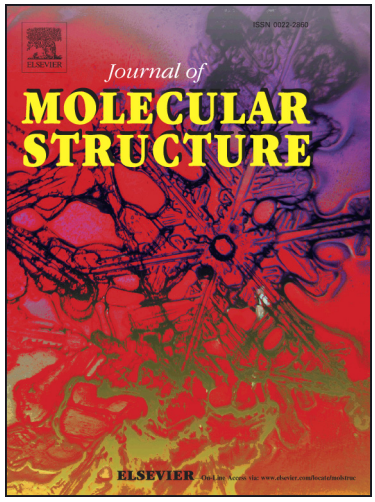


X-ray diffraction and VT-NMR studies of (*E*)-3-(piperidinyl)-1-(2′-hydroxy-phenyl)-prop-2-en-1-one

Seunghyun Choi, YunHye Kim, Bernie Byeonghoon Park, Suzie Park, Jonghyun Park, Kiwon Ok, JaeHyung Koo, Yong Woo Jung, Young Ho Jeon, Eun Hee Lee, Ken S. Lee, Youngjoo Byun

PII: S0022-2860(14)00835-7
DOI: http://dx.doi.org/10.1016/j.molstruc.2014.08.016
Reference: MOLSTR 20876

To appear in: *Journal of Molecular Structure*

Received Date: 29 May 2014
Revised Date: 5 August 2014
Accepted Date: 5 August 2014

Please cite this article as: S. Choi, Y. Kim, B.B. Park, S. Park, J. Park, K. Ok, J. Koo, Y.W. Jung, Y.H. Jeon, E.H. Lee, K.S. Lee, Y. Byun, X-ray diffraction and VT-NMR studies of (*E*)-3-(piperidinyl)-1-(2′-hydroxyphenyl)-prop-2-en-1-one, *Journal of Molecular Structure* (2014), doi: http://dx.doi.org/10.1016/j.molstruc.2014.08.016

Aug 5, 2014

Re: Cover letter for L05-77-14

Dear Dr. Jaan Laane

Attached are further corrections and improvements to our manuscript, *X-ray diffraction and VT-NMR studies of* (*E*)-3-(piperidinyl)-1-(2′-hydroxyphenyl)-prop-2-en-1-one, performed in response to the comments of Reviewers. The rigor of the reviewers has challenged us to improve the quality of the manuscript greatly. We have answered all queries and comments.

If further information is required, please do not hesitate to contact me. Thank you for the very careful review and the opportunity to provide these corrections and re-submit to *Journal of Molecular Structure.*

Yours sincerely,

Youngjoo Byun, Ph. D.

College of Pharmacy, Korea University

2511 Sejong-ro, Jochiwon-eup, Sejong 339-700, South Korea

Tel: 82-41-860-1619, Fax: 82-41-860-1606, E-mail: yjbyun1@korea.ac.kr

X-ray diffraction and VT-NMR studies of (*E*)-3-(piperidinyl)-1-(2′-hydroxyphenyl)-prop-2-en-1-one

Seunghyun Choi,[a,#] YunHye Kim,[a,#] Bernie Byeonghoon Park,[a] Suzie Park,[a] Jonghyun Park,[a] Kiwon Ok, [a] JaeHyung Koo,[b] Yong Woo Jung,[a] Young Ho Jeon,[a] Eun Hee Lee,[a] Ken S. Lee,[c] Youngjoo Byun [a,d,*]

[a]College of Pharmacy, Korea University, 2511 Sejong-ro, Jochiwon-eup, Sejong 339-700, South Korea.

[b]Department of Brain Science, Daegu Gyeongbuk Institute of Science & Technology, 50-1 Sang-Ri, Hyeonpung-Myeon, Dalseong-Gun, Daegu, 711-873, South Korea

[c]Department of Chemistry & Biochemistry, Jackson State University, 1400 J. R. Lynch Street, Jackson, MS 39217, USA

[d]Biomedical Research Center, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 152-703, South Korea

[#]Equal contribution

*Corresponding author:

Youngjoo Byun, Ph.D.

College of Pharmacy, Korea University, 2511 Sejong-ro, Jochiwon-eup, Sejong 339-700, South Korea.

Tel.: 82-44-860-1619; Fax: 82-44-860-1607; E-mail: yjbyun1@korea.ac.kr

Abstract

A series of 1-aryl-3-(cyclicamino)-prop-2-en-1-one analogs was synthesized from commercial acetophenones in 2 or 3 steps. Compound **6**, (*E*)-3-(piperidinyl)-1-(2′-hydroxyphenyl)-prop-2-en-1-one, exhibited the unique shape and intensity of the C_{sp2}-N-CH_2 peaks in the ^{1}H- and ^{13}C-NMR spectra. Variable temperature (VT) nuclear magnetic resonance (NMR) and X-ray diffraction (XRD) studies of **6** revealed that the piperidine ring has a lower energy barrier to rotation than the 5-membered pyrrolidine **9** due to the less effective πelectron delocalization along the C_{sp2}-N bond.

Key Words: Enaminones, X-ray diffraction, VT-NMR, Flexible rotation

Research Highlights

- (E)-Selective synthesis of 3-(piperidinyl)-1-(2′-hydroxyphenyl)-prop-2-en-1-one.
- 3D structure determination of the compound by X-ray diffraction.
- Spectroscopic characterization of the compounds by 1D and 2D NMR.
- Flexible rotation of the compound along the C-N bond explained by VT-NMR studies.

1. Introduction

Enaminones, consisting of the conjugated N-C=C-C=O system, are attractive functional groups in the field of medicinal chemistry because of their versatile utilization as intermediates for the synthesis of pharmacologically active agents [1-3]. They have been widely used as important intermediates and building blocks for preparing heterocyclic moieties, including quinolones, indoles, isoxazoles, and pyridines, because they can act not only as nucleophiles but also as electrophiles in a variety of chemical reactions [4-9]. Some of the enaminone-containing molecules were used as key intermediates for the synthesis of FDA-approved drugs such as ciprofloxacin and imatinib [10, 11]. Despite the importance of enaminone systems in synthetic chemistry and medicinal chemistry, few reports have been published on the structural analysis of enaminone systems by X-ray crystal analysis and variable-temperature (VT)-nuclear magnetic resonance (NMR) experiments [12-16].

In general, substituted enaminones are classified into *(E)* and *(Z)* geometrical isomers based on the relative position of substituents with higher priorities of the carbon-carbon double bond. They are also classified into s-*cis* and s-*trans* conformational isomers based on the relationship of alkene and carbonyl groups around the central single C-C bond. For example, 3-(dimethylamino)-1-(2′-hydroxyphenyl)prop-2-en-1-one (Figure 1) has four possible isomeric forms: (*E*)-s-*trans*, *(Z)*-s-*trans*, (*E*)-s-*cis,* and *(Z)*-s-*cis*. In this study, we synthesized 1-aryl-3-(cyclicamino)-prop-2-en-1-one analogs and fully analyzed the chemical structure of (*E*)-3-(piperidinyl)-1-(2′-hydroxyphenyl)prop-2-en-1-one, one of the analogs, by means of X-ray crystallography and VT NMR spectroscopy.

2. Experimental

General

Chemicals and solvents were purchased from Aldrich and Acros. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER Biospin AVANCE 600 MHz and 300 MHz spectrometer. Chemical shifts are reported as δ values downfield from internal TMS in appropriate organic solvents. Mass spectra were recorded on Agilent 6530 Accurate mass Q-TOF LC/MS spectrometer. HPLC were recorded on Agilent HPLC 1260 Infinity. Silica gel column chromatography experiments were performed using Merck Silica Gel F_{254}. VT NMR experiments were carried out by cooling and heating the probe. For VT NMR studies the sample was placed in the probe and allowed to equilibrate to the required temperature for 30 min.

Synthesis of compounds 6 and 9

*(E)-3-(Dimethylamino)-1-(2´-hydroxyphenyl)-prop-2-en-1-one (**5**)*

To a solution of 2'-hydroxyacetophenone (2.73 g, 20 mmol) in *p*-xylene (20 mL) was added dimethylformamide-dimethylacetal (DMF-DMA) (2.34 g, 20 mmol). The reaction mixture was stirred under reflux for 2 hr. After monitoring the progress of the reaction by TLC, the excessive solvent was removed under reduced pressure. The precipitate solid was collected by filtration and washed with ethanol. Crystallization from ethanol afforded the compound **5** (hexane/ethyl acetate = 1.5:1, R_f = 0.22) in 79% yield as orange-red solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ2.97 (s, 3H, NCH_3), 3.19 (s, 3H, NCH_3), 5.78 (d, 1H, *J* = 12.2 Hz, =CH-), 6.82 (m, 1H, *J* = 1.2, 8.1 Hz, Ar-H), 6.93 (dd, 1H, *J* = 1.0, 8.3 Hz, Ar-H), 7.32-7.38 (m, 1H, *J* = 1.6, 7.3, 8.7 Hz, Ar-H), 7.69 (dd, 1H, *J* = 1.6, 8.0 Hz, Ar-H), 7.90 (d,

1H, *J* = 12.1 Hz, =CH-), 13.93 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ37.39 (NCH_3), 45.33 (NCH_3), 90.13 (=CH-), 117.95, 118.24, 120.36, 128.21, 133.94, 154.71, 162.98, 191.56 (C=O). HRMS (ESI): $[M+H]^+$, calcd for $C_{11}H_{14}NO_2$ (*m/z*): 192.1025, found: 192.1018.

*3-Acetyl-4H-chromen-4-one (**8**)*

To a solution of compound **5** (1.90 g, 10 mmol) in acetonitrile (30 mL) was added pyridine (25 mL) and acetic anhydride (4.8 g, 40 mmol). The reaction mixture was refluxed for 4 hr. After monitoring the progress of the reaction by TLC, the excessive solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (100 mL) and washed with 1 N HCl solution (100 mL x 2). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica-gel chromatography (hexane/ethylacetate = 5:1, R_f = 0.33) afforded the compound **8** in 52% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ2.77 (s, 3H, $COCH_3$), 7.28-7.50 (m, 2H, *J* = 0.9, 7.1 Hz, Ar-H), 7.53 (d, 1H, *J* = 8.4 Hz), 7.72-7.77 (m, 1H, *J* = 1.4, 8.5 Hz, Ar-H), 8.31 (d, 1H, *J* = 7.9 Hz, Ar-H), 8.63 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ31.54 ($CO\underline{C}H_3$), 118.27, 122.86, 125.43, 126.29, 126.47, 134.33, 155.88, 161.67, 175.32, 196.68 (C=O). HRMS (ESI): $[M+H]^+$, calcd for $C_{11}H_9O_3$ (*m/z*): 189.0552, found: 189.0504.

*(E)-1-(2´-Hydroxyphenyl)-3-(piperidin-1-yl)-prop-2-en-1-one (**6**)*

To a solution of compound **8** (0.262 g, 1.4 mmol) in chloroform (30 mL) was added piperidine (14 mmol). The reaction mixture was stirred under reflux for 6 hr. After monitoring the progress of the reaction by TLC, the excessive solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (50 mL) and washed with 1 N

HCl solution (50 mL x 2). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate=5:1, R_f = 0.26) provided compound **6** in 32% yield in white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (s, 6H, $N(CH_2)_2(C\underline{H}_2)_3$), 3.41 (s, 4H, $N(C\underline{H}_2)_2(CH_2)_3$), 5.88 (d, 1H, *J* = 12.3 Hz, =CH-), 6.81 (dd, 1H, *J* = 7.6 Hz, Ar-H), 6.93 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.27-7.37 (m, 1H, *J* = 1.1, 7.1, 8.3 Hz, Ar-H), 7.67 (d, 1H, *J* = 1.1, 8.0 Hz, Ar-H), 7.86 (d, 1H, *J* = 12.3 Hz, =CH-), 14.02 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ23.97, 30.89, 44.81, 89.09, 117.89, 118.25, 120.51, 128.08, 133.83, 153.44, .162.93, 191.81 (C=O). HRMS (ESI): $[M+H]^+$, calcd for $C_{11}H_{14}NO_2$ (*m/z*): 232.1338, found: 232.1346.

*(E)-1-(2´-Hydroxyphenyl)-3-(pyrrolidin-1-yl)-prop-2-en-1-one (**9**)*

Compound **9** was prepared according to the procedure described for compound 6 using pyrrolidine instead of piperidine.

Yield: 22% R_f = 0.37 (hexane/ethyl acetate=3:2), ^{1}H NMR (300 MHz, $CDCl_3$): δ1.93-2.01 (m, 2H, $NCH_2C\underline{H}_2$), 2.03-2.12 (m, 2H, $NCH_2C\underline{H}_2$), 3.33 (t, 2H, *J* = 6.9 Hz, $NC\underline{H}_2CH_2$), 3.61 (t, 2H, *J* = 6.6 Hz, $NC\underline{H}_2CH_2$), 5.74 (d, 1H, *J* = 12.1 Hz, =CH-), 6.79-6.84 (m, 1H, *J* = 1.2,7.3, 8.0 Hz, Ar-H), 6.93 (d, 1H, *J* = 1.0, 8.3 Hz, Ar-H), 7.32-7.38 (m, 1H, *J* = 1.6, 7.3, 8.5 Hz, Ar-H), 7.69 (dd, 1H, *J* = 1.5, 8.0 Hz, Ar-H), 8.10 (d, 1H, *J* = 12.1 Hz, =CH-), 14.03 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.17 ($NCH_2\underline{C}H_2$), 47.17 ($N\underline{C}H_2CH_2$), 52.69 ($N\underline{C}H_2CH_2$), 90.92, 117.90, 118.21, 120.38, 128.21, 133.84, 150.42, 162.97, 191.23 (C=O). HRMS (ESI): $[M+H]^+$, calcd for $C_{11}H_{14}NO_2$ (*m/z*): 218.1181, found: 218.1180.

X-ray crystallography

X-ray intensity data for compounds **6** and **9** were collected on a Bruker SMART APEX-II CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at a

temperature of 296 K or 173 K. The structures were solved by applying the direct method using a SHELXS-97 and refined by full-matrix least-squares calculation on F^2 using SHELXL-97. All non-hydrogen atoms were refined anisotropically. Amine H atoms were located in a difference map and refined freely [refined distances; N-H = 0.73 (3) and 0.96 (2) Å]. Other H atoms were positioned geometrically and refined using a riding model, with C-H = 0.93-0.98 Å with U_{iso} = 1.2 U_{eq} (carrier C) for aromatic- and methylene-H, and 1.5 U_{eq}(carrier C) for methyl-H atoms. Crystallographic details for compounds **6** and **9** are summarized in Table 1.

3. Results and Discussion

3′-Hydroxyphenylenaminone analogs were prepared by using the synthetic procedure shown in Scheme 1. Briefly, the reaction of *N,N*-dimethylformamide-dimethylacetal (DMF-DMA) with 3′-hydroxyacetophenone in *p*-xylene under reflux afforded (*E*)-3-(dimethylamino)-1-(3′-hydroxyphenyl)prop-2-en-1-one (**2**). Treatment of **2** with pyrrolidine or piperidine under acidic conditions gave the corresponding (*E*)-3-(pyrrolidinyl)-1-(3′-hydroxyphenyl)-prop-2-en-1-one (**3**) and(*E*)-3-(piperidinyl)-1-(3′-hydroxyphenyl)-prop-2-en-1-one(**4**) in 65% and 52% yield, respectively. In the case of 2′-hydroxyacetophenone analogs, however, a mixture of geometrical (*E*) isomer **6** and (*Z*) isomer **7** was obtained in 5:4 ratio (Scheme 1). The pure isomer could not be isolated from a (*E/Z*) mixture by normal silica-gel column chromatography due to the complete overlap of the two isomers. The (*E*) and (*Z*) composition ratio was calculated based on the integration and coupling constant of vicinal hydrogens of the alkene group from ^{1}H NMR experiment.

In order to prepare the (*E*)-isomer **6** exclusively, we used the alternative synthetic

route shown in Scheme 2. (*E*)-1-(2′-hydroxyphenyl)-3-(piperidin-1-yl)-prop-2-en-1-one (**6)** was synthesized from 2′-hydroxyacetophenone in 3 steps. The key intermediate, 3-acetylchromone **8,** was prepared by reacting **5** with acetic anhydride in pyridine by modifying the published synthetic procedure [17]. Treatment of **8** with piperidine in chloroform under reflux induced the ring opening of the pyrone ring to afford the (*E*)-isomer **6** exclusively without generating the (*Z*)-isomer **7** in 32% yield. When compound **8** was reacted with pyrrolidine and piperazine instead of piperidine under the same conditions, the corresponding enaminones **9** and **10** were obtained in (*E*)-isomeric form. The electron-withdrawing acetyl group of **8** decreases the electron density of the C-2 atom and acts as a 1,4-addition reaction acceptor. Nucleophilic attack of cyclic amines induces the concomitant opening of the pyrone ring, followed by deacetylation under reflux.

Compound **6** was fully analyzed by ^{1}H, ^{13}C, and 2D NMR experiments. ^{1}H NMR shows each proton's peak, as expected, with a proper integration. The proton of the hydroxyl group appeared at 14.1 ppm. Two olefin hydrogen atoms at 7.86 ppm and 5.88 ppm were confirmed by correlation spectroscopy (COSY) experiment and its coupling constant (J = 12.3 Hz) proved that the compound has (*E*) conformation. Six protons of the piperidine ring gave peaks at 1.69 ppm (6Hs) and 3.41 ppm (4Hs, two of –N-C**H**$_2$-), which were a broad singlet, but the COSY experiment confirmed that were coupled with each other. Five carbons of the piperidine ring are observed at 23.9 ppm, 25.1 ppm, 26.4 ppm, 46.5 ppm and 55.0 ppm in ^{13}C NMR, but all except that at 23.9 ppm were relatively weak. Heteronuclear correlation spectroscopy (HETCOR) experiment between ^{1}H and ^{13}C showed that the hydrogen at 3.41 ppm was correlated with the peaks at 46.5 ppm and 55.0 ppm, which were attributed to the methylene group next to nitrogen (-N-C**H$_2$-**) in the piperidine ring, and that the broad peak at 1.69 ppm was crossed with three carbon peaks at 23.9 ppm, 25.1 ppm, and 26.4 ppm, which

were the remaining methylene groups in the piperidine ring. The broadness of the proton peaks in ^{1}H NMR and the small peaks in ^{13}C NMR revealed that the piperidine ring was quickly rotating along the C-N bond. Therefore, we quickly conducted VT ^{1}H and ^{13}C NMR experiments from 6.2 ^{o}C to 40 ^{o}C. The carbon peaks presented a sharper and taller shape as the temperature was decreased. In the ^{1}H NMR results, the peaks at 3.41 ppm with two triplets at 6.2 ^{o}C were changed into a sharp singlet at 40 ^{o}C. We observed the coalescence temperature of N-C**H$_2$** located at 25 ^{o}C (298K) on ^{1}H NMR spectrum and the calculated activation rotational energy was 15.0 kcal/mol (see supporting information for details).

VT ^{1}H NMR indicated that the piperidine ring of compound **6** is rotating fast enough to show its broadness at room temperature. However, such fast rotation has not been observed in other enaminone systems substituted with 5-membered pyrrolidine (**9**) or acyclic *N,N*-dimethylamine. The proton peaks of the two methyl groups next to the nitrogen were separated clearly in the pyrrolidine and *N,N*-dimethyl analogs (see all spectra in the supporting information), which revealed that they are not rotating that fast at room temperature. However, the ^{1}H and ^{13}C NMR spectra of the enaminone of 6-membered piperazine analog **10** showed broad and weak intensity peaks similar to those of compound **6**. These results indicated that the delocalization of pi-electrons from the nitrogen to carbonyl may differ different between the 6-membered ring system and the 5-membered or acyclic systems. The nitrogen in piperidine would not participate in the delocalization as much as the dimethylamino or pyrrolidine compound would.

To analyze the molecular structure of compound **6** more accurately, its X-ray crystal structure was determined. The exhibited planar structure shows the hydrogen bonding between the oxygen of the carbonyl group and the hydrogen of the hydroxyl group on the phenyl ring, as shown in Figure 3. The distance between the oxygen of the carbonyl group

and the hydrogen of OH was 1.666Å, which is in the range of normal hydrogen bonding reported previously with substituted phenyl chalcones [12]. The planarity of compound **6** was probably due to the delocalized πelectron system from the carbonyl to the nitrogen of the piperidine ring. The torsional angles around the nitrogen (C8-C7-N1-C6 or C2) of compound **6** were -0.6° and 168.8°, respectively. The bond lengths and the bond angles around the nitrogen supported the participation of nitrogen in long conjugation of the πelectron, which was extended to the carbonyl group at least. The bond angles around nitrogen were 120.3°, 123.0°, and 115.7° and the bond lengths from the nitrogen to the neighboring C_{sp2} and C_{sp3} carbons were 1.327 Å and 1.470 Å, respectively. The normal bond lengths for C-N bonds in the planar structure are in the range of 1.336 Å and 1.473 Å, respectively. The bond lengths around the carbonyl carbon were 1.491 Å and 1.427 Å for the adjacent carbons, which are within the range of reported values. However, the bond to the unsaturated carbon was shorter than the other, since it was involved in the conjugation, as indicated by the bond length of the carbonyl bond, which at 1.267 Å was slightly longer than that of a non-conjugated carbonyl group.

Compound **6** exhibited a similar structural feature to the previously reported crystal structure of (*E*)-1-(2′-hydroxyphenyl)-3-(*N,N*-dimethylamino)-prop-2-en-1-one (**5**). The striking differences between the two compounds were the intermolecular hydrogen interactions for packing. The dimethylamino group showed its weak intermolecular hydrogen interactions between the oxygen of the hydroxyl group and the two C-H units of the αcarbon and *ortho* position of the aromatic ring, 2.387 Å and 2.405 Å, respectively. Such interactions influenced the hydrogen bond by making it stronger. The X-ray results of **6** showed that the OH bonds with the neighboring carbonyl group were longer (1.032 Å) and shorter (1.500 Å) than usual. However, the results also showed weak intermolecular interactions between the

oxygen of the hydroxyl group and the two hydrogen atoms from two piperidine rings of two different molecules, with distances of 2.545 Å and 2.478 Å. The revealed X-ray crystal structure indicated that the contribution of the nitrogen in piperidine to the delocalization of the enaminone was not as much as that of dimethylamine or pyrrolidine compounds. The enaminone of the dimethylamino group has a shorter distance in hydrogen bonding, 1.50 Å, compared to 1.666 Å for piperidine. This indicates that the oxygen in the carbonyl is less negatively charged due to a partial conjugation of πelectron from the nitrogen.

The proton peaks of the two N-CH_2 in the pyrrolidine **9** appeared as two sharp triplet centered at 3.60 and 3.33 ppm, respectively (see the supporting information), indicating that the two N-CH_2 are in different chemical environments. In the X-ray crystal structure of **9** as shown in Figure 5, the shorter N(1)-C(6) [1.308 Å] bond distance was observed as compared to N(1)-C(7) [1.327 Å] for compound **6**. This result indicated that the C-N bond of **9** is less flexible than that of **6** because the delocalization of π electrons in the enaminone system substituted with the pyrrolidine is more effective than that in the related piperidine **6**.

4. Conclusions

We synthesized a series of (*E*)-1-aryl-3-(cyclicamino)-prop-2-en-1-one analogs and analyzed their structures by means of ^{1}H and ^{13}C NMR and liquid chromatography–mass spectrometry (LC/MS). We developed a synthetic strategy for preparing (*E*)-1-(2′-hydroxyphenyl)-3-(piperidin-1-yl)-prop-2-en-1-one (**6**) and analyzed its structural characteristics by X-ray crystallography and VT-NMR. The rotational flexibility of the piperidine ring in compound **6** at room temperature produced the unique shape and intensity of the C-N-CH_2 peaks in ^{1}H-NMR and ^{13}C-NMR. The X-ray structure of **6** revealed that the piperidine ring has more flexible rotation along the C-N bond than the 5-membered

pyrrolidine **9** due to the less effective πelectron delocalization of the enaminone system.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea Government (No. 2014R1A4A1007304 and No. 2012R1A1A11010000).

Appendix A. Supplementary material

Supplementary data associated with this article and cif files for **6** and **9** can be found at http://

References

[1] R. Pena, S. Jimenez-Alonso, G. Feresin, A. Tapia, S. Mendez-Alvarez, F. Machin, A.G. Ravelo, A. Estevez-Braun, J Org Chem, 78 (2013) 7977-7985.

[2] C.O. Okoro, J. Apraku, E.O. Okoromoba, O.O. Fadeyi, Lett Drug Des Discov, 10 (2013) 1024-1031.

[3] C.A. Engelhart, C.C. Aldrich, J Org Chem, 78 (2013) 7470-7481.

[4] A. Salomone, F.M. Perna, F.C. Sassone, A. Falcicchio, J. Bezensek, J. Svete, B. Stanovnik, S. Florio, V. Capriati, J Org Chem, 78 (2013) 11059-11065.

[5] J.C. Liermann, M.H. Elnagdi, H. Meier, Magnetic Resonance in Chemistry, 51 (2013) 16-18.

[6] N.A. Hamdy, W.M. El-Senousy, Acta Pol Pharm, 70 (2013) 99-110.

[7] M.A. El-Borai, H.F. Rizk, D.M. Beltagy, I.Y. El-Deeb, Eur J Med Chem, 66 (2013) 415-422.

[8] D.X. Xiang, X.Q. Xin, X. Liu, R. Zhang, J.M. Yang, D.W. Dong, Org Lett, 14 (2012) 644-647.

[9] A.S. Shawali, Arkivoc, (2012) 383-431.

[10] J. Zimmermann, E. Buchdunger, H. Mett, T. Meyer, N.B. Lydon, P. Traxler, Bioorg Med Chem Lett, 6 (1996) 1221-1226.

[11] D.T.W. Chu, P.B. Fernandes, A.K. Claiborne, E. Pihuleac, C.W. Nordeen, R.E. Maleczka, A.G. Pernet, J Med Chem, 28 (1985) 1558-1564.

[12] A.K. Pleier, E. Herdtweck, S.A. Mason, W.R. Thiel, Eur J Org Chem, (2003) 499-506.

[13] P. Simunek, V. Bertolasi, A. Lycka, V. Machacek, Org Biomol Chem, 1 (2003) 3250-3256.

[14] P. Simunek, V. Bertolasi, M. Peskova, V. Machacek, A. Lycka, Org Biomol Chem, 3 (2005) 1217-1226.

[15] Y.C. Shi, Y.Y. Hu, J Coord Chem, 62 (2009) 1302-1312.

[16] P. Simunek, M. Svobodova, V. Bertolasi, L. Pretto, A. Lycka, V. Machacek, New J Chem, 31 (2007) 429-438.

[17] I. Yokoe, K. Maruyama, Y. Sugita, T. Harashida, Y. Shirataki, Chem Pharm Bull, 42 (1994) 1697-1699.

Legends

Figure 1. Geometrical and conformational isomers of 3-(dimethylamino)-1-(2′-hydroxyphenyl)prop-2-en-1-one

Figure 2. Variable temperature (VT) NMR spectra: Full screen (a) and expanded spectra around 3.4 ppm (c) in ^{1}H NMR of temperature control, and full screen (b) and expanded spectra around 40 ppm (d) in ^{13}C NMR of temperature control

Figure 3. Crystal structure of *(E)*-1-(2′-hydroxyphenyl)-3-(piperidin-1-yl)-prop-2-en-1-one (**6**). Selected bond lengths [Å] and angles [deg]; N(1)-C(7) 1.327Å, N(1)-C(6) 1.470Å, N(1)-C(2) 1.470Å, C(16)-O(17) 1.349Å, C(16)-O(17)-H(17) 102.5°, O(10)-H(17) 1.666Å (est).

Figure 4. The packing diagram of compound **6**

Figure 5. Crystal structure of *(E)*-1-(2′-hydroxyphenyl)-3-(pyrrolidin-1-yl)-prop-2-en-1-one (**9**). Selected bond lengths [Å] and angles [deg]; N(1)-C(6) 1.309Å, N(1)-C(5) 1.461Å, N(1)-C(2) 1.463Å, C(15)-O(16) 1.347Å, C(15)-O(16)-H(16) 107.4 °, O(9)-H(16) 1.572Å (est).

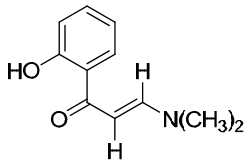
Figure 6. The packing diagram of compound **9**

Scheme 1. Synthesis of (*E*)-3′-hydroxyphenylenaminones

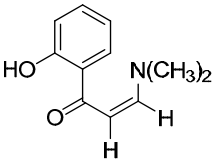
Scheme 2. Synthesis of (*E*)-2′-hydroxyphenylenaminones

Table 1. Crystal and structure refinement for compounds **6** and **9**

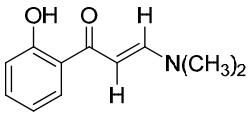
Figure 1.



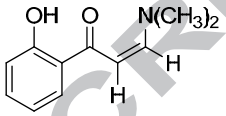
(E) **-s-*trans***



(Z)*-s-*trans



(E)*-s-*cis



(Z)*-s-*cis

Figure 2.

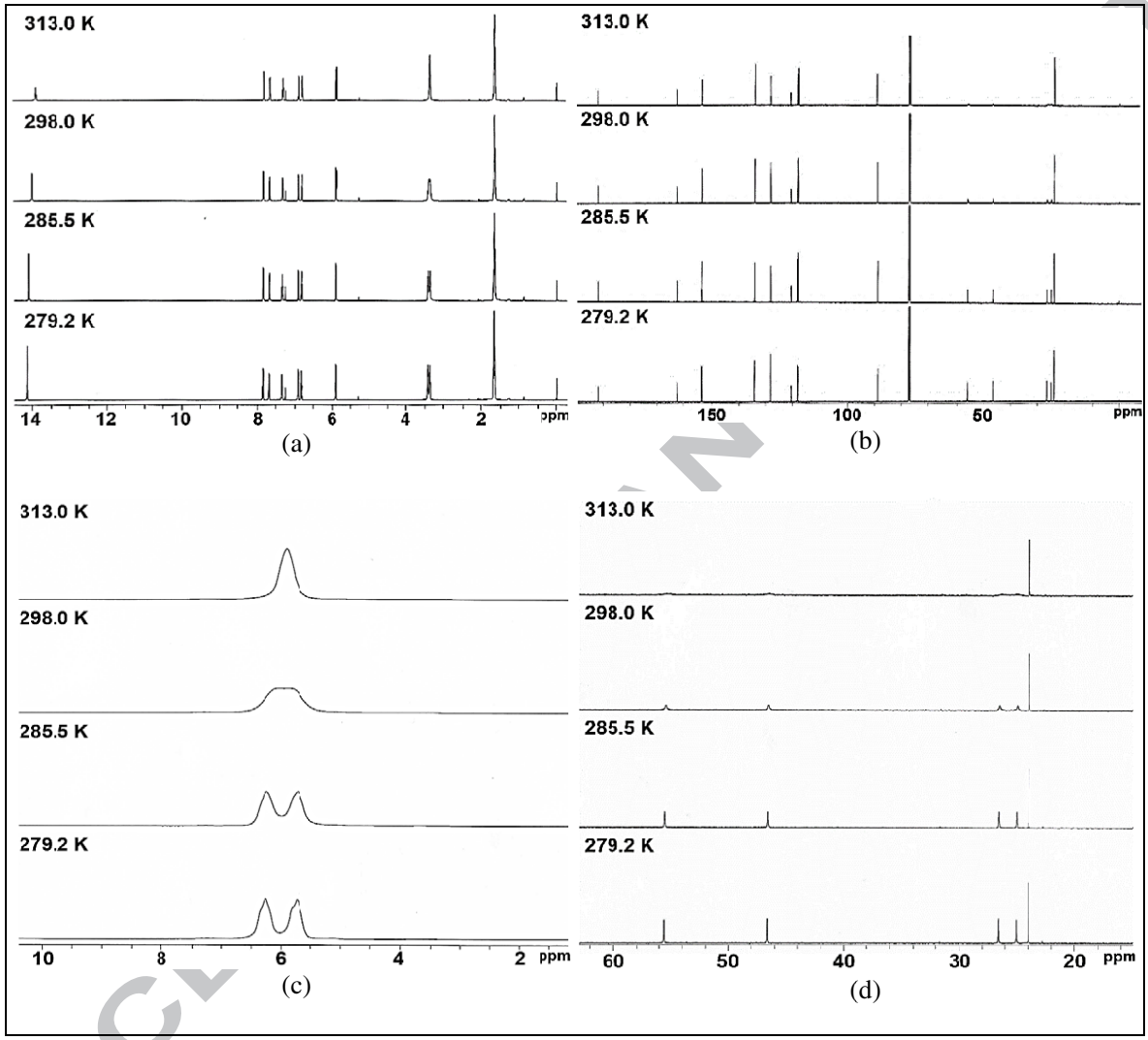


Figure 3.

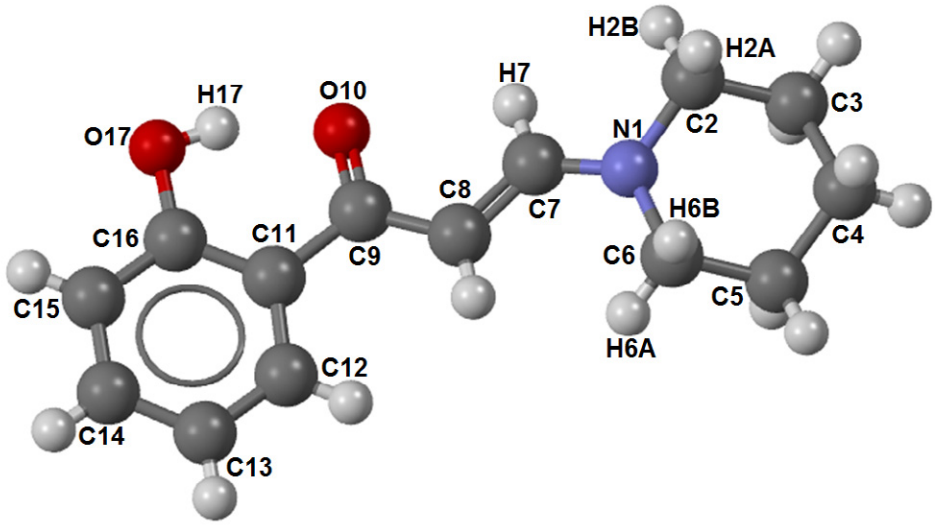


Figure 4.

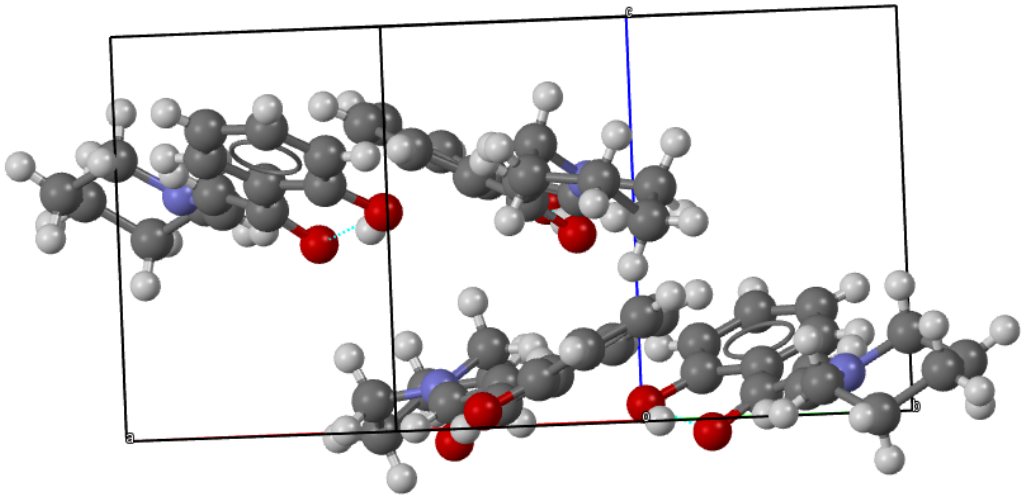


Figure 5.

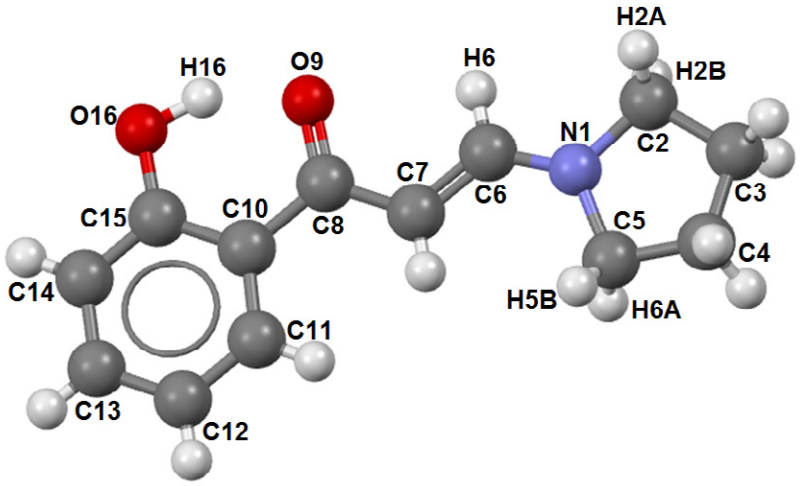
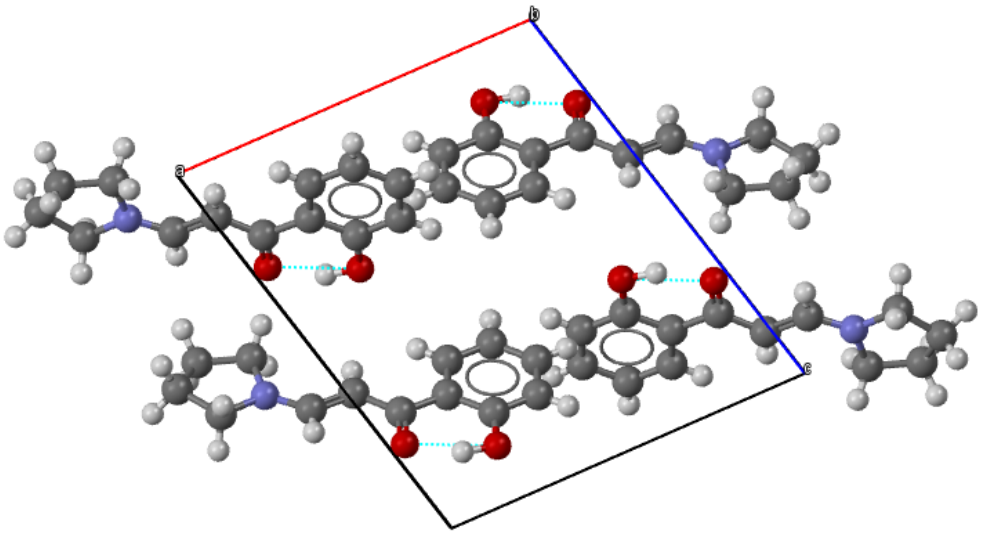
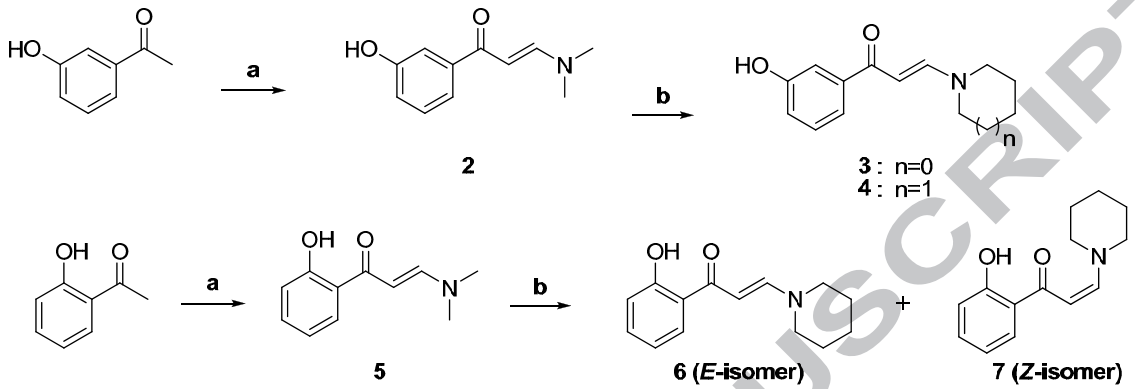


Figure 6.

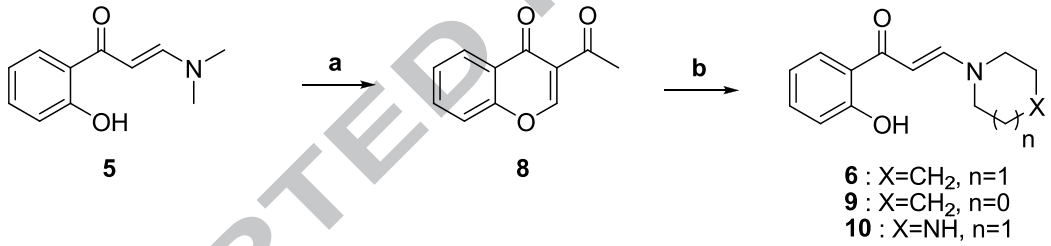


Scheme 1.



Reagents and conditions: (a) DMF-DMA, xylene, reflux, 12 hr; (b) piperidine/pyrrolidine, AcOH, EtOH, reflux, 3 hr

Scheme 2.

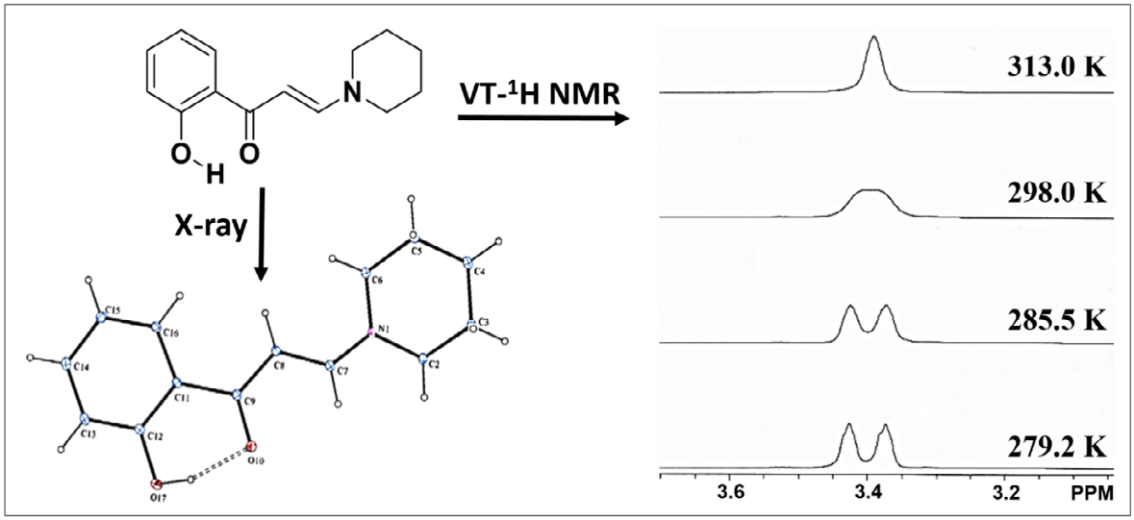


Reagents and conditions: (a) acetic anhydride, pyridine, reflux, 4 hr; (b) amines, chloroform, reflux, 6 hr

Table 1.

Compound	**6**	**9**
Empirical formula	$C_{14}H_{17}NO_2$	$C_{13}H_{15}NO_2$
Formula weight	231.28	217.26
Temperature (K)	173(2)	296 (2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic
Space group	$Pna2_1$	$P2_1/c$
Unit cell dimensions (Å), (°)	a = 10.9878(2) , α = 90.000 b = 13.5883(4) , β= 90.000 c = 7.9410(10) , γ = 90.000	a = 10.3245(16), α = 90.000 b = 9.4867(14) , β= 104.257(2) c = 11.9731(19) , γ = 90.000
Volume ($Å^3$)	1185.64(4)	1136.6(3)
Z, Calculated density (mg m^{-3})	4, 1.296	4, 1.270
Absorption coefficient (mm^{-1})	0.086	0.086
Crystal size	0.23 x 0.22 x 0.22 mm	0.23 x 0.22 x 0.20 mm
Theta range for data collection	2.384 to 28.309 deg.	2.035 to 28.274 deg.
Limiting indices	-14 ≤ h ≤ 14, -18 ≤ k ≤ 18, -10 ≤ l ≤ 10	-13 ≤ h ≤ 13, -12 ≤ k ≤ 12, -15 ≤ l ≤ 15
Reflections collected / unique	30904 / 2954 [R(int) = 0.0412]	17102 / 2818 [R(int) = 0.0324]
Completeness to theta = 25.242	100.0 %	100.0 %
Final R indices [I>2 sigma(I)]	R1 = 0.0323, wR2 = 0.0851	R1 = 0.0688, wR2 = 0.1916

Graphical abstract



Highlights

- (E)-Selective synthesis of 3-(piperidinyl)-1-(2′-hydroxyphenyl)-prop-2-en-1-one.
- 3D structure determination of the compound by X-ray diffraction.
- Spectroscopic characterization of the compounds by 1D and 2D NMR.
- Flexible rotation of the compound along the C-N bond explained by VT-NMR studie s.