Synthesis of 1,3-Disubstituted *N*-Amino-1,2,3,4-tetrahydroisoquinolines

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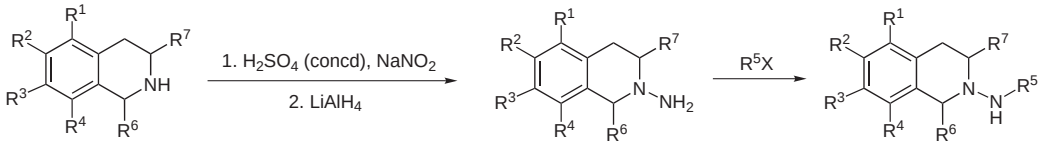
Abstract: The synthesis of 1,3-disubstituted *N*-amino-1,2,3,4-tetrahydroisoquinolines from the corresponding hydrazide intermediate via Pictet−Spengler reaction is described and the effect of the aldehyde on the stereoconfiguration of the products is discussed.

Key words: quinolines, aldehydes, heterocycles, reduction, ring closure

Tetrahydroisoquinolines (THIQs) have become attractive targets for organic synthesis due to their widespread occurrence in nature, interesting chemical properties, and diverse biological activities. This includes functioning as calcium antagonists,[1] cardiovascular,[2] antibacterial,[3] antitumor antibotics[4] and neuromodulation effects.[5] Their neuromodulating effects, in particular, related to pathogenic processes in the central nervous system[6] make THIQs a new class of noncompetitive AMPAR [2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid receptor] antagonists[7] and have received considerable attention. Much effort has been devoted to the modification[8] of THIQs in order to afford more potent and selective ligands.

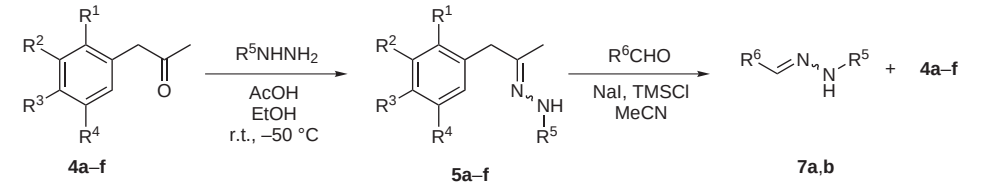
The *N*-amino-substituted THIQs **3** (Scheme 1), which appear to be structurally similar to THIQs **1**, can dramatically change the electronic property of the nitrogen atom in the molecule, and may present interesting physical and biological properties. Due to the electronic feature of N–N bond, the synthesis of *N*-amino-substituted THIQs **3** cannot be easily achieved.[9a] The chemistry for preparation of *N*-amino THIQs **3**[9] can start from THIQs **1** (Scheme 1) by



1 **2** **3a–n**

R^1–R^4 = H or MeO
R^5 = PhCO
R^6 = H, Pr, *c*-Hex, Ph, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-Furyl, 2-Thienyl, 4-Pyridinyl
R^7 = H or Me
X = Halogen

Scheme 1



4a–f **5a–f** **7a,b** **6a–f** **3a–n**

R^1–R^4 = H or MeO
R^5 = PhCO
R^6 = H, Pr, *c*-Hex, Ph, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-Furyl, 2-Thienyl, 4-Pyridinyl

Scheme 2

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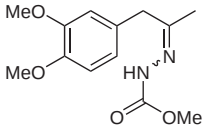
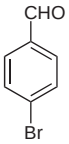
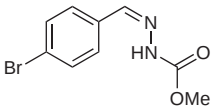
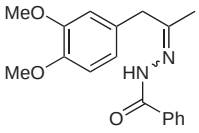
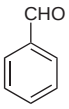
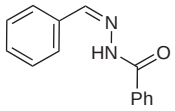
Table 1 Exchange Reaction of Hydrazones with Aldehydes

Entry	Substrate	*syn*/*anti*[a]	Aldehyde	Product	Yield (%)
1	 **5a**	1:6		 **7a**	25
2	 **5b**	1:11		 **7b**	30

[a] Ratio was determined by 500 MHz ^{1}H NMR spectroscopy.

using a multi-step procedure (N-nitrosation, $LiAlH_4$ reduction, and alkylation/acylation). The method is good for a wide variety of substrates, but the yield is poor due to the generation of byproducts during the nitrating step and alkylation/acylation steps. Moreover, the synthesis of the THIQ-skeleton-containing compounds is often achieved by using the Pictet–Spengler reaction, and it would be very desirable to study this reaction for the direct preparation of *N*-amino THIQ derivatives, although the scope and usefulness of this kind of Pictet–Spengler reaction have not been reported before.

In this letter, we present a simple approach to the synthesis of 1,3-disubstituted *N*-amino-THIQs starting from hydrazones **5** (Scheme 2),[10,11] through the reduction to hydrazides **6**,[10,12] and finally the Pictet−Spengler reaction[4,13] to give a series of a new type of THIQs **3**. All reactions took place at room temperature and all reagents are commercially available or easy to prepare in the laboratory. The conditions are mild and easy to control. It should be pointed out that the reduction of C=N (hydrazone) to C−N (hydrazide) was necessary in order to effect the ring closure. If this reduction step was not performed, under the Pictet−Spengler reaction conditions compound **5** underwent an aldehyde-exchange reaction to form compound **7**.[14] Further, compound **5** is a mixture of two geometric isomers which could be attributed to their *anti*- and *syn*-geometric isomers (Table 1).

The Pictet–Spengler reaction using hydrazides **6** and aldehydes gave product **3** which possessed two chiral centers (C-1 and C-3; with the exception of formaldehyde) and therefore could exist as *cis* or *trans* diastereoisomers (Tables 2 and 3). There are four aspects that should be pointed out: (a) the electron-donating methoxy group is very important and works only if it is *meta*-substituted with respect to the hydrazine moieties (i.e. compound **6c**). The addition of another methoxy group at the *para* position in compound **6d** further strengthens this electronic effect, whereas one more methoxy group at position 5 (i.e. compound **6e**) sterically hindered the electrophilic addition. These effects can be seen by the results listed in Table 2. (b) The R^6 group of the aldehydes greatly influences the steric configuration of products **3**. When R^6 was aryl or a substituted aryl group, the *trans*-1,3-disubstituted *N*-amino tetrahydroisoquinolines were formed as major products. The *trans*/*cis* ratios were as high as 60:1 such that the minor *cis* isomer could not be detected by the NMR spectroscopy (see Table 2 entries 3 and 4, and Table 3 entries 1−6). However, when R^6 was aliphatic or a heterocyclic group such as butyl, cyclohexyl, 2-thienyl or 2-furyl, these groups did not appear to give product with high diastereoselectivity (*trans*/*cis* products ratio of 3:1). The absolute configuration of the major isomer of compound **3b** was also confirmed by the X-ray crystal structure analysis (Figure 1).[15,16] (c) The hydrogen atoms on C-1 or C-3 gave a broad ^{1}H NMR signal. This was probably due to a restricted rotation of the *N*-hydrazide bond.[17] (d) On the basis of the molecular modeling study,[18] some of these new 1,3-disubstituted *N*-amino THIQs (products **3a**–**g** and **3k**) fit the preliminary pharmacophore model[18] well, which consists of four features corresponding to one hydrogen acceptor group (carbonyl group), one aromatic ring function (benzene ring) and two hydrophobic group regions (dimethoxy), so theoretically they could be the lead candidates of a novel series of noncompetitive AMPAR antagonists.

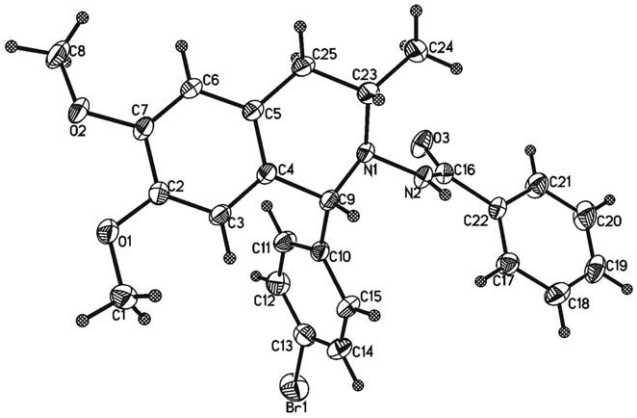
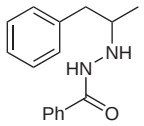
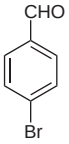
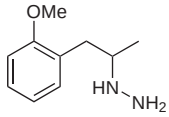
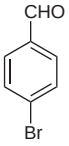
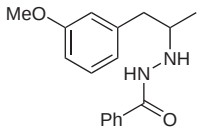
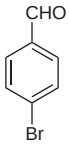
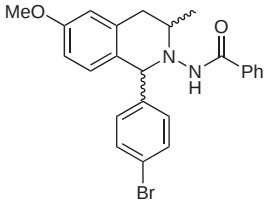
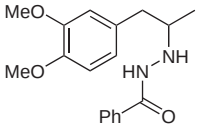
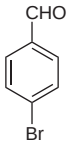
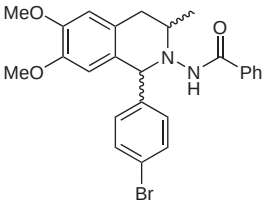
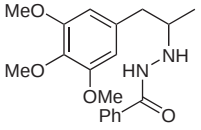
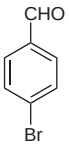
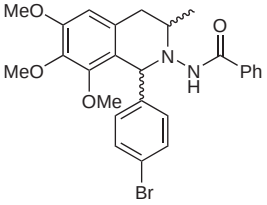
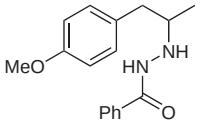
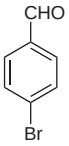


Figure 1 X-ray of compound **3b** (*trans*)

Table 2 Coupling of Compounds **6a–f** with Aldehydes via Pictet–Spengler Reaction

Entry	Substrate	Aldehyde	Product yield[a]	*trans*/*cis*[b]
1	 **6a**		n.r.	–
2	 **6b**		n.r.	–
3	 **6c**		 **3a** (71%)	60:1
4	 **6d**		 **3b** (83%)	60:1
5	 **6e**		 **3c** (78%)	1.5:1
6	 **6f**		n.r.	–

[a] Isolated yield; n.r.: no reaction.
[b] Ratio of *trans*/*cis* was calculated by the ^{1}H NMR spectrum.

Table 3 Coupling of Hydrazide **6d** with Aldehydes via Pictet–Spengler Reaction

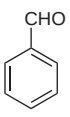
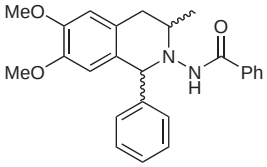
Entry	Substrate	Aldehyde	Product yield[a]	*trans*/*cis*[b]
1	**6d**		 **3d** (75%)	20:1

Table 3 Coupling of Hydrazide **6d** with Aldehydes via Pictet–Spengler Reaction (continued)

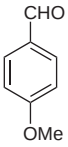
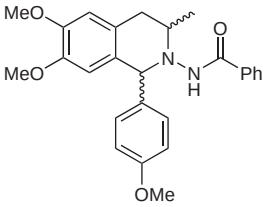
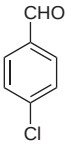
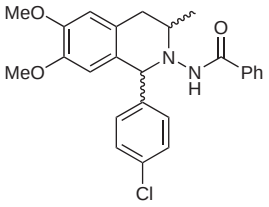
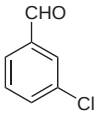
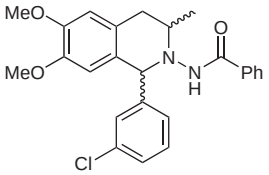
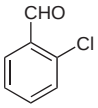
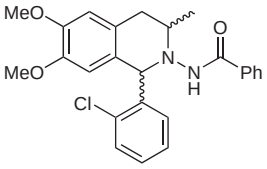
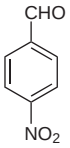
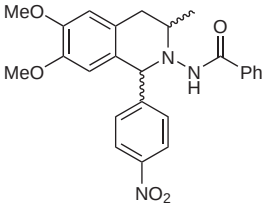
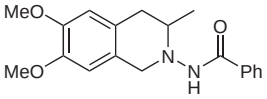
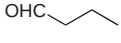
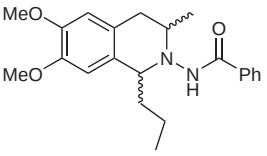
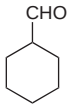
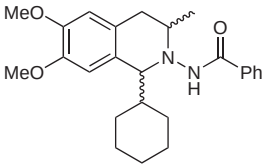
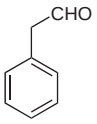
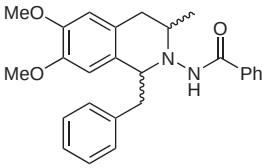
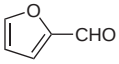
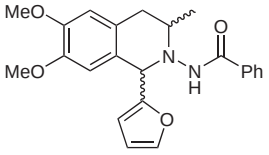
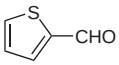
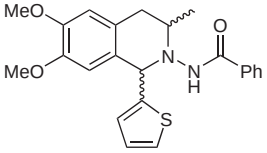
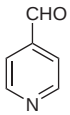
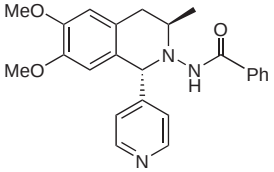
Entry	Substrate	Aldehyde	Product yield[a]	*trans*/*cis*[b]
2	**6d**		 **3e** (87%)	6.6:1[c]
3	**6d**		 **3f** (*p*) (90%)	8.2:1[c]
4	**6d**		 **3f** (*m*) (86%)	9.3:1[c]
5	**6d**		 **3f** (*o*) (80%)	4.6:1[c]
6	**6d**		 **3g** (91%)	65:1
7	**6d**	HCHO	 **3h** (87%)	–
8	**6d**		 **3i** (84%)	3.3:1

Table 3 Coupling of Hydrazide **6d** with Aldehydes via Pictet–Spengler Reaction (continued)

Entry	Substrate	Aldehyde	Product yield[a]	*trans*/*cis*[b]
9	**6d**		 **3j** (69%)	3.3:1
10	**6d**		 **3k** (82%)	4:1
11	**6d**		 **3l** (83%)	3.3:1
12	**6d**		 **3m** (51%)	3:1
13	**6d**		 **3n** (30%)	*trans*

[a] Isolated yield.
[b] Ratio of *trans*/*cis* was calculated by the ^{1}H NMR spectrum.
[c] Ratio of *trans*/*cis* was calculated by isolated yield.

Acknowledgment

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References and Notes

(1) Dong, H.; Sheng, J. Z.; Wong, T. M. *Br. J. Pharmacol.* **1993**, *109*, 109.
(2) Dong, H.; Lee, C. M.; Huang, W. L.; Peng, S. X. *Br. J. Pharmacol.* **1992**, *107*, 262.
(3) Chandrasekhar, S.; Mohanty, P. K.; Harikishan, K.; Sasmal, P. K. *Org. Lett.* **1999**, *1*, 877; and references cited therein.
(4) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.
(5) Vecchietti, V.; Clarke, G. D.; Colle, R.; Giardina, G.; Petrone, G.; Sbacchi, M. *J. Med. Chem.* **1991**, *34*, 2624.
(6) (a) Gremmen, C.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett.* **2001**, *42*, 8885. (b) Kotake, Y.; Tasaki, Y.; Makino, Y.; Ohta, S.; Hirobe, M. *J. Neurochem.* **1995**, *65*, 2633. (c) Grunewald, G. L.; Sall, D. J.; Monn, J. A. *J. Med. Chem.* **1998**, *31*, 824.
(7) (a) Gitto, R.; Barreca, M. L.; De Luca, L.; De Sarro, G.; Ferreri, G.; Quartarone, S.; Russo, E.; Constanti, A.; Chimirri, A. *J. Med. Chem.* **2003**, *46*, 197. (b) Ferreri, G.; Chimirri, A.; Russo, E.; Gitto, R.; Gareri, P.; De Sarro, A.; De Sarro, G. *Pharmacol. Biochem. Behav.* **2004**, *77*, 85.
(8) (a) Gray, N. M.; Cheng, B. K.; Mick, S. J.; Lair, C. M.; Contrera, P. C. *J. Med. Chem.* **1989**, *32*, 1242. (b) Horiguchi, Y.; Kodama, H.; Nakamura, M.; Yoshimura, T.; Hanezi, K.; Hamada, H.; Saitoh, T.; Sano, T. *Chem. Pharm. Bull.* **2002**, *50*, 253.

(9) (a) Zalán, Z.; Martinek, T. A.; Lázár, L.; Sillanpää; Fülöp, F. *Tetrahedron* **2006**, *62*, 2883. (b) Biel, J. H. US Patent, 3037984, **1962**; *Chem. Abstr*. **1962**, *57*, 15082a. (c) Biel, J. H. US Patent, 2932646, **1960**; *Chem. Abstr*. **1960**, *54*, 17435h.

(10) Dutta, A. S.; Morley, J. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1712.

(11) All melting points were determined on a Kofler hot-plate microscope apparatus and are uncorrected. Mass spectra ESI were recorded on Q-TOF Micromass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz instrument.
Selected data of compounds **5**:
5a: mp 109−110 °C. ^{1}H NMR ($CDCl_3$): δ = 7.76 (br s, 1 H, *anti*), 7.85 (br s, 1 H, *syn*), 6.79−6.83 (m, 2 H, 2 isomers), 6.75−6.77 (m, 2 H, *anti*), 6.66–6.68 (m, 2 H, *syn*), 6.74 (s, 1 H, *anti*), 6.62 (br s, 1 H, *syn*), 3.85−3.87 (m, 9 H, 2 isomers), 3.57 (d, *J* = 4.0 Hz, 2 H, *anti*), 3.52 (br s, 2 H, *syn*), 1.71 (d, *J* = 1.0 Hz, 3 H, *anti*), 2.06 (d, *J* = 6.5 Hz, 3 H, *syn*). MS (ESI): *m*/*z* = 267.0 [M + H]$^+$. **5b**: mp 144−146 °C. ^{1}H NMR ($CDCl_3$): δ = 8.75 (br s, 1 H, *anti*), 8.99 (br s, 1 H, *syn*), 7.83 (br s, 2 H, *anti*), 7.60 (d, *J* = 16.0 Hz, 2 H, *syn)*, 7.52–7.54 (m, 1 H, *anti*), 7.49–7.52 (m, 2 H + 1 H′), 7.36 (t, *J* = 7.5 Hz, 2 H, *syn*), 6.81 (s, 3 H, *anti*), 6.71 (s, 3 H, *syn*), 3.86 (s, 3 H, *anti*), 3.88 (s, 3 H, *syn*), 3.85–3.86 (m, 3 H, 2 isomers), 3.63–3.69 (m, 2 H, 2 isomers), 1.86 (s, 3 H, *anti*), 2.15 (s, 3 H, *syn*). MS (ESI): *m*/*z* = 313.0 [M + H]$^+$.

(12) Selected data of compounds **6**:
6a: mp 114−116 °C. ^{1}H NMR ($CDCl_3$): δ = 7.60 (d, *J* = 7.0 Hz, 2 H), 7.49 (t, *J* = 2.0 Hz, 1 H), 7.40 (t, *J* = 2.5 Hz, 2 H), 7.30−7.32 (m, 2 H), 7.20–7.26 (m, 3 H), 4.49 (br s, 1 H), 3.40 (sext, *J* = 6.5 Hz, 1 H), 2.83 (q, *J* = 6.5 Hz, 1 H), 2.67 (q, *J* = 7.0 Hz, 1 H), 1.13 (d, *J* = 6.0 Hz, 3 H). MS (ESI): *m*/*z* = 255.2 [M + H]$^+$. **6b**: ^{1}H NMR ($CDCl_3$): δ = 7.16 (td, *J* = 8.0, 9.5 Hz, 1 H), 7.16 (dd, *J* = 1.5, 7.5 Hz, 1 H), 6.86 (td, *J* = 7.5, 8.5 Hz, 1 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 4.01 (sext, *J* = 6.0 Hz, 1 H), 3.73 (s, 3 H), 2.71–2.76 (m, 2 H), 1.16 (s, 3 H). MS (ESI): *m*/*z* = 181.4 [M + H]$^+$. **6f**: mp 82−84 °C. ^{1}H NMR ($CDCl_3$): δ = 7.61−7.63 (m, 2 H), 7.48−7.52 (m, 1 H), 7.39−7.42 (m, 2 H), 7.68−7.87 (m, 2 H), 7.14−7.17 (m, 2 H), 3.79 (s, 3 H), 3.37 (sext, *J* = 6.5 Hz, 1 H), 2.78 (q, *J* = 7.0 Hz, 1 H), 2.64 (q, *J* = 6.5 Hz, 1 H), 1.14 (d, *J* = 6.5 Hz, 3 H). MS (ESI): *m*/*z* = 285.4 [M + H]$^+$.

(13) (a) Bates, H. A. *J. Org. Chem.* **1983**, *48*, 1932. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (c) Nakamura, S.; Tanaka, M.; Taniguchi, T.; Uchiyama, M.; Ohwada, T. *Org. Lett.* **2003**, *5*, 2087. (d) Magnus, P.; Matthews, K. S.; Lynch, V. *Org. Lett.* **2003**, *5*, 2181. (e) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 4607.

(14) Compound **7a**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.21 (br s, 1 H), 7.99 (s, 1 H), 7.57−7.63 (m, 4 H) 3.69 (s, 3 H). **7b**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.87 (br s, 1 H), 8.47 (s, 1 H), 7.92 (d, *J* = 7.5 Hz, 2 H), 7.74 (d, *J* = 5.4 Hz, 2 H), 7.46−7.61 (m, 6 H).

(15) **3b**: Crystallized in triclinic, space group *P*–1 with cell parameters: *a* = 5.2532(11) Å, *b* = 10.676(2) Å, *c* = 20.717(4) Å, *α* = 101.19°, *β* = 93.87°, *γ* = 102.61°, *V* = 1104.9(4) Å^3, D_c = 1.447 g/cm^3, *Z* = 2.

(16) Synthesis of compound **3**: To the mixture of compound **6a** (200 mg, 0.64 mmol) and 4-bromobenzaldehyde (118 mg, 0.64 mmol) in MeCN (8 mL), anhyd NaI (334 mg, 2.23 mmol) was added under stirring at r.t., followed by TMSCl (0.28 mL, 2.23 mmol). After 40 min, the reaction was concentrated and the products were purified by column chromatography (10–30% EtOAc–PE). Unless otherwise indicated, each product was separated as an enantiomeric mixture and characterized by NMR spectroscopy.

Selected data of compounds **3**:
3a: mp 227−229 °C. ^{1}H NMR ($CDCl_3$): δ = 7.43−7.47 (m, 1 H), 7.39−7.42 (m, 4 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 6.96 (br s, 1 H), 6.63 (d, *J* = 2.5 Hz, 1 H), 6.59 (dd, *J* = 2.5, 8.5 Hz, 1 H), 6.49 (d, *J* = 8.5 Hz, 1 H), 5.81 (br s, 1 H), 4.12 (br s, 1 H), 3.76 (s, 3 H), 3.00 (br s, 1 H), 2.88 (dd, *J* = 3.5, 16.0 Hz, 1 H), 1.29 (d, *J* = 6.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 167.65, 158.03, 142.74, 135.33, 133.78, 131.56, 131.51, 131.19, 129.34, 128.65, 126.64, 121.45, 112.37, 112.25, 66.56, 55.19, 54.11, 39.01, 19.70. MS (ESI): *m*/*z* = 451.2, 453.2 [M + H]$^+$. **3b**: mp 216−217 °C. ^{1}H NMR ($CDCl_3$): δ = 7.41−7.47 (m, 5 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.23 (d, *J* = 7.5 Hz, 2 H), 6.99 (br s, 1 H), 6.59 (s, 1 H), 6.04 (s, 1 H), 5.83 (br s, 1 H), 4.14 (br s, 1 H), 3.85 (s, 3 H), 3.59 (s, 3 H), 2.96 (br s, 1 H), 2.82 (dd, *J* = 2.5, 15.5 Hz, 1 H), 1.28 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 167.65, 147.78, 147.26, 142.61, 133.75, 131.56, 131.50, 131.21, 129.39, 128.65, 126.65, 126.41, 121.50, 111.08, 110.45, 66.38, 55.90, 55.84, 53.84, 38.38, 19.67. MS (ESI): *m*/*z* = 481.0, 483.0 [M + H]$^+$. **3c**: mp 171−172 °C. ^{1}H NMR ($CDCl_3$): δ = 7.40−7.56 (m, 5 H, 2 isomers), 7.15−7.18 (*trans*), 7.03−7.05 (m, 4 H, *cis*), 6.70 (br s, 1 H, 2 isomers), 6.43 (s, 1 H, *trans*), 6.49 (s, 1 H, *cis*), 5.69 (br s, 1 H, *trans*), 5.37 (s, 1 H, *cis*), 4.00 (br s, 1 H, *trans*), 3.24–3.26 (m, 1 H, *cis*), 3.86 (s, 3 H, *trans*), 3.87 (s, 3 H, *cis*), 3.73 (s, 3 H, *trans*), 3.79 (s, 3 H, *cis*), 3.14 (s, 3 H, *trans*), 3.46 (s, 3 H, *cis*), 2.95 (br s, 1 H, 2 isomers), 2.74−2.83 (m, 1 H, 2 isomers), 1.23 (d, *J* = 6.0 Hz, 3 H, *trans*), 1.17 (d, *J* = 6.0 Hz, 3 H, *cis*). ^{13}C NMR ($CDCl_3$): δ (*trans*/*cis*) = 166.35/167.48, 152.56/153.22, 150.70/151.06, 140.57/144.76, 140.46/139.35, 133.75/134.04, 131.61/131.45, 131.17/130.87, 130.81/130.77, 128.67/129.32, 126.76/127.04, 121.61/123.79, 120.43/119.81, 106.14/106.56, 64.05/60.71, 60.50/60.38, 59.12/60.16, 55.87/55.93, 48.52/53.08, 39.53/32.95, 19.63/18.86. MS (ESI): *m*/*z* = 511.1, 513.1 [M + H]$^+$. **3d**: mp 215−218 °C. ^{1}H NMR ($CDCl_3$): δ = 7.42 (t, *J* = 7.5 Hz, 1 H), 7.34−7.36 (m, 4 H), 7.27−7.33 (m, 5 H), 6.95 (br s, 1 H), 6.59 (s, 1 H), 6.09 (s, 1 H), 5.79 (br s, 1 H), 4.13 (br s, 1 H), 3.85 (s, 3 H), 3.56 (s, 3 H), 2.97 (br s, 1 H), 2.83 (dd, *J* = 3.5, 15.5 Hz, 1 H), 1.30 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 167.75, 147.63, 147.14, 143.33, 134.07, 131.36, 130.08, 129.52, 128.53, 128.38, 127.65, 126.68, 126.38, 113.31, 110.38, 68.07, 55.83, 54.06, 38.46, 19.73. MS (ESI): *m*/*z* = 403.3 [M + H]$^+$. **3e** (*trans*): mp 210−211 °C. ^{1}H NMR ($CDCl_3$): δ = 7.42−7.45 (m, 3 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 6.91 (br s, 1 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 6.58 (s, 1 H), 6.10 (s, 1 H), 5.73 (br s, 1 H), 4.10 (br s, 1 H), 3.85 (s, 3 H), 3.78 (s, 3 H), 3.58 (s, 3 H), 2.96 (br s, 1 H), 2.82 (dd, *J* = 3.5, 15.5 Hz, 1 H), 1.29 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 167.79, 158.98, 147.60, 147.12, 135.37, 134.12, 131.36, 130.59, 130.29, 128.55, 126.70, 126.37, 113.69, 111.34, 110.33, 55.86, 55.21, 38.39, 19.78. MS (ESI): 433.1 [M + H]$^+$. **3e** (*cis*): mp 210−211 °C. ^{1}H NMR ($CDCl_3$): δ = 7.66 (d, *J* = 7.5 Hz, 2 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 9.0 Hz, 2 H), 6.75 (s, 1 H), 6.66 (s, 1 H), 6.39 (s, 1 H), 5.18 (s, 1 H), 3.90 (s, 3 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.36 (sept, *J* = 6.0 Hz, 1 H), 2.90 (dd, *J* = 5.0, 17.0 Hz, 1 H), 2.82 (dd, *J* = 10.0, 17.0 Hz, 1 H), 1.17 (d, *J* = 6.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 166.18, 159.10, 148.23, 147.70, 134.18, 132.46, 131.50, 131.21, 128.60, 127.02, 126.20, 125.72, 113.54, 111.46, 110.84, 67.83, 55.87, 55.27, 49.04, 33.05, 18.26. MS (ESI): *m*/*z* = 433.1 [M + H]$^+$. **3f** (*p*, *cis*): mp 202−204 °C. MS (ESI): *m*/*z* = 437.1, 439.1 [M + H]$^+$. **3f** (*m*, *trans*): mp 182−183 °C. MS (ESI): *m*/*z* = 437.1, 439.1 [M + H]$^+$. **3f** (*o*): mp 99−101 °C. MS (ESI): *m*/*z* = 437.1, 439.1 [M + H]$^+$. **3g**: mp 203−206 °C. ^{1}H NMR (DMSO-d_6): δ = 9.43 (br s, 1 H), 8.12

(d, *J* = 8.5 Hz, 2 H), 7.63 (br s, 2 H) 7.49 (d, *J* = 7.5 Hz, 2 H) 7.45 (t, *J* = 7.5 Hz, 1 H), 7.36 (t, *J* = 7.5 Hz, 2 H), 6.74 (s, 1 H), 6.02 (s, 1 H), 5.24 (br s, 1 H), 3.71 (s, 3 H), 3.42 (s, 3 H), 3.23 (br s, 1 H), 2.91 (br s, 1 H), 2.83 (dd, *J* = 3.0, 16.0 Hz, 1 H), 1.17 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 167.40, 151.23, 148.08, 147.46, 147.41, 133.33, 131.70, 130.25, 128.63, 126.56, 126.49, 123.53, 110.83, 110.73, 67.78, 55.88, 55.83, 54.47, 38.29, 19.48. MS (ESI): *m*/*z* = 448.2 $[M + H]^+$. **3h**: mp 158−160 °C. ^{1}H NMR ($CDCl_3$): δ = 7.72 (d, *J* = 7.0 Hz, 2 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.08 (br s, 1 H), 6.60 (s, 1 H), 6.52 (s, 1 H), 4.36 (d, *J* = 10.0 Hz, 1 H), 4.12 (d, *J* = 15.0 Hz, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.45 (br s, 1 H), 2.73−2.84 (m, 2 H), 1.30 (d, *J* = 6.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 166.65, 147.85, 147.63, 133.81, 131.49, 128.49, 126.97, 125.04, 123.97, 111.13, 109.32, 56.94, 55.80, 55.45, 33.13, 18.69. MS (ESI): *m*/*z* = 327.1 $[M + H]^+$. **3i** (*trans*): mp 184−186 °C. ^{1}H NMR ($CDCl_3$): δ = 7.71 (d, *J* = 7.5 Hz, 2 H), 7.51 (t, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 2 H), 6.82 (br s, 1 H), 6.68 (s, 1 H), 6.57 (s, 1 H), 4.31 (br s, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.46 (br s, 1 H), 2.77−2.82 (m, 1 H), 2.67 (dd, *J* = 3.5, 16.5 Hz, 1 H), 1.93−2.00 (m, 1 H), 1.73−1.80 (m, 1 H), 1.56−1.63 (m, 1 H), 1.40 (m, 1 H), 1.27 (d, *J* = 6.5 Hz, 3 H), 0.90 (t, *J* = 6.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 167.18, 147.67, 147.60, 134.21, 131.53, 128.68, 128.43, 126.92, 110.92, 109.34, 64.22, 56.06, 55.85, 35.84, 35.19, 19.82, 18.31, 14.57. MS (ESI): *m*/*z* = 369.3 $[M + H]^+$. **3i** (*cis*): mp 183–184 °C. MS (ESI): *m*/*z* = 369.3 $[M + H]^+$. **3k** (*trans*): mp 170−172 °C. ^{1}H NMR ($CDCl_3$): δ = 7.59 (d, *J* = 7.0 Hz, 2 H), 7.48−7.51 (m, 1 H), 7.39−7.42 (m, 2 H), 7.23−7.26 (m, 4 H), 7.14−7.17 (m, 1 H), 7.01 (br s, 1 H), 6.53 (s, 1 H), 6.46 (s, 1 H), 4.73 (br s, 1 H, H_a), 3.84 (s, 3 H), 3.63 (s, 3 H), 3.54−3.56 (m, 1 H, H_e), 3.28 (dd, J_{ee} = 5.0 Hz, J_{ea} = 14.0 Hz, 1 H, H_e), 3.09 (dd, J_{aa} = 6.5 Hz, J_{ae} = 14.0 Hz, 1 H, H_a), 2.65 (dd, J_{aa} = 11.0 Hz, J_{ae} = 16.0 Hz, 1 H, H_a), 2.59 (dd, J_{ea} = 3.5 Hz, J_{ea} = 16.0 Hz, 1 H, H_e), 1.23 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 167.14, 147.41, 147.20, 139.87, 133.79, 131.61, 129.61, 129.03, 128.59, 128.30, 126.87, 126.81, 126.04, 110.63, 109.99, 66.23, 55.82, 55.69, 55.06, 43.72, 36.26, 20.04. MS (ESI): *m*/*z* = 417.3 $[M + H]^+$. **3m**: mp 195−196 °C. ^{1}H NMR ($CDCl_3$): δ = 7.44−7.51 (m, 3 H + 1 H′), 7.71 (d, *J* = 7.5 Hz, 2 H, *cis*), 7.34−7.37 (m, 2 H, *trans*), 7.41 (t, *J* = 7.5 Hz, 2 H, *cis*), 7.26 (d, *J* = 4.0 Hz, 1 H, *trans*), 7.31 (d, *J* = 4.0 Hz, 1 H, *cis*), 7.19 (br s, 1 H, 2 isomers), 7.11 (d, *J* = 3.0 Hz, 1 H, *trans*), 6.84 (d, *J* = 3.0 Hz, 1 H, *cis*), 6.91 (dd, *J* = 3.5, 5.5 Hz, 1 H, *trans*), 6.98 (dd, *J* = 3.5, 5.5 Hz, 1 H, *cis*), 6.58 (s, 1 H, *trans*), 6.63 (s, 1 H, *cis*), 6.32 (s, 1 H, *trans*), 6.48 (s, 1 H, *cis*), 6.17 (br s, 1 H, *trans*), 5.50 (s, 1 H, *cis*), 4.11 (br s, 1 H, *trans*), 3.42−3.49 (m, 1 H, *cis*), 3.86 (s, 1 H, *trans*), 3.88 (s, 1 H, *cis*), 3.64 (s, 1 H, *trans*), 3.75 (s, 1 H, *cis*), 2.84−2.96 (m, 1 H, 2 isomers), 2.80 (dd, *J* = 3.5, 15.5 Hz, 1 H, 2 isomers), 1.30 (d, *J* = 6.5 Hz, 3 H, *trans*), 1.24 (d, *J* = 6.5 Hz, 3 H, *cis*). ^{13}C NMR ($CDCl_3$): δ (*trans*/*cis*)= 167.85/166.05, 147.87/148.48, 147.24/147.60, 133.88/133.92, 131.49/131.58, 128.58/128.61, 127.47/127.00, 126.75/126.55, 125.96/125.92, 125.85/125.36, 110.96/111.11, 110.37/110.58, 63.68/62.86, 55.80/55.85, 49.77/54.66, 38.11/34.52, 19.74/18.78. MS (ESI): *m*/*z* = 409.4 $[M + H]^+$. **3n** (*trans*): mp 192−194 °C. ^{1}H NMR ($CDCl_3$): δ = 8.44 (d, *J* = 5.5 Hz, 2 H), 7.61 (br s, 1 H), 7.43−7.55 (m, 3 H), 7.30–7.34 (m, 2 H), 7.27−7.28 (m, 2 H), 6.61 (s, 1 H), 6.02 (s, 1 H), 5.86 (br s, 1 H), 4.00 (br s, 1 H), 3.85 (s, 3 H), 3.58 (s, 3 H), 2.95 (br s, 1 H), 2.82 (dd, *J* = 3.5, 15.5 Hz, 1 H), 1.27 (d, *J* = 6.0 Hz, 3 H). MS (ESI): *m*/*z* = 404.4 $[M + H]^+$.

(17) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901.

(18) (a) Rezessy, B.; Sólyom, S. *Lett. Drug Des. Discov.* **2004**, *1*, 217. (b) Barreca, M. L.; Gitto, R.; Quartarone, S.; De Luca, L.; De Sarro, G.; Chimirri, A. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 651.