Graphical Abstract

Better than nature: facile synthesis of tryptophan derivatives

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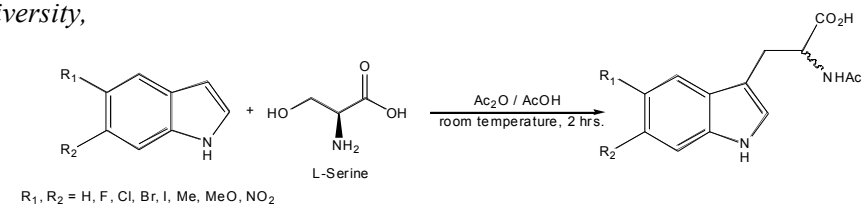
Tryptophan derivatives can be easily synthesised at room temperature using a a wide range of indole derivatives.



R_1, R_2 = H, F, Cl, Br, I, Me, MeO, NO_2

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LETTERS

Better than nature: facile synthesis of tryptophan derivatives

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Abstract—Tryptophan is an essential amino acid important as protein building block, for the anchoring and binding of membrane proteins, substrate in biosynthetic reactions, and as versatile label in protein folding and location studies. As fluorescent molecules, tryptophan derivatives are especially useful in the exact determination of 3-dimensional protein structure in solution and in bound states. This study reports a facile method to synthesise a variety of tryptophan derivatives that are difficult to prepare using alternative enzymatic approaches.

Introduction

Tryptophan is a ubiquitous essential amino acid. A building block of nonribosomal peptides and alkaloids, it has been recognised that tryptophan plays an important role in the binding and anchoring of membrane proteins to the lipid bilayer of cells.[i] Furthermore, molecular tryptophan is also a substrate for the biosynthesis of molecules such as the antifungal, pyrrolnitrin, which proceeds *via* the cleavage of 7-chlorotryptophan.[ii] Due to their fluorescent properties, tryptophan derivatives, are commonly used as probes to determine the 3 dimensional structures and intra- as well as inter molecular distances within proteins and protein complexes.[iii,iv]

Derivatisation of natural products as simple as mono-substitutions and the commonly found introduction of halogen atoms can dramatically impact on the compounds bioactivity and bioavailability.[v] Halogenated amino acids are also activated as possible substrates for further selective functionalisation through reactions such as the Suzuki and the Sonogashira coupling.

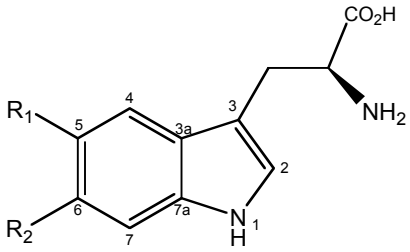

Figure 1: Tryptophan .structures synthesised, where R_1 = H, F, Cl, Br, I, MeO, NO_2; R_2 = H, F, Cl, Br, Me, MeO, NO_2

Tryptophan can be synthesised using a variety of chemical and enzymatic methods; amongst the latter, tryptophan synthase has received much attention.[vi] This enzyme uses indole-3-glycerol phosphate and *L*-serine as substrates to produce *L*-tryptophan in two sequential reactions. Although a variety of substrates is accepted, the accessibility of the enzyme active site places restrictions on the production of a wide range of tryptophan derivatives. Mono-substituted indoles on position 4 and 7 on the indole ring (Figure 1) are normally poor substrates.[vi] A range of substitutions on the ring positions 5 and 6 is tolerated but bulky groups like

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Keywords: Tryptophan derivatives, Acylase, *L*-Serine, Indole
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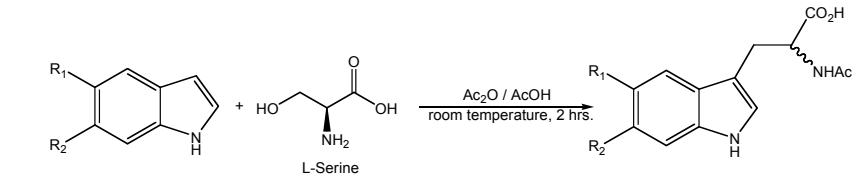
iodo or nitro-substituents or extended alkyl groups cannot be accommodated by the enzyme.



R1, R2 = H, F, Cl, Br, I, Me, MeO, NO2

Table 1. 5-Indole reaction with *L*-serine

No.	Indole Derivative	Ac_2O (equiv)	Yield (%)
1	R_1 = F	2.0	82
2	R_1 = Cl	2.0	86
3	R_1 = Br	2.0	77
4	R_1 = I	1.5	74
5	R_1 = MeO	1.0	80
6	R_1 = NO_2	2.5	44[a]

[a] Lower yield due to electron withdrawing nitro group.

Chemical synthesis can be achieved by a classical S_N2 nucleophilic attack of the C3 indole carbon on an activated electrophile, followed by E1 elimination to restore aromaticity of the ring. The nucleophilic attack is site-specific and stabilised through resonance. If serine is used as electrophile, under the appropriate conditions the resulting product will be a simple tryptophan analogue. Using the right stoichiometry, near quantitative reaction can be achieved, while excess electrophile will be directed onto the C2 position. Using such a chemical approach has the advantage that there are virtually no restrictions in terms of the indole derivates that may be used, giving access to a wide range of products. In this article, we describe the synthesis of a range of 5- and 6-substituted tryptophan derivatives by electrophilic substitution and their subsequent resolution using enzymatic methods.

Results

Using a chemical approach, a wide range of tryptophan derivatives was produced. The products cover a broad spectrum of electron density on the indole ring demonstrating the feasibility of the reaction for a range of indole derivatives. Reaction yields of up to 98% were achieved for the initial preparation of N^{α}-acetylated tryptophan derivatives (Tables 1 and 2). The enzymatic separation of enantiomers made both the free *L*-amino acid and the corresponding N^{α}-acetyl *D*-enantiomer readily available. The *L*-tryptophan derivative could be used directly for further derivatisation such as the introduction of an Fmoc protecting group rendering it as a good substrate for standard solid phase peptide chemistry.

The *D*-enantiomer can be both used to study the naturally less abundant enantiomer of the amino acid or racemised and recycled to produce more *L*-enantiomer.

Table 2. 6-Indole reaction with *L*-serine

No.	Indole Derivative	Ac_2O (equiv)	Yield (%)
7	R_2 = F	2.0	98
8	R_2 = Cl	2.0	86
9	R_2 = Br	2.0	73
10	R_2 = Me	1.5	73
11	R_2 = MeO	1.0	77
12	R_2 = NO_2	2.5	58[a]

[a] Lower yield due to electron withdrawing nitro group.

Discussion

The feasibility and applicability of the synthesis method depends on the electron density distribution on the indole ring. Electron rich indole derivatives such as **5** and **11** were found to be highly reactive towards electrophilic attack. The less electron rich indoles **6** and **12** were less reactive and an excess of the electrophile had to be used to achieve moderate yields. The most likely side-reaction was found to be a double-attachment of the electrophile on position C2 and C3 on the indole ring. These are the classical sites for reactions on the indole ring as the partial electron density is highest on these carbon centres. The side-reaction could be minimized by adjusting the stoichiometry accordingly by increasing the amount of electrophiles slightly for electron deficient indole compounds and reducing the amount of electrophiles for electron rich indole derivatives. Multiple substitution might also be achieved by dilution of the sample.

In contrast to this chemical approach, enzymatic approaches to the synthesis of tryptophan derivatives are limited by the substrate restrictions posed by the enzyme. In tryptophan synthase, indole must first enter the α subunit and pass through a 2.5 nm long tunnel before it reaches the active site in the β subunit.[vii] Indoles with substitutions on the 4 or 7 position will have the greatest width and therefore, may be blocked or hindered. The reported yields for such substrates were poor.[vi] Other sterically hindered substrates such as iodo- or nitro-substituted compounds may not be converted at all.

The yields of the chemical reaction could be improved by recycling unreacted indole starting material from the organic extraction.

A drawback of the reaction is racemisation of the amino acid stereocentre under the coupling conditions. Working under strongly acidic conditions implied that the observed racemization neither proceeded *via* oxazolone formation, nor *via* a classical direct enolization of the serine, both of which require the presence of a base. The mechanism by which the reaction might proceed has been discussed: it was proposed that in the enzymatic pathway of tryptophan synthase, the reactive *L*-serine intermediate is an aminoacrylate.[viii] A patent was filed claiming a reaction between indole derivatives and *N*-acetylated aminoacrylic acid in 1954.[ix] However, there is another paper suggesting a different route.ref

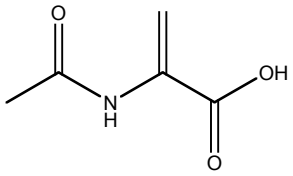


Figure 2: 2-acetamido acrylic acid crystal structure.

2-Acetamido acrylic acid (Figure 2) was identified as a by-product of the reaction in our case, being isolated from reactions with less reactive indoles such as 5- and 6-nitroindole. This suggested that it was an intermediate in the reaction, consistent with the loss of the stereocentre. It was believed to have formed *via* an elimination reaction of serine through loss of AcOH from the acylated intermadiate. However, when *L*-serine was reacted with an excess of acetic anhydride (5 equiv.) in glacial acetic acid, the major product was found to be doubly acetylated *D,L*-serine. No presence of 2-acetamido acrylic was detected in this control experiment in the absence of an indole derivative. This indicates that the acrylic acid is likely to be an unstable reaction product, which, under the reaction conditions with acetic anhydride in vast excess, reacted to form the more stable N_{α}-acetyl-O_{β}-acetyl serine (Ac-Ser(Ac)-OH).

Experimental

Chemicals and Reagents. Chemicals and reagents of the were obtained from Sigma Aldrich or Fisher Scientific UK if not stated otherwise. All reagents were of the highest quality and were used without further purification. Deuterated solvents were used as supplied from GOSS. The enzyme "Amano Acylase" was used as purchased from Amano Enzyme Inc., Nagoya, Japan.

Synthesis 5- & 6-mono-substituted tryptophan derivatives. *L*-serine (0.2 mmol) was dissolved in a solution of the substituted indole (0.1 mmol) in acetic acid (0.24 ml) and acetic anhydride (0.9 mmol). The mixture was stirred under argon at 73 °C for 2 h. Upon cooling the solution was treated with diethyl ether (2 ml), adjusted to pH 11 using 30% sodium hydroxide solution and further diluted with ether (3 ml). The layers were partitioned and treated separately. The ether layer was further extracted with 1 *N* sodium hydroxide solution (2 x 2 ml) and a small amount of sodium thiosulphate $Na_2S_2O_4$ was added. The aqueous solutions were combined, neutralized to pH 7 using concentrated hydrochloric acid and the volume reduced to 50% by evaporation under vacuum. If precipitation occurred, samples were stored at 4 °C for 24 hours to allow further precipitation. Precipitates were filtered and dried under vacuum. The filtrate was further concentrated to half its original volume and any further precipitates collected. Otherwise the filtrates were acidified to pH 3 with 5% hydrochloric acid, extracted with ethyl acetate (3 x 7 ml) and dried over magnesium sulphate. After filtration, the solvent was removed under vacuum and the residue treated with benzene and re-evaporated to yield the desired mono-substituted *D,L*-tryptophan derivative. The ether layer was dried over magnesium sulphate. Removal of the solvent under vacuum recovered unreacted indole starting material.

Enzymatic resolution of 5- & 6-mono-substitued D,L-*tryptophan derivatives*. Borate buffer solution was prepared from sodium tetraborate decahydrate (1.9 g, 0.05 M) in deionised water (100 ml). The pH was adjusted to pH 8.00 using concentrated hydrochloric acid. Cobalt(II) chloride hexahydrate (0.5 mg, 3.9 μmol) was added to a final concentration of 0.125 mM.

N-acetylated-*D,L*-tryptophan amino acid (0.40 mmol) was dissolved in borate buffer solution (5 ml). A solution of acylase (100 mg) in borate buffer (10 ml) was added under stirring. The reaction mixture was stirred at 37 °C for 48 hours. The reaction was quenched by adjusting the pH to 5 using 10% hydrochloric acid. Subsequently the mixture was filtered through a celite pad and the filtrate extracted into ethyl acetate (3 x 25 ml). The organic layer was dried over magnesium sulphate, filtered and the solvent removed under vacuum to afford the crude unreacted *N*-acetyl-*D*-tryptophan derivative. The aqueous phase was purified by ion-exchange chromatography using DOWEX® Resin 50X2-200. The resin was prepared prior to the run through deprotonation and protonation via 0.1 *M* sodium hydroxide solution and 0.1 *M* hydrochloride solution respectively. Water and methanol eluents were used to wash the resin before its application. The column was prepared for loading by protonation of the acceptor sites with 0.1 *M* HCl solution. The product, dissolved in the aqueous phase, was then applied to the column and eluted first with water (150 ml) and then with 10% ammonia in methanol (200 ml). Fractions which showed UV activity and responded positively to a ninhydrin test were collected and the solvent removed under vacuum to afford the *L*-enantiomer of the free amino acid.

Methyl-Esterification: *N*-Acetylated-*L*-tryptophan amino acid (0.1 mmol) was dissolved in excess methanol (5 ml). Concentrated sulphuric acid (0.15 ml) was added as a

catalyst. The reaction mixture was refluxed for 2 hours and neutralized upon cooling using 0.5 *M* aqueous sodium carbonate solution. The solvents were removed under vacuum and the residues re-dissolved in deionised water (2 ml). The product was extracted from the aqueous phase using dichloromethane (3 x 2 ml). The organic layer was separated and washed with 0.5 *M* aqueous sodium carbonate solution (2 ml) and deionised water (2 x 2 ml). The DCM mixture was then dried over magnesium sulphate, filtered and the solvent removed under vacuum to yield the crude product which was used without further purification for the ethyl amidation reaction.

Ethyl amidation. The *N*-acetylated-*L*-tryptophan methyl ester derivative (0.1 mmol) was dissolved in a solution of ethylamine in methanol (50 % v/v) (5 ml). The reaction was carried out at 0 °C for 24 hours. Solvents were removed under vacuum and reaction was repeated to improve the yield. The crude product was purified by silica flash column chromatography (95% DCM, 5% EtOH).

Experimental Data Analysis. Purity of compounds was checked with Varian Unity 300 and Varian Unity 400 NMR spectrometers. Liquid chromatography coupled with mass spectroscopy was employed for further analysis of compounds. Electro spray (ES+) was used as ionisation mode. A Micromass LCT mass spectrometer and a LC Waters 2795 instrument were used.

Conclusion

Various mono-substituted tryptophan analogues were synthesised using a combined acylation-resolution methodology. A wide range of substrates demonstrated the feasibility of the methodology. Using a variety of indole derivatives it was shown that this synthesis provides a facile route to protein chemistry precursors such as *L*- and *D*-Fmoc-protected tryptophan analogues. Mimics of the amino acid as it is as a residue in proteins were synthesised in good yield and optical purity.

Acknowledgments

EPSRC and Durham University are gratefully acknowledged for funding.

Supporting Information

N-Acetyl-5-fluoro-*D,L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.90 (s, 3H), 3.11 (dd, *J* = 7.6, 15.6, 1H), 3.26 (d, *J* = 6.0 , 1H), 4.68 (dd, *J* = 5.2, 7.6, 1H), 6.84 (dt, *J* = 2.8, 8.4, 1H), 7.14 (s, 1H), 7.21 (dd, *J* = 2.0, 10.0, 1H), 7.26 (dd, 1H, J = 3.6, 8.4 Hz). ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.38, 28.44, 54.71, 103.77, 110.31, 110.57, 112.95, 113.05, 126.38, 134.56, 157.80, 160.11, 173.18. MS (ES+) *m/e* 287.1 $[m+Na]^+$. Mp

N-Acetyl-5-chloro-*D,L*-tryptophan

^{1}H NMR (400 MHz, Acetone – d_6): δ 1.90 (s, 3H), 3.17 (dd, 1H, J = 7.0, 15.0 Hz), 3.30 (dd, 1H, J = 5.5, 15.0 Hz), 4.77 (dd, 1H, J = 5.5, 13.0 Hz), 7.06 (d, 1H, J = 7.5 Hz), 7.24 (s, 1H), 7.27 (d, 1H, J = 7.5 Hz), 7.60 (s, 1H); ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.40, 28.32, 54.75, 108.27, 111.51, 112.19, 120.35, 124.44, 124.75, 130.56, 136.02, 173.18, 175.11,; **MS** (ES+) *m/e* 303.2 $[m+Na]^+$, 305.2 $[m+Na]^+$

N-Acetyl-5-bromo-*D,L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.91 (s, 3H), 3.12 (dd, 1H, J = 6.4, 12 Hz), 3.30 (dd, 1H, J = 4.4, 11.6 Hz), 4.70 (dd, 1H, J = 4.0, 6.0 Hz), 6.98 (dt, 1H, J = 1.6, 6.8 Hz), 7.10 (s, 1H), 7.31 (d, 1H, J = 1.2 Hz), 7.49 (d, 1H, J = 2.8 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.41, 28.28, 54.81, 111.02, 112.99, 113.92, 121.94, 125.08, 125.93, 130.76, 136.62, 173.18, 175.23; MS (ES+) *m/e* 347.1 $[m+Na]^+$, 349.1 $[m+Na]^+$, 325.1 $[m+H]^+$, 327.1 $[m+H]^+$

N-Acetyl-5-iodo-*D,L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.92 (s, 3H), 3.10 (dd, 1H, J = 8.0, 14.8 Hz), 3.31 (dd, 1H, J = 5.2, 14.8 Hz), 4.67 (dd, 1H, J = 5.2, 8.0 Hz), 7.07 (s, 1H), 7.14 (d, 1H, J = 8.4 Hz), 7.32 (dd, 1H, J = 1.6, 8.4 Hz), 7.88 (d, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.46, 28.23, 54.83, 82.75, 110.69, 114.43, 125.58, 128.37, 130.67, 131.61, 137.01, 173.18, 174.95; MS (ES+) *m/e* 395.1 $[m+Na]^+$

N-Acetyl-5-methoxy-*D,L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.91 (s, 3H), 3.12 (dd, 1H, J = 7.6, 14.8 Hz), 3.30 (dd, 1H, J = 5.2, 14.4 Hz), 3.82 (s, 3H), 4.70 (dd, 1H, J = 5.2, 7.2 Hz), 6.74 (dd, 1H, J = 2.0 Hz, 8.8 Hz), 7.05 (s, 2H), 7.20 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.44, 30.68, 54.74, 56.23, 101.09, 110.82, 112.72, 112.92, 125.06, 129.06, 133.23, 155.09, 173.19, 175.28; MS (ES+) *m/e* 299.1 $[m+Na]^+$

N-Acetyl-5-nitro-*D,L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.92 (s, 3H), 3.22 (dd, 1H, J = 7.6, 14.8 Hz), 3.39 (dd, 1H, J = 5.2, 14.8 Hz), 4.74 (dd, 1H, J = 5.2, 7.6 Hz), 7.31 (s, 1H), 7.43 (d, 1H, J = 7.2 Hz), 8.01 (dd, 1H, J = 2.0, 8.8 Hz), 8.56 (d, 1H, J = 2.4 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.39, 28.14, 54.70, 112.45, 114.26, 116.82, 116.82, 117.84, 128.25, 141.01, 142.46, 173.21, 174.65; MS (ES+) *m/e* 314.1 $[m+Na]^+$

N-Acetyl-6-fluoro-*D,L*-tryptophan

^{1}H NMR (500 MHz, MeOH – d_4): δ 1.90 (s, 3H), 3.12 (dd, 1H, J = 8.0, 14.5 Hz), 4.69 (dd, 1H, J = 5.5, 10 Hz), 6.79 (dt, 1H, J = 2.5 Hz, 10.0 Hz), 7.01 (dd, 1H, J = 2.0 Hz, 10.0 Hz), 7.07 (s, 1H), 7.45 (dd, 1H, J = 5.5 Hz, 9.0 Hz); ^{13}C

NMR (125 MHz, MeOH – d_4): δ 22.37, 28.43, 54.71, 108.09, 110.14, 111.40, 120.14, 124.79, 125.60, 137.87, 160.23, 173.18, 175.12; MS (ES+) *m/e* 287.1 $[m+Na]^+$, 265.1 $[m+H]^+$

N-Acetyl-6-chloro-*D,L*-tryptophan

^{1}H NMR (500 MHz, MeOH – d_4): δ 1.89 (s, 3H), 3.12 (dd, 1H, J = 8.0, 15 Hz), 4.70 (dd, 1H, J = 5.0, 7.5 Hz), 6.98 (dd, 1H, J = 2.0, 8.5 Hz), 7.10 (s, 1H), 7.31 (d, 1H, J = 1.5 Hz), 7.50 (d, 1H, J = 6.5 Hz); ^{13}C NMR (125 MHz, MeOH – d_4): δ 22.38, 28.33, 54.69, 111.50, 112.03, 120.28, 120.34, 125.3, 127.59, 128.29, 138.33, 173.17, 175.07; MS (ES+) *m/e* 303.1 $[m+Na]^+$, 305.1 $[m+Na]^+$, 281.1 $[m+H]^+$, 283.1 $[m+H]^+$

N-Acetyl-6-bromo-*D,L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.89 (s, 3H), 3.12 (dd, 1H, J = 8.0, 14.4 Hz), 4.69 (dd, 1H, J = 4.2, 8.4 Hz), 7.09 (s, 1H), 7.11 (dd, 1H, J = 2.0, 8.8 Hz), 7.45 (s, 1H), 7.47 (m, 1H); ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.38, 28.30, 54.66, 111.80, 112.34, 120.97, 121,26, 125,83, 127.92, 128.34, 138.55, 173.18, 175.10; MS (ES+) *m/e* 347.2 $[m+Na]^+$, 349.2 $[m+Na]^+$

N-Acetyl-6-methyl-*D,L*-tryptophan

^{1}H NMR (500 MHz, MeOH – d_4): δ 1.89 (s, 3H), 2.40 (s, 3H), 3.11 (dd, 1H, J = 8.0, 14.5 Hz), 4.69 (dd, 1H, J = 5.0, 8.0 Hz), 6.85 (d, 1H, J = 8.5 Hz), 6.99 (s, 1H), 7.11 (s, 1H), 7.42 (d, 1H, J = 9.0 Hz), 7.63 (s, 1H); ^{13}C NMR (125 MHz, MeOH – d_4): δ 21.78, 22.39, 28.55, 54.80, 110.90, 112.12, 118.93, 121.54, 123.61, 126.83, 132.02, 138.49, 173.18, 175.28; MS (ES+) *m/e* 283.2 $[m+Na]^+$, 261.2 $[m+H]^+$

N-Acetyl-6-methoxy-*D,L*-tryptophan

^{1}H NMR (500 MHz, MeOH – d_4): δ 1.90 (s, 3H), 3.09 (dd, 1H, J = 8.0, 14.5 Hz), 3.29 (dd, 1H, J = 6.0, 14.5 Hz), 3.78 (s, 3H), 4.67 (dd, 1H, J = 5.0, 7.5 Hz), 6.67 (dd, 1H, J = 8.0 Hz), 6.80 (d, 1H, J = 8.5 Hz), 7.36 (s, 1H), 7.63 (s, 1H); ^{13}C NMR (125 MHz, MeOH – d_4): δ 22.44, 30.68, 55.18, 57.12, 94.50, 108.62, 110.01, 118.78, 121.64, 125.06, 136.30, 155.21, 169.27, 173.63 ; MS (ES+) *m/e* 283.2 $[m+Na]^+$, 261.2 [m+H]

N-Acetyl-6-nitro-*D,L*-tryptophan

^{1}H NMR (500 MHz, MeOH – d_4): δ 1.90 (s, 3H), 3.09 (dd, 1H, J = 8.0, 14.5 Hz), 3.29 (dd, 1H, J = 6.0, 14.5 Hz), 3.78 (s, 3H), 4.67 (dd, 1H, J = 5.0, 7.5 Hz), 6.67 (dd, 1H, J = 8.0 Hz), 6.80 (d, 1H, J = 8.5 Hz), 7.36 (s, 1H), 7.63 (s, 1H); ^{13}C NMR (125 MHz, MeOH – d_4): δ 22.44, 30.68, 55.18, 57.12, 94.50, 108.62, 110.01, 118.78, 121.64, 125.06, 136.30, 155.21, 169.27, 173.63 ; MS (ES+) *m/e* 283.2 $[m+Na]^+$, 261.2 [m+H]

N-acetyl-5-fluoro-*D*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.90 (s, 3H), 3.11 (dd, 1H, J = 7.6, 14.8 Hz), 3.26 (d, 1H, J = 6.0 Hz), 4.68 (dd, 1H, J = 5.2, 7.6 Hz), 6.84 (dt, 1H, J = 2.4, 9.2 Hz), 7.14 (s, 1H), 7.21 (dd, 1H, J = 2.4, 10.4 Hz), 7.27 (dd, 1H, J = 4.8, 8.8 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.38, 28.45, 54.71, 103.77, 110.31, 111.34, 112.96, 126.38, 129.27, 134.57, 157.81, 173.18, 175.13; MS (ES+) *m/e* 265.2 $[m+H]^+$

N-acetyl-5-chloro-*D*-tryptophan

^{1}H NMR (500 MHz, MeOH – d_4): δ 1.91 (s, 3H), 3.11 (dd, 1H, J = 10.0, 18.5 Hz), 3.29 (dd, 1H, J = 5.5, 18.5 Hz), 4.69 (dd, 1H, J = 6.5, 10.5 Hz), 7.11 (dt, 1H, J = 3.0, 11.5 Hz), 7.15 (s, 1H), 7.23 (dd, 1H, J = 3.0, 12.0 Hz), 7.68 (dd, 1H, J = 6.0, 11.0 Hz); ^{13}C NMR (125 MHz, MeOH – d_4): δ 22.42, 28.23, 54.76, 110.91, 112.98, 113.90, 121.89, 125.06, 125.91, 130.68, 136.53, 173.18, 175.27; MS (ES+) *m/e* 282.2 $[m+H]^+$, 284.2 $[m+H]^+$

N-acetyl-5-bromo-*D*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.91 (s, 3H), 3.11 (dd, 1H, J = 8.0, 14.4 Hz), 3.30 (dd, 1H, J = 5.2, 14.8 Hz), 4.69 (dd, 1H, J = 5.2, 7.6 Hz), 7.12 (s, 1H), 7.16 (dd, 1H, J = 2.0, 8.8 Hz), 7.24 (d, 1H, J = 8.8 Hz), 7.68 (d, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.41, 28.27, 54.78, 111.00, 112.99, 113.93, 121.93, 125.09, 130.75, 136.61, 173.19, 174.98; MS (ES+) *m/e* 325.2 $[m+H]^+$, 327.2 $[m+H]^+$

N-acetyl-5-iodo-*D*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.92 (s, 3H), 3.11 (dd, 1H, J = 8.0, 14.8 Hz), 3.32 (dd, 1H, J = 5.2, 14.8 Hz), 4.69 (dd, 1H, J = 5.2, 8.0 Hz), 7.07 (s, 1H), 7.14 (d, 1H, J = 8.4 Hz), 7.32 (dd, 1H, J = 1.6, 8.4 Hz), 7.88 (d, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.48, 28.25, 54.85, 82.73, 110.71, 114.40, 125.61, 128.39, 130.69, 131.65, 137.05, 173.20, 174.91; MS (ES+) *m/e* 395.1 $[m+Na]^+$

N-acetyl-5-methyl-*D*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.90 (s, 3H), 2.40 (s, 3H), 3.10 (dd, 1H, J = 8.0, 14.8 Hz), 3.31 (dd, 1H, J = 4.8, 14.8 Hz), 4.69 (dd, 1H, J =5.2, 8.0 Hz), 6.91 (dd, 1H, J = 2.0, 8.0 Hz), 7.03 (s, 1H), 7.19 (d, 1H, J = 8.0 Hz), 7.33 (t, 1H, J = 0.8 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 21.69, 22.39, 28.49, 54.84, 110.53, 111.95, 118.86, 124.00, 124.38, 128.80, 129.10, 136.40, 173.18, 175.31; MS (ES+) *m/e* 261.2 $[m+H]^+$

N-acetyl-5-methoxy-*D*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.91 (s, 3H), 3.12 (dd, 1H, J = 8.0, 14.8 Hz), 3.30 (dd, 1H, J = 4.8, 14.8 Hz), 3.81 (s, 3H), 4.69 (dd, 1H, J = 5.2, 8.0 Hz), 6.74 (dd, 1H, J = 2.4, 8.8 Hz), 7.05 (s, 2H), 7.20 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 20.75, 22.44, 28.52, 54.73, 56.24, 101.10, 110.81, 112.72, 125.07, 129.17,

133.22, 155.08, 173.19, 175.28; MS (ES+) *m/e* 276.1 $[m+H]^+$

N-acetyl-5-nitro-*D*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.91 (s, 3H), 3.21 (dd, 1H, J = 7.6, 14.8 Hz), 3.37 (dd, 1H, J = 5.6, 14.8 Hz), 4.76 (dd, 1H, J = 5.6, 7.6 Hz), 7.32 (s, 1H), 7.43 (d, 1H, J = 7.2 Hz), 8.01 (dd, 1H, J = 2.4, 8.4 Hz), 8.57 (d, 1H, J = 2.4 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 22.41, 28.16, 54.74, 112.52, 114.28, 116.85, 116.84, 117.86, 128.28, 141.05, 142.44, 173.24, 174.63; MS (ES+) *m/e* 314.1 $[m+Na]^+$

N-acetyl-6-fluoro-*D*-tryptophan

^{1}H NMR (500 MHz, DMSO – d_6): δ 1.78 (s, 3H), 2.96 (dd, 1H, J = 9.5, 16 Hz), 3.11 (dd, 1H, J = 5.0, 15.0 Hz), 4.43 (m, 1H), 6.83 (dd, 1H, J = 2.0 Hz, 9.5 Hz), 7.09 (dd, 1H, J = 2.5, 10.0 Hz), 7.12 (d, 1H, J = 2.5 Hz), 7.48 (dd, 1H, J = 5.0, 7.0 Hz), 8.15 (d, 1H, J = 10.0 Hz), 10.90 (s, br, 1H); ^{13}C NMR (125 MHz, DMSO – d_6): δ 20.39, 27.03, 52.89, 97.19, 97.39, 106.71, 106.90, 119.19, 124.08, 135.90, 157.86, 169.20, 173.47; MS (ES+) *m/e* 287.1 $[m+Na]^+$

N-acetyl-6-chloro-*D*-tryptophan

^{1}H NMR (400 MHz, DMSO – d_6): δ 1.78 (s, 3H), 2.96 (dd, 1H, J = 8.8, 14.8 Hz), 3.12 (dd, 1H, J = 5.2, 14.8 Hz), 4.42 (sex, 1H, J = 3.2, 6.8, 16.8 Hz), 6.98 (dd, 1H, J = 2.0, 8.4 Hz), 7.17 (d, 1H, J = 2.4 Hz), 7.36 (d, 1H, J = 1.6 Hz), 7.51 (d, 1H, J =8.4 Hz), 8.14 (d, 1H, J = 2.0 Hz), 10.98 (s, br, 1H); ^{13}C NMR (100 MHz, DMSO – d_6): δ 20.78, 26.95, 52.91, 110.39, 110.98, 118.69, 119.60, 124.74, 125.67, 126.06, 136.42, 170.37, 173.45; MS (ES+) *m/e* 281.2 $[m+H]^+$, 283.2 $[m+H]^+$

N-acetyl-6-bromo-*D*-tryptophan

^{1}H NMR (500 MHz, DMSO – d_6): δ 1.78 (s, 3H), 2.96 (dd, 1H, J = 9.0, 15 Hz), 3.11 (dd, 1H, J = 5.0, 14.0 Hz), 4.42 (dd, 1H, J = 7.0, 11.0 Hz), 7.10 (dd, 1H, J = 2.0, 8.5 Hz), 7.16 (d, 1H, J = 2.5 Hz), 7.47 (d, 1H, J = 9.0 Hz), 7.50 (d, 1H, J = 1.5 Hz), 8.11 (d, 1H, J = 7.5 Hz), 10.65 (s, br, 1H); ^{13}C NMR (125 MHz, DMSO – d_6): δ 20.76, 26.92, 52.89, 110.40, 113.68, 113.90, 120.00, 121.21, 124.66, 126.29, 136.92, 170.34, 173.40; MS (ES+) *m/e* 347.1 $[m+Na]^+$, 349.1 $[m+Na]^+$

N-acetyl-6-methyl-*D*-tryptophan

^{1}H NMR (500 MHz, DMSO – d_6): δ 1.78 (s, 3H), 2.36 (s, 3H), 2.93 (dd, 1H, J = 8.5, 14.5 Hz), 3.10 (dd, 1H, J = 5.5, 15.0 Hz), 4.42 (dd, 1H, J = 7.0, 9.5 Hz), 6.80 (dd, 1H, J = 4.0, 8.0 Hz), 7.02 (d, 1H, J = 2.0 Hz), 7.10 (s, 1H), 7.38 (d, 1H, J = 8.0 Hz), 8.11 (d, 1H, J = 9.5 Hz), 10.65 (s, br, 1H); ^{13}C NMR (100 MHz, DMSO – d_6): δ 20.77, 22.41, 27.22, 52.98, 109.80, 111.18, 117.88, 120.12, 122.77, 125.16, 129.87, 136.53, 170.36, 173.59; MS (ES+) *m/e* 261.2 $[m+H]^+$

N-acetyl-6-methoxy-*D*-tryptophan

^{1}H NMR (500 MHz, DMSO – d_6): δ 1.78 (s, 3H), 2.94 (dd, 1H, J = 8.5, 14.5 Hz), 3.06 (dd, 1H, J = 5.5, 14.5 Hz), 3.73 (s, 3H), 4.40 (dd, 1H, J = 7.0, 9.5 Hz), 6.63 (dd, 1H, J = 3.0, 11.0 Hz), 6.81 (d, 1H, J = 3.0 Hz), 7.34 (d, 1H, J = 3.0, 11.0 Hz), 8.11 (d, 1H, J = 9.5 Hz), 10.62 (s, br, 1H); ^{13}C NMR (100 MHz, DMSO – d_6): δ 22.43, 27.24, 55.15, 59.79, 94.45, 108.60, 109.98, 118.77, 121.60, 122.09, 136.79, 155.48, 170.39, 173.62; MS (ES+) *m/e* 276.2 $[m+H]^+$

5-Fluoro-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 3.14 (dd, 1H, J = 8.8 Hz, 15.2 Hz), 3.82 (dd, 1H, J = 4.0 Hz, 9.2 Hz), 6.88 (dt, 1H, J = 1.6, 9.2 Hz), 7.24 (s, 1H), 7.31 (dd, 1H, J = 4.8, 8.4 Hz), 7.40 (dd, 1H, J = 2.4 Hz, 10.0 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 28.34, 56.54, 104.05, 109.73, 110.71, 113.24, 127.18, 128.83, 134.91, 160.26, 174.33; MS (ES+) *m/e* 223.1 $[m+H]^+$

(Lit.[x] ^{1}H NMR (300 MHz, MeOD) δ 3.14 (βH), 3.84 (αH), 6.87 (H-6), 7.21 (H-2), 7.27 (H-7), 7.33 (H-4); ^{13}C NMR[xiii] (75.5 MHz, D_2O) δ 26.8, 57.8, 103.5, 108.0, 110.8, 113.1, 127.0, 127.3, 131.2, 159.4, 175.0; MS[xiii] (EI) *m/e* 222 $[M]^+$)

5-Chloro-*L*-tryptophan

^{1}H NMR (500 MHz, MeOH – d_4): δ 3.14 (dd, 1H, J = 9.0, 15.0 Hz), 3.43 (dd, 1H, J = 4.0, 15.0 Hz), 3.83 (dd, 1H, J = 4.5, 9.0 Hz), 7.07 (d, 1H, J = 2.0, 9.0 Hz), 7.25 (s, 1H), 7.32 (d, 1H, J = 9.0 Hz), 7.73 (d, 1H, J = 2.0 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 28.22, 57.9, 109.47, 113.64, 118.95, 122.87, 126.00, 126.94, 129.68, 136.71, 174.36; MS (ES+) *m/e* 239.1 $[m+H]^+$, 241.1 $[m+H]^+$

(Lit.[x] ^{1}H NMR (300 MHz, MeOD) δ 2.90 (αH), 3.26 (βH), 3.54 (βH), 7.05 (H-6), 7.20 (H-2), 7.31 (H-7), 7.73 (H-4); MS[xiv] (EI) *m/e* 238 $[M]^+$, 240 $[M]^+$)

5-Bromo-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 3.08 (dd, 1H, J = 8.8, 15.4 Hz), 3.43 (dd, 1H, J = 4.0 Hz, 15.4 Hz), 3.80 (dd, 1H, J = 4.4 Hz, 9.2 Hz), 7.19 (d, 1H, J = 2.0 Hz), 7.21 (m, 1H), 7.28 (d, 1H, J = 8.8 Hz), 7.90 (d, 1H, J = 1.6 Hz); MS (ES+) *m/e* 283.0 $[m+H]^+$, 285.1 $[m+H]^+$, 305.1 $[m+Na]^+$, 307.1 $[m+Na]^+$

(Lit.[x] ^{1}H NMR (300 MHz, D_2O) δ 2.90 (αH), 3.26 (βH), 3.54 (βH), 7.05 (H-6), 7.20 (H-2), 7.31 (H-7), 7.73 (H-4); MS[xiv] (EI) *m/e* 238 $[M]^+$, 240 $[M]^+$)

5-Iodo-*L*-tryptophan

^{1}H NMR (500 MHz, MeOH – d_4): δ 3.11 (dd, 1H, J = 9.0, 15.0 Hz), 3.43 (dd, 1H, J = 4.0 Hz, 15.0 Hz), 3.83 (dd, 1H, J = 4.0 Hz, 9.0 Hz), 7.18 (d, 1H, J = 2.0 Hz), 7.19 (s, 1H), 7.36 (dd, 1H, J = 2.0, 9.0 Hz), 8.09 (d, 1H, J = 1.5 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 28.20, 56.56, 83.13.

109.10, 114.59, 126.35, 128.43, 130.00, 131.06, 137.36, 174.40; MS (ES+) *m/e* 331.1 $[m+H]^+$

(Lit.[xi] ^{1}H NMR (500 MHz, DMSO) δ 2.96 (αH, dd, J = 8.3, 15.0 Hz), 3.22 (βH, dd, J = 4.2, 15.0 Hz), 3.39 (βH, dd, J = 4.2, 8.3 Hz), 7.20 (H-6, s), 7.21 (H-2, d, J = 8.4 Hz), 7.31 (H-7, dd, J = 1.6, 8.4 Hz), 7.92 (H-4, d, J = 1.6 Hz); MS[xi] (CI) *m/e* 331.0 $[m+H]^+$)

5-Methyl-*L*-tryptophan

^{1}H NMR (300 MHz, MeOH – d_4): δ 2.42 (s, 3H), 3.09 (dd, 1H, J = 9.0, 15.2 Hz), 3.49 (dd, 1H, J = 4.5, 15.2 Hz), 3.84 (dd, 1H, J = 4.5, 9.3 Hz), 6.94 (d, 1H, J = 4.8 Hz), 7.13 (s, 1H), 7.23 (d, 1H, J = 4.8 Hz), 7.50 (s, 1Hz); ^{13}C NMR (125 MHz, MeOH – d_4): δ 21.64, 28.54, 56.74, 109.08, 112.15, 118.95, 124.39, 125.18, 128.68, 129.26, 136.77, 174.45; MS (ES+): 219.1 $[m+H]^+$

(Lit. ^{1}H NMR[xii] (300 MHz, MeOD) δ 2.43, 2.85, 3.32, 3.57, 6.94, 7.09, 7.25, 7.51; MS[xiii] (EI) *m/e* 218 $[M^+]$)

5-Methoxy-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 3.10 (dd, 1H, J = 5.6, 15.2 Hz), 3.47 (dd, 1H, J = 3.6, 15.2 Hz), 3.83 (s, 3H), 6.76 (dd, 1H, J = 2.4 Hz, 8.8 Hz), 7.15 (s, 1H), 7.23 (d, 1H, J = 0.8 Hz), 7.24 (d, 1H, J = 4.8 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 28.62, 56.25, 56.51, 101.09, 109.34, 113.13, 113.24, 125.85, 128.73, 133.53, 155.36, 174.63; MS (ES+): *m/e* 234.1 $[m+H]^+$

Lit.[xiv] ^{1}H NMR (D_2O): δ 3.0 - 3.7 (2H, m, CH_2), 3.8 – 4.2 (2H, m, CH), 3.85 (3H, s, OCH3), 6.80 (1H, dd, J = 2, 9 Hz, C(6)-H), 7.20 (1H, s, C(2)-H), 7.20 (1H, d, J = 2 Hz, (C(4)-H), 7.30 (1H, d, J = 9 Hz, C(7)-H); MS *m/e* (EI) 234 $[m^+]$

5-Nitro-*L*-tryptophan

^{1}H NMR (500 MHz, MeOH – d_4): δ 3.27 (dd, 1H, J = 8.5, 15.5 Hz), 3.50 (dd, 1H, J = 4.0, 15.5 Hz), 3.88 (dd, 3H, J = 4.5, 8.5 Hz), 7.42 (s, 1H), 7.45 (s, 1H), 8.04 (d, 1H, J = 9.0 Hz), 8.78 (d, 1H, J = 2.0 Hz); ^{13}C NMR (125 MHz, MeOH – d_4): δ 27.91, 56.52, 110.56, 112.56, 117.09, 118.14, 126.70, 128.07, 129.02, 142.71, 174.08; MS (ES+): *m/e* 234.1 $[m+H]^+$

Lit. ^{1}H NMR[xiv] (D_2O): δ 3.12 (1H, dd, J = 7.5, 15.1 Hz, CH), 3.29 (1H, dd, J = 4.2, 15.1 Hz, CH2), 3.44 (1H, dd, J = 4.5, 7.4 Hz, CH2), 7.44 (1H, s, C(2)-H), 7.51 (1H, d, J = 9.0 Hz, C(6)-H), 7.97 (1H, dd, J = 2.2, 9.0 Hz, (C(7)-H), 8.63 (1H, d, J = 2.2 Hz, C(4)-H)

6-Fluoro-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 3.11 (dd, 1H, J = 9.2, 15.6 Hz), 3.45 (dd, 1H, J = 4.4, 15.6 Hz), 3.80 (dd, 1H, J = 4.0 Hz, 9.2 Hz), 6.82 (dt, 1H, J = 2.0, 6.1 Hz), 7.04 (dd, 1H, J = 2.4, 10.0 Hz), 7.17 (s, 1H), 7.65 (dd, 1H, J = 5.2, 8.8 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 28.69, 56.67, 98.14, 98.39, 108.36, 108.61, 120.35, 125.26, 125.62, 135.26, 174.91; MS (ES+) *m/e* 235.1 $[m+H]^+$

Lit.[x] ^{1}H NMR (300 MHz, MeOH – d_4): δ 3.13, 3.47, 3.84, 6.82, 7.05, 7.17, 7.64; ^{13}C NMR (60 MHz, MeOH – d_4): δ 98.3, 108.5, 109.8, 120.4, 125.2, 125.6, 138.3, 161.4

6-Chloro-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 3.15 (dd, 1H, J = 9.2, 15.6 Hz), 3.46 (dd, 1H, J = 4.0, 15.6 Hz), 3.82 (dd, 1H, J = 4.0 Hz, 9.2 Hz), 7.00 (dd, 1H, J = 2.0 Hz, 8.8 Hz), 7.21 (s, 1H), 7.35 (d, 1H, J = 1.6 Hz), 7.65 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 28.26, 56.58, 110.02, 115.26, 116.18, 120.96, 123.21, 126.09, 127.53. 139.19, 174.28; MS (ES+) *m/e* 222 $[m\text{-}NH_3]^+$, 239 $[m+H]^+$

Lit.: ^{1}H NMR[xii] (300 MHz, MeOH – d_4): δ 2.93, 3.27, 3.55, 6.99, 7.18, 7.35, 7.67; ^{13}C NMR[xii] (60 MHz, MeOH – d_4): δ 32.5, 57.9, 111.9, 112.9, 120.9, 125.5, 127.8, 128.2, 138.5, 182.2; MS[xv] *m/e* (EI) 238.0 $[m^+]$

6-Bromo-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 3.15 (dd, 1H, J = 7.2, 12.4 Hz), 3.46 (dd, 1H, J = 3.2, 12.4 Hz), 3.82 (dd, 1H, J = 3.6, 7.2 Hz), 7.14 (dd, 1H, J = 1.2, 6.8 Hz), 7.19 (s, 1H), 7.52 (d, 1H, J = 1.2 Hz), 7.61 (d, 1H, J = 6.8 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 28.21, 56.49, 109.89, 112.22, 120.54, 120.60, 126.31, 127.23, 128.59, 138.68, 174.57; MS (ES+) *m/e* 283.2 $[m+H]^+$, 285.2 $[m+H]^+$

6-Methyl-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 3.08 (dd, 1H, J = 8.0, 12.2 Hz), 3.34 (s, 3H), 3.48 (dd, 1H, J = 2.8, 12.2 Hz), 3.83 (dd, 1H, J = 3.2, 7.6 Hz), 6.88 (d, 1H, J = 6.4 Hz), 7.10 (s, 1H), 7.15 (s, 1H), 7.57 (d, 1H, J = 6.4 Hz); ^{13}C NMR (125 MHz, MeOH – d_4): δ 21.79, 28.57, 56.68, 109.41, 112.29, 119.07, 121.87, 124.48, 126.39, 132.47, 138.87, 174.48; MS (ES+) *m/e* 219.1 $[m+H]^+$, 241.1 $[m+Na]^+$

Lit.:[xii] ^{1}H NMR (300 MHz, MeOH – d_4): δ 2.43, 2.88, 3.31, 3.56, 6.86, 7.06, 7.14, 7.58; ^{13}C NMR (60 MHz, MeOH – d_4): δ 112.0, 112.3, 119.4, 121.4, 124.8, 127.0, 131.7

6-Methoxy-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 3.11 (dd, 1H, J = 6.0, 15.2 Hz), 3.44 (dd, 1H, J = 4.0, 15.2 Hz), 3.79 (s, 3H), 6.76 (dd, 1H, J = 2.4 Hz, 8.4 Hz), 6.86 (s, 1H), 7.24 (d, 1H, J = 0.8 Hz), 7.26 (d, 1H, J = 4.8 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 28.85, 55.21, 58.24, 101.15, 109.40, 113.18, 113.27, 125.83, 128.76, 133.52, 155.46, 174.65; MS (ES+) *m/e* 235.2 $[m+H]^+$, 259.2 $[m+Na]^+$

Fmoc-5-F-*L*-tryptophan

^{1}H NMR (300 MHz, MeOH – d_4): δ 3.12 (dd, 1H, J = 8.7, 14.7 Hz), 4.15 (dd, 1H, J = 6.9, 14.1 Hz), 4.22-4.33 (m, 2H), 4.47 (dd, 1H, J = 4.8, 8.4 Hz), 6.85 (dt, 1H, J = 2.4,

9.0 Hz), 7.14 (s, 1H), 7.21-7.30 (m, 4H), 7.36 (t, 2H, J = 7.5), 7.57 (d, 2H, J = 7.5), 7.76 (d, 2H, J = 7.5); MS (ES+) *m/e* 445.4 $[m+Na]^+$

Fmoc-5-MeO-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 3.12 (m, 1H), 4.15 (m, 2H), 4.68 (m, 1H), 6.72 (dd, 1H, J = 2.2 Hz, 0.6 Hz), 7.05 (dd, 1H, J = 3.8 Hz, 0.5 Hz), 7.20 (m, 1.5H), 7.34 (m, 1H), 7.55 (d, 1H, J = 1.6 Hz), 7.57 (d, 1H, J = 1.9Hz); ^{13}C NMR (100MHz, MeOH – d_4): δ 28.71, 56.22, 56.36, 68.04, 101.18, 112.66, 112.94, 120.87, 125.21, 126.27, 126.36, 128.17, 128.74, 142.52, 145.25; MS (ES+) *m/e* 465.2 $[m+Na]^+$

N-acetyl-5-methoxy-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.91 (s, 3H), 3.12 (dd, 1H, J = 8.0, 14.8 Hz), 3.30 (dd, 1H, J = 4.8, 14.8 Hz), 3.81 (s, 3H), 4.69 (dd, 1H, J = 5.2, 8.0 Hz), 6.74 (dd, 1H, J = 2.4, 8.8 Hz), 7.05 (s, 2H), 7.20 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, MeOH – d_4): δ 20.75, 22.44, 28.52, 54.73, 56.24, 101.10, 110.81, 112.72, 125.07, 129.17, 133.22, 155.08, 173.19, 175.28; MS (ES+) *m/e* 276.2 $[m+H]^+$

Lit.:[xiv] ^{1}H NMR (400 MHz, $CDCl_3$): δ

N-acetyl-5-nitro-*L*-tryptophan

^{1}H NMR (400 MHz, MeOH – d_4): δ 1.92 (s, 3H), 3.15 (dd, 1H, J = 8.4, 14.8 Hz), 3.31 (dd, 1H, J = 5.2, 14.8 Hz). 4.65 (dd, 1H, J = 5.6, 8.4 Hz), 7.19 (dd, 1H, J = 2.4, 8.8 Hz), 7.45 (d, 1H, J = 2.4 Hz), 8.08 (s, 1H), 8.13 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.74, 29.97, 55.18, 109.79, 112.15, 114.60, 122.52, 125.78, 129.12, 132.72, 144.16, 171.67, 174.44; MS (ES+) *m/e* 314.1 $[m+Na]^+$

N-Ac-*L*-W-OMe

^{1}H NMR (500 MHz, MeOH – d_4): δ 1.91 (s, 3H), 3.14 (dd, 1H, J = 8.0, 14.5 Hz), 3.27 (dd, 1H, J = 6.0, 14.5 Hz), 3.64 (s, 3H), 4.71 (dd, 1H, J = 6.0, 7.5 Hz), 7.00 (dt, 1H, J = 1.0, 7.5 Hz), 7.06 (s, 1H), 7.08 (dt, 1H, J = 1.0, 7.5 Hz), 7.31 (d, 1H, J = 8.0 Hz), 7.50 (d, 1H, J = 1.0, 8.0 Hz); ^{13}C NMR (125 MHz, MeOH – d_4): δ 22.31, 28.50, 52.64, 55.02, 110.73, 112.30, 119.09, 119.80, 122.43, 124.32, 128.72, 138.04, 173.21, 174.05; mp.: 144 °C

Lit.: mp[xvi].: 155-156 °C

N-Ac-5-F-*L*-W-OMe

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05 (s, 3H), 3.23 (dd, 1H, J = 7.6, 14.6 Hz), 3.37 (dd, 1H, J = 5.8, 14.6 Hz), 3.79 (s, 3H), 4.83 (dd, 1H, J = 6.0, 7.4 Hz), 6.97 (dt, 2H, J = 2.4, 9.0 Hz), 7.27 (d, 1H, J = 2.4 Hz), 7.32 (d, 1H, J = 2.4 Hz), 7.39 (d, 1H, J = 4.6 Hz), 7.43 (d, 1H, J = 2.4 Hz); MS (ES+) *m/e* 279.1 $[m+H]^+$, 301.1 $[m+Na]^+$

N-Ac-5-MeO-*L*-W-OMe

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (3H, s), 3.22-3.32 (2H, m), 3.69 (3H, s), 3.83(3H, s), 4.93 (1H, dquart, J = 2.4, 6.8 Hz), 6.00 (1H, d, J = 8.8 Hz), 6.84 (1H, dd, J = 2.4, 8.8 Hz), 6.93 (1H, d, J = 2.4 Hz), 6.96 (1H, d, J = 2.4 Hz), 7.221 (1H, d, J = 8.8 Hz), 7.99 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.30, 29.61, 54.40, 55.00, 102.13, 111.85, 114.01, 114.68, 125.33, 130.14, 133.18, 156.29, 171.75, 174.42; MS (ES+) *m/e* 291.1 $[m+H]^+$, 313.1 $[m+Na]^+$

N-Ac-5-NO_2-*L*-W-OMe

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (3H, s), 3.22-3.32 (2H, m), 3.68 (3H, s), 4.96 (1H, dq, J = 2.4, 6.8 Hz), 7.18 (1H, d, J = 8.8 Hz), 7.38 (1H, dd, J = 2.4, 8.8 Hz), 7.44 (1H, d, J = 2.4 Hz), 8.05 (1H, s), 8.11 (1H, d, J = 8.8 Hz), 8.33 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.98, 30.01, 52.43, 54.81, 109.74, 112.11, 114.57, 122.43, 125.87, 129.15, 132.68, 144.13, 171.64, 174.43; MS (ES+) *m/e* 306.1 $[m+H]^+$, 328.1 $[m+Na]^+$

N-Ac-*L*-W-NEt

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 3H, 7.4 Hz), 1.96 (s, 3H), 3.02 – 3.13 (m, 3H), 3.27 (dd, 1H, J = 5.2, 14.2 Hz), 4.65 (quartett, 1H, J = 5.2 Hz), 5.55 (s, br, 1H), 6.46 (d, 1H, J = 5.2 Hz), 7.02 (d, 1H, J = 2.4 Hz), 7.10 (dt, 1H, J = 1.2, 7.0 Hz), 7.18 (dt, 1H, J = 1.2, 7.0 Hz), 7.34 (d, 1H, J = 7.2 Hz), 7.68 (d, 1H, J = 7.2 Hz), 8.26 (s, br, 1H); ^{13}C NMR (125 MHz, MeOH – d_4): δ 14.81, 22.56, 30.12, 34.75, 53.71, 110.73, 111.38, 119.09, 119.82, 122.45, 124.30, 128.75, 138.07, 173.25, 174.07; MS (ES+) *m/e* 274.2 $[m+Na]^+$

Lit.:[xvii] MS (EI) *m/e* 273.2 $[m]^+$

N-Ac-5-F-*L*-W-NEt

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (3H, t, J = 7.2 Hz), 2.00 (3H, s), 3.01 (1H, dd. J = 9.2, 14.4 Hz), 3.04-3.17 (2H, m), 3.28 (1H, dd, J = 4.8, 14.4 Hz), 3.87 (3H, s), 4.60-4.65 (1H, m), 5.39 (1H, s, br), 6.39 (1H, d, J = 7.2 Hz), 6.85 (1H, dd, J = 2.4, 8.8 Hz), 7.01 (1H, d, J = 2.4 Hz), 7.22 (1H, d, J = 2.4 Hz), 7.24 (1H, d, J = 8.8 Hz), 8.00 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.43, 25.36, 30.96, 36.34, 54.34, 55.81, 102.28, 112.88, 114.01, 115.01, 125.58, 130.14, 133.17, 156.35, 172.87; MS (ES+) *m/e* 326.1 $[m+Na]^+$

N-Ac-5-MeO-*L*-W-NEt

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J = 7.2 Hz), 2.00 (3H, s), 3.01 (1H, dd. J = 9.2, 14.4 Hz), 3.04-3.17 (2H, m), 3.28 (1H, dd, J = 4.8, 14.4 Hz), 3.87 (3H, s), 4.60-4.65 (1H, m), 5.39 (1H, s, br), 6.39 (1H, d, J = 7.2 Hz), 6.85 (1H, dd, J = 2.4, 8.8 Hz), 7.01 (1H, d, J = 2.4 Hz), 7.22 (1H, d, J = 2.4 Hz), 7.24 (1H, d, J = 8.8 Hz), 8.00 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.43, 25.36, 30.96, 36.34, 54.34, 55.81, 102.28, 112.88, 114.01, 115.01, 125.58, 130.14, 133.17, 156.35, 172.87; MS (ES+) *m/e* 326.1 $[m+Na]^+$

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