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ARTICLE

Synthesis and Antimicrobial Activity of Novel Oxothiazolidine Derivatives

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Asian Journal of Organic & Medicinal Chemistry

Volume: 5 Year: 2020
Issue: 2 Month: April–June
pp: 91–96
DOI: https://doi.org/10.14233/ajomc.2020.AJOMC-P248

Received: 9 January 2020
Accepted: 17 April 2020
Published: 2 July 2020

ABSTRACT

In this article, acid hydrazide **2**, a functional group, was synthesized by the reaction of (4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diaza-cyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid ethyl ester (**1**) with hydrazine yield (4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid hydrazide (**2**) is discussed. The reactive acid hydrazide compound **2** was utilized for the synthesis of amides **3**, Schiff's bases **4** and thiazolidine **5** derivatives. The structures of target compounds were confirmed by elemental analysis and spectral data. The antimicrobial activity of new compounds were studied against *Streptococcus* sp., *Bacillus megaterium*, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus*, *Bacillus subtilis*, *Proteus valgaris* and *Pseudomonas aeroginosa* by the agar well diffusion method. Compounds **4b**, **5a, 5b** and **5c** showed good antimicrobial activity.

KEYWORDS

Oxothiazolidines, Heterocyclic amines, Antimicrobial activity.

INTRODUCTION

Thiazolidinone and hydrazide hydrazone derivatives are important class of heterocyclic compounds, which attract researchers to synthesize and biological evaluation of their activities. The hydrazide hydrazones mainly acts as chemotherapeutic agents, which are also useful as a building block for the synthesis of verity of heterocyclic derivatives. Thiazolidinones is a important five membered heterocyclic ring compound having sulfur at 1-position, the nitrogen at 3-position and carbonyl group at 2, 4 or 5 position. However, the hetero atoms like sulfur, nitrogen and oxygen present in the penicillin was first time recognize and characterize its occurrence in the nature [1]. The ring structure of thiazolidinone is a core component of penicillin derivatives, which shows broad spectrum of therapeutic activities. Numerous reports in the literature survey highlight their use and chemistry. The compounds of giltazones or thiazolidinone diones act as insulin sensitizers and used for the treatment of type second diabetes. Diabetic disorder is initiated due to the metabolic action caused by hyperglycemia, which is characterized due to insulin secretion deficiency [2]. An aryl thiazolidinone derivative shows hypolipidemic and hypoglycemic activities againt type 2 diabetes [3,4].

There are different types of human pathogen like *S. aureus* asymptomatically colonizing 30% of the human population.

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Escherichia coli virulent strain causes infections like gastroenteritis, urinary tract infections, *etc*. Similarly, *Bacillus cereus* is a Gram-positive, beta hemolytic bacterium commonly found in soil and food are harmful to humans to cause food borne illness. To control such types of infections there are several drugs are used. The thiazolidinone derivatives showed wide spectrum of activities such as anti-hyperglycemic and anti-hyperlipidemic [5], antimicrobial [6,7], antitubercular [8], antifungal [9], anti-inflammatory [10,11], anticancer [12] and virus type 1 (HIV-1) activities [13]. 4-Tiazolidinone derivatives were reported as novel class of inhibitors of the bacterial enzyme Mur B, which was precursor for the biosynthesis of peptidoglycan [14].

Several methods were used for the synthesis of thiazolidinone derivatives are widely reported in the literature. The synthesis of thiazolidinones involves three components such as carbonyl compound, mercapto acid and amine. In the past years, the synthesis reported can be either condensation of three components in one pot or two step process. In this reaction first formation of imine derivatives by the condensation of aldehydes or ketones with amines, which undergoes attack with mercapto acid followed by intramolecular cyclization and elimination of water molecule, gives thiazolidinones [15]. Thiazolidinone derivatives also synthesized by one pot cyclocondensation of maleic acid, substituted aldehyde, thiosemicarbazide and catalytic amount of *p*-toluenesulfonic acid in dry toluene was irradiated in microwave at 100-120 ºC [16].

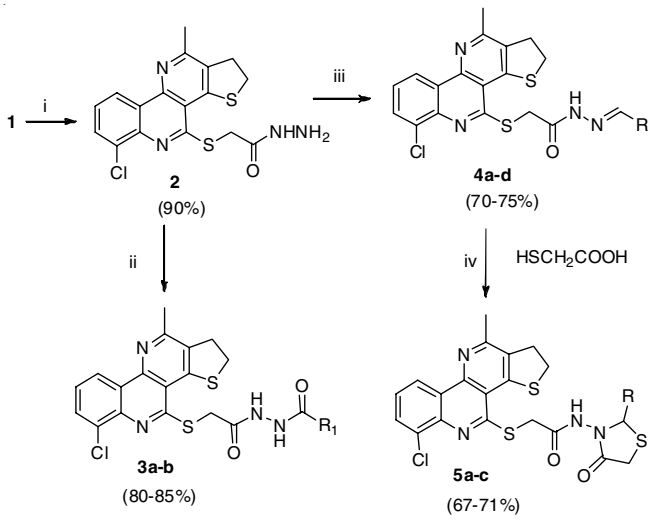
In view of all these facts, the synthesis of bioactive heterocyclic derivatives using α-acetyl γ-butyrolactone and heterocyclic amines [17-23], enthused us to investigate new derivatives of benzo[*h*][1,6]naphthyridine for medicinal purpose. In this work, the synthesis and antimicrobial activity of novel thiazolidinone ring on the side chain of benzo[*h*]naphthyridine derivatives are reported.

EXPERIMENTAL

The melting points were measured on melting point apparatus Barnstead Electro Thermal 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 ºC. 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 (δ scale) are quoted in parts per million (ppm).

Compound **1** was synthesized according to our reported work [17].

(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid hydrazide (2): A reaction mixture of (4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-acetic acid ethyl ester (**1**) (4.04 mL, 0.01 mol), hydrazine (0.384 g, 0.012 mol) and five drops of acetic acid in absolute ethanol was refluxed for 20 h. The reaction progress was continuously checked by TLC using toluene/ethyl acetate (2:8) till the reactant was consumed. After completion of the reaction, the obtained product was filtered and washed with little ethanol (**Scheme-I**). Compound **2** was recrystallized in DMF gave yellow coloured prisms (3.12 g, 80%, mp 201 ºC); R_f 0.29 (ethyl acetate/toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): 3292 (NH), 3203 (NH_2), 2916, 2829, 1662 (C=O), 1545, 1483, 1307, 1084, 775; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.76 (s, 3H, CH_3), 3.47 (t, *J* = 7.4 Hz, 2H, CH_2C-H_2S), 3.57 (t, *J* = 7.4 Hz, 2H, CH_2CH_2S), 4.28 (s, 2H, CH_2), 4.42 (s, 2H, NH_2, exchangeable with D_2O), 7.40 (t, *J* = 8.0 Hz, 1H, C_2H), 7.73 (d, *J* = 8.0 Hz, 1H, C_3H), 8.91 (d, *J* = 8.0Hz, 1H, C_1H), 9.31 (s, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 392 (M+2, 50), 390 (M+, 90), 323 (100), 232 (45), 199 (40), 116 (30), 100 (10). Anal. calcd. (found) % for $C_{17}H_{15}N_4OS_2Cl$ (m.w. 390.92): C, 52.23 (52.32); H, 3.87 (3.89); N, 9.07 (9.02).



3a: R^1=4-MeC_6H_4 **4a:** R=C_6H_5 **5a:** R= C_6H_5
3b: R^1=3-ClC_6H_4 **4b:** R=3,4-$OMeC_6H_3$ **5b:** R=3,4-$OMeC_6H_3$
3c: R^1=C_6H_4 **4c:** R=3-$NO_2C_6H_4$ **5c:** R=3-$NO_2C_6H_4$
3d: R^1=4-ClC_6H_4 **4d:** R=4-ClC_6H_4

Scheme-I: Reagents and conditions: (i) NH_2NH_2, EtOH, AcOH, reflux, 20 h; (ii) ArCOOH, AcOH, reflux, 3 h; (iii) ArCHO, EtOH, AcOH, 80 ºC, 5 h; (iv) EtOH, Anhydrous $ZnCl_2$, reflux, 5 h

4-Chloro-12-methyl-7-(phenyl-[1,3,4]-oxadiazol-2-ylmethylsulfanyl)-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene (3a-d): A solution of (4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid hydrazine (**2**) (0.390 g, 0.001 mol), respective aryl acid (0.0012 mol) and sulfuric acid (1 mL) was refluxed for 5 h in 10 mL acetic acid. The reaction progress was continuously monitored by using TLC in toluene/ethyl acetate (2:8) till the reactant was consumed. The reaction mixture was cooled to room temperature after completion. The solid was filtered, recrystallized in DMF to give compound **3a-d** (**Scheme-I**).

4-Chloro-12-methyl-7-(5-*p*-tolyl-[1,3,4]oxadiazol-2-ylmethylsulfanyl)-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene (3a): Pink prisms; yield (0.416 g, 85%, m.p. 323 ºC); R_f 0.28 (ethyl acetate/toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): 3188, 3130 (NH), 1656, 1647 (C=O), 1548, 1330, 802; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 3.49 (t, *J* = 7.2 Hz, 2H, CH_2CH_2S), 3.53 (t, *J* =

7.2 Hz, 2H, CH_2CH_2S), 4.35 (s, 2H, CH_2), 7.12 (d, *J* = 7.5 Hz, 2H, ArH), 7.38 (d, *J* = 7.5 Hz, 2H, ArH), 7.51 (t, *J* = 7.3 Hz, 1H, C_2H), 7.81 (d, *J* = 7.3 Hz, 1H, C_3H), 8.92 (d, *J* = 7.3 Hz, 1H, C_1H), 9.91 (s, 1H, NH, exchangeable with D_2O), 9.95 (S, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 510 (M+2, 30), 508 (M+, 100), 473 (20), 389 (30), 359 (40), 317 (50), 191 (80), 149 (30), 119 (20). Anal. calcd. (found) % for $C_{25}H_{21}N_4O_2S_2Cl$ (m.w. 509.05): C, 58.99 (58.91); H, 4.16 (4.18); N, 11.01 (11.04).

4-Chloro-7-(5-(3-chlorophenyl)[1,3,4]oxadiazol-2-ylmethylsulfanyl)-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene (3b): Pink prisms; Yield: 0.408 g, 80%), m.p. 319 ºC); R_f 0.29 (ethyl acetate/toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): 3178, 3141 (NH), 3045, 1654, 1643 (C=O), 1556, 1332, 804; ^1H NMR (300 MHz, DMSO-d_6): δ 2.73 (s, 3H, CH_3), 3.45 (t, *J* = 7.4 Hz, 2H, CH_2CH_2S), 3.55 (t, *J* = 7.4 Hz, 2H, CH_2CH_2S), 4.36 (s, 2H, CH_2), 7.08-7.32 (m, 3H, ArH), 7.20 (s, 1H, ArH), 7.53 (t, *J* = 7.6 Hz, 1H, C_2H), 7.77 (d, *J* = 7.6 Hz, 1H, C_3H), 8.91 (d, *J* = 7.6 Hz, 1H, C_1H), 9.93 (s, 1H, NH, exchangeable with D_2O), 9.97 (S, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 532 (M+4, 20), 530 (M+2, 40), 528 (M+, 100), 458 (30), 389 (40), 359 (30), 325 (30), 211 (90), 169 (60), 139 (70). Anal. calcd. (found) % for $C_{24}H_{18}N_4O_2S_2Cl_2$ (m.w. 529.47): C, 54.44 (54.40); H, 3.43 (3.38); N, 10.58 (10.47).

4-Chloro-7-(5-phenyl[1,3,4]oxadiazol-2-ylmethylsulfanyl)-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene (3c): Faint pink coloured prisms; yield: 0.356 g, 70%; m.p. 305 ºC; R_f 0.23 (ethyl acetate/toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): 3140, 3096 (NH), 3024, 1659, 1650 (C=O), 1543, 1320, 807; ^1H NMR (300 MHz, DMSO-d_6): δ 2.68 (s, 3H, CH_3), 3.38 (t, *J* = 7.3 Hz, 2H, CH_2CH_2S), 3.52 (t, *J* = 7.3 Hz, 2H, CH_2CH_2S), 4.20 (s, 2H, CH_2), 7.02-7.20 (m, 5H, ArH), 7.51 (t, *J* = 6.5 Hz, 1H, C_2H), 7.70 (d, *J* = 6.5 Hz, 1H, C_3H), 8.90 (d, *J* = 6.5 Hz, 1H, C_1H), 9.92 (s, 1H, NH, exchangeable with D_2O), 9.95 (S, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 496 (M+2, 40), 494 (M+, 100), 390 (40), 324 (30), 178 (40), 138 (60). Anal. calcd. (found) % for $C_{24}H_{19}N_4O_2S_2Cl$ (m.w. 494.06): C, 58.23 (58.10); H, 3.87 (3.80); N, 11.32 (11.29).

4-Chloro-7-(5-(4-chlorophenyl)[1,3,4]oxadiazol-2-ylmethylsulfanyl)-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthrene (3d): Faint brown coloured prisms; yield: 0.343 g, 65%, m.p. 296 ºC); R_f 0.32 (ethyl acetate /toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): 3159, 3120 (NH), 3010, 1656, 1643 (C=O), 1542, 1350, 810; ^1H NMR (300 MHz, DMSO-d_6): δ 2.60 (s, 3H, CH_3), 3.36 (t, *J* = 7.4 Hz, 2H, CH_2CH_2S), 3.47 (t, *J* = 7.4 Hz, 2H, CH_2CH_2S), 4.30 (s, 2H, CH_2), 7.18-7.30 (m, 4H, ArH), 7.46 (t, *J* = 6.8 Hz, 1H, C_2H), 7.68 (d, *J* = 6.8 Hz, 1H, C_3H), 8.95 (d, *J* = 6.8 Hz, 1H, C_1H), 9.85 (s, 1H, NH, exchangeable with D_2O), 9.90 (S, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 532 (M+4, 25), 530 (M+2, 30), 528 (M+, 100), 456 (20), 390 (30), 324 (30), 178 (30), 168 (50), 139 (60). Anal. calcd. (found) % for $C_{24}H_{18}N_4O_2S_2Cl_2$ (m.w. 529.47): C, 54.44 (54.50); H, 3.43 (3.48); N, 10.58 (10.52).

(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid substituted benzylidene-hydrazide (4a-d): A solution of (4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]-phenanthren-7-ylsulfanyl)acetic acid hydrazide (**2**) (1.95 g, 0.005 mol), aryl aldehyde (0.006 mol) and five drops of acetic acid in absolute ethanol (15 mL) was heated to reflux for 3.5 h. The progress of the reaction was checked by using TLC in toluene/ethyl acetate (2:8) till the reactant was consumed. After completion, the solid obtained was suction filtered and washed with ethanol, recrystallized in DMF to give compounds **4a-d** in good yield (**Scheme-I**).

(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid benzylidene-hydrazide (4a): Pink prisms; yield: 1.79 g, 75%; m.p.: 265-266 ºC); R_f 0.68 (ethyl acetate/toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): 3244 (NH), 1679 (CO), 1610, 1552, 1438, 1166, 954; ^1H NMR (300 MHz, DMSO-d_6): δ 3.34 (s, 3H, CH_3), 3.48 (t, *J* = 7.2 Hz, 2H, CH_2CH_2S), 3.60 (t, *J* = 7.2 Hz, 2H, CH_2CH_2S), 4.85 (s, 2H, CH_2), 7.34-7.47 (m, 3H, ArH), 7.54 (t, *J* = 7.8 Hz, 1H, C_2H), 7.67-7.73 (m, 2H, ArH), 7.85 (d, *J* = 7.7 Hz, 1H, C_3H), 8.04 (s, 1H, N=CH), 8.84 (d, *J* = 7.8 Hz, 1H, C_1H), 11.67 (s, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 481 (M+2, 20), 479 (M+, 100), 375 (30), 360 (40), 320 (40), 318 (60), 201 (40), 161 (70), 119 (70). Anal. calcd. (found) % for $C_{24}H_{19}N_4OS_2Cl$ (m.w. 479.03): C, 60.18 (60.14); H, 4.01 (4.07); N, 11.71 (11.64).

(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid (3,4-dimethoxy benzylidene)hydrazide (4b): Pink prisms; yield: 1.88 g, 70%; m.p. 244-245 ºC); R_f 0.70 (ethyl acetate/toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): 3213 (NH), 3043, 2898, 1666 (CO), 1550, 1506, 1297, 1024; ^1H NMR (300 MHz, DMSO-d_6): δ 3.38 (S, 3H, CH_3), 3.50 (t, *J* = 7.3 Hz, 2H, CH_2CH_2S), 3.61 (t, *J* = 7.3 Hz, 2H, CH_2CH_2S), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.82 (s, 2H, CH_2), 6.97 (d, *J* = 7.0 Hz, 1H, ArH), 7.21-7.27 (m, 2H, ArH), 7.53 (t, *J* = 8.4 Hz, 1H, C_2H), 7.87 (d, *J* = 8.4 Hz, 1H, C_3H), 7.97 (s, 1H, N=CH), 8.81 (d, *J* = 8.4 Hz, 1H, C_1H), 11.83 (s, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 541 (M+2, 30), 539 (M+, 100), 508 (40), 477 (50), 375 (40), 252 (50), 220 (90), 178 (80), 121 (40). Anal. calcd. (found) % for $C_{26}H_{23}N_4O_3S_2Cl$ (m.w. 539.08): C, 57.93 (57.88); H, 4.30 (4.35); N, 10.39 (10.35).

(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-acetic acid (3-nitro-benzylidene)hydrazide (4c): Pink prisms; yield: 1.83 g, 70%; m.p. 251-252 ºC); R_f 0.68 (ethyl acetate/toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): 3215 (NH), 3030, 2910, 1680 (CO), 1606, 1530, 1295, 1020; ^1H NMR (300 MHz, DMSO-d_6): δ 3.36 (s, 3H, CH_3), 3.51 (t, *J* = 7.2 Hz, 2H, CH_2CH_2S), 3.60 (t, *J* = 7.2 Hz, 2H, CH_2CH_2S), 4.86 (s, 2H, CH_2), 7.53 (t, *J* = 8.1 Hz, 1H, C_2H), 7.70 (t, *J* = 6.8 Hz, 1H, ArH), 7.83 (d, *J* = 7.9 Hz, 1H, C_3H), 8.18 (s, 1H, N=CH), 8.20-8.35 (m, 3H, ArH), 8.84 (d, *J* = 7.9 Hz, 1H, C_1H), 11.91 (s, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 527 (M+2, 30), 525 (M+, 60), 479 (30), 444 (30), 376 (50), 208 (60), 206 (100), 178 (40), 125 (50). Anal. calcd. (found) % for $C_{24}H_{20}N_5O_3S_2Cl$ (m.w. 526.04): C, 54.80 (54.85); H, 3.83 (3.79); N, 13.31 (13.36).

(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid (4-chlorobenzylidene)hydrazide (4d): Pink prisms; yield (1.86 g, 73%, mp 281 ºC); R_f 0.73 (ethyl acetate/toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): 3240 (NH), 3203, 3068, 1676 (CO), 1600,

1515, 1438, 1166, 954; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.36 (s, 3H, CH_3), 3.49 (t, *J* = 7.4 Hz, 2H, CH_2CH_2S), 3.60 (t, *J* = 7.4 Hz, 2H, CH_2CH_2S), 4.82 (s, 2H, CH_2), 7.43-7.53 (m, 3H, ArH, C_2H), 7.71-7.75 (m, 2H, ArH), 7.83 (d, *J* = 7.8 Hz, 1H, C_3H), 8.11 (s, 1H, N=CH), 8.81 (d, *J* = 7.9 Hz, 1H, C_1H), 11.71 (s, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 517 (M+4, 20), 515 (M+2, 80), 513 (M+, 90), 369 (20), 368 (30), 367 (100), 339 (15), 324 (15), 311 (10). Anal. calcd. (found) % for $C_{24}H_{18}N_4OS_2Cl_2$ (m.w. 513.47): C, 56.14 (56.11); H, 3.53 (3.56); N, 10.91 (10.87).

2-(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-*N*-(2-(phenyl-4-oxo-2-phenyl-thiazolidin-3-yl)acetamide (5a-c): Compound **4a-c** (0.553 g, 0.001 mol) was refluxed with thioglycolic acid (0.138 g, 0.002 mol) in presence of anhydrous $ZnCl_2$ (0.135 g, 0.001 mol) in dry ethanol (25 mL) for 5 h. The reaction progress was checked by TLC in toluene/ethyl acetate (2:8) till the reactant was consumed. After completion the mixture of reaction was cooled, the solid obtained was filtered and recrystallized in DMF to furnished compound **5a-c** in good yield (**Scheme-I**).

2-(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-*N*-(4-oxo-2-phenyl-thiazolidin-3-yl)acetamide (5a): Pink prisms; yield: 0.392 g, 71%; m.p.: 239-241 ºC); R_f 0.30 (ethyl acetate/toluene 8:2);IR (KBr, ν_{max}, cm^{-1}): 3320 (NH), 3010, 2917, 1730 (C=O), 1703 (C=O), 1546, 1309, 1170, 952; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.33 (s, 3H, CH_3), 3.48 (t, *J* = 7.0 Hz, 2H, CH_2CH_2S), 3.59 (t, *J* = 7.0 Hz, 2H, CH_2CH_2S), 4.30 (s, 2H, CH_2), 4.83 (s, 2H, CH_2), 4.93 (s, 1H, CH), 7.27-7.39 (m, 3H, ArH), 7.53 (t, *J* = 7.7 Hz, 1H, C_2H), 7.61-7.71 (m, 2H, ArH), 7.83 (d, *J* = 7.7 Hz, 1H, C_3H), 8.91 (d, *J* = 7.6 Hz, 1H, C_1H), 11.89 (s, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 555 (M+2, 20), 553 (M+, 40), 518 (30), 476 (20), 366 (30), 235 (100), 193 (90), 178 (70), 122 (40). Anal. calcd. (found) % for $C_{26}H_{21}N_4O_2S_3Cl$ (m.w. 553.13): C, 56.47 (56.40); H, 3.82 (3.80); N, 10.12 (10.15).

2-(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diaza-cyclopenta[*a*]phenanthren-7-ylsulfanyl)-*N*-[2-(3,4-dimethoxyphenyl)-4-oxothiazolidin-3-yl)-acetamide (5b): Pink prisms; yield: 0.410 g, 67%, m.p.: 243-244 ºC); R_f 0.40 (ethyl acetate/toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): *v* 3309 (NH), 2912, 1714 (C=O), 1703 (C=O), 1546, 1307, 1085, 950; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.36 (s, 3H, CH_3), 3.51 (t, *J* = 7.4 Hz, 2H, CH_2CH_2S), 3.60 (t, *J* = 7.4 Hz, 2H, CH_2CH_2S), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2), 4.83 (s, 2H, CH_2), 4.97 (s, 1H, CH), 7.05-7.21 (m, 3H, ArH), 7.55 (t, *J* = 7.8 Hz, 1H, C_2H), 7.85 (d, *J* = 7.8 Hz, 1H, C_3H), 8.81 (d, *J* = 7.8 Hz, 1H, C_1H), 11.91 (s, 1H, NH, exchangeable with D_2O); MS: *m/z* (%): 615 (M+2, 20), 613 (M+, 60), 551 (40), 313 (60), 281 (100), 239 (40), 224 (30), 137 (40). Anal. calcd. (found) % for $C_{28}H_{25}N_4O_4S_3Cl$ (m.w. 613.18): C, 54.85 (54.86); H, 4.11 (4.16); N, 9.14 (9.16).

2-(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diazacyclopenta[*a*]phenanthren-7-ylsulfanyl)-*N*-[2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)-acetamide (5c): Pink prisms; yield: 0.426 g, 71%; m.p. 354 ºC); R_f 0.43 (ethyl acetate /toluene 8:2); IR (KBr, ν_{max}, cm^{-1}): 3188 (NH), 3047, 2950, 1695 (C=O), 1666 (C=O), 1533, 1433, 1271, 954; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.37 (s, 3H, CH_3), 3.50 (t, *J* = 7.3 Hz, 2H, CH_2CH_2S), 3.61 (t, *J* = 7.3 Hz, 2H, CH_2CH_2S), 4.40 (s, 2H, CH_2), 4.82 (s, 2H, CH_2), 5.03 (s, 1H, CH), 7.54 (t, *J* = 8.1 Hz, 1H, C_2H), 7.69 (t, *J* = 6.5 Hz, 1H, ArH), 7.88 (d, *J* = 8.1 Hz, 1H, C_3H), 8.22-8.40 (m, 3H, ArH), 8.82 (d, *J* = 8.0 Hz, 1H, C_1H), 11.91 (s, 1H, NH, exchangeable with D_2O) ; MS: *m/z* (%): 601 (M+2, 20), 599 (M+, 70), 425 (20). 317 (20), 208 (100), 166 (60), 151 (70). Anal. calcd. (found) % for $C_{26}H_{22}N_5O_4S_3Cl$ (m.w. 600.14): C, 52.04 (52.01); H, 3.70 (3.74); N, 11.67 (11.65).

Antibacterial activity: Antibacterial 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/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), 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). Test samples prepared in DMF (10 mg/mL) were loaded into the wells of the plates. 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. The test was performed three times for each bacterium culture. Ampicilin and streptomycin was used as antibacterial standard drugs.

RESULTS AND DISCUSSION

(4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diaza-cyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid ethyl ester **1** on reaction with hydrazine hydrochloride in acidic medium gave acid hydrazide derivative **2** in 80% yield. No reaction progress was observed in absence of acid catalyst. The structure of newly synthesized compounds was established by analytical and spectral data. The IR spectrum of compound **2** shows stretching frequency at 1662 (C=O), 3292 (NH), 3203 cm^{-1} (NH_2). The ^{1}H NMR spectrum in DMSO-d_6 of compound **2** showed the broad singlet at δ 4.42 ppm was assignable for NH_2 and at δ 9.31 ppm was assignable for NH protons. The CH_2 group was deshields at 4.28 ppm due to attach with electro negative sulfur and carbonyl group. The doublet at 2.76 & 3.47 ppm was assignable for the protons of CH_2CH_2S group respectively. The remaining protons showed expected splitting pattern and chemical shifts. Compound **2** on reaction with aromatic acid in presence of small amount of sulfuric acid in AcOH as solvent furnished compound **3a-b** in 80-85% yield. Here also the reaction does not observed in absence of H_2SO_4 catalyst. The same reaction in $POCl_3$ furnishes inseparable mixture of products. The IR spectrum of compound **3a** shows stretching frequency at 1647, 1656 (C=O), 3188-3130 cm^{-1} (NH). The ^{1}H NMR spectrum in DMSO-d_6 of compound **3a** showed the resonance singlet at δ 9.91 & 9.95 ppm was assignable for NH protons. On refluxing compound **2** with aryl aldehydes in presence of AcOH in dry ethanol furnished compound **4a-c** in 70-75% yields. The structures of **4a-c** were established by analytical

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

Compd. No.	Antibacterial inhibition zone diameter (mm)							
	P. aeroginosa	*B. subtilis*	*E. coli*	*S. aureus*	*B. cereus*	*P. valgaris*	*B. megaterium*	*Streptococcus* sp
2	–	–	–	–	–	–	–	–
3a	–	–	–	–	–	–	–	–
3b	–	–	–	–	–	–	–	–
3c	–	–	8	–	–	–	–	–
3d	–	–	–	–	8	–	–	–
4a	–	8	10	–	-	–	–	–
4b	–	14	13	–	10	17	15	8
4c	–	13	–	8	–	–	–	–
4d	–	–	–	–	–	–	–	–
5a	16	17	13	12	10	16	16	10
5b	8	16	8	17	16	11	–	8
5c	–	15	–	16	13	–	40	–
Ampicillin	45	40	35	45	33	34	15	40
Streptomycin	–	15	–	13	40	34	–	–

& spectral data. IR of **4a** showed stretching at 1680-1666 cm^{-1} (amide) and 3244-3213 cm^{-1} (NH). The ^1H NMR (DMSO-d_6) spectrum of compound **4a** showed the resonance singlet at δ 8.04 ppm was assignable for N=CH and at δ 11.67 ppm was assignable for NH, the remaining protons showed expected splitting pattern and chemical shifts. The EIMS showed M+ (479) and M+2 (481) *m/z*, indicating the presence of one chlorine atom. 4-Chloro-12-methyl-16,17-dihydro-15-thia-6,11-diaza-cyclopenta[*a*]phenanthren-7-ylsulfanyl)acetic acid benzylidene hydrazides **4a-c** on refluxing with thioglycolic acid in presence of one equivalent anhydrous $ZnCl_2$ in ethanol furnished compound **5a-c** in good yields. The excess amount of catalyst $ZnCl_2$ do not alter the rate of reaction but create difficulty in product purification, while lower amount than 1 equivalent decrease the rate of reaction. Other catalyst $AlCl_3$ or H_2SO_4 gave mixture of inseparable mixture of products. The IR spectrum of compound **5a** shows carbonyl stretching frequency at 1703, 1730 cm^{-1} and NH at 3320 cm^{-1}. The ^1H NMR spectrum in DMSO-d_6 of compound **5a** showed the highly deshielded singlet at δ 11.89 ppm was assignable for NH protons. The remaining protons showed expected splitting pattern and chemical shifts.

Antimicrobial activity: The synthesized compounds screened against the cultures of different bacterial species, namely, *Bacillus megaterium*, *Staphylococcus aureus*, *Proteus valgaris*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeroginosa*, *Bacillus cereus* and *Streptococcus* sp. were screen for antimicrobial activity. The agar well diffusion technique was used to study antimicrobial activities. Compounds **4b**, **5a**, **5b** and **5c** showed good activity against the diffrent bacterial strains. The bacterial organisms were screened in solutions of compound having concentration; 1.0 mg/mL. Ampicillin and streptomycin as a reference compounds were used against antibacterial species to evaluate the activity of synthesized compounds under similar conditions. The minimum inhibitory concentrations (MIC) of the synthesized compounds were measured by two-fold dilution method. The screening results are depicted in Table-1. Compound **5a, 5b** and **5c** having pharmacologically active thiazolidin ring on side chain of cyclopenta[*a*]phenanthrene. Also the substituent 3-phenyl, 3,4-dimethoxyphenyl and 3-nitrophenyl on thiazolidin ring showed increasing activity. Compound **5c** showed good activity against *Bacillus megaterium* species than the standard ampicillin and streptomycin.

Conclusion

A 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 disclosed. The synthesized thiazolidine derivative on the side chain of cyclopenta[*a*]phenanthren moiety was achieved by FGI reaction. The antimicrobial activity study revealed that compounds **3d, 3h** and **5a-c** exhibited a good antimicrobial activity. Thiazolidine derivative **5c** showed excellent activity against *Bacillus megaterium*.

ACKNOWLEDGEMENTS

The author thanks to U.G.C. New Delhi and B.C.U.D. University of Pune, India for financial support to this research project. Author also thanks to Department of Chemistry, University of Pune, IIT Mumbai and Principal K.T.H.M. College Nashik, India for spectral and analytical facilities.

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