Synthesis and Characterization of New Fused Heterocyclic Compounds Consisting of Benzodiazepine, Quinoxaline, Benzimidazole and Thiazole Rings

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Abstract

In this study, new heterocyclic compounds were synthesized through the cyclization reactions of *o*-phenylenediamine (**1**) with various organic reagents. Benzodiazepine derivatives (**2-4**) were obtained by reaction of (**1**) with ethylacetoacetate, malonic acid and acetyl acetone.Treatment of compound (**1**) with chloroacetamide, chloroacetic acid, *p*-bromophenacyl bromide and oxalic acid dihydrate afforded quinoxaline derivatives (**5-8**), respectively. Reaction of compound (**1**) with benzoic acid, piperonal, cyclohexanone and carbon disulfide resulted in the formation of compounds (**9-12**), respectively. Finally, reaction of compound (**12**) with chloroacetic acid in the presence of potassium hydroxide produced compound (**13**).

Keywords: Benzodiazepine, Quinoxaline, Benzimidazole and Thiazole, Cyclization Reactions.

Introduction

Nitrogen containing heterocycles are frequently found in privileged structures (pharmacophores) but their incorporation sometimes possess special problems (multi step sequence, lack of generality, preparation from cyclic precursors,etc);thus,only a limited number of strategies have been successfully applied in the synthesis of heterocyclic scaffolds.The development of new, rapid and clean synthetic routes toward focused libraries of such compounds is therefore of great importance to both medicinal and synthetic chemists.Consequently,the design and development of procedures for the generation of new heterocycles receive growing interest.The benzimidazole ring is of a crucial pharmacophore in drug discovery. Benzimidazoles show different biological activities, such as anticancer ,antimicrobial,or anthelmintic activities[1].Benzimdazole derivatives are a unique broad-spectrum class of antirhino/enteroviral agents. Benzimidazoles exhibit cytomegalovirus (HCMV)[2].A number of synthetic methods have beendeveloped in recent years to uncover a variety of new reagents for the synthesis of benzimidazole derivatives

Benzimidazoles can be synthesized by a number of methods, usually involving formation of the N-C-N unit as the key step. One of the formally utilized general routs to benzimidazoles involves the reaction of aldehydes and ketones with *o*-phenylenediamine[3]. Although there are several routs leading to 2-substituted benzimidazoles,a typical procedure involves heating *o*-phenylenediamine with a substituted carboxylic acid in the presence of a mineral acid[4].

Brown rot, caused by the fungal *Monilina fructicola*(G.Wint.).Chemical control of brown rout is an important strategy for the management of this disease. The Benzimidazole fungicides like Benomyl ,Carbendazine,Chlorofenazole,Thiophanat, etc. have been widely used for controlling the disease[5].

Benzodiazepines are a family of prescription drugs that are used mainly to relieve anxiety and to help people to sleep.These are sedative drugs, which reduce activity in certain parts of your brain,resulting in a calming effect Xanax (alprazolam), Rivotril (clonazepam), Valium (diazepam) , Dalmane (flurazepam) ,

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Ativan(lorazepam),Restoril (temazepam),Halcion (triazolam),etc,are examples of benzodiazepine drugs[6].

Other uses of benzodiazepines include :inducing sedation for sur-gical and other medicinal procedures treatment of alco- hol withdrawal controlling seizures relaxation of skeletal muscles, such as the back and neck[7].

Among the various classes of heterocyclic compounds, quinoxaline form an important component of pharmacologically active compounds. Quinoxaline ring is a part of various antibiotics such as Echinomycine, Levomycine and Actnomycine that are known to inhibit the growth of Gram positive bacteria and are active against varioustrans plantable tumors[8]. Quinoxalinediones and their derivatives are important members of heterocyclic compounds that are widely applied in many fields, as curatorial intermediates, bactericides and inseticides[9].One-pot efficient synthesis of quinoxaline-dione derivatives may permit the development of novel therapies for the treatment of epilepsy, pain and other neurodegenerative disorders[10].

Because of its synthetic utility and broad rang of pharmacological activities,the thiazole nucleus is an important heterocyclic ring.Some thiazole derivatives with different pharmacological effects,including anti HIV, antihistaminic,antiulcer,cardiotonic,antihypertensive and neuroleptic,are in clinical use[11]. In order to obtain more effective chemotherapeutic agents, a variety of reports have been presented on the synthesis and biological evolution of new thiazole derivatives[12].

Experimental

General

Melting points were determined on Gallen Kamp melting point apparatus and were uncorrected. The IR spectra of the compounds were recorded on Shimadzu FTIR-8300 spectrometer as KBr disc; results are given in cm^{-1}.^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300.131 and 75.47 MHz, respectively,in DMSO-d_6 for all compo- unds on a Bruker AMX-400 NMR spectro- meter. The chemical shifts are reported in part per million (ppm) downfield from internal tetramethylsilane (TMS) (chemical shift in δ values).Thin layer chromatography was carried out using Fertigfollen precoated sheets type Polygram SilG, the plates were developed with iodine vapour.^{1}H-and ^{13}C-NMR were made at Medicinal and Health Analytical Center, Peking University, China.

Synthesis of 4-methyl-1,3-dihydro-2H-1,5-benzodiazepin -2-one (2)

A mixture of *o*-phenylenediamine(**1**) (0.015mol) and (0.015mol) of ethylacetoa cetate, in 20ml abs. ethanol was reflux for 24h. The excess solvent was removed under reduced pressure, the reaction mixture was cooled and the formed precipitate was filtered off and recrystallized from ethanol to give the desired products. M.P. 158-159C°, Yield 85%.

Synthesis of 1H-1,5-benzo diazepine-2,4(3H,5H)-dione (3)

The same procedure as for the synthesis of compound **2** but use malonic acid instead of ethylacetoacetate.M.P.187-189C°, Yield 70%.

Synthesis of 2,4-dimethyl-3H-1,5-benzodia zepine (4)

The same procedure as for the synthesis of compound **2** but use acetylactone instead of ethylacetoacetate.M.P.115-117C°, Yield 75%.

Synthesis of 3,4-dihydroquinoxalin-2-amine (5)

A solution of (0.01mol) of compound **1** and (0.01mol) of potassium hydroxide in 15ml abs. ethanol was added to (0.01mol) of chloroacetamide.The reaction mixture was heated under reflux for 24h, and then the solid that formed was separated by filtration and recrystallized from chloroform to give the final products. M.P. 198-200C°, Yield 60%.

Synthesis of 3,4-dihydroquinoxalin-2(1*H*)-one (6)

A solution of (0.01mol) of compound **1** and (0.01mol)of potassium hydroxide in 15ml abs. Ethanol was added to (0.01mol) of chloroacetic acid. The reaction mixture was heated under reflux for 24h, and then the solid that formed was separated by filtration and recrystallized from chloroform to give the final products.M.P. 170-172C°, Yield 70%.

Synthesis of 3 - (4 – bromophenyl) -1 , 2 - dihydroquinoxaline (7)

A mixture of compound **1** (0.015mol) and *p*-bromophenacyl bromide (0.015mol) in 25ml abs. ethanol was refluxed for 24h; then

the solvent was reduced to one third its volume under reduced pressure and then cooled. The solid that separated was recrystallized from dichloromethane. M.P. 78-80C˚, Yield 80%.

Synthesis of 1,4-dihydroquinoxaline-2,3-dione (8)[10]

A mixture of oxalic acid dihydrate (0.012mol) and *o*-phenylenediamine (0.012 mol) was thoroughly ground with a pestle in a mortar at R.T. In an open atmosphere until the mixture turned into a melt.The mixture continued to be ground occasionally for 1/2h. Then the melt was crystallized from water/ethanol (1:1) mixture to get the pure product. M.P.155 -157C˚, Yield 80%.

Synthesis 2-phenyl-1H-benzimidazole (9)

To (0.01mol) of compound **1**, a mixture of (0.01mol) of benzoic acid with few drops of conc. hydrochloric acid in 15ml abs. ethanol was added. Then the reaction mixture was heated under reflux for 15h. The crude product was isolated by filtration and recrystallized from acetone. M.P.210-212C˚, Yield 65%.

Synthesis of 2-(1,3-benzodioxol-5-yl)-2,3-dihydro-1*H*-benzimidazole (10)

A mixture of compound **1** (0.012mol), 25ml abs. ethanol and piperonal (0.012mol) was heated under reflux for 24h. The reaction mixture was filtered off and recrystallized from chloroform. M.P. 230-232C˚,Yield 75%.

Synthesis of 1 , 3-dihydrospiro [benzim idazol -2,1'-cyclohexane] (11)

A mixture of (0.015mol) of compound **1** and (0.015mol) of cyclohexanone in 20ml glacial acetic acid was heated under reflux for 24h, and then the mixture was filtered off to obtain the desired product. M.P. 220-222C˚, Yield 60%.

Synthesis of 1H-benzimidazole-2-thiol (12)

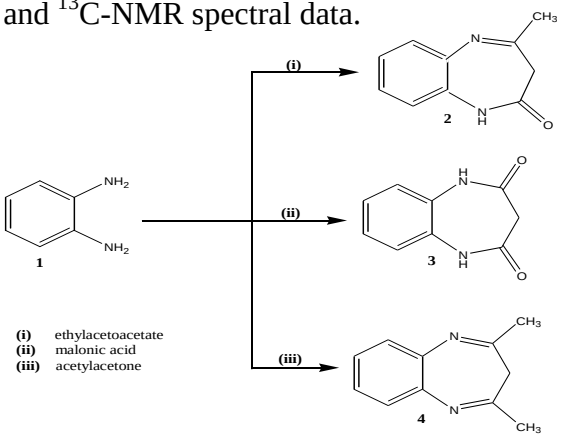
o-Phenylenediamine (0.01mol) (**1**) and (0.02mol) of CS_2 was mixed together in 20 ml abs. ethanol. The reaction mixture was refluxed for 18h. The crude product was obtained by filtration, washed with water and recrystallized from benzene. M.P. 90-92C˚, Yield 70%.

Synthesis of [1,3] thiazolo [3 , 2 - a] benzim idazol-3(2H)-one (13)

To a warmed sodium hydroxide solution prepared by dissolving of sodium hydroxide (0.01mol) and (0.01mol) of compound **12** in 15ml abs. ethanol, (0.01mol) of chloroacetic acid was added. The reaction mixture was refluxed for 24h.The solid precipitate was formed after the solvent was reduced to one third its volume under reduced pressure.Crude product was obtained by filtration and recrystallized from benzene. M.P. 112-114C˚, Yield 80%.

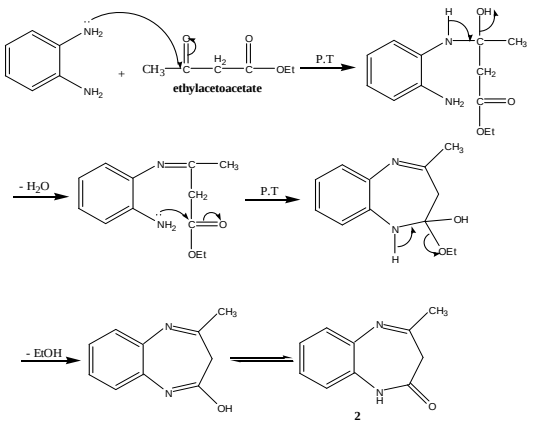
Results and Discussion

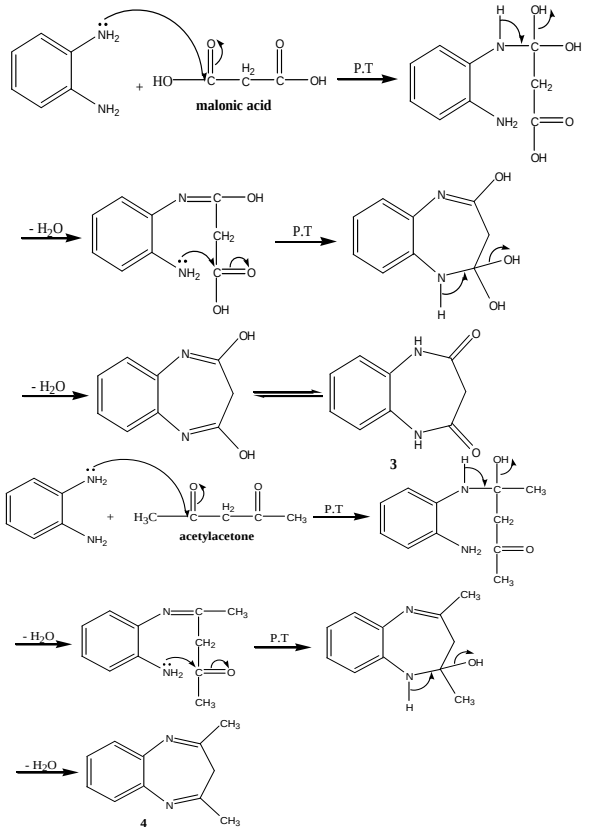
In the current study,*o*-phenelenediamine (**1**) was chosen as starting material. One of our aims was to use the two nucleophilic center of this material in synthesis an interesting heterocyclic compounds. One of the two amino groups will be reacting in a normal manner and an intermolecular attack by the other amino group at ortho position was suggested to take place. In the first part of these synthetic procedures, compounds **2-4** were obtained from the reaction of compound **1** with ethylacetoacetate, malonic acid and acetyl acetone, respectively **(Scheme I)**. Their structures were confirmed by FT-IR,[1]H-NMR and [13]C-NMR spectral data.



Scheme I

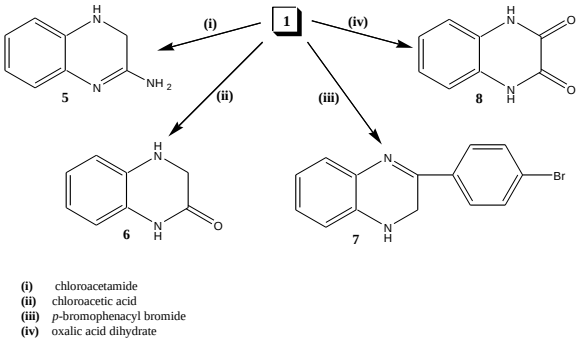
The mechanism of the reaction for the synthesis of compounds **2-4** is outlined below in





Scheme II

The IR spectra of compounds 4-methyl-1,3-dihydro-2H-1,5-benzodiazepin -2-one **(2)** and 1H-1,5-Benzodiazepine-2,4(3H,5H)-dione **(3)** (**Fig. 1**) showed characteristic bands at 3400-3300, 2900-2800 and 1650-1700 due to stretching vibrations of OH, CH aliphatic and C=O groups, respectively. From this we can say that these two compounds can exist in two tautomeric forms keto and enol forms. The signals corresponding to aliphatic protons, NH and OH protons were recorded at 1.14(s,3H,CH_3),8.32(s,1H,NH)(D_2Oexchange), 9.21(s,1H,OH) (D_2O exchange) for compound **2** and at 2.10(s, 2H, CH_2), 8.44 and 8.71(s, 1H, NH) (D_2O exchange), 9.35(s, 1H, OH) (D_2O exchange), for compound **3**, in ^{1}H-NMR spectra. The C=O signal appear at 170.1and 164.7,168. 3 for compounds **2** and **3,** respectively,in ^{13}C-NMR analysis. Compound **4** displayed bands in its IR spectrum at 2900 and 1610 belonging to CH aliphatic and C=N stretching vibrations. ^{1}H-NMR spectrum showed signals at 1.21 (s, 6H, $2CH_3$) and 6.89-7.56 (m, 4H, aromatic protons), these two groups appeared at 14.6, 15.7(2C, CH_3), and 132.0-136.4(6C, aromatic carbons) in the ^{13}C-NMR spectrum.In the second step of this study, quinoxaline derivatives **5-8** were obtained by the reaction of compound **1** with chloroacetamide, chloroacetic acid,*p*-bromophenacyl bromide and oxalica cid dihydrate,respectively,**(Scheme III)**.

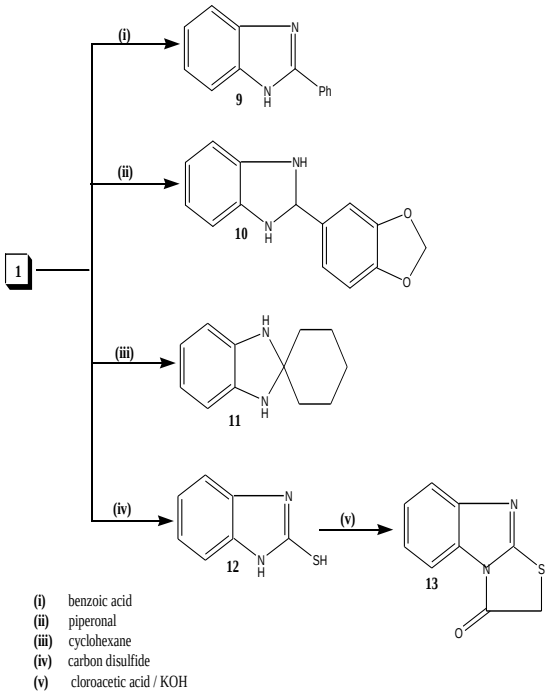


(i) chloroacetamide
(ii) chloroacetic acid
(iii) *p*-bromophenacyl bromide
(iv) oxalic acid dihydrate

Scheme III

In the IR spectra of compounds **5-8**, **Fig. 2** show FT-IR spectrum of compound **8** , the stretching multiple bands derived from $-NH_2$ group of *o*-phenylenediamine were absent. In addition, signal derived from C=O was observed, at 168.7 and 170.7, 172.4 in the ^{13}C-NMR spectra of compounds **6** and **8**, respectively. Beside this, the signal corresponding to –NH group was recorded at the range 8.21-8.55 in the ^{1}H-NMR spectra of these compounds which were disappear with D_2O exchange. Furthermore, ^{1}H-NMR spectra of compounds **5** and **7** showed signals at 8.71 which was integrated for two protons corresponding to $-NH_2$ group of compound **5**, this was disappeared with D_2O exchange, while the structure of compound **7** was confirmed by a multiple signal at 6.81–7.44 due to aromatic protons. In the last part of the synthesis reactions,compound **1** was treated with benzoic acid ,piperonal ,cyclohexanone and carbon disulfide ;

2 -phenyl-1H–benzimidazole **(9) ,**2-(1,3-benzodioxol-5-yl)-2,3-dihydro-1*H*-benzimidazole**(10),**1,3-dihydrospiro[benzimidazol-2,1'-cyclohexane]**(11)** and 1H-benzimidazole-2-thiol **(12)** were formed respectively. Then compound **(12)** was converting to [1,3]thiazolo[3,2-a]benzimidazol -3(2H)-one **(13)** by treating with chloroacetic acid in abs. ethanol **(Scheme IV)**.



(i) benzoic acid
(ii) piperonal
(iii) cyclohexane
(iv) carbon disulfide
(v) cloroacetic acid / KOH

Scheme IV

The ^{1}H-NMR spectra of compound **9** and **10** showed characteristic signals at 8.30-8.84(s, 1H, NH) which was further characterized by D_2O exchange. Beside this, in the ^{1}H-NMR spectrum of compound **11**, there were a multiple signals at 1.80-2.05 belonging to $–CH_2$- group of cyclohexane ring. On the other hand, ^{1}H-NMR spectrum of compound **12** showed signal at 5.51 due to –SH group which was disappear with D_2O. When compound **12** was converted to compound **13**, signal of -SH group was disappear and a new signal at 2.25 was shown which represent $–CH_2$- group, in ^{1}H-NMR spectrum. Furthermore, ^{13}C-NMR spectra of compounds **9-13** give a good support for the IR and ^{1}H-NMR data of these compounds. **Table I** summarize physical properties of the synthesized compounds; **Table II** shoes characteristic spectral data of these compounds.

Table I: Physical properties of compounds 2-13

Compound No.	M.P/°C	%Yield
2	158-159	85
3	187-189	70
4	115-117	75
5	198-200	60
6	170-172	70
7	78-80	80
8	55-157	80
9	210-212	65
10	230-232	75
11	220-222	60
12	90-92	70
13	112-114	80

Table II:spectral data of compounds 2-13

Com No	FT-IR	^{1}H-NMR	^{13}C-NMR
2	3361(OH),3100,(NH),3050(CH aromatic),2987 and2810(CH aliphatic),1668,(C=O),734 (aromatico-disubstituted)	1.14(s, 3H, CH_3), 1.86 (s, 2H,CH_2), 6.75-7.21(m, 4H, aromatic protons), 8.32(s, 1H, NH) (D_2O exchange, disappear), 9.21(s, 1H, OH) (D_2O exchange, disappear)	13.4(1C, CH_3), 18.2(1C, CH_2), 26.8(1C, N=C), 130.2-135.4(6C, aromatic carbons), 170.1 (1C, C=O)
3	3400(OH), 3249(NH), 3060(CH aromatic), 2823(CH aliphatic), 1685(C=O),758(aromatic *o*-disubstituted)	2.10(s, 2H, CH_2), 7.12-7.45(m, 4H, aromatic protons), 8.44 and 8.71(s, 1H, NH) (D_2O exchange, disappear), 9.35 (s, 1H, OH) (D_2O exchange, disappear)	0.1(1C, CH_2), 128.3-131. 5(6C, aromatic carbons), 164.7and 168.3(2C, C=O)
4	3080(CH aromatic), 2900(CH aliphatic), 1610(C=N), 752 (aromatico-disubstituted)	1.21(s, 6H, $2CH_3$), 1.78(s, 2H, CH_2), 6.89-7.56(m, 4H,aromaticprotons)	14.63 and 15.7(2C, CH_3), 18.4(1C, CH_2), 132.0-136.4(6C, aromatic carbons)
5	3300-3200 (NH_2), 3180(NH), 2941(CH aliphatic),1600(C=N), 772(aromatic *o*-disubstituted)	2.10(s, 2H, CH_2), 7.11-7.54(m, 4H, aromatic protons),8.22(s, 1H,NH)(D_2O exchange, disappear), 8.71(s, 2H, NH_2) (D_2O exchange, disappear)	17.1(1C, CH_2), 40.2(1C, C-NH_2), 130.5-134.1(6C, Aromaticcarbons)
6	3398(b, OH), 3222(NH), 3030 (CH aromatic), 2860(CH aliphatic),1672(C=O), 769(aromatic *o*-disubstituted)	2.03(s, 2H, CH_2), 7.20-7.69(m, 4H, aromatic protons), 8.21 and 8.35 (s, 1H, NH) (D_2O exchange, disappear), 9.21(s, 1H, OH) (D_2O exchange, disappear)	20.2(1C, CH_2), 132.5-136.9(6C, aromatic carbons), 168.7(1C, C=O)
7	3300(NH), 3080(CH aromatic), 2900(CH aliphatic), 1614(C=N), 877(aromatic*p*-substituted), 758(aromatico-disubstituted)	2.05(s, 2H, CH_2), 6.81-7.44(m, 8H, aromatic protons), 8.09 (s, 1H, NH) (D_2O exchange, disappear)	18.2(1C, CH_2), 22.5(1C, C= N), 128.4-133.3(12C, aromatic carbons)
8	3390(OH), 3255(NH), 3028(CH aromatic),1670(C=O),779 (aromatico-disubstituted)	7.27-7.60(m, 4H, aromatic protons), 8.24 and 8.55(s, 1H, NH)(D_2O exchange, disappear), 9.06(s, 2H, OH) (D_2O exchange, disappear)	131.1-135.5(6C, aromatic carbons),170.7 and 172.4(2C, C=O)
9	3230(NH), 3100(CH aromatic),1605(C=N), 1566 (C=C), 757 (aromatic *o*-disubstituted), 735 and 705 (aromatic mono substituted)	7.05-7.87(m, 9H, aromatic protons), 8.33(s, 1H, NH) (D_2O exchange, disappear)	32.4(1C, C=N), 128.9-132.2(12C, aromatic carbons)
10	3230(NH), 3100(CH aromatic), 2900(CH aliphatic),760(aromatic *o*-disubstituted)	2.08(s, 2H, CH_2), 2.77(s, 1H, CH),7.22-7.98 (m, 7H, Aromatic protons), 8.73 and 8.84 (s, 1H, NH) (D_2O exchange, disappear)	20.1(1C, CH_2), 24.8(1C, N-C-N), 129.3-135.5(12C, aromatic carbons)
11	3280(NH), 3050(CH aromatic), 2920(CHaliphatic), 1530(C=C), 755(aromatic o-disubstituted)	1.80-2.05(m, 10H, 5CH2), 7.10-7.48(m, 4H, Aromatic protons),8.44 and 8.69(s, 1H, NH)(D2Oexchange, disappear)	20.5-24.8(5C, CH2 cyclohexane carbons), 26.6(1C, N-C-N), 133.1-138.5(6C, aromatic carbons)
12	3230(NH),3080(CH aromatic), 2600(SH),1620(C=N),1550(C=C),352(C=S), 730(aromatic o-substituted), 653(C-S)	5.51(s, 1H, SH)(D2O exchange,disappear), 6.66-7.45(m, 4H, aromatic protons), 8.15(s, 1H, NH) (D2O exchange, disappear)	24.3(C=N),132.3136.0(6C, aromaticcarbons)
13	3400(OH), 3080(CH aromatic) , 2916(CH aliphatic),1660(C=O), 1600(C=N),1502(C=C),744(aro matic o-disubstituted), 678(C-S)	2.25(s, 1H, CH2), 7.33-7.67(m, 4H, aromatic protons)	17.3(1C, CH2),23.4(C=N), 128.8-133.1(6C, aromatic carbons), 172.5(1C, C=O)

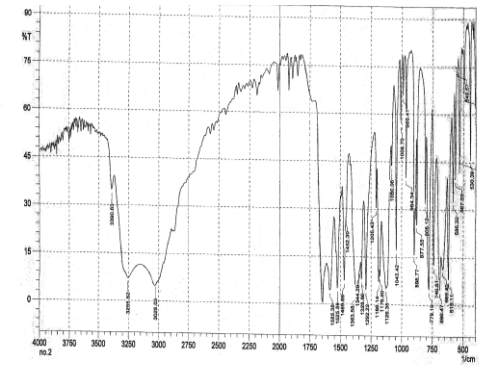


Fig. 1: FT-IR spectrum of compound 3

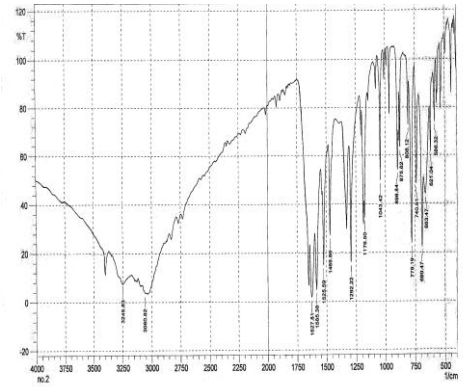


Fig. 2: FT-IR spectrum of compound 8

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تحضير وتشخيص مركبات حلقية غير متجانسة ملتحمة جديدة جديدة تحتوي على حلقات البنزودايأيزوأبين، الكوينوكزالين، البنزايمدازول والثايزول

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الخلاصة

لقد تم في هذا البحث تحضير عدد من المركبات الحلقية الغير متجانسة الجديدة من خلال تفاعلات الغلق للـ أورثو فنيلين داي أمين (**1**) مع عدد من الكواشف العضوية المختلفة. لقد تم الحصول على مشتقات البنزو داي أيزوأبين (**2-4**) من خلال مفاعلة المركب (**1**) مع أثيل أسيتوأستيت, حامض المالونك, أسيتايل أسيتون. ان معاملة المركب (**1**) مع الكلوروأستيماید, كلوروأستيك أسد, بارا برومو فيناسيل بروماید, حامض الأوكزالك ثنائي الهيدريد أعطى مشتقات الكوينوكزالين (**5-8**) على التوالي. وكذلك عومل المركب (**1**) مع حامض البنزويك, ببرونال, سايكلوهكسانون, ثنائي كبريتيد الكاربون أنتج المركبات (**9-12**) على التوالي. وأخيرا فوعل المركب (**12**) مع كلوروأستيك أسد بوجود هيدروكسيد البوتاسيوم ليعطي المركب (**13**).