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A Facile Synthesis of Squamosamide Cyclic Analogs

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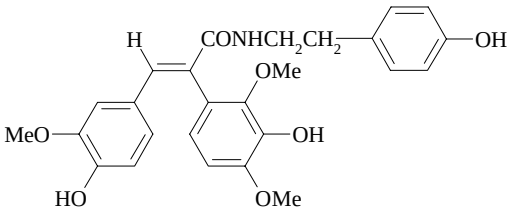
Abstract: A series of novel cyclic derivatives have been synthesized by utilizing a nickel powder mediated radical cyclization as the key step. The structures of the new compounds were confirmed by ^{1}H-NMR and MS.

Keywords: Squamosamide, radical cyclization, synthesis.

Squamosamide **I**, a potentially bioactive new compound, was isolated from *Annona squamosa*[1]. The total synthesis of squamosamide and its analogues had been accomplished in our group[2]. Some of them show good anti-oxidant and nerve growth factor enhancing activity, and are expected to be useful in treatment or prevention of degenerative nervous system disorders such as senile dementia and Alzheimer's disease. In order to find better bioactive compounds for structure-activity-relationship studies, we designed a series of new cyclic derivatives. An effective synthetic path has been explored to obtain these compounds as shown in **Scheme 1**.



Squamosamide **I**

Passing hydrogen chloride gas to a solution of *p*-hydroxyphenylacetic acid in methanol gave compound **2**. Compound **2** was treated with anhydrous K_2CO_3 and benzyl bromide in DMF to form compound **3**. Compound **3** was hydrolyzed by potassium hydroxide to give compound **4** in 77% yield. Condensation of **4** and *p*-methoxy aniline in the presence of DCC in dichloromethane gave compound **5** in 68% yield. **5** was reduced by borane-methyl sulfide in THF to give compound **6**. **6** condensed with trichloroacetic acid by DCC in CH_2Cl_2 to generate compound **7** in 65%

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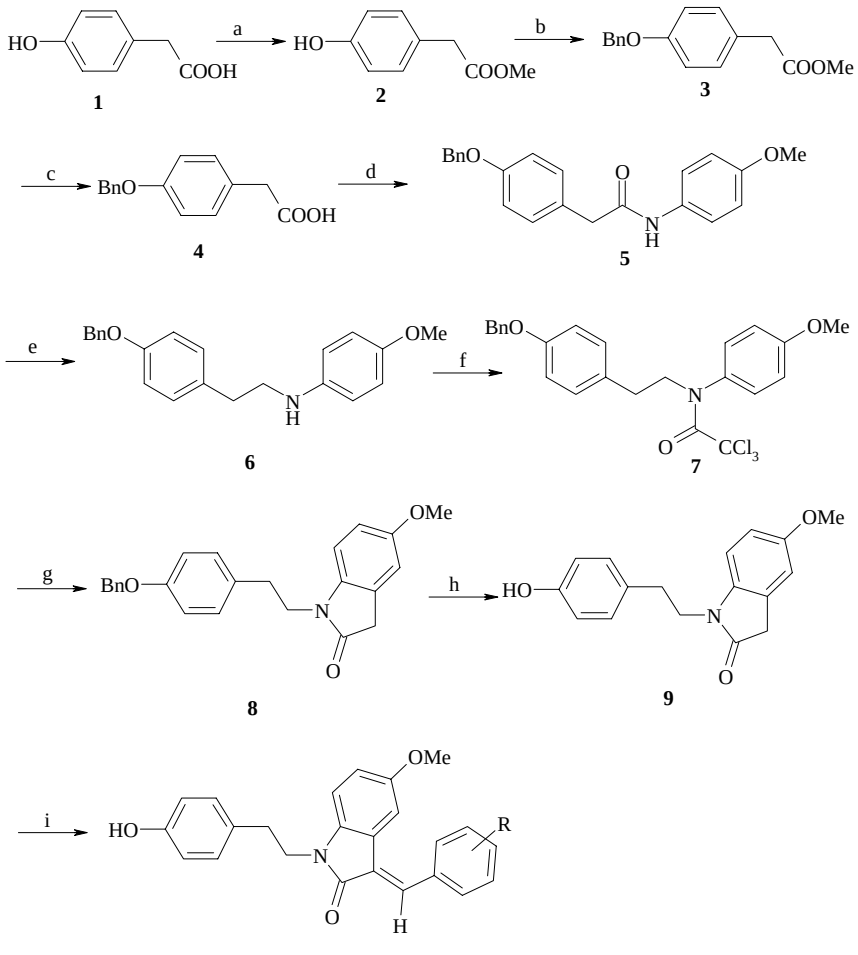
yield. In the presence of excessive Ni powder and acetic acid, **7** was cyclized to form 1-*O*-phenylethyl-6-methoxy-2H-indol-2-one **8,** which was the key intermediate, in 64% yield[3]. The debenzylation of **8** by H_2/Pd-C in ethanol gave compound **9** in 90% yield. Aldol condensation of **9** and aldehydes gave a series of 2H-indol-2-one derivatives. The structures of the target compounds and the main intermediates were determined by ^{1}H-NMR and MS.

Scheme 1



Reagents and conditions: a) HCl/CH_3OH; b) K_2CO_3, BnBr, DMF; c) KOH/H_2O; d) *p*-methoxy aniline, DCC, CH_2Cl_2; e) $BH_3 \bullet (CH_3)_2S$, THF; f) CCl_3COOH, DCC, CH_2Cl_2; g) Ni, HOAc, *i*-propanol; h) H_2, Pd-C, ethanol; i) piperridine, R-CHO, ethanol.

Table 1 Chemical structures and physical data of the compounds **10-14**

compound	R	configuration	Yield(%)
10	4″-methoxyl	E	80.0
11	3″,4″-methylenedioxy	E	87.6
12	4″-isopropyl	E	65.0
13	3″, 5”-dimethoxyl	E	72.4
14	2″, 4″, 5″-trimethoxyl	E	73.6

Acknowledgment

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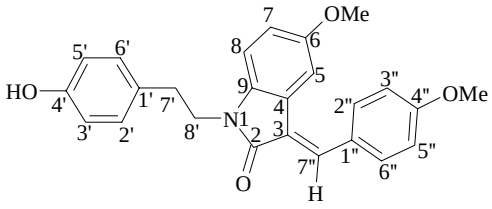
References and Notes

1. X. J. Yang, L. Z. Xu, N. J. Sun, S. C. Wang, Q. T. Zheng, *Acta Pharma. Sinica*, **1992**, *27* (3), 185.
2. X.S. Ji, X. T. Liang, *Chin. Chem. Lett.*, **1993**, *4* (4), 297.
3. J. Boivin, M. Yousfi, S. Z. Zard, *Tetrahedron Lett.*, **1994**, *35* (31), 5629.
4. Selected data of compounds: **7**. White solid, mp 98-100°C, ^{1}H-NMR(300Hz, $CDCl_3$, δppm, J Hz), 7.44-6.88 (m, 13H), 5.04 (s, 2H), 3.90 (br., 2H), 3.83 (s, 3H), 2.91 (t, 2H, J=8.1Hz). **8**. ^{1}H-NMR(300Hz, $CDCl_3$, δppm, JHz), 7.44-6.66 (m, 12H), 5.04 (s, 2H), 3.87 (t, 2H, J=7.6H), 3.79 (s, 3H), 3.48 (s, 2H), 2.89 (t, 2H, J=7.6Hz). EI-Ms *m/z* (%): 373 (62), 176 (62), 163 (77), 148 (88), 91 (100). **10**. Orange solid, mp 210-210°C, ^{1}H-NMR(300Hz, DMSO, δppm, JHz), 9.14 (s, 1H, -OH), 7.69 (d, 2H, J=9Hz, H-2″, H-6″), 7.61(s, 1H, H-7″), 7.23 (d, 1H, J=2.4Hz, H-5), 7.09 (d, 2H, J=8.7Hz, H-3″, H-5″), 7.02 (d, 2H, J=7.2Hz, H-2′, H-6′), 6.96 (d, 1H, J=8.4Hz, H-8), 6.85 (dd, 1H, J_1=8.4Hz, J_2=2.4Hz, H-7), 6.63 (d, 2H, J=8.1Hz, H-3′, H-5′), 3.86-3.64 (m, 8H, 2xOCH_3, H-8′), 2.76 (t, 2H, J=7.5Hz, H-7′). EI-Ms *m/z* (%): 401 (30), 294 (100), 66 (65).
5. The configuration of compounds was confirmed by NOE. For example, When irradiating H-7″ (7.61 ppm) of **10**, H-5 (7.23ppm) had no NOE enhancement, and When irradiating H-2″ and H-6″ (7.69ppm) of **10**, H-7″ (7.611 ppm), H-5 (7.23ppm) and H-3″, H-5″ (7.09ppm) had NOE enhancement. So **10** has E configuration as shown in **Figure 1**.

Figure 1



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