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SYNTHESIS AND CHARACTERIZATION OF SOME NEW PYRROLIDINE-2,5-DIONE DERIVATIVES USING ANTHRANILIC ACID

تحضير وتشخيص بعض المشتقات الجديدة للبرولدين5,2-ثنائي الكيتون بواسطة استخدام حامض الانثرانلك

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ABSTRACT

Depending on anthranilic acid as a starting material tow amides 1 and 2 were synthesized through the nucleophilic substitution reaction with both *2*-chloro- benzoylchloride and acetic anhydride respectively, which were then reacted with hydrazine hydrate or phenylenediamine respectively to produce the corresponding quinazolinones (3 and 4). These compounds in turn were reacted with phthalic anhydride and succinic anhydrides respectively to produce the corresponding pyrrolidine-2,5-dione derivatives (5, 6, 7 and 8). All the synthesized compounds were characterized through their physical properties and identified using the spectroscopic techniques which is: FT- IR and ^{1}H NMR techniques.

الخلاصــة

بالاعتماد على حامض الانثرانلك كمادة اولية تم تحضير الامايدين 1و2 من خلال تفاعل التعويض النيوكليوفيلي مع كل من مركب 2-كلورو كلوريد البنزويل و انهدريد الخليك على التوالي بعدها تم مفاعلة المركبات 1و2 مع الهيدرازين المائي او مركب بارا فنيلين ثنائي الامين على التوالي لتحضير الكويناز ولينونات المقابة 3و 4 على التوالي والتي بدورها تم مفاعلتها مع كل من انهيدريد الفثاليك والسكسنيك على التوالي فتم تحضير مشتقات البايروليدين ثنائية الكيتون المقابلة 5و6و7و8 على التوالي. جميع المركبات المحضرة تم تشخيصها من خلال صفاتها الفيزياوية ومن خلال استعمال التقنيات الطيفية المتمثلة بتقنية الاشعة تحت الحمراء FT-IR وتقنية الرنين النووي المغناطيسي ^{1}H NMR.

INTRODUCTION

Quinazolinones (benzopyrimidine derivative) are a large family of heterocyclic compounds with wide spectrum of biological activities, including: anti-cancer, anti convulsant, anti-inflammatory, anti-tubercular and anti-bacterial activities [1-7].

A highly employed method for synthesis of 4(3*H*)-quinazolinone is based on the condensation of anthranilic acid with acetic anhydride [8]. This reaction containing ring closure to afford the corresponding 1,3-benzoxazin-4-one (benzoxazinone) which will be treated with different amines to give 4(3*H*)-quinazolinone derivatives[9]. 4(3*H*)-quinazolinone also can be prepared by acylation with acid chloride or anhydride followed by ring closure which done by direct condensation with hydrazine hydrate, phenylhydrazine, or phenylinediamine [10,11].

Pyrrolidine-2,5-dione moiety can be acquired by the reaction of 3-aminoquinazolin-4(3*H*)-one derivatives with different acid anhydrides. The pyrrolidine ring is considered as a source for a broad range of bioactive natural and synthesized products, it presents in large number of pharmaceutical agents, and recently it is used as organocatalysts as well as ligands for a wide range of metal-mediated enantioselective protocols [12].

The present study plans to synthesize some new quinazolinone derivatives that contain pyrrolidine-2,5-dione moiety using anthranilic acid as starting material.

Experimental

Materials:

All chemical materials and solvents were purchased from BDH, Scharlau and Himedia and were used without further purification.

Instruments:

Melting points were measured on a Gallan Kamp MFB-600 Melting point apparatus and were uncorrected. FTIR spectra were recorded as potassium bromide (KBr) disk on FTIR-8400S Fourer Transform Infrared Spectrophotometer "SHIMADZU". ^{1}H NMR spectra were recorded on Burker DMX- 500 NMR (300-600 MHz) Spectrophotometer with using DMSO as a solvent in Jordan University.

Preparation of compound 1 [11]

2-{[(2-chlorophenyl)carbonyl]amino}benzoic acid

2-chlorobenzoylchloride (3.5g, 0.02 mol) was added drop-wise to a stirring solution of anthranilic acid (2.74 g, 0.02 mol) in dry benzene. The mixture was heated for 15 minutes to produce a precipitate which was filtered of, dried and recrystallized from absolute ethanol, as a white solid (70%), mp =200-202^{0}C.

Preparation of compound 2 [13]

2-(acetylamino)benzoic acid

Anthranilic acid (2.74 g, 0.02 mol) was dissolved in acetic anhydride and heated under reflux for 15 minutes. The mixture was cooled to room temperature, poured onto cold water (50 mL) and stirred until the oil was solidified to produce a precipitate which was collected by filtration and washed with cold water (4*50 ml). The precipitated solid was dried as an off white solid, (80%) mp =192- 194^{0}C.

Preparation of compound 3 [14]

3-amino-2-(2-chlorophenyl)quinazolin-4(3*H*)-one

Compound 1 (2.57g, 0.01 mol) was dissolved in hydrazine hydrate (80%) and refluxed for 6 hrs to produce a precipitate, which was collected by filtration,then it was recrystallized from absolute ethanol, as a yellow solid, (65%), mp =157-159^{0}C.

Preparation of compound 4 [13]

3-(4-aminophenyl)-2-methylquinazolin-4(3*H*)-one

p-phenylenediamine (1.07g, 0.01 mol) was added to a hot solution of compound 2 (1.79g, 0.01 mol) in absolute ethanol and refluxed for 2 hrs to produce a precipitated solid which was filtered off and then recrystallized from ethanol, as an off white solid (75%), mp = 177- 178^{0}C.

Preparation of compounds 5 and 6 [15]

2-[2-(2-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]-1*H*-isoindole-1,3(2*H*)-dione and
1-[2-(2-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]-1*H*-pyrrole-2,5-dione respectively

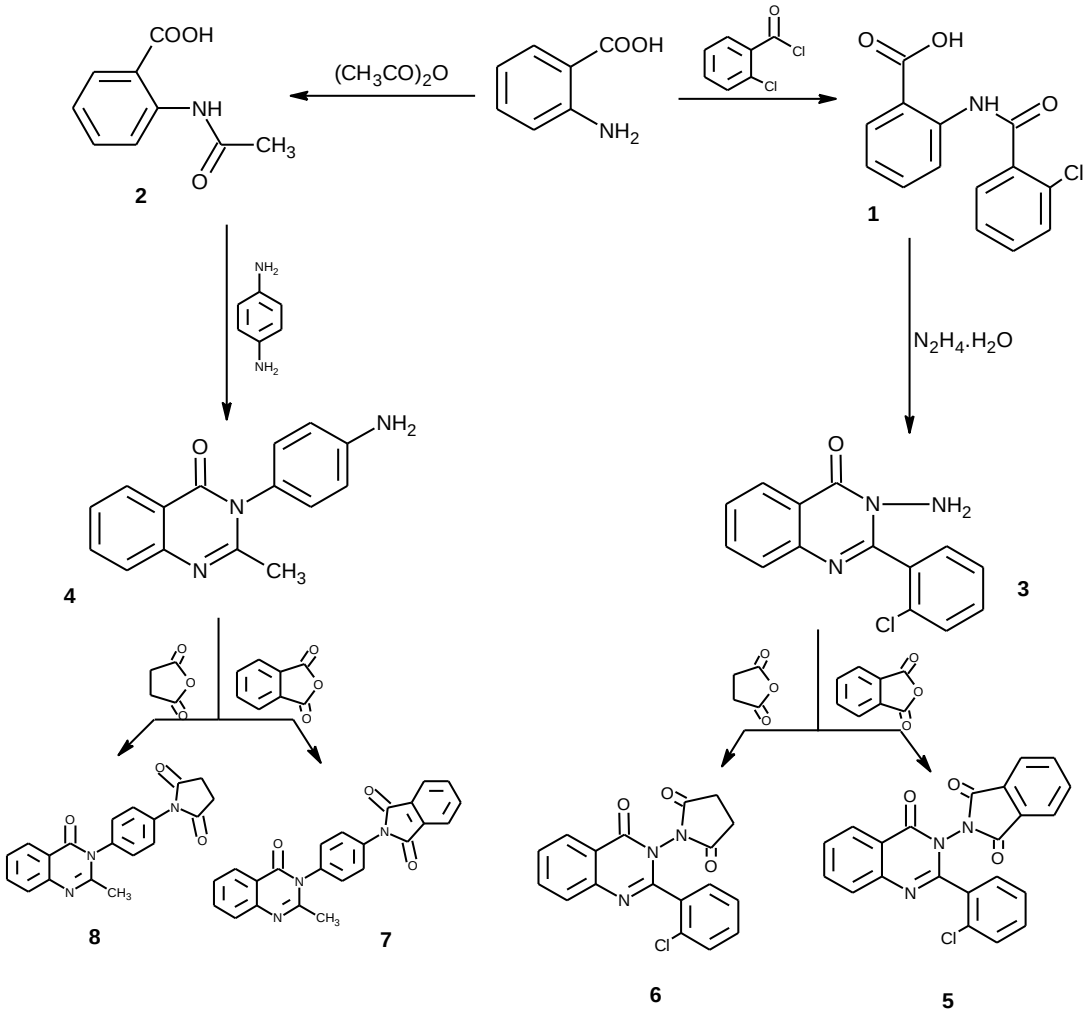
Phthalic anhydride and succinic anhydride (0.01 mol) was added to a hot solution of compound 3 (1.36g, 0.005 mol) in acetic acid and refluxed for 6 hrs. The produced solid was collected by filtration and washed with cold water then it was recrystallized from ethanol to produce an off white solid, (60%), mp = 173- 174^{0}C for compound 5 and (65%), mp = 172-173^{0}C for compound 6.

Preparation of compounds 7 and 8 [15]

2-[4-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenyl]-1*H*-isoindole-1,3(2*H*)-dione and
1-[4-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenyl]pyrrolidine-2,5-dione respectively

Phthalic anhydride and succinic anhydride (0.01 mol) was added to a hot solution of compound 4 (0.48g, 0.005 mole) in acetic acid and refluxed for 6 hrs. The produced solid was collected by filtration and washed with cold water then it was recrystallized from ethanol to produce an off white solid, (60%), mp = 308- 310^{0}C for compound 7 and (65%), mp =302- 303^{0}C for compound 8.

RESULTS AND DISCUSSION



Compound **1** was prepared through the nucleophilic substitution of 2-chlorobenzoylchloride with anthranilic acid using dry benzene as a solvent. This compound is diagnosed by FTIR spectrum which shows the appearance of a sharp band at 1664 cm^{-1} attributed to amide carbonyl group[16] in addition to another sharp band at 1699 cm^{-1} indicates the presence of the original carboxylic carbonyl, beside the disappearance of the doublet band that related to the original NH_2 group of anthranilic acid. A broad band at 3167 cm^{-1} indicates the presence of the original carboxylic OH group of anthranilic acid.

Compound **2** was prepared through the acetylation of anthranilic acid by acetic anhydride. This reaction was carried out without using a solvent. This compound was diagnosed by the FTIR spectrum that shows the appearance of a strong band at 1666 cm^{-1} attributed to the carbonyl of the acetamide group in addition to another strong band at 1699 cm^{-1} attributed to the original carboxylic carbonyl group. It also shows the disappearance of the doublet band that attributed to the original NH_2 group of anthranilic acid and appearance of a single band at 3345 cm^{-1} related to amidic NH. A broad band at 3167 cm^{-1} indicates the presence of original carboxylic OH of the anthranilic acid.

Compounds **3** and **4** was prepared through the cyclization reaction that achieved by addition of hydrazine hydrate and *p*-phenylendiamine respectively. These compounds were confirmed by FTIR spectra. The spectrum of compound 3 shows appearance of two sharp bands at 3282 cm^{-1} & 3442 cm^{-1} which indicate the presence of NH_2 group in the synthesized compound, beside the disappearance of the broad band that attributed to OH group of compound **1**. It also shows that bands that related to the carboxylic carbonyl and to the amidic carbonyl are disappeared and replaced by a strong band at 1674 cm^{-1} for the lactamic carbonyl. The spectrum of

compound **4** shows appearance of a two sharp bands at 3320 cm^{-1} & 3387 cm^{-1} which indicate the presence of NH_2 group in the synthesized compound, beside the disappearance of the broad band that attributed to OH group of compound **2**. It also shows that bands that related to the carboxylic carbonyl and to the amidic carbonyl are disappeared and replaced by a strong band at 1680 cm^{-1} for the lactamic carbonyl group.

Compounds **5**,**6**,**7** and **8** were prepared through the condensation reaction between compounds **3** and **4** with phthalic anhydride and succinic anhydride respectively. These compounds were confirmed by their FTIR and ^{1}H NMR spectra. FTIR spectra for compound **5**& **6** show appearance of a sharp band at 1721 cm^{-1} for compound **5** and at 1723 cm^{-1} for compound **6** that represent new imide carbonyl groups in the synthesized compounds beside the disappearance of the two bands that attributed to NH_2 group in compound **3**. ^{1}H NMR spectra for compounds **5**& **6** show peaks at: 7.15-8.42 ppm (12H,Ar-H) for compound 5 and 2.503 ppm refers to the distinguishing peaks of DMSO solvent and the following protons apparently also presence in this area (4H, $2CH_2$ of pyrrolidine-2,5-dione ring) and 7.18-8.49 ppm (8H,Ar-H) for compound 6.

FTIR spectra for compound **7**& **8** show appearance of a sharp band at 1719 cm^{-1} for compound **7** and at 1724 cm^{-1} for compound **8** that represent the new imide carbonyl groups in the synthesized compounds beside the disappearance of the two bands that attributed to NH_2 group in compound 4. ^{1}H NMR spectra for compound **7**& **8** show peaks at: 2.151 ppm (3H, CH_3) and 7.17-7.966 ppm (12H, Ar-H) for compound **7** and 2.152 ppm (3H, CH_3), 2.503 ppm refers to the distinguishing peaks of DMSO solvent and the following protons is apparently also presence in this area (4H, 2 CH_2 of pyrrolidine-2,5-dione ring) and 7.342-7.968 ppm (8H,Ar-H) for compound **8**.

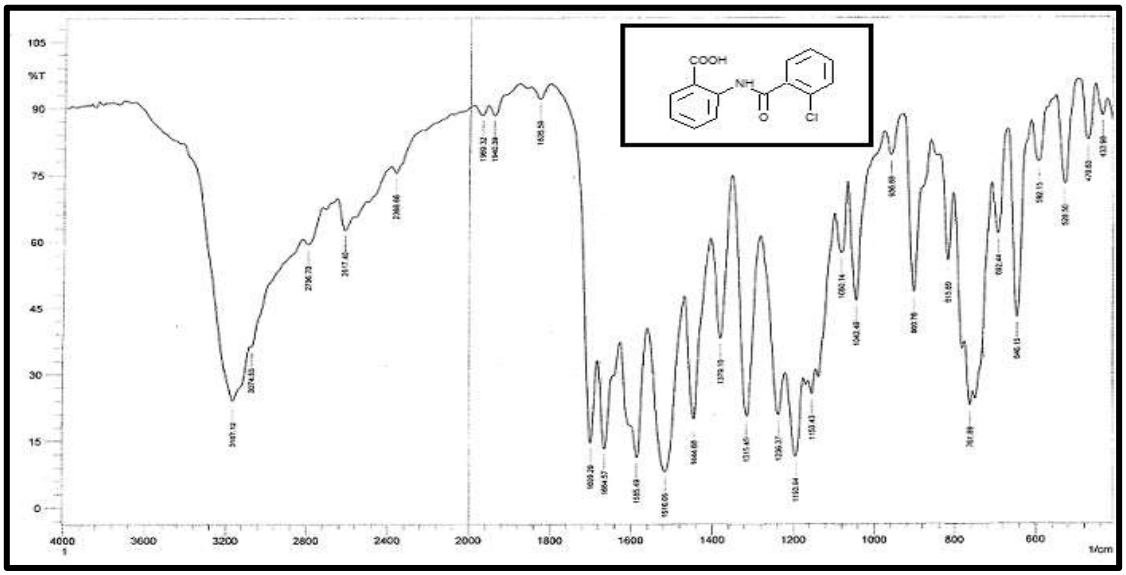


Fig.1: FTIR spectrum for compound 1

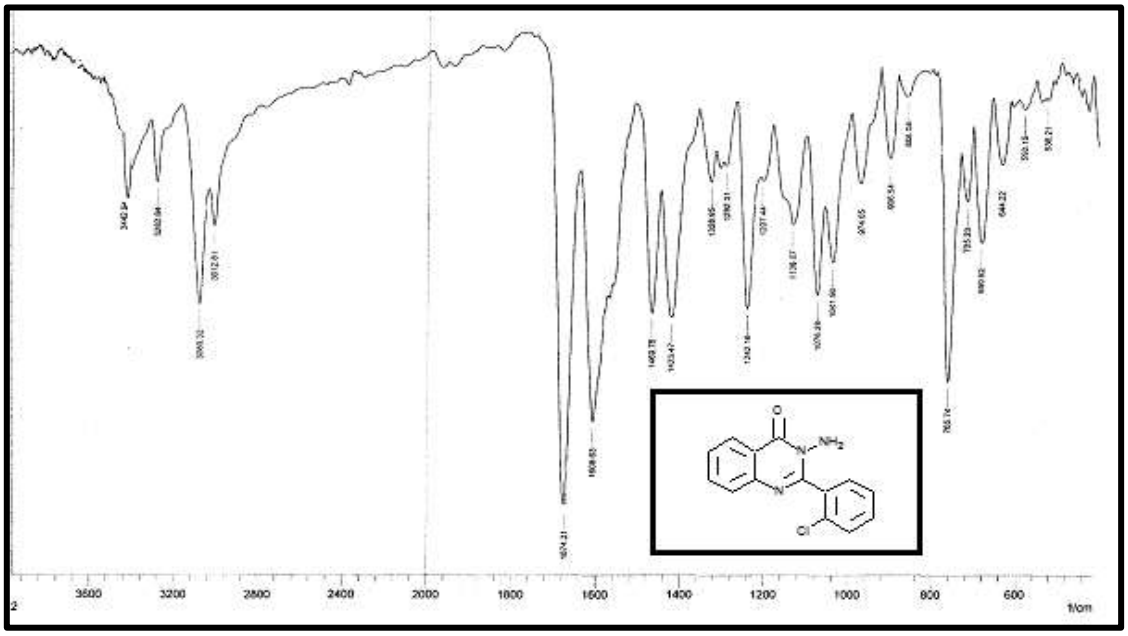


Fig.1: FTIR spectrum for compound 3

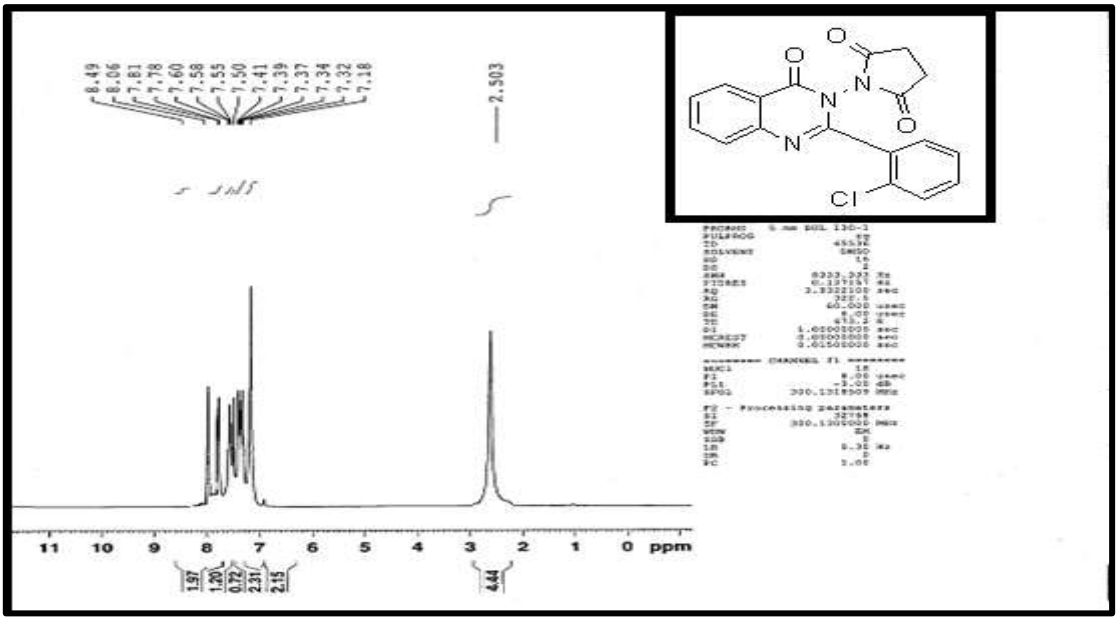


Fig.3: ^{1}HNMR spectrum for compound 6

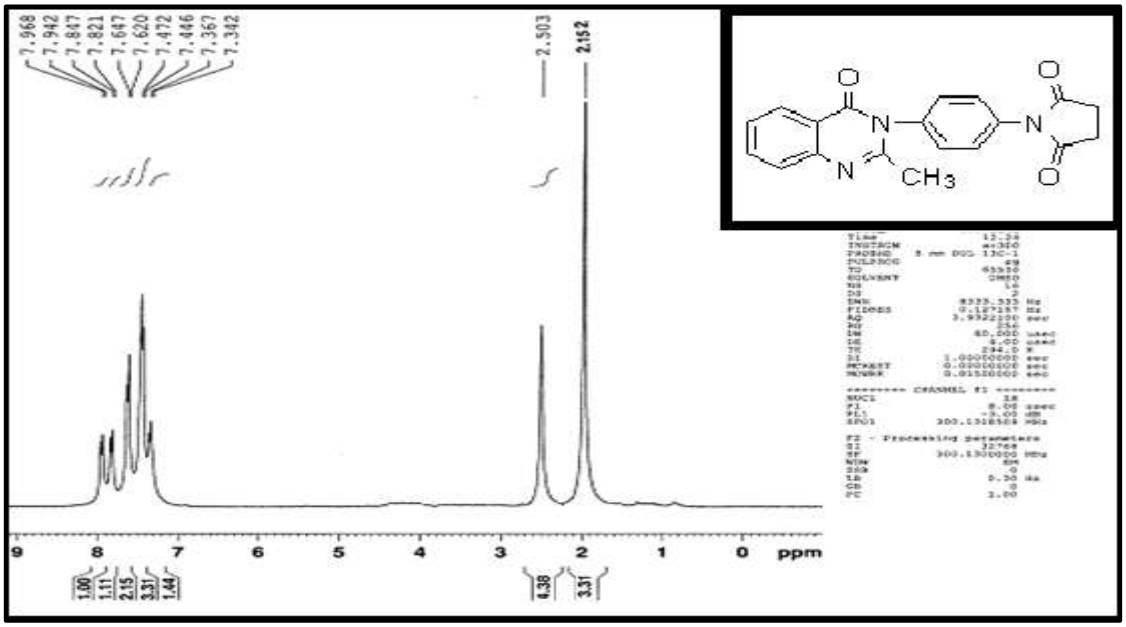


Fig.4: ^{1}HNMR spectrum for compound 8

Table 1 FTIR spectral data for the synthesized compounds

Comp. No.	Characteristic bands of FT-IR(cm^{-1} KBr disk)			
	ν (N-H)	ν (C=O)	ν (=C-H)= Ar ν (-C-H)= ali	ν (others)
1	3100	1699,1664	Ar. =3074	ν (C-O) =1193 ν (O-H)=3167 ν (C-Cl) =1043 ν (C=C) =1585
2	3345	1698,1666	Ar. =3057 ali.=2989	ν (C-O)=1147 ν (O-H)=3223 ν (C=C) =1600
3	3282, 3442	1674	Ar. =3080 3072	ν (C=N) =1608 ν (C-O) =1136 ν (C-N) =1242
4	3320, 3387	1680	Ar. =3078 ali.=2729	ν (C=N) =1620 ν (C-O) =1132 ν (C-N) =1390
5	-------	1721	Ar. =3080, 3077	ν (C=N) =1624 ν (C-N) = 1259
6	-------	1723	Ar. =3072, 3068	ν (C=N)= 1625 ν (C-N) =1224
7	-------	1724	Ar. =3043, 3038 ali.=2974	ν (C=N) =1620 ν (C-N) =1254
8	-------	1719	Ar. =3068, 3054 ali.=2974	ν (C=N) =1600 ν (C-N) =1283

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