Bioorganic & Medicinal Chemistry Letters 18 (2008) 3652–3655

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design and synthesis of tetrahydroisoquinoline derivatives as potential multidrug resistance reversal agents in cancer

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ARTICLE INFO

Article history:
Received 6 January 2008
Revised 22 March 2008
Accepted 19 April 2008
Available online 11 May 2008

Keywords:
Tetrahydroisoquinoline derivatives
Multidrug resistance
P-glycoprotein

ABSTRACT

Exploration for new MDR-modulator utilizing tetrahydroisoquinoline as scaffold disclosed 6,7-dimethoxy-1-(3,4-dimethoxy)benzyl-2-(*N*-*n*-octyl-*N*′-cyano)guanyl-1,2,3,4-tetrahydroisoquinoline (**7**) as a readily accessible medicinal lead. Compound **7** possessed potent MDR reversal activity in the range of the reference compound verapamil, and had not cardiovascular activity compared to verapamil.

Multidrug resistance (MDR)[1] is a major problem in cancer treatment. The typical MDR in tumor cells is mainly associated with a reduced intracellular drug accumulation and an increased cellular drug efflux. This phenomenon can be related to the overexpression of the energy-dependent efflux pump, P-glycoprotein (P-gp),[2] a 170-kDa protein that belongs to the ATP-binding cassette superfamily of transporters. Intense efforts to overcome MDR by influencing transporter expressions via signal transduction pathways or by direct transcriptional control have not been successful in clinical trials.[3] A number of compounds, so-called chemosensitizers, are able to reverse the effect of Pgp on MDR.[4] Tsuruo and coworkers[5] were the first to demonstrate the ability of the calcium channel blocker, verapamil, to reverse MDR. The cardiovascular action of verapamil derivatives has always represented a problem in the development of MDR modulators possessing this structure and many efforts have been devoted to identifying more selective compounds.

Several bisbenzylisoquinoline alkaloids as tetrandrine and berbamine show anti-MDR properties and calcium antagonistic activity in various degrees.[6] More than 100 tetrahydroisoquinoline derivatives were designed and synthesized for the search of novel calcium channel blockers by simplifying and optimizing tetrandrine in our group.[7–12] A series of *N*-cyanoguanyl-substituted tetrahydroisoquinoline derivatives had strong calcium antagonistic activities but showed almost no cardiovascular activities. Their MDR reversal activities in vitro were evaluated, and the results showed that these compounds exerted different degrees of MDR reversal activities. Particularly, the activity of 6,7-dimethoxy-1-(3,4-dimethoxy)benzyl-2-(*N*-*n*-octyl-*N*′-cyano)guanyl-1,2,3,4-tetrahydro-isoquinoline (**7**) was comparable to that of the control verapamil.[13]

In this letter, the representative compound **7** was synthesized and evaluated in several assays of MDR reversal and cardiovascular activities in vitro and in vivo.

The synthetic route to the target compound **7** is outlined in Scheme 1. The synthesis of compound **7** utilized 3,4-dimethoxyphenylethyamine **1** and 3,4-dimethoxy-phenylacetic acid **2** as the starting material, which were converted to**3** at 190 °C under N_2 protection in 84% yield. Treatment of **3** with $POCl_3$ in toluene under reflux provided **4** in 97% yield, followed by reduction with the yield of 64%. Next, the reaction at the N-position of compound **5** was achieved with dimethyl cyanocarbonimidodithioate in 25% yield. Reaction of key intermediate **6** with *n*-octylamine in toluene under reflux gave **7** with the yield of 34%. Compound **7** was characterized by IR, ^{1}HNMR, mass spectra, and elemental analysis.[14]

The in vitro MDR reversal activities of compound **7** against MCF-7, MCF-7/ADR, and K562/A02 cell lines were evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) colorimetric assay[15] with verapamil as reference drug (Tables 1 and 2). The results showed that compound **7** exhibited a well-defined trend in MDR reversal activities.

The in vivo efficacy of compound **7** was evaluated by using the resistant K562/A02 cell xenografts SCID nude mice.[16] The results displayed that compound **7** had no direct effect on K562/A02 cell growth. The antitumor activity of adriamycin (ADM) was signifi-

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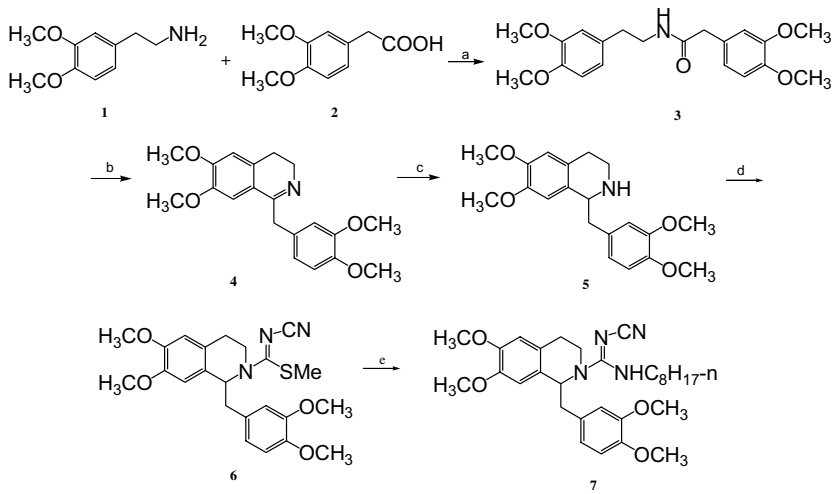
doi:10.1016/j.bmcl.2008.04.082



Scheme 1. Reagents and conditions: (a) N_2, 190 °C, 3 h; (b) $POCl_3$, toluene, N_2, 110 °C, reflux, 2.5 h; (c) KBH_4, diethylamine, methanol, rt, 22 h; (d) dimethyl cyanocarbonimidodithioate, toluene, reflux, 30–50 h; (e) n-$C_8H_{17}NH_2$, toluene, reflux, 14–72 h.

Table 1
Inhibitory effects of compound **7** on the proliferation of MCF-7 cell line and MCF-7/ADR cell line by MTT assay($\bar{X} \pm s, n = 5$)

Compound[#]	IC_{50}[*] MCF-7	MCF-7[##]	IC_{50}[*] MCF-/ADR	MCF-7/ADR[##]
Control[**]	96.2 ± 2.6		6864.2 ± 4.9	
Verapamil	92.8 ± 1.8	1.0	689.2 ± 8.6	10.0
7	79.7 ± 0.9	1.2	226.8 ± 3.5	30.3

[*] IC_{50} of adriamycin (nmol/L).
[**] 0.01‰ DMSO.
[#] Compounds were tested at 10 μmol/L.
[##] Reversal fold.

Table 2
Inhibitory effects of compound **7** on the proliferation of K562/A02 cell line by MTT assay($\bar{X} \pm s, n = 5$)

Compound[#]	Reversal adriamycin		Reversal vincristine	
	IC_{50}[*]	[##]	IC_{50}[*]	[##]
Control[**]	18.13 ± 1.2		12.23 ± 0.4	
Verapamil	0.40 ± 0.2	45.30	1.55 ± 0.1	7.90
7	0.38 ± 0.3	47.71	1.33 ± 0.1	9.20

[*] IC_{50} of adriamycin (μmol/L).
[**] 0.01‰ DMSO.
[#] Compounds were tested at 10 μmol/L.
[##] Reversal fold.

Table 3
The effects of compound **7** on K562/A02 cell growing of bearing cancer mice ($\bar{X} \pm s, n = 8$)

Group	Dose (mg/kg)	Tumor weight (g)	Inhibitory ratio (%)
0.9% NaCl	—	3.54±1.1[*]	−63.1
0.9% NaCl + ADM	—	2.15±0.4[#]	0.9
Verapamil	8	3.61±1.2[*]	−66.4
Verapamil + **7**	8	0.3±0.2[**,##]	86.2
ADM	2	2.17 ± 0.4[#]	
7	8	3.46±1.2[*]	−59.5
	2	3.52±1.1[*]	−62.2
7 + ADM	8	0.32±0.2[**,##]	85.3
	4	0.4±0.3[**,##]	81.6
	2	0.64±0.3[**,##]	70.5

[*] $P < 0.05$.
[**] $P < 0.01$ vs ADM.
[#] $P < 0.05$.
[##] $P < 0.01$ vs 0.9%NaCl.

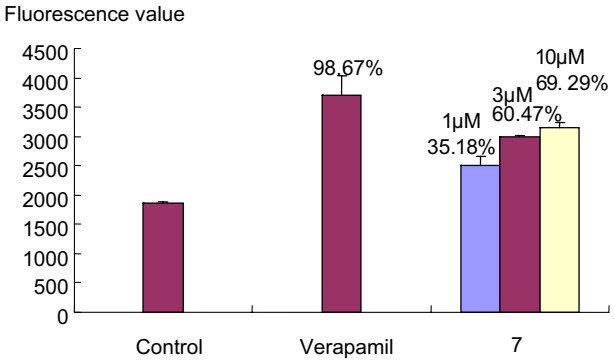


Figure 1. The effects of compound **7** on cellular Rh123 accumulation in MCF-7/ADM ($n = 3$).

cantly potentiated by the coadminstration of compound **7** (8, 4 and 2 mg/kg) in SCID nude mice (Table 3).

The rhodamine 123 (Rh123) accumulation assay was used to measure the P-gp inhibitory activity of compound **7**. The uptake of Rh123 in cells was followed by monitoring the fluorescence signal with the method described.[17] The results showed that fluorescence value of compound **7** was increased obviously compared to

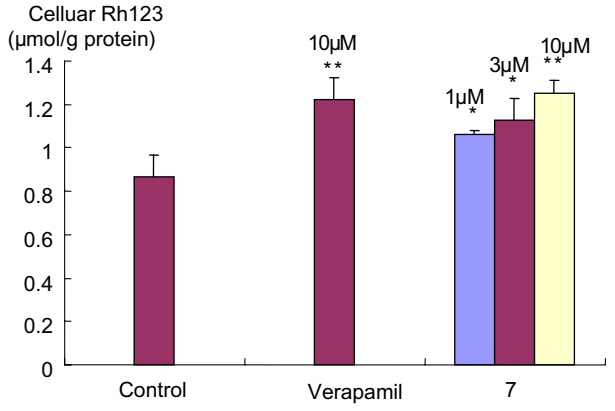


Figure 2. The effects of compound **7** on Rh123 accumulation in RBMEC ([*]$P < 0.05$, [**]$P < 0.01$ vs control) ($n = 3$).