DJS Vol. 45(1) (2022) pp. 141-150 - ISSN: 1012-5965

Delta Journal of Science

Available online at **https://djs.journals.ekb.eg/**

Research Article **CHEMISTRY**

Asymmetric synthesis of α-alkylated carbonyl compounds and their biological applications

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Received: 26/12/2022 accepted: 23/1/2023

KEY WORDS

Asymmetric reagents, diastereomers, enantiomers, HPLC.

ABSTRACT

Creation of asymmetric centers is the fundamental basis of asymmetric synthesis as the resulting diastereomers or enantiomers are formed in unequal ratio. This is obtained by the creation of novel asymmetric centers either in a chiral molecule or in molecules already containing asymmetric centers, which lead to formation of new diastereomers in unequal ratio. Biological activity is associated with the interactions of a specific stereoisomer with a biological receptor. The vast majority of commercially produced drugs that include one or more stereocenters, but only one of the stereoisomers may biologically active whilst the other may be ineffective. This study included a novel idea for the synthesis of asymmetric reagents by employing quinazolinone derivative. This quinazolinone was interact with ketone's derivatives, creating quinazolinone Schiff bases which upon deprotonation, subsequently alkylation with alkyl halide led to production of α-alkylated quinazolinone Schiff bases. This Schiff base was then hydrolyzed to give α-alkylated carbonyl compounds that converted to diastereomeric Schiff bases and separated via HPLC using silica gel column. In addition, the target products were tested *in-vitro* against different types of bacteria and fungi.

Introduction

Heterocyclic substances are organic cyclic substances with at least one element in their ring structures other than carbon. Nowadays, heterocyclic compounds pay attention due to their biological activity as many drugs are heterocycles **(Noser *et al*., 2022; Rizk *et al*., 2022; Ibrahim *et al*., 2022).** In order to create quinazolinones, a benzene ring must fuse with 4-pyrimidinone ring. These products are referred to as quinazolin-4(3H)-one. Due to their wide spectrum of biological functions and presence in 200 or more naturally occurring alkaloids, quinazolinones are an important class of fused heterocyclic scaffolds **(Radwan *et al*., 2020; Kshirsagar *et al*., 2015).** In addition, quinazolinones used previously in asymmetric synthesis. **(Noser *et al*., 2020; Rodriguez *et al*., 2022).**

One of the most crucial reactions in organic synthesis and one that has greatly influenced the advancement of organic chemistry as a whole is the creation of a new carbon-carbon bond alpha (α) to a carbonyl group. Ketones are frequently used in this regard. This is unquestionably a result of the variety of enolate chemistry obtained from ketones and the number of substituted ketones (and derivatives) in physiologically active systems. An important topic of study for organic chemists is the creation of new catalytic asymmetric techniques for organic transformations. Alkylation of carbonyl compounds is a particularly advantageous method for forming C-C bonds among many chemical processes **(Cano *et al*., 2017; Song *et al*., 2012).**

It is essential and helpful to prepare enantiomerically pure molecules. Resolution of a racemic mixture and asymmetric synthesis can be used as preparation techniques. It took more than a century of research, to establish the fundamental ideas behind the two categories of methods as they are recognized today. A chiral auxiliary that is momentarily incorporated into the substrate, included in the reagent, or present in the catalyst is required for asymmetric synthesis. Asymmetric synthesis has been a theory for more than eighty years. Emil Fischer postulated in 1894 that plants produce optically active sugars from carbon dioxide and water through the action of chlorophyll as an asymmetric catalyst **(Kagan *et al*., 2011; ApSimon *et al*., 1979).**

In our previous studies, inter- and intramolecular cyclopropanations of various diazoacetates were attempted using Ru(II)-pheox catalyst and the product was chemically transformed to the corresponding chiral cyclopropyl ketone with high yield with unaltered

enantioselectivity. (**Mandour *et al.*, 2017**) The purpose of this study is to create α-alkylated acids using quinazolinone derivative, and to investigate the impact of temperature and steric hindrance on enantioselectivity.

Experimental

Chemistry

All reagents of analytical quality were purchased from Sigma-Aldrich. All melting points were measured without adjustments on Gallen Kamp melting point equipment. On a Perkin-Elmer FTIR 1430 spectrophotometer, the Fourier transform infrared spectroscopy (FTIR) spectra were captured. On a Bruker AC spectrometer (400 MHz), the ^{1}H nuclear magnetic resonance (NMR) spectra were captured at 25^{o}C in DMSO-d_6, with TMS serving as an internal standard. Chemical shifts were given in parts per million as values, and the ^{13}C NMR was set at 101 MHz. Except where otherwise noted, elemental investigations for C, H, and N were also carried out, and the outcomes were found to be within 0.4% of theoretical values. Thin layer chromatography was employed to monitor the reaction's development. The separation of diastereomers was carried out using the HPLC technique with a silica gel column, eluent, petroleum ether/ ethyl acetate 8:2, F (flow rate =1 mL/ min), detector: UV 254nm.

Synthesis of 3-amino-2-phenylquinazolin-4(3H)-one (2)

According to Alagarsamy's illustration, Compound 2 was prepared. **(Alagarsamy *et al.*, 2003)**

General procedure for the Synthesis of quinazolinone Schiff bases (3 I, II)

A mixture of 3-amino-2-phenylquinazolin-4(*3H*)-one **(2)** (3.5 mmol, 0.83 g), ketones (3.8 mmol), an hydrous magnesium sulphate (4.2 mmol, 0.499 g), few drops of glacial acetic acid in ethanol (20 mL) was refluxed for 16 h (TLC control), finally the reaction mixture was cooled and filtrated.

(Z)-3-(hexan-2-ylideneamino)-2-phenylquinazolin-4(3H)-one (3 I)

White powder, yield 89.6% ; IR (KBr) v/cm^{-1}: 3068 (Arom-H), 2924 (aliph-H), 1661 (C=O), 1566 (C=N); ^{1}H NMR (DMSO-d_6)δ ppm: 0.82 (t, 3H, CH_3), 1.03-1.19 (m, 4H, $2CH_2$), 1.82 (t, 2H, CH_2), 2.04 (s, 3H, CH_3), 7.45-8.16 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 11.70, 17.90, 20.20, 24.07, 39.87, 120.60, 126.56, 127.27, 127.93, 130.02, 130.14, 134.82, 135.42, 147.24, 156.29, 161.74, 169.20 ; elemental analysis [calculated for $C_{20}H_{21}N_3O$ (319.40) : C: 75.21%, H: 6.63%, N: 13.16%] ; founded [C: 74.90%, H: 6.30%, N: 12.76%].

(Z)-3-(pentan-2-ylideneamino)-2-phenylquinazolin-4(3H)-one (3 II)

White powder, yield 88 % ; IR (KBr) v/cm^{-1}: 3067 (Arom-H), 2922 (aliph-H), 1660 (C=O), 1565 (C=N); ^{1}H NMR (DMSO-d$_6$)δ ppm: 1.02 (t, 3H, CH_3), 1.20 (m, 2H, CH_2), 1.88 (t, 2H, CH_3), 2.03 (s, 3H, CH_3), 7.46-7.81 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d$_6$) δppm: 11.90, 14.00, 20.10, 39.80, 120.60, 126.57, 127.27, 127.94, 130.02, 130.14, 134.82, 135.42, 147.25, 156.33, 161.75, 169.80; elemental analysis [calculated for ($C_{19}H_{19}N_3O$: C: 74.73%, H: 6.27%, N: 13.76%] ; founded [C: 74.50%, H: 5.90% , N: 13.4%].

Synthesis of 3-(3-ethylhexan-2-ylideneamino)-2-phenylquinazolin-4(3H)-one (4a-d)

A mixture of compounds **3I, II** (3.5 mmol) was dissolved in THF (20 mL), then adding cyclohexyl isopropyl amine (CHIPA) (6.00 mmol, 0.605 mL) at -96 ^{o}C and -80 ^{o}C, after that adding *n*-BuLi (6.00 mmol, 0.383 mL) drop wise with stirring, the reaction mixture still stirred for 1h subsequently adding alkyl halide (7.04 mmol), the reaction mixture leave to stirr over night at room temperature, filtrated of to give **4a-d.**

White powder; yield 75-85%; IR (KBr) v/cm^{-1}: 3067 (Arom-H), 2924 (aliph-H), 1658 (C=O), 1566 (C=N); ^{1}H NMR (DMSO-d$_6$) δ ppm: 0.70 (t, 6H, $2CH_3$), 1.19-1.40 (m, 8H, $4CH_2$), 1.79 (s, 3H, CH_3), 7.46-7.81 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d$_6$) δ ppm: 9.80, 12.20, 19.40, 20.50, 22.80, 28.40, 39.90, 120.61, 126.57, 127.28, 127.93, 130.02, 130.14, 134.83, 147.25, 152.00, 156.32, 161.74, 166.20; elemental analysis [calculated for $C_{22}H_{25}N_3O$ (347.45): C: 76.05%, H: 7.25%, N: 12.09%]; Founded [C: 75.75%, H: 6.85%, N: 11.89%].

Synthesis of 3-ethylhexan-2-one (5a-d)

In 100 mL round bottom flask, a mixture of **4a-d** (0.47mmol) was dissolved in THF (15mL in the presence of methane sulphonic acid (0.30g), after that, the reaction mixture was refluxed for 12 h, then compounds **5a-d** was extracted with methylene chloride.

Yellow liquid; yield 86-88% ; IR (KBr) v/cm^{-1}: 2922 (aliph-H), 1739 (C=O); ^{1}H NMR (DMSO-d$_6$) δ ppm: 0.81 (t, 6H, $2CH_3$), 1.19-1.41 (m, 6H, $3CH_2$), 1.95 (s, 3H, CH_3), 2.19 (m, H, CH); ^{13}C NMR (DMSO-d$_6$) δ ppm: 10.00, 16.00, 17.90, 19.00, 29.00, 31.90, 55.41, 212.00; elemental analysis [calculated for $C_8H_{16}O$ (128.21): C: 74.94%, H: 12.58%]; Founded [C: 74.50%, H: 12.30%].

Synthesis of diastereomeric compounds (6a-d)

In 100mL round bottom flask, reflux a mixture of compound **5a-d** (2.0 ml, 15 mmol), (*R*)-phenyl glycinol (0.2 g, 2.1 mmol), ethanol (20 mL), few drops of glacial acetic acid for 10 h. (TLC control), then extraction the diastereomeric Schiff base **6a-d** using 10 ml methylene chloride.

Yellow Liquid, Yield 84-86%; IR (KBr) v/cm^{-1}: 3460 (OH), 3097 (Arom-H), 2920 (Aliph-H), 1600 (C=N). ^{1}H NMR (DMSO-d_6) δ ppm: 0.82 (t, 6H, $2CH_3$), 1.16-1.24 (m, 7H, $3CH_2$, CH), 1.83 (d, 2H, CH_2), 2.01 (s, 3H, CH_3), 3.43 (s, H, OH), 4.10 (t, 1H, CH), 7.33-7.52 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6) δ ppm: 10.89, 13.86, 20.30, 21.10, 22.50, 29.50, 32.00, 60.44, 77.01, 126.78, 127.90, 128.80, 138.80, 171.47; elemental analysis [calculated for $C_{16}H_{25}NO$ (247.38): C: 77.68%, H: 10.19%, N: 5.66%]; founded [C: 77.43%, H: 10.08%, N: 5.20%].

Separation of compounds 6a-d.

Compounds **6a-d** were separated via silica gel column (250×4.60 mm/Si 60-5 Mm) using HPLC, 1 mL/min (flow rate), petroleum ether: ethyl acetate 8:2 (mobile phase), UV 254 nm (detector)**.**

Biological evaluation

Antimicrobial activity of compounds 5a-d

Detailed methodology of the antimicrobial screening is illustrated by Stylianakis **(Stylianakis *et al*., 2003)**

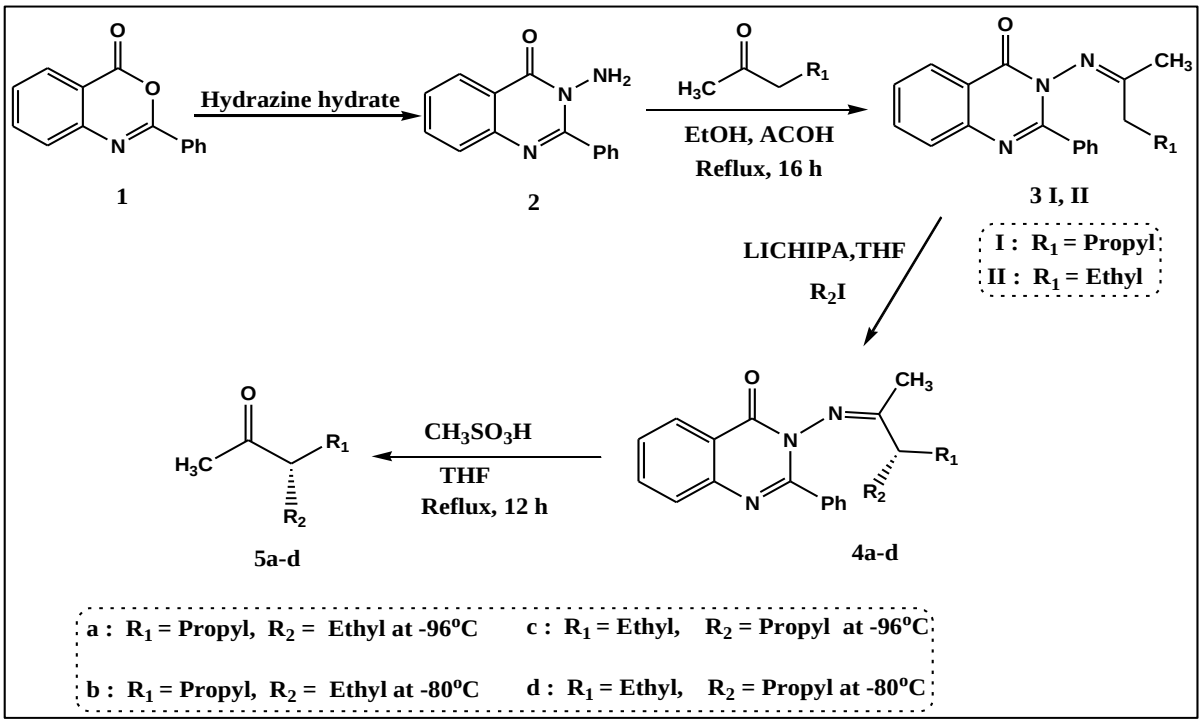
Results and Discussion

The compounds that were synthesized can be seen in **Schemes 1, 2**. **In scheme 1**, compound **1** was reacted with hydrazine hydrated with adding ethanol and few drops of glacial acetic acid to give 3-amino-2-phenylquinazolin-4(3H)-one (**2**) which can be illustrated by spectral analysis, the FT-IR spectra of **2** illustrated the absorptions band of NH_2 group at 3300 cm^{-1}, CO stretching at 1690 cm^{-1} and C=N stretching at 1630 cm^{-1}.

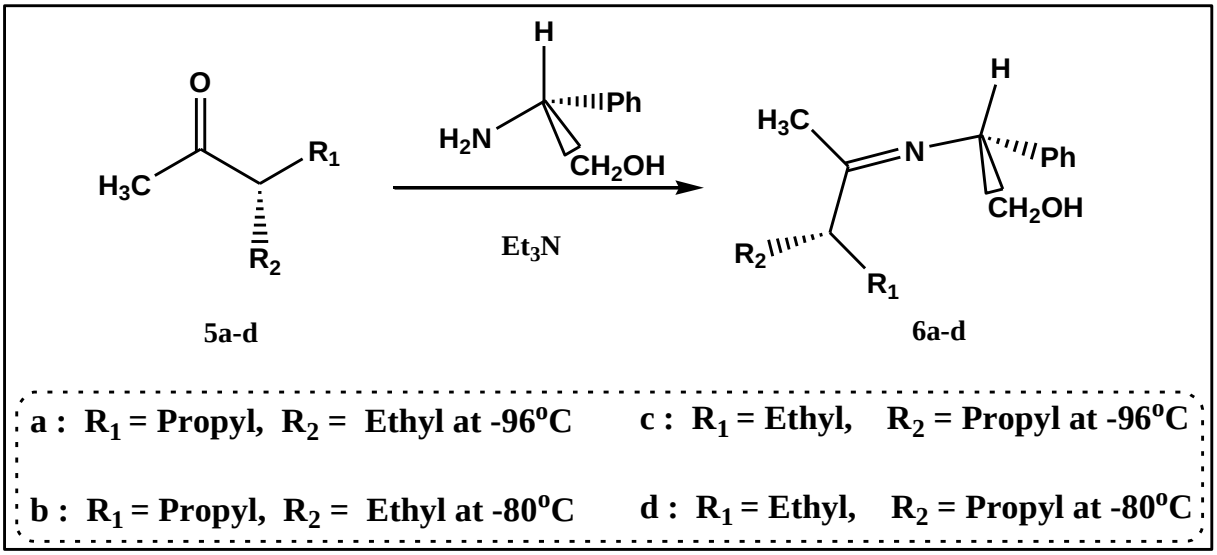
Compound Z-3-(4-hexan-2-ylideneamino) phenyl)-2-phenylquinazolin-4-(3H)-one (**3 I**) was synthesized via reaction of 2-hexanone with compound **2** (**scheme 1**) while compound Z-3-(4-pentan-2-ylideneamino) phenyl)-2-phenylquinazolin-4-(3H)-one (**3 II**) was prepared through the reaction of compound **2** with 2-pentanone in presence of magnesium sulfate and ethanol in acidic medium. The structure of compounds **3 I, II** was illustrated by different spectroscopic techniques. The FT-IR spectrum showed stretching bands at 1565-1566 cm^{-1} corresponding to C=N group and disappearance of NH_2 stretching.

Compounds **3I, II** were deprotonated at different temperatures (-96 ^{o}C and -80 ^{o}C) via adding lithium cyclohexyl isopropyl amine (LICHIPA) subsequently adding alkyl halide to form α-alkylated compounds **4 a-d**. Elemental analysis and spectral data were used to confirm the structure of the synthesized compounds.

Additionally, the hydrolysis of **4a-d** led to formation of α-alkylated carbonyl compound (**5a-d**) as described in **Scheme 1**. Elemental analysis and spectral data were used to confirm the structure of compounds **5a-d**. The FT-IR spectra showed complete loss of C=N stretching and appearance of CO stretching at 1739 $^{-1}$cm.



Scheme 1: Synthesis of compounds **2-5**



Scheme 2: Synthesis of compounds **6a-d**

Furthermore, **in Scheme 2**, the reaction of compound **5a-d** with optically active ethanolic solution of (*R*)-phenyl glycinol led to formation of compound **6a-d.**

As shown in **Table (1)**, compounds **6a-d** were separated using HPLC using a silica gel column, and the results described two factors which effect on both the value of enantiomeric purity and our configuration. the first one is the effect of the temperature of deprotonation of compounds **3I, II** during the synthesis of compounds **4a-d** which showed that compound **6a** gave the highest value of enantiomeric purity with 94% e.e that prepared at -96 ^{o}C. the second one is the effect of order of addition of alkyl group which affect on the configuration of the target product as we found that compounds **6a, b** have (*S)* configuration while compound **6 c, d** have (*R*) configuration.

Anti-microbial activity

Due to the importance of asymmetric synthesis in biological applications as we found that sometimes one isomer gives high biological activities while the other isomer gives no activity as described by Selim **(Selim *et al*., 2014).**

In-vitro antibacterial activity of the produced compounds **5b** (*S*-isomer) and **5c** (*R*-isomer) were evaluated against a panel of two gramme positive bacteria (*Staphylococcus aurous*, *Bacillus subtilis*), and one Gram-negative bacteria (*Escherichia coli*). Additionally, their effectiveness against fungi was assessed (*Candida albicans, Aspergillus flavus*). The reference medications Ampicillin and Clotrimazole were used to compare the diameter of the inhibition zones of the newly created compounds. Compound **5b (*S*-isomer)** showed better results than compound **5c (*R*-isomer) (Table (2), Fig. (1)** Proving that the antibacterial activity was significantly influenced when the configuration of the produced compounds changed from *(S)* configuration to (*R*) configuration, proving the importance of asymmetric synthesis.

Table (1): Effect of temperature in enantiomeric excess

Compound	Temperature (^{o}C)	Enantiomeric excess (e.e) (%)	Configuration
6a	-96	94	S
6b	-80	93	S
6c	-96	88	R
6d	-80	91	R

Table 2. antimicrobial activities of compounds **5b, c** against different tested bacteria and fungi

Compound	*E. coli*	*S. aureus*	*Bacillus subtilis*	*Candida albicans*	*Aspergillus flavus*
	inhibition zone (mm)	inhibition zone (mm)	inhibition zone (mm)	inhibition zone (mm)	inhibition zone (mm)
5b	7	12	11	10	8
5c	4	9	8	9	6
Ampicillin	23	21	23	----	----
Clotrimazole	----	----	----	24	25

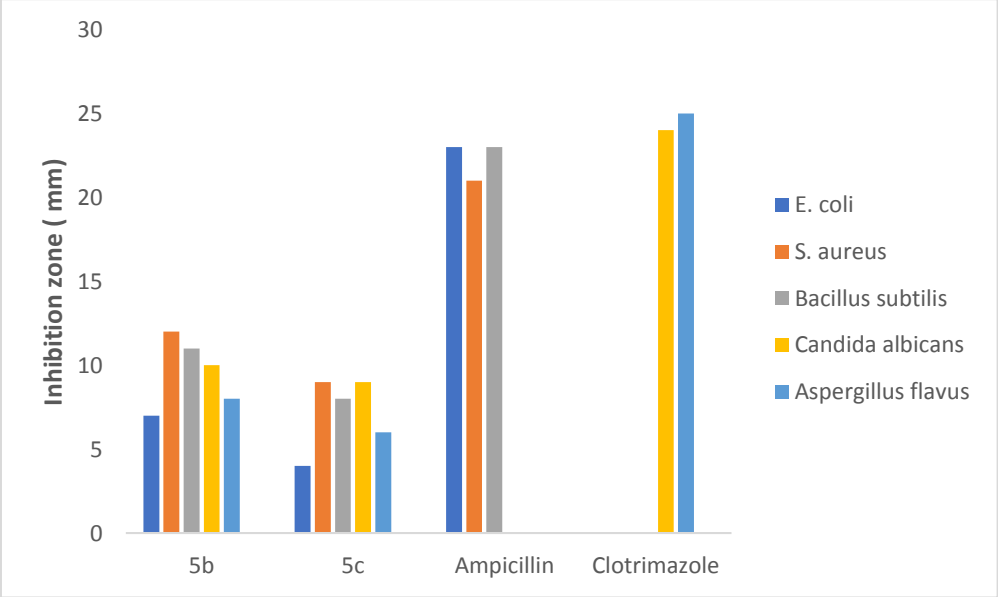


Figure 1. antimicrobial activities of compounds **5b, c** against different tested bacteria and fungi

Conclusion

In conclusion, the quinazolinone asymmetric reagent enabled the development of an effective technique for the asymmetric synthesis of α-alkylated carbonyl compounds. The results described the effect of deprotonation temperature during the synthesis of compounds **4a-d** which showed that compound **6a** gave the highest value of enantiomeric purity.

In addition, the order of addition of alkyl group effect on the configuration of the target product as we found that compounds **6a, b** have (*S*) configuration while compound **6c, d** have (*R*) configuration. Additionally, the synthetic compounds were tested *in-vitro* against several types of bacteria and fungi demonstrating that only (*S*) isomer give a good result.

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التوليف الغير متماثل لمركبات الفا الكيل الكربونيل وتطبيقاتها البيولوجية

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يعتبرانشاء المراكز الغير متماثلة هو المبدأ الاساسي للتوليف الغير متماثل حيث يتم تحضير الايزوميرات بنسبة غير متماثلة. يتم الحصول على هذا من خلال إنشاء مراكز غير متماثلة جديدة إما في جزيء غير متماثل أو في جزيئات تحتوي بالفعل على مراكز غير متماثلة ، مما يؤدي إلى تكوين دياستيريوميرات جديدة بنسب غير متساوية. الغالبية العظمى من الأدوية المنتجة تجاريًا تحتوى على واحد أو أكثر من الايزوميرات المختلفة ، ولكن واحدًا فقط من الأيزومرات الغير متماثلة فراغيا قد يكون نشطًا بيولوجيًا بينما الآخر قد يكون غير فعال. تضمنت هذه الدراسة فكرة جديدة لتخليق الفا الكيل الكربونيل فى صورة نقية ضوئيا باستخدام مشتق الكينازولينون. تم تحديد نسبة النقاء الضوئى عبر جهاز HPLC. بالإضافة إلى دراسة تاثير بعض المركبات المحضره ضد أنواع مختلفة من البكتيريا والفطريات واعطت نتائج جيدة.

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