Bioorganic & Medicinal Chemistry Letters 21 (2011) 2302–2304

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Design, synthesis and cytotoxic activities of novel β-amino alcohol derivatives

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ARTICLE INFO

Article history:
Received 30 January 2011
Revised 21 February 2011
Accepted 23 February 2011
Available online 26 February 2011

Keywords:
β-Amino alcohol
Cytotoxic activity
Structure–activity relationship
MTT

ABSTRACT

Three series of novel β-amino alcohols possessing an *N*-anthranyl group have been obtained using tryptophan as the major starting material. These compounds were screened for cytotoxic activity against five human cancer cell lines in vitro by MTT assay, and some of them exhibited potential ability to be anticancer agents. Structure–activity relationship was carefully investigated. Only the compounds possessing small substituents (H or CH_3) at C-6 position showed the same activity as cisplatin (DDP) did.

β-Amino alcohol is a big class of compounds with a wide range of bioactivities, such as antiplasmodial,[1] antileishmanial,[2] antiproliferative,[3] antimicrobial.[4] In recent decades, plenty of compounds, which were synthesized and used in the treatment of cancers, have an indole moiety.[5–8] Some compounds had tryptophan moiety, such as β-carboline,[9,10] tetrahydro-β-carboline,[11,12] which showed strong cytotoxic activity. In our previous work, chiral secondary and tertiary β-amino alcohols derived from tryptophan or abrine (*N*-methyl tryptophan) have been synthesized and used as catalysts in enantioselective additions of diethylzinc to aldehydes. However, their bioactivities were not investigated.[13–16] We wonder if such kinds of β-amino alcohols derived from tryptophan have whether any potential ability to be anticancer agents or not. Indeed, simple structures with strong cytotoxic activity as the same as cisplatin (DDP) will be of much more attraction in pharmaceutical industry.

Herein, we report the synthesis of series of β-amino alcohols derived from tryptophan (Scheme 1). The *N*-anthoranyl group was employed as a substituent of amino group in view of that the flat rigid structure may be of benefit to a high cytotoxic activity. The experimental conditions that were reported for *N*-akylation were modified slightly in our *N*-akylation experiments to give *N*-anthryl-L-tryptophan methyl ester (**2**).[17] Intermediates **3a** and **3b** were obtained through indole *N*-alkylation using sodium hydride as a reduction reagent, and **4a, 4b** through *N*-acetylation in presence of triethylamine as a base. Then a series of amino alcohols **5a–5e**, **6a–6j** and **7a–7d** were synthesized via additions of methyl esters **2–4** with different Grignard reagents, respectively (Scheme 1). All compounds were characterized by ^{1}H NMR, ^{13}C NMR and MS.

The typical procedure for synthesis of **5** was introduced. To the solution of **2** (100 mg, 0.25 mmol) in a dried THF was added methylmagnesium bromide (4.0 equiv) by syringe under nitrogen protection cooled with an external ice-bath. The solution was then warmed to room temperature for 10 h (checked with TLC), and then quenched with saturated NH_4Cl under ice-bath. The mixture was extracted with ethyl acetate and the combined organic layers were dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure. The residue was purified by chromatography (silica gel) eluting with petroleum ether/EtOAc (3:1) to give a pale yellow powder **5b** (85 mg, 85% yield). The specific data are listed in Ref. 18. Other experimental procedures are summarized in Supplementary data.

Total 19 synthesized amino alcohols **5a–5e, 6a–6j, 7a–7d** were screened in vitro for study of cytotoxic activity against five human cancer cell lines, HL-60, SMMC-7721, A-549, MCF-7 and SW480, in order to study the structure–activity relationship (SAR). The MTT assay was used in antitumor activity study. The cell lines were cultured in DMEM medium supplemented with 10% fetal bovine serum at 37 °C in humidified air containing 5% CO_2. The cytotoxic activity results are summarized in Table 1.

For **5a–5e**, compounds **5b**, **5c** and **5d**, which featured methyl, ethyl and *n*-propyl, respectively, exhibited quite strong activities against all of the five cancer cell lines. Among the three compounds, **5b** had the smallest group (methyl) at C-6 position

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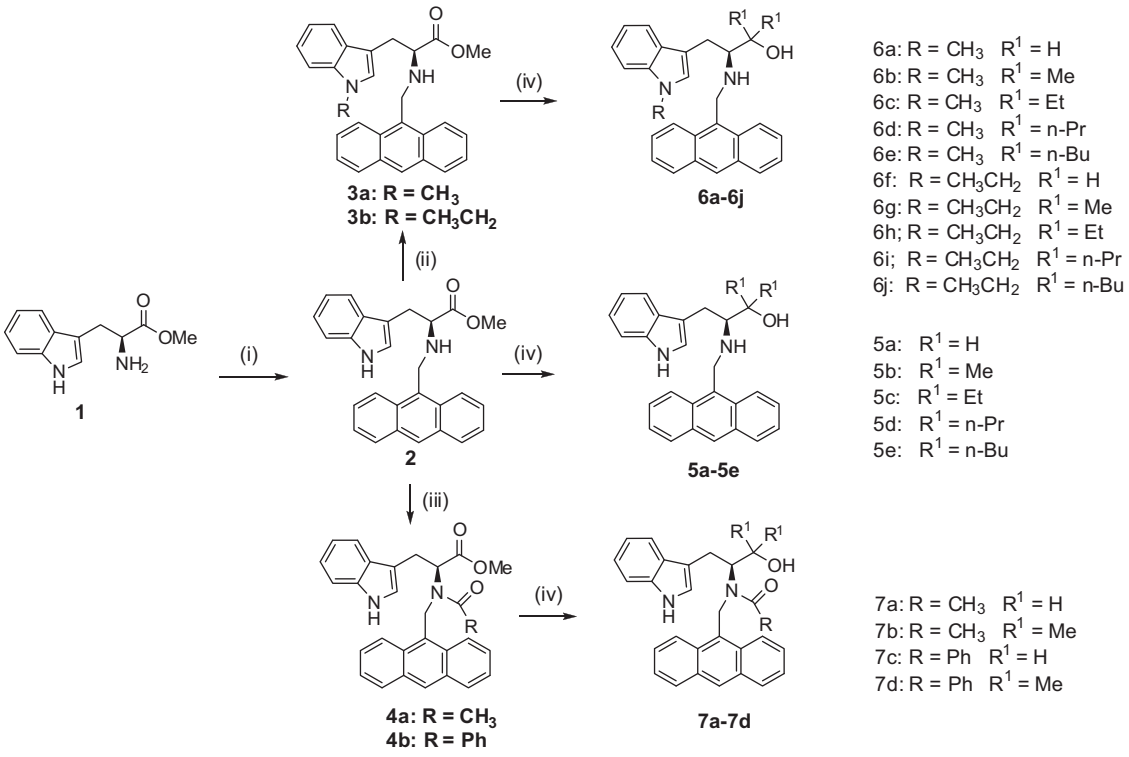
doi:10.1016/j.bmcl.2011.02.087



Scheme 1. Reagents and conditions: (i) anthraldehyde, CH_2Cl_2, molecular sieve, rt, a week. then $NaBH_4$, CH_3OH, rt, 10 min; (ii) CH_3I or CH_3CH_2Br, K_2CO_3, DMF, rt, 12 h; (iii) CH_3COCl or PhCOCl, Et_3N, CH_2Cl_2, rt. (iv) Grignard reagents, THF, rt, 6–10 h; for R^1 = H, $LiAlH_4$, THF, rt, 1 h.

Table 1
Inhibition activity against five human cancer cell lines by MTT assay

Compound	HL-60 IC_{50} (μM)	SMMC-7721 IC_{50} (μM)	A-549 IC_{50} (μM)	MCF-7 IC_{50} (μM)	SW480 IC_{50} (μM)
5a	>40	>40	>40	>40	>40
5b	9.55	13.39	11.04	12.50	11.71
5c	12.16	12.97	11.58	24.26	>40
5d	13.18	17.32	10.86	23.86	>40
5e	>40	>40	>40	>40	>40
6a	4.48	14.99	16.51	16.63	13.49
6b	4.78	15.48	11.77	15.24	15.13
6c	>40	>40	>40	>40	>40
6d	>40	>40	>40	>40	>40
6e	>40	>40	>40	>40	>40
6f	6.18	17.05	16.51	14.94	17.42
6g	5.44	13.61	14.99	13.90	17.56
6h	>40	>40	>40	>40	>40
6i	>40	>40	>40	>40	>40
6j	>40	>40	>40	>40	>40
7a	3.64	14.05	15.23	16.07	17.30
7b	6.49	11.96	14.51	15.60	17.24
7c	7.03	20.68	13.18	17.38	30.66
7d	>40	>40	>40	>40	>40
DDP	1.04	14.99	6.81	24.70	24.34

and inhibited the cancer growth rate by 50% or more at a concentration of 10 μM, which displayed the greatest activity equivalent to DDP except for HL-60 cancer. In contrast, proton or more bulky group (e.g., *n*-butyl) resulted in lower activity against all of the cancer cell lines.

Further investigation of influence of indole group on anticancer activity was carried out using the same methods in cytotoxic activity investigation for **6a–6j**, which had indole *N*-methyl or *N*-ethyl, respectively. Compounds **6a, 6b, 6f** and **6g** possessed the same substituent R as **6c–6e, 6h–6j** did, but different R^1. It is found that the former compounds **6a, 6b, 6f, 6g** had higher inhibitory activity against the five cancer cell lines than the **6c–6e** and **6h–6j** did (Table 1). A small R^1 substituent such as H or methyl had more activity than bulky group did when R is either methyl or ethyl. Subsequently, the SAR of the amino was investigated by introducing acyl groups. Substitution on amino with an acetyl and benzoyl group resulted in no any loss in cytotoxic activity against all the cell lines for compounds **7a–7c** except for **7d**. It exhibited that this position is not the sensitive point.

The overall cytotoxic activity studies of these compounds indicated that the compound with H or methyl group (e.g., **5b**, **6a**, **6b**, **6f**, **6g**, **7a–7c**) possess a better activity than with a more bulky group. In addition, indole and substituent on amino nitrogen do not have apparent effect on the antitumor activity except for **5a** and **7d**.

More experimental procedures can be found in Supplementary data including all of the molecular information, for example, ^1H, ^{13}C NMR data.

In summary, three series of novel β-amino alcohols are derived from tryptophan, and some of them exhibited relatively strong cytotoxicity as the same as DDP did against the five tumor cell lines. It is interesting to develop derivatives from amino acids for treatment of the corresponding tumors. To design more efficient derivatives from amino acids based on the current study may successfully lead to development of a potent anticancer agent. Further developments involving cyclization to afford a six-membered heterocycle via the Pictet–Spengler reaction, preparation of analogs with a *N*-phenanthyl or *N*-naphthyl group, and replacement with other amino acids are in progress.

Acknowledgments

The work was supported by the NSFC (30873141), 973 Program (2009CB522300), program of recruited science and technology talents (2009C1120), the State Key Laboratory of Phytochemistry and Plant Resources in West China, and Hebei University.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.02.087.

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18. For compound **5b** (85% yield). A pale yellow powder. ESI-MS *m*/*z*: 409 $[M+H]^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.24 (s, 3 H), 1.54 (s, 3H), 2.65 (m, 2H), 3.26 (m, 3H), 4.30 (d, 1H, *J* = 12.0 Hz, ArC*H*NH), 4.49 (d, 1H, *J* = 12.0 Hz, ArC*H*NH), 6.98 (s, 1H), 7.20 (t, 1H, *J* = 7.4 Hz), 7.27–7.38 (m, 5H), 7.47 (d, 1H, *J* = 8.0 Hz), 7.62 (d, 2H, *J* = 8.8 Hz), 7.77 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 2H, *J* = 8.5 Hz), 8.27 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 27.9, 28.1, 47.3, 67.5, 72.2, 111.5, 113.4, 118.9, 119.7, 122.4, 122.8, 123.9, 124.7, 125.8, 127.2, 127.4, 128.9, 129.9, 131.3, 131.4, 136.7. For **6b**. ESI-MS *m*/*z*: 423 $[M+H]^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (s, 3H), 1.55 (s, 3H), 2.60 (m, 2H), 3.26 (m, 3H), 3.70 (s, 3H, NCH_3), 4.30 (d, 1H, *J* = 12.0 Hz, ArC*H*NH), 4.49 (d, 1H, *J* = 12.0 Hz, ArC*H*NH), 6.83 (1H, s), 7.18 (t, 1H, *J* = 7.7 Hz), 7.27–7.40 (m, 6H), 7.64 (d, 2H, *J* = 8.9 Hz), 7.70 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 2H, *J* = 8.0 Hz), 8.28 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.3, 27.8, 28.2, 47.4, 67.6, 72.1, 109.5, 111.8, 119.0, 119.1, 122.0, 124.0, 124.7, 125.8, 127.1, 127.5, 127.8, 128.9, 129.3, 129.7, 131.3, 137.4. For **7b**: ESI-MS *m*/*z*: 473 $[M+Na]^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.22 (s, 3H), 0.78 (s, 3H), 2.71 (s, 3H, COCH_3), 3.07 (dd, 1H, *J* = 15.2, 2.3 Hz), 3.26 (dd, 1H, *J* = 10.8, 2.3 Hz), 3.54 (m, 1H), 4.69 (d, 1H, *J* = 14.7 Hz, ArC*H*NH), 5.10 (d, 1H, *J* = 14.6 Hz, ArC*H*NH), 6.87 (s, 1H), 7.11 (t, 1H, *J* = 7.7 Hz), 7.21 (t, 1H, *J* = 7.5 Hz), 7.27 (d, 1H, *J* = 7.8 Hz), 7.30 (d, 1H, *J* = 7.9 Hz), 7.39 (m, 4H), 7.46 (d, 2H, *J* = 8.8 Hz), 7.90 (d, 2H, *J* = 8.4 Hz), 8.32 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.2, 24.5, 28.5, 48.1, 69.8, 71.1, 111.3, 113.6, 118.9, 119.5, 122.1, 122.8, 123.4, 124.8, 125.3, 126.6, 127.6, 129.2, 129.4, 130.9, 131.4, 136.2, 172.5. See Supplementary data for more details about other new compounds' data.