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Development and Characterization of Novel Amino acid Conjugates of Aceclofenac

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Abstract: The emphasis of present research work is to improve solubility behavior of NSAID by different water insoluble amino acid conjugation and to overcome general side effects of NSAID. Almost all the currently available NSAIDs share the undesirable properties and become cause for major adverse reactions. Present conjugate approach stands for modification to overcome pharmaceutical barrierslike solubility behavior. The prodrugs designed by classical approach increase lipophilicity of the drug, which decreases the water solubility thus decreasing the concentration gradient, which controls drug absorption. Toovercome the limitations of traditional prodrug approach, water soluble conjugates are designed by addingselected amino acid to the drug moiety that are thesubstrates for the enzyme located at the intestinal brushborder thus overcoming pharmaceutical problem withoutcompromising bioavailability.Amino acid conjugate of Aceclofenac was synthesized by conventional coupling method using N,N-dicyclohexylcarbodiimide and it was characterizedby melting point, TLC, UV, FT-IR, NMR and MASS spectroscopy.*Alanin-Aceclofenac conjugate* has maximum water solubility, while in methanol and chloroform solubility of remaining synthesized compounds shows greater result than parent compound. The partition coefficient of the synthesized compound in octanol/water system was found to be more than the parent drug. Present research work indicates that conjugates synthesized with amino acid possess more water solubility. From the pH rate profile it was found that all the synthesized compounds, are stable at low pH value (pH 1.2), while undergo hydrolysis as the pH is increased (pH 7.4). This indicates that the synthesized compounds will be hydrolyzed and subsequently absorbed through intestine. In future this approach can be applied to other NSAIDs having free carboxyl functional group as well as in vivo bioavailability study can be undertaken in animals and can be correlated in humans.

Keywords: Aceclofenac, Prodrug, conjugates and Synthesis.

Introduction:

Almost all the currently available agents which are non-selective COX-1 and COX-2 inhibitors, shares the undesirable properties of producing effect to gastric and intestinal mucosa, resulting in erosion, ulcers and gastric bleeding and represent the major adverse reactions to the use of NSAIDs. NSAIDs induce gastric damage by dual insult mechanism, they are acidic in nature damage the GI tract by changing the permeability of cell membrane allowing a back diffusion of hydrogen ions, causing cell damage; on the other hand the nonselective inhibition of prostaglandin biosyntheses in the GI tract prevents the prostaglandin from exerting their protective mechanism on gastric mucosa. Their therapeutic efficacy can be improved or eliminating the undesirable properties while retaining the desirable ones with the approach of drug design.[1-4] This can be achieved through biological, physical or chemical

means. The biological approach is to alter the route of administration. The physical approach is to modify the design of dosage form, such as controlled drug delivery system. The third and best approach is to enhance drug selectivity while minimizing its toxicity is the chemical approach. Prodrug approach is one of the chemical approaches for optimizing the drugs therapeutics.[4]

A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent compound. Chemical modification of a drug via the attachment of promoiety generates the prodrug. The properties of the prodrug enable it to cross the limiting barrier and it is designed ideally to be cleaved efficiently by enzymatic or non-enzymatic processes. This is followed by rapid elimination of the released promoiety.

The term is a chemically modified inert drug precursor, which upon biotransformation prior to eliciting a pharmacological response. These definition Includes metabolites if administered drugs that are true active drugs as well as latentiated drugs.[5]

Soft drugs are pharmacologically active but undergo controlled and predictable conversion *in vivo*, generating non-toxic metabolites after having its therapeutic effect. Double-prodrug approach a more advanced prodrug design is applied to overcome the stability problems the seldom occur in the formulations of carriers linked prodrug. This is also termed as pro-prodrug.

The major objectives behind prodrug design are improved formulation, improved chemical stability, improved patient acceptance, improved bioavailability, prolonged action, selectivity and reduced toxicity. Prodrug design, therefore aims to overcome numbers of barriers of the drug usefulness like- Taste and odor, Slow dissolution rate, Poor solubility, Irritation/pain (Pharmaceutical barrier) and Insufficient oral absorption, Short duration, Pre-systemic metabolism, Unfavorable distribution, Non specificity (Pharmacokinetic barriers), Toxicity or side effects (Pharmacodynamic barrier)[6-9]

Objectives:

From the light of literature, it was through worthwhile to synthesis the amide conjugates of aceclofenac, an aryl acetic acid derivative containing free carboxylic acid group to decrease the adverse effects and to increase solubility behavior and also characterized other physicochemical parameter of synthesis compounds.

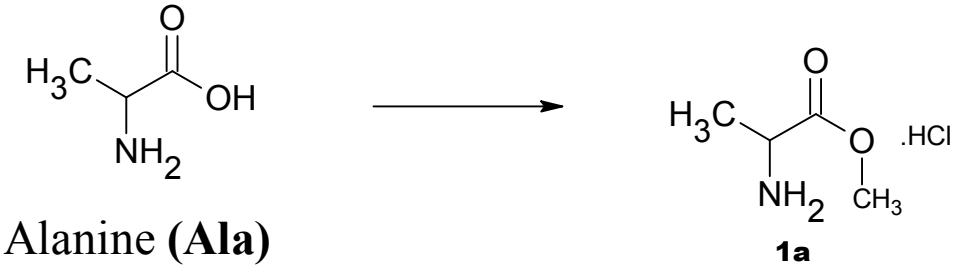
Materials and Experimental Techniques:

All the research chemicals and solvents were procured from commercial sources and purified by standard procedures described in the literature. Aceclofenac, was procured as gift sample from Suyash Laboratories Ltd, Tarapur India, All the chemicals and solvents used in studies were of GR grade, dried and purified before use. Melting points were obtained using DBK programmed melting point apparatus and are uncorrected. The purification of synthesized compounds was performed by recrytallization with appropriate solvent system. The purity of the compounds was checked using TLC technique, spots were developed by exposure to iodine vapors and UV cabinet, **UV absorbance** of the synthesized compound was carried out on UV 2401(PC) S 220V double beam UV spectrophotometer in methanol. **Infrared spectra** were recorded on FTIR spectrophotometer 8400S, Shimadzu corporation. **Mass spectra** were recorded in QP-2010 PLUS GC-MS system. **Nuclear Magnetic Resonance spectra** were recorded with AVANCE 300MHz, using $CDCl_3$ and D_2O. **Solubility and partition coefficient study:** by using three different systems, Concentration of the drug was determined by measuring the UV absorbance at the λ max of the individual conjugate.

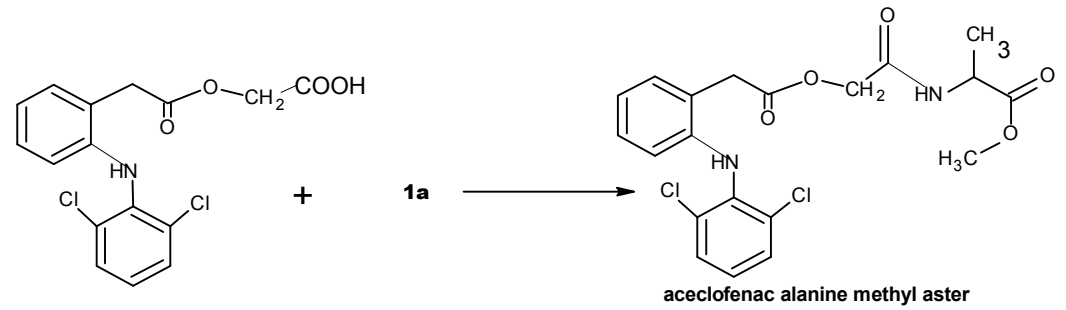
A) Scheme for Synthesis:

Scheme I:

ALANINE CONJUGATE:



Alanine **(Ala)** **1a**

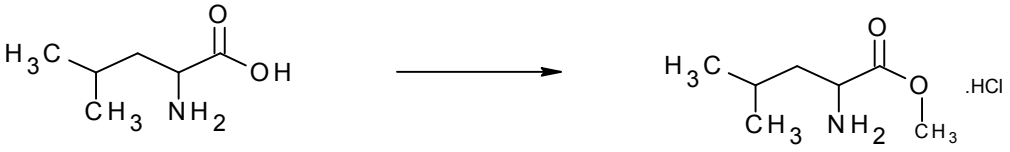


aceclofenac alanine methyl aster

1b

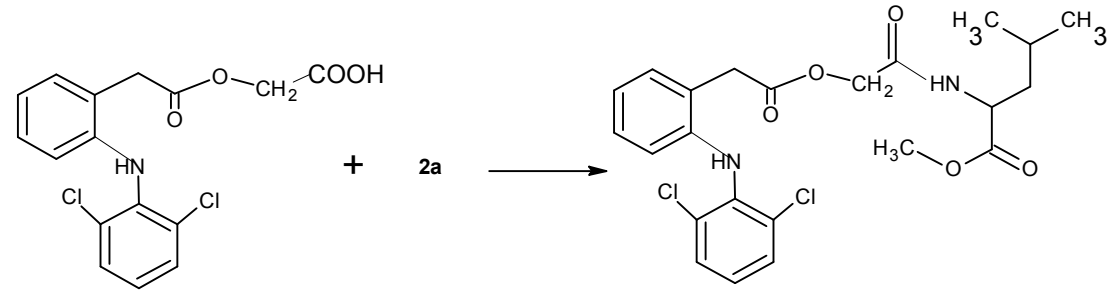
Scheme II :

LEUCINE CONJUGATE:



Leucine **(Leu)**

2a

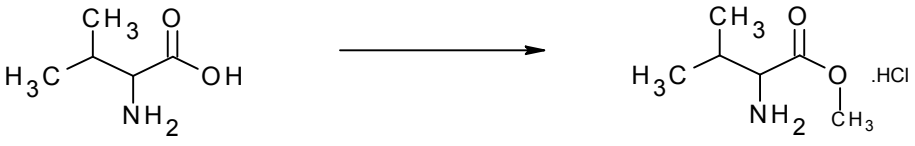


Aceclofenac leucine methyl aster

2b

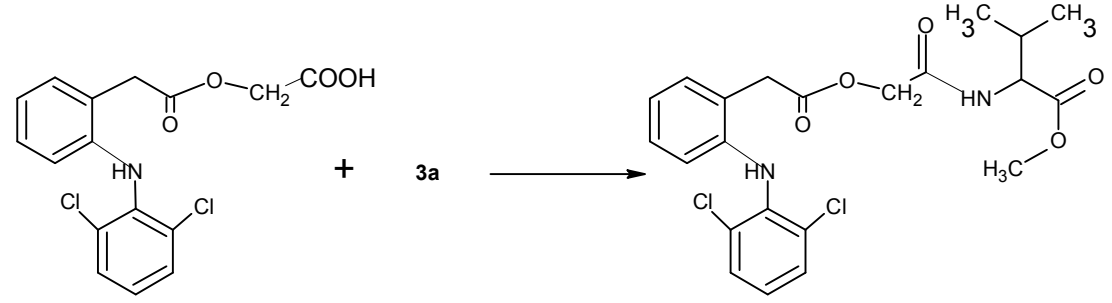
Scheme III :

VELINE CONJUGATE:



Valine **(Val)**

3a

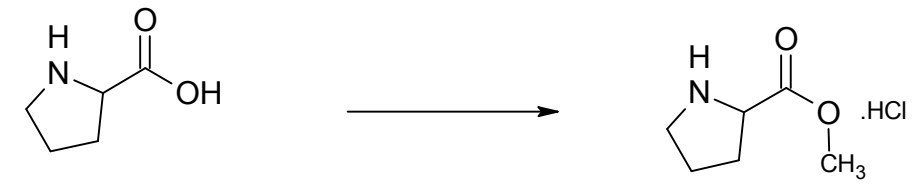


Aceclofenac valine methyl aster

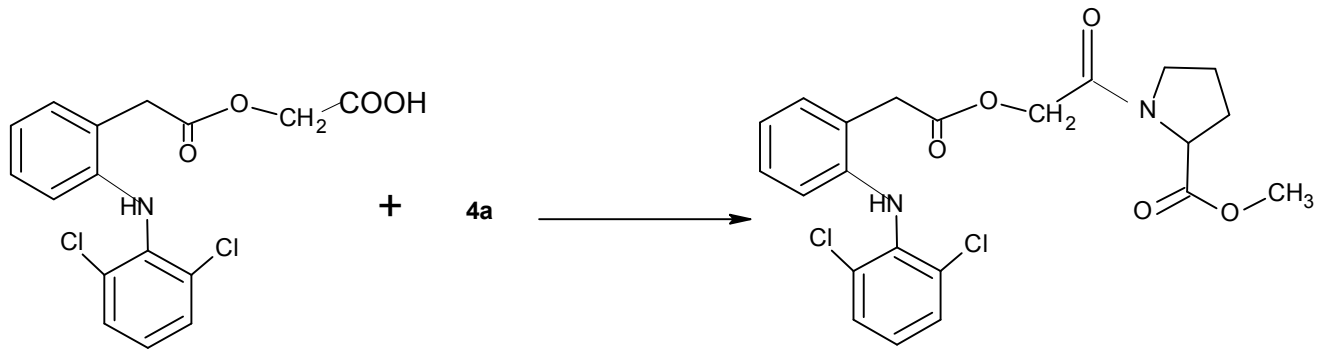
3b

Scheme IV :

PROLINE CONJUGATE:



Proline **(Pro)** **4a**



Aceclofenac proline methyl aster

4b

B) Procedure for Synthesis[10] (1b-4b):

Mixture of thionyl chloride and methanol with respective amino acids was refluxed for 6 hr. at 60-70 ^{0}C with continuous stirring. Crude product is obtained after removal of excess of thionyl chloride. It was triturate with 20 ml portion of cold ether at low temperature. The resulting solid product was dried under vacuum and was recrystallized from hot methanol. Crystals were collected on next day. These crystals further dissolved in methanol and triethylamine was added slowly and stirred for 2 hr. at low temp. The reaction mixture was then filtered and methanol distilled off to get sticky ester. The ester was then dried. Mixture of N, N', dicyclohexyl carbodiimide, Aceclofenac and N hydroxyl succiniimide in dry dichloromethane was prepared. Subsequently, ester adds to dichloromethane and was mixed with it. The reaction mixture stirred for 36 hr. The organic layer was dried with anhydrous sodium sulphate to give Aceclofenac Amino Acid methyl esters.

Thin layer chromatography was performed on silica gel G glass plates using suitable solvents systems to ascertain the purity of these compounds. The percentage yield, melting point and analytical data of the synthesized compounds are listed in Table 2.

Table 1: Mobile phase used for determination of $R_f$value of synthesized compounds.

Compound No.	Mobile phase
I	Chloroform : ethanol : acetic acid (90 : 10 : 1)
1b	Benzene : ethyl acetate (70 : 30)
2b	Benzene : ethyl acetate (70 : 30)
3b	Chloroform : ethanol (90 : 10)
4b	Benzene : ethyl acetate (70 : 30)

Table 2: Synthesized conjugates with physical constants

Compound	M.P. (^{0}C)	Yield (%)	R_f Value	Mol. Wt	Elemental analysis (%) (C, H, N)
1b	480-482	62	0.68	439.29	54.68, 4.59, 16.14, 6.38, 18.21
2b	504-506	60	0.60	481.37	57.39, 5.44, 14.73, 5.82, 16.62
3b	516-518	58	0.55	467.34	56.54, 5.18, 15.17, 5.99, 17.12
4b	448-450	54	0.74	465.33	56.78, 4.77, 15.24, 6.02, 17.19

Solubility studies

Aqueous solubility: The aqueous solubility of synthesized compounds were determined by stirring 200 mg accurately weighed compounds in water (10 ml) with a magnetic stirrer for 4 hrs. in a sealed flask. The solvent was filtered through Whatman filter paper No.42 and the portion of the filtrate was suitably diluted with water. The concentration of the compounds was determined by measuring the UV absorbance at λ max in water. The solubility was calculated mg/ml. Results of aqueous solubility of synthesized compounds are given in Table 3.

Solubility in methanol, ethanol and chloroform

The solubilities of the synthesized compounds were determined by stirring 500 mg accurately weighed synthesized compounds in methanol, ethanol and chloroform, respectively (5 ml) with a magnetic stirrer for 4 hrs. in a sealed flask. The solvent was filtered through Whatman filter paper No. 42 and 1 ml filtrate was taken in the previously weighed china dish. The solvent was evaporated off and the weight of the residue determined. The solubility was calculated in mg/ml. The solubility in different solvents are given in Table 3.

Partition coefficient studies

The partition coefficients of the compound were determined in three systems, i.e. Octanol/water, Octanol/hydrochloric acid (pH 1.2) and Octanol /phosphate buffer (pH 7.4). Results of partition coefficient of synthesized compound are given in table 4.

Table 3: Solubility data of compounds in various solvents

Solvent	Water	Methanol	Ethanol	Chloroform
Compound	**Solubility (mg/ml)**			
1b	16.48	21.45	25.56	42.28
2b	11.32	24.98	26.05	41.92
3b	12.47	17.42	23.55	40.67
4b	15.43	26.62	27.42	49.04
Aceclofenac	1.02	10.47	13.93	33.48

Table 4: Partition coefficients data of the synthesized prodrug compounds

Compounds	Solvent system		
	Octanol-Water (1:1)	Octanol-Hydrochloric acid (pH 1.2)	Octanol-Phosphate Buffer (pH 7.4)
1b	3.25	0.003	4.73
2b	4.49	0.08	6.19
3b	4.14	0.06	5.66
4b	3.67	0.005	5.39
aceclofenac	3.65	8.52	4.74

***In Vitro* hydrolysis kinetic studies**

The kinetics of chemical hydrolysis of the synthesized compounds was studied at 37 ± 1^{0}C in aqueous buffer solutions of pH 1.2 and pH 7.4, the buffer were prepared by the procedure as per I.P., the total buffer concentration was generally 0.05 M and a constant ionic strength (μ) of 0.5 was maintained for each buffer by adding a calculated amount of potassium chloride. The reaction was monitored by UV for the increase in concentration of free drug with time and the order of reaction and half-life ($t_{1/2}$) were calculated.

Scanning of aceclofenac for λ max

Scanning was performed in ethyl acetate.

Procedure for scanning

The solution containing 50 μg/ml of aceclofenac was prepared in ethyl acetate and scanned over range of 200 nm to 400 nm against ethyl acetate as a blank using double beam UV spectrophotometer.

Hydrolysis in 0.05 M hydrochloric acid buffer (pH 1.2)

10 mg of the synthesized compounds (**1b-4b**) were introduced separately in 900 ml of HCl buffer (pH 1.2) taken in the basket and was kept in a constant temperature bath at 37 ±1 ^{0}C. The solution was occasionally stirred and 5 ml aliquot portion was withdrawn at various time intervals and was transferred to separating funnel containing ethyl acetate. Free Aceclofenac, which was released after hydrolysis, was extracted with 5 ml portions of ethyl acetate. The ethyl acetate layer was estimated on UV spectrophotometer at 274 nm for free Aceclofenac release.

Hydrolysis in 0.05 M phosphate buffer (pH 7.4)

10 mg of the synthesized compounds (**1b-4b**) were introduced separately in 900 ml of phosphate buffer (pH 7.4) taken in the basket and was kept in a constant temperature bath at 37 ±1 ^{0}C. The solution was occasionally stirred and 5ml aliquot portion were withdrawn at various time interval and were transferred to separating funnel containing ethyl acetate. Free Aceclofenac, which was released after hydrolysis, was extracted with 5ml portions of ethyl acetate. The ethyl acetate layer was estimated on UV spectrophotometer at 274 nm for free Aceclofenac release. The hydrolysis data of synthesized compounds are given in Table 5-8 and figure 1-2.

Table 5: Hydrolysis data of compound 1b

Time (h)	pH 7.4		pH 1.2	
	a	a-x	a	a-x
0	0	100	0	100
0.5	42.37	57.62	11.18	88.81
1	53	46.99	16.14	83.85
2	62.21	37.78	35.99	64
3	66.46	33.53	45.91	54.08
4	85.59	14.4	52.29	47.7
5	92.68	7.31	64.23	35.66
6	95.51	4.48	70	29.99

Table 6: Hydrolysis data of compound 2b

Time (h)	pH 7.4		pH 1.2	
	A	a-x	a	a-x
0	0	100	0	100
0.5	31.74	68.25	9.77	90.22
1	43.07	56.92	14.02	85.97
2	59.37	40.62	24.65	75.34
3	81.34	18.65	28.9	71.09
4	85.59	14.4	36.7	63.29
5	88.43	11.56	52.29	47.7
6	92.68	7.31	77.8	22.19

Table 7: Hydrolysis data of compound 3b

Time (h)	pH 7.4		pH 1.2	
	A	a-x	a	a-x
0	0	100	0	100
0.5	35.28	64.71	10.19	89.8
1	50.87	49.12	17.21	82.78
2	67.88	32.11	25.71	74.28
3	77.09	22.9	35.4	64.85
4	81.34	18.65	46.33	53.66
5	91.26	8.73	55.4	44.59
6	94.81	5.18	70.09	22.9

Table 8: Hydrolysis data of compound 4b

Time (h)	pH 7.4		pH 1.2	
	A	a-x	a	a-x
0	0	100	0	100
0.5	28.19	71.8	10.55	89.44
1	45.2	54.79	12.81	87.18
2	60.79	39.2	17.21	82.78
3	73.55	26.44	22.98	77.01
4	81.34	18.65	33.03	68.96

Where,
a = Concentration of drug at t = 0
a-x = Concentration of drug yet to undergo reaction at time t.

Figure 1: Kinetic data of compounds 1b-4b in pH 7.4

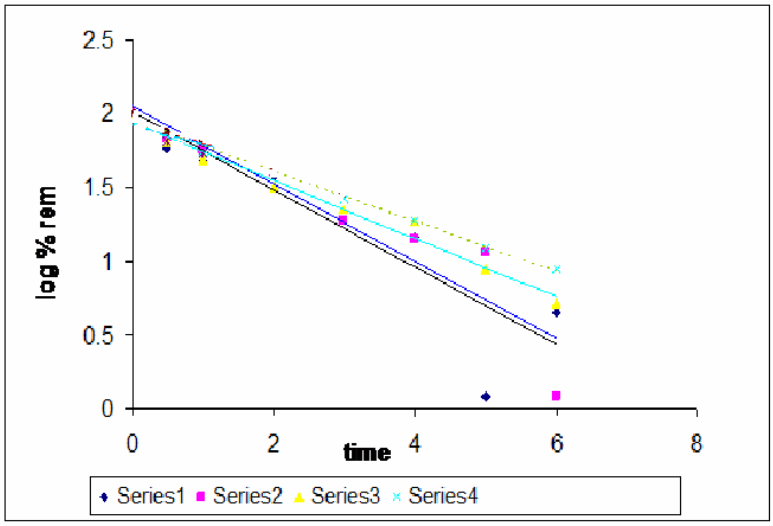
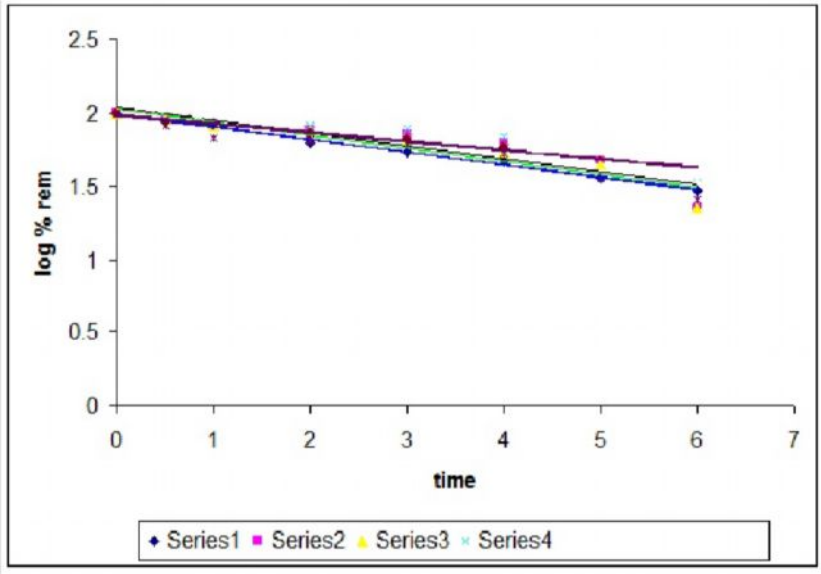


Figure 2: Kinetic data of compounds 1b-4b in pH 1.2



The hydrolysis data obtained followed first order kinetics by using following equation:

$$\textbf{Log C = Log } C_0 \textbf{- Kt / 2.303}$$

Where:

C- Concentration of drug yet to undergo reaction at time t.

C_0 - Concentration of drug at t = 0

A semi logarithmic plot of equation (I) yields a straight line with slope = - K / 2.303

and y-intercept = Log C_0

First order half life:

$$t_{1/2} = 0.693 / K$$

Result:

SPECTRAL DATA

A. Methyl 2-(2-(2-(2-((2,6-dichlorophenyl)amino) phenyl)acetoxy)acetamido)propanoate(1b) (Aceclofenac alanine conjugate)

λmax :284

I.R. (KBr, cm^{-1}):3320 (-NHstr), 1734 (ester carbonyl group), 1620 (amide carbonyl bend), 1446, 1421 (asymmetric bend, $-CH_3$)1394 (symmetrical bend $-CH_3$),

NMR (CDCl3) :δ 8.55, 7.37, 7.22, 7.10, 7.10, 7.08, 6.91, 6.73, 5.33, 4.96, 4.96, 4.56, 3.81, 3.81, 3.81, 3.47, 3.47, 1.51, 1.51, 1.51.

MS (m/z):438.07 (100.0%), 440.07 (63.9%), 439.08 (22.1%), 441.08 (14.5%), 442.07 (10.3%), 440.08 (3.5%), 443.07 (2.3%), 442.08 (2.1%)

B. methyl 2-(2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetoxy)acetamido)-4-methyl pentanoate (2b) (Aceclofenac leucine conjugate)

λ max : 286

I.R. (KBr, cm-1):. 3320 (-NHstr), 1734 (ester carbonyl group), 1620 (amide carbonyl bend), 1446, 1421 (asymmetric bend, $-CH_3$)1394 (symmetrical bend $-CH_3$),

NMR (CDCl3) : δ 7.99, 7.36, 7.22, 7.09, 7.09, 7.08, 6.91, 6.75, 4.85, 4.85, 4.85, 4.63, 3.82, 3.82, 3.82,

3.41, 3.41, 1.73, 1.72, 1.66, 0.99, 0.99, 0.99, 0.99, 0.99, 0.99.
MS (m/z):480.12 (100.0%), 482.12 (64.1%), 481.13 (25.4%), 483.12 (16.5%), 484.12 (11.0%), 482.13 (4.1%), 485.12 (2.6%), 484.13 (2.0%)

C. methyl 2-(2-(2-(2-((2,6-dichlorophenyl)amino) phenyl)acetoxy)acetamido)-3-methyl butanoate (3b) (Aceclofenac velline conjugate)

λ max : 290

I.R. (KBr, cm-1): 3405 (-NH str), 1730 (ester carbonyl group), 1685 (amide carbonyl) 1446, 1421 (asymmetric bend, -CH_3), 1394 (symmetrical bend –CH_3),
NMR (CDCl3) : δ 7.34, 7.21, 7.13, 7.13, 6.99, 6.89, 6.82, 6.13, 4.91, 4.91, 4.61, 4.45, 3.67, 3.67, 3.67, 3.57, 3.57, 2.31, 1.06, 1.06, 1.06, 1.06, 1.06, 1.06.
MS (m/z):466.11 (100.0%), 468.10 (63.9%), 467.11 (24.3%), 469.11 (15.8%), 470.10 (10.3%), 468.11 (4.0%), 471.10 (2.5%), 470.11 (2.5%)

D. methyl 1-(2-(2-(2-((2,6-dichlorophenyl)amino) phenyl)acetoxy)acetyl)pyrrolidine-2-carboxylate (4b) (Aceclofenac proline conjugate)

λ max : 294
I.R. (KBr, cm-1):3320 (-NHstr), 1734 (ester carbonyl group), 1620 (amide carbonyl bend), 1446, 1421 (asymmetric bend, -CH_3)1394 (symmetrical bend –CH_3),
NMR (CDCl3) : δ 7.54, 7.34, 7.24, 7.15, 7.06, 7.06, 6.92, 6.72, 5.03, 5.03, 4.29, 3.86, 3.75, 3.75, 3.75, 3.57, 3.35, 3.35, 2.44, 2.20, 2.11, 2.02.
MS (m/z):464.09 (100.0%), 466.09 (65.1%), 465.09 (24.7%), 467.09 (15.5%), 468.08 (10.2%), 466.10 (2.8%), 468.09 (2.5%), 469.09 (2.5%).

Discussion

The term conjugation is used to describe compounds, which undergo biotransformation, before exerting their pharmacological action. This type of derivatization not only is helpful for improving the pharmacokinetic profile of the parent compound, but also may give a synergistic effect. In the present study conjugates in the form of esters and amide were synthesized by linking alanine, leucine, valline, and proline with Aceclofenac as per the procedures described in schemes. The parent drug Aceclofenac is practically insoluble in water, and literature revealed that the conjugates improve the water solubility. The compound 1b has maximum water solubility i.e. 16.48 mg/ml. While in methanol and chloroform solubility of synthesized compound is greater than parent compound. A drug's partition coefficient is a measure of its distribution in a lipophilic/hydrophilic phase system, and is indicative of its ability to penetrate biological multiphase system. The values of partition coefficient range from 3.25 to 4.49 in Octanol/water system. The value of partition coefficient range from 0.003 to 0.08 in Octanol/hydrochloric acid (pH 1.2) system and the value of partition coefficient range from 4.73 to 6.19 in Octanol /phosphate buffer (pH 7.4).IR and NMR spectra confirmed the structure of the compounds. IR spectra exhibited characteristic absorption bands of N-H stretching, C=O stretching and C-H stretching functional groups vibrations., All conjugates showed IR absorption frequency for N-H stretching in between 3405 to 3220.40 cm-1, C-H stretching in between 2998.05 to 2918.05 cm-1 and C=O stretching in between 1770.53 to 1730.96 and 1685 to 1620 for amide carbonyl, 1446 to 1394 for asymmetric bend of -CH_3.

The hydrolysis studies conducted at selected pH values (1.2 and 7.4) at 37±1 ^{0}C provide useful information relation to the likely stability of the compounds in the gastrointestinal tract. Graphs were plotted with time in hours on X-axis and log of amount remaining (a-x) on Y- axis. From the pH rate profile it was found that all the synthesized compounds, are stable at low pH value (pH 1.2), while undergo hydrolysis as the pH is increased (pH 7.4). This indicates that the synthesized compounds will be hydrolyzed and subsequently absorbed through intestine. At pH 1.2 the t ½ of the compounds were in between 7.86 to 3.31 h., while at pH 7.4 the t ½ were in between 1.77 to 1.35 h, the *in vitro* hydrolysis data are shown in Table 5-8 and half life of the synthesized compounds are given in Table-9 for pH 1.2 and pH 7.4.

Table 9: Showing K value and calculated half life of synthesized compounds.

Compound.	pH 1.2		pH 7.4	
	K value	**$t_{1/2}$ (h)**	**K value**	**$t_{1/2}$ (h)**
IV a	0.1412	4.90	0.5131	1.35
IV b	0.2091	3.31	0.4223	1.63
IV c	0.1419	4.88	0.3912	1.77
IV d	0.0881	7.86	0.4846	1.43

Conclusion

The conjugates of Aceclofenac were synthesized using simple synthetic route in good yields and their structure were confirmed by spectral analysis, the solubility of the compounds were found to be more in organic phase as compared to aqueous phase this indicates the lipoidal nature of the synthesized compounds. All conjugates have more water solubility then parent compound, the compound 1b have highest solubility in water. The partition coefficients of the synthesized compounds found more in Octanol/ phosphate buffer (pH 7.4) as compared to Octanol / water and Octanol /Hydrochloric acid buffer (pH 1.2). The partition coefficient of 2b, 3b and 4b were found to be remarkably high in two of the three systems as compared as to other conjugates. The partition coefficient of the synthesized compounds 2b, 3b, and 4b in Octanol /water system was found to be more than the parent drug. From the partition coefficient study, results indicate that the synthesized compounds are liable to absorb from small intestine rather than from stomach as in parent compound. Hydrolysis kinetics of synthesized conjugate showed that they were chemically stable in buffer with lower value (pH 1.2), while the compounds showed significant hydrolysis at pH 7.4. The half-life ranges in between 3.31 h to 7.86 h for pH 1.2 while 1.35 h to 1.77 h in pH 7.4. The compounds were found to stable at acidic pH as there was little hydrolysis of the synthesized compounds into parent compound, and hence may not produce gastric irritation of gastrointestinal tract. The synthesized molecules may have the potential as conjugate of aceclofenac.

Future Scope

- The synthesized compounds can be subjected to in-vivo analgesic, anti-inflammatory and anti-ulcerogenic activity study.
- *In vivo* bioavailability study can be undertaken in animals and can be correlated in humans.
- Stability studies of the compounds as per ICH guideline can perform.
- This approach can be applied to other NSAIDs having free carboxyl functional group.

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