# Synthesis of Benzo[*h*][1,6]naphthyridine derivatives and Study of their antimicrobial activity

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**Abstract:**
*The polysubstituted iminoether derivatives **3** and N-alkyl benzo[h][1,6]naphthyridine **4** were synthesized by the reaction of 4,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridin-5(6H)-one **2** with various N-phenyl bromoacetamides. The antimicrobial activity of new compounds were studied against Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeroginosa, Proteus valgaris, Bacillus cereus, Streptococcus sp and Bacillus megaterium by the agar well diffusion method. Compounds **3h,** showed good antimicrobial activities against Escherichia coli, Bacillus cereus and Bacillus megaterium species.*

**Keywords:** benzo[*h*][1,6]naphthyridine

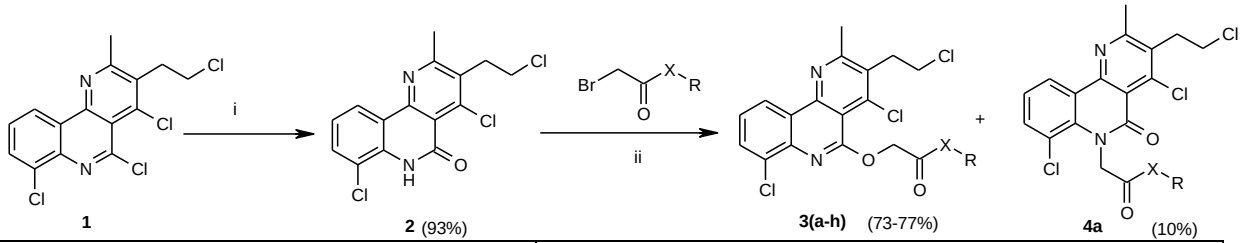
## INTRODUCTION

Several antimalarial candidates possessing usable $C_4$ substitution in tricyclic heteroaromatic nucleus[1] were synthesized by chloride substitution of benzo[*h*][1,6] naphthyridines with various nucleophiles e.g. *N*-alkyl-4-piperidinyl methanolates.[2] The benzo[*h*][1,6] naphthyridines showed broad spectrum of biological activities[3-7] including high affinity on 5-$HT_4$ receptors and high selectivity versus other receptors.[8-9] Recent SAR studies of overlay iminoether derivatives with pharmacophore 5-$HT_4$ receptors, showed that the cyclic iminoether group could be considered as a bioisoester of ester function found in 5-$HT_4$ antagonist structures.[10] The availability of the cloned 5-$HT_4$ receptors stimulated more interest in the search of new ligands. Recently, new 5-$HT_4$ antagonists which possessed a side chain centered on a piperidine ring system.[11-13] In this paper, we report the synthesis of $C_5$-iminoether linkers to benzo[*h*][1,6]naphthyridines.

## MATERIALS AND METHODS

### *Chemistry*

The iminechloride (-N=C-Cl) moiety in 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo *h*][1,6] naphthyridine **1**[14] was converted to lactum cabonyl[15] by refluxing in glacial acetic acid to yield 4,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6]naphthyridin-5(*6H*)-one **2** in 93% yield, which showed lactum carbonyl (C=O) stretching at 1676 $cm^{-1}$ and NH at 3339 $cm.^{-1}$




| | |
|---|---|
| **3a:** X=O, R=$C_2H_5$ | **3e:** X= NH, R=2,4-$ClC_6H_3$ |
| **3b:** X=NH, R=4-$MeC_6H_4$ | **3f:** X=NH, R=2-Cl,6-$FC_6H_3$ |

| | |
|---|---|
| **3c:** X=NH, R=4-$FC_6H_4$ | **3g:** X=NH, R=3-Cl,4-$CF_3C_6H_3$ |
| **3d:** X=NH, R=4-$ClC_6H_4$ | **3h:** X=NH, R=2,4-$CF_3C_6H_3$ |
| **4a:** X=O, R=$C_2H_5$ | |

**Scheme.** Reagents and conditions: (i) AcOH, reflux, 15 min; (ii) $K_2CO_3$, DMF, 25 $^oC$, 2 h.

The alkylation reaction on compound **2** with bromoester or substituted *N*-phenyl bromoacetamide[16] in presence of anhydrous $K_2CO_3$ in DMF at room temperature afford mixture of compound **3a** in 73-77% and **4a** in 10% respectively, which were separated by column chromatography eluting with toluene. The predominant *O*-alkylation over *N*- alkylation was observed due to higher contribution of enaminol than amide tautomer in compound **2** at room temperature. The structure of compounds **3a** and **4a** were assigned using spectroscopic and analytical methods. For instance IR of **3a** showed ester (C=O) stretching at 1749 $cm^{-1}$ and absence of lactum carbonyl while compound **4a** showed ester (C=O) at 1731 $cm^{-1}$ and lactum (C=O) at 1664 $cm.^{-1}$

***Antimicrobial activity***

| Compd. No. | Antibacterial inhibition zone diameter (mm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *S. aureus* | *E. coli* | *B. subtilis* | *P. aeroginosa* | *P. valgaris* | *B. cereus* | *Streptoc occus sp* | *B. megaterium* |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3a | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3c | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12 |
| 3d | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 8 |
| 3e | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 |
| 3f | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 8 |
| 3g | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3h | 0 | 8 | 0 | 0 | 0 | 10 | 0 | 10 |
| 4a | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 8 |
| *Ampicillin | 45 | 35 | 40 | 45 | 34 | 33 | 40 | 15 |
| *Streptomycin | 13 | 0 | 15 | 0 | 34 | 40 | 0 | 0 |

All the compounds were screened against cultures of eight bacterial species, namely, *Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeroginosa, Proteus valgaris, Bacillus cereus, Streptococcus sp and Bacillus megaterium* to detect antimicrobial activities. The antimicrobial activity was biologically assayed using agar well diffusion technique. The organisms were tested in solutions with concentration; 1.0 mg/ml of each compound using inhibition zone diameter (IZD) in mm for antimicrobial activity. Ampicillin and Streptomycin as an antibacterial agent were used as references to evaluate the potency of the tested compounds under similar conditions. The minimum inhibitory concentrations (MIC) of the biologically active compounds were measured by two-fold serial dilution method. The benzo[*h*][1,6]naphthyridine **3(a-h)** do not showed considerable antibacterial activity. All of the other compounds exhibited no activity against the tested species.

Antimicrobial activity of chemical substances tested.

** Ampicillin and Streptomycin are used as standard antibacterial agents*

## EXPERIMENTAL

### *General*

Common reagents grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. The melting points were measured on Barnstead Electro Thermal melting point apparatus Mod. No. IA-9200 in open capillary tubes and are uncorrected. Elemental analyses were determined using Thermo Quest Model No. flash EA 1112-Elemental Analyzer. The IR spectra of compounds were recorded on Shimadzu IR-408, instrument in potassium bromide pellets. The mass spectra were recorded on Mat 112 Varian Mat Bremen mass spectrometer. $^{1}$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded on VARIAN XL-300 instrument at 25 $^{o}$C. The measurements were done using solvents-$CDCl_3$ and DMSO-$d_6$ with TMS as an internal standard reference. Coupling constants ($J$) are quoted to the nearest 0.1 Hz and chemical shift ($\delta$-scale) are quoted in parts per million (ppm) and following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was performed using silica gel with particle size (60-120 mesh, Merck). All reactions were monitored by TLC carried out 0.2 mm silica gel 60 $F_{254}$ (Merck) plates using 254 and 366 nm UV light for detection.

***Synthetic procedures***

***4,7-Dichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridin-5(6H)-one (2).*** A mixture of 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6]naphthyridine **1** (3.60 g, 0.01 mol) in glacial acetic acid (25 mL) was refluxed for 15 min. After cooling to room temperature, methanol (50 mL) was added, the crude product obtained was collected by suction filtration, dried and recrystallized from ethanol/DMF (9:1) to yield title compound **2** (3.17 g, 93%) as pink colored prisms; $R_f$ (toluene/ethyl acetate 9:1) 0.51, mp 254 $^{o}$C; IR (KBr): $\nu$ 3339 (NH), 3186, 3143, 1676 (C=$O_{lactum}$), 1249, 734 cm$^{-1}$; $^{1}$H NMR ($CDCl_3$): $\delta$ 2.91 (s, 3H, $CH_3$), 3.57 (t, $J$ = 7.1 Hz, 2H, $CH_2CH_2Cl$), 3.83 (t, $J$ = 7.1 Hz, 2H, $CH_2CH_2Cl$), 7.59 (t, $J$ = 7.5 Hz, 1H, $C_9H$), 7.77 (d, $J$ = 7.5 Hz, 1H, $C_8H$), 8.1 (s, 1H, NH, $D_2O$ exchangeable), 8.97 (d, $J$ = 7.5 Hz, 1H, $C_{10}H$); $^{13}$C NMR ($CDCl_3$): $\delta$ 23.26, 30.95, 42.65, 119.40, 121.72, 122.14, 126.75, 128.00, 128.20, 128.63, 128.74, 136.66, 142.23, 161.54, 170.61; MS: *m/z* (%): 347 (M+6, 10), 345 (M+4, 30), 343 (M+2, 50), 341 (M, 100), 274 (20), 198 (20), 99 (10); Anal. Calcd for $C_{15}H_{11}Cl_3N_2O$ (341.62): C, 52.74; H, 3.25; N, 8.20. Found: C, 52.47; H, 3.31; N, 8.29.

***2-[4,7-Dichloro-3-(2-chloro-ethyl)-2-methyl-5-oxo-5H-benzo[h][1,6]naphthyridine-6-yl]-N-substituted-phenyl acetamide (3a-h).*** Anhydrous potassium carbonate (0.136 g, 0.001 mol) was added to the stirred solution of 4,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6] naphthyridine-5-(*6H*)-one **2** (0.341 g, 0.001 mol) and 2-bromo-*N*-phenyl-acetamide (0.0012 mol) in DMF at 25 $^{o}$C. The resulting reaction mixture was kept stirring for 2 h. The progress of the reaction was monitored by TLC (toluene/ethyl acetate 8:2) till the reactant was consumed. After completion, the reaction mixture was poured in cold water (100 mL). The obtained solid was filtered washed with water, dried and purified by column chromatography eluting with toluene gave title compound **3** and **4**.

***[4,7-Dichloro-3-(2-chloro-ethyl)-2-methyl-5-oxo-5H-benzo[h][1,6]naphthyridin-6-yl]-acetic acid ethyl ester (3a).*** Yellow prisms; yield (0.328 g, 77%); $R_f$ (toluene/ethyl acetate 8:2) 0.53, mp 211 $^{o}$C; IR (KBr): $\nu$ 2977, 2898, 1749 (C=O), 1589, 1562, 1375, 1213, 1060, 748 cm$^{-1}$; $^{1}$H NMR ($CDCl_3$): $\delta$ 1.31 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$), 2.92 (s, 3H, $CH_3$), 3.53 (t, $J$ = 7.5 Hz, 2H, $CH_2CH_2Cl$), 3.81 (t, $J$ = 7.5 Hz, 2H, $CH_2CH_2Cl$), 4.28 (q, $J$ = 7.2 Hz, 2H, $OCH_2CH_3$), 5.20 (s, 2H, $CH_2$), 7.44 (t, $J$ = 7.8 Hz, 1H, $C_9H$), 7.76 (d, $J$ = 7.8 Hz, 1H, $C_8H$), 8.88 (d, $J$ = 7.8 Hz, 1H, $C_{10}H$); MS: *m/z* (%): 432 (M+6, 10), 430 (M+4, 15), 428 (M+2, 30), 426 (M+, 40) , 391 (30), 381 (50), 341 (60), 91 (40), 85 (100), 77 (30). Anal. Calcd for $C_{19}H_{17}Cl_3N_2O_3$ (427.72): C, 53.36; H, 4.01; N, 6.55. Found: C, 53.39; H, 4.07; N, 6.51.

***2-[4,7-Dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h][1,6]naphthyridin-5-yloxy]-N-p-tolyl-acetamide (3b).*** Yellow needles; yield (0.374 g, 77%); $R_f$ (toluene/ethyl acetate 8:2) 0.51, mp 218 $^oC$; IR (KBr): *v* 3390 (NH), 2962, 2926, 2854, 1681 (C=O), 1589, 1537, 1300, 1184, 1037 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.34 (s, 3H, $CH_3$), 2.95 (s, 3H, $CH_3$), 3.58 (t, *J* = 7.8 Hz, 2H, $CH_2CH_2Cl$), 3.84 (t, *J* = 7.8 Hz, 2H, $CH_2CH_2Cl$), 5.35 (S, 2H, $CH_2$), 7.19 (d, *J* = 8.7 Hz, 2H, ArH), 7.49-7.52 (m, 3H, ArH, $C_9H$), 7.82 (d, *J* = 7.5 Hz, 1H, $C_8H$), 8.82 (s, 1H, NH, $D_2O$ exchangeable), 8.91 (d, *J* = 7.5 Hz, 1H, $C_{10}H$); MS: *m/z* (%): 493 (M+6, 10), 491 (M+4, 10), 489 (M+2, 15), 487 (M+, 30), 452 (20), 381 (80), 341 (50), 325 (60), 147 (100), 106 (65), 91 (80), 77 (90). Anal. Calcd for $C_{24}H_{20}Cl_3N_3O_2$ (488.80): C, 58.97; H, 4.12; N, 8.60. Found: C, 59.02; H, 4.11; N, 8.64.

***2-[4,7-Dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h][1,6]naphthyridin-5-yloxy]-N-(4-fluoro-phenyl)-acetamide (3c).*** Yellow needles; yield (0.369 g, 75%); $R_f$ (toluene/ethyl acetate 8:2) 0.80, mp 121 $^oC$; IR (KBr): *v* 3354 (NH), 3273, 2926, 1670 (C=O), 1595, 1590, 1317, 1224, 833 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.95 (s, 3H, $CH_3$), 3.57 (t, *J* = 7.2 Hz, 2H, $CH_2CH_2Cl$), 3.84 (t, *J* = 7.2 Hz, 2H, $CH_2CH_2Cl$), 5.35 (s, 2H, $CH_2$), 7.11 (d, *J* = 7.2 Hz, 2H, ArH), 7.49 (t, *J* = 7.2 Hz, 1H, $C_9H$), 7.61 (d, *J* = 7.2 Hz, 2H, ArH), 7.85 (d, *J* = 7.5 Hz, 1H, $C_8H$), 8.91 (d, *J* = 7,5 Hz, 1H, $C_{10}H$), 9.21 (s, 1H, NH, $D_2O$ exchangeable); $^{13}C$ NMR ($CDCl_3$): $\delta$ 25.09, 29.66, 41.16, 66.78, 115.67, 115.96, 119.20, 121.66, 122.23, 123.52, 123.98, 125.72, 128.27, 128.80, 129.19, 131.39, 133.33, 155.14; MS: *m/z* (%): 497 (M+6, 15), 495 (M+4, 20), 493 (M+2, 30), 491 (M+, 40), 456 (20), 482 (30), 342 (40), 325 (50), 149 (100). 91 (40), 77 (40). Anal. Calcd for $C_{23}H_{17}Cl_3FN_3O_2$ (492.77): C, 56.06; H, 3.48; N, 8.53. Found: C, 56.12; H, 3.42; N, 8.56.

***N-(4-Chloro-phenyl)-2-[4,7-dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h][1,6] naphthayridin-5-yloxy]-acetamide (3d).*** Yellow needles; yield (0.371 g, 73%); $R_f$ (toluene/ethyl acetate 8:2) 0.82, mp 231-232 $^oC$; IR (KBr): *v* 3355 (NH), 2926, 2840, 1683 (C=O), 1594, 1510, 1318, 1224, 850 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.72 (s, 3H, $CH_3$), 3.46 (t, *J* = 7.6 Hz, 2H, $CH_2CH_2Cl$), 3.57 (t, *J* = 7.6 Hz, 2H, $CH_2CH_2Cl$), 4.41 (s, 2H, $CH_2$), 7.35 (d, *J* = 8.3 Hz, 2H, ArH), 7.54 (t, *J* = 7.8 Hz, 1H, $C_7H$), 7.61 (d, *J* = 8.3 Hz, 2H, ArH), 7.83 (d, *J* = 7.8 Hz, 1H, $C_8H$), 8.85 (d, *J* = 7.8 Hz, 1H, $C_6H$), 9.81 (s, 1H, NH, $D_2O$ exchangeable); MS: *m/z* (%): 515 (M+8, 10), 513 (M+6, 10), 511 (M+4, 15), 509 (M+2, 20), 507 (M+, 40), 472 (30), 381 (30), 341 (30), 325 (100), 166 (80). Anal. Calcd for $C_{23}H_{17}Cl_4N_3O_2$ (509.22): C, 54.25; H, 3,37; N, 8.25. Found: C, 54.30; H, 3.35; N, 8.27.

***2-[4,7-Dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h][1,6]naphthyridin-5-yloxy]-N-(2,4-dichloro-phenyl)-acetamide (3e).*** Yellow needles; yield (0.423 g, 77%); $R_f$ (toluene/ethyl acetate 8:2) 0.90, mp 110 $^oC$; IR (KBr): *v* 3389 (NH), 3226, 2924, 2852, 1672 (C=O), 1589, 1525, 1305, 1143, 1053, 779 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.95 (s, 3H, $CH_3$), 3.57 (t, *J* = 7.8 Hz, 2H, $CH_2CH_2Cl$), 3.81 (t, *J* = 7.8 Hz, 2H, $CH_2CH_2Cl$), 5.45 (s, 2H, $CH_2$), 7.30 (m, 2H, ArH), 7.38 (d, *J* = 7.2 Hz, 1H, ArH), 7.49 (t, *J* = 8.1 Hz, 1H, $C_9H$), 7.84 (d, *J* = 8.1 Hz, 1H, $C_8H$), 8.41 (d, *J* = 8.1 Hz, 1H, $C_{10}H$), 8.90 (s, 1H, NH, $D_2O$ exchangeable); MS: *m/z* (%): 551 (M+10, 10), 549 (M+8, 10), 547 (M+6, 15), 545 (M+4, 20), 543 (M+2, 25), 541 (M+, 30), 506 (30), 498 (20), 452 (40), 324 (20), 217 (20), 201 (100), 159 (90). Anal. Calcd for $C_{23}H_{16}Cl_5N_3O_2$ (543.67): C, 50.81; H, 2.97; N, 7.73. Found: C, 50.85; H, 2.93; N, 7.70.

***N-(2-Chloro-6-fluoro-phenyl)-2-[4,7-dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h] [1,6]naphthyridin-5-yloxy]-acetamide (3f).*** Yellow needles; yield (0.405 g, 77%); $R_f$ (toluene/ethyl acetate 8:2) 0.70, mp 215 $^oC$; IR (KBr): *v* 3385 (NH), 3230, 2930, 2852, 1674 (C=O), 1589, 1516, 1310, 1145, 830 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.90 (s, 3H, $CH_3$), 3.55 (t, *J* = 7.6 Hz, 2H, $CH_2CH_2Cl$), 3.82 (t, *J* = 7.6 Hz, 2H, $CH_2CH_2Cl$), 5.43 (s, 2H, $CH_2$), 7.33-7.38 (m, 4H, ArH), 7.49 (t, *J* = 8.0 Hz, 1H, $C_9H$), 7.83 (d, *J* = 8.0 Hz, 1H, $C_8H$), 8.45 (d, *J* = 8.0 Hz, 1H, $C_{10}H$), 8.96 (s, 1H, NH, $D_2O$ exchangeable); Anal. Calcd for $C_{23}H_{16}Cl_4FN_3O_2$ (527.21): C, 52.40; H, 3.06; N, 7.97. Found: C, 52.32; H, 3.11; N, 7.90.

***N-(3-chloro-4-trifluoromethyl-phenyl)-2-[4,7-dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h][1,6]naphthyridin-5-yloxy]-acetamide (3g).*** Yellow needles; yield (0.455 g, 79 %); $R_f$ (toluene/ethyl acetate 8:2) 0.80, mp 218 $^oC$; IR (KBr): *v* 3370 (NH), 2923, 2850, 1690 (C=O), 1597, 1510, 1270, 850 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.93 (s, 3H, $CH_3$), 3.59 (t, *J* = 7.8 Hz, 2H, $CH_2CH_2Cl$), 3.82 (t, *J* = 7.8 Hz, 2H, $CH_2CH_2Cl$), 5.42 (s, 2H, $CH_2$), 7.43-7.47 (m, 2H, ArH), 7.49 (t, *J* = 7.8 Hz, 1H, $C_9H$), 7.64 (s, 1H, ArH), 7.83 (d, *J* = 7.8 Hz, 1H, $C_8H$), 8.51 (d, *J* = 7.8 Hz, 1H, $C_{10}H$), 8.95 (s, 1H, NH, $D_2O$ exchangeable); $^{13}C$ NMR ($CDCl_3$): $\delta$ 25.15, 29.68, 33.48, 41.22, 118.77, 123.46, 123.59, 123.76, 124.28, 124.92, 125.18, 125.84, 130.77, 130.92, 131.41, 131.62, 132.11, 136.14, 139.64, 141.18, 151.14, 155.30, 163.34, 166.32; MS: *m/z* (%): Anal. Calcd for $C_{24}H_{16}Cl_4F_3N_3O_2$ (577.22): C, 49.94; H, 2.79; N, 7.28. Found: C, 56.32; H, 3.31; N, 8.64.

***N-(2,4-Bis-trifluoromethyl-phenyl)-2-[4,7-dichloro-3-(2-chloro-ethyl)-2-methyl-benzo [h][1,6]naphthyridin-5-yloxy]-acetamide (3h).*** Yellow needles; yield (0.445 g, 73%); $R_f$ (toluene/ethyl acetate 8:2) 0.82, mp 230 $^oC$; IR (KBr): *v* 3390 (NH), 3254, 2924, 1674 (C=O), 1593, 1539, 1319, 1178, 481 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.96 (s, 3H, $CH_3$), 3.58 (d, *J* = 7.2 Hz, 2H, $CH_2CH_2Cl$), 3.85 (d, *J* = 7.2 Hz, 2H, $CH_2CH_2Cl$), 5.37 (s, 2H, $CH_2$), 7.47-7.53 (m, 3H, ArH, $C_9H$), 7.84 (d, *J* = 7.8 Hz, 1H, $C_8H$), 7.97 (d, *J* = 7.0 Hz, 1H, ArH), 8.95 (d, *J* = 7.8 Hz, 1H, $C_{10}H$), 9.12 (s, 1H, NH, $D_2O$ exchangeable); MS: *m/z* (%): 615 (M+, 10), 613 (M+4, 20), 611 (M+, 30), 609 (M+, 50), 575 (30), 543 (20), 477 (30), 410 (100), 370 (40), 91 (20). Anal. Calcd for $C_{25}H_{16}Cl_3F_6N_3O_2$ (610.77): C, 49,16; H, 2.64; N, 6.88. Found: C, 49.11; H, 2.73; N, 6.85.

***[4,7-Dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h][1,6]naphthyridin-5-yloxy]-acetic acid ethyl ester (4a).***Yellow needles; yield (0.0426 g, 10%); $R_f$ (toluene/ethyl acetate 8:2), mp 237 $^oC$; IR (KBr): *v* 2993, 2960, 1731 (C=O), 1664 (C=O), 1533, 1394, 1253, 1126, 786 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.30 (t, *J* = 6.9 Hz, 3H, $OCH_2CH_3$), 2.89 (s, 3H, $CH_3$), 3.46 (t, *J* = 7.2 Hz, 2H, $CH_2CH_2Cl$), 3.78 (t, *J* = 7.2 Hz, 2H, $CH_2CH_2Cl$), 4.28 (q, *J* = 6.9 Hz, 2H, $OCH_2CH_3$), 5.27 (s, 2H, $CH_2$), 7.29 (t, *J* = 8.1 Hz, 1H, $C_9H$), 7.61 (d, *J* = 8.1 Hz, 1H, $C_8H$), 8.90 (d, *J* = 8.1 Hz, 1H, $C_{10}H$); MS: *m/z* (%): 432 (M+6, 10), 430 (M+4, 15), 428 (M+2, 30), 426 (M+, 100), 391 (30), 381 (50), 341 (60), 91 (50), 85 (90), 77 (40). Anal. Calcd for $C_{19}H_{17}Cl_3N_2O_3$ (427.72): C, 53.36; H, 4.01; N, 6.55. Found: C, 53.39; H, 4.07; N, 6.51.

### *Antibacterial studies*

Atibacterial activities were investigated using agar well diffusion method. The activity of tested samples was studied against the eight bacteria species, namely, *Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeroginosa, Proteus valgaris, Bacillus cereus, Streptococcus sp aureus* and *Bacillus megaterium.* Centrifuged pellets of bacteria from a 24 h old culture containing approximately $10^4$-$10^6$ CFU (colony forming unit) per mL were spread on the surface of Nutrient agar (typetone 1%, yeast extract 0.5%, NaCl 0.5%, agar 1%, 1000 mL of distilled water, PH 7.0) which was autoclaved under 121 $^oC$ for at least 20 min. Wells were created in medium with the help of a sterile metallic bores and then cooled down to 45 $^oC$. The activity was determined by measuring the diameter of the inhibition zone (in mm). 100 µl of the tested samples (10 mg/mL) were loaded into the wells of the plates. All compounds was prepared in N,N-dimethyl formamide (DMF), DMF was loaded as control. The plates were kept for incubation at 37 $^oC$ for 24 h and then the plates were examined for the formation of zone of inhibition. Each inhibition zone was measured three times by caliper to get an average value. The test was performed three times for each bacterium culture. Ampicilin and Streptomycin was used as antibacterial standard drugs. Zone of inhibition were determined for compounds **1** to **4** the results are summarized in Table 1.

## CONCLUSION

The convenient synthesis of benzo[*h*][1,6]naphthyridines and cyclopenta[*a*]phenanthrens as a useful tool in the development of iminoether derivatives was disclosed. The synthesized

benzo[*h*][1,6]naphthyridines on the side chain of cyclopenta[*a*]phenanthren moiety was achieved by FGI reaction. The antimicrobial activity study revealed that compounds **3h,** showed good antimicrobial activity.

## ACKNOWLEDGEMENTS

The authors thank to UGC New Delhi and BCUD Savitribai Phule Pune University, Pune, India for financial support to this research project. Author also thanks to Department of Chemistry University of Pune, IIT-Powai Mumbai and Principal K.T.H.M. College Nashik, for spectral and analytical facilities.

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