Synthesis and Characterization of Some New Dioxoisoindolin Compounds Containing Thiazine, Azetidine, Thiazolidine and Amide Moities

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Abstract

A compound (1) was done through thiosemicarbazide cyclization in presence of (CS_2) and anhydrous of (Na_2CO_3) in ethylalcohol. Compound (1) was treated with substituted aromatic aldehydes to produced 2- [(subrogateed benzyliden) amino] 1,3,4-thiadiazole (2). Schiff bases prepared by reaction of 2-carboxy thiophenol with (Et_3N) to give compound (4). Then the compound (4) was interact with chloro acetyl chloride in Et_3N to collect the compound (3). Compound (5) 4- (1,3-dioxoisoindolin-2-yl) benzoic acid was prepared from reaction between p-amino benzoic acid and phthalic anhydride in acetic acid and then converted into the 4 - (1,3-dioxoisoindolin-2-yl) benzoyl chloride (6) by use thionyl chloride. The reaction of acyl chloride with appropriate primary amine gives amide derivatives (14a-i) while the reaction of acyl compound (6) with thiol derivatives gave compounds (7,8 and 9). Compound (12) was synthesized by the reaction of compound (6) with hydrazine hydrate. Then reacted with appropriate benzaldehyde to give compound (13). The reaction between 4- (1,3-dioxoisoindolin-2-yl) benzoic acid (5) and one mole of thiosemicarbazide in presence of phosphorousoxychloride give compound (10) which reacted with p-nitrobenzaldehyde to afford compound (11).

Keywords: thiazine, azetidine, thiazolidine, Schiff bases

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تحضير وتشخيص مركبات داي اوكسوايزواندولين المحتوية على الثايازين، ازتدين، ثايازولدين ومجاميع الامايد

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الخلاصة

المركب- 2 امينو- 5 -مركبتو 1 -و 3 و– 4 ثايادايازول (1)) تم تحضيره بواسطة الغلق الحلقي الناتج من تفاعل الثايوسيميكاربازايد مع ثنائي كبريتيد الكاربون باستخدام كاربونات الصوديوم اللامائية في الايثانول.المركب (1) تم مفاعلته مع مجموعة من الالدهايدات المعوضة ليعطي مركب رقم (2) وهومشتق- 2 بنزلدين امينو (1 و 3 و- 4 ثايادايازول.)مركبات قاعدة شف تم مفاعلتها مع مركب2 --مركبتو حامض البنزويك باستخدام قطرات من ثلاثي اثيل امين لينتج مركب رقم (4) وهو مشتق الثايازين.تم مفاعلة مركبات قاعدة شف ايضا مع كلورواستيل كلورايد حيث انتجت مشتقات لحلقة الازتدين (3) اما المركب (5) فقد تم تحضيره بتفاعل بارا-امينو بنزويك اسيد مع انهدريد الفثالك وباستخدام حامض الخليك. بعد ذلك تم تفاعل مركب (5) مع كلوريد الثايونيل اعطى مشتق كلويد الحامض (6). تم مفاعلة مركب (6) مع مجموعة مشتقات الامين الاولي حيث اعطى مشتقات الامايد الحلقي (14) بينما تفاعل مركب (6) مع مشتقات الثايول اعطى المركبات (9-7).المركب (12) تم تحضيره من تفاعل مركب (6) مع الهيدرازين المائي بعدها تم مفاعلته مع مجموعة من الالدهايدات المعوضة ليعطي مركب (13). تفاعل بين المركب (5) مع الثايوسيميكاربازايد باستعمال $POCl_3$ اعطى مركب (10) الذي تم مفاعلته معبارا-نايترو بنزالديهايد الذي اعطى مركب (11).

الكلمات المفتاحية: ثايازين، ازتدين، ثايازولدين، قواعد شف

Introduction

Phthalimide which has a structural features –CO-N(R)-CO-and an cyclic imide ring, this makes them useful biologically and pharmaceutically [1]. Some imide compounds can be derivate to be a bioactive group compounds displaying activated sense antagonists, anti-inflammatory, anti-viral. anxiolytic, antibacterial ,and antitumor activity [2] Though their usage in many applications, their production methods are confined [3]. The dehydrative intensification of an

anhydride and an amine at high heat and the amic acid cyclization with acidic reagents are perfect techniques [4]

Studies reported that phthalimide and some of its derivatives have interest biological effects same or higher than known pharmacological molecules, thus, their biological activity is being a subject of biomedical research [5-8].

Paracetamol is a widely used analgesic, antipyretic drug, post –surgical pain and in treatment of advanced cancer [9]. Other studies suggested that Phthalimide derivatives revealed important pharmaceutical effects as analgesic [10], anti-inflammatory [11] and antiviral activities [12]. According to these properties, it was considered interest to synthesize phthalimide derivatives which could be exhibit similar potency to that of paracetamol itself.

Experimental section

1. Instrumentation and chemicals:

All the chemical materials used were procedures from fluka and Aldrich. melting point compounds were recorded by Digital MPA 161 (MSRS) electronic. Infrared spectra (FT-IR) for all compounds were recorded on Shimadzu type 8400 Spectrophotometer. Proton-NMR spectra were recorded on Bruke, model: Ultra shield 300 MH_Z, with tetra methyl saline as internal standard in DMSO-d_6 as a solvent, measurement were made at chemistry department, Ahl-Albayt University. Jordan**,** UV-Visible shimadzu.

2. Synthesis methods

2.1 synthesis of compound (1) [13]

Aminothiourea (2g,0.02 mol.) with (2.33g, 0.02 mol) of anhydrous Na_2CO_3 were mixed in 25 ml. of absolute ethyl alcohol. Carbon disulphide (3.2 g , 0.04 mol.) was later gathered to this solution, which refluxed for 10 hrs. Sol. was cooled at room temperature and the solvent was evaporated through reducing pressure then it was used 20 ml of distilled water to solve the rest. Acidification was done on the sol. with cold conc. HCl in order to create pallid yellow residue to be then ready for filtering and washing with water. The precipitate was submitted to a recrystallization process from hot water to produce the desired material as yellow needles, gained (75%), m.p 230-232 ^oC,Rf=0.65.

2.2 General synthesis method for compound (2) [14]**:**

A mixture of equimolar amounts (0.09 mol.) of appropriate aldehyde and compound [1] in 15ml of ethanol absolute then it was added three drops of icy ethanoic acid. The solution was put in a reflux (water bath) for eight hours then refrigerated at room temperature. Results were under filtering, drying and recrystallization from ethylalcohol to obtain yellow crystals which was (90%), m.p. 220-222 ^{0}C.

2.3 Synthesis of 3-chloro-4-(4-(N, N-dimethyl amino) phenyl)-1-(5-mercapto-1,3,4-thiadiazol-azetidin-2-one [15]

It was added (0.01mol.) of Et_3N in (10ml.) dioxin to chloroacetyl chloride (0.01mol.) in 10ml cooled dioxin (0-5) C^o. Schiff bases (0.01mol.) in 10ml of dioxin was slowly added and warmed in water bath for 12hours. When the reaction was ended- (identified by TLC), the mixture was put into ice-cold water for producing solid residue. Filtering, drying and recrystalizing process to the results by ether and benzene (50-50), yield (64%), m.p.200-202C^0

2.4 General synthesis method for the compound (4) [16]:

Schiff base (2) (0.01mol.) and 30 ml. of benzene was mixed with 2-carboxythiophenol (0.01mol.) then it was added three drops of Et_3N. The mixture was refluxed for six hours. The dissolvent was vaporized through reducing pressure. the remaining precipitate was cleaned with 10% of ($NaHCO_3$), again the compound was filtered and recrystallizing with dioxan was made to the results, gained was (78%), m.p.240-242 ^{0}C.

2.5 General synthesis method for compound [5], [17]:

A mixture of equimolar amouts (0.001mole) of phthalic anhydride with p-aminobenzoic acid in presence of ethanoic acid (15ml). The mixture was warmed under refluxed for (3.5-5) hours .Aliquate of 25ml. of ice cold distilled water was added to the reaction medium and the compounds was filtered ,dried and recrystallized from ethylalcohol, yield(91%),m.p.291-293 ^{0}C.

2.6 General synthesis method for compound (6) [18]:

A compound [5] (0.01mole) and thionyl chloride (5ml.) in benzene (10ml.) was warmed under refluxed for 7 hours. After cooling, excess of thionyl chloride and benzene were removed under vacuum. The product was yellowish crystals, yield (80%) , m.p254-257 ^{o}C .

2.7 General synthesis method for compounds [7,8,9,12,14 and 18] :

The compounds which containing (-NH_2) and (-SH) groups (0.01mle) was dissolved in dry benzene (10ml). Compound [6] was put and the combination was refluxed for 7h. The product was cooled and the resolve was set aside under vaccum pressure , water was added , filtered ,dried and recrystallized from ethylalcohol to offer products . It can be seen in table (1) the nomenclature ,m.ps , structural & molecular formula for prepared compounds.

2.8 General synthesis method for compound (10)[19] :

An equimolar mixture of compounds [5](0.01moe) and thiosemicabazide was refluxed in the presence of phosphorousoxychloride (5ml.) for four hours, then the product was cooled and diluted with cold water (10ml) . The product was neutralized with potassium hydroxide solution 40% . The precipitate was filtered off and recrystallized from ethyl alcohol to give solid product, m.p 184^{o}C decomposition ,yield (25%).

2.9 General method for the synthesis of compounds (11 and 13)[20]

A mixture of equimolar amounts (0.01mole) of appropriate aldehyde and compounds [10and12] in absolute ethanol (15ml.). Three drops of glacial ethanoic acid were added and put in water bath (refluxed) for eight hours then was cooled at room temperature,drying and filtering process was done to the results. Recrystallization to the precipitate from ethyl alcohol was made for obtaining yellow crystals. Nomenclature, m.ps, structural and molecular formula for prepared compound are presented in table (1).

Results and Discussion:

The compound[1]structure was characterized by its m.p. and Fourier-Transform infrared spectroscopy which its compound[1]displays two peaks at(3394)and(3277)cm^{-1} belong to symmetric and asymmetric vibration of primary amine group, an absorption peak at(3091)cm^{-1} was attributed of the(N-H)(tautomeric form). Peak at (3174) cm^{-1}, the intra-molecularly hydrogen bonded of (-NH) group led to the band. The band of (-SH) stretching band was seen

as weak band at (2358) cm^{-1}. (C=N) of the thiadiazole ring moiety stretching caused a band at (1604) cm^{-1} and 1597 cm^{-1}. The band at (1533 cm^{-1}) and (1330 cm^{-1}) were related to the (-NH) and (C-N) stretching vibration [21,22]. Other band appeared at 1055 cm^{-1} related to the (C=S)group. FT-IR spectra [2] demonstrated the vanishing of the two absorption bands due to ($-NH_2$) stretching of amino1,2,3- thiadiazole derivatives as example ,showed all the suggested bonds for (C-H)olefinic , (C=C) aromatic, (C=N)endocyclic and exocyclic imine group. Expansion vibrations in addition to out of plane bending of substituted aromatic ring. All the prepared compounds (Schiff bases) exhibited the stretching band near the region (1200-1250) cm^{-1} this due to (-C=N-N=C-) cyclic group.

Chloro acetylchloride were reacted with Schiff compounds and Et_3N was added .The new compounds which were characterized by their melting points,FT-IR,UV-Vis,^{1}H-NMR spectroscopy and checked by TLC. The FT-IR spectra of compound [3] , display appearance of identified band at (1683) cm^{-1} due to of stretching vibration of (C=O) azetidinone ring. The Fourier-Transform Infrared spectrum illustrate (C-H)olefinic ,aromatic (C=C) . ^{1}H-NMR spectrum for compound [23] [3] showed the chemical shift ,(Dimethylsulfoxide) ppm , the proton in azetidine-2-one ring [3] seemed as two signs (doublet) at (3.77-3.79) ppm and (CH) proton was combined with chloro (doublet) at (4.27-4.46) ppm and δ (8.1-8.4) ppm for proton aromatic phenyl ring .This compound's proton [3] looked as multiple at (7.1-7.7) ppm, singlet signal at δ (3.3) ppm associated with (S-H) proton , (CH) proton in azetidione was shown as 2 signals (doublet) at δ (3.71-3.76) ppm and (CH) proton was integrated with chloro (doublet) at δ (3.98-4.03)ppm. The (UV-Vis)compound's spectrum [3], demonstrated the absorption peaks at (332-285)nm, this might be refered to(n - π*) and (π-π*) transmission.

Thiazine derivatives were made by the Schiff bases interaction and 2-carboxythiophenol in dry benzene. Results were confirmed by UV-Vis, IR , ,proton-NMR spectroscopy all results were identified and their melting points were tested by T.L.C. for compounds. It was noticed that the thiazines carbonyl group appeared at (1662-1683) cm-1 and the (C=N) group was absent in (1610-1620) cm-1 while the (O-H) broad band stretching vibration disappearing was at 3450 cm-1 of 2- carboxythiophenol 1H-NMR compound's spectrum [4] displayed the following characteristic chemical shifts (DMSO-d6 , ppm) : the proton of aromatic ring was shown as

multiple at (6.6-8.81) ppm , signal at δ (10.1) related to the (C-H) in thiazine as singlet .The (UV-vis) compound's spectrum [4], demonstrates the absorption peaks at (351-295) nm and this might be according to (n- π*) and (π-π*) transition. Compound [5] was prepared by the reaction of p-aminobenzoic acid with phthalic anhydride in glacial acetic acid .The compound was confirmed by IR and melting point .The FT-IR spectrum showed absorption bands disappearing of two bands (C=O) (anhydride) with existence of two (C=O) (cyclic amide) at (1716-1778) cm^{-1} , band at (1687) cm^{-1} due to of carbonyl group of carboxylic acid .

The compound structure [6] was prepared by the condensation of [5] with thionyl chloride in dry benzene . The compound was characterized by melting point and FT-IR spectrum. FT-IR spectrum of compound (6), appeared the disappearance of absorption peak at (1687 Cm-1) due to of (carbonyl) of carboxylic acid and (2549-3088) cm^{-1}due to of (O-H) of carboxylic acid with appearance of band at (1751) cm^{-1} ,for carbonyl group of acyl chloride.

It was set compounds [7] and [8] by the interaction of compound [3] and [4] with compound [6] in benzene as solvent. These compounds were confirmed by FT-IR and 1H-NMR spectrums, these compounds were specified. FT-IR compound's spectrum [7], displayed the band absent at (1751) cm-1because of (C=O) acid chloride with appearing of absorption of two (C=O) (cyclic amide) in the area (1716-1774) cm-1 and band appearance at (1668) cm-1 due to (C=O) to benzothioate carbonyl group.

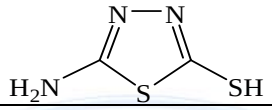
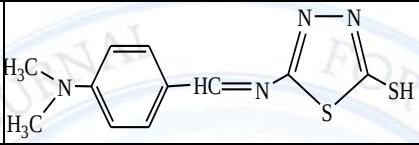
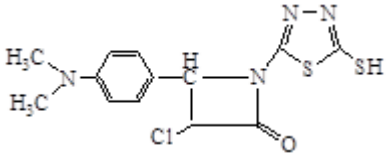
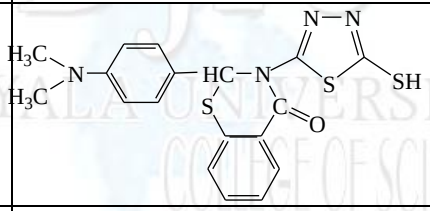
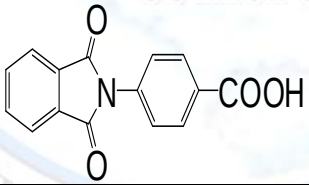
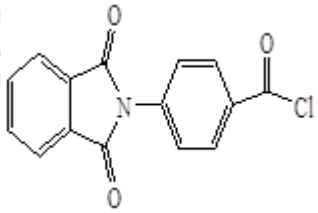
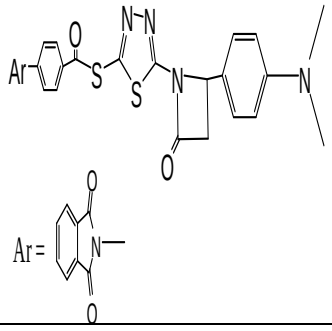
FT-IR compound's spectrum [9] displayed vanishing absorption peak at (1751)cm-1 because of (C=O) group in acid chloride with absorption band apparition of (C=O) (cyclic amide) at zone (1716-1774) cm-1 and of absorotion band appearing at (1668)cm-1 because of absorption of carbonyl group for benzothioate. The^{1}H-NMR compound's spectrum [9] performed the following characteristic chemical transfers (dmso-d6) ppm: the compound's aromatic ring proton [9] was clarified as multiple δ (7.18-8.16) ppm due to of protons benzene ring. Compound [10] was prepared the compound [10] by condensation of compound [5] with thiosemicarbazide in 5ml of POCl3 . It was studied the structure of this compound confirmed by FT-IR,melting point, 1H-NMR . The FT-IR spectrum of compound [10] displayed the absorption bands vanishing of band (C=O) of carboxylic acid with absorption bands appearing associated of (-NH_2) amine at (3338-3217) cm-1. .FT-IR spectra demonstrated absorption

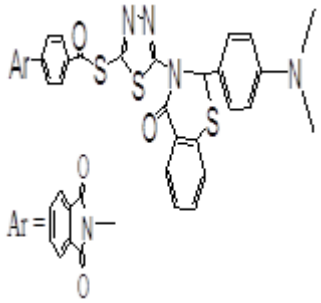
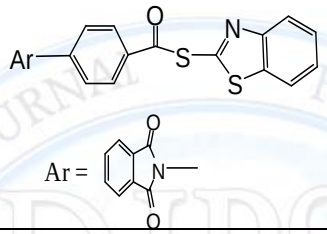
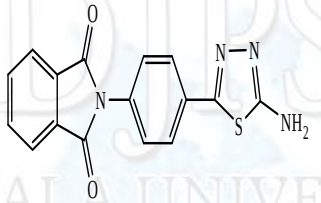
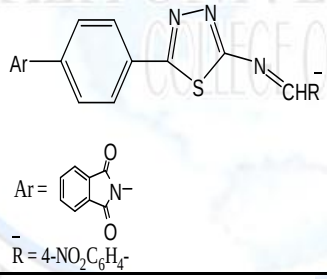
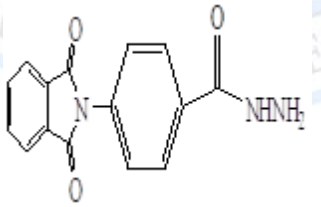
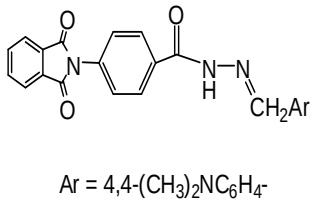
bands, including band at (1714-1784)cm^{-1} ,(1643)cm^{-1}, (1604)cm^{-1} , (1535)cm^{-1} , (1313-1375)cm^{-1} due to (C=O)imide , (C=N) ,(C=C) , (C-N) imide and (C-S). The 1H-NMR compounds' spectrum [10] displayed the chemical trasfers (DMSO-d6) ppm: the aromatic ring protons of this compound seemed as multiple (6.90-8.23) ppm and δ (5.25-5.36) br. s,2H of (NH_2) .Compound [12] was produced by the treated of compound [6] with 80% of hydrazine hydrate in absolute of ethyl alcohol . The compound was identified by FT-IR and ^{1}H-NMR spectra . IR spectrum of compound [12] , showed the disappearance of carbonyl group at (1751) cm^{-1} and appearance peak at(3348-3243) cm^{-1} related to asymmetric and symmetric stretching vibration of (-NH_2) group and at (1662) cm^{-1} for (C=O) group of amide . ^{1}H-NMR spectrum of compound [12],showed the following characteristic chemical shifts , (DMSO-d6) ppm : the protons of aromatic ring compound [12] appeared as multiple at δ (6. 97- 8.09) ppm , signal at δ (4.10)ppm due to the(-NH_2) proton and protons of (-NH) appeared at δ (10-5.6) ppm .

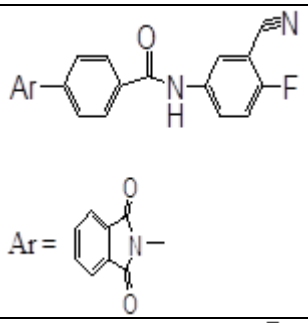
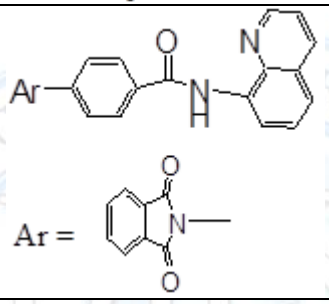
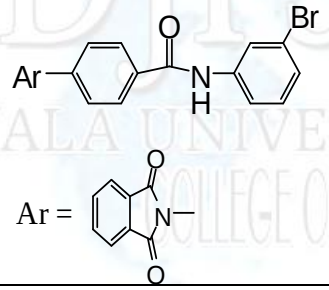
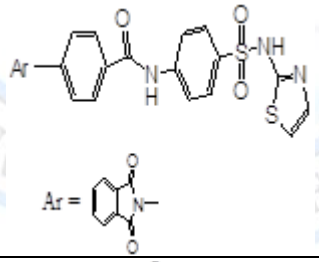
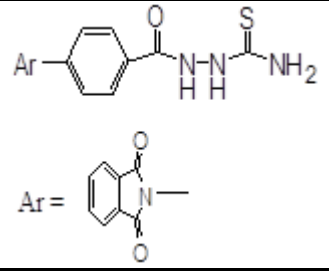
The intensification interaction of the compound isothermal quantity [10] and [12] with $C_7H_5NO_3$ was the main technique of preparing Schiffs bases .The product structure evaluation were based on its melting point, FT-IR and 1H-NMR spectrum . (FT-IR) Schiff base spectrum [11],[13] displayed appearancing of characteristic absorption bands at the area (1653-1647) cm-1 region associated with (C=N) stretching vibration for C17H13NO8S2 band aside from the vanishing of the absorption band at the area (3348-3243) cm-1 belong to the identical and non-identical stretching vibration of the (-NH_2) group. The 1H-NMR compound's spectrum [13] displayed the following characteristic chemical shifts, (DMSO) pare per million as it can be seen in Fig (21): the aromatic ring protons was shown as a multiple at δ (6. 60- 8.69) ppm , signal at δ (10.13) ppm because of (C-H) Schiff. While (-NH) protons were noticed at δ (12.14) ppm . Amides compounds were synthesized by the compound interaction [6] with primary amine in dry benzene . It was characterized compounds by FT-IR and 1H-NMR spectrum. FT-IR compound's spectrum [14] revealed two absorption band vanishing, yhis was because of (-NH2) stretching vibration of amino group with absorption appearing of 2 (C=O) (cyclic amide) at the area (1716-1784) cm-1 and band appearance at (1660)cm-1 due to (C=O) to carbonyl group of amide . In table (2), the compound characteristic bands [14a-i] can be shown .The1H-NMR compounds' spectrum [14] demonstrated the following characteristic

chemical transfers (DMSO-d6) part per million : the aromatic ring proton of compound [14] that was seen in multiple δ (6.78-8.27) ppm and signal at δ (10.52) linked to (NH).

Table 1: Show the nomenclature, melting points, structural and molecular formula for compounds

Comp No.	Nomenclature	Structural formula	Molecular formula	M.p. C°	Color
1	2-amino-5-mercapto-1,3,4-thiadiazole		$C_2H_3N_3S_2$	230-232	Yellow
2	5-(4-(dimethylamino) benzylideneamino)-1,3,4-thiadiazole-2-thiol		$C_{11}H_{12}N_4S_2$	264-266	Orange
3	3-chloro-4-(4-(dimethyl amino)phenyl)-1-(5-mercapto-1,3,4-thiadiazol-azetidin-2-one		$C_{13}H_{13}ON_4S_2Cl$	340-342	Brown
4	2-(4-(dimethylamino) phenyl)-2,3-dihydro-3-(5-mercapto-1,3,4-thiadiazol-2-yl)benzo[1,3-e]thiazin-4-one.		$C_{18}H_{16}ON_4S_3$	390-392	Yellow
5	4-(N-phthalimide)benzoic acid		$C_{15}H_9NO_4$	288-290	White
6	4-(N-phthalimide)benzoyl chloride		$C_{15}H_8ClNO_3$	254-257	Off – white
7	S-5-(2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-yl)-1,3,4-thiadiazol-2-yl 4-(1,3-dioxoisoindolin-2-yl)benzothioate		$C_{27}H_{22}N_5O_4S_2$	146-148	Brown

8	S-5-(2-(4-(dimethylamino)phenyl)-4-oxo-2H-benzo[e][1,3]thiazin-3(4H)-yl)-1,3,4-thiadiazol-2-yl 4-(1,3-dioxoisoindolin-2-yl)benzothioate		$C_{32}H_{24}N_5O_4S_3$	233-235	Yellow
9	S-benzo[d]thiazol-2-yl 4-(1,3-dioxoisoindolin-2-yl)benzothioate		$C_{22}H_{12}N_2O_3S_2$	224-226	Pale brown
10	2-(4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl)isoindoline-1,3-dione		$C_{16}H_{10}N_4O_2S$	184-186	Brown
11	(E)-2-(4-(5-(4-nitrobenzylideneamino)-1,3,4-thiadiazol-2-yl)phenyl)phthalimide		$C_{23}H_{13}N_5O_4$	109-111	Yellow
12	4-(N-phthalimide)benzohydrazide		$C_{15}H_{11}N_3O_3$	272-275	White
13	(E)-N-(4-(dimethylamino)benzylidene)-4-(1,3-dioxoisoindolin-2-yl)benzamide		$C_{24}H_{20}N_4O_3$	240-243	Yellow

14a	N-(3-cyano-4-fluorophenyl)-4-(phthalimide)benzamide		$C_{22}H_{11}FN_3O_3$	94-96	Silver
14b	4-(phthalimide)-N-(quinolin-8-yl)benzamide		$C_{24}H_{15}N_3O_3$	235-237	Pale brown
14c	N-(3-bromophenyl)-4-(phthalimide)benzamide		$C_{21}H_{13}BrN_2O_3$	273-275	Yellow
14d	4-(1,3-dioxoisoindolin-2-yl)-N-(4-(N-thiazol-2-ylsulfamoyl)phenyl)benzamide		$C_{24}H_{16}N_4O_5S_2$	230 -233	White
14e	2-(4-(1,3-dioxoisoindolin-2-yl)benzoyl)hydrazinecarbothioamide		$C_{16}H_{12}N_4O_3S$	187-189	White

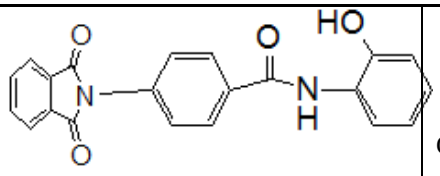
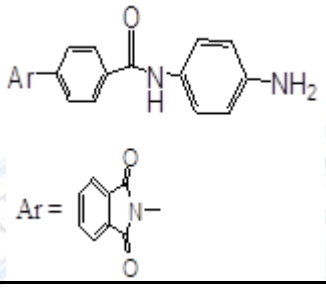
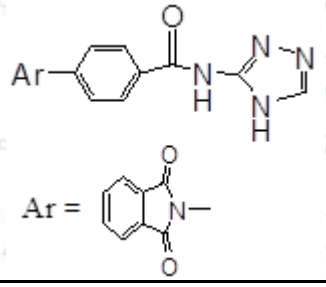
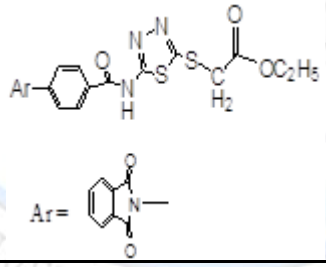
14f	4-(phthalimide)-N-(2-hydroxyphenyl)benzamide		$C_{21}H_{14}N_2O_4$	282-284	White
14g	N-(4-aminophenyl)-4-(1,3-dioxoisoindolin-2-yl)benzamide		$C_{21}H_{15}N_3O_3$	240-243	Off-white
14h	4-(1,3-dioxoisoindolin-2-yl)-N-(4H-1,2,4-triazol-3-yl)benzamide		$C_{17}H_{11}N_5O_3$	295-297	White
14i	ethyl 2-(5-(4-(phthalimide)benzamido)-1,3,4-thiadiazol-2-ylmercapto)acetate		$C_{21}H_{16}N_4O_5S_2$	252-254	Off-white

Table 2: FT-IR data of amides compounds [14 a-i]

Compounds number	υ (C=O)cm^{-1} amide	υ (C=O)cm^{-1} imide	υ (C=C)cm^{-1}arom.	υ (N-H)cm^{-1}
14a	1660	1710-1786	1527	3346
14b	1678	1718-1787	1539	3369
14c	1660	1705-1778	1589	3373
14d	1660	1716-1788	1595	3321
14e	1674	1716-1788	1533	3363
14f	1629	1707-1786	1598	3323
14g	1651	1712-1788	1570	3334
14h	1662	1720-1784	1548	3309
14i	1658	1716-1784	1537	3159

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