SHORT PAPER

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Reactions of ketonic Mannich bases with malononitrile and malononitrile dimer†

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The reaction of malononitrile with the tertiary Mannich base hydrochloride derived from acetophenone and some related compounds **1**, **3**, **5** and **7**, in piperidine at 50°C afforded the pyrido[1,2-*a*]pyrimidine derivatives **2**, tetrahydronaphthalene derivative **4** substituted quinolines **6** and benzopyran derivatives **8**. While the condensation of malononitrile dimer with acetophenone, cyclohexanone and/ or α-tetralone Mannich bases hydrochloride **1**, **3** and **9** gave the pyridine, isoquinoline and benzo[f]isoquinoline derivatives **10–12** in moderate to good yield.

Keywords: ketonic Mannich bases, malononitrile, malononitrile dimer

Ketonic Mannich bases are β-bifunctional reactive synthons. These compounds have been widely used as good alkylating agents for acyclic, alicyclic ketones,[1-4] β-ketoesters,[5] phenoles and aromatic amines.[6] We have reported the reaction of some Mannich bases with different cyclic ketones.[7-11] To the best of our knowledge, only one example has been reported of the use of Mannich bases as alkylating agents for activated nitriles.[12] We describe in this paper the synthesis of some new heterocycles and naphthalene derivatives via reaction of various acyclic and cyclic ketonic Mannich bases with malononitrile and its dimer.

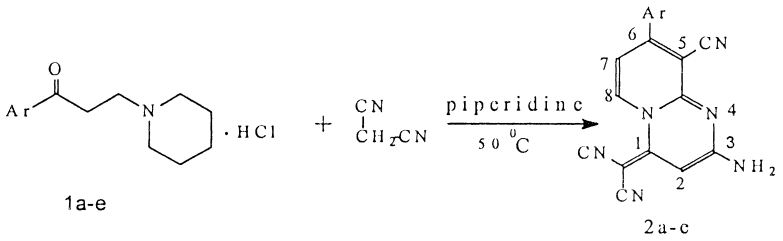
Thus, heating ketonic Mannich bases hydrochloride **1a–f** with malononitrile in piperidine at 50°C gave the 6-arylpyrido[1,2-a]pyrimidine derivatives **2a–f** in moderate to good yields. These compounds were assigned their structures on the basis of their elemental analyses and spectroscopic data, which indicated the interaction of each molecule of Mannich base with three molecules of malononitrile. The IR spectra of **2a–e** showed characteristic absorption bands for (NH_2) groups 3450–3354 cm^{-1} and strong bands for (CN) groups at 2215–2188 cm^{-1} . The ^{1}H- NMR spectrum of compound **2a** showed a broad singlet at δ 6.8 for an amino group, an AB system with a coupling constant 8 Hz (ortho coupling) at δ 7.2, δ 8.4 for 7-H and 8-H respectively, a multiplet at δ 7.5–7.7 for phenyl ring and a singlet for the 2-H at δ 7.8.

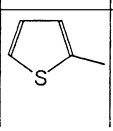
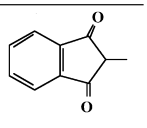
The formation of compounds **2a–f** may be rationalised in terms of a carbanion attack at the carbonyl carbon atom of the Mannich base to give the dicyanomethylidene intermediate (A) which underwent transamination by the malononitrile dimer (which is formed under the same reaction condition) followed by tandem bicyclisation and auto-oxidation to give compounds **2a–f** (Scheme 2).

The cyclohexanone tertiary Mannich base hydrochlorides **3a,b** on treatment with equimolar amount of malononitrile in piperidine at 50 °C afforded the tetrahydro-naphthalene derivatives **4** (Scheme 3).

The tetrahydronaphthalene derivative **4** was formed via a successive Knoevenagel condensation and C-alkylation reactions of cyclohexanone Mannich bases **3a,b** by two molecules of malononitrile to give the intermediate A, which upon cyclisation and removal of hydrogen cyanide gave compound **4** in good yield. This mechanism finds support in the formation of the same compound from Mannich bases with different amine moieties (Scheme 3). Also, the formation of substituted aromatic rings from the reaction of arylidene-malononitrile derivatives and cycolopentanone has been reported previously.[13]

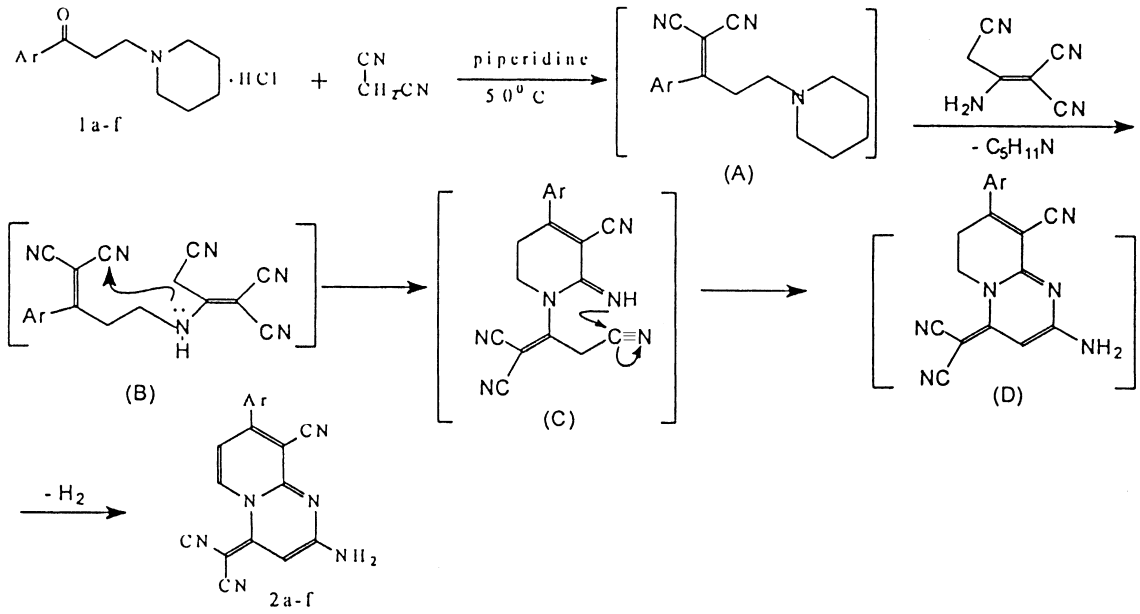
The structure of compound **4** was based on microanalytical and spectroscopic data. The IR spectrum of compound **4** showed absorption bands at 3473,3353 cm^{-1} for the -NH_2



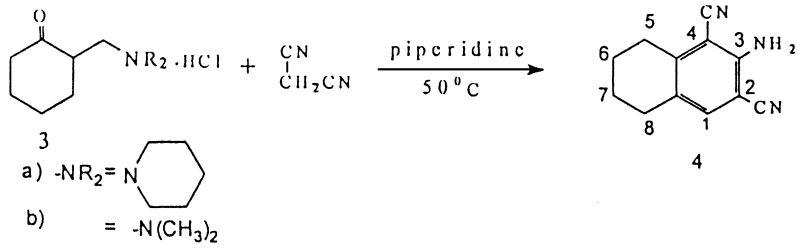
1,2	a	b	c	d	e	f
Ar	C_6H_5 -	p-HO-C_6H_4-	p-CH_3O-C_6H_4-	p-C_6H_5-C_6H_4-		

Scheme 1

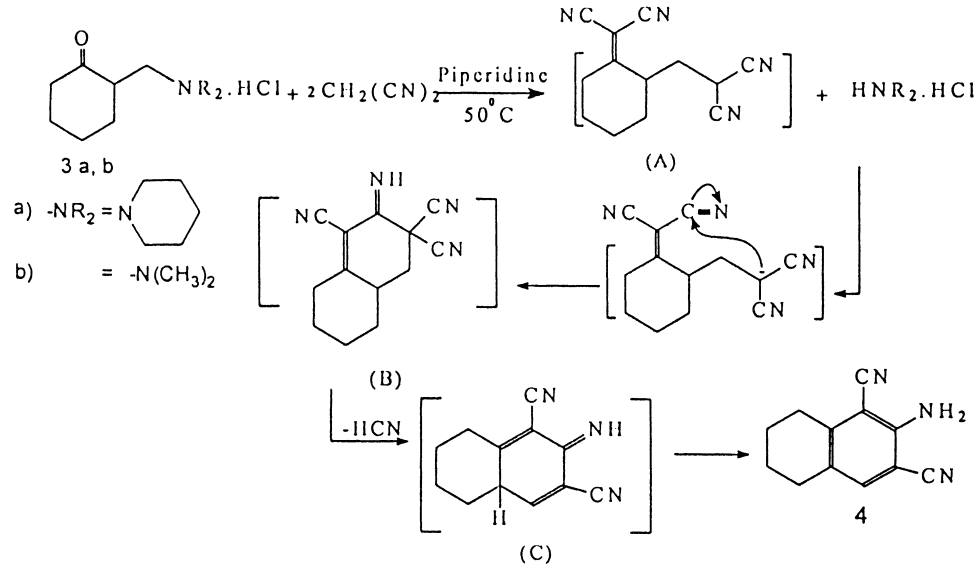
* To receive any correspondence.
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2



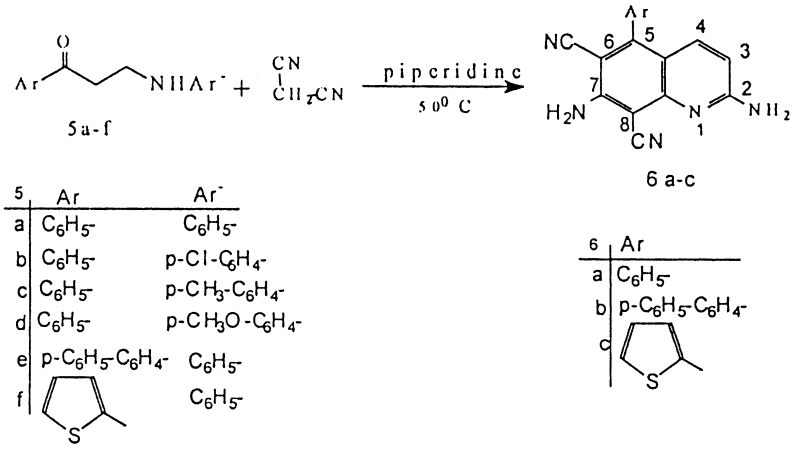
Scheme 3



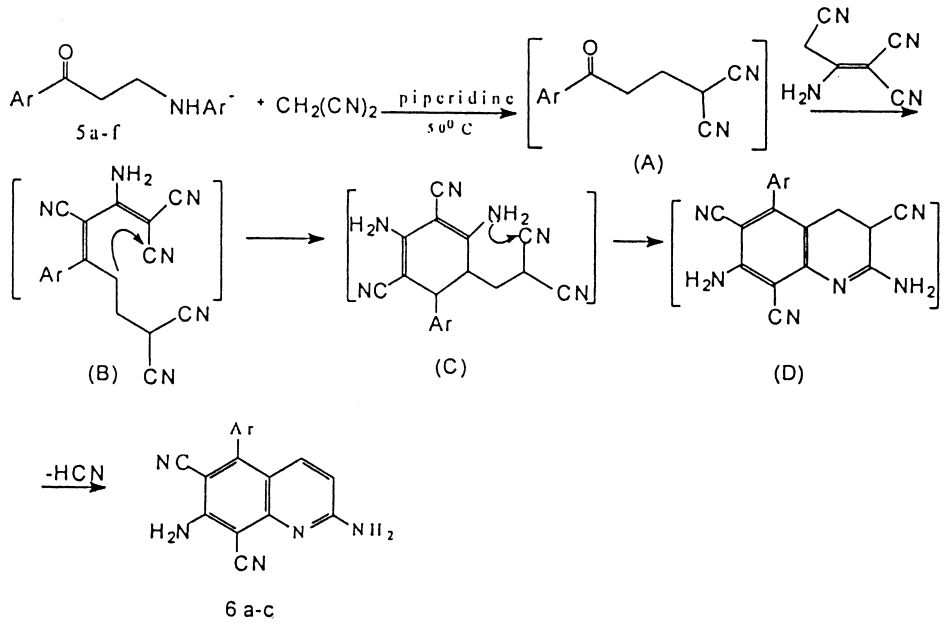
Scheme 4

groups and at 2217 cm^{-1} for the -CN groups. In addition the structure of **4** was supported by the ^1H- NMR which showed two triplets of two protons each at δ 2.6, 2.85 for (8-H_2) and (5-H_2) respectively and one aromatic hydrogen singlet at δ 7.29 for (1-H).

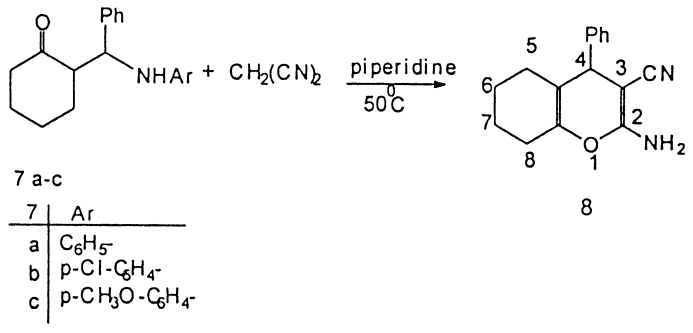
Unexpectedly, acyclic ketonic secondary Mannich bases under the same condition afforded the 2-aminoquinoline derivatives **6a–c** (Scheme 5). The key intermediate for these compounds is the C-alkylation product (A) which underwent Knoevenagel condensation with malononitrile dimer (which is formed under the reaction condition) to give the intermediate (B). Tandem bicyclisation and removal of hydrogen cyanide produced 2-aminoquinoline derivatives **6a–c** via the intermediates (C) and (D) (Scheme 6).



Scheme 5



Scheme 6



Scheme 7

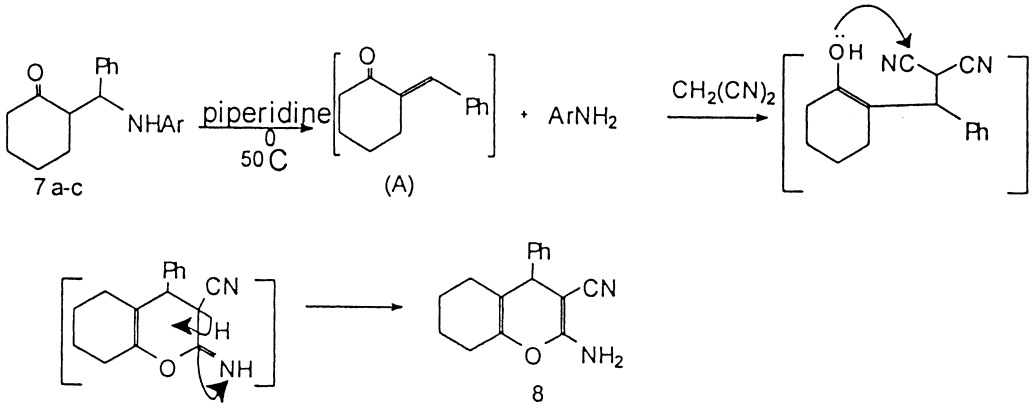
The ^{1}H-NMR of **6a** revealed two broad singlets at δ 3.8 and 8.1 attributed to two amino groups. The mass spectrum of this compound showed the parent peak at *m/z* 285 which fitted with the calculated mass.

2-(Arylaminobenzyl) cyclohexanone **7a–c,** which can be considered as secondary ketonic Mannich bases, on treatment with malononitrile in piperidine at 50 °C afforded 2- amino-3-cyano-4 -phenyl-5, 6, 7, 8-tetrahydro-4H-benzopyrane **8.** The ^{1}H-NMR of compound **8** displayed a multiplet at δ 1.65 for 6-H_2, a multiplet at δ 1.8 for 7-H_2, two triplets two protons each at δ 2.28, 2.95 for 5-H_2, 8-H_2, a singlet at δ 5.0 for NH_2 and 4-H and a multiplet at δ 7.3–7.48 for five aromatic protons.

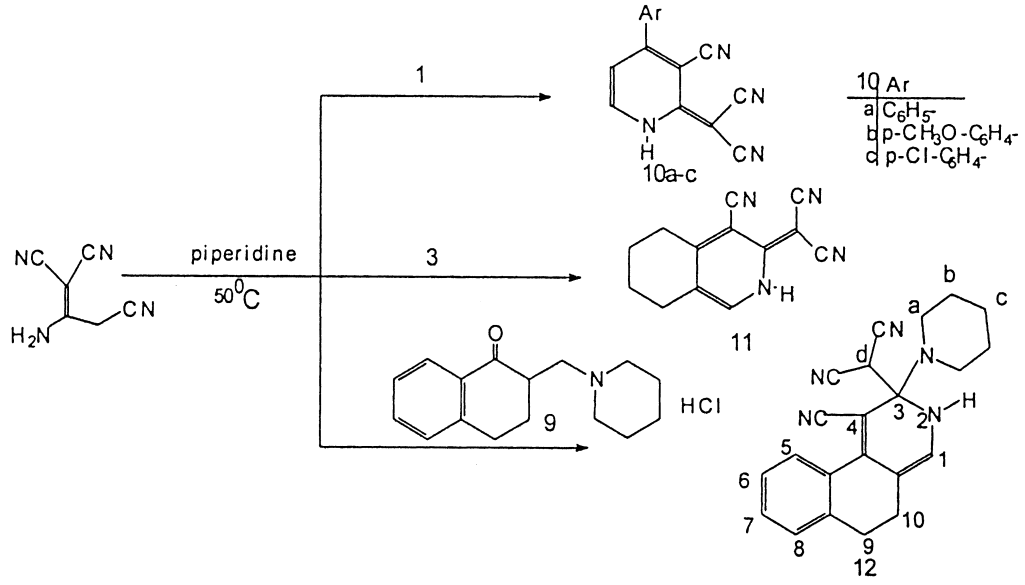
The formation of compound **8** may proceed according to the mechanism depicted in Scheme 8. The 2-benzylidenecyclohexanone (A) was postulated as an intermediate which underwent Michael addition with malononitrile followed by cyclisation.

The easy formation of compounds **2, 4, 6** and **8** under mild condition in one pot reaction encouraged us to investigate the reaction of various Mannich bases with malononitrile dimer under the same conditions. Although, cyclic, acyclic ketonic tertiary and secondary Mannich bases showed different behaviour towards malononitrile, a variety of Mannich bases hydrochloride showed similar behaviour towards malononitrile dimer. Treatment of acetophenone Mannich bases hydrochloride **1a, b** and **1g** with malononitrile dimer in piperidine at 50 °C afforded 2-dicyanomethylidenepyridine derivatives **10** (Scheme 9).

The formation of **10** may be explained by the reaction pathway depicted in Scheme 10. The Mannich bases **1** underwent Knoevenagel condensation with malononitrile dimer to give



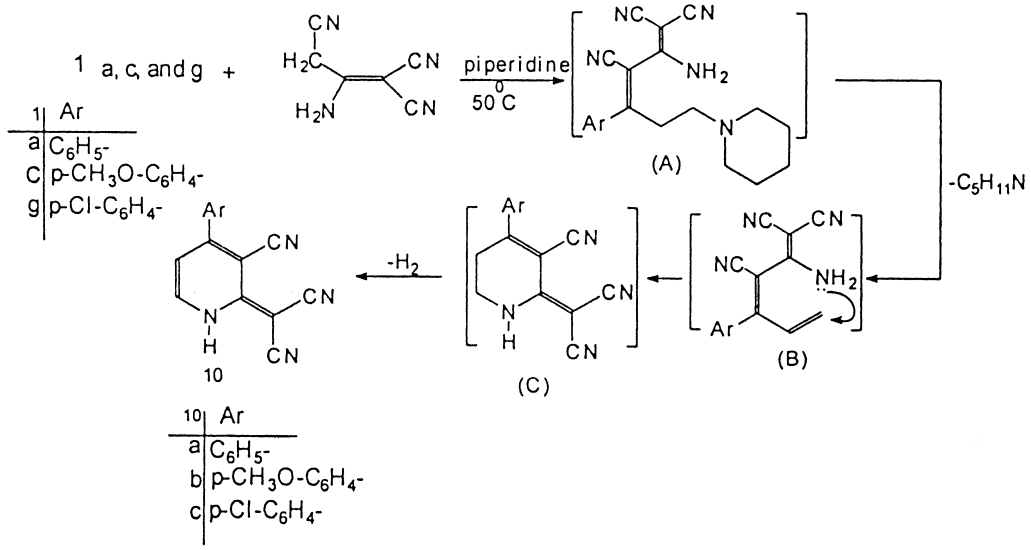
Scheme 8



Scheme 9

Table 1 Characterisation data of compounds **2a–f**, **4**, **6a–c**, **8**, **10a–c**, **11** and **12**

Compd No.	Yield %	M.p. °C	Formula M. wt.	Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
2a	60	> 300	$C_{18}H_{10}N_6$	69.65	3.25		69.73	3.55	
2b	60	> 300	$C_{18}H_{10}N_6O$	66.23	3.09		66.72	3.34	
2c	62	> 300	$C_{19}H_{12}N_6O$	67.05	3.55		67.28	3.70	
2d	65	> 300	$C_{24}H_{14}N_6$	74.60	3.65		74.80	3.76	
2e	50	> 300	$C_{16}H_8N_6S$	60.75	2.55		60.84	2.75	
2f	60	> 300	$C_{21}H_{10}N_6O_2$	66.67	2.66		66.46	2.80	
4	60	154–155	$C_{12}H_{11}N_3$	73.06	5.62	21.32	73.45	5.75	21.55
6a	40	> 300	$C_{17}H_{11}N_5$	71.57	3.89		71.81	3.77	
6b	45	> 300	$C_{23}H_{15}N_5$	76.44	4.18		76.70	4.57	
6c	60	> 300	$C_{15}H_9N_5S$	61.84	3.11		61.97	3.25	
8	70	240–241	$C_{16}H_{16}N_2O$	76.16	6.39		76.48	6.53	
10a	65	235–236	$C_{15}H_8N_4$	73.76	3.30	22.94	73.90	3.54	22.50
10b	65	246(dec.)	$C_{16}H_{10}N_4O$	70.07	3.67	20.43	70.40	3.90	20.25
10c	65	283–285	$C_{15}H_7N_4Cl$	64.64	2.53	20.10	64.05	2.88	19.96
11	70	260–262	$C_{13}H_{10}N_4$	70.26	4.54		70.45	4.75	
12	75	270-272	$C_{22}H_{21}N_5$	74.34	5.96	19.70	74.51	6.03	19.56



Scheme 10

the nonisolable intermediate (A). This lost a piperidine molecule to give the vinyl intermediate (B) which cyclised into the pyridine intermediate(C). The intermediate (C) was readily oxidised to the final isolable stable compound **10** (Scheme 10).

Similarly, cyclohexanone and α–tetralone Mannich bases hydrochloride gave the isoquinoline **11** and benzo[f]isoquinoline derivatives **12** in good yield. Compound **12** was formed via addition of a piperidine molecule into the corresponding dicyanomethylidene derivatives. The structures of compounds **10–12** were established on the bases of their elemental analyses and spectral data (*cf*. Experimental).

Experimental

Melting points (°C) (uncorrected) were determined using Griffin melting point apparatus. IR spectra were recorded on MATTSON 5000 FTIR Spectrometer. NMR spectra were run at ^{1}H-NMR Varian-Gemini (200 MHz) and Brucker FTNMR (200 MHz) Spectrometer using ($CDCl_3$) and (DMSO-D_6) as solvents. MS were recorded on G.C. MSQP-1000 EX Shimidazu (Japan) Mass Spectrometer. Elemental analyses were carried out at the microanalytical unit, Faculty of Science, Mansoura University.

β-(piperidino) propiophenone hydrochloride derivatives (**1a–d**): These compounds were prepared according to the reported methods.[14]

β-(piperidinoethyl)-2-thienyl ketone hydrochloride (**1e**): This compound was prepared according to the reported method.[15]

2-β-(piperidinopropanoyl)indan-1,3-dione (**1f**): This compound was prepared according to the reported method.[7]

2-(N-piperidinomethyl)cyclohexanone hydrochloride (**3a**) *and 2-(N,N-dimethyl amino methyl)cyclohexanone hydrochloride* (**3b**): These compounds were prepared according to the reported method.[16]

β-(Arylamino)propiophenone derivatives (**5a–f**): These compounds were prepared according to the reported method.[17]

2-(piperidinomethyl)tetral-1-one hydrochloride (**9**): This compound was prepared according to reported method.[18]

1,1,3-Tricyano-2-amino-1-propene(malononitrile dimer): This compound was prepared according to reported method.[19]

2-(Arylaminobenzyl) cyclohexanone (**7a –c**): These compounds were prepared according to the reported method.[20]

*Pyrido[1,2-a]pyrimidine derivatives (***2a–f***), 2-amino-1,3-dicyano-5,6,7,8-tetra hydro naphthalene* (**4**), *2,7-diamino-6,8-dicyano-5-arylquinoline* (**6a–c**) *and 2-amino-3-cyano-4-phenyl-5,6,7,8-tetrahydro-4H-benzopyrane* (**8**).

General procedure: To a mixture of tertiary Mannich bases hydrochloride **(1a–f), (3a,b)** or secondary Mannich bases **(5a–f), (7a–c)** (5mmol) and malononitrile (6 mmol) was added piperidine (5 ml). The reaction mixture was heated at 50 °C for 24 hours, cooled, poured onto ice-cold water and acidified with dilute HCl (1:1) to pH=5. The solid products were filtered off, dried and crystallised from ethanol.

Compound (**2a**): IR (KBr) 3448-3339(NH_2), 3063(C-H aromatic), 2216 (CN) and 1635 cm^{-1} (C=C); ^{1}H-NMR (DMSO): δ 6.8(s, 2H, NH_2), 7.2(d, 1H, 7-H), 7.6(m, 5H, phenyl ring) and 7.8(s, 1H, 2-H), 8.4(d, 1H, 8- H).

(**2b**): IR (KBr) 3440(OH), 3356,3234(NH_2) and a broad band centered at 2209–2180 cm^{-1} (CN); ^{1}H-NMR (DMSO): δ 6.5(s, 2H, NH_2), 7.1 (d, 2H, ArH), 7.3(d, 2H, ArH), 7.6(s, 1H, 2-H), 7.7(s, 1H, phenolic-OH), 7.8(d, 1H, 7-H), 8.3(d, 1H, 8-H).

(**2c**): IR (KBr) 3436,3345(NH_2), 3098(C-H aromatic), 2965(C-H aliphatic), 2208, 2184, 2148 cm^{-1} (three CN groups); ^{1}H-NMR ($CDCl_3$/DMSO): δ 3.9 (s, 3H, OCH_3), 6.25(s, 2H, NH_2), 7.3–7.5(4H, ArH), 7.7(d, 1H, 7-H), 7.8(s, 1H, 2-H), 8.35(d, 1H, 8-H).

(**2d**): IR (KBr) 3463, 3337(NH_2), 2206(CN) and 1630 cm^{-1} (C=C).

(**2e**): IR (KBr) 3457,3349(NH_2), 3100(C-H aromatic) and 2205 cm^{-1} (CN); ^{1}H-NMR (DMSO): δ 4.2(br, 2H, NH_2), 7.3(d, 1H, 7-H) and 7.59–7.95(m, 3H, thiophene ring), 8.54 (d, 1H, 8-H), 8.6 (s, 1H, 2-H); MS: *m/z* (%): 317(M+1, 1.4), 291(M^+-CN, 100), 226(M^+-C_4HN_3, 15.2), 210(M^+ -$C_4H_2N_4$, 1.8), 129 (M^+ - $C_8H_3N_4S$).

(**2f**) IR (KBr) 3400, 3365 (NH_2), 3080(C-H aromatic), 2935(C-H aliphatic), 2195(CN), 1708 (C=O) and 1610 cm^{-1} (C=C).

(**4**): IR (KBr) 3473, 3353(NH_2), 2943(C-H aliphatic) and 2217 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$): δ 1.8(m, 4H, 6-H_2, 7-H_2), 2.6(t, 2H, 8-H_2), 2.86(t, 2H, 5-H_2), 4.95(br, 2H, NH_2), 7.29(s, 1H, ArH); Ms (*m/z*, %) 197 (M^+, 92), 170(M^+- HCN,100), 143(M^+- $C_2H_2N_2$, 13).

(**6a**): IR (KBr) 3459, 3334 (NH_2), 3059(C-H aromatic), 2214(CN) and 1636 cm^{-1} (C=C); ^{1}H-NMR (DMSO): δ 3.8(br, 2H, NH_2), 7.3(d, 1H, 3-H), 7.6(m, 5H, ArH), 8.1(br, 2H, NH_2), and 8.5(d, 1H, 4-H); MS (*m/z*, %): 286(M^++1, 19.4), 285(M^+, 100), 258(M^+ -HCN, 5), 231(M^+-$C_2H_2N_2$, 1.1), 215(M^+ -$C_2H_4N_3$, 4), 138(M^+ -$C_8H_9N_3$, 3).

(**6b**): IR (KBr) 3445, 3350(NH_2), 2208(CN), and 1651 cm^{-1} (C=C); MS (*m/z*, %): 362(M^++1,100), 335(M^+ -HCN, 3), 308(M^+ -$C_2H_2N_2$, 0.9), 292(M^+ - $C_2H_3N_3$, 1.3), 139(M^+ -$C_{14}H_{14}N_3$, 1.4).

(**6c**): IR (KBr) 3447, 3346(NH_2) and 2204–2188 cm^{-1} (two CN groups).

(**8**): IR (KBr): 3420, 3330 (NH_2), 2943(C-H aliphatic), 2214(CN) and 1640 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$): δ 1.65(m, 2H, 6-H_2), 1.8(m, 2H, 7-H_2), 2.28(t, 2H, 5-H_2), 2.95(t, 2H, 8-H_2), 5(br, 4-H+ NH_2) and 7.3–7.48(m, 5H, phenyl ring).

Reaction of tertiary Mannich bases hydrochloride (**1a,c** *and* **g**), (**3a,b**) *and* (**9**) *with mlononitrile dimer. Synthesis of 2-dicyanomethylidene-3-cyano-4-aryl-1, 2-dihydropyridine* (**10a–c**), *isoqunoline derivative* (**11**) *and benzo[f]isoqunoline* (**12**).

General procedure: To a mixture of Mannich bases hydrochloride (**1a,c** and **g**), (**3a,b**) and (**9**) (5 mmol) and malononitrile dimer (6mmol) was added 5 ml piperidine dimer. The reaction mixture was heated at 50 °C for 24 hours, cooled, poured onto crushed ice with stirring, followed by acidification with dilute HCl (1:1) to pH=5. The solid products were collected by filtration and crystallised from ethanol to give:

(10a): IR (KBr) 3325(NH), 2195(CN) and 1618 cm^{-1} (C=C).); ^{1}H-NMR (DMSO): δ 7.1(d, 1H, 5-H) 7.4(s, 1H, NH), 7.6(d, 1H, 6- H), 7.8 (m, 5H, ArH).

(10b): IR (KBr) 3241(NH), 3034(C-H aromatic), 2963(C-H aliphatic), 2205, 2180(two CN groups) and 1620 cm^{-1} (C=C); MS (*m*/*z*, %): 274 (M^+, 100), 243(M^+ -OCH_3, 5.3), 179(M^+ -$C_4H_3N_2O$, 3.6), 152(M^+-$C_5H_4N_3O$, 5.4).

(10c): IR (KBr) 3399, (NH), 3095(C-H aromatic), 2208, 2183(two CN groups) and 1626 cm^{-1} (C=C).

(11): IR (KBr) 3356(NH), 3027(C-H aromatic), 2939(C-H aliphatic), 2199(CN) and 1620 cm^{-1} (C=C); MS (*m*/*z*, %): 223(M^++1,18.2), 222(M^+, 100), 196(M^+ -CN, 35.1), 170(M^+ -C_2N_2, 5.1), 130(M^+ - $C_4H_2N_3$, 6.1), 103(M^+-$C_5H_3N_4$).

(12): IR (KBr) 3385 (NH), 2931(C-H aliphatic) and 2195 cm^{-1} (CN); ^{1}H-NMR (DMSO): δ 1.54(br, 6H, 2×b-H_2 and c-H_2), 2.82(br, 4H, 2×a-H_2), 3.69(br, 4H, 9-H_2 and 10-H_2), 6.1(s, 1H, d-H), 7.1(m, 4H, ArH), 7.8(s, 1H, NH), 8.4(S, 1H, 1-H); MS (*m*/*z*, %): 356(M^++1, 100), 272(M^+-C_5H_9N, 17.6), 205(M^+-$C_8H_{12}N_3$, 2), 179(M^+-$C_9H_{12}N_4$, 7.6), 128(M^+-$C_{12}H_{11}N_5$, 1.5).

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