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# Synthesis and Characterization of Some New Compounds of Imide Moiety and Their Antibacterial Evaluating

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## Abstract

In the present study, a series of novel phthalimide derivatives are synthesized because of its potent antibacterial activity. structurally modified phthalimide derivatives are prepared through condensation of 4-(1,3-dioxoisoindolin-2-yl) benzoyl chloride with corresponding furan-2-carbohydrazide , 5-(isopropylthio)-1,3,4-thiadiazole -2-amine,5-(4-chloro phenyl)-1,3,4-thiadiazole-2-amine and 4,7-dichlorobenzo[d]thiazol-2-amine with variable yields. structures of the prepared compounds were confirmed by spectroscopic methods including FT-IR and $^{1}$H-NMR. Finally antibacterial activity of some of the prepared new cyclic imides are evaluated against two types of bacterial *Eschericha-coli* and *Staphylococcus aureus* and the results show that the most of the tested imides posses good biological activity against these organisms.

Key Words:- Thiadiazole ,Furan ,Phtalimide derivatives.

# تحضير وتشخيص بعض المركبات الجديدة لوحدة الامايد ودراسة الفعالية البايولوجية لها

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**الخلاصة:-**

في هذه الدراسة حضرت سلسلة من مشتقات الفثالامايد الجديدة وذلك لانها تمتلك فعالية عالية ضد بعض انواع البكتريا. حضرت مشتقات من الفثالامايد المحورة تركيبيا عن طريق تكثيف٤-(١و٣-ثنائياوكسواندولين-٢-يل)كلوريد البنزويل مع مركبات فيوران-٢-كاربوهيدرازايد و ٥-(ايزوبروبايل ثايو)-١و٣و٤-ثايادايزول-٢-امينو٤,٧-ثنائي كلوروبنزو [d] ثيازول -٢-امين وبنسب نواتج مختلفة. تم اثبات صحة تراكيب المركبات المحضرة بالاعتماد على استخدام الطرق الطيفية ،مطيافية الاشعة تحت الحمراء والرنين النووي المغناطيسي.واخيرا تم تقدير الفعالية البايولوجية لبعض الايميدات الحلقية ضد نوعين من البكتريا هما *Eschericha-coli*، *Staphylococcus aureus* واظهرت النتائج ان اغلب الايميدات المحضرة تمتلك فعالية بايولوجية جيدة ضد الانواع المذكورة من البكتريا.

الكلمات المفتاحية:-

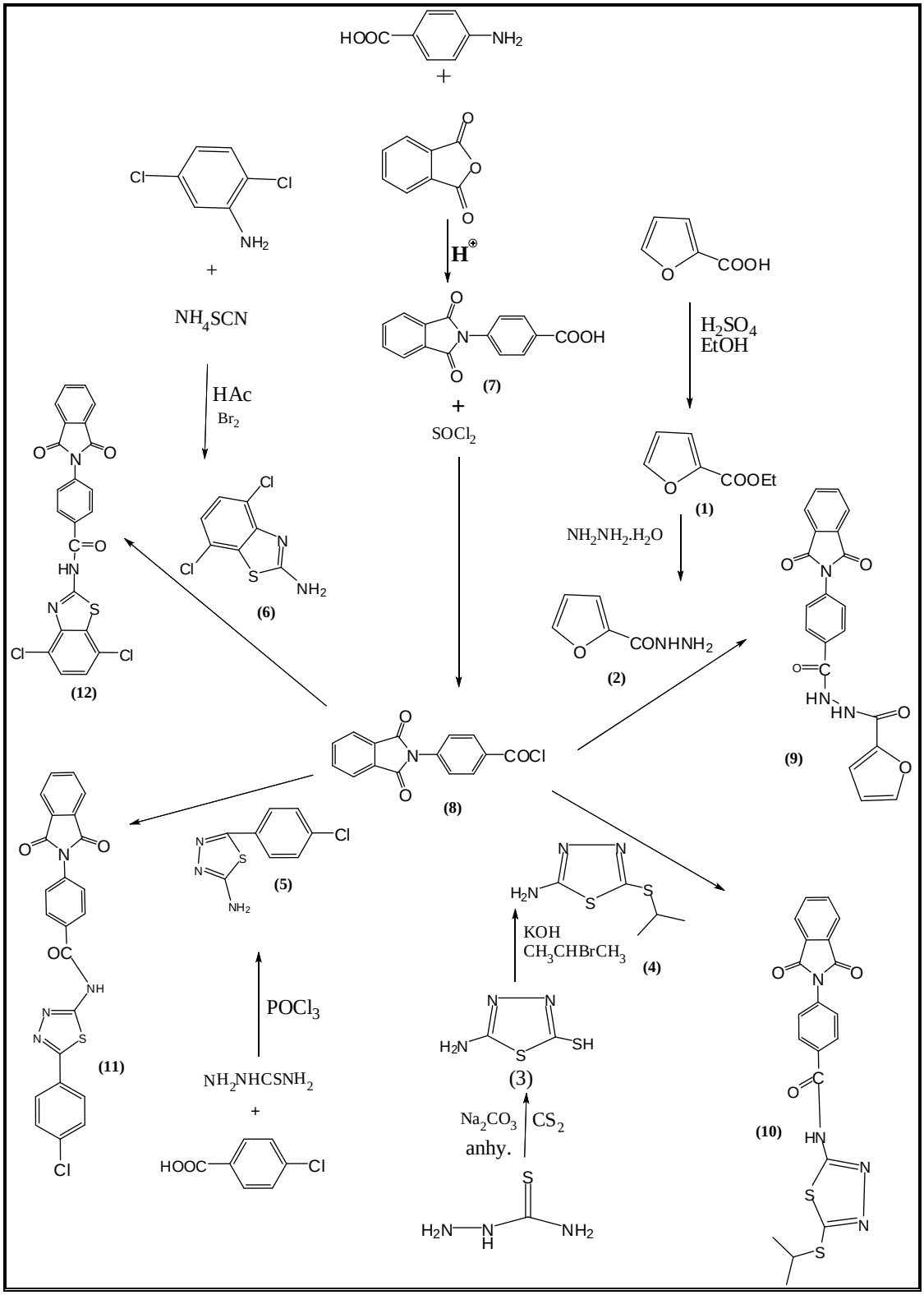
الثايادايزول، الفيوران، مشتقات الفثالامايد.

## Introduction

Small molecules and macromolecules containing imide groups exhibit great electrical properties, good solubility in polar media ,resistance to hydrolysis and high thermal stability. Due to their excellent properties many efforts have been made to produce different compounds containing imide groups consisting of two carbonyl groups bound to nitrogen[(1)].

Imides and their derivatives are also used in polymer chemistry. Today various routes are a vailable for the synthesis of imides which involve either Lewis-acid mediated condensation of an amine with maleic ,phthalic anhydride or N-alkylation of the corresponding imide with halides or alcohols[(2)]. On the other hand naphthalimides first discovered

by Brana and Coworkers[3,4] are DNA-targeted chemotherapeutic agents acting primairly by attacking DNA at some level (synthesis ,replication or processing) thus may naphtalimides have shown high anticancer activity[5,6] against a variety of murine and tumor cells , therefore plenty of naphthalimide based anticancer drugs[7-10]have been synthesized and promising results have been obtained .


HOOC
NH2
+
Cl
Cl
NH2
+
NH4SCN
HAc
Br2
H⊕
O
O
O
COOH
N
(7)
+
SOCl2
H2SO4
EtOH
COOEt
(1)
NH2NH2.H2O
CONHNH2
(2)
(6)
(12)
(8)
COCl
(9)
(5)
(11)
POCl3
NH2NHCSNH2
+
HOOC
Cl
KOH
CH3CHBrCH3
(4)
(3)
Na2CO3
anhy.
CS2
SH
(10)

**Scheme (1)**

## Experimental

Chemicals used in this work are supplied from BDH and Fluka companies and are used without further purification. Melting points was recorded by digimelt MPA161 (MSRS) electronic and was uncorrected. FT-IR spectra were recorded on SCHIMADZU FT-IR 8400 Fourier Transformer infrared spectrophotometer using KBr disc. $^{1}$H-NMR spectra were recorded on Bruker ultra shield 300MHz instrument using DMSO – d6 as a solvent and TMS as internal reference.

**- Synthesis of ethyl furan-2-carboxylate [1][(11)]**

A mixture of 2-furoic acid (0.01 mol.) with absolute ethanol absolute and (3ml) of sulfuric acid and the reaction mixture was heated under reflux for 4 hr. The reaction mixture was then allowed to cool down at room temperature ,extracted with ethyl acetate then the extraction solution was evaporat to yield [1].

**Synthesis of ethyl furan-2-carbohydrazide [2][(12)]**

To a stirring mixture of corresponding compounds [1] (0.01 mol.) and 80% hydrazine hydrate (0.05 mol.) in dry benzene (15ml.) was refluxed for 4h. After cooling , the solvent and excess hydrazine hydrate were removed under reduce pressure , the residue was washed with ether , then recrystallized from ethanol to give solid products , yield (81%) .m.p(74)C$^{o}$,lit(76) C$^{o}$.

**Synthesis of 2-amino-5-mercapto-1,3,4-thiadiazole[3][(13)] .**

A mixture of (2g , 0.02 mol.) of thiosemicarbazide and (2.33g , 0.02mol.) of anhydrous sodium carbonate were dissolved in 25 ml. absolute. ethanol . To this solution (3.2g , 0.04 mol.) of carbon disulphide was added.

The resulting mixture was heated under reflux for 10 h.,the reaction mixture was then allowed to cool down at room temperature . Most of

solvent was removed under reduced pressure and the residue was dissolved in (20ml.) distilled water, carefully acidified with cold conc. hydrochloric acid to give pale yellow precipitate . The crude product was filtered and washed with cold water , recrystallized from hot water to give the desired product as yellow needles , yield (75%),m.p(230-232)$C^o$. lit.(230)$C^o$ .

**Synthesis of 2-amino-5-alkylthio-1,3,4-thiadiazole[4][(14)].**

Compound [1],(0.001mol.) containing (-SH) group was dissolved in (10ml.)dioxan , which contained(0.001mol.) potassium hydroxide. Alkylhalide (0.001mol.) was added using separating funnel dropwise with stirring . The reactants were refluxed for 5 hrs. The solvent was evaporated under reduced pressure ,water was added, and the crude product was extracted with ethyl acetate and dried with anhydrous magnesium sulphate evaporation of the organic layer gave solid products , recrystallized from dioxin to give the desired product , m.p (139-140)$C^o$, yield (80.5%) .

**Synthesis of 5-(4-chlorophenyl)-1,3,4-thiadiazole -2-amine[5][(15)]**

An equimolar mixture (0.01moe) of compound [4-chlorobenzoic acid] with thiosemicabazide was refluxed in the presence of phosphorous oxychloride (5ml.) for 4h. After then the mixture was cooled and diluted with water (10ml.) .The mixture was filtered and the filtrate was neutralized with potassium hydroxide solution . The precipitate was filtered off and recrystallized from ethanol to give solid product ,m.p (225-227)$C^o$ , yield(75%) .

**Synthesis of 4,7-dichlorobenzo[d]thiazol-2-amine[6][(16).]**

2,5-dichloroaniline (0.001mol.) dissolved in acetic acid with stirring, ammonium thiocyanate (0.001mol.) dissolved in acetic acid with stirring and mixed the two solutions with stirring for two hours. Then (0.001mol.) of bromine in acetic acid was added to the mixture with stirring and dissolved in water, filtered, neutralized with potassium hydroxide to produce white precipitate, m.p.(245-247) ,yield (78%).

**Synthesis of 4-(1,3-dioxoisoindolin-2-yl)benzoic acid[7][(17)]**

A mixture of equimolar amounts (0.001mol.) of commercially available phthalic anhydride and p-amino benzoic acid in presence of (15ml) of glacial acetic acid . The mixture was refluxed for (4 h.) , then 25ml of ice cold distilled water was added to the reaction medium and the compounds were filtered ,dried and recrystallized from ethanol m.p(293)$^0$C yield(69%).

**Synthesis of 4-(1,3-dioxoisoindolin-2-yl)benzoyl chloride [8][(18)].**

A mixture of compound [7] (0.01mole) and thionyl chloride (10ml.) in dry benzene (5ml.) was refluxed for 3h . After cooling the excess of thionyl chloride and benzene were removed under vacuum . The product was crystals, yield (80%) ,m.p(254-257)C$^o$ .

**General method for synthesis of compounds** [9-12].

The compounds which contain (-$NH_2$) groups (0.01mol) were dissolved in dry benzene (10ml.) . Compound [8] was added and refluxed for (4-5h) . After cooling , the solvent was removed under reduced pressure , water was added , filtered , dried and recrystallized from ethanol to give products table(1) .

Biological study

The cup plate agar diffusion method was employed in studying the antibacterial activities of the prepared imides against two types of bacteria ,*staphylococcus Aureous and Eschericha* (E.Coli) as a grame negative in nutrient agar medium.DMSO was used as solvent. All the synthesized compounds(50µg/ml)were placed serially in the cavities with the help of micro pipette and allowed to diffuse for 1 hour. Then plates were incubated at 37$^{o}$C for 24 hr. The zone of inhibition observed around the cups after respective incubation was measured in mm. and the results was shown in table 3

**Results and Discussion**

Scheme (1)summarized the performed reactions in this work. Ethyl furan -2-carboxylate(1), was prepared by reaction of 2-furoic acid in absolute ethanol. The formation of this compound (1) was identified by the presence in its IR spectrum of the (C=O)of ester at 1735 $cm^{-1}$, combined with the disappearance of the both absorption stretching bands at 1678 $cm^{-1}$ and (2500-3200) $cm^{-1}$ for (C=O) group and (OH) group respectively.

Compound (2) was synthesized by the reaction of compound (1) with 80% of hydrazine hydrate. The FT-IR spectrum of compound (2) showed the appearance of characteristic absorption bands in (3313) $cm^{-1}$,(3269) $cm^{-1}$ and (3149) $cm^{-1}$ due to the asymmetric , symmetric stretching of (-$NH_2$) group and (-NH)group respectively,The appearance of a band at (1685) $cm^{-1}$ may refer to stretching vibration of carbonyl amide group.

2-amino-5-mercapto-1,3,4-thiadiazole (3)was prepared through the reaction of thiosemicarbazide with carbon disulphide in presence of anhydrous sodium carbonate. The FT-IR spectrum showed the azomethine (C=N) and thiol(SH) stretching bands at (1640) $cm^{-1}$ and (2600) $cm^{-1}$(weak) .

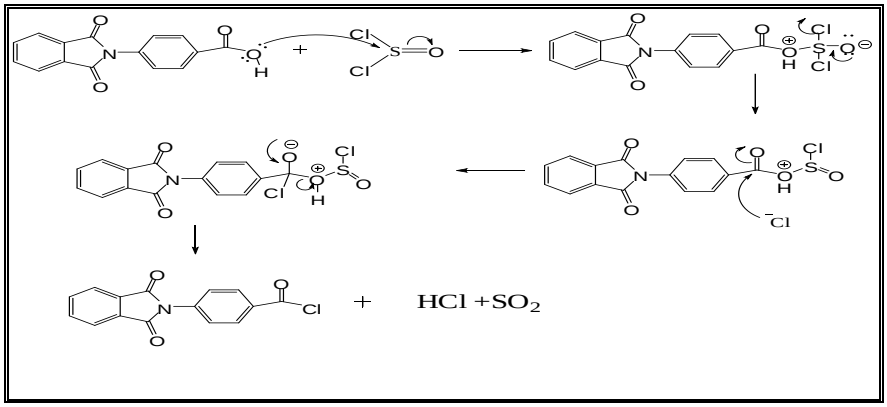
The chemical reactivity of the (SH) group at position (5) in compound (4) plays a significant role in using this compound as a key intermediate for the synthesized of target compounds. Thus ,when compound(4) was treated with ethyl iodide in basic medium (KOH). The FT-IR spectrum showed the(S-CH($CH_3$)$_2$) stretching absorptionnear(1411,1327) $cm^{-1}$.

Compound (5) was synthesized by the condensation of 4-chlorobenzoic acid with thiosemicarbazide in 5 ml of phosphorousoxychloride. The FT-IR spectrum of compound(5) showed disappearance of absorption band for (C=O) group of carboxylic acid with appearance of absorption bands belong to (-$NH_2$)amine at (3277,3101) $cm^{-1}$ .Also ,FT-IR spectrum showed absorption bands at(1633) $cm^{-1}$ ,(1568) $cm^{-1}$ ,(1336,1379) $cm^{-1}$ which may due to (C=N),(C=C) and (C-S) respectively.

Reaction between 2,5-dichloroaniline dissolved in acetic acid, ammonium thiocyanate dissolved in acetic acid and bromine in acetic acid gave compound[6]. The FT-IR spectrum of this compound showed appearance of absorption band at (1635) $cm^{-1}$ due to (C=N) group, absorption band at (3269-3456) $cm^{-1}$ attributed to the (-$NH_2$)group.

4-(1,3-dioxoisoindolin-2-yl)benzoic acid (7) was prepared by the reaction of ρ-amino benzoic acid with phthalic anhydride in glacial acetic acid . The FT-IR showed the disappearance of absorption bands of two (C=O) (anhydride)band with appearance of two (C=O) (cyclic imide) at (1716-1778)$cm^{-1}$, and band at (1687)$cm^{-1}$ which may assign to (C=O) of carboxylic acid.

The compound (8) was prepared by condensation of compound(7) with thionylchloride . a mechanism for this reaction may be outlined as followed :




Scheme(2)

The FT-IR showed disappearance of absorption band at (1687)$cm^{-1}$ might be due to the carboxylic (C=O) and (2549-3088) $cm^{-1}$owing to (O-H) of carboxylic acid with appearance of a band at (1751)$cm^{-1}$bearing to the carbonyl group of the acyl chloride .

The prepared compounds (9-12) are colored solids and afforded in high percent yields. Structures of these compounds were confirmed by FT-IR and $^{1}$H-NMR. FT-IR spectra of all the prepared amides showed disappearance of two absorption bands at (3301-3456) $cm^{-1}$ which belongs to the (-$NH_2$) group with appearance of band at (1662-1691) $cm^{-1}$ refers to the carbonyl group of amide. The $^{1}$H-NMR spectrum of compound (9)showed clear signals at δ(7.21-8.11)ppm which belong to the aromatic ring protons, a singlet at δ(9.98)ppm owing to the (NH) and protons of furan at δ(6.51-6.55)ppm.

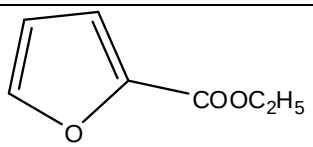
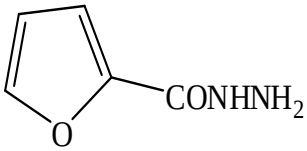
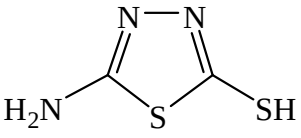
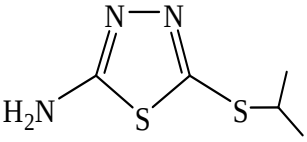
Finally $^{1}$H-NMR spectrum of compound (10) showed many multiplet at δ (7. 21- 8.25) ppm, singlet at (13.02)ppm due to the (NH), triple signal at δ (1.38) ppm for the methyl group and a multiplet at δ (3.7) ppm belongs to (C-H) group.

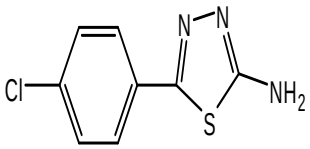
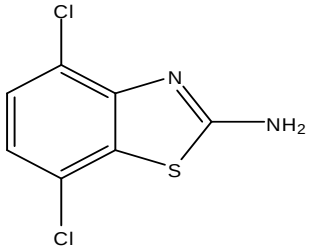
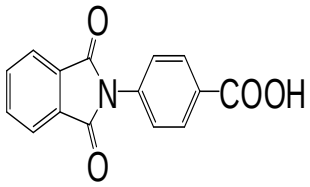
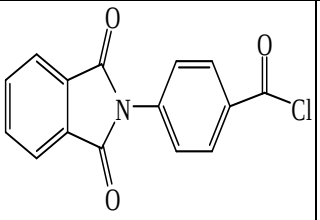
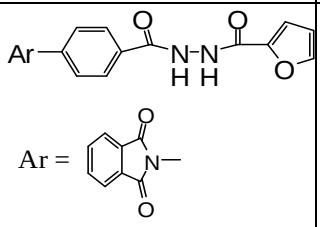
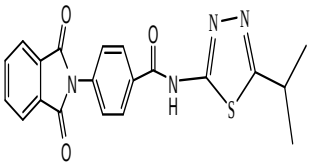
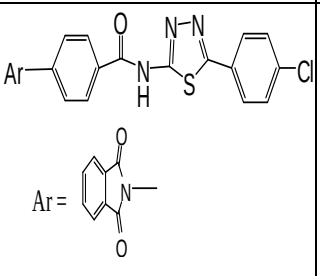
**Biological activity**

The results of antibacterial activities of some synthesized compounds against two microorganisms (*E. coli* , *S. aureus*) are presented in table (3) which the zone of inhibition was measured in mm. The results revealed that compounds showed varying degrees of inhibition against the tested microorganism. In general the compounds [3,4,5] exhibited potent activity against (*E. coli* , *S. aureus*) bacteria. These compounds showed high activity against *E.Coli* .

The compounds [9-12] showed good activity against *S.aureous* (+Gr), while compounds [1.2,6,7,8,10] did not show any activity against (*E. coli* , *S. aureus*) when compared with the two standard drugs.

Table (1): physical properties of the prepared compounds

| No | Name of compound | Structural formula | M.p. C$^{o}$ | Yield % | Color |
|---|---|---|---|---|---|
| 1- | ethyl furan-2-carboxylate |  | **Liquid** | **78** | Yellow |
| 2- | furan-2-carbohydrazide |  | **74** | **81** | White |
| 3- | 2-amino-1,3,4-thiadiazole-5-thiol |  | **230-232** | **75** | Yellow |
| 4- | 5-(isopropylthio)-1,3,4-thiadiazol-2-amine |  | **139-140** | **80.5** | White |

| | | | | | |
|---|---|---|---|---|---|
| **5-** | 5-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine |  | **225-227** | **75** | Brown |
| **6-** | 4,7-dichlorobenzo[d]thiazol-2-amine |  | **245-247** | **78** | White |
| **7-** | 4-(1,3-dioxoisoindolin-2-yl)benzoic acid |  | **293** | **91** | White |
| **8-** | 4-(1,3-dioxoisoindolin-2-yl)benzoyl chloride |  | **254-257** | **80** | Off – white |
| **9-** | N'-(4-(1,3-dioxoisoindolin-2-yl)benzoyl)furan-2-carbohydrazide |  | **288-289** | **64** | White |
| **10-** | 4-(1,3-dioxoisoindolin-2-yl)-N-(5-isopropyl-1,3,4-thiadiazol-2-yl)benzamide |  | **270-272** | **71** | Off – white |
| **11-** | N-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)-4-(1,3-dioxoisoindolin-2-yl)benzamide |  | **298-300** | **75** | yellow |

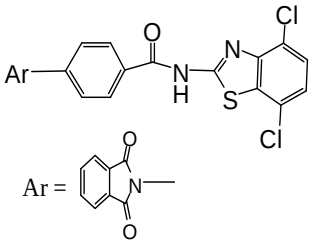
| | | | | | |
|---|---|---|---|---|---|
| **12-** | N-(4,7-dichlorobenzo[d]thiazol-2-yl)-4-(1,3-dioxoisoindolin-2-yl)benzamide |   | **296** | **83** | Off-white |

Table ( 2 ) : FT-IR spectral data of the prepared compounds

| Comp.No. | ν (C-H) arom. | ν (C=O) imide | ν (C=C) arom. | ν (C=O) amide | ν (N-H) $NH_2$ | ν (C=N) |
|---|---|---|---|---|---|---|
| 1 | | | | | | |
| 2 | | 1595 | 1685 | | 3313,3269 | |
| 3 | | | | | 3396,3277 | 1604,1564 |
| 4 | | | | | 3282,3105 | 1633 |
| 5 | 3010 | | 1597 | | 3277,3101 | 1633 |
| 6 | 3070 | | | | 3458,3269 | |
| 7 | 3020 | 1716,1778 | 1583 | | | |
| 8 | | 1711,1734 | 1554 | | | |
| 9 | 3050 | 1714,1737 | 1583 | 1691 | 3322,3287 | |
| 10 | 3080 | 1716,1735 | 1604 | 1662 | 3120 | 1604 |
| 11 | 3053 | 1718,1739 | 1598 | 1674 | 3269 | 1629 |
| 12 | 3040 | 1739,1768 | 1591 | 1664 | 3456,3269 | 1608 |

Table (3):Antibacterial activity for some of the prepared compounds.

| Compounds | *E.coli-(mm)* | *s.aureous-(mm)* |
|---|---|---|
| Penicillin | 16 | 22 |
| Azithromycine | 20 | 30 |
| DMSO | Nil | Nil |
| 1 | 0 | 0 |
| 2 | 0 | 0 |
| 3 | 20 | 20 |
| 4 | 19 | 20 |
| 5 | 11 | 12 |
| 6 | 0 | 0 |
| 7 | 0 | 0 |
| 8 | 0 | 0 |
| 9 | 7 | 10 |
| 10 | 0 | 0 |
| 11 | 9 | 12 |
| 12 | 10 | 11 |

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