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Research Article

Kinetic Study of Some Naproxen Derivatives

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Abstract

It was known that Salicylic acid is an analgesic compound but the presence of OH of the carboxyl group cause corrosion to the blood vessels so it was converted into ester to overcome this phenomena and becomes a pro drug. it was also known that procaine is a good anesthetic but because of its ester moiety which is easily hydrolyzed making this compound inefficient for this purposes compared to Lidocaine because Lidocaine is an amide compound which takes more time to be hydrolyzed (more stable), so it is used as analgesic instead of Procaine in locally anesthetic applications. In this study we have synthesized some esters and amide of Naproxen (Naproxen Pro drug) these compounds include P-hydroxy phenyl, Methyl, Butyl and p- amino benzoate of Naproxen which are pro drug 1, pro drug 2, 3 and pro drug 4 respectively. The results of their kinetic hydrolysis studies are discussed therein.

Keywords: Kinetic; Study; Naproxen; Derivatives

Introduction

Literature survey

Naproxen [2-(6-Methoxynaphthyl) Propionic acid] belongs to (Non-Steroidal Anti-inflammatory Drugs) [1] this compound thought to inhabit (Cyclooxygenase) [2] which is responsible for the production of (Prostaglandins) these compounds were excreted by the body when it was infected which cause the pain and heat so Naproxen is used for heat depression such as headache and teeth ache and also it was used for treatment of muscle infection and arthritis and also in treatment of other infections Rheumatoid Arthritis, Osteoarthritis [3,4], Tendinitis and so other infections. Naproxen is one of the drugs which cause problems to the digestive system such as stomach infections and also sometimes used in high level doses for treatment of Gastric ulcer.

The prodrug is a biologically neutral primary drug to protect the action of terminal (Carboxylic Moiety) in Naproxen [6,7] in order to reduce the side effects cause by this group as mentioned above. The following scheme showed the action of Cyclooxygenase using (Non Steroidal anti- inflammatory Drug.

In 1981 Richard M. and his coworkers have prepared a compound similar to Naproxen from its contents having (S character) [8]. In 1987 Noyori and his team have prepared Naproxen by hydrogenation of (2-methyl naphthyl alkenyl propenoic acid) using ((Ruthenium) as a catalyst [9]. In 1989 Oreste Piccolo and et-al have prepared Naproxen from (6- Methoxy Naphthalene) and (Propronic acid chloride) using Lewis as a catalyst. The final compound (ketone) of the above reaction was reacted via Friedel-Crafts giving the Naproxen isomer (S) [10].

It is worth noting here that Claudio and his coworkers in 1989 have prepared Naproxen through the protection of the Ethynyl ketone by dicarbonyl diol getting Naproxen with (S) configuration

[11]. in 1990 Monsanto company has produced Naproxen from Hydroxy Naproxen with 9% yield using acidic catalyst for production of the above acid which has (S) configuration by Asymmetric Hydrogenation of the ene acid [12]. In 1993 Giordano and his coworkers have developed the stated patent above for the production of Naproxen having (S) configuration which is the same work as previously mentioned by Claudio [13]. In 2017 Ammar Y. A et-al have prepared Naproxen by reacting 1-(6-Methoxy 2-Naphyl) ethanol with acetyl chloride getting the corresponding ketone then esterification using $H_2So_4$and then Sodium Hydride while the third step is the Hydrolysis with NaOH forming DL Naproxen. The (S) Naproxen was isolated from this isomeric mixture using (Cinchonidine). In the same year some scientists have prepared the isomer (S) type Naproxen by bromination of (6-Hydroxy Naphthalene) then the product was treated with $NaHSO_3$ then methylation of phenol with methyl chloride. The reaction of the final compound with Grignard reagent afford DL mixture of isomers. The isolation of (S) isomer using)N-alkylglucamine) [14].

Among the main reactions of Naproxen found in literature are the following reactions: Esters of Naproxen, when Peter PÖchlauer and his team in 1998 have prepared (N- succinimidyl Naproxen) using chlorophosphate catalyst [15].

In 2001 Barkin Berk and his coworkers have prepared (triazolo Naproxen) and studied their Anti-inflammatory activity using DCC coupling agent [16]. In 2010 Zbigniew Ochal have prepared Aryl ethyl ester of aromatic compounds using TOSCl in Tri ethyl amine for the reaction of the corresponding tosylate with some substituted phenols using microwave [17]. In the same year some researchers have prepared Naproxyl hydrazones from the reaction of the corresponding Naproxyl esters with hydrazine then the products were converted ito hydrazones using PEG - 400 instead of using microwave [18]. In 2012 Jimenez-Estrada Manuel and his coworkers have prepared some fused ring phenolic esters of Naproxen [19]. In 2013 Bassem Sadek., *et al*. have prepared some Naproxen amides and Naproxenoyl triazoles using amino acid ester such as proline methyl ester [20]. In 2017 Monther F. Mahdi and his colleagues were succeeded to prepare some Naproxen triazole from the corresponding Naproxen hydrazides using alcoholic $CS_{2.}$ these compounds have showed anti-inflammatory activities *in vivo* using mice for this study and it was revealed that these hydrazones are more active than Naproxen [21]. In 2019 Ahmed A. and his colleagues have prepared Naproxen Isocyanates of Naproxen and were allowed to react with amino acids forming the corresponding amides. these amides were proved their anti-inflammatory actions [22].

The kinetic studies of naproxen: During the last years [23], it was found that the pro drug resulting from the conversion of the original drug into esters or amide becomes inert toward the human body and during the physiological body actions these pro drugs released their derivatives of either amine or alcohol forming the original drug. these derivatives usually used to reduce the side effects of the original drug or increasing its solubility and improving the drug uptake and taste [24,25].

The study of Lateefa Alkhateeb and her team on the adsorption of non-steroidal drugs (Nanoghraphene, Ibuprofen, Ketoprofen, Naproxen, Dichlorofenal)on graphine revealed that these pro drugs adsorbed within minutes on graphine at r.t and increase in increasing the temperature [26]. It was found that Naproxene pro drug when taken orally and passed through the digestive system caused to hydrolyzed into Naproxene drug due the gastric fluids [27]. In 2018 Noor Hatef Naser has studied the kinetic of (Gatifloxacin NSAIDs as Mutual Prodrugs), her study was revealed that these pro drugs having stability in pH 1.2, pH 7.4 without having water hydrolysis characters for stomach and gastric fluids while the hydrolysis yield of 80% in blood plasma hydrolysis by the impact of Esterase enzyme [28]. In 2020 Nuha Wazzan [29] has studied the adsorption of NSAID, the study revealed that the adsorption was following the increasing of the activation energy and finally the adsorption system resulted from Nanographene (Ng) with the pro drugs according to the following order: NAP-NG DIC-NG < IBU-NG < KETO-NG < NAP-NG < IBU-NG < KETO-NG < DIC-NG.

Due to limited kinetic studies of the pro drugs, we are here to present our kinetic study of some prepared esters and amide of Naproxen derivatives hope to find their advantages for other researchers and useful for drug companies development.

Experimental

All melting points were uncorrected using Stuart SMP300 type melting point apparatus. IR spectra were recorded using Shimadzu type. Uv spectra measurements were performed using Shimadzu UV 1800 spectrophotometer. Naproxen compound was supplied by Sammara Company for drug industry-Sammara –Iraq as pure and

used as it is without further purifications. The pH = 1.0 was prepared from (HCl 0.1M) and other acidic derivatives were prepared using phosphate buffered solution [30] the other pH were prepared using buffer phosphate solution [31]. Naproxenoyl chloride was prepared following an elsewhere procedure [20]. Naproxen Methyl and Ethyl esters were prepared using the same published procedure [32]. Paracetamol was prepared using the published procedure [33]. N-succinimidal Naproxene was prepared according to the well-known procedure [16].

Synthesis of 2-(6-Methoxynaphthyl) Propionoyl P-hydroxyBenzamide.

Pro drug 1

P-amino phenol (0.001mol., 1.1g) was dissolved in 25 ml of THF and (0.001 mol., 2.6g) of Naproxenoyl chloride was then added with (0.001 mol, 0.1g.) of triethyl amine The reaction mixture was stirred at r.t for one hour. The reaction mixture as then filtered of. Addition of 40 mil. Of chloroform and 10 mil of saturated solution of NaCl. The organic layer was then separated, dried on anhydrous sodium sulfate. Evaporation of the solvent gave the amide. Recrystallization from minimum amount of chloroform gave pure compound with 70 % yield and melting point of 138 - 140^{0}C.

Synthesis of methyl and n-Butyl esters of Naproxene pro drug 2 and 3:

- The same published procedure was used for the synthesis of these compounds [30].
- Synthesis of 2-(6-Methoxynaphthyl) Propionic p-Amino Benzoate [31].

Pro drug 4

N-succinimidyl Naproxen (4.6 gram) was dissolved in (40 ml) chloroform then Paracetamol (2.1 gram) was then added. the mixture was stirred for 24 hour after that (50 ml) of distilled water was added. The organic layer was separated and dried on $MgSO_4$ anhydrous filtered off and the filtrate was evaporated under reduced pressure using rotary evaporator till dryness. the solid residue was recrystallized from a mixture of chloroform ether 1:1 yield % melting point (158 - 160^{0}C).

Hydrolysis kinetics

The hydrolysis of the prepared pro drugs (1 - 4) was achieved using pH of (1.2, 5.8, 6.4, 7.4) which are the pH of stomach, large and small intestine of human body using UV spectrophotometer at λ_{max} of 231 nm. it was prepared pH =1 from 0.1 M HCl [30,31].

The hydrolysis was performed for the above pHs after completion of the solution to (100 ml) using volumetric flask at temperature of (37 ± 0.1^{0}C). Stock solution of 10^{-3} from pro drugs (1-4) in Aceto nitrile against (0.6 ml) of the pro drugs with (2.4 ml) of the buffer solution at pH under study. The absorbents (A_0) was measured before applying the water bath at (initial Time =0) then the absorbents A_t at time interval of (30 min) was then measured at temperature of (37^{0}C) in a total time of (150 min) for each sample. The blank buffer solution which contains (0.6 ml) of Aceto nitrile with (2.4 ml) of buffer solution against the buffer hydrolysis solution. the absorbents was measured at λ_{max} of Naproxene (231 nm).

Table 2 represents the studied compound (Pro drugs 1-4) along with their chemical structures and their molecular weights:

- X ml of 0.2M of Na_2HPO_4.
- 50-X ml of 0.2M NaH_2PO_4.

Results and Discussion

Pro drug 1 was prepared from Naproxen acyl chloride and para amino phenol according the procedure mentioned in the experimental part above. The IR spectrum showed that the absorption band belongs to the carboxylic acid group which is broad band is replaced by a hydroxyl one absorbed at 3508 cm^{-1} along with the appearance of amide group absorbed at 1737.81cm $^{-1}$.The original Naproxene carbonyl group before reaction was appeared at 1725.17. Pro drug 2 and 3 were prepared according to the published procedure [32].The IR spectra showed the following absorption bands:1735.81cm^{-1} for carbonyl methyl ester and 1726.17cm^{-1} for n-Butyl ester.

N- [2-(6-methoxy-2-naphthyl)-propanoyloxy]succinimide.

This compound was prepared according the well non procedure [16] with some modification as it was presented in the experimental part. The Ir absorption bands were as follows cm^{-1}: 1785 for C=O ester,1628 for amide,1269,1205for C-O ester.

pH	X	50-X
5.8	4.5	46
6.4	13.25	36.75
7.4	40.5	9.5

Table 1: The prepared phosphate buffered solution.

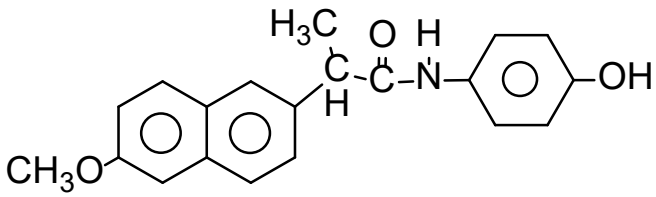
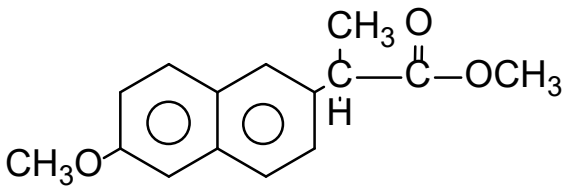
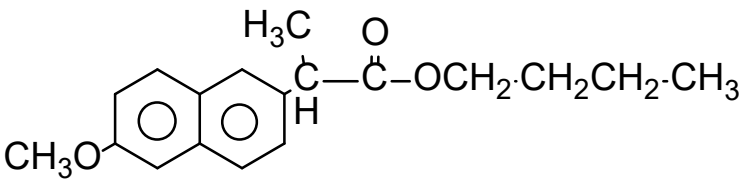
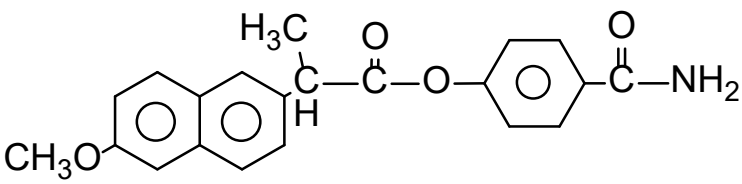
Prodrug No.	Compound	Chemical Structure	M.Wt
1	2-(6-Methoxynaphthyl) Propionic P-hydroxyBenza-mide		321
2	2-(6-Methoxynaphthyl) Propionic acid Methyl ester		244
3	2-(6-Methoxynaphthyl) Propionic acid Butyl ester		283
4	2-(6-Methoxynaphthyl) Propionic P-Amido Benzoate		349

Table 2: The studied pro drugs 1-4.

N-- [2- (6-methoxy-2-naphthyl)-propanoyloxy] -4-phenyloxy acet amide (Pro drug 4).

This compound showed the disappearance of the carboxyl absorption band and the presence of new band of ester at 1735.81cm^{-1}and the acet-amide carbonyl at 1650 cm^{-1}.

Kinetic studies

As it was shown below table 2 the absorption of pro drugs 1-4 at λ max= 231(nm) and pH of (37^{0}C).

The graphical results between (Log A^0/At vs. time) give a linear relationship and the statistical data as a result from the value of slope, intersection and the rate constant (R_2) which showed a linear relationship as shown in table 3.

Table 4 shows the value of the K_{obs} hydrolytic velocity constant. The apparent and half-life value (t1/2) calculated from the first order equation for the reaction:

$t_{1/2} = 0.693/K_{obs.}$

And it was shown from table 4 that the value of the reaction rate constant for the Pro drug 1 has the same value at pH 5.8 as well as at pH 6.4, while it became twice the value at pH 7.4.

The Pro drug 2 showed stability of K_{obs} values. at (pH1.0, pH5.8, pH6.4), while its value doubled at pH7.4.

For Pro drug 3, its stability increased with the increase of pH values, while the values of K_{obs} for Pro drug 4 is approximately remain stable at different pHs.

The relationship between LogK and pH for each compound (Pro drug 1-4) was plotted, as shown in table 5 and figure 5, and it was found that for Pro drug 1 compound, the hydrolysis decreases with increasing pH values from (1.0) to (7.4).

A_o	3.280		3.303	3.220		3.280	
λ_{max}	231		231	231		231	
	pH 1.0		pH 5.8	pH 6.4		pH 7.4	
Time(min.)	A_t	A_o/A_t	A_t	A_o/A_t	A_t	A_o/A_t	A_t	A_o/A_t
30	3.081	1.064	3.275	1.008	3.126	1.032	3.218	1.019
60	3.062	1.071	3.245	1.017	3.028	1.063	3.207	1.022
90	3.029	1.082	3.198	1.032	3.000	1.073	3.152	1.040
120	3.004	1.091	3.163	1.044	2.980	1.080	2.926	1.120
150	2.990	1.096	3.079	1.072	2.909	1.106	2.907	1.128

Prodrug 1

A_o	3.275		3.283	3.183		3.259	
λ_{max}	231		231	231		231	
	pH 1.0		pH 5.8	pH 6.4		pH 7.4	
Time(min.)	A_t	A_o/A_t	A_t	A_o/A_t	A_t	A_o/A_t	A_t	A_o/A_t
30	3.221	1.016	3.232	1.015	3.103	1.025	3.244	1.004
60	3.155	1.038	3.191	1.028	3.052	1.042	3.207	1.015
90	3.078	1.064	3.145	1.043	3.033	1.049	3.101	1.050
120	3.069	1.067	3.072	1.068	2.984	1.066	2.999	1.086
150	3.008	1.088	3.035	1.081	2.973	1.070	2.972	1.096

Prodrug 2

A_o	3.207		3.197		3.150		3.230	
λ_{max}	231		231		231		231	
	pH 1.0		pH 5.8		pH 6.4		pH 7.4	
Time(min.)	A_t	A_o/A_t	A_t	A_o/A_t	A_t	A_o/A_t	A_t	A_o/A_t
30	3.146	1.019	3.170	1.008	3.083	1.021	3.220	1.003
60	3.131	1.024	3.151	1.014	3.021	1.042	3.172	1.018
90	3.110	1.031	3.081	1.037	2.977	1.058	2.998	1.077
120	3.071	1.044	3.008	1.062	2.909	1.082	2.892	1.116
150	3.030	1.058	2.958	1.080	2.855	1.103	2.789	1.158

Prodrug 3

A_o	3.326		3.220		3.236		3.143	
λ_{max}	231		231		231		231	
	pH 1.0		pH 5.8		pH 6.4		pH 7.4	
Time(min.)	A_t	A_o/A_t	A_t	A_o/A_t	A_t	A_o/A_t	A_t	A_o/A_t
30	3.202	1.038	3.191	1.009	3.124	1.035	3.052	1.029
60	3.188	1.043	3.169	1.016	3.078	1.051	3.031	1.036
90	3.177	1.046	3.117	1.033	3.070	1.054	2.990	1.051
120	3.164	1.064	3.094	1.040	3.033	1.066	2.914	1.078
150	3.133	1.061	3.047	1.056	3.020	1.071	2.892	1.086

Prodrug 4

Figure 1: Rate of hydrolysis of pro dug 1 at different pH and at (37^0C).

Figure 2: Rate of hydrolysis of pro dug 2 at different pH and at (37^0C).

Figure 3: Rate of hydrolysis of pro dug 3 at different pH and at (37^0C).

Figure 4: Rate of hydrolysis of pro dug 4 at different pH and at (37^0C).

Prodrug No.	pH	Intercept	Slope	R^2
1	1.0	0.0237	1×10^{-4}	0.9833
	5.8	0.0046	2×10^{-4}	0.9603
	6.4	0.0087	2×10^{-4}	0.9323
	7.4	0.0111	4×10^{-4}	0.8653
2	1.0	0.0017	2×10^{-4}	0.9595
	5.8	0.0013	2×10^{-4}	0.9884
	6.4	0.0074	2×10^{-4}	0.9631
	7.4	0.0104	4×10^{-4}	0.9623
3	1.0	0.0028	1×10^{-4}	0.9578
	5.8	0.0069	3×10^{-4}	0.9731
	6.4	0.0009	3×10^{-4}	0.9862
	7.4	0.0188	5×10^{-4}	0.9795
4	1.0	0.0046	2×10^{-4}	0.8151
	5.8	0.0019	2×10^{-4}	0.9835
	6.4	0.0128	1×10^{-4}	0.9529
	7.4	0.0046	2×10^{-4}	0.9586

Table 3: The graphical results between (Log A^0/At vs. time and the statistical data results for compounds 1-4 at different pH values.

Prodrug No.	pH	$K_{obs.}$ (min^{-1}.)	$t_{1/2}$ (min.)
1	1.0	1×10^{-4}	6.930
	5.8	2×10^{-4}	3.465
	6.4	2×10^{-4}	3.465
	7.4	4×10^{-4}	1.732
2	1.0	2×10^{-4}	3.465
	5.8	2×10^{-4}	3.465
	6.4	2×10^{-4}	3.465
	7.4	4×10^{-4}	1.732
3	1.0	1×10^{-4}	6.930
	5.8	3×10^{-4}	2.310
	6.4	3×10^{-4}	2.310
	7.4	5×10^{-4}	1.386
4	1.0	2×10^{-4}	3.465
	5.8	2×10^{-4}	3.465
	6.4	1×10^{-4}	6.930
	7.4	2×10^{-4}	3.465

Table 4: The values of the reaction rate constant (hydrolysis) and the half-life of the prepared derivatives.

Log $K_{obs.}$	pH 1.0	pH 5.8	pH 6.4	pH7.4
1	-4	-3.6989	-3.6989	-3.3979
2	-3.6989	-3.6989	-3.6989	-3.3979
3	-4	-3.5228	-3.5228	-3.3010
4	-3.6989	-3.6989	-4	-3.6989

Table 5: The relationship between LogK and pH for each studied compound.

Figure 5: The relationship between Log K_{obs} against the pH of each derivative (Prodrug 1, 2, 3, 4).

Conclusions

In conclusion for the above study it was found that Pro drug 2 showed stability at (pH1.0) to (pH6.4), then the stability of this compound increased at (pH7.4), and for Pro drug 3 its stability was almost stable, while in case of Pro drug 4 it showed constant stability at each (pH1.0, 5.8, 7.4) compared to the other pro. drugs studied.

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