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BIOACTIVE NUCLEOSIDE DERIVATIVE OF 3- (2- PHENYL- PYRIDIN- 3- YL) -5A, 9A- DIHYDRO - 4H - 11- THIA-1, 2, 3A, 4, 5, 10- HEXAAZACYCLOPENTA [B] ANTHRACENE

Chemistry

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ABSTRACT

Target compound 2-Hydroxymethyl-5- [3- (2-phenyl- pyridin -3- yl) - 5a, 9a, dihydro - 11-thia, 1, 2, 3a, 4, 5, 10-hexaaza- cyclopenta [b] anthracen-4-y]- tetrahydro-furan-3,4-diol was obtained by glycosylation followed by deacetylation of potential bioactive compound 3- (2- Phenyl- pyridin- 3- yl) -5a, 9a- dihydro - 4H - 11- thia-1, 2, 3a, 4, 5, 10- hexaazacyclopenta [b] anthracene , which has been synthesized by the reaction of o-phenylenediamine and 3- (2-Phenyl- pyridin- 3- yl) - 1, 8a-dihydro- [1, 2, 4] triazolo [3, 4-b] [1, 3, 4] thiadiazine -6, 7- dione.

KEYWORDS

Antiviral, 3- (2- Phenyl- pyridin- 3- yl) -5a, 9a- dihydro - 4H - 11- thia-1, 2, 3a, 4, 5, 10- hexaazacyclopenta [b] anthracene , 2-Hydroxymethyl-5- [3- (2-phenyl- pyridin -3- yl) - 5a, 9a, dihydro - 11-thia, 1, 2, 3a, 4, 5, 10-hexaaza- cyclopenta [b] anthracen-4-y]- tetrahydro-furan-3,4-diol.

INTRODUCTION With the enormous global burden of increasing bacterial infections which is the major cause of the most of the threatening diseases led to the alarming rise in the number of clinical isolates displaying drug resistance or increased virulence [1]. The problem of resistance has necessitated research into the design and synthesis of most bioactive nucleoside derivatives. Among various synthetic compounds, substituted 1, 2, 4-triazolo-1, 3, 4-thiadiazines are reported to possess antifungal, antibacterial and anticancer activities [2-4]. Additional bioactivities shown by such molecules include antitubercular, anti-inflammatory and antimolluscicidal etc. [5-6]. And various substituted 1, 2, 4-triazolo [3, 4-*b*]- 1, 3, 4-thiadiazines and schiff's bases are associated with diverse pharmacological activities, such as analgesic, anthelmintic, antitubercular, plant growth regulating, antiviral, antifungal and anticancer properties [7-10].

EXPERIMENTAL

General

All chemicals were used as received without further purification. NMR spectra were recorded on a Bruker Advance DPX-400400 FT spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C) using $CDCl_3$as solvent and TMS as an internal reference. Mass spectra were recorded on a JEOL SX-102 (FAB) mass spectrometer at 70eV. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. Silica gel-G was used for TLC. Melting points were determined by open glass capillary method and are uncorrected.

I. Synthesis of N'- (2-Phenyl – pyridine -3- carbonyl) - hydrazine carbodithioic acid potassium salt:

To a solution of 2-Phenyl-nicotinic acid hydrazide (2.19 mmol) in ethanol was added KOH solution (2.36 mmol) in ethanol, the resulting solid was treated with CS_2(3.28 mmol) and was stirred for about 18 hrs at room-temperature under nitrogen atmosphere then diluted with diethyl ether.

II. Synthesis of 4-Amino- 5 (2-phenyl- pyridin- 3- yl) - 4H- [1, 2, 4] triazole -3- thiol:

A solution of I (1.4 mmol), in water was treated with hydrazine hydrate (7.30mmol) the resulting solution was refluxed for about 1hr. The resulting mixture was cooled and diluted with water and acidified with glacial acetic acid. The precipitate thus obtained was filtered and washed with cold water and recrystallised from ethanol.

III. Synthesis of 3- (2-Phenyl- pyridin- 3- yl) - 1, 8a-dihydro- [1, 2, 4] triazolo [3, 4-b] [1, 3, 4] thiadiazine -6, 7- dione:

To a solution of II (1 mmol) in dry benzene was added oxalyldichloride (1 mmol) the resulting solution was heated under reflux for about 6 hrs solvent was removed under pressure. Then cooled at room-temperature, poured into the crushed ice. The precipitate was filtered, dried and recrystallised from ethanol.

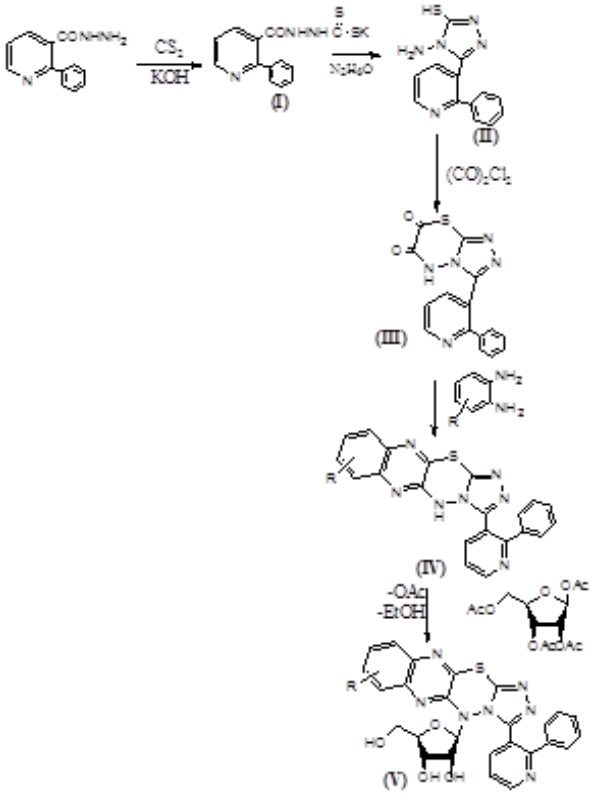
IV. Synthesis of 3- (2- Phenyl- pyridin- 3- yl) -5a, 9a- dihydro - 4H - 11- thia-1, 2, 3a, 4, 5, 10- hexaazacyclopenta [b] anthracene:

To a solution of compound III (1 mmol) in acetonitrile was added o-phenylenediamine (1 mmol) was heated under reflux for about 6-8 hrs. The precipitate was filtered, dried and recrystallised from ethanol.

V. Synthesis of 2-Hydroxymethyl-5- [3- (2-phenyl- pyridin -3- yl) - 5a, 9a, dihydro - 11-thia, 1, 2, 3a, 4, 5, 10-hexaaza- cyclopenta [b] anthracen-4- y]- tetrahydro-furan-3 ,4- diol:

A mixture of compound IV (0.002 mol), 1, 2, 3, 5-tetracetyl -β- D -O-ribofuranose (0.002mol) and iodine (0.002mol) was dissolved in minimum amount of dioxane. The mixture was refluxed for 4-7 hrs. After cooling the mixture was poured into aqueous solution of sodium thiosulphate to remove excess of iodine. The acylated nucleoside, thus, obtained was filtered, washed with water and dried. The compound was crystallized from mixture of ethanol and ethylacetate to obtain pure compound. For deacetylation the compound was dissolved in 20ml of dry methanol and 1ml sodium methoxide. The mixture was allowed to stand for 4-5 hours, with occasional shaking. The solution was neutralized with dilute HCl .The product, thus, precipitated was filtered, washed and crystallized from absolute ethanol **V (a-f).**

Scheme :



R= H, 3-Cl, 3-Br, 3-NO_2, 3-CH_3, 2-CH_3

Characterization of the synthesized compounds V (a-f):

Compound V (a)

Yield: 86%; M.p: 90 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.7-8.1

(m, 4H, ArH), 7.28-7.99 (m, 5H, ArH), 7.04-8.52 (m, 3H, ArH) 4.81 (d, 1H, C-1'H), 3.65-3.89 (m, 2H, C-2'H & C-3'H), 3.91 (m, 1H,C-4'H), 3.66 (m, 2H, C-5'H), 2.0 (s, 3H, 3xOHexchangeable with D_2O); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ :61.9, 70, 73, 75.7, 88.1, 120.7, 125, 126, 127.1, 128, 129, 132.2, 135.4, 136, 139.7, 143, 148, 148.3, 157, 162EIMS: (m/z): 527.14 (M+). Anal. calcd. For $C_{26}H_{21}N_7O_4S$ C: 59.19, H: 4.01, N: 18.59, O: 12.13, S: 6.08 %

Compound V (b)

Yield: 92%; M.p:112 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.9-8.5 (m, 3H, ArH), 7.20-7.90 (m, 5H, ArH), 7.10-8.60 (m, 3H, ArH) 4.88 (d, 1H, C-1'H), 3.67-3.99 (m, 2H, C-2'H & C-3'H), 3.97 (m, 1H,C-4'H), 3.72 (m, 2H, C-5'H), 2.5 (s, 3H, 3xOHexchangeable with D_2O); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ :61.9, 70, 73, 75.7, 88.1, 120.7, 125, 127.1, 129, 130, 132.2,134, 135.4, 136, 139.7, 143, 148, 148.3, 157, 163 EIMS: (m/z): 561.10 (M+). Anal. calcd. For $C_{26}H_{20}ClN_7O_4SC$: 55.57, H: 3.59, Cl: 6.31, N: 17.45, O: 11.39, S: 5.71 %

Compound V (c)

Yield: 74%; M.p: 100 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.0-8.8 (m, 3H, ArH), 7.32-7.93 (m, 5H, ArH), 7.14-8.48 (m, 3H, ArH) 4.76 (d, 1H, C-1'H), 3.61-3.83 (m, 2H, C-2'H & C-3'H), 3.88 (m, 1H,C-4'H), 3.69 (m, 2H, C-5'H), 2.2 (s, 3H, 3xOHexchangeable with D_2O); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ :61.9, 70, 73, 75.7, 88.1, 120.7, 122, 127.1, 128, 129, 130, 132.2, 135.4, 136, 137, 139.7, 141, 148, 148.3, 157, 162 EIMS: (m/z): 607.05 (M+). Anal. calcd. For $C_{26}H_{20}BrN_7O_4SC$: 51.49, H: 3.32, Br: 13.18, N: 16.17, O: 10.55, S: 5.29 %

Compound V (d)

Yield: 82%; M.p: 115 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 8.3-9.0 (m, 3H, ArH), 7.22-7.99 (m, 5H, ArH), 7.07-8.58 (m, 3H, ArH) 4.89 (d, 1H, C-1'H), 3.71-3.90 (m, 2H, C-2'H & C-3'H), 3.93 (m, 1H,C-4'H), 3.75 (m, 2H, C-5'H), 2.7 (s, 3H, 3xOHexchangeable with D_2O); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ :61.9, 70, 73, 75.7, 88.1, 118, 120.7, 123, 127.1, 129, 130, 132.2, 135.4, 138, 139.7, 140,142, 148, 148.3, 149, 157, 164 EIMS: (m/z): 572.12 (M+). Anal. calcd. For $C_{26}H_{20}N_8O_6SC$: 54.54, H: 3.52, N: 19.57, O: 16.77, S: 5.60 %

Compound V (e)

Yield: 97%; M.p: 86 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.1-8.2 (m, 3H, ArH), 7.22-7.96 (m, 5H, ArH), 7.11-8.66 (m, 3H, ArH), 2.35 (s, 3H, -CH_3), 4.88 (d, 1H, C-1'H), 3.56-3.94 (m, 2H, C-2'H & C-3'H), 3.94 (m, 1H,C-4'H), 3.71 (m, 2H, C-5'H), 2.3 (s, 3H, 3xOHexchangeable with D_2O); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ :20.9, 61.9, 70, 73, 75.7, 88.1, 120.7, 125, 127, 127.1, 129, 132.2, 134, 135, 135.4, 138,139.7, 143, 148, 148.3, 157, 161 EIMS: (m/z): 541.15 (M+). Anal. calcd. For $C_{27}H_{23}N_7O_4S$ C: 59.88, H: 4.28, N: 18.10, O: 11.82, S: 5.92 %

Compound V (f)

Yield: 80%; M.p: 106 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.8-8.5 (m, 3H, ArH), 7.33-7.99 (m, 5H, ArH), 7.01-8.48 (m, 3H, ArH), 2.28 (s, 3H, -CH_3), 4.81 (d, 1H, C-1'H), 3.61-3.83 (m, 2H, C-2'H & C-3'H), 3.86 (m, 1H,C-4'H), 3.69 (m, 2H, C-5'H), 2.1 (s, 3H, 3xOHexchangeable with D_2O); ^{13}CNMR (100MHz, $CDCl_3$ / TMS) δ :16.2, 61.9, 70, 73, 75.7, 88.1, 120.7, 125, 126, 127.1, 129,132, 132.2, 135, 135.4, 136, 139.7, 142, 148, 148.3, 157, 161 EIMS: (m/z): 541.15 (M+). Anal. calcd. For $C_{27}H_{23}N_7O_4S$ C: 59.88, H: 4.28, N: 18.10, O: 11.82, S: 5.92 %

Antiviral activity:

Some derivatives of the titled compound were subjected for their assay against two animal viruses *viz.* (HSV-1) and HAV. Analysis followed standard method by a virus plaque reduction assay. It was found that some of them posses moderate to good antiviral activity

Compd.	Conc. (µg/mL)	Inhibition(%)	
		HSV-1	HAV
Va	20	61.5	53.6
Vb	30	73.2	71.8
Ve	40	58.2	45.8

CONCLUSION:

An efficient synthesis has been developed for the titled compound, which has good antiviral activity against two animal viruses *viz. (HSV-1)* and *HAV.*

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