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Synthesis and *In Vitro* Antiviral Activities of Some New 2-Arylthiomethyl-4-tertiaryaminomethylsubstituted Derivatives of 6-Bromo-3-ethoxycarbonyl-5-hydroxyindoles

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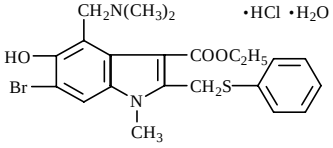
Abstract: Some new derivatives of 3-ethoxycarbonyl-6-bromo-5-hydroxyindoles were designed and prepared, their antiviral activity were determined in cell culture with virus cytopathic effect assay. The results showed compound **Ⅶ b**, **Ⅶ h** exhibited potential antiviral activity.

Keywords: 3-Ethoxycarbonyl-6-bromo-5-hydroxyindoles, antiviral, synthesis.

Influenza virus infection and acute respiratory viral infection (ARVI) remain a serious seasonal health concern. In this connection, chemotherapy is of great importance in the treatment of influenza and ARVI.

Substituted 6-bromo-3-ethoxycarbonyl-5-hydroxyindoles have been known to exhibit various biological activities such as antiviral activity for influenza virus, interferon-inducing effects and so on[1~4]. Abidol **1** has been developed and licensed for the treament and prophylaxis of influenza and other acute respiratory viral infection in Russia[5]. Hence, with Abidol as the leading compound, it was thought of considerable interest to synthesize its new analogs to evaluate their antiviral activities. Based on the structure of Abidol, we made some modifications. At the 2 positon of indole nucleus, the phenyl group was substituted by the strong electron-withdrawing fluoro group or the strong electron- donating methoxy group. At the 4 position, besides dimethylamino group, diethylamino group and some alicyclic amino groups such as piperidinyl, piperazinyl, morpholinyl were introduced. At the *N*-1 position, substituents containing more than one atom, especially, ethyl group were introduced. Thus, some new 2-arylthio methyl-4-tertiaryaminomethylsubstituted derivatives of 6-bromo-3-ethoxycarbonyl-5-hydroxyindoles were synthesized.

A process for preparing new derivatives was shown in **Scheme 1**: The key intermediate, 1, 2-dimethyl-3-ethoxycarbonyl-5-hydroxyindole Ⅱ was prepared by Nenitzescu



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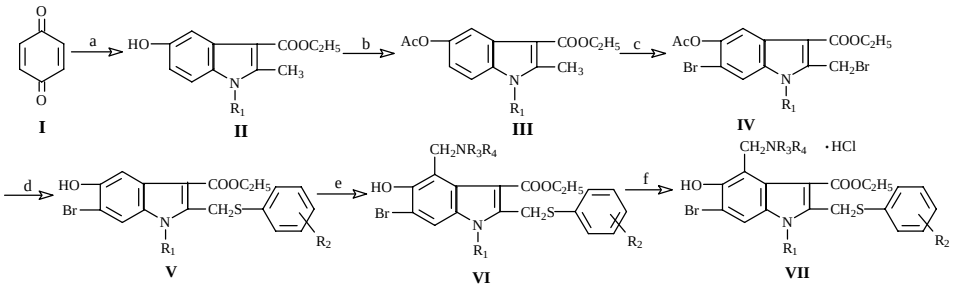
reaction[5]. II was acylated with acetic chloride affording the *O*-acyl derivative III, which was brominated to the corresponding dibromide IV with bromine. The reaction of IV with thiophenol or substituted thiophenol in the presence of an alkali metal hydroxide yielded V, which were reacted with formaldehyde and secondary amines in acetic acid, under 60℃ to refluxing temperature to give Mannich base VI. VI was treated with ethanolic solution of hydrochloric acid to give the target compoud VII.

With the above general procedure, compound VII **a~j** were prepared, and their structures, melting points and ^{1}H NMR data were listed in **Table 1.**

Scheme 1 The synthetic route of 6-bromo-3-ethoxycarbonyl-2-substitutedphenyl thiomethyl-4-tertiaryaminomethyl-5-hydroxyindoles



a. $CH_3(NHR_1)C{=}CHCOOC_2H_5$/$ClCH_2CH_2Cl$, reflux ; b. CH_3COCl/pyridine/CH_3COCH_3, 40-45℃; c. Br_2/CCl_4, reflux; d. R_2-substituted thiophenol/KOH/CH_3OH, r. t.; e. 37% HCHO/HNR_3R_4/ CH_3COOH, 60℃-reflux; f. HCl/C_2H_5OH/CH_3COCH_3, r. t.

Experimental

5-Acetoxy-1-alkyl-2-methyl-3-ethoxycarbonylindole(III)

To 500 mL of acetone were added 0.35 mol of II[6] and 0.7 mol of pyridine, and then was added dropwise 0.7 mol of acetic chloride with good stirring under 40-45℃ The resulting solution was stirred at this temperature for 4-5 h and then cooled. The solution was poured into 500 mL of water, the precipitate was collected by filtration and washed with water.

6-Bromo-3-ethoxycarbonyl-2-substitutedphenylthiomethyl-4-alkylsubstitutedtertiary aminomethyl-5-Hydroxyindoles (VI)

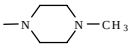
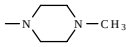
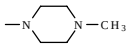
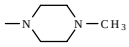
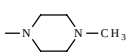
To a 225 mL of acetic acid was successively added 0.7 mol of a secondary amine, 0.3 mol of a 37.7% solution of formaline, and 0.27 mol of V[7]. The reaction mixture was stirred at 60°C to refluxing temperature for 8 h. The solvent was evaporated *in vacuo*, and 500 mL of water was added in one portion. The resultant mixture was adjusted pH to 12 with trimethylamine and extracted with methylene chloride. The organic phase was dried over sodium sulfate, and evaporated *in vacuo* to yield a yellow oil in most circumstances*.

* Exclusively, compoud VI **h** and VI **i** precipitated as crystal after the mixture was alkalized to pH 12 and so they can be obtained directly by filtration.

*6-Bromo-3-ethoxycarbonyl-2-substitutedphenylthiomethyl-4-alkylsubstitutedtertiaryam inomethyl-5-hydroxyindole hydrochloride (*VII)

To a solution containing 0.05 mol of VI in 500 mL of acetone was added 0.065 mol of ethanolic solution of hydrochloride acid. The mixture was allowed to stand for 0.5-1 h, the precipitate was obtained and recrystallized from a mixture of acetone and ethanol.

Table 1 The structures, melting point and ^{1}H NMR data of compounds **Ⅶ a~j**

Compd	R_1	$-R_2$	$-NR_3R_4$	Mp(℃)	^{1}H NMR (δ , ppm)
Ⅶ a	$-CH_3$	-H		198-200 (dec)	$CDCl_3$: 1.35 (t, 3H), 1.41-1.46 (m, 1H), 1.73-1.89 (m, 3H), 2.20- 2.34 (m, 2H), 2.86-2.97 (m, 2H), 3.30-3.34 (m, 2H), 3.58 (s, 3H), 4.21 (q, 2H), 4.54 (s, 2H), 5.19 (d, 2H), 7.22-7.32 (m, 5H), 7.63 (s, 1H), 10.27 (br s, 2H)
Ⅶ b	$-CH_3$	*p*-F		208-210	DMSO-d_6: 1.26 (t, 3H), 2.78 (br s, 3H), 3.43-3.94 (m, 8H), 3.69 (s, 3H), 4.19 (q, 4H), 4.70 (s, 2H), 4.98 (br s, 2H), 7.19 (dd, 2H), 7.39 (dd, 2H), 8.04 (s, 1H), 12.20 (br s, 2H)
Ⅶ c	$-CH_3$	*p*-F		130-132	DMSO-d_6: 1.24 (t, 3H), 2.71 (s, 6H), 3.68 (s, 3H), 4.14 (q, 2H), 4.67 (s, 2H), 4.88 (s, 2H), 7.15 (dd, 2H), 7.36 (dd, 2H), 8.02 (s, 1H), 9.12 (br s, 1H), 9.43 (br s, 1H)
Ⅶ d	$-CH_3$	*m*-OCH_3		166-168	DMSO-d_6: 1.25 (t, 3H), 2.78 (br s, 3H), 3.25-3.45 (m, 8H), 3.69 (s, 3H), 3.71 (s, 3H), 4.21 (q, 2H), 4.74 (s, 2H), 4.81 (br s, 2H), 6.86-6.96 (m, 3H), 7.26 (t, 1H), 8.01 (s,1H), 9.54 (br s, 1H), 12.05 (br s, 1H)
Ⅶ e	$-CH_3$	*m*-OCH_3		168-170	$CDCl_3$: 1.36 (t, 3H), 3.20-3.27 (m, 4H), 3.62 (s, 3H), 3.69 (s, 3H), 3.87-3.91 (m, 2H), 4.19-4.33 (m, 4H), 4.57 (s, 2H), 5.29 (d, 2H), 6.78-6.90 (m, 3H), 7.18 (t, 1H), 7.66 (s,1H), 8.39 (br s, 1H), 11.21 (br s, 1H)
Ⅶ f	$-C_2H_5$	-H		180-182	$CDCl_3$: 1.32 (t, 3H), 1.39 (t, 3H), 2.87 (s, 3H), 3.40- 3.44 (m, 2H), 3.61-3.65 (m, 2H), 4.06-4.09 (m, 4H), 4.30 (m, 4H), 4.60 (s, 2H), 5.38 (s, 2H), 7.30 (s, 5H), 7.62 (s, 1H), 11.62 (br s, 1H), 13.70 (br s, 1H)
Ⅶ g	$-C_2H_5$	*p*-F		208-210	DMSO-d_6: 1.22 (t, 3H), 1.25 (t, 3H), 2.77 (s, 3H), 3.30-3.48 (m, 8H), 4.18 (q, 2H), 4.24 (q, 2H), 4.65 (s, 2H), 5.02 (br s, 2H), 7.18 (t, 2H), 7.39 (dd, 2H), 8.00 (s, 1H), 9.69 (br s, 1H), 11.70 (br s, 1H)
Ⅶ h*	$-C_2H_5$	*p*-F		194-196	DMSO-d_6: 1.23 (t, 3H), 1.29 (t, 3H), 2.38 (s, 6H), 4.11 (q, 2H), 4.20 (s, 2H), 4.22 (q, 2H), 4.60 (s, 2H), 7.15 (t, 2H), 7.35 (dd, 2H), 7.80 (s, 1H), 8.01 (br s, 1H)
Ⅶ i*	$-C_2H_5$	*m*-OCH_3		159-161	$CDCl_3$: 1.33 (t, 3H), 1.38 (t, 3H), 2.66 (m, 4H), 3.69 (s, 3H), 3.72-3.77 (m, 4H), 4.09 (q, 2H), 4.21 (s, 2H), 4.22 (q, 2H), 4.51 (s, 2H), 6.79 (s, 1H), 6.81 (d, 2H), 6.94 (d, 2H), 7.19 (dd, 1H), 7.45 (s, 1H)
Ⅶ j	$-C_2H_5$	*m*-OCH_3		188-190	$CDCl_3$: 1.33 (t, 3H), 1.40 (t, 3H), 2.88 (s, 3H), 3.44- 3.48 (m, 2H), 3.62-3.66 (m, 2H), 3.72 (s, 3H), 4.07- 4.14 (m, 4H), 4.14-4.36 (m, 4H), 4.60 (s, 2H), 5.39 (s, 2H), 6.81 (s, 1H), 6.83 (d, 1H), 6.91 (d, 1H), 7.21 (dd, 1H), 7.63 (s, 1H), 11.55 (br s, 1H), 13.55 (br s, 1H)

*: Compouds **Ⅶ h** and **Ⅶ i** were free- bases.

Antiviral activity

The activities of compound **Ⅶ a~j** *in vitro* against laboratory-passaged isolates of human influenza A3 and respiratory syncytial virus (RSV) were examined, respectively in MDCK cell culture and HeLa cell culture with virus cytopathic effect assay in comparison with amantadine and Abidol. The 50% inhibitory concentration (IC_{50}) and the minimum inhibitory concentration (MIC) for the tested compouds against the above two virus were calculated with Reed and Muench Method, and therapeutic index (TI) was obtained. The results were shown in **Table 2**.

Table 2 Iihibition of virus cytopathic effect by laboratory-passaged influenza A3 virus and RSV*

Compoud	IC_{50} (μ g/ml)		TI	
	influenza A3	RSV	influenza A3	RSV
Ⅶ a	<3.9±0	3.9±0	64	32
Ⅶ b	<3.9±0	3.9±0	512	256
Ⅶ c	7.8±0	7.8±0	4	4
Ⅶ d	250±0	250±0	4	4
Ⅶ e	15.6±0	15.6±0	32	32
Ⅶ f	<3.9±0	3.9±0	128	64
Ⅶ g	3.9±0	7.8±0	64	16
Ⅶ h	3.9±0	<3.9±0	256	513
Ⅶ i	7.8±0	3.9±0	8	2
Ⅶ j	7.8±0	31.3±0	16	16
amantadine	0.97±0	0.97±0	128	256
Abidol	3.9±0	7.8±0	32	32

*The results were the mean ± standard deriviation IC_{50} of two independent determinations.

Discussions and conclusion

In vitro antiviral activity assay showed compouds **Ⅶ b**, **Ⅶ h** bearing *p*-fluorophenyl moiety at the 2 position of the indole nucleus had potent antiviral activity with TI higher than control drugs amantadine and Abidol, while compounds **Ⅶ d**, **Ⅶ e**, **Ⅶ i**, **Ⅶ j** bearing *m*-methoxyphenyl moiety at the same position exhibited least antiviral activity. From these facts, we may draw a conclusion that electronic character of substituents of the benzene-ring at the 2 position exert influence on pharmacological activity of the tested compounds. Electron-withdrawing group increased antiviral effect while electron- donating group weakened it. This conclusion was made just based on small scale research, more extensive study would be needed until precise conclusion could be made.

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