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PREPARATION AND CHARACTERIZATION OF MEDICAL COMPOUNDS OF ESTERS

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ABSTRACT : The research involves the preparation of previously unprepared esters compounds, which have been characterized by measurement of fusion degree, infrared spectrum (FT_IR) and magnetic resonance spectrum (1HNMR).

1. **Synthesis Of hexyl 1-((2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate.**
2. **Synthesis Of butyl 1-((2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate**

Key words : Candesartan, ^{13}C- NMR, FTIR, ^{1}H-NMR, direct esterification.

INTRODUCTION

Candesartan

Candesartan Cilexetil (CC) prodrug is quickly and fully biaoactivated by hydrolysis of the ester when the ester link to produce active Can throughout absorption from the gastrointestinal tract (GI) McClellan Oral administration of can reveals poor bioavailability (Ishizuka *et al*, 2013).

Increased blood pressure is one of the world's leading causes of disability and death. Annually, a number of 7.6 million premature fatalities and 92 million of disabilities, keeping blood pressure under control and preventing complications such as; damage of the eye, kidney failure, stroke and coronary heart disease, are considered the primary goals for hypertension treatment. The United States in April 2002 OM for treating hypertension The study was approved by the Food and Drug Administration (FDA). In an expanding class, the seventh of antihypertensive agents is known as receptor blockers of angiotensin II (Wright *et al*, 2007). The drug functions by inhibiting the impacts of angiotensin II, a powerful vasoconstrictor and one of the main cardiovascular and renal disease contributors. OM is a prodrug that contains an ester moiety that is quickly and entirely cleaved during absorption from the gastrointestinal tract to release the active metabolite olmesartan. The potential benefits of this drug involve one-day dosage, a lack of significant backward reactions, cost-effective and a well-tolerated side-effect profile (Guang *et al*, 2012).

Natural esters

Natural esters are found in many fruits, flowers and vegetables, and they are responsible for the pleasant smell, taste and aroma. These esters are fairly volatile, as a result of their low molecular weights. Aroma or fragrance is a chemical compound that has a scent or perfume. Aroma of oranges, for example, contains 30 different esters along with carboxylic acids, aldehydes, alcohols, ketones and hydrocarbons. Examples of natural esters (Surburg and Panten, 2016).

Structure and Preparation Esters

Esters are carboxylic acid derivatives that occur by adding an "ether" moiety (-OR) instead of (OH) group part of COOH group:

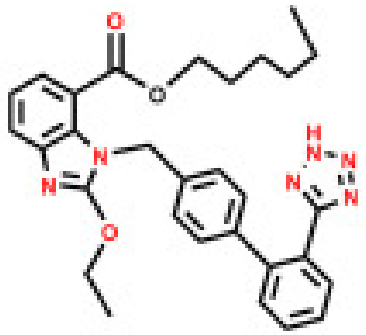
The replacing process mentioned above eliminates the parent structure's (acid) acidic feature forming a non-acidic compounds (esters) (neutral but polar somewhat). Moreover, Esters can be even more classified as aliphatic, aromatic or cyclic (called "lactones") based on their overall composition as demonstrated in the examples given in Fig. 2.

The functionality of ester does not create an asymmetry center and therefore does not result in optical and geometric isomerism. The functionality of ester (carbonyl and ether oxygen) consists of sp2 hybridized carbon so that it is not possible to be chiral, thus Free rotation is observed around Ethers possess geometric isomers and bonds, it is also not feasible the center of sp2 (Carey and Sundberg, 2007).

MATERIALS AND METHODS

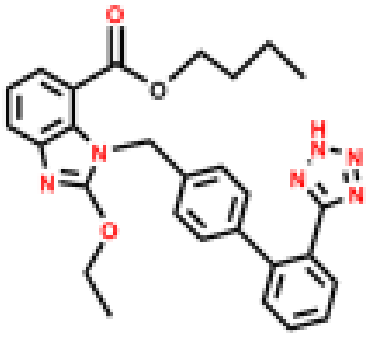
Direct Esterification

Synthesis of (E1)



This compound was synthesized according to the method: 0.2 g Candesartan was dissolved in 8 mL of acetone, after that 0.15 g potassium carbonate was added In the room the same temperature and stir to 2 hours. Then 1 mL of Hexanol was added in the drops form. The analytical data for compounds is summarized as below: (E1) [115,116]. Yield 75%, m.p 135-140°C, Molecular Weight: 608.73, IR: (cm^{-1}) : 1705, (C=O), 1356, (C=N), 2935, 2829 (CH aliph.), 1610 (C=C), 1282(C - O) 1240 (O – C – O) (Satturwar *et al*, 2007).

Synthesis of (E2)



This compound was synthesized according to the method : 0.2 g of Candesartan was dissolved in 8 mL of acetone, after that 0.1 g potassium carbonate was added In the room the same temperature and stir to for 2 hours. Then 1 mL of butanol was added in the drops form. The analytical data for compounds is summarized as below: (E2). yield 80%, m.p 155-160°C, Molecular Weight: 580.68, IR: (cm-1) : 3419 (OH), 1705, (C=O), 1346, (C=N), 2935, 2829 (CH aliph.), 1620 (C=C), 1282(C - O) 1240 (O – C – O) (Satturwar *et al*, 2007).

RESULTS AND DISCUSION

Characterization of compounds (E_1, E_2)

The direct esterification method was used to prepare the compounds by dissolving the carboxylic acid by using polar solvent and other factors to ensure the conversion of carboxyl group to carbonyl ester. 75% of the E_1 compound was obtained by dissolving the carboxylic acid in acetone, also another factor as potassium carbonate (K_2CO_3) and hexanol was used to complete the ester

Table 1 : The main candesartan drugs have been reported to interact with.

Drug	Interaction
Amiloride	Increased risk of hyperkalemia
Drospirenone	Increased risk of hyperkalemia
Lithium	The ARB increases serum levels of lithium
Potassium	Increased risk of hyperkalemia
Spironolactone	Increased risk of hyperkalemia
Tobramycin	Increased risk of nephrotoxicity
Trandolapril	The angiotensin II receptor blocker, Candesartan, may increase the adverse effects of Trandolapril.
Treprostinil	Additive hypotensive effect. Monitor antihypertensive therapy during concomitant use.
Triamterene	Increased risk of hyperkalemia

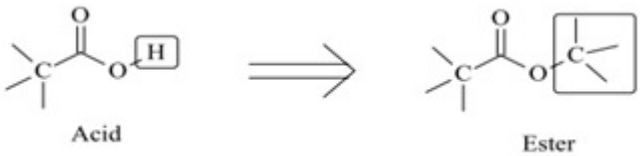


Fig. 1 : Conversion acid to ester by O'fallon *et al* (2007).

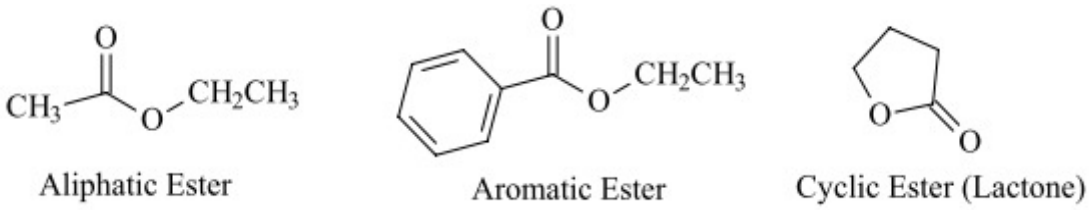
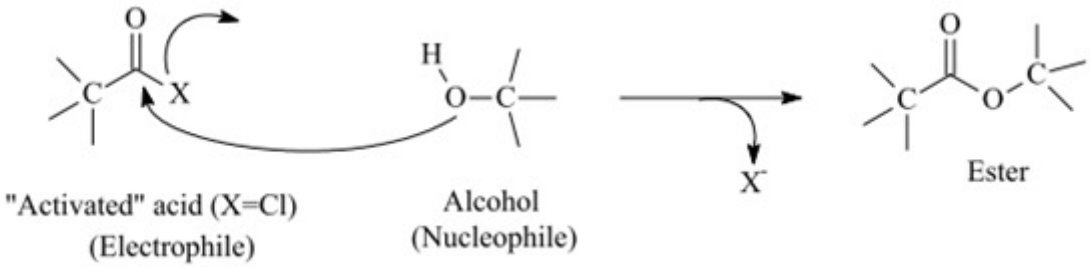


Fig. 2 : Type of esters by Dang *et al* (2012).



Scheme 1 : Mechanism formation of Esters.

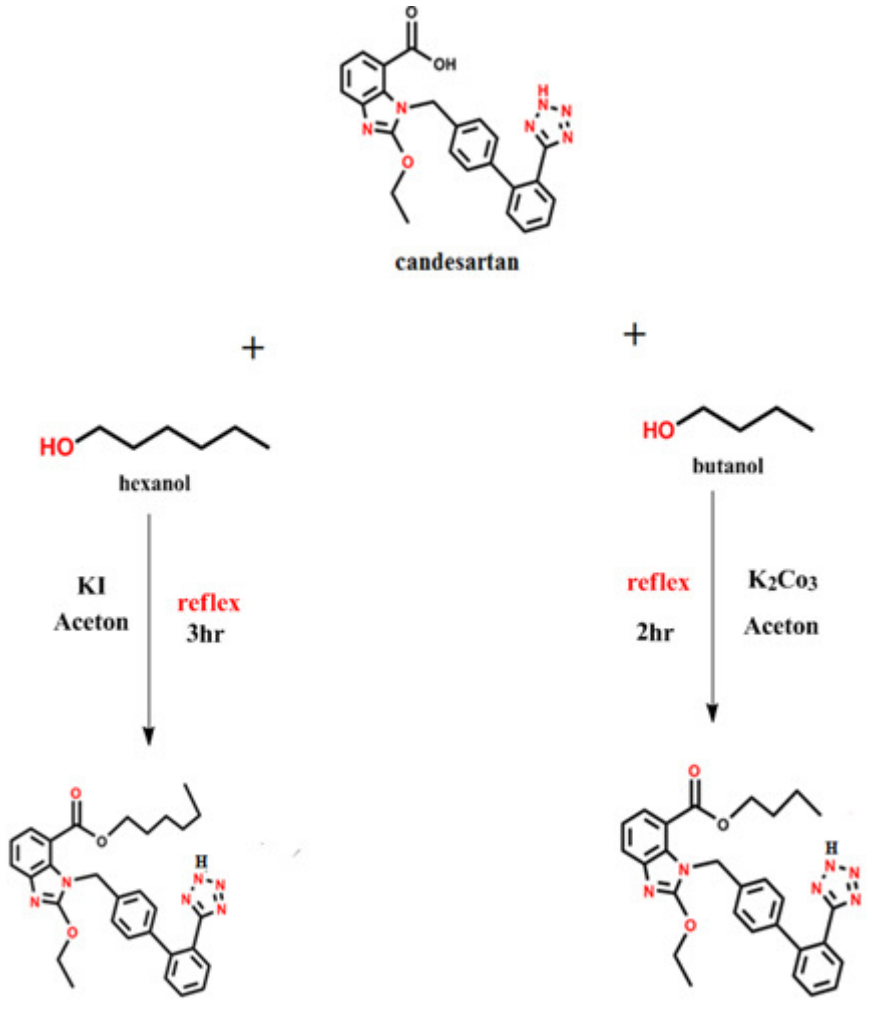


Fig. 3 : General scheme for synthesis compounds (E_1-E_2).

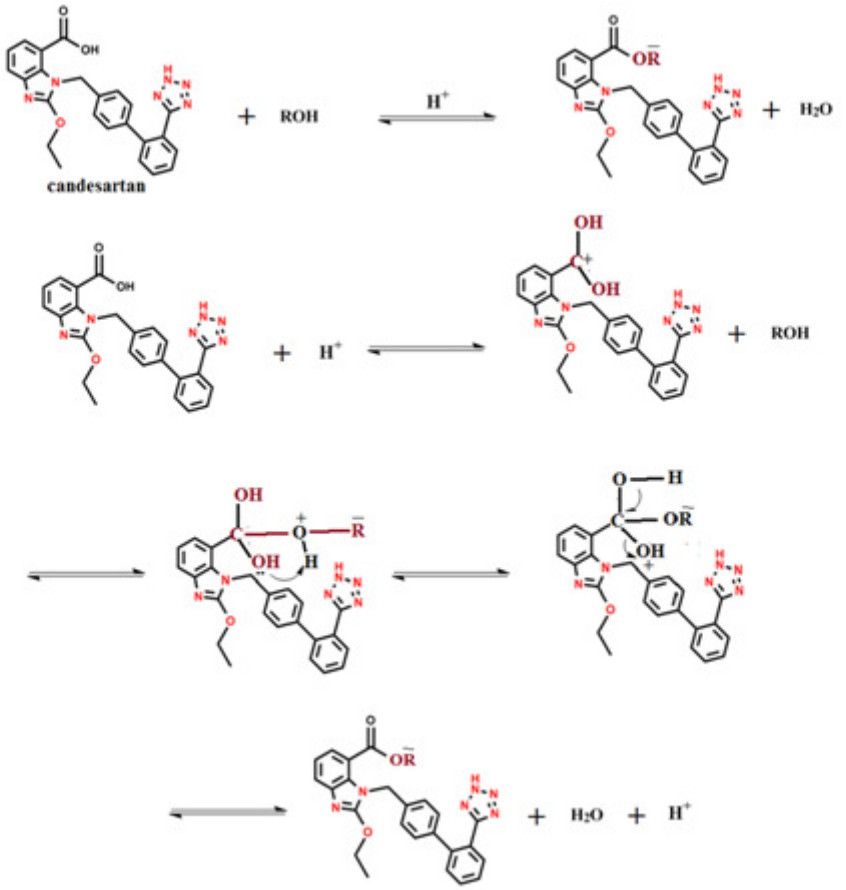


Fig. 4 : Mechanism formation of ester.

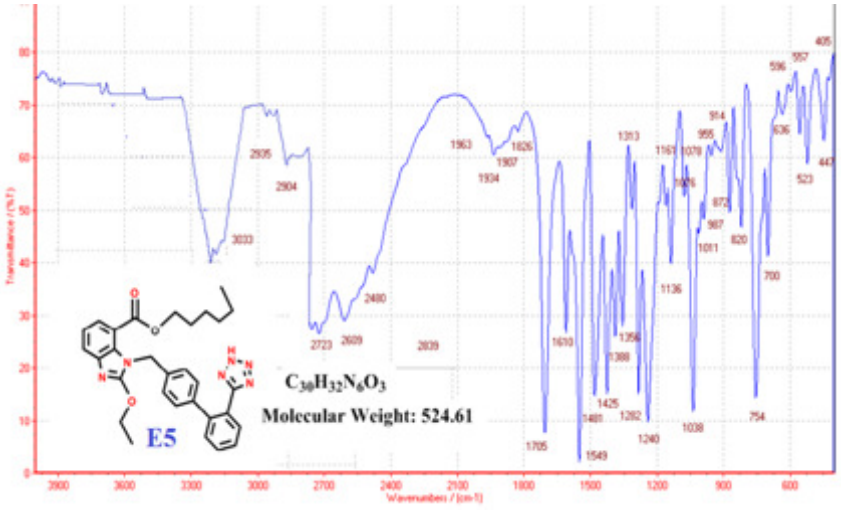


Fig. 5 : FT-IR E1.

process. In addition of the characterization of the melting point of E_5, which reached (135–140°C). This is a positive indication of the decrease of the temperature of the compound compared to the carboxylic acid with a melting point (180 °C). This proves the success of the test, which confirms with the previous literature.

The yield of the compound E_1 had very limited quantity, which led to the identification of the types of tests and did not test the characterization of pharmaceutical reaction. The compound was characterized by infrared radiation, where the compound showed an absorption set of 1705 cm^{-1} (Goyal and Suleria, 2019).

(E1) Yield (75 %.) FT-IR (d., cm^{-1}) : 3312 (CH), 1705.5 (C=0),. 'H NMR (DMSO2.489 ppm). 1.75-1.70 (8H, m, $4CH_2$), 3.34-3.38 (4H, $2CH_2$) 4.25(1H, s, CH),

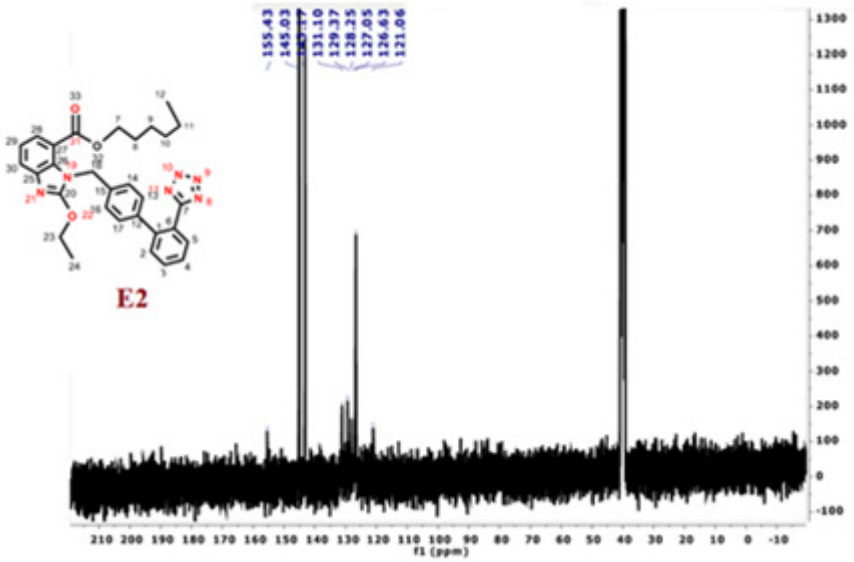


Fig. 6 : 13C-NMR spectrum for compound E1.

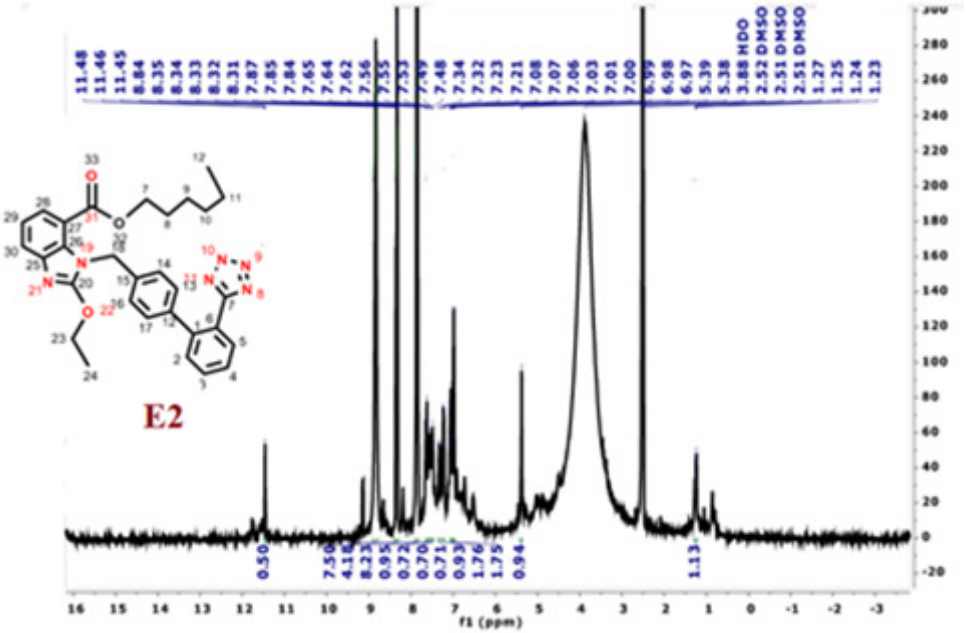


Fig. 7 : ^{1}H-NMR E_1.

4.57 (1H, s, CH), 7.26 (1H., s, arH), 13C NMR (DMSO-d6, 8 ppm): 40.60 (CH_2)), arC: [123.75 (CH), 122.10 (CH), 126.85 (CH_2), 140.02 (C), 139.85 (C)],), 145.52 (tatriazole C-4), 155.23 (C=O) (Cebeci *et al*, 2019; Jansson and Kay, 2019).

The yield of the compound E_2 was 75%, which is relatively considered a limited quantity compared to thionyl chloride method, which led to use the preceding method. E_6 compound was achieved by dissolving the carboxylic acid in acetone, also another factor as potassium carbonate (K_2CO_3) and butanol, which were used to complete the ester process.

The compound was characterized by infrared radiation, where the compound showed an absorption set of 1705 cm^{-1}, the melting point of E_2, which reached (155-160°C) and light yellow color appeared (Cebeci *et al*, 2019; Jansson and Kay, 2019).

(E2) Yield 80 % FT-IR (D. cm^{-1}) : 3312 (CH-H), 1701.1 (C=O),. 'H NMR (DMS0-2.489 p p m): .1.22-1.25 (10H, m, 5CH_2), 3.30-3.40 (6H, m, 3CH_2) 4.25 (1H, s, CH), 4.58 (1H, s, CH), 7.26 (1H, S, arH), 7.51 (1H, S, arH), 13C NMR (DMSO-d6, 8 ppm): 40.60 (CH2), 68.63 (CH), ar C: [122.10 (CH), 123.75 (CH), 126.85 (CH), 139.02 (C), 140.85 (C)], 146.52 (tetriazole C-4), 164.23 (C=O) (Cebeci *et al*, 2019; Jansson and Kay, 2019).

CONCLUSION

1. New esters compounds were prepared

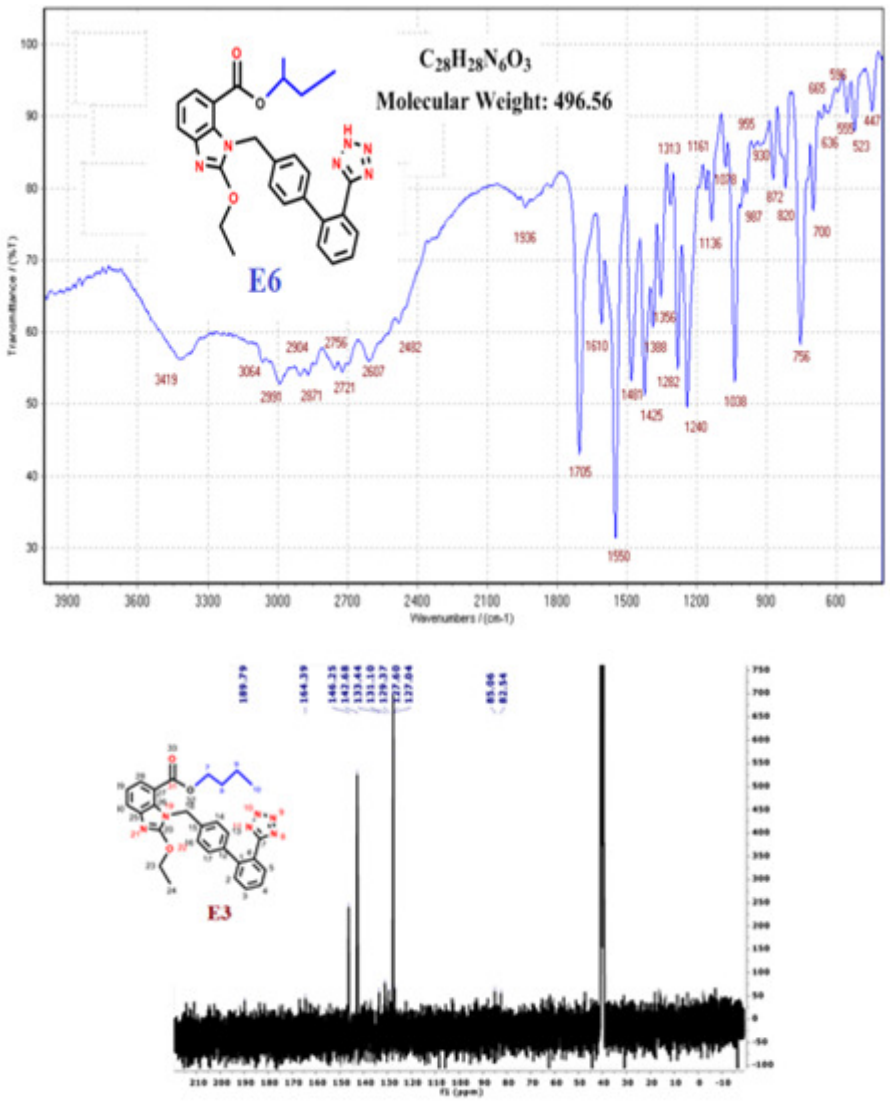


Fig. 8 : ^{13}C-NMR spectrum for compound E_2.

Fig. 9 : ^{1}H-NMR spectrum for compound E_2.

2. Structure properties of new compounds esters were studied

3. The results of the studies of the compounds prepared in the research plan were consistent with the theoretical framework of the research.

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