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Synthesis of Isatine Derivatives Considering Pfitzinger Reaction Part I

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Abstract: ***In this work neuteric quinoline-4- carboxylic acid derivatives have been compilation from isatin. Onset, quinoline -4-carboxylic derivatives were designed from the reaction of isatin with different ketone (benzophenone, acetylacetone and acetone) in presence of powerful base (KOH) under Pfitzinger reaction case to obtain corresponding derivatives (1-3). Secondly, derivatives (4-6) have prepared by reflux of compounds (1-3) with p-hydroxybenzaldehyde in presence of few drops of concentrated sulfuric acid, and then the products were refluxed respectively with guanine to give desired compounds (7-9). Furthermore, carboxamide derivatives (10-12) have been prepared by refluxing of compounds (1-3) with o-phenylenediamine (benzene-1, 2-diamine) in ethanol solvent. Finally, derivatives (16-18) have been prepared by reaction of synthesized derivatives (13-15) that prepared from the reaction of compounds (1 - 3) with thionyl chloride followed by conversion into corresponding quinoline-8-yl (substituted quinoline-4- carboxylic acid (16-18) by reaction with quinolin-8-ol in acetone. All structures of newly synthesized compounds have been characterize and identified via of their physical properties and spectral data analysis (^{1}H-NMR, FT-IR and U.V.).***

Keywords: Pfitzinger reaction, powerful base, o-phenylenediamime, quinoline-8-yl, thionyl chloride.

1. Introduction

The quinoline nucleus [1, 2, 3] is an important structural moiety on a number of kink chemotherapeutic agents. A lot of quinoline derivatives are known to own hypotensive, analgesic, anti-leishmanial, anti-fungal and anti-inflammatory [4-9]. Quinoline -4-carboxylic acid and their isotopes have a large variety of medicinal properties involving anti-tumor, anti-viral and anti-bacterial activities [10, 11]. The Pfitizinger reactions offer a very adequate synthetic entry to quinoline 4-carboxylic acids derivative from isatin. The enclosable conjugated ketone compounds intensive with isatin in strongly alkaline medium and posterior cyclize to give the quinoline products. This reaction stock a very facile one tube synthetic route to quinoline-4-carboxylic acid derivatives from conjugated ketone. Profiteering of isatin moiety on antiviral and anticonvulsant region has been especially fruitful [12]. As recent days, derivatives of quinoline carboxylic acid have been studied as potential HIV-I contraindication [13]. It has elevated a renovated interest in these molecules from yet another perspective.

2. Materials and Methods

- Melting points were determined on Gallen Kamp melting point apparatus MFB-600-Olof and uncorrected.
- FT-IR spectra were recorded using solid KBr disc by testing Shimadzu FT –IR 8000 series Fourier transform infrared spectrophotometer.
- Ultra violet spectra were recorded using Shmazue (UV-Vis)-160 recording spectrophotometer using DMSO as a solvent.
- All the chemicals used were supplied by BDH and Fluka chemicals.

Experimental:
Physical and other properties of the following synthesized compounds are outlined in table 1.

Synthesis of {2, and 2, 3-substitutedlquinoline-4-carboxylic acid} (1-3)[14]:
A (5.9 g, 0.01 mol) of potassium hydroxide was dissolved in absolute ethanol / distil water (20: 5ml),Isatin (1.47g, 0.01 mol) was add and refluxed for 1 hr, then an appropriate ketones (1.2g, 0.01mol) was add slowly to the mixture and then the mixture was heated under reflux for 13hr. Finally the solution was poured on crush- ice and carefully acidified with concentrated hydrochloric acid (PH= 1-2). The excess of solvent was evaporated until the solid brown precipitate appeared. The crude product was recrysallized from ethanol.

Synthesis of {4-formylphenyl-2and 2, 3-substitutionquinoline-4-carboylate} compounds (4-6) [15]:
A mixture of compounds (1-3) (0.0018 mol) respectively and 4-hydroybenzaldehyde (0.0018 mol) in (15 ml) of acetone and few drops of concentration H_2SO_4 was heated under reflux on oil-bath at 140-160°C for 3hours. The reaction mixture was concenetrated , cooled and recrystallized from ethanol.

Synthesis of {4-(((6-oxo-4, 5, 9, 9-tetrahydro-1H-purin-2-yl) imino) methyl) 2, and 2, 3-substituted quinoline-4-carboylate} (7-9):
To a solution of guanine (0.0003 mol) in (15 ml) of absolute ethanol, compounds (4-6), (0.0003 mol) respectively were added, with few drops of glacial acetic acid. The mixture was refluxed for 4 hours, cooled filtered and recrysallized from ethanol.

Synthesis of {N-(2-aminophenyl)-2 and 2, 3-substitutedquinoline-4-carboxamide} (10-12):
To (0.001 mol) of compounds (1-3) respectively in ethanol, (0.001mol) of o-phenylenediamine was added and refluxed for 4hr. The precipitate was poured in crash –ice and recrystilized from ethanol.

Synthesis of {2 and 2, 3-substitutedquinoline-4-carbonyl chloride} derivatives (13-15) [16]:
(0.19g) of thionyl chloride was add drop wise to a mixture of (0.0016 mol) of quinoline carboxylic acid derivatives (1-3) in (15) ml of chloroform (CH_2Cl_2). The mixture was refluxed

pending the evolution all of hydrogen chloride gas and the acids chloride were used in the next reactions without further purification.

Synthesis of {quinolin-8-yl (2- and 2, 3-substitutedquinoline-4-carboxylate} compounds (16-18):

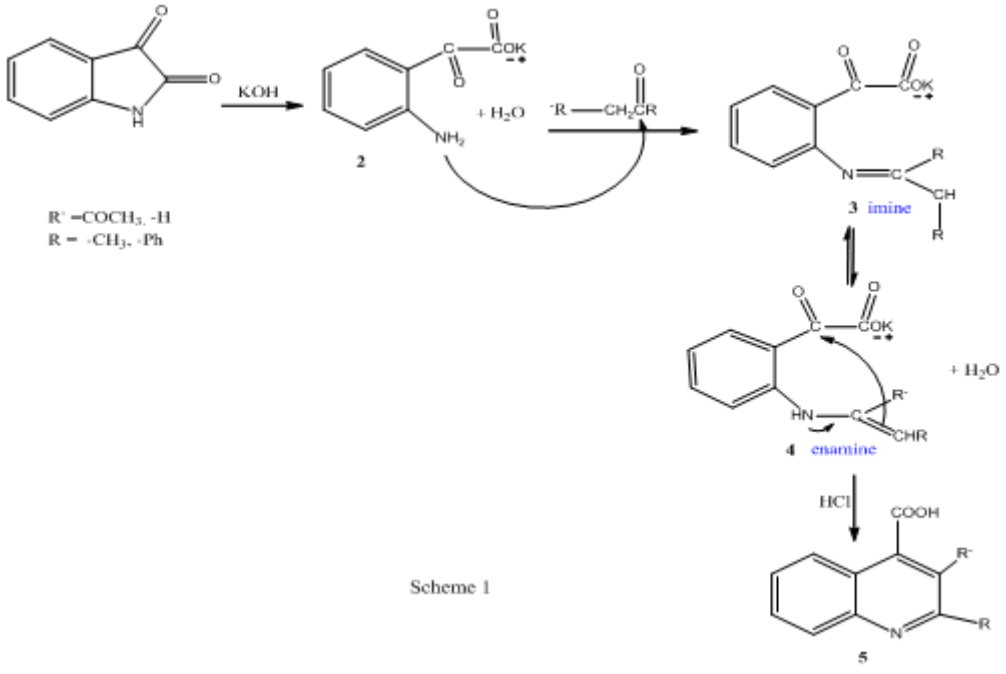
To a solution of componds (13-15) (0.005 mol, 1.23 g) in dry benzene (20 ml) quinolin-8-ol (0.005 mol, 1.23 g) was added, the mixture was refluxed for 6 hours.

Table 1: The physical properties of compounds (1-18)

Compound No.	Molecular formula	Melting Point	Color	Solvent	Yield
1	$C_{16}H_{11}NO_2$	214-215	brown	Ethanol/Water	94
2	$C_{13}H_{11}NO_3$	208-210	Dark brown	Ethanol/Water	87
3	$C_{11}H_9NO_2$	216-218	brown	Ethanol/Water	89
4	$C_{23}H_{15}NO_2$	166-168	brown	Dry Benzene	91
5	$C_{20}H_{15}NO_3$	196-198	brown	Dry Benzene	86
6	$C_{18}H_{13}NO_2$	162-165	yellow	Dry Benzene	94
7	$C_{28}H_{20}N_6O_2$	278-280	Red	Ethanol	77
8	$C_{25}H_{20}N_6O_3$	254-255	Red	Ethanol	73
9	$C_{23}H18N_6O_2$	250-252	Red	Ethanol	64
10	$C_{22}H_{17}N_3O$	120-122	Red	Ethanol	65
11	$C_{19}H_{17}N_3O_2$	112-114	Red	Ethanol	80
12	$C_{17}H_{15}N_3O$	103-105	Red	Ethanol	82
13	$C_{16}H_{10}ClNO$	192-194	Pale -brown	Dichloromethane	75
14	$C_{13}H_{10}ClNO_2$	141-143	Pale -brown	Dichloromethane	78
15	$C_{11}H_8ClNO$	145-147	Pale -brown	Dichloromethane	60
16	$C_{25}H_{16}N_2O_2$	97-99	Brown	Acetone	78
17	$C_{22}H_{16}N2O_3$	118-120	Reddish-brown	Acetone	81
18	$C_{20}H_{14}N_2O_2$	133-135	Reddish-brown	Acetone	85

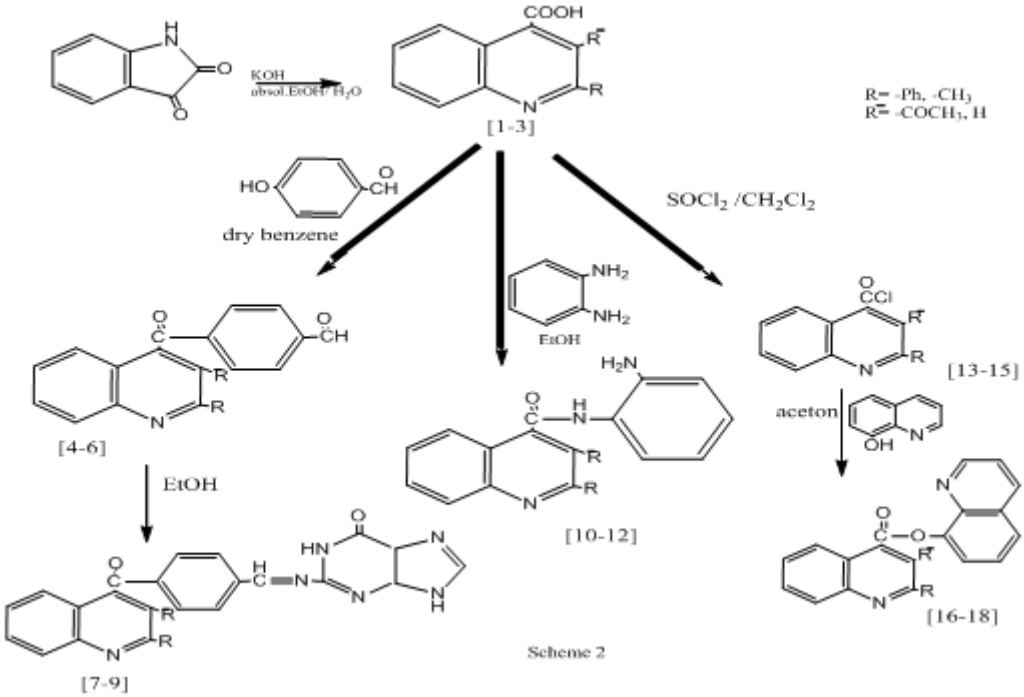
3. Results and Discussion

The reaction of isatin with a base like potassium hydroxide hydrolyses the amide bond to give the keto-ester (2). This intermediate can be secluded, but is habit not. A ketone will react with the aniline to produce imine (3) and the enamine (4).The enamine will cyclize and dehydrate to give desired substituted quinoline -4-carboxylic acid [17, 18, 19, 20].



Scheme 1

For the synthesis of the target (2, and 2, 3-substituted quinoline-4-carboxylic acid derivatives in this work, the raction squences are summed up in scheme (2).

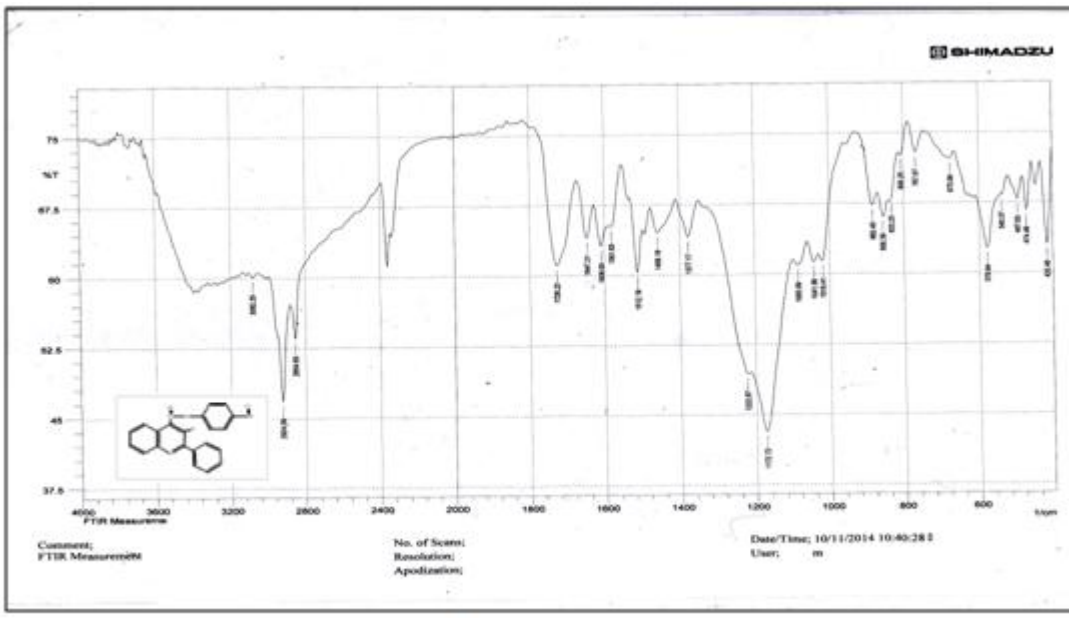


Scheme 2

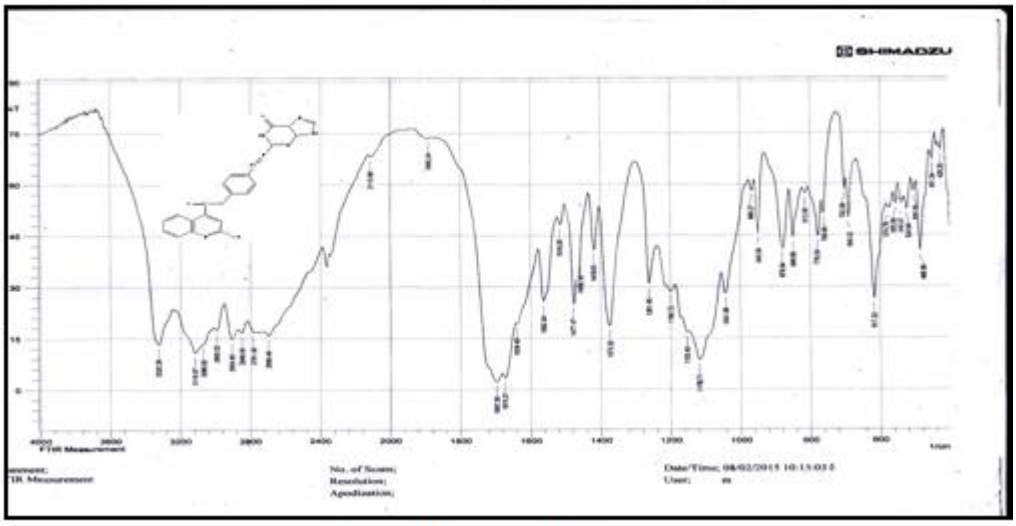
The FT-IR spectrum of compounds (**1-3**) figure (1) shown disappearance of band of stretching [20] (*v* NH) at (3190.26) cm^{-1} and appearance of a broad stretching band of (*v* OH) at (3356.14, 3379.29 and 3367.71) cm^{-1}, and characteristic bands at (1724.36, 1720.50, 1712.79) cm^{-1} for (C=O) of carboxylic acid respectively. Furthermore, a bands at (1604.77, 1608.63 and 1608. 63) cm^{-1} for (*v* C=N) respectively. U.V. spectrum of compounds (2and 3), have λmax (DMF) at (335, 270) and (302) nm responsible for (π- π^*) and (n- π^*) respectively. The IR spectrum of compounds **(4-6)**,figur (2) shows the disappearance both of the broad bond of (*v* OH) carboxylic acid and the sharp bands of (*v* C=O) carbonyl compounds and appearances of new bands at 1728.22 over coming from the overlapping of (*v* C=O) of carbonyl group of ester and (*v* C=O) of aldehyde functional group, and for compounds (**5**) appearances of two stretching bands at (1739.79-1720) cm^{-1} due to the both carbonyl (*v* C=O) for ester and aldehyde functional groups. Two bands at the range (1724-1705) cm^{-1} was due to the carbonyl (*v* C=O) stretching vibration for both ester and aldehyde functional groups. The spectrums for compounds (4, 5 and 6), figure (3) also shows a new absorptions bands at (1647, 1639and1639 cm^{-1}) referring to (*v* C=N) stretching respectively. U.V. proved the structures of compound(5) and (6) respectivelly by revealing absorption bands at 280 nm and 273nm for (π- π^*) and λ_{max} at 345 nm represent (n-π^*) for compound (6). The FT-IR spectrum of compound **(7-9)** shows disappearances of (v C=O) for aldehyde functional group and appearances of a new bands at (1674) cm^{-1} attributed to *v* (C=O) of ring and band at (1701and 1697) cm^{-1}due to *v* (C=O) of ester, an absorption bands at (3300, 3113and 3116) cm^{-1} was due to the –NH stretching of purin ring [10]. Furthermore, bands at (1562) cm^{-1} due to (*v* C=N) stretching vibrations of imine groups. U.V. spectrum showed electronic transition peak at (291 nm) (π-π^*) for compound (7) and two electronic transitions peak at (271 nm) (π-π^*) and (345 nm) (n- π^*) (DMF) as a solvent. The ^{1}H.NMR spectrum of compound (7) absorption δ 3.7 (s,1H, NH) and δ 6.4 (s, 1H, CH a) δ 6.6 (s, 1H, CH b) δ(7.29-7.84) (d*d, 2H, CH c&d), δ8.35-9.33 (m, 14H, CH aromatic), δ11.3 (bs, 1H, HN-CO) δ2.5 (S, DMSO-d_6) The FT-IR spectrum of compouns (**10-12**) shows absorption bands at (3300-3450 cm^{-1}) due to (*v* NH_2) stretching vibration [21], and (*v* OH) bands due to the tautomeric at (3398, 3479 and 3425 cm^{-1}) respectivelly. The ^{1}H.NMR spectrum of compound (12) absorption δ1.4 (s, 3H, CH_3), absorption δ3.04 (s, 2H, NH_2 rapid exchange), δ 6.94-8.66 (m, 9H, CH aromatic) δ8.8(s, 1H, HN-CO) δ2.5 DMSO-d_6. U.V. spectrum exhibited for compounds (11 and 12) λ_{max} at (339 and 301 nm) (n-π^*) respectivelly and (270 nm) (π-π^*) for compound 11. The FT-IR spectrum of compouns (**13-15**) shows the disappearance of the hydroxyl group of starting material and appearance of the new (C=O) band at (1743 and 1720 cm-1) for the acetyl chloride. The spectrum also shows an absorption band at (767 and 752 cm^{-1}) for compounds (13 and 14) respectively, referring to (C-Cl) [12] band. Compound **(16-18)** were prepared by treatment of compound **(13-15)** respectively with thionyl chloride in acetone as a solvent to produced quinolin-8-yl –substituted quinoline-4-carboxylate. TheFT- IR spectrums of compound **(16-18)**, shows absorption band at (1716, 1701 and 1716 cm^{-1}) due to (C=O) of ester vibration and stretching bands due to two (C=N) at (1597, 1554), (1597, 1550) and (1597, 1550) for compounds (16, 17 and 18) respectively. U.V. spectrum for compounds (16-18) respectively showed absorption for exaited electron Pi and non-bonding electrons at (296, 269 nm) (π-π^*) and (301, 304 nm) (n- π^*).

Table 2: Spectral data for compounds (1-18)

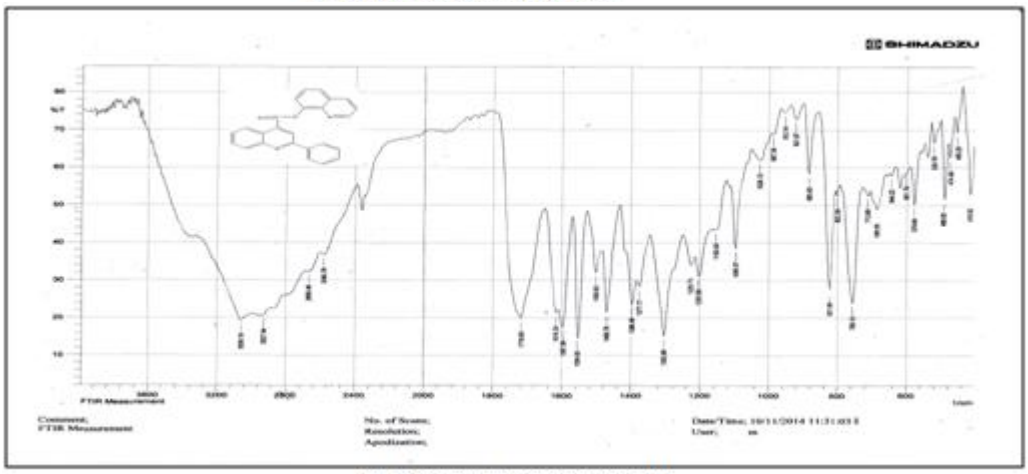
Compound Number	UV λmax	ν(C=O)	ν(C=C)	ν(C=N)	ν(C-H)aliphatic ν(C-H)aromatic	Others
1	----	1724(acid)	1635	1604	(2978) asy (3066)$_{aroma.}$	3356 (OH)st.
2	(335)$_{n-\pi^*}$ (270) $_{\pi-\pi^*}$	1720(acid)	1631	1608	(2997)asy,(2862) sy (3039) $_{arm.}$	3379 (O-H)$_{st.}$
3	(302)$_{n-\pi^*}$	1712(acid)	1643	1608	(2981)asy,(2908) sy 3074arom.	3367(O-H)st
4	(345) $_{n-\pi^*}$ (273) $_{\pi-\pi^*}$	1728(ester) Interfere withaldehy d.)	1608	1581	(2924)a ,(3082)$_{arm.}$	-------
5	-------	1739(ester) interfere with (aldehyde) 1693(acetyl)	1612	1539	(2924)asy (2854)sy	-------
6	(280) $_{\pi-\pi^*}$	1724(ester) 1705(aldehyde)	1608	1512	(2924)asy (2854)sy	-------
7	(345) $_{n-\pi^*}$ (271) $_{\pi-\pi^*}$	1674 (ringr) 1701 (ester)	1612	1562	-----	(NH) 3325
8	------	1674 (ring) 1697 (ester)	--------	1562	2908$_{asym.}$ 2850$_{sym.}$	(NH) 3325
9	(291) $_{\pi-\pi^*}$	1674 (ring) 1697 (ester)	1639	1562	2904 $_{asym.}$ 2846 $_{sym.}$	(NH) 3325
10	(344) $_{n-\pi^*}$ (266) $_{\pi-\pi^*}$	1692(amide)	1608	1550	3078-3035$_{aroma.}$	(NH_2)stinterfere with (OH)st. and (NH)$_{str.}$ 3398
11	(339) $_{n-\pi^*}$ (270) $_{\pi-\pi^*}$	1681(amide) 1716(acetyl)	1618	------	2958 (3174-3043)$_{arm.}$	(3410-3348) (NH)st (NH) interfere with (OH) Tautomeric 3479
12	(301) $_{n-\pi^*}$	1654(amide)	1635	1539	(2931) $_{asym}$ (2850)$_{sym.}$	(NH) st interfere with(OH)$_{ST.}$tautomeric and (NH) 3200-3425
13	-----	1743(acid chloride)	1616	1535	(3116)$_{arm.}$	C-Cl 752 1160(C-O-C) 3350 (NH)st
14	-----	1762(acid chloride) 1720 (acetyl)	1600	1558	2924 (3070)$_{arm.}$	C-Cl 767
16	(296) $_{\pi-\pi^*}$	1716(ester)	1616	1597(quinoline) 1554$_{(substituted}$	(2927)$_{asy}$ (3059)$_{arm.}$	1153(C-O-C)
17	(304) $_{n-\pi^*}$ (269) $_{\pi-\pi^*}$	1743(ester) 1701(acetyl)	1627	1597 quinoline) 1550$_{(substituted}$ quinoline	(2920)asy (2850)sy (3080)$_{arm}$	1195(C-O-C)
18	(301) $_{n-\pi^*}$	1716(ester)	1627	1597 quinoline) 1550$_{(substituted}$	(2924) asy (2854) sy (3050)$_{arm.}$	1168(C-O-C)



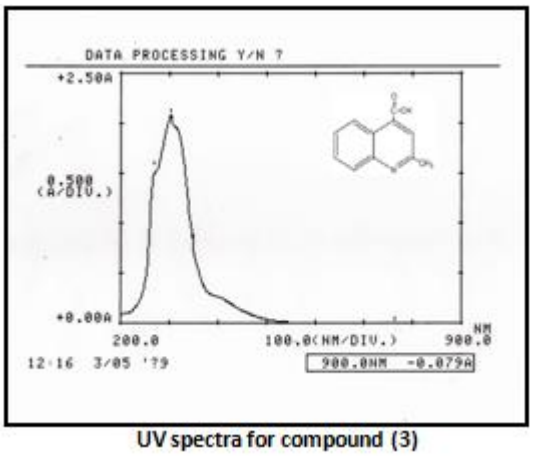
FT-IR spectra for compound (4)



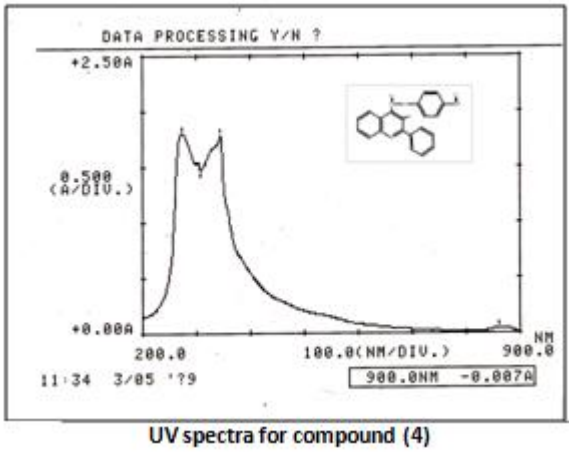
FT-IR spectra for compound (9)



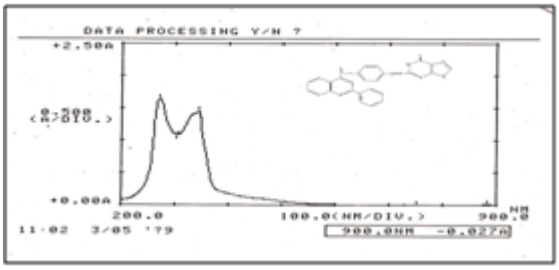
FT-IR spectra for compound (16)



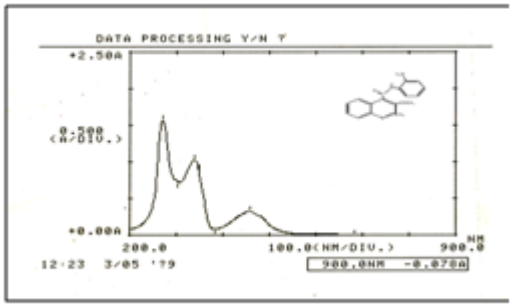
UV spectra for compound (3)



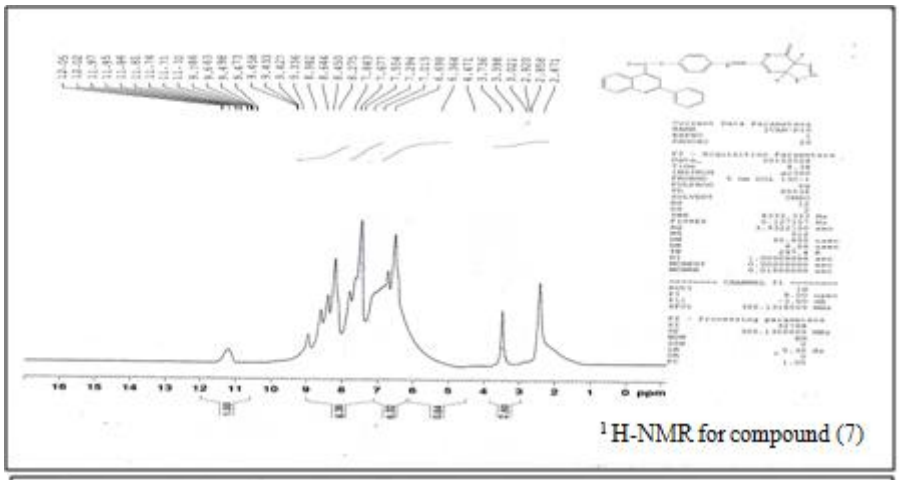
UV spectra for compound (4)



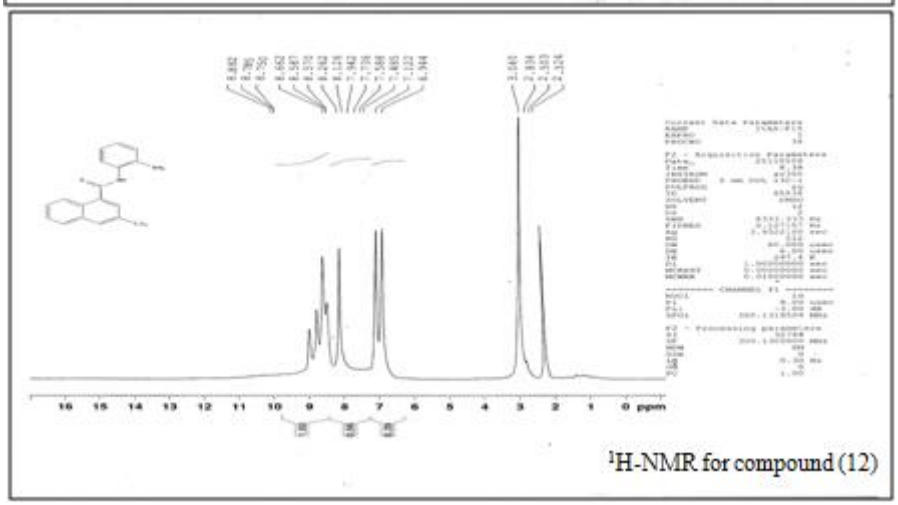
UV spectra for compound (7)



UV spectra for compound (11)



^{1}H-NMR for compound (7)



^{1}H-NMR for compound (12)

References

[1] Gerd Collin; Hartmut Höke (2005), "Quinoline and Isoquinoline", *Ullmann's Encyclopedia of Industrial Chemistry*.
[2] Eno E. Ebenso1, Ime B. Obot and L. C. Murulana Int. *J. Electrochem. Sci*., 2010, 5, 1574 – 1586
[3] H. Ashassi-Sorkhabi, B. Masoumi, P. Ejbari, E. Asghari, J. Appl. *Electrochem*. 2009, 39, 1497.
[4] Savini L, Chiasserini L, Pellerano C, Filippelli W &Falcone G, II Farmaco, 2001, 56, 939.
[5] Claret P A, in *Coprehensive Organic Chemistry*, Vol. 4, edited by D H R Barton & W D Eills, (Pergamon Press, New York), 1979, 198.
[6] Vaitilingam B, Nayyar A, Palde P B, Monya V, Jain R, Kaur S & Singh P P. *Bioorg Med Chem*., 2004, 12, 4187.
[7] Benard C, Zouhiri F, Bayle M N, Danet M, Desmade D, Leh H, Mouscadet J F, Mbemba G, Thomas C M, Bret M L & D Angelo J, Bioorg *M ed Chem Lett.*, 2004, 14, 2473.
[8] Bala M, Naparzewska A & Chojnaka W, *J. Pharmacal Pharm*, 38, 1986,222; *Chem. Abstr*., 1986, 105, 164770.
[9] VS Hursky; AM Bernard KE .Price; P Siminoff; *Antimicrob Agents Chemothev*, 1973, *3*,742.
[10] A Lásiková; J Strigáčová; D Hudecová; L' Varečka;; D Végh; SV Nielson; EB Pederson;*Hert. Chem*., 2008, 305-309.
[11] KN Singh; SN Panday; V Manjusha; JP Sables; *Acta. .Pharm*, 2004, *54*, 49-56.
[12] G .Mathé; E Chenu; C Bourut; S Orbach-Arbouys; *Biomed. & Pharmacother*. 1993, 47(10), 457-460.
[13] http://en.wikipedia.org/wiki/Pfitzinger_reaction.
[14] Rafah F.Al-Smaisim, Redha E.Al-Bayati and Abdul Hussain K. Sharba. *AJPS*, 2011, Vol. 9, No.1.
[15] Mc, Murry. John. "*Organic Chemistry*",5th Edition, Cornel Universitypress, (2002).
[16] Pfitizinger, W.*J Prakt. Chem*. 1886, 33, 100.
[17] Pfitizinger, W.*J Prakt. Chem*. 1888, 38, 582.
[18] *J. Med. Chem.*, 1988, *31* (5), pp 983–991
[19] Parikh, V. M. "*Absorption Spectroscopic of Organic Molecules*" Translated by A. H. Khuthier, J. M. A. Al-Rawi, M. A. Al-Iraqi, Mousul University (1985).
[20] March, J."*Advanced Organic Chemistry*" Ed., Jhon Wiely and Sons, New York, (1985).
[21] *J. A. Knight, H. K. Porter and Paul k. Calaway J. Am. Chem. Soc., 66* (11), 1944, pp 1893–1894