to exhibit this activity.





Apart from blocking the free carboxylic acid group into ester functionality as aminoesters, the existence of anticholinergic activity in the derivatives were expected to provide the following advantages over the reported simple ester prodrugs of NSAIDs in literature.

1) The designed aminoesters would block the free carboxylic group of NSAIDs like any other reported ester/amide.

2) The aminoester derivatives will be in the protonated form (as salts of amines) in the acidic pH of the stomach along with a blocked carboxyl group and hence there would be neither any absorption of the ionized compounds nor local gastric irritation (due to absence of free carboxyl group).

3) The protonated derivatives would revert back into the free aminoesters in the alkaline pH of the intestine where, they are expected to be absorbed since they would be in unionized form (more lipophilic than the parent NSAIDs).

4) Further, besides the blocked carboxyl group, the possession of anticholinergic activity would have the added advantage of decreasing the mucosal damage by decreasing the gastric acid secretion and peristaltic movement of GIT.

5) After absorption into the system, the aminoesters would be cleaved enzymatically /non-enzymatically into the parent NSAIDs, thereby eliciting the normal pharmacodynamics of NSAIDs.

Hence, in contrast to the simple esters reported earlier, which simply prevent the local GI irritation by blocking the carboxyl group, our designed aminoesters are proposed to

prevent GI irritation by two mechanisms. The first mechanism would be by preventing the exposure of stomach mucosa to the acidic functionality of NSAIDs and secondly by inhibition of gastric acid secretion due to the inherent property of possessing the anticholinergic activity.

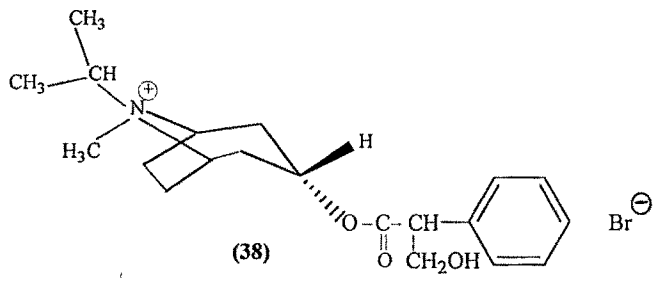
The combination of these two properties of being anticholinergic when intact and anti-inflammatory after hydrolysis may lead to a much wider scope for these esters with possible indication in ophthalmic inflammatory conditions and in conditions of respiratory disorders.

i) Indication in Opthalmology

NSAIDs in general, have found less use in the inflammatory conditions of eye due to their highly polar nature leading to poor absorption. The aminoesters are expected to be readily absorbed into the eye due to their availabilitiy as non-ionic form in the slightly alkaline pH of the eye. The anticholinergic activity should cause mydriasis, aiding in the ophthalmic disc examination by the surgeon. Further, after cleavage the liberated parent NSAID will elicit the normal anti-inflammatory activity.

ii) Indication in Respiratory Disorders

Asthma is now being considered to be an inflammatory disorder and NSAIDs like. sodium cromoglycate, ketotifen are considered important for prophylactic purposes[94, 95]. Ipratropium **(38)** is an inhalational anticholinergic drug used in chronic obstructive pulm-



(38)

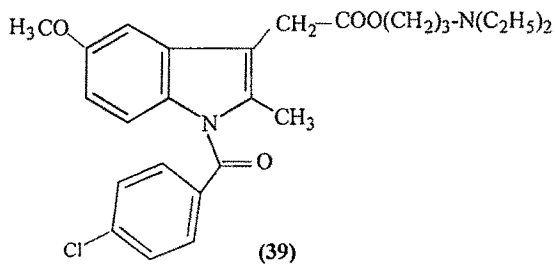
onary disease like asthma, alongwith various β_2-agonists. Our synthesized aminoesters could be of use in such respiratory disorders due to their dual action.

Above all, the expected good aqueous solubility of the hydrochloride salt of these esters could be exploited in formulating parenteral and ophthalmic dosage forms of these NSAIDs.

It was thought of interest to carry out the derivatization of some clinically used NSAIDs to different N,N-disubstitutedaminoethyl esters, to evaluate their stability in buffers of pH 2.0 and pH 7.4 (to stimulate gastric and intestinal pH) and their enzymatic susceptibility in 80% human plasma for releasing the parent drug. It was also planned to perform the pharmacological evaluation for determining the anti-inflammatory, analgesic and the anticholinergic activities and the ulcerogenic potential of the synthesized derivatives.

It would be appropriate here to mention that during the course of this work survey of literature indicated existence of reports wherein many aminoalcohol esters of acidic NSAIDs have been synthesized and evaluated for decreasing the GI toxicity (the 'Topical effect') or for improving the physicochemical properties. Various such reports are described below.

A novel indomethacin ester, 3-(N,N-diethylamino)propyl indomethacin prodrug **(39)** was synthesized[96] and studied for its anti-inflammatory and analgesic effects. The prodrug

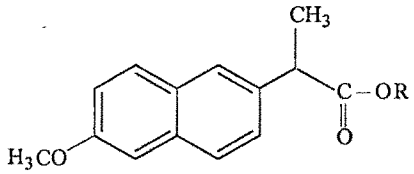


(39)

was found to be potent anti-inflammatory agent with lower ulcerogenicity in the stomach.

Morpholinyl and piperazinyl esters **(40a-e)** of naproxen were synthesized and evaluated[97] *in vitro* for their properties as bioreversible topically administered dermal prodrugs of naproxen. A four to nine fold enhancement of permeation was observed for

40b and **40d** when compared to naproxen itself at pH 7.4 and a 4 fold better permeation



(40 a-e)

(a) $(CH_2)_2-N$ NH **(b)** $(CH_2)_2-N$ NCH_3

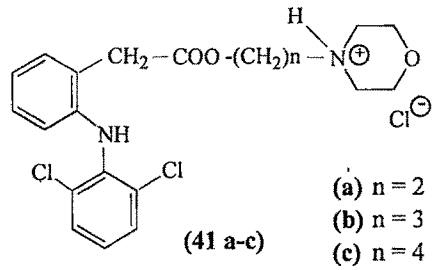
(c) $(CH_2)_4-N$ O **(d)** $(CH_2)_4-N$ NCH_3

(e) $(CH_2)_6-N$ NCH_3

was observed for **40b** at pH 5.0. These esters proved to be promising prodrugs for topical drug delivery of naproxen.

Morpholinoalkyl esters of naproxen and indomethacin were synthesized and evaluated[98] *in vitro* and *in vivo* for their potential use as prodrugs for oral delivery. The prodrugs were found to be 30-36% more bioavailable orally than the parent drugs and were significantly less irritating to gastric mucosa than the parent drugs following single-dose and chronic oral administration in rats.

A series of morpholinoalkyl ester prodrugs **(41a-c)** of diclofenac were synthesized by Tamara *et al* [99] and evaluated *in vitro* and *in vivo* for their potential use as prodrugs for



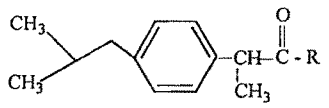
(41 a-c)

(a) n = 2
(b) n = 3
(c) n = 4

oral delivery. All the esters were reported to exhibit a rapid bioconversion to the parent compound in rat plasma and were significantly less irritating to the gastric mucosa than the parent drug.

Many ester **(42a-d)**, **(43a-d)** and amide **(42e-h)**, **43e** prodrugs of ibuprofen and naproxen were synthesized and evaluated by Shanbhag *et al*[100] for anti-inflammatory activity and

gastrointestinal toxicity. The ulcerogenic activitiy of the prodrugs **42a**, **43a**, **42h**, and **43d** was less than the respective parent drugs. All the prodrugs were found to be less



(42 a-h)

R

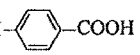
(a) $O(CH_2)_2 N(CH_3)_2$ HCl

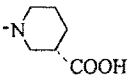
(b) $O(CH_2)_2 N(C_2H_5)$ HCl

(c) $O(CH_2)_2$N-morpholine HCl

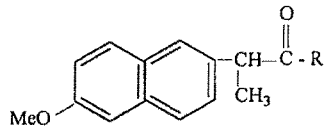
(d) $O(CH_2)_2$ N-piperidine HCl

(e) $-NH(CH_2)_3N(C_2H_5)_2$

(f) 

(g) 

(h) $-NHCH_2COOH$



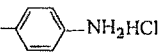
(43 a-e)

R

(a) $O(CH_2)_2 N(CH_3)_2$ HCl

(b) $O(CH_2)_3N(CH_3)_2$ HCl

(c) $O(CH(CH_3)CH_2N(CH_3)_2HCl$

(d) 

(e) $-NH-CH_2COOH$

active than the parent compounds in their anti-inflammatory efficacy.

It is amply clear that the above mentioned esters were synthesized with the sole aim of preventing the local effect of NSAIDs by blocking the acidic carboxyl group and to convert the parent compounds into water soluble derivatives.

The following given NSAIDs were chosen for the current study:

1. Biphenylacetic acid (an active acid metabolite of fenbufen which is three times more active than the parent compound).
2. Flurbiprofen
3. Diclofenac
4. Indomethacin
5. Aspirin
6. Ketorolac

Further, we would like to emphasize here that it would be inappropriate to call our designed aminoester derivatives as prodrugs of their respective parent NSAIDs because unlike prodrugs, which by themselves have no pharmacological activity, our conceived compounds would be bioactive even in the intact form. These are expected to exhibit anticholinergic activity till they remain intact in their chemically modified form.