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SYNTHESIS OF SOME NEW OXIMES, THIOCARBAMATES, PYRAZOLYLOXY, ISOXAZOLYLOXY, PYRIMIDYLOXY AND PYRIDYLOXY QUINOLINES

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مركبات جديدة لمشتقات ٨ - كينولين - أوكسي أسيتيل أوكزيم - ثيوكربامات - أزولات - بريميدينات والنيكوتينونيتريل

علي عبد الحافظ

يتفاعل مركب ٥ - مورفولينوسلفونيل - ٨ - كينولينو أوكسي اسيتيل مورفولين (١) وكذلك شالكونات (3a -c) مع هيدروكسيل آمين عند درجة الغليان في البيريدين معطياً الأوكزيمات المقابله (2) ، (5a - c) والتي تتفاعل بدورها مع فينيل أيزوثيوسيانات لتعطي مشتقات الثيوكربامات المقابلة (4) و(6a c) . وقد أمكن تخليق سلسله جديده من مشتقات ٥ - موفولينوسلفونيل ٨ - [٥ - اريل - $\Delta^{٢}$ - بيرازولين - ٤ - ويلوكس] - كينولين (7a - f) ، ٥ - مورفولينو سلفونيل - ٨ - [$\Delta^{٢}$ - أيزواكزازولين - ٤ - ديلوكسي] - كينولين (8a -c) ٥ - مورفولينوسلفونيل - ٨ - ٢ - اكزو (ثيواوكزو) - ٤ - مورفولينو - ١ ، ٢ ، ٥ ، ٦ - رباعي هيدروبيريميدين - ٥ - ويلوكسي - كينولين (9a - f) ، ٥ - مورفولينوسلفونيل ٨ - [٢ - أمينو - ٤ - اريل -٣- سيانو - ٦ - مورفولينوبيريدين - ٥ - ويلوكس)] - كينولين (10a, b) وذلك بتفاعل الشالكونات (3a - c) مع الهيدرازين - هيدروكسيل آمين - يوريا - ثيويوريا والمالونونيتريل على الترتيب . وقد تم دراسة التأثير البيولوجي للمركبات الجديدة على بعض أنواع من البكتريا المختاره مثل *باسيلس سيريوس* ، *كليبسيلانومونيا* ، *سيراتيامارسينس* وكذلك بعض من الفطريات المختارة مثل *اسبيرجليس فلافس* ، *بينيسيلام كريسوجينوم* ، *ستاكيبفريس كارتافوم* ، *كانديدا البيكانس* وقد أظهرت الدراسة أن المشتقات 3a ,c لها نشاط فعال على *باسيلس سيريوس* بينما المركبات 3b , 5b , 5c , 7d , 9d لها تأثير على *سيراتيا مارسينس* ولكن كل المركبات ليس لها أي تأثير *كليسيلا نومونيا* . ومن ناحية أخرى أظهرت الدراسة أن كل المركبات ليس لها أي تأثير على الثلاثة أنواع الأولى من الفطريات ولكن عشرة مركبات فقط منها وهم 2, 3a - c, 5b - c, 6b, 7a, 9a, 9d لها تأثير واضح وفعال على النوع الحساس من الفطريات وهو *كانديدا البيكانس* .

Key Words: Quinolinoximes, Thiocarbamatquinolines, Azolyloxyquinolines, Pyrimdyloxyquinolines, Pyridyloxyquinolines

ABSTRACT

The reaction of 1 or its corresponding chalcones 3a-c with hydroxylamine in boiling pyridine gave the oximes 2 or 5a-c respectively in almost quantitative yield. When both 2 and 5a-c were reacted with phenylisothiocyanate, the corresponding thiocarbamates 4 and 6a-c were achieved. A new series of pyrazolyloxy 7a-f, isoxazolyloxy 8a-c, pyrimidyloxy 9a-f and pyridyloxy 10a,b quinolines were obtained from the reaction of 3a-c with hydrazines, hydroxylamine, urea, thiourea and malononitrile respectively. The in vitro antibacterial and antifungal activity were screened for all the compounds prepared, some of the compounds tested showed interesting results.

INTRODUCTION

It has been known that oximes, carbamates, thiocarbamates, pyrazolines, isoxazoline, pyrimidines and nicotinonitriles possess interesting biological activity[1-7]. In view of the above findings and in continuation to our previous work[7-17] directed to the synthesis of new oximes, carbamates and other heterocycles derived from quinoline we report herein a new variety of the title compounds.

EXPERIMENTAL

All melting points are uncorrected, Infrared spectra (KBr) were determined on a Perkin Elmer 599 B spectrophotometer and NMR spectra on a Varian EM (60 MHz) spectrometer.

N-(5-Morpholinosulfonyl-8-quinolinylacetyl) morpholine (1)

A mixture of ethyl 5-(morpholinosulfonyl)-8-quinolinylacetate (0.01 mol) and morpholine (0.02 mol) in absolute ethanol (50 ml) was heated under reflux for 5 h. The reaction mixture was cooled and diluted with water (50 ml). The precipitate was filtered off and recrystallized from methanol.

N-[2-(5-Morpholinosulfonyl-8-quinolinyl-oxy)cinnamoyl] morpholine derivatives (3a-c)

N-5-(Morpholinosulfonyl-8-quinolinyloxyacetyl)-morpholine (1) and the selected aldehydes in equimolar ratio were dissolved in absolute ethanol and few drops of piperidine as catalyst added and the mixture was refluxed for 8 h. The reaction mixture was then evaporated under vacuum, and the resulting precipitate filtered off washed with alcohol and recrystallized from ethanol.

Reaction of N-(5-morpholinosulfonyl-8-quinolinyloxyacetyl)morpholine(1) and its chalcone derivatives 3a-c with hydroxylamine hydrochloride

A solution of N-(5-morpholinosulfonyl-8-quinolinyloxyacetyl)morpholin(1) and or corresponding chalcones 3a-c (0.01 mol) and hydroxylamine hydrochloride (0.015 mol) in dry pyridine (20 ml) was heated under reflux for 5 hours. The reaction mixture was poured onto crushed ice and the precipitated solid was filtered off and recrystallized from the suitable solvent to give the corresponding oximes 2 and 5a-c respectively. The results are given in Table 1.

Reaction of oximes 2 and 5a-c with phenyl isothiocyanate

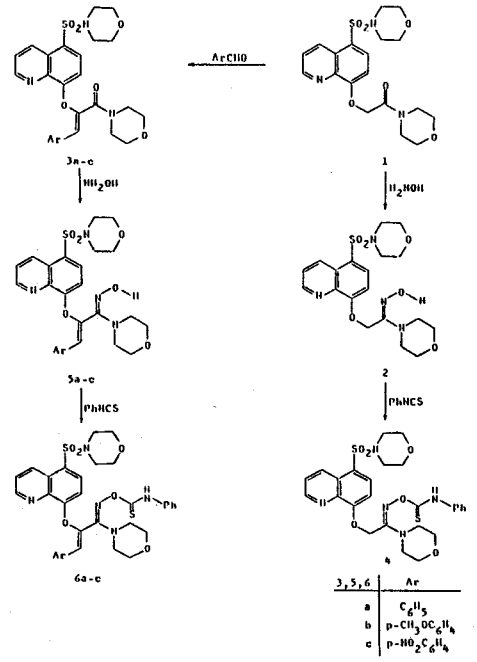
A solution of the oximes 2 and 5a-c (0.01 mol) phenyl isothiocyanate (0.01 mol) in dry benzene (25 ml) containing triethylamine (0.5 ml) was heated under reflux for 4 hours. The separated crystalline solid was filtered off, washed with ether and recrystallized from dioxane to give the corresponding thiocarbamate derivatives 4 and 6a-c, respectively. The results are given in Table 1.

5-Morpholinosulfonyl-8-[1-acetyl-5-aryl-Δ^2-pyrazolin-4-yloxy]quinolines (7a-c)

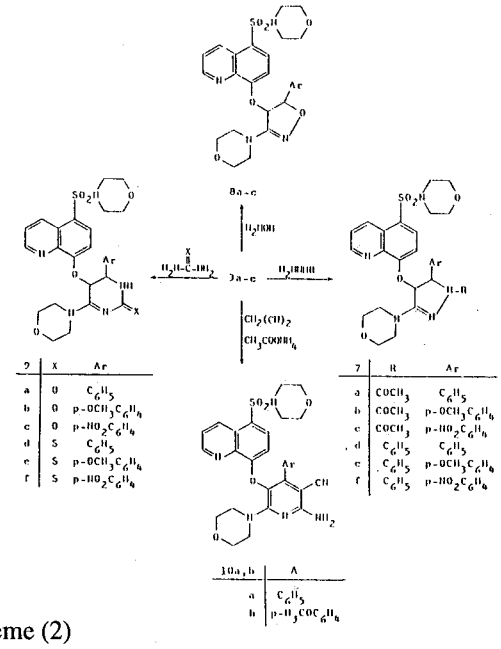
A mixture of the chalcones 3a-c (0.01 mol) and hydrazine hydrate (1.5 ml, 98) in glacial acetic acid (30 ml) was refluxed for 7 hours. The reaction mixture was cooled and the resulting solid was washed with alcohol and recrystallized from acetic acid.

5-Morpholinosulfonyl-8-[5-aryl-1-phenyl-Δ^2-pyrazolin-4-yloxy]-quinolines (7d-f)

A solution of the chalcones 3a-c (0.01 mol) in absolute ethanol (30 ml) phenylhydrazine (1 ml) and piperidine (2 drops) was refluxed for 5 h. The resulting solid was washed with alcohol and recrystallized from methanol.



Scheme (1)



Scheme (2)

5-Morpholinosulfonyl-8-[5-Aryl-Δ^2isoxazolin-4-yloxy]-quinolines (8a-c)

A mixture of the chalcones 3a-c (0.01 mol), hydroxylamine hydrochloride (0.06 mol) and NaOH (0.2 g) in absolute ethanol (50 ml) was refluxed for 6 h. The reaction mixture was then concentrated, neutralised with dilute HCl and the resulting solid was washed with water and recrystallized from ethanol (Table 1).

Table 1.
Physical and spectral data of compounds 1-10

Compd.	Yield	%	Molecular* formula	Spectral data IR (cm^{-1}) & ^1H NMR (d ppm)
1	72	238-40	$C_{19}H_{23}N_3O_6S$	IR: 1650 (CO), 1330 (SO_2 asym), 1160 (SO_2 sym).
2	75	313-15	$C_{19}H_{24}N_4O_6S$	IR: 1600(C=N), 3200 (OH, oxime).
3a	68	>300	$C_{26}H_{27}N_3O_6S$	IR: 1690 (CO). ^{1}HMNR (DMSO-d_6): 2.5-3.6 (m, 16H, 2-morpholine ring), 6.4-6.9 (m, 5H, aromatic + CH), 7.3-8.1 (m, 5H, quinoline).
3b	70	230-32	$C_{27}H_{29}N_3O_7S$	IR: 1690 (CO), 1350 (SO_2 asym), 1170 (SO_2 sym).
3c	65	280-82	$C_{26}H_{26}N_4O_8S$	IR: 1685 (CO), 1360 (SO_2 asym), 1160 (SO_2 sym). ^{1}H NMR (DMSO-d_6): 2.4-3.4 (m, 16H, morpholine), 6.3-6.8 9m, 4H, aromatic + CH), 7.2-7.9 (m, 5H, quinoline).
4	77	296-98	$C_{26}H_{29}N_5O_6S_2$	IR: 3230(NH), 1200(CS), 1370(SO_2 asym), 1150(SO_2 sym).
5a	71	>330	$C_{26}H_{28}N_4O_6S$	IR: 3120(OH-oxime), 1350 (SO_2 asym), 1160(SO_2 sym). ^{1}H NMR (DMSO-d_6): 2.3 (s, 1H, OH), 4.4 (s, 2H, CH_2), 2.7-3.6 (m, 16H, morph), 6.4-6.9(m, 5H, aromatic + CH), 7.4-8.1 (m, 5H, quinoline).
5b	74	248-50	$C_{27}H_{30}N_4O_7S$	IR: 2850-3100 (OH-oxime), 1590(C=N), 1360(SO_2 asym), 1170(SO_2 sym).
5c	68	>300	$C_{26}H_{27}N_5O_8S$	^{1}H NMR ($CDCl_3$): 2.4 (s, 1H, OH), 4.3 (s, 2H, CH_2), 2.6-3.7(m, 16H, morph), 6.5-7.1 (m, 4H, aromatic + CH), 7.5-8.5 (m, 5H, quinoline).
6a	66	298-300	$C_{33}H_{33}N_5O_6S_2$	IR: 3250(NH), 1190(CS), 1360(SO_2 asym), 1160(SO_2 sym). ^{1}H NMR ($CDCl_3$): 2.7-3.4(m, 16H, morph), 9.5(s, 1H, NH), 6.2-7.1(m, 5H aromatic + CH), 7.4-8.3 (m, 5H, quinoline).
6b	70	>300	$C_{33}H_{33}N_5O_6S_2$	IR: 3260(NH), 1185(CS), 1370(SO_2 asym), 1170(SO_2 sym).
6c	64	322-24	$C_{33}H_{32}N_6O_8S_2$	IR: 3240(NH), 1200(CS), 1370(SO_2 asym), 1170(SO_2 sym). ^{1}H NMR (DMSO-d_6): 2.5-3.3 (m, 16H, morph), 9.6(s, 1H, NH), 6.1-6.9(m, 4H, aromatic + CH), 7.2-8.1(m, 5H, quinoline).
7a	67	>330	$C_{28}H_{31}N_5O_6S$	IR: 1600(C=N), 1700(CO), 1360(SO_2 sym). ^{1}H NMR ($CDCl_3$): 2.3 (s, 3H, CH_3), 2.6-3.2(m, 16H, morph), 6.1-6.8(m, 5H, arom), 7.3-8.2(m, 5H, quinoline), 3.5(d, 2H, CH_2), 5.6(t, 1H, CH).
7b	72	324-26	$C_{29}H_{33}N_5O_7S$	IR: 1595(C=N), 1710(CO), 1370(SO_2 asym), 1170(SO_2 sym).
7c	62	328-30	$C_{28}H_{30}N_6O_8S$	IR: 1600(C=N), 1700(CO), 1385(SO_2 asym), 1165(SO_2 sym). ^{1}H NMR ($CDCl_3$): 2.4(s, 3H, CH_3), 2.5-3.3(m, 16H, morph), 6.3-6.9(m, 4H, arom), 7.4-8.5(m, 5H, quinoline), 3.6 (d, 2H, CH_2), 5.5 (t, 1H, CH).
7d	77	296-98	$C_{32}H_{33}N_5O_5S$	IR: 1600(C=N), 1380(SO_2 sym). ^{1}H NMR (DMSO-d_6): 2.4-3.1(m, 16H, morph), 6.5-7.4(m, 10H, arom), 7.6-8.5(m, 5H, quinoline), 3.7(d, 2H, CH_2), 5.7(t, 1H, CH).
7e	81	248-50	$C_{33}H_{35}N_5O_6S$	IR: 1590(C=N), 1370(SO_2 asym), 1170(SO_2 sym).
7f	65	320-22	$C_{32}H_{32}N_6O_7S$	IR: 1600(C=N), 1370(SO_2 asym), 1170(SO_2sym), ^{1}H NMR (DMSO-d_6): 2.4-3.2 (m, 16H, morph), 6.3-7.4(m, 9H, arom), 7.7-8.6 (m, 5H, quinoline), 3.55(d, 2H, CH_2), 5.65(t, 1H, CH).
8a	61	303-5	$C_{26}H_{28}N_4O_6S$	^{1}H NMR($CDCl_3$): 2.3-3.3(m, 16H, morph), 6.4-7.3(m, 5H, arom), 7.6-8.4 (m, 5H, quinoline), 3.6(d, 2H, CH_2), 5.6(t, 1H, CH).
8b	66	318-20	$C_{27}H_{30}N_4O_7S$	IR: 1190-1050(isoxazolone ring), 1370(SO_2 asym), 1170(SO_2 sym).
8c	62	308-10	$C_{26}H_{27}N_5O_8S$	IR: 1360(SO_2 asym), 1160(SO_2 sym), 1190(1050(isoxazoline ring), ^{1}H NMR (DMSO-D_6): 2.4-3.4(m, 16H, morph), 6.3-7.2(m, 4H, arom), 7.4-8.1 (m, 5H, quinoline), 3.55(d, 2H, CH_2), 5.65(t, 1H, CH).
9a	57	303-5	$C_{27}H_{29}N_3O_7S$	IR: 3150(NH), 1710(CO), 1365(SO_2 asym), 1165(SO_2 sym). ^{1}H NMR (DMSO-d_6): 2.2-3.2(m, 16H, morph), 6.4-7.3(m, 5H, arom), 7.6-8.4m, 5H, quinoline), 3.5(s, 1H, NH), 3.6(d, 2H, CH_2), 5.6(t, 1H, CH).
9b	60	>330	$C_{28}H_{31}N_5O_7S$	IR: 3130(NH), 1700(CO), 1370(SO_2 asym), 1170(SO_2 sym).
9c	55	324-26	$C_{27}H_{28}N_6O_8S$	^{1}H NMR (DMSO-d_6): 2.2-3.3(m, 16H, morph), 6.3-7.1(m, 4H, arom), 7.4-8.1(m, 5H, quinoline), 3.55(s, 1H, NH), 3.65(d, 2H, CH_2), 5.65(t, 1H, CH).

Table 1 Contd.

Compd.	Yield	%	Molecular* formula	Spectral data IR (cm^{-1}) & ^1H NMR (d ppm)
9d	56	330	$C_{27}H_{29}N_5O_5S_2$	IR: 3170(NH), 1190-1070(CS), 1490(CNS), 1375(SO_2 asym), 1165 (SO_2 sym). ^1H NMR ($CDCl_3$): 2.3-3.4(m, 16H, morph), 6.3-7.2(m, 5H, arom), 7.5-8.2(m, 5H, quinoline), 3.7 (d, 2H, CH_2), 5.7(t, 1H, CH).
9e	61	>330	$C_{28}H_{31}N_5O_6S_2$	IR: 3150(NH), 1190-1050(CS), 1485(CNS), 1370(SO_2 asym), 1160 (SO_2 sym).
9f	54	>330	$C_{27}H_{28}N_6O_7S_2$	^1H NMR (DMSO-d_6): 2.4-3.5(m, 16H, morph), 6.4-7.3(m, 4H, arom), 7.6-8.3(m, 5H, quinoline), 3.5(s, 1H, NH), 3.7(d, 2H, CH_2), 5.7(t, 1H, CH).
10a	56	318-20	$C_{29}H_{28}N_6O_5S$	IR: 3240, 3180(NH_2), 2200(CN), 1370(SO_2 asym), 1175(SO_2 sym). ^1H NMR (CF_3COOH): 2.2-3.1(m, 16H, morph), 6.2-7.2(m, 5H, arom), 7.4-8.1 (m, 5H, quinoline).
10b	68	270-72	$C_{30}H_{30}N_6O_6S$	IR: 3210, 3190(NH_2), 2200(CN), 1370(SO_2 asym), 1180(SO_2 sym). ^1H NMR (CF_3 COOD): 2.3-3.3(m, 16H, morph), 2.4(s, 3H, CH_3), 6.4-7.5(m, 5H, arom), 7.7-8.4(m, 5H, quinoline).

*All compounds gave satisfactory elemental analyses C, ± 0.27; H, ± 0.15; N, ± 0.22; S, ± 0.24

5-Morpholinosulfonyl-8-[6-aryl-4-morpholino-2-oxo(thioxo)-1,2,5,6-tetrahydropyrimidin-5-yloxyl-quinolines (9a-f)

A mixture of the chalcones 3a-c (0.01 mol), urea and/or thiourea (0.01 mol) and potassium hydroxide (0.1 g) in absolute ethanol (50 ml) was refluxed for 12 h. The reaction mixture was concentrated, neutralised with dilute HCl, and the resulting solid was washed with water and recrystallized from alcohol.

5-Morpholinosulfonyl-8-[2-amino-4-Aryl-3-cyano-6-morpholinopyridin-5-yloxy]-quinolines (10a,b)

A mixture of the chalcones 3a, b (0.01 mol) malononitrile (0.01 mol) ammonium acetate (0.02 mol) and n-butanol (10 ml) was refluxed for 8 h. The reaction mixture was cooled and the resulting solid was air-dried and recrystallized from ethanol.

Biological Screening

All the compounds prepared were screened for their antimicrobial activity against different strains of bacteria and fungi using the usual cupplate agar diffusion technique[18]. The antibacterial screening against Bacillus cereus, Klebsiella pneumonia and Serratia marcescens revealed that compounds 3a,c were only active against Bacillus cereus with inhibition zones of 16 and 12 mm, respectively, whereas compounds 3b, 5, 5c, 7d and 9d showed inhibition zones around 8-a0 mm against Serratia marcescens only. However Klebsiella pneumoniae was resistant to all the compounds tested.

On the other hand the compounds under investigation were tested for their antifungal potency against Aspergillus flavus, Penicillium chrysogenum, Stachybotrys chartavum and Candida Albicans. All the compounds under testing were inactive against the first three fungi, however ten derivatives out of them (2, 3a, 3b, 3c, 5b, 6b, 7a, 9a and 9d) proved to be remarkedly potent against Candida Albicans with inhibition zones ranging from 8-14 mm (cf. Table 2.).

Table 2

Antimicrobial screening of the synthesized compounds.

Compd No.	Antibacterial activity			Antifungal activity			
	Bacillus cereus	Klebsiella pneumoniae	Serratia marcescens	Aspergillus flavus	Penicillium chrysogenum	Stachybotrys chartovum	Candida albicans
2	-	-	-	-	-	-	10
3a	16	-	-	-	-	-	12
3b	-	-	8	-	-	-	10
3c	12	-	-	-	-	-	8
4a	-	-	-	-	-	-	-
4b	-	-	-	-	-	-	-
4c	-	-	-	-	-	-	-
5a	-	-	-	-	-	-	-
5b	-	-	8	-	-	-	12
5c	-	-	8	-	-	-	10
6a	-	-	-	-	-	-	-
6b	-	-	-	-	-	-	15
6c	-	-	-	-	-	-	-
7a	-	-	-	-	-	-	8
7b	-	-	-	-	-	-	-

Table 2 Contd.

	Antibacterial activity			Antifungal activity			
Compd No.	Bacillus cereus	Klebsiella pneumoniae	Serratia marcescens	Aspergillus flavus	Penicillium chrysogenum	Stachybotrys chartovum	Candida albicans
7c	-	-	-	-	-	-	-
7d	-	-	10	-	-	-	-
7e	-	-	-	-	-	-	-
8a	-	-	-	-	-	-	-
8b	-	-	-	-	-	-	-
8c	-	-	-	-	-	-	-
9a	-	-	-	-	-	-	8
9b	-	-	-	-	-	-	-
9c	-	-	-	-	-	-	-
9d	-	-	8	-	-	-	14
9e	-	-	-	-	-	-	-
9f	-	-	-	-	-	-	-
10a	-	-	-	-	-	-	-
10b	-	-	-	-	-	-	-

RESULTS AND DISCUSSION

Interaction of 1 and the chalcones 3a-c with hydroxylamine hydrochloride gave the corresponding oximes 2 and 5a-c respectively.

The IR spectra of compound 2 and 5a-c showed a broad band at 3200-2800 cm^{-1} characteristic to the oxime hydroxyl group in addition to nC=N group. The ^{1}H-NMR ($CDCl_3$) of compound 2 revealed signals at d 2.4 (s,1H, OH), d4.4 (s, 2H, OCH2), d2.8-3.70 (m, 16H, 2-morpholine ring), d7.4-8.3(m, 5H quinoline).

Phenyl isothiocyanate react readily with the oximes 2 and 5a-c in boiling dry benzene in presence of triethylamine to afford the corresponding thiocarbamates 4 and 6a-c in good yields. The structure of the thiocarbamates 4 and 6a-c was assigned on both analytical and spectral data. The IR spectra of thiocarbamates showed the lack of (nOH) and presence of (nNHO as a single band in 3200 cm^{-1} region and (C=S) in the region 1200-1080 cm^{-1}. The ^{1}H-NMR spectra of 4 showed signals at d2.6-3.5 m, 16H, 2-morpholine ring), d4.3 (s, 2H, OCH2), 9.8 (s, 1H, NH), d7.3-8.1 (m. 5H, quinoline), 6.1-6.9 (m, 5H, aromatic).

Interaction of 1 with the selected aldehydes in ethanol using piperidine as basic catalyst gave new series of the corresponding chalcones 3a-c. These compounds were identified by elemental analysis as well as by IR and ^{1}H NMR spectral data. IR spectra showed bands at 1680-1660 (COCH=CH). Cyclization of 3a-c with hydrazines, hydroxylamine, urea, thiourea and malononitrile under the experimental conditions gave the corresponding pyrazole, isoxazol, pyrimidine, pyrimidinethione and nicotinonitrile quinoline derivatives (7-10). IR spectra showed band at 1600-1580 cm-1 (nC=N), 1730-1700 (nC=O) for N-acetylpyrazoline derivatives (7a-c); at 1600 cm-1 (nC=N), 1280 (nC-N) for N-phenylpyrazolin derivatives (7d-f) at 1190-1050 cm-1 (isoxazolin ring) for compounds (8a-c); at 1190-1170 cm-1 (C=S), 1490 cm-1 (nC-N-S) for pyrimidinethione derivatives (9d-f) and at 1600 cm-1 (nC=N), 3240-3130 cm-1 (NH2), 2200 cm-1 (nC=N) for nicotinonitrile derivatives (10a, b) (cf. Table 1).

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