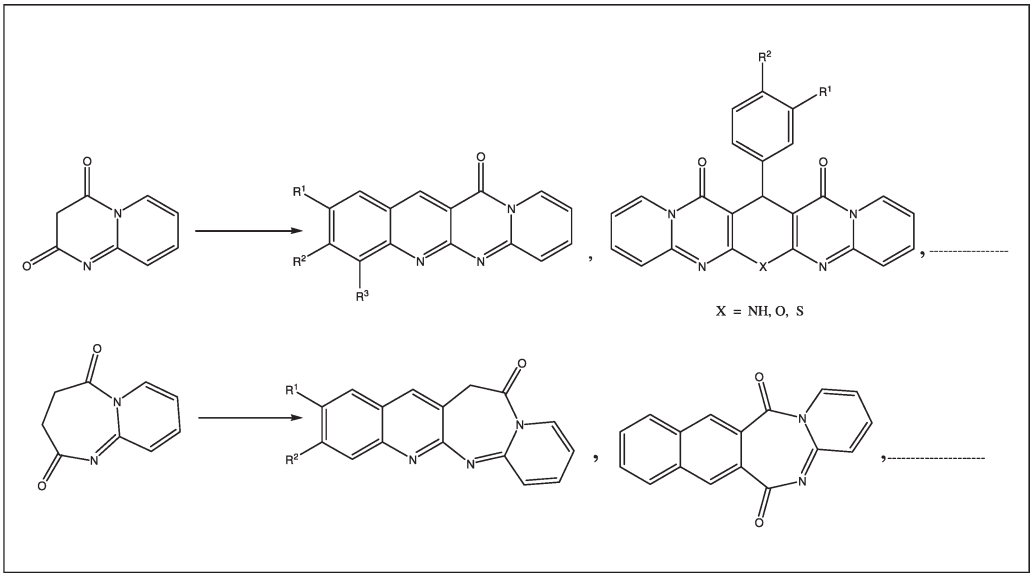
Synthesis of Novel and Biologically Potent Heteropolycyclics Containing Bridge Head Nitrogen

Poonam Gupta, Shallu Gupta, Anand Sachar, and R. L. Sharma*

Department of Chemistry, University of Jammu, Jammu 180006, India
*E-mail: rlsharma_hod@rediffmail.com

Received July 3, 2009
DOI 10.1002/jhet.465
Published online 26 July 2010 in Wiley Online Library (wileyonlinelibrary.com).



A facile one pot synthesis of 2,3,4,5-tetrahydropyrido [1,2-*a*] [1,3] diazepine-2,5-dione **2** and 3,4-dihydro-2*H*-pyrido [1,2-*a*] pyrimidine-2,4-dione **3** has been achieved. Condensation of **3** with *o*-aminobenzaldehydes produced the linear product **4** and not the angular one **5**. Cyclocondensation of **3** with 1,5-diketones afforded a tricyclic linear system **6**, a bis assembly system **7** and two novel heterotetracyclic nitrogen bridged linear systems **8** and **10**. Condensation of *o*-aminobenzaldehydes with **2** produced a novel linear system **12** and a new doubly fused hexacyclic system **11**. Cyclodehydration of **2** with 1,2-dicarbaldehydes produced **1**, **13**, and a new heterotetracyclic nitrogen bridged system **14**. Condensation of **3** with aromatic aldehydes in presence of ethylene glycol as solvent without the use of catalyst generated the doubly nitrogen bridged linear pentacyclic systems **15–17**. The synthesized compounds have been adequately characterized and screened for bronchodilatory and antimicrobial activities with promising results.

J. Heterocyclic Chem., **47**, 1188 (2010).

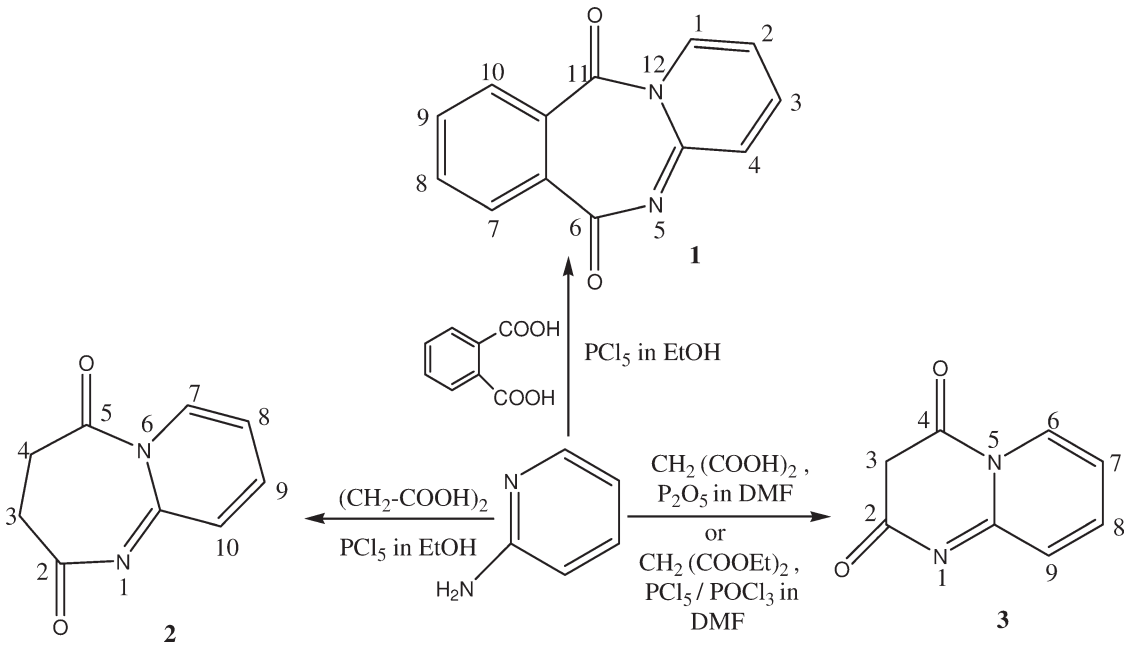
INTRODUCTION

Diazepines and benzodiazepines are known to exhibit a wide variety of biological activities such as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, and hypnotic activity [1–3]. Some of the benzodiazepine derivatives particularly 7-(*p*-methoxyphenyl)-8-phenoxy-1, 5-benzo-3-azanonem (1,5-BDZ-OMe) and 7-phenyl-8-phenoxy-1,5-benzo-3-azanonem (1,5-BDZ-H) possess hypnotic activity [4]. Pyrrolo [2,1-*c*] [1,4] benzodiazepines such as anthramycin and DC-81 are well-known antitumor antibiotics (PBDS) derived from streptomyces species [5].

Compounds possessing quinazoline and quinazolinone nuclei show potent biological activities including bronchodilatory, anticancer, anticonvulsant, antibacterial, anti-HIV properties [6,7], anthelmintic [8], antiparkinsonium [9], antitubercular [10], hypoglycemic [11], antiviral [12], anticoagulant [13], antifibrillatory [14], cardiac stimulant [15], CNS depressant [16], neuroleptic [17], and hypnotic [18]. Vasicine and vasicinone, the two known alkaloids and a synthetic compound 7,8,9,10-tetrahydroazepino [2,1-*b*] quinazolin-12(6*H*)-one (RLX) all bearing quinazoline moiety have been evaluated as potent bronchodilatory and oxytocic agents [19–22]. The latter compound has been found to be six times more potent than aminophylline [23].

Quinoline and its derivatives are known for their antimalarial and therapeutic properties. A number of quinoline derivatives are known to possess antitumour, antibacterial, antifungal, hypotensive, anti-HIV, analgesic,

Scheme 1



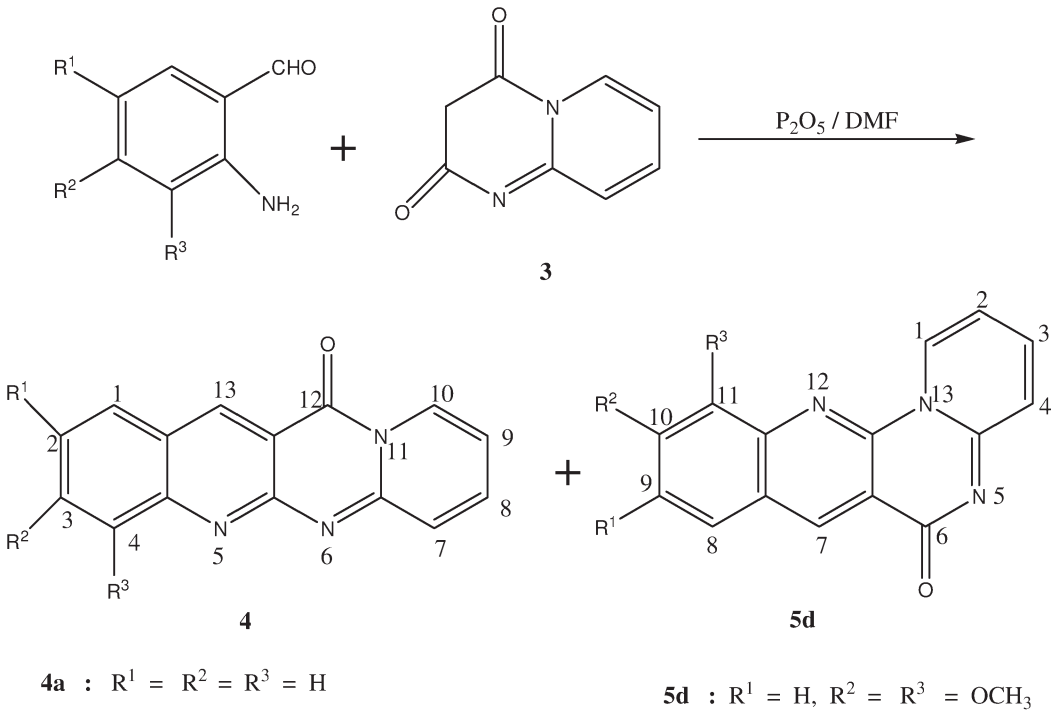
anti-Leishmanial, and anti-inflammatory activities [24]. In addition, the synthesis of pyrido [1,2-*a*] pyrimidin-4-ones provided a wide spectrum of biological activities [25–31] such as tranquilizer, antiallergic, antiulcerative, antiasthmetic and bronchodilatory activity, analgesic activity, and human platelet aggregation inhibitory properties. Biologically active evaluations of these constituent moieties in the recent years encouraged us to generate the novel condensed heteropolycyclic systems containing bridge head nitrogen atom, most of them hitherto unknown in literature and comprising of one or more than one of these moieties. Such novel systems might expectedly prove to be the potent therapeutic agents in near future.

RESULTS AND DISCUSSION

In this work, 6*H*,11*H*-pyrido[1,2-*b*][2,4]benzodiazepine-6,11-dione **1** and 2,3,4,5-tetrahydropyrido[1,2-*a*] [1,3]diazepine-2,5-dione **2** were designed and generated by the condensation of 2-aminopyridine with phthalic acid and succinic acid, respectively, both in presence of PCl_5 in ethanol. An active methylene heterocycle, 3,4-dihydro-2*H*-pyrido [1,2-*a*] pyrimidine-2,4-dione **3** was produced by the condensation of 2-aminopyridine either with malonic acid in presence of anhydrous P_2O_5 in DMF or with diethyl malonate in the presence of PCl_5/ $POCl_3$ in DMF (Scheme 1). Compound **3** has been known in literature, having been prepared through other approaches [32–34]. Literature m.p, analytical data, and spectral data confirmed the structure assigned to it in this study. Presence of peculiar bands between 1590 to 1600 cm^{-1} and 1675 to 1710 cm^{-1} in IR spectra of compounds **1** and **2** favored the presence of C=N and CON< (tertiary amide) functionalities. Presence of signal of aromatic protons only for compound **1**, a downfield multiplet due to two methylene groups around δ 2.35 to 2.43 ppm for compound **2**, and the absence of any D_2O exchangable proton in ^1H NMR spectra of either of these two compounds confirmed the heterocyclisation and their structures unambigously.

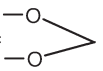
The active methylene compound **3** was put to Knoevenagel condensation with some *o*-aminobenzaldehydes followed by subsequent heterocyclodehydration affording a single product (**4a–c**) and in one case affording the main product **4d** associated with another very minor product (TLC). The compounds **4a–d** have been characterized as 12*H*-pyrido [1′,2′:1,2] pyrimido [4,5-*b*] quinolin-12-ones belonging to a linear ''ortho fused'' system. The minor product which could not be separated from **4d** might be the angular product, 6*H*-pyrido [1′, 2′:1, 2] pyrimido [4,5-*b*] quinolin-6-one **5d** (Scheme 2). The literature report [35] regarding compound **4a** confirmed its structure by comparing m.p, analytical, and spectral data of **4a** of this study with that known in literature. The appearance of peaks of methylenedioxy protons at δ 6.10 ppm in **4c**, two methoxyl group protons at δ 3.70 and 3.75 ppm in compound **4b**, and two methoxyl group protons at δ 3.72 and δ 3.78 ppm for compound **4d** in ^1H NMR spectra confirmed their structures unequivocally. Other signals in ^1H NMR spectra of **4b–d** were almost identical with those for compound **4a**.

Scheme 2



4a : $R^1 = R^2 = R^3 = H$

4b : $R^1 = R^2 = OCH_3$; $R^3 = H$

4c : $R^1 + R^2 =$  ; $R^3 = H$

4d : $R^1 = H$, $R^2 = R^3 = OCH_3$

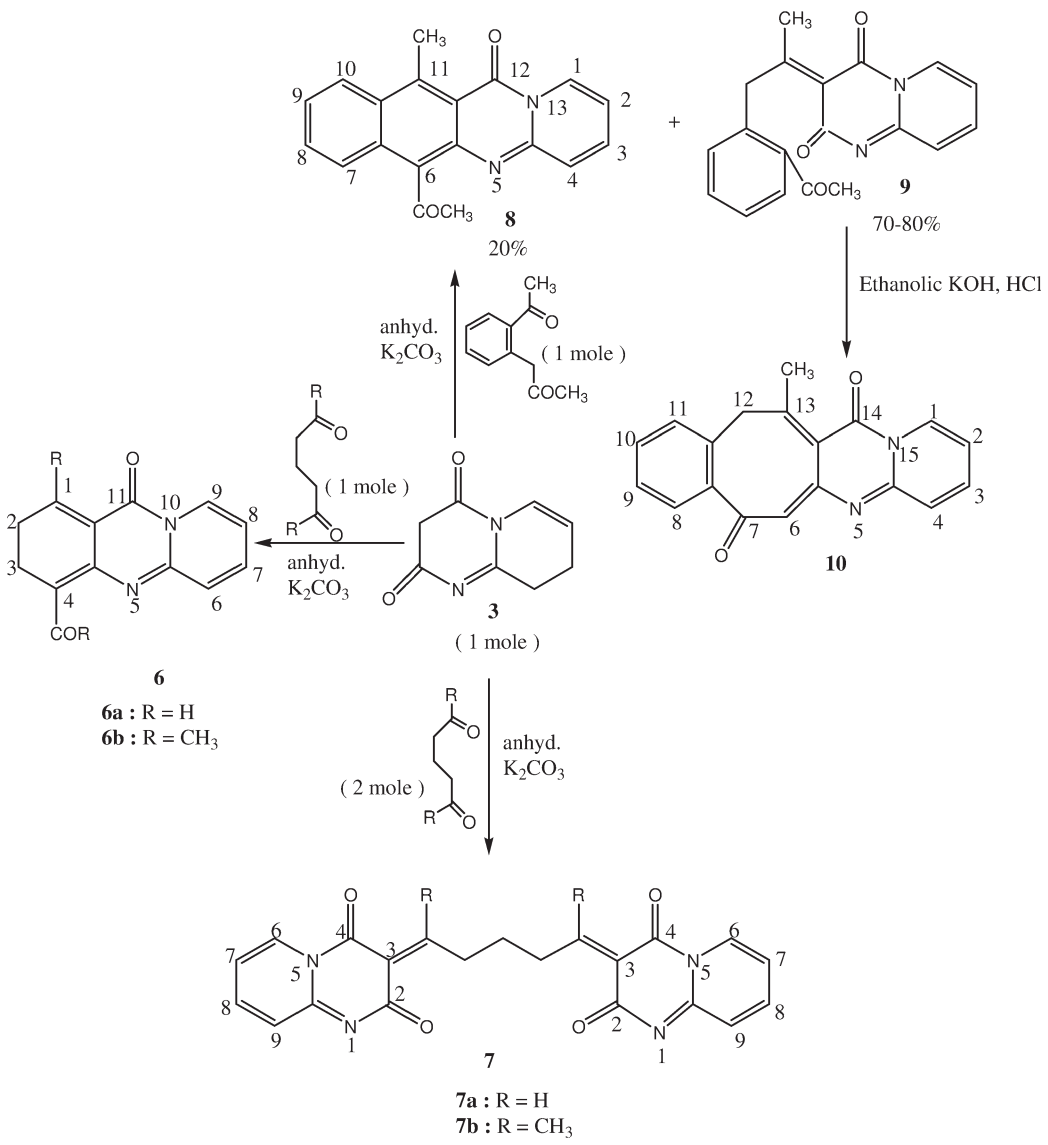
5d : $R^1 = H$, $R^2 = R^3 = OCH_3$

Working on the similar route of synthesis, cyclocondensation of **3** with 1,5-dicarbonyl compounds like glutaraldehyde and heptane-2,6-dione in the mole ratio of 1:1 and 1:2 in presence of anhydrous K_2CO_3 was carried producing two entirely different product systems, a quinazoline based linearly fused tricyclic system, 4-acyl-2,3-dihydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one **6a–b**, and a bis heterocyclic ring assembly system, 1,5-bis (2,4-dioxo-3,4-dihyro-2*H*-pyrido [1,2-*a*] pyrimidin-3-ylidine) pentane **7a–b**, respectively, in each case. The compound **6a** obtained from 1:1 condensation showed a characteristic downfield singlet at δ 9.96 ppm due to proton of CHO at C-4, a downfield triplet at δ 5.70 ppm due to ethylenic proton at position 1, and a multiplet at δ 1.7 to 1.85 ppm due to four methylenic protons besides four aromatic protons as multiplet in its ^{1}H NMR spectrum. The compound **6b** had two prominent singlets of three protons each at δ 2.43 and 2.15 ppm due to $COCH_3$ and CH_3 protons, respectively. The appearance of a multiplet due to six protons of three methylene groups and a triplet due to two ethylenic protons in the acyclic portion confirmed unequivocally the structure of **7a**. Similarly, 6-aceto-12*H*-11-methylbenzo [*g*] pyrido[2,1-*b*]quinazolin-12-one **8** and 12*H,14H*-13-methylbenzo [5,6] [8] annuleno [1,2-*d*] pyrido [1,2-*a*] pyrimidine-7,14-dione **10** were also generated from compound **3**, the latter through the intermediacy of **9** (Scheme 3).

Under slightly different conditions, a highly hybrid quinoline-based doubly fused hexacyclic system, tetrasubstituted pyrido[1′,2′:1,2]quino [3″,2″:6,7][1,3] diazepino[4,5-*b*] quinoline **11** and a novel linear disubstituted system, pyrido[1′,2′:1,2] [1:3] diazepino[4,5-*b*]quinolin-12(13*H*)-one **12** were generated from **2** whose characterization was done as usual (details in experimental part). Again, cyclodehydration of **2** with malealdehyde and succinaldehyde produced **1** and its dihydro analogue **13**, respectively, and the condensation between **2** and phthalaldehyde produced a new heterotetracyclic system 6*H*,13*H*-pyrido[1,2-*a*]naphtho[2,3-*e*] [1,3] diazepine-6,13-dione **14** (Scheme 4).

In extension of our earlier work [36,37], it was thought worthwhile to study the condensation of active methylene compound **3** with aromatic aldehydes in ethylene glycol as solvent without the use of catalyst. Knoevenagel condensation, Michael addition, and cyclodehydration took place simulataneously resulting in the formation of a novel linear and heteropentacyclic system **16** containing a central pyran ring. The

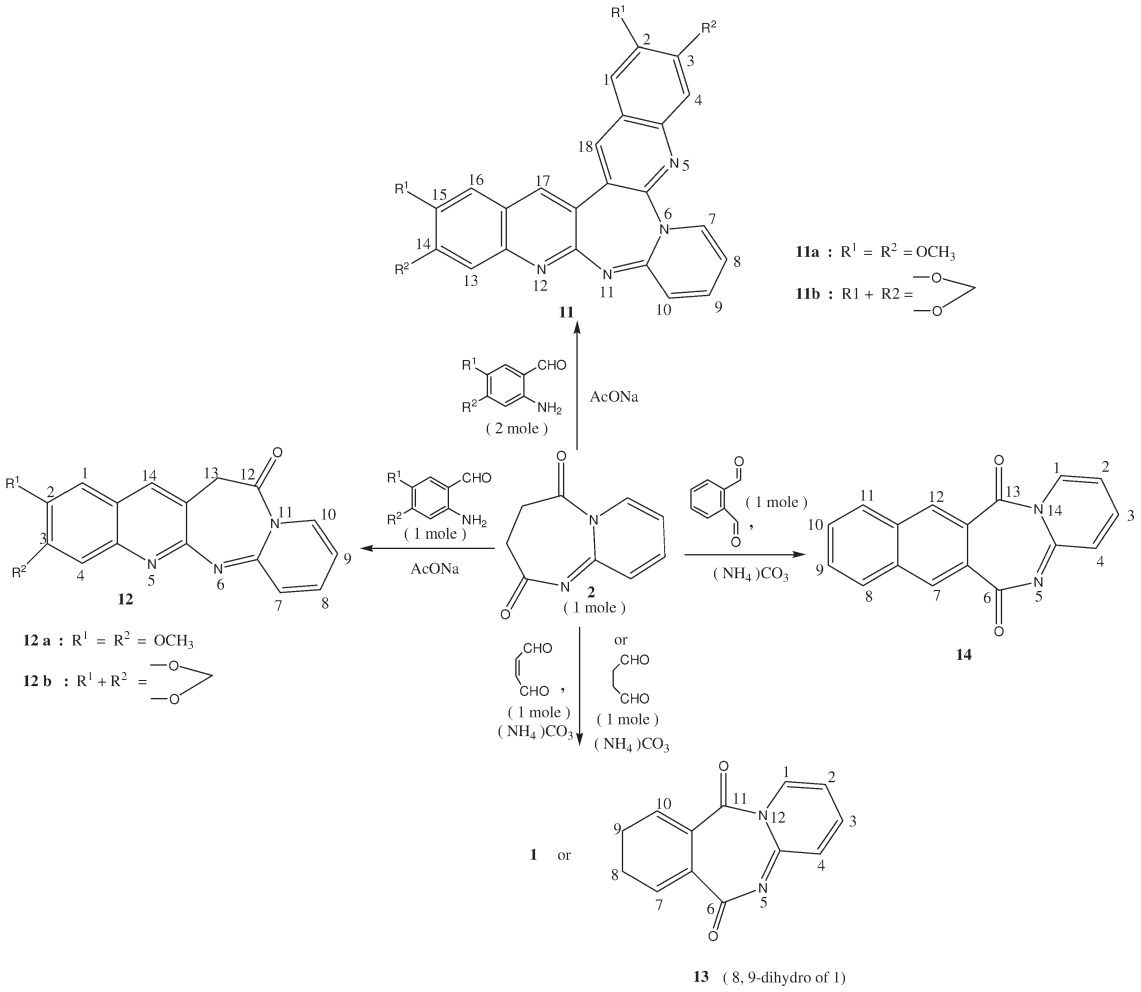
Scheme 3



intermediates could not be isolated but the second intermediate after the two transformations seemed to be more interesting for exploitation in the ring closure heterocyclising reaction. Hence, compound **3** was treated with different aromatic aldehydes in ethylene glycol producing compound **16** and refluxed in DMF in presence of ammonium acetate, P_2O_5 and P_2S_5 giving similar results in each case producing three novel linear heteropentacyclic systems **15**, **16**, and **17** with pyridine, pyran, and thiopyran central ring, respectively (Scheme 5). The characterization has been made for these systems on the basis of elemental analysis and spectral studies. The present exposition has twofold importance, firstly the study of the versatility and reactions of compound **3** and **2** with different aldehydes under different conditions resulting in generation of various novel-fused heterocyclic systems most of which are hitherto unknown in literature and secondly the study of physiological nature of these systems.

Pharmacology. On preliminary pharmacological investigations, the compounds **4a–d**, **6a–b**, **8**, **11a–b**, and **12a–b** have been found to be promising bronchodilatory and oxytocic agents having activities comparable to those of alkaloid vasicine and its natural and synthetic analogues. The detailed study of the evaluation of these biological activities is under active exploration from our research laboratory. The drugs employed in this study are 7,8,9,10-tetrahydroazepino [2,1-*b*] quinazolin-12(6*H*)-one; Aminophyllin injection I.P (Burroughs Welcome & Co.); Histamine diphosphate (Sigma); Adrenaline tartarate (IP); Propanolol HCl (ICI); 5-hydroxytryptamine; and Egg albumin (BDH).

Scheme 4



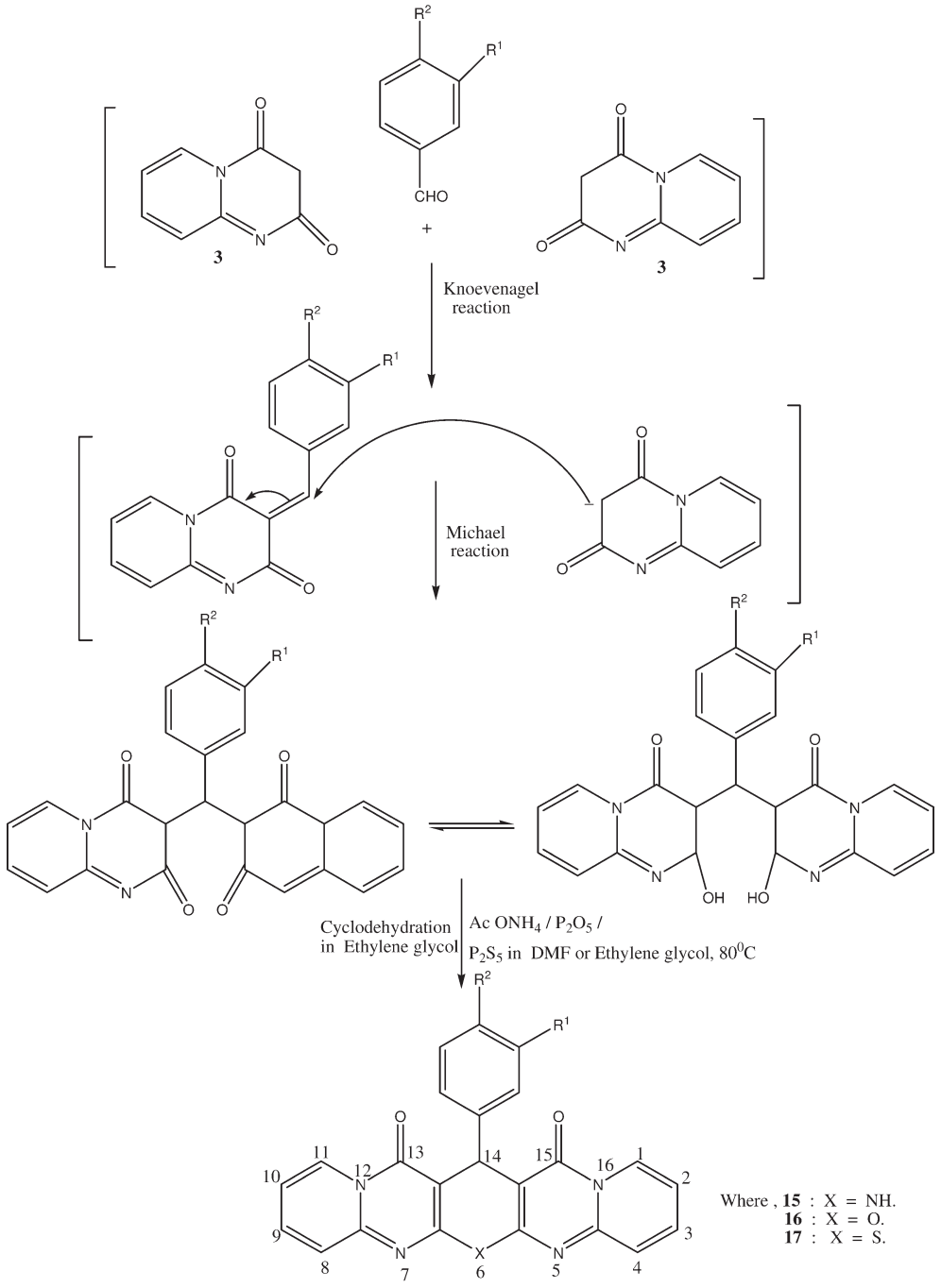
The comparative SAR of various compounds [38] and the results of other details regarding these activities are being currently determined. The compounds **4a–d**, **6a–b**, **8**, **11a–b**, and **12a** have been found to be weakly to moderately active antimicrobial agents. Compounds **4a–d**, **6a–b**, **11a–b**, and **12a** have been found to be highly promising, as regards ''Tracheal smooth muscle activity'' and ''Antitussive activity.''

Antimicrobial activity. The compounds **3**, **7a–b**, **15a–d**, and **4a–d** have been screened for their antifungal activity against Aspergillus, Penicillium, and Cladosporium species. For antibacterial activity, these compounds have been screened against *E.coli*, *Bacillus subtilis*, and *Bacillus cereus*. Both the activities were evaluated at the same concentration of 1000 μg and through well diffusion technique. The standard antifungal agent fluconazole and the antibacterial agent norfloxacin were also screened under similar conditions for a comparative study. The inhibition zones formed were measured in mm and are listed in (Table 1).

Broncodilatory activity

Tracheal smooth muscle activity. Preparation of tissue was similar to that described by Castillow and de Beer [39] except that the tracheal ring was opened by severing the cartilage. Guineapigs (350–500 g) of either sex were sacrificed by a blow to the head and the tracheae rapidly excised. The tracheal chain was prepared and suspended in a 20 mL tissue bath containing Krebs-henselet solution (KHS) continuously aerated with 95% O_2 and 5% CO_2 and maintained at 37°. The composition (mM) of (KHS) was NaCl 118, KCl 4.7, $MgSO_4 \cdot 7H_2O$ 1.2, $CaCl_2$ 2.2, KH_2PO_4 1.2, $NaHCO_3$ 24.9, and (+)-glucose 11.1. The responses were recorded isotonically on a kymograph. The tissue was adjusted to an initial tension of 1.5 g and allowed to equilibrate (60–90) min. Relaxation effect of the drug was studied on tracheal chain precontracted with histamine diphosphate (1×10^{-6} g/mL) or acetylcholine chloride (1×10^{-6} g/mL). The test drugs were added 8 min after the tonic contraction reached plateau. The responses were calculated as percent to relaxing of

Scheme 5



15a, 16a, 17a : R^1 = H, R^2 = OCH_3 **15b, 16b, 17b :** R^1 = H, R^2 = CH_3

15c, 16c, 17c : R^1 = R^2 = OCH_3 **15d, 16d, 17d :** $R^1 + R^2$ =

precontracted muscle back to base line tension (10% relaxation). If there was relaxation to muscle slightly below the base line, it was also taken as 100% relaxation.

Antitussive activity. Kobayshi's [40] method was used in this study. Guineapigs (300–400 g) were aneasthetised by I/P urethane (6.5 mL/kg; 25%) and fixed in

Table 1

Antimicrobial activity of compounds **3**, **7a–b**, **15a–d**, and **4a–d**.

	Antibacterial activity			Antifungal activity		
Compd. No	*E. coli*	*B. subtilis*	*B. cereus*	*A. niger*	*P. species*	*C. species*
3	14	12	17	17	13	16
7a	15	13	16	14	12	17
7b	17	11	18	18	16	17
15a	20	22	19	19	18	20
15b	19	23	23	21	22	23
15c	20	19	23	23	24	24
15d	20	18	21	20	19	20
4a	19	17	14	17	18	19
4b	18	16	16	19	18	19
4c	20	19	18	20	17	17
4d	21	19	17	17	21	20
NR	28	26	28	–	–	–
Flu	–	–	–	32	25	23

Note: 10 mm, inactive; 11–15 mm, weakly active; 16–22 mm, moderately active; 22–25 mm, highly active.
NR, norfloxacin; Flu, fluconazole.

dorsal position. The trachea was exposed and a small incision made at a distance of 1.5 cm from the clavicle. A fine and very thin polythene tube was inserted into the incision as deep as 3 cm to give the stimulus. The stimulus was applied two times before and 15, 30, 45, 60, 90 and 120 min after the drug administration by oral route. If no coughing occurred in two or more out of five trails after drug administration, the drug was estimated as effective percent inhibition was recorded. Results are shown in (Table 2) as follows:

EXPERIMENTAL

General. Melting points were measured in open capillaries on perfit melting point apparatus and are uncorrected. IR spectra on KBr were recorded on Brucker—4800 infrared spectrometer. NMR and EIMS/HRMS spectra were recorded on Brucker AC-400 (400 MHz and 100 MHz) and JEOL D-300 mass spectrometer, respectively. Elemental analysis was carried out on simple CHNS analyzer (CHNS-932, LECO Corporation, USA). ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) as internal standard. All experiments were performed in oven dried glass

Table 2

Bronchodilatory and antitussive activities[a] of compounds **4a–d**, **6a–b**, **8**, **11a–b**, and **12a–b**.

	In vitro guinea pig trachea % relaxation			Antitussive activity (guinea pig)	
Compd.	Histamine	Acetylcholine	Concn (μ/mL)	% cough inhibition	Dose (mg/kg)
4a	60	–	–	–	10
4b	80	70	30	80[b]	10
4c	60–80	40–50	9	60[b]	10
	70–90	70–80	20	80[b]	
	90	80–90	40	80[b]	
4d	80	–	40	100[b]	10
6a	80	80–85	9	100[c]	10
6b	–	60	70	80[c]	10
8	80	80–15	30	60[c]	10
11a	40–50	40–50	30	100[d]	10
1b	50–60	50–60	40	100[d]	10
12a	40–50	40–50	30	100[e]	10
Bromhexine hydrochloride				40–80[e]	2
				100[e]	4

[a] Minimium of four experiments for each group.
[b] Onset of action after 45 min and duration of 3 h.
[c] Onset of action after 45 min and duration >3 h.
[d] Onset of action after 30 min and duration >3 h .
[e] Onset of action after 15 min and duration >3 h.

apparatus. SISCO silica was used as adsorbent for TLC (0.5 mm thick plates) and TLC plates were eluted with 1:9 ratios of ethyl acetate and *n*-hexane. The column chromatography was performed over silica gel (60–120 mesh) with graded solvent systems of ethyl acetate-pet ether (60–80).

General procedure for the synthesis of 1–3. A mixture of 2-aminopyridine (0.01 mole) and appropriate dibasic acid/ester (0.01 mole) was initially grinded for about 20 min and then fused or refluxed as such for about 1 h without any solvent in a round bottom flask and finally refluxed on water bath in presence of 15 mL of ethanol and PCl_5 or at 150–160°C in presence of anhydrous $POCl_3/PCl_5$ in 20 mL of DMF or P_2O_5 in 20 mL of DMF. After the reaction time (TLC), the solvent was evaporated under reduced pressure and 100 mL of H_2O was added. The precipitates obtained were filtered, dried, and then crystallized from hot ethanol to generate pure 1–**3**.

6H,11H-Pyrido [1,2-b] [2,4]benzodiazepine-6,11-dione (1). It was obtained from phthalic acid (8.30 g, 0.01 mole) and 2-aminopyridine (4.70 g, 0.01 mole) as colorless solid; m.p.150–152°C ; yield 78%; IR (KBr) ν/cm^{-1}: 1320–1325 (C—N), 1600 (C=N), 1610–1620 (C=C), 1675 (C=O); MS: m/z = 224 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 7.01–7.81 (m, 8H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 110.2, 114.0, 125.4, 126.8, 128.7, 130.4, 132.4, 133.7, 135.1, 136.1, 154.1, 158.9, 162.8. Anal. Calcd. for $C_{13}H_8N_2O_2$: C, 69.6; H, 3.5; N, 12.5. Found: C, 68.9; H, 3.3; N, 12.1.

2,3,4,5-Tetrahydrohyropyrido [1,2-a] [1,3] diazepine-2,5-dione (2). It was obtained from succinic acid (5.90 g, 0.01 mole) and 2-aminopyridine (4.70 g, 0.01 mole); m.p. 102–104°C; yield 72%; IR (KBr) ν/cm^{-1}: 1305–1320 (C—N), 1594 (C=N), 1685–1710 (C=O); MS: m/z = 176 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 2.35–2.43 (m, 4H, 2×CH_2), 7.2–7.6 (m, 4H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δppm) = 25.7, 31.2, 110.4, 115.5, 120.3, 124.5, 162.9, 165. 8, 180.7. Anal. Calcd for $C_9H_8N_2O_2$. C, 61.3; H, 4.5; N, 15.9. Found: C, 58.2; H, 4.4; N, 15.4.

3,4-Dihydro-2H-pyrido [1,2-a] pyrimidine-2,4-dione (3). Crystallized from DMF, m.p. 301–303°C, (literature m.p. 296–298°C [32]; 295–298°C [33]; 305–308°C [34]).The observed analytical and spectral data were found in complete conformity with the literature values.

General procedure for the synthesis of 4. Dissolved (0.01 mole) of substituted *o*-aminobenzaldehyde in 40 mL of hot rectified spirit and added to it a solution of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine-2,4-dione (0.01 mole) **3** in 25 mL of rectified spirit and 0.02 mole of fused anhydrous sodium acetate. Swirled to mix and set aside for 5–6 h and finally refluxed the mixture for an hour. Distilled off the ethanol and added 100 mL of H_2O. Filtered, washed, the crystalline product with water twice and with a little cold ethanol and crystallized from about 100 mL of hot rectified spirit to obtain the pure and dry product 4.

12H-Pyrido[1′,2′:1,2]pyrimido[4,5-b]quinolin-12-one (4a). Crystallized from butanone, m.p. 272–273°C. The observed and literature [35] analytical and spectral data were in complete agreement with each other, thus conforming the structure of the synthesized compound.

12H-2,3-Dimethoxypyrido[1′,2′:1,2]pyrimido[4,5-b]quinolin-12-one (4b). It was obtained from 6-aminoveratraldehyde (1.81 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 246–248°C; yield 67%; IR (KBr) ν/cm^{-1}: 1320–1330 (C—N), 1590 (C=N), 1692 (C=O); MS: m/z = 307 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 7.10–7.90 (m, 7H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 56.0, 56.3, 110.1, 120.3, 121.4, 122.7, 123.6, 128.9, 130.1, 140.2, 145.7, 158.2, 159.4, 164.3, 165.6, 169.8, 189.0. Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.2; N, 13.6. Found: C, 66.41; H, 4.0; N, 13.8.

12H-[1,3]Dioxolo[4,5-g]pyrido[1′,2′:1,2]pyrimido[4,5-b]quinolin-12-one (4c). It was obtained from 6-aminopiperonal (1.65 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 190–192°C; yield 64%; IR (KBr) ν/cm^{-1}: 1305–1320 (C—N), 1620 (C=N), 1690 (C=O); MS: m/z = 291 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 6.10 (s, 2H, CH_2O_2), 7.20–7.92 (m, 7H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$) : δ (ppm) = 90.5, 108.0, 108.3, 110.1, 114.6, 120.2, 124.1, 124.8, 136.6, 137.1, 140.2, 151.2, 155.3, 162.3, 163.5, 165.4. Anal. Calcd. for $C_{16}H_9N_3O_3$: C, 65.97; H, 3.0; N, 14.4. Found: C, 64.12; H, 2.9; N, 14.7.

12H-3,4-Dimethoxypyrido[1′,2′:1,2]pyrimido[4,5-b]quinolin-12-one (4d). It was obtained from 2-aminoveratraldehyde (1.81 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 242–244°C; yield 68%; IR (KBr) ν/cm^{-1}: 1320–1330 (C—N), 1590 (C=N), 1692 (C=O); MS: m/z = 307 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 3.71(s, 3H, OCH_3), 3.75 (S, 3H, OCH_3), 6.92–7.90 (m, 7H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 54.2, 54.3, 105.8, 110.5, 118.8, 120.2, 121.3, 122.5, 125.7, 130.8, 132.3, 135.6, 137.8, 140.5, 145.3, 162.5, 165.2. Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.2; N, 13.6. Found: C, 66.38; H, 4.16; N, 13.42.

General procedure for the synthesis of 6–9. Dissolved (0.01/0.02 mole) of appropriate aldehyde or ketone in 40 mL of hot rectified spirit, added a solution of 3,4-dihydro-2*H*-pyrido [1,2-*a*] pyrimidine-2,4-dione (0.01 mole) 3 in 25 mL of rectified spirit and added (0.02/0.04 mole) of anhydrous potassium carbonate. Swirled to mix and set aside for 5–6 h. The reaction mixture was finally refluxed for 3 h. Distilled off the ethanol and added 100 mL of H_2O. Filtered, washed the crystalline product first with water, and finally with a little cold ethanol and recrystallized from about 100 mL of hot rectified spirit to obtain the product **6–9**.

3,11-Dihydro-2H-11-oxopyrido[2,1-b]quinazoline-4-carbaldehyde (6a). It was obtained from glutaraldehyde (1.00 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 80–82°C; yield 62%; IR (KBr) ν/cm^{-1}: 1305–1320 (C—N), 1610 (C=N), 1695 (C=O); MS: m/z = 226 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 1.7–1.85 (brs, 4H, 2×CH_2), 5.7 (s, 1H, CH-1), 6.87–7.90 (m, 4H, ArHs), 9.96 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 22.3, 25.5, 110.8, 114.7, 120.3, 135.0, 135.2, 136.8, 138.9, 156.9, 160.2, 163.4, 189.3. Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.04; H, 4.42; N, 12.38. Found: C, 68.05; H, 4.37; N, 12.42.

4-Aceto-3,11-dihydro-2H-1-methyl pyrido [2,1-b]quinazolin-11-one (6b). It was obtained from heptane-2,6-dione (1.28 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 88–90°C; yield 66%; IR (KBr) ν/cm^{-1}: 1305–1320 (C—N), 1615 (C=N), 1690 (C=O); MS: m/z = 254 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 1.78–2.02 (brs, 4H, 2×CH_2), 2.15 (s, 3H, CH_3), 2.43 (s, 3H, $COCH_3$), 6.92–7.23 (m, 4H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 15.6, 20.7, 21.8, 31.7, 112.1, 115.6, 126.3, 128.2, 134.3, 136.1, 144.5, 147.1, 160.2,

162.4, 194.5. Anal Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.56; H, 5.51; N, 11.02. Found: C, 70.42; H, 5.42; N, 11.0.

1,5-Bis(2,4-dioxo-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-3-ylidene)pentane (7a). It was obtained from gluteraldehyde (2.00 g, 0.02 mole) and **3** (1.62 g, 0.01 mole); m.p. 74–76°C; yield 72%; IR (KBr) ν/cm^{-1}: 1310–1320 (C—N), 1615 (C=N), 1700 (C=O); MS: m/z = 388 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.52–2.20 (m, 6H, 3×CH_2), 5.2 (t, 2H, methine protons), 6.92–7.25 (m, 8H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 15.2, 15.8, 24.3, 24.5, 26.2, 110.5, 110.0, 114.0, 114.8, 122.3, 122.5, 135.5, 138.8, 155.3, 155.7, 158.2,159.3, 160.2, 162.3, 180.5, 180.8. Anal. Calcd. for $C_{21}H_{16}N_4O_4$: C, 64.94; H, 4.12; N, 14.43. Found: C, 63.10; H, 4.11; N, 14.01.

1,5-Dimethyl-1,5-bis(2,4-dioxo-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-3-ylidene) pentane (7b). It was obtained from heptane-2,6-dione (2.56 g, 0.02 mole) and **3** (1.62 g, 0.01 mole); m.p. 80–82°C; yield 70%; IR (KBr) ν/cm^{-1}: 1300–1320 (C—N), 1620 (C=N), 1705 (C=O); MS: m/z = 416 (M^+);^{1}H NMR(200 MHz, $CDCl_3$): δ(ppm) = 1.40–2.32 (m, 6H, 3×CH_2), 2.32 (s, 6H, 2×CH_3), 6.68–7.20 (m, 8H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 14.2, 14.4, 22.2, 30.4, 30.6, 110.8, 114.8, 115.2, 120.3, 120.8, 131.3, 131.6, 133.2, 133.8, 160.2, 160.4, 164.0,164.5, 165.2, 166.2, 180.5, 180.9. Anal. Calcd. for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.80; N, 13.46. Found: C, 65.84; H, 4.78; N, 13.10.

6-Aceto-12H-11-methylbenzo [g] pyrido [2,1-b] quinazolin-12-one (8). It was obtained from *o*-acetophenylpropan-2-one (1.76 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 85–87°C; yield 64%; IR (KBr) ν/cm^{-1}: 1300–1315 (C—N), 1620 (C=N), 1705 (C=O); MS: m/z = 302 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 1.80–2.05 (m, 4H, 2 × CH_2), 2.22 (s, 3H, CH_3), 2.50 (s, 3H, $COCH_3$), 5.73 (t, 1H, methine proton), 5.78 (t, 1H, methine proton), 7.42–7.84 (m, 4H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 13.1, 22.1, 110.2, 114.4, 120.6, 122.8, 124.6, 124.9, 125.5, 125.8, 126.5, 128.8, 130.3, 136.7, 140.1, 144.7, 160.4, 161.5, 186.5. Anal. Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.49; H, 4.63; N, 9.27. Found: C, 75.31; H, 4.62; N, 9.19.

3-(1-o-Acetobenzylethylidene)-3,4-dihydro-2H-pyrido[1,2-a] pyrimidine-2,4-dione (9). It was obtained from *o*-acetophenylpropan-2-one (1.76 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 84–86°C; yield 78%; IR (KBr) ν/cm^{-1}: 1300–1338 (C—N), 1585 (C=N), 1680–1710 (C=O); MS: m/z = 320 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 1.70 (s, 3H, CH_3), 2.35 (s, 3H, $COCH_3$), 2.8–3.0 (brs, 2H, CH_2), 6.94–7.28 (m, 7H, ArHs), 8.1 (d, 1H, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): (ppm) = 13.5, 111.1, 115.7, 125.6, 125.8, 126.4, 126.5, 126.8, 129.5, 129.8, 130.1, 130.5, 136.8, 142.1, 147.7, 150.1, 184.4, 190.5, 196.5. Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.25; H, 5.0; N, 8.75. Found: C, 71.18; H, 4.8; N, 8.71.

Procedure for the synthesis of 10. Dissolved 9 (0.01 mole) in 40 mL of hot rectified spirit, added 20 mL 10% ethanolic KOH and refluxed for about 3 h and distilled off the ethanol. The reaction mixture was cooled, acidified with very dilute HCl to the pH 5–6 and set aside for 5–6 h. Colorless crystalline compound was formed, filtered, washed the crystalline product first with water twice and finally with a little cold ethanol and recrystallized from about 100 mL of hot rectified spirit to obtain the product **10**. It was characterized as follows:

12,14-Dihydro-7H-13-methylbenzo [5,6] [8] annuleno [1,2-d] pyrido [1,2-a] pyrimidine-7,14-dione. m.p. 78–80°C; yield 20%; IR (KBr) ν/cm^{-1}: 1300–1310 (C—N), 1625 (Cdsbond]N), 1700 (C=O); MS: m/z = 302 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 2.22 (s, 3H, CH_3), 2.6–2.8 (brs, 2H, CH_2), 6.90–7.25 (m, 8H, ArHs), 7.95 (d, 1H, CH-1); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 15.2, 30.8, 111.5, 119.5, 120.3, 126.7, 126.8, 128.2, 129.2, 132.2, 136.8, 137.4, 138.8, 140.2, 151.6, 156.5, 169.5, 175.5. Anal. Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.49; H, 4.63; N, 9.27. Found: C, 75.38; H, 4.50; N, 9.25.

General procedure for the synthesis of 11–12. Dissolved appropriate 2-aminobenzaldehyde in 40 mL of hot rectified spirit, added a solution of 2,3,4,5-tetrahydropyrido [1,2-*a*] [1,3] diazepine-2,5-dione (0.01 mole) **2** in 25 mL of rectified spirit, and added 0.02 mole of fused sodium acetate. Swirled to mix and set aside for 5–6 h. The reaction mixture was finally refluxed for 3 h. Distilled off the ethanol and added 100 mL of H_2O. Filtered, washed the crystalline product first with water thrice and finally with a little cold ethanol, and recrystallized from about 100 mL of hot rectified spirit to obtain the product **11–12**.

2,3,14,15-Tetramethoxypyrido [1′,2′:1,2] quino [3″,2″:6,7] [1,3] diazepino [4,5-b] quinoline (11a). It was obtained from 4,5-dimethoxy-2-aminobenzaldehyde (6-amino veratraldehyde) (3.62 g, 0.02 mole) and **2** (1.76 g, 0.01 mole); m.p. 230–232°C; yield 52%; IR (KBr) ν/cm^{-1}: 1300–1325 (C—N), 1605 (C=N), 1695 (C=O); MS: m/z = 466 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.72–3.82 (overlappedpeaks, 12H, 4×OCH_3), 6.92–7.25 (m, 10H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 55.2, 55.8, 56.2, 56.3, 103.5, 104.8, 105.5, 106.7, 106.8, 107.5, 110.5, 121.5, 121.8, 123.5, 123.9, 124.0, 130.8, 132.4, 132.7, 136.5, 144.2, 142.3, 145.4, 150.0, 152.2, 160.2, 164.8. Anal. Calcd. for $C_{27}H_{22}N_4O_4$: C, 69.52; H, 4.72; N, 12.01. Found: C, 69.41; H, 4.71; N, 12.0.

2,3;14,15-Bismethylenedioxypyrido[1′,2′:1,2]quino[3″,2″:6,7][1,3]diazepino [4,5-b] quinoline (11b). It was obtained from 4,5-methylenedioxy-2-aminobenzaldehyde(6-aminopiperonal) (3.30 g, 0.02 mole) and **2** (1.76 g, 0.01 mole); m.p. 238–240°C; yield 50%; IR (KBr) ν/cm^{-1}: 1305–1315 (C—N), 1625 (Cdsbond]N), 1690 (C=O); MS: m/z = 434 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 5.95 (s, 2H, CH_2O_2), 6.05 (s, 2H, CH_2O_2), 6.90–7.25 (m, 10H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 90.2, 91.3, 102.1, 105.2, 106.9, 107.4, 108.2, 110.2, 122.1, 123.5, 123.8, 124.2, 130.1, 132.5, 135.4, 135.8, 136.5, 142.2, 145.2, 148.2, 152.5, 153.8, 155.2, 165.4, 166.2. Anal. Calcd. for $C_{25}H_{14}N_4O_4$: C, 69.12; H, 3.22; N, 12.90. Found: C, 69.10; H, 3.20; N, 12.88 .

2,3-Dimethoxypyrido [1′,2′:1,2] [1:3] diazepino [4,5-b] quinolin-12(13H)-one (12a). It was obtained from 4,5-dimethoxy-2-aminobenzaldehyde (6-amino veratraldehyde) (1.81 g, 0.01 mole) and **2** (1.76 g, 0.01 mole); m.p. 151–153°C; yield 56%; IR (KBr) ν/cm^{-1}: 1300–1325 (C—N), 1600 (C=N), 1690 (C=O); MS: m/z = 309 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.65–2.85 (brs, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.9–7.28 (m, 7H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 34.3, 56.3, 56.5, 106.3, 108.0, 111.1, 116.1, 121.9, 124.3, 134.2, 137.4, 144.1, 150.8, 152.8, 164.4, 167.7, 170.8. Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.85; N, 13.59. Found: C, 65.09 ; H, 4.83; N, 13.51.

[1,3]Dioxolo[4,5-g]pyrido [1′,2′:1,2] [1:3] diazepino [4,5-b] quinolin-12(13H)-one (12b). It was obtained from 4,5-methylenedioxy-2-aminobenzaldehyde (6-aminopiperonal) (1.65 g, 0.01 mole) and **2** (1.76 g, 1 mole); m.p. 140–142°C; yield 62%; IR (KBr) ν/cm^{-1}: 1305–1315 (C—N), 1625 (C=N), 1692 (C=O); MS: m/z = 293 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.68–2.83 (brs, 2H, CH_2), 5.9 (s, 2H, CH_2O_2), 6.80–7.25 (m, 7H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 34.5, 91.2, 106.3, 108.2, 110.3, 114.3, 120.8, 123.0, 124.2, 132.3, 134.2, 140.1, 150.2, 152.4, 160.2, 168.8, 170.2. Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.52; H, 3.75; N, 14.33. Found: C, 65.48; H, 3.70; N, 14.01.

General procedure for the synthesis of 1, 13, and 14. Dissolved (0.01 mole) of **2** in 40 mL of hot rectified spirit, added to it a solution of malealdehyde or succinaldehyde or *o*-phthaldehyde (0.01 mole) in 25 mL of rectified spirit, and added 0.02 moles of $(NH_4)_2CO_3$, a few drops of dilute NH_3 and two drops of piperidene. Swirled to mix and set aside for 5–6 h. The reaction mixture was finally refluxed for 3 h, distilled off the ethanol, and added dilute HCl till a pH between 5 and 6 of the reaction was achieved. Filtered, washed the crystalline product first with water twice and finally with a little cold ethanol and recrystallized from about 100 mL of hot rectified spirit to obtain the product **1**, **13**, and **14**.

6H,11H-Pyrido[1,2-b][2,4]benzodiazepine-6,11-dione (1) M.p. 152–154°C; yield 76% and superimposable IR with that of authentic sample obtained through (Scheme 1).

6,8,9,11-Tetrahydropyrido[1,2-b][2,4]benzodiazepine-6,11-dione (13). It was obtained from succinaldehyde (0.86 g, 0.01 mole) and 2 (1.76 g, 0.01 mole); m.p. 140–142°C; yield 75%; IR (KBr) ν/cm^{-1}: 1310–1315 (C—N), 1610–1625 (C=C), 1625 (C=N), 1680–1715 (C=O); MS: m/z = 226 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 1.90–2.10 (m, 4H, 2×CH_2), 6.85–7.85 (m, 6H, ArHs and two methine protons); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 25.6, 26.8, 110.8, 114.8, 124.2, 135.2, 135.7, 137.2, 140.8, 146.2, 160.2, 162.4, 180.2. Anal.Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.86; N, 12.38. Found: C, 69.06; H, 4.85; N, 12.33.

6H,13H-Pyrido[1,2-a]naphtho[2,3-e][1,3]diazepine-6,13-dione (14). It was obtained from *o*-phthaldehyde (1.34 g, 0.01 mole) and **2** (1.76 g, 0.01 mole); m.p. 234–236°C; yield 55%; IR (KBr) ν/cm^{-1}: 1305–1315 (C—N), 1605 (C=N), 1685 (C=O); MS: m/z = 274 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 7.20–8.40 (m, 10H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 110.2, 115.4, 124.3, 128.6, 128.8, 129.0, 129.6, 130.1, 130.2, 132.1, 132.5, 134.0, 134.4, 137.1, 164.2, 164.6, 180.2. Anal. Calcd. for $C_{17}H_{10}N_2O_2$: C, 74.45; H, 3.64; N, 10.21. Found; C, 74.40; H, 3.63; N, 10.18.

General procedure for the synthesis of 15a–15d. A mixture of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine-2,4-dione (3.24 g, 20 mmol) **3** and the aromatic aldehyde (10 mmol) in ethylene glycol (30 mL) in presence of ammonium acetate (20 mmol) was heated at 140°C for about 4–5 h and then cooled to room temperature. The reaction mixture was poured into 300 mL water. The solid was filtered and then washed with water twice to remove excess of ammonium acetate. The crude solid was crystallized from 80–85% EtOH.

6,13,14,15-Tetrahydro-14-(4-methoxyphenyl)dipyrido[1,2-a:1′, 2′-a′] pyrido[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (15a). It was obtained from **3** (1.62 g, 10 mmole) and *p*-anisaldehyde (0.60 mL, 5 mmol); m.p. 244–246°C; yield 76%; IR (KBr) ν/cm^{-1}: 1320–1330 (C—N), 1590 (C=N), 1670 (C=O), 3280 (NH); MS: m/z = 423 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 3.71 (s, 3H, OCH_3), 5.18 (s, 1H,6-CH), 6.92–7.23 (m, 12H, ArHs), 9.26 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.4, 50.8, 54.3, 56.2, 62.4, 108.4, 110.5, 114.2, 114.3, 115.2, 115.7, 124.2, 124.3, 128.3, 128.5, 130.1, 135.5, 136.5, 152.4, 128.8, 162.5, 165.0, 166.2, 168.5. Anal. Calcd. for $C_{24}H_{17}N_5O_3$: C, 68.08; H, 4.01; N, 16.54. Found: C, 67.10; H, 4.0; N, 16.10.

6,13,14,15-Tetrahydro-14-(4-methylphenyl)dipyrido[1,2-a:1′, 2′-a′] pyrido[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (15b). It was obtained from **3** (1.62 g, 10 mmole) and *p*-tolualdehyde (0.58 ml, 5 mmol); m.p. 238–240°C; yield 77%; IR (KBr) ν/cm^{-1}: 1305–1315 (C—N), 1662 (C=N), 1670 (C=O), 3240 (NH); MS: m/z = 407 (M^+); ^{1}H NMR (200 MHz,$CDCl_3$): δ (ppm) = 2.30 (s, 3H, CH_3), 5.20 (s, 1H, 6-CH), 6.90–7.20 (m, 12H, ArHs), 9.01 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 20.2, 24.3, 50.2, 64.3, 106.8, 110.2, 111.0, 115.2, 115.8, 124.1, 124.3, 128.2, 128.4, 129.5, 129.7, 135.0, 135.5, 137.2, 137.8, 150.8, 160.2, 160.4, 162.5, 168.8. Anal. Calcd. for $C_{24}H_{17}N_5O_2$: C, 70.76; H, 4.17; N, 17.19. Found: C, 69.58; H, 4.09 ; N, 17.12.

6,13,14,15-Tetrahydro-14-(3,4-dimethoxyphenyl)dipyrido[1, 2-a:1′,2′-a′] pyrido[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (15c). It was obtained from 3 (1.62 g, 10 mmole) and veratraldehyde (0.83 g, 5 mmol); m.p.244–246°C; yield 83%; IR (KBr) ν/cm^{-1}:1320–1330 (C—N), 1590 (C=N), 1670 (C=O), 3410 (NH); MS: m/z = 453 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.90 (s, 1H, 6-CH), 6.9–7.21 (m, 11H, ArHs), 9.56 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.3, 50.8, 56.2, 56.5, 64.2, 108.1, 110.1, 111.3, 114.8, 115.3, 116.8, 120.1, 122.3, 122.5, 132.1, 135.6, 142.8, 147.5, 150.2, 155.8, 160.5, 162.4, 164.0, 164.2, 170.2. Anal. Calcd. for $C_{25}H_{19}N_5O_4$: C, 66.22; H, 4.19; N, 15.45. Found: C, 65.90; H, 4.17; N, 15.12.

6,13,14,15-Tetrahydro-14-[1,3]benzodioxol-5yldipyrido[1,2-a:1′,2′-a′] pyrido[2″,3″-d:6″,5″-d′] dipyrimidine-13,15-dione (15d). It was obtained from **3** (1.62 g, 10 mmole) and piperonal (0.75 mL, 5 mmol); m.p. 238–240°C; yield 75%; IR (KBr) ν/cm^{-1}: 1315–1325 (C—N), 1615 (C=N), 1670 (C=O), 3410 (NH); MS: m/z = 437 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.89 (s, 1H, 6-CH), 6.10 (s, 2H, CH_2O_2), 6.90–7.25 (m, 11H, ArHs), 9.28 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.2, 50.8, 56.4, 64.2, 90.2, 107.2, 110.1, 111.3, 114.7, 115.1, 116.2, 116.8, 120.2, 122.3, 122.5, 132.1, 135.5, 140.2, 147.2, 152.2, 160.2, 160.5, 163.5, 168.8. Anal. Calcd. for $C_{24}H_{15}N_5O_4$: C, 65.90; H, 3.43; N, 16.01. Found: C, 64.70; H, 3.41; N, 15.85.

General procedure for the synthesis of 16a–16d. A mixture of 3, 4-dihydro-2*H*-pyrido [1,2-*a*] pyrimidine-2,4-dione (3.24 g, 20 mmol) 3 and the aromatic aldehyde (10 mmol) in ethylene glycol (30 mL) in presence of P_2O_5 (20 mmol) was heated at 140°C for about 4–5 h and then cooled to room temperature. The reaction mixture was poured into 300 mL water cautiously and slowly. The solid formed was filtered and, then washed with water twice to remove excess of adhered materials. The crude solid was recrystallized from 80–85% EtOH.

14,15-Dihydro-13H-14-(4-methoxyphenyl)dipyrido[1,2-a:1′, 2′-a′] pyrano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (16a). It was obtained from 3 (1.62 g, 10 mmole) and anisaldehyde

(0.60 mL, 5 mmol); m.p. 270–272°C; yield 69%; IR (KBr) ν/cm^{-1}: 1315–1330 (C—N), 1595 (C=N), 1675 (C=O); MS: m/z = 424 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 3.70 (s, 3H, OCH_3), 4.63 (s, 1H, 6-CH), 6.92–7.32 (m, 12H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 23.7, 54.1, 56.7, 77.7, 90.5, 110.5, 111.1, 114.3, 114.7, 115.2, 115.5, 124.1, 124.2, 128.3, 128.5, 134.7, 135.1, 136.1, 136.4, 160.2, 162.1, 163.4, 164.2, 168.3. Anal. Calcd. for $C_{24}H_{16}N_4O_4$: C, 67.92; H, 3.77; N, 13.20. Found: C, 67.96; H, 3.76; N, 13.17.

14,15-Dihydro-13H-14-(4-methylphenyl)dipyrido[1,2-a:1′,2′-a′]pyrano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (16b). It was obtained from **3** (1.62 g, 10 mmole) and *p*-tolualdehyde (0.58 mL, 5 mmol); m.p. 264–266°C; yield 66%; IR (KBr) ν/cm^{-1}: 1300–1310 (C—N), 1598 (C=N), 1675 (C=O); MS: m/z = 408 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.30 (s, 3H, CH_3), 4.93 (s, 1H, 6-CH), 6.72–7.41 (m, 12H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 20.2, 23.3, 50.5, 77.2, 90.2, 110.2, 111.0, 114.5, 114.9, 124.2, 124.7, 128.1, 128.5, 129.5, 129.5, 134.8, 135.2, 136.2, 136.5, 160.1, 162.2, 163.5, 164.0, 168.2. Anal. Calcd. for $C_{24}H_{16}N_4O_3$: C, 70.58; H, 3.92; N, 13.72. Found: C, 70.55; H, 3.91; N, 13.78.

14,15-Dihydro-13H-14-(3,4-dimethoxyphenyl)dipyrido[1,2-a:1′,2′-a′] pyrano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (16c). It was obtained from **3** (1.62 g, 10 mmol) and veratraldehyde (0.83 g, 5 mmol); m.p. 280–282°C; yield 70%; IR (KBr) ν/cm^{-1}: 1320–1330 (C—N), 1620 (C=N), 1675 (C=O); MS: m/z = 454(M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm) = 3.72 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.70 (s, 1H, 6-CH), 6.90-7.25 (m, 11H,ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 27.1, 52.0, 52.3, 55.4, 74.6, 94.6, 95.2, 98.9, 110.1, 110.4, 115.8, 115.9, 120.8, 122.3, 122.8, 136.5, 137.1, 154.1, 157.1, 159.1, 160.5, 163.1, 164.0, 164.2, 175.6. Anal. Calcd. for $C_{25}H_{18}N_4O_5$: C, 66.12; H, 4.21; N, 11.00. Found: C, 65.22; H, 4.19; N, 10.6.

14,15-Dihydro-13H-14-dipyrido[1,2-a:1′,2′-a′]pyrano[2″,3″-d:6″,5″-d′] dipyrimidine-13,15-dione (16d). It was obtained from **3** (1.62 g, 10 mmol) and piperonal (0.75 mL, 5 mmol); m.p. 245–247°C; yield 64%; IR (KBr) ν/cm^{-1}: 1310–1320 (C—N), 1620 (C=N), 1675 (C=0); MS: m/z = 438 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ(ppm)= 5.52 (s, 1H, 6-CH), 5.98 (s, 2H, CH_2O_2), 7.01–7.80 (m, 11H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 22.4, 50.5, 77.2, 90.3, 95.5, 110.1, 110.3, 114.8, 115.1, 115.5, 115.8, 120.8, 124.1, 124.3, 130.2, 135.5, 135.7, 142.5, 144.3, 160.5, 160.8, 164.2, 165.2, 170.0. Anal. Calcd.for $C_{24}H_{14}N_4O_5$: C, 65.75; H, 3.19; N, 12.78. Found: C, 65.12; H, 3.18; N, 12.52.

General procedure for the synthesis of 17a–17d. A mixture of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine-2,4-dione(3.24 g, 20 mmol) **3** and the aromatic aldehyde (10 mmol) in ethylene glycol (30 mL) in presence of P_2S_5 (20 mmol) was heated at 140°C for about 4–5 h and then cooled to room temperature. The reaction mixture was poured into 300 mL of water. The solid was filtered and then washed with water twice to remove excess of P_2S_5. The crude solid was crystallized from 80–85% EtOH.

14,15-Dihydro-13H-14-(4-methoxyphenyl)dipyrido[1,2-a:1′,2′-a′] thiopyarano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (17a). It was obtained from **3** (1.62 g, 10 mmol) and *p*-anisaldehyde (0.60 mL, 5 mmol); m.p. 240–242°C; yield 62%; IR (KBr) ν/cm^{-1}: 1168 (C—S), 1320–1330 (C—N), 1590 (C=N), 1678 (C=O); MS: m/z = 408 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.72 (s, 3H, OCH_3), 4.64 (s, 1H, 6-CH), 7.01–7.20 (m, 12H, ArHs); ^{13}C–NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.5, 52.1, 54.3, 56.2, 110.5, 110.8, 114.1, 114.5, 115.5, 115.8, 118.2, 124.1, 124.3, 128.2, 128.5, 130.2, 135.5, 135.7, 154.0, 158.2, 160.0, 160.2, 162.1, 168.5. Anal. Calcd. for $C_{24}H_{16}N_4O_3S$: C, 70.58; H, 3.92; N, 13.72; S, 7.84. Found: C, 70.55; H, 3.91; N, 13.6; S, 7.67.

14,15-Dihydro-13H-14-(4-methylphenyl)dipyrido[1,2-a:1′,2′-a′] thiopyarano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (17b). It was obtained from 3 (1.62 g, 10 mmol) and *p*-tolualdehyde (0.58 mL, 5 mmol); m.p. 252–254°C; yield 66%; IR (KBr) ν/cm^{-1}: 1185 (C—S), 1305–1315 (C—N), 1630 (C=N), 1678 (C=O); MS: m/z = 424 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.32 (s, 3H, CH_3), 5.50 (s, 1H, 6-CH), 6.90–7.30 (m, 12H, ArHs); ^{13}C NMR (50 MHZ, $CDCl_3$): δ (ppm) = 20.2, 25.3, 52.0, 54.1, 111.0, 111.2, 114.3, 114.5, 115.1, 115.3, 118.3, 124.3, 124.5, 128.1, 128.3, 130.1, 135.3, 135.5, 154.2, 158.1, 160.1, 160.3, 162.3, 169.3. Anal. Calcd. for $C_{24}H_{16}N_4O_2S$: C, 67.92; H, 3.77; N, 13.20; S, 7.54. Found: C, 66.81; H, 3.76; N, 12.80; S, 7.16

14,15-Dihydro-13H-14-(3,4-dimethoxyphenyl)dipyrido[1,2-a:1′,2′-a′] thiopyarano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (17c). It was obtained from **3** (1.62 g,10 mmol) and veratraldehyde (0.83 g, 5 mmol); m.p. 260–262°C; yield 76%; IR (KBr) ν/cm^{-1}: 1180 (C—S), 1320–1330 (C—N), 1595 (C=N), 1678 (C=O); MS: m/z = 470 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.74 (s, 1H, 6-CH), 6.70–7.20 (m, 11H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.4, 50.4, 56.1, 56.4, 64.4, 108.0, 110.0, 111.2, 114.5, 115.1, 115.5, 116.7, 120.0, 122.7, 132.0, 134.3, 135.5, 142.7,147.3, 150.2, 155.4, 160.5, 162.4, 164.0, 170.5. Anal. Calcd. for $C_{25}H_{18}N_4O_4S$: C, 63.82; H, 3.82; N, 11.90; S, 6.80. Found: C, 62.80; H, 3.81; N, 11.10; S, 5.90.

14,15-Dihydro-13H-14-[1,3]benzodioxol-5yldipyrido[1,2-a:1′,2′-a′] thiopyarano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (17d). It was obtained from 3 (1.62 g, 10 mmol) and piperonal (0.75 mL, 5 mmol); m.p. 250–252°C; yield 72%; IR (KBr) ν/cm^{-1}: 1178 (C—S), 1310–1330 (C—N), 1625 (C=N), 1678 (C=O); MS: m/z = 454 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.74 (s, 1H, 6-CH), 6.05 (s, 2H, CH_2O_2), 7.10–7.30 (m, 11H, ArHs); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.3, 50.7, 64.1, 90.1, 107.1, 110.2, 111.2, 115.0, 115.5, 116.1, 116.6, 120.1, 122.2, 122.4, 132.0, 135.4, 140.1, 147.3, 152.3, 160.3, 160.3, 163.4, 164.3, 170.2. Anal. Calcd. for $C_{24}H_{14}N_4O_4S$: C, 63.43; H, 3.08; N, 12.33; S, 7.04. Found: C, 62.13; H, 2.82; N, 12.12; S, 6.20.

Acknowledgments. The authors are thankful to the Department of Chemistry, University of Jammu, Jammu and IIIM Jammu for providing research and library facilities.

REFERENCES AND NOTES

[1] Posha, M. A.; Jayashankara, V. P. Indian J Heterocycl Chem 2006, 15, 397.

[2] Fryer, R. I. In Bicyclic Diazepines in the Chemistry of Heterocyclic Compounds; Taylor, E., Ed.; Wiley: New York, 1991; Vol. 50, Chapter II.

[3] Haris, R. C.; Straley, J. M. U.S. Pat. 1,537,757; Chem Abstr 1970, 173, 100054 w.

[4] Guerreo, F. A.; Blanco, C.; Guevara, U.; Martinez, R. J.; Campo, A. E. Proc West Pharmacol Soc 1992, 35, 153.

[5] Remers, W. A.; Mabilia, M.; Hopfinger, A. J. J Med Chem 1986, 29, 2492.

[6] Pellon, P. F.; Carrasco, R.; Rodes, L. Synth Commun 1996, 26, 3869.

[7] Murugan, V.; Padmavathy, N. P.; Ramasarma, G. V. S.; Sharma, S. V.; Suresh, V. Indian J Chem 2003, 13, 143.

[8] Brown, D. J. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 148.

[9] Gupta, D. P.; Ahmad, S. A.; Shankar, K. Indian J Chem 1988, 27B, 106.

[10] Parmar, S. S.; Singh, S. P. J Heterocycl Chem 1979, 16, 448.

[11] Ram, V. J.; Srimal, R. C.; Kuschwaha, D. S.; Mishra, L. J Prakt Chem 1990, 332, 629.

[12] Srivastava, V. K.; Singh, S.; Gulati, A.; Shankar, H. Indian J Chem 1987, 26B, 652.

[13] Pandey, V. K.; Gupta, M.; Mishra, D. Indian Drugs 1996, 33, 409.

[14] Umio, S.; Kariyone, K.; Zenno, H.; Kamiya, T. Jpn. Pat. 12,670 (1970); Chem Abstr 1968, 68, 2195.

[15] Shetty, B. V. U.S. Pat. 2,549,634 (1970); Chem Abstr 1971, 75, 5940.

[16] Otto, H.; Houlohan, W. W. Swiss Pat. 499,544 (1971); Chem Abstr 1971, 75, 20435.

[17] Saksena, R. K.; Amin Khan, M. Indian J Chem 1989, 28B, 443.

[18] Mukerji, M. L.; Nautiyal, S. R.; Prasad, C. R.; Dhwan, B. N. Indian J Med Res 1980, 71, 480.

[19] Malhotra, S.; Koul, S. K.; Sharma, R. L.; Anand, K. K.; Gupta, O. P.; Dhar, K. L. Indian J Chem 1988, 27, 937.

[20] Gupta, O. P.; Sharma, M. L.; Ray Ghatak, B. J.; Atal, C. K. Indian J Med Res 1977, 66, 680.

[21] Gupta, O. P.; Sharma, M. L.; Ray Ghatak, B. J.; Atal, C. K. Indian J Med Res 1977, 66, 865.

[22] Gupta, O. P.; Wakhloo, R. L.; Sharma, M. L.; Atal, C. K. J Obstet Gynaecol India 1979, 29, 935.

[23] Atal, C. K. A Text Book of Chemistry and Pharmacology of Vasicine; Regional Research Laboratory: Jammu, 1980; pp 1–155.

[24] Holla, B. S.; Poojary, K. N.; Poojary, B.; Subramanaya, K.; Suchetha, N. Indian J Chem 2005, 44, 2114.

[25] Smith, R. L.; Barret, R. J.; Bush, E. S. J Pharmacol Exp Ther 1995, 275, 1050.

[26] (a) Awouters, F.; Vermeire, J.; Smeyers, F.; Vermote, P.; Vanbeek, R.; Niemegeers, C. J. E. Drug Dev Res 1986, 8, 95; (b) Hermeez, I.; Breining, T.; Debreczy, L. V.;Rodriguer. L. J Med Chem 1983, 26, 1494.

[27] Matsutani, S.; Mizushima, Y. Eur. Pat. Appl. 89-102635 (1989).

[28] Yanagihara, Y.; Kassai, H.; Kawashima, T.; Shida, T. Jpn J Pharmacol 1988, 48, 91.

[29] Hermeez, I.; Kokosi, J.; de Vos, C.; Rodriguez, L. J Med Chem 1987, 30, 1543.

[30] Knoll, K.; Meszaros, Z.; Szentmiklosi, P.; Furst, S. Arzneim Forsch 1971, 21, 717.

[31] (a) Roma, G.; Cinone, N.; Dibraceio, M.; Grossi, G.; Leoncini, G.; Signorello, M. G.; Carotti, A. Bio Org Med Chem 2000, 8, 751; (b) Leoncini, G.; Signorello, M. G.; Roma, G.; Di Braccio, M. Biochem Pharmacol 1997, 53, 1667.

[32] Abass, M.; Mayas, A;, S. Heteroatom Chem 2007, 18, 19.

[33] Lappin, G. R.; Petersen, Q. R.; Wheeler, C. E. J Org Chem 1950, 15, 377.

[34] Shur, M.; Israeltam, S. S. J Org Chem 1968, 33, 3015.

[35] Roma, G.; Di Braccio, M.; Babli, A.; Mazzei, M.; Ermili, A. J Heterocycl Chem 1987, 24, 329.

[36] Sharma, R. L.; Kumar, S.; Kour, D.; Singh, J. J Heterocycl Chem 2006, 43, 1177.

[37] Sachar, A.; Gupta, P.; Gupta, S.; Sharma, R. L. Indian J Chem 2009, 48B, 1187.

[38] Wooley, R. E.; Blue, J. L. J Med Microbiol 1975, 8, 189.

[39] Castillow, J. C.; Debeer, E. J. J Pharm Exp Ther 1947, 90, 104.

[40] Kobayshi, S.; Hasebawa, K.; Muri, M.; Takagi, H. Arzneim Forech Drug Res 1970, 20, 43.