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Synthesis and Anti-influenza Virus Activity of Ethyl 6-Bromo-5-hydroxyindole-3-carboxylate Derivatives

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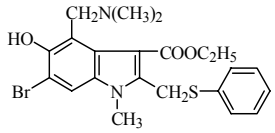
Abstract: A series of ethyl 6-bromo-5-hydroxyindole-3-carboxylate derivatives were synthesized and their *in vitro* anti-influenza virus activity was evaluated. All the compounds were characterized by ^{1}H NMR and MS.

Keywords: Ethyl 6-bromo-5-hydroxyindole-3-carboxylate derivatives, synthesis, anti-influenza virus activity.

Worldwide influenza pandemics have occurred at irregular and unpredictable intervals throughout history. The impact of pandemic influenza is substantial in terms of morbidity, mortality and economic cost. The chemotherapy options were limited to admantidine or rimantidine, which are only effective against influenza A and often cause side-effects and rapid viral resistance. Recently the launch of the neuraminidase inhibitors zanamivir and oseltamivir give a new option. Nevertheless, the improvement of these options still remains need[1].



The structure of arbidol

Arbidol is an antiviral and immunostimulatory agent launched in the Russian Federation for the prophylaxis and treatment of influenza A and B and other acute respiratory viral infections[2]. To improve its antiviral properties and broaden its antiviral spectrum, a number of different ethyl 6-bromo-5-hydroxyindole-3-carboxylate derivatives were designed and synthesized. As a part of our efforts to develop new antiviral compounds, Wang Dun[3] *et al.* synthesized a series of 4-tertiaryaminomethyl substituted derivatives. Herein, we designed a new series of ethyl 6-bromo-5-hydroxy-indole-3-carboxylate derivatives to investigate the influence of different groups at 1, 4 positions and the phenyl ring on the antiviral activity. Guanidine and imidazole have

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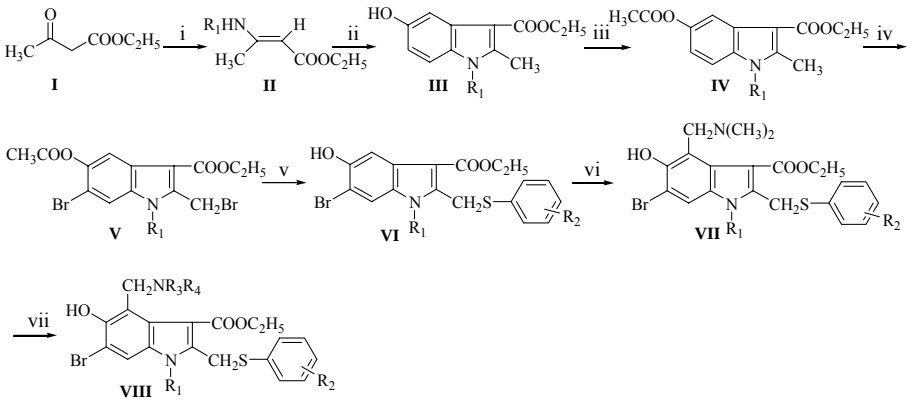
different basicity and affinity with enzyme and protein, so several structural changes were introduced, including guanidinyl, imidazolyl and 2-methyl-imidazol-1-yl substitutions on 4-postion, fluorine and chloride substitutions on the phenyl ring, replacement of methyl on 1-position by cyclopropyl. All the compounds were evaluated their antiviral activity *in vitro*, and some of them appeared to be potent inhibitors of influenza A3 and RSV replication and have low toxicity to the cells.

The title compounds ethyl 6-bromo-5-hydroxyindole-3-carboxylate derivatives were obtained as described in **Scheme 1,** and their structures were characterized by ^{1}H NMR and MS. The substituents of compounds **Ⅷa-j** and their physical data were shown in **Table 1**.

Scheme 1 The synthetic route of ethyl 6-bromo-5-hydroxyindole-3-carboxylate derivatives



Reagents and conditions: i. R_1NH_2, 35~45°C, 6 h; ii. 1,4-benzoquinone, $ClCH_2CH_2Cl$, 40~45°C; iii. CH_3COCl, $(C_2H_5)_3N$, acetone, rt, 4 h; iv. Br_2/CCl_4, benzoyl peroxide, reflux, 4 h. v. R_2-substituted thiophenol, NaOH, CH_3OH, rt, 8 h; vi. dimethylamine (33%), HCHO (37%), C_2H_5OH, CH_3COOH, 40~45°C, 6 h; vii. HNR_3R_4, C_2H_5OH, reflux, 4 h.

Table 1 The substitutents and physical data of compounds **Ⅷa-j**

Compd.	R_1	R_2	NR_3R_4	mp (°C)	Yield* (%)
Ⅷa	CH_3	H	2-methylimidazole-1-yl	140-142	20
Ⅷb	cyclopropyl	H	guanidinyl	182-184	24
Ⅷc	CH_3	H	guanidinyl	192-194	22
Ⅷd	CH_3	H	imidazole-1-yl	210-212	19
Ⅷe	CH_3	3′-F, 4′-F	guanidinyl	194-196	26
Ⅷf	CH_3	3′-F, 4′-F	2-methylimidazole-1-yl	166-168	19
Ⅷg	cyclopropyl	2′-Cl, 6′-Cl	imidazole-1-yl	208-210	20
Ⅷh	cyclopropyl	2′-Cl, 6′-Cl	guanidinyl	168-170	23
Ⅷi	cyclopropyl	4′-F	guanidinyl	180-182	24
Ⅷj	cyclopropyl	4′-F	imidazole-1-yl	202-204	21

*Overall yield from I.

The antiviral activity *in vitro* of compounds **VIIIa-j** was carried out in cell culture experiments. The viruses were human influenza A3 in MDCK (Madin-Darby canine kidney) cells and respiratory syncytial virus (RSV) in HeLa (human cervical carcinoma) cells respectively with the control amantadine and arbidol. The experimental results were shown in **Table 2**.

Compounds **VIIIa, c, j** showed potent antiviral activity and low cell toxicity according to their therapeutic index. Further investigation was underway.

Table 2 The antiviral activity of compounds **VIIIa-j** on influenza A3 virus and RSV

Compounds	IC_{50} (μg/mL)		TI	
	influenza A3	RSV	influenza A3	RSV
VIIIa	1.5±0	0.8±0	341	870
VIIIb	<5.8±0	1.7±0	85	213
VIIIc	3.9±0	3.9±0	128	128
VIIId	31.3±0	31.3±0	16	16
VIIIe	5.8±0	3.7±1.0	85	160
VIIIf	11.7±0	7.0±0	21	53
VIIIg	11.7±0	5.8±1.0	43	106
VIIIh	0.7±0	0.4±0	42	104
VIIIi	5.8±0	<3.1±0	106	213
VIIIj	2.9±0	1.6±0	417	426
Admantidine	0.97±0	0.97±0	128	256
Arbidol	3.9±0	3.9±0	32	32

IC_{50}: 50% inhibitory concentration; TI: therapeutic index. The results were the mean ± standard deviation IC_{50} of two independent determinations, calculated with Reed and Muench Method.

Experimental

*General procedures for the preparation of compounds **VIIIa-j**:*

Compound **II** 3-substituted aminocrotonate was prepared according to the literature[4] from commercially available **I** and appropriate alkyl substituted amine. Nentizescu condensation of **II** and 1,4-benzoquinone give the key intermediate **III**[5].

Acetic chloride (0.5 mol) was added dropwise into the stirred solution of **III** (0.05 mol) and triethylamine (0.1 mol) in 50 mL of acetone in cooling. The reaction mixture was then stirred at 25°C for 4 h before quenching by the addition of cooled water. The resulting precipitate was collected by filtration, rinsed with water, and dried to give **IV** in 85% yield.

Starting from **IV**, compound **VII** was synthesized in three steps by bromination with bromine, substitution by appropriately thiophenol, and Manncich reaction with dimethylamine. The synthetic procedure was according to the literature[6].

A mixture of **VII** (0.05 mol), HNR_3R_4 (0.15 mol) in 80 mL of ethanol was refluxed

for 4 h. After cooling, the resultant precipitate was collected by filtration and washed with ether and ethanol, then recrystallized with methanol to give the title compounds **VIIIa~j**[7].

Acknowledgment

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References and Notes

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5. S. A. Monti, *J. Org. Chem.*, **1966**, *31*, 2669.
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7. Melting points were determined with capillary tube method, and the thermometer was uncorrected. Mass spectra were obtained with a Finnigan LCQ HPLC-MS instrument. ^{1}H NMR spectra were run on a Bruker ARX-300 instrument and the solvents were DMSO-d_6.
VIIIa: [MH^+] (*m/z*): 514.1 (Br=79), 516.0 (Br=81); ^{1}H NMR: δppm: 1.07 (t, 3 H, J=7.2 Hz), 2.33 (s, 3 H), 3.71 (s, 3 H), 3.99 (q, 2 H, J=7.2 Hz), 4.65 (s, 2 H), 5.52 (s, 2 H), 6.27 (s, 1 H), 6.52 (s, 1 H), 7.29 (m, 5 H), 7.88 (s, 1 H), 8.95 (br s, 1 H); **VIIIb**: [MH^+] (*m/z*): 517.1 (Br=79), 519.1 (Br=81); ^{1}H NMR: δppm: 0.98 (m, 2 H), 1.13 (m, 2 H), 1.23 (t, 3 H, J=7.2 Hz), 2.91 (s, 1 H), 4.19 (q, 2 H, J=7.2 Hz), 4.51 (d, 2 H, J=5.3 Hz), 4.73 (s, 2 H), 6.60 (s, 2 H), 6.93 (s, 1 H), 7.36 (m, 5 H), 7.53 (s, 1 H), 13.13 (br, 1 H); **VIIIc**: [MH^+] (*m/z*): 491.0 (Br=79), 493.0 (Br=81);^{1}H NMR: δppm: 1.23 (t, 3 H, J=7.2 Hz), 3.51 (s, 3 H), 4.17 (q, 2 H, J=7.2 Hz), 4.55 (d, 2 H, J=5.2 Hz), 4.65 (s, 2 H), 6.62 (s, 2 H), 6.93 (s, 1 H), 7.28~7.39 (m, 5 H), 7.48 (s, 1 H); **VIIId**: [MH^+] (*m/z*): 500.0 (Br=79), 502.0 (Br=81); ^{1}H NMR: δppm: 1.28 (t, 3 H, J=7.2 Hz), 3.61 (s, 3 H), 4.17 (q, 2 H, J=7.2 Hz), 4.54 (s, 2 H), 6.01 (s, 2 H), 7.09 (s, 1 H), 7.19 (s, 1 H), 7.27-7.35 (m, 6 H), 7.53 (s, 1 H), 8.02 (br s, 1 H); **VIIIe**: [MH^+] (*m/z*): 527.0 (Br=79), 529.0 (Br=81); ^{1}H NMR: δppm: 1.22 (t, 3 H, J=7.1 Hz), 3.54 (s, 3 H), 4.16 (q, 2 H, J=7.1 Hz), 4.52 (s, 2 H), 4.66 (s, 2 H), 6.89 (m, 4 H), 6.89 (s, 1 H), 7.18 (m, 1 H), 7.39 (m, 1 H), 7.43 (s, 1 H), 7.45 (m, 1 H), 13.12 (br s, 1 H); **VIIIf**: [MH^+] (*m/z*): 550.0 (Br=79), 552.0 (Br=81); ^{1}H NMR: δppm: 1.06 (t, 3 H, J=7.2 Hz), 2.30 (s, 3 H), 3.77 (s, 3 H), 3.98 (q, 2 H, J=7.2 Hz), 4.65 (s, 2 H), 5.48 (s, 2 H), 6.23 (s, 1 H), 6.51 (s, 1 H), 7.11 (m, 1 H), 7.29~7.42 (m, 1 H), 7.89 (s, 1 H), 9.99 (br s, 1 H); **VIIIg**: [MH^+] (*m/z*): 596.4; ^{1}H NMR: δppm: 1.06 (m, 2 H), 1.09 (t, 3 H, J=7.1 Hz), 1.24 (m, 2 H), 3.25 (m, 1 H), 3.93 (q, 2 H, J=7.1 Hz), 4.66 (s, 2 H), 5.60 (s, 2 H), 6.73 (d, 1 H, J=8.9 Hz), 7.28 (s, 1 H), 7.39 (m, 1 H), 7.49 (m, 2 H), 7.84 (s, 1 H), 9.03 (br s, 1 H); **VIIIh**: [MH^+] (*m/z*): 587.4; ^{1}H NMR: δppm: 0.95 (m, 2 H), 1.09 (m, 2 H), 1.24 (t, 3 H, J=7.1 Hz), 2.97 (s, 1 H), 3.42 (m, 1 H), 4.08 (q, 2 H, J=7.1 Hz), 4.67 (s, 2 H), 4.74 (s, 2 H), 6.7 (s, 2 H), 6.87 (s, 1 H), 7.39 (m, 1 H), 7.50 (m, 2 H), 7.56 (s, 1 H); **VIIIi**: [MH^+] (*m/z*): 535.0 (Br=79), 537.0 (Br=81); ^{1}H NMR: δppm: 0.97 (m, 2 H), 1.13 (m, 2 H), 1.25 (t, 3 H, J=7.1 Hz), 2.88 (m, 1 H), 4.19 (q, 2 H, J=7.1 Hz), 4.53 (s, 2 H), 4.69 (s, 2 H), 6.68 (s, 2 H), 6.94 (s, 1 H), 7.22 (m, 2 H), 7.40~7.47 (m, 3 H), 7.54 (s, 1 H); **VIIIj**: [MH^+] (*m/z*): 544.0 (Br=79), 546.0 (Br=81); ^{1}H NMR: δppm: 1.06 (m, 2 H), 1.09 (t, 3 H, J=7.1 Hz), 1.23 (m, 2 H), 3.12 (m, 1 H), 3.99 (q, 2 H, J=7.1 Hz), 4.67 (s, 2 H), 5.78 (s, 2 H), 7.13 (m, 2 H), 7.33 (m, 2 H), 7.42 (s, 1 H), 7.59 (s, 1 H), 7.92 (s, 1 H), 8.83 (s, 1 H), 9.35 (s, 1 H), 14.61 (br s, 1 H).

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