Synthises of 3 – glucosyl ibuprofen ester derivative

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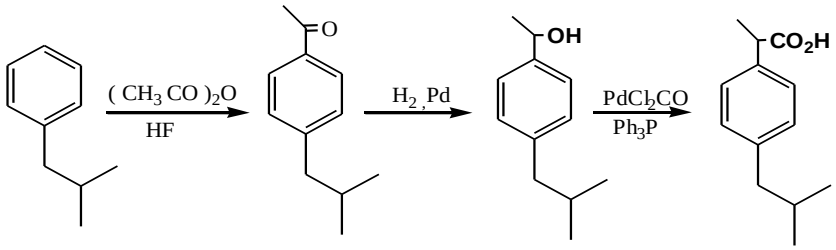
Abstract :-

3-glucosyl ibuprofen ester was synthesized by esterification of ibuprofen carb-oxylic acid group to obtaine a new ibuprofen derivative that may have more water– solubility than ibuprofen and may also be possible to reduce the dose by effectively delivering the drug inside the cell.

Introduction:-

Ibuprofen (**1**) is anon steroid anti-inflammatory agent used to controll pain and inflammation with reduction in the milder gastrointestinal side effect, [1,2]



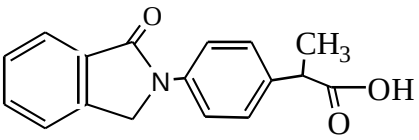
(1)

(Fig.1)

Its synthesis (fig. 1) begins with the reaction of isobutyl benzene with acetic anhydride using hydrofluric acid (HF) as the solvent ,

This is the variation for the Friedel-Crafts acylation in which the anhydride serves as the source of an acylium ion. The second step is an addition reaction, catalytic hydrogenation of acetone to an alcohol. The final step is an insertion of carbon monoxide into a benzylic C-O bond to give the carboxylic acid (ibuprofen) [3] . Ibuprofen is known to block cycloxgenase, which then reduces metabolites produced by this enzyme that are at least partially responsible for inflammation [4,5]. Saveral resurch teste the relation ship between the strauctur and the activity with compound similar to ibuprofen, including indoprofen [6] (**2**) ketoprofen [7,8]

(**3**), flurbiprofen[9] (**4**) and fenoprofen[10,11] (**5**) .



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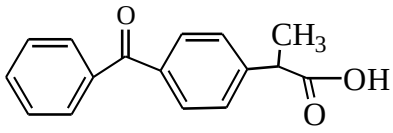

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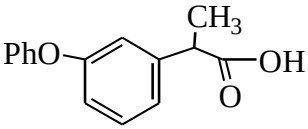

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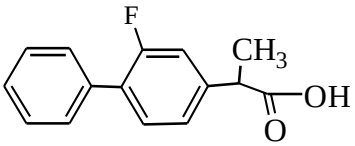
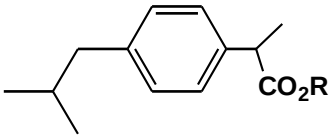


(4)

The ester derivatives of ibuprofen (**6**) would reduce its side effects and also be possibl to reduce the dose by effectively delivering the drug inside the cell [12] .



(6)

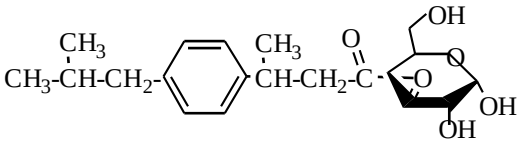
In the last few years, carbohydrate mimetics have become an emerging area in drug design. Several applications of carbohydrate mimetics are currently on clinical trial to increase the activity, bioavilability and the selectivety of drugs [13,14].

Results and Disccusion:-

The context of the research:Synthises of 3-glucosyl ibuprofen ester (7) .

This study deals with the synthises of a new carbohydrate ibuprofen ester derivative (7) by esterification of its carboxylic acid by one of the glucose hydroxyl groups, this may increase the solubility since glucose has many free-OH groups. It is hoped that the new synthesized

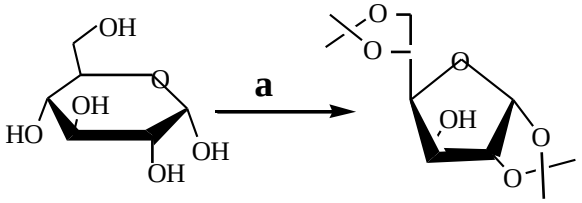
derivative may possess the activity with high solubility than parent drug.



(7)

Scheme (1). Synthises of 1,2:5,6-di-O-isopropylidine□□-*D*-glucofuranose(8)

This compound was synthesized in one step, reaction of anhydrous –D-glucose with dry acetone in the presence of sulfuric acid, afforded compound (8) in 50 % yield,



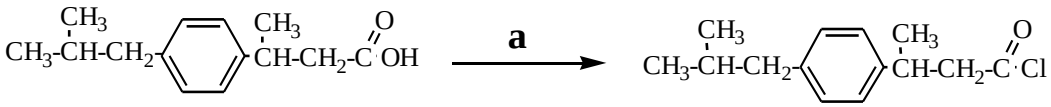
(8)

Scheme 1- Reagents and condition:

(a) 1/ (CH3)2CO , H2SO4 , 25^0 C , 5 h 2/ NaOH

Synthises of ibuprofenoyl chloride (9)
scheme (2)

Carboxylic acid group of ibuprofen was converted to its chloride by reaction with dry thionyl chloride gives compound (9) in 45.4 % yield.



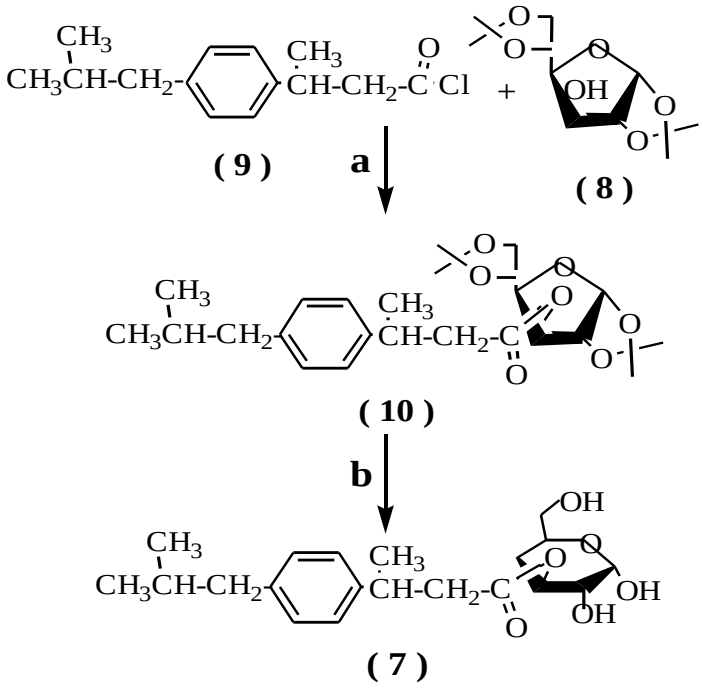
(1) **(9)**

Scheme 2- Reagents and condition:

(a) 1/ SOCl2 , 70^0 C , 3 h.

Synthises of 3-glucosyl ibuprofen ester (7)
scheme -3-

Compound (8) was reacted with ibuprofenoyl chloride (9) in the presence of pyridine for 24 h. to give in (40 % yield) 3-diacetone glucosyl ibuprofen ester (10) , then stirring with SnCl2 for 5 hr.to produce 3-glucosyl ibuprofen ester (7) in 50 % yield .



Scheme 2- Reagents and condition:

(a) pyridine , 25^0 C, 24 h . (b) 1/ SnCl2, 25^0 C,5 h . 2/ Na2CO3

Experimental

General methods:-

For anhydrous reaction, glassware was dried over night in an oven at 100^0 C and colled in a desicator over anhydrous CaCl2 or silicagel. Reagents were purchased from fluca (switzerland) or sigma (st. Louis.USA). Solvents ,

incuding dry chloroform, acetone, thionyl chlorid and cyclohexane were obtained by distillation over the CaCl2 . Other solvents including pyridine was refluxed with K2CO3

for 5 h . then fractional distillation over anhydrouse K2CO 3. Absolute ethanol was purchased from Merck (Germany) and used as receiver. Melting points were obtained with Buch , 510 melting point appartus. Infrared (FTIR) spectra were recording on a Beckman I. R-8 spectrophotometer.The wave numbers reported are referenced to the 200 Cm^{-1} of chloroform . Ibuprofen unhydrous was supplied from Samarra drug industries. Samarra,Iraq , the purity of this compound is checked according to m.p and Meric index . UV spectra were carrid out using an 845 2A diode array spectrophotometer. Purification on silicagel refers to gravity column chromatography on Merck Silicagel 60 (particle size 230-400 mesh) . Analytical TLC was performed on precoated plates purched from Merck (Silicagel 60 F 254) . Compounds were visualized by using U.V light , I2 vapor 2.5 % phospho molybic acid in ethanol with heating.

1,2:5,6-di-O-isopropylidine-□-*D* glucofuranose (8).

To the solution of anhydrous-D-glucose (10 gm , 0.05 mol) in dry acetone (200 mL) was added (8mL) concentrated sulfuric acid with stirring for 5 h. at 25 ^{0}C. Asuspension of 50 % NaOH was added with stirring to near neutrality the mixture was filtered under suction , then the solution was concentrated under reduced pressure to a thick syrup that is dissolved in chloroform on water bath, the solutic 6 extracted with water , dried over MgSO4 then evaporated to give white crystal wl as recrystalized from cyclohexane to yield compound (8) in 50% yield. M.p 105 ^{0}C ; Rf [CH2Cl2 : CH3OH , 1: 0.5] (0.23) ; FTIR (KBr disk) (cm^{-1})(fig.2) ,3400 (OH strech.),2800 (C-H aliphatic)1250-1100 of the acetal (C-O-C) .

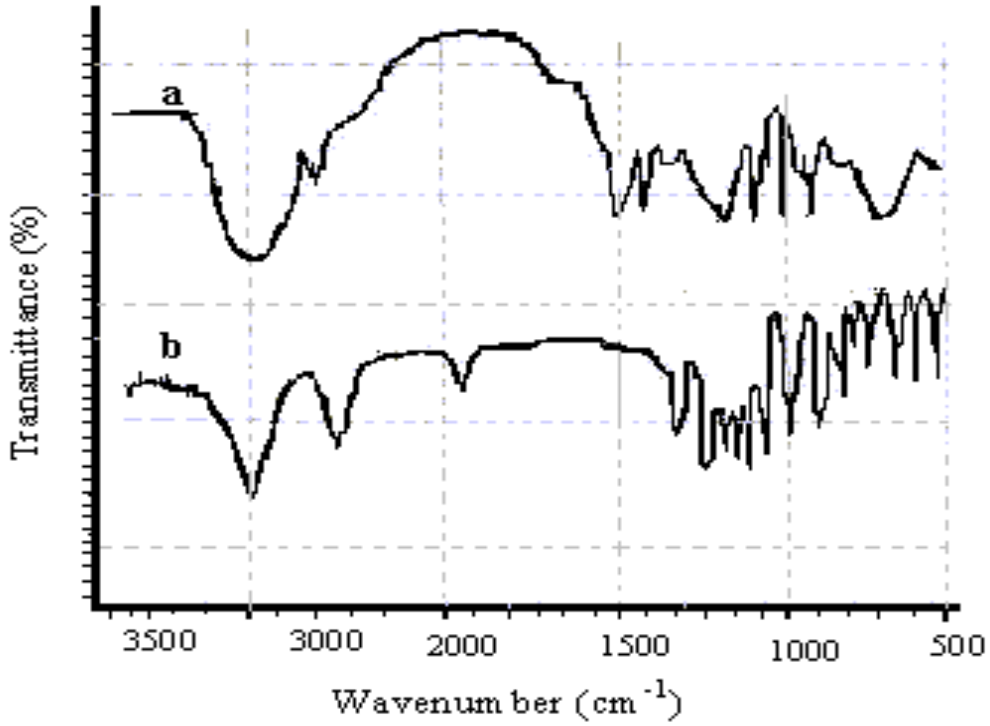


Fig. 2. Comparison between FTIR spectra of : a) □-D-glucose, and b) diacetone glucose (8)

Ibuprofenoyl chloride (9).

Dry powdered ibuprofen (1.02 gm , 5 mmol) was placed in disstillation flask, redistilled thionyl chloride was added . The mixture was then refluxed with shaking for 3 h ., the flask , was cooled the condenser deta 7 d the flask was heated carefully over the hot plate at 60 ^{0} C with accasional shaking for 20 minutes, afforded compound (9) in 45.4 % yield as syrup ; Rf (CH2OH,C6H6 2:10) (0.7);FTIR (film) (cm^{-1})(fig.3) 1800 for acid chloride 3040 (C-H aromatic) , 2950 (C-H aliphatic) and 655 (C-Cl). U.V(chloroform)□□ max at 238 nm.

3-diacetone glucosyl ibuprofen ester (10).

Compound (8) (1.2 gm, 4.5 m. mol) was dissolved in anhydrous pyridine (10 mL), ibuprofen chloride (9) (1.0 gm , 4.5 m. mol) was added , stirred for 24 h. at room tempercture, a mixture of water-chloroform (30 mL) (1:2), filtered and the organic layer was separated, washed with water dried over MgSO4 and filtered, evaporation under reduced pressure and purification of residue by using column chromatography (CH2Cl2) give compound (10) as syrup in 40 % yield, Rf [EtOH : CH3OH 1:5] (0.8) , FTIR (film)(cm^{-1}) (fig.3) 3024 (C-H aromatic) 2985 (C-H aliphatic) 1739 (C=O ester) and 1250-1050 of the acetal (C-O-C).

3-glucosyl ibuprofen ester (7).

Compound (10) (1.3gm, 5m mol) was dissolved in (10 mL) of chloroform, then added (0.2 gm) SnCl2, with stirring for 3h. at 25 ^{0}C . 50 % of KHCO3 , was added with stirring, the reaction mixture was poured on to cold water (50 mL) and extracted with chloroform , washed with water , dried over MgSO4 and filtered, the solution was concentrated then added to silicagel column, the column was eluted with chloroform . The major fraction was evaporated to afforde compound (7) in 50 % yield as syrup; Rf (EtOA: CH3OH 5:1) (0.65);FTIR (film)(cm^{-1}) (fig.3) 3380 (O-H), 1739 (C=O ester). 3024 (C-H aromatic) 2985 (C-H aliphatic).

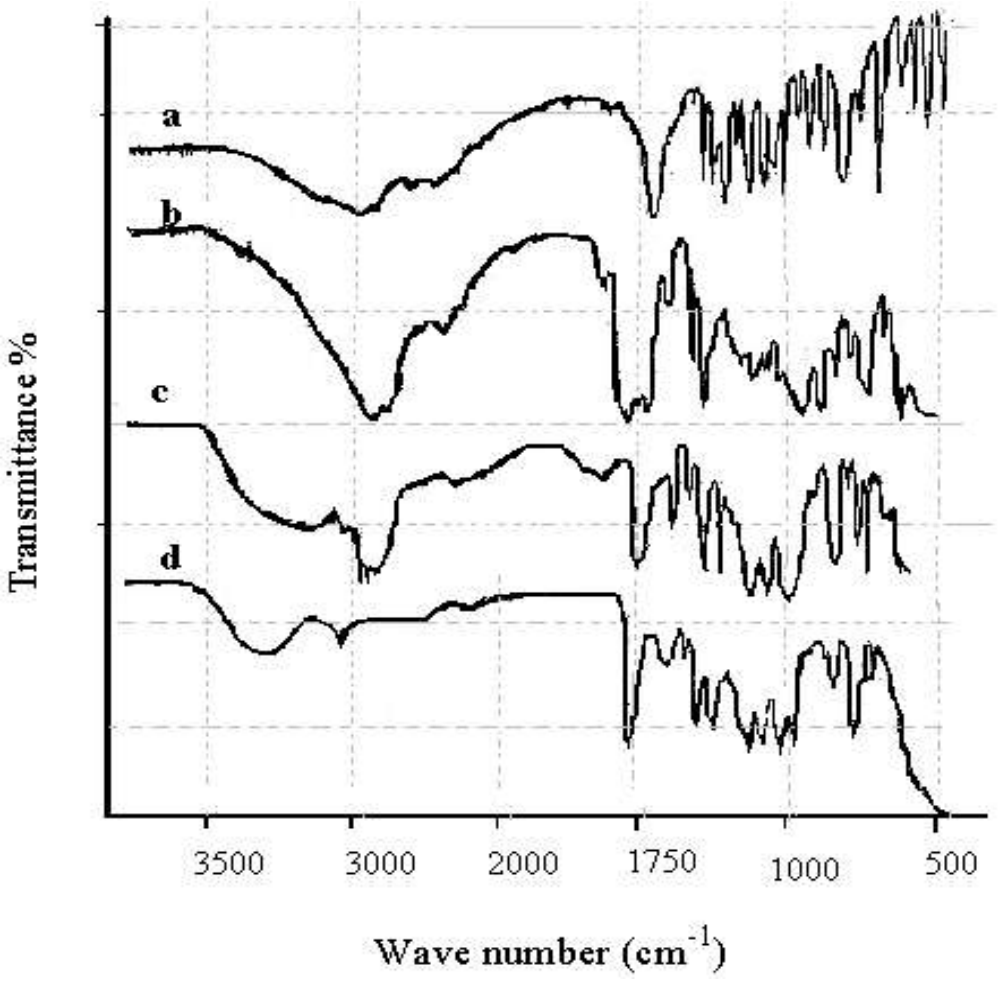


Fig. 3. Comparison of FTIR spectra of : a) ibuprofen, b) ibuprofen chlorid (9) , c) compound (10) and compound (7)

Acknowledgements

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References

1. S. Keady, A. Grosso and F. Maguire, **Hospital Pharmacist** , 12,(2005) : 273-274.

2. M. Etminan and A 9 i, **The Lancet** 361 ,(2003):1558.

3. Z. Qian, **The China Papers**, (2004) :39-42

4. T. A. Trappe, F. White, C. P. Lambert, D. Cesar, M. Hellerstein, and W. J. Evans, **Am. J. Physiol Endrocrinol Metab** 282,(2002):551-556. **5.** R. A. Sheldon, **Pure Appl. Chem**., 72 ,(2000):1233-1246.

6. M. R. Lunn, D. E. Root, A. M. Martino, S. P. Flaherty, B. P. Kelley, D. D. Coovert, A. H. Burghes, N. T. Man, G. E. Morris, J. Zhou, E. J. Androphy, C. J. Sumner, and B. R. Stockwell, **Chemistry and biology**, 11 (2004):1489-1493.

7. M. Zovko, B. Zorc, M. J. M. Takac, B. Metelko, and P. Novak, Croatica **Chemica Acta**, 76,(2003):335-341.

8. C. Ramminger, D. Zim, V. R. Lando, V. Fassina and A. L. Monteiro, J. **Braz. Chem Soc.** 11,(2000):105-111.

9. S. V. Bhandarkar, and S. H. Neau, Electronic **J. Biotechnology** 3 ,(2000) :195-201.

10. M. Zovko, M. Barbaric, B. Zorc, A. Hafner, J. F. Grcic, **Acta Pharm**. 55 ,(2005):169- 176.

11. G. Kumaraswamy, N. Jena, M. N. V. Sastry, and G. Ramakrishna **ARKIVOC** , 94**,** (2005):53-58.

12. P. Koihe, J. Khandare, O. Pillai, S. Kannan, M. L. Lai, and R. Kannan, **Pharmace. Research**, 21,(2004):2185-2195.

13. P.Sears and C.Wong, **Proc.Natl. Acad. Sci. USA**, 93,(1996):12086-12093.

14. A. P. Lam, **Tichnical Report**, 2 ,(1998):1-19