Synthesis of some new heterocyclic compounds derived from 2-Chloro-3-formyl quinoline

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الخلاصة

يتضمن هذا البحث تحضير عدد من معوضات 2- كلورو -3- فورميل كوينولين(2a – d) من خلال تفاعل معوضاتالاسيتنالايد او 1- (4- معوضاتالفنيل) ايثانوناوكسيم مع $POCl_3$ في ثنائي مثيل فورماميد من خلال تحولقفلزمايرـهوك. ان تكاثف 2- كلورو-3- فورميل كوينولين مع بارا هيدروكسي اسيتوفينون, 2- استيل بريدين, 2- استيل فيوران او 3- استيل اندول من خلال تكاثف كلايسنـشميدت يعطي جالكوناتالكوينولين(4a – d). تم تحضير مشتقات جديدة للبارازولين من خلال تكاثف الجالكون (4a) مع الهيدرازين المائي او مع فنيل هيدرازين (10, 11) تم الحصول على مركب الاوكسازول (12) منتفاعلالمركب (4a) وهيدروكلورايدهيدروكسيل امين في الوسط القاعدي.ان تفاعل الجالكون (4a) مع اليوريا, الثايويوريا او معهيدروكلورايدالكواندين يعطي مركبات البريميدين-2-اون (7) و البريميدين-2-ثايون (8) او 2- امينو بريميدين (9). حضر الاوكسيران (6)من خلال تفاعل الجالكون (4a) مع بيروكسيد الهيدروجين في الوسط القاعدي. ان تفاعل الجالكون (4a) مع البروم يعطي مركب ثنائي البروميد(5).تم تشخيص تراكيب المركبات المحضرة باستخدام الطرق الطيفية والفيزياوية.

ABSTRACT

In this paper the Synthesis of some substituted 2-Chloro-3-formyl quinoline (2a–d) by treating various substituted acetanilide or 1-(4-substituted phenyl) ethanone oxime with $POCl_3$ in dimethyl formamide. It proceeds through Vilsmeier – Haack cyclization. The condensation of 2-chloro-3-formylquinoline with *p*-Hydroxyacetophenone, 2-acetyl pyridine, 2-acetyl furan or 3-acetyl indole via Claisene– Schmiatcondensations gives quinolinylchalcone (4a – d). Newpyrazoline derivatives were synthesized by condensing the appropriate chalcone (4a) with hydrazine hydrate or phenylhydrazine (10 – 11). Oxazole (12) is reported from compound (4a) and hydroxyl amine hydrochloride is in basic medium. The reaction of chalcone (4a) with urea, thiourea or quinidine hydrochloride gives pyrimidine-2-one (7), pyrimidine-2-thiol (8) or 2- amino pyrimidine (9) respectively.Oxirane (6) prepared from reaction of chalcone (4a) with hydrogen peroxide in basic medium. The reaction of chalcone (4a) with bromine gives dibromide (5). The structures of synthesized compounds were confirmed by spectral and physical methods.

* ***Presented at the second conference on Chemistry, University of Mosul, college of Education, 17-18 Novamber-2013.***

INTRODUCTION

Quinoline, also known as L-azanaphthalene, 1-benzaine or benzo(b)pyridine is an aromatic nitrogen compound characterized by a double ring structure contain a benzene fused pyridine at two adjacent carbon. Quinoline family compounds are widely used as a parent compound to make drug especially anti-malarial [1], anti-inflammatory [2,3], anti-bacterial [3,4,5], anti-fungal [6], anti-microbial agent [7], anti-tumor [8], analgesic [9]. The plant family have been known to be the rich source of quinoline alkaloids [10], pyranoquinoline alkaloids gained importance due to their several pharmacological activities like anti-coagulant [11]. Several quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use. Indeed quinoline derivatives are some of the oldest compounds which have been utilized for the treatment of a variety of disease.The bark of the cinchona plant containing quinine was utilized to treat palpitations [12]. There are many methods available for functionalized quinolines the Vilsmeier approach is found to be among the most efficient for achieving useful transformations and hetero annulations, in fact 2-chloro-3-formyl quinoline the primary intermediate, is a good starting material for the preparation of different quinoline derivatives.

MATERIALS AND METHODS

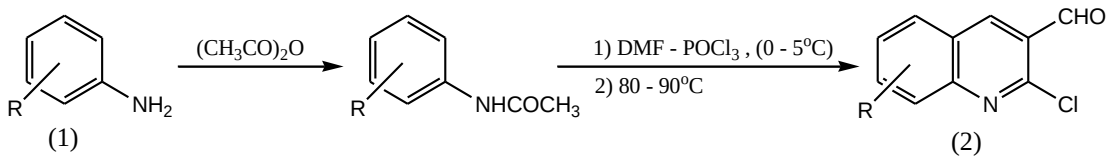
Melting point were recorded on electrothermal SMP30 melting point apparatus and are uncorrected, IR spectra were recorded on infrared spectrophotometer model tensor, Bruker Co. Germany by using KBr discs.^{13}C,^{1}H NMR spectra were recorded on a JEol 400MH, using Tetramethyl saline (TMS) as internal standard.

EXPERIMENTAL

The starting material, substituted acetanilide (I_a, I_b) was readily prepared from the reaction of corresponding anilines with acetic anhydride in aqueous medium [13].

General procedure for the Synthesis of substituted 2-Chloro-3-formyl quinoline (2a and 2b) [14].

To a solution of I_a and I_b (5 mmoles) in dry DMF (15 mmoles) at (0-15) °C with stirring $POCl_3$ (35 mmoles) was added drop wise. The mixture stirred at (80-90°C) for 16 *hrs*. The mixture was poured into crushed ice, stirred for 1 *hr*. and the resulting solid filtered, washed well with water and dried; the compounds were purified by recrystallizationfrom ethyl acetate. The melting point was (148-151°C) and (179-181°C) with 36% yield. The IR spectra and physical properties are listed in Table 1. (Scheme 1).



Scheme 1: Synthesis of 2-Chloro-3-formyl quinoline (2a – b)

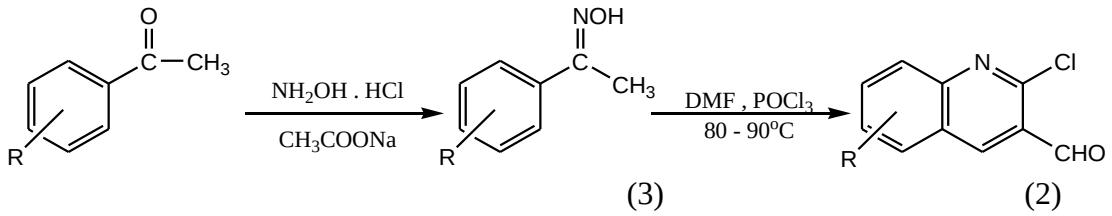
(1)	R	(2)	R	m.p °C
A	H	**a**	H	148-151
b	*m*-CH_3	**b**	7- CH_3	179-181

General procedure for the Synthesis of 1-(4-substituted phenyl) ethanone oxime (3a – d):

The 1-(4-substituted phenyl) ethanone oximes were synthesized from different substituted acetophenone (0.1mol), hydroxyl amine hydrochloride (0.12mol) and sodium acetate (0.12mol) using method reported by Chon *et al.* [14].

General procedure for the Synthesis of 2-Chloro-3-formyl quinoline from oxime (2a – d) [1, 3]:

To dry DMF (0.15mol) cooled to (0 – 5°C), $POCl_3$ (0.35mol) was added drop wise under stirring, and then the respective oxime (0.05mol) was added portion-wise. The reaction mixture was heated at (80 – 90°C) for 12 *hrs.* . It was then poured into ice water (300 mL) and stirred for 1*hr*. The substituted 2-Chloro-3-formyl quinoline was filtered and recrystallized from ethyl acetate. The IR spectra and physical properties are listed in Table 1. (Scheme 2).



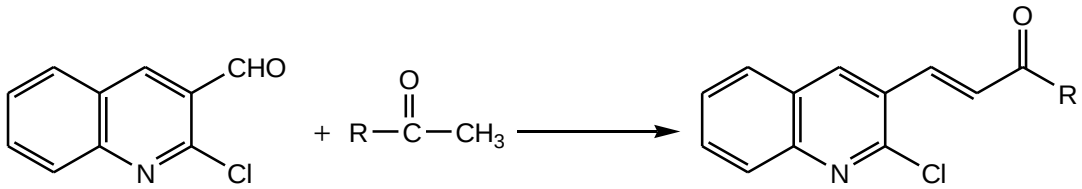
Scheme 2: Synthesis of 2-Chloro-3-formyl quinoline from oxime (2a – d)

(3)	R	(2)	R	m.p °C
a	H	**a**	H	147-152
b	4-NH_2	**b**	6-NH_2	216-220
c	4-OH	**c**	7-OH	140-142
d	2-OH, 4-OCH_3	**d**	5-OH ,7-OCH_3	144-146

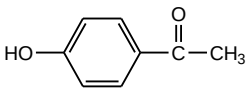
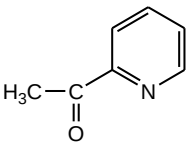
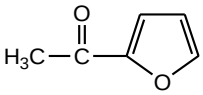
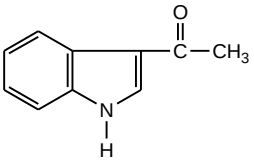
General procedure for Synthesis of Quinolinyle chalcones (4a – d) [15]:

2-Chloro-3-formyl quinoline (0.01mol) was added to an ethanolic (15mL) solution of *p*-Hydroxy acetophenone, 2-acetyl pyridine, 2-acetyl furan or 3-acetyl indole (0.01mol).

To the above reactionmixture, aqueous NaOH (40%, 0.03mol, 3mL) was added drop-wise with stirring. The reaction mixture was kept overnight, then acidified with cold dilute HCl, and the resulting solid filtered, washed well with water and dried. The IR spectra and physical properties are listed in Table 1. (Scheme 3).



Scheme 3: Synthesis of quinolinyle chalcone (4a – d)

		R	m.p °C
4a	(E)-3-(2-Chloroquinolin-3-yl)-1-(4-hydroxy phenyl)prop-2-en-1-one		185-187
4b	(E)-3-(2-Chloroquinolin-3-yl)-1-(pyridine-3-yl)prop-2-en-1-one		278-280 d
4c	(E)-3-(2-Chloroquinolin-3-yl)-1-(furan-2-yl)prop-2-en-1-one		160-162
4d	(E)-3-(2-Chloroquinolin-3-yl)-1-(1H-indol-3-yl)prop-2-en-1-one		254-256 d

3-(2-Chloroquinolin-3-yl)-1-(4-hydroxy phenyl)-2,3-dibromo-1-one (5):

To a stirred mixture of compound (4a) ($5x10^{-4}$mol, 0.36gm.)in 15mL ethanol was slowly added (1mL) of bromine. The reaction mixture was kept overnight at room temperature. The precipitate formed was collected, washed with water. The melting point was 192-195°C. The physical properties are listed in Table 1.

3-(2-Chloroquinolin-3-yl)-1-(4-hydroxyphenyl)-2,3-epoxy-1-propanone(6)[16]:

To solution of compound 4a (0.5mol, 0.86gm) in 25mL of methanol at 30°C, was added (1 mL) of 30% hydrogen peroxide, then (0.5 mL)of 16% Sodium hydroxide was added drop by drop with stirring

for (3 *hr*.). The mixture was cooled and left overnight at room temperature; precipitate was formed, recrystallized from ethanol. The melting point was (121-124°C). The physical properties are listed in Table 1.

4-(2-Chloroquinolin-3-yl)-6-(4-hydroxyphenyl)-3,4-dihydropyrimidine–2(1H)-one(7) [17]:

A solution of compound 4a (0.02mol, 0.61gm) in 15 mL ethanol was added to solution of Sodium ethoxide and urea (0.02mol, 0.34gm). The reaction mixture was heated under reflux for 2*hrs*. , the mixture was cooled and diluted with water and left overnight. The resulting product was filtered off, washed with 20 mL of a mixture of water / ethanol (1:1 v/v). The melting point was (154-156°C). The physical properties are listed in Table 1.

4-(2-Chloroquinolin-3-yl)-6-(4-hydroxyphenyl)-3,4-dihydropyrimidine–2(1H)-thione (8) [17]:

Compound 4a (0.02mol, 0.61gm) was added to Sodium ethoxide solution (0.1gm of Sodium metal in 20 mL of absolute ethanol). Then thiourea (0.02mol, 0.38gm) was added. The reaction mixture was refluxed for 4*hrs*. The precipitate which separated on cooling washed with ethanol. The melting point was (175-177°C). The physical properties are listed in Table 1.

2-Amino-4-(2-chloroquinolin-3-yl)-6-(4-hydroxyphenyl)-3,4-dihydro pyrimidine (9) [18]:

In a 100 mL two necked round bottomed flask equipped with a dropping funnel which charged with a solution of Sodium hydroxide (0.4gm in 5 mL of water), a mixture of 4a (0.0048mol, 0.58gm) and quainidine hydrochloride (0.0048mol, 0.86gm), in 20 mL of ethanol was refluxed while the solution of Sodium hydroxide was added drop by drop with stirring during 2*hrs*. . The mixture was reflux for 10*hrs*. . Let the mixture at room temperature then diluted with water and left overnight, precipitate was formed washed with 20 mL of a mixture of water/ethanol (1:1 v/v) then recrystallized from benzene to give compound (9).The melting point was (194-196°C). The physical properties are listed in Table 1.

3-(2-Chloroquinolin-3-yl)-5-(4-hydroxyphenyl)-2,3-dihydropyrazoline(10)[19]:

A mixture of compound 4a ($5x10^{-3}$mol, 1gm) and hydrazine hydrate ($5x10^{-3}$mol, 2 mL) in 20 mL ethanol was refluxed for 4*hrs*. . The reaction mixture was concentrated to half under vacuum, then left to cool, the precipitate which separated was collected, washed with water and recrystallized from ethanol.The melting point was (186-188°C). The physical properties are listed in Table 1.

1-Phenyl-2-(2-chloroquinolin-3-yl)-4-(4-hydroxyphenyl)-1,2-dihydropyrazoline(11)[19]:

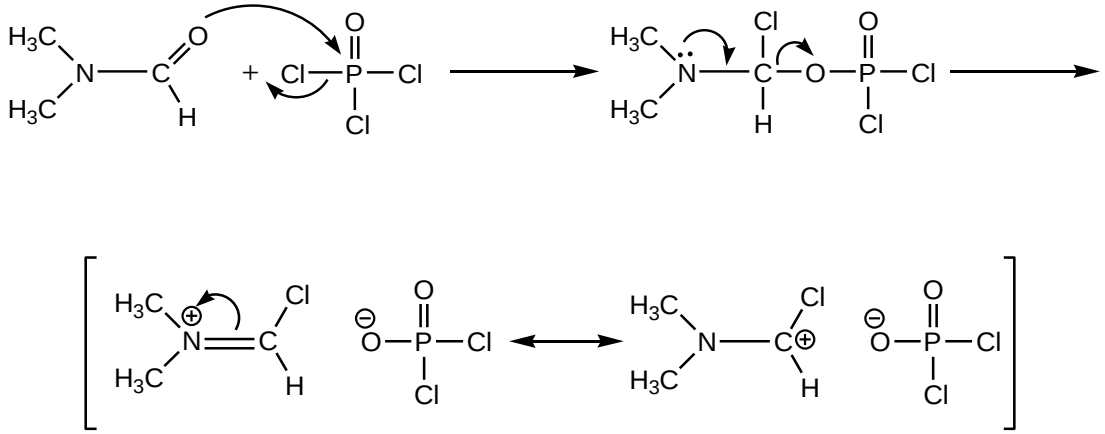
A mixture of compound 4a ($25x10^{-4}$mol, 0.61gm) and phenyl hydrazine ($25x10^{-4}$mol, 0.27gm) in ethanol was refluxed for 24*hrs*. . The reaction mixture was concentrated to half under vacuum. The precipitate which separated on cooling was recrystallized from ethanol.The melting point was (192-195°C). The physical properties are listed in Table 1.

3-(2-Chloroquinolin-3-yl)-5-(4-hydroxyphenyl)-4,5-dihydroOxazole(12)[20]:

A solution of compound 4a ($5.2x10^{-3}$mol, 0.63gm) in 10 mL ethanol was added to the mixture of hydroxyl amine hydrochloride (0.014mol, 2.30gm) and Sodium hydroxide (10%). The reaction mixture was refluxed for 1*hr*. in water bath. The precipitate which separated on cooling was washed with cold water and recrystallized from ethanol.The melting point was (154-159°C). The physical properties are listed in Table 1.

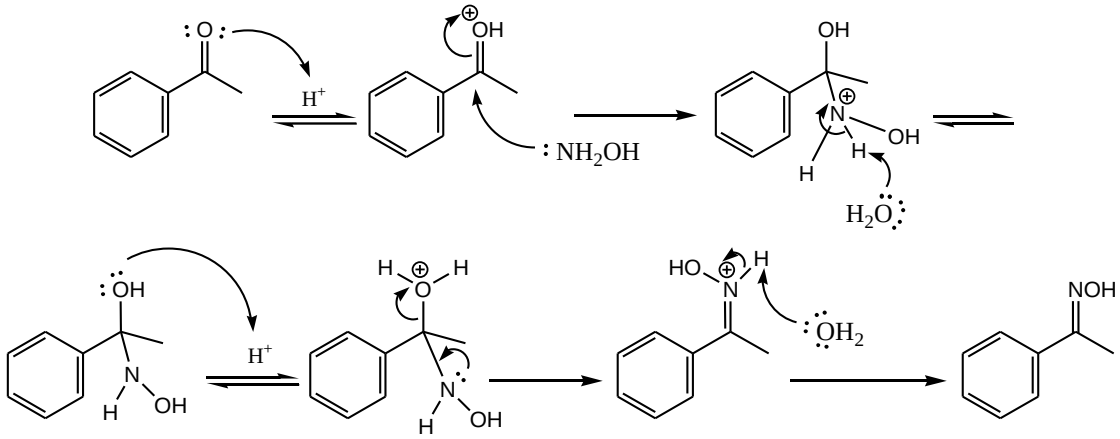
RESULTS AND DISCUSSION

Although many routes have been developed for functionalized quinoline [21, 22, and 23] the Vilsmeier approach is found to be among the most efficient for achieving useful transformation and hetero annulation. Thus in the communication is reported the Synthesis of substituted2-Chloro-3-formylquinolines from the reaction of substituted acetanilide with Vilsmeier reagent and transformation of2-Chloro and 3-formyl group into different functionalities. The Vilsmeier cyclization of substituted acetanilides was carried out by adding $POCl_3$ to the substrate in DMF at 0–5°C followed by heating to 90°C to afford2-Chloro-3-formylquinoline. The mechanism of reaction work according to the Scheme 4.



Scheme 4: The mechanism of Vilsmeier – Haack reaction

Another method to prepared substituted 2-Chloro-3-formylquinolines from the reaction of substituted phenyl ethanone oxime with $POCl_3$ in the presence of DMF using the Vilsmeier – Haack reaction method [24], and the mechanism of formation of phenyl ethanone oxime according to Scheme 5.

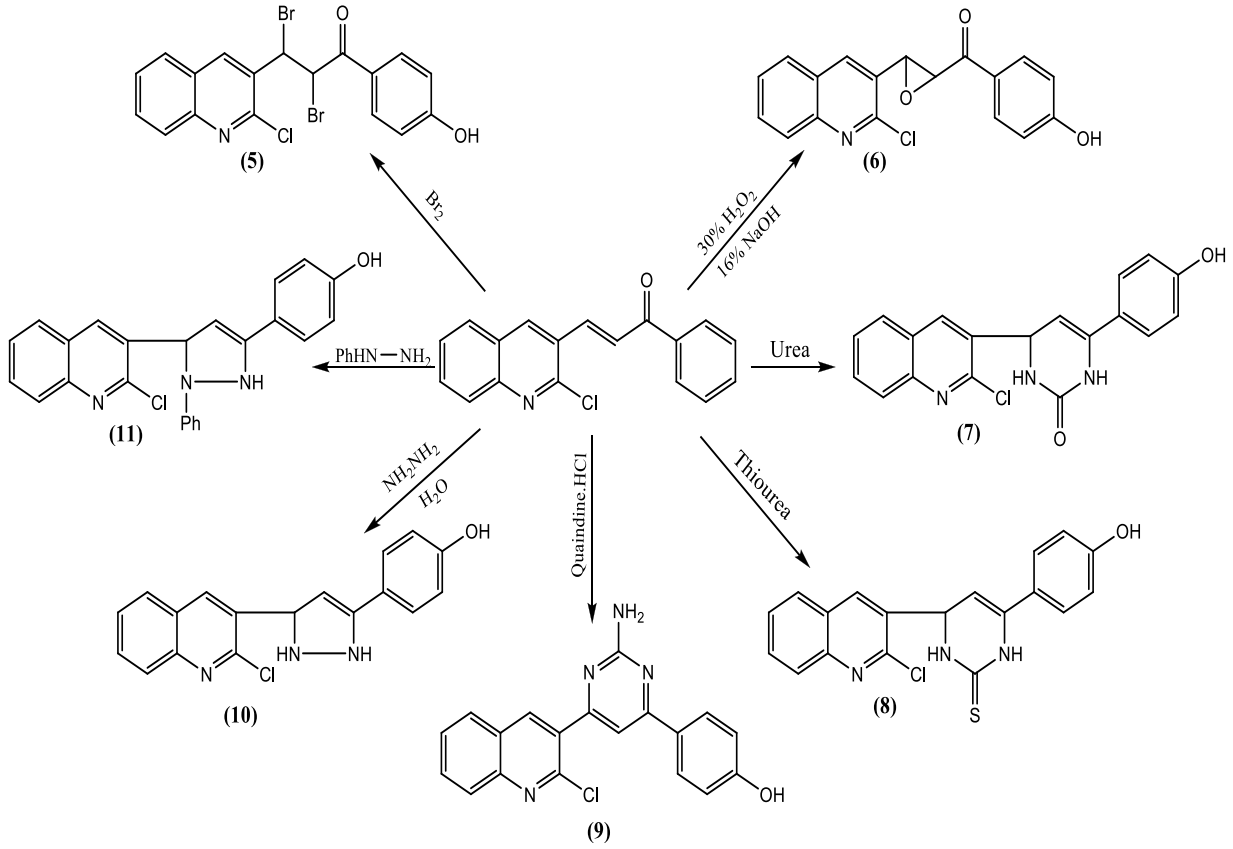


Scheme 5: The mechanism of oxime formation

Structures of the synthesized compounds were elucidated by mean of physical and spectral data (Table 1). The IR spectra of compounds (2a–d) showed characteristic absorption band in the reign (1664-1686 cm^{-1}) for C=O function and at reign (1552-1571 cm^{-1}) for C=N function and at(780-756 cm^{-1}) for C–Clfunction (Fig. 1).The ^{1}H NMR spectra for compound (2a) in $CDCl_3$ (Fig.2, Table 2) showed significant peak as the following triplet at 7.61-7.68 for **H-7**, triplet at 7.84-7.91 for **H-6**, doublet at 7.97-8.02 for **H-8**, doublet at 8.06-8.10 for **H-5**, singlet at 8.73 for **H-4** and singlet at 10.5 for aldehydic proton. The ^{13}C NMR spectra of this compound (Fig.3, Table 2) showed a carbonyl peak at 189.2.

Compounds (4a-d) have been prepared via Claisen-Schmidt condensation in ethanolic solution of 2-Chloro-3-formyl quinoline with *p*-Hydroxy acetophenone, 2-acetyl pyridine, 2-acetyl furan and 3-acetyl indole. The IR spectra of these compounds showed a strong absorption bands observed at reign (1642-1695 cm^{-1}) were attributable to the carbonyl, (C=O), at (1579-1615 cm^{-1}) suggested the presence of C=C group. In addition, bands were observed at (1560-1581 cm^{-1}) and at 747 cm^{-1} corresponding to C=N and C–Cl groups (Table 1). The ^{1}H NMR spectra for compound (4c) in $CDCl_3$(Fig. 4 and 5) (Table 2) showed significant peak as the following, singlet at 8.17 for **H-4**, doublet at 8.01-7.99 for **H-5**, doublet at 7.77-7.75 for $\mathbf{H_{\beta}}$, triplet at 7.67-7.53 for**H-6**, multiplet at 7.53-7.51 for **H-8**, multiplet at 7.25-7.22 for $\mathbf{C_7}$ and $\mathbf{H_{\alpha}}$, multiplet at 6.504-6.500, doublet at 6.32 and doublet at 4.54-4.52 for $\mathbf{H_2}$, $\mathbf{H_3}$ and $\mathbf{H_4}$ respectively for furan ring. The ^{13}C NMR spectra of this compound (Fig. 6, Table 2) showed a carbonyl peak at 186.9. The compound (5) was prepared from reaction of chalcone (4a) with bromine (Scheme 6). The IR spectral data for the compound exhibit an absence of absorption at about 1601 cm^{-1} for C=C and a presence of a strong absorption at about1698 cm^{-1}which attributed to carbonyl group. The reaction between compound (4a) and 30% hydrogen peroxide in basic medium can formed compound (6) (Scheme 6). The IR spectral data exhibit an absence of absorption at about 1601cm^{-1} for C=C and a presence of a strong absorption at 1702cm^{-1} attributed to the C=O group. A medium absorption at 1584 cm^{-1} for aromatic C=N, and absorption at 1029 cm^{-1} duo toC–O–C of epoxide ring. The ^{1}H NMR spectra for compound (6) in $CDCl_3$ (Fig.7 and 8) (Table 2) showed significant peak as the following, singlet at 8.68 for **H-4**, doublet at 8.11-8.13 for **H-5**, triplet at 7.88-7.90 for **H-6**, triplet at 7.41-7.43 for **H-7**, doublet at 7.69-7.71 for **H-8**, multiplet at 7.06-7.41 for **Ar-H**, singlet at 6.53 for phenolic proton and multipletat 4.33 and doublet at 4.993-4.997 for **H-2** and**H-3** for epoxide ring.The ^{13}CNMR spectra for this compound (Fig.9, Table 2) in $CDCl_3$ showed a carbonyl peak at 193.53. The pyrimidine compound (7) was synthesized from reaction of chalcone (4a) and urea in Sodium ethoxide solution (Scheme 6). The IR spectra data for compound showed the absence of two important absorptions, the first is absorption of carbonyl group at 1673 cm^{-1} and the other is the absorption of olefinic double bond at 1601 cm^{-1}. A strong absorption at 1686 cm^{-1} due to carbonyl group in the pyrimidine ring, a medium absorption at 1586 cm^{-1} and 1477 cm^{-1} for C=N and C=C corresponding to aromatic system. The reaction of compound (4a) with thiourea can formed compound (8). The IR spectral data showed the absence of absorption at 1673 cm^{-1} and at 1607 cm^{-1} for C=O group and olefinic double bond respectively. New absorption appeared at 1155 cm^{-1} for C=S group in pyrimidine ring, a

medium absorption at 1558 cm^{-1} and at 1448 cm^{-1} for C=N and C=C corresponding to aromatic system. The IR spectral data for compound (9) showed the disappearance of absorption at 1673 cm^{-1} and 1601 cm^{-1} corresponding to C=O group and for olefinic double bond, and exhibited absorption at 3487 cm^{-1} for N–H group. The reaction of chalcone (4a) with hydrazine hydrate and phenyl hydrazine can formed pyrazoline (10, 11). The IR spectra of these compounds (Table 1) showed the disappearance of absorption of C=O group and olefinic double bond and exhibited absorption at 3359 cm^{-1} for N–H group. And absorption appeared at 1577 cm^{-1} and 754 cm^{-1} for C=N and C–Cl group. The reaction of chalcone (4a) with hydroxylamine hydrochloride can form Oxazole (12). The IR spectral data (Table 1) showed the disappearance of absorption of carbonyl group at 1673 cm^{-1} and absorption at 1601cm^{-1} for olefinic double bond (Table 1).



Scheme 6: Synthesis of chalcone derivatives (5-12)

Table 1: Physical and IR spectral data of compounds (1-12)

Com. No	m.p °C	% yield	Formula	IR data (cm^{-1})								
				C=O	C=C olefinic	OH	C=N	C=C aromatic	N–H	C–Cl	C–O–C	C=S
2a	147-152	36	$C_{10}H_6NOCl$	1686	---	---	1562	1470	---	746	---	---
2b	216-220	13	$C_{10}H_8N_2OCl$	1664	---	---	1571	1491	3421	756	---	---
2c	140-142	55	$C_{11}H_9NOCl$	1680	---	---	1552	1490	---	780	---	---
2d	144-146	50	$C_{11}H_8O_2NCl$	1685	---	3335	1562	1495	---	760	---	---
3a	60-63	47	C_8H_9NO	---	---	3238	1542	1496	---	---	---	---
3b	150-153	80	$C_8H_{10}N_2O$	---	---	3354	1577	1492	3295	---	---	---
3d	144-146	92	$C_8H_9O_2N$	---	---	3334	1496	1496	3319	---	---	---
3c	42-45	52	$C_9H_{11}O_3N$	---	---	---	---	---	---	---	---	---
4a	185-187	53	$C_{18}H_{14}NO_2Cl$	1673	1601	3444	1561	1469	---	747	---	---
4b	278-280	77	$C_{17}H_{14}N_2OCl$	1695	1618	---	1587	1490	---	749	---	---
4c	160-162	92	$C_{16}H_{12}NO_2Cl$	1666	1593	---	1562	1467	---	750	---	---
4d	254-256	73	$C_{20}H_{12}N_2OCl$	1642	1616	---	1541	1480	---	741	---	---
5	192-195	57	$C_{17}H_{12}NOBr_2Cl$	1698	---	3354	1562	1466	---	784	---	---
6	121-124	94	$C_{18}H_{12}NO_3Cl$	1702	---	3384	1584	1480	---	750	1029	---
7	154-156	80	$C_{19}H_{13}N_3O_2Cl$	1686	1586	3420	1586	1473	3420	750	---	---
8	175-177	43	$C_{19}H_{13}N_3OClS$	---	---	3386	1558	1447	3359	754	---	1155
9	194-196	84	$C_{19}H_{13}N_4OCl$	---	---	3487	1572	1488	3410	758	---	---
10	186-188	66	$C_{18}H_{13}N_3OCl$	---	---	3433	1577	1489	3359	754	---	---
11	192-195	34	$C_{24}H_{17}N_3OCl$	---	---	3456	1576	1498	---	746	---	---
12	154-159	76	$C_{17}H_{13}N_2O_2Cl$	---	---	3300	1586	1474	---	756	---	---

Table 2: ^{13}C, ^{1}H NMR spectral data of compounds (2a, 4c, 6)

Comp. No.	^{1}H NMR Chemical shift ($CDCl_3$, δ, ppm)	^{13}C NMR ($CDCl_3$)
2a	7.61-7.65(1H,t,C_7),7.84-7.91(1H,t,C_6),7.95-8.00(1H,d,C8),8.04-8.08(1H,d,C_5),8.73-8.76 (1H,s,C_4),10.5(H,S,HC=O).	126.46 (C_3), 126.62 (C_6), 128.23 (C_8), 128.64 (C_5), 129.81 (C_9), 133.70 (C_7), 140.39 (C_4), 149.67 (C_{10}), 150.19 (C_2), 189.20(C=O).
4c	8.17(1H,s,C_4), 7,99-8.01(1H,d,C_5), 7.75-7.77(1H,d,H_β),7.53-7.67(1H,t,C_6), 7.518-7.539(1H,m,C_8), 7.25-7.32(1H,m,H_α), 6.500-6.509(1H,m,$\acute{C}_{2furan}$),6.32 (1H,d,$\acute{C}_{3furan}$), 4.527-7.544(1H,d,$\acute{C}_{4furan}$).	112 ($\acute{C}_3$), 117 ($\acute{C}_4$), 146.5 ($\acute{C}_5$), 146.7 ($\acute{C}_2$), 146.5 (C_4), 146.7 (C_{10}), 127.4 (C_6 and C_α), 127.8 (C_7, C_β), 130.5 (C_8, C_9), 146.0 (C_{10}), 146.5 (C_4), 152.4 (C_2), 186.9 (C=O)
6	4.33(1H,m,$C_{2epoxide}$), 4.993-4.997(1H,d,$C_{3epoxide}$), 6.53(1H,s,$OH_{phenolic}$), 7.06-7.41(4H,m,Ar-H), 7.69-7.71 (1H,d,C_8),7.41-7.43(1H,t,C_7),7.88-7.90(1H,t,C_6), 8.11-8.13(1H,d,C_5), 8.68(1H,s,C_4).	58.55 ($\acute{C}_{2\ epoxide}$), 57.83($\acute{C}_{3\ epoxide}$), 148.2 ($\acute{C}_{4\ benzene}$),137 ($C_{1\ benzene}$), 122.49 (C_3, $C_{5\ benzene}$), 135 (C_2, $C_{6\ benzene}$), 127.1 (C_7), 127.8 (C_5), 128 (C_6), 129.6 (C_8), 129.3 (C_9),147.0 (C_4), 149.3 (C_{10}), 150.0 (C_2), 193.53 (C=O).

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