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Research Article

CHEMISTRY

Enantioselective synthesis, characterization and biological evaluation of α-alkylated acids

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Enantiomerically pure, Asymmetric synthesis, chiral auxiliaries, enantiomeric excess

ABSTRACT

All living organisms produce only one enantiomer so we found that all natural compounds are presented in enantiomerically pure form. Asymmetric synthesis is highly spread in pharmaceutical industry because enantiomerically pure drugs are highly applicable. Most of traditional drugs that used for treatment of many diseases are usually undergo racemic modifications of two enantiomers, and the side effect of these drugs is due to presence of the un wanted enantiomer. The asymmetric synthesis has become very important to increase the enantioselectivity of synthesized compounds via different methods. This study demonstrated the enantioselective synthesis of (*S*)-2-ethylpentanoic acid (**5a, b**) and (*R*)- 2-ethylpentanoic acid (**5c, d**) using quinazolinone derivative **(2)** as chiral auxiliaries. The enantiomeric excess was determined via HPLC using silica gel column and ranging from 90-98 depending on different factors. Some of the synthesized compounds were examined *in-vitro* against different types of bacteria and fungi and give a good result.

Introduction

Nowadays, heterocyclic compounds merit attention for a variety of reasons, the most important of which is their biological activity. In addition, many drugs are heterocycles **(Atmaram *et al*., 2022; Noser *et al*., 2022; Jul *et al*., 2022; Rizk *et al*., 2022; Ibrahim *et al*., 2022).** Quinazolinones are a type of fused heterocyclic that have high biological activities, including anticancer, anticonvulsant and hypotensive actions **(Liu *et al*., 2022; Noser *et al*., 2021)**. Quinazolinones are pharmacological activities that have attracted a lot of interest from medicinal chemists for the creation of new therapies or drug candidates **(Wahan *et al*., 2022)**. quinazolinone and other biologically active pharmacophores may be used to create hybrid analogues that will produce medications with greater potency and decreased drug resistance, and due to the moiety of quinazolinone is found in a variety of synthetic and natural product-based medications that are used in clinical settings to treat a wide range of medical problems **(Noser *et al*., 2020; Li *et al*., 2022)**. The synthesis of a large number of enantiomerically pure compounds can be controlled and enabled by chiral auxiliaries, which are typically regarded as dependable substances with well-known configurations **(Diaz *et al*., 2019)**. The development and expansion of asymmetric synthesis have, in fact, been greatly influenced by the development of efficient chiral auxiliaries. Amino acids, carbohydrates, terpenes, and other naturally occurring substances are the sources from which the majority of chiral auxiliaries are obtained. They may be utilized in the same form as when they were separated or after certain structural alterations. **(Diaz *et al*., 2019; Baś *et al*., 2022)** Asymmetric synthesis is now recognized as the ideal method for the enantioselective synthesis of desired targets, particularly those exhibiting biological activity **(Ziarani *et al*., 2018; Selim *et al*., 2014).**

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 analytical grade reagents were acquired from Sigma-Aldrich and utilized without additional purification unless otherwise stated. On Gallenkamp melting point equipment, all melting points were measured without modifications. Using the KBr disc approach, the Fourier transform infrared spectroscopy (FT-IR) spectra were

recorded on a Perkin-Elmer FT-IR 1430 spectrophotometer. The ^{1}H nuclear magnetic resonance (NMR) spectra were recorded at 25 ^{o}C in DMSO-d6 with TMS as an internal standard on a Bruker AC spectrometer (400 MHz), and chemical shifts were reported in parts per million as δ values; ^{13}C NMR was set at 101 MHz. Elemental studies for C, H, and N were also performed, and the results were found to be within 0.4 percent of theoretical values unless otherwise stated. Thin layer chromatography was used to track the reaction's progress.

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

Noser prepared Compound **2** previously **(Noser *et al*., 2020).**

Synthesis of quinazolinone esters (3I, II)

In 100 mL round bottom flask using Dean–Stark trap, compound **2** (3.14 g, 10 mmol), carboxylic acid derivatives (20 mmol), methane sulphonic acid (0.1 g) and 50 mL benzene were heated for 6 h and the reaction process was controlled via thin layer chromatography (TLC), then the products was basified with sodium carbonate, filtered, dried to give compounds **3I, II**.

4-(4-oxo-2-phenylquinazolin-3(4H)-yl) phenyl pentanoate (3I)

Dark brown powder; m.p 200 ^{o}C ; yield 82% ; IR (cm^{-1}) , 3062 (Ar-CH) , 2958 (Aliph-CH), 1665 (CO) ; ^{1}H NMR (DMSO.d_6), δ7.2- 7.82 (m, 13H, Ar) , δ 2.17 (t, 2H, CH_2) , δ 1.04-1.66 (m , 4H , $2CH_2$), δ 0.80 (t, 3H, CH_3); ^{13}C NMR (DMSO.d6), δ 173.006, 165.19, 155.21, 142.17, 132.47, 132.33, 129.36, 179.54, 128.66, 127.54, 123.06, 122.85, 29.006, 22.02, 13.8; Anal. Calculated for $C_{25}H_{22}N_2O_3$ (398.45); C, 75.36%; H, 5.57%; N, 7.01 % Founded; C, 74.96%; H, 5.17%; N, 6.91%.

4-(4-oxo-2-phenylquinazolin-3(4H)-yl) phenyl butyrate (3II)

Brown powder; m.p 235 $^{\circ}C$; Yield 90%; IR (cm^{-1}); 3040 (Ar-CH), 2970 (Aliph-CH), 1664 (CO); $^{1}HNMR$ (DMSO. d_6), δ 7.25 - 7.79 (m, 13H, Ar), δ 2.15 (t, 2H, CH_2), δ 1.29 (m, 2H, CH_2), δ 0.82 (t, 3H, CH_3); 13C NMR (DMSO. d6), δ 172.3, 164, 160.9, 151.3, 147, 133.5, 129.6, 128.9, 128.8, 128.7, 127.4, 126.10, 126.1, 122.4, 122, 120.9, 27.3, 22.2, 13.8; Anal. Calculated for $C_{25}H_{22}N_2O_3$ (384.43); C, 74.98%; H, 5.24 %; N, 7.20%; Founded; C, 74.67%; H, 5.13%; N, 7.08%.

Synthesis of 4-(4-oxo-2- phenylquinazolin-3(4H)-yl) phenyl 2-ethylpentanoate (4a-d)

To a mixture of compound **3I** or **3II** (26.0 mmol) in 20 mL THF, Cyclohexyl iso propyl amine (CHIPA) (0.4 mL, 3.9 mmol) was added drop by drop at both -96°C and -80°C, followed by addition of *n*-butyl lithium (*n*-BuLi) (0.6 mL, 5.9 mmol) and stirring for 1 h. finally alkyl

halide (7.0 mmol) was added drop by drop at -40°C and stirred for 10 h, the desired product was then filtered off and dried.

Brown powder; m.p 230 ^{o}C; yield 82%; IR (cm^{-1}), 3062 (Ar-CH), 2958 (Aliph-CH), 1665 (CO); ^{1}H NMR (DMSO.d_6), δ 7.40 -7.62 (m, 13H, Ar), δ 2.31 (m, 1H, CH), δ 1.33-1.52 (m, 6H, $3CH_2$), δ 0.96 (t, 6H, $2CH_3$); ^{13}C NMR (DMSO.d_6); δ 176, 164, 160.9, 151.3, 133.5, 129.6, 128.9, 127.4, 122.4, 122.0, 120.9; Anal. calculated for $C_{27}H_{26}N_2O_3$ (426.51); C, 76.03%, H, 6.14 %, N, 6.57%; Founded; C, 75.9 %; H; 5.48 %; N; 6.37 %.

Synthesis of 2-ethylpentanoic acid (5a-d)

Compound **4a-d** (11.09 g, 26 mmol) and methanesulphonic acid (0.1 g) in Tetrahydrofuran (THF) (20 mL) were heated for 12 h. Finally, the reaction mixture was cooled, filtered, then compound **5a-d** was extracted by dichloromethane (20 mL), dried to give pale yellow liquid.

IR (cm^{-1}); 3477 (OH), 1647 (CO); ^{1}H NMR (DMSO.d_6); δ 11 (s, 1H, COOH), δ 3.61 (m, 1H, CH), δ 1.33-1.39 (m, 6H, $3CH_2$); ^{13}C NMR (DMSO.d_6), δ 178.5, 40.5, 34.7, 16.6, 14.1, 7.16; Anal. Calculated for $C_7H_{14}O_2$ (130.18); C, 64.58%; H, 10.84%; Founded; C, 64.18 %; H, 10.54 %.

Synthesis of 2-ethyl-N-((*R*)-2-hydroxy-1-phenylethyl) pentanamide (6a-d)

A mixture of **5a-d** (1.30 g, 10 mmol) and thionyl chloride (3.62 mL, 50 mmol) were heated for 4 h to give the acid chloride which then dissolved in 10 mL THF and added drop by drop to a solution of (*R*)-phenyl glycinol (1.50 g, 11 mmol) in10 mL THF, then the reaction mixture was refluxed for 5 h, the diastereomeric amide (**6a-d)** was then extracted via dichloromethane, washed with 1 N HCl and 1N NaOH, filtered and dried.

IR (cm^{-1}) 3415 (NH), 3240 (OH), 1725 (CO); ^{1}H NMR (DMSO.d_6); δ 8.0 (s ,1H , NH), δ 7.25 - 7.79 (m, 5H, Ar), δ 4.91 (t, 1H, CH), δ 3.69 (d, 2H, CH_2), δ 2.3 (m , 1H, CH), δ 2.0 (s, 1H, OH), δ 1.24 -1.29 (m, 6H, $3CH_2$), δ 0.88 (t, 6H , $2CH_3$); ^{13}C NMR (DMSO.d_6); δ 175.1, 128.6, 127.0, 126.8, 64.8, 55.6, 35.6, 19.3, 17.7, 13.5 ; Anal . Calculated for $C_{15}H_{23}NO_2$ (249.35); C, 72.25 %; H, 9.30 %; N, 5.62%; Founded; C, 72.85 %; H, 9.1 %; N, 5.52 %.

Separation of diastereomeric amides (6a-d)

By using high performance liquid chromatography (HPLC), compounds **6a-d** were separated via 250× 4.6 mm/Si 60 5 Mm silica gel column, detector: UV 254 nm, mobile phase: Petroleum ether: Ethyl acetate 8:2 with 1 mL/min flow rate.

Results and discussion

Compound **2** was synthesized through the reaction of compound **1** with *P*- amino phenol in acidic medium (**Scheme 1**). The structure of **2** was established based on elemental analyses and spectral data. The FT-IR spectrum revealed absorption band at 3062 cm^{-1} characteristics of the (Ar-CH), 2958 cm^{-1} for (Aliph-CH) and at 1665 cm^{-1} due to CO group.

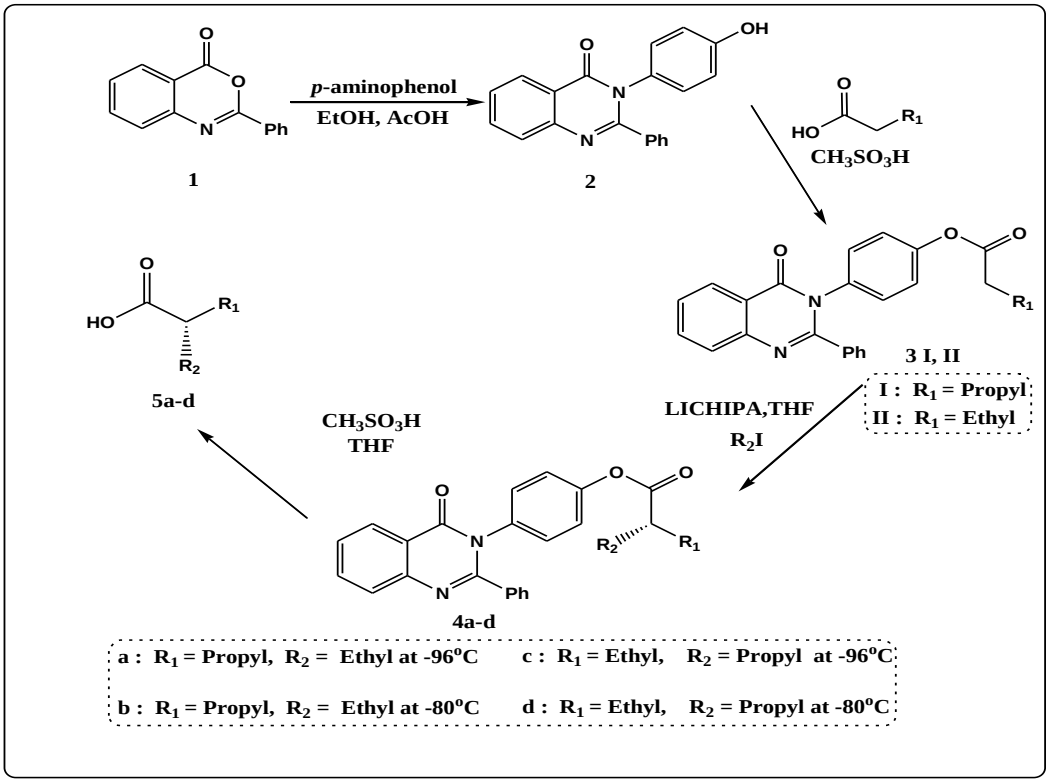
As illustrated in **Scheme 1**, the reaction of **2** with pentanoic acid with the aid of methanesulphonic acid using dean stark trap gave compound **3I**. Its FT-IR spectrum revealed absorption at 1660 cm^{-1} which belonged to CO and a complete loss of OH stretching. Its ^1H NMR spectrum revealed the presence of triplet signals at δ 2.17 ppm characteristic of CH_2 protons, multiple signals at δ 1.04 - 1.66 ppm assigned to $2CH_2$ protons and triplet signals at δ 0.80 ppm assigned to CH_3 protons. In addition, the reaction of **2** with butyric acid led to formation of compound **3II** whose structure was confirmed as described in experimental part.

The asymmetric α-alkylation of **3I** was occurred through deprotonation with lithium cyclohexyl iso propyl amine (LICHIPA) at -96^oC and -80^oC followed by addition of ethyl iodide to give compounds **4a, b** respectively. Similarly, the α-alkylation of compound **3II** was occurred through deprotonation with LICHIPA at -96^oC and -80^oC followed by alkylation with propyliodide to give **4c, d** respectively.

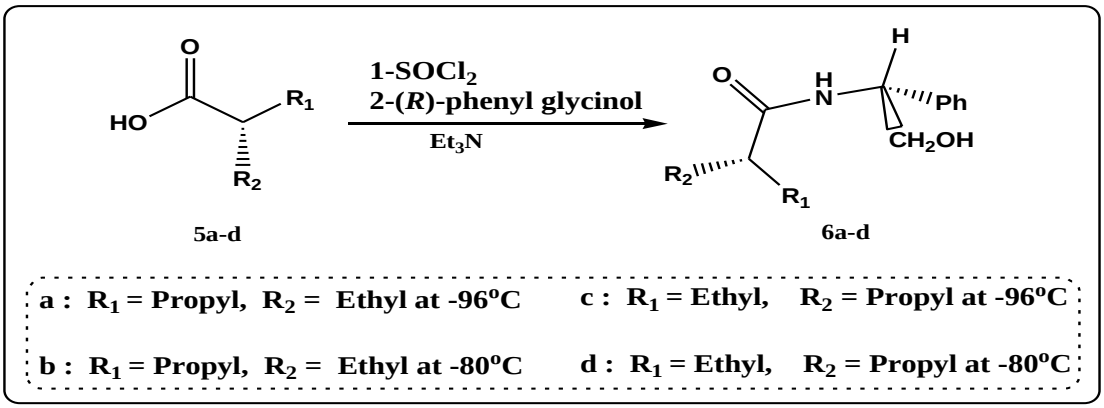
Further modification of compound **4a, b** with methanesulphonic acid led to formation of (*S*)-2-ethylpentanoic acid (**5a, b**). While the hydrolysis of **4c, d** gave (*R*)- 2-ethylpentanoic acid (**5c, d**). The IR spectrum revealed band at 1725 cm^{-1} corresponding to CO group and at 3400 cm^{-1} corresponding to OH group.

The treatment of compound **5a, b** with thionyl chloride give (*S*)-2-ethylpentanoyl chloride which added to optically active (*R*) phenyl glycinol to give **6a, b** respectively. In addition, the reaction of **5c, d** with thionyl chloride give (*R*)-2-ethylpentanoyl chloride which on reaction with (*R*) phenyl glycinol give diastereomeric amides **6c, d** respectively. (**Scheme 2**).

As illustrated in Table (1), diastereomers 6a-d were separated using HPLC with silica gel column, and they give different values of enantiomeric purity with different configuration. We founded that compound 6c gave the highest enantiomeric value with 98% e.e that prepared at -96^oC with R configuration.



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



Scheme 2: Synthesis of compounds 6a-d

Table (1): The enantiomeric excess of compounds **6a-d** at different temperatures.

Compound	Temperature	Configuration	Enantiomeric excess (e.e) (%)
6a	-96 ˚C	S	96
6b	-80 ˚C	S	93
6c	-96 ˚C	R	98
6d	-80 ˚C	R	90

Anti-microbial activity

Compounds **5a (*S*-isomer) and 5c (*R*-isomer)** were tested *in-vitro* antibacterial activities against four types of bacteria (*Proteus mirabilis, Kluyvera ascorbata, Pantoea agglomerans* and *Klepsiela ornithinolytica)*. Also, they were examined for their antifungal activity against (*Candida parapsilosis*).

The diameter of inhibition zones of compounds **5a, c** were compared with the reference drugs Ampicillin and Clotrimazole. All compounds showed a good antifungal activity against *Candida parapsilosis* but showed no antibacterial activity against all tested types of bacteria. As mentioned in **Table (2).**

Table (2): Inhibition zones (mm) of compounds **5a, c**

Compound	***Proteus mirabilis***	***Kluyvera ascorbata***	***Pantoea agglomerans***	***Klepsiela ornithinolytica***	***Candida parapsilosis***
	Inhibition zone (mm)	Inhibition zone (mm)	Inhibition zone (mm)	Inhibition zone (mm)	Inhibition zone (mm)
5c	NA	NA	NA	NA	1.2
5a	NA	NA	NA	NA	1.5

(NA): No Activity

Conclusion

In summary, an efficient method for enantioselective synthesis of α-alkylated acids was achieved via 3-(4-hydroxyphenyl)-2-phenylquinazolin-4(3H)-one as chiral auxiliaries. Various factors affecting on the configuration and enantiomeric purity of the synthesized compounds as order of addition of alkyl group and deprotonation temperature were described. In addition, some of the synthesized α-alkylated acids were tested *in-vitro* against different types of bacteria and fungi and give different results.

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التوليف الانتقائي والتوصيف والتقييم البيولوجي لالفا الكيل الحمض

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من المعروف ان جميع الكائنات الحية تقوم بانتاج ايزومير واحدًا فقط ، لذلك وجدنا أن جميع المركبات الطبيعية يتم تقديمها في شكل نقي ضوئيا. ينتشر التخليق الغير متماثل بشكل كبير في صناعة الادوية المختلفة لأن الأدوية النقية ضوئيا قابلة للتطبيق بشكل كبير. عادة ما تخضع معظم الأدوية التقليدية التي تستخدم لعلاج العديد من الأمراض للتعديلات بحيث يكون الناتج عباره عن ايزومير واحد فقط حيث يرجع التأثير الجانبي لهذه الأدوية إلى وجود احد الايزومير غير المرغوب فيه. أصبح التخليق غير المتماثل مهمًا جدًا لزيادة نسبة النقاء الضوئى للمركبات المختلفة. أوضحت هذه الدراسة التوليف الانتقائي للحمض (S)-2-ethylpentanoic و (R)-2-ethylpentanoic acid باستخدام مشتق الكينازولينون كعامل مساعد للتخليق الغير متماثل. تم تحديد نسبة النقاء الضوئى لهذه العينات عن طريق جهاز HPLC والتى تتراوح نسبتها من ٩٠ الى ٩٨% اعتمادًا على العوامل المختلفة التى تم عرضها خلال البحث. ايضا تم دراسة تأثير بعض المركبات المحضرة ضد أنواع مختلفة من البكتيريا والفطريات واعطت نتائج جيدة.