Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2018, 7 (1): 71-76

(International Peer Reviewed Journal)

Design and Synthesis of Possible Mutual Prodrugs of Naproxen and Acetylsalicylic Acid with Gemcitabine

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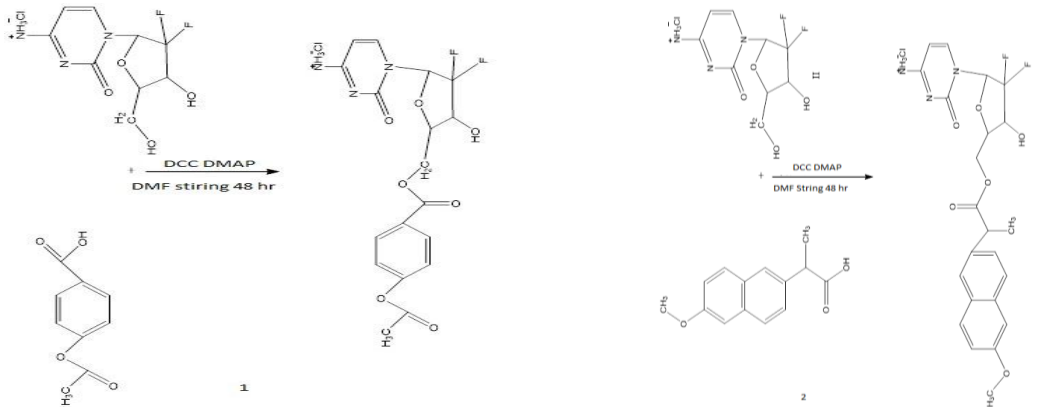
Accepted on 10th January 2018, Published online on 27th January 2018

ABSTRACT

'Non-steroidal anti-inflammatory' (NSAIDs) drugs are most commonly used type of medications and its long period of use result in unwanted side effect like (GI) ulceration. (COX-II) have an important role all over oncogenesis and so I explain the cause of using (NSAID) (naproxen and Acetylsalicylic acid) together with cytotoxic drug [Gemcitabine] in the management of cancer. The research outlines the designing and synthesis of mutual prodrug of (NSAID) and (gemcitabine), which is nominated to create the interdependent pharmacological action as a single pharmacological unit with enhanced drug targeting. The synthesized products was advised by (FTIR) chart, (CHNS) analysis and physiochemical properties. The synthesized prodrug is supposed to diminish the undesirable effect of (NSAIDs) on the (GI) tract with amendment of the bioavailability and cancer targeting for (gemcitabine).

Graphical Abstract



The synthesis schemes of (Naproxen Gemcitabine and Aspirin Gemcitabine prodrug} (1 and 2).

Keywords: Naproxen, Acetylsalicylic acid (ASA), gemcitabine, drug targeting, mutual prodrug.

INTRODUCTION

NSAIDs are widely used drugs in the world, because of their anti-inflammatory, pain killing and fever reducing properties [1]. Yet, their use result in many serious side effects the most one is GI ulceration and perforation. The side effects are the use of "traditional" NSAIDs results in serious upper gastrointestinal, GI adverse events e.g. ASA and naproxen [2]. Non-steroidal anti-inflammatory drugs NSAIDs are associated with gastrointestinal side effects particularly stomach ulceration, bleeding and perforation. The side effects caused by NSAIDs are supposed to be due to two reasons: direct effect by direct contact with (GI) mucosa and the second one is due to systemic action by suppression the COX-I that provide cytoprotection to the (GI) lumen [3-7]. Thus, need of safer NSAID still remains. Prodrug approach is one of many strategies to overcome this problem, also to get good solubility, stability and targeting for these drugs, the mutual prodrug concept normally composed of two pharmacologically active drugs joined together either directly or through spacer and each one act as carrier for the other one [8,9].

Directing the [NSAIDs] toward the inflammation is an interesting approach for cancer therapy and prevention. There is evidence that NSAIDs have the ability to suppress cancer progress in many areas. So such results give a great attention in cancer targeting studies [10]. As well to the confirmed performance of COX-II in inflammatory process, the newly studies explain that the isoform could be associates in many events throughout the tumorigenic growth. Also many studies demonstrate the role of NSAIDs in diminishing the dangerous of many case of cancer [11]. Curiously, significant clinical information illustrates the performance of NSAIDs in avoidance and preventing a wide range of tumors, specifically when mixed with cytotoxic drugs [12, 13]. [NSAIDs] perhaps have the ability to reduce the insecure of tumors such as in breast cancer, ovarian cancer, pancreas, lung, prostate and stomach cancer [14].

[NSAIDs] are pull a considerable attention as a new type of antitumor drug. [15, 16] cancer growth suppression by [NSAIDs] perhaps due to intra and extra cellular activity, these activities relate to the ability of [NSAID] to compensate the apoptosis process and suppression of angiogenesis [17].

Prodrug is a drug molecule undergo chemical or/and enzymatic biotransformation inside the body to release the pharmacologically active parents drug [18]. The strategy used to amend the bioavailability and perform a specific cancer targeting is of great importance in prodrug approach since the last years [19].
Purposely the anticancer drugs became increasingly sophisticated, although there is no cytotoxic drug can heal the caner completely. The entrance of prodrug molecules inside tumor cells undergo both cellular resistance and sensitivity. Like any dosage regimen combination, the both drugs will target that specific area at same time individually and so they will increase the cytotoxicity [20].

The purpose of this study was to design and synthesize of new compounds (I, II) as possible mutual prodrugs for targeting cancer tissue.

MATERIALS AND METHODS

Materials: All materials and solvent (anhydrous) used as received from the commercial provider (Merck; Germany, Reidel De-Haen, Germany, Sigma, Aldrich, Germany and BDH; England). Naproxen and ASA was bought from the SDI Company, Iraq.

Synthesis of [Naproxen-Gemcitabine] and [Aspirin-Gemcitabine] prodrug: Naproxen 460.5 mg (2 mmol) or Aspirin 360.3 mg (2 mmol) dissolved in (20 mL) of [chloroform] then add (DCC) (N,N'-Dicyclohexylcarbodiimide) 412 mg (2 mmol). The blend was on stirrer at laboratory temp for about 1 hr and this is solution (A). Then [Gemcitabine] 600 mg (2mmol) and 20 mg of [DMAP] have been dissolved in 30 mL [DMF] and this is solution (B). After that mixed the both solutions (A) and (B) and put it on stirrer for 48hrs at laboratory temp. Then all the precipitate of DCU (N, N′-Dicyclohexylurea) were filtered

and then the filtrated solution in rotary evaporator to remove the solvent under reduced pressure. Then by using cold water (150 mL) will gain the product precipitate which recrystallized by using ethanol was filtered off and solvent of filtrate was removed under reduced pressure.

Compound analyzing: Product M.P (melting point) was obtained by using electrical (M.P) apparatus, SMP30 Stuart; England. Using of ascending thin layer chromatograph (TLC) for checking the purity and reaction progression, this is done by using DCKartan_SI alumina 0.2 mm) plates. The compound was identified by using (U.V) detector and the chromatogram was eluted by [Chloroform: Methanol is 8.5:1.5]. The compound IR spectra were recorded by using [(FTIR) Spectrophotometer Shimadzu] as (KBr) disks. The compound (CHNS) analysis data was done by using a [Euro(EA 3000) elemental analyzer apparatus].

RESULTS AND DISCUSSION

The scheme of synthesis is presented in (Figure 1). The procedure used in synthesis of products is explained in these schemes.

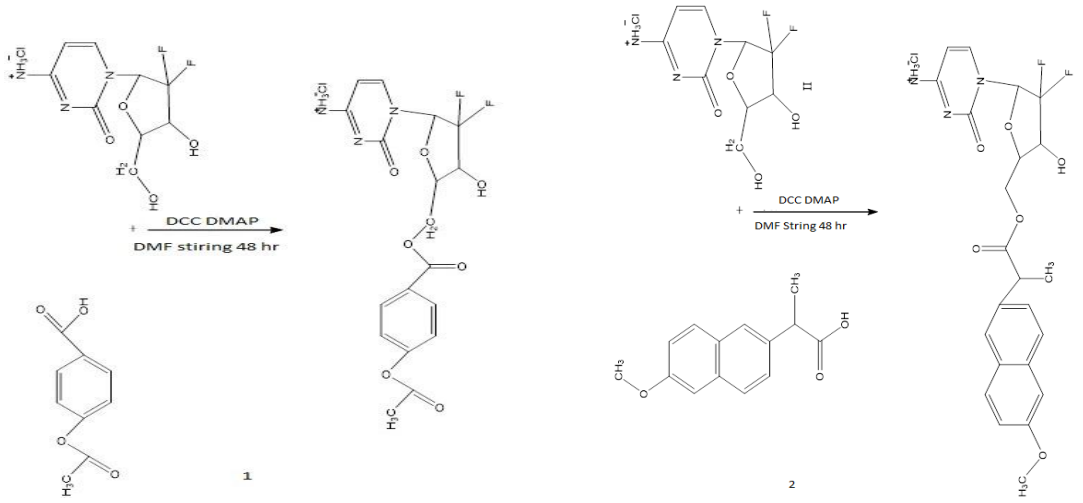


Figure 1: The synthesis schemes of (Naproxen-Gemcitabine and Aspirin-Gemcitabine prodrug (I and II).

The percent of yield, melting point, physical appearance and TLC results of the synthesized compounds were listed in table 1.

The calculated Elemental Analysis for compound I were: C= 46.82; H= 3.39; N= 9.10 and the observed results were: C= 45.1; H= 2.95; N= 8.73.

The calculated Elemental Analysis for compound II were: C= 53.96; H= 4.73; N= 8.21 and the observed Elemental Analysis were: C=53.32; H= 5.12; N= 7.9. The results of (FT-IR) charts are recorded in table 2.

Table 1. The physical appearance, percent yield, melting point and (Rf) values of the synthesized products.

Compound	*Chemical formula*	*Mwt*	*Description*	*% yield*	*Melting point oC*	*Rf value*
I (ASA-G)	C18H18ClF 2N3O7	461.80	Faint yellow	72	semisolid	0.63
II (Nap-G)	C23H24ClF 2N3O6	511.9	yellow	61	127-130	0.71

Pharmacological studies explain that COX-II inhibitors have the ability to suppress cancer growth and this action related to its doses in different animal types. Significantly, many research shown that COX-II inhibitor may act cooperatively with presently used anticancer targeted drugs. In this part I explain that COX-II inhibitors have great function in oncogenesis by prevention or/and management of tumor as unique drug or in mixture with cytotoxic [21]. Gemcitabine act by two strategies, the first one is by replacing on strand and so suppress cancer development, the other one is by targeting on the ribonucleotide reductase enzymes (RNR). The diphosphate form of gemcitabine tie on RNR active position and so inhibit this enzyme irreversibly. At a time RNR is suppressed the cell will not be able to generate (deoxyribonucleotides) that needed for replication and repairing of (DNA), and so cell lysis is evoked [22].

Table 2. [(IR) characteristic bands] for the designed compounds.

Compound	Bands (cm^{-1})	Interpretation
Compound I	3329 3072 2928,2851 1751 1736 1707 1494, 1573, 1451 1629 ;1089 748.38	*(N- H) stretching vibration of ammonuim* *(C -H) stretching of aromatic* *.(C –H) stretching for[CH2&CH3]* *(C═O) stretching of ester* *(C═O) stretching of ester* *(C═O) stretching of ketone* *(C=C) stretching of aromatic overlap with (N-H) bending vibration* *(C=N) stretching (Ar-Cl) stretching vibration* *(C- H) bending vibration out of plane of aromatic*
Compound II	3327 2927,2850 1738 1705 1577,1492, 1452 1627 1089 748	*(N-H) stretching of 2ndary amine.* *(C-H) stretching for CH2&CH_3.* *(C-O) stretching of ester* *(C=O) stretching of ketone.* *(C-H) stretching of aromatic .* *(C=C) stretching of aromatic overlap with(N-H) bending vibration .(C=N) stretching vibration.* *(Ar-Cl) stretching vibration.* *(C-H) bending vibration out of plane of aromatic.*

The synthesized prodrugs are directed toward three paths:

1) Modification of (COOH) group of [NSAID] by conversion into ester derivative will terminate its ability for inhibition of COX-I without any effect on its COX-II suppression activity result in reducing its irritation effect on stomach.

2) The anticancer drug Gemcitabine is undergo first pass metabolism, so must be given to patient by intravenous rout, so when modified as prodrug by conjugation with NSAID as single drug it thought to improve its oral bioavailability of the parent drug. As in the prodrug of [NSAID] with (5_FU), it enhances the oral bioavailability of 5_FU [23].

3) The study reveals that up to 80% of COX-II is expressed in cancerous cells, the strength and percent of expression is very high in cancerous cell in comparison with normal cells. Furthermore, the highly differentiated cancerous cells have higher percent of expression for COX-II than slowly differentiated one. On the other hand, there is no appearance of COX-II in the vessels of healthy organs and tissues, so, the designed prodrugs of [NSAIDs-Gemcitabine] are adjusted cancer cells targeting. [24].

CONCLUSIONS

The designated and synthesized derivative of NSAIDs (Naproxen and Aspirin) with cytotoxic antimetabolite drug Gemcitabine as possible mutual pro-drug have been anticipated to improve the oral bioavailability of Gemcitabine and site-specific targeting.

ACKNOWLEDGEMENTS

I am appreciative to staff members of department of pharmaceutical chemistry in faculty of pharmacy/ university of Kufa for giving me all the available facilities to complete the research.

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