Synthesis of the new carbohydrate Ibuprofen ester as possible prodrug

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Abstract:
Synthesis of new ibuprofen ester (5) is described. Ester formation was achieved by esterification of ibuprofen carboxylic acid (1) with diacetone fructose (3). The structure of synthesized compounds were characterized by means of FTIR and UV. Preliminary results showed that the prepared fructose-drug conjugates underwent hydrolysis and released the pound ibuprofen and fructose. However, detailed kinetic studies of chemical and potential enzyme hydrolysis still remain to be done.

الخلاصة:
تضمن البحث تحظير مشتق استري جديد لدواء الأيبوبروفين في حزما جذور الينس. سكر الفركتوز وذالذ يتحو مجموعة
الحامض للأيبوبروفين إلى كلوستيد الحامض ثم ادخال أسترة مباشرة مع مجموعة الكحول. سكر الفركتوز المحمي في
الموقع رقم 1 زيادة كل من الدواء نية والأنتصاصية للأيبوبروفين مما يمكن من تقليل كمية الدواء المعطي للمرض والمقليل
من أعراض الجانبية. تم تشخيص المركبات المحظرة بواسطة طيف الأشعة تحت الحمراء والأشعة فوق البنفسجية وكانت
النتائج مطابقة لما هو متوقع.

INTRODUCTION
The term "prodrug" or "proagent" was first introduced by Albert1 to signify pharmacologically inactive chemical derivatives that could be used to alter the physicochemical properties of drugs, in a temporary manner, to increase their usefulness and/or to decrease associated toxicity. Since Albert discussed the concept of prodrugs in the late 1950s, the use of the term implies a covalent link between a drug and a chemical moiety, though some authors also use it to characterize some forms of salts of the active drug molecule. Although there is no strict universal definition for a prodrug itself, and the definition may vary from author to author, generally prodrugs can be defined as pharmacologically inert chemical derivatives that can be converted in vivo to the active drug molecules, enzymatically or nonenzymatically, to exert a therapeutic effect. Ideally, the prodrug should be converted to the original drug as soon as the goal is achieved, followed by the subsequent rapid elimination of the released derivatizing group2-4.
Carbohydrate-drug conjugates connected by potentially metabolisable sacrificial linkages, such as esters, have high potential utility as prodrugs in which the glycan moiety affords both protection and specific transport properties5.
This prodrugs have been prepared to increase the bioavailability \(^6\), solubility \(^7\), activity \(^8\), and the selectivity \(^9,10\). Ibuprofen, a potent nonsteroidal anti-inflammatory drug, has been widely used in the treatment of pain and inflammation. \(^11,12\) Unfortunately, like other nonsteroidal anti-inflammatory agents, ibuprofen carries some side effects such as gastrointestinal irritation \(^13,14\). Therefore, the ester prodrugs of ibuprofen were synthesized with the intention of reducing the side effects \(^15,16\). It is known that some carbohydrate ester prodrugs have antibiotic activity. In the light of these results, I aimed to develop carbamate-linked sugars (fructose) with ibuprofen because this linkage is stable in aqueous solution and could be hydrolyzed by glycosidases \(^17\) and no other toxic groups are released from the linkage portion of the molecule. Also, this may reduce the side effects of ibuprofen and increasing the tissue distribution.

**EXPERIMENTAL**

Melting points were determined on Buch 510 melting point apparatus and remained uncorrected. Infrared (FTIR) spectra were recorded on a Beckman I.R–8 spectrophotometer UV spectra were carried out using an Hp 845 2A diode array spectrophotometer, and the wave numbers reported are referenced to the 200 n.m. Cm\(^{-1}\) of chloroform. TLC was performed on silica gel plates kieselgel 60 F245 (Merck, Germany) and the following solvents and solvent mixtures were used: CH2Cl2: CH3OH, CH2OH,C6H6 (2:10), EtOA: CH3OH (1:5), EtOA: CH3OH (5:1). Spots were visualized by short-wave UV light and iodine vapor. Chromatography was performed on silica gel eluent with chloroform. Ibuprofen anhydrous was supplied from Samarra drug industries Samarra, Iraq. The purity of this compound is checked according to m.p and Meric index. All solvents were distilled and dried prior to use. Pyridine was refluxed with K2CO3 for 5 h. Then fractional distillation over anhydrous K2CO3, glass ware was dried over night in an oven at 130\(^0\) C and cooled in a desicator over anhydrous CaCl2 or silica gel.

**General procedure for the compounds synthesis**

2, 3 : 4 , 5 -di-O-isopropylidene\(-\)D fructopyranose (3).

Compound (3) was synthesized from\(-\)-D –fructose in acetone following the published procedure. \(^18\)

**Ibuprofenoyl chloride (2).**

Dry powdered of ibuprofen (1 gm, 5 m mol) was placed in distillation flask, redistilled thionyl chloride was added. The mixture was then refluxed with shaking for 3 h. The flask, was cooled the condenser detached and the flask was heated carefully over the hot plate at 60 \(^0\) C with accessional shaking for 20 minutes.

**1-diacetone fructosyl ibuprofen ester (4).**

Compound (3)(1 gm, 3.8 m.mol)’ solved in anhydrous pyridine (10 mL), ibuprofen chloride (2) (0.85 gm, 3.8 m.mol) was stirred for 24 h. at room temperature, a mixture of water-chloroform (30 mL) (1:2), filtered and the organic layer was separated, washed with water dride over MgSO4, filtered, evaporation under reduced pressure.

**1-fructocyl ibuprofen ester (5).**

Compound (4) (1 gm, 2.3 m. mol) was dissolved in 10 mL of chloroform, then stirring with 0.5 N (HCl) for 3h. at 25 \(^0\) C.
RESULTS

In this paper, a new and convenient method of ibuprofen ester preparation via \( \square \)-D-fructose was reported. In the first step, carboxylic acid group of ibuprofen was converted to its chloride (2) by reaction with dry thionyl chloride in 45.4% yield, then reacted with 2,3:4,5-di-O-isopropylidene-\( \square \)-D-fructopyranose (3). 1-diacetone fructocyl ibuprofen ester (4) was formed, then stirring with 0.5 N of HCl giving the corresponding ester in 50% (Scheme 1). The following compounds were synthesized: (2), (3), (4) and (5). All except (3), are new compounds. Compound (3) was previously synthesised, but the literature report\textsuperscript{18} gave no spectroscopic characterisation. Therefore, its spectroscopic data are reported here, together with the data for the new compounds.

\[
\text{(5)} \quad \text{CH}_2\text{CH} \quad \text{CH}_3\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O} \quad \text{CH}_3 \quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O} \quad \text{CH}_3 \quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O} \\
\text{(2)} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{O} \quad \text{CH}_3 \quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O} \quad \text{CH}_3 \quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O} \\
\text{(4)} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{O} \quad \text{CH}_3 \quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O} \quad \text{CH}_3 \quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O} \\
\text{(6)} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{O} \quad \text{CH}_3 \quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O} \quad \text{CH}_3 \quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O} \\
\text{(1)} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{O} \quad \text{CH}_3 \quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O} \quad \text{CH}_3 \quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \quad \text{O}
\]

Scheme 1: i) acetone, 36 C°, FeCl\textsubscript{3}, 10 h. : ii) SOCl\textsubscript{2}, 60 C°, 3 hr. : iii) pyridine, 25° C 24 hr. : vi) (0.5 N) HCl, 6 h.

The ester preparation proceeded in mild condition, at room temperature spectral assignment of all synthesized confirmed their structures. FTIR spectra of (5) showed the characteristic absorption bands for OH at \( \nu \) 3400, \( \nu \) C-H aliphatic at 2800, \( \nu \) C=O ester 1739. The parallel display of FTIR spectra of ibuprofen (1), ibuprofen chloride (2), 1-diacetone fructosyl ibuprofen ester (4), and 1-fructocyl ibuprofen ester (5) is presented in (Figure 1,2). Reaction conditions, yields, physical, FTIR spectroscopic, UV and Rf are given in (Table 1).
Figure 1. FTIR spectra of a/ibuprofen (1) and b/ibuprofen chloride (2).

Figure 2. FTIR spectra of c/compound (4), and d/compound (5).
Figure / 3. UV spectra of compounds (2, 4, 5)
TABLE 1. Preparation and analytical data of compounds (2-5)

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<tr>
<th>Comp. No</th>
<th>Molecular formula ((M_r))</th>
<th>Rf</th>
<th>M. P (C^0)</th>
<th>Time (h)</th>
<th>Yield %</th>
<th>Solvent</th>
<th>FTIR (\nu_{max}/\text{cm}^{-1})</th>
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<td>3</td>
<td>C12H20O6 ((260))</td>
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<td>-</td>
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<td>45.4</td>
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<td>33</td>
<td>Pyridin</td>
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</tr>
<tr>
<td>5</td>
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<td>CH2Cl2</td>
<td>3380, 1740, 3024, 2985,</td>
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CONCLUSIONS

In this work fructose was used to synthesize a new carbohydrate ibuprofen ester (5) by esterification of its carboxylic acid group by one of the fructose hydroxyl groups. Preliminary results showed that the prepared fructose-drug conjugates underwent hydrolysis and released the compound ibuprofen and fructose. However, detailed kinetic studies of chemical and potential enzyme hydrolysis still remain to be done.

Acknowledgements

This work was supported by chemistry Department / college of Science Baghdad university.

Reference