Indian Journal of Chemistry
Vol. 48B, May 2009, pp. 697-704

Synthesis and antimicrobial evaluation of some alkoxyphthalimide derivatives of naphthyridine

Dinesh Bhambi, Vijay Kumar Salvi, Archita Bapna, Gangotri Pemawat & G L Talesara*

Synthetic Organic Chemistry Laboratory, Department of Chemistry, M. L. Sukhadia University, Udaipur 313 001, India

E-mail: gtalesara@yahoo.com

Received 8 July 2008; accepted (revised) 5 January 2009

5-(4-Substitutedphenyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-7*H*-one **1a-e** have been converted to their *N*-substituted alkoxyphthalimide derivatives using two alternative pathways. In route one, **1a-e** are treated with formalin (37%) to yield 5-(4-substitutedphenyl)-10-(hydroxymethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one **2a-e**, which is further changed to corresponding chloro derivatives **3a-e** by the treatment with thionyl chloride. Condensation of **3a-e** with *N*-hydroxyphthalimide furnished the final compounds 2-{[5-(4-substitutedphenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridin-10-5*H*-yl]methoxy}phthalimide **4a-e**. In another route, **1a-e** is directly condensed with ω-bromoalkoxyphthalimide to yield higher homologues of **4a-e** *i. e.* 2-{2-[5-(4-substituted phenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridin-10-5*H*-yl]ethoxy} phthalimide derivatives **5a-e**. Structures of all the synthesized compounds have been established on the basis of elemental analysis and spectral studies. All the synthesized compounds have been screened for antibacterial and antifungal activities.

Keywords: Naphthyridine, ω-bromoalkoxyphthalimide, multicomponent condensation, antimicrobial activity, *N*-hydroxyphthalimide

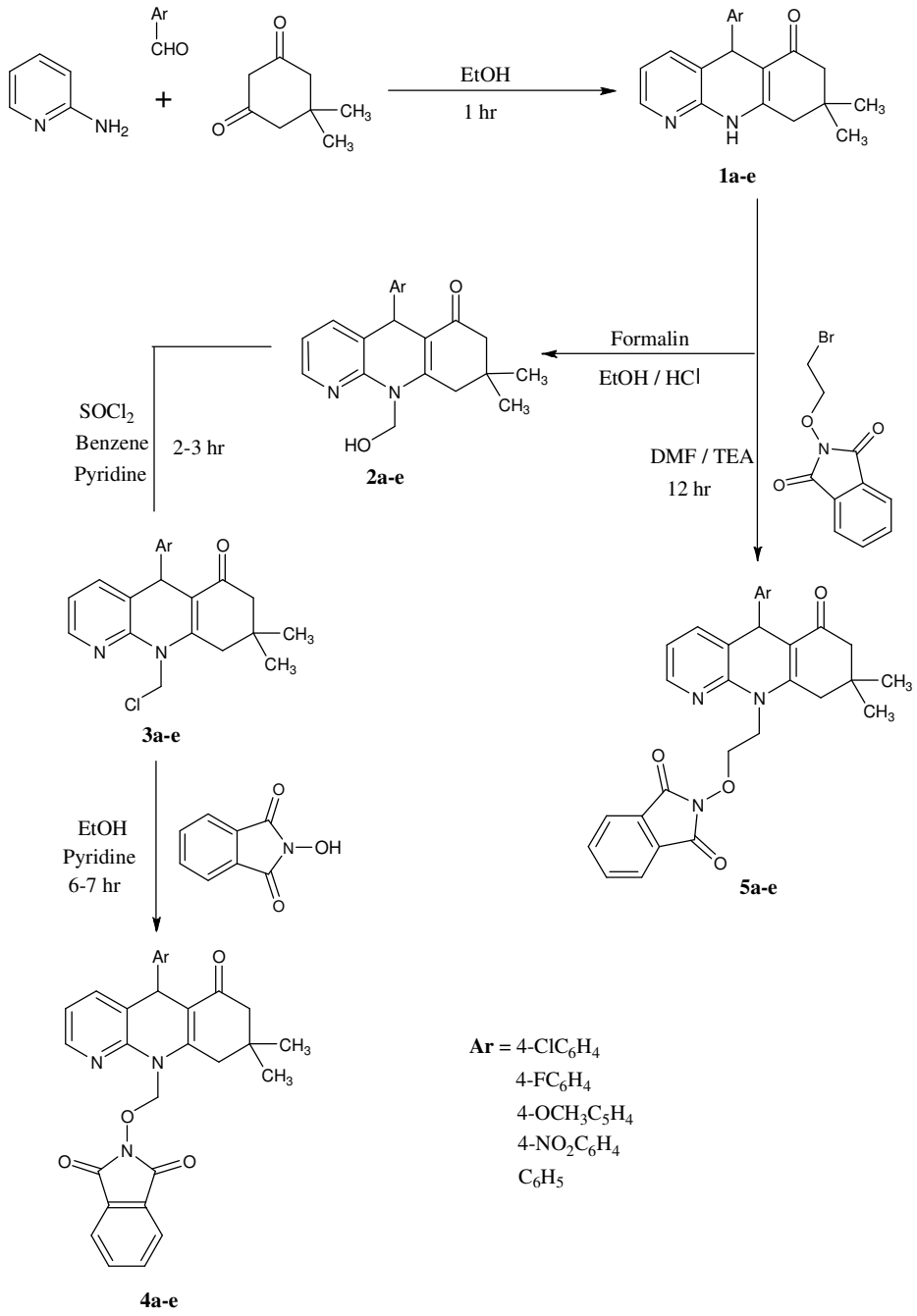
Naphthyridine derivatives have been reported to possess antibacterial[1], antimicobacterial[2], anti-tumoral[3], anti-inflammatory[4,5], antiplatelet[6] , gastric antisecretary[7], antiallergic[8] , local anaesthetic[9] and benzodiazepine receptor activities[10]. 1,8-Naphthyridine derivatives are also reportedly associated with positive ionotropic[11], β-adrenergic blocking[12] and antihypertensive[13] activities. A series of naphthyridine carboxamide attached to triazole have been synthesized, found to possess anti-inflammatory activity[14] and its analogues have been found to be very useful intermediate for the synthesis of molecular building blockes[15-21]. Antimalarial[22], antihypertensive[23], antimicrobial[24] and HIV-I inhibitor[25] activities are reported in the literature for 1,8-naphthyridine derivatives. 2-Fluronaphthyridine containing ketolides have been assayed[26] for inhibition of protein synthesis. Effect on topoisomerase targeting activity and cytotoxicity has been studied[27] by Singh *et al.* on nitro and amino substituted dibenzonaphthyridine-6-ones.

Alkoxyphthalimide derivatives are used as potent anticonvulsant[28], diuretic[29], fungicidal[30] and trypanocidal[31] agents. These have ability to inhibit growth of malarial parasite *Plasmodium falsiparum*[32].

Earlier work on the synthesis of alkoxyphthalimide derivative of various heterocycles has been very useful to achieve enhanced biological activity[33,34] of particular molecule. In the present investigation the derivatives of naphthyridines have been prepared and evaluated for their bioactivity.

Result and Discussion

The Synthetic route for obtaining the final products is presented in **Scheme I**. The cyclocondensation of 2-amino pyridine with dimedone and substituted aromatic aldehydes yielded 5-(4-substitutedphenyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one **1a-e**. The structure of the compounds **1a-e** was assigned on the basis of their spectral and analytical data. In addition, to the characteristic NH band in the region 3214 cm^{-1}, the IR spectra of the compound **1a** revealed C=O and C=N absorption band in the region of 1690 and 1634 cm^{-1} respectively. ^1H NMR spectra of all compounds exhibited two characteristic singlet of NH and CH proton. Further 5-(4-substitutedphenyl)-10-(hydroxylmethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one **2a-e** were obtained from tetrahydronapthyridine **1a-e** and formalin *via* condensation reaction.



Scheme I

Disappearance of sharp absorption band NH and appearance of broad band at 3407 cm^{-1} for OH group were obtained in IR spectra. The ^1H NMR spectra of compound **2a** revealed the absence of NH proton and the presence of two new singlets at δ 4.51 and 3.93 of CH_2 and OH group respectively. Hydroxynaphthyridine **2a-e** were further converted into their chloride derivatives 5-(4-substitutedphenyl)-10-(chloromethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one **3a-e** by reaction with thionylchloride. Formation of the product was confirmed by the disappearance of characteristic OH signals in IR and ^1H NMR spectra. Subsequently, the chlorine atom in N-CH_2-Cl was replaced by the phthalimidoxy group to give 2-{[5-(4-substituted-phenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo-[*b*][1,8]naphthyridin-10-5*H*-yl]methoxy}phthalimide **4a-e**. Stretching of CO-N-CO around 1725 cm^{-1}

confirming the presence of imidoxy moiety in **4a**, this was further supported by molecular ion peak in the mass spectrum.

In order to synthesize 2-{2-[5-(4-substitutedphenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*]-[1,8]naphthyridin-10-5*H*-yl]ethoxy}phthalimide derivatives **5a-e,** tetrahydronaphthyridines **1a-e** were treated with phthalimidoxyethyl bromide in the presence of DMF/TEA. Disappearance of sharp NH band in the IR spectrum and presence of two triplets at δ 4.45 and 3.52 for OCH_2 and NCH_2 respectively in ^{1}H NMR spectrum confirmed the formation of final compound **5a**. Physical and analytical data of synthesized compounds are summarized in **Table I**.

Antimicrobial Activity

Ten compounds have been tested for their biological activity against four bacteria and two fungi using 50 µg/mL concentration in DMF by cup and well method[35,36]. The micro-organisms used as antibacterial are *Proteus mirabilis*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Escherichia coli* and *Candida albicans* and *Aspergillus fumigatus* as fungal strains. The activity is presented as zone of inhibition in mm and compared with activity of controls C_1 and C_2 (for antibacterial activity C_1=ciprofloxacin, C_2=roxithromycin and for antifungal activity C_1= amphotericin and C_2= flucanazole) to gave activity index value.

From the data presented in **Table II**, it is clear that majority of the compounds show moderate to strong activity as compared to the standard drug. These compounds show better activity on *E. coli*, *B. subtilis* as antibacterial and on both the pathogenic fungal strains. Compound **4d**, **5d** and **5e** show weak inhibition whereas **4b** and **5b** show strong activity in general. All the compounds except **5e** show good activity against *C. albicans*. Antifungal activity against *A. fumigatus* is stronger then standard for all the compounds. Conclusively, these compounds show weak antibacterial but strong antifungal agents.

Experimental Section

Melting points of all synthesized compounds were determined in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 1300 FT IR spectrometer and ^{1}H NMR spectra were recorded on a Bruker WM-400 (400 MHz FT NMR) spectrometer using TMS as internal standard. Mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer. All compounds gave satisfactory micro analytical results. Homogeneity of the synthesized compounds was checked by TLC using silica gel-G plates, *n*-hexane-ethyl acetate as developing solvent and the spots were visualized using iodine vapor. *N*-Hydroxyphthalimide[37], phthalimidoxy ethyl bromide[38] were prepared by reported methods.

Synthesis of 5-(4-substitutedphenyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one, 1a

A solution of 2-aminopyridine (0.01 mole), dimedone (0.01 mole) and aromatic aldehydes (0.01 mole) in absolute ethanol (20 mL) was refluxed for 1 hr. The product was separated by cooling followed by filtration, washing with ethanol, drying and purified by recrystallization from absolute ethanol.

IR (KBr): 3214 (N-H str.), 3054 (C-H str., Ar-H), 2953 (C-H str., CH_3), 1690 (C=O str.), 1634 (C=N str.), 749 cm^{-1} (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ 9.59 (s, 1H, NH), 7.88-7.26 (m, 7H, ArH), 5.31 (d, 1H, CH, *J* = 6.7 Hz), 2.51 (s, 2H, =C-CH_2), 2.20 (s, 2H, CH_2-CO), 1.09 (s, 6H, CH_3).

Similarly, other compounds **1b-e** were also been synthesized. Their characterization spectral data are given below:

5 - (4 - Florophenyl) - 8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one, 1b

IR (KBr): 3204 (N-H str.), 3062 (C-H str., Ar-H), 2958 (C-H str., CH_3),1684 (C=O str.), 1625 (C=N str.), 1172 cm^{-1} (C-F str.); ^{1}H NMR ($CDCl_3$): δ 9.52 (s, 1H, NH), 7.75-7.14 (m, 7H, ArH), 5.32 (d, 1H, CH, *J* = 6.9 Hz), 2.53 (s, 2H, =C-CH_2), 2.02 (s, 2H, CH_2-CO), 1.03 (s, 6H, CH_3).

5-(4-Methoxyphenyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one, 1c

IR (KBr): 3221 (N-H str.), 3059 (C-H str., Ar-H), 2949 (C-H str., CH_3), 1687 (C=O str.), 1622 (C=N str.), 1092 cm^{-1} (C-O str.); ^{1}H NMR ($CDCl_3$): δ 9.49 (s, 1H, NH), 7.80-7.19 (m, 7H, ArH), 5.29 (d, 1H, CH, *J* = 6.4 Hz), 3.92 (s, 3H, OCH_3), 2.50 (s, 2H, =C-CH_2), 2.15 (s, 2H, CH_2-CO), 1.12 (s, 6H, CH_3).

5-(4-Nitrophenyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one, 1d

IR (KBr): 3229 (N-H str.), 3050 (C-H str., Ar-H), 2951 (C-H str., CH_3), 1679 (C=O str.), 1622 (C=N

Table I —-Physical and analytical characterization data of compounds **1a-e**, **2a-e**, **3a-e**, **4a-e** and **5a-e**

Compd	Mol. formula	Mol. Wt.	Ar	Yield (%)	m.p. °C	Found (Calcd) % N
1a	$C_{20}H_{19}ClN_2O$	338.50	4-ClC_6H_4	80	205	8.17 (8.27)
1b	$C_{20}H_{19}ClN_2O$	322	4-FC_6H_4	73	178	8.57 (8.69)
1c	$C_{21}H_{22}N_2O_2$	334	4-$OCH_3C_6H_4$	69	192	8.34 (8.38)
1d	$C_{20}H_{19}N_2O$	349	4-$NO_2C_6H_4$	64	220	11.92 (12.03)
1e	$C_{20}H_{20}N_2O$	304	C_6H_5	71	210	9.11 (9.21)
2a	$C_{21}H_{21}ClN_2O_2$	368	4-ClC_6H_4	76	142	7.51 (7.59)
2b	$C_{21}H_{21}FN_2O_2$	352	4-FC_6H_4	70	122	7.84 (7.95)
2c	$C_{22}H_{24}N_2O_3$	364	4-$OCH_3C_6H_4$	62	115	7.58 (7.69)
2d	$C_{21}H_{21}N_3O_4$	379	4-$NO_2C_6H_4$	58	164	11.01 (11.08)
2e	$C_{21}H_{22}N_2O_2$	334	C_6H_5	68	105	8.29 (8.38)
3a	$C_{21}H_{20}Cl_2N_2O$	387	4-ClC_6H_4	67	129	7.17 (7.23)
3b	$C_{21}H_{20}ClFN_2O$	370	4-FC_6H_4	62	115	7.51 (7.55)
3c	$C_{22}H_{23}ClN_2O_2$	382	4-$OCH_3C_6H_4$	58	108	7.27 (7.32)
3d	$C_{21}H_{20}ClN_3O_3$	397	4-$NO_2C_6H_4$	53	136	10.47 (10.56)
3e	$C_{21}H_{21}ClN_2O$	352	C_6H_5	60	101	7.88 (7.94)
4a	$C_{29}H_{24}ClN_3O_4$	513	4-ClC_6H_4	61	129	8.04 (8.17)
4b	$C_{29}H_{24}FN_3O_4$	497	4-FC_6H_4	56	115	8.39 (8.45)
4c	$C_{18}H_{15}N_5O$	509	4-$OCH_3C_6H_4$	54	108	8.18 (8.25)
4d	$C_{19}H_{18}N_6$	524	4-$NO_2C_6H_4$	51	136	10.58 (10.68)
4e	$C_{17}H_{12}N_6O_2$	479	C_6H_5	58	102	8.69 (8.76)
5a	$C_{30}H_{26}ClN_3O_4$	527.50	4-ClC_6H_4	62	141	7.91 (7.96)
5b	$C_{30}H_{26}FN_3O_4$	511	4-FC_6H_4	57	132	8.14 (8.21)
5c	$C_{31}H_{29}N_3O_5$	523	4-$OCH_3C_6H_4$	64	114	7.93 (8.03)
5d	$C_{30}H_{26}N_4O_6$	538	4-$NO_2C_6H_4$	52	157	10.32 (10.40)
5e	$C_{30}H_{27}N_3O_4$	493	C_6H_5	59	111	8.44 (8.51)

Table II — Antimicrobial activity of the synthesized compounds **4a-e** and **5a-e**.

Compd. No.	Antibacterial Activity				Antifungal Activity	
	Proteus mirabilis	*Klebsiella pneumoniae*	*Escherichia coli*	*Bacillus subtilis*	*Candida albicans*	*Aspergillus fumigatus*
4a	9	NA	15	13	13	6
4b	12	4	12	7	11	8
4c	9	3	10	8	10	7
4d	7	5	8	6	7	4
4e	9	10	7	11	10	11
5a	10	11	9	12	9	12
5b	12	9	11	10	11	10
5c	11	7	12	12	13	11
5d	8	NA	14	9	11	9
5c	6	9	10	10	NA	7
C_1	14	12	12	11	12	6
C_2	10	6	10	6	6	3

Zone of inhibition (mm) (activity index)$^{std.}$
(Activity index) = Inhibition zone of compound/Inhibition zone of the standard drug.
For antibacterial activity: C_1 = ciprofloxacin, C_2 = roxithromycin
For antifungal activity: C_1 = amphotericin B, C_2 = flucanazole
NA = Nil activity

str.), 1542, 1349 cm^{-1} (NO_2 str.); ^1H NMR ($CDCl_3$): δ 9.59 (s, 1H, NH), 7.83-7.29 (m, 7H, ArH), 5.31 (d, 1H, CH, *J* = 6.6 Hz), 2.47 (s, 2H, =C-CH_2), 2.07 (s, 2H, CH_2-CO), 1.11 (s, 6H, CH_3).

5-(4-Phenyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one, 1e

IR (KBr): 3210 (N-H str.), 3060 (C-H str., Ar-H), 2948 (C-H str., CH_3), 1676 (C=O str.), 1621 cm^{-1} (C=N str.); ^1H NMR ($CDCl_3$): δ 9.53 (s, 1H, NH), 7.78-7.21 (m, 8H, ArH), 5.27 (d, 1H, CH, *J* = 6.4 Hz), 2.44 (s, 2H, =C-CH_2), 2.04 (s, 2H, CH_2-CO), 1.10 (s, 6H, CH_3).

Synthesis of 5-(4-chlorophenyl)-10-(hydroxymethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]-naphthyridin-6-7*H*-one, 2a

Compound **1a** (0.01 mole) was suspended in ethanol (25 mL) then formalin (37%, 1 mL) and HCl in catalytic amount were added with vigorous stirring. The reaction-mixture was scratched, kept overnight and the separated solid was filtered, washed thoroughly with water, dried and purified by recrystallization from ethanol.

IR (KBr): 3410 (b, O-H str.), 2952, 2819 (C-H str., CH_3), 1682 (C=O str.), 1633 cm^{-1} (C=N str.); ^1H NMR ($CDCl_3$): δ 7.54-7.18 (m, 7H, ArH), 5.30 (s, 1H, CH), 4.51 (s, 2H, N-CH_2), 3.93 (s, 1H, -OH), 2.57 (s, 2H, =C-CH_2), 2.18 (s, 2H, CH_2-CO), 0.99 (s, 6H, CH_3).

Compounds **2b-e** were also prepared by similar method with minor change in reaction conditions. Spectral data of these compounds are given below:

5-(4-Florophenyl)-10-(hydroxymethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8] naphthyridin-6-7*H*-one, 2b

IR (KBr): 3396 (b, O-H str.), 2959, 2824 (C-H str., CH_3), 1679 (C=O str.), 1629 (C=N str.), 1168 cm^{-1} (C-F str.); ^1H NMR ($CDCl_3$): δ 7.59-7.17 (m, 7H, ArH), 5.25 (s, 1H, CH), 4.47 (s, 2H, N-CH_2), 3.94 (s, 1H, -OH), 2.52 (s, 2H, =C-CH_2), 2.21 (s, 2H, CH_2-CO), 1.09 (s, 6H, CH_3).

5-(4-Methoxyphenyl)-10-(hydroxymethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8] naphthyridin-6-7*H*-one, 2c

IR (KBr): 3402 (b, O-H str.), 2950, 2811 (C-H str., CH_3), 1677 (C=O str.), 1628 (C=N str.), 1092 cm^{-1} (C-O str.); ^1H NMR ($CDCl_3$): δ 7.63-7.24 (m, 7H, ArH), 5.33 (s, 1H, CH), 4.42 (s, 2H, N-CH_2), 3.88 (s, 1H, -OH), 3.42 (s, 3H, OCH_3), 2.49 (s, 2H, =C-CH_2), 2.16 (s, 2H, CH_2-CO), 1.02 (s, 6H, CH_3).

5-(4-Nitrophenyl)-10-(hydroxymethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8] naphthyridin-6-7*H*-one, 2d

IR (KBr): 3416 (b, O-H str.), 2947, 2817 (C-H str., CH_3), 1676 (C=O str.), 1619 (C=N str.), 1546, 1352 cm^{-1} (NO_2 str.); ^1H NMR ($CDCl_3$): δ 7.76-7.29 (m, 7H, ArH), 5.28 (s, 1H, CH), 4.40 (s, 2H, N-CH_2), 3.84 (s, 1H, -OH), 2.52 (s, 2H, =C-CH_2), 2.12 (s, 2H, CH_2-CO), 0.96 (s, 6H, CH_3).

5-(4-Phenyl)-10-(hydroxymethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8] naphthyridin-6-7*H*-one, 2e

IR (KBr): 3386 (b, O-H str.), 2957, 2831 (C-H str., CH_3), 1679 (C=O str.), 1613 cm^{-1} (C=N str.); ^1H NMR ($CDCl_3$): δ 7.71-7.24 (m, 8H, ArH), 5.22 (s, 1H, CH), 4.49 (s, 2H, N-CH_2), 3.81 (s, 1H, -OH), 2.50 (s, 2H, =C-CH_2), 2.08 (s, 2H, CH_2-CO), 1.11 (s, 6H, CH_3).

Synthesis of 5-(4-chlorophenyl)-10-(chloromethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one, 3a

A mixture of **2a** (0.01 mole) and thionylchloride (0.02 mole) was refluxed in benzene (30 mL) in presence of pyridine (1 mL) for 2-3 hr. Excess of solvent and thionylchloride was removed under reduce pressure. On cooling, the solid obtained was crystallized from absolute alcohol to afford chloromethyl naphthyridine.

IR (KBr): 3069 (CH str, ArH.), 2933 (C-H str., CH_3), 1688 (C=O str.), 1635 (C=N str.), 760 cm^{-1} (C-Cl str.); ^1H NMR ($CDCl_3$): δ 7.60-7.10 (m, 8H, ArH), 5.45 (s, 1H, CH), 4.75 (s, 2H, N-CH_2), 2.62 (s, 2H, =C-CH_2), 2.20 (s, 2H, CH_2-CO), 0.98 (s, 6H, CH_3).

Similarly, other compounds **3b-e** were also synthesized. Their characterization spectral data are given below:

5-(4-Fluorophenyl)-10-(chloromethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8] naphthyridin-6-7*H*-one, 3b

IR (KBr): 3063 (CH str, ArH.), 2924 (C-H str., CH_3), 1672 (C=O str.), 1626 (C=N str.), 1186 cm^{-1} (C-F str.) 880 cm^{-1} (Ar-H bend, 1,4-disubs.); ^1H NMR ($CDCl_3$): δ 7.73-7.12 (m, 7H, ArH), 5.38 (s, 1H, CH), 4.69 (s, 2H, N-CH_2), 2.57 (s, 2H, =C-CH_2), 2.16 (s, 2H, CH_2-CO), 1.09 (s, 6H, CH_3).

5-(4-Methoxyphenyl)-10-(chloromethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8]naphthyridin-6-7*H*-one, 3c

IR (KBr): 3088 (CH str, ArH.), 2938 (C-H str., CH_3), 1679 (C=O str.), 1621 (C=N str.), 1072 cm^{-1} (C-O str.) 887 cm^{-1} (Ar-H bend, 1,4-disubs.); ^1H NMR ($CDCl_3$): δ 7.67-7.19 (m, 7H, ArH), 5.28 (s, 1H, CH), 4.58 (s, 2H, N-CH_2), 3.86 (s, 3H, OCH_3), 2.24 (s, 2H, CH_2-CO), 1.10 (s, 6H, CH_3).

5-(4-Nitrophenyl)-10-(chloromethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8] naphthyridin-6-7*H*-one, 3d

IR (KBr): 3073 (CH str, ArH.), 2929 (C-H str., CH_3), 1680 (C=O str.), 1631 (C=N str.), 1560, 1348 cm^{-1} (NO_2 asym. & sym. Str.), 887 cm^{-1} (Ar-H bend, 1,4-disubs.); ^1H NMR ($CDCl_3$): δ 7.80-7.29 (m, 7H, ArH), 5.41 (s, 1H, CH), 4.60 (s, 2H, N-CH_2), 2.50 (s, 2H, =C-CH_2), 2.13 (s, 2H, CH_2-CO), 1.02 (s, 6H, CH_3).

5-(Phenyl)-10-(chloromethyl)-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[*b*][1,8] naphthyridin-6-7*H*-one, 3e

IR (KBr): 3070 (CH str, ArH.), 2948 (C-H str., CH_3), 1688 (C=O str.), 1614 cm^{-1} (C=N str.); ^1H NMR ($CDCl_3$): δ 7.84-7.31 (m, 7H, ArH), 5.21 (s, 1H, CH), 4.52 (s, 2H, N-CH_2), 2.59 (s, 2H, =C-CH_2), 2.17 (s, 2H, CH_2-CO), 0.96 (s, 6H, CH_3).

2-{[5-(4-Chlorophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridin-10-5*H*-yl]methoxy}phthalimide, 4a

N-Hydroxyphthalimide (0.01 mole) was added to a well stirred solution of chloromethyl naphthyridine **3a** (0.01mole) in ethanol (30 mL) containing pyridine (0.01 mole) as a base. The reaction-mixture was refluxed for 6-7 hr., filtered and the filtrate was poured into crushed ice. The precipitated solid was collected and recrystallized from absolute ethanol.

IR (KBr): 3001 (CH str, ArH.), 2954, 2839 (C-H str., CH_3), 1725 (C=O str., CO-N-CO), 1690 (C=O str.), 1634 (C=N str.), 957 (N-O str.), 829 (Ar-H bend, 1,4-disubs.), 751 cm^{-1} (C-Cl str.); ^1H NMR ($CDCl_3$): δ 7.87-7.16 (m, 11H, ArH), 5.47 (s, 1H, CH), 4.50 (s, 2H, N-CH_2), 2.57 (s, 2H, =C-CH_2), 2.10 (s, 2H, CH_2-CO), 1.10 (s, 6H, CH_3); MS: *m/z* 515 $[M]^{+\cdot}$, 513, 497, 493, 415, 356, 342, 162, 132, 111, 104, 76.

Compounds **4b-e** were also prepared by similar method with minor change in reaction conditions. Spectral data of these compounds are given below:

2-{[5-(4-Fluorophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridin -10-5*H*-yl]methoxy}phthalimide, 4b

IR (KBr): 3006 (CH str, ArH.), 2950, 2831 (C-H str., CH_3), 1722 (C=O str., CO-N-CO), 1683 (C=O str.), 1627 (C=N str.), 1666 (C-F str.), 950 (N-O str.), 822 cm^{-1} (Ar-H bend, 1,4-disubs.); ^1H NMR ($CDCl_3$): δ 7.82-7.10 (m, 11H, ArH), 5.42 (s, 1H, CH), 4.51 (s, 2H, N-CH_2), 2.53 (s, 2H, =C-CH_2), 2.13 (s, 2H, CH_2-CO), 1.04 (s, 6H, CH_3); MS: *m*/*z* 497 $[M]^{+\cdot}$, 481, 467, 399, 340, 326, 162, 132, 104, 76.

2-{[5-(4-Methoxyphenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*][1,8] naphthyridin-10-5*H*-yl]methoxy}phthalimide, 4c

IR (KBr): 2996 (CH str, ArH.), 2942, 2836 (C-H str., CH_3), 1715 (C=O str., CO-N-CO), 1678 (C=O str.), 1631 (C=N str.), 941 (N-O str.), 816 cm^{-1} (Ar-H bend, 1,4-disubs.); ^1H NMR ($CDCl_3$): δ 7.85-7.17 (m, 11H, ArH), 5.43 (s, 1H, CH), 4.47 (s, 2H, N-CH_2), 3.82 (s, 3H, OCH_3), 2.52 (s, 2H, =C-CH_2), 2.17 (s, 2H, CH_2-CO), 1.13 (s, 6H, CH_3); MS: *m*/*z* 509 $[M]^{+\cdot}$, 493, 479, 411, 352, 338, 162, 132, 104, 76.

2-{[5-(4-Nitrophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridin-10-5*H*-yl]methoxy}phthalimide, 4d

IR (KBr): 3012 (CH str, ArH.), 2959, 2834 (C-H str., CH_3), 1720 (C=O str., CO-N-CO), 1680 (C=O str.), 1621 (C=N str.), 1550, 1338 (NO_2 asymm. and symm. Str.), 947 (N-O str.), 817 cm^{-1} (Ar-H bend, 1,4-disubs.); ^1H NMR ($CDCl_3$): δ 7.91-7.16 (m, 11H, ArH), 5.41 (s, 1H, CH), 4.48 (s, 2H, N-CH_2), 2.56 (s, 2H, =C-CH_2), 2.10 (s, 2H, CH_2-CO), 1.07 (s, 6H, CH_3); MS: *m*/*z* 524 $[M]^{+\cdot}$, 508, 494, 426, 367, 353, 162, 132, 122, 104, 76.

2-{[5-(Phenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridin-10-5*H*-yl]methoxy}-phthalimide, 4e

IR (KBr): 2995 (CH str, ArH.), 2945, 2830 (C-H str., CH_3), 1728 (C=O str., CO-N-CO), 1688 (C=O str.), 1630 cm^{-1} (C=N str.); ^1H NMR ($CDCl_3$): δ 7.72-7.16 (m, 11H, ArH), 5.41 (s, 1H, CH), 4.50 (s, 2H, N-CH_2), 2.49 (s, 2H, =C-CH_2), 2.09 (s, 2H, CH_2-CO), 0.98 (s, 6H, CH_3); MS: *m*/*z* 479 $[M]^{+\cdot}$, 463, 449, 381, 322, 308, 162, 132, 104.

Synthesis of 2-{2-[5-(4-Chlorophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*] [1,8]naphthyridin-10-5*H*-yl]ethoxy}phthalimide, 5a

To a stirred solution of **1a** (0.01 mole) and triethylamine (0.01 mole) in DMF, phthalimidoxyethyl bromide (0.01 mole) was added portion wise. The reaction-mixture was refluxed for 12 hr. It was cooled and precipitate of triethylamine hydrobromide was filtered off. The filtrate was poured into crushed ice with constant stirring. The solid obtained was recrystallized from absolute ethanol.

IR (KBr): 3066 (CH str, ArH.), 2983, 2814 (C-H str., CH_3), 1722 (C=O str., CO-N-CO), 1692 (C=O str.), 1642 (C=N str.), 940 (N-O str.), 805 (Ar-H bend, 1,4-disubs.), 773 cm^{-1} (C-Cl str.); ^1H NMR ($CDCl_3$): δ 8.45-7.26 (m, 11H, ArH), 5.40 (s, 1H, CH), 4.45 (t, 2H, O-CH_2), 3.52 (t, 2H, -NCH_2), 2.52 (s, 2H, =C-CH_2), 2.16 (s, 2H, CH_2-CO), 1.16 (s, 6H, CH_3); MS: *m*/*z* 527 $[M]^{+\cdot}$, 527, 511, 497, 485, 429, 336, 190, 162, 132, 111, 104, 76.

Compounds **5b-e** were prepared by the similar method with minor change in reaction conditions. Their spectral data are given below:

2-{2-[5-(4-Fluorophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[b][1,8] naphthyridin-10-5*H*-yl]ethoxy}phthalimide, 5b

IR (KBr): 3060 (CH str, ArH.), 2978, 2811 (C-H str., CH_3), 1727 (C=O str., CO-N-CO), 1687 (C=O str.), 1636 (C=N str.), 946 (N-O str.), 802 (Ar-H bend, 1,4-disubs.), 1172 cm^{-1} (C-F str.); ^1H NMR ($CDCl_3$): δ 8.51-7.22 (m, 11H, ArH), 5.43 (s, 1H, CH), 4.39 (t, 2H, O-CH_2), 3.50 (t, 2H, -NCH_2), 2.48 (s, 2H, =C-CH_2), 2.13 (s, 2H, CH_2-CO), 1.14 (s, 6H, CH_3); MS: *m*/*z* 511 $[M]^{+\cdot}$, 495, 481, 469, 413, 320, 190, 162, 132, 104, 76.

2-{2-[5-(4-Methoxyphenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*][1,8] naphthyridin-10-5*H*-yl]ethoxy}phthalimide, 5c

IR (KBr): 3056 (CH str, ArH.), 2986, 2807 (C-H str., CH_3), 1725 (C=O str., CO-N-CO), 1684 (C=O str.), 1639 (C=N str.), 1068 (C-O str.), 945 (N-O str.), 801 cm^{-1} (Ar-H bend, 1,4-disubs.); ^1H NMR ($CDCl_3$): δ 8.41-7.14 (m, 11H, ArH), 5.45 (s, 1H, CH), 4.40 (t, 2H, O-CH_2), 3.38 (s, 3H, OCH_3), 3.48 (t, 2H, -NCH_2), 2.46 (s, 2H, =C-CH_2), 2.06 (s, 2H, CH_2-CO), 1.11 (s,

6H, CH_3); MS: *m/z* 523 $[M]^{+\cdot}$, 507, 495, 481, 425, 332, 190, 162, 132, 104, 76.

2-{2-[5-(4-Nitrophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*][1,8] naphthyridin-10-5*H*-yl]ethoxy}phthalimide, 5d

IR (KBr): 3059 (CH str, ArH.), 2970, 2804 (C-H str., CH_3), 1718 (C=O str., CO-N-CO), 1682 (C=O str.), 1631 (C=N str.), 1550, 1342 (NO_2 asym. and sym. Str.), 941 (N-O str.), 800 cm^{-1} (Ar-H bend, 1,4-disubs.); ^1H NMR ($CDCl_3$): δ 8.72-7.11 (m, 11H, ArH), 5.38 (s, 1H, CH), 4.33 (t, 2H, O-CH_2), 3.55 (t, 2H, -NCH_2), 2.42 (s, 2H, =C-CH_2), 2.16 (s, 2H, CH_2-CO), 1.04 (s, 6H, CH_3); MS: *m/z* 538 $[M]^{+\cdot}$, 522, 508, 496, 440, 347, 190, 162, 132, 122, 104, 76.

2-{2-[5-(Phenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridin-10-5*H*-yl]ethoxy}phthalimide, 5e

IR (KBr): 3062 (CH str, ArH.), 2981, 2804 (C-H str., CH_3), 1713 (C=O str., CO-N-CO), 1688 (C=O str.), 1633 (C=N str.), 933 cm^{-1} (N-O str.); ^1H NMR ($CDCl_3$): δ 8.40-7.19 (m, 11H, ArH), 5.34 (s, 1H, CH), 4.41 (t, 2H, O-CH_2), 3.51 (t, 2H, N(CH_2)$_2$), 2.47 (s, 2H, =C-CH_2), 2.10 (s, 2H, CH_2-CO), 1.14 (s, 6H, CH_3); MS: *m/z* 493 $[M]^{+\cdot}$, 477, 463, 351, 395, 451, 395, 302, 190, 162, 132, 104.

Acknowledgements

Authors are thankful to the Head, Department of Chemistry, M.L. Sukhadia University, Udaipur for providing Laboratory facilities and to the Director, RSIC, CDRI, Lucknow, India for providing spectral and analytical data. Authors are grateful to Antimicrobial Research Laboratory, particularly to Dr. Kanika Sharma, Department of Botany, M. L. Sukhadia University for evaluating antimicrobial activity. Three of the authors (D B, V K S and A B) are thankful to UGC and CSIR, New Delhi respectively for providing necessary financial assistance.

References

1 Bouzard D, Di Cesare P, Essiz M, Jacquet J P, Ledoussal B, Remuzon P, Kessler R E & Fung-Tomc J, *J Med Chem*, 35, **1992**, 518.
2 Ferrarini P L, Manera C, Mori C, Badawneh M & Saccomanni G, *Farmaco*, 53, **1998**, 741.
3 Zhang S X, Bastow K F, Tachibana Y, Kuo S C, Hamel E, Mauger A, Narayanan V L & Lee K H, *J Med Chem*, 42, **1999**, 4081.
4 Kuroda T, Suzuki F, Tamura T, Ohmori K & Hosoe H, *J Med Chem*, 35, **1992**, 1130.
5 Chiara D, Massimo C, Margheri G, Mario D B, Giorgio R & Robert F, *J of Inflammation*, 34, **2006**, 1.
6 Ferrarini P L, Badawneh M, Franconi F, Manera C, Miceli M, Mori C & Saccomanni G, *Farmaco*, 56, **2001**, 311.
7 Santilli A A, Scotese A C, Bauer R F & Bell S C, *J Med* Chem, 30, **1987**, 2270.
8 Kuo S C, Tsai S Y, Li H T, Wu C H, Ishii K & Nakamura H, *Chem Pharm Bul*, 36, **1988**, 4403.
9 Ferrarini P L, Mori C & Tellini N, *Farmaco*, 45, **1990**, 385.
10 Da Settimo A, Primofiore G, Da Settimo F, Simorini F, Barili P L, Senatore G, Martini C & Lucacchini A, *Drug Des Discov*, 11, **1994**, 307.
11 Herzig S, Heber D, Mescheder A, Reifenstein-Herzig U, Thormann T, Verborg M & Mohr K, *Arzneimittel Forschung*, 44, **1994**, 937.
12 Ferrarini P L, Mori C, Badawneh M, Calderone V, Greco R, Manera C, Martinelli A, Nieri P & Saccomanni G, *Eur J Med Chem*, 35, **2000**, 815.
13 Leonard J T, Gangadhar R, Gnanasam S K, Ramachandran S, Saravanan M & Sridhar S K, *Biol Pharm Bull*, 25, **2002**, 798.
14 Roma G, Di Braccio M, Grossi G, Mattioli F & Ghia M, *Eur J Med Chem*, 35, **2000**, 1021.
15 Ligthart G B W L, Ohkawa H, Sijbesma R P & Meijer E W, *J Am Chem Soc*, 127, **2005**, 810.
16 Li X Q, Feng D J, Jiang X K & Li Z T, *Tetrahedron*, 60, **2004**, 8275.
17 Wang X Z, Li X Q, Shao X B, Zhao X, Deng P, Jiang X K & Chen Y K, *Chem Eur J*, 9, **2003**, 2904.
18 Al Jamal J A & Badawneh M, *Arch Pharm Med Chem*, 336, **2003**, 285.
19 Corbin P S & Zimmerman S C, *J Am Chem Soc*, 122, **2000**, 3779.
20 Corbin P S, Lawess L J, Witmer M J & Zimmerman S C, *Proc Natl Acad Sci USA*, 99, **2002**, 5099.
21 Brammer S, Luning U & Kuhl C, *Eur J Org Chem*, **2002**, 4045.
22 Balin G B & Tan W L, *Aus J Chem*, 37, **1984**, 1065.
23 Ferrarini M, Clendio M, Calderone U & Lovella G, *Eur J Med Chem*, 33, **1998**, 383.
24 Ramesh D & Sreenivasulu B, *Indian J Chem*, 43B, **2004**, 897.
25 Linghang Z, John S W, Mark W E, Thorsten E, Melissa S E & Linda S P, *J Med Chem*, 46, **2003**, 453.
26 Darren A, Glenda W, Barbara F, Y Li Mark M, Deborab M, Ellyh W & Karen B, *Antimicrobial Agents and Chemotherapy*, 49(1), **2005**, 309.
27 Sudhir K S, Alexander L R, Tsai K, Angela L, Lerory F L & Edmond J L, *J Med Chem*, 46, **2003**, 2254.
28 Loscher W G, *Eur J Pharmacol*, 51, **1946**, 342.
29 Cornish E J, Lee G E & Wargg W R, *J Pharmacol*, 18, **1966**, 65.
30 Kaunowasky H, Cherwat R, Delage B & Jondet A, *Chem Thera*, **1966,** 209.
31 Finley W H & Carlson W C, *J Med Sci*, 1, **1946**, 1657.
32 Mamalis P, *Xenobiotica*, 1, **1971**, 569.
33 Banu T, Rajora S, Khatri D & Talesara G L, *J Indian Chem Soc*, 77, **2000**, 300.
34 Singh B, Mehta D, Baregama L K & Talesara G L, *Indian J Chem*, 43B, **2004**, 1306.
35 Bisen P S & Verma K, *Hand Book of Microbiology*, 1st Edn, (CBS Publication and Distributors) New Delhi, **1998**.
36 Joon S E, *Clinical Bacteria*, 4th Edn, (Edward Arnold London) **1975,** 226.
37 Orndroff W R & Pratt D S, *J Am Chem*, 47, **1912**, 1604.
38 Bauer L & Suresh K S, *J Org Chem*, 28, **1963**, 1604.