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Ligands with dual vitamin D_3-agonistic and androgen-antagonistic activities

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Abstract—Ligands possessing dual vitamin D_3-agonistic (estimated as HL-60 monocytic cell differentiation induction) and androgen-antagonistic (estimated as testosterone-induced SC-3 cell growth inhibition) activities with various activity spectra were prepared based on a substituted bis-phenylmethane skeleton. Some of them were revealed to be potent androgen antagonists with a nonsecosteroidal vitamin D_3 skeleton.

1. Introduction

A relationship between vitamin D_3 and prostate cancer has been well documented.[1–4] For example, epidemiological evidence suggests that low exposure to sunlight and vitamin D deficiency may be risk factors for prostate cancer mortality.[1,2] In addition, 1α,25-dihydroxyvitamin D_3 (1,25-D_3), which is an active metabolite of vitamin D_3 and a ligand of nuclear vitamin D_3 receptor (VDR), has been reported to induce apoptosis or differentiation in many cell types, including prostate tumor cell lines.[3–6] Well-established activities elicited by 1,25-D_3 are induction of monocytic cell differentiation of human leukemia cell line HL-60 and growth inhibition of androgen-dependent human prostate tumor cell lines.[3,7–10] Although the 1,25-D_3-induced cell differentiation of HL-60 is mediated by direct binding and activation of VDR by 1,25-D_3, the molecular mechanism and the role of VDR in 1,25-D_3-induced growth inhibition of androgen-dependent cell lines remain obscure.[3,9,10]

During our structural development studies of nuclear receptor antagonists, including vitamin D_3 antagonists and androgen antagonists,[11–15] we noticed that 1,25-D_3 potently inhibits androgen-induced cell growth of Shionogi Carcinoma SC-3 cells. This led us to suspect that 1,25-D_3 might be an antagonistic ligand for nuclear androgen receptor (AR). In fact, we found that 1,25-D_3 binds to AR in a competitive manner with its cognate ligand, testosterone (details will be published elsewhere). The calculated K_i value of 1,25-D_3 for binding to AR was 2.2 μM, which is 244 times larger than that for binding to VDR. In spite of this, that is the affinity ratio of 1,25-D_3 toward AR and VDR being 1:244, the specific binding of 1,25-D_3 to AR might have some biological meaning, especially in the case of 1,25-D_3-induced cell growth inhibition of androgen-dependent prostate tumor cell lines. Moreover, this result suggests that 1,25-D_3 can act as a dual ligand for both VDR and AR, though its activity toward the latter is antagonistic.

A group at Ligand Pharmaceuticals has developed the so-called nonsecosteroidal vitamin D_3 agonists, including LG190155 (**1**) and LG190178 (**7**) (Table 1), with a bis-phenol skeleton.[16,17] These compounds have been reported to act as vitamin D_3 agonists by binding and activating VDR.[16,17] We suspected that these compounds might also act as androgen antagonists, as 1,25-D_3 does. Therefore, we prepared several nitrogen-containing derivatives of LG190155 (**1**)/LG190178 (**7**), and examined their biological activities. One of authorized and specific biological activity of vitamin D_3 is HL-60 monocytic cell differentiation-inducing activity.[16,17] This activity was defined as vitamin D_3 agonistic activity in this paper. Similarly, inhibition of

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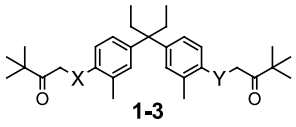
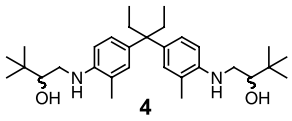
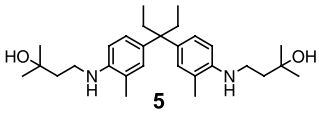
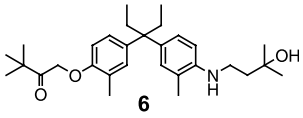
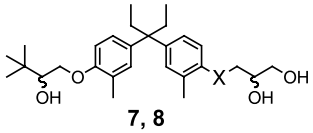
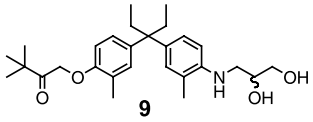
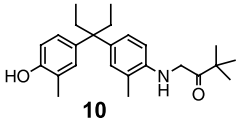
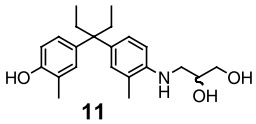
Table 1. Structures and results of biological assays of bis-phenylmethane derivatives **1**–**11**

	Vitamin D_3 agonistic activity (ED_{50}, nM)[a]	Androgen antagonistic activity (IC_{50}, nM)[b]	Activity ratio[c] (ED_{50}[a]/IC_{50}[b])	AR-binding affinity (K_i, nM)
 **1-3**				
1: X = O, Y = O (LG190155)	410	1900	0.22	ND
2: X = O, Y = NH	450	1200	0.38	ND
3: X = NH, Y = NH	450	1000	0.45	ND
 **4**				
4	1200	1000	1.20	ND
 **5**  **6**				
5	900	6800	0.13	3380
6	370	820	0.45	2900
 **7, 8**				
7: X = O (LG190178)	44	19	2.31	ND
8: X = NH	52	9.0	5.78	1508
 **9**				
9	110	7.6	14.5	1170
 **10**  **11**				
10	1500	3500	0.43	ND
11	ND	ND	—	ND

ND: not detected.

[a] Vitamin D_3 agonistic activity was estimated as ED_{50} values of HL-60 monocytic cell differentiation induction measured by NBT-positivity.

[b] Androgen antagonistic activity was estimated as IC_{50} values on testosterone-induced cell growth of SC-3 cells.

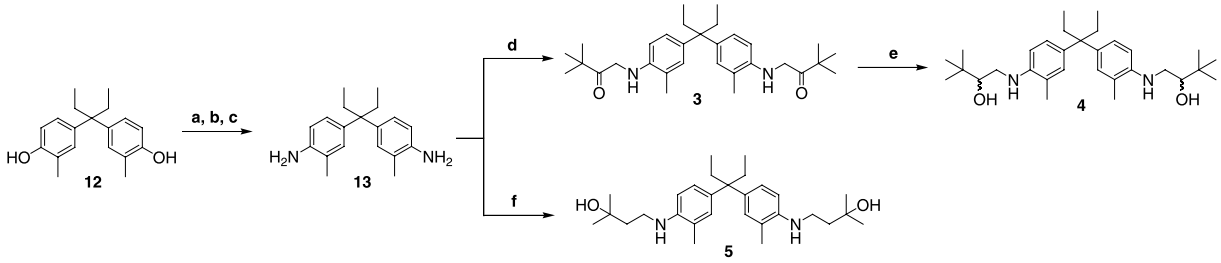
[c] Activity ratio was defined as vitamin D_3 activity (ED_{50} value)/androgen antagonistic activity (IC_{50} value).

androgen-induced cell growth of SC-3 cells was defined as androgen-antagonistic activity.[12,13,15]

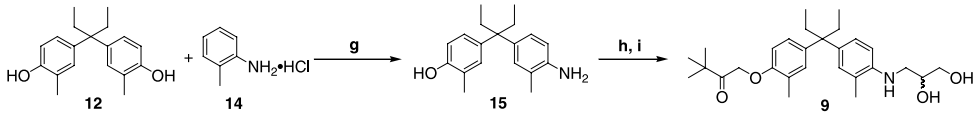
2. Chemistry

First we designed nitrogen analogs of LG190155 (**1**)/LG190178 (**7**), that is, **2**, **3**, and **8**, in order to allow introduction of a substituent at the nitrogen atom, aiming at eventual conversion of the compounds to antagonists, based on our earlier development studies on nitrogen-containing vitamin D_3 antagonists, DLAMs.[11,14] Next, we designed (i) the reduced analog of **3**, that is, compound **4**, (ii) compounds possessing hydroxyl groups at various positions (like the 25-hydroxyl group of the side chain of 1,25-D_3), that is, compound **5** and its hybrid compound with **1/2** (**6**), (iii) the oxidized analog of **8**, that is, compound **9**, and (iv) compounds which possess a free phenolic hydroxyl group derived from **2** and **8**, that is, compounds **10** and **11**, respectively. These compounds were obtained by usual organic synthetic methods, and the structures were confirmed by the spectroscopic data.[18–26] A typical synthetic scheme (for the synthesis of compounds **3**–**5**) is shown in Scheme 1.

It is noteworthy that direct substitution reaction of the bisphenol derivative **12** with an aniline derivative **14** proceeded efficiently to yield compound **15** (Scheme 2).



Scheme 1. Reagents and conditions: (a) Tf_2O, Et_3N, CH_2Cl_2, 2 h, 97%; (b) $BnNH_2$, $Pd(OAc)_2$, 2-(di-*tert*-butylphosphino)biphenyl, Cs_2CO_3, toluene, 100 °C, 14 h, 54%; (c) H_2, $Pd(OH)_2/C$, DMF, 16 h, 95%; (d) 1-chloropinacolone, KI, Et_3N, DMF, 24 h, 59%; (e) $NaBH_4$, *sec*-BuOH, 30 min, 98%; (f) 4-bromo-2-methyl-2-butanol, Et_3N, DMF, 60 °C, 22 h, 31%.



Scheme 2. Reagents and conditions: (g) neat, 180 °C, 2.5–15 h, 72%; (h) 1-chloropinacolone, NaH, DMF, 1 h, 97%; (i) glycidol, EtOH, 19 h, 57%.

This reaction seems to be general, because the substitution reaction of **12** with various aniline derivatives of **14** gave the corresponding adducts in good yields (generally 50–80%; details will be published elsewhere). A similar reaction, that is, transalkylation of 4,4′-(1-methylethylidene)bisphenol with 2,6-diphenylphenol, was reported by Wang and Hay, though the reaction proceeds in the presence of methanesulfonic acid.[27]

3. Cell biological assays

Vitamin D_3-agonistic activity of the compounds was evaluated by measurement of HL-60 cell differentiation as described previously.[14,28] Briefly, HL-60 cells were incubated in RPMI 1640 medium in the presence or absence of a test compound for three days. Treated HL-60 cells were mixed with phosphate-buffered saline (PBS) containing 0.2% nitroblue tetrazolium (NBT) and 20 nM 12-*O*-tetradecanoylphorbol 13-acetate (TPA) in a 1:1 (v/v) ratio and incubated at 37 °C for 20 min. NBT positivity was measured by counting 200–300 cells. The cell differentiation was also confirmed morphologically by microscopy after Wright–Giemsa staining. Of course, the percentage values differed from experiment to experiment, but the results were basically reproducible. A typical set of ED_{50} values is presented in Table 1.

Androgen-antagonistic activity of the compounds was evaluated by measurement of inhibition of androgen-induced SC-3 cell growth, as described previously.[12,13,15] Briefly, SC-3 cells were cultured in MEM medium supplemented with 10% FBS and 10 nM testosterone in the presence or absence of a test compound for three days at 37 °C under 5% CO_2. The number of cells with testosterone alone was defined as 100%. The concentration of test compounds that inhibited by 50% the increase of the cell number induced by 10 nM testosterone was quantified (IC_{50}) (Table 1). Androgen-agonistic activity can be evaluated in the same cell line, but none of the prepared compounds (**1**–**11**) showed androgen-agonistic activity (growth promotion of SC-3 cells). The binding affinity of the compounds toward AR was also evaluated as described previously.[12,13,15] Briefly, recombinant AR was prepared from cytosol of *Escherichia coli* transformed with a human AR LBD expression vector (GST-hARLBD), which encodes amino acids 627–919 of human AR fused with GST protein under the lac promoter.[29] The binding activity of the GST-hARLBD thus prepared for [^{3}H]testosterone, that is, the K_d (dissociation constant) value, was determined to be 1.4 nM by Scatchard analysis, and this value is close to that of AR prepared from intact SC-3 cells. Although, the amino acid sequences of mouse AR and human AR are slightly different from each other, they possess basically the same ligand selectivity as far as examined.[12,15] The binding activity of a test compound was determined by incubation of GST-hARLBD with [^{3}H]testosterone in the presence of various concentrations of the test compound. The concentration of a test compound that inhibits [^{3}H]testosterone binding by 50% (IC_{50} value) was determined, and the K_i value was calculated based on the K_d value of [^{3}H]testosterone (Table 1).

4. Results and discussion

As shown in Table 1, LG190155 (**1**) showed moderate HL-60 cell differentiation-inducing activity (vitamin D_3-agonistic activity) with an EC_{50} value of 410 nM, which is consistent with the reported activity.[16,17] We found that this compound also possesses SC-3 cell growth-inhibitory activity (androgen-antagonistic activity), as we suspected, though the activity was weak (IC_{50} value of 1900 nM). Though LG190155 (**1**) possesses both vitamin D_3-agonistic and androgen-antagonistic activities, the activity ratio (ratio of ED_{50} value for vitamin D_3-agonistic activity and IC_{50} value for androgen-antagonistic activity) was 0.22, meaning that this compound can be regarded primarily as a vitamin D_3 agonist, rather than an androgen antagonist.

Exchange of the one or two phenolic oxygen atom(s) of LG190155 (**1**) with a nitrogen atom(s), resulting in compounds **2** and **3**, respectively, slightly lowered the vitamin D_3 activity and increased the androgen-antagonistic activity. The androgen-antagonistic activity of these three compounds increased in the order of the number of oxygen–nitrogen exchange(s), that is, **1** < **2** < **3**. The activity ratio values of **2** and **3** were 0.38 and 0.45, respectively.

Reduction of **3**, giving **4**, resulted in a lower vitamin D_3 activity but the androgen-antagonistic activity was not affected, and its activity ratio value was further raised to 1.20. Consequently, compound **4** can be regarded as a dual ligand possessing both vitamin D_3 activity and androgen-antagonistic activity, although AR binding affinity could not be observed under the experimental conditions used.

Translocation of two hydroxyl groups of **4**, giving **5**, resulted in a slight increase of vitamin D_3 activity, but the androgen-antagonistic activity was greatly lowered. Consequently, at least in terms of the cell biological assays performed here, compound **5** can be recognized as almost a pure vitamin D_3 agonist (the activity ratio is 0.13). A hybrid compound of **5** with **1/2**, that is, **6**, showed a further increase of vitamin D_3-agonistic activity and great potentiation of androgen-antagonistic activity. It should be noted that both **5** and **6** possess moderate binding affinity toward AR. Although we cannot interpret this lack of a precise correlation between AR affinity and androgen-antagonistic activity evaluated in terms of SC-3 cell growth inhibitory activity at this stage, AR affinity is not necessarily correlated with androgen-antagonistic activity, especially for AR antagonists, and lack of such a relationship is often observed.[12,13] One possible interpretation is different efficacy among AR/androgen antagonist complexes in recruiting corepressor(s).

LG190178 (**7**) showed very potent vitamin D_3 activity, as reported.[16,17] We found that LG190178 (**7**) possess a potent androgen-antagonistic activity with an IC_{50} value of 19 nM, as we had suspected. Its activity ratio was 2.31, so, it can be recognized as a dual ligand possessing both vitamin D_3 activity and androgen-antagonistic activity. For the aza analog of LG190178 (**7**), that is, compound **8**, the vitamin D_3 activity was slightly lowered, but the androgen-antagonistic activity was potentiated, as was found in the case of nitrogen–oxygen exchange(s) in compounds **1**–**3**. Compound **8** possess potent binding affinity toward AR with a K_i value of 1508 nM, which is comparable with that of the well-known androgen antagonist, hydroxyflutamide (K_i = 936 nM), and its activity ratio was 5.78, meaning that compound **8** can be regarded as an androgen antagonist rather than vitamin D_3 agonist.

Although detailed structure–activity relationship studies remain to be performed, some features could be extracted from the results presented here, that is, (1) exchange of a phenolic oxygen atom(s) with a nitrogen atom(s) seems to lower vitamin D_3-agonistic activity and to enhance androgen-antagonistic activity (comparisons among **1**–**3**, and between **7** and **8**), (2) a 1,2-diol group seems to be important for potent vitamin D_3-agonistic activity (comparison of **1**–**6** vs compounds **7**–**9**), and (3) exchange of the phenolic oxygen atom-containing side chain of **6** with a nitrogen atom-containing side chain with reduction and translocation of a hydroxyl group, giving **5** seems to weaken both vitamin D_3-agonistic activity and androgen-antagonistic activity, but the effect is much greater for the latter activity. These results prompted us to evaluate a hybrid compound **9** (Scheme 2).

Compound **9** was revealed to possess very potent androgen-antagonistic activity with an IC_{50} value of 7.6 nM, which is 24 times more potent than hydroxyflutamide (IC_{50} = 180 nM). Although **9** possess moderate vitamin D_3-agonistic activity with an EC_{50} value of 110 nM, the activity ratio is 14.5, and it also possesses rather potent AR-binding affinity (K_i value of 1170 nM). Therefore, **9** can be regarded as a potent androgen antagonist with additional vitamin D_3-agonistic activity. The tertiary butylcarbonylmethyl group of **9** seems to be important for both vitamin D_3-agonistic and androgen-antagonistic activities because its removal, giving **11**, resulted in disappearance of the activities. Interestingly, compound **10**, a de-butylcarbonylmethylated analog of **2** with a free phenolic hydroxyl group, possesses both vitamin D_3 and androgen-antagonistic activities, though they are very weak compared with those of **2**.

In conclusion, several compounds with a bis-phenylmethane skeleton (**2**–**6** and **8**–**11**) were derived from nonsecosteroidal vitamin D_3 [LG190155 (**1**) and LG190178 (**7**)]. The prepared compounds showed various activity ratio values ranging from 0.13 to 14.5. For convenience, these compounds can be classified into three categories, that is, vitamin D_3 agonists (compounds with activity ratio values of less than 0.4), androgen antagonists (compounds with activity ratio values of more than 2.5), and dual ligands (compounds with activity ratio values of 0.4–2.5). Then, compounds **1**, **2**, and **5** are vitamin D_3 agonists, compounds **3**, **4**, **6**, and **7** are dual ligands, and compounds **8** and **9** are androgen antagonists (with activity ratios of 5.78 and 14.5, respectively). In particular, compound **9** is a very potent and selective androgen antagonist with a nonsecosteroidal vitamin D_3 skeleton. Further structural development studies and investigation of structure–activity relationships are in progress.

Acknowledgments

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18. 1-(4-{3-[4-(3,3-Dimethyl-2-oxobutylhydroxy)-3-methylphenyl]pentan-3-yl}-2-methylphenylamino)-3,3-dimethylbutan-2-one (**2**): mp 106 °C. HRMS: 479.3392 (calcd 479.3399). ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 6.93–6.89 (m, 3H), 6.83 (br s, 1H), 6.49 (d, J = 8.1 Hz, 1H), 6.39 (d, J = 8.1 Hz, 1H), 4.82 (s, 2H), 4.50 (br s, 1H), 4.13 (d, J = 4.3 Hz, 2H), 2.23 (s, 3H), 2.16 (s, 3H), 1.99 (q, J = 7.3 Hz, 4H), 1.25 (s, 9H), 1.24 (s, 9H), 0.59 (t, J = 7.3 Hz, 6H). Anal. Calcd N, 2.80; C, 77.39; H, 9.37. Found: N, 2.92; C, 77.62; H, 9.46.
19. 3,3-Bis[4-(3,3-Dimethyl-2-oxobutylamino)-3-methylphenyl]pentane (**3**): HRMS: 478.3562 (calcd 478.3559). ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 6.95 (dd, J = 8.5, 2.1 Hz, 2H), 6.85 (d, J = 2.1 Hz, 2H), 6.39 (d, J = 8.5 Hz, 2H), 4.50 (br s, 2H), 4.13 (s, 4H), 2.16 (s, 6H), 1.99 (q, J = 7.3 Hz, 4H), 1.24 (s, 18H), 0.59 (t, J = 7.3 Hz, 6H).
20. 3,3-Bis[4-(2-hydroxy-3,3-dimethylbutylamino)-3-methylphenyl]-pentane (**4**): HRMS: 482.3878 (calcd 482.3872). ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 6.95 (dd, J = 8.6, 2.1 Hz, 2H), 6.85 (br s, 2H), 6.53 (d, J = 8.6 Hz, 2H), 3.52 (d, J = 10.3 Hz, 2H), 3.37 (dd, J = 12.4, 2.6 Hz, 2H), 2.99 (dd, J = 12.4, 10.3 Hz, 2H), 2.10 (s, 6H), 2.00 (q, J = 7.3 Hz, 4H), 0.99 (s, 9H), 0.60 (t, J = 7.3 Hz, 6H).
21. 3,3-Bis[4-(3-Hydroxy-3-methylbutylamino)-3-methylphenyl]pentane (**5**): HRMS: 454.3562 (calcd 454.3559). ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 6.95–6.90 (m, 3H), 6.81 (d, J = 1.7 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 6.49 (d, J = 8.6 Hz, 1H), 4.82 (s, 2H), 3.30 (t, J = 6.6 Hz, 2H), 2.24 (s, 3H), 2.07 (s, 3H), 2.00 (q, J = 7.3 Hz, 4H), 1.85 (t, J = 6.6 Hz, 2H), 1.31 (s, 6H), 1.25 (s, 9H), 0.59 (t, J = 7.3 Hz, 6H).
22. 1-(4-{3-[4-(3-Hydroxy-3-methylbutylamino)-3-methylphenyl]pentan-3-yl}-2-methylphenoxy)-3,3-dimethylbutan-2-one (**6**): HRMS: 467.3388 (calcd 467.3399). ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 6.95–6.90 (m, 3H), 6.81 (d, J = 1.7 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 6.49 (d, J = 8.6 Hz, 1H), 4.82 (s, 2H), 3.30 (t, J = 6.6 Hz, 2H), 2.24 (s, 3H), 2.07 (s, 3H), 2.00 (q, J = 7.3 Hz, 4H), 1.85 (t, J = 6.6 Hz, 2H), 1.31 (s, 6H), 1.25 (s, 9H), 0.59 (t, J = 7.3 Hz, 6H).
23. 3-(4-{3-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]pentan-3-yl}-2-methylphenylamino)- propane-1,2-diol (**8**): HRMS: 457.3190 (calcd 457.3192). ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 6.97–6.92 (m, 3H), 6.83 (d, J = 1.7 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.55 (d, J = 6.9 Hz, 1H), 4.10–4.07 (m, 1H), 4.01 (m, 1H), 3.87–3.81 (m, 2H), 3.71–3.67 (m, 2H), 3.33 (dd, J = 12.8, 4.3 Hz, 1H), 3.25–3.21 (m, 1H), 2.17 (s, 3H), 2.11 (s, 3H), 2.01 (q, J = 7.3 Hz, 4H), 1.01 (s, 9H), 0.60 (t, J = 7.3 Hz, 6H).
24. 1-(4-{3-[4-(2,3-Dihydroxypropylamino)-3-methylphenyl]-pentan-3-yl}-2-methylphenoxy)-3,3-dimethylbutan-2-one (**9**): HRMS: 455.3040 (calcd 455.3036). ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 6.94–6.89 (m, 3H), 6.82 (d, J = 2.1 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 6.49 (d, J = 8.1 Hz, 1H), 4.83 (s, 2H), 4.01 (m, 1H), 3.82(dd, J = 11.1, 3.4 Hz, 1H), 3.70–3.66 (m, 1H), 3.33 (dd, J = 12.8, 4.3 Hz, 1H), 3.25–3.21 (m, 1H), 2.23 (s, 3H), 2.11 (s, 3H), 2.00 (q, J = 7.3 Hz, 4H), 1.25 (s, 9H), 0.59 (t, J = 7.3 Hz, 6H).
25. 1-{4-[3-(4-Hydroxy-3-methylphenyl)pentan-3-yl]-2-methylphenylamino}-3,3-dimethylbutan-2-one (**10**): HRMS: 381.2658 (calcd 381.2668). ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 6.94–6.87 (m, 3H), 6.84 (d, J = 2.1 Hz, 1H), 6.64 (d, J = 8.6 Hz, 1H), 6.40 (d, J = 8.1 Hz, 1H), 4.53 (br s, 1H), 4.13 (s, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.00 (q, J = 7.3 Hz, 4H), 1.24 (s, 9H), 0.59 (t, J = 7.3 Hz, 6H).
26. 4-{3-[4-(2,3-Dihydroxypropylamino)-3-methylphenyl]pentan-3-yl}-2-methylphenol (**11**): HRMS: 357.2344 (calcd 357.2304). ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 6.95–6.83 (m, 4H), 6.64 (d, J = 8.6 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 4.01 (m, 1H), 3.82 (dd, J = 11.1, 3.4 Hz, 1H), 3.70–3.66 (m, 1H), 3.32 (dd, J = 12.8, 4.3 Hz, 1H), 3.25–3.21 (m, 1H), 2.22 (s, 3H), 2.10 (s, 3H), 2.00 (q, J = 7.3 Hz, 4H), 0.60 (t, J = 7.3 Hz, 6H).
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