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SYNTHESIS SOME NEW QUINOLINE DERIVATIVE INCORPORATED WITH OTHER HETEROCYCLIC COMPOUNDS

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Abstract

Reaction of 2-(quinolin-8-yloxy)acetohydrazide 1with phenyl isothiocyanate, carbon dsulphide, nitrous acid,active methylene compound and aromastic aldehydes afforded different heterocyclic compounds containing quinoline moiety 2-11. The structures of the new compounds confirmed by elemental analyses,spectroscopic measurements and chemical reactions.

Introduction

The chemistry of quinoline derivatives has been of increasing interest since many of these compounds have found useful application as chemotherapeutic agents against malaria parasites and microbes[1-4].Also,it has been reported that many other heterocycles such as 1,3-thiazolidine, triazole, pyrazole and oxadiazole derivatives possess biological activity[5-7].From this point of view it was very interesting to synthesis some new quinolines derivative incorporated into such heterocyclic .

Results and Discussion

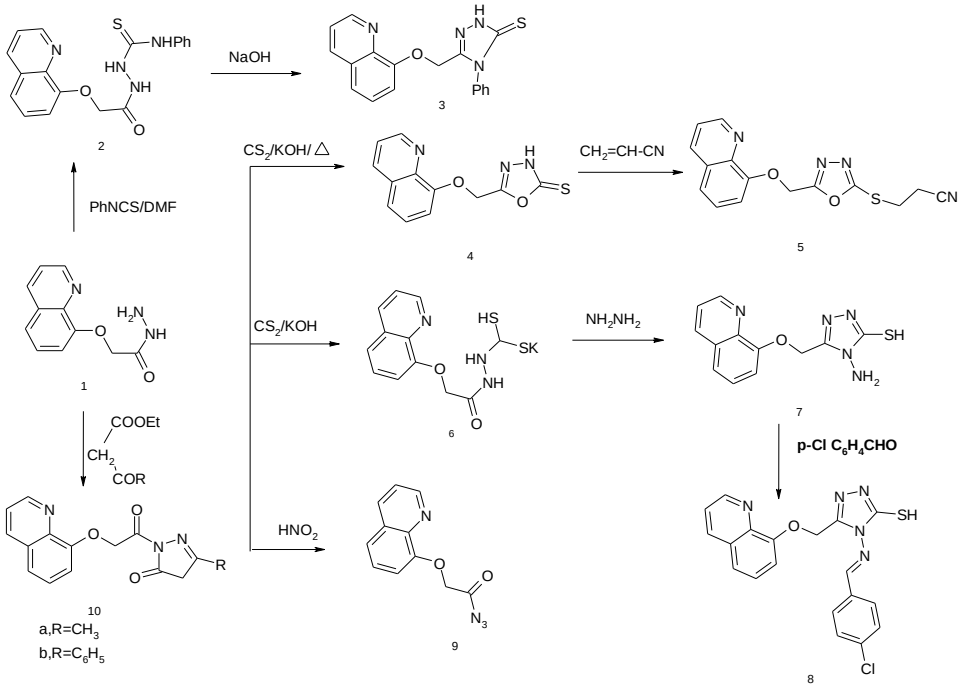
Reaction of 2-(quinolin-8-yloxy)acetohydrazide 1 with phenyl isothiocyanate in DMF[8] afforded thiosemicarbazide derivative 2.The structure of 2 was established by IR spectra which absence of NH_2 group (present in starting 1) but show absorption band at 1243cm^{-1}(C=S). Reaction 2 with sodium hydroxid [9] afforded 1,2,4-triazole-3-thione derivative 3 .

The reaction of acid hydrazide 1 with carbon disulphide yielded different products[10]according to the reaction conditions.Thus, acid hydrazide 1 when reacted with carbon disulphide in boiling alcoholic potassium hydroxide yielded 1,3,4-oxadiazole-2-thione derivative 4.While the potassium dithiocarbazide 5 was obtained when the reaction takes place at room temperature. IR spectrum of compound 4 showed absorption bands at 3230 cm^{-1}due to NH group and 1258cm^{-1} due to C=S group. ^{1}H-NMR spectrum of compounds 4 showed a broad signal at δ 9.27ppm corresponding to (NH) protone (Table 1).Reaction of 1,3,4-oxadiazole-2-

thione derivative 4 with acrylonitrile[11]afforded 2-(cyanoethylthio)-1,3,4-oxadiazole 6.IR spectrum of compounds 6 showed absorption band at 2230 cm^{-1} due to CN group and the disappearance of absorption band at 1258 cm^{-1}(C=-S).Reaction of 5 with hydrazine hydrate led to the formation of 4-amino-1,2,4-triazole-3-thiol derivative 7.Compound 7existed in thiol-thione tautomers as indicated by their IR spectra which showed a bands due to SH and N-C=S. The ^{1}H-NMR spectrum of 7 indicated the predominance of thiol tautomer DMSO-d_6 since thy showed D_2O exchangeable signal at δ13.88ppm du to SH. Furthermore compound 7 was reacted with p-chlorobenzaldehyde in boiling ethanol[12] to yield 4-[(*p*-chloro-benzylidene)amino]-4H-1,2,4-triazole deriva-tive 8 (Scheme 1).Compounds 8 was characterized by the absence of NH_2 band in their IR spectra and the presence of arylidene proton N=CH at δ 8.87 pmm in the ^{1}H-NMR.

Condensation of acid hydrazide 1 with nitrous acid[13-15]and active methylene compounds such as ethyl acetoacetate and ethyl benzoyacetate in ethanol[16]afforded the corresponding (quinolin-8-yloxy)acetyl azid 9 and 5-substituted-pyrazol-3-one derivatives 10a,b. The structure of compound 9 and 10 were proved by both elemental analyses and spectral data .

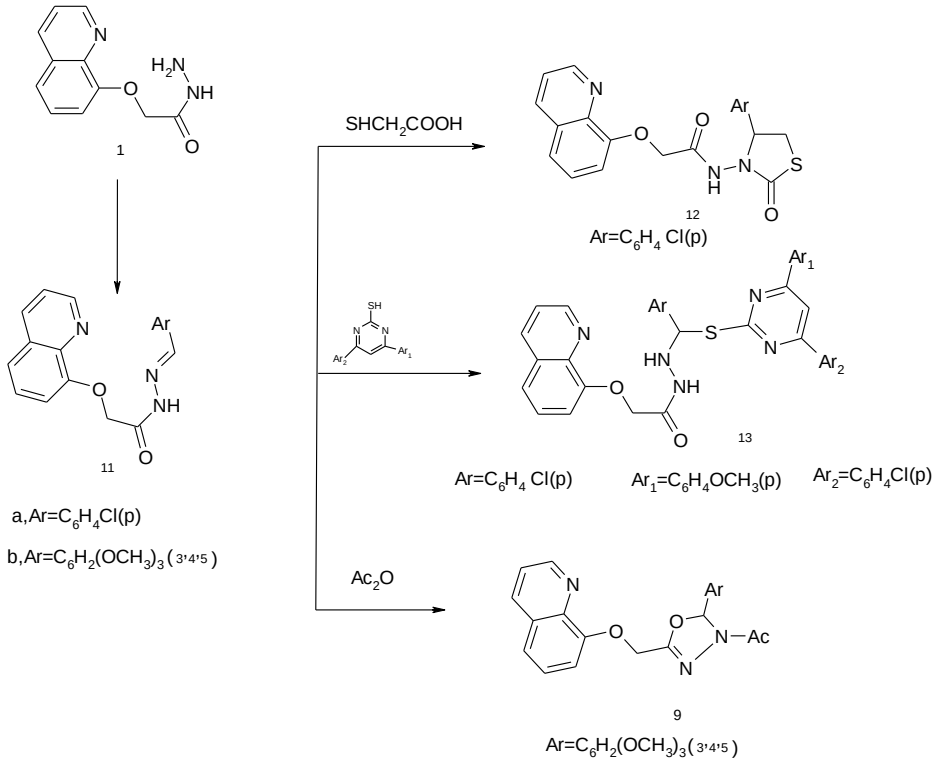
Scheme 1



Reaction of acid hydrazide 1 with aromatic aldehydes afforded arylidene derivatives 11a,b.^{1}H-NMR spectra of compound 11a recorded a signal at δ 8.73 and 11.75 ppm du to (N = CH) and (NH) protones (Table 1).Condensation of 11a with thioglycolic acid [17] afforded N-[2-(*p*-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(quinolin-8-loxy)acetamide 12.

Condensation of arylidene acetohydrazide 11a with 4-(*p*-chlorophenyl)-6-(*p*-methoxyphe-nyl)pyrimidine-2(1H)-thione afforded N-[(*p*-chlorophenyl)(pyrimidin-2-yl)mercapto methyl]-2-quinoline-8-yloxy)acetohydrazide 13. 4 Acetyl -1,3,4-oxadiazole 14 was abtained via cetyla- tion and cyclization of arylidene acetohydrazide 11b using acetic anhydride (Scheme2).

Scheme 2



Experimental

All melting points were determined in open glass capillaries on a Gallenkamp apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on a Pye-Unicam spectrophotometer type 1200 using KBr discs.^{1}H–NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using TMS as an internal standard and DMSO-d_6 as a solvent .Chemical shifts were expressed in δ(ppm)values .Elemental analysis were determined using a Parkin–Elmer 240C Microanalyser. The microanalyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University. The physical data of the synthesized compounds were give in Table 1.

4-Phenyl-1-[(quinolin -8-yloxy)acetyl]thiosemicarbazide 2.

A mixture of 1 (0.01mol) and phenyl isothiocyanate (0.01 mol) in DMF was refluxed for 6 h . The solvent was evaporated under reduced pressure. The solid that formed was filtered off, washed with water, and crystallized from n-butanol, m.p. 222-225 ^{o}C; yie ld:75%

4-Phenyl-5-[(quinolin -8-yloxy)]-4H-1,2,4-triazole-3-thione 3.

Compound 2 (0.01mol) was refluxed with NaOH solution (4%,25 ml) for 3 h. The res- ulting solution was treated with charcoal, filtered and cooled .The filtrate was acidified with HC l to PH 5-6. The resulting solid was crystallized from DMF,m.p.257-260 ^{o}C; yield:60 %.

5-[(Quinolin -8-yloxy)methyl]-1,3,4-oxadiazole-2(3H)thione 4

To a mixture of 1 (0.01mol) in ethanolic KOH(0.01 mol in 30 ml ethanol), was added carbone disulphide (0.02 mol).The reaction mixture was refluxed for 8 h. The solvent was evaporated under reduced pressure. The residue was diluted with water and acidified with HCl. The formed solid was filtered ,washed with water and crystallized from methanol, m.p. 218-220 ^{o}C; yield: 75 % .

(Quinolin -8-yloxy)dithiocarbazate potassium salt 5

Carbone disulphide (0.15mol) was added dropwise to an ice-cold solution of 1 (0.1mol) in ethanolic KOH(0.15 mol, in 50 ml ethanol).The whole mixture was stirred at r.t. for 12 h. Dry ether (50 ml) was added and the separated solid was

filtered and washed with ether. The product obtained was employed in next reaction without further purification.

2-(Cyanoethylthio)-5-[(quinolin-8-yloxy)methyl]-1,3,4-oxadiazole 6

Equimolar mixture of compound 4 and acroylonitrile (0.01 mol of both) was refluxed in dry pyridine (30 ml) for 6 h.The mixture was cooled and poured into ice/HCl . The formed solid was filtered and crystallized from methanol,m.p. 94-96 ^{o}C; yield: 65%.

4-Amino-5-[(quinolin-8-yloxy)methyl]-4H-1,2,4-triazole-3-thiol 7

A suspension of 5 (0.05 mol) and hydrazine hydrate (0.01 mol,95%) was heated under reflux at 140 ^{o}C for one hour.After cooling ,water (5 ml) was added ,the whole mixture was neutralized with conc.HCl. The formed solid was filtered ,washed with water and crystallized from methanol,m.p. 283-285 ^{o}C; yield: 85%.

4-[(p-Chlorobenzylidene)amino]-5-[(quinolin-8-yloxy)methyl]-4H-1,2,4-triazole-3-thiol 8

A mixture of 7 (0.01 mol) and p-chlorobenzaldehyde (0.01 mol) in dioxane(30 ml) was heated under refluxed for 6 h . After cooling, the resulting solid was collected by filtration, washed with water ,dried and crystallized from propan-2-ol,m.p. 254-257 ^{o}C; yield: 80%.

(Quinolin-8-yloxy) acetyl azid 9

To a cooled solution of 1 (0.01mol) in acetic acid (20 ml), was added dropwise with stirring a solution of sodium nitrite (0.7 g in 2 ml H_2O).After addition was finished the stirring was continued for another one hour and the mixture was allowed to stand for 3 h. The formed solid was filtered ,washed with water and crystallized from n-butanol,m.p. 244-247 ^{o}C; yield: 85%.

4-Substituted -2-[(quinolin-8-yloxy)acetyl]-2,4-dihydro-pyrazol-3-one 10a,b

A mixture of 1 (0.05 mol) ,ethylacetoacetate and/ or ethylbenzoylacetate (0.05 mol) in ethanol (30 ml) was refluxed for 6 h.After cooling, the resulting solid was collected by filtration and crystallized from suitable solvent .

a,R=CH_3, Crystallized from benzene,m.p. 80-81 ^{o}C; yield: 65%.

b,R=C_6H_5, Crystallized from mixture of ethanol and benzene,m.p. 202-204^oC; yield: 70 %.

N-(Substituted benzylidene) -2-(quinolin-8-yloxy)acetohydrazide 11a,b

A mixture of 1 (0.01 mol) and appropriate aldehyde (0.01 mol) in abs.ethanol (30 ml) was refluxed for 5h.The excess of solvent was evaporated under reduced pressure and the obtained solid was crystallized from suitable solvent .

a,R=C_6H_4 Cl (4), Crystallized from ethanol,m.p. 190-192 ^oC; yield: 65%.

b,R=C_6H_2 $(OCH_3)_3$(3,4,5), Crystallized from mixture of ethanol and benzene,m.p. 270-272^oC; yield: 70 %.

N-[2-(p-Chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(quinolin-8-yloxy)acetamide 12

To a solution of 11a (0.01mol) in dioxane (50 ml) ,thioglycolic acid (0.01 mol)was added, the reaction mixture was refluxed for 8-10 h. Excess of solvent was evaporated under reduced pressure and the resulting residue was pourd in ice-cold water .The solid obtained was washed with sodium bicarbonate solution and crystallized from chlorform .m.p. 218-220^oC; yield:70%

N-[(*p*-Chlorophenyl)(4-(*p*-chloropheny)-6-(*p*-methoxyphenyl)pyrimidin-2 yl)mercapto methyl]-2-(quinolin-8-yloxy)acetohydrazide 13

A mixture of 11a (0.01mol) and 4-(*p*-chlorophenyl)-6-(*p*-methoxy-phenyl)pyrimidine-2(1H)-thione in dry benzene (30 ml) containing few drops of piperidine was refluxed for 3 h. The solid that separated ofter cooling was collected and crystallized from ethanol .m.p. 160-165 ^oC; yield: 75 %.

8-[4-Acetyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)metho-xy]quino-line 14

A mixture of 11b (0.01mol) and acetic anhydride (3ml)was refluxed for one hour.The excess of solvent was evaporated under reduced pressure and the obtained solid crystallized from ethanol.m.p. 250-253 ^oC; yield: 75 %.

Table 1: Physical data of the prepared compound 2-13

Compd .No.	Mol.Formula	Element Analyses Calcd./ Found					IR spectra(cm^{-1})	^{1}H-NMR
		C	H	N	S	Cl		
2	$C_{18}H_{16}N_4OS$	61.35	4.58	15.90	9.10		3289(NH),1644(C=O),3043,	6.94-7.60(9H,m,Ar-H and $C_{3,5,6,7}$-H Quinoline),8.31(1H,d,
	352.42	61.38	4.62	15.93	9.14		2918(CH),1243(C=S)	C_4-H Quinoline),8.91(1H,d,C_2-H Quinoline),5.17(2H,s,CH_2), 9.90(2H,br s,NH-CS-NH),10.59(1H,br s,CONH).
3	$C_{18}H_{14}N_4OS$	64.65	4.22	16.75	9.59		3110(NH),1616(C=N),3055,	7.12-7.63(9H,m,Ar-H and $C_{3,5,6,7}$-H Quinoline),8.33(1H,d,
	334.4	64.68	4.25	16.78	9.61		2917(CH),1259(C=S).	C_4-H Quinoline),8.81(1H,d,QuinolineC_2-H),10.2(1H,br s,NH), 5.18(2H,s,CH_2)
4	$C_{12}H_9N_3O_2S$	55.59	3.50	16.21	12.37		3230(NH),1258(C=S),3038	7.21-7.61(4H,m, $C_{3,5,6,7}$-H Quinoline),8.19(1H,d,C_4-H
	259.29	55.62	3.54	16.25	12.40		2989(CH),1632(C=N).	Quinoline),8.83(1H,d,C_2-H Quinoline),5.90(2 H,s,CH_2),9.72 (1H,br s,NH).
6	$C_{15}H_{12}N_4O_2S$	57.68	3.87	17.94	10.27		2230(CN),3040,2980(CH),	7.22-7.79 (4H,m, $C_{3,5,6,7}$-H Quinoline),8.15(1H,d,C_4-Hquin-
	312.35	57.71	3.89	17.97	10.30		1610(C=N).	oline),8.81(1H,d,C_2-H Quinoline),5.60(2H,s,CH_2),2.91- 3.08(4H,m,S-CH_2CH_2.CN).
7	$C_{12}H_{11}N_5OS$	52.73	4.06	25.62	11.73		1260(C=S),3046,2917(CH),	7.14-7.63 (4H,m, $C_{3,5,6,7}$-H Quinoline),8.45(1H,d,C_4-H
	273.32	52.75	4.09	25.64	11.76		3257,3131(NH_2),2372(SH). 1601(C=N).	Quinoline),8.90(1H,d,C_2-H Quinoline),5.37(2H,s,CH_2),13.88 (1H,s,SH),5.52(2H,br s,NH_2).
8	$C_{19}H_{14}ClN_5OS$	57.65	3.56	17.69	8.1	8.96	1618(C=N),1618(C=N),2374	7.40-7.58(8 H,m,Ar-H and $C_{3,5,6,7}$-H Quinoline),8.34(1H,d,
	395.87	57.67	3.59	17.71	8.12	8.99	(SH).	C_4-HQuinoline),8.47(1H,d,C_2-H Quinoline),8.87(1H,s,CH=N) 5.36(2H,br s,NH_2),13.78(1H,s,SH)
9	$C_{11}H_8N_4O_2$	57.89	3.53	24.55			2107(N_3),1645(C=O),1604	7.48-7.97(4 H,m,$C_{3,5,6,7}$-HQuinoline),8.01(1H,d,C_4-H Quin-
	228.21	57.92	5.56	24.58			(C=N),2936,2848(CH).	oline),8.95(1H,d,C_2-H Quinoline),5.11(2H,s,CH_2).
10a	$C_{15}H_{13}N_3O_3$	63.6	4.63	14.83			1683(C=O),1702(C=O),	7.27-7.85(4 H,m,$C_{3,5,6,7}$-H Quinoline),8.31(1H,d,C_4-HQuin-
	283.29	63.63	4.66	14.86			1603(C=N).	oline),8.88(1H,d,C_2-H Quinoline),4.91(2H,s,CH_2),3.43(2H,s, CH_2Pyrazole),2.50(3H,m,CH_3).

Continued Table(1)

Compd .No.	Mol.Formula	Element Analyses Calcd./ Found C	H	N	S	Cl	IR spectra(cm^{-1})	^{1}H-NMR
10b	$C_{20}H_{15}N_3O_3$ 345.36	69.56 69.59	4.38 4.40	12.17 12.19			1652(C=O),1694(C=O), 1596(C=N).	7.26-7.63(9 H,m,$C_{3,5,6,7}$-H Quinoline),8.34(1H,d,C_4-HQuinoline),8.89(1H,d,C_2-H Quinoline),4.91(2H,s,CH_2),3.92(2H,s, CH_2 Pyrazole).
11a	$C_{18}H_{14}ClN_3O_2$ 339.78	63.63 63.66	4.15 4.17	12.37 12.40		10.43 10.47	3212(NH),1672(C=O),3090, 2993,2913(CH).	7.27-7.66(9 H,m,$C_{3,5,6,7}$-HQuinoline),8.36(1H,d,C_4-H Quinoline),8.85(1H,d,C_2-H Quinoline),5.42(2H,s,CH_2),8.73(1H,s, N=CH)11.75(1H,be s,NH).
11b	$C_{21}H_{21}N_3O_5$ 395.42	63.79 63.75	5.35 5.32	10.63 10.60			3183(NH),1680(C=O),3090, 2919(CH).	7.01-7.99(6 H,m,Ar-H and $C_{3,5,6,7}$-H Quinoline),8.18(1H,d, C_4-H Quinoline),8.66(1H,d,C_2-H Quinoline),5.48(2H,s,CH_2), 8.58(1H,s,N=CH)11.70(1H,be s,NH),3.87(9H,s,$(OCH_3)_3$).
12	$C_{20}H_{16}ClN_3O_3S$ 413.89	58.04 58.00	3.90 3.88	10.15 10.11	7.75 7.72	8.57 8.55	1599(C=N),2922,2852(CH), 31798(NH),1722,1684 (C=O).	7.10-7.73(8 H,m,Ar-H and $C_{3,5,6,7}$-H Quinoline),8.24(1H,d, C_4-H Quinoline),8.88(1H,d,C_2-H Quinoline),4.84(2H,s,CH_2), 6.48(1H,s,C_2-HOxathiazolidine),10.85(1H,br s,NH),3.98(2H, s,C_5-H Oxathiazolidine).
13	$C_{35}H_{27}Cl_2N_5O_3S$ 668.61	62.88 62.90	4.07 4.10	10.47 10.50	4.80 4.82	10.61 10.63	1598(C=N),2924,2852(CH), 3469,3189(NH)	6.10-7.73(17 H,m,Ar-H,$C_{3,5,6,7}$-H Quinoline and CH Pyrimidine),8.24(1H,d,C_4-H Quinoline),8.35(1H,d,C_2-H Quinoline), 5.11(2H,s,CH_2),11.71(1H,br s,NH),12.06(1H,br s,NH),3.62 (3H,s,OCH_3),4.05(1H,s,CH-NH).
14	$C_{23}H_{23}N_3O_6$ 437.46	63.15 63.17	5.30 5.32	9.61 9.62			1597(C=N),1660(C=O), 2843,2914(CH).	7.10-7.72(7 H,m,Ar-H,$C_{3,5,6,7}$-HQuinoline and C_5Oxadiazole), 8.24(1H,d,C_4-H Quinoline),8.35(1H,d,C_2-H Quinoline),3.80 (9H,s,$(OCH_3)_3$),4.11(2H,s,CH_2),3.32(3H,s,$COCH_3$).

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