Heterocyclic Fused Rings with Bridgehead Nitrogen Atoms: Single Step Synthesis of Several Polyfunctionally Substituted Fused Pyridines

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Abstract: The synthesis of several new polyfunctionally substituted fused pyridines via reaction of benze[g] 4-amino, 3-cyano, 2-methyl, 1H quinolino, 4,5-dione [1] and 4-amino, 3-cyano, 2-methyl 1,4-piperidino [2,3-b] benz [g] 1,2,3,4-tetrahydroquinoline 4,5,10 trione [2] with different reagents is described.

INTRODUCTION

Polyfunctionally substituted heteroaromatics are biologically interesting molecules and their synthesis has recently received considerable attention[1-3]. In previous work we have reported several synthesis of azoles[4], azines[5], and benzoazines[6], which are required as potential biodegradable agrochemicals. Among these are the considerable biological activities of pyridines and pipridinopyridines as antischistosomal agents[7] and antimetabolities[8]. As a part of a biological chemistry project in our laboratories, samples of certain polyfunctionally substituted fused pyridines were required.

RESULTS AND DISCUSSION

Synthesis of 4-amino, 3-cyano, 2-methyl, 1H quinolino 4,5-dione [1] and 4-amino, 3-cyano, 2-methyl, 4-piperidene [2,3-b] benz [g] 1,2,3,4-tetrahydroquinoline 4,5,10 trione [2].

Compound [1] was prepared by cycloaddition reaction of equimolcular amount of appropriate alkalidene malononitrile and 1,4 naphthoquinine in ethanol in the presence of piperidine as basic catalyst. Also, with the same pathway we synthesised compound [2] by cyclocondensation reaction of benz[g] 1,2,3,4 tetrahydroquinoline 4,5,10-trione which was prepared in our laboratory as reported in earlier publication[9] with equimolecular ratio of qppropriate alkylidene malononitrile in ethanol in the presence of piperidine as basic catalyst.

The structures of the newly synthesised compounds [1,2] were confirmed by their Elemental analysis, IR, ^{1}H NMR and Mass Spectral data [C.F. Table 1,2]. The activity of the methyl group at C_3 which due to its adjacent to the nitrile group at C_2 with its inflammatory effect prompted us to explore the possibility of the reactions of 1 and 2 with Arylidine malononitrile derivatives. The formation of compounds 5a, 10a from the reaction of 3a and 1,2 is assumed to proceed via initrial addition of the active methyl group in 1,2 to the activated double bond and subsequent attack of the cyano function into 5a, 10a. Attempts to isolate the cyclic intermediate for the reaction in order to provide evidence failed. However, in the Michael adduct by ring nitrogen atom affording 5a, 10a. The proposed structure 5a, 10a was supported by its independent synthesis from 1,2 and the phenyl methylidenecyanothioacetamide (3f) via elimination of hydrogen sulfide (mf; mixed mp; elemental and spectral analysis).

Similar to the behaviour of 1,2 with (3a), compound 1,2 reacted with ethyl benzylidenecyanoacetate (3b) to yield 5b, 10b. The formation of 5b and 10b in this reaction is assumed to proceed via a sequence similar to that discussed above for the

reaction of 1,2 and 3a. Thus ^{1}H NMR for all reaction products revealed a down field shifted amino function (cf. Table 2).

Compound 1,2 reacted also with α-cyanochalcon (3c) to yield pyridine derivatives 6,11. The formation of 6,11 is assumed to proceed via an initial formation of the Michael adduct 4c, 9c which then undergoes intermolecular cyclocondensation, through elimination of water to yield the final isolable 6 and 11. Both elemental analysis and spectral data were in complete agreement with the assigned structure.

Similarly compound 1 and 2 reacted with 3d-g to yield the corresponding 5d-g and 10d-g. The structure proposed for the reaction products was established based on analytical and spectral data. Thus, ^{1}H NMR for all reaction products revealed a down field shifted amino function (Scheme 1,2).

The reaction of 1 and 2 with alkylidenemalononitrile derivatives (14a-f; prepared in citu from the corresponding aliphatic aldehyde and active methylene reagent was also investigated. Thus, it has been found that 1 and 2 reacts with 14a prepared from a mixture of acetaldehyde and malononitrile in refluxing pyridine to yield compounds 16a and 25a. Also two isomeric products were considered. Thus 16a and 25a was considered most likely based on 1H NMR spectrum which revealed broad signal at 8.2 ppm for the amino function. If the reaction product was the isomeric 18a and 27a one would expected amino function at δ = 3.14 - 3.39

Similarly, 14b-d reacted with 1 and 2 to afford 16b-d and 25b-d. The reaction of 14e,f with 1 and 2 was also investigated. Two isomeric products seems also possible (cf. 23, 23) and (31, 32). Compound 22 and 31 were established for the reaction product based on elemental analysis IR spectra, Mass spectra and ^{1}H NMR spectra which reveals the amino function at 8.2 ppm.

EXPERIMENTAL SECTION

Melting point was measured on a Galllenkamp melting point apparatus. The Infrared spectra were recorded in potassium bromide on a Pye-Unicam Sp. 3-300 Infrared spectrophotometer. The ^{1}H NMR spectra were recorded in deuterated chloroform or DMSO-d_6 on a Varian Gemini 200 NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were recorded on a GCMS-Qp 1000EX mass spectrometer at 70 eV Microanalyses was carried out at the Microanalytical Center, University of Cairo, Giza, Egypt.

Benz[g] 4-amino; 3-cyano; 2-methyl; 1H quinoline-5,10-dione 91):

A solution of the appropriate acetamidine malononitrile (1-amino-1-methyl methylene malononitrile) was prepared in citu from the reaction of the acetamide and malononitrile (0.1 mole) in ethanol (20 ml) containing two drops of piperidine was treated with 1,4-naphthoquinone (0.01 mole). The reaction mixture was heated under reflux for 8-10 hr. The solvent was then evaporated under reduced pressure. Pour onto ice/water acidified by HCl, the solid product so formed was collected by filtration and crystallized from ethanol.

4-Amino; 3-cyano; 2-methyl; 1,2,3-trihydropiperidino [2,3-b] benz [g] 1,2,3,4-tetrahydroquinoline-4,5,10-trione (2):

A solution of the appropriate acetamidine malononitrile was prepared in citu from the reaction of the acetamide and malononitrile (0.01 mole) in ethanol (30 ml) containing

two drops of piperidine was treated with benz[g] 1,2,3,4-tetrahydroquinoline (0.01 mole). The reaction mixture was heated under reflux for 8-10 hr. The solvent was then evaporated under reduced pressure. Pour onto ice/water acidified by HCl, the solid product so formed was collected by filtration and crystallized from ethanol.

Reaction of Benz [g] 4-amino; 3-cyano; 2-methyl; 1H quinoline-5,10-dione (1) with cinnamonitriles (3a-g):

A suspension of 1 (2.65 g, 0.01 mole) and the appropriate cinnamonitriles (3a-g) (0.01 mol) in ethanol (30 ml) was treated with piperidine (1 ml). The reaction mixture was refluxed for 7-8 h., the solvent was then evaporated in vacuo. The remaining solid was triturated with water (20 ml) and acidified with conc. hydrochloric acid (if necessary). The product was collected by filtration and finally recrystallised from the appropriate solvent to afford the corresponding 5a-g.

Reaction of 4-Amino; 3-cyano; 2-methyl; 1,2,3-trihydropiperidino [2,3-b] benz[g] 1,2,3,4-tetrahydroquinoline 4,5-trione [2] with cinnamonitriles (3a-g):

A solution of 2 (3.34 g, 0.01 mole) and the appropriate cinnamonitriles (3a-g) (0.01 mol) in ethanol (30 ml) was treated with piperidine (1 ml). The reaction mixture was refluxed for 8-9 h., the solvent was then evaporated in vacuo. The remaining solid was triturated with water (20 ml) and acifified with conc. hydrochloric acid (if necessary). The product was collected by filtration and finally recrystallised from the appropriate solvent to afford the corresponding 10a-g.

Reaction of Benz[g] 4-amino; 3-cyano; 2-methyl; 1H quinoline 5,10-dione (1) with alkylidenemalononitrile derivatives (14a-f):

General procedure:

A solution of the appropriate alkylidenemalononitrile derivatives (14a-f) (0.01 mol); prepared in citue from the corresponding aliphatic aldehyde and active methylene reagent in pyridine (30 ml) was treated with compound 1 (2.65 g, 0.01 mole). The reaction mixture was refluxed for 8-9 h., the solvent was then evaporated in vacuo. The remaining solid was triturated with ice water and acidified with conc. hydrochloric acid. The solid product, so formed was collected by filtration, washed with cold water, dried and finally recrystallised from the proper solvent to afford the corresponding 16a,b and 20a,b and 22e-f respectively.

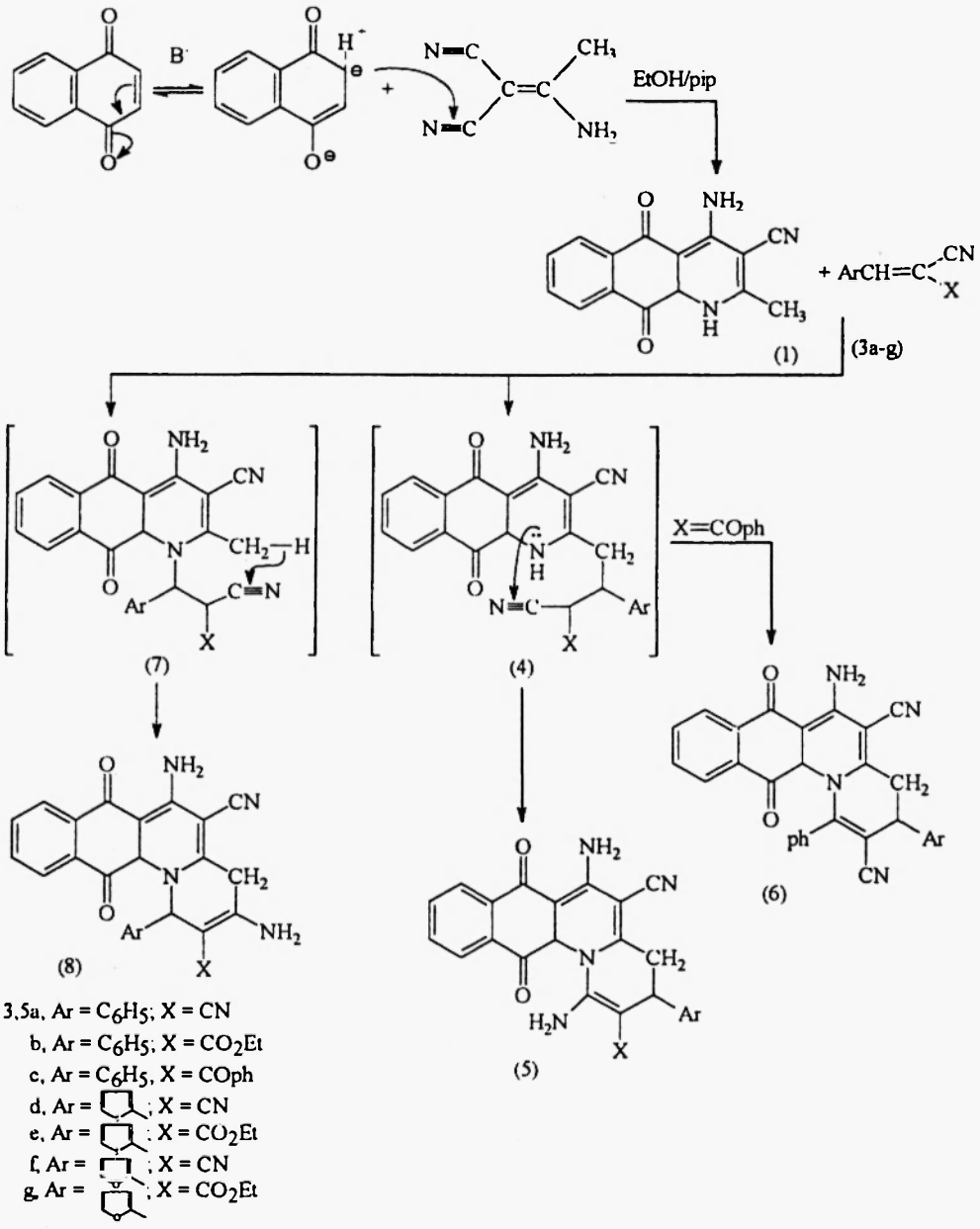
Reaction of 4-Amino; 3-cyano; 2-methyl; 1,2,3-trihydropiperidino [2,3-b] benz[g] 1,2,3,4-tetrahydroquinoline 4,5,10-trione (2) with alkylidenemalononitrile derivatives (14a-f):

General procedure:

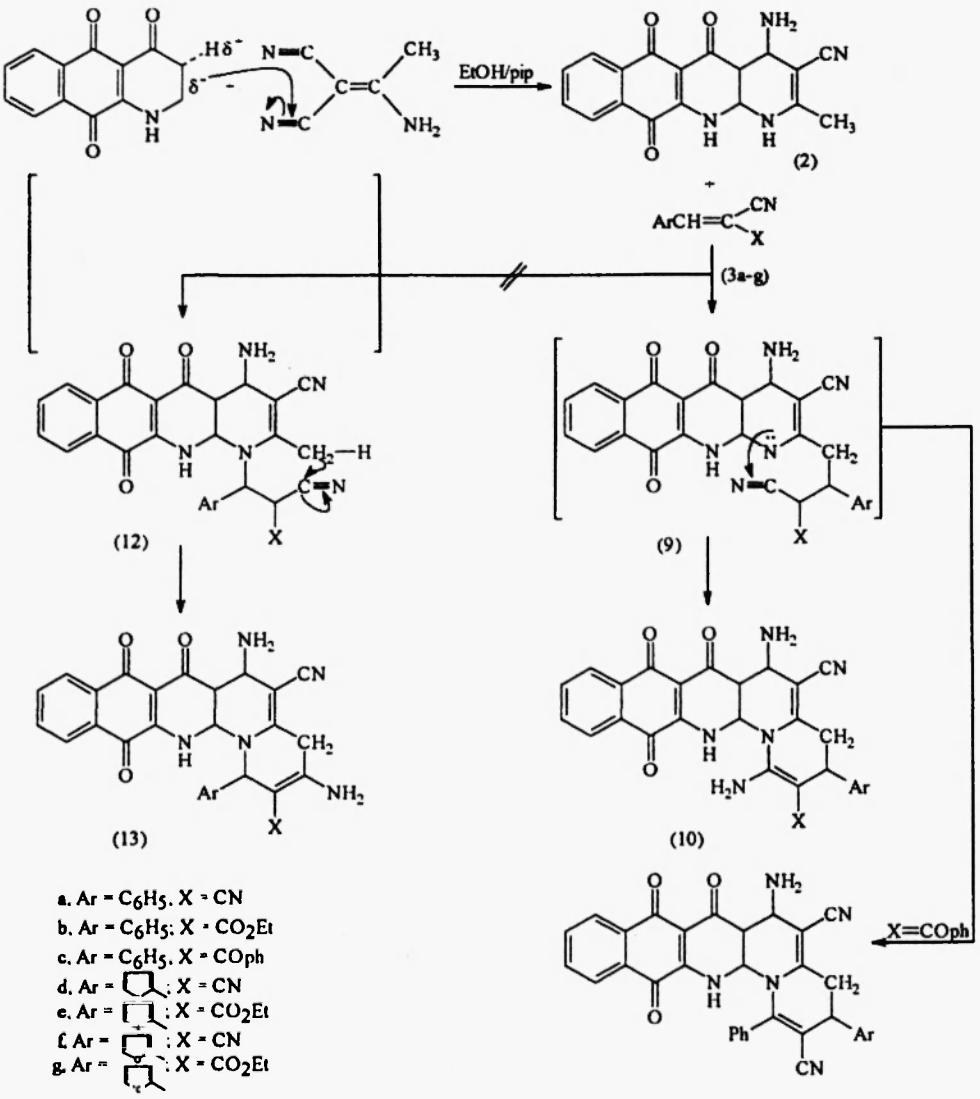
A solution of the appropriate alkylidenemalononitrile derivatives (14a-f) (0.01 mol); prepared in citue from the corresponding aliphatic aldehyde and active methylene reagent in pyridine (30 ml) was treated with compound 2 (3.34 g, 0.01 mol). The reaction mixture was refluxed for 8-9 h., the solvent was then evaporated in vacuo. The remaining solid was triturated with ice water and acidified with conc. hydrochloric acid. The solid product, so formed was collected by filtration, washed with cold water, dried and finally recrystallised from the proper solvent to afford the corresponding 25a-b, 29a-b, and 31e-f respectively.

Table 1

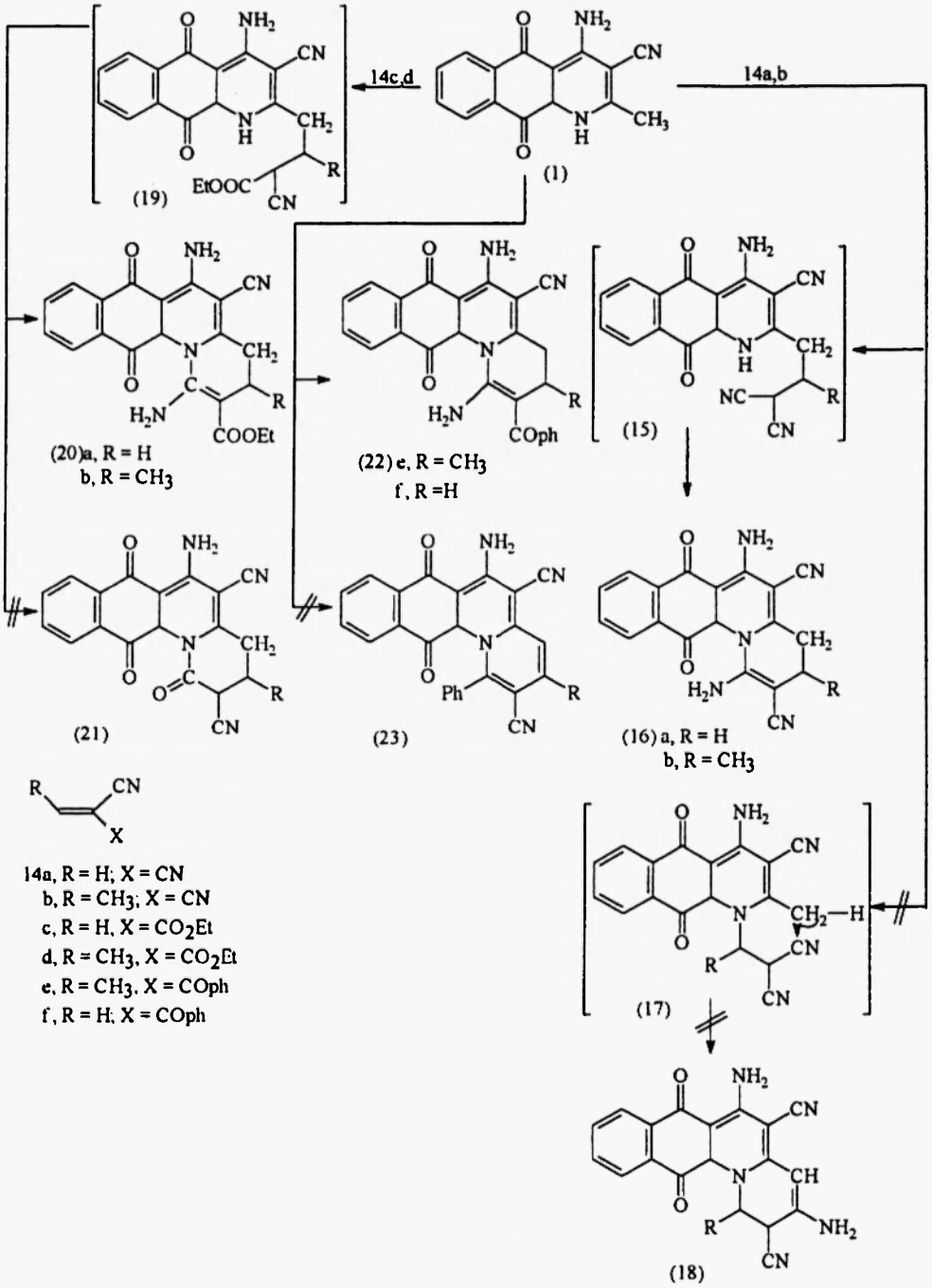
Comp No.	IR (ν max/cm^{-1})	^{1}H NMR	(Calcd.) Found			
			C	H	N	S
1	2216 (C≡N), 3400-2100 NH, NH_2	3.43 (d, 3H), 8.1-7.3 (m, 4H), 6.7(brs, NH_2), 10.2(S, NH)	(67.92) 67.90	(4.18) 4.15	(15.84) 15.80	--
2	2206 (C≡N), 3350-3200 (NH, NH_2)	2.44 (d, 3H), 5.73 (brs, NH_2), 8.01-7.48 (m,7H),12.41(S, NH)	(64.70) 64.65	(4.22) 4.10	(16.77) 16.66	--
5a	2200-2220 (C≡N), 3400-3100 NH_2	3.4 (tr, 2H), 3.6(tr, 1H), 4.5(dbrs, $2NH_2$) 1.2(t, 3H), 2.5(q,2H)	(71.59) 71.55	(4.09) 4.06	(16.698) 16.691	--
5b	2209-2215 (C≡N), 1740 C=O(ester)	3.42 (t, 2H), 3.6(t, 1H), 4.5(dbrs,$2NH_2$), 7.1-8.2 (m, 4H)	(69.52) 69.50	(4.75) 4.73	(12.01) 12.00	--
6	2219-2225 (C≡N), 3400-3100 NH_2	1.32(d, 1H), 1.52(d, 1H), 6.1(S, NH_2), 8.1-7.1 (m, 6H)	(77.81) 77.80	(3.79) 3.76	(11.708) 11.70	--
5d	2200-2215 (C≡N), 3400-3100 NH_2	3.41 (t, 1H), 1.5 (d, 2H), 6.1(S, NH_2), 8.2-7.01 (m, 8H0	(64.93) 64.90	(3.55) 3.54	(16.64) 16.45	(7.54) 7.52
5e	2210-2220 (C≡N), 3390-3100 NH_2	3.42 (t, 1H), 1.53 (d, 1H), 6.1 (brs, NH_2), 4.2(q, 2H), 1.55 (t, 3H), 7.5 (m, 8H)	(63.55) 63.53	(4.27) 4.25	(11.86) 11.85	(6.79) 6.77
5f	2190-2206 (C≡N), 3400-3150 NH_2	3.41 (t, 1H), 1.53 (d, 1H), 6.5 (brs, NH_2), 7.6 (m, 8H)	(67.48) 67.46	(44.07) 44.05	(17.11) 17.10	--
5g	2200-2220 (C≡N), 3400-3100 NH_2	3.43 (t,2H), 1.51 (d, 1H),4.2(q,2H),1.55(t 3H),8.1-7.01(m, 8H)	(65.78) 65.76	(4.42) 4.41	(12.27) 12.25	--
10a	2206-2215 (C≡N), 3390-3190 (NH, NH_2)	3.43 (t, 2H), 3.5 (t, 1H), 5.1 (brs, NH_2), 8.01-7.1 (m, 8H)	(68.85) 68.83	(4.13) 4.11	(17.20) 17.19	--
10b	2210-2216(C≡N), 3400-3100 (NH, NH_2),1740 (C=O) ester	3.42(t, 2H), 3.5(t, 1H), 5.1(brs, NH), 1.5(t, 3H), 4.2(q, 2H), 7.5(m, 8H)	(67.28) 67.23	(4.60) 4.69	(13.08) 13.06	--
11	2209-2220(C≡N), 3395-3100(NH, NH_2)	1.31(d, 1H), 1.52(d, 1H), 6.2(brs, NH_2), 8.01-7.1(m, 6H)	(74.58) 74.57	(3.87) 3.85	(12.79) 12.77	--
10d	2200-2215(C≡N), 34000-3100 (NH, NH_2)	3.4(t, 1H), 1.5(d, 2H), 6.2(brs, NH_2), 8.01-7.1 (m, 8H)	(63.15) 63.14)	(3.67) 3.65	(16.99) 16.97	(6.48) 6.46
10e	2215-2220(C≡N), 3390-3095(NH,NH_2) 1745 (C=O) ester	4.2 (q, 2H), 1.55 (t, 3H), 8.1-7.01 (m, 8H)	(62.097) 62.08	(4.28) 4.26	(12.93) 12.91	(5.92) 5.90



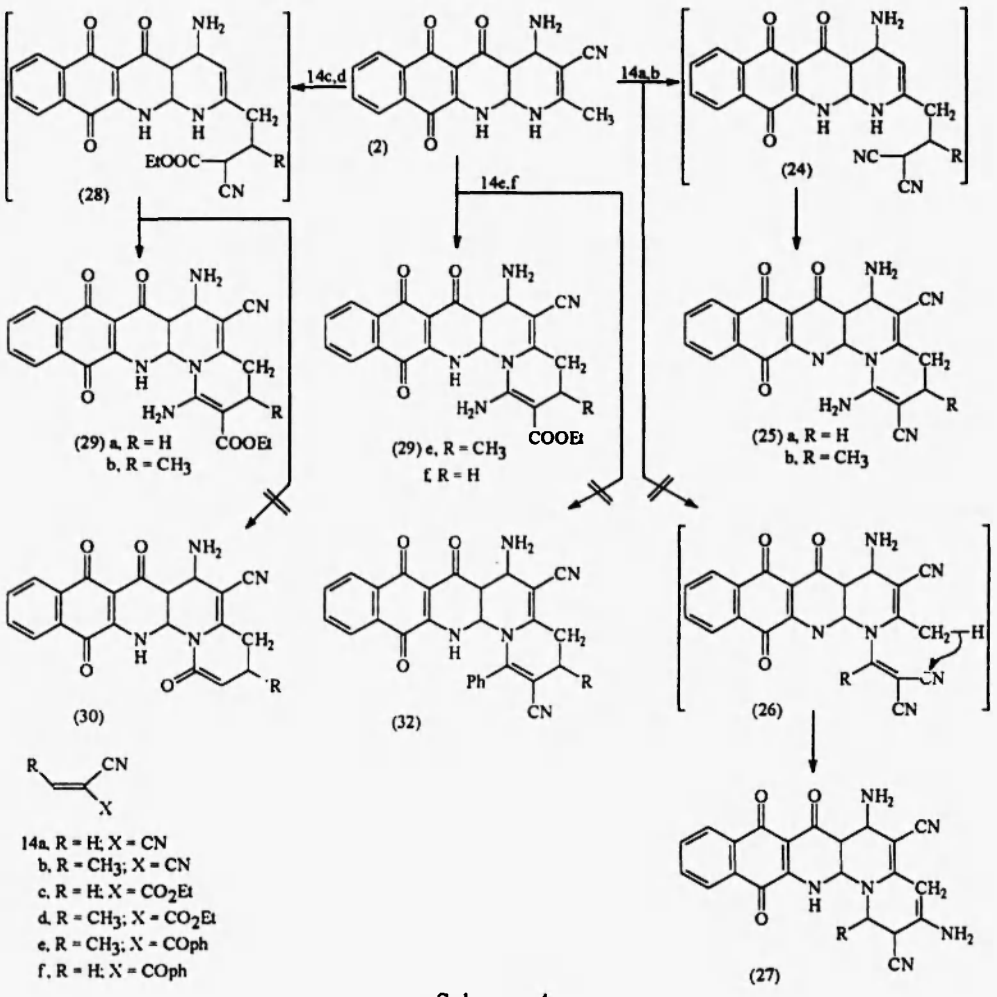
(Scheme 1)



(Scheme 2)



Scheme (3)



Scheme 4

Table 1

Comp No.	IR (ν max/cm^{-1})	^{1}H NMR	(Calcd.) Found			
			C	H	N	S
10f	2200-2215 (C≡N), 3400-3100 (NH, NH_2)	3.4(t, 1H), 1.52(d, 1H), 6.2(brs, NH_2), 7.5(m, 8H)	(65.27) 65.25	(3.79) 3.78	(17.56) 17.55	--
10g	2200-2215(C≡N), 3400-3100(NH, NH_2)	3.43(t, 1H), 1.5(d, 1H), 4.2(q, 2H), 1.6(t, 3H), 8.01-7.1 (m, 8H)	(63.995) 63.98	(4.41) 4.40	(13.33) 13.32	--
16a	2200-2220(C=N), 3400-3100(NH_2)	5.6(brs, NH_2), 8.01-7.1 (m, 9H)	(66.50) 66.52	(3.82) 3.84	(20.41) 20.42	--
16b	2210-2220(C≡N), 3400-3100(NH_2)	1.5(s, 3H), 5.65(brs, NH_2), 8.1-7.01 (m, 8H)	(67.22) 67.21	(4.20) 4.19	(19.596) 19.59	--
20a	2200-2220(C≡N), 3400-3100(NH_2), 1745(C=O)	4.3(q, 2H), 1.8(t, 3H), 6.1(brs, NH_2), 8.01-7.1(m, 9H)	(69.41) 69.40	(4.99) 4.97	(15.42) 15.41	--
20b	2206-2220(C=N), 3400-3100(NH_2), 1735-1740(C=O)	1.5(S, 3H), 4.32(q, 2H), 1.8(t, 3H), 6.02 (brs, NH_2), 8.01-7.1 (m, 8H)	(65.34) 65.32	(4.98) 4.96	(13.85) 13.84	--
22e	2200-2220(C≡N), 3400-3100(NH_2)	1.5(S, 3H), 6.1(brs, NH_2), 8.1-7.01(m, 8H)	(68.83) 68.81	(4.16) 4.15	(12.84) 12.82	
22f	2210-2220((C=N), 3400-3100 NH_2	6.2(brs, NH_2), 8.1-7.01(m, 9H)	(69.35) 69.34	(4.48) 4.47	(12.44) 12.43	--
25a	2190-2220(C=N), 3400-3100(NH, NH_2)	6.1(brs, NH_2), 8.01-7.1(m, 10H)	(64.07) 64.05	(3.91) 3.90	(20.38) 20.37	--
25b	2206-2215(C≡N), 3400-3100(NH,NH_2)	1.5(S, 3H), 6.2(brs, NH_2), 8.1-7.01(m, 9H)	(64.78) 64.77	(4.25) 4.23	(19.71) 19.7	--
29a	2200-2220(C=N), 3400-3100(NH, NH_2), 1740(C=O)	1.55(t, 3H), 4.2(q, 2H), 6.1(brs, NH_2), 8.1-7.01(m, 10H)	(62.74) 62.72	(4.61) 4.59	(15.24) 15.23	--
29b	2200-2215(C≡N), 3400-3100(NH, NH_2)	1.56(t, 3H), 4.2(q, 2H), 6.2(brs, NH_2), 8.1-7.01(m, 9H)	(63.42) 63.41	(4.895) 4.90	(14.79) 14.78	--
31e	2195-2215(C=N), 3400-3100(NH, NH_2)	1.5(S, 3H), 6.1(brs, NH_2), 8.1-7.01(m, 9H)	(68.90) 68.91	(4.59) 4.50	(13.85) 13.86	--
31f	2200-2215(C=N), 3400-3100(NH, NH_2)	6.2(brs, NH_2), 8.1-7.01 (m, 10H)	(68.42) 68.41	(4.31) 4.3	(14.25) 14.23	--

Table 2

Comp. No.	Yield %	mp.	Crystal solvent	Mol. Formula	(Mol. Wt)	MS
1	65	270	EtOH	$C_{15}H_{11}O_2N_3$	(265.270	266 M+1
2	70	190	EtOH	$C_{18}H_{14}O_3N_4$	(334.15)	338 M+4
5a	73	240	EtOH	$C_{25}H_{17}O_2N_5$	(419.44)	419
5b	75	130	EtOH	$C_{27}H_{22}O_4N_4$	(466.495)	466
6	76	195	EtOH	$C_{31}H_{18}O_2N_4$	(478.51)	478
5d	77	200	EtOH	$C_{23}H_{15}O_2N_5S$	(425.46)	425
5e	70	210	EtOH	$C_{25}H_{20}O_4N_4S$	(472.517)	472
5f	75	215	EtOH	$C_{23}H_{15}O_3N_5$	(409.403)	409
5g	73	220	EtOH	$C_{25}H_{20}O_5N_4$	(456.457)	456
10a	75	145	EtOH	$C_{28}H_{20}O_3N_6$	(488.488)	488
10b	70	200	EtOH	$C_{30}H_{25}O_5N_5$	(535.558)	535
11	70	215	EtOH	$C_{34}H_{21}O_3N_5$	(547.57)	547
10d	65	225	EtOH	$C_{26}H_{18}O_3N_6S$	(494.527)	494
10e	77	210	EtOH	$C_{28}H_{23}O_5N_5S$	(541.58)	541
10f	60	190	EtOH	$C_{26}H_{18}O_4N_6$	(478.466)	478
10g	66	195	EtOH	$C_{28}H_{23}O_6N_5$	(525.519)	525
16a	70	>300	EtOH	$C_{19}H_{13}O_2N_5$	(343.154)	344 M+1
16b	60	>300	EtOH	$C_{20}H_{15}O_2N_5$	(357.37)	357
20a	65	>300	EtOH	$C_{21}H_{18}O_4N_4$	(363.397)	363
20b	75	>300	EtOH	$C_{22}H_{20}O_4N_4$	(404.424)	408 M+4
22e	66	>300	EtOH	$C_{25}H_{18}O_3N_4$	(436.259)	436
22f	68	>300	EtOH	$C_{26}H_{20}O_3N_4$	(450.286)	450
25a	65	150	EtOH	$C_{22}H_{16}O_3N_6$	(412.41)	412
25b	70	160	EtOH	$C_{23}H_{18}O_3N_6$	(426.434)	426
29a	75	175	EtOH	$C_{24}H_{21}O_5N_5$	(459.46)	459
29b	65	185	EtOH	$C_{25}H_{23}O_5N_5$	(473.49)	473
31e	80	186	EtOH	$C_{29}H_{23}O_4N_5$	(505.53)	505
31f	66	170	EtOH	$C_{28}H_{21}O_4N_5$	(491.505)	491

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