AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Synthesis of Mutual Pro-drugs through coupling of Etodolac And Tolmetin by Sulfa drugs

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ABSTRACT

[NSAIDs] "non-steroidal anti-inflammatory drugs" always enter in the management of chronic diseases associated with inflammation, but it have many unwanted side effects, one of them is stomach irritation and ulceration. The Co-drug approach is a strategy used to solve this problem. The mutual Pro-drug composed of two therapeutically active materials coupled to each other via covalent bond. Because of the infection always lead to inflammation. So [NSAID] could be coupled with sulfa drugs together as single drug via amide linkage. Here the carrier molecules "sulfonamides" could be helpful to counteract part of side effects of prime drug especially (GI) ulceration. By this work I wish to explain the procedure that I used in coupling of Etodolac and Tolmetin with different sulfa drugs to create amide containing products. Therefor the synthesized products could be useful in the management of infection and inflammations.

Key words: Mutual prodrug, Etodolac, Tolmetin [NSAID], Drugs [Sulfa Drug].

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Received 12 December 2017, Accepted 02 January 2018

Please cite this article as: Alibeg AA *et al.*, Synthesis of Mutual Pro-drugs through coupling of Etodolac And Tolmetin by Sulfa drugs. American Journal of PharmTech Research 2018.

INTRODUCTION

[NSAIDs] are always exhausted in the management of chronic inflammatory diseases to reduce "inflammation, swelling, pain, rheumatoid arthritis, and osteoarthritis". But their long period of using is un acceptable because of their (GI) side effects. The most serious one is (GI) ulceration[1-2] . [NSAIDs] have the ability to suppress the cyclooxygenases enzyme activity [COXs], which have role in the synthesis of [prostaglandin H2]. As we know that "COX" found in two isoforms formula, [COX-I] and [COX-II], which are organized variously[3] . There is abundant information that suppression of [Cox-I] is more than that of [Cox-II] which result in gastric irritation[4] . [COX-I] is basically assert in stomach to give protection for cell in the (GIT)[5] . The prodrug approach is a strategy used to solve the problem of drawback. Mutual prodrug is a type of many kind of this strategy, where the carrier moiety that used is pharmacologically active drug contrary to inert moiety[6] . A mutual prodrug compose of two biologically active agent linked to each other and so each one act as a moiety for the other and conversely. Mutual prodrug designing strategy is not quite different from the process of drug discovery, where a unique materials is observed to have the recommended biological effects, and knowing of its physiochemical properties use in the synthesis of more beneficial drug. It is of high importance area for researching, and its entrance in human pharmacological treatment has pron huge results in developing the clinical and therapeutic efficacy of drugs having unwanted properties that Mutual prodrugs of [ketoprofen, flurbiprofen, ibuprofen and diclofenac] [7-9] with activity against arthritis when coupled with [D-glucosamine] have been noticed and reported with decreased (GI) ulceration, greater anti inflammatory - analgesic effects and higher activity against arthritis. Where [Glucosamine] was used in the treatment of arthritis and nutritional supplement in many conditions such as stiffness of joints, movement restriction, ache and sever pain [10] .

[NSAIDs] largely used for the emblematic treatment of inflammation associated with many diseases but are incapable to defeat the main cause of that disease. The prolong use of [NSAIDs] cause (GI) side effects. Generally the infection constantly cause inflammation[11] . So sulfa drugs (antibacterial) may be use through coupling with [NSAIDs]. By this manner the carrier moiety (sulfonamides drugs) is helpful to reduce a part of undesirable effect of original drug especially (GI) ulceration. Sulfonamides are antibacterial agents conflict with the production and/or action of folate, sulfonamide consider as bacteriostatic because it suppress bacterial growth not kill them [12] . So sulfa molecules perhaps conjugate with [NSAIDs] so that these mutual prodrugs can be used for infections as well as for inflammation.

Sulfonamide with varying physical, chemical, pharmacological and antibacterial properties are produced by attacking substituents to the amido group (-SO2-NH-R-) or the amine group (-NH2) of the sulfanilamide nucleus[13] . Example sulfadiazine .

Etodolac and tolmetin They might offer significant advantages over aspirin , indomethacin and other NSAIDs for many patients as they are well tolerated[14] .

MATERIALS AND METHOD

The entire materials and anhydrous solvents were of analytical grade, were used as earned from the commercial supplier [Reidal Dehean Germany, Sigma-Aldrich Germany, BDH England]. Etodolac and Tolmetin was purchased from china , Sulfadiazine was received from the SDI Company in Iraq. Melting points (uncorrected) recorded by capillary method by using Thomas hoover apparatus (England). Determination of infrared spectra by using F.T.IR-spectrophotometer, were done at the College of Pharmacy, University of Kufa, the recording of spectra taken were done by using (KBr) disc. (TLC) The ascending thin layer chromatography was run on (DC-Kartan) SI Alumina 0.2 mm for checking the cleanliness and reaction progression. The (CHN) analysis was determined by (CHNS) analyzer [Euro-vector EA_3000A (Italy)]. The recognition of products was carried by using the vapor of iodine and the chromatograms were determined by: [chloroform]:[ethyl acetate]:[ether] (10:5:1).

Chemical synthesis

Coupling reaction of sulfa drugs with chloroacetylchloride compound 1a: The mixture of 0.02 M of sulfadiazine, (30 ml) benzene and (3ml) of triethylamine (TEA), then the mixture was stirred on ice bath, chloroacetylchloride (CAC) 0.02 M (1.6ml in 30ml of benzene) was added gradually (drop wise) then the blend was on reflux for (2 hrs). The excess of benzene was vaporized under vacuum then the precipitate was washed with sodium carbonate (2%), HCl (5%) and distilled water; then recrystallized by ethanol[15] , white brown crystalline product was obtained.

Coupling reaction of NSAIDs with compounds 1a:

Mixture of compound 1a (0.01mole), NSAIDs (0.01mole), TEA (0.01mole), sodium iodide (0.01mole) in (Dimethylformamide DMF) (25ml) was on stirrer over night at the laboratory temperature. Then the blend was flowed into bruised ice with continuous stirring then extract the product with chloroform (5*25ml). Then the mixed organic layer was scrubbed with sodium thiosulphate (2%, 4*50ml), (HCL) (5%, 4*50ml), (NAOH) (5%, 4*50ml) and then with brine solution (3*25ml). Then use anhydrous sodium sulfate for drying the organic layer, finally by

filtration and removing the solvent by using the rotary evaporator (removing the solvent by reduction the pressure) I get the product[16] .

Table 1: Physical data, percentage of yield, melting points and Rf values of intermediates and final compounds

Compounds	Chemical formula	Molecular weight	Description	% yield	Melting point C°	Rf value
Ia	$C_{12}H_{11}ClN_4O_3S$	326.7	White brown crystals	64	196-199	0.8
I	$C_{27}H_{25}N_5O_6S$	547.5	Pale yellow crystals	59	189-191	0.86
II	$C_{29}H_{31}N_5O_6S$	577.6	Yellow crystals	61.5	187-190	0.84

Table 2: Elemental microanalysis results of compounds I and II

Compound	Chemical formula	Elemental microanalysis %		
		Element	Calculated	Observed
I	$C_{27}H_{25}N_5O_6S$	C	59.2	60.214
		H	4.60	4.732
		N	12.79	12.967
		S	5.86	6.216
II	$C_{29}H_{31}N_5O_6S$	C	60.30	60.741
		H	5.41	5.936
		N	12.12	12.831
		S	5.55	6.131

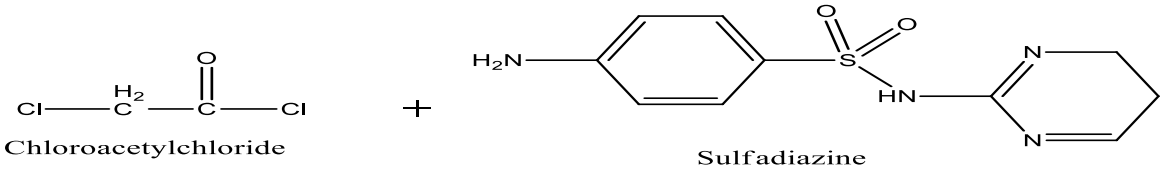
Table 3: FT IR characteristic bands of the synthesized compounds

Compounds	Band (cm-1)	Interpretation
Compound 1a	3329	(N-H) stretching of amide
	1674	(C=O) of amide
	1445	(N-H) bending vibration of secondary amide
	1316,1157	(O=S=O) sulfonamide two bands
Compound I	3332	(N-H) stretching of amide
	1749	(C=O) of ester
	1685	(C=O) of secondary amide
	1614	(C=C) aromatic
	1356,1170	(O=S=O) sulfonamide two bands
	1278	(C-O) stretching of ester
Compound II	3333	(N-H) stretching of amide
	1751	(C=O) of ester
	1639	(C=O) of secondary amide
	1627	(C=C) aromatic
	1349,1132	(O=S=O) sulfonamide two bands
	1269	(C-O) stretching of ester

RESULTS AND DISCUSSION

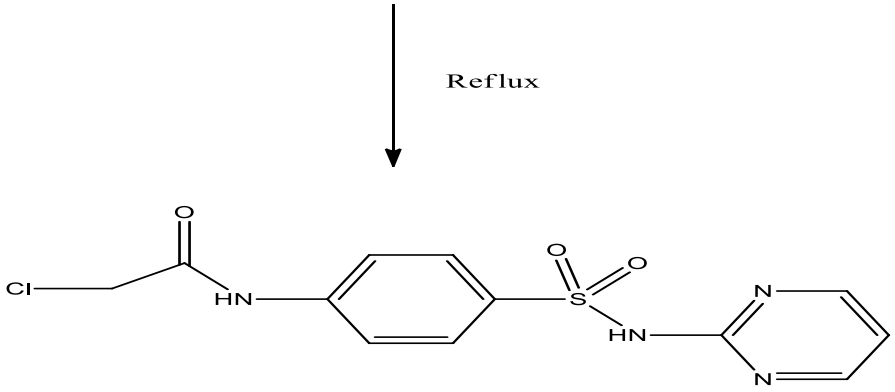
Compound (I,II) was synthesized by coupling of compound (Ia) with sulfonamide and the yield was moderate to good percent, the results are illustrated in the [table-1] and The structures of the final products where settled by spectral data .

Tolmetin and Etodolac have free (COOH) that altered into different amide derivatives. The using of Sulfadiazine molecules resulted in covering the (COOH) group. Accordingly these mutual prodrugs perhaps used to overcome the side effects like (GI) irritation and ulceration further other components of sulfa drug may be used in treatment of infection. Yet, more pharmaceutical studies are required to sketch the ultimate conclusion.



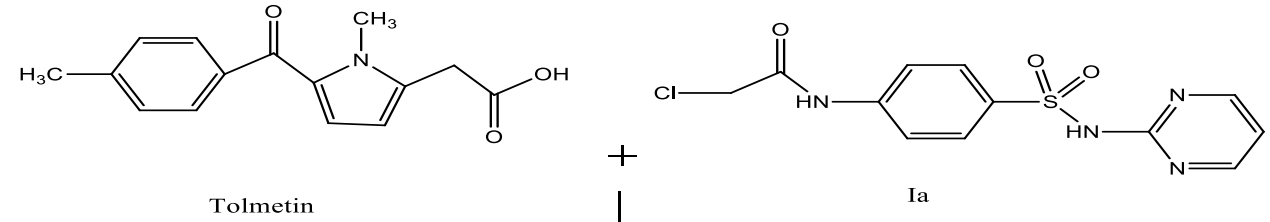
Chloroacetylchloride

Sulfadiazine



Reflux

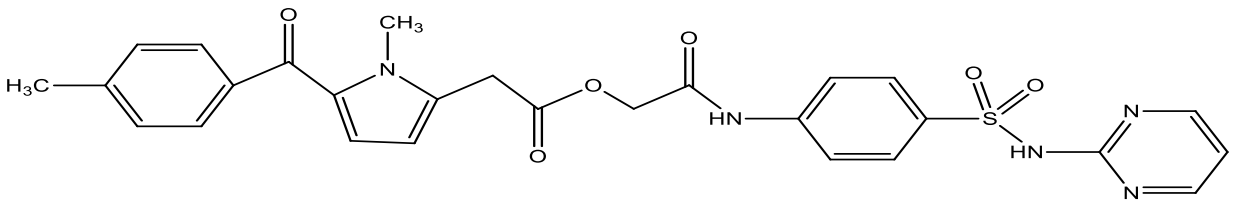
Ia



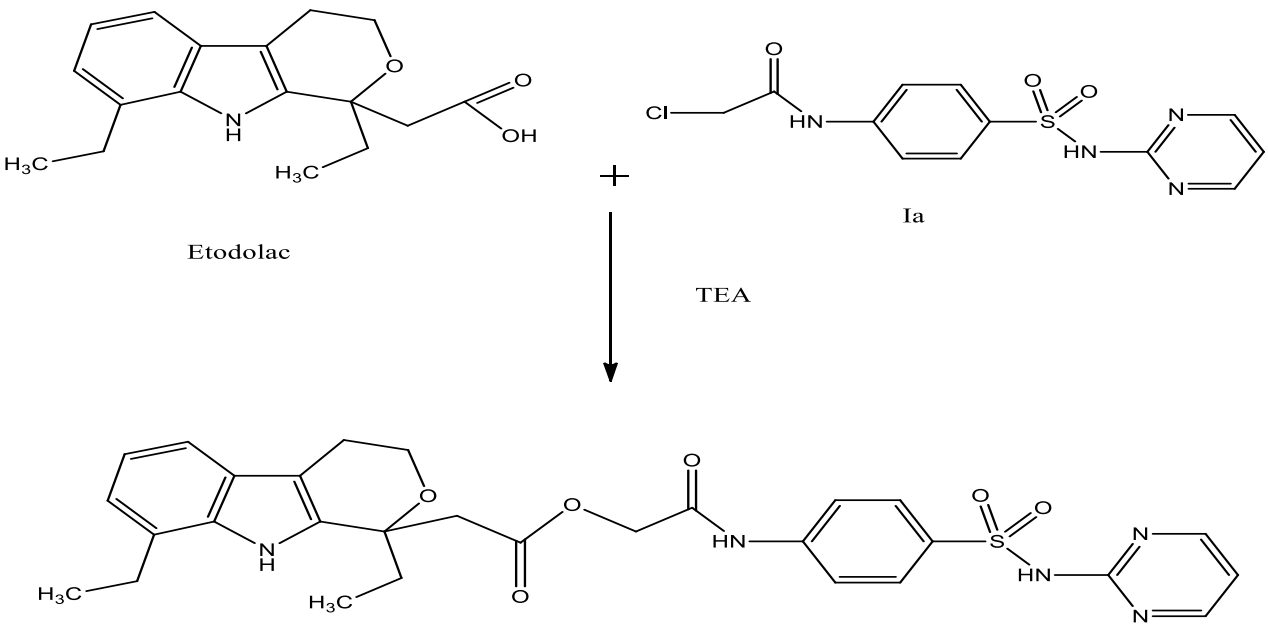
Tolmetin

Ia

TEA



I



CONCLUSION

The constructed compounds was synthesized profitably as demonstrated in (scheme **1)** and their chemical structures were proved, by using infrared spectroscopy (IR spectra), elemental microanalysis (CHN) and its purity was settled by their physical data (color, consistency, melting points and Rf attitude).

ACKNOWLEDGEMENTS

Praise is to almighty Allah gracious for enabling me finish what I started and for helping me to present this work. I grateful to the staff members and the department of Pharmaceutical Chemistry, College of Pharmacy, University of Kufa.

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