AN ABSTRACT OF THE THESIS OF

Yuelong Ma for the degree of Master of Science in Chemistry presented on August 24, 2006.

Title: Synthetic Studies on Indolic Enamide Natural Products: 1. Total Syntheses of Coscinamide A, Concinamide B and Igzamide. 2. Synthetic Studies towards the Synthesis of Halocyamine B

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Abstract approved: _____

Kevin P. Gable

The 3-substituded indolic enamide moiety has been found in many marine compounds over the past 20 years. These indolic enamides exhibit various biological properties such as cytotoxic, anthelmintic, antimicrobial and HIV-inhibitory activities. Among these indolic enamides, some are (*E*)-enamides, like coscinamide A and coscinamide B, others are (*Z*)-configuration in their natural form, like igzamide and halocyamine B.

A general method to selectively construct (*E*)- and (*Z*)-indolic enamides was devised through an hydroxyl amide formed from amino alcohol followed by a thermally assisted dehydration as the key step. Solvent effects were tested for the dehydration reaction. (*Z*)-Indolic enamides could be obtained in a moderate yield with xylene as the solvent for the dehydration reaction. (*E*)-Indolic enamides were the main products with *N*, *N*-dimethylformamide as the solvent.

Total syntheses of three indolic enamides: coscinamide A, coscinamide B and igzamide have been described. The (*E*)- or (*Z*)-isomers of these natural compounds were obtained during the syntheses as well. A synthetic study of halocyamine B is also reported in this thesis.

Synthetic Studies on Indolic Enamide Natural Products: 1. Total Syntheses of Coscinamide A, Concinamide B and Igzamide. 2. Synthetic Studies towards the Synthesis of Halocyamine B

by
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APPROVED:

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Major Professor, representing Chemistry

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Yuelong Ma, Author

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TABLE OF CONTENTS

SYNTHETIC STUDIES ON INDOLIC ENAMIDE NATURAL PRODUCTS: 1. TOTAL SYNTHESES OF COSCINAMIDE A, CONCINAMIDE B AND IGZAMIDE. 2. SYNTHETIC STUDIES TOWARD THE SYNTHESIS OF HALOCYAMINE B

CHAPTER 1. INTRODUCTION

The marine environment, covering 70% of the earth's surface and 95% of its tropical biosphere, provides a fascinating variety of biodiversity. The molecular diversity produced by marine organisms is unprecedented. One important aspect is that marine products can incorporate elements like bromine that are not readily available to terrestrial species.[1] The research of marine products in various areas including chemistry, physiology, pharmacology and medicine attracts worldwide attention.

Indolic enamides represent a group of indole-based alkaloids which are extracted from marine organisms, including sponges, tunicates, red alga, acorn worms, and symbiotic bacteria, etc. Natural indolic enamides exhibit various biological properties, such as cytotoxic, anthelmintic, antimicrobial and HIV-inhibitory activities.[2-10] The representative structure of an indolic enamide is shown in Figure 1.1. Most of the natural indolic enamides are 3-substituted enamides. They could have substitutions, like halogens or hydroxyl groups on the indole ring which brings structural variety to these natural products. Some of the natural products are (*E*)-enamides, like coscinamide A, B, C,[2] chondriamide A, B[3] and aspergillamide B[4]. Others are (*Z*)-enamides in their natural form, like igzamide[5], terpeptin[6], aspergillamide A[4] and halocyamine A, B[7]. (Figure **1.2**)

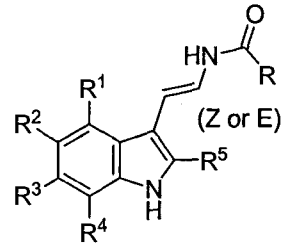
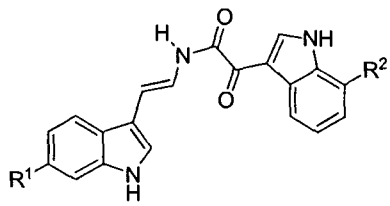
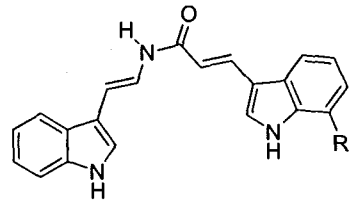


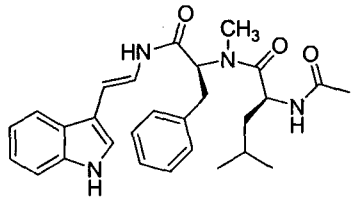
Figure 1.1 A representative structure for indolic enamide



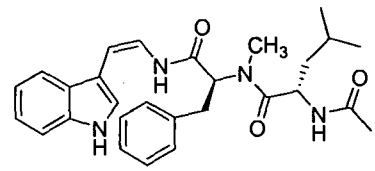
R^1 = Br, R^2 = H Coscinamide A
R^1 = R^2 = H Coscinamide B
R^1 = Br, R^2 = OH Coscinamide C



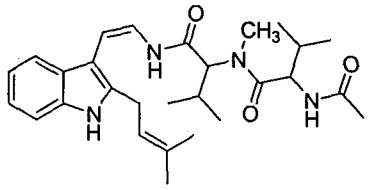
R = H Chondriamide A
R = OH Chondriamide B



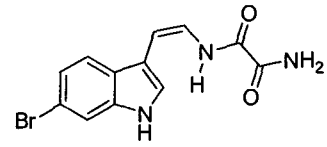
Aspergillamide B



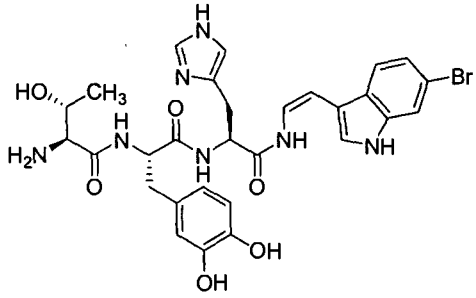
Aspergillamide A



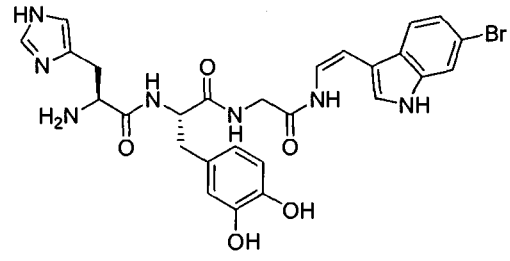
Terpeptin



Igzamide



Halocyamine B



Halocyamine A

Figure 1.2 Indolic enamides

Among these indolic enamides, coscinamides and chondriamides are bis-indolic natural products which are quite rare in nature.[8] Terpeptin, aspergillamides and halocyamines are polypeptide-like substances. Due to the significant activity that they have elicited in cancer or cytotoxicity assays, great interdisciplinary attention has been paid on the structure elucidation, synthesis, and pharmacology of indolic enamides recently.

Coscinamide A, B and C were first reported by Boyd, et al. in 2000.[2] Coscinamides were isolated from an extract of marine sponge *Coscinoderma* sp. in Papua, New Guinea and their structure was determined from spectroscopic techniques. The pure coscinamides have been reported to exhibit partial cytoprotection against HIV in the NCI assay.

Igzamide, a brominated tryptamine derivative, was isolated in 1993 by Andersen and co-workers from the extract of the sponge *Plocamissa igzo* at Anthony Island, B.C.[5] Structure elucidation was accomplished by spectroscopic analysis. Igzamide showed very weak cytotoxicity against L1210 (ED_{50} 19 μg/mL) murine leukemia cell line.

Halocyamine A and halocyamine B were isolated from *Halocynthia roretzi* by Yokosawa and co-workers in 1990.[7] The peptide composition and sequence were determined by amino acid analyzer and automatic protein sequencer together with spectroscopic techniques. Both halocyamines showed antimicrobial activities against several kinds of bacteria and yeast together with cytotoxic activities against neural cells cultured from rat fetal brain, mouse neuroblastoma N-18 cells, and human hepatoma Hep-G2 cells.

Chondriamide A and B were first isolated from red alga *Chondria* by Seldes and co-workers.[3] The structures of chondriamides were determined by spectroscopic data. Chondriamide A and B have moderate cytotoxicity activity against LOVO cells (colon cancer) besides antiviral and antifungal activity. Manta also isolated these two indolic enamides together with other indole derivatives in 1998 and reported that they showed moderate anthelmintic activity (EC_{80} value of chondriamide A: 0.26 mM).[9]

Terpeptin was isolated from the cultured broth of *Aspergillus terreus* 95F-1, which was extracted from a soil sample collected at Naha city, Okinawa, Japan.[6]

Terpeptin's skeleton was elucidated by spectral analyses. It was reported to have cell cycle inhibitory activity with a minimum inhibitory concentration of 62.5 μM.

Aspergillamide A and B are two isomeric linear peptides which were isolated from mycelium of a cultured marine fungus of the genus *Aspergillus*. This fungus was grown in static culture in a seawater-based fermentation medium in a saline lake on Acklins Island, the Bahamas. The structure was determined by comprehensive 2D NMR methods. Aspergillamide A showed modest in vitro cytotoxicity toward the human colon carcinoma cell line HCT-116 (IC_{50} = 16 μg/mL).[4]

Reference:

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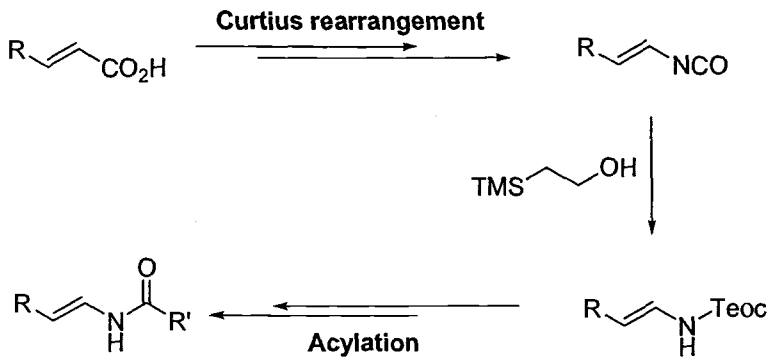
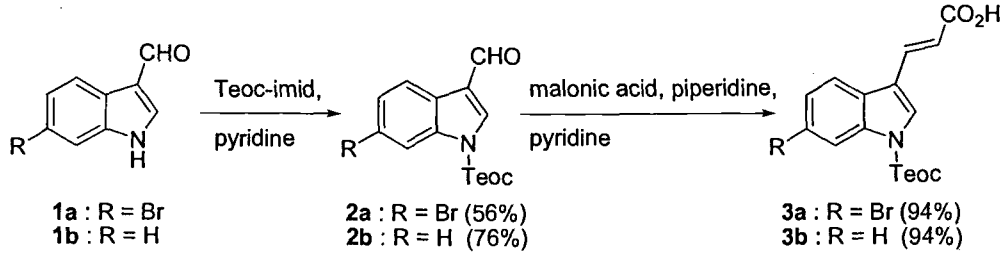
CHAPTER 2. BACKGROUND

Although enamides are a common functional group that has been studied extensively as synthons in organic synthesis, synthetic studies of the stereoselective construction of indolic enamides, especially (*Z*)-indolic enamides are scarce. [1a] There are only several methods for the construction of indolic enamides which have been reported, including three stereo-selective syntheses of (*E*)-indolic enamides and one selective synthesis of (*Z*)-indolic emanides. Kitahara reported the syntheses of several (*E*)-indolic enamides using an aldol/Curtius rearrangement approach.[1] Benhida synthesized (*E*)-indolic enamide aspergillamide B via an acid catalyzed dehydration reaction.[2] Chakrabarty reported the synthesis of (*E*)-indolic enamide coscinamide B through a bromination-dehydrobromination sequence.[3] An oxidative decarboxylation-elimination procedure was reported by Porco to construct (*Z*)-indolic enamides.[4]

Kitahara reported the first total syntheses of coscinamide A and coscinamide B based on the Curtius rearrangement and acylation of alkenylcarbamates (Scheme 2.1).[1] This methodology also has been used in the total synthesis of (+)-salicylihalamide by Smith III[5] and (+)-crocacin D by Rizzacasa[6]. The (*E*)-alkene moiety in the indolic enamide was obtained from indolylacrylic acid which was prepared from an aldol reaction between an indolic aldehyde and malonic acid.



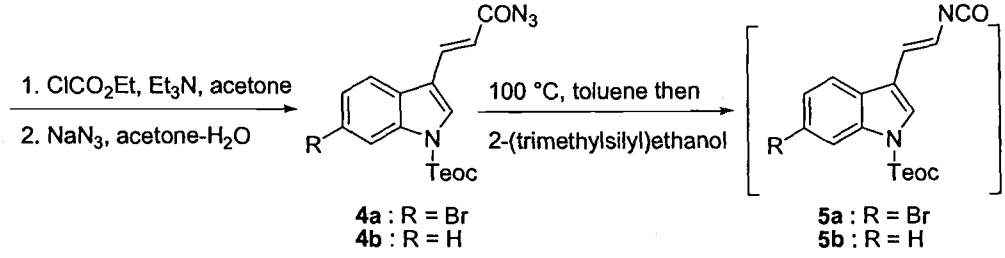
Scheme 2.1



1a : R = Br
1b : R = H

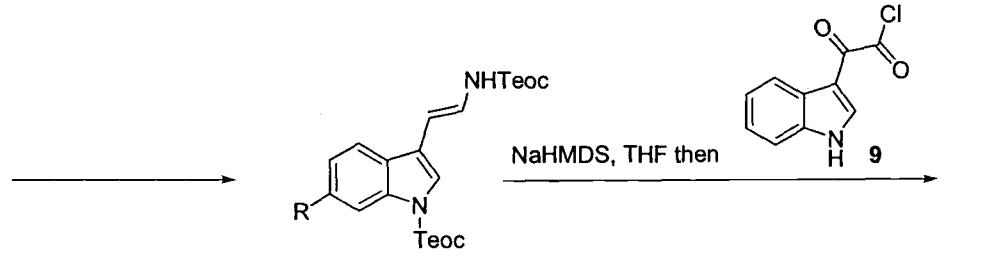
2a : R = Br (56%)
2b : R = H (76%)

3a : R = Br (94%)
3b : R = H (94%)

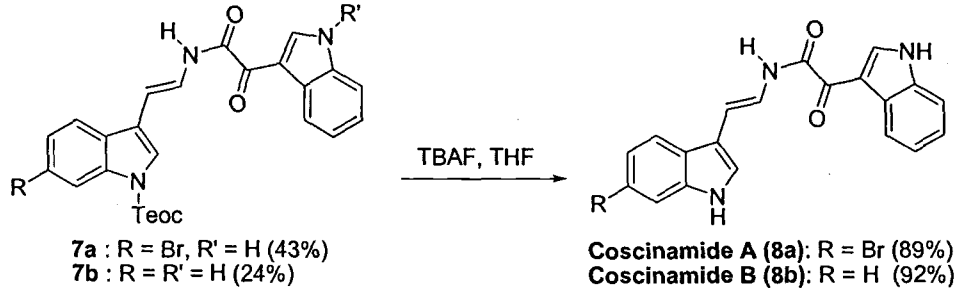


4a : R = Br
4b : R = H

5a : R = Br
5b : R = H



6a : R = Br (84% in 3 steps)
6b : R = H (85% in 3 steps)

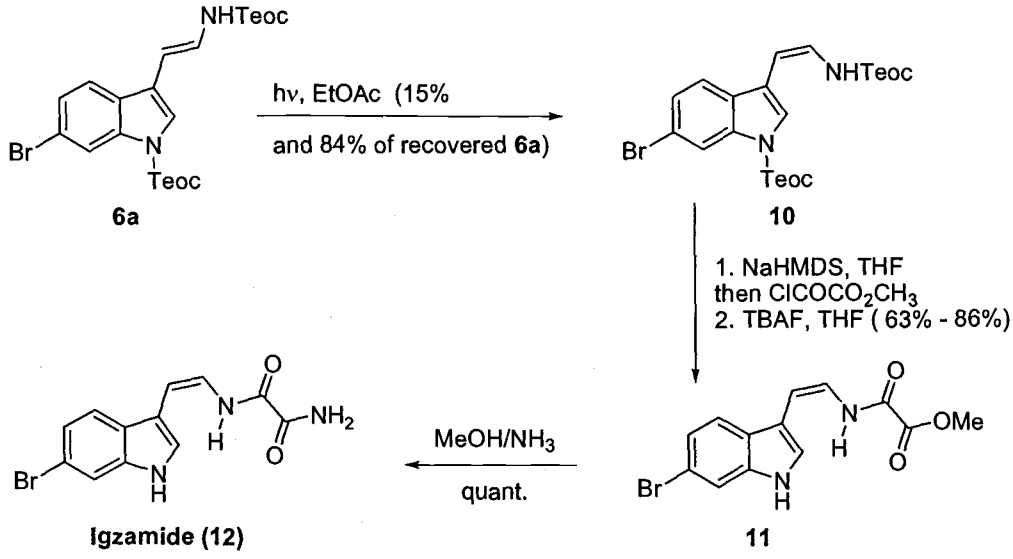


7a : R = Br, R' = H (43%)
7b : R = R' = H (24%)

Coscinamide A (8a): R = Br (89%)
Coscinamide B (8b): R = H (92%)

Scheme 2.2 Kitahara's syntheses of coscinamide A and B

Kitahara's syntheses of coscinamide B was initiated from indole-3-carbaldehyde **1b**. Protection **1b** with Teoc group and condensation with malonic acid provided (*E*)-N-Teoc-3-indole-acrylic acid **2b** which contains the (*E*)-alkene moiety. Acid **3b** was transformed to acyl azide **4b** by a two-step protocol. Following thermal decomposition of the azide **4b**, the resulting isocyanate **5b** was trapped with 2-(trimethyl-silyl)ethanol *in situ* to give *N*-Teoc-alkenylcarbamate **6b**. Treatment of **6b** with NaHMDS followed by addition of 3-indole-glyoxyl chloride **9** gave **7b** after which deprotection of the Teoc group using TBAF afforded coscinamide B (**8b**). Coscinamide A (**8a**) was prepared via the same methodology from 6-bromoindole-3-carboaldehyde **1a**. (Scheme 2.2)

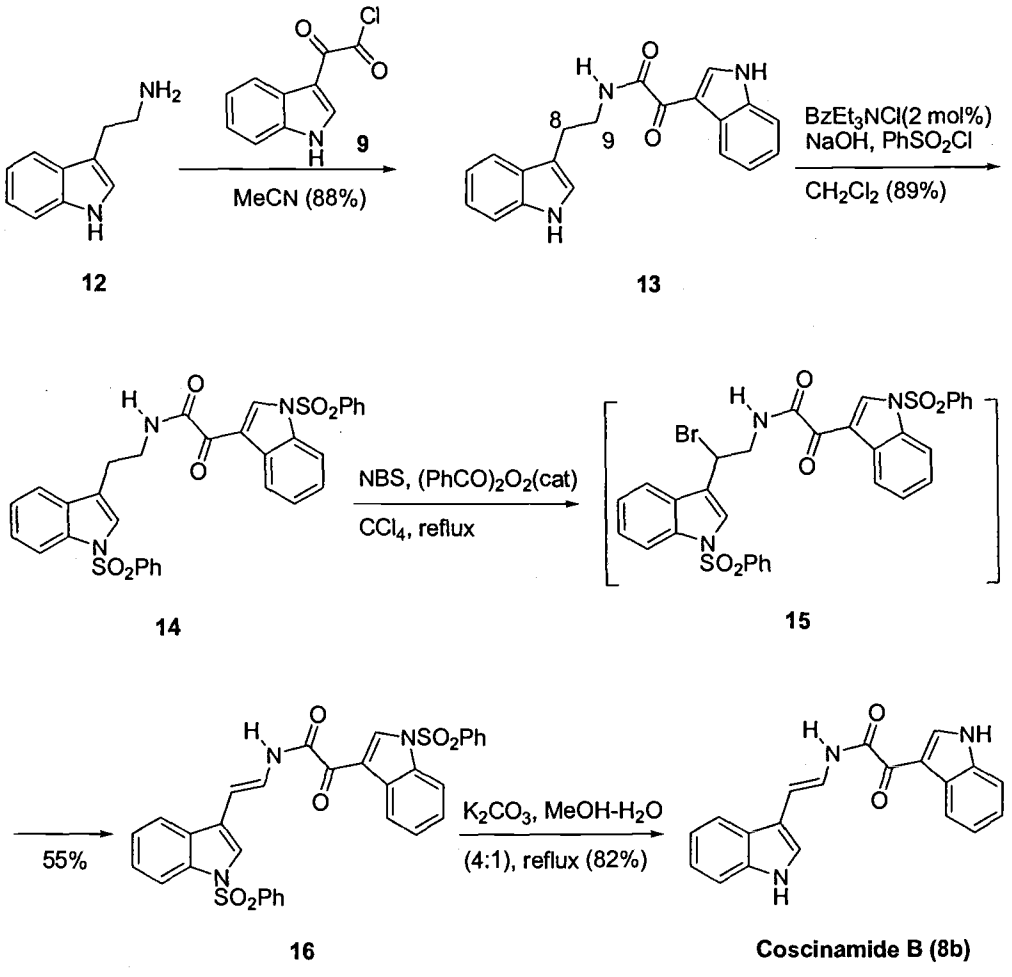


Scheme 2.3 Kitahara's synthesis of igzamide

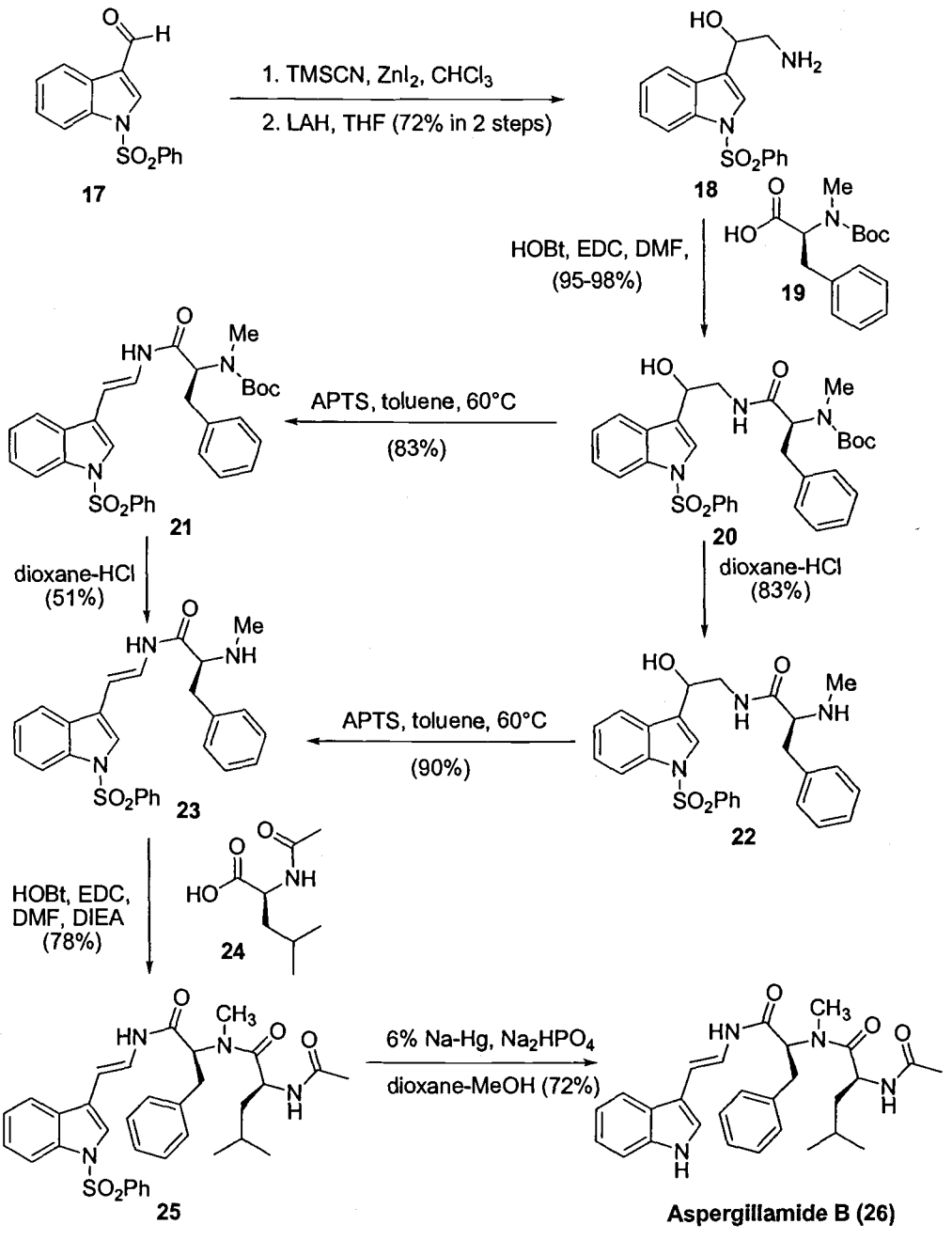
Kitahara obtained the (*Z*)-alkene moiety, although not directly, by photoisomerization of (*E*)-isomer in the synthesis of igzamide (Scheme 2.3).[1a] Starting from the *N*-Teoc-alkenylcarbamate **6a**, (Z)-enecarbamate **10** was generated via photoisomerization in 15% yield with 84% recovery of **6a**. Condensation of **10** with methyl chlorooxoacetate under the treatment with NaHMDS in THF followed by cleavage of Teoc group afforded **11**. Finally, treatment of **11** with MeOH-liq. NH_3 (1 : 1) gave igzamide (**12**) with a quantitative yield.

The syntheses of chondriamide A and chondriamide C were also reported by Kitahara using the same methodology.[1a]

Another synthesis of coscinamide B was reported by Chakrabarty in 2003 using a one-pot benzylic bromination and subsequent *in situ* dehydrobromination reaction (Scheme 2.4).[3] Condensation of tryptamine **12** with 3-indole-glyoxyl chloride **9** afforded **13**. Then the corresponding derivative *N,N'*-bis (benzenesulfonyl) **14** was refluxed with NBS in the presence of a catalytic amount of benzoyl peroxide which provided *N,N'*-bis(benzenesulfonyl) coscinamide B (**16**). Sulfonamide **16** was believed to originate via intermediate 8-bromodihydro derivative **15**. Hydrolysis of *N, N'*- bis(benzenesulfonyl) coscinamide B (**16**) furnished coscinamide B (**8b**).



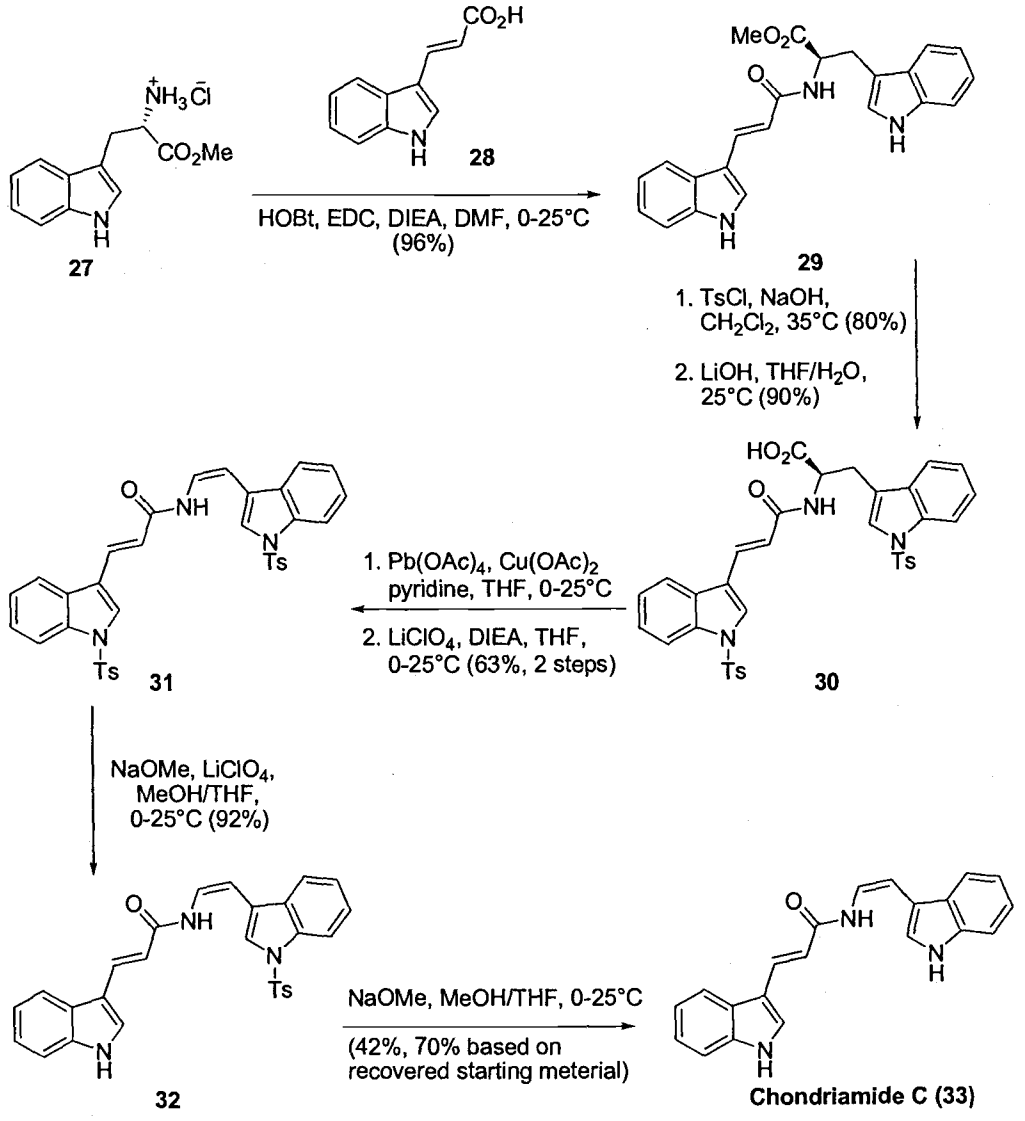
Scheme 2.4 Chakrabarty's synthesis of coscinamide B



Scheme 2.5 Benhida's synthesis of aspergillamide B

Benhida reported the selective synthesis of (*E*)-indolic enamide, aspergillamide B (**26**) (Scheme 2.5).[2] The key step in this strategy is the acid catalyzed dehydration reaction. Treatment of aldehyde **17** with TMSCN and ZnI_2 generated the cyanohydrin intermediate. Subsequent reduction with $LiAlH_4$

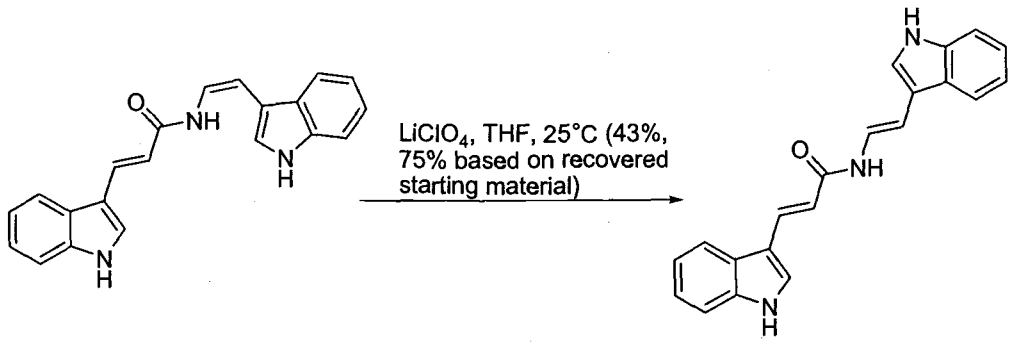
provided compound **18**. Next, the coupling of aminoalcohol **18** with *N*-Boc, *N*-Me-phenylalanine (**19**) gave **20**. Then a two-step sequence either began with the dehydration reaction under acidic treatment (8-aminopyrene-1,3,6-trisulfonic acid(APTS)-toluene) followed by removal of Boc-protection group or vice versa and provided (*E*)-indolic enamide product **23**. The coupling of **23** with *N*-acetyl-leucine (**24**) yielded the protected aspergillamide B (**25**). The benzenesulfonyl group was removed by treatment with Na-Hg to provide aspergillamide B (**26**).



Scheme 2.6 Porco's synthesis of chondriamide C

Porco reported the selective syntheses of several (*Z*)-indolic enamides containing alkaloids via oxidative decarboxylation-elimination procedure. Scheme 2.6 is the synthesis of chondriamide C (**33**).[4a] Tryptophan methyl ester hydrochloride (**27**) was acylated with trans-3-indoleacrylic acid (**28**) to afford 3-indole-acryltryptophan methyl ester (**29**). Bis tosylation followed by ester hydrolysis produced **30**. Oxidative decarboxylation and elimination of **30** provided compound **31** with a (*Z*) : (*E*) ratio of 14 : 1. Removal of the two tosyl groups stepwise furnished chondriamide C (**33**).

Isomerization of chondriamide C to chondriamide A was also accomplished by Porco under treatment with $LiClO_4$ (Scheme 2.7). The isomerization using $LiClO_4$ requires the existence of both tryptophan and conjugated acrylamide moieties.



Chondriamide C (33) **Chondriamide A (34)**

Scheme 2.7 Porco's synthesis of chondriamide A

Other (*Z*)-indolic enamides such as aspergillamide A and terpeptin were also prepared by this methodology with different selectivities and yields.[4b]

In 2000, Dömling reported the syntheses of a library of aspergillamide analogues using an Ugi multicomponent reaction.[7] This multicomponent reaction gave a mixture of diastereoisomers.

Considering the intriguing biological properties of indolic enamides and the relatively few synthetic methods to these natural products, finding a concise general method to construct indolic enamides, especially (*Z*)-indolic enamides has attracted

our attention. We focused our first synthetic targets on a few representative compounds, bisindolic enamides coscinamide B, its brominated derivative coscinamide A, the brominated tryptamine derivative igzamide and a peptide enamide halocyamine B.

Reference:

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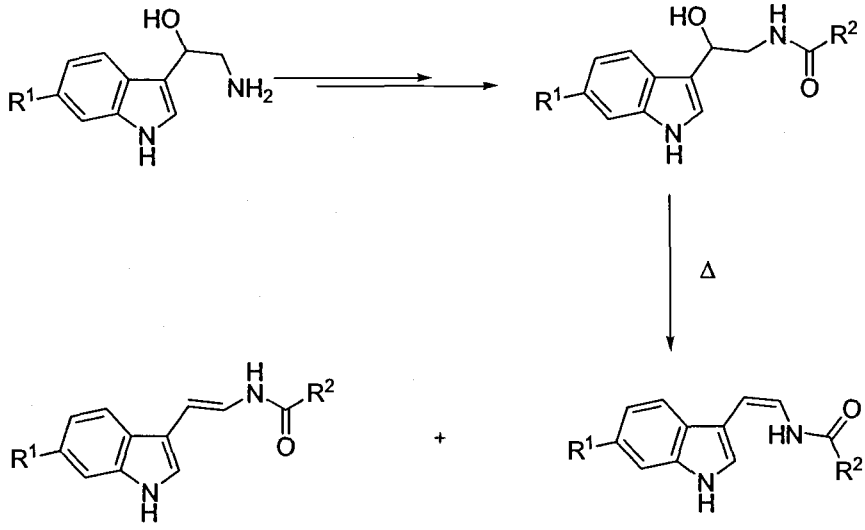
CHAPTER 3. SYNTHETIC STUDIES ON INDOLIC ENAMIDE NATURAL PRODUCT

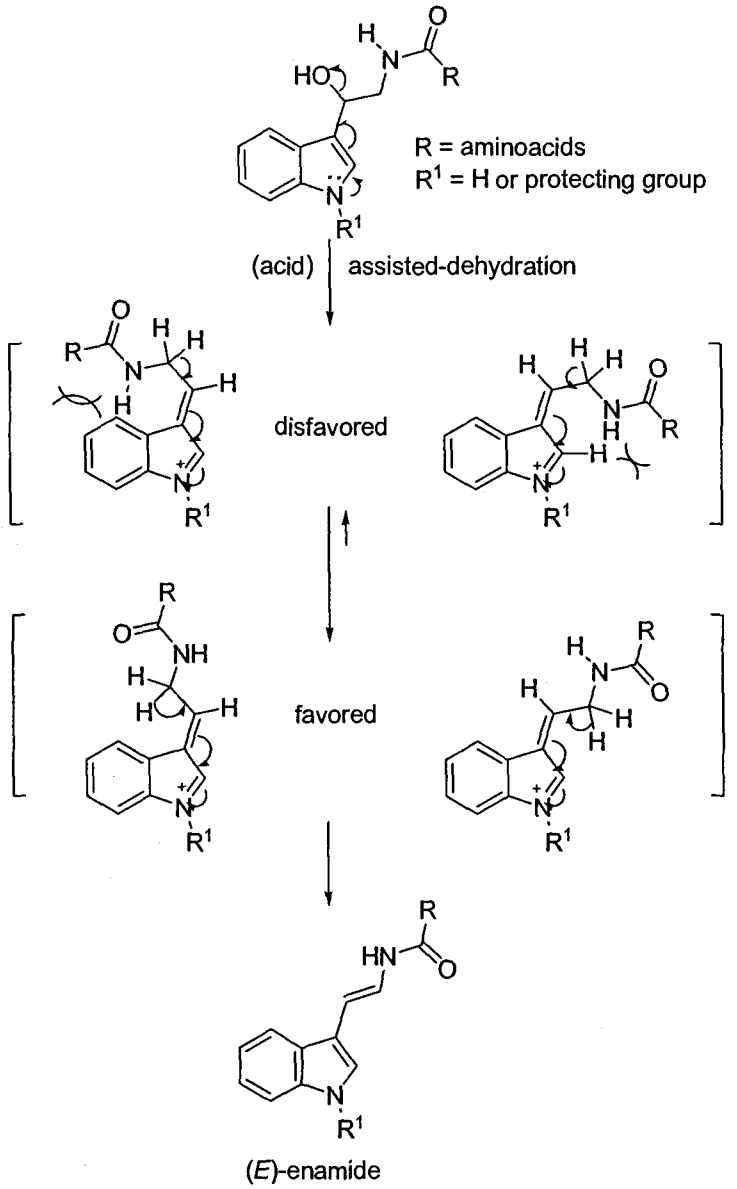
3.1 TOTAL SYNTHESES OF COSCINAMIDE A, CONCINAMIDE B AND IGZAMIDE

Our approach to introduce the (*Z*)- and (*E*)-enamide moieties is outlined in Scheme 3.1. It is based on developing a selective thermally assisted dehydration reaction to generate both (*Z*)- and (*E*)-enamide products. This synthetic strategy is based in part on previous work in our group on the syntheses of tryptamine derivatives. [1,2]



Scheme 3.1 Outline of the synthetic strategy

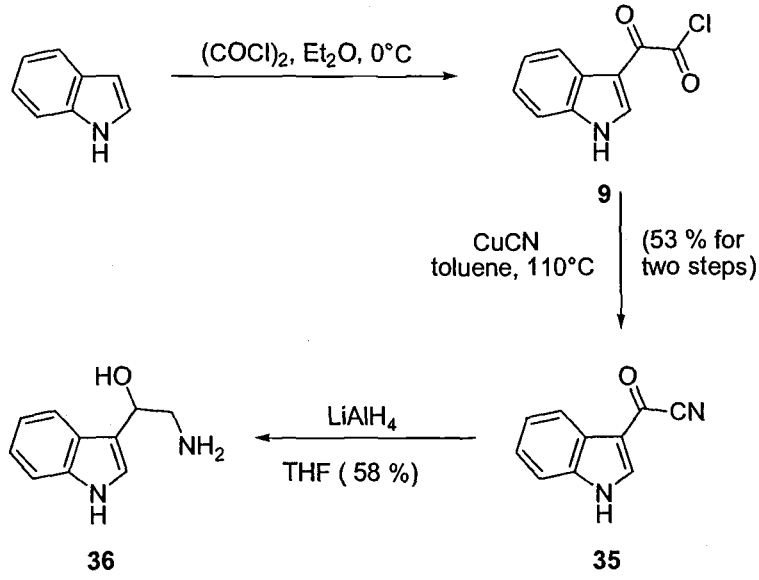
It was proposed by Benhida and co-workers in the synthesis of aspergillamide B that the electron rich indole unit might assist water elimination to provide the enamide moiety.[3] The results of their experiments showed that acid (APTS-toluene) catalyzed elimination reaction can yield the single (*E*)-enamide product without the (*Z*)-isomer in the total synthesis of aspergillamide B (Scheme 3.2). These results suggested that an acid-catalyzed procedure would not be suitable for the formation of (*Z*)-indolic enamides.



Scheme 3.6 The mechanism of elimination reaction proposed by Benhida

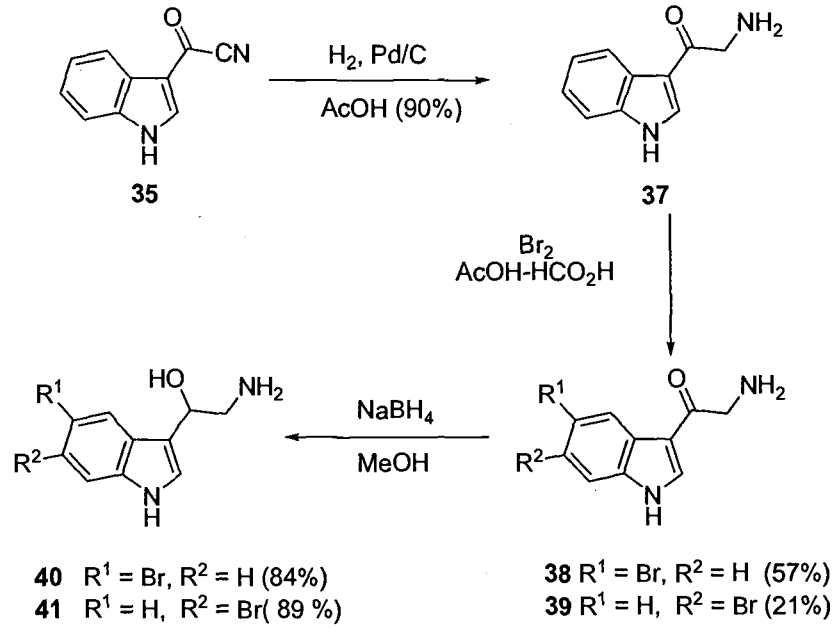
An initial goal of our research work was to determine the relative ratio of the formation of (*E*)- and (*Z*)-isomers under the thermally assisted dehydration reaction conditions through the total syntheses of several natural indolic enamides and their derivatives. Furthermore, we desired to develop a general method to access either (*E*)- or (*Z*)-indolic enamides, selectively. The initial synthetic targets were coscinamide B, coscinamide A, igzamide and halocyamine B.

The syntheses of an appropriate amino alcohol intermediate for the synthesis of coscinamide B is shown in Scheme 3.2. Starting from indole, acyl cyanide **35** was prepared according to the procedure of Hogan and Sainsbury with a moderate yield in a one pot reaction.[4] The 3-indole-glyoxyl chloride **9** could also be isolated with a yield of 95 %[6]. Reduction of acyl cyanide **35** with $LiAlH_4$ gave the amino alcohol **36**.[5]



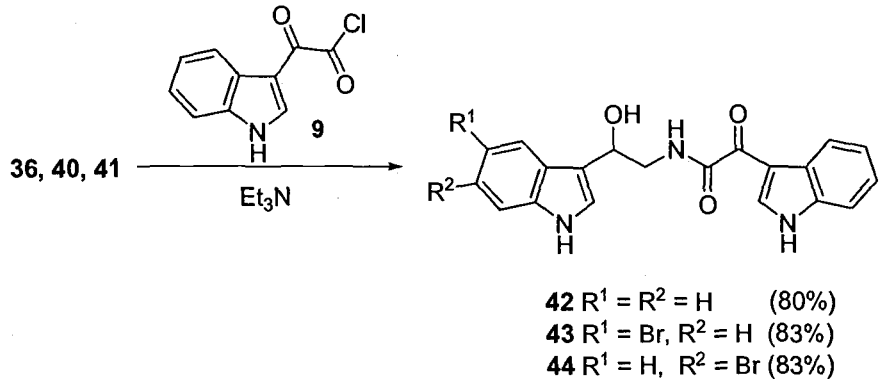
Scheme 3.2

The syntheses of bromo-substituted amino alcohols are shown in Scheme 3.3. Starting from acyl cyanide **35**, hydrogenation over Pd/C gave oxotryptamine **37**.[1] Direct bromination of **37** produced an isomeric mixture of 5- and 6-substituted oxotryptamine derivatives **38** and **39** in an approximate 2:1 ratio, respectively.[1] Brominated oxotryptamines **38** and **39** can be separated by flash chromatography. Further reduction of **38** and **39** by $NaBH_4$ provided 5-substituded amino alcohol **40** and 6-substituded amino alcohol **41**.



Scheme 3.3

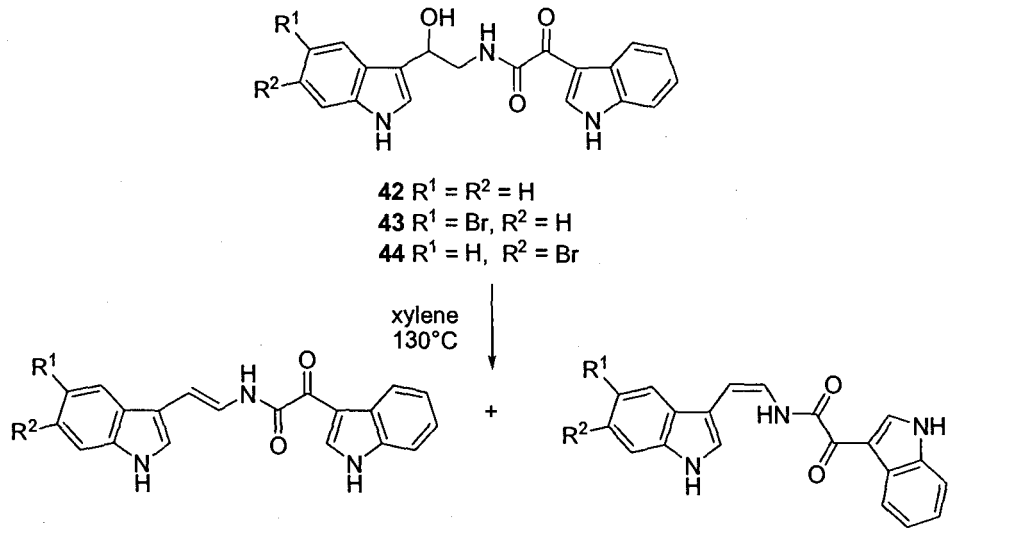
Reaction of amino alcohol **36**, **40** and **41** with 3-indoleglyoxyl chloride **9** gave amides **42, 43** and **44,** respectively in an approximate yield of 80 % (Scheme 3.4). With these amides in hand, we next investigated their transformation into (*Z*)- or (*E*)-indolic enamides using thermally assisted dehydration reactions.



Scheme 3.4

When xylene was used as the solvent, the dehydration reaction of hydroxyl amide **42** could be accomplished at 130 °C for 16 hours giving both (*E*)- and (*Z*)-isomers of coscinamide B. From the crude NMR, the ratio of coscinamide B (**8b**) and its (*Z*)-isomer (**46**) was 5 : 3. The total yield of both isomers after column was 69 % with a small amount of unassigned side products and 5 % recovery of starting material amide **42** (Scheme 3.5).

If (*Z*)-coscinamide B was maintained in DMSO-d_6 at 45°C for 2 days, 80 % of the (*Z*)-isomer was converted to the natural (*E*)-configuration. This observation prompted us to use an aprotic polar solvent for the dehydration reaction in order to get a higher (*E*) / (*Z*) ratio. When the hydroxyl amide **42** was kept under 130 °C for 24 hours in DMF, the dehydration reaction provided an (*E*) : (*Z*) ratio of 5 : 1 for the formation of coscinamide B. The TLC and crude NMR showed that the dehydration reaction in DMF is cleaner than the one in xylene. The yield of both enamides is approximately 90%.



Coscinamide B (**8b**) $R^1 = R^2 = H$ (49%)
5-Bromocoscinamide B (**45**) R^1 = Br, R^2 = H (42%)
Coscinamide A (**8a**) R^1 = H, R^2 = Br (43%)

(*Z*)-Coscinamide B (**46**) $R^1 = R^2 = H$ (20%)
(*Z*)-5-Bromocoscinamide B (**47**) R^1 = Br, R^2 = H (15%)
(*Z*)-Coscinamide A (**48**) R^1 = H, R^2 = Br (17%)

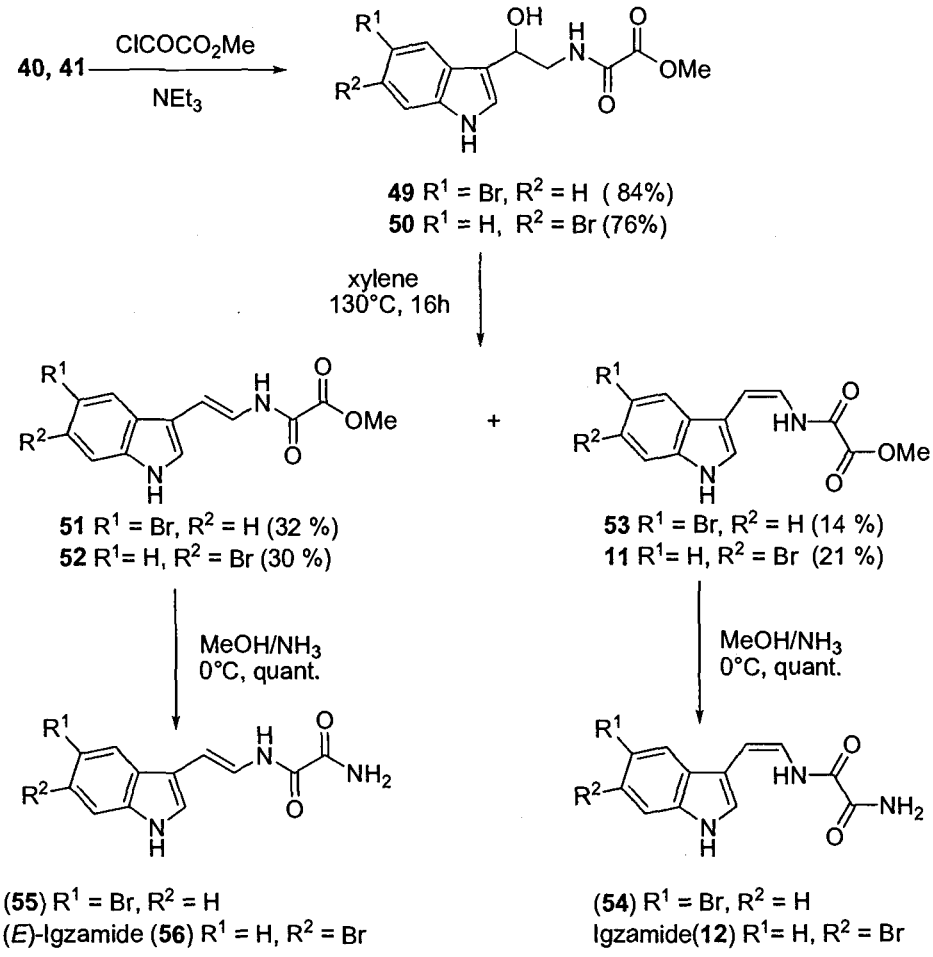
Scheme 3.5

The thermally assisted dehydration reaction of 5- and 6-bromo substituted hydroxyltryptamine in xylene gave similar results and yielded 5-bromo coscinamide B (**45**), coscinamide A (**8a**) with their (*Z*)-isomers (Scheme 3.5). The relative (*E*) : (*Z*) ratio of these reactions is apprommately 5 : 3 based on crude NMR data and the yield of both isomers is approximately 70 % after chromatography. The corresponding reaction in DMF also provided similar results to that of coscinamide B with an (*E*) : (*Z*) ratio around 5 : 1 based on crude NMR data. These results indicate a better selectivity for (*E*)-indolic enamide in DMF than in xylene (5 : 3 ratio of (*E*) : (*Z*) configuration in xylene).

Based on the above observations, we continued our research for the synthesis of (*Z*)-natural indolic emanides. The first target was igzamide, or its precursor **11.** According to Kitahara's synthesis, the conversion from intermediate **11** to igzamide is quantitative (Scheme 2.3). We expected to get a moderate selectivity of (*Z*)-isomer of **11** through the thermally assisted dehydration reaction using xylene as the solvent.

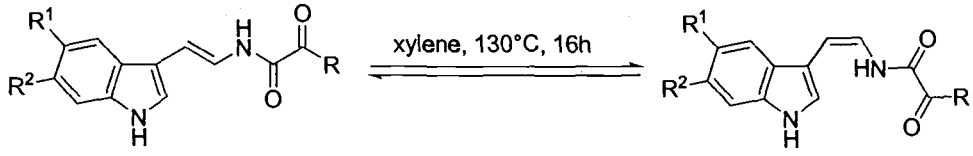
The syntheses of igzamide and its (*E*)-isomer are shown in Scheme 3.6. Treatment of 6-bromo aminoalcohol **41** and methyl chlorooxoacetate with Et_3N in THF produced amide **50** in 76 % yield after flash chromatography. Heating hydroxyl amide **50** in xylene under 130°C yielded a mixture of (*E*)- and (*Z*)-enamides **52** and **11** in a 3 : 2 ratio as expected with a total yield of 51 % after chromatography using CH_2Cl_2 : MeOH (19:1) as eluent. Subsequent transformations to igzamide and its (*E*)-isomer were achieved in quantitative yield by the addition of saturated ammonia methanol. The 5-bromo derivatives were generated using the same protocol starting from 5-bromo substituted aminoalcohol **40**.

The dehydration reaction of hydroxyl amide **49** and **50** in DMF at 120-130 °C for 24 hours provided a higher selectivity of (*E*)-configuration, with a (*E*) : (*Z*) ratio of 4 : 1 and 5 : 1 (checked by crude NMR data), respectively.



Scheme 3.6

When (*E*)-indolic enamide **52** was resubjected to xylene at 130 °C for 16 hours, an equilibrium between the (*E*)- and (*Z*)-indolic enamide was obtained. The (*E*)-enamide was converted into a mixture of both configurations with a (*E*) : (*Z*) ratio around 3 : 2 (Scheme 3.7). The TLC and crude NMR is similar to that of the original dehydration reaction. The 5-bromo derivative **51**, coscinamide B (**8a**), coscinamide A (**8b**) and the (*E*)-5-bromo derivative **45** were tested using the same protocol and gave similar results to that of the corresponding original dehydration reactions (Scheme 3.8).

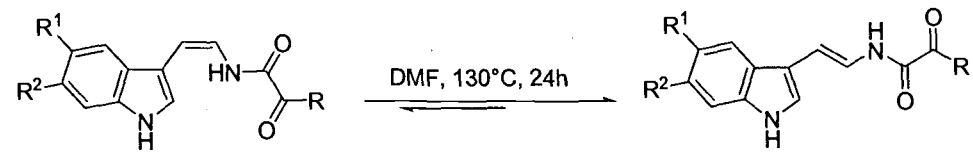


8b $R^1 = R^2 = H$, R = indolyl
45 R^1 = Br, $R^2 = H$, R = indolyl
8a $R^1 = H$, R^2 = Br, R = indolyl
51 R^1 = Br, $R^2 = H$, R = methoxyl
52 $R^1 = H$, R^2 = Br, R = methoxyl

46 $R^1 = R^2 = H$, R = indolyl
47 R^1 = Br, $R^2 = H$, R = indolyl
48 $R^1 = H$, R^2 = Br, R = indolyl
53 R^1 = Br, $R^2 = H$, R = methoxyl
11 $R^1 = H$, R^2 = Br, R = methoxyl

Scheme 3.7

In addition, when (*Z*)-indolic enamides **53** and **11** were resubjected to DMF under 120-130 °C for 24 hours, a mixture of both configurations with a (*E*) : (*Z*) ratio around 5 : 1 was obtained. The TLC and crude NMR data were similar to the corresponding original dehydration reactions. The similar results were given with (*Z*)-indolic enamides **46, 47** and **48,** provided the conversion to (*E*)-indolic enamides with a (*E*) : (*Z*) ratio similar to the original dehydration reactions in DMF (Scheme 3.8). All the reactions have not yet been optimized. Further investigations into the reaction conditions are in progress.

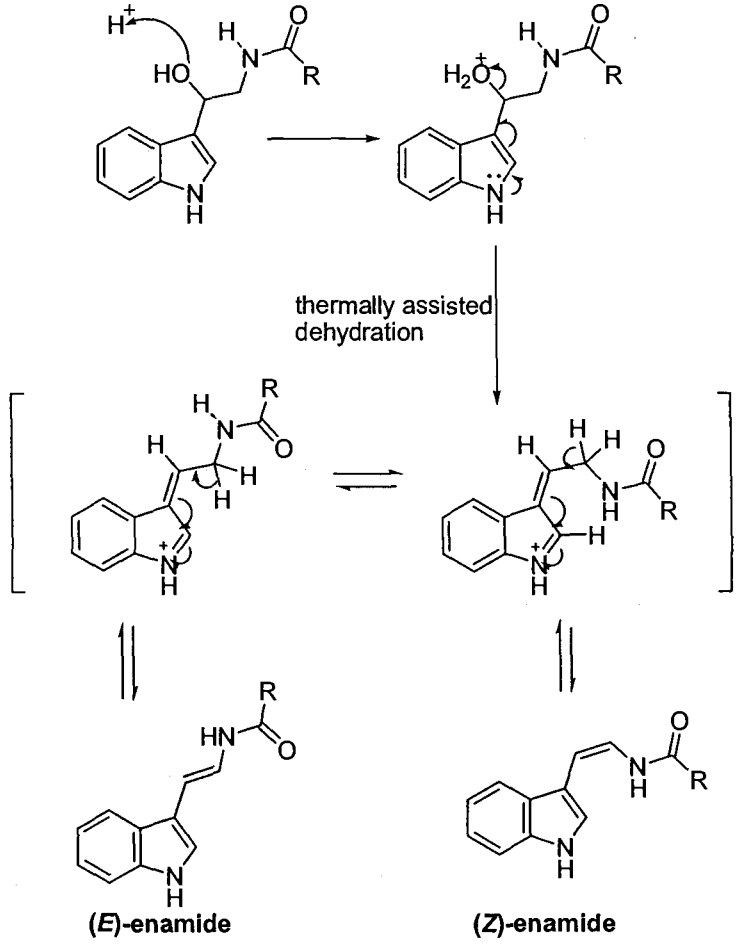


46 $R^1 = R^2 = H$, R = indolyl
47 R^1 = Br, $R^2 = H$, R = indolyl
48 $R^1 = H$, R^2 = Br, R = indolyl
53 R^1 = Br, $R^2 = H$, R = methoxyl
11 $R^1 = H$, R^2 = Br, R = methoxyl

8b $R^1 = R^2 = H$, R = indolyl
45 R^1 = Br, $R^2 = H$, R = indolyl
8a $R^1 = H$, R^2 = Br, R = indolyl
51 R^1 = Br, $R^2 = H$, R = methoxyl
52 $R^1 = H$, R^2 = Br, R = methoxyl

Scheme 3.8

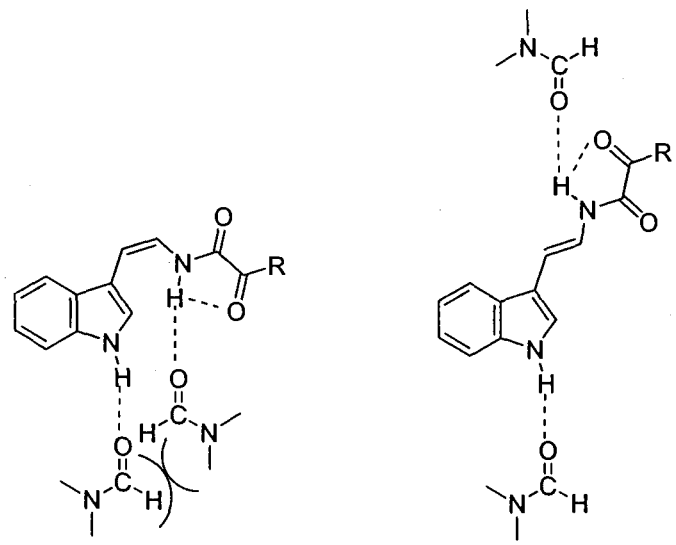
The observation above suggested a possible mechanism for the thermally assisted dehydration reaction (Scheme 3.9). The trace amount of proton from the glassware might assist the dehydration reaction. The equilibrium between (*E*)/(*Z*) configuration and their intermediates drives the reaction to provide the more stable isomer as the major product. The relative ratio of the two configurations was determined by the relative stability of (*E*)- and (*Z*)-indolic enamides in different solvent systems.



Scheme 3.9 A possible mechanism of the thermally assisted dehydration reaction

An explanation for the higher selectivity of (*E*)-indolic enamide in DMF than in xylene is shown in Scheme 3.10. In either case, (*E*)-configuration is the more thermodynamically stable product. In xylene, because of the nonpolar property of

the solvent, the solvent effect was not tremendous. The relative stability of the two configurations is more close to that in the gas phase. DMF or DMSO, however, as hydrogen-bond acceptor solvents, provides more solvation energy to both configurations. However, the solvation energy of (*E*)-indolic enamide is higher due to the better arrangement or less hindrance between the solvent molecules of (*E*)-indolic enamide -DMF system (Scheme 3.10 **b**) than that of (*Z*)-configuration (Scheme 3.10 **a**). Thus, the solvent effect makes the energy difference between (*E*)- and (*Z*)-isomer larger with DMF than with xylene which explained that with xylene, the dehydration reaction provides an (*E*)/(*Z*) ratio about 3 : 2 while with DMF, the selectivity of (*E*)-configuration is higher and with a (*E*)/(*Z*) ratio about 5 : 1.



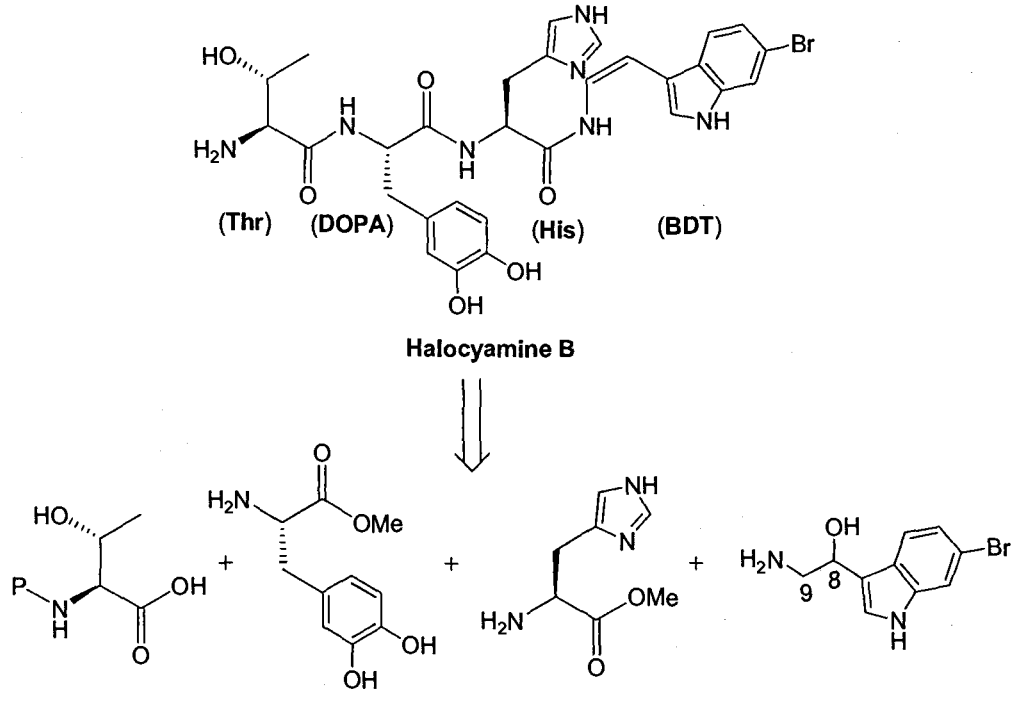
a **b**

Scheme 3.10

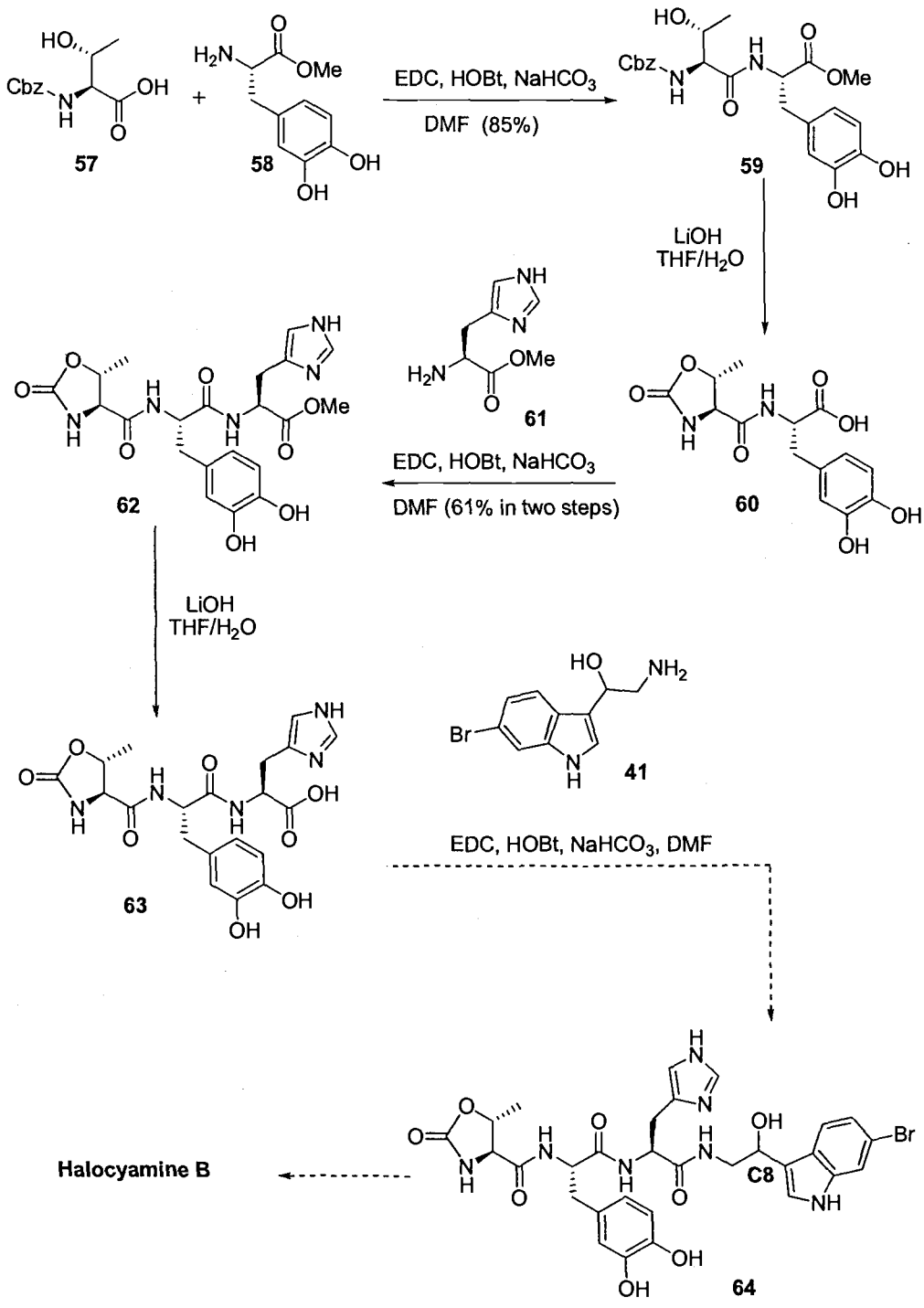
3.2 SYNTHETIC STUDIES TOWARDS THE SYNTHESIS OF HALOCYAMINE B

Based on the foregoing observations for the synthesis of the simple (Z)-indolic enamide natural product, igzamide, and bis-indolic enamide coscinamide A, B, we sought to apply this methodology to the synthesis of a more complex structure, the (Z)-peptide indolic enamide halocyamine B. This natural compound was isolated in 1990; however, no synthetic work on this compound has been reported.

Structurally, halocyamine B consists of four subunits, L-threonine (Thr), L-3,4-dihydroxy-phenylalanine (DOPA), L-histidine (His), and a 6-bromo-8,9-didehydrotryptamine chromophore (BDT).[7] The retrosynthetic analysis is shown in Scheme 3.11.



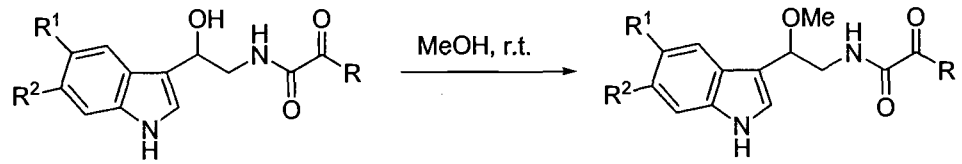
Scheme 3.11


57
58
EDC, HOBt, NaHCO3
DMF (85%)
59
LiOH
THF/H2O
60
61
EDC, HOBt, NaHCO3
DMF (61% in two steps)
62
LiOH
THF/H2O
63
41
EDC, HOBt, NaHCO3, DMF
64
C8
Halocyamine B

Scheme 3.12

Our synthetic strategy is outlined in Scheme 3.12. Our synthesis started with the construction of the Thr-DOPA-His tripeptide. Coupling of Cbz-protected threonine **57** with methylated DOPA **58**[8] proceeded smoothly under EDC/HOBt and $NaHCO_3$ conditions[9] with a yield of 85 %. Subsequent hydrolysis of methyl ester dipeptide **59** with LiOH[10] under inert atmospheric condition gave carboxylic acid **60**. Under the condition of LiOH, the Cbz protecting group at the N-terminus reacted with the adjacent hydroxyl group and formed an N-terminal oxazolidinone. Subsequent coupling of dipeptide **60** with methylated histidine **61** produced **62**. Treatment of **62** with LiOH, again under inert atmosphere afforded methyl ester tripeptide **63**. Due to difficulty of purification, we decided to move on to the next step directly from the residue of the ester hydrolysis step after removal of solvent. 5-Bromo derivative **40** was used instead of 6-bromo substituted amino alcohol **41**, which is shown in our synthetic strategy, for the coupling reaction under the treatment of EDC and HOBt. After chromatography using an eluent of 19 : 1 aceone/H_2O, an inseparable mixture of diastereoisomers at C8 in the indolic aminoalcohol sequence were observed, with a yield of 78 % over two steps.

Unfortunately, the attempt at the dehydration reaction was unsuccessful, giving only a mixture of unassigned products with greater polarity than the starting material amide. A possible explanation for these observations is the existence of the diphenol groups which reacted with the hydroxyl amide and made a dimeric or even more complex structure. This possibility could be supported by the fact that hydroxyl amide intermediates will convert to the corresponding methoxyl substituted amide slowly in methanol even at room temperature.



42 $R^1 = R^2 = H$, R = indolyl
43 R^1 = Br, R^2 = H, R = indolyl
44 R^1 = H, R^2 = Br, R = indolyl
49 R^1 = Br, R^2 = H, R = methoxyl
50 R^1 = H, R^2 = Br, R = methoxyl

65 $R^1 = R^2 = H$, R = indolyl
66 R^1 = Br, R^2 = H, R = indolyl
67 R^1 = H, R^2 = Br, R = indolyl
68 R^1 = Br, R^2 = H, R = methoxyl
69 R^1 = H, R^2 = Br, R = methoxyl

Scheme 3.13

Further investigations are in progress about the synthesis of halocyamine B. Different protecting groups to avoid the formation of oxazolidinone, or protecting groups on the diphenol groups are possibilities.

Reference:

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CHAPTER 4. CONCLUSION

Concise syntheses of coscinamide A, B, igzamide have been accomplished from readily available starting materials. A general method for the preparation of (*E*)- and (*Z*)-indolic enamides was devised from amino alcohols by thermally assisted dehydration processes. Although (*E*)-configuration is the more thermodynamically stable product in most cases, (*Z*)-indolic enamides could be obtained in a moderate yield when using xylene as the solvent for the dehydration reaction. A better selectivity for (*E*)-indolic enamide could be obtained in DMF. A balance between the (*E*)- and (*Z*)-indolic enamides could be obtained when either configuration was resubjected to the same reaction condition of the dehydration reaction, which provides the possibility of the conversion between each configuration.

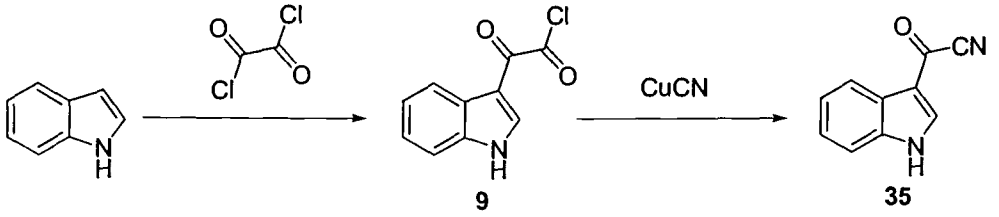
A synthetic study of halocyamine B was outlined including the synthesis of the precursor for the dehydration reaction. The attempt of the dehydration reaction, however, was unsuccessful. Further work is in progress.

CHAPTER 5. EXPERIMENTAL

General Procedures:

All reactions were carried out under nitrogen atmosphere. Starting materials and reagents were purchased from commercial suppliers and usually used without further purification. Unless otherwise stated, concentration under reduced pressure refers to a rotatory evaporator at water aspirator pressure.

Infrared spectra were recorded on a Nicolet 5DXB spectrometer. ^{1}H and ^{13}C spectra were recorded in Fourier transform mode at the field strength specified either on a Bruker AC300 or AM400 spectrometer. Spectra were obtained on DMSO-d_6 or acetone-d_6 solutions in 5mm diameter tubes, and the chemical shift in ppm is quoted relative to the residue signals of DMSO (δ_H 2.50 ppm, or δ_C 40.4 ppm) or Acetone (δ_H 2.05 ppm, or δ_C 28.9 ppm). Multiplicities in the ^{1}H NMR spectra are describes as: s = single, d = double, t = triplet, q = quartet, m = multiplet, b = broad; Low-resolution FAB mass spectra (LRMS) and high-resolution FAB mass spectra (HRMS) were measured on a Kratos MS 50 TC spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units.



9 35

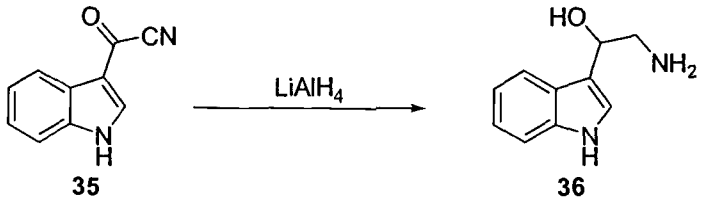
Indolyl-3-carbonyl chloride 9[2] and indolyl-3-carbonyl nitrile 35[1]

To a stirred solution of indole (10.0 g, 85.0 mmol) in 150 mL anhydrous ether was added oxalyl chloride (8.2 mL, 97.4 mmol) dropwise at 0 °C, and the mixture was stirred for 1h at 0 °C, then copper cyanide (14.2 g, 158.4 mmol), acetonitrile (10 mL) and toluene (150 mL) was added at 23 °C. The mixture was heated at 110 °C for 7 h. The solid was filtered over a pad of celite and washed with THF. The filtrate was treated with activated charcoal and boiled for a few minutes, again filtrated and finally evaporated under reduced pressure to yield a brown crude product. Flash chromatography with CH_2Cl_2 afforded **35** as a yellow solid (7.7 g, 53 %).

Compound **9** could also be isolated after the mixture of indole and oxalyl chloride was stirred for 1 h at 0 °C. Filtration and washed with dry ether provided a light yellow solid indolyl-3-carbonyl chloride **9** (95 %).

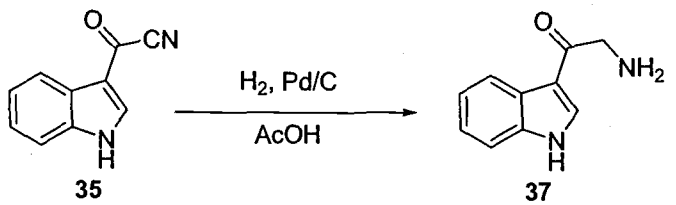
9: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.35 (bs, 1H), 8.41 (d, J = 3.3 Hz, 1H), 8.16 (m, 1H), 7.53 (m, 1H), 7.26 (m, 2H).

35: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.90 (bs, 1H), 8.63 (s, 1H), 8.03 (m, 1H), 7.57 (m, 1H), 7.34 (m, 2H).



β-Hydroxyl tryptamine 36[3]

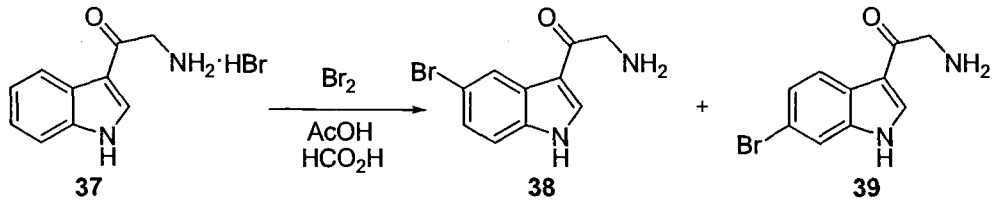
$LiAlH_4$ (1.3 g, 35.3 mmol) was added slowly to a stirred solution of carbonyl nitrile **35** (2.0 g, 11.8 mmol) in 100 mL THF. The mixture was stirred at 23 °C for 1 h prior to being quenched with EtOH, then filtered and washed with EtOH. The solvent was removed under reduced pressure. Flash chromatography of the resulting residue (CH_2Cl_2 : MeOH saturated with NH_3 = 9:1) yielded compound **36** as a light yellow solid (1.19 g, 58 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.86 (bs, 1H), 7.60 (bd, J = 7.9 Hz, 1H), 7.33 (bd, J = 8.0 Hz, 1H), 7.19 (d, J = 2.2 Hz, 1H), 7.04 (td, J = 8.1, 1.0 Hz, 1H), 6.94 (td, J = 8.0, 1.1 Hz, 1H), 4.95 (bs, 1H), 4.72 (dd, J = 6.9, 5.0 Hz, 1H), 2.84 (dd, J = 12.7, 5.0 Hz, 1H), 2.79 (dd, J = 12.7, 6.9 Hz, 1H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ 137.3, 126.8, 123.0, 121.7, 120.2, 119.1, 118.5, 112.2, 69.8, 39.8.



β-Oxotryptamine 37[3]

A mixture of indole-3-carbonyl nitrile **35** (3.1 g, 18.2 mmol) and 20 % Pd/C (0.6 g) in acetic acid 150 mL was stirred vigorously at 23 °C under a hydrogen balloon overnight. The reaction mixture was filtered over celite. The filtrate was evaporated under reduced pressure. The residue was treated with the mixture of 10 mL MeOH

and $HBr•H_2O$ (48 % w/w, 2.5 mL) and concentrated. EtOH was added to the resulting residue and concentrated under reduced pressure. This EtOH addition/evaporation sequence was repeated three times. Addtion of 5 mL EtOH and then filtration provide 3.0 g light pink solid **37**•HBr in 65 % yield. Flash chromatography of the filtrate using CH_2Cl_2 : MeOH saturated with NH_3 (9:1) as the eluent yielded 0.8 g (26 %) of **37** as free base. **37**•HBr ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.25 (bs, 1H), 8.49 (d, J = 3.1 Hz, 1H), 8.16 (m, 1H), 8.13 (bs, 3H), 7.52 (m, 1H), 7.25 (m, 2H), 4.37 (bs, 2H).

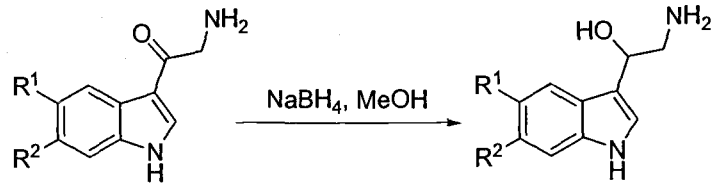


5-Bromo-β-oxotryptamine 38[3] and 6-Bromo-β-oxotryptamine 39[3]

To a stirred solution of **37**•HBr (1.7g, 6.7 mmol) in 150 mL acetic acid/formic acid (1 : 1) was added bromine dropwise (0.34 mL, 6.7 mmol) at 23 °C, then the resulting solution was stirred overnight. The solvent was evaporated under reduced pressure. Flash chromatography ($CHCl_3$: MeOH saturated with NH_3 9:1) provided 6-bromoxotryptamine **39** (0.35 g, 21 %) as an orange solid and 5-bromoxotryptamine **38** (0.96 g, 57 %) as a yellow solid sequentially.

38: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.38 (s, 1H), 8.31 (dd, J = 1.8 Hz, 0.5 Hz, 1H), 7.44 (dd, J = 8.6 Hz, 0.5 Hz, 1H), 7.33 (dd, J = 8.6 Hz, 2.0 Hz, 1H), 3.87 (s, 2H).

39: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.35 (s, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 1.8 Hz, 1H), 7.32 (dd, J = 8.5 Hz, 1.8 Hz, 1H), 3.87 (s, 2H).



38 R^1 = Br, R^2 = H
39 R^1 = H, R^2 = Br

40 R^1 = Br, R^2 = H
41 R^1 = H, R^2 = Br

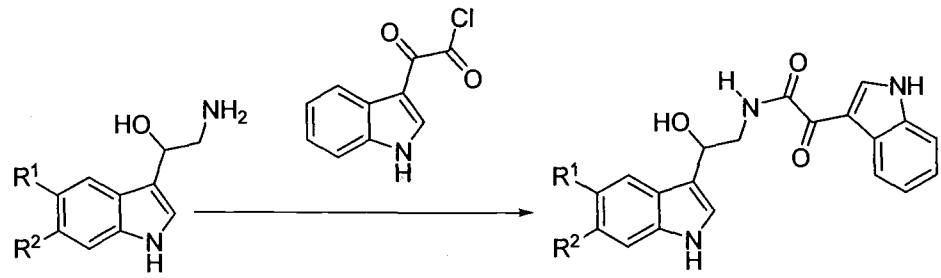
5-Br-β-hydroxyl tryptamine 40

To a stirred solution of **38** (0.96 g, 3.8 mmol) in methanol 150 mL was added $NaBH_4$ (1.43 g, 38.0 mmol) at 0 °C. The solution was warmed to 23 °C and stirred for 20 min. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2 : MeOH saturated with NH_3 9:1) to give **40** as a yellow solid (0.82 g, 84 %). IR (KBr) ν_{max} 3428, 3366, 3176, 3166, 1466, 1452, 1046, 950, 854, 795 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.08 (bs, 1H), 7.78 (d, J = 1.8 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.25 (bs, 1H), 7.15 (dd, J = 8.6, 1.8 Hz, 1H), 5.03 (bs, 1H), 4.66 (dd, J = 6.8, 5.3 Hz, 1H), 2.80 (dd, J = 12.7, 4.9 Hz, 1H), 2.75 (dd, J = 12.7, 7.1 Hz, 1H), 1.58 (bs, 2H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 135.9, 128.7, 124.6, 124.1, 122.5, 118.4, 114.2, 111.7, 69.8, 49.8; HRFABMS m/z calcd for $C_{10}H_{12}N_2O^{79}Br$ $[M+H]^+$: 255.0133; found: 255.0145.

6-Br-β-hydroxyl tryptamine 41

To a stirred solution of **39** (0.53 g, 2.1 mmol) in methanol 80 mL was added $NaBH_4$ (0.79 g, 20.8 mmol) at 0 °C. The solution was warmed to 23 °C and stirred for 20 min. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2 : MeOH saturated with NH_3 9:1) to give **41** as a yellow solid (0.47 g, 89 %). IR (KBr) ν_{max} 3415, 3359, 3286, 1435, 1331, 1049, 894, 803 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.02 (bs, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.22 (bs, 1H), 7.08 (dd, J = 8.5, 1.8 Hz, 1H), 5.00 (bs, 1H), 4.96 (dd, J = 7.1, 5.0 Hz, 1H), 2.81 (dd, J = 12.8, 5.0 Hz, 1H), 2.76 (dd, J =

12.8, 7.1 Hz, 1H), 1.89 (bs, 2H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 138.1, 125.8, 124.0, 122.0, 121.95, 118.9, 114.8, 114.5, 69.8, 49.7; HRFABMS m/z calcd for $C_{10}H_{11}N_2O^{79}Br$ M^+: 254.00548; found: 254.00486.



36 $R^1 = R^2 = H$
40 $R^1 = Br, R^2 = H$
41 $R^1 = H, R^2 = Br$

42 $R^1 = R^2 = H$
43 $R^1 = Br, R^2 = H$
44 $R^1 = H, R^2 = Br$

Compound 42

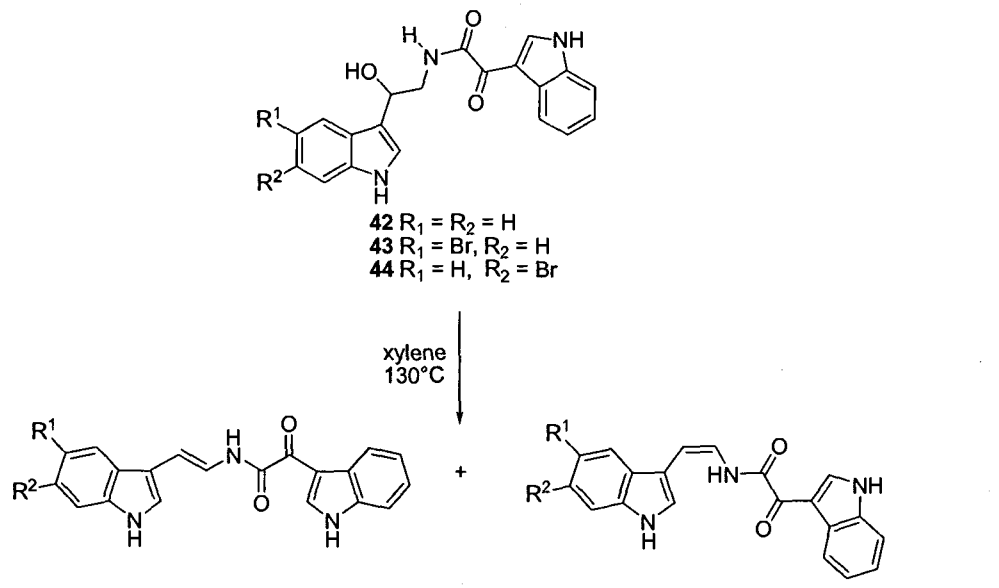
To a stirred solution of **36** (0.67 g, 3.8 mmol) and triethyl amine (0.80 mL, 5.7 mmol) in 100 mL THF was added indolyl-3-carbonyl chloride (0.95 g, 4.5 mmol) at 23 °C. The reaction was stirred for 1 h. The solvent was removed under reduced pressure. Addition of small amount of ethanol to this residue and filtration yielded amide **42** as a colorless solid (1.05 g, 80 %). IR (KBr) ν_{max} 3375, 3251, 1657, 1601, 1499, 1430 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.22 (bs, 1H), 10.92 (bs, 1H), 8.80 (d, J = 3.1 Hz, 1H), 8.57 (t, J = 5.8 Hz, 1H), 8.24 (m, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.53 (m, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.26 (m, 2H), 7.08 (td, J = 7.1, 1.0 Hz, 1H), 6.99 (td, J = 7.4, 1.0 Hz, 1H), 5.32 (d, J = 4.8 Hz, 1H), 5.08 (m, 1H), 3.71 (m, 1H), 3.53 (m, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 182.7, 164.2, 139.5, 137.3, 137.1, 127.1, 126.7, 124.3, 123.4, 123.1, 122.2, 121.9, 120.1, 119.3, 117.8, 113.4, 113.0, 112.3, 66.4, 46.6; HRFABMS m/z calcd for $C_{20}H_{17}N_3O_3$ M^+: 347.1270; found: 347.1280.

Compound 43

To a stirred solution of **40** (0.70 g, 2.7 mmol) and triethyl amine (0.58 mL, 4.1 mmol) in 100 mL THF was added indolyl-3-carbonyl chloride (0.65 g, 3.3 mmol) at 23 °C. The reaction was stirred for 1 h. The solvent was removed under reduced pressure. Addition of small amount of ethanol to this residue and filtration yielded amide **43** as a light yellow solid (0.96 g, 83 %). IR (KBr) ν_{max} 3379, 3251, 1658, 1601, 1496, 1445, 1431, 1055 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.25 (bs, 1H), 11.16 (bs, 1H), 8.75 (s, 1H), 8.60 (t, J = 6.0 Hz, 1H), 8.23 (m, 1H), 7.87 (d, J = 1.9 Hz, 1H), 7.53 (m, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.26 (m, 2H), 7.18 (dd, J = 8.6, 2.0 Hz, 1H), 5.40 (d, J = 4.8 Hz, 1H), 5.04 (m, 1H), 3.56 (m, 2H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 182.3, 163.8, 139.1, 136.7, 135.6, 128.2, 126.7, 124.3, 123.9 (2C), 123.0, 122.1, 121.8, 117.2, 113.9, 113.0, 112.6, 111.5, 65.7, 46.1.

Compound 44

To a stirred solution of **41** (0.29 g, 1.1 mmol) and triethyl amine (0.23 mL, 1.7 mmol) in 50 mL THF was added indolyl-3-carbonyl chloride (0.27 g, 1.3 mmol) at 23 °C. The reaction was stirred for 1 h. The solvent was removed under reduced pressure. Addition of small amount of ethanol to this residue and filtration yielded amide **44** as a light yellow solid (0.39 g, 83 %). IR (KBr) ν_{max} 3372, 3251, 1660, 1600, 1492, 1440, 1436, 1064 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.22 (bs, 1H), 11.07 (bs, 1H), 8.75 (d, J = 3.2 Hz, 1H), 8.58 (t, J = 5.8 Hz, 1H), 8.21 (m, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.52 (m, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.25 (m, 2H), 7.11 (dd, J = 8.5, 1.8 Hz, 1H), 5.37 (d, J = 4.9 Hz, 1H), 5.04 (m, 1H), 3.63 (m, 1H), 3.49 (m, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 182.3, 163.8, 139.1, 137.7, 136.7, 126.7, 125.4, 123.9, 123.8, 123.0, 121.7 (2C), 121.5, 117.7, 114.5, 114.3, 113.0, 112.6, 65.7, 46.2.



Coscinamide B (8b) $R^1 = R^2 = H$
5-Bromocoscinamide B (45) R^1 = Br, R^2 = H
Coscinamide A (8a) R^1 = H, R^2 = Br

(*Z*)-Coscinamide B (46) $R^1 = R^2 = H$
(*Z*)-5-Bromocoscinamide B (47) R^1 = Br, R^2 = H
(*Z*)-Coscinamide A (48) R^1 = H, R^2 = Br

Coscinamide B (8b) and (*Z*)-coscinamide B (46)

A suspension of **42** (0.10 g, 0.29 mmol) in xylene 10 mL was heated in a sealed tube at 130 °C for 16 h under nitrogen with the exclusion of air. After cooling to room temperature, the solvent was evaporated under reduced pressure. Flash chromatography (CH_2Cl_2 : MeOH saturated with NH_3 19:1) of the resulting residue gave (*Z*)-coscinamide B (**46**) (0.020 g, 20 %) as a red solid and coscinamide B (**8b**) (0.047 g, 49 %) as an orange solid sequentially.

Coscinamide B (8b)[4, 5, 6]: IR (KBr) ν_{max} 3436, 3227, 1650, 1597, 1542, 1490, 1442, cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.30 (bs, 1H), 11.21 (bs, 1H), 10.83 (d, *J* = 10.1 Hz, 1H), 8.84 (d, *J* = 3.1 Hz, 1H), 8.28 (m, 1H), 7.69 (bd, *J* = 6.9 Hz, 1H), 7.55 (m, 1H), 7.49 (d, *J* = 2.5 Hz, 1H), 7.42 (dd, *J* = 14.8, 10.1 Hz, 1H), 7.39 (bd, *J* = 6.8 Hz, 1H), 7.28 (m, 2H), 7.12 (m, 2H), 6.85 (d, *J* = 14.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 182.0, 161.2, 139.5, 137.8, 137.2, 127.1, 125.7, 125.2, 124.4, 123.5, 122.5, 122.2, 120.3, 119.9, 119.5, 113.5, 113.2, 112.8, 112.5, 110.9; HRFABMS m/z calcd for $C_{20}H_{15}N_3O_2$ M^+: 329.1164; found: 329.1158.

46: IR (KBr) ν_{max} 3304, 3051, 1672, 1610, 1535, 1483, 1433, 742 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.37 (bs, 1H), 11.45 (bs, 1H), 9.69 (d, J = 11.1 Hz, 1H), 8.93 (bs, 1H), 8.24 (m, 1H), 7.66 (bs, 1H), 7.64 (bd, J = 8.1 Hz, 1H), 7.56 (m, 1H), 7.45 (bd, J = 8.0, 1H), 7.28 (m, 2H), 7.17 (bt, J = 7.5 Hz, 1H), 7.08 (bt, J = 7.4 Hz, 1H), 6.82 (dd, J = 11.1, 9.2 Hz, 1H), 6.23 (d, J = 9.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 180.6, 160.7, 140.1, 137.2, 136.7, 127.3, 127.1, 124.6 * 2, 123.7, 122.8, 122.2, 120.3, 119.3, 118.2, 113.6, 112.8, 112.6, 110.5, 106.8; HRFABMS m/z calcd for $C_{20}H_{15}N_3O_2$ M^+: 329.1164; found: 329.1168.

5-Bromo coscinamide A (45), (*Z*)-5-bromo coscinamide A (47),

A suspension of **43** (0.50 g, 1.2 mmol) in xylene 50 mL was heated in a sealed tube at 130 °C for 16 h under nitrogen with the exclusion of air. After cooling to room temperature, the solvent was evaporated under reduced pressure. Flash chromatography (CH_2Cl_2 : MeOH saturated with $NH_3$19:1) of the resulting residue gave (*Z*)-5-bromo coscinamide A (**47**) (0.070 g, 15 %) as a red solid and 5-bromo coscinamide A (**45**) (0.20 g, 42 %) as an orange solid sequentially.

45: IR (KBr) ν_{max} 3432, 3320, 1669, 1654, 1604, 1543, 1487, 1424, 1114 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.32 (bs, 1H), 11.44 (bs, 1H), 10.85 (d, J = 10.1 Hz, 1H), 8.86 (s, 1H), 8.28 (m, 1H), 7.79 (bd, J = 1.6 Hz, 1H), 7.58 (d, J = 2.3 Hz, 1H), 7.55 (m, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.37 (dd, J = 14.8, 10.1 Hz, 1H), 7.27 (m, 3H), 6.82 (d, J = 14.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 181.9, 161.3, 139.6, 137.2, 136.4, 127.5, 127.1, 126.6, 124.9, 124.4, 123.6, 122.2, 122.0, 120.1, 114.8, 113.5, 113.1, 112.8, 112.3, 110.0; HRFABMS m/z calcd for $C_{20}H_{15}N_3O_2{}^{79}Br$ M^+: 407.0269; found: 407.0264.

47: IR (KBr) ν_{max} 3350, 1673, 1613, 1487, 1437, 1128 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.37 (bs, 1H), 11.63 (bs, 1H), 9.71 (d, J = 11.0 Hz, 1H), 8.90 (s, 1H), 8.24 (m, 1H), 7.84 (d, J = 1.9 Hz, 1H), 7.73 (d, J = 2.5 Hz, 1H), 7.56 (m, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.28 (m, 3H), 6.80 (dd, J = 11.0, 9.2 Hz, 1H), 6.23 (d, J = 9.2

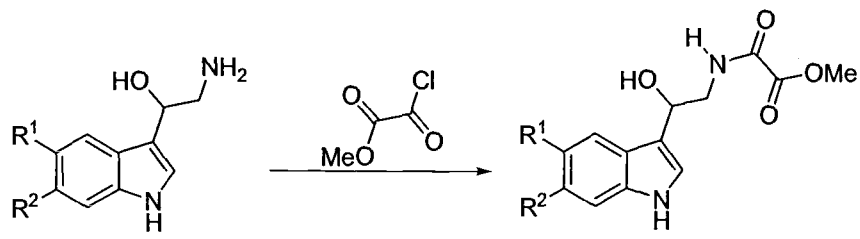
Hz, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 180.8, 161.0, 140.0, 137.2, 135.3, 129.2, 127.1, 126.1, 125.3, 124.6, 123.7, 122.2, 121.8, 118.7, 114.6, 113.6, 112.9, 112.8, 110.4, 106.2; HRFABMS m/z calcd for $C_{20}H_{14}N_3O_2{}^{79}Br$ M^+: 407.0269; found: 407.0273.

Coscinamide A (8a) and (*Z*)-coscinamide A (48)

A suspension of **44** (0.38 g, 0.29 mmol) in xylene 50 mL was heated in a sealed tube at 130 °C for 16 h under nitrogen with the exclusion of air. After cooling to room temperature, the solvent was evaporated under reduced pressure. Flash chromatography (CH_2Cl_2 : MeOH saturated with NH_3 19:1) of the resulting residue gave (*Z*)-coscinamide A (**48**) (0.060 g, 17 %) as a red solid and coscinamide A (**8a**) (0.16 g, 43 %) as an organic solid sequentially.

Coscinamide A (8a)[4, 5]**:** IR (KBr) ν_{max} 3354, 1664, 1617, 1539, 1488, 1423, 1109 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.32 (bs, 1H), 11.35 (bs, 1H), 10.87 (d, *J* = 10.1 Hz, 1H), 8.84 (s, 1H), 8.29 (m, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.59 (d, *J* = 1.2 Hz, 1H), 7.57 (m, 1H), 7.55 (d, *J* = 2.6 Hz, 1H), 7.41 (dd, *J* = 14.7, 10.1 Hz, 1H), 7.29 (m, 2H), 7.25 (dd, *J* = 1.7, 8.5 Hz, 1H), 6.83 (d, *J* = 14.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 181.5, 160.9, 139.1, 138.2, 136.8, 126.7, 125.6, 124.3, 124.0, 123.1, 122.7, 121.8, 121.2, 119.8, 114.9, 114.7, 113.1, 112.7, 112.4, 109.7; HRFABMS m/z calcd for $C_{20}H_{14}N_3O_2{}^{79}Br$ M^+: 407.0269; found: 407.0258.

(*Z*)-coscinamide A (48): IR (KBr) ν_{max} 3311, 1668, 1621, 1600, 1531, 1483, 1436 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.39 (bs, 1H), 11.58 (bs, 1H), 9.70 (d, *J* = 10.8 Hz, 1H), 8.92 (s, 1H), 8.25 (m, 1H), 7.70 (d, *J* = 2.5 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.57 (m, 1H), 7.30 (m, 2H), 7.21 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.84 (dd, *J* = 10.8, 9.2 Hz, 1H), 6.21 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 180.3, 160.5, 139.7, 137.1, 136.8, 126.7, 125.9, 125.2, 124.2, 123.3, 122.7, 121.8, 120.8, 118.5, 115.2, 114.8, 113.2, 112.4, 110.4, 105.8; HRFABMS m/z calcd for $C_{20}H_{14}N_3O_2{}^{79}Br$ M^+: 407.0269; found: 407.0273.



40 R^1 = Br, R^2 = H
41 R^1 = H, R^2 = Br

49 R^1 = Br, R^2 = H
50 R^1 = H, R^2 = Br

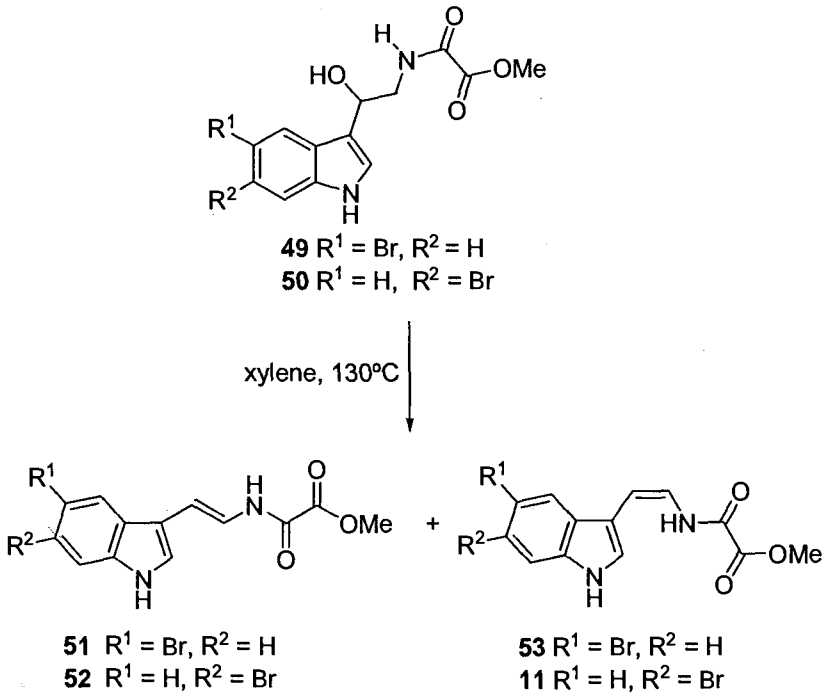
Compound 50

To a stirred solution of 6-bromo aminoalcohol **41** (0.15 g, 0.59 mmol) and triethyl amine (0.12mL, 0.88 mmol) in 25 mL THF was added methyl chloro acetate (0.06 mL 0.65 mmol) at 23°C. The reaction was stirred for 1 h. The solvent was removed under reduced pressure. Flash chromatography (CH_2Cl_2 : MeOH saturated with $NH_3$19:1) of the resulting residue gave 6-bromo amide **50** (0.15 g, 76 %) as a colorless solid. IR (KBr) ν_{max} 3415, 3311, 1741, 1686, 1212 cm^{-1}; ^1H NMR (Acetone-d_6, 300 MHz) δ 10.32 (bs, 1H), 8.10 (bs, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 1.8 Hz, 0.5 Hz, 1H), 7.38 (dd, J = 2.5, 0.8 Hz, 1H), 7.18 (dd, J = 8.5, 1.8 Hz, 1H), 5.20 (m, 1H), 4.55 (d, J = 4.4 Hz, 1H), 3.82 (s, 3H), 3.79 (m, 1H), 3.60 (m, 1H); ^{13}C NMR (Acetone-d_6, 300 MHz) δ 161.2, 156.6, 137.8, 125.1, 123.1, 121.8, 121.0, 117.4, 114.5, 114.2, 66.2, 52.4, 46.3; HRFABMS m/z calcd for $C_{13}H_{13}N_2O_4{}^{79}Br$ M^+: 340.0059; found: 340.0044.

Compound 49

To a stirred solution of 5-bromo aminoalcohol **40** (0.25 g, 0.98 mmol) and triethyl amine (0.20 mL, 1.4 mmol) in 30 mL THF was added methyl chloro acetate (0.10 mL 1.1 mmol) at 23°C. The reaction was stirred for 1 h. The solvent was removed under reduced pressure. Flash chromatography (CH_2Cl_2 : MeOH saturated with $NH_3$19:1) of the resulting residue gave 5-bromo amide **49** (0.29 g, 84 %) as a yellow solid. IR (KBr) ν_{max} 3417, 3305, 1730, 161, 1042 cm^{-1}; ^1H NMR (DMSO-d_6,

300 MHz) δ 11.14 (bs, 1H), 8.84 (t, J = 5.7 Hz, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 1.9 Hz, 1H), 7.18 (dd, J = 8.6, 1.9 Hz, 1H), 5.34 (d, J = 4.8 Hz, 1H), 4.97 (m, 1H), 3.78 (s, 3H), 3.45 (m, 2H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 161.7, 157.3, 135.5, 128.2, 124.3, 123.9, 122.0, 117.0, 113.9, 111.5, 65.4, 52.3, 46.6.



Compound 11[5] and compound 52

A suspension of **50** (0.092 g, 0.27 mmol) in xylene 25 mL was heated in a sealed tube at 130 °C for 16 h under nitrogen with the exclusion of air. After cooling to room temperature, the solvent was evaporated under reduced pressure. Flash chromatography (CH_2Cl_2 : MeOH = 19 : 1) of the resulting residue gave (*Z*)-indolic enamide **11** (0.018 g, 21 %) and (*E*)-indolic enamide **52** (0.026 g, 30 %), sequentially as light yellow solids.

11: IR (KBr) ν_{max} 3303, 1751, 1697, 1533, 1285 cm^{-1}; ^{1}H NMR (Acetone-d_6, 300 MHz) δ 10.74 (bs, 1H), 9.20 (d, J = 11.9 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.63 (m,

2H), 7.27 (dd, J = 8.5, J = 1.8 Hz, 1H), 6.85 (dd, J = 11.1, 9.2 Hz, 1H), 6.22 (d, J = 9.2 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (Acetone-d_6, 300 MHz) δ 160.8, 153.4, 137.1, 125.7, 124.1, 122.8, 120.3, 118.4, 115.4, 114.5, 110.5, 105.3, 52.9; HRFABMS m/z calcd for $C_{13}H_{11}N_2O_3{}^{79}Br$ M^+: 321.9953; found: 321.9960.

52: IR (KBr) ν_{max} 3337, 1733, 1668, 1544, 1273 cm^{-1}; ^{1}H NMR (Acetone-d_6, 300 MHz) δ 10.53 (bs, 1H), 10.02 (bs, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 1.8, 1H), 7.54 (d, J = 2.5 Hz, 1H), 7.42 (dd, J = 14.8, 10.2 Hz, 1H), 7.28 (dd, J = 8.5, 1.8 Hz, 1H), 6.90 (d, J = 14.8 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (Acetone-d_6, 300 MHz) δ 160.8, 153.3, 138.1, 124.7, 124.4, 122.7, 120.8, 119.1, 114.9, 114.6, 112.4, 109.5, 52.6; HRFABMS m/z calcd for $C_{13}H_{11}N_2O_3{}^{79}Br$ M^+: 321.9953; found: 321.9946.

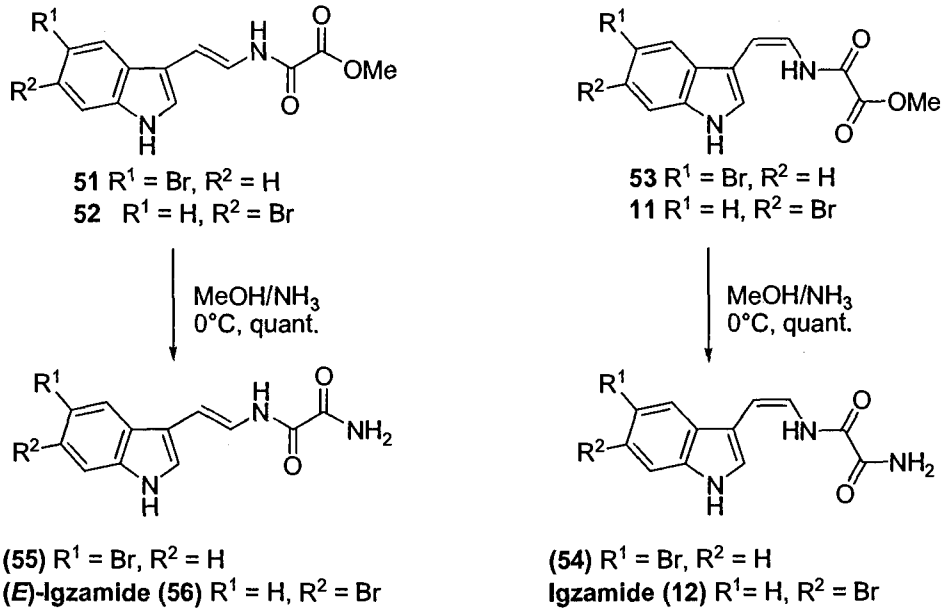
Compound 51 and compound 53

A suspension of **49** (0.070 g, 0.21 mmol) in xylene 20 mL was heated in a sealed tube at 130 °C for 16 h under nitrogen with the exclusion of air. After cooling to room temperature, the solvent was evaporated under reduced pressure. Flash chromatography (CH_2Cl_2 : MeOH = 19 : 1) of the resulting residue gave (*Z*)-indolic enamide **53** (0.009 g, 14 %) and (*E*)-indolic enamide **51** (0.021 g, 32 %), sequentially as light yellow solids.

53: IR (KBr) ν_{max} 3415, 3248, 1691, 1286 cm^{-1}; ^{1}H NMR (Acetone-d_6, 300 MHz) δ 10.81 (bs, 1H), 9.19 (d, J = 9.2 Hz, 1H), 7.84 (d, J = 1.9 Hz, 1H), 7.67 (bs, 1H), 7.47 (dd, J = 8.6, J = 0.5 Hz, 1H), 7.32 (dd, J = 8.6, 1.9 Hz, 1H), 6.85 (dd, J = 11.0, 9.2 Hz, 1H), 6.23 (dd, J = 9.2, 0.8 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (Acetone-d_6, 300 MHz) δ 160.8, 153.5, 135.1, 128.6, 125.0, 124.7, 121.2, 118.4, 113.5, 112.6, 110.0, 105.3, 52.7.

51: IR (KBr) ν_{max} 3391, 3329, 1730, 1677, 1271, 931 cm^{-1}; ^{1}H NMR (Acetone-d_6, 300 MHz) δ 10.59 (bs, 1H), 10.03 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.59 (d, J = 2.6 Hz, 1H), 7.43 (dd, J = 8.6, J = 0.4 Hz, 1H), 7.39 (dd, J = 14.9, 10.2

Hz, 1H), 7.29 (dd, J = 8.6, 1.9 Hz, 1H), 6.90 (dd, J = 14.8, 0.5 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (Acetone-d_6, 300 MHz) δ 160.7, 153.3, 135.9, 127.3, 125.0, 124.5, 121.5, 119.1, 113.6, 112.5, 111.9, 109.3, 52.6.



Igzamide (12)[5, 7]

A solution of **11** (8.0 mg, 0.022 mmol) in a solvent of methanol saturated with NH_3 (4 mL) was stirred at 0 °C for 30 min. The solvent was evaporated under reduced pressure to give igzamide **12** (7.0 mg, quant.) as a light yellow solid. IR (KBr) ν_{max} 3391, 3372, 3329, 3233, 1662, 1528, 1040, cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.56 (bs, 1H), 9.48 (d, J = 11.5 Hz, 1H), 8. 39 (bs, 1H), 8.09 (bs, 1H), 7.63 (d, J = 1.7 Hz, 1H), 7.57 (d, J = 8.9, 1H), 7.56 (bs, 1H), 7.20 (dd, J = 8.6, J = 1.7 Hz, 1H), 6.70 (dd, J = 11.3, 9.4 Hz, 1H), 6.17 (d, J = 9.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 161.9, 157.7, 137.1, 125.8, 124.9, 122.8, 120.8, 118.5, 115.2, 114.8, 110.3, 105.8; HRFABMS m/z calcd for $C_{12}H_{10}N_3O_2{}^{79}Br$ M^+: 306.9956; found: 306.9944.

(*E*)-igzamide (56)

A solution of **52** (5.4 mg, 0.016 mmol) in a solvent of methanol saturated with NH_3 (2.3 mL) was stirred at 0 °C for 30 min. The solvent was evaporated under reduced pressure to give (*E*)-igzamide (**56**) (5.1 mg, quant.) a light yellow solid. IR (KBr) ν_{max} 3453, 3384, 3298, 3277, 1638, 1544, 1109 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.33 (bs, 1H), 10.77 (d, J = 10.0 Hz, 1H), 8.19 (bs, 1H), 7.90 (bs, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.4Hz, 1H), 7.22 (dd, J = 10.1, J = 14.7 Hz, 1H), 7.22 (dd, J = 8.8, 1.6 Hz, 1H), 6.84 (d, J = 14.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 162.0, 157.9, 138.1, 125.4, 124.4, 122.7, 121.1, 119.7, 114.9, 114.7, 112.2, 109.8.

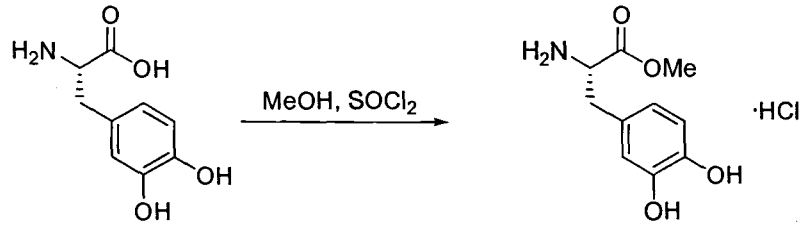
Compound 54

A solution of **53** (16.6 mg, 0.050 mmol) in a solvent of methanol saturated with NH_3 (6.9 mL) was stirred at 0 °C for 30 min. The solvent was evaporated under reduced pressure to give compound **54** (16.1 mg, quant.) a light yellow solid. IR (KBr) ν_{max} 3406, 3348, 3301, 3255, 1664, 1534, 1459, 796 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.63 (bs, 1H), 9.50 (d, J = 11.3 Hz, 1H), 8.40 (bs, 1H), 8.10 (bs, 1H), 7.81 (d, J = 1.7 Hz, 1H), 7.59 (d, J = 2.5, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.27 (dd, J = 8.6, J = 1.9 Hz, 1H), 6.68 (dd, J = 11.3, 9.2 Hz, 1H), 6.20 (d, J = 9.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 161.7, 157.7, 134.9, 128.6, 125.3, 125.0, 121.4, 118.2, 114.2, 112.5, 109.8, 105.8.

Compound 55

A solution of **51** (17.7 mg, 0.054 mmol) in a solvent of methanol saturated with NH_3 (7.4 mL) was stirred at 0 °C for 30 min. The solvent was evaporated under reduced pressure to give compound **55** (16.9 mg, quant.) a light yellow solid. IR (KBr) ν_{max} 3438, 3377, 3286, 3209, 1693, 1647, 1548, 1107, 934 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.43 (bs, 1H), 10.75 (d, J = 10.1 Hz, 1H), 8. 20 (bs, 1H),

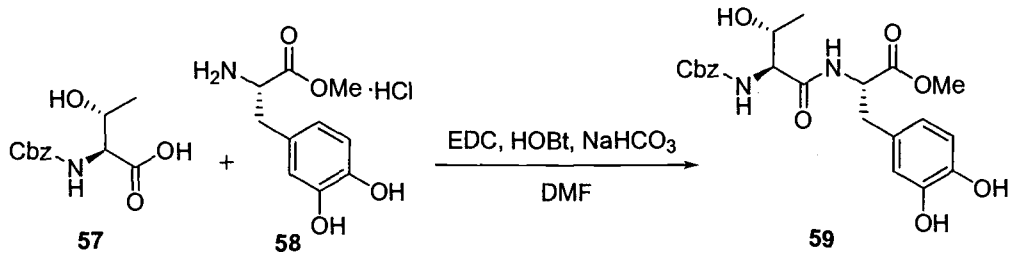
7.92 (bs, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.24 (dd, J = 8.5, 1.8 Hz, 1H), 7.20 (dd, J = 14.8, 10.1 Hz, 1H), 6.83 (d, J = 14.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 162.2, 157.9, 135.9, 127.1, 125.9, 124.5, 121.4, 119.6, 114.4, 112.4, 111.7, 109.7.



58

L-DOPA methyl ester hydrochloride 58[8]

Thionyl chloride (0.8 mL, 10.96 mmol) was added drop by drop to a suspension of L-DOPA (1.1 g, 5.58 mmol) in 25 mL MeOH at 0 °C. The solution was refluxed for 1.5 h, and then the solvent was evaporated carefully under vacuum pressure to get 1.4 g L-DOPA methyl ester hydrochloride **58** as white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.97 (s, 1H), 8.94 (s, 1H), 8.52 (bs, 3H), 6.68 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 1.4 Hz, 1H), 6.45 (dd, J = 8.0, 1.4 Hz, 1H), 4.13 (dd, J = 6.0, 6.5 Hz, 1H), 3.69 (s, 3H), 2.99 (dd, J = 14.1, 5.6 Hz, 1H), 2.91 (dd, J = 14.1, 7.0 Hz, 1H).



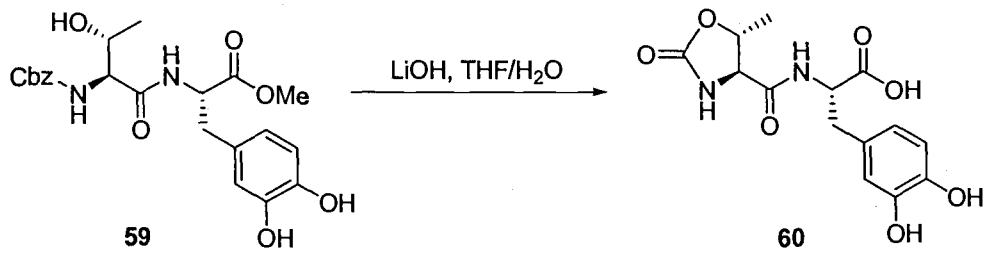
57 58 59

N-Cbz-L-Thr-L-DOPA methyl ether 59

A solution of L-DOPA methyl ester hydrochloride **58** (0.2 g, 0.808 mmol) in DMF 10 mL was treated sequentially with $NaHCO_3$ (0.068 g, 0.808 mmol), HOBt (0.27g,

2.02 mmol), N-Cbz-L-Thr (0.20 g, 0.808 mmol), and EDC (0.341 g, 1.78 mmol) at 0 °C, then stirred overnight at room temperature.

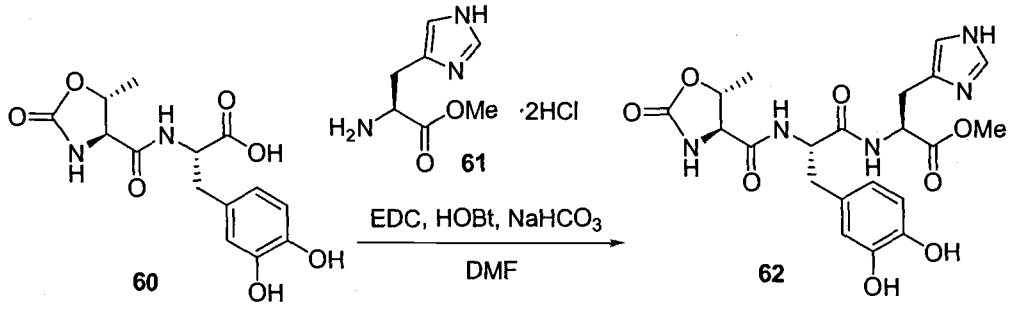
After removal of the solvent *in vacuo*, H_2O (10 mL) and AcOEt (30 mL) were added to the residue. The aqueous phase was extracted with AcOEt (3 X 10 mL). The combined organic layers were washed with H_2O, saturated aqueous $NaHCO_3$, brine, then dried with $MgSO_4$ and concentrated *in vacuo*. The residue after chromatography ($CHCl_3$: MeOH = 19 : 1) afforded dipeptide methyl ester **59** as a white solid (0.31 g, 85 %). IR (KBr) ν_{max} 3406, 3290, 1759, 1679, 1649, 1542 cm^{-1};^1H NMR (DMSO-d_6, 300 MHz) δ 8.76 (s, 1H), 8.72 (s, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.36 (m, 5H), 6.96 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 7.9 Hz, 1H), 6.55 (d, J = 1.9 Hz, 1H), 6.43 (dd, J = 8.0, 1.7 Hz, 1H), 5.04 (d*2, J = 15.0, 14.8 Hz, 2H), 4.83 (d, J = 5.6 Hz, 1H), 4.39 (m, 1H), 3.95 (dd, J = 8.7, 5.3 Hz, 1H), 3.82 (m, 1H), 3.55 (s, 3H), 2.78 (m, 2H), 1.01 (d, J = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 172.3, 170.6, 156.4, 145.4 144.4, 137.4, 128.8 (2C), 128.3, 128.2 (2C), 127.8, 120.3, 116.8, 115.8, 67.3, 66.0, 60.9, 54.3, 52.1, 37.0, 20.0.



Compound 60

To a solution of the above dipeptide N-Cbz-L-Thr-L-DOPA methyl ether **59** (1.13 g, 2.53 mmol) in degassed THF (15 mL), LiOH (0.21g, 5.06 mmol) in H_2O (15 mL) was added at 0 °C. The reaction was stirred at room temperature overnight with bubbling nitrogen into the solution. 1.2 N HCl was added for acidification to pH 2. The aqueous phase was washed with small amount of Et_2O. Then AcOEt was used

to extract the aqueous layer, and got the acid **60** as a white solid (0.40g). The aqueous layer was concentrated *in vacuo*. EtOH was added to the residue and the filtration was carried to remove the inorganic salt. After removal of the solvent, the residue of the filtrate afforded another potion of **60**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.75 (bs, 1H), 8.76 (s, 1H), 8.72 (s, 1H), 8.33 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 2.8 Hz, 1H), 6.46 (dd, J = 8.0, 2.1 Hz, 1H), 4.34 (m, 2H), 3.85 (dd, J = 4.9, 0.8 Hz, 1H), 2.91 (dd, J = 14.0, 5.0 Hz, 1H), 2.73 (dd, J = 14.0, 9.2 Hz, 1H), 1.34 (d, J = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 173.2, 170.5, 158.7, 145.4, 144.4, 128.5, 120.3, 116.8, 115.8, 76.1, 60.7, 54.4, 36.4, 21.0.

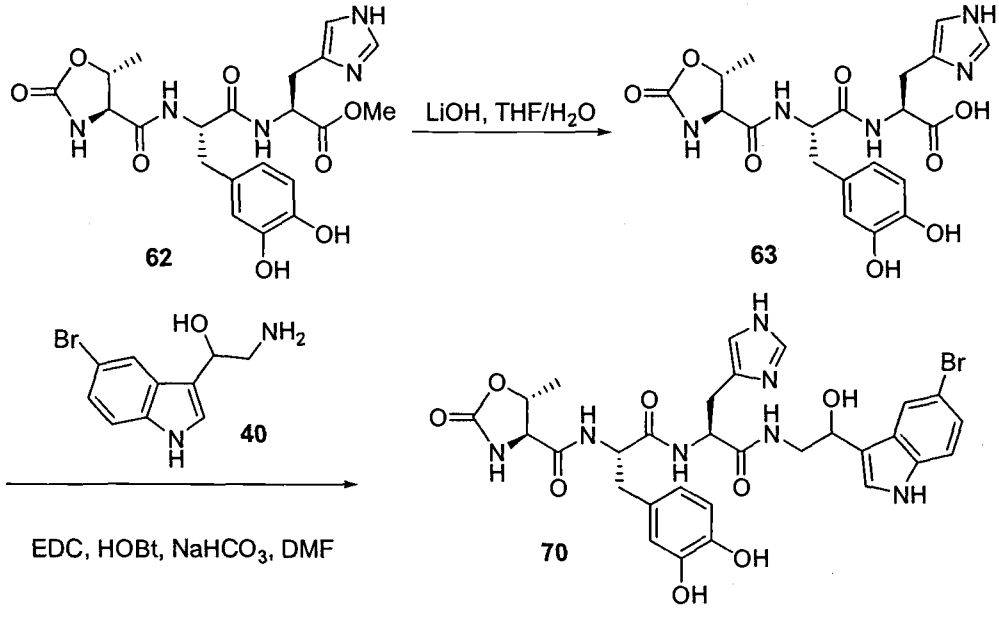


Compound 62:

A solution of L-His methyl ester hydrochloride **61** (0.030g, 0.127 mmol) in DMF 5 mL was treated sequentially with $NaHCO_3$ (0.021 g, 0.255 mmol), HOBt (0.019g, 0.139 mmol), dipeptide acid **60** (0.037g, 0.115 mmol), and EDC (0.027 g, 0.139 mmol) at 0 °C, then stirred overnight at room temperature.

The solvent was removed *in vacuo*. The residue after chromatography (CH_2Cl_2 : MeOH = 19 : 1) afforded tripeptide **62** as a white solid (0.0331g, 61 %). IR (KBr) ν_{max} 3225, 1744, 1660, 1529 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.95 (bs, 1H), 8.74 (bs, 2H), 8.48 (d, J = 7.1 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.55 (s, 1H), 6.84 (bs, 1H), 6.65 (d, J = 1.8 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.48 (dd, J = 8.0, 1.8 Hz, 1H), 4.49 (m, 2H), 4.29 (m, 1H), 3.83 (d, J = 4.9 Hz, 1H), 3.60 (s,

3H), 2.92 (m, 3H), 2.64 (m, 1H), 1.34 (d, J = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 172.2, 171.5, 170.3, 158.6, 145.3, 144.2, 135.4, 128.8, 120.4, 117.1, 115.7, 76.2, 60.9, 54.7, 53.0, 52.3, 37.2, 29.5, 21.0; HRFABMS m/z calcd for $C_{21}H_{26}N_5O_8$ $[M+H]^+$: 476.1781; found: 476.1774.



Compound 70:

To a solution of the above tripeptide methyl ether **62** (0.087 g, 0.18 mmol) in degassed THF (5 mL), the LiOH (0.015g, 0.36 mmol) in H_2O (5 mL) was added at 0 °C. The reaction was stirred at room temperature overnight with bubbling nitrogen into the solution. 1.2 N HCl was added for acidification to pH 2. The solution was solidified in dry ice acetone bath, and then H_2O and THF was removed under reduced pressure.

The residue got from above was dissolved in DMF (5 mL) and then treated sequentially with HOBt (0.048g, 0.36 mmol), $NaHCO_3$ (0.030 g, 0.36 mmol), amino alcohol 9 (0.084 g, 0.33 mmol), and EDC (0.069 g, 0.36 mmol) at 0 °C, then stirred overnight at room temperature.

The solvent was removed *in vacuo*. The residue after chromatography (Acetone : H_2O = 19 : 1) afforded a light yellow solid (0.099g, 78 %). ^1H NMR (DMSO-d_6, 300 MHz) δ 11.91 (bs, 1H), 11.14 (bs, 1H), 8.71 (bs, 1H), 8.69 (bs, 1H), 8.28 (t, J = 8.4 Hz, 1H), 8.15 (d, J = 7.7 Hz, 0.5H), 8.07 (m, 1H), 7.94 (m, 0.5 H), 7.83 (m, 2H), 7.58 (d, J = 3.2 Hz, 1H), 7.34 (dd, J = 8.6, 1.8 Hz, 1H), 7.29 (dd, J = 4.5, 2.0 Hz, 1H), 7.19 (dd, J = 8.6, 1.9 Hz, 1H), 6.83 (bd, J = 8.3 Hz, 1H), 6.66 (t, J = 2.5 Hz, 1H), 6.61 (dd, J = 8.0, 1.8 Hz, 1H), 6.49 (m, 1H), 4.88 (m, 1H), 4.47 (m, 2H), 4.28 (m, 1H), 3.83 (m, 1H), 3.55 (m, 0.5H), 3.34 (m, 1H), 3.17 (m, 0.5), 2.88 (m, 3H), 2.59 (m, 1H), 1.35 (dd, J = 6.2, 2.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 171.0, 170.4, 158.6, 145.3, 144.2, 135.6, 135.1, 128.9, 128.1, 124.3, 124.2, 123.9, 122.2, 120.4, 117.0, 115.6, 113.9, 111.5, 76.2, 66.3, 60.9, 55.0, 53.4, 53.0, 46.4, 37.1, 21.0.

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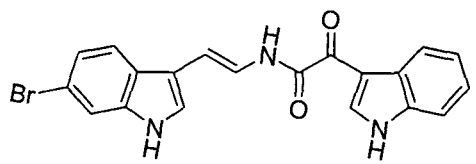
APPENDIX: ^{1}H AND ^{13}C NMR SPECTRA



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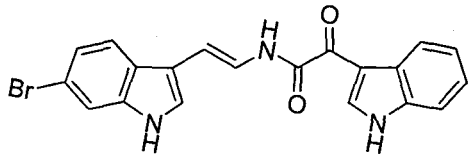

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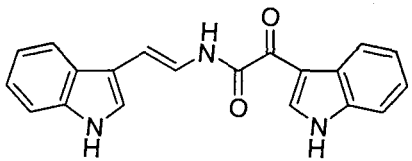

Coscinamide B (8b)
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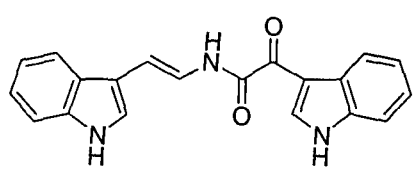

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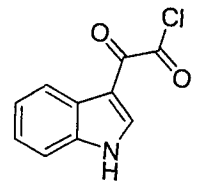

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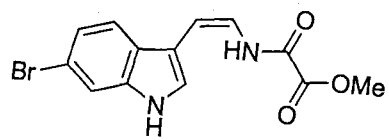
DMSO-d_6, 300 MHz



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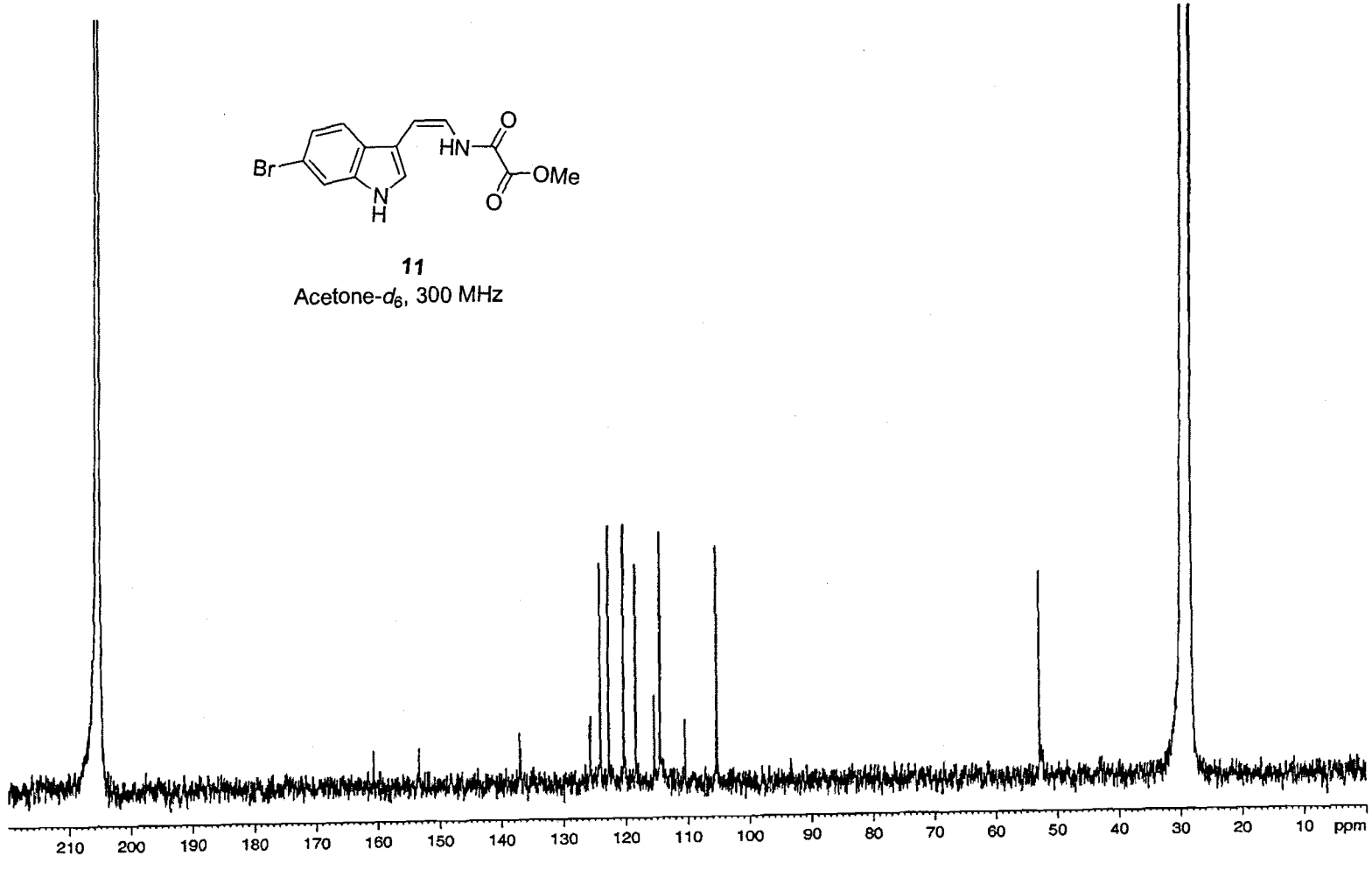
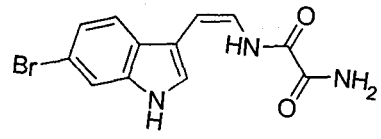
Acetone-d_6, 300 MHz

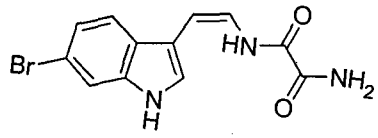


11

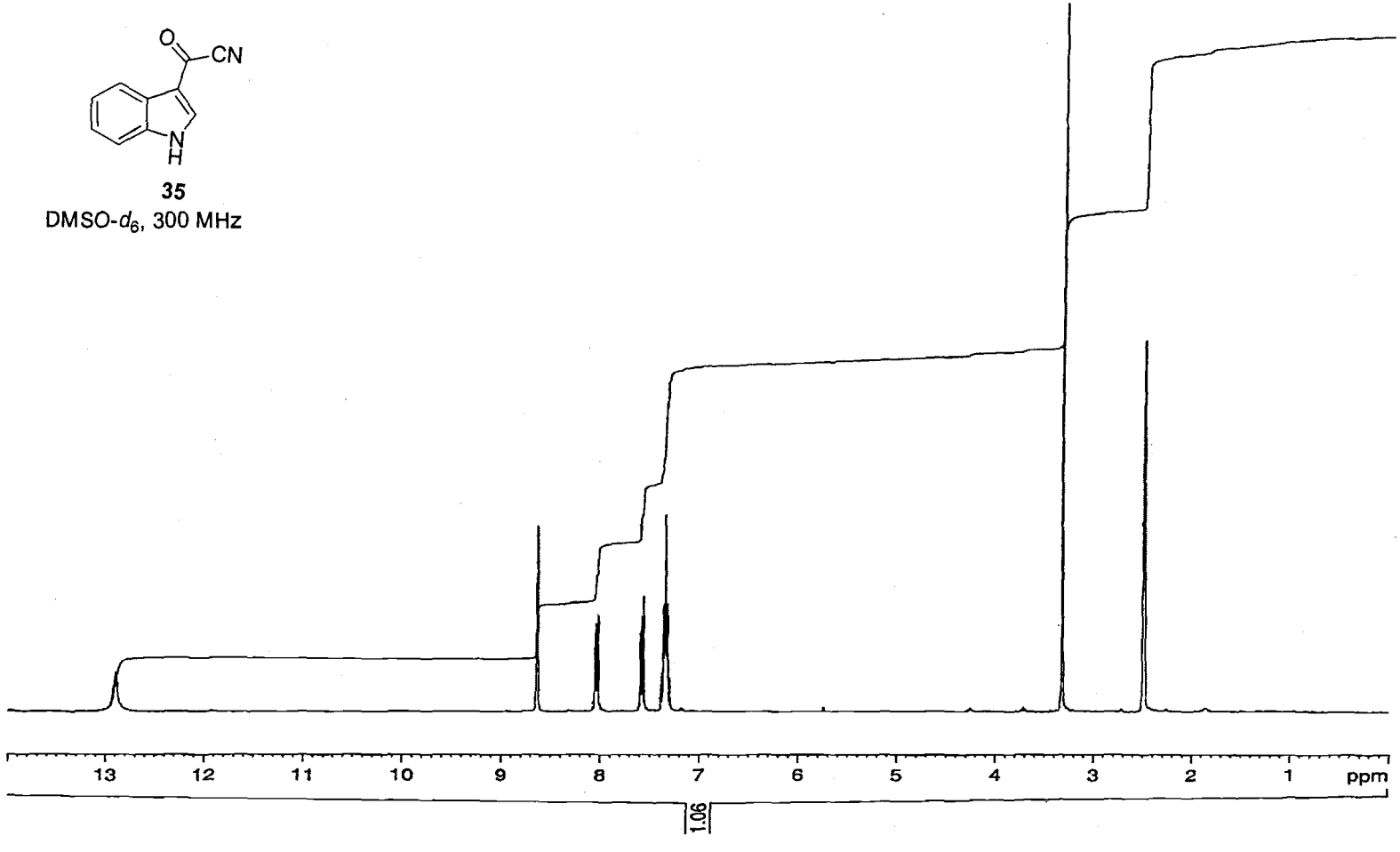
Acetone-d_6, 300 MHz

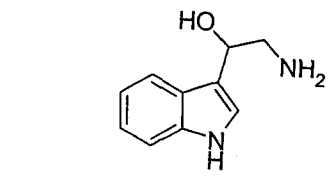


Igzamide (12)
DMSO-d_6, 300 MHz



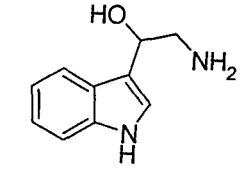
Igzamide (12)
DMSO-d_6, 400 MHz


O
CN
N
H
35
DMSO-d_6, 300 MHz
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.06



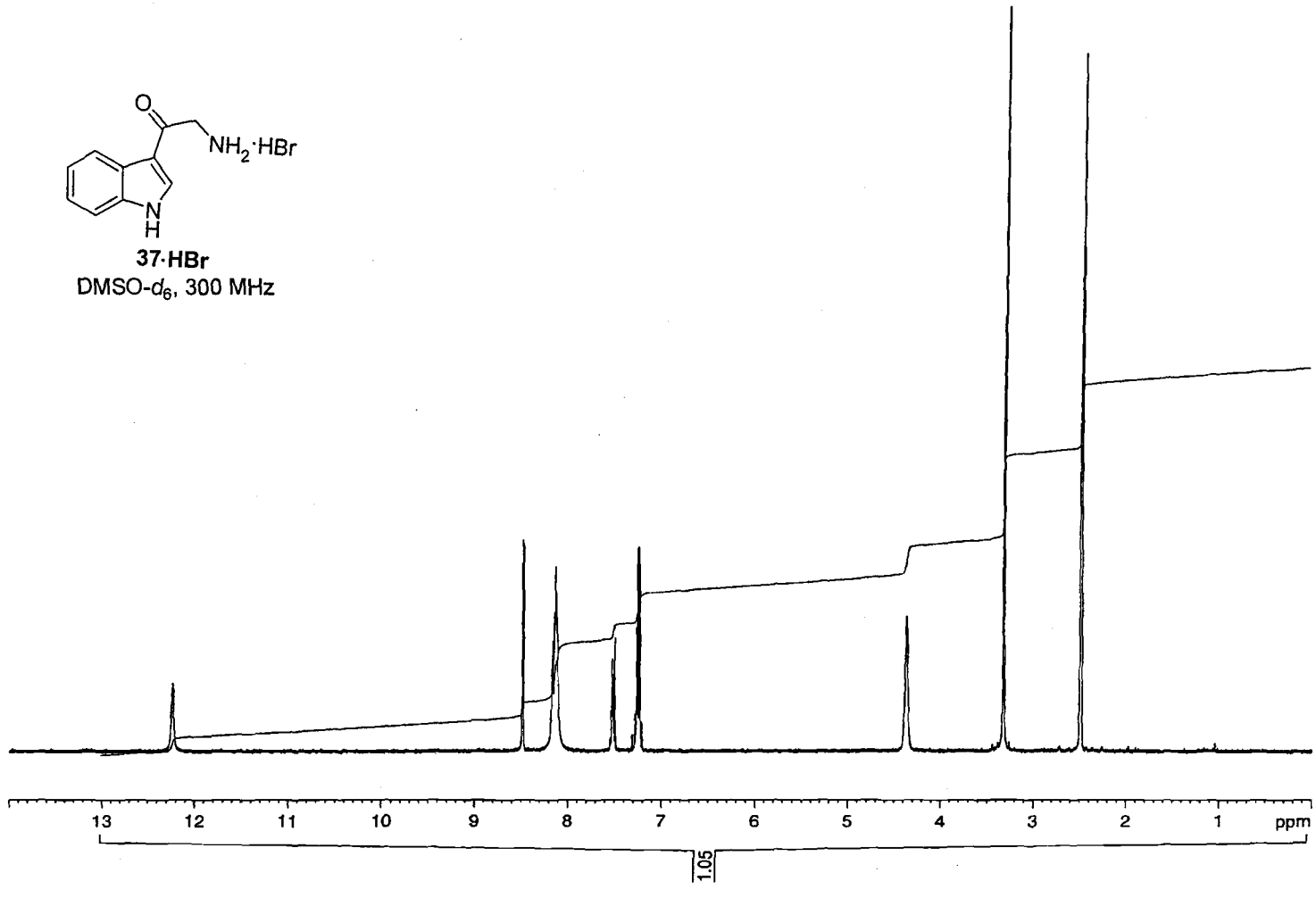
36

DMSO-d_6, 300 MHz

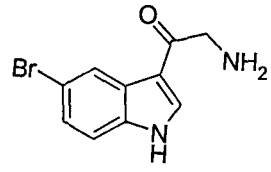


36

DMSO-d_6, 400 MHz

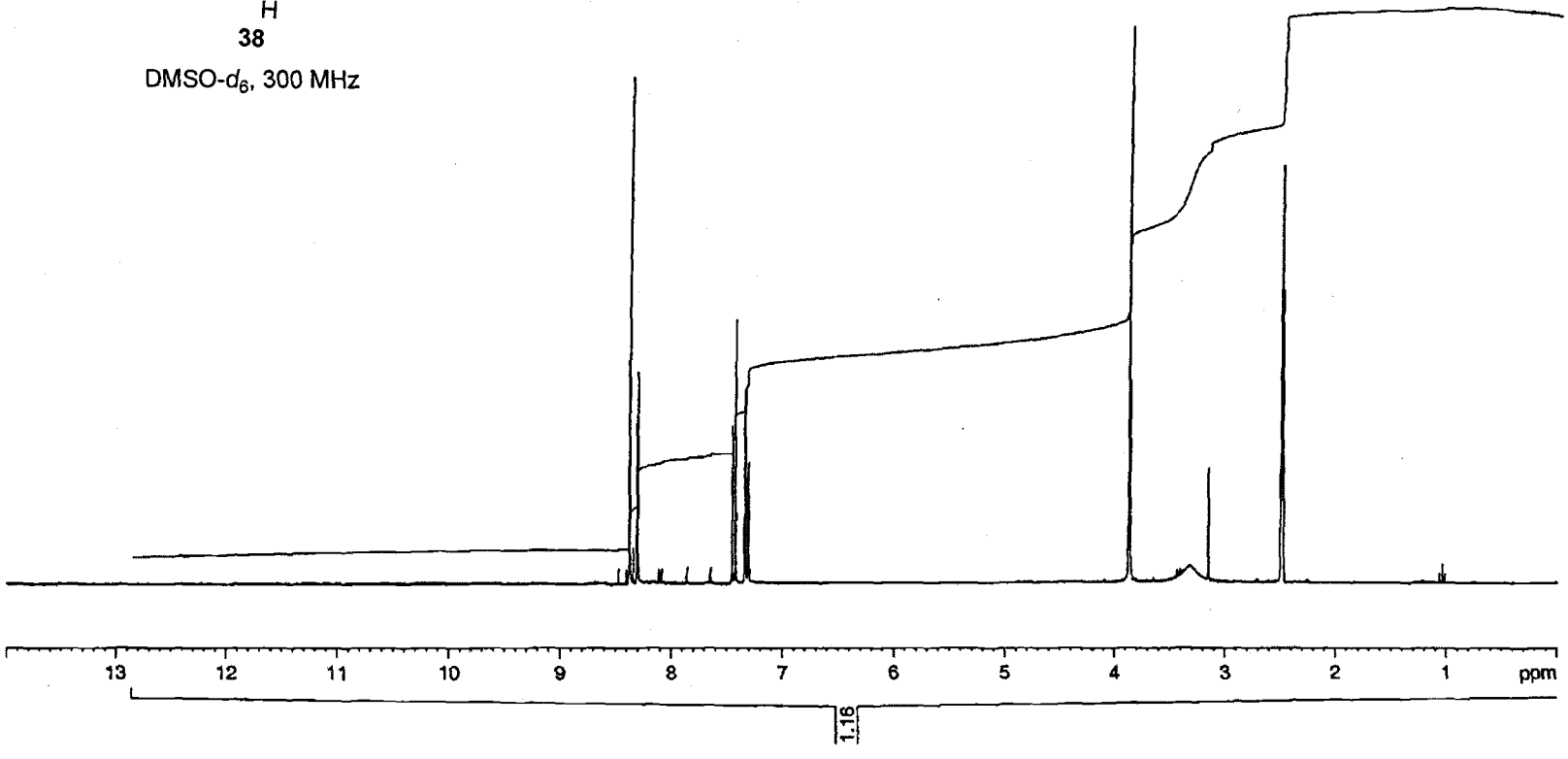


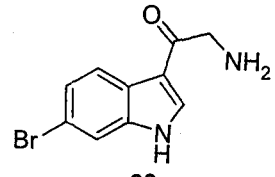
37·HBr
DMSO-d_6, 300 MHz



38

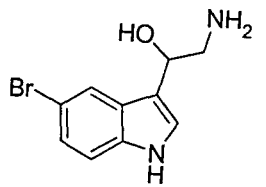
DMSO-d_6, 300 MHz





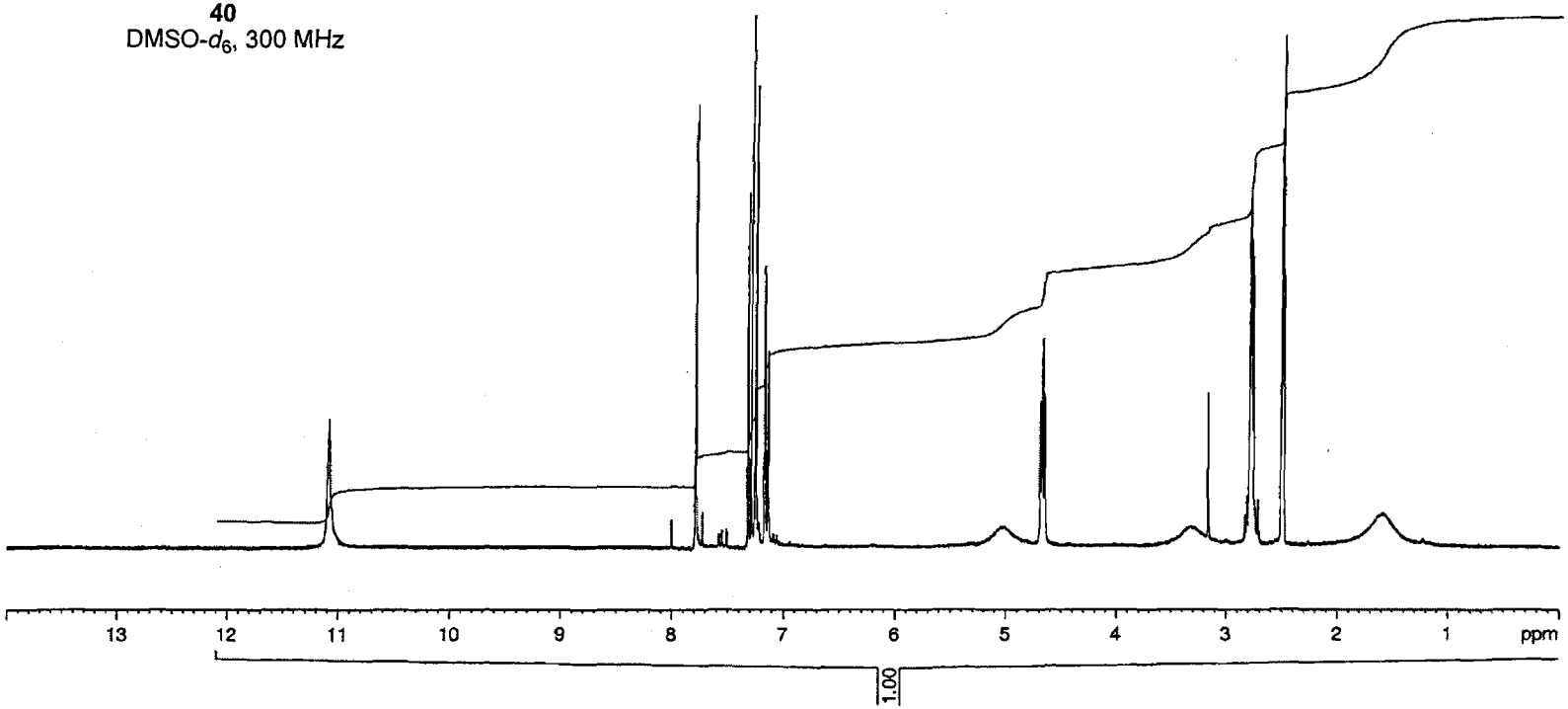
39

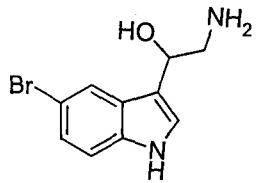
DMSO-d_6, 300 MHz



40

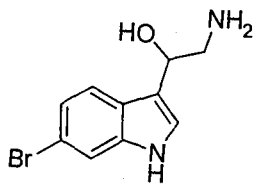
DMSO-d_6, 300 MHz





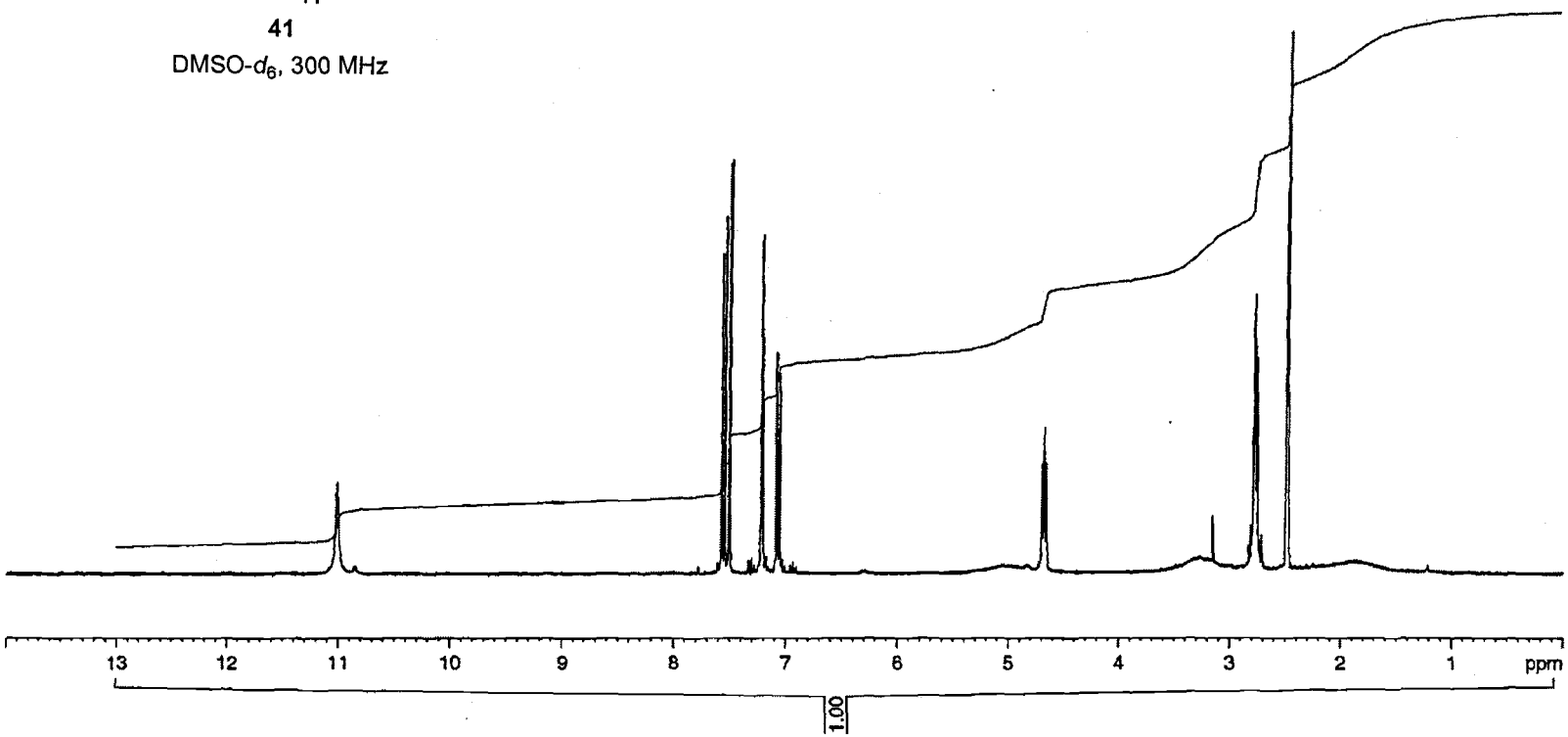
40

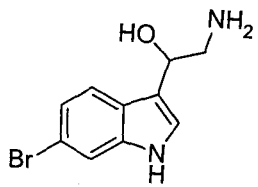
DMSO-d_6, 300 MHz



41

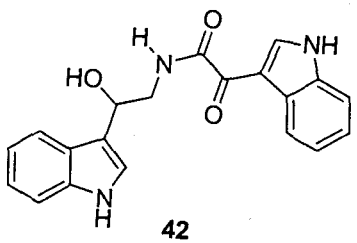
DMSO-d_6, 300 MHz





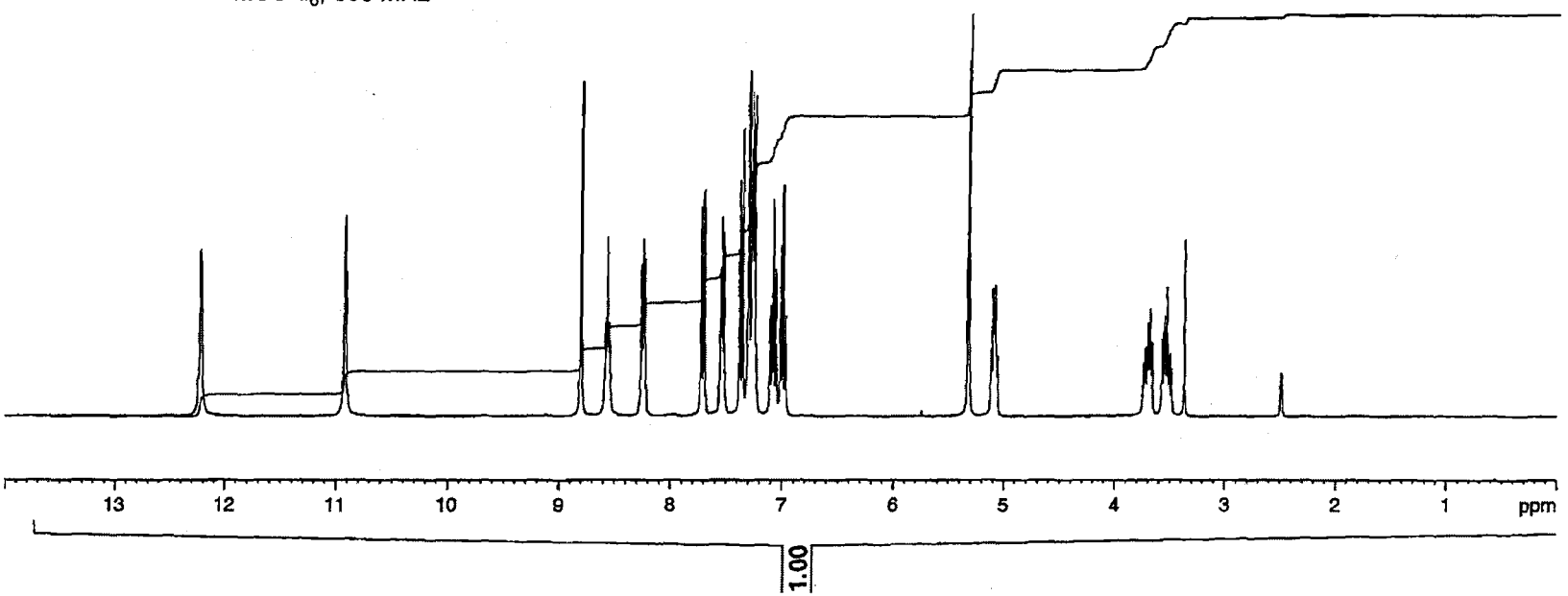
41

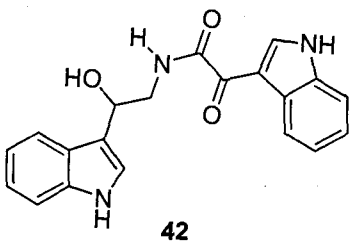
DMSO-d_6, 300 MHz



42

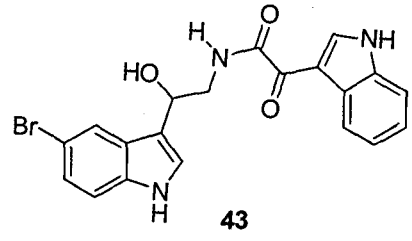
DMSO-d_6, 300 MHz





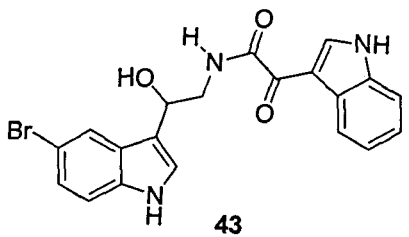
42

DMSO-d_6, 300 MHz



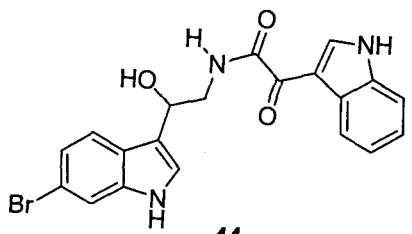
43

DMSO-d_6, 300 MHz



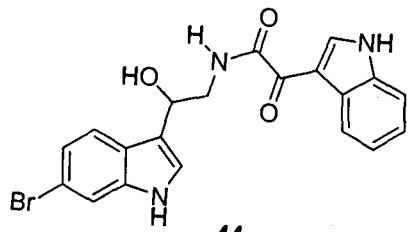
43

DMSO-d_6, 300 MHz



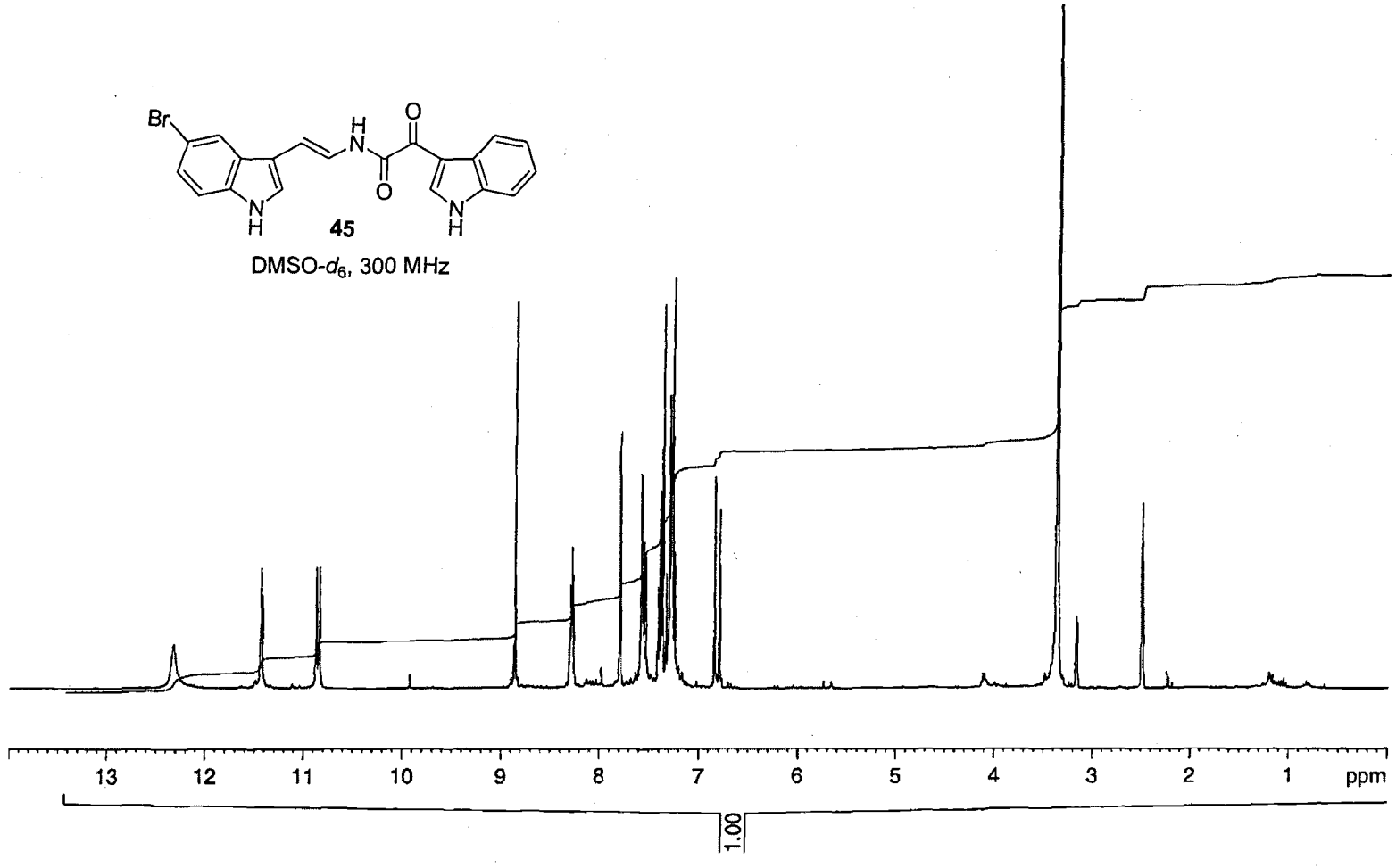
44

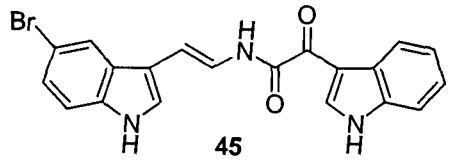
DMSO-d_6, 300 MHz



44

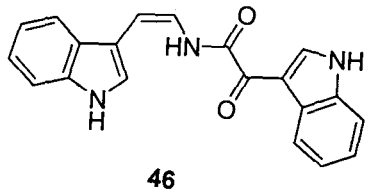
DMSO-d_6, 300 MHz


Br
H
N
O
O
N
H
N
H
45
DMSO-d_6, 300 MHz
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00



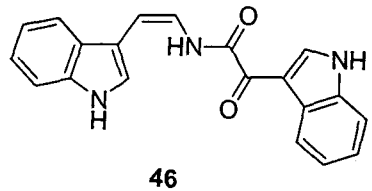
45

DMSO-d_6, 300 MHz



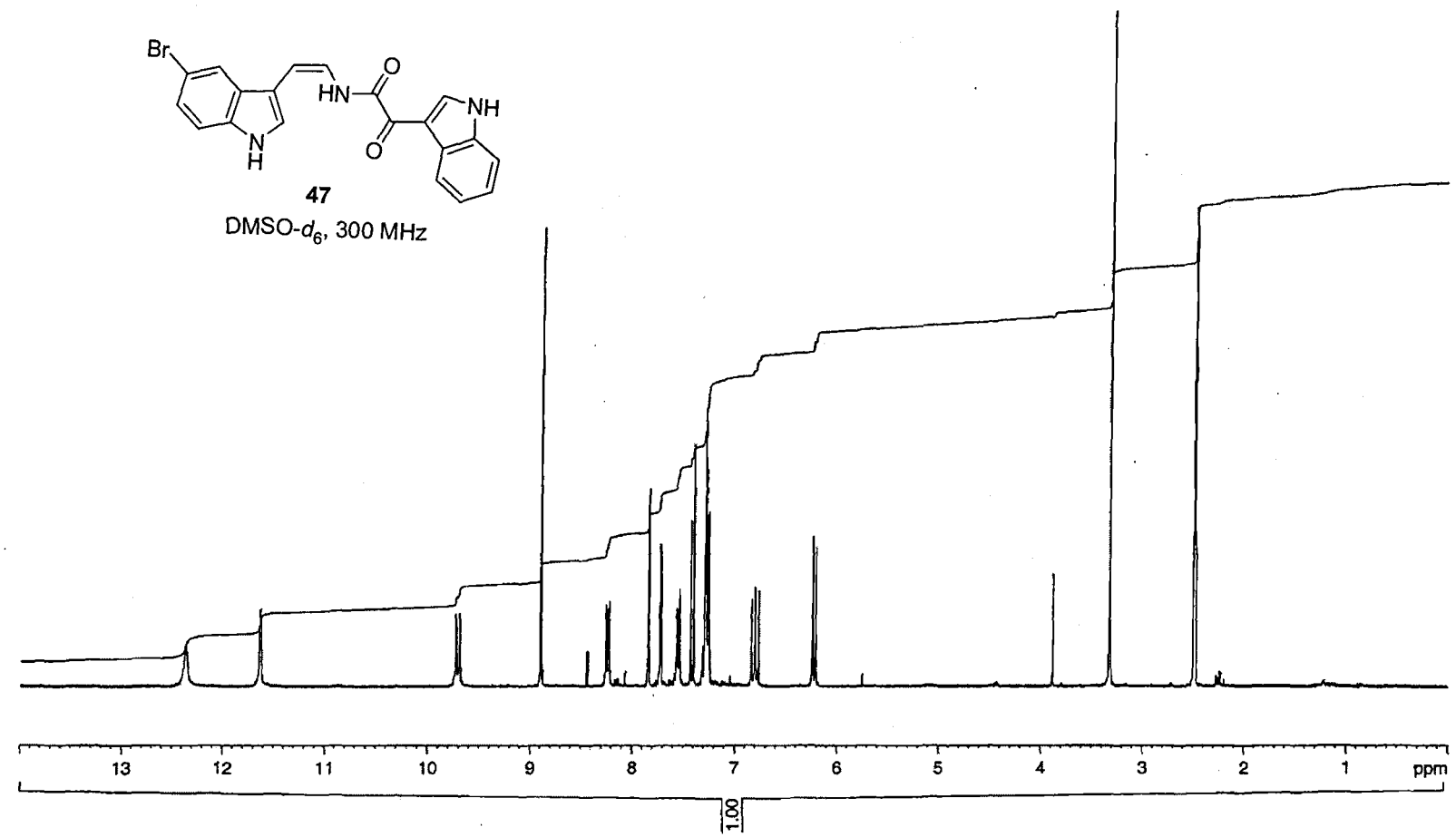
46

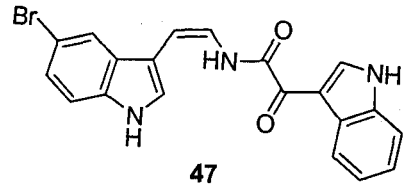
DMSO-d_6, 300 MHz



46

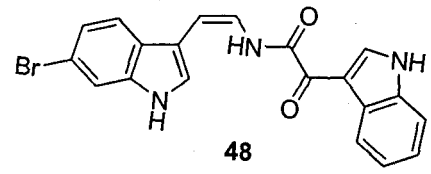
DMSO-d_6, 300 MHz


Br
HN
O
O
NH
N
H
47
DMSO-d_6, 300 MHz
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00



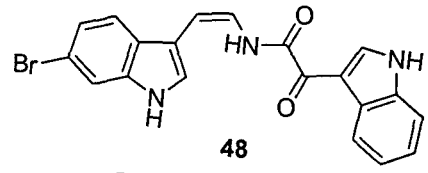
47

DMSO-d_6, 300 MHz



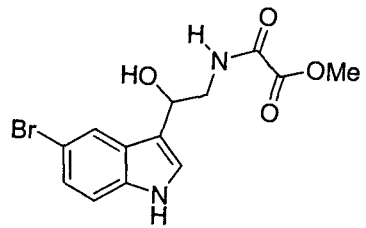
48

DMSO-d_6, 300 MHz

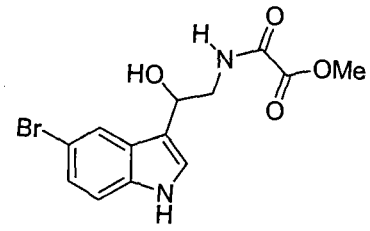


48

DMSO-d_6, 400 MHz

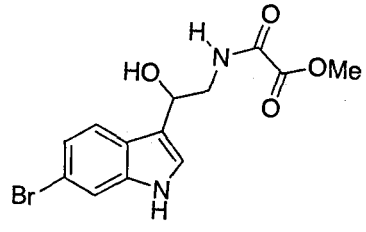


49
DMSO-d_6, 300 MHz



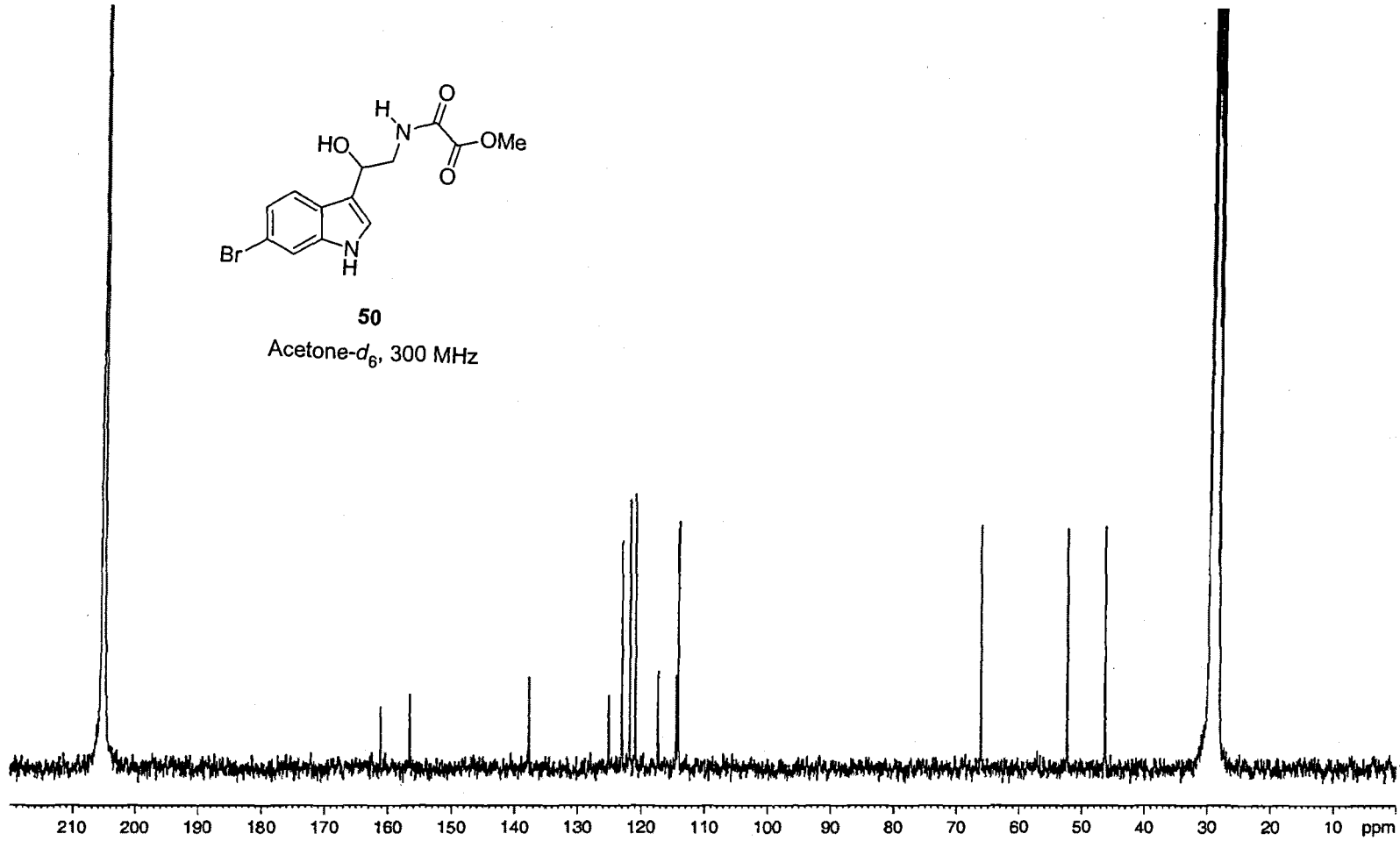
49

DMSO-d_6, 400 MHz



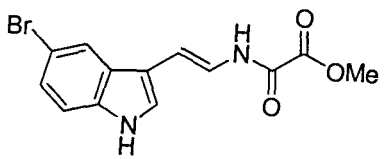
50

Acetone-d_6, 300 MHz



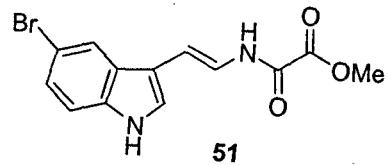
50

Acetone-d_6, 300 MHz



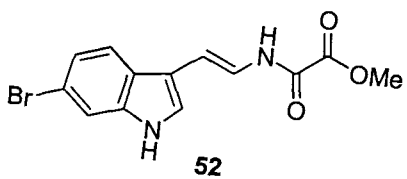
51

Acetone-d_6, 300 MHz



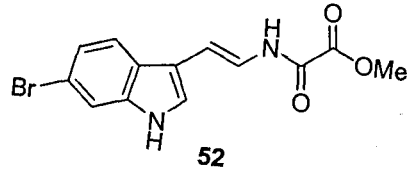
51

Acetone-d_6, 300 MHz



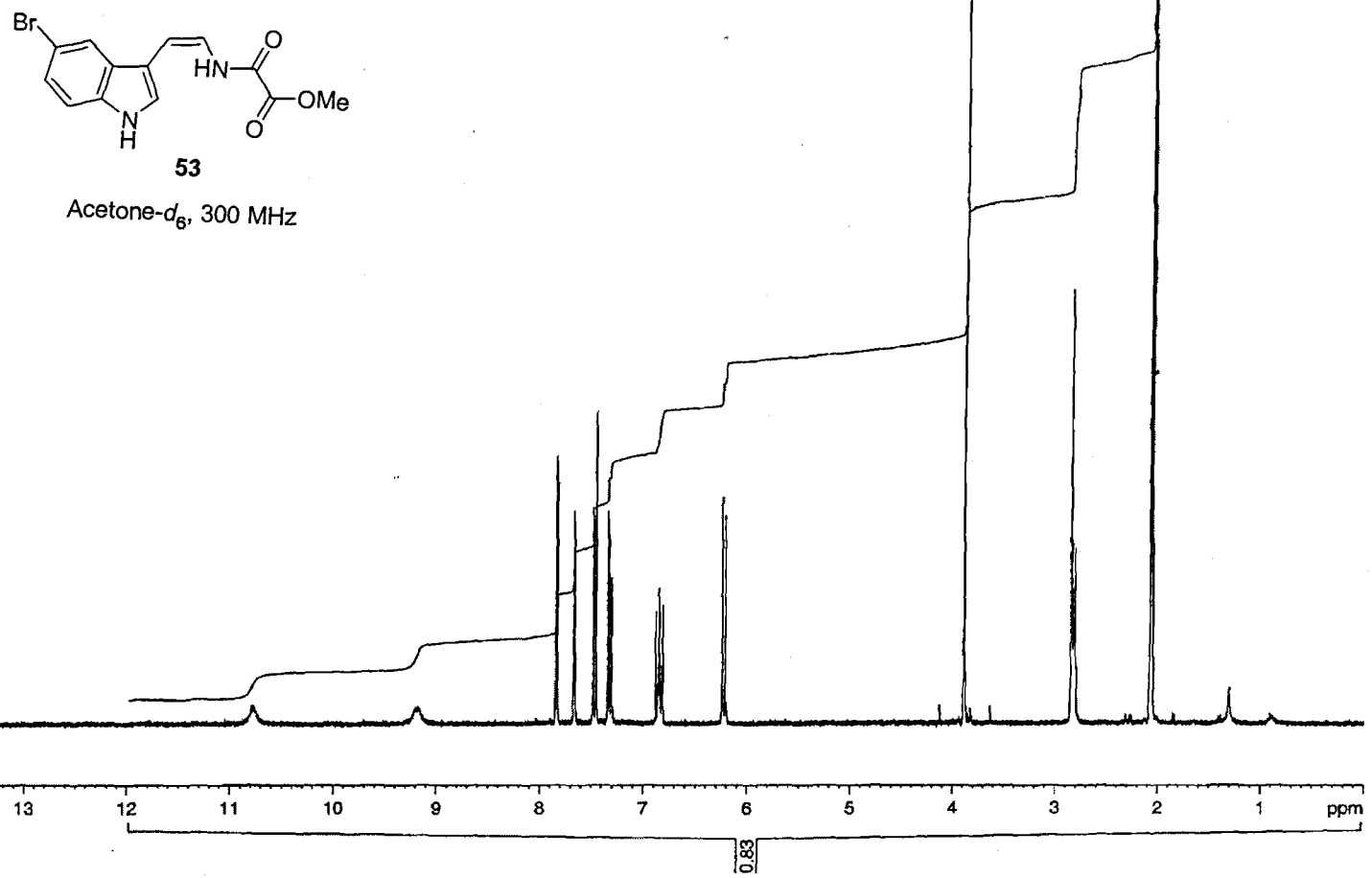
52

Acetone-d_6, 300 MHz



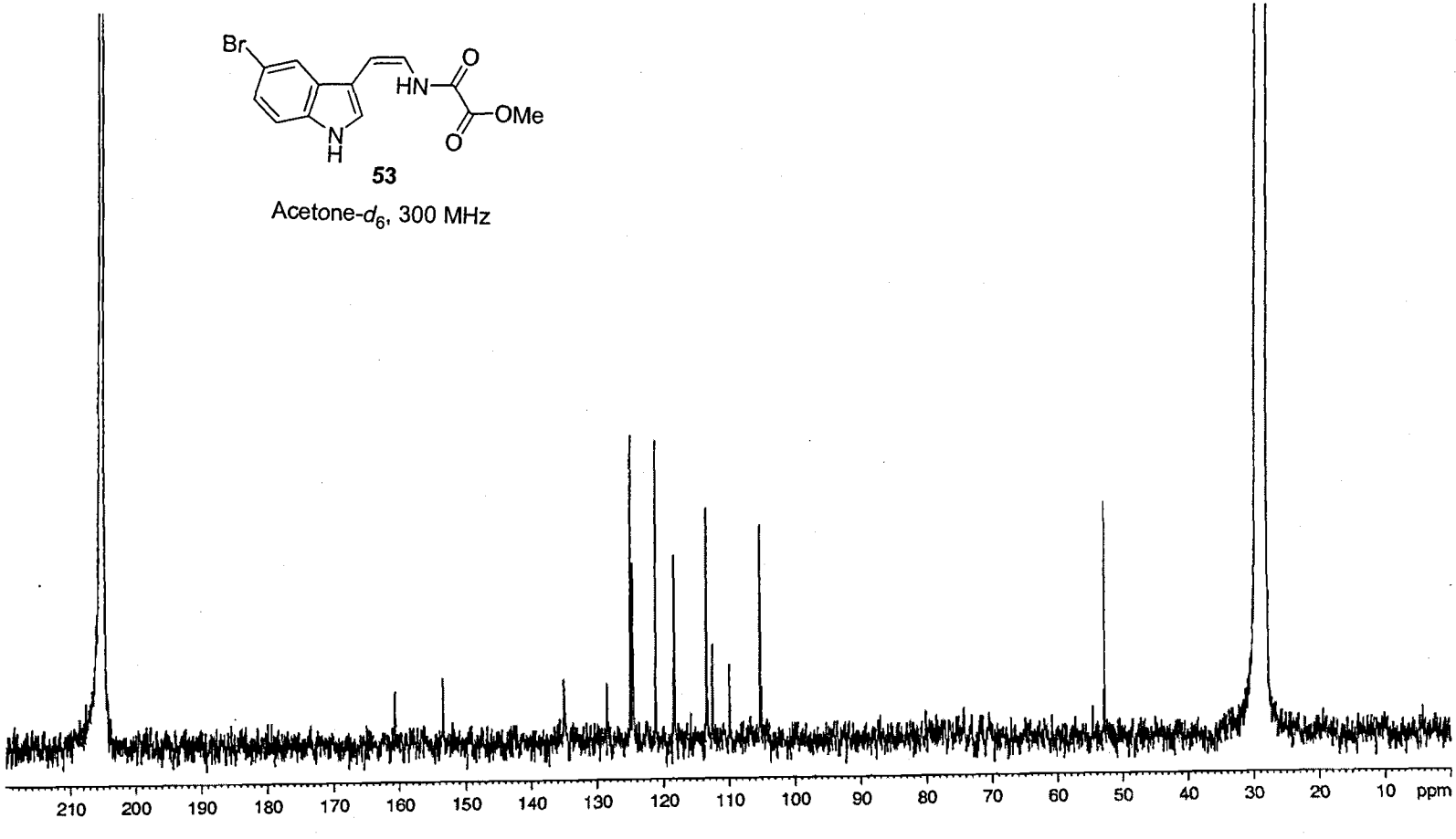
52

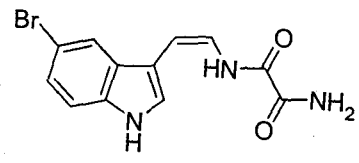
Acetone-d_6, 300 MHz



53

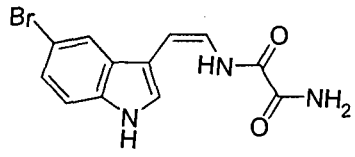
Acetone-d_6, 300 MHz


Br
HN
O
OMe
O
N
H
53
Acetone-d_6, 300 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



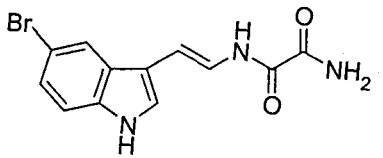
54

DMSO-d_6, 300 MHz



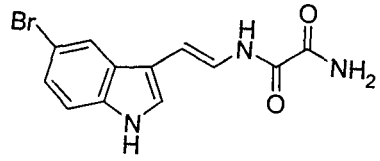
54

DMSO-d_6, 300 MHz



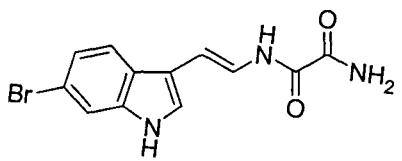
55

DMSO-d_6, 300 MHz



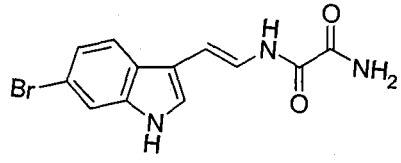
55

DMSO-d_6, 300 MHz



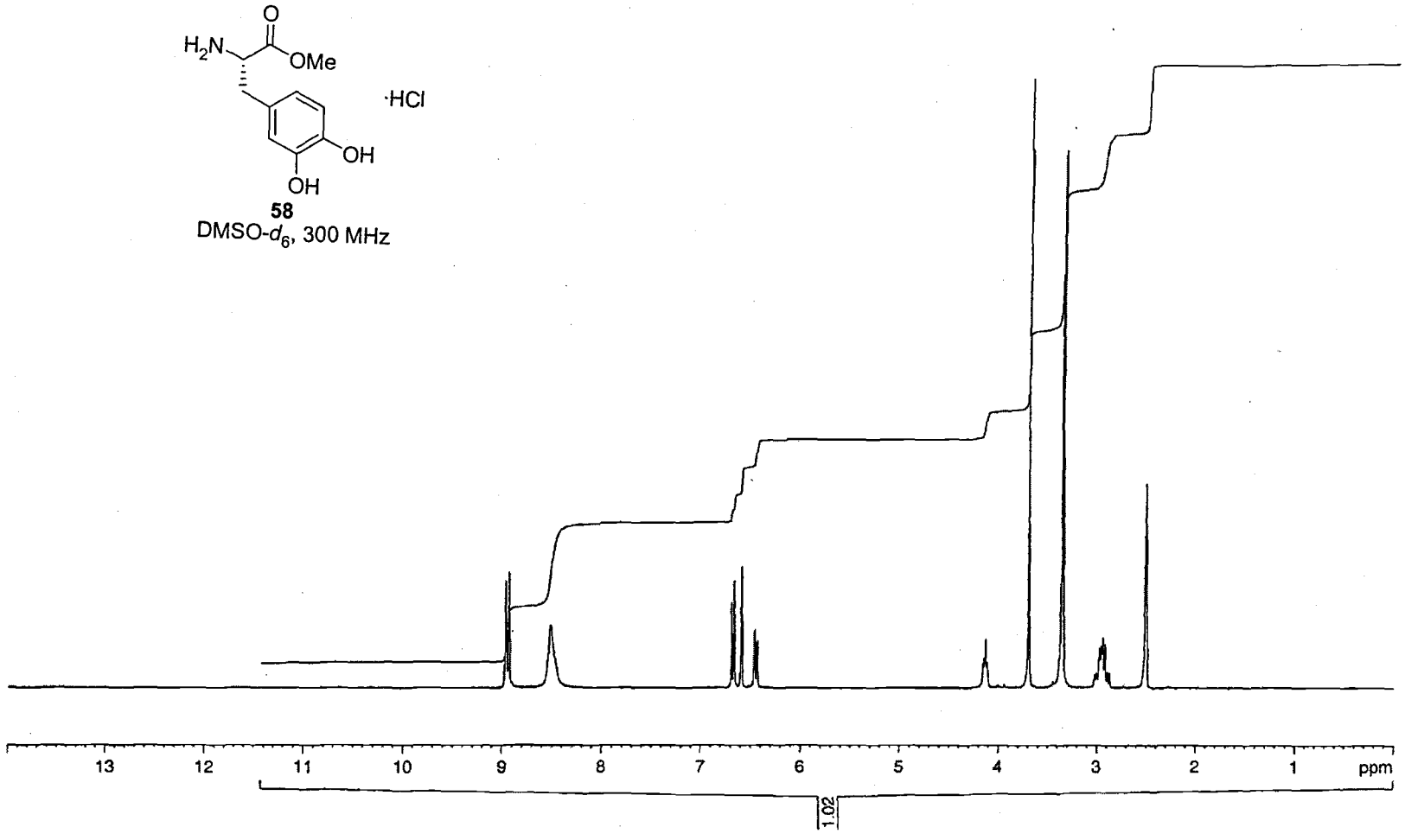
56

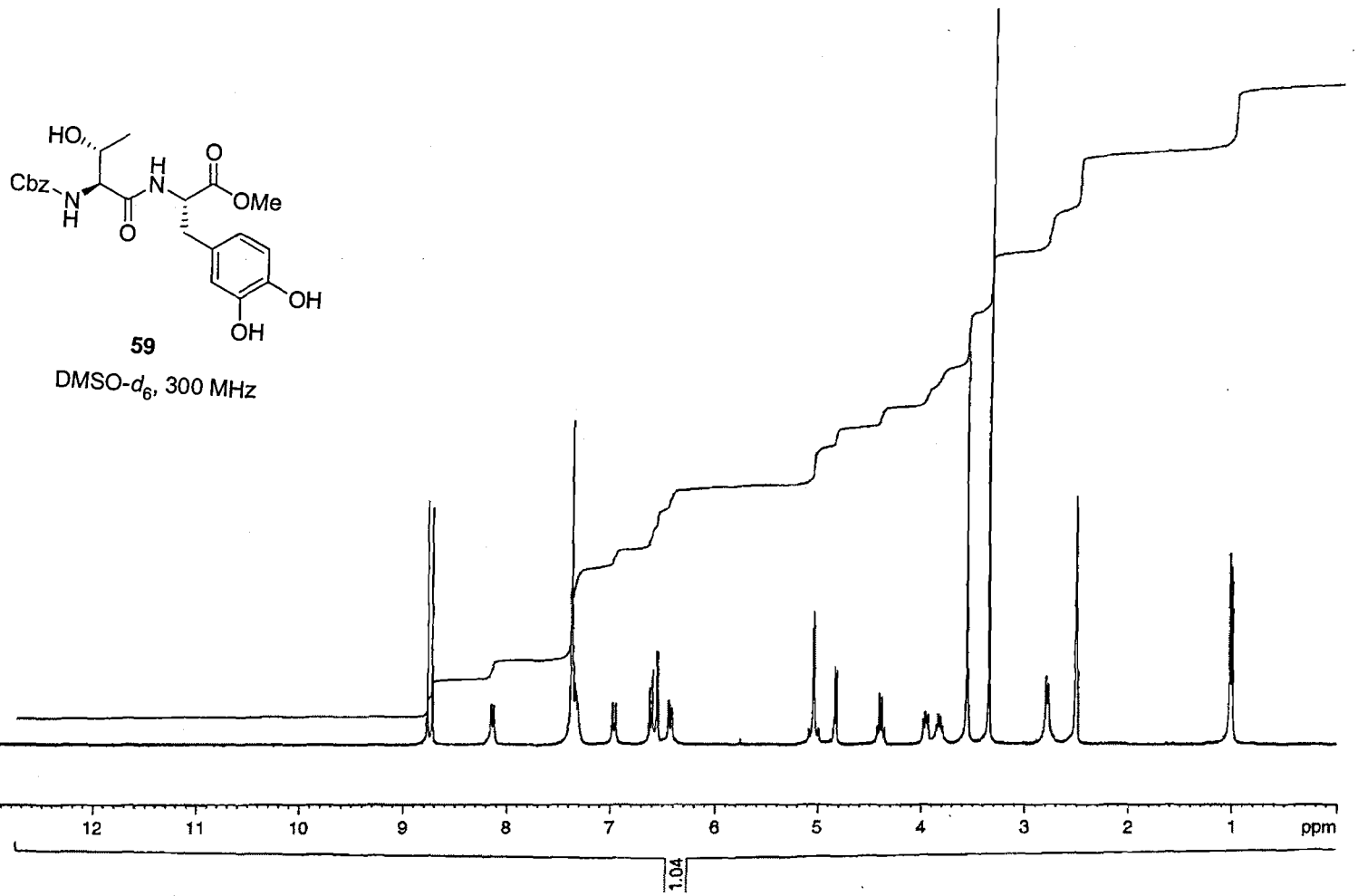
DMSO-d_6, 300 MHz



56

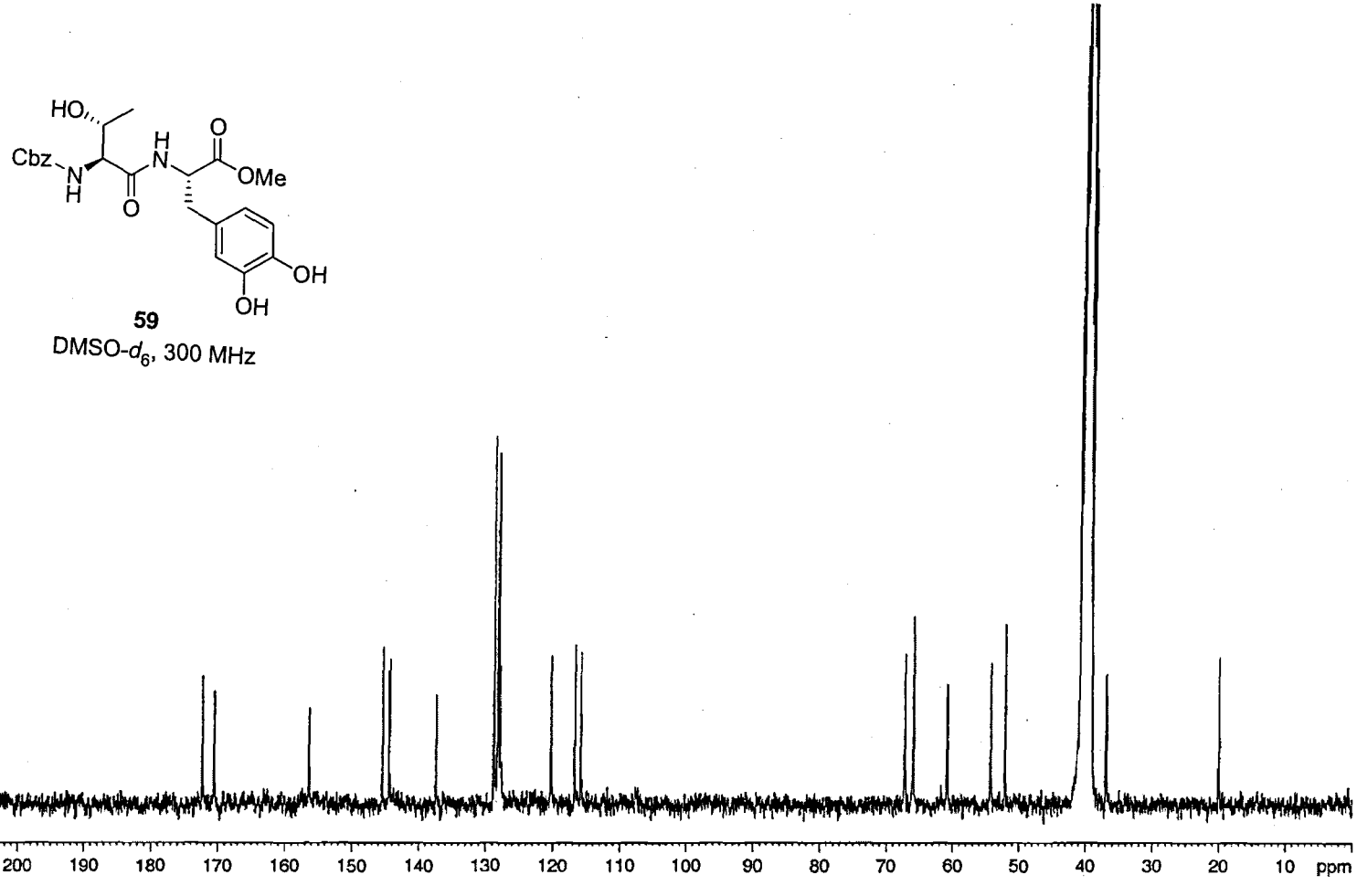
DMSO-d_6, 300 MHz


O
H2N
OMe
·HCl
OH
OH
58
DMSO-d6, 300 MHz
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
20.1



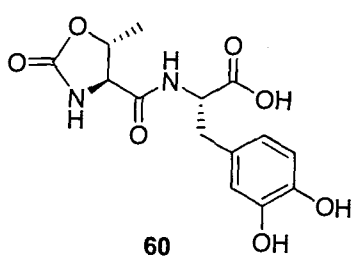
59

DMSO-d_6, 300 MHz



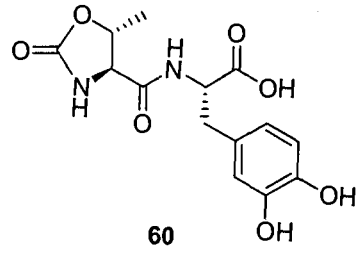
59

DMSO-d_6, 300 MHz



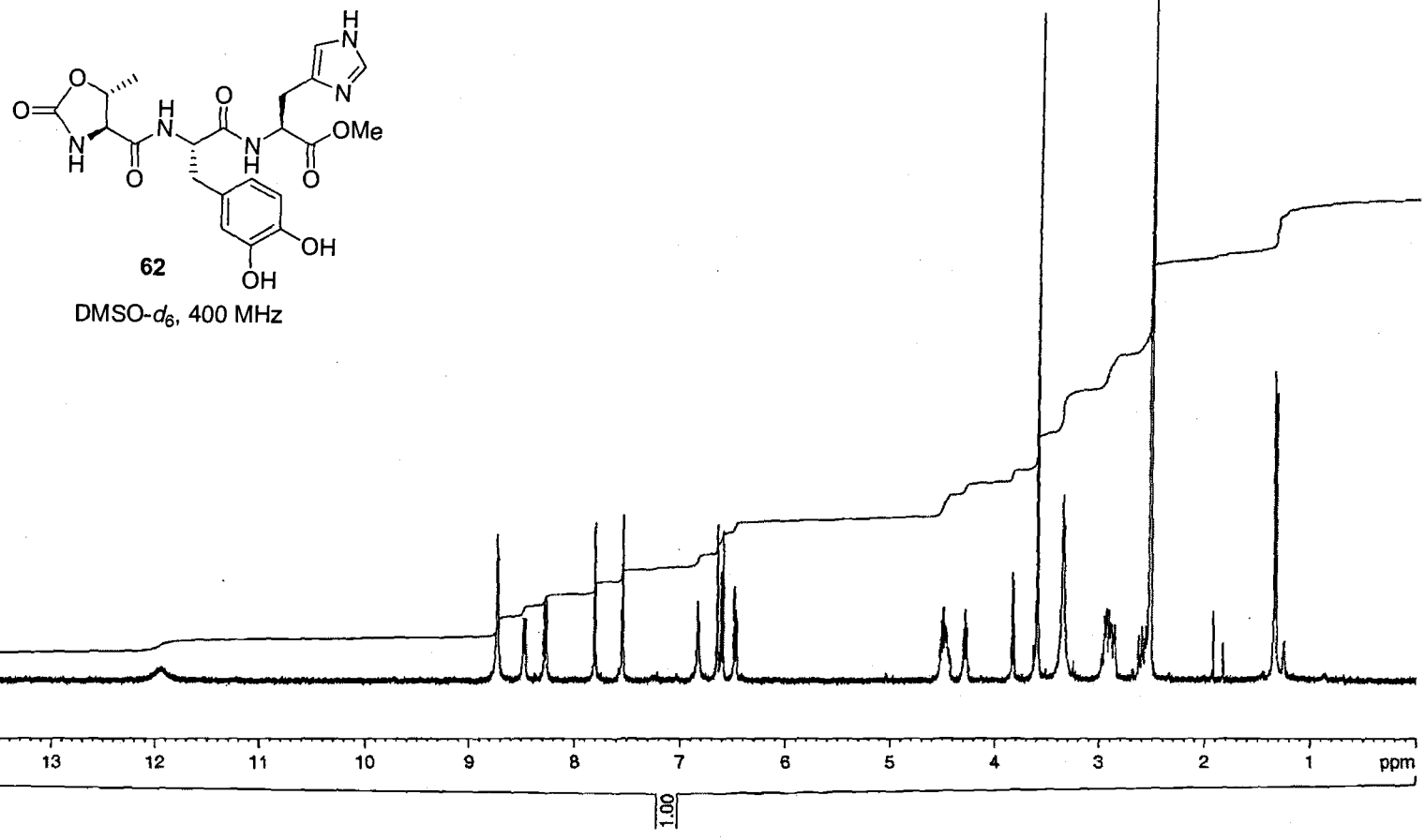
60

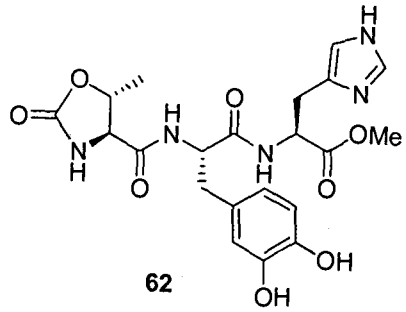
DMSO-d_6, 300 MHz



60

DMSO-d_6, 400 MHz


62
DMSO-d_6, 400 MHz
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00



62

DMSO-d_6, 400 MHz