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INNOVATIVE SYNTHESIS OF DERIVATIVES OF 4-ETHYLBENZOIC ACID AND 4-ETHYLCYCLOHEXANECARBOXYLIC ACID

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Abstract:

This research aims to prepare new derivatives of 4-ethylbenzoic acid and 4-ethylcyclohexanecarboxylic acid using a variety of organic reactions including amine esterification and hydrogenation. First, 4-ethylbenzoic acid was prepared by oxidation of 4-ethyltoluene with potassium permanganate in basic medium, and then this compound was hydrogenated to obtain 4-ethylcyclohexanecarboxylic acid. Then, ester and amine derivatives were prepared by substitution reactions using catalysts to modify the chemical properties of the resulting compounds. The chemical structures of the prepared compounds were confirmed by elemental analysis (CHN) and using infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy techniques, which showed that the analytical data were consistent with the expected structures. The results in previous studies indicate that derivatives containing amino groups may possess strong antibacterial properties. This research is a step towards exploring the pharmaceutical and chemical applications of these acid derivatives, as the prepared compounds can be used in developing drugs or chemicals with improved properties. It also opens the way for further studies related to the biological and chemical activity of these compounds in the future.

Keywords: 4-Ethylbenzoic**,** 4-ethylcyclohexanecarboxylic acid, pharmaceutical industry, catalytic agents.

تخليق مبتكر لمشتقات حمض 4-إيثيل بنزويك وحمض 4-إيثيل سيكلوهكسان كاربوكسيليك

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الملخص:

يهدف هذا البحث إلى تحضير مشتقات جديدة من حمض 4-إيثيل بنزويك وحمض 4-إيثيل سيكلوهكسان كاربوكسيليك باستخدام مجموعة متنوعة من التفاعلات العضوية بما في ذلك استرة الأمين والهدرجة .أولاً، تم تحضير حمض 4-إيثيل بنزويك بأكسدة 4-إيثيل تولوين مع برمنجنات البوتاسيوم في وسط قاعدي، ثم تمت هدرجة هذا المركب للحصول على حمض 4-إيثيل سيكلوهكسان كاربوكسيليك .بعد ذلك، تم تحضير مشتقات الإستر والأمين عن طريق تفاعلات الاستبدال باستخدام المحفزات لتعديل الخصائص الكيميائية للمركبات الناتجة .تم تأكيد التركيب الكيميائي للمركبات المحضرة من خلال التحليل العنصري (CHN) واستخدام تقنيات التحليل الطيفي بالأشعة تحت الحمراء (IR) والرنين النووي المغناطيسي (NMR)، والتي أظهرت أن البيانات التحليلية كانت متسقة مع التركيب المتوقع . وتشير النتائج في الدراسات السابقة إلى أن المشتقات التي تحتوي على مجموعات أمينية قد تمتلك خصائص مضادة للبكتيريا قوية . ويعد هذا البحث خطوة نحو استكشاف التطبيقات الصيدلانية والكيميائية لهذه المشتقات الحمضية، حيث يمكن استخدام المركبات المحضرة في تطوير الأدوية أو المواد الكيميائية ذات الخصائص المحسنة، كما يفتح الطريق لمزيد من الدراسات المتعلقة بالنشاط البيولوجي والكيميائي لهذه المركبات في المستقبل.

الكلمات المفتاحية: 4-إيثيل بنزويك, حمض 4-إيثيل سيكلوهكسان كاربوكسيليك, صناعة الأدوية, عوامل محفزة.

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1. Introduction:

Benzoic acid is an organic hydrocarbon acid and is inexpensive in its crude form. This acid can be hydrogenated into several compounds, including cyclohexanecarboxylic acid, which is an important product of the acid and is used as an organic intermediate. This compound and its derivatives, such as cyclohexyl-methylcarbamate and *trans*-4-isopropylcyclohexyl carboxylic acid, are used in the synthesis of many chemical and pharmaceutical products.

Hongjun Wang and Fengyu Zhao said, “Hydrogenation of benzoic acid (BA) is an important industrial reaction as its product cyclohexanecarboxylic acid (CCA) is a very important and excellent chemical or pharmaceutical intermediate. The production of cyclohexanecarboxylic acid by catalytic hydrogenation of benzoic acid is well known, but it endures some disadvantages in both technical and economic aspects, which inhibit their application on a commercial scale. Cyclohexanecarboxylic acid can be produced from hydrogenation of molten benzoic acid without any solvent, but the reaction temperature and pressure are relatively high" [1]. The hydrogenation of aromatic carboxylic acids is a very versatile reaction as it contains aromatic ring and carboxylic group which can be hydrogenated. And selective hydrogenation of benzoic acid to cyclohexane carboxylic acid can be obtained by using Ni-Zr-B amorphous alloy catalyst with 90.6% selectivity [2]. Methods have been developed for the synthesizing derivatives of 4-ethylbenzoic and 4-ethylcyclohexane-carboxylic acids using liquid-phase catalytic oxidation and hydrogenation. Esters and *N*- aryl amides were obtained based on the acid chloride of 4-ethylbenzoic acid, and the corresponding *N*- aryl amides were obtained based on the acid chloride of 4-ethylcyclohexanecarboxylic acid. Derivatives of 4-ethylbenzoic and 4-ethylcyclohexanecarboxylic acids can serve as raw materials for the creation of new drugs, being of interest to the pharmaceutical industry. *Trans* -Isomers of 4-ethylcyclohexa-carboxylic acid and its derivatives can be used as synthons for liquid crystalline compositions [3,4]. 4-Ethylbenzoic acid is obtained by acylation of ethyl benzene with acetyl chloride followed by oxidation of the ketone group with alkali metal hypobromites [5]. Methods for the preparation of *trans* -4-ethylcyclohexacarboxylic acid are limited. The preparation of a wide range of alkyl benzoic acids containing tertiary and secondary hydrogen atoms in the α-position of the alkyl group became possible thanks to the methods we developed for liquid-phase selective oxidation and hydrogenation of aromatic compounds. 4-Ethylbenzoic acid (I) was obtained by selective oxidation of the methyl group of para- ethyltoluene with oxygen in acetic acid in the presence of an initiator - acetaldehyde and a catalyst - cobalt acetate (II) with a concentration above 0.1 mol/l. At high concentrations acetate cobalt (II) there is an inversion of the reactivity of alkyl groups during the oxidation of alkyl aromatic hydrocarbons: in acetic acid, the methyl group in 4-ethyltoluene reacts 1.7 times faster than the ethyl group, and 7.6 times faster than the isopropyl group in 4 isopropyl toluene [6] . The oxidation of hydrocarbons by metal-oxo species has received much attention in recent years because of its fundamental interest and its relevance to a number of industrial and biological processes. The oxidation of toluene by CrO_2Cl_2 in cyclohexane solution also occurs by hydrogen atom transfer [7]. K. van der Wiel, B.J. van den Berg said: “The partial oxidation of toluene is among the most extensively investigated systems because it has been chosen as a model reaction for the study of oxidation kinetics” [8]. R. A. Sheldon and J. K. Kochi said, “Concerning the mechanisms of toluene oxidation, it is well known that dioxygen, with its triplet ground spin state, does not react easily with hydrocarbons (i.e. toluene) at mild conditions since they exist in a singlet ground state. One could therefore initiate an auto-oxidation if a hydrocarbon radical is produced by breaking a C–H bond since the radical would then react rapidly with triplet dioxygen at room temperature” [9].

2. Expremental:

NMR spectra ^1H recorded on a Bruker spectrometer AC -200 P with an operating frequency of 200 MHz in deuterated $CDCl_3$, and TMS as an internal standard - hexamethyldisiloxane. IR spectra were measured on an IKS A-301 instrument for samples in the form of a suspension in Vaseline oil. Elemental analyses were performed using a Perkin–Elmer 2400 CHN elemental analyzer. All Solvents used were dried according to standard procedures.

4-Ethylbenzoic acid (Ia). 8 g of 4-ethyltoluene was added to a mixture of 1.18 g of $Co(OAc)_2$. $4H_2O$ and 60 ml of acetic acid. Then 1 ml of acetaldehyde was added and oxygen was supplied at a rate of 3.2 l/h. This moment was considered the beginning of the reaction. During the reaction at 95 ^{o} C, 1 ml of acetaldehyde was added 5 times after every hour. After the completion of the reaction, by-products of the process were distilled off from the oxidate. The remainder was poured into ice water. The precipitate that formed was filtered off and dried in vacuum at 80 ^{o}C. We obtained 4.9 g (60 %) of acid (Ia), heat of fusion 196 ^{o} C.

4-Ethylcyclohexacarboxylic acid (IX), 20 g of acid (Ia) was converted into a potassium salt (up to pH 13-14) by the action of a 10% KOH solution, placed in a reactor, then 2 g of RNC-5 catalyst was added to the reactor and hydrogen was supplied to a pressure of 3410-4900 kPa. The temperature in the reactor rose to 150 ^{o}C, and hydrogenation was carried out at this temperature. The end of hydrogenation was determined by the moment the hydrogen pressure in the reactor dropped. At the end of the reaction, acid (IX) was released from the hydrogenate by acidifying it with 10% hydrochloric acid. The precipitate that formed was filtered off and dried. The yield of4-ethylcyclohexanecarboxylic acid (IX) (a mixture *of cis and trans* isomers in a ratio of 3:2) was 95%.

4-Biphenyl-4-ethylbenzoate (III) was obtained by reacting acid chloride (II) with 4-hydroxybiphenyl, heat of fusion 175-185 ^{o}C. IR spectrum (cm^{-1}) 1720 (C=O), 1280, 1200 (C-O-C). Found, %: C 83.39; H 6.10; O 10.54. $C_{21}H_{18}O_2$. _ Calculated, %: C 83.42; H 6.00; O 10.58.

4-Chlorophenyl-4-ethylbenzoate (IV), obtained by reacting acid chloride (II) with 4-chlorophenol, heat of fusion 58-59 ° C. IR spectrum (cm^{-1}): 1738 (C=O), 1260, 1200 (C-O-C). ^{1}HNMR spectrum (δ, ppm): 1.18 t (CH_3), 2.65 k (CH_2), 6.99 d (2H, m- Cl), 7.16 d (2H , *o*-C_2H_5), 7.24 (H, *m*-Cl), 7.97 (2H , *m*-C_2H_5). Found, %: C 69.0; H 4.95; Cl 13.5. C_{15}H13ClO_2. _ Calculated, %: C 69.10; H 5.03; Cl 13.6.

4-(*tert*-Octyl)phenyl-4-ethylbenzoate (V) was obtained by reacting acid chloride (II) with 4- *tert*-octylphenyl, heat of fusion 148-152 ° C. IR spectrum (cm^{-1}): 1730 (C=O), 1260, 1200 (C-O-C). Found, %: C 81.5; H 8.90. $C_{23}H_{30}O_2$. _ Calculated, %: C 81.61; H 8.93.

8-Quinolyl-4-ethyl benzoate (VI) was obtained by reacting acid chloride (II) with 8-hydroxyquinoline, heat of fusion 153-163 °C. IR spectrum (cm^{-1}): 1738 (C=O), 1265, 1230 (C-O-C). ^{1}HNMR spectrum (δ, ppm): 1.20 t (CH_3), 2.65 k (CH_2), 7.27 d (2H, *o*-C_2H_5), 7.40-8, 13 m (5H, $H_{quinoline}$), 8.18 d (2H , *m*-C_2H_5), 8.80 k (1H, CH=N). Found, %: C 77.10; H 5.40; N 5.25. $C_{17}H_{15}NO_2$. Calculated, %: C 77.26; H 5.034; N 5.30.

4-Pentanoil- ethylbenzoate (VII) was obtained by reacting acid chloride (II) with 4-valerylphenyl, heat of fusion 95-103 °C. IR spectrum (cm^{-1}): 1720 (C=O, ester), 1680 (C=O, ketone) 1270, 1220, 1180 (C-O-C). Found, %: C 77.28; H 7.20. $C_{20}H_{22}O_3$. _ Calculated, %: C 77.39; H 7.14.

N-(4-Hydroxyphenyl)-4-ethylbenzamide (VIII) was obtained by reacting acid chloride (II) with 4-aminophenil, heat of fusion 204-206 °C. IR spectrum (cm^{-1}): 3370 (OH), 3300 (NH), 1640 (C=O, I_{amide}), 1235 (C-O), 1530 (NH, II_{amide}). Found, %: C 74.52; H 6.15; N 5.78. $C_{15}H_{15}NO_2$. Calculated, %: C 74.67; H 6.27; N 5.81.

N-(4-Bromophenyl)-4-ethylcyclohexanecarboxamide (XI) was obtained by reacting acid chloride (X) with 4-bromoaniline, heat of fusion 85-88 °C.

IR spectrum (cm^{-1}): 3250 (NH), 1645 (C=O, I_{amide}), 1520 (NH, II_{amide}).. ^{1}HNMR spectrum (δ, ppm): 0.92 t (CH_3), 1.23 m (C_2H_5), 1.38 m ($C\underline{H}C_2H_5$), 1.55 m ($2C\underline{H}_2CHCH_2$), 1.88 m ($2C\underline{H}_2CHCO$, 2, 27 t (CHCO), 7.34 d (2H, *m*-Br), 7.54 d (2H, *o*-Br), 9.88 s (NH). Found, %: C 57.55; H 6.60; Br 25.71; N 4.55. $C_{15}H_{20}BrNO$. _Calculated, %: C 58.07; H 6.50; Br 25.76; N 4.52.

N-(4-Methoxyphenyl)-4-ethylcyclohexanecarboxamide (XII) was obtained by reacting acid chloride (X) with 4-methoxyaniline, heat of fusion 154-161 ^oC. IR spectrum (cm^{-1}): 3280 (NH), 1650 (C=O I_{amide}), 1250, 1035 (OCH_3) 1530 (NH, II_{amide}). Found, %: C 73.45; H 8.85; N 5.41. $C_{16}H_{23}NO_2$. Calculated, %: C 73.53; H 8.85; N 5.36.

N-(4-Tolyl)-4-ethylcyclohexanecarboxamide(XIII) was obtained by reacting acid chloride (X) with 4-toluidine, heat of fusion 144-152 ^oC. IRspectrum (cm^{-1}): 3290 (NH), 1650 (C= O, I_{amide}), 1530 (NH, II_{amide}). ^{1}HNMR spectrum (δ, ppm): 0.92 t (CH_3), 1.23 m (C_2H_5), 1.38 m ($CH\underline{C}_2H_5$), 1.53 m ($2C\underline{H}_2CHCH_2$), 1.85 m ($2C\underline{H}_2CHCO$), 2.17 s (CH_3, Ph), 2.23 t (CHCO), 6.97 d (2H, *o*-CH_3), 7.41 (2H, m -CH_3), 9.65 (NH). Found, %: C 78.71; H 9.41; N 5.68. $C_{16}H_{23}NO$. Calculated, %: C 78.32; H 9.45; N 5.71.

N-(2-Naphthyl)-4-ethylcyclohexanecarboxamide (XIV) was obtained by reacting acid chloride (X) with 2-naphthylamine, heat of fusion 157-158 ^oC. IR spectrum (cm^{-1}): 3260 (NH), 1650 (C=O, I_{amide}), 1540 (NH, II_{amide}). ^{1}HNMR spectrum (δ, ppm): 0.92 t (CH_3), 1.23 m (C_2H_5), 1.39 m ($CH\underline{C}_2H_5$), 1.55 m ($2C\underline{H}_2$ $CHCH_2$), 1.88 m ($2C\underline{H}_2CHCO$), 2.27 t (CHCO), 7.26-8.24 m (7H, H naphthalene), 9.88 (NH). Found, %: C 80.95; H 8.18; N 5.68. $C_{19}H_{23}NO$. Calculated, %: C 81.10; H 7.69; N 5. 09.

N-(4-Carboxyphenyl)-4-ethylcyclohexanecarboxamide (XV) was obtained by reacting acid chloride (X) with 4-aminobenzoic acid, heat of fusion 165 °C. IR spectrum (cm^{-1}): 3300 (NH), 2250, 2650 (OH), 1680 (C=O), 1640 (C=O, I_{amide}), 1525 (NH, II_{amide}), 940 (OH). Found, %: C 69.75; H 7.61; N 5.11. $C_{16}H_{21}NO_3$. Calculated, %: C 69.71; H 7.69; N 5.09.

3. Result And Discussion:

This is explained by the reaction proceeding through the mechanism of one-electron oxidation with the intermediate formation of radical ion transition states in the limiting stage of the process, which makes it possible to carry out the targeted synthesis of alkyl benzoic acids by oxidation of the methyl group to a carboxyl group with a high degree of selectivity.

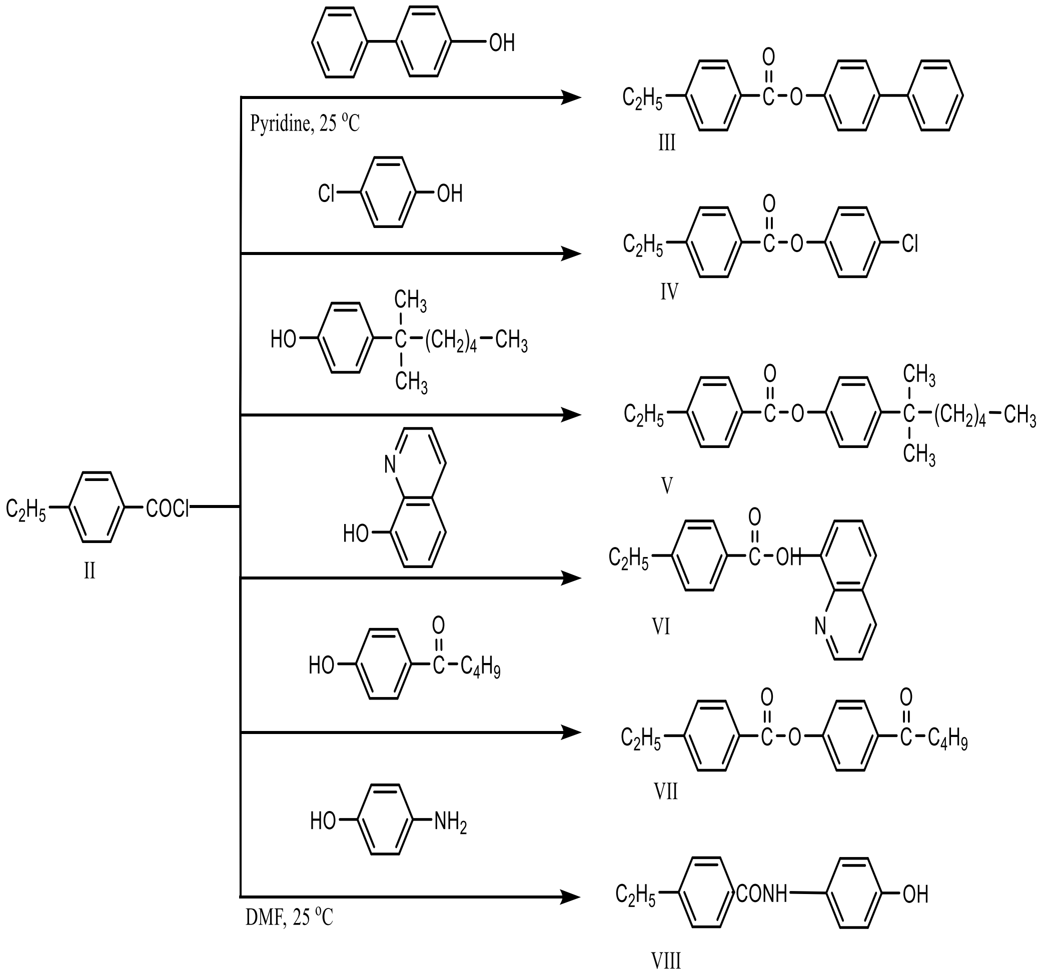
$$4\text{-}RC_4H_4Me + 1/2\ O_2 \xrightarrow[AcOH,\ MeCHO]{Co(OAc)_2 \cdot H_2O} 4\text{-}RC_4H_4CO_2H + H_2O$$

Ia,b

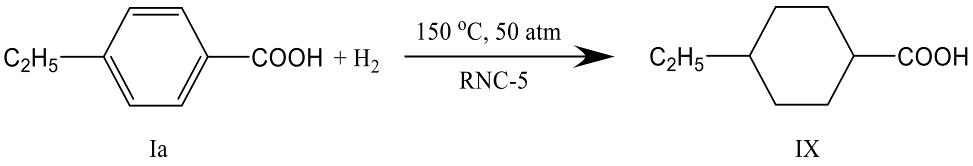
R = Et (a), i-Pr (b)

The action of thionyl chloride on acid (Ia) its acid chloride (II) was obtained, on the basis of which esters and N - acrylamides were synthesized using methods known in the literature. The composition and structure of compounds (I-VIII) were established using elemental analysis data from IR and ^{1}HNMR spectroscopy.

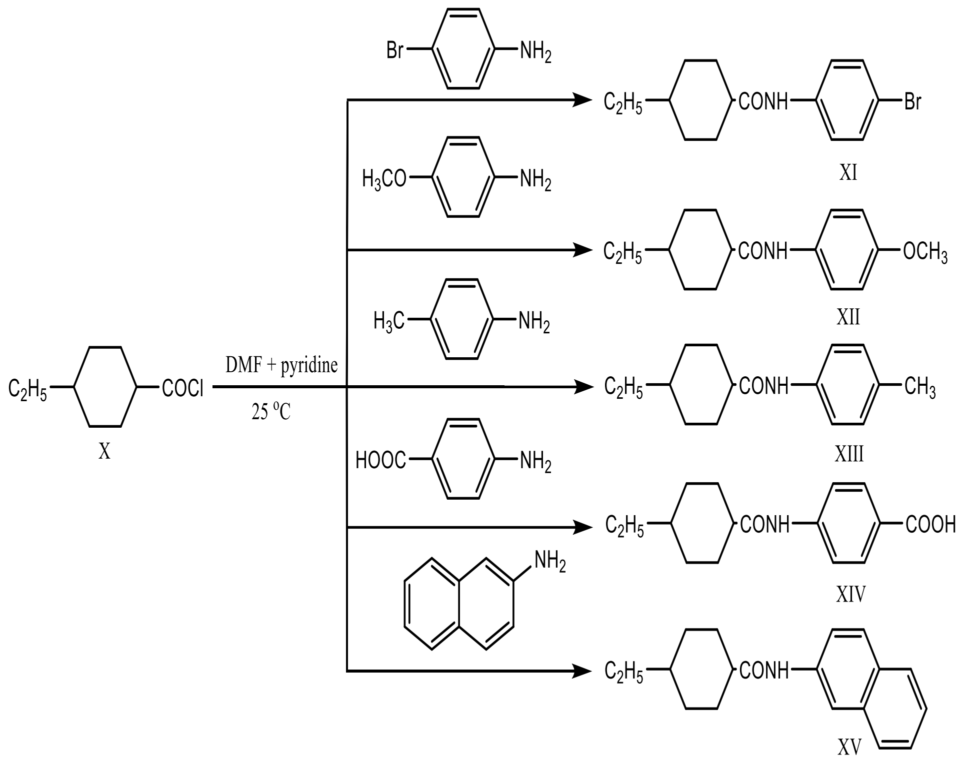
Trans-4-ethylcyclohexanecarboxylic acid and its derivatives are of significant interest. Interest in these compounds is due to the appearance of a cyclohexane fragment in the structure of the molecule, which leads to the manifestation of new unique properties in the compounds. The production of trans-alkylcyclohexanecarboxylic acids became accessible thanks to the method we developed of catalytic selective hydrogenation on the RNC-5 catalyst (ruthenium-nickel supported on coal) and the organization of pilot production of acids on this basis.



4-Ethylcyclohexacarboxylic acid (IX) was obtained by hydrogenation of 4-ethylbenzoic acid (Ia) with hydrogen under pressure in an aqueous-alkaline medium on an RNC -5 catalyst [10].



The reaction of thionyl chloride with acid (IX) resulted in the formation of its acid chloride (X). This intermediate was subsequently utilized to synthesize the corresponding *N*-aryl amides (XI–XV) through well-known methods.



The composition and structural characteristics of compounds (XI-XV) were carefully determined using infrared (IR) spectroscopy and proton nuclear magnetic resonance (1H NMR) spectroscopy, in conjunction with elemental analysis. These analytical techniques provided critical insights into the molecular structures, functional groups, and overall purity of the compounds, allowing for a comprehensive understanding of their chemical properties.

4. Conclusion:

Derivatives of 4-ethylbenzoic acid and 4-ethylcyclohexanecarboxylic acid were prepared by various organic reactions and the chemical structures of the prepared compounds were confirmed using different analyses, which showed that the analytical data were consistent with the expected structures.

The prepared compounds can be used in the development of pharmaceutical industry and some chemicals with improved properties. These compounds can be developed to open the way for further studies related to the biological and chemical activity of these compounds in the future.

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