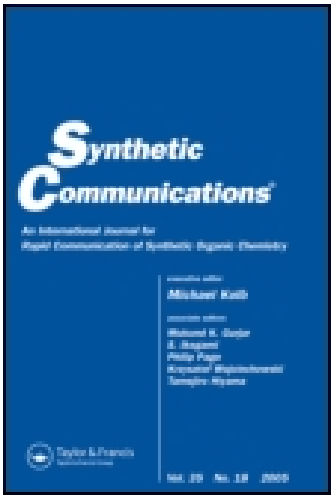


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

First Synthesis of Dopamine and Rotigotin Analogue 2-Amino-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene

Süleyman Yılmaz [a] & Süleyman Göksu [a]

[a] Department of Chemistry, Faculty of Science , Atatürk University , Erzurum , Turkey

Accepted author version posted online: 08 Nov 2013.Published online: 19 Mar 2014.

To cite this article: Süleyman Yılmaz & Süleyman Göksu (2014) First Synthesis of Dopamine and Rotigotin Analogue 2-Amino-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:8, 1058-1065, DOI: 10.1080/00397911.2013.841939

To link to this article: http://dx.doi.org/10.1080/00397911.2013.841939

Synthetic Communications®, 44: 1058–1065, 2014

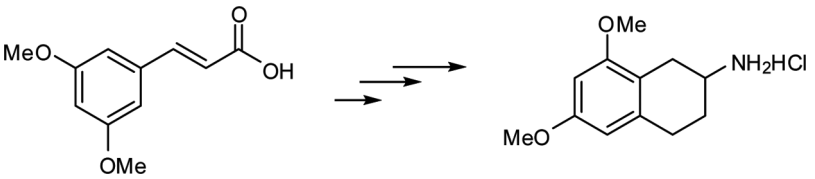
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.841939

FIRST SYNTHESIS OF DOPAMINE AND ROTIGOTIN ANALOGUE 2-AMINO-6,8-DIMETHOXY-1, 2,3,4-TETRAHYDRONAPHTHALENE

Süleyman Yılmaz and Süleyman Göksu

Department of Chemistry, Faculty of Science, Atatürk University, Erzurum, Turkey

GRAPHICAL ABSTRACT



Abstract *The title compound was synthesized starting from 3-(3,5-dimethoxyphenyl)acrylic acid in 11 steps with 30% total yield. The reaction sequence hydrogenation of acrylic acid, reduction of acid to alcohol derivative with $LiAlH_4$, reaction of alcohol with CBr_4/PPh_3, substitution reaction of alkyl halide to nitrile derivative with NaCN, hydrolysis of nitrile with NaOH, cyclization reaction of acid with PPA to give 1-tetralone, α-carboxylation of tetralone with Me_2CO_3 in the presence of NaH, reduction of ketone group with Et_3SiH, hydrolysis of ester, Curtius rearrangement of acid with diphenylphosphoryl azide followed by conversion to carbamate, and finally hydrogenolysis of carbamate afforded 2-amino-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene hydrogen chloride salt.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords 2-Aminotetralin; Curtius rearrangement; dopamine; neurotransmitter; rotigotin analogue; synthesis

INTRODUCTION

Monoamine hormone dopamine (**1**) is a neurotransmitter and is very important in the central nervous system (CNS).[1] It has been reported that many chemical compounds show dopaminergic activities.[2] Dopamine-like compounds, especially 2-aminotetralin derivatives 2-amino-1,2,3,4-tetrahydronaphthalene-6, 7-diol (6,7-ADTN; **2**),[3] 2-amino-1,2,3,4-tetrahydronaphthalene-5,6-diol (5,6-ADTN; **3**),[4] and (S)-2-N,N-dipropylamino-1,2,3,4-tetrahydronaphthalen-5-ol (5-OH-DPAT,

Received July 25, 2013.

Address correspondence to Süleyman Göksu, Department of Chemistry, Faculty of Science, Atatürk University, Erzurum 25240, Turkey. E-mail: sgoksu@atauni.edu.tr

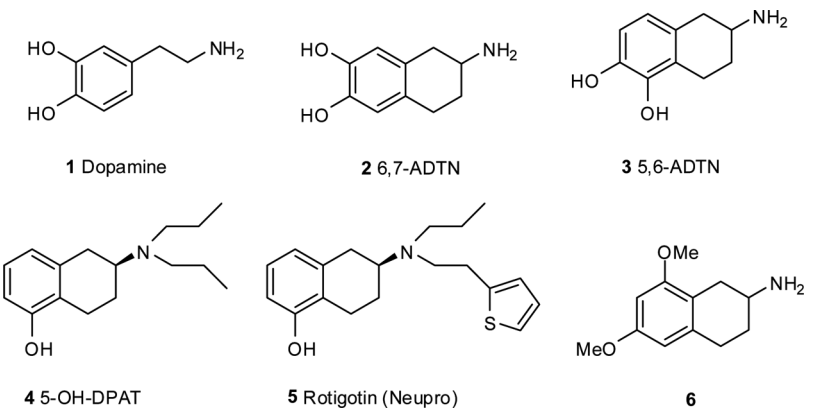


Figure 1. Dopamine (**1**), some selected dopaminergic compounds **1–5**, and novel compound **6**.

4),[5] are potential agonists at dopamine receptors. Dopamine agonist drug rotigotin (**5**), commercially known as Neupro, is a derivative of 5-OH-DPAT (**4**). Rotigotin (**5**) is used in the treatment of Parkinson's disease[6] and restless legs syndrome[7] as transdermal patch (Fig. 1).

In addition, 2-aminotetralin derivatives have some other beneficial biological activities, including phenylethanolamine N-methyltransferase inhibition;[8] antifungal activity;[9] 11β-hydroxylase inhibition;[10] α-adrenergic[11] melatonin-like activity;[12] prolactin secretion inhibition;[13] antihypertensive,[14] sedative and analgesic,[15] and 5-hydroxytryptaminergic activity,[16] AChE and MAO inhibition,[17] GlyT1 inhibition,[18] B-Raf mutant tumor growth inhibition,[19] μ-selective opioid activity;[20] and pain management;[21] antihyperlipidemic, antiatherosclerotic,[22] and seratonergic[23] activities. A lot of other biological activities of 2-aminotetralin derivatives have been reported.

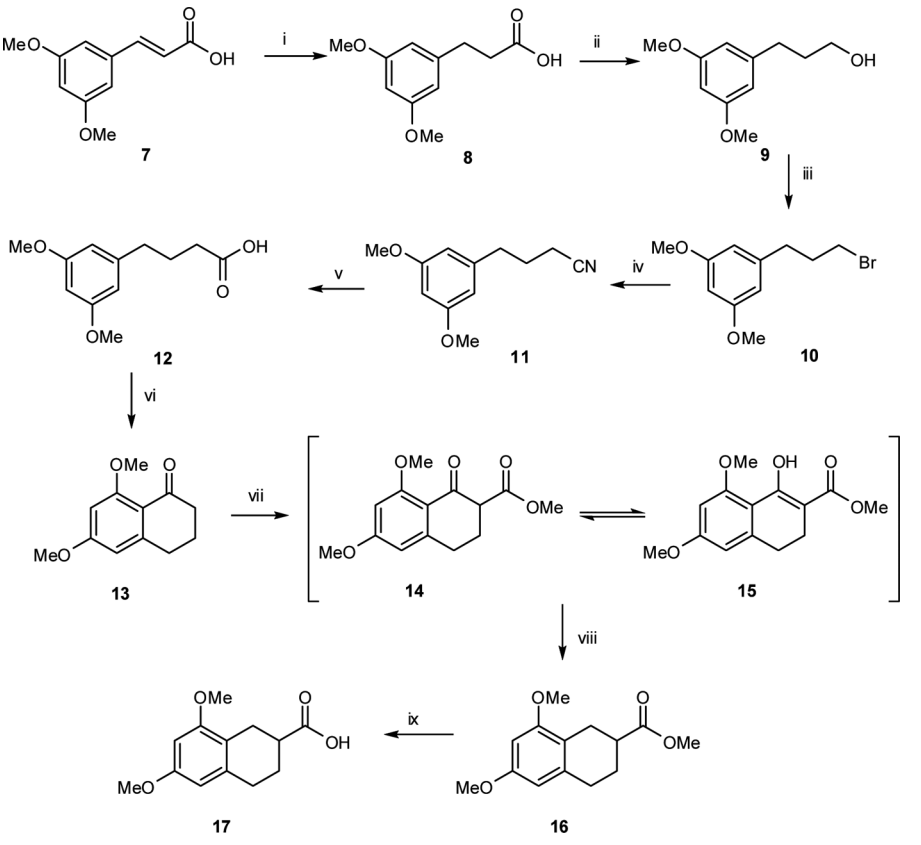
Because of the important biological activities of 2-aminotetralin derivatives, the synthesis of novel dopamine analogues or convenient synthesis of known dopaminergic compounds would be useful for further synthetic and biological purposes. For this reason, we have already achieved the synthesis of 6,7-ADTN (**2**),[24] 5,6-ADTN (**3**),[25] the main component of compound **4**,[26] and some 2-aminoindane derivatives.[27]

It is well known that substituents on the phenyl rings of dopamine-related compounds can lead to different selective biological activities against receptors. Therefore, in the present study we focused on the first synthesis of potential biologically active 2-aminotetralin **6**. The synthesis of **6** was accomplished starting from 3-(3,5-dimethoxyphenyl)acrylic acid (**7**) in 11 steps with an overall yield of 30%.

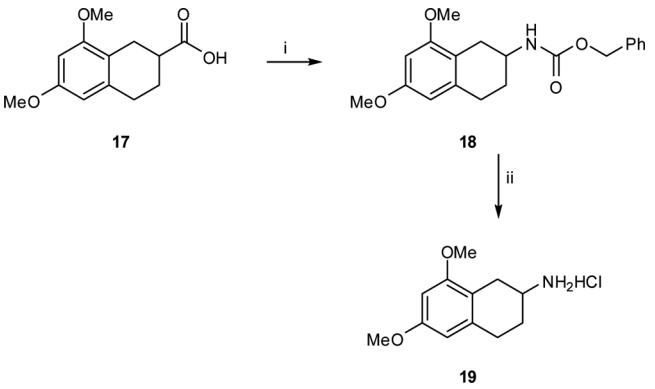
RESULTS AND DISCUSSION

The synthesis of the title compound was started from 3-(3,5-dimethoxyphenyl) acrylic acid (**7**). 3-(3,5-Dimethoxyphenyl)propanoic acid (**8**) was synthesized via Pd-C-catalyzed hydrogenation of compound **7** according to the procedure described by Zhao et al.[28] The reduction of acid **8** with $LiAlH_4$ gave 3-(3,5-dimethoxyphenyl) propan-1-ol (**9**).[29] The conversion of **9** to nitrile **11** can be achieved by the reaction

of **9** with MsCl, PBr_3/Et_3N, or CBr_4/PPh_3 and then reacting the resulting product with NaCN. Here, we saw that the latter procedure was the most convenient one. Therefore, alcohol **9** was reacted with CBr_4/PPh_3 to give alkyl halide **10** according to the procedure described by Jamie and Richards.[29c] Substitution reaction of **10** with NaCN gave novel 4-(3,5-dimethoxyphenyl)butanenitrile (**11**) in good yield. Hydrolysis of **11** with 6 M NaOH at 78 °C furnished 4-(3,5-dimethoxyphenyl)butanoic acid (**12**)[30] by an alternative method. Polyphosphoric acid (PPA) prepared from phosphoric acid and P_2O_5- catalyzed acylation or alkylation of aromatic compounds have been used in the literature.[31] Following the same procedure, reaction of **12** with PPA at 78 °C yielded tetralone **13**.[30a] Conversion of 1-tetralones to their α-carbonyl derivatives with Me_2CO_3 in the presence of NaH has been given in the literature.[32] Applying the same procedure to **13** gave a mixture of the desired new compound **14** and its tautomer **15**. The mixture of **14** and **15** was reacted with Et_3SiH in CF_3CO_2H to give novel methyl 6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate



Scheme 1. Synthesis of acid **17**: (i) H_2/Pd-C, THF, 25 °C, 48 h, 95%; (ii) $LiAlH_4$, THF, 0–25 °C, 24 h, 88%; (iii) CBr_4/PPh_3, CH_3CN, 80 °C, 2 h, 92%; (iv) NaCN, DMF, 50 °C, 24 h, 85%; (v) 6 M NaOH, EtOH, 78 °C, 24 h, then conc. HCl, 0 °C, 90%; (vi) PPA prepared from P_2O_5/H_3PO_4, 80 °C, 45 min., 90%; (vii) Me_2CO_3/NaH, THF, 65 °C, 24 h; (viii) Et_3SiH, CF_3CO_2H, 72 °C, 2.5 h, 80%; and (ix) 10% aqueous NaOH, MeOH, 25 °C, 24 h, then conc. HCl, 0 °C, 87%.



Scheme 2. Synthesis of dopamine and rotigotin analogue **19**: (i) $(PhO)_2PON_3/NEt_3$, C_6H_6, 80 °C, 6 h, then $PhCH_2OH$, 80 °C, 30 h, 85%; and (ii) H_2/Pd-C, $CHCl_3$-MeOH, 25 °C, 24 h, 94%.

(**16**), which was hydrolyzed to corresponding acid derivative **17**[32b] with a solution of NaOH in H_2O-MeOH and then acidified with dilute HCl (Scheme 1).

In our previous research, we have converted carboxylic acids to their carbamate derivatives via Curtius reaction of acids with diphenylphosphoryl azide followed by addition of benzyl alcohol.[24–26] In a similar approach, the Curtius reaction of **17** with diphenylphosphoryl azide in the presence of Et_3N in benzene at 80 °C for 6 h, followed by treatment with benzyl alcohol at the same temperature for 30 h, afforded carbamate **18**. Pd-C-catalyzed hydrogenolysis of **18** in the presence of $CHCl_3$ (for in situ production of HCl)[24–27] in MeOH gave novel dopamine analogue **6** as amine hydrochloride salt (**19**) in excellent yield (Scheme 2). The structures of all synthesized compounds were characterized by ^1H and ^{13}C NMR. Nitrile and azide functional groups were characterized by infrared (IR).

In summary, the title compound 2-amino-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (**6**) was synthesized as hydrochloride salt **19** from commercially available 3-(3,5-dimethoxyphenyl)acrylic acid (**7**) in 11 steps and with 30% total yield for the first time. Because of the similar structure of compound **6** with other dopamine analogues, it may be very useful for further biological and pharmacological purposes. In addition, 4-(3,5-dimethoxyphenyl)butanenitrile (**11**) and benzyl 6,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-ylcarbamate (**18**) were synthesized for the first time and carboxylic acid **12** was synthesized by an alternative method.

EXPERIMENTAL

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Melting points were determined on a capillary melting apparatus (Buchi 530) and are uncorrected. IR spectra were obtained from solutions in 0.1-mm cells with a Perkin-Elmer spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on 400- (100-) MHz Varian and Bruker spectrometers with δ in ppm and Me_4Si as the internal standard. Elemental analyses were performed on a Leco CHNS-932 apparatus. All column chromatography

was performed on silica gel (60 mesh, Merck) using preparative thick-layer chromatography (PLC) and 1 mm of silica gel 60 PF (Merck) on glass plates.

Acid **8**,[28] alkyl halide **10**,[29c] and tetralone **13**[30a] were synthesized according to the literature procedure.

4-(3,5-Dimethoxyphenyl)butanenitrile (11)

NaCN (1.08 g, 22.02 mmol) was added to a solution of alkyl bromide **10** (1.90 g, 7.34 mmol) in DMF (25 ml) at 50 °C. The reaction mixture was stirred at the same temperature for 24 h. After the mixture was cooled to room temperature, EtOAc (80 ml) and H_2O (20 ml) were added to this mixture. The organic layer was separated and extracted with H_2O (3×20 ml). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. Chromatography of the residue on a silica-gel column (30 g) with 30% EtOAc–hexane gave colorless liquid nitrile **11** (1.28 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 3H, Ar-H), 3.77 (s, 6H, $2OCH_3$), 2.71 (t, 2H, CH_2, $J = 7.4$ Hz), 2.31 (t, 2H, CH_2, $J = 7.4$ Hz), 1.96 (quintet, 2H, CH_2, $J = 7.4$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.22 (2C), 142.30 (C), 119.80 (CN), 106.41 (2CH), 98.50 (CH), 55.52 ($2OCH_3$), 34.84 (CH_2), 26.94 (CH_2), 16.59 (CH_2). IR (CH_2Cl_2, cm^{-1}): 3001, 2939, 2840, 2246, 1732, 1597, 1463, 1430, 1349, 1325, 1294, 1255, 1205, 1154, 1071, 940. Anal. calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.18; H, 7.39; N, 6.80.

Methyl 6,8-Dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (16)

NaH (0.35 g, 14.6 mmol) and a solution of Me_2CO_3 (1.31 g, 14.6 mmol) in dry THF (10 ml) were added to a stirred solution of ketone **13** (1.20 g, 5.83 mmol) in dry THF (30 ml) under N_2(g) at rt. The mixture was refluxed for 24 h under N_2(g). After AcOH (2 ml) was added to the cooled reaction mixture, most THF was evaporated. CH_2Cl_2 (60 ml) and a solution of Na_2CO_3 (50 ml) were added to the residue. The organic layer was separated and washed with Na_2CO_4 (2×30 ml) and H_2O (30 ml). After drying over Na_2SO_4 and evaporation of CH_2Cl_2, column chromatography of the residue on silica gel (30 g) with 30% EtOAc–hexane afforded an inseparable mixture of **14** and **15**, which were directly converted to **16** without further characterization. CF_3CO_2H (10 ml) and Et_3SiH (1.43 g, 12.31 mmol) were added to a mixture of **14** and **15** (1.30 g, 4.92 mmol). The reaction mixture was refluxed for 2.5 h under N_2(g). The reaction mixture was cooled to rt and CF_3CO_2H was evaporated. Concentrated $NaHCO_3$ solution in H_2O (40 ml) and EtOAc (40 ml) were added to the residue, and the organic layer was separated. The H_2O phase was extracted with EtOAc (2×40 ml) and the combined organic layers were washed with H_2O (30 ml). Organic phase was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Oily compound **16** was obtained by eluting of the residue on a silica-gel column with 5%, 10%, and 30% EtOAc–hexane (1.16 g, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, 1H, Ar-H, $J = 2.0$ Hz), 6.2 (d, 1H, Ar-H, $J = 2.0$ Hz), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.08–2.96 (m, 1H), 2.82–2.78 (m, 2H), 2.70–2.64 (m, 2H), 2.20–2.13 (m, 1H), 1.80 (dddd, 1H, $^3J = 6.9$, $^3J = 10.8$, $^3J = 12.4$, $^2J = 17.7$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$)

δ 176.4 (CO), 158.7 (C), 158.5 (C), 137.7 (C), 116.5 (C), 104.2 (CH), 96.2 (CH), 55.4 (2C, OCH_3), 51.9 (OCH_3), 40.1 (CH), 29.4 (CH_2), 25.8 (CH_2), 25.5 (CH_2). IR (CH_2CI_2, cm^{-1}): 3006, 2996, 2949, 2839, 1735, 1609, 1596, 1492, 1458, 1436, 1360, 1342, 1301, 1273, 1256, 1236, 1196, 1170, 1148, 1105, 1052, 1027, 1052, 1027, 962, 937. Anal. calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.12; H, 7.28.

Benzyl 6,8-Dimethoxy-1,2,3,4-tetrahydronaphthalen-2-ylcarbamate (18)

Diphenylphosphoryl azide (2.80 g, 10.16 mmol) and Et_3N (1.03 g, 10.16 mmol) were added to a stirred solution of acid **17** (2.00 g, 8.47 mmol) in anhydrous benzene (40 ml) at rt. The mixture was heated at reflux temp for 6 h. Benzyl alcohol (2.75 g, 25.41 mmol) was added to the reaction mixture, and it was refluxed for 30 h. After the mixture was cooled to rt, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (40 g) with 20% EtOAc–hexane. The latest solid was crystallized with EtOAc–hexane, and carbamate **18** was obtained as white crystals (2.46 g, 85% yield). Mp 129–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.30 [m, 5H, Ar-H, (Ph)], 6.28 (d, 1H, Ar-H, $J = 2.2$ Hz), 6.23 (d, 1H, Ar-H, $J = 2.2$ Hz), 5.11 (s, 2H, OCH_2), 4.84 (d, 1H, NH, $J = 7.1$ Hz), 4.05–3.96 (m, 1H, CH), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.00 (A part of AB, dd, 1H, $^2J = 16.7$, $^3J = 5.2$ Hz), 2.85–2.81 (m, 2H), 2.38 (B part of AB, dd, 1H, $^2J = 16.7$, $^3J = 8.2$ Hz), 2.06–2.00 (m, 1H), 1.82–1.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0 (CO), 158.7 (C), 156.0 (C), 137.5 (C), 136.9 [CH (Ph)], 128.8 [3CH (Ph)], 128.3 [2CH (Ph)], 115.6 (C), 104.2 (CH), 96.3 (CH), 66.8 (OCH_2), 55.53 (OCH_3), 55.47 (OCH_3), 47.0 (CH), 29.7 (CH_2), 28.9 (CH_2), 28.0 (CH_2). IR (CH_2CI_2, cm^{-1}): 3684, 3317, 2943, 2880, 2838, 1692, 1595, 1519, 1493, 1455, 1424, 1342, 1306, 1271, 1212, 1194, 1147, 1097, 1050, 934. Anal. calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.35; H, 6.80; N, 4.13.

2-Amino-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene Hydrogen Chloride (19)

Pd/C (80 mg) and carbamate **18** (2.00 g, 5.87 mmol) in MeOH (60 ml) and $CHCl_3$ (4 ml, for producing HCl) were placed in a 100-mL flask. A balloon filled with H_2 gas (3 L) was fitted to the flask. The mixture was deoxygenated by flushing with H_2. The mixture was hydrogenated for 24 h at rt. After the catalyst was removed by filtration, evaporation of the solvent and recrystallization of the residue from MeOH-Et_2O afforded amine hydrochloride salt **19** (1.86, 94% yield). Colorless solid. Mp 280–282 °C. ^{1}H NMR (400 MHz, D_2O): δ 6.30 (s, 1H, Ar-H), 6.27 (s, 1H, Ar-H), 4.65 (bs, 3H of NH_3 and H_2O of D_2O), 3.66 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.45–3.37 (m, 1H, CH), 2.93 (dd, 1H, $^2J = 16.4$ Hz, $^3J = 5.5$ Hz), 2.73–2.69 (m, 2H), 2.36 (dd, 1H, $^2J = 16.4$, $^3J = 9.6$ Hz), 2.06–1.98 (m, 1H), 1.66 (dddd, 1H, $^3J = 7.5$, $^3J = 10.3$, $^3J = 12.2$, $^2J = 17.3$ Hz). ^{13}C NMR (100 MHz, D_2O): δ 158.5 (C), 158.1 (C), 137.3 (C), 113.9 (C), 105.0 (CH), 96.6 (CH), 55.7 (OCH_3), 55.5 (OCH_3), 47.6 (CH), 27.0 (CH_2), 26.8 (CH_2), 26.4 (CH_2). Anal. calcd. for $C_{12}H_{18}ClNO_2$: C, 59.14; H, 7.44; N, 5.75. Found: C, 59.10; H, 7.47; N, 5.74.

FUNDING

The authors are indebted to the Scientific and Technological Research Council of Turkey (TÜBİTAK, Grant No. 109 T/241) and Atatürk University for financial support of this work.

SUPPORTING INFORMATION

Full experimental detail and ^{1}H and ^{13}C NMR spectra can be found via the "Supplementary Content" section of this article's Web page.

REFERENCES

1. Haadsma-Svensson, S. R.; Svensson, K. A. *CNS Drug Rev.* **1998**, *4*, 42–53.
2. Cannon, J. G. *Prog. Drug Res.* **1985**, *29*, 303–414.
3. (a) Woodruff, G. N. *Comp. Gen. Pharmacol.* **1971**, *2*, 439–455; (b) Abel, M. S.; Clement-Cormier, Y. *Pharmacologist* **1978**, *20*, 241.
4. (a) McDermed, J. D.; McKenzie, G. M.; Phillips, A. P. *J. Med. Chem.* **1975**, *18*, 362–367; (b) Cannon, J. G.; Lee, T.; Goldman, H. D.; Costall, B.; Naylor, R. J. *J. Med. Chem.* **1977**, *20*, 1111–1116.
5. (a) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* **1976**, *19*, 547–549; (b) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469–1475; (c) van Vliet, L. A.; Tepper, P. G.; Dijkstra, D.; Damsma, G.; Wikström, H.; Pugsley, T. A.; Akunne, H. C.; Heffner, T. G.; Glase, S. A.; Wise, L. D. *J. Med. Chem.* **1996**, *39*, 4233–4237.
6. (a) Giladi, N.; Boroojerdi, B.; Korczyn, A. D.; Burn, D. J.; Clarke, C. E.; Schapira, A. H. *Mov. Disord.* **2007**, 2398–2404; (b) Chen, J. J.; Swope, D. M.; Dashtipour, K.; Lyons, K. E. *Pharmacother.* **2009**, *29*, 1452–1467.
7. Sixel-Döring, F.; Trenkwalder, C. *Expert Opin Pharmacother.* **2010**, *11*, 649–656.
8. Ye, Q.; Grunewald, G. L. *J. Med. Chem.* **1989**, *32*, 478–486.
9. Yao, B.; Ji, H.; Cao, Y.; Zhou, Y.; Zhu, J.; Lu, J.; Li, Y.; Chen, J.; Zheng, C.; Jiang, Y.; Liang, R.; Tang, H. *J. Med. Chem* **2007**, *50*, 5293–5300.
10. Singh, P. *Arzneim.-Forsch* **1986**, *36*, 1437–1439.
11. (a) Holz, W. C.; Hieble, J. P.; Gill, C. A.; De Marinis, R. M.; Pendleton, R. G. *Psychopharmacol.* **1982**, *77*, 259–267; (b) DeMarinis, R. M.; Shah, D. H.; Hall, R. F.; Hieble, J. P.; Pendleton, R. G. *J. Med. Chem.* **1982**, *25*, 136–141.
12. Copinga, S.; Tepper, P. G.; Grol, C. J.; Horn, A. S.; Dubocovich, M. L. *J. Med. Chem.* **1993**, *36*, 2891–2898.
13. Rusterholz, D. B.; Barfknecht, C. F.; Clemens, J. A. *J. Med. Chem.* **1976**, *19*, 99–102.
14. (a) Sharabi, F. M.; Long, J. P.; Rusterholz, D. B.; Barfknecht, C. F. *Res. Commun. Chem. Pathol. Pharmacol.* **1978**, *19*, 37–55; (b) Clark, R. D.; Caroon, J. M.; Repke, D. B.; Strosberg, A. M.; Whiting, R. L.; Brown, C. M. *J. Pharm. Sci.* **1986**, *75*, 80–82.
15. Rusterholz, D. B.; Dryer, S. E.; Long, J. P.; Barfknecht, C. F.; Mott, J. *Eur. J. Pharmacol.* **1980**, *65*, 201–211.
16. Hacksell, U.; Arvidsson, L. E.; Johansson, A. M.; Nilsson, J. L.; Sanchez, D.; Lindberg, P.; Wikström, H.; Svensson, K.; Hjorth, S.; Carlsson A. *Acta Pharm. Suec.* **1986**, *23*, 77–90.
17. Sterling, J.; Herzig, Y.; Goren, T.; Finkelstein, N.; Lerner, D.; Goldenberg, W.; Miskolczi, I.; Molnar, S.; Rantal, F.; Tamas, T.; Toth, G.; Zagyva, A.; Zekany, A.; Lavian, G.;

Gross, A.; Friedman, R.; Razin, M.; Huang, W.; Krais, B.; Chorev, M.; Youdim, M. B.; Weinstock, M. *J. Med. Chem.* **2002**, *45*, 5260–5279.
18. Amberg, W.; Ochse, M.; Lange, U.; Kling, A.; Behl, B.; Hornberger, W.; Mezler, M.; Hutchins, C. PCT Int. Appl. WO2010092180 2010; *Chem. Abstr.* **2010**, *153*, 333740.
19. Gould, A. E.; Adams, R.; Adhikari, S.; Aertgeerts, K.; Afroze, R.; Blackburn, C.; Calderwood, E. F.; Chau, R.; Chouitar, J.; Duffey, M. O.; England, D. B.; Farrer, C.; Forsyth, N.; Garcia, K.; Gaulin, J.; Greenspan, P. D.; Guo, R.; Harrison, S. J.; Huang, S. C.; Iartchouk, N.; Janowick, D.; Kim, M. S.; Kulkarni, B.; Langston, S. P.; Liu, J. X.; Ma, L. T.; Menon, S.; Mizutani, H.; Paske, E.; Renou, C. C.; Rezaei, M.; Rowland, R. S.; Sintchak, M. D.; Smith, M. D.; Stroud, S. G.; Tregay, M.; Tian, Y.; Veiby, O. P.; Vos, T. J.; Vyskocil, S.; Williams, J.; Xu, T.; Yang, J. J.; Yano, J.; Zeng, H.; Zhang, D. M.; Zhang, Q.; Galvin, K. M. *J. Med. Chem.* **2011**, *54*, 1836–1846.
20. Roy, C.; Li, T.; Krasik, P.; Gilbert, M. J.; Pelletier, C.; Gagnon, D.; Robert, E.; Ducharme, J.; Storer, R.; Lavallee, J. F. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3141–3143.
21. Dixit, D.; Bednarski, K.; Li, T.; Roberts, E.; Storer, R.; Wang, W. PCT Int. Appl. WO2000037438, 2000; *Chem. Abstr.* **2000**, *133*, 58533.
22. Trivedi, B. K. Eur. Pat. Appl. EP 335375, 1989; *Chem. Abstr.* **1990**, *112*, 178376.
23. Westkaemper, R. B.; Yousif, M.; Teitler, M.; Glennon, R. A. *Med. Chem. Res.* **1992**, *2*, 482–490.
24. Göksu, S.; Kazaz, C.; Sütbeyaz, Y.; Seçen, H. *Helv. Chim. Acta* **2003**, *86*, 3310–3313.
25. (a) Göksu, S.; Uğuz, M. T.; Özdemir, H.; Seçen, H. *Turk. J. Chem.* **2005**, *29*, 199–205; (b) Göksu, S.; Seçen, H.; Sütbeyaz, Y. *Helv. Chim. Acta* **2006**, *89*, 270–273.
26. Öztaşkın, N.; Göksu, S.; Seçen, H. *Synth. Commun.* **2011**, *41*, 2017–2024.
27. (a) Göksu, S.; Seçen, H. *Tetrahedron* **2005**, *61*, 6801–6807; (b) Şentürk, M.; Ekinci, D.; Göksu, S.; Supuran, C. T. *J. Enzyme Inhib. Med. Chem.* **2012**, *27*, 365–369.
28. Zhao, H.; Neamati, N.; Mazumder, A.; Sunder, S.; Pommier, Y.; Burke, T. R. J. *J. Med. Chem.* **1997**, *40*, 1186–1194.
29. (a) Nikas, S. P.; Thakur, G. A.; Makriyannis, A. *Synth. Commun.* **2002**, *32*, 1751–1756; (b) Crocker, P. J.; Saha, B.; Ryan, W. J.; Wiley, J. L.; Martin, B. R.; Ross, R. A.; Pertwee, R. G.; Razdan, R. K. *Tetrahedron* **1999**, *55*, 13907–13926; (c) Jamie, J. F.; Rickards, R. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3613–3622.
30. (a) El-Feraly, F. S.; Cheatham, S. F.; McChesney, J. D. *Can. J. Chem.* **1985**, *63*, 2232–2236; (b) Davies, J. E.; King, F. E.; Roberts, J. C. *J. Chem. Soc.* **1955**, 2782–2786.
31. (a) Akbaba, Y.; Balaydın, H. T.; Göksu, S.; Şahin, E.; Menzek, A. *Helv. Chim. Acta* **2010**, *93*, 1127–1135; (b) Balaydın, H. T.; Gülçin, I.; Menzek, A.; Göksu, S.; Sahin, E. *J. Enzyme Inhib. Med. Chem.* **2011**, *25*, 685–695; (c) Balaydın, H. T.; Akbaba, Y.; Menzek, A.; Şahin, E.; Göksu, S. *Arkivoc* **2009**, *14*, 75–97; (d) Balaydın, H. T.; Durdağı, S.; Ekinci, D.; Şentürk, M.; Göksu, S.; Menzek, A. *J. Enzyme Inhib. Med. Chem.* **2012**, *27*, 467–475; (f) Akbaba, Y.; Balaydın, H. T.; Menzek, A.; Göksu, S.; Şahin, E.; Ekinci, D. *Arch. Pharm. Chem. Life Sci.* **2013**, *346*, 447–454; (g) Balaydın, H. T.; Şentürk, M.; Göksu, S.; Menzek, A. *Eur. J. Med. Chem.* **2012**, *54*, 423–428.
32. (a) House, H. O.; Hudson, C. B. *J. Org. Chem* **1970**, *35*, 647–651. (b) Morris, J. C.; Mander, L. N.; Hockless, D. C. R. *Synthesis* **1998**, 455–467.