Facile and One Pot Synthetic Routes for Various Novel, Differently Fused and Promising Heteropolycycles

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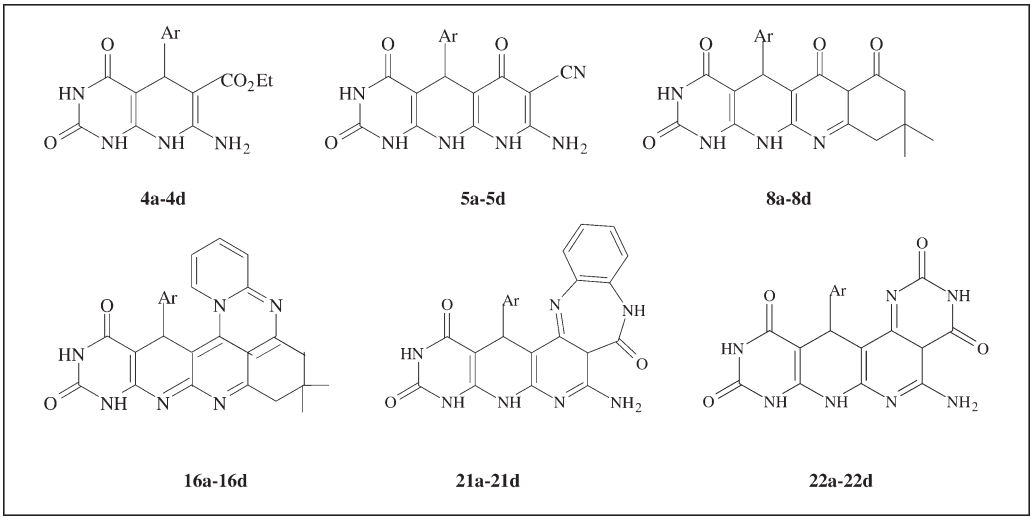

Four-component one pot cyclocondensation of aromatic aldehydes 1, ethyl cyanoacetate 2, barbituric acid 3 and ammonium acetate in methanol gave substituted and functionalised pyrido[2,3-d]pyrimidine derivatives 4 and 4′ after initial Knoevenagel, subsequent Micheal and final heterocyclization reactions. Compounds 4 on reaction with different active methylene compounds resulted in the formation of again functionalized and diversly substituted pyrimidonaphthyridines 5-7, 9 and benzo[b] pyrimidonaphthyridines 8. The various compounds of systems 7 and 8 on further condensation with the reactive and mostly the bifunctional moieties like urea/thiourea, and 2-aminopyridine generated the novel and differently fused dipyrimidonaphthyridines 10/11 and pyrimidonaphthyridinoquinazolines 13/14, and pyrido-pyrimido- pyrimido[1,8]naphthyridines 15 and pyrimidonaphthyridino- pyridoquinazolines 16, respectively, hitherto unknown in literature. Compounds 7 on condensation with *o*-phenylenediamine produced novel pyrimidonaphthyridinobenzodiazepines 12. Other novel systems like pyrido[2,3-d;6,5-d′]dipyrimidines 17, dipyrimido[4,5-b:5′,4′-g][1,8]naphthyridines 18, 1,3,4,6,7,8,9,11-octazabenzo[de]-naphthacenes 19, dipyrimido[4,5-b:5′,4′-g][1,8]naphthyridines 20, pyrimido[5′,4′:6,7][1,8]naphthyridino[4,3-b][1,5]benzodiazepines 21, dipyrimido[4,5-b:4′,5′-f][1,8]naphthyridines 22 and dipyrimido [4,5-b:5′,4′-g][1,8] naphthyridines 23 have also been generated in this study.

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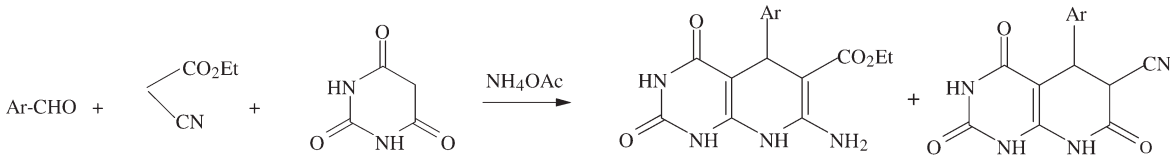
INTRODUCTION

The benzodiazepines are a class of drugs with hypnotic [1], anxiolytic, anticonvulsant, amnestic, and muscle relaxant properties. They serve as cholecystokinin A and B antagonists [2], opioid receptor ligands [3], platelet-activating factor antagonists [4], HIV inhibitors [5], and farnesyltransferase inhibitors [6]. Benzodiazepines [7] can be used in anxiety disorders, insomnia, involuntary movement disorders, and in detoxification from alcohol and other substances. The pyridopyrimidines are very popularly and widely known compounds as a consequence of their activity against a variety of pathogenic bacteria and have potential activity such as antipyretic, diuretic, bacteriostatic, sedative, and coronary dilating agents [8]. The chemical transformations of the pyridopyrimidine ring system by the introduction and assemblage of different substituents and heterocyclic rings in fused form have allowed expansion of the research to the structure activity relationship to afford new insight into the molecular interactions at the receptor level. Many heterocyclic compounds having pyrido-pyrimidine nucleus are also known to have a wide range of biological activities [9]. Condensed system having 1,8-naphthyridine and a pyrimidine nucleus constitutes a

Scheme 1



1 **2** **3** **4a-4d** **4′a-4′d**

a; Ar = 4-CH $_3$O-C_6H_4
b; Ar = 3,4-(CH $_3$O)$_2$-C_6H_3
c; Ar = 4-CH $_3$-C_6H_4
d; Ar = 3,4-OCH $_2$O-C_6H_3

group of important compounds because of their vital pharmacological properties. Members of this family have wide applications in medicinal chemistry, being used to have antibacterial [10], antithrombic [11], and anticonvulsant behavior [12]. The quinazoline ring system is a commonly encountered structural core in a number of natural and synthetic molecules with a wide range of biological activities [13]. Many of the quinazoline derivatives are known to exhibit anti-inflammatory [14], anthelmentic [15], analgesic [16], CNS-depressant [17], and anticonvulsive activities [18]. Metolazone and quinethazone are two quinazoline-based drugs that are used currently as diuretics in medicines [19]. Vasicine and related naturally occurring quinazoline alkaloids, and other quinazoline bearing natural metabolites including a number of tryptoquivalines are the famous broncodilators [20], oxytocics, and antifungals being used since time immemorial. The bacterial and bacteriolytic activities have not been extensively studied in pyrimidine, quinazoline, naphthyridine, and benzo[b]diazepine systems in both isolation and in fused assemblages. Literature survey reveals that a fair amount of work has been published in the condensation reactions of barbituric acid, dimedone, and other active methylene carbocyclic and heterocyclic compounds. Because of long standing interest in our laboratory in the condensation reactions of active methylene compounds [21–23] and generation of new fused (''ortho'' and ''ortho and peri''), bridged [23], spiro [24], ring assembly and cyclophane [25] heterocyclic compounds, we have extended our synthetic activity along these lines to include the synthesis of some pyridopyrimidine, pyrimidonaphthyridine, benzo[b]pyrimidonaphthyridine, dipyrimidonaphthyridine, pyrimidonaphthyridinoquinazoline, pyrimidonaphthyridinobenzodiazepine, pyridopyrimido- pyrimido- naphthyridine, pyrimidonaphthyridino-pyridoquinazoline, and 1,3,4,6,7,8,9,11-octazabenzo[de]naphthacene systems.

It was interesting to study these di- and tri- and unknown and unreported tetra-, penta-, and hexa- cyclic heterocyclic systems containing various vital nitrogen heterocyclic moieties, expectedly enriched with potential antimicrobial, antifungal, and other important biological activities. To prepare these novel classes of compounds, we synthesized and used ethyl 7-amino-2,4-diketo-5-aryl-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate **4** as the key intermediate synthon.

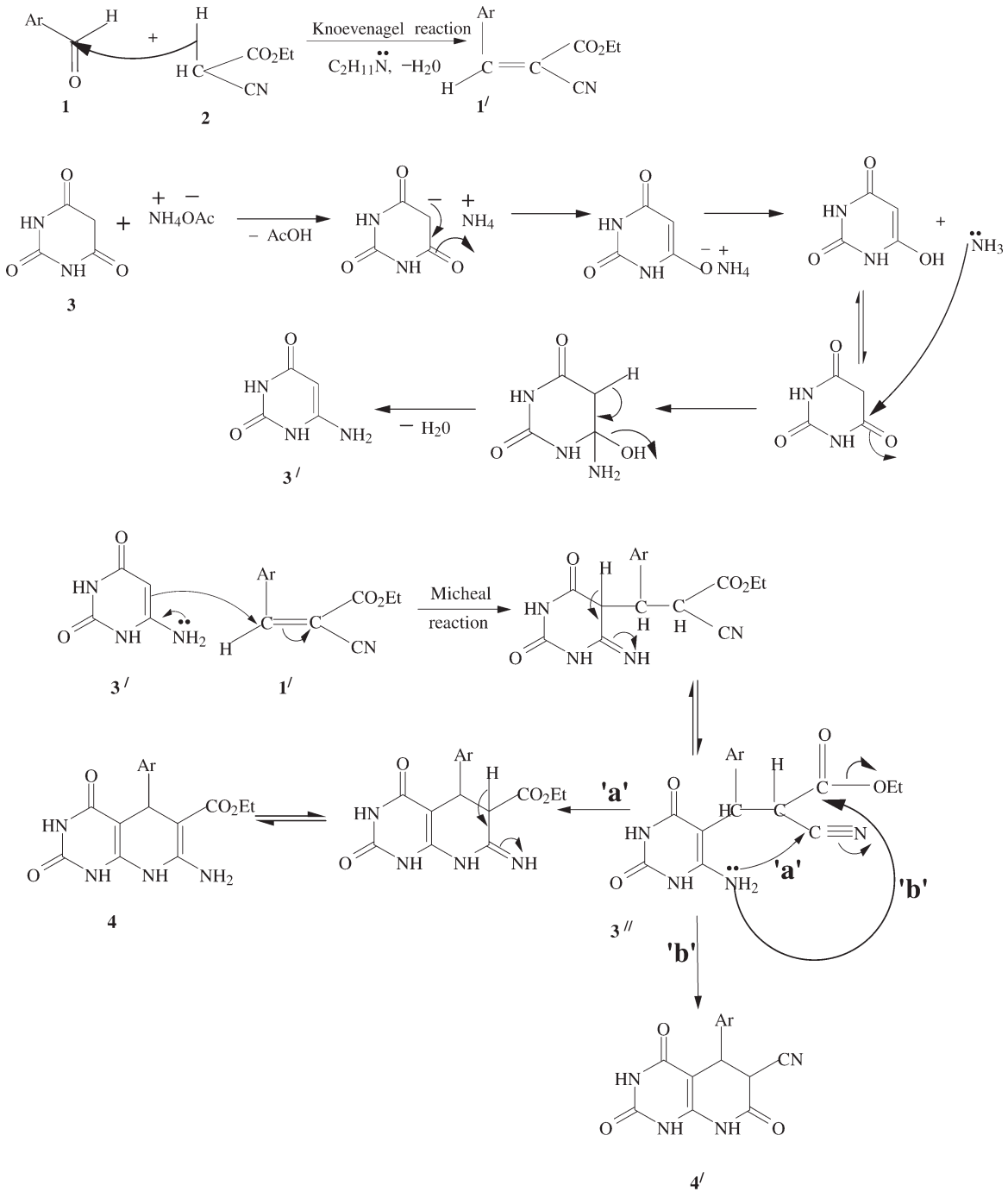
RESULTS AND DISCUSSION

The key intermediates **4a–4d** used as starting materials [26] have been prepared in better yields by refluxing the aromatic aldehydes **1**, ethyl cyanoacetate **2**, barbituric acid, **3** and excess of ammonium acetate in methanol though some traces of compound **4′** in each case were formed. The main product **4** was separated by fractional crystallization and from the mother liquor a pale yellow colored side product **4′** was isolated in each case that was characterized as 6-cyano-5-aryl-1,2,3,4,5,6,7,8-octahydropyrido[2,3-d]pyrimidine-2,4,7-trione. The formation of these key intermediates **4** and mechanism of their formation have been exhibited (Scheme 1 and 2 respectively).

The reaction sequence in the formation of **4** may be proceeding via initial formation of ethyl arylidenecyanoacetate **1′** by reaction of aromatic aldehyde **1** and ethyl cyanoacetate **2** through typical Knoevenagel condensation. Subsequently, the intermediate **1′** reacts with 6-amino uracil **3′** obtained through the aminodehydration of barbituric acid **3** to produce another intermediate **3″** which on cyclocondensation results in the formation of **4** and **4′** (Scheme 2).

The structure of **4a** was established on the basis of elemental analysis, IR and ^{1}H NMR spectral data. The IR spectrum of compound **4a** showed strong absorption bands at υ 3333 and 3423 cm^{-1} for amino group and at υ 1675, 1682, 1690 cm^{-1} for (C=O) group. Its ^{1}H NMR spectrum showed as usual a quartet and a triplet

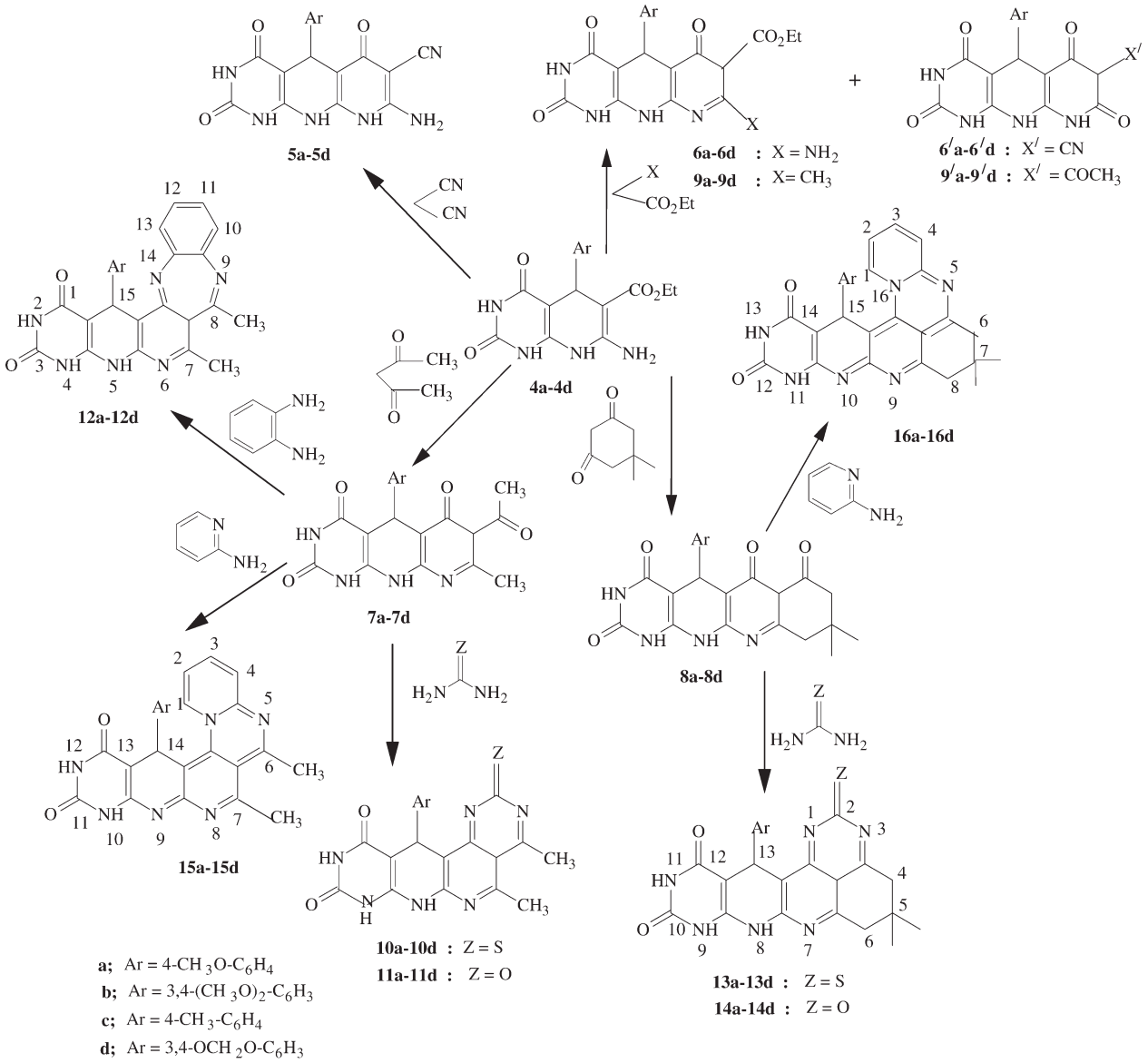
Scheme 2



due to CH_2 and CH_3 protons respectively of the ethyl ester functionality besides other protons including a multiplet of aromatic proton, a singlet of chiral proton, a singlet at δ 3.75 due to OCH_3 group and D_2O exchangeable protons. Treatment of compounds **4a–4d** with malononitrile under refluxing in DMF in the presence of catalytic amount of piperidine gave products identified as 8-amino-7-cyano-5-aryl-1,2,3,4,5,6,9,10-octahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6-triones **5a–5d** (Scheme 3). The structures of these products were established on the basis of their analytical and spectral data.

Condensation of compounds **4a–4d** with ethyl cyanoacetate under similar conditions gave major products identified as 8-amino-7-ethoxycarbonyl-5-aryl-1,2,3,4,5,6, 7,10-octahydro-pyrimido[4,5-b][1,8]naphthyridine-2,4,6-triones

Scheme 3



6a–6d and minor products identified as 7-cyano-5-aryl-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6,8-tetraones **6′a–6′d**. Their structures were established as usual on the basis of elemental and spectral data. Similar condensation of compounds **4a–4d** with acetylacetone [27] under refluxing in DMSO in the presence of catalytic amount of P_2O_5 gave the enamine ketones in good yields. The enamine ketones were then cyclized in presence of K_2CO_3 and copper powder in refluxing dry acetone giving substituted pyrimidonaphthyridine derivatives **7a–7d**. Condensation of compounds **4a–4d** with other active methylene compounds like dimedone and ethyl acetoacetate resulted in the formation of substituted benzo[b] pyrimidonaphthyridine **8a–8d** and substituted pyrimidonaphthyridine compounds **9a–9d** and **9′a–9′d**, respectively. The structures of all these compounds were established as usual by elemental analysis and spectral studies, details of which are given in the experimental section. Cyclocondensation of compounds **7a–7d** with urea/thiourea separately resulted in the formation of substituted dipyrimidonaphthyridines **10a–10d** and **11a–11d** and similar treatment of **8a–8d** resulting in the formation of pyrimidonaphthyridinoquinazoline derivatives **13a–13d** and **14a–14d**. On condensation with *o*-phenylenediamine, compounds **7a–7d** resulted in the formation of substituted pyrimidonaphthyridinobenzodiazepine compounds **12a–12d**. The ^{1}H NMR data of compound **12b** showed two singlets at δ 3.73 and 3.78 indicating the presence of two methoxyl groups, a singlet at δ 4.74 indicating the presence of chiral CH proton, peaks at δ 8.79, 8.95 and 9.74 due to three D_2O

exchangeable (NH) protons. The three aromatic protons of 3,4-dimethoxyphenyl group appeared at δ 6.64–6.95 as a multiplet and another multiplet was located at δ 7.13–7.32 due to four aromatic protons of the benzodiazepine moiety. A singlet at δ 2.47 due to methyl group attached to diazepine ring and another very highly downfield singlet at δ 2.83 revealed the presence of methyl group attached to pyridine ring. These assignments richly characterized the compound **12b** as 7,8-dimethyl-15-(3,4-dimethoxy phenyl)-2,3,4,5,7a,15-hexahydro-1*H*-pyrimido[5′,4′:6,7][1,8]naphthyridino[4,3-b][1,5]benzo- diazepine-1,3-dione. Further, compounds **7a–7d** and **8a–8d** on similar cyclocondensations with 2-aminopyridine were attributed to generate substituted pyrido[2′,1′:2,3]pyrimido[4,5-f] pyrimido[4,5-b][1,8]naphthyridine-11,13-diones **15a–15d** and substituted pyrimido [5′,4′:6,7] [1,8]naphthyridino[4,3,2-de] pyrido[2,1-b]quinazolines **16a–16d**, respectively, on the grounds that the ^{1}H NMR data of compound **15c** revealed the presence of two D_2O exchangeable (NH) protons at δ 8.96 and 9.74, a singlet at δ 2.22 due to methyl group of *p*-methylphenyl ring, a singlet at δ 4.74 indicating the presence of chiral CH proton, a double doublet at δ 6.80–6.95 and 6.65–6.67 with ortho coupling indicating the presence of *p*-methylphenyl ring, a multiplet at δ 6.39–6.62 showing the presence of another set of four aromatic protons and two sharp singlets at δ 2.29 and 2.72 due to other two methyl groups in the compound; and ^{1}H NMR data of compound **16d** showing peaks due to two D_2O exchangeable (NH) protons at δ 8.97 and 9.79, two singlet at δ 1.88 and 2.12 due to two methylene groups, a singlet at δ 1.11 due to six protons of two gem dimethyl groups, a singlet at δ 4.74 due to chiral CH proton, a multiplet at δ 6.49–6.62 showing the presence of four protons of Nitrogen bridged pyrimidine ring, a sharp singlet at δ 5.87 due to two methylenedioxy protons and a multiplet at δ 6.47–6.89 due to three aromatic protons of the methylenedioxyphenyl group.

Compounds **4, 5** and **6** on condensation with formamide could close the recurring generation of the COOR/CN group at adjacent position to NH_2 group in the same ring resulting in the production of pyrido[2,3-d;6,5-d′]dipyrimidines **17**, dipyrimido[4,5-b:5′,4′-g][1,8]naphthyridines **18** which subsequently generated 1,3,4,6,7,8,9,11-octaza benzo[de]naphthacenes **19** with more of formamide and dipyrimido[4,5-b:5′,4′-g][1,8]naphthyridines **20**, respectively. In addition, compound **6** on treatment with *o*-phenylenediamine produced a novel pentacyclic heterocyclic system, pyrimido [5′,4′:6,7] [1,8]naphthyridino[4,3-b][1,5]benzodiazepines **21**, and on heating with thiourea, it produced dipyrimido[4,5-b:4′,5′-f][1,8]naphthyridine **22** and dipyrimido[4,5-b:5′,4′-g][1,8]naphthyridine **23** the two differently fused systems (Scheme 4). The compounds **22** and **23** have been distinguished on the basis of analytical and spectral data. In the ^{1}H NMR spectra, the singlet at δ 2.26 ppm due to the proton on the fused tertiary carbon atom (C-4a) of the structure **22** (experimental data given for **22b**) does not appear as downfield as the singlet at δ 3.92 ppm due to the proton on the fused tertiary carbon atom (C-6a) of the structure **23** (experimental details given for **23a**), latter is flanked on either side by C═O groups. There is a marked D_2O exchangeable singlet at δ 3.85 ppm for **22b** due to NH_2 group in the ^{1}H NMR spectrum. Such chemical shift value is absent in ^{1}H NMR spectrum of **23a**. Analytical data of **22a** and **23a** (with same aryl substituents) have revealed their molecular formulae to be $C_{19}H_{15}N_7O_4S$ and $C_{19}H_{14}N_6O_5S$, respectively, which are same as calculated for their proposed structures. So, structure **22** is a $H_{15}N_7O_4$ compound without aryl groups, whereas structure **23** is a $H_{14}N_6O_5$ compound without aryl groups. The observed % of Nitrogen in former is 22.54 and in latter 19.19. Same is true for the other pairs, i.e., **22b** and **23b**, **22c** and **23c**, and **22d** and **23d**. The m/z for the parent peak (M^+) could also speak for different molecular masses of the two structures **22** and **23**.

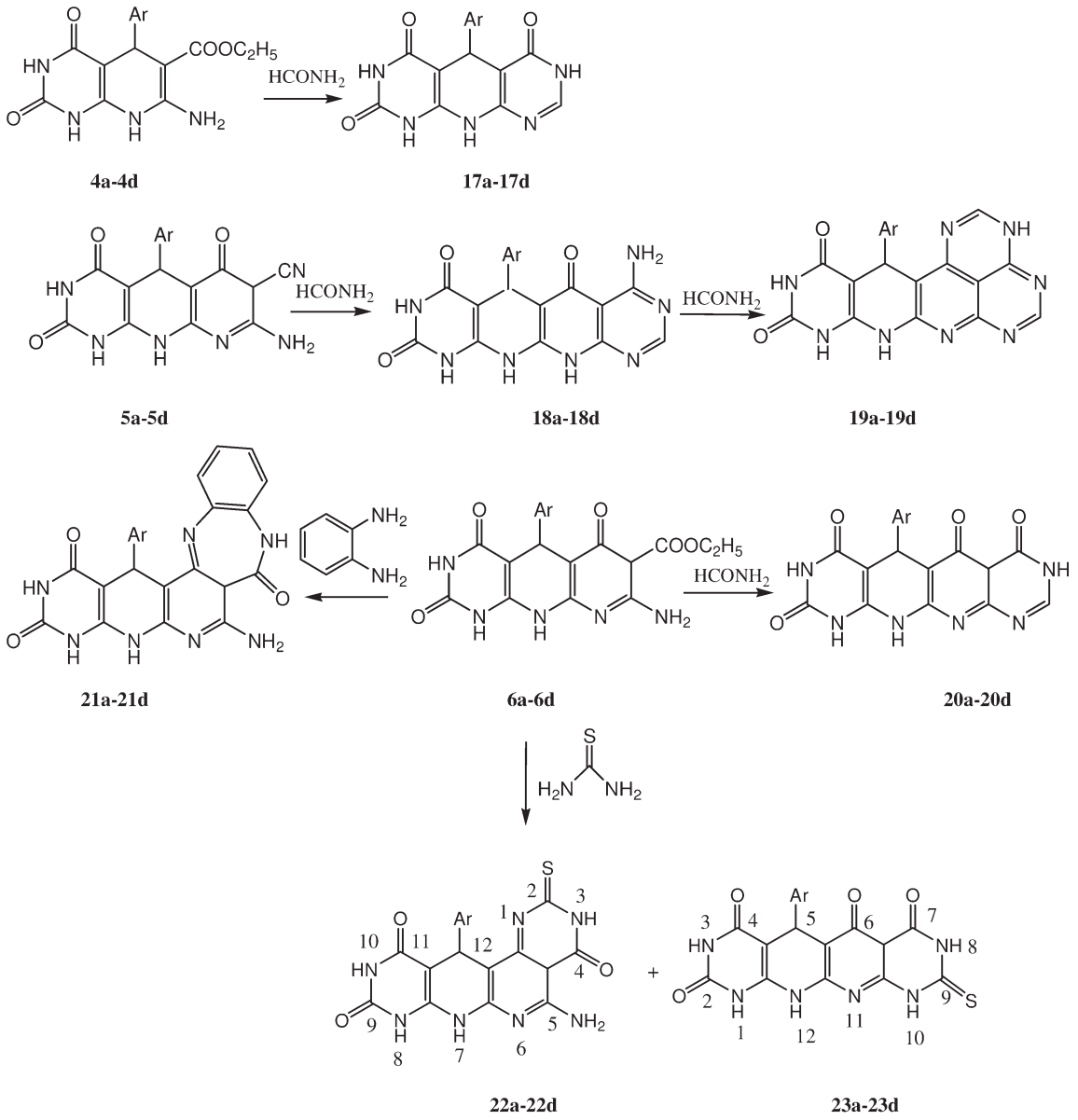
In compound **23a**, the pure ketonic group on Carbon-6 shows C═O stretching frequency 1715 cm^{-1}, higher than the other carbonyl stretching frequencies (1660–1680cm^{-1}) of lactam and thiolactam rings present in structures **22** and **23**. This higher valued carbonyl stretching frequency is absent in the IR spectrum of structure **22b**. The free amino group on the unsaturated carbon atom shows marked N—H stretching frequency (3200–3500cm^{-1}) in structures **22** and this is lacking in IR spectrum of structure **23a**.

The preliminary tests of the keto compound like formation of 2,4-dinitrophenyl hydrazone, phenylhydrazone, semicarbazone, and oxime could be confirmed only for structure **23** (keto group at C-6). Structure **22** could not respond to these tests as it contains carbonyl groups only in the form of lactam and thiolactam functionalities. Similarly, Structures **22** give all the preliminary tests of free amino group.

All the other products were similarly characterized by ^{1}H NMR and ^{13}C NMR data, and their elemental analysis data was also in complete agreement with the assigned structures. The structural formulae, m.ps, yield, molecular formulae, and elemental analysis for these compounds are shown in tabular form (Table 1).

The novel fused heterocyclic systems belonging to compounds **8a–8d**, **10a–10d**, **12a–12d**, **13a–13d**, **15a–15d**, **16a–16d**, **18a–18d**, and **19a–19d** are highly fascinating and interesting and are being reported for the first time in literature especially as regards their generation. The heterocyclic compounds **8** and **18** with linear, ''ortho'' fused structures; **10, 12**, and **15** with angular ''ortho'' fused structures; and compounds **13, 16**, and **19**

Scheme 4



a; Ar = 4-CH $_3$O-C$_6$H$_4$
b; Ar = 3,4-(CH $_3$O)$_2$-C$_6$H$_3$
c; Ar = 4-CH $_3$-C$_6$H$_4$
d; Ar = 3,4-OCH $_2$O-C$_6$H$_3$

with ''ortho'' and ''ortho and peri'' fused structures contain various component heterocyclic moieties like pyrimidine, pyridine, quinazoline, quinoline, [1,8]naphthyridine, and benzodiazepine present in different modes of combinations and all known for their remarkable, varied, and highly useful physiological activities.

From the study of the key reactions discussed in the present exposition for transformation of an active methylene cyclic compound into a polycyclic ring system containing one six-membered ring more than the substrate, it can be summarily concluded that a reaction of an active methylene compound like malononitrile, ethyl cyanoacetate, and ethyl acetoacetate with a cyclic system having NH_2 and groups like CN/COOH/COOR in adjacent position to each other can serve as a recurring contributor for the transformation of a linear system into another linear system having one more ring till the reaction gets stopped due to very high cyclicity (7,8,9. . .membered) and molecular weight or availability of very small amount of substrates to proceed further

Table 1

Differently substituted compounds with mp's, yields, and molecular formulae.

Compound	Ar	Mp's (°C)	Yield (%)	Mol. formulae (M^+)	Calcd. formula% / Obsd. formula% C	H	N	S
4a	4-$CH_3O.C_6H_4$	294	83	$C_{17}H_{18}N_4O_5$	56.97	5.06	15.63	–
					56.92	5.02	15.75	
4b	3,4-$(CH_3O)_2.C_6H_3$	275	86	$C_{18}H_{20}N_4O_6$	55.66	5.19	14.42	–
					55.58	5.17	14.50	
4c	4-$CH_3.C_6H_4$	210	84	$C_{17}H_{18}N_4O_4$	59.64	5.29	16.36	–
					59.60	5.32	16.42	
4d	3,4-$OCH_2O.C_6H_3$	298	85	$C_{17}H_{16}N_4O_6$	54.83	4.33	15.04	–
					54.88	4.35	15.12	
4′a	4-$CH_3O.C_6H_4$	205	70	$C_{15}H_{12}N_4O_4$	57.69	3.87	17.94	–
					57.75	3.89	17.87	
4′b	3,4-$(CH_3O)_2.C_6H_3$	202	69	$C_{16}H_{14}N_4O_5$	56.14	4.12	16.36	–
					56.10	4.09	16.48	
4′c	4-$CH_3.C_6H_4$	218	72	$C_{15}H_{12}N_4O_3$	60.80	4.08	18.91	–
					60.76	4.09	18.98	
4′d	3,4-$OCH_2O.C_6H_3$	220	74	$C_{15}H_{10}N_4O_5$	55.22	3.08	17.17	–
					55.17	3.12	17.25	
5a	4-$CH_3O.C_6H_4$	145	70	$C_{18}H_{14}N_6O_4$	57.14	3.73	22.21	–
					57.12	3.72	22.28	
5b	3,4-$(CH_3O)_2.C_6H_3$	149	72	$C_{19}H_{16}N_6O_5$	55.88	3.94	20.57	–
					55.85	3.97	20.65	
5c	4-$CH_3.C_6H_4$	135	69	$C_{18}H_{14}N_6O_3$	59.66	3.89	23.19	–
					59.60	3.86	23.25	
5d	3,4-$OCH_2O.C_6H_3$	141	71	$C_{18}H_{12}N_6O_5$	55.10	3.08	21.42	–
					55.07	3.09	21.47	
6a	4-$CH_3O.C_6H_4$	187	70	$C_{20}H_{19}N_5O_6$	56.46	4.50	16.46	–
					56.43	4.52	16.54	
6b	3,4-$(CH_3O)_2.C_6H_3$	188	68	$C_{21}H_{21}N_5O_7$	55.38	4.64	15.37	–
					55.32	4.62	15.43	
6c	4-$CH_3.C_6H_4$	189	65	$C_{20}H_{19}N_5O_5$	58.67	4.67	17.10	–
					58.62	4.69	17.16	
6d	3,4-$OCH_2O.C_6H_3$	182	63	$C_{20}H_{17}N_5O_7$	54.67	3.90	15.93	–
					54.63	3.92	15.97	
6′a	4-$CH_3O.C_6H_4$	201	68	$C_{18}H_{13}N_5O_5$	56.99	3.45	18.46	–
					56.93	3.42	18.55	
6′b	3,4-$(CH_3O)_2.C_6H_3$	206	69	$C_{19}H_{15}N_5O_6$	55.74	3.69	17.10	–
					55.73	3.61	17.13	
6′c	4-$CH_3.C_6H_4$	209	71	$C_{18}H_{13}N_5O_4$	59.50	3.60	19.27	–
					59.46	3.64	19.32	
6′d	3,4-$OCH_2O.C_6H_3$	205	73	$C_{18}H_{11}N_5O_6$	54.96	2.81	17.80	–
					54.93	2.79	17.85	
7a	4-$CH_3O.C_6H_4$	188	68	$C_{20}H_{18}N_4O_5$	60.91	4.60	14.20	–
					60.84	4.65	14.25	
7b	3,4-$(CH_3O)_2.C_6H_3$	172	70	$C_{21}H_{20}N_4O_6$	59.43	4.75	13.20	–
					59.40	4.78	13.24	
7c	4-$CH_3.C_6H_4$	174	71	$C_{20}H_{18}N_4O_4$	63.48	4.79	14.80	–
					63.56	4.77	14.82	
7d	3,4-$OCH_2O.C_6H_3$	179	73	$C_{20}H_{16}N_4O_6$	58.82	3.94	13.72	–
					58.85	3.92	13.70	
7′a	4-$CH_3O.C_6H_4$	215	62	$C_{23}H_{22}N_4O_5$	63.58	5.10	12.89	–
					63.63	5.08	12.92	
7′b	3,4-$(CH_3O)_2.C_6H_3$	211	64	$C_{24}H_{24}N_4O_6$	62.06	5.20	12.06	–
					62.08	5.23	12.14	
7′c	4-$CH_3.C_6H_4$	203	61	$C_{23}H_{22}N_4O_4$	66.01	5.29	13.38	–
					66.08	5.25	13.41	
7′d	3,4-$OCH_2O.C_6H_3$	245	62	$C_{23}H_{20}N_4O_6$	61.60	4.49	12.49	–
					61.58	4.51	12.48	
9a	4-$CH_3O.C_6H_4$	218	59	$C_{21}H_{20}N_4O_6$	59.43	4.75	13.20	–
					59.39	4.76	13.28	

(*Continued*)

Table 1
(*Continued*)

Compound	Ar	Mp's (°C)	Yield (%)	Mol. formulae (M^+)	Calcd. formula% / Obsd. formula% C	H	N	S
9b	3,4-$(CH_3O)_2.C_6H_3$	202	57	$C_{22}H_{22}N_4O_7$	58.14	4.88	12.32	–
					58.17	4.89	12.38	
9c	4-$CH_3.C_6H_4$	206	58	$C_{21}H_{20}N_4O_5$	61.75	4.93	13.71	–
					61.83	4.94	13.68	
9d	3,4-$OCH_2O.C_6H_3$	228	56	$C_{21}H_{18}N_4O_7$	57.53	4.13	12.78	–
					57.65	4.11	12.77	
9′a	4-$CH_3O.C_6H_4$	249	53	$C_{19}H_{16}N_4O_6$	57.57	4.06	14.13	–
					57.58	4.08	14.25	
9′b	3,4-$(CH_3O)_2.C_6H_3$	245	52	$C_{20}H_{18}N_4O_7$	56.33	4.25	13.14	–
					56.42	4.22	13.15	
9′c	4-$CH_3.C_6H_4$	221	56	$C_{19}H_{16}N_4O_5$	59.99	4.24	14.73	–
					59.95	4.22	14.78	
9′d	3,4-$OCH_2O.C_6H_3$	233	51	$C_{19}H_{14}N_4O_7$	55.61	3.43	13.65	–
					55.65	3.41	13.74	
10a	4-$CH_3O.C_6H_4$	295	55	$C_{21}H_{18}N_6O_3S$	58.05	4.17	19.34	7.38
					58.09	4.14	19.28	7.44
10b	3,4-$(CH_3O)_2.C_6H_3$	>300	52	$C_{22}H_{20}N_6O_4S$	56.88	4.34	18.09	6.90
					56.83	4.30	18.15	6.94
10c	4-$CH_3.C_6H_4$	>300	54	$C_{21}H_{18}N_6O_2S$	60.27	4.33	20.08	7.66
					60.23	4.30	20.16	7.69
10d	3,4-$OCH_2O.C_6H_3$	>300	55	$C_{21}H_{16}N_6O_4S$	56.24	3.59	18.74	7.15
					56.21	3.62	18.79	7.18
11a	4-$CH_3O.C_6H_4$	284	54	$C_{21}H_{18}N_6O_4$	60.28	4.33	20.08	–
					60.23	4.30	20.15	
11b	3,4-$(CH_3O)_2.C_6H_3$	296	51	$C_{22}H_{20}N_6O_5$	58.92	4.49	18.74	–
					58.98	4.55	18.70	
11c	4-$CH_3.C_6H_4$	299	49	$C_{21}H_{18}N_6O_3$	62.68	4.50	20.88	–
					62.73	4.46	20.92	
11d	3,4-$OCH_2O.C_6H_3$	>300	47	$C_{21}H_{16}N_6O_5$	58.33	3.73	19.43	–
					58.36	3.76	19.38	
12a	4-$CH_3O.C_6H_4$	>300	48	$C_{26}H_{22}N_6O_3$	66.94	4.75	18.01	–
					66.98	4.77	18.10	
12b	3,4-$(CH_3O)_2.C_6H_3$	310	46	$C_{27}H_{24}N_6O_4$	65.31	4.87	16.92	–
					65.36	4.86	16.96	
12c	4-$CH_3.C_6H_4$	306	46	$C_{26}H_{22}N_6O_2$	69.32	4.92	18.65	–
					69.34	4.96	18.69	
12d	3,4-$OCH_2O.C_6H_3$	298	48	$C_{26}H_{20}N_6O_4$	64.99	4.19	17.49	–
					64.93	4.23	17.56	
13a	4-$CH_3O.C_6H_4$	290	45	$C_{24}H_{22}N_6O_3S$	60.74	4.67	17.71	6.75
					60.70	4.65	17.76	6.79
13b	3,4-$(CH_3O)_2.C_6H_3$	285	47	$C_{25}H_{24}N_6O_4S$	59.51	4.79	16.65	6.35
					59.62	4.76	16.63	6.37
13c	4-$CH_3.C_6H_4$	288	47	$C_{24}H_{22}N_6O_2S$	62.86	4.83	18.32	6.99
					62.87	4.81	18.34	6.97
13d	3,4-$OCH_2O.C_6H_3$	296	48	$C_{24}H_{20}N_6O_4S$	59.00	4.12	17.20	6.56
					59.04	4.14	17.26	6.58
14a	4-$CH_3O.C_6H_4$	276	43	$C_{24}H_{22}N_6O_4$	62.87	4.83	18.33	–
					62.85	4.85	18.42	
14b	3,4-$(CH_3O)_2.C_6H_3$	279	45	$C_{25}H_{24}N_6O_5$	61.46	4.95	17.20	–
					61.43	4.97	17.29	
14c	4-$CH_3.C_6H_4$	288	44	$C_{24}H_{22}N_6O_3$	65.14	5.01	18.99	–
					65.19	5.05	18.97	
14d	3,4-$OCH_2O.C_6H_3$	>300	45	$C_{24}H_{20}N_6O_5$	61.01	4.26	17.78	–
					61.05	4.29	17.87	
15a	4-$CH_3O.C_6H_4$	>300	44	$C_{25}H_{20}N_6O_3$	66.36	4.45	18.57	–
					66.32	4.49	18.63	
15b	3,4-$(CH_3O)_2.C_6H_3$	>300	42	$C_{26}H_{22}N_6O_4$	64.72	4.59	17.41	–
					64.74	4.52	17.53	

(*Continued*)

Table 1
(*Continued*)

Compound	Ar	Mp's (°C)	Yield (%)	Mol. formulae (M^+)	Calcd. formula% / Obsd. formula% C	H	N	S
15c	4-CH_3.C_6H_4	>300	44	$C_{25}H_{20}N_6O_2$	68.79	4.61	19.25	–
					68.76	4.64	19.32	
15d	3,4-OCH_2O.C_6H_3	>300	46	$C_{25}H_{18}N_6O_4$	64.37	3.89	18.01	–
					64.31	3.83	18.09	
16a	4-CH_3O.C_6H_4	>300	38	$C_{28}H_{24}N_6O_3$	68.28	4.91	17.06	–
					68.20	4.87	17.09	
16b	3,4-$(CH_3O)_2$.C_6H_3	>300	39	$C_{29}H_{26}N_6O_4$	66.65	5.01	16.08	–
					66.63	5.03	16.14	
16c	4-CH_3.C_6H_4	>300	43	$C_{28}H_{24}N_6O_2$	70.57	5.07	17.63	–
					70.61	5.09	17.67	
16d	3,4-OCH_2O.C_6H_3	>300	45	$C_{28}H_{22}N_6O_4$	66.39	4.37	16.59	–
					66.36	4.35	16.61	
17a	4-CH_3O.C_6H_4	198	55	$C_{16}H_{13}N_5O_4$	56.63	3.86	20.64	–
					56.58	3.89	20.70	
17b	3,4-$(CH_3O)_2$.C_6H_3	206	58	$C_{17}H_{15}N_5O_5$	55.28	4.09	18.96	–
					55.20	4.07	18.99	
17c	4-CH_3.C_6H_4	215	52	$C_{16}H_{13}N_5O_3$	59.44	4.05	21.66	–
					59.40	4.08	21.68	
17d	3,4-OCH_2O.C_6H_3	195	54	$C_{16}H_{11}N_5O_5$	54.39	3.13	19.82	–
					54.25	3.14	19.87	
18a	4-CH_3O.C_6H_4	267	51	$C_{19}H_{15}N_7O_4$	56.29	3.73	24.18	–
					56.23	3.74	24.15	
18b	3,4-$(CH_3O)_2$.C_6H_3	251	53	$C_{20}H_{17}N_7O_5$	55.17	3.93	22.51	–
					55.15	3.90	22.48	
18c	4-CH_3.C_6H_4	276	50	$C_{19}H_{15}N_7O_3$	58.60	3.88	25.18	–
					58.57	3.85	25.26	
18d	3,4-OCH_2O.C_6H_3	289	52	$C_{19}H_{13}N_7O_5$	54.41	3.12	23.38	–
					54.37	3.10	23.45	
19a	4-CH_3O.C_6H_4	284	48	$C_{20}H_{14}N_8O_3$	57.97	3.40	27.04	–
					57.92	3.38	27.09	
19b	3,4-$(CH_3O)_2$.C_6H_3	298	47	$C_{21}H_{16}N_8O_4$	56.75	3.62	25.21	–
					56.78	3.60	25.28	
19c	4-CH_3.C_6H_4	>300	44	$C_{20}H_{14}N_8O_2$	60.29	3.54	28.12	–
					60.32	3.51	28.17	
19d	3,4-OCH_2O.C_6H_3	>300	46	$C_{20}H_{12}N_8O_4$	56.07	2.82	26.15	–
					56.03	2.80	26.23	
20a	4-CH_3O.C_6H_4	290	44	$C_{19}H_{14}N_6O_5$	56.16	3.47	20.68	–
					56.11	3.44	20.72	
20b	3,4-$(CH_3O)_2$.C_6H_3	>300	42	$C_{20}H_{16}N_6O_6$	55.04	3.69	19.25	–
					55.00	3.68	19.32	
20c	4-CH_3.C_6H_4	287	45	$C_{19}H_{14}N_6O_4$	58.46	3.61	21.52	–
					58.41	3.58	21.57	
20d	3,4-OCH_2O.C_6H_3	>300	42	$C_{19}H_{12}N_6O_6$	54.29	2.87	19.99	–
					54.24	2.84	20.23	
21a	4-CH_3O.C_6H_4	298	46	$C_{24}H_{19}N_7O_4$	61.40	4.07	20.88	–
					61.48	4.10	20.94	
21b	3,4-$(CH_3O)_2$.C_6H_3	292	41	$C_{25}H_{21}N_7O_5$	60.11	4.23	19.63	–
					60.15	4.19	19.69	
21c	4-CH_3.C_6H_4	>300	43	$C_{24}H_{19}N_7O_3$	63.57	4.22	21.62	–
					63.62	4.20	21.65	
21d	3,4-OCH_2O.C_6H_3	>300	45	$C_{24}H_{17}N_7O_5$	59.62	3.54	20.28	–
					59.65	3.55	20.33	
22a	4-CH_3O.C_6H_4	274	41	$C_{19}H_{15}N_7O_4S$	52.16	3.45	22.41	7.33
					52.07	3.48	22.54	7.30
22b	3,4-$(CH_3O)_2$.C_6H_3	289	42	$C_{20}H_{17}N_7O_5S$	51.38	3.66	20.97	6.86
					51.41	3.60	20.98	6.92
22c	4-CH_3.C_6H_4	>300	42	$C_{19}H_{15}N_7O_3S$	54.15	3.58	23.26	7.60
					54.19	3.60	23.29	7.64

(*Continued*)

Table 1
(*Continued*)

Compound	Ar	Mp's (°C)	Yield (%)	Mol. formulae (M^+)	Calcd. formula% Obsd. formula% C	H	N	S
22d	3,4-$OCH_2O.C_6H_3$	>300	44	$C_{19}H_{13}N_7O_5S$	50.55	2.90	21.71	7.10
					50.60	2.94	21.70	7.14
23a	4-$CH_3O.C_6H_4$	>300	40	$C_{19}H_{14}N_6O_5S$	52.05	3.21	19.16	7.31
					52.09	3.28	19.19	7.35
23b	3,4-$(CH_3O)_2.C_6H_3$	>300	41	$C_{20}H_{16}N_6O_6S$	51.28	3.44	17.94	6.84
					51.32	3.46	17.95	6.87
23c	4-$CH_3.C_6H_4$	>300	44	$C_{19}H_{14}N_6O_4S$	54.02	3.34	19.89	7.59
					54.08	3.36	19.86	7.66
23d	3,4-$OCH_2O.C_6H_3$	>300	42	$C_{19}H_{12}N_6O_6S$	50.44	2.67	18.57	7.08
					50.47	2.68	18.59	7.04

due to large number of steps having occurred till then or the reaction is terminated intentionally according to desirability of the required cyclicity by closing the reaction by condensation of the product with formamide and finally generating another terminal pyrimidine ring (Scheme 4).

All the compounds under various heterocyclic systems discussed herein were obtained either as a racemic mixture of a pair of enantiomers or as a mixture of two racemates or as only enantiomer or a diastereomer of unknown stereochemistry. The resolution of the racemic mixtures into the chiral enantiomers could not be carried in this study, and the compounds were used and characterized as obtained.

Pharmacology. One compound each from the systems synthesized in this study was subjected to bactericidal and bacteriolytic activity against *Escherichia coli*. The clinical syndromes associated with human beings are urinary track infections, neonatal meningitis, and gastroenteritis.

The bactericidal and bacteriolytic activity. The compounds under study (20mg) were dissolved in 500 IL of DMSO. Five microlitres (0.2 mg approx) of the stock solution was taken and 95 IL bacterial suspension in Tris buffer saline (0.8 OD at 580 nm) was added to it. The mixture was incubated at 14°C for 14 h. After incubation, it was subjected to plating in TCBS agar (Thiosulphate, Citric, Bile salt, Sucrose agar). After 12 h, the culture plate was observed for bacterial growth.

For bacteriolytic activity, bacterial suspension in TBS was prepared with an optical density of 0.8 OD at 580 nm (double beam UV spectrometer). TBS (Tris buffer saline) served as the blank. The test compound (10mg) was dissolved in 150 L of DMSO and 2850 IL of bacterial suspension in TBS was added to it. The initial OD of the sample was recorded. The mixture was incubated for 90 min at 23°C. Final OD of the mixture was recorded. The initial OD minus the final OD gives the bacteriolytic activity. The —NH— group and the —O— group on the given moieties may bind with the negatively charged phosphate group on phospholipids present on the wall of bacteria. This causes inhibition of the activities of lysosomal phospholipases because of the neutralization of the negative charges of phospholipid bilayer, leading to potential antibacterial activity.

Observations. The active compounds exhibited a range between mild to strong bactericidal activity against gram-negative bacteria *Escherichia coli* (Table 2). The compounds were also subjected to bacteriolytic activity against *E. coli*. The compounds **4d**, **5d**, **6d**, **8d**, **11d**, **18d**, **20d**, **21d**, and **22d** showed mild bacteriolytic activity; compounds **9d**, **10d**, **13d**, **14d**, **15d**, **17d**, **19d**, and **23d** exhibited moderate bacteriolytic activity; and compounds **7d**, **12d**, and **16d** showed strong bacteriolytic activity against *E. coli* (Table 3). Ciprofloxacin was used as standard antibiotic in this study.

EXPERIMENTAL

General. The melting points were determined in open capillary tubes in Perfit melting point apparatus and are uncorrected. The purity of the products was checked on TLC plates coated with silica gel-G and detected by iodine vapors. The IR spectra were recorded on Perkin Elmer Infrared model S99-B and on Shimdzu IR-435 spectrophotometer (υ_{max} in cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a varian unity 200 MHz NMR spectrophotometer using ppm on δ scale). Elemental analysis was performed on a simple CHNS analyzer (model: CHNS-932, LECO Corporation, USA; IR Technology Services).

General procedure for the synthesis of ethyl 7-amino-2,4-diketo-5-aryl-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylates 4a–4d and 6-cyano-5-aryl-1,2,3,4,5, 6,7, 8-octahydropyrido[2,3-d]pyrimidine-2,4,7-trione 4′a–4′d. A mixture of equimolar amounts (0.01 moles) of aromatic aldehydes **1**, ethyl cyanoacetate **2**, and barbituric acid **3** along with

Table 2

In vitro screening of bactericidal activity of compounds against *E. coli*.

Entry	Compounds	B.A. against *E.coli*
1	**4d**	+
2	**5d**	+
3	**6d**	+
4	**7d**	+
5	**8d**	++
6	**9d**	+
7	**10d**	++
8	**11d**	++
9	**12d**	+++
10	**13d**	++
11	**14d**	++
12	**15d**	+++
13	**16d**	+++
14	**17d**	+
15	**18d**	+
16	**19d**	+++
17	**20d**	++
18	**21d**	+++
19	**22d**	++
20	**23d**	++
21	**Ciprofloxacin**	+++

Bacterial activity: B.A.
Concentration is 2 mg/mL.
(+): mild bacterial activity was observed.
(++): moderate bacterial activity was observed.
(+++): strong bacterial activity was observed.

excess of ammonium acetate in methanol was refluxed on water bath for 8–10 h. After the reaction is over as monitored on TLC, the reaction mixture was concentrated and cooled at room temperature. The solid products **4** was separated by fractional crystallization as a major product and from the mother liquor a pale yellow colored solid product **4′** was isolated on prolonged cooling as a minor product. The spectral data along with IUPAC names of the products and names of the starting materials for some of the compounds is mentioned below:

Ethyl 7-amino-2,4-diketo-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,8-hexahydropyrido[2,3-d] pyrimidine-6-carboxylate (4b). It was obtained using veratraldehyde. IR(KBr,υ,cm^{-1}): 1605 (C=C), 1675, 1682, 1695 (C=O), 3254 (NH_2), 3334–3410 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, CH_3), 2.94 (q, 2H, OCH_2), 3.73 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.72 (s, 1H, 5-CH), 5.58 (s, 2H, NH_2), 6.74–6.96 (m, 3H, ArH's), 8.76–9.86 (br.s, 3H, NH).

Ethyl 7-amino-2,4-diketo-5-(3,4-methylenedioxyphenyl)-1,2,3,4,5,8-hexahydropyrido [2,3-d]pyrimidine-6-carboxylate (4d). It was obtained using piperonal. IR(KBr,υ,cm^{-1}): 1605 (C=C), 1675, 1680, 1695 (C=O), 3256 (NH_2), 3334–3412 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, CH_3), 2.94 (q, 2H, OCH_2), 4.72 (s, 1H, 5-CH), 5.58 (s, 2H, NH_2), 5.79 (s, 2H, O_2CH_2), 6.57–6.67 (m, 3H, ArH's), 8.78–9.89 (br.s, 3H, NH).

6-Cyano-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrido [2,3-d]pyrimidine-2,4,7-trione (4′a). It was obtained using anisaldehyde as a minor product along with **4a** as major product. IR(KBr,υ,cm^{-1}): 1605 (C=C), 1670, 1680, 1692 (C=O), 2195 (C=N), 3333–3405 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 3.74 (s, 3H, OCH_3), 4.25 (s, 1H, CH), 4.42 (s, 1H, 5-CH), 6.83–6.95 (d, 2H, ArH's), 6.64–6.69 (d, 2H, ArH's), 8.75–9.85 (br.s, 3H, NH, D_2O exchangeable).

6-Cyano-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrido[2,3-d]pyrimidine-2,4,7-trione (4′b). It was obtained using veratraldehyde as a minor product along with **4b** as major product. IR(KBr,υ,cm^{-1}): 1605 (C=C) 1670, 1682, 1690 (C=O), 2194 (C=N), 3333–3405 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.25 (s, 1H, CH), 4.52 (s, 1H, 5-CH), 6.46–6.54 (m, 3H, ArH's), 8.71–9.83 (br.s, 3H, NH).

General procedure for the synthesis of 8-amino-7-cyano-5-aryl-1,2,3,4,5,6,9,10-octahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6-triones 5a–5d. A mixture of **4** (10 mmoles) and malononitrile (10 mmoles) in DMF (20 mL) containing piperidine (0.1 mL) was refluxed for 5–6 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid product **5** so formed was collected by filtration and crystallized from acetic acid as brown crystals.

8-Amino-7-cyano-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,9,10-octahydropyrimido[4,5-b][1,8] naphthyridine-2,4,6-trione (5b). It was obtained from **4b**. IR(KBr,υ,cm^{-1}): 1605 (C=C), 1610, 1635, 1674 (C=O), 2223 (C=N), 3430 (NH_2), 3445–3538 (4NH),cm^{-1}; ^{1}H NMR($CDCl_3$): δ 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.74 (s, 1H, 5-CH), 6.78–6.95 (m, 3H, ArH's), 7.98 (s, 2H, NH_2), 8.82–9.89 (br.s, 4H, NH).

8-Amino-7-cyano-5-(3,4-methylenedioxyphenyl)-1,2,3,4,5,6,9,10-octahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6-trione (5d). It was obtained from **4d**. IR(KBr,υ,cm^{-1}): 1605 (C=C), 1612, 1625, 1674 (C=O), 2198 (C=N), 3423 (NH_2), 3425–3536 (4NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.74 (s, 1H, 5-CH), 5.86 (s, 2H, O_2CH_2), 6.54–6.68 (m, 3H, ArH's), 7.95 (s, 2H, NH_2), 8.83–9.87 (br.s, 4H, NH).

General procedure for the synthesis of substituted pyrimido[4,5-b][1,8]naphthyridines 6a–6d, 6′a–6′d, 9a–9d, and 9′a–9′d. A mixture of **4** (10 mmoles) and ethyl cyanoacetate/ethyl acetoacetate (10 mmoles) in DMF (20 mL) containing piperidine (0.1 mL) was refluxed for 6–8 h yielding **6, 6′** and **9, 9′**, respectively. The reaction was left to cool at room temperature and then poured on to ice-cold water. The solid product so formed was collected by filtration and crystallized from acetic acid. Using ethyl cyanoacetate, the main product **6** separated out first and from the mother liquor another minor product **6′** separated on keeping in refrigerator. Similarly, **9** and **9′** were separated as major and minor products, respectively, while using ethyl acetoacetate.

8-Amino-7-ethoxycarbonyl-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6-trione (6a). It was obtained from **4a** as a major product. IR(KBr,υ,cm^{-1}): 1076 (C—O—C), 1528 (C⋯⋯C of aromatic ring), 1645, 1658, 1672, 1695 (C=O), 2926 (C—H, aliphatic), 3047 (C—H, aromatic), 3336–3486 (3NH), 3428 (NH_2) cm^{-1}; ^{1}H NMR($CDCl_3$): δ 1.37 (t, 3H, CH_3), 2.92 (q, 2H, OCH_2), 3.73 (s, 3H, OCH_3), 4.21 (s, 1H, CH), 4.42 (s, 1H, 5-CH), 6.65–6.67 (d, 2H, ArH's), 6.70–6.93 (d, 2H, ArH's), 7.89 (s, 2H, NH_2), 8.80–9.86 (br.s, 3H, NH).

8-Amino-7-ethoxycarbonyl-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido [4,5-b][1,8]naphthyridine-2,4,6-trione (6b). It was obtained from **4b** as a major product. IR(KBr,υ,cm^{-1}): 1078 (C—O—C), 1527 (C⋯⋯C of aromatic ring), 1647, 1662, 1680, 1690 (C=O), 2928 (C—H, aliphatic), 3048 (C—H, aromatic), 3425 (NH_2), 3436–3538 (3NH)cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, CH_3), 2.92 (q, 2H, OCH_2),

Table 3

In vitro screening of bacteriolytic activity of compounds against *E. coli*.

Entry	Compounds	Bacterial suspension in optical density (OD)	Bacteriolytic test			B.A.
			Initial (OD)	Final (OD)	Activity (OD)	
1	**4d**	0.8	0.833	0.787	0.046	+
2	**5d**	0.8	0.833	0.788	0.045	+
3	**6d**	0.8	0.833	0.786	0.047	+
4	**7d**	**0.8**	**0.833**	**0.770**	**0.063**	+++
5	**8d**	0.8	0.833	0.788	0.045	+
6	**9d**	**0.8**	**0.833**	**0.778**	**0.055**	++
7	**10d**	**0.8**	**0.833**	**0.780**	**0.053**	++
8	**11d**	0.8	0.833	0.788	0.045	+
9	**12d**	**0.8**	**0.833**	**0.773**	**0.060**	++
10	**13d**	**0.8**	**0.833**	**0.775**	**0.058**	++
11	**14d**	**0.8**	**0.833**	**0.776**	**0.057**	++
12	**15d**	**0.8**	**0.833**	**0.777**	**0.056**	++
13	**16d**	**0.8**	**0.833**	**0.770**	**0.063**	+++
14	**17d**	**0.8**	**0.833**	**0.775**	**0.058**	++
15	**18d**	0.8	0.833	0.788	0.045	+
16	**19d**	**0.8**	**0.833**	**0.774**	**0.059**	++
17	**20d**	0.8	0.833	0.788	0.045	+
18	**21d**	0.8	0.833	0.786	0.047	+
19	**22d**	0.8	0.833	0.788	0.045	+
20	**23d**	**0.8**	**0.833**	**0.778**	**0.055**	++

Bacterial activity: B.A.
Concentration is 2 mg/mL.
(+): mild bacterial activity was observed.
(++): moderate bacterial activity was observed.
(+++): strong bacterial activity was observed.

3.74 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.18 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 6.67–6.90 (m, 3H, ArH's), 8.12 (s, 2H, NH_2), 8.87–9.87 (br.s, 3H, NH).

7-Cyano-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b][1,8] naphthyridine-2,4,6,8–tetraone (6′a). It was obtained from **4a** as a minor product along with **6a**. IR(KBr,υ,cm^{-1}): 1527 (C⋯C of aromatic ring), 1627, 1640, 1675, 1694 (C=O), 2198 (C=N), 2926 (C—H, aliphatic), 3045 (C=H, aromatic), 3448–3535 (4NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.73 (s, 3H, OCH_3), 4.25 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 6.65–6.69 (d, 2H, ArH's), 6.70–6.72 (d, 2H, ArH's), 8.73–11.93 (br.s, 4H, NH).

7-Cyano-5-(3,4-methylenedioxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b][1,8] naphthyridine-2,4,6,8–tetraone (6′d). It was obtained from **4d** as a minor product along with **6d**. IR(KBr,υ,cm^{-1}): 1598 (C=C), 1605, 1635, 1672, 1695 (C=O), 2198 (C=N), 2829 (C—H, aliphatic), 3048 (C—H, aromatic), 3448–3535 (4NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.25 (s, 1H, CH), 4.68 (s, 1H, 5-CH), 5.89 (s, 2H, O_2CH_2), 6.49–6.57 (m, 3H, ArH's), 9.89–11.98 (br.s, 4H, NH).

7-Ethoxycarbonyl-8-methyl-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido [4,5-b][1,8]naphthyridine-2,4,6-trione (9b). It was obtained from **4b** as a major product. IR(KBr,υ,cm^{-1}): 1078 (C—O—C), 1525 (C⋯C of aromatic ring), 1627, 1657, 1672, 1694 (C=O), 2928 (C—H, aliphatic), 3048 (C—H, aromatic), 3428 (NH_2), 3435–3536 (3NH)cm^{-1}; ^{1}H NMR ($CDCl_3$): δ1.36 (t, 3H, CH_3), 2.95 (q, 2H, OCH_2), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.58 (s, 1H, CH), 4.72 (s, 1H, 5-CH), 6.70–6.74 (m, 3H, ArH's), 8.88–9.85 (br.s, 3H, NH).

7-Ethoxycarbonyl-8-methyl-5-(4-methylphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6-trione (9c). It was obtained from **4c** as a major product. IR(KBr,υ,cm^{-1}): 1079 (C—O—C), 1525 (C⋯C of aromatic ring), 1605, 1625, 1635, 1674 (C=O), 2935 (C—H, aliphatic), 3045 (C—H, aromatic), 3424 (NH_2), 3435–3537 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 3H, CH_3), 1.38 (t, 3H, CH_3), 2.74 (q, 2H, OCH_2), 4.52 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 6.64–6.68 (d, 2H, ArH's), 6.72–6.74 (d, 2H, ArH's), 8.89–9.75 (br.s, 3H, NH).

7-Aceto-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b][1,8] naphthyridine-2,4,6,8–tetraone (9′a). It was obtained from **4a** as a minor product along with **9a**. IR(KBr,υ,cm^{-1}): 1527 (C⋯C of aromatic ring), 1647, 1659, 1678, 1694 (C=O), 2926 (C—H, aliphatic), 3045 (C—H, aromatic), 3425 (NH_2), 3448–3535 (4NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 4.22 (s, 1H, CH), 4.72 (s, 1H, 5-CH), 6.65–6.67 (d, 2H, ArH's), 6.70–6.73 (d, 2H, ArH's), 8.89–11.95 (br.s, 4H, NH).

7-Aceto-5-(3,4-methylenedioxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b] [1,8]naphthyridine-2,4,6,8–tetraone (9′d). It was obtained from **4d** as a minor product along with **9d**. IR(KBr,υ,cm^{-1}): 1528 (C⋯C of aromatic ring), 1647, 1662, 1678, 1694 (C=O), 2928 (C—H, aliphatic), 3048 (C—H, aromatic), 3458–3538 (4NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.27

(s, 3H, CH_3), 4.24 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 5.78 (s, 2H, O_2CH_2), 6.70–6.76 (m, 3H, ArH's), 8.86–11.95 (br.s, 4H, NH).

General procedure for the synthesis of substituted pyrimido[4,5-b][1,8]naphthyridine-2,4,6-triones 7a–7d and substituted benzo[b]pyrimido[5,4-g][1,8]naphthyridine-2,4,6,7-tetraones 8a–8d. A suspension of **4** (0.02 mole), the appropriate active methylene compounds, i.e., acetylacetone/dimedone (0.02 mole) and P_2O_5 (0.10 g) in dry toluene 20 mL was refluxed for 4 h, and the water was collected in a Dean Stark trap. After cooling, the reaction mixture was filtered. The filtrate was evaporated to dryness. The resulting residue (enamine ketone) was crystallized from ethyl acetate. To (0.03 mole) of the residue was added K_2CO_3 (2.0 mmole) and copper powder (0.03 mole) in dry acetone (10 mL) and refluxed for 5–6 h. After completion of reaction, the warm reaction solution was filtered. The filtrate was evaporated to dryness and crystallized from hot ethanol to get **7** and **8**, respectively.

7-Aceto-8-methyl-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido[4,5-b][1,8] naphthyridine-2,4,6-trione (7a). It was obtained from **4a**. IR(KBr,υ,cm^{-1}): 1625 (C⋯C of aromatic ring), 1638, 1675, 1680, 1695 (C=O), 2932 (C—H, aliphatic), 3048 (C—H, aromatic), 3335–3485 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.68 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.76 (s, 1H, CH), 4.71 (s, 1H, 5-CH), 6.62–6.65 (d, 2H, ArH's), 6.73–6.94 (d, 2H, ArH's), 8.80–9.83 (br.s, 3H, NH).

7-Aceto-8-methyl-5-(3,4-methylenedioxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido [4,5-b][1,8] naphthyridine-2,4,6-trione (7d). It was obtained from **4d**. IR(KBr,υ,cm^{-1}): 1595 (C⋯C of aromatic ring), 1657, 1675, 1685, 1694 (C=O), 2898 (C—H, aliphatic), 3045 (C—H, aromatic), 3338–3483 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 3.76 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 5.75 (s, 2H, O_2CH_2), 6.64–6.67 (m, 3H, ArH's), 8.92–9.85 (br.s, 3H, NH).

9,9-Dimethyl-5-(4-methoxyphenyl)-1,2,3,4,5,6,6a,7,8,9,10,12-dodecahydrobenzo[b] pyrimido[5,4-g][1,8]naphthyridine-2,4,6,7-tetraone (8a). It was obtained from **4a**. IR(KBr,υ,cm^{-1}): 1625 (C⋯C of aromatic ring), 1657, 1663, 1675, 1690 (C=O), 2928 (C—H, aliphatic), 3025 (C—H, aromatic), 3330–3484 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.54 (d, 2H, CH_2), 2.98 (d, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.83 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 6.64–6.67 (d, 2H, ArH's), 6.73–6.98 (d, 2H, ArH's), 8.83–9.53 (br.s, 3H, NH).

9,9-Dimethyl-5-(4-methylphenyl)-1,2,3,4,5,6,6a,7,8,9,10,12-dodecahydrobenzo[b] pyrimido[5,4-g][1,8]naphthyridine-2,4,6,7-tetraone (8c). It was obtained from **4c**. IR(KBr,υ,cm^{-1}): 1625 (C⋯C of aromatic ring), 1645, 1669, 1680, 1695 (C=O), 2925 (C—H, aliphatic), 3048 (C—H, aromatic), 3338–3480 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 6H, $2CH_3$), 2.52 (s, 3H, CH_3), 2.56 (d, 2H, CH_2), 2.96 (d, 2H, CH_2), 3.85 (s, 1H, CH), 4.72 (s, 1H, 5-CH), 6.62–6.67 (d, 2H, ArH's), 6.72–6.95 (d, 2H, ArH's), 8.87–9.58 (br.s, 3H, NH).

General procedure for the synthesis of substituted dipyrimido[4,5-b;4′,5′-f] [1,8]naphthyridines 10a–10d and 11a–11d. A mixture of **7** (10 mmoles) and thiourea/urea (10 mmoles) in DMF (20 mL) was melted and refluxed for 5–6 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid products so formed, **10** and **11**, respectively, were collected by filtration and crystallized from ethanol as light brown crystals.

4,5-Dimethyl-12-(4-methoxyphenyl)-2-thioxo-2,4a,7,8,9,10,11,12-octahydrodipyrimido [4,5-b;4′,5′-f] [1,8]naphthyridine-9,11-dione (10a). It was obtained from **7a** using thiourea. IR(KBr,υ,cm^{-1}): 1605 (C⋯C of aromatic ring), 1640, 1670 (C=O), 2925 (C—H, aliphatic), 3052 (C—H, aromatic), 3334–3485 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, CH_3), 2.24 (s, 1H, CH), 2.52 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 4.74 (s, 1H, 12-CH), 6.64–6.67 (d, 2H, ArH's), 6.74–6.96 (d, 2H, ArH's), 8.78–9.84 (br.s, 3H, NH).

4,5-Dimethyl-12-(3,4-methylenedioxyphenyl)-2-thioxo-2,4a,7,8,9,10,11,12-octahydrodi pyrimido[4,5-b;4′,5′-f] [1,8]naphthyridine-9,11-dione (10d). It was obtained from **7d** using thiourea. IR(KBr,υ,cm^{-1}): 1645, 1670 (C=O), 1605 (C⋯C of aromatic ring), 2850 (C—H, aliphatic), 3048 (C—H, aromatic), 3333–3484 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H, CH_3), 2.26 (s, 1H, CH), 2.53 (s, 3H, CH_3), 4.74 (s, 1H, 12CH), 5.79 (s, 2H, O_2CH_2), 6.65–6.69 (m, 3H, ArH's), 8.78–9.76 (br.s, 3H, NH).

4,5-Dimethyl-12-(3,4-dimethoxyphenyl)-2,4a,7,8,9,10,11,12-octahydrodipyrimido[4,5-b; 4′,5′-f][1,8]naphthyridine-2,9,11-trione (11b). It was obtained from **7b** using urea. IR(KBr,υ,cm^{-1}): 1595, 1605, 1648 (C=O), 1605 (C⋯C of aromatic ring), 2850 (C—H, aliphatic), 3042 (C—H, aromatic), 3330–3488 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H, CH_3), 2.26 (s, 1H, CH), 2.54 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.75 (s, 1H, 12-CH), 6.67–6.72 (m, 3H, ArH's), 8.78–9.76 (br.s, 3H, NH). ^{13}C NMR ($CDCl_3$):16.1, 24.7, 30.1, 56.3, 79.7, 94.8, 115.0, 115.8, 122.6, 130.0, 140.5, 144.6, 145.2, 147.5, 151.6, 161.0, 162.2, 164.1, 164.6, 165.1, 194.5.

4,5-Dimethyl-12-(4-methylphenyl)-2,4a,7,8,9,10,11,12-octahydrodipyrimido[4,5-b;4′,5′-f] [1,8]naphthyridine-2,9,11-trione (11c). It was obtained from **7c** using urea. IR(KBr,υ,cm^{-1}): 1605 (C⋯C of aromatic ring), 1594, 1645, 1670 (C=O), 2926 (C—H, aliphatic), 3054 (C—H, aromatic), 3334–3487 (3NH)cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, CH_3), 2.24 (s, 1H, CH), 2.36 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.73 (s, 1H, 12-CH), 6.62–6.67 (d, 2H, ArH's), 6.74–6.98 (d, 2H, ArH's), 8.76–9.86 (br.s, 3H, NH).

General procedure for the synthesis of substituted pyrimido[5′,4′:6,7] [1,8]naphthyridino[4,3-b][1,5]benzodiazepine-1,3-diones 12a–12d. A mixture of **7** (10 mmoles) and *o*-phenylenediamine (10 mmoles) in DMF (20 mL) was refluxed for 8–10 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid product **12** so formed was collected by filtration and crystallized from ethanol.

7,8-Dimethyl-15-(4-methoxyphenyl)-2,3,4,5,7a,15-hexahydro-1H-pyrimido[5′,4′:6,7][1,8] naphthyridino[4,3-b][1,5]benzodiazepine-1,3-dione (12a). It was obtained from **7a**. IR(KBr,υ,cm^{-1}): 1595 (C⋯C of aromatic ring), 1675, 1690 (C=O), 2923 (C—H, aliphatic), 3059 (C—H, aromatic), 3328–3484 (3NH)cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.57 (s, 1H, CH), 2.47 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 4.71 (s, 1H, 15-CH), 6.64–6.67 (d, 2H, ArH's), 6.74–6.95 (d, 2H, ArH's), 7.13–7.35 (m, 4H, ArH's), 8.88–9.76 (br.s, 3H, NH). ^{13}C NMR ($CDCl_3$): 16.1, 16.5, 24.7, 26.2, 28.3, 56.0, 79.7, 95.0, 114.0, 123.3, 128.3, 129.6, 130.3, 142.5, 143.0, 145.2, 151.5, 159.1, 164.1, 164.6.

7,8-Dimethyl-15-(3,4-methylenedioxyphenyl)-2,3,4,5,7a,15-hexahydro-1H-pyrimido[5′,4′: 6,7] [1,8]naphthyridino[4,3-b][1,5]benzodiazepine-1,3-dione (12d). It was obtained from

7d. IR(KBr,υ,cm^{-1}): 1640, 1695 (C=O), 1605 (C⋯C of aromatic ring), 2850 (C—H, aliphatic), 3048 (C—H, aromatic), 3333–3485 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.52 (s, 1H, CH), 2.47 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 4.74 (s, 1H, 15-CH), 5.76 (s, 2H, O_2CH_2), 6.68–6.72 (m, 3H, ArH's), 7.13–7.32 (m, 4H, ArH's), 8.86–9.78 (br.s, 3H, NH).

General procedure for the synthesis of substituted pyrimido[5′,4′:6,7] [1,8]naphthyridino[4,3,2-de]quinazolines 13a–13d and 14a–14d. A mixture of **8** (10 mmoles) and thiourea/urea (10 mmoles) in DMF (20 mL) was refluxed for 5–6 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid products **13** and **14**, respectively, so formed were collected by filtration and crystallized from ethanol as light brown crystal.

5,5-Dimethyl-13-(4-methoxyphenyl)-2-thioxo-4,5,6,8,9,10, 11,12,13,13c-decahydro-2H-pyrimido[5′,4′:6,7][1,8]naphthyridino [4,3,2-de]quinazoline-10,12-dione (13a). It was obtained from **8a** using thiourea. IR(KBr,υ,cm^{-1}): 1605 (C⋯C of aromatic ring), 1672, 1685 (C=O), 2925 (C—H, aliphatic), 3052 (C—H, aromatic), 3334–3485 (3NH)cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.48 (s, 2H, CH_2), 2.81 (s, 2H, CH_2), 2.86 (s, 1H, CH), 3.74 (s, 3H, OCH_3), 4.74 (s, 1H, 13-CH), 6.64–6.67 (d, 2H, ArH's), 6.74–6.96 (d, 2H, ArH's), 8.75–9.87 (br.s, 3H, NH).

5,5-Dimethyl-13-(4-methylphenyl)-2-thioxo-4,5,6,8,9,10,11,12, 13,13c-decahydro-2H-pyrimido[5′,4′:6,7][1,8]naphthyridino[4,3,2-de]quinazoline-10,12-dione (13c). It was obtained from **8c** using thiourea. IR(KBr,υ,cm^{-1}): 1598 (C⋯C of aromatic ring), 1645–1680 (C=O), 2928 (C—H, aliphatic), 3047 (C—H, aromatic), 3336–3483 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.34 (s, 3H, CH_3), 2.48 (s, 2H, CH_2), 2.81 (s, 2H, CH_2), 2.86 (s, 1H, CH), 4.74 (s, 1H, 13-CH), 6.67–6.68 (d, 2H, ArH's), 6.74–6.98 (d, 2H, ArH's), 8.79–9.88 (br.s, 3H, NH). ^{13}C NMR ($CDCl_3$): 19.6, 20.9, 27.1, 27.9, 45.1, 45.9, 79.7, 94.8, 128.6, 129.4, 134.7, 141.8, 145.2, 151.6, 164.4, 164.9, 235.8.

5,5-Dimethyl-13-(3,4-dimethoxyphenyl)-4,5,6,8,9,10,11,12, 13,13c-decahydro-2H-pyrimido[5′,4′:6,7] [1,8]naphthyridino[4,3,2-de]quinazoline-2,10,12-trione (14b). It was obtained from **8b** using urea. IR(KBr,υ,cm^{-1}): 1595, 1638, 1658 (C=O), 1605 (C⋯C of aromatic ring), 2850 (C—H, aliphatic), 3044 (C—H, aromatic), 3330–3486 (3NH)cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.27 (s, 2H, CH_2), 2.43 (s, 2H, CH_2), 2.88 (s, 1H, CH), 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.75 (s, 1H, 13-CH), 6.87–6.96 (m, 3H, ArH's), 8.78–9.76 (br.s, 3H, NH).

5,5-Dimethyl-13-(3,4-methylenedioxyphenyl)-4,5,6,8,9,10,11,12, 13,13c-decahydro-2H-pyrimido[5′,4′:6,7][1,8]naphthyridino[4,3,2-de]quinazoline-2,10,12-trione (14d). It was obtained from **8d** using urea. IR(KBr,υ,cm^{-1}): 1595, 1635, 1648 (C=O), 1605 (C⋯C of aromatic ring), 2850 (C—H, aliphatic), 3333–3484 (3NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.23 (s, 2H, CH_2), 2.53 (s, 2H, CH_2), 2.86 (s, 1H, CH), 4.74 (s, 1H, 13-CH), 5.74 (s, 2H, O_2CH_2), 6.68–6.82 (m, 3H, ArH's), 8.81–9.82 (br.s, 3H, NH).

General procedure for the synthesis of substituted pyrido[2′,1′:2,3]pyrimido[4,5-f] pyrimido[4,5-b][1,8]naphthyridine-11,13-diones 15a–15d. A mixture of **7** (10 mmoles) and 2-aminopyridine (10 mmoles) in DMF (20 mL) was refluxed for 8–10 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid products so formed, **15** were collected by filtration and crystallized from ethanol.

6,7-Dimethyl-14-(4-methoxyphenyl)-11,12,13,14-tetrahydro-10H-pyrido[2′,1′:2,3] pyrimido[4,5-f]pyrimido[4,5-b][1,8]naphthyridine-11,13-dione (15a). It was obtained from **7a**. IR(KBr,υ,cm^{-1}): 1595 (C⋯C of aromatic ring), 1675, 1695 (C=O), 2923 (C—H, aliphatic), 3059 (C—H, aromatic), 3329–3481 (2NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 4.45 (s, 1H, 14-CH), 6.47–6.62 (m, 4H, ArH's), 6.64–6.67 (d, 2H, ArH's), 6.74–6.95 (d, 2H, ArH's), 8.88–9.78 (br.s, 2H, NH). ^{13}C NMR ($CDCl_3$): 26.9, 27.7, 48.1, 48.8, 56.6, 81.7, 115.0, 115.8, 116.7, 120.6, 122.4, 130.1, 144.6, 147.5, 151.3, 155.6, 157.0, 157.2, 159.1, 161.6, 164.4, 168.9.

6,7-Dimethyl-14-(4-methylphenyl)-11,12,13,14-tetrahydro-10H-pyrido[2′,1′:2,3]pyrimido [4,5-f]pyrimido[4,5-b][1,8]naphthyridine-11,13-dione (15c). It was obtained from **7c**. IR(KBr,υ,cm^{-1}): 1590 (C⋯C of aromatic ring), 1670, 1695 (C=O), 2926 (C—H, aliphatic), 3054 (C—H, aromatic), 3333–3480 (2NH)cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 4.74 (s, 1H, 14-CH), 6.39–6.62 (m, 4H, ArH's), 6.65–6.67 (d, 2H, ArH's), 6.80–6.95 (d, 2H, ArH's), 8.96–9.74 (br.s, 2H, NH). ^{13}C NMR ($CDCl_3$): 16.2, 18.2, 20.9, 96.5, 100.4, 106.9, 116.8, 121.6, 126.7, 128.5, 129.0, 129.4, 134.7, 137.5, 140.3, 141.6, 149.5, 151.5, 159.1, 164.0, 164.6.

General procedure for the synthesis of substituted pyrimido[5′,4′:6,7] [1,8]naphthyridino[4,3,2-de]pyrido[2,1-b]quinazoline-10,12-diones 16a–16d. A mixture of **8** (10 mmoles) and 2-aminopyridine (10 mmoles) in DMF (20 mL) was refluxed for 8–10 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid products **16** so formed were collected by filtration and crystallized from ethanol.

7,7-Dimethyl-15-(4-methoxyphenyl)-6,7,8,11,12,13,14,15-octahydropyrimido[5′,4′:6,7][1,8]naphthyridino[4,3,2-de]pyrido[[2,1-b]quinazoline-12,14-dione (16a). It was obtained from **8a**. IR(KBr,υ,cm^{-1}): 1595 (C⋯C of aromatic ring), 1665, 1685 (C=O), 2927 (C—H, aliphatic), 3058 (C—H, aromatic), 3336–3487 (2NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.48 (s, 2H, CH_2), 2.81 (s, 2H, CH_2), 3.42 (s, 3H, OCH_3), 4.74 (s, 1H, 15-CH), 6.47–6.62 (m, 4H, ArH's), 6.64–6.67 (d, 2H, ArH's), 6.74–6.96 (d, 2H, ArH's), 8.75–9.87 (br.s, 2H, NH).

7,7-Dimethyl-15-(3,4-methylenedioxyphenyl)-6,7,8,11,12,13,14, 15-octahydropyrimido [5′,4′:6,7][1,8]naphthyridino[4,3,2-de]pyrido[[2,1-b]quinazoline-12,14-dione (16d). It was obtained from **8d**. IR(KBr,υ,cm^{-1}): 1595 (C⋯C of aromatic ring), 1638, 1680 (C=O), 2890 (C—H, aliphatic), 3049 (C—H, aromatic), 3333–3485 (2NH)cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 1.88 (s, 2H, CH_2), 2.12 (s, 2H, CH_2), 4.74 (s, 1H, 15-CH), 5.87 (s, 2H, O_2CH_2), 6.17–6.59 (m, 3H, ArH's), 6.49–6.62 (m, 4H, ArH's), 8.97–9.79 (br.s, 2H, NH). ^{13}C NMR ($CDCl_3$): 21.1, 27.1, 45.6, 47.8, 91.3, 100.4, 106.9, 115.0, 115.8, 116.9, 120.1, 122.7, 126.6, 131.4, 138.5, 140.2, 143.1, 144.6, 147.5, 149.6, 151.5, 161.2, 163.6, 164.0, 164.8.

General procedure for the synthesis of substituted pyrido[2,3-d;6,5-d′]dipyrimidine-2,4,6-triones 17a–17d. A mixture of equimolar quantity of **4** (0.01 moles) and formamide (0.01 moles) was refluxed on a water bath for 6 h. After the completion of the reaction, the reaction mixture was poured into

ice-cold water with stirring. The solid product was collected by filtration and crystallized from hot methanol to afford **17**.

5-(4-methoxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrido[2,3-d;6,5-d′]dipyrimidine-2,4,6-trione (17a). It was obtained from **4a**. ^{1}H NMR ($CDCl_3$): δ 3.73 (s, 3H, OCH_3), 4.74 (s, 1H, 5-CH), 6.63–6.65 (d, 2H, ArH's), 6.85–6.95 (d, 2H, ArH's), 7.48 (s, 1H, CH), 8.50–11.95 (br.s, 4H, NH). ^{13}C NMR ($CDCl_3$): 39.1, 55.9, 79.7, 100.9, 114.2, 114.9, 129.1, 130.1, 134.5, 150.1, 150.5, 151.2, 157.0, 157.7, 162.5, 163.8.

General procedure for the synthesis of substituted dipyrimido[4,5-b:5′,4′-g] [1,8]naphthyridine-2,4,6-trione 18a–18d. A mixture of equimolar quantity of **5** (0.01 moles) and formamide (0.01 moles) was refluxed on a water bath for 6 h. After the completion of the reaction, the reaction mixture was poured into ice-cold water. The solid product was collected by filtration and crystallized from hot methanol to produce **18**. On the other hand, a mixture of **5** and formamide (1:2 ratios) was refluxed on a water bath for 6–8 h. After the completion of the reaction, the reaction mixture was poured into the ice-cold water. The solid product was collected by filtration and crystallized from hot methanol to produce **19** as the main product. From the mother liquor a minor product was also separated on cooling which was exactly identical with **18**.

7-Amino-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,11,12-octahydrodipyrimido[4,5-b;5′,4′-g] [1,8]naphthyridine-2,4,6-trione (18b). It was obtained from **5b**. ^{1}H NMR ($CDCl_3$): δ 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.74 (s, 1H, 5-CH), 5.92 (s, 2H, NH_2), 6.52–6.58 (m, 3H, ArH's), 7.85 (s, 1H, CH), 8.85–11.92 (br.s, 4H, NH). ^{13}C NMR ($CDCl_3$): 36.5, 56.2, 56.8, 79.5, 85.6, 99.3, 114.5, 115.2, 122.6, 135.5, 146.7, 150.2, 150.9, 151.5, 154.5, 155.9, 163.8, 172.6, 183.5.

13-(3,4-Methylenedioxyphenyl)-8,9,10,11,12,13-hexahydro-3H-1,3,4,6,7,8,9,11-octaza- benzo[de]naphthacene-10,12-diones (19d). It was obtained from **5d**. ^{1}H NMR ($CDCl_3$): δ 4.72 (s, 1H, 13-CH), 5.82 (s, 2H, O_2CH_2), 6.48–6.59 (m, 3H, ArH's), 7.50 (s, 1H, 5-CH), 8.37 (s, 1H, 2-CH), 8.71–11.92 (br.s, 4H, NH). ^{13}C NMR ($CDCl_3$): 32.8, 81.7, 100.2, 101.4, 111.4, 114.1, 115.2, 122.4, 128.4, 145.8, 146.3, 148.7, 150.5, 155.2, 155.9, 156.0, 156.9, 158.0, 158.7, 163.8.

General procedure for the synthesis of substituted dipyrimido[4,5-b:5′,4′-g] [1,8]naphthyridines 20a–20d. A mixture of equimolar quantity of **6** (0.01 moles) and formamide (0.01 moles) was refluxed on a water bath for 6 h. After the completion of the reaction, the reaction mixture was poured into ice-cold water with stirring. The solid product was collected by filtration and crystallized from hot methanol to produce **20**.

5-(4-Methoxyphenyl)-1,2,3,4,5,6,6a,7,8,12-decahydrodipyrimido[4,5-b;5′,4′-g][1,8]naphthyridine-2,4,6,7-tetraone (20b). It was obtained from **6b**. ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H, OCH_3), 3.98 (s, 1H, 6a-CH), 4.48 (s, 1H, 5-CH), 6.63–6.65 (d, 2H, ArH's), 6.85–6.95 (d, 2H, ArH's), 7.89 (s, 1H, 9-CH), 8.59–11.72 (br.s, 4H, NH). ^{13}C NMR ($CDCl_3$): 36.5, 55.1, 55.9, 79.5, 107.5, 114.2, 114.8, 130.0, 130.6, 134.5, 150.2, 150.5, 150.9, 155.9, 157.8, 163.8, 164.2, 170.5, 196.5.

General procedure for the synthesis of substituted pyrimido[5′,4′:6,7] [1,8]naphthyridino[4,3-b][1,5]benzodiazepine-1,3,8-triones 21a–21d. A mixture of 6 (10 mmoles) and *o*-phenylenediamine (10 mmoles) in DMF (20mL) was refluxed for 8–10 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid product 21 so formed was collected by filtration and crystallized from ethanol.

7-Amino-15-(4-methoxyphenyl)-2,3,4,5,7a,8,9,15-octahydro-1H-pyrimido[5′,4′:6,7][1,8] naphthyridino[4,3-b[1,5]benzodiazepine-1,3,8-trione (21a). It was obtained from **6a**. ^{1}H NMR($CDCl_3$): δ 1.59 (s, 1H, 7a-CH), 3.74 (s, 3H, OCH_3), 3.89 (s, 2H, NH_2), 4.72 (s, 1H, 15-CH), 6.64–6.67 (d, 2H, ArH's), 6.74–6.95 (d, 2H, ArH's), 7.23–7.58 (m, 4H, ArH's), 8.85–11.90 (br.s, 4H, NH). ^{13}C NMR ($CDCl_3$) : 37.5, 39.2, 55.9, 79.5, 93.0, 114.8, 114.1, 122.5, 122.9, 125.6, 127.4, 130.1, 130.6, 132.5, 134.7, 142.6, 150.4, 151.2, 151.6, 157.7, 163.8, 164.0, 164.8, 168.2.

General procedure for the synthesis of substituted dipyrimido[4,5-b;4′,5′-f] [1,8]naphthyridines 22a–22d and substituted dipyrimido[4,5-b;5′,4′-g] [1,8]naphthyridines 23a–23d. A mixture of **6** (10 mmoles) and thiourea (10 mmoles) in DMF (20 mL) was refluxed for 5–6 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid product so formed, a mixture of **22** and **23** was collected by filtration and separated by column chromatography (eluant:Pet ether:Methanol::90:10; Pet ether: Methanol::85:15).

5-Amino-12-(3,4-dimethoxyphenyl)-2-thioxo-2,3,4,4a,7,8,9,10, 11,12-decahydro dipyrimido[4,5-b; 4′,5′-f][1,8]naphthyridine-4,9,11-trione (22b). It was obtained from **6a** using thiourea. IR(KBr,υ,cm^{-1}): 1625 (C⋯⋯C of aromatic ring), 1660, 1670, 1675 (C═O), 2890 (C—H, aliphatic), 3049 (C—H, aromatic), 3235 (NH_2), 3330–3400 (4NH)cm^{-1}; ^{1}H NMR($CDCl_3$): δ 2.26 (s, 1H, 4a-CH), 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.85 (s, 2H, NH_2), 4.74 (s, 1H, 12-CH), 6.67–6.72 (m, 3H, ArH's), 8.85–11.92 (br.s, 4H, NH). ^{13}C NMR ($CDCl_3$): 36.5, 38.9, 55.6, 79.6, 93.2, 114.2, 114.8, 130.1, 130.6, 134.5, 150.6, 151.0, 151.8, 157.6, 159.8, 163.8, 164.0, 164.8, 170.7. MS: m/z, 467 (M^+).

5-(4-Methoxyphenyl)-9-thioxo-1,2,3,4,5,6,6a,7,8,9,10,12-dodecahydrodipyrimido[4,5-b; 5′,4′-g][1,8]naphthyridine-2,4,6,7-tetraone (23a). It was obtained from **6a** using thiourea. IR(KBr,υ,cm^{-1}): 1605 (C⋯⋯C of aromatic ring), 1657, 1665, 1678, 1715 (C═O), 2895 (C—H, aliphatic), 3042 (C—H, aromatic), 3330–3470 (5NH)cm^{-1}; ^{1}H NMR($CDCl_3$): δ 3.92 (s, 1H, 6a-CH), 4.43 (s, 1H, 5-CH), 6.63–6.67 (d, 2H, ArH's), 6.85–6.95 (d, 2H, ArH's), 8.69–11.92 (br.s, 5H, NH). ^{13}C NMR ($CDCl_3$): 36.5, 55.8, 56.9, 79.5, 107.5, 114.2, 114.8, 130.0, 131.6, 134.5, 150.5, 151.2, 152.9, 155.8, 157.6, 163.8, 164.2, 170.7, 196.5. MS: m/z, 438 (M^+).

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