A SIMPLE AND EFFICIENT SYNTHESIS OF FUSED HETEROCYCLIC QUINOLINE DERIVATIVES

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Abstract : The reaction of arylidenemalononitrile **2a-e** with 5-chloro-8-quinolinol 1 gave the corresponding pyrane derivatives **3a-e** .Their cyclization with acetic anhydride/pyridine, formamide, triethylorthoformate then with aniline, ethyl cyanoacetate, and nitrous acid afforded a series of poly cyclic heterocycles containing pyrimidine and triazine rings.
Key words : Triazino pyranoquinolines, Pyrimidopyranoquinolines, antibacterial activities.

Introduction

Several quinoline possess abroad spectrum of therapeutic activity Members of this class were used as antihypertensive (1), cardiovascular (2), inhibiters of MEK enzymes (3), antibacterials (4), antiulcer agents (5), anti-tumor, anti-atheroselerosis, antipsoriasis, antidiabetes, anti-arthritis activities (6), and as anti-malarialacitivities (7). Pyrimidines were used as tyrosine kinase inhibitors (8), herbicides and agrochemical fungicides (9), anticancer (10), gonadotropin releasing hormone antagonists (11) and for treatment of erectile dysfunction (12). Pyrans are useful in the treatment of LTB_4 induced illnesses (13). In this respect and in continuation of our interest in the synthesis of heterocyclic systems (14-19), we report herein the synthesis of the title compounds in the hope that member of them would find interesting biological activities.

Experimental

The time required for completion of each reaction was monitored by TLC. Melting points are uncorrected. NMR (δ,ppm) spectra were measured on an EM-360 90-MHz spectrometer using TMS as internal standard. ^{13}CNMR (δ,ppm) were measured on a Varian FT-80 spectrophotometer IR(v,cm^{-1}) spectra were recorded on a Nicolet Jeol Technique in the rang of 4000-400 cm^{-1} 205 FTIR with KBr. Elemental analyses were determined on a Perkin Elmer 240 C microanalyser. Mass spectra were recorded on Jeol JMS 600 instrument.

2-Amino-4aryl-6-chloro-4H-pyrano[3,2-h]quinolines (3a-e) (Scheme-1)

General procedure :

A mixture of arylidenemalononitriles 2a-e (0.01 mol) and 5-chloro-8-quinolinol (0.01mol) was heated under reflux in absolute ethanol (50 ml) using a catalytic amount of piperidine for 6h. The solvent was evaporated under reduced pressure, cool and poured into ice cold water. The solid products were collected, washed several times with water and recrystallized from ethanol (Table-1).

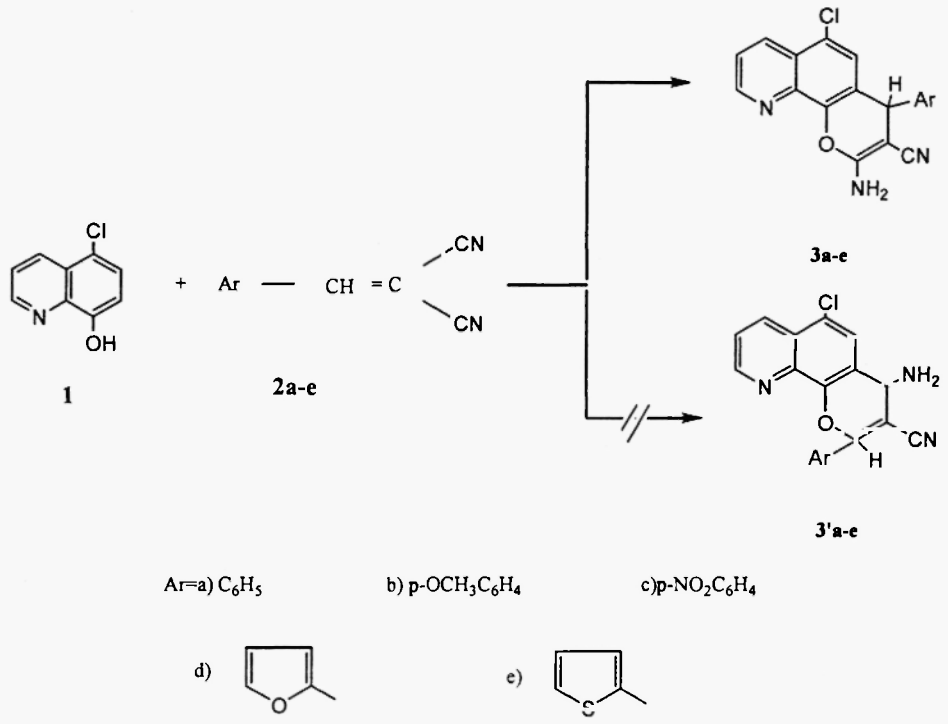
7-Aryl-5-chloro-10-methyl-8-oxo8,9dihydro-7H-pyrimido[4',5':6,5]pyrano[3,2h]quinolines(4a-e) (Scheme-2)

General procedure:

A solution of 3a-e (0.01) in acetic anhydride/pyridine mixture (20 ml, 2:1 v/v) was heated under reflux on a steam path for 8h and poured into ice cold water. The products were collected, washed several times with water and recrystallized from dioxane (Table-1).

8-Amino-7-aryl-5-chloro-7H-pyrimido[4',5' : 6,5]pyrano[3,2-h]quinolines (5a-e) (Scheme-2)

General procedure:
A mixture of 3a-e (0.01 mol) and formamide (25 ml) was heated under reflux for 5h. The reaction mixture was allowed to cool and the product was collected and recrystallized from methanol (Table-1).



Scheme-1

7-Aryl-5-chloro-8-oxo-8,9-dihydro-7H-pyrimido[4',5':6,5]pyrano[3,2-h]quinolines (6a-e) (Scheme-2)

General procedure:
A mixture of 3a-e (0.01 mol) and formic acid (7 ml) in formamide (25 ml) was heated under reflux for 4h. The reaction mixture was allowed to cool, poured into ice cold water and the precipitated solid was collected and recrystallized from dioxane (Table-1).

4-Aryl-6-chloro-3-cyano-2-(ethoxymethylenamino)-4H-pyrano[3,2-h]quinolines (7a-e) (Scheme-2)

General procedure:
A mixture of 3a-e (0.01 mol) and triethyl orthoformate (3 ml) in acetic anhydride (15 ml) was heated under reflux for 2h. The solid product was collected and recrystallized from methanol (Table-1).

7-Aryl-5-chloro-8-imino-9-phenyl-7H-pyrimido[4',5': 6,5]pyrano[3,2-h]quinolines (8a-e) (Scheme-2)

General procedure:
A mixture of 7a-e (0.01 mol) and aniline (0.01 mol) in absolute ethanol (50 ml) was reflux for 3h. The precipitate was collected and recrystallized from ethanol (Table-1).

8-amino-7-aryl-5-chloro-9-cyano-10-oxo-pyrido[2',3' :6,5]pyrano[3,2-h]quinolines(9a-e) (Scheme-2)

General procedure:
A mixture of 3a-e (0.01 mol) and ethyl cyanoacetate (0.01 mol) was fused for 3h. The solid product was collected and recrystallized from dioxane.

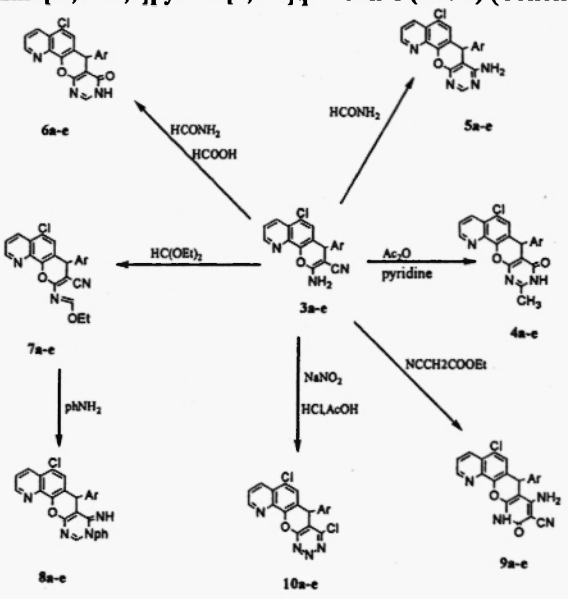
Table-1 : Physical Data of pyrano derivatives (3a-e), pyranopyrimidines (4a-e – 8a-e), pyranopyridines (9a-e), and pyranotriazines (10a-e).

Comp. No.	Yield (%)	Mp (C°)	Molecular Formula	IR(γ,cm^{-1}) (KBr)and MS	NMR(δ,ppm) (solvent) ^{13}(NMR($CDCl_3$)	Anal.Calcd/(found)%				
						C	H	N	S	Cl
3a	68	123	$C_{19}H_{12}N_3OCl$	2192(CN),3324-3180(NH_2),3057 (CH arom.)m/z 333,335	($CDCl_3$):4.90(1H,s),8.8(2H,s), 6.90-8.10(9H,m),^{13}CNMR: 158.86,148.34,133.44, 129.18,127.44,126.81,122.56, 115.09,111.79,92.13,77.30,76.67, 55.77	68.36 (68.47)	3.62 3.69	12.59 (12.48)	- -	10.64 (10.70)
3b	73	73	$C_{20}H_{14}N_3O_2Cl$	2192(CN),3300-3190(NH_2),3030 (CHarom.)m/z363, 365	($CDCl_3$):5.00(1H,s),3.6(3H,s), 6.90-8.10(8H,m),8.15(2H,s)	66.02 (66.17)	3.88 (3.91)	11.55 11.64)	- -	9.76 (9.81)
3c	77	85	$C_{19}H_{11}N_4O_3Cl$	2180(CN),3318-3062(NH_2),3020 (CHarom.),m/z 378,380	($CDCl_3$):4.90(1H,s), 6.90-8.10(8H,m),8.15(2H,s)	60.24 (60.37)	2.93 (2.89)	14.79 (14.66)	- -	9.37 (9.44)
3d	85	117	$C_{17}H_{10}N_3O_2Cl$	2217(CN),3324-3196(NH_2),3025 (CH arom.)	($CDCl_3$):5.00(1H,s),6.70-8.00 (7H,m),8.10(2H,s)^{13}CNMR:	63.06 (63.22)	3.11 (3.16)	12.98 (12.20)	- -	10.96 (10.84)
3e	82	111	$C_{17}H_{10}N_3OClS$	2212(CN),3318-1396(NH_2),3020 (CH arom),m/z 339,341	($CDCl_3$):5.00(1H,s),6.70-8.00(7H,m),8.10(2H,s)	60.07 (60.24)	2.97 (2.89)	12.37 (12.46)	9.45 (9.54)	10.45 (10.55)
4a	76	170	$C_{21}H_{14}N_3O_2Cl$	1654(C=O),3390 (NH)	(CF_3COOD):5.00(1H,s)3.40 (3H,s),7.00-8.20(9H,m)	67.10 (67.23)	3.76 (3.82)	11.18 (11.26)	- -	9.45 (9.53)
4b	78	196	$C_{22}H_{16}N_3O_3Cl$	1700(C=O),3432 (NH)	(CF_3COOD):4.40(1H,s)3.4 (3H,s),7.00-8.20(8H,m)	65.10 (65.26)	3.97 (3.91)	10.63 (10.28)	- -	8.75 (8.69)
4c	80	126	$C_{21}H_{13}N_4O_4Cl$	1710(C=O),3273 (NH)	(CF_3COOD):4.90(1H,s)3.4 (3H,s),7.00-8.20(8H,m)	59.93 (59.80)	3.11 (3.19)	13.32 (13.41)	- -	8.44 (8.51)
4d	88	130	$C_{19}H_{12}N_3O_3Cl$	1696(C=O),3421 (NH)	(CF_3COOD):4.9(1H,s)3.4 (3H,s),6.70-8.15(7H,m)	62.38 (62.25)	3.31 (2.35)	11.49 (11 57)	- -	9.70 (9.62)
4e	85	175	$C_{19}H_{12}N_3O_2ClS$	1685(C=O),3421 (NH)	(CF_3COOD):4.9(1H,s)3.4 (3H,s),6.70-8.15(7H,m)	59.75 (59.64)	3.17 (3.12)	11.01 (11.22	8.41 (8.47)	9.30 (9.22)
5a	65	110	$C_{20}H_{13}N_4OCl$	3440-3340(NH_2), 3020(CHarom.), m/z 360,362	(DMSO-d_2):5.00(1H,s),8.25 (2H,s),7.25-8.10(10H,m)	66.57 (66.47)	3.63 (3.70)	15.53 (15.64)	- -	9.84 (9.78)
5b	69	109	$C_{21}H_{15}N_4O_2Cl$	3440-3340(NH_2), 3020(CH arom.)	(DMSO-d_2):5.00(1H,s),8.25 (2H,s),7.25-8.10(9H,m), 4.6(3H,s)	64.35 (64.44)	3.35 (3.41)	14.34 (14.42)	- -	9.08 (9.16)
5c	71	135	$C_{20}H_{12}N_5O_3Cl$	3420-3310(NH_2), 3020(CHarom), m/z 405,407	(CF_3COOD):4.9(1H,s), 7.25-8.40 (9H,m)	59.18 (59.03)	2.98 (2.95)	17.26 (17.33)	- -	8.75 (8.81)
5d	78	>300	$C_{18}H_{11}N_4O_2Cl$	3440-3340(NH_2), 3020(CH arom.)	(CF_3COOD):5.00(1H,s),6.70-8.00(8H,m)	61.62 (61.73)	3.16 (3.24)	15.97 (15.88)	- -	10.12 (10.22)
5e	74	116	$C_{18}H_{11}N_4OClS$	3440-3340(NH_2), 3020(CH arom.)	(CF_3COOD):5.00(1H,s),6.70-8.00(8H,m)	58.92 (58.83)	3.12 (3.08)	15.27 (15.35)	8.75 (8 61)	9.68 (9.60)
6a	63	115	$C_{20}H_{12}N_3O_2Cl$	3100(NH),11690 (C=O),3010 (CH arom.),m/z 361,363	(CF_3COOD):4.90(1H,s),7.15-8.20(10H,m)	66.39 (66.50)	3.34 (3.29)	11.62 (11.54)	- -	9.81 (9.75)
6b	66	88	$C_{21}H_{14}N_3O_3Cl$	3100(NH),1700 (C=O),3010 (CH arom.),m/z 391,393	(CF_3COOD):4.90(1H,s),3.5 (3H,s),7.15-8.20(9H,m)	64.36 (64.23)	3.60 (3.54)	10.73 (10.67)	- -	9.06 (9.14)
6c	69	105	$C_{20}H_{11}N_4O_4Cl$	3100(NH),1700 (C=O),3010 (CH arom),m/z 406,408	(CF_3COOD):4.80(1H,s),7.15-8.20(9H,m)	59.04 (59.16)	2.73 (2.67)	13.78 (13.84)	- -	8.73 (8.81)
6d	74	235	$C_{18}H_{10}N_3O_3Cl$	3100(NH),1700 (C=O),3010 (CHarom.)	(CF_3COOD):5.00(1H,s),6.60-7.80(8H,m)	61.45 (61.56)	2.87 (2.92)	11.95 (11.89)	- -	10.09 (10.15)
6e	68	101	$C_{18}H_{10}N_3O_2ClS$	3100(NH),1700 (C=O),3010 (CHarom.)	(CF_3COOD):5.00(1H,s),6.60-7.80(8H,m)	58.76 (58.67)	2.74 (2.62)	11.43 (11.51)	8.73 (8.79)	9.65 (9.73)
7a	71	247	$C_{22}H_{16}N_3O_2Cl$	3000(CH arom.), 2920(CH aliph.), 2208(CN),m/z 389.88	($CDCl_3$):4.95(1H,s),1.80(3H,t, j=7.2Hz),4.20(2H,q,j=7.2Hz),7.20-8.30(10H,m)	67.77 (67.66)	4.14 (4.22)	10.78 (10.69)	- -	9.11 (9.21)

Table-1 (Continued) : Physical Data of pyrano derivatives (3a-e), pyranopyrimidines (4a-e – 8a-e), pyranopyridines (9a-e), & pyranotriazines (10a-e).

Comp. No.	Yield (%)	Mp (C°)	Molecular Formula	IR(γ,cm^{-1}) (KBr)and MS	NMR(δ,ppm) (solvent) ^{13}(NMR($CDCl_3$)	Anal.Calcd/(found)%				
						C	H	N	S	Cl
7b	61	220	$C_{23}H_{18}N_3O_3Cl$	3000(NH),2920 (CH aliph.),2208 (CN),m/z 420,427	($CDCl_3$):4.95(1H,s),1.6(3H,t, j=6.90Hz),4.10(2H,q,j=6.90Hz) 7.20-8.30(9H,m)	65.79 (65.66)	4.32 (4.29)	10.01 (10.12)	- -	8.45 (8.51)
7c	64	129	$C_{22}H_{15}N_4O_4Cl$	3000(CH arom), 2940(CH aliph), 2218(CN),m/z 434.88	($CDCl_3$):4.95(1H,s),1.95(3H,t, j=7.40Hz),7.20-8.30(9H,m), 4.30(2H,q,j=7.40Hz)^{13}CNMR: 158.85,150.87,148.3,133.42, 129.28,123.98,115.09,77.30, 72.66,69.90,63.66,61.47, 55.76,53.84,40.74,30.69	60.76 (60.85)	3.48 (3.54)	12.89 (12.97)	- -	8.16 (8.24)
7d	77	>300	$C_{20}H_{14}N_3O_3Cl$	3000(CH arom), 2900(CH aliph), 2300(CN)	($CDCl_3$):5.00(1H,s),1,8 (3H,t, j=7.10 Hz), 4.10(2H,q,j=7.10 Hz),6.60-7.80(8H,m)	63.24 (63.14)	3.72 (3.69)	11.07 (11.14)	- -	9.35 (9.40)
7e	73	256	$C_{20}H_{14}N_3O_2ClS$	3078(CH arom.), 2919(CH aliph), 2218(CN)	($CDCl_3$):5.00(1H,s),1,8 (3H,t, j=7.10 Hz), 4.10(2H,q,j=7.10 Hz),6.60-7.80(8H,m)	60.67 (60.56)	3.56 (3.49)	10.62 (10.73)	8.11 (8.03)	8.97 (8.86)
8a	58	109	$C_{26}H_{17}N_4OCl$	3191(NH),3000 (CH arom.), m/z 437,439	(CF_3COOD):4.90(1H,s),7.10-8.20(15H,m)	71.47 (71.57)	3.92 (3.88)	12.83 (12.91)	- -	8.13 (8.22)
8b	64	251	$C_{27}H_{19}N_4O_2Cl$	3400(NH),3000 (CH arom.), m/z 466.96	(CF_3COOD):4.90(1H,s), 3.40(3H,s),7.10-8.20(14H,m)	69.44 (69.32)	4.10 (4.05)	12.00 (12.10)	- -	7.60 (7.53)
8c	61	244	$C_{26}H_{16}N_5O_3Cl$	3319(NH),3000 (CH arom.), m/z 482,484	(CF_3COOD):4.90(1H,s), 7.10-8.25(14H,m).^{13}CNMR: 158.44,148.33,133.42,129.16, 122.64,114.42,76.98,72.66, 70.38,63.66,61.47,55.76, 53.84,40.74,30.89	64.79 (64.88)	3.35 (3.40)	14.54 (14.60)	- -	7.37 (7.44)
8d	71	127	$C_{24}H_{15}N_4O_2Cl$	3319(NH),3058 (CH arom.)	(CF_3COOD):5.00(1H,s),6.60-7.80(13H,m)	67.52 (67.41)	3.54 (3.61)	13.13 (13.24)	- -	8.32 (8.26)
8e	66	109	$C_{24}H_{15}N_4OClS$	3334(NH),3026 (CH arom.), m/z 443,445	(CF_3COOD):5.00(1H,s),6.60-7.80(13H,m)	65.07 (65.19)	3.41 (3.33)	12.65 (12.54)	7.25 (7.34)	8.01 (8.12)
9a	60	155	$C_{22}H_{13}N_4O_2Cl$	3334-3210(NH_2), 3000 (CH arom.), 2203 (CN), m/z 400.84	(CF_3COOD):4.95(1H,s),7.00-8.10(9H,m)	65.91 (65.82)	3.27 (3.32)	13.98 (13.92)	- -	8.86 (8.93)
9b	61	195	$C_{23}H_{15}N_4O_3Cl$	3329-3186(NH_2), 3093(CH arom.), 2208(CN)	(CF_3COOD):4.95(1H,s),7.00-8.10(8H,m),3.40(3H,s)	64.11 (64.23)	3.51 (3.46)	13.01 (13.11)	- -	8.24 (8.31)
9c	68	130	$C_{22}H_{12}N_5O_4Cl$	3191-3104(NH_2), 3319(NH),3000 (CH arom.), 2200(CN)	(CF_3COOD):4.95(1H,s),7.00-8.10(8H,m)	59.26 (59.15)	2.71 (2.78)	15.71 (15.60)	- -	7.96 (7.87)
9d	72	137	$C_{20}H_{11}N_4O_3Cl$	3319-3191(NH_2), 3000(CH arom.), 2218(CN)	(CF_3COOD):5.00(1H,s),6.70-7.85(7H,m)	61.46 (61.56)	2.84 (2.80)	14.34 (14.42)	- -	9.08 (9.17)
9e	66	>300	$C_{20}H_{11}N_4O_2ClS$	3191-3093(NH_2), 3339(NH),3000 (CH arom.),2208 (CN)	(CF_3COOD):5.00(1H,s),6.70-7.85(7H,m)	59.03 (59.13)	2.73 (2.77)	13.77 (13.84)	7.89 (7.96)	8.72 (8.67)
10a	64	170	$C_{19}H_{10}N_4OCl_2$	3000(CH arom.), m/z 381,383	($CDCl_3$):7.20-8.30(9H,m), 4.90(1H,s)	59.84 (59.98)	2.64 (2.71)	14.70 (14.61)	- -	18.62 (18.51)
10b	69	114	$C_{20}H_{12}N_4O_2Cl_2$	2945(CH arom.), m/z 411,413	($CDCl_3$):4.90(1H,s),3.50(3H,s), 7.20-8.30(8H,m)	58.40 (58.26)	2.94 (2.90)	13.62 (13.50)	- -	17.26 (17.32)
10c	58	187	$C_{19}H_9N_5O_3Cl_2$	3000(CH arom.), m/z 426,428	($CDCl_3$):4.90(1H,s),7.20-8.30(8H,m)	53.53 (53.62)	2.13 (2.18)	16.43 (16.54)	- -	16.66 (16.58)
10d	55	250	$C_{17}H_8N_4O_2Cl_2$	3083(CH arom), m/z 371,373	($CDCl_3$):5.00(1H,s),6.60-7.80(7H,m)	54.99 (54.88)	2.17 (2.22)	15.09 (15.18)	- -	19.12 (19.05)
10e	57	200	$C_{17}H_8N_4OCl_2S$	3000(CH arom.), m/z 387,389	($CDCl_3$):5.00(1H,s),6.60-7.80(7H,m)	52.71 (52.84)	2.08 (2.15)	14.47 (14.35)	8.29 (8.38)	18.33 (18.22)

5-Aryl-4,7-dichloro-[1,2,3]triazino[5',4' :5,6]pyrano[3,2-h]quinolines (10a-e) (Scheme-2)



Scheme-2

General Procedure:

To an ice cold solution of 3a-e (0.01 mol) in a mixture of acetic acid (20 ml) and hydrochloric acid (10 ml), sodium nitrite (0.01 mol in 10 ml H_2O) was added with stirring for 30 min and the stirring was continued for 3h. The product was collected and recrystallized from diluted acetic acid (Table-1).

Antimicrobial Activity

The antimicrobial activity of the synthesized compounds was tested against *Escherichia coli* and *staphylococcus aurous* using the agar cup diffusion technique (22) and the results are given in (Table-2). The data showed that most of the newly synthesized compounds exhibited remarkable effects.

Table-2 : Antibacterial screening of compounds 3a-e-10a-e (Inhibition zones mm)

Comp. No.	Escherichia Coli	Staphylococcus Aurens	Comp.No.	Escherichia Coli	Staphlococcus Aureus
3a	22	16	7d	19	19
3b	28	23	7e	36	29
3c	21	19	8a	22	24
3d	33	22	8b	21	23
3e	44	27	8c	23	15
4a	23	26	8d	21	19
4b	28	31	8e	25	33
4c	-	19	9a	31	32
4d	23	19	9b	24	35
4e	36	22	9c	21	15
5a	22	18	9d	23	20
5e	18	25	9e	31	19
5c	16	16	10b	26	17
5e	29	34	10c	-	28
6a	20	-	10d	19	21
6b	19	21	10e	26	32
6c	23	18	Tetracycline	12	15
6d	-	18			
6e	19	-			
7a	18	18			
7b	26	26			
7c	-	-			

Results and Discussions

5-chloro-8-quinolinol 1 reacts with arylidenemalononitrile 2a-e in boiling ethanol containing few drops of piperidine for which two products 3a-e and 3a'-e seemed possible. Structures 3a-e were established for the reaction products based on ^{1}H-NMR spectra which revealed the presence of 4H-pyran proton at 5.00-5.10ppm, thus the structures 3a'-e were ruled out (20,21).

Compounds 3a-e proved to be a useful key intermediate in the synthesis of fused heterocyclic systems. Thus the pyrimido[4',5' :6,5]]pyrano[3,2-h] quinolines 4a-e -6a-e were produced when compounds 3a-e were reacted with acetic anhydride/pyridine mixture, formamide/formic acid mixture respectively. 4-Aryl-3-cyano-6-chloro-2-(ethoxymethylenamino)-4H-pyrano [3,2-h] quinolines 7a-e were obtained by refluxing compounds 3a-e with ethyl orthofomate. The IR (KBr,cm^{-1}) spectrum of compound 7a showed absorption bands at 3000 (CH arom.), 2920 (CH aliph.), 2208(CN); m/z 389,391. The ^{1}HNMR spectrum of 7a ($CDCl_3$/TMS) showed the following signals : δ 4.95 (1H,s), 1.8(3H,t, j=7.2 Hz), 4.2(2H,q, j=7.2 Hz), 7.20-8.30 (10H,m). Compounds 7a-e underwent aminolysis and cyclization by treatment with aniline to give in "one step reacton" 7-aryl-5-chloro-8-imino-9-phenylpyrimido [4',5 : 6,5] pyrano [3,2-h] quinolines 8a-e. Furthermore compounds 3a-e gave the corresponding 8-amino-7-aryl-5-chloro-9-cyano-10-oxo-pyrido [2',3' : 6,5] pyrano [3,2-h] quinolines 9a-e when 3a-e were reacted with ethyl cyanoacetate. Finally, 3a-e gave the corresponding triazine derivatives 10a-e by means of diazotization with sodium nitrite in a mixture of hydrochloric and acetic acid (Scheme 2). Compounds 8a-e – 10a-e were identified by conventional methods such as elemental and spectral analyses (Table-1).

Conclusions

This work reports a facile method for the synthesis of pyrimidopyranoquinoline derivatives.

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