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Design and Synthesis of Possible Mutual Prodrugs of (Nsaid) Etodolac and Tolmetin with (Cytotoxic) Gemcitabine

Ammar Abdul Aziz Alibeg[1*], Abbas H. Abdulsada[2], Noor H. Nasser[3], Karrar Abdil Aziz Ali beg[4]

[1,3] Department of Pharmaceutical chemistry, College of pharmacy, Kufa University, Iraq
[2]Department of Pharmaceutical chemistry, College of pharmacy, Babylon University, Iraq
[4]College of medicine, Jabir Ibn Hayyan Medical University
Corresponding Author: ammara.alibeck@uokufa.edu.iq

ABSTRACT

[NSAIDs] Non-steroidal anti-inflammatory drugs consider an important group of drugs due to their properties as anti-inflammatory and it have both antipyretic and pain killer activities. [COX-II] plays an important role all over oncogenesis and here we attempt the same thing to search the use of [NSAID] (Etodolac & tolmetin) in conjugation with current cytotoxic agent (Gemcitabine) for the prevention and/or management of cancer. This study distinguishes the designing and synthesis of mutual prodrug of [NSAID] & gemcitabine, which is specified to create the concomitantly pharmacological action as a one chemical entity with amend of targeting of drug. The synthesized compound was conferred by TLC, CHNS, FTIR and physicochemical properties. The newly synthesized prodrug is predicted to reduce the adverse effects of [NSAIDs] on the (GIT) gastrointestinal tract with enhancement of gemcitabine oral bioavailability and its targeting.

Keywords: Etodolac, tolmetin, gemcitabine, drug targeting, mutual prodrug.

Correspondence:
Ammar Abdul Aziz Alibeg
Department of Pharmaceutical chemistry, College of pharmacy, Kufa University, Iraq

*Corresponding author: Ammar Abdul Aziz Alibeg email-address:
ammara.alibeck@uokufa.edu.iq

INTRODUCTION

[NSAIDs] Non-steroidal anti-inflammatory drugs consider an important group of drugs which are highly prescribed throughout the world because of additionally to their anti-inflammatory effects, this class of drugs possess both analgesic and antipyretic activities[(1)].[NSAIDs] are widely used to cure inflammation, rheumatoid arthritis and pain. But long period of using of [NSAIDs] have been associated with many (GIT)sides effects [(2)].The (NSAIDs) side effects are many especially on stomach such as ulcer formation, perforation of stomach wall and bleeding. These adverse effects that caused by [NSAIDs] are suggested to be because of two reasons: the first one is the direct effect due to their contact with (GI) mucosa directly while the second reason is due to the systemic effect by inhibition the cyclooxygenases [COX-I] enzyme that supply protection to the lumen cell of the (GI) [(3-7)]. The mechanism of action of [NSAIDs] involves inhibition of certain enzyme which is [COX] enzymes that initiate the prostaglandin formation [(3)].[COX] enzyme subdivided into three subtypes: [COX-I] enzyme which is consider as cytoprotective enzyme since it expressed in stomach to provide protection for stomach cells, [COX-II] which is consider the major factor in induction of inflammatory processes, and the isozymic [COX-III][(8,9)].

The targeting of inflammation with [NSAIDs] is an attractive argument to prevent cancer development. There is plentiful experimental and epidemiological evidence that [NSAIDs] have the power to inhibit the development of tumor in many organs such as stomach cancer, , lung, pancreas, ovarian, breast cancer especially when combined with cytotoxic drugs so these group of drugs have great results in scientific intervention researches [(10,11)].

[NSAIDs] have great care as a new kind of antitumor agents. [(12,13)]Inhibition of cancer growth by [NSAIDs]may be due to extracellular and intracellular activity, these activities assort to the [NSAID]ability to counterbalance the process of apoptosis and prevention of angiogenesis [(14)].

Thus, the demand for safer [NSAIDs] still required. One of many strategy to counteract this trouble is the Prodrug approach, also to get acceptable drugs properties like stability, solubility and site targeting, the mutual prodrug approach is consist of two therapeutically active molecules coupled and their connection is either by direct way or indirect via linker and so each molecules act as carrier group for the other [(15,16)] .

Prodrug is a drug molecule subjected to enzymatic and/or chemical process of modification inside the body to liberate the parent's drug which is therapeutically active molecules [(17)]. In the last years the strategy of enhancing the bioavailability site specific targeting is of high importance in prodrug development [(18)]. The anticancer drugs became highly informed; even there is no ability for complete cancer improvement by anticancer drugs. When the prodrug molecule enters inside the tumor cell it will subject to both cellular sensitivity and resistance. So, the increasing in the cytotoxicity will gained from entrance of the two drugs together at the same time and site [(19)].

MATERIALS AND METHODS

Materials

The entire materials with solvents [anhydrous] were of absolute grade used as gained from the provider (BDH. England, sigma Aldrich. Germany and Merck. Germany). Etodolac and Tolmetin was purchased from china. Melting points (uncorrected readings) recorded via capillary method throughout using (England) Thomas hover equipment. infrared spectrum was determined by using the F.T.IR-spectrophotometer, were done at the university of kufa -faculty of Pharmacy. The progression of reaction of synthesis was check cleanliness through using [DC_Kartan type SIAlumina 0.2 mm] thin layer chromatography (TLC). [C, H, N] analysis was determined by using [CHNS] analyzer of type [Euro vector EA_3000A (Italy)]. Recognition of products done by using vapor of iodine and by using system of solvents: (chloroform-ethyl acetate-ether)[10:5:1] the chromatogram was

determined.

Synthesis of [Etodolac, Tolmetin - Gemcitabine] prodrugs: Etodolac (2 mmol) 574 mg or Tolmetin (2 mmol)514 mg were dissolved in chloroform [20 mL] then after complete dissolving and get clear solution add [N,N'-Dicyclohexylcarbodiimide](DCC) (2 mmol)412 mg. Solution of mixture putted on stirrer at room temp for 1 hour and this blend is named mixture (A). After that (2mmol) 600 mg of Gemcitabine putted in round flask and dissolved in 30 ml of DMF after that adding the DMAP 20 mg and this blend is named mixture (B). And then combine the two blends in one flask and stirring the whole mixture (A+B) at room temperature for two days. After that the (N, N′-Dicyclohexylurea) DCC precipitate were removed by filtration and the solvent residue were removed under vacuum by using rotary evaporator. After that we use 150 ml of cold water to get the precipitate of products the recrystallized through using ethanol.

RESULTS AND DISCUSSION

The table 1 explains the yield percentage, physical appearance, and melting point and TLC value of the final created compounds.

The value of compound (I) of CHN analysis were: [C= 54.88; H= 5.49; N= 9.85]while the results that observed were: [C= 54.23; H= 5.15; N= 9.73].

The value of compound (II) of CHN analysis were: C= 53.49; H= 4.68; N= 10.4while the results that observed were: C=53.321; H= 5.12; N= 9.93.

The (FT-IR) charts values of synthesized compound are recorded in table 2.

Table 1: physiochemical properties, percentage of yield, melting points and R_f values of final compounds

Compound	*Chemical formula*	*Mwt*	*Description*	*% yield*	*Melting point oC*	*R_f value*
I (Eto-G)	C26H31ClF2N4O6	569.00	Yellow crystal	71	162-164	0.84
II (Tol-G)	C24H25ClF2N4O6	538.93	Faint yellow crystal	63	189-191	0.86

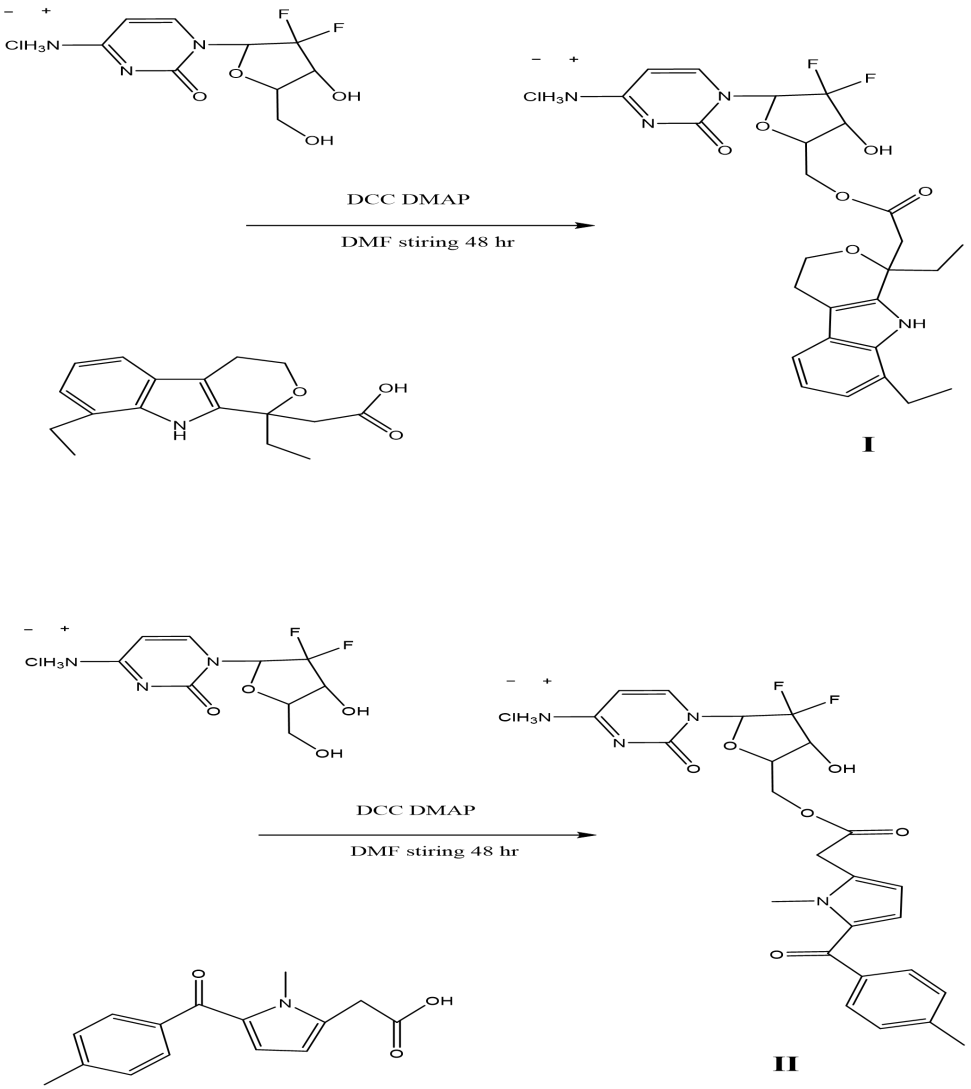

Figure 1: chemical structure of synthesized compounds

FT IR characteristic bands of the synthesized compounds

Table 2: The characteristic FT_ IR bands of the synthesized compounds

Compounds	*Band (cm-1)*	*Interpretation*
Compound (I)	3326	(N- H) ammonuim stretching
	3075	(C-H) aromatic stretching
	2924.91,2847.5	(C-H) CH_2&CH_3 stretching
	1749	(C=O) ester stretching
	1706	(C=O) ketone stretching
	1492, 1571, 1454	(C=C) aromatic stretching overlap with (N-H) bending
	1623	(C=N) stretching
	744.54	(C-H) aromaticstretching out of plane
Compound (II)	3326.21	(N-H) ammonuim stretching
	2923 , 2852	(C-H) CH2&CH3 stretching
	1745	(C=O) ester stretching
	1170	(C=O) ketone stretching
	1222	(C-O) ester stretching
	752.4	(C- H) aromatic out plane bending

For Compound I

1H NMR (CDCl3 d ppm) δ 8.11 – 8.04 (m, 2H), 7.92 (d, J = 10.8 Hz, 1H), 7.80 (s, 1H), 7.32 – 7.23 (m, 3H), 6.67 – 6.53 (m, 3H), 5.44 (q, J = 6.9 Hz, 1H), 4.72 (dd, J = 12.4, 7.0 Hz, 1H), 4.31 – 4.10 (m, 3H), 4.02 (dd, J = 12.4, 7.0 Hz, 1H), 3.72 (s, 3H), 2.30 (s, 2H), 2.30 (d, J = 2.1 Hz, 1H), 1.57 (d, J = 4.9 Hz, 1H).

For Compound II

1H NMR (CDCl3 d ppm) δ 8.75 (s, 1H), 7.92 (d, J = 10.8 Hz, 1H), 7.34 (dd, J = 7.4, 1.5 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.75 (dd, J = 7.5, 1.5 Hz, 1H), 6.64 (d, J = 10.8 Hz, 1H), 5.50 (s, 1H), 4.58 (dt, J = 6.9, 5.4 Hz, 1H), 4.47 – 4.32 (m, 2H), 4.23 (dd, J = 12.4, 5.4 Hz, 1H), 4.08 (dt, J = 12.5, 5.2 Hz, 1H), 3.88 (dt, J = 12.5, 5.3 Hz, 1H), 2.81 (dt, J = 12.9, 5.3 Hz, 1H), 2.80 – 2.70 (m, 1H), 2.72 – 2.62 (m, 3H), 2.46 (d, J = 12.5 Hz, 1H), 1.92 (q, J = 8.1 Hz, 1H), 1.57 (d, J = 4.9 Hz, 1H), 1.42 (q, J = 8.0 Hz, 1H), 1.25 (t, J = 8.0 Hz, 3H), 0.90 (t, J = 8.0 Hz, 3H).

The scientific studies show that the molecules that cause inhibition for [COX-II] enzymes have the power to decrease the growth of cancer and this ability doses in different types of animal. Significantly, many studies and researches explain that the inhibitors of [COX-II] enzyme may act synergistically together with used targeted cytotoxic drugs. So In this part we explain that the inhibitors of [COX-II] enzymes have high benefit in the development of cancer by improvement or prevention of tumors as single [COX_II] inhibitors or in together with antineoplastic [20]. Gemcitabine cytotoxic drug act through two strategies, either through changing single (DNA) strand and by this way it will inhibit cancer growth, or by focusing on specific enzyme which is (RNR) the reductase enzymes of rib nucleotide. The diphosphate configuration of gemcitabine joined on the active site of (RNR) enzymes and by this manner it will irreversibly inhibit the previous enzyme. At the suppression time of (RNR) the cell will became unable to generate the necessary (deoxyribonucleotides) which is very important for (DNA) repairing and replication, and this will lead to lysis of the cell [21].

The synthesized compounds are directed for:

1.Changing the carboxyl group [COOH] of Etodolac and tolmetin [NSAIDs] through transformation into ester which is more tolerable and by this transformation the inhibition of [COX_I] enzyme will be terminated , while its ability for inhibition of [COX-II] enzyme is not affected by this modification and so this will lead to decrease its irritating effect on (GIT).

2. Gemcitabine is have low oral bioavailability due to it undergo rapid metabolism , for this reason it used parentally only , but when synthesized as mutual prodrug through conjugation with [NSAIDs] as one unit of drug molecule it expected to increase its bioavailability through oral dose. Such as in the creation of mutual prodrug of [5_FU] with [NSAIDs], it enhances the bioavailability of [5_FU] after oral dosing [22].

* The researches explain that there is high percent of [COX_II] enzyme approximately (80%) found in tumor cells in comparison healthy one. Further, the extremely differentiated cells of cancer cells have percent high level [COX-II] enzyme in comparison with the moderately differentiated cells. While, in the healthy tissues or organs cells there is no finding of [COX-II] enzyme, so, the synthesized prodrugs are designated for targeting the tumor cells [23].

CONCLUSIONS

The synthesized prodrug compounds which are [NSAIDs] derivatives of Etodolac and Tolmetin and cytotoxic drug (Gemcitabine) are expected to give us three benefits which are : the first one is diminish the undesirable side effect of [NSAIDs] on the gastrointestinal tract, the second one is the improvement of gemcitabine oral bioavailability and the third is getting drug targeting for its specific site of action so decrease the systemic side effects .

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