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Synthesis of novel 6-unsubstituted 2-aminodihydropyrimidines by Sc(OTf)$_3$-mediated amination and their antiproliferative effect on HL-60 cells

Yoshio Nishimura [a,*], Hidetomo Kikuchi [b], Takanori Kubo [a], Ibuki Nakakita [a], Mari Oguni [a], Misaki Ohta [a], Rie Arai [c], Bo Yuan [b], Katsuyoshi Sunaga [b], Hidetsura Cho [d]

[a] Faculty of Pharmacy, Yasuda Women's University, 6-13-1, Yasuhigashi, Asaminami-ku, Hiroshima 731-0153, Japan
[b] Faculty of Pharmacy and Pharmaceutical Sciences, Josai University, 1-1, Keyakidai, Sakado, Saitama 350-0295, Japan
[c] Futaba Nutrition College, 2-11-2, Kichijojihoncho, Musashino-shi, Tokyo 180-0004, Japan
[d] Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

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ABSTRACT

An efficient method of synthesis of novel 6-unsubstituted 2-aminodihydropyrimidines **9** has been developed. The substitution reaction of 2-methylthiodihydropyrimidines **7** and primary amines in the presence of a catalytic amount of Sc(OTf)$_3$ with heating proceeds smoothly to give **9** in good to high yields. This amination protocol can be applied to various aryl- and alkylamines. Other 2-methylthiodihydropyrimidines **10** having different substituent patterns at 4- and 6-positions also reacted with aniline under the same conditions to give corresponding 2-anilinodihydropyrimidines **11** in high yields. These compounds **9** were assessed for their antiproliferative effect on the human promyelocytic leukemia cell line HL-60. The 2-benzyl derivative **9i** showed a relatively high activity with an IC$_{50}$ of <100 nM. The high activity of **9i** was comparable to that of all-*trans* retinoic acid (223.1 nM). The results of the trypan blue exclusion test of **9i** indicated that necrosis-like cell death occurred.

Introduction

Dihydropyrimidines (DPs) show a wide range of biological activities for medicinal applications. They display calcium channel inhibitory, anticancer, antiviral, antibacterial, antifungal, antimicrobial, anti-HIV, antimalarial, anti-inflammatory, antihypertensive, and antioxidation activities. Many reviews on the development of synthetic methods for these heterocycles and their biological activities have recently been published, which suggest their great and significant potential as leading compounds for developing medicines [1–7].

Multisubstituted DPs such as **1** have been well investigated because of their accessibility and synthetic and biological studies on these compounds have been well documented (Fig. 1). For the synthesis of **1**, a three-component reaction known as the Biginelli reaction involving urea or thiourea, aldehydes, and β-dicarbonyl compounds has been generally used [1–7]. On the other hand, methods of synthesis of 6-unsubstituted 2-oxo and 2-thioxo DPs **2** (Y = O, S) have rarely been reported. A few methods of synthesis of **2** have been reported, in which a 3,3-dialkoxypropanoate, alkyl propiolate, or alkyl enaminoate is used instead of a β-dicarbonyl compound in a three-component reaction [8–14]. As for 6-unsubstituted 2-amino DP **3**, no synthetic study has been conducted; to the best of our knowledge, the general formula of **3** has not been reported.

Previously, we developed an efficient method of synthesis of **2** (Y = O, S) [15]. In three-component reactions, urea or thiourea, aldehydes, and ethyl dimethylaminoacrylate in the presence of $AlCl_3$ proceeded smoothly to give **2** in high yields. Additionally, the antiproliferative effect of these compounds on the human promyelocytic leukemia cell line HL-60 was examined; we found a related 6-methyl DP derivative showing high activity with an IC$_{50}$ of 952 nM. To expand the structural diversity of DP and carry out further structure–activity relationship studies, we need to synthesize hitherto unavailable **3**.

Conventionally, 2-amino DPs having 6-substituent have been synthesized using a multicomponent condensation reaction [16–20], or a nucleophilic substitution reaction of DPs with the amines at the 2-position [21–27]. Generally, the nucleophilic substitution reactions for synthesis of 6-substituted 2-amino DPs employed 2-methoxy, 2-alkylthio, or 2-pyrazoyl DPs as electrophiles, in which

* Corresponding author.
E-mail address: nishimura-y@yasuda-u.ac.jp (Y. Nishimura).

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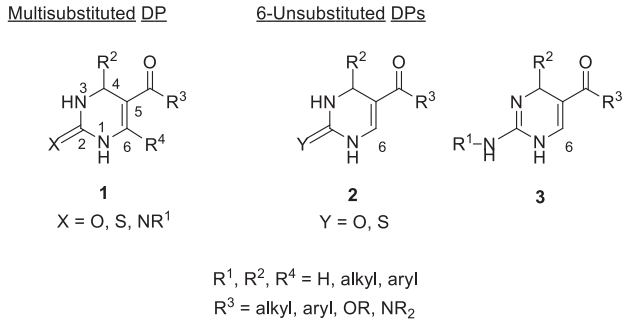
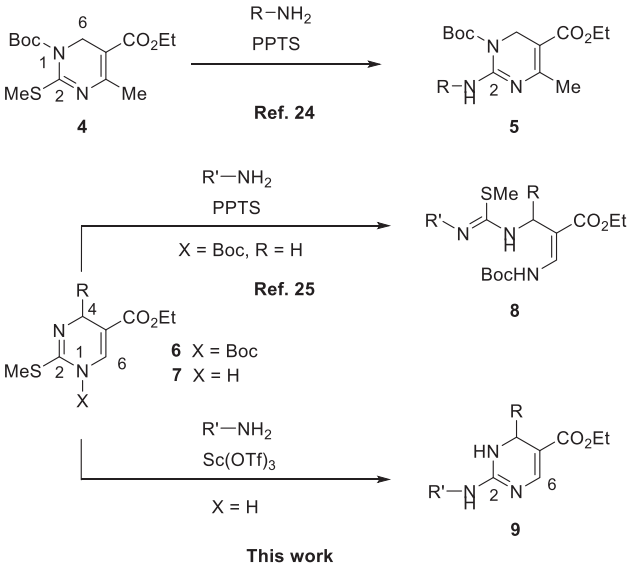


Fig. 1. Multisubstituted DP **1** and 6-unsubstituted DPs **2** and **3**.

the reactions were promoted by simple heating or microwave irradiation. To obtain a variety of 2-aryl- or 2-alkylamino DPs **3** convergently, we employed nucleophilic substitution of 2-methylthio DPs prepared from **2** (Y = S). We developed a nucleophilic substitution reaction of 6-unsubstituted 2-methylthio DP **4** protected by a Boc group at N1-position with amines for the synthesis of 2-amino DPs **5** (Scheme 1) [27]. In this reaction, the introduction of a Boc group on the nitrogen of **4** increased the reactivity of the amination reaction. However, in the case of the reaction of 4,6-unsubstituted 2-methylthio DP **6** (R = H) protected by a Boc group at N1-position with amines, it did not give 2-amino DP, but rather an unexpected product **8** by ring cleavage between the N1–*C*2 bond [28]. Thus, the effect of a Boc group in the reaction of 1,4-DP should be clarified; we found that the introduction of a Boc group only induced the ring opening to give **8** in the reaction of **6**. Consequently, a suitable substrate for nucleophilic substitution of 1,4-DP was determined to be *N*-unprotected DP **7**. As part of our studies on the synthesis of less substituted DPs [29–33], we realized that $Sc(OTf)_3$ acted as an effective mediator to promote the amination reaction of **7** to give 2-amino DP **9** in this article. The *in vitro* antiproliferative effect of these compounds on HL-60 cells was also evaluated.

Initially, we confirmed our previous finding that the reaction of 1,4-DP **6a** (R = H) with 4-methoxyaniline in the presence of 0.1 eq of pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2 at reflux for 24 h



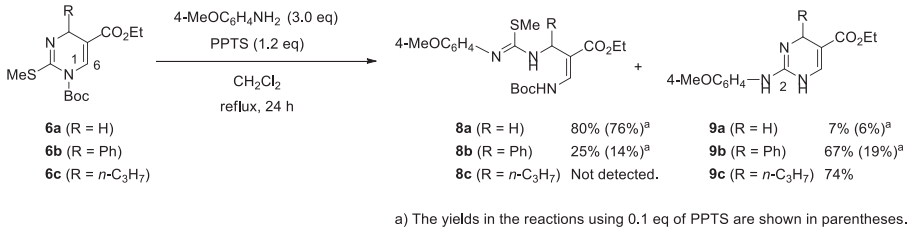
Scheme 1. Reactions of *N*-Boc substituted 1,6-DP **4**, *N*-Boc substituted 1,4-DP **6**, and *N*-unsubstituted 1,4-DP **7** with amines.

gave the ring opening product **8a** (R = H) in 76% yield (Scheme 2) [28]. Careful analysis of the reaction revealed the 2-substituted product **9a** (R = H) having no Boc group, albeit in a low yield of 6%. Increased amount of PPTS (1.2 eq) in the reaction of **6a** showed no effect; **8a** and **9a** were obtained in 80% and 7% yields, respectively. Encouraged by these results, we turned our attention to the effect of 4-substituents on the reactivity to improve the yield of **9**. In the reaction of **6b** (R = C_6H_5) with 4-methoxyaniline in the presence of PPTS (0.1 eq), **8b** (R = C_6H_5) and **9b** (R = C_6H_5) were obtained in 14% and 19% yields, respectively, with recovery of **6b** in 66%. The reaction of **6b** with the amine in the presence of PPTS (1.2 eq) gave **9b** in 67% yield accompanied by **8b** in 25% yield. The reaction of **6c** (R = *n*-C_3H_7) with the amine exclusively gave **9c** (R = *n*-C_3H_7) in 74% yield with no **8c** detected. These results indicate that the 2-substitution reactions of **6b** and **6c** with amine proceeded smoothly in contrast to that of **6a**. Different 4-substituents (H, C_6H_5, *n*-C_3H_7) had a masked effect on the reactivity; the preference for 2-substitution over ring opening is *n*-C_3H_7 > C_6H_5 ≫ H; the reason for this preference is not clear.

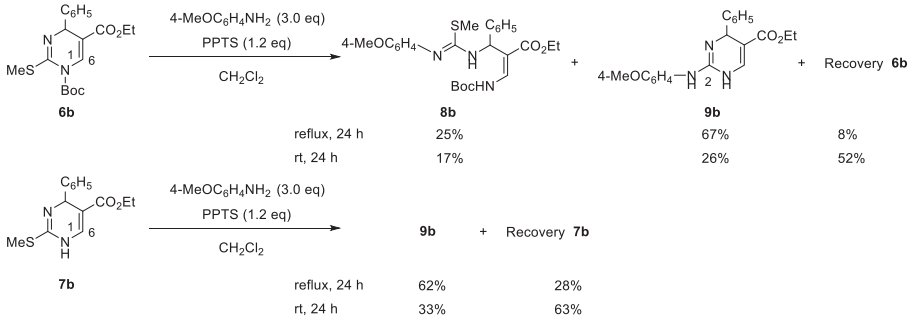
In our previous report, the introduction of a Boc group on the nitrogen at the 3-position of 1,6-dihydropyrimidine increased the reactivity of the 2-substitution reaction [27]. In this reaction, no ring opening product such as **8** was detected at all. To determine a suitable substrate for the 2-substitution reaction of 1,4-DP, we compared the reactivities of *N*-Boc substituted **6b** and *N*-unsubstituted **7b** (Scheme 3). In the reactions of **6b** and **7b** with 4-methoxyaniline in the presence of PPTS at room temperature, the yields of **9b** were 26% and 33%, respectively. In the reactions of **6b** and **7b** at reflux, the yields of **9b** were 67% and 62%, respectively. Although the reaction of **6b** gave a considerable amount of **8b** (17% at rt, 25% at reflux), no such byproduct was detected in the reaction of **7b**. These results indicate that the reactivities in the 2-substitution reactions of **6b** and **7b** are about the same; the introduction of a Boc group on the nitrogen at the 1-position only induces the ring opening reaction. Thus, a suitable substrate was determined to be **7b** for the 2-substitution reaction of 1,4-DP.

Next, we examined and optimized the reaction conditions in the reaction of **7b** with aniline. The reaction in 1,2-dichloroethane at reflux for 3 h gave the corresponding 2-substituted product **9d** in only 4% yield (Table 1, entry 1). The addition of an acid was evaluated in an attempt to improve the yield and determine its effect. All catalysts including protonic acids and Lewis acids improved the yield of **9d** to some extent. Metal triflates such as $Sc(OTf)_3$, $Y(OTf)_3$, or $Yb(OTf)_3$ effectively promoted the reaction to give **9d** in good yields. (entries 9–11). The highest yield of 41% was achieved using $Sc(OTf)_3$ while the reaction using $Yb(OTf)_3$ showed relatively better mass balance among the three reactions (entries 9–11). Subsequently, effect of $Sc(OTf)_3$ and $Yb(OTf)_3$ was further compared, and other conditions including reaction time, concentration, and amounts of reagents were optimized. The detail was shown in Supplementary Material (Table S1). As a result, the reaction using $Sc(OTf)_3$ at higher concentration for 15 h gave **9b** in high yield of 86% (entry 13). The reaction using reduced amounts of aniline (1.5 eq) and $Sc(OTf)_3$ (10 mol%) resulted in a satisfactory yield of 85% (entry 14).

Under the optimized reaction conditions (Table 1, entry 14), various primary aryl- and alkylamines were subjected to the reaction to assemble 6-unsubstituted 2-amino DPs **9**; the results are summarized in Table 2 [34]. Electron-rich 4-methoxyaniline showed high reactivity, and the corresponding products **9b** and **9c** were obtained in high yields (entries 1 and 2). Although arylamines having electron-withdrawing groups showed relatively lower reactivity than aniline, their reactions gave **9e** and **9f** in good yields (entries 4 and 5). 1-Naphthylamine was also applicable to the reaction to give **9g** in acceptable yield (entry 6). The reactions using alkylamines such as *n*-decylamine, benzylamine, and cyclo-

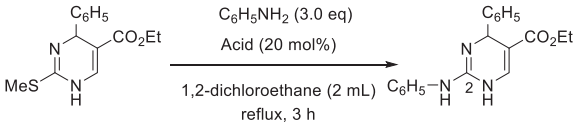


Scheme 2. Effect of 4-substituents of **6** on the reactivity.



Scheme 3. Comparison of reactivity of **6b** and **7b** for 2-substitution reaction.

Table 1
Screening of acid catalyst, and optimization of other reaction conditions.

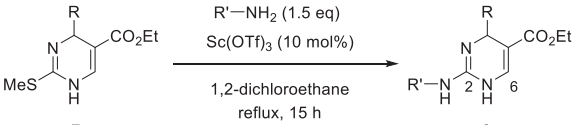


Entry	Acid	Yield of **9b** (%)[a]	Recovery of **7b** (%)[a]
1	None	4	96
2	PPTS	27	72
3	CF_3CO_2H	30	64
4	$BF_3{\cdot}Et_2O$	21	75
5	$AlCl_3$	24	71
6	$InCl_3$	25	66
7	$CeCl_3$	8	91
8	AgOTf	21	74
9	$Sc(OTf)_3$	41	47
10	$Y(OTf)_3$	39	48
11	$Yb(OTf)_3$	39	56
12	$La(OTf)_3$	18	80
13[a]	$Sc(OTf)_3$	86	3
14[a,b]	$Sc(OTf)_3$	85	10

[a] For 15 h. 1,2-dichloroethane (0.5 mL) was used.
[b] $C_6H_5NH_2$ (1.5 eq) and $Sc(OTf)_3$ (10 mol%) were used.

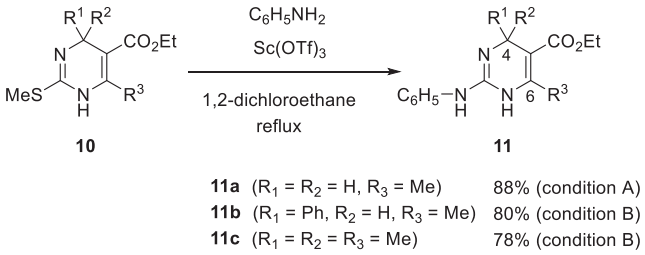
hexylamine proceeded smoothly to afford the corresponding products **9h**–**9j** in good to high yields (entries 7–9). The reactions using relatively hindered 1-naphthylamine, cyclohexylamine, or electron-deficient aniline needed to employ increased amount of the amines (3.0 eq) and $Sc(OTf)_3$ (20 mol%) for 40 h to achieve good yields (entries 5, 6 and 9). In the case of 4,6-unsubstituted DP in entry 10, the reaction was sluggish, and the desired product **9k** was obtained in a low yield of 28%. This result is probably due to the instability of **9k** and the starting material. Regarding as for the synthesis of 4,6-unsubstituted derivatives such as **9k**, successive reactions previously reported by our group provide alternative and useful approach [28]. We also tested the reaction using a sec-

Table 2
Synthesis of 6-unsubstituted 2-amino DPs **9** using $Sc(OTf)_3$-mediated amination.



Entry	R	R'	**9**	Yield (%)
1	C_6H_5	4-$CH_3OC_6H_4$	**9b**	92
2	*n*-C_3H_7	4-$CH_3OC_6H_4$	**9c**	74
3	C_6H_5	C_6H_5	**9d**	85
4	C_6H_5	4-ClC_6H_4	**9e**	74
5[a]	C_6H_5	4-$MeO_2CC_6H_4$	**9f**	62
6[a]	C_6H_5	1-Naphthyl	**9g**	52
7	C_6H_5	*n*-$C_{10}H_{21}$	**9h**	79
8	C_6H_5	$C_6H_5CH_2$	**9i**	75
9[a]	C_6H_5	*cyclo*-C_6H_{11}	**9j**	59
10[b]	H	C_6H_5	**9k**	28

[a] For 40 h. $Sc(OTf)_3$ (20 mol%) and amine (3.0 eq) were used.
[b] For 5 h.



Scheme 4. Synthesis of a variety of 2-amino DPs **11** using $Sc(OTf)_3$-mediated amination.

ondary amine, *N*-methylaniline; however, the amination gave a corresponding product in low yield of <17%. Although application of such hindered amine was difficult using the optimized condition, further examination to overcome the problem is in progress. As shown in Table 2, we demonstrated that the amination using the $Sc(OTf)_3$ mediator proceeded efficiently to give a variety of novel derivatives **9**.

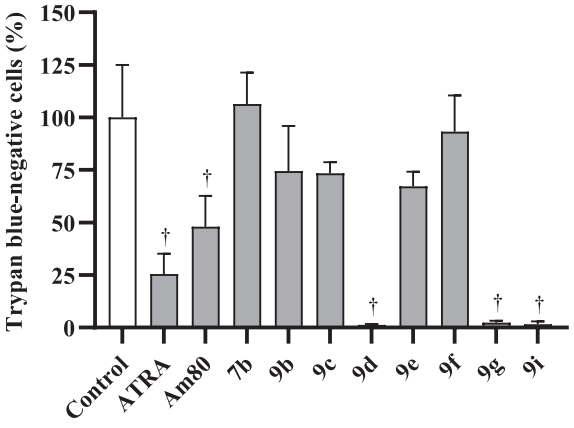


Fig. 2. Antiproliferative effects of ATRA, Am80, **7b**, **9b**–**9g**, and **9i** on HL-60 cells. After treatment for 96 h with each compound at 1000 nM, the cell viability of HL-60 cells was determined by TB exclusion test as described in "Supplementary Material". Relative cell viability was calculated as the ratio of TB-negative cells of each treatment group against those of the corresponding untreated control group. Data are shown as the means and SD (standard deviation) from three independent experiments. $^{\dagger}p < 0.01$ vs. control.

The $Sc(OTf)_3$-mediated amination protocol was applied to the synthesis of other 2-amino DPs **11** with different substituent patterns at the 4- and 6-positions. As shown in Scheme 4, the 4-unsubstituted 6-substituted derivative **11a**, 4,6-disubstituted derivative **11b**, and 4,4,6-trisubstituted derivative **11c** were obtained in high yields employing condition A or B. In the case of **11b** and **11c** having both 4- and 6-substituents, condition B using increased amounts of reagents was required. The cyclic guanidino structures of **9** and **11** are unique and might have promising biological activity.

To explore the antiproliferative effect of the eight compounds of **7b**, **9b**–**9g**, and **9i** in comparison with all-*trans* retinoic acid (ATRA) and Am80 on HL-60 cells, the viability of the cells after treatment for 96 h with each compound at 1000 nM was determined by the trypan blue (TB) exclusion test [15]. As shown in Fig 2, **9d, 9g,** and **9i** showed higher antiproliferative activities than Am80 ($p < 0.01$, 0.05, and 0.05, respectively), although there was no significant difference between these DPs and ATRA.

To determine the accurate IC_{50} values of ATRA, **9d**, **9g**, and **9i**, HL-60 cells were further treated for 96 h with various concentrations (100, 300, 700, and 1,000 nM) of each compound. As shown in Fig. 3 (left), a dose-dependent decrease in the number of TB-negative cells (viable cells) was observed in ATRA-, **9d**-, **9g**-, and **9i**-treated HL-60 cells. The IC_{50} values of ATRA, **9d**, and **9g** were 223.1 nM (95% confidence interval, 120.3–383.3; R^2 = 0.7726), 320.8 nM (95% confidence interval, 255.9–412.1; R^2 = 0.8913), and 328.6 nM (95% confidence interval, 262.3–397.3; R^2 = 0.9206), respectively. Among the tested DPs, the antiproliferative activity of **9i** was the highest with an IC_{50} of < 100 nM. In addition, a dose-dependent increase in the ratio of TB-positive cells (dead cells)/TB-negative cells in HL-60 cells treated with ATRA, **9d**, **9g**, and **9i** was observed [Fig. 3 (right)], indicating that necrosis-like cell death occurred in the treated cells.

In summary, a $Sc(OTf)_3$-mediated amination reaction of 2-methylthio DPs has been developed. This method is general and

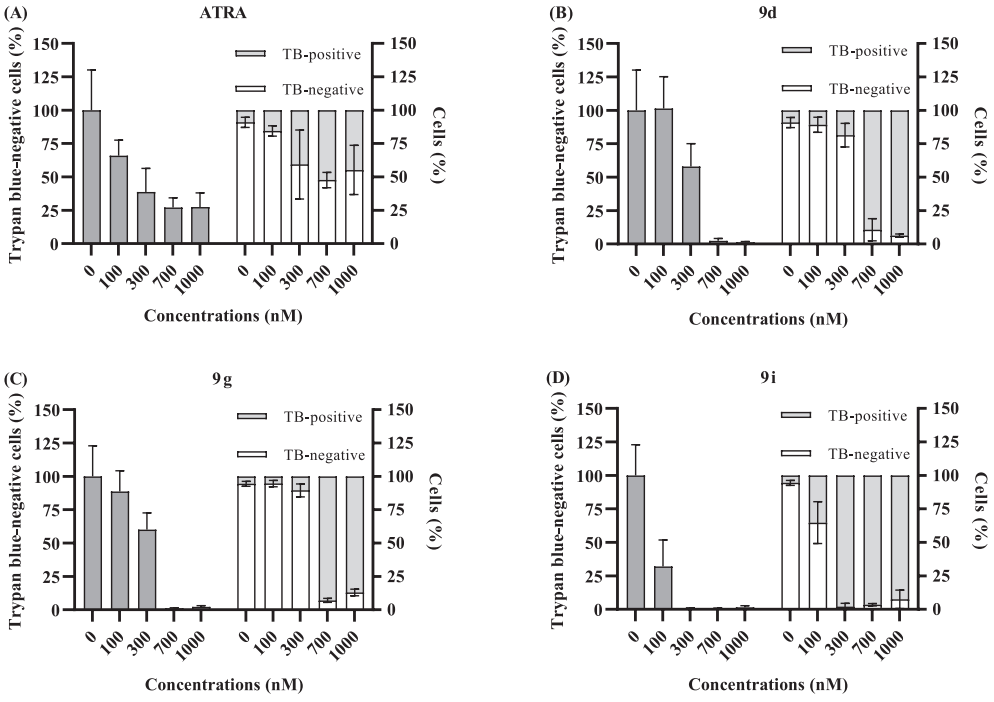


Fig. 3. A dose-dependent decrease in cell viability of HL-60 cells treated by ATRA, **9d**, **9g**, and **9i**. Following treatment with various concentrations of ATRA (A), **9d** (B), **9g** (C), and **9i** (D) for 96 h, the cell viability of HL-60 cells was determined by TB exclusion test as described in "Supplementary Material". (Left) Relative cell viability was calculated as the ratio of TB-negative cells of each treatment group against those of the corresponding untreated control group. (Right) the ratio of TB-positive cells to TB-negative cells in HL-60 cells treated with each concentration of ATRA, **9d**, **9g**, and **9i** were calculated. Data are shown as the means and SD from three independent experiments.

efficient for the synthesis of various 6-unsubstituted 2-aryl and 2-alkylamino DPs **9** in good to high yields. The method is also applicable to the synthesis of other 2-amino DPs **11** with different substituent patterns at the 4- and 6-positions. Their *in vitro* antiproliferative effect on HL-60 cells was also evaluated. The activities of **9d**, **9g**, and **9i** were higher than those of ATRA and Am80. The results of the TB exclusion test of **9d**, **9g**, and **9i** indicated that necrosis-like cell death occurred. Further structure–activity relationship and biological studies using **9i** as the main compound are underway.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152760.

References

[1] L.H.S. Matos, F.T. Masson, L.A. Simeoni, M. Homem-de-Mello, Eur. J. Med. Chem. 143 (2018) 1779–1789.
[2] R. Kaur, S. Chaudhary, K. Kumar, M.K. Gupta, R.K. Rawal, Eur. J. Med. Chem. 132 (2017) 108–134.
[3] H. Nagarajaiah, A. Mukhopadhyay, J.N. Moorthy, Tetrahedron Lett. 57 (2016) 5135–5149.
[4] H. Cho, Heterocycles 87 (2013) 1441–1479.
[5] J.S. Sandhu Suresh, ARKIVOC i (2012) 66–133.
[6] C.O. Kappe, A. Stadler, Org. React. 63 (2004) 1–116.
[7] C.O. Kappe, Eur. J. Med. Chem. 35 (2000) 1043–1052.
[8] A. Stadler, C.O. Kappe, J. Comb. Chem. 3 (2001) 624–630.
[9] J.C. Barrow, P.G. Nantermet, H.G. Selnick, K.L. Glass, K.E. Rittle, K.F. Gilbert, T.G. Steele, C.F. Homnick, R.M. Freidinger, R.W. Ransom, P. Kling, D. Reiss, T.P. Broten, T.W. Schorn, R.S.L. Chang, S.S. O'Malley, T.V. Olah, J.D. Ellis, A. Barrish, K. Kassahun, P. Leppert, D. Nagarathnam, C. Forray, J. Med. Chem. 43 (2000) 2703–2718.
[10] P.A. Evans, J. Qin, J.E. Robinson, B. Bazin, Angew. Chem. Int. Ed. 46 (2007) 7417–7419.
[11] J.-P. Wan, Y. Lin, K. Hu, Y. Liu, Beilstein J. Org. Chem. 10 (2014) 287–292.
[12] S. Terentjeva, D. Muceniece, V. Lusis, Chem. Heterocycl. Comp. 49 (2014) 1757–1769.
[13] E.S. Darwish, I.A. Abdelhamid, M.A. Nasra, F.M. Abdel-Gallil, D.H. Fleita, Helv. Chim. Acta 93 (2010) 1204–1208.
[14] J.-P. Wan, Y.-J. Pan, Chem. Commun. (2009) 2768–2770.
[15] Y. Nishimura, H. Kikuchi, T. Kubo, Y. Gokurakuji, Y. Nakamura, R. Arai, B. Yuan, K. Sunaga, H. Cho, Tetrahedron Lett. 61 (2020) 151967.
[16] F. Felluga, F. Benedetti, F. Berti, S. Drioli, G. Regini, Synlett 29 (2018) 1047–1054.
[17] M.J. Ahmed, S.F. Hassan, R.U. Nisa, K. Ayub, M.S. Nadeem, S. Nazir, F.L. Ansari, N.A. Qureshi, U. Rashid, Med. Chem. Res. 25 (2016) 1877–1894.
[18] S.S. Mansoor, S.S. Shafi, S.Z. Ahmed, Arab. J. Chem. 9 (2016) S846–S851.
[19] B. Ahmed, R.A. Khan, Habibullah, M. Keshari, Tetrahedron Lett. 50 (2009) 2889–2892.
[20] J.J.V. Eynde, N. Hecq, O. Kataeva, C.O. Kappe, Tetrahedron 57 (2001) 1785–1791.
[21] K.S. Atwal, G.C. Rovnyak, B.C. O'Reilly, J. Schwartz, J. Org. Chem. 54 (1989) 5898–5907.
[22] B.L. Nilsson, L.E. Overman, J. Org. Chem. 71 (2006) 7706–7714.
[23] M. Matloobi, C.O. Kappe, J. Comb. Chem. 9 (2007) 275–284.
[24] S. Khan, V. Tyagi, R. Mahar, V. Bajpai, B. Kumar, P.M.S. Chauhan, Synthesis 24 (2013) 2405–2412.
[25] D.M. Arnold, M.G. LaPorte, S.M. Anderson, P. Wipf, Tetrahedron 69 (2013) 7719–7731.
[26] Y. Guo, Z. Gao, K. Wang, J. Li, X. Bi, L. Guo, H. Liu, E. Shi, J. Xiao, Asian J. Org. Chem. 9 (2020) 626–630.
[27] H. Cho, Y. Nishimura, Y. Yasui, S. Kobayashi, S. Yoshida, E. Kwon, M. Yamaguchi, Tetrahedron 67 (2011) 2661–2669.
[28] H. Cho, E. Kwon, Y. Yasui, S. Kobayashi, S. Yoshida, Y. Nishimura, M. Yamaguchi, Tetrahedron Lett. 52 (2011) 7185–7188.
[29] Y. Nishimura, T. Kubo, Y. Okamoto, H. Cho, Tetrahedron Lett. 58 (2017) 4236–4239.
[30] Y. Nishimura, T. Kubo, Y. Okamoto, H. Cho, Tetrahedron Lett. 57 (2016) 4492–4495.
[31] Y. Nishimura, H. Cho, Synlett 26 (2015) 233–237.
[32] Y. Nishimura, H. Cho, Tetrahedron Lett. 55 (2014) 411–414.
[33] Y. Nishimura, Y. Yasui, S. Kobayashi, M. Yamaguchi, H. Cho, Tetrahedron 68 (2012) 3342–3350.
[34] To a mixture of **7** (R = C_6H_5) (69 mg, 0.250 mmol), 4-methoxyaniline (47 mg, 0.382 mmol) in 1,2-dichloroethane (0.5 mL) was added $Sc(OTf)_3$ (12 mg, 0.0244 mmol) at room temperature, and the reaction mixture was stirred at reflux for 15 h. To the mixture was added EtOAc (20 mL) and saturated $NaHCO_3$ aqueous solution (5 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (10 mL), and the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [*n*-hexane-EtOAc (1:1) to EtOAc-MeOH-Et_3N (200:10:1)] to give **9b** (80.7 mg, 0.230 mmol, 92%) as colorless crystals.