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[Research article]

Synthesis, Anti-HIV activity and Cytotoxicity of N-Substituted Phthalimide derivatives

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ABSTRACT

A series of novel N-substituted phthalimide derivatives have been synthesized by condensation of phthalic anhydride and primary amines. Their chemical structures were assigned by means of spectral analysis (FT-IR and ^{1}H-NMR). Synthesized compounds were screened for antiviral activity against HIV-1 and -2 replication in MT-4 cells. Cytotoxicity was also investigated in uninfected MT-4 cells. All the synthesized compounds exhibited cytotoxicity in MT-4 cells (CC_{50}: 84-125 µg/ml).

KEYWORDS: N-Substituted phthalimide, Antiviral activity against HIV-1 and -2

INTRODUCTION

Phthalimide is a versatile lead molecule for the designing of potential therapeutic agents and its derivative, thalidomide used to treat various cancer, dermatological, neurological and inflammatory diseases[1]. N-Substituted phthalimide derivatives were tested for anti-HIV activity[2,3,4,5,6], some of their derivatives have also shown significant activity against HIV virus replication and HIV Reverse Transcriptase enzymatic activity[6]. Phthalimide react with p-nitrobenzoyl chloride yields the P-nitrobenzoyl phthalimide. A series of novel N-substituted phthalimide derivatives have been synthesized by condensation of phthalic anhydride and compounds with primary aromatic amino group (Scheme-1). Present work is to investigate the anti-HIV activity and cytotoxicity of newly synthesized phthalimide derivatives by using MT-4/MTT assay.

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Anti-HIV activity and Cytotoxicity

Synthesized compounds were tested for anti-HIV activity against the replication of HIV-1(III_B) and HIV-2(ROD) in MT-4 cells. Inhibitory effects of the compounds on HIV-1 and HIV-2 replication were monitored by inhibition of virus-induced cytopathic effect in MT-4 cells[7,8]. Cytotoxicity of the compounds for mock- infected MT-4 cells was assessed by the MTT method. Anti-HIV activity and cytotoxicity of standard AZT were also performed by a similar method in MT-4 cells (Table 1). All synthesized compounds exhibited cytotoxicity in MT-4 cells (CC_{50}: 84-125 µg/ml) and compound PH-2A4PT (CC_{50}: 84 ±2.49 µg/ml) toxic in this series.

EXPERIMENTAL

Melting points were determined using open ended capillary tube method and are uncorrected. FT-IR

recorded on Perkin Elmer–1605 series FT-IR in KBr disc. ^{1}H NMR Spectra were recorded at 400 MHz on Bruker FT-NMR spectrophotometer.

Synthesis of P-nitrobenzoyl phthalimide (PH-PNBOC)

An equimolar (0.01 mol) mixture of phthalimide and p-nitrobenzoyl chloride was dissolved with 20 ml of pyridine and refluxed for 4 hrs. The mixture was cooled to room temperature and poured into crushed ice, filter and then washed with water. The solid thus obtained was recrystallized from ethanol.

2-(4-Nitrobenzoyl)-isoindole-1,3-dione(PH-PNBOC)

IR(KBr):1670(C=0),1596(C=C), 690 (Ar-H); PMR (DMSO-d_6): 7.2-8.2 (m, 8H, Ar-H).

Synthesis of N-substituted Phthalimide derivatives

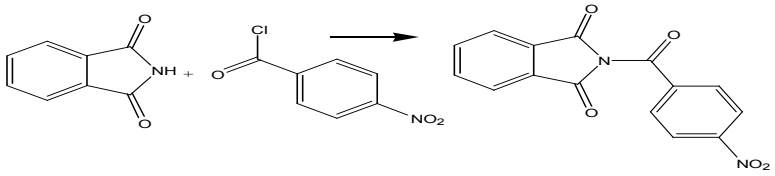
An equimolar (0.01 mol) mixture of phthalic anhydride and aromatic primary amine containing compounds (2-amino-4-phenylthiazole, 2-amino-benzthiazole and p-amino- benzoic acid) was dissolved in 10 ml of glacial acetic acid refluxed for 6 hrs. The mixture was cooled to room temperature and poured into crushed ice, filter and then washed with water. The solid thus obtained was recrystallized from ethanol.

4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-benzoic acid(PH-PABA):IR(KBr) :3134(OH), 1695(C=O), 1580 (C=C); PMR (DMSO-d_6): 9.02 (s,1H,-COOH), 6.5-7.8 (m, 8H, Ar-H).

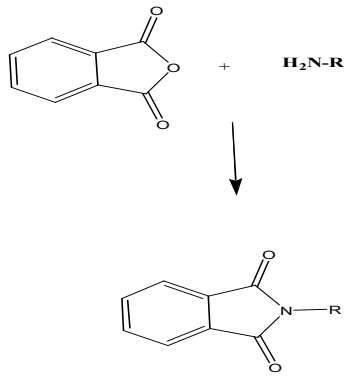
2-Benzothiazol-2-yl-isoindole-1,3-dione(PH2ABT) :IR(KBr):1620(C=O),1566(C=N), 1510 (C=C), 670 (Ar-H); PMR (DMSO-d_6): 6.5-7.8 (m, 8H, Ar-H).

2-(2-Phenyl-thiazol-4-yl)-isoindole-1,3-dione(PH-2A4PT):IR(KBr):1690(C=O),1574(C=N),1526(C=C), 670 (Ar-H); PMR (DMSO-d_6): 6.5 (s, 1H, CH-thiazole), 6.9-8.2 (m, 8H, Ar-H).

Synthesis of N-p-nitrobenzoyl phthalimide



Synthesis of N-substituted phthalimide derivatives



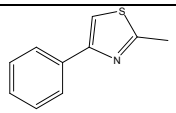
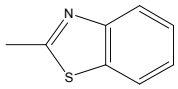
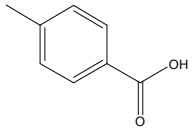
COMPOUND CODE	Substitution = R
PH-2A4PT	
PH-2ABT	
PH-PABA	

Table 1. PHYSICAL, ANTI-HIV ACTIVITY DATA OF SYNTHESIZED COMPOUNDS

Compound	M.P	Yield (%)	Strain	IC_{50}[a] (µg/ml)	CC_{50}[b] (µg/ml)
Phthalimide	-	-	III_B	>107.80	107.80±15.39
	-	-	ROD	>107.80	107.80±15.39
P-nitrobenzoyl chloride	-	-	III_B	>125	>125
	-	-	ROD	>125	>125
PH-PNBOC	210	67	III_B	>125	>125
	-	-	ROD	≥56.30	>125
PH-2ABT	243	62	III_B	>88.10	88.10±12.25
	-	-	ROD	>88.10	88.10±12.25
PH-2A4PT	205	56	III_B	>84.38	84.38±2.49
	-	-	ROD	>84.38	84.38±2.49
PH-PABA	278	74	III_B	>101	≥101
	-	-	ROD	>101	≥101
AZT (STD)	-	-	III_B	0.0015	>25
	-	-	ROD	0.0016	>25

[a] Concentrations required to inhibit the cytopathic effect of HIV-1(III_B) in MT-4 cells by 50%.
[b] Concentrations required to cause cytotoxicity to 50% of the MT-4 cells.
whereas HIV-1 = (IIIB), HIV-2 = (ROD). All the value of SD of two independent experiments.

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