Synthesis and Antimicrobial Activities of Iminothioether Linkers on Cyclopenta[*a*]phenanthrene Derivatives

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The reaction of methylbenzo[*h*][1,6]naphthyridine (**1**) with thiourea yield 4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene-7-thiol (**2**). The chemistry of compound **2** is explored to obtain iminothioether derivatives (**3a-h**) in good yields. The structures of newly synthesized compounds were confirmed by spectral data and elemental analysis. The antimicrobial activity of newly synthesized compounds were studied against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Bacillus cereus*, *Streptococcus sp.* and *Bacillus megaterium* by the agar well diffusion method. Compounds **3d**, **3f** and **3h** showed moderate antimicrobial activity.

Keywords: Benzo[*h*][1,6]naphthyridine, cyclopenta[*a*]phenanthrene, Antimicrobial.

INTRODUCTION

Benzo[1,6]naphthyridine derivatives are class of fused heterocyclic compounds that exhibit broad spectrum of biological activities such as antimalarial [1], inhibitor of HIV-1 integrase [2-5], HCMV [6,7], FGF receptor-1 tyrosine kinase [8] and the enzyme acetyl cholinesterase [9,10]. The SAR studies of these types of compounds were having quinoline nucleus as carrier of several cytotoxic agents [11,12]. Recent discovery of benzo[1,6]naphthyridine as selective highly potent mammalian inhibitor of rapamycin (mTOR) for the treatment of cancer cell [13,14]. In view of all these reports we have synthesized bioactive naphthyridine heterocyclic derivatives using α -acetyl γ -butyrolactone and heterocyclic amines, [15-21] to investigate new derivatives of benzo[*h*][1,6]naphthyridines. In this present communication we report the synthesis of C₇-iminotioether linkers to cyclopenta[*a*]phenanthrene-7-yl-sulfanyl)-*N*-phenyl acetamide.

EXPERIMENTAL

Commercially available common reagents was used for synthesis or synthesized by standard literature known methods. Open capillary tube method was used to measure melting points on Barnstead Electro Thermal apparatus Mod. No. IA-

9200. The thermo Quest flash EA 1112-Elemental Analyzer was used for elemental analysis of synthesized compounds. The IR spectra were recorded on Shimadzu IR 408 instrument and the mass spectra recorded on Varian Mat Bremen mass spectrometer Mat 112. The ¹H NMR spectra (300 MHz) and ¹³C NMR (75 MHz) were run on VARIAN XL-300 in CDCl₃ or DMSO-*d*₆ using TMS as an internal standard. Chemical shift (δ) are measured in ppm, coupling constants (*J*) in Hz. All reactions were checked by using TLC 0.2 mm silica gel 60 F₂₅₄ plates using UV light for detection 254 and 366 nm.

Synthetic procedures

4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene-7-thiol (2**):** A mixture of compound **1** (3.60 g, 0.01 mol) and thiourea (0.98 g, 0.013 mol) in acetic acid (20 mL) was refluxed for 20 min. The reaction completion was monitored by using TLC (toluene/ethyl acetate 8:2) and reaction mixture was slowly poured in 300 mL stirred ice cold water. The crude product was isolated by suction filtration and recrystallized by using ethanol and DMF gave 4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene-7-thiol (**2**); Yield (2.86 g, 90 %); m.p.: 242 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3350 (SH), 3330 (NH), 2923, 2852, 1660 (C=S), 1543, 1432, 1214, 766; ¹H NMR in

CDCl_3 : δ 2.61 (s, 3H, CH_3), 3.34 (t, $J = 7.0$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 3.38 (t, $J = 7.0$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 7.38 (t, $J = 6.9$ Hz, 1H, C_2H), 7.59 (d, $J = 6.9$ Hz, 1H, C_3H), 8.73 (d, $J = 6.9$ Hz, 1H, C_1H), 10.41 (s, 1H, SH); MS: m/z (%): 320 (M+2, 40), 318 (M, 100), 283 (30), 248 (20), 159 (10); Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{S}_2\text{Cl}$ (318.85): C, 56.51; H, 3.48; N, 8.79. Found: C, 56.42; H, 3.37; N, 8.74.

(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid ethyl ester (3a): Anhydrous potassium carbonate (2.04 g, 0.015 mol) was added to the stirred solution of 4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene-7-thiol (**2**) (4.77 g, 0.015 mol) and ethyl bromoacetate (3.6 mL, 0.018 mol) in DMF (50 mL) at 25 °C. Stirring the resulting solution for 2 h and the progress of reaction was confirmed by using TLC. After completion, the resulting solution was slowly added in cold water 500 mL. The precipitated solid was collected by suction filtration, washed with water and recrystallized in DMF/ethanol (2:8) to yield compound **3a**; Yield (5.51 g, 91 %); m.p.: 163 °C; IR (KBr, ν_{max} , cm^{-1}): 2976, 2929, 1739 (C=O), 1543, 1296, 1159, 954; ^1H NMR (CDCl_3): δ 1.29 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 2.67 (s, 3H, CH_3), 3.45 (t, $J = 7.8$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 3.56 (t, $J = 7.8$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 4.25 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 4.29 (s, 2H, CH_2), 7.43 (t, $J = 8.1$ Hz, 1H, C_2H), 7.74 (d, $J = 8.1$ Hz, 1H, C_3H), 8.90 (d, $J = 8.1$ Hz, 1H, C_1H); MS: m/z (%): 407 (M+2, 50), 405 (M+, 100), 311 (20), 195 (30), 134 (70), 100 (10). Anal. Calcd. for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_2\text{S}_2\text{Cl}$ (404.94): C, 56.36; H, 4.23; N, 6.92. Found: C, 56.30; H, 4.20; N, 6.94.

2-(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-N-substituted phenyl acetamide (3b-h): Anhydrous potassium carbonate (0.136 g, 0.001 mol) was added to the stirred solution of 4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene-7-thiol (**2**) (0.318 g, 0.001 mol) and 2-bromo-*N*-phenyl-acetamide (0.0012 mol) in DMF at 25 °C. Stirring the resulting solution for 2h and the progress of reaction was confirmed by using TLC. After completion, the resulting solution was slowly added in cold water (100 mL) and the solid obtained was recrystallized in DMF/ethanol (2:8) to yield iminothioether derivatives (**3b-h**).

2-(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-N-*p*-tolyl-acetamide (3b): Yield (0.396 g, 85 %); m.p.: 266 °C; IR (KBr, ν_{max} , cm^{-1}): 3338 (NH), 2918, 1685 (C=O), 1600, 1543, 1440, 1257, 1166, 1126, 950; ^1H NMR (CDCl_3): δ 2.24 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.47 (t, $J = 7.2$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 3.56 (t, $J = 7.2$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 4.30 (s, 2H, CH_2), 7.03 (d, $J = 7.8$ Hz, 2H, ArH), 7.37 (d, $J = 7.8$ Hz, 2H, ArH), 7.52 (t, $J = 7.8$ Hz, 1H, C_2H), 7.85 (d, $J = 7.8$ Hz, 1H, C_3H), 7.98 (d, $J = 7.8$ Hz, 1H, C_1H), 9.77 (s, 1H, NH); ^{13}C NMR (CDCl_3): δ ; MS: m/z (%): 468 (M+2, 20), 466 (M+, 31), 340 (50), 318 (100), 202 (50), 160 (40), 91 (30). Anal. Calcd. for $\text{C}_{24}\text{H}_{20}\text{N}_3\text{OS}_2\text{Cl}$ (466.03): C, 61.86; H, 4.33; N, 9.02. Found: C, 61.84; H, 4.30; N, 9.04.

2-(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-N-(4-fluorophenyl)acetamide (3c): Yield (0.408 g, 87 %); m.p.: 256 °C;

IR (KBr, ν_{max} , cm^{-1}): 3348 (NH), 2918, 1685 (C=O), 1545, 1506, 1404, 1211, 1165, 950; ^1H NMR (CDCl_3): δ 2.71 (s, 3H, CH_3), 3.46 (t, $J = 7.0$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 3.56 (t, $J = 7.0$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 4.40 (s, 2H, CH_2), 7.31 (d, $J = 8.2$ Hz, 2H, ArH), 7.51 (t, $J = 7.6$ Hz, 1H, C_2H), 7.67 (d, $J = 8.2$ Hz, 2H, ArH), 7.83 (d, $J = 7.6$ Hz, 1H, C_3H), 8.91 (d, $J = 7.6$ Hz, 1H, C_1H), 10.01 (s, 1H, NH); MS: m/z (%): 471 (M+2, 20), 469 (M+, 40), 418 (30), 361 (40), 319 (70), 151 (100), 91 (30). Anal. Calcd. for $\text{C}_{23}\text{H}_{17}\text{FN}_3\text{OS}_2\text{Cl}$ (469.99): C, 58.78; H, 3.65; N, 8.94. Found: C, 58.72; H, 3.64; N, 8.96.

2-(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-N-(4-chloro-phenyl)acetamide (3d): Yield (0.398 g, 82 %); m.p.: 262 °C; IR (KBr, ν_{max} , cm^{-1}): 3355 (NH), 2926, 2840, 1683 (C=O), 1594, 1510, 1318, 1224, 850; ^1H NMR (CDCl_3): δ 2.72 (s, 3H, CH_3), 3.46 (t, $J = 7.6$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 3.57 (t, $J = 7.6$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 4.41 (s, 2H, CH_2), 7.35 (d, $J = 8.3$ Hz, 2H, ArH), 7.54 (t, $J = 7.8$ Hz, 1H, C_2H), 7.61 (d, $J = 8.3$ Hz, 2H, ArH), 7.82 (d, $J = 7.8$ Hz, 1H, C_3H), 8.85 (d, $J = 7.8$ Hz, 1H, C_1H), 9.81 (s, 1H, NH); MS: m/z (%): 489 (M+4, 10), 487 (M+2, 40), 485 (M+, 70), 450 (30), 415 (20), 361 (50), 325 (100), 168 (90), 125 (75). Anal. Calcd. for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{OS}_2\text{Cl}_2$ (486.45): C, 56.79; H, 3.52; N, 8.64. Found: C, 56.73; H, 3.55; N, 8.67.

2-(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-N-(2,4-dichlorophenyl)acetamide (3e): Yield (0.468 g, 90 %); R_f (toluene/ethyl acetate 8:2) 0.71, m.p.: 229 °C; IR (KBr, ν_{max} , cm^{-1}): 3244 (NH), 2920, 2850, 1683 (C=O), 1546, 1514, 1442, 1305, 1168, 954; ^1H NMR (CDCl_3): δ 2.78 (s, 3H, CH_3), 3.57 (t, $J = 6.9$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 3.64 (t, $J = 6.9$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 4.49 (s, 2H, CH_2), 7.23-7.27 (m, 2H, ArH), 7.56 (t, $J = 8.1$ Hz, 1H, C_2H), 7.84 (d, $J = 8.1$ Hz, 1H, C_3H), 8.30 (d, $J = 7.9$ Hz, 1H, ArH), 9.01 (d, $J = 8.1$ Hz, 1H, C_1H), 9.81 (s, 1H, NH); MS: m/z (%): 526 (M+6, 20), 524 (M+4, 30), 522 (M+2, 50), 520 (M+, 90), 368 (40), 367 (100), 325 (20), 135 (20), 116 (15); Anal. Calcd. for $\text{C}_{23}\text{H}_{16}\text{N}_3\text{OS}_2\text{Cl}_3$ (520.89): C, 53.04; H, 3.10; N, 8.07. Found: C, 53.07; H, 3.06; N, 8.10.

N-(2-Chloro-6-fluorophenyl)-2-(4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)acetamide (3f): Yield (0.438 g, 87 %); m.p.: 263 °C; IR (KBr, ν_{max} , cm^{-1}): 3250 (NH), 3041, 2922, 1685 (C=O), 1546, 1444, 1280, 1168, 952; ^1H NMR (CDCl_3): δ 2.74 (s, 3H, CH_3), 3.51 (t, $J = 6.7$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 3.59 (t, $J = 6.7$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 4.51 (s, 2H, CH_2), 7.24-7.32 (m, 4H, ArH), 7.55 (t, $J = 8.0$ Hz, 1H, C_2H), 7.91 (d, $J = 8.0$ Hz, 1H, C_3H), 8.85 (d, $J = 8.0$ Hz, 1H, C_1H), 10.06 (s, 1H, NH); MS: m/z (%): 507 (M+4, 10), 505 (M+2, 30), 503 (M+, 100), 436 (40), 393 (20), 361 (40), 319 (30), 196 (80), 142 (50). Anal. Calcd. for $\text{C}_{23}\text{H}_{16}\text{N}_3\text{OS}_2\text{Cl}_2\text{F}$ (504.44): C, 54.77; H, 3.20; N, 8.33. Found: C, 54.74; H, 3.23; N, 8.36.

2-(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-N-(3-chloro-4-trifluoromethylphenyl)acetamide (3g): Yield (0.448 g, 81 %); m.p.: 243 °C; IR (KBr, ν_{max} , cm^{-1}): 3317 (NH), 2922, 1691 (C=O), 1545, 1483, 1223, 1130, 950; ^1H NMR (CDCl_3): δ 2.70 (s, 3H, CH_3), 3.50 (t, $J = 7.2$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 3.57 (t, $J = 7.2$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{S}$), 4.29 (s, 2H, CH_2), 7.34 (d, $J = 8.4$

Hz, 1H, ArH), 7.53-7.63 (m, 2H, ArH, C₂H), 7.87-7.89 (m, 2H, ArH, C₃H), 9.03 (d, *J* = 8.4 Hz, 1H, C₁H), 10.21 (s, 1H, NH); Anal. Calcd. for C₂₄H₁₆N₃OS₂Cl₂F₃ (554.44): C, 51.99; H, 2.91; N, 7.58. Found: C, 52.03; H, 2.90; N, 7.55.

N-(2,4-bis-trifluoromethylphenyl)-2-(4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]-phenanthren-7-ylsulfanyl)acetamide (3h): Yield (0.531 g, 91 %); m.p.: 150 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3244 (NH), 2918, 2850, 1678 (C=O), 1546, 1433, 1142, 1042, 954; ¹H NMR (CDCl₃): δ 2.72 (s, 3H, CH₃), 3.50 (t, *J* = 6.5 Hz, 2H, CH₂CH₂S), 3.60 (t, *J* = 6.5 Hz, 2H, CH₂CH₂S), 4.43 (s, 2H, CH₂), 7.42-7.51 (m, 2H, ArH, C₂H), 7.60 (d, *J* = 8.1 Hz, 1H, C₃H), 7.74 (d, *J* = 6.9 Hz, 1H, ArH), 8.42 (s, 1H, ArH), 8.98 (d, *J* = 8.1 Hz, 1H, C₁H), 9.64 (s, 1H, NH); Anal. Calcd. for C₂₆H₁₉N₃OS₂ClF₅ (584.03): C, 51.70; H, 3.34; N, 6.96. Found: C, 51.73; H, 3.30; N, 6.94.

Antibacterial studies: Eight bacterial species such as *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Proteus vulgaris*, *Streptococcus sps*, *Bacillus megaterium* and *Pseudomonas aeruginosa* were tested for antimicrobial activity by agar well diffusion method. Nutrient agar (tryptone 1 %, yeast extract 0.5 %, NaCl 0.5 %, agar 2.5 %, 1000 mL of distilled water, PH 7.0) which was autoclaved under 121 °C for at least 20 min was inoculated by spread plate technique with bacteria from 24 h old culture having approximately 10⁴-10⁶ CFU (colony forming unit) per mL. After inoculation wells were made by sterile metallic boarer and the compound to be tested were loaded (100 μ L) in the well. The plates were incubated for 24 h and the activity was determined by measuring zone of inhibition around the well. All compounds was prepared in N,N-dimethyl formamide

(DMF), DMF was loaded as control. The average value of inhibition zone was calculated. All the experiment was carried out in triplicate for each bacterial culture. Ampicillin and streptomycin were used as antibacterial standard drugs. Zone of inhibition were determined for compounds **2** to **3(a-h)** the results are mentioned in Table-1.

RESULTS AND DISCUSSION

We already reported the synthesis of methylbenzo-[*h*][1,6]-naphthyridines (**1**) by using 4-aminoquinolines and α -acetyl γ -butyrolactone [15]. The iminechloride moiety was converted into thiol by refluxing compound **1** with thiourea in acetic acid furnished 4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene-7-thiol (**2**) in 90 % yield [22,23]. The structure of compound **2** showed thiol (SH) stretching at 3350, NH at 3330 cm⁻¹ and (C=S) at 1660 cm⁻¹ in its IR spectra. It was observed that alkylation reaction on compound **2** with bromoester/substituted *N*-phenyl bromoacetamide in presence of anhydrous K₂CO₃ in DMF at room temperature gave only *S*-alkylated compound **3** in 82-91 % yield, which showed absence of (C=S) stretching frequency indicates the *S*-alkylation in **3**. The ¹H NMR spectrum in CDCl₃ of **3a** showed triplets at δ 3.45 and δ 3.56 ppm with *J* = 8.1 Hz were designate for CH₂CH₂S. The up field triplet at δ 1.28 ppm and down field quartet at δ 4.25 ppm with *J* = 7.2 Hz were designate for OCH₂CH₃. The peak at δ 4.29 ppm was assigned for methylene protons, the other aromatic protons were resonance at expected splitting pattern and chemical shifts. The EIMS of compound **3a** showed M⁺ at 405 and M+2 at 407 *m/z*, corresponds to chlorine atom (**Scheme-I**).

TABLE-1
ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS TESTED AGAINST BACTERIAL SPECIES

Compd. No.	Antibacterial inhibition zone in diameter (mm)							
	<i>S. aureus</i>	<i>E. coli</i>	<i>B. subtilis</i>	<i>P. aeruginosa</i>	<i>P. vulgaris</i>	<i>B. cereus</i>	<i>Streptococcus sp</i>	<i>B. megaterium</i>
2	–	–	–	–	–	–	–	–
3a	–	–	–	–	–	–	–	–
3b	–	–	–	–	–	–	–	–
3c	–	–	–	–	–	–	–	–
3d	–	14	–	–	–	–	–	–
3e	–	–	–	–	–	–	–	–
3f	–	08	–	–	–	–	–	11
3g	–	–	–	–	–	–	–	–
3h	–	08	–	–	–	–	–	08
*Ampicillin	45	35	40	45	34	33	40	15
*Streptomycin	13	00	15	00	34	40	00	00

*Ampicillin and streptomycin are used as standard antibacterial agents.

3a: X=O, R=C₂H₅; **3b:** X=NH, R=4-MeC₆H₄; **3c:** X=NH, R=4-FC₆H₄; **3d:** X=NH, R=4-ClC₆H₄; **3e:** X=NH, R=2,4-ClC₆H₃; **3f:** X=NH, R=2-Cl,6-FC₆H₃; **3g:** X=NH, R=3-Cl,4-CF₃C₆H₃; **3h:** X=NH, R=2,4-CF₃C₆H₃

Scheme-I

Antimicrobial activities: To detect antimicrobial activities of compounds were screened against cultures of eight bacterial species, namely, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Bacillus cereus*, *Streptococcus sp* and *Bacillus megaterium* by agar well diffusion technique. Tested compounds showed moderate activity against the bacterial strains was mentioned in Table-1. Inhibition zone diameter (IZD in mm) was measured with solution concentration of each compound was 1.0 mg/mL. Streptomycin and ampicillin were used as an reference antibiotics antibacterial agents to evaluate the potency of tested compounds. The inhibitory concentration (MIC) of the biologically active compounds was determined by using two-fold dilution method. The results of newly synthesized compounds were obtained are shown in Table-1. The cyclopenta[*a*]phenanthren **3(a-h)** derivatives were showed antibacterial activity against *E. coli* and *B. megaterium* species.

Conclusion

The convenient synthesis of benzo[*h*][1,6]naphthyridines and cyclopenta[*a*]phenanthrens as a useful tool in the development of iminoether and iminothioether derivatives was developed. The antimicrobial activity study revealed that compounds **3d**, **3f** and **3h** showed moderate antimicrobial activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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