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Ethylenediamine diacetate (EDDA)-catalyzed one-pot synthesis of tetrahydroquinolines by domino Knoevenagel/hetero Diels–Alder reactions from 1,3-dicarbonyls

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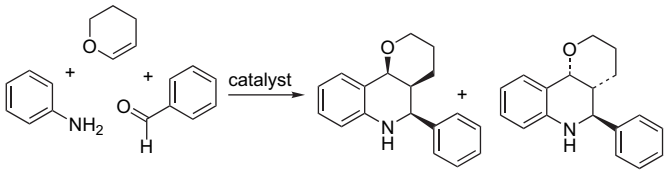
ABSTRACT

This paper describes new and efficient synthetic approaches for biologically interesting tetrahydroquinoline analogues. The key strategies involve the ethylenediamine diacetate-catalyzed cyclization of 1,3-dicarbonyls to aminobenzaldehydes through domino Knoevenagel/hetero Diels–Alder reactions. These reactions provide a rapid route for the synthesis of novel polycycles with the tetrahydroquinoline moiety.

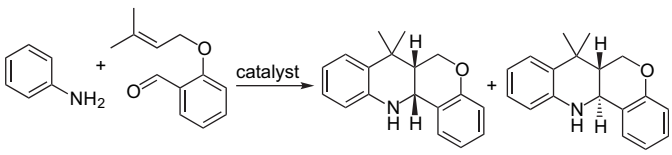
1. Introduction

Tetrahydroquinolines with a variety of substituents show a wide range of psychotropic, anti-allergic, anti-inflammatory, and estrogenic activities.[1] A number of methodologies for synthesizing tetrahydroquinones with substituents have been reported. Among these, hetero Diels–Alder reactions between *N*-aldimines and electron-rich dienophiles are a powerful synthetic tool for preparing tetrahydroquinoline derivatives.[2] First, intermolecular imino Diels–Alder reactions using a three-component condensation of *N*-anilines with benzaldehydes to electron-rich olefins provided tetrahydroquinolines with a variety of substituents (Scheme 1).[3] These reactions have been studied extensively using Lewis acids, such as $InCl_3$,[3] $FeCl_3$/NaI,[4] and $BF_3{\cdot}OEt_2$,[5] Brønsted acids, such as TFA and *p*-TsOH,[6] and lanthanide triflates including $Ln(OTf)_3$, $Sc(OTf)_3$, and $Yb(OTf)_3$.[7] Montmorillonite KSF,[8] $GdCl_3$,[9] $ZrCl_4$,[10] $LiBF_4$,[11] $SbCl_3$,[12] and $LiClO_4$[13] have been used as catalysts in the synthesis of tetrahydroquinolines. These strategies allow for the facile synthesis of tetrahydroquinoline derivatives. However, these reactions mainly give a mixture of diastereomers as products.

Second, intramolecular imino Diels–Alder reactions between *N*-arylamines and *O*-allyl derivatives of salicylaldehyde also provide multiple opportunities for synthesizing tetrahydroquinolines (Scheme 2). These reactions have been also catalyzed by TFA,[14] $BiCl_3$,[15] $LiClO_4$,[16] and triphenylphosphonium perchlorate.[17] However, these reactions often produce a mixture of diastereomers, require strong acidic conditions and long reaction times, and produce products in low yields.



Scheme 1.



Scheme 2.

Domino Knoevenagel/hetero Diels–Alder reactions have been used extensively for the synthesis of heterocyclic compounds.[18] These reactions provide a rapid synthetic route for assembling polycyclic structures.[19] The simplicity and utility of these reactions for the synthesis of polycycles prompted us to examine the use of

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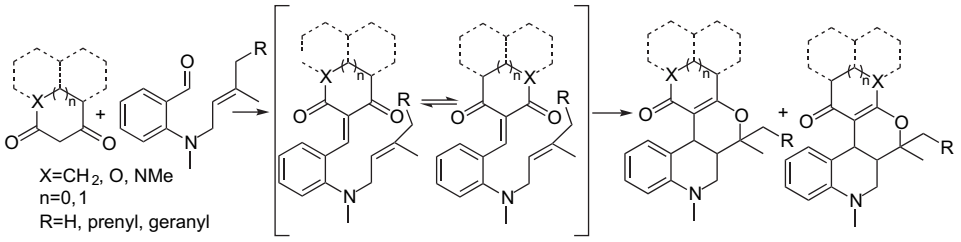


Scheme 3.

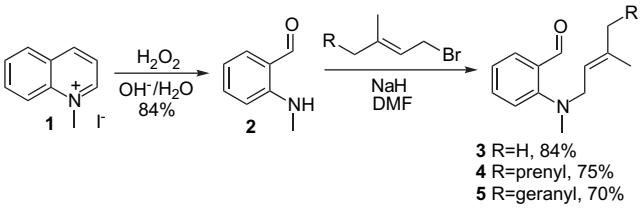
these reactions. The scope and limitation of these reactions in the synthesis of tetrahydroquinoline derivatives were investigated. There are no reports on domino Knoevenagel/hetero Diels–Alder cyclizations between 1,3-dicarbonyls and *N*,*N*-dialkylated aminobenzaldehydes.

Recently, the Brønsted acids and bases have demonstrated their potent to serve as active catalysts for a variety of synthetically useful reactions in organic chemistry.[20] In particular, we have developed a new and useful methodology for preparing a variety of benzopyrans using ethylenediamine diacetate (EDDA) as effective Brønsted acid and base catalysts.[21] These reactions involve a formal [3+3]-cycloaddition through a 6π-electrocyclization. This methodology provides a rapid route for synthesizing benzopyran derivatives with a variety of substituents on the pyranyl ring.[22]

As a part of an ongoing study into the synthetic efficacy of this methodology, this study investigated EDDA-catalyzed domino Knoevenagel/hetero Diels–Alder reactions of cyclic 1,3-dicarbonyls and 2-aminobenzaldehydes to afford tetrahydroquinolines, as shown in Scheme 3. We report the efficient one-pot synthesis of tetrahydroquinoline analogues with a variety of substituents on the pyranyl rings.

2. Results and discussion

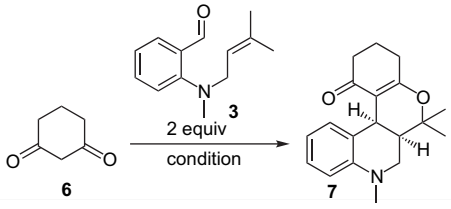
As starting materials, *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**), *N*-methyl-*N*-geranyl-2-aminobenzaldehyde (**4**), and *N*-methyl-*N*-farnesyl-2-aminobenzaldehyde (**5**) were first prepared from 1-methylquinolinium iodide (**1**) in a two-step reaction, as shown in Scheme 4. Treatment of methylquinolinium iodide (**1**) with hydrogen peroxide in aqueous sodium hydroxide afforded *N*-methyl-2-aminobenzaldehyde (**2**) in 84% yield.[23] A reaction of *N*-methyl-2-aminobenzaldehyde (**2**) with prenyl bromide in the presence of NaH in DMF gave *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) in 84% yield. Similarly, treatment of compound **2** with geranyl bromide gave compound **4** in 75% yield. On the other hand, a reaction with *trans*,*trans*-farnesyl bromide afforded compound **5** in 70% yield.



Scheme 4.

To produce a variety of tetrahydroquinoline analogues, reaction of 1,3-cyclohexanedione (**6**) with 2.0 equiv of *N*,*N*-methylprenyl-2-aminobenzaldehyde (**3**) was attempted under several conditions (Table 1). Indium(III) chloride (20 mol %) as a Lewis acid catalyst in refluxing acetonitrile gave no adduct, whereas ytterbium(III) triflate (20 mol %) afforded product **7** in only 10% yield. No products were obtained using pyridine as the reactant and solvent at 140 °C for 24 h. However, adduct **7** was obtained using ethylenediamine diacetate (20 mol %) as a catalyst. This reaction is solvent-dependent with the best yield (75%) being obtained in refluxing xylene for 24 h.

Table 1
Reaction of 1,3-cyclohexanedione (**6**) with aminobenzaldehyde **3** under several conditions

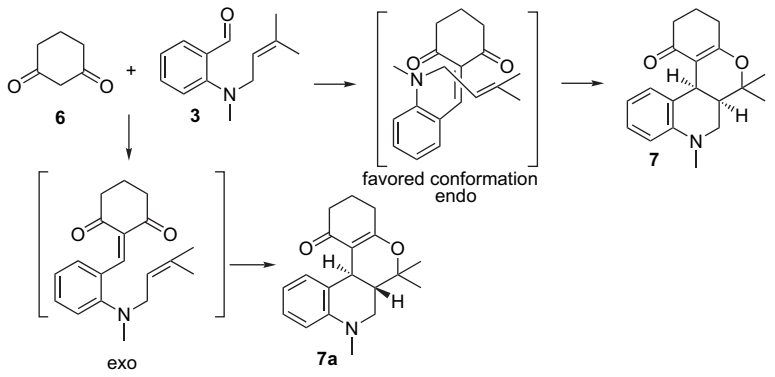


Condition		Yield (%)
$InCl_3$ (20 mol %)	Acetonitrile, reflux, 12 h	0
$Yb(OTf)_3$ (20 mol %)	Acetonitrile, reflux, 12 h	10
Pyridine (excess)	140 °C, 24 h	0
EDDA (20 mol %)	Methylene chloride, rt, 24 h	33
EDDA (20 mol %)	Benzene, reflux, 24 h	42
EDDA (20 mol %)	Xylene, reflux, 24 h	75
EDDA (20 mol %)	Ethyl acetate, rt, 24 h	60

Compound **7** was easily separated by column chromatography and the cis-stereochemistry of compound **7** was confirmed based on the coupling constant of ^{1}H NMR and by a direct comparison with reported data.[19c,24] The signal of the benzylic methine on the pyranyl ring in compound **7** appears as a doublet (J=6.0 Hz) at δ 3.91. In the cis-fused cycloadducts of these types of other known tetracycles, the signals of benzylic methine are observed as a doublet with a coupling constant J=4–6 Hz, whereas those of trans-fused adducts appear as a doublet with a coupling constant J=9–11 Hz.[19c,24]

The stereospecificity of compound **7** may be explained by the *endo*-transition structure as shown in Scheme 5. In the process of the hetero Diels–Alder reaction, the *endo*-transition structure must have been more favorable than the *exo*-transition structure due to an sp^2-geminal effect according to the phenomenon of 1,3-allylic strain.[25] This is in agreement with Tietze's work, who reported the synthesis of tetracycles using intramolecular hetero Diels–Alder cycloaddition of 1,3-dicarbonyl compounds and *O*-allyl ether of salicylic aldehydes.[26]

In order to extend the utility of this methodology, further reactions of several types of cyclic 1,3-dicarbonyls were carried out in the presence of ethylenediamine diacetate (20 mol %) in refluxing xylene for 12–24 h. The results are summarized in Table 2. First, the reactions of symmetrical cyclic 1,3-dicarbonyl compounds were examined. A reaction of 1,3-cyclopentanedione (**8**) of a five-membered ring with 2.0 equiv of *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) in refluxing xylene for 12 h afforded adduct **16** in



Scheme 5.

85% yield (entry 1). Similarly, a reaction of 5,5-dimethyl-1,3-cyclohexanedione (**9**) with **3** gave adduct **17** in 83% yield, whereas a reaction with 3-hydroxy-1*H*-phenalen-1-one (**10**) afforded product **18** in 76% yield (entries 2 and 3). In particular, the structure and cis-stereochemistry of compound **18** were confirmed by X-ray single crystal analysis, as shown in Figure 1. The cycloaddition reactions were also successful with other unsymmetrical cyclic 1,3-dicarbonyls. A reaction of 4-hydroxycoumarin (**11**) with compound

Table 2
Reactions of symmetrical or unsymmetrical 1,3-dicarbonyls with aminobenzaldehyde **3**[a]

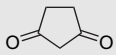
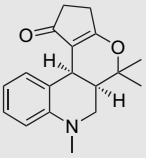
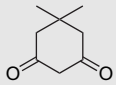
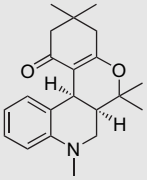
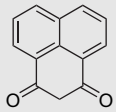
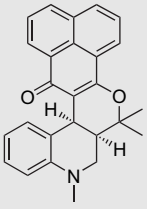
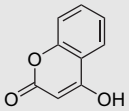
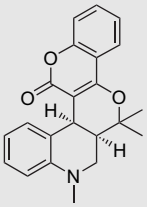
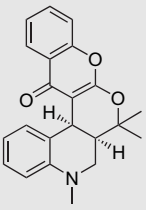
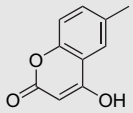
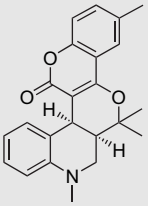
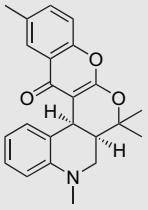
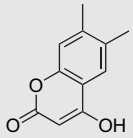
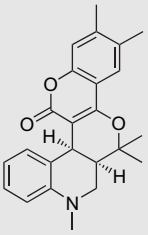
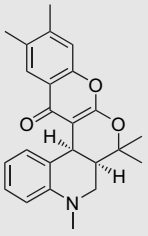
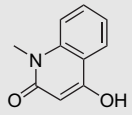
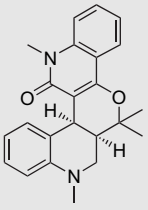
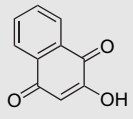
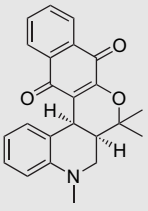
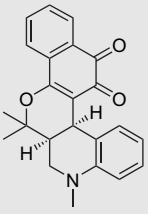
Entry	1,3-Dicarbonyls		Aminoaldehyde	Time (h)	Product		Yield (%)
1		**8**	**3**	12		**16**	85
2		**9**	**3**	12		**17**	83
3		**10**	**3**	12		**18**	76
4		**11**	**3**	24		**19**	60
						**20**	24

Table 2 (*continued*)

Entry	1,3-Dicarbonyls		Aminoaldehyde	Time (h)	Product		Yield (%)
5		**12**	**3**	24		**21**	58
						**22**	22
6		**13**	**3**	24		**23**	54
						**24**	20
7		**14**	**3**	24		**25**	75
8		**15**	**3**	12		**26**	57
						**27**	32

[a] Conditions: starting material (1.0 mmol) and **3** (2.0 mmol) under EDDA (20 mol %) in refluxing xylene.

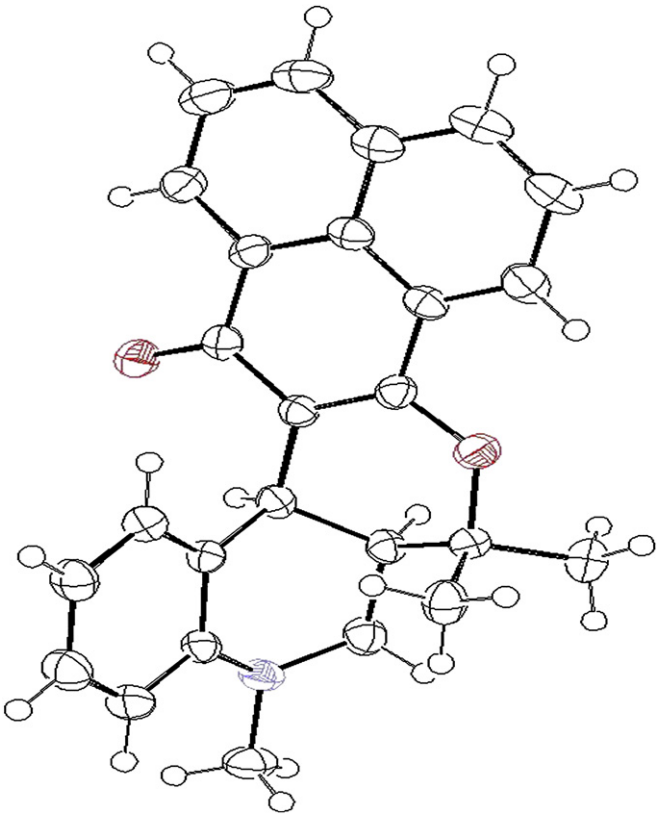
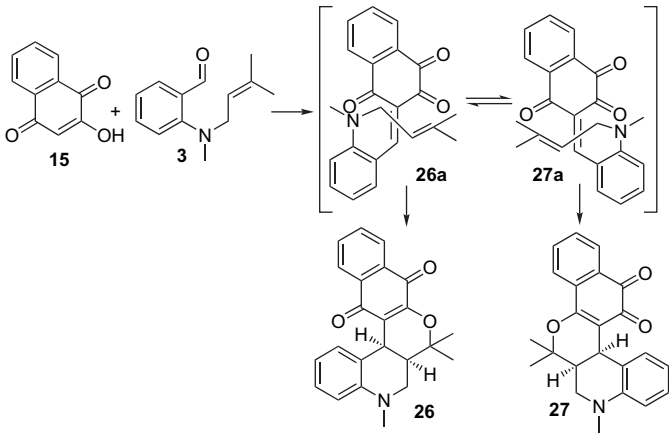


Figure 1. X-ray structure of compound **18**.

3 in refluxing xylene for 24 h afforded two regioisomers **19** and **20** in 60 and 24% yields, respectively (entry 4). These two compounds were easily separated by column chromatography and were assigned by the spectral data. In the IR spectra, the ester carbonyl absorption of compound **19** was observed at 1705 cm^{-1}, whereas the carbonyl absorption was observed at 1618 cm^{-1} in the case of compound **20**. Further support for distinguishing between the coumarin and chromone structures came from the carbonyl carbon in the ^{13}C NMR spectrum, which appeared at δ 162.7 for compound **19** with a coumarin skeleton, and at δ 177.9 for compound **20** with a chromene moiety. Similarly, reactions of 4-hydroxycoumarins **12** and **13** with substituents on the benzene ring gave also products **21**–**24** (entries 5 and 6) in moderate yields. Interestingly, in the cases of entries 5 and 6 with substituents such as methyl and dimethyl on the benzene ring, the yield and selectivity of the obtained products were somewhat decreased. Unlike 4-hydroxycoumarins **11**–**13**, 4-hydroxy-2-quinolone (**14**) gave product **25** in 75% yield as a sole compound. In order to examine the usefulness of these reactions, the other reaction using 2-hydroxy-1,4-naphthoquinone (**15**) was studied. Treatment of compound **15** with **3** in refluxing xylene for 12 h provided two products **26** and **27** in 57 and 32% yields, respectively. The products were easily separated by column chromatography and the structures of two isomers were determined from their spectroscopic data. The ^{1}H NMR spectrum of compound **26** showed the aromatic protons of symmetrical 1,4-naphthoquinone moiety as two parts with chemical shifts at δ 8.09–8.04 (2H, m) and 7.71–7.61 (2H, m), whereas compound **27** showed aromatic peaks separately as four parts at δ 8.07 (1H, d, J=7.5 Hz), 7.84 (1H, d, J=7.8 Hz), 7.64 (1H, dd, J=7.8, 7.5 Hz), 7.51 (1H, dd, J=7.5, 7.5 Hz) due to unsymmetrical 1,2-naphthoquinone skeleton. The ^{13}C NMR spectra of compound **26** showed two signals at δ 184.2 and 179.9 due to the presence of two carbonyl groups, and compound **27** showed two carbonyl signals at δ 179.8 and 179.0. The formation of compounds **26** and **27** can be explained by the sequence through intermediates **26a** and **27b** as shown in Scheme 6.



Scheme 6.

Based on these successful results, additional domino Knoevenagel/intramolecular hetero Diels–Alder reactions between cyclic 1,3-dicarbonyl compounds and aminobenzaldehydes **4**–**5** with geranyl or farnesyl group were examined (Table 3). A reaction of 1,3-cyclohexanedione (**6**) with aminobenzaldehyde **4** using 20 mol % of ethylenediamine diacetate as a catalyst in refluxing xylene for 24 h gave product **28** (68%), whereas a reaction with aminobenzaldehyde **5** afforded product **29** in 65% yield (entries 1 and 2). Similarly, treatment of compound **9** with aminobenzaldehyde **4** or **5** in the presence of 20 mol % of ethylenediamine diacetate in refluxing xylene for 24 h gave product **30** (72%) or **31** (68%) (entries 3 and 4), respectively. These reactions provide a rapid route for the synthesis of tetrahydroquinolines with long chain substituents on the pyranyl ring.

In conclusion, we report a new and efficient methodology for synthesizing biologically interesting tetrahydroquinoline derivatives via domino Knoevenagel/hetero Diels–Alder reactions from 1,3-dicarbonyls and aminoaldehydes. These reactions provide a rapid route for the synthesis of novel types of polycycles with the tetrahydroquinoline moiety.

3. Experimental section

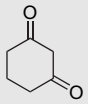
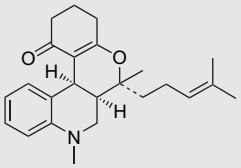
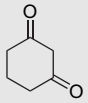
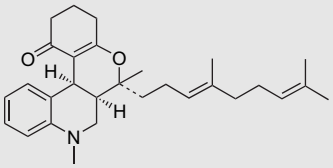
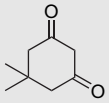
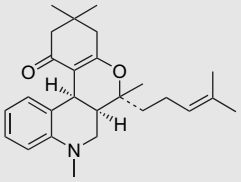
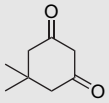
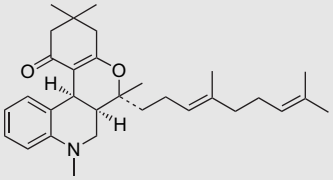
3.1. General

All the experiments were carried out in a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ using δ=7.24 and 77.0 ppm as the solvent chemical shift. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. The HRMS and MS spectra were carried out at the Korea Basic Science Institute.

3.2. *N*-Methyl-2-aminobenzaldehyde (2)

To a stirred mixture of potassium hydroxide (8.30 g, 0.148 mol) in water (30 mL) and 1,2-dichloroethane (30 mL) at 0 °C was added hydrogen peroxide (6.4 mL, 35%, 0.074 mol) in water (4 mL). 1-Methylquinolinium iodide (**1**) (4.065 g, 0.015 mol) in water (10 mL) was added dropwise over 45 min at 0 °C, which was then stirred at room temperature for 48 h. Thiodiethanol (0.5 g) was added and the layers were separated. The aqueous phase was extracted with

Table 3
Reactions of 1,3-dicarbonys with aminobenzaldehydes **4**–**5**[a]

Entry	1,3-Dicarbonyls		Aminoaldehyde	Time (h)	Product		Yield (%)
1		**6**	**4**	24		**28**	68
2		**6**	**5**	24		**29**	65
3		**9**	**4**	24		**30**	72
4		**9**	**5**	24		**31**	68

[a] Conditions: starting materials (1.0 mmol) and aminobenzaldehydes **4**–**5** (2.0 mmol) under EDDA (20 mol %) in refluxing xylene.

dichloromethane (30 mL×3), washed with water (30 mL) and saturated sodium sulfite solution (30 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 20:1) to give **2** (1.703 g, 84%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (1H, s), 7.45 (1H, dd, J=7.8, 1.5 Hz), 7.42–7.38 (1H, m), 6.70–6.66 (1H, m), 6.66 (1H, d, J=8.9 Hz), 2.92 (3H, d, J=5.5 Hz); IR (neat) 3345, 2908, 2829, 2744, 1658, 1577, 869, 752 cm^{-1}; m/z (EI) 135 (M^+, 59), 134 (100), 119 (20), 105 (35); HRMS m/z (M^+) calcd for C_8H_9NO: 135.0684. Found: 135.0687.

3.3. *N*-Methyl-*N*-prenyl-2-aminobenzaldehyde (3)

To a solution of **2** (2.0 g, 14.8 mmol) in DMF (20 mL) was added sodium hydride (1.776 g, 60%, 44.4 mmol) at 0 °C. After 20 min, prenyl bromide (2.426 g, 16.3 mmol) in DMF (3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 12 h and water (30 mL) was added slowly at 0 °C. The reaction mixture was extracted with ethyl acetate (30 mL×3), washed with water (30 mL) and saturated NH_4Cl solution (30 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 20:1) to give **3** (2.527 g, 84%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (1H, s), 7.75 (1H, dd, J=7.7, 1.7 Hz), 7.47–7.43 (1H, m), 7.07–6.97 (2H, m), 5.29–5.26 (1H, m), 3.67 (2H, d, J=6.7 Hz), 2.80 (3H, s), 1.71 (3H, s), 1.59 (3H, s); IR (neat) 2855, 1686, 1597, 1483, 1453, 1381, 1283, 1192, 1080, 928, 831, 764 cm^{-1}; HRMS m/z (M^+) calcd for $C_{13}H_{17}NO$: 203.1310. Found: 203.1312.

3.4. *N*-Methyl-*N*-geranyl-2-aminobenzaldehyde (4)

To a solution of **2** (2.0 g, 14.8 mmol) in DMF (20 mL) was added sodium hydride (1.776 g, 60%, 44.4 mmol) at 0 °C. After 20 min, geranyl bromide (3.539 g, 16.3 mmol) in DMF (3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 12 h and water (30 mL) was added slowly at 0 °C. The mixture was extracted with ethyl acetate (30 mL×3), washed with water (30 mL) and saturated NH_4Cl solution (30 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 20:1) to give **4** (3.012 g, 75%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.3 (1H, s), 7.76 (1H, dd, J=7.7, 1.7 Hz), 7.45 (1H, ddd, J=7.2, 7.2, 1.7 Hz), 7.06–6.98 (2H, m), 5.30–5.26 (1H, m), 5.06–5.02 (1H, m), 3.69 (2H, d, J=6.7 Hz), 2.81 (3H, s), 2.05–2.01 (4H, m), 1.67 (3H, s), 1.59 (3H, s), 1.58 (3H, s); IR (neat) 2968, 2924, 1688, 1597, 1483, 1453, 1381, 1283, 1190, 1107, 932, 831, 764 cm^{-1}; HRMS m/z (M^+) calcd for $C_{18}H_{25}NO$: 271.1936. Found: 271.1934.

3.5. *N*-Methyl-*N*-farnesyl-2-aminobenzaldehyde (5)

To a solution of **2** (2.0 g, 14.8 mmol) in DMF (20 mL) was added sodium hydride (1.776 g, 60%, 44.4 mmol) at 0 °C. After 20 min, *trans*,*trans*-farnesyl bromide (4.650 g, 16.3 mmol) in DMF (3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 12 h and water (30 mL) was added slowly at 0 °C. The mixture was extracted with ethyl acetate (30 mL×3), washed with water (30 mL) and saturated NH_4Cl solution (30 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 20:1) to give **5** (3.517 g, 70%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (1H, s), 7.77 (1H, dd, J=7.7, 1.7 Hz), 7.46 (1H, ddd, J=7.2, 7.2, 1.7 Hz), 7.10–7.02 (2H, m), 5.38–5.27 (1H, m), 5.12–5.01 (2H, m), 3.95 (2H, s, J=6.7 Hz), 2.85 (3H, s), 2.13–1.96 (8H, m), 1.64 (6H, s), 1.57 (6H, s); IR (neat) 2967, 1688, 1597, 1484, 1453, 1381, 1283, 1109, 831, 761 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{33}NO$: 339.2562. Found: 339.2560.

3.6. General procedure for the synthesis of tetrahydroquinolines

Ethylenediamine diacetate (36 mg, 0.2 mmol) was then added to a solution of cyclic 1,3-diketones (1.0 mmol) and aminobenzaldehydes (2.0 mmol) in xylene (10 mL) at room temperature. The reaction mixture was stirred in refluxing xylene for 12–24 h. The removal of the solvent under reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give the products.

3.6.1. Compound **7**

A reaction of compound **6** (112 mg, 1.0 mmol) with *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) (406 mg, 2.0 mmol) in refluxing xylene (10 mL) for 24 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 7:1) afforded compound **7** (223 mg, 75%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (1H, dd, J=7.8, 7.5 Hz), 6.8 (1H, d, J=7.5 Hz), 6.64 (1H, dd, J=8.0, 7.8 Hz), 6.54 (1H, d, J=8.0 Hz), 3.91 (1H, d, J=6.0 Hz), 3.49 (1H, dd, J=11.9, 8.0 Hz), 2.86–2.80 (4H, m), 2.58–2.50 (1H, m), 2.41–2.37 (2H, m), 2.35–2.29 (2H, m), 2.03–1.97 (2H, m), 1.32 (3H, s), 0.92 (3H, m); IR (neat) 2943, 1649, 1612, 1503, 1454, 1379, 1262, 1171, 1125, 1086, 1047, 1001, 928, 853, 748 cm^{-1}; m/z (EI) 297 (M^+, 100), 296 (19), 282 (13), 255 (17), 254 (84), 242 (13), 241 (36), 198 (11), 186 (40), 185 (15), 184 (12), 144 (24); HRMS m/z (M^+) calcd for $C_{19}H_{23}NO_2$: 297.1729. Found: 297.1731.

3.6.2. Compound ***16***

A reaction of compound **8** (146 mg, 1.0 mmol) with *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) (406 mg, 2.0 mmol) in refluxing xylene (10 mL) for 12 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded compound **16** (203 mg, 85%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, J=7.8 Hz), 7.09 (1H, dd, J=7.8, 7.5 Hz), 6.72 (1H, dd, J=7.6, 7.5 Hz), 6.60 (1H, d, J=7.6 Hz), 3.84 (1H, d, J=4.0 Hz), 3.35 (1H, dd, J=11.7, 4.8 Hz), 2.93 (1H, dd, J=11.7, 4.8 Hz), 2.87 (3H, s), 2.47–2.46 (2H, m), 2.39–2.34 (2H, m), 2.17–2.12 (1H, m), 1.39 (3H, s), 1.33 (3H, s); IR (neat) 2926, 1689, 1609, 1510, 1435, 1381, 1302, 1278, 1201, 1144, 1121, 1082, 1020, 907, 858, 810, 741 cm^{-1}; m/z (EI) 283 (M^+, 100), 282 (13), 240 (52), 228 (11), 227 (24), 203 (19), 198 (16), 186 (31), 184 (11), 158 (12), 145 (12), 144 (32), 143 (11); HRMS m/z (M^+) calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1774.

3.6.3. Compound ***17***

A reaction of compound **9** (140 mg, 1.0 mmol) with *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) (406 mg, 2.0 mmol) in refluxing xylene (10 mL) for 12 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 7:1) afforded compound **17** (270 mg, 83%) as an solid: mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (1H, dd, J=7.5, 7.4 Hz), 6.7 (1H, d, J=7.4 Hz), 6.65 (1H, dd, J=8.0, 7.5 Hz), 6.54 (1H, d, J=8.0 Hz), 3.90 (1H, d, J=6.0 Hz), 3.47 (1H, dd, J=11.8, 8.1 Hz), 2.85–2.80 (4H, m), 2.44–2.22 (5H, m), 1.32 (3H, s), 1.12 (3H, s), 1.06 (3H, s), 0.93 (3H, m); IR (KBr) 2957, 2893, 1639, 1610, 1508, 1375, 1339, 1298, 1127, 1092, 1030, 862, 745 cm^{-1}; m/z (EI) 325 (M^+, 100), 324 (19), 310 (15), 283 (21), 282 (93), 270 (14), 269 (39), 186 (37), 185 (14), 184 (11), 144 (22); HRMS m/z (M^+) calcd for $C_{21}H_{27}NO_2$: 325.2042. Found: 325.2045.

3.6.4. Compound ***18***

A reaction of compound **10** (196 mg, 1.0 mmol) with *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) (406 mg, 2.0 mmol) in refluxing xylene (10 mL) for 12 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 7:1) afforded compound **18** (290 mg, 76%) as a solid: mp 196–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (1H, d, J=7.4 Hz), 8.21 (1H, d, J=7.4 Hz), 8.09 (1H, d, J=8.0 Hz), 7.99 (1H, d, J=8.0 Hz), 7.69 (1H, dd, J=8.0, 7.4 Hz), 7.58 (1H, d, J=8.0, 7.4 Hz), 7.11–7.05 (2H, m), 6.67 (1H, dd, J=7.5, 7.3 Hz), 6.61 (1H, d, J=8.0 Hz), 4.34 (1H, d, J=6.1 Hz), 3.61 (1H, dd, J=11.8, 8.4 Hz), 2.91 (1H, dd, J=11.8, 8.4 Hz), 2.87 (3H, s), 2.62–2.55 (1H, m), 1.52 (3H, s), 1.08 (3H, s); IR (KBr) 2903, 1632, 1574, 1508, 1417, 1377, 1298, 1242, 1223, 1121, 1024, 937, 785, 742 cm^{-1}; HRMS m/z (M^+) calcd for $C_{26}H_{23}NO_2$: 381.1729. Found: 381.1730.

3.6.5. Compounds ***19*** and ***20***

A reaction of compound **11** (162 mg, 1.0 mmol) with *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) (406 mg, 2.0 mmol) in refluxing xylene (10 mL) for 24 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 7:1) afforded compounds **19** (208 mg, 60%) and **20** (83 mg, 24%).

Compound **19**: mp 170–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, d, J=7.8 Hz), 7.65 (1H, dd, J=7.8, 7.5 Hz), 7.47–7.37 (2H, m), 7.34–7.24 (2H, m), 6.87 (1H, dd, J=7.5, 7.2 Hz), 6.76 (1H, d, J=7.8 Hz), 4.27 (1H, d, J=4.2 Hz), 3.69 (1H, dd, J=11.4, 8.3 Hz), 3.06 (1H, dd, J=11.4, 8.3 Hz), 2.99 (3H, s), 2.73–2.68 (1H, m), 1.65 (3H, s), 1.26 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 159.1, 152.7, 146.7, 131.5, 128.1, 127.3, 124.0, 123.5, 122.8, 117.7, 116.3, 115.8, 110.9, 101.0, 81.2, 51.0, 40.7, 38.6, 31.7, 28.0, 23.0; IR (KBr) 2978, 2847, 1705, 1626, 1574, 1495, 1454, 1393, 1279, 1136, 1086, 1038, 972, 897, 855, 748 cm^{-1}; m/z (EI) 347 (M^+, 100), 346 (11), 305 (11), 304 (51), 291 (19), 186 (39), 185 (15), 184 (12), 160 (22), 149 (15), 144 (25), 129 (17), 121 (11), 83 (11), 71 (13), 69 (18), 57 (19), 55 (14); HRMS m/z (M^+) calcd for $C_{22}H_{21}NO_3$: 347.1521. Found: 347.1523.

Compound **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (1H, d, J=8.2 Hz), 7.56 (1H, dd, J=8.2, 7.8 Hz), 7.38–7.33 (2H, m), 7.11–7.07 (2H, m), 6.69 (1H, dd, J=7.2, 7.0 Hz), 6.60 (1H, d, J=8.2 Hz), 4.33 (1H, d, J=6.2 Hz), 3.61 (1H, dd, J=12.0, 7.8 Hz), 2.95 (1H, dd, J=12.0, 7.8 Hz), 2.87 (3H, s), 2.55–2.49 (1H, m), 1.51 (3H, s), 1.14 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 162.9, 153.0, 146.3, 132.7, 128.2, 127.2, 126.0, 124.8, 124.3, 122.8, 118.1, 116.9, 111.0, 97.4, 85.1, 51.1, 40.9, 38.9, 30.8, 28.2, 22.9; IR (neat) 2982, 1618, 1564, 1499, 1468, 1414, 1302, 1121, 1086, 972, 824, 758 cm^{-1}; m/z (EI) 347 (M^+, 100), 346 (20), 332 (13), 305 (19), 304 (88), 292 (20), 291 (58), 278 (13), 249 (10), 186 (33), 185 (11), 184 (20), 172 (16), 161 (16), 160 (19), 158 (14), 144 (39), 130 (17), 128 (10), 121 (29), 118 (32), 91 (13), 77 (14); HRMS m/z (M^+) calcd for $C_{22}H_{21}NO_3$: 347.1521. Found: 347.1519.

3.6.6. Compounds ***21*** and ***22***

A reaction of compound **12** (176 mg, 1.0 mmol) with *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) (406 mg, 2.0 mmol) in refluxing xylene (10 mL) for 24 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded compounds **21** (209 mg, 58%) and **22** (83 mg, 22%).

Compound **21**: mp 172–174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, s), 7.33–7.05 (4H, m), 6.72 (1H, dd, J=7.5, 7.2 Hz), 6.62 (1H, d, J=8.1 Hz), 4.11 (1H, d, J=5.7 Hz), 3.54 (1H, dd, J=11.4, 8.7 Hz), 2.90 (1H, dd, J=11.4, 8.7 Hz), 2.96 (3H, s), 2.58–2.52 (1H, m), 2.40 (3H, s), 1.50 (3H, s), 1.11 (3H, s); IR (KBr) 2980, 1709, 1626, 1582, 1499, 1385, 1277, 1121, 1090, 1047, 1011, 924, 820, 735 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{23}NO_3$: 361.1678. Found: 361.1674.

Compound **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (1H, s), 7.32 (1H, d, J=8.4 Hz), 7.17 (1H, d, J=8.4 Hz), 7.03–6.98 (2H, m), 6.59 (1H, dd, J=7.2, 7.0 Hz), 6.51 (1H, d, J=7.8 Hz), 4.24 (1H, d, J=5.7 Hz), 3.53 (1H, dd, J=11.4, 8.7 Hz), 2.85 (1H, dd, J=11.4, 8.7 Hz), 2.79 (3H, s), 2.47–2.42 (1H, m), 2.34 (3H, s), 1.43 (3H, s), 1.05 (3H, s); IR (neat) 2982, 1615, 1568, 1454, 1397, 1298, 1208, 1121, 818, 735 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{23}NO_3$: 361.1678. Found: 361.1682.

3.6.7. Compounds ***23*** and ***24***

A reaction of compound **13** (190 mg, 1.0 mmol) with *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) (406 mg, 2.0 mmol) in refluxing xylene (10 mL) for 24 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded compounds **23** (203 mg, 54%) and **24** (75 mg, 20%).

Compound **23**: mp 175–177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, s), 7.16–7.09 (2H, m), 7.08 (1H, s), 6.70 (1H, dd, J=7.5, 7.4 Hz), 6.59 (1H, d, J=8.1 Hz), 4.08 (1H, d, J=5.8 Hz), 3.53 (1H, dd, J=11.8, 8.2 Hz), 2.89 (1H, dd, J=11.8, 8.2 Hz), 2.84 (3H, s), 2.57–2.50 (1H, m), 2.32 (3H, s), 2.29 (3H, s), 1.49 (3H, s), 1.09 (3H, s); IR (KBr) 2978, 1709, 1628, 1572, 1503, 1454, 1387, 1186, 1123, 1088, 1034, 864, 779 cm^{-1}; HRMS m/z (M^+) calcd for $C_{24}H_{25}NO_3$: 375.1834. Found: 375.1836.

Compound **24**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (1H, s), 7.15 (1H, s), 7.127–7.05 (2H, m), 6.67 (1H, dd, J=7.4, 7.0 Hz), 6.59 (1H, d, J=8.2 Hz), 4.31 (1H, d, J=6.1 Hz), 3.61 (1H, dd, J=12.0, 7.8 Hz), 2.92 (1H, dd, J=12.0, 7.8 Hz), 2.87 (3H, s), 2.56–2.52 (1H, m), 2.35 (3H, s), 2.32 (3H, s), 1.50 (3H, s), 1.11 (3H, s); IR (neat) 2980, 1618, 1559, 1501, 1464, 1435, 1391, 1300, 1200, 1123, 976, 874, 737 cm^{-1}; HRMS m/z (M^+) calcd for $C_{24}H_{25}NO_3$: 375.1834. Found: 375.1832.

3.6.8. Compound **25**

A reaction of compound **14** (175 mg, 1.0 mmol) with *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) (406 mg, 2.0 mmol) in refluxing xylene (10 mL) for 24 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 10:1) afforded compound **25** (270 mg, 75%) as a solid: mp 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (1H, dd, J=8.1, 1.5 Hz), 7.55 (1H, ddd, J=7.2, 7.0, 1.8 Hz), 7.34 (1H, d, J=8.4 Hz), 7.21–7.18 (1H, m), 7.12–7.07 (2H, m), 6.75–6.68 (2H, m), 4.23 (1H, d, J=6.3 Hz), 3.84–3.54 (5H, m), 2.92 (3H, s), 2.59–2.52 (1H, m), 1.47 (3H, s), 1.03 (3H, s); IR (KBr) 2978, 1632, 1503, 1462, 1385, 1327, 1196, 1119, 1044, 754 cm^{-1}; m/z (EI) 360 (M^+, 100), 359 (15), 345 (25), 318 (18), 317 (74), 305 (14), 304 (24), 226 (29), 186 (15), 144 (18), 129 (11), 57 (10); HRMS m/z (M^+) calcd for $C_{23}H_{24}N_2O_2$: 360.1838. Found: 360.1841.

3.6.9. Compounds **26** and **27**

A reaction of compound **15** (174 mg, 1.0 mmol) with *N*-methyl-*N*-prenyl-2-aminobenzaldehyde (**3**) (406 mg, 2.0 mmol) in refluxing xylene (10 mL) for 12 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 10:1) afforded compounds **26** (205 mg, 57%) and **24** (115 mg, 32%).

Compound **26**: mp 169–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–8.04 (2H, m), 7.71–7.61 (2H, m), 7.13–7.04 (2H, m), 6.70 (1H, dd, J=7.5, 7.2 Hz), 6.60 (1H, d, J=8.1 Hz), 4.24 (1H, d, J=5.7 Hz), 3.48 (1H, dd, J=11.4, 8.1 Hz), 2.94 (1H, dd, J=11.4, 8.1 Hz), 2.84 (3H, s), 2.46–2.41 (1H, m), 1.48 (3H, s), 1.14 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 179.9, 154.4, 146.7, 134.0, 132.8, 132.5, 131.0, 129.0, 127.6, 126.4, 126.1, 124.2, 121.1, 117.7, 111.0, 81.2, 50.9, 40.5, 38.6, 31.8, 27.6, 23.4; IR (KBr) 2930, 1680, 1612, 1500, 1370, 1273, 1125, 982, 727 cm^{-1}; m/z (EI) 359 (M^+, 100), 358 (49), 317 (21), 316 (48), 278 (21), 263 (16), 227 (46), 144 (44), 120 (12), 77 (13); HRMS m/z (M^+) calcd for $C_{23}H_{21}NO_3$: 359.1521. Found: 359.1524.

Compound **27**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (1H, d, J=7.5 Hz), 7.84 (1H, d, J=7.8 Hz), 7.64 (1H, dd, J=7.8, 7.5 Hz), 7.51 (1H, dd, J=7.5, 7.5 Hz), 7.08 (1H, dd, J=8.0, 7.5 Hz), 6.99 (1H, d, J=7.5 Hz), 6.66 (1H, dd, J=8.0, 7.5 Hz), 6.60 (1H, d, J=8.0 Hz), 4.21 (1H, d, J=6.3 Hz), 3.55 (1H, dd, J=12.0, 9.0 Hz), 2.96 (1H, dd, J=12.0, 9.0 Hz), 2.86 (3H, s), 2.53–2.47 (1H, m), 1.53 (3H, s), 1.15 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 179.0, 161.7, 146.5, 134.7, 132.6, 130.9, 130.5, 129.7, 128.6, 127.4, 124.6, 123.7, 117.8, 114.6, 110.9, 82.5, 51.0, 40.3, 38.7, 30.5, 28.2, 23.4; IR (neat) 2930, 1647, 1602, 1568, 1502, 1454, 1373, 1290, 1122, 1089, 735 cm^{-1}; m/z (EI) 359 (M^+, 100), 358 (30), 317 (19), 316 (72), 304 (19), 274 (21), 259 (31), 231 (21), 203 (17), 186 (30), 144 (41), 120 (27); HRMS m/z (M^+) calcd for $C_{23}H_{21}NO_3$: 359.1521. Found: 359.1518.

3.6.10. Compound **28**

A reaction of compound **6** (112 mg, 1.0 mmol) with *N*-methyl-*N*-geranyl-2-aminobenzaldehyde (**4**) (543 mg, 2.0 mmol) in refluxing xylene (10 mL) for 24 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded compound **28** (249 mg, 68%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (1H, dd, J=8.0, 7.4 Hz), 6.90 (1H, d, J=7.4 Hz), 6.66 (1H, dd, J=8.0, 7.4 Hz), 6.56 (1H, d, J=8.0 Hz), 5.10–5.05 (1H, m), 3.91 (1H, d, J=6.0 Hz), 3.45 (1H, dd, J=11.8, 8.2 Hz), 2.86–2.79 (4H, m), 2.58–2.47 (1H, m), 2.45–2.33 (4H, m), 2.05–1.96 (4H, m), 1.67 (3H, s), 1.59 (3H, s), 1.53 (2H, m), 0.90 (3H, s); IR (neat) 2959, 1653, 1618, 1504, 1452, 1377, 1140, 754 cm^{-1}; m/z (EI) 365 (M^+, 100), 297 (11), 296 (51), 294 (19), 282 (12), 264 (13), 255 (16), 254 (68), 242 (13), 241 (32), 212 (10), 198 (11), 184 (29), 144 (29); HRMS m/z (M^+) calcd for $C_{24}H_{31}NO_2$: 365.2355. Found: 365.2353.

3.6.11. Compound **29**

A reaction of compound **6** (112 mg, 1.0 mmol) with *N*-methyl-*N*-farnesyl-2-aminobenzaldehyde (**5**) (679 mg, 2.0 mmol) in refluxing xylene (10 mL) for 24 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded compound **29** (282 mg, 65%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (1H, dd, J=7.8, 7.5 Hz), 6.91 (1H, d, J=7.5 Hz), 6.67 (1H, dd, J=7.8, 7.5 Hz), 6.58 (1H, d, J=7.8 Hz), 5.15–5.05 (2H, m), 3.91 (1H, d, J=6.3 Hz), 3.46 (1H, dd, J=11.4, 9.3 Hz), 2.83 (3H, s), 2.80 (1H, dd, J=11.4, 9.3 Hz), 2.60–2.47 (1H, m), 2.46–2.33 (2H, m), 2.05–1.96 (10H, m), 1.65 (3H, s), 1.64–1.58 (2H, m), 1.58 (6H, s), 0.91 (3H, s); IR (neat) 2924, 1651, 1615, 1505, 1453, 1379. 1262, 1101, 802, 748 cm^{-1}; m/z (EI) 433 (M^+, 74), 365 (17), 364 (63), 322 (15), 296 (35), 254 (33), 241 (22), 184 (18), 182 (41), 167 (100), 144 (19), 69 (14); HRMS m/z (M^+) calcd for $C_{29}H_{39}NO_2$: 433.2981. Found: 433.2983.

3.6.12. Compound **30**

A reaction of compound **9** (140 mg, 1.0 mmol) with *N*-methyl-*N*-geranyl-2-aminobenzaldehyde (**4**) (543 mg, 2.0 mmol) in refluxing xylene (10 mL) for 24 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded compound **30** (283 mg, 72%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (1H, dd, J=7.7, 7.4 Hz), 6.90 (1H, d, J=7.4 Hz), 6.72–6.62 (2H, m), 5.09–5.05 (1H, m), 3.92 (1H, d, J=6.1 Hz), 3.46 (1H, dd, J=11.8, 8.3 Hz), 2.85 (3H, s), 2.82 (1H, dd, J=11.3, 8.3 Hz), 2.57–2.31 (2H, m), 2.46–2.19 (4H, m), 2.07–1.99 (3H, m), 1.67 (3H, s), 1.59 (3H, s), 1.12 (3H, s), 1.07 (3H, s), 0.91 (3H, s); IR (neat) 2959, 2928, 1505, 1453, 1377, 1298, 1242, 1161, 1140, 748 cm^{-1}; m/z (EI) 393 (M^+, 100), 325 (13), 324 (53), 322 (19), 310 (13), 292 (12), 283 (17), 282 (59), 270 (14), 269 (33), 254 (27), 240 (12), 184 (28), 144 (28); HRMS m/z (M^+) calcd for $C_{26}H_{35}NO_2$: 393.2668. Found: 393.2670.

3.6.13. Compound **31**

A reaction of compound **9** (140 mg, 1.0 mmol) with *N*-methyl-*N*-farnesyl-2-aminobenzaldehyde (**5**) (679 mg, 2.0 mmol) in refluxing xylene (10 mL) for 24 h and purification by column chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded compound **31** (314 mg, 68%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (1H, dd, J=7.8, 7.5 Hz), 6.89 (1H, d, J=7.5 Hz), 6.70 (1H, dd, J=7.8, 7.5 Hz), 6.61 (1H, d, J=7.8 Hz), 5.11–5.04 (2H, m), 3.92 (1H, d, J=6.0 Hz), 3.47 (1H, dd, J=11.7, 8.4 Hz), 2.84 (3H, s), 2.82 (1H, dd, J=11.7, 8.4 Hz), 2.44–2.37 (2H, m), 2.31–2.28 (4H, m), 2.08–1.94 (7H, m), 1.66 (3H, s), 1.63 (3H, s), 1.59 (3H, s), 1.13 (3H, s), 1.07 (3H, s), 0.91 (3H, s); IR (neat) 2926, 1653, 1618, 1504, 1452, 1377, 1298, 1242, 1161, 1140, 748 cm^{-1}; m/z (EI) 461 (M^+, 100), 393 (32), 392 (89), 324 (49), 322 (28), 283 (14), 282 (48), 270 (16), 269 (29), 184 (23), 149 (28), 144 (210), 69 (18); HRMS m/z (M^+) calcd for $C_{31}H_{43}NO_2$: 461.3294. Found: 461.3291.

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