Original Research Paper Chemistry

Antiviral Agent 5-(β-D-O-Ribofuranosyl)-1-[4-(1-Methyl- 1H- Benzoimidazol-2-Yl)- Phenyl] -3, 6-Diphenyl -4- Thioxo- [1, 3, 5] Triazinan-2-One

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ABSTRACT

Desired compound 5-(β-D-O-ribofuranosyl)-1- [4-(1-Methyl- 1H- benzoimidazol-2-yl)- phenyl] -3, 6- diphenyl -4- thioxo- [1, 3, 5] triazinan-2-one was obtained by glycosylation followed by deacetylation of compound of a novel compound 1- [4-(1-Methyl- 1H- benzoimidazol-2-yl)- phenyl] -3, 6- diphenyl -4- thioxo- [1, 3, 5] triazinan-2-one, which has been synthesized by the reaction of arylisocyanate and isothiocyanato-phenyl-methyl-[4-(1-methyl-1H-benzoimidazol-2yl)-phenyl]-amine.

KEYWORDS

1- [4-(1-Methyl- 1H- benzoimidazol-2-yl) - phenyl] -3, 6- diphenyl -4- thioxo- [1, 3, 5] triazinan-2-one, 1, 2, 3, 5-tetracetyl-β-D-O-ribofuranose, Japanese encephalitis virus (JEV) and Herpes simplex virus-1 (HSV-1).

INTRODUCTION

Resistance to antibacterial agents is a significant problem since last three decades [1-2]. As multidrug-resistant bacterial strains proliferate, the necessity for effective therapy has stimulated research into the design and synthesis of novel antimicrobial molecules. Among various synthetic compounds, triazines have been found to be potential candidates for antiviral agents [3-4].

The chemistry of [1, 3, 5] triazine compounds has been studied intensively and is the subject of many reviews [5]. The triazine scaffold possess potent antiprotozoal [6], anticancer [7], antimalarial [8], antiviral activity [9] and antimicrobial activity [10]. The benzimidazole core is 'privileged substructures' for a variety of enzymes and protein receptors [11]. They have emerged as potent non nucleoside inhibitors of HIV-1 reverse transcriptase [12] and specific inhibitors of the NS5B polymerase of the hepatitis C virus (HCV).[13]

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 70 eV. 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 4-(1-Methyl-1H-benzoimidazol-2-yl)-phenylamine:

Benzimidazoles, was readily prepared from substituted N-Methyl-benzene-1, 2-diamines and p-aminobenzaldehydes using chlorotrimethylsilane in DMF as a promoter and water-acceptor agent, followed by oxidation with air oxygen. S. V. Ryabukhin, A. S. Plaskon, D. M. Volochnyuk, A. A. Tolmachev, *Synthesis*, **2006**, 3715-3726.

II. Synthesis of Benzylidene- [4-(1-methyl-1H-benzoimidazol-2-yl)-phenyl]-amine:

A mixture of I (0.01mole), substituted aldehyde (0.01mole) and DMF (5drops) was subjected to microwave irradiation at 200w intermittently at 10 sec. intervals for the specified time. On completion of the reaction, as monitored by TLC, the reaction mixture was cooled and digested with cold water. The solid thus obtained was filtered, washed with water and purified by recrystallization from ethanol.

III. Synthesis of Isothiocyanato-phenyl-methyl-[4-(1-methyl-1H-benzoimidazol-2yl)-phenyl]-amine:

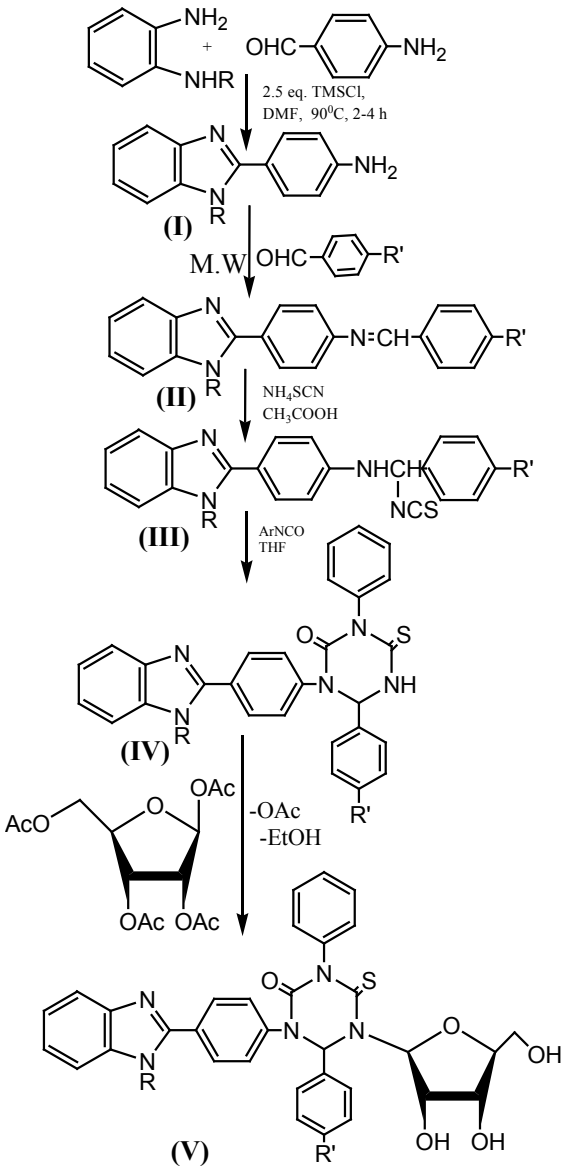
To a stirred solution of II (a-f) (0.01mole) in glacial acetic acid was added ammonium thiocyanate (0.015mole). After stirring for 4hrs the solid thus obtained was filtered, washed with water, dried and purified by recrystallization from ethanol.. Synthesis of 1- [4-(1-Methyl- 1H- benzoimidazol-2-yl) - phenyl] -3, 6- diphenyl -4- thioxo- [1, 3, 5] triazinan-2-one:

A solution of arylisocyanate (0.01mole) in THF was added dropwise to a solution of III (a-f) (0.01mole) in THF at reflux. The reaction mixture was refluxed for 10hrs. The solvent on evaporation resulted in crude product, which was filtered and purified by recrystallization from methanol.

V. Synthesis of 5-(β-D-O-ribofuranosyl)-1- [4-(1-Methyl-1H- benzoimidazol-2-yl)- phenyl] -3, 6- diphenyl -4- thioxo- [1, 3, 5] triazinan-2-one:

Compound IV (0.001mol), 1,2,3,5-tetracetyl-β-D-O-ribofuranose(0.001mol) and p-TsOH (0.003g) were mixed thoroughly in an agar mortar. Then the mixture was put into microwave oven for 8-15min. The progress of the reaction was monitored by TLC at every 3min. The resulting oil was dissolved in 1.5ml absolute ethanol. A solid was formed upon standing for about 1.5 hr. The crude product obtained by filteration was recrystallized from absolute methanol, and dried in vacuum to obtain the acetylated nucleosides. For deacetylation the compound was dissolved in 20ml of dry methanol and 1ml sodium methoxide. The mixture was allowed to stand for 2-4 hours, with occasional shaking. The solution was neutralized with dilute HCl .The product, thus, precipitated was filtered, washed and crystallized from absolute ethanol.

Scheme 1: 5-(β-D-O-ribofuranosyl)-1- [4-(1-Methyl- 1H- benzoimidazol-2-yl)- phenyl] -3, 6- diphenyl -4- thioxo- [1, 3, 5] triazinan-2-one



R'= H, Cl, CH_3, OH, OCH_3 and NO_2, R= CH_3

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

Compound V (a)

Yield: 80%; M.p: 86 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.26-7.70 (m, 4H, ArH), 3.63 (s, 3H, -CH_3), 7.46-7.70 (m, 4H, ArH), 6.01 (s, 1H, -CH), 7.06-7.14 (m, 5H, ArH), 7.24-7.64 (m, 5H, ArH), 4.96 (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); EIMS: (m/z): 621.20 (M+). Anal. calcd. For $C_{34}H_{31}N_5O_5S$ C: 65.68, H: 5.03, N: 11.26, O: 12.87, S: 5.16 %

Compound V (b)

Yield: 92%; M.p: 113 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.30-7.62 (m, 4H, ArH), 3.25 (s, 3H, -CH_3), 7.40-7.60 (m, 4H, ArH), 5.88 (s, 1H, -CH), 7.00-7.15 (m, 4H, ArH), 7.20-7.52 (m, 5H, ArH),5.02 (d, 1H, C-1'H), 3.70-3.92 (m, 2H, C-2'H & C-3'H), 3.89 (m, 1H,C-4'H), 3.68 (m, 2H, C-5'H), 2.4 (s, 3H, 3xOHexchangeable with D_2O); EIMS: (m/z): 655.17 (M+). Anal. calcd. For $C_{34}H_{30}ClN_5O_5S$ C: 62.24, H: 4.61, Cl: 5.40, N: 10.67, O: 12.19, S: 4.89 %

Compound V (c)

Yield: 90%; M.p: 79 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.28-7.77 (m, 4H, ArH), 3.58 (s, 3H, -CH_3), 7.37-7.79 (m, 4H, ArH), 6.05 (s, 1H, -CH), 7.12-7.17 (m, 4H, ArH), 2.35 (s, 3H, -CH_3), 7.14-7.44 (m, 5H, ArH),4.88 (d, 1H, C-1'H), 3.68-3.90 (m, 2H, C-2'H & C-3'H), 3.80 (m, 1H,C-4'H), 3.60 (m, 2H, C-5'H), 2.1 (s, 3H, 3xOHexchangeable with D_2O); EIMS: (m/z): 635.22 (M+). Anal. calcd. For $C_{35}H_{33}N_5O_5S$ C: 66.12, H: 5.23, N: 11.02, O: 12.58, S: 5.04 %

Compound V (d)

Yield: 88%; M.p: 90 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.36-7.69 (m, 4H, ArH), 3.62 (s, 3H, -CH_3), 7.44-7.70 (m, 4H, ArH), 5.90 (s, 1H, -CH), 7.00-7.12 (m, 4H, ArH), 5.0 (s, IH, -OH), 7.18-7.60 (m, 5H, ArH),4.88 (d, 1H, C-1'H), 3.60-3.86 (m, 2H, C-2'H & C-3'H), 3.95 (m, 1H,C-4'H), 3.55 (m, 2H, C-5'H), 2.3(s, 3H, 3xOHexchangeable with D_2O); EIMS: (m/z): 637.20 (M+). Anal. calcd. For $C_{34}H_{31}N_5O_6S$ C: 64.04, H: 4.90, N: 10.98, O: 15.05, S: 5.03 %

Compound V (e)

Yield: 80%; M.p: 99 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.16-7.66 (m, 4H, ArH), 3.60 (s, 3H, -CH_3), 7.36-7.79 (m, 4H, ArH), 6.03 (s, 1H, -CH), 7.07-7.19(m, 4H, ArH), 3.73(s, lH, -OCH_3), 7.19-7.54 (m, 5H, ArH), 4.92 (d, 1H, C-1'H), 3.55-3.78 (m, 2H, C-2'H & C-3'H), 3.88 (m, 1H,C-4'H), 3.68 (m, 2H, C-5'H), 2.04 (s, 3H, 3xOHexchangeable with D_2O); EIMS: (m/z): 651.22 (M+). Anal. calcd. For $C_{35}H_{33}N_5O_6S$ C: 64.50, H: 5.10, N: 10.75, O: 14.73, S: 4.92 %

Compound V (f)

Yield: 89%; M.p: 103 ^{O}C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ : 7.32-7.79 (m, 4H, ArH), 3.59 (s, 3H, -CH_3), 7.52-7.73 (m, 4H, ArH), 5.89 (s, 1H, -CH), 7.10-7.21 (m, 4H, ArH), 7.29-7.69(m, 5H, ArH), 4.86 (d, 1H, C-1'H), 3.55-3.99 (m, 2H, C-2'H & C-3'H), 3.86 (m, 1H,C-4'H), 3.59 (m, 2H, C-5'H), 2.5 (s, 3H, 3xOHexchangeable with D_2O); EIMS: (m/z): 666.19 (M+). Anal. calcd. For $C_{34}H_{30}N_6O_7S$ C: 61.25, H: 4.54, N: 12.61, O: 16.80, S: 4.81 %

Antiviral activity:

Some derivatives of the titled compound were subjected for their assay against two animal viruses viz. *Japanese encephalitis virus* (JEV) and *Herpes simplex virus-1* (HSV-1). Cytotoxicity and antiviral assays of the compounds were performed by the standard method. It was found that some of them posses moderate to good antiviral activity.

Compd.	**Anti-JEV *invitro* Conc.125 (µ/mL)**	**Anti-HSV-1 *invitro* Conc.125 (µ/mL)**
	Inhibition (%)	Inhibition (%)
Va	20	10
Vb	30	25
Vc	25	20

CONCLUSION:

A novel method of synthesis has been developed for 5-(β-D-O-ribofuranosyl)-1- [4-(1-Methyl- 1H- benzoimidazol-2-yl)- phenyl] -3, 6- diphenyl -4- thioxo- [1, 3, 5] triazinan-2-one, which has good antiviral activity against two animal viruses viz. *Japanese encephalitis virus* (JEV) and *Herpes simplex virus-1* (HSV-1).

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